eman ta zabal zazu

Universidad del País Vasco
Euskal Herriko Unibertsitatea

ORGANOCATALYTIC α-FUNCTIONALIZATION OF CARBONYL COMPOUNDS: CHEMO-, REGIO- AND STEREOSELECTIVITY

DOCTORAL THESIS

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Eskerrak

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de San Sebastián, Universidad del País Vasco (UPV-EHU), bajo la dirección del Dr. Claudio Palomo Nicolau y el Dr. Mikel Oiarbide Garmendia, a quienes expreso mi más sincero agradecimiento primero por darme la oportunidad de desarrollar esta tesis doctoral en este departamento y por su dedicación y esfuerzo durante el desarrollo de este trabajo. La financiación de este trabajo ha provenido de una beca predoctoral del Gobierno Vasco, así como la ayuda para la realización de estancias predoctorales en centros distintos al de aplicación para el personal investigador en formación.

I also want to thank Dr. Jonathan Clayden and his group for giving me the opportunity to do a short but unforgettable stay in his laboratory at the School of Chemistry in the University of Bristol and to participate in one of their research projects. Thank you very much for your hospitality.

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Noski, departamentuko lagunei ere eskerrak eman nahi dizkiet, bai ni baino lehen alde egin dutenei eta baita oraindik hor jarraitzen dutenei ere, garrasi asko egin arren beti laguntzeko prest agertzeagatik, baina batez ere kafe eta bazkalorduetan igarotako momentu onengatik.

I am thankful for having the best possible housemates (my English best friends and Hanz) while I was in Bristol. You made me like the UK far more than I would have ever expected. Thank you for all those Saturdays at the Anchor.

Eskerri kasko nire lagun gertukoenei asteburu guzti hauetan zertan ari naizen entzuteagatik eta burua beste zerbaitetan jartzen laguntzeagatik, ezinbestekoa izan da.

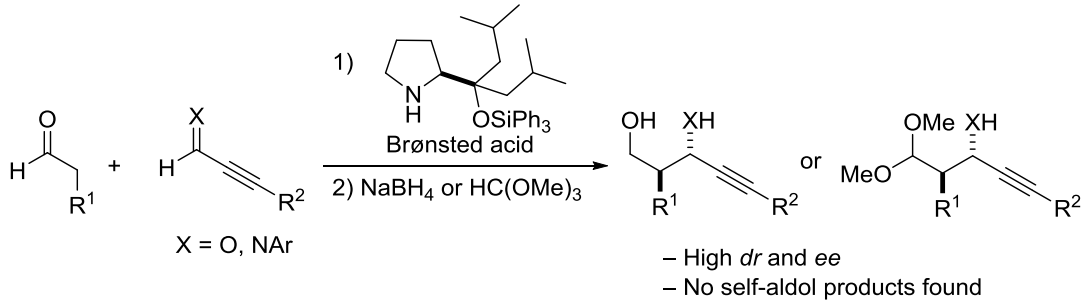
Nere eskerrik beroenak familiakoei, aita, ama eta Aimarri bereziki, nire lanaren inguruan interesa azaltzeagatik gaia beraientzat guztiz arrotza izan arren. Baita aitona-amona, osaba-izeba eta lengusuei, eta baita Wendyren familiari ere, beti alboan egoteagatik. Azkenik eta bereziki, Wendyri eman nahi dizkiot eskerrak, egunetik egunera onean eta txarrean nire ondoan egoteagatik. Entzundako aurkezpen guztiekin irabazia duzu zerua.

Eskerrik asko denoi

Summary

Many natural products and bioactive substances bear a stereogenic center adjacent to a carbonyl group. Therefore, great efforts have been made to develop stereocontrolled methods for the preparation of such structural motifs with a predefined configuration. One of the main approaches consists on the stereocontrolled addition of an enolate or equivalent species to a suitable electrophile. This approach is extremely versatile due to the array of procedures available for the formation of enolate equivalents and the set of electrophiles amenable for the reaction.

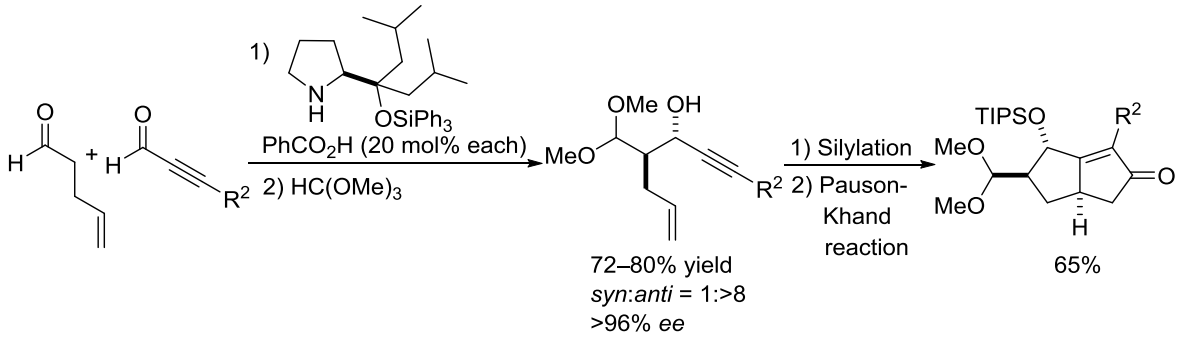
The addition of enolizable carbonyl compounds to propargylic imines, aldehydes or ketones is an interesting reaction owing to the synthetic versatility of the acetylenic adducts formed. Nevertheless, both propargyl imines and aldehydes/ketones have remained mostly overlooked in this context. Our group has employed these electrophiles in the direct aldol and Mannich reactions for the first time. In both reactions, the catalyst developed in the group (see Scheme A) together with participation of a Brønsted acid cocatalyst are key for the reactions via enamine to proceed smoothly and in high stereoselectivity.



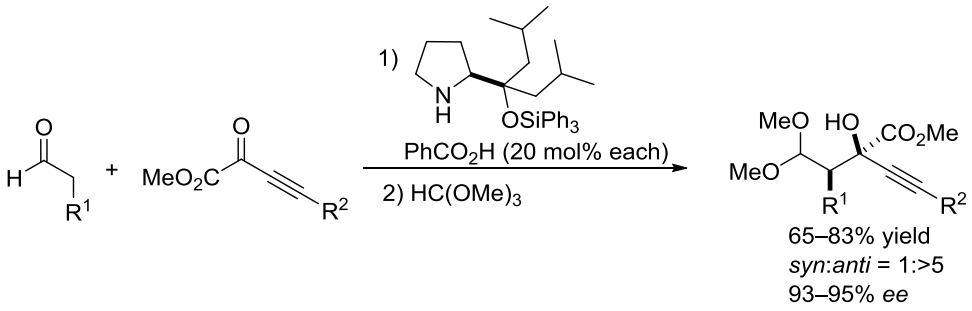
Scheme A

In this Doctoral Thesis it has been studied, on the one hand, the particular case of the use of ω-unsaturated aldehydes as donors in the aldol reaction mentioned above and the subsequent Pauson-Khand reaction of the resulting 1,ω-enynes (Scheme Ba). On the other hand, the behaviour of alkynyl ketones (ynones) as acceptors in such aldol reactions has also been studied (Scheme Bb).

a) Aldol reaction of ω-unsaturated enolizable aldehydes with ynals

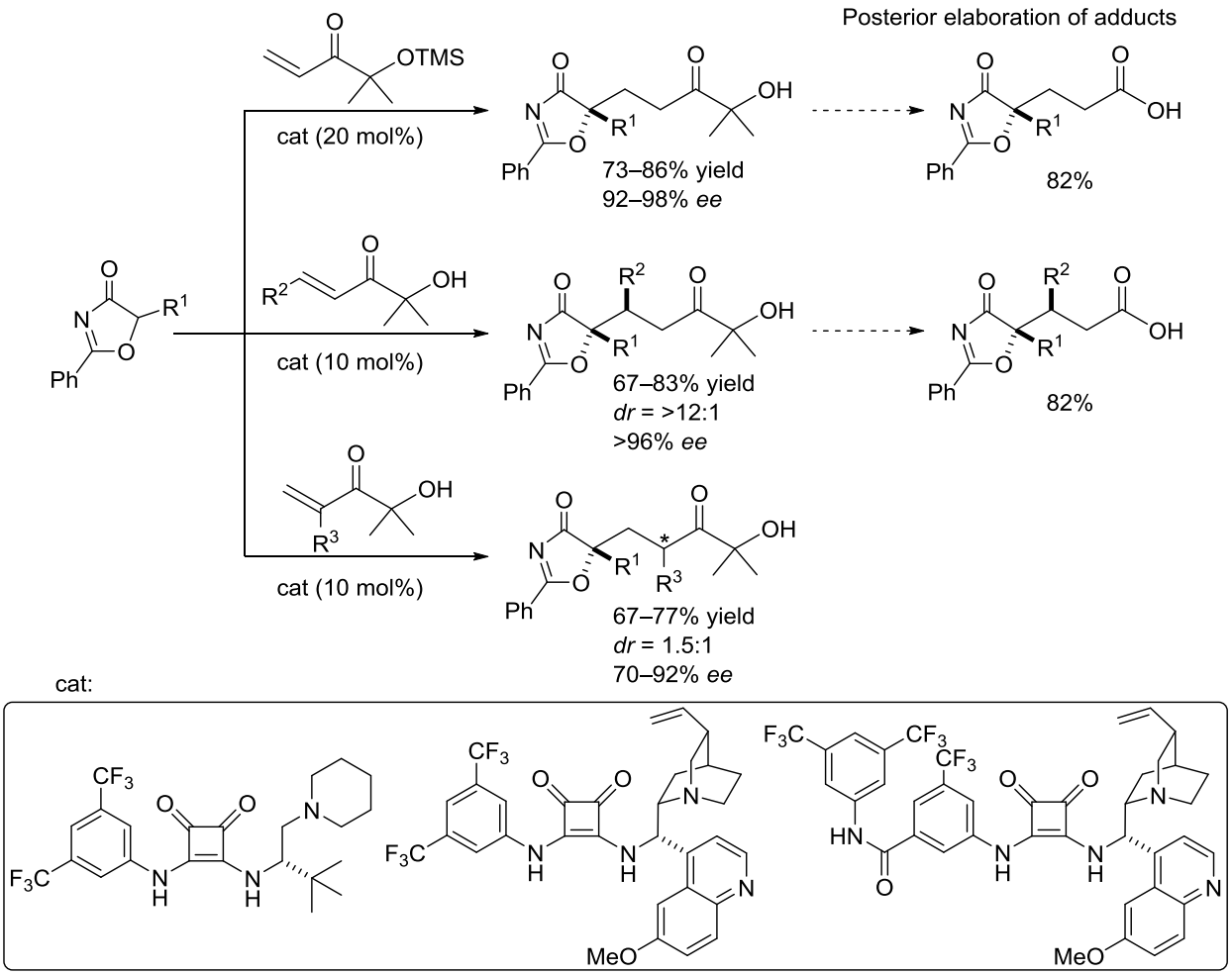


b) Aldol reaction of enolizable aldehydes with ynones



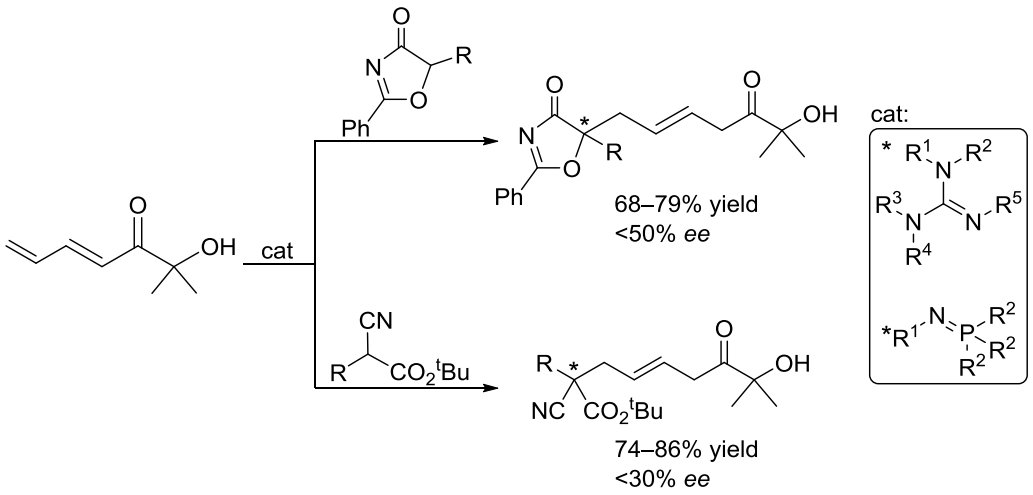
Scheme B

In a second chapter of this Doctoral Thesis, new catalytic systems based on Brønsted bases (BB) for the stereoselective generation of new tetrasubstituted carbon stereocenters have been studied. Based on previous results in our group using α'-oxy enones as acrylate equivalents in metal-catalyzed processes, their use as Michael acceptors in Brønsted base-catalyzed enantioselective processes has been studied. Specifically, the conjugate addition of oxazolones has been investigated, for which catalysts shown in Scheme C happened to be the optimal ones. Three situations have been addressed: a) addition to the unsubstituted enone (the *O*-$SiMe_3$ derivative resulting superior), b) addition to β-substituted enones, where not only the attenuated reactivity, but also the control of both contiguous stereogenic centers formed should be addressed, and c) addition to α-substituted hydroxyenones, in which case the control of diastereoselectivity during the generation of two non-adjacent stereocenters must be addressed. It should be noted that only scarce direct asymmetric methods exist for the access to this type of structures.



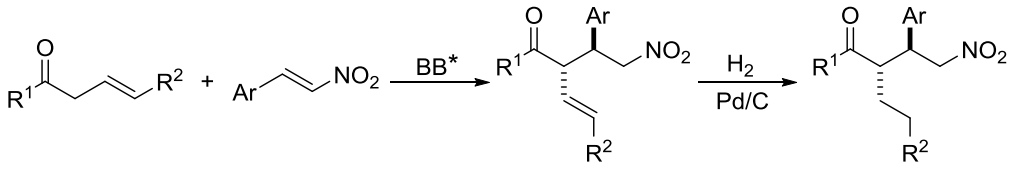
Scheme C

After the good results obtained with the α'-hydroxy enone as Michael acceptor, the corresponding conjugated α'-hydroxy dienones have been studied with the aim to ascertain to which extent both the stereoselectivity, and the regioselectivity (1,4-addition vs. 1,6-addition) of the process could be controlled. For this purpose, new chiral guanidine and phosphanimines were synthetized, which happened to efficiently control the regioselectivity, but not stereoselectivity (Scheme D).



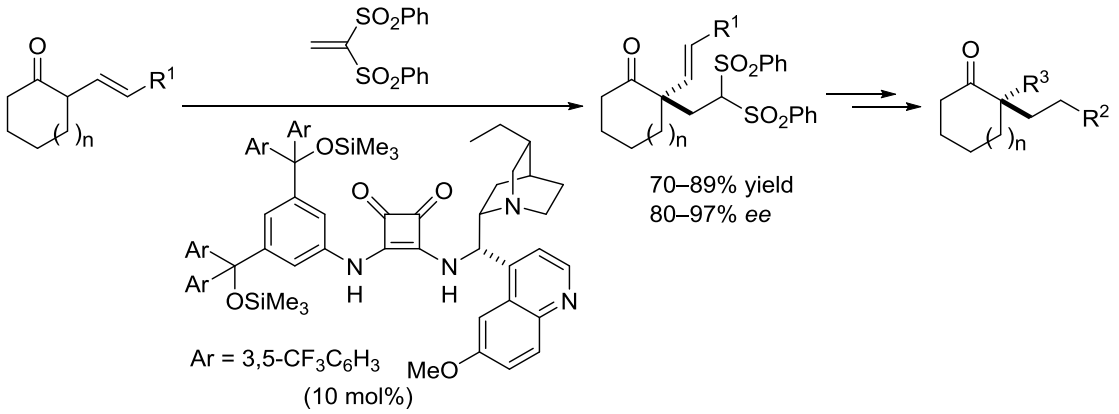
Scheme D

In a third chapter of this Thesis, the behaviour of vinylogous ketone enolates generated under catalytic conditions has been studied. Our laboratory has found that these ketones react in a highly regioselective manner with nitroalkenes and vinylsulfones through C_α in the presence of certain Brønsted bases, in contrast to most precedents in the literature, that describe reactions through C_γ (Scheme E). By this way adducts with two new contiguous stereocenters are accessible in high control, and can be subsequently elaborated in diverse ways.



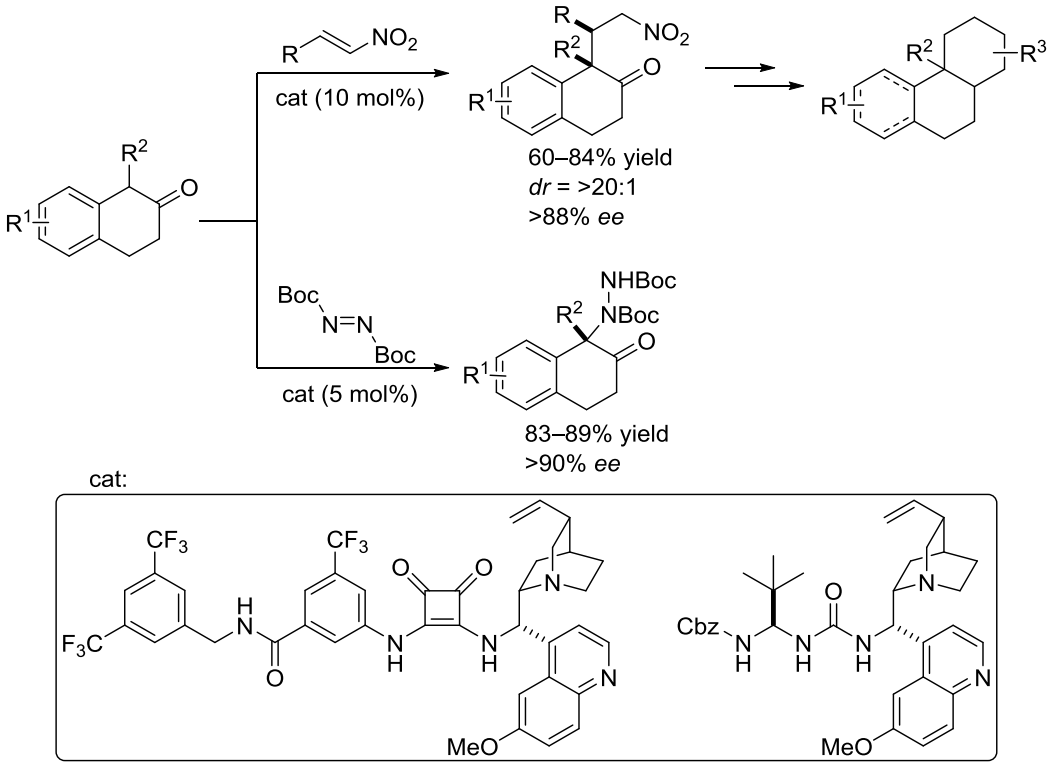
Scheme E.

In this Thesis, the method has been successfully extended to α-branched cyclic ketones giving access to the corresponding α,α-disubstituted (quaternary) ketones in good yield and overall high selectivity. The method was demonstrated to be robust, admitting cycloalkanones with different ring-sizes (n = 0, 1, 2, 3) and constituting a significant advance on scope (Scheme F).



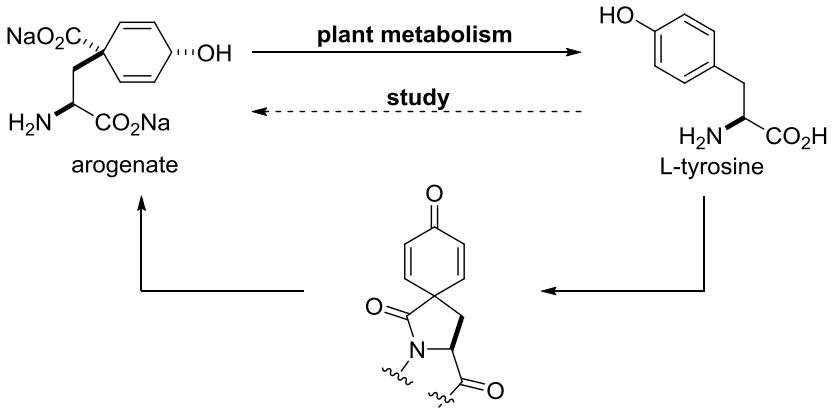
Scheme F

In the same context, the completely regio- and stereoselective functionalization of α-substituted β-tetralones through the bifunctional Brønsted base-catalyzed Michael reaction with nitroalkenes and addition to azodicarboxylates have been achieved (Scheme G). The absence of previous direct and catalytic methods for this transformation should be noted.



Scheme G

During the last part of this Thesis a short stay was performed in the group of Prof. Jonathan Clayden in the School of Chemistry of the University of Bristol, in which routes to the synthesis of arogenate from the natural amino acid L-tyrosine have been studied (Scheme H). Arogenate is a direct precursor of aromatic amino acids in the metabolism of certain plants and its derivatives are potential selective herbicides. However, only scarce procedures for its synthesis exist to date.

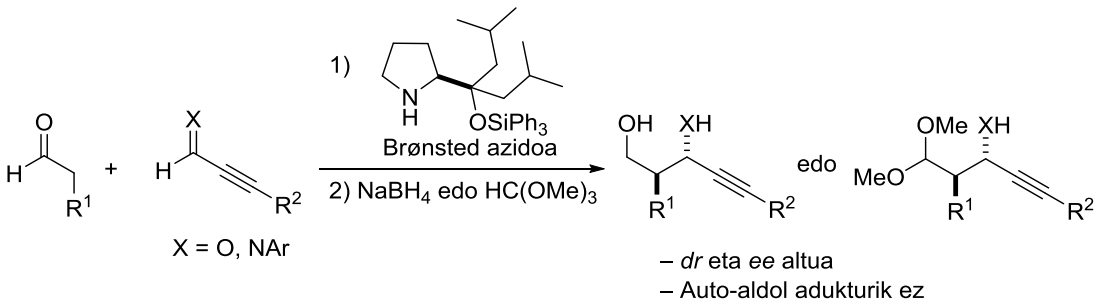


Scheme H

Laburpena

Produktu natural eta sustantzia bioaktibo askok zentru estereogeniko bat dute karbonilo taldearen alboko karbonoan (C_α). Ondorioz, esfortzu handia egin da egitura hauen prestaketa ahalbidetuko duten prozedura estereokontrolatuen garapenean. Estrategia ohikoenetako bat enolato edo baliokide bat eta elektrozale baten arteko adizio estereokontrolatuan datza. Planteamendu hau oso baliagarria suertatzen da enolato eta enolato baliokideen sorrerarako prozedura bat baino gehiago daudelako eta parte har dezaketen elektrozaleak askotarikoak izan daitezkeelako.

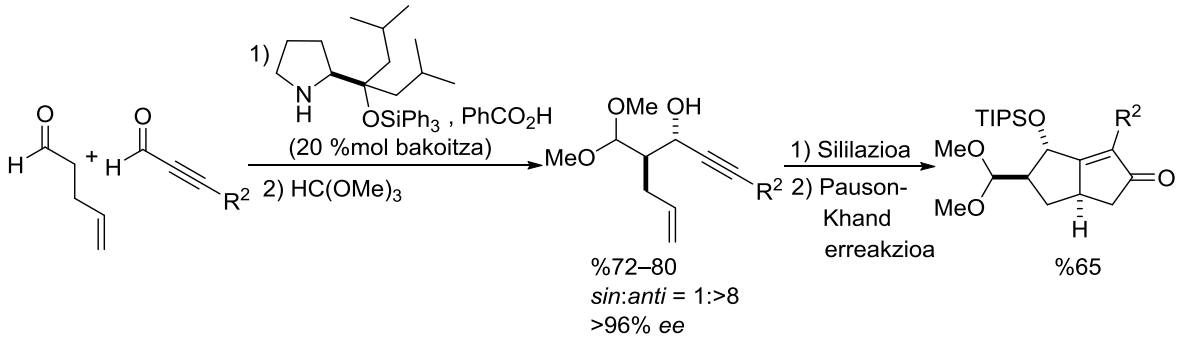
Konposatu karboniliko enolizagarrien eta imina, aldehido edo zetona propargilikoeen arteko adizio erreakzioak interesgarriak dira lortutako produktu azetilenikoen erabilgarritasun zabala dela eta. Hala ere, bai imina eta bai aldehido/zetona propargilikoak oso gutxi aztertuak izan dira testuinguru honetan. Gure ikerketa taldeak elektrozale hauek Mannich erreakzioan eta erreakzio aldolikoan erabili ditu lehen aldiz. Bietan, taldean garatutako aminokatalizatzailearen eta Brønsted azido kokatalizatzailearen partehartzeak oinarrizkoak dira enamina bidezko erreakzioa modu garbian eta estereokontrol onarekin eman dadin (A Eskema).



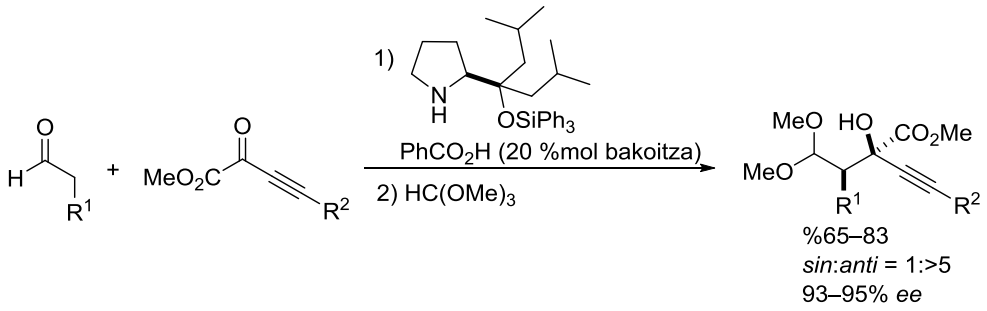
A Eskema

Doktore Tesi honetan aztertu da, alde batetik, aldehido ω-asegabeek emaile gisa goian aipatutako erreakzio aldolikoan duten portaera, eta, besterik, sortutako produktuen (1,ω-eninoen) portaera ondorengo Pauson-Khand erreakzioan (Ba Eskema). Bestalde, alkinil zetonen (inonen) portaera aztertu da hartzaile moduan erreakzio aldolikoan (Bb Eskema).

a) Aldehido ω-asegabe enolizagarrien eta inalen arteko erreakzio aldolikoa

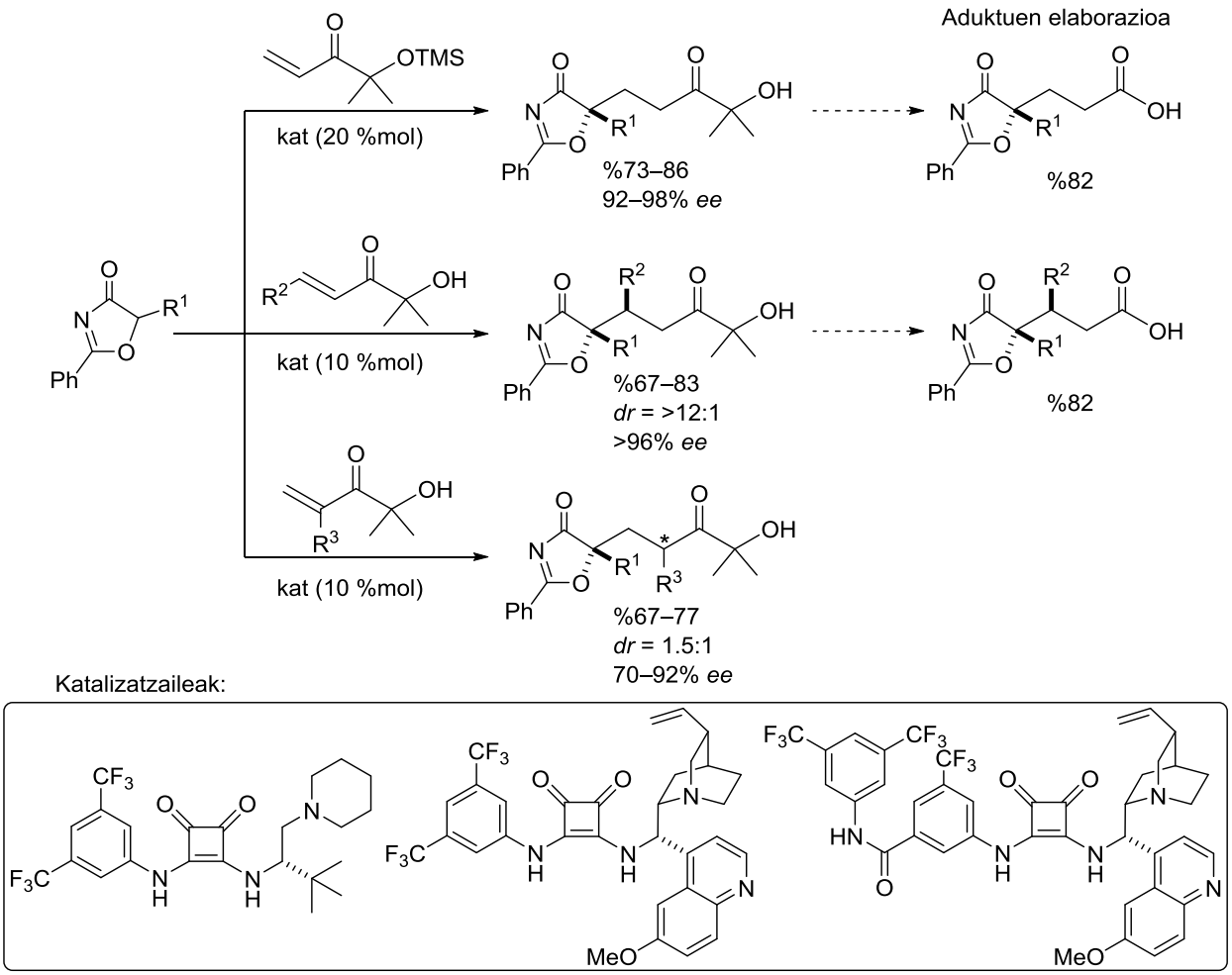


b) Aldehido enolizagarrien eta inonen arteko erreakzio aldolikoa



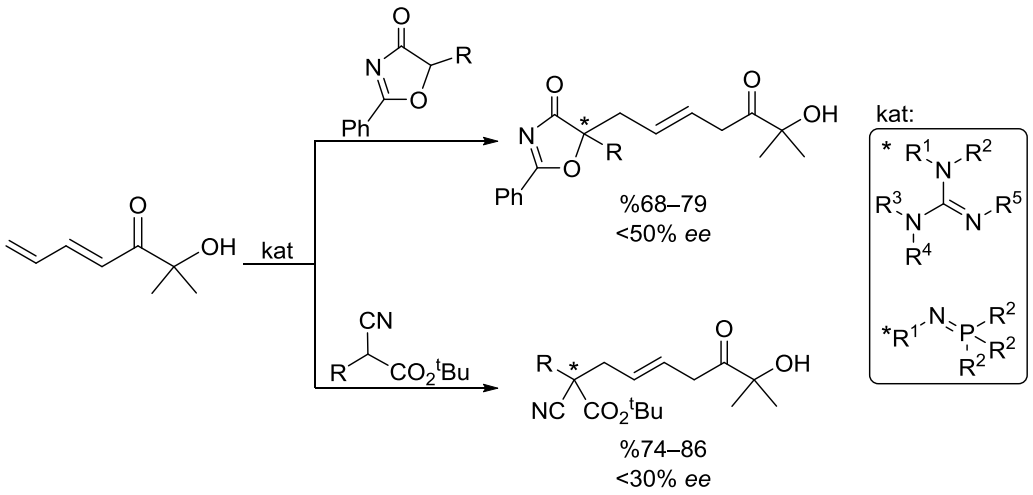
B Eskema

Doktore Tesi honen bigarren atal batean, Brønsted baseetan (BB) oinarritutako sistema katalitiko berriak aztertu dira tetraordezkatutako zentro estereogenikoen sorrera estereoselektiboa bideratzeko. Gure taldean α'-oxi enonak akrilato baliokide gisa aurrez aztertuak izan dira metalek katalizatutako erreakzioetan. Honetan oinarriturik, α'-oxi enonen erabilera aztertu da Brønsted baseek katalizatutako prozesu enantioselektiboetan. Zehazki, oxazolonen adizio konjokatua aztertu da, erreakzio honetarako C Eskemako katalizatzaileak izan direlarik eraginkorrenak. Hiru egoera aztertu dira: a) enona ordezkatu gabearekin (*O*-SiMe$_3$ deribatua egokiena delarik), b) enona β-ordezkatuekin, erreaktibitate baxuagoa izateaz gain sortutako bi zentro estereogeniko jarraien kontrola beharrezkoa delarik, eta c) enona α-ordezkatuekin, bi zentro estereogeniko ez jarraien sorreran diastereoselektibitatearen kontrola zailtasun gehigarri bat delarik. Esan beharra dago zuzeneko prozedura asimetriko gutxi daudela egitura mota hauen sorrerarako.



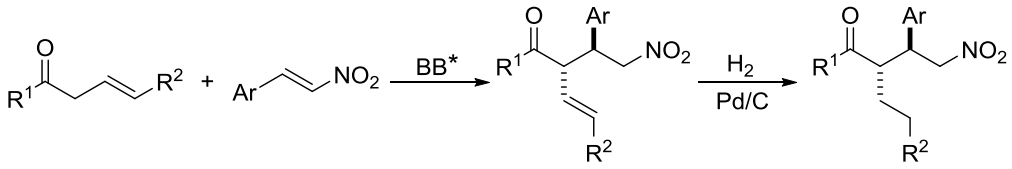
C Eskema

α'-Hidroxi enonak Michael hartzaile gisa erabiliaz lortutako emaitza hauen ondoren, dagokion α'-hidroxi dienonak aztertu dira prozesuaren estereoselektibotasuna eta erregioselektibotasuna (1,4-adizioa 1,6-adizioaren aurka) noraino kontrola daitezkeen argitzeko asmoz. Honetarako guanidina eta fosfanimina motako molekula kiral berriak sintetizatu dira, aipatutako erreakzioen erregioselektibotasunaren kontrolean eraginkorrak direla frogatu delarik, baina ez estereoselektibotasunaren kontrolean (D Eskema).



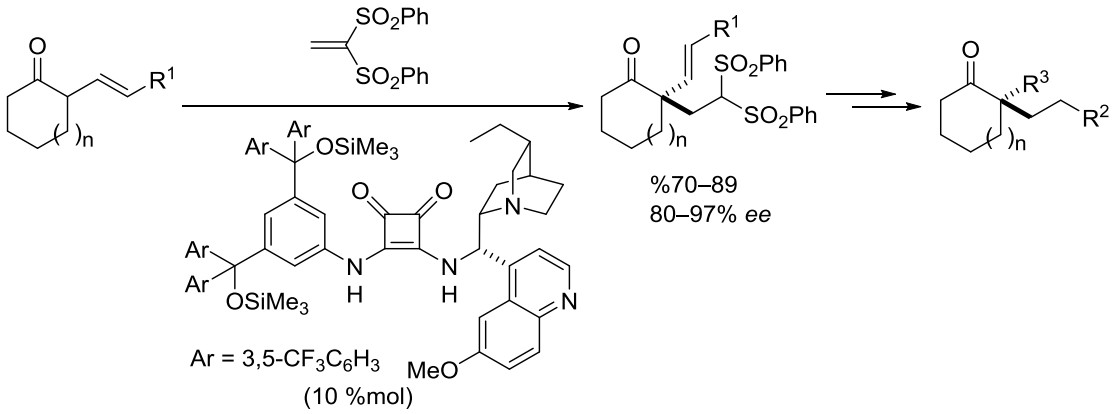
D Eskema

Doktore Tesi honen hirugarren atal batean, baldintza katalitikoetan sortutako zetona enolato binilogoen jokaera aztertu da. Gure laborategian enolato binilogo hauek Brønsted base izaera duten katalizatzaile batzuen eraginez sor daitezkela eta nitroalkeno zein binil sulfonekin erregioselektibotasun altuan erreakzionatzen dutela aurkitu da, α-bidea jarraituz, bibliografian deskribatutako aurrekari gehienek C_γ bidez erreakzionatzen duten bitartean (E Eskema). Erreakzioan bi zentro estereogeniko berri bata bestearen alboan dituzten aduktuak lor daitezke kontrol maila altuan, ondoren modu ezberdinetan eraldatuak izan daitezkeenak.



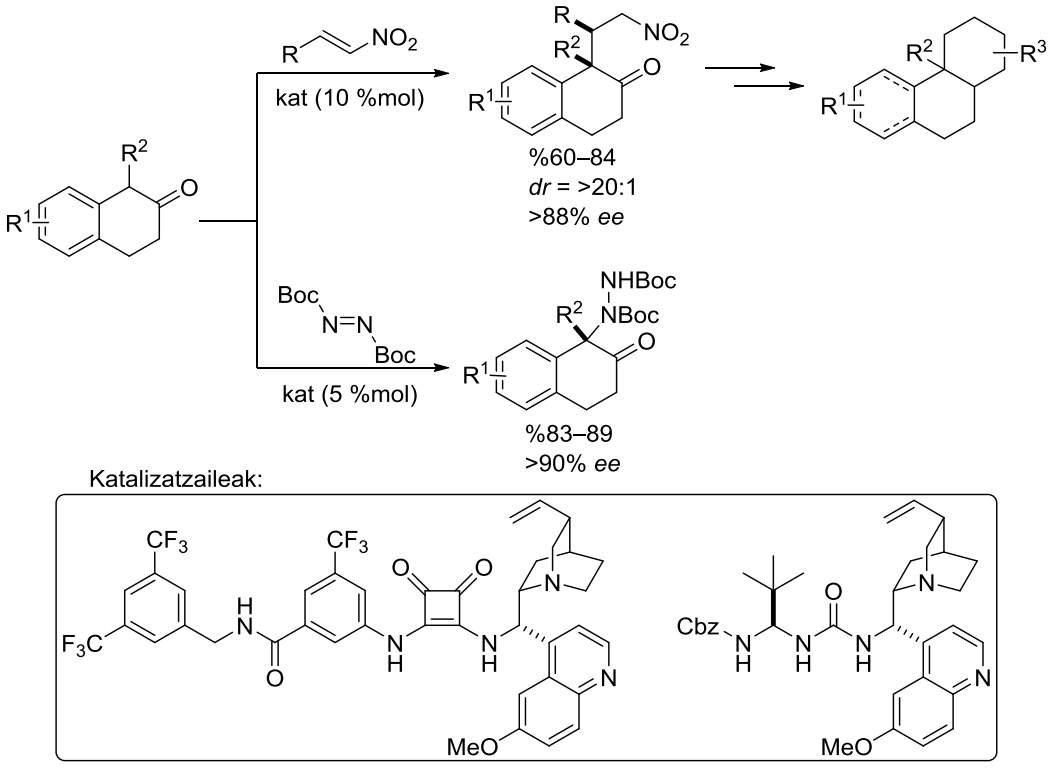
E Eskema

Tesi honetan prozedura hau arrakastaz zabaldu da α-adarkatutako zetona ziklikoetara, dagokion zetona α,α-biordezkatuak (kuaternarioak) etekin onean eta selektibotasun handian lortzea ahalbidetuz. Prozedura honen sendotasuna ere frogatu da tamaina ezberdinetako (n = 0, 1, 2, 3) zikloalkanonak erabiliz, garapen honek orainarteko esparruaren zabalkuntza nabarmena dakarrelarik (F Eskema).



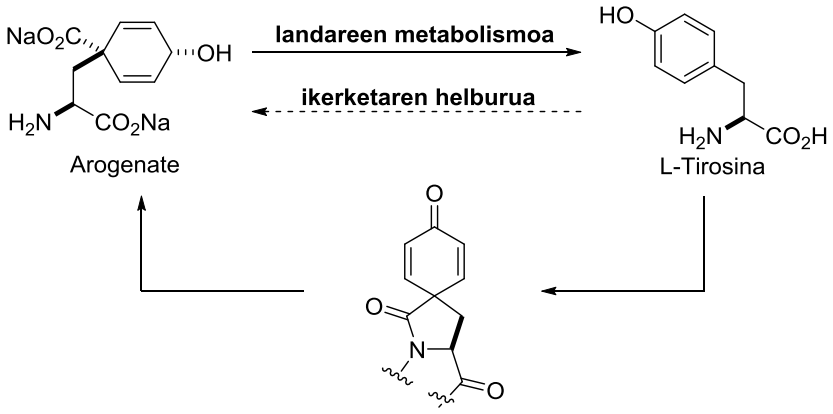
F Eskema

Testuinguru berean, β-tetralona α-ordezkatuen funtzionalizazio guztiz erregio- eta estereoselektiboa lortu da Brønsted baseek katalizatutako Michael erreakzioan oinarriturik, nitroalkenoak eta azodikarboxilatoak hartzaile moduan erabiliz (G Eskema). Kontuan hartu beharrekoa da oraindaino transformazio hau egiteko prozedura katalitikorik ez dagoela deskribatua.



G Eskema

Tesi honen azken atalean University of Bristol-eko School of Chemistry-ko Jonathan Claydenen taldean egindako egonaldi labur batean garatutako lana biltzen da. Bertan L-tirosina aminoazido naturaletik abiatuta arogenateren sintesirako zenbait bide aztertu dira (H Eskema). Arogenate amino azido aromatikoen aurrekaria da landare batzuen metabolismoan eta bere deribatuak herbizida selektibo potentzialak dira. Hala ere, gaur egun bere sintesirako prozedura gutxi dago.

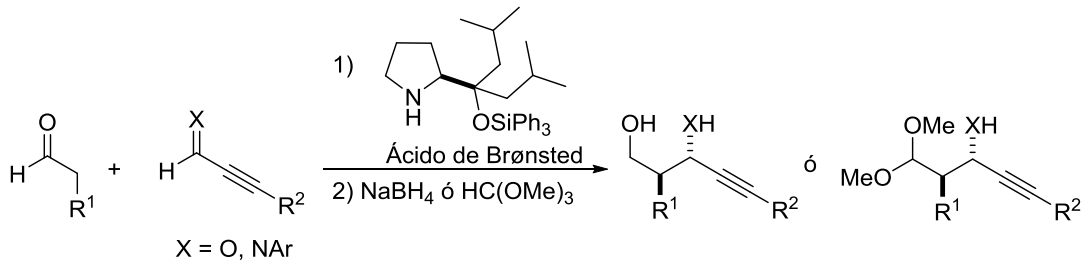


H Eskema

Resumen

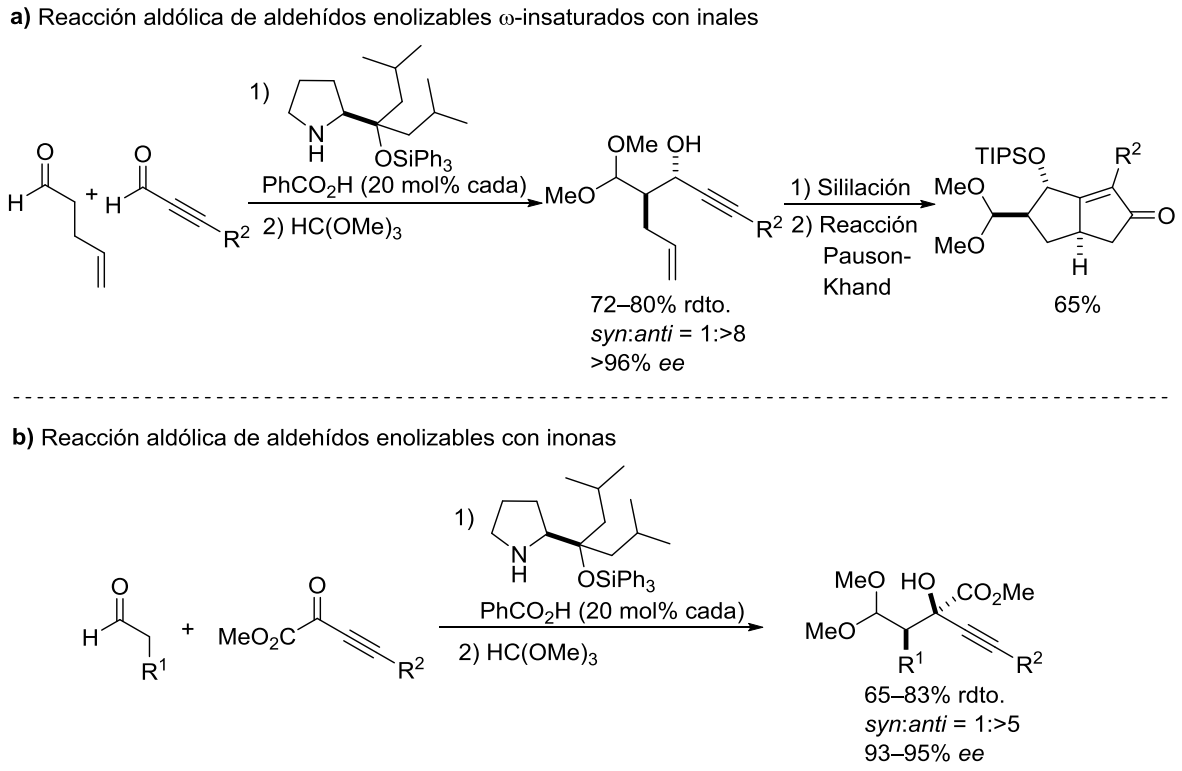
Muchos productos naturales y sustancias bioactivas contienen un centro estereogénico adyacente a un grupo carbonilo. Como consecuencia, se han realizado grandes esfuerzos para desarrollar métodos estereocontrolados que permitan la preparación de este tipo de estructuras con una configuración predefinida. Una de las aproximaciones más comunes consiste en la reacción estereocontrolada de un anión enolato o equivalente con un electrófilo. Esta aproximación resulta extremadamente versátil gracias a la variedad de procedimientos disponibles para la formación de equivalentes de enolato y el gran número de electrófilos que se prestan para esta reacción.

La adición de compuestos carbonílicos enolizables a iminas y aldehídos/cetonas propargílicos es una reacción interesante debido a las posibilidades sintéticas de los aductos acetilénicos obtenidos. Sin embargo, tanto las iminas como los aldehídos/cetonas propargílicas han sido poco estudiados en este contexto. Nuestro grupo ha empleado estos electrófilos por primera vez en las reacciones aldólica y de Mannich directas. En ambos casos, para que las reacciones vía enamina transcurran de forma limpia y con elevada estereoselectividad ha sido clave el uso del catalizador mostrado desarrollado en el grupo (Esquema A) en conjunción con un ácido de Brønsted.



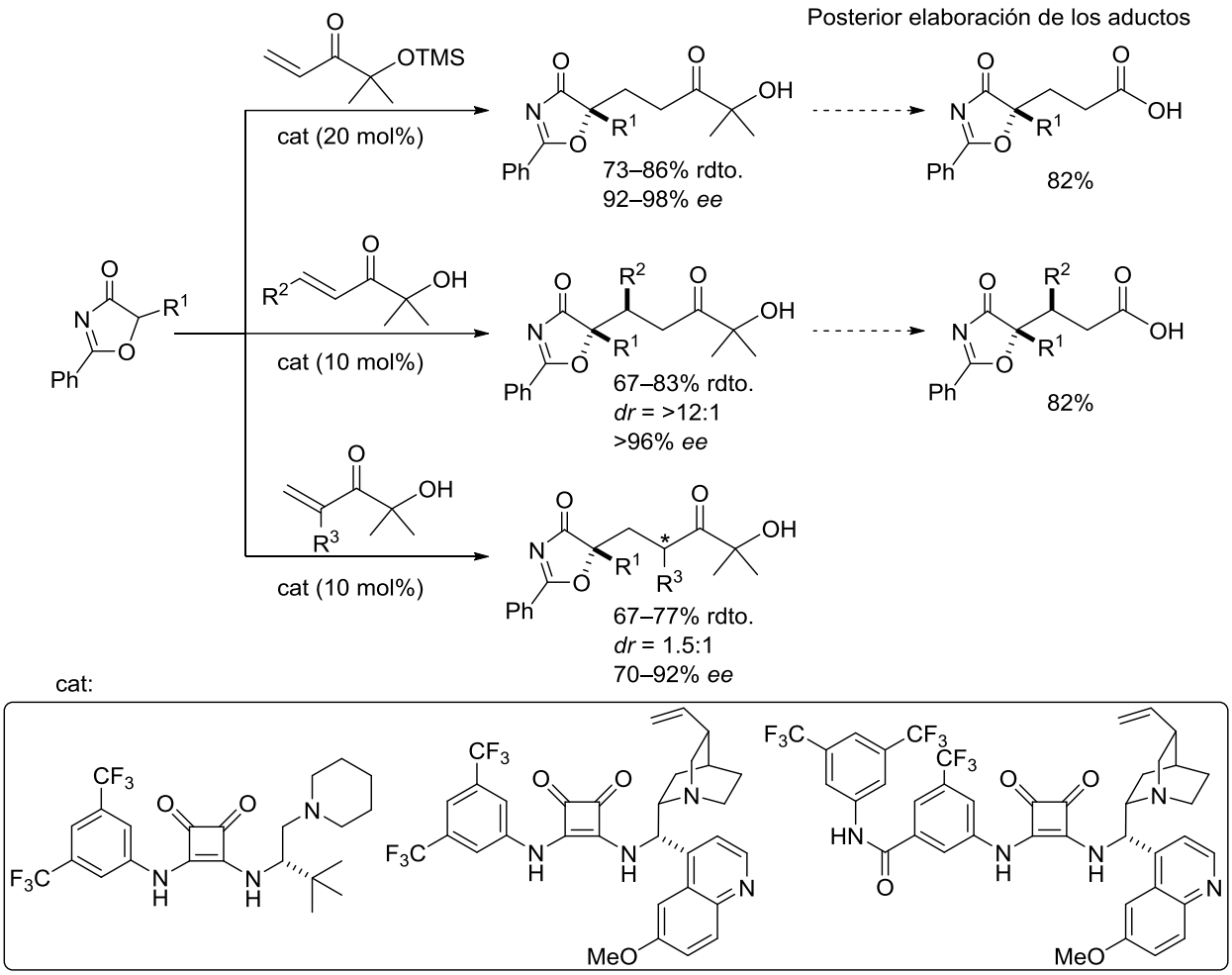
Esquema A

En esta Tesis Doctoral se ha estudiado, por un lado, el caso particular de la utilización de aldehídos ω-insaturados como dadores de la reacción aldólica arriba mencionada y la posterior reacción de Pauson-Khand de los 1,ω-eninos resultantes (Esquema Ba). Por otro lado, se ha estudiado el comportamiento de alquinil cetonas (inonas) en dichas reacciones aldólicas vía enamina (Esquema Bb).



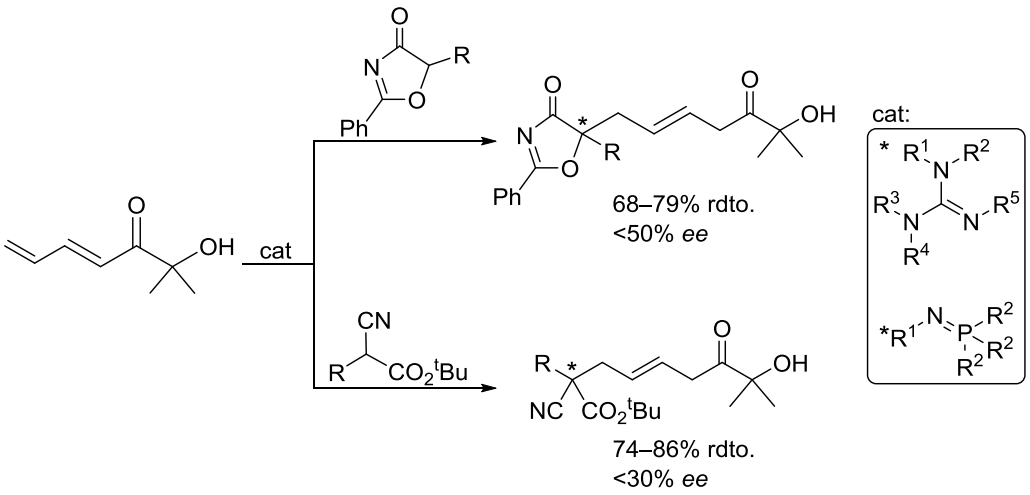
Esquema B

En un segundo apartado de esta Tesis Doctoral se han estudiado nuevos sistemas catalíticos basados en bases de Brønsted (BB) para la generación enantioselectiva de compuestos de interés con un carbono tetrasustituido. Sobre la base de resultados previos del grupo en la utilización de α'-oxi enonas como equivalentes de acrilatos en procesos catalizados por metales, se ha estudiado su utilización como aceptores de Michael en procesos catalizados por bases de Brønsted quirales. De forma específica, se ha estudiado la adición conjugada de oxazolonas, reacción para la que han resultado óptimos los catalizadores de escuaramida mostrados (Esquema C). Se han abordado tres situaciones: a) la adición a la enona no sustituida (en cuyo caso el derivado *O*-$SiMe_3$ ha resultado superior), b) la adición a enonas β-sustituidas, donde además de la atenuada reactividad un segundo aspecto crucial ha sido el control de los dos centros estereogénicos contiguos que se forman, y c) la adición a hidroxienonas α-sustituidas, en cuyo caso ha de abordarse el control de la diastereoselectividad durante la generación de dos centros estereogénicos no contiguos. Conviene destacar que apenas existen métodos directos y asimétricos para el acceso a este tipo de estructuras.



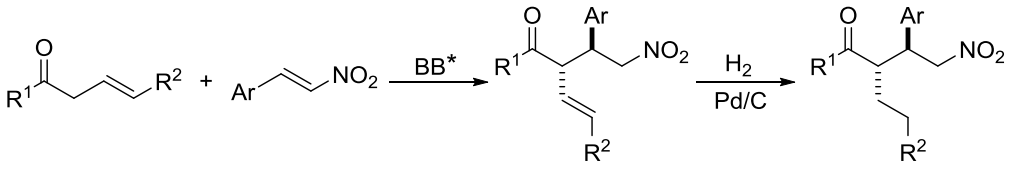
Esquema C

Tras los buenos resultados obtenidos con la α'-hidroxi enona como aceptor de Michael, posteriormente se ha explorado el comportamiento de las correspondientes α'-hidroxi dienonas conjugadas, con objeto de averiguar hasta qué punto se puede controlar no sólo la estereoselectividad del proceso con estos sustratos, sino también la regioselectividad (adición 1,4 frente a adición 1,6). Para este propósito se han preparado nuevas guanidinas y fosfaniminas quirales, las cuales han resultado ser catalizadores eficientes en el control de la regioselectividad, pero no en el de la estereoselectividad (Esquema D).



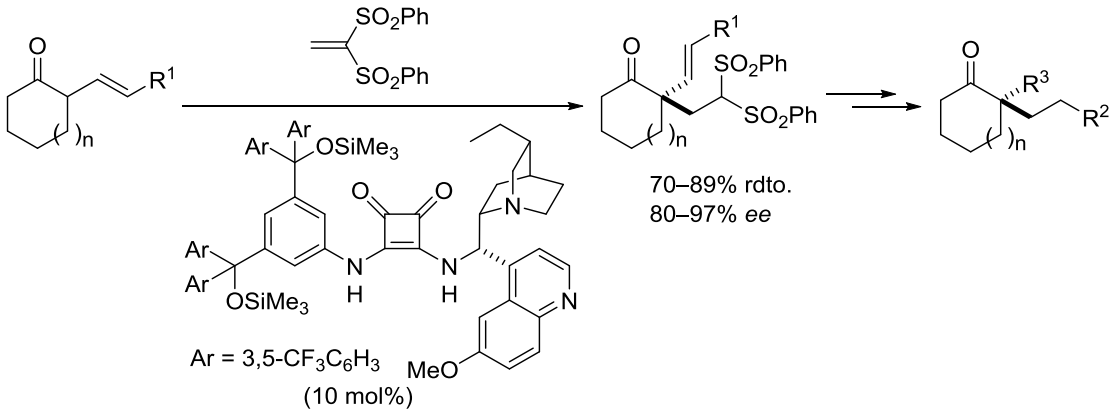
Esquema D

En un tercer apartado de esta Tesis, se ha estudiado el comportamiento de enolatos de cetona vinílogos generados en condiciones catalíticas. Se ha encontrado que estas cetonas en presencia de ciertas bases de Brønsted reaccionan de forma altamente regioselectiva con nitroalquenos y vinilsulfonas a través del C_α, en contraste a la mayoría de casos previamente descritos en la bibliografía, que lo hacen por C_γ (Esquema E). Esta circunstancia permite acceder a aductos con dos nuevos estereocentros contiguos con un grado de control notable y que pueden ser posteriormente elaborados de diversas maneras.



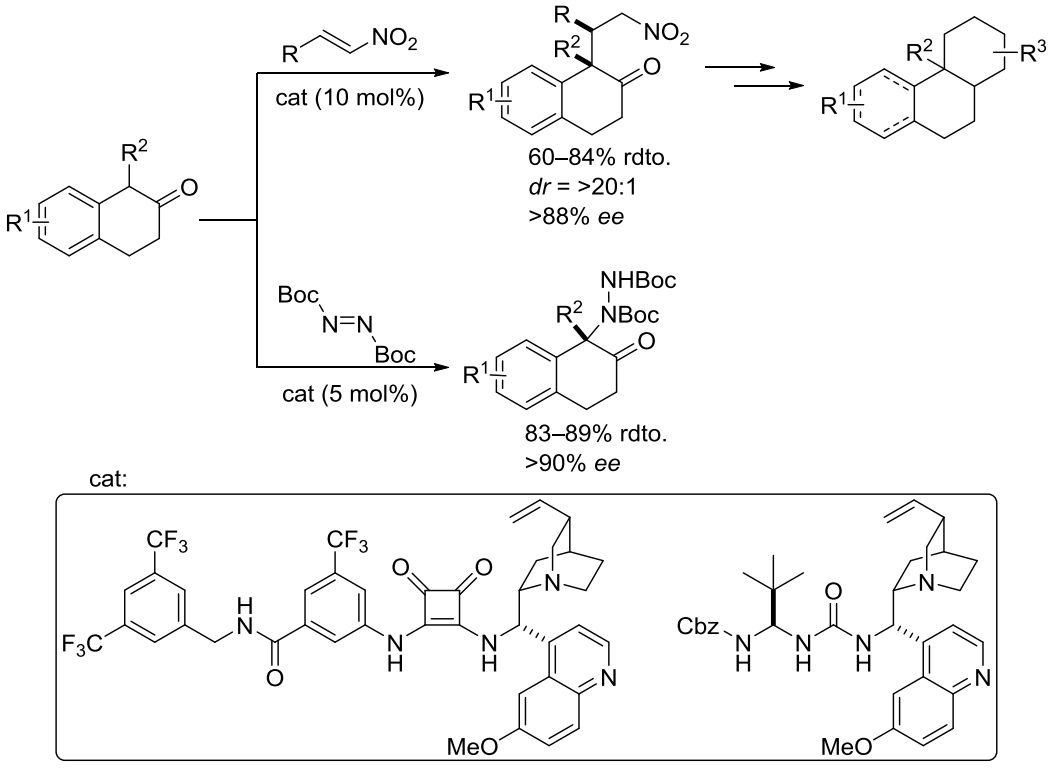
Esquema E

Ha sido posible extender esta metodología a cetonas cíclicas con un grupo alquenilo en C_α obteniéndose las correspondientes cetonas α,α-disustituidas (cuaternarias) con buenos rendimientos y selectividades elevadas en general. El método ha resultado ser muy robusto, admitiendo cicloalcanonas con tamaños de ciclo variable (n = 0, 1, 2, 3) y constituyendo un avance significativo sobre lo realizado hasta la fecha (Esquema F).



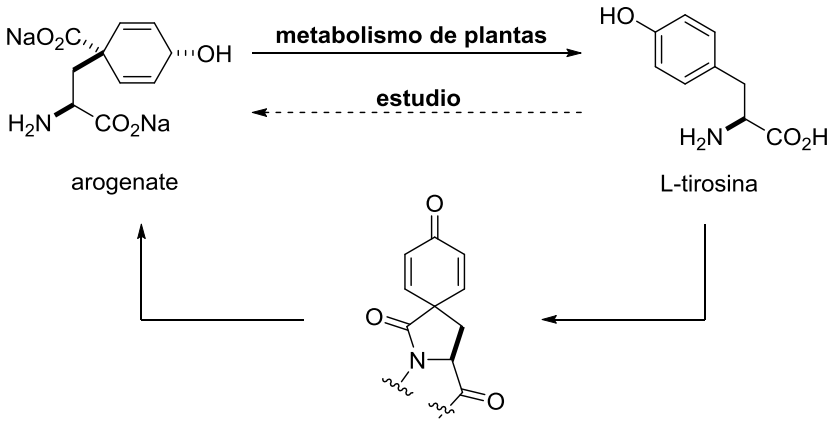
Esquema F

En este mismo contexto, se ha logrado llevar a cabo la funcionalización de forma totalmente regio- y estereoselectiva de β-tetralonas α-sustituidas tanto mediante reacción de Michael con nitroalquenos como mediante adición a azodicarboxilatos catalizadas por bases de Brønsted bifuncionales (Esquema G). Conviene señalar la ausencia de métodos directos y catalíticos previos para esta transformación.



Esquema G

Durante el último tramo de la Tesis se ha desarrollado una breve estancia en el grupo del Prof. Jonathan Clayden del School of Chemistry de la University of Bristol, donde se han estudiado algunas rutas de síntesis del arogenate a partir del aminoácido natural L-tirosina (Esquema H). El arogenate es un precursor inmediato de aminoácidos aromáticos en el metabolismo de algunas plantas y sus derivados son potenciales herbicidas selectivos. Sin embargo, hasta la fecha existen escasos procedimientos de síntesis.



Esquema H

Abbreviations and acronyms

AAA	Aromatic amino acid
Ac	Acetyl
aq.	Aqueous
Ar	Aryl
Å	Angstrom
BA	Benzoic acid
BB*	Chiral Brønsted base
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BINOL	1,1’-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOX	Bisoxazoline
^{n}Bu	*n*-Butyl
^{i}Bu	Isobutyl
^{t}Bu	*tert*-Butyl
CAN	Cerium(VI) ammonium nitrate
cat	Catalyst
Cbz	Bencyloxicarbonyl
CDI	1,1-Carbonyldiimidazol
*m*CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphorsulfonic acid
quant.	Quantitative
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane

DBE	Dibromoethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
$(DHQD)_2PYR$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
DIBALH	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DSC	*N,N*'-Disuccinimidyl carbonate
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
h	Hour(s)
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate

HFIP	Hexafluoroisopropanol
HMDS	bis(Trimethylsilyl)amide
HOBT	1-hydroxybenzotriazole
HPLC	High-performance liquid chromatography
Im	Imidazole
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
LG	Leaving group
M	Metal
Me	Methyl
m. p.	Melting point
min	Minutes
Ms	Methanesulfonyl
MS	Mass spectrometry
M.S.	Molecular sieve
MTBE	Methyl *tert*-butyl ether
MVK	Methyl vinyl ketone
Naph	Naphthyl
n. d.	Not determined
n. r.	No reaction
*p*NBA	*para*-Nitrobenzoic acid
NCA	*N*-Carboxyanhydride
NMM	*N*-Methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide

NMR	Nuclear magnetic resonace
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
o.n.	Overnight
ORTEP	Oak ridge thermal ellipsoid plot
PG	Protecting group
Ph	Phenyl
Phth	Phthalic anhydride
^{n}Pr	*n*-Propyl
^{i}Pr	Isopropyl
pyr	Pyridine
quant.	Quantitative
Rac.	Racemic
Ref.	Reference
RT	Room temperature
t	Time
t_R	Retention time
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
Tf	Trifluoroacetate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

TLC	Thin layer chromatography
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
TMSO	3-(Trimethylsilyl)-2-oxazolidinone
TPP	Triphenylphosphine
triton B	Benzyltrimethylammonium hydroxyde
Ts	*para*-toluenesulfonyl
*p*TSA	*para*-Toluenesulfonic acid
UV	Ultraviolet

Index

Chapter 1:

Introduction

1. Introduction

Introduction

1.1. α-Substituted carbonyl compounds

Molecules containing carbonyl groups with an adjacent stereocenter are widespread within natural products and biologically active compounds, like the ones depicted in Figure 1.[1] Therefore, methods capable of accessing such moieties in high selectivity are most sought after.

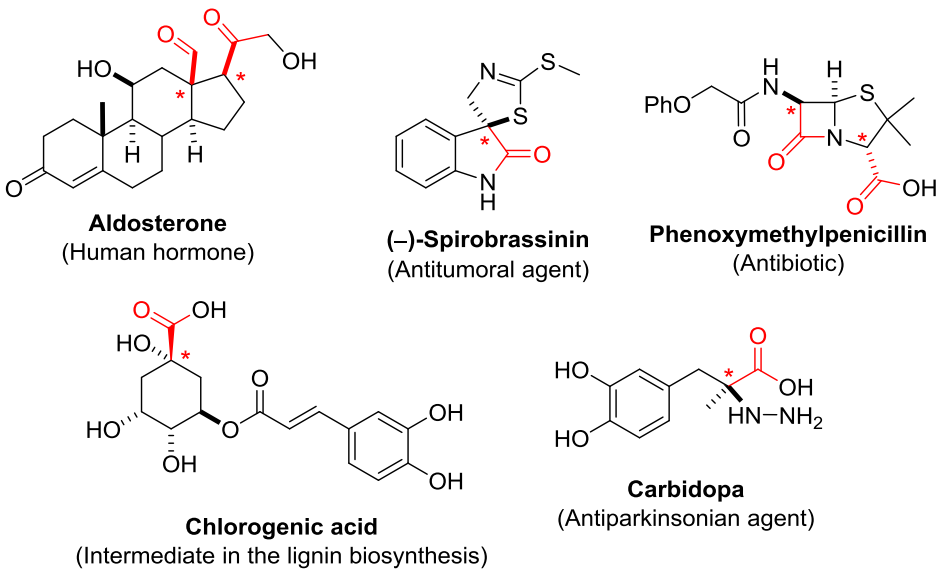
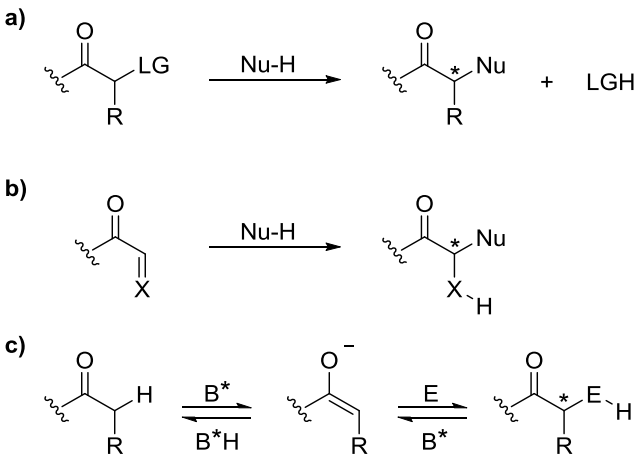


Figure 1.

Three main approaches for the stereoselective formation of a stereogenic center in the α-position of a carbonyl compound are shown in Scheme 1. Among them, the present thesis is focused on approach c), that is, reaction of an electrophile with an enolate anion or equivalent under proton transfer conditions.

[1] Aldosterone: F. Jaisser, N. Farman, *Farmacol. Rev.* **2016**, *68*, 49–75. (–)-Spirobrassinin: L. Liu, S.-L. Zhang, F. Xue, G.-S. Lou, H.-Y. Zhang, S.-C. Ma, W. Duan, W. Wang, *Chem. Eur. J.* **2011**, *17*, 7791–7795. Phenoxymethylpenicillin: J. Colloway, A. Couch, F. Foster, W. Hunter, V. Knight, A. C. White, *Antibiotics Annu.* **1955**, *3*, 490–501. Chlorogenic acid: W. Boerjan, J. Ralph, M. Baucher, *Annu. Rev. Plant Biol.* **2003**, *54*, 519–546. Carbidopa: G. C. Davis, A. C. Williams, S. P. Markey, M. H. Ebert, E. D. Caine, C. M. Reichert, I. J. Kopin, *Psychiatry. Res.* **1979**, *1*, 249–254.



Scheme 1.

Approach c) is extremely versatile owing to three main aspects among others:[2] i) there are several procedures to generate enolate equivalents (Figure 2); ii) enolates and equivalents are highly nucleophilic, so they can react with a variety of electrophiles; and iii) the approach is well suited for the generation of two contiguous stereocenters when both nucleophile and electrophile are prostereogenic.

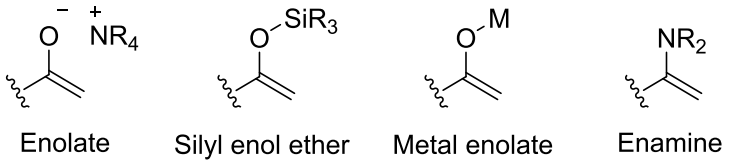


Figure 2.

Two main approaches, namely the use of chiral auxiliaries and catalytic methods, are suitable strategies to control the stereogenical outcome of the reactions leading to a carbonyl compound with an α-stereocenter.

As usual, initial developments in this area were based on the use of covalently bound chiral auxiliaries. Chiral auxiliaries must be capable of transferring the chiral information during the new bond formation event and easily cleavable from the obtained adducts for the procedure to be practical.

Chiral secondary amines were among the first chiral auxiliaries developed for this endeavour, which upon condensation with ketones and aldehydes form enamine

[2] a) C. Spino, *Org. Prep. Proced. Int.* **2003**, 35, 1–120. a) W. Carruthers, I. Coldham, *Modern Methods of Organic Synthesis*, Ed. Cambridge University Press, Cambridge, **2004**, 1–45. b) F.A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Ed. Springer, Heildeberg, **2007**, vol. B. c) P. Knochel, G. A. Molander, *Comprehensive Organic Synthesis II*, Ed. Elsevier, Amsterdam, **2014**, vol. 1.

intermediates with enhanced nucleophilicity. In 1969 Yamada et al.[3] reported the first examples in a series of investigations on the alkylation of chiral enamines derived from L-proline esters. With this methodology, the products of the formal addition of cyclohexanone to methyl acrylate and acrylonitrile, as well as from the reaction with strongly electrophilic alkyl halides were obtained, although unfortunately, with very low yields (<25%) and *ee* values (<60%). Subsequent work by other groups identified other chiral amines that performed superior for different asymmetric alkylations. These developments were focused on cyclohexanone-derived enamines as substrates almost exclusively (Figure 3).

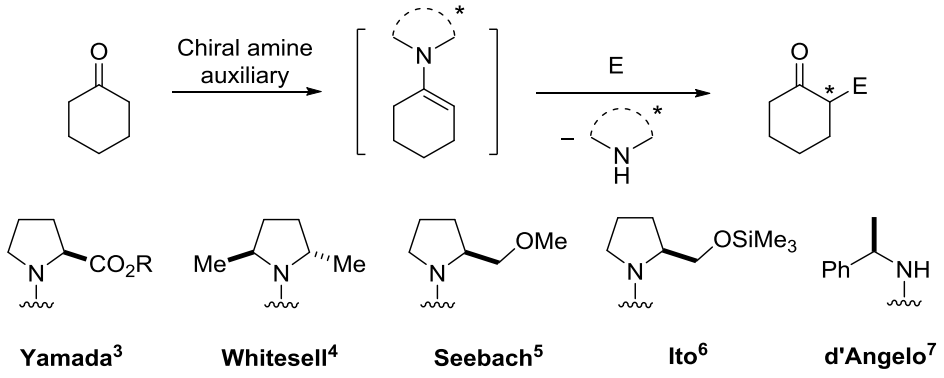


Figure 3.

Hydrazines are another functional group that can condense with aldehydes and ketones, leading to the formation of hydrazones, which are good nucleophiles upon deprotonation.[8] In this context, Enders[9] explored in depth the usefulness of chiral hydrazones derived from (S)-1-amino-2-methoxymethylpyrrolidine for the α-functionalization of aldehydes and ketones (Figure 4).

[3] a) S.-I. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett.* **1969**, *10*, 4233–4236. For more information on the subject see: b) P. W. Hichmott, *Tetrahedron.* **1982**, *38*, 1975–2050.

[4] J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **1977**, *42*, 1663–1664.

[5] a) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 1637–1654. For more references on the subject see: b) W. Miltz, W. Steglich, *Synthesis* **1990**, 750–751.

[6] Y. Ito, M. Sawamura, K. Kominami, T. Saegusa, *Tetrahedron Lett.* **1985**, *26*, 5303–5306.

[7] a) M. Pfau, G. Revial, A. Guigant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273–274. For further references on the subject see: b) J. Y. Kang, R. C. Johnson, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629–3637.

[8] E. J. Corey, D. Enders, *Tetrahedron Lett.* **1976**, *17*, 3–6.

[9] For an example of: Alkylation: a) D. Enders, H. Eichenauer, *Angew. Chem. Int. Ed.* **1976**, *15*, 549–551. Aldol reaction: b) D. Enders D. L. Whitehouse, *Synthesis* **1996**, *38*, 621–626 For a review on asymmetric reactions of hydrazones see: c) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.

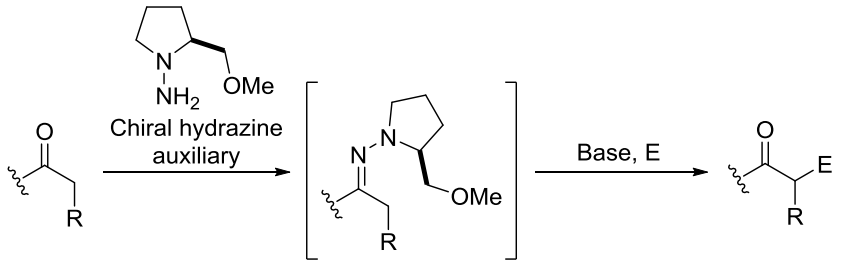


Figure 4.

A different strategy to achieve the asymmetric α-functionalization of carbonyl compounds is the use of chiral ligand-bearing metal enolates as nucleophilic intermediates. An advantage of this approach compared to enamine- and hydrazone-mediated approaches is that not only aldehydes and ketones, but also carboxylic acid derivatives such as esters and thioesters can be used as enolizable substrates. As representative examples of this strategy, some boron ligands employed in chiral ligand mediated enolate reactions are shown in Figure 5.[10]

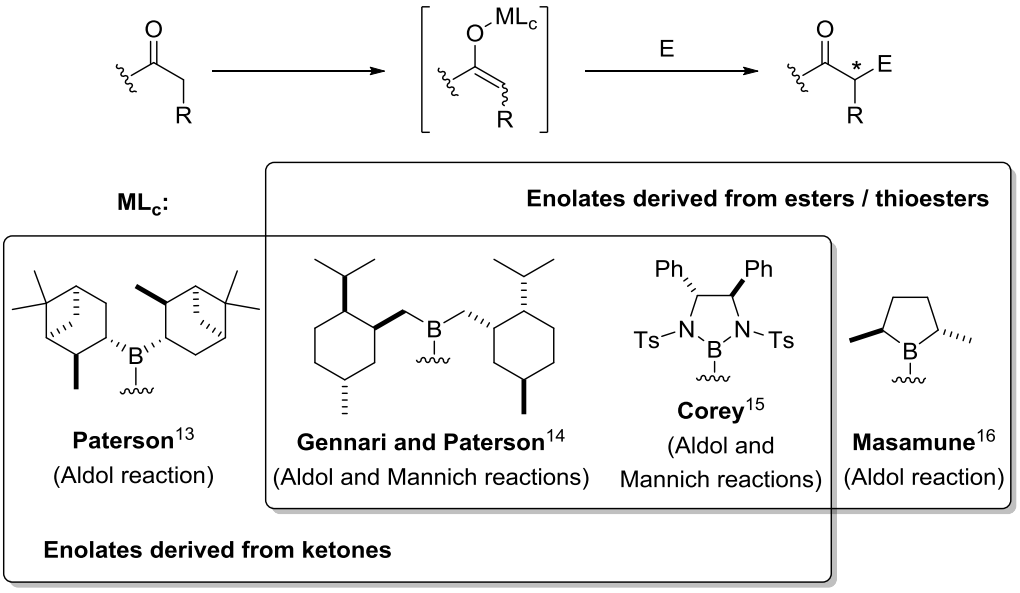


Figure 5.

[10] For further information on the subject see: a) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200. b) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947. c) I. Paterson, C. J. Cowden, D. J. Wallace, *Modern Carbonyl Chemistry*, Ed. Wiley-VCH, Weinheim, **2000**, 249–297. d) A. Abiko, *Boron Reagents in synthesis*, Ed. American Chemical Society, Washington DC, **2016**, 123–171.

[11] a) I. Paterson, M. S. Lister, C. K. McClure, *Tetrahedron Lett.* **1986**, *27*, 4748–4790. b) I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumman, C. K. McClure, R. D. Norcross, *Tetrahedron Lett.* **1990**, *46*, 4663–4684.

[12] For an example of: Aldol reaction of ketones: a) C. Gennari, C. T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J. M. Goodman, I. Paterson, *J. Org. Chem.* **1992**, *57*, 5173–5177. Aldol reaction of thioesters: b)

For substrates in the carboxylic acid oxidation state, a chiral auxiliary can be covalently bound to the acyl system. Upon enolization, subsequent reaction with an electrophile would be controlled by the auxiliary intramolecularly (diastereoselective process). One advantage of this method is that the removal of the chiral auxiliary can afford either carboxylic acid derivatives, aldehydes or ketones depending on the scission conditions employed, thus giving access to a broad variety of products from a common optically active intermediate (or adduct).

In 1981, Evans and coworkers[15,16] reported the use of chiral oxazolidinones as auxiliaries for the asymmetric formation of a stereogenic center in the α-position of acyl systems via alkylation and aldol-type reactions. Following this ground marking work, many other chiral auxiliaries[23-21] were reported for different reactions leading to α-stereogenic carboxylic acid derivatives (Figure 6).[23]

C. Gennari, A. Vulpetti, D. Moresca, *Tetrahedron Lett.* **1994**, *35*, 4857–4860. Mannich reaction of thioesters: d) C. Gennari, A. Vulpetti, M. Donghi, N. Mongelli, N. E. Vanotti, *Angew. Chem. Int. Ed.* **1996**, *35*, 1723–1725. For further references see: e) F. Lang, D. Zewge, Z. J. Song, M. Biba, P. Dormer, D. Tschaen, R. P. Volate, P. J. Reider, *Tetrahedron Lett.* **2003**, *44*, 5285–5288 and references herein.

[13] For an example of: Aldol reaction of ketones: a) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495. Aldol reaction of esters: b) E. J. Corey, S. S. Kim, *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977. Mannich reaction of thioesters: c) E. J. Corey, C. P. Decicco, R. C. Newbold, *Tetrahedron Lett.* **1991**, *32*, 5287–5495.

[14] S. Masamune, T. Sato, B. M. Kim, T. A. Wollman, *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281.

[15] D. A. Evans, J. Bartroli, T. L Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

[16] For an example of: Aldol reaction: a) D. A. Evans, J. Bartroli, T. L Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. Amination: b) D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397. Mannich reaction: c) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. For further references see: e) E. H. Tallmadge, J. Jermaks, D. B. Collum, **2016**, *138*, 345–355 and references herein.

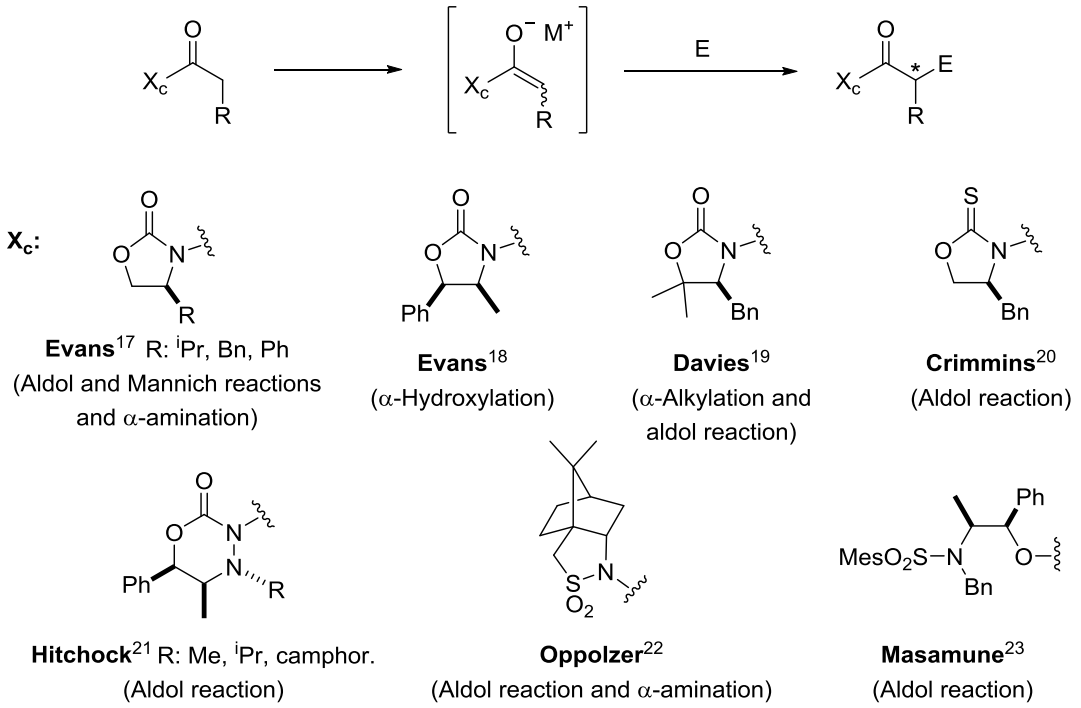


Figure 6.

Methods based on covalently bound chiral auxiliaries despite being very effective need a stoichiometric amount of the chiral agent and additional steps are required for the attachment and ulterior detachment of the auxiliary which compromise

[17] D. A. Evans, M. M. Morressey, R. L. Dorow, *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

[18] For an example of: Alkylation: a) S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee, A. D. Smith, *Tetrahedron: Asymmetry* **2000**, *11*, 3475–3479. Aldol reaction: b) S. G. Davies, I. A. Hunter, R. L. Nicholson, P. M. Roberts, E. D. Savory, A. D. Smith, *Tetrahedron* **2004**, *60*, 7553–7557. For further references see: c) J. Alvarado, A. T. Herrmann, A. Zakarian, *J. Org. Chem.* **2014**, *79*, 6206–6220; d) A. Gómez-Palomino, M. Pellicena, J. M. Romo, R. Solà, P. Romea, F. Urpí, M. Font-Bardia, *Chem. Eur. J.* **2014**, *20*, 10153–10159 and references herein.

[19] M. T. Crimmins, B. W. King, E. A. Tabet, *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884.

[20] a) D. M. Casper, J. R. Burgenson, J. M. Esken, G. M. Ferrence, S. R. Hitchock, *Org. Lett.* **2002**, *4*, 3739–3742. For further references see: A. R. Leise, N. Comas, D. Harrison, D. Patel, E. G. Whitemiller, J. Wilson, J. Timms, I. Golighty, C. G. Hamaker, S. R. Hitchock, *Tetrahedron: Asynnmetry* **2017**, *28*, 1154–1162 and references herein.

[21] For an example of: Aldol reaction: a) W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. Amination: b) W. Oppolzer, O. Tamura, J. Deerberg, *Hel. Chim. Acta* **1992**, *75*, 1965–1968. For further references see: L. Zhang, L. Zhu, J. Yang, J. Luo, R. Hong, *J. Org. Chem.* **2016**, *81*, 3890–3900 and references herein.

[22] A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587.

[23] For further information on the subject see: a) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947. b) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev*. **2004**, *33*, 65–75. c) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131–173. d) M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2014**, *25*, 1061–1090.

atom and step economy. Asymmetric catalytic procedures, in which a substoichiometric amount of a chiral inductor is enough to accomplish the reaction with high chemo-, regio- and stereoselectivity, are more convenient from the point of view of atom economy and procedural simplicity.[24]

Procedures based on the use of previously generated (preformed) enolates or enolate equivalents, namely *directed* methods, in combination with a chiral Lewis acid catalyst have been studied in depth. Among them, silyl enol ethers are by far the most prominent, and their addition reaction to carbonyl compounds, namely the Mukaiyama aldol reaction, is the most representative example of their potential for the formation of C–C bonds in a stereocontrolled manner. [25]

In 1989 Mukaiyama described the first catalytic enantioselective reaction of silyl enol ethers derived from esters[26] and thioesters[27] employing a tin(II)-chiral diamine complex as the catalyst. Following this seminal work, several chiral Lewis acids have been developed for the catalytic enantioselective Mukaiyama reaction.[28] The most representatives are shown in Figure 7.

[24] For detailed information on this concept see: B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

[25] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011–1014. b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. For further information on the subject see: a) M. B. Boxer, B. J. Albert, H. Yamamoto, *Aldrichimi. Act.* **2009**, *42*, 3–15. b) T. Kitanosono, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 3095–3118. c) S. B. Jennifer Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108. d) J.-I. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118.

[26] S. Kobayashi, T. Sano, T. Mukaiyama, *Chem. Lett.* **1989**, 1319–1322.

[27] S. Kobayashi, T. Mukaiyama, *Chem. Lett.* **1989**, 297–300.

[28] For reviews on Mukaiyama reaction see: a) E. M. Carreira, *Modern Carbonyl Chemistry*, Ed. Wiley-VCH, Winheim, **2000**, 227–248. b) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086–9096. c) S. B. Jennifer Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108. d) J.-I. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118. e) T. Kitanosono, S. Kobayashi, *Chem. Rec.* **2014**, *14*, 130–143. f) W. Gati, H. Yamamoto, *Acc. Chem. Res.* **2016**, *49*, 1757–1768.

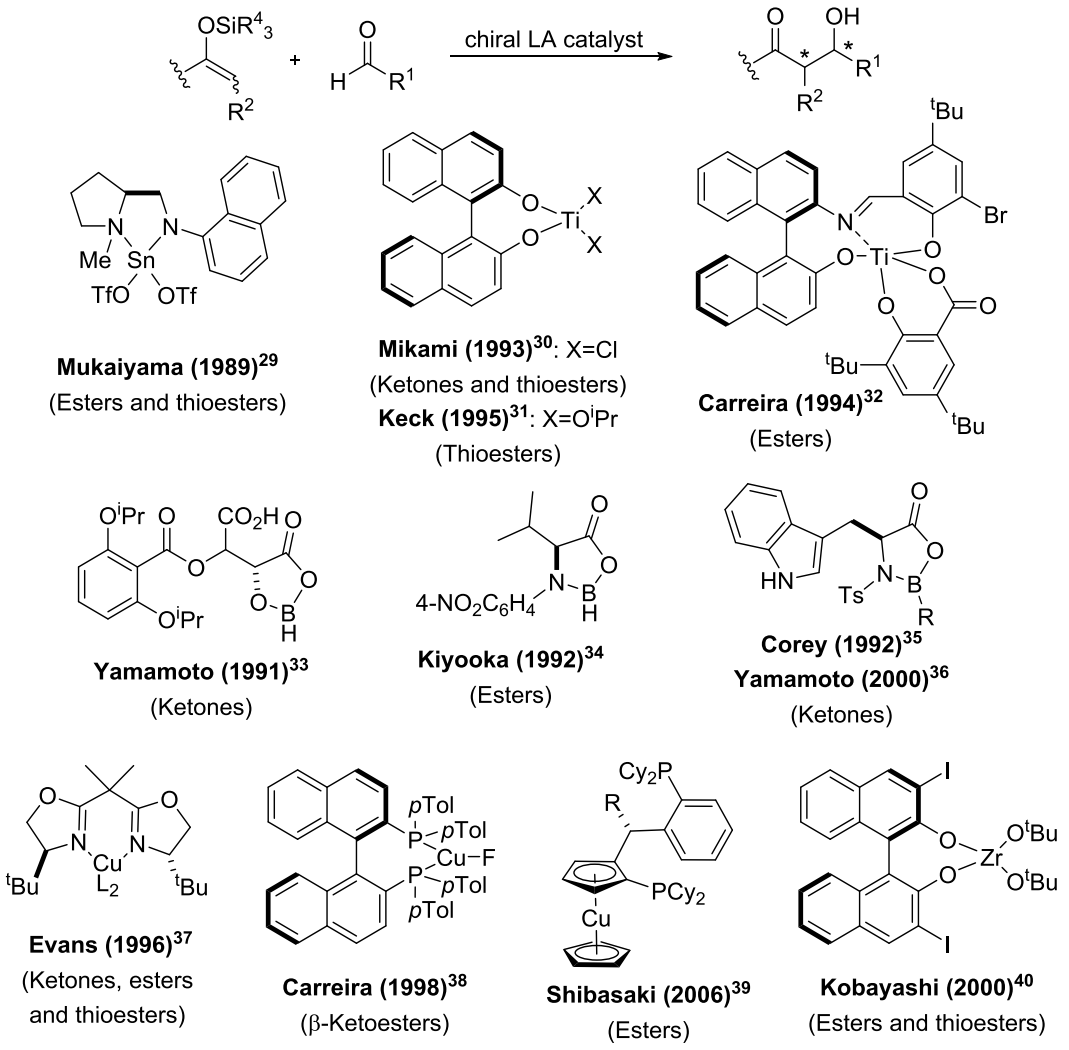


Figure 7.

[29] For pioneering examples of reaction with: Esters: a) S. Kobayashi, I. Shiina, J. Izumu, T. Mukaiyama, *Chem. Lett.* **1992**, 373–376. Thioesters: c) T. Mukaiyama, H. Uchiro, S. Kobayashi, *Chem. Lett.* **1989**, 1757–1760.

[30] For pioneering examples of reaction with: Ketones: a) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.* **1993**, *115*, 7039–7040. Thioesters: b) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.* **1994**, *116*, 4077–4078. For further references see: c) F. Fang, F. Xie, H. Yu, H. Zhang, B. Yang, W. Zhang, *Tetrahedron Lett.* **2009**, *50*, 6672–6675 and references herein.

[31] G. E. Keck, D. Krishnamurthy, *J. Am. Chem. Soc.* **1995**, *117*, 2363–2364.

[32] E. M. Carreira, R. A. Singer, W. J. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 8837–8838.

[33] K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042.

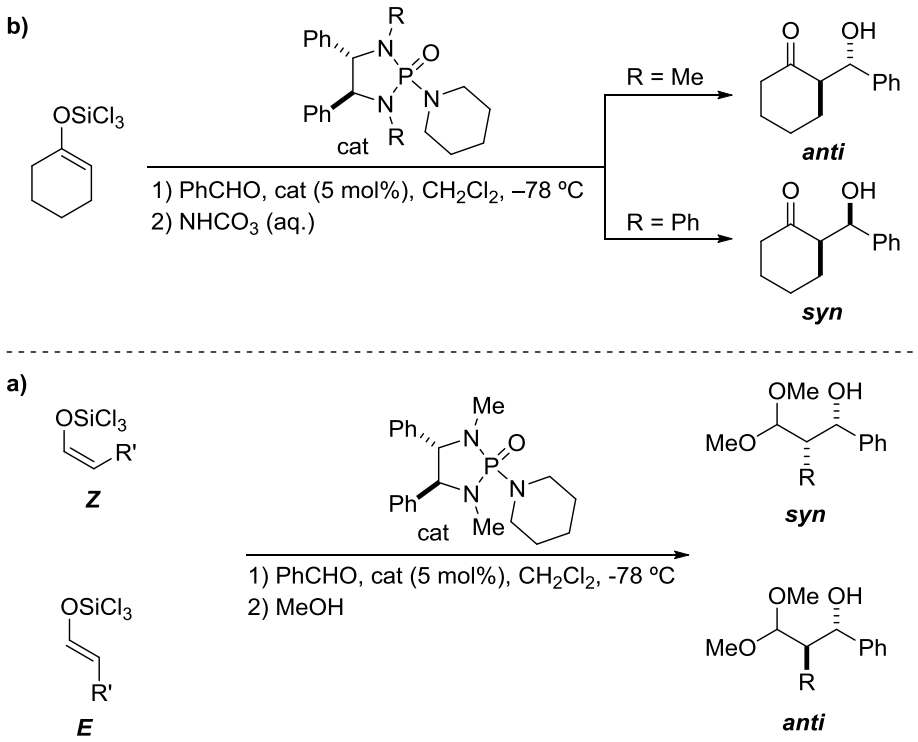
[34] S. Kiyooka, Y. Kaneko, K. Kume, *Tetrahedron Lett.* **1992**, *33*, 4927–4930.

[35] E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6910.

[36] K. Ishihara, S. Kondo, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 9125–9128.

[37] a) D. A. Evans, C. Kozlowski, J. A. Murry, *J. Am. Chem. Soc.* **1996**, *121*, 669–685. b) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335 and references herein.

On the other hand, Denmark and coworkers[41] reported a distinct strategy for the catalytic asymmetric directed aldol reaction based on the activation of trichlorosilyl enol ethers by a chiral phosphoramide Lewis base catalyst. Contrary to the Lewis acid-catalyzed processes, which tend to provide the *syn*-adducts, this methodology is stereospecific and can provide either *syn*- or *anti*-adducts selectively by judicious choice of the catalyst or the *E* or *Z* configuration of the starting silyl enolate for ketones (Scheme 2a) and aldehydes (Scheme 2b) respectively.[42]



Scheme 2.

Whereas some methods with the "Mukaiyama reaction scheme" are quite efficient and general, and proceed with high stereocontrol (both absolute and relative), preparation of the silyl enolate in a previous and irreversible synthetic operation employing stoichiometric quantities of reagents constitutes an important drawback.[43] In

[38] For a pioneering example of reaction with β-ketoesters: J. Krüger, E. M. Carreira, *J. Am. Chem. Soc*. **1998**, *120*, 837–838.

[39] K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2006**, *128*, 7164–7165.

[40] Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292–3302.

[41] a) S. E. Denmark, S. B. D. Winter, X. Su, K.-T. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405.

[42] For further information on this observation see: a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991. b) S. E. Denmark, S. K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762. For a review on Lewis base-promoted Mukaiyama reactions see: c) Ref. 28a.

[43] For approaches to catalytic methods see: J. M. García, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2011**, *50*, 8790–8792.

contrast, *direct* methods that allow the reaction of unmodified carbonyl compounds with the corresponding electrophiles are particularly attractive, especially if a substoichiometric amount of a chiral promoter is sufficient to attain good yield and selectivity. An overview of these approaches is described next.

1.2. Direct catalytic asymmetric α-functionalization of carbonyl compounds

It is well known that enzymes are able to trigger the α-functionalization of unmodified carbonyl compounds with extremely high efficiency and selectivity. Thus, enzymes meet perfectly the atom and step economy principles, doing their work with high efficiency and selectivity most often by activating both the donor and acceptor components of a given reaction concurrently. Following a similar principle of concomitant substrate activation, chemists have developed synthetic catalysts capable of promoting α-functionalization of carbonyl compounds leading to the formation of a stereogenic center in the α-position in a direct fashion with considerable success. Main developments in this field are briefly described next according to two categories: metal-based methods and organocatalyst-based methods.

1.2.1. Methods based on metal catalysts

A significant breakthrough in this area came from the laboratories of Shibasaki and Trost, who independently introduced new bifunctional Lewis acid/Brønsted base metal complexes capable of catalysing some fundamental C–C bond forming reactions.[44]

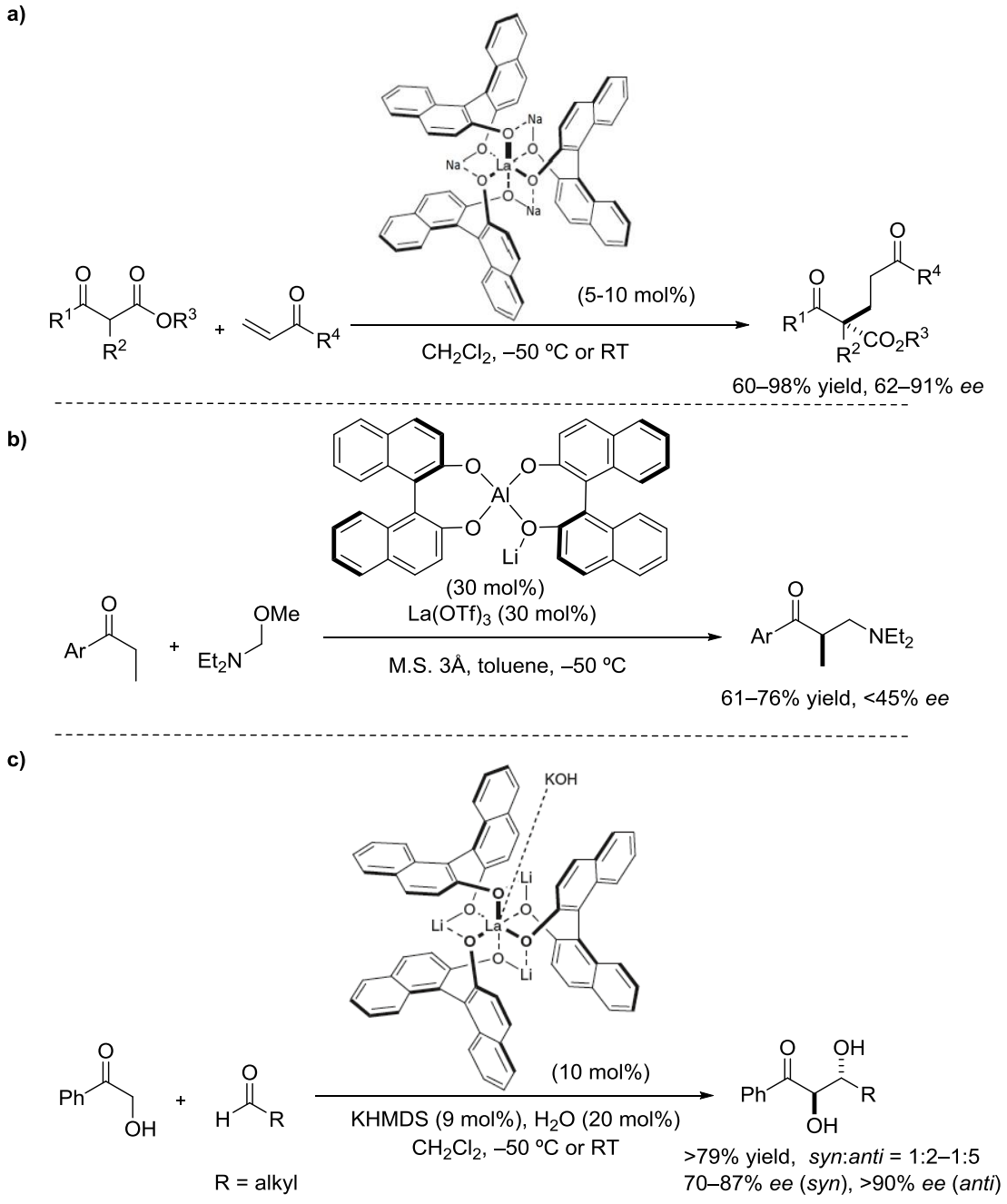
In 1996, Shibasaki[45] and coworkers used a bifunctional heterobimetallic catalyst to perform the Michael addition of cyclic β-ketoesters to methyl vinyl ketone and acrylates obtaining moderate to very good enantioselectivities (Scheme 3a). Later, the group developed similar catalysts for the Mannich reaction between aromatic ketones and aminoethyl ethers (in low enantioselectivity and high catalyst loading, Scheme 3b),[46] and the aldol reaction of 2-hydroxyacetophenone with aliphatic unbranched

[44] For the concept of bifunctional metal complexes see: a) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406. b) M. Shibasaki, M. Kanai, S. Matsunaga, *Acc. Chem. Res.* **2009**, *42*, 1117–1127. c) J. Ito, H. Nishiyama, *Bifunctional Molecular Catalysis. Topics in organometallic Chemistry*, Ed. Springer, Berlin **2011**, vol. 37.

[45] H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 5561–5564.

[46] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307–310.

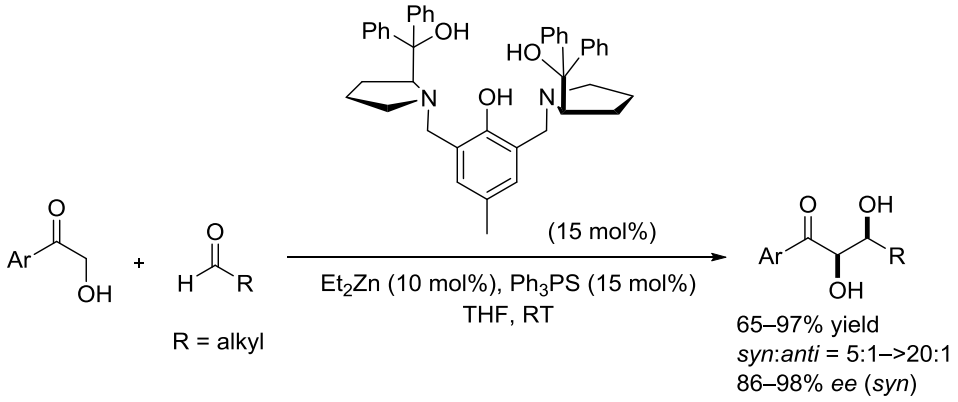
aldehydes (Scheme 3c),[47] which had not been previously used in direct aldol reactions, presumably due to their tendency towards enolization. The main concept involved in these researches is that the metal complexes have a basic site and an acidic site which can work in concert for the activation of both the donor and the acceptor reaction components.



Scheme 3.

[47] N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467.

On the other hand, Trost and coworkers reported the aldol reaction of 2-hydroxyacetophenone with aliphatic aldehydes, including the more challenging unbranched aldehydes, catalyzed by a bifunctional dinuclear Zn catalyst which proceeds with high enantio- and diastereoselectivities (Scheme 4).[48] This catalyst could be later applied to a related Mannich reaction.[49]



Scheme 4.

Following these first examples, there have been several other reports dealing with the α-functionalization of enolizable carbonyl compounds based on chiral metallic catalysts.[50]

Despite several kinds of α-functionalization procedures using metallic catalysts have been described to give rise very good yield and stereocontrol, direct procedures are still limited to the use of activated carbonyl compounds, mainly those bearing an electron withdrawing group at the α-position or in some instance having an aryl substituent. Furthermore, many of these methods rely on the use of rare (and toxic) metals of limited availability and are often highly sensitive to the presence of traces of water or oxygen in the reaction medium.

[48] B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368.

[49] B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

[50] For reviews on bifunctional metal complexes see: a) C. Nájera, J. M. Sansano, J. M. Saá, *Eur. J. Chem.* **2009**, 2385–2400. b) T. Ikariya, I. D. Gridnev, *Top. Catal.* **2010**, *53*, 894–901. c) B. Ramasamy, P. Ghosh, *Eur. J. Inorg. Chem.* **2016**, 1448–1465.

1.2.2. Methods based on organocatalysts

With the renaissance of organocatalysis at the beginning of this millennium, new opportunities appeared for achieving the selective α-functionalization of enolizable carbonyl compounds.[51] Two main ways for the activation of the enolizable carbonyl substrate have been exploited: activation via enamine formation (aminocatalysis) and activation via enolization (Brønsted base catalysis).

1.2.2.1. Activation via enamine formation (covalent)

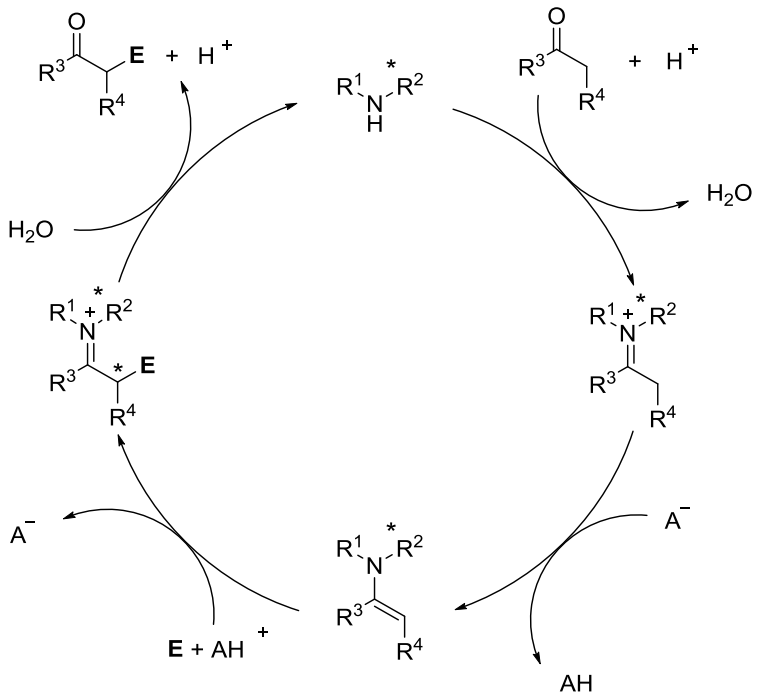
Small primary or secondary amines can condense with carbonyl compounds, more specifically aldehydes or ketones, leading to enamines which have increased nucleophilicity and are capable of reacting with a variety of electrophilic reagents. In the classical stoichiometric procedure (see Figure 3 above), the chiral enamine is isolated and then reacted with an electrophile. The adduct thus obtained can be hydrolysed aftermaths under acidic conditions affording the desired α-substituted carbonyl compound and recovering the starting chiral amine.[52]

In enamine mediated catalysis, the same process happens within a catalytic cycle that contains as the main steps the following (Scheme 5): i) condensation of the chiral amine catalyst and the enolizable carbonyl compound, forming an iminium-ion; ii) deprotonation of the iminium leading to an enamine intermediate; iii) the stereochemistry-determining C–C bond formation by reaction of the enamine with an electrophile; and iv) hydrolysis of the resulting iminium species to afford the desired α-functionalized carbonyl product with regeneration of the chiral amine catalyst, which can then re-enter the catalytic cycle.[53]

[51] For reviews on asymmetric organocatalysis see: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. b) H. Pellissier, *Tetrahedron.* **2007**, *63*, 9267–9331. c) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. d) H, Pellissier, *Recent Developments in Asymmetric Organocatalysis*, ACS Publishing, Cambridge **2010**. e) B. List, K. Maruoka, Science of Synthesis: A*symmetric Organocatalysis*, Ed. Thieme, Stuttgart **2010**.

[52] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Ed. Springer, New York **2007**, vol. B, 46-55.

[53] I. Ojima, *Catalytic Asymmetric Synthesis*, Ed. John Wiley & Sons, New York, **2010**.



Scheme 5. Catalytic cycle for enamine mediated processes. All reactions are reversible, but one-way arrows are depicted for simplicity.

As established, the rate-determining step of this process is the formation of the enamine, which implies the abstraction of an α-proton.[54] Thus, protic additives and polar solvents play a critical role accelerating the deprotonation and stabilizing ionic charges respectively.

On the other hand, the principles that govern stereochemistry during the key C–C bond forming step and so determine the configuration of the newly formed α-stereocenter obey to two general models as represented in Figure 8. According to the model on the left (H-bond as control element) the hydrogen-bond donor group of the catalyst directs the approach of the electrophile towards one of the sides of the prostereogenic C_α, while according to the model on the right (steric control) bulky substituents of the catalyst force the approach of the electrophile to be from the side opposite to the "obese" substituent of the enamine, with the enamine adopting the *E-anti* configuration preferentially.

[54] a) K. N. Rankin, J. W. Gaud, R. J. Boyd, *J. Phis. Chem.* **2002**, *106*, 5155–5159. b) F. R. Clemente, K. N. Houk, *Angew. Chem. Int. Ed.* **2004**, *43*, 5766–5768. For a review on mechanisms in aminocatalysis see: c) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen *Chem. Commun.* **2011**, *47*, 632–649.

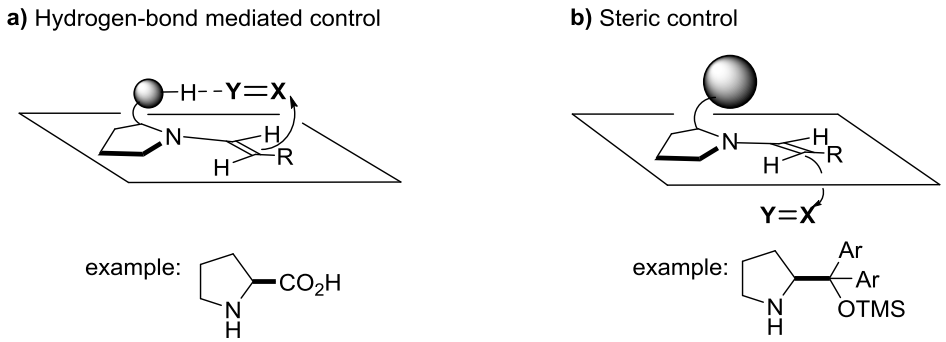


Figure 8.

In these models, an important assumption concerns enamine configuration. From the four possible configurations (Figure 9), in the case of aldehydes (R' = H) the *E-anti* configuration is favoured. For ketones (R'=CH_2-), the *E-syn* configuration is assumed to be the most stable.[55]

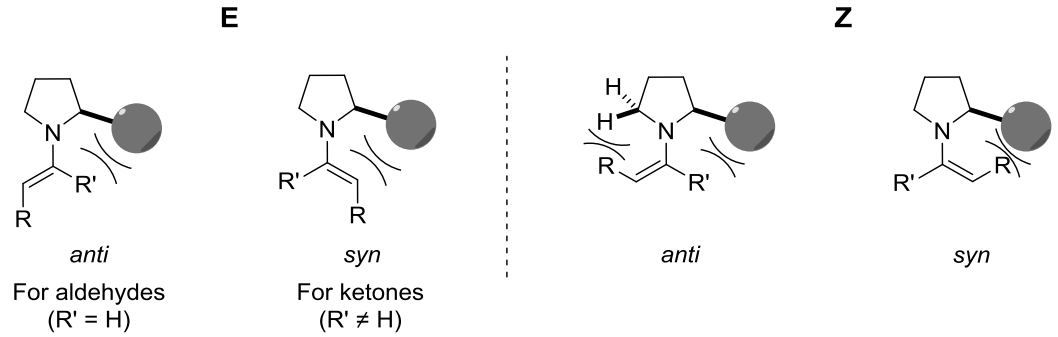


Figure 9.

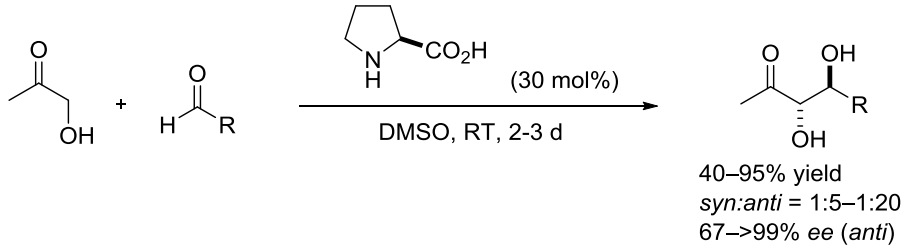
Following the discovery by List and Barbas in 2000[56] of the potential of proline as a catalyst in the asymmetric intermolecular aldol reaction, the field of aminocatalysis has experienced an impressive growth,[57] and enamine mediated catalysis has demonstrated to be an especially valuable tool for the introduction of α-stereogenicity in aldehydes and ketones.

[55] a) S. Seebach, J. Golinski, *Helv. Chim. Act.* **1981**, *64*, 1413–1423. b) P. Dinér, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122–127. c) D. Seebach, U. Groselj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Act.* **2008**, *91*, 1999–2034. d) U. Groselj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Act.* **2009**, *92*, 1225–1259. e) T. Huch, D. Seebach, A. K. Beck, M. Reiher, *Helv. Chim. Act.* **2017**, *100*, e1700182.

[56] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

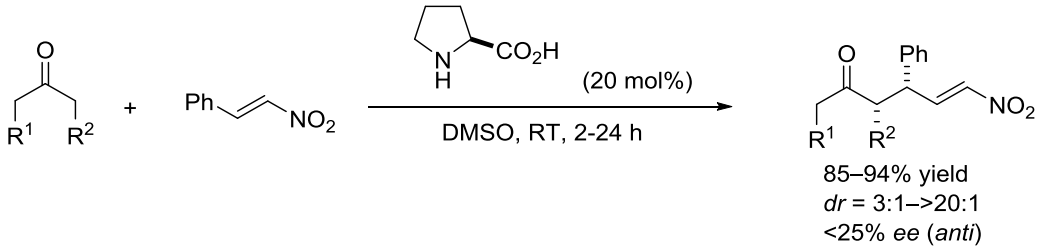
[57] For reviews on aminocatalysis see: a) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569. b) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. c) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. d) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649. e) B. M. Paz, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2015**, *21*, 1846–1853.

Notz and List reported the first example of the enamine-mediated asymmetric formation of an α-stereogenic center in an aldol reaction using α-hydroxyacetone as the donor compound. Given the easy enolization of aliphatic aldehydes the reaction is limited to aromatic or α-branched aldehydes as acceptor components, affording the *anti*-aldol products in variable yields and diastereoselectivity, but in an overall excellent enantioselectivity (Scheme 6).[58]



Scheme 6.

List[59] and Maruoka[60] extended the method to the addition of cyclic ketones to aldehydes and α-ketoesters, respectively, with good results. List et al. were also the first to report the proline-catalyzed Michael[61] reaction yielding products with a stereogenic center in C_α, albeit the enantioselectivity obtained was very low (Scheme 7).



Scheme 7.

Whereas these first examples demanded the use of a large excess of donor ketone compound, high catalyst loadings and prolonged reaction times, they demonstrated the true potential of aminocatalysis, and therefore a fast-paced era of proline-catalyzed reaction exploration began. In few years, a big amount of relevant proline-catalyzed procedures for the asymmetric reactions of ketones and aldehydes were disclosed.[62]

[58] W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

[59] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.

[60] O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 5103–5105.

[61] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.

[62] For reviews on proline-catalyzed reactions see: a) S. S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5568. b) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*,

Meanwhile, in an attempt to overcome the limitations encountered when using proline, new and more efficient catalysts started to emerge, and the first approaches were mainly centered in the modification of the proline structure. The substitution of the carboxylic acid of proline for other functional groups resulted in catalysts with improved solubility in organic solvents and easier structural fine tune to better adapt to each particular substrate, thus improving the reactivity and the stereocontrol. Some of the most representative proline-based catalyst families used in the asymmetric α-functionalization of aldehydes and ketones are shown in Figure 10.[63] Of these catalysts, prolinol silyl ethers (Figure 10, **F**) have demonstrated the most versatile and general, catalysing a broad array of asymmetric reactions via either enamine or iminium activation.[64]

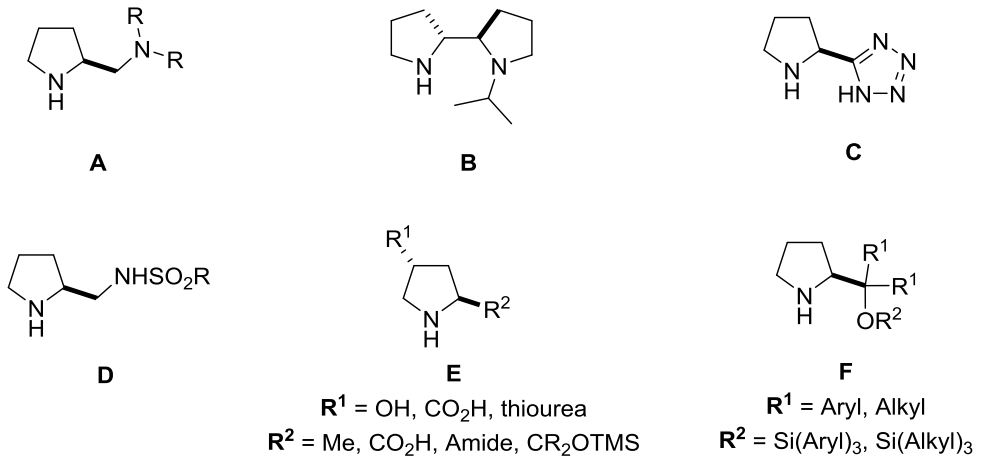


Figure 10.

Naturally available primary amines and their derivatives have also been used, mainly for asymmetric reactions involving ketones as donors.[65] For example, Córdova

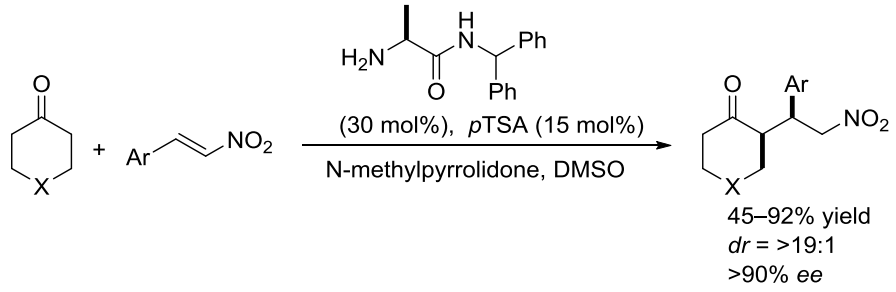
493–529. c) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757–797. c) S. K. Panday, *Tetrahedron: Asymmetry* **2011**, *22*, 1817–1847.

[63] For a recent review on proline-based secondary amine catalysts see: J. Liu, W. Lei, *Synthesis* **2017**, *49*, 960–972.

[64] For reviews on α,α-diarylprolinol silyl ether catalysts see: a) A. Mielgo, C. Palomo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880. b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948. c) K. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264. d) B. Donslud, T. K. Johansen, P. H. Pernille, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874. e) L. Klier, F. Tur, P. H. Pernille, K. A. Jørgensen, *Chem. Soc. Rev.* **2017**, *46*, 1080–1102.

[65] For reviews on primary amine catalysts see: a) Y.-C. Chen, *Synlett* **2008**, 1919–1930. b) P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770. c) L. Zhang, N. Fu, S. Luo, *Acc. Chem. Res.* **2015**, *48*, 986–997.

et al. used a primary amine catalyst derived from the natural amino acid L-alanine for the Michael addition of cyclic ketones to aromatic nitroalkenes (Scheme 8).[66]



Scheme 8.

De novo design secondary cyclic amines have also been demonstrated useful as aminocatalysts for activation via enamine formation. In particular, Maruoka et al. developed binaphtyl derived amine catalysts for the *anti*-Mannich and *syn*-aldol reactions, contributing to fill an important gap in asymmetric synthesis.[67] The same group later extended the utility of these catalysts to the Michael addition using aldehydes as donors.[68]

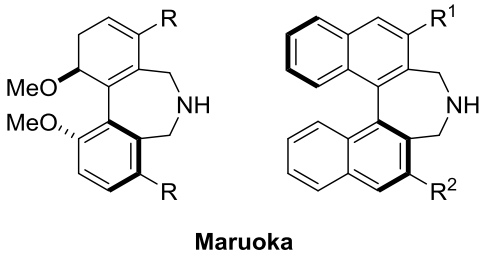


Figure 11.

To sum up, impressive progress has been done during the last two decades in the development of enamine-based asymmetric α-functionalization of carbonyl compounds. However, some recalcitrant problems regarding substrate scope, regio- and stereocontrol as well as some practical issues still remain. Indeed, the procedures

[66] Y. Xu, A. Córdova, *Chem. Commun.* **2006**, *42*, 460–462.

[67] a) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409. b) T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 1738–1740. For reviews on these catalysts see: c) T. Kano, K. Maruoka, *Chem. Commun.* **2008**, *44*, 5465–5473. d) T. Kano, K. Maruoka, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1421–1438.

[68] a) T. Kano, H. Sugimoto, O. Tokuda, K. Maruoka, *Chem. Commun.* **2013**, *49*, 7028–7030. b) T. Kano, H. Maruyama, R. Sakamoto, K. Maruoka, *Chem. Commun.* **2015**, *51*, 10062–10065. c) T. Kano, H. Sugimoto, H. Maruyama, K. Maruoka, *Angew. Chem. Int. Ed.* **2015**, *54*, 8462–8465. d) S. B. J. Kan, H. Maruyama, M. Akakura, T. Kano, K. Maruoka, *Angew. Chem. Int. Ed.* **2017**, *56*, 9487–9491.

described so far are limited to aldehyde and ketone donors, and the use of sterically hindered ketones still remains challenging. Furthermore, unsymmetrical ketones have been scarcely used due to the difficulties in controlling the regiochemistry of the reaction and low diastereomeric ratios are obtained in many examples where two stereogenic centers are formed.

On the one hand, chemoselectivity is still an issue in cross aldol reactions involving aldehydes: these reactions may lead to two homoaldol and two cross-aldol products, and so use of large excesses of one of the components is usually required in order to obtain good yields and selectivity. On the other hand, sterically hindered carbonyl compounds have been scarcely used in enamine catalysis, due to their lower tendency towards formation of enamines.

1.2.2.2. Activation via base-promoted enolization (noncovalent)

The α-deprotonation of enolizable carbonyl compounds by action of a base to yield the corresponding enolate is one of the most elemental mechanisms for carbonyl compound activation.[69] Upon the subsequent reaction of the enolate with a suitable electrophile the base might get restored again, allowing to re-enter the activation pathway and render the process catalytic. Accordingly, a general catalytic cycle as that shown in Figure 12 could be invoked in which proton transfer events occur repeatedly.

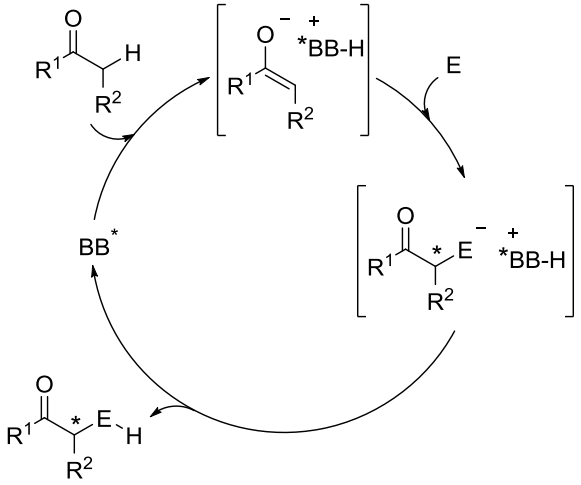


Figure 12.

[69] For further information on Brønsted base-catalyzed α-functionalization of carbonyls see: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev*. **2009**, *38*, 632–653. b) I. Ojima, *Catalytic Asymmetric Synthesis*, Ed. John Wiley & Sons, New York, **2010**. c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem*. **2010**, *291*, 145–200. d) K. Maruoka, *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Ed. Thieme, Stuttgart, **2012**.

In such a process, the chirality transfer from the base (catalyst) to the product takes place during the key C_α-E bond forming reaction and implies information transfer throughout a non-covalent substrate-catalyst ion-pairing complex. This constitutes a significant difference if compared with enamine catalysis described above, where a substrate-catalyst covalent complex is formed. The intrinsic nondirectional nature of electrostatic interactions in ion-pairing complexes makes predicting the sense of the stereoinduction exerted from the catalyst difficult. In this sense, molecules that combine a site acting as a base and another site with hydrogen-bond donor ability, namely bifunctional Brønsted base/H-bond donor catalysts,[70] can anchor both nucleophilic and electrophilic components in the transition state. As a result, more active catalysts are obtained, and a higher degree of stereochemical order is achieved in the transition state (Figure 13).

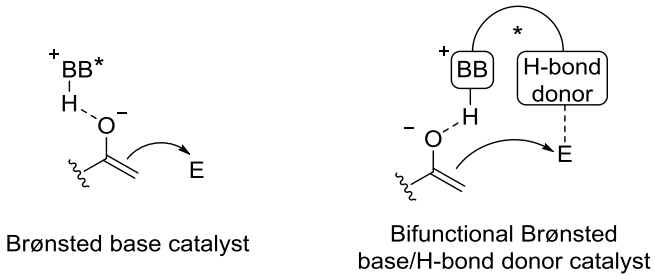


Figure 13.

Different nitrogen-containing functionalities have been employed for the design of chiral BB catalysts. Among them, tertiary amines are the most prominent, but also guanidines, amidines, and imidazoles are used (Figure 14).

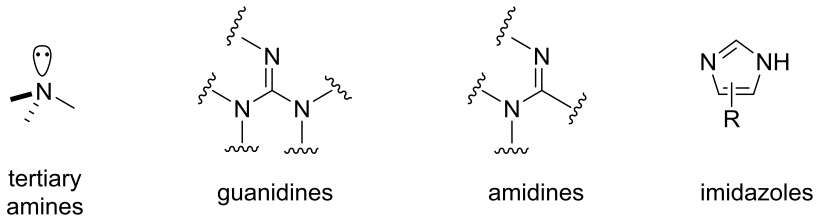


Figure 14.

The selection of the chiral basic unit is highly dependent on the availability of the corresponding optically pure precursors from the chiral pool. In this context, alkaloids and in particular cinchona family are a straightforward source of enantiopure BB catalyst candidates (Figure 15). Furthermore, simple chemical modifications of the

[70] For further information on the concept of bifunctional organocatalysts see: L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, 23, 490–508.

parent alkaloid structure provide a rapid access to stereochemically related architectures. Thus, these cinchona and cinchona-derived catalysts were the earliest bifunctional BB catalysts applied to the α-functionalization of easily enolizable carbonyl compounds, usually bearing an EWG at the α-carbon.[71]

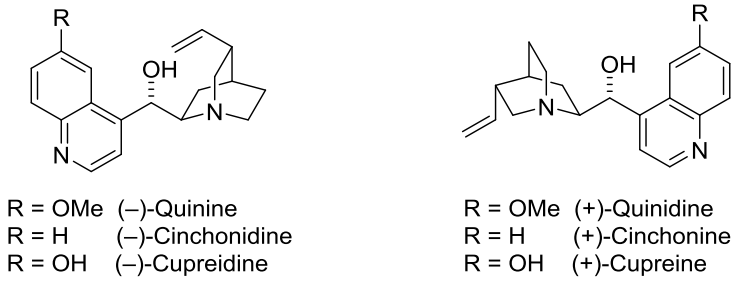
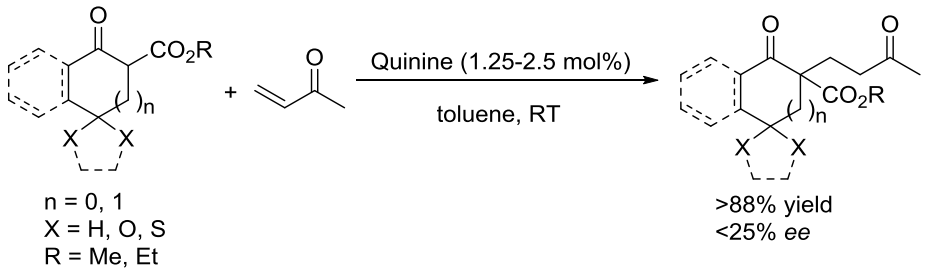


Figure 15.

Wynberg and coworkers, in the 70's were pioneers in this field and recognized the activation and stereoinduction capacity of cinchona alkaloid-derived catalysts, mainly for the Michael-type reactions. Although they obtained remarkable results for some transformations, such as the conjugate addition of thiols,[72] poor enantioselectivities were reported for the conjugate addition of enolizable C-nucleophiles (Scheme 9).[73]



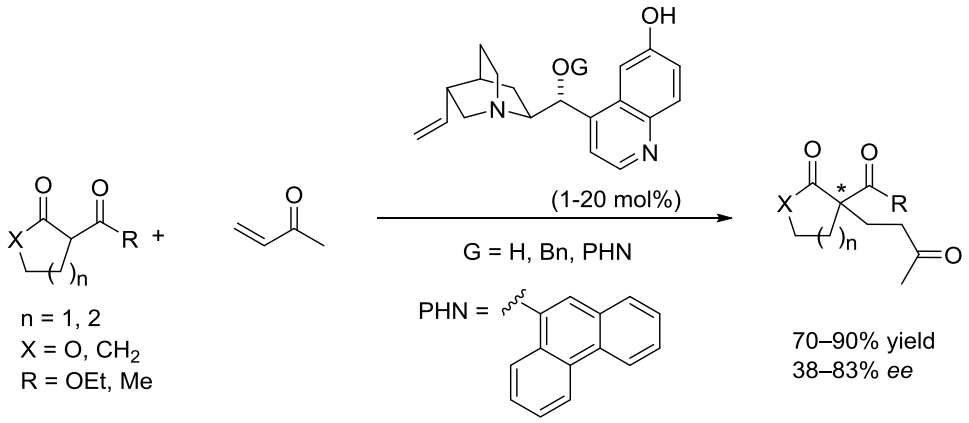
Scheme 9.

[71] For reviews on cinchona alkaloids in asymmetric organocatalysis see: a) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, 45, 7496–7504. b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279. c) E. M.O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron*. **2011**, 1725–1762. d) L. A. Bryant, R. Fanelli, A. J. A. Cobb, *Beilstein J. Org. Chem.* **2016**, *12*, 429–443.

[72] a) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430. b) H. Hiemstra, H. Wynberg, E: G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 168–173.

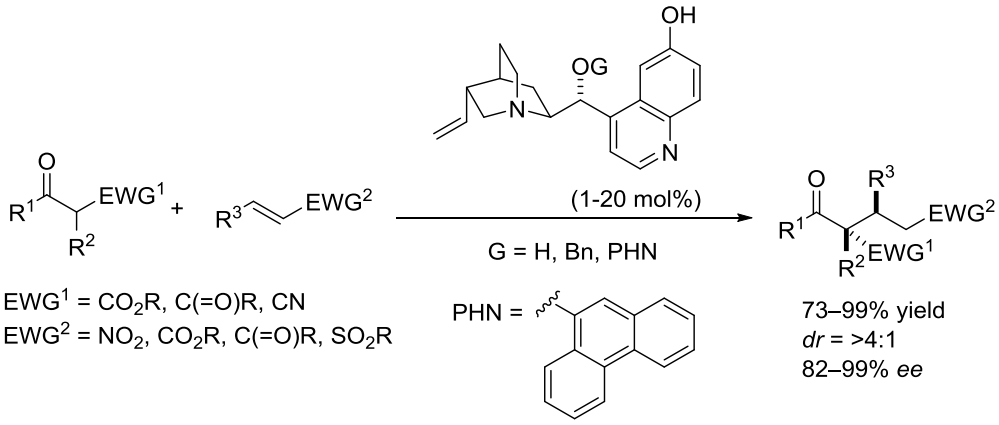
[73] a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4058. b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.

Some years later, Szöllösi[74] tested several cinchona alkaloid derivatives for the conjugate addition of different β-dicarbonyl compounds to methyl vinyl ketone, obtaining substantially better results (*ee* up to 83%, Scheme 10).



Scheme 10.

In a series of papers published from 2004 to 2006, Deng and coworkers[75] studied the bifunctional BB-catalyzed conjugate addition of easily enolizable carbonyl compounds quite extensively employing a broad spectrum of Michael acceptors and bifunctional cupreine and derived catalysts (Scheme 11). Excellent yields and diatereo- and enantioselectivities were obtained and they demonstrated the critical role of the 6'-OH group of cupreine as a H-bond donor site, as both catalyst activity and enantioselectivity vary drastically when moving from cupreine to quinidine.[75a]

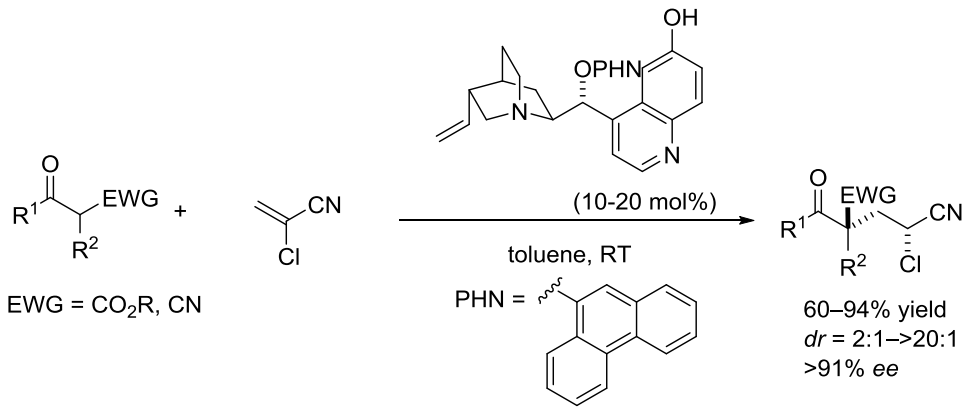


Scheme 11.

[74] G. Szöllösi, M. Bartók, *Chirality* **2001**, *13*, 614–618.

[75] a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907. b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108. c) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949. d) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 947–950. e) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301–4305.

The use of α-chloroacrylonitrile as Michael acceptor by the same group[76] is worth of mention. In this reaction two nonadjacent stereogenic centers are formed in a domino process with overall excellent results (Scheme 12). According to the authors, the cinchona catalyst first directs the addition of the nucleophile and then performs a stereoselective protonation of the resulting intermediate.



Scheme 12.

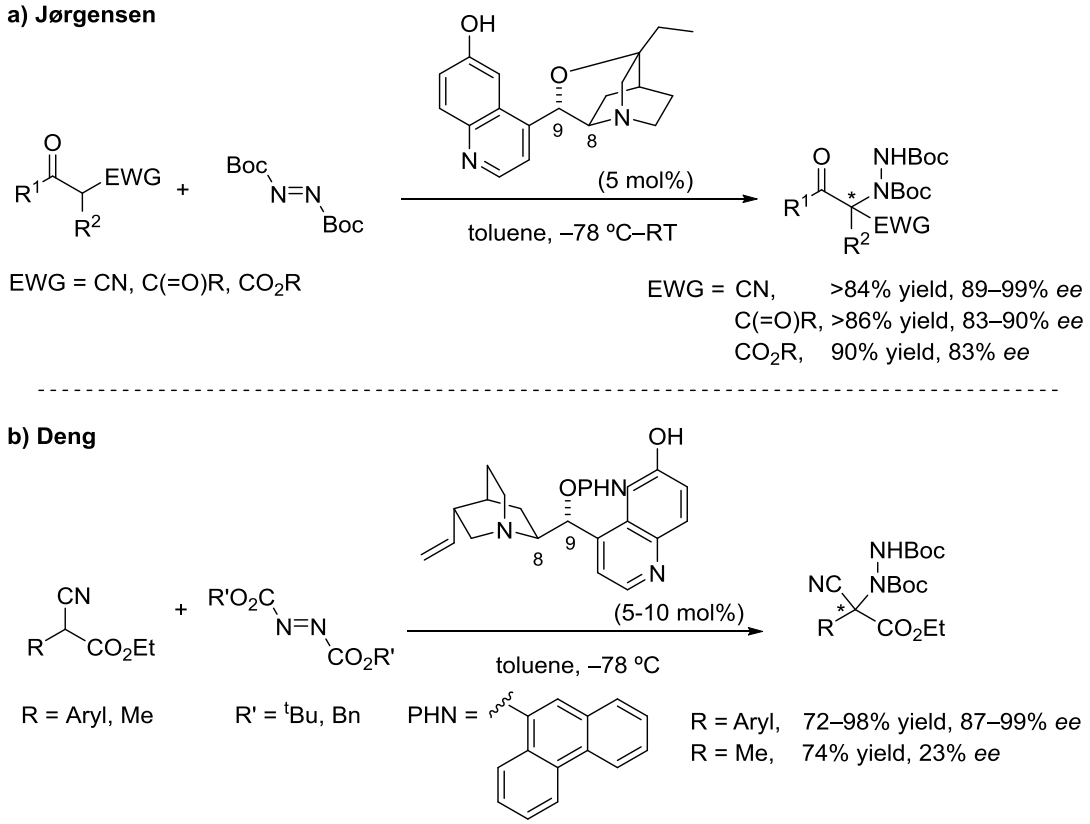
The α-amination of carbonyl compounds represents another reaction category for which BB-catalysis has been successfully applied. Pikho and coworkers[77] reported the first example with β-ketoesters using dibenzyl azodicarboxylate as the electrophile and cinchonine or cinchonidine as the catalyst, although enantioselectivity could not be higher than 88% *ee*. Almost at the same time, the group of Jørgensen[78] achieved the highly enantioselective α-amination reacting α-aryl-α-cyanoacetates with di-*tert*-butyl azodicarboxylate in the presence of a cinchona-alkaloid derivative. However, they obtained slightly lower selectivities when using β-diketones and β-ketoesters as pronucleophiles (Scheme 13a). Later Deng and coworkers[79] also used these cupreine-derived catalysts for the same reaction obtainig comparable results (Scheme 13b).

[76] Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930.

[77] P. M. Pikho, A. Pohjakallio, *Synlett* **2004**, 2115–2118.

[78] S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.

[79] a) X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, *7*, 167–169. b) X. Liu, B. Sun, L. Deng, *Synlett* **2009**, 1685–1689.



Scheme 13.

The quest for new and efficient bifunctional catalysts headed to the design and synthesis of enantiomerically pure amine derivatives bearing a range of H-bond donor sites. The most successful strategies to date merge a readily available chiral amine and an efficient H-bond donor group, such as a urea, thiourea, squaramide or sulphonamide (Figure 16). These modifications have led to increasingly active and selective bifunctional BB catalysts.

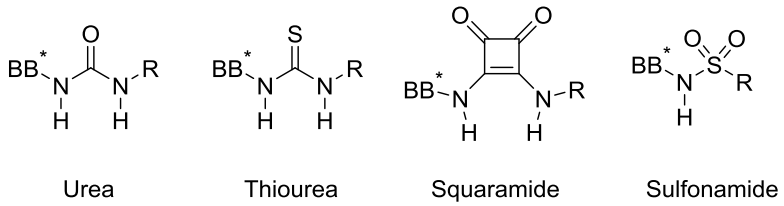
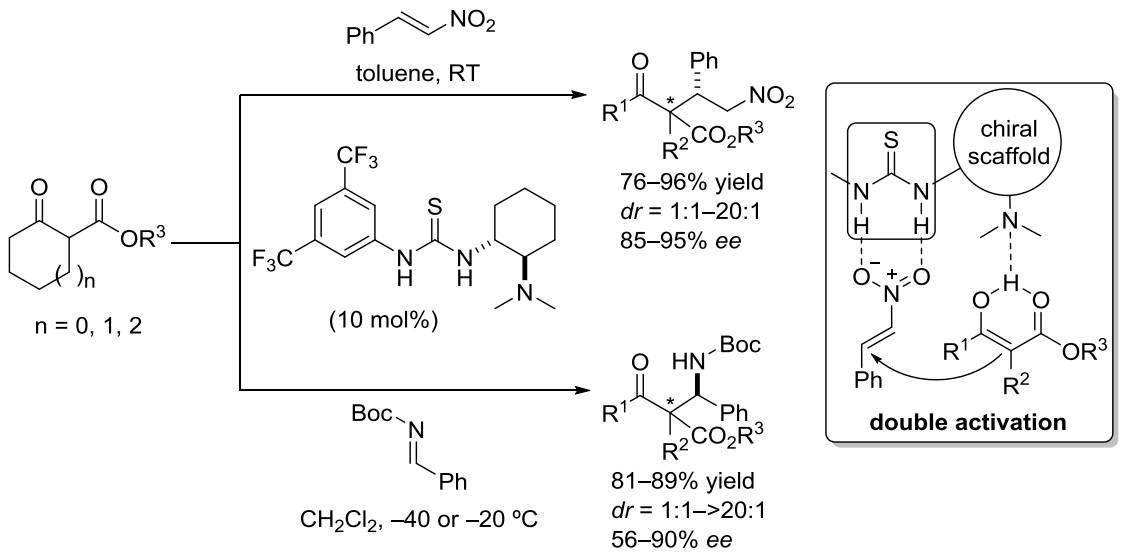


Figure 16.

In 2003, Takemoto et al.[80] presented the first highly enantioselective catalyst based on these principles, a thiourea derived from 1,2-diaminocyclohexane, for the Michael addition of malonates to nitroalkenes. The same group later used the catalyst for the Michael and Mannich reactions of cyclic β-ketoesters generating adducts which

[80] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

bear a tertiary or quaternary stereocenter at C_α (Scheme 14).[81] According to the authors, the catalyst activates the nucleophile through the amino group while the thiourea moiety activates the electrophile, forcing both components to approach in a stereospecific manner.[82]



Scheme 14.

Other thiourea catalysts derived from diamines with C_2-symmetry were also developed for the asymmetric α-functionalization of carbonyl compounds,[83] but because of the availability and versatility of cinchona-alkaloids, the thiourea-cinchona alkaloid catalysts soon became the most popular bifunctional catalysts in the area.[84] For instance, between 2005 and 2006 Connon,[85] Deng,[86] Dixon,[87] Soós[88] and Wang[89] independently

[81] a) T. Okino, Y. Hoashi, T. Furakawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125. b) Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, 2571–2575.

[82] a) Ref. 81a. Later Pápai and Zhong proposed that the nucleophile coordinates to the NH-bonds of the thiourea moiety and the nitrostyrene is activated by the protonated tertiary amine based on DFT and 1H-NMR studies: b) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160. c) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, 2682–2685.

[83] For a review on thiourea catalysts derived from diamines with C_2-symmetry see: Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601.

[84] For reviews on cinchona-based thiourea organocatalysts see: a) S. J. Connon, *Chem. Commun.* **2008**, *44*, 2499–2510. b) Y. Xi, X. Shi, *Chem. Commun.* **2013**, *49*, 8583–8585.

[85] A. H. McCooney, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370, Michael reaction.

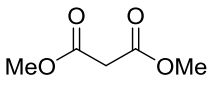
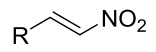
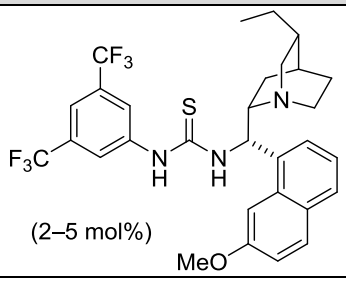
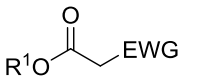
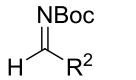
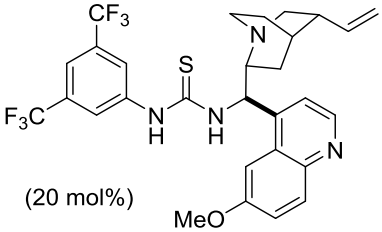
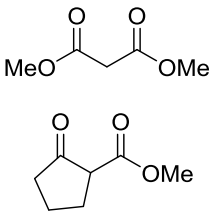
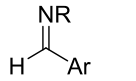
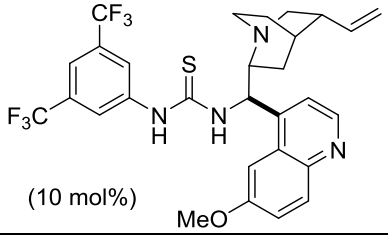
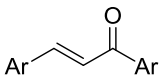
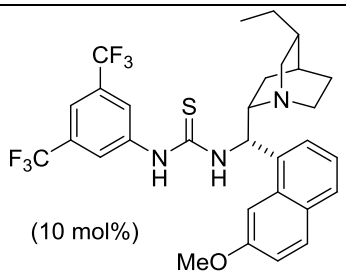
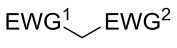
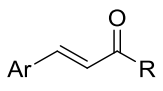
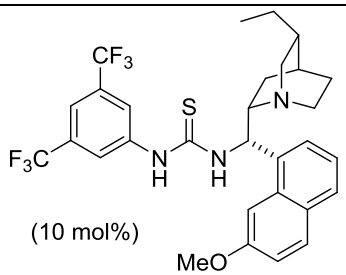
[86] a) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6084–6085, Mannich reaction. b) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157, Friedel-Crafts reaction.

[87] A. L. Tillman, J. Ye, D. Dixon, *Chem Commun.* **2006**, *42*, 1191–1193, Mannich reaction.

[88] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969, Michael reaction.

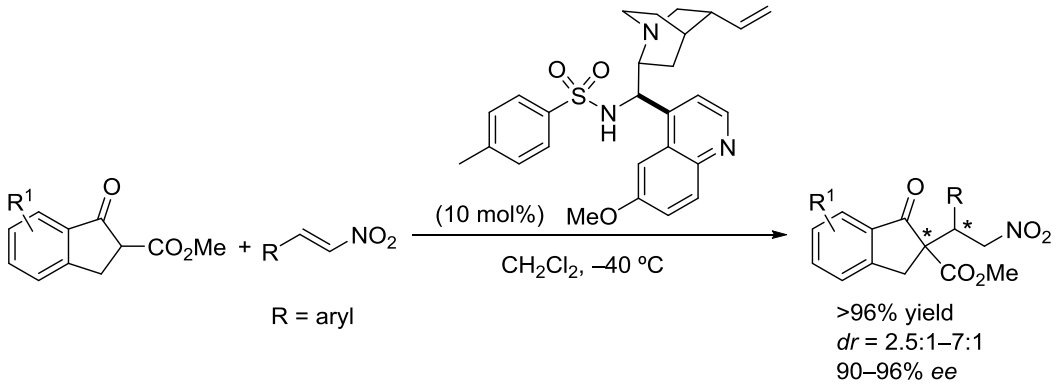
reported first thiourea-cinchona alkaloid catalysts for reactions involving soft carbon nucleophiles, as summarised in Table 1.

Table 1. Pioneering thiourea-cinchona alkaloid-catalyzed reactions

Donor	Acceptor	Catalyst	Yield (%) dr *ee* (%)	Author, Ref.
	 R = aryl, alkyl	 (2–5 mol%)	88–95% >86% *ee*	Connon, 85 (2005)
 R^1 = Me, Bn, allyl EWG = ketone, ester	 R^2 = aryl, alkyl	 (20 mol%)	>64% <3:1 *dr* >89% *ee*	Deng, 86 (2006)
	 R = Boc, Cbz	 (10 mol%)	>81% >16:1 *dr* 84–97% *ee*	Dixon, 87 (2006)
$MeNO_2$		 (10 mol%)	8094% 89–98% *ee*	Sóos, 88 (2005)
 EWG = ester, ketone CN, NO_2	 R = aryl, Me	 (10 mol%)	>61% <1.5:1 *dr* >95–98% *ee*	Wang, 89 (2006)

[89] J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653, Michael reaction.

In 2008, Song and coworkers[90] introduced a bifunctional cinchona alkaloid-sulphonamide catalyst, for the desymmetrization of cyclic anhydrides. However, catalysts bearing a sulphonamide group have been scarcely used in the asymmetric α-functionzalization of enolizable compounds, and so far they have been limited to the Michael reaction with nitroolefins.[91] Lu et al.[91a] reported the asymmetric α-functionzalization of cyclic β-ketoesters derived from 1-indanone using this kind of catalyst (Scheme 15). Adducts were obtained in excellent yield and enantioselectivity and good diastereoselectivity, although *ee*'s were eroded when varying the rig-size or removing the fused aromatic ring.



Scheme 15.

The same year, Rawal and coworkers[92] introduced the squaramide function as efficient double H-bond donor site in asymmetric catalysis. Both (thio)urea and squaramides are structurally rigid, although there are some differences. On the one hand, squaramides contain two hydrogen-bond donors (*N–H*) and two carbonyl acceptors (*C=O*), showing one more acceptor than thioureas. On the other hand, the cyclobutenedione ring induces a convergent orientation of the *N–H* groups, and the distance between them is estimated to be bigger (2.71 Å)[92] than in the case of thioureas (2.13 Å) (Figure 17a).[93] Both functionalities have the possibility of delocalizing the nitrogen lone pair through the carbon-heteroatom double bond, but in the case of squaramides further delocalization can occur through the cyclobutenedione system

[90] S. H. Oh, H. S. Rho, J. w. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem. Int. Ed.* **2008**, *47*, 7872–7875.

[91] a) J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437–440. b) H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee, C. E. Song, *Chem. Commun.* **2011**, 9621–9623. c) C. Reiter, S. López-Molina, B. Schmid, C. Neiss, A. Görling, S. B. Tsogoeva, *ChemCatChem.* **2014**, *6*, 1324–1332.

[92] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[93] T. Okino, Y. Hoashi, T. Fukurawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

(Figure 17b),[94] thus making the *N–H* acidity of the squaramide catalysts higher compared to the thiourea analogs.[95] Accordingly, squaramides can form stronger hydrogen bonds, which may account for their comparatively higher activity, even at relatively low catalyst loadings.

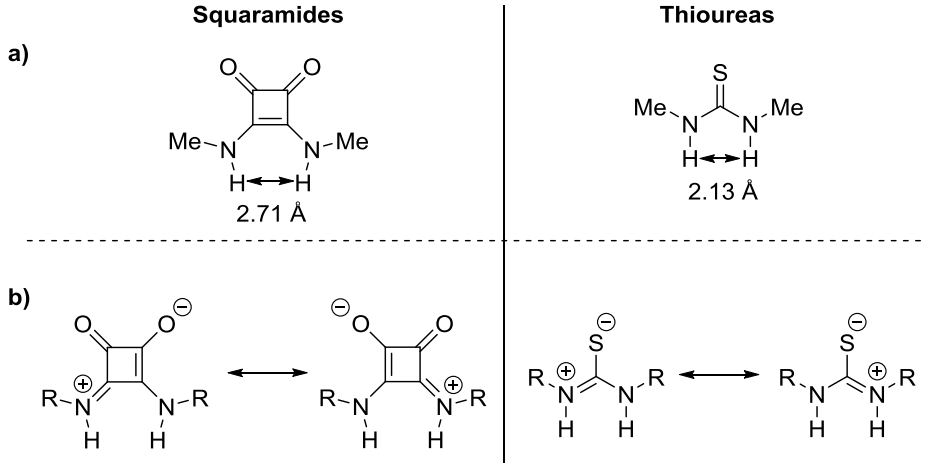
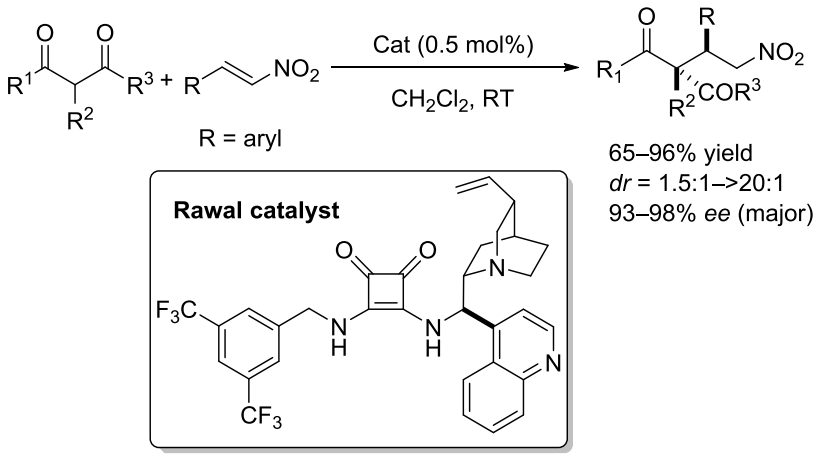


Figure 17.

Cinchonine derivatives bearing a squaramide group proved to be good promoters for the Michael addition of β-ketoesters and β-diketones to β-arylnitroalkenes (Scheme 16).[92] The corresponding adducts were obtained in excellent yield and enantioselectivity, but the most remarkable aspect of this reaction is the low catalyst loading (as low as 0.1 mol%) needed for effective stereocontrol.



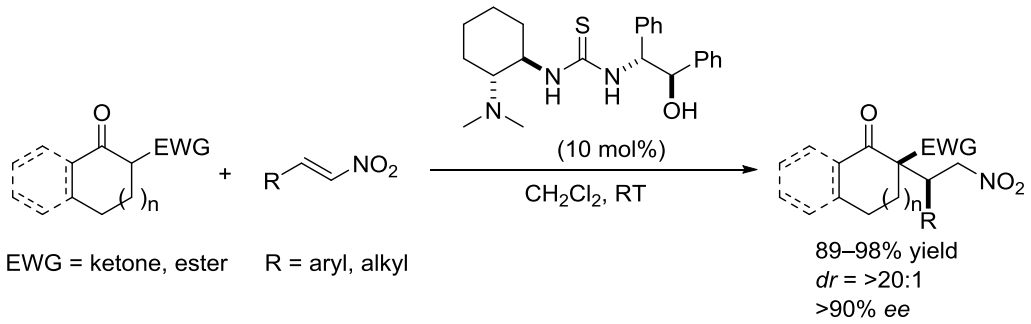
Scheme 16.

[94] S. Tomàs, R. Prohens, M. Vega, M. C. Rotger, P. M. Deyá, A. Costa, *J. Org. Chem.* **1996**, *61*, 9394–9401.

[95] X. Ni, X. Li, Z. Wang, J. P. Cheng, *Org. Lett.* **2014**, *16*, 1786–1789.

Encouraged by this unusual activity, in the following years many new squaramide catalysts were employed in different reactions,[96] with special success in domino and tandem processes.[97]

On the other hand, Wang et al. developed a different kind of bifunctional organocatalyst based on bifunctional amine-thioureas bearing three hydrogen-bond donor sites. The undelaying idea is that one more interaction site would lead to the formation of additional hydrogen bonds, thus improving the efficiency of the catalyst.[98] This group demonstrated the utility of these catalysts for the Michael reaction of β-ketoesters and β-diketones with nitroalkenes, obtaining the corresponding adducts in excellent yield, diastereo- and enantioselectivity (Scheme 17).[99]



Scheme 17.

Shortly before beginning this Thesis work, our research group introduced a new type of bifunctional BB catalyst based on the presence of a ureidopeptide unit as the H-bond donor site.[100] These catalysts were demonstrated to be very efficient in the Michael addition to nitroolefins and the amination of 5*H*-thiazol-4-ones (Scheme 18). These catalysts, which offer three independently modifiable parts, outperformed cinchona alkaloids and the Takemoto catalyst. It is worth noting that this was the first time 5*H*-thiazol-4-ones were used in asymmetric synthesis.

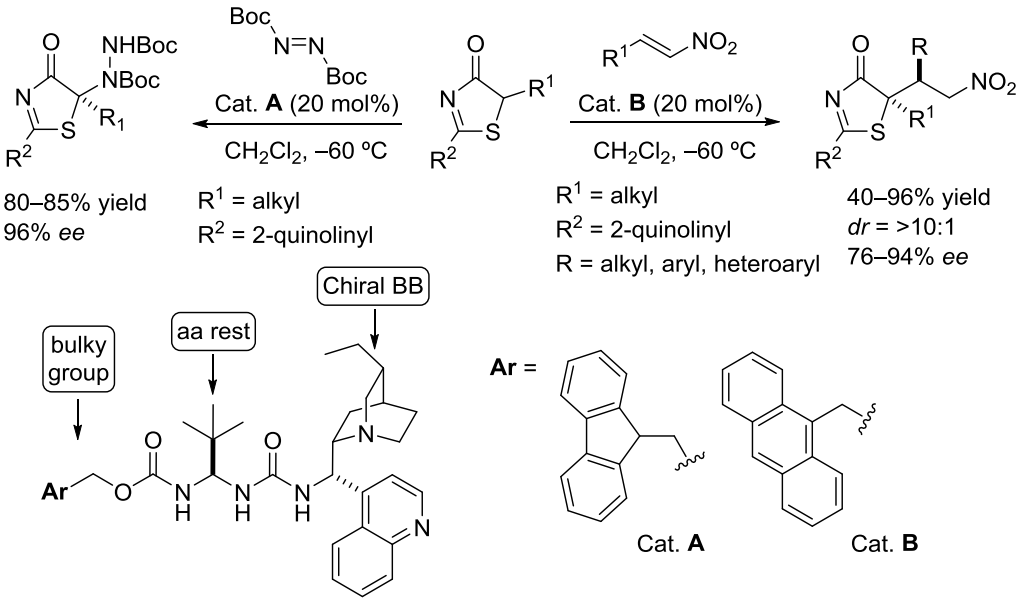
[96] For reviews on squaramide-based catalysts see: a) J. Alemán, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899. b) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906. c) B.-L. Zhao, J.-H. Li, S.-M. Du, *Chem. Rec.* **2017**, *17*, 994–1018.

[97] For a review on squaramide-catalyzed domino and tandem reactions see: P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 254–281.

[98] For a review on these catalysts see: X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197.

[99] Z.-H. Zhang, X.-Q. Dong, C.-J. Wang, *Chem. Eur. J.* **2008**, *14*, 8780–8783.

[100] a) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizaola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851. For further utility of these catalysts see: Mannich reaction: b) S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531. c) I. Bastida, M. San Segundo, R. López, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 13332–13336. Aldol reaction: d) I. Lapuerta, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2016**, *22*, 7229–7237. e) H. Etxabe, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.



Scheme 18.

On the other hand, guanidines represent another class of BB-catalysts. Guanidines can be categorized as organic superbases, owing to the stability of their conjugated acids (Figure 18), and therefore they are capable of catalysing various base-mediated organic reactions.[101] Another feature of guanidines is that the bidentate group may activate both the nucleophile and the electrophile concomitantly (Figure 18).[102]

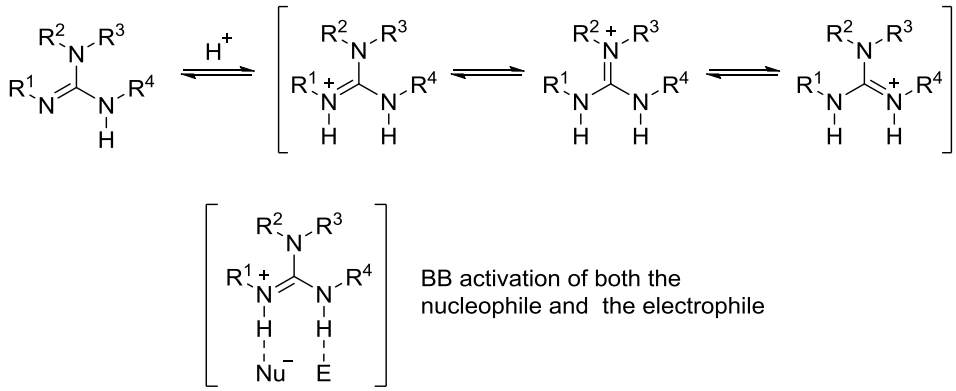
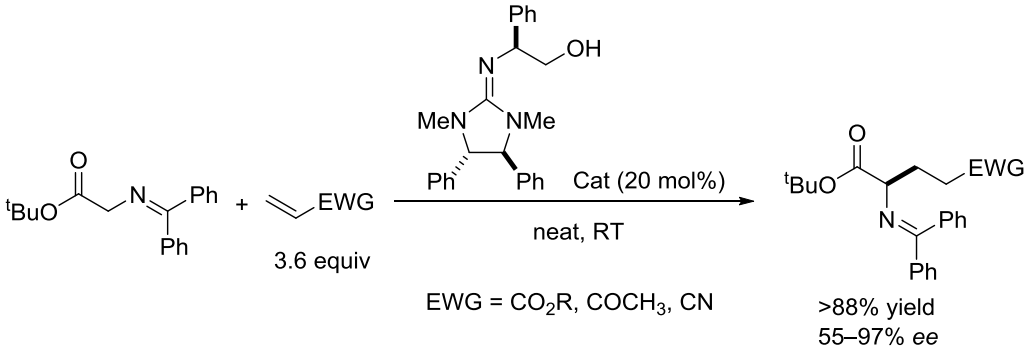


Figure 18.

[101] For further information on guanidine-catalyzed reactions see: a) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–725. b) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488–507. c) D. Mailhol, M. M. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 3523–3532.

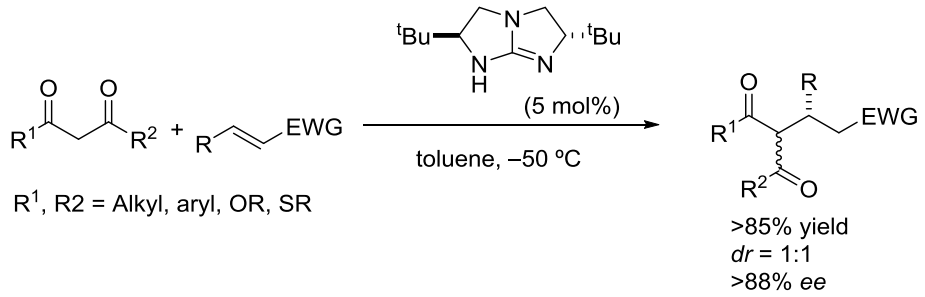
[102] P. I. Dalko, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Ed. Wiley-VCH Verlag GmbH & Co., **2013**.

In 2001, Ishikawa and coworkers[103] reported the first highly effective BB catalyzed Michael reaction using a 1,2-diphenylethylenediamine-derived chiral guanidine. The Michel reaction under neat conditions between glycine imine and several different acceptors afforded up to 97% *ee*, but a big excess of the acceptor was required in order to obtain a good yield (Scheme 19).



Scheme 19.

The bicyclic C_2-symmetric chiral guanidine introduced by the group of Corey[104] in 1999 is one of the most popular guanidine catalysts. In 2007, Tan and Jiang[105] reported the Michael reaction between different Michael acceptors and active methylene compounds to afford excellent yield and *ee* values, but zero diastereoselectivity, presumably due to subsequent epimerization of the α-carbon (Scheme 20).



Scheme 20.

To conclude, although BB catalysis has been successfully employed in the α-functionalization of an array of enolizable carbonyl compounds, most of the methods are restricted to easily enolizable nucleophiles typically bearing an EWG at the α-position like malonates, cyanoacetates, β-ketoesters, etc. In addition, most asymmetric

[103] T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, T. Isobe, *Chem. Commun.* **2001**, 245–246.

[104] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.

[105] a) W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2452–2458. For further examples by the same group see: b) L. Huang, J. Li, Y. Zhao, X. Ye, Y. Liu, L. Yan, C.-H. Tan, H. Liu, Z. Jiang, *J. Org. Chem.* **2015**, *80*, 8933–8941 and references herein.

procedures reported to date lead to the formation of a single stereogenic center or provide two consecutive new stereogenic centers with variable diastereoselectivity. On the other hand, among the Michael acceptors used so far, α,β-unsaturated carboxylic acid equivalents (enoates) remain little explored.

1.3. Limitations and general objectives

As can be seen in the previous sections, procedures for the direct asymmetric α-functionalization of carbonyl compounds still have some important limitations regarding the scope of nucleophiles and electrophiles suitable for attaining high reactivity and selectivity.

On the one hand, the enamine mediated cross-aldol reactions between two enolizable compounds remain troublesome due to the potential formation of up to four distinct aldol products, especially when using aldehydes as nucleophiles (Figure 19a). On the other hand, the use of α,β-unsaturated carbonyl compounds as electrophiles in asymmetric C–C bond forming catalysis has been little explored, in part owing to competitive 1,2- versus 1,4-addition pathways (Figure 19b).

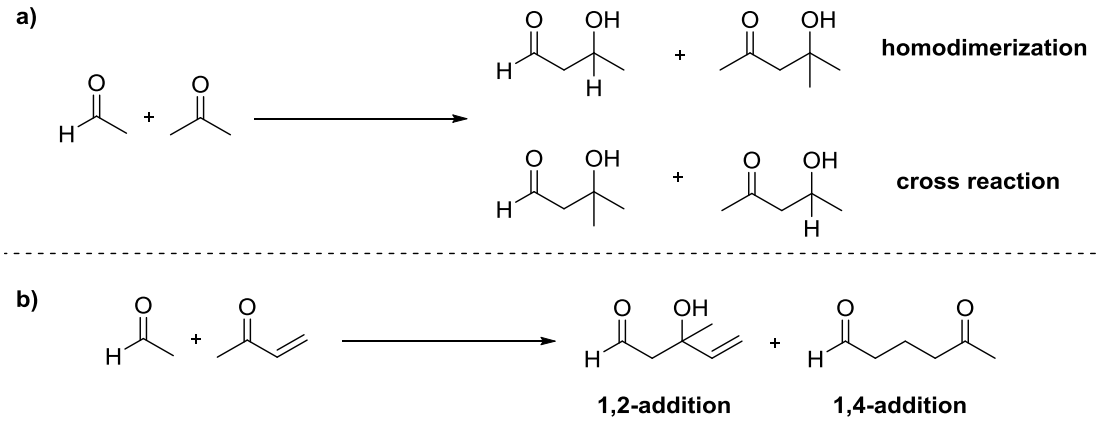


Figure 19.

These and other yet problematic issues, such as the creation of quaternary stereocenters or two adjacent stereocenters in an enatio- and diastereoslective manner, have been addressed in the present investigation. More specifically, we hypothesized that the use of propargylic carbonyl compounds as acceptors might provide a solution to the problematic cross-aldol reaction with enolizable aldehydes. As will be outlined later, these aldehydes have not been previously employed as acceptors in direct aldol reactions. The total or partial reduction of the triple C≡C bond in adducts should afford products that are formally derived from a troublesome cross-aldol reaction. Two

additional characteristics of this realization would be: i) the simultaneous formation of two contiguous stereogenic centers; and ii) the production of densely functionalized building-blocks, appropriate for ulterior application in the synthesis of structurally complex molecules.

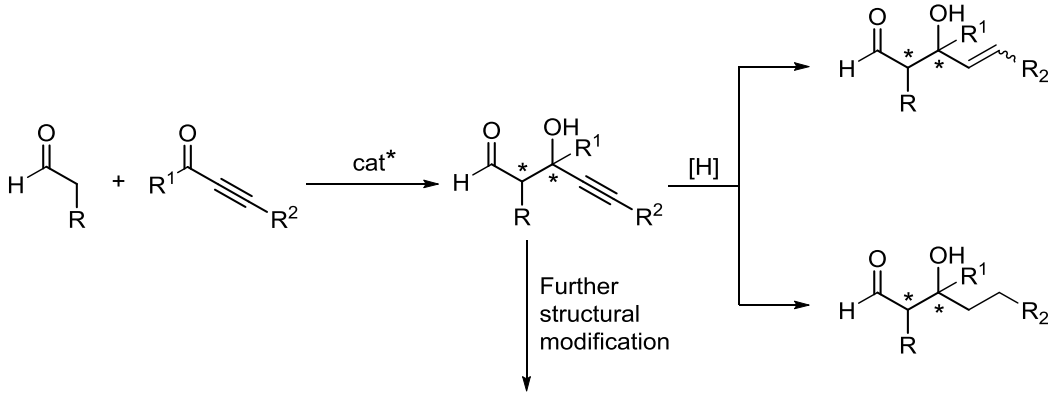


Figure 20.

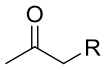
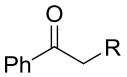
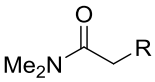
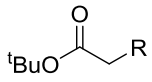
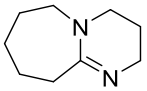
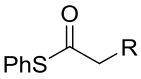
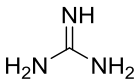
At the outset, this plan faced several challenges:

- Selective activation of the propargyl aldehyde as electrophile
- Suppression of the homodimerization of the enolizable aldehyde
- Control of the 1,2- vs 1,4- addition to ynones
- Control of the diastereo- and enantioselectivity

In a second part, we focused on some problems inherent to BB-catalyzed α-functionalization of carbonyl compounds. In particular, one limitation of the existing methods, as mentioned before, is the need for an additional EWG being attached to the α-carbon, which makes the α-carbon more acidic (13–18 pK_a range)[106] and therefore suitable for enolization by common organic bases (Table 2). In contrast, unactivated carbonyl compounds display higher pK_a values and thus are more challenging substrates for activation by Brønsted base catalysis.

[106] For a webpage of Bordwell pKa Table (acidities in DMSO) of different compounds, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

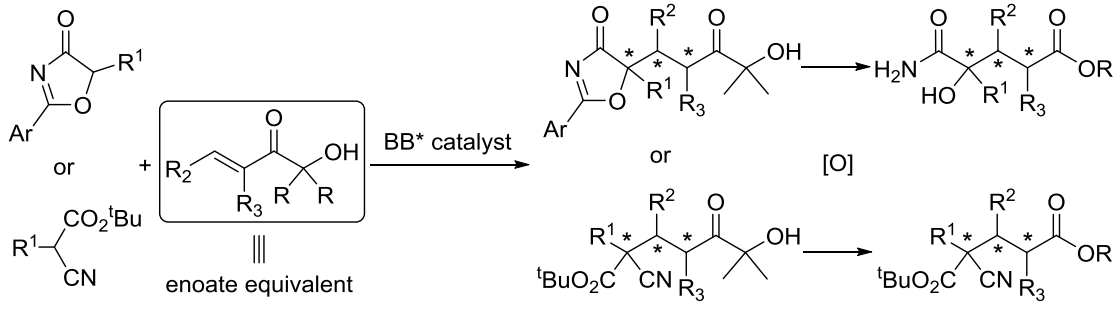
Table 2. pK_a values in DMSO for representative carbonyl compounds and organic BB.[106]

Carbonyls	pK_a		Bases	pK_a of conjugated acid
	R = H	R = Ph		
	26.5	19.8		8.9
	24.7	17.7	TEA	9.0
	35	25.9		9.8
	30.3	23.6		12.0
	-	16.9		13.6

On the other hand, the regioselective α-functionalization of ketones with two enolizable positions (α vs α'), and the stereoselective conjugate additions to enoates or equivalents also remain problematic.

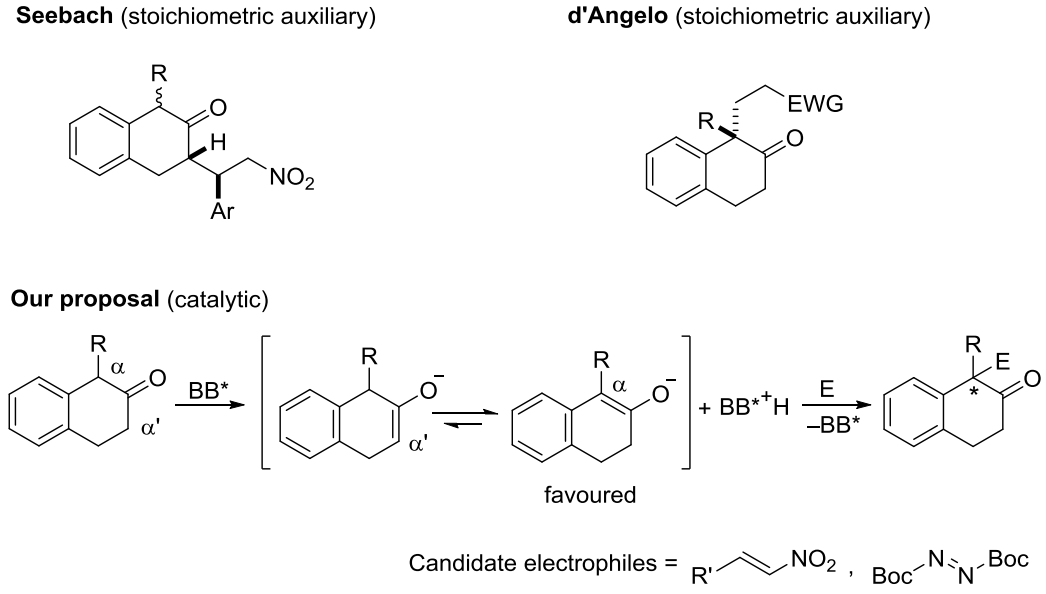
Figure 21.

In this context, our proposal was the use of α'-hydroxy enones in asymmetric organocatalysis for the first time. We hypothesized that chiral bifunctional BB catalysts might be able to trigger the Michael addition of pronucleophiles like 5*H*-oxazol-4-ones and cyanoacetates to these electrophiles, allowing the generation of chiral tertiary alcohols and all-carbon tetrasubstituted stereogenic centers, respectively.



Scheme 21.

A third problem we addressed during this Thesis concerns the regioselective α-functionalization of enolizable ketones. Following the work by Seebach[107] and d'Angelo[108] using enamine chemistry, we decided to take β-tetralones as a case study for achieving their regio- and stereoselective functionalization with the help of chiral bifunctional BB catalysts. The idea was that the fused aromatic ring in the molecule would induce preferential enolization at C_α, thus directing the functionalization towards that position.



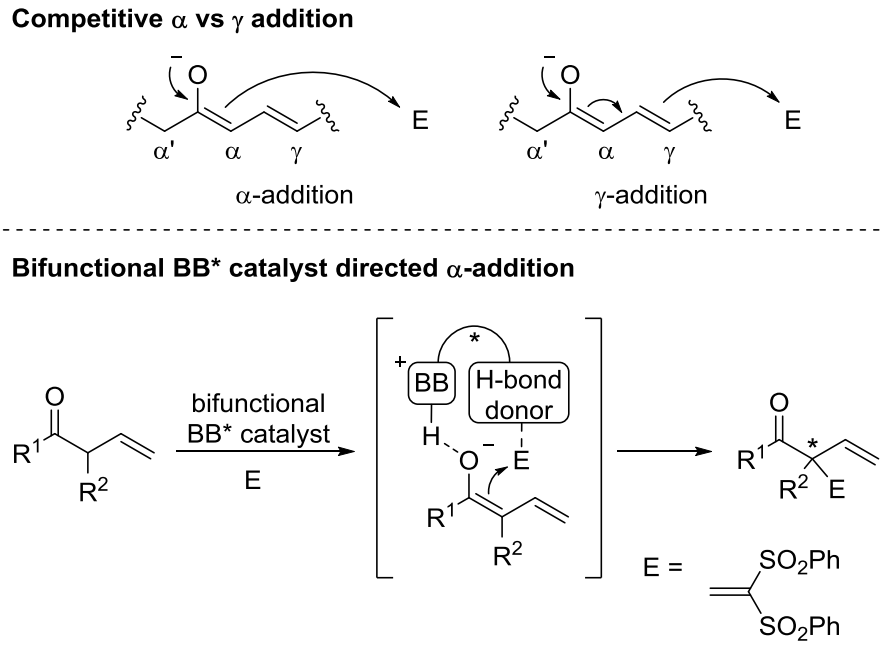
Scheme 22.

In this particular development, several problems were apparent at the outset: i) control of the α/α' selectivity, ii) suppression of the double addition (over addition products), and iii) control of diastereo- and enantioselectivity.

As another relevant situation where regioselectivity is an issue, we also decided to investigate the BB-catalyzed functionalization of alkenyl ketones. Here a vinylogous enolate would be formed and so there is a double selectivity problem: α vs α' vs γ. With these types of substrates, enamine-mediated catalysis usually provides the γ-addition adducts preferentially. We reasoned that bifunctional Brønsted base/H-bond catalysis might direct the approach of the electrophile through the α-position.

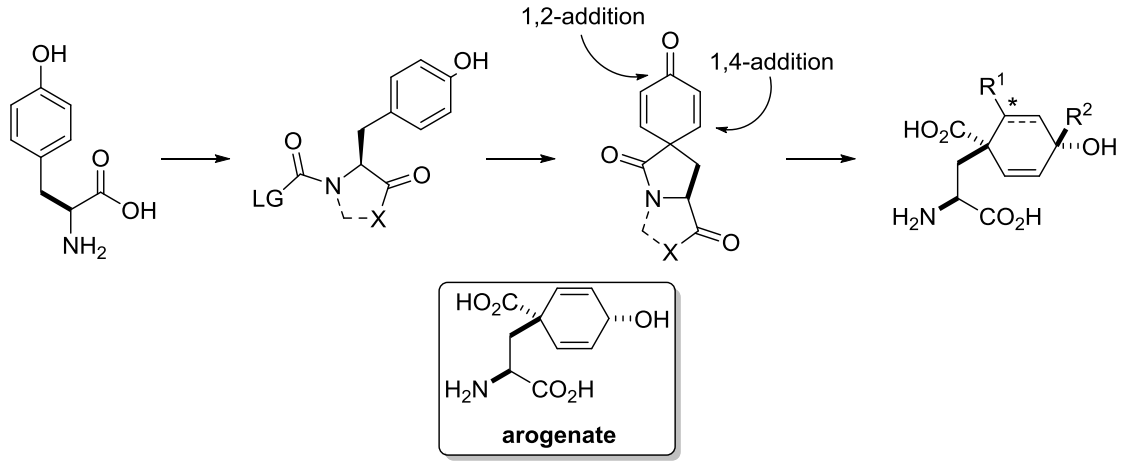
[107] a) S. J. Blarer, W. D. Seebach, *Chem. Ber.* **1982**, *116*, 3086–3096.

[108] a) T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.* **1987**, *28*, 2367–2370. b) J. d'Angelo, G. Revial, T. Volpe, M. Pfau, *Tetrahedron Lett.* **1988**, *29*, 4427–4430.



Scheme 23.

In the last part of my Doctoral research period, a short stay was carried out under the supervision of Prof. Jonathan Clayden in the School of Chemistry of the University of Bristol in the United Kingdom. The research project there was focused on the preparation of arogenate derivatives starting from the natural amino acid tyrosine. Arogenate derivatives are potential candidates for application as selective herbicides, and the development of an efficient and reproducible synthetic route to arogenate involving stable and modifiable intermediates is of current interest.



Scheme 24.

Chapter 2:

Enamine-mediated aldol reactions of aldehydes with propargylic aldehydes and ketones

2. Enamine-mediated aldol reactions of aldehydes with propargylic aldehydes and ketones

Enamine-mediated aldol reaction of aldehydes with propargylic aldehydes and ketones

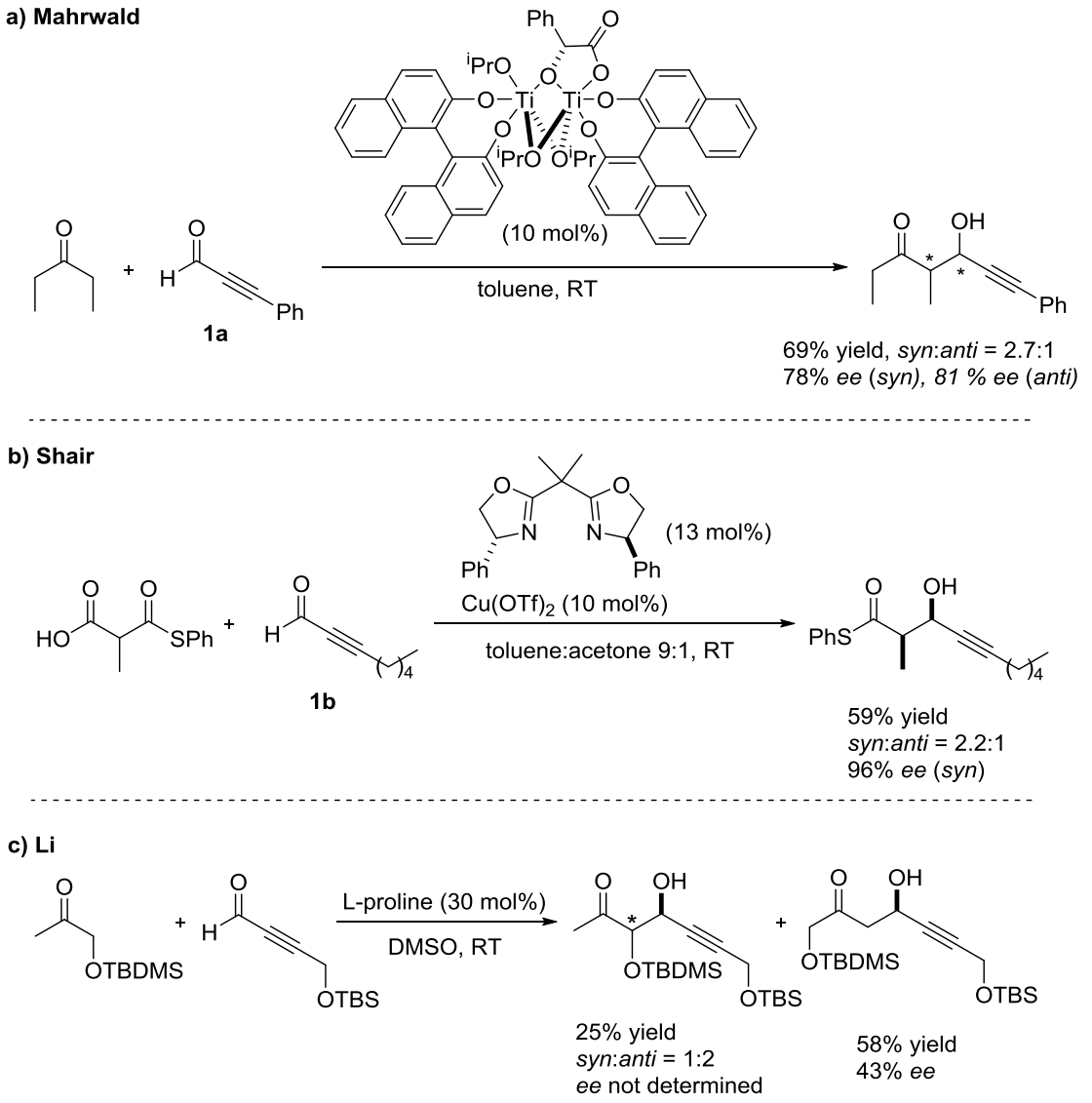
2.1. Precedents and objectives

Propargylic carbonyl compounds are attractive acceptors in C–C bond forming reactions, not only because the acetylenic system in the resulting adduct is an interesting scaffold for synthetic purposes, but also because they might be viewed as surrogates of simple enolizable aldehydes and α,β-enals given the ease with which the alkyne moiety may be easily transformed (upon total or partial reduction of the triple bond) into the corresponding alkyl and alkenyl units, respectively.

Despite the aldol reaction is one of the most extensively studied C–C bond forming transformations, at the beginning of this project there were only three examples of asymmetric catalytic direct aldol reactions involving propargylic aldehydes. The first two examples, reported by the groups of Mahrwald[109] and Shair,[110] were based on the use of metal complexes. Mahrwald used a titanium-BINOL complex for the asymmetric addition of a symmetric linear ketone to propargylic aldehyde **1a** (Scheme 1a), obtaining the corresponding aldol adduct in good yield, low *syn*/*anti* selectivity and good enantioselectivity. On the other hand, Shair et al. developed a Cu-catalyzed decarboxylative aldol addition of a malonic acid half thioester to propargylic aldehyde **1b** (Scheme 1b), which yielded the aldol reaction product in moderate yield, low diastereoselectivity and excellent enantioselectivity.

[109] a) R. Mahrwald, *Org. Lett.* **2000**, *2*, 4011–4012. b) R. Mahrwald, B. Ziemer, *Tetrahedron Lett.* **2002**, *43*, 4459–4461. c) R. Mahrwald, B. Schetter, *Org. Lett.* **2006**, *8*, 281–284. d) B. Schetter, B. Ziemer, G. Schnakenburg, R. Mahrwald, *J. Org. Chem.* **2008**, *73*, 813–819.

[110] D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2005**, *127*, 7284–7285.



Scheme 1.

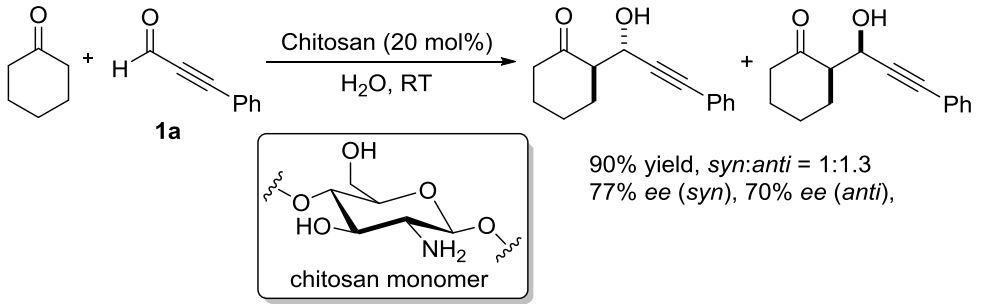
Li et al.[111] reported in 2003 the third and only organocatalytic example described before the beginning of this project (Scheme 1c). The L-proline catalyzed reaction of TBDMS-protected hydroxyacetone with a propargylic aldehyde afforded a mixture of aldol adducts with low selectivity.

While our investigation was in progress, Ricci, Quignard et al.[112] published the aldol reaction of cyclohexanone with different aldehydes, including propargylic

[111] H. Liu, L. Peng, T. Zhang, Y. Li, *New J. Chem.* **2003**, *27*, 1159–1160.

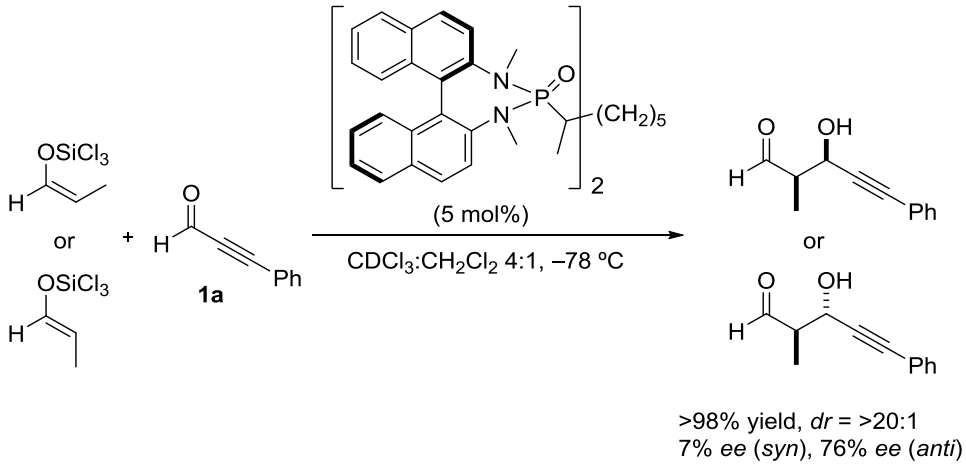
[112] C. Gioia, A. Ricci, L. Bernardi, K. Bourahla, N. Tanchoux, M. Robitzer, F. Quignard, *Eur. J. Org. Chem.* **2013**, 588–594.

aldehydes, catalyzed by a chitosan aerogel. When phenylpropargyl aldehyde **1a** was employed, very low diastereoselectivity and moderate *ee* were obtained (Scheme 2).



Scheme 2.

The control of chemoselectivity is especially troublesome in aldol reactions involving linear aldehydes as donor components, given the likelihood to have competitive undesired self-aldol processes. To our knowledge, the sole previous example of catalytic asymmetric aldol reaction using enolizable aldehydes as donor components was reported by Denmark and Ghosh[113] and involves trichlorosilyl enol ethers derived from aldehydes as nucleophiles and a phosphoramide catalyst (Scheme 3). Although cross-aldol products were obtained in excellent yield and diastereoselectivity, the enantioselectivity turned out to be of 76% *ee* at best.



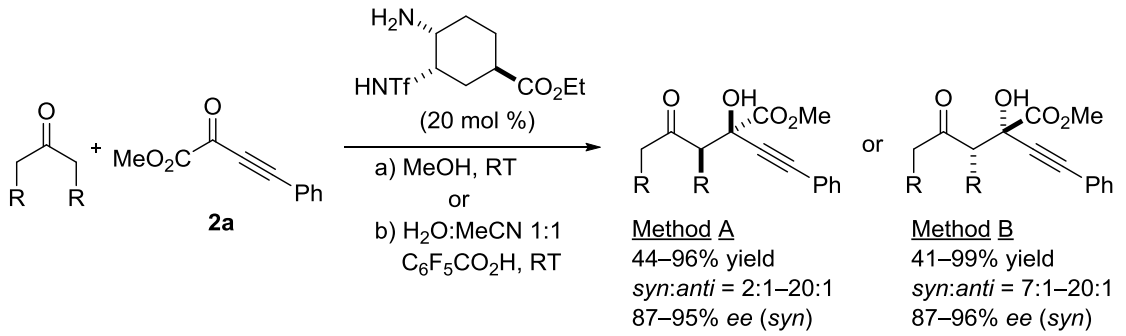
Scheme 3.

As to the use of propargylic ketones as electrophiles in asymmetric catalytic aldol reaction, the only example to date has been reported by Maruoka et al.,[114] who during the progress of this project documented the aldol reaction of symmetric ketones

[113] S. E. Denmark, S. K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762.

[114] S. A. Moteki, J. Han, S. Arimitsu, M. Akakura, K. Nakayama, K. Maruoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 1187–1190.

with a single propargylic α-ketoester **2a** employing a chiral primary amine catalyst. The corresponding adducts were obtained selectively with the C_α-alkyl and the C_β-OH groups in the *syn*- relative position in excellent yield and enantioselectivity. An interesting aspect of this development is that the enantioselectivity could be inverted by addition of an achiral Brønsted acid (Scheme 4).

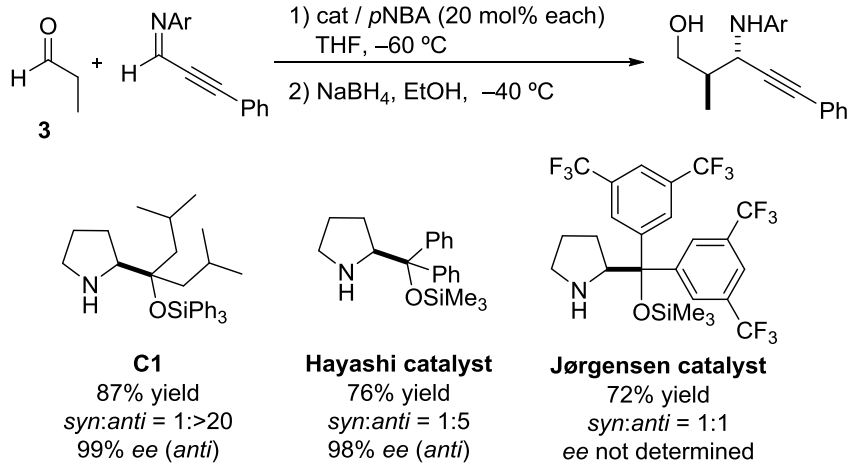


Scheme 4.

In this same context, I. Otazo and I. Lapuerta during their Thesis work and S. Vera, in our group reported a general procedure for the asymmetric direct Mannich reaction between aldehydes and unactivated imines,[115] including propargylimines (Scheme 5), promoted by certain silylprolinol ether catalysts.[116] These catalysts, exemplified by **C1**, bear two geminal α,α-alkyl groups instead of the gem-α,α-diaryl groups present in the commonly employed α,α-diaryl prolinol ethers (Jørgensen and Hayashi catalysts). During this development, it was observed that while these catalysts conducted the Mannich reaction with high efficiency and selectivity in the presence of a Brønsted acid cocatalyst (i.e. *p*NBA), no appreciable amounts of self-aldol product was formed at the low reaction temperatures utilized (~ –60 ºC). This result was explained assuming that the imine component would be selectively activated by the added Brønsted acid (protonated imine) even at low temperature, thus skipping the problem of aldehyde self-condensation.

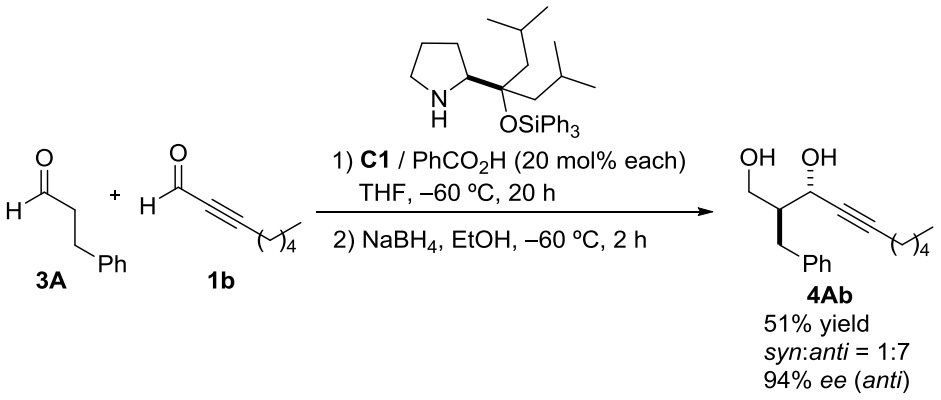
[115] E. Gómez-Bengoa, S. Jiménez, I. Lapuerta, A. Mielgo, M. Oiarbide, I. Otazo, I. Velilla, S. Vera, C. Palomo, I. Velilla, *Chem. Sci.* **2012**, *3*, 2949–2957.

[116] For further examples of the use of these catalysts in the group see: a) C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem. Int. Ed.* **2007**, *46*, 8054–8056. b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente, S. Vera, *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435. c) A. Landa, M. Maestro, C. Masdeu, Á. Puente, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *7*, 1562–1565. d) E. Gómez-Bengoa, M. Maestro, A. Mielgo, I. Otazo, C. Palomo, I. Velilla, *Chem. Eur. J.* **2010**, *8*, 5333–5342. e) A. Mielgo, I. Velilla, E. Gómez-Bengoa, C. Palomo, *Chem. Eur. J.* **2010**, *8*, 7496–7602. f) S. Jiménez, A. Landa, A. Lizarraga, M. Maestro, A. Mielgo, M. Oiarbide, I. Velilla, C. Palomo, *J. Org. Chem.* **2012**, *77*, 747–753.



Scheme 5.

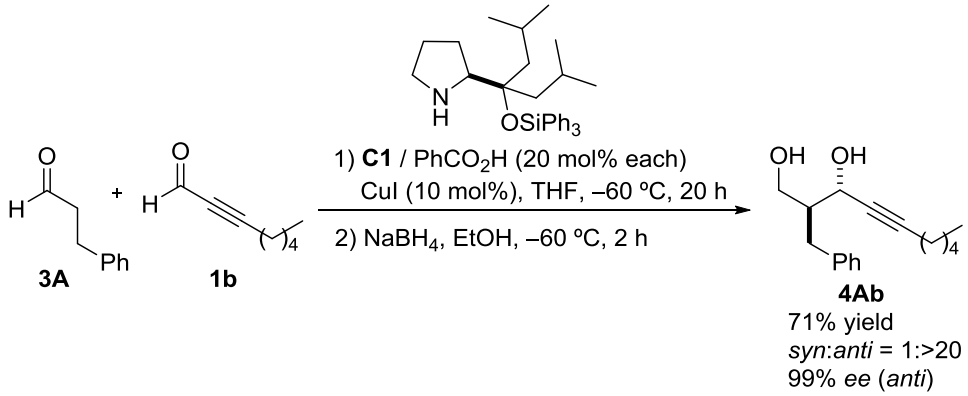
Following this previous work and taking into consideration the few precedents described on the direct asymmetric catalytic aldol reaction involving propargylic carbonyl compounds, and especially the lack of methods employing aldehydes as donor carbonyl compounds in the direct catalyzed version of the reaction, we set out to study the aldol reaction between enolizable aldehydes and propargylic carbonyl compounds with the aim of developing an efficient organocatalytic system. However, only moderate yield and diastereoselectivity were obtained following the procedure described for propargylic imines (Scheme 6).



Scheme 6.

With the aim to improve this result, it was reasoned that an efficient and selective activation of propargylic aldehydes as acceptors might be achieved by a simple metal cocatalyst capable of coordinating to ynals. Thus, it was found that when adding

10 mol% of the CuI metal salt to the reaction both the yield and the diastereoselectivity of the reaction were significantly improved (Scheme 7).[117]

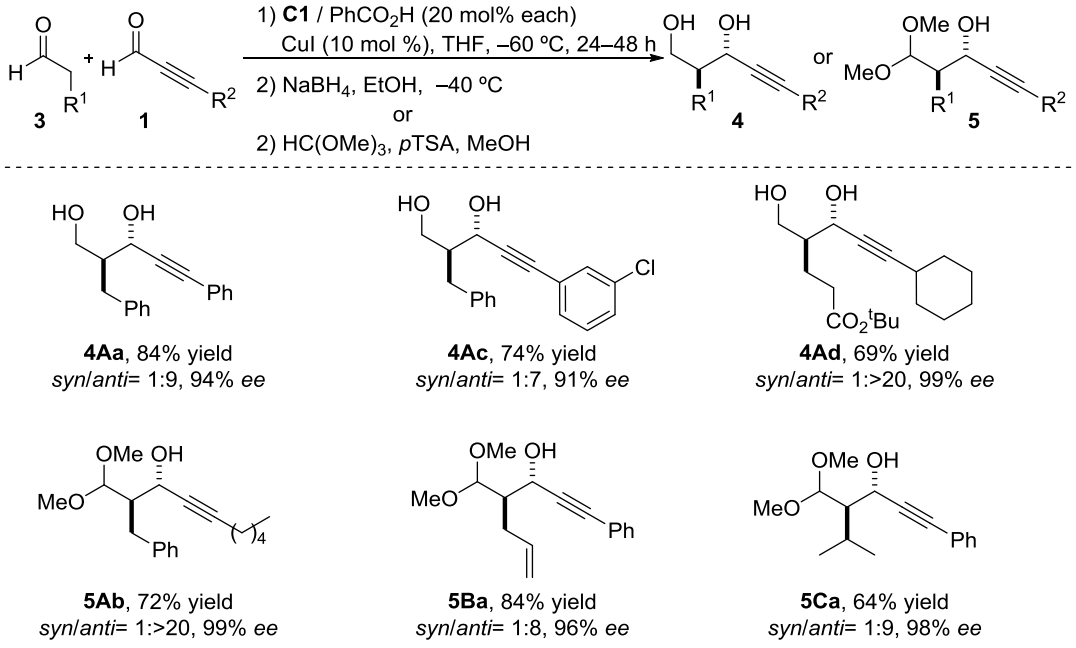


Scheme 7.

Some of the most representative examples of the reaction scope, part of the doctoral Thesis of I. Lapuerta, are shown in Table 1. As it can be seen, the reaction proceeded smoothly and in good yield and the corresponding adducts were isolated either as diols or acetals to avoid epimerization of C_α. The reaction tolerated well both aromatic (**4Aa** and **4Ac**) and aliphatic (**4Ad** and **5Ab**) propynals and donor ramified aldehydes (**5Ca**) or aldehydes with additional functional groups (**4Ad** and **5Ba**). Furthermore, the *syn*/*anti* ratios were higher than 1:5 in all cases, and *ee* values for the major isomer (*anti*) were above 90% *ee*.

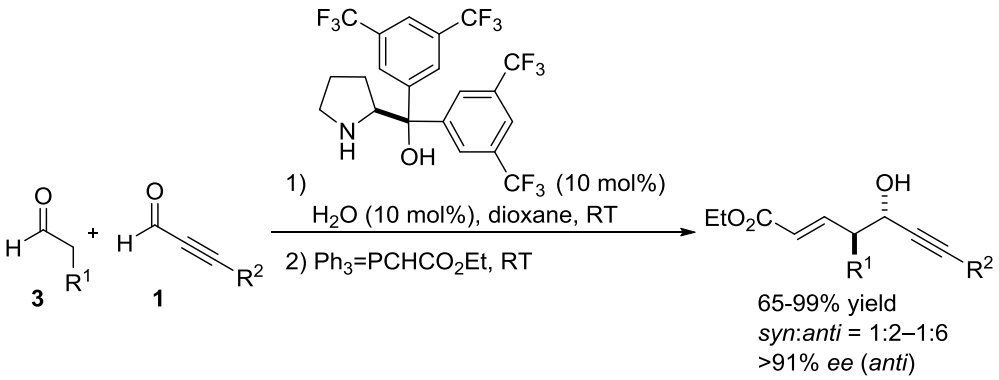
[117] E. Gómez-Bengoa, J. M. García, S. Jiménez, I. Lapuerta, A. Mielgo, J. M. Odriozola, I. Otazo, J. Razkin, I. Urruzuno, S. Vera, M. Oiarbide, C. Palomo, *Chem. Sci.* **2013**, *4*, 3198–3204.

Table 1. Cross-aldol reaction scope between saturated and propargylic aldehydes[a]



[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**3**/**1**/**C1**/$PhCO_2H$/CuI molar ratio = 1.5:1:0.2:0.2:0.1). Combined yield of syn/anti adducts after chromatography. *syn*:*anti* values determided by ^1H NMR spectroscopy and corroborated by HPLC. *ee* of major (*anti*) isomer, determined by chiral HPLC.

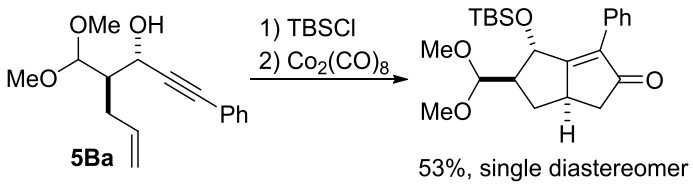
It should be noted that shortly after these preliminary results were disclosed, Hayashi and coworkers[118] reported the direct aldol reaction between aldehydes and propargylic aldehydes employing a prolinol catalyst and water as the only additive (Scheme 8). This method, which applies a subsequent Wittig reaction, requires a large excess (5 equiv.) of the donor aldehyde and provides modest *syn*/*anti* selectivity (1:2–1:6 while our method afforded typically 1:>9 *syn*/*anti* ratios).



Scheme 8.

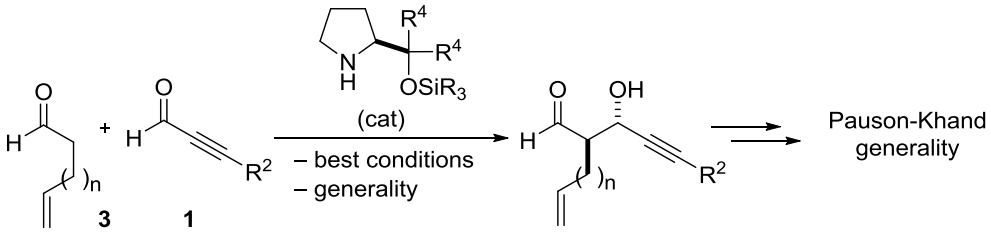
[118] Y. Hayashi, M. Kojima, Y. Yasui, Y. Kanda, T. Mukaiyama, H. Shomura, D. Nakamura, Ritmanleni, I. Sato, *Chem. Cat. Chem.* **2013**, *5*, 2887–2892.

When the donor aldehyde bears a ω-olefin function (i.e. **3b**), the resulting adduct (i.e. **5Ba**) is an 1,ω-enyne and therefore could participate in a Pauson-Khand intramolecular reaction. This type of oxygenated 1,ω-enyne systems have been previously reported in the literature to provide upon Pauson-Khand reaction bicyclic [m.3.0] rings,[119] which are found as subunits of natural sesquiterpene products.[120] We indeed observed that the treatment of the silylated derivative of **5Ba** under Pauson-Khand reaction conditions afforded the corresponding bicyclic [3.3.0] compound in moderate yield and as a single isomer (Scheme 9).



Scheme 9.

Based on these precedents, we set out to study the reaction generality for a range of ω-unsaturated aldehydes as donors in order to apply the aldol reaction to the preparation of hydroxyl Pauson-Khand precursors, commencing by examining the best reaction conditions for these particular substrates.

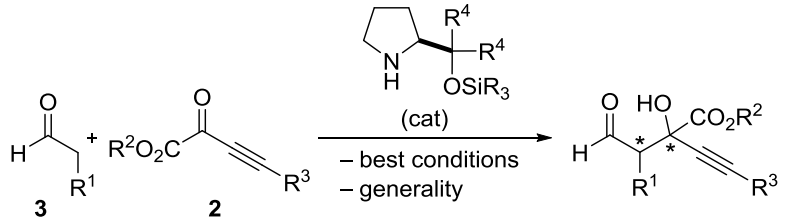


Scheme 10.

We planned to study also the suitability of the approach for acetylenic ketones (ynones) as acceptors. If successful, this development would considerably expand the pool of accessible compounds including those with a tertiary carbinol, which are considerably more challenging to obtain in a stereoselective manner.

[119] a) C. Mukai, J. S. Kim, H. Sonobe, M. Haneoka, *J. Org. Chem.* **1999**, *64*, 6822–6832. b) T. Kozaka, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2007**, *72*, 10147–10154. c) Y. Otsuka, F. Inagaki, C. Mukai, *J. Org. Chem.* **2010**, *75*, 3420–3426. d) M. Turlington, Y. Yue, X.-Q. Yu, L. Pu, *J. Org. Chem.* **2010**, *75*, 6941–6952. e) M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat, L. Pu, *J. Am. Chem. Soc.* **2011**, *133*, 11780–11754. f) W. Chen, J.-H. Tay, J. Ying, M. Sabat, X.-A. Yu, L. Pu, *Chem. Commun.* **2013**, *49*, 170–172. g) W. Chen, J.-H. Tay, J. Ying, X.-A. Yu, L. Pu, *J. Org. Chem.* **2013**, *78*, 2256–2265. h) N. Itoh, T. Iwata, H. Sughihara, F. Iragaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665–8672.

[120] a) B. M. Fraga, *Nat. Prod. Rep.* **1999**, *16*, 21–38. b) B. M. Fraga, *Nat. Prod. Rep.* **2003**, *20*, 392–413.



Scheme 11.

2.2. Enamine-mediated aldol reaction of ω-unsaturated aldehydes with propargylic aldehydes

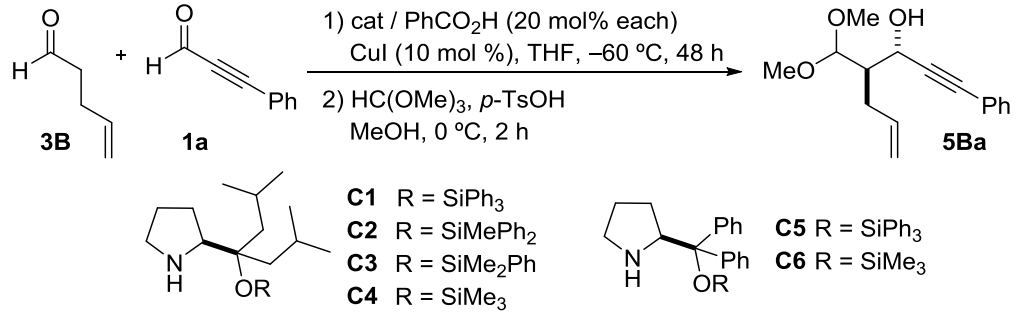
2.2.1. Initial experiments and reaction optimization

Initially a study of the best reaction conditions for these types of unsaturated donor aldehydes was carried out with the reaction between 4-pentenal (**3B**) and phenylpropinal (**1a**) taken as a model. The data of the most representative experiments are shown in Table 2. First reactions were carried out under the general conditions previously established in the group for the direct asymmetric reaction of enolizable aldehydes with ynals[117] (1.5 equiv. of donor aldehyde, 20 mol% **C1**, 20 mol% benzoic acid and 10 mol% CuI at –60 ºC) (Table 2, entry 1) and after 48 h and subsequent acetalization, the desired adduct **5Ba** was obtained in good yield and very high diastereo- and enantioselectivity. When running the reaction without any benzoic acid cocatalyst, low conversions (<30 %) were obtained (Table 2, entry 2), corroborating the crucial role played by this cocatalyst. However, when running the reaction in the absence of CuI (Table 2, entry 3), only a little erosion in diastereoselectivity was observed. On the other hand, lowering the loading of the amine catalyst and the benzoic acid to 10 mol% resulted in low conversion after 48 h (Table 2, entry 4).

Next, we studied the performance of the purposely synthesised related amine catalysts **C2**–**4**, which bear different *O*-protecting groups. When using catalyst **C2** (R = $SiPh_2Me$; Table 2, entry 5), the yield and enantioselectivity were similar to those values obtained with **C1**, but the *syn*/*anti* ratio turned out to be only moderate (*syn*/*anti* = 1:4). Moreover, using CuI in combination with **C2** the same results were obtained (Table 2, entry 6). Amine **C3** also rendered adduct **5Ba** in similar results (Table 2, entry 7) without any metal salt, but when the reaction was run in the presence of CuI (Table 2, entry 8) very low conversion of the reaction was observed. The reactivity and selectivity observed when using catalyst **C4** (Table 2, entry 9) in the absence of the metal was once again similar to **C2** and **C3**, but when carrying out the reaction in the presence of CuI

(Table 2, entry 10) eroded yields were obtained. These results indicate a correlation between the silyl group of the catalyst and the reaction selectivity, given that changing the triphenylsily group of **C1** for a less sterically demanding silyl group severely eroded the *syn*/*anti* ratio. Furthermore, whilst the effect of added CuI in the reaction seems to vary with the nature of the silyl substituent of the aminocatalyst, in neither case it plays a beneficial role in terms of reactivity or selectivity.

Table 2. Catalyst screening for the reaction between **3B** and **1a**[a]



Entry	cat	Metal	Conv. (%)[b]	Yield (%)[c]	syn/anti[d]	*ee* (%)[e]
1	**C1**	CuI	96	67	1:14	98
2	**C1**	CuI	<30[f]	n.d.	n.d.	n.d.
3	**C1**	-	96	61	1:11	98
4	**C1**	-	45[g]	n.d.	n.d.	n.d.
5	**C2**	-	90	67	1:4	94
6	**C2**	CuI	86	65	1:4	92
7	**C3**	-	92	62	1:4	96
8	**C3**	CuI	30	n.d.	n.d	n.d.
9	**C4**	-	95	63	1:4	96
10	**C4**	CuI	79	53	1:4	94
11	**C5**	-	93	68	1:4	99
12	**C5**	CuI	72	51	1:1.5	99
13	**C6**	-	93	66	1:4	98
14	**C6**	CuI	33	n.d.	1:6	91

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**3B**/**1a**/cat/$PhCO_2H$/CuI molar ratio = 1.5:1:0.2:0.2:0.1). [b] Determined by ^1H NMR spectroscopy on reaction aliquots before workup. [c] Combined yield of *syn*/*anti* adducts after chromatography. [d] Determided by ^1H NMR spectroscopy and corroborated by HPLC. [e] *ee* of major (*anti*) isomer, determined by chiral HPLC. [f] Reaction conducted without $PhCO_2H$. [g] Reaction conducted with 10 mol% of the amine catalyst and $PhCO_2H$.

We also tested the α,α-diaryl catalysts **C5** and **C6** (Table 2, entries 11 and 13) which indeed did promote the cross-aldol reaction with similar efficiency but with

lower *syn*/*anti* selectivity as compared with **C1**. Again, when performing the reaction in the presence of 10 mol% CuI (Table 2, entries 12 and 14), a lower reactivity of the catalytic system was observed. Moreover, for **C5** the use of the metal salt also led to a loss of diastereoselectivity (Table 2, entry 12).

From these results it could be deduced that the amine / Brønsted acid combination was crucial for the reaction, being amine catalyst **C1** the optimum, and that the use of a metal cocatalyst would not lead to any improvement in the case of aldehyde **3B**.

Both the reaction conversion and *syn*/*anti* ratios were determined by ^{1}H NMR (300 MHz) analysis of untreated and treated samples of the reaction (Figure 1 and 2, respectively). Thus conversions were measured by comparison of the peak areas of the protons linked to the carbonyl group of both the propargylic aldehyde **1a** (9.43 ppm, 1 H) and adduct **5Ba** (both *syn* and *anti*; 9.89 ppm, 1 H) respectively. The signal at 9.78 ppm corresponds to the donor aldehyde **3B**.

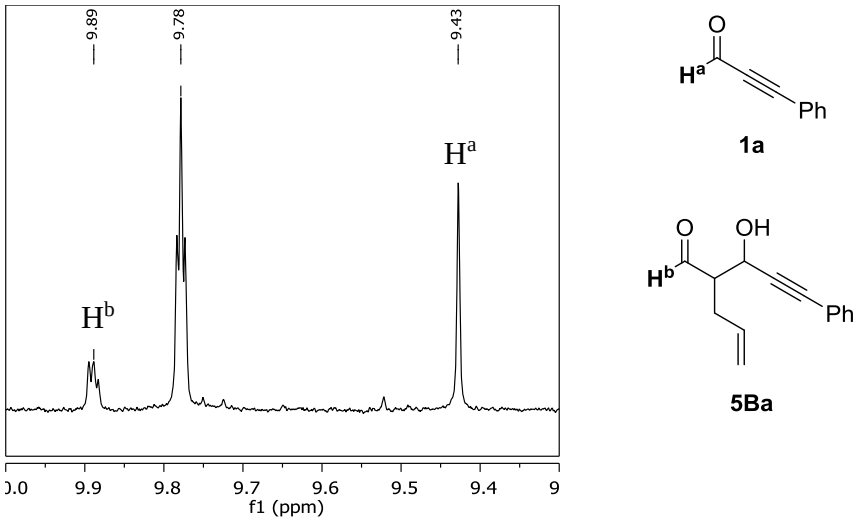
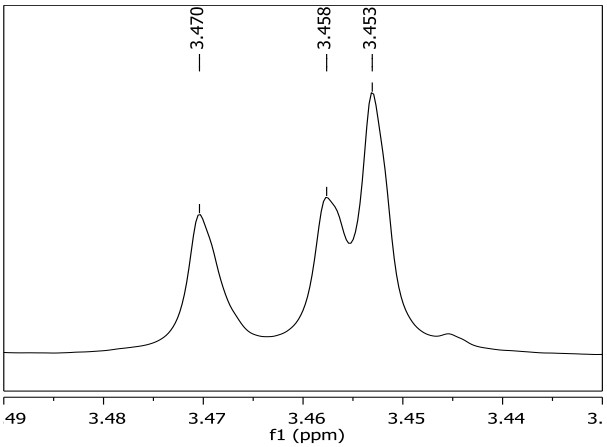
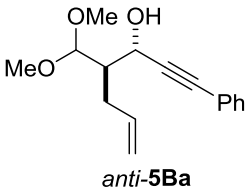


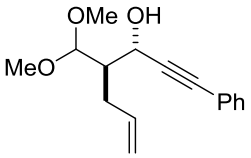
Figure 1.

On the other hand, the *syn*/*anti* ratio was determined by comparing the peak areas of the protons present in the methoxy groups of the acetal. The signals at 3.470 ppm (3 H) and 3.458 ppm (3 H) correspond to the *anti* adduct (major), and the signal at 3.453 ppm (6 H) corresponds to *syn* adduct (minor).





anti-**5Ba**



syn-**5Ba**

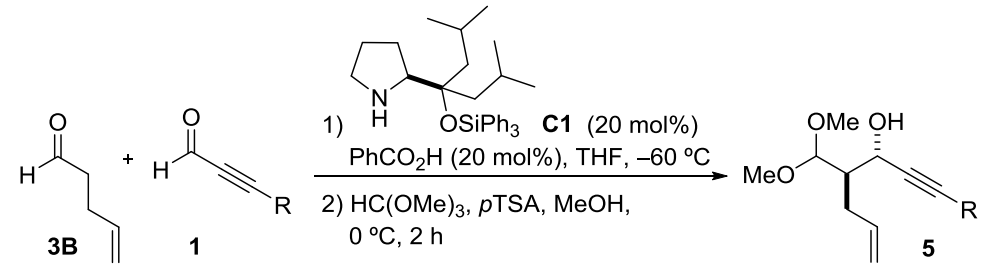
Figure 2.

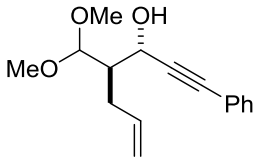
2.2.2. Reaction scope

Once the optimization of the model reaction was performed, the reaction of aldehyde **3B** with a selection of four propargylic aldehydes was carried out following the next standard procedure: the acceptor ynal was dissolved in THF (1 M) at –60 °C and 1.5 equivalents of the donor aldehyde and 20 mol% of each the catalyst **C1** and benzoic acid were added. The reaction mixture was stirred at the same temperature, and after verifying by ^{1}H NMR analysis of untreated aliquots that the reaction stopped (24–48 h), the mixture was treated with $HC(OCH_3)_3$ (3 equivalents) in the presence of 20 mol% *p*TSA at 0 °C for 2 h. The corresponding dimethyl acetal products were isolated by flash column chromatography on silica gel eluting with hexane/EtOAc mixtures.

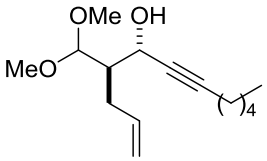
The results in Table 3 show that the reactions proceeded in good yield with either aromatic (**5Ba**), aliphatic (**5Bb**), or heteroaromatic (**5Bd**) propynals. In addition, the reaction was performed in a 5 mmol scale to afford adduct **5c** in excellent diastereo- and enantioselectivity, although the yield was only moderate due to a lower conversion of the reaction. Furthermore, the *syn*/*anti* ratio varies from minimum of 1:8 to 1:20, and the lowest enantioselectivity for the major isomer (*anti*) was 96% *ee*.

Table 3. Cross-aldol reaction scope between saturated and propargylic aldehydes[a]

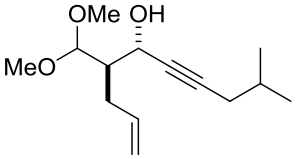




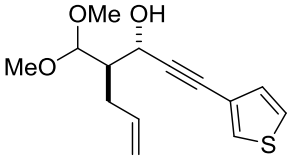
5Ba, 72% yield
syn/*anti*= 1:8, 99% *ee*



5Bb, 80% yield
syn/*anti* = 1:13, 96% *ee*



5Bc, 50%[b] yield
syn/*anti* = 1:20, 99% *ee*



5Bd, 72% yield
syn/*anti* = 1:9, 99% *ee*

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**3B**/**1**/**C1**/$PhCO_2H$ molar ratio = 1.5:1:0.2:0.2). Combined yield of *syn*/*anti* adducts after chromatography. *dr* values determided by ^1H NMR spectroscopy and corroborated by HPLC. ee of major (*anti*) isomer, determined by chiral HPLC. [b] Reaction run at 5 mmol scale.

2.2.3. Elaboration of the adducts: Pauson-Khand reaction

The Pauson-Khand reaction, introduced in 1971,[121] is a formal [2π + 2π + 2π] cycloaddition between an alkyne, an alkene, and carbon monoxide to afford a β-cyclopentanone, catalyzed by cobalt (usually dicobalt octacarbonyl).

For the reaction to be efficient, high stereo- and regioselectivity must be obtained. In the case of an intramolecular reaction, two isomeric bicyclic products (*exo* and *endo*) can be formed, as depicted in Figure 3.

[121] a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc. D.* **1971**, 36–36b. b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc. Perkin Trans. 1* **1973**, 975–977. c) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977–981.

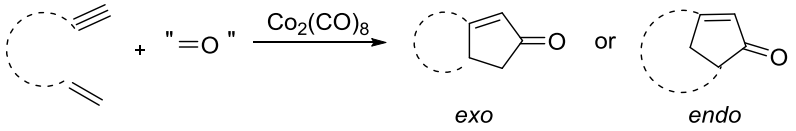


Figure 3. General scheme of the intramolecular Pauson-Khand reaction

At the outset it had been reported that unprotected propargylic alcohols are not suitable substrates for the Pauson-Khand reaction,[122] and that protection of the alcohol as a silyl ether allows the Pauson-Khand reaction to proceed.

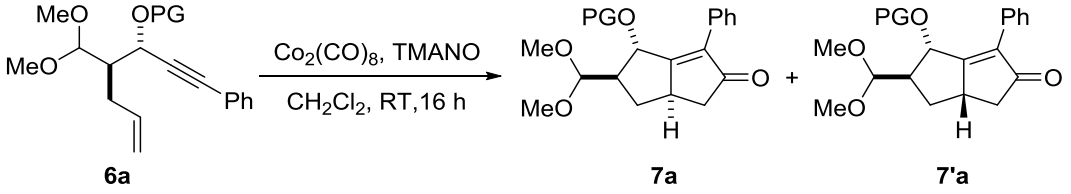
Considering this, a preliminary study to establish the ideal protecting group and reaction conditions for the formal [2+2+2] cycloaddition process was performed.[123] Trimethylamine *N*-oxide (TMANO) was added to oxidize the CO liberated in the coordination of the cobalt to the alkyne, forming CO_2 and rendering the step irreversible, thus allowing the use of milder reaction conditions.[124] As the data summarized in Table 4 show, the bulkiest silyl groups (Si^iPr_3, $Si(SiMe_3)_3$) turned out to be the most efficient, giving rise to the desired cycloadducts essentially as a sole diastereomer (Table 4, entries 4 and 5). The reaction also proceeded with yields around 65–70% when using the less bulky groups ($SiMe_3$, $SiPh_3$, $SiMe_2{}^tBu$) but led to diastereomeric mixtures (Table 4, entries 1, 2 and 3). In every case the corresponding cycloadducts were obtained in a completely *exo*-selective manner.

[122] a) C. Mukai, J. S. Kim, H. Sonobe, M. Haneoka, *J. Org. Chem.* **1999**, *64*, 6822–6832. b) M. Turlington, Y. Yue, X.-Q. Yu, L. Ou, *J. Org. Chem.* **2010**, *75*, 6941–6952. c) N. Itoh, T. Iwata, H. Sughihara, F. Iragaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665–8672.

[123] This study was carried out in collaboration with the group of J. M. García, in Universidad Pública de Navarra.

[124] S. Shambayani, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289–5292.

Table 4. Effect of the protecting group in the Pauson-Khand reaction stereoselectivity[a]



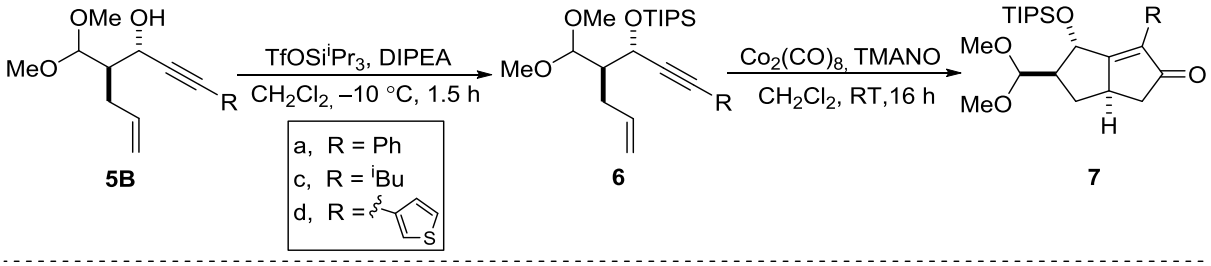
6a **7a** **7'a**

Entry	Protecting group (PG)	Yield (%)[b]	7a/7'a[c]
1	$SiMe_3$	65	5:1
2	$SiPh_3$	66	4:1
3	$SiMe_2{}^tBu$	67	3:1
4	$Si(SiMe_3)_3$	60	>20:1
5	Si^iPr_3	65	>20:1

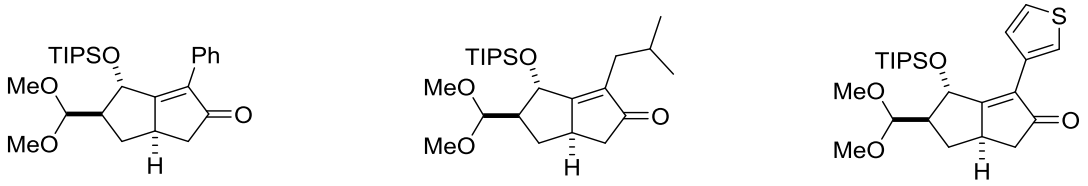
[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of CH_2Cl_2. [b] Combined yield of *exo*/*endo* adducts after chromatography. [c] Determided by ^1H NMR spectroscopy.

Next, the conditions optimized for enyne **5Ba** were applied to the adducts **5Bc** and **5Bd.** As shown in Table 5, the desired bicyclic adducts were obtained satisfactorily with aliphatic (**7c**) and heteroaromatic (**7d**) R groups in good yield and essentially as a single diastereomer.

Table 5. Pauson-Khand reaction scope[a]



5B **6** **7**



7a, 65%
dr = >20:1

7c, 64%
dr = >20:1

7d, 65%
dr = >20:1

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of CH_2Cl_2. *dr* determided by ^1H NMR spectroscopy.

The configuration of the major and minor diastereomers was deduced by ^1H NMR chemical shift correlation (Figure 3). It was previously established that for this kind of bicycles with the H^a and H^c in a *trans* relationship, H^a resonates more up-field

than in the corresponding *cis* isomer.[125] Accordingly, using the trimethylsilyl protected adducts (5:1 *dr*), the major isomer was assigned as *trans* H^a-H^c (H^a signal at 4.8 ppm) and the minor as *cis* (H^a signal at 5.2 ppm). Finally, it was observed that H^b also follows the same trend (5.1 ppm for the major isomer and 5.6 for the minor).

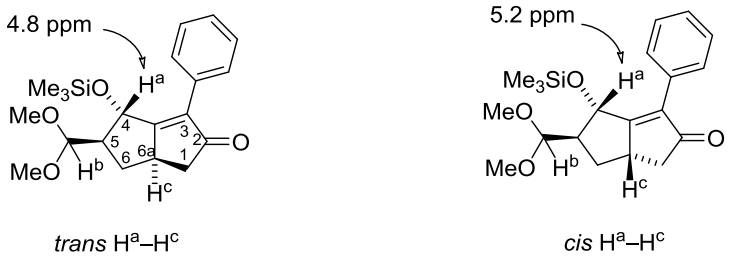
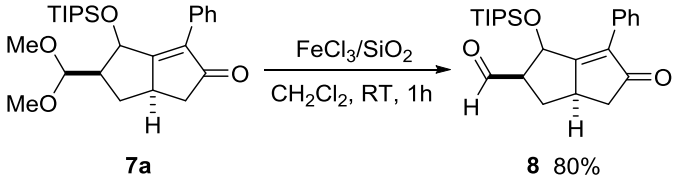


Figure 4.

Finally, the unprotected aldehyde **8** was obtained from the cycloadduct **7a** upon exposure to Mori's conditions ($FeCl_3/SiO_2$)[126] in methylene chloride (Scheme 12). Although hydrolysis was not complete, the unreacted dimethyl acetals could be easily recovered by column chromatography and recycled, obtaining good yields after two reaction cycles. Other attempted methods for the hydrolysis were the use of Amberlyst-15 in acetone, which led to no reaction, and the use of HCl in acetone / water, which led to very low yields due to undesired side-reactions.



7a **8** 80%

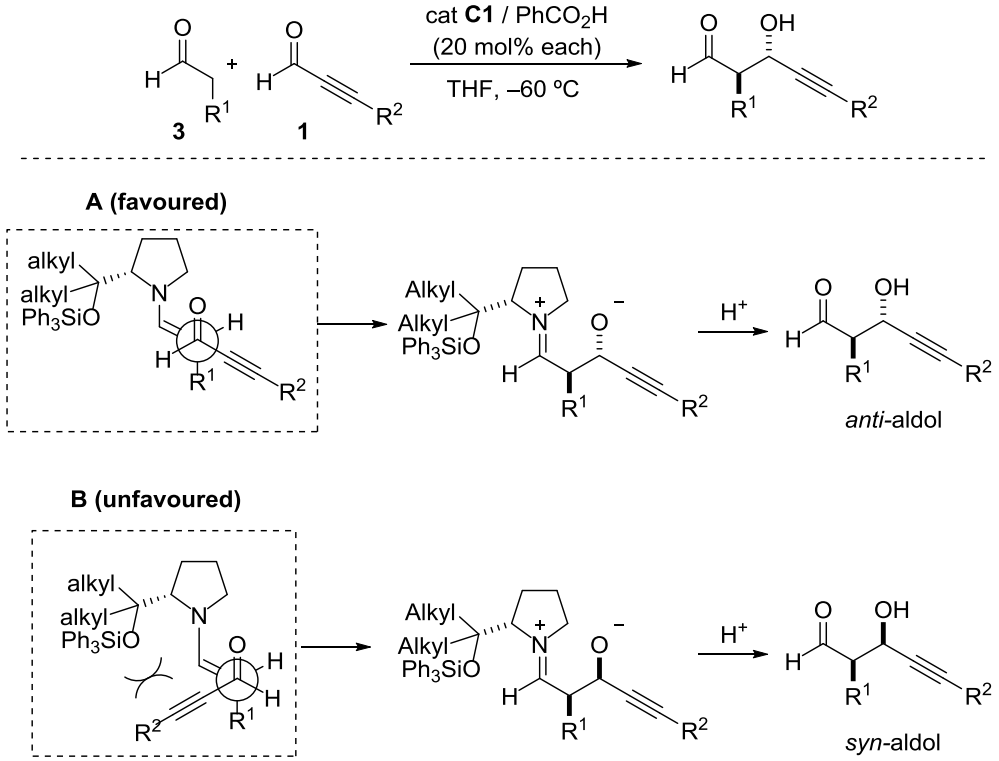
Scheme 12.

[125] Similar well-characterized bicyclic products: a) P. Magnus, L. M. Principe, *Tetrahedron Lett.* **1985**, *26*, 4851–4854. b) C. Mukai, M. Uchiyama, S. Sakamoto, M. Hanaoka, *Tetrahedron Lett.* **1995**, *36*, 5761–5764. c) J. Castro, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron* **1995**, *51*, 6541–6556. d) C. Mukai, J. S. Kim, M. Uchiyama, S. Sakamoto, M. Hanaoka, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2903–2915. e) C. Mukai, J. S. Kim, M. Uchiyama, M. Hanaoka, *Tetrahedron Lett.* **1998**, *39*, 7909–7912. f) P. M. Breczinski, A. Stumpf, H. Hope, M. E. Krafft, J. A. Casalnuovo, N. E. Schore, *Tetrahedron* **1999**, *55*, 6797–6812.

[126] T. Nishimata, Y. Sato, M. Mori, *J. Org. Chem.* **2004**, *69*, 1837–1843.

2.2.4. Reaction stereochemistry

The stereochemical results obtained in the aldol reaction can be explained through the two competing open models **A** and **B** presented in Scheme 13. In **B** overlapping of the bulky substituents of amine **C1** and the propargylic group of the ynone **1** would lead to an unfavourable approaching, thus leading towards the preferential formation of the *anti*-adduct.



Scheme 13.

The observed reaction stereochemistry in the Pauson-Khand reaction can be explained through the chair-like models **C** and **D** presented in Figure 5. A destabilizing pseudo-1,3-diaxial interaction between the hydrogen at C_α and the coordinated metal in model **D** could determine the positioning of the metal complex, and thus the final configuration of the adduct (**7**).

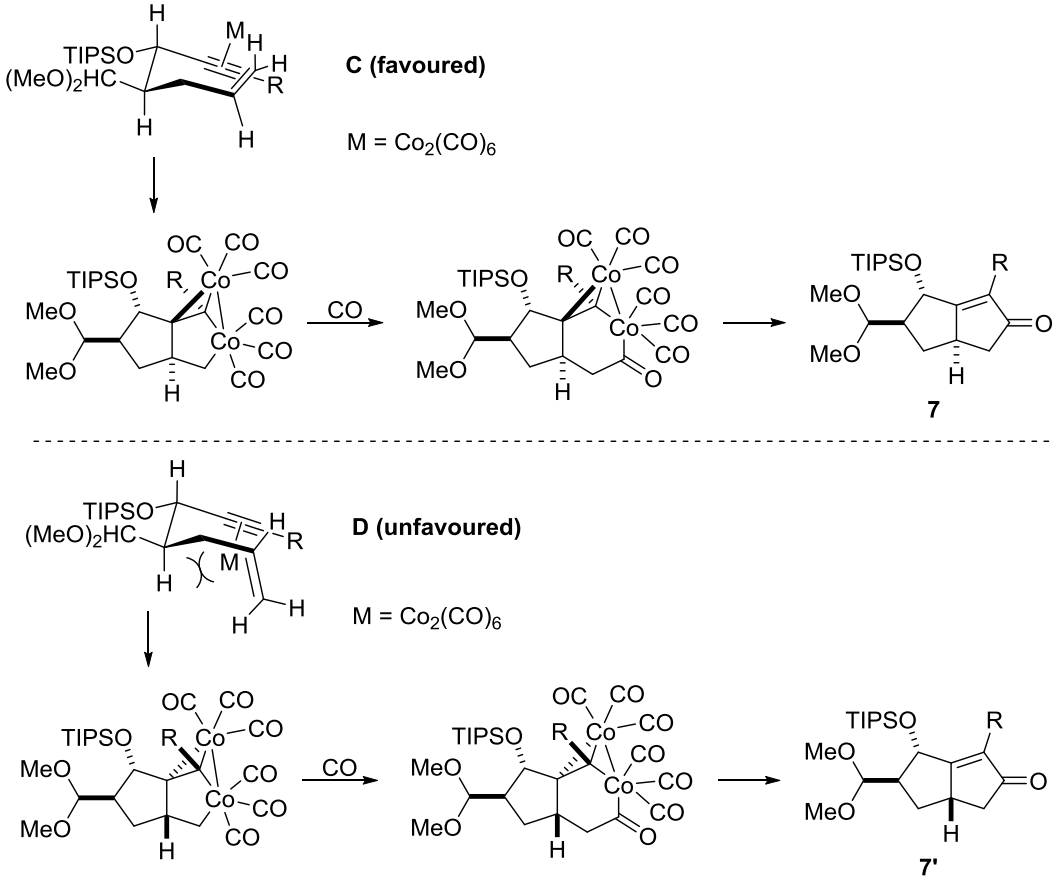


Figure 5.

2.3. Enamine-mediated cross aldol reaction of aldehydes with propargylic α-ketoesters

2.3.1. Initial experiments and reaction optimization

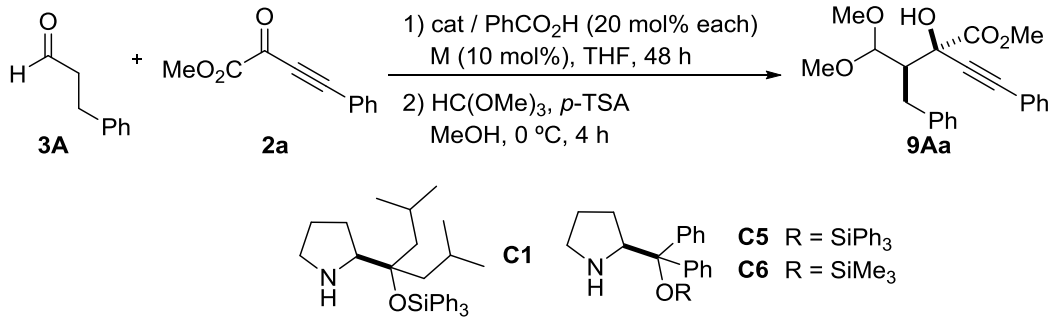
The purpose was to explore the possibility of extending the above method to ynones as acceptors. Initially, the reaction between hydrocinnamaldehyde (**3A**) and ynone **2a** was studied using the conditions developed in the previous section (Table 6, entry 1), and low conversions were obtained after 20 h. This result might be ascribed to either the lower solubility or the lower inherent reactivity of these ynones as compared with the parent ynals. Then the reaction temperature was raised to –40 ^{o}C, which allowed the reaction conversion to be essentially complete after 48 h (Table 6, entry 2), affording, after subsequent acetalization, the desired adduct **9Aa** in good yield and high diastereo- and enantioselectivity. Further increase in temperature led to a lower *ee* (Table 6, entry 6). Furthermore, no significant improvement of reactivity or stereoselectivity was observed when using CuI or Cu(OAc) as additive (Table 6, entries

4 and 5 vs. 2). On the other hand, lowering the loading of the amine catalys and the benzoic acid to 10 mol% yielded low conversions after 48 h (Table 6, entry 3).

Next, the performance of the parent α,α-diaryl catalysts **C5** and **C6** was studied. Once again, both were equally efficient in terms of reactivity and enantioselectivity, but led to a diminished *dr* (from 5:1 in entry 2 to nearly equimolecular in entry 7 and 8).

The yields when employing ynone **2a** as the acceptor happened to be higher as compared with the parent ynals (see Table 3 for a comparison). This could be attributed to a large extent to the higher conversion rates obtained in the reactions involving propargylic ketoester **2a**.

Table 6. Catalyst screening for the reaction between **3A** and **2a**



Entry	cat	Metal	T (ºC)	Conv. (%)[b]	Yield (%)[c]	syn/anti[d]	*ee* (%)[e]
1	**C1**	-	–60	33	n.d.	n.d.	n.d.
2	**C1**	-	–40	100	83	5:1	93
3	**C1**	-	–40	62[f]	n.d.	n.d.	n.d.
4	**C1**	CuI	–40	98	79	6:1	95
5	**C1**	Cu(OAc)	–40	98	80	6:1	96
6	**C1**	-	–20	100	81	4:1	90
7	**C5**	-	–40	86	75	1.5:1	99
8	**C6**	-	–40	92	78	1.2:1	97

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**3A**/**2a**/cat/$PhCO_2H$/M molar ratio = 1.5:1:0.2:0.2:0.1). [b] Determined by ^1H NMR spectroscopy on reaction aliquots before workup. [c] Combined yield of *syn*/*anti* adducts after chromatography. [d] Determided by HPLC analysis of the reaction crude. [e] *ee* of major (*syn*) isomer, determined by chiral HPLC. [f] Reaction conducted with 10 mol% of the amine catalyst and $PhCO_2H$.

The conversion was determined by ^1H NMR (300 MHz) analysis of untreated samples of the reaction (Figure 6) comparing the peak areas of the protons of the methyl ester groups of both propargylic ketoester **2a** (3.96 ppm, 3 H) and adduct **9Aa** (both *syn* and *anti*, 3.89 ppm, 3 H).

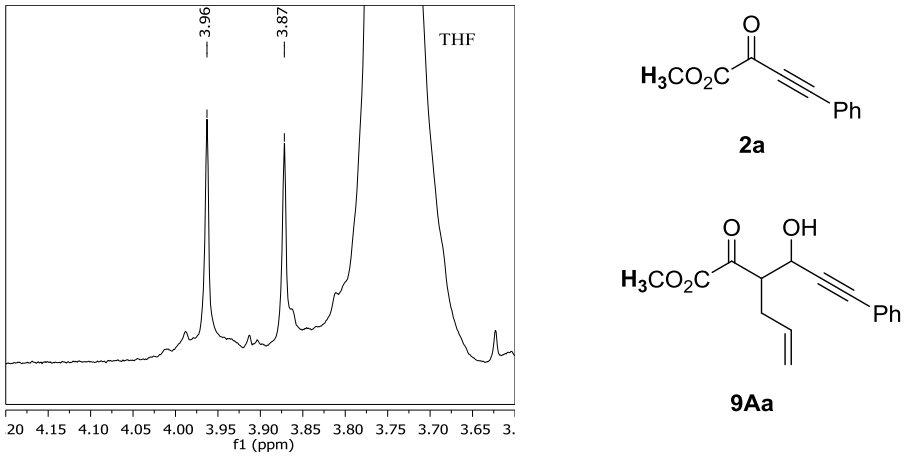


Figure 6.

The *syn*/*anti* ratio was determined by chiral HPLC analysis (Chiralpack IA, hex:^{i}Pr 95:5, 0.5 mL/min, λ = 240 nm) of the reaction crude (Figure 7) comparing the peak areas of the *syn*- (major, 20.9 and 29.3 min) and *anti*-adduct (minor, 24.7 min and 32.8 min).

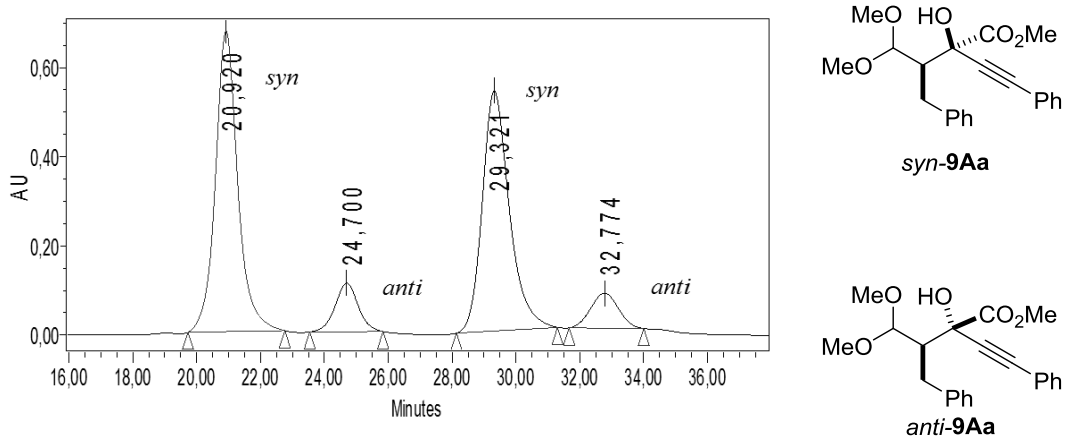
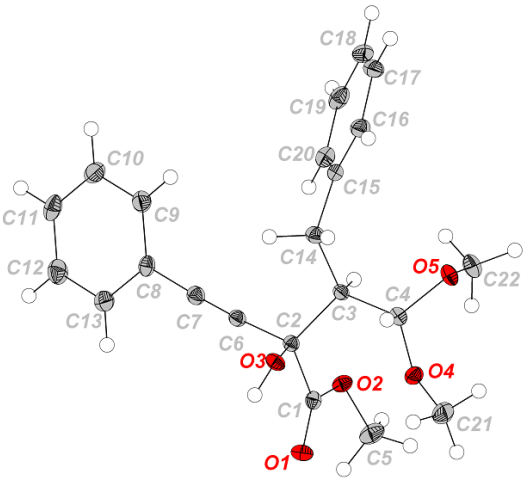
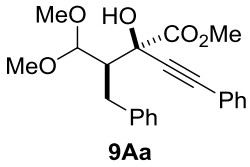


Figure 7.

The absolute configuration of compound **9Aa** was established by a single crystal X-ray analysis and for the remaining adducts was assumed based on a uniform reaction mechanism. The configuration of the molecule happened to be (2*S*,3*S*), as it is shown in the ORTEP diagram of the molecule in Figure 8.





9Aa

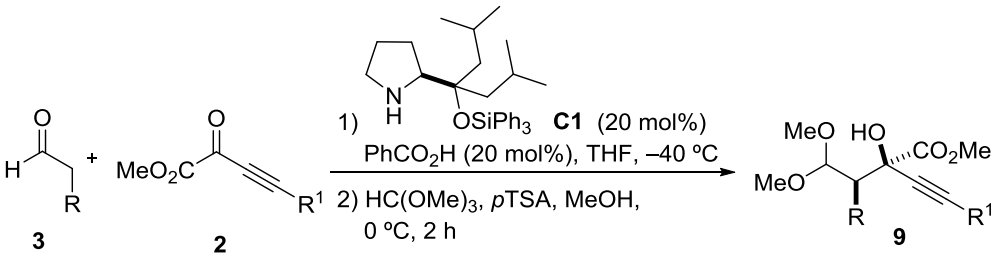
Figure 8.

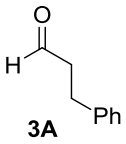
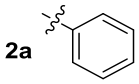
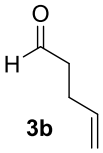
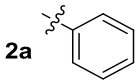
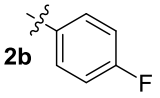
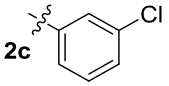
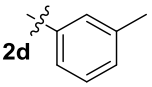
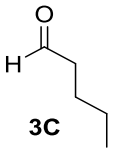
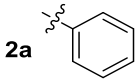
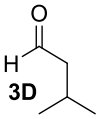
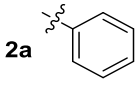
2.3.2. Reaction scope

The generality of the method was explored using a selection of propargylic ketoesters (**2**) with a range of enolizable aldehydes (**3),** under the optimized conditions, namely: the acceptor ynone was dissolved in THF (1 M) at –40 °C and 1.5 equivalents of the donor aldehyde and 20 mol% of each catalyst **C1** and benzoic acid were added. The reaction mixture was stirred at the same temperature, and after verifying by ^{1}H NMR analysis of an untreated reaction sample that the reaction finished (48 h), the mixture was treated with $HC(OCH_3)_3$ (3 equivalents) in the presence of *p*TSA at 0 °C for 2 h. The corresponding dimethyl acetal products were isolated by flash column chromatography on silica gel eluting with hexane/THF mixtures.

As data in Table 7 show, the reactions proceeded smoothly with various donor aldehydes **3**, affording the corresponding tertiary propargylic alcohols in good yield, diastereoselectivity of 1:5 or higher, and enantioselectivities above 93% *ee* in most cases. These examples include ynones bearing substituents at the *ortho* or *metha* positions of the phenyl ring (Table 7, entries 2 and 3). However, *meta*-tolyl susbsituted ynone **2d** (Table 7, entry 4) was an exception and led to the corresponding adduct **9Ad** with decreased enantioselectivity.

Table 7. Cross-aldol reaction scope between enolizable aldehydes and propargylic α-ketoesters[a]



Entry	Aldehyde	Ynone (R^1)	Product	Yield, %[b]	syn/anti[c]	ee, %[c]
1	 **3A**	 **2a**	**9Aa**	83	5:1	93
2	 **3b**	 **2a**	**9Ba**	74	6:1	94
3		 **2b**	**9Bb**	77	8:1	93
4		 **2c**	**9Bc**	65	5:1	94
5		 **2d**	**9Bd**	72	13:1	80
6	 **3C**	 **2a**	**9Ca**	65	8:1	93
7	 **3D**	 **2a**	**9Da**	70	5:1	95

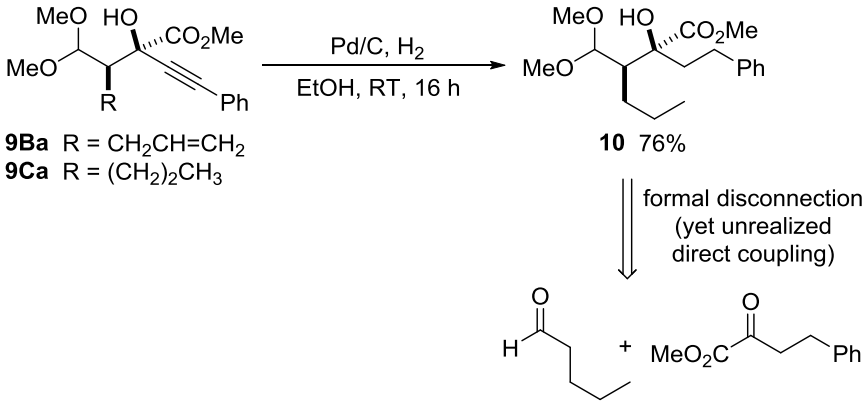
[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**3**/**2**/**C1**/$PhCO_2H$ molar ratio = 1.5:1:0.2:0.2). [b] Combined yield of *syn*/*anti* adducts after chromatography. [c] *dr* values determided by HPLC analysis of the crude product. [d] *ee* of major (*syn*) isomer, determined by chiral HPLC.

2.3.3. Elaboration of adducts

Once a method for the stereoselective cross-aldol reaction between enolizable aldehydes and propargylic α-ketoesters was developed, some possibilities for the transformation of the adducts were briefly explored.

*2.3.3.1. Reduction of adducts **9Aa** and **9Ca***

As stated in the Introduction, the alkyne moiety could in principle be transformed into the corresponding alkyl and alkenyl units via total or partial reduction, respectively. To corroborate this assertion, adduct **9Ca** was submitted to hydrogenation over Pd on charcoal (Scheme 14) to afford the reduction product **10** in 76% yield. The same process applied to adduct **9Ba** also produced an identical adduct, which proved the stereochemical uniformity of the adducts. It is worth noting that **10** is the adduct formally derived from the cross-aldol reaction between two enolizable carbonyl compounds, a reaction that cannot be carried out efficiently in a direct manner so far.

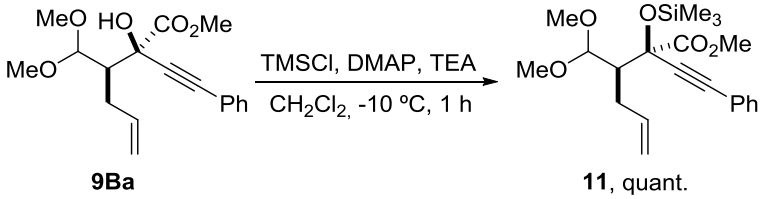


Scheme 14.

2.3.3.2. Pauson-Khand reaction

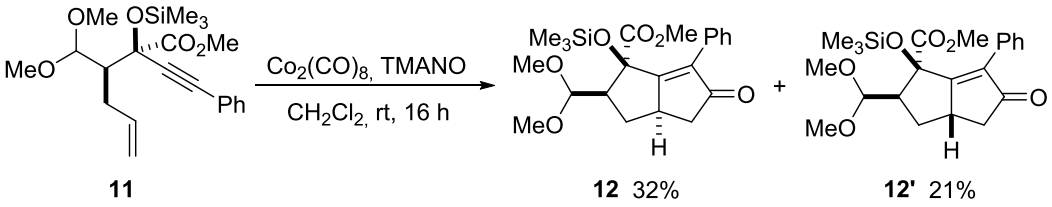
Following the successful intramolecular Pauson-Khand cyclization reaction developed using secondary propargylic carbinols, the corresponding transformation using tertiary alcohol **9Aa** was attempted.

The first problem was the protection of the tertiary alcohol, which turned out to be a challenging task. Indeed, we were unable to get the corresponding TIPS derivative, even at room temperature. Thus protection of the tertiary alcohol with the TMS group was performed instead, using TMSCl, DMAP and TEA (Scheme 15), which led to the protected alcohol **11** quantitatively.



Scheme 15.

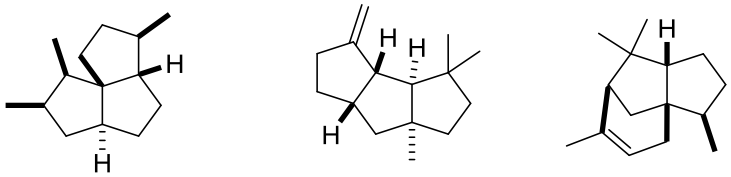
The Pauson-Khand reaction was then performed under the previously described conditions, thus treatment of **11** with dicobalt octacarbonyl and TMANO in dichloromethane at room temperature afforded a diastereomeric mixture of bicyclic products **12** and **12'** in 32% and 21% isolated yields, respectively.



11 **12** 32% **12'** 21%

Scheme 16.

Thus, this study gives a convenient entry to fused cyclopentene rings, structural frameworks present in natural sesquiterpene products (Figure 9).[120]



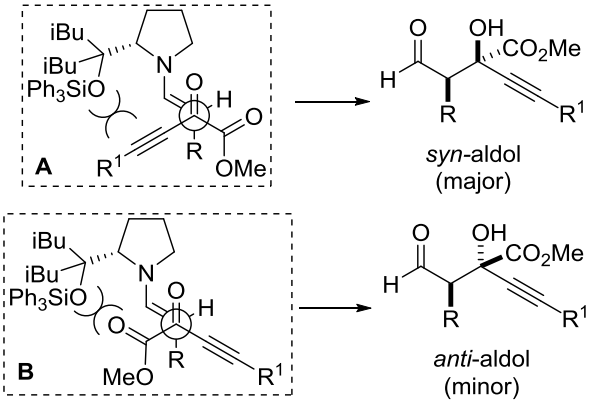
Silphiperfolane Capnellene Cedrene

Figure 9.

2.3.4. Reaction stereochemistry

Based on previous stereochemical models for related enamine mediated aldol reactions,[127] we propose an open model similar to that proposed before for ynals (Scheme 13, page 67) that explains the observed stereoselectivity (Scheme 17). Assuming that the enamine adopts preferentially the most stable *E-anti* conformation two possible approaching orientations **A** and **B** should be considered. From these models **A** appears to be sterically less congested owing to the presumed higher interaction of the ester group with the bulky substituents of the enamine as compared to the alkyne group, with linear geometry. This model is in good agreement with the observed preferential formation of the *syn*-aldol.

[127] a) S. A. Moteki, J. Han, S. Arimitsu, M. Akakura, K. Nakayama, K. Maruoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 1187–1190. b) E. Gómez-Bengoa, J. M. García, S. Jiménez, I. Lapuerta, A. Mielgo, J. M. Odriozola, I. Otazo, J. Razkin, I. Urruzuno, S. Vera, M. Oiarbide, C. Palomo, *Chem. Sci.* **2012**, *3*, 2949–2957. c) Y-Hua Deng, J.-Q. Chen, L. He, T.-R. Kang, Q.-Z. Liu, S.-W. Luo, W.-C. Yuan, *Chem. Eur. J.* **2013**, *19*, 7143–7150.



Scheme 17.

2.4. Conclusions

In this Chapter we have demonstrated that the direct cross-aldol reaction of enolizable aldehydes with propargylic aldehydes can be performed efficiently and with very good diastereo- and enantioselectivity via enamine activation. Key for this development is the concurrent use of α,α-dialkylprolinol ether / Brønsted acid catalytic system. The method is quite general with respect to the propargylic aldehyde substrate, and has been extended to the unprecedented reaction of aldehydes with propargylic ketoesters, affording the corresponding tertiary propargylic alcohols in good yield and selectivity.

In addition, the observed stereochemical outcome of the aldol reaction can be explained by involving open models similar to previously reported for related aldol reactions.

Furthermore, the use of ω-unsaturated aldehydes as nucleophiles afforded the corresponding 1,ω-enyne adducts, which bear an additional alkene group compared to adducts obtained from simple aliphatic aldehydes, thus making feasible the application of these adducts in a wider variety of transformations.

In this sense, transformation of the resulting 1,6-enyne structures to the corresponding polisubstituted bicyclic enones through an intramolecular Pauson-Khand reaction has been realized. This reaction proceeds with essentially perfect diastereoselectivity in the case of ynal-derived adducts when using the *O*-TIPS protected propargylic alcohols and less selectively with an *O*-TMS protected tertiary enyne alcohol studied.

Finally, the hydrogenation of the triple (and double) bonds in adducts have been performed successfully, demonstrating the validity of the method for obtaining adducts that are formally derived from a cross-aldol reaction that cannot yet be performed directly in an efficient manner.

Chapter 3:

Brønsted base-catalyzed α-functionalization of carbonyl compounds

3. Brønsted base-catalyzed α-functionalization of carbonyl compounds

Brønsted base-catalyzed α-functionalization of carbonyl compounds

3.1. Development of α'-oxy enones as acrylate equivalents

3.1.1. Precedents and objectives

As stated in the introduction, asymmetric catalyzed conjugate additions to simple α,β-unsaturated esters and amides remain challenging, mainly due to their attenuated reactivity. In order to overcome this limitation, one of the working approaches is the development of α,β-unsaturated ester and amide surrogates possessing certain qualities: i) enhanced activation of the substrate towards nucleophilic attack, ii) improved coordination to the catalyst, and iii) easy removal of the activating group.

The underlying idea is that coordination of one lone pair of the oxygen in the template to the catalyst (a Lewis acid or H-bond donor) would trigger the reaction. In this sense, monodentate acyl templates may lead to two possible substrate-catalyst geometries, complicating stereocontrol. On the contrary, bidentate templates would not only coordinate more efficiently, but also skip such degeneracy forming one preferential cyclic geometry, thus facilitating good reaction stereocontrol (Figure 1).

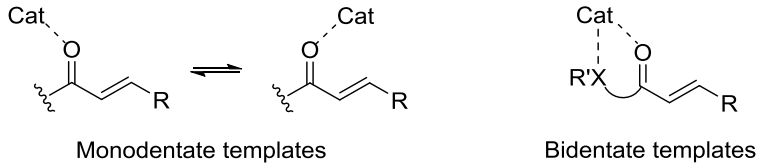


Figure 1.

Following this idea, several two-point binding α,β-unsaturated acyl templates have been developed during the last years,[128] which may be divided in two categories: heteroatom-linked templates (Figure 2a) and carbon-linked templates (Figure 2b). However, at the outset of this project only scarce examples of conjugate addition of enolizable carbonyl compounds to these enoate surrogates leading to the formation of a stereogenic center at C_α were reported.

[128] For a review on the use of these templates in organocatalysis see: D. Monge, H. Jiang, Y. Álvarez-Casao, *Chem. Eur. J.* **2015**, *21*, 4494–4504.

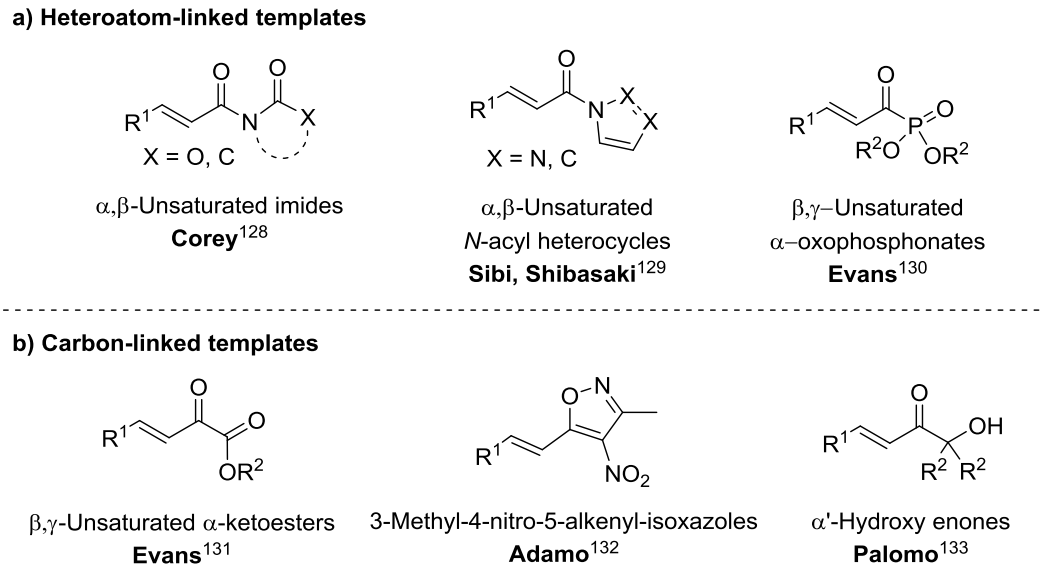


Figure 2.

Whilst efforts to control stereoselectivity from α,β-unsaturated carbonyl compounds have been mainly focused on carboxylic acid derivatives, essentially no reports concerning the use of ketones have been described in the literature. One exception is the strategy developed by Enders,[135] where hydrazones are used as ketone surrogates. In this context, some years ago, our group reported chiral α'-oxy ketones and enones as acyl equivalents useful for several diastereoselective reactions.[136] The

[129] E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.

[130] a) M. P. Sibi, J. J. Shay, J. Ji, *Tetrahedron Lett.* **1997**, *38*, 5955–5958. b) T. Nemoto, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9474–9475.

[131] D. A. Evans, J. S. Hohnson, *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896.

[132] D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem. Int. Ed.* **1998**, *37*, 3372–3375.

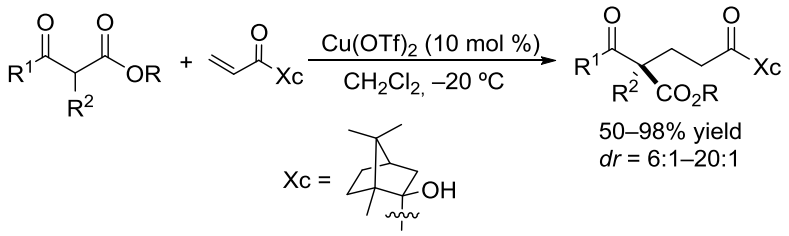
[133] A. Baschieri, L. Bernardi, A. Ricci, S. Suresh, M. F. A. Adamo, *Angew. Chem. Int. Ed.* **2009**, *48*, 9342–9345.

[134] C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

[135] For a review on hydrazine chiral auxiliaries see: A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.

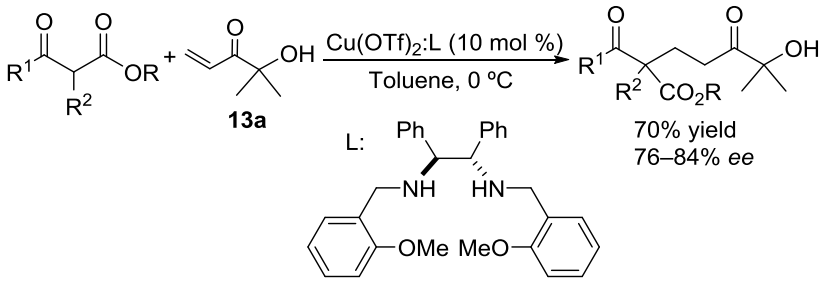
[136] Aldol reaction: a) C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez, A. Linden, *Angew. Chem. Int. Ed.* **1998**, *37*, 180–182. b) C. Palomo, M. Oiarbide, J. M. Aizpurua, A. González, J. M. García, C. Landa, I. Odriozola, A. Linden, *J. Org. Chem.* **1999**, *64*, 8193–8200. c) C. Palomo, M. Oiarbide, E. Gómez-Bengoa, A. Mielgo, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, P. Bañuelos, A. Linden, *ARKIVOC* **2005**, 377–392. Mannich reaction: d) C. Palomo, M. Oiarbide, M. C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden, *Angew. Chem. Int. Ed.* **2000**, *39*, 1063–1066. e) C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martín-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637–8643. Conjugate addition: f) C. Palomo, J. M. Aizpurua, M. Oiarbide, J. M. García, A. González, I. Odriozola, A. Linden, *Tetrahedron Lett.* **2001**, *42*, 4829–4831. g) C. Palomo, M. Oiarbide, J. M. García,

diastereoselective Michael addition of β-ketoesters to chiral α'-hydroxy enones resulting on the formation of challenging quaternary stereocenters is shown in Scheme 1 as a representative example.[136g]



Scheme 1.

On the other hand, *achiral* α'-hydroxy enones have also been developed in our group as acrylate equivalents in chiral Lewis acid-catalyzed enantioselective reactions. For instance, an enantioselective version of the conjugate addition of β-ketoesters above mentioned was reported[136g] employing a C_2-symmetric diamine-copper complex as the catalyst (Scheme 2).



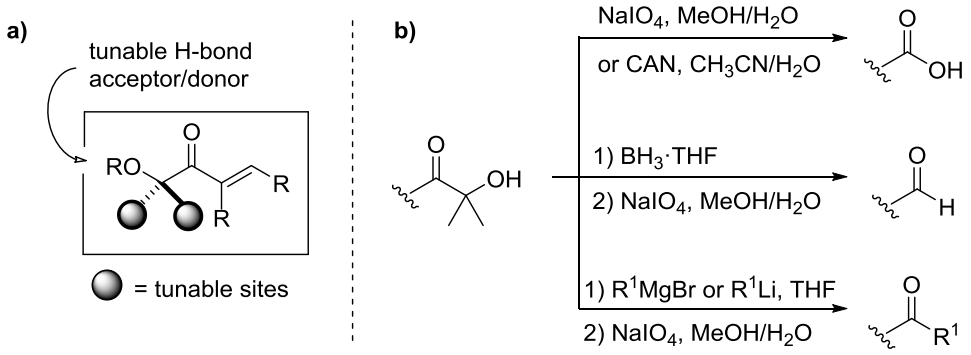
Scheme 2.

This and additional research from this laboratory has revealed that achiral α'-hydroxy enones are excellent bidentate Michael acceptors for metal-catalyzed

A. González, P. Bañuelos, J. M. Odriozola, J. Razkin, A. Linden, *Org. Lett.* **2008**, *10*, 2637–2640. h) J. M. García, M. A. Maestro, M. Oiarbide, J. M. Odriozola, J. Razkin, C. Palomo, *Org. Lett.* **2009**, *11*, 3826–3829. Diels-Alder reaction: i) C. Palomo, M. Oiarbide, J. M. García, A. González, A. Lecumberri, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 10288–10289. j) P. Bañuelos, J. M. García, E. Gómez-Bengoa, A. Herrero, J. M. Odriozola, M. Oiarbide, C. Palomo, *J. Org. Chem.* **2010**, *75*, 1458–1473. Alkylation: k) C. Palomo, M. Oiarbide, A. Mielgo, A. González, J. M. García, C. Landa, A. Lecumberri, A. Linden, *Org. Lett.* **2001**, *3*, 3249–3252. Darzens reaction: l) C. Palomo, M. Oiarbide, A. K. Sharma, M. C. González-Rego, A. Linden, J. M. García, A. González, *J. Org. Chem.* **2000**, *65*, 9007–9012.

asymmetric transformations,[137] specially for the 1,4-addition of *N*- and *C*-centered nucleophiles.[138]

Interesting features of the α'-hydroxyketone template are: i) The salient behaviour in asymmetric catalysis due to the ability of the α-hydroxy carbonyl (or ketol) moiety for efficient 1,4-metal binding; ii) the gem-dialkylcarbinol framework of the template can be easily modified for optimal performance (Scheme 3a), and ii) the Michael adducts can be further elaborated under smooth oxidative conditions (Scheme 3b) affording carboxylic acids, aldehydes and ketones from a single common intermediate.



Scheme 3.

Despite these features, however, construction of quaternary centers[139] through Michael reactions was still problematic with these enones, especially under Lewis acid catalysis as noted above. In general, this reaction is limited to highly active donor substrates, that is, substrates capable of easily generating the enol form, such as β-ketoesters. Generation of the more nucleophilic enolate species through deprotonation by a tertiary amine base is usually unfruitful because of self-quenching of the Lewis acid-Lewis base pair. With very few exceptions, this combined use of a base and acid for concomitant substrate activation is a general problem that still remains not well

[137] For a review on α'-hydroxy ketones see: C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2012**, *41*, 4150–4164.

[138] For an example of 1,4-addition reaction with: Carbamates: a) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. Pyrroles/indoles: b) C. Palomo, M. Oiarbide, B. Kadar, J. M. García, *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155. Nitroalkanes: c) C. Palomo, R. Pazos, M. Oiarbide, J. M. García, *Adv. Synth. Catal.* **2006**, *348*, 1161–1164.

[139] For reviews on asymmetric synthesis of quaternary stereocenters see: a) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597. b) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. c) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396. d) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295–7306. e) K. W. Quasdorf, L. E. Overmann, *Nature* **2014**, *516*, 181–191. f) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stolz, *Acc. Chem. Rev.* **2015**, *48*, 740–751. g) J. Feng, M. Holmes, M. J. Krische, *Chem. Rev.* **2017**, *117*, 12564–12580.

resolved.[140] A practical solution to this problem is suppressing the Lewis acid and carrying out the reaction in the presence of a bifunctional Brønsted base/H-bond donor catalyst. In this instance, the electrophile would be activated by hydrogen bonding whilst the donor substrate would be activated by the Brønsted base through a model that resembles that of the Lewis acid, as shown in Figure 3.

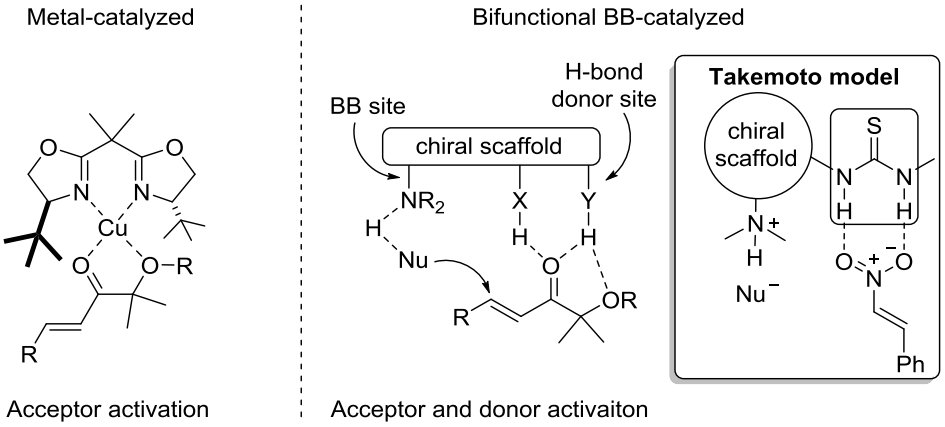


Figure 3.

3.1.1.1. Preparation of the α'-oxy enones used in the study

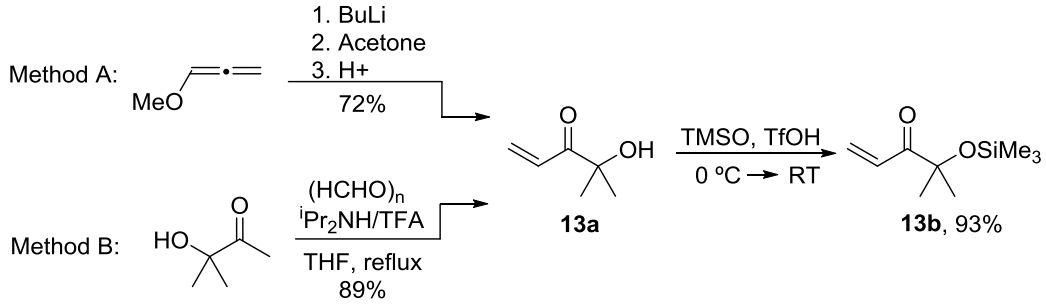
An interesting practical aspect of these enones is that they may be readily prepared from commercially available compounds, in the majority of the cases in few steps, and purified by simple flash column chromatography to be obtained as colourless oils, which can be stored for several months at –30 ºC. For example, α'-hydroxy enone **13a** was synthesised starting from methoxypropadiene through addition of its lithium salt to acetone and subsequent acid treatment in good yield (Scheme 4, method A).[141] Alternatively, it could also be prepared in high yield from commercially available 3-hydroxy-3-methyl-2-butanone via aldol condensation with formaldehyde, formed *in situ* from paraformaldehyde[142] (Scheme 4, method B). Enone **13a** was silylated by mixing it with 3-(trimethylsilyl)-2-oxazolidinone (TMSO)[143] and a few drops of trifluoroacetic acid and stirring at room temperature without any solvent, affording α'-silyloxy enone **13b** in excellent yield.

[140] For a review on Lewis acid/Brønsted base cooperative catalysis see: L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.* **2012**, *3*, 942–958.

[141] C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

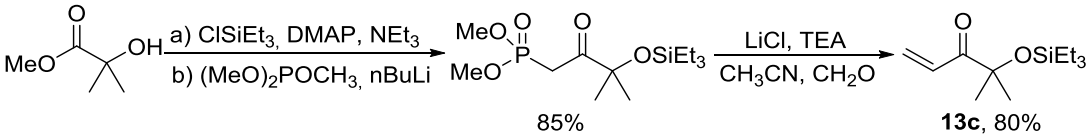
[142] A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* **2010**, *46*, 1715–1717.

[143] J. M. Aizpurua, C. Palomo, A. L. Palomo, *Can. J. Chem.* **1984**, *62*, 336–340.



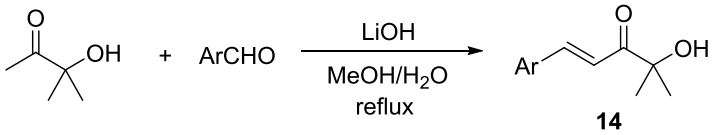
Scheme 4.

The *O*-triethylsilyl substituted enone **13c** was prepared starting from methyl 2-hydroxyisobutyrate.[144] In a first step, the alcohol was protected as the corresponding triethyl silyl ether, and the resulting product was converted into the dimethyl phosphoester intermediate. The Wittig-Horner reaction with formaldehyde afforded the desired enone **13c** in good overall yield (Scheme 5).



Scheme 5.

β-Aryl α'-hydroxyenones **14a-14d** were obtained by aldol condensation of the commercially available 3-hydroxy-3-methyl-2-butanone with the corresponding aryl aldehyde (Scheme 6).[144] The reaction was carried out under reflux using lithium hydroxide as the base and a mixture of MeOH/water as the solvent, affording exclusively the corresponding *E*-enones in high yield.

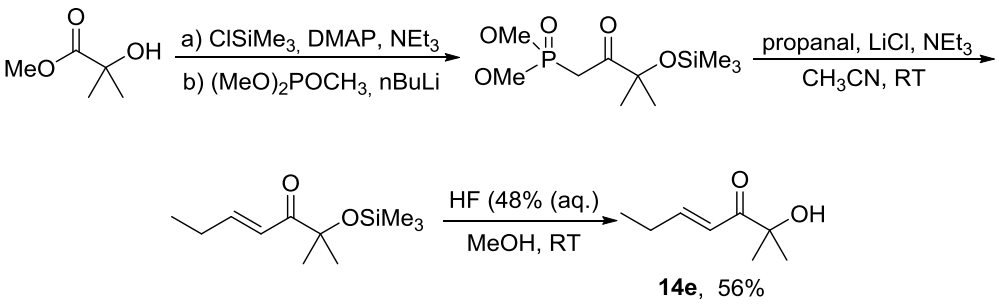


a Ar = 4-MeC_6H_4, 85% yield
b Ar = 4-BrC_6H_4, 75% yield
c Ar = 3-MeC_6H_4, 85% yield
d Ar = Ph, 95% yield

Scheme 6.

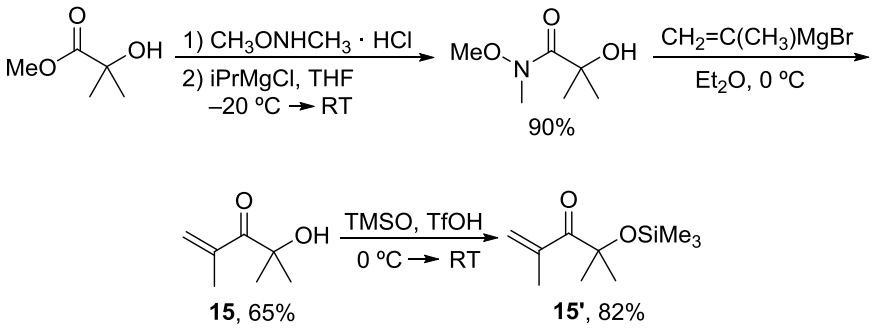
[144] a) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. b) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

β-Alkyl α'-hydroxyenone **14e** was obtained in an overall moderate yield following the procedure described above for enone **13c**, employing trimethylsilyl chloride in the first step and performing the Wittig-Horner reaction with propanal, followed by desilylation with hydrofluoric acid in methanol (Scheme 7).[144]



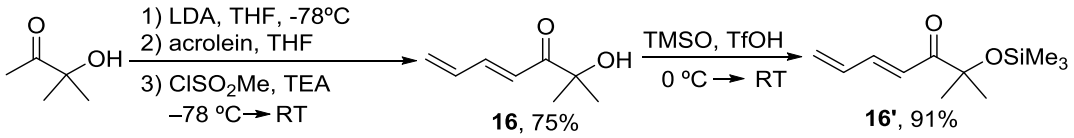
Scheme 7.

For the synthesis of α-methyl α'-hydroxy enone **15**, the commercially available 2-methoxy-2-propanoate was transformed into the Weinreb amide, which was then reacted with isopropenyl magnesium bromide, yielding the desired enone in moderate yield after two steps (Scheme 8). Posterior silylation under the conditions previously employed for the formation of unsubstituted enone **13b** afforded enone **15'** in good yield.



Scheme 8.

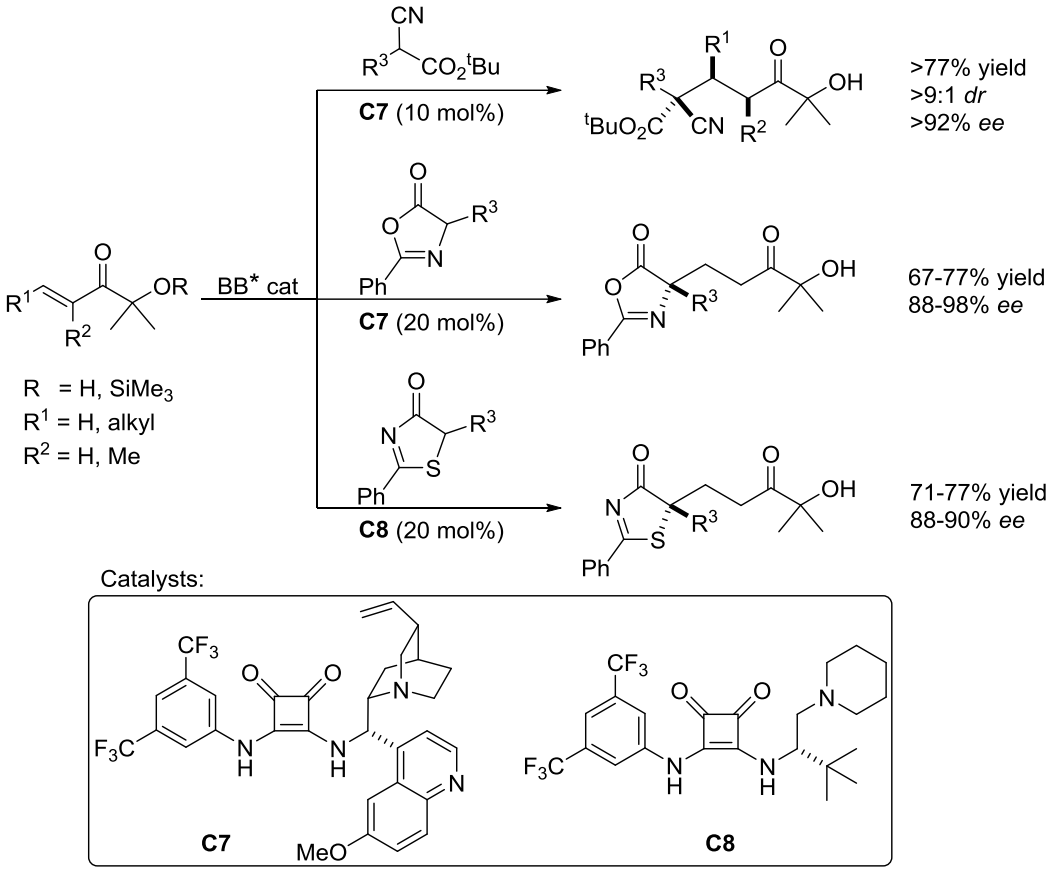
Dienone **16** was prepared in good yield starting from 3-hydroxy-3-methyl-2-butanone through aldol reaction with acrolein and *in situ* mesylation and elimination. The posterior silylation of **16** with TMSO afforded **16'** in excellent yield.



Scheme 9.

3.1.2. Conjugate additions: Previous results from this laboratory

With these templates in hand, their behaviour in organocatalytic reactions with several nucleophiles was studied in parallel. Dr. Badiola and Dr. Olaizola from this laboratory studied their reactions with α-cyanoacetates, azlactones and 5*H*-thiazol-4-ones respectively (Scheme 10).[145]



Scheme 10.

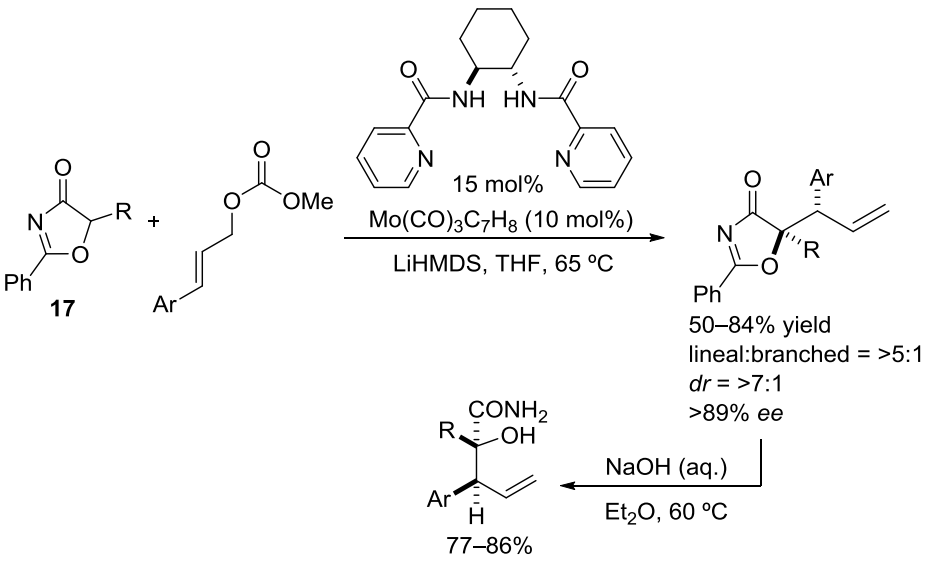
3.1.3. 1,4-Addition of oxazolones to α'-oxy enones

To complete these studies and with the aim to show the potential scope of these enones in asymmetric conjugate additions, we planned to evaluate the reaction with 5*H*-oxazol-4-ones (oxazolones), which would generate α-hydroxy carboxylic acid derivatives with a tetrasubstituted stereogenic center. These compounds are important

[145] E. Badiola, B. Fiser, E. G-B, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.

building blocks in pharmaceutical products and biologically active compounds.[146] 5*H*-oxazol-4-ones were first introduced in asymmetric catalysis by Trost and subsequently used by several other groups.

In 2004 Trost and coworkers[147] reported the Mo-catalyzed asymmetric allylic alkylation of oxazolones (Scheme 11), which yielded 5,5-dialkyl oxazol-4-ones in high yield, good regio- and diastereoselectivity and high enantioselectivity. Posterior basic hydrolysis of the adducts afforded the corresponding chiral α-hydroxyamides.



Scheme 11.

Examples of catalytic asymmetric aldol[148] and Mannich-type[149] reactions of oxazolones have also been seldom reported. However, the conjugate addition has been studied more exhaustively as shown in the examples that follow.

Misaki and Sugimura[150] performed the 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds catalyzed by chiral guanidines (Scheme 12Table 3),

[146] For more information on the subject see: a) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, G. S. Bates, *J. Am. Chem. Soc.* **1975**, *97*, 3512–3513. b) S. Hatakeyama, Y. Matsui, M. Suzuki, K. Sakurai, S. Takano, *Tetrahedron Lett.* **1985**, *26*, 6485–6488. c) H. Shao, J. K. Rueter, M. Goodman, *J. Org. Chem.* **1998**, *63*, 5240–5244.

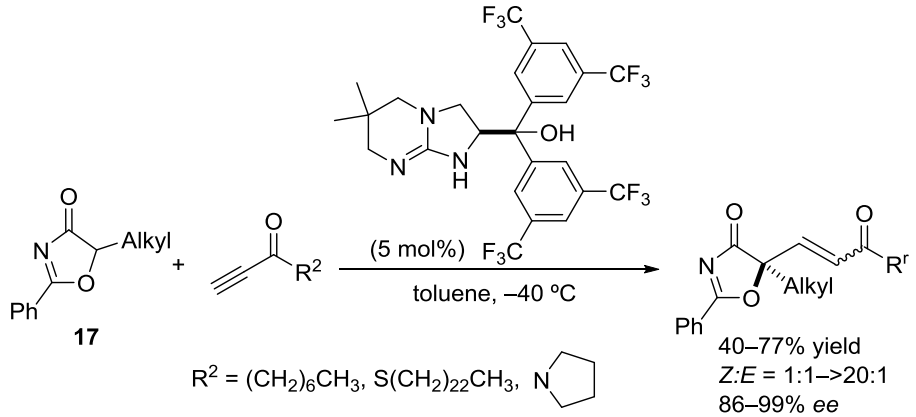
[147] B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945.

[148] T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.

[149] For an example of metal catalysis see: a) D. Zhao, L. Eang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527. For an example of organocatalysis see: b) Z. Han, W. Yang, C.-H. Tan, Z. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 1505–1511.

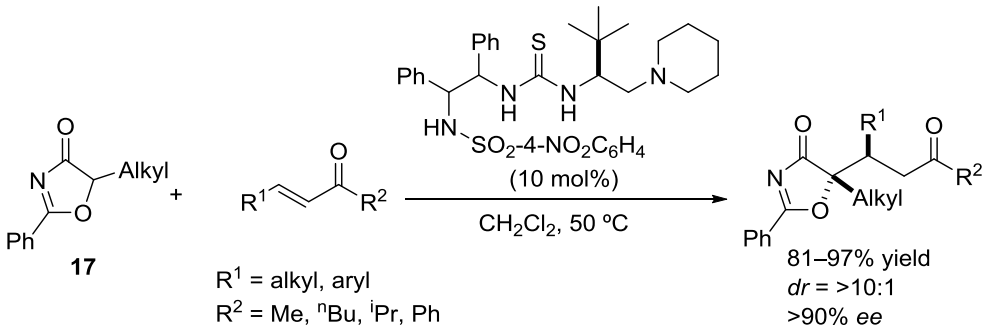
[150] a) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695–5697. For other reports of this group concerning the Michael reaction of oxazolones see: b) N. Jin, T. Misaki T. Sugimura, *Chem.*

obtaining the corresponding conjugate addition adducts in moderate yield, variable *E*/*Z* selectivity and high enantioselectivity.



Scheme 12.

In another relevant example, Ye et al.[151] reported the bifunctional Brønsted base-catalyzed Michael addition of oxazolones to α,β-unsaturated ketones (Scheme 13). The thiourea-sulfonamide catalyst rendered the Michael reaction adducts in excellent yield, diastereo- and enantioselectivity.



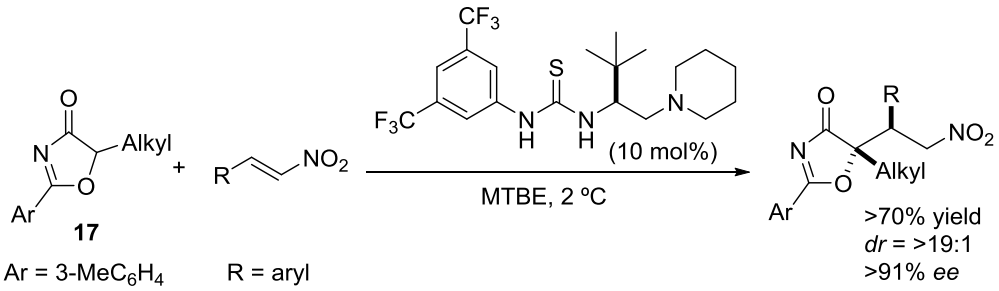
Scheme 13.

In 2013 and using a similar thiourea catalyst lacking the sulfonamide group the group of Jiang[152] reported the conjugate addition of oxazolones to aromatic nitroalkenes that proceeds in excellent yield, diastereo- and enantioselectivity (Scheme 14).

Lett. **2013**, *42*, 894–896. c) A. Morita, T. Misaki, T. Sugimura, *Tetrahedron Lett.* **2015**, *56*, 264–267. d) T. Misaki, N.-R. Choi, A. Morita, T. Sugimura, *Tetrahedron Lett.* **2015**, *56*, 5063–5066.

[151] H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461–463.

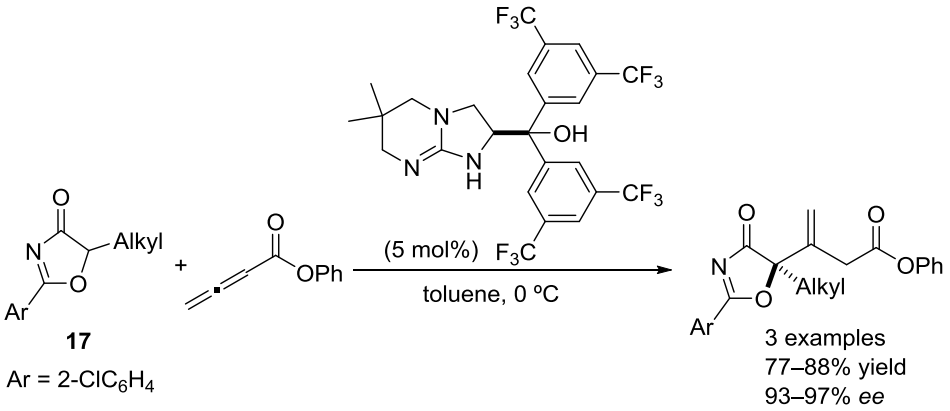
[152] a) B. Qiao, Y. An, Q. Liu, W. Yang, H. Liu, J. Shen, L. Yan, Z. Jiang, *Org. Lett.* **2013**, *15*, 2358–2361. For other reports of this group concerning the Michael reaction of oxazolones see: b) Q. Liu, B. Qiao, K. F. Chin, C.-H. Tan, Z. Jiang, *Adv. Synth. Catal.* **2014**, *256*, 3777–3783. c) B. Zhu, R. Lee, J. Li, X. Ye, S.-N. Hong, S. Qiu, M. L. Coote, Z. Jiang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1299–1303. d) J. Li, S. Qui, X. Ye, B. Zhu, H. Liu, Z. Jiang, *J. Org. Chem.* **2016**, *81*, 11916–11923.



Scheme 14.

However, to the best of our knowledge, at the outset of this project no examples had been reported on the catalytic asymmetric conjugate addition of oxazolones to unsaturated esters or equivalents. Only two examples were described in the literature during the progress of this Thesis.

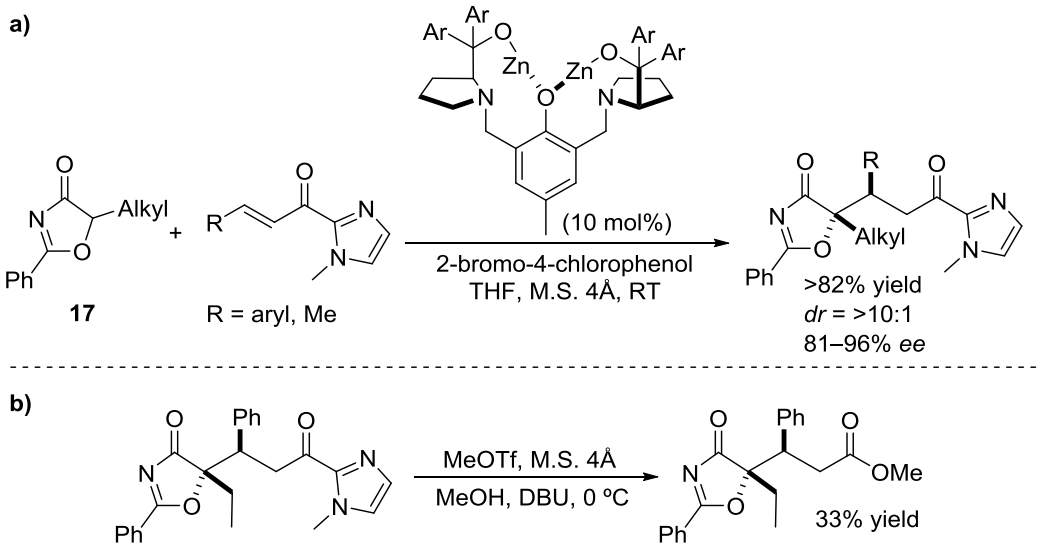
In the first one, Misaki and Sugimura[150b] described the 1,4-addition reaction of oxazolones to an allenic phenyl ester catalyzed by a chiral guanidine/alcohol in excellent yield and enantioselectivity (Scheme 15).



Scheme 15.

The second work appeared just after our initial results were published.[145] Wang et al.[153] reported the conjugate addition of oxazolones to α,β-unsaturated acyl imidazoles catalyzed by a dinuclear zinc complex, obtaining the corresponding adducts in high yield, diastereo- and enantioselectivity (Scheme 16a). They also performed the transformation of an adduct to the corresponding carboxylic methyl ester, affording the product in low yield (Scheme 16b).

[153] B. Zhang, F. Han, L. Wang, D. Li, D. Yang, X. Yang, J. Yang, X. Li, D. Zhao, R. Wang, *Chem. Eur. J.* **2015**, *21*, 17234–17238.



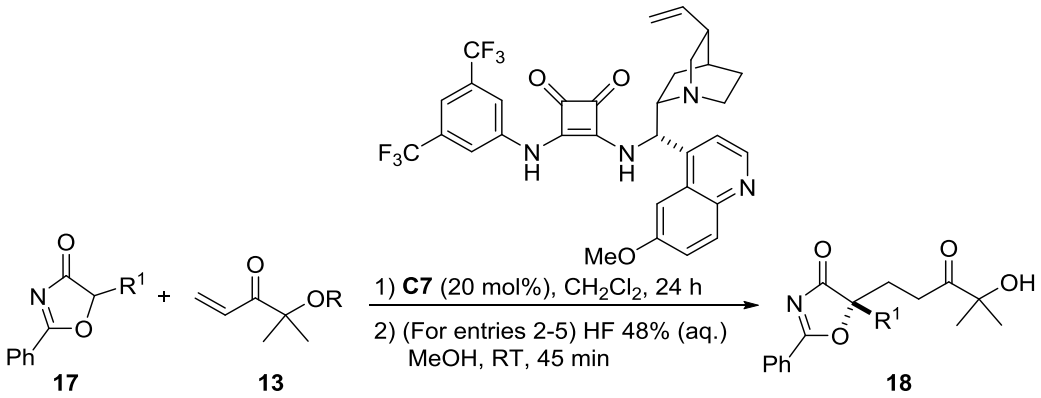
Scheme 16.

3.1.3.1. Unsubstituted α'-oxy enones as electrophiles

Initially the reaction of oxazolone **17A** with a variety of unsubstituted α'-oxy enones (**13a-13c**) catalyzed by a squaramide catalyst was investigated. For this purpose **C7**,[154] the optimal catalyst for α-cyanoacetates,[145] was taken as a model in order to find the optimum structure of the Michael acceptor (Table 1). Reaction with the free hydroxyl enone **13a** at –40 ºC yielded an almost racemic addition product (Table 1, entry 1). In its turn, reaction with the *O*-TMS substituted enone **13b** afforded, after subsequent desilylation, the desired adduct **18A** in good yield and moderate *ee* (Table 1, entry 2). An increase of the temperature from –40 to –20 ºC was found to be beneficial both for the yield and enantioselectivity of the reaction (entries 3 and 4), perhaps due to the better solubilisation of the catalyst. Enone **13c**, bearing a bulkier *O*-protecting group, was also examined but the product was obtained in low enantiomeric excess (entry 5). Thus reaction with α'silyloxy enone **13b** at RT was selected for further optimization.

[154] a) W. Yang, D. M. Du, *Org. Lett.* **2010**, *12*, 5450–5453. For pioneering work on squaramides see: b) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. c) V. B. Gondi, K. Hagihara, V. H. Rawal, *Angew. Chem. Int. Ed.* **2009**, *48*, 776–779. d) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

Table 1. Screening of template structure for the **C7**-catalyzed reaction with oxazolone **17A** (R^1 = ^{i}Bu)[a]



A R^1 = ^{i}Bu
B R^1 = ^{n}Pr
C R^1 = Bn
D R^1 = Me
E R^1 = $(CH_2)_5CH_3$

a R = H
b R = $OSiMe_3$
c R = $OSiEt_3$

Entry	Enone	R	T	Yield of **18A** (%)[b]	*ee* (%)[c]
1	**13a**	H	–40 ºC	68	10
2	**13b**	$SiMe_3$	–40 ºC	78	60
3	**13b**	$SiMe_3$	–20 ºC	85	73
4	**13b**	$SiMe_3$	RT	80	73
5	**13c**	$SiEt_3$	RT	86	34

[a] Reactions conducted on a 0.3 mmol scale in 0.9 mL of CH_2Cl_2 (**17A**/**13**/**C7** molar ratio = 1:1.5:0.2). [b] Isolated yield after chromatography. [c] Determined by chiral HPLC.

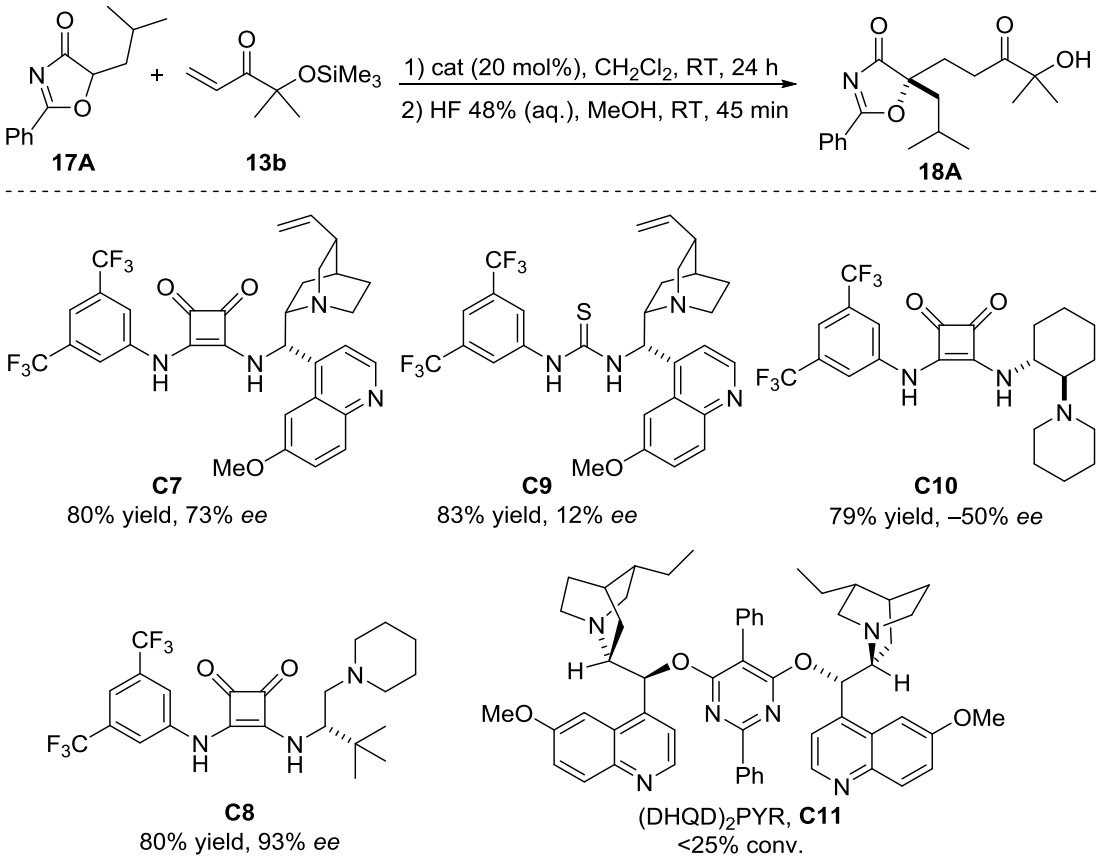
Next, a variety of Brønsted base-catalysts for the reaction of oxazolone **17A** with α'-silyloxy enone **13b** were tested at RT (Table 2). Using thiourea catalyst **C9**,[155] compound **18A** was obtained in good yield but in very low *ee*. Then, other chiral scaffolds were tested: Using **C10**,[156] derived from a chiral diamine with C_2-symmetry, the desired product was obtained in good yield and moderate *ee*. To our delight catalyst **C8**,[157] derived from L-*tert*-leucine, afforded the Michael reaction adduct **18A** in good yield and excellent *ee*. When using $(DHQD)_2PYR$ (**C11**) as the catalyst a very low conversion was observed, suggesting that the H-bond donor functionality of the catalyst is necessary for the activation of the reaction substrates.

[155] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967–1969.

[156] W. Yang, D.-M Du, *Adv. Synth. Catal*. **2011**, *353*, 1241–1246.

[157] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

Table 2. Catalyst screening for the reaction of **17A** with α'-oxy enone **13b**[a]

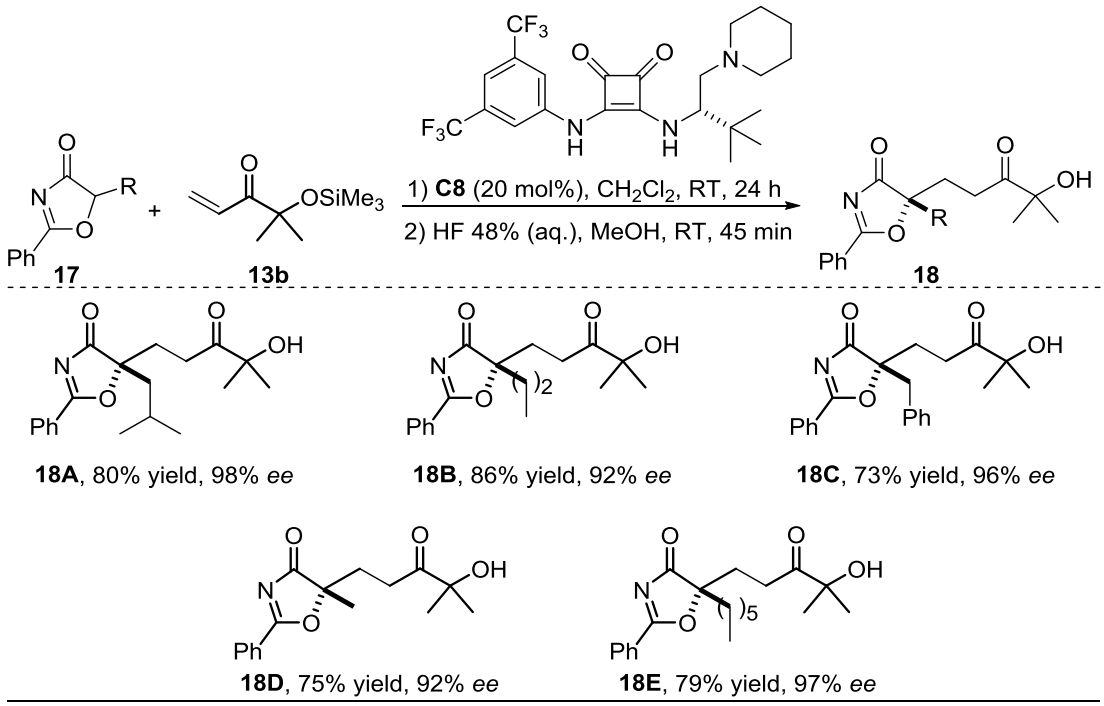


[a] Reactions conducted on a 0.3 mmol scale in 0.9 mL of CH_2Cl_2 (**17A**/**13b**/cat. molar ratio = 1:1.5: 0.2). Isolated yield after chromatography. ee determined by chiral HPLC.

After performing the optimization of conditions for the model reaction, the reaction of oxazolones **17A-17E** with α'-oxy enone **13b** was carried out following the next standard procedure: the oxazolone was dissolved in CH_2Cl_2 (0.33 M) and 1.5 equivalents of the enone and 20 mol% of the catalyst **C8** were added. The reaction mixture was stirred at room temperature, and after verifying total conversion (TLC monitoring, 24–48 h), the mixture was treated with HF 48% (aq.) at the same temperature for 45 min. The corresponding Michael reaction adducts were isolated by flash column chromatography on silica gel eluting with hexane/acetate mixtures.

As the results in Table 3 show, the reaction proceeded in good yield with different alkyl-substituted oxazolones, including those with *n*-alkyl (**18B-18D**) and benzyl substituents (**18E**), and the lowest enantioselectivity was 92% *ee*.

Table 3. Michael reaction scope between oxazolones and α'-oxy enone **13b**[a]



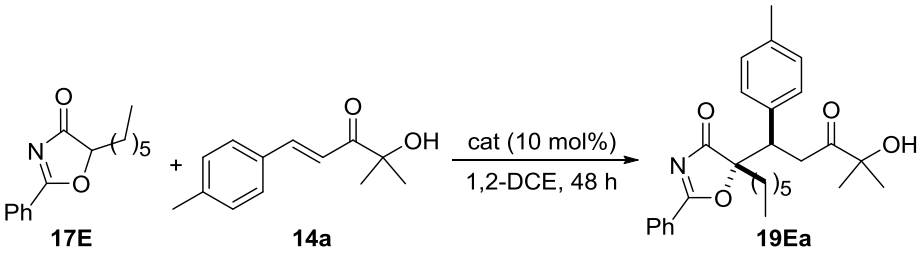
[a] Reactions conducted on a 0.3 mmol scale in 0.9 mL of CH_2Cl_2 (**17**/**13b**/**C8** molar ratio = 1:1.5:0.2). Isolated yield after chromatography. *ee* determined by chiral HPLC.

3.1.3.2. β-Substituted α'-oxy enones as electrophiles

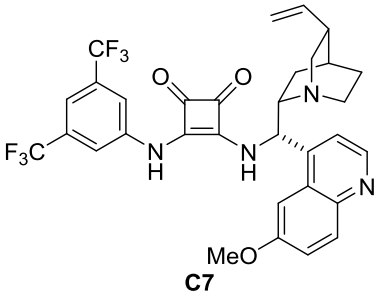
Following the study on the Michael addition of oxazolones to unsubstituted α'-oxy enones, we decided to study the addition to β-substitutted α'-oxy enones. Now a relatively diminished reactivity of the enone was expected as compared with the unsubstituted analogue, and on the other hand, the problem of the relative configuration of the newly generated tetra- and trisubstituted contiguous stereocenters arises. This time the reaction between oxazolone **17E** and β-aryl α'-hydroxy enone **14a** was taken as a model to test a variety of catalysts (Table 4). 1,2-Dichloroethane was used as the solvent so the reaction could be performed at temperatures higher than 40 ºC in order to compensate for the expected lower reactivity of β-substitutted α'-oxy enones. When using squaramide **C7** as the catalyst at room temperature a very low conversion was observed after 48 h (Table 4, entry 1). When increasing the temperature from RT to 50 ºC only moderate conversion was observed after 48 h, but good diastereoselectivity and enantioselectivity were obtained (Table 4, entry 2). Very low conversions were obtained with the analogous thiourea **C9** (entry 4) and also with the L-*tert*-leucine derived squaramide **C8** (entry 3). The reaction with catalyst **C12**[154b] afforded the Michael addition product **19Ea** in similar selectivity to catalyst **C7**, but a slightly lower

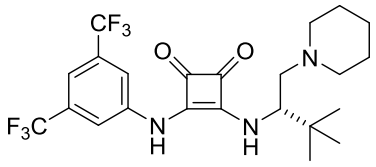
reactivity was observed (entry 5). On the other hand, increasing the reaction temperature to 70 ºC when using catalyst **C7** allowed the reaction to proceed to complete conversion within 48 h affording the desired Michael addition adduct **19Ea** in high yield and excellent diastereo- and enantioselectivity.

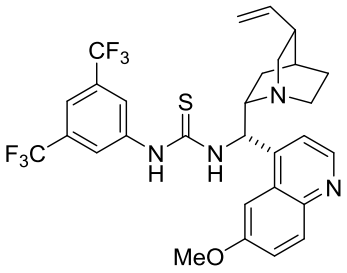
Table 4. Condition optimization for the reaction of **17E** with α'-oxy enone **14a** [a]

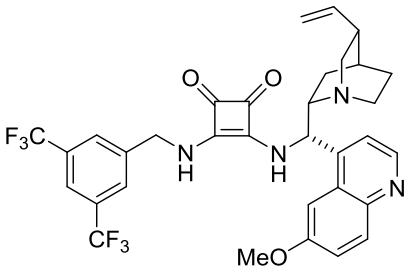


Entry	cat	T (ºC)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee* (%)[e]
1	**C7**	15	<20	n.d.	n.d.	n.d.
2	**C7**	50	83	67	11:1	80
3	**C8**	50	21	n.d.	n.d.	n.d.
4	**C9**	50	20	n.d.	n.d.	n.d.
5	**C12**	50	50	38	11:1	79
6	**C7**	70	100	80	13:1	96


C7


C8


C9


C12

[a] Reactions conducted on a 0.3 mmol scale in 0.9 mL of 1,2-DCE (**17E**/**14a**/cat molar ratio = 1:3:0.1). [b] Determined by ^{1}H NMR spectroscopy on reaction aliquots before workup. [c] Combined yield of both isomers after chromatography. [d] Determined by ^{1}H NMR spectroscopy. [e] *ee* of major isomer, determined by chiral HPLC.

The conversion was determined by ^{1}H NMR (300 MHz) analysis of untreated samples of the reaction (Table 4, entry 4; Figure 4). Comparing the peak areas of the

C_α-proton of oxazolone **17E** (4.77 ppm, 1 H), and the protons of the methyl substituent at the aromatic ring of adduct **19Ea** (2.24 ppm, 3 H).

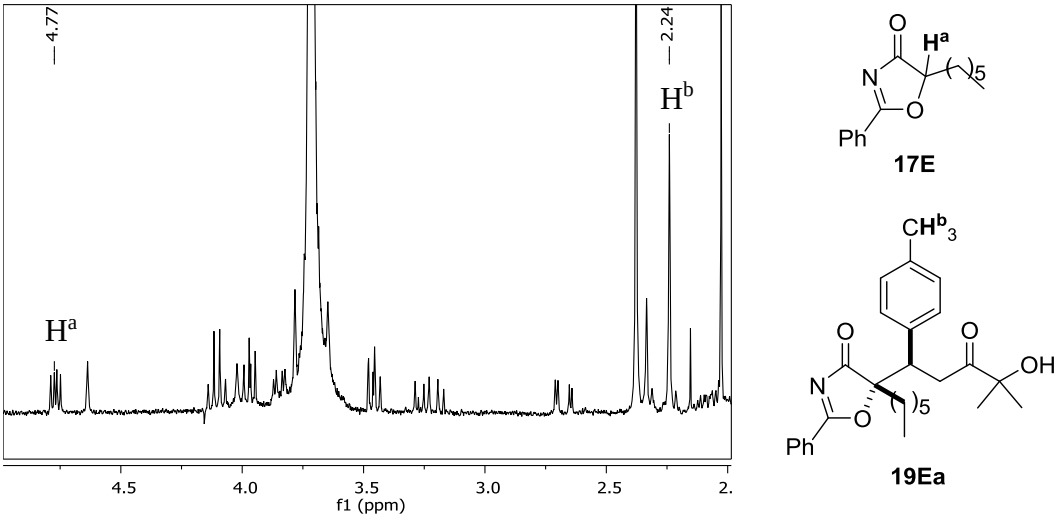


Figure 4.

The diastereomeric ratio was determined by ^{1}H NMR (300 MHz) analysis of the reaction crude (Figure 5) comparing the peak areas of the protons of the methyl substituent at the aromatic ring of the adduct (2.24 ppm for major and 2.21 ppm for minor).

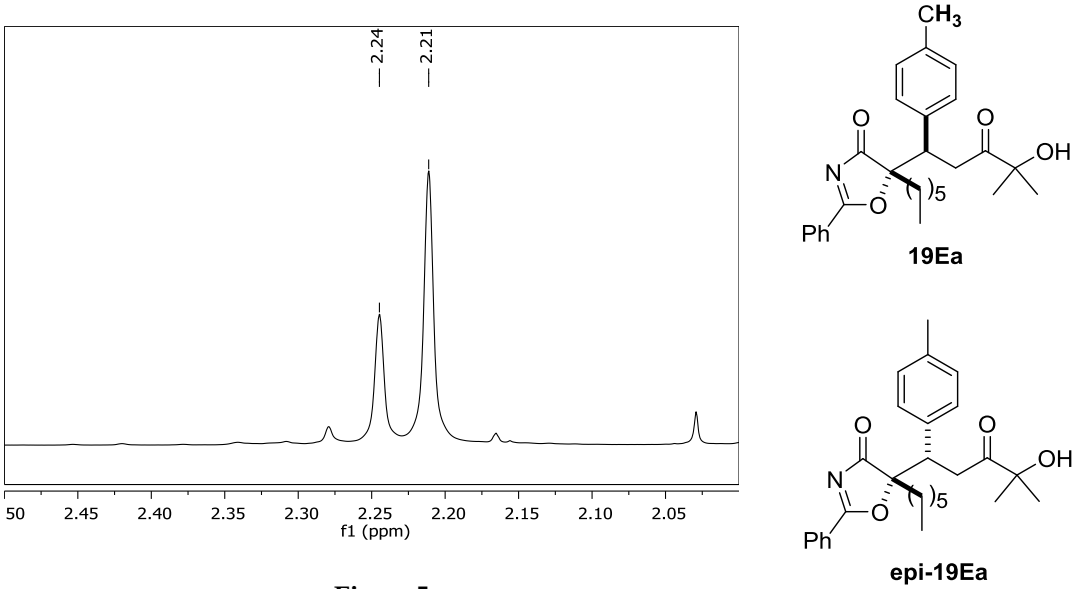


Figure 5.

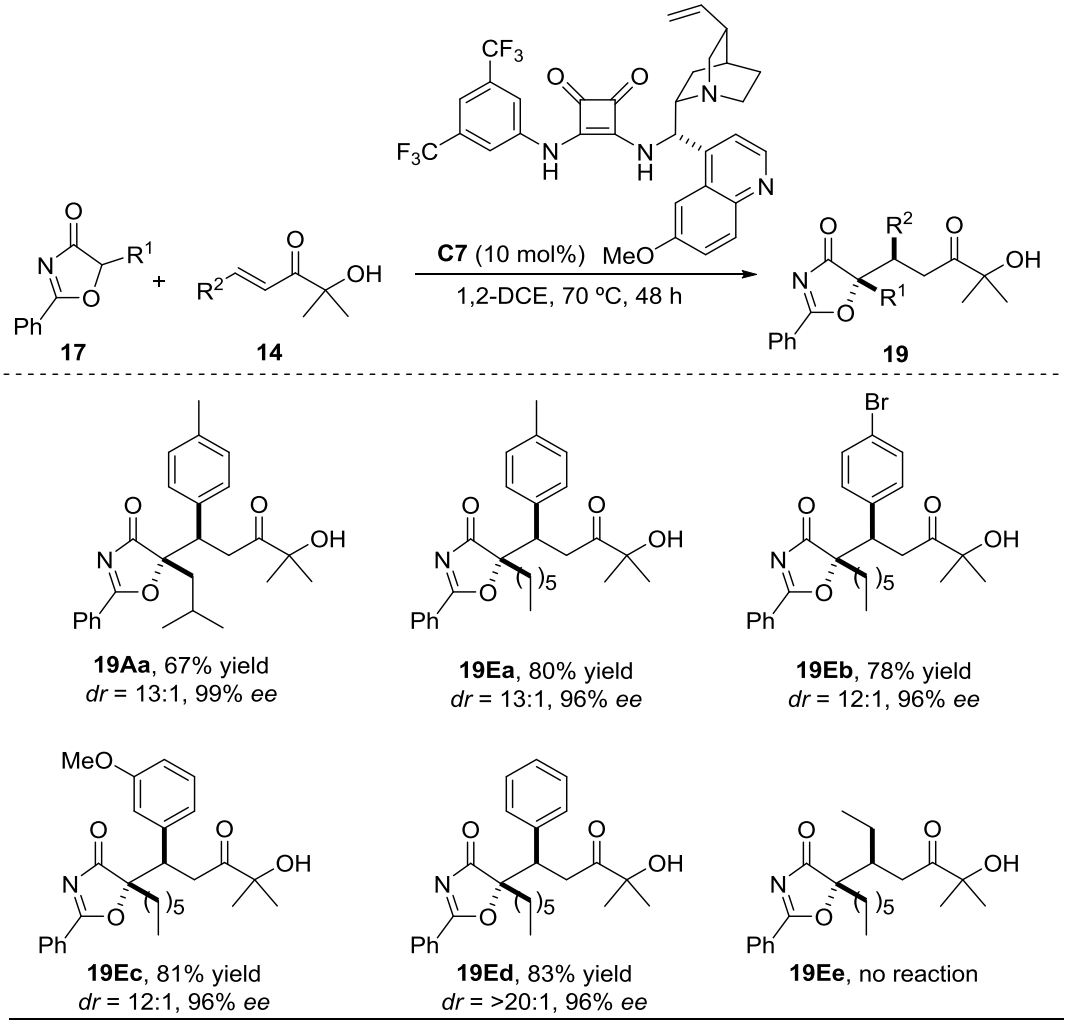
Once the optimized conditions were found, the reaction of oxazolones **17A** and **17E** with α'-hydroxy enones **14a-14d** was carried out following the next standard procedure: the oxazolone was dissolved in 1,2-dichloroethane (0.33 M) and 3

equivalents of the enone and 10 mol% of the catalyst **C7** were added. The reaction mixture was stirred at 70 ºC, and after verifying reaction completion (TLC monitoring, 48 h), the corresponding Michael adduct was isolated as a mixture of diastereomers by flash column chromatography on silica gel eluting with hexane/acetate mixtures.

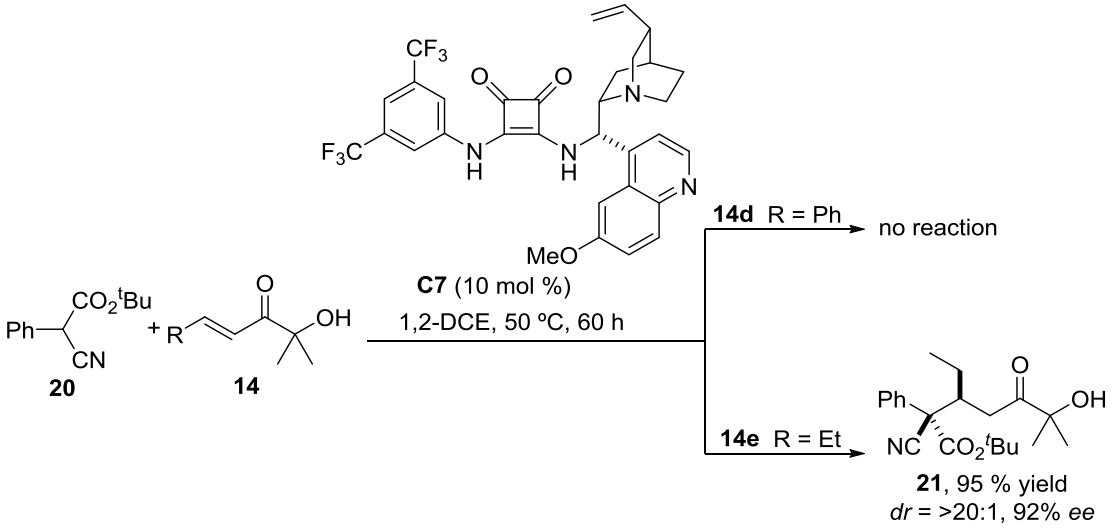
The data in Table 5 show that the reaction also proceeded in good yield for the 5-*iso*-butyl substituted oxazolone (adduct **19Aa**), although a slightly lower yield was obtained as a consequence of an incomplete conversion. Higher steric impediment of the alkyl chain of **17A** as compared to the alkyl chain of **17E** could be a possible cause. On the other hand, β-aryl α'-hydroxy enones with electron-donor (**19Ec**) and withdrawing (**19Eb**) groups were well tolerated. Furthermore, the *dr* was higher than 12:1 in all cases, and the lowest enantiomeric excess for the major diastereomer was 96%. Unexpectedly, β-alkyl substituted α'-hydroxy enones seemed to be unreactive under these reaction conditions (**19Ee**). This is especially curious taking into account that the trend for the reaction with α-cyanoacetates is just the opposite, with β-alkyl substituted α'-hydroxy enones being the most reactive (Scheme 17).[158]

[158] For more information on the organocatalytic asymmetric Michael addition of cyanoacetates to α'-hydroxy enones see the doctoral Thesis of Eider Badiola, *UPV/EHU*, Donostia, **2016** .

Table 5. Michael reaction scope between oxazolones and β-substituted α'-hydroxy enones[a]



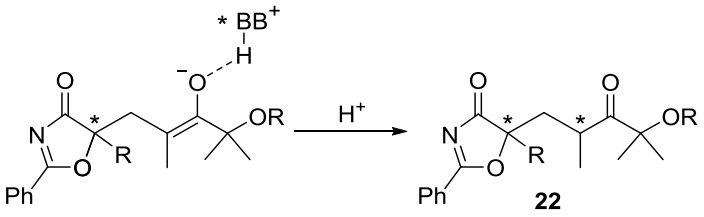
[a] Reactions conducted on a 0.15 mmol scale in 0.45 mL of 1,2-DCE (**17**/**14**/**C7** molar ratio = 1:3:0.1). Combined yield of both isomers after chromatography. *dr* determined by ^{1}H NMR spectroscopy. *ee* of major isomer determined by chiral HPLC.



Scheme 17.

3.1.3.3. α-Substituted α'-oxy enones as electrophiles

The method was also extended to the reaction with α-substituted α'-oxy enones. This reaction would lead to the formation of two nonadjacent stereogenic centers which, unlike in the case of α'-oxy enones examined above, are created in two different steps. The stereogenic center at C_α-atom of oxazolone is formed during the addition step (C–C bond forming step), and the second stereocenter is subsequently formed upon protonation of the resulting enolate. This is a complication since here asymmetric induction from the diol substrate and the catalyst may or may not be convergent. In the protonation step, the asymmetric induction of both the catalyst and the stereogenic center of the substrate are expected to play an important role (Scheme 18).

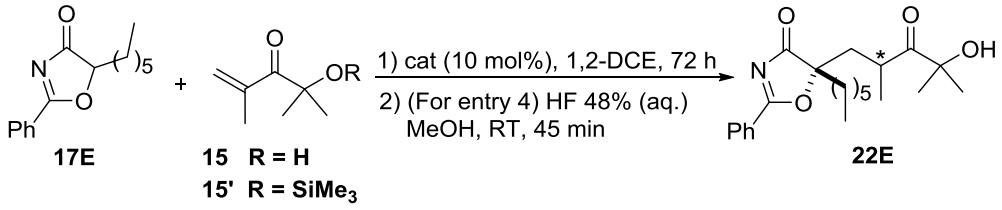


Scheme 18. Protonation step

Initially the reaction between oxazolone **17E** and α-methyl α'-oxy enones (**15, 15'**) in the presence of catalyst **C7** was taken as a model to optimize the Michael reaction conditions (Table 6). The reaction at room temperature led to low conversions, even after 72 h (Table 6, entry 1). By increasing the temperature to 50 ºC better conversions were obtained, and the desired adduct **22E** was obtained in moderate yield, low diastereoselectivity, and moderate enantioselectivity (Table 6, entry 2). Further increase of the temperature afforded similar results, but with a slightly lower diastereoselectivity (Table 6, entry 3). When the reaction was attempted with the *O*-trimethylsilyl derivative **15'** no reaction was observed (Table 6, entry 4).

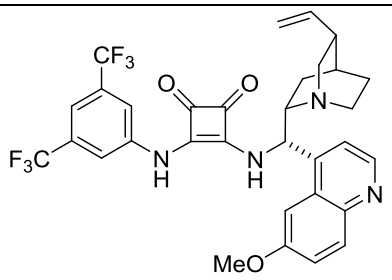
Next, we tested a selection of catalysts, starting with the squaramide catalyst **C8**, which afforded the desired adduct **22E** in similar selectivity to **C7**, but in conversions lower than 50% (Table 6, entry 5). Thiourea catalyst **C9** exhibited an inferior catalytic capacity (Table 6, entry 6). It was gratifying to observe that using catalyst **C13**, which bears an additional amide group for further H-bonding, a good conversion was observed and the corresponding product was obtained in very good enantioselectivity (92 %) (Table 6, entry 7). Unfortunately, none of the tested catalysts afforded diastereomeric ratios higher than 2:1.

Table 6. Condition optimization for the reaction of **17E** with α-methyl α'-oxy enones[a]

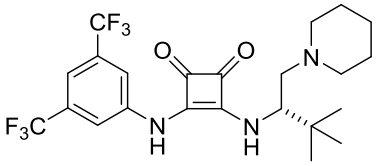


17E **15 R = H** **15' R = $SiMe_3$** **22E**

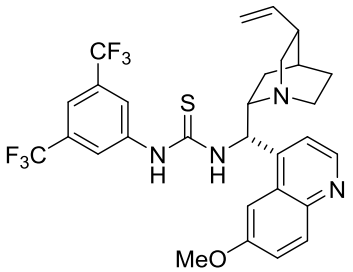
Entry	cat	Enone	T (°C)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee* (%)[e]
1	**C7**	15	15	<35	n.d.	n.d.	n.d.
2	**C7**	15	50	70	61	2:1	72
3	**C7**	15	70	80	64	1.5:1	72
4	**C7**	15'	50	0	-	-	-
5	**C8**	15	50	42	n.d.	2:1	75
6	**C9**	15	50	23	n.d.	n.d.	n.d.
7	**C13**	15	50	89	67	2:1	92



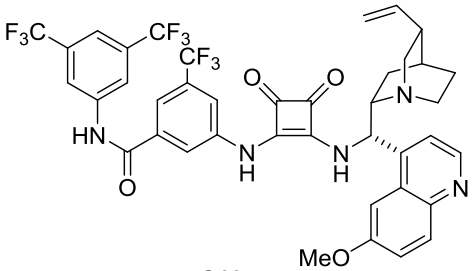
C7



C8



C9



C13

[a] Reactions conducted on a 0.15 mmol scale in 0.45 mL of 1,2-dichloroethane (**17E**/enone/cat molar ratio = 2:1:0.1). [b] Determined by ^{1}H NMR spectroscopy on reaction aliquots before workup. [c] Combined yield of both isomers after chromatography. [d] Determined by ^{1}H NMR spectroscopy. [e] *ee* of major isomer, determined by chiral HPLC.

The diastereomeric ratio was determined by ^{1}H NMR (300 MHz) analysis of the reaction crude (Figure 6) comparing the peak area of the proton at the α-position of the diastereomer adducts (3.27 ppm for minor and 3.13 ppm for major).

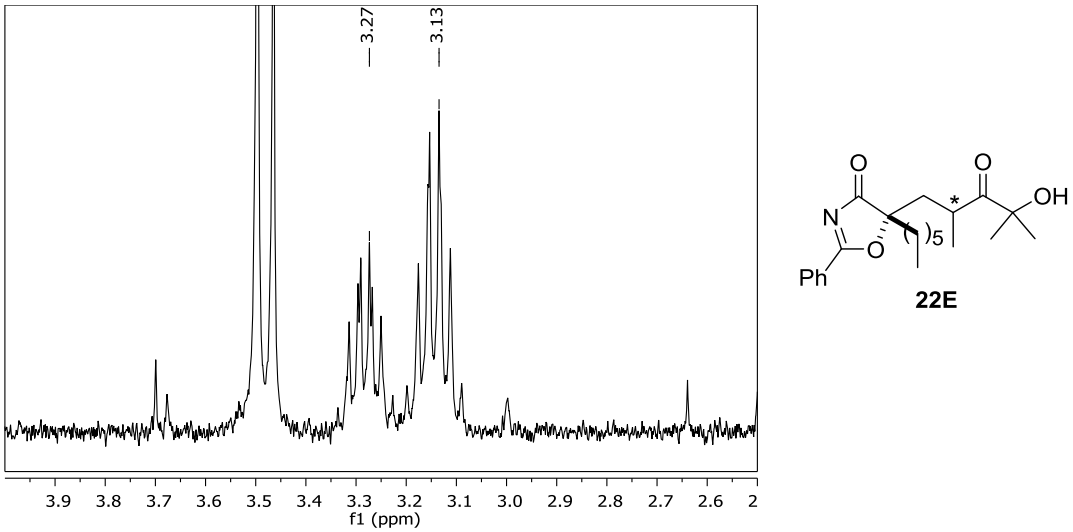
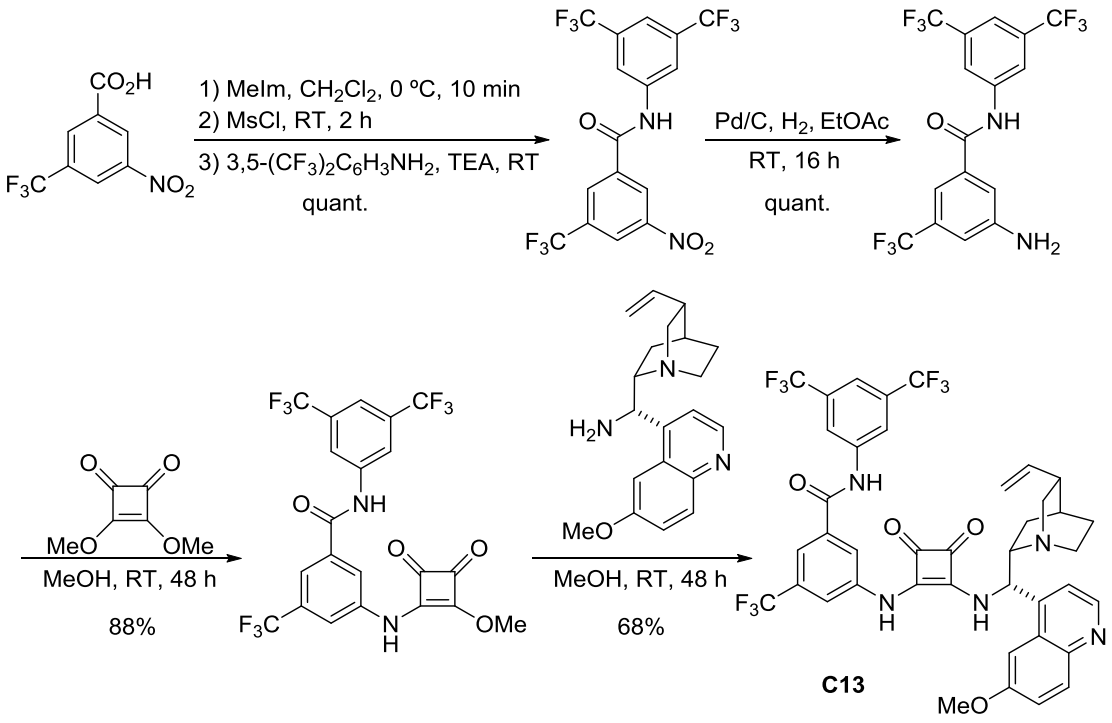


Figure 6.

Catalyst **C13** was prepared in good yield in four routinely steps according to the method described in Scheme 19.[159]



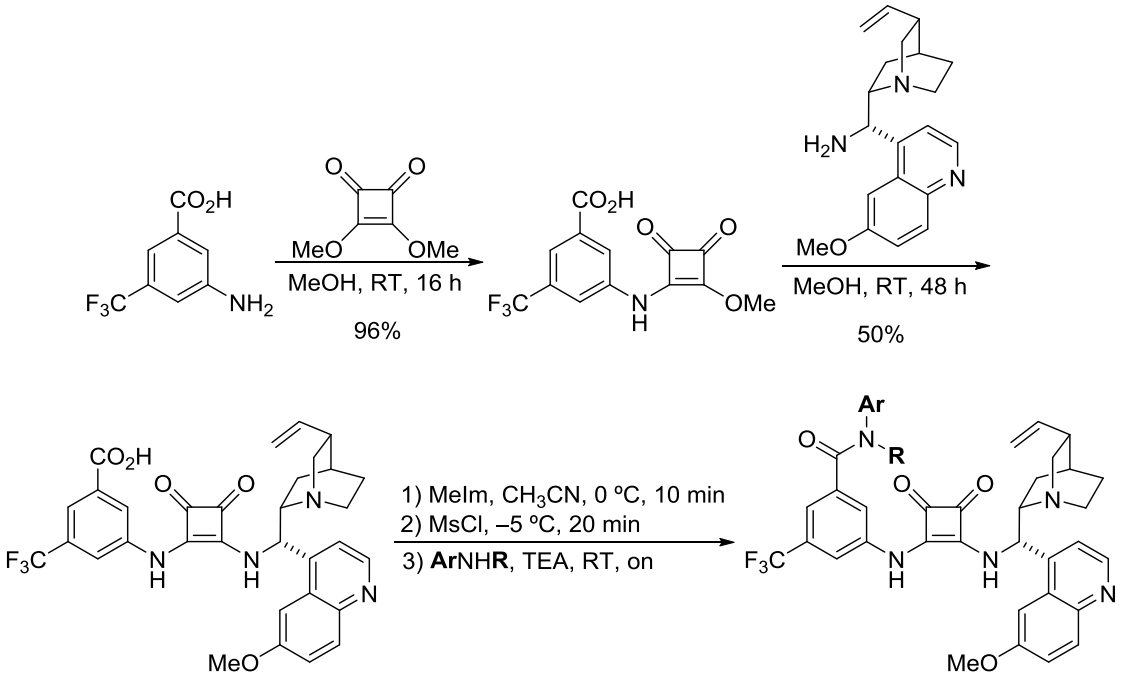
Scheme 19.

As illustrated in Scheme 20, an alternative approach was also developed in our group[160] for the synthesis of **C13**. This approach takes the advantage that different

[159] For detailed information on the synthesis of catalysts see the Experimental Section.

[160] E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185–8195.

catalysts of this type may be prepared via a single common squaramide carboxylic acid precursor.

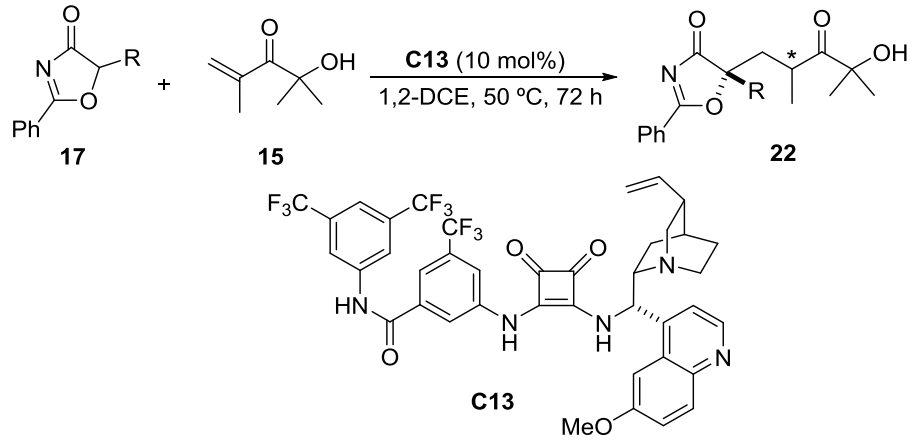


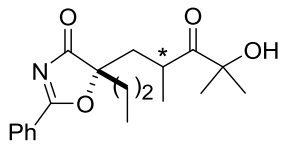
Scheme 20.

Once the optimized conditions were found, the reaction of oxazolones **17B-E** with α'-hydroxy enone **15** was carried out following the next standard procedure: the enone was dissolved in 1,2-dichloroethane (0.33 M) and 2 equivalents of the oxazolone and 10 mol% of the catalyst **C13** were added. The reaction mixture was stirred at 50 ºC, and after verifying that the reaction stopped (^{1}H NMR monitoring, 72 h), the crude material was purified by flash column chromatography on silica leading to a mixture of diastereomers.

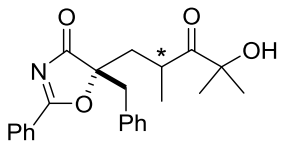
The results in Table 7 show that the reaction proceeded in good yield for the four different oxazolones tested. However, enantioselectivity seems to be very substrate-dependent, as oxazolones with a longer alkyl chain (Bn, 90% *ee*; hex, 92% *ee*) provided the highest enantioselectivity, while oxazolones with a small side chain afforded lower selectivity (Pr, 80% *ee*; Me, 70% *ee*). Furthermore, the *dr* was lower or equal to 2:1 in all cases.

Table 7. Michael reaction scope between oxazolones and α-methyl α'-hydroxy enone **15**[a]

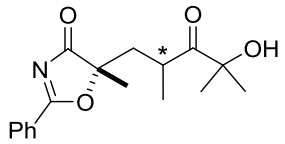




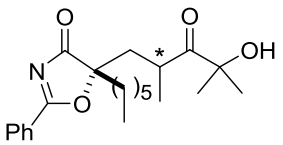
22B, 69% yield
dr = 1.5:1, 80% *ee*



22C, 77% yield
dr = 1.5:1, 90% *ee*



22D, 74% yield
dr = 1.5:1, 70% *ee*

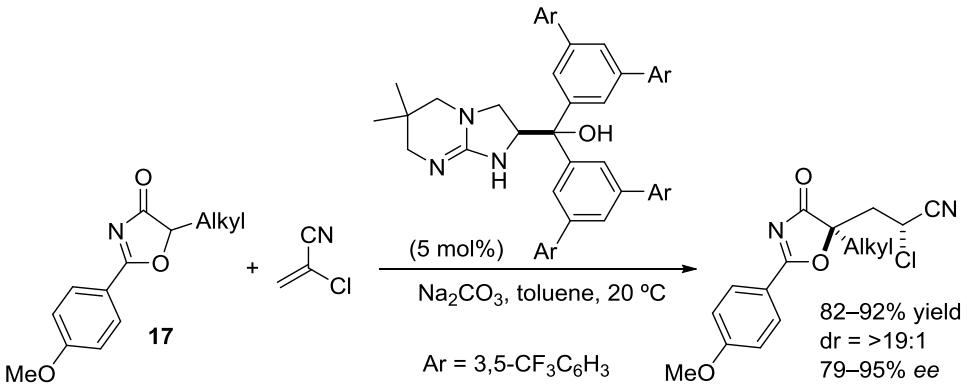


22E, 67% yield
dr = 2:1, 92% *ee*

[a] Reactions conducted on a 0.15 mmol scale in 0.45 mL of 1,2-DCE (**17**/**15**/**C13** molar ratio = 2:1:0.1). Combined yield of both isomers after chromatography. *dr* determined by ^{1}H NMR spectroscopy. *ee* of major isomer determined by chiral HPLC.

While this work was ongoing, Misaki and Sugimura[161] reported the asymmetric conjugate addition of oxazolones to α-chloroacrylonitrile, obtaining the corresponding α-chloronitriles in excellent yield and diastereoselectivity and high enantioselectivity (Scheme 21).

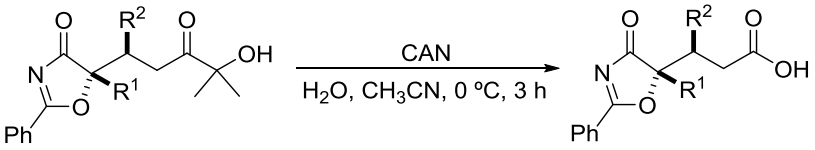
[161] T. Misaki, N.-R. Choi, A. Morita, T. Sugimura, *Tetrahedron Lett.* **2015**, *56*, 5063–5066.



Scheme 21.

3.1.3.4. Elaboration of adducts

In order to validate the α'-hydroxy ketone functionality as a carboxylic acid surrogate, the oxidation of the ketol moiety by using cerium ammonium nitrate (CAN) was carried out. The corresponding carboxylic acids **23**–**26** were obtained in high yield and without loss of optical purity (Scheme 22).

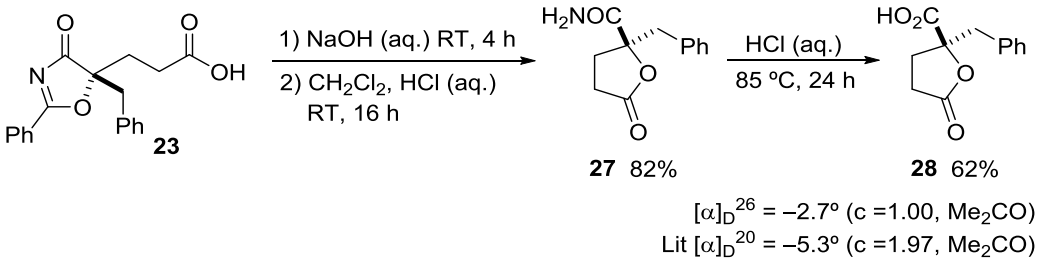


18C	$R^1 = CH_2Ph$,	$R^2 = H$	96% *ee*	**23**, 84% yield
18E	$R^1 = (CH_2)_5CH_3$,	$R^2 = H$	97% *ee*	**24**, 82% yield, 96% *ee*
19Eb	$R^1 = (CH_2)_5CH_3$,	$R^2 = 4\text{-}BrC_6H_4$	96% *ee*	**25**, 82% yield, 95% *ee*
19Ed	$R^1 = (CH_2)_5CH_3$,	$R^2 = C_6H_5$	96% *ee*	**26**, 82% yield, 96% *ee*

Scheme 22.

Carboxylic acid **23** was further derivatized to afford known γ-lactone **28**,[162] which served to determine the configuration of adduct **23** and its precursor **18C** as *R* (Scheme 23). Configuration of the remaining adducts **18** was assigned by assuming a uniform reaction mechanism.

[162] A. Paju, M. Laos, A. Jõgi, M. Päri, R. Jäälaid, T. Pehk, T. Kanger, M. Lopp, *Tetrahedron Lett.* **2006**, *47*, 4491–4493.



Scheme 23.

A crystalline sample of adduct **19Eb** was obtained by crystallisation from a mixture of hexane/ethyl acetate and then its absolute configuration was established by a single crystal X-ray analysis thus confirming initial assignment (Figure 7).

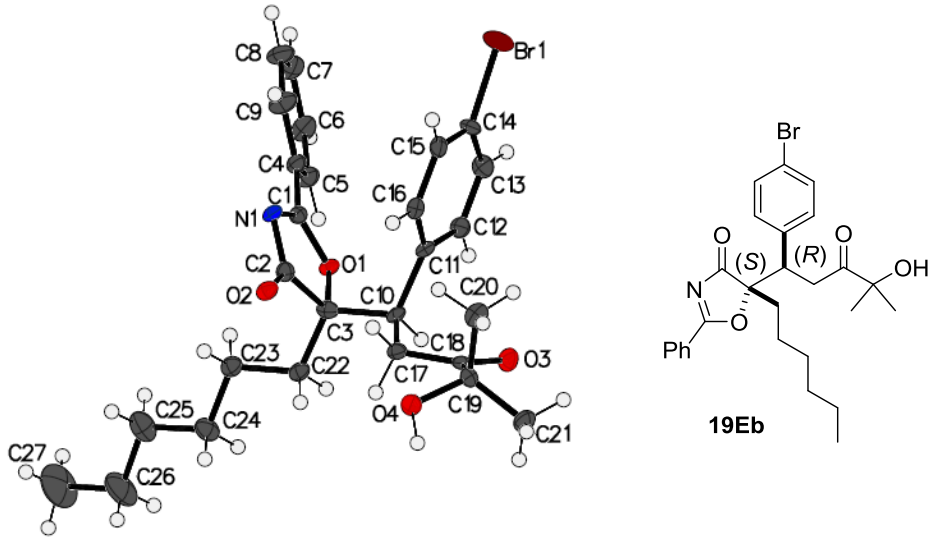
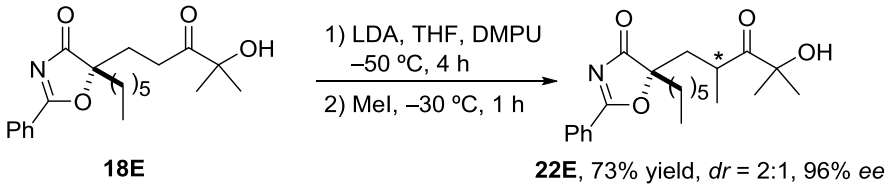


Figure 7.

On the other hand, chemical correlation between adduct **18E** and **22E** as indicated in Scheme 24 demonstrated again that the newly generated stereocenter at the oxazolone C5 position is the same in both reactions.



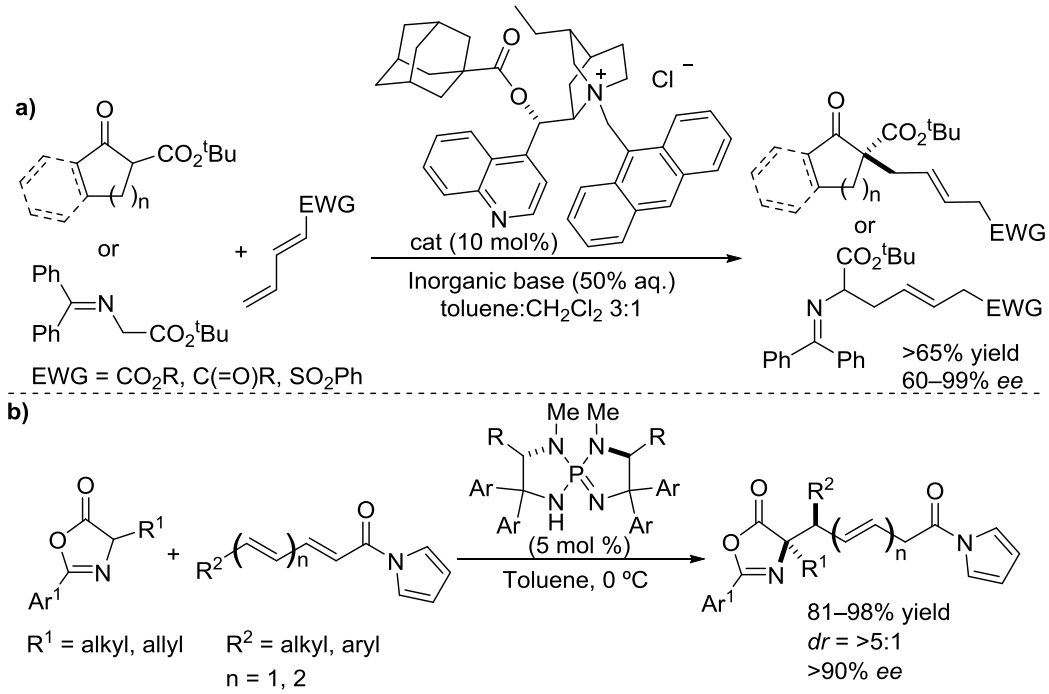
Scheme 24.

3.2. 1,6-Additions to α'-oxy dienones

After developing a robust method for the asymmetric 1,4-addition reactions, the investigation of the nucleophilic addition at more remote positions of polyunsaturated α'-oxy ketones was the next logical step.

3.2.1. Precedents and objectives

At the outset of this project there were only two precedents in the literature involving catalyst-controlled direct stereoselective 1,6-addition reactions of enolizable nucleophiles leading to the formation of a stereogenic center at C_α: On the one hand, Jørgensen and coworkers[163] reported the regio- and stereoselective addition of cyclic β-ketoesters and iminoesters to diverse unsubstituted diunsaturated electrophiles under phase-transfer conditions with excellent results (Scheme 25a). On the other hand, Ooi et al.[164] performed the 1,6- and 1,8-addition of azlactones to polyunsaturated γ- and ζ-alkyl *N*-acylpyrroles respectively catalyzed by a triaminophosphorane catalyst with high levels of regio- and stereocontrol, and later extended the substrate scope to diunsaturated γ-aryl *N*-acylpyrroles (Scheme 25b).[165]



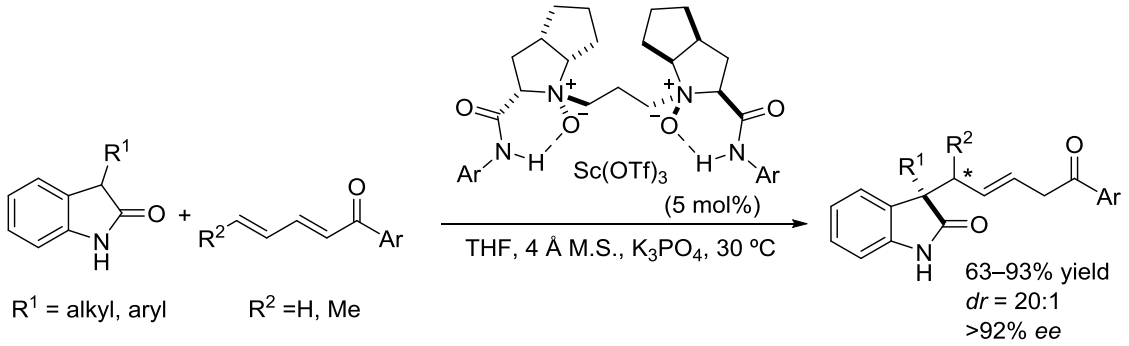
Scheme 25.

[163] L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.

[164] a) D. Uraguchi, K. Yoshioka, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370–19373. b) D. Uraguchi, K. Yoshioka, T. Ooi, *Nature Commun.* DOI: 10.1038/ncomms14793.

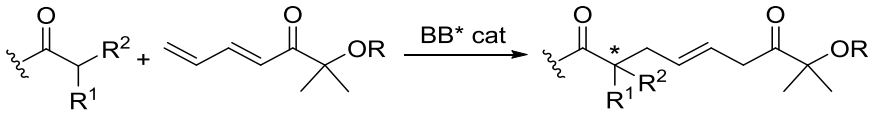
[165] For further information on conjugate 1,6-addition reactions see: a) A. G. Csákÿ, G. Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080–4102. b) E. M. P. Silve, A. M. S. Silva, **2012**, 44, 3109–3128.

Moreover, while the project was ongoing Feng and coworkers reported the scandium-catalyzed asymmetric 1,6-addition of 3-substituted oxindoles to dienyl ketones in excellen selectivity (Scheme 26).



Scheme 26.

Taking into account the scarcity of methods, the viability of the asymmetric 1,6-conjugate addition of enolizable carbonyl compounds to α'-oxy dienones was attempted (Scheme 27).



Scheme 27.

The realization of this objective possessed several challenges to overcome: i) the control of the face selectivity at sites remote from the coordination point, ii) the diminished reactivity of α'-oxy dienones as compared to the parent unsubstituted α'-oxy enones and iii) the control of the 1,4 vs 1,6 addition.

The goal was to identify the factors that govern the different reactivity and selectivity aspects of this transformation.

3.2.2. Oxazolones as nucleophiles

The suitability of a catalytic 1,6-addition process involving our dienones was first evaluated by using oxazolone **17E** and α'-oxy dienones **16** and **16'** in the presence of several Brønsted base catalysts (Table 8). In a first run the reaction was carried out under the conditions developed for the Michael reaction of oxazolones with β-aryl α'-hydroxy enones. Under these conditions (**C7** 10 mol%, 70 ºC) a 2:1 mixture of the 1,6- and 1,4-addition products was obtained in low stereoselectivity (Table 8, entry 1). In

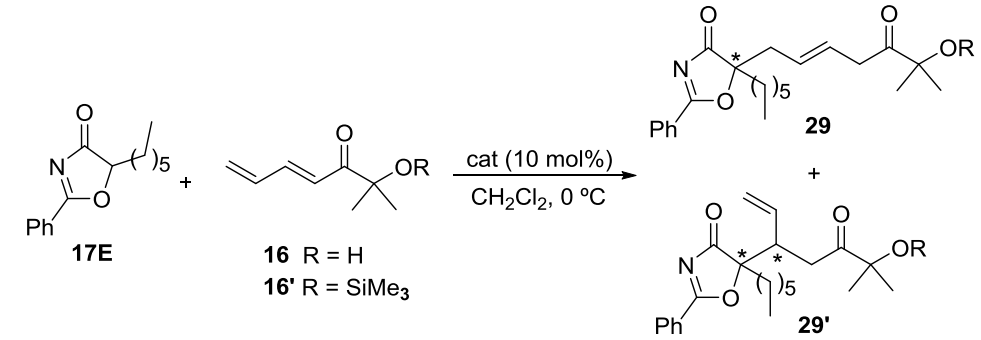
light of this result, we decided to change the tertiary amine by a stronger basic functionality. The idea was that a stronger base would increase the amount of enolate present in the reaction media, thus accelerating the reaction and making feasible its performance under kinetic control, hopefully favouring the addition at the least sterically-hindered position (δ).

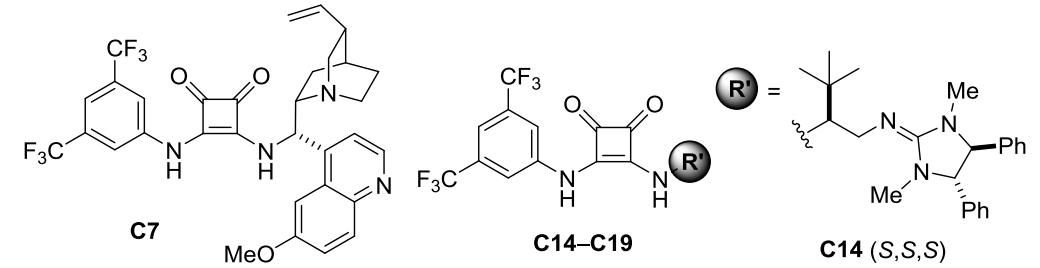
For that goal, a set of novel guanidine catalysts (**C14-C18**) and phosphanimine **C19** were synthesised. The reactions at 0 ºC with guanidine catalysts **C14-C18**, afforded the 1,6-addition adduct exclusively. However, enantioselectivity remained suboptimal in all the cases. For example guanidine **C14**, similar to the ones developed by Ishikawa,[166] afforded the desired product in an almost racemic manner (Table 8, entry 2). Moreover, the use of catalysts **C15-C17**, including variations in the relative disposition of the stereogenic centers did not lead to substantial improvement of the enantioselection (entries 3, 5 and 7, respectively). The silylated dienone **16'** was also tested in the reaction with catalysts **C15-C17** (entries 4, 6 and 8, respectively), but reaction times became longer and similar *ee* values to the ones obtained with dienone **16** were observed. When chiral guanidine **C18**, similar to the one described by Wang and Qu,[167] was tested in the reaction (Table 8, entry 9), similar results were obtained. Finally, phosphanimine catalyst **C19** was also employed in the reaction (Table 8, entry 10), but low conversion rates were observed.

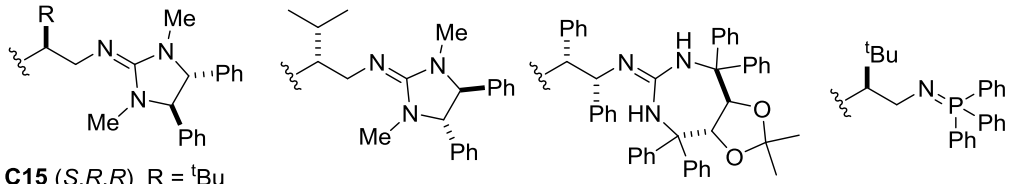
[166] T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, T. Isobe, *Chem. Commun.* **2001**, 245–246.

[167] L. Zou, B. Wang, H. Mu, H. Zhang, Y. Song, J. Qu, *Org. Lett.* **2013**, *15*, 3106–3109.

Table 8. Catalyst screening for the reaction of oxazolone **17E** with α'-oxy dienones[a]



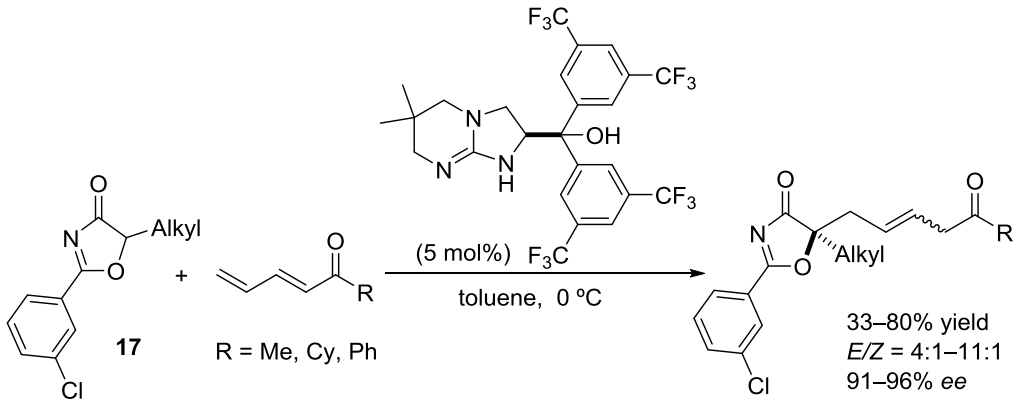




Entry	cat	Enone	R	t (h)	Yield (%)[b]	**29**:**29'**[c]	*ee* (%)[d]
1	**C7**	28	H	48[e]	68	2:1	15
2	**C14**	28	H	24	76	>20:1	13
3	**C15**	28	H	24	74	>20:1	–22
4	**C15**	28'	$SiMe_3$	72	56	>20:1	–35
5	**C16**	28	H	24	72	>20:1	–27
6	**C16**	28'	$SiMe_3$	72	45	>20:1	–36
7	**C17**	28	H	24	79	>20:1	40
8	**C17**	28'	$SiMe_3$	72	73	>20:1	45
9	**C18**	28	H	24	78	>20:1	-40
10	**C19**	28	H	72	<25	n.d.	n.d.

[a] Reactions conducted on a 0.15 mmol scale in 0.45 mL of CH_2Cl_2 (**17E**/dienone/cat molar ratio = 1:2:0.1). [b] Yield of combined isomers after chromatography. [c] Determined by ^1H NMR spectroscopy. [d] *ee* of compound **29**, determined by chiral HPLC. [e] Reaction carried out at 70 ºC using 1,2-DCE as the solvent.

While this study was ongoing, Misaki and Sugimura[168] reported a similar work where they performed the conjugate 1,6-addition of oxazolones to simple dienones. The corresponding adducts were obtained in variable yield and excellent enantioselectivity as a mixture of *E*/*Z* isomers (Scheme 28).



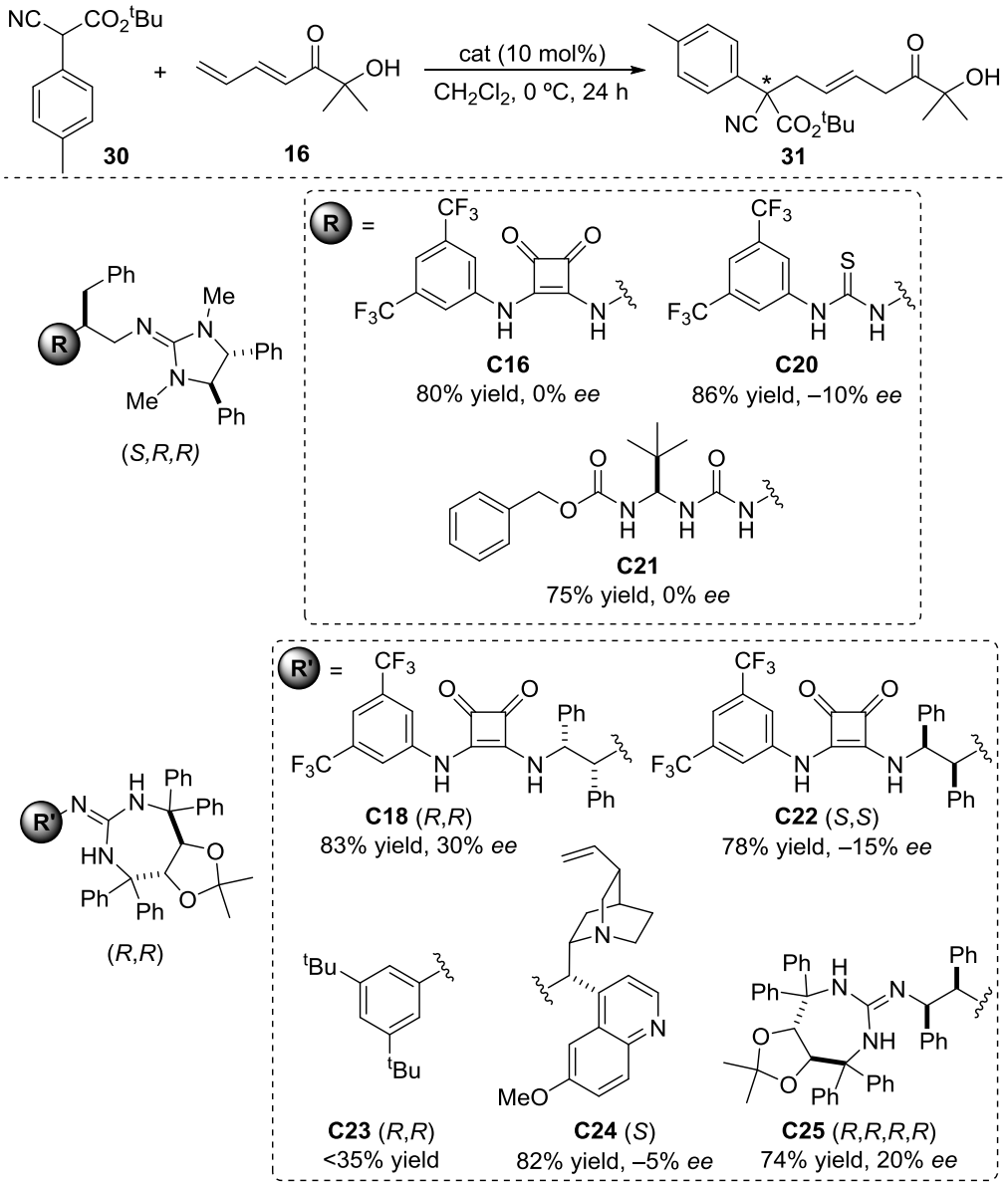
Scheme 28.

3.2.3. α-Cyanoacetates as nucleophiles

At this point, we decided to switch from oxazolones to α-cyanoacetates as nucleophiles, and the reaction of cyanoacetate **30** with α'-oxy dienone **16** was taken as a model to perform the catalyst screening (Table 9). Also some new catalysts **C20**-**C25** were synthesised. To begin with, guanidine catalysts bearing the squaramide (**C16**), thiourea (**C20**) and ureidopeptide (**C21**) motifs were employed in the reaction, and although the 1,6-addition adduct was formed exclusively, enantioselectivity near zero was obtained. When catalyst **C18** was used for the reaction, some stereoselectivity was observed and therefore different catalysts bearing the same chiral guanidine structure were synthesised and tested. First, catalyst **C22**, with a different relative configuration, rendered the adduct in lower *ee*. On the other hand, catalyst **C23**, not bearing additional H-bonding groups, turned out to be an inefficient catalyst for the reaction. Finally, catalysts **C24** and **C25**, with additional basic functionalities, rendered the desired product in good yield, but very low enantioselectivity.

[168] a) A. Morita, T. Misaki, T. Sugimura, *Chem Lett.* **2014**, *43*, 1826–1828. b) A. Morita, T. Misaki, T. Sugimura, *Tetrahedron Lett.* **2015**, 56, 264–267.

Table 9. Catalyst screening for the reaction of cyanoacetate **30** with α'-hydroxy dienone **16**[a]



[a] Reactions conducted on a 0.15 mmol scale in 0.45 mL of CH_2Cl_2 (**30**/**16**/cat molar ratio = 1:2:0.1). Isolated yield after chromatography. *ee* determined by chiral HPLC.

At this point, seeing the difficulties we were encountering in our quest for a catalyst that could effectively control the enantioselectivity of the 1,6-addition reaction, we decided to provisionally put the project aside to focus on other goals.

3.3. Regio-, diastereo- and enantioselective functionalization of unactivated cyclic ketones

3.3.1. Precedents and objectives

Despite the great synthetic interest of chiral ketones, the direct asymmetric α-functionalization of enolizable ketones remains challenging. This situation aggravates in the case of non-symmetrical unactivated ketones with two sites for deprotonation, in which the procedures for the catalytic asymmetric α-carbofunctionalization are mostly limited to the use of either chiral auxiliaries or preformed enolates and equivalents. For instance, to the best of our knowledge, the direct catalytic stereoselective α-arylation[169] of these ketones is yet to be achieved, and only scarce examples of allylation[170] and alkylation[171] reactions have been reported so far.

Successful strategies for the α-alkylation involving the use of primary amine catalysts have been independently reported by the groups of Carter[172] and Kotsuki,[173] but they require a high catalyst loading and harsh reaction conditions (Scheme 29). Furthermore, the substituent at C_α is limited to the methyl, ethyl, *n*-propyl and benzyl groups, affording the adducts of the latter two in low yield (<35%).

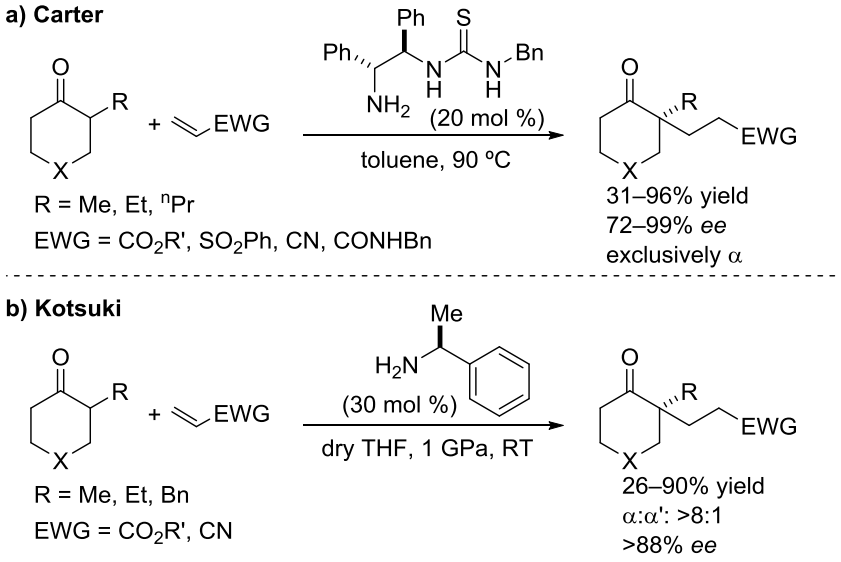
[169] For reviews on the arylation of carbonyl compounds see: a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676–707. b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082–1146.

[170] For a metal-catalyzed example of this reaction see: a) W. Chen, M. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 15825–15828. For reviews on the allylation of carbonyl compounds see: b) S. Oliver, P. A. Evans, *Synthesis* **2013**, *45*, 3179–3198. c) J. C. Hethcox, S. E. Shockley, B. M. Stolz, *ACS Catal.* **2016**, *6*, 6207–6213.

[171] For a recent review on the direct asymmetric alkylation of ketones see: R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.* **2017**, *56*, 9278–9290.

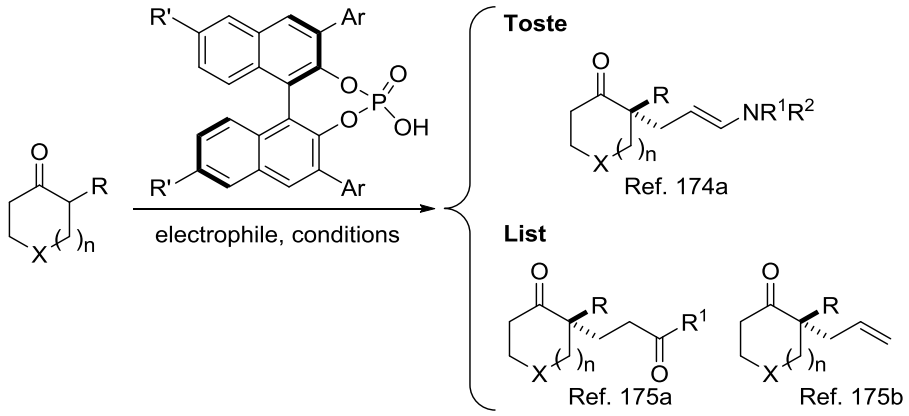
[172] a) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178–3181. b) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, *81*, 3629–3637.

[173] R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457–4463.



Scheme 29.

On the other hand, Toste[174] and List[175] have independently demonstrated the utility of chiral phosphoric acids as Brønsted acid catalysts for the regioselective asymmetric α-carbofunctionalization of cyclic ketones with allenamides, allylic alcohols and α'-branched α,β-unsaturated ketones (Scheme 30).



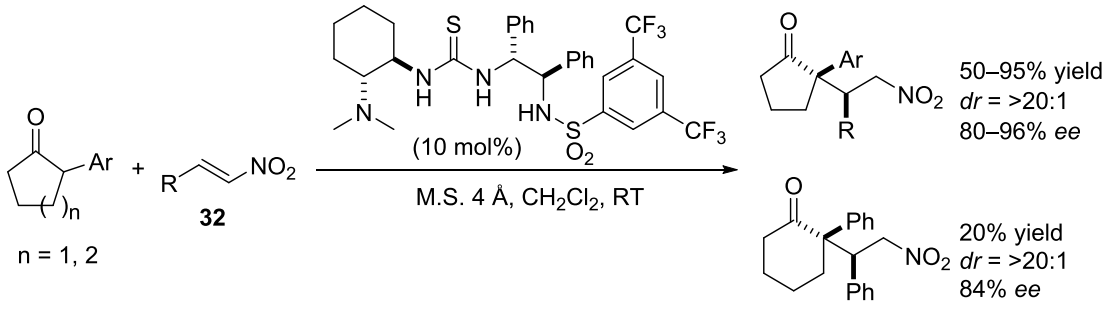
Scheme 30.

At the outset of this project, the only direct Brønsted base-catalyzed example in the literature for the regio- and stereoselective functionalization of ketones with two

[174] a) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653–2656. For examples of heterofunctionalization reactions see: b) X. Yang, R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5225–5228. c) X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205–3208.

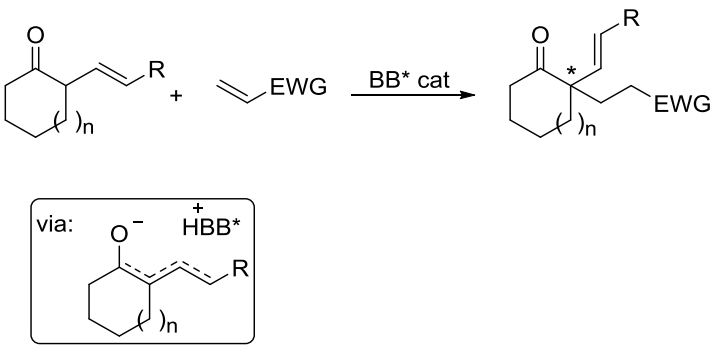
[175] a) I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960–1964. b) G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed.* **2016**, *55*, 6099–6102. For an example of amination reaction see: c) G. A. Shevchenko, G. Pupo, B. List, *Synlett* **2015**, *26*, 1413–1416.

distinct sites for deprotonation was the one reported by Wang,[176] where the Michael reaction of α-aryl substituted cyclopentanones with nitroalkenes was catalyzed by a chiral thiourea-sulfonamide catalyst (Scheme 31). The corresponding α-alkylation adducts were obtained exclusively and in excellent yield, diastereo- and enantioselectivity. However, α-phenyl cyclohexanone behaved sluggishly.



Scheme 31.

We decided to explore alternative strategies to provide a methodology for the α-functionalization of either cyclic or acyclic α-substituted ketones. The major handicaps in developing direct regio- and enantioselective C-C bond forming reactions at C_α position of α-branched ketones under proton transfer conditions stem from: i) the relatively high pK_a value of the ketone substrate and ii) the steric constraints imposed by the carbonyl α-substituent, which difficult proton abstraction and decreases nucleophilicity. We envisioned that an alkenyl group installed at the α-position of the carbonyl function, that is an α-alkenyl cycloalkanone, would not only provide synthetic versatility to the resulting adducts, but, most importantly, also charge delocalization during enolization. As a result, a weak base catalyst might suffice to trigger the reaction while securing regioselective α- vs α'-enolization (Scheme 32).

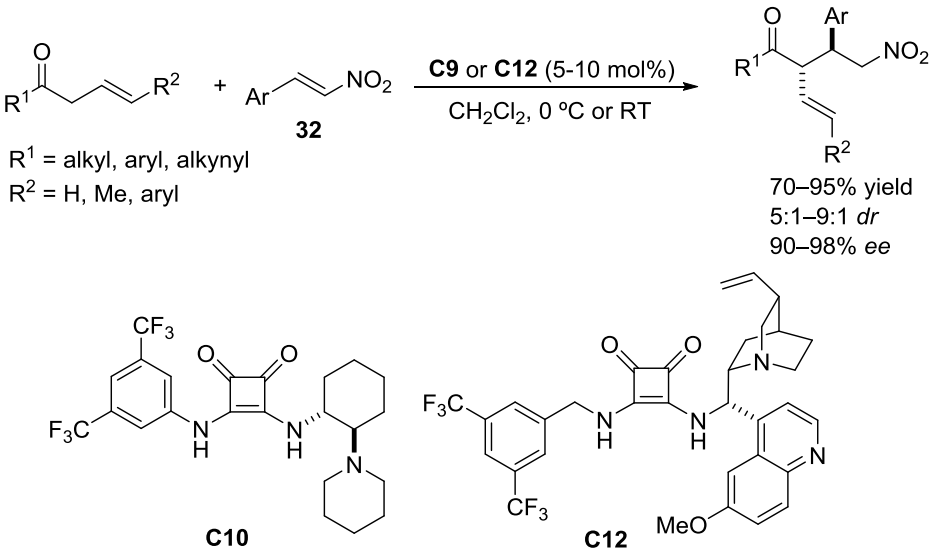


Scheme 32.

[176] X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem Commun.* **2010**, *46*, 6840–6842.

However, in that design the Brønsted base should also be effective in controlling both the α- vs γ-reactivity of the transiently formed vinylogous enolate and the reaction stereoselectivity during generation of the quaternary stereogenic center.

Recently, I. Iriarte, O. Olaizola and Dr. Vera from this laboratory[177] have addressed this latter problem in acyclic systems and found that conjugate additions of β,γ-unsaturated ketones to nitroalkenes catalyzed by bifunctional Brønsted bases provided only the α-addition adducts (Scheme 33).



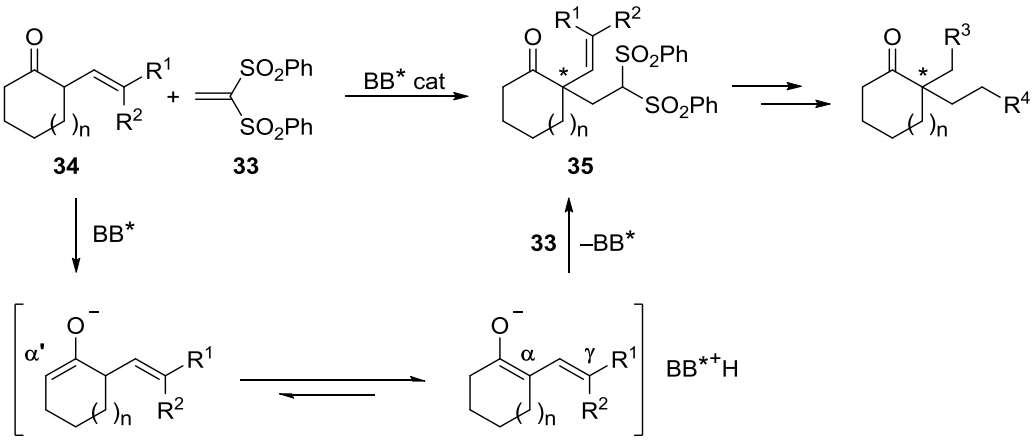
Scheme 33.

3.3.2. α-Functionalization of α-alkenyl cycloalkanones

On this basis, our study was initiated with the reaction of α-alkenyl cycloalkanones with vinyl sulphones under similar conditions, addressing the double α/α'/γ regioselectivity problem. We elected to use vinyl sulphones as acceptors because, upon double bond hydrogenation and desulfonylation, products from a formal α-alkylation of α-alkyl cycloalkanones would result in a concise, simple way (Scheme 34). Such products are otherwise difficult to achieve.[178]

[177] I. Iriarte, O. Olaizola, S. Vera, I. Gamboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.

[178] For an approach involving protection of α'-position, α-alkylation and α'-deprotection see: a) T. Hamada, A. Chieffi, J. Ahman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. b) T. Kano, Y. Hayashi, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 7134–7137.



Scheme 34.

3.3.2.1. Catalyst screening

Initially the reaction between 2-styrylcyclohexanone (**34A**) and 1,1-bis(phenylsulfonyl)ethylene (**35**) was taken as a model to find the optimal catalyst for the α-alkylation reaction of cyclic α-alkenylketones (Table 10). In a first run, the reaction catalyzed by thiourea **C9** afforded exclusively the desired α-addition product **35A** in good yield, but in an almost racemic manner. Urea catalysts **C26**[179] and **C27**[180] afforded the adduct in better, but still low enantioselectivity. On the other hand, $(DHQD)_2PYR$ (**C11**) and squaramide catalysts **C7**[154a] and **C12**[154b] rendered the addition product in high yield and moderate *ee* values (60–73% *ee*). When using the less basic amine **C10**[156] as the catalyst low conversions were observed, even at room temperature. Moreover, the new squaramide catalysts bearing an amide group as an additional H-bond donor functionality (**C13** and C**28**[181]) led to no improvement as compared to **C7**. However, using a more sterically demanding catalyst such as **C29**[182] the desired adduct was obtained in excellent yield and enantioselectivity (96% *ee*). Furthermore, catalyst **C30**, synthesised from hydrogenated quinine, afforded adduct **35A** in even higher enantioselectivity (98% *ee*). Remarkably, no formation of α'- or γ-addition adducts was observed with any of the catalyst.

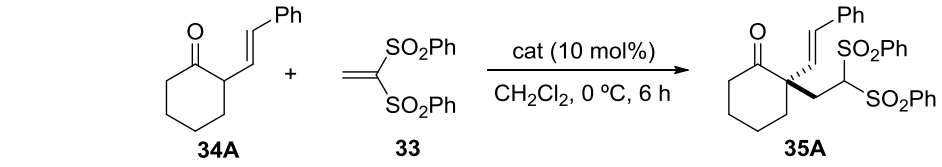
[179] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886.

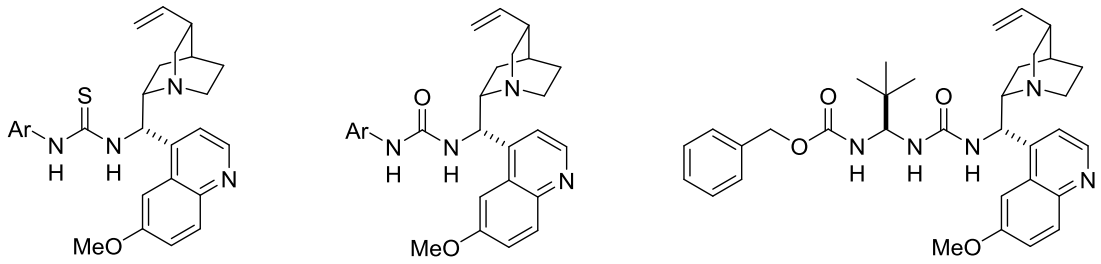
[180] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.

[181] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.

[182] A. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 12758–12762.

Table 10. Catalyst screening for the reaction between **34A** and **33**[a]

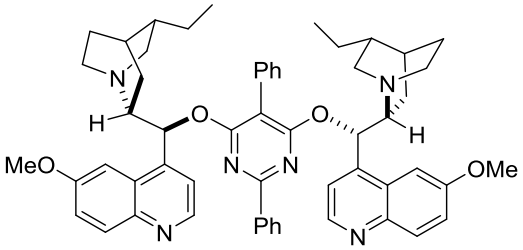




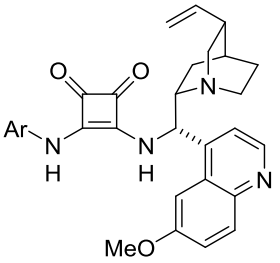
C9
72% yield,10% *ee*

C26
79% yield, 40% *ee*

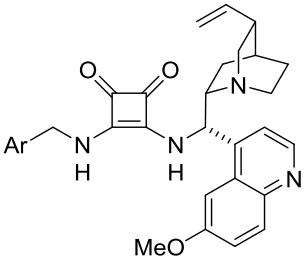
C27
83% yield, 40% *ee*



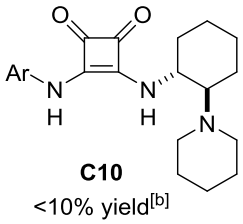
(DHQD)$_2$PYR, C11
86% yield, 60% *ee*



C7
88% yield, 73% *ee*

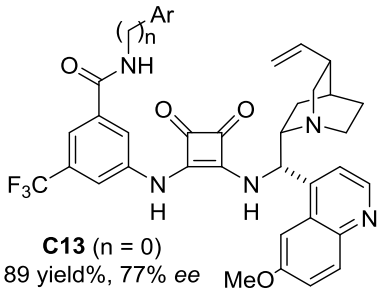


C12
83 yield%, 60% *ee*



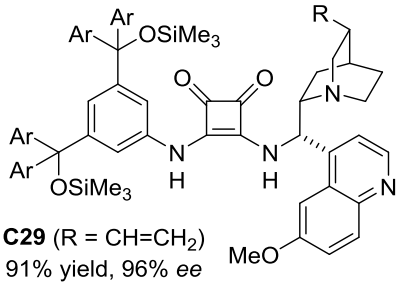
C10
<10% yield[b]

Ar = 3,5-$CF_3C_6H_3$



C13 (n = 0)
89 yield%, 77% *ee*

C28 (n = 1)
81 yield%, 72% *ee*



C29 (R = $CH{=}CH_2$)
91% yield, 96% *ee*

C30 (R = CH_2CH_3)
89% yield, 98% *ee*

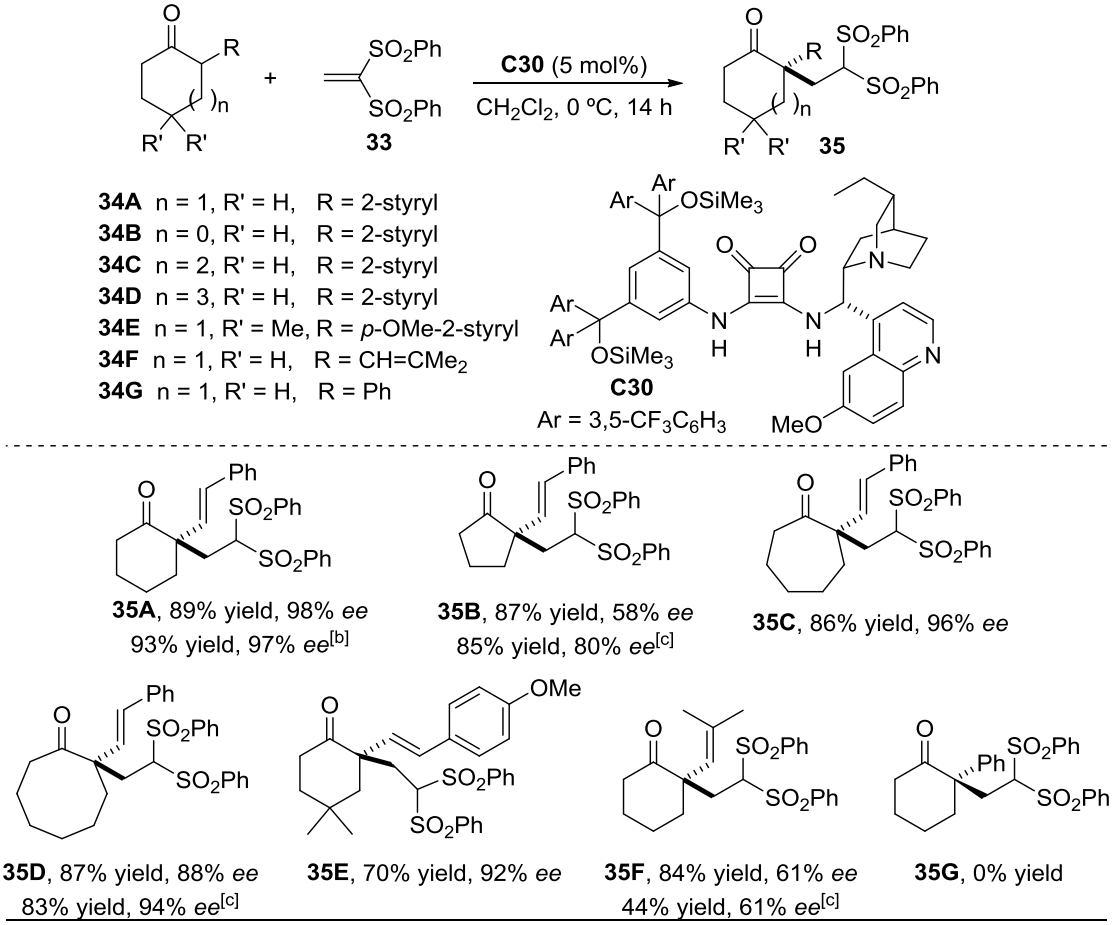
[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**34A**/**33**/cat molar ratio = 1:1.5:0.1). Yield of isolated product after chromatography. *ee* determined by chiral HPLC. [b] Reaction conducted at RT.

3.3.2.2. Reaction scope

Once the optimal catalyst for the reaction model was found, the reaction of cyclic α-alkenyl ketones **34** with bisulfone **33** was conducted following the next standard procedure: the donor ketone was dissolved in CH_2Cl_2 (0.5 M) and 1.5 equivalents of 1,1-bis(phenylsulfonyl)ethylene (**35**) and 5 mol% of the catalyst **C30** were added. The reaction mixture was stirred at 0 ºC, and after verifying that the reaction finished (TLC monitoring, 14 h), the reaction mixture was submitted to flash column chromatography on silica gel eluting with hexane/EtOAc mixtures.

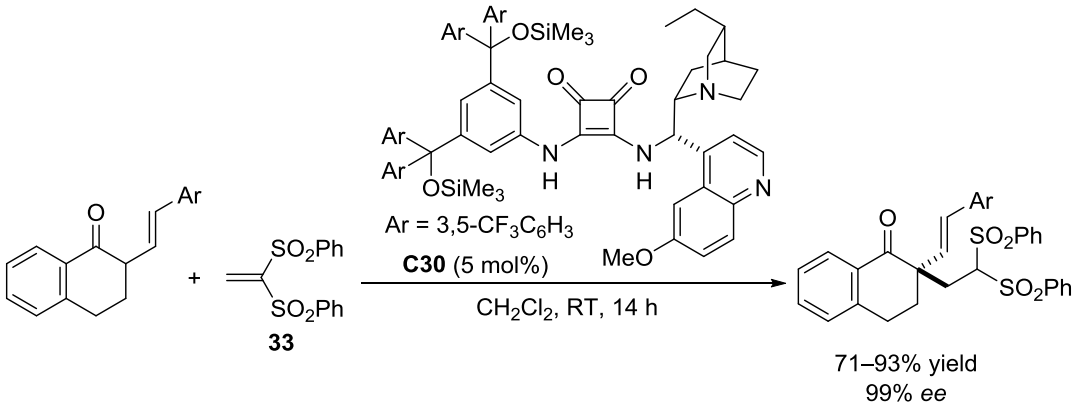
As data in Table 11 show, the reaction tolerated well the different ring-sized cycloalkanones (**34B**–**34D**), affording the corresponding alkylation products **35B**–**35D** in high yield and excellent enantioselectivity except for the cyclopentanone derivative **35B**, which was obtained in lower selectivity. It is noteworthy that in the case of adducts **35B** and **35D** switching the solvent to toluene resulted in an increase of stereoselectivity. Moreover, compound **35E**, bearing substituents at the cyclohexanone ring and with a more electron-rich alkenylic group was also obtained with equally good results. However, product **35F**, not having a styril group, was obtained in lower *ee* values. Curiously, when α-phenyl cyclohexanone (**35G**) was tested in the reaction for a comparison, no reaction was observed, probably due to the bigger steric hindrance present at the α-position as compared to the other substrates. In addition, the scalability of the reaction was demonstrated by performing the reaction at 3 mmol scale, obtaining adduct **35A** with similar results. Importantly, in every case exclusively the α-addition product was formed.

Table 11. Reaction scope between α-alkenyl ketones and **33**[a]



[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (**34**/**33**/**C30** molar ratio = 1:1.5:0.05). Yield of isolated product after chromatography. *ee* determined by chiral HPLC. [b] Reaction conducted at 3 mmol scale. [c] Reaction conducted at RT using toluene as the solvent.

In parallel to our work, O. Mugica from this laboratory found that vinyl sulphones are suitable acceptors for the conjugate addition reaction with α-alkenyl α-tetralones, and was able to obtain the addition products in high yield and almost perfect enantioselectivity by using "bulky" Brønsted base catalyst **C30** (Scheme 35).

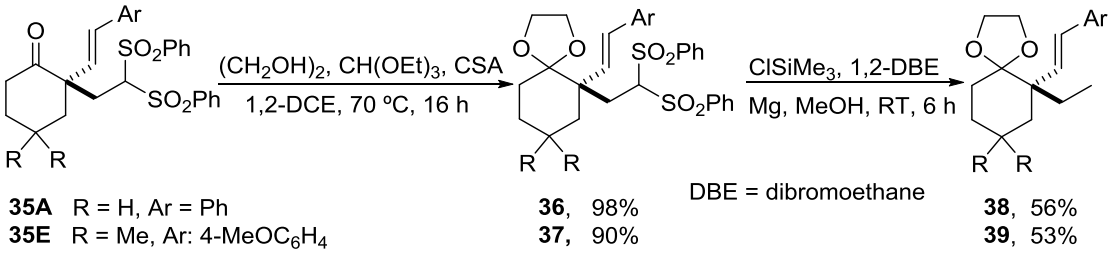


Scheme 35.

3.3.2.3. Elaboration of adducts

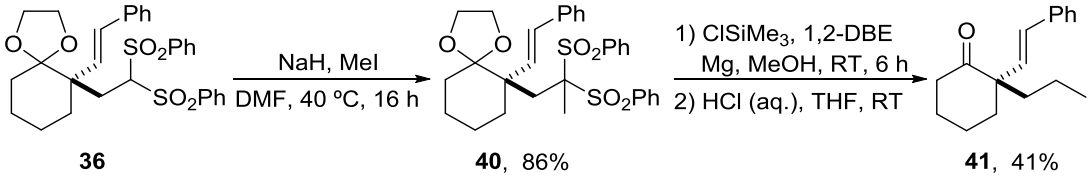
Once an efficient and highly selective procedure for the α-alkylation was obtained, some possibilities for the transformation of the adducts were briefly explored.

First, the desulfonylation of adducts **35A** and **35E** was performed with magnesium in methanol after ketalization of the carbonyl to avoid its non-stereoselective reduction (Scheme 36). The desired desulfonylated products **38** and **39** were obtained in moderate yield.



Scheme 36.

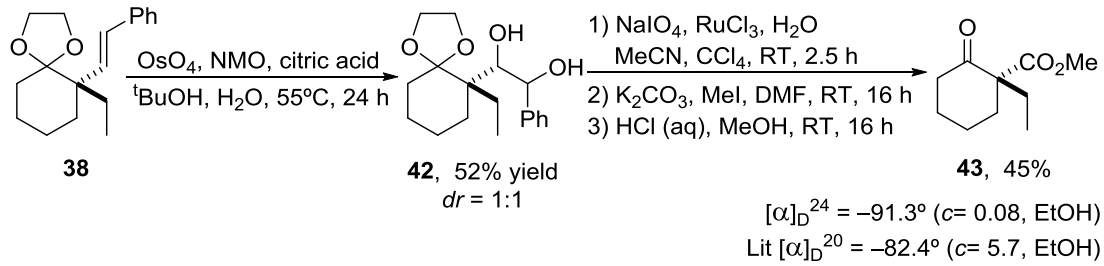
Moreover, alkylation of product **36** was performed with methyl iodide and sodium hydride obtaining the methylated product **40** in high yield, and upon subsequent desulfonylation and deprotection α,α-disubstituted ketone **41** was obtained in moderate yield (Scheme 37). Unfortunately, preliminary attempts on benzylation and allylation of **36** under the same reaction conditions were unsuccessful.



Scheme 37.

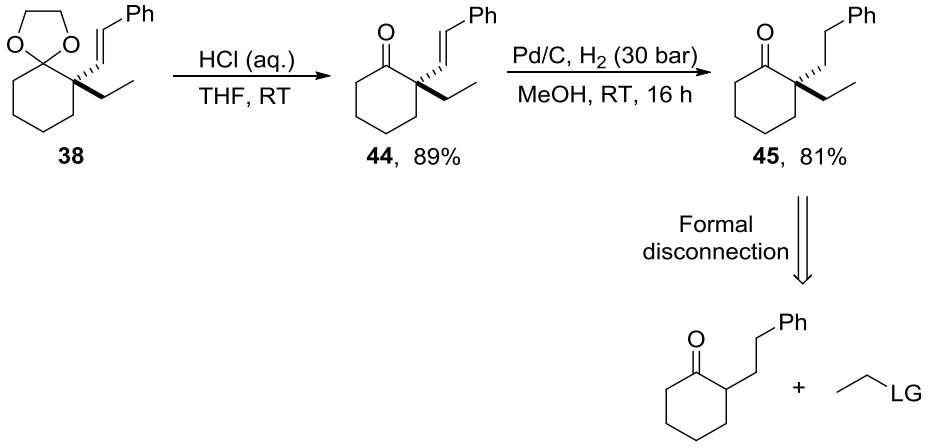
In another transformation, compound **38** was derivatized to afford known β-ketoester **43**,[183] which served to determine the configuration of adduct **38** and its precursor **35A** as *R* (Scheme 38). Configuration of remaining adducts was assumed based on a uniform reaction mechanism.

[183] S. Pinheiro, A. Guingant, D. Desmaële, D. d'Angelo, *Tetrahedron: Asymmetry* **1992**, *3*, 1003–1006.



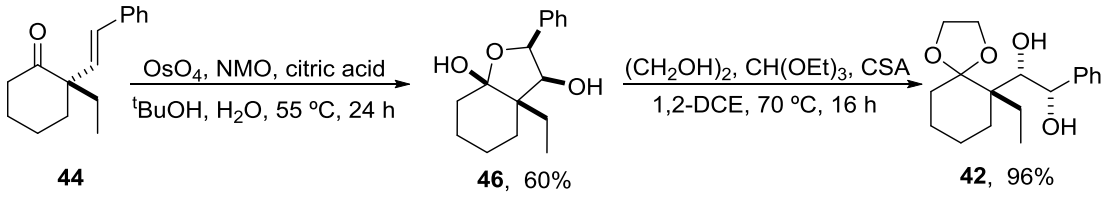
Scheme 38.

On the other hand, the branched cycloalkanone **45** was synthesised in high yield from **38** via hydrolysis of the ketal and reduction of the double bond with H_2/Pd (Scheme 39). The former is the adduct formally derived from the asymmetric alkylation of an α-alkyl cycloalkanone, which is difficult to achieve regio- and stereoselectivily.



Scheme 39.

Intermediate **44** was also used for the preparation of the β,γ-dihydroxy ketone derivative **42** (Scheme 40). In a first step ketone **44** was oxidized with osmium tetroxide and *N*-methylmorpholine *N*-oxide affording the hemiketal **46**, and after conversion to the ketal the desired diol **42** was obtained in good yield and as a single isomer.



Scheme 40.

Additionally, a crystalline sample of adduct **46** was obtained by crystallization from a mixture of hexane/dichloromethane and thus the absolute configuration of compound **46** was established by a single crystal X-ray analysis. The configuration of

the molecule happened to be (1*S*, 6*S*, 7*S*, 8*S*), with both hydroxyl groups on the same side of the tetrahydrofurane ring (Figure 8).

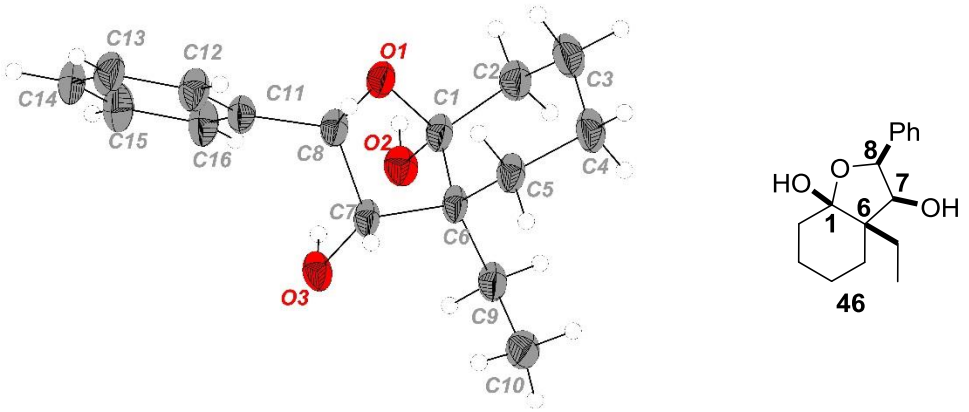
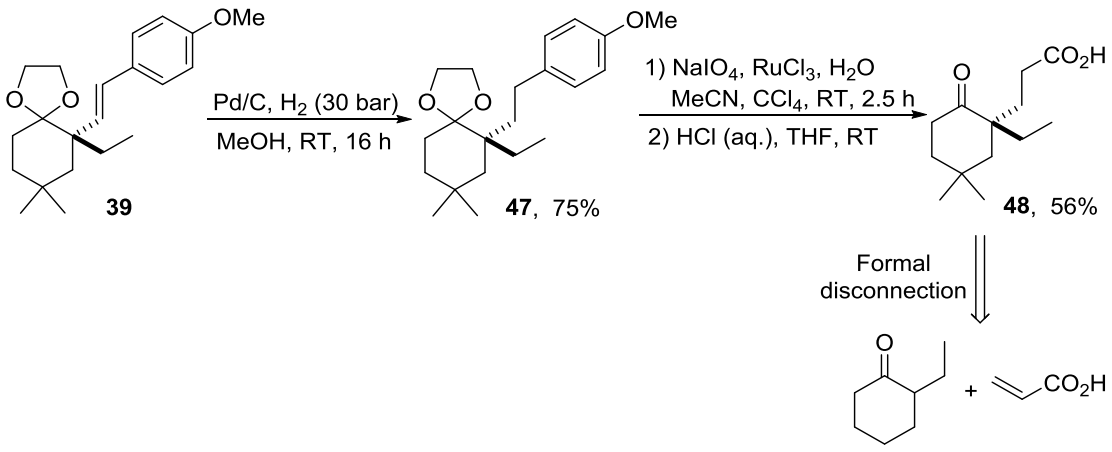


Figure 8.

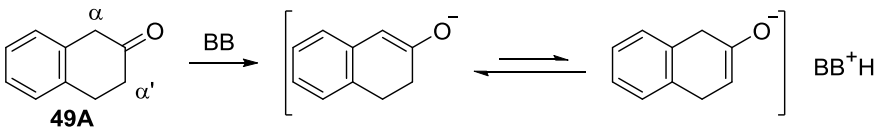
Finally, compound **39** was reduced with H_2/Pd leading to the α,α-dialkyl ketal intermediate **47**, which after subsequent oxidative scission and deprotection of the ketone afforded product **48** (Scheme 41). It is worth noting that **48** is the adduct formally derived from the asymmetric Michael reaction between an α-alkyl cycloalkanone and an enoate, a reaction for which no direct Brønsted base-catalyzed procedures have yet been reported.



Scheme 41.

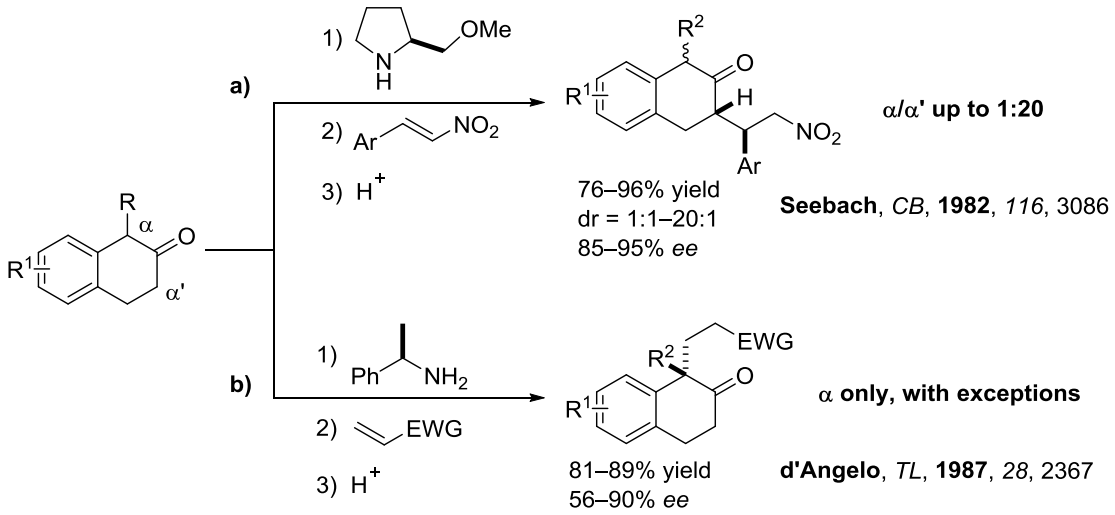
3.3.3. α-Alkylation of β-tetralone derivatives

Given these results, we next explored the behaviour of β-tetralones in this type of reations. We hypothesised that the fused aromatic ring in β-tetralones might induce preferential enolization at C_{α} rather than $C_{\alpha'}$ (Scheme 42), and that in the presence of a Brønsted base relatively high concentrations of the enolic form would be expected, thus eventually driving the catalytic process forward. Moreover, not only alkenyl, but also alkyl groups at this position might be equally tolerated.



Scheme 42.

The only previous asymmetric procedures for the α'- and α-functionalization of β-tetralone derivatives described by Seebach[184] and d'Angelo[185] respectively rely on the use of chiral amine auxiliaries, affording the corresponding adducts in good yield but variable diastereo- and enantioselectivity (Scheme 43). Most importantly, in these examples the regioselectivity of the reaction is strongly substrate-dependent.



Scheme 43.

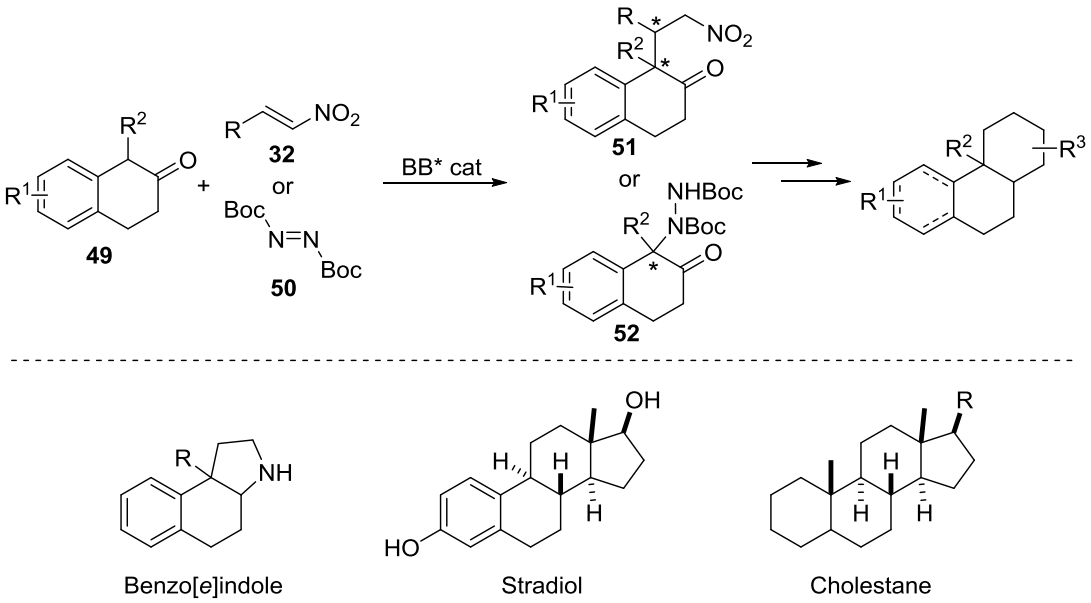
In this context, the use of a chiral Brønsted base would not only enable the use of catalytic amounts of the chiral compound for the selective α-functionalization of β-tetralones, but, compared to the previous procedures employing chiral amine auxiliaries,

[184] a) S. J. Blarer, W. D. Seebach, *Chem. Ber.* **1982**, *116*, 3086–3096.

[185] a) T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.* **1987**, *28*, 2367–2370. b) J. d'Angelo, G. Revial, T. Volpe, M. Pfau, *Tetrahedron Lett.* **1988**, *29*, 4427–4430.

would also avoid the need for additional steps for the formation of the nucleophilic species and the recovery of the final carbonyl compound.

Indeed, whilst O. Mugica from this laboratory demonstrated that β-tetralones can be selectively substituted at C_α in the presence of a Brønsted base catalyst employing vinyl sulphones as electrophiles,[186] we have found that nitroolefins and azodicarboxylates are also suitable substrate acceptors for this reaction leading to attractive building-blocks of products of relatively greater complexity, as it has been shown in previous works (Scheme 44).[187]



Scheme 44.

3.3.3.1. Initial experiments and reaction scope

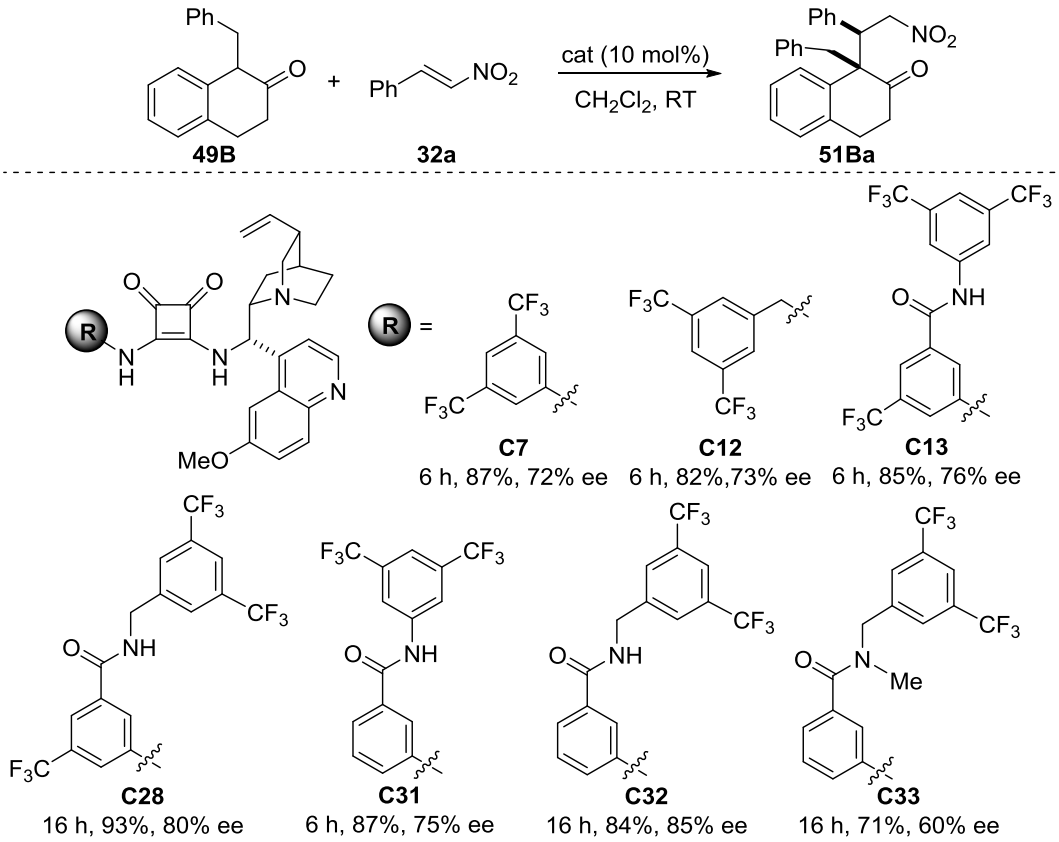
Initially the reaction between β-tetralone **49B** and nitrostyrene (**32a**) at 0 ºC was taken as a model in order to find the optimal Brønsted base catalyst to render the corresponding α,α-disubstituted β-tetralones. As the most representative experiments summarised in Table 12 show, all catalysts afforded the α-addition adduct exclusively in a completely diastereoselective manner. However, stereoselectivity happened to be

[186] Results not published yet.

[187] For the synthesis of: Homoerythrina alkaloids: a) M. A. Le Dréau, D. Desmaele, F. Dumas, J. O'Angelo, *J. Org. Chem.* **1993**, *58*, 2933–2935. Morphan derivatives: b) G. Lim, J. W. Hooper, US Patent 4, 017,493; Apr. 12, **1997**. Glucocorticoid receptors: c) B. P. Morgan, A. G. Swick, D. M. Hargrove, J. A. LaFlame, M. S. Moybihan, R. S. Carrol, K. A. Martin, G. Lee, D. Decosta, J. Bordner, *J. Med. Chem.* **2002**, *45*, 2417–2424. Stradiols: d) Y. Bouali, F. Nique, J.-G. Teutsch, P. Van de Velde, US Patent 6, 207,657BI, Mar 27, **2001**. e) J. P. Larkin, C. Whrey, P. Boffelli, H. Lagraulet, G. Lamaitre, A. Nedelec, D. Prat, *Org. Process Res. Dev.* **2002**, *6*, 20–27.

highly catalyst-dependent. Catalysts bearing the squaramide H-bonding structure (**C7**, **C12**, **C13**, **C28**, **C31-C33**) exhibited a superior enantiocontrol when compared to catalysts with other functionalities such as urea (**C26**[179]), thiourea (**C9**[155]) and ureidopeptide (**C35**[188]), or catalysts not bearing this kind of H-bond donor moieties (**C11** and **C34**), which all rendered adduct **51Ba** in low *ee* (<50%). **C7**[154a] and **C12**[154b] afforded the adduct in similar enantioselectivity, while catalysts **C13** and **C31**[189] provided slightly higher *ee*. Catalysts bearing a benzylic group instead of an arylic group at the amide functionality (**C28**[181] and **C32**) rendered the product in improved enantioselectivity, although longer reaction times (16 h) were required. Furthermore, the use of *N*-methylated catalyst (**C33**) leaded to a significant loss of enantioselectivity, thus suggesting that the amide group is involved in some H-bond interaction during the reaction.

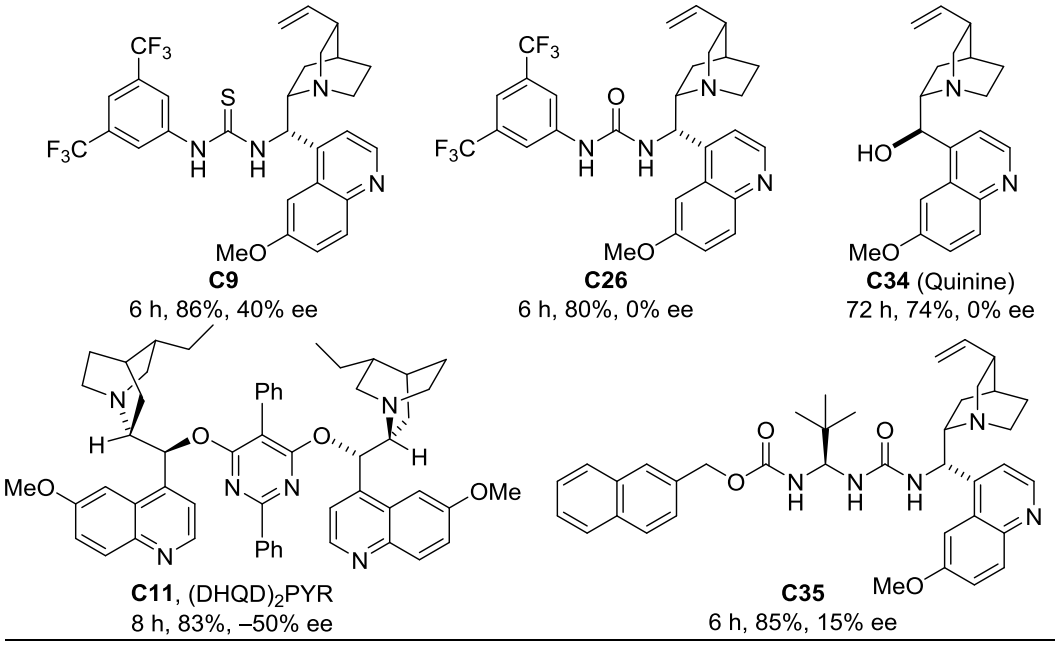
Table 12. Catalyst screening for the reaction between **49B** and **32a**[a]



[188] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizaola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[189] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.

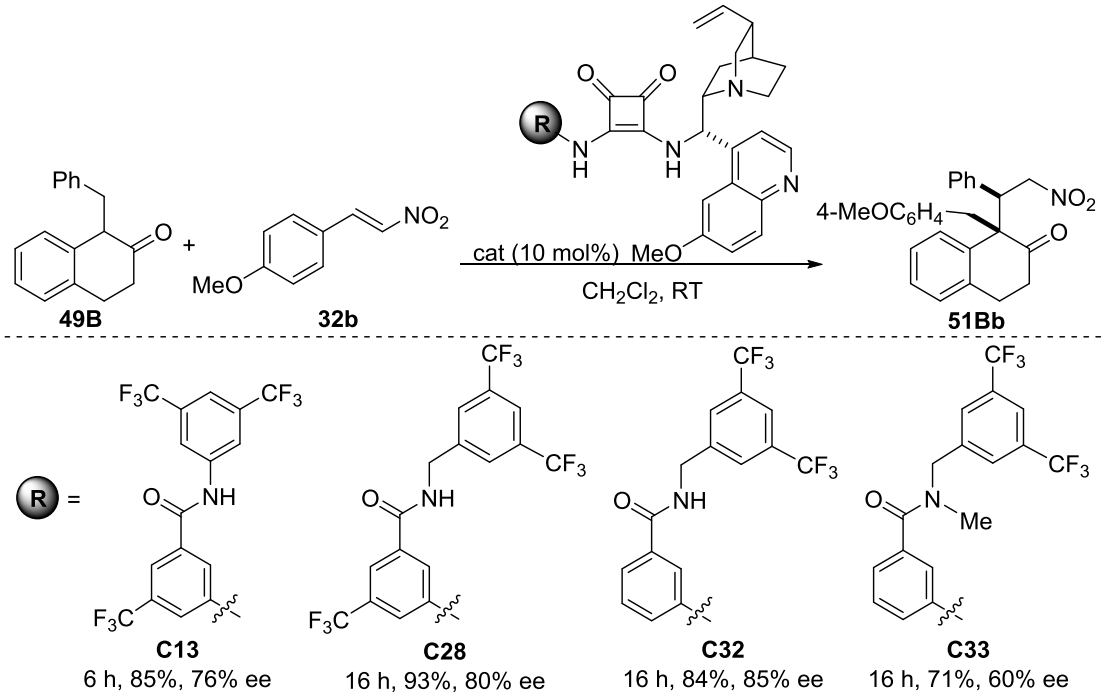
Continuation of **Table 12**



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49B**/**32a**/cat molar ratio = 1:1.2: 0.1). Yield of isolated product after chromatography. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC.

Next, to ensure that stereoselectivity was not substrate-dependent catalysts with the squaramide motif (**C13**, **C28**, C**32** and **C33**) were tested in the reaction between β-tetralone **49B** and the more electron-rich nitroalkene **32b** (Table 13). The results were similar to the ones above obtained.

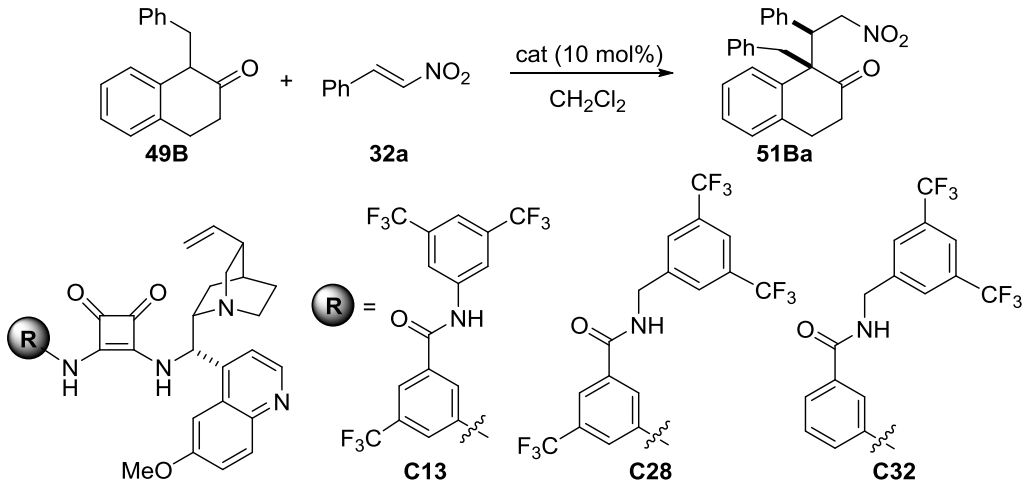
Table 13. Catalyst screening for the reaction between **49B** and **32b**[a]



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49B**/**32b**/cat molar ratio = 1:1.2:0.1). Yield of isolated product after chromatography. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC.

In light of the preliminary results, catalysts **C13**, **C28** and **C32** were chosen for the study of the effect of temperature in the reaction between β-tetralone **49B** and nitrostyrene (**32a**) (Table 14). Lowering the temperature from 15 to 0 ºC improved the enantioselectivity obtained with catalyst **C13**, although reaction times became longer (entry 1 vs. 2). Further decrease in temperature to –20 ºC allowed to obtain adduct **51Ba** in 90% *ee* (Table 14, entry 3). Conducting the reaction with catalyst **C28** at –10 ºC instead of 15 ºC also improved the stereoselectivity (entry 4 vs. 5), and afforded comparable results to the ones obtained with catalysts **C13** at –20 ºC (entry 3 vs. 5). An improvement in enantioselectivity was also observed with catalyst **C32** when using it at 0 ºC as compared to the same reaction at 15 ºC (entry 6 vs. 7). However, the low solubility of catalyst **C32** made it behave sluggishly when decreasing the temperature bellow 0ºC, affording the product in similar yield and enantioselectivity, but after longer reaction times (72 h) (Table 14, entry 8). Thus, **C28** was chosen as the optimal catalyst for the reaction of α-substituted β-tetralones with nitroalkenes (**32**).

Table 14. Study of the effect of temperature in the reaction between **49B** and **32a**[a]



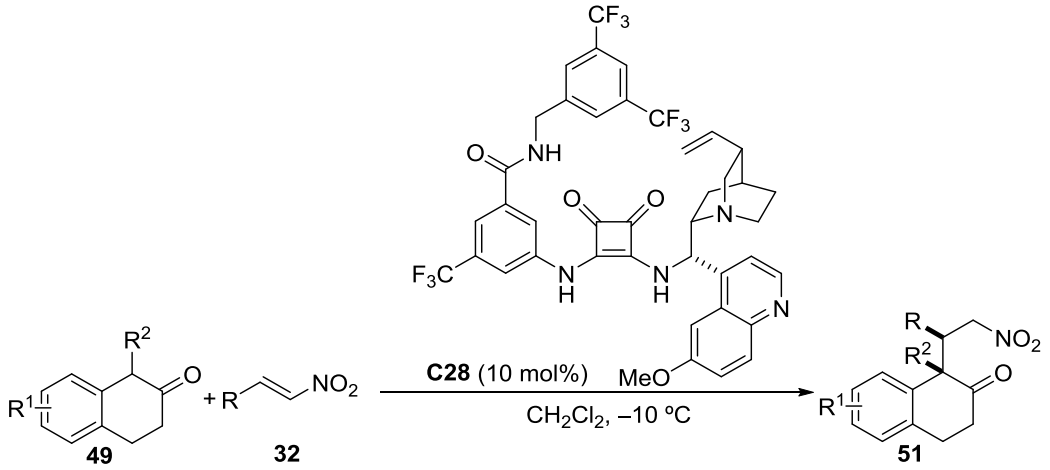
Entry	cat	T (ºC)	t (h)	Yield (%)[b]	*ee* (%)[c]
1	**C13**	15	6	85	76
2	**C13**	0	16	84	86
3	**C13**	–20	24	84	90
4	**C28**	15	16	93	80
5	**C28**	–10	24	82	90
6	**C32**	15	16	84	85
7	**C32**	0	24	86	89
8	**C32**	–10	72[d]	80	90

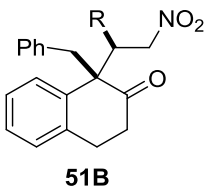
[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49B**/**32a**/cat molar ratio = 1:1.2:0.1). *dr* = >20:1 in all cases. [b] Yield after chromatography. [c] *ee* of major isomer, determined by chiral HPLC. [d] Low solubility of the catalyst.

With the optimized conditions in hand, the reaction of β-tetralone derivatives **49B-49D** with a set of nitroalkenes (**32)** was carried out following the next standard procedure: the donor was dissolved in CH_2Cl_2 (0.5 M) and 1.2 equivalents of the acceptor nitroalkene and 10 mol% of the catalyst **C28** were added. The reaction mixture was stirred at –10 ºC, and after verifying that the reaction finished (TLC monitoring, 16–64 h) the reaction mixture was submitted to flash column chromatography on silica gel eluting with hexane/EtOAc mixtures.

As the results in Table 15 show, the reaction proceeds smoothly for the differently substituted aromatic nitroalkenes (**32a-32d**) affording the corresponding adducts (**51Ba**–**51Bd**) in high selectivity (90–92% ee). Furthermore, heteroaromatic (**32h**) and aliphatic (**32i**) nitroalkenes afforded the corresponding adducts (**51Bh** and **51Bi**) with similarly good yield and enantioselectivity. α-Subsituted tetralones bearing additional functionality (**49C** and **49D**) were also successfully employed in the reaction with equally good yields and *ee* values (products **51Ce** and **51Df**). The reaction also tolerates β-tetralones bearing electron donating or withdrawing groups at the aromatic ring, which were equally efficient (adducts **51Fg**, **51Ga** and **51Hj**). Importantly, in every case no traces of products from the reaction at the α'-carbon atom were found, and the adducts were obtained essentially as a sole diastereomer. It must be noted that for the formation of some adducts (**51Ce**, **51Fg** and **51Ga**) in high yield the use of the more active catalyst **C13** was necessary.

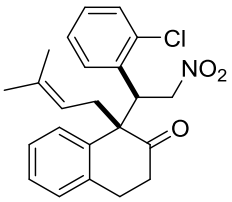
Table 15. Michael reaction scope between α-substituted β-tetralones and nitroalkenes[a]



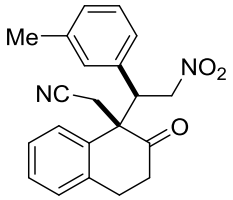


51B

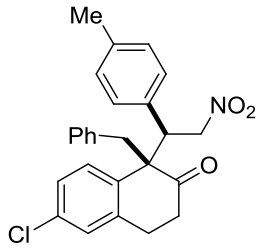
51Ba	R = C_6H_5	82% yield, 90% *ee*
51Bb	R = 4-$MeOC_6H_4$	82% yield, 91% *ee*
51Bc	R = 4-BrC_6H_4	85% yield, 91% *ee*
51Bd	R = 3-$MeOC_6H_4$	80% yield, 91% *ee*[b]
51Bh	R = 2-Furyl	60% yield, 92% *ee*[b]
51Bi	R = $CH_3(CH_2)_2$	72% yield, 88% *ee*



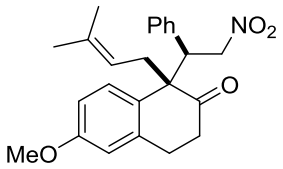
51Ce, 80% yield, 99% *ee*[c]



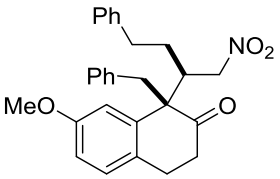
51Df 78% yield, 91% *ee*



51Fg, 84% yield, 90% *ee*[c]



51Ga, 79% yield, 98% *ee*[d]



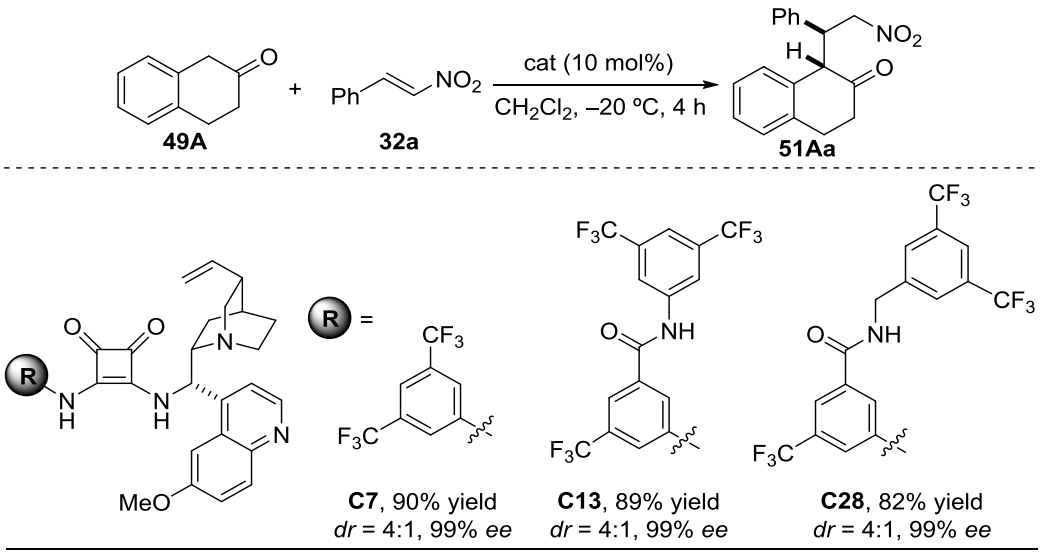
51Hj, 81% yield, 90% *ee*

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49**/**32**/**C28** molar ratio = 1:1.2:0.1). Yield of isolated product after chromatography. *dr* = >20:1 in all cases. *ee* determined by chiral HPLC. [b] Reaction conducted at –20 ºC. [c] Reaction conducted at –20 ºC with catalyst **C13**. [d] Reaction conducted at RT with catalyst **C13**.

In light of the good results obtained with α-substituted β-tetralones, the behaviour of the parent α-unsubstituted β-tetralone **49A** was investigated under similar reaction conditions. A selection of bifunctional Brønsted base catalysts bearing the squaramide functional unit (**C7**, **C13** and **C28**) were tested in the reaction of **49A** with nitrostyrene (**32a**) (Table 16). In all the cases the desired adduct **51Aa** with a tertiary stereocenter at C_α was obtained in high yield, good diastereoselectivity and almost

perfect enantioselectivity. Importantly, no α,α-double addition or α'-addition adducts were observed in any of the cases.

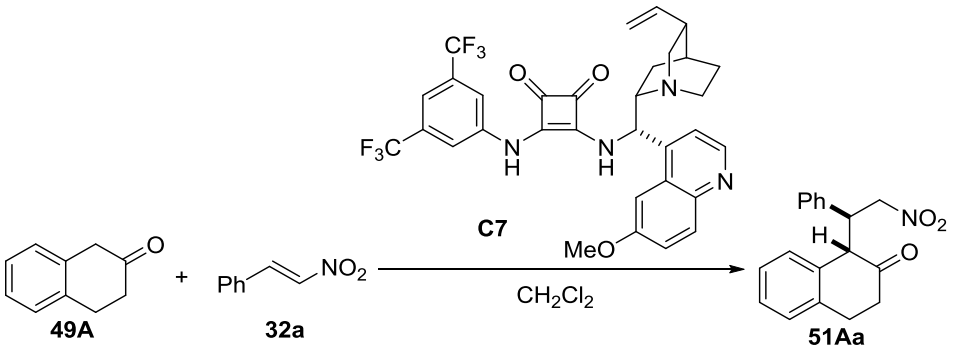
Table 16. Catalyst screening for the reaction between **35A** and **34a**[a]



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49A**/**32a**/cat molar ratio = 1:1.2: 0.1). Yield of isolated product after chromatography. *dr* determined by ^{1}H NMR spectroscopy. *ee* determined by chiral HPLC.

Next, the effect of temperature and the **C7** loading in the reaction of **49A** with nitrostyrene (**32a**) were examined (Table 17). Almost perfect enantioselectivity was obtained at 0, –20 and –40 ºC (Table 17, entries 1, 2 and 4, respectively), but higher temperatures (Table 17, entry 1) and prolonged reaction times (Table 17, entries 3 and 4) were detrimental for the diastereomeric ratio, likely due to the tendency of the adduct to further deprotonate in the presence of the catalyst, resulting in epimerization. Furthermore, reactions with 5, 2 and 1 mol% **C7** loadings afforded adduct **51Aa** in equally good results (entries 5, 6 and 7, respectively).

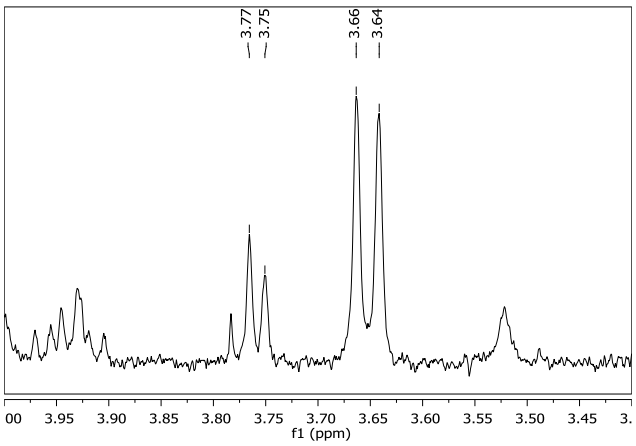
Table 17. Study of the effect of temperature in the reaction between **49A** and **32a** catalyzed by **C7**[a]



Entry	**C7** (mol%)	T (ºC)	t (h)	Yield (%)[b]	*dr* (%)[c]	*ee* (%)[d]
1	10	15	1	74	1:1	99
2	10	–20	2	85	4:1	99
3	10	–20	8	81	1:1	99
4	10	–40	16	75	2:1	99
5	5	–20	4	82	4:1	99
6	2	–20	8	83	4:1	99
7	1	–20	16	82	4:1	98

[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49A**/**32a** molar ratio = 1:1.2). [b] Combined yield of isomers after chromatography. [c] Determined by ^{1}H NMR spectroscopy of an untreated reaction sample and confirmed by HPLC. [d] *ee* determined by chiral HPLC, same for both isomers.

The diastereomeric ratio was determined by ^{1}H NMR (300 MHz) analysis of the reaction crude (Figure 9) comparing the peak areas of the protons at C_α of adduct **51Aa** (3.76 ppm for minor and 3.65 ppm for major).



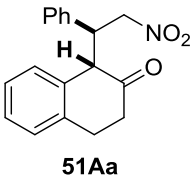
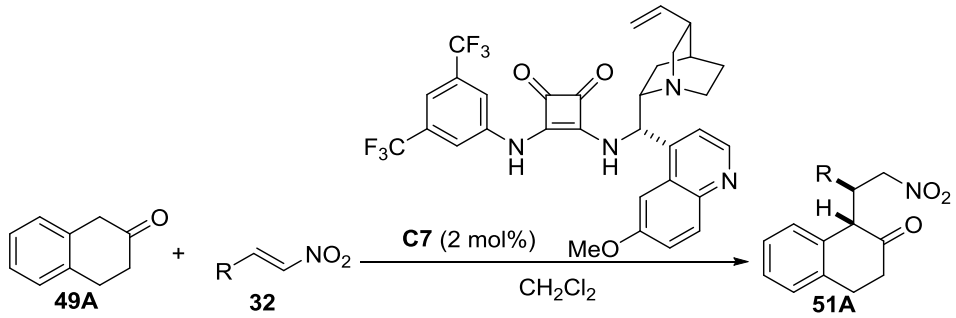


Figure 9.

Once the optimized conditions were found, the reaction of β-tetralone **49A** with nitroalkenes **(32)** was carried out following the next standard procedure: the donor was dissolved in CH_2Cl_2 (0.5 M) and 1.2 equivalents of the acceptor nitroalkene and 2 mol% of the catalyst **C7** were added. The reaction mixture was stirred at –20 ºC for the aromatic nitroalkenes, and at room temperature for the aliphatic ones. After verifying that the reaction finished (TLC monitoring, 8–24 h) the reaction mixture was submitted to flash column chromatography, isolating the corresponding adduct **51A** as a mixture of diastereomers.

As results in Table 18 show, the reaction was again found to be completely regioselective for all the nitroalkenes tested. Furthermore, the corresponding Michael addition products **51A** were obtained from both aryl- (**51Aa-51Ae**) and alky-substituted (**51Ai-51Aj**) nitroalkenes in high yield and in excellent enantioselectivity. Furthermore, diastereoselectivity was good (4:1 or higher) with the only exception of the 2-furyl substituted nitroalkene **32h**, which afforded a 1:1 diastereomeric mixture (entry 6). The reaction was also scaled up to a 2 mmol scale for adduct **51Aa** obtaining equally good results (entry 10).

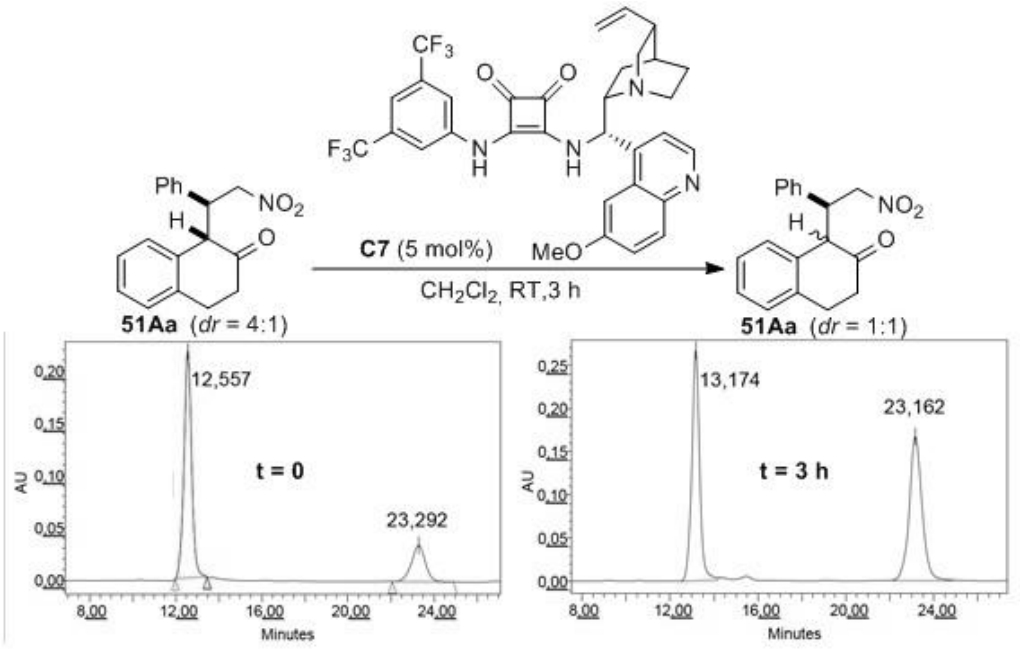
Table 18. Michael reaction scope between β-tetralone **49A** and nitroalkenes[a]



Entry	Product	R	T (ºC)	t (h)	Yield (%)[b]	*dr* (%)[c]	*ee* (%)[d]
1	**51Aa**	Ph	–20	8	83	4:1	99
2	**51Ab**	4-$MeOC_6H_4$	–20	8	85	8:1	99
3	**51Ac**	4-BrC_6H_4	–20	8	88	4:1	99
4	**51Ad**	3-$MeOC_6H_4$	–20	8	80	4:1	99
5	**51Ae**	2-ClC_6H_4	–20	8	84	>20:1	99
6	**51Ah**	2-furyl	–20	8	86	1:1	98
7	**51Ai**	$CH_3(CH_2)_2$	RT	16	81	5:1	99
8	**51Aj**	$Ph(CH_2)_2$	RT	16	83	5:1	99
9	**51Ak**	C_6H_{11}	RT	24	80	4:1	99
10	**51Aa**	Ph	–20	8	83	4:1	98[e]

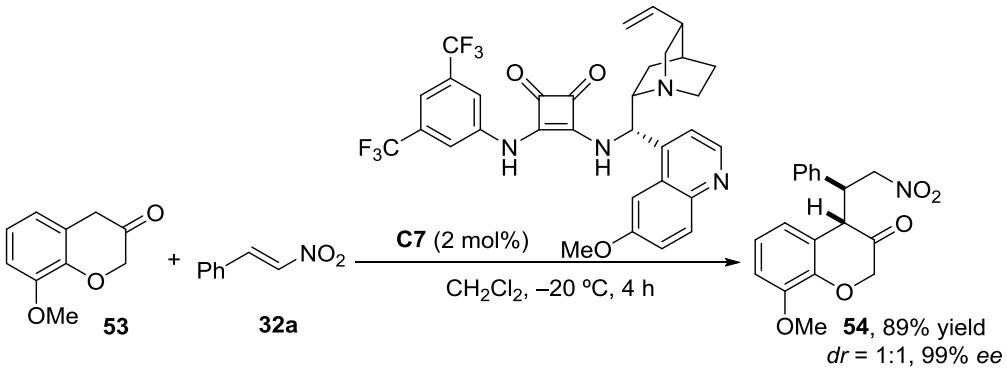
[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49A**/**32**/**C7** molar ratio = 1:1.2:0.02). [b] Combined yield of isomers after chromatography. [c] Determined by ^{1}H NMR spectroscopy of an untreated reaction sample. [d] *ee* determined by chiral HPLC, same for both isomers. [e] Reaction conducted at a 2 mmol scale.

Control experiments were carried out to study the tendency of adducts **51A** towards epimerization. Thus, when compound **51Aa** (*dr* = 4:1) was exposed to 5 mol% of **C7** at room temperature in dichloromethane for 3 h an equimolar mixture of diastereomers was obtained, as could be monitored by HPLC (Scheme 45). However, in the absence of **C7**, no epimerization was observed, even after 24 h at 80 ºC.



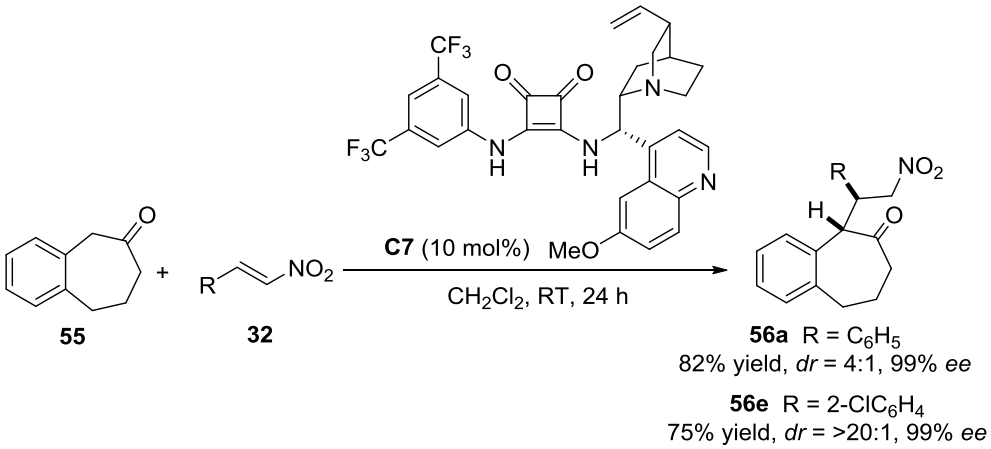
Scheme 45.

Later, the suitability of this method for the site- and stereoselective α-functionalization of related ketone substrates was investigated. Indeed, the aromatic ring-fused cycloalkanone **53** with an oxygen heteroatom in the cycle was equally competent undergoing the regioselective Michael addition under described catalytic conditions (Scheme 46). The desired adduct **54** was obtained in high yield and excellent enantioselectivity as a 1:1 diastereomeric mixture. The diastereoselective formation of the product **54** was observed when lowering the reaction temperature to –60 ºC, but upon flash column chromatography on silica gel the 1:1 mixture was again obtained.



Scheme 46.

Cycloalkanone **55**, with a 7-membered ring, was also found suitable for the reaction although it needed to be conducted at room temperature and with a 10 mol% catalyst loading (Scheme 47). The corresponding adducts were obtained in good yield, good diastereoselectivity (4:1 or higher) and excellent enantioselectivity. Again, no double addition nor α'-addition products were observed.

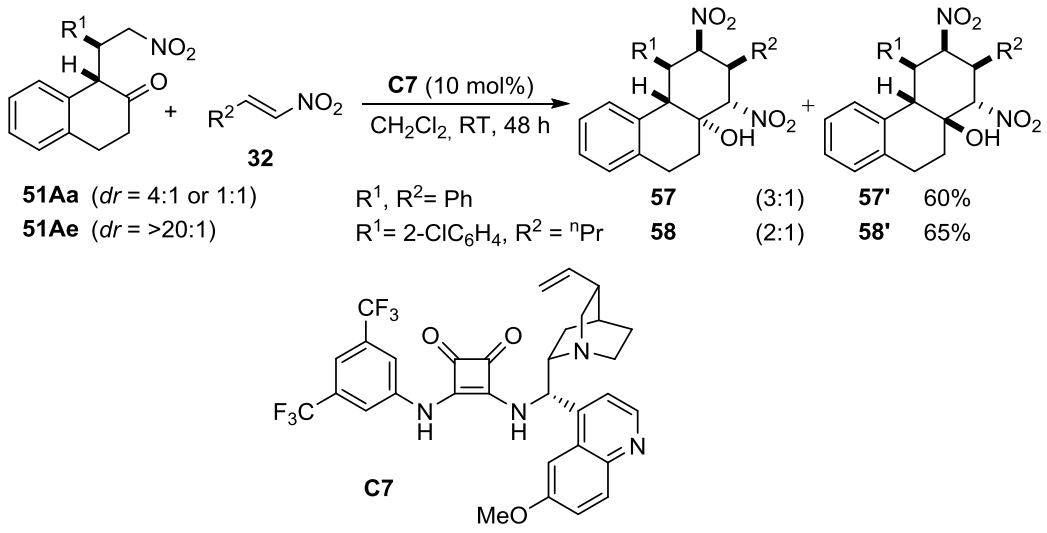


Scheme 47.

3.3.3.2. Elaboration of adducts

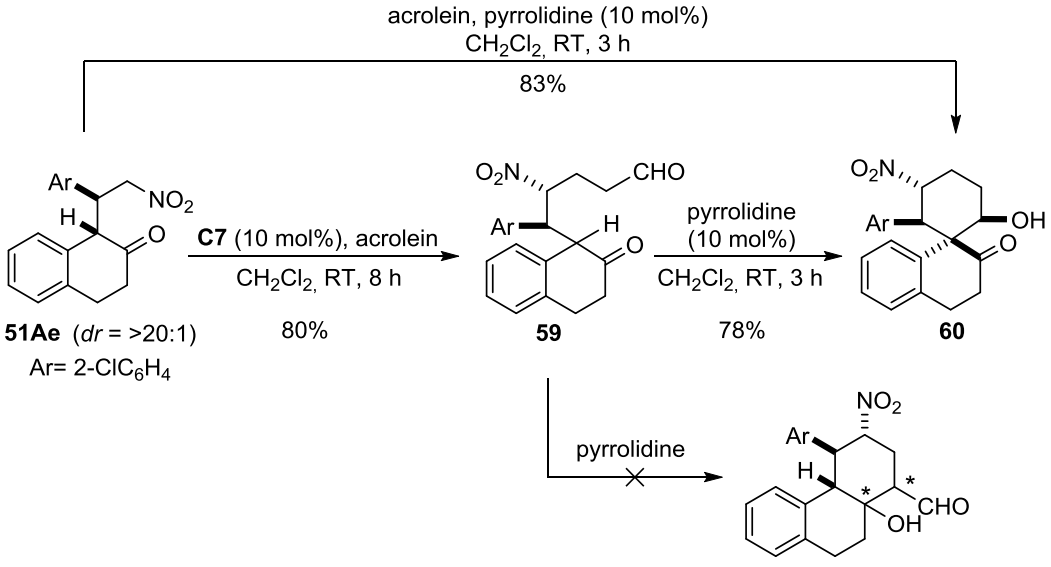
Once an efficient and highly regio- and stereoselective procedure for the Michael addition of β-tetralones to nitroalkenes was obtained, some possibilities for the transformation of the adducts into more complex polycyclic structures were explored.

First, adducts **51Aa** and **51Ae** were reacted with nitroalkenes **32a** and **32i**, respectively, in the presence of 10 mol% **C7**, as shown in Scheme 48. As a result, the tricyclic systems **57**/**57'** and **58**/**58'** were obtained in moderate combined yield. Remarkably, with this procedure only two out of the possible 64 stereoisomers are obtained. Furthermore, no cyclization product derived from the minor isomer of **51A** was observed in neither of the cases, and the isomeric composition of the isolated product was found to be independent of the initial mixture of **51A**. These results suggest that formation of the tricycles through a Michael/Henry cascade reaction involves some kinetic resolution process.



Scheme 48.

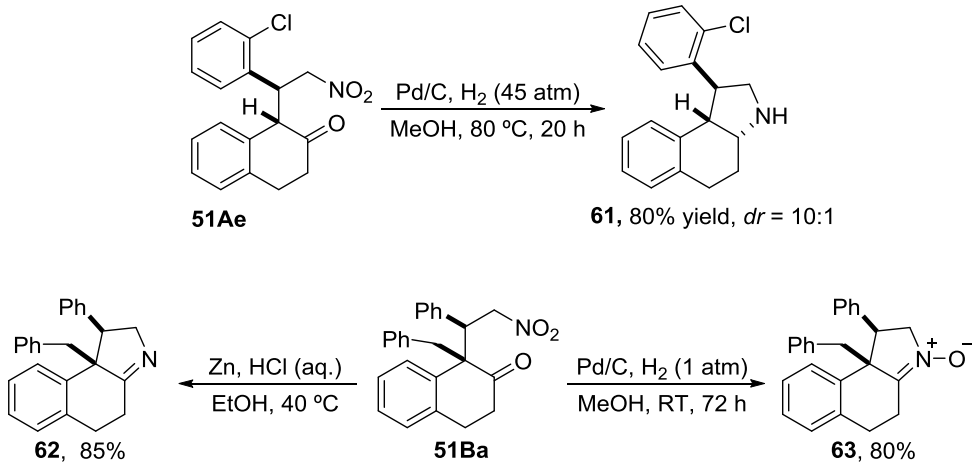
When **51Ae** was treated with acrolein in the presence of **C7** at room temperature, the Michael addition product **59** was isolated. Then, the aldol-reaction-mediated cyclization to **60** was achieved employing 10 mol% pyrrolidine. Otherwise, direct transformation of **51Ae** to the spirocyclic aldol **60** could also be achieved by treatment with acrolein in the presence of 10 mol% pyrrolidine. Both ways **60** was produced as essentially a single diastereomer. It should be noted that the course of the reaction is quite unexpected, taking into account that cycloalkanones under similar reaction conditions have been reported to afford substituted decalins instead.[190]



Scheme 49.

[190] S. Anwar, H.-J. Chang, K. Chen, *Org. Lett.* **2011**, *13*, 2200–2203.

Moreover, the reduction of adducts **51** afforded in very good yield hexahydrobenzo[*e*]indoles, heterocyclic cores present in many biologically active compounds (Scheme 50).[191] For instance, reduction of the adduct **51Ae** with H_2/Pd provided amine **61** in a highly selective manner. On the other hand, adduct **51Ba** was also reduced with either Zn/H^+ or H_2/Pd, providing imine **62** and imine *N*-oxide **63**, respectively.

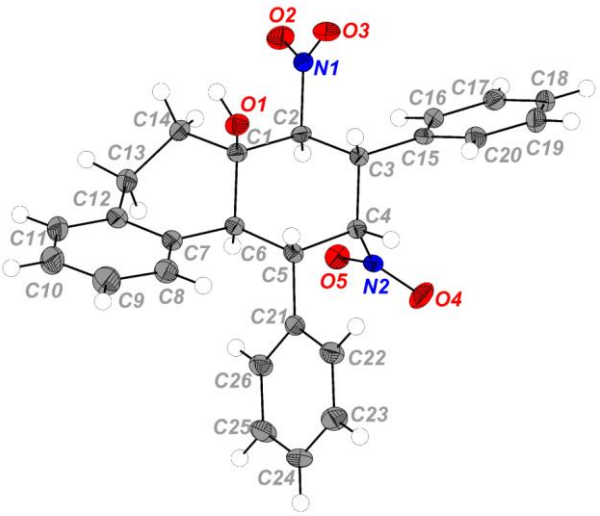


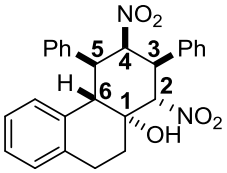
Scheme 50.

3.3.3.3. Determination of the absolute configuration

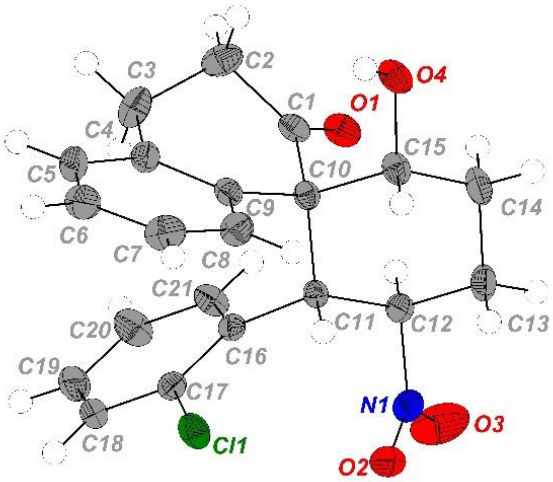
The absolute configuration of compounds **57**, **60** and **63** was established by a single crystal X-ray analysis and for the remaining compounds derived from β-tetralones and related cyclic ketones was assumed based on a uniform reaction mechanism. The ORTEP diagrams of the molecules are shown in Figure 10.

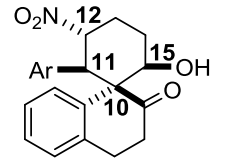
[191] C. H. Lin, S. R. Haadsma-Svensson, G. Phillips, R. B. McCall, M. F. Piercey, M. W. Smith, K. Svensson, A. Carlsson, C. G. Chidester, P. F. Von Voigtlander, *J. Med. Chem.* **1993**, *36*, 2208–2218.



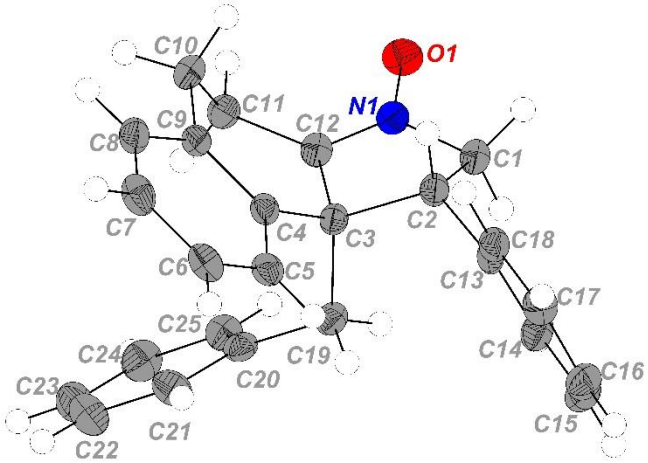


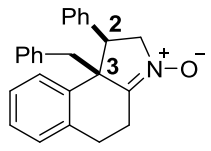
57 (1*R*, 2*S*, 3*R*, 4*R*, 5*S*, 6*S*)





60 (10*S*, 11*R*, 12*R*, 15*R*)



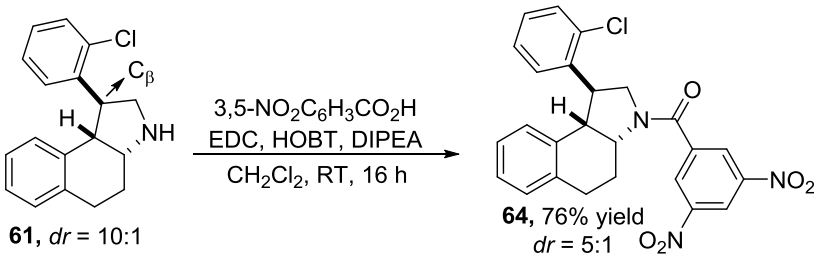


63 (2*R*, 3*S*)

Figure 10.

Knowing the configuration of the C_β, the absolute configuration of **61** was established by a NOESY analysis of its amide derivative **64** (Scheme 51). Irradiation at

3.80 ppm (H^2) (Figure 11) revealed the proximity of H^1 (NOESY >2%), indicating that both protons are on the same side of the pyrrolidine ring. On the other hand, only a small signal from H^3 was detected (<0.5%), thus indicating that H^2 and H^3 are on opposite sides of the pyrrolidine ring. Therefore, the configuration of the molecule was assigned as (1*R*, 2*S*, 3*S*).



Scheme 51.

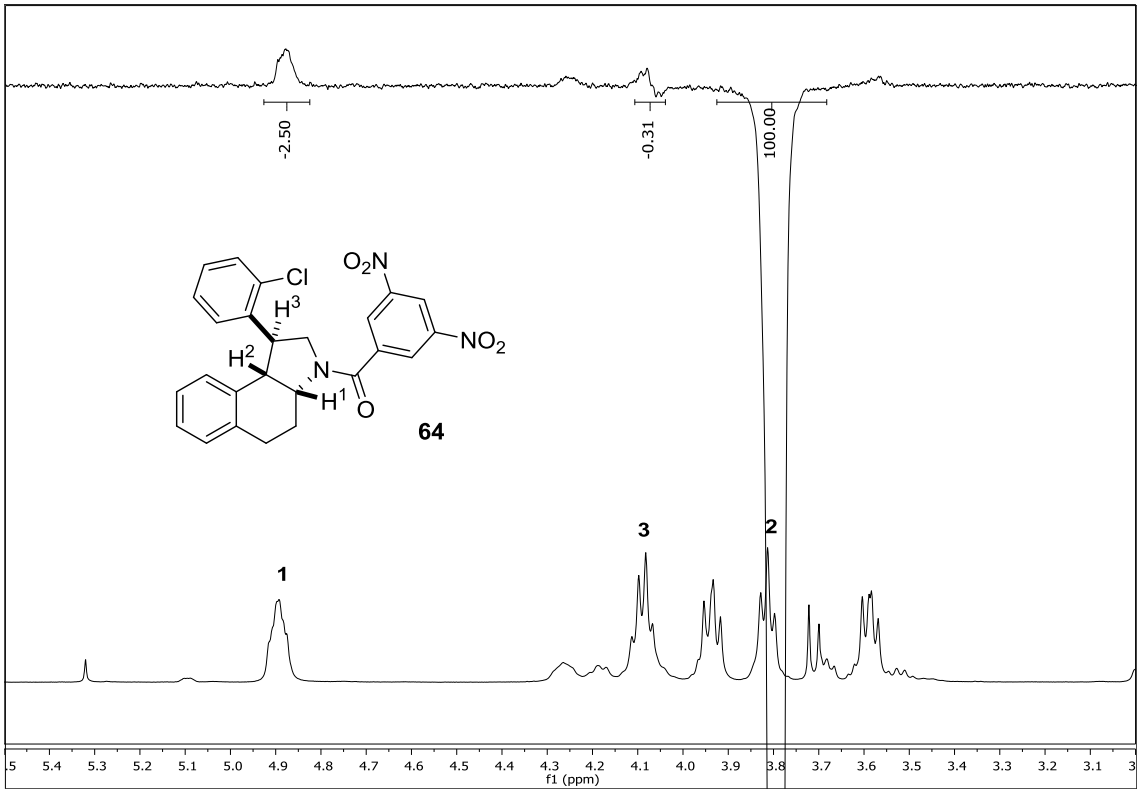


Figure 11.

On the other hand, the configuration of **57'** was established by a NOESY analysis, and for product **58'** was assumed based on a uniform reaction mechanism. Irradiation at 3.82 ppm (H^5) (Figure 12) revealed the proximity of H^3 and H^4 (NOESY >1.5%), indicating that both protons are on the same side of the ring. On the other hand, H^1, H^2 and H^6, gave almost no signal (<0.30%), thus suggesting that these protons are

on the other side. Therefore, the configuration of the molecule was deduced to be (1*S*, 2*S*, 3*R*, 4*R*, 5*S*, 6*S*).

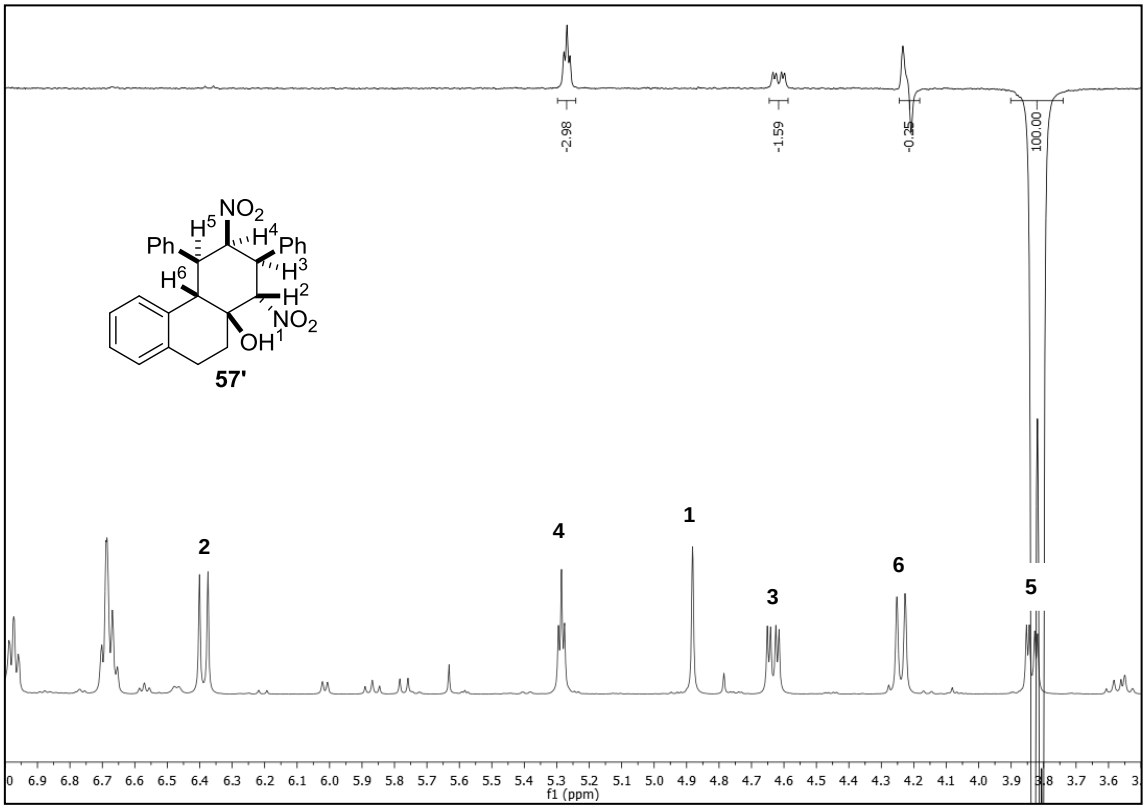


Figure 12.

3.3.4. α-Amination of β-tetralone derivatives

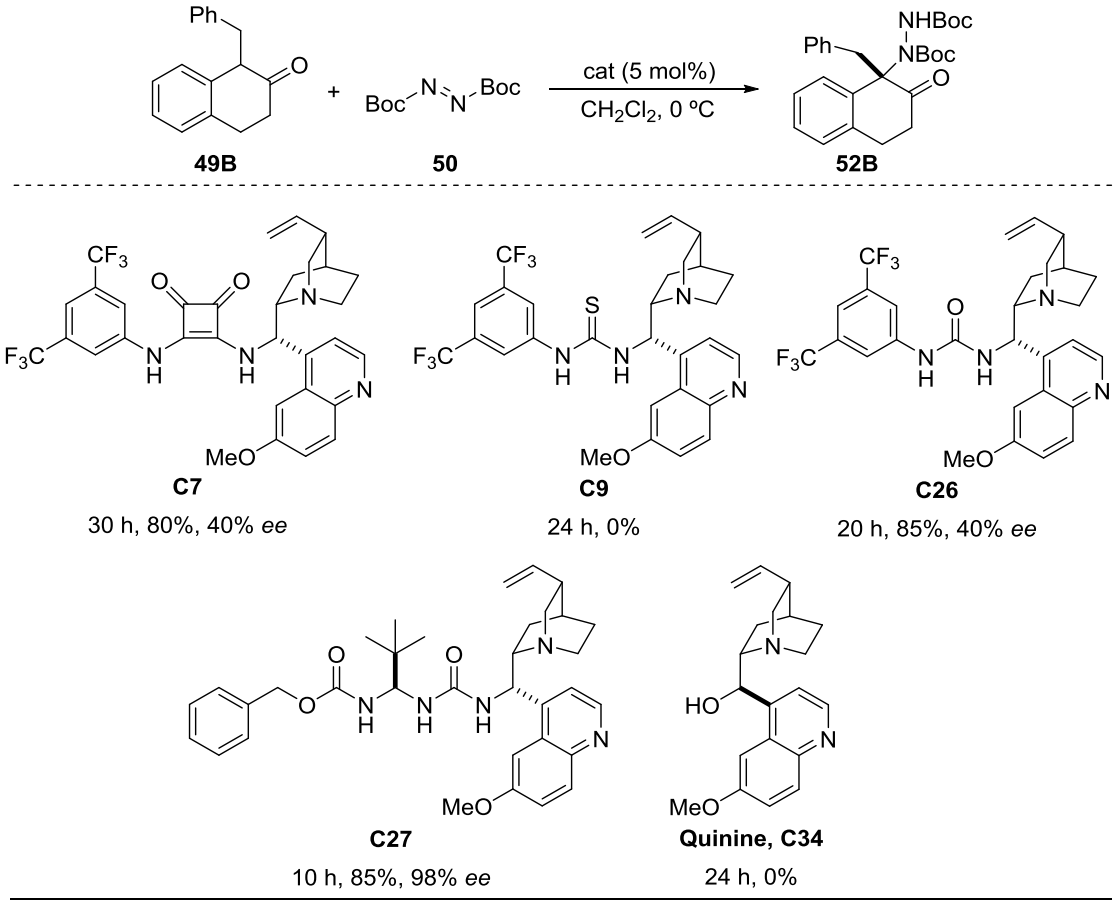
Given these results, we decided to further extend the regioselective functionalizaiton of β-tetralones. Thus, we explored the behaviour of β-tetralones in the amination reaction using azodicarboxylates as acceptors under similar reaction conditions.

3.3.4.1. Catalyst screening

Initially the reaction between β-tetralone **49B** and di-*tert*-butyl azodicarboxylate (**50**) was taken as a model to find the optimum Brønsted base catalyst for the reaction to afford α-amino β-tetralones in a stereoselective manner (Table 19). We began by comparing catalysts **C7**, **C9** and **C26** in order to determine the most suited *H*-bond donor group for the reaction. In a first run, reaction with squaramide catalyst **C7**[154a] afforded the desired adduct **52B** in complete regioselectivity and good yield, but low stereoselectivity. Unexpectedly, using the parent thiourea **C9**[155] no addition product was

observed even after 24 h. The use of urea **C26**[179] in the reaction allowed to shorten the reaction times, but low enantioselectivity was obtained. On the other hand, when ureidopeptide **C27**[180] was employed the reaction finished in only 10 h and in excellent stereoselectivity. Finally, no reaction was observed when quinine (**C34**) was used as the catalyst.

Table 19. Catalyst screening for the reaction between **49B** and **50**[a]



[a] Reactions conducted on a 0.30 mmol scale in 0.6 mL of CH_2Cl_2 (**49B**/**50**/cat molar ratio = 1:2: 0.05). Yield of isolated product after chromatography. *ee* determined by chiral HPLC.

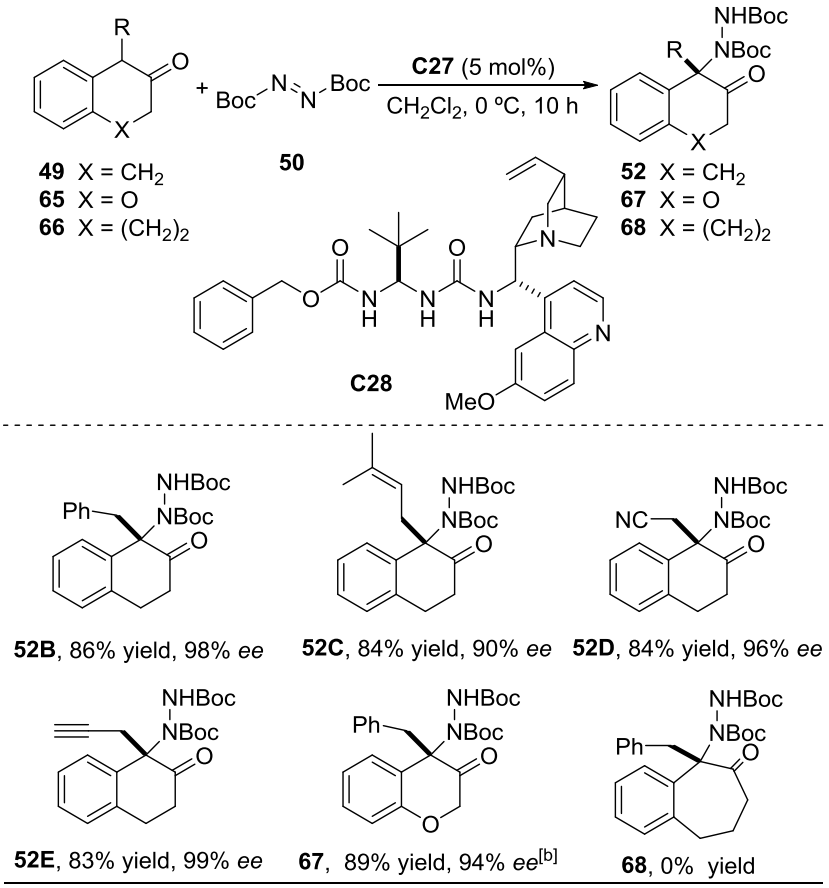
3.3.4.2. Reaction scope

The study of the generality of the method was addressed by carrying out the reaction of β-tetralones **49B**-**49E** and related ketone substrates **65** and **66** with **50**. As standard reaction conditions, the ketone was dissolved in CH_2Cl_2 (0.5 M) and 2.0 equivalents of **50** and 5 mol% of the catalyst **C27** were added. The reaction mixture was stirred at 0 ºC, and after verifying that the reaction finished (TLC monitoring, 10 h), the

mixture was submitted to flash column chromatography on silica gel eluting with hexane/EtOAc mixtures.

As the results in Table 20 show, the reaction proceeded in good yield and excellent enantioselectivity with a variety of α-substituted β-tetralones (adducts **52B-52E**). Furthermore, the aromatic ring-fused cycloalkanone **67** with an oxygen heteroatom in the cycle was equally competent undergoing the amination reaction, although lower temperatures were needed in order to obtain good stereocontrol due to the higher reactivity of the nucleophile as compared to β-tetralones. On the other hand, reaction with the 7-membered ring cycloalkanone **66** did not happen, even after 24 h at room temperature. Importantly, no addition at the α'-carbon was observed in any of the cases.

Table 20. α-Amination reaction of β-tetralones and related ketone substrates[a]



[a] Reactions conducted on a 0.15 mmol scale in 0.3 mL of CH_2Cl_2 (donor/**50**/**C27** molar ratio = 1:2:0.05). Yield of isolated product after chromatography. *ee* determined by chiral HPLC. [b] Reaction conducted at –60 ºC.

3.4. Conclusions

In summary, the highly stereoselective generation of tetrasubstituted carbon stereocenters at C_α of several enolizable carbonyl compounds has been realized via bifunctional Brønsted base-catalyzed Michael reaction.

On the one hand the addition of oxazolones with differently substituted α'-oxy enones as key enoate surrogates has been preformed and it was demonstrated that the resulting α'-oxy ketone adducts can be smoothly converted into the corresponding carboxylic acid through simple oxidative cleavage of the ketol unit.

In addition, a set of novel catalysts were developed for the 1,6-addition reaction of oxazolones and cyanoacetates to α'-oxy dienones, obtaining the desired adducts in good yield and virtually perfect regioselectivity using chiral guanidines as catalysts. Unfortunately, low enantioselectivity was obtained in all cases.

On the other hand, the asymmetric Brønsted base-catalyzed regio-, diastereo- and enantioselective functionalization of cyclic unactivated ketones (not bearing a strongly EWG at α-carbon) has been studied. In this context, the α-functionalization of cyclic α-alkenyl ketones was achieved in a highly diastereo- and enantioselective manner and with complete regioselectivity, leading to the formation of quaternary carbon stereocenters at C_α. Furthermore, some possibilities for the transformation of these adducts were explored.

Moreover, the method was successfully extended to the α-functionalization of β-tetralone derivatives. Once again the reaction proceeded with complete regioselectivity, obtaining exclusively the α-substitution adducts in high diastereo- and enantioselectivity, and leading to the formation of either a tri- or tetrasubstituted stereogenic carbon atom. In addition, the synthetic utility of the method was demonstrated by easy transformation of adducts into diverse polycyclic compounds featuring up to six contiguous stereogenic centers.

Chapter 4:

Synthesis of arogenate by dearomatising cyclisation of a L-tyrosine derivative

4. Synthesis of arogenate by dearomatising cyclisation of a L-tyrosine derivative

Synthesis of arogenate by dearomatising cyclisation of a L-tyrosine derivative

4.1. Arogenate: Origin, structure and interest

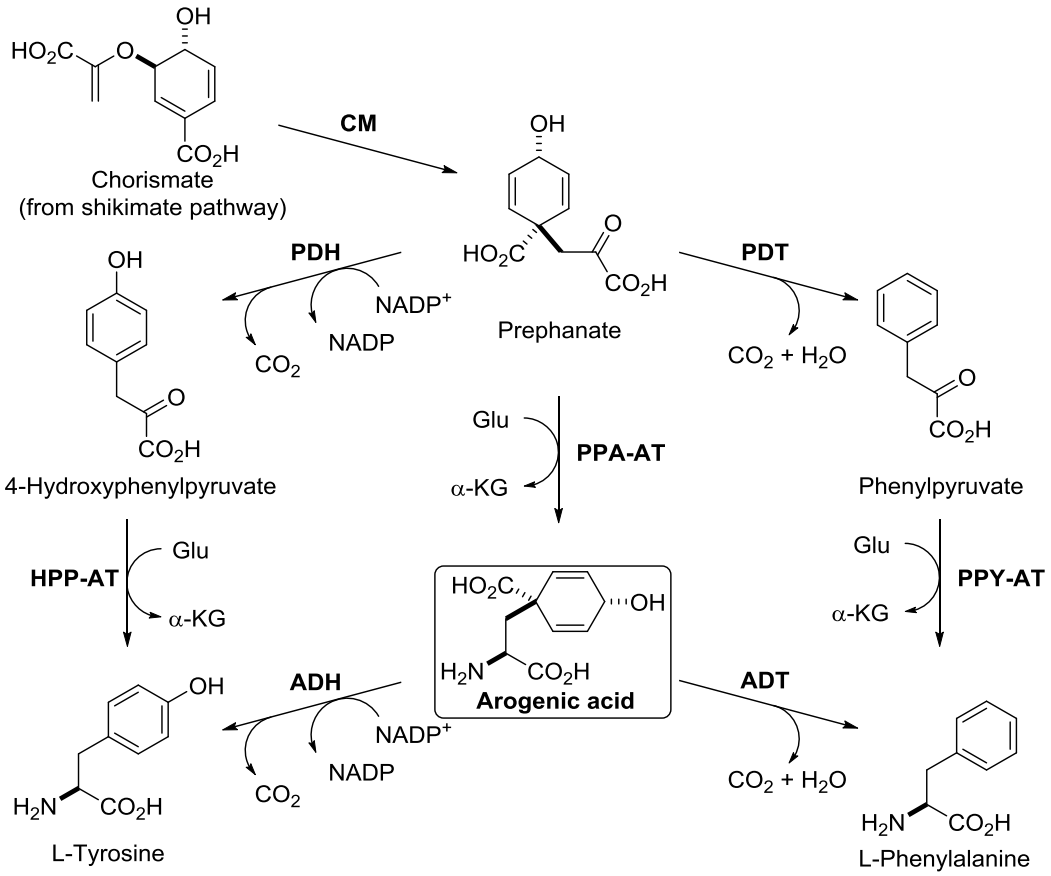
Arogenate [L-(8*S*)-β-(carboxy-4-hydroxy-2,5-cyclohexadien-1-yl)alanine]$^{2-}$ is a precursor in the biosynthesis of aromatic amino acids (AAA) in some microorganisms[192] and plants.[193] Although it is an immediate precursor of L-phenylalanine and L-tyrosine in the shikimate pathway, organisms can alternatively obtain these amino acids through the phenylpyruvate route, as shown in Scheme 1.[194]

Unlike in plants, pathways for the synthesis of AAA are inexistent in animals, and therefore enzymes involved in their biosynthesis are usual targets for the development of safe herbicides. Indeed, depending on the exact plant species, either one or both arogenate and phenylpyruvate routes are used to produce AAA, and thus this metabolic diversity might provide a source for discriminative herbicides through the selective inhibition of one of the pathways. In this context, herbicides structurally related to arogenate could inhibit either arogenate dehydrogenase (ADH) or arogenate dehydratase (ADT) (Scheme 1).

[192] Selected examples: S. L. Stenmark, D. L. Pierson, G. I. Glover, R. A. Jensen, *Nature (London)* **1974**, *247*, 290–292. b) S. L. Stenmark, D. L. Pierson, G. I. Glover, R. A. Jensen, *Nature (London)* **1974**, *254*, 667–671. c) A. M. Fazel, R. A. Jensen, *J. Bacteriol.* **1979**, *138*, 805–815. d) R. Borde, D. Birnbaum, *Biochem. Physiol. Pflanzen.* **1978**, *173*, 44–49.

[193] Selected examples: N. Patel, S. Stenmark-Cox, R. A. Jensen, *J. Biol. Chem.* **1978**, *253*, 2972–2978. b) E. Jung, L. O. Zamir, R. A Jensen, *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 7231–7245.

[194] H. Maeda, N. Dudareva, *Annu. Rev. Plant Biol.* **2012**, *63*, 73–105.



Scheme 1.

Arogenate presents a chirality axis located in the future aromatic ring in addition to the stereocenter at C_α of natural α-amino acids, making it a small but rather complex molecule. Furthermore, the free acid (arogenic acid; see Scheme 1) is highly unstable and it is quantitatively transformed into L-phenylalanine,[195] and arogenate salts are stable at pH 7.5 in the solid state, but decompose when exposed to heat or to a strong base.[196]

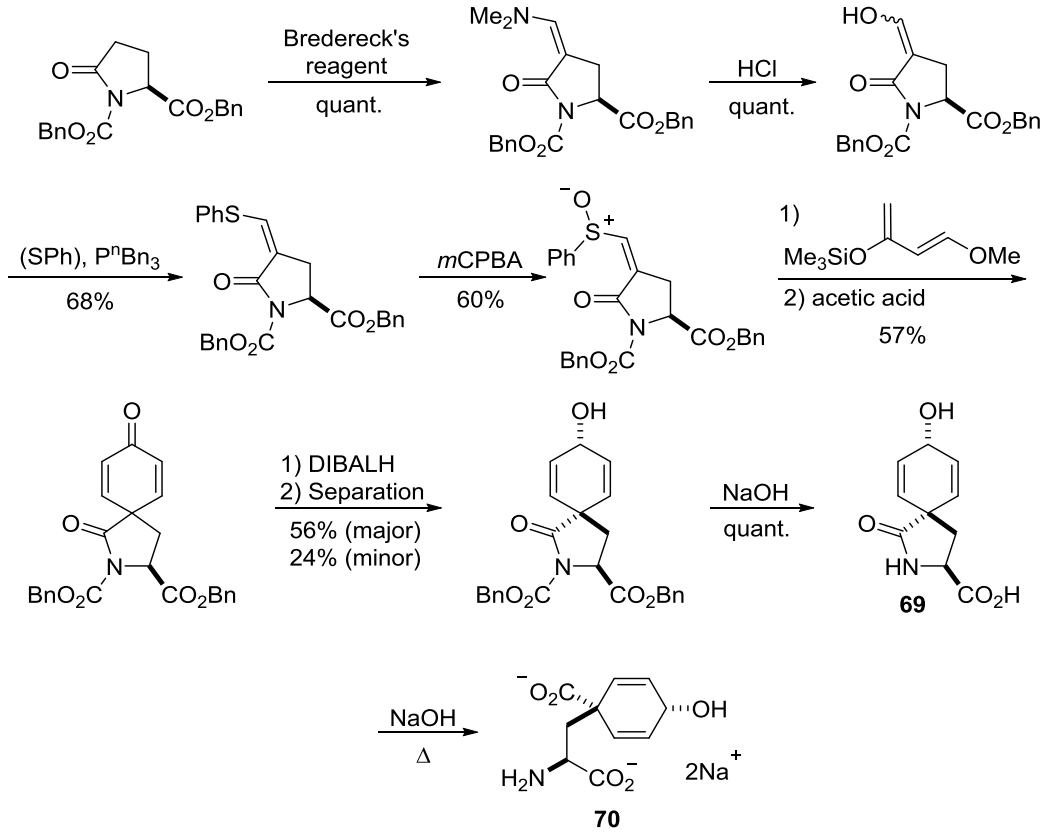
[195] L. O. Zamir, R. A. Jensen, B. H. Arison, A. W. Douglas, G. Albers-Schönberg, J. R. Bowen, *J. Am. Chem. Soc.* **1980**, *102*, 4499–4504.

[196] M. J. Crossley, R. C. Reid, *J. Chem. Soc., Chem. Commun.* **1994**, 2237–2238.

4.2. Previous approaches towards the synthesis of arogenate

In light of the precarious stability of arogenate along with its difficult isolation from natural sources,[195] a total synthesis seems to be a more appropriate alternative for the obtainment of arogenate and its structural analogues. Surprisingly, however, arogenate has received little synthetic attention, with only two published syntheses.

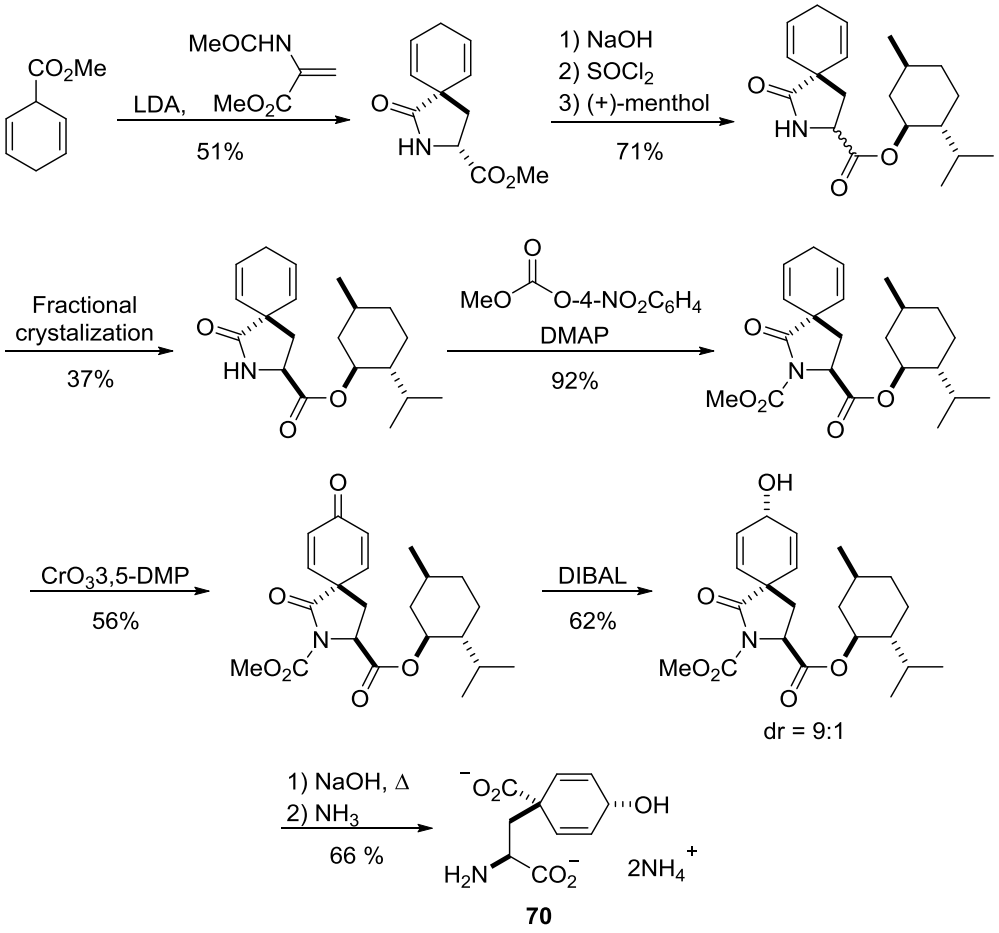
In 1981 Danishefsky and coworkers[197] described the first total synthesis of arogenate starting from a glutamic acid derivative in 8 steps, via a key Diels-Alder reaction (Scheme 2). However, the yield of the final step was not reported.



Scheme 2.

On the other hand, Crossley and Reid[196] performed its synthesis in 7 steps in an overall 2.8% yield from methyl 2,5-diene-1-carboxylate through a key Michael addition and resolution (Scheme 3).

[197] S. Danishefsky, J. Morris, L. A. Clizbe, *J. Am. Chem. Soc.* **1981**, *103*, 1602–1604.



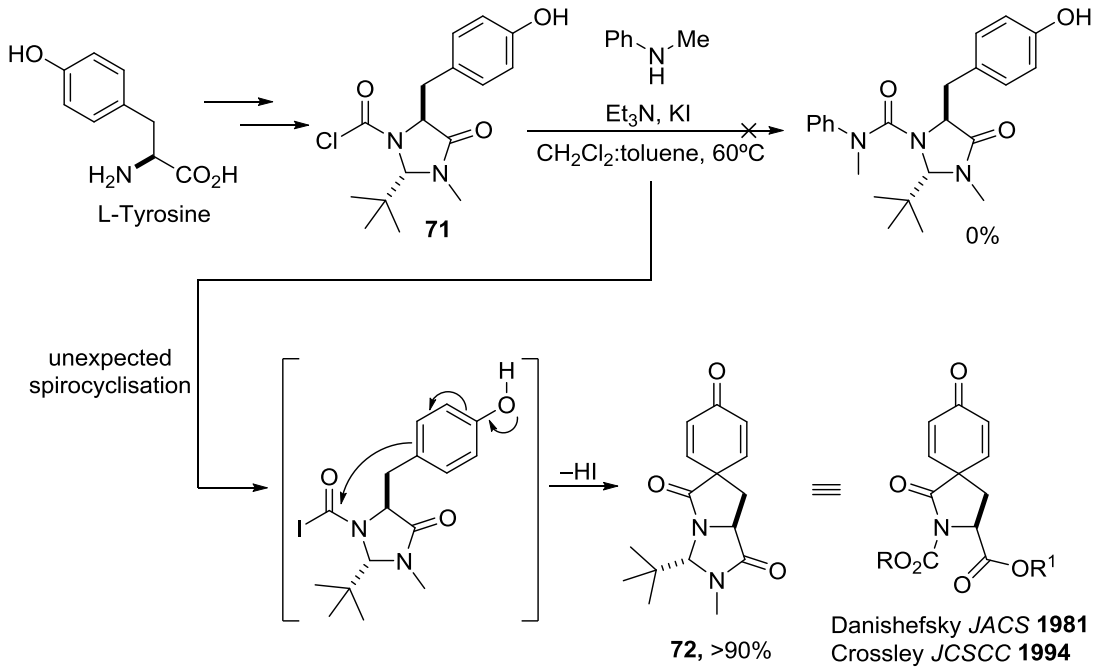
Scheme 3.

In both approaches, the diastereoselective reduction of a cyclohexadienone spyrolactam intermediate is the key step for the formation of the chirality axis of the cyclohexadiene ring present in arogenate, and in both cases a mixture of diastereomers is formed.

Surprisingly, neither of these syntheses employ the obvious starting material to arogenate: tyrosine itself.

4.3. Group precedents and objectives

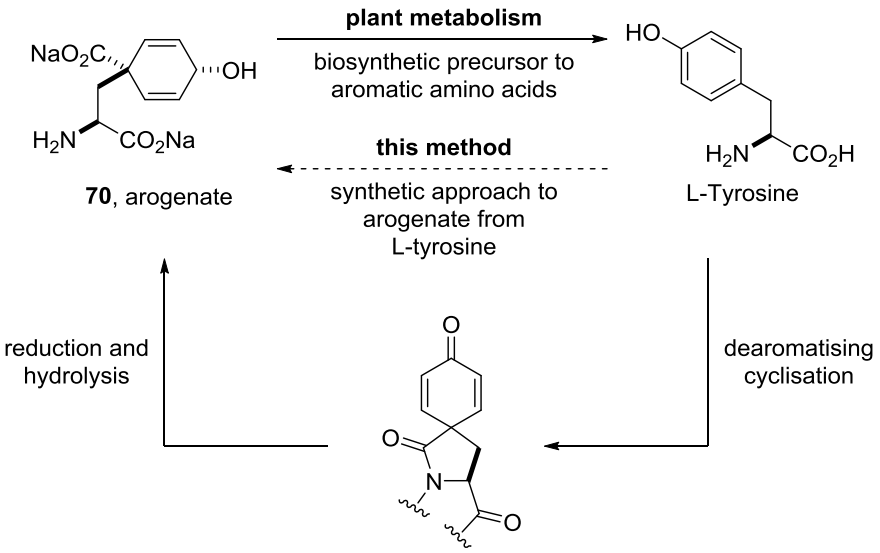
Previous work in the Clayden group in the context of another project involving a development of Seebach's self-regeneration of stereocenters[198] explored the coupling of tyrosine-derived carbamoyl chloride **71** with *N*-methylaniline to form the corresponding urea. However, the alternative spirocyclic imidazolidinone **72** was obtained in high yield instead (Scheme 4). The intramolecular nucleophilic dearomatizing spirocyclisation reaction seemingly proceeds through the formation of a carbamoyl iodide intermediate, as low yield was obtained in the absence of the iodine salt. The spirocyclisation of the diastereomeric isomer of **71** was also attempted but no reaction was observed, most probably because the steric hindrance of the *tert*-butyl group avoided the approach of the phenol ring to the carbamoyl group.



Scheme 4.

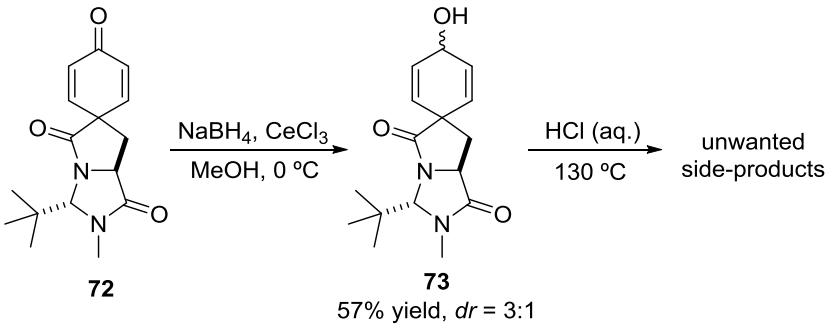
Compound **72** is structurally closely related to the spirocyclic lactam intermediates described in the previously reported synthetic methods (see Scheme 2 and Scheme 3), and therefore it was thought that the dearomatising spirocyclisation reaction may open a pathway for the synthesis of arogenate and related compounds from the natural amino acid L-tyrosine, inverting the biological path for AAA metabolism (Scheme 5).

[198] For a review see: D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748.



Scheme 5.

The Luche reduction of compound **72** was performed before this stay, affording a 3:1 diastereomeric mixture of alcohol **73** in moderate yield (Scheme 6). Unfortunately, attempts to hydrolyse the three C–N bonds in the product under acid conditions without compromising the integrity of the fragile cyclohexadienone to afford arogenate were unsuccessful.



Scheme 6.

In light of this result, alternative synthetic pathways were proposed involving alternative heterocyclic structures, namely oxazolidinone and hydantoin, that may make feasible the use of milder hydrolysis conditions leading to arogenate (Figure 1).

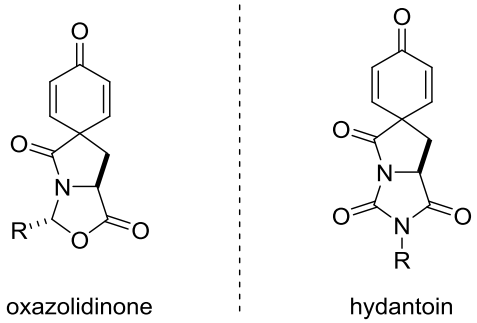
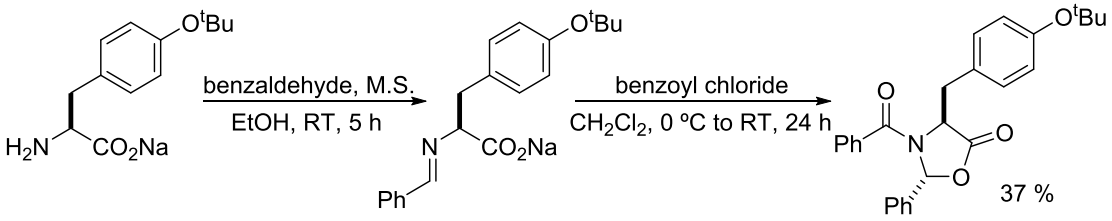


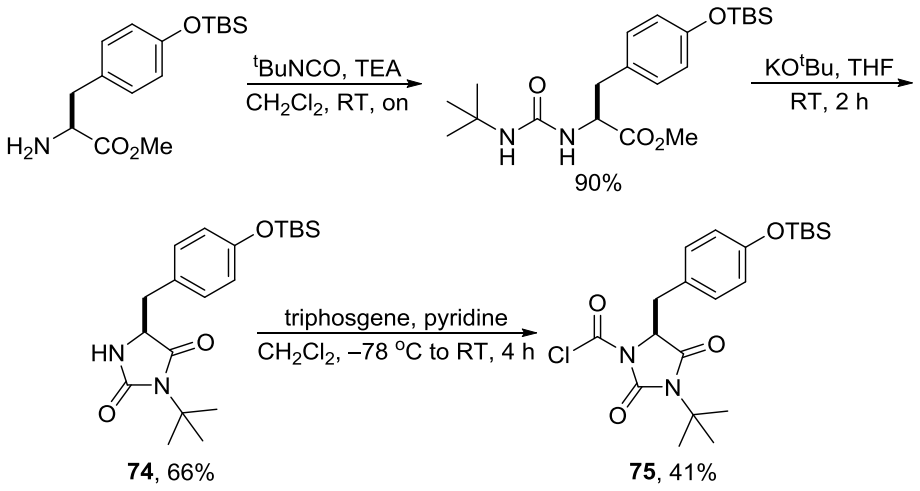
Figure 1.

A preparatory work on the formation of the oxazolidinone structure from L-tyrosine was carried out in the Clayden group by L. Eagling (Scheme 7). *O-tert*-Butyl-L-tyrosine was condensed with benzaldehyde forming the imine, which upon reaction with benzoyl chloride afforded the *N*-benzoyl substituted oxazolidinone in low yield.



Scheme 7.

On the other hand, in a preliminary work with the hydantoin structure, L. Eagling achieved the synthesis of hydantoin **75**, which possessed the carbamoyl chloride moiety, from L-tyrosine methyl ester (Scheme 8). *O*-TBS L-tyrosine methyl ester was reacted with *tert*-butyl isocyanate to form the corresponding urea, and it was then treated with potassium *tert*-butoxyde to form hydantoin **74** in moderate yield. Finally, reaction with triphosgene afforded the *N*-substituted hydantoin **75** in low yield.



Scheme 8.

At the outset of this doctoral stay, the development of a reproducible method for the synthesis of modifiable spirocyclic compounds that could subsequently be reduced and hydrolysed leading to arogenate was a priority, as it was essential for the posterior preparation of arogenate-based potential herbicides (Figure 2).

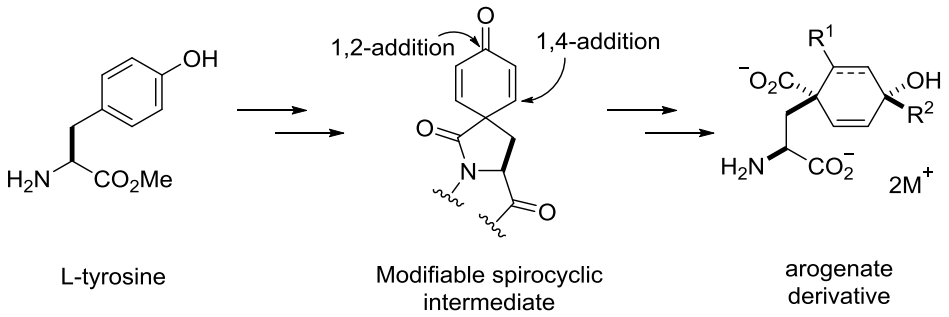
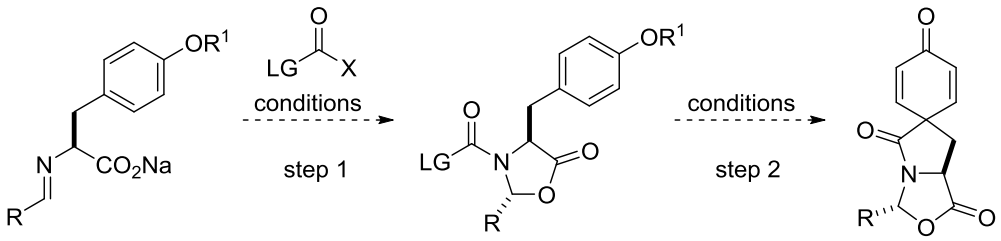


Figure 2.

With this aim, the series of possible synthetic routes described below were proposed.

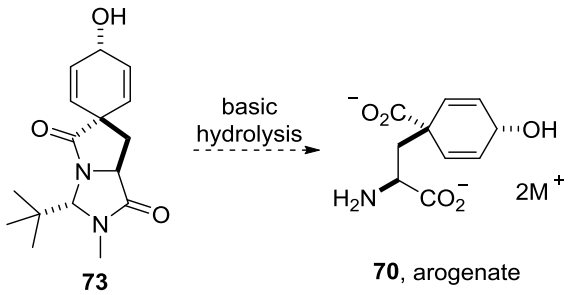
4.4.Synthetic plan

The synthesis of arogenate through oxazolidinone intermediates was taken as the first alternative, following the preliminary work carried out in the Clayden group (see Scheme 7). However, at the outset two main challenges of this synthetic route were patent: i) the formation and isolation of an *N*-carbamoyl oxazolidinone (Scheme 9, step 1); and ii) the yet unrealised dearomatising spirocyclisation of this oxazolidinone intermediate (Scheme 9, step 2).



Scheme 9.

On the other hand, further exploration on the hydrolysis of spirocyclic imidazolidinone **73** was taken as a second option, this time under basic conditions given the low stability of arogenate at low pH (Scheme 10).



Scheme 10.

In addition, the importance of the cyclic imidazolidinone structure for the stabilization of the carbamoyl moiety and the spirocyclisation reaction was also investigated by comparison with the parent acyclic ester and amide (Figure 3).

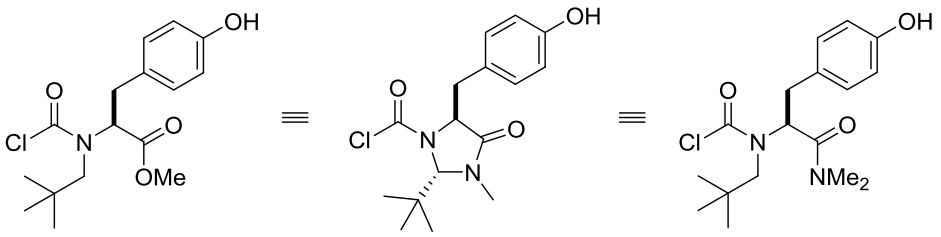
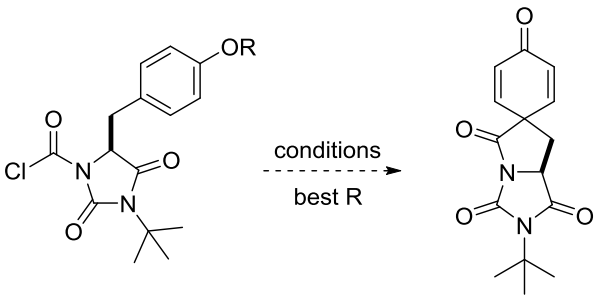


Figure 3.

Finally, the suitability of the hydantoin structure for the spirocyclisation reaction was addressed. The main challenge here was finding a suitable protecting group for the phenol functionality that would ideally be automatically cleaved during the spirocyclisation step, or alternatively in a previous step without affecting the integrity of the carbamoyl chloride moiety (Scheme 11).

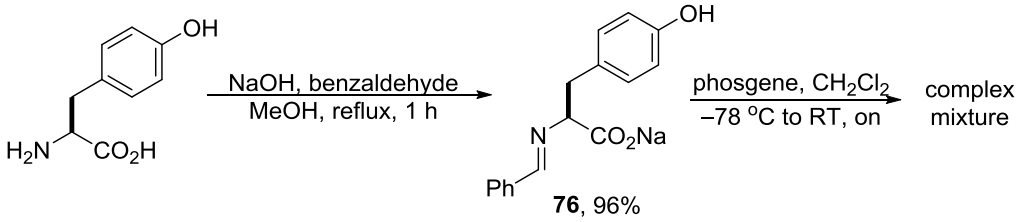


Scheme 11.

4.5. Results and discussion

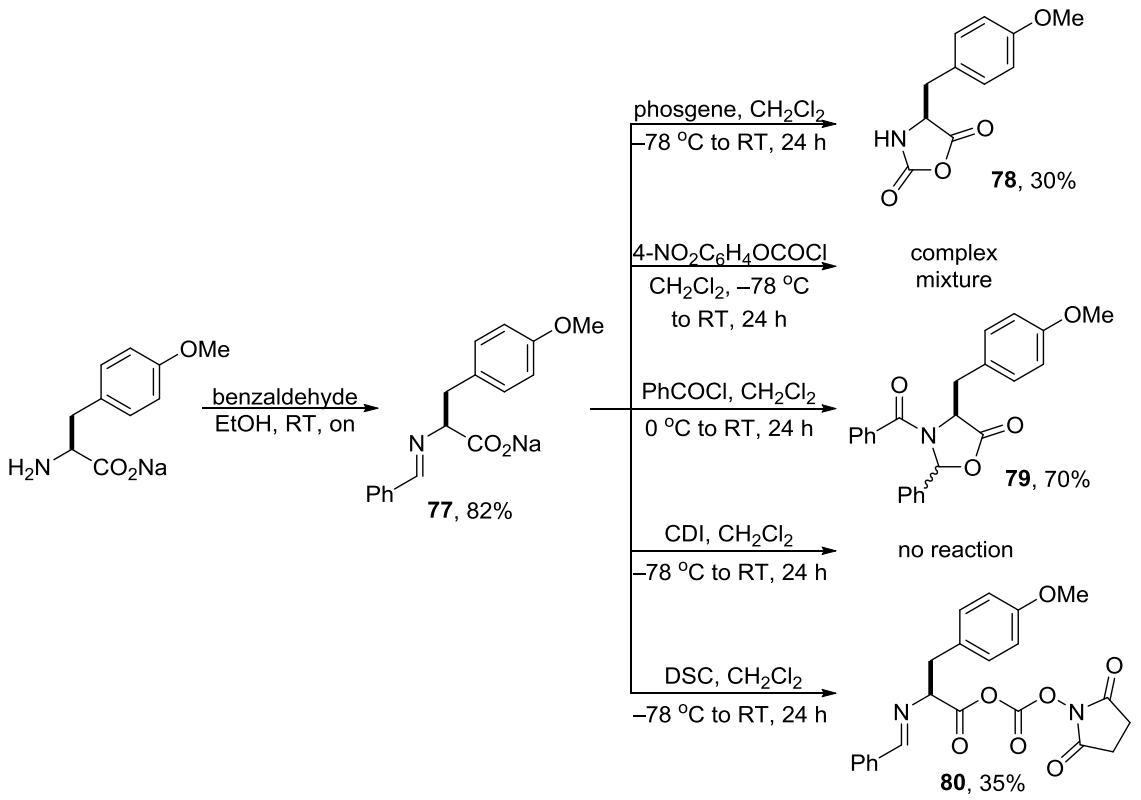
4.5.1. Oxazolidinone route

In a first try, *O*-unprotected L-tyrosine was tested following the preliminary experiments on the oxazolidinone route in an attempt to avoid an additional deprotection step prior to the spirocyclisation. With that aim, l-tyrosine was condensed with benzaldehyde affording imine **76** in excellent yield. Unfortunately, when imine **76** was submitted to the reaction conditions previously used for the preparation of oxazolidinones, a complex mixture of unknown compounds was obtained (Scheme 12). In a first instance it was assumed to be due to the participation of the unprotected phenol group in the reaction.



Scheme 12.

Next, imine **77** was prepared in good yield from the commercially available *O*-methyl L-tyrosine for its reaction with a number of active carbonyl compounds to afford the corresponding *N*-carbonyl oxazolidinones (Scheme 13). In a first run, the imine was reacted with phosgene, but instead of the expected *N*-carbamoyl chloride substituted oxazolidinone, NCA (*N*-carboxyanhydride) **78** was isolated as the major product in low yield. In a second run, 4-nitrophenyl chloroformate was used instead of phosgene, but a complex product mixture was obtained, and no formation of the desired oxazolidinone product was observed. At this point, the reaction was repeated with benzoyl chloride in order to ensure the reproducibility of the reaction performed in the preliminary work (see Scheme 7), affording the oxazolidinone **79** in good yield. On the other hand, when 1,1'-carbonyldiimidazole (DCI) was used instead of a an acyl chloride, no reaction was observed, even after 24 h at room temperature. Finally, in the reaction with *N*,*N*'-disuccinimidyl carbonate (DSC), the unstable compound **80** was isolated as the major product in low yield. This result suggested that the reaction was not proceeding as expected because in most cases the addition to the electrophile occurred through the oxygen atom at the carboxylic salt instead of the nitrogen of the imine, therefore rendering impossible the formation of the oxazolidinone.

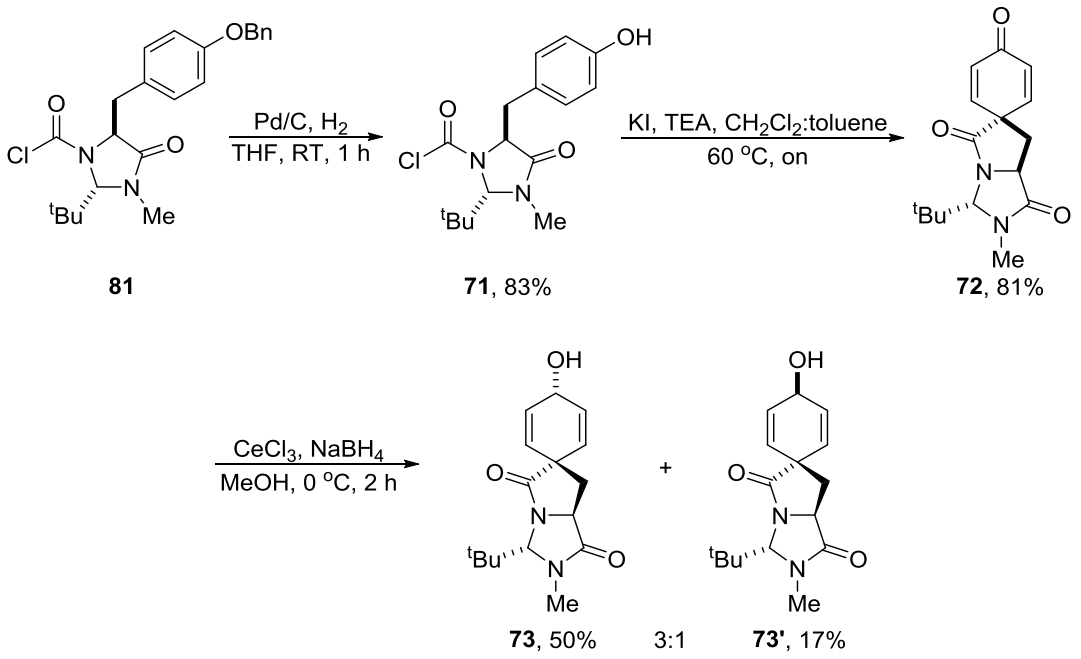


Scheme 13.

In light of these results, the oxazolidinone route was discarded as a viable option for the synthesis of arogenate.

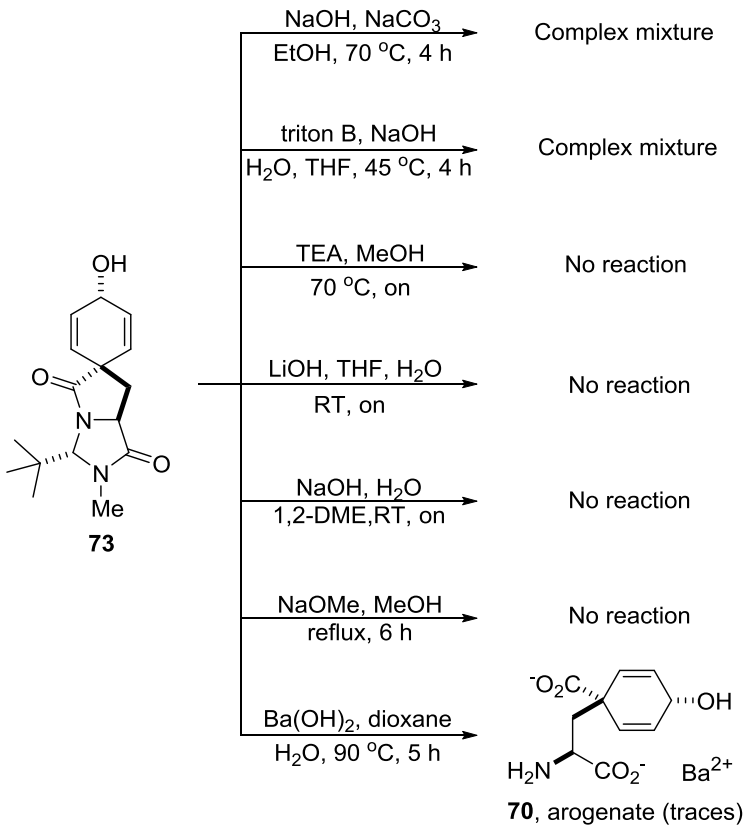
4.5.2. Imidazolidinone route

As stated in the group precedents of section 4.3, the spirocyclisation reaction using imidazolidinone **71** had previously been performed in the Clayden group and only the final hydrolysis step was lacking. Therefore, polycyclic compound **73** was synthesised following the previously established procedure from a small amount of *O*-benzyl imidazolidinone **81** provided by L. Eagling (Scheme 14). Deprotection of **81** with H_2/Pd in THF afforded the desired unprotected alcohol **71** without observing reduction of the acyl choride, and it was subsequently cyclised to afford dienone **72** in high yield. The posterior Luche reduction afforded the corresponding alcohol as a 3:1 mixture of diastereomers **73**:**73'** in good overall yield.



Scheme 14.

The major isomer **73** was then submitted to hydrolysis. In order to avoid acid reaction conditions, which would compromise the integrity of arogenate, a set of basic hydrolysis conditions were tested for the cleavage of the C–N bonds (Scheme 15). In a first attempt, hydrolysis with sodium hydroxide and sodium carbonate in ethanol at 70 ºC afforded a complex product mixture, in which no traces of arogenate were found by ^{1}H NMR. In a second run, reaction with triton B (benzyltrimethylammonium hydroxide) and sodium hydroxide in a water and THF mixture afforded similar results. Triethylamine was also tested as a base for hydrolysis, but no reaction occurred. Similarly, no change was observed in the reaction mixture when **73** was treated with lithium hydroxide or sodium hydroxide at room temperature. The treatment with sodium methoxide in methanol did not lead to any transformation either. On the other hand, when oxazolidinone **73** was treated with barium hydroxide in a dioxane / water mixture at 90 ºC, peaks matching the ones expected for arogenate were observed by ^{1}H NMR.



Scheme 15.

An initial attempt for the purification of arogenate was performed employing Sephadex A-25 ion exchange resin (chlorine form), but no separation of the reaction products was achieved. In a second trial arogenate (**70**) was purified by reverse phase column chromatography eluting with TFA / MeCN mixtures, obtaining traces of the desired compound. The chemical shifts observed in the ^{1}H NMR (400 MHz) spectra (Figure 4) were consistent with the data found in the literature,[199] thus confirming the formation of arogenate (**70**) and the configuration of intermediate **73**.

[199] S. Danishefsky, J. Morris, L. A. Clizbe, *J. Am. Chem. Soc.* **1981**, *103*, 1602-1604.

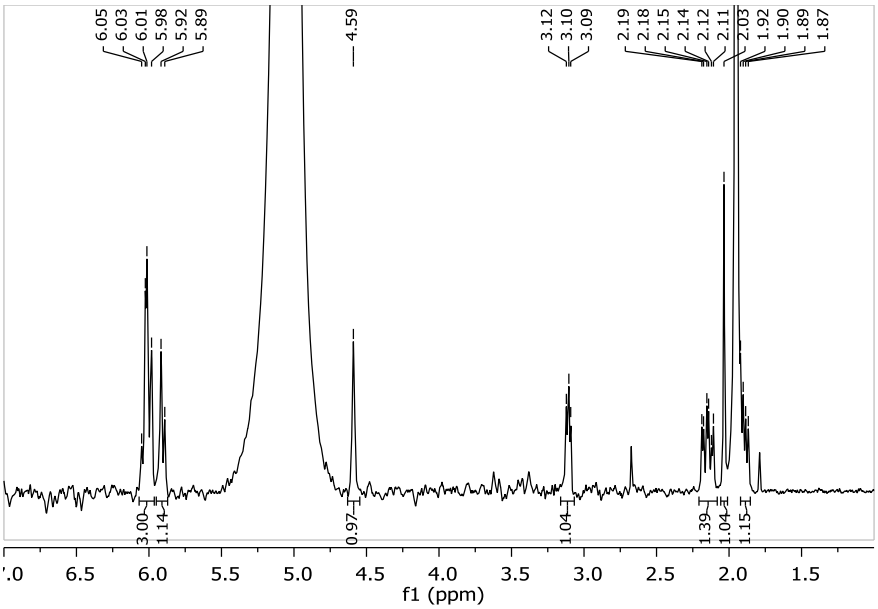
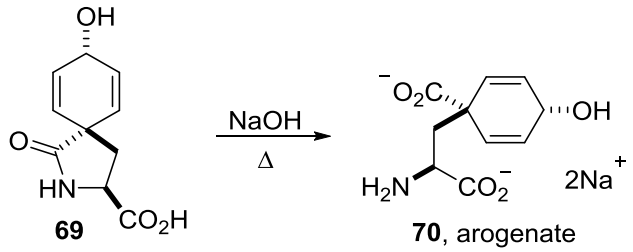


Figure 4.

Interestingly, a posterior thorough study by L. Eagling in the Clayden group revealed that spiro-arogenate (**69**),[200] which is the product from the penultimate step in Danishefsky's synthesis of arogenate (see Scheme 2 in page 151), was the main product of this reaction, therefore further supporting the validity of this route for the synthesis of arogenate (Scheme 16).



Scheme 16. Last setp of Danishefsky's synthesis of arogenate

The study of the imidazoline route is still ongoing in the Clayden group.

[200] L. O. Zamir, R. Tiberio, E. Jung, R. Jensen, *J. Biol. Chem.* **1983**, *258*, 6486–6491.

4.5.3. Acyclic route

As no investigation on the use of acyclic molecules for the spirocyclisation reaction had been performed, we set out to synthesise the ester and amide analogues of imidazolidinone **71** to determine whether the cyclic structure offered any real advantages for the synthesis of arogenate (Figure 5).

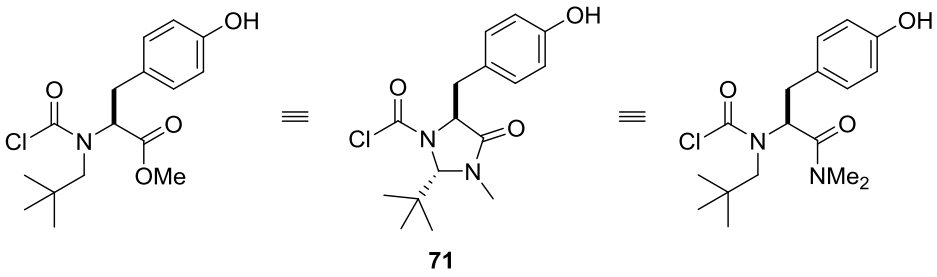
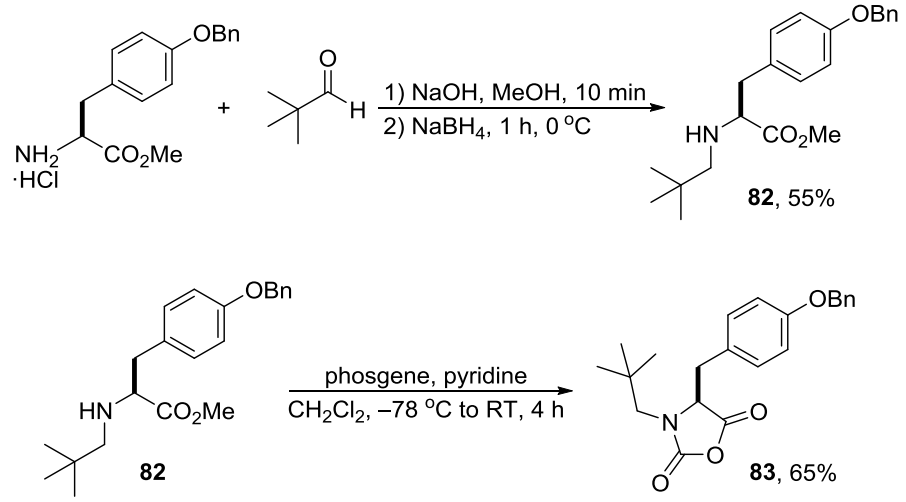


Figure 5.

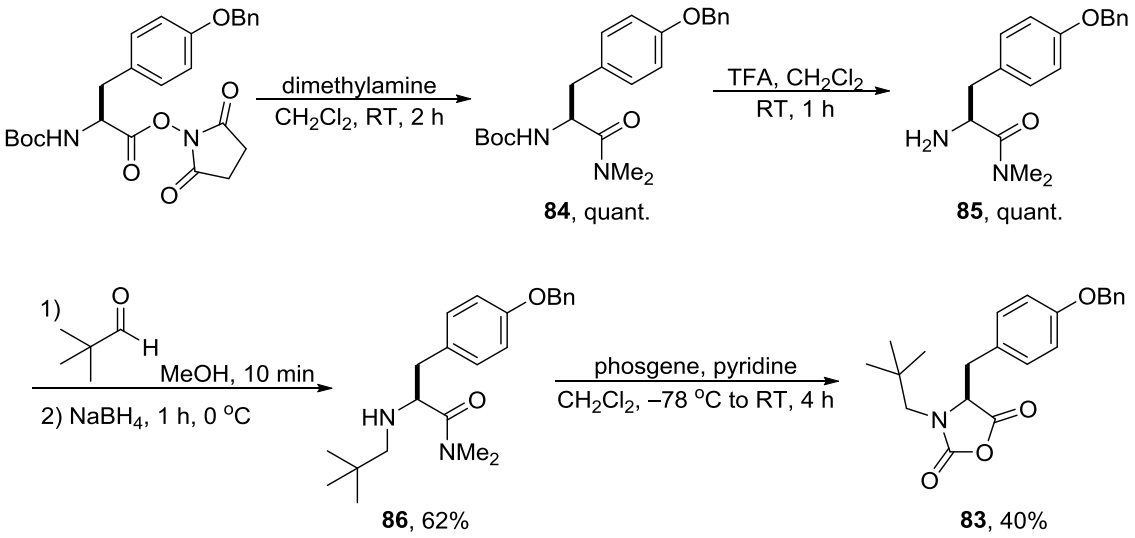
We started by attempting to prepare the ester (Scheme 17), and in a first step the commercially available *O*-benzyl-L-tyrosine methyl ester was submitted to reductive amination with trimethylacetaldehyde, affording amine **82** in moderate yield. However, when the insertion of the *N*-carbamoyl chloride functionality was attempted employing the reaction conditions previously used for imidazolidinone **71**, NCA **83** was obtained instead of the desired acyclic ester.



Scheme 17.

Next, the preparation of the amide was addressed. The readily available *Boc*-*O*-benzyl-L-tyrosine hydroxysuccinimide ester was reacted with dimethylamine affording amide **84**, and subsequently decarboxylated affording the unprotected amine **85** quantitatively. The reductive amination with trimethylacetaldehyde afforded compound

86 in moderate yield, which was submitted to the same *N*-funtionalization conditions used for imidazolidinone **71**. Unfortunately, although untreated ^{1}H NMR aliquots of the reaction looked promising, only NCA **83** was isolated upon purification by silica gel column chromatography.

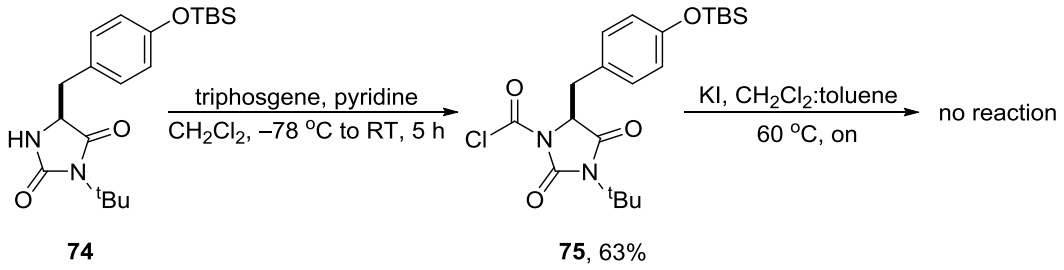


Scheme 18.

In light of these results, we could conclude that the rigidity of the cyclic structure of imidazolidinone provides the essential stability that mantains the carbamoyl chloride functionality intact under isolation or mild reaction conditions.

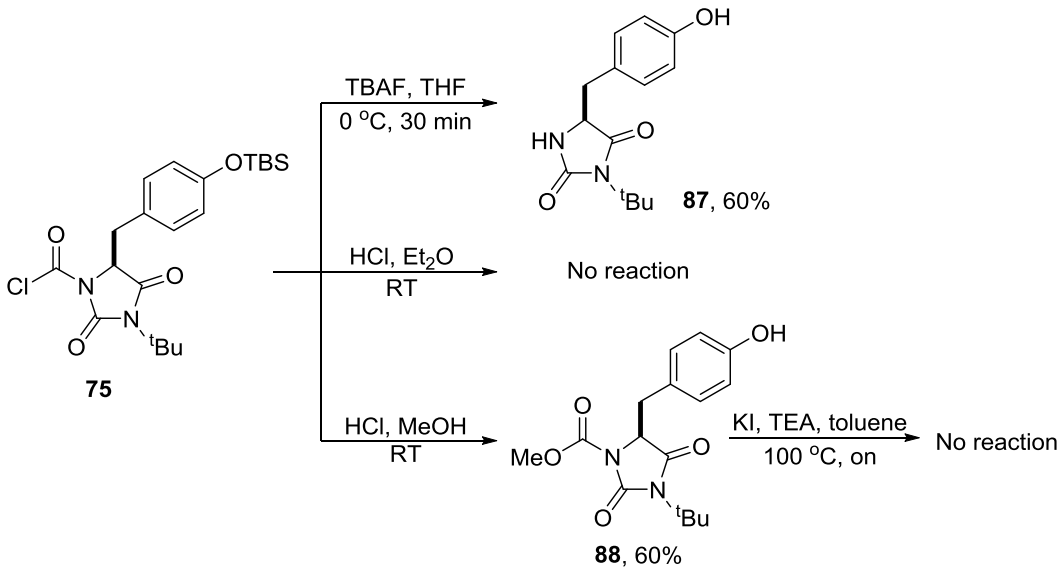
4.5.4. Hydantoin route

As stated in the group precedents of Section 0, hydantoin **75** had previously been synthesised in the Clayden group. Therefore, it was prepared following the previously established procedure from a small amount of *O*-TBS hydantoin **74** provided by L. Eagling in moderate yield. The dearomatising cyclisation reaction was then attempted with the *O*-TBS protected compound **75**, but no reaction occurred, as shown in Scheme 19.



Scheme 19.

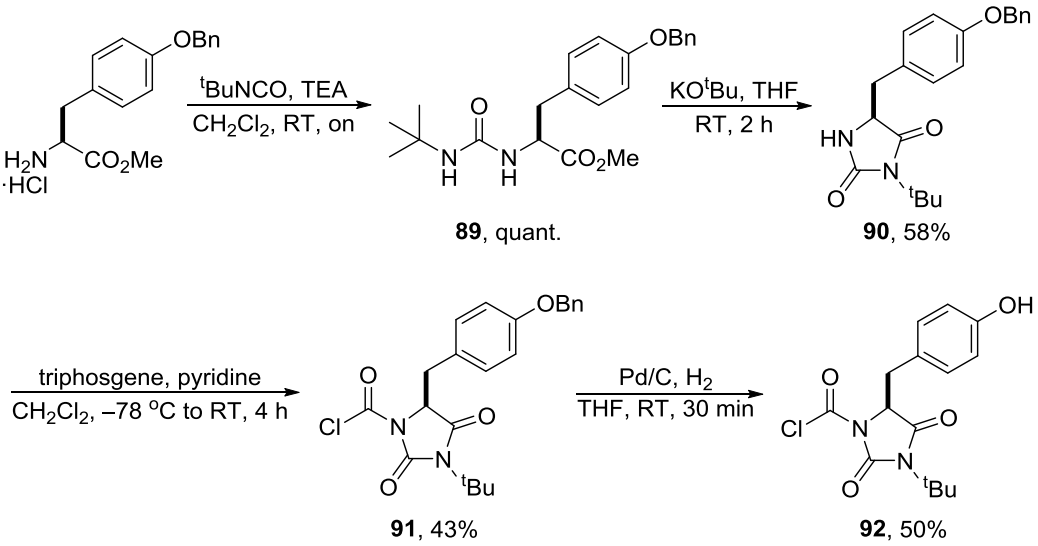
In consequence, the desilylation of **75** was addressed, as it was expected that the free alcohol would be able to undergo the intramolecular spirocyclisation reaction. Unfortunately, the carbamoyl moiety exhibited a higher reactivity than the TBS group, and therefore the selective deprotection of the alcohol could not be performed (Scheme 20). Indeed, when **75** was treated with TBAF (tetrabutylammonium fluoride), the *N*-unsubstituted hydantoin **87** was obtained in moderate yield. In a second run, HCl in Et_2O was employed, but no reaction was observed. On the other hand, when HCl in MeOH was used, the product resulting from the nucleophilic addition of methanol to the carbamoyl group (**88**) was obtained. Despite having a worse leaving group than its precursor, as the phenol group was now unprotected, the spirocyclisation of compound **88** was attempted in toluene at 100 ºC, but no reaction was observed even after 24 h.



Scheme 20.

In order to allow the deprotection of the phenol group without compromising the integrity of the carbamoyl moiety, the use of an *O*-benzyl substituted intermediate was besought based on the previous work with imidazolidinones (see Scheme 14). Thus, compound **91** was synthesised in three steps starting from the commercially available

O-benzyl-L-tyrosine methyl ester (Scheme 21). First, urea **89** was formed reacting the starting amine hydrochloride with *tert*-butyl isocyanate, and it was then reacted with potassium *tert*-butoxyde to form hydantoin **90** in moderate yield. Reaction with triphosgene afforded the *N*-substituted hydantoin **91** in low yield. As expected, the deportection of the alcohol with H_2/Pd in THF proceeded smoothly affording hydantoin **92** as the major product in moderate yield.



Scheme 21.

The dearomatising cyclisation of **92** was not attempted within the stay in the Clayden group.

4.6. Conclusions

In summary, oxazolidinones, imidazolidinones and hydantoins have been studied as intermediates for the synthesis of arogenate via an intramolecular dearomatising cyclisation reaction starting from the natural amino acid L-tyrosine. During the investigation, it was shown that the oxazolidinone route was not suitable for the formation of the necessary *N*-carbonyl substituted intermediates, and important advances were made in the hydantoin route. Furthermore, the importance of the cyclic structure of intermediates for the stabilization of the carbamoyl chloride functionality was demonstrated, and the total synthesis of arogenate was achieved for the first time employing imidazolidinone intermediates.

Chapter 5:

Experimental section

5. Experimental section

Experimental section

5.1. Material and techniques

5.1.1. Reagents and solvents

Reagents were purchased from different commercial suppliers (Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

Triethylamine, DBU, DIPA and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at –30 ºC under nitrogen.

When anhydrous solvents were required, they were dried following established procedures.[201] Dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma aldrich) columns.

5.1.2. General experimental

All non-aqueous reactions were performed under inhert atmosphere using oven-dried glassware and were magnetically stirred. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Heat requiring reactions were performed using a hotplate with a sand bath and a condenser. Reactions requiring low temperatures were performed using cooling bath circulators *Huber* T100E and acetone or isopropanol baths.

Organic layers washed with aqueous phases were dried over $MgSO_4$ or Na_2SO_4 and filtered through cotton.

Organic solvents were evaporated under reduced pressure using rotavapors Büchi R-110, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (~0.5 mmHg) was employed.

[201] Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals* 3rd Edition Butterworth-Heinemann, Oxford **1988**.

5.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Bioblock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 ml of water (limited lifetime), followed by heating.

Chromatographic purification was performed on Merck ROCC 60 silica gel 40-63 μm as stationary phase and a suitable mixture of solvents (typically hexane/ethyl acetate, pentane/diethyl ether or dichloromethane/methanol) as eluent.

5.1.4. Optical rotation

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg·cm^2·g^{-1}; concentrations (*c*) are quoted in g/100 mL; $_D$ refers to the D-line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

5.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

5.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), Varian 400 MR (400 MHz for ^{1}H, 100 MHz for ^{13}C) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

5.1.7. Mass spectra

MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) or in the Chemistry School in the University of Bristol.

5.1.8. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

5.1.9. Determination of enantiomeric excesses

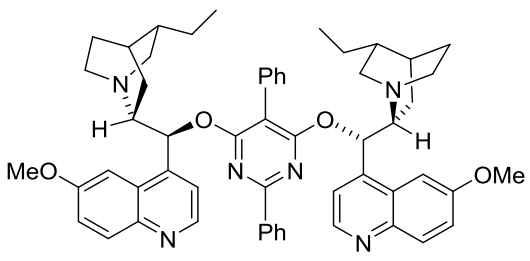
Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on either a Waters 600 (equipped with Photodiode Array Detector Waters 2996). The used columns were Chiralpack AD-H, AY-H, IA, IB and IC; and flow/solvent conditions are given for each compound.

5.1.10. X-Ray diffraction analysis

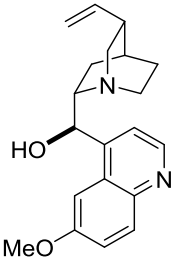
The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

5.2. Preparation of catalysts

Catalysts **C11** [$(DHQD)_2PYR$] and **C34** (quinine) are commercially available and were purchased from commercial suppliers. The remaining catalysts were prepared as follows.



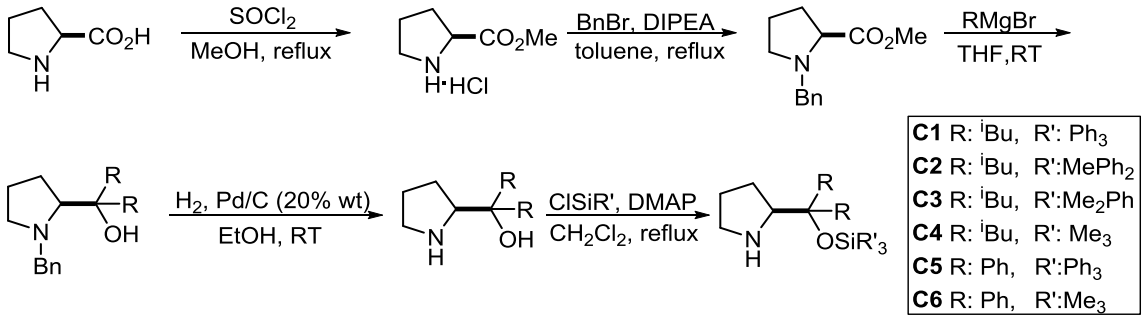
C11, $(DHQD)_2PYR$



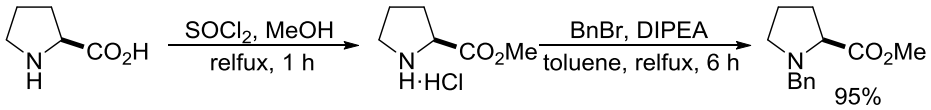
C34, quinine

5.2.1. Preparation of proline-based aminocatalysts C1-C6

Known catalysts **C1**,[202] **C5**[203] and **C6**[204] and the newly prepared catalysts **C2-C4** were prepared according to the following synthetic sequence:



Preparation of (*S*)-1-(1-benzylpyrrolidin-2-yl)ethan-1-one



[202] E. Gómez-Bengoa, S. Jiménez, I. Lapuerta, A. Mielgo, M. Oiarbide, I. Otazo, I. Velilla, S. Vera, C. Palomo, I. Velilla, *Chem. Sci.* **2012**, *3*, 2949–2957.

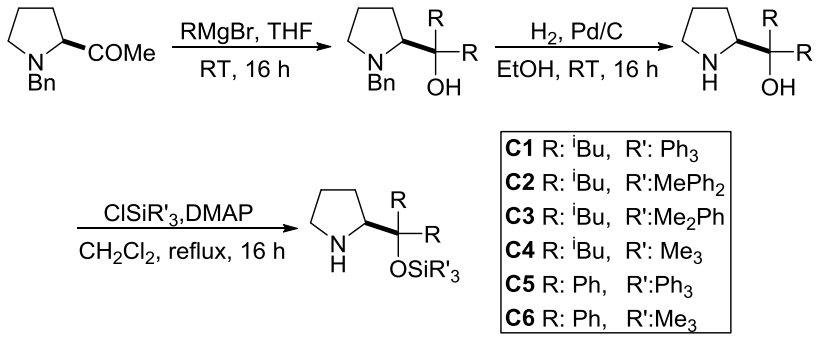
[203] E. Gómez-Bengoa, A. Landa, A. Lizarraga, A. Mielgo, M. Oiarbide, C. Palomo, I. Velilla, *Chem. Sci.* **2011**, *2*, 353–357.

[204] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angewandte Chem. Int. Ed.* **2005**, *44*, 794–797.

1st step:[205] Thionyl chloride (4.0 mL, 55 mmol, 1.1 equiv.) was added dropwise over 5 min to a suspension of L-proline (5.76 g, 50 mmol, 1 equiv.) in methanol at 0 ºC, and the resulting solution was stirred at reflux for 1 h. Then, the solvent and excess thionly chloride were eliminated under reduced pressure, affording the crude product as a yellow oil, which was used in the next step without further purification.

2nd step:[206] Benzyl bromide (6.5 mL, 55 mmol, 1.1 equiv.) was added dropwise to a solution of the crude product previously obtained (8.28 g, 50 mmol, 1 equiv.) and DIPEA (26.1 mL, 150 mmol, 3 equiv.) in toluene (50 mL) at 0 ºC, and the resulting solution was stirred at reflux for 6 h. Then, the reaction mixture was cooled to 0 ºC and a saturated solution of $NaHCO_3$ (40 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was eliminated under reduced pressure to afford the crude (*S*)-1-(1-benzylpyrrolidin-2-yl)ethan-1-one as a brown oil, which was used in the next step without further purification. Yield: 95% (10.3 g, 47.5 mmol). All data were consistent with those previously reported.[207] **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.34, (m, 5H), 5.15 (m, 2H), 4.35 (m, 1H), 3.86-3.40 (m, 5H), 2.30 -1.80 (m, 4H).

General procedure for the preparation of catalysts C1-C6



1st step:[208] A solution of the corresponding alkyl or aryl bromide magnesium bromide (3 equiv.) was added dropwise to a stirred solution of the crude ester (4.38 g, 20 mmol, 1 equiv.) in dry THF (40 mL) at 0 ºC. The reaction mixture was let to stir at room temperature for 16 h before being cooled to 0 ºC to quench the reaction by adding a saturated solution of NH_4Cl (30 mL). The resulting salts were filtered over a path of celite and rinsed with dichloromethane (3 × 20 mL). The combined organic phases were

[205] P. N. Confalone, E. H. Huie, S. S. Ko, G. H. Cole, *J. Org. Chem*. **1988**, *53*, 482–487.

[206] Adapted from: K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed*. **2003**, *42*, 5489–5492.

[207] D. Gray, C. Concellón, T. Gallagher, *J. Org. Chem.* **2004**, *69*, 4849–4851.

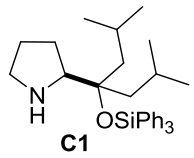
[208] Adapted from: K. Soai, H, Hachida, N. Yokota, *J. Chem. Soc. Perkin. Trans I* **1987**, 1909–1914.

washed with brine and dried over $MgSO_4$, and the solvent was eliminated under reduced pressure. The desired alcohol was purified by flash column chromatography on silica gel eluting with a 95:5 mixture of hexane/EtOAc.

2nd step:[202] The product resulting from the previous step and palladium on activated charcoal (10% wt.) (20% wt.) were stirred in EtOH (1 mL/mmol) under an hydrogen atmosphere. The resulting suspension was filtered over a pad of celite and the solvent was eliminated under reduced pressure affording the crude unprotected amine, which was used in the next step without further purification.

3rd step:[202] The crude product obtained in the previous step (10 mmol, 1 equiv.) was dissolved in dichloromethane (20 mL), and DMAP (2.43 g, 20 mmol, 2 equiv.) and the corresponding silyl chloride (17.5 mmol, 1.75 equiv.) were added at 0 ºC. The resulting solution was refluxed for 16 h, and after cooling to room temperature water (25 mL) was added. The layers were separated, the aqueous phase was extracted with dichloromethane (3 × 25 mL), and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (40 mL). The organic phase was then dried over $MgSO_4$, and the solvent was eliminated under reduced pressure. Catalysts **C1-C6** were purified by silica gel flash column chromatography eluting with CH_2Cl_2/MeOH mixtures. The pure product was then dissolved in dichloromethane (20 mL), washed with a saturated solution of $NaHCO_3$ (20 mL) and the organic phase was dried over $MgSO_4$. The solvent was eliminated under reduced pressure to afford the corresponding pure and basified catalyst.

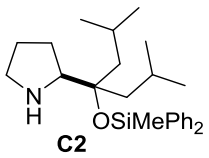
(*S*)-2-(2,6-Dimethyl-4-((triphenylsilyl)oxy)heptan-4-yl)pyrrolidine (C1)[202]



C1

C1 was prepared starting from L-proline according to the general procedure described above using ^{i}BuMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and Ph_3SiCl (5.18 g, 17.5 mmol) in the silylation step. White solid. m. p.: 112–115 ºC. Yield after 5 steps: 61%. All data were consistent with those previously reported. $[\alpha]_D^{25}$ = +20.3º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 6H), 7.45-7.33 (m, 9H), 3.24 (t, *J* = 7.4 Hz, 1H), 2.74 (dt, J_1 = 6.4 Hz, J_2 = 12.7 Hz, 1H), 2.69-2.60 (m, 1H), 1.97-1.79 (m, 2H), 1.74 (dd, J_1 = 5.6 Hz, J_2 = 14.4 Hz, 2H), 1.59 (dd, J_1 = 3.4 Hz, J_2 = 10.9 Hz, 2H), 1.55-1.48 (m, 2H), 1.50 (bs, 1H), 1.33 (dd, J_1 = 5.7 Hz, J_2 = 14.2, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 2.5 Hz, 3H), 0.88 (d, *J* = 2.5 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 137.4, 135.8, 129.3, 127.5, 84.2, 65.7, 47.0, 44.8, 27.2, 26.3, 25.3, 25.1, 24.9, 23.8, 23.4. **MS:** calculated for $C_{31}H_{42}NOSi$ ($M + H^+$): 472.3035; found: 472.3039.

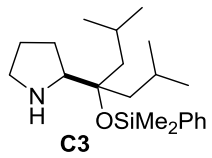
(*S*)-2-(2,6-Dimethyl-4-((methyldiphenylsilyl)oxy)heptan-4-yl)pyrrolidine (C2)



C2

C2 was prepared starting from L-proline according to the general procedure described above using ^{i}BuMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and $MePh_2SiCl$ (3.20 g, 17.5 mmol) in the silylation step. Yellow oil. Yield after 5 steps: 54%. $[\alpha]_D^{20}$ = +7.4° (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 4H), 7.38 – 7.29 (m, 6H), 2.99 (t, *J* = 7.2 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.65 – 2.55 (m, 1H), 1.86 – 1.72 (m, 2H), 1.67 – 1.45 (m, 7H), 1.41 (dd, *J* = 14.1, 4.9 Hz, 1H), 0.92 (ddd, *J* = 7.5, 6.6, 1.8 Hz, 12H), 0.76 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 139.7, 134.8, 129.5, 127.9, 83.3, 66.7, 47.3, 47.0, 46.2, 27.1, 26.3, 25.7, 25.6, 25.5, 25.3, 24.4, 24.1, 1.3. **MS:** calculated for $C_{31}H_{42}NOSi$ (M, H^+): $C_{26}H_{39}NOSi$ (M + H^+), 410.2789; found, 410.2868.

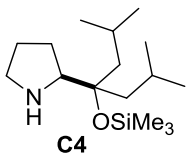
(*S*)-2-(4-((Dimethyl(phenyl)silyl)oxy)-2,6-dimethylheptan-4-yl)pyrrolidine (C3)



C3

C3 was prepared starting from L-proline according to the general procedure described above using ^{i}BuMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and $Me_2PhSiCl$ (2.12 g, 17.5 mmol) in the silylation step. Yellow oil. Yield after 5 steps: 50%. $[\alpha]_D^{20}$ = –5.2° (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.37 – 7.32 (m, 3H), 2.94 (t, *J* = 7.2 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.65 (dt, *J* = 10.5, 6.3 Hz, 1H), 1.82 – 1.68 (m, 2H), 1.68 – 1.54 (m, 5H), 1.52 – 1.37 (m, 3H), 0.99 – 0.89 (m, 12H), 0.44 (s, 3H), 0.43 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 140.7, 133.3, 128.9, 127.6, 82.0, 66.4, 46.8, 46.4, 46.0, 26.5, 25.8, 25.2, 25.1, 24.9, 24.9, 24.0, 23.9, 2.1, 1.9. **MS:** calculated for $C_{21}H_{37}NOSi$ (M + H^+), 348.2722; found, 348.2717.

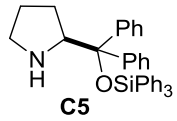
(*S*)-2-(2,6-Dimethyl-4-((trimethylsilyl)oxy)heptan-4-yl)pyrrolidine (C4)



C4

C4 was prepared starting from L-proline according to the general procedure described above using ^{i}BuMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and Me_3SiCl (3.20 mL, 17.5 mmol) in the silylation step. Yellow oil. Yield after 5 steps: 65%. $[\alpha]_D^{25}$ = –6.2° (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.55 – 3.31 (m, 2H), 3.23 – 3.07 (m, 1H), 2.11 (tt, *J* = 14.1, 7.0 Hz, 6H), 2.00 – 1.89 (m, 3H), 1.82 (dd, *J* = 14.0, 4.9 Hz, 1H), 1.46 – 1.24 (m, 12H), 0.54 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 81.2, 66.5, 47.0, 46.2, 26.5, 26.0, 25.2, 25.1, 24.9, 24.9, 23.9, 3.2. **MS:** calculated for $C_{21}H_{37}NOSi$ (M + H^+), $C_{20}H_{34}NOSi$ (M, H+), 286.2566; found, 286.2548.

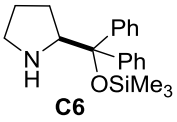
(*S*)-2-(Diphenyl((triphenylsilyl)oxy)methyl)pyrrolidine (C5)[203]



C5

C5 was prepared starting from L-proline according to the general procedure described above using PhMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and Ph_3SiCl (5.18 g, 17.5 mmol) in the silylation step. White solid. m. p.: 147–150 ºC. Yield after 5 steps: 75%. All data were consistent with those previously reported. $[\alpha]_D^{25}$ = –24.4º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.47-7.41 (m, 8H), 7.39–7.22 (m, 11H), 7.20–7.08 (m, 6H), 3.98 (t, *J* = 7.6 Hz, 1H), 2.74–2.66 (m, 1H), 2.63–2.49 (m, 1H), 1.88–1.68 (m, 1H), 1.60–1.38 (m, 3H), 1.30 (t, *J* = 10.6 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 146.3, 145.1, 136.3, 135.1, 129.3, 129.1, 127.8, 127.4, 127.0, 126.7, 85.0, 65.3, 46.9, 28.0, 25.0.

(*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (C6)[204]

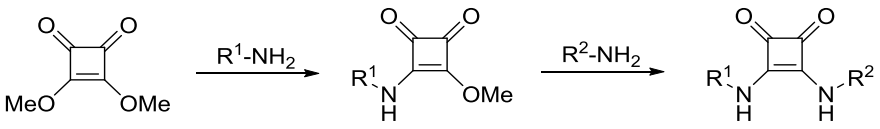


C6

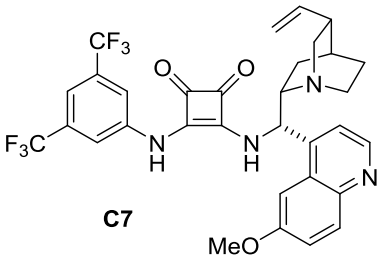
C6 was prepared starting from L-proline according to the general procedure described above using PhMgBr (2 M solution in Et_2O, 30 mL, 60 mmol) in the Grignard reaction and Me_3SiCl (3.20 mL, 17.5 mmol) in the silylation step. Yellow oil. Yield after 5 steps: 78%. All data were consistent with those previously reported. $[\alpha]_D^{25}$ = +20.3º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 2H), 7.26 – 7.17 (m, 4H), 4.04 (t, *J* = 7.4 Hz, 1H), 2.91 – 2.65 (m, 2H), 1.62 – 1.50 (m, 3H), 1.42 – 1.31 (m, 1H), -0.10 (s, 9H).

5.2.2. Preparation of squaramide-based Brønsted base catalysts

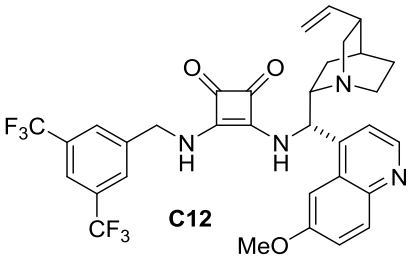
Squaramide-based catalysts were prepared according to the following synthetic sequence:



*5.2.2.1. Preparation of catalysts **C7** and **C12***



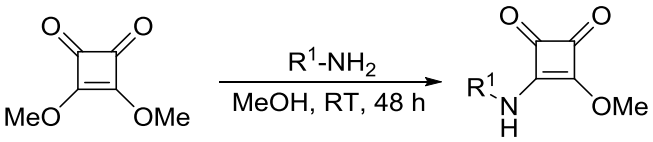
C7



C12

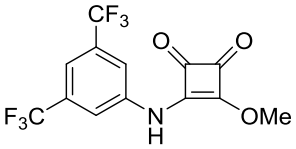
Known catalysts **C7**[209] and **C12**[210] were synthesised as follows:

Preparation of squaric ester monoamides



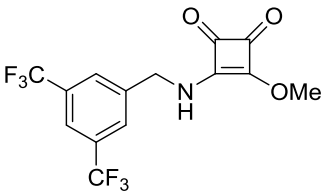
To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (280 mg, 2.0 mmol) in MeOH (20 mL) was added the corresponding amine (2.0 mmol) and the reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give the squaric ester monoamide.

3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione[211]



The title compound was prepared according to the general procedure described above using 3,5-bis(trifluoromethyl)aniline (310 mg, 2.0 mmol) as the amine. Yield: 68% (463, 1.36 mmol). All spectroscopic data were identical to those reported in literature. **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

3-((3,5-bis(Trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione[212]



The title compound was prepared according to the general procedure described above using 3,5-bis(trifluoromethyl)benzylamine (486 mg, 2.0 mmol) as the amine. Yield: 62% (438, 1.24 mmol). All spectroscopic data were identical to those reported in literature. **^{1}H-NMR** (300

[209] W. Yang, D. M. Du, *Org. Lett*. **2010**, *12*, 5450–5453.

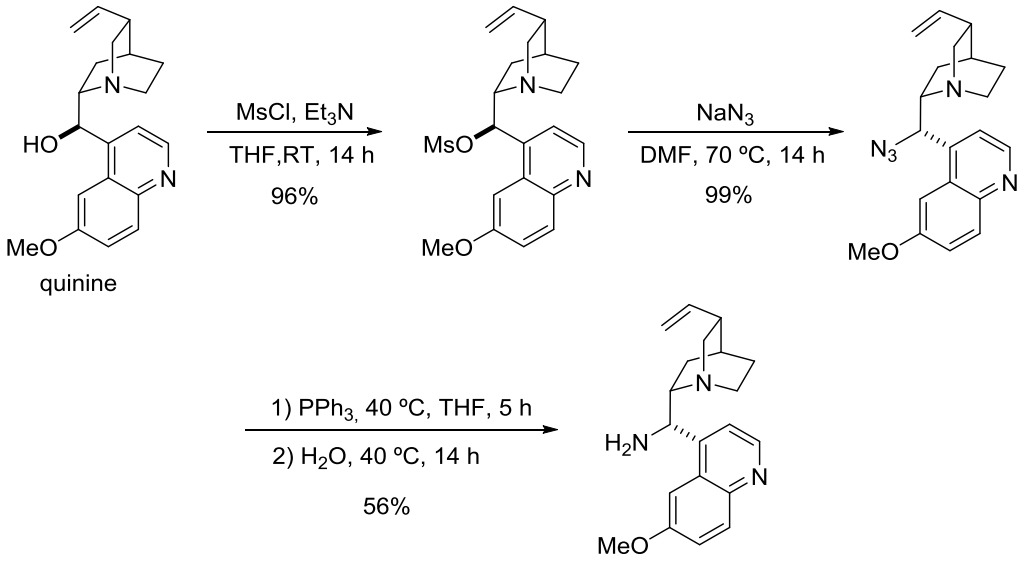
[210] J. P. Malerich, K. Hagihara, V. H. Rawal. *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417.

[211] Yang, W.; Du, D. M. *Org. Lett*. **2010**, *12*, 5450–5453.

[212] J. P. Malerich, K. Hagihara, V. H. Rawal. *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417.

MHz, DMSO-d_6) δ 8.94 (br s, 1H), 7.09 (s, 2H), 7.94 (s, 1H), 4.78 (br s, 2H), 4.26 (s, 3H).

Preparation of 9-amino-(9-deoxy)epiquinine[213]



1st step:[214] A mixture of quinine (16.2 g, 50 mmol, 1 equiv.) and triethylamine (25.1 mL, 180 mmol, 3.6 equiv.) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (7.0 mL, 90 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and a saturated solution of $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford the crude product in 96% yield, which was used in the next step without further purification.

2nd step:[215] The crude product (19.3 g, 48 mmol, 1 equiv.) was dissolved in DMF (150 mL). The solution was cooled to 0 ºC and NaN_3 (6.2 g, 96 mmol, 2 equiv.) was added in portions. The mixture was stirred at 70 ºC for 16 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with brine (10 × 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield, which was used in the next step without further purification.

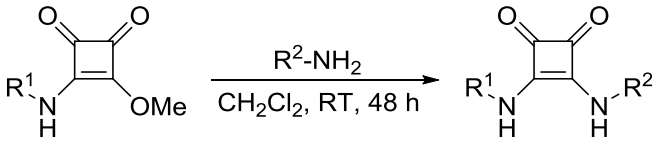
[213] Adapted from: H. Brunner, J. Büegler, B. Nuber, *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

[214] Adapted from: M. Zielinska-Blajet, M. Kucharska, J. Skarzewski, *Synthesis*, **2006**, *7*, 4383–4387.

[215] Adapted from: U. Sudermeier, C. Döbler, G. M. Mehltretter, W. Baumann, M. Beller, *Chirality*, **2003**, *15*, 127–134.

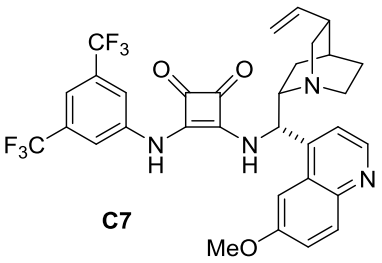
3rd step:[215] The crude product was dissolved in THF (250 mL) and PPh_3 (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated to 40 ºC and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 ºC. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 × 100 mL). Then the aqueous layer was cooled to 0 ºC and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with CH_2Cl_2 (3 × 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 56% (8.7 g, 26.9 mmol). All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

Coupling with squaric ester monoamide



To a suspension of the corresponding squaric ester monoamide prepared above (1.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added 9-amino-(9-deoxy)*epi*quinine (323 mg, 1.0 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography (eluting hexane/EtOAc 50:50 → 0:100).

3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C7)[209]

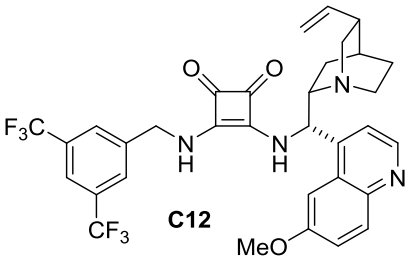


C7

The title compound was prepared according to the general procedure described above from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (339 mg, 1.0 mmol). Yellow solid. m. p. 223–225 ºC. Yield: 70% (441 mg, 0.70 mmol). All spectroscopic data were identical to those reported in literature. **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s,

3H), 3.52-3.42 (m, 1H), 3.30- 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H)..

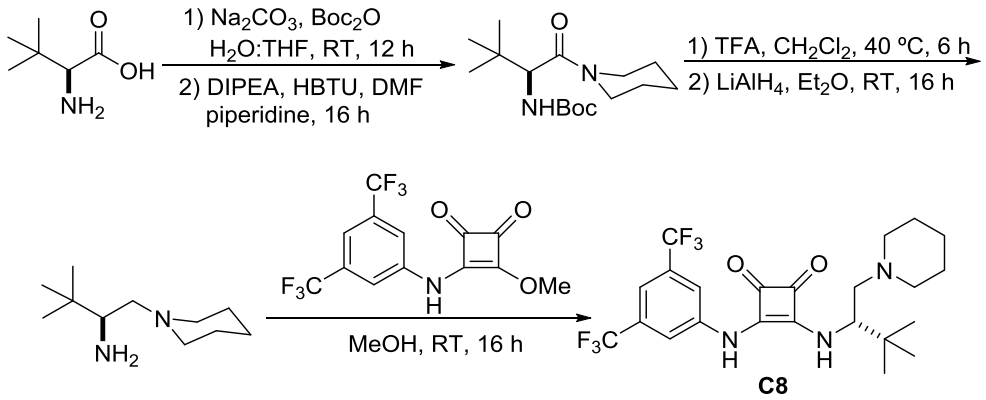
3-((3,5-bis(Trifluoromethyl)benzyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C12)[210]



The title compound was prepared according to the general procedure described above from 3-((3,5-bis(Trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (353 mg, 1.0 mmol, 1 equiv.). Yield: 64% (413, 0.64 mmol). All spectroscopic data were identical to those reported in literature. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 8.90 (d, *J* = 4.5 Hz, 1H), 8.39 (d, *J* = 8.3 Hz, 1H), 7.93-8.07 (m, 5H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.74 (br s, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 4.4 Hz, 1H), 6.06 (brs, 1H), 5.79 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 4.82 (m, 2H), 3.27 (q, *J* = 9.4 Hz, 1H), 3.07 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.89 (t, *J* = 12.2 Hz, 1H), 2.81 (m, 1H), 2.74 (dd, *J* = 14.4, 10.5 Hz, 1H), 2.17 (q, *J* = 8.0 Hz, 1H), 1.40-1.55 (m, 3H), 0.83-0.99 (m, 2H).

*5.2.2.2. Preparation of catalyst **C8***

Known catalyst **C8**[216] was prepared according to the following synthetic sequence:



1st step:[217] Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3 g, 15 mmol, 1.5 equiv.) were added to a solution of L-*tert*-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL)

[216] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

and THF (5 mL) at 0 ºC. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aqueous phases were combined, washed with brine (50 mL) and dried over $MgSO_4$. After removing the solvent under reduced pressure, the resulting residue was redissolved in dry DMF (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 g, 15 mmol, 1.5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were combined and washed with HCl 1 M and brine (20 mL) and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 8:/15) to afford *tert*-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 82% (2.5 g, 8.3 mmol). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62 (m, 6H), 3.46 – 3.69 (m, 4 H), 4.54 (d, *J* = 9.7 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H).

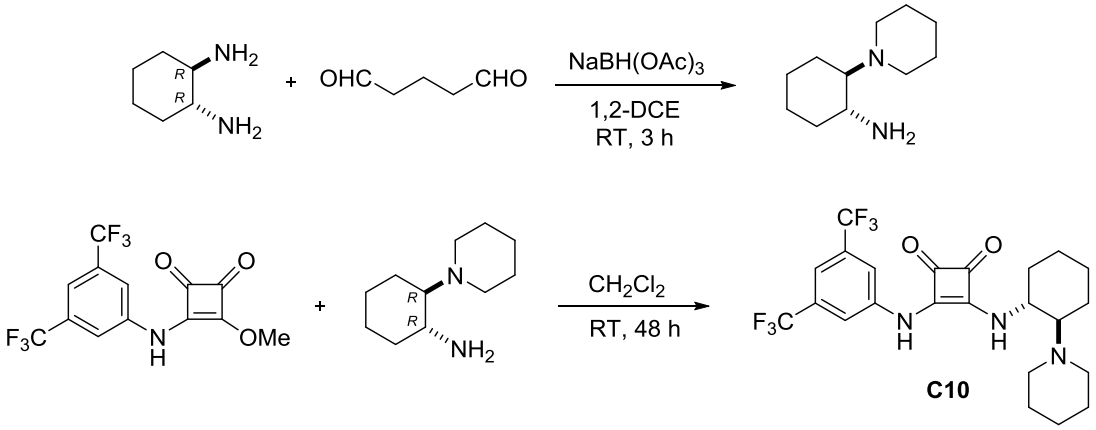
2nd step:[217] The previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 ºC until no more starting material was observed by TLC (eluting with hexane/EtOAc 70:30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40 %), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 ºC under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched by the addition of water (5 mL) and NaOH 15 % (1.2 mL) at 0 ºC. The resulting mixture was filtered and the filtrate was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 1:1) to afford (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 92% (1.16 g, 6.8 mmol). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.52 (d, *J* = 12.3 Hz, 4H), 2.28 (dd, *J* = 12.3, 2.8 Hz, 3H), 2.13 (dd, *J* = 12.1, 11.2 Hz, 1H), 1.61-1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

[217] Y. Gao, Q. Ren, L. Wang, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13068–13071.

3rd step:[216] To a solution of the diamine (780 mg, 4.6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4.6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The formed white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure **C8** as a white solid. m. p. 246–248 ºC. Yield: 59% (1.29 g, 2.6 mmol). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (s, 2H), 7.64 (s, 1H), 4.07 – 3.93 (m, 1H), 2.49 – 2.04 (m, 5H), 1.51 – 1.22 (m, 6H), 0.93 (s, 9H).

*5.2.2.3. Preparation of catalyst **C10***

Known catalyst **C10**[218] was prepared according to the following synthetic sequence:



1st step:[219] Glutaraldehyde (50 wt% in H_2O, 1.90 mL, 10.4 mmol, 1.04 equiv.) was added dropwise into a mixture of diamine (1.140 g, 10 mmol, 1 equiv.) and $NaBH(OAc)_3$ (8.500 g, 40 mmol, 4 equiv.) in 1,2-dichloroethane (60 mL) at room temperature. The resulting mixture was stirred at room temperature for 3h, and quenched with NaOH 6 M (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated. The residue was then redissolved in 50 mL CH_2Cl_2, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give the product as a yellow liquid. Yield: 89% (1.622 g, 8.9 mmol). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 – 2.68 (m, 1H), 2.67 – 2.49 (m, 3H), 2.41 – 2.19 (m, 2H), 2.16 – 1.92 (m, 2H), 1.88 – 1.34 (m, 8H), 1.31 – 0.97 (m, 4H).

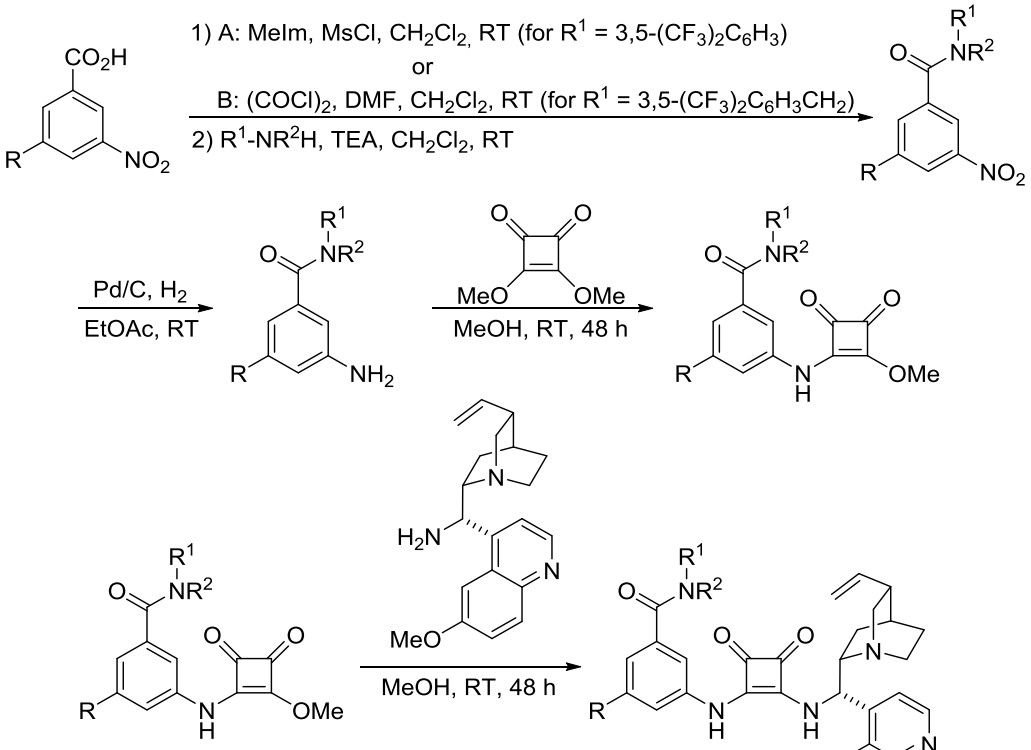
[218] W. Yang, D.-M Du, *Adv. Synth. Catal*. **2011**, *353*, 1241–1246.

[219] Y. Zhu, J. P. Malerich,.V. H. Rawal, *Angew. Chem. Int. Ed*. **2010**, *49*, 153–156.

2nd step:[218] To a suspension of the squaric ester monoamide described above in section 5.2.2.1 (339 mg, 1.0 mmol, 1 equiv.) in 5 mL of CH_2Cl_2 was added 2-(piperidin-1-yl)cyclohexanamine (379 mg, 1.0 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature. After solvent evaporation the desired product was obtained by silica gel column chromatography (eluting with CH_2Cl_2/MeOH, 98:2). White solid. m. p. 134–136 °C. Yield: 71% (347 mg, 0.71 mmol). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.43 (s, 1H), 4.00 – 3.80 (m, 1H), 2.66 – 2.49 (m, 2H), 2.39 – 2.14 (m, 3H), 1.93 – 1.59 (m, 4H), 1.48 – 0.98 (m, 10H).

*5.2.2.4. Preparation of catalysts **C13, C28** and **C31-C33***

Amide group-bearing squaramide-based catalysts **C13**, **C28** and **C31-C33** were prepared according to the following synthetic sequence. Catalyst **C31**[220] was previously described in in our group and the rest were synthesised for the first time:



[220] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.

1st step: Method A:[221] 1-Methylimidazole (1.0 mL, 1.25 mmol, 2.5 equiv.) was added to a slurry of the corresponding 3-nitrobenzoic acid (5 mmol, 1 equiv.) in CH_2CL_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (0.58 mL, 7.5 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL) was added to the mixture under –5 °C. After the resulting mixture was stirred under that temperature for 20 min and then 3,5-bis(trifluoromethyl)aniline (0.78 mL, 5 mmol, 1 equiv.) was added. The mixture was stirred at room temperature for 2 h. H_2O (50 mL) was then added and a solid precipitated, which was solved in EtOAc (50 mL). The organic layer was washed with brine (3 × 25 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the desired amide as a white solid in quantitative yield.

Method B: Oxalyl chloride (0.47 mL, 5.5 mmol, 1.1 equiv.) was added to a suspension of the corresponding 3-nitrobenzoic acid (5 mmol, 1 equiv.) in dichloromethane (5 mL) at 0 ºC under nitrogen atmosphere. DMF (1 drop) was then added and the mixture was allowed to stir at room temperature for 2 h, observing the complete dissolution of the solid. The resulting crude was concentrated under reduced pressure and slowly added to a solution of the corresponding benzylamine (5 mmol, 1 equiv.) and triethylamine (2.1 mL, 15 mmol, 3 equiv.) in dichloromethane (15 mL) at 0 ºC under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and EtOAc (30 mL) was added. The organic phase was washed with aqueous HCl (1 M) (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure affording the desired amide as a white solid in quantitative yield.

2nd step: To a solution of the previous benzamide (5 mmol) in EtOAc (15 mL) under inert atmosphere, Pd/C was added (230 mg, Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product quantitatively, which was used for the preparation of the corresponding squaric ester monoamide without further purification.

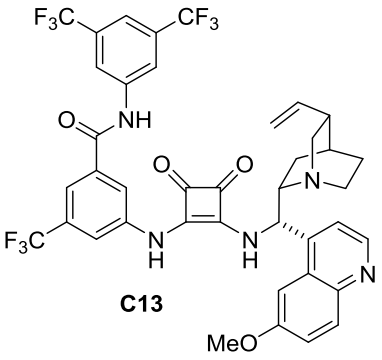
3rd step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (280 mg, 2.0 mmol) in MeOH (20 mL) was added the corresponding amine (2.0 mmol) and the reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give the squaric ester monoamide.

4th step: To a suspension of the corresponding squaric ester monoamide prepared above (1.0 mmol) in CH_2Cl_2 (5 mL) was added 9-amino-(9-deoxy)*epi*quinine (323 mg, 1.0

[221] Adapted from: L. Mao, Z. Wang, Y. Li, X. Han, W. Zhou, *Synlett* **2011**, *1*, 129–133.

mmol) and the reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography (eluting hexane/EtOAc 50:50 → 0:100), affording the catalysts corresponding catalyst.

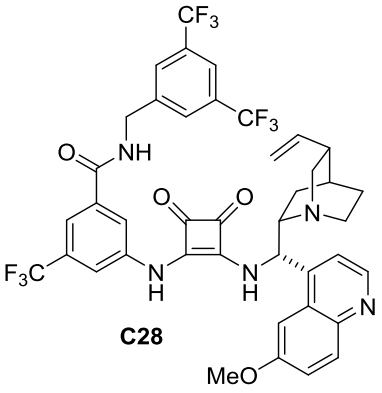
N-(3,5-bis(Trifluoromethyl)phenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C13)



C13

The title compound was prepared according to the general procedure described above starting from 3-nitro-5-(trifluoromethyl)benzoic acid (1.2 g, 5 mmol, 1 equiv.) and 3,5-bis(trifluoromethyl)aniline (1.1 g, 5 mmol, 1 equiv.). Yellow solid. Yield of 4th step: 68% (555 mg, 0.68 mmol). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 9.24 (s, 1H), 8.13 (d, J = 4.6 Hz, 1H), 7.81 (s, 2H), 7.55 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.21 – 6.67 (m, 8H), 5.48 – 5.16 (m, 2H), 4.46 – 4.19 (m, 2H), 3.29 (s, 3H), 2.89 – 2.58 (m, 3H), 2.15 – 1.90 (m, 2H), 1.61 (s, 1H), 1.08 – 0.65 (m, 4H), -0.02 (s, 1H). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ 184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3, 143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.7, 27.3, 26.0. **MS:** calculated for $C_{40}H_{42}NO_4F_9$ ($M + H^+$): 472.3035; found: 472.3039.

N-(3,5-bis(trifluoromethyl)benzyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C28)

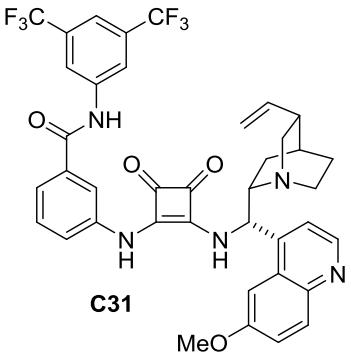


C28

The title compound was prepared according to the general procedure described above starting from 3-nitro-5-(trifluoromethyl)benzoic acid (1.2 g, 5 mmol, 1 equiv.) and 3,5-bis(trifluoromethyl)benzylamine (1.2 g, 5 mmol, 1 equiv.). Yellow solid. Yield of 4th step: 84% (698 mg, 0.84 mmol). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.38 (t, J = 5.9 Hz, 1H), 8.80 (d, J = 4.5 Hz, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 8.02 (s, 2H), 8.01–7.94 (m, 2H), 7.92 (t, J = 1.8 Hz, 1H), 7.84 (s, 1H), 7.75 (d, J = 2.7 Hz, 1H), 7.66 (d, J = 4.6 Hz, 1H), 7.44 (dd, J = 9.2, 2.5 Hz, 1H), 5.97 (ddd, J = 17.6, 10.2, 7.7 Hz, 2H), 5.15–4.89 (m, 2H), 4.66 (d, J = 5.8 Hz, 2H), 3.95 (s, 3H), 3.33–3.08 (m, 3H), 2.81–2.55 (m, 2H), 2.34–2.18 (m, 1H), 1.69–1.40 (m, 4H), 0.77–0.59 (m, 1H). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ 184.6, 180.0, 168.4, 164.8, 163.1,

157.9, 147.8, 144.3, 143.1, 142.8, 142.1, 140.1, 136.0, 131.5 (q), 130.5 (q), 130.2, 128.3, 128.3, 127.4, 125.5, 125.2, 121.9, 121.6, 120.9, 120.8, 120.8, 120.7, 117.3, 117.3, 117.1, 114.4, 101.5, 58.9, 55.7, 42.2, 27.3, 26.0. **MS:** calculated for $C_{41}H_{35}N_5O_4F_9$ ($M + H^+$): 832.2545; found: 832.2559.

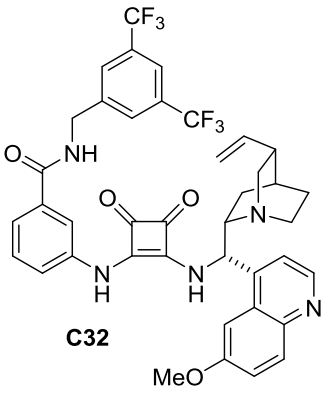
N-(3,5-bis(Trifluoromethyl)phenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C31)



C31

The title compound was prepared according to the general procedure described above starting from 3-nitrobenzoic acid (840 mg, 5 mmol, 1 equiv.) and 3,5-bis(trifluoromethyl)aniline (1.1 g, 5 mmol, 1 equiv.). White solid. Yield of 4th step: 68% (510 mg, 0.68 mmol). All spectroscopic data were identical to those reported in literature. **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, J = 4.5 Hz, 1H), 8.47 (d, J = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, J = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, J = 4.6 Hz, 1H), 7.45 (dd, J = 9.2, 2.4 Hz, 1H), 6.22–5.82 (m, 2H), 5.30–4.81 (m, 2H), 3.96 (s, 3H), 3.56–3.06 (m, 4H), 2.85–2.55 (m, 2H), 2.28 (q, J = 8.0, 7.2 Hz, 1H), 1.84–1.34 (m, 4H), 0.68 (s, 1H).

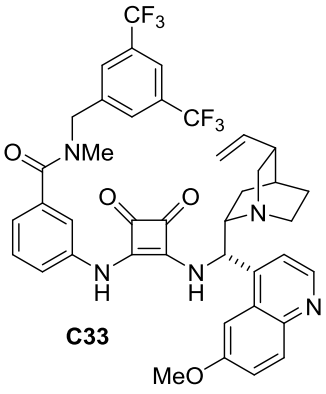
N-(3,5-bis(Trifluoromethyl)benzyl)-3-((2-(((1*S*)-(6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C32)



C32

The title compound was prepared according to the general procedure described above starting from 3-nitrobenzoic acid (840 mg, 5 mmol, 1 equiv.) and 3,5-bis(trifluoromethyl)benzylamine (1.2 g, 5 mmol, 1 equiv.). Yellow solid. Yield of 4th step: 90% (686 mg, 0.90 mmol). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.14 (s, 1H), 8.79 (d, J = 4.5 Hz, 1H), 8.39 (s, 1H), 8.04–7.95 (m, 3H), 7.77 (d, J = 9.0 Hz, 2H), 7.71–7.63 (m, 2H), 7.54–7.36 (m, 3H), 6.13–5.86 (m, 2H), 5.09–4.86 (m, 2H), 4.71–4.56 (m, 2H), 3.95 (s, 3H), 3.46 (dd, J = 18.2, 9.3 Hz, 1H), 3.19 (dd, J = 13.4, 10.1 Hz, 1H), 2.82–2.58 (m, 2H), 2.27 (t, J = 9.1 Hz, 1H), 1.52 (t, J = 20.0 Hz, 4H). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ 184.2, 179.8, 168.1, 166.2, 163.6, 157.8, 147.8, 144.3, 143.2, 142.1, 139.0, 135.1, 131.5, 130.4, 129.9, 129.4, 128.1, 127.4, 125.1, 121.9, 121.1, 120.6, 117.4, 114.3, 101.5, 55.7, 55.6, 42.0, 30.7, 27.3, 26.0. **MS:** calculated for $C_{40}H_{36}N_5O_4F_6$ ($M + H^+$): 764.2671; found: 764.2676.

N-(3,5-bis(Trifluoromethyl)benzyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-N-methylbenzamide (C33)



C33

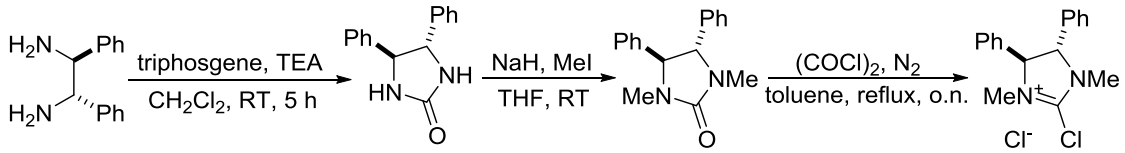
The title compound was prepared according to the general procedure described above starting from 3-nitrobenzoic acid (840 mg, 5 mmol, 1 equiv.) and 3,5-bis(trifluoromethyl)benzylmethylamine[222] (1.3 g, 5 mmol, 1 equiv.). Yellow solid. Yield of 4th step: 90% (700 mg, 0.90 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.1 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 16.0 Hz, 2H), 7.54–7.28 (m, 4H), 6.98 (s, 2H), 6.89–6.73 (m, 1H), 6.22 (s, 1H), 5.87–5.69 (m, 1H), 5.04–4.87 (m, 2H), 4.85–4.54 (m, 2H), 3.95 (s, 3H), 3.63–3.34 (m, 2H), 3.17 (t, *J* = 11.4 Hz, 1H), 2.87 (s, 3H), 2.81–2.63 (m, 2H), 2.35–2.19 (m, 1H), 1.75–1.42 (m, 4H), 0.78–0.64 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 183.7, 181.3, 171.5, 168.7, 163.3, 158.7, 147.2, 144.5, 143.4, 141.0, 139.3, 138.5, 136.0, 132.2, 131.8, 131.3, 129.4, 127.9, 127.0, 124.8, 122.6, 121.7, 121.2, 120.4, 118.7, 117.4, 114.7, 101.1, 77.2, 59.7, 55.9, 50.4, 40.7, 39.3, 37.4, 27.4, 26.1. **MS:** calculated for $C_{40}H_{36}N_5O_4F_6$ ($M + H^+$): 764.2671; found: 764.2676.

*5.2.2.5. Preparation of catalysts **C14-C17***

New catalysts **C14-C17** were synthesised as follows:

Preparation of the imidazolium chlorides

Known imidazolium salt intermediates were prepared according to a previously reported synthetic sequence:[223]



[222] Prepared following the procedure previously described: A. Arasappan *et al.*, *PCI Int. Appl.* **2011**, 2011103441.

[223] T. Ma, X. Fu, C. W. Kee, L. Zong, Y. Pan, K. Huang, C. Tan, *J. Am. Chem. Soc.* **2011**, *133*, 2828–2831.

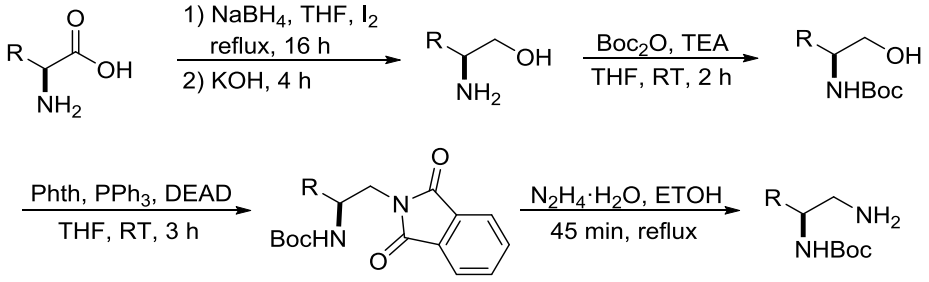
1st step: Triphosgene (2.93 g, 10 mmol, 1 equiv.) was slowly added to a solution of the corresponding 1,2-iphenylethylenediamine (6.36 g, 30 mmol, 1 equiv.) and triethylamine (12.3 mL, 90 mmol, 3 equiv.) in CH_2Cl_2 (75 mL) at 0 ºC. The reaction was then stirred for 5 h at room temperature and quenched adding H_2O (60 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the desired intermediate as a yellow solid quantitatively, which was subsequently used without further purification. All spectroscopic data were identical to those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.3 Hz, 5H), 7.31 – 7.25 (m, 5H), 5.03 (s, 2H), 4.59 (s, 2H).

2nd step: The solid obtained in the previous step was dissolved in dry THF (45 mL) and it was slowly added to a suspension of NaH (2.2 g, 90 mmol, 3 equiv.) in THF (60 mL). The reaction mixture was stirred at room temperature for 30 min and iodomethane (6.9 mL, 111 mmol, 3.7 equiv.) was added. After completion of the reaction (TLC monitoring) the resulting mixture was filtered through celite and the reaction crude was concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc 60:40), affording the dimethylated intermediate as a white solid. Yield: 66% (5.2g, 20 mmol). All spectroscopic data were identical to those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 5.0, 2.0 Hz, 6H), 7.18 (dt, *J* = 6.1, 2.4 Hz, 4H), 4.12 (s, 2H), 2.74 (s, 6H).

3rd step: To a solution of the previously obtained solid (5.2 g, 20 mmol, 1 equiv.) in toluene (130 mL) oxalyl chloride (16.8 mL, 200 mmol, 10 equiv.) was added and the reaction mixture was refluxed for 16 h. The solvent was eliminated under reduced pressure with big care to avoid contact of the compound with air and the resulting white solid was stored under Ar in a desiccator until it was submitted to the next step. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.47 – 7.41 (m, 6H), 5.30 (s, 2H), 3.21 (s, 6H).

Preparation of Boc-protected diamines

Previously known Boc-protected diamine intermediates were prepared according to the following synthetic sequence:



1st step:[224] The corresponding amino acid (50 mmol, 1 equiv.) was added to a suspension of $NaBH_4$ (4.78 g, 125 mmol, 2.5 equiv.) in THF (120 mL), and the resulting mixture was cooled to 0 ºC before I_2 (12.7 g, 50 mmol, 1 equiv.) in THF (30 mL) was added over a 30 min period. Then, the reaction mixture was allowed to warm to room temperature, and after the evolution of gas ceased it was refluxed for 16 h. The reaction was quenched by slow addition of MeOH at 0 ºC, and the solvent was removed under reduced pressure. The solid residue was dissolved in KOH (20%; 100 mL), stirring at room temperature for 4 h and the resulting solution was extracted with CH_2Cl_2 (5 x 50 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the corresponding aminoalcohol as a colourless oil, which was used in the next step without further purification. Yield: Cuantitative.

2nd step:[225] To a solution of the previously obtained aminoalcohol (30 mmol, 1 equiv.) and triethylamine (4.2 mL, 30 mmol, 1 equiv.) in THF (90 mL) Boc_2O (6.54 g, 30 mmol, 1 equiv.) was added at 0 ºC, and the resulting mixture was allowed to stir at room temperature for 2 h. The solvent was removed under vacuum and the solid residue was redissolved in EtOAc (75 mL), washed with H_2O (2 x 75 mL) and brine (75 mL). The organic phase was then dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the corresponding *N*-boc aminoalcohol, which was subsequently used without further purification. Yield: Cuantitative.

3rd step:[226] A solution of phthalic anhydride (3.35 g, 22.8 mmol, 1.5 equiv.), triphenylphosphine (11.9 g, 45 mmol, 3 equiv.) and the alcohol above obtained (15 mmol, 1 equiv.) in dry THF (150 mL) was cooled to 0 ºC and diethylazodicarboxylate (DEAD; 5.95 mL, 37.5 mmol, 2.5 equiv.) was slowly added. The resulting mixture was

[224] M. Nakamura, T. Hatakeyama, K. Hara, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 6362–6363.

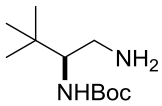
[225] C. Ebner, A. Pfaltz, *Tetrahedron.* **2011**, *67*, 10287–10290.

[226] C. A. Busacca, D. Grossbach, E. Spinelli, *Tetrahedron: Asymmetry* **2000**, *11*, 1907–1910.

let to warm to room temperature and it was stirred at the same temperature for 3 h. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (eluting with hexane/EtOAc 80:20), affording the corresponding phthalimide as a white solid. Yield: 80–90%.

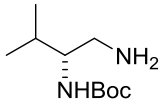
4th step:[226] Hydrazine monohydrate (2.43 mL, 50 mmol, 5 equiv.) was added to a solution of the previously obtained solid (10 mmol, 1 equiv.) in EtOH (85 mL) and the mixture was refluxed for 45 min, observing the formation of a white solid. After cooling to room temperature, the mixture was filtered through a pad of celite and the filtrate was washed with Et_2O (150 mL). The liquid phase was then washed with H_2O (100 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure affording the Boc-protected diamine as a white solid, which was used in the next step without further purification. Yield: 80–85%.

***tert*-Butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate**[227]



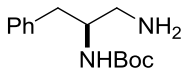
Prepared starting from L-*tert*-leucine (1.8 g, 8.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.40 (d, *J* = 10.3 Hz, 1H), 3.33 (td, *J* = 10.3, 3.1 Hz, 1H), 2.95 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.39 (dd, *J* = 13.3, 10.3 Hz, 1H), 1.45 (s, 9H), 1.06 (bs, 2H), 0.90 (s, 9H).

***tert*-Butyl (*R*)-(1-amino-3-methylbutan-2-yl)carbamate**[226]



Prepared starting from D-valine (1.6 g, 8.0 mmol).**^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.54 (s, 0H), 3.39 (s, 0H), 2.83 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.65 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.78 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.48 (s, 6H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

***tert*-Butyl (*S*)-(1-amino-3-phenylpropan-2-yl)carbamate**[228]

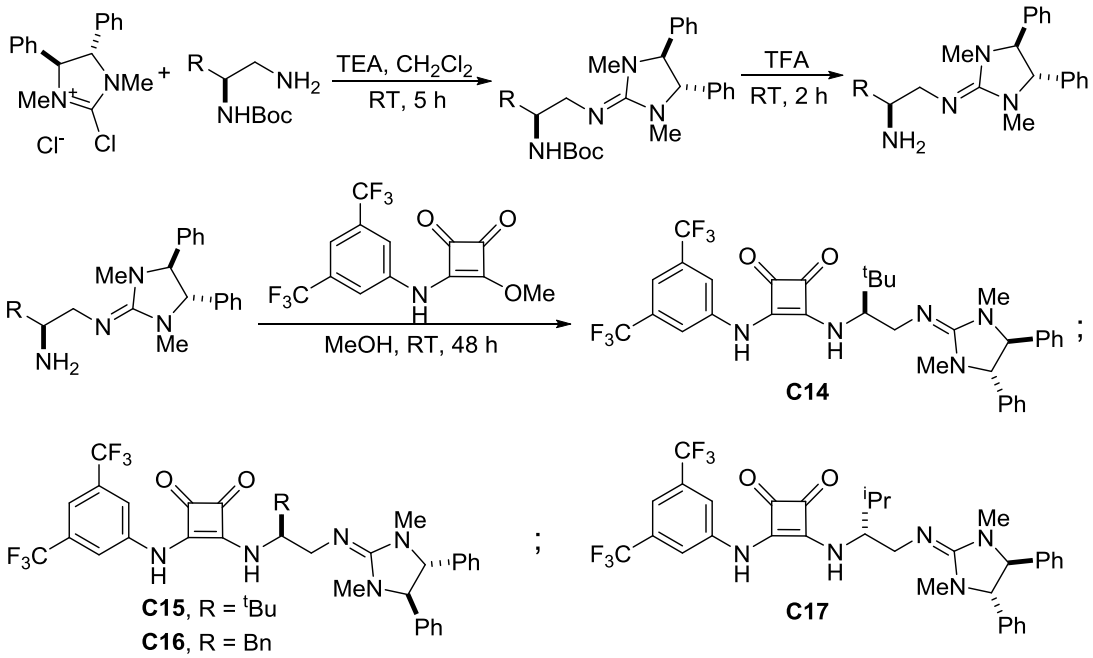


Prepared starting from L-phenylalanine (2.1 g, 8.4 mmol).**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 5H), 4.66 (bs, 1H), 3.86 – 3.72 (m, 1H), 2.83 – 2.56 (m, 4H), 1.41 (s, 9H), 1.17 (bs, 2H).

[227] H. Cho *et al.*, *PCI Int. Appl.* **2002**, 2002014324.

[228] G. Kokotos, V. Constantinou-Kokotou, *J. Chem. Res.* **1992**, *12*, 391.

Preparation of catalysts C14-C17

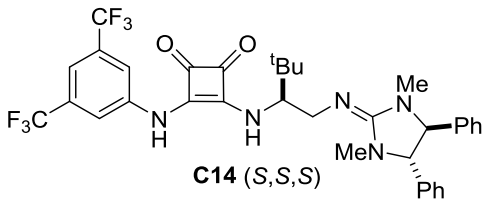


1st step: A solution of the above prepared amine (1 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added to a solution of the previously obtained imidazolium salt (1.5 mmol, 1.5 equiv.) in CH_2Cl_2 (5 mL) and TEA (1.25 mL, 9 mmol, 9 equiv.) was added to the resulting solution. The reaction mixture was stirred at room temperature for 5 h making sure that the reaction media remained basic, and then the reaction was quenched by adding HCL 3 M. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the crude product, which was subsequently purified by flash column chromatography (CH_2Cl_2/MeOH 90:10) affording the pure product as a viscous oil. Yield: 60–70%.

2nd step: The guanidine above obtained (0.6 mmol) was dissolved in TFA and the resulting solution was stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (5 mL). The solution was washed with NaOH 2 M (5 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the crude product, which was used in the next step without further purification. Yield: Cuantitative.

3rd step: To a suspension of the squaric ester monoamide prepared above (Section 5.2.2.1, 170 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added the previously obtained amine (0.5 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography (eluting CH_2Cl_2/MeOH 95:5).

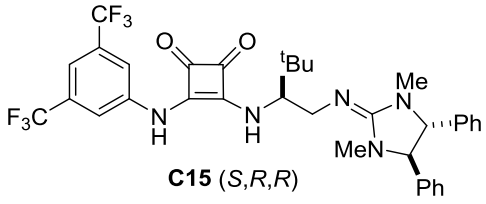
3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((*S*)-1-(((4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3,3-dimethylbutan-2-yl)amino)cyclobut-3-ene 1,2-dione (C14)



C14 (*S*,*S*,*S*)

The title compound was prepared from *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate (182 mg, 0.5 mmol) and the *S*,*S*-imidazolium salt. Yellow solid. m. p. = 137–141 ºC. Yield: 15%, (50 mg, 0.075 mmol). **[α]$_D^{23}$**= +30.7º (*c* = 0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.49 – 7.08 (m, 11H), 4.39 (d, *J* = 15.7 Hz, 1H), 4.17 (t, *J* = 24.9 Hz, 2H), 4.05 – 3.70 (m, 1H), 3.05 – 2.70 (m, 6H), 1.10 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 185.4, 180.1, 169.5, 165.1, 160.7, 141.1, 135.4, 135.0, 132.2, 129.7, 129.5, 126.8, 125.0, 121.3, 118.2, 115.3, 77.2, 75.9, 73.1, 63.8, 42.9, 36.1, 26.4. **MS:** calculated for $C_{35}H_{36}N_5O_2F_6$ ($M + H^+$), 672.2773; found, 672.2775.

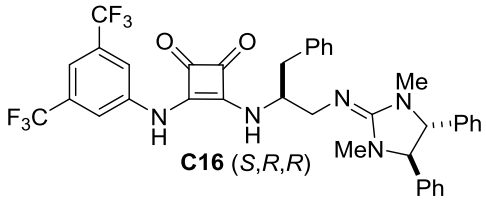
3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((*S*)-1-(((4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3,3-dimethylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (C15)



C15 (*S*,*R*,*R*)

The title compound was prepared from *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate (182 mg, 0.5 mmol) and the *R*,*R*-imidazolium salt. Yellow solid. m. p. = 162–165 ºC. Yield: 70%, (235 mg, 0.35 mmol). **[α]**$_D^{24}$= – 25.0º (*c* = 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.46 – 7.26 (m, 7H), 7.11 (dd, *J* = 22.0, 7.9 Hz, 4H), 4.34 (s, 1H), 4.30 – 4.18 (m, 1H), 4.08 – 3.97 (m, 1H), 3.96 – 3.82 (m, 1H), 3.00 (s, 6H), 2.85 (s, 1H), 2.72 – 2.63 (m, 1H), 1.12 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.1, 180.8, 170.2, 165.7, 161.4, 141.8, 136.1, 135.7, 132.9, 130.4, 130.2, 127.5, 125.6, 122.0, 118.9, 115.9, 77.9, 76.6, 73.8, 64.5, 43.6, 36.8, 27.1. **MS:** calculated for $C_{35}H_{36}N_5O_2F_6$ ($M + H^+$), 672.2773; found, 672.2775.

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((*S*)-1-(((4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3-phenylpropan-2-yl)amino)cyclobut-3-ene-1,2-dione (C16)

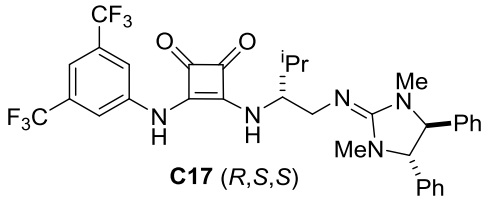


C16 (*S*,*R*,*R*)

The title compound was prepared from *tert*-Butyl (*S*)-(1-amino-3-phenylpropan-2-yl)carbamate (202 mg, 0.5 mmol) and the *R*,*R*-imidazolium salt. Yellow solid. m. p. = 140–145 ºC. Yield: 84%, (296 mg, 0.42 mmol). **[α]**$_D^{24}$=

9.2º (*c* = 1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.48 – 7.08 (m, 15H), 6.81 (s, 2H), 4.68 (bs, 1H), 4.48 (bs, 1H), 4.34 – 4.19 (m, 1H), 4.05 (bs, 1H), 3.90 – 3.78 (m, 1H), 3.36 – 3.06 (m, 1H), 2.86 (s,3H), 2.58 (s, 3H), 1.38 – 1.19 (m, 2H), 0.96 – 0.78 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.4, 180.9, 169.8, 165.2, 165.0, 164.3, 159.3, 158.9, 141.7, 137.3, 136.6, 135.2, 134.8, 132.1, 129.4, 128.6, 127.1, 126.9, 126.6, 124.9, 121.3, 118.7, 118.4, 115.0, 76.4, 73.9, 57.5, 56.8, 40.4, 33.2, 29.4. **MS:** calculated for $C_{38}H_{34}N_5O_2F_6$ (M, H^+), 706.2617; found, 706.2632.

3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((*R*)-1-(((4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3-methylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (C17)



C17 (*R*,*S*,*S*)

The title compound was prepared from *tert*-butyl *tert*-Butyl (*R*)-(1-amino-3-methylbutan-2-yl)carbamate (175 mg, 0.5 mmol) and the *S*,*S*-imidazolium salt. Yellow solid. m. p. = 150–154 ºC. Yield: 60%, (197 mg, 0.30 mmol). **[α]**$_D^{23}$= +31.5º (*c* = 0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, CH_2Cl_2) δ 8.17 (s, 1H), 7.38 – 7.23 (m, 7H), 7.09 (d, *J* = 5.6 Hz, 4H), 4.39 (s, 2H), 4.19 – 3.96 (m, 3H), 3.04 (s, 6H), 2.30 – 2.11 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 185.1, 180.48 , 169.7, 165.0, 160.0, 141.4, 135.4, 129.5, 129.4, 126.7, 125.0, 121.3, 118.3, 114.9, 74.1, 60.9, 45.1, 34.7, 31.1, 29.6, 18.9, 18.5. **MS:** calculated for $C_{34}H_{34}N_5O_2F_6$ (M + H^+), 658.2617; found, 658.2625.

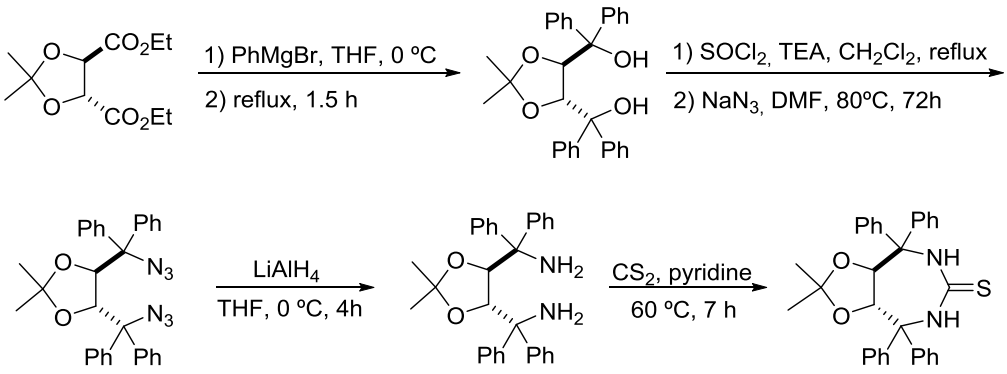
*5.2.2.6. Preparation of catalysts **C18** and **C22***

New catalysts **C18** and **C22** were synthesised as follows:

Preparation of the thiourea intermediate

The known thiourea intermediate was prepared following a previously described synthetic sequence:[229]

[229] L. Zou, X. Bao, Y. Ma, Y. Song, J. Qu, B. Wang, *Chem. Commun.* **2014**, *50*, 5760–5762.



1st step: A solution of diethyl(2*R*,3*R*)-2,3-*O*-isopropildentartrate (14.8 g, 60 mmol, 1 equiv.) in THF (15 mL) was slowly added to phenylmagnesium bromide (3 M in THF; 100 mL, 300 mmol, 5 equiv.) at 0 ºC, and the reaction mixture was refluxed for 1.5 h. After cooling, a saturated solution of NH_4Cl (400 mL) was added, and the organic phase was separated. The aqueous phase was then extracted with EtOAc (1 x 150 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the crude product, which was purified by recrystallization from CH_2Cl_2/hexane, affording the diol as a white solid. All spectroscopic data were identical to those reported in the literature. Yield: 95% (27 g, 57 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.35 (m, 16H), 4.61 (s, 2H), 3.95 (s, 2H), 1.05 (s, 6H).

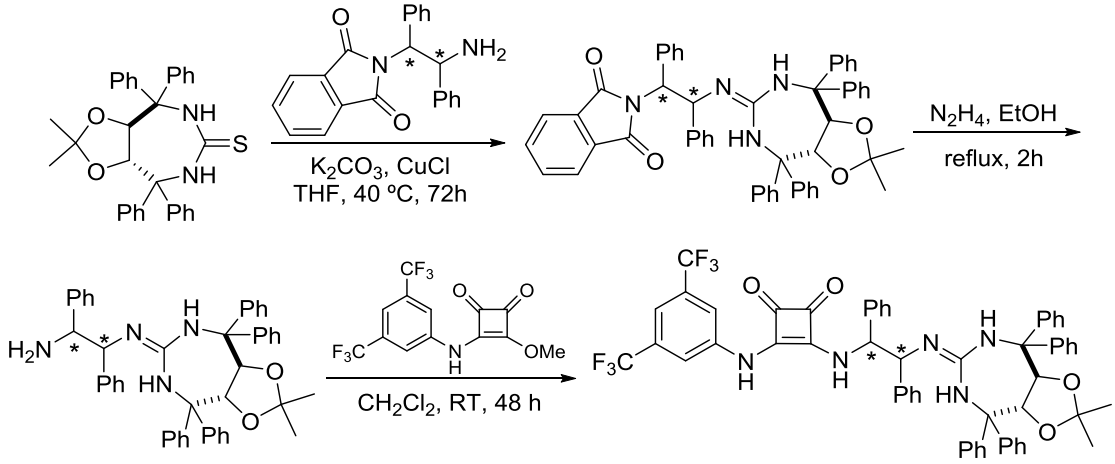
2nd step: To a solution of the diol (4.7 g, 10 mmol, 1 equiv.) in CH_2Cl_2 (60 mL) at room temperature thionyl chloride was added (1.8 g, 30 mmol, 3 equiv.) and the mixture was warmed to reflux and TEA (4.2 g, 42 mmol, 4.2 equiv.) in CH_2Cl_2 (60 mL) was added during a 3 h period. The reaction mixture was stirred until complete consumption of the starting material was observed by TLC, and the solvent was eliminated under reduced pressure. The residue was dissolved in DMF (50 mL) and to this solution sodium azide (2.6 g, 40 mmol, 4 equiv.) was added and the reaction mixture was stirred at 80 ºC for 72 h. After cooling to room temperature, H_2O (150 mL) was added and the aqueous solution was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with water (3 x 100 mL) dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography (eluting hexane /acetate 80:20) to afford the diazide as a yellow solid. All spectroscopic data were identical to those reported in the literature. Yield: 84% (3.9 g, 8.4 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (m, 20H), 4.64 (s, 2H), 1.07 (s, 6H).

3rd step: To a solution of the above obtained diazide (3.6 g, 7 mmol, 1 equiv.) in dry THF (40 mL) at 0 ºC was added dropwise a suspension of $LiAlH_4$ (1,6 g, 42 mmol, 6 equiv.) in dry THF (40 mL) and the reaction mixture was stirred at the same temperature for further 4 h. Then, NaOH 1M (5 mL) was added dropwise, the mixture

was diluted with Et_2O (200 mL) and $Na_2SO_4 \cdot 10\ H_2O$ (20 g) was added. The mixture was stirred for 2 h at room temperature before being filtered, and the filtrate was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the crude product. The product was purified by flash column chromatography (eluting CH_2Cl_2/MeOH 80:20) to afford the diamine as a white solid. All spectroscopic data were identical to those reported in the literature. Yield: 53% (1.72 g, 3.7 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (m, 4H), 7.35 (m, 6H), 7.19 (m, 10 H), 4.28 (s, 2H), 2.32 (brs, 4H), 1.12 (s, 6H).

4th step: To a solution of the diamine obtained above (1.4 g, 3.0 mmol 1 equiv.) in pyridine (5 mL) was added carbon disulphide (361 µL, 6.0 mmol, 2 equiv.) and the resulting mixture was stirred at 60 ºC for 7 h. Then CH_2Cl_2 (20 mL) and H_2O (10 mL) were added and the pH was adjusted to 2 adding HCl 1 M dropwise. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with NaOH 1 M (1 x 50 mL) and brine (1 x 50 mL), subsequently. The organich phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the crude product, which was crushed with a hexane/CH_2Cl_2 mixture and filtered, affording the pure thiourea as a white solid. All spectroscopic data were identical to those reported in the literature. Yield: 81% (1.2 g, 2.4 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.42 (m, 6H), 7.28 (m, 6H), 7.15 (m, 4H), 6.85 (s, 2H), 4.59 (s, 2H), 1.20 (s, 6H).

Preparation of catalysts C18 and C22



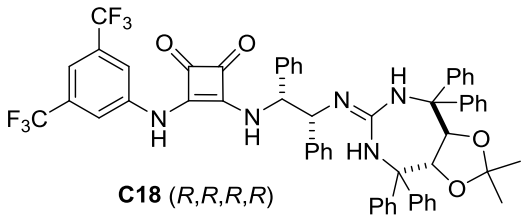
1st step:[229] The thiourea intermediate above prepared (250 mg, 0.50 mmol, 1 equiv.) was added to a suspension of K_2CO_3 (1.0 g, 7.5 mmol, 15 equiv.) and CuCl (1.0 g, 1.05 mmol, 2.1 equiv.) in dry THF (5 mL) and the resulting mixture was stirred for 10 min at room temperature before adding the corresponding *N*-phthaloyl-1,2-

diphenylethylenediamine[230] (171 mg, 0.5 mmol, 1 equiv.). The reaction mixture was then stirred at 40 ºC for 72 h and a saturated solution of NH_4Cl (2 mL) was added. Then HCl 1 M was added dropwise until pH 5 was reached, the mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic phase was washed with brine (1 x 10 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography (eluting CH_2Cl_2/MeOH 95:5) to afford the guanidine intermediate as a yellow solid. Yield: 60–70%.

2nd step: Hydrazine monohydrate (0.38 mL, 3.0 mmol, 10 equiv.) was added to a solution of the previously obtained solid (245 mg, 0.3 mmol, 1 equiv.) in EtOH (1 mL) and the mixture was refluxed for 45 min, observing the formation of a white solid. After cooling to room temperature, the mixture was filtered through a pad of celite and the filtrate was washed with Et_2O (15 mL). The liquid phase was then washed with H_2O (10 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure affording the crude amine, which was crushed in MeOH and filtered to afford the pure intermediate. Yield: 75–85%.

3rd step: To a suspension of the squaric ester monoamide prepared above (Section 5.2.2.1, 68 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added the previously obtained amine (0.5 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography (eluting hexane/EtOAc 50:50).

3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((1*R*,2*R*)-2-(((3a*R*,8a*R*)-2,2-dimethyl-4,4,8,8-tetraphenylhexahydro-6*H*-[1,3]dioxolo[4,5-e][1,3]diazepin-6-ylidene)amino)-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (C18)



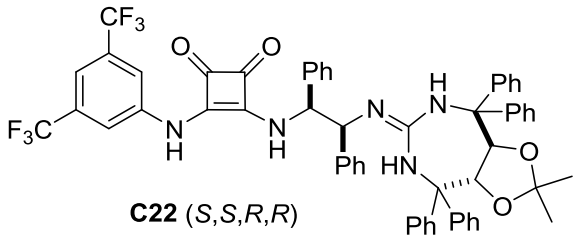
C18 (*R*,*R*,*R*,*R*)

The title compound was prepared according to the general procedure above described. Yellow solid. m. p. = 178–182 ºC. Yield after 3 steps: 12%, (47 mg, 0.070 mmol). $[\alpha]_D^{24}$= +38.8º (*c* = 1.00, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.66 – 7.48 (m, 9H), 7.45 – 7.23 (m, 16H), 7.16 (d, *J* = 3.2 Hz, 7H), 6.98 (s, 2H), 4.69 (s, 1H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.23 (s, 1H), 4.02 (d, *J* = 8.0 Hz, 1H), 1.24 (s, 3H), 0.74 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.2, 188.4, 176.1, 157.9, 149.2, 141.7, 129.8, 129.6, 129.0, 128.8, 128.4, 128.1, 127.3, 126.7, 126.3, 117.6, 113.8, 108.3, 83.9, 81.0, 68.2, 66.1, 62.2, 27.2, 26.6.

[230] Prepared following the procedure previously described: M. Kaik, J. Gawronski, *Chem. Commun.* **2003**, *14*, 1559–1563.

MS: calculated for $C_{46}H_{45}N_4O_2$ (M – squaric ester monoamide), 685.3537; found, 685.3533.

3-((3,5-bis(Trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-(((3a*R*,8a*R*)-2,2-dimethyl-4,4,8,8-tetraphenylhexahydro-6*H*-[1,3]dioxolo[4,5-e][1,3]diazepin-6-ylidene)amino)-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione (C22)

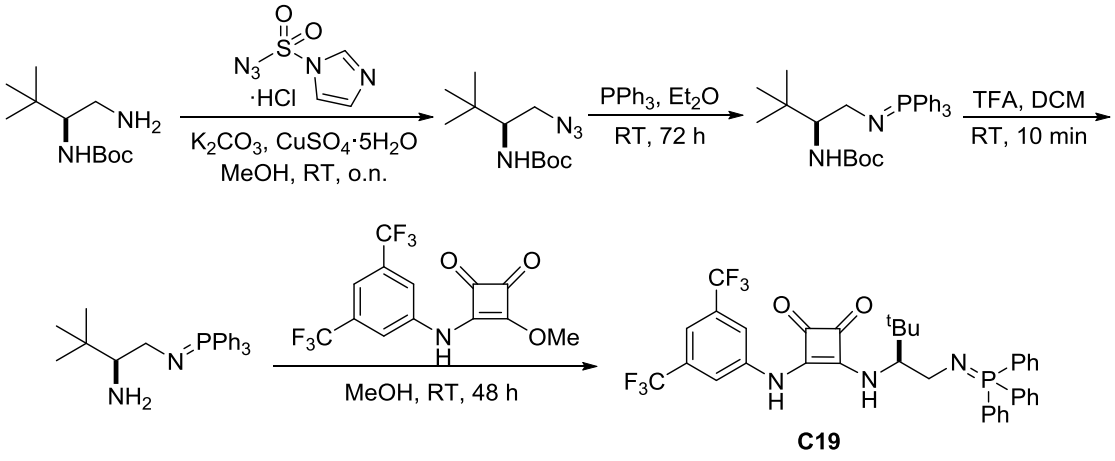


C22 (*S*,*S*,*R*,*R*)

The title compound was prepared according to the general procedure above described. Yellow solid. m. p. = 187–192 ºC. Yield after 3 steps: 18%, (60 mg, 0.090 mmol). $[\alpha]_D^{24}$= +9.7º (*c* = 1.00, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.87 (s, 1H), 7.99 (s, 1H), 7.74 (d, *J* = 7.0 Hz, 2H), 7.64 – 7.50 (m, 8H), 7.46 – 7.09 (m, 22H), 6.56 (d, *J* = 5.6 Hz, 2H), 4.69 (d, *J* = 8.0 Hz, 2H), 4.54 – 4.38 (m, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 1.25 (s, 3H), 1.22 (s, 3H).). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.5, 189.7, 177.4, 159.2, 150.5, 143.0, 131.1, 131.0, 130.3, 130.1, 129.7, 129.4, 128.6, 128.0, 127.6, 118.9, 115.1, 109.6, 85.3, 82.45, 69.5, 67.4, 63.5, 28.6, 27.9. **MS:** calculated for $C_{46}H_{45}N_4O_2$ (M – squaric ester monoamide), 685.3537; found, 685.3533.

*5.2.2.7. Preparation of catalyst **C19***

New catalyst **C19** was prepared according to the following synthetic sequence:



C19

1st step:[231] To a solution of the *N*-Boc diamine above prepared (Section 5.2.2.5; 324 mg, 1.5 mmol, 1 equiv.), K_2CO_3 (351 mg, 2.6 mmol, 1.7 equiv.) and $CuSO_4·5H_2O$ (3.9

[231] M. G. Núñez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

mg, 1 mol %) in MeOH (9 mL) at 0 ºC 1*H*-Imidazole-1-sulfonyl azide hydrochloride[232] (372 mg, 1.8 mmol, 1.2 equiv.) was added carefully in small portions and the reaction mixture was allowed to stir at room temperature overnight. The resulting mixture was concentrated under reduced pressure without heating and was diluted with H_2O (25 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography (eluting hexane/EtOAc 90:10). White solid. All spectroscopic data were identical to those reported in the literature. Yield: 82%, (300 mg, 1.23 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.53 (d, *J* = 8.5 Hz, 1H), 3.71 – 3.54 (m, 1H), 3.47 (dd, *J* = 12.6, 3.5 Hz, 1H), 3.22 (dd, *J* = 12.4, 8.2 Hz, 1H), 1.46 (s, 9H), 0.93 (s, 9H).

2nd step:[232] To a solution of the azide above prepared (242 mg, 1.0 mmol, 1 equiv.) in Et_2O (2.5 mL) was added triphenylphosphine (262 mg, 1.0 mmol, 1 equiv.) and the resulting solution was stirred until the complete disappearance of the azide was observed (TLC monitoring). The solvent was eliminated under reduced pressure affording the desired product as a white foam, which was subsequently used without further purification. Yield: Cuantitative. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.61 (m, 6H), 7.57 – 7.39 (m, 9H), 4.82 (s, 1H), 3.44 – 3.22 (m, 2H), 3.12 – 2.89 (m, 1H), 1.43 (s, 9H), 0.82 (s, 9H).

3rd step:[232] The compound obtained in the previous step (238 mg, 0.5 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 and TFA (1:1, 5 mL) and the resulting solution was stirred at room temperature for 10 min. Then the solvent was eliminated under reduced pressure, and the residue was redissolved in CH_2Cl_2 (5 mL) and washed with NaOH 2 M (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure affording the crude product as a yellow solid, which was used in the next step without further purification.

4th step: To a suspension of the squaric ester monoamide prepared above (Section 5.2.2.1, 200 mg, 1.5 mmol, 3 equiv.) in MeOH (5 mL) was added the previously obtained crude amine (0.5 mmol, 1 equiv.) and the reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography (eluting CH_2Cl_2/MeOH 90:10). White solid. Yield after 2 steps: 32%, (110 mg, 0.16 mmol). **[α]**$_D^{24}$= –25.0º (*c* = 1.00, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.78 (s, 1H), 8.15 (s, 2H), 7.83 – 7.71 (m, 9H), 7.71 – 7.62 (m, 6H), 7.43 (s, 1H), 3.95 – 3.79 (m, 1H), 3.57 – 3.39 (m, 1H), 3.21 – 3.08 (m, 1H), 0.84 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.6, 180.4, 170.5, 164.1, 141.0,

[232] T. Wang, D. Y. W. Ng, Y. Wu, J. Thomas, T. TamTran, T. Weil, *Chem. Commun.* **2014**, *50*, 1116–1118.

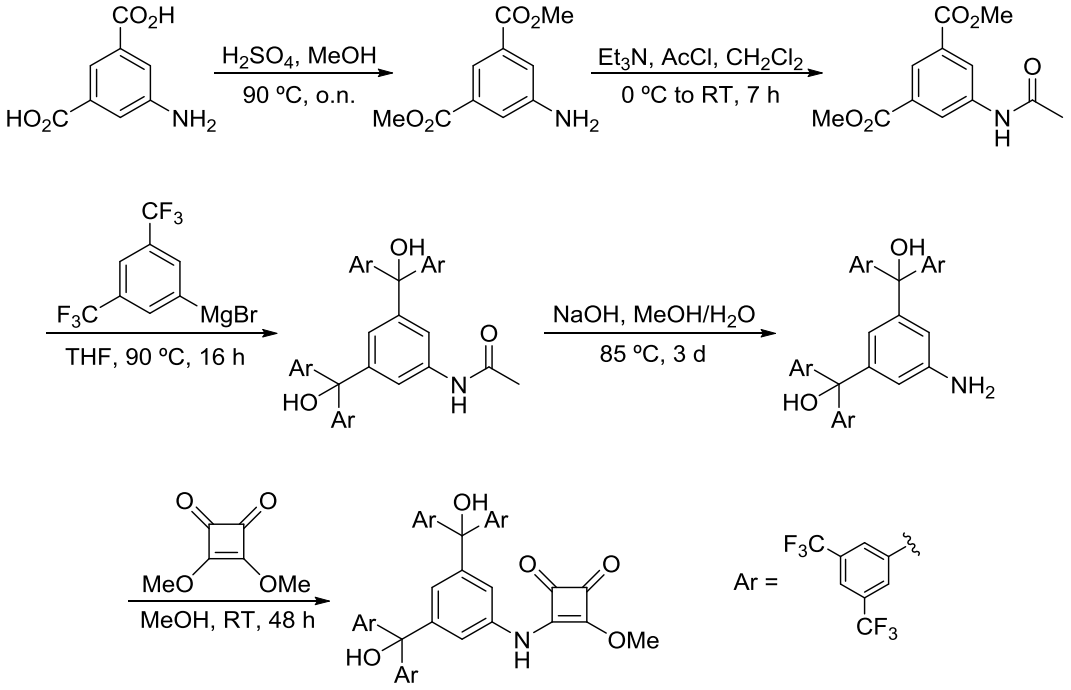
135.2, 133.5, 133.4, 132.1, 131.9, 130.2, 130.0, 128.6, 128.4, 65.1, 42.6, 34.4, 26.0. **MS:** calculated for $C_{36}H_{33}N_3O_2F_6P$ ($M + H^+$), 684.2215; found, 684.2232.

*5.2.2.8. Preparation of catalysts **C29** and **C30***

Catalyst **C29,**[233] previously described in our group, and new catalyst **C30** were synthesised as follows:

Preparation of the squaric ester monoamide

The squaric ester monoamide required for the preparation of catalysts **C29** and **C30** was prepared according to the synthetic sequence previously reported by our group:[233]



1st step: To a solution 5-aminoisophthalic acid (1.81 g, 10 mmol, 1.0 equiv.) in MeOH (20 mL) was added concentrated H_2SO_4 (4.32 mL, 80 mmol, 8 equiv.). The reaction mixture was stirred for 24 h at 90 °C. After allowing the mixture to reach room temperature, the solvent was removed under reduced pressure. Then, water (10 mL) and NaOH 2 M was added until pH 7 and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was obtained as white solid and used

[233] A. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 12758–12762.

without further purification. Yield: 68% (1.54 g, 6.84 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.05 (t, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 2H), 3.92 (s, 6H).

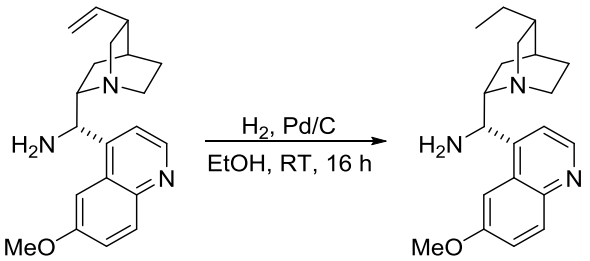
2nd step: To a solution of the crude dimethyl 3-aminophtalate (1.54 g, 6.84 mmol, 1 equiv.) and Et_3N (1.0 mL, 6.84 mmol, 1 equiv.) in CH_2Cl_2 (33 mL) was added dropwise at 0 °C acetyl chloride (0.54 mL, 7.52 mmol, 1.1 equiv.). After stirring for 7 h at room temperature, the reaction mixture was filtered and the solid was washed with cool CH_2Cl_2 (2 × 10 mL) to provide the title compound as white solid which was used in the next step without further purification. Yield: 90% (1.55 g, 6.16 mmol). **^{1}H-NMR** (300 MHz, DMSO-*d*$_6$) δ 10.39 (s, 1H), 8.46 (d, *J* = 1.4 Hz, 2H), 8.21 – 8.10 (m, 1H), 3.89 (s, 6H), 2.08 (s, 3H).

3rd step: A solution of the acetamide ester product obtained above (520 mg, 2.0 mmol, 1 equiv.) in THF (5 mL) was added dropwise at 0 °C to a solution of 3,5-bis(trifluoromethyl)phenyl magnesium bromide (3.2 mL, 0.5M in THF, 8 equiv.) and the mixture was stirred at 90 °C 16 h. The reaction was cooled to room temperature, quenched with a saturated solution of NH_4Cl and solvent evaporated under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 7:3) to give the title compound as a brown solid. Yield: 79% (1.03 g, 1.57 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 4H), 7.64 (d, *J* = 1.7 Hz, 8H), 7.44 (d, *J* = 1.7 Hz, 2H), 7.34 (s, 1H), 2.03 (s, 3H).

4th step: To a solution of the amide obtained above (522 mg, 0.5 mmol, 1 equiv.) in MeOH (4.0 mL) and water (0.5 mL) was added NaOH (400 mg, 10 mmol, 20 equiv.) and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized by slow addition of HCl 1M until pH 7, and then it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the primary amine as a brown solid, which was used in the next step without further purification. Yield: 85% (431 mg, 0.43 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 4H), 7.68 (d, *J* = 1.7 Hz, 8H), 6.52 (d, *J* = 1.6 Hz, 2H), 6.08 (t, *J* = 1.7 Hz, 1H).

5th step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (60 mg, 2.43 mmol) in MeOH (20 mL) was added the above obtained amine (430 mg, 0.43 mmol) and the reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give the squaric ester monoamide. **^{1}H-NMR** (300 MHz, MeOH-*d*$_4$) δ 8.02 – 7.89 (m, 4H), 7.76 (d, *J* = 1.8 Hz, 8H), 7.49 (t, *J* = 2.4 Hz, 2H), 6.68 (s, 1H), 4.27 (s, 3H). Yield: 81% (387 mg, 0.35 mmol).

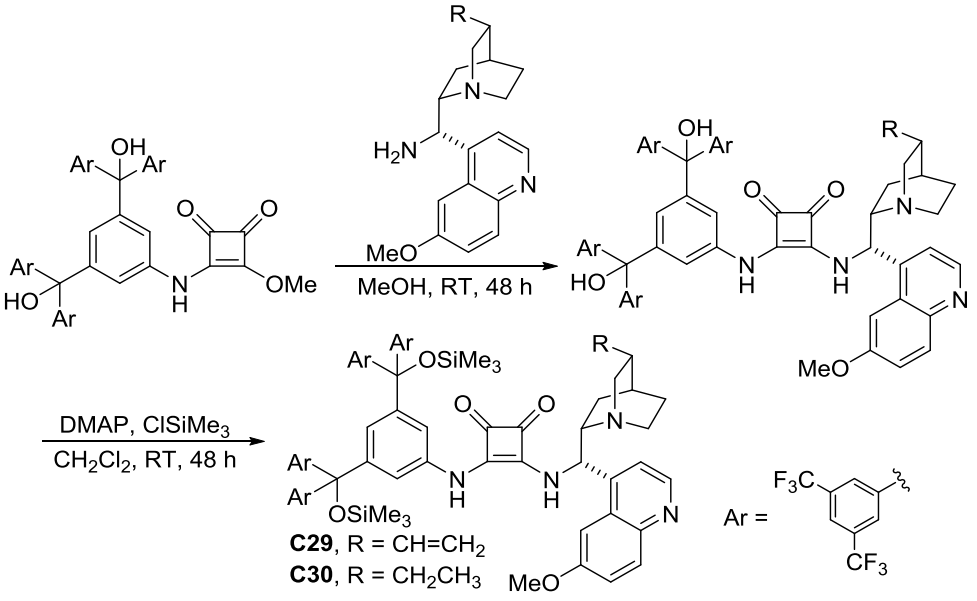
Preparation of 9-amino-10,11-dihydro-(9-deoxy)epiquinine[234]



9-amino-(9-deoxy)epiquinine (647 mg, 2 mmol) and palladium on activated charcoal (10% wt.) (130 mg, 20% wt.) were stirred in EtOH (1 mL/mmol) under an hydrogen atmosphere (1 atm). The resulting suspension was filtered over a pad of celite and the solvent was eliminated under reduced pressure affording the crude amine, which was used in the next step without further purification. Yield: Cuantitative. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.75 – 7.61 (m, 1H), 7.53 – 7.45 (m, 1H), 7.39 (dd, *J* = 9.2, 2.7 Hz, 1H), 4.60 (d, *J* = 10.3 Hz, 1H), 3.97 (s, 3H), 3.32 – 3.17 (m, 2H), 3.13 – 2.97 (m, 1H), 2.79 (ddd, *J* = 14.7, 10.2, 5.4 Hz, 1H), 2.53 (ddd, *J* = 13.7, 4.6, 2.5 Hz, 1H), 1.62 – 1.48 (m, 2H), 1.38 – 1.27 (m, 2H), 1.27 – 1.23 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

Preparation of catalysts C29 and C30

Catalysts **C29** and **C30** were prepared from the squaric ester monoamide intermediate above synthesised according to the synthetic sequence previously described in our group:[233]

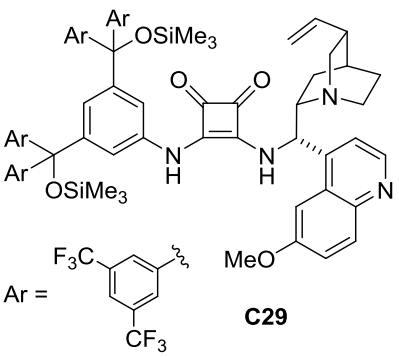


[234] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizaola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

1st step: To a solution of the squaric ester monoamide prepared above (218 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added the corresponding amine (0.20 mmol) and the reaction mixture was stirred for 48 h at room temperature. The solvent was evaporated, and the crude product was subsequently used without further purification.

2nd step: To a suspension of the previously prepared diol-squaramide (0.20 mmol, 1 equiv.) and DMAP (80 mg, 0.60 mmol, 3 equiv.) in CH_2Cl_2 (0.8 mL) was added dropwise chlorotrimethylsilane (80 μL, 0.60 mmol, 3 equiv.) and the reaction mixture was stirred for 14 h at room temperature. Then, additional CH_2Cl_2 (4 mL) was added and the mixture was washed with water (2 × 4 mL) and HCl 1 M (2 × 4 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was subjected to purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH 98:2) affording the pure catalyst.

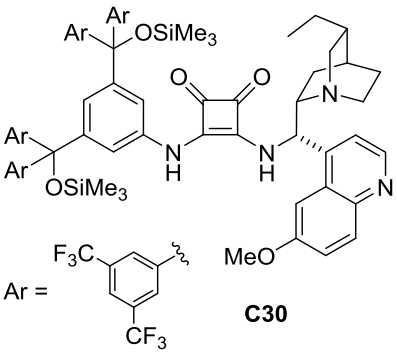
3-((3,5-bis(bis(3,5-bis(Trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)phenyl) amino)-4-(((1*S*)-(6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C29)[233]



C29

The title compound was prepared according to the general procedure described above using 9-amino-(9-deoxy)epiquinine (65 mg, 0.2 mmol, 1 equiv.). Yellow solid. m. p. = 160–168 ºC. Yield of after 2 steps: 47% (145 mg, 0.094 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 13H), 7.71 (s, 1H), 7.65 – 7.37 (m, 2H), 7.40 – 7.24 (m, 1H), 7.24 – 7.12 (m, 1H), 7.12 – 7.03 (m, 1H), 6.14 (s, 1H), 5.85 – 5.61 (m, 1H), 5.11 – 4.92 (m, 2H), 3.95 (s, 3H), 3.43 – 3.03 (m, 3H), 2.43 – 2.27 (m, 1H), 1.79 – 1.58 (m, 3H), 1.49 (t, *J* = 12.0 Hz, 1H), 1.37 – 1.21 (m, 1H), 0.78 (td, *J* = 17.3, 13.8, 6.5 Hz, 1H), -0.28 (s, 18H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 185.1, 180.5, 168.1, 164.9, 159.7, 148.2, 147.4, 147.0, 145.1, 140.8, 140.6, 132.7, 129.4, 129.0, 128.7, 125.4, 124.0, 122.7, 121.8, 118.2, 118.1, 115.9, 101.6, 84.0, 60.7, 59.4, 56.7, 56.3, 41.3, 39.2, 31.6, 30.4, 27.6, 26.5, 1.7. **MS:** calculated for $C_{70}H_{59}N_4O_5F_{24}Si_2$ ($M + H^+$): 1547.3641; found: 1747.3595.

3-((3,5-bis(bis(3,5-bis(Trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)phenyl) amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C30)

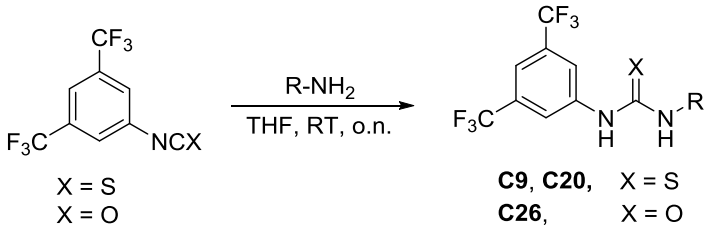


C30

The title compound was prepared according to the general procedure described above using 9-amino-(9-deoxy)epiquinine (65 mg, 0.2 mmol, 1 equiv.). Yellow solid. m. p. = 155–160 ºC. Yield of after 2 steps: 65% (202 mg, 0.13 mmol). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ 8.73 (d, J = 4.6 Hz, 1H), 8.21 (s, 1H), 7.96 (d, J = 3.9 Hz, 4H), 7.93 (s, 1H), 7.89 (d, J = 4.9 Hz, 8H), 7.72 – 7.63 (m, 1H), 7.59 – 7.54 (m, 1H), 7.46 (s, 2H), 7.36 (dd, J = 9.2, 2.5 Hz, 1H), 6.85 (s, 1H), 5.96 (s, 1H), 3.88 (s, 3H), 3.53 – 3.45 (m, 1H), 3.27 – 3.06 (m, 2H), 2.62 – 2.53 (m, 1H), 2.39 (d, J = 13.4 Hz, 1H), 1.61 – 1.17 (m, 8H), 0.90 – 0.75 (m, 3H), 0.62 (s, 1H), -0.33 (s, 18H). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ 183.9, 179.2, 168.1, 162.9, 157.8, 147.5, 145.4, 144.3, 140.1, 131.4, 130.9, 130.5, 130.1, 127.8, 124.6, 121.9, 121.0, 120.3, 117.2, 101.1, 82.9, 78.4, 72.0, 70.0, 60.3, 55.4, 36.7, 26.8, 25.8, 24.9, 11.8, 0.6. **MS:** calculated for $C_{70}H_{61}N_4O_5F_{24}Si_2$ (M + H^+): 1549.3797; found: 1749.3822.

5.2.3. Preparation of thiourea- and urea-based Brønsted base catalysts C9, C20 and C26

Known thiourea/urea-based catalysts **C9**[235] and **C26**[236] and new thiourea-based catalyst **C26** were prepared according to the following synthetic procedure:[237]



To a solution of the corresponding amine (5 mmol, 1 equiv.) in THF (7.5 mL) at 0 ºC, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.5 g, 5.5 mmol, 1.1 equiv.) or bis(trifluomethyl)phenyl isocyanate (0.6 mL, 5.5 mmol, 1.1 equiv.) in THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column

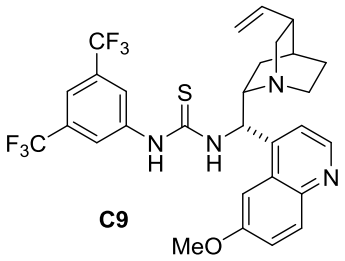
[235] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.

[236] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886.

[237] Adapted from: B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.

chromatography on silica gel (eluting with hexane/ ethyl acetate 80:20 → 0:100) to afford compounds **C9**, **C20** and **C26**.

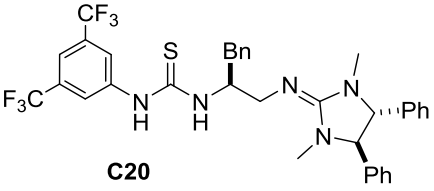
1-(3,5-bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (C9)[235]



C9

C9 was prepared from bis(trifluomethyl)phenyl isothiocyanate (1.5 g mL, 5.5 mmol) using 9-amino-(9-deoxy)*epi*quinine (1.6 g, 5 mmol, 1 equiv.) as the amine, according to the general procedure described above. White solid. m. p.: 123–125 ºC. Yield: 88% (2.6 g, 4.4 mmol). All data were consistent with those previously reported. **^{1}H-NMR** (300 MHz, MeOH-d_4) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38–2.35 (m, 1H), 1.71–1.68 (m, 2H), 1.64–1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

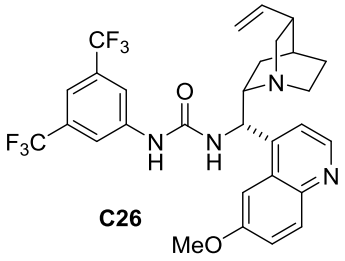
1-(3,5-bis(Trifluoromethyl)phenyl)-3-((*S*)-1-(((4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3-phenylpropan-2-yl)thiourea (C20)



C20

C20 was prepared from bis(trifluomethyl)phenyl isothiocyanate (50 µL, 0.27 mmol, 1.1 equiv.) using the corresponding amine above prepared (section 5.2.2.5, 92 mg, 0.23 mmol, 1 equiv.) as the amine, according to the general procedure described above. White solid. Yield: 25% (39 mg, 0.06 mmol). **[α]$_D^{23}$**= +2.5º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, MeOH-d_4) δ 8.17 (s, 1H), 7.73 (s, 1H), 7.50 – 7.30 (m, 10H), 7.24 – 7.17 (m, 5H), 7.05 (s, 1H), 4.80 – 4.66 (m, 1H), 4.49 (dd, *J* = 12.0, 6.2 Hz, 1H), 4.17 (s, 2H), 4.13 – 4.05 (m, 1H), 3.02 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.88 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.72 (s, 1H), 2.60 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.7, 177.8, 157.4, 151.2, 139.8, 137.6, 135.1, 129.3, 129.0, 128.7, 127.6, 127.2, 124.3, 122.0, 119.6, 112.9, 73.2, 57.2, 52.9, 41.4, 34.1. **MS:** calculated for $C_{35}H_{34}N_5SF_6$ (M + H^+): 670.2439; found: 670.2439.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (C26)[236]

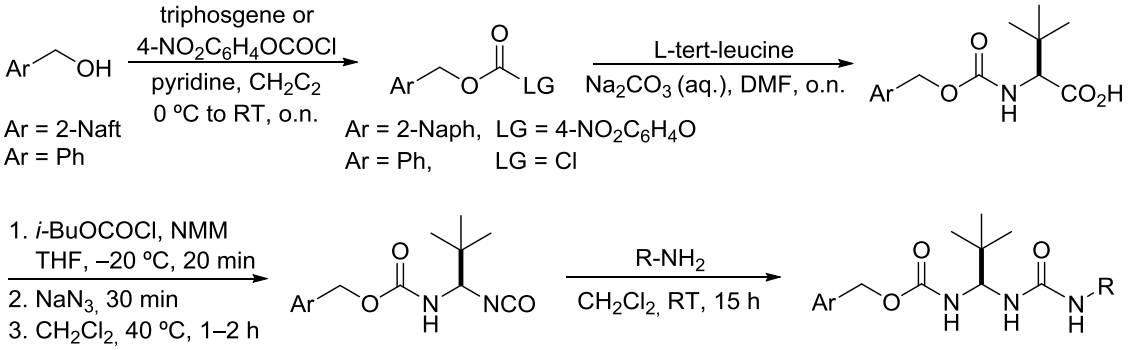


C26

C26 was prepared from bis(trifluomethyl)phenyl isocyanate (0.6 mL, 5.5 mmol) using 9-amino-(9-deoxy)*epi*quinine (1.6 g, 5 mmol, 1 equiv.) as the amine, according to the general procedure described above. White solid. m. p.: 132–135 ºC. Yield: 82% (2.4 g, 4.1 mmol). All data were consistent with those previously reported. **^{1}H-NMR** (300 MHz, MeOH-d_4) δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.84–7.90 (m, 3H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 5.83–5.89 (m, 1H), 5.65 (bs, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 3.03–3.15 (m, 4H), 2.41–2.43 (m, 1H), 1.40–1.73 (m, 3H), 1.17–1.25 (m, 3H).

5.2.4. Ureidopeptide-like Brønsted base catalysts C21, C27 and C35

New catalyst **C21** and known catalysts **C27**[238] and **C35**[234] were prepared according to the synthetic sequence previously reported by our group:[234]



1st step:[239] To a stirred solution of the aryl alcohol (10 mmol, 1 equiv.) in dichloromethane (50 mL) at 0 ºC was added pyridine (0.92 mL, 11.5 mmol, 1.15 equiv.) followed by triphosgene (1.2 g, 4 mmol, 0.4 equiv.) or *p*-nitropheylchloroformate (2.2 g, 11 mmol, 1.1 equiv.). The resulting mixture was stirred at room temperature overnight, and then it was partially evaporated at reduced pressure and diluted with hexane (50 mL). The solids were removed by filtration and the filtrate was evaporated to afford the corresponding chloroformate in quantitative yield, which was used for the next step without further purification.

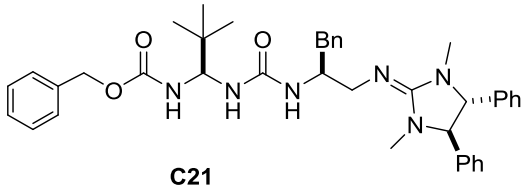
[238] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.

[239] Adapted from: L. Fang, F. Yang, *Org. Lett.* **2010**, *12*, 3124–3127.

2nd step:[240] To a stirred solution of the *L-tert*-leucine (1.3 g, 10 mmol, 1 equiv.) in 10% aqueous Na_2CO_3 (26 mL), and dioxane (10 mL) was slowly added at 0 ºC a solution of the previous chloroformate (1.4 mL, 10 mmol, 1 equiv.) in dioxane (30 mL). The mixture was stirred at the same temperature for 1 h and then allowed to warm to room temperature. The solution was subsequently stirred overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered off and the solvent evaporated under reduced pressure to afford the corresponding L-*tert*-leucine derivative in quantitative yield, which was used for the next step without further purification.

3rd step:[241] The previously obtained acid (5.0 mmol, 1 equiv.) was dissolved in THF (20 mL), and isobutyl chloroformate (0.65 mL, 5 mmol1 equiv.) and *N*-methylmorpholine (0.6 mL, 5 mmol1 equiv.) were added. Then, the mixture was stirred at–20 ºC for 20 min and a suspension of NaN_3 (0.48 g, 7.5 mmol, 1.5 equiv.,) in H_2O (5 mL) was added. After 30 min at the same temperature, the organic layer was separated, diluted with CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil which was redissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 ºC under nitrogen until completion (reaction monitored by IR analysis until disappearance of the isocyanate band, 1–2 h). Then, the corresponding amine was added (3.5 mmol, 0.7 equiv.) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluting with dichloromethane/MeOH 90:10) to afford the corresponding catalyst.

Naphthalen-2-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C21)



C21

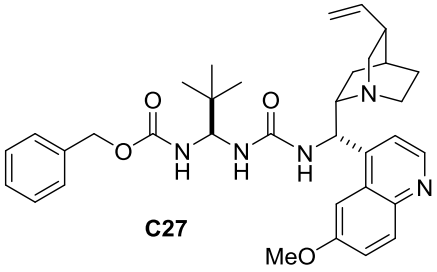
C21 was prepared from benzyl alcohol (1.0 g, 10 mmol) according to the general procedure using triphosgene (1.2 g, 4.0 mmol, 0.4 equiv.) in the first step and the corresponding amine above prepared (section 5.2.2.5, 140 mg, 3.5 mmol, 1 equiv.) as the amine. Yield: 30% (70 mg, 0.11 mmol). **[α]**$_D^{23}$= –8.9º (*c* = 1.00, CH_2Cl_2).**^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.10 (m, 20H), 6.89 (s, 1H), 5.37 (bs, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.76 – 4.64 (m, 1H), 4.38 – 4.20

[240] Adapted from: b) J. D. Bain, D. A. Wacker, E. E. Kuo, A. R. Chamberlin, *Tetrahedron* **1991**, *47*, 2389–2400.

[241] Adapted from: Suresh Babu, V. V.; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705.

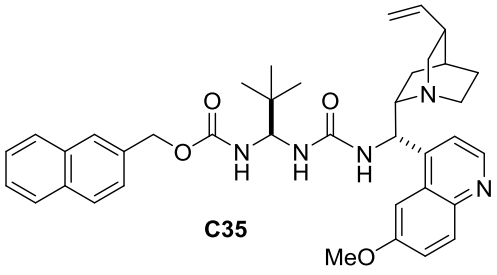
(m, 3H), 3.51 (d, *J* = 6.7 Hz, 2H), 3.15 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.86 (s, 1H), 2.65 (s, 6H), 0.98 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.7, 158.4, 155.7, 138.5, 136.4, 135.8, 129.2, 128.5, 128.2, 127.7, 127.4, 126.4, 77.2, 74.0, 66.1, 51.4, 47.1, 40.1, 36.0, 33.6, 25.5. **MS:** calculated for $C_{40}H_{49}N_6O_3$ ($M + H^+$): 661.3866; found: 661.3865.

Benzyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C27)[238]



C27 was prepared from benzyl alcohol (1.0 g, 10 mmol) according to the general procedure using triphosgene (1.2 g, 4 mmol, 0.4 equiv.) in the first step and 9-amino-(9-deoxy)*epi*quinine (1.12 g, 3.5 mmol, 1 equiv.) as the amine. Yield: 72% (1.48 g, 2.5 mmol). All data were consistent with those previously reported. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.3, 1H), 8.01 (d, *J* = 9.2, 1H), 7.74 (d, *J* = 2.6, 1H), 7.39 (d, *J* = 2.7, 1H), 7.37–7.34 (m, 5H), 7.22 (d, *J* = 4.4, 1H), 6.48–6.35 (bs, 1H), 5.84–5.73 (m, 1H), 5.32–5.29 (m, 1H), 5.20 (d, *J* = 9.4, 1H), 5.08–5.05 (m, 2H), 5.04–4.95 (m, 3H), 3.97 (s, 3H), 3.30–3.23 (m, 2H), 3.12–2.99 (m, 1H), 2.80–2.70 (m, 2H), 2.34–2.27 (s, 1H), 1.68–1.64 (m, 2H), 1.62–1.56 (m, 1H), 1.45–1.38 (m, 1H), 0.82 (s, 10H).

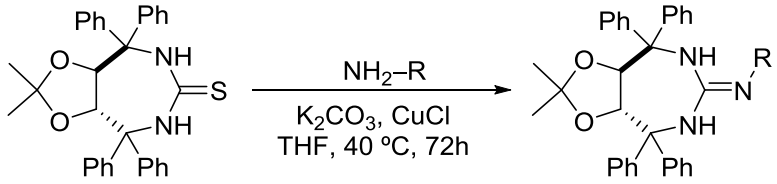
Naphthalen-2-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C35)[234]



C35 was prepared from 2-nafthalenemethanol (1.6 g, 10 mmol) according to the general procedure using *p*-nitropheylchloroformate (2.2 g, 11 mmol, 1.1 equiv.) in the first step and 9-amino-(9-deoxy)*epi*quinine (1.12 g, 3.5 mmol, 1 equiv.) as the amine. Yield: 86% (1.9 g, 3.0 mmol). All data were consistent with those previously reported. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.87–7.67 (m, 5H), 7.35 (dd, *J* = 9.2, 2.7 Hz, 4H), 7.24 (d, *J* = 4.6 Hz, 1H), 6.42–6.24 (bs, 1H), 5.85–5.66 (m, 1H), 5.33–5.22 (bs, 1H), 5.12–4.85 (m, 4H), 3.95 (s, 3H), 3.33–2.98 (m, 3H), 2.87–2.57 (m, 2H), 2.35–2.22 (m, 1H), 1.94–1.78 (m, 1H), 1.69–1.30 (m, 4H), 0.86 (s, 9H).

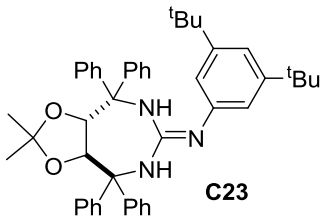
5.2.5. Preparation of catalysts C23-C25

New catalysts **C23-C25** were synthesised according to a previously described synthetic procedure:[242]



The thiourea intermediate above prepared (Section 5.2.2.6, 250 mg, 0.50 mmol, 1 equiv.) was added to a suspension of K_2CO_3 (1.0 g, 7.5 mmol, 15 equiv.) and CuCl (1.0 g, 1.05 mmol, 2.1 equiv.) in THF (5 mL) and the resulting mixture was stirred for 10 min at room temperature before adding the corresponding amine (0.50 mmol, 1 equiv.). The reaction mixture was then stirred at 40 ºC for 72 h and a saturated solution of NH_4Cl (2 mL) was added. Then HCl 1 M was added dropwise until pH 5 was reached, the mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic phase was washed with brine (1 x 10 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography (eluting CH_2Cl_2/MeOH 95:5) to afford the pure catalyst.

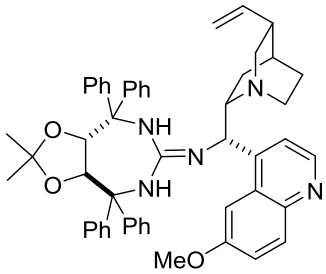
(3a*R*,8a*R*)-*N*-(3,5-di-tert-Butylphenyl)-2,2-dimethyl-4,4,8,8-tetraphenylhexahydro-6*H*-[1,3]dioxolo[4,5-*e*][1,3]diazepin-6-imine (C23)



C23

The title compound was prepared following the general procedure above desctibed using 3,5-di-tert-butylaniline (103 mg, 0.50 mmol, 1 equiv.) as the amine. Yellow solid. Yield: 64% (214 mg, 0.32 mmol). $[\alpha]_D^{23}$= +53.9º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.7 Hz, 2H), 7.55 (s, 2H), 7.49 – 7.32 (m, 8H), 7.28 (s, 5H), 7.15 (s, 3H), 7.03 (d, *J* = 9.1 Hz, 3H), 6.85 (s, 2H), 4.75 (d, *J* = 14.1 Hz, 2H), 1.34 (s, 3H), 1.24 (s, 18H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.1, 145.3, 144.9, 141.8, 141.2, 129.0, 128.3, 127.7, 127.6, 127.4, 127.0, 117.3, 116.8, 110.2, 81.2, 80.0, 66.2, 65.6, 34.7, 31.3, 27.0, 26.6. **MS:** calculated for $C_{46}H_{52}N_3O_2$ ($M + H^+$), 678.4060; found, 678.4056.

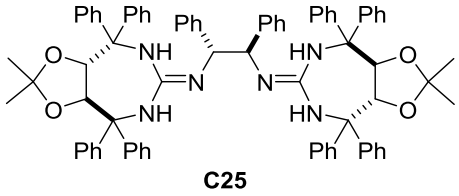
(3a*R*,8a*R*)-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-2,2-dimethyl-4,4,8,8-tetraphenylhexahydro-6*H*-[1,3]dioxolo[4,5-*e*][1,3]diazepin-6-imine (C24)



C24

The title compound was prepared following the general procedure above desctibed using 9-amino-(9-deoxy)*epi*quinine (194 g, 0.50 mmol, 1 equiv.) as the amine. Yellow solid. Yield: 64% (254 mg, 0.32 mmol). **[α]**$_D^{23}$= +95.5º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.2 Hz, 1H), 7.73 – 7.29 (m, 16H), 7.21 (s, 6H), 7.02 – 6.83 (m, 2H), 6.59 (s, 2H), 5.81 – 5.58 (m, 1H), 5.02 – 4.86 (m, 2H), 4.78 (s, 1H), 4.17 (s, 1H), 3.51 (s, 3H), 3.09 (s, 1H), 2.66 (d, *J* = 39.9 Hz, 2H), 2.22 (s, 2H), 1.58 (s, 6H), 1.32 – 1.17 (m, 2H), 1.11 – 0.49 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.1, 147.3, 144.4, 141.2, 131.9, 131.8, 131.1, 129.5, 128.4, 128.2, 127.3, 127.0, 121.5, 114.2, 111.1, 55.5, 55.0, 40.3, 39.4, 27.9, 27.3, 26.5, 25.2. **MS:** calculated for $C_{52}H_{54}N_5O_3$ ($M + H^+$), 796.4227; found, 796.4223.

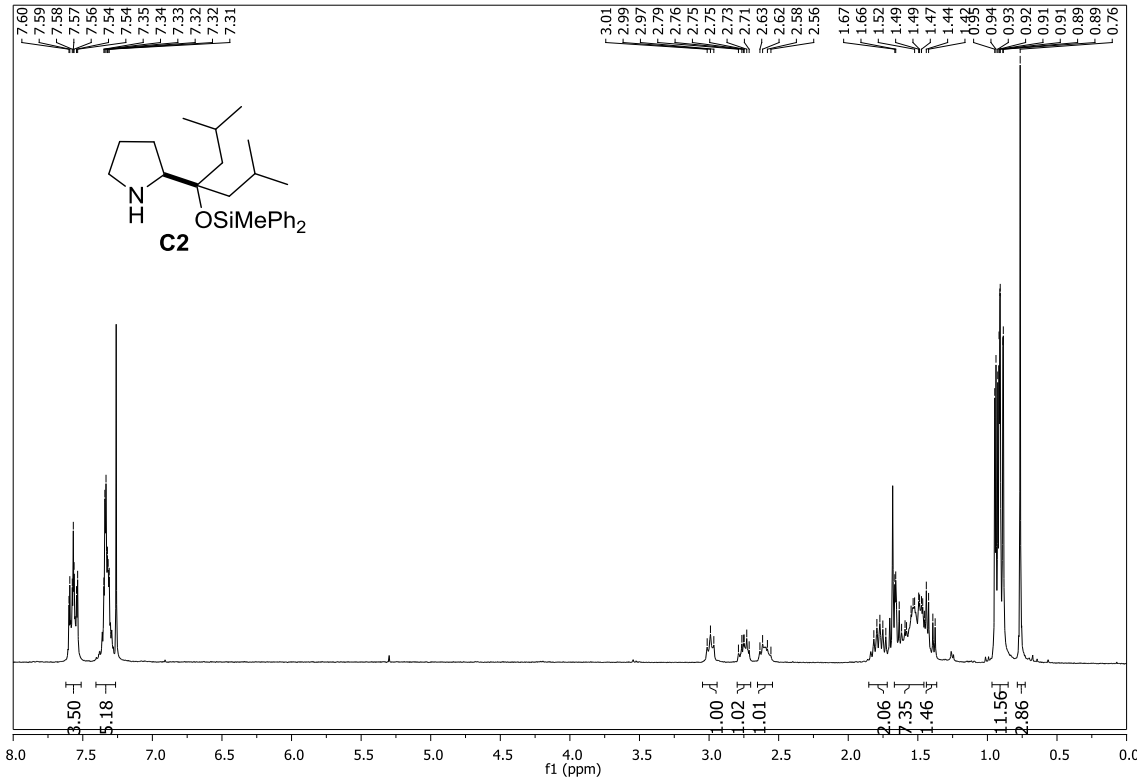
(3a*R*,3a'*R*,8a*R*,8a'*R*)-*N*,*N*'-((1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl)bis(2,2-dimethyl-4,4,8,8-tetraphenylhexahydro-6*H*-[1,3]dioxolo[4,5-e][1,3]diazepin-6-imine) (C25)

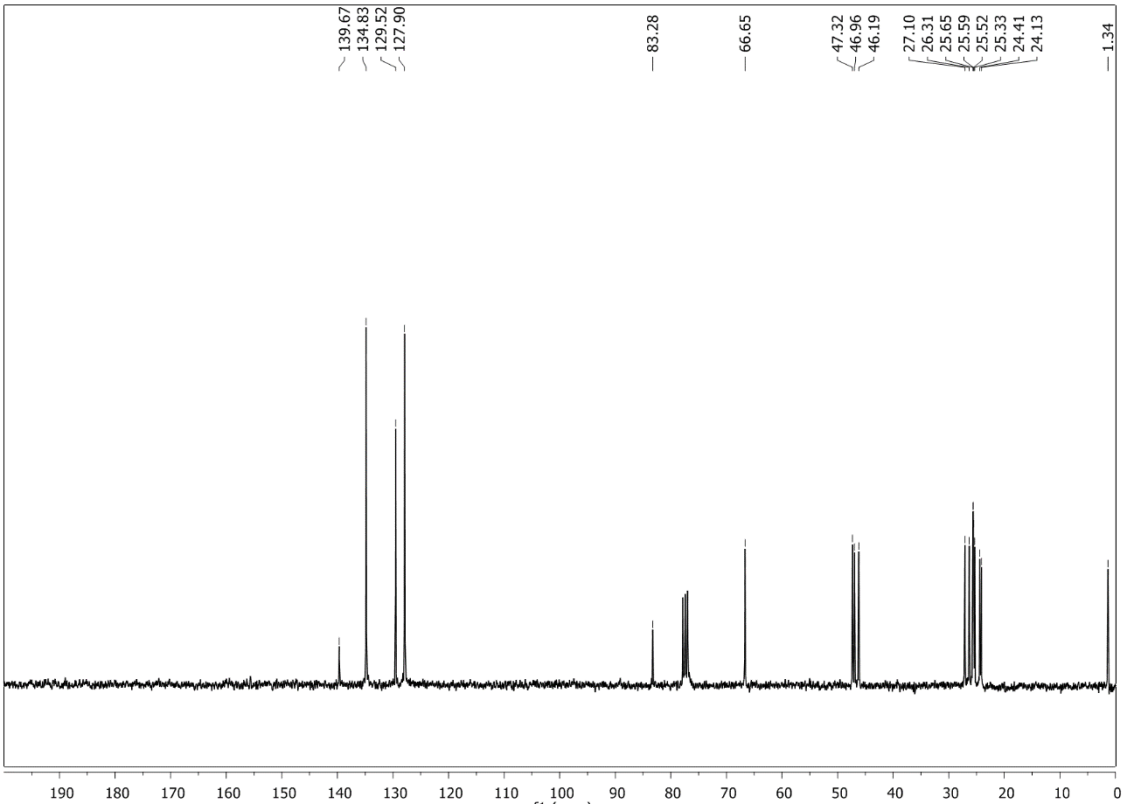


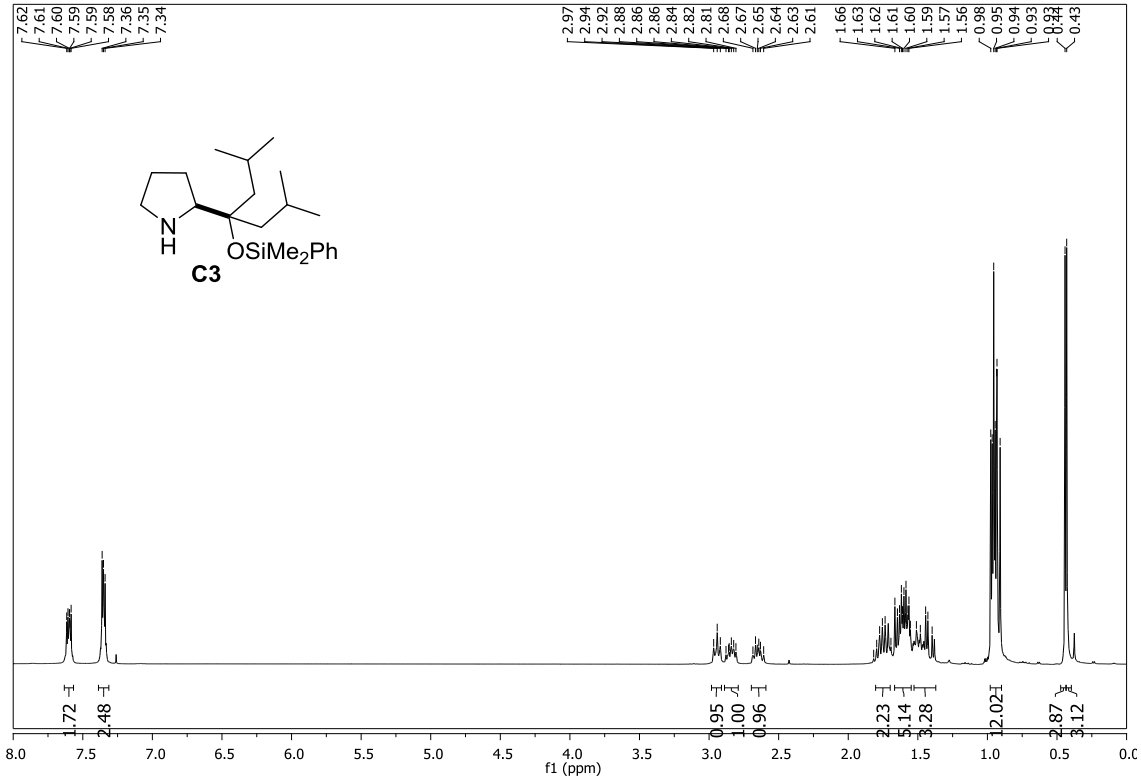
C25

The title compound was prepared following the general procedure above desctibed using 1,2-diphenylethylenediamine (53 g, 0.25 mmol, 0.5 equiv.) as the amine. Yellow solid. Yield: 60% (173 mg, 0.15 mmol). **[α]**$_D^{23}$= +135.5º (*c* = 1.00, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 8H), 7.46 – 7.39 (m, 12H), 7.31 – 7.25 (m, 12H), 7.22 – 7.15 (m, 8H), 6.81 (s, 2H), 6.65 (s, 2H), 5.23 (s, 3H), 4.60 (s, 3H), 1.30 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9, 144.2, 140.5, 128.7, 128.3, 127.7, 127.5, 127.4, 127.2, 109.6, 78.8, 65.6, 26.6. **MS:** calculated for $C_{78}H_{73}N_6O_4$ ($M + H^+$), 1157.5688; found, 1157.5705.

5.2.6. Representative NMR spectra



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7.59
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7.58
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7.35
7.34
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2.86
2.86
2.84
2.82
2.81
2.68
2.67
2.65
2.64
2.63
2.61
1.66
1.63
1.62
1.61
1.60
1.59
1.57
1.56
0.98
0.95
0.94
0.93
0.43
0.43
N
H
OSiMe2Ph
C3
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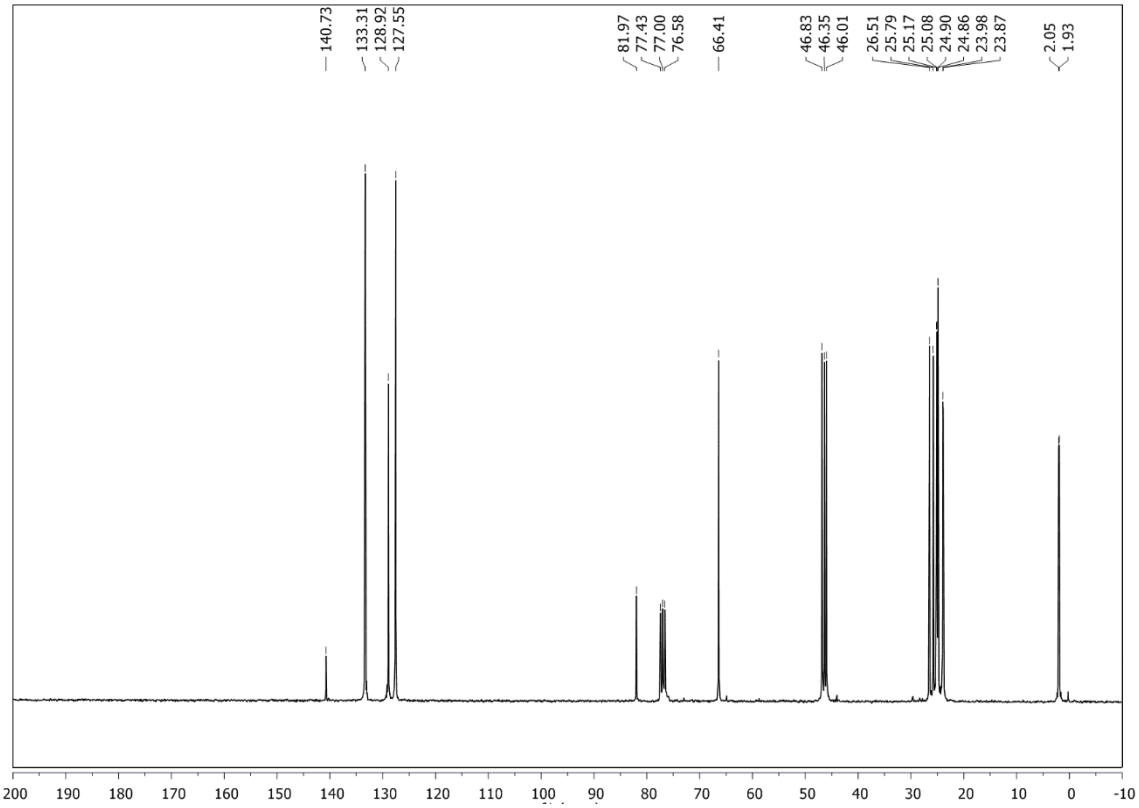
0.95
1.00
0.96
2.23
5.14
3.28
12.02
2.87
3.12
f1 (ppm)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127.55
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77.43
77.00
76.58
66.41
46.83
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46.01
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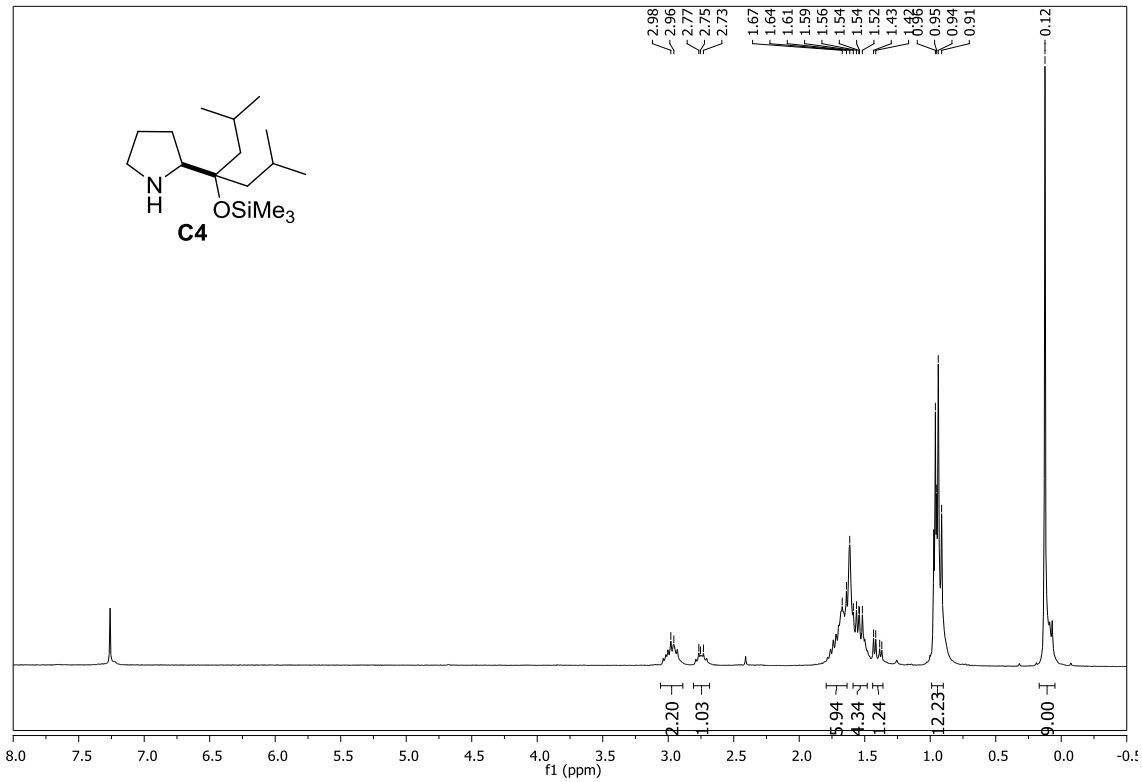
24.90
24.86
23.98
23.87
2.05
1.93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1.61
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1.54
1.54
1.52
1.43
0.96
0.95
0.94
0.91
0.12
N
H
OSiMe3
C4
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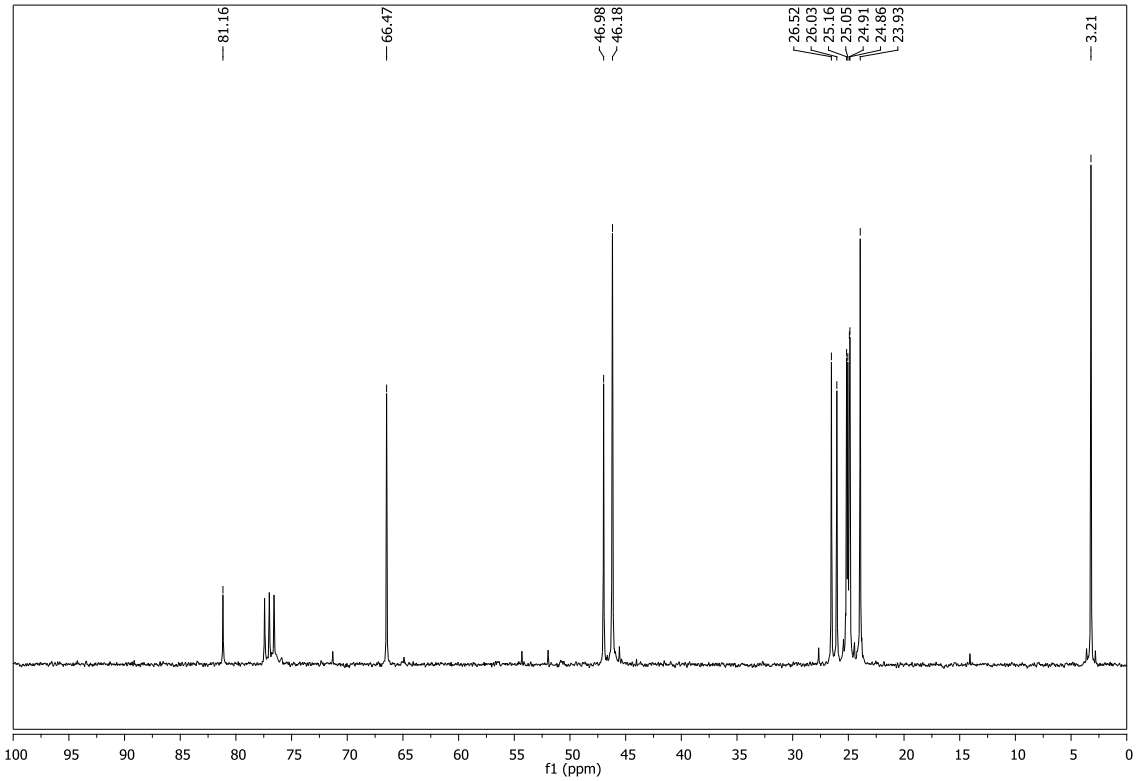
1.03
5.94
4.34
1.24
12.23
9.00
f1 (ppm)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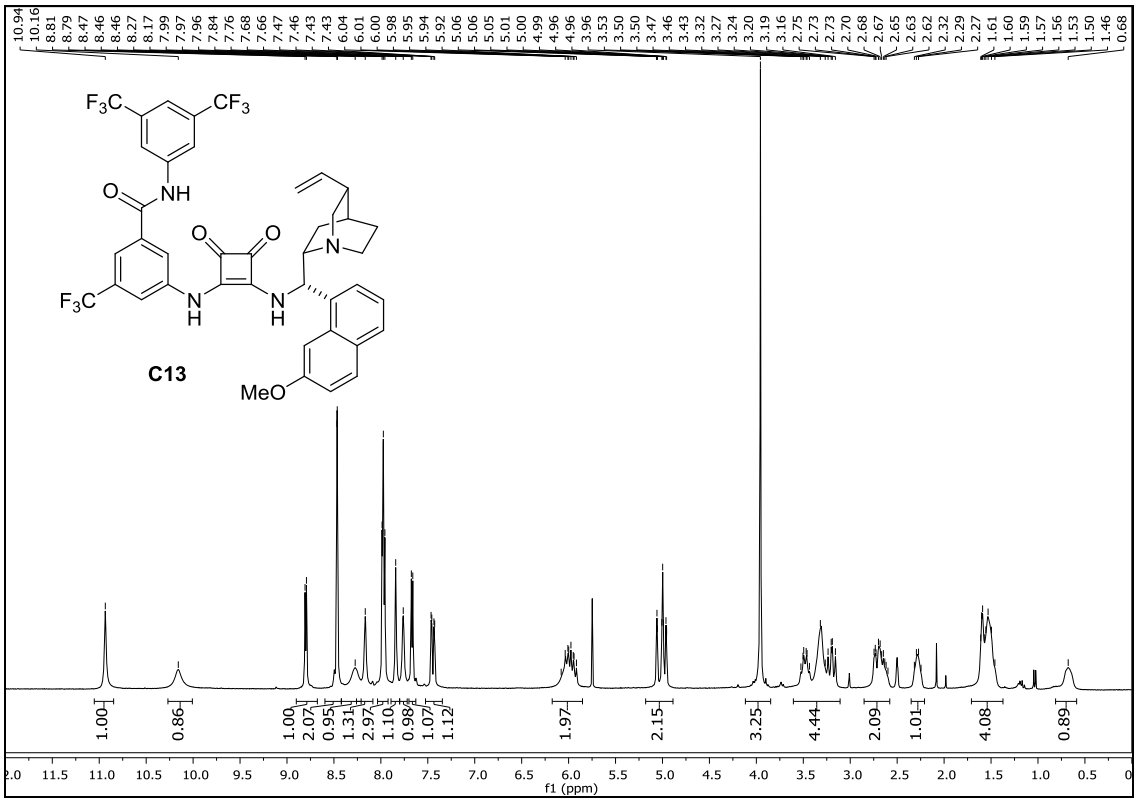
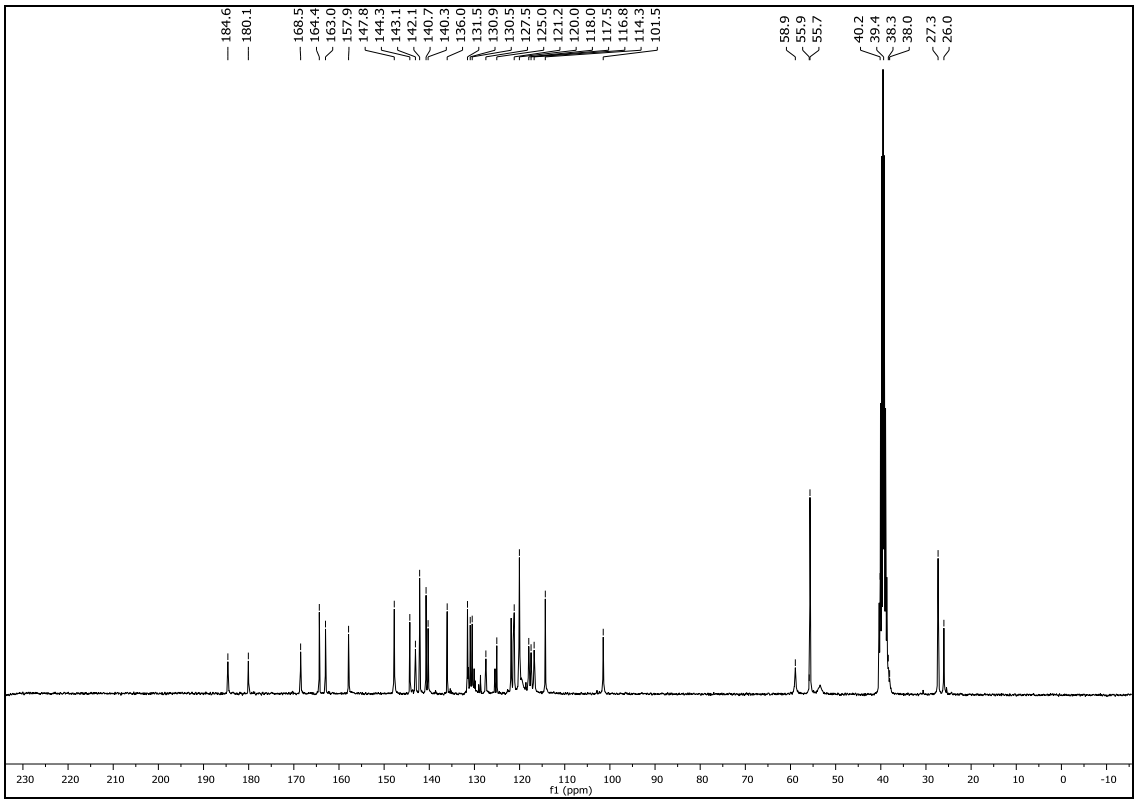
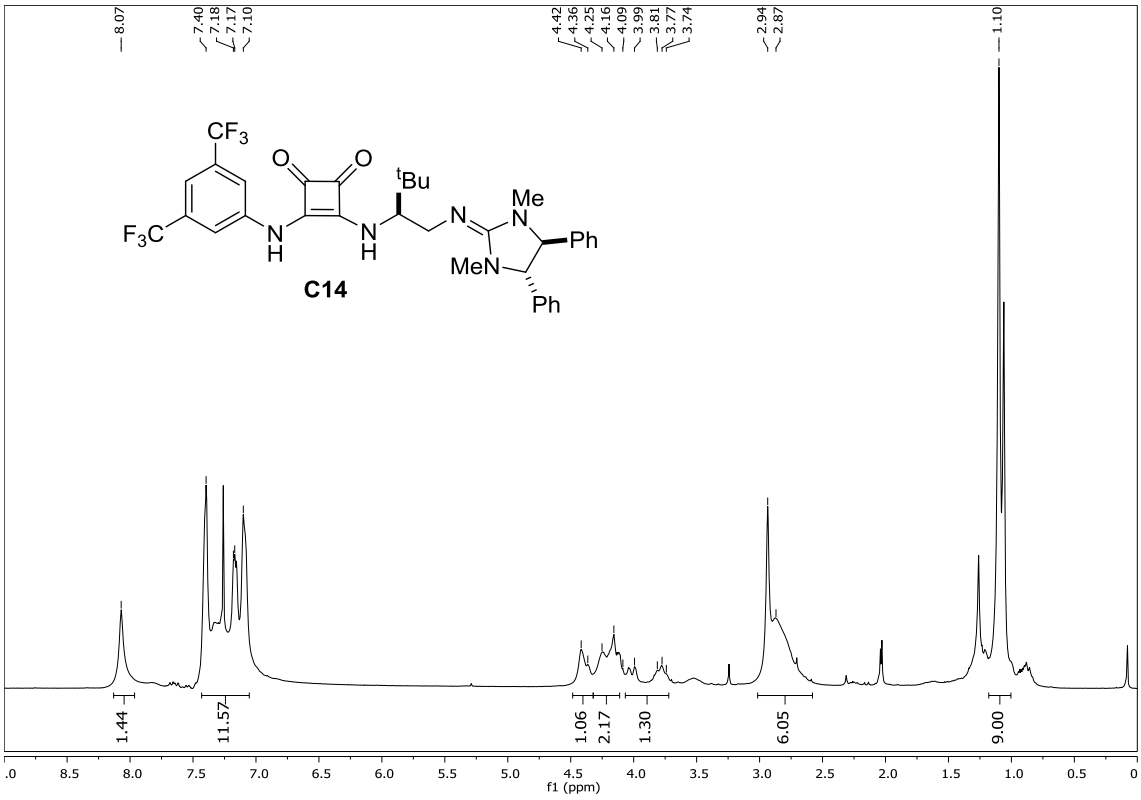
46.18
26.52
26.03
25.16
25.05
24.91
24.86
23.93
3.21
f1 (ppm)


C13
f1 (ppm)


f1 (ppm)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3.74
2.94
2.87
1.10
CF3
F3C
O
O
N
H
N
H
tBu
N
Me
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Ph
MeN
Ph
C14
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11.57
1.06
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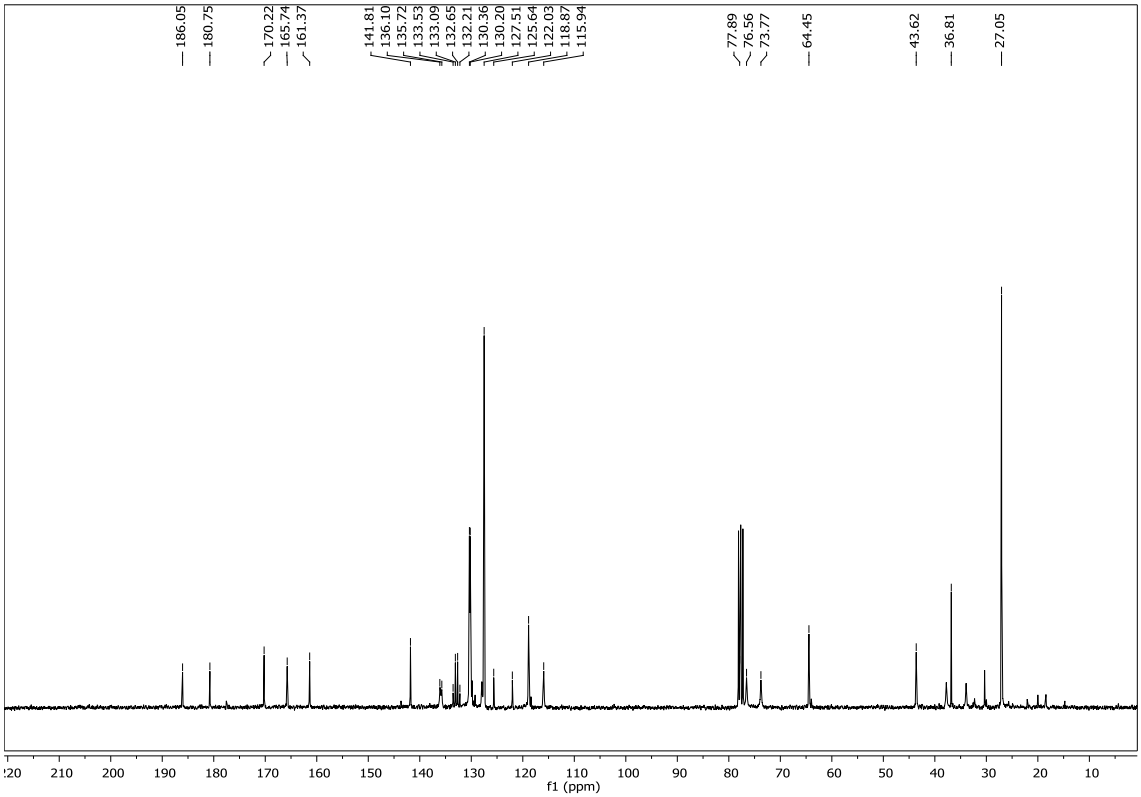
1.30
6.05
9.00
f1 (ppm)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130.20
127.51
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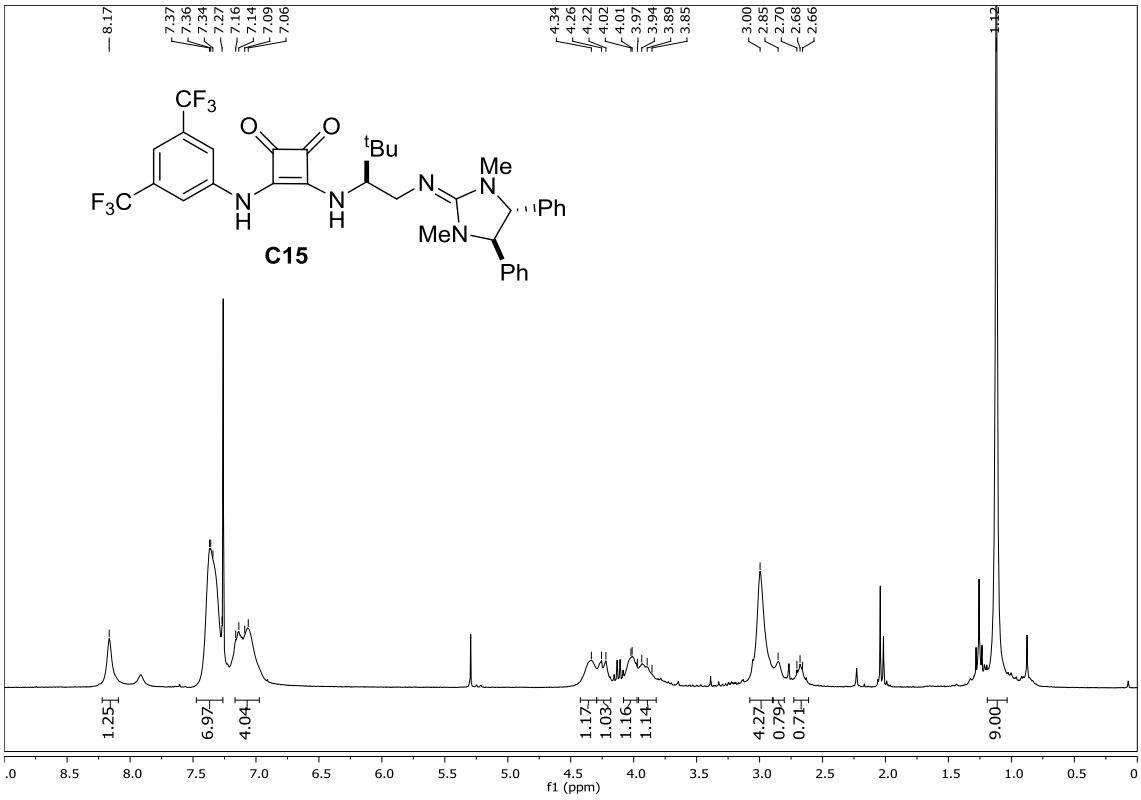
27.05
f1 (ppm)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7.06
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3.00
2.85
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2.68
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N
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tBu
N
Me
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Ph
MeN
Ph
C15
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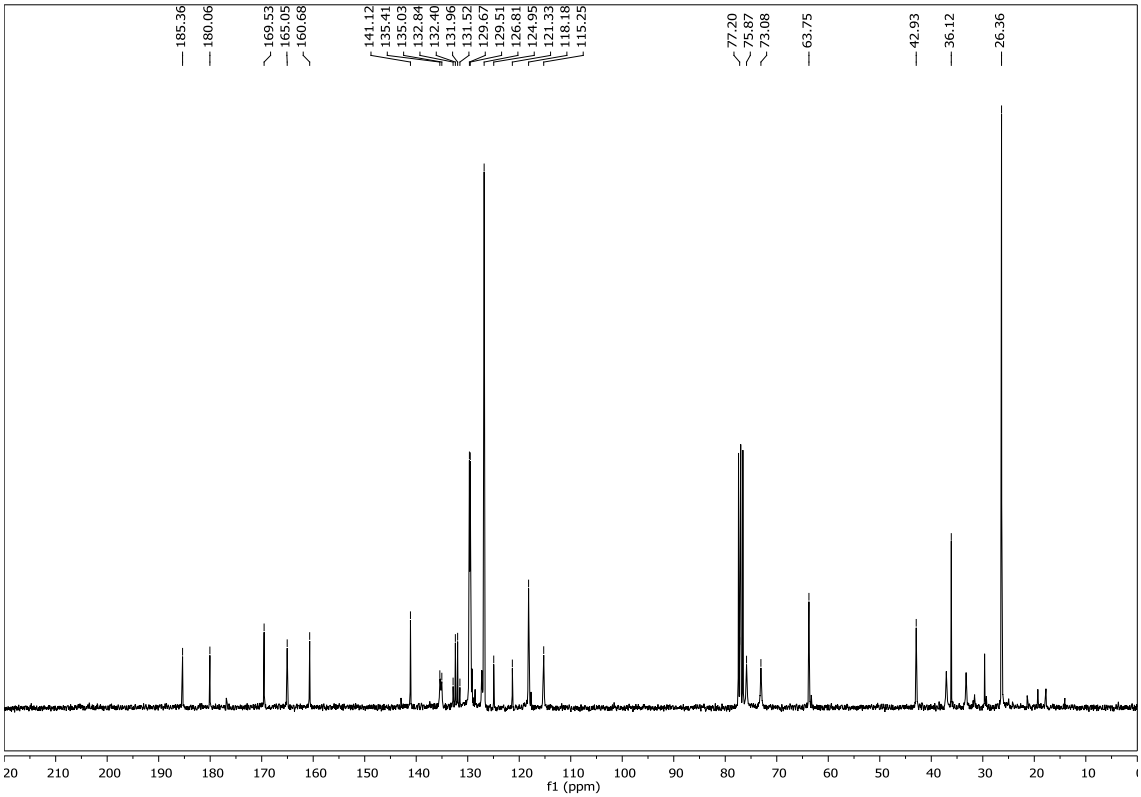
f1 (ppm)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129.51
126.81
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42.93
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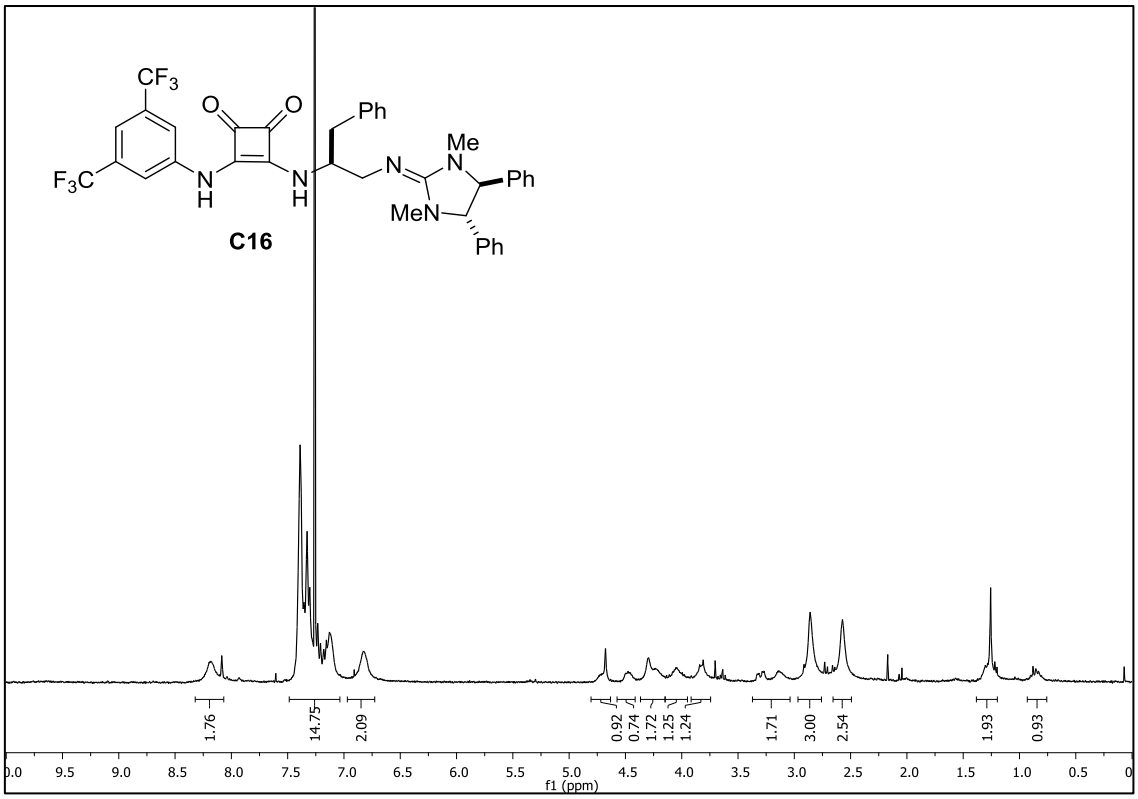
26.36
f1 (ppm)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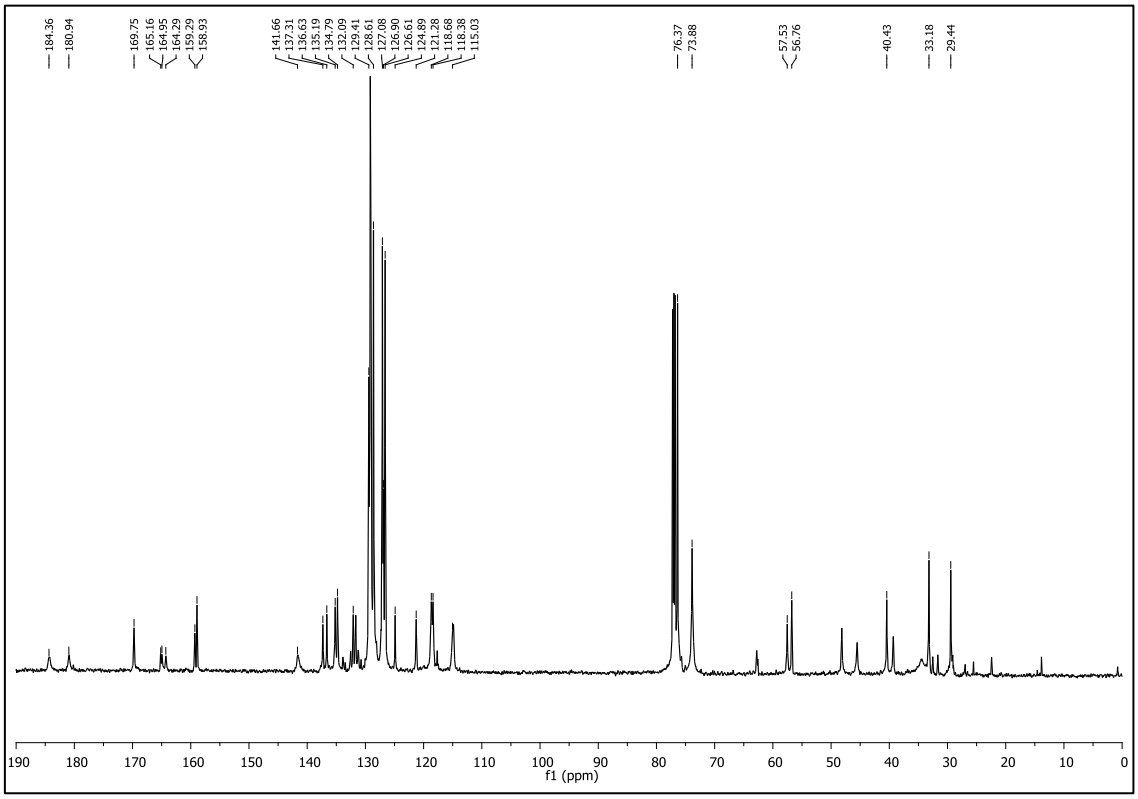
f1 (ppm)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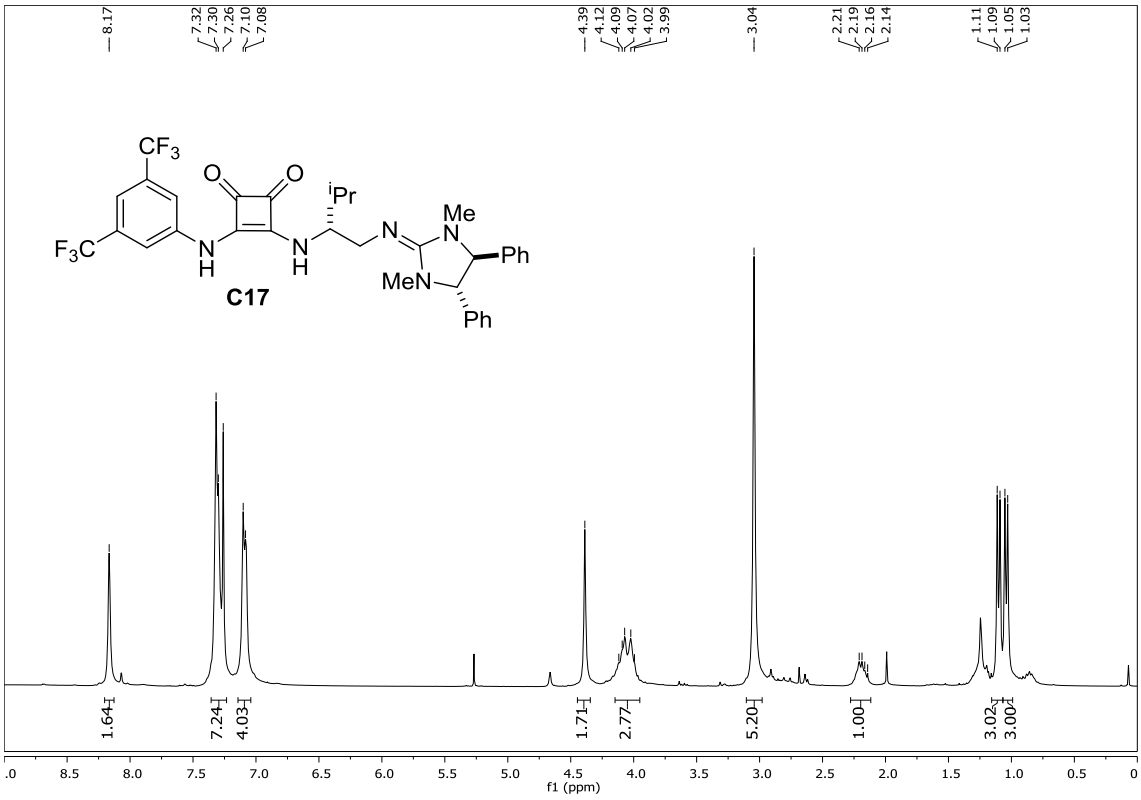
f1 (ppm)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1.09
1.05
1.03
CF3
F3C
O
O
iPr
N
H
N
H
N
Me
N
Ph
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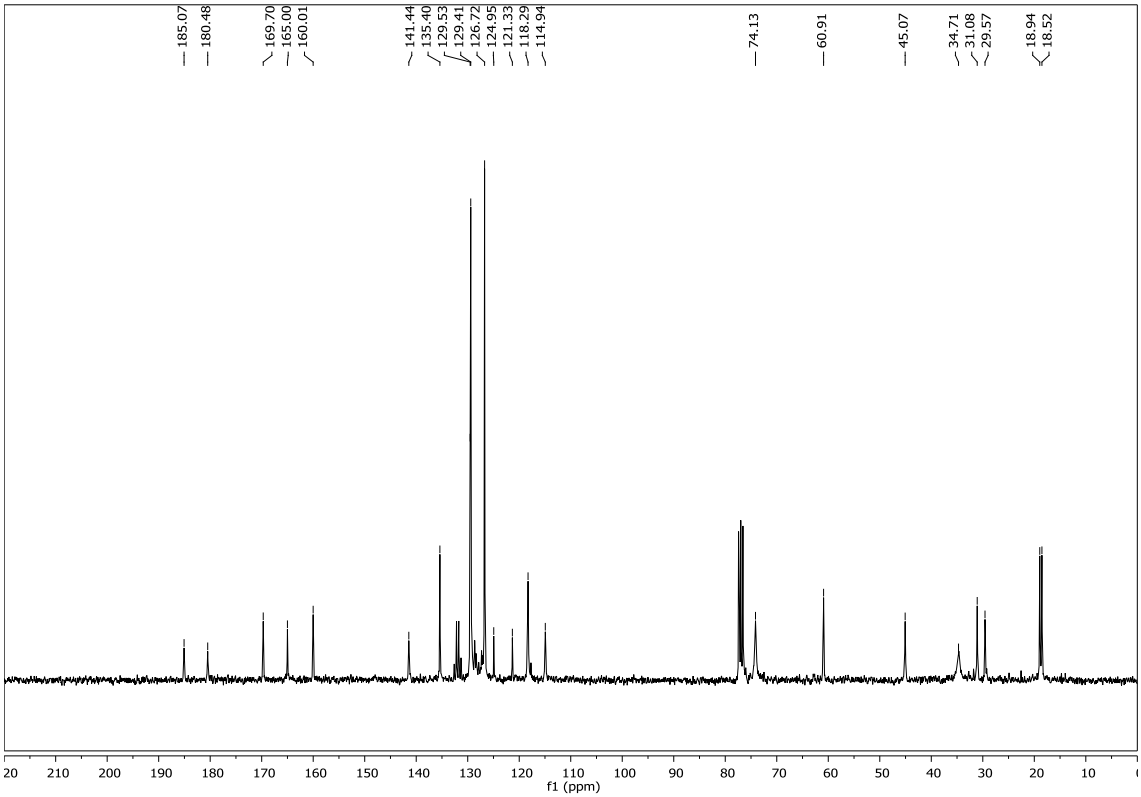
f1 (ppm)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165.00
160.01
141.44
135.40
129.53
129.41
126.72
124.95
121.33
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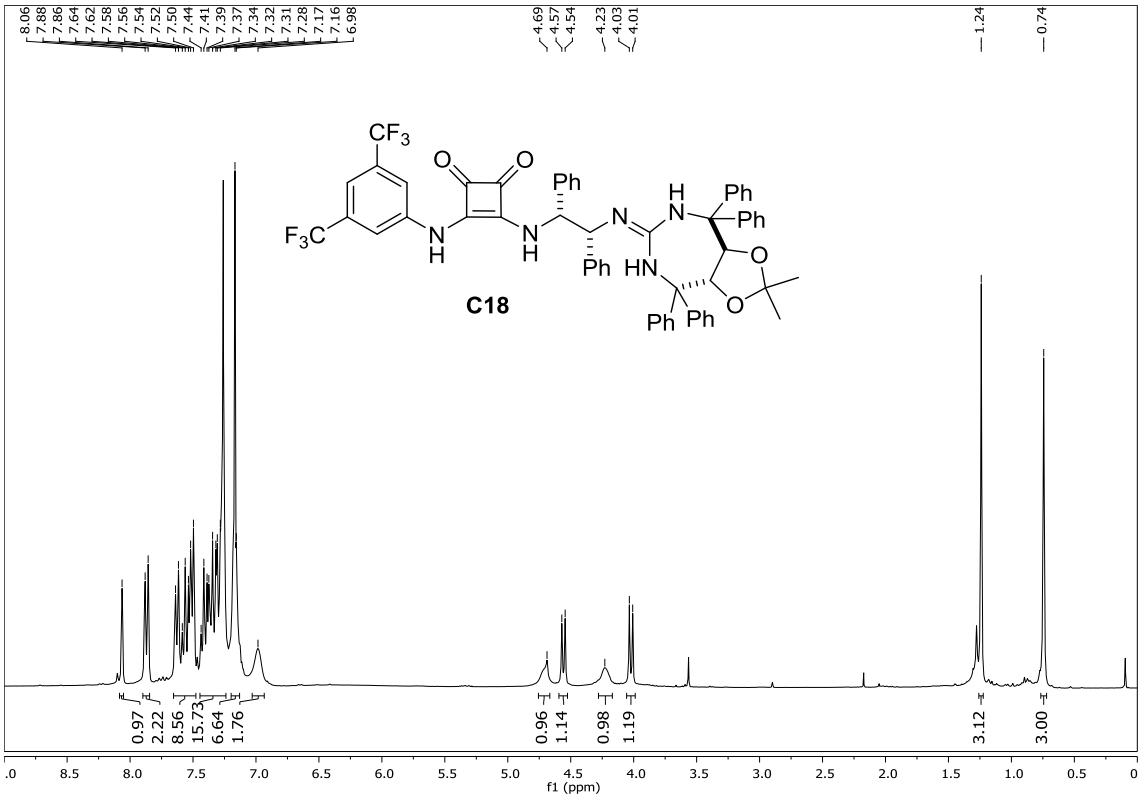
74.13
60.91
45.07
34.71
31.08
29.57
18.94
18.52
f1 (ppm)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7.88
7.86
7.64
7.62
7.58
7.56
7.54
7.52
7.50
7.44
7.41
7.39
7.37
7.34
7.32
7.31
7.28
7.17
7.16
6.98
4.69
4.57
4.54
4.23
4.03
4.01
1.24
0.74
CF3
F3C
O
O
N
H
N
H
Ph
N
H
N
Ph
Ph
Ph
HN
O
O
Ph
Ph
C18
0.97
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1.14
0.98
1.19
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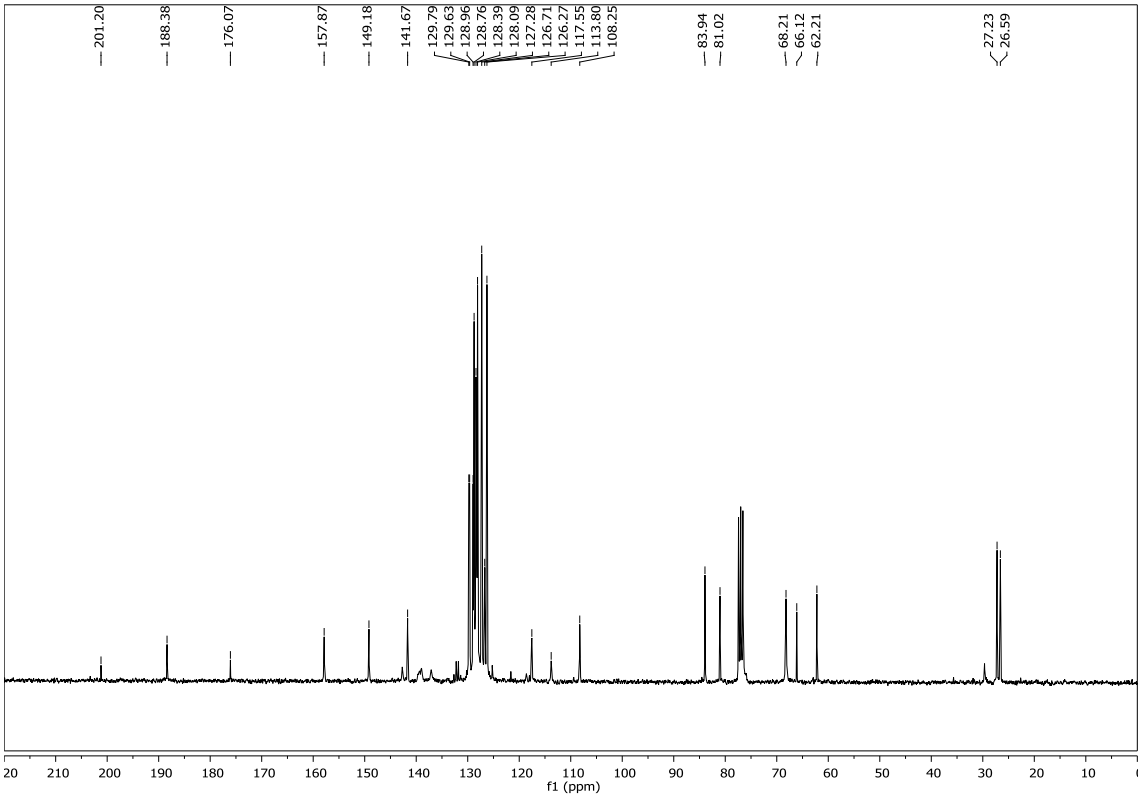
3.00
f1 (ppm)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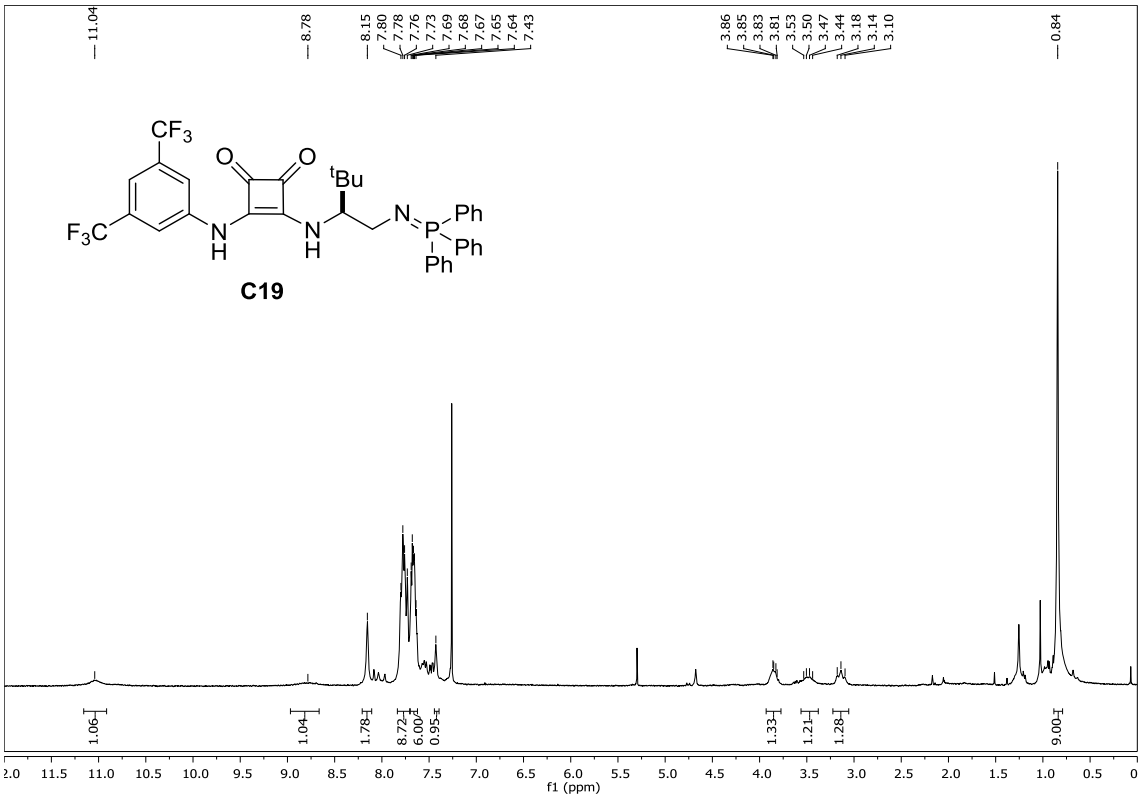
188.38
176.07
157.87
149.18
141.67
129.79
129.63
128.96
128.76
128.39
128.09
127.28
126.71
126.27
117.55
113.80
108.25
83.94
81.02
68.21
66.12
62.21
27.23
26.59
f1 (ppm)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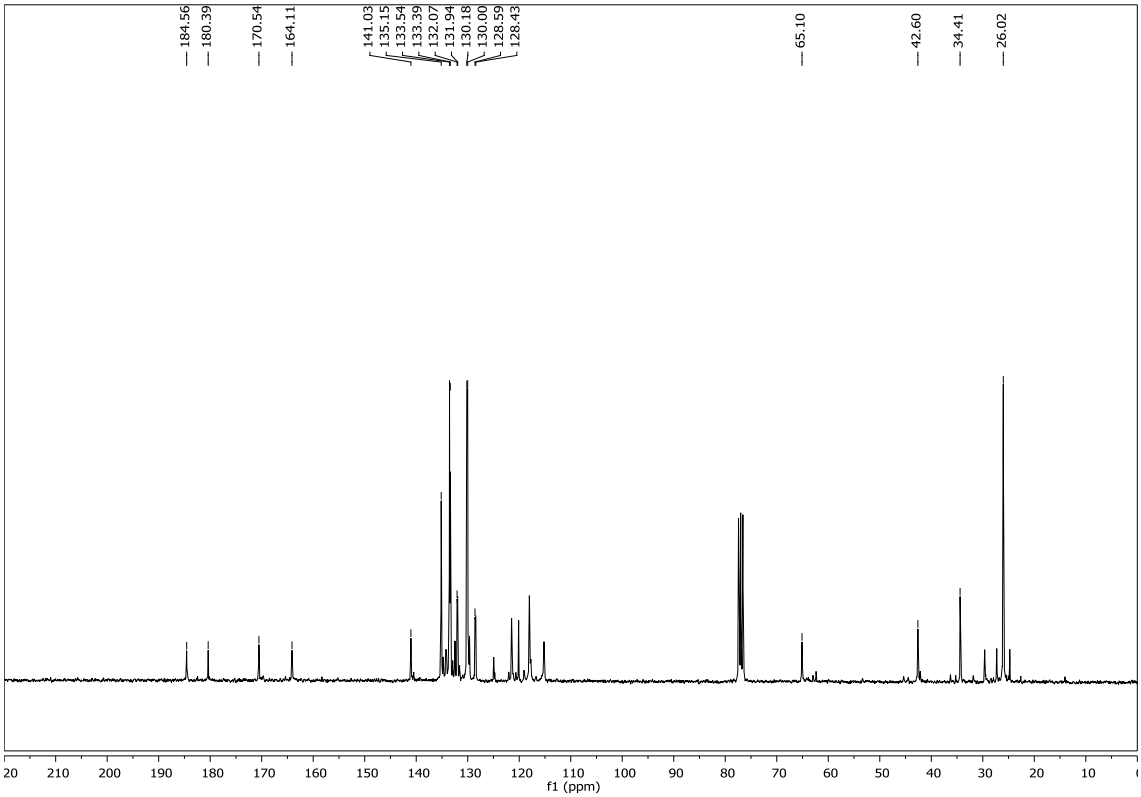
8.15
7.80
7.78
7.76
7.73
7.69
7.68
7.67
7.65
7.64
7.43
3.86
3.85
3.83
3.81
3.53
3.50
3.47
3.44
3.18
3.14
3.10
0.84
CF3
F3C
O
O
tBu
N
H
N
H
N
P
Ph
Ph
Ph
C19
1.06
1.04
1.78
8.72
6.00
0.95
1.33
1.21
1.28
9.00
f1 (ppm)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180.39
170.54
164.11
141.03
135.15
133.54
133.39
132.07
131.94
130.18
130.00
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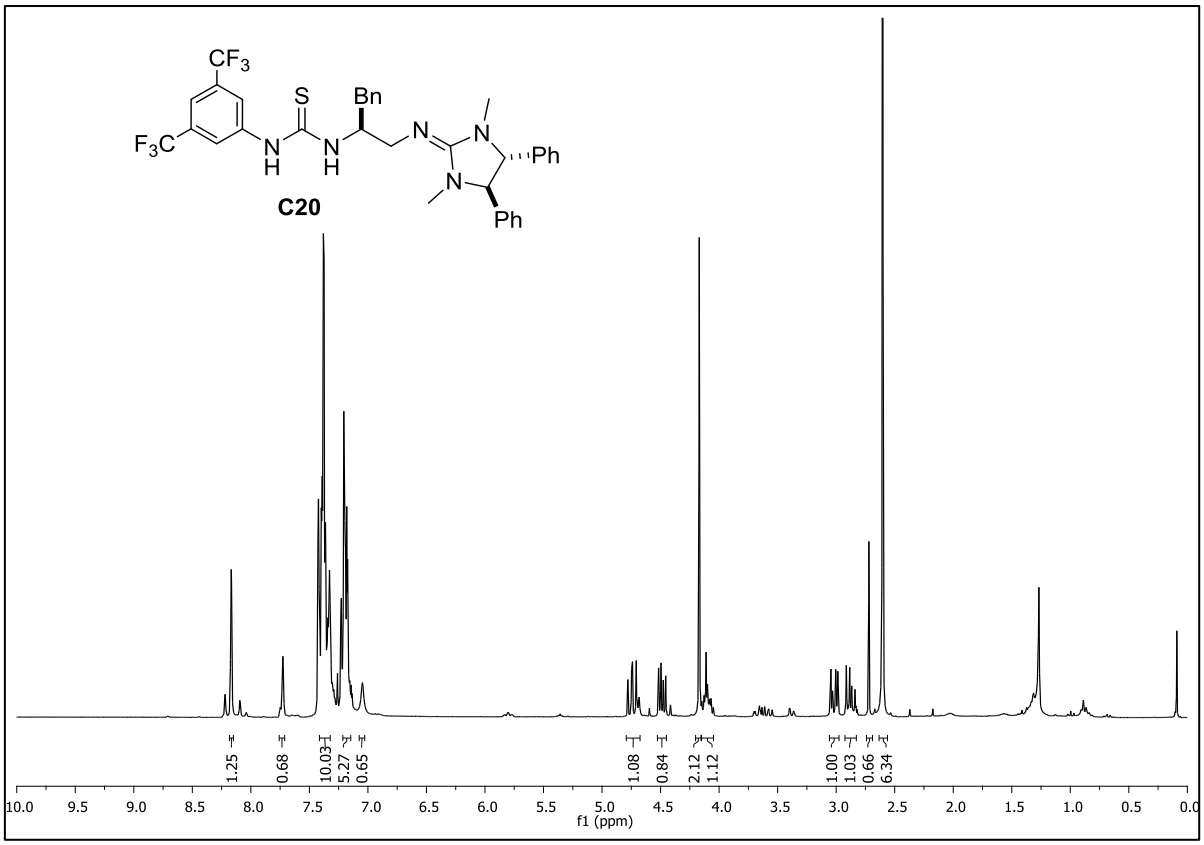
128.43
65.10
42.60
34.41
26.02
f1 (ppm)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F3C
S
Bn
N
H
N
H
N
N
Ph
N
Ph
C20
1.25
0.68
10.03
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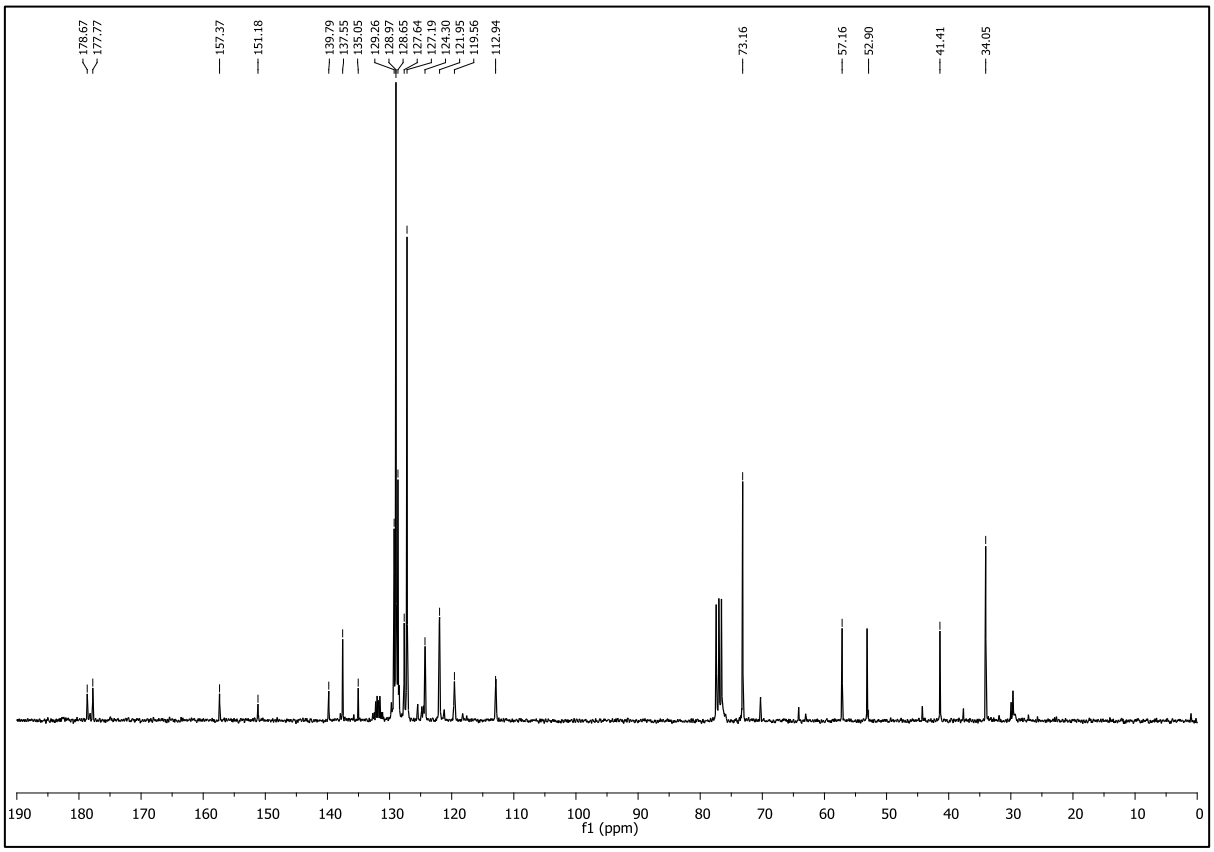
1.08
0.84
2.12
1.12
1.00
1.03
0.66
6.34
f1 (ppm)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177.77
157.37
151.18
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137.55
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129.26
128.97
128.65
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127.19
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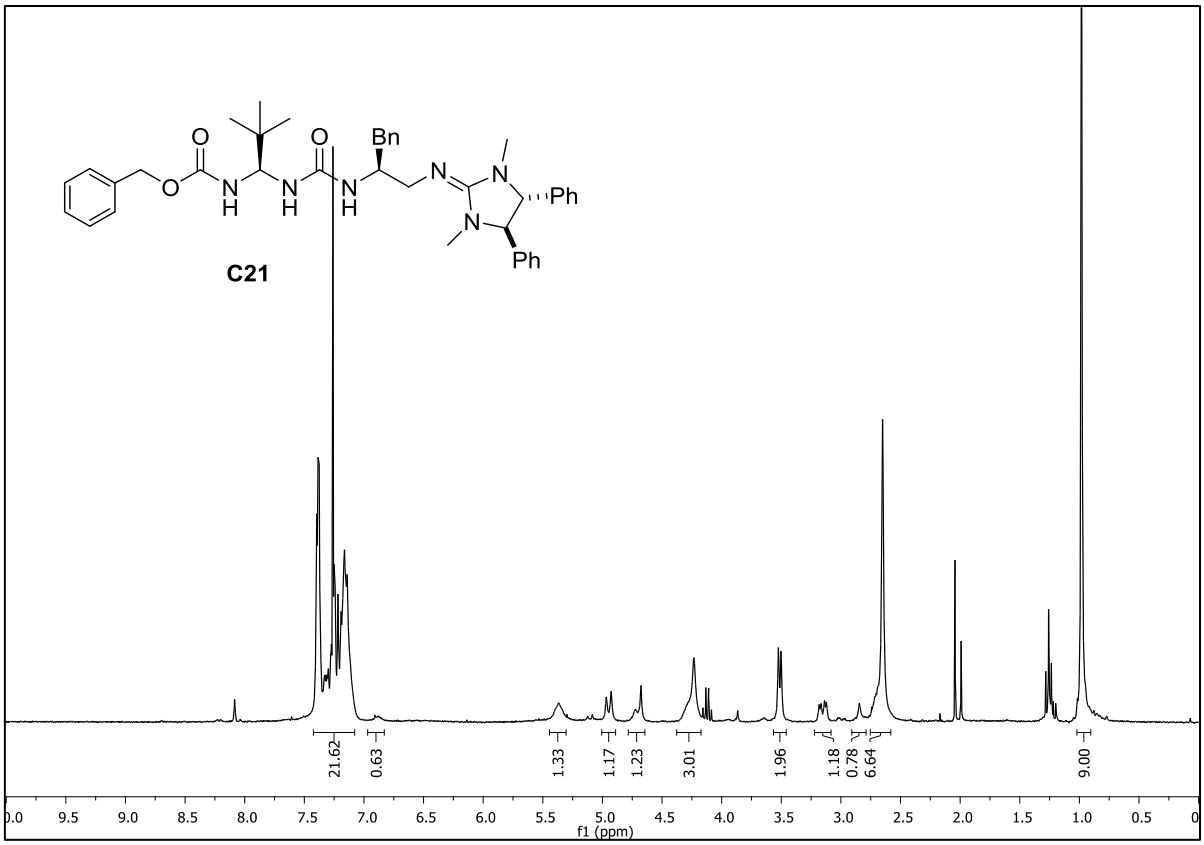
57.16
52.90
41.41
34.05
f1 (ppm)


C21
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1.17
1.23
3.01
1.96
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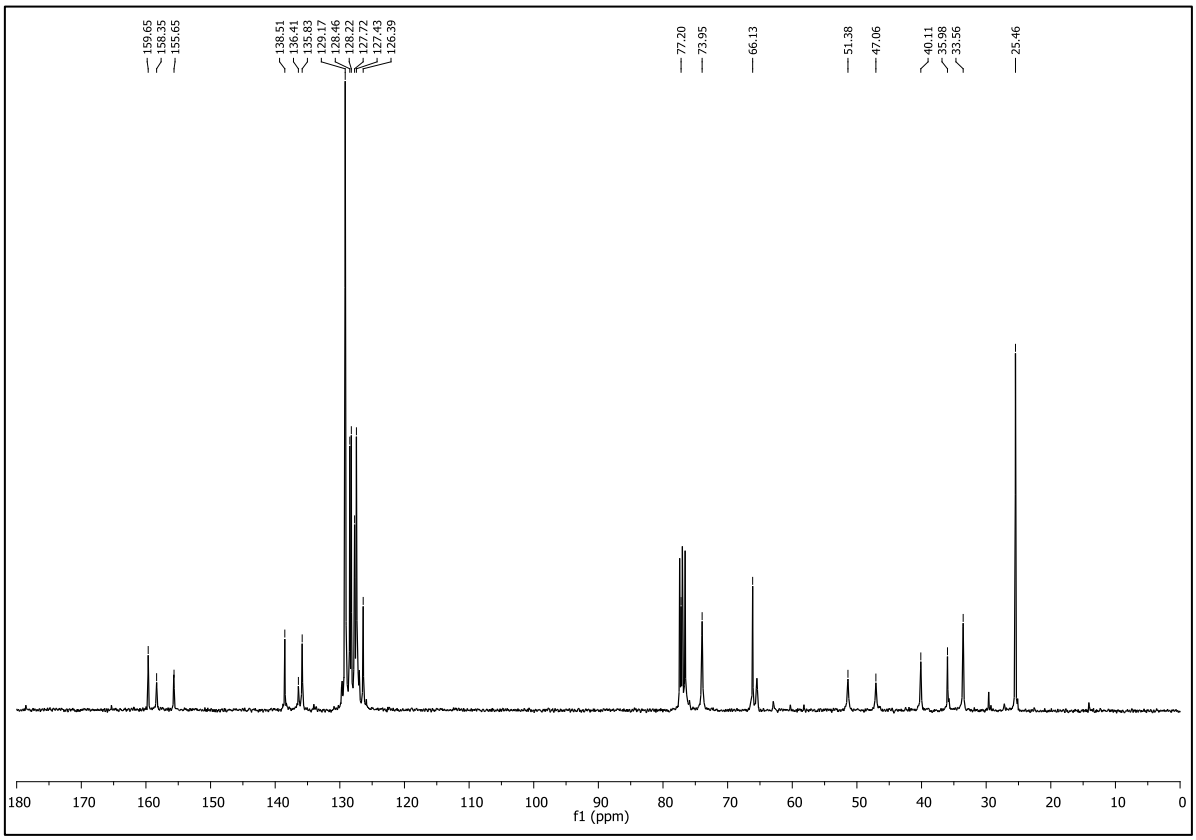
6.64
9.00
f1 (ppm)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136.41
135.83
129.17
128.46
128.22
127.72
127.43
126.39
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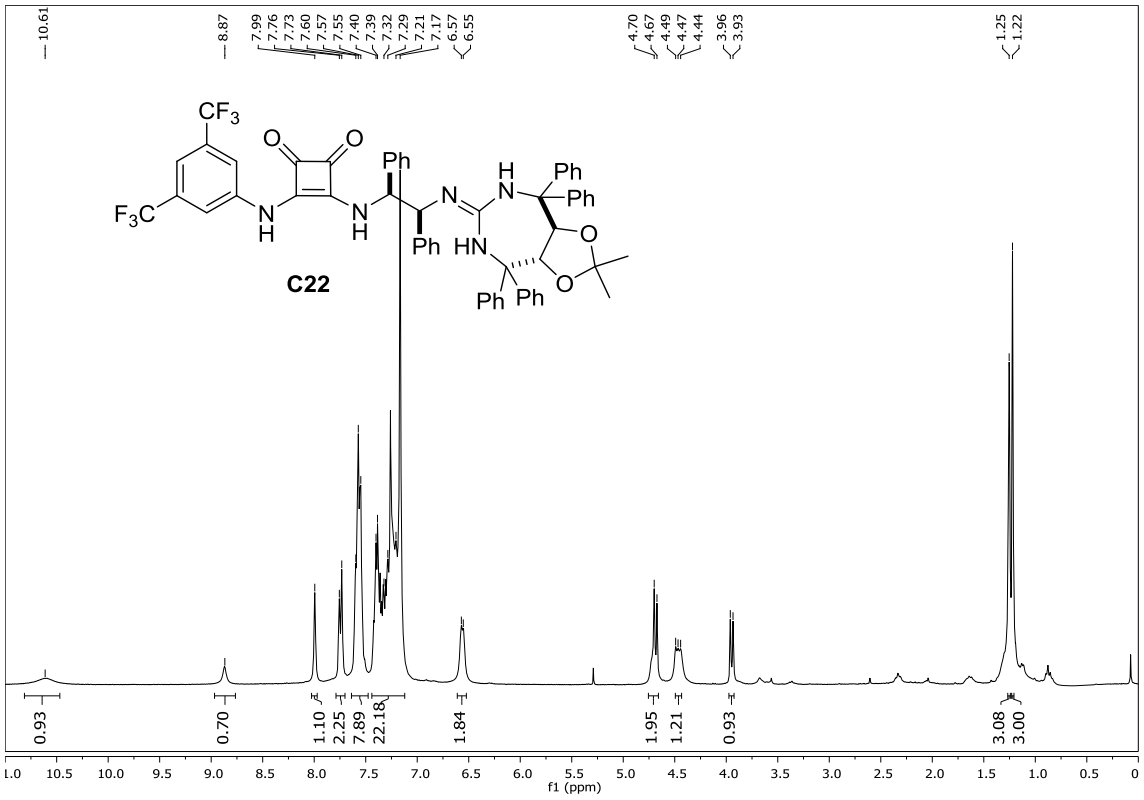
73.95
66.13
51.38
47.06
40.11
35.98
33.56
25.46
f1 (ppm)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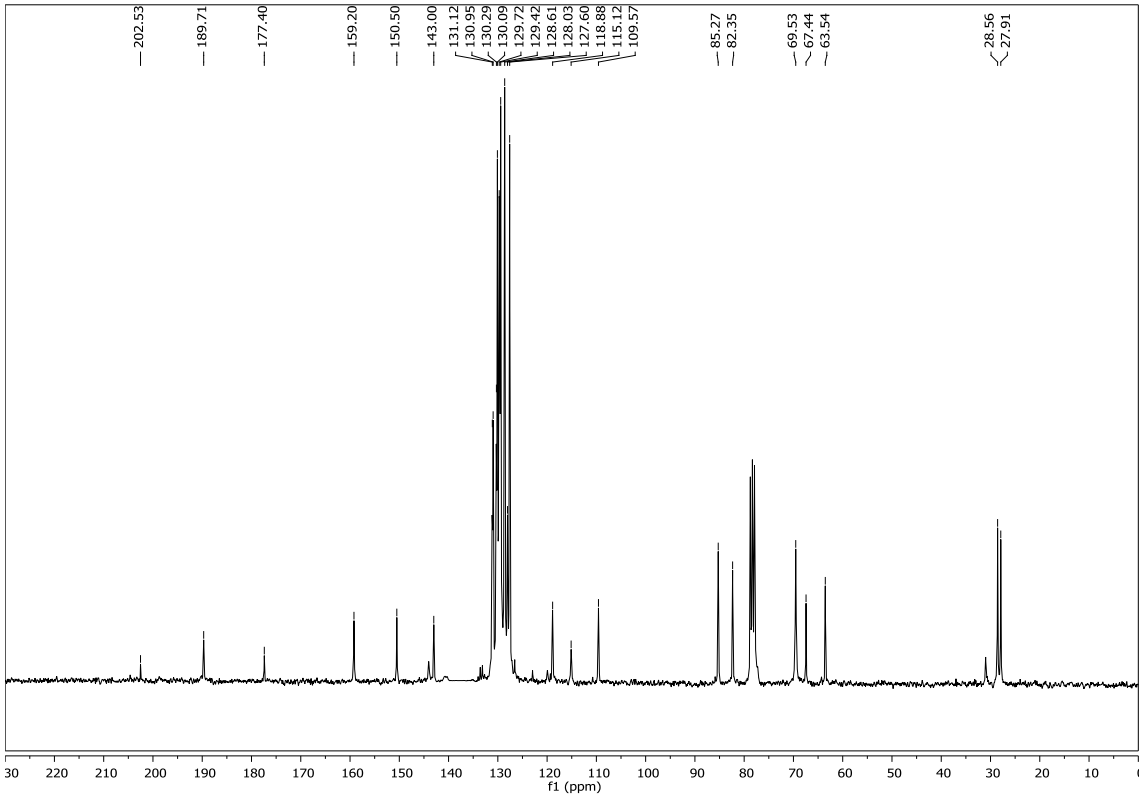
7.55
7.40
7.39
7.32
7.29
7.21
7.17
6.57
6.55
4.70
4.67
4.49
4.47
4.44
3.96
3.93
1.25
1.22
CF3
F3C
O
O
N
H
N
H
Ph
Ph
N
H
N
H
Ph
Ph
Ph
HN
O
O
Ph
Ph
C22
0.93
0.70
1.10
2.25
7.89
22.18
1.84
1.95
1.21
0.93
3.08
3.00
f1 (ppm)


202.53
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177.40
159.20
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143.00
131.12
130.95
130.29
130.09
129.72
129.42
128.61
128.03
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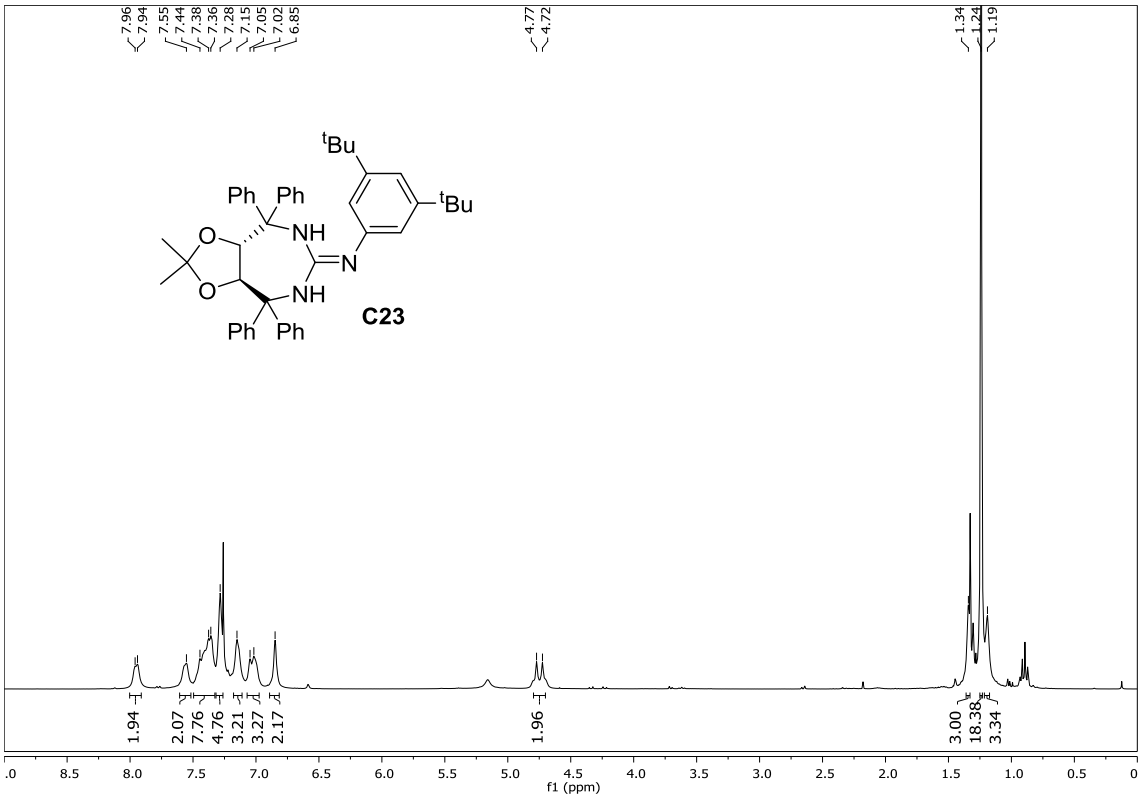
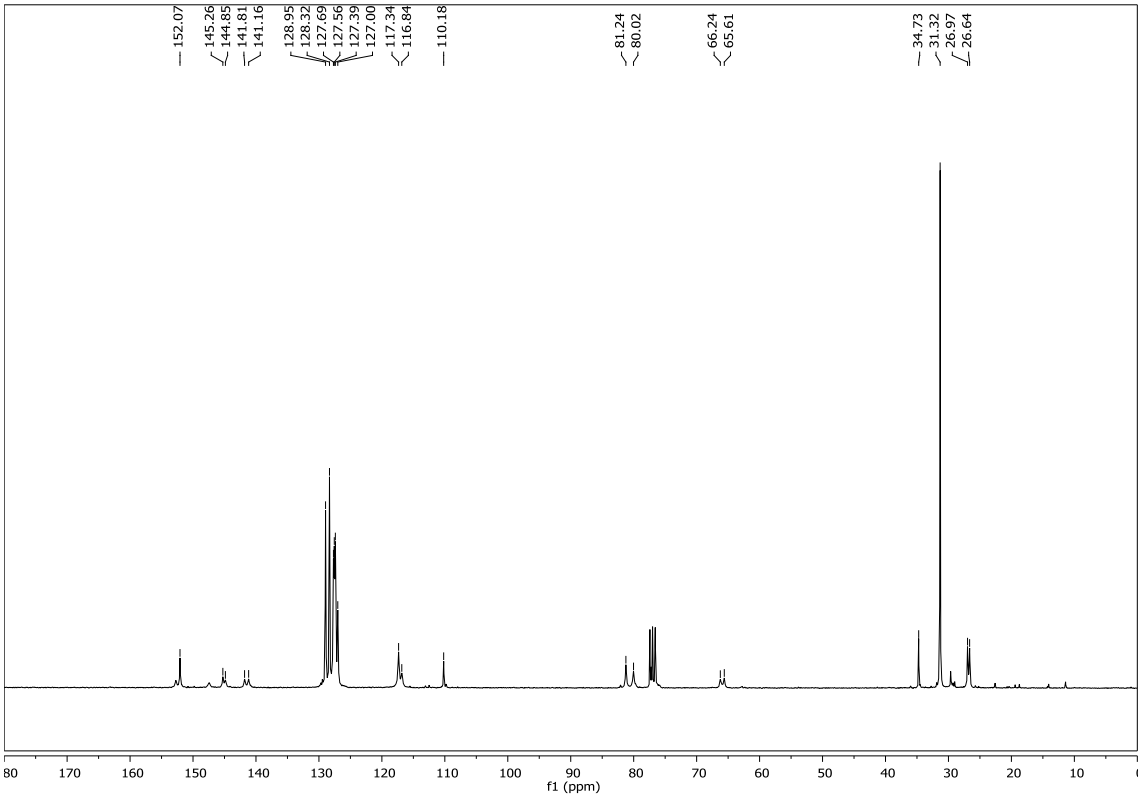
67.44
63.54
28.56
27.91
f1 (ppm)


7.96
7.94
7.55
7.44
7.38
7.36
7.28
7.15
7.05
7.02
6.85
4.77
4.72
1.34
1.24
1.19
tBu
tBu
Ph
Ph
NH
N
NH
O
O
Ph
Ph
C23
1.94
2.07
7.76
4.76
3.21
3.27
2.17
1.96
3.00
18.38
3.34
f1 (ppm)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128.32
127.69
127.56
127.39
127.00
117.34
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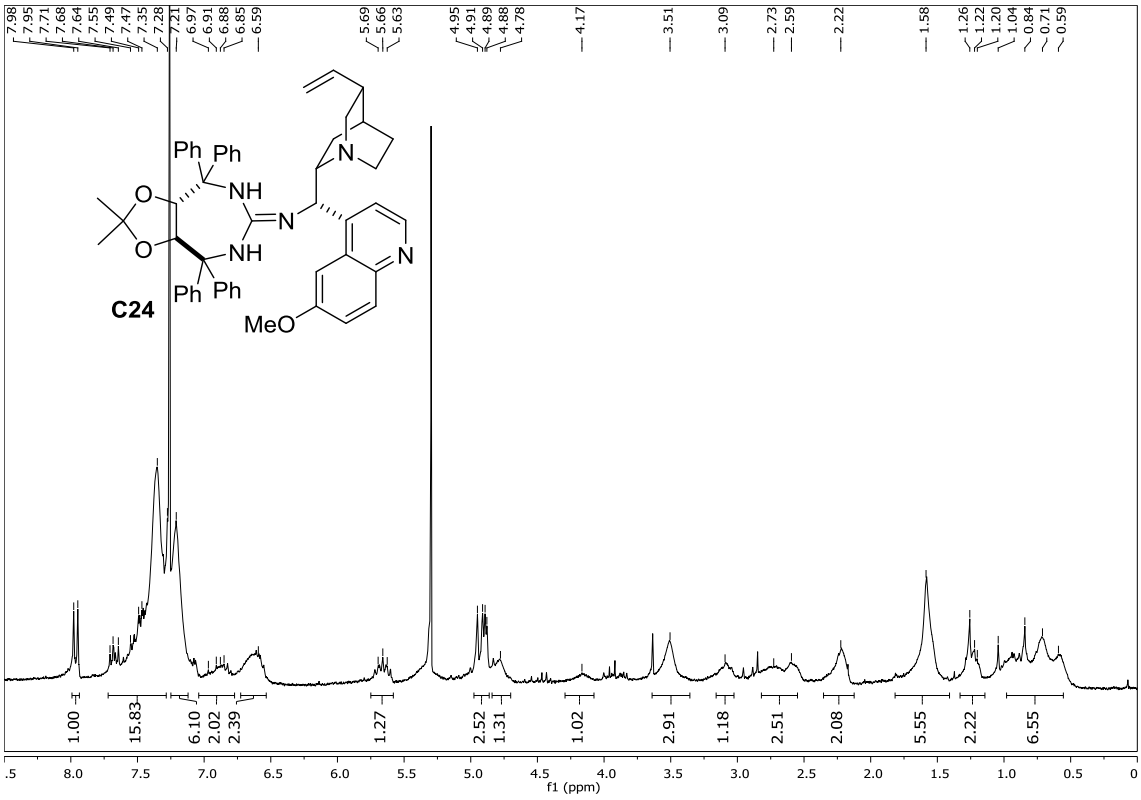
110.18
81.24
80.02
66.24
65.61
34.73
31.32
26.97
26.64
f1 (ppm)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Ph
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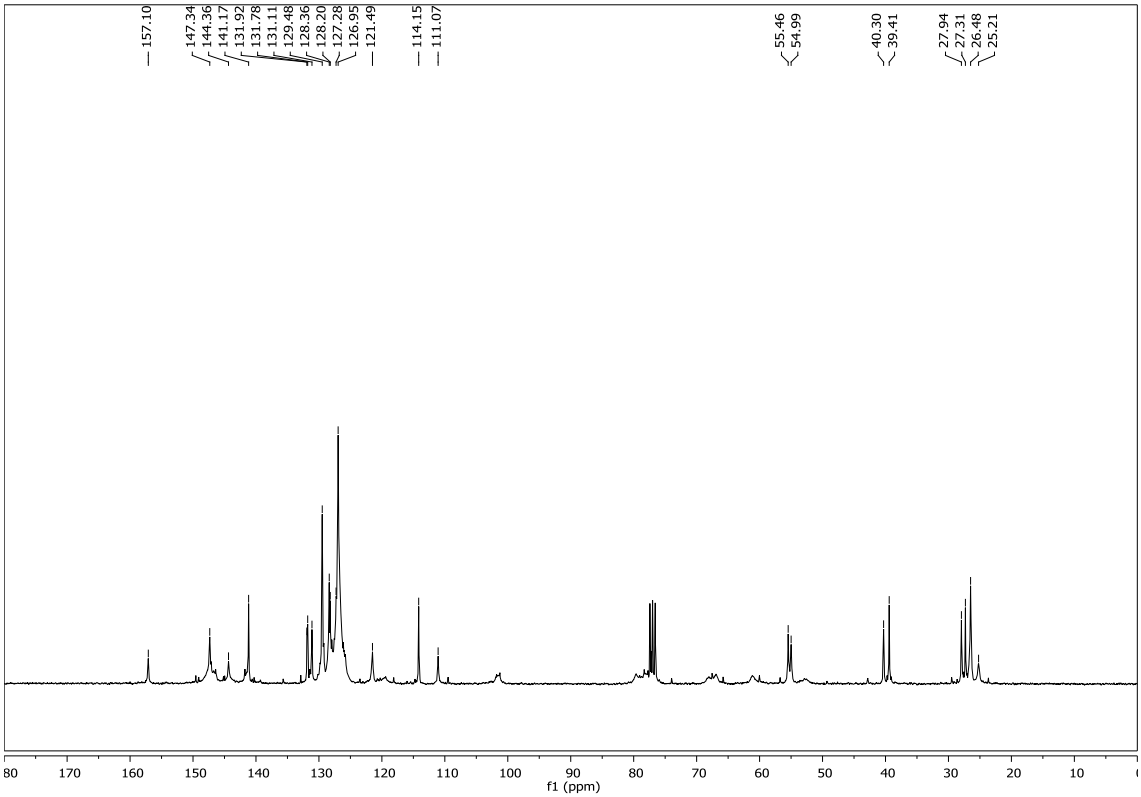
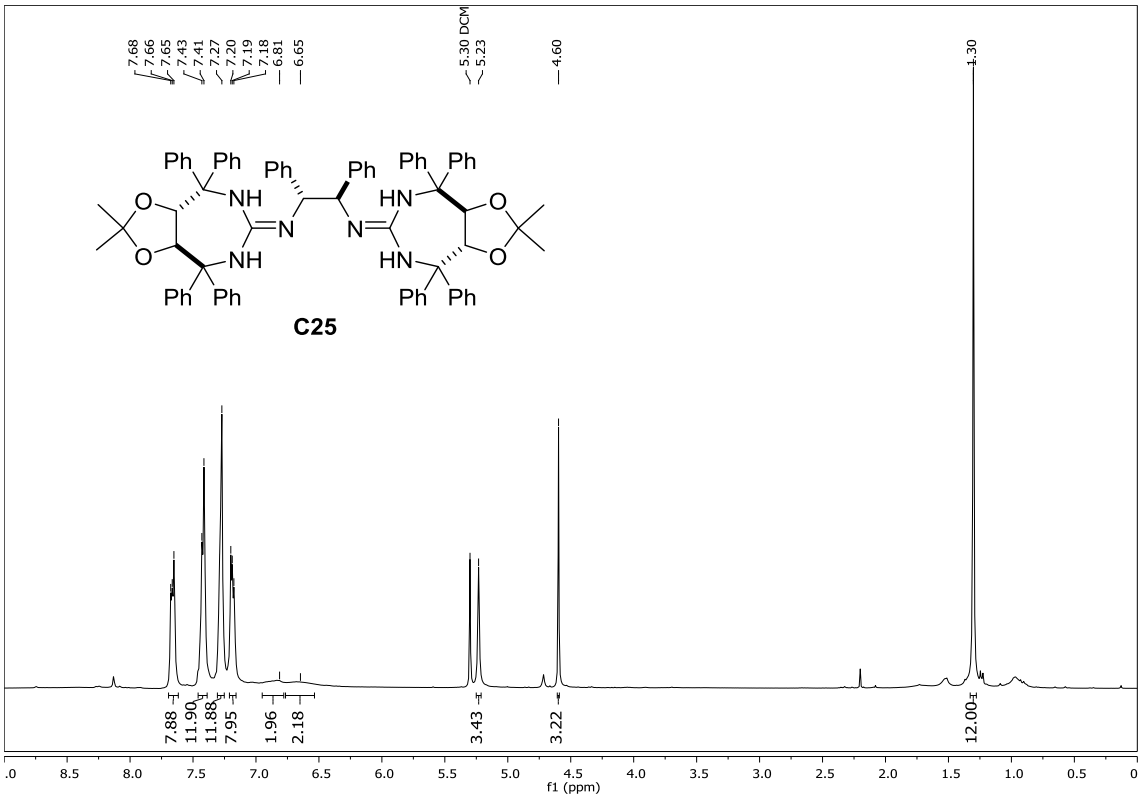
N
O
O
NH
Ph
Ph
N
MeO
f1 (ppm)


f1 (ppm)


7.68
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7.65
7.43
7.41
7.27
7.20
7.19
7.18
6.81
6.65
5.30 DCM
5.23
4.60
1.30
Ph
NH
N
HN
O
C25
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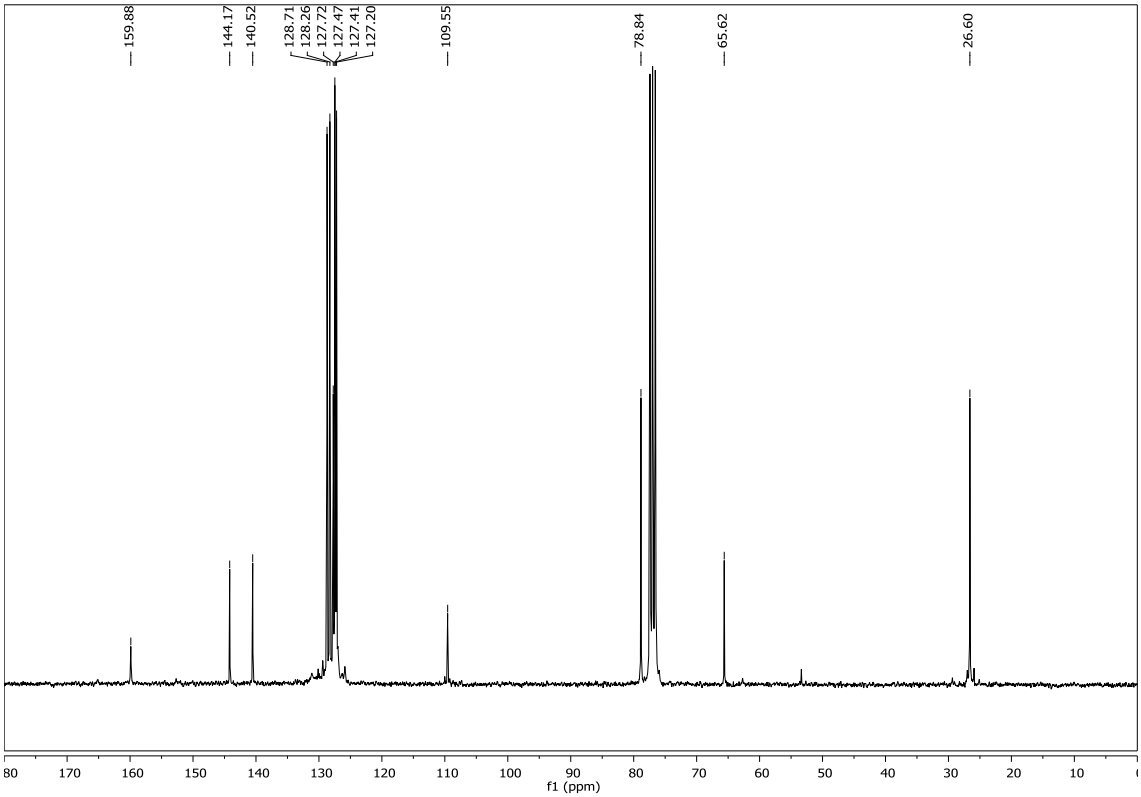
11.90
11.88
7.95
1.96
2.18
3.43
3.22
12.00
f1 (ppm)


159.88
144.17
140.52
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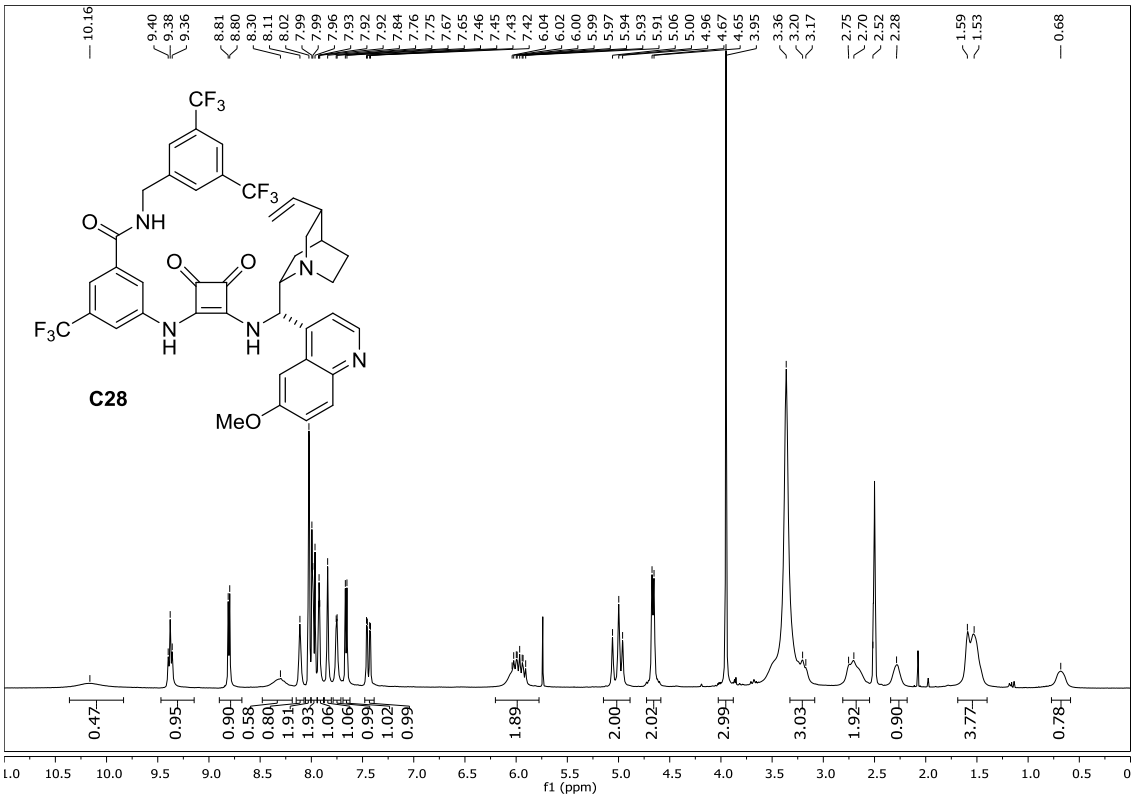
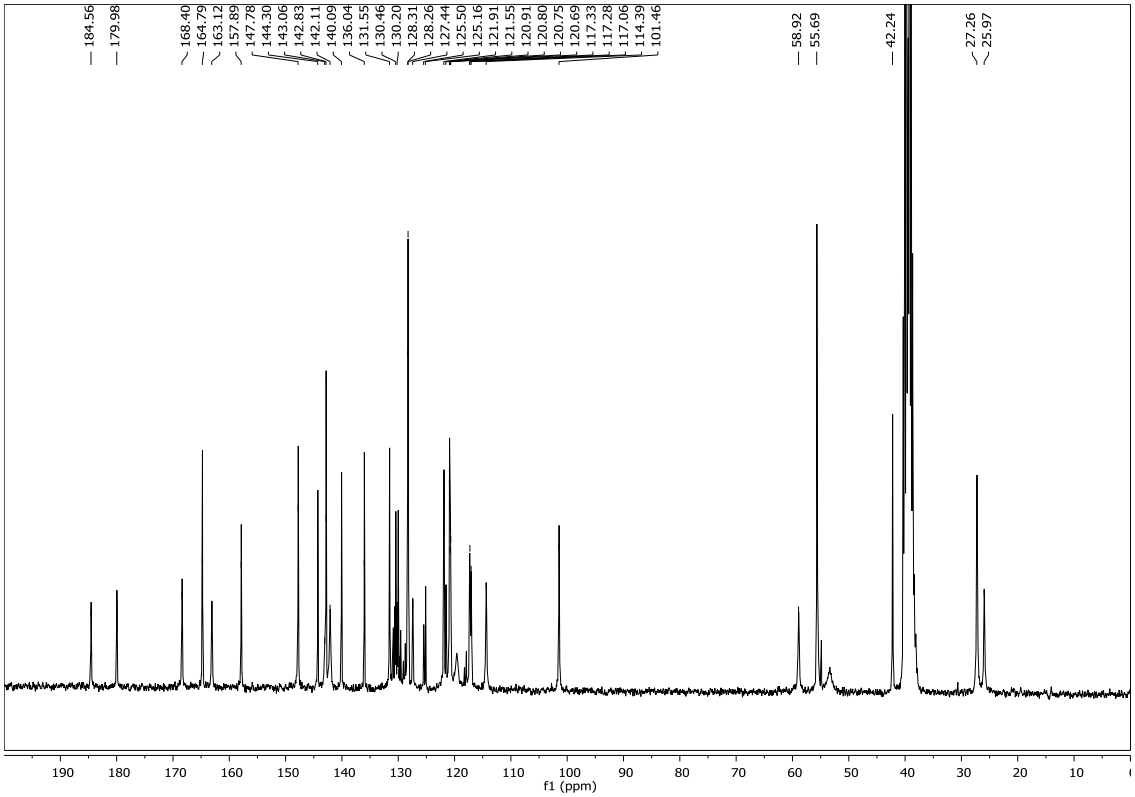
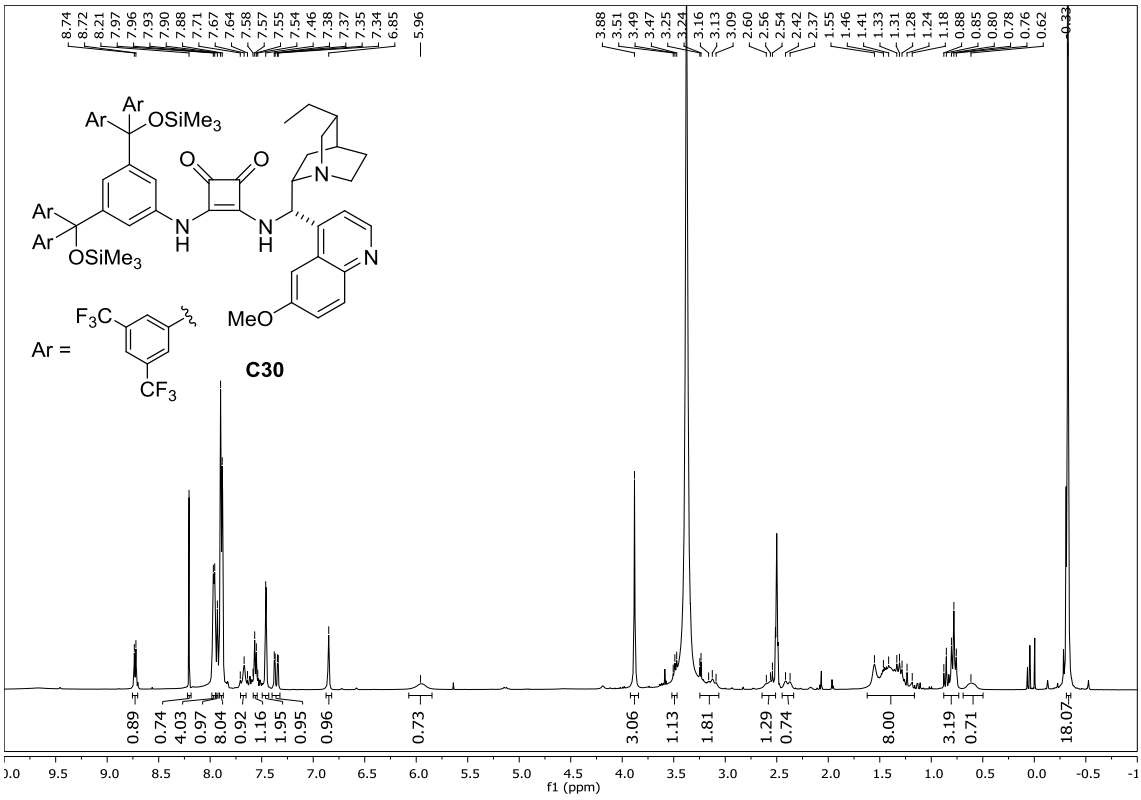
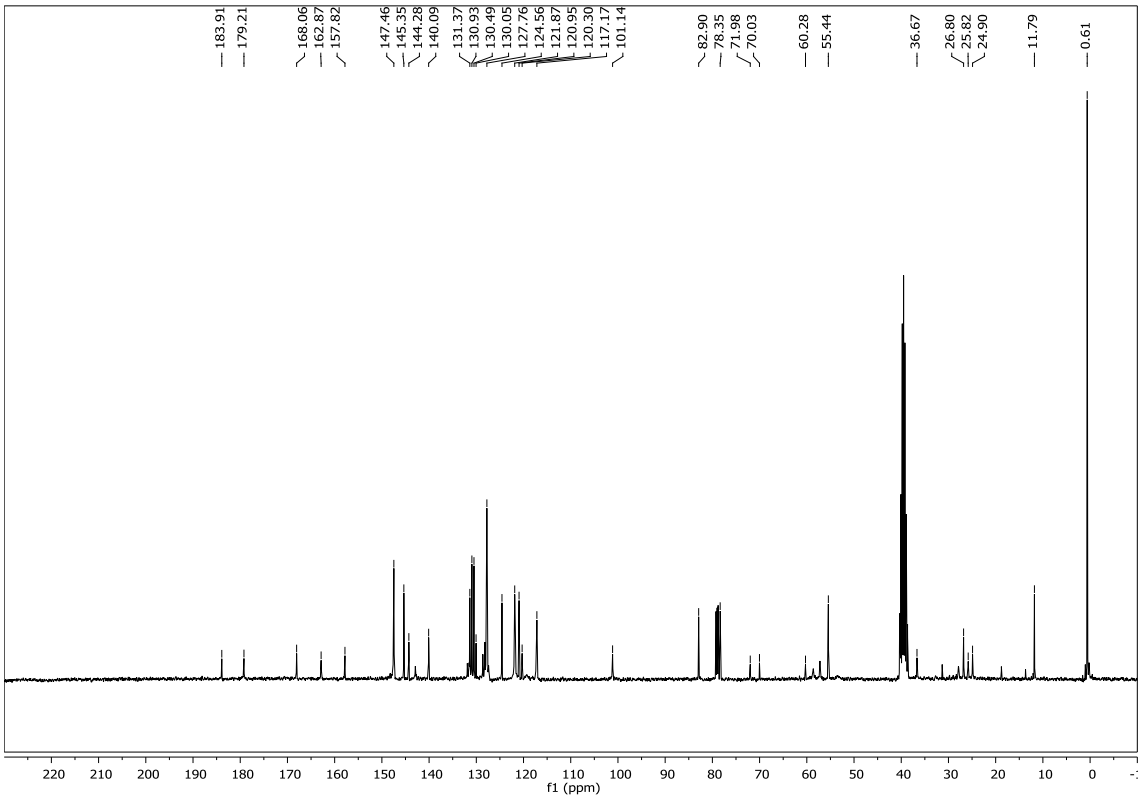
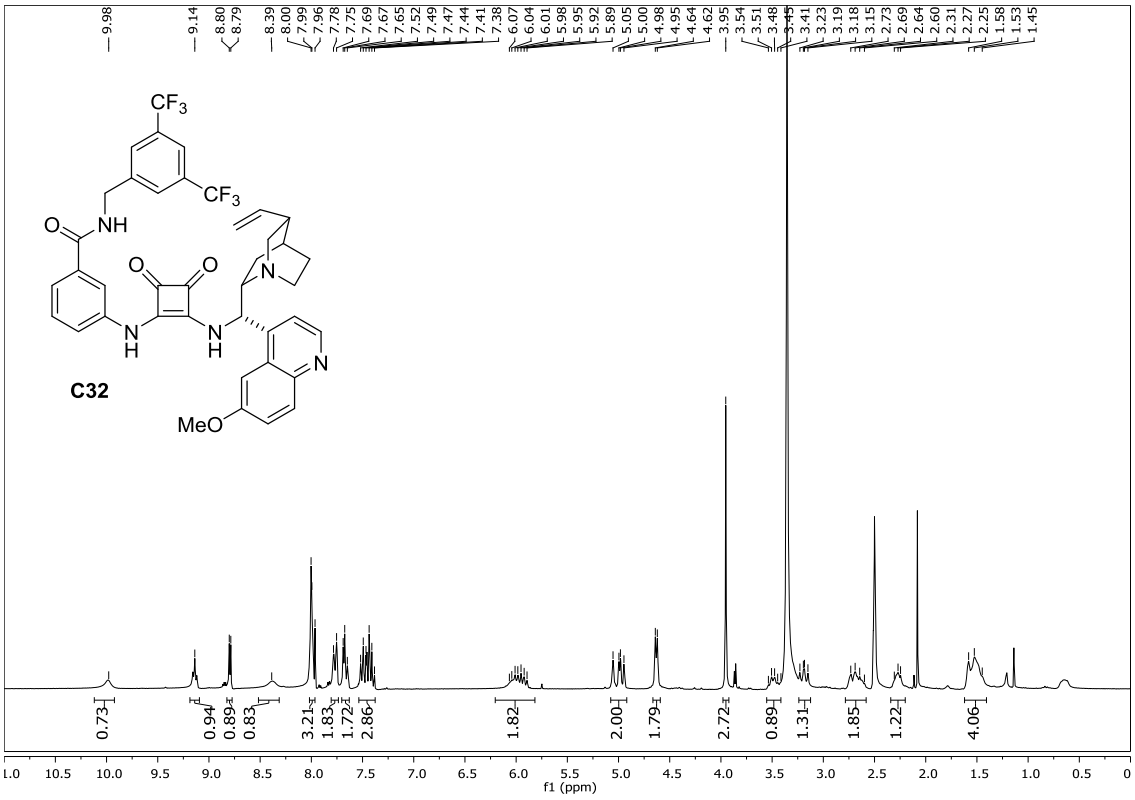
128.26
127.72
127.47
127.41
127.20
109.55
78.84
65.62
26.60
f1 (ppm)

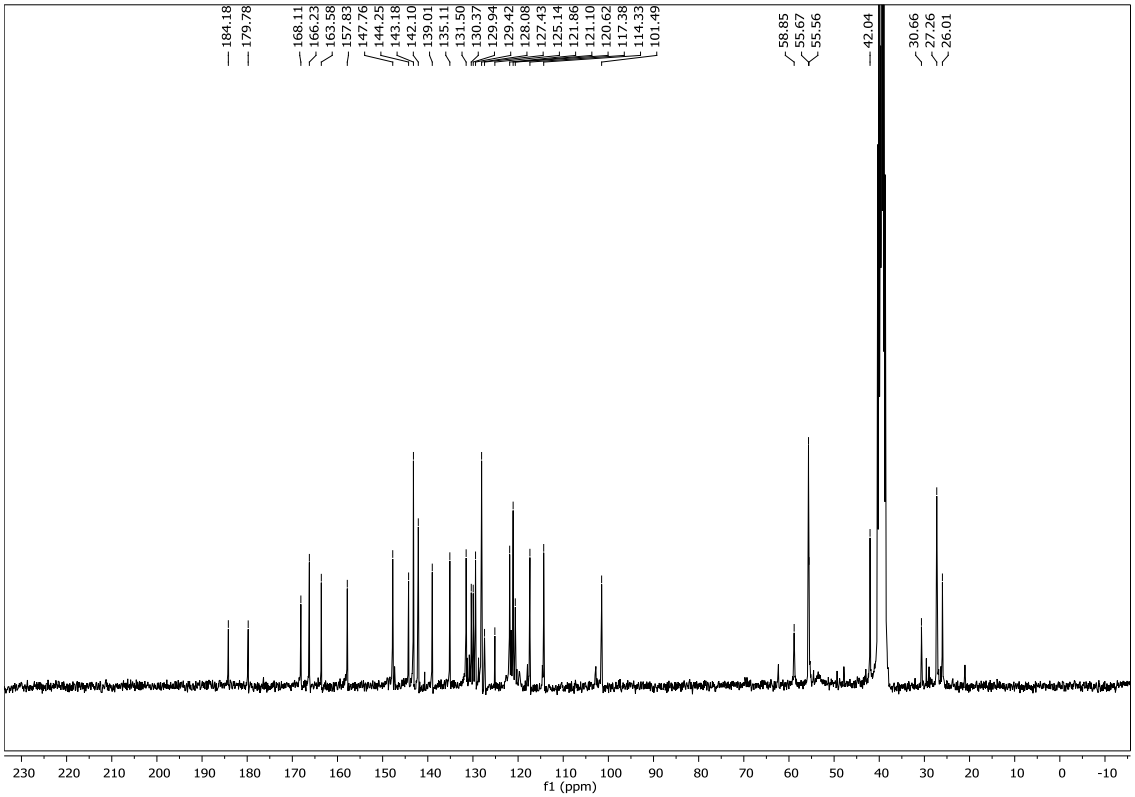

CF3
CF3
O
NH
O
O
N
F3C
N
H
N
H
N
MeO
C28
f1 (ppm)

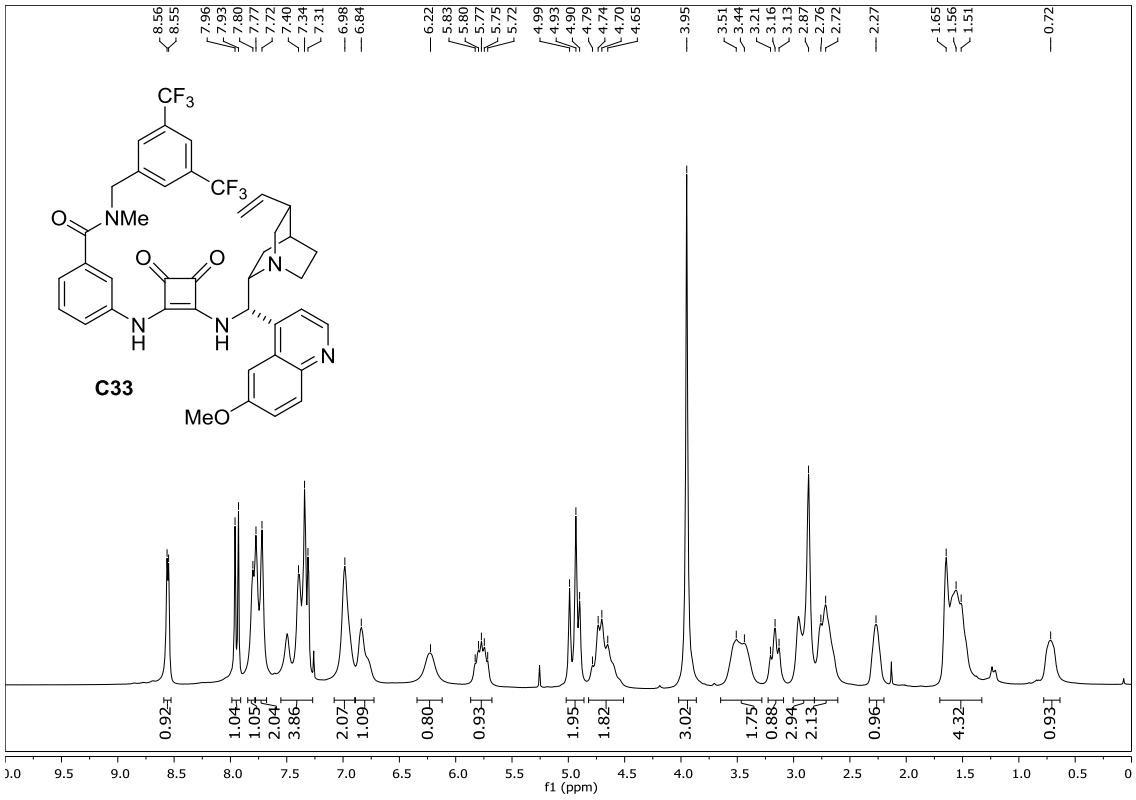

f1 (ppm)


8.74 8.72 8.21 7.97 7.96 7.93 7.90 7.88 7.71 7.67 7.64 7.58 7.57 7.55 7.54 7.46 7.38 7.37 7.35 7.34 6.85 5.96
3.88 3.51 3.49 3.47 3.25 3.24 3.16 3.13 3.09 2.60 2.56 2.54 2.42 2.37 1.55 1.46 1.41 1.33 1.31 1.28 1.24 1.18 0.88 0.85 0.80 0.78 0.76 0.62 0.33
Ar
OSiMe3
O
O
N
Ar
Ar
OSiMe3
N
H
N
H
N
MeO
F3C
Ar =
CF3
C30
0.89 0.74 4.03 0.97 8.04 0.92 1.16 1.95 0.95 0.96 0.73 3.06 1.13 1.81 1.29 0.74 8.00 3.19 0.71 18.07
f1 (ppm)


183.91 179.21 168.06 162.87 157.82 147.46 145.35 144.28 140.09 131.37 130.93 130.49 130.05 127.76 124.56 121.87 120.95 120.30 117.17 101.14
82.90 78.35 71.98 70.03 60.28 55.44 36.67 26.80 25.82 24.90 11.79 0.61
f1 (ppm)


CF3
CF3
O
NH
O
O
N
N
H
N
H
N
MeO
C32
f1 (ppm)


f1 (ppm)


8.56
8.55
7.96
7.93
7.80
7.77
7.72
7.40
7.34
7.31
6.98
6.84
6.22
5.83
5.80
5.77
5.75
5.72
4.99
4.93
4.90
4.79
4.74
4.70
4.65
3.95
3.51
3.44
3.21
3.16
3.13
2.87
2.76
2.72
2.27
1.65
1.56
1.51
0.72
CF3
CF3
O
NMe
O
O
N
N
H
N
H
N
C33
MeO
0.92
1.04
1.05
2.04
3.86
2.07
1.09
0.80
0.93
1.95
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3.02
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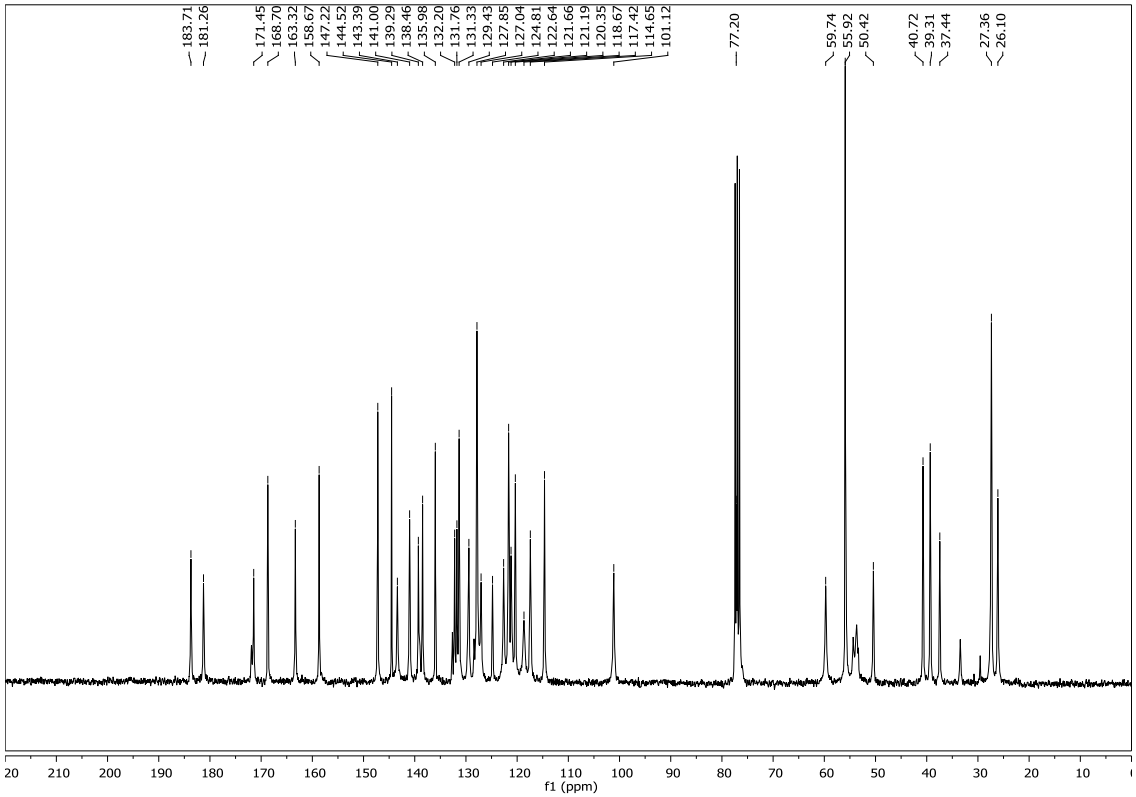
2.94
2.13
0.96
4.32
0.93
f1 (ppm)


183.71
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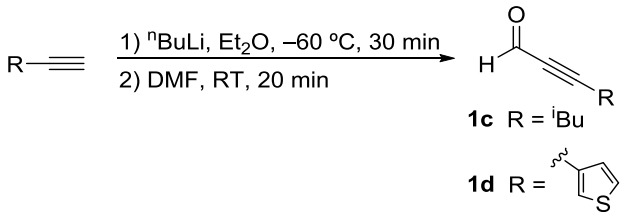
168.70
163.32
158.67
147.22
144.52
143.39
141.00
139.29
138.46
135.98
132.20
131.76
131.33
129.43
127.85
127.04
124.81
122.64
121.66
121.19
120.35
118.67
117.42
114.65
101.12
77.20
59.74
55.92
50.42
40.72
39.31
37.44
27.36
26.10
f1 (ppm)

5.3. Experimental section of Chapter 2

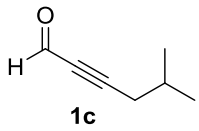
5.3.1. Synthesis of propargylic aldehydes 1

Phenyl propynal (**1a**) and octynal (**1b**) are commercially available and were purchased from commercial suppliers. New propargylic aldehydes **1c** and **1d** were synthesised as described bellow:[242]



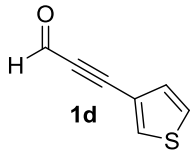
To a round bottomed flask filled with Et_2O (50 mL) and cooled to –60 ºC were successively added dropwise ^nBuLi (50 mmol, 20 mL, 2.5 M in hexane) and the corresponding alkyne (50 mmol). The reaction mixture was stirred at that temperature for 30 min after which DMF (4.3 mL, 62.5 mmol) was added slowly. The resulting mixture was removed from the bath, warmed slowly to room temperature and stirred at this temperature for 20 min. Then, the reaction mixture was poured into a cold solution of water (25 mL) and concentrated HCl (4 mL) and a solution of saturated $NaHCO_3$ was added dropwise until pH 6-7. The organic layer was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was eliminated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the corresponding pure ynone **1**.

5-Methylhex-2-ynal (1c)



The compound was prepared according to the general procedure, starting from 4-methylpent-1-yne (1.4 mL, 10 mmol). Black oil. Yield: 63% (700 mg, 7.0 mmol). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 2.35 (dd, *J* = 6.5, 0.7 Hz, 2H), 2.04 – 1.89 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H).

3-(Thiophen-3-yl)propiolaldehyde (1d)

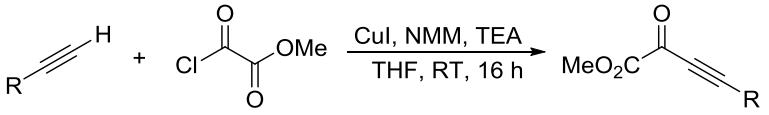


Prepared according to the general procedure, starting from 3-ethynylthiophenone (0.98 mL, 10 mmol). Black oil. Yield: 45% (610 mg, 4.5 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.82 (d, *J* = 1.7 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.26 (d, *J* = 5.0 Hz, 1H).

[242] L. Bradsma, Preparative acetylenic chemistry (Studies in Organic Chemistry 34); Elsevier, Amsterdam, **1988**, 97–112.

5.3.2. Synthesis of propargylic ketoesters 2[243]

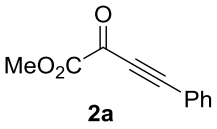
Known ketoester **2a** and new ketoesters **2b-2d** were synthesised according to the following synthetic procedure:



2a, R = Ph
2b, R = 4-FC_6H_4
2c, R = 3-ClC_6H_4
2d, R = 3-MeC_6H_4

To a mixture of copper (I) iodide (100 mg, 0.5 mmol, 5 mol%) and triethylamine (2.8 mL, 20 mmol, 2 equiv.) in THF (50 mL) the corresponding alkyne (10 mmol, 1 equiv.) and methyl oxalyl chloride (1.8 mL, 20 mmol, 2 equiv.) were successively added and the mixture was allowed to stir at room temperature for 16 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (50 mL) and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The organic phases were combined, dried over $MgSO_4$, and the solvent was eliminated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5) obtaining the pure desired product.

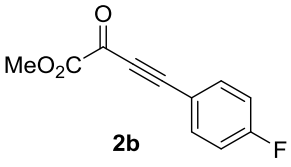
Methyl 2-oxo-4-phenylbut-3-ynoate (2a)[244]



2a

The compound was prepared according to the general procedure, starting from phenylacetylene (1.1 mL, 10 mmol). Yellow solid. Yield: 61% (990 mg, 6.1 mmol). All data were consistent with those previously reported. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.56 – 7.51 (m, 1H), 7.45 – 7.40 (m, 2H), 3.97 (s, 3H).

Methyl 4-(4-fluorophenyl)-2-oxobut-3-ynoate (2b)



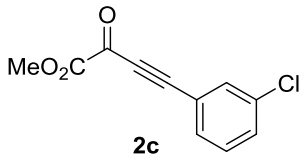
2b

The compound was prepared according to the general procedure, starting from 1-ethynyl-1-fluorobenzene (1.2 mL, 10 mmol). Yellow solid. Yield: 50% (1.0 g, 5.0 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 2H), 7.18 – 7.08 (m, 2H), 3.96 (s, 3H).

[243] Adapted from: W. Yao, L. Pan, Y. Zhang, G. Wang, X. Wang, C. Ma, *Angew. Chem. Int. Ed.* **2010**, *49*, 9210–9214.

[244] M. Ueda, Y. Ikeda, A. Sato, Y. Ito, M. Kakiuchi, H. Shono, T. Miyoshi, T. Naito, O. Miyata, *Tetrahedron*, **2011**, 67, 4612–4615.

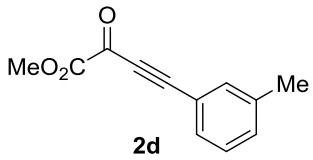
Methyl 4-(3-chlorophenyl)-2-oxobut-3-ynoate (2c)



2c

The compound was prepared according to the general procedure, starting from 3-chloro-1-ethynylbenzene (1.4 g, 10 mmol). Brown solid. Yield: 22% (500 mg, 2.2 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.66 (t, *J* = 1.8 Hz, 1H), 7.56 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.50 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 3.97 (s, 3H).

Methyl 4-(3-methylphenyl)-2-oxobut-3-ynoate (2d)

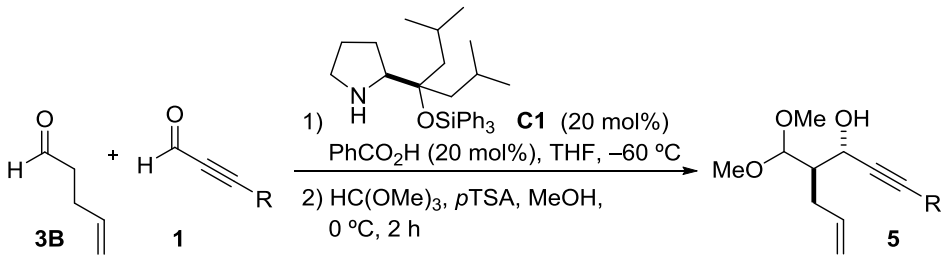


2d

The compound was prepared according to the general procedure, starting from 1-ethynyl-3-methylbenzene (1.2 g, 10 mmol). Brown solid. Yield: 58% (1.2 mg, 5.8 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 6.4, 1.4 Hz, 2H), 7.32 (dd, *J* = 6.2, 1.1 Hz, 2H), 3.96 (s, 3H), 2.38 (s, 3H).

5.3.3. Cross-aldol reaction of α,β-ynals

5.3.3.1. General procedure

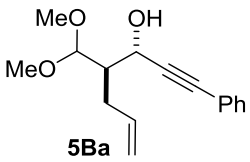


To a solution of the amine catalyst **C1** (47 mg, 0.1 mmol, 20 mol%) in THF (0.5 mL) at –60 ºC were successively added 4-pentenal (**3B**, 74 µL, 0.75 mmol, 1.5 equiv.), benzoic acid (12 mg, 0.1 mmol, 20 mol%) and the corresponding ynal **1** (0.5 mmol, 1 equiv.). The resulting solution was stirred at –60 ºC for 24–48 h until the reaction stopped (^{1}H NMR monitoring), and to the mixture MeOH (4.5 mL), trimethyl orthoformate (0.16 mL, 1.5 mmol, 3 equiv.) and *p*TSA (20 mg, 0.1 mmol, 20 mol%) were successively added at –60 ºC. The mixture was allowed to reach 0 ºC and, after 2 h stirring, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (2 × 4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 90:10), thus allowing in each case separation of *anti* (major) and *syn* (minor) aldol diastereomers.

Racemic reactions were conducted following the procedure for the asymmetric version, but using **(±)1C** (20 mol%) as the catalyst.

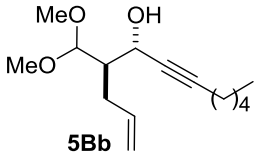
*5.3.3.2. Characterization data for compounds **5B***

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-phenylhept-6-en-1-yn-3-ol (5Ba)



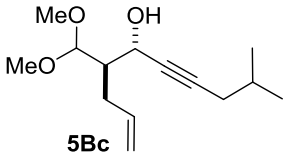
The compound was obtained following the general procedure using ynal **1a** (61 µL, 0.5 mmol). Yellow oil. The adduct was obtained in a 1:8 *syn*/*anti* ratio. Yield: 72% (93 mg, 0.36 mmol). $[\alpha]_D^{24}$ = –8.2º (*c* = 1.05, 94% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.51 – 7.31 (m, 5H), 5.94 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.27 – 5.07 (m, 2H), 4.80 (d, *J* = 5.9 Hz, 1H), 4.64 (d, *J* = 4.9 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 2.55 – 2.37 (m, 2H), 2.20 (ddd, *J* = 10.7, 7.4, 5.7 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 136.5, 130.0, 128.9, 125.3, 117.2, 106.7, 88.5, 81.0, 63.2, 56.1, 55.0, 46.3, 30.4. **MS:** calculated for $C_{16}H_{20}O_3$ ($M + H^+$), 261.1446; found, 261.1440. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak AD-H, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 19.8 min (minor), 22.0 min (major)).

(4*R*,5*S*)-4-(Dimethoxymethyl)dodec-1-en-6-yn-5-ol (5Bb)



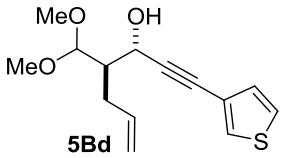
The compound was obtained following the general procedure using ynal **1b** (0.71 mL, 5.0 mmol). Yellow oil. The adduct was obtained in a 1:20 *syn*/*anti* ratio. Yield: 50% (640 mg, 2.5 mmol). $[\alpha]_D^{24}$ = +13.4º (*c* = 1.00, 99% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.04 – 5.66 (m, 1H), 5.30 – 4.99 (m, 2H), 4.56 (d, *J* = 5.1 Hz, 2H), 3.47 (s, 3H), 3.45 (s, 3H) 2.38 (dd, *J* = 13.7, 7.1 Hz, 2H), 2.27 (td, *J* = 7.0, 2.0 Hz, 2H), 2.09 – 2.02 (m, 1H), 1.55 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.46 – 1.35 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 137.1, 117.1, 107.0, 86.9, 80.1, 63.1, 56.1, 55.0, 46.7, 31.4, 30.6, 28.7, 22.5, 19.1, 14.3. **MS:** calculated for $C_{14}H_{23}O_2$ ($M - OMe^-$), 223.1704; found, 223.1696. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the corresponding *O*-benzoylate derivative (Daicel Chiralpak IC, hexane/isopropanol, 99:1; flux = 1 mL/min; retention times: 5.9 min (major), 8.2 min (minor)).

(4*R*,5*S*)-4-(dimethoxymethyl)-9-methyldec-1-en-6-yn-5-ol (5Bc)



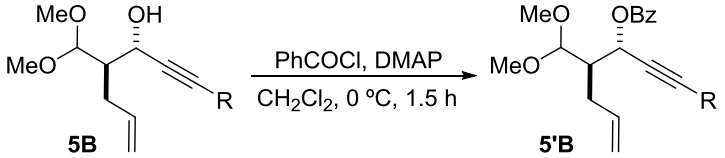
The compound was obtained following the general procedure using ynal **1c** (0.71 mL, 5.0 mmol). Yellow oil. The adduct was obtained in a 1:20 *syn*/*anti* ratio. Yield: 50% (640 mg, 2.5 mmol). $[\alpha]_D^{24}$ = +14.3º (*c* = 1.00, 99% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.04 – 5.66 (m, 1H), 5.30 – 4.99 (m, 2H), 4.56 (d, *J* = 5.1 Hz, 2H), 3.47 (s, 3H), 3.45 (s, 3H) 2.38 (dd, *J* = 13.7, 7.1 Hz, 2H), 2.27 (td, *J* = 7.0, 2.0 Hz, 2H), 2.09 – 2.02 (m, 1H), 1.55 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.46 – 1.35 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 137.1, 117.1, 107.0, 86.9, 80.1, 63.1, 56.1, 55.0, 46.7, 31.4, 30.6, 28.7, 22.5, 19.1, 14.3. **MS:** calculated for $C_{13}H_{21}O_2$ (M – OMe^-), 209.1547; found, 209.1523. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the corresponding *O*-benzoylate derivative (Daicel Chiralpak IC, hexane/isopropanol, 98:2; flux = 0.75 mL/min; retention times: 6.5 min (major), 7.5 min (minor)).

(3*S*,4*R*)-4-(dimethoxymethyl)-1-(thiophen-3-yl)hept-6-en-1-yn-3-ol (5Bd)



The compound was obtained following the general procedure using ynal **1d** (52 mg, 0.5 mmol). Yellow oil. The adduct was obtained in a 1:9 *syn*/*anti* ratio. Yield: 72% (96 mg, 0.36 mmol). $[\alpha]_D^{24}$ = +21.6º (*c* = 1.00, 99% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.26 (s, 1H), 7.11 (d, *J* = 3.9 Hz, 1H), 6.03 – 5.74 (m, 1H), 5.16 (d, *J* = 16.0 Hz, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 4.74 (s, 1H), 4.58 (d, *J* = 4.7 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.48 – 2.33 (m, 2H), 2.15 – 1.12 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 136.5, 131.6, 128.3, 128.2, 122.4, 117.0, 106.7, 88.9, 85.7, 63.0, 55.9, 54.8, 46.3, 30.3. **MS:** calculated for $C_{13}H_{15}O_2S$(M, – OMe^-), 235.0798; found, 235.0784. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak AD-H, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 25.8 min (minor), 26.7 min (major)).

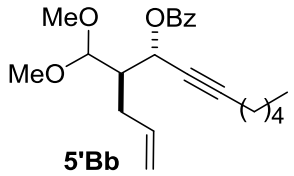
5.3.3.3. Benzoylation of adducts for ee determination by HPLC



The *ee* of adducts **5Bb** and **5Bc** was determined on their benzoylated derivative, prepared as follow. To a solution of alcohol **5B** (0.15 mmol) in CH_2Cl_2 (0.5 mL) at 0 ºC

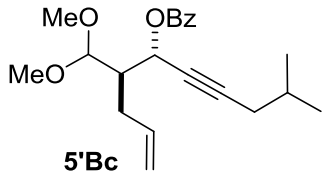
were successively added DMAP (55 mg, 0.45 mmol, 3 equiv.) and benzoyl chloride (32 mg, 0.23 mmol, 1.5 equiv.). The resulting mixture was stirred at 0 ºC for 3 h, diluted with CH_2Cl_2 (10 mL) and the organic solution was washed with a saturated solution of NH_4Cl (2 × 5 mL) and a saturated solution of $NaHCO_3$ (2 × 5 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5) to afford the pure benzoylated product.

(4*R*,5*S*)-4-(Dimethoxymethyl)dodec-1-en-6-yn-5-yl benzoate (5'Bb)



The product was prepared as described above starting from adduct **5Bb** (38 mg, 0.15 mmol, 1 equiv.). Yellow oil. Yield: 95% (51 mg, 0.14 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 2H), 7.60 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 6.07 – 5.92 (m, 1H), 5.84 (dd, *J* = 4.3, 2.1 Hz, 1H), 5.15 – 4.95 (m, 3H), 4.43 (d, *J* = 7.2 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 4H), 2.56 – 2.41 (m, 3H), 2.34 – 2.28 (m, 1H), 2.23 (ddd, *J* = 7.1, 4.5, 2.1 Hz, 3H), 1.55 – 1.48 (m, 2H), 1.40 – 1.31 (m, 4H), 0.92 – 0.86 (m, 3H).

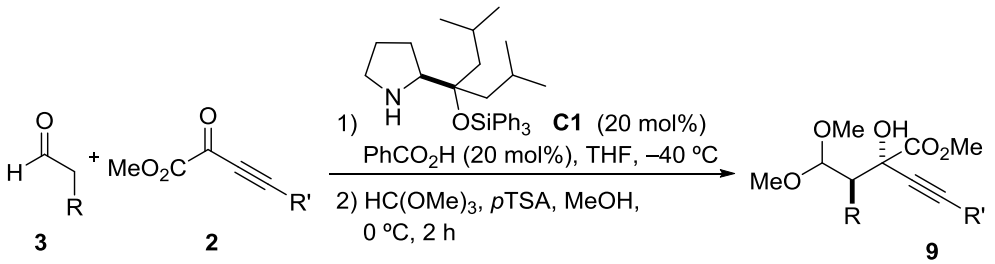
(4*R*,5*S*)-4-(Dimethoxymethyl)-9-methyldec-1-en-6-yn-5-yl benzoate (5'Bc)



The product was prepared as described above starting from adduct **5Bc** (36 mg, 0.15 mmol, 1 equiv.). Yellow oil. Yield: 95% (51 mg, 0.14 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.16 – 7.94 (m, 2H), 7.61 – 7.52 (m, 1H), 7.47 – 7.42 (m, 2H), 6.10 – 5.90 (m, 1H), 5.86 (dt, *J* = 4.2, 2.0 Hz, 1H), 5.15 – 4.90 (m, 2H), 4.44 (d, *J* = 7.3 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.59 – 2.39 (m, 2H), 2.37 – 2.27 (m, 1H), 2.14 (dd, *J* = 6.5, 2.0 Hz, 2H), 1.91 – 1.72 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H).

5.3.4. Cross-aldol reaction of α,β-ynones

5.3.4.1. General procedure



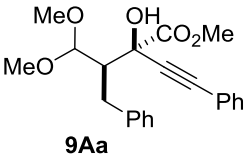
3A, R = CH_2Ph **2a**, R = Ph
3B, R = $CH_2CH{=}CH_2$ **2b**, R = 4-FC_6H_4
3C, R = $(CH_2)_2CH_3$ **2c**, R = 3-ClC_6H_4
3D, R = $CH(CH_3)_2$ **2d**, R = 3-MeC_6H_4

To a solution of the amine catalyst **C1** (47 mg, 0.1 mmol, 20 mol%), benzoic acid (12 mg, 0.1 mmol, 20 mol%) and the corresponding ynone **2** (0.5 mmol, 1 equiv.) in THF (0.5 mL) at –40 ºC the corresponding aldehyde **3** (0.75 mmol, 1.5 equiv.) was added. The resulting solution was stirred at –40 ºC for 48 h until the reaction stopped (^{1}H NMR monitoring), and to the mixture MeOH (4.5 mL), trimethyl orthoformate (0.16 mL, 1.5 mmol, 3 equiv.) and *p*TSA (20 mg, 0.1 mmol, 20 mol%) were successively added at –60 ºC. The mixture was allowed to reach 0 ºC and, after 2 h stirring, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (2 × 4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/THF 92:8), thus allowing in each case separation of *syn* (major) and *anti* (minor) aldol diastereomers.

Racemic reactions were conducted following the procedure for the asymmetric version, but using **(±)1C** (20 mol%) as the catalyst.

*5.3.4.2. Characterization data for compounds **9***

Methyl (*R*)-2-((*R*)-1,1-dimethoxy-3-phenylpropan-2-yl)-2-hydroxy-4-phenylbut-3-ynoate (9Aa)

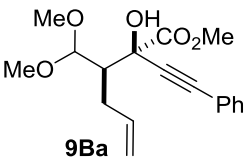


9Aa

The compound was obtained following the general procedure from aldehyde **3A** (97 µL, 0.75 mmol) and ynone **2a** (94 mg, 0.5 mmol). White solid. The adduct was obtained in a 5:1 *syn*/*anti* ratio. m. p.: 123–127ºC. Yield: 83% (153 mg, 0.42 mmol). $[\alpha]_D^{25}$ = –69.5º (*c* =

1.00, 95% *ee*, CH_2Cl_2). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.36 – 7.27 (m, 6H), 7.22 – 7.13 (m, 2H), 4.33 (d, *J* = 6.2 Hz, 1H), 3.81 (s, 3H), 3.52 (s, 1H), 3.41 (dd, *J* = 7.4, 6.1 Hz, 1H), 3.34 (s, 3H), 3.10 (s, 3H), 2.93 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.89 – 2.81 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 172.6, 140.8, 132.0, 131.9, 129.2, 129.2, 129.1, 128.7, 128.6, 128.5, 128.2, 128.2, 125.9, 106.2, 87.7, 85.9, 73.6, 56.7, 53.5, 53.2, 50.1, 33.3. **MS:** calculated for $C_{20}H_{17}O_3$ (M – $(OMe)_2^-$), 305.1178; found, 305.1189. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 0.5 mL/min; retention times: 20.2 min (major), 27.5 min (minor)).

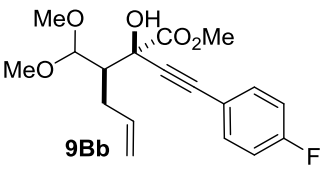
Methyl (2*R*,3*R*)-3-(dimethoxymethyl)-2-hydroxy-2-(phenylethynyl)hex-5-enoate (9Ba)



9Ba

The compound was obtained following the general procedure from aldehyde **3B** (74 µL, 0.75 mmol) and ynone **2a** (94 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 6:1 *syn*/*anti* ratio. Yield: 74% (117 mg, 0.37 mmol). **[α]**$_D^{25}$ = –83.0º (*c* = 1.00, 94% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.37 – 7.22 (m, 3H), 6.05 (td, *J* = 10.1, 5.0 Hz, 1H), 5.17 – 4.96 (m, 2H), 4.42 (d, *J* = 7.0 Hz, 1H), 4.04 (s, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.77 – 2.66 (m, 1H), 2.62 – 2.50 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 173.1, 137.5, 132.3, 129.1, 128.7, 122.5, 116.4, 106.3, 87.8, 86.1, 73.7, 57.4, 54.2, 53.8, 48.6, 32.2. **MS:** calculated for $C_{16}H_{15}O_3$ (M – $(OMe)_2^-$), 255.1021; found, 255.1039. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 11.6 min (major), 13.1 min (minor)).

Methyl (2*R*,3*R*)-3-(dimethoxymethyl)-2-((4-fluorophenyl)ethynyl)-2-hydroxyhex-5-enoate (9Bb)

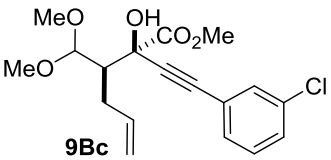


9Bb

The compound was obtained following the general procedure from aldehyde **3B** (74 µL, 0.75 mmol) and ynone **2b** (102 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 8:1 *syn*/*anti* ratio. Yield: 77% (129 mg, 0.39 mmol). **[α]**$_D^{21}$ = –80.9º (*c* = 1.00, 93% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.9, 5.4 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.15 – 5.90 (m, 1H), 5.15 – 4.99 (m, 2H), 4.39 (d, *J* = 6.9 Hz, 1H), 4.04 (s, 1H), 3.82 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.76 – 2.64 (m, 1H), 2.62 – 2.44 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ172.6, 164.4, 161.1, 137.0, 133.8, 133.7, 115.9, 115.7, 115.4, 105.8, 87.1, 84.6, 73.2, 56.9, 53.8, 53.3, 48.1, 31.7. **MS:** calculated for $C_{16}H_{14}FO_3$ (M – $(OMe)_2^-$), 273.0927; found, 273.0916. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the

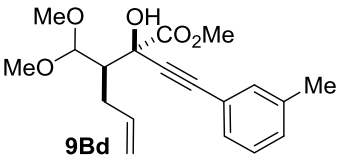
crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 7.3 min (major), 8.0 min (minor)).

Methyl (2*R*,3*R*)-2-((3-chlorophenyl)ethynyl)-3-(dimethoxymethyl)-2-hydroxyhex-5-enoate (9Bc)



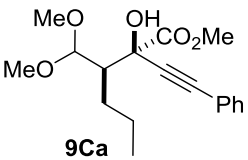
The compound was obtained following the general procedure from aldehyde **3B** (74 µL, 0.75 mmol) and ynone **2c** (111 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 5:1 *syn*/*anti* ratio. Yield: 65% (115 mg, 0.33 mmol). **[α]**$_D^{21}$ = –18.3º (*c* = 1.00, 94% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.42 (t, *J* = 1.8 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 6.02 (td, *J* = 10.1, 5.0 Hz, 1H), 5.16 – 4.97 (m, 2H), 4.40 (d, *J* = 6.9 Hz, 1H), 4.05 (s, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 2.74 – 2.65 (m, 1H), 2.62 – 2.48 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 172.5, 136.9, 134.1, 131.7, 130.0, 129.5, 129.0, 125.5, 116.1, 105.8, 88.6, 84.2, 73.2, 57.0, 53.8, 53.4, 48.1, 31.8. **MS:** calculated for $C_{18}H_{21}ClO_5$ (M – $(OMe)_2^-$), 261.0318; found, 261.0763. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 9.5 min (major), 11.5 min (minor)).

Methyl (2*R*,3*R*)-3-(dimethoxymethyl)-2-hydroxy-2-(m-tolylethynyl)hex-5-enoate (9Bd)



The compound was obtained following the general procedure from aldehyde **3B** (74 µL, 0.75 mmol) and ynone **2d** (101 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 13:1 *syn*/*anti* ratio. Yield: 72% (120 mg, 0.36 mmol). **[α]**$_D^{21}$ = –83.0º (*c* = 1.00, 80% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.08 (m, 5H), 6.06 (ddd, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.19 – 4.95 (m, 2H), 4.41 (d, *J* = 7.0 Hz, 1H), 4.02 (s, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.81 – 2.66 (m, 1H), 2.67 – 2.45 (m, 2H), 2.31 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 173.1 , 138.3 , 137.5 , 132.8 , 130.0 , 129.3 , 128.5 , 125.9 , 122.2 , 116.3 , 106.3 , 87.4 , 86.3, 73.6 , 57.3 , 54.1 , 53.7 , 48.5 , 32.2 , 30.7 , 21.5. **MS:** calculated for $C_{18}H_{21}ClO_5$ (M – $(OMe)_2^-$), 261.0318; found, 261.0763. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 6.7 min (major), 8.0 min (minor)).

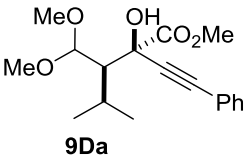
Methyl (2*R*,3*R*)-3-(dimethoxymethyl)-2-hydroxy-2-(phenylethynyl)hexaneate (9Ca)



9Ca

The compound was obtained following the general procedure from aldehyde **3C** (74 µL, 0.75 mmol) and ynone **2a** (94 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 8:1 *syn*/*anti* ratio. Yield: 65% (120 mg, 0.36 mmol). **[α]**$_D^{21}$ = –21.0º (*c* = 1.00, 93% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.34 – 7.27 (m, 3H), 4.39 (d, *J* = 7.4 Hz, 1H), 4.01 (d, *J* = 0.4 Hz, 1H), 3.83 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.45 (dt, *J* = 7.3, 4.8 Hz, 1H), 1.89 (ddd, *J* = 11.9, 8.4, 3.5 Hz, 1H), 1.73 – 1.50 (m, 3H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 173.4, 132.2, 129.0, 128.6, 125.9, 122.6, 107.0, 88.1, 85.5, 73.9, 58.7 – 57.4, 54.3, 53.7, 48.5, 30.7, 30.0, 22.1, 15.0. **MS:** calculated for $C_{17}H_{21}O_4$ (M – OMe^-), 289.1434; found, 289.1427. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA+IC, hexane/isopropanol, 95:5; flux = 0.5 mL/min; retention times: 29.7 min (major), 34.6 min (minor)).

Methyl (2*R*,3*R*)-3-(dimethoxymethyl)-2-hydroxy-4-methyl-2-(phenylethynyl)pentanoate (9Da)



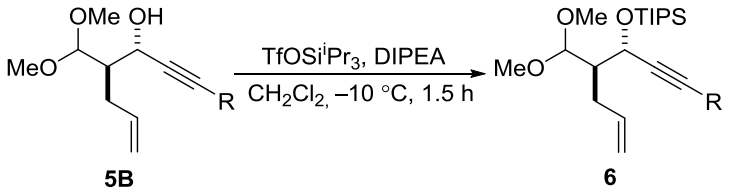
9Da

The compound was obtained following the general procedure from aldehyde **3D** (74 µL, 0.75 mmol) and ynone **2a** (94 mg, 0.5 mmol). Colourless oil. The adduct was obtained in a 5:1 *syn*/*anti* ratio. Yield: 70% (112 mg, 0.35 mmol). **[α]**$_D^{22}$ = –33.4º (*c* = 1.00, 95% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.33 – 7.26 (m, 3H), 4.52 (d, *J* = 8.1 Hz, 1H), 3.98 (d, *J* = 0.7 Hz, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.68 – 2.56 (m, 1H), 2.47 – 2.40 (m, 1H), 1.16 (dd, *J* = 7.1, 3.2 Hz, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 173.3, 131.7, 129.0, 128.6, 128.2, 128.2, 105.2, 88.1, 85.7, 74.2, 57.1, 53.3, 53.2, 51.6, 27.7, 23.2, 19.1. **MS:** calculated for $C_{16}H_{17}O_3$ (M – $(OMe)_2^-$), 257.11782; found, 257.1216. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 9.2 min (major), 11.2 min (minor)).

5.3.5. Elaboration of adducts 5 and 9

5.3.5.1. Silylation of adducts

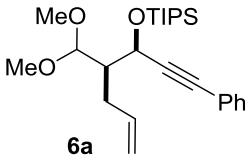
General procedure for the silylation of adducts 5



5B **6**

To a solution of alcohol **5** (0.5 mmol) in CH_2Cl_2 (2 mL) at –10 ºC were successively added DIPEA (194 mg, 1.5 mmol, 3 equiv.) and triisopropylsilyl trifluoromethanesulfonate (184 mg, 0.6 mmol, 1.2 equiv.). The resulting mixture was stirred at –10 ºC for 1 h, diluted with CH_2Cl_2 (15 mL), and the organic solution was washed with a saturated solution of NH_4Cl (2 × 10 mL) and saturated $NHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5) to afford the pure silyl ether compound as a yellow oil.

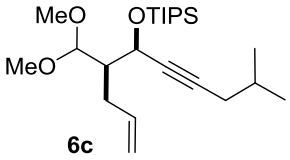
(((3*R*,4*R*)-4-(Dimethoxymethyl)-1-phenylhept-6-en-1-yn-3-yl)oxy)triisopropylsilane (6a)



6a

The compound was prepared as described above from adduct **5a** (130 mg, 0.5 mmol). Yield: 72% (150 mg, 0.36 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.35 – 7.33 (m, 3H), 6.24 – 5.97 (m, 1H), 5.16 – 5.04 (m, 1H), 5.04 – 4.96 (m, 1H), 4.94 (d, *J* = 4.8 Hz, 1H), 4.47 (d, *J* = 7.5 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 2.57 (dt, *J* = 15.7, 7.0 Hz, 1H), 2.39 (dt, *J* = 14.5, 7.8 Hz, 1H), 2.19 (dt, *J* = 13.0, 5.5 Hz, 1H), 1.23 – 1.11 (m, 21H).

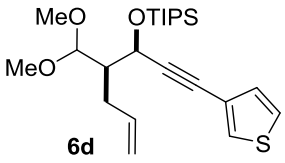
(((4*R*,5*R*)-4-(dimethoxymethyl)-9-methyldec-1-en-6-yn-5-yl)oxy)triisopropylsilane (6c)



6c

The compound was prepared as described above from adduct **5c** (120 mg, 0.5 mmol). Yield: 68% (135 mg, 0.34 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.14 – 6.00 (m, 1H), 5.05 (dd, *J* = 17.1, 2.3 Hz, 1H), 4.99 – 4.87 (m, 1H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.68 – 2.43 (m, 1H), 2.36 – 2.21 (m, 1H), 2.14 (d, *J* = 2.0 Hz, 1H), 2.12 (d, *J* = 2.0 Hz, 1H), 2.10 – 2.04 (m, 1H), 3.15 – 3.10 (m, 21H), 1.01 (d, *J* = 6.6 Hz, 6H).

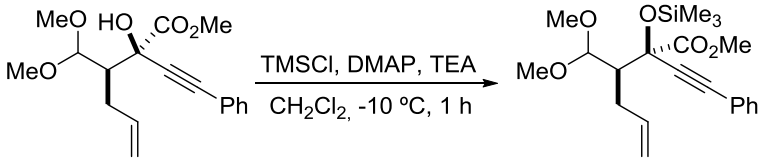
(((3*R*,4*R*)-4-(Dimethoxymethyl)-1-(thiophen-3-yl)hept-6-en-1-yn-3-yl)oxy)triisopropylsilane (6d)



6d

The compound was prepared as described above from adduct **5d** (133 mg, 0.5 mmol). Yield: 70% (144 mg, 0.35 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.35 – 7.33 (m, 3H), 6.24 – 5.97 (m, 1H), 5.16 – 5.04 (m, 1H), 5.04 – 4.96 (m, 1H), 4.94 (d, *J* = 4.8 Hz, 1H), 4.47 (d, *J* = 7.5 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 2.57 (dt, *J* = 15.7, 7.0 Hz, 1H), 2.39 (dt, *J* = 14.5, 7.8 Hz, 1H), 2.19 (dt, *J* = 13.0, 5.5 Hz, 1H), 1.23 – 1.11 (m, 21H).

Silylation of adduct 9Aa

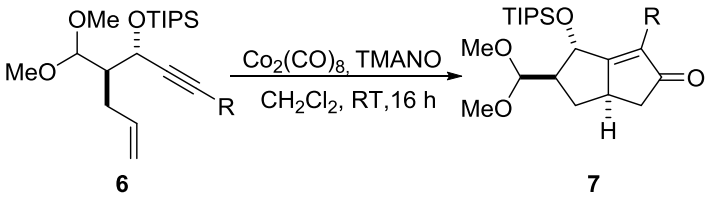


9Aa **11**

To a solution of tertiary alcohol **9Aa** (159 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) at –10 ºC were successively added DMAP (6.1 mg, 0.05 mmol, 10 mol%), TEA (0.2 mL, 1.5 mmol, 3 equiv.) and trimethylchlorosilane (134 µL, 1 mmol, 2 equiv.). The resulting mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (15 mL), and the organic solution was washed with a saturated solution of NH_4Cl (2 × 10 mL) and saturated $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5) to afford the pure silyl ether compound as a yellow oil. Yield: Cuantitative (195 mg, 0.5 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.39 – 7.33 (m, 3H), 6.09 (ddd, *J* = 13.9, 10.1, 7.2 Hz, 1H), 5.17 – 4.95 (m, 2H), 4.38 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.73 – 2.55 (m, 2H), 2.53 – 2.42 (m, 1H), 0.30 (s, 9H).

5.3.5.2. Intramolecular Pauson-Khand reaction

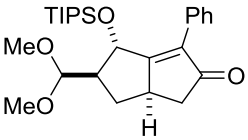
Intramolecular Pauson-Khand reaction of compounds 6



6 **7**

$[Co_2(CO)_8]$ (341 mg, 1 mmol, 2 equiv.) was added to a solution of the corresponding sylilated propargylic alcohol **6** (0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) at room temperature and was stirred for 30 min. Then trimethylamine *N*-oxide (TMANO) (226 mg, 3 mmol, 6 equiv.) was added at –10 ºC and the mixture was allowed to warm to room temperature until the initially formed Co complex disappeared (16 h), at which time usually a purple precipitate had formed. The mixture was passed through a small plug of silica gel and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc 95:5, affording the desired bicyclic compound as a yellow oil.

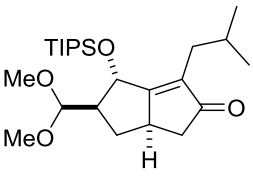
(4*S*,5*R*,6a*R*)-5-(dimethoxymethyl)-3-phenyl-4-((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (7a)



7a

The compound was obtained following the general procedure from silylated propargylic alcohol **6a** (208 mg, 0.5 mmol). Yellow oil. The adduct was obtained in a >20:1 *dr*. Yield: 65% (144 mg, 0.33 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 5.06 (s, 1H), 4.09 (d, *J* = 6.4 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.85 (dd, *J* = 18.3, 6.6 Hz, 1H), 2.70 (dd, *J* = 14.4, 6.5 Hz, 1H), 2.40 (dt, *J* = 12.9, 9.1 Hz, 1H), 2.24 (dd, *J* = 18.4, 2.7 Hz, 1H), 1.23 – 1.16 (m, 1H), 0.97 – 0.89 (m, 21H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 209.2, 180.2, 134.2, 131.4, 128.4, 128.2, 127.9, 106.2, 69.6, 54.9, 53.8, 53.2, 42.7, 39.0, 30.1, 17.8, 17.8, 12.2. **MS:** calculated for $C_{26}H_{40}O_4Si$ (M + H^+), 445.2774; found: 445.2726.

(4*S*,5*R*,6a*R*)-5-(dimethoxymethyl)-3-isobutyl-4-((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (7c)

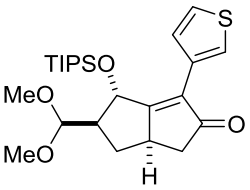


7c

The compound was obtained following the general procedure from silylated propargylic alcohol **6c** (127 mg, 0.32 mmol). Yellow oil. The adduct was obtained in a >20:1 *dr*. Yield: 64% (87 mg, 0.32 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.01 (d, *J* = 7.4 Hz, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 2.67 (dd, *J* = 18.3, 6.4 Hz,

2H), 2.36 – 2.27 (m, 1H), 2.26 – 2.18 (m, 1H), 2.11 – 2.01 (m, 1H), 1.97 (d, *J* = 13.1 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.09 – 1.02 (m, 21H), 1.00 – 0.92 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 211.5, 179.2, 134.7, 105.9, 69.8, 54.5, 53.7, 52.9, 42.4, 39.4, 33.1, 30.8, 27.1, 22.9, 22.4, 18.0, 18.0, 12.5. **MS:** calculated for $C_{24}H_{44}O_4Si$ ($M + H^+$), 425.3087; found: 425.3053.

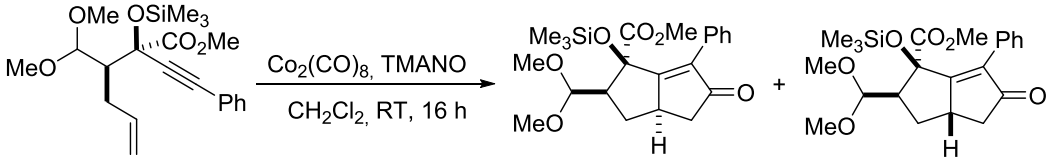
(4*S*,5*R*,6a*R*)-5-(dimethoxymethyl)-3-(thiophen-3-yl)-4-((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (7d)



7d

The compound was obtained following the general procedure from silylated propargylic alcohol **6d** (76 mg, 0.18 mmol). Yellow oil. The adduct was obtained in a >20:1 *dr*. Yield: 65% (52 mg, 0.33 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$), 7.70 – 7.65 (m, 1H), 7.35 – 7.28 (m, 2H), 5.16 (s, 1H), 4.04 (d, *J* = 6.5 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.83 (dd, *J* = 18.3, 6.6 Hz, 1H), 2.70 (dd, *J* = 14.8, 6.6 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.21 (dd, *J* = 18.3, 2.7 Hz, 1H), 1.23 – 1.10 (m, 1H), 1.03 – 0.90 (m, 21H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 209.2, 178.5, 127.0, 125.2, 124.3, 106.2, 70.1, 54.9, 53.8, 53.2, 42.8, 39.0, 30.1, 17.9, 17.8, 12.3. **MS:** calculated for $C_{24}H_{38}O_4SSi$ ($M + H^+$), 452.338; found: 451.2318.

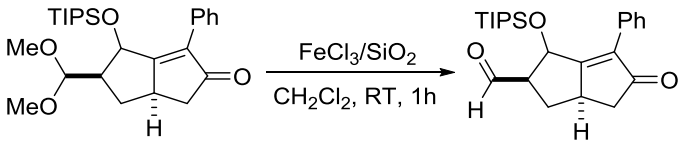
Intramolecular Pauson-Khand reaction of compound 11



11 **12** 32% **12'** 21%

The intramolecular Pauson-Khand reaction of compound **11** (195 mg, 0.5 mmol) was conducted following the procedure described above for secondary silylated propargylic alcohols **6**, obtaining the bicyclic product as a 1.5:1 mixture of diastereomers. Combined yield: 53% (97 mg, 0.27 mmol). Data of major isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.37 (ddd, *J* = 8.7, 7.8, 6.1 Hz, 3H), 7.26 – 7.16 (m, 2H), 4.54 (d, *J* = 8.5 Hz, 1H), 3.54 – 3.43 (m, 1H), 3.30 (s, 3H), 3.30 (s, 3H), 3.07 – 2.89 (m, 2H), 2.86 (s, 3H), 2.36 (dd, *J* = 18.0, 3.7 Hz, 1H), 2.16 (ddd, *J* = 13.4, 11.4, 9.3 Hz, 1H), 1.72 (ddd, *J* = 13.7, 10.2, 5.3 Hz, 1H), 0.32 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 208.5, 177.5, 171.1, 135.1, 130.3, 129.2, 128.2, 128.0, 104.8, 80.9, 55.5, 53.4, 52.0, 51.2, 44.7, 39.8, 29.0, 2.5. **MS:** calculated for $C_{24}H_{44}O_4Si$ ($M + H^+$), 419.1890; found, 419.1869.

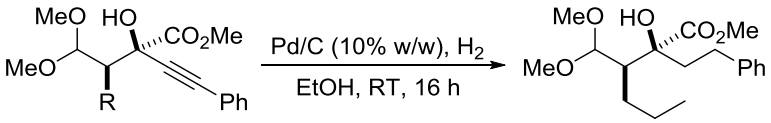
*5.3.5.3. Hydrolysis of the acetal **7a***



7a **8**

To a solution of the acetal **7a** (355 mg, 0.80 mmol) in CH_2Cl_2 (40 mL) 7.4 wt% $FeCl_3$ on SiO_2 (80 mg) was added, and the resulting suspension was stirred vigorously for 1 h. Then aqueous $NaHCO_3$ (1 mL) was added, and the organic phase was washed with brine, dried over $MgSO_4$ and concentrated. Flash column chromatography on silica gel (hexane/EtOAc 95:5) of the residue afforded the pure aldehyde **8** (yellow oil; 65%, 206 mg, 0.52 mmol) along with unreacted starting material **7a** (15%, 54 mg, 0.12 mmol). Effective yield of isolated **8** based on recovered starting material: 80%. **^{1}H-NMR** (300 MHz, $CDCl_3$) 9.74 (d, *J* = 1.1 Hz, 1H), 7.44 – 7.30 (m, 5H), 5.42 (s, 1H), 3.45 (ddd, *J* = 16.2, 9.4, 2.8 Hz, 1H), 3.39 – 3.30 (m, 1H), 2.90 (dd, *J* = 18.4, 6.6 Hz, 1H), 2.60 (dt, *J* = 12.8, 9.1 Hz, 1H), 2.30 (dd, *J* = 18.4, 2.8 Hz, 1H), 1.51 (ddd, *J* = 12.9, 9.8, 7.5 Hz, 1H), 1.07 – 0.84 (m, 21H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 208.3, 199.6, 177.2, 135.7, 130.7, 128.6, 128.4, 128.3, 68.0, 62.9, 42.6, 39.3, 29.3, 18.0, 17.9, 12.3. **MS:** calculated for $C_{24}H_{35}O_3Si$ ($M + H^+$), 399.2355; found, 399.2328.

*5.3.5.4. Reduction of adducts **9Ba** and **9Ca***



9Ba R = $CH_2CH{=}CH_2$
9Ca R = $(CH_2)_2CH_3$

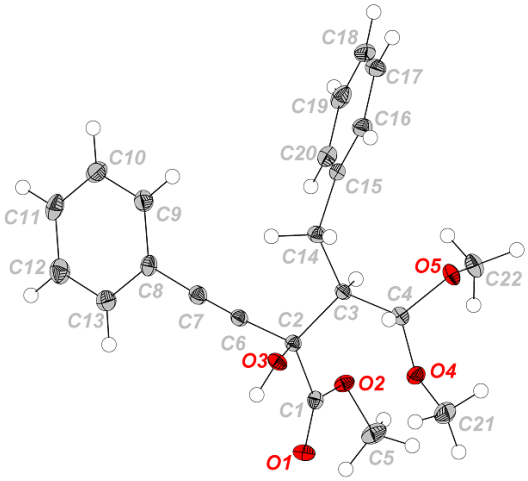
10 76%

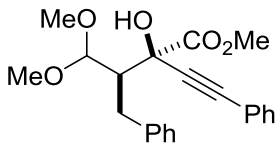
To a solution of **9Ba** or **9Ca** (0.2 mmol) in EtOH (0.8 mL) Pd 10% wt. on activated carbon (20 wt%) was added. The mixture was allowed to stir under hydrogen atmosphere (1 atm) for 16 h. The mixture was then filtered over celite (2 cm) and the solvent was eliminated under reduced pressure yielding the desired product **10** as colourless oil. Yield: 76% (49 mg, 0.15 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.31 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.28 (d, *J* = 5.8 Hz, 1H), 3.75 (s, 3H), 3.73 (d, *J* = 0.8 Hz, 1H), 3.35 (s, 3H), 3.35 (s, 3H), 2.76 (td, *J* = 12.8, 4.6 Hz, 1H), 2.35 – 2.20 (m, 1H), 2.15 – 2.01 (m, 2H), 1.99 – 1.85 (m, 1H), 1.60 – 1.43 (m, 3H), 1.41 – 1.25 (m, 1H), 0.89 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 176.9, 141.82,128.43

128.4, 125.9, 78.3, 56.7, 54.63, 52.2, 47.6, 39.4, 29.7, 27.4, 22.2, 14.6. **MS:** calculated for $C_{17}H_{25}O_4Si$ (M – OMe^-), 293.1753; found, 293.1768.

5.3.6. ORTEP diagram of compound 9Aa

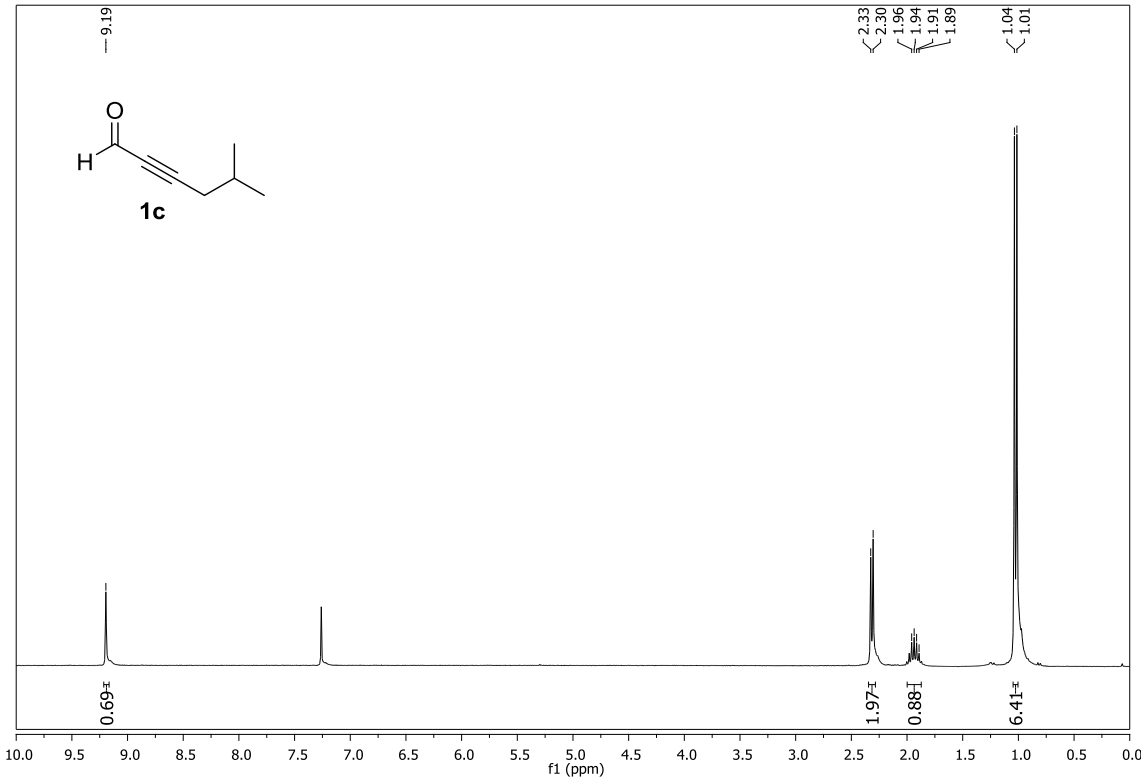
CCDC-930356 contains the supplementary crystallographic data for the structural analysis of **9Aa**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

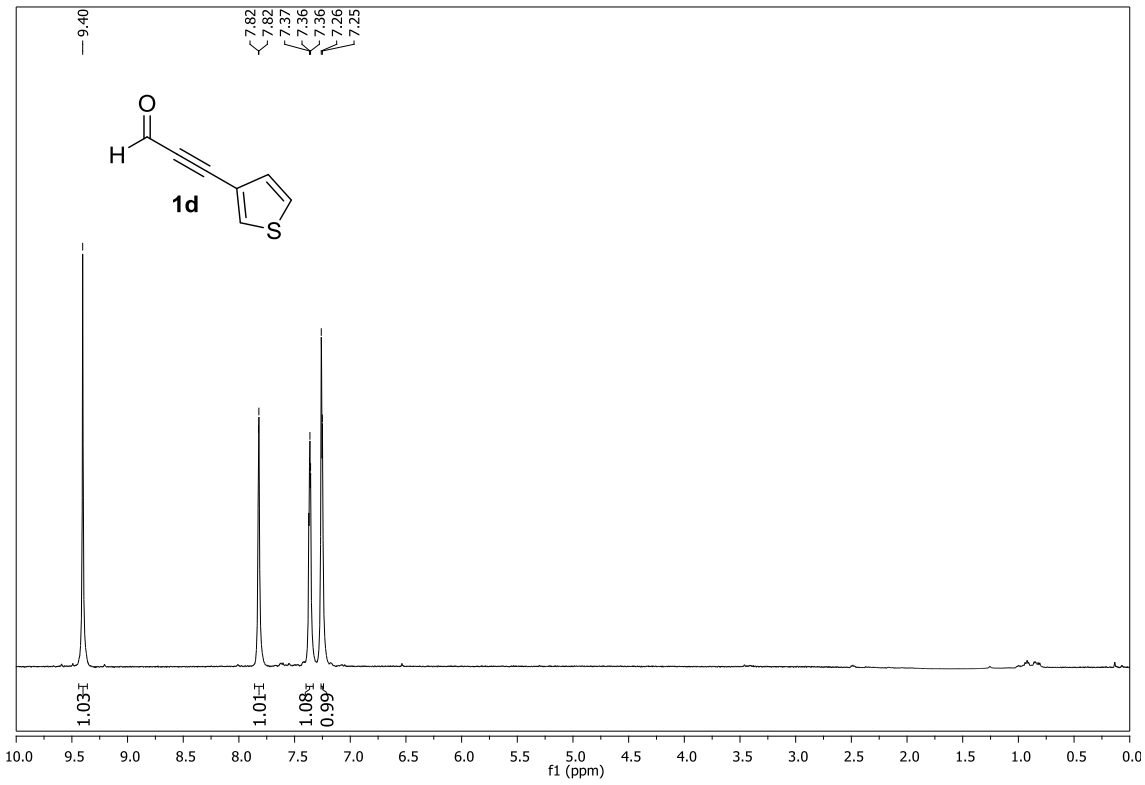


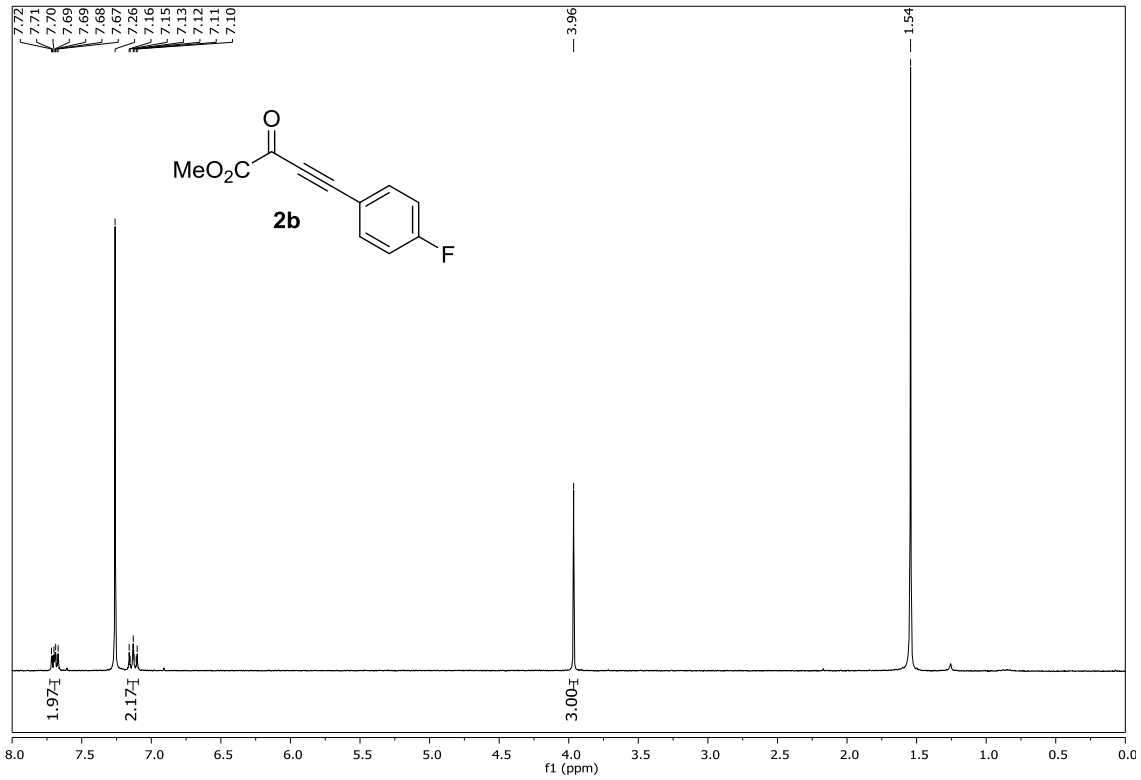


9Aa

5.3.7. Representative NMR spectra



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F
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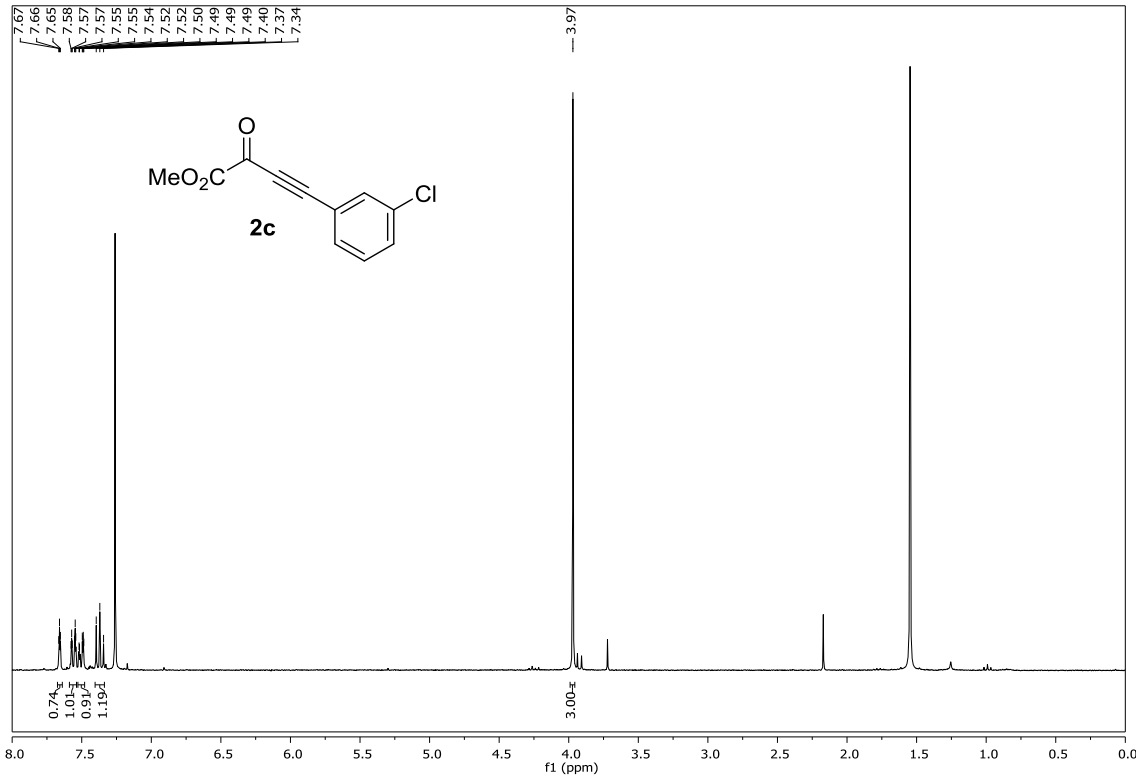
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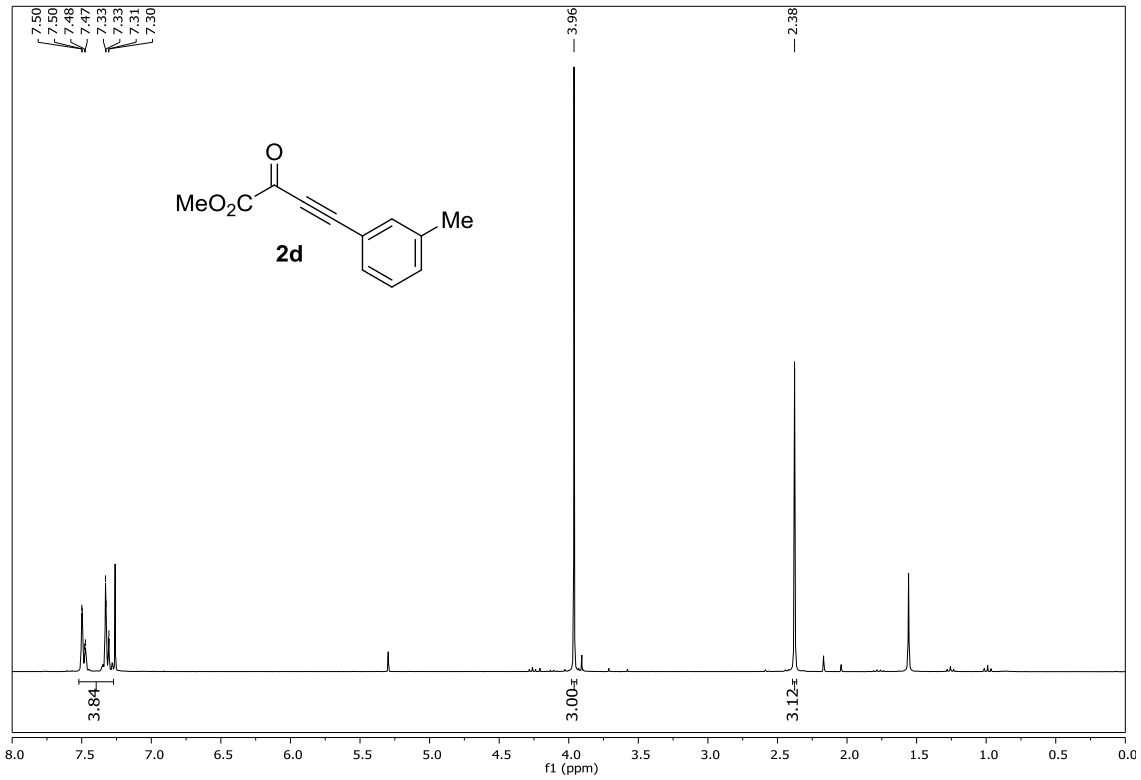
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6.0
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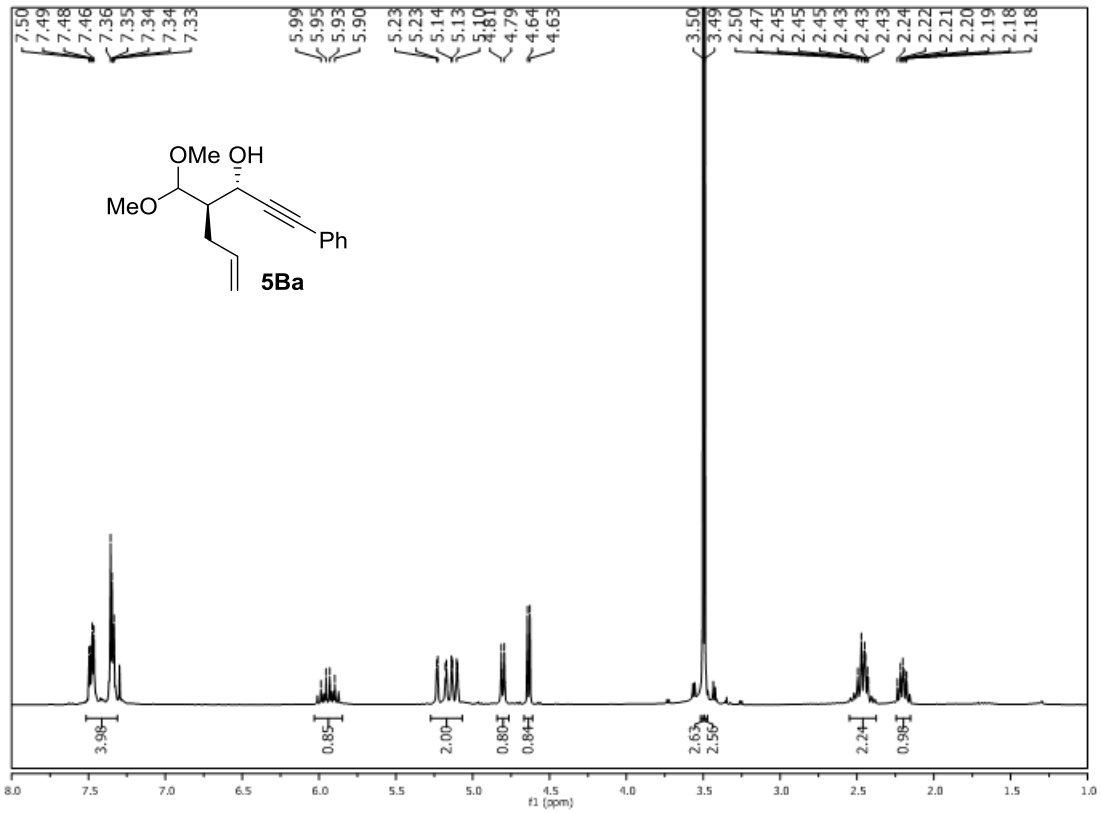
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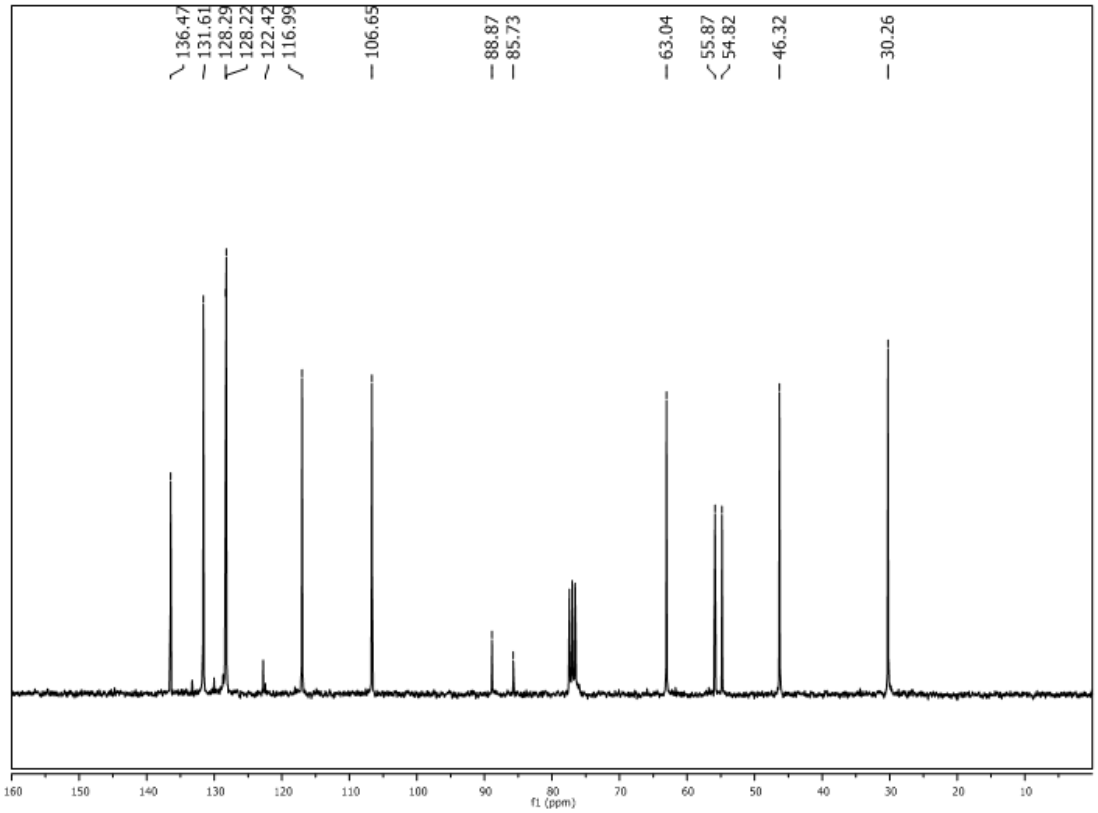
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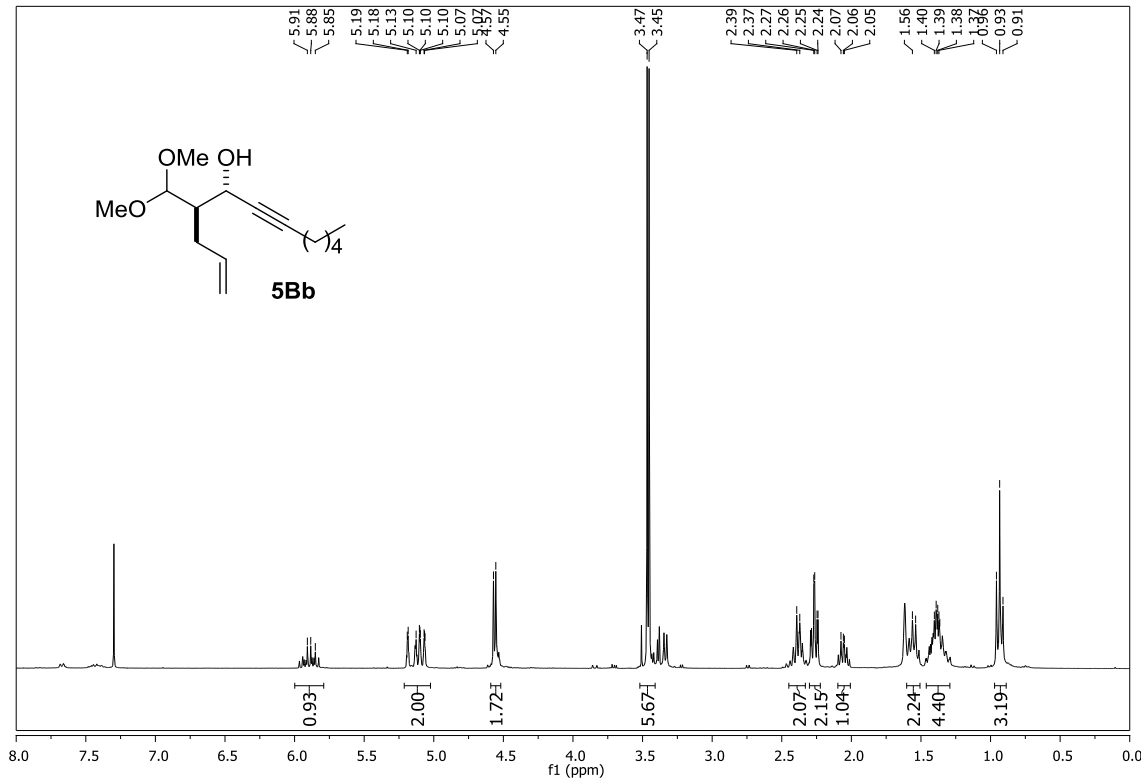
f1 (ppm)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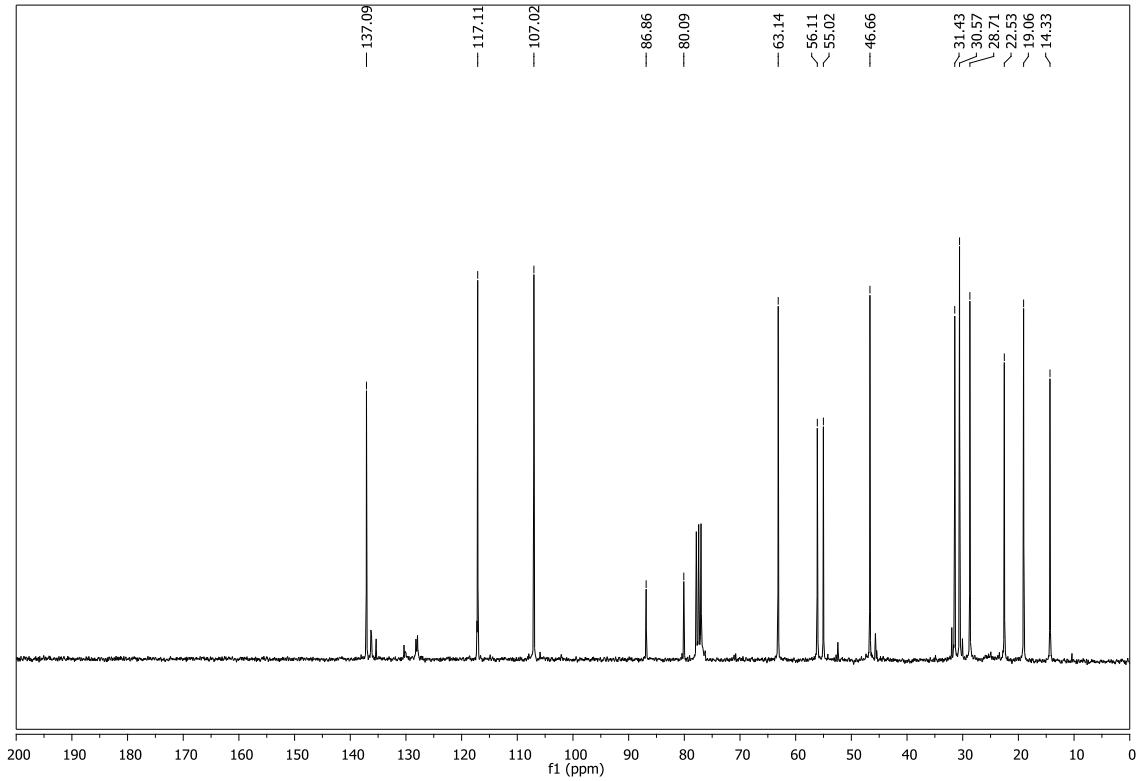
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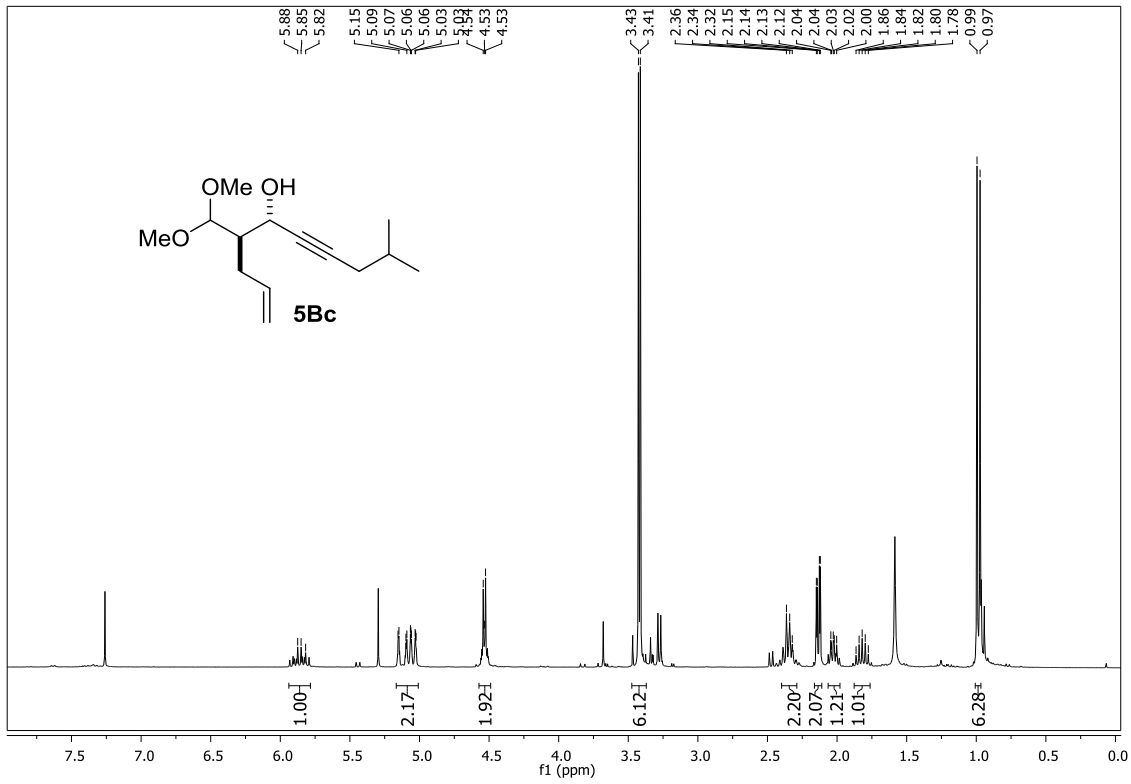
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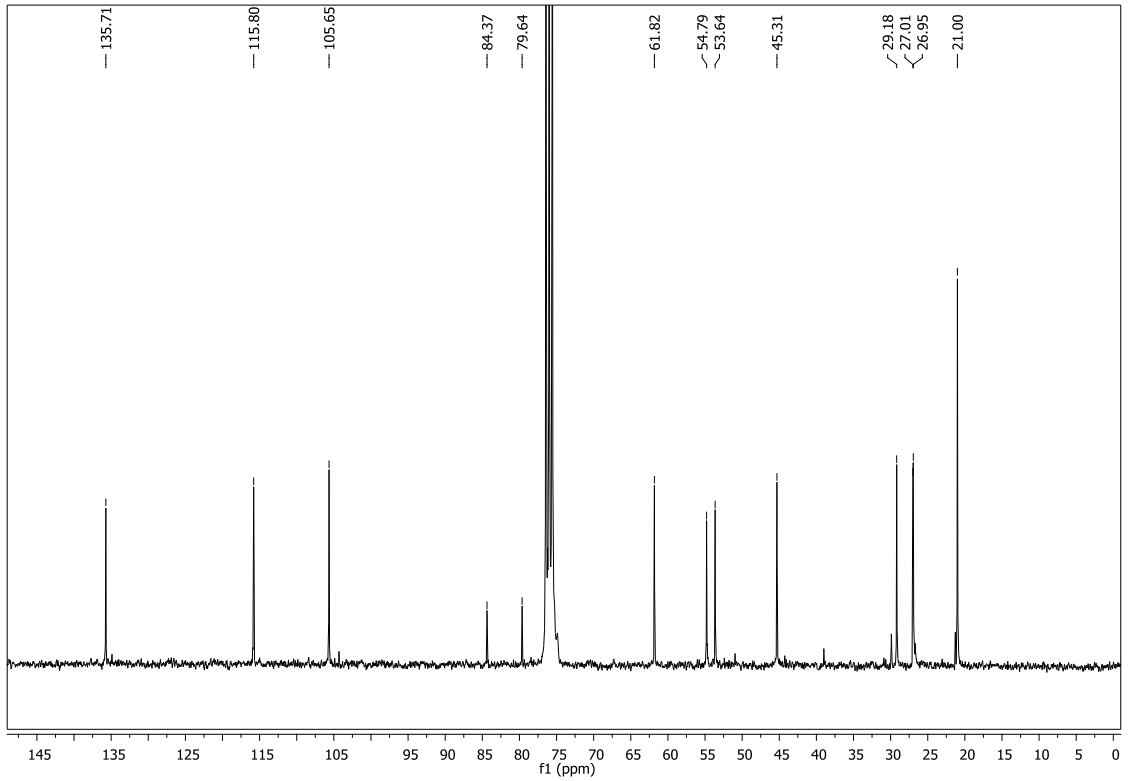
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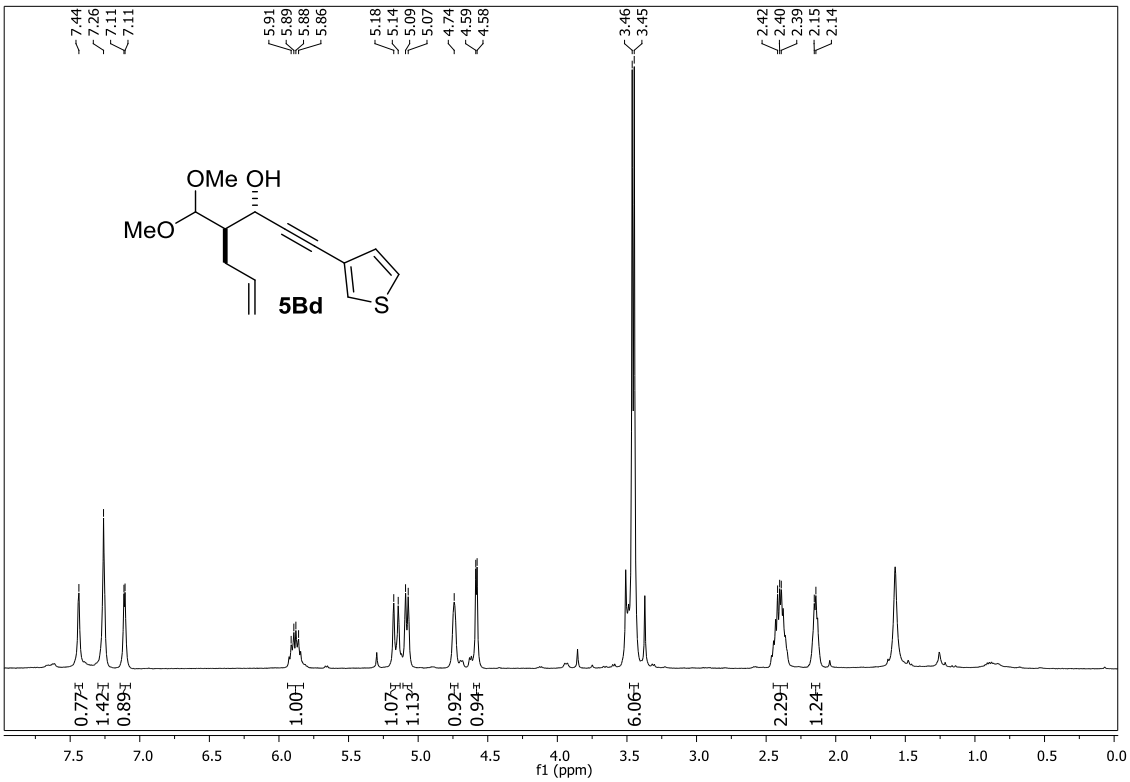
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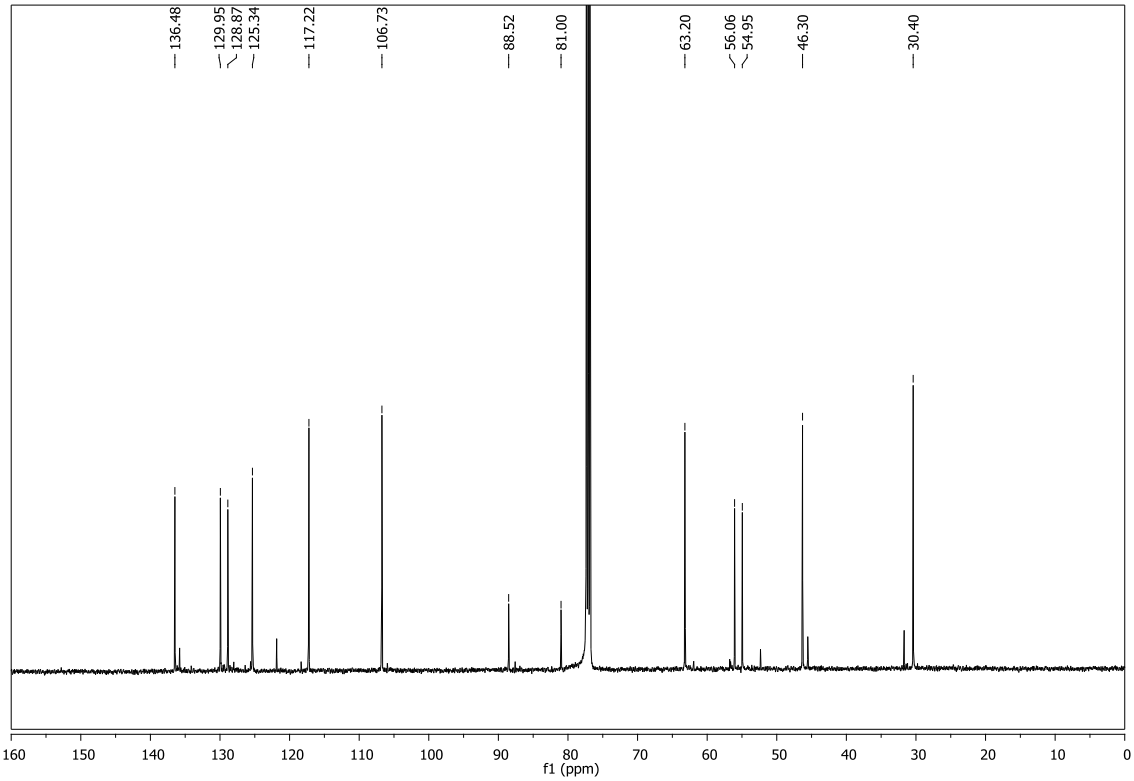
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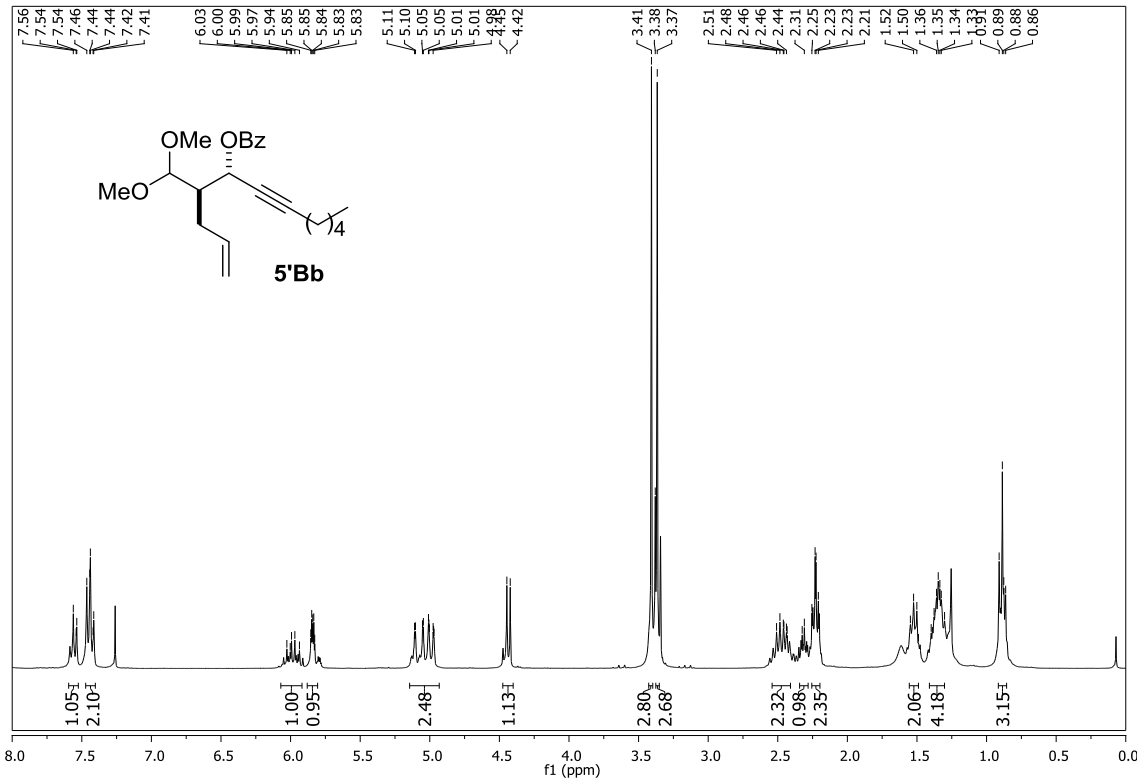
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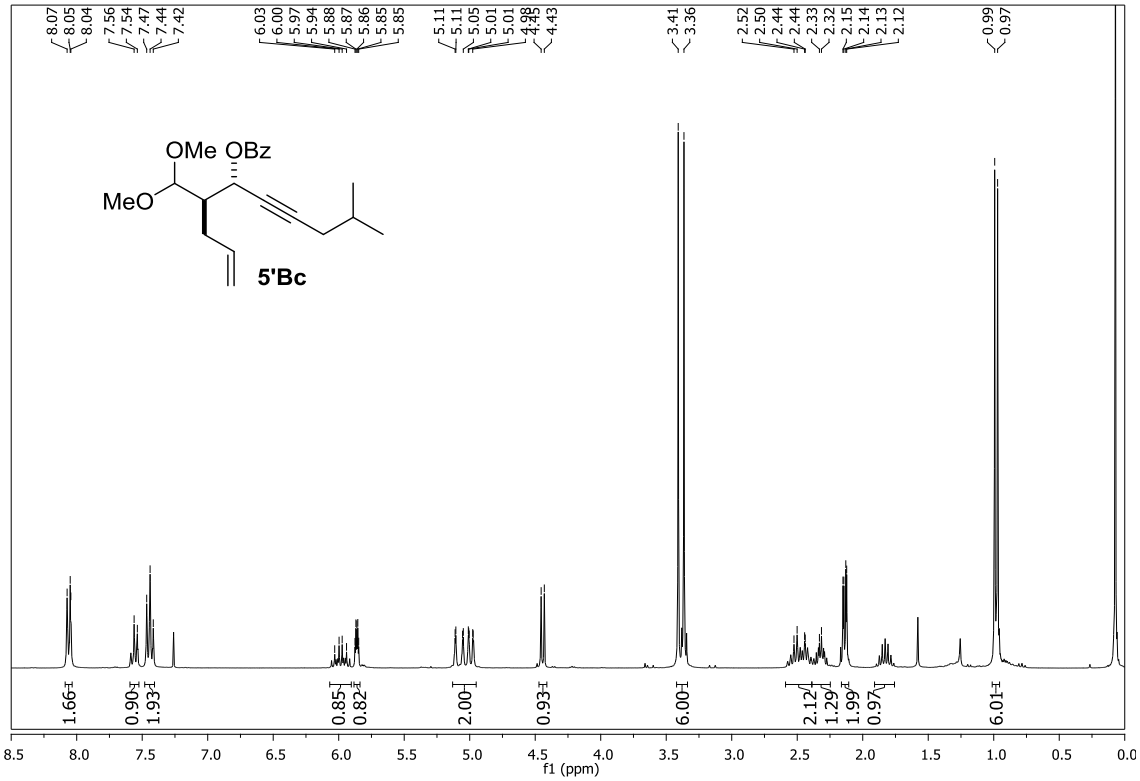
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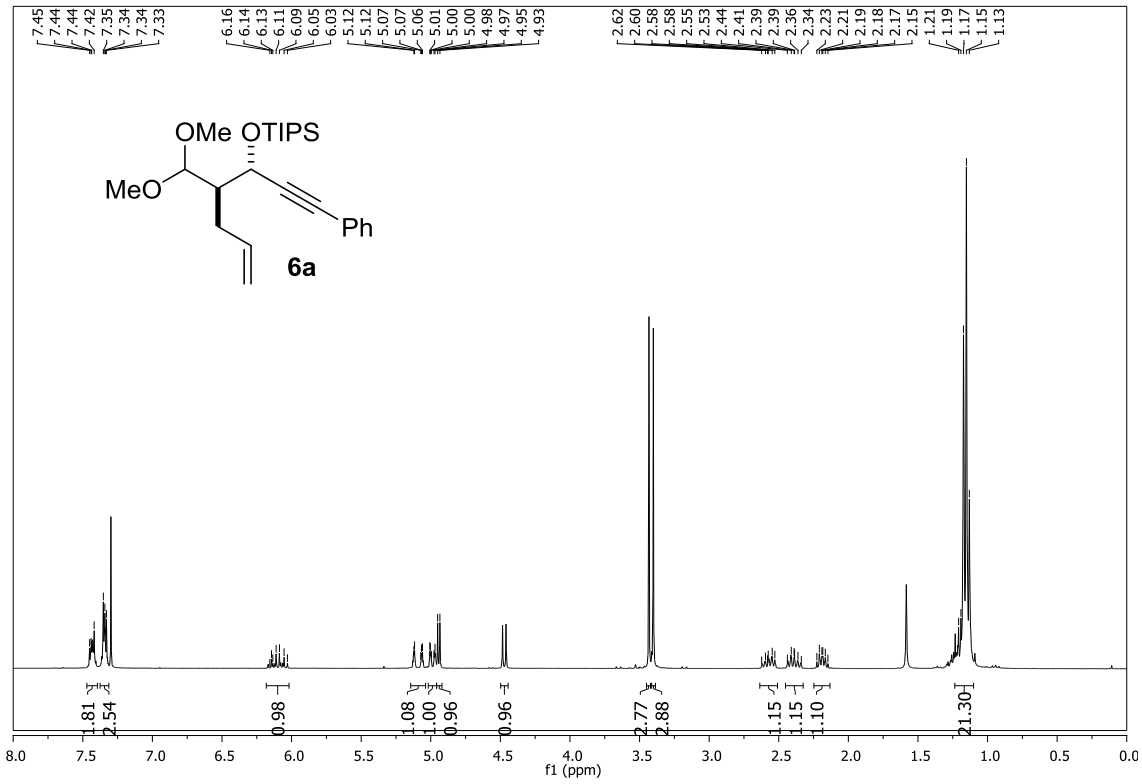
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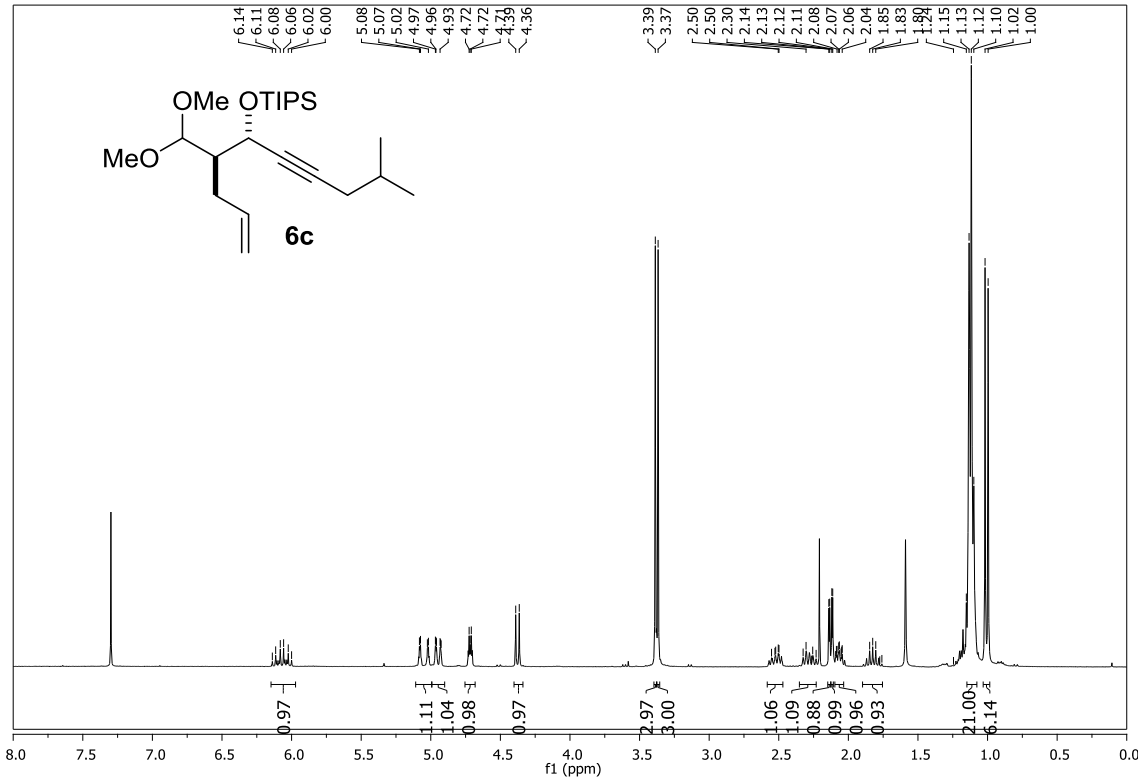
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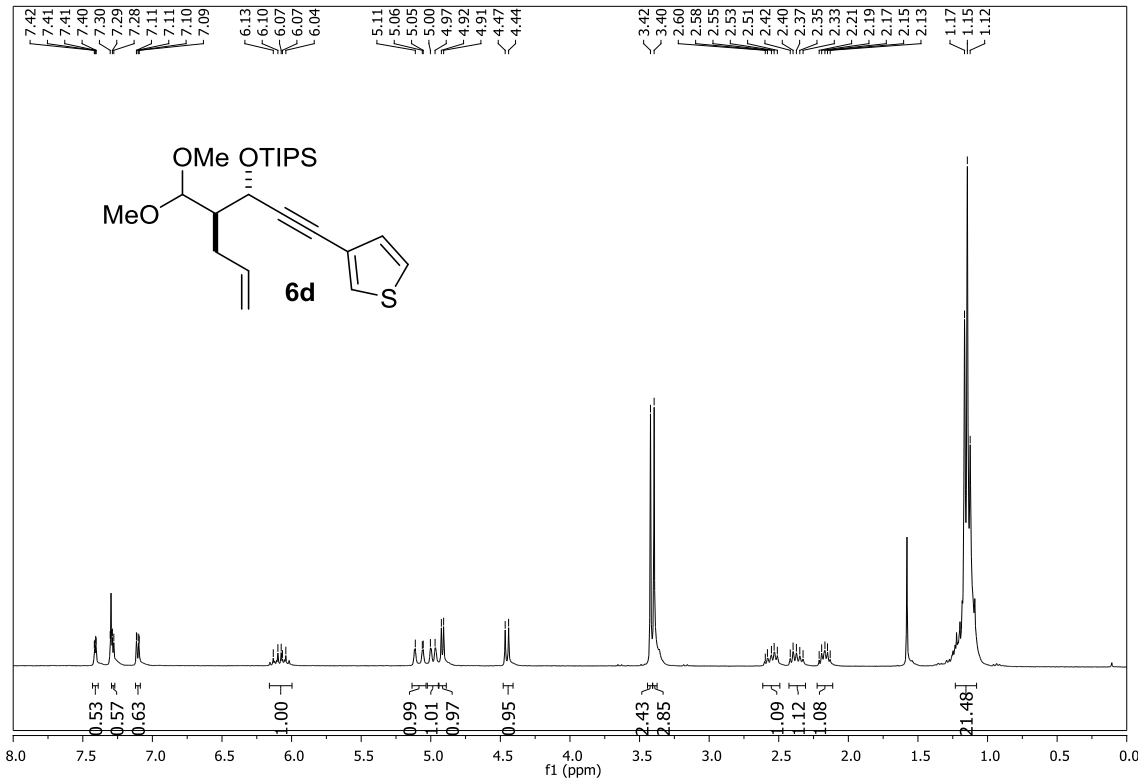
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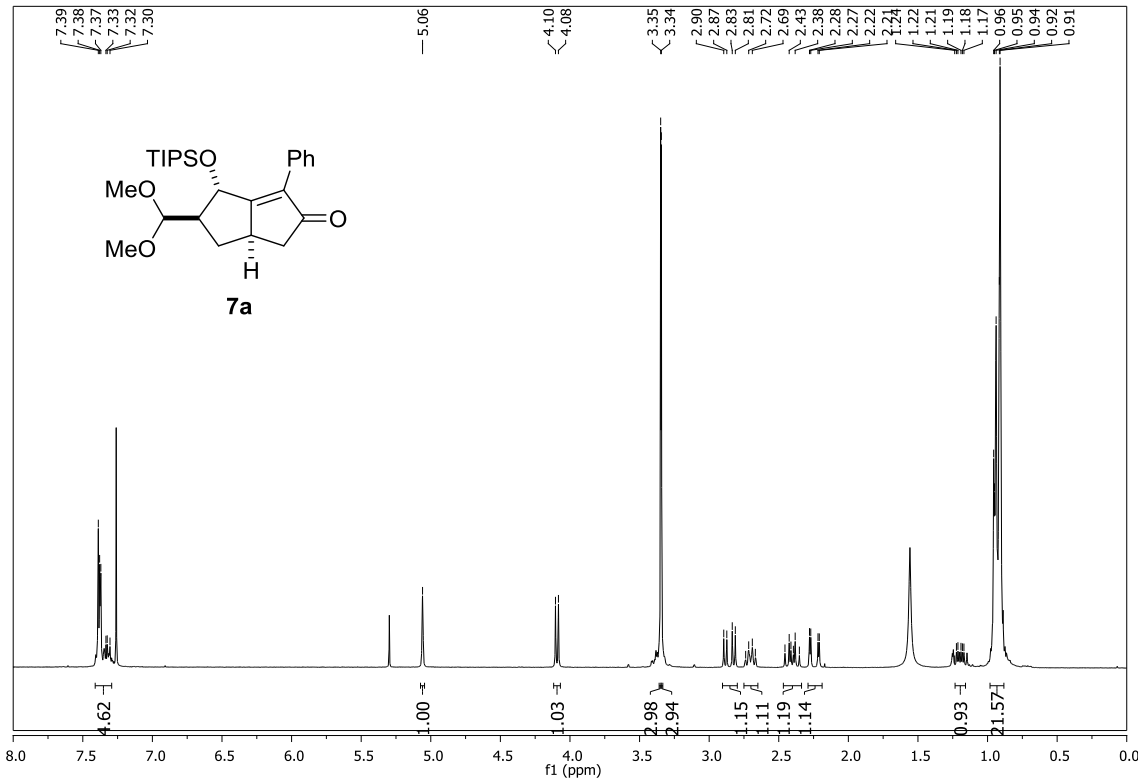
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1.22
1.21
1.19
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MeO
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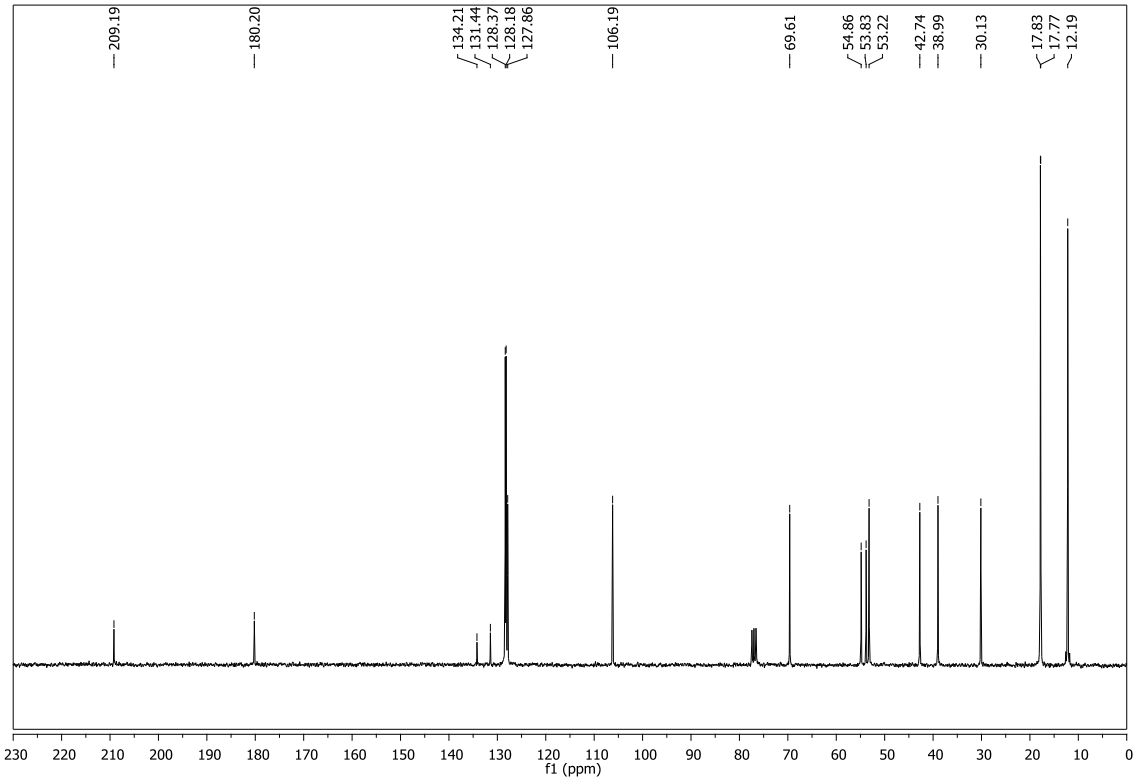
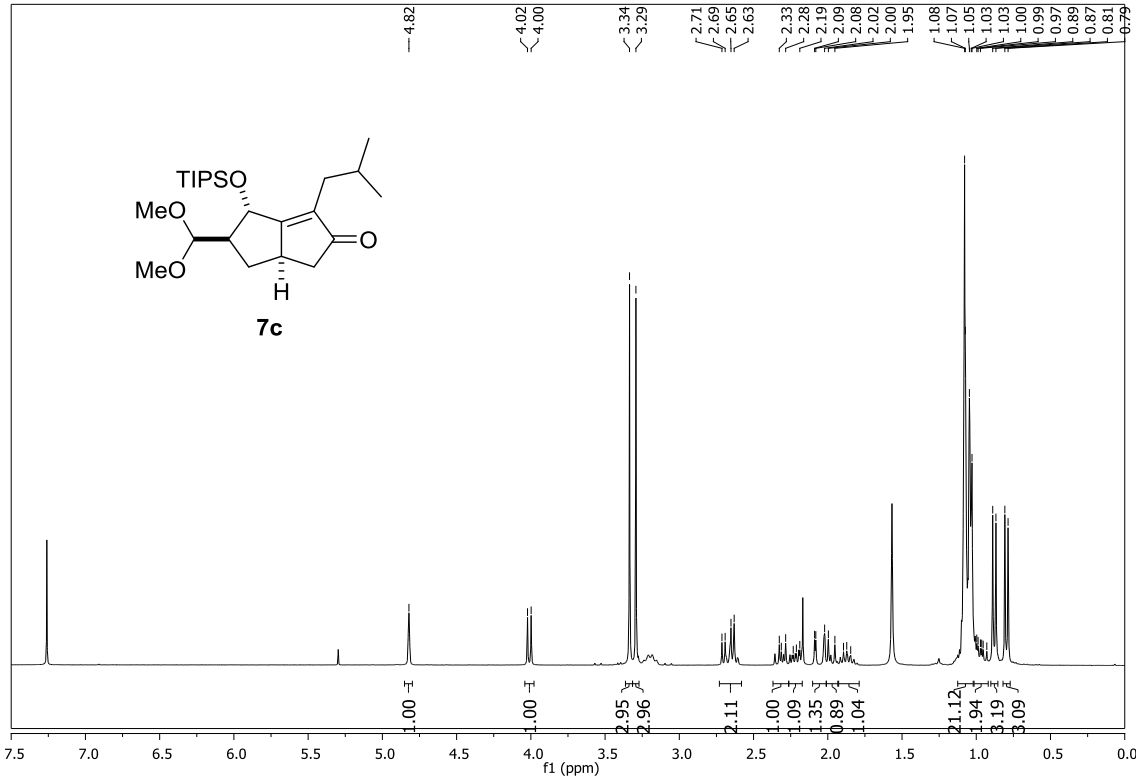
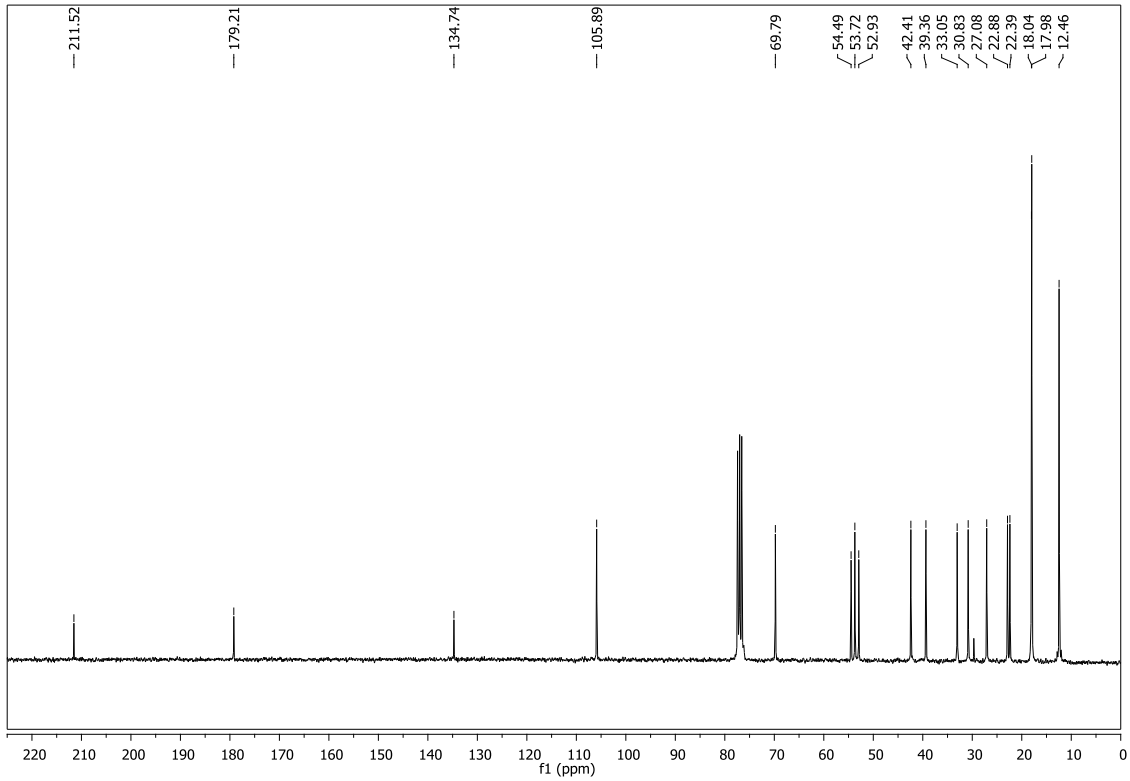
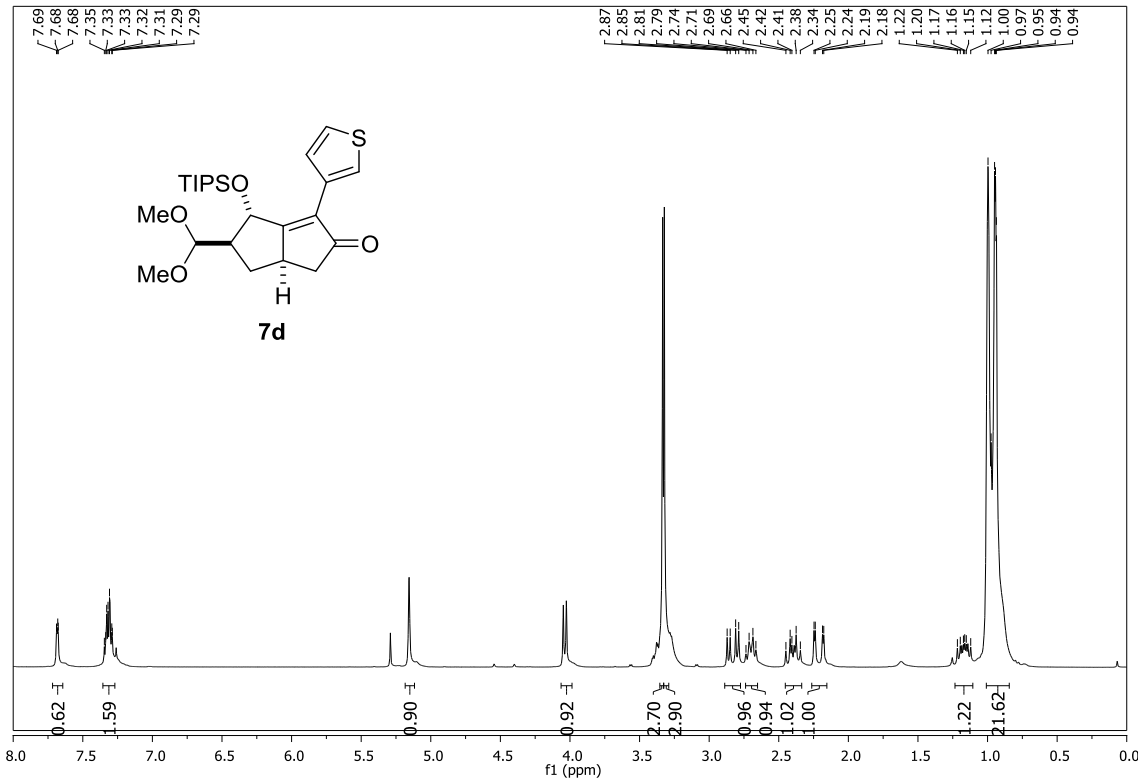
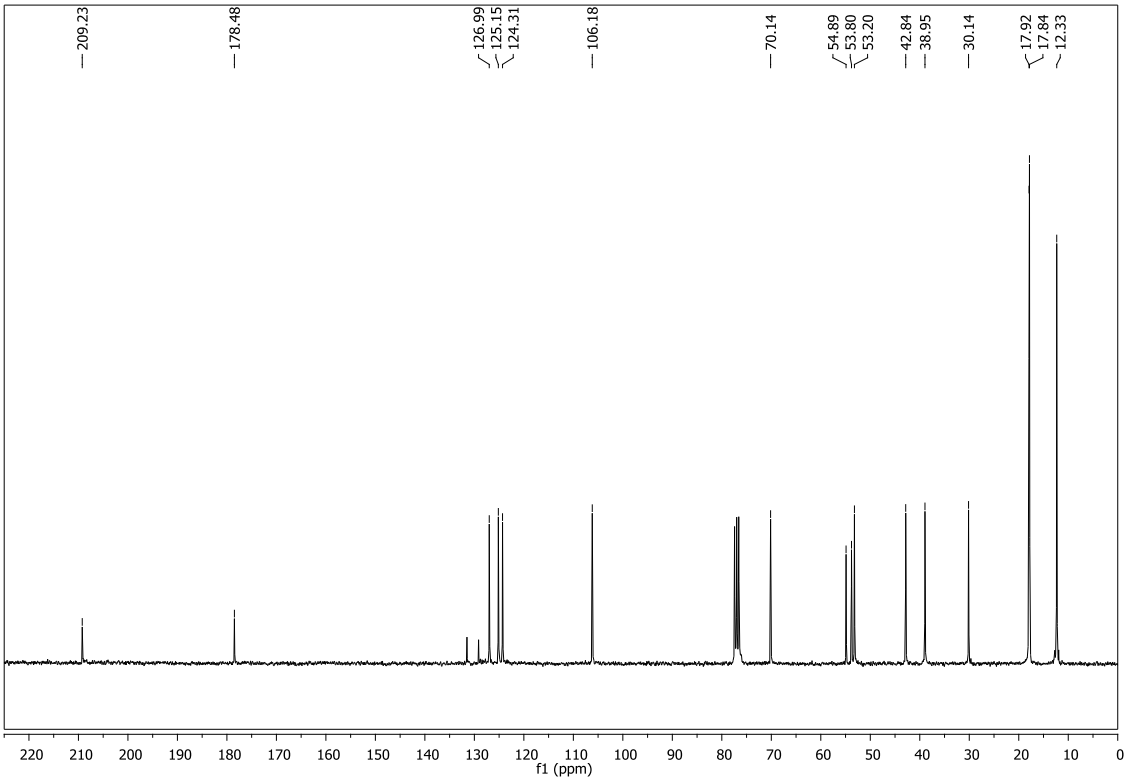
21.57
f1 (ppm)

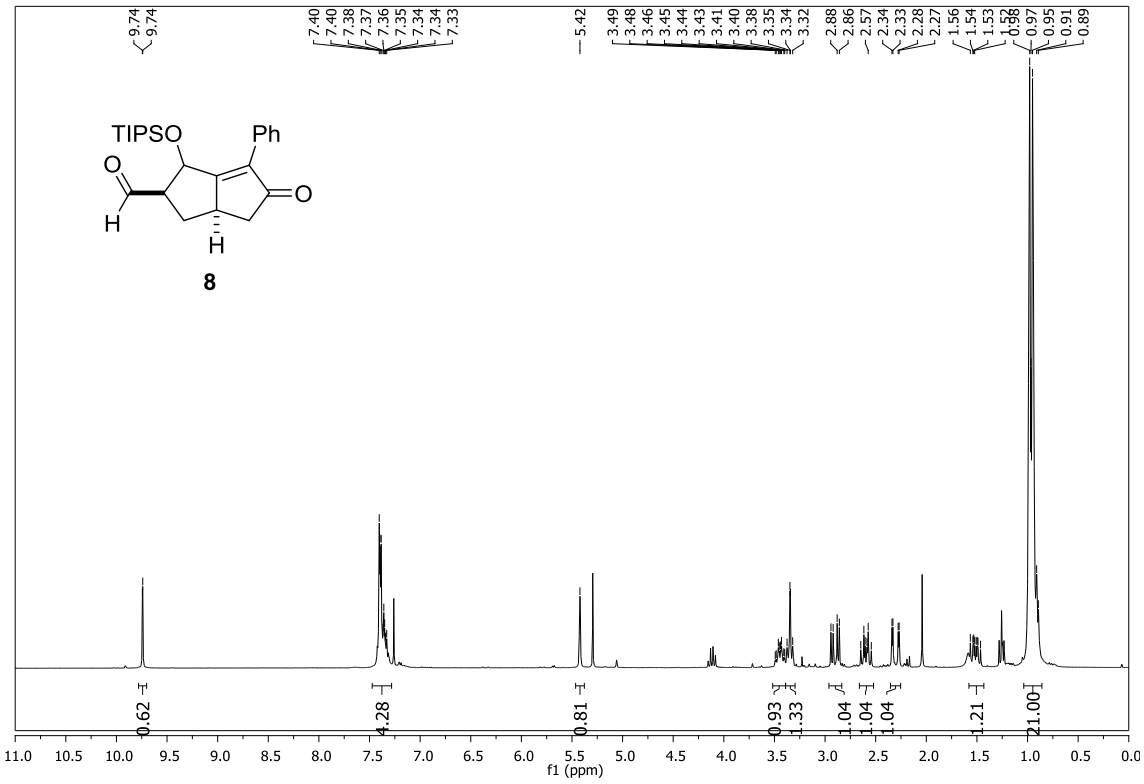

209.19
180.20
134.21
131.44
128.37
128.18
127.86
106.19
69.61
54.86
53.83
53.22
42.74
38.99
30.13
17.83
17.77
12.19
f1 (ppm)

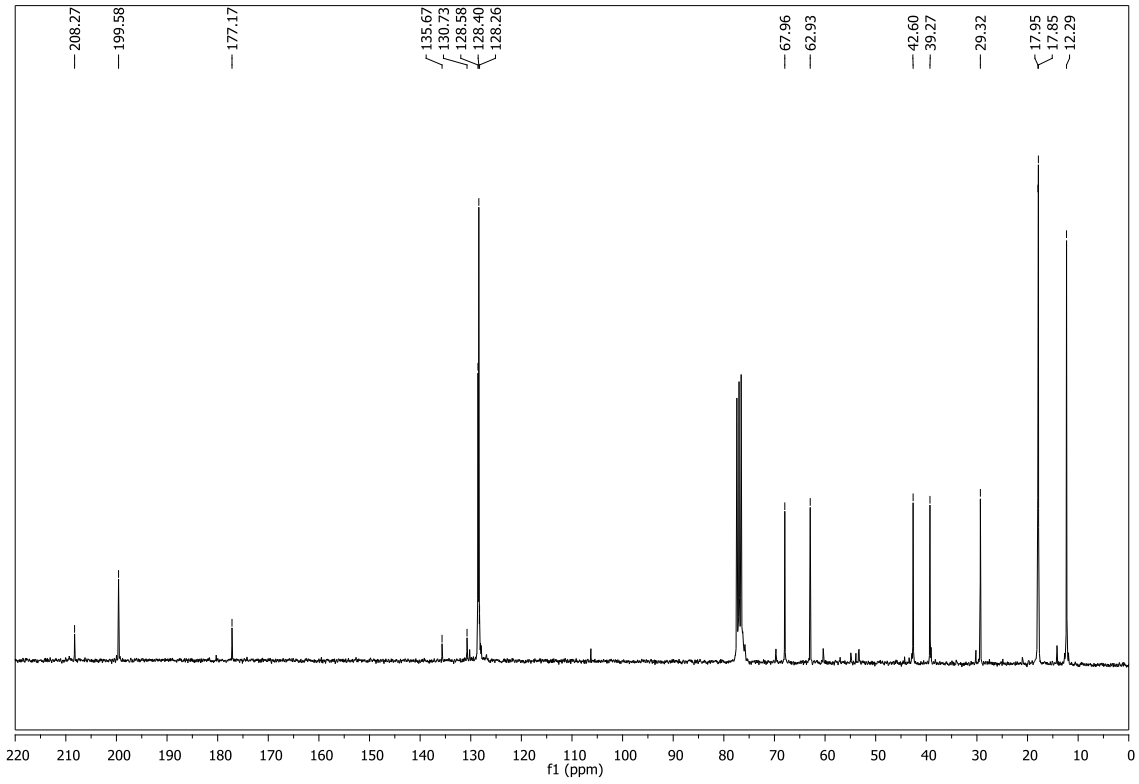

TIPSO
MeO
MeO
O
H
7c
f1 (ppm)

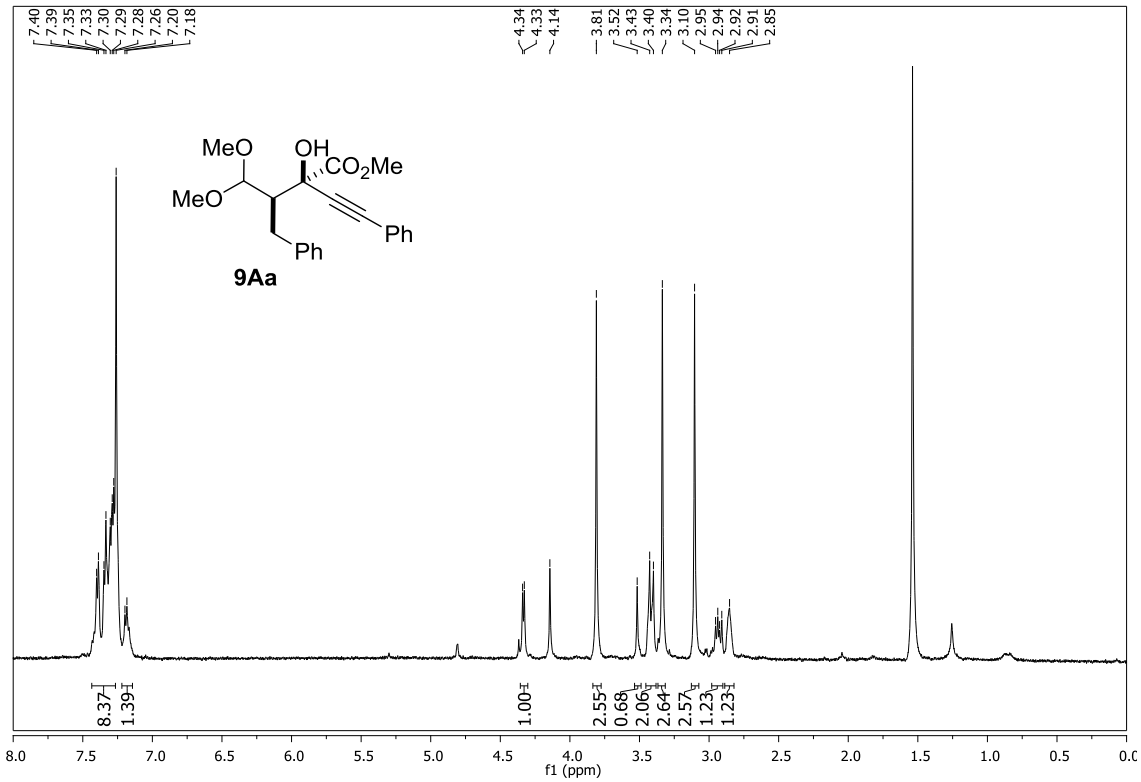

f1 (ppm)

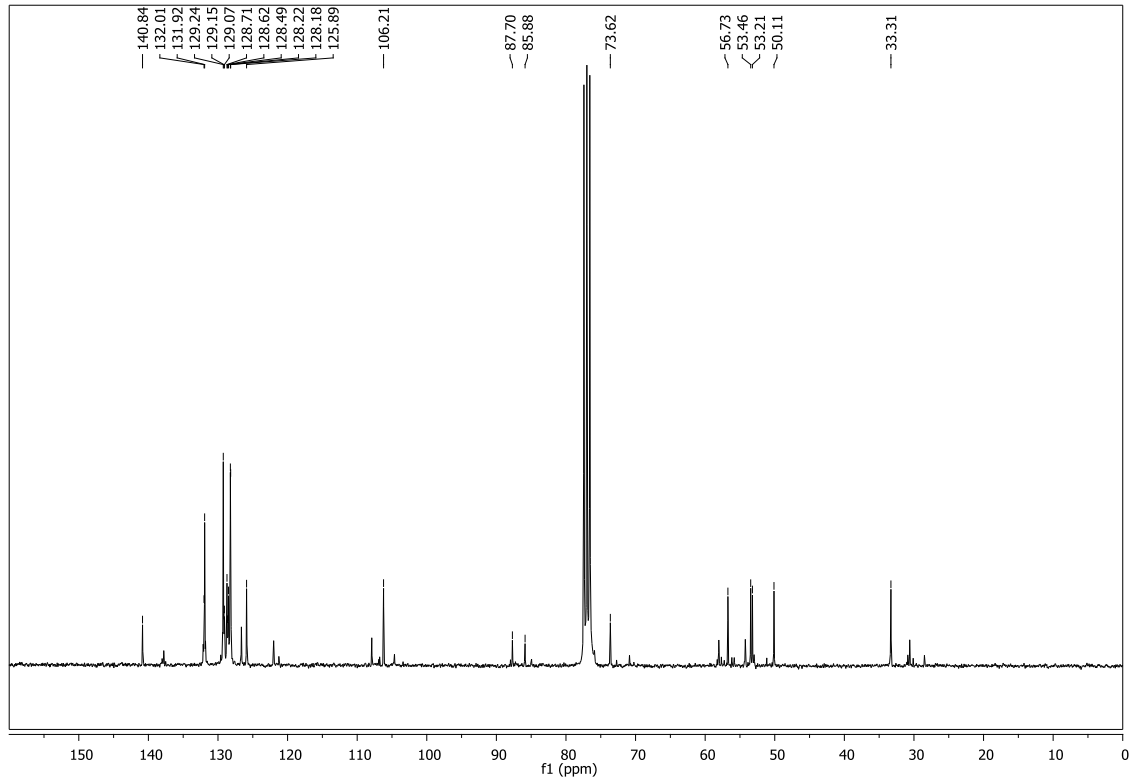

7.69
7.68
7.68
7.35
7.33
7.33
7.32
7.31
7.29
7.29
2.87
2.85
2.81
2.79
2.74
2.71
2.69
2.66
2.45
2.42
2.41
2.38
2.34
2.25
2.24
2.19
2.18
1.22
1.20
1.17
1.16
1.15
1.12
1.00
0.97
0.95
0.94
0.94
S
TIPSO
MeO
MeO
O
H
7d
0.62
1.59
0.90
0.92
2.70
2.90
0.96
0.94
1.02
1.00
1.22
21.62
f1 (ppm)

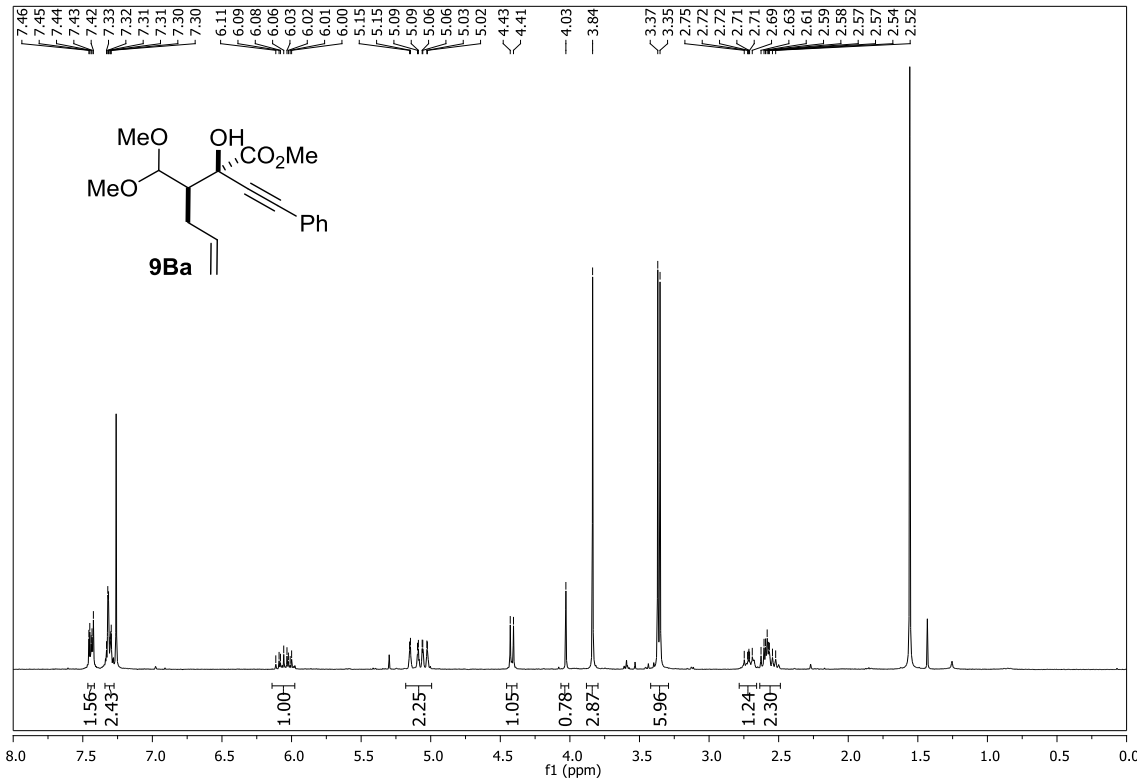

209.23
178.48
126.99
125.15
124.31
106.18
70.14
54.89
53.80
53.20
42.84
38.95
30.14
17.92
17.84
12.33
f1 (ppm)

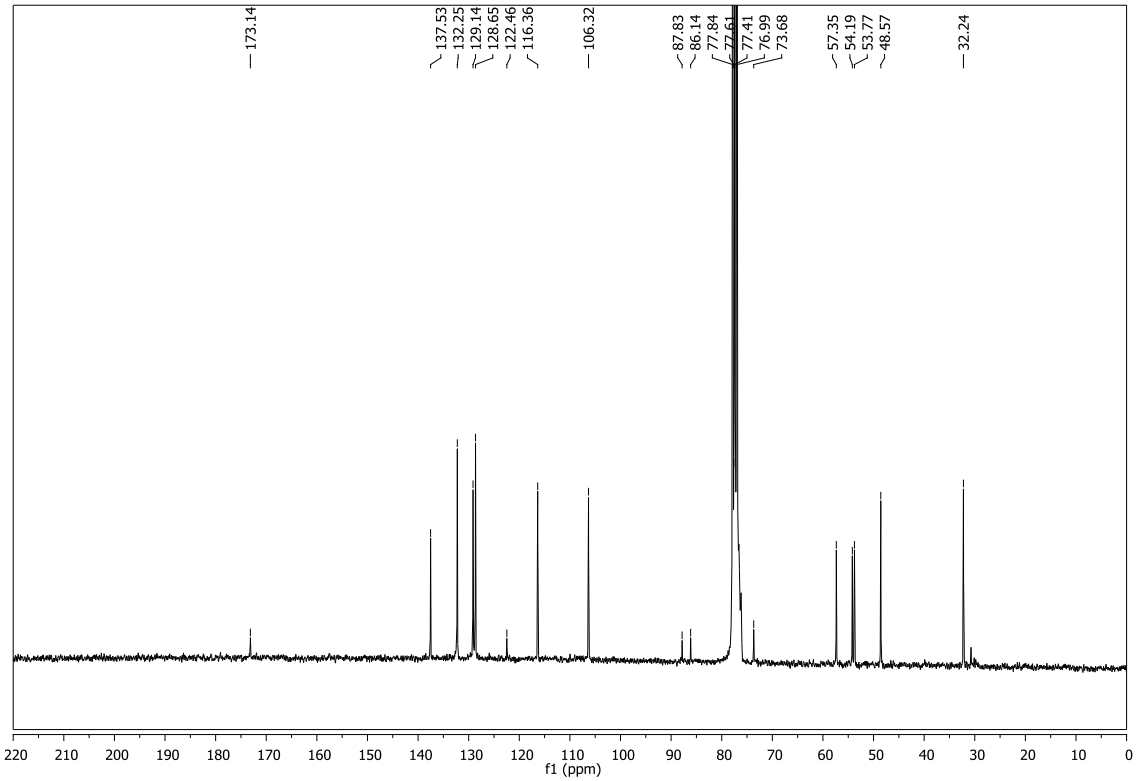

TIPSO
Ph
O
O
H
H
8
f1 (ppm)

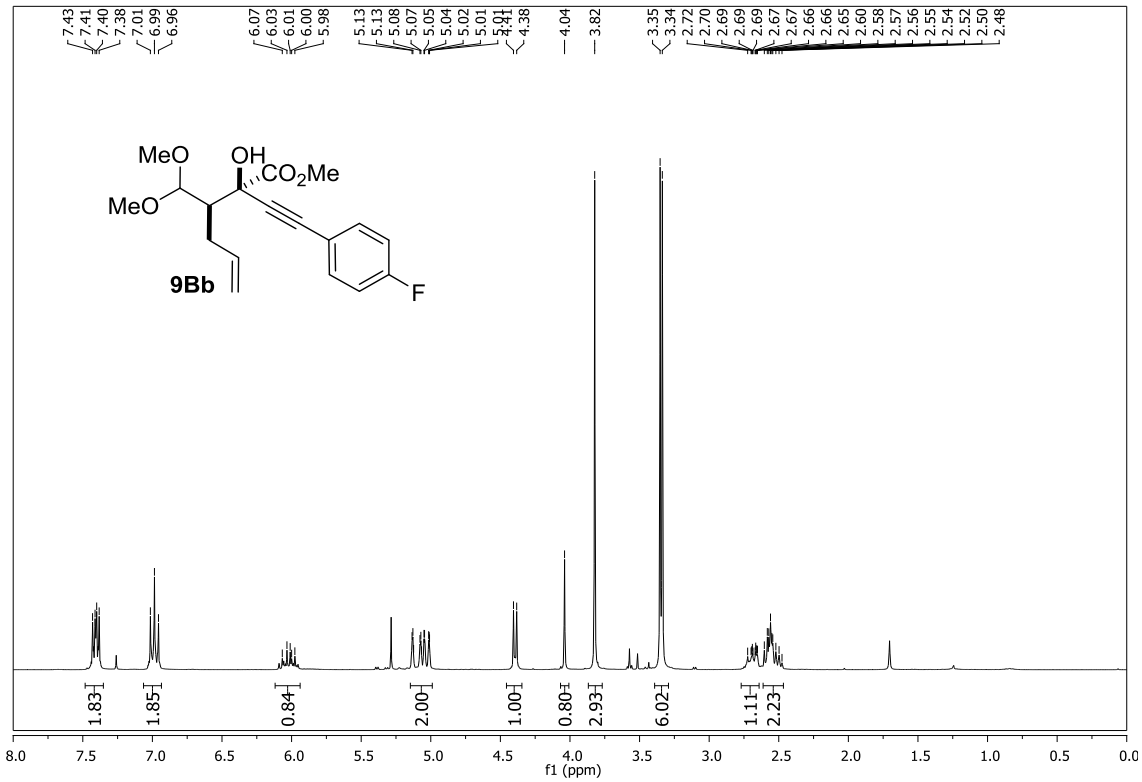

f1 (ppm)

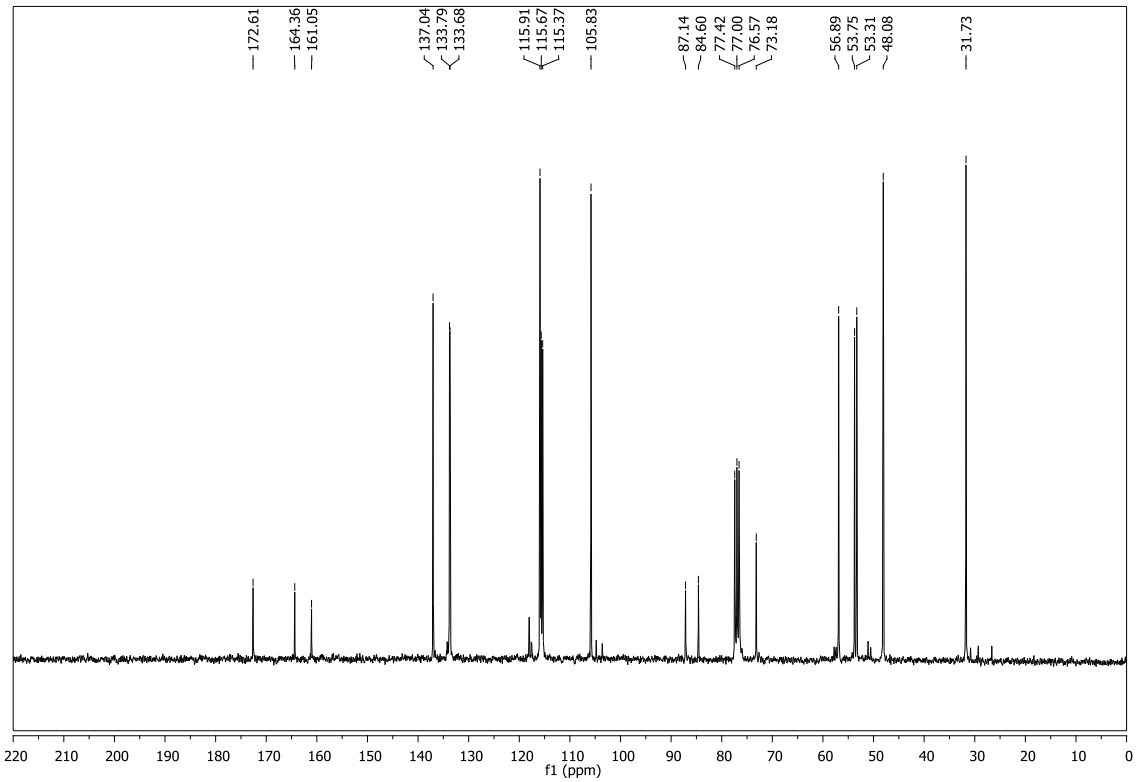

7.40
7.39
7.35
7.33
7.30
7.29
7.28
7.26
7.20
7.18
4.34
4.33
4.14
3.81
3.52
3.43
3.40
3.34
3.10
2.95
2.94
2.92
2.91
2.85
MeO
OH
CO2Me
MeO
Ph
Ph
9Aa
8.37
1.39
1.00
2.55
0.68
2.06
2.64
2.57
1.23
1.23
f1 (ppm)

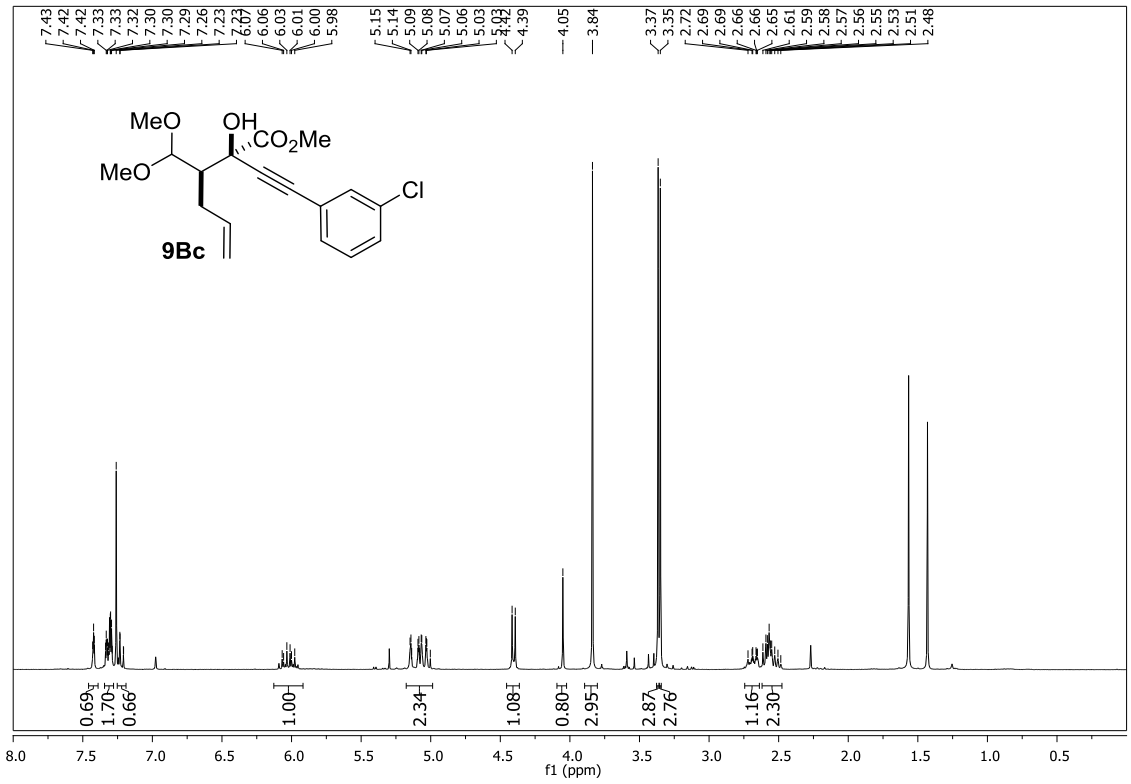

140.84
132.01
131.92
129.24
129.15
129.07
128.71
128.62
128.49
128.22
128.18
125.89
106.21
87.70
85.88
73.62
56.73
53.46
53.21
50.11
33.31
f1 (ppm)

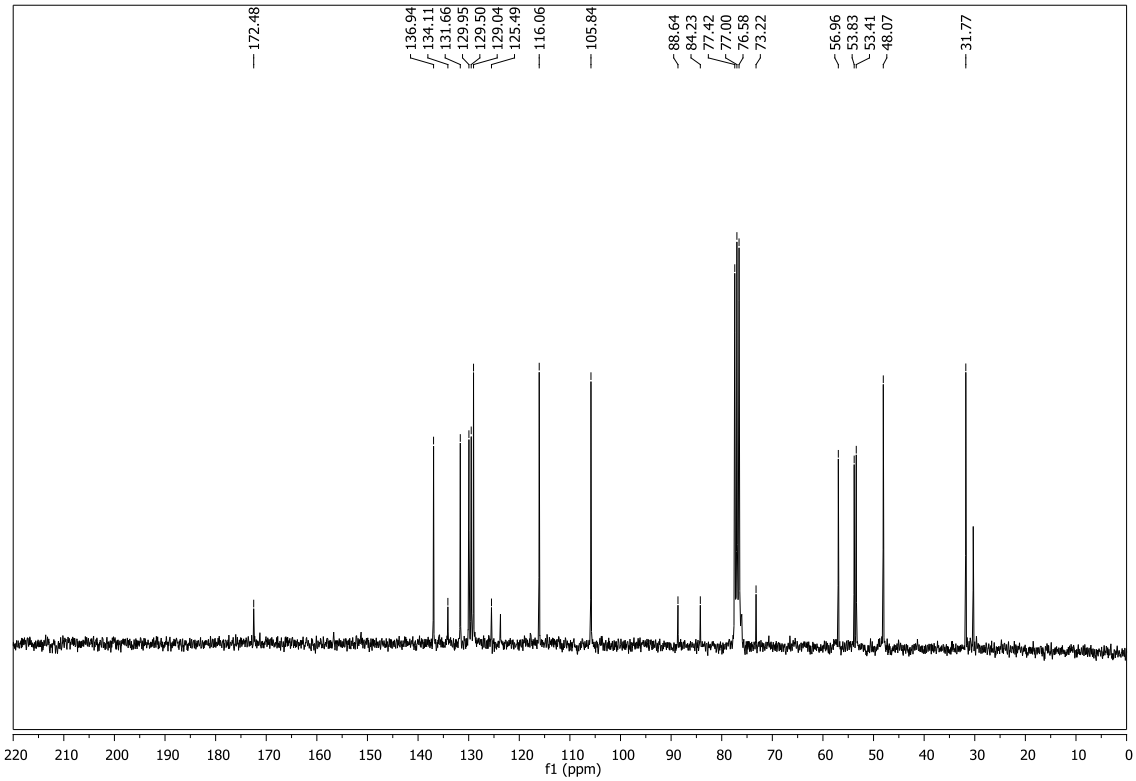

MeO
OH
CO2Me
MeO
Ph
9Ba
f1 (ppm)

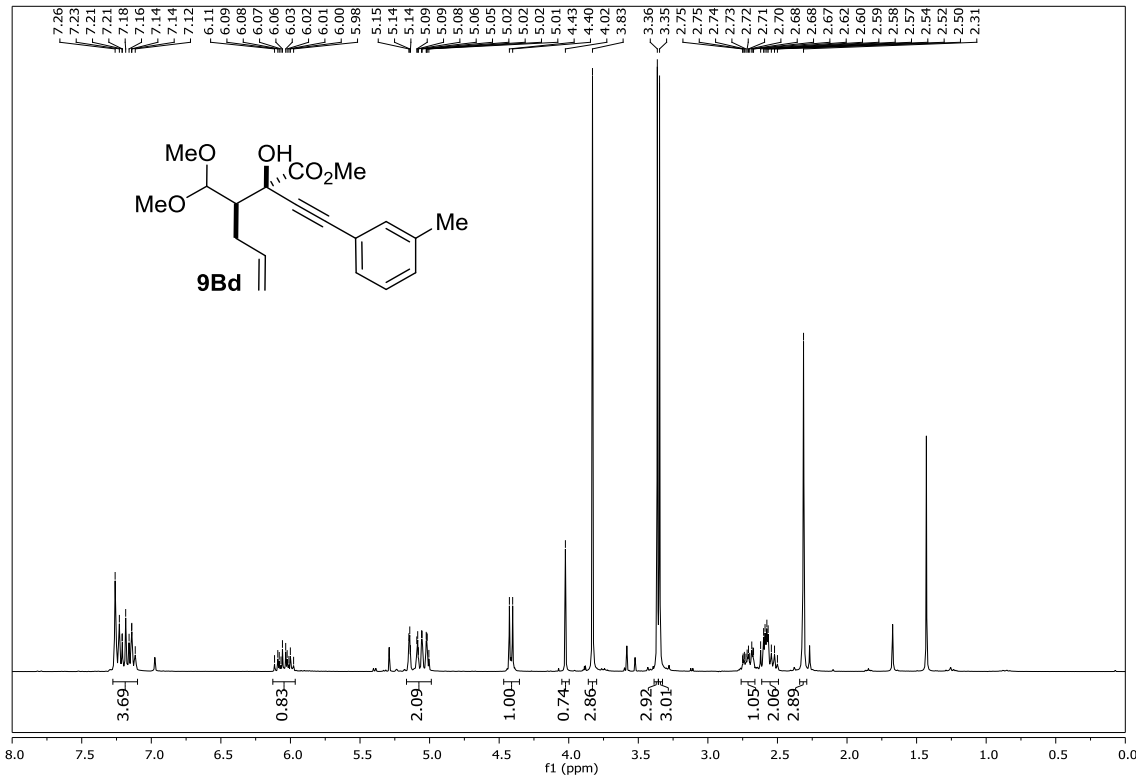

f1 (ppm)

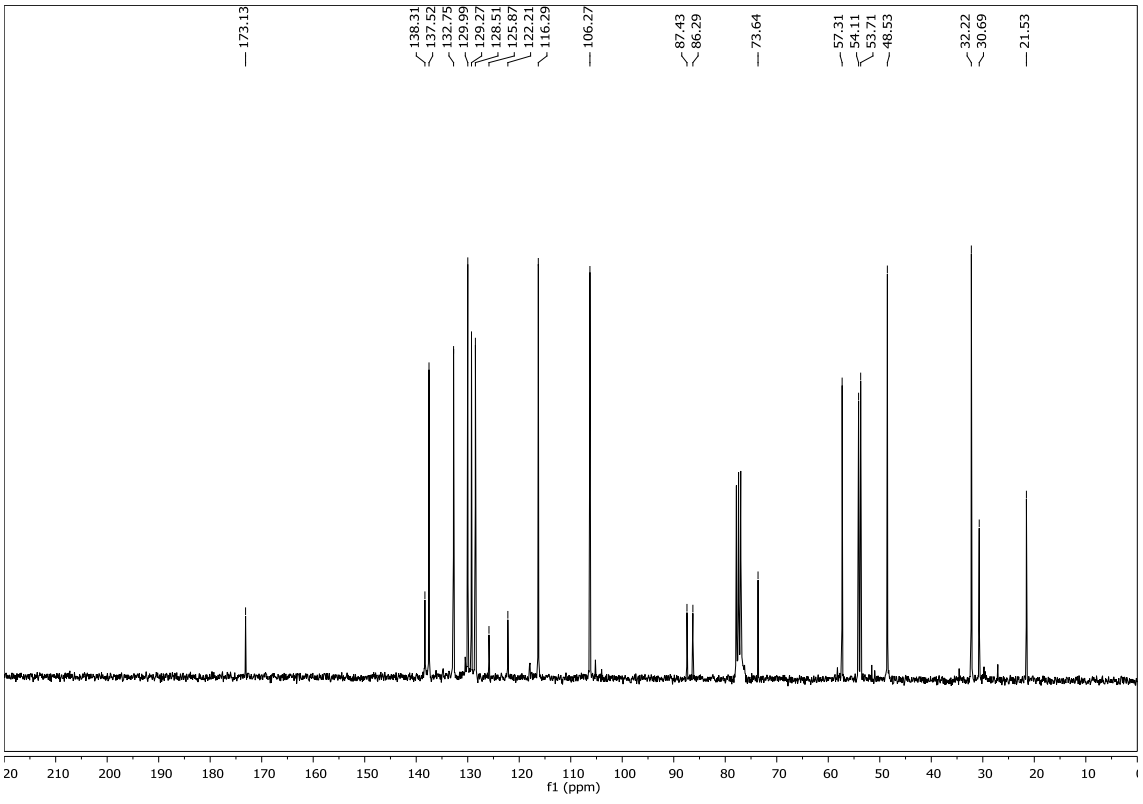

MeO
OH
CO2Me
MeO
9Bb
F
f1 (ppm)

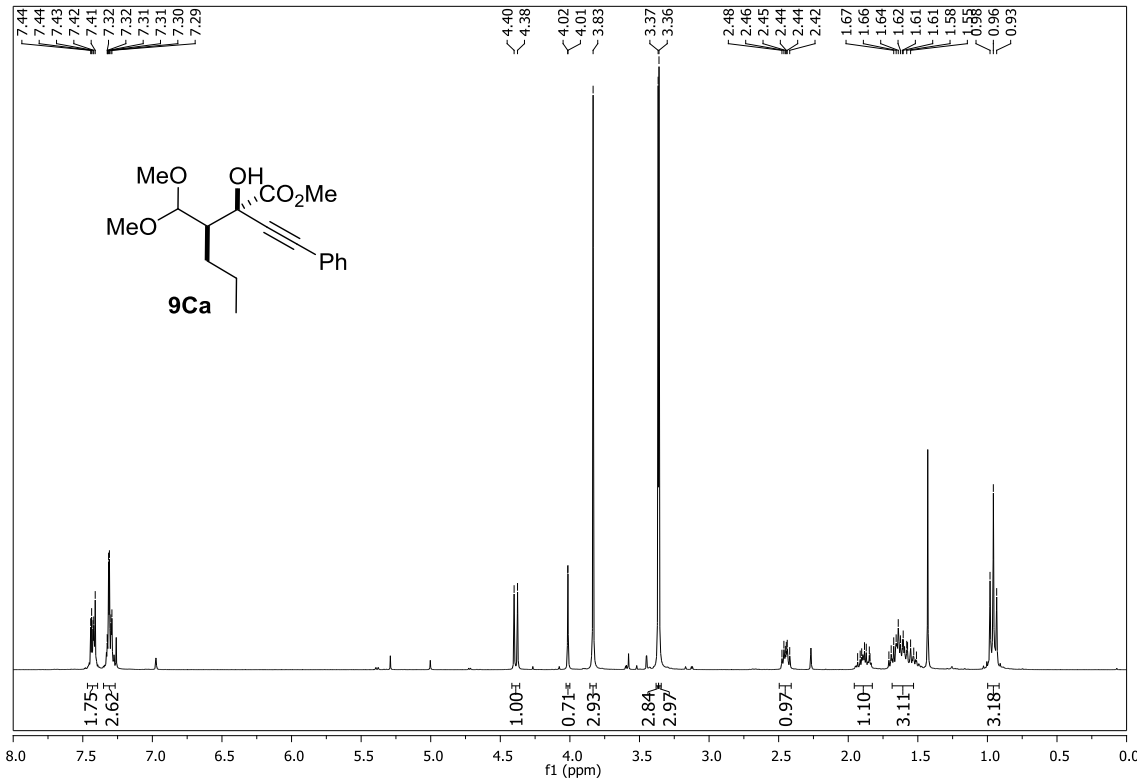

f1 (ppm)

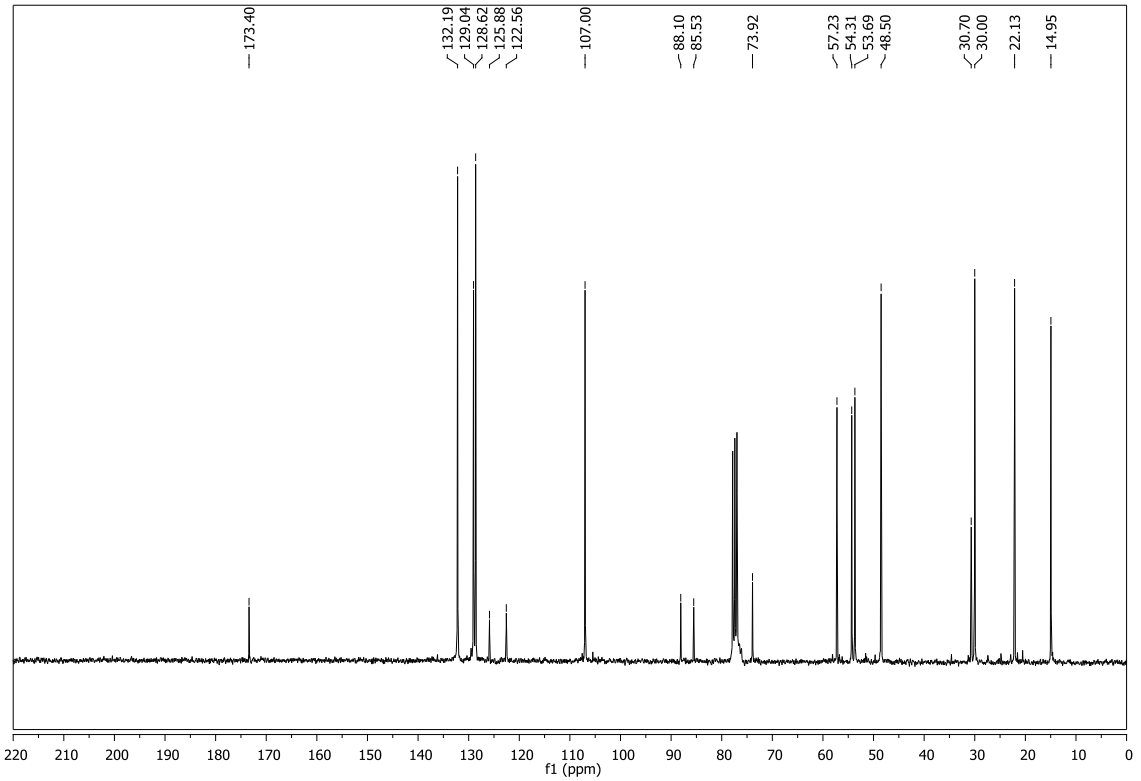

MeO
OH
CO2Me
MeO
Cl
9Bc
f1 (ppm)

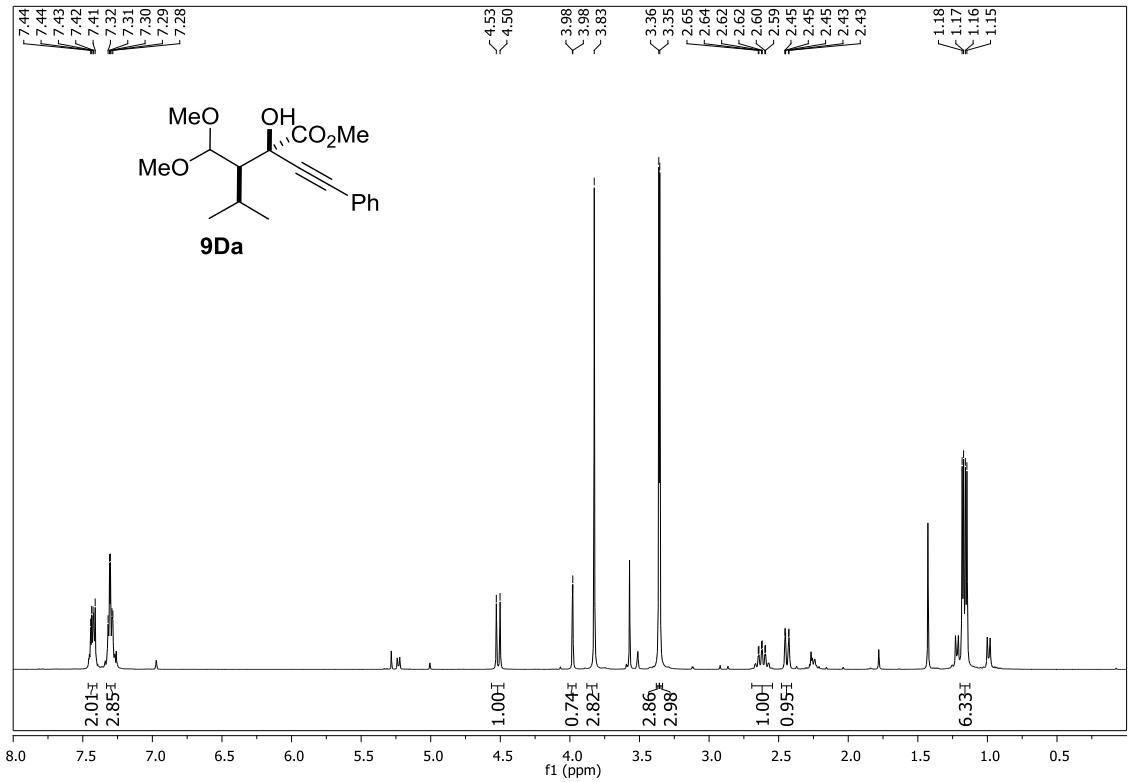

f1 (ppm)

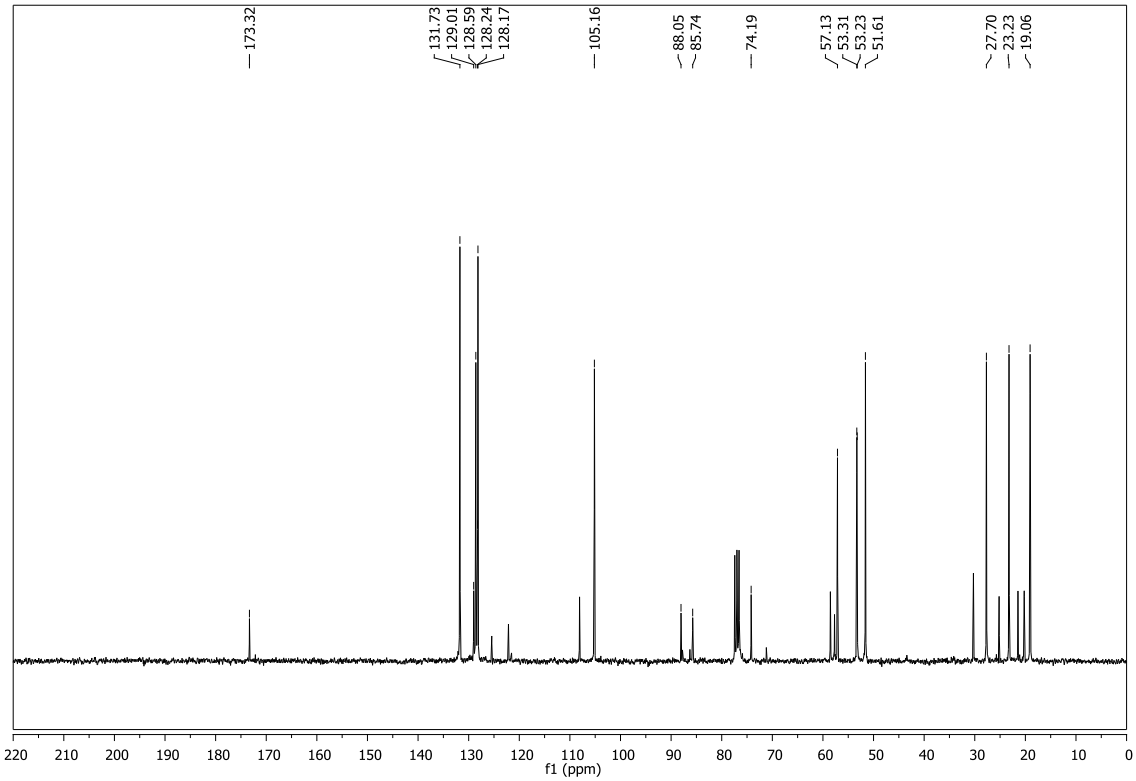

MeO
OH
CO2Me
MeO
Me
9Bd
f1 (ppm)

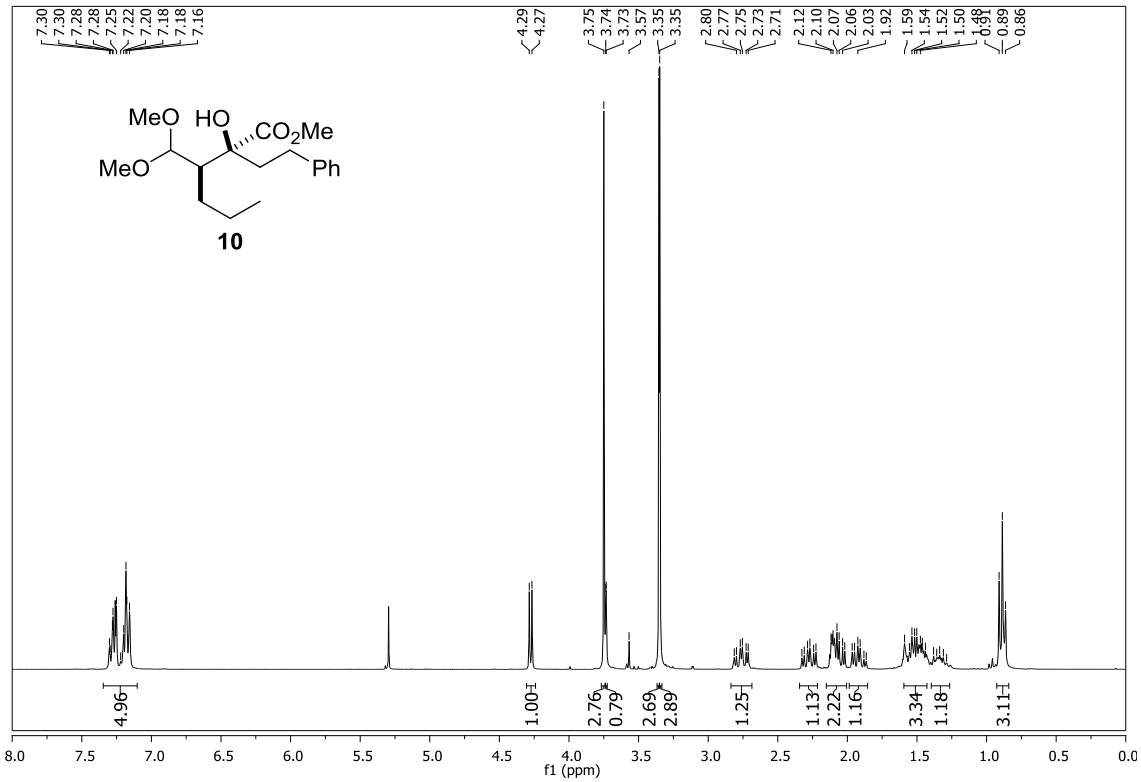

f1 (ppm)

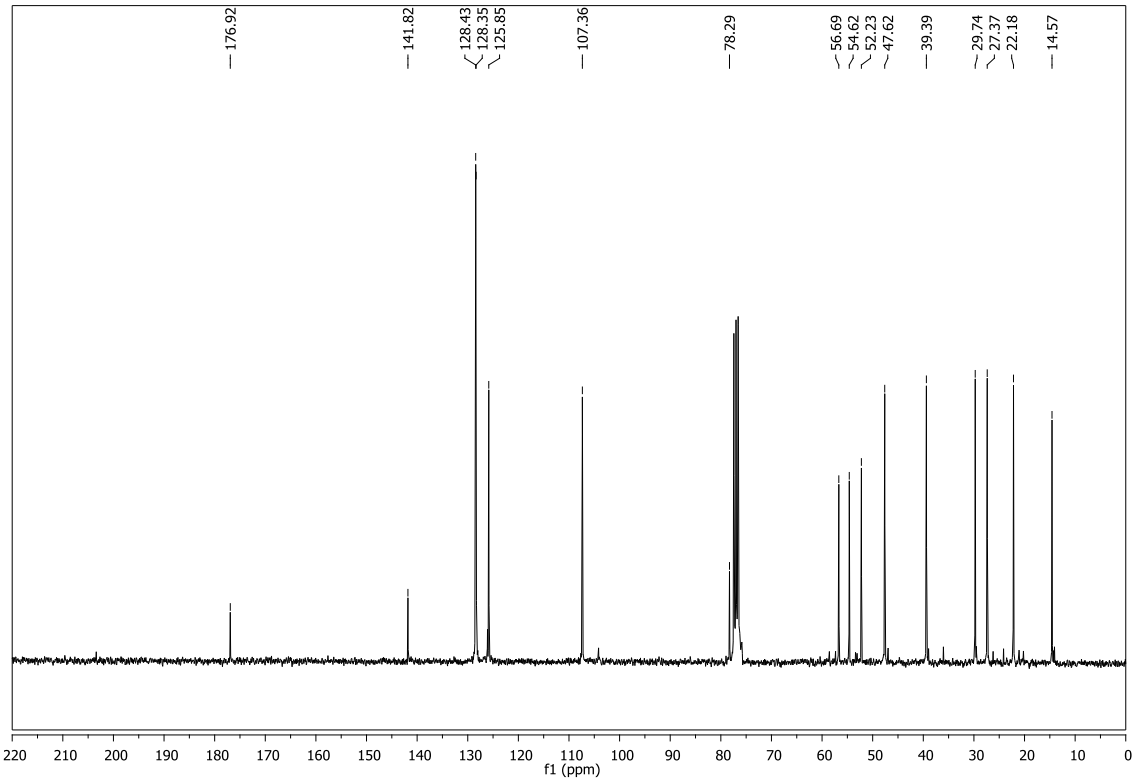

MeO
OH
CO2Me
MeO
Ph
9Ca
f1 (ppm)

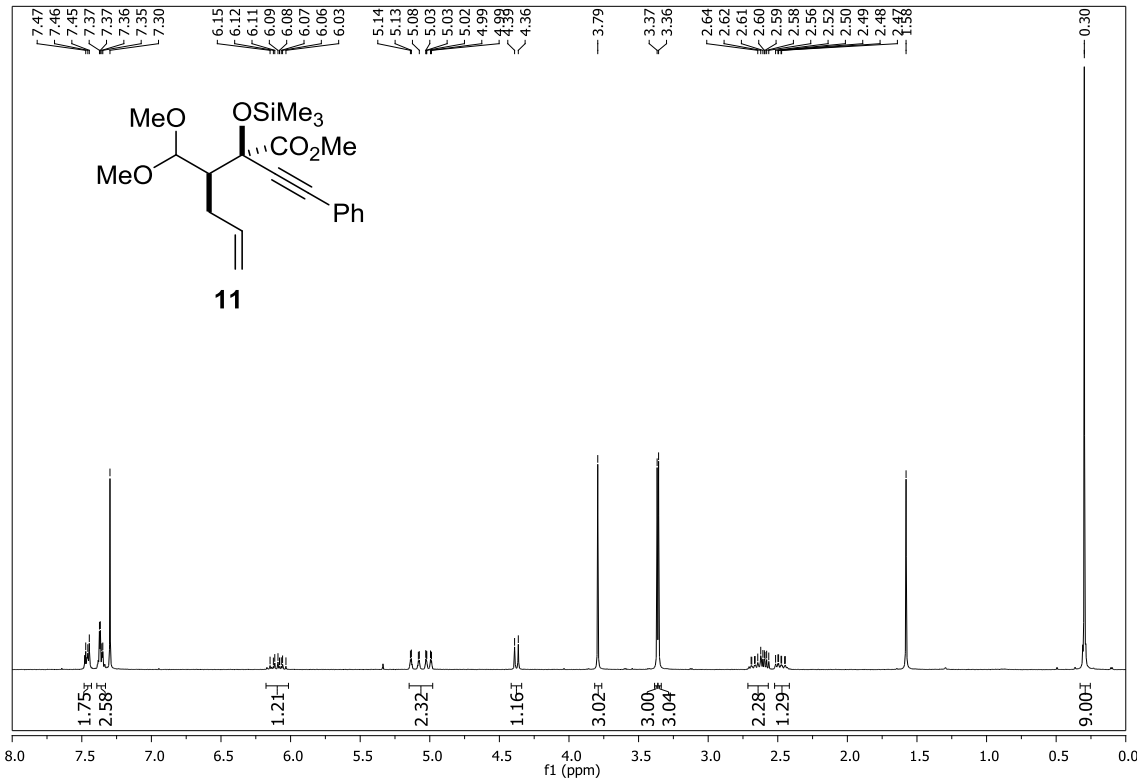

f1 (ppm)

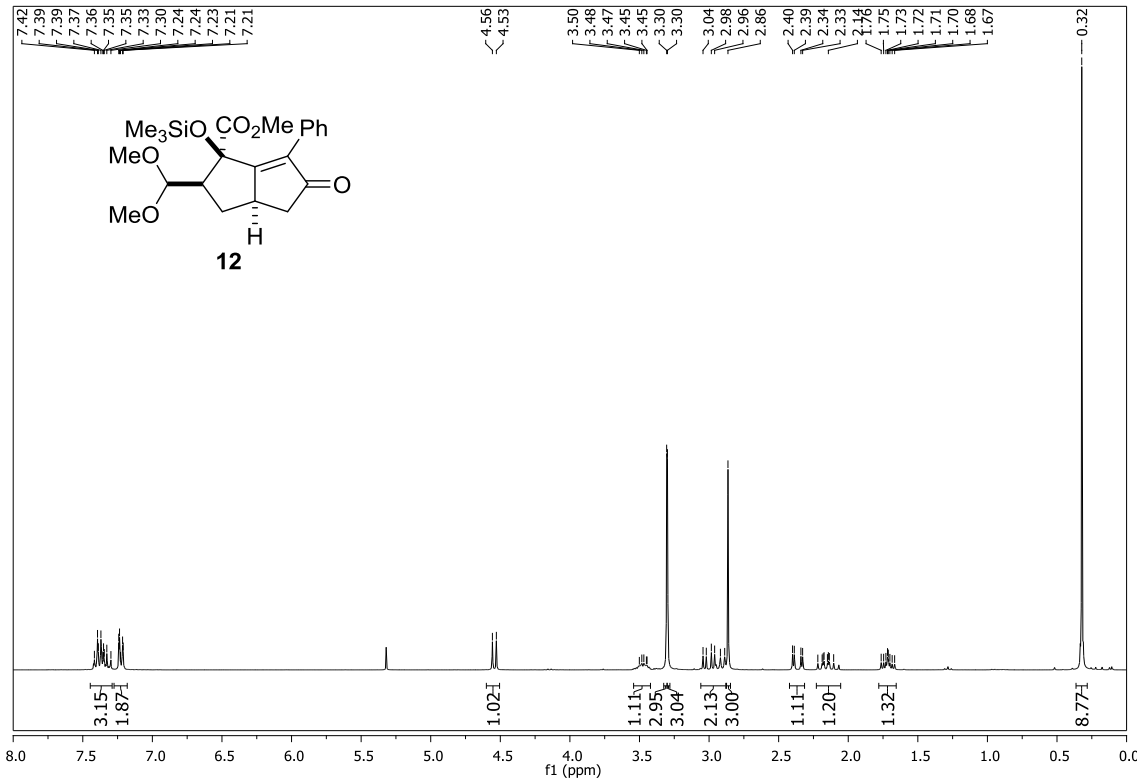

7.44
7.44
7.43
7.42
7.41
7.32
7.31
7.30
7.29
7.28
4.53
4.50
3.98
3.98
3.83
3.36
3.35
2.65
2.64
2.62
2.62
2.60
2.59
2.45
2.45
2.45
2.43
2.43
1.18
1.17
1.16
1.15
MeO
OH
CO2Me
MeO
Ph
9Da
2.01
2.85
1.00
0.74
2.82
2.86
2.98
1.00
0.95
6.33
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

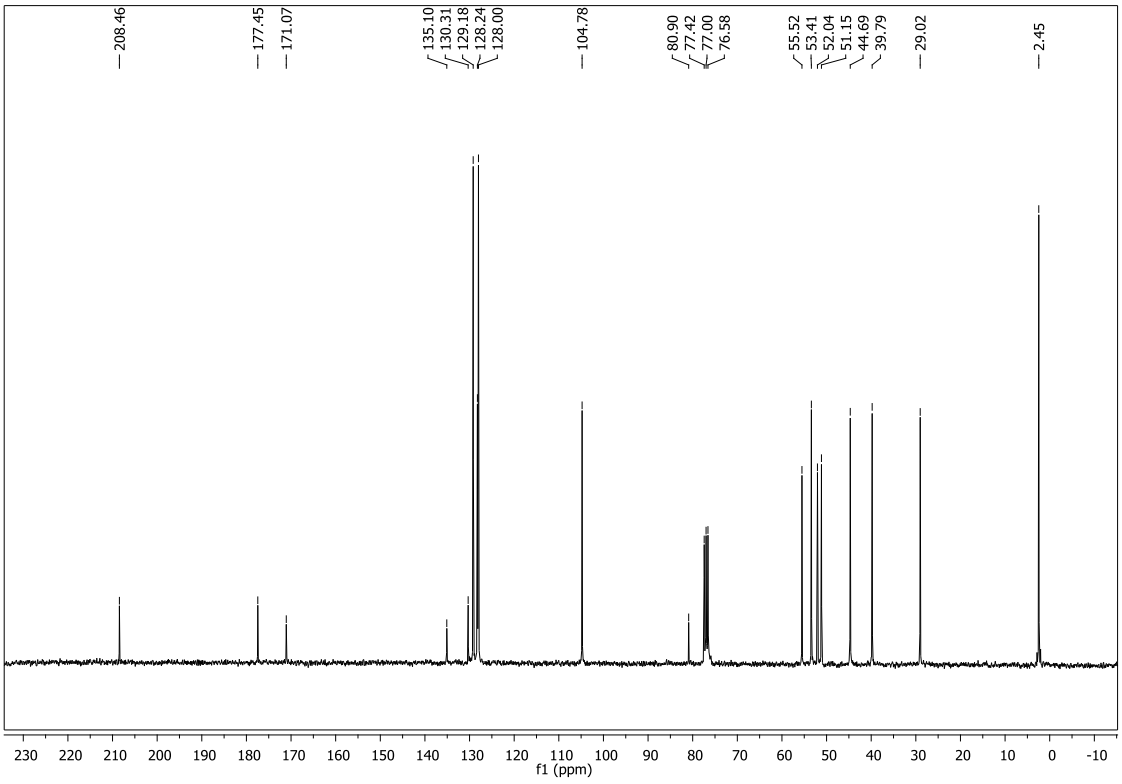

173.32
131.73
129.01
128.59
128.24
128.17
105.16
88.05
85.74
74.19
57.13
53.31
53.23
51.61
27.70
23.23
19.06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
HO
CO2Me
MeO
Ph
10
f1 (ppm)


f1 (ppm)

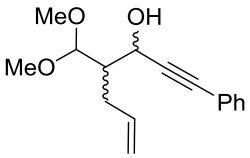

MeO
OSiMe3
CO2Me
MeO
Ph
11
f1 (ppm)


Me3SiO
CO2Me
Ph
MeO
MeO
O
H
12
f1 (ppm)


f1 (ppm)

5.3.8. HPLC chromatograms

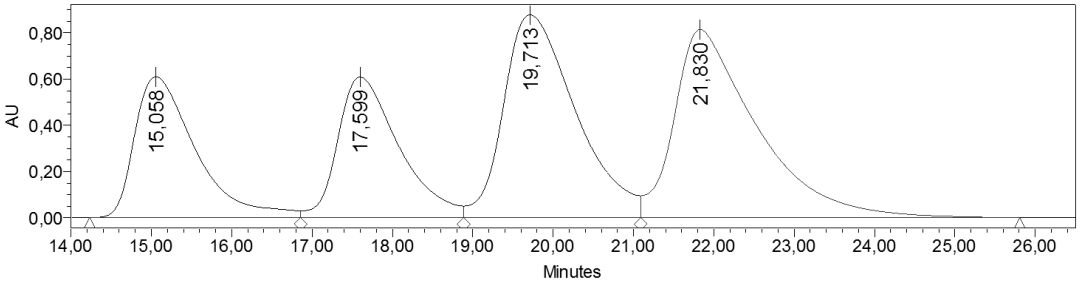
Chiralpack AD-H, 0.5 mL/min, hexane/isopropanol 95:5, λ = 240 nm

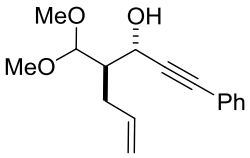


(±)*anti*-5Ba

Processed Channel Descr.: PDA 240,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240,0 nm	19,713	54485396	48,46	876391
2	PDA 240,0 nm	21,830	57958813	51,54	812794

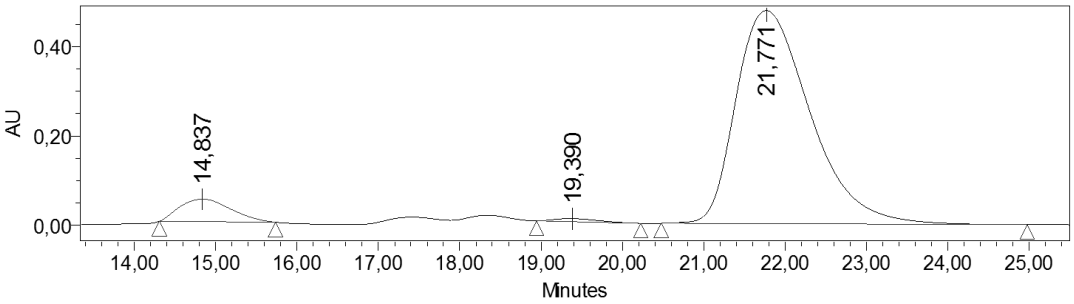




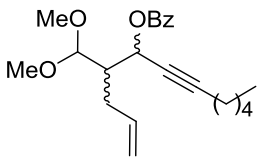
5Ba

Processed Channel Descr.: PDA 240,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240,0 nm	14,837	1867869	5,78	46220
2	PDA 240,0 nm	19,390	253914	0,79	6882
3	PDA 240,0 nm	21,771	30176798	93,43	476827



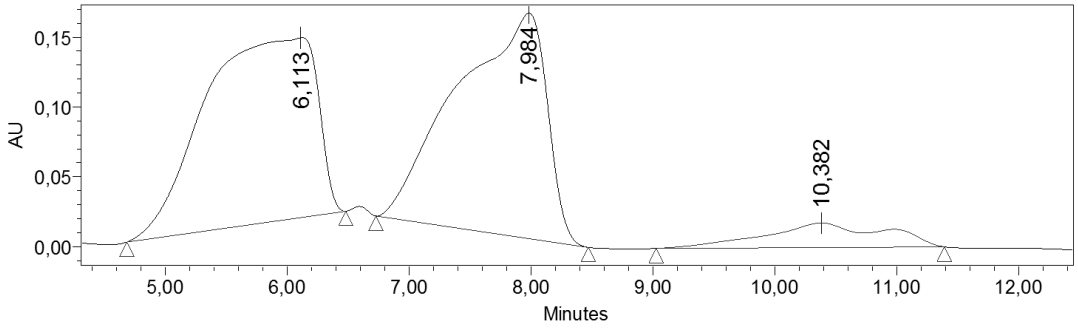
Chiralpack IC, 1 mL/min, hexane/isopropanol 99:1, λ = 230 nm

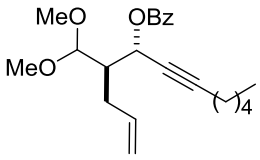


(±)5'Bb

Processed Channel Descr.: PDA 230,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 230,0 nm	6,113	8446113	47,40	128768
2	PDA 230,0 nm	7,984	8183307	45,92	161503
3	PDA 230,0 nm	10,382	1190755	6,68	17673

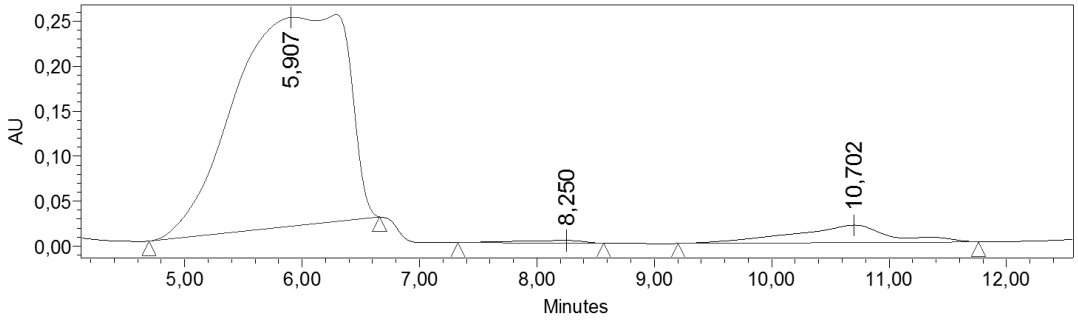




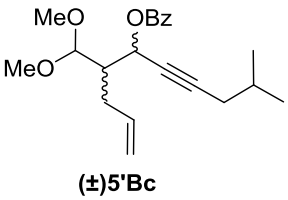
5'Bb

Processed Channel Descr.: PDA 230,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 230,0 nm	5,907	15611356	92,69	231874
2	PDA 230,0 nm	8,250	116019	0,69	3083
3	PDA 230,0 nm	10,702	1115683	6,62	19410



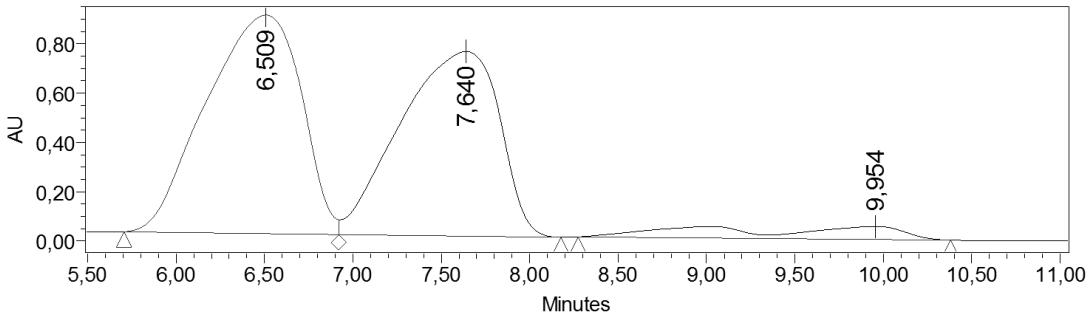
Chiralpack IC, 0.75 mL/min, hexane/isopropanol 98:2, λ = 230 nm

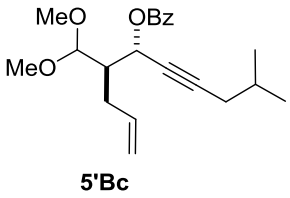


(±)5'Bc

Processed Channel Descr.: PDA 230,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 230,0 nm	6,509	33160798	50,22	886928
2	PDA 230,0 nm	7,640	29233937	44,27	749378
3	PDA 230,0 nm	9,954	3633509	5,50	53056

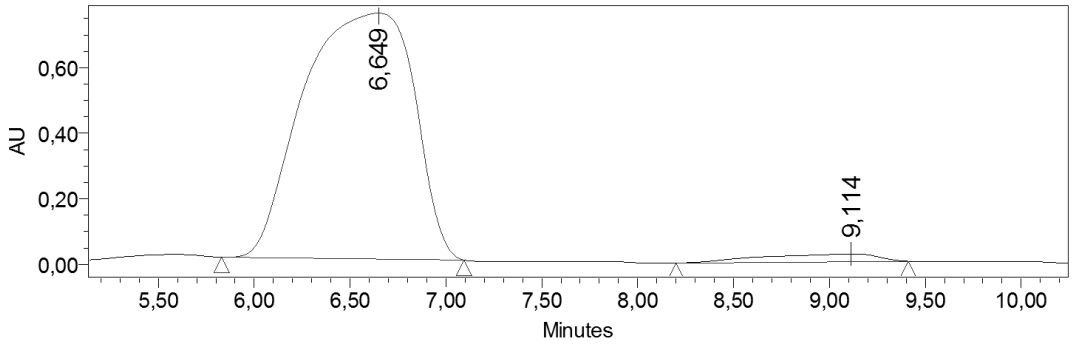




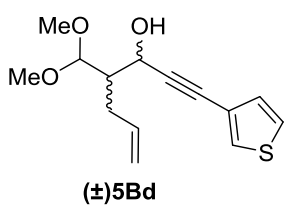
5'Bc

Processed Channel Descr.: PDA 230,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 230,0 nm	6,649	30155346	96,73	750486
2	PDA 230,0 nm	9,114	1019514	3,27	23823



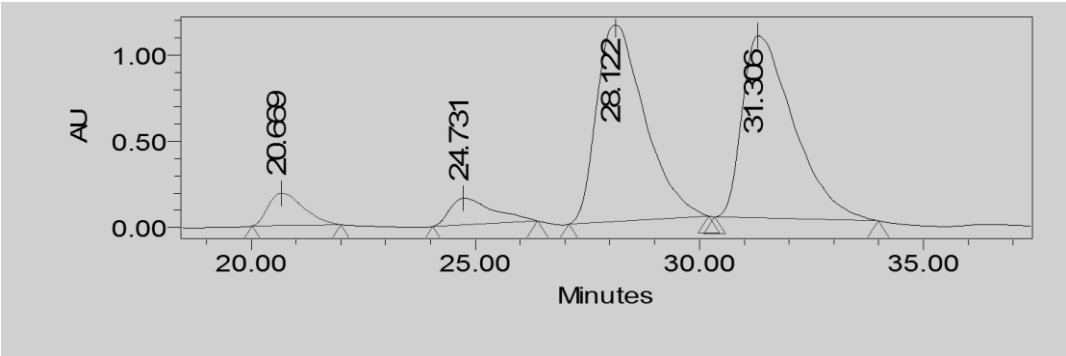
Chiralpack AD-H, 0.5 mL/min, hexane/isopropanol 95:5, λ = 210 nm

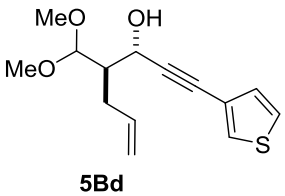


(±)5Bd

Processed Channel Descr.: PDA 210.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 210.0 nm	20.669	10242257	5.39	188530
2	PDA 210.0 nm	24.731	10313789	5.42	154674
3	PDA 210.0 nm	28.122	85234923	44.82	1138277
4	PDA 210.0 nm	31.306	84378901	44.37	1054890

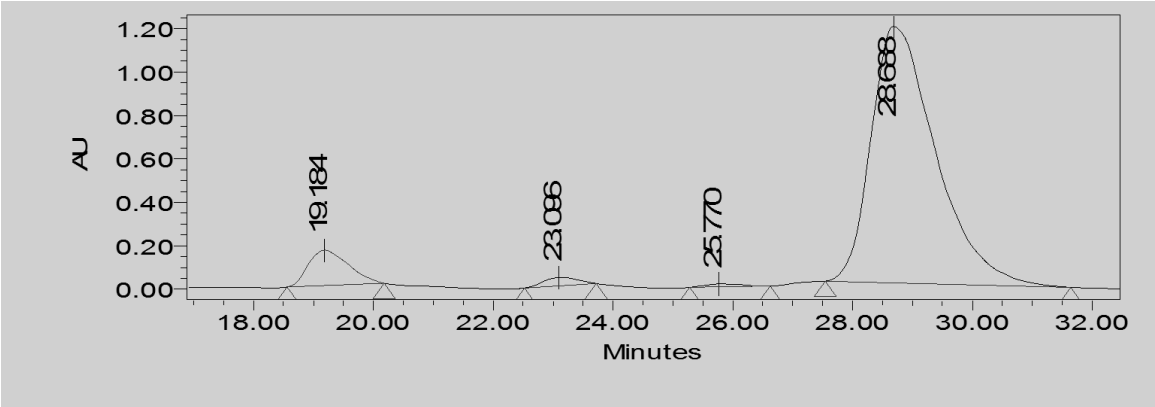




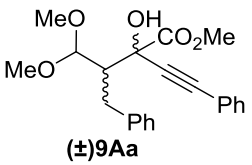
5Bd

Processed Channel Descr.: PDA 210.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 210.0 nm	19.184	7537894	7.68	162782
2	PDA 210.0 nm	23.096	1521590	1.55	38097
3	PDA 210.0 nm	25.770	535894	0.55	13100
4	PDA 210.0 nm	28.688	88537752	90.22	1180664



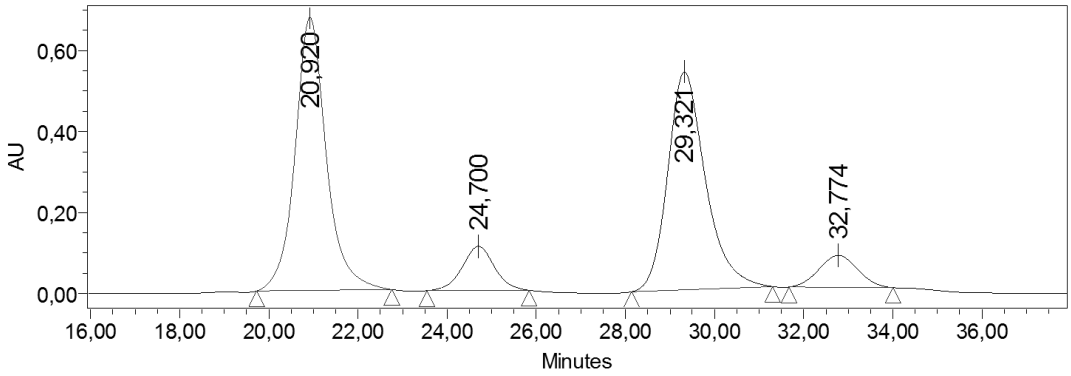
Chiralpack IA, 0.5 mL/min, hexane/isopropanol 95:5, λ = 240 nm

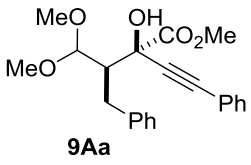


(±)9Aa

Processed Channel Descr.: PDA 240,0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240,0 nm	20,920	32358655	44,13	672652
2	PDA 240,0 nm	24,700	4600339	6,27	101396
3	PDA 240,0 nm	29,321	31755766	43,31	539156
4	PDA 240,0 nm	32,774	4608434	6,29	77586

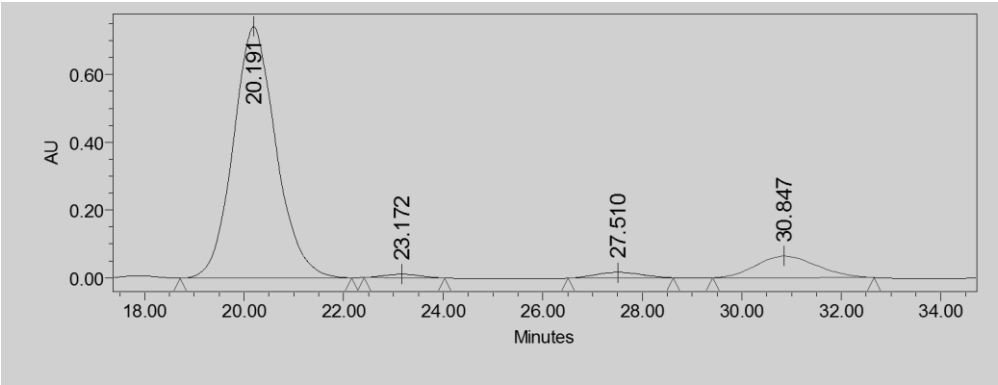




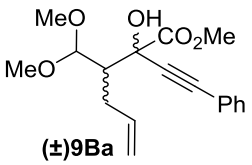
9Aa

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	20.191	44285958	86.19	742397
2	PDA 240.0 nm	23.196	495576	0.96	9827
3	PDA 240.0 nm	27.510	1156904	2.25	17594
4	PDA 240.0 nm	30.847	5442010	10.59	63927



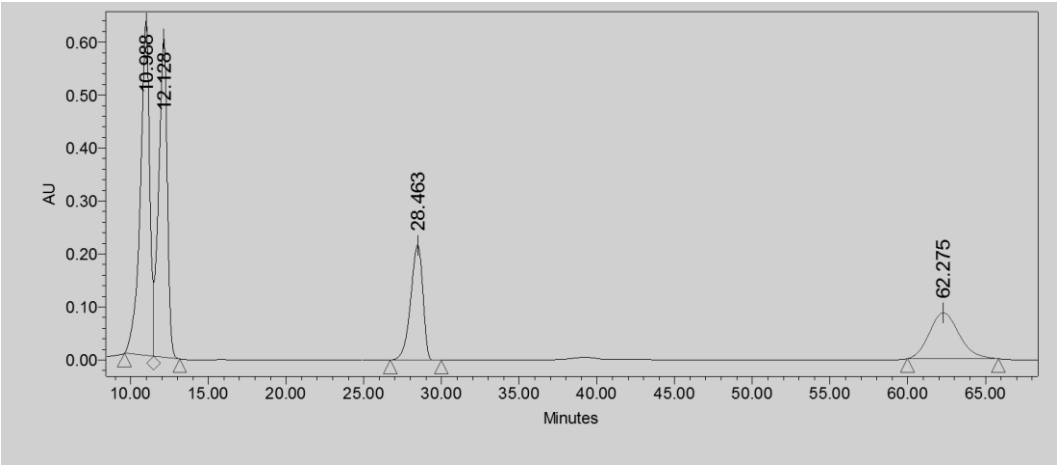
Chiralpack IC, 1 mL/min, hexane/isopropanol 98:2, λ = 240 nm

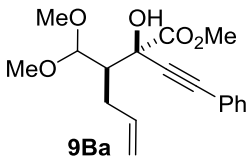


(±)9Ba

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	10.988	26376065	36.14	631480
2	PDA 240.0 nm	12.128	23210408	31.80	601370
3	PDA 240.0 nm	28.463	11872546	16.27	217112
4	PDA 240.0 nm	62.275	11526108	15.79	86494

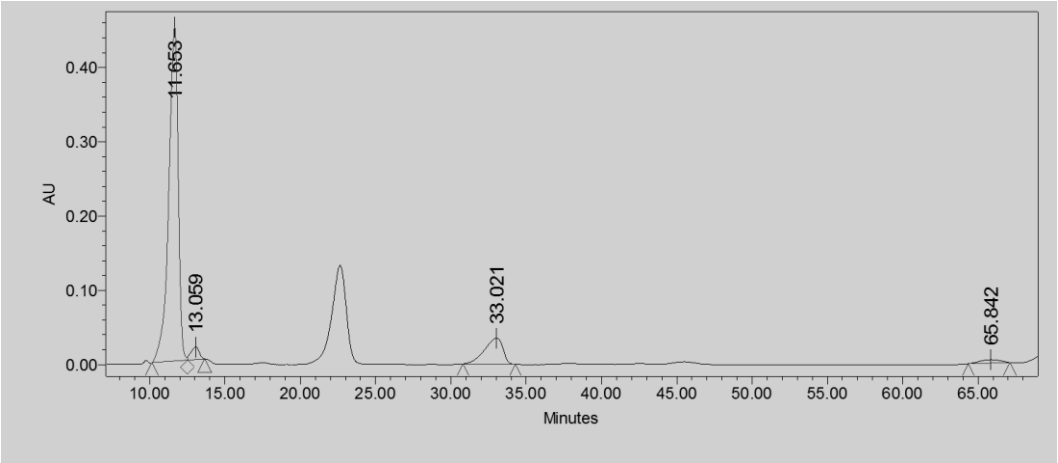




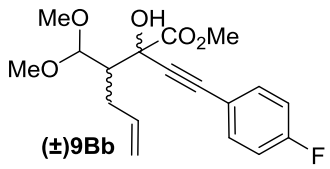
9Ba

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	11.653	19711169	82.84	449486
2	PDA 240.0 nm	13.059	650517	2.73	17062
3	PDA 240.0 nm	33.021	2997867	12.60	35167
4	PDA 240.0 nm	65.842	435404	1.83	4690

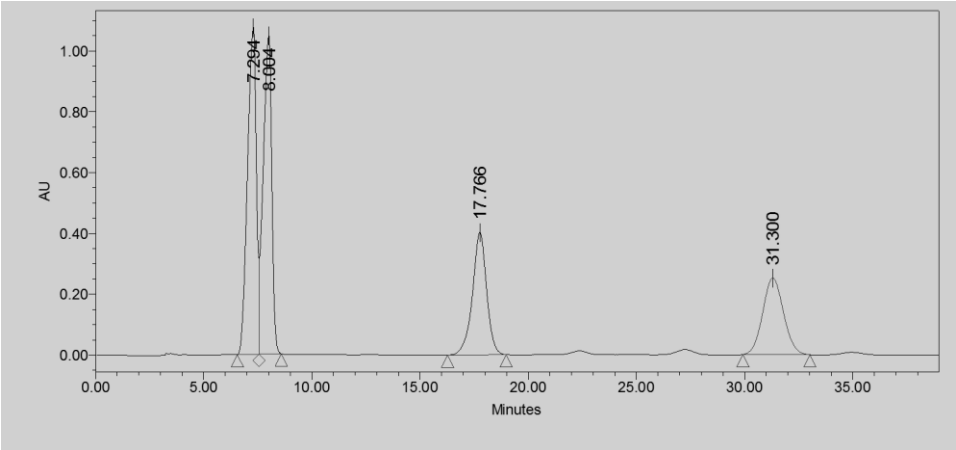


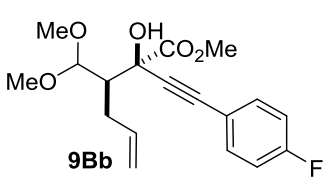
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 240 nm



Processed Channel Descr.: PDA 240.0 nm

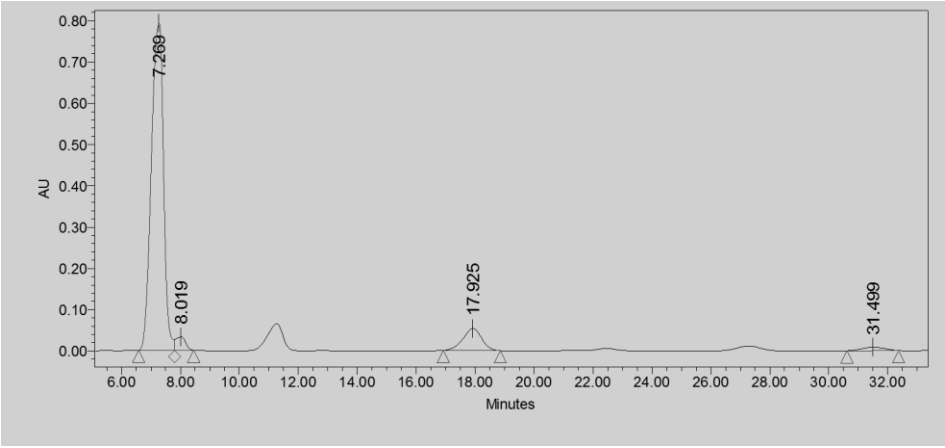
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	7.294	30573165	32.36	1076580
2	PDA 240.0 nm	8.004	28740020	30.42	1046771
3	PDA 240.0 nm	17.766	18301481	19.37	402898
4	PDA 240.0 nm	31.300	16875813	17.86	252570



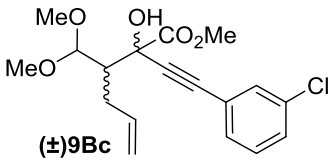


Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	7.269	22833895	86.42	793155
2	PDA 240.0 nm	8.019	761417	2.88	32542
3	PDA 240.0 nm	17.925	2373096	8.98	53688
4	PDA 240.0 nm	31.499	454142	1.72	8243



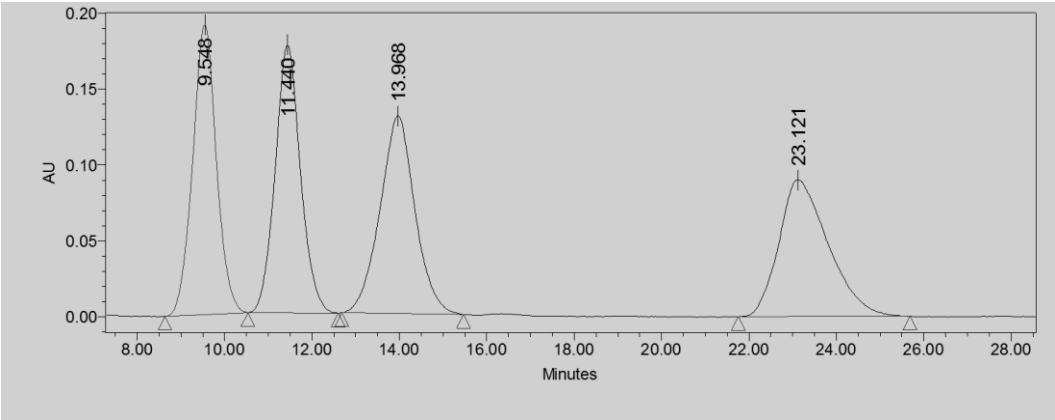
Chiralpack IA, 1 mL/min, hexane/isopropanol 98:2, λ = 240 nm

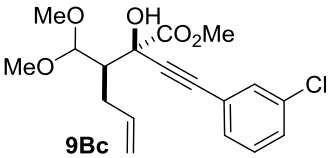


(±)9Bc

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	9.548	7214579	25.23	191129
2	PDA 240.0 nm	11.440	7117159	24.89	176535
3	PDA 240.0 nm	13.968	7237087	25.31	130142
4	PDA 240.0 nm	23.121	7027872	24.58	89901

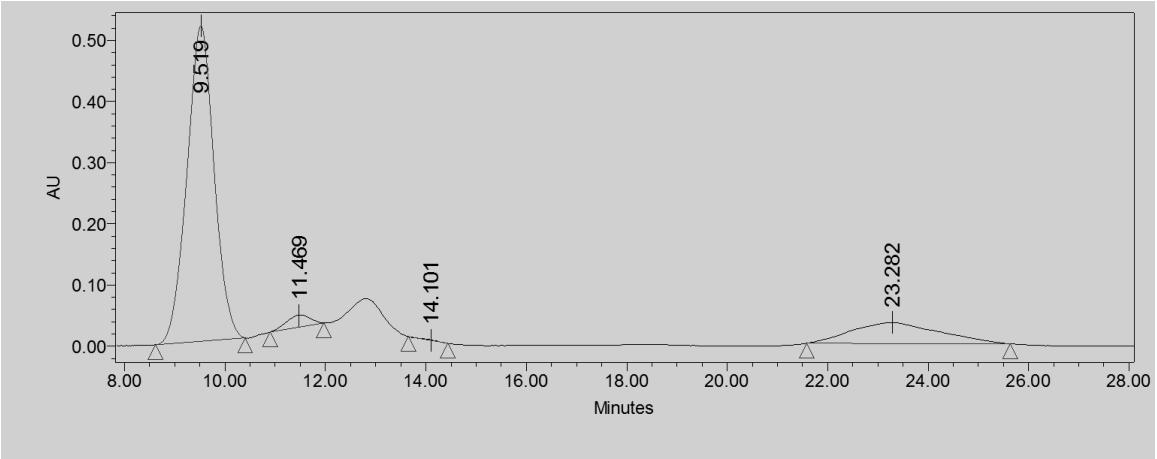




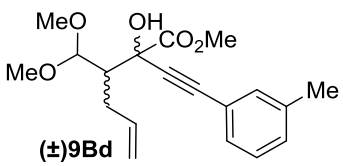
9Bc

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	9.519	19384078	80.15	515536
2	PDA 240.0 nm	11.469	649975	2.69	19827
3	PDA 240.0 nm	14.101	22237	0.09	1082
4	PDA 240.0 nm	23.282	4129133	17.07	34350



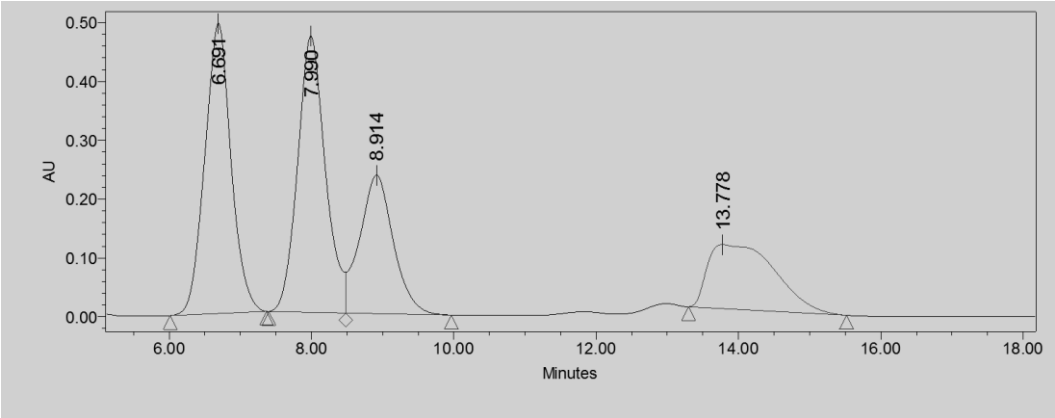
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 240 nm

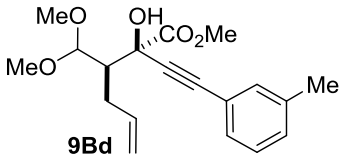


(±)9Bd

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	6.691	12657325	31.36	493516
2	PDA 240.0 nm	7.990	12728317	31.53	469344
3	PDA 240.0 nm	8.914	7718122	19.12	235502
4	PDA 240.0 nm	13.778	7260473	17.99	108776

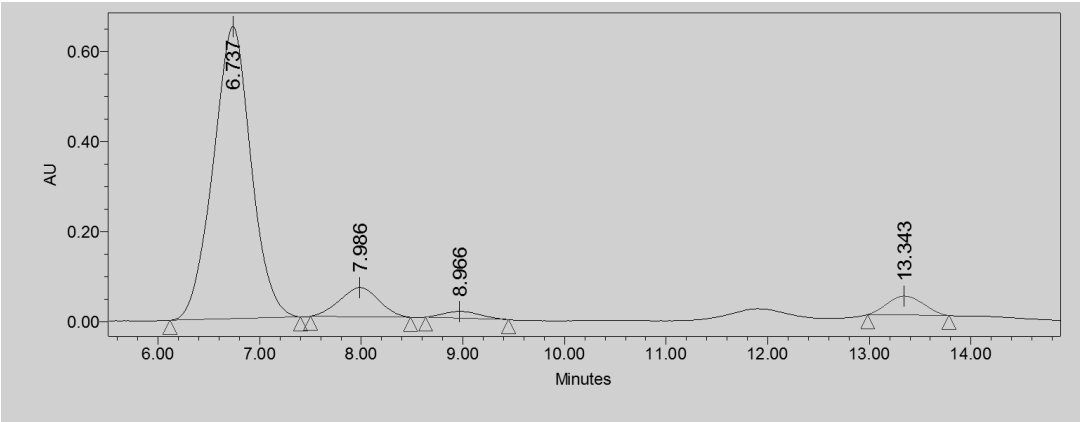




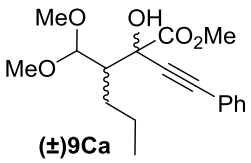
9Bd

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	6.737	16831525	84.41	649780
2	PDA 240.0 nm	7.986	1739804	8.73	65061
3	PDA 240.0 nm	8.966	370867	1.86	14944
4	PDA 240.0 nm	13.343	997829	5.00	40987



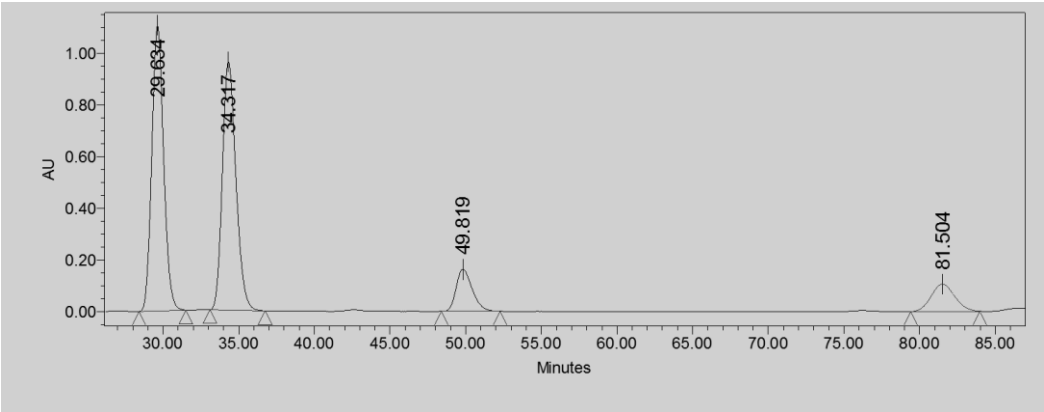
Chiralpack IA+IC, 0.5 mL/min, hexane/isopropanol 95:5, λ = 240 nm

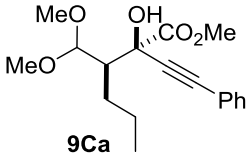


(±)9Ca

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	29.634	59910118	41.90	1104286
2	PDA 240.0 nm	34.317	59611453	41.69	961736
3	PDA 240.0 nm	49.819	11986622	8.38	163342
4	PDA 240.0 nm	81.504	11462676	8.02	105853

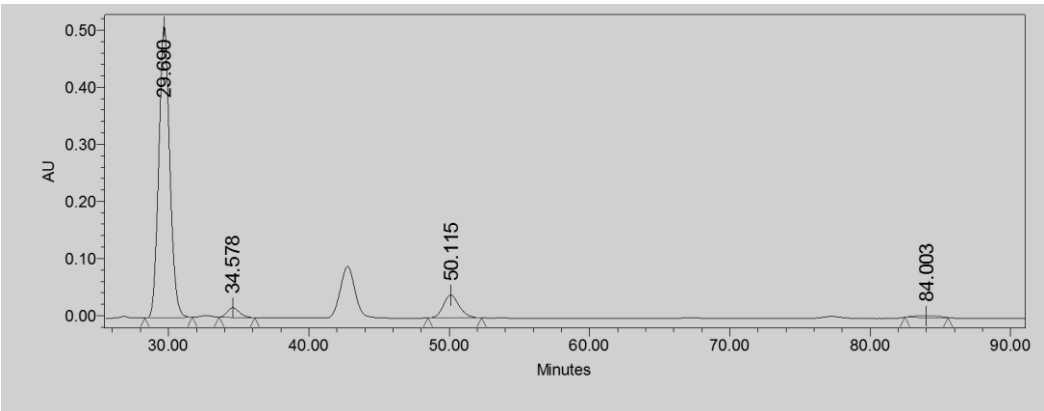




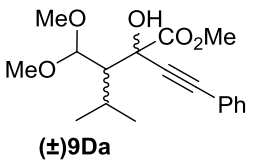
9Ca

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	29.690	27757285	85.96	510413
2	PDA 240.0 nm	34.578	1012296	3.13	16887
3	PDA 240.0 nm	50.115	3151359	9.76	40312
4	PDA 240.0 nm	84.003	370359	1.15	2894



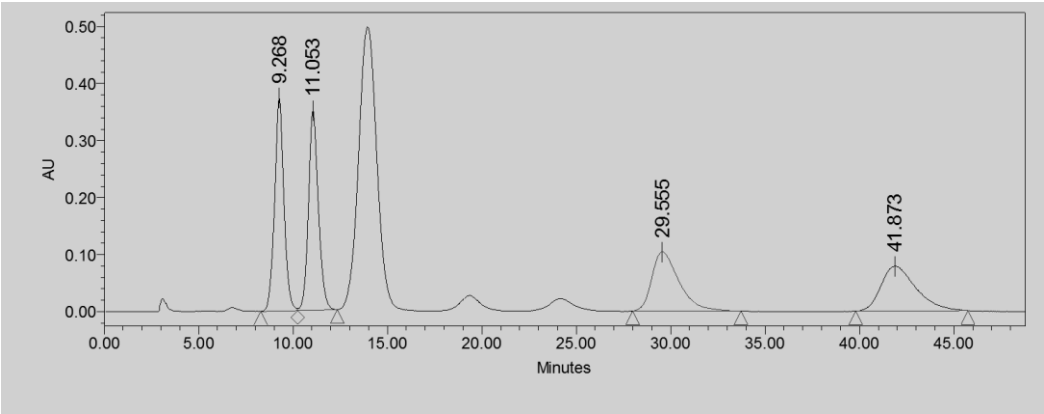
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 240 nm

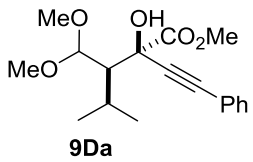


(±)9Da

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	9.268	12843977	27.89	373802
2	PDA 240.0 nm	11.053	12763738	27.72	350351
3	PDA 240.0 nm	29.555	10333342	22.44	103814
4	PDA 240.0 nm	41.873	10106513	21.95	78515

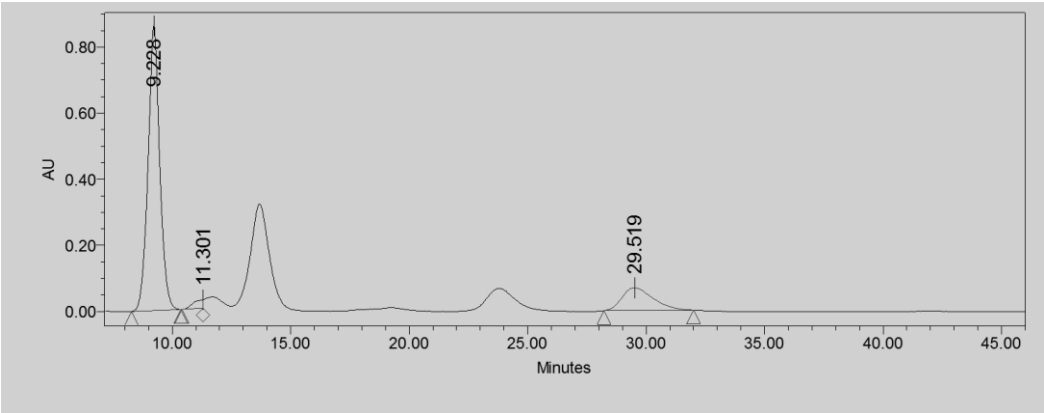




9Da

Processed Channel Descr.: PDA 240.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 240.0 nm	9.228	29525344	80.88	862259
2	PDA 240.0 nm	11.234	615855	1.69	23827
3	PDA 240.0 nm	29.519	6366024	17.44	69414



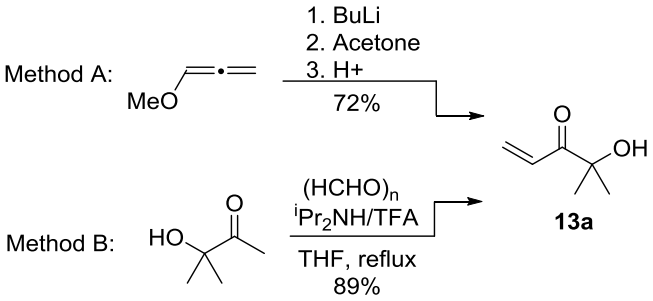
5.4. Experimental section of Chapter 3

5.4.1. General procedures for the synthesis of α'-oxy enones

*5.4.1.1. Preparation of α'-oxy enones **13***

Preparation of α'-hydroxy enone 13a

Known enone **13a** was prepared according to either of the following previously described procedures:

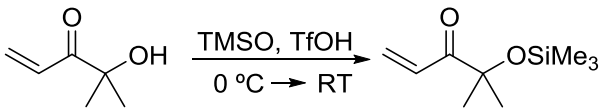


Method A:[245] To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at –40 °C, *n*BuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction mixture was stirred at –40 °C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction mixture was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid, which was added dropwise to 5% aq H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time, the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 x 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid. Yield: 88% (4.42 g, 38.7 mmol). All data were consistent with those previously reported. b.p. = 45 ºC (13 mmHg). **^{1}H NMR** ($CDCl_3$) δ 6.73 (dd, *J* = 9.5, 16.8 Hz, 1H), 6.50 (dd, *J* = 2.2, 16.8 Hz, 1H), 5.82 (dd, *J* = 2.2, 10.3 Hz, 1H), 1.38 (s, 6H). **^{13}C NMR** ($CDCl_3$) δ 202.3, 131.1, 128.8, 75.4, 26.1.

[245] C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc*. **2003**, *125*, 13942–13943.

Method B:[246] Commercially available 3-hydroxy-3-methyl-2-butanone (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde (2 equiv., 3 g, 100 mmol) were added to a solution of $^{i}Pr_2NH$ (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure (230 mbar/ bath 40 ºC). The residue was purified by flash column chromatography on silica gel (eluent: diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one as colorless oil. Yield: 89% (5.0 g, 44.5 mmol).

Preparation of α'-trimethylsilyloxy enone 13b[247]



13a **13b**

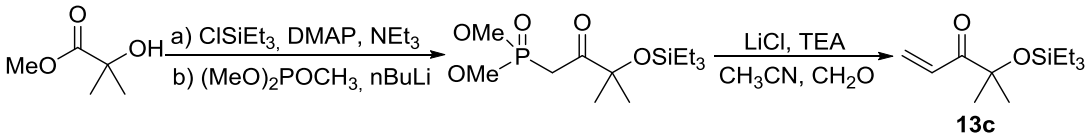
3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (3.4 mL, 22.5 mmol, 1.5 equiv.) and 3 drops of trifluoromethanesulfonic acid were added to enone **13a** (1.68 g, 15 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 2 h, diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was then dried over with $MgSO_4$ and concentred under reduced pressure to afford the title compound **13b** as a colorless oil. Yield: 93% (2.6 g, 14.0 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.8, 130.7, 129.2, 79.3, 27.2, 2.3.

Preparation of α'-triethylsilyloxy enone 13c

The title compound **13c** was prepared according to the following synthetic sequence:

[246] Adapted from: A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun*. **2010**, *46*, 1715–1717.

[247] Adapted from: J. M. Aizpurua, C. Palomo, A. L. Palomo, *Can. J. Chem*. **1984**, *62*, 336–340.



1st step:[248] Methyl 2-hydroxyisobutyrate (6.9 mL, 60 mmol, 1.2 equiv.) was added under a nitrogen atmosphere to a solution of dimethyl amino pyridine (1.22 g, 10 mmol, 0.2 equiv.), triethylamine (10 mL, 50 mmol, 1 equiv.) and triethylchlorosilane (6.7 mL, 50 mmol, 1 equiv.) in 50 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 24 hours. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1 x 50 mL). The solvent was removed under reduced pressure to give the corresponding triethylsilyl ether, which was used as such without further purification. Dimethyl methyl phosphonate (13.8 mL, 130 mmol, 2.5 equiv.) in dry THF (40 mL) was added dropwise to a cold solution of *n*BuLi (1.6 M in hexanes, 79 mL, 130 mmol, 2.5 equiv.) in dry THF (80 mL) at –78 °C under a nitrogen atmosphere. After 30 min of stirring at the same temperature, a solution of the crude triethylsilyl ether (16 g, 50 mmol, 1 equiv.) in dry THF (100 mL) was added dropwise at –78 °C. The mixture was stirred at the same temperature (–78 °C) for 3 h and then quenched at this temperature with a saturated NH_4Cl solution (200 mL). The reaction mixture was allowed to reach room temperature, it was extracted with diethyl ether (3 x 250 mL) and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure to get phosphonic acid dimethyl ester, which was used for the next step without further purification. Yield: 99%, (16.0 g, 49.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.79 (d, *J* = 11.2 Hz, 6H), 3.39 (d, *J* = 20.7 Hz, 2H), 1.36 (s, 6H), 1.05 – 0.86 (m, 9H), 0.74 – 0.56 (m, 6H).

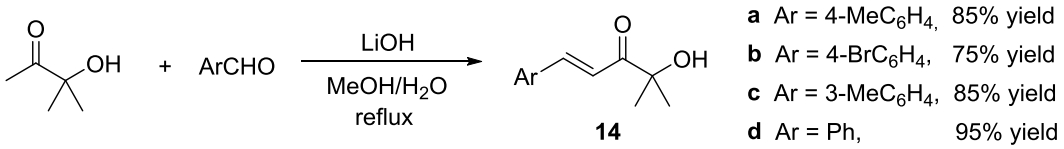
2nd step: Dried LiCl (1.17 g, 27 mmol, 1 equiv.) and Et_3N (3.8 mL, 27 mmol, 1 equiv.) were added successively to a solution of (3-methyl-2-oxo-3-triethylsilyloxybutyl)phosphonic acid dimethyl ester (8.7 g, 27 mmol) in dry MeCN (67 mL). The resulting milky suspension was stirred for 15 min at room temperature and the formaldehyde (37% in water; 5.4 mL, 54 mmol, 2 equiv.) was added dropwise. The mixture was stirred for 40 h, diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. to afford the crude product that was purified by flash silica gel chromatography (hexane/EtOAc, 95:5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.37 (dd, *J* = 17.4, 2.1 Hz, 1H), 5.71 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.36 (s, 6H), 1.06 – 0.85 (m, 9H), 0.71 – 0.53 (m, 6H).

[248] Adapted from: a) P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem.* **1986**, *51*, 2525–2529. b) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll, S. E. Lawrence, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667–3675.

*5.4.1.2. Preparation of β-substituted α'-hydroxy enones **14***

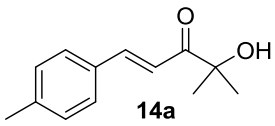
Preparation of β-aryl substituted α'-hydroxy enones 14a-14d

Enones **14a-14d** were synthesised following the procedure previously described in our group:[249]



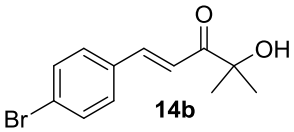
3-Hydroxy-3-methyl-2-butanone (5.0 g, 30 mmol, 1 equiv.) was dissolved in a mixture of MeOH (90 mL) and H_2O (30 mL). Freshly distilled aldehyde (60 mmol, 2 equiv.) was then added followed by $LiOH \cdot H_2O$ (5.0 g, 120 mmol, 4 equiv.). The reaction mixtue was stirred at reflux for 3 h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$ and concentrated, and the crude product was purified by column chromatography (silca gel, hexane/EtOAc 90:10).

(*E*)-4-hydroxy-4-methyl-1-(p-tolyl)pent-1-en-3-one (14a)



The title compound **14a** was prepared using 4-methylbenzaldehyde (3.4 mL, 60 mmol, 2 equiv.) according to the general procedure. Yellow oil. Yield: 75% (4.4 g, 23 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.6 Hz, 1H), 7.50 (dd, *J* = 7.3, 1.1 Hz, 2H), 7.29 – 7.16 (m, 2H), 6.99 (d, *J* = 15.7 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 202.3, 145.2, 141.2, 131.4, 129.4, 128.8, 128.4, 126.7, 117.3, 75.3, 26.2, 21.2.

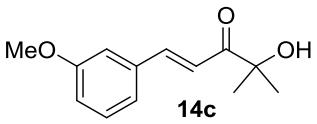
(*E*)-1-(4-bromophenyl)-4-hydroxy-4-methylpent-1-en-3-one (14b)



The title compound **14c** was prepared using 4-methylromobenzaldehyde (10 g, 60 mmol, 2 equiv.) according to the general procedure. Yellow oil. Yield: 85% (6.5 g, 25.5 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 15.8 Hz, 1H), 7.52 – 7.31 (m, 4H), 7.09 (d, *J* = 15.7 Hz, 1H), 4.11 (s, 1H), 1.41 (s, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 202.1, 143.4, 132.9, 131.8, 129.6, 124.8, 119.0, 75.5, 26.1.

[249] a) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189. b) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

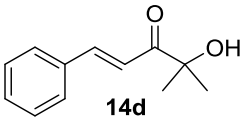
(*E*)-4-hydroxy-1-(3-methoxyphenyl)-4-methylpent-1-en-3-one (14c)



14c

The title compound **14d** was prepared using 3-methoxybenzaldehyde (6.6 mL, 60 mmol, 2 equiv.) according to the general procedure. Yellow oil. Yield: 75% (4.6 g, 24 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 15.7 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.15 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.92 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 4.04 (s, 1H), 3.79 (s, 3H), 1.43 (s, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 202.3, 159.7, 145.1, 135.5, 129.8, 121.0, 118.6, 116.4, 113.5, 75.5, 55.1, 26.3.

(*E*)-4-hydroxy-4-methyl-1-phenylpent-1-en-3-one (14d)[250]

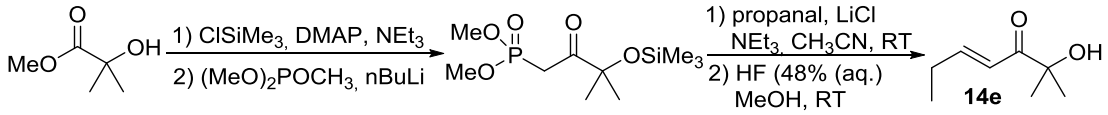


14d

The title compound **14b** was prepared using benzaldehyde (6.1 mL, 60 mmol, 2 equiv.) according to the general procedure. Yellow oil. All data were consistent with those previously reported. Yield: 95% (5.4 g, 28 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, *J* =15.7 Hz, 1H), 7.58 (m, 2H), 7.40 (m, 3H), 7.02 (d, *J* =15.4 Hz, 1H), 4.00 (s, 1H), 1.45 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 7.83 (d, *J* =15.7 Hz, 1H), 7.58 (m, 2H), 7.40 (m, 3H), 7.02 (d, *J* =15.4 Hz, 1H), 4.00 (s, 1H), 1.45 (s, 6H).

Preparation of (E)-2-hydroxy-2-methylhept-4-en-3-one (14e)

Known compound **14e**[251] was prepared according to the following synthetic sequence:



14e

1st step:[252] Methyl 2-hydroxyisobutyrate (6.9 mL, 60 mmol, 1.2 equiv.) was added under a nitrogen atmosphere to a solution of dimethyl amino pyridine (1.22 g, 10 mmol, 0.2 equiv.), triethylamine (10 mL, 50 mmol, 1 equiv.) and trimethylchlorosilane (6.3 mL, 50 mmol, 1 equiv.) in 50 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 24 hours. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1

[250] C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

[251] A. R. Katritzky, D. Feng, H. Lang, *J. Org. Chem*. **1997**, *62*, 706–714.

[252] Adapted from: a) P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem*. **1986**, *51*, 2525–2529. b) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll, S. E. Lawrence, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667–3675.

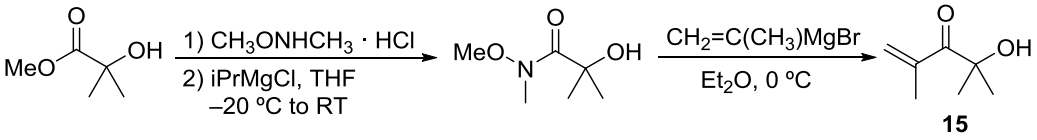
x 50 mL) and water (1 x 50 mL). The solvent was removed under reduced pressure to give the trimethylsilyl ether, which was used as such without further purification. Dimethyl methyl phosphonate (13.8 mL, 130 mmol, 2.5 equiv.) in dry THF (40 mL) was added dropwise to a cold solution of *n*BuLi (1.6 M in hexanes, 79 mL, 130 mmol, 2.5 equiv.) in dry THF (80 mL) at –78 °C under a nitrogen atmosphere. After 30 min of stirring at the same temperature, a solution of the crude triethylsilyl ether (16 g, 50 mmol, 1 equiv.) in dry THF (100 mL) was added dropwise at –78 °C. The mixture was stirred at the same temperature (–78 °C) for 3 h and then quenched at this temperature with a saturated NH_4Cl solution (200 mL). The reaction mixture was allowed to reach room temperature, it was extracted with diethyl ether (3 x 250 mL) and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure to get phosphonic acid dimethyl ester, which was used for the next step without further purification. Yield: 99%, (14.6 g, 49.5 mmol).

2nd step: Dried LiCl (1.17 g, 27 mmol, 1 equiv.) and Et_3N (3.8 mL, 27 mmol, 1 equiv.) were added successively to a solution of (3-methyl-2-oxo-3-trimethylsilyloxybutyl)phosphonic acid dimethyl ester (8.0 g, 27 mmol) in dry MeCN (67 mL). The resulting milky suspension was stirred for 15 min at room temperature and the propanal (3.9 mL, 54 mmol, 2 equiv.) was added dropwise. The mixture was stirred for 40 h, diluted with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude was dissolved in methanol (200 mL) and a solution of hydrofluoric acid (HF) (48% in water, 5 mL) was added. The resulting mixture was stirred for 0.5 h at room temperature and then was neutralized by addition of a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude desilylated product that was purified by flash silica gel chromatography (hexane/EtOAc, 98:2). Colourless oil. All spectroscopic data were consistent with those previously reported. Yield: 75% (3.2 mg, 20 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 1H), 6.46 (d, *J* = 15.4 Hz, 1H), 4.09 (s, 1H), 2.30 –2.20 (m, 2H), 1.55 – 1.43 (m, 2H), 1.40 (s, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

*5.4.1.3. Preparation of α-methyl α'-oxy enones **15***

Preparation of α-methyl α'-hydroxy enone 15

Known enone **15**[253] was prepared according to the following procedure:



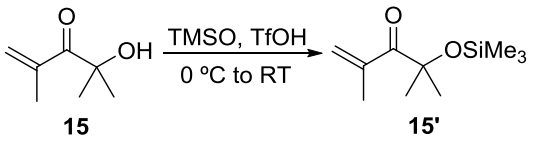
1st step: To a solution of methyl 2-hydroxy-2-methylpropanoate (1.77 g, 15 mmol, 1 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv.) in dry THF (50 mL), ^{i}PrMgCl (2 M in THF; 60 mmol, 4 equiv.) was added at –20 ºC and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried over $MgSO_4$ and filtered and the solvent was evaporated under reduced pressure and crude material was purified by flash column chromatography (hexane/EtOAc, 80:20) to obtain the desired amide product as colourless oil. Yield: 90% (1.99 g, 13.5 mmol). All spectroscopic data were consistent with those previously reported.[254] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.29 (s, 1H), 3.73 (s, 3H), 3.28 (s, 3H), 1.47 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.2, 72.1, 61.0, 33.6, 26.5.

2nd step: To a solution of the starting amide (1.85 g, 10 mmol, 1 equiv.) in Et_2O (20 mL), isopropenyl magnesium bromide (0.5 M in THF; 60 mL, 3 equiv.) was added at –20 ºC, and the resulting mixture was stirred at 0 ºC for 16 h. The reaction was quenched with a saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O 95:5) to obtain the desired product **15** as a colourless oil. Yield: 65% (833 mg, 6.5 mmol). All spectroscopic data were consistent with those previously reported. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.75 (s, 1H), 4.11 (s, 1H), 1.86 (s, 3H), 1.42 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.3, 140.3, 125.6, 72.0, 28.3, 19.9.

[253] A. Basheer, M. Mishima, I. Marek, *Org. Lett.* **2011**, *13*, 4076–4079.

[254] F. Miege, B. M. Trost, *J. Am. Chem. Soc*. **2014**, *136*, 3016–3019.

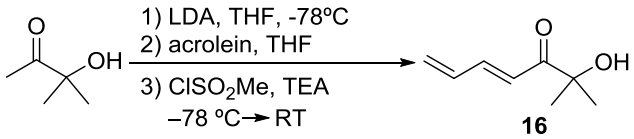
Preparation of α-methyl α'-trimethylsilyloxy enone 15



3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (1.1 mL, 7.5 mmol, 1.5 equiv.) and a drop of trifluoromethanesulfonic acid were added to enone **15** (640 mg, 5.0 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 2 h, diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was then dried over with $MgSO_4$ and concentred under reduced pressure to afford the title compound **15'** as a yellow oil. Yield: 82% (820 mg, 4.1 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.78 (s, 1H), 1.89 (s, 3H), 1.46 (s, 6H), 0.10 (s, 9H).

*5.4.1.4. Preparation of α'-oxy dienones **16***

Preparation of α'-hydroxy dienone 16[255]

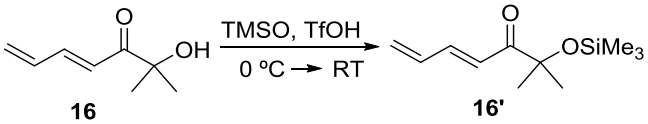


3-Hydroxy-3-methyl-2-butanone (2.1 mL, 20 mmol, 1 equiv.) in THF (2.5 mL) was slowly added to a solution of *n*-butyllithium (1.6 M in Et_2O; 32 mL, 50 mmol, 2.5 equiv.) and diisopropylamine (7.7 mL, 50 mmol, 1.5 equiv.) in THF (25 mL) at –78 ºC and the resulting solution was stirred at the same temperature for 5 min. Next, acrolein (1.23 g, 22 mmol, 1.1 equiv.) in THF (2.5 mL) was added over a 10 min period and then *p*-toluenesulfonyl chloride (1.84 mL, 24 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred until completion of the reaction (TLC monitoring). The solvent was eliminated under reduced pressure and the residue was redissolved in CH_2Cl_2 (80 mL). The organic phase was then washed with water (80 mL) and a saturated solution of NH_4Cl (80 mL), dried over with $MgSO_4$ and concentred under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (eluting hexane/EtOAc 80:20). Yellow oil. Yield: 75% (2.1 g, 15 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 –

[255] Adapted from: L. Bernardi, J. López-Cantero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.

7.36 (m, 1H), 6.59 – 6.42 (m, 2H), 5.79 – 5.59 (m, 2H), 3.94 (s, 1H), 1.39 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.7, 145.4, 134.9, 128.0, 122.6, 75.4, 26.3.

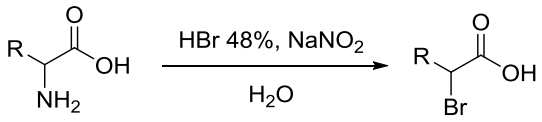
Preparation of α'-trimethylsilyloxy dienone 16'

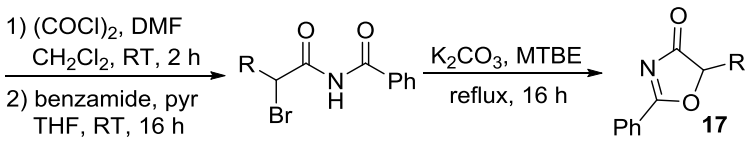


3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (1.1 mL, 7.5 mmol, 1.5 equiv.) and a drop of trifluoromethanesulfonic acid were added to dienone **16** (700 mg, 5.0 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 2 h, diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was then dried over with $MgSO_4$ and concentred under reduced pressure to afford the title compound **16'** as a yellow oil. Yield: 88% (934 mg, 4.4 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 15.4, 11.0 Hz, 1H), 6.81 (d, *J* = 15.4 Hz, 1H), 6.62 – 6.42 (m, 1H), 5.76 – 5.50 (m, 2H), 1.37 (s, 6H), 0.14 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.2, 143.5, 135.6, 126.3, 124.6, 30.9, 27.2, 2.2.

5.4.2. Preparation of 5*H*-oxazol-4-ones (oxazolones) 17

Known oxazolones **17A-17D** and new oxazolone **17E** were prepared according to the synthetic sequence described by Misaki and Sugimura:[256]





1st step:[257] The corresponding amino acid (40 mmol, 1 equiv.) is solubilized in 48% HBr (40 mL) and 36 mL water. The reaction mixture was cooled to 0 °C and a solution of $NaNO_2$ (4.4 g, 64 mmol, 1.6 equiv.) in 10 mL water was added dropwise. The mixture was stirred for 2.5 h at room temperature, then concentrated to remove acid

[256] T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.

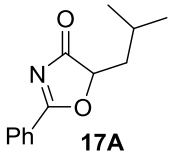
[257] Z. P. Kortylewicz, R. E. Galardy, *J. Med. Chem.* **1990**, *33*, 263-273.

vapour, and extracted with Et_2O (4 x 10 mL). The organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure yielding the corresponding 2-bromo-carboxylic acid as colorless oil, which was used without further purification.

2nd step:[258] A solution of oxalyl chloride (1.0 mL, 12 mmol, 1.2 equiv.) in dry dichloromethane (6 mL) was added slowly to a stirred solution of the corresponding bromoacid (10 mmol, 1 eq.) in dichloromethane (0.5 mL/mmol) at 0 ºC, then 2 drops of DMF were added. Gas evolution was observed, and the system was allowed to stir at room temperature for 2 additional hours. Volatiles were removed under reduced pressure and the resulting crude material was added over 5 min to a suspension of benzamide (1.2 g, 10 mmol, 1.0 eq.) and pyridine (0.81 mL, 10 mmol, 1.0 eq.) in THF (12.5 mL) at 0 °C. The resulting suspension was stirred overnight at room temperature and diluted with EtOAc. The mixture was acidified to pH 2 with HCl 1 M and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with water (3 x 20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered. Volatiles were removed under reduced pressure. The imide product was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 90:10).

3rd step:[256] A suspension of K_2CO_3 (2.0 g, 20 mmol, 2.0 equiv.) in methyl tert-butylether (MTBE) (20 mL) was refluxed for 2 h to remove water using a Dean-Stark trap. The suspension was cooled to room temperature and the corresponding imide was added in one portion. The resulting mixture was refluxed overnight and cooled to room temperature. Inorganic salts were filtered through a celite pad with suction and the filter cake was washed with EtOAc. The combined organic layers were concentrated in vacuo and the crude material was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 80:20).

5-isobutyl-2-phenyloxazol-4(5*H*)-one (17A) [259]



17A

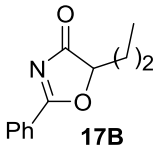
The title compound **17A** was prepared from 2-bromo-4-methylpentanoic acid (2.0 g, 10 mmol) according to the general procedure. White solid. All data were consistent with those previously reported. m. p. = 57–59 ºC. Yield: 54% (1.2 g, 5.4 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.15 (m, 2H), 7.74 – 7.63 (m, 1H), 7.59 – 7.47 (m, 2H), 4.79 (dd, *J* = 10.0, 3.5 Hz, 1H), 2.11 – 1.82 (m, 2H), 1.77 – 1.62 (m, 1H), 1.04 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR** (75 MHz,

[258] Adapted from: T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.

[259] D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527.

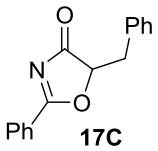
$CDCl_3$), δ 192.2, 186.3, 135.1, 130.0, 128.9, 125.9, 80.8, 40.2, 25.5, 22.8, 21.9. **MS:** calculated for $C_{13}H_{16}NO_2$ ($M + H^+$), 218.1181; found, 218.1183.

2-phenyl-5-propyloxazol-4(5*H*)-one (17B)[260]



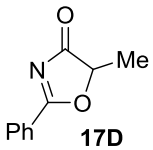
The title compound **17B** was prepared from 2-bromopentanoic acid (1.8 g, 10 mmol) according to the general procedure. White solid. All data were consistent with those previously reported. m. p. = 55–56 ºC. Yield: 24% (480 mg, 2.4 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 2H), 7.76 – 7.65 (m, 1H), 7.60 – 7.47 (m, 2H), 4.79 (dd, *J* = 7.7, 4.5 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.93 – 1.78 (m, 1H), 1.56 (dq, *J* = 14.8, 7.5 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 192.3, 186.9, 135.5, 130.5, 129.4 126.3, 82.2, 33.6, 18.5, 14.0. **MS:** calculated for $C_{12}H_{14}NO_2$ ($M + H^+$), 204.1021; found, 204.1024.

5-benzyl-2-phenyloxazol-4(5*H*)-one (17C)[261]



The title compound **17C** was prepared from 2-bromo-3-phenylpropanoic acid (2.3 g, 10 mmol) according to the general procedure. All data were consistent with those previously reported. White solid. m. p. = 97–98 ºC. Yield: 34% (850 mg, 3.4 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.70 – 7.62 (m, 1H), 7.49 (dd, *J* = 10.6, 4.8 Hz, 2H), 7.29 – 7.20 (m, 5H), 4.98 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.43 (dd, *J* = 14.8, 4.0 Hz, 1H), 3.12 (dd, *J* = 14.8, 7.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 190.9, 186.4, 135.2, 134.6, 130.0, 129.3, 128.9, 128.6, 127.3, 125.6, 81.9, 37.3. **MS:** calculated for $C_{16}H_{14}NO_2$ ($M + H^+$), 252.1025; found, 252.1024.

5-methyl-2-phenyloxazol-4(5*H*)-one (17D)[256]

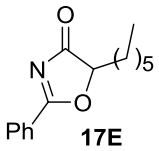


The title compound **17D** was prepared from 2-bromopropanoic acid (1.5 g, 10 mmol) according to the general procedure. White solid. All data were consistent with those previously reported. m. p. = 68–70 ºC. Yield: 62% (1.1 g, 6.2 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.15 – 7.99 (m, 2H), 7.64 – 7.46 (m, 1H), 7.46 – 7.35 (m, 2H), 4.72 (q, 1H), 1.49 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 192.0, 185.8, 134.8, 129.6, 128.5, 125.4, 77.6, 16.0. **MS:** calculated for $C_{10}H_{10}NO_2$ ($M + H^+$), 176.0712; found, 176.0717.

[260] H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461–463.

[261] B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945.

5-pentyl-2-phenyloxazol-4(5*H*)-one (17E)

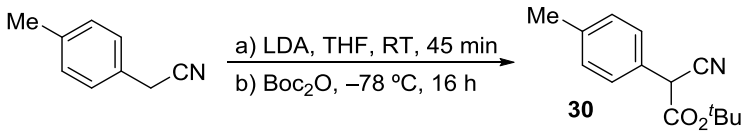


17E

The title compound **17E** was prepared from 2-bromopropanoic acid (1.5 g, 10 mmol) according to the general procedure. White solid. m. p. = 69–70 ºC. Yield: 44% (1.1 g, 4.4 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.76 – 7.63 (m, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 4.78 (dd, *J* = 7.6, 4.5 Hz, 1H), 2.19 – 2.00 (m, 1H), 1.86 (td, *J* = 14.8, 7.6 Hz, 1H), 1.51 (dt, *J* = 15.7, 6.9 Hz, 2H), 1.33 (ddd, *J* = 11.2, 8.1, 4.5 Hz, 6H), 0.87 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$), δ 8.23 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.76 – 7.63 (m, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 4.78 (dd, *J* = 7.6, 4.5 Hz, 1H), 2.19 – 2.00 (m, 1H), 1.86 (td, *J* = 14.8, 7.6 Hz, 1H), 1.51 (dt, *J* = 15.7, 6.9 Hz, 2H), 1.33 (ddd, *J* = 11.2, 8.1, 4.5 Hz, 6H), 0.87 (t, *J* = 6.7 Hz, 3H). **MS:** calculated for $C_{15}H_{20}NO_2$ ($M + H^+$), 246.1494; found, 246.1494.

5.4.3. Preparation of α-cyanoacetate 30

α-Cyanoacetate **30** was synthesised according to the procedure previously described in the literature:[262]



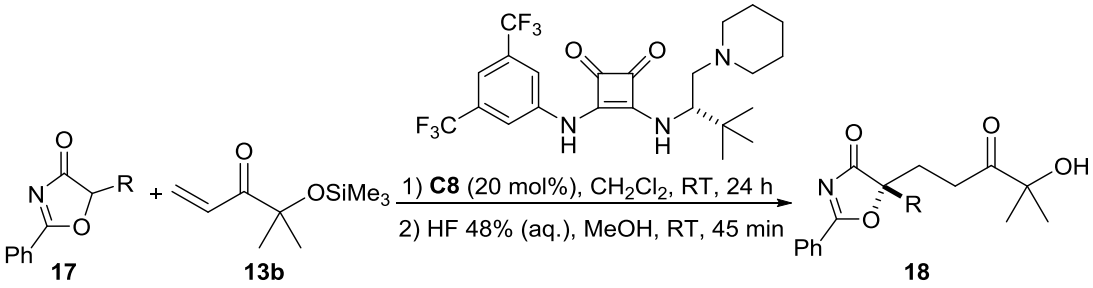
30

A solution of 2-(p-tolyl)acetonitrile (1.3 g, 10 mmol, 1 equiv.) in THF (10 mL) was added dropwise to a solution of LDA (3.1 mL, 25 mmol, 2.5 equiv.) in THF (30 mL) cooled to −78 ºC. The reaction mixture was allowed to stir at –78 ºC for 45 min. and then at room temperature for an additional 45 minutes. Then it was cooled to −78 ºC and a solution of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise *via* syringe. After stirring at −78 ºC for 16 hours, the mixture was quenched with saturated ammonium chloride (20 mL) and extracted with Et_2O (3 x 50 mL). The organic layer was washed with 1 N HCl (30 mL), brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified by silica gel flash chromatography (hexane/EtOAc 95:5) to yield the desired cyanoester **30** as a clear oil. The characterization data were coincident with the previously reported. Yield: 75% (1.7 g, 7.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.56 (s, 1H), 2.36 (s, 3H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3, 139.1, 130.1, 127.8, 116.3, 84.5, 44.6, 27.8, 21.3.

[262] S. Jautze, R. Peters, *Angew. Chem. Int. Ed.* **2008**, *47*, 9284–9288.

5.4.4. 1,4-addition of oxazolones to unsubstituted α'-silyloxy enone 13b

5.4.4.1. General procedure

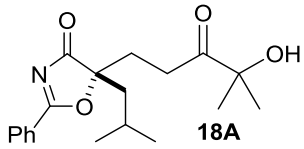


To a mixture of the corresponding oxazolone **17** (1 equiv., 0.3 mmol) and the enone **13b** (83.9 mg, 3.0 equiv., 0.9 mmol), in CH_2Cl_2 (0.9 mL) at room temperature the catalyst **C8** (20 mol%) was added. The resulting suspension was stirred at the same temperature until consumption of the oxazolone (monitored by ^{1}H-NMR). Then, 3 mL of methanol and 0.6 mL of aqueous HF 48% were added and the mixture was stirred for 45 min. The reaction was treated at 0 ºC with saturated solution of $NaHCO_3$ until pH 7. The product was extracted from the aqueous phase with CH_2Cl_2 (3 x 3 mL) and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the title products **18**, which were purified by flash column chromatography (eluting hexane/EtOAc 80:20).

Racemic reactions were conducted following the procedure for the asymmetric version using enone **13a** (3 equiv.) and TEA (20 mol%) as the catalyst.

*5.4.4.2. Characterization data for compounds **18***

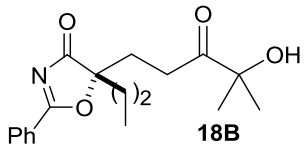
(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-2-phenyloxazol-4(5*H*)-one (18A)



The title compound was obtained following the general procedure from oxazolone **17A** (65 mg, 0.30 mmol). Colourless oil. Yield: 80% (79 mg, 0.24 mmol). **[α]**$_D^{22}$ = +10.7º (*c* = 1.00, 93% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.22 – 8.09 (m, 2H), 7.73 – 7.61 (m, 1H), 7.57 – 7.46 (m, 2H), 3.56 (s, 1H), 2.57 – 2.47 (m, 1H), 2.38 – 2.23 (m, 1H), 2.22 – 2.08 (m, 1H), 2.04 – 1.84 (m, 2H), 1.82 – 1.64 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H), 0.88 (dd, *J* = 10.0, 6.4 Hz, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 212.7, 193.4, 185.6, 130.0, 129.0, 125.4, 90.2, 76.4, 60.3, 44.4, 29.7, 29.0, 26.4, 23.9, 23.3, 14.1. **MS:** calculated for $C_{19}H_{26}NO_4$ (M + H $^+$), 332.1862;

found, 332.1866. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 85:15; flux = 1 mL/min; retention times: 18.1 min (major), 22.4 min (minor)).

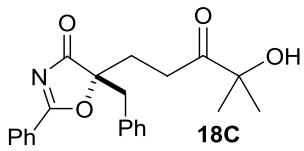
(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-2-phenyl-5-propyloxazol-4(5*H*)-one (18B)



18B

The title compound was obtained following the general procedure from oxazolone **17B** (61 mg, 0.30 mmol). Colourless oil. Yield: 86% (52 mg, 0.26 mmol). **[α]**$_D^{22}$ = +58.4º (*c* = 1.00, 92% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.29 – 8.15 (m, 2H), 7.77 – 7.64 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 3.62 (s, 1H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.40 – 2.13 (m, 2H), 1.93 (ddd, *J* = 10.0, 5.8, 4.0 Hz, 2H), 1.40 – 1.15 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 212.7, 193.1, 185.7, 135.3, 130.0, 128.9, 125.3, 90.3, 76.3, 37.9 29.4, 29.1, 26.4, 16.2, 13.7. **MS:** calculated for $C_{18}H_{24}NO_4$ (M + H $^+$), 318.1705; found, 318.1697. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 36.3 min (major), 39.5 min (minor)).

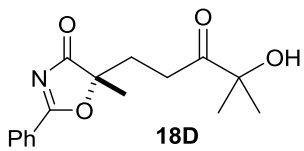
(*R*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (18C)



18C

The title compound was obtained following the general procedure from oxazolone **17C** (75 mg, 0.30 mmol). Colourless oil. Yield: 73% (80 mg, 0.22 mmol). **[α]**$_D^{22}$ = +44.6º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 6.0 Hz, 5H), 3.61 (s, 1H), 3.20 (s, 2H), 2.60 (dd, *J* = 10.8, 5.3 Hz, 2H), 2.34 (dd, *J* = 15.2, 7.5 Hz, 2H), 1.26 (s, 3H), 1.22 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 212.6, 192.4, 185.4, 135.2, 132.8, 129.8, 128.8, 128.3, 127.4, 125.2, 90.1, 76.4, 42.2, 29.3, 29.2, 26.4. **MS:** calculated for $C_{22}H_{24}NO_4$ (M + H $^+$), 366.1705; found, 366.1708. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 85:15; flux = 1 mL/min; retention times: 28.0 min (minor), 32.8 min (major)).

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenyloxazol-4(5*H*)-one (18D)

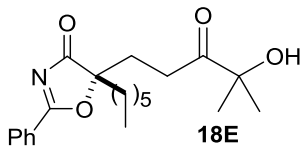


18D

The title compound was obtained following the general procedure from oxazolone **17D** (53 mg, 0.30 mmol). Colourless oil. Yield: 86% (52 mg, 0.26 mmol). **[α]**$_D^{22}$ = –25.6º (*c* = 1.00, 92% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.30 – 8.14 (m, 2H), 7.77 – 7.66 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 2.59 (t, *J* =

7.5 Hz, 2H), 2.46 – 2.13 (m, 3H), 1.62 (s, 4H), 1.32 (s, 3H), 1.28 (s, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 212.5, 193.4, 185.4, 135.4, 130.2, 129.1, 87.1, 30.4, 29.4, 26.6, 22.3. **MS:** calculated for $C_{16}H_{20}NO_4$ (M + H $^+$), 290.1392; found, 290.1381. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 89.1 min (major), 102.1 min (minor)).

(*S*)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (18E)

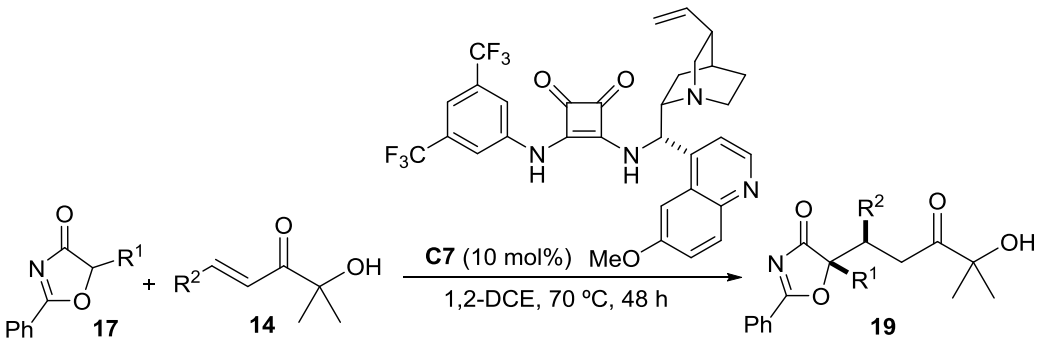


18E

The title compound was obtained following the general procedure from oxazolone **17E** (84 mg, 0.30 mmol). Colourless oil. Yield: 79% (61 mg, 0.21mmol). **[α]**$_D^{22}$ = +10.6º (*c* = 1.00, 97% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.07 (m, 2H), 7.76 – 7.60 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.41 – 2.09 (m, 2H), 1.89 (d, *J* = 3.9 Hz, 2H), 1.34 – 1.08 (m, 14H), 0.78 (t, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 213.4, 193.8, 186.3, 135.9, 130.7, 129.6, 126.0, 91.0, 77.0, 36.6, 31.9, 30.0, 29.8, 29.5 27.1, 23.3, 22.9, 14.5. **MS:** calculated for $C_{21}H_{30}NO_4$ (M + H $^+$), 360.2175; found, 360.2170. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 66.6 min (major), 72.7 min (minor)).

5.4.5. 1,4-addition of oxazolones to β-substituted α'-hydroxy enones 14

5.4.5.1. General procedure



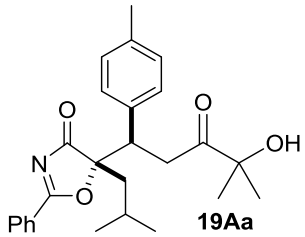
To a mixture of the corresponding oxazolone **17** (0.15 mmol, 1 equiv.) and the corresponding enone **14** (0.45 mmol, 3.0 equiv.), in 1,2-dichloroethane (0.45 mL) at 70 ºC, catalyst **C7** (9.5 mg, 10 mol%) was added. The resulting mixture was stirred at the same temperature until consumption of the starting oxazolone as monitored by ^{1}H-

NMR. The crude product was purified by flash column chromatography (eluting hexane/EtOAc 80:20).

The same above procedure was followed except that reactions were run at 50 ºC and DBU was used as the catalyst instead of **C7**.

*5.4.5.2. Characterization data for compounds **19***

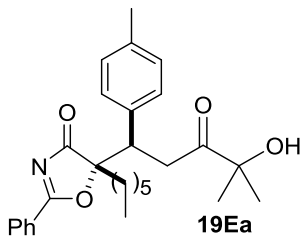
(*S*)-5-((*R*)-4-Hydroxy-4-methyl-3-oxo-1-(p-tolyl)pentyl)-5-isobutyl-2-phenyloxazol-4(5*H*)-one (19Aa)



19Aa

The title compound was obtained following the general procedure from oxazolone **17A** (33 mg, 0.15 mmol) and enone **14a** (92 mg, 0.45 mmol) in a 13:1 *dr*. Yellow oil. Yield: 67% (43 mg, 0.10 mmol). Data of major isomer: $[\alpha]_D^{25}$ = –45.4º (*c* = 1.00, 99% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.18 – 8.08 (m, 2H), 7.74 – 7.62 (m, 1H), 7.52 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.17 – 7.08 (m, 2H), 7.05 – 6.95 (m, 2H), 3.85 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.45 – 3.24 (m, 2H), 2.72 (dd, *J* = 17.5, 3.3 Hz, 1H), 2.21 (s, 3H), 1.80 (dd, *J* = 6.2, 4.2 Hz, 2H), 1.64 – 1.52 (m, 1H), 1.23 (s, 3H), 1.04 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 211.1, 193.4, 185.7, 137.2, 135.2, 134.0, 129.9, 129.0, 128.8, 125.4, 92.8, 76.3, 46.3, 43.6, 35.8, 26.0, 24.1, 23.8, 20.9. **MS:** calculated for $C_{26}H_{32}NO_4$ (M + H $^+$), 422.2331; found, 422.2314. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IB, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 18.8 min (minor), 18.8 min (major)).

(*S*)-5-Hexyl-5-((*R*)-4-hydroxy-4-methyl-3-oxo-1-(p-tolyl)pentyl)-2-phenyloxazol-4(5*H*)-one (19Ea)

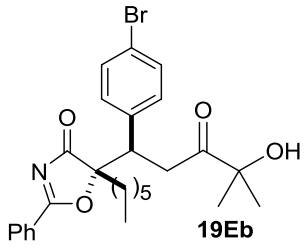


19Ea

The title compound was obtained following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) and enone **14a** (92 mg, 0.45 mmol) in a 13:1 *dr*. Yellow oil. Yield: 80% (55 mg, 0.12 mmol). Data of major isomer: $[\alpha]_D^{25}$ = –53.6º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.23 – 8.13 (m, 2H), 7.78 – 7.63 (m, 1H), 7.60 – 7.48 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 3.86 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.27 (dd, *J* = 17.4, 10.8 Hz, 1H), 2.70 (dd, *J* = 17.4, 3.3 Hz, 1H), 2.24 (s, 3H), 1.21 (s, 3H), 1.13 (m, 8H), 1.04 (s, 3H), 0.81 – 0.72 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 210.9, 193.2,

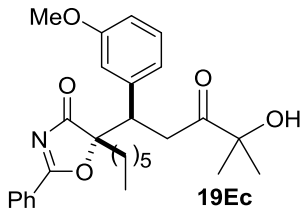
185.8, 137.3, 135.3, 134.3, 130.0, 129.1, 129.0, 128.8, 125.3, 93.2, 76.3, 45.8, 36.1, 35.2, 31.3, 28.9, 26.0, 22.7, 22.3, 21.0, 13.8. **MS:** calculated for $C_{28}H_{36}NO_4$ (M + H $^+$), 450.2666; found, 450.2626. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 80:20; flux = 1 mL/min; retention times: 9.5 min (minor), 11.2 min (major)).

(*S*)-5-((*R*)-1-(4-Bromophenyl)-4-hydroxy-4-methyl-3-oxopentyl)-5-hexyl-2-phenyloxazol-4(5*H*)-one (19Eb)



The title compound was obtained following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) and enone **14b** (115 mg, 0.45 mmol) in a 12:1 *dr*. White soldi. m. p. = 125-127 ºC. Yield: 78% (60 mg, 0.12 mmol). Data of major isomer: **[α]**$_D^{25}$ = –57.3º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.68 – 7.59 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.82 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.69 (s, 1H), 3.30 (dd, *J* = 18.0, 10.9 Hz, 1H), 2.76 (dd, *J* = 17.9, 3.1 Hz, 1H), 1.88 – 1.85 (m, 1H), 1.70 – 1.57 (m, 1H), 1.10 – 1.00 (m, 14H), 0.75 – 0.65 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 210.9, 192.6, 185.7, 136.6, 135.3, 131.2, 130.5, 129.8, 128.9, 124.8, 121.4, 92.6, 76.3, 45.3, 35.9, 34.9, 31.0, 28.6, 25.8, 25.8, 22.4, 22.1, 13.6. **MS:** calculated for $C_{27}H_{33}BrNO_4$ (M + H $^+$), 514.1593; found, 514.1594. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 14.2 min (minor), 19.7 min (major)).

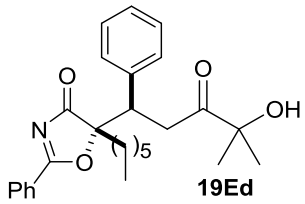
(*S*)-5-Hexyl-5-((*R*)-4-hydroxy-4-methyl-3-oxo-1-(p-tolyl)pentyl)-2-phenyloxazol-4(5*H*)-one (19Ec)



The title compound was obtained following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) and enone **14c** (103 mg, 0.45 mmol) in a 12:1 *dr*. Yellow oil. Yield: 81% (57 mg, 0.12 mmol). Data of major isomer: **[α]**$_D^{25}$ = –54.4º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.74 – 7.64 (m, 1H), 7.54 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.16 (t, *J* = 7.9 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.72 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.86 (dd, *J* = 10.6, 3.3 Hz, 1H), 3.74 (s, 3H), 3.41 (s, 1H), 3.26 (dd, *J* = 17.5, 10.7 Hz, 1H), 2.69 (dd, *J* = 17.4, 3.3 Hz, 1H), 1.94 – 1.80 (m, 1H), 1.79 – 1.64 (m, 1H), 1.20 (s, 3H), 1.17 – 1.06 (m, 8H), 1.05 (s, 3H), 0.80 – 0.73 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 210.8, 193.0, 185.99, 159.3, 139.0, 135.3, 130.0, 129.3, 129.0, 125.3, 121.2, 115.2, 112.7, 93.0, 76.3, 55.1.0, 46.2, 36.0, 35.1, 31.3, 28.9, 26.0, 22.7, 22.3, 13.8. **MS:**

calculated for $C_{27}H_{33}NO_4$ (M + H $^+$), 466.2593; found, 466.2577. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IB, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 11.9 min (minor), 14.0 min (major)).

(*S*)-5-Hexyl-5-((*R*)-4-hydroxy-4-methyl-3-oxo-1-phenylpentyl)-2-phenyloxazol-4(5*H*)-one (19Ed)

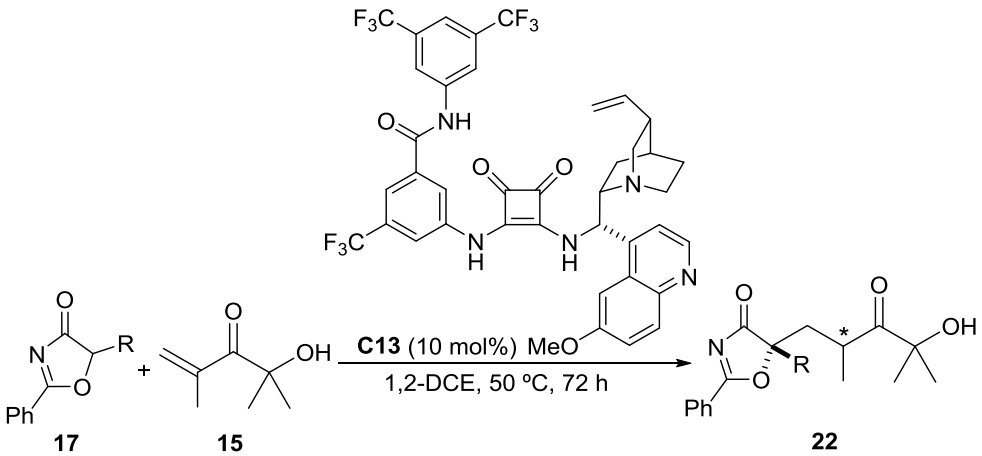


19Ed

The title compound was obtained following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) and enone **14d** (79 mg, 0.45 mmol) in a 12:1 *dr*. White soldi. m. p. = 125-127 ºC. Yield: 73% (47 mg, 0.11 mmol). Data of major isomer: $[\alpha]_D^{25}$ = –49.9º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.22 – 8.10 (m, 2H), 7.74 – 7.65 (m, 1H), 7.58 – 7.48 (m, 2H), 7.32 – 7.12 (m, 5H), 3.90 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.39 (s, 1H), 3.30 (dd, *J* = 17.5, 10.7 Hz, 1H), 2.74 (dd, *J* = 17.5, 3.3 Hz, 1H), 2.00 – 1.81 (m, 1H), 1.81 – 1.64 (m, 1H), 1.21 (s, 3H), 1.18 – 1.07 (m, 8H), 1.03 (s, 3H), 0.82 – 0.71 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 210.9, 193.0, 185.8, 137.4, 135, 123.0, 129.0, 128.4, 127.7, 125.3, 93.0, 76.3, 46.2, 36.0, 35.2, 31.3, 28.9, 26.0, 22.7, 22.3, 13.8. **MS:** calculated for $C_{27}H_{34}NO_4$ (M + H $^+$), 436.2488; found, 436.2275. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 18.7 min (minor), 20.5 min (major)).

5.4.6. 1,4-addition of oxazolones to α-substituted α'-hydroxy enone 15

5.4.6.1. General procedure



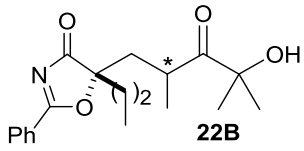
17 **15** **22**

To a mixture of the corresponding oxazolone **17** (0.30 mmol, 2 equiv.) and enone **15** (0.15 mmol, 1 equiv.), in 1,2-dichloroethane (0.45 mL) at 50 ºC, catalyst **C13** (12.3 mg, 10 mol%) was added. The resulting mixture was stirred at the same temperature until consumption of the starting oxazolone as monitored by ^{1}H-NMR. The crude product was submitted to flash column chromatography (eluting hexane/EtOAc 80:20), affording the desired adduct as a mixture of diastereomers.

The same above procedure was followed except DBU was used as the catalyst instead of **C13**.

*5.4.6.2. Characterization data for compounds **22***

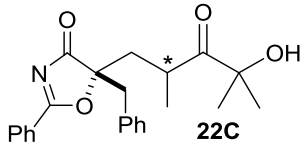
(5*S*)-5-(4-Hydroxy-2,4-dimethyl-3-oxopentyl)-2-phenyl-5-propyloxazol-4(5*H*)-one (22B)



22B

The title compound was obtained following the general procedure from oxazolone **17B** (61 mg, 0.30 mmol) in a 1:1 *dr*. Yellow oil. Yield: 69% (34 mg, 0.10 mmol). Data of major isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 2H), 7.82 – 7.64 (m, 1H), 7.59 – 7.48 (m, 2H), 3.53 (s, 1H), 3.21 – 3.06 (m, 1H), 2.31 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.04 (dd, *J* = 15.0, 6.7 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 1.26 – 1.20 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.8, 193.1, 185.8, 135.4, 130.1, 129.0, 125.6, 90.8, 76.9, 38.8, 38.3, 34.7, 26.7, 26.6, 19.5, 16.2, 13.8. Data of minor isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 3.35 – 3.24 (m, 1H), 2.45 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.00 – 1.95 (m, 1H), 1.96 – 1.78 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 1.26 – 1.20 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.5, 193.7, 185.8, 135.4, 130.1, 129.0, 125.6, 90.4, 76.8, 39.0, 38.1, 34.2, 26.9, 26.6, 12.0, 16.2, 13.8. **MS:** calculated for $C_{19}H_{26}NO_4$ ($M + H^+$), 332.1862; found, 332.1866. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IB, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 17.5 min (major), 28.0 min (minor)).

(5*R*)-5-Benzyl-5-(4-hydroxy-2,4-dimethyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (22C)

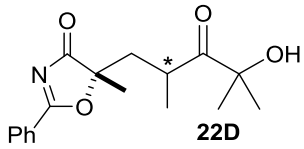


22C

The title compound was obtained following the general procedure from oxazolone **17C** (75 mg, 0.30 mmol) in a 1.5:1 *dr*. Yellow oil. Yield: 77% (44 mg, 0.12 mmol). Data of major

isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.72 – 7.61 (m, 1H), 7.60 – 7.42 (m, 2H), 7.21 – 7.04 (m, 5H), 3.46 (s, 1H), 3.22 (s, 2H), 3.30 – 3.09 (m, 1H), 2.43 (dd, *J* = 15.0, 5.2 Hz, 1H), 2.13 (dd, *J* = 15.0, 7.0 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H).. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.7, 192.4, 185.5, 135.3, 132.7, 129.9, 129.0, 128.4, 127.5, 125.4, 90.6, 76.9, 42.6, 38.5, 34.9, 29.7, 26.7, 26.6, 19.3. Data of minor isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.72 – 7.61 (m, 1H), 7.60 – 7.42 (m, 2H), 7.21 – 7.04 (m, 5H), 3.39 – 3.26 (m, 1H), 3.17 (s, 2H), 2.56 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.07 (dd, *J* = 14.8, 4.7 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.4, 193.0, 185.5, 135.3, 132.8, 129.9, 128.9, 128.4, 127.5, 125.5, 90.2, 77.2, 42.5, 38.8, 34.4, 29.7, 27.0, 26.7, 20.1. **MS:** calculated for $C_{23}H_{25}NO_4$ ($M + H^+$), 379.1784; found, 379.1775. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 51.7 min (major), 112.0 min (minor)).

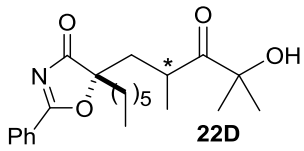
(5*S*)-5-(4-Hydroxy-2,4-dimethyl-3-oxopentyl)-5-methyl-2-phenyloxazol-4(5*H*)-one (22D)



22D

The title compound was obtained following the general procedure from oxazolone **17D** (53 mg, 0.30 mmol) in a 1:1 *dr*. Yellow oil. Yield: 74% (34 mg, 0.11 mmol). Data of major isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.31 – 7.98 (m, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.65 – 7.49 (m, 2H), 3.53 (s, 1H), 3.21 (dt, *J* = 13.1, 6.0 Hz, 1H), 2.36 (dd, *J* = 15.0, 6.3 Hz, 1H), 2.02 (dd, *J* = 14.8, 6.1 Hz, 1H), 1.57 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.7, 193.4, 185.3, 135.4, 130.1, 129.0, 127.8, 87.5, 75.1, 39.6, 34.8, 26.8, 26.7, 22.3, 19.6. Data of minor isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.14 (m, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.64 – 7.50 (m, 2H), 3.49 (s, 1H), 3.30 (dt, *J* = 12.7, 6.3 Hz, 1H), 2.44 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.97 (dd, *J* = 14.5, 5.5 Hz, 1H), 1.59 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.4, 193.4, 185.3, 132.8, 130.1, 129.0, 128.8, 127.8, 87.5, 75.1, 39.8 34.5, 26.9, 26.7, 22.4, 19.7. **MS:** calculated for $C_{17}H_{22}NO_4$ ($M + H^+$), 304.1549; found, 304.1552. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA+AY-H, hexane/isopropanol, 80:20; flux = 0.5 mL/min; retention times: 33.2 min (major), 57.8 min (minor)).

(5*S*)-5-Hexyl-5-(4-hydroxy-2,4-dimethyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (22B)

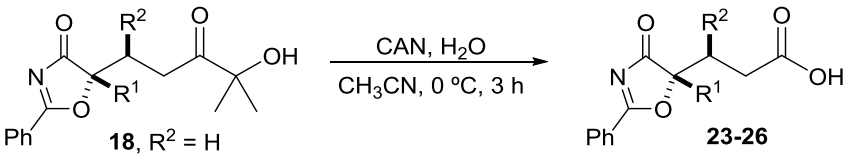


22D

The title compound was obtained following the general procedure from oxazolone **17E** (74 mg, 0.30 mmol) in a 1.5:1 *dr*. Yellow oil. Yield: 67% (32 mg, 0.10 mmol). Data of major isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.27 – 8.14 (m, 2H), 7.81 – 7.66 (m, 1H), 7.64 – 7.52 (m, 2H), 3.50 (s, 1H), 3.21 – 3.09 (m, 1H), 2.31 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.12 – 1.84 (m, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.26 – 1.19 (m, 8H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 216.8, 193.1, 185.8, 135.4, 130.1, 129.1, 125.6, 76.9, 38.9, 36.2, 34.7, 31.3, 28.9, 26.7, 26.6, 22.6, 22.4, 19.5, 13.9. Data of minor isomer: **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.27 – 8.14 (m, 2H), 7.81 – 7.66 (m, 1H), 7.64 – 7.52 (m, 2H), 3.46 (s, 1H), 3.35 – 3.23 (m, 1H), 2.46 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.12 – 1.84 (m, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.26 – 1.19 (m, 8H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 217.0, 194.2, 186.2, 135.8, 130.5, 129.5, 126.0, 90.9, 77.2, 39.5, 36.5, 34.6, 31.8, 30.1, 27.3, 27.0, 23.1, 22.8, 20.4, 14.3. **MS:** calculated for $C_{22}H_{32}NO_4$ ($M + H^+$), 374.2331; found, 374.2333. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 14.6 min (major), 24.8 min (minor)).

5.4.7. Elaboration of adducts 18 and 19

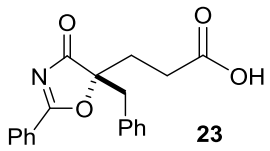
*5.4.7.1. Transformation of adducts to carboxylic acids **23-26***



To a stirred solution of the ketol (0.8 mmol, 1 equiv.) in acetonitrile (10 mL) at 0 ºC a solution of cerium ammonium nitrate (CAN) (3 equiv., 1.46 g, 2.7 mmol) in water (5 mL) was added dropwise and the mixture was stirred at the same temperature until starting material disappeared (TLC hexane/EtOAc 60:40). Water was then added (3 mL) and the mixture was extracted with CH_2Cl_2 (2 x 10 mL), after which the organic phases were combined, dried over $MgSO_4$ and concentrated. The crude material was purified

by flash chromatography on silica gel (eluting with CH_2Cl_2/MeOH 95:5) obtaining the desired product.

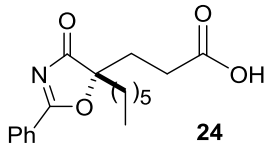
(*R*)-3-(5-benzyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (23)



23

The title compound was obtained from adduct **18C** according to the procedure above described. Yellow oil. Yield: 84% (217 mg, 0.67 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.02 (m, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.17 (s, 5H), 3.22 (s, 2H), 2.41 – 2.29 (m, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 192.6, 185.9, 177.2, 135.6, 133.1, 130.2, 129.2, 128.7, 127.8, 90.3, 42.3, 30.6, 28.4. **MS:** calculated for $C_{19}H_{18}NO_4$ (M + H $^+$), 324.1236; found, 324.1227.

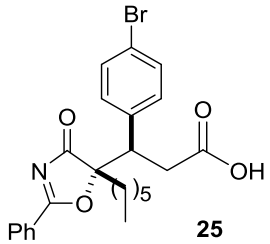
(*S*)-3-(5-Hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (24)



24

The title compound was obtained from adduct **18D** according to the procedure above described. Yellow oil. Yield: 82% (208 mg, 0.66 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 2.37 – 2.27 (m, 2H), 1.96 – 1.84 (m, 2H), 1.34 – 1.14 (m, 10H), 0.81 (t, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 193.0, 185.8, 176.9, 135.4, 130.1, 129.0, 127.4, 125.4, 90.2, 35.8, 31.3, 30.6, 28.9, 28.0, 22.7, 22.4, 13.9. **MS:** calculated for $C_{18}H_{24}NO_4$ (M + H $^+$), 318.1705; found, 318.1691. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane:ethanol, 70:30; flux = 0.5 mL/min; retention times: 16.8 min (major), 18.2 min (minor)).

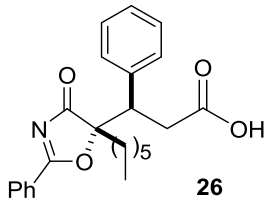
(*R*)-3-(4-Bromophenyl)-3-((*S*)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (25)



25

The title compound was obtained from adduct **19Eb** according to the procedure above described. Yellow oil. Yield: 80% (301 mg, 0.64 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 2H), 7.78 – 7.67 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 3.64 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.75 (dd, *J* = 16.2, 11.2 Hz, 1H), 2.61 (dd, *J* = 16.2, 3.9 Hz, 1H), 1.81 (dt, *J* = 14.5, 6.7 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.20 – 1.06 (m, 8H), 0.77 (t, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 192.6 , 185.9, 175.1, 136.0, 135.6.0, 131.7, 130.7, 130.0, 129.1, 125.0, 121.9, 92.4, 46.5, 34.9, 34.6, 31.3, 28.9, 22.6, 22.3, 13.9. **MS:** calculated for $C_{24}H_{27}BrNO_4$ (M + H $^+$), 472.1123; found, 472.1109.

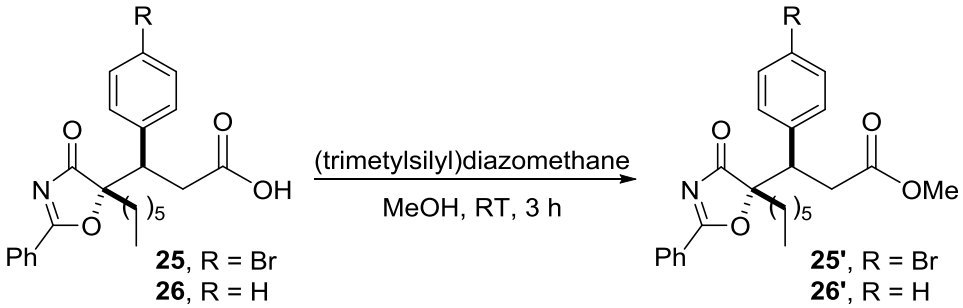
(*R*)-3-((*S*)-5-Hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)-3-phenylpropanoic acid (26)



26

The title compound was obtained from adduct **19Eb** according to the procedure above described. Yellow oil. Yield: 86% (275 mg, 0.69 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 8.21 – 8.13 (m, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.18 (m, 5H), 3.68 (dd, *J* = 11.2, 3.8 Hz, 1H), 2.79 (dd, *J* = 16.1, 11.2 Hz, 1H), 2.61 (dd, *J* = 16.1, 3.8 Hz, 1H), 1.91 – 1.76 (m, 1H), 1.72 – 1.55 (m, 1H), 1.19 – 1.05 (m, 8H), 0.76 (t, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 192.8, 185.8, 175.6, 136.7, 135.3, 129.9, 128.9, 128.3, 127.7, 125.1, 92.7, 47.0, 34.8, 34.6, 31.2, 28.8, 22.5, 22.2, 13.7. **MS:** calculated for $C_{25}H_{27}NO_4$ ($M + H^+$), 394.2018; found, 394.2003.

Elaboration of the carboxylic acids 25 and 26 to carboxylic esters 25' and 26'

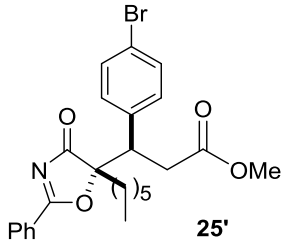


25, R = Br
26, R = H

25', R = Br
26', R = H

The corresponding carboxylic acid (0.25 mmol, 1 equiv.) was dissolved in MeOH (7.5 mL) and a solution of (trimethylsilyl)diazomethane in diethyl ether (2 M; 0,38 mL, 0.75 mmol, 3 equiv.) was added dropwise, observing the coloration of the mixture. The reaction mixture was stirred for further 3 h and disappearance of the acid was checked by TLC (hexane/EtOAc 1:1). The reaction mixture was concentrated and the crude material was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 90:10) obtaining the desired product.

(*R*)-3-(4-Bromophenyl)-3-((*S*)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (25')

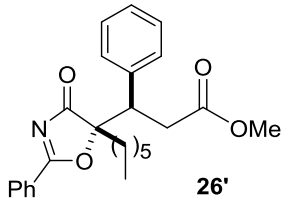


25'

The title compound was obtained from compound **25** according to the procedure above described. Yellow oil. Yield: 87% (103 mg, 0.22 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.19 (m, 2H), 7.80 – 7.71 (m, 1H), 7.59 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.73 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.50 (s, 3H), 2.79 (dd, *J* = 15.8, 11.3 Hz, 1H), 2.65 (dd, *J* = 15.8, 4.1 Hz, 1H), 1.95 – 1.79 (m, 1H), 1.74 – 1.58 (m, 1H), 1.25 – 1.07 (m, 8H), 0.81 (t, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 192.6, 185.9, 170.7, 136.2,

135.5, 131.6, 130.7, 130.0, 129.1, 125.2, 121.8, 92.3, 51.8, 46.8 , 35.0, 34.6, 31.3, 28.9, 22.6, 22.3, 13.8. **MS:** calculated for $C_{25}H_{29}BrNO_4$ (M + H $^+$), 486.1280; found, 486.1258. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 80:20; flux = 1 mL/min; retention times: 14.2 min (minor), 15.8 min (major)).

(*R*)-3-((*S*)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)-3-phenylpropanoic acid (26')

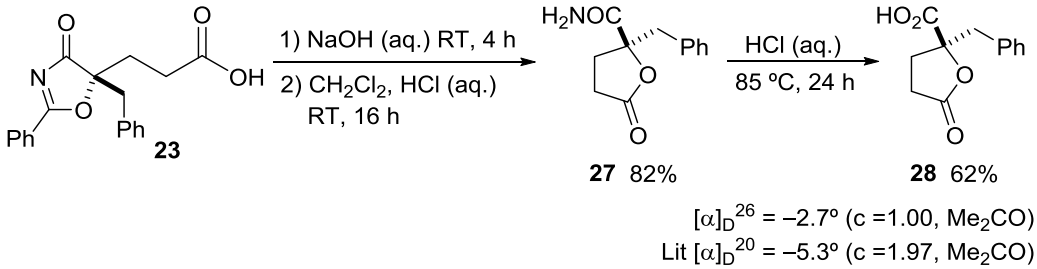


26'

The title compound was obtained from compound **26** according to the procedure above described. Yellow oil. Yield: 97% (99 mg, 0.24 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.12 (m, 2H), 7.74 – 7.63 (m, 1H), 7.53 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.34 – 7.17 (m, 5H), 3.72 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.42 (s, 3H), 2.79 (dd, *J* = 15.6, 11.2 Hz, 1H), 2.62 (dd, *J* = 15.7, 4.1 Hz, 1H), 1.91 – 1.76 (m, 1H), 1.70 – 1.55 (m, 1H), 1.21 – 1.04 (m, 8H), 0.75 (t, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 192.9, 185.8, 170.8, 137.0, 135.2, 129.9, 128.9, 128.3, 127.7, 125.2, 92.6, 51.5, 47.4, 34.9, 34.7, 31.2, 28.8, 22.5, 22.2, 13.7. **MS:** calculated for $C_{25}H_{30}NO_4$ (M + H $^+$), 408.2175; found, 408.2155. The enantiomeric purity was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 80:20; flux = 1 mL/min; retention times: 18.6 min (minor), 24.5 min (major)).

*5.4.7.2. Synthesis of γ-lactone **28***

Known γ-lactone **28** was prepared according to the following synthetic sequence:



1st step:[263] The acid **23** (0.6 mmol) was dissolved in a 2.5 M aqueous solution of NaOH (6 mL) and stirred at room temperature for 4 h. Then CH_2Cl_2 was added and the mixture

[263] Adapted from: a) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287. b) A. Paju, M. Laos, A. Jõgi, M. Päri, R. Jäälaid, T. Pehk, T. Kanger, M. Lopp, *Tetrahedron Lett.*. **2006**, *47*, 4491–4493.

was acidified to pH 1 using a concentrated aqueous solution of HCl. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic phases were united and the solvent was eliminated under reduced pressure. The crude was then redissolved in CH_2Cl_2 (12 mL) and a concentrated aqueous solution of HCl (0.12 mL) was added, letting the mixture to stir at room temperature overnight. The organic phase was washed with a saturated solution of $NaHCO_3$ (3 x 10 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure, obtaining (*R*)-2- benzyl-5-oxotetrahydrofuran-2-carboxamide **27** as a white solid, which was used in the next step without further purification. Yield: 85% (112 mg, 0.51 mmol). m. p. = 165–168 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 5H), 6.26 (s, 1H), 5.66 (s, 1H), 3.29 (d, *J* = 14.1 Hz, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.49 (m, 1H), 2.49 – 2.27 (m, 2H), 2.18 – 1.97 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.4, 174.2, 133.9, 130.4, 128.6, 127.5, 87.7, 43.4, 29.9, 28.1. **MS:** calculated for $C_{12}H_{14}NO_3$ (M, H^+), 220.0974; found, 220.0981.

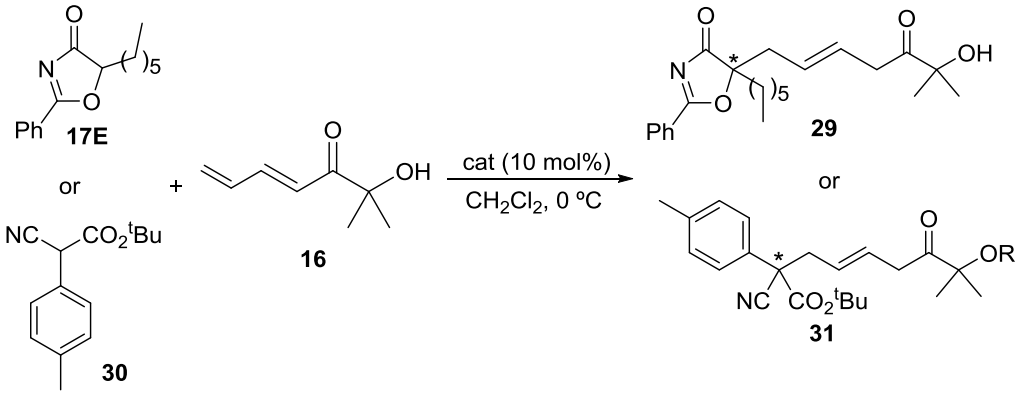
2nd step:[264] The above obtained adduct **28** (0.31 mmol) was dissolved in an aqueous concentrated HCl solution (2 mL) and heated at 85 ºC in a sealed tube for 24 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$ and the solvent eliminated under reduced pressure obtaining a brown solid. The solid was triturated with Et_2O obtaining the desired carboxylic acid **30** as a white solid. Yield: 62% (43 mg, 0.19 mmol). m. p. = 101–104 ºC. **[α]**$_D^{26}$= –2.73° (*c* = 1.00, acetone) **([α]**$_D^{20}$ Lit[265] = –5.3° (*c* = 1.97, acetone). All spectroscopic data were identical to those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 5H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.15 (d, *J* = 14.4 Hz, 1H), 2.57 – 2.43 (m, 2H), 2.39 – 2.25 (m, 1H), 2.24 – 2.06 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.67, 175.49, 133.42, 130.57, 128.64, 127.62, 85.80, 42.14, 29.96, 27.93.

[264] S. Caille, S. Cui, T.-L. Hwang, X. Wang, M. M. Faul, *J. Org. Chem.* **2009**, *74*, 3833–3842.

[265] A. Paju, M. Laos, A. Jõgi, M. Päri, R. Jäälaid, T. Pehk, T. Kanger, M. Lopp, *Tetrahedron Lett.* **2006**, *47*, 4491–4493.

5.4.8. 1,6-addition to α'-oxy dienones

5.4.8.1. General procedure

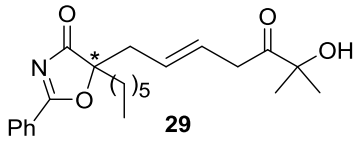


To a mixture of the corresponding nucleophile (0.15 mmol, 1 equiv.) and dienone **16** (42 mg, 0.30 mmol, 3.0 equiv.), in CH_2Cl_2 (0.45 mL) at 0 ºC, the selected catalyst (10 mol%) was added. The resulting mixture was stirred at the same temperature until consumption of the starting nucleophile as monitored by ^{1}H-NMR. The crude product was purified by flash column chromatography (eluting hexane/EtOAc 80:20).

For the racemic version of the reaction the same procedure was followed using DBU as the catalyst.

*5.4.8.2. Characterization data for compounds **29** and **31***

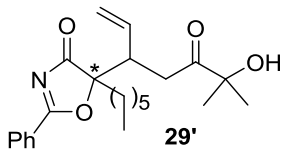
(*E*)-5-Hexyl-5-(6-hydroxy-6-methyl-5-oxohept-2-en-1-yl)-2-phenyloxazol-4(5*H*)-one (29)



The title compound was obtained following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) employing catalyst **C17**. Colourless oil. Yield: 79% (39 mg, 0.12 mmol). $[\alpha]_D^{23}$ = –3.9º (*c* = 0.80, 40% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.17 (m, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.60 – 7.51 (m, 2H), 5.73 (dt, *J* = 13.9, 6.8 Hz, 1H), 5.40 (dt, *J* = 15.4, 7.2 Hz, 1H), 3.23 – 3.14 (m, 2H), 2.71 – 2.63 (m, 2H), 1.99 – 1.88 (m, 2H), 1.37 – 1.18 (m, 14H), 0.84 (t, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 211.8, 193.1, 185.5, 145.4, 141.8, 135.1, 130.0, 128.9, 127.8, 125.4, 124.2, 90.6, 76.2, 39.1, 35.5, 31.4, 29.0, 26.9, 26.2, 25.3, 22.8, 22.4, 13.9. **MS:** calculated for $C_{23}H_{32}NO_4$ (M + H $^+$), 386.2331; found, 386.2342. The enantiomeric purity of the major isomer was determined by chiral HPLC

analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 34.7 min (major), 37.4 min (minor)).

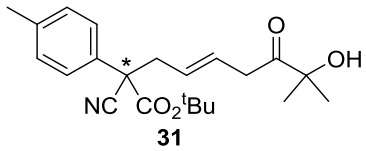
(*E*)-5-Hexyl-5-(6-hydroxy-6-methyl-5-oxohept-2-en-1-yl)-2-phenyloxazol-4(5*H*)-one (29')



29'

The title compound was obtained as a byproduct following the general procedure from oxazolone **17E** (37 mg, 0.15 mmol) but at 70 ºC in 1,2-dichloroethane and employing catalyst **C7**. Colourless oil. Yield: 23% (11 mg, 0.034 mmol). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 2H), 7.77 – 7.68 (m, 1H), 7.61 – 7.52 (m, 2H), 5.64 – 5.44 (m, 1H), 5.26 – 5.08 (m, 2H), 3.37 (td, *J* = 9.8, 3.1 Hz, 1H), 2.90 (dd, *J* = 17.2, 10.2 Hz, 1H), 2.58 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.01 – 1.88 (m, 2H), 1.33 (s, 3H), 1.28 (s, 3H), 1.22 (dd, *J* = 13.3, 6.6 Hz, 8H), 0.82 (t, *J* = 7.1 Hz, 3H). **MS:** calculated for $C_{23}H_{32}NO_4$ (M + H $^+$), 386.2331; found, 386.2342.

tert-Butyl (*E*)-2-cyano-8-hydroxy-8-methyl-7-oxo-2-(p-tolyl)non-4-enoate (31)



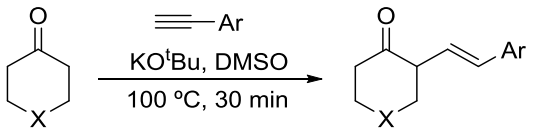
31

The title compound was obtained following the general procedure from α-cyanoacetate **30** (69 mg, 0.15 mmol) employing catalyst **C18**. Colourless oil. Yield: 83% (46 mg, 0.12 mmol). **[α]**$_D^{23}$ = +3.1º (*c* = 1.00, 30% *ee*, CH_2Cl_2). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 2H), 7.01 – 6.88 (m, 2H), 5.81 (dt, *J* = 13.8, 6.7 Hz, 1H), 5.52 (dt, *J* = 14.5, 7.1 Hz, 1H), 3.82 (s, 3H), 3.53 (s, 1H), 3.31 (d, *J* = 6.7 Hz, 2H), 3.06 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.9, 6.9 Hz, 1H), 1.42 (s, 9H), 1.36 (s, 3H), 1.35 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 211.8, 165.9, 159.6, 128.2, 127.2, 126.9, 126.2, 118.4, 114.2, 84.2, 76.3, 55.2, 54.1, 40.6, 39.2, 27.5, 26.5. **MS:** calculated for $C_{22}H_{29}NO_5Na$ (M + Na^+), 410.1943; found, 410.1938. The enantiomeric purity of the major isomer was determined by chiral HPLC analysis of the crude reaction mixture (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 31.0 min (major), 35.8 min (minor)).

5.4.9. Preparation of α-alkenyl cycloalkanones 34

Preparation of α-styryl cycloalkanones (34A-34E)

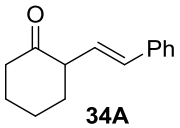
Known cycloalkanones **34A** and **34B** and new cycloalkanones **34C-34E** were synthesised following the procedure reported by Trofimov:[266]



34A-34E

A solution of the corresponding cyclic ketone (8 mmol, 1 equiv.), the corresponding alkyne (8 mmol, 1 equiv.) and potassium tert-butoxyde (900 mg, 8 mmol, 1 equiv.) in DMSO (20 mL) was stirred at 100 ºC for 30 min in a sealed tube under argon. Te reaction mixture was then cooled to room temperature, water (20 mL) was added and the mixture was neutralized with a saturated solution of NH_4Cl. The resulting biphasic mixture was extracted with Et_2O (4 x 20 mL) , the combined organic extract was washed with water (2 x 20 mL) and dried over $MgSO_4$, and volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/CH_2Cl_2 1:1).

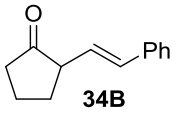
(*E*)-2-Styrylcyclohexan-1-one (34A)[266]



34A

The title compound was obtained following the general procedure above described starting from cyclohexanone (0.83 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow solid. Yield: 50% (800 mg, 4.0 mmol). All data were consistent with those previously reported. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.52 – 6.31 (m, 2H), 3.26 – 3.15 (m, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.32 (m, 1H), 2.25 – 2.13 (m, 1H), 2.13 – 2.01 (m, 1H), 1.99 – 1.86 (m, 1H), 1.85 – 1.68 (m, 3H).

(*E*)-2-Styrylcyclopentan-1-one (34B)[267]



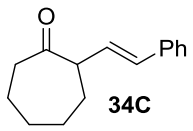
34B

The title compound was obtained following the general procedure above described starting from cyclopentanone (0.71 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 62% (1.3 g, 6.9 mmol). All data were consistent with those previously reported. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 6.92 (m, 5H), 6.47 (d, *J* = 16.1 Hz, 1H), 6.24 (dd, *J* =

[266] B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem*. **2012**, *77*, 6880–6886.
[267] L.-L. Zhu, X.-X. Li, W. Zhou, X. Li, Z. Chen, *J. Org. Chem*. **2011**, *76*, 8814–8823.

16.1, 6.2 Hz, 1H), 3.02 – 2.87 (m, 1H), 2.45 – 2.02 (m, 5H), 1.97 – 1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 136.9, 131.9, 128.4, 127.3, 126.2, 126.0, 52.4, 37.8, 29.7, 20.7.

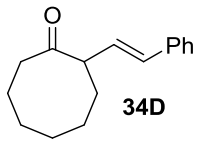
(*E*)-2-Styrylcycloheptan-1-one (34C)



34C

The title compound was obtained following the general procedure above described starting from cycloheptanone (0.94 mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 67% (1.2 g, 5.4 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 7.39 – 7.24 (m, 2H), 7.25 – 7.18 (m, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 6.32 (dd, *J* = 16.0, 7.2 Hz, 1H), 3.35 (ddd, *J* = 11.0, 7.2, 4.0 Hz, 1H), 2.66 – 2.45 (m, 2H), 2.06 – 1.82 (m, 4H), 1.77 – 1.57 (m, 2H), 1.54 – 1.38 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.7, 137.0, 130.8, 128.5, 128.4, 127.3, 126.2, 56.2, 42.4, 31.5, 29.7, 27.9, 24.8. **MS:** calculated for $C_{15}H_{19}O$ (M + H^+), 215.1436; found, 215.1432.

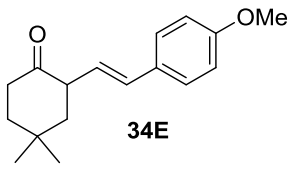
(*E*)-2-Styrylcyclooctan-1-one (34D)



34D

The title compound was obtained following the general procedure above described starting from cyclooctanone (1.0 g mL, 8 mmol, 1 equiv.) and phenylacetylene (0.88 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 74% (1.4 g, 5.9 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.39 – 7.18 (m, 5H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 7.7 Hz, 1H), 3.39 (ddd, *J* = 11.2, 7.7, 3.7 Hz, 1H), 2.60 – 2.23 (m, 2H), 2.11 – 1.79 (m, 4H), 1.79 – 1.63 (m, 2H), 1.60 – 1.37 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.7, 136.9, 130.9, 128.4, 128.3, 127.3, 126.1, 55.0, 40.7, 32.4, 26.9, 26.1, 25.8, 24.5. **MS:** calculated for $C_{16}H_{21}O$ (M + H^+), 229.1592; found, 229.1604.

(*E*)-2-(4-Methoxystyryl)-4,4-dimethylcyclohexan-1-one (34E)

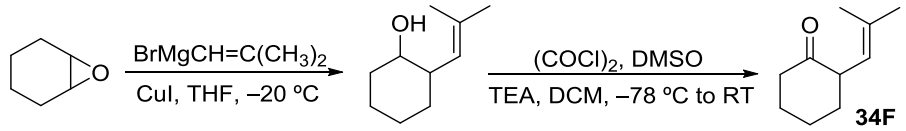


34E

The title compound was obtained following the general procedure above described starting from 4,4-dimethylcyclohexanone (1.01g mL, 8 mmol, 1 equiv.) and 4-ethynylanisole (1.04 mL, 8 mmol, 1 equiv.) as a yellow oil. Yield: 27% (490 mg, 1.9 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.40 – 6.21 (m, 2H), 3.82 (s, 2H), 3.37 – 3.24 (m, 1H), 2.64 – 2.46 (m, 1H), 2.41 – 2.30 (m, 1H), 1.95 – 1.64 (m, 3H), 1.29 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 159.0, 130.6, 130.0, 127.4, 125.4, 113.6, 55.3, 49.7, 47.2, 38.2, 31.4, 30.8, 24.6. **MS:** calculated for $C_{17}H_{23}O_2$ (M + H^+), 259.1698; found, 259.1711.

Preparation of 2-(2-methylprop-1-en-1-yl)cyclohexan-1-one (34F)

Cycloalkanone **34F** was prepared according to the synthetic procedure reported by Toste:[268]



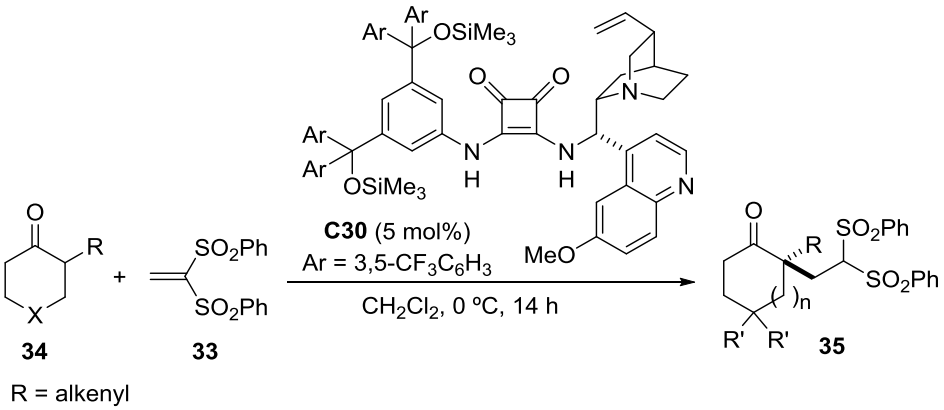
1st step: To a solution of CuI (380 mg, 2 mmol, 0.1 equiv.) in THF (20 mL) and 2-methyl-1-propenylmagnesium bromide (0.5 M in THF; 52 mL, 26 mmol, 1.3 equiv.) was added at –78 ºC. After stirring for 30 min cyclohexene oxide (2.0 mL, 20 mmol, 1 equiv.) was added, and the resulting mixture was further stirred for 2 h at –20 ºC. The reaction was quenched by adding a saturated solution of NH_4Cl (50 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extract was washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 80:20). Yield: 55% (1.7 g, 11 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.99 (d, *J* = 9.3 Hz, 0H), 3.81 (qd, *J* = 6.8, 3.5 Hz, 1H), 2.64 – 2.45 (m, 1H), 2.02 – 1.82 (m, 1H), 1.82 – 1.49 (m, 6H), 1.37 – 1.20 (m, 1H).

2nd step: DMSO (1.1 mL, 15 mmol, 3 equiv.) was added to a solution of $(COCl)_2$ (0.64 mL, 7.5 mmol, 1.5 equiv.) in CH_2Cl_2 (15 mL) at –78 ºC. After stirring for 30 min a solution of the alcohol obtained above (5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was slowly added and the mixture stirred for further 2 h at the same temperature before slowly warming it to room temperature. The mixture was stirred for an additional hour and the reaction was quenched by adding a saturated solution of NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extract was washed with brine (50 mL) and dried over $MgSO_4$, and volatiles were removed under reduced pressure (400 bat at 35 ºC) to obtain the crude compound, which was purified by silica gel flash column chromatography (hexane/Et_2O 95:5). Yellow oil. All data were consistent with those previously reported. Yield: 40% (400 mg, 2.0 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.99 (d, *J* = 8.3 Hz, 1H), 3.14 – 2.78 (m, 1H), 2.40 – 1.96 (m, 5H), 1.95 – 1.70 (m, 5H), 1.70 – 1.56 (m, 4H).

[268] X. Yang, F. D. Toste, *J. Am. Chem. Soc*. **2015**, *137*, 3205–3208.

5.4.10. α-Functionalization of α-alkenyl cycloalkanones

5.4.10.1.General procedure

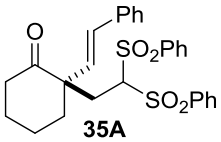


Catalyst **C30** (11.5 mg, 5 mol%) was added over a solution of the corresponding α-alkenyl cycloalkanone **34** (0.15 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (**33**) (69 mg, 0.23 mmol, 1.5 equiv.) in CH_2Cl_2 at 0 ºC. The resulting solution was stirred until the reaction was completed (monitored by TLC hexane/EtOAc 80:20). Then the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 85:15), affording the corresponding adducts as essentially pure compound.

The racemic version of the reaction was performed following the asymmetric reaction procedure except the reaction was conducted at room temperature and TEA (20 mol%) was used as the catalyst.

*5.4.10.2.Characterization data of compounds **35***

(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-styrylcyclohexan-1-one (35A)

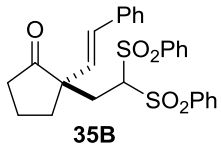


35A

The adduct was obtained according to the general procedure described above using (*E*)-2-styrylcyclohexan-1-one (**34A**) (30 mg, 0.15 mmol, 1 equiv.). White solid. m. p. = 92–93 ºC. Yield: 91% (69 mg, 0.136 mmol). $[\alpha]_D^{23}$= –95.8º (*c* = 1.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.85 (m, 2H), 7.71 – 7.61 (m, 3H), 7.57 – 7.45 (m, 3H), 7.45 – 7.25 (m, 7H), 6.42 (d, *J* = 16.6 Hz, 1H), 6.12 (d, *J* = 16.6 Hz, 1H), 4.56 (t, *J* = 4.3 Hz, 1H), 3.18 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.49 – 2.37 (m, 2H), 2.26 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.06 – 1.69 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 138.3, 137.3, 136.1, 134.5, 134.1, 132.6, 130.3, 130.2, 129.5, 128.9, 128.8,

128.3, 126.6, 80.8, 54.4, 39.7, 36.1, 31.1, 27.0, 21.3. **MS:** calculated for $C_{28}H_{32}NO_5S_2$ ($M + NH_4^+$), 526.6855; found, 526.1727. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux = 1 mL/min; retention times: 17.6 min (minor), 18.9 min (major)).

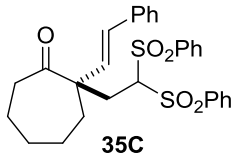
(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-styrylcyclopentan-1-one (35B)



35B

The adduct was obtained according to the general procedure described above using (*E*)-2-styrylcyclopentan-1-one (**34B**) (28 mg, 0.15 mmol, 1 equiv.) in toluene instead of dichloromethane. White solid. m. p. = 154–156 ºC. Yield: 85% (62 mg, 0.128 mmol). $[\alpha]_D^{23}$= –36.0º (*c* = 0.75, 80% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 4H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.37 (m, 4H), 7.35 – 7.25 (m, 5H), 6.37 (d, *J* = 16.3 Hz, 1H), 5.93 (d, *J* = 16.3 Hz, 1H), 4.89 (t, *J* = 4.2 Hz, 1H), 2.91 (dd, *J* = 16.4, 4.3 Hz, 1H), 2.49 – 2.25 (m, 4H), 2.23 – 1.87 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.0, 140.3, 138.3, 137.2, 136.2, 134.9, 134.5, 134.2, 131.5, 129.9, 129.5, 128.9, 128.6, 128.0, 126.7, 79.5, 53.7, 37.9, 35.1, 31.4, 18.7. **MS:** calculated for $C_{27}H_{27}O_5S_2$ ($M + H^+$), 495.1300; found, 495.1299. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux = 1 mL/min; retention times: 15.0 min (major), 16.9 min (minor)).

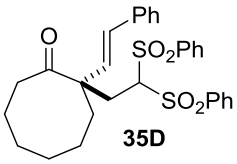
(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-styrylcycloheptan-1-one (35C)



35C

The adduct was obtained according to the general procedure described above using (*E*)-2-styrylcycloheptan-1-one (**34C**) (32 mg, 0.15 mmol, 1 equiv.). White foam. Yield: 86% (67 mg, 0.129 mmol). $[\alpha]_D^{23}$= –123.0º (*c* = 1.00, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.55 (q, *J* = 7.3 Hz, 2H), 7.51 – 7.16 (m, 9H), 6.51 (d, *J* = 16.5 Hz, 1H), 6.14 (d, *J* = 16.5 Hz, 1H), 4.63 (t, *J* = 4.0 Hz, 1H), 3.12 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.61 – 2.50 (m, 1H), 2.30 (dd, *J* = 16.5, 3.5 Hz, 1H), 2.20 – 1.99 (m, 2H), 1.68 (dp, *J* = 31.2, 11.0, 9.1 Hz, 5H), 1.52 – 1.38 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.9, 138.5, 137.1, 136.5, 134.5, 134.0, 132.4, 130.5, 130.1, 129.5, 128.9, 128.8, 128.7, 128.0, 126.7, 80.5, 57.0, 41.1, 32.6, 30.2, 29.9, 26.5, 24.4. **MS:** calculated for $C_{29}H_{31}O_5S_2$ ($M + H^+$), 523.1613; found, 523.1620. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 50:50; flux = 1 mL/min; retention times: 33.4 min (minor), 49.5 min (major)).

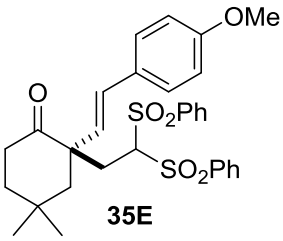
(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-styrylcyclooctan-1-one (35D)



35D

The adduct was obtained according to the general procedure described above using (*E*)-2-styrylcyclooctan-1-one (**34D**) (34 mg, 0.15 mmol, 1 equiv.) in toluene instead of dichloromethane. White foam. Yield: 88% (69 mg, 0.132 mmol). $[\alpha]_D^{23}$= –87.6º (*c* = 1.00, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.41 (m, 4H), 7.41 – 7.26 (m, 5H), 6.63 (d, *J* = 16.6 Hz, 1H), 6.23 (d, *J* = 16.6 Hz, 1H), 3.19 (dd, *J* = 16.7, 4.2 Hz, 1H), 2.85 – 2.68 (m, 1H), 2.46 – 2.26 (m, 4H), 2.25 – 2.14 (m, 1H), 1.87 – 1.62 (m, 5H), 1.58 – 1.38 (m, 2H), 1.25 – 1.07 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.9, 138.4, 137.3, 136.4, 134.4, 134.0, 132.8, 130.1, 129.8, 129.5, 128.8, 128.8, 128.2, 126.7, 81.3, 56.6, 38.0, 30.0, 29.4, 26.7, 26.2, 24.7, 24.2. **MS:** calculated for $C_{30}H_{33}O_5S_2$ (M + H^+), 137.1769; found, 137.1766. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 50:50; flux = 1 mL/min; retention times: 20.6 min (minor), 26.5 min (major)).

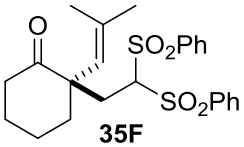
(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-styrylcyclohexan-1-one (35E)



35E

The adduct was obtained according to the general procedure described above using (*E*)-2-(4-methoxystyryl)-4,4-dimethylcyclohexan-1-one (**34E**) (39 mg, 0.15 mmol, 1 equiv.). White solid. m. p. = 107 ºC. Yield: 91% (69 mg, 0.136 mmol). $[\alpha]_D^{23}$= +10.8º (*c* = 1.00, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 4H), 7.66 – 7.51 (m, 2H), 7.49 – 7.22 (m, 6H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.13 (d, *J* = 16.7 Hz, 1H), 5.98 (d, *J* = 16.7 Hz, 1H), 4.89 – 4.80 (m, 1H), 3.83 (s, 3H), 2.98 (d, *J* = 20.0 Hz, 1H), 2.74 – 2.54 (m, 1H), 2.42 – 2.32 (m, 1H), 2.32 – 2.21 (m, 1H), 2.13 (d, *J* = 14.2 Hz, 1H), 1.75 (d, *J* = 14.2 Hz, 1H), 1.68 (dd, *J* = 9.1, 4.6 Hz, 2H), 1.16 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 159.6, 138.3, 134.1, 134.1, 130.8, 130.3, 129.7, 129.7, 129.1, 128.8, 128.8, 127.7, 114.2, 80.9, 55.3, 52.5, 51.0, 38.3, 36.3, 33.0, 32.1, 30.9, 27.3. **MS:** calculated for $C_{31}H_{35}O_6S_2$ (M + H^+), 567.1875; found, 567.1882. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 70:30; flux = 1 mL/min; retention times: 16.7 min (minor), 23.2 min (major)).

(*R*,*E*)-2-(2,2-bis(Phenylsulfonyl)ethyl)-2-(2-methylprop-1-en-1-yl)cyclohexan-1-one (35F)



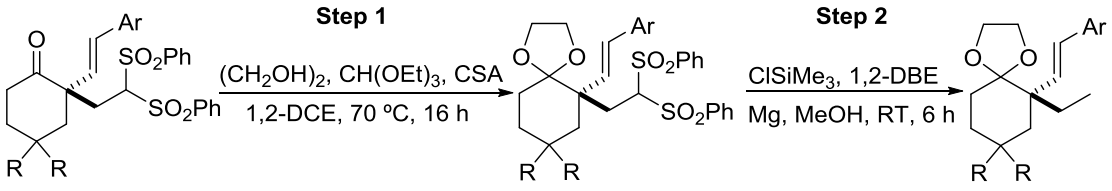
35F

The adduct was obtained according to the general procedure described above using 2-(2-methylprop-1-en-1-yl)cyclohexan-1-one (**34F**) (23 mg, 0.15 mmol, 1 equiv.). Colourless oil. Yield: 84% (58 mg, 0.126 mmol). $[\alpha]_D^{23}$= –36.1º (*c* = 1.00, 61% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.69 – 7.58 (m, 1H), 7.56 – 7.47 (m, 3H), 5.00 (s, 0H), 4.96 (dd, *J* = 5.3, 3.2 Hz, 1H), 2.81 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.37 (dd, *J* = 16.2, 3.2 Hz, 1H), 2.32 – 2.20 (m, 1H), 2.19 – 2.12 (m, 2H), 2.06 – 1.96 (m, 1H), 1.56 (s, 2H), 1.52 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.6, 138.7, 138.2, 137.6, 134.5, 134.1, 129.9, 129.5, 129.0, 128.9, 124.9, 79.1, 51.7, 38.8, 37.4, 31.0, 27.1, 19.8, 18.7. **MS:** calculated for $C_{24}H_{29}O_5S_2$ ($M + H^+$), 461.6105; found, 461.6100. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol, 70:30; flux = 1 mL/min; retention times: 9.3 min (minor), 10.4 min (major)).

5.4.11. Elaboration of adducts 35

*5.4.11.1.Synthesis of **38** and **39***

Ketals **38** and **39** were prepared according to the following synthetic sequence:



35A R = H, Ar = Ph
35E R = Me, Ar: 4-MeOC$_6$H$_4$

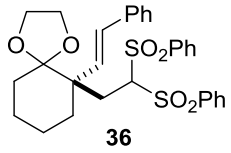
36
37

38
39

Step 1: Protection of the ketone moiety (36 and 37)

The above obtained ketone **35** (0.25 mmol, 1 equiv.), etylenglycol (60 µL, 1.0 mmol, 4 equiv.) and triethyl orthoformate (80 µL, 0.50 mmol, 2 equiv.) were dissolved in 1,2-DCE (0.6 mL) and camphorsulphonic acid (16 mg, 0.07 mmol, 0.28 equiv.) was added. The resulting solution was stirred at 70 ºC overnight before being directly submitted to silica gel flash column chromatography (hexane/EtOAc 80:20).

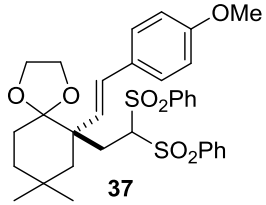
(*R*,*E*)-6-(2,2-bis(Phenylsulfonyl)ethyl)-6-styryl-1,4-dioxaspiro[4.5]decane (36)



36

The ketal was obtained from adduct **35A** (125 mg, 0.25 mmol, 1 equiv.) following the procedure described above. White solid. m. p. = 67–69 ºC. Yield: 98% (135 mg, 0.244 mmol). $[\alpha]_D^{23}$= –69.0º (*c* = 1.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.72 – 7.65 (m, 1H), 7.60 – 7.52 (m, 4H), 7.50 – 7.44 (m, 3H), 7.42 – 7.34 (m, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.37 (d, *J* = 4.4 Hz, 3H), 4.43 (t, *J* = 4.0 Hz, 2H), 4.04 – 3.80 (m, 4H), 2.79 (dd, *J* = 16.2, 4.0 Hz, 1H), 2.34 (dd, *J* = 16.2, 4.0 Hz, 2H), 2.05 (d, *J* = 14.1 Hz, 2H), 1.82 – 1.43 (m, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.9, 137.6, 137.3, 134.7, 134.1, 132.3, 131.2, 130.8, 129.6, 129.0, 128.9, 128.9, 127.9, 126.8, 111.7, 81.4, 65.2, 65.1, 49.5, 32.5, 30.4, 27.9, 23.5, 21.0. **MS:** calculated for $C_{30}H_{36}N_2O_5S_2$ ($M + NH_4^+$), 570.7385; found, 570.1994.

(*R*,*E*)-6-(2,2-bis(Phenylsulfonyl)ethyl)-6-(4-methoxystyryl)-8,8-dimethyl-1,4-dioxaspiro[4.5]decane (37)



37

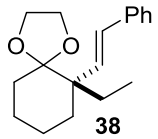
The ketal was obtained from adduct **35E** (283 mg, 0.5 mmol, 1 equiv.) following the procedure described above. White solid. m. p. = 90–93 ºC. Yield: 90% (274 mg, 0.45 mmol). $[\alpha]_D^{23}$= –45.9 (*c* = 1.00, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.61 – 7.45 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 4H), 7.29 (t, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 16.9 Hz, 1H), 6.22 (d, *J* = 16.9 Hz, 1H), 4.77 (t, *J* = 3.7 Hz, 1H), 4.15 – 3.85 (m, 4H), 3.80 (s, 3H), 2.82 (dd, *J* = 16.3, 3.0 Hz, 1H), 2.19 (dd, *J* = 16.3, 4.9 Hz, 1H), 1.83 – 1.43 (m, 5H), 1.29 – 1.18 (m, 1H), 0.97 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0, 140.2, 138.4, 137.9, 134.7, 134.0, 133.7, 130.8, 130.2, 129.9, 129.6, 129.6, 128.5, 128.4, 128.2, 127.5, 113.9, 111.7, 81.3, 64.1, 63.7, 55.1, 48.0, 45.7, 36.1, 33.9, 30.8, 29.4, 28.2, 27.8. **MS:** calculated for $C_{33}H_{39}O_7S_2$ ($M + H^+$), 611.2137; found, 611.2125.

Step 2: Desulfonylation of ketals 36 and 37 to afford 38 and 39

The above obtained ketal (0.25 mmol, 1 equiv.) was dissolved in MeOH (2 mL) and magnesium powder (61 mg, 2.5 mmol, 10 equiv.) was added. The resulting suspension was cooled to 0 ºC and a drop of trimethylsilylchloride and a drop of 1,2-dibromoethane were added. The resulting mixture was warmed to room temperature observing the formation of hydrogen, and the reaction was followed by TLC (hexane/EtOAc 80:20). After completion of the reaction the mixture was filtered

through a pad of celite and washed with MeOH. The solvent was eliminated under reduced pressure and the residue was dissolved in dichloromethane (10 mL). The organic solution was washed with water (2 x 10 mL), dried over $MgSO_4$, volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 95:5).

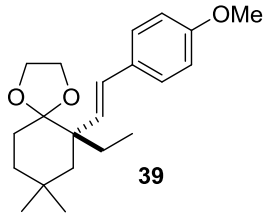
(*R*,*E*)-6-Ethyl-6-styryl-1,4-dioxaspiro[4.5]decane (38)



38

The product was obtained from **36** (138 mg, 0.25 mmol, 1 equiv.) following the procedure described above as a colourless oil. Yield: 56% (38 mg, 0.14 mmol). $[\alpha]_D^{23}$= –16.2º (*c* = 0.80, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.34 (d, *J* = 16.7 Hz, 1H), 6.23 (d, *J* = 16.7 Hz, 1H), 4.03 – 3.82 (m, 4H), 1.94 – 1.82 (m, 1H), 1.74 – 1.51 (m, 8H), 1.51 – 1.38 (m, 1H), 0.74 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.9, 134.4, 130.3, 129.1, 128.8, 127.4, 126.7, 126.1, 113.3, 65.9, 65.6, 49.0, 32.7, 29.8, 25.7, 24.2, 21.3, 8.4. **MS:** calculated for $C_{18}H_{25}O_2$ ($M + H^+$), 273.3955; found, 273.1722.

(*S*,*E*)-6-Ethyl-6-(4-methoxystyryl)-8,8-dimethyl-1,4-dioxaspiro[4.5]decane (39)

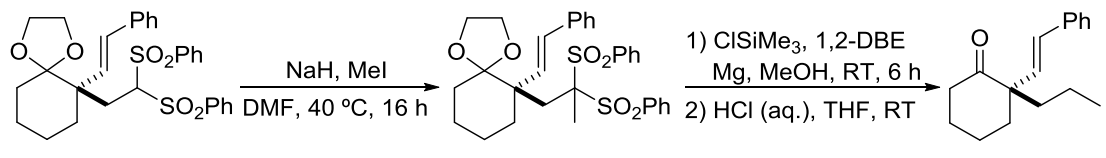


39

The product was obtained from **37** (270 mg, 0.40 mmol, 1 equiv.) following the procedure described above. Colourless oil. Yield: 53% (70 mg, 0.21 mmol). $[\alpha]_D^{26}$= –13.7º (*c* = 0.50, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 16.7 Hz, 1H), 6.12 (d, *J* = 16.7 Hz, 1H), 4.09 – 3.89 (m, 4H), 3.81 (s, 3H), 1.78 – 1.59 (m, 5H), 1.59 – 1.41 (m, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.82 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 132.8, 129.4, 128.5, 127.0, 113.8, 64.8, 64.7, 55.2, 47.8, 43.5, 36.4, 31.4, 30.6, 30.5, 28.9, 27.5, 8.2.

*5.4.11.2.Synthesis of compound **41***

Ketone **41** was synthesised from ketal **36** according to the following synthetic sequence:



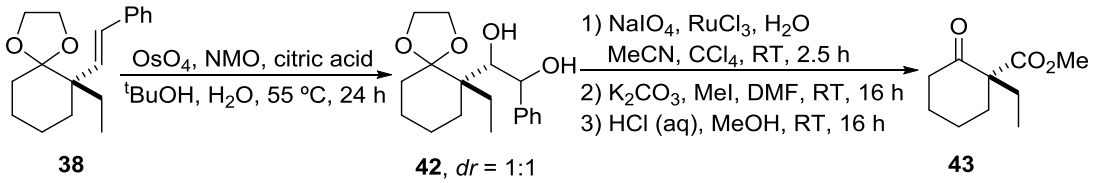
36 **40** **41**

1st step: Sodium hydride (60% wt in oil) (9.5 mg) was added to a solution of the above obtained ketal **58** (116 mg, 0.20 mmol, 1 equiv.) in dry DMF (0.5 mL) at 0 ºC. The mixture was stirred at room temperature for 30 min and was recooled to 0 ºC to slowly add iodomethane (75 µL, 0.6 mmol, 3 equiv.). The resulting solution mas stirred overnight at 40 ºC. The reaction was quenched by adding a saturated solution of NH_4Cl, and the resulting aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic layer was washed with brine (5 x 5 mL), dried over $MgSO_4$, and volatiles were removed under reduced pressure to obtain crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 80:20) obtaining product **62** as a white foam. Yield: 86% (99 mg, 0.172 mmol). $[\alpha]_D^{25}$= –59.3º (*c* = 1.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 7.3 Hz, 2H), 7.75 – 7.45 (m, 6H), 7.25 (dt, *J* = 24.9, 7.6 Hz, 5H), 6.46 – 6.26 (m, 1H), 5.90 (d, *J* = 16.8 Hz, 1H), 3.99 – 3.72 (m, 4H), 2.34 – 2.20 (m, 1H), 1.96 (dt, *J* = 14.0, 6.7 Hz, 1H), 1.88 (s, 3H), 1.69 – 1.48 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.4, 136.8, 136.1, 134.2, 132.3, 131.8, 131.5, 128.6, 128.4, 128.4, 127.2, 126.1, 112.3, 89.8, 64.8, 49.2, 31.3, 31.1, 23.1, 20.9, 16.4.

2nd step: The methylated adduct **40** (142 mg, 0.25 mmol) was submitted to the desulfonylation procedure described above (Section 5.4.11.1), and the resulting ketal was dissolved in a mixture of THF (0.5 mL) and aqueous HCl (6 M) (0.5 mL) and stirred at room temperature overnight. THF was eliminated under reduced pressure and the remaining aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to obtain crude compound **41**, which was purified by silica gel flash column chromatography (hexane/CH_2Cl_2 60:40). Yield: 41% (25 mg, 0.102 mmol). $[\alpha]_D^{25}$= +48.0º (*c* = 0.30, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.18 (m, 5H), 6.38 (d, *J* = 16.6 Hz, 1H), 6.28 (d, *J* = 16.6 Hz, 1H), 2.64 – 2.49 (m, 1H), 2.46 – 2.32 (m, 1H), 2.18 – 2.08 (m, 1H), 2.01 – 1.89 (m, 1H), 1.90 – 1.73 (m, 4H), 1.70 – 1.52 (m, 2H), 1.41 – 1.19 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.2, 137.1, 133.5, 130.3, 128.6, 127.5, 126.1, 54.6, 40.1, 39.6, 36.7, 27.3, 21.7, 17.1, 14.8. **MS:** calculated for $C_{17}H_{23}O$ ($M + H^+$), 243.1749; found, 243.1752.

*5.4.11.3.Preparation of β-ketoester **43***

Known β-ketoester **43**[269] was synthesised according to the following synthetic sequence:



38 **42**, *dr* = 1:1 **43**

1st step:[270] Alkene **38** (68 mg, 0.25 mmol, 1 equiv.) was dissolved in a mixture of *tert*-butanol (3 mL) and water (1 mL) and citric acid (72 mg, 0.75 mmol, 3 equiv.). To the resulting solution *N*-methylmorpholine *N*-oxide (136 mg, 0.75 mmol, 3 equiv.) and osmium tetraoxide (2.5 wt% in ^{t}BuOH) (0.6 mL, 0.05 mmol, 0.2 equiv.) were added and the reaction mixture was stirred at 55 ºC for 24 h. Part of the solvent was eliminated under reduced pressure and the aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and volatiles were removed under reduced pressure to obtain the crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 85:15). The desired diol **42** was obtained as a mixture of two isomers at a 1:1 ratio. Yield: 52% (40 mg, 0.13 mmol).

2nd step:[271] The diol **42** obtained in the previous step (37 mg, 0.12 mmol, 1 equiv.) was dissolved in a 2:2:3 mixture of CH_3CN, CCl_4 and H_2O (2 mL) and sodium metaperiodate (205 mg, 0.96 mmol, 8 equiv.) and ruthenium(III) chloride (0.6 mg, 2.5 mol%) were added. The resulting mixture was vigorously stirred for 2.5 h before being diluted with dichloromethane (2 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude obtained was dissolved in dry DMF (1.6 mL) and potassium carbonate (66 mg, 0.48 mmol, 4 equiv.) was added. The mixture was stirred for 30 min at room temperature before adding iodomethane (0.10 mL, 0.72 mmol, 6 equiv.) and letting to stir overnight. The mixture was poured over HCl (1 M) and diethylether and the aqueous layer was extracted with diethylether (5 x 2 mL). The combined organic layers were washed with brine (10 x 2 mL), dried over $MgSO_4$ and volatiles were removed under reduced pressure. The reaction crude was then redissolved in methanol (3.6 mL) and aqueous

[269] K. Umemura, H. Matsuyama, N. Watanabe, M. Kobayashi, N. Kamigata, *J. Org. Chem*. **1989**, *59*, 2374–2383.

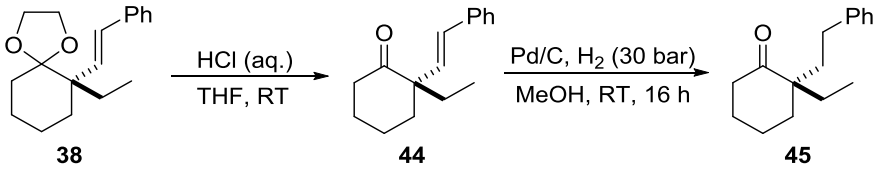
[270] Adapted from: J-J. Wu, Y. Shi, W-S. Tian, *Tetrahedron Lett*. **2017**, *58*, 923–925.

[271] a) S. H. Jacobo, C-T. Chang, G-J. Lee, J. A. Lawson, W. S. Powel, D. Pratico, G. A. FitzGerald, J. Rokach, *J. Org. Chem*. **2006**, *71*, 1370–1379. b) G. Song, X. Shen, S. Li, Y. Li, H. Si, J. Fan, J. Li, E. Gao, S. Liu, *Eur. J. Med. Chem.* **2016**, 199, 109–121.

HCl (3 M) (0.7 mL) was added. The resulting solution was stirred at room temperature overnight and diluted with an aqueous solution of $NaHCO_3$ (5%). The mixture was extracted with Et_2O (3 x 5 mL) and the combined organic layers were washed with brine (10 x 2 mL), dried over $MgSO_4$ and volatiles were removed under reduced pressure to obtain the crude ketoester **63**, which was purified by silica gel flash column chromatography (hexane/EtOAc 97:3). All data were consistent with those previously reported. Yield: 45% (10 mg, 0.054 mmol). The absolute configuration of the molecule was determined by comparison of the [α] value.[272] **$[\alpha]_D^{23}$**= –91.3º (*c*= 0.08, 98% *ee*, EtOH), (**$[\alpha]_D^{20}$** Lit[272] = –82.4° (*c* = 5.7, EtOH). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.56 – 2.39 (m, 3H), 2.06 – 1.87 (m, 2H), 1.78 – 1.52 (m, 4H), 1.50 – 1.37 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.0, 172.5, 61.3, 52.2, 41.2, 35.5, 29.7, 27.6, 22.5, 8.8. **MS:** calculated for $C_{10}H_{17}O_3$ ($M + Na^+$), 185.1178; found, 185.1183.

*5.4.11.4.Preparation of cycloalkanone **45***

α,α-Dialkyl cycloalkanone **45** was synthesised according to the following synthetic sequence:



38 **44** **45**

1st step: Ketal **38** obtained above (16 mg, 0.6 mmol, 1 equiv.) was dissolved in a mixture of THF (0.5 mL) and aqueous HCl (6 M) (0.5 mL) and stirred at room temperature overnight. THF was eliminated under reduced pressure and the remaining aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to obtain the desired ketone **44** as an essentially pure liquid compound. Yield: 89% (12.2 mg, 0.053 mmol). **$[\alpha]_D^{23}$**= –30.3º (*c* = 0.50, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 4H), 7.26 – 7.22 (m, 1H), 6.30 (d, *J* = 3.9 Hz, 2H), 2.62 – 2.47 (m, 1H), 2.42 – 2.29 (m, 1H), 2.14 – 2.04 (m, 1H), 1.99 – 1.59 (m, 7H), 0.84 (t, *J* = 7.5 Hz, 3H). **^{13}C**

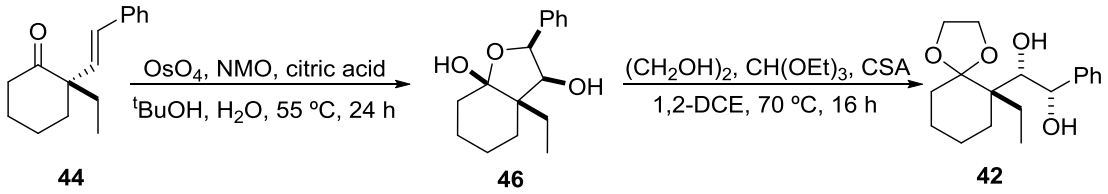
[272] For the same isomer: a) $[\alpha]_D^{20}$ = –9.0º (11% *ee*, EtOH), K. Umemura, H. Matsuyama, N. Watanabe, M. Kobayashi, N. Kamigata, *J. Org. Chem*. **1988**, *54*, 2374–2383. b) $[\alpha]_D^{20}$ = –82.4º (*c* = 5.7, 94% *ee*, EtOH), S. Pinheiro, A. Guingant, D. Desmaële, J. d'Angelo, *Tetrahedron: Asymmetry*. **1992**, 3, 1003–1006. For the other isomer: $[\alpha]_D^{20}$ = +13.6º (*c* = 0.43, 16% *ee*, EtOH), M. Kobayashi, K. Umemura, N. Watanabe, H. Matsuyama, *Chem. Lett*. **1985**, 1067–1070.

NMR (75 MHz, $CDCl_3$) δ 213.2, 137.1, 133.2, 130.6, 128.6, 127.5, 126.1, 54.8, 39.6, 36.0, 30.3, 27.3, 21.6, 8.2.

2nd step: The previously obtained desulfonylated product **44** (11 mg, 0.5 mmol, 1 equiv.) and palladium on activated charcoal (10% wt.) (20% wt, 2.2 mg) were stirred under an hydrogen atmosphere at 30 bar overnight. The resulting suspension was filtered over a pad of celite and the solvent was eliminated under reduced pressure. The α,α-dialkyl cycloalkanone **45** was purified by silica gel flash column chromatography (hexane/EtOAc 95:5). Colourless oil. Yield: 81% (9.3 mg, 0.040 mmol). $[\alpha]_D^{23}$= –19.6º (*c* = 0.25, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.12 (m, 3H), 2.53 (td, *J* = 12.9, 5.1 Hz, 1H), 2.44 – 2.27 (m, 3H), 1.99 – 1.69 (m, 9H), 1.65 – 1.51 (m, 1H), 0.82 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.3, 142.7, 128.4, 128.3, 125.8, 51.7, 39.2, 36.4, 36.1, 30.0, 27.2, 27.0, 20.8, 7.8. **MS:** calculated for $C_{16}H_{23}O$ ($M + H^+$), 231.1749; found, 231.1755.

*5.4.11.5.Synthesis of hemiketal **46** and diastereopure diol **42***

Compound **42** was prepared in a diastereopure manner according to the following synthetic sequence:



44 **46** **42**

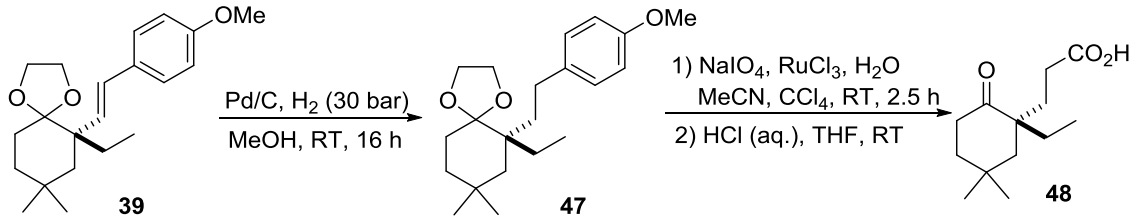
1st step:[270] Compound **44** (62 mg, 0.25 mmol, 1 equiv.) was dissolved in a mixture of *tert*-butanol (36 mL) and H_2O (1 mL) and citric acid (72 mg, 0.75 mmol, 3 equiv.). To the resulting solution *N*-methylmorpholine *N*-oxide (136 mg, 0.75 mmol, 3 equiv.) and osmium tetraoxide (2.5 wt % in ^{t}BuOH) (1.2 mL, 0.1 mmol, 0.2 equiv.) were added and the reaction mixture was stirred at 55 ºC for 24 h. Part of the solvent was eliminated under reduced pressure and the aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to obtain the crude compound which was purified by silica gel flash column chromatography (hexane/EtOAc 85:15). The hemiketal **46** was obtained as a single diastereomer and its structure was confirmed by X-ray analysis. Yield: 60% (38 mg, 0.150 mmol). $[\alpha]_D^{26}$= –18.1º (*c* = 1.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 – 7.34 (m, 4H), 7.34 – 7.24 (m, 1H), 5.49 (d, *J* = 4.2 Hz, 1H), 3.99 (d, *J* = 2.5 Hz, 2H), 2.12 – 1.78 (m, 3H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.66 – 1.17 (m, 8H), 0.96

(t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2, 128.6, 127.7, 126.7, 107.7, 83.3, 79.1, 51.9, 31.9, 27.2, 22.5, 20.6, 18.8, 8.9. **MS:** calculated for $C_{16}H_{21}O_2$ ($M - OH^-$), 245.1536; found, 245.1551.

2nd step: Diol **42** was obtained following the acetalization procedure described above (Section 5.4.11.1) starting from the hemiketal **46** obtained in the previous step (25 mg, 0.10 mmol). White foam. Yield: 96% (29 mg, 0.096 mmol). **[α]$_D^{25}$**= +20.1º (*c* = 0.50, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 5H), 5.54 (d, *J* = 4.7 Hz, 1H), 4.04 – 3.87 (m, 2H), 3.73 – 3.61 (m, 3H), 2.80 (d, *J* = 10.7 Hz, 1H), 2.35 – 2.21 (m, 1H), 2.08 – 1.95 (m, 1H), 1.89 (d, *J* = 13.3 Hz, 2H), 1.74 – 1.67 (m, 1H), 1.62 – 1.50 (m, 2H), 1.49 – 1.36 (m, 3H), 1.32 – 1.20 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.1, 128.0, 126.9, 126.4, 83.6, 79.0, 62.1, 61.7, 52.7, 28.7, 27.9, 22.7, 20.6, 18.8, 8.7. **MS:** calculated for $C_{18}H_{27}O_5$ ($M + H^+$), 307.1904; found, 307.1917.

*5.4.11.6.Synthesis of cycloalkanone **48***

α,α-Dialkyl cycloalkanone **48** was synthesised according to the following synthetic sequence:

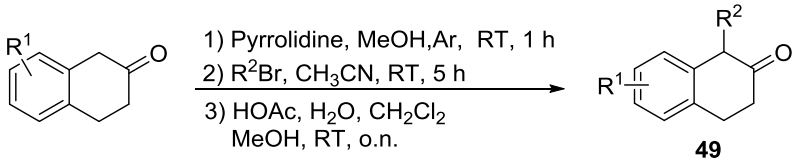


1st step: The previously obtained desulfonylated compound **39** (70 mg, 0.20 mmol, 1 equiv.) and palladium on activated charcoal (10% wt.) (20% wt, 14 mg) were stirred under an hydrogen atmosphere at 30 bar overnight. The resulting suspension was filtered over a pad of celite and the solvent was eliminated under reduced pressure. Product **47** was purified by silica gel flash column chromatography (hexane/EtOAc 95:5). White foam. Yield: 75% (51 mg, 0.15 mmol). **[α]$_D^{23}$**= –18.0º (*c* = 0.50, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.03 – 3.89 (m, 4H), 3.79 (s, 3H), 2.60 – 2.47 (m, 2H), 1.98 – 1.73 (m, 2H), 1.71 – 1.39 (m, 6H), 1.36 (s, 2H), 1.01 (s, 6H), 0.95 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 136.0, 129.1, 113.7, 64.1, 55.2, 46.2, 43.6, 36.4, 35.8, 31.3, 30.6, 30.5, 29.7, 27.8, 25.6, 8.8.

2nd step:[273] The product above obtained (40 mg, 0.12 mmol, 1 equiv.) was dissolved in a 2:2:3 mixture of CH_3CN, CCl_4 and H_2O (2 mL), and sodium metaperiodate (107 mg, 1.2 mmol, 10 equiv.) and ruthenium(III) chloride (0.6 mg, 2.5 mol%) were added. The resulting mixture was vigorously stirred for 2.5 h before being diluted with dichloromethane (2 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The residue was then dissolved in a mixture of THF (0.5 mL) and aqueous HCl (6 M) (0.5 mL) and stirred at room temperature overnight. THF was eliminated under reduced pressure and the remaining aqueous phase was extracted with dichloromethane (3 x 2 mL). The combined organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to afford the desired ketone **48**. Yield: 56% (15.2 mg, 0.067 mmol). $[\alpha]_D^{25}$= +8.2° (*c* = 1.00, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.49 – 2.32 (m, 2H), 2.32 – 2.13 (m, 2H), 1.95 – 1.74 (m, 2H), 1.74 – 1.62 (m, 3H), 1.62 – 1.48 (m, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.78 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.1, 179.4, 49.8, 47.6, 37.3, 35.7, 30.6, 30.6, 30.3, 30.0, 29.4, 28.9, 8.0. **MS:** calculated for $C_{13}H_{23}O_3$ ($M + H^+$), 227.1647; found, 227.1658.

5.4.12. General procedure for the synthesis of *rac* 1-substituted β-tetralones 49

New β-tetralones **49B-H** where synthesised following the procedure previously reported by McNally.[274] **49A** was commercially available.



49

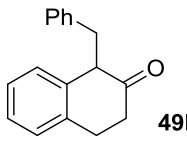
49A R^1 = H, R^2 = H
49B R^1 = H, R^2 = Bn
49C R^1 = H, R^2 = $CH_2CHC(CH_3)_2$
49D R^1 = H, R^2 = CH_2CN
49E R^1 = H, R^2 = CH_2CCH
49F R^1 = 6-Cl, R^2 = Bn
49G R^1 = 6-OMe, R^2 = $CH_2CHC(CH_3)_2$
49H R^1 = 7-OMe, R^2 = Bn

[273] Adapted from: I. Comomer, R. C. Barcelos, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2016**, *55*, 4748–4752.

[274] M. A. Youngman, N. M. Willard, S. L. Dax, J. J. McNally, *Synth. Commun.* **2003**, *33*, 2215–2227.

Pyrrolidine (0.46 mL, 6 mL, 1.2 equiv.) was added to a solution of the corresponding β-tetralone (5 mmol, 1 equiv.) in MeOH under argon and the resulting mixture was stirred for 1 h at room temperature, observing the precipitation of the enamine. The solvent was evaporated and 1,2-dichloroethane (10 mL) was added and evaporated to eliminate the excess pyrrolidine. The residue was dissolved in acetonitrile (10 mL) and the corresponding bromide (6 mmol, 1.2 equiv.) was added. The resulting solution was stirred at room temperature for 5 h and the solvent was eliminated under reduced pressure. The obtained crude was dissolved in a mixure of dichloromethane (7 mL), water (7 mL), methanol (15 mL) and acetic acid (1 mL) and the mixture was stirred at room temperature overnight. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The corresponding products were purified by flash column chromatography (hexane/EtOAc 90:10).

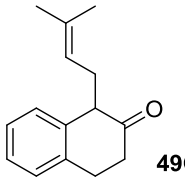
1-Benzyltetralone (49B)



49B

The adduct was obtained following the general procedure. Yellow oil. Yield: 68% (803 mg, 3.4 mmol). The spectral data was coincidental with the one described in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22–7.08 (m, 6H), 6.99–6.86 (m, 3H), 3.74 (t, *J* = 6.4 Hz, 1H), 3.23 (d, *J* = 2.8 Hz, 1H), 3.21 (d, *J* = 1.9 Hz, 1H), 2.90–2.75 (m, 1H), 2.69–2.39 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 138.1, 136.9, 136.4, 129.4, 128.5, 128.1, 127.6, 126.8, 126.6, 126.4, 55.0, 39.0, 38.3, 27.2.

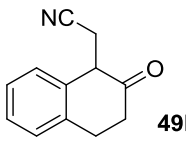
1-(3-Methylbut-2-en-1-yl)-tetralone (49C)



49C

The adduct was obtained following the general procedure. Yellow oil. Yield: 82% (879 mg, 4.1 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24–7.11 (m, 1H), 5.06 (m, 1H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.15 (m, 1H), 3.01 (m, 1H), 2.59 (m, 4H), 1.65 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5, 137.2, 136.6, 134.3, 128.3, 127.8, 126.8, 126.7, 120.5, 53.8, 37.9, 30.8, 27.9, 25.8, 17.7. **MS:** calculated for $C_{15}H_{19}O$ ($M + H^+$), 215.1436; found, 215.1433.

2-(2-Oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (49D)

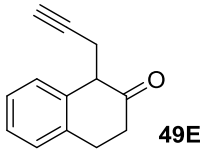


49D

The adduct was obtained following the general procedure. Yellow oil. Yield: 43% (394 mg, 2.1 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 1H), 3.85–3.80 (m, 0H), 3.15–2.98 (m, 1H), 2.80–2.70 (m, 0H), 2.53 (ddd, *J* = 17.6, 8.7, 6.2 Hz, 1H). **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 207.7, 137.3, 133.1, 128.2, 128.0, 127.7, 125.8, 118.3, 48.9, 37.2, 27.9, 16.9. **MS:** calculated for $C_{13}H_{13}O$ ($M + H^+$), 185.0966; found, 185.0958.

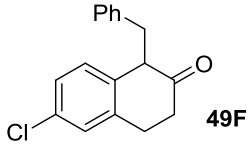
1-(Prop-2-yn-1-yl)-tetralone (49E)



49E

The adduct was obtained following the general procedure. Yellow oil. Yield: 70% (645 mg, 3.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 4H), 3.64 (m, 1H), 3.16–3.06 (m, 1H), 3.01–2.78 (m, 1H), 2.73–2.50 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.9, 137.3, 135.3, 127.8, 127.2, 127.2, 127.1, 81.7, 70.4, 51.5, 37.8, 27.9, 19.4. **MS:** calculated for $C_{13}H_{13}O$ ($M + H^+$), 185.0966; found, 185.0958.

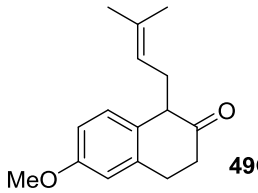
1-Benzyl-6-chlorotetralone (49F)



49F

The adduct was obtained following the general procedure. Yellow oil. Yield: 56% (758 mg, 2.8 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20–7.15 (m, 3H), 7.15–7.10 (m, 2H), 6.87 (dd, *J* = 6.4, 3.1 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 3.70 (t, *J* = 6.4 Hz, 1H), 3.22–3.16 (m, 2H), 2.83–2.74 (m, 1H), 2.62–2.54 (m, 1H), 2.53–2.40 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.4, 138.6, 137.7, 134.9, 132.5, 130.0, 129.3, 128.2, 127.7, 126.7, 126.6, 54.5, 39.2, 37.9, 27.0. **MS:** calculated for $C_{17}H_{19}OCl$ ($M + H^+$), 271.0890; found, 271.0895.

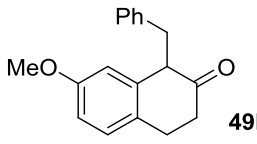
6-Methoxy-1-(3-methylbut-2-en-1-yl)-tetralone (49G)



49G

The adduct was obtained following the general procedure. Yellow oil. Yield: 46% (561 mg, 2.3 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.86–6.65 (m, 2H), 5.04 (t, *J* = 7.3 Hz, 1H), 3.79 (s, 3H), 3.36 (t, *J* = 6.6 Hz, 1H), 3.17–3.02 (m, 1H), 3.02–2.87 (m, 1H), 2.67–2.40 (m, 4H), 1.63 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5, 158.2, 137.7, 134.0, 129.1, 120.5, 113.1, 112.1, 55.2, 52.9, 37.7, 30.8, 28.0, 25.6, 17.6. **MS:** calculated for $C_{15}H_{19}O_2$ ($M + H^+$), 231.1385; found, 231.1372.

1-Benzyl-7-methoxytetralone (49H)



49H

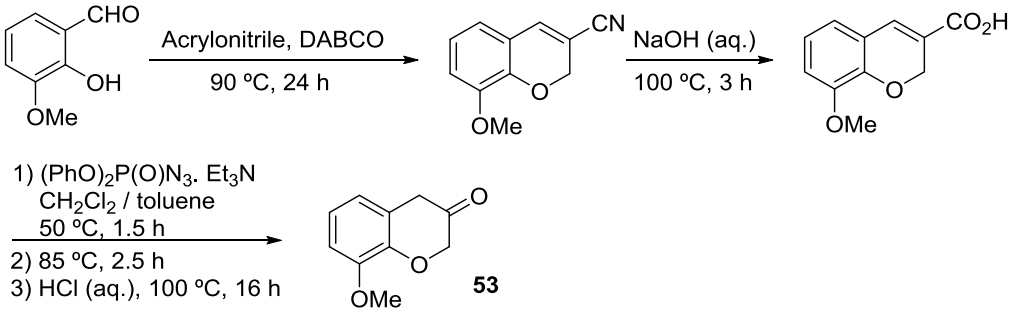
The adduct was obtained following the general procedure. Yellow oil. Yield: 60% (799 mg, 3.0 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25–7.10 (m, 4H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.73 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 3.66 (s, 3H), 3.29–3.08 (m, 2H), 2.87–2.73 (m, 1H), 2.69–2.35 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 158.2, 138.1, 137.5, 129.4, 128.8, 128.6,

128.1, 126.4, 113.6, 112.7, 55.2, 39.1, 38.5, 26.4. **MS** (ESI, m/z): calculated for $C_{18}H_{19}O_2$ ($M + H^+$), 167.1385; found, 167.1392.

5.4.13. Preparation of chroman-3-ones 53 and 65

8-Methoxychroman-3-one (53)

The title compound was synthesised according to the following synthetic sequence as described in the literature:[275]



1st step: *o*-Vanilin (1.5 mL, 10 mmol, 1 equiv.), acrylonitrile (3.28 mL, 50 mmol, 5 equiv.) and DABCO (247 mg, 2.2 mmol, 0.22 equiv.) were stirred for 24 h at 90 °C and the course of the reaction was followed by TLC on silica (hex:CH_2Cl_2 70:30). After the aldehyde disappeared. the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 (30 mL) and washed with a saturated solution of $NaHCO_3$ and brine. The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure, affording the crude nitrile, which was purified by column chromatography on silica gel (hexane/EtOAc 80:20). Yield: 67% (1.0 g, 6.7 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 1.3 Hz, 1H), 6.94 (d, *J* = 1.3 Hz, 1H), 6.92 (s, 1H), 6.74 (dd, *J* = 5.1, 4.0 Hz, 1H), 4.87 (d, *J* = 1.4 Hz, 2H), 3.88 (s, 3H).

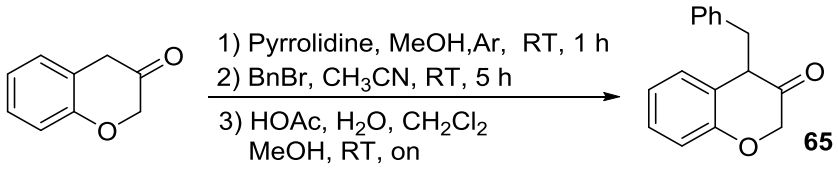
2nd step: An aqueous solution of NaOH (10%, 23 mL) was added to the 2*H*-chromenecarbonitrile above obtained (1.0 g, 10 mmol, 1 equiv.). The reaction mixture was heated to 100 °C for 3 h. The course of the reaction was followed by TLC on silica (hex:CH_2Cl_2 1:1) and after completion, the reaction mixture was cooled to room temperature and an aqueous solution of HCl (3 N) was carefully added dropwise until pH 3 was reached. The product precipitated as a pale yellow solid, which was filtered,

[275] D. Pressnitz, C. S. Fuchs, J. H. Sattler, T. Knaus, P. Macheroux, F. G. Mutti, W. Kroutil. *ACS Catal.* **2013**, *3*, 555−559.

recrystallized from MeOH and dried over night over $CaCl_2$ in a dessicator. Yield: 77% (1.4 g, 7.7 mmol).

3rd step: The 2*H*-chromenecarboxylic acid obtained in the previous step (5 mmol, 1 equiv.) was suspended in CH_2Cl_2 (11.5 mL). After addition of Et_3N (0.9 mL, 6.5 mmol, 1.3 equiv.), a homogeneous solution was obtained. Then, a solution of $(PhO)_2P(O)N_3$ (1.19 mL, 5.5 mmol, 1.1 equiv.) in toluene (5 mL) was added dropwise to the reaction mixture over a period of 15 minutes. Afterwards, the solution was heated to 50 °C for 1.5 h. Another aliquot of toluene (11.5 mL) was added and the solution was heated subsequently to 85 °C for 2.5 h. The quantitative formation of the isocyanate intermediate was followed by TLC on silica (hexane/CH_2Cl_2 20:80). Finally, the reaction mixture was cooled down and an aqueous solution of HCl (6 N, 50 mL) was added. The biphasic system was heated under reflux for 16 h. The course of the reaction was controlled by TLC on silica gel (hexane/CH_2Cl_2 20:80). Then, the layers were separated; the organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The product was purified by column purification on silica gel (hexane/EtOAc 90:10). Pale yellow solid. m. p. = 81–82 ºC. Yield: 48% (430 mg, 2.4 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.02 – 6.91 (m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.41 (s, 2H), 3.86 (s, 3H), 3.56 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.1, 149.1, 143.4, 123.2, 122.5, 120.3, 110.7, 72.9, 55.8, 40.5. **MS:** calculated for $C_{10}H_{11}O_3$ ($M + H^+$), 179.0708; found, 179.0708.

4-(2-Methylprop-1-en-1-yl)chroman-3-one (65)

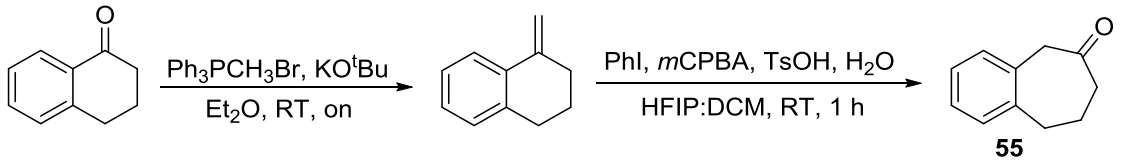


The same procedure employed for the synthesis of *rac* 1-substituted β-tetralones (Section 5.4.12) was used starting from the commercially available 5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (740 mg, 5 mmol), obtaining compound **65** as a yellow oil. Yield: 30% (360 mg, 1.5 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 4H), 7.07 – 6.87 (m, 4H), 6.77 (d, *J* = 7.5 Hz, 1H), 4.51 (d, *J* = 17.8 Hz, 1H), 4.35 (d, *J* = 17.8 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.25 (dd, *J* = 13.5, 5.5 Hz, 1H), 3.09 (dd, *J* = 13.5, 8.7 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.1, 154.4, 137.4, 129.2, 129.1, 128.6, 128.3, 126.6, 123.0, 117.6, 72.7, 52.6, 38.0.

5.4.14. Preparation of seven-membered cycloalkanones 55 and 66

5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (55)

Known cycloalkanone **55**[276] was prepared according to the following synthetic sequence:



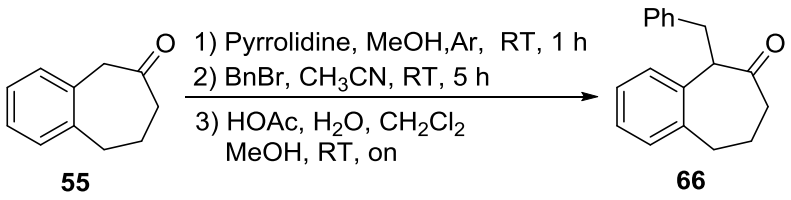
1st step:[277] Under argon atmosphere, potassium *tert*-butoxide (1.35 g, 12 mmol, 1.2 equiv.) was added to a mixture of methyltripheylphosphonium bromide (4.29 g, 12 mmol, 1.2 equiv.) in anhydrous Et_2O. The resulting mixture was stirred at rt for 1 h and a solution of α-tetralone (1.3 mL, 10 mmol, 1 equiv.) in Et_2O (5 mL) was slowly added. The resulting mixture was allowed to stir overnight, passed through a pad of celite and washed with Et_2O. The solvent was eliminated under reduced pressure and the crude was diluted with hexane before passing it again trough a pad of celite. The alkene was purified by flash column chromatography (hexane/EtOAc 99:1). The spectroscopic data were identical to those reported in the literature. Yield: Cuantitative. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 1H), 7.18 – 7.13 (m, 2H), 7.13 – 7.06 (m, 1H), 5.62 – 5.27 (m, 1H), 4.95 (d, *J* = 1.3 Hz, 1H), 2.85 (t, *J* = 6.3 Hz, 2H), 2.61 – 2.46 (m, 2H), 1.89 (p, *J* = 6.3 Hz, 2H).

2nd step:[276] Iodobenzene (1.3 mL, 11.5 mmol, 1.15 equiv.), *meta*-chloroperbenzoic acid (70%) (2.6 g, 11.5 mmol, 1.15 equiv.) and *para*-toluenesulfonic acid monohydrate (2.2 g, 11.5 mmol, 1.15 equiv.) were stirred together in hexafluoroisopropanol (HFIP)/CH_2Cl_2 (1:6) (50 mL) for 30 min before the previously obtained alkene was added at 0 ºC. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with $NaHCO_3$, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The desired ketone **55** was purified by flash column chromatography (hexane/EtOAc 92:8). Yellow oil. Yield: 90% (1.44 g, 9.0 mmol). The spectroscopic data were identical to those reported in the literature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24–7.12 (m, 4H), 3.73 (s, 2H), 3.10–2.80 (m, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.00 (dt, *J* = 13.2, 6.6 Hz, 2H).

[276] A. Ahmad, P. Scarassati, N. Jalalian, B. Olofsson, L. F. Silva Jr., *Tetrahedron Lett.* **2013**, *54*, 5818–5820.

[277] D. H. T. Phan, K. G. M. Kou, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16354–16355.

5-benzyl-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (66)

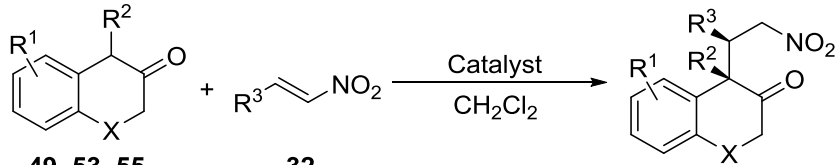


55 **66**

The same procedure employed for the synthesis of *rac* 1-substituted β-tetralones (Section 5.4.12) was used starting compound **55** (801 mg, 5 mmol), affording new product **66** as a yellow oil. Yield: 64% (803 mg, 3.2 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.06 (m, 8H), 7.02 (d, *J* = 6.3 Hz, 1H), 4.15 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.65 (dd, *J* = 13.4, 7.9 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.79 (ddd, *J* = 14.1, 9.3, 4.0 Hz, 1H), 2.67 – 2.53 (m, 1H), 2.53 – 2.43 (m, 1H), 2.15 – 2.00 (m, 1H), 1.98 – 1.80 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.88 , 140.08 , 139.71 , 136.56 , 129.35 , 129.21 , 128.15 , 127.85 , 127.27 , 126.88 , 126.05 , 58.67 , 43.70 , 35.02 , 32.72 , 27.88 . **MS:** calculated for $C_{18}H_{19}O_5$ ($M + H^+$), 251.1436; found, 251.1436.

5.4.15. α-Alkylation of β-tetralones and related ketones with nitroalkenes

5.4.15.1.General procedure



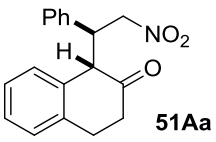
49, 53, 55 **32** **51, 54, 56**

The selected catalyst (2 mol% for R^2 = H; 10 mol% for $R^2 \neq$ H) was added to a solution of the corresponding cycloalkanone **49**, **53** or **55** (0.3 mmol, 1 equiv.) and nitroalkene **32** (0.36 mmol, 1,2 equiv.) in CH_2Cl_2 at the specified temperature. The resulting solution was stirred at the specified temperature until the reaction was completed (monitored by TLC hexane/EtOAc 80:20) and the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 90:10), affording the corresponding α-alkylation adducts as essentially pure compound.

The racemic version of the reaction was performed following the asymmetric reaction procedure except the reaction was conducted at room temperature and TEA (20 mol%) was used as the catalyst.

*5.4.15.2.Characterization data for compounds **51**, **54** and **56***

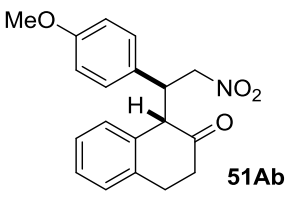
(*S*)-1-((*S*)-2-Nitro-1-phenylethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Aa)



51Aa

The adduct was obtained as a 4:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), nitrostyrene **32a** (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 83% (75 mg, 0.251 mmol). Major diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (dq, *J* = 22.2, 7.5 Hz, 6H), 6.84 (d, *J* = 7.0 Hz, 1H), 6.71 (d, *J* = 6.9 Hz, 2H), 4.94 (dd, *J* = 13.4, 7.7 Hz, 1H), 4.72 (dd, *J* = 13.4, 7.7 Hz, 1H), 4.27 (q, *J* = 7.6 Hz, 1H), 3.65 (d, *J* = 6.3 Hz, 1H), 2.68–2.45 (m, 2H), 2.45–2.27 (m, 1H), 2.14–1.99 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.4, 138.1, 135.8, 132.9, 129.6, 128.6, 128.2, 128.1, 127.6, 126.6, 77.2, 56.6, 46.3, 38.5, 26.3. Minor diastereomer (*R*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (dq, *J* = 22.2, 7.5 Hz, 6H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.0 Hz, 2H), 5.30 (dd, *J* = 13.8, 7.3 Hz, 1H), 5.03 (dd, *J* = 13.8, 8.0 Hz, 1H), 4.01–3.87 (m, 1H), 3.76 (d, *J* = 4.5 Hz, 1H), 2.68–2.45 (m, 2H), 2.45–2.25 (m, 1H), 1.81–1.63 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.8, 137.3, 135.3, 132.9, 129.1, 128.6, 128.2, 127.9, 127.5, 127.3, 77.6, 54.8, 49.8, 39.4, 26.1. **MS:** calculated for $C_{18}H_{18}NO_3$ ($M + H^+$), 296.1287; found, 296.1284. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times of major diastereomer: 12.6 min (major), 13.8 min (minor). Retention times of minor diastereomer: 10.4 min (minor), 23.3 min (major)).

(*S*)-1-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ab)

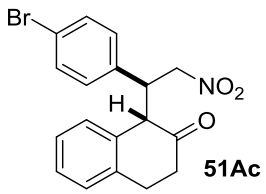


51Ab

The adduct was obtained as a 8:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), *p*-methoxynitrostyrene (**32b**) (65 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 85% (83 mg, 0.255 mmol). Major diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.08 (m, 3H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.71–6.57 (m, 4H), 4.89 (dd, *J* = 13.2, 7.8 Hz, 1H), 4.66 (dd, *J* = 13.2, 7.8 Hz, 1H), 4.31–4.16 (m, 1H), 3.74 (s, 3H), 2.65–2.45 (m, 2H), 2.42–2.22 (m, 1H), 2.14–1.97 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.6, 159.3, 138.2, 133.0, 129.6, 129.3, 128.2, 127.6, 127.5, 126.6, 113.9, 77.9, 56.5, 55.1, 45.8, 38.6, 26.3. Minor diastereomer (*R*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.08 (m, 3H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.71–6.57 (m, 4H), 5.32–5.21 (m, 1H), 4.99 (dd, *J* = 13.6, 8.1 Hz, 1H), 3.93–3.84 (m, 1H), 3.74 (s, 3H), 2.65–2.45 (m, 1H), 2.42–2.22 (m, 2H), 1.88–1.73 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.6,

159.3, 138.2, 133.0, 129.6, 129.3, 128.2, 127.6, 127.5, 126.6, 113.9, 77.9, 56.5, 55.1, 45.8, 38.6, 26.3. **MS:** calculated for $C_{19}H_{20}NO_4$ (M + H^+), 348.1212; found, 348.1207. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times of major diastereomer: 11.3 min (major), 12.6 min (minor). Retention times of minor diastereomer: 9.5 min (minor), 34.2 min (major)).

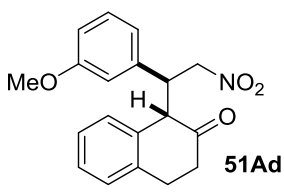
(*S*)-1-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ac)



51Ac

The adduct was obtained as a 4:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), *p*-bromonitrostyrene (**32c**) (82 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 88% (99 mg, 0.264 mmol). Major diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35–7.11 (m, 5H), 6.84 (d, *J* = 6.8 Hz, 1H), 6.62 (dd, *J* = 15.2, 8.4 Hz, 2H), 4.90 (dd, *J* = 13.4, 7.3 Hz, 1H), 4.70 (dd, *J* = 13.4, 8.2 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 1H), 3.64 (d, *J* = 6.3 Hz, 1H), 2.72–2.50 (m, 2H), 2.45–2.27 (m, 1H), 2.22–2.08 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.0, 138.0, 134.9, 132.6, 131.7, 129.9, 129.5, 128.3, 127.9, 127.4, 122.3, 77.5, 56.3, 45.7, 38.5, 26.5. Minor diastereomer (*R*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35–7.11 (m, 5H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.62 (dd, *J* = 15.2, 8.4 Hz, 2H), 5.25 (dd, *J* = 13.8, 7.0 Hz, 1H), 5.03 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.97–3.87 (m, 1H), 3.76 (d, *J* = 4.5 Hz, 1H), 2.72–2.50 (m, 1H), 2.45–2.27 (m, 2H), 1.92–1.78 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.5, 137.1, 135.0, 134.4, 131.7, 129.8, 129.0, 128.1, 127.7, 126.8, 122.3, 77.5, 54.6, 49.2, 39.5, 26.4. **MS:** calculated for $C_{18}H_{17}NO_3Br$ (M + H^+), 396.0211; found, 396.0217. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times of major diastereomer: 14.9 min (minor), 17.9 min (major). Retention times of minor diastereomer: 9.0 min (minor), 31.0 min (major)).

(*S*)-1-((*S*)-1-(3-Methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ad)

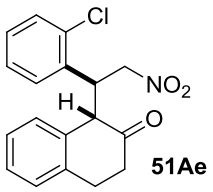


51Ad

The adduct was obtained as a 4:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), *m*-methoxynitrostyrene (**32d**) (65 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 80% (78 mg, 0.240 mmol). Major diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz,

$CDCl_3$) δ 7.39–7.34 (m, 1H), 7.32–7.05 (m, 3H), 6.91 (d, *J* = 6.9 Hz, 1H), 6.84–6.76 (m, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.20 (dt, *J* = 4.2, 2.1 Hz, 1H), 4.96 (dd, *J* = 13.5, 7.9 Hz, 1H), 4.74 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.34–4.23 (m, 1H), 3.68 (d, *J* = 6.2 Hz, 1H), 3.63 (s, 3H), 2.72–2.47 (m, 2H), 2.47–2.28 (m, 1H), 2.24–2.10 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.4, 159.5, 138.2, 137.2, 133.0, 129.6, 129.6, 128.1, 127.7, 127.3, 120.6, 114.0, 113.5, 77.1, 56.5, 54.7, 46.4, 38.6, 26.3. Minor diastereomer (*R*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39–7.34 (m, 1H), 7.32–7.05 (m, 4H), 6.84–6.76 (m, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 6.20 (dt, *J* = 4.2, 2.1 Hz, 1H), 5.32 (dd, *J* = 13.9, 7.4 Hz, 1H), 5.05 (dd, *J* = 13.9, 7.9 Hz, 1H), 3.95 (td, *J* = 7.6, 4.5 Hz, 1H), 3.79 (d, *J* = 4.4 Hz, 1H), 3.61 (s, 3H), 2.72–2.47 (m, 1H), 2.47–2.28 (m, 2H), 1.82 (ddd, *J* = 16.6, 11.2, 6.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.8, 159.4, 137.4, 136.7, 135.4, 129.6, 129.1, 127.9, 127.5, 126.6, 119.9, 114.2, 113.8, 77.5, 55.0, 55.0, 49.9, 39.5, 26.2. **MS:** calculated for $C_{19}H_{20}NO_4$ (M + H^+), 348.1212; found, 348.1207. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times of major diastereomer: 14.0 min (major), 15.2 min (minor). Retention times of minor diastereomer: 12.7 min (minor), 20.0 min (major)).

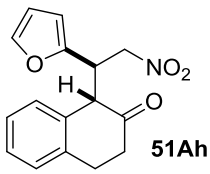
(*S*)-1-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ae)



51Ae

The adduct was obtained as single isomer by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), *o*-chloronitrostyrene (**32e**) (66 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 86% (85 mg, 0.258 mmol). **[α]**$_D^{23}$= –36.0º (*c* = 2.00, 99% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28–7.08 (m, 7H), 6.99–6.91 (m, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 5.05–4.86 (m, 2H), 4.77–4.63 (m, 1H), 3.73 (d, *J* = 9.5 Hz, 1H), 3.32 (ddd, *J* = 16.8, 11.7, 5.5 Hz, 1H), 2.98 (ddd, *J* = 15.8, 6.6, 2.9 Hz, 1H), 2.77 (ddd, *J* = 18.5, 5.5, 2.9 Hz, 1H), 2.49 (ddd, *J* = 18.5, 11.7, 6.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.1, 137.4, 134.6, 133.1, 130.0, 129.0, 128.9, 128.8, 127.9, 127.6, 127.0, 126.5, 76.4, 57.3, 40.5, 37.7, 27.1. **MS:** calculated for $C_{18}H_{16}NO_3ClNa$ (M + Na^+), 352.0716; found, 352.0721. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 17.5 min (major), 22.1 min (minor)).

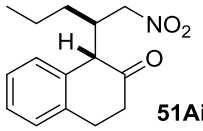
(*S*)-1-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ah)



51Ah

The adduct was obtained as a 1:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), 2-(2-nitrovinyl)furan (**32h**) (50 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –20 ºC. Foam. Yield: 84% (72 mg, 0.252 mmol). *dr* = 1:1. Diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37–7.07 (m, 4H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.25–6.22 (m, 1H), 5.81 (d, *J* = 3.2 Hz, 1H), 5.07 (dd, *J* = 13.9, 6.6 Hz, 1H), 4.91 (dd, *J* = 17.2, 7.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 1H), 3.80–3.72 (m, 1H), 2.90–2.23 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.5, 149.1, 142.3, 137.0, 134.7, 128.8, 128.0, 127.5, 127.2, 110.9, 108.8, 76.2, 53.3, 42.8, 39.0, 26.6. Diastereomer (*R*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37–7.07 (m, 5H), 6.20 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.85 (d, *J* = 3.1 Hz, 1H), 4.86 (dd, *J* = 17.0, 7.5 Hz, 1H), 4.76 (dd, *J* = 13.7, 8.0 Hz, 1H), 4.14 (ddd, *J* = 8.3, 6.8, 4.8 Hz, 1H), 3.80–3.72 (m, 1H), 2.90–2.23 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.8, 149.3, 142.3, 137.4, 133.0, 129.0, 128.1, 127.7, 126.7, 110.6, 108.7, 75.5, 55.2, 39.8, 38.3, 26.6. **MS:** calculated for $C_{15}H_{15}NO_4Na$ (M + Na^+), 308.0899; found, 308.0896. The enantiomeric purity was determined by chiral HPLC analisys (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times of diastereomer A: 9.7 min (minor), 10.7 min (major). Retention times of diastereomer B: 13.9 min (minor), 14.3 min (major)).

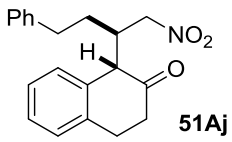
(*S*)-1-((*R*)-1-Nitropentan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ai)



51Ai

The adduct was obtained as a 5:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), 1-nitropent-1-ene (**32i**) (41 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at room temperature. Foam. Yield: 81% (88 mg, 0.243 mmol). Major diastereomer (*S*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 4H), 4.82 (dd, *J* = 13.5, 7.8 Hz, 1H), 4.53–4.47 (m, 1H), 3.49 (d, *J* = 6.8 Hz, 1H), 3.32–3.10 (m, 1H), 3.08–2.84 (m, 2H), 2.72–2.42 (m, 2H), 1.58–1.15 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.3, 137.4, 134.4, 128.6, 128.3, 127.5, 127.1, 76.8, 55.0, 38.3, 38.1, 32.2, 27.7, 19.6, 13.8. Minor diastereomer (*R*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 4H), 4.58–4.23 (m, 2H), 3.57 (d, *J* = 5.2 Hz, 1H), 3.32–3.10 (m, 1H), 3.08–2.84 (m, 2H), 2.72–2.42 (m, 2H), 1.58–1.15 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.3, 136.7, 135.5, 128.6, 128.3, 127.3, 127.2, 77.5, 53.3, 41.4, 39.1, 30.5, 27.9, 20.1, 13.8. **MS:** calculated for $C_{15}H_{19}NO_3Na$ (M + H^+), 284.1263; found, 284.1270. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times of major diastereomer: 21.9 min (major), 22.9 min (minor). Retention times of minor diastereomer: 12.7 min (minor), 14.1 min (major)).

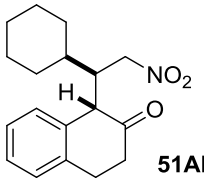
(*R*)-1-((*R*)-1-Nitro-4-phenylbutan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (51Aj)



51Aj

The adduct was obtained as a 5:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), (4-nitrobut-3-en-1-yl)benzene (**32j**) (62 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at room temperature. Foam. Yield: 83% (81 mg, 0.249 mmol). Major diastereomer (*S*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.01 (m, 9H), 4.94–4.43 (m, 2H), 3.55 (d, *J* = 7.0 Hz, 1H), 3.24–3.05 (m, 1H), 3.04–2.87 (m, 2H), 2.74–2.42 (m, 4H), 2.03–1.87 (m, 1H), 1.81–1.65 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.6, 140.1, 136.9, 133.9, 128.2, 128.1, 127.9, 127.7, 127.2, 126.8, 125.8, 76.4, 54.5, 37.6, 37.5, 32.4, 31.3, 27.3. Minor diastereomer (*R*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.01 (m, 9H), 4.68–4.43 (m, 2H), 3.61 (d, *J* = 5.6 Hz, 1H), 3.24–3.05 (m, 1H), 3.04–2.87 (m, 2H), 2.74–2.42 (m, 4H), 2.03–1.87 (m, 1H), 1.81–1.65 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.7, 139.2, 136.3, 133.7, 128.2, 128.1, 127.9, 127.8, 127.0, 126.8, 125.8, 77.0, 53.2, 39.8, 38.4, 32.6, 29.6, 27.5. **MS:** calculated for $C_{20}H_{21}NO_3Na$ (M + Na^+), 346.1419; found, 346.1418. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times of major diastereomer: 30.1 min (major), 34.5 min (minor). Retention times of minor diastereomer: 15.9 min (minor), 18.4 min (major)).

(*S*)-1-((*R*)-1-Cyclohexyl-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ak)

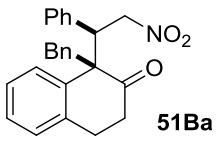


51Ak

The adduct was obtained as a 4:1 mixture of diastereomers by using β-tetralone **49A** (40 µL, 0.3 mmol, 1 equiv.), (2-nitrovinyl)cyclohexane (**32k**) (41 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at room temperature. Foam. Yield: 80% (72 mg, 0.240 mmol). Major diastereomer (*S*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40–7.00 (m, 4H), 4.73–4.26 (m, 2H), 3.55 (d, *J* = 8.4 Hz, 1H), 3.36 (ddd, *J* = 16.1, 10.8, 5.6 Hz, 1H), 3.11–2.91 (m, 1H), 2.83–2.72 (m, 1H), 2.72–2.58 (m, 1H), 2.59–2.36 (m, 1H), 1.85–1.44 (m, 6H), 1.35–0.77 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 137.5, 134.9, 129.0, 128.4, 127.6, 127.1, 74.7, 55.2, 42.5, 38.0, 37.7, 31.8, 27.7, 27.5, 26.3, 26.2. Minor diastereomer (*R*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40–7.00 (m, 4H), 4.73–4.26 (m, 2H), 3.55 (d, *J* = 8.4 Hz, 1H), 3.36 (m, 1H), 3.11–2.91 (m, 1H), 2.83–2.72 (m, 1H), 2.72–2.58 (m, 1H), 2.59–2.36 (m, 1H), 1.85–1.44 (m, 6H), 1.35–0.77 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.3, 137.0, 135.1, 129.1, 128.4, 127.7, 127.2, 75.5, 54.1, 44.9, 38.3, 38.0, 31.9, 28.6, 27.6, 26.5, 26.0. **MS:** calculated for $C_{18}H_{23}NO_3Na$ (M + Na^+), 324.1576; found, 324.1576. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times of major diastereomer:

30.7 min (major), 32.6 min (minor). Retention times of minor diastereomer: 15.1 min (minor), 15.9 min (major)).

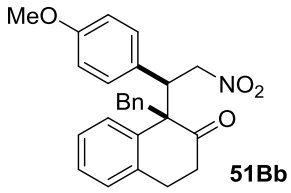
(*S*)-1-Benzyl-1-((*R*)-2-nitro-1-phenylethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ba)



51Ba

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), nitrostyrene (**32a**) (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28** and carrying out the reaction at –10 ºC. Foam. Yield: 82% (95 mg, 0.261 mmol). Carrying out the reaction in the presence of 10 mol% catalyst **C13** at –20 ºC, compound **51Ba** with essentially identical *dr* and *ee* was obtained in 80% isolated yield. $[\alpha]_D^{23}$= –105.7º (*c* = 2,00, 92% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.3 Hz, 1H), 7.54–7.42 (m, 1H), 7.36–7.24 (m, 1H), 7.20–7.09 (m, 1H), 7.08–7.00 (m, 5H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.84–6.74 (m, 2H), 6.53 (d, *J* = 7.3 Hz, 2H), 5.10 (dd, *J* = 12.4, 4.2 Hz, 1H), 4.85 (t, *J* = 12.0 Hz, 1H), 4.63 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.60 (d, *J* = 12.5 Hz, 1H), 3.35 (d, *J* = 12.6 Hz, 1H), 2.16–2.04 (m, 2H), 1.28–1.12 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 139.9, 135.6, 135.2, 134.9, 130.3, 129.5, 128.7, 128.0, 128.0, 127.8, 127.7, 127.6, 126.7, 126.4, 76.5, 60.4, 52.1, 43.3, 40.3, 26.1. **MS:** calculated for $C_{25}H_{23}NO_3Na$ (M + Na^+), 408.1576; found, 408.1587. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times: 11.8 min (minor), 14.7 min (major)).

(*S*)-1-Benzyl-1-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Bb)

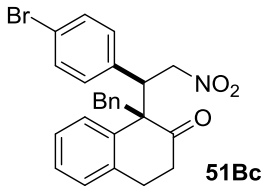


51Bb

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), *p*-methoxynitrostyrene (**32b**) (65 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at –10 ºC for 24 h. Foam. Yield: 79% (98 mg, 0.24 mmol). $[\alpha]_D^{23}$= –114.7º (*c* = 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.09–7.00 (m, 3H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.82–6.76 (m, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 6.43 (d, *J* = 8.0 Hz, 2H), 5.06 (dd, *J* = 12.1, 4.1 Hz, 1H), 4.78 (t, *J* = 12.0 Hz, 1H), 4.57 (dd, *J* = 11.9, 4.2 Hz, 1H), 3.70 (s, 3H), 3.57 (d, *J* = 12.5 Hz, 1H), 3.33 (d, *J* = 12.6 Hz, 1H), 2.22–2.01 (m, 2H), 1.42–1.07 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 159.1, 139.9, 135.7, 135.0, 130.6, 130.3, 128.7, 128.0, 127.7, 127.6, 127.0, 126.6, 126.4, 113.3, 76.8, 60.4, 55.1, 51.5, 43.3, 40.3, 26.2. **MS:** calculated for $C_{26}H_{25}NO_4Na$ (M + Na^+), 438.1681; found, 438.1687. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC,

hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 21.4 min (major), 29.3 min (minor)).

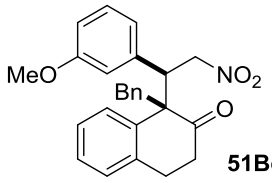
(*S*)-1-Benzyl-1-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Bc)



51Bc

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), *p*-bromonitrostyrene (**32c**) (82 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at –10 ºC for 24 h. Foam. Yield: 85% (118 mg, 0.26 mmol). $[\alpha]_D^{23}$= –138.9º (*c* = 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.12–7.00 (m, 3H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 9.3 Hz, 2H), 6.40 (d, *J* = 8.0 Hz, 2H), 5.08 (dd, *J* = 12.3, 4.0 Hz, 1H), 4.79 (t, *J* = 12.2 Hz, 1H), 4.60 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.58 (d, *J* = 12.5 Hz, 1H), 3.30 (d, *J* = 12.5 Hz, 1H), 2.25–2.13 (m, 1H), 2.13–2.02 (m, 1H), 1.39–1.11 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 139.7, 135.3, 134.7, 134.3, 131.1, 130.2, 128.9, 128.1, 127.8, 127.6, 126.8, 126.6, 122.1, 76.4, 60.1, 51.5, 43.5, 40.2, 26.3. **MS:** calculated for $C_{25}H_{22}NO_3BrNa$ (M + Na^+), 486.0681; found, 486.0682. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 12.5 min (major), 19.4 min (minor)).

(*S*)-1-Benzyl-1-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Bd)

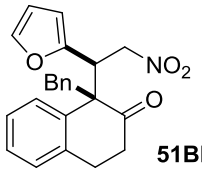


51Bd

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), *m*-methoxynitrostyrene (**32d**) (66 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28** carrying out the reaction at –20 ºC. Foam. Yield: 80% (100 mg, 0.258 mmol). Carrying out the reaction in the presence of 10 mol% catalyst **C13**, compound **51Bd** with essentially identical *dr* and *ee* was obtained in 86% isolated yield. $[\alpha]_D^{23}$= –78.5º (*c* = 2.00, 91% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.09–7.00 (m, 3H), 7.00–6.92 (m, 2H), 6.79 (d, *J* = 7.0 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.18 (d, *J* = 7.4 Hz, 1H), 5.98 (s, 1H), 5.10 (dd, *J* = 12.4, 4.2 Hz, 1H), 4.83 (t, *J* = 12.0 Hz, 1H), 4.61 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.59 (d, *J* = 12.5 Hz, 1H), 3.53 (s, 3H), 3.34 (d, *J* = 12.5 Hz, 1H), 2.26–2.00 (m, 2H), 1.37–1.09 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.0, 158.91 , 140.0, 136.7, 135.6, 135.1, 130.3, 129.0, 128.8, 128.0, 127.7, 127.6, 126.7, 126.4, 122.2, 114.2, 76.5, 60.4, 54.9, 52.0, 43.3, 40.3, 26.2. **MS:** calculated for $C_{26}H_{26}NO_4$ (M + H^+), 416.1862; found, 416.1870. The enantiomeric purity was determined by chiral

HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 11.0 min (minor), 15.4 min (major)).

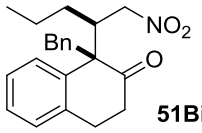
(*S*)-1-Benzyl-1-((*R*)-1-(furan-2-yl)-2-nitroethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Bh)



51Bh

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), 2-(2-nitrovinyl)furan (**32h**) (50 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at –20 ºC. Foam. Yield: 60% (68 mg, 0.216 mmol). Carrying out the reaction in the presence of 10 mol% catalyst **C13**, compound **51Bh** with essentially identical *dr* and *ee* was obtained in 72% isolated yield. $[\alpha]_D^{23}$= –9.0º (*c* = 2.00, 90% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 7.03 (d, *J* = 24.3 Hz, 4H), 6.71 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.01–5.93 (m, 1H), 4.89–4.74 (m, 2H), 4.65 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.48–3.31 (m, 2H), 2.27 (ddt, *J* = 16.4, 10.8, 5.2 Hz, 2H), 2.11–1.96 (m, 1H), 1.66–1.52 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.5, 149.7, 142.3, 138.6, 135.6, 130.3, 128.6, 128.0, 127.5, 127.4, 126.7, 110.6, 109.7, 74.8, 59.3, 46.4, 43.5, 40.5, 26.7. **MS:** calculated for $C_{23}H_{22}NO_4$ (M + H^+), 376.1549; found, 376.1555. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 17.0 min (major), 24.4 min (minor)).

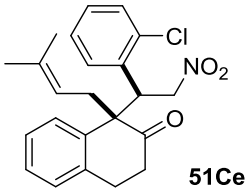
(*S*)-1-Benzyl-1-((*R*)-1-nitropentan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (51Bi)



51Bi

The adduct was obtained by using 1-benzyl-β-tetralone **49B** (70 mg, 0.3 mmol, 1 equiv.), 1-nitropent-1-ene (**32i**) (42 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at room temperature for 48 h. Colourless oil. Yield: 72% (77 mg, 0.22 mmol). $[\alpha]_D^{23}$= +53.7º (*c* = 2.00, 88% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 8.3 Hz, 1H), 7.28–7.21 (m, 1H), 7.19–7.13 (m, 1H), 7.09–6.98 (m, 3H), 6.62 (d, *J* = 7.7 Hz, 2H), 4.57 (dd, *J* = 13.0, 4.1 Hz, 1H), 4.19 (dd, *J* = 13.0, 8.3 Hz, 1H), 3.48 (d, *J* = 12.6 Hz, 1H), 3.31 (dq, *J* = 8.1, 4.1 Hz, 1H), 3.13 (d, *J* = 12.6 Hz, 1H), 2.87–2.72 (m, 1H), 2.40–2.23 (m, 2H), 1.88–1.64 (m, 2H), 1.34–1.10 (m, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.1, 137.6, 136.9, 135.7, 129.8, 129.0, 128.3, 127.4, 127.0, 126.9, 126.6, 126.1, 76.2, 58.8, 54.5, 45.9, 43.8, 40.1, 32.2, 27.1, 20.9, 13.7. **MS:** calculated for $C_{22}H_{26}NO_3$ (M + H^+), 352.1913; found, 352.1928. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 9.4 min (minor), 12.1 min (major)).

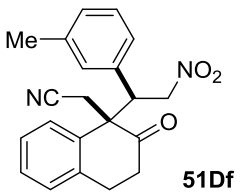
(*S*)-1-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-1-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ce)



51Ce

The adduct was obtained by using 1-(3-methylbut-2-en-1-yl)-β-tetralone **49C** (64 mg, 0.3 mmol, 1 equiv.), *o*-chloronitrostyrene (**32e**) (66 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C13**, and carrying out the reaction at –20 ºC. Foam. Yield: 80% (95 mg, 0.240 mmol). Carrying out the reaction in the presence of 10 mol% catalyst **C28**, compound **51Ce** with essentially identical *dr* and *ee* was obtained in 77% isolated yield. $[\alpha]_D^{23}$= –59.7º (*c* = 2.00, 99% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 7.23–7.09 (m, 3H), 6.90 (d, *J* = 7.5 Hz, 1H), 4.99 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.91–4.70 (m, 2H), 4.58 (t, *J* = 7.1 Hz, 1H), 2.94–2.73 (m, 3H), 2.70–2.53 (m, 2H), 2.49–2.33 (m, 1H), 1.51 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.8, 138.4, 137.0, 136.2, 135.4, 133.5, 130.0, 129.5, 129.0, 128.4, 127.4, 127.0, 126.3, 117.8, 76.6, 57.5, 46.1, 40.5, 34.8, 27.7, 25.7, 18.0. **MS:** calculated for $C_{23}H_{25}NO_3Cl$ (M + H^+), 398.1523; found, 398.1536. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 19.1 min (major), 25.8 min (minor)).

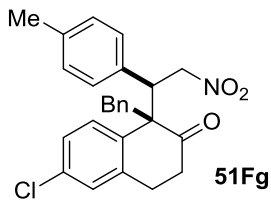
2-((*S*)-1-((*R*)-2-Nitro-1-(m-tolyl)ethyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (51Df)



51Df

The adduct was obtained by using 1-cyanomethyl-β-tetralone **49D** (56 mg, 0.3 mmol, 1 equiv.), *o*-chloronitrostyrene (**32f**) (58 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at –10 ºC for 24 h. Foam. Yield: 78% (82 mg, 0.23 mmol). $[\alpha]_D^{23}$= –31.5º (*c* = 2.00, 91% *ee*, dr= >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 2H), 7.23–7.17 (m, 1H), 7.10–6.97 (m, 3H), 6.49–6.37 (m, 1H), 6.30 (s, 1H), 4.80–4.60 (m, 2H), 4.18 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.19 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.85–2.73 (m, 1H), 2.72–2.56 (m, 2H), 2.16 (s, 3H), 2.22–2.08 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.9, 138.3, 138.2, 133.2, 130.1, 129.4, 129.1, 128.6, 128.4, 127.3, 126.8, 126.2, 116.4, 75.4, 56.6, 50.0, 38.9, 26.7, 24.2, 21.2. **MS:** calculated for $C_{18}H_{18}NO_3$ (M + H^+), 371.1372; found, 371.1372. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 13.4 min (minor), 15.4 min (major)).

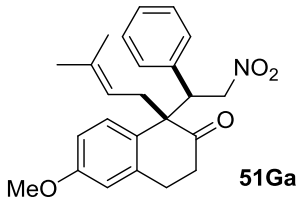
(*S*)-1-Benzyl-6-chloro-1-((*R*)-2-nitro-1-(p-tolyl)ethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Fg)



51Fg

The adduct was obtained by using 1-benzyl-6-chloroβ-tetralone **49F** (81 mg, 0.3 mmol, 1 equiv.), *p*-bromonitrostyrene (**32g**) (58 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C13**, and carrying out the reaction at –20 ºC. Foam. Yield: 84% (109 mg, 0.252 mmol). $[\alpha]_D^{23}$= –162º (*c* = 2.00, 90% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.20–6.99 (m, 4H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.77 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.44 (d, *J* = 7.8 Hz, 2H), 5.04 (dd, *J* = 12.2, 4.3 Hz, 1H), 4.77 (t, *J* = 11.9 Hz, 1H), 4.56 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.50 (d, *J* = 12.7 Hz, 1H), 3.35 (d, *J* = 12.7 Hz, 1H), 2.23 (s, 3H), 2.14–2.01 (m, 2H), 1.30–1.10 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.9, 142.4, 138.4, 136.0, 134.4, 134.0, 132.4, 130.9, 129.9, 129.8, 129.5, 129.2, 128.7, 127.4, 127.2, 77.0, 60.9, 52.3, 43.8, 40.5, 26.6, 21.6. **MS:** calculated for $C_{26}H_{24}NO_3ClNa$ (M + Na^+), 456.1342; found, 456.1346. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 12.8 min (minor), 17.9 min (major)).

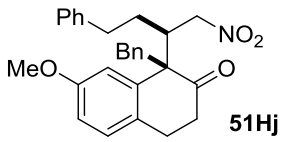
(*S*)-6-Methoxy-1-(3-methylbut-2-en-1-yl)-1-((*R*)-2-nitro-1-phenylethyl)-3,4-dihydronaphthalen-2(1*H*)-one (51Ga)



51Ga

The adduct was obtained by using 6-methoxy-1-cyanomethyl-β-tetralone **49G** (72 mg, 0.3 mmol, 1 equiv.), nitrostyrene (**32a**) (54 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C13**, and carrying out the reaction at –20 ºC for 16 h. Foam. Yield: 79% (86 mg, 0.237 mmol). $[\alpha]_D^{23}$= –81.9º (*c* = 2.00, 98% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 4.2 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.93 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64–6.48 (m, 3H), 5.02 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.81–4.66 (m, 2H), 4.40 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.89 (s, 3H), 3.00 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.77 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.47–2.30 (m, 2H), 2.18–2.02 (m, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.36–1.16 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.8, 158.6, 141.2, 135.5, 129.5, 128.3, 128.0, 127.8, 127.1, 117.9, 113.5, 112.3, 76.4, 58.2, 55.3, 51.4, 40.4, 35.7, 26.5, 25.8, 18.0. **MS:** calculated for $C_{24}H_{28}NO_4$ (M + H^+), 394.2023; found, 394.2018. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 12.7 min (minor), 18.3 min (major)).

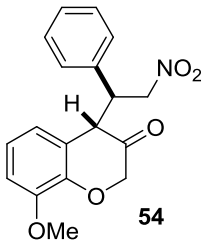
(*S*)-1-Benzyl-7-methoxy-1-((*R*)-1-nitro-4-phenylbutan-2-yl)-3,4-dihydronaphthalen-2(1*H*)-one (51Hj)



51Hj

The adduct was obtained by using 1-benzyl-7-methoxy-β-tetralone **49H** (80 mg, 0.3 mmol, 1 equiv.), (4-nitrobut-3-en-1-yl)benzene (**32j**) (64 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C28**, and carrying out the reaction at 0 ºC. Foam. Yield: 81% (108 mg, 0.243 mmol). Carrying out the reaction in the presence of 10 mol% catalyst **C13**, compound **51Hj** with essentially identical *dr* and *ee* was obtained in 81% isolated yield. $[\alpha]_D^{23}$= +45.6º (*c* = 2.00, 89% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.23–7.10 (m, 3H), 7.10–6.98 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.63 (d, *J* = 6.7 Hz, 2H), 4.59 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.28 (dd, *J* = 12.8, 8.5 Hz, 1H), 3.88 (s, 3H), 3.42 (d, *J* = 11.7 Hz, 1H), 3.34–3.23 (m, 1H), 2.95 (d, *J* = 12.7 Hz, 1H), 2.74–2.45 (m, 3H), 2.39–2.08 (m, 3H), 1.95–1.78 (m, 1H), 1.67–1.50 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.3, 158.5, 141.0, 138.5, 135.9, 131.5, 130.2, 129.6, 128.5, 128.4, 127.9, 126.6, 126.2, 113.0, 112.9, 78.1, 59.0, 55.4, 45.8, 44.0, 40.8, 34.4, 32.2, 26.7. **MS:** calculated for $C_{28}H_{30}NO_4$ (M + H^+), 444.2175; found, 444.2176. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 11.4 min (major), 18.7 min (minor)).

(*S*)-8-Methoxy-4-((*S*)-2-nitro-1-phenylethyl)chroman-3-one (54)

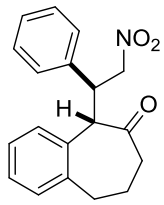


54

The adduct was obtained by using **53** (54 mg, 0.3 mmol, 1 equiv.), nitrostyrene (**32a**) (56 mg, 0.36 mmol, 1.2 equiv.) and catalyst **C7**, and carrying out the reaction at –40 ºC. Foam. 1:1 mixture of diastereomers. Combined yield: 89% (88 mg, 0.267 mmol). Diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 6.88–6.77 (m, 2H), 6.21 (dd, *J* = 6.4, 2.7 Hz, 1H), 4.88 (dd, *J* = 13.7, 7.1 Hz, 1H), 4.76 (dd, *J* = 13.7, 7.9 Hz, 1H), 4.44 (dd, *J* = 100.2, 18.2 Hz, 2H), 4.11 (q, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 3.68 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.8, 149.4, 144.0, 135.5, 128.7, 128.3, 127.8, 123.1, 121.4, 111.7, 76.9, 73.0, 56.0, 54.8, 45.5. Diastereomer (*R*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30–7.25 (m, 3H), 7.11–6.89 (m, 3H), 6.74 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.24–6.19 (m, 1H), 4.92–4.72 (m, 2H), 4.44–4.15 (m, 2H), 4.16–4.03 (m, 1H), 3.88 (s, 3H), 3.80 (d, *J* = 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.5, 149.5, 143.8, 135.1, 128.9, 128.5, 127.7, 123.7, 120.9, 111.9, 77.1, 72.9, 56.0, 53.6, 47.2. **MS:** calculated for $C_{18}H_{17}NO_5Na$ (M + Na^+), 250.1004; found, 250.0992. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 80:20; flux = 1 mL/min;

retention times of major diastereomer: 29.0 min (major), 35.5 min (minor). Retention times of minor diastereomer: 17.3 min (major), 26.1 min (minor)).

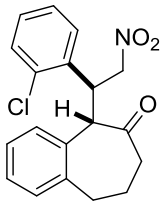
(*S*)-5-((*S*)-2-Nitro-1-phenylethyl)-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (56a)



56a

The adduct was obtained by using **55** (48 mg, 0.3 mmol, 1 equiv.), nitrostyrene (**32a**) (54 mg, 0.36 mmol, 1.2 equiv.) and 10 mol% catalyst **C7**, and carrying out the reaction at room temperature for 24 h. Foam. 4:1 mixture of diastereomers. Combined yield: 82% (76 mg, 0.25 mmol). Major diastereomer (*S*,*S*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.23–7.09 (m, 4H), 6.89–6.82 (m, 1H), 4.86 (dd, *J* = 12.8, 5.0 Hz, 1H), 4.70 (dd, *J* = 12.9, 9.5 Hz, 1H), 4.39 (td, *J* = 9.3, 4.9 Hz, 1H), 4.28 (d, *J* = 9.3 Hz, 1H), 2.81 (dt, *J* = 14.6, 5.0 Hz, 1H), 2.69–2.56 (m, 1H), 2.50–2.39 (m, 2H), 1.97–1.85 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.0, 141.0, 137.0, 133.7, 130.4, 129.1, 128.8, 128.4, 128.3, 128.0, 127.6, 78.8, 61.1, 44.4, 43.2, 32.9, 28.2. Minor diastereomer (*R*,*R*): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.23–7.09 (m, 4H), 7.06–6.99 (m, 1H), 4.88–4.80 (m, 1H), 4.76–4.64 (m, 1H), 4.45–4.34 (m, 1H), 4.15 (d, *J* = 5.7 Hz, 1H), 2.88–2.76 (m, 1H), 2.69–2.56 (m, 1H), 2.50–2.39 (m, 2H), 1.97–1.85 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.4, 141.0, 136.2, 133.2, 129.9, 129.8, 128.7, 128.3, 128.2, 127.7, 126.9, 78.5, 58.9, 42.3, 41.0, 31.4, 27.8. **MS:** calculated for $C_{19}H_{19}NO_3Na$ (M + Na^+), 332.1263; found, 332.1265. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 95:5; flux = 1 mL/min; retention times of major diastereomer: 14.3 min (major), 23.2 min (minor). Retention times of minor diastereomer: 10.6 min (major), 10.8 min (minor)).

(*S*)-5-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (56e)

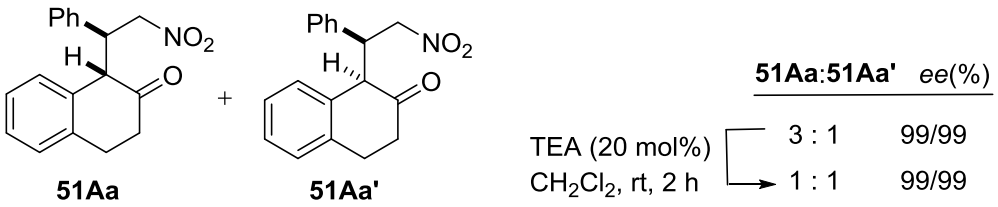


56e

The general procedure was applied starting from **55** (48 mg, 0.3 mmol, 1 equiv.), *o*-chloronitrostyrene (**32e**) (66 mg, 0.36 mmol, 1.2 equiv.) and 10 mol% catalyst **C7**, and carrying out the reaction at room temperature for 32 h. Foam. Single diastereomer.Yield: 75% (77 mg, 0.23 mmol). **[α]**$_D^{23}$= –23.1º (*c* = 2.00, 99% *ee*, *dr* = >20:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.9 Hz, 1H), 7.18–7.11 (m, 1H), 7.11–6.94 (m, 5H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.00–4.76 (m, 4H), 3.25 (ddd, *J* = 13.7, 10.4, 2.8 Hz, 1H), 3.06–2.87 (m, 2H), 2.68 (ddd, *J* = 12.3, 5.2, 3.4 Hz, 1H), 2.33–2.18 (m, 1H), 1.95–1.77 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.1, 141.5, 134.3, 134.1, 132.8, 130.2, 129.5, 128.9, 128.6, 127.6, 127.3, 127.2, 77.5, 54.7, 45.4, 38.7, 33.4, 28.7. **MS:** calculated for $C_{19}H_{18}ClNO_3Na$ (M + Na^+), 366.0873; found, 366.0869. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA,

hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 7.2 min (major), 8.4 min (minor)).

5.4.16. Base-promoted epimerization of β-tetralone 51Aa

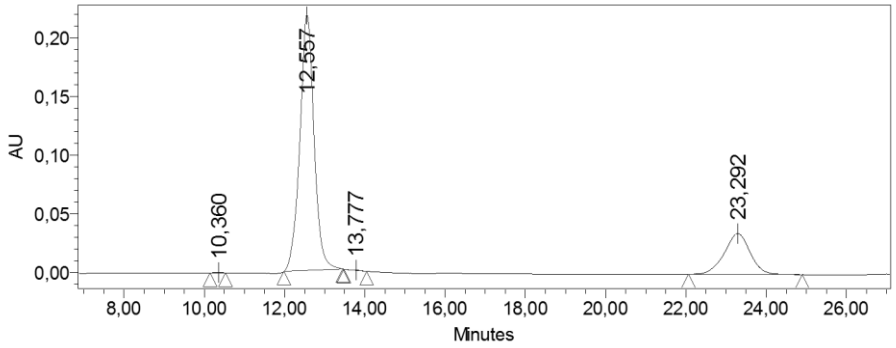


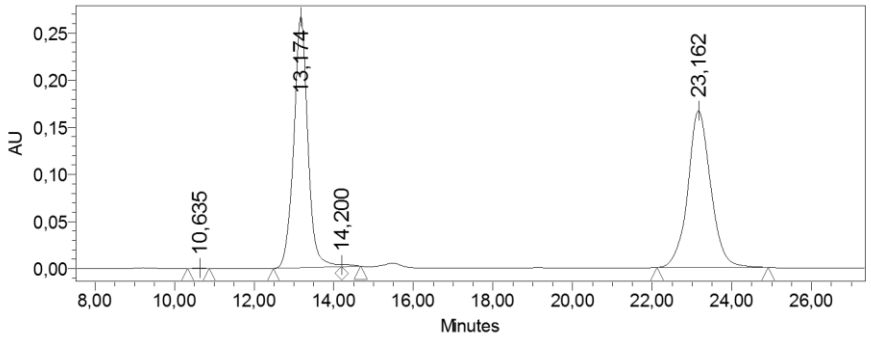
Triethylamine (2.5 µL, 0.02 mmol, 20 mol%) was added over a solution of the **51Aa/51Aa'** mixture previously obtained (*dr* = 3:1, 99% *ee*; 30 mg, 0.1 mmol, 1 equiv.) in CH_2Cl_2 (0.3 mL) and the mixture was stirred at room temperature for 2 h. The resulting product was purified by flash column chromatography (hexane/EtOAc 90:10). Yield: 95% (29 mg, 0.95 mmol). The enantiomeric and diastereomeric purity were determined by chiral HPLC analysis.

Chromatograms before and after epimerization:

Retention Time	% Area
10,360	0,09
12,557	77,43
13,777	0,07
23,292	22,41

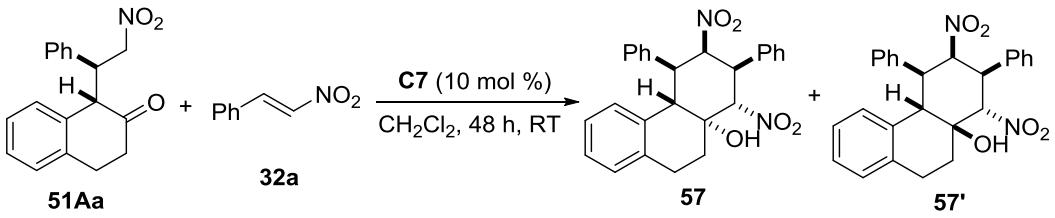
Retention Time	% Area
10,635	0,08
13,174	49,36
14,200	0,30
23,162	50,26





5.4.17. Elaboration of adducts 51

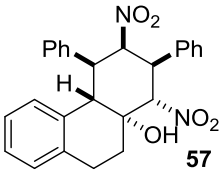
*5.4.17.1.Synthesis of tricyclic compounds **57/57'** and **58/58'***



starting from	**57** : **57'**
51Aa (dr= 3:1)	3 : 1
51Aa (dr= 1:1)	2.8 : 1

Nitrostyrene (60 mg, 0.4 mmol, 2 equiv.) was added to a solution of adduct **51Aa** (59 mg, 0.2 mmol, 1 equiv.) and catalyst **C7** (12.6 mg, 0.02 mmol, 10 mol %) in dichloromethane (0.6 mL) and the resulting mixture was stirred for 48 h at room temperature. Then the mixture was directly submitted to a flash column chromatography (hexane/CH_2Cl_2 75:25) from which essentially pure compounds **57** and **57'** were obtained separately as white solids.

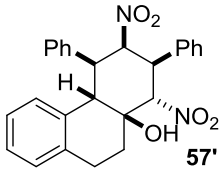
(4b*S*,5*S*,6*R*,7*R*,8*S*,8a*R*)-6,8-Dinitro-5,7-diphenyl-5,6,7,8,9,10-hexahydrophenanthren-8a(4b*H*)-ol (57)



The product was obtained following the general procedure from adduct **51Aa** and nitrostyrene (**32a**). Major isomer. Diastereomeric ratio 3:1. Yield: 45% (40 mg, 0.09 mmol). Structure confirmed by x-ray analysis. $[\alpha]_D^{23}$= –38.3º (*c* = 0.30, 99% *ee*, acetone). **^{1}H NMR** (300 MHz, acetone-d_6) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.46–7.28 (m, 6H), 7.25–7.16 (m, 2H), 7.15–7.04 (m, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.19 (d, *J* = 12.5 Hz, 1H), 5.56 (t, *J* = 4.8 Hz, 1H), 4.73 (dd, *J* = 12.5, 4.7 Hz, 1H), 4.44 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.14 (d, *J* = 12.3 Hz, 1H), 4.06 (s, 1H), 3.25–3.10 (m, 1H), 3.10–2.99 (m, 1H), 2.99–2.87 (m, 1H), 1.80 (ddd,

J = 14.4, 10.3, 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, acetone-d_6) δ 140.4, 140.1, 137.6, 137.1, 130.9, 130.3, 130.0, 129.6, 129.4, 128.8, 128.6, 128.1, 127.3, 126.7, 97.5, 92.5, 74.9, 44.5, 43.4, 43.0, 36.7, 29.2, 27.6. **MS:** calculated for $C_{25}H_{26}NO_3$ (M - H^+), 443.1612; found, 443.1604.

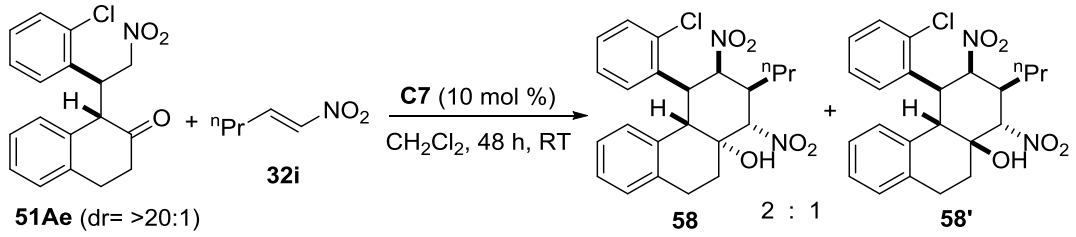
(4b*S*,5*S*,6*R*,7*R*,8*S*,8a*S*)-6,8-Dinitro-5,7-diphenyl-5,6,7,8,9,10-hexahydrophenanthren-8a(4b*H*)-ol (57')



57'

The product was obtained following the general procedure from adduct **51Aa** and nitrostyrene (**32a**). Minor isomer. Diastereomeric ratio 3:1. Yield: 15% (39 mg, 0.061 mmol). Relative stereochemistry determined by NOESY. **[α]**$_D^{23}$= +111.1º (*c* = 0.60, 99% *ee*, acetone). **^{1}H NMR** (300 MHz, Acetone-d_6) δ 7.41–7.28 (m, 5H), 7.24–7.18 (m, 3H), 7.18–7.09 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.00–6.92 (m, 1H), 6.66 (dd, *J* = 6.0, 1.4 Hz, 2H), 6.37 (d, *J* = 13.1 Hz, 1H), 5.27 (t, *J* = 4.8 Hz, 1H), 4.86 (s, 1H), 4.61 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.22 (d, *J* = 14.0 Hz, 1H), 3.82 (dd, *J* = 12.8, 4.5 Hz, 1H), 3.14–3.00 (m, 2H), 2.96–2.83 (m, 1H), 2.04–1.94 (m, 1H). **^{13}C NMR** (75 MHz, acetone-d_6) δ 137.6, 136.1, 135.9, 135.3, 133.2, 129.9, 129.6, 129.3, 129.1, 128.8, 128.1, 127.2, 125.1, 95.3, 93.3, 74.3, 50.9, 47.6, 46.0, 25.5, 24.1. **MS:** calculated for $C_{25}H_{26}NO_3$ (M - H^+), 443.1612; found, 443.1604.

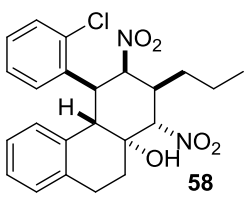
The same procedure as above was followed starting from **51Ae** (66 mg, 0.2 mmol, 1 equiv.) and nitroalkene **32i** (46 mg, 0.4 mmol, 2 equiv.).



51Ae (dr= >20:1)

58 2 : 1 **58'**

(4b*S*,5*S*,6*R*,7*R*,8*S*,8a*R*)-5-(2-Chlorophenyl)-6,8-dinitro-7-propyl-5,6,7,8,9,10-hexahydrophenanthren-8a(4b*H*)-ol (58)



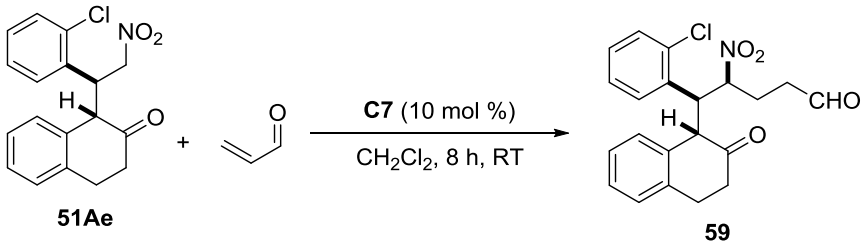
58

The product was obtained following the general procedure from adduct **51Ae** and 1-nitro-1-propene (**32i**). Diastereomeric ratio 2:1. Major isomer: Yield: 44% (40 mg, 0.088 mmol). **[α]**$_D^{23}$= –16.1º (*c* = 0.20, 99% *ee*, acetone). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.27–7.05 (m, 4H), 7.01–6.88 (m, 2H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.50 (d, *J* = 12.1 Hz, 1H), 5.44 (t, *J* = 4.6 Hz, 1H), 4.54 (dd, *J* = 12.2, 4.8 Hz, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.20–3.05 (m, 1H), 2.98–2.82 (m, 1H), 2.69–2.53 (m, 2H), 1.75–1.56 (m, 2H), 1.42–1.25 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ 138.2, 134.6, 134.5, 133.5, 130.3, 129.3, 128.0, 127.6, 127.2, 127.2, 126.9, 126.4, 93.5, 88.6, 73.2, 41.6, 38.6, 37.4, 36.2, 30.2, 26.5, 19.7, 13.6. **MS**: calculated for $C_{23}H_{25}N_2O_5ClNa$ ($M + Na^+$), 467.1350; found, 467.1357.

*5.4.17.2.Synthesis of spirocyclic compound **60***

(4*S*,5*S*)-5-(2-chlorophenyl)-4-nitro-5-((S)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)pentanal (59)

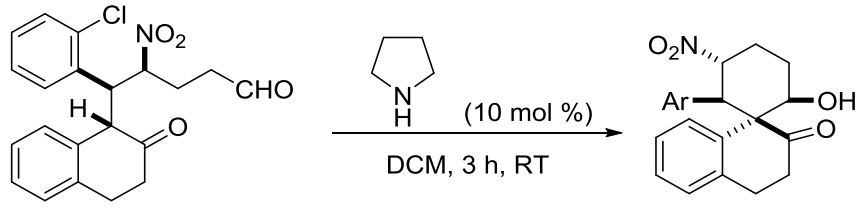


51Ae **59**

Catalyst **C7** (13 mg, 0.02 mmol, 10 mol%) was added to a solution of acrolein (27 µL, 0.4 mmol, 2 equiv.) and the previously obtained nitroketone **51Ae** (67 mg, 0.2 mmol, 1 equiv.) in CH_2Cl_2 (0.4 mL) and the resulting solution was stirred at room temperature for 8 h. The product was purified by flash column chromatography (hexane/EtOAc 90:10) obtaining the addition compound as a sole diastereomer. Foam. Yield: 80% (62 mg, 0.16 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.18 (ddd, *J* = 40.5, 22.9, 9.2 Hz, 6H), 6.87 (d, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 5.12 (dt, *J* = 13.3, 6.7 Hz, 1H), 4.85 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.54 (d, *J* = 5.7 Hz, 1H), 2.69–2.56 (m, 2H), 2.52–2.42 (m, 2H), 2.39–2.23 (m, 2H), 1.85 (q, *J* = 6.8 Hz, 2H).

(1*R*,2*S*,3*R*,6*R*)-2-(2-Chlorophenyl)-6-hydroxy-3-nitro-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-naphthalen]-2'-one (60)

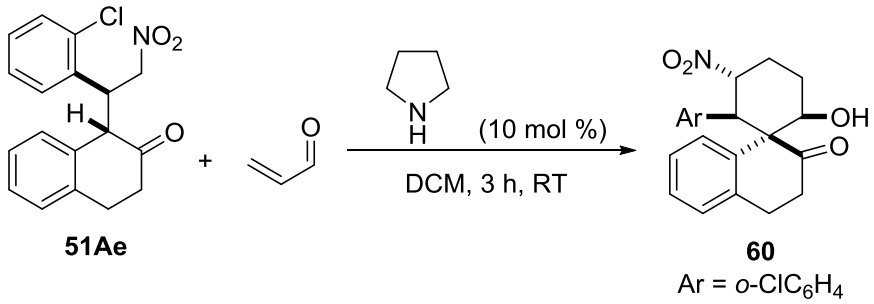
METHOD A:



59 **60**
Ar = *o*-ClC_6H_4

Pyrrolidine (1.1 mg, 0.015 mmol, 10 mol%) was added to a solution of adduct **59** (48 mg, 0.15 mmol, 1 equiv.) in dichloromethane (0.3 mL) and the resulting solution was stirred at room temperature for 3 h. Then the mixture was directly submitted to a flash column chromatography (CH_2Cl_2/EtOAc 95:5) from which the spirocyclic compound **60** was obtained essentially pure. White solid. Yield: 78% (68 mg, 0.117 mmol).

METHOD B:



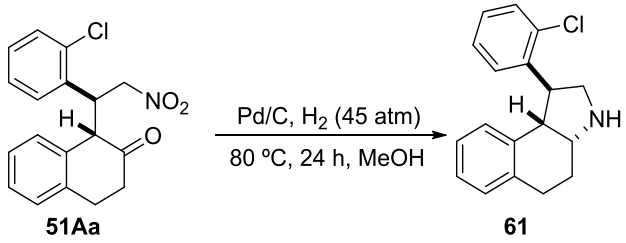
51Ae **60**

Ar = *o*-ClC_6H_4

Pyrrolidine (1.4 mg, 0.02 mmol, 10 mol%) was added to a solution of acrolein (27 µL, 0.4 mmol, 2 equiv.) and adduct **51Ae** (67 mg, 0.2 mmol, 1 equiv.) in dichloromethane (0.4 mL) and the resulting solution was stirred at room temperature for 3 h. Then the mixture was directly submitted to a flash column chromatography (CH_2Cl_2/EtOAc 95:5) from which the spirocyclic compound **60** was obtained essentially pure as a white solid. Yield: 83% (64 mg, 0.166 mmol). Structure confirmed by X-ray analysis. $[\alpha]_D^{23}$= +184.0º (*c* = 2.00, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.38–7.30 (m, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.13–7.05 (m, 1H), 7.05–6.95 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.02 (td, *J* = 11.4, 4.4 Hz, 1H), 4.70–4.58 (m, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 2.66–2.46 (m, 4H), 2.40–2.21 (m, 1H), 2.15–2.06 (m, 1H), 1.96–1.82 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.6, 139.9, 136.9, 136.5, 134.1, 130.7, 130.2, 129.8, 128.7, 128.5, 128.0, 127.5, 87.5, 77.0, 61.7, 50.7, 44.3, 30.5, 28.0, 27.8. **MS:** calculated for $C_{21}H_{20}NO_4ClNa$ (M + Na^+), 408.0977; found, 408.0979.

*5.4.17.3.Synthesis of tricyclic compounds **61-64***

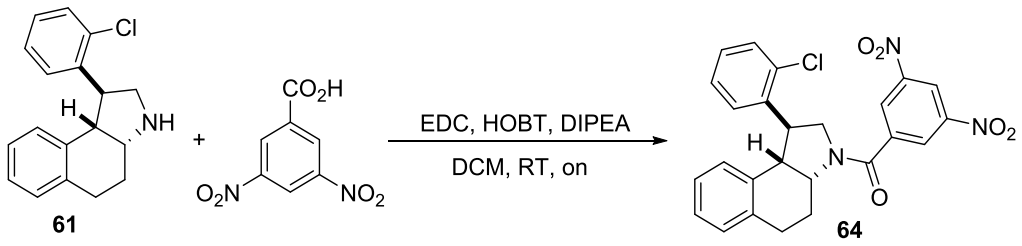
(1*S*,3a*R*,9b*S*)-1-(2-Chlorophenyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole (61)[278]



51Aa 61

Nitroalkane **51Aa** (132 mg, 0.40 mmol, 1 equiv.) was suspended on MeOH (4 mL) and Pd (10% wt. on charcoal) (26 mg, 20% weight) was added. The reaction mixture was stirred under hydrogen atmosphere (45 atm) at 80 ºC for 24 h. The resulting mixture was filtered over a 2 cm path of celite and the solvent was eliminated under reduced pressure. The product was purified by flash column chromatography (CH_2Cl_2/MeOH 90:10) to afford the amine as a colourless oil. Diastereomeric ratio 10:1. Yield: 80% (90 mg, 0.32 mmol). $[\alpha]_D^{23}$= +6.6º (*c* = 2.00, 99% *ee*, *dr* = 10:1, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.37–7.30 (m, 2H), 7.25–7.17 (m, 1H), 7.13–7.05 (m, 2H), 6.99–6.91 (m, 1H), 6.63 (s, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 4.08 (q, *J* = 7.5 Hz, 1H), 3.83 (q, *J* = 9.2 Hz, 1H), 3.70–3.59 (m, 2H), 3.31–3.19 (m, 1H), 3.04–2.91 (m, 1H), 2.82–2.70 (m, 1H), 2.15–1.99 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2, 135.9, 134.6, 129.8, 128.7, 128.4, 128.2, 128.0, 127.4, 126.3, 126.1, 57.7, 51.4, 49.4, 48.5, 26.8, 26.7. **MS:** calculated for $C_{18}H_{19}NCl$ ($M + H^+$), 284.1206; found, 284.1224.

((1*S*,3a*R*,9b*S*)-1-(2-Chlorophenyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(3,5-dinitrophenyl)methanone (64)



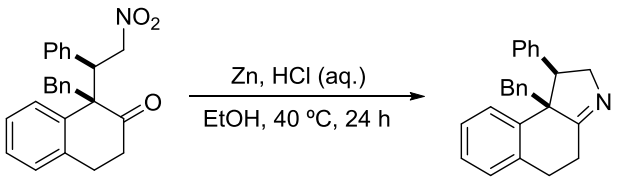
61 64

N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) (38 mg, 0.2 mmol, 1.3 equiv.) and 1-hydroxybenzotriazole hydrate (HOBT) (27 mg, 0.18 mmol, 1.2 equiv.) were added to a stirred solution of 3,5-dinitrobenzoic acid (32 mg, 0.15

[278] X. Dong, H. Teng, M. Tong, H. Huan, H. Tao, C. Wang, *Chem. Commun*. **2010**, *46*, 6840–6842.

mmol, 1 equiv.), diisopropylethylamine (80 µL, 0.23 mmol, 3 equiv.) and amine **61** (0.15 mmol, 1 equiv.) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to stir at room temperature overnight and the reaction was quenched adding water (2 mL). The aqueous phase was extracted with dichloromethane (3 x 2 mL) and the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 85:15) to afford the amide as a white solid. Diastereomeric ratio 5:1. Yield: 76% (73 mg, 0.152 mmol). Relative stereochemistry of major isomer determined by NOESY. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.71 (s, 2H), 7.43–7.29 (m, 3H), 7.29–7.21 (m, 1H), 7.20–7.11 (m, 2H), 7.08–6.96 (m, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 4.93–4.80 (m, 1H), 4.13–4.04 (m, 1H), 3.92 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.79 (t, *J* = 7.8 Hz, 1H), 3.57 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.98–2.87 (m, 2H), 2.45–2.33 (m, 1H), 2.27–2.12 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 148.4, 140.0, 137.1, 136.3, 135.0, 134.4, 130.3, 128.8, 128.7, 128.4, 128.1, 127.5, 127.3, 126.8, 126.3, 119.8, 57.6, 54.4, 48.3, 45.9, 27.2, 24.8. **MS:** calculated for $C_{25}H_{21}NO_5Cl$ ($M + H^+$), 478.1170; found, 478.1172.

(1*R*,9b*S*)-9b-Benzyl-1-phenyl-2,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole (62)[279]



37Ba **62**

To a suspension of nitroalkane **51Ba** (0.25 mmol) on EtOH (2.5 mL) zinc powder (235 mg, 3.75 mmol, 15 equiv.) was added and the suspension was stirred at 40 ºC for 10 min. Then aqueous HCl (4 M) (1.6 mL) was added and the reaction mixture was allowed to stir for 24 h making sure the pH was betw*ee*n 0 and 1. The reaction mixture was concentrated under vacuum, aqueous NaOH (3 M) (5 mL) were added and the reaction mixture was stirred for further 5 min. CH_2Cl_2 (20 mL) was then added and the suspension was filtrated on celite. The aqueous and organic layer were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The product was purified by flash column chromatography (EtOAc) to afford the imine **62** as a white solid. Yield: 88% (75 mg, 0.22 mmol). **[α]**$_D^{23}$= –27.9º (*c* = 1.00, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47–7.33 (m, 5H), 7.24–7.14 (m,

[279] X. Dong, H. Teng, M. Tong, H. Huan, H. Tao, C. Wang, *Chem. Commun*. **2010**, *46*, 6840–6842.

2H), 7.11–6.95 (m, 5H), 6.62–6.55 (m, 2H), 4.31 (ddd, *J* = 14.7, 11.2, 3.4 Hz, 1H), 4.16 (dd, *J* = 15.0, 7.4 Hz, 1H), 3.50 (dd, *J* = 11.2, 7.4 Hz, 1H), 3.15 (d, *J* = 13.0 Hz, 1H), 2.90–2.63 (m, 3H), 2.42 (ddd, *J* = 12.9, 5.3, 2.2 Hz, 1H), 1.40 (dddd, *J* = 12.8, 10.1, 7.1, 3.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 183.3, 140.6, 137.4, 136.9, 136.2, 130.7, 129.9, 128.8, 128.1, 128.0, 127.9, 127.4, 126.5, 126.4, 126.1, 61.9, 58.2, 57.6, 41.4, 31.4, 29.8. **MS:** calculated for $C_{25}H_{24}NO_3$ ($M + H^+$), 338.1909; found, 338.1919.

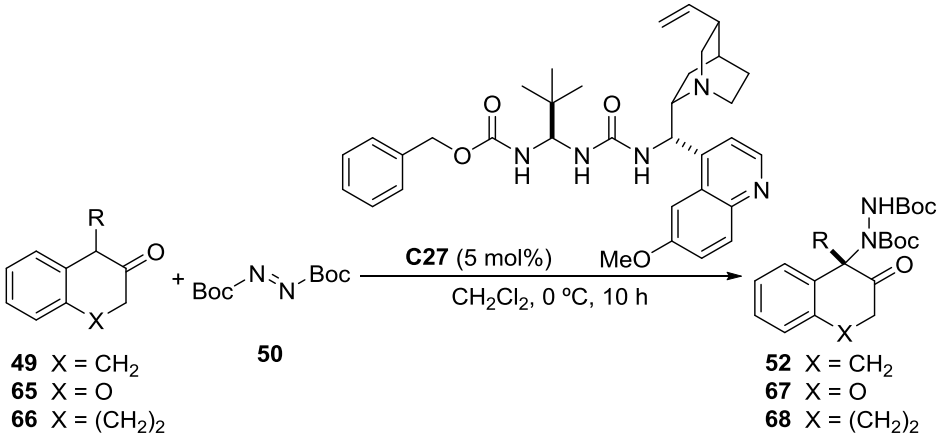
(1*R*,9b*S*)-9b-Benzyl-1-phenyl-2,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole *N*-oxide (63)

51Ba **63**

Nitroalkane **51Ba** (0.3 mmol) was disolved in EtOAc (0.45 mL) and Pd (10% wt. on charcoal) (24 mg, 20% weight). The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 3 days. The resulting mixture was filtered over a 2 cm path of celite and the solvent was eliminated under reduced pressure. The product was purified by flash column chromatography (CH_2Cl_2/MeOH 80:20) to afford the imine N-oxide **63** as a white solid. Yield: 80% (85 mg, 0.24 mmol). $[\alpha]_D^{23}$= –24.6º (*c* = 0.10, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52–7.40 (m, 5H), 7.24–7.15 (m, 2H), 7.09 (d, *J* = 7.3 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 3H), 6.54 (d, *J* = 7.0 Hz, 2H), 4.79 (td, *J* = 13.1, 3.2 Hz, 1H), 4.21 (dd, *J* = 13.2, 8.6 Hz, 1H), 3.83 (dd, *J* = 12.0, 8.5 Hz, 1H), 3.32 (d, *J* = 12.9 Hz, 1H), 3.07 (ddd, *J* = 15.3, 6.9, 3.2 Hz, 1H), 2.84 (d, *J* = 12.9 Hz, 1H), 2.72 (ddd, *J* = 17.1, 10.6, 7.0 Hz, 1H), 2.32 (ddd, *J* = 16.4, 7.3, 3.1 Hz, 1H), 1.38 (dddd, *J* = 14.3, 10.1, 7.4, 2.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.3, 139.2, 136.3, 136.1, 134.2, 130.5, 129.9, 128.9, 128.6, 128.3, 128.0, 127.1, 126.7, 126.4, 65.6, 54.1, 53.1, 43.4, 28.3, 21.3. **MS:** calculated for $C_{25}H_{24}NO$ ($M + H^+$), 354.1858; found, 354.1862.

5.4.18. α-Amination of β-tetralones and related ketones

5.4.18.1.General procedure

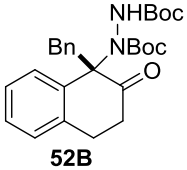


Catalyst **C27** (4.4 mg, 5 mol%) was added to a solution of the corresponding nucleophile **49**, **65** or **66** (0.15 mmol, 1 equiv.) and di-*tert*-butyl azodicarboxylate (**50)** (0.30 mmol, 2 equiv.) in CH_2Cl_2 at 0 ºC. The resulting solution was stirred at the same temperature until the reaction was completed (monitored by TLC hexane/EtOAc 80:20) and the mixture was directly submitted to a flash column chromatography (hexane/EtOAc 90:10), affording the corresponding α-amination adducts as essentially pure compound.

The racemic version of the reaction was performed following the asymmetric reaction procedure except the reaction was conducted at room temperature and TEA (20 mol%) was used as the catalyst.

*5.4.18.2.Characterization data for compounds **52** and **67***

di-tert-Butyl (*S*)-1-(1-benzyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (52B)

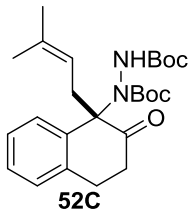


52B

The adduct was obtained by using 1-benzyl-β-tetralone (**49B**) (35 mg, 0.15 mmol, 1 equiv.), di-*tert*-butyl azodicarboxylate (69 mg, 0.30 mmol, 2 equiv.) and catalyst **C27** (4.4 mg, 5 mol%) and carrying out the reaction at 0 ºC. Yellow oil. Yield: 86% (60 mg, 0.129 mmol). $[\alpha]_D^{22}$= –296.6º (*c* = 3.00, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.10 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.78 (s, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 3.60 (d, *J* = 12.0 Hz, 1H), 2.97 (d, *J* = 12.0 Hz, 1H), 2.65 – 2.38 (m, 2H), 2.31 – 2.09 (m, 1H), 1.54 (s, 9H), 1.30 –

1.21 (m, 1H), 1.18 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.6, 156.3, 154.5, 139.3, 135.2, 133.8, 130.9, 127.8, 127.2, 127.0, 1269, 82.3, 81.0, 71.1, 46.6, 37.4, 28.3, 27.9, 25.8. **MS:** calculated for $C_{27}H_{34}N_2O_5Na$ (M + Na^+), 489.2365; found, 489.2374. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol, 98:2; flux = 1 mL/min; retention times: 8.9 min (minor), 17.3 min (major)).

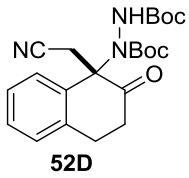
di-tert-Butyl (*S*)-1-(1-(3-methylbut-2-en-1-yl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (52C)



52C

The adduct was obtained by using 1-(3-methylbut-2-en-1-yl)-tetralone (**49C**) (30 mg, 0.15 mmol, 1 equiv.), di-*tert*-butyl azodicarboxylate (69 mg, 0.30 mmol, 2 equiv.) and catalyst **C27** (4.4 mg, 5 mol%) and carrying out the reaction at 0 ºC. Yellow oil. Yield: 84% (56 mg, 0.126 mmol). **[α]**$_D^{23}$= –32.9º (*c* = 1.50, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.21 – 7.15 (m, 1H), 7.14 – 7.08 (m, 1H), 6.64 (s, 1H), 4.80 (t, *J* = 6.7 Hz, 1H), 3.23 – 2.96 (m, 2H), 2.77 – 2.65 (m, 3H), 2.52 – 2.40 (m, 1H), 1.59 – 1.43 (m, 15H), 1.30 – 1.18 (m, 9H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.8, 156.0, 154.8, 135.7, 127.4, 127.2, 127.0, 126.6, 117.2, 82.0, 808, 37.0, 36.9, 28.3, 28.1, 27.9, 27.6, 25.8, 17.5. **MS:** calculated for $C_{25}H_{36}N_2O_5Na$ (M + Na^+), 467.2522; found, 467.2529. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 4.9 min (minor), 11.3 min (major)).

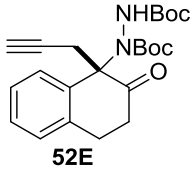
di-tert-Butyl (*S*)-1-(1-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (52D)



52D

The adduct was obtained by using 2-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**49D**) (28 mg, 0.15 mmol, 1 equiv.), di-*tert*-butyl azodicarboxylate (69 mg, 0.30 mmol, 2 equiv.) and catalyst **C27** (4.4 mg, 5 mol%) and carrying out the reaction at 0 ºC. Yellow oil. Yield: 84% (52 mg, 0.126 mmol). **[α]**$_D^{22}$= –55.9º (*c* = 2.00, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.21 – 7.86 (m, 1H), 7.48 – 7.30 (m, 2H), 7.28 – 7.18 (m, 1H), 6.66 (s, 1H), 3.72 – 2.57 (m, 6H), 1.50 (d, *J* = 14.4 Hz, 9H), 1.36 – 1.25 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.4, 155.9, 134.6, 129.5, 128.9, 128.4, 127.6, 126.9, 116.0, 83.2, 81.8, 68.8, 36.3, 28.1, 27.9, 27.8, 26.6. **MS:** calculated for $C_{22}H_{30}N_3O_5$ (M + H^+), 416.2185; found, 416.2191. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 11.4 min (minor), 20.6 min (major)).

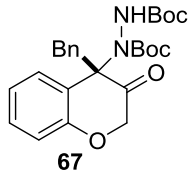
di-tert-Butyl (*S*)-1-(2-oxo-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (52E)



52E

The adduct was obtained by using 1-(Prop-2-yn-1-yl)-tetralone **49E** (28 mg, 0.15 mmol, 1 equiv.), di-*tert*-butyl azodicarboxylate (69 mg, 0.30 mmol, 2 equiv.) and catalyst **C27** (4.4 mg, 5 mol%) and carrying out the reaction at 0 ºC. Yellow oil. Yield: 83% (52 mg, 0.125 mmol). $[\alpha]_D^{23}$= –48.8º (*c* = 2.00, 99% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.23 (m, 1H), 7.26 – 7.10 (m, 2H), 6.64 (s, 1H), 3.29 – 3.16 (m, 2H), 3.02 – 2.73 (m, 3H), 1.97 (s, 1H), 1.52 – 1.46 (m, 9H), 1.28 – 1.19 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.0, 155.8, 154.4, 134.3, 127.5, 127.3, 127.1, 82.3, 80.9, 78.7, 72.3, 36.9, 28.8, 28.2, 27.8. **MS:** calculated for $C_{23}H_{30}N_2O_5Na$ (M + Na^+), 437.0252; found, 437.0251. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 7.0 min (minor), 14.7 min (major)).

di-tert-Butyl (*S*)-1-(4-benzyl-3-oxochroman-4-yl)hydrazine-1,2-dicarboxylate (67)

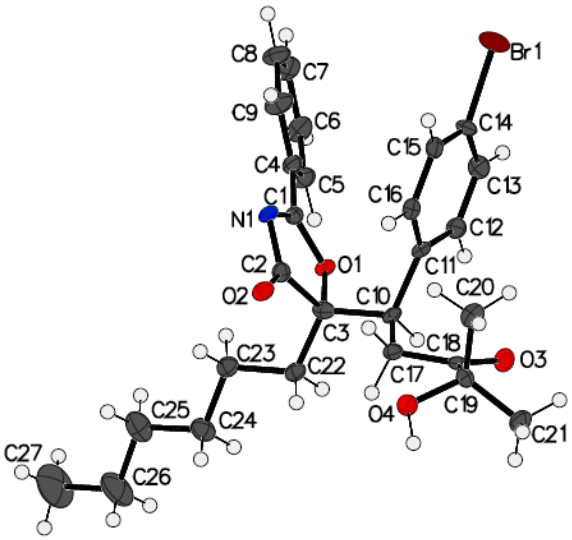


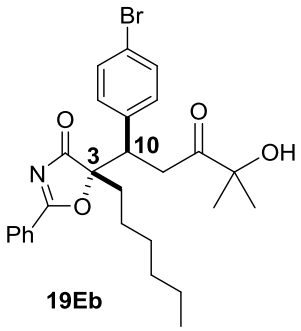
67

The adduct was obtained by using 4-benzylchroman-3-one **65** (28 mg, 0.15 mmol, 1 equiv.), di-*tert*-butyl azodicarboxylate (69 mg, 0.30 mmol, 2 equiv.) and catalyst **C27** (4.4 mg, 5 mol%) and carrying out the reaction at –60 ºC. Yellow oil. Yield: 89% (63 mg, 0.134 mmol). $[\alpha]_D^{23}$= –98.7º (*c* = 1.50, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.5 Hz, 1H), 7.27 – 6.90 (m, 6H), 6.77 – 6.47 (m, 3H), 4.34 (d, *J* = 17.9 Hz, 1H), 3.97 (d, *J* = 17.9 Hz, 1H), 3.50 (d, *J* = 12.2 Hz, 1H), 3.02 (d, *J* = 12.2 Hz, 1H), 1.56 (s, 9H), 1.33 – 1.19 (m, 9H). ^{13}C **NMR** (75 MHz, $CDCl_3$) δ 210.6, 156.2, 152.8, 132.9, 130.4, 128.6, 127.9, 127.4, 127.2, 122.8, 116.6, 82.8, 81.3, 71.6, 45.5, 28.2, 27.9. **MS:** calculated for $C_{26}H_{32}N_2O_6Na$ (M + Na^+), 491.218; found, 491.2154. The enantiomeric purity was determined by chiral HPLC analysis (Daicel Chiralpak ADH, hexane/isopropanol, 90:10; flux = 1 mL/min; retention times: 5.9 min (minor), 10.8 min (major)).

5.4.19. ORTEP diagram of compound 19Eb

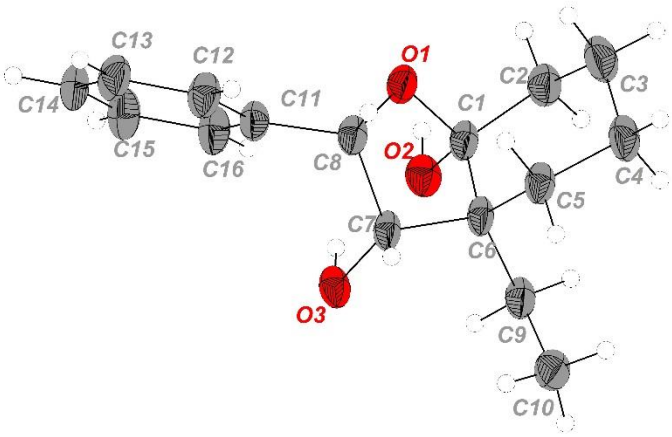
CCDC-1025058 contains the supplementary crystallographic data for the structural analysis of **19Eb**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

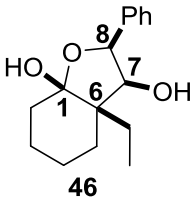




5.4.20. ORTEP diagram of compound 46

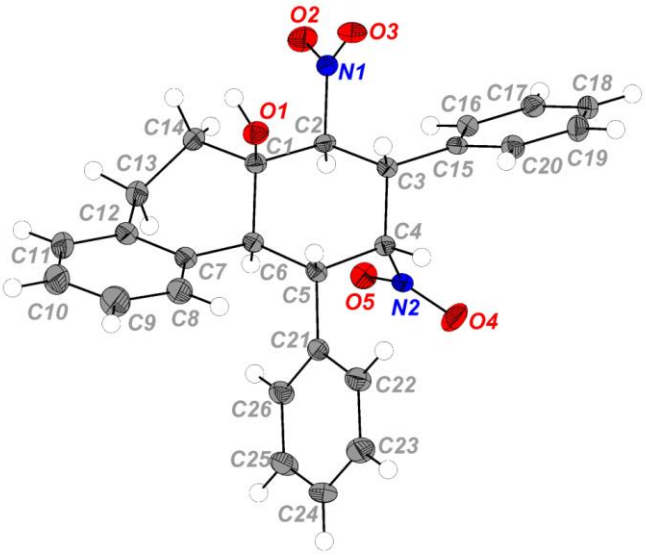
CCDC-1821643 contains the supplementary crystallographic data for the structural analysis of **46**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

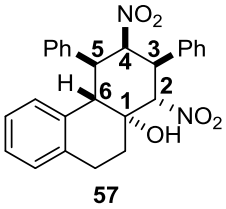




5.4.21. ORTEP diagram of compound 57

CCDC-1511199 contains the supplementary crystallographic data for the structural analysis of **57**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

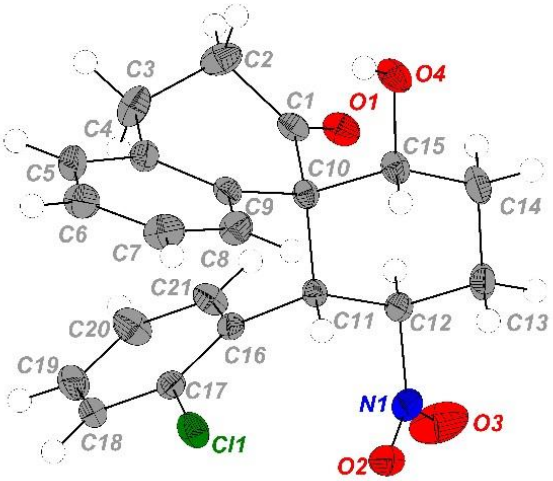


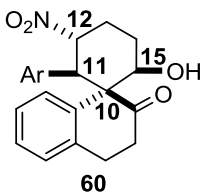


57

5.4.22. ORTEP diagram of compound 60

CCDC-1511200 contains the supplementary crystallographic data for the structural analysis of **60**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

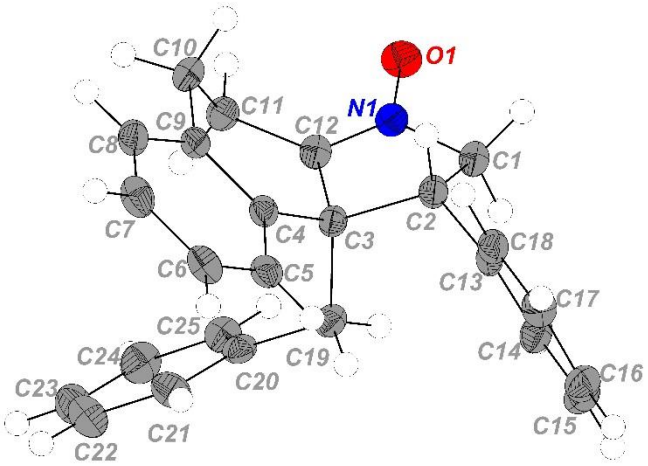


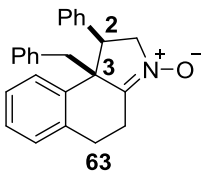


60

5.4.23. ORTEP diagram of compound 63

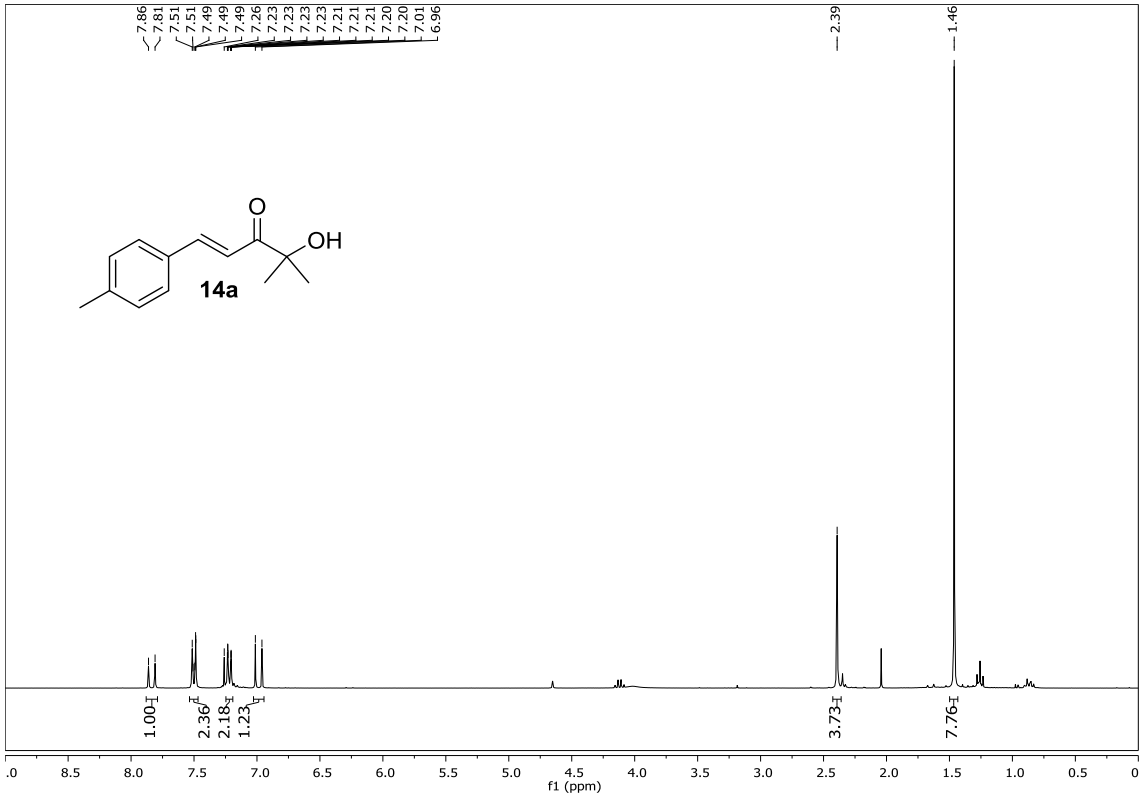
CCDC-1511201 contains the supplementary crystallographic data for the structural analysis of **63**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

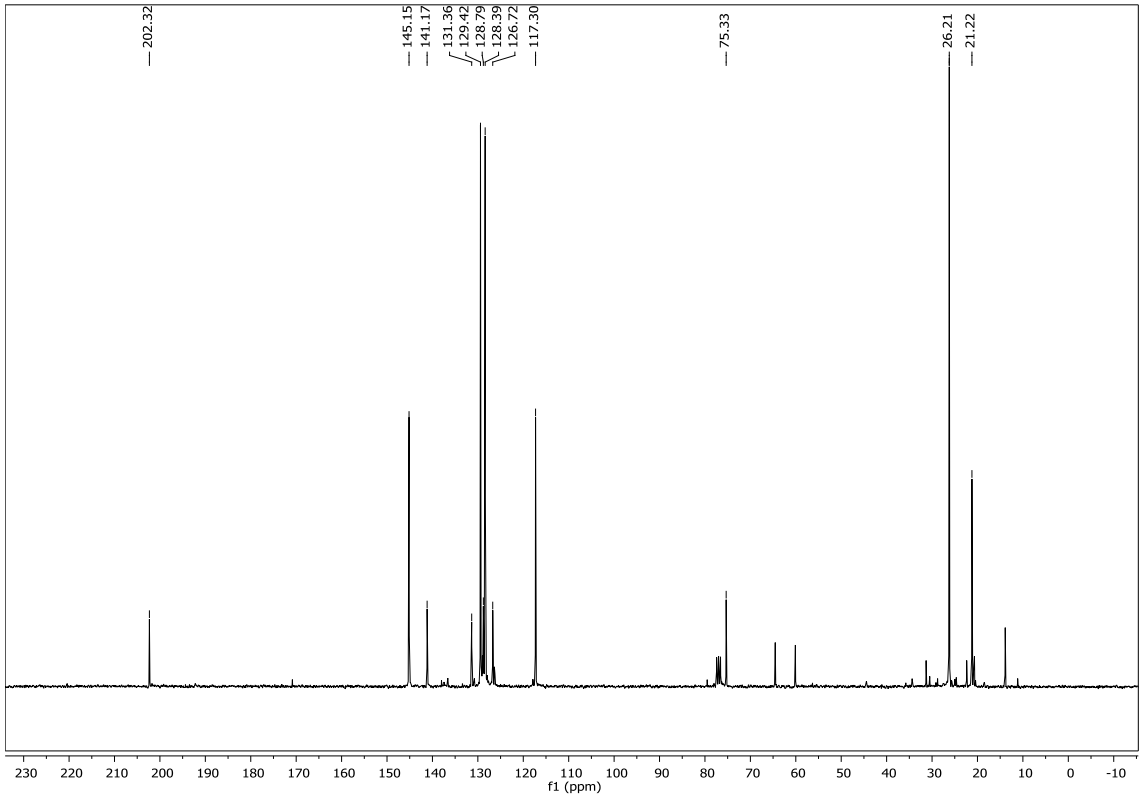

C10
O1
C11
N1
C9
C12
C8
C1
C7
C4
C3
C2
C18
C6
C5
C13
C17
C25
C24
C19
C14
C16
C23
C20
C21
C15
C22

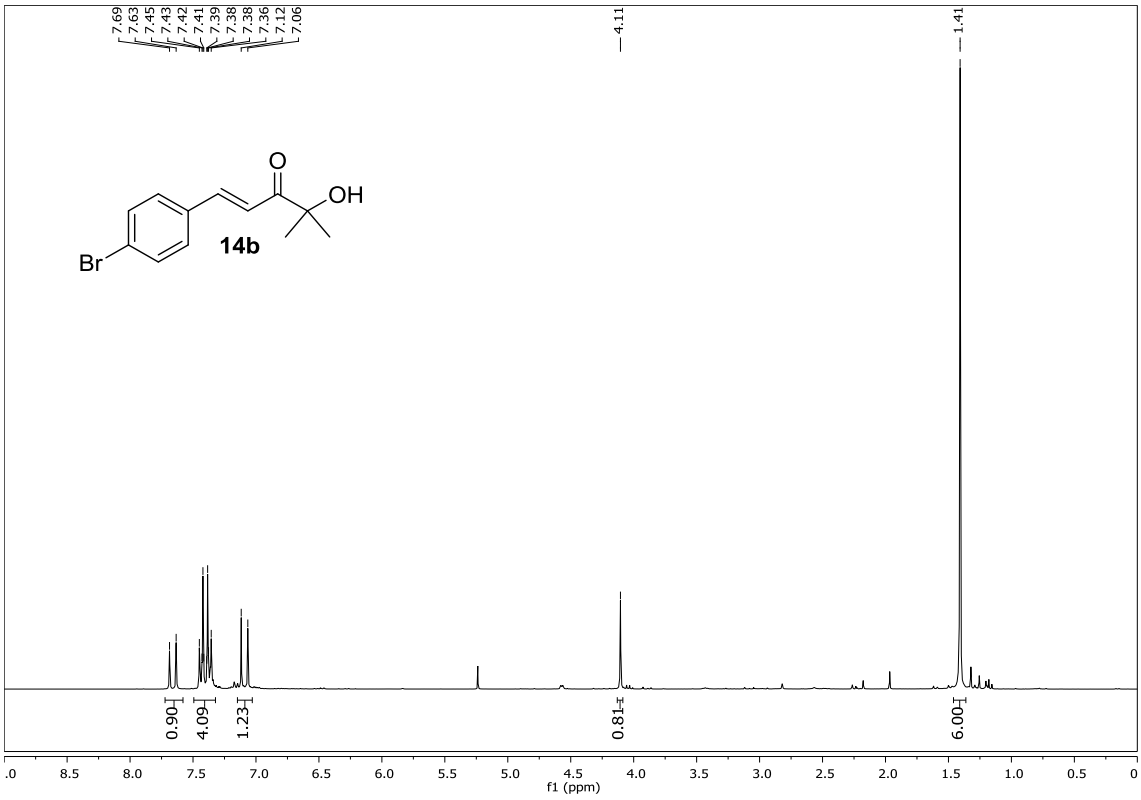

Ph
2
Ph
3
N
O

63

5.4.24. Representative NMR spectra



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7.45
7.43
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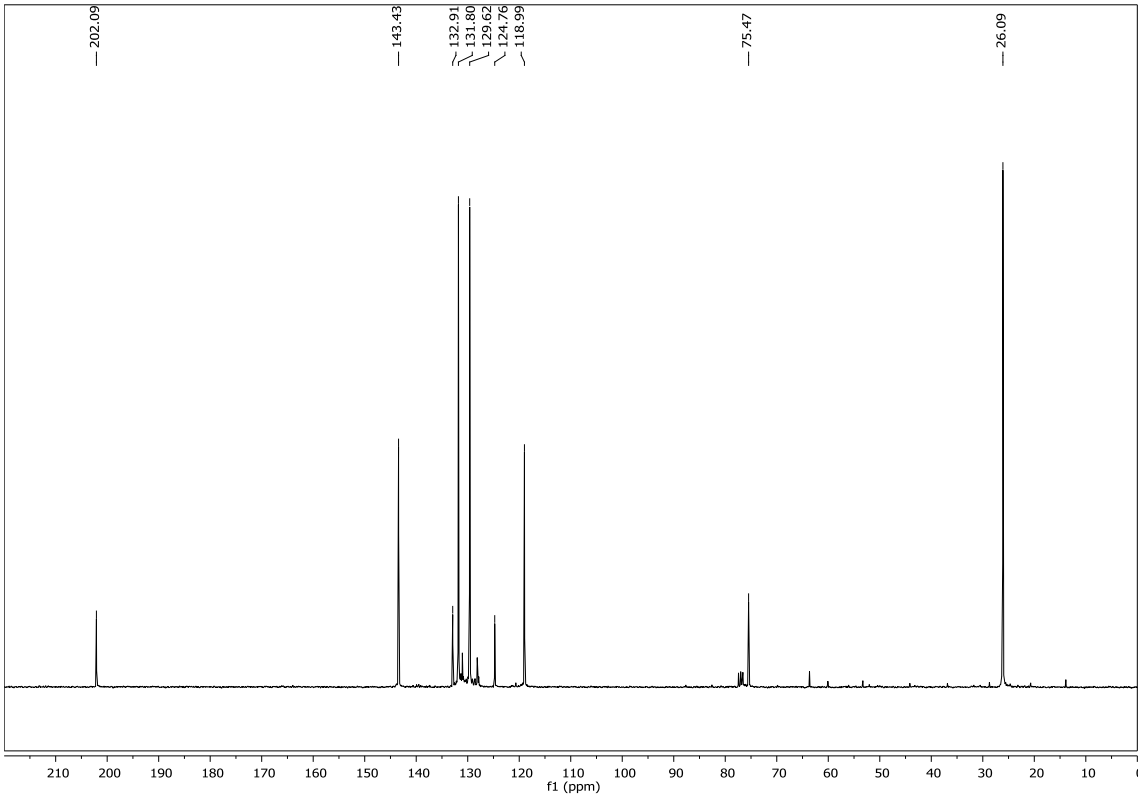
7.41
7.39
7.38
7.38
7.36
7.12
7.06
4.11
1.41
O
OH
Br
14b
0.90
4.09
1.23
0.81
6.00
f1 (ppm)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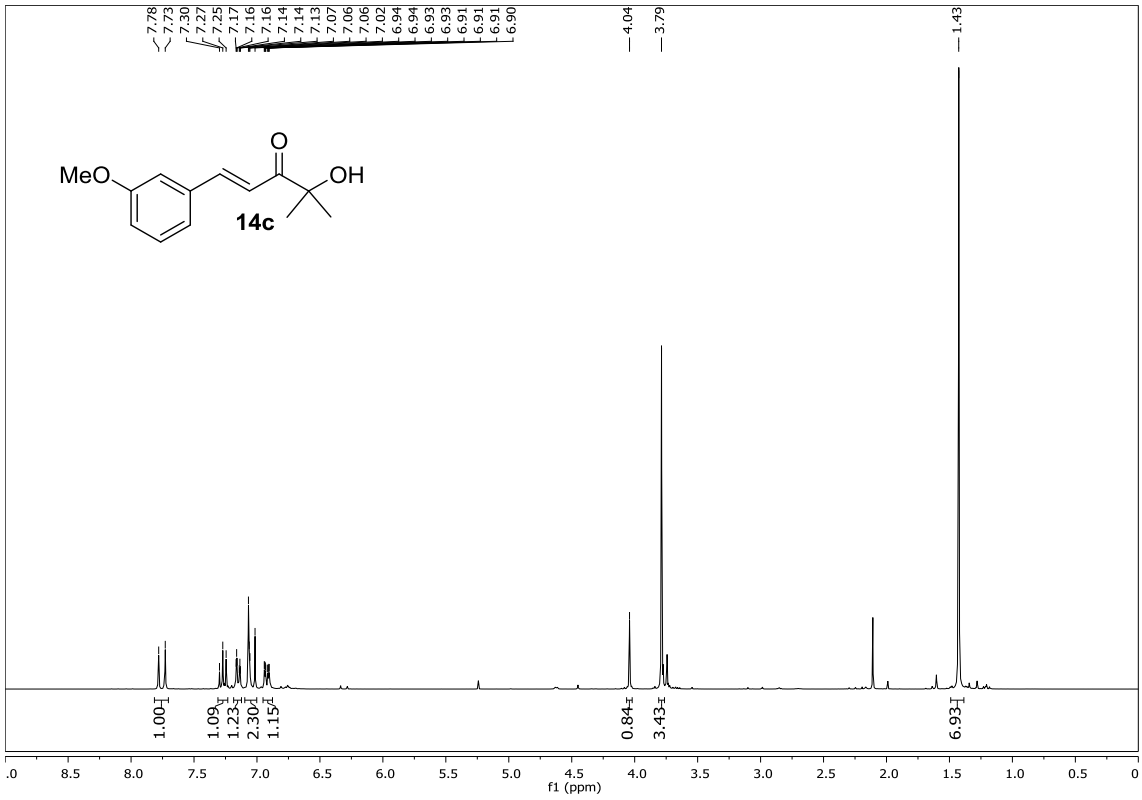
143.43
132.91
131.80
129.62
124.76
118.99
75.47
26.09
f1 (ppm)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7.73
7.30
7.27
7.25
7.17
7.16
7.16
7.14
7.14
7.13
7.07
7.06
7.06
7.02
6.94
6.94
6.93
6.93
6.91
6.91
6.91
6.90
4.04
3.79
1.43
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MeO
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1.00
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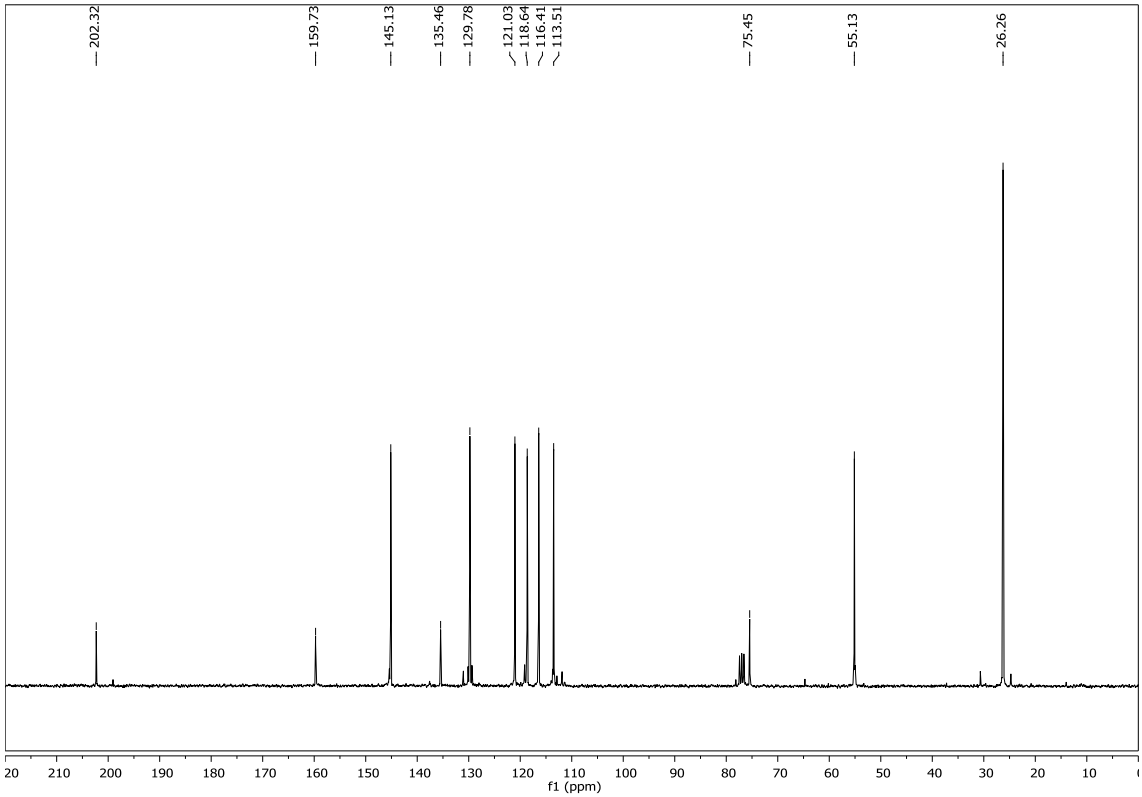
1.23
2.30
1.15
0.84
3.43
6.93
f1 (ppm)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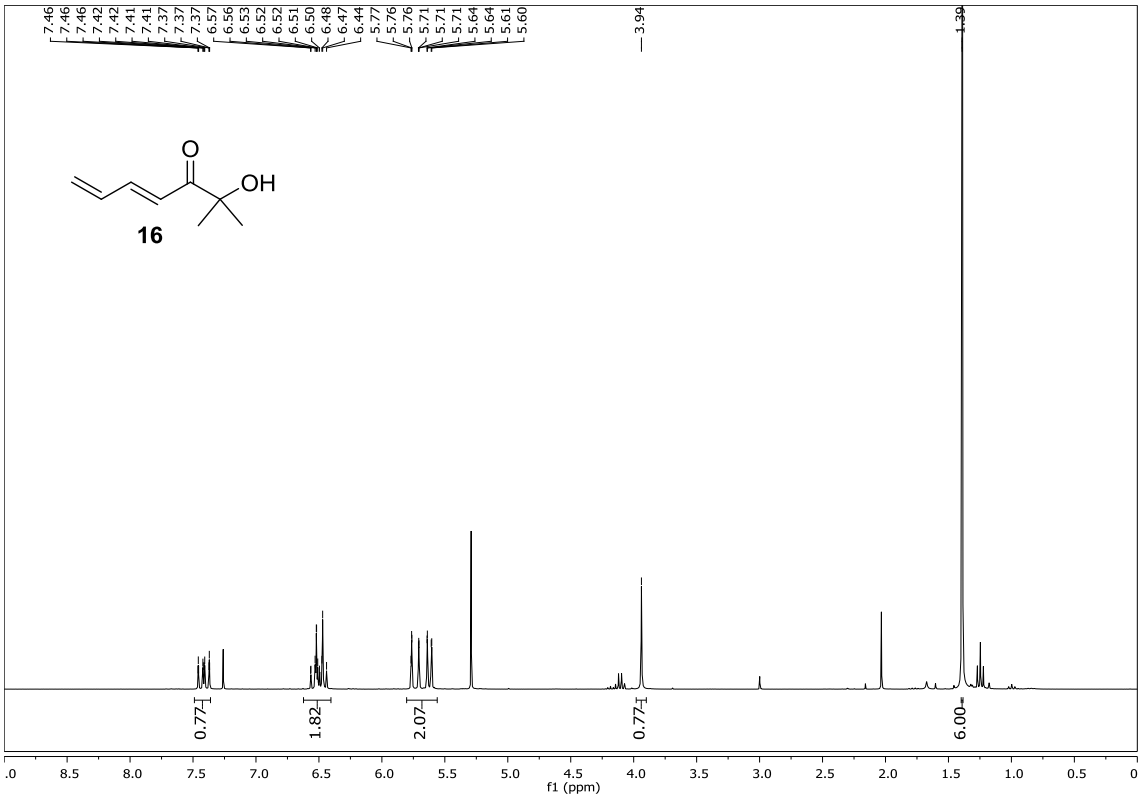
159.73
145.13
135.46
129.78
121.03
118.64
116.41
113.51
75.45
55.13
26.26
f1 (ppm)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7.46
7.46
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7.42
7.41
7.41
7.37
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7.37
6.57
6.56
6.53
6.52
6.52
6.51
6.50
6.48
6.47
6.44
5.77
5.76
5.76
5.71
5.71
5.71
5.64
5.64
5.61
5.60
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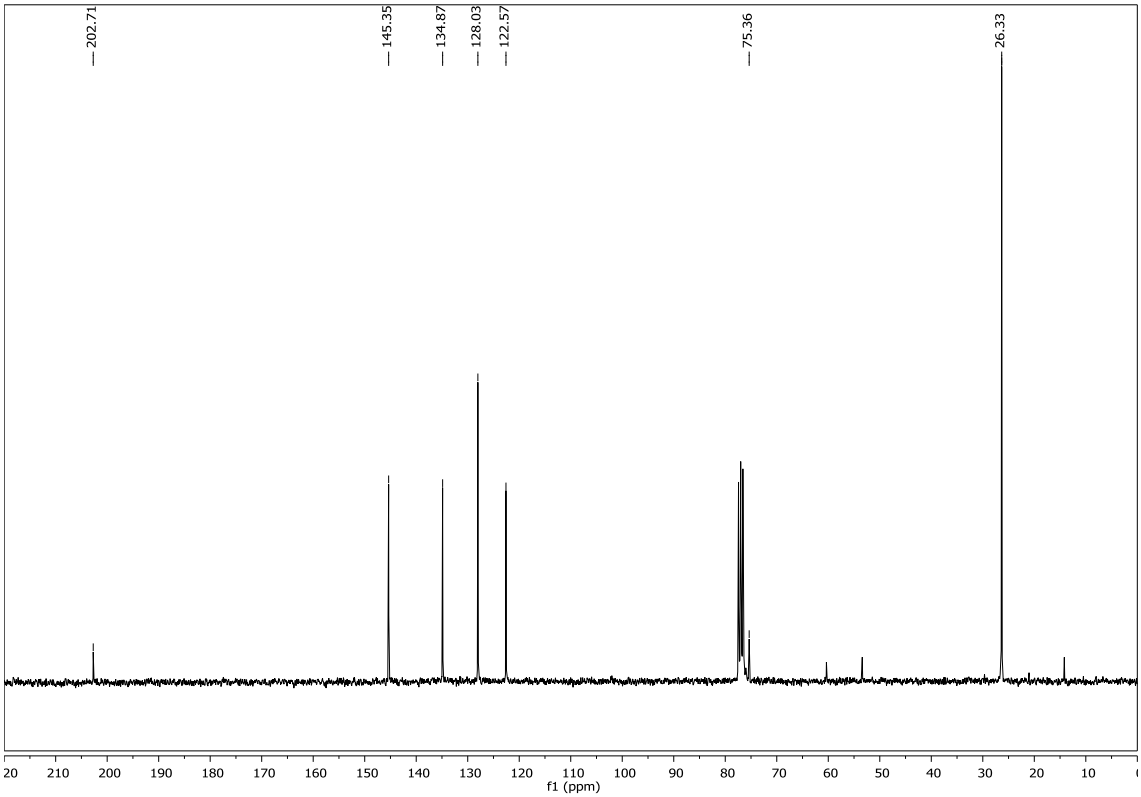
1.39
O
OH
16
0.77
1.82
2.07
0.77
6.00
f1 (ppm)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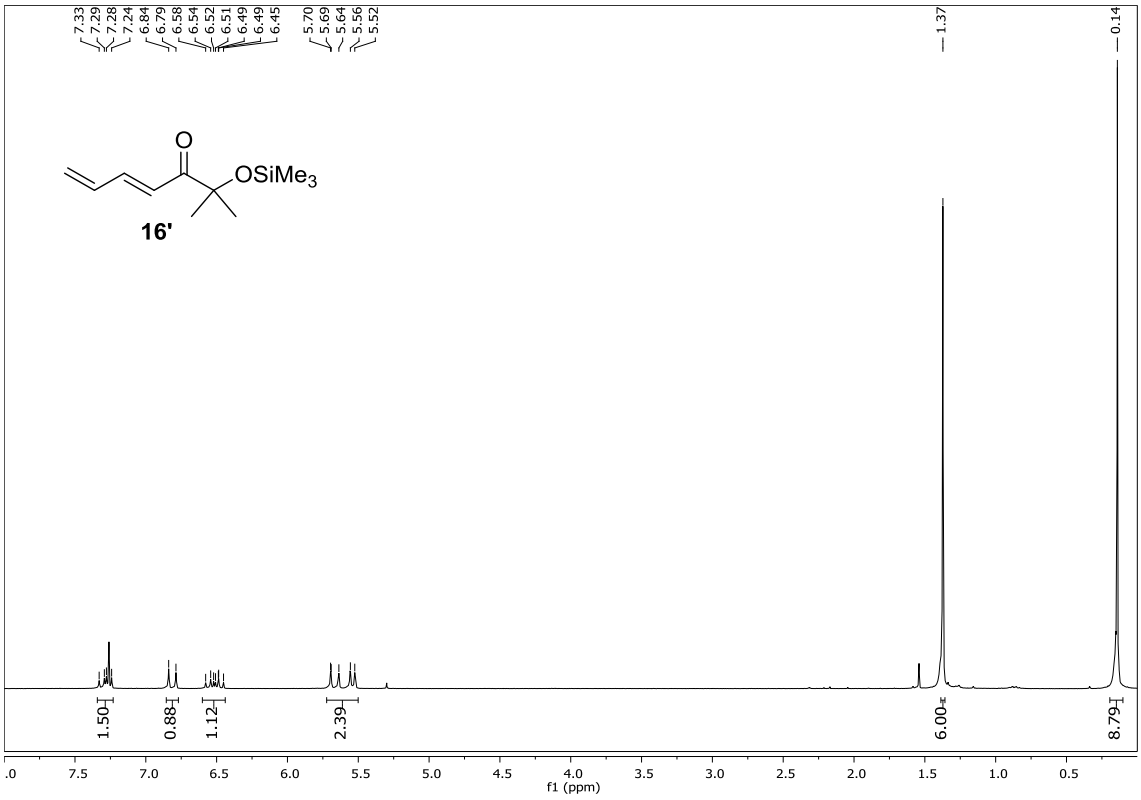
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7.28
7.24
6.84
6.79
6.58
6.54
6.52
6.51
6.49
6.49
6.45
5.70
5.69
5.64
5.56
5.52
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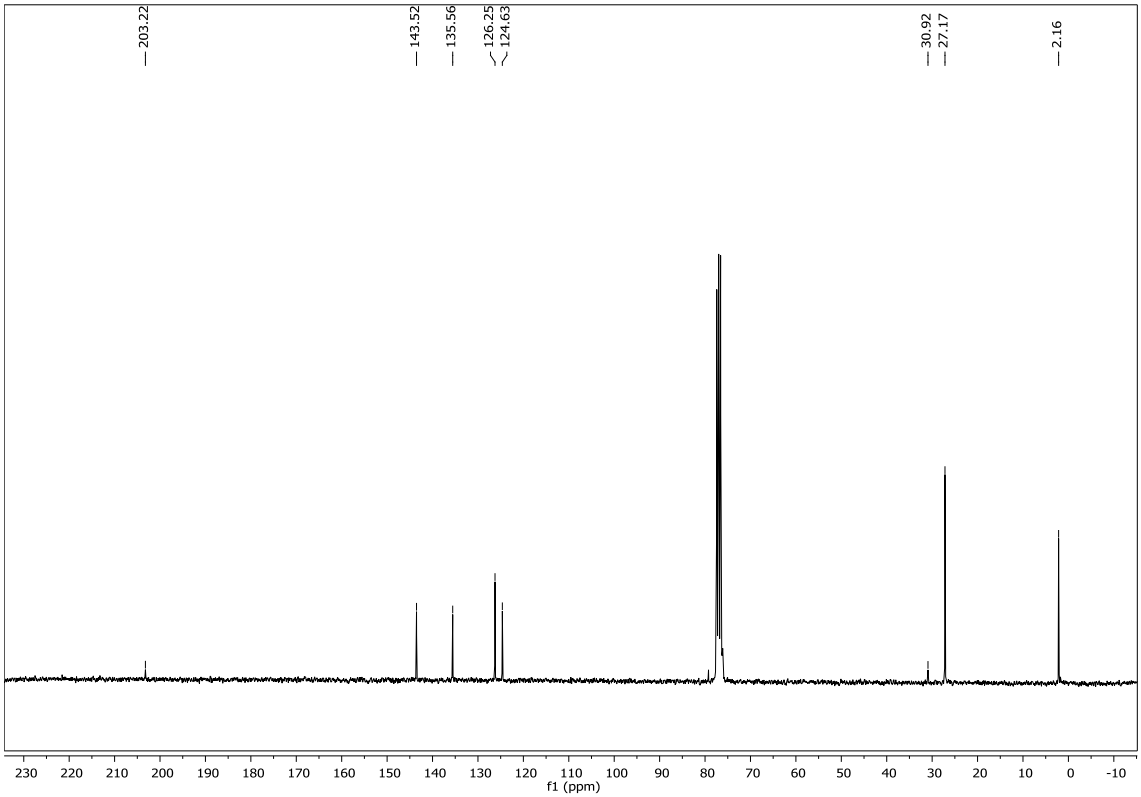
0.14
O
OSiMe3
16'
1.50
0.88
1.12
2.39
6.00
8.79
f1 (ppm)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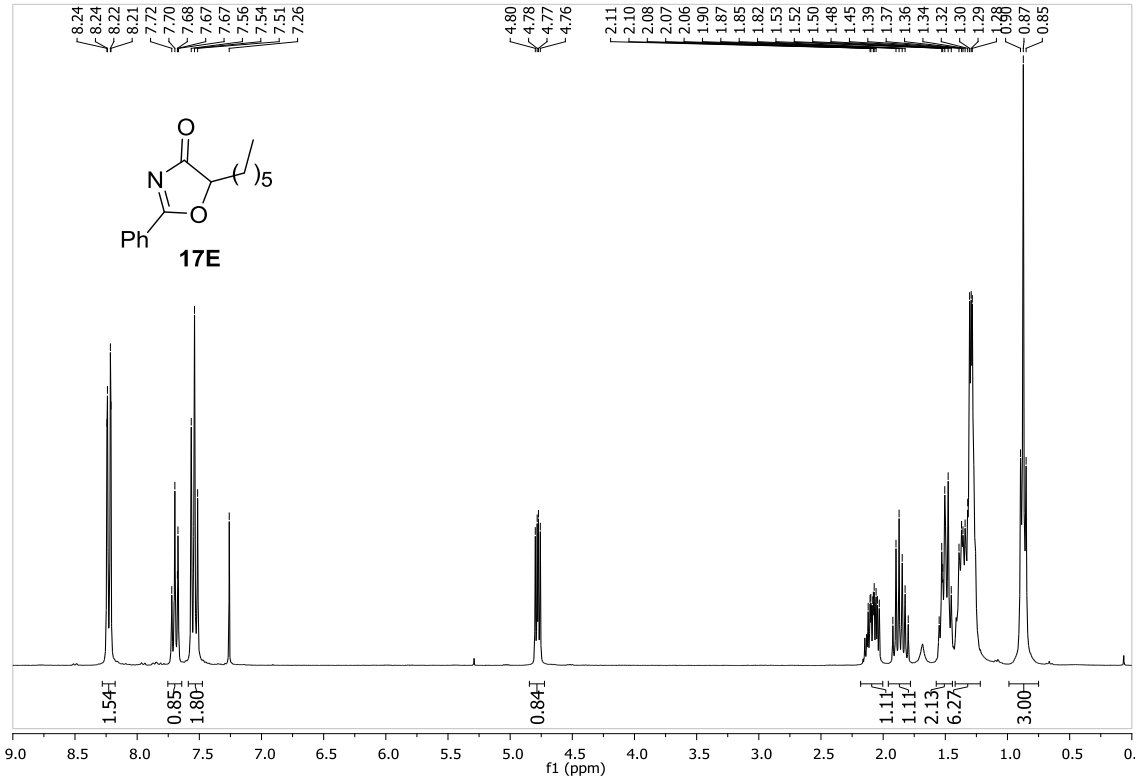
f1 (ppm)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8.22
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7.54
7.51
7.26
4.80
4.78
4.77
4.76
2.11
2.10
2.08
2.07
2.06
1.90
1.87
1.85
1.82
1.53
1.52
1.50
1.48
1.45
1.39
1.37
1.36
1.34
1.32
1.30
1.29
0.87
0.85
O
N
O
Ph
5
17E
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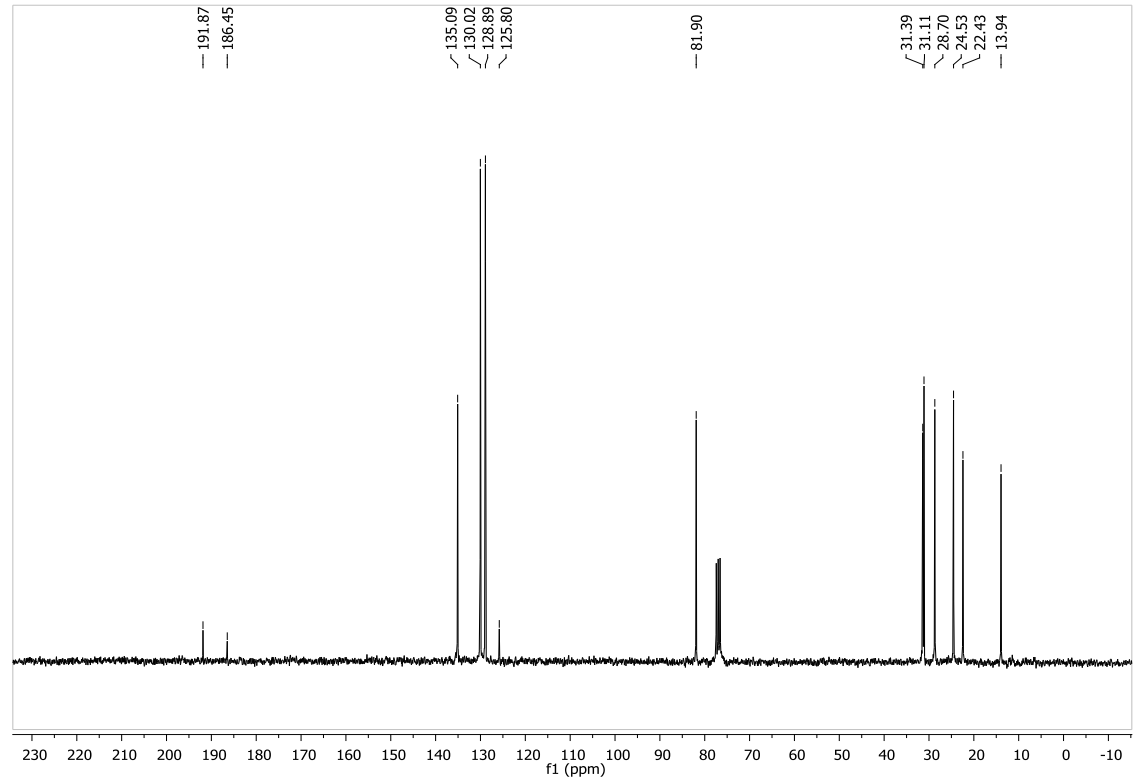
0.85
1.80
0.84
1.11
1.11
2.13
6.27
3.00
f1 (ppm)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186.45
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125.80
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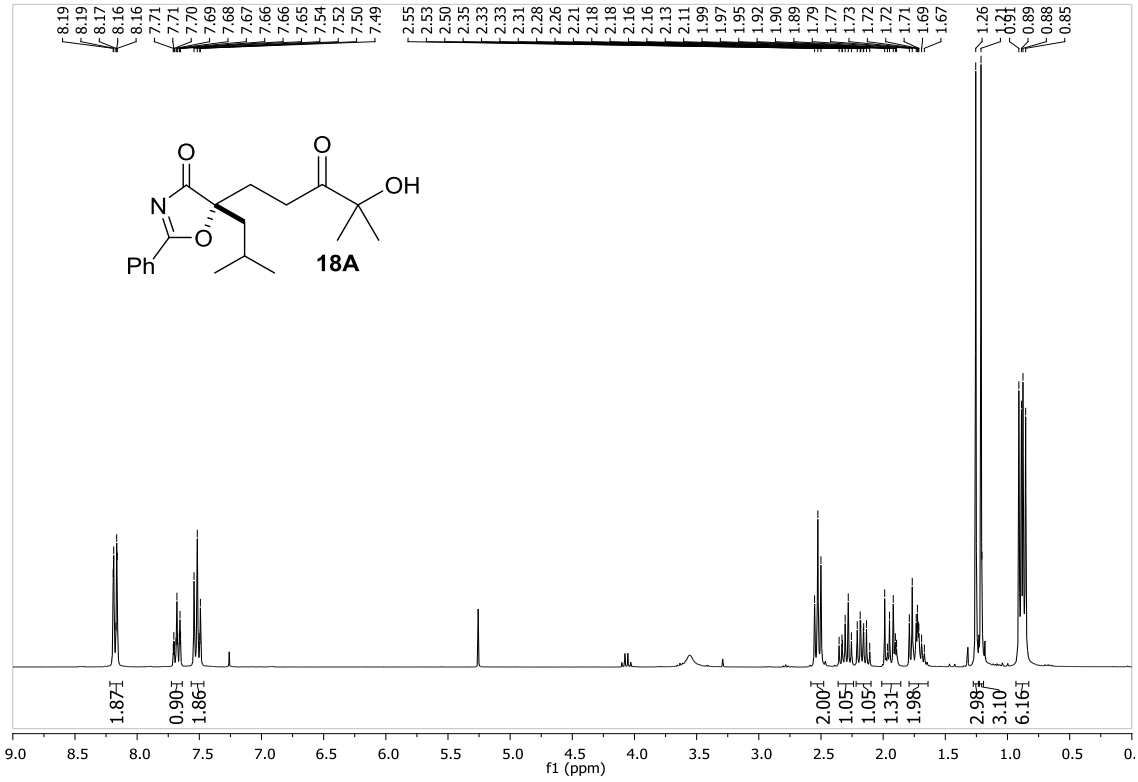
31.39
31.11
28.70
24.53
22.43
13.94
f1 (ppm)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7.66
7.66
7.65
7.54
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7.50
7.49
2.55
2.53
2.50
2.35
2.33
2.33
2.31
2.28
2.26
2.21
2.18
2.18
2.16
2.16
2.13
2.11
1.99
1.97
1.95
1.92
1.90
1.89
1.79
1.77
1.73
1.72
1.72
1.71
1.69
1.67
1.26
1.21
0.91
0.89
0.88
0.85
O
O
OH
N
O
Ph
18A
1.87
0.90
1.86
2.00
1.05
1.05
1.31
1.98
2.98
3.10
6.16
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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2.5
2.0
1.5
1.0
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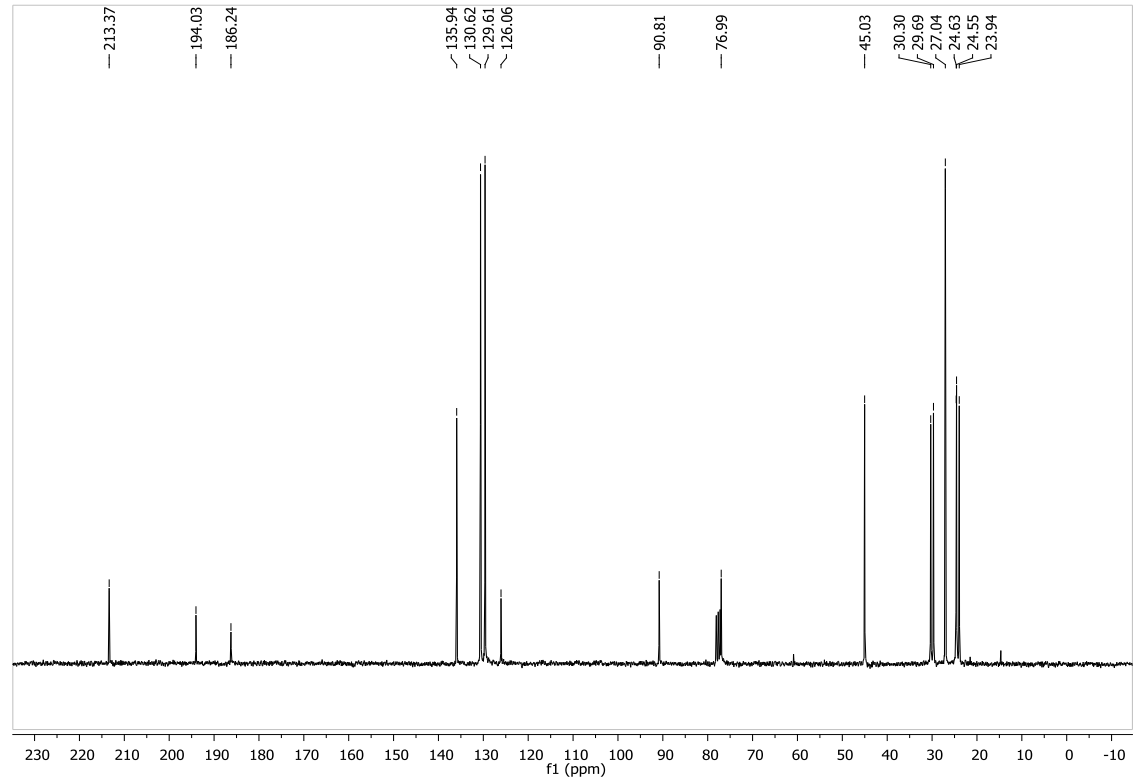
0.
f1 (ppm)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45.03
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29.69
27.04
24.63
24.55
23.94
230
220
210
200
190
180
170
160
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140
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120
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100
90
80
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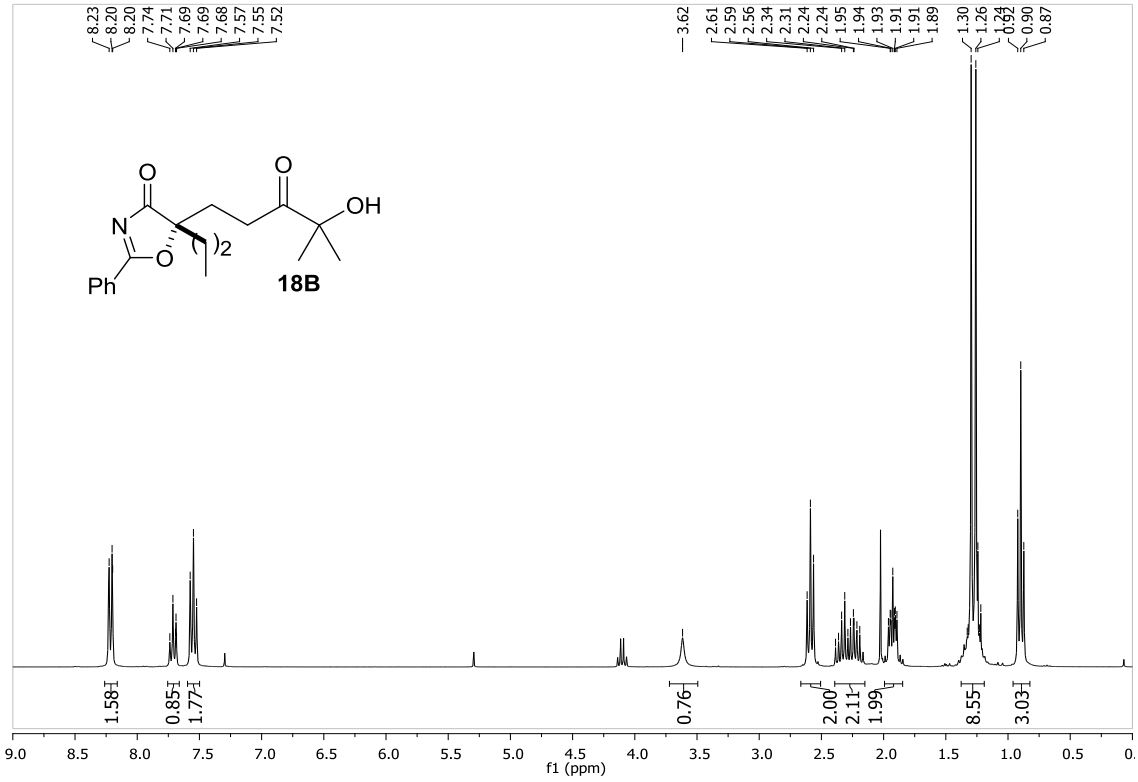
60
50
40
30
20
10
0
-10
f1 (ppm)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2.59
2.56
2.34
2.31
2.24
2.24
1.95
1.94
1.93
1.91
1.91
1.89
1.30
1.26
1.24
0.92
0.90
0.87
O
O
N
O
OH
)2
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0.85
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0.76
2.00
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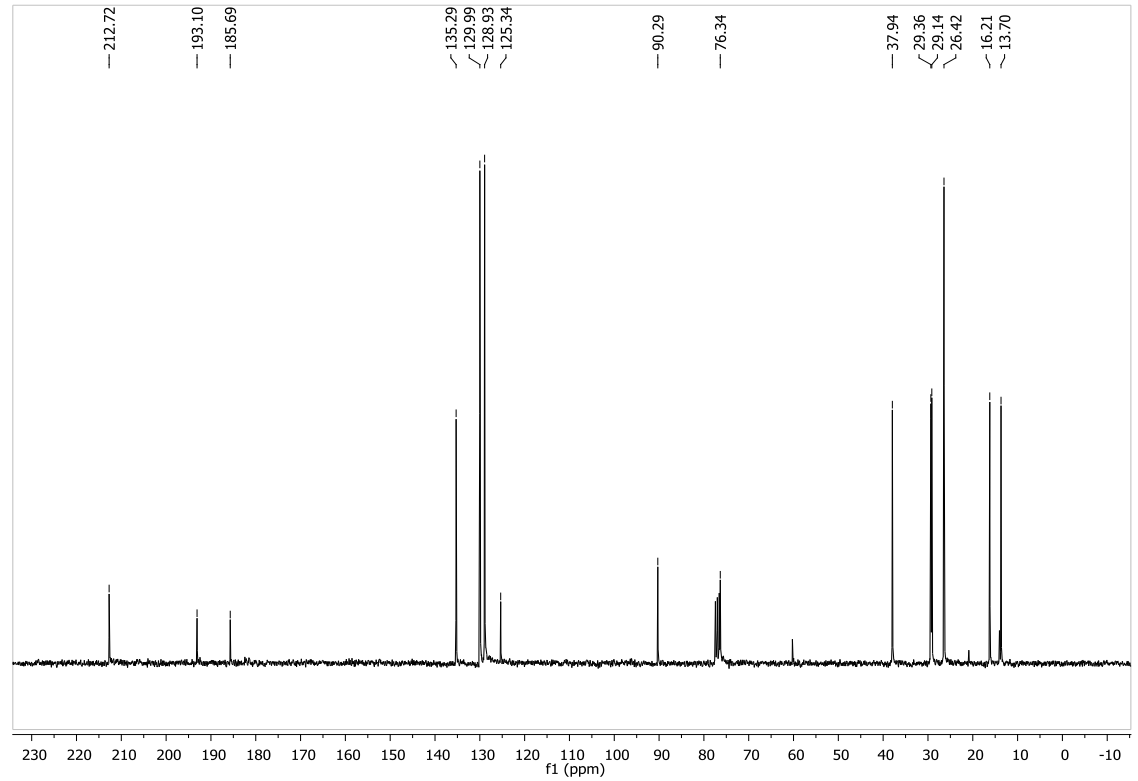
1.99
8.55
3.03
f1 (ppm)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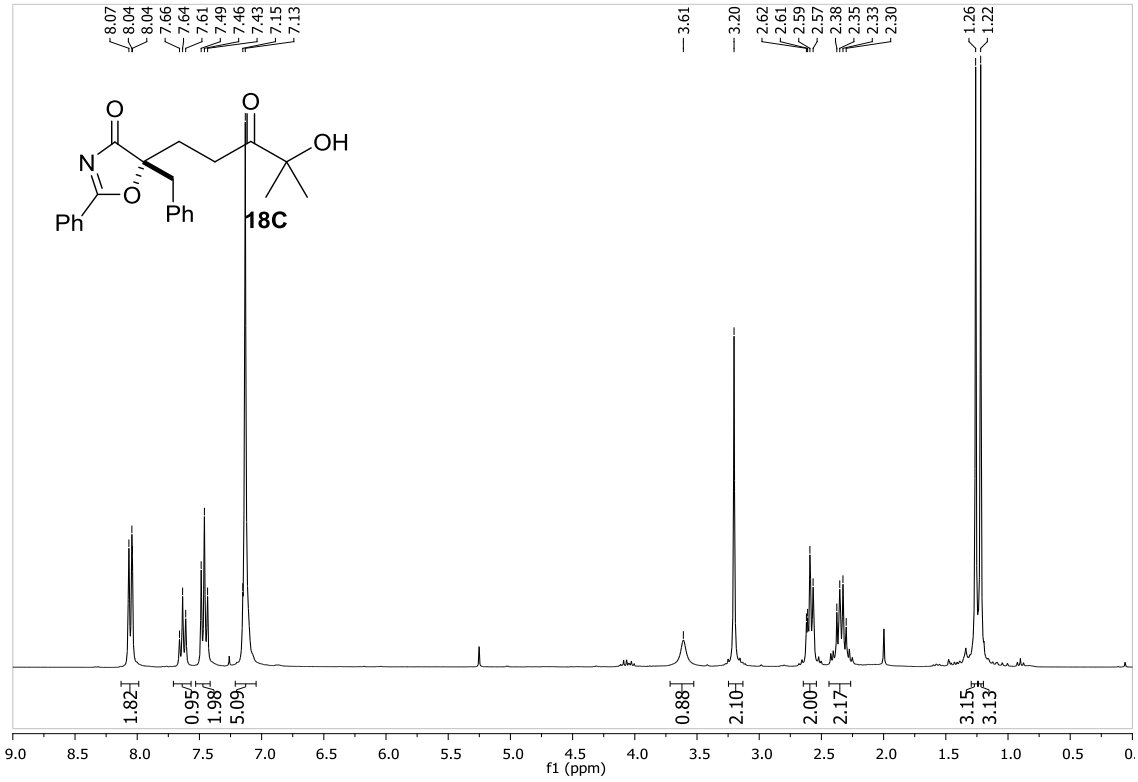
13.70
f1 (ppm)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7.13
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2.62
2.61
2.59
2.57
2.38
2.35
2.33
2.30
1.26
1.22
O
O
N
O
OH
Ph
Ph
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0.88
2.10
2.00
2.17
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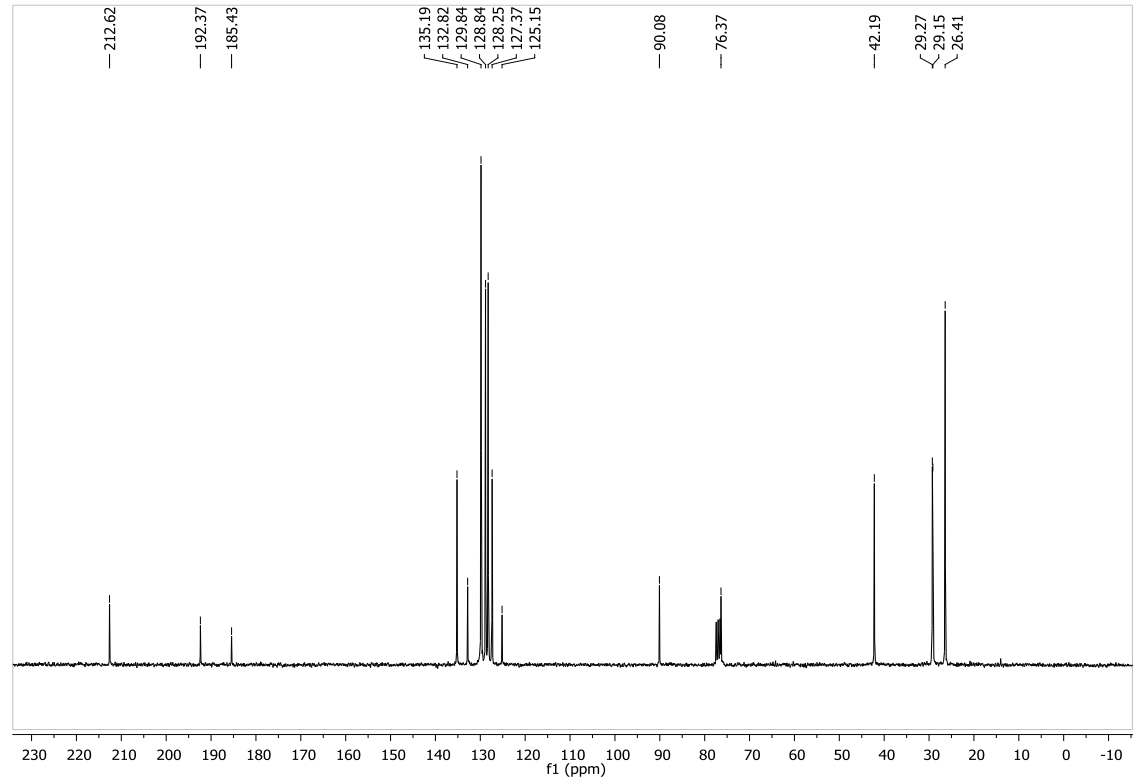
3.13
f1 (ppm)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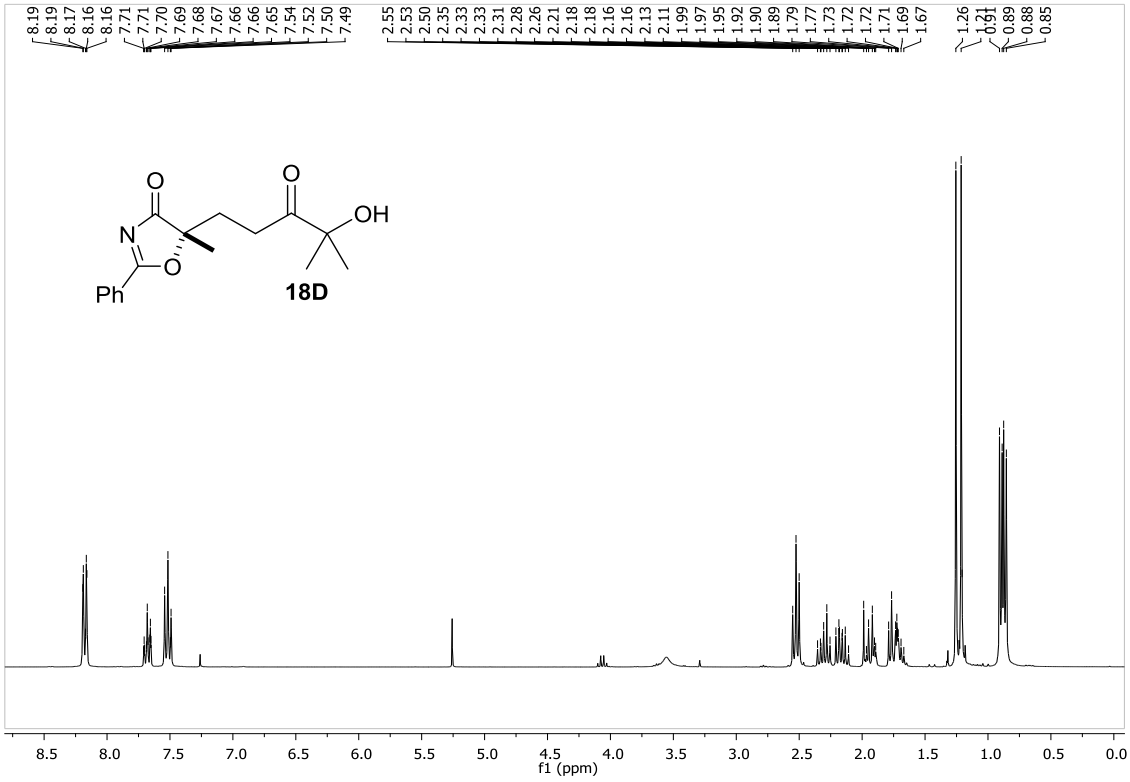
26.41
f1 (ppm)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7.50
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2.18
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2.16
2.13
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1.90
1.89
1.79
1.77
1.73
1.72
1.72
1.71
1.69
1.67
1.26
0.91
0.89
0.88
0.85
O
O
N
O
OH
Ph
18D
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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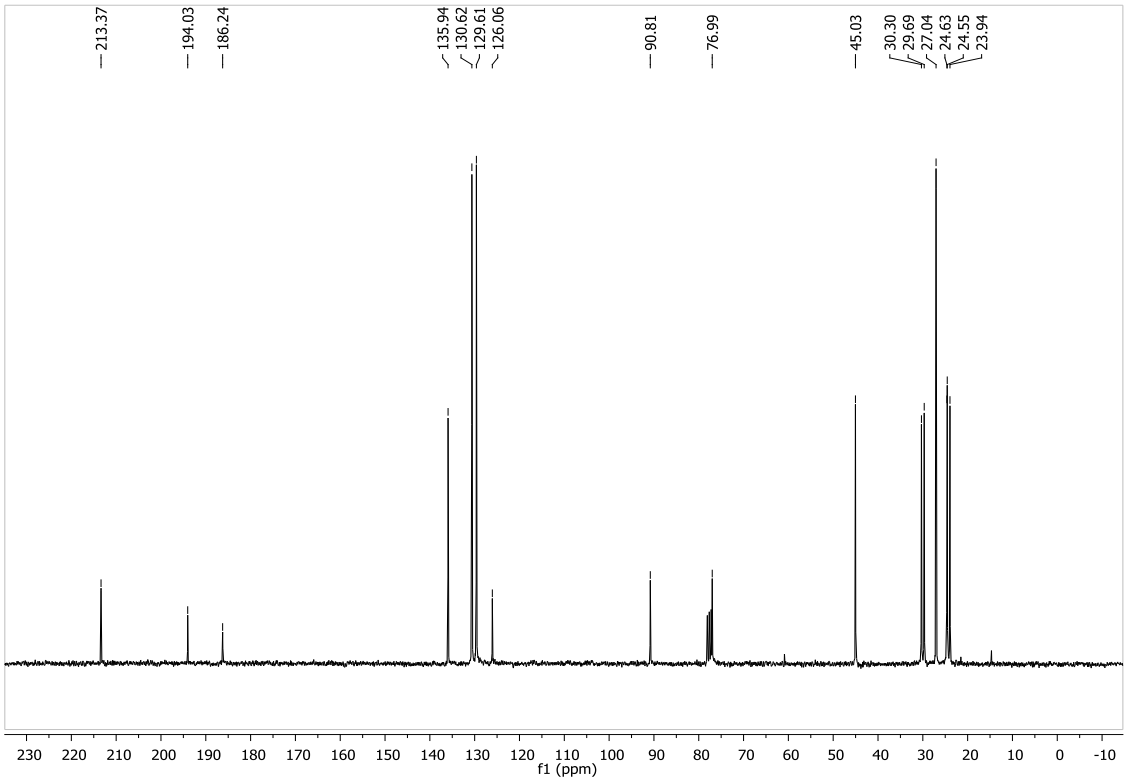
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30.30
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24.63
24.55
23.94
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200
190
180
170
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100
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80
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60
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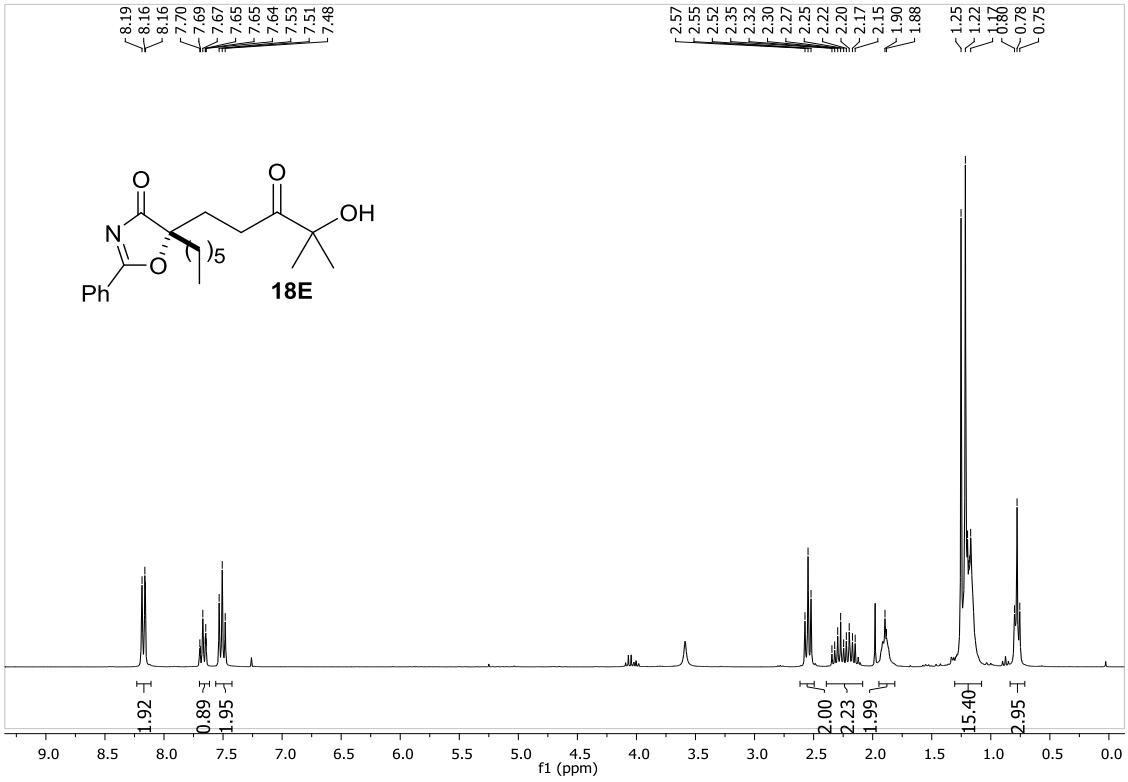
40
30
20
10
0
-10
f1 (ppm)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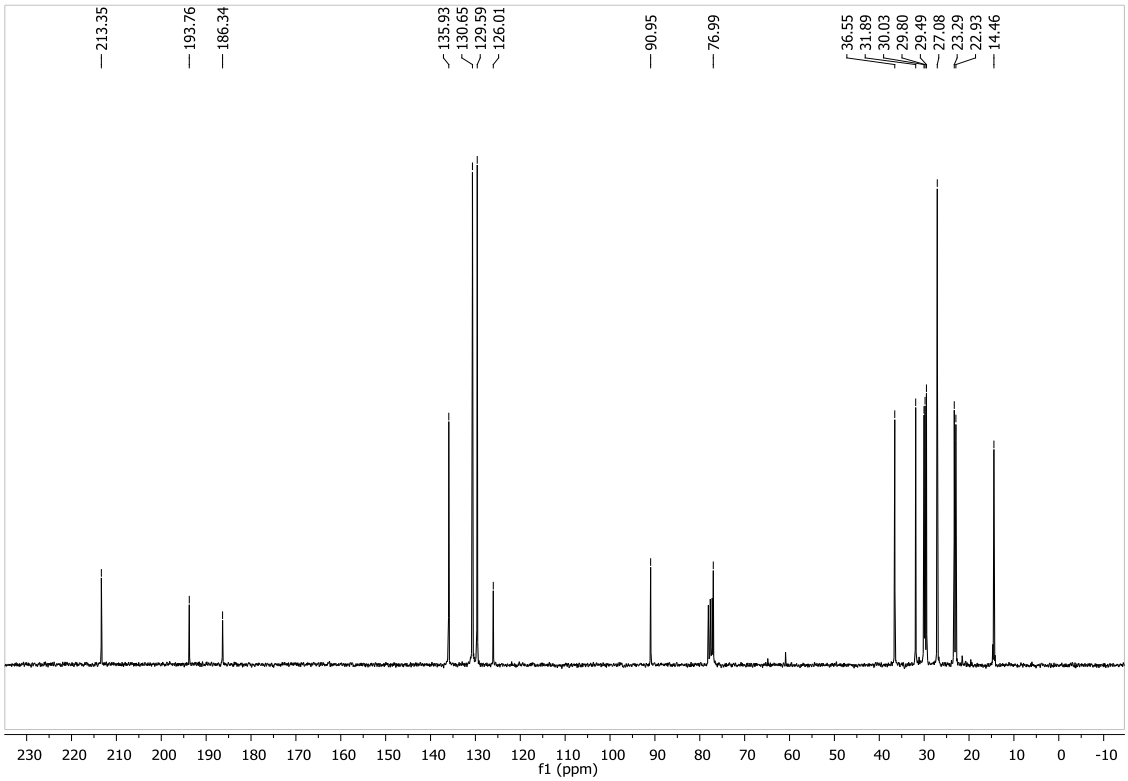
2.30
2.27
2.25
2.22
2.20
2.17
2.15
1.90
1.88
1.25
1.22
1.17
0.80
0.78
0.75
O
O
OH
N
O
)5
Ph
18E
1.92
0.89
1.95
2.00
2.23
1.99
15.40
2.95
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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135.93
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129.59
126.01
90.95
76.99
36.55
31.89
30.03
29.80
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27.08
23.29
22.93
14.46
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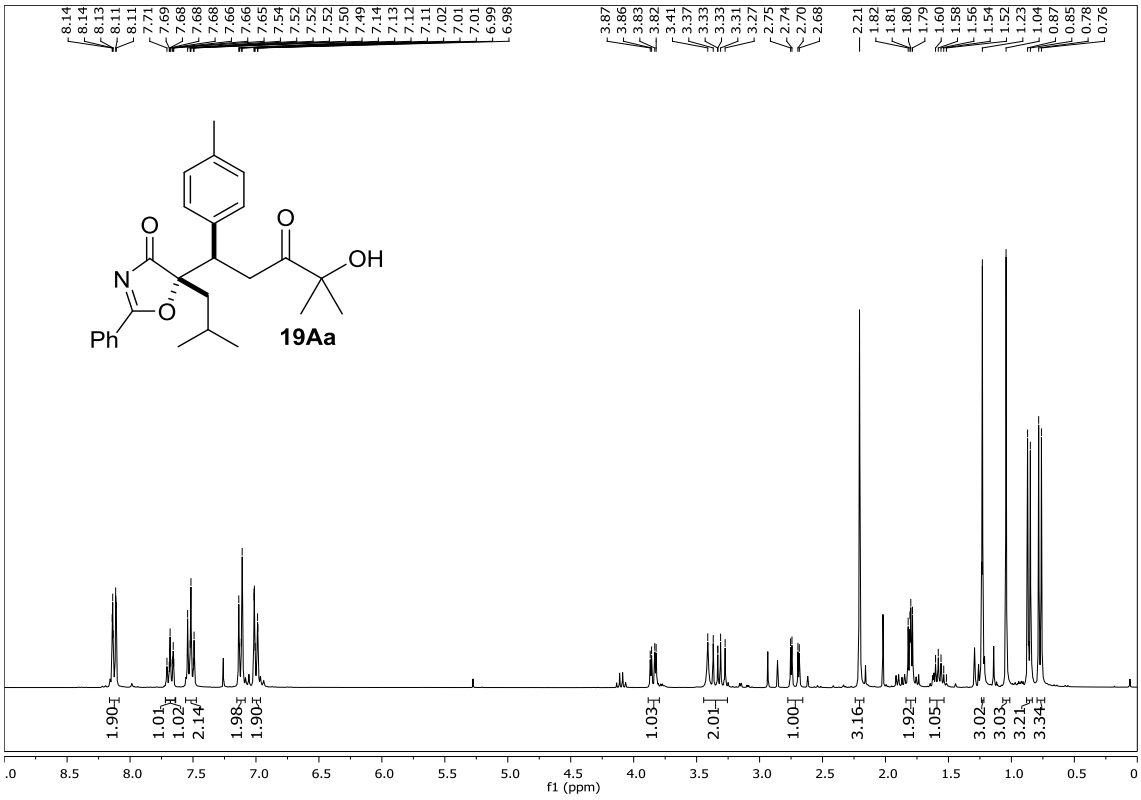
f1 (ppm)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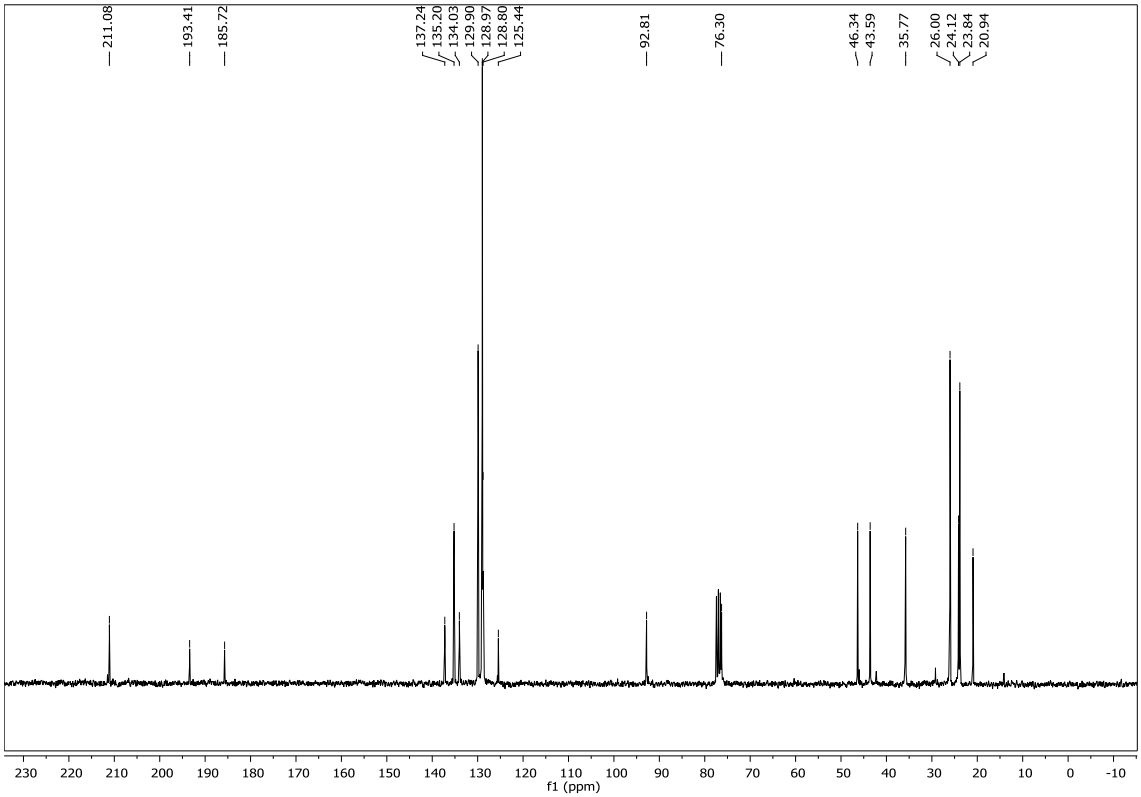
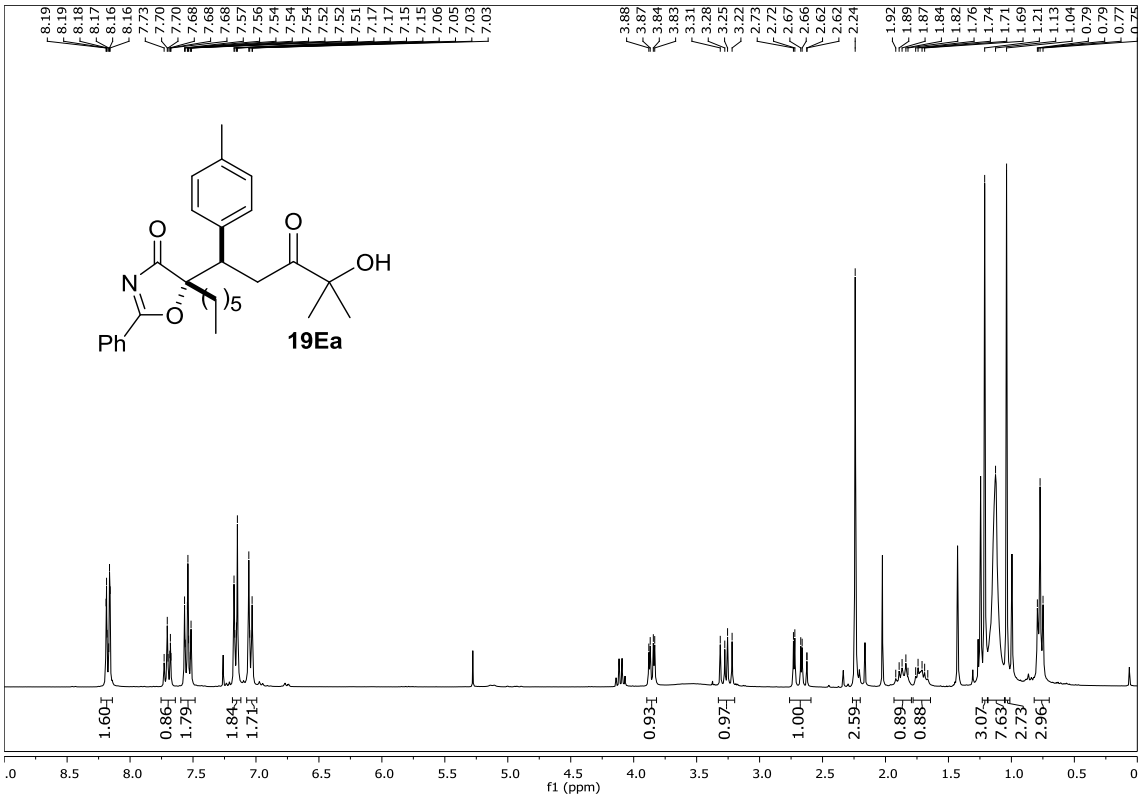
3.87 3.86 3.83 3.82 3.41 3.37 3.33 3.33 3.31 3.27 2.75 2.74 2.70 2.68
2.21 1.82 1.81 1.80 1.79 1.60 1.58 1.56 1.54 1.52 1.23 1.04 0.87 0.85 0.78 0.76
O
O
OH
N
O
Ph
19Aa
1.90 1.01 1.02 2.14 1.98 1.90
1.03 2.01 1.00 3.16 1.92 1.05 3.02 3.03 3.21 3.34
f1 (ppm)


211.08 193.41 185.72
137.24 135.20 134.03 129.90 128.97 128.80 125.44
92.81 76.30
46.34 43.59 35.77 26.00 24.12 23.84 20.94
f1 (ppm)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7.03
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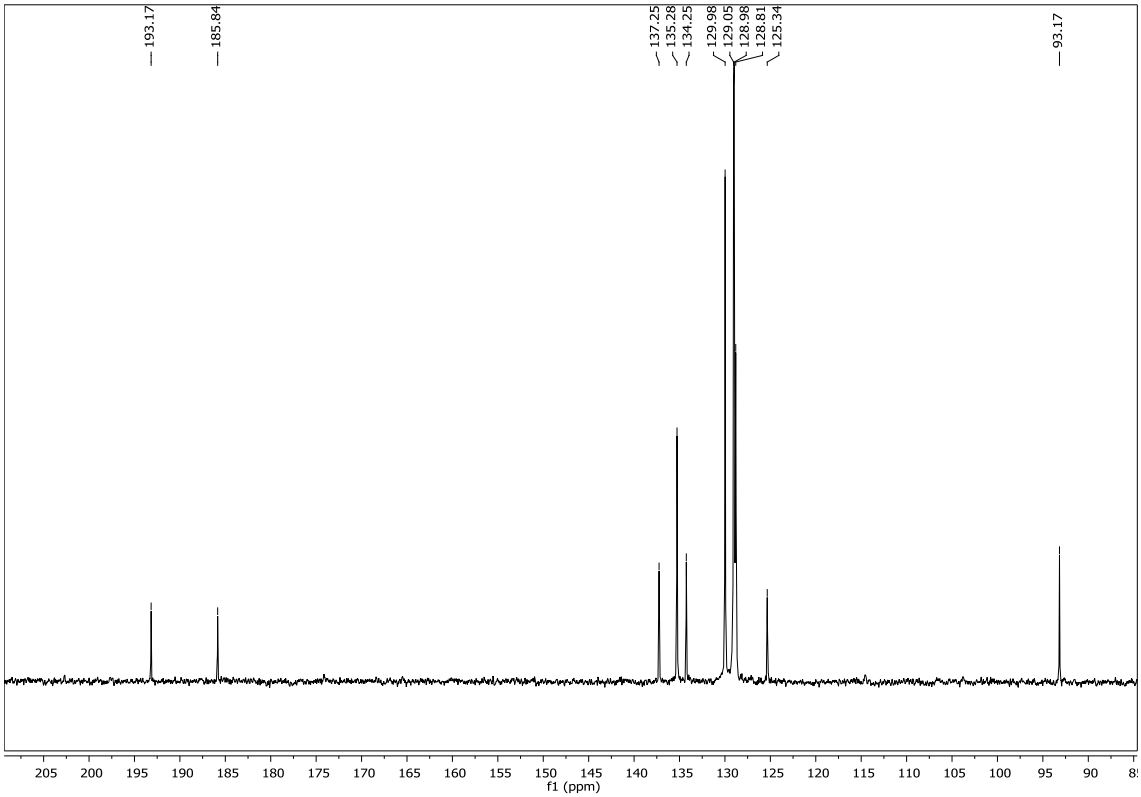
1.92
1.89
1.87
1.84
1.82
1.76
1.74
1.71
1.69
1.21
1.13
1.04
0.79
0.79
0.77
O
O
N
O
OH
5
Ph
19Ea
1.60
0.86
1.79
1.84
1.71
0.93
0.97
1.00
2.59
0.89
0.88
3.07
7.63
2.73
2.96
f1 (ppm)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129.05
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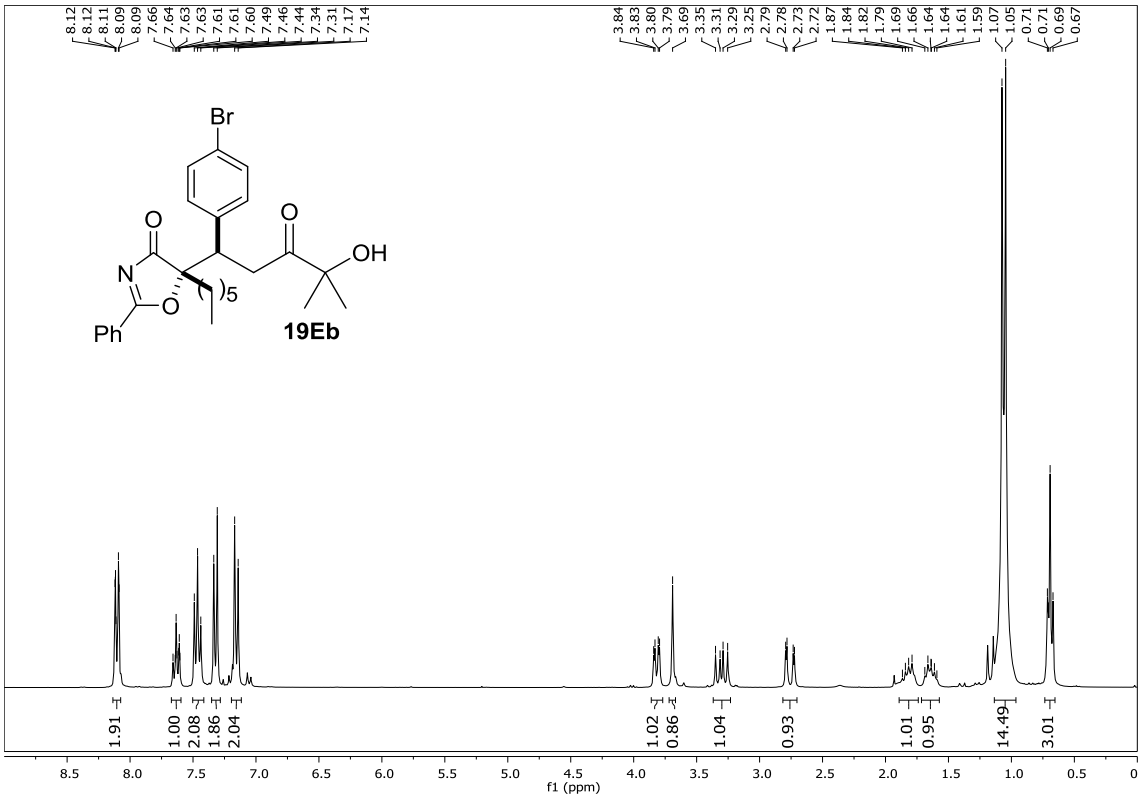
93.17
f1 (ppm)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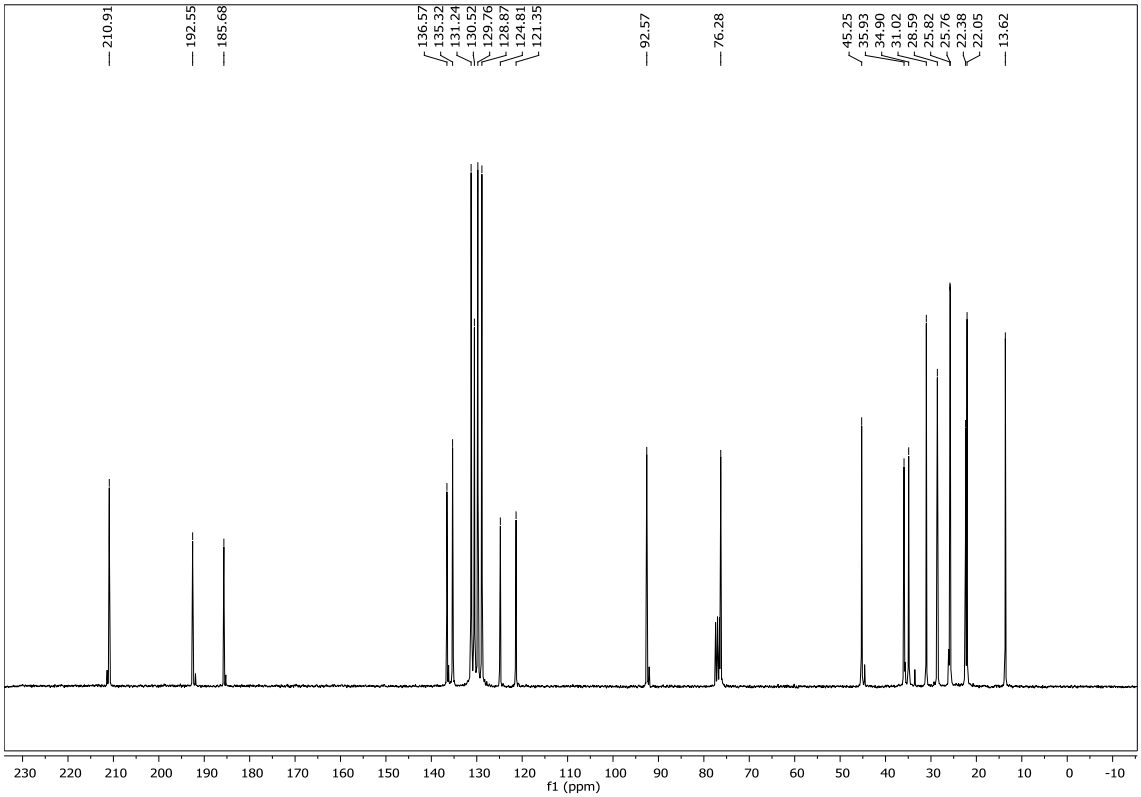
OH
N
O
)5
Ph
19Eb
f1 (ppm)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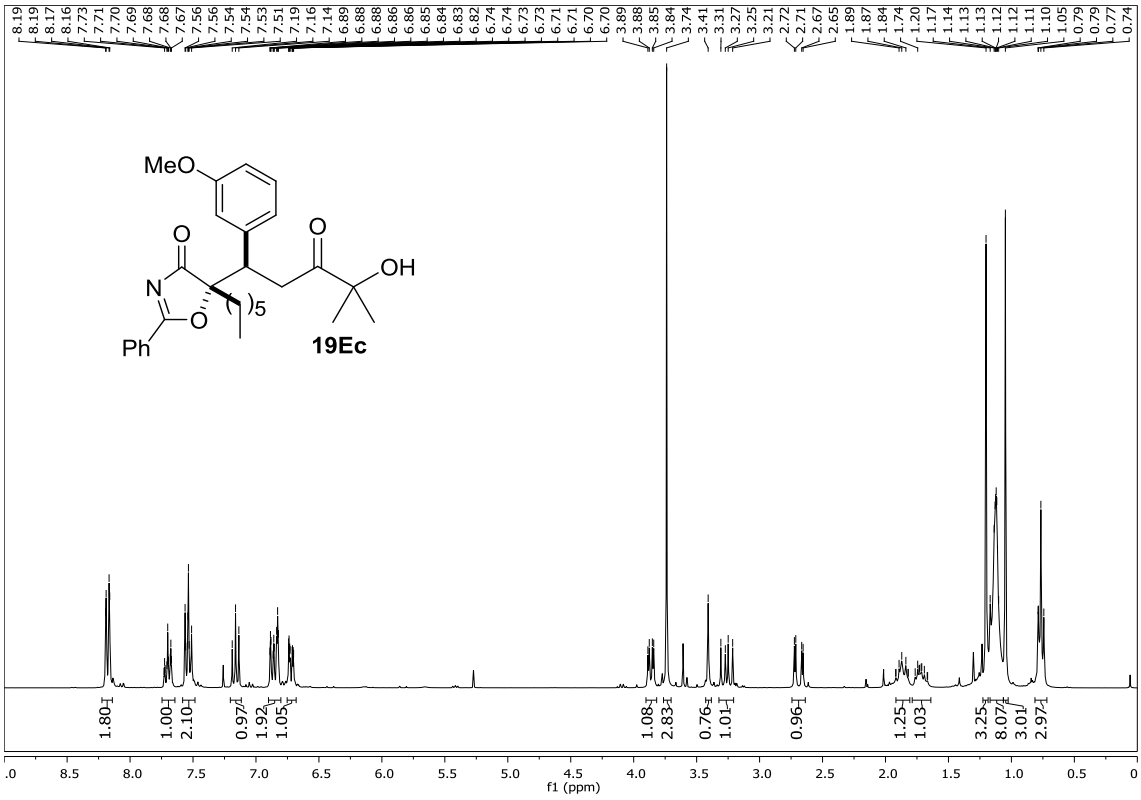
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OH
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Ph
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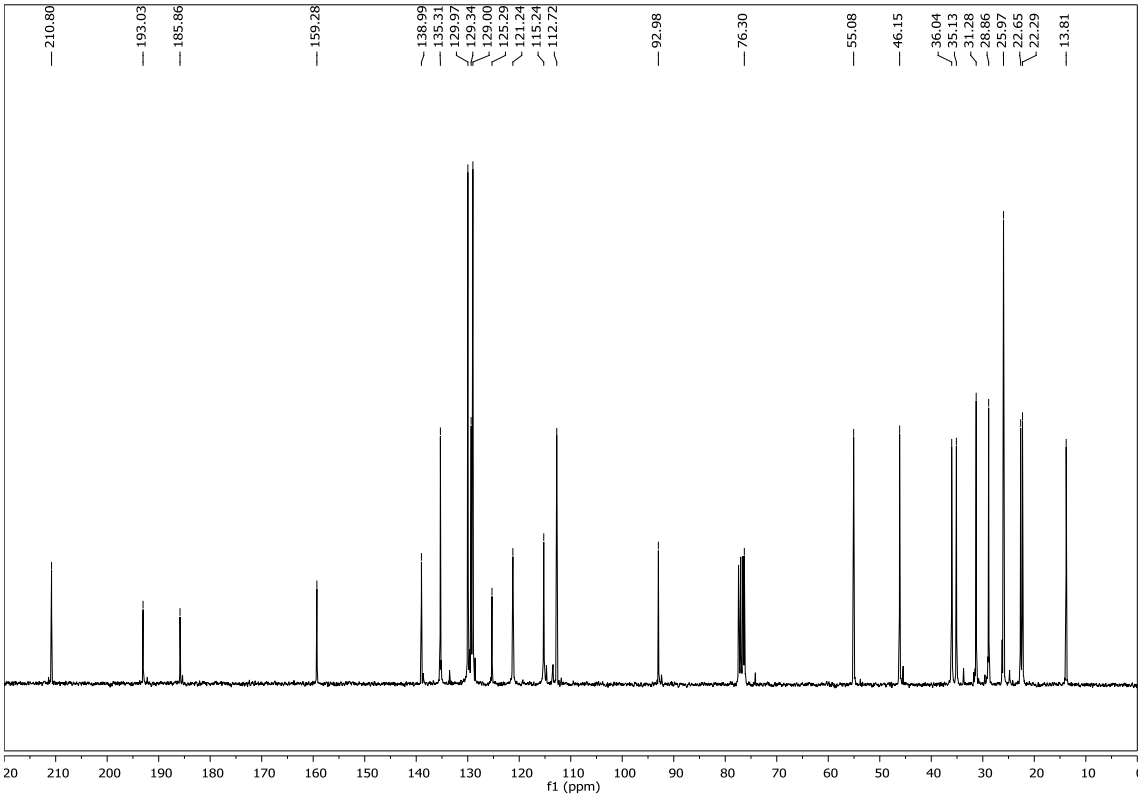
f1 (ppm)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121.24
115.24
112.72
92.98
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31.28
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25.97
22.65
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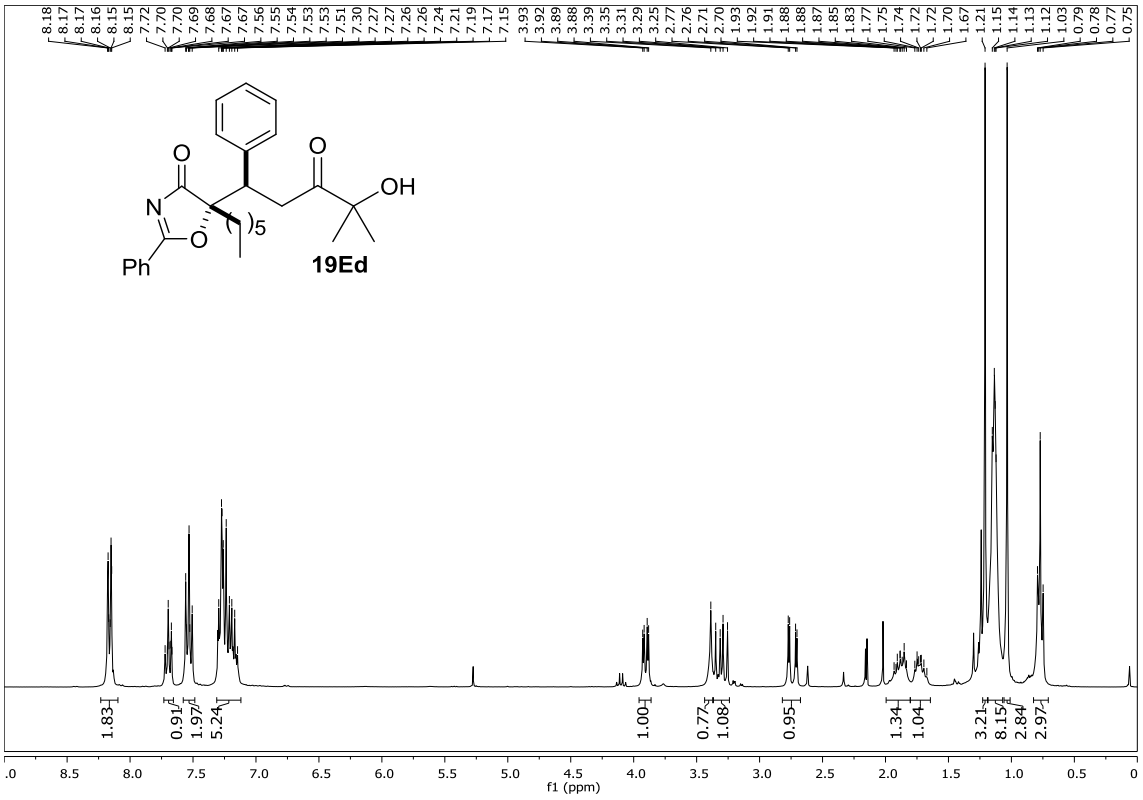
13.81
f1 (ppm)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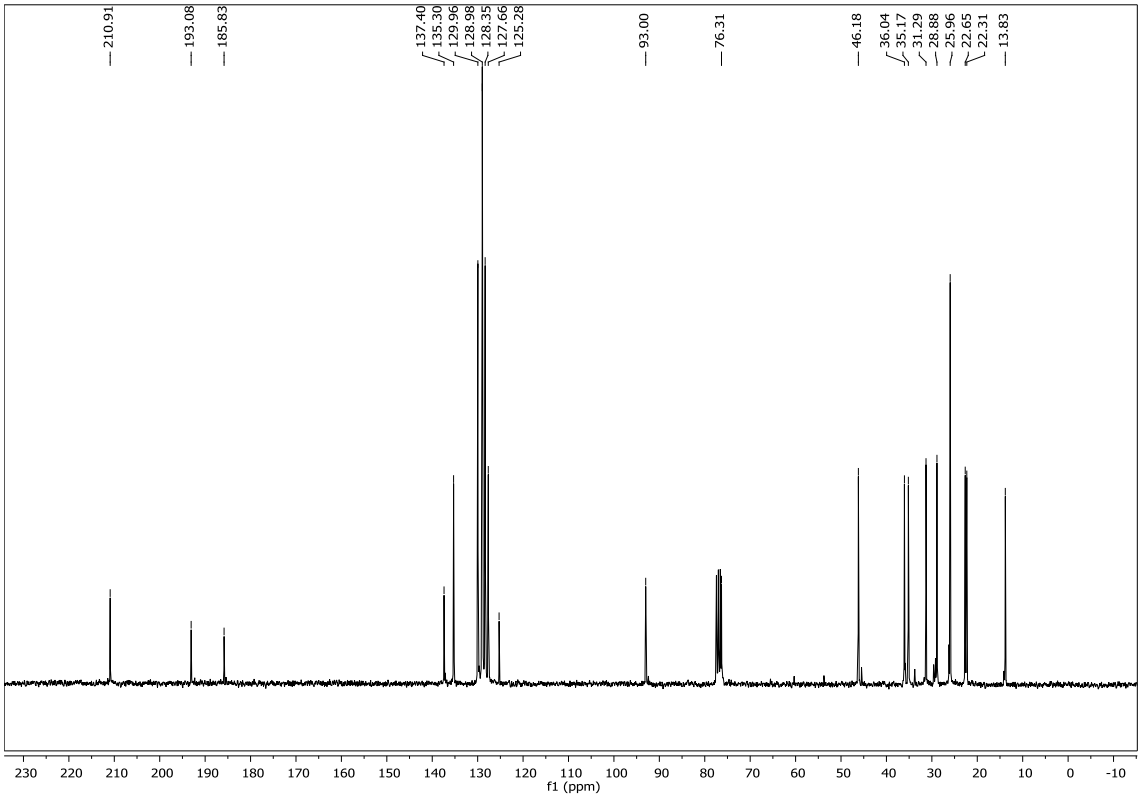
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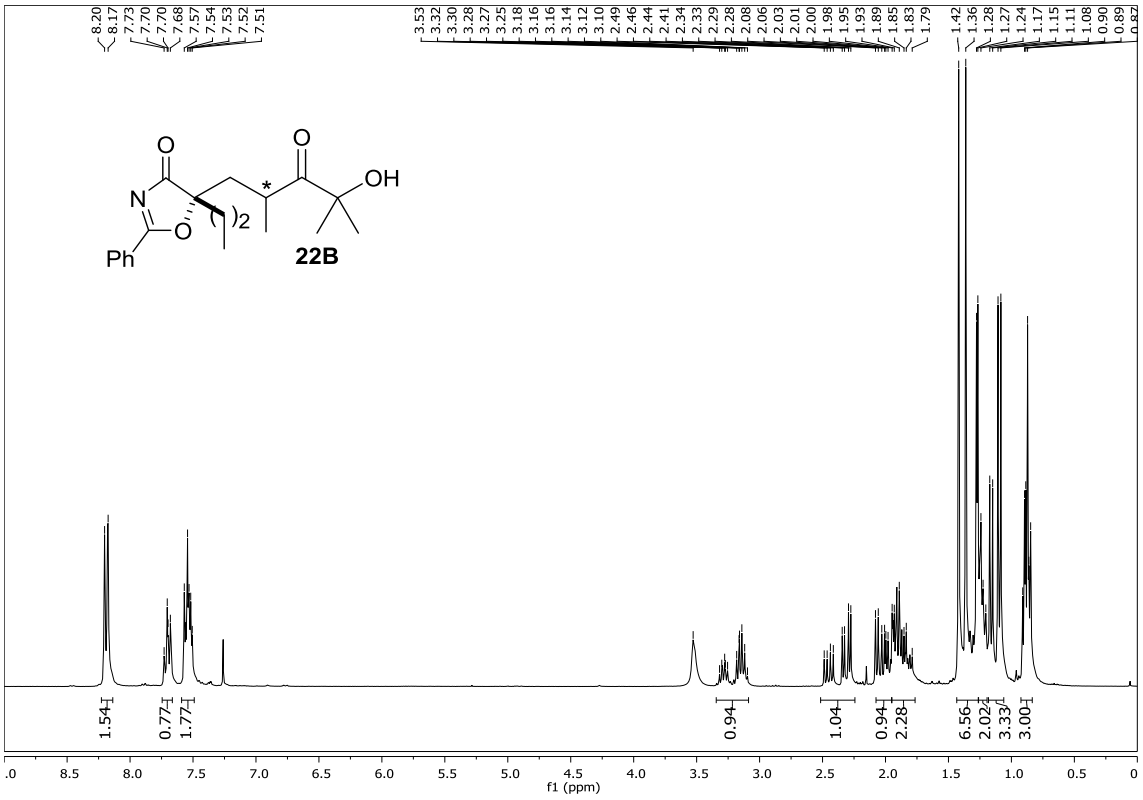
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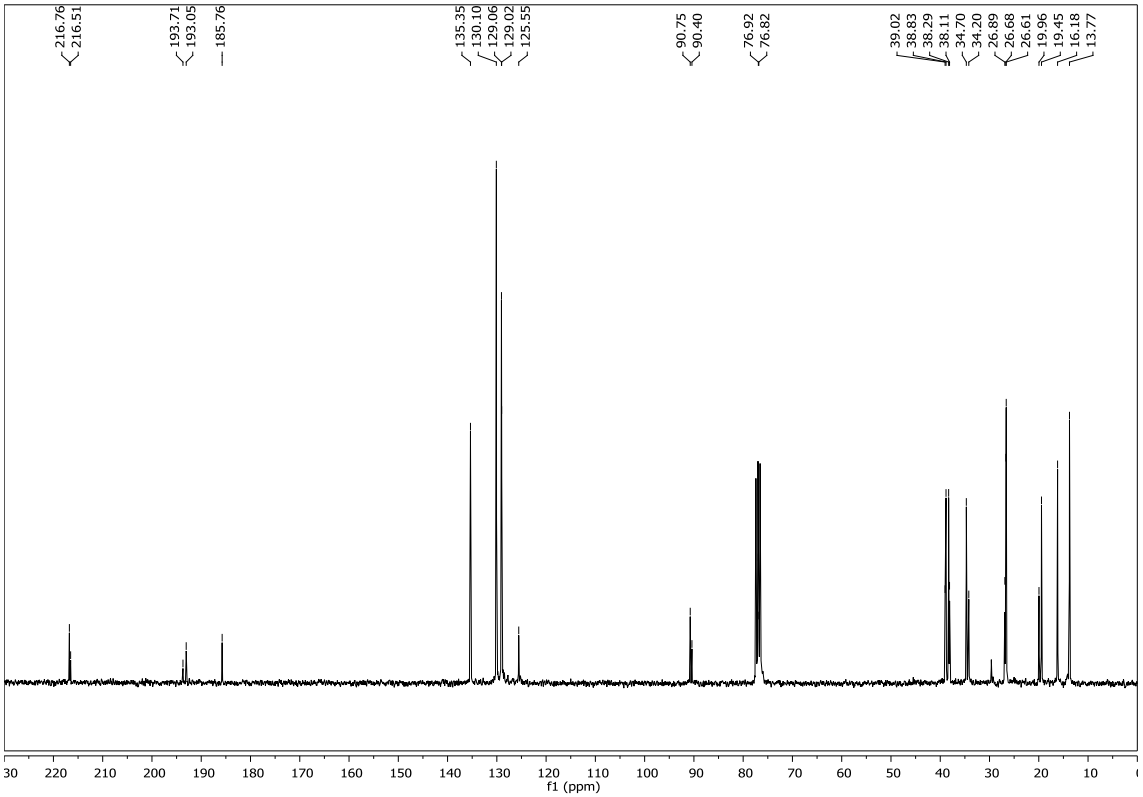
f1 (ppm)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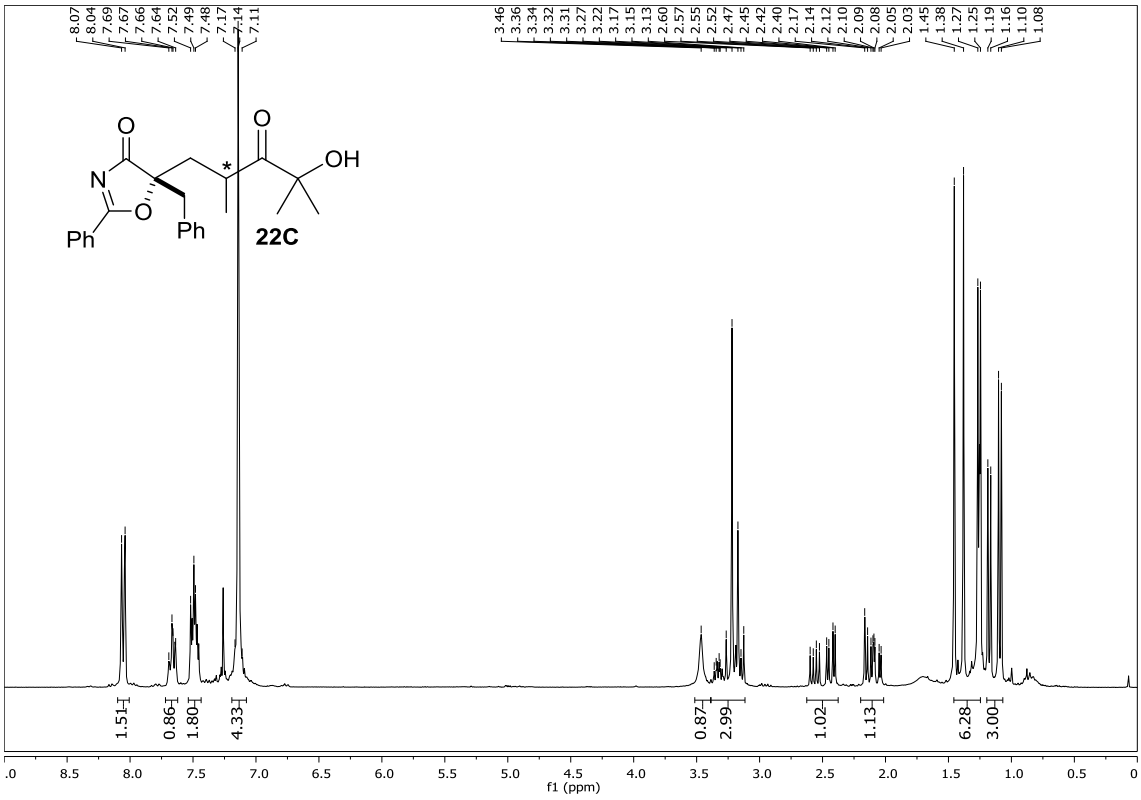
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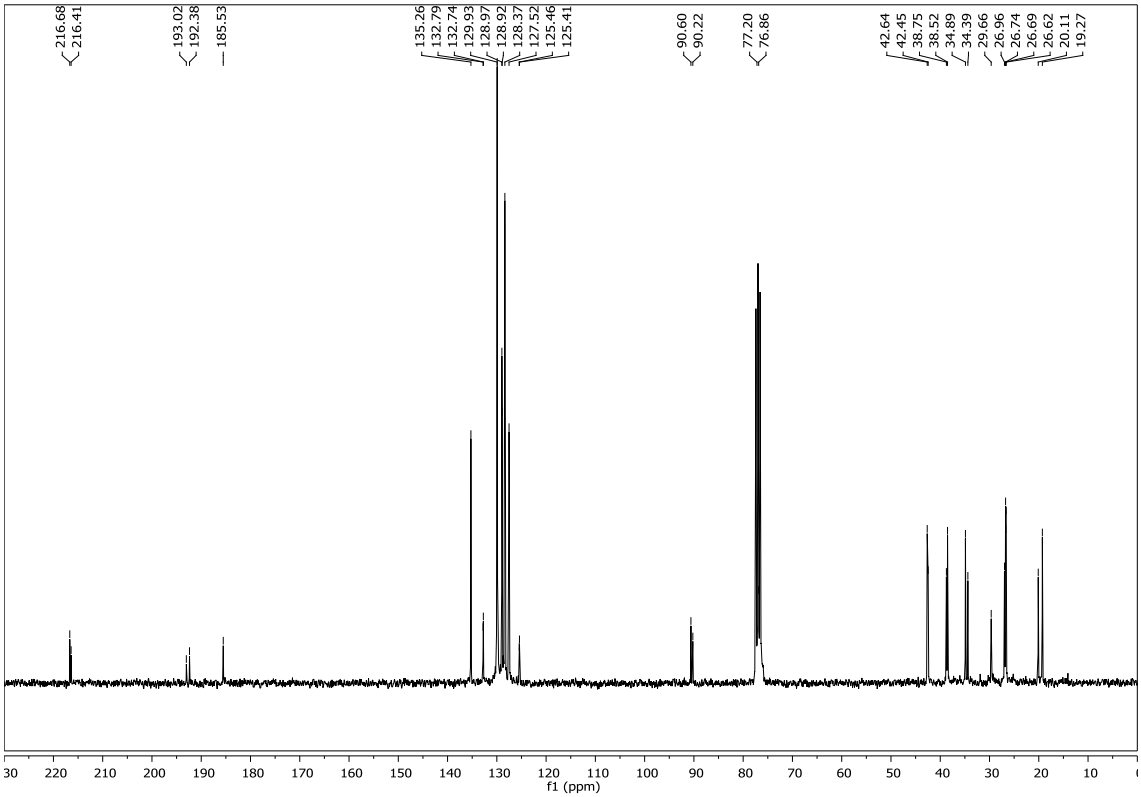
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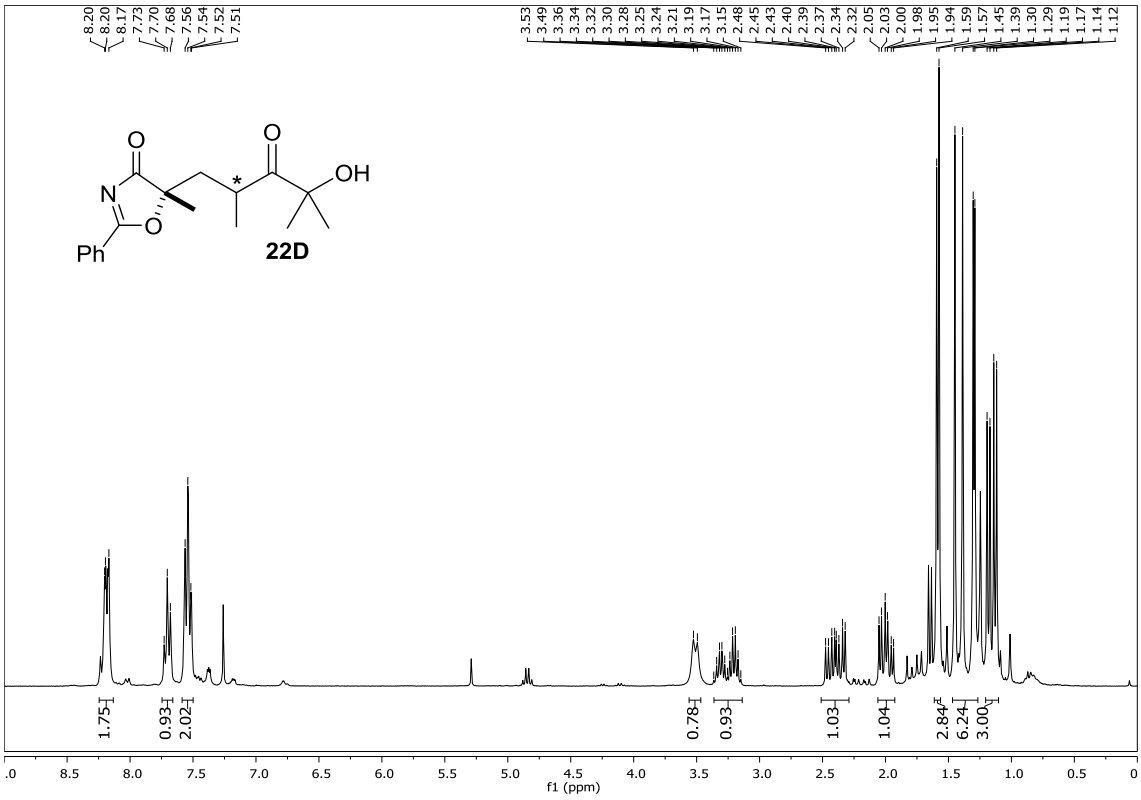
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7.56
7.54
7.52
7.51
3.53
3.49
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3.34
3.32
3.30
3.28
3.25
3.24
3.21
3.19
3.17
3.15
2.48
2.45
2.43
2.40
2.39
2.37
2.34
2.32
2.05
2.03
2.00
1.98
1.95
1.94
1.59
1.57
1.45
1.39
1.30
1.29
1.19
1.17
1.14
1.12
O
O
N
O
Ph
*
OH
22D
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2.02
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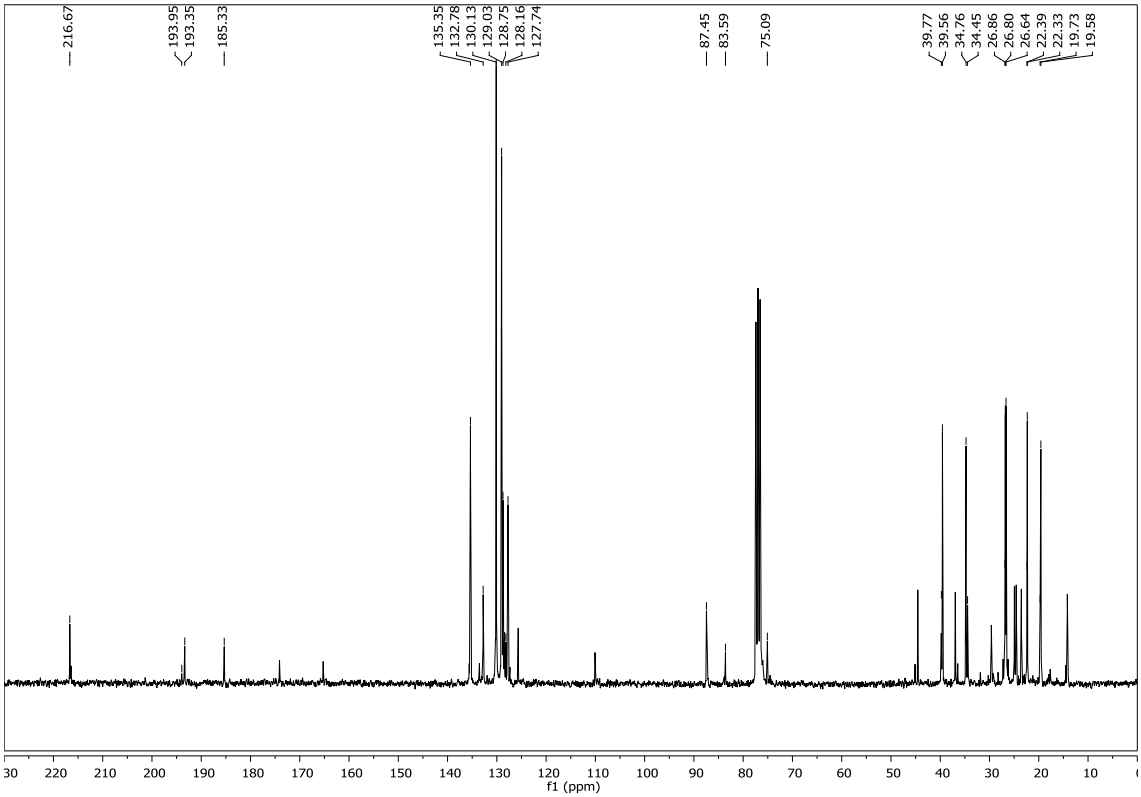
0.93
1.03
1.04
2.84
6.24
3.00
f1 (ppm)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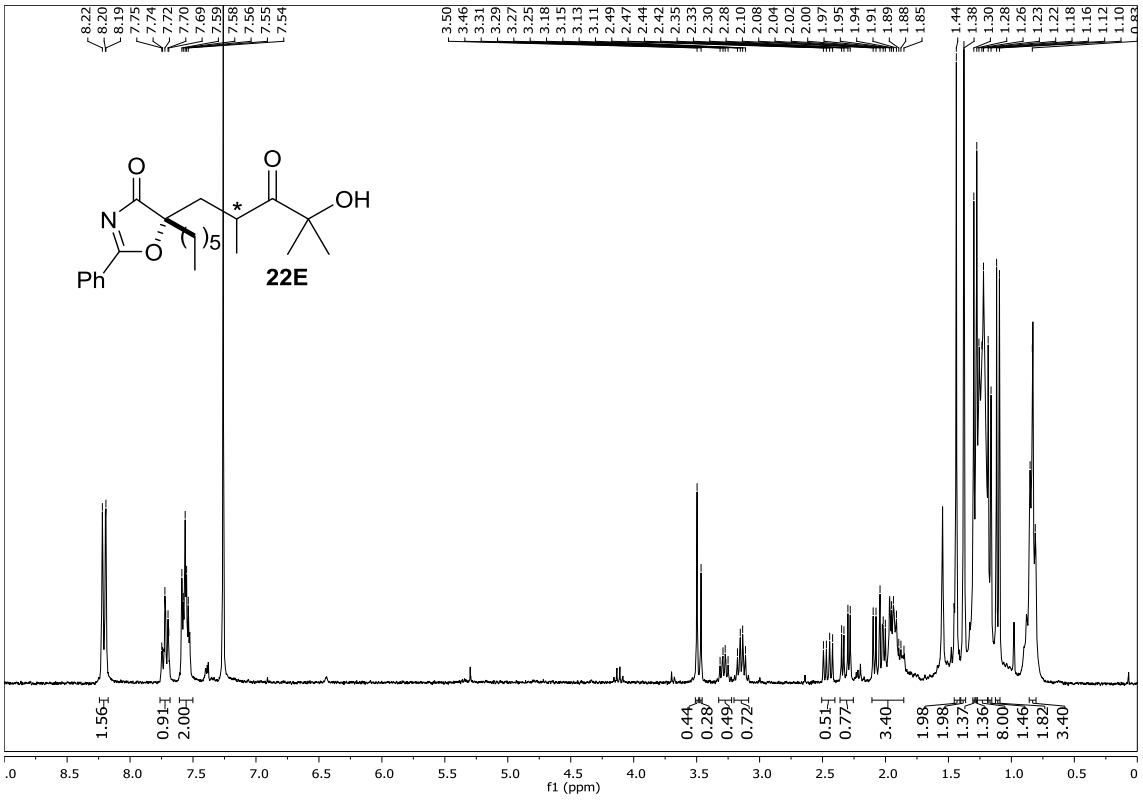
128.75
128.16
127.74
87.45
83.59
75.09
39.77
39.56
34.76
34.45
26.86
26.80
26.64
22.39
22.33
19.73
19.58
f1 (ppm)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7.69
7.59
7.58
7.56
7.55
7.54
3.50
3.46
3.31
3.29
3.27
3.25
3.18
3.15
3.13
3.11
2.49
2.47
2.44
2.42
2.35
2.33
2.30
2.28
2.10
2.08
2.04
2.02
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1.97
1.95
1.94
1.91
1.89
1.88
1.85
1.44
1.38
1.30
1.28
1.26
1.23
1.22
1.18
1.16
1.12
1.10
O
N
O
Ph
)5
*
O
OH
22E
1.56
0.91
2.00
0.44
0.28
0.49
0.72
0.51
0.77
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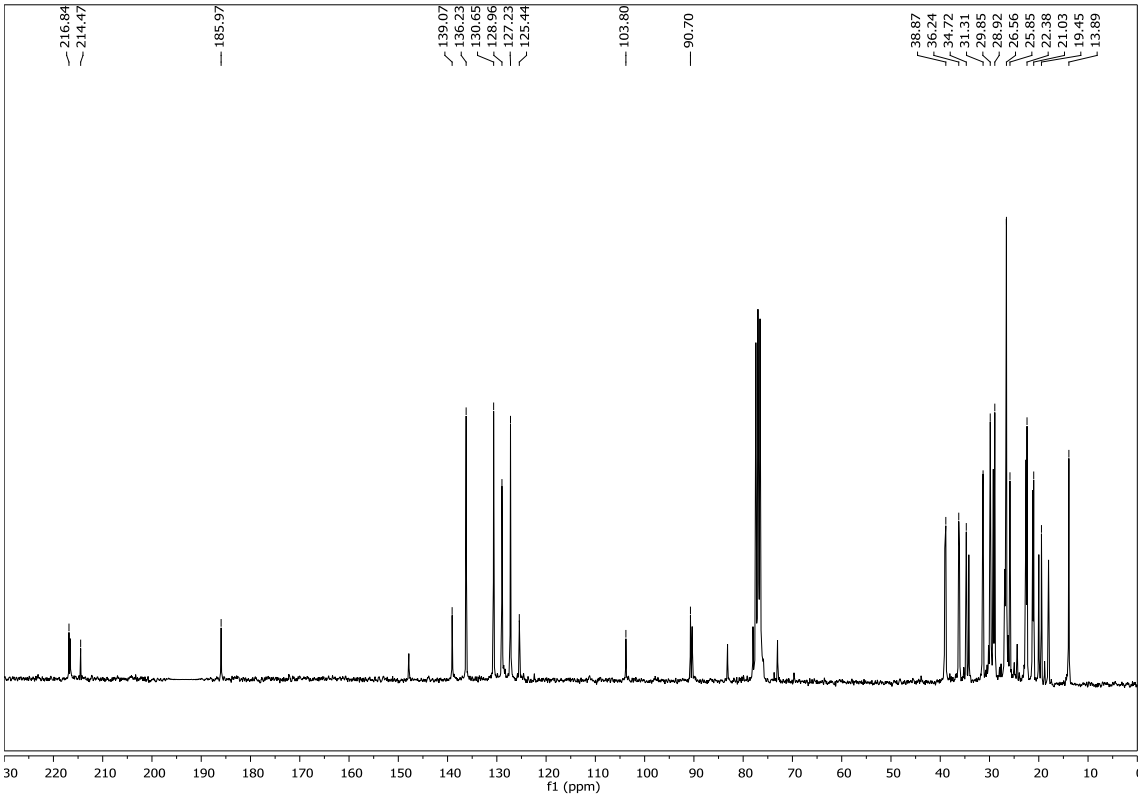
1.98
1.37
1.36
8.00
1.46
1.82
3.40
f1 (ppm)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127.23
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103.80
90.70
38.87
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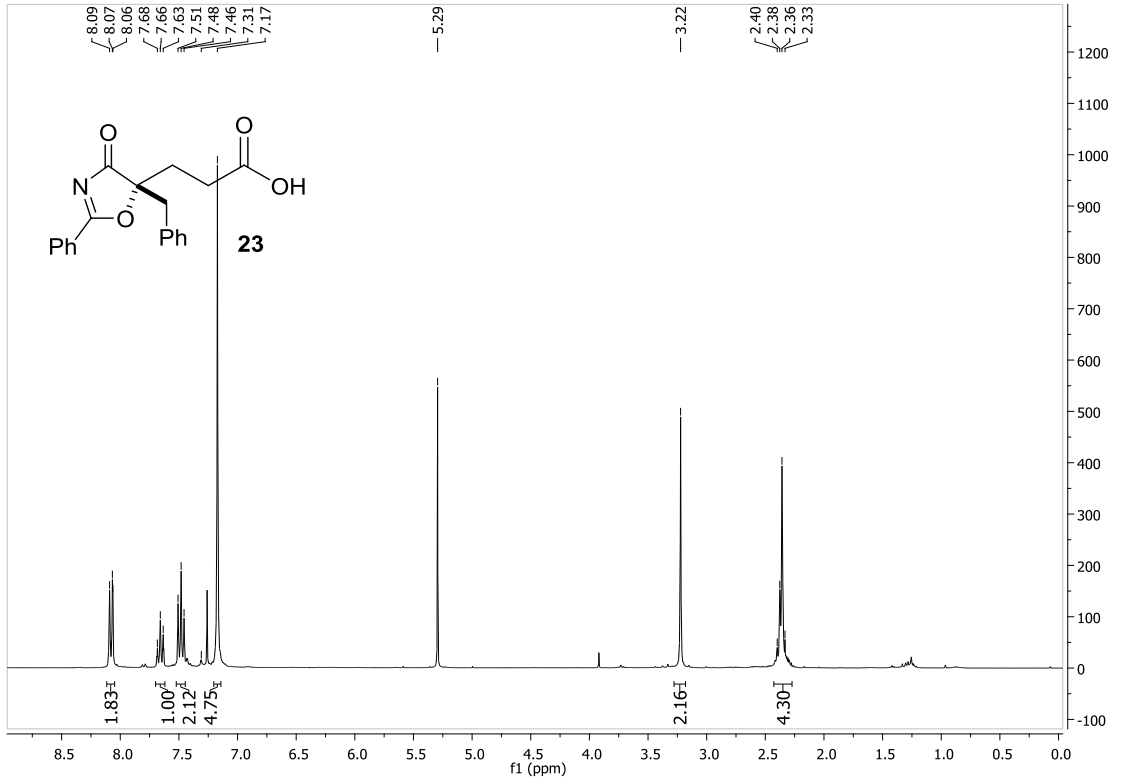
34.72
31.31
29.85
28.92
26.56
25.85
22.38
21.03
19.45
13.89
f1 (ppm)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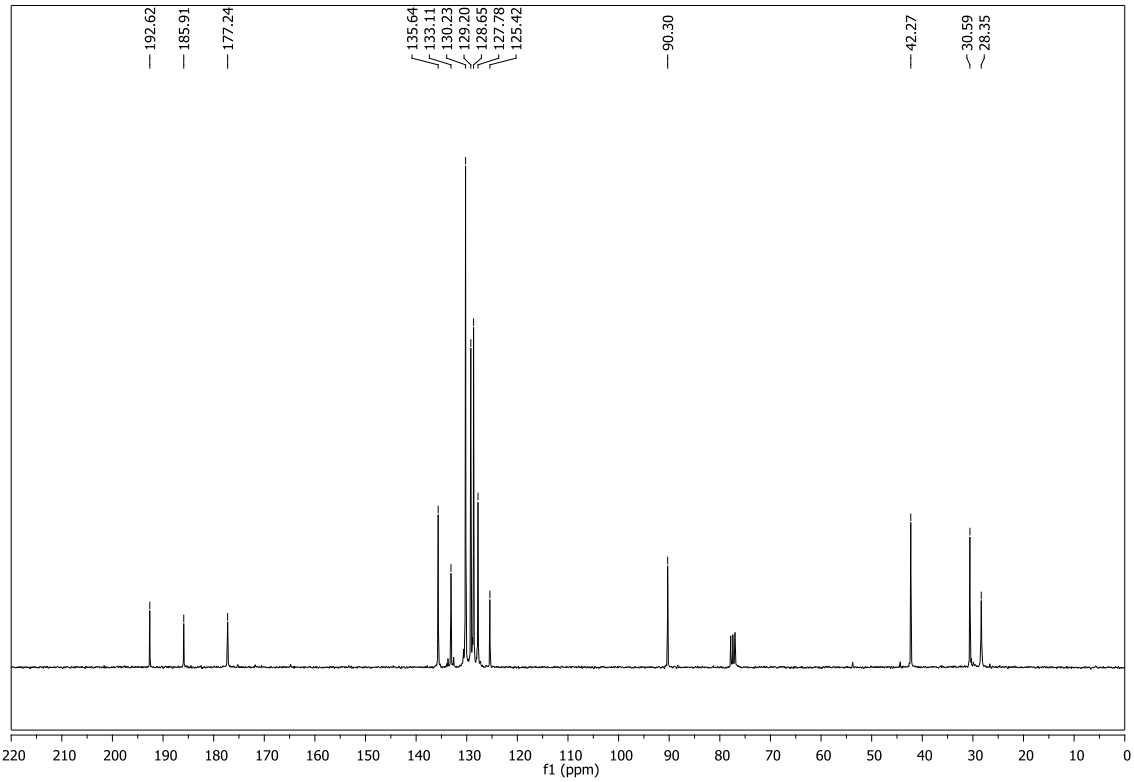
7.48
7.46
7.31
7.17
5.29
3.22
2.40
2.38
2.36
2.33
O
O
N
OH
O
Ph
Ph
23
1.83
1.00
2.12
4.75
2.16
4.30
f1 (ppm)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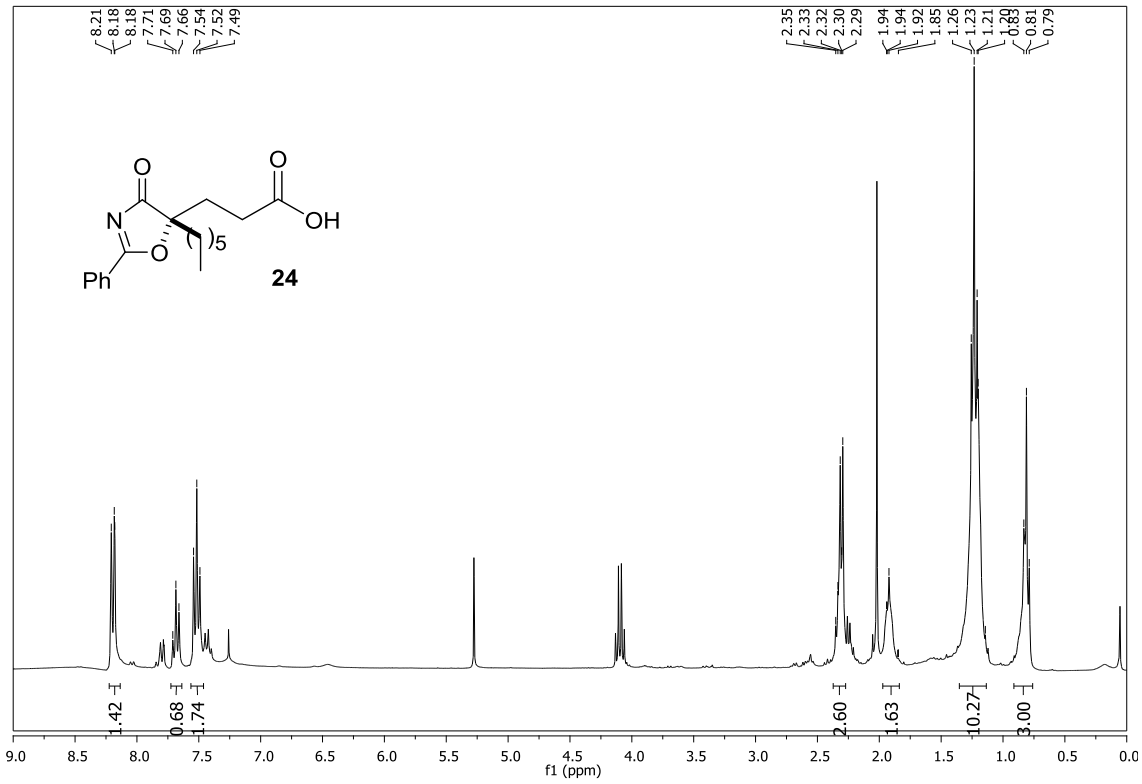
128.65
127.78
125.42
90.30
42.27
30.59
28.35
f1 (ppm)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8.18
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7.66
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7.49
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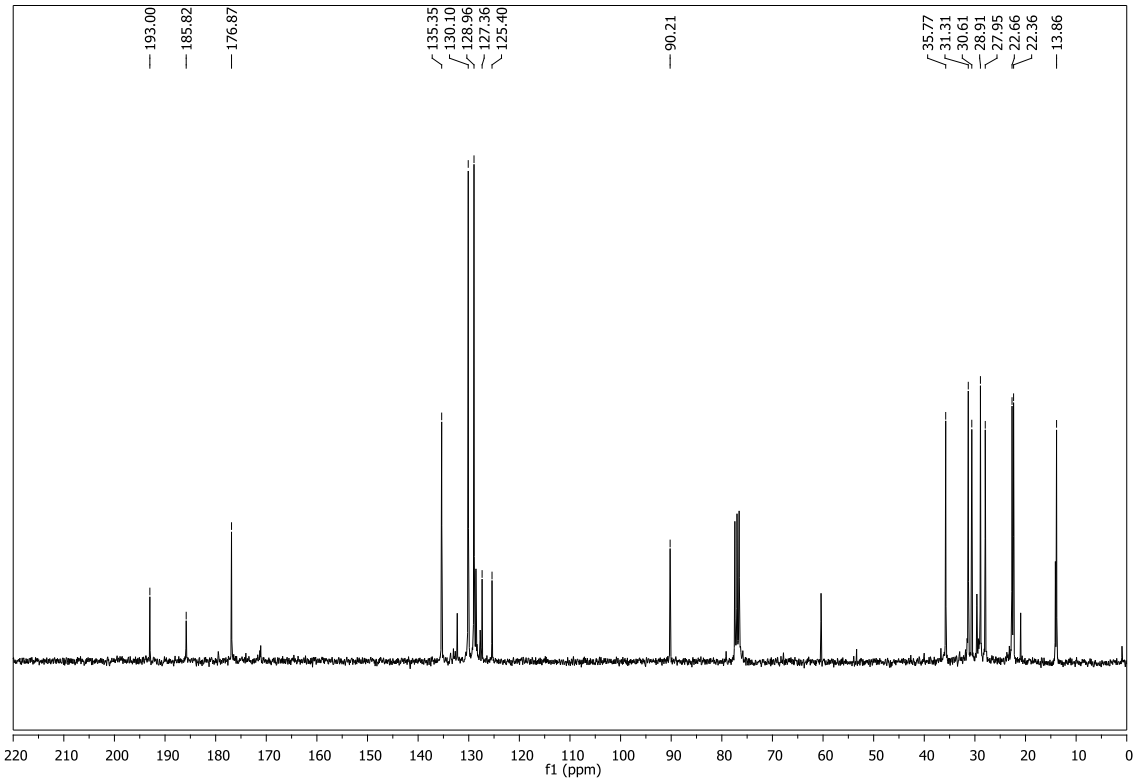
2.33
2.32
2.30
2.29
1.94
1.94
1.92
1.85
1.26
1.23
1.21
1.20
0.83
0.81
0.79
O
O
N
O
OH
5
Ph
24
1.42
0.68
1.74
2.60
1.63
10.27
3.00
f1 (ppm)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30.61
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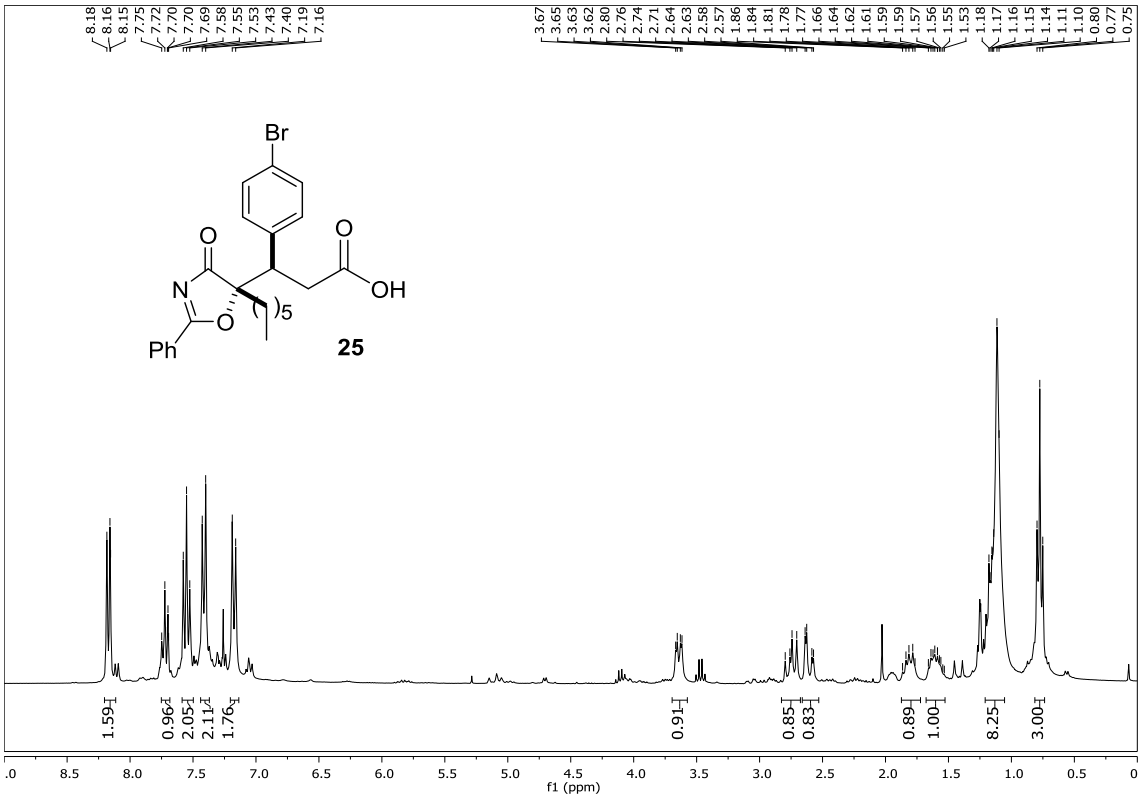
27.95
22.66
22.36
13.86
f1 (ppm)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O
N
O
OH
5
Ph
25
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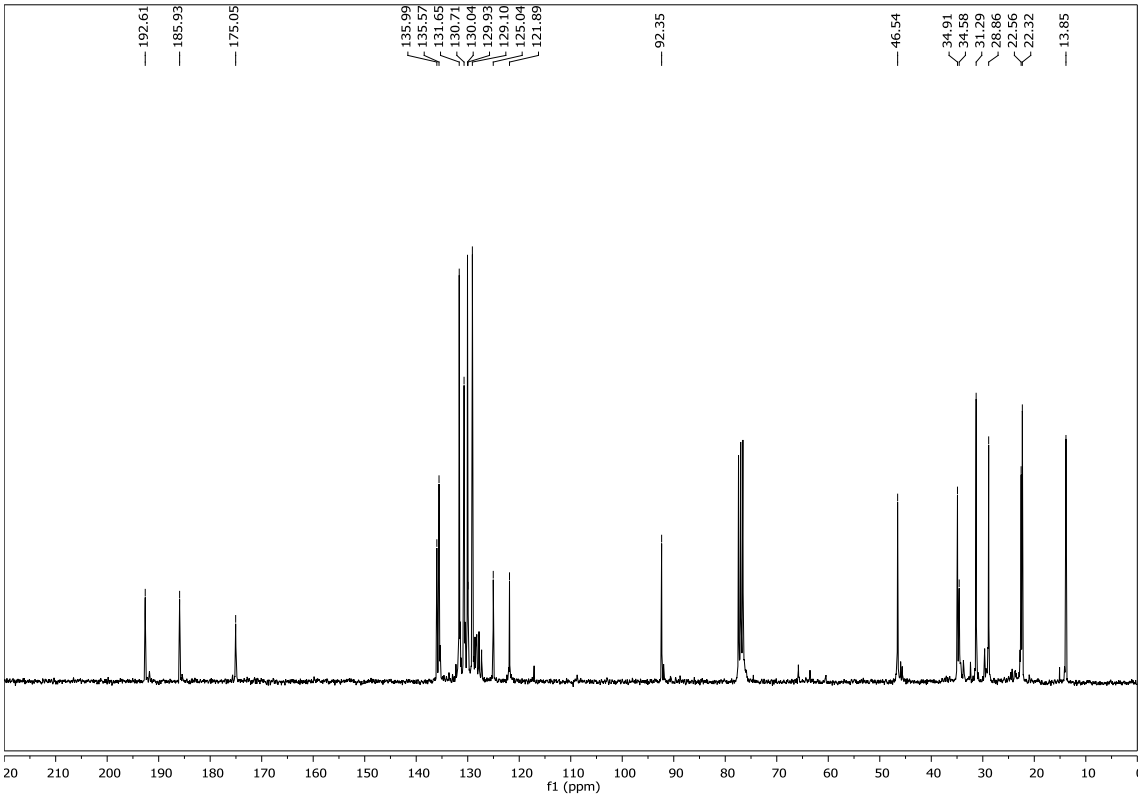
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129.10
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121.89
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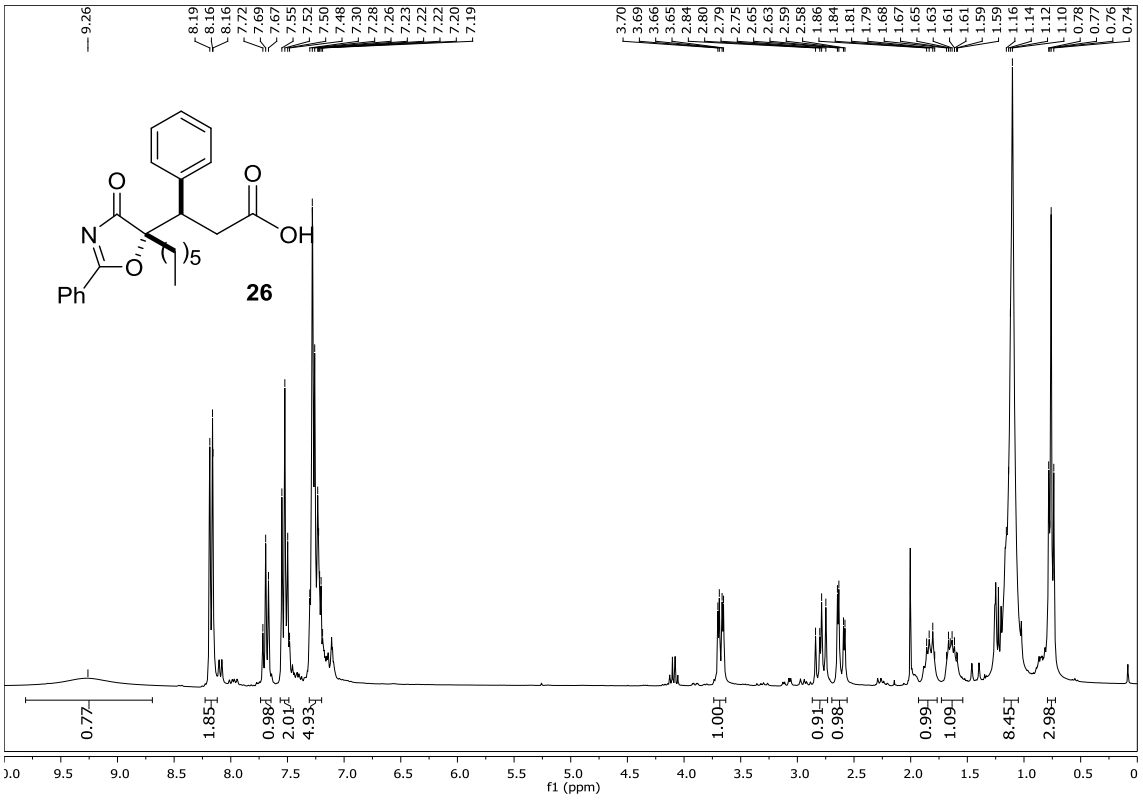
28.86
22.56
22.32
13.85
f1 (ppm)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7.48
7.30
7.28
7.26
7.23
7.22
7.22
7.20
7.19
3.70
3.69
3.66
3.65
2.84
2.80
2.79
2.75
2.65
2.63
2.59
2.58
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1.68
1.67
1.65
1.63
1.61
1.61
1.59
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1.16
1.14
1.12
1.10
0.78
0.77
0.76
0.74
O
N
O
O
OH
5
Ph
26
0.77
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0.91
0.98
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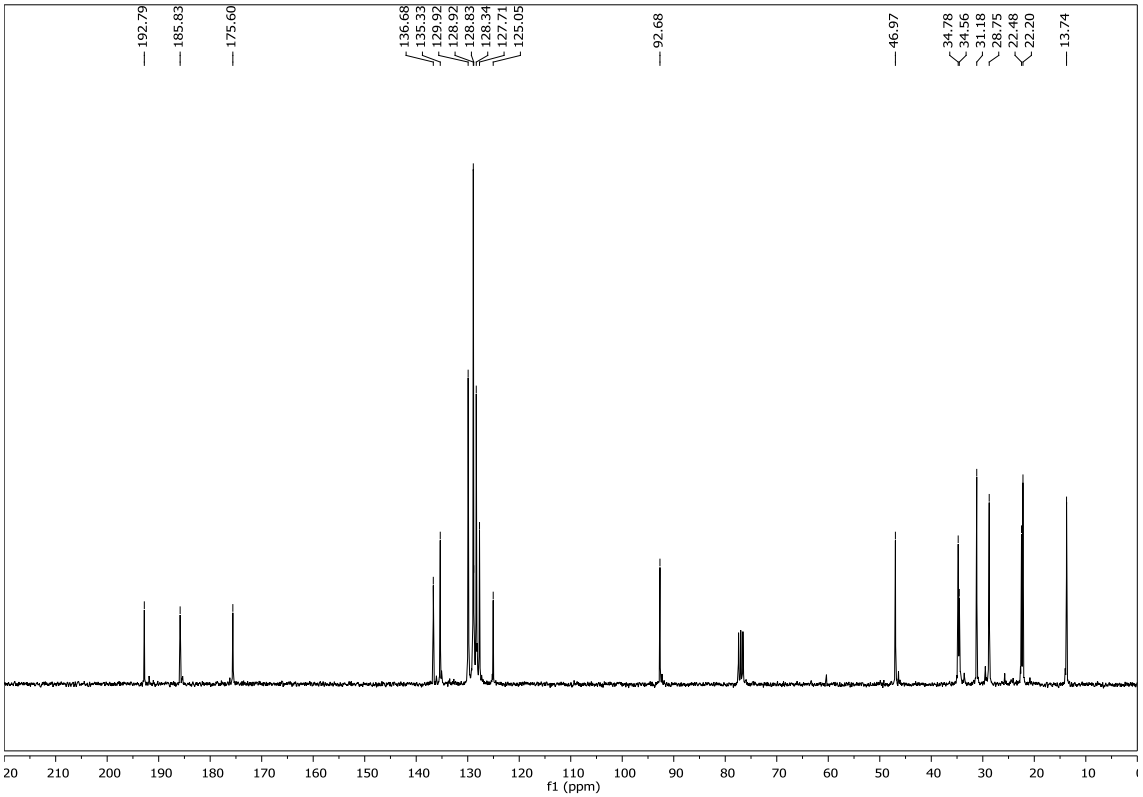
1.09
8.45
2.98
f1 (ppm)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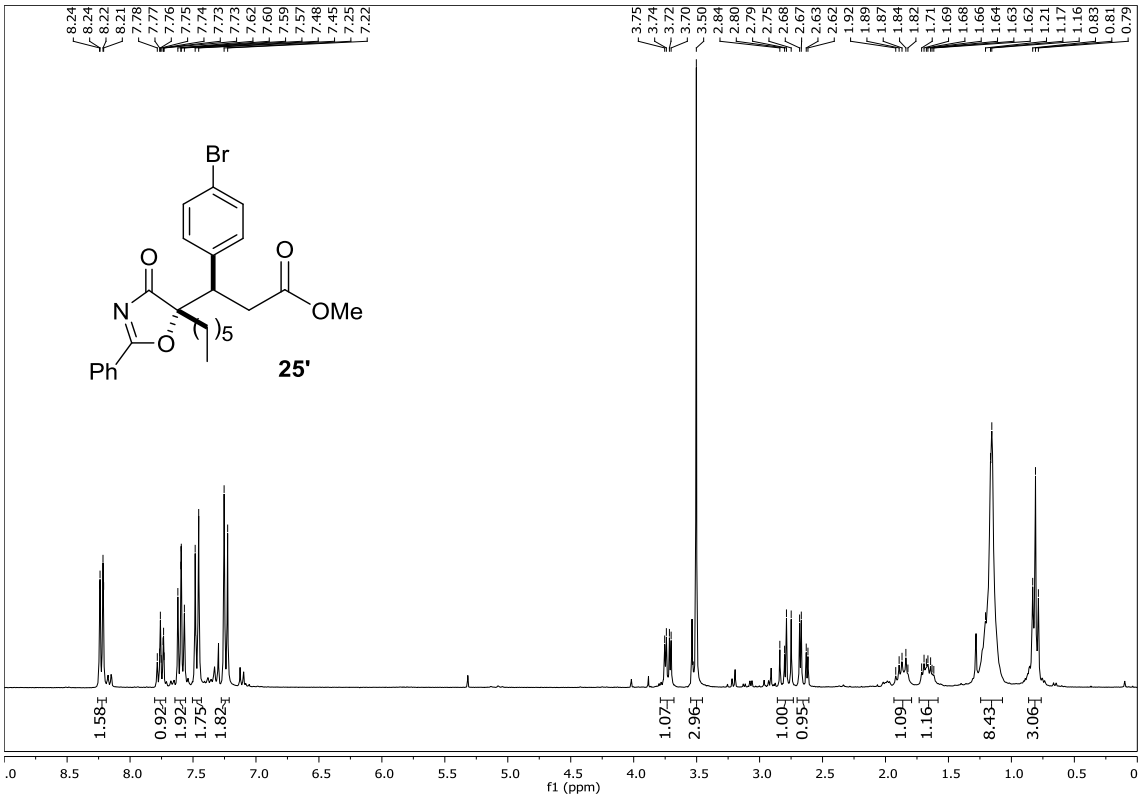
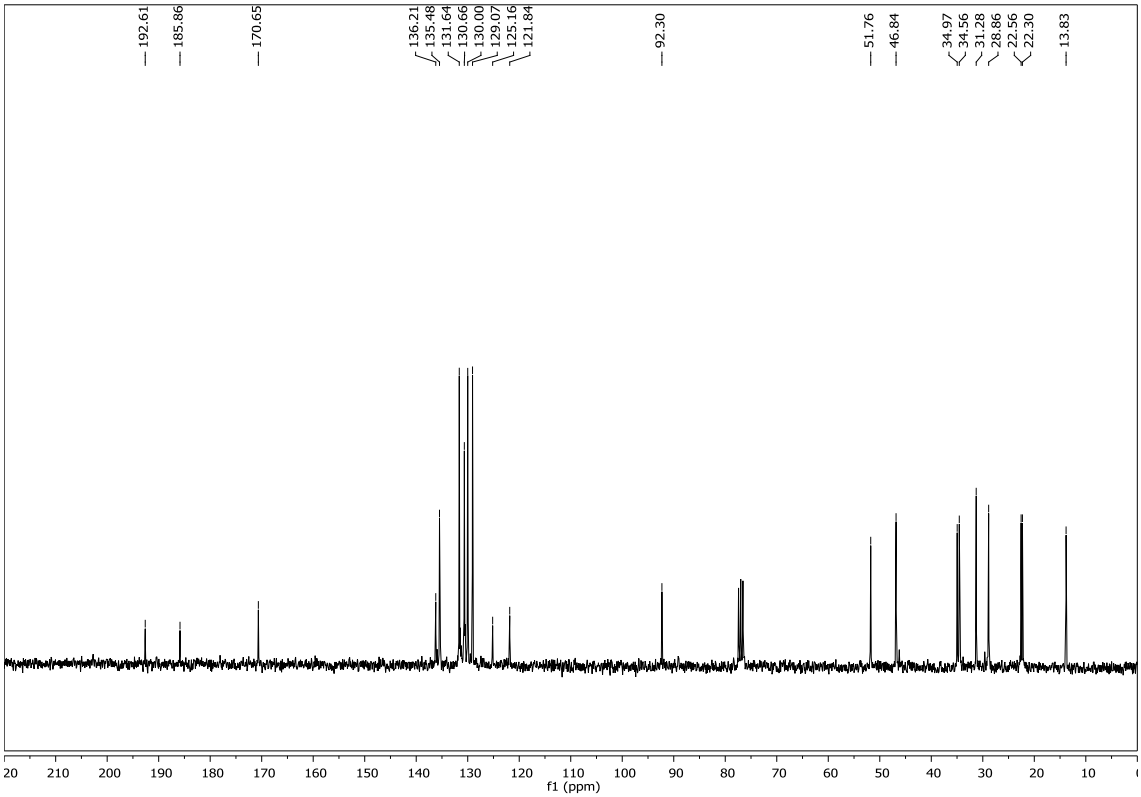
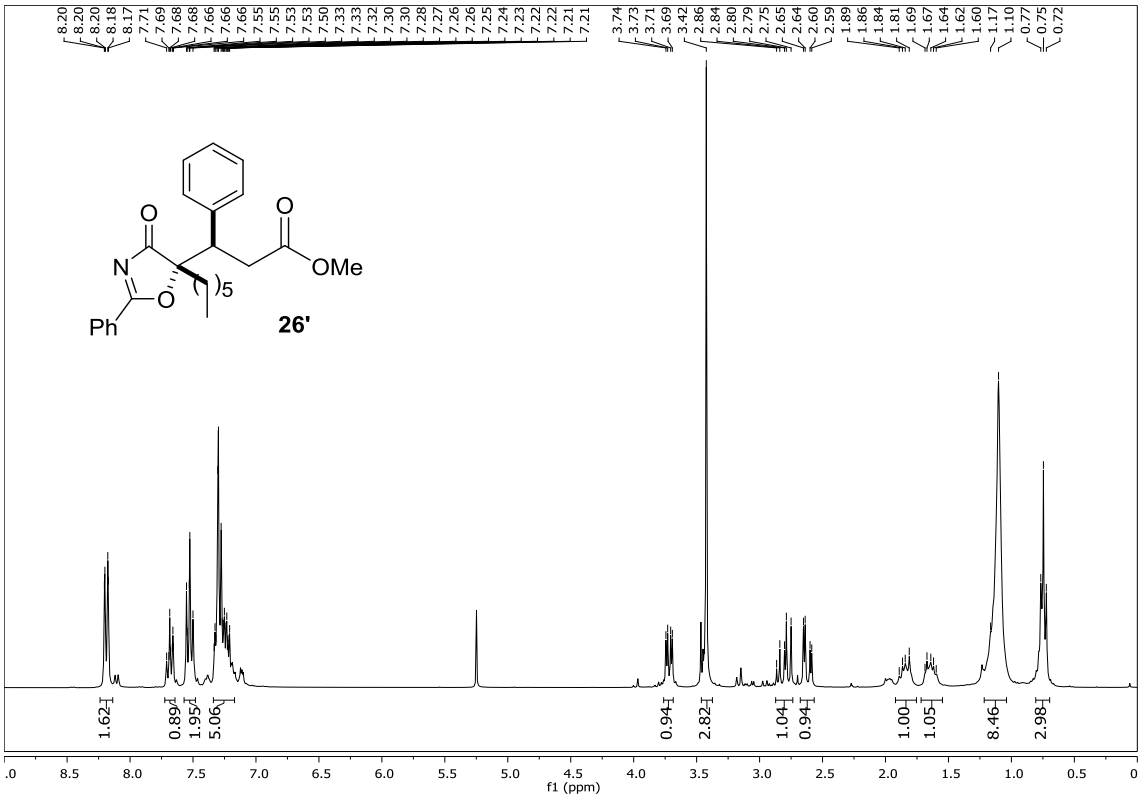
28.75
22.48
22.20
13.74
f1 (ppm)


Br
O
O
N
O
)5
OMe
Ph
25'
f1 (ppm)


f1 (ppm)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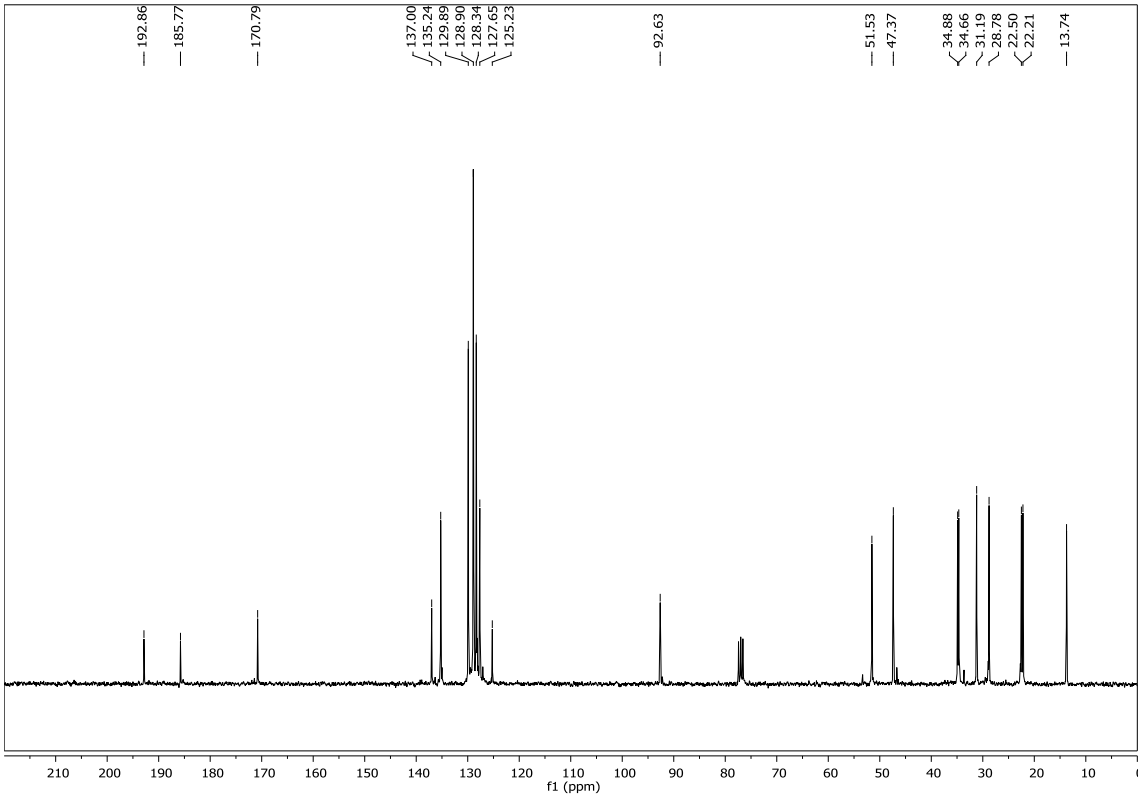
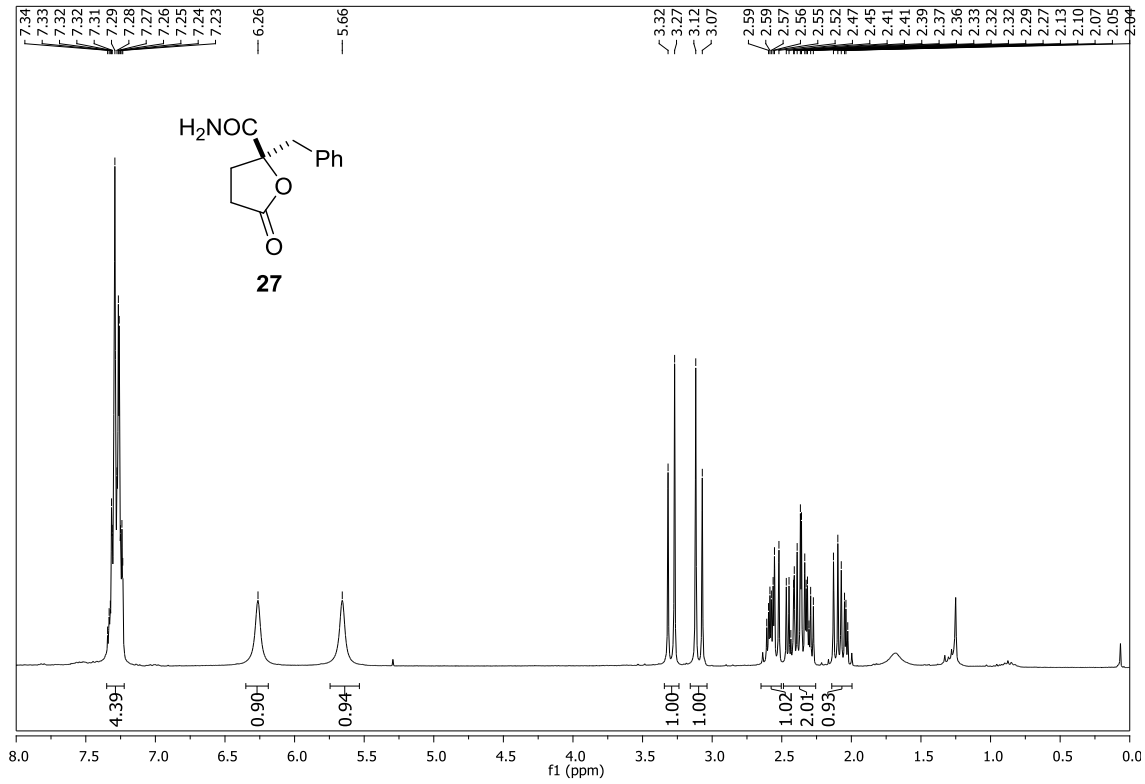
3.74 3.73 3.71 3.69 3.42 2.86 2.84 2.80 2.79 2.75 2.65 2.64 2.60 2.59 1.89 1.86 1.84 1.81 1.69 1.67 1.64 1.62 1.60 1.17 1.10 0.77 0.75 0.72
O
O
N
O
OMe
5
Ph
26'
1.62 0.89 1.95 5.06 0.94 2.82 1.04 0.94 1.00 1.05 8.46 2.98
f1 (ppm)


192.86 185.77 170.79 137.00 135.24 129.89 128.90 128.34 127.65 125.23 92.63 51.53 47.37 34.88 34.66 31.19 28.78 22.50 22.21 13.74
f1 (ppm)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7.26
7.25
7.24
7.23
6.26
5.66
3.32
3.27
3.12
3.07
2.59
2.59
2.57
2.56
2.55
2.52
2.47
2.45
2.41
2.41
2.39
2.37
2.36
2.33
2.32
2.32
2.29
2.27
2.13
2.10
2.07
2.05
2.04
H2NOC
Ph
O
O
27
4.39
0.90
0.94
1.00
1.00
1.02
2.01
0.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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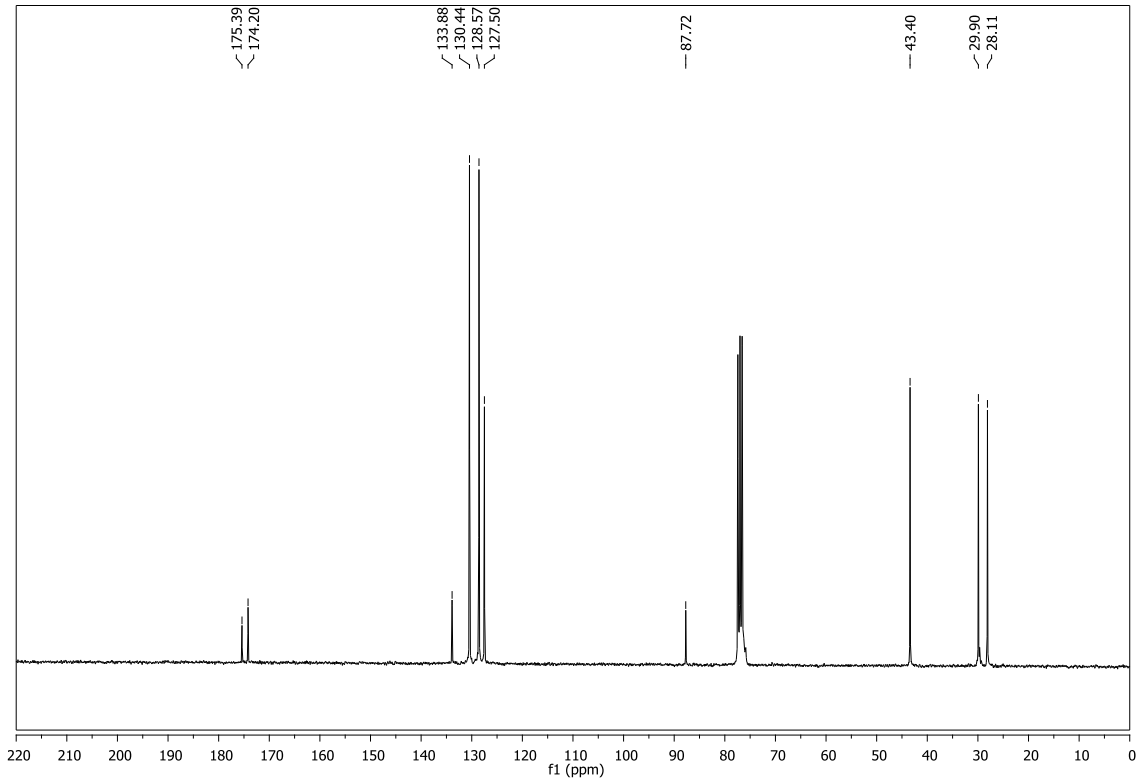
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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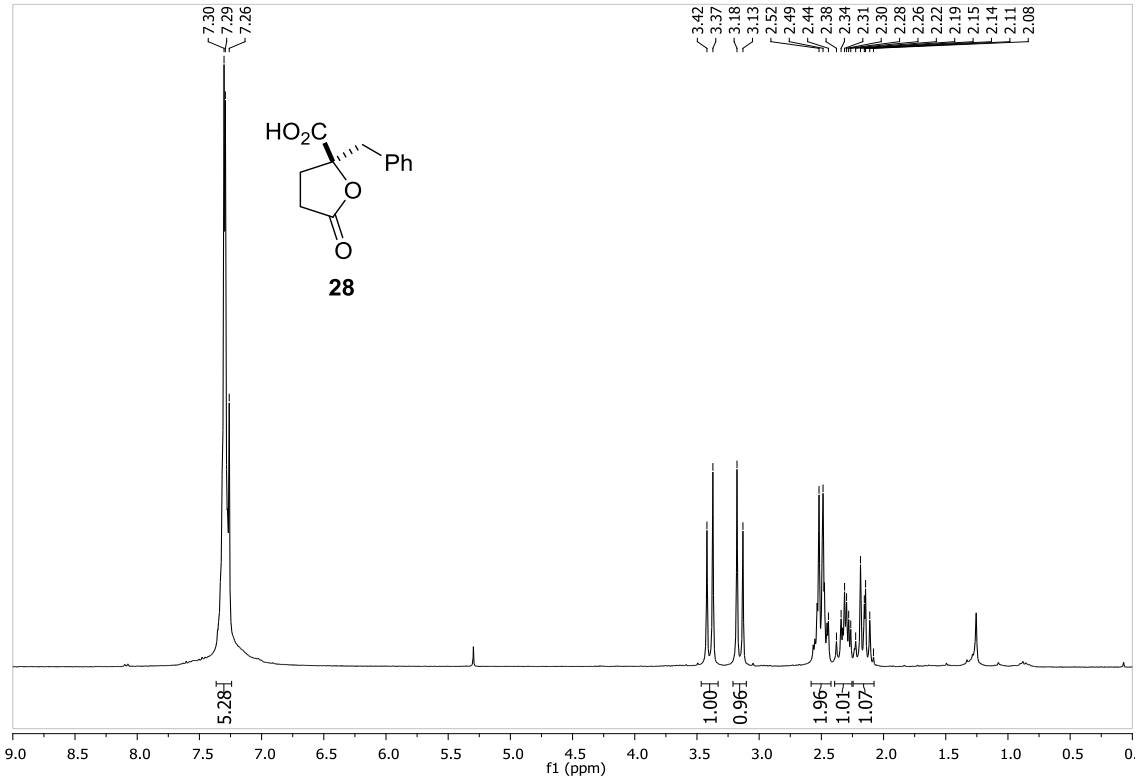
133.88
130.44
128.57
127.50
87.72
43.40
29.90
28.11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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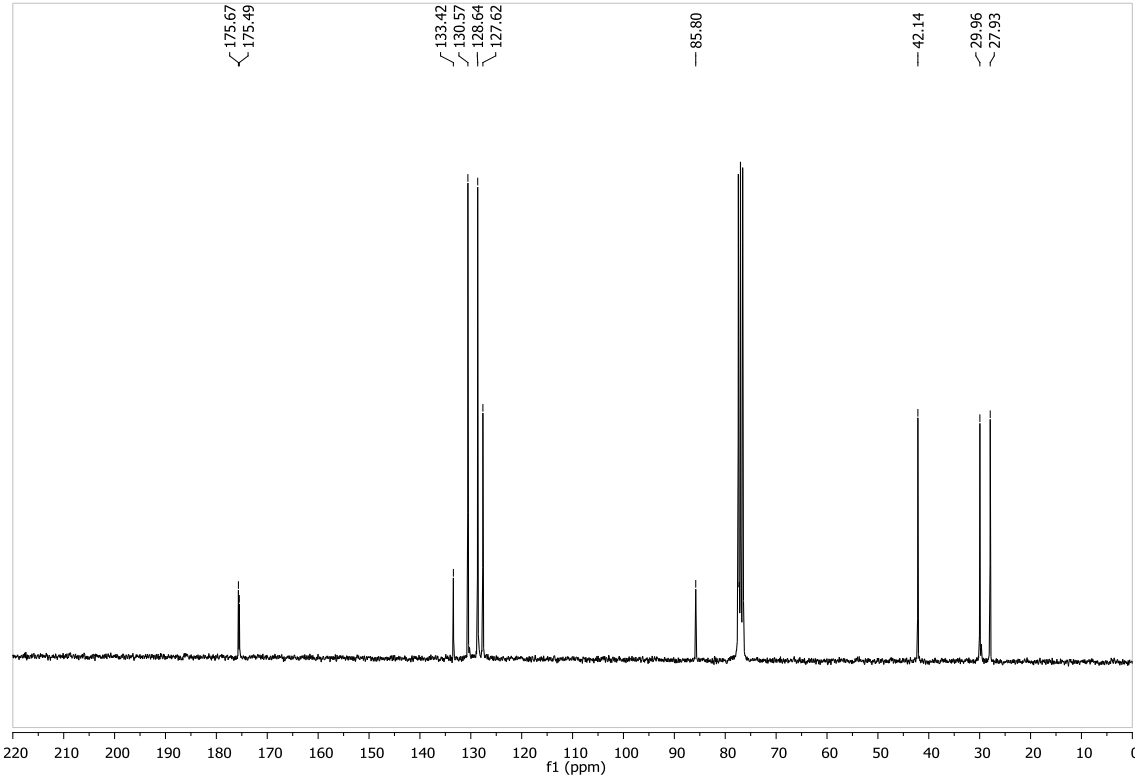
7.29
7.26
3.42
3.37
3.18
3.13
2.52
2.49
2.44
2.38
2.34
2.31
2.30
2.28
2.26
2.22
2.19
2.15
2.14
2.11
2.08
HO2C
Ph
O
O
28
5.28
1.00
0.96
1.96
1.01
1.07
f1 (ppm)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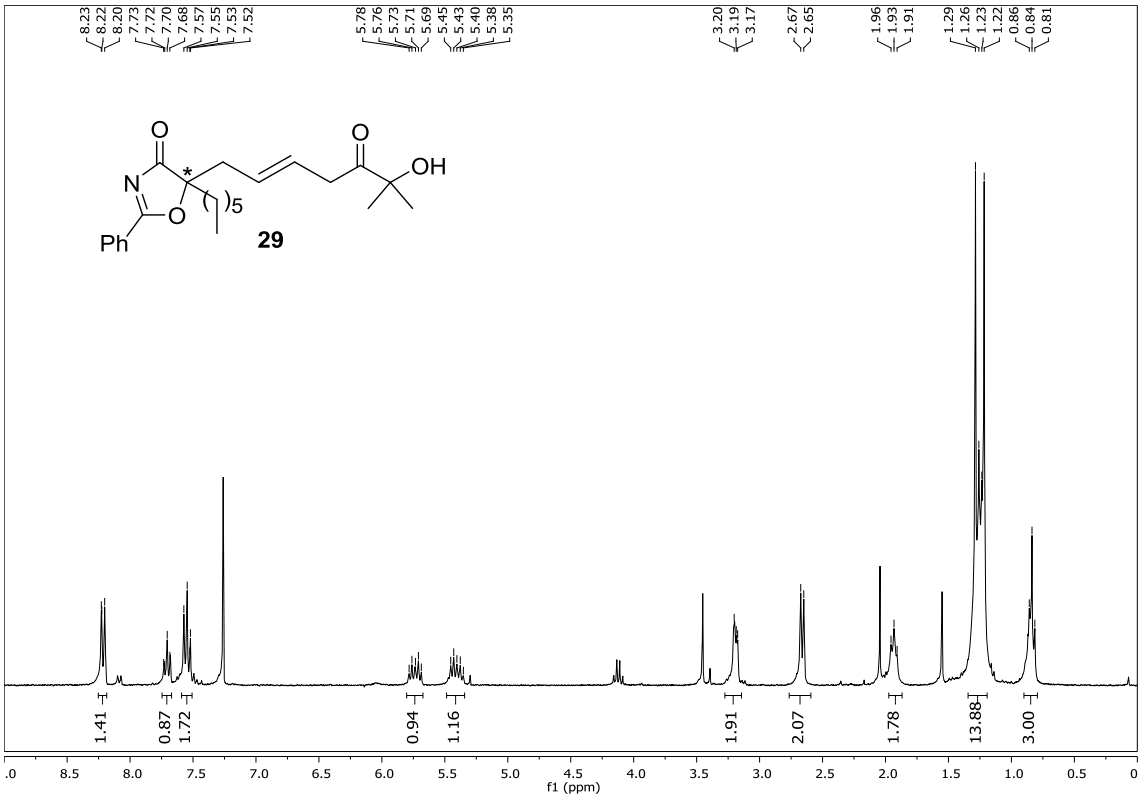
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5.76
5.73
5.71
5.69
5.45
5.43
5.40
5.38
5.35
3.20
3.19
3.17
2.67
2.65
1.96
1.93
1.91
1.29
1.26
1.23
1.22
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0.84
0.81
O
N
O
O
OH
*
5
Ph
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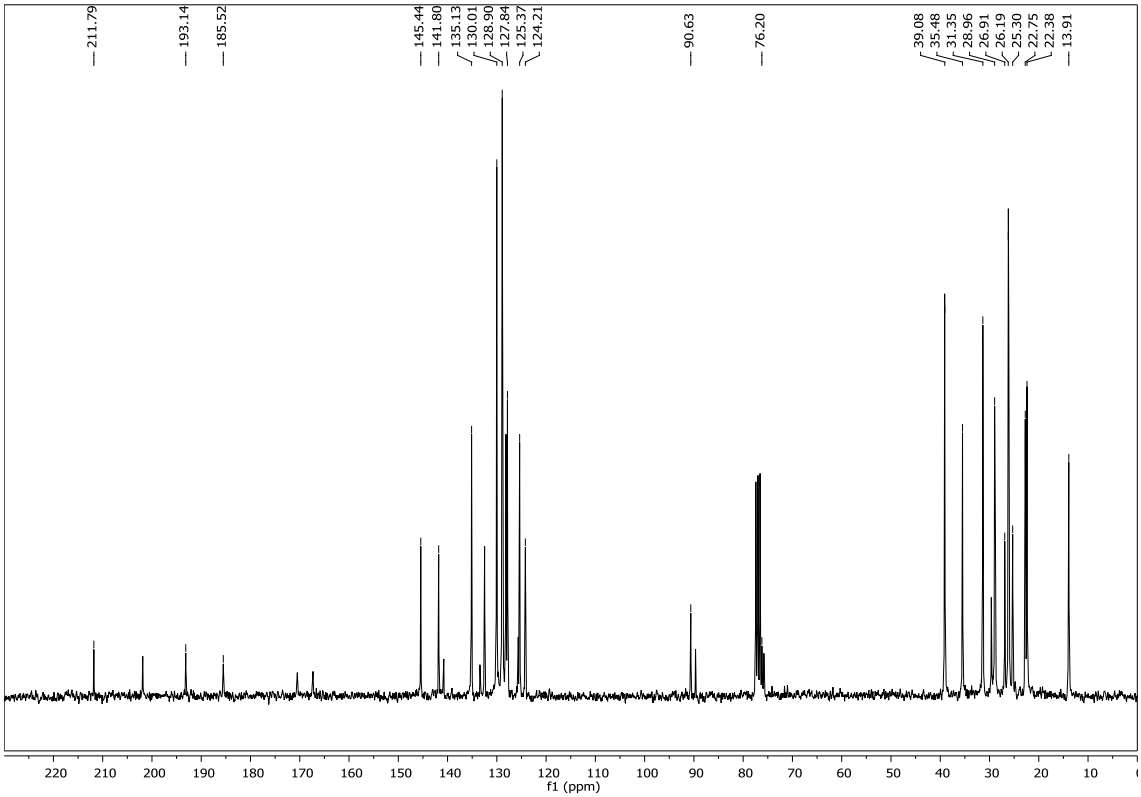
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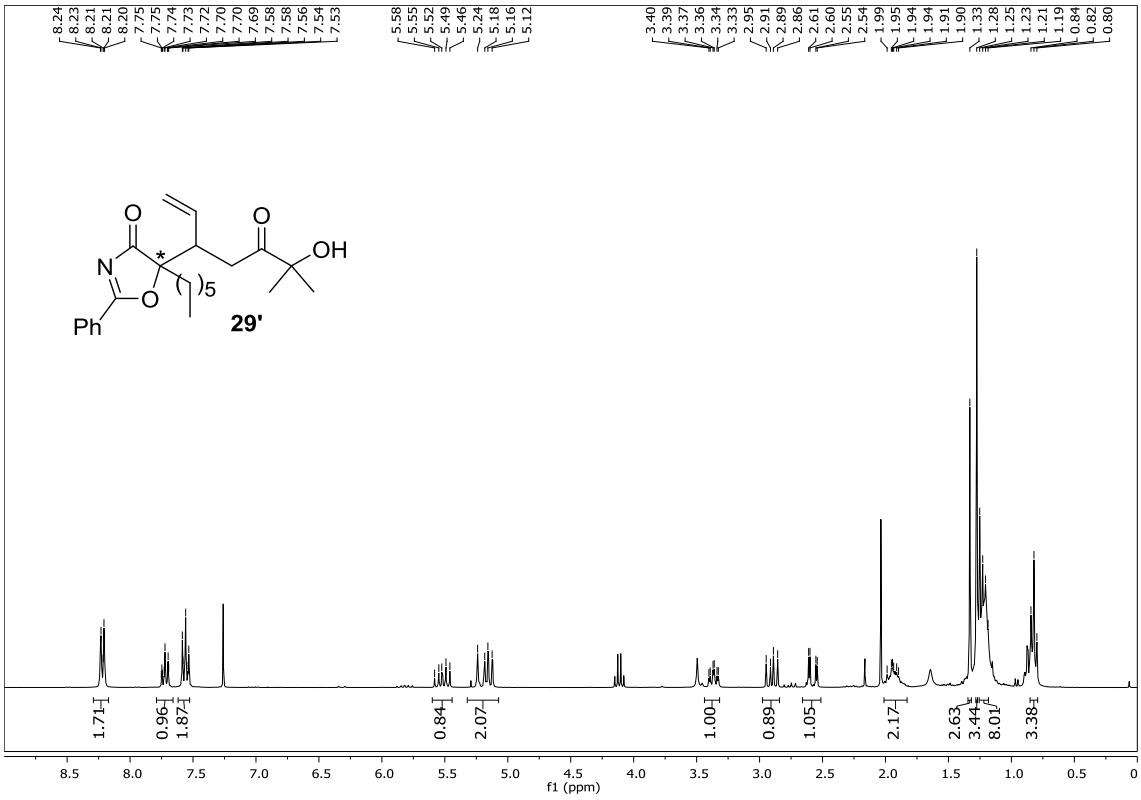
13.91
f1 (ppm)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7.53
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5.55
5.52
5.49
5.46
5.24
5.18
5.16
5.12
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3.39
3.37
3.36
3.34
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2.54
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1.23
1.21
1.19
0.84
0.82
0.80
O
O
N
*
OH
O
5
Ph
29'
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0.96
1.87
0.84
2.07
1.00
0.89
1.05
2.17
2.63
3.44
8.01
3.38
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7.5
7.0
6.5
6.0
5.5
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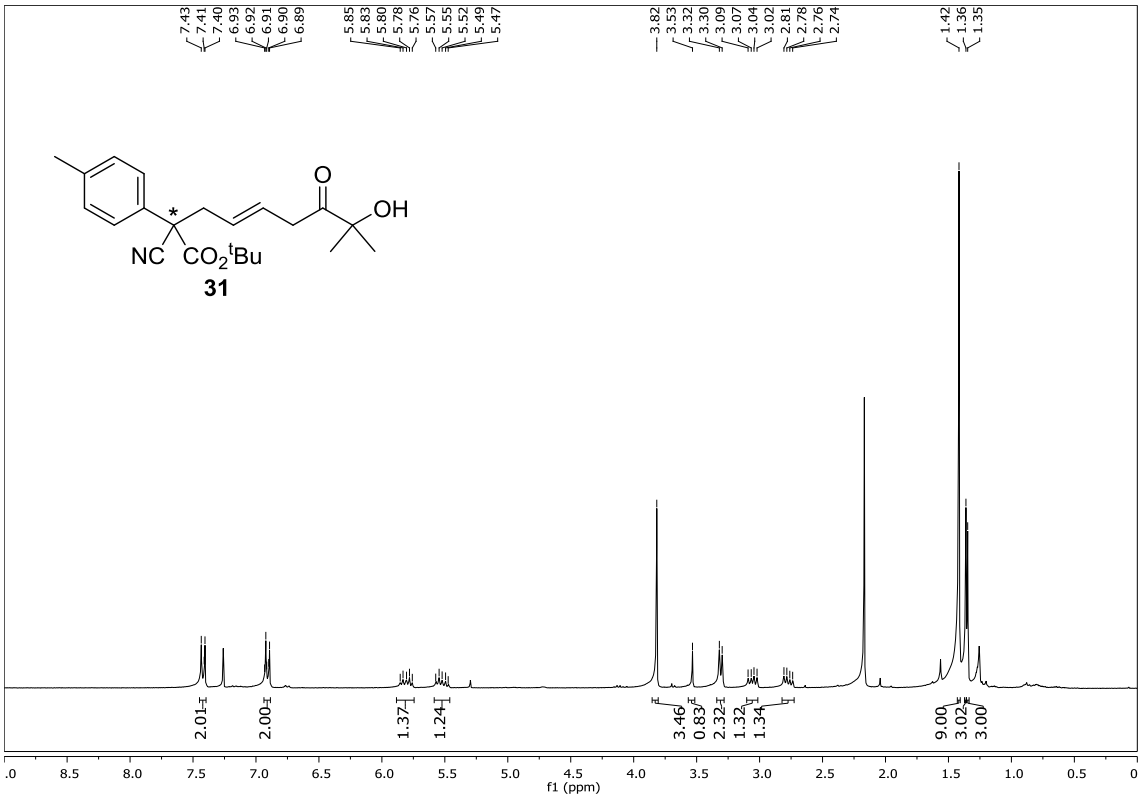
f1 (ppm)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5.76
5.57
5.55
5.52
5.49
5.47
3.82
3.53
3.32
3.30
3.09
3.07
3.04
3.02
2.81
2.78
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1.36
1.35
O
OH
*
NC
CO2tBu
31
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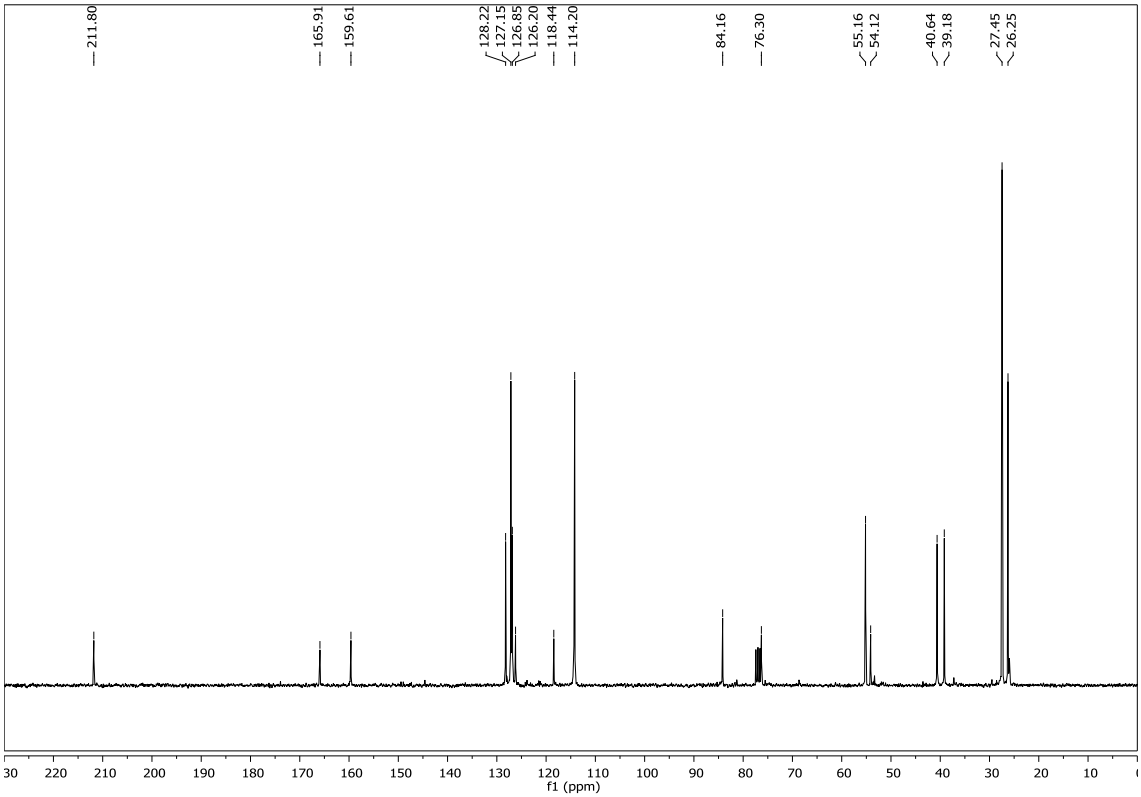
3.00
f1 (ppm)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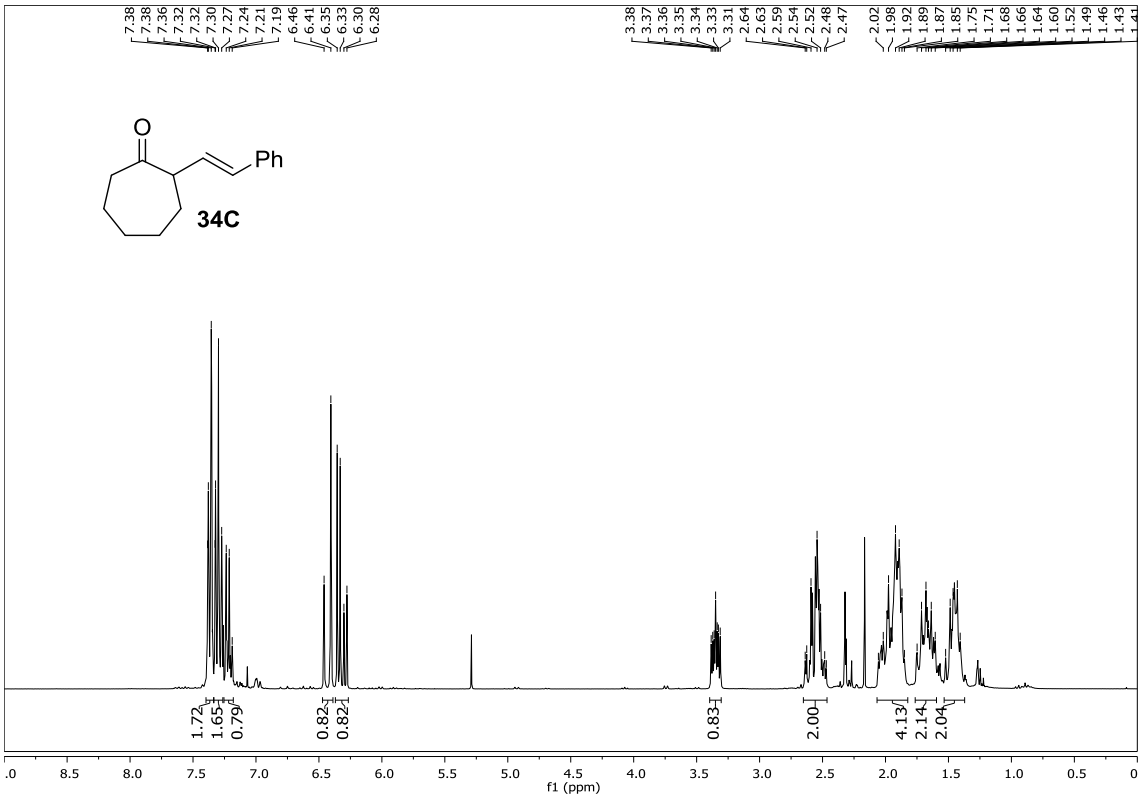
54.12
40.64
39.18
27.45
26.25
f1 (ppm)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2.48
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1.60
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1.49
1.46
1.43
1.41
O
Ph
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0.82
0.83
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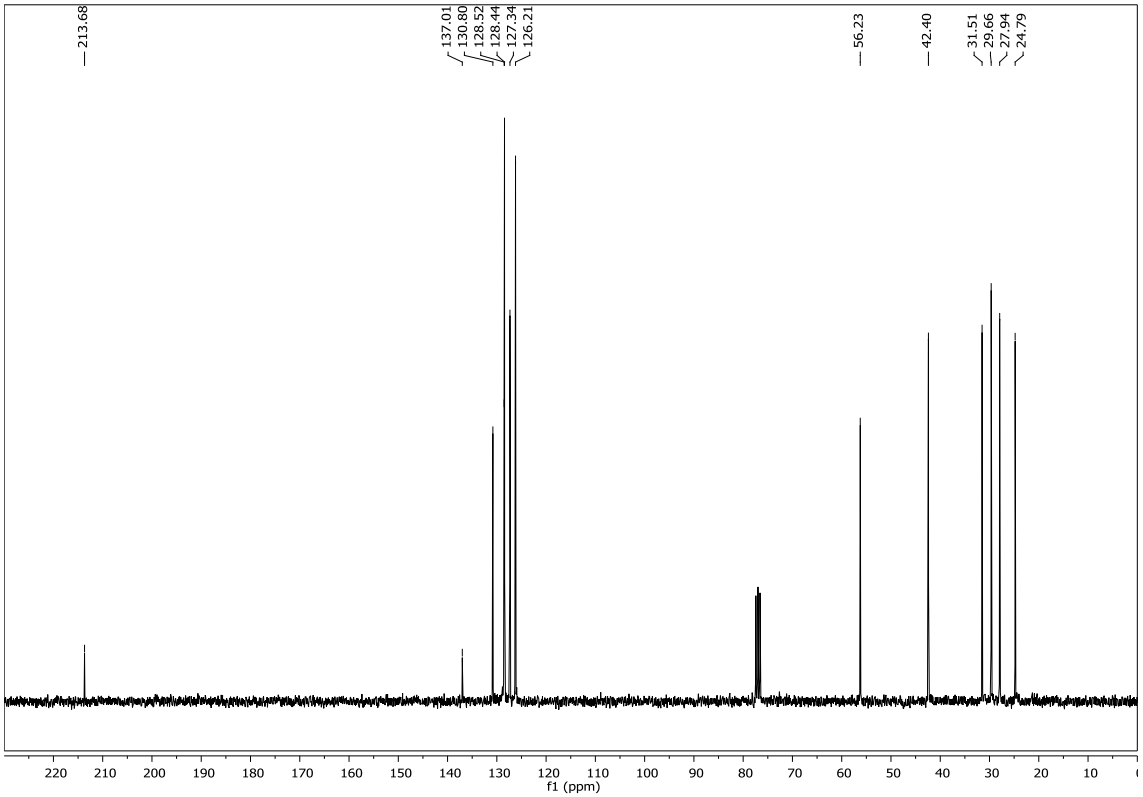
2.04
f1 (ppm)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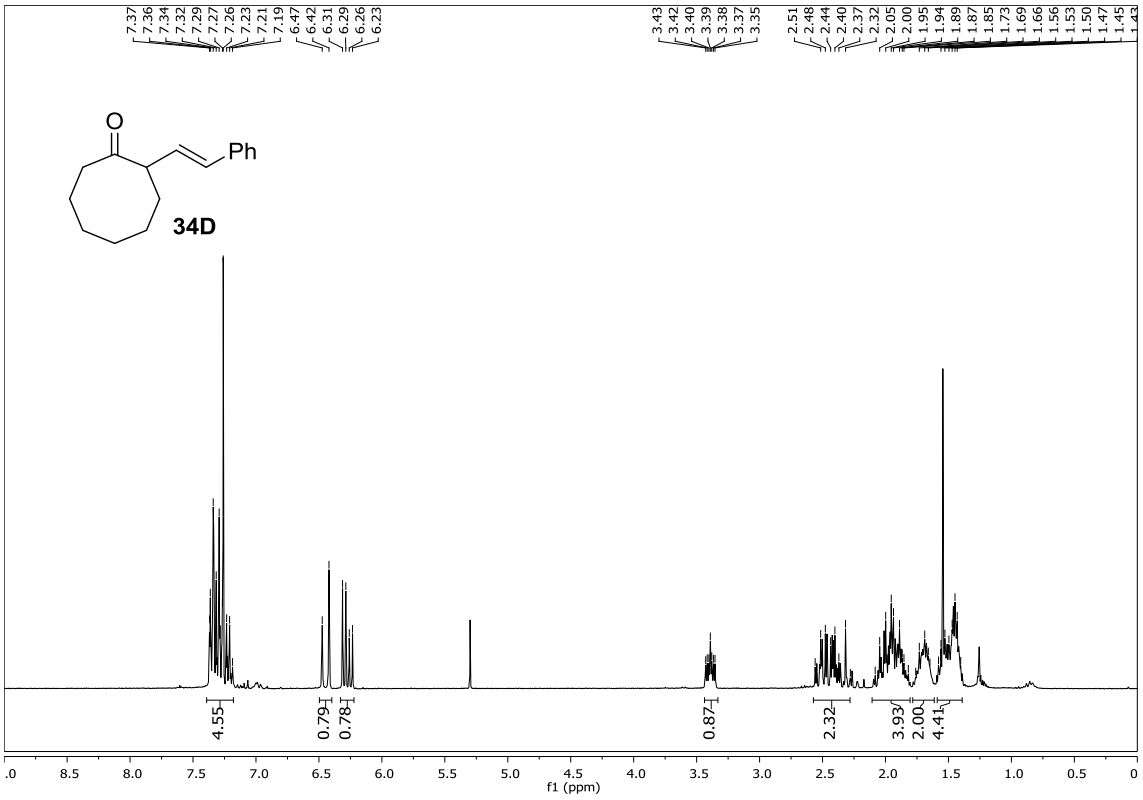
31.51
29.66
27.94
24.79
f1 (ppm)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1.66
1.56
1.53
1.50
1.47
1.45
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Ph
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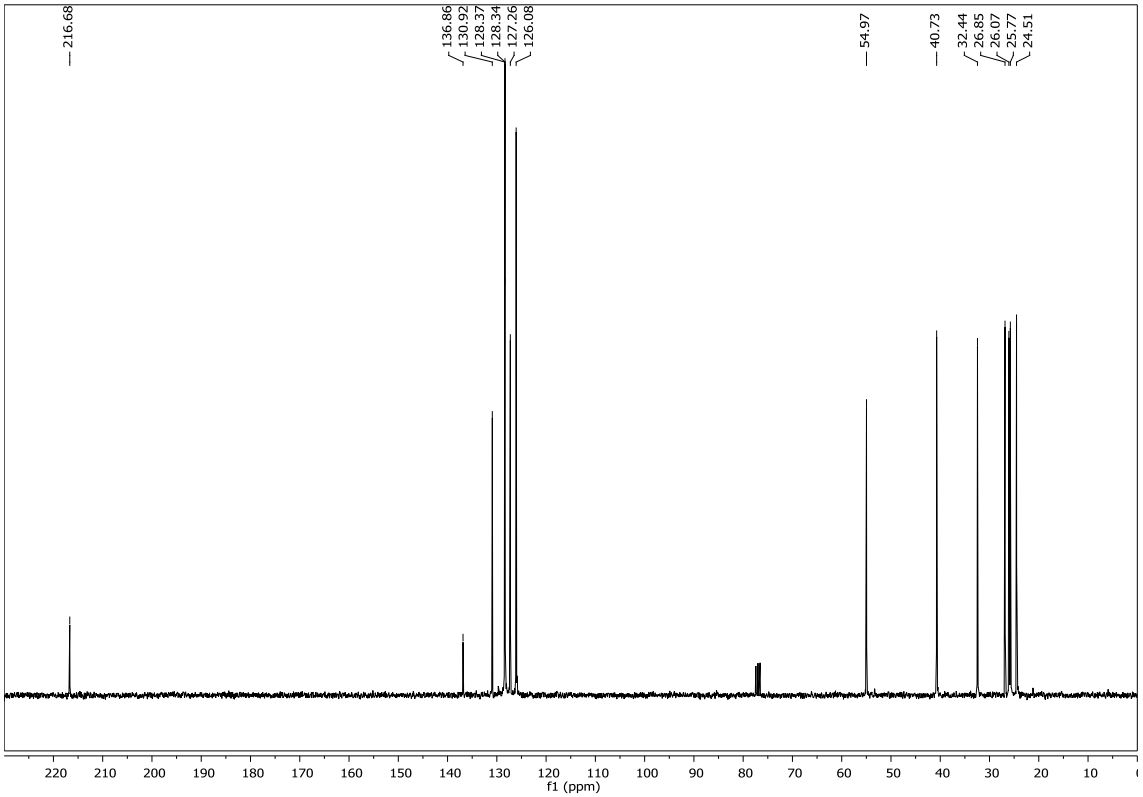
3.93
2.00
4.41
f1 (ppm)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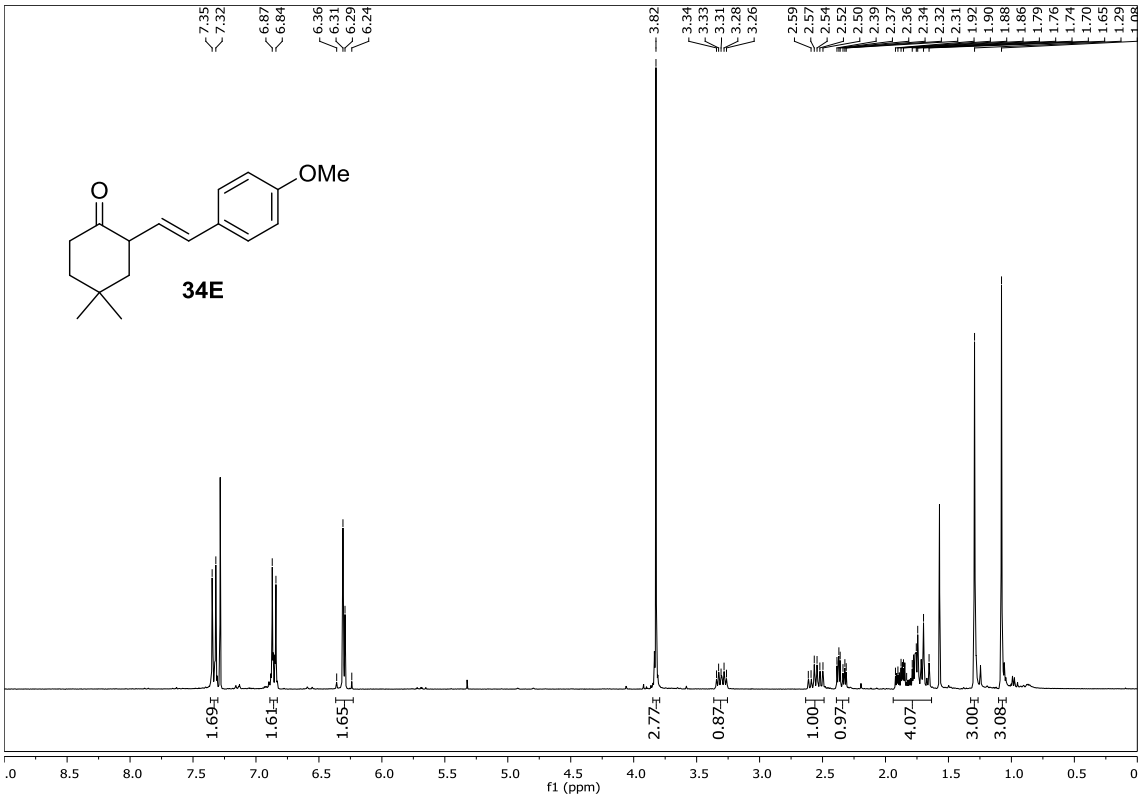
32.44
26.85
26.07
25.77
24.51
f1 (ppm)


OMe
O
34E
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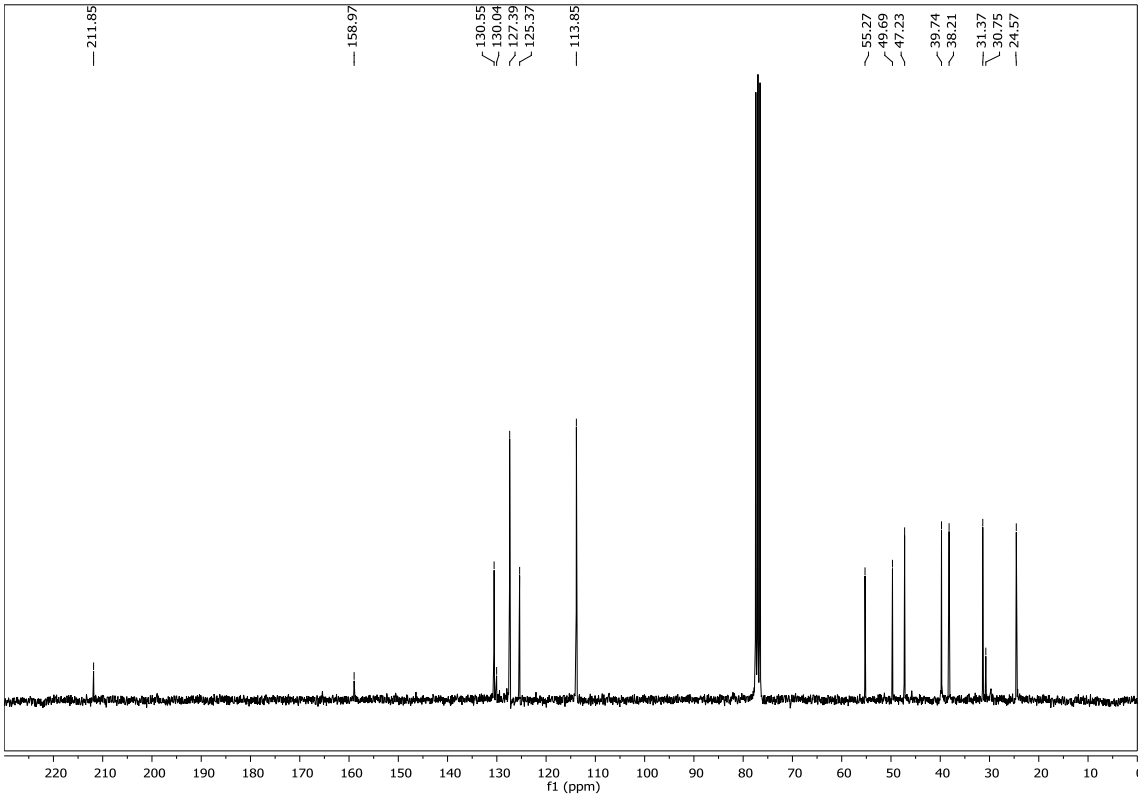
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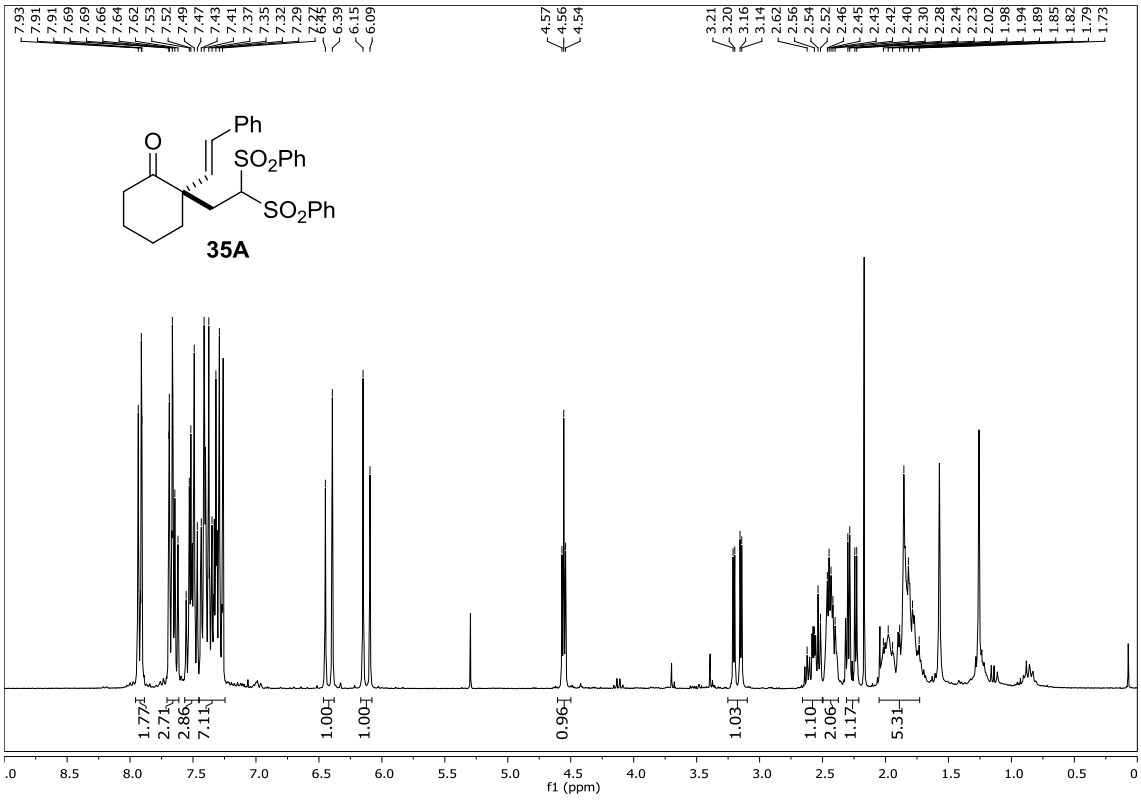
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7.52
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7.43
7.41
7.37
7.35
7.32
7.29
6.39
6.15
6.09
4.57
4.56
4.54
3.21
3.20
3.16
3.14
2.62
2.56
2.54
2.52
2.46
2.45
2.43
2.42
2.40
2.30
2.28
2.24
2.23
2.02
1.98
1.94
1.89
1.85
1.82
1.79
1.73
O
Ph
SO2Ph
SO2Ph
35A
1.77
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1.00
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1.03
1.10
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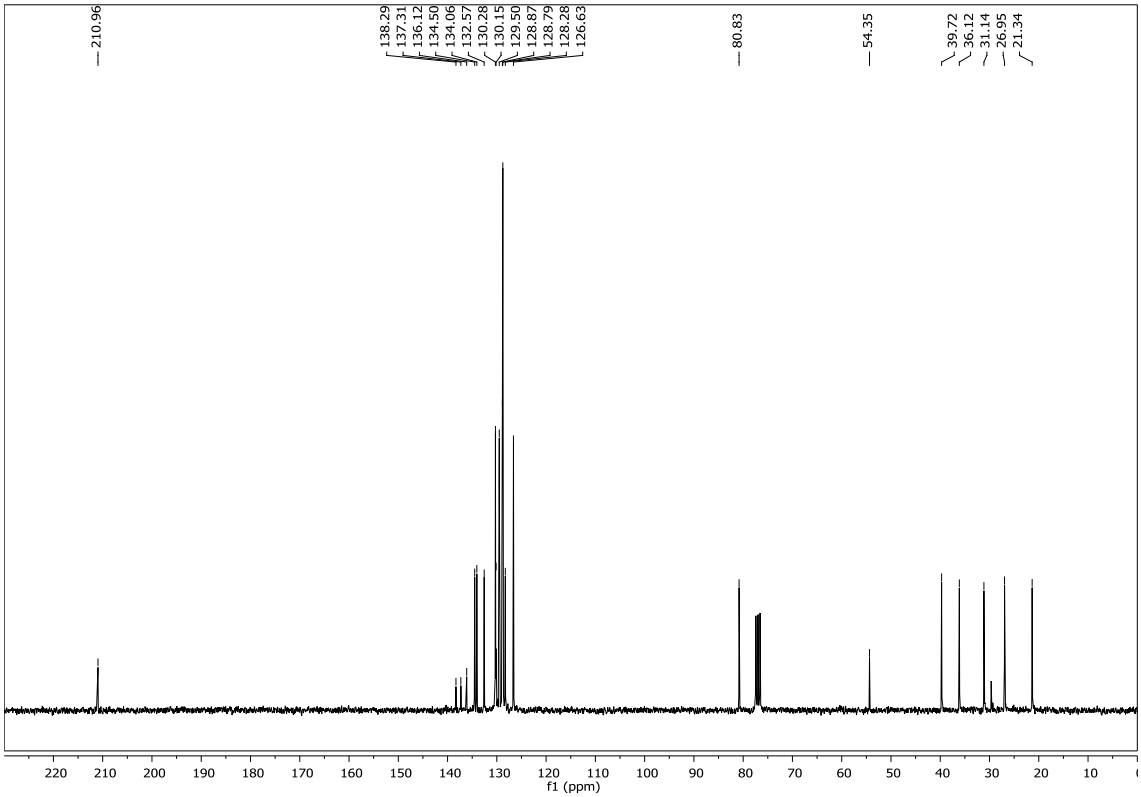
5.31
f1 (ppm)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129.50
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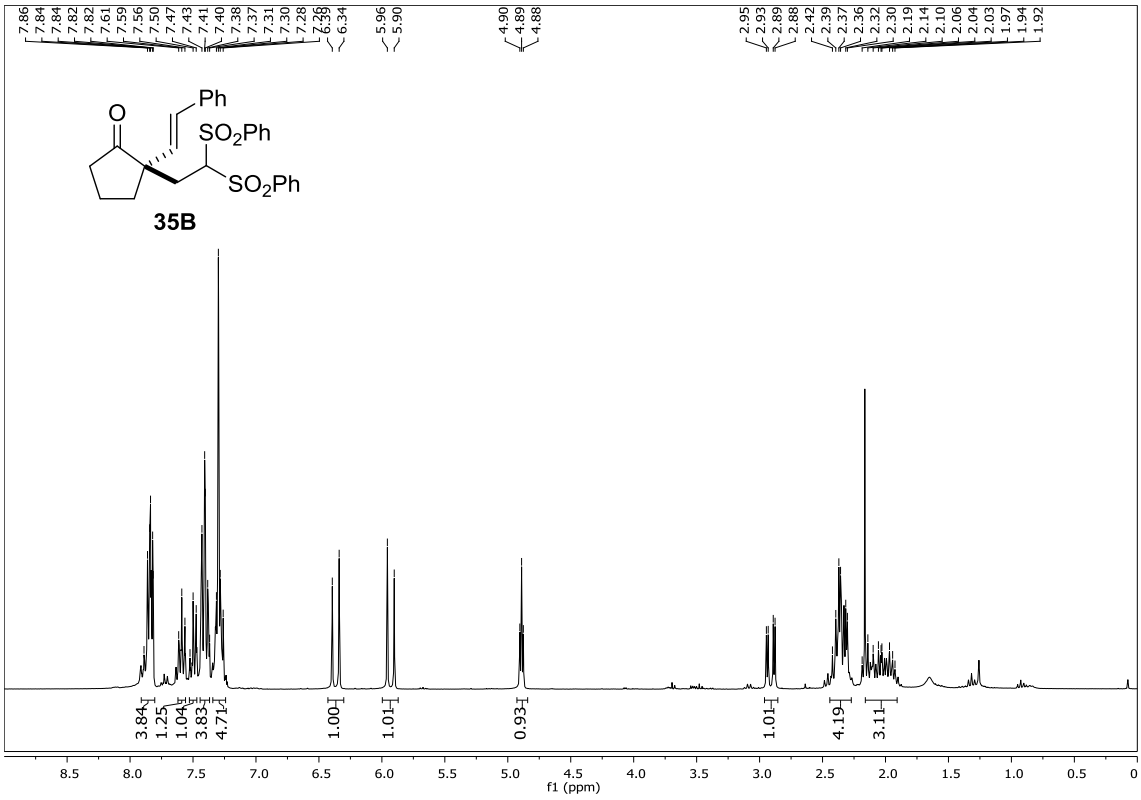
31.14
26.95
21.34
f1 (ppm)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7.43
7.41
7.40
7.38
7.37
7.31
7.30
7.28
6.39
6.34
5.96
5.90
4.90
4.89
4.88
2.95
2.93
2.89
2.88
2.42
2.39
2.37
2.36
2.32
2.30
2.19
2.14
2.10
2.06
2.04
2.03
1.97
1.94
1.92
O
Ph
SO2Ph
SO2Ph
35B
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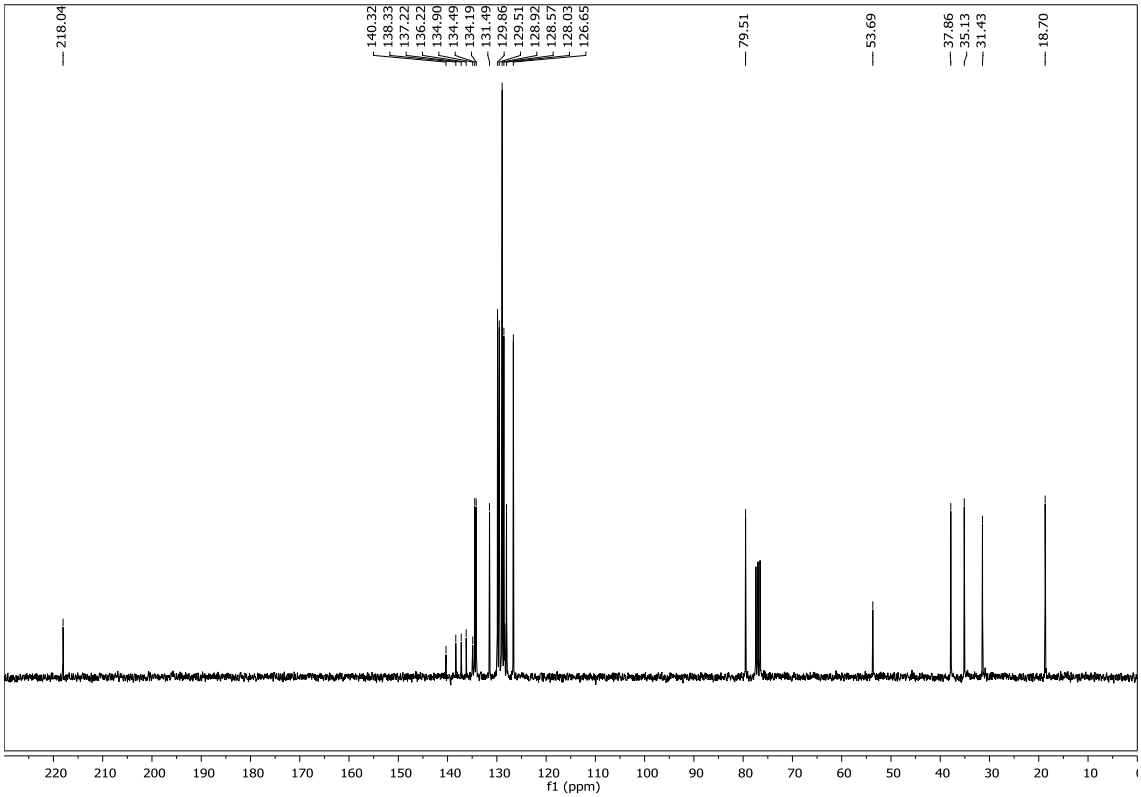
3.11
f1 (ppm)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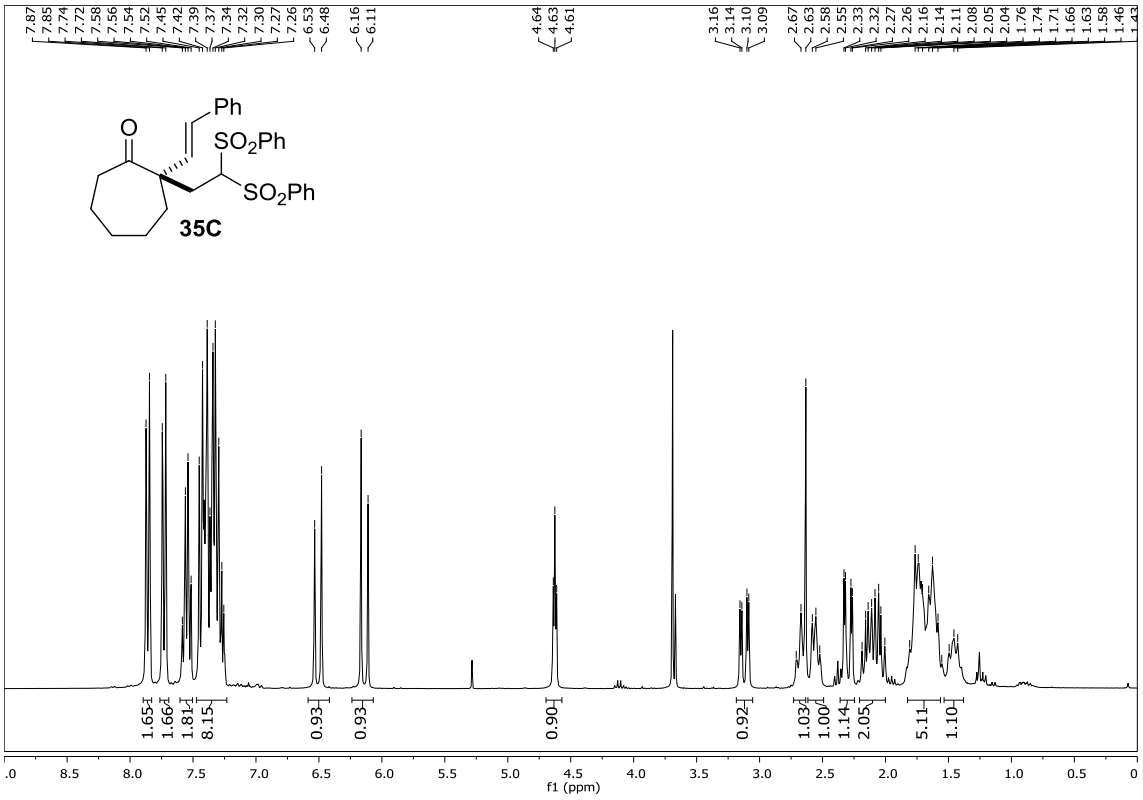
35.13
31.43
18.70
f1 (ppm)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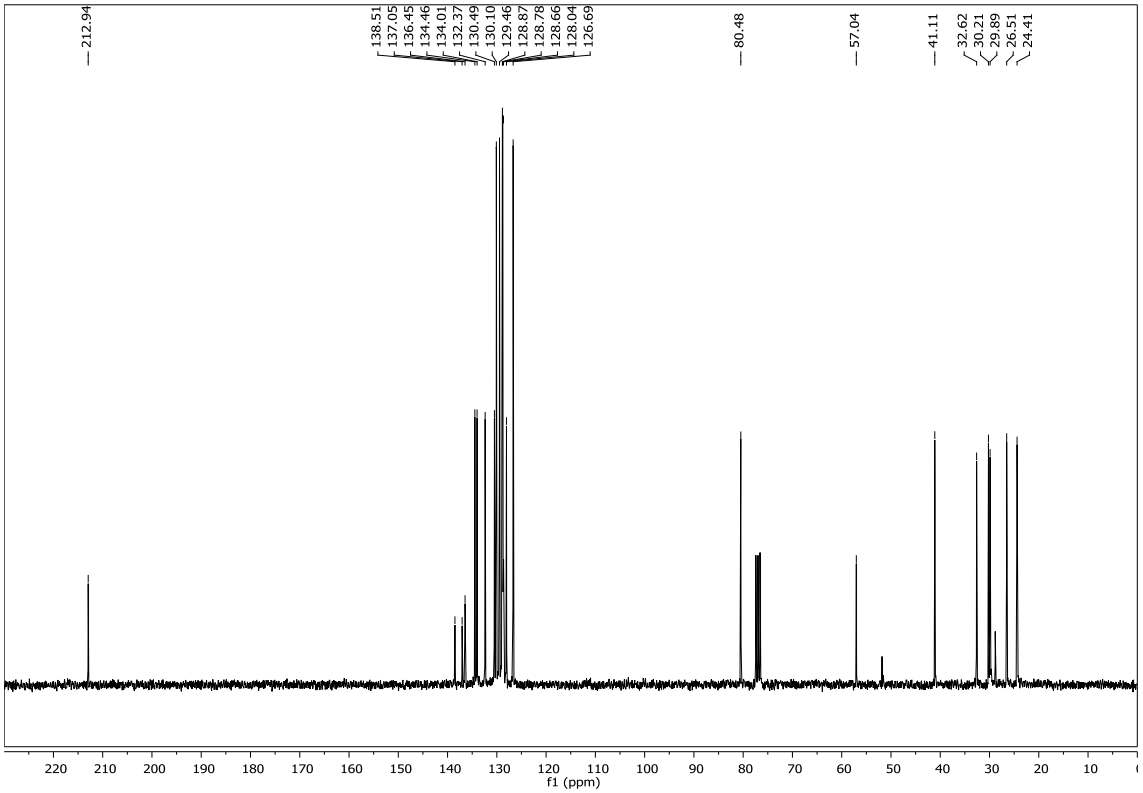
SO2Ph
SO2Ph
35C
f1 (ppm)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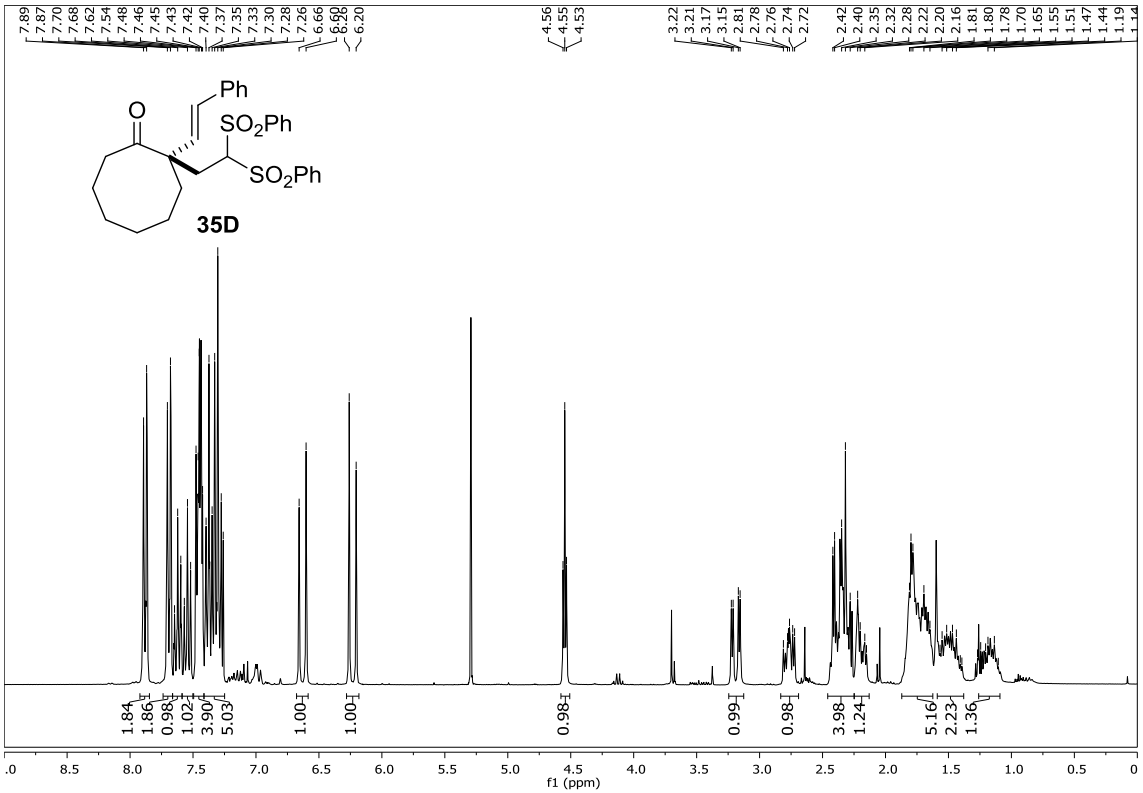
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SO2Ph
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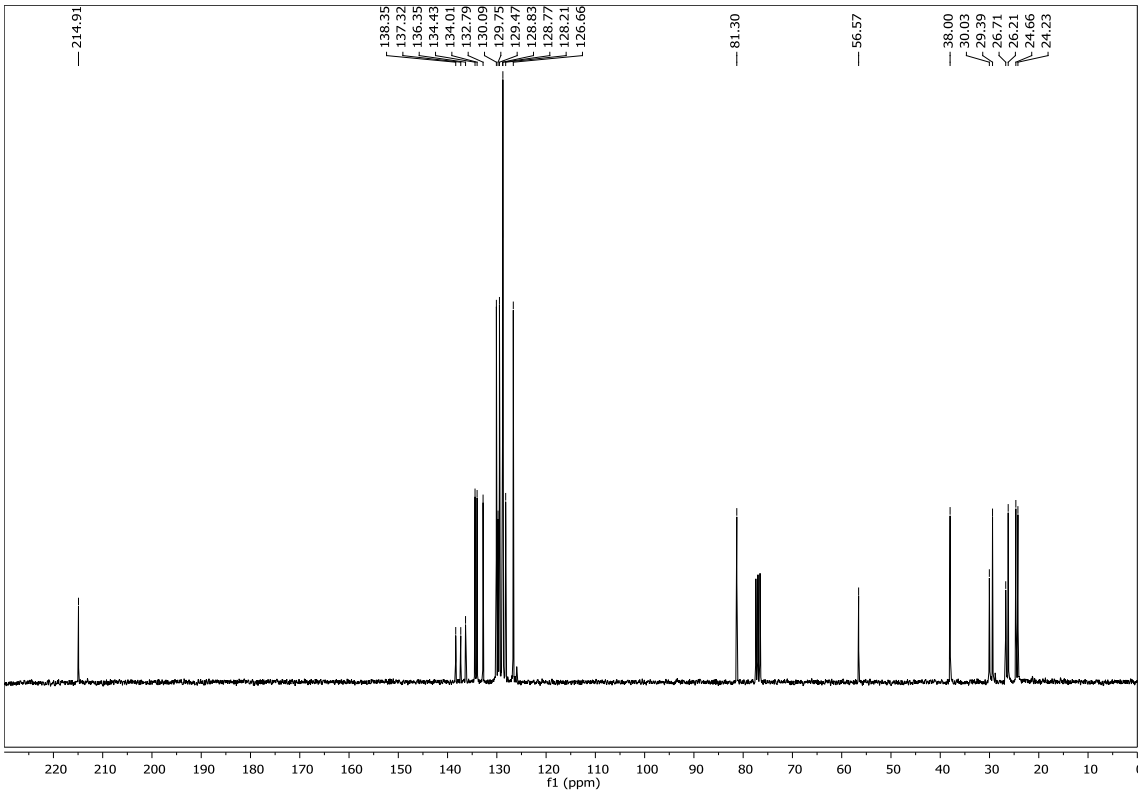
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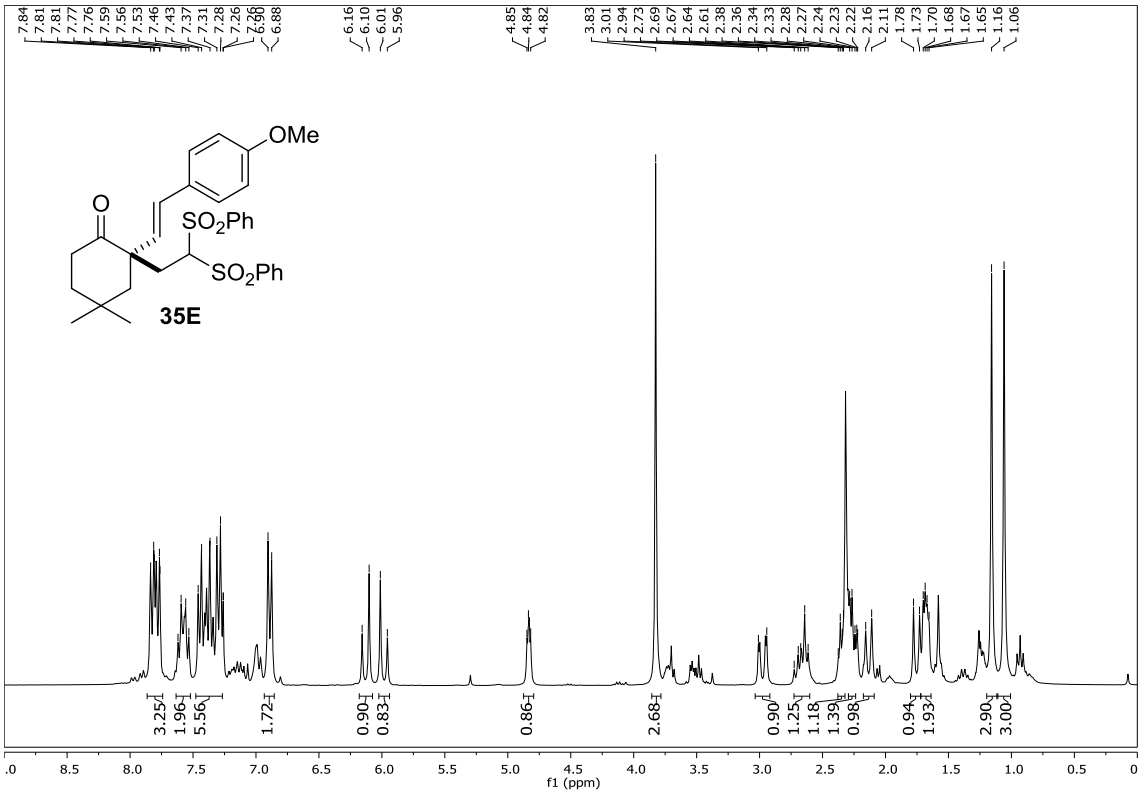
26.71
26.21
24.66
24.23
f1 (ppm)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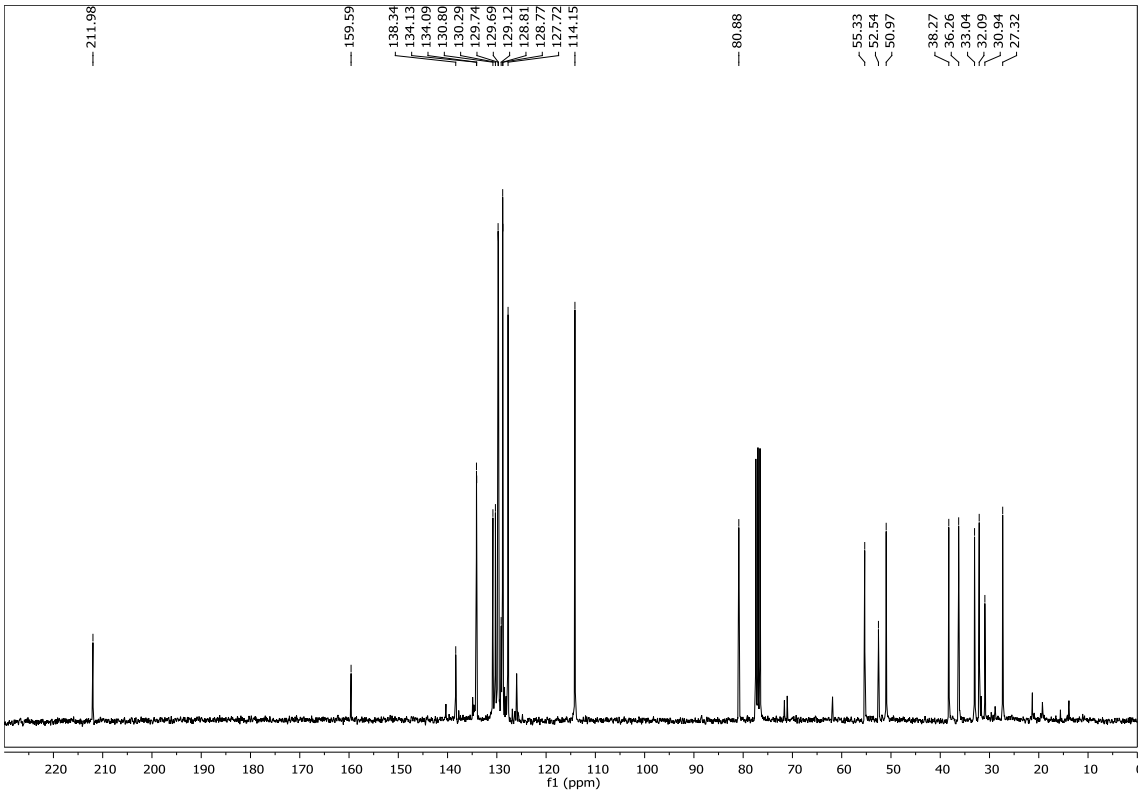
SO2Ph
SO2Ph
35E
f1 (ppm)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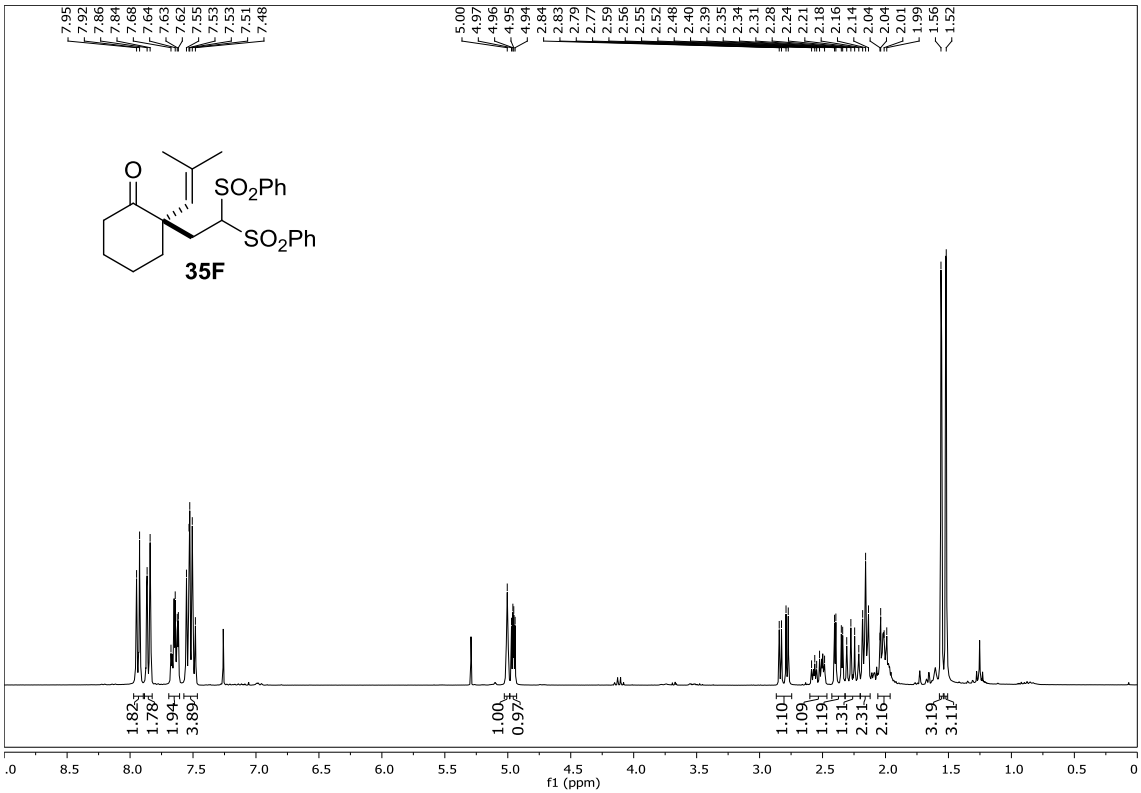
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2.01
1.99
1.56
1.52
O
SO2Ph
SO2Ph
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1.78
1.94
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1.09
1.19
1.31
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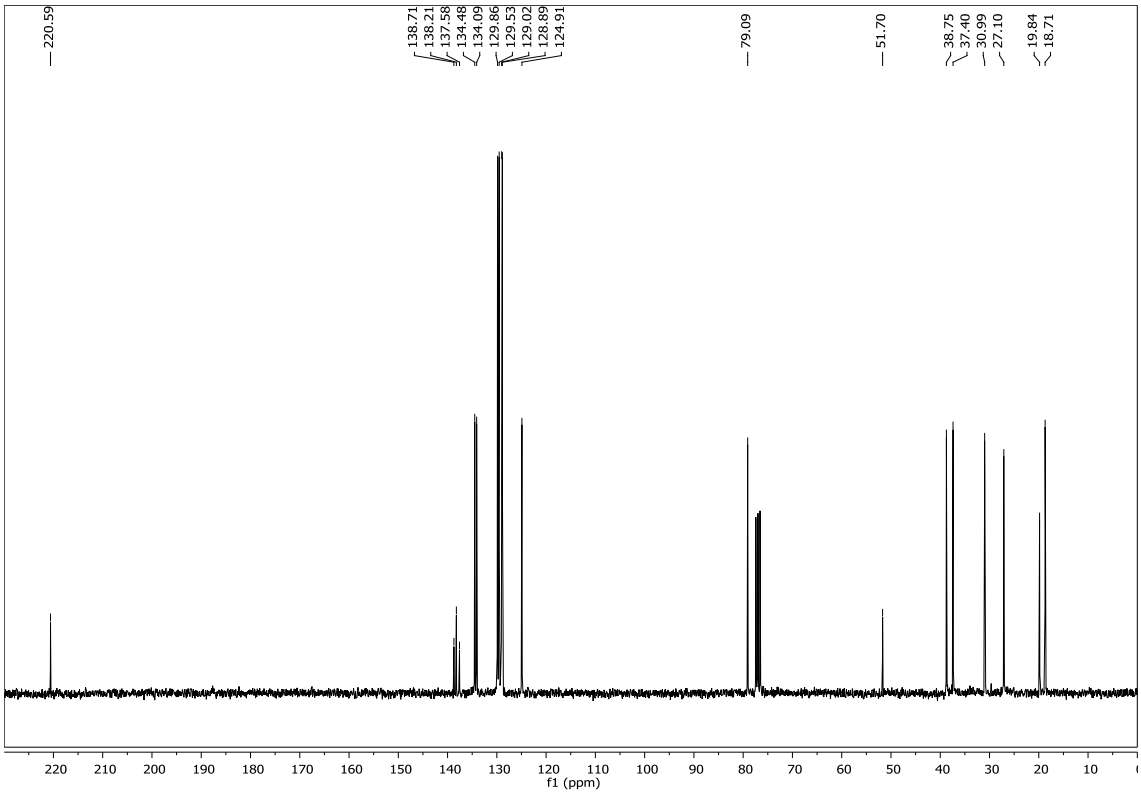
2.16
3.19
3.11
f1 (ppm)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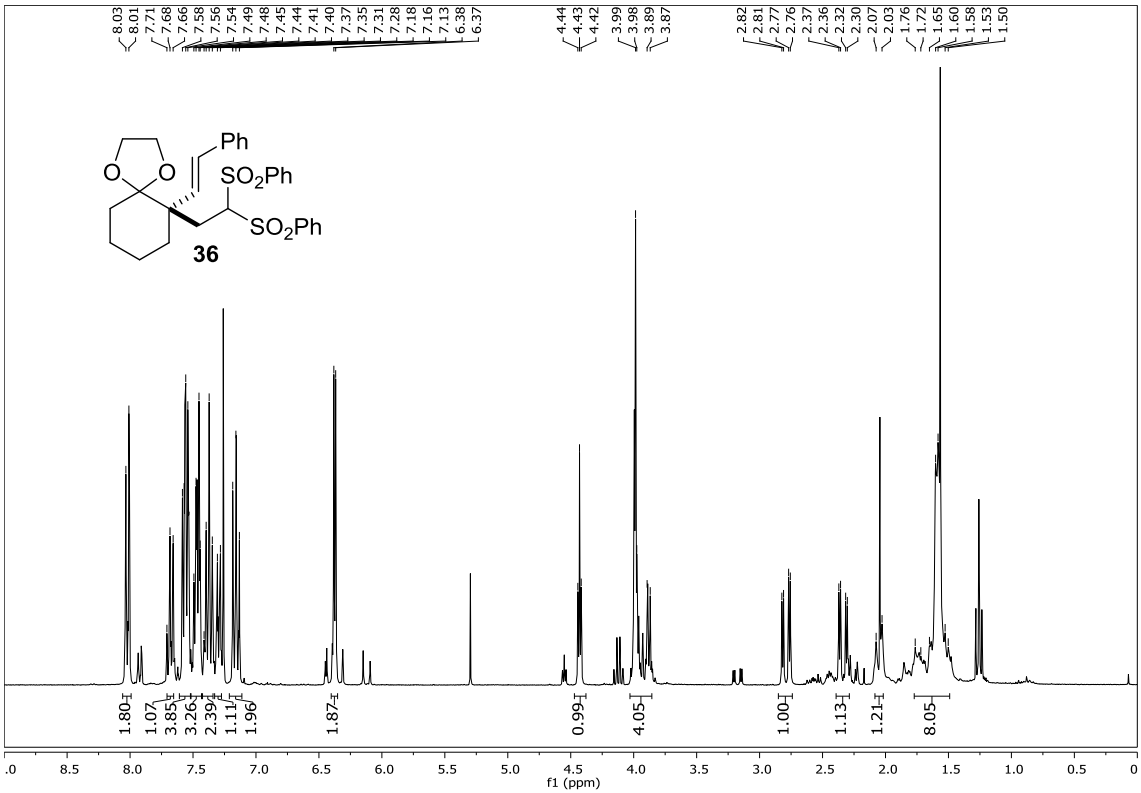
27.10
19.84
18.71
f1 (ppm)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7.45
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7.40
7.37
7.35
7.31
7.28
7.18
7.16
7.13
6.38
6.37
4.44
4.43
4.42
3.99
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3.89
3.87
2.82
2.81
2.77
2.76
2.37
2.36
2.32
2.30
2.07
2.03
1.76
1.72
1.65
1.60
1.58
1.53
1.50
Ph
O
O
SO2Ph
SO2Ph
36
1.80
1.07
3.85
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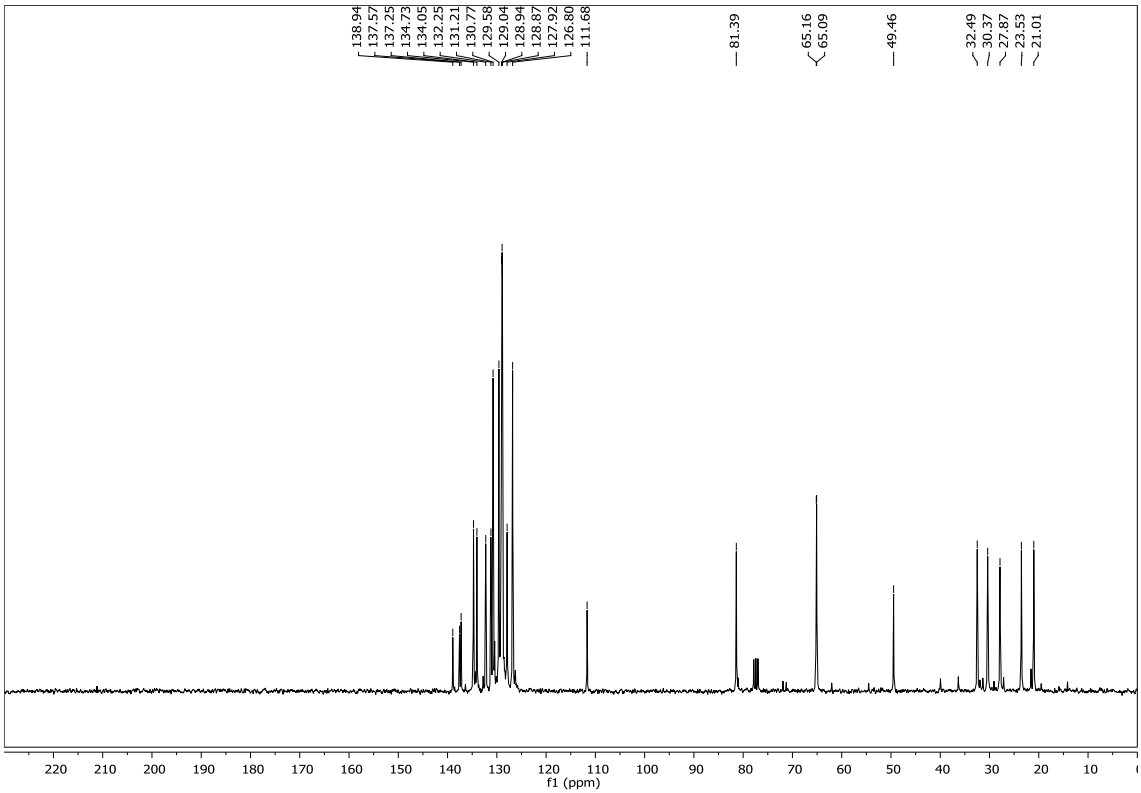
8.05
f1 (ppm)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128.87
127.92
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32.49
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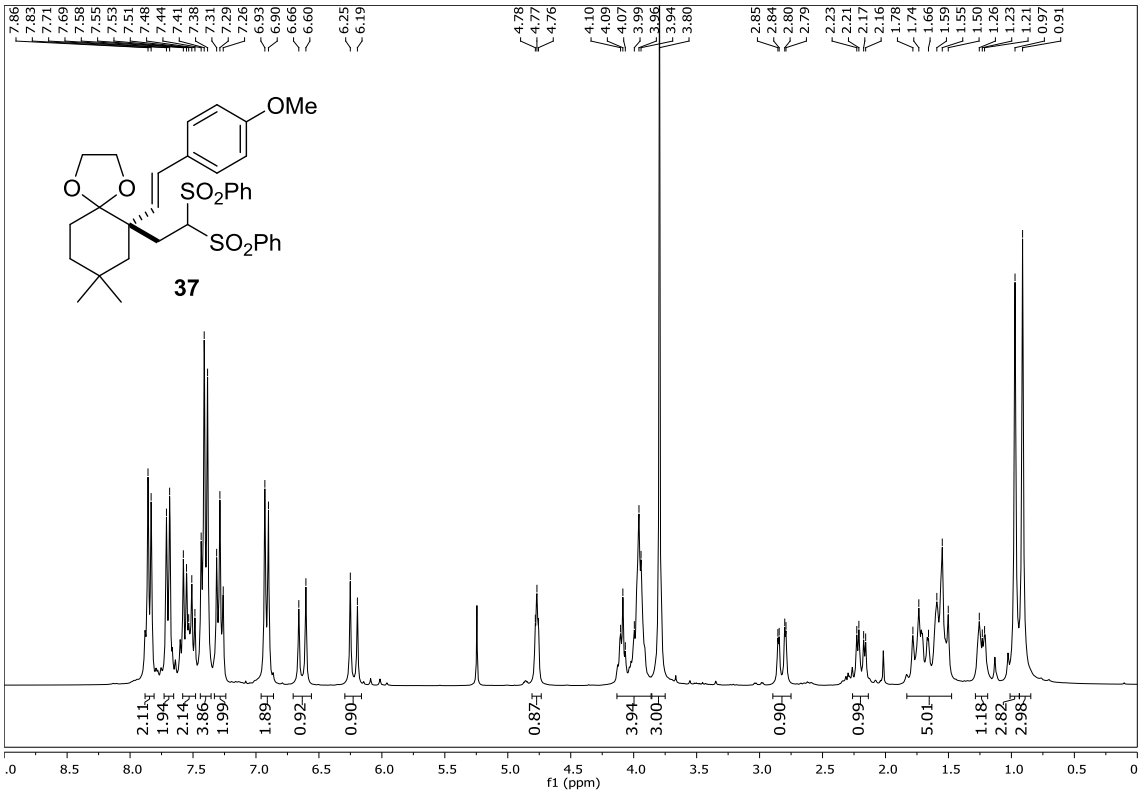
27.87
23.53
21.01
f1 (ppm)


OMe
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O
SO2Ph
SO2Ph
37
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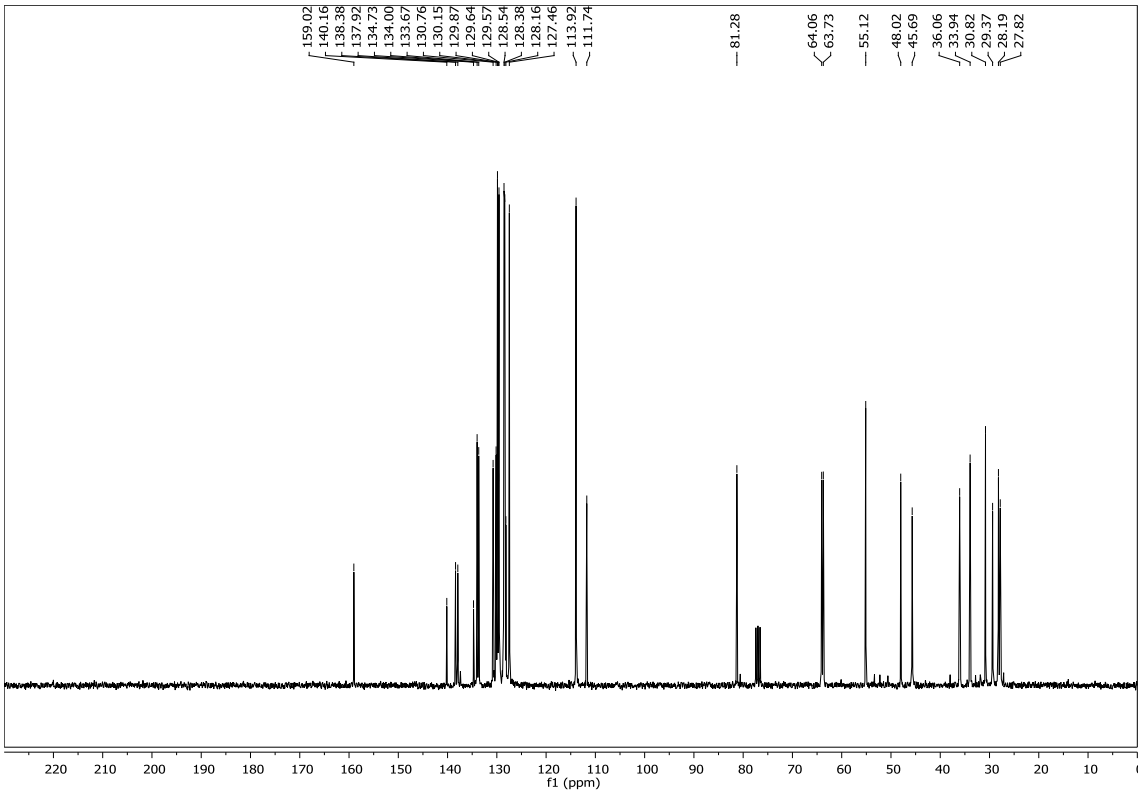
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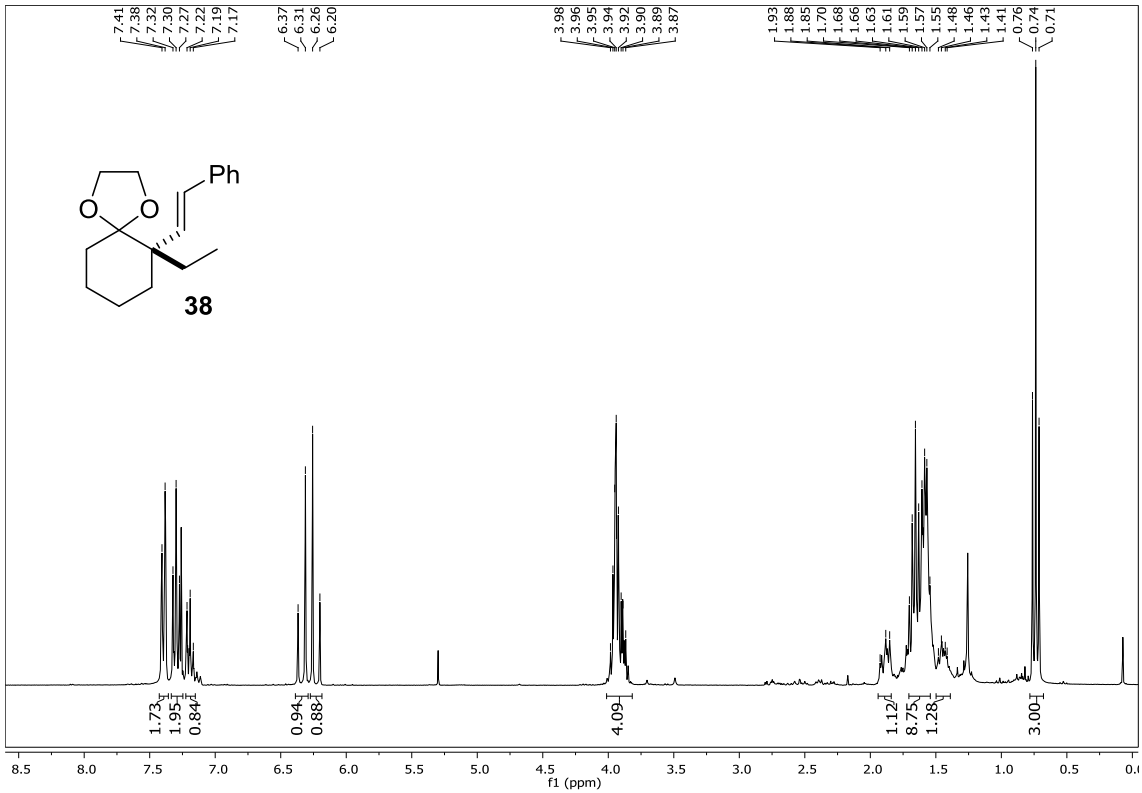
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3.96
3.95
3.94
3.92
3.90
3.89
3.87
1.93
1.88
1.85
1.70
1.68
1.66
1.63
1.61
1.59
1.57
1.55
1.48
1.46
1.43
1.41
0.76
0.74
0.71
Ph
O
O
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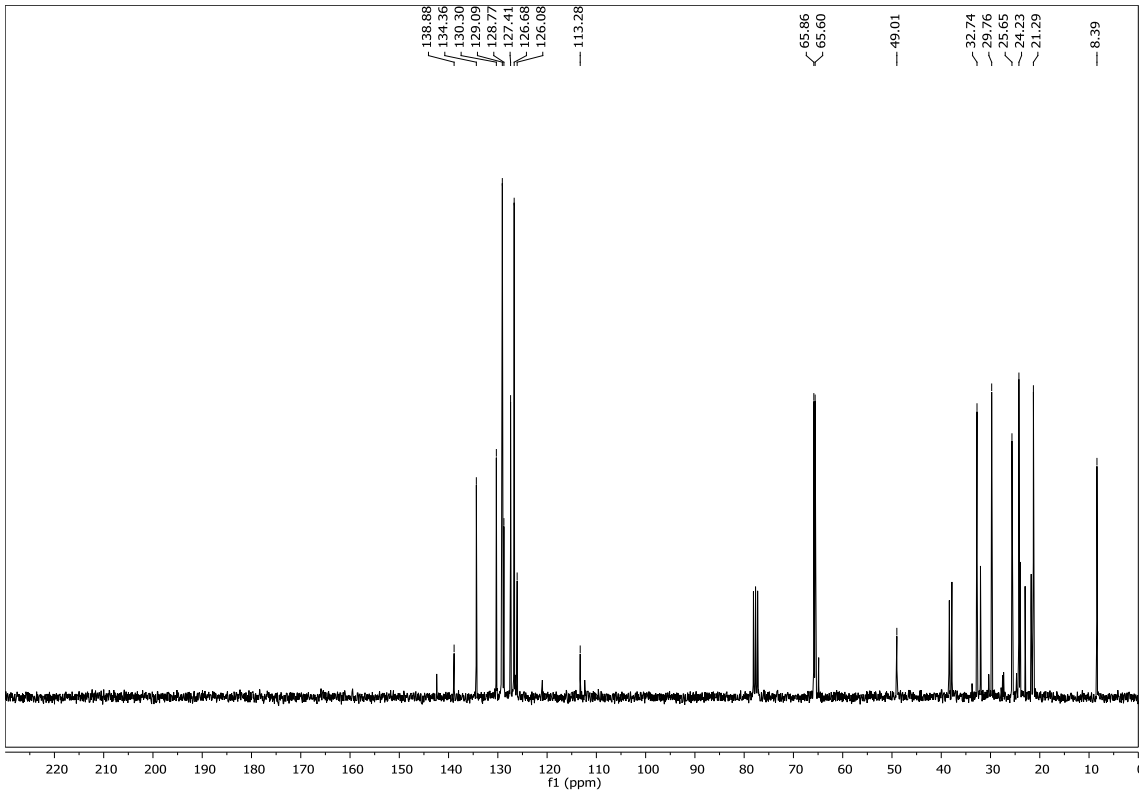
0.94
0.88
4.09
1.12
8.75
1.28
3.00
f1 (ppm)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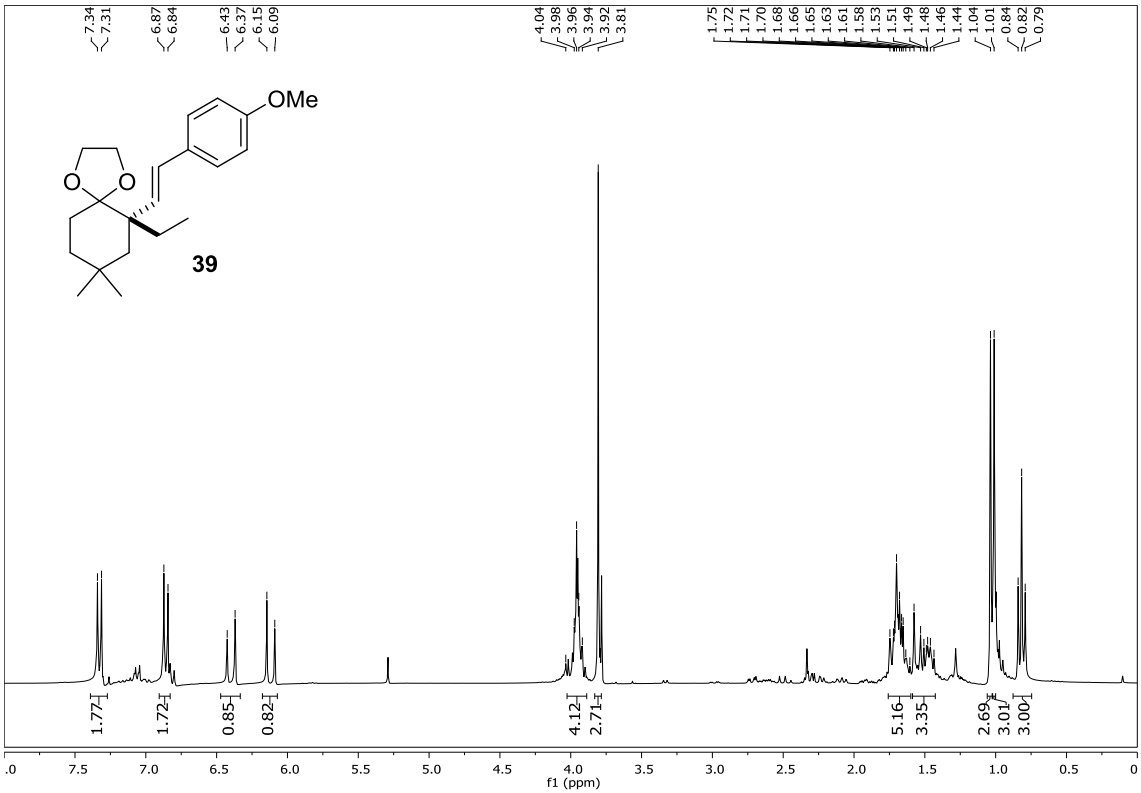
f1 (ppm)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1.63
1.61
1.58
1.53
1.51
1.49
1.48
1.46
1.44
1.04
1.01
0.84
0.82
0.79
OMe
O
O
39
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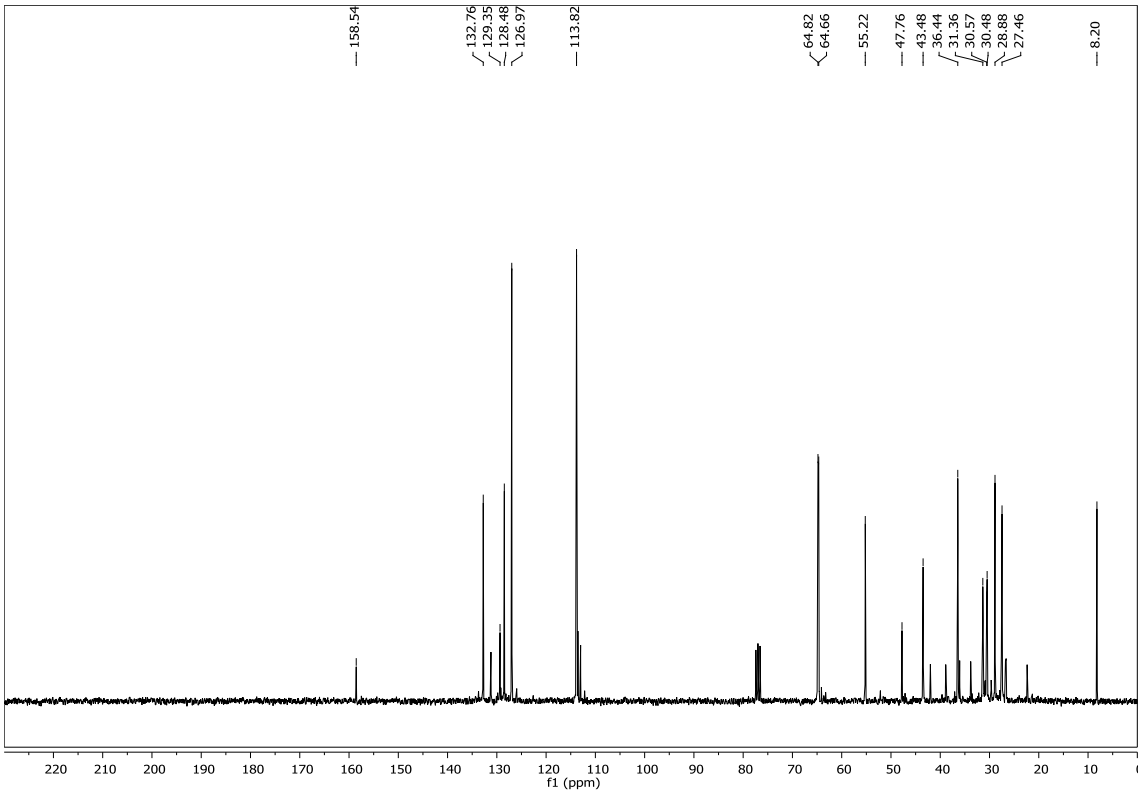
0.82
4.12
2.71
5.16
3.35
2.69
3.01
3.00
f1 (ppm)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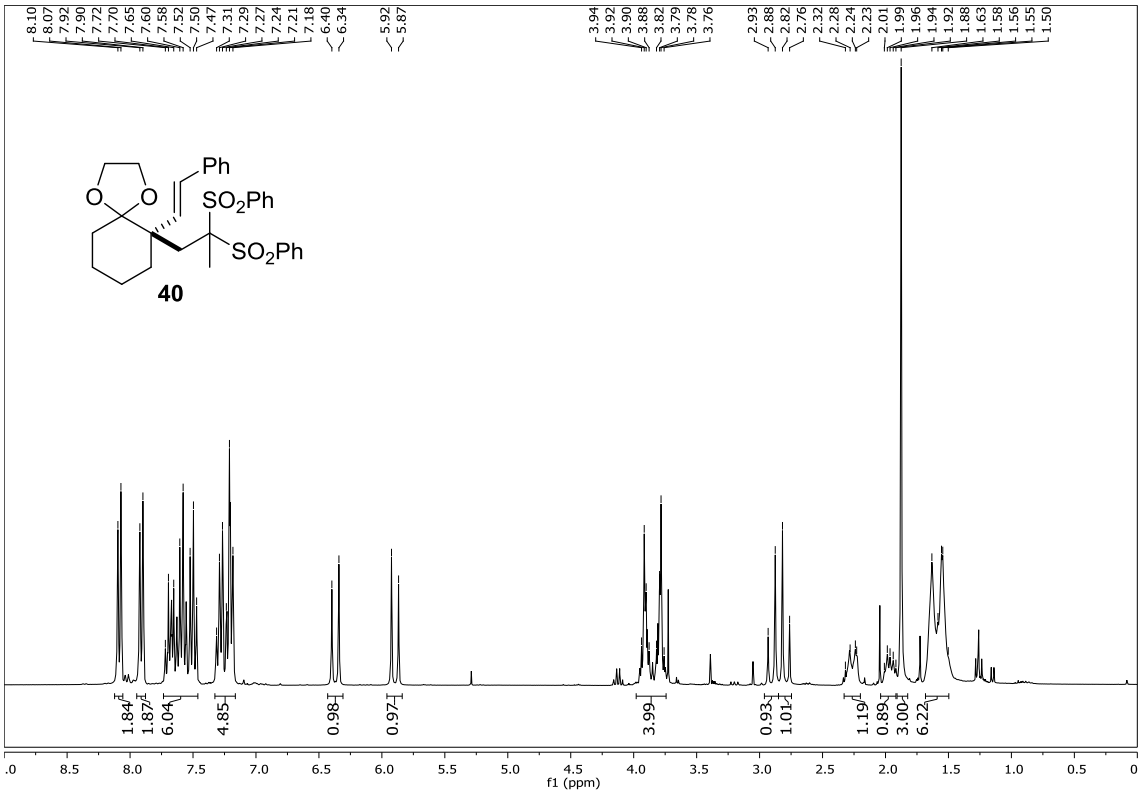
36.44
31.36
30.57
30.48
28.88
27.46
8.20
f1 (ppm)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7.29
7.27
7.24
7.21
7.18
6.40
6.34
5.92
5.87
3.94
3.92
3.90
3.88
3.82
3.79
3.78
3.76
2.93
2.88
2.82
2.76
2.32
2.28
2.24
2.23
2.01
1.99
1.96
1.94
1.92
1.88
1.63
1.58
1.56
1.55
1.50
Ph
SO2Ph
SO2Ph
40
1.84
1.87
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0.97
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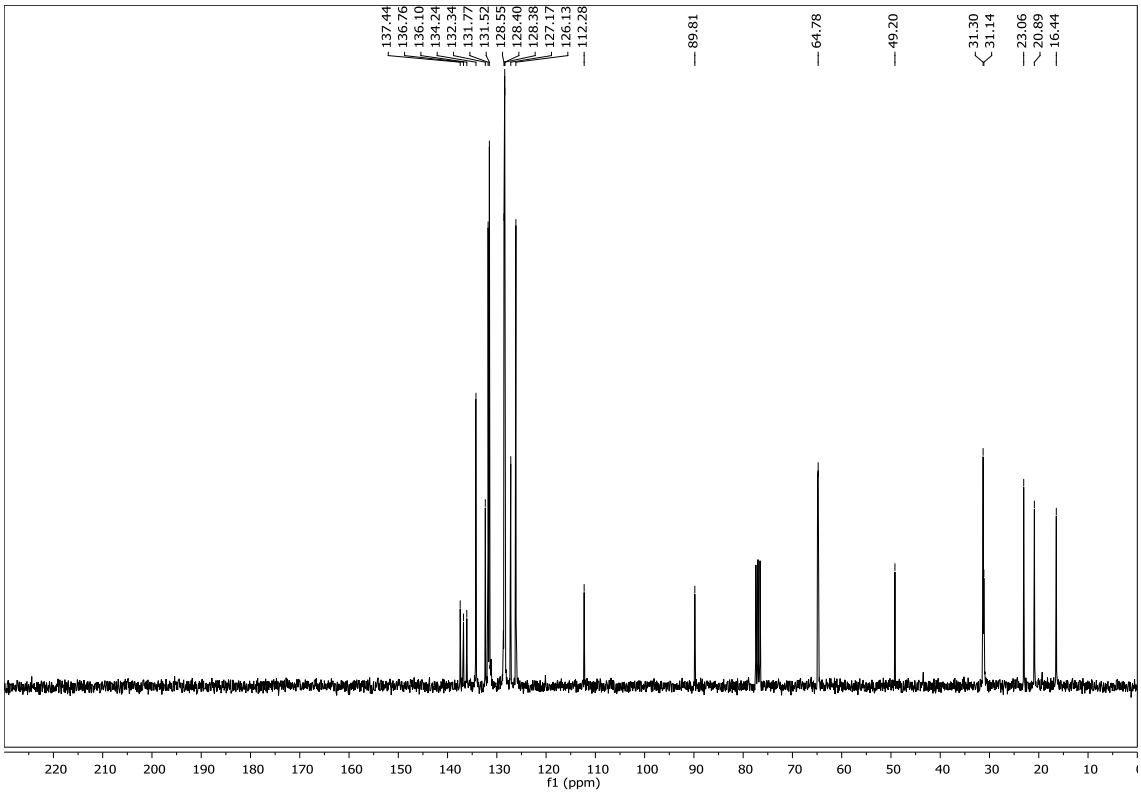
0.93
1.01
1.19
0.89
3.00
6.22
f1 (ppm)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131.77
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128.38
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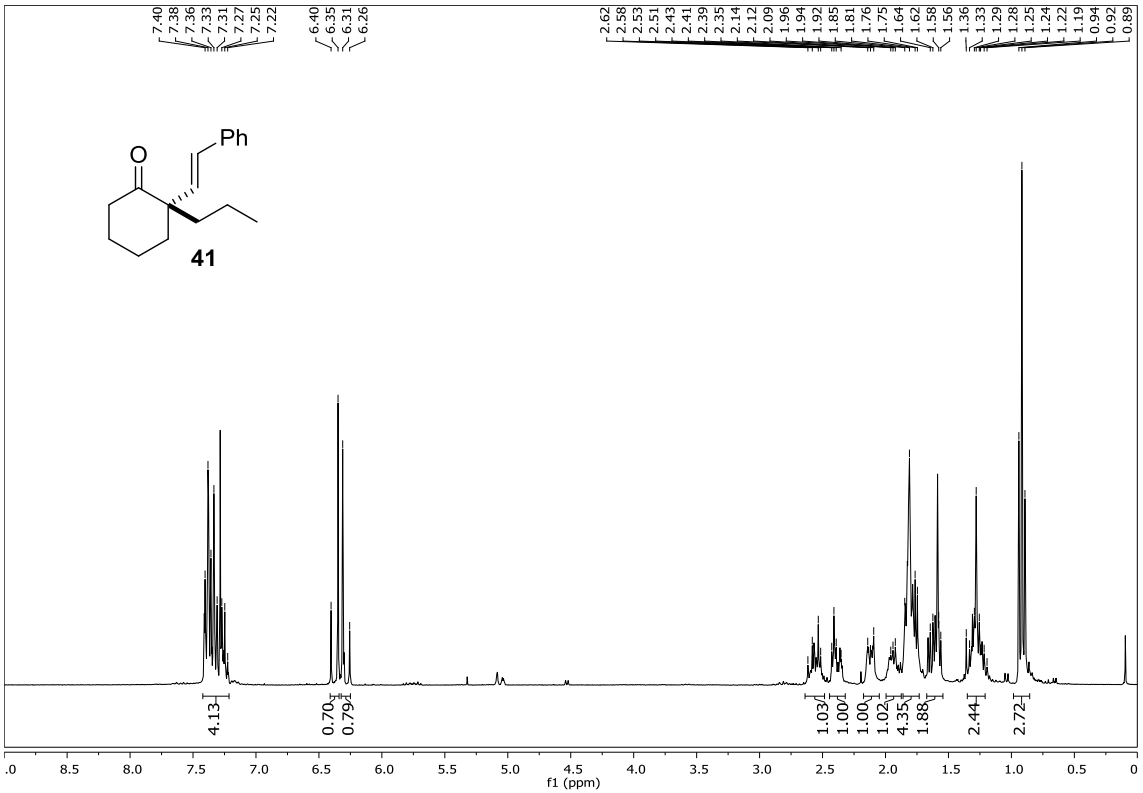
112.28
89.81
64.78
49.20
31.30
31.14
23.06
20.89
16.44
f1 (ppm)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6.31
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2.53
2.51
2.43
2.41
2.39
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2.14
2.12
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1.96
1.94
1.92
1.85
1.81
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1.58
1.56
1.36
1.33
1.29
1.28
1.25
1.24
1.22
1.19
0.94
0.92
0.89
O
Ph
41
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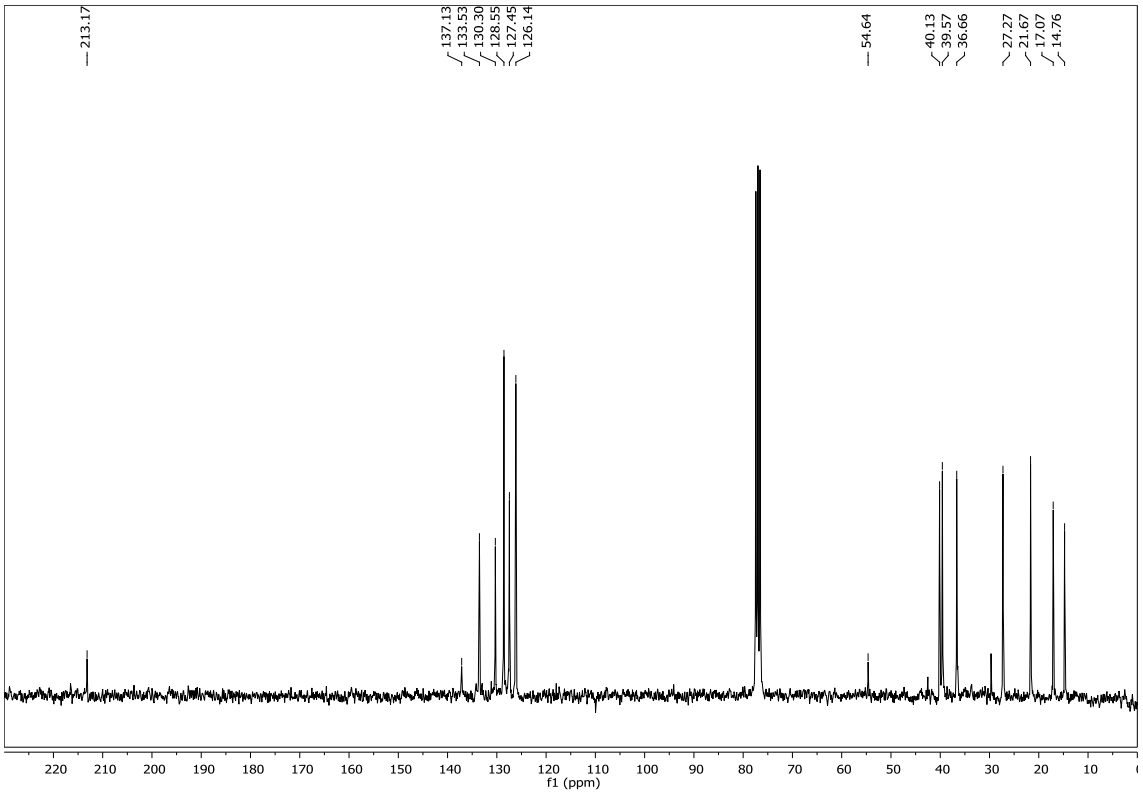
1.00
1.02
4.35
1.88
2.44
2.72
f1 (ppm)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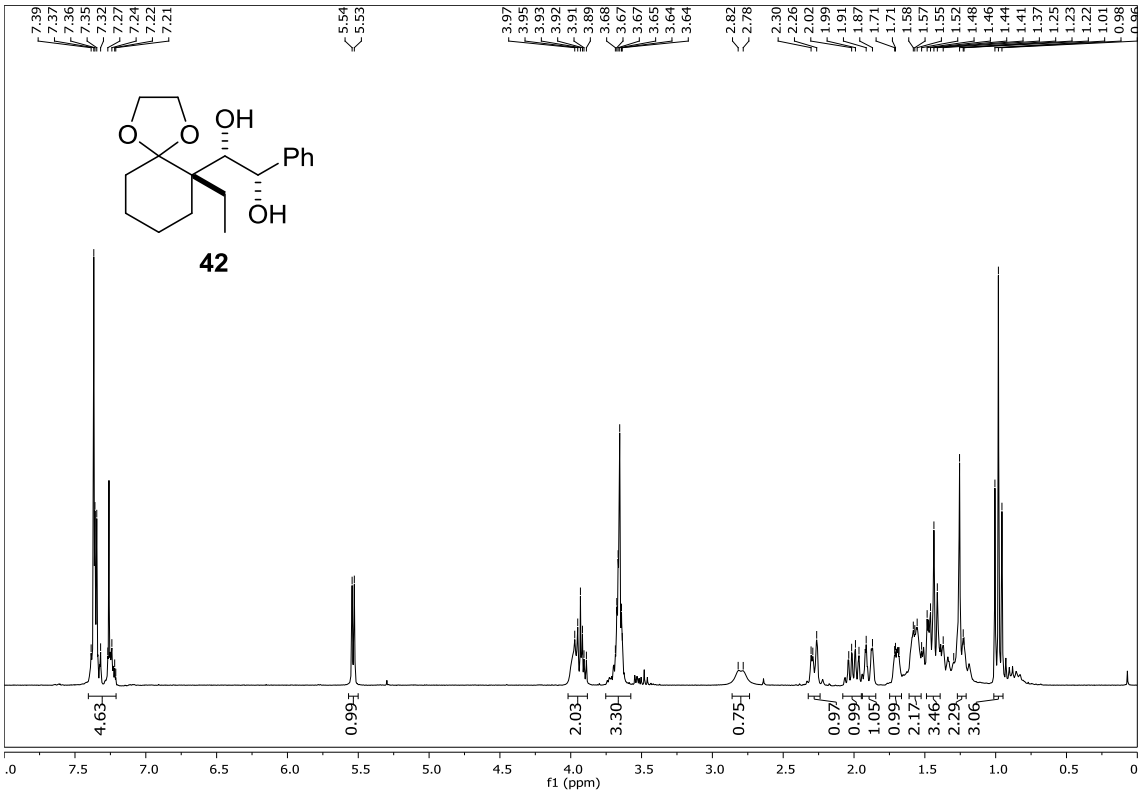
40.13
39.57
36.66
27.27
21.67
17.07
14.76
f1 (ppm)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3.97
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3.93
3.92
3.91
3.89
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3.67
3.67
3.65
3.64
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2.82
2.78
2.30
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2.02
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1.25
1.23
1.22
1.01
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OH
O
O
Ph
OH
42
4.63
0.99
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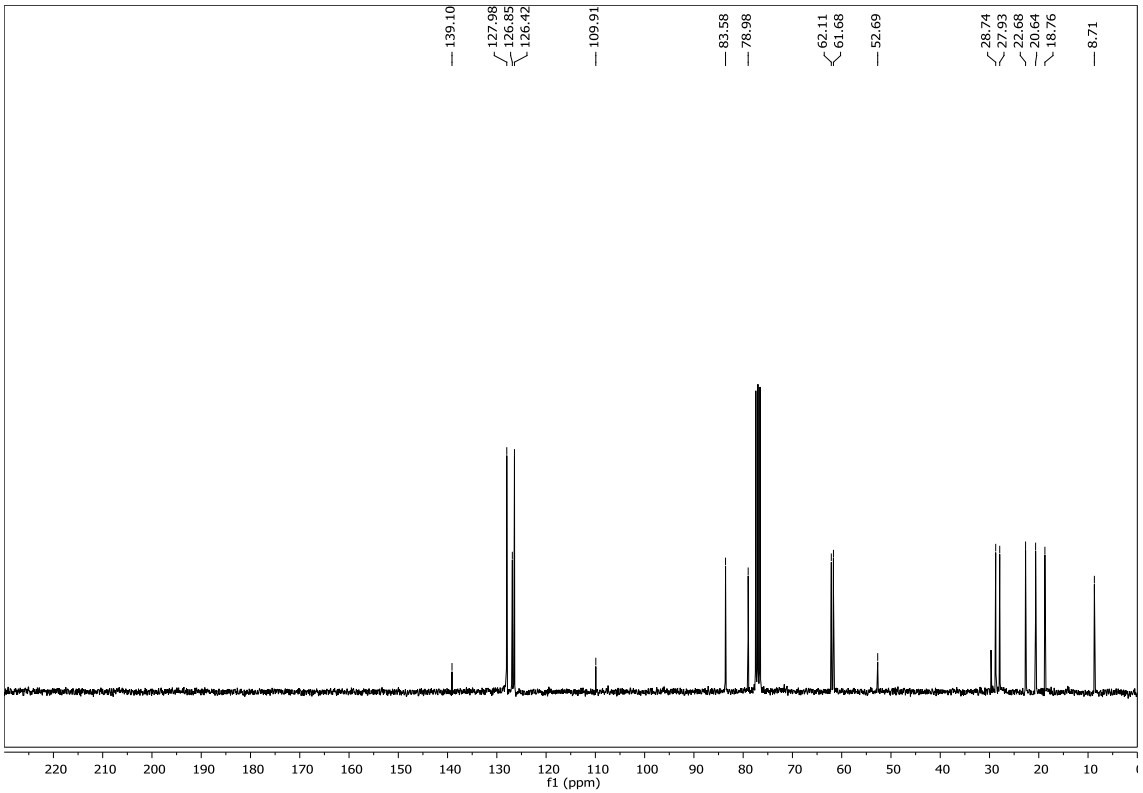
0.99
1.05
0.99
2.17
3.46
2.29
3.06
f1 (ppm)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109.91
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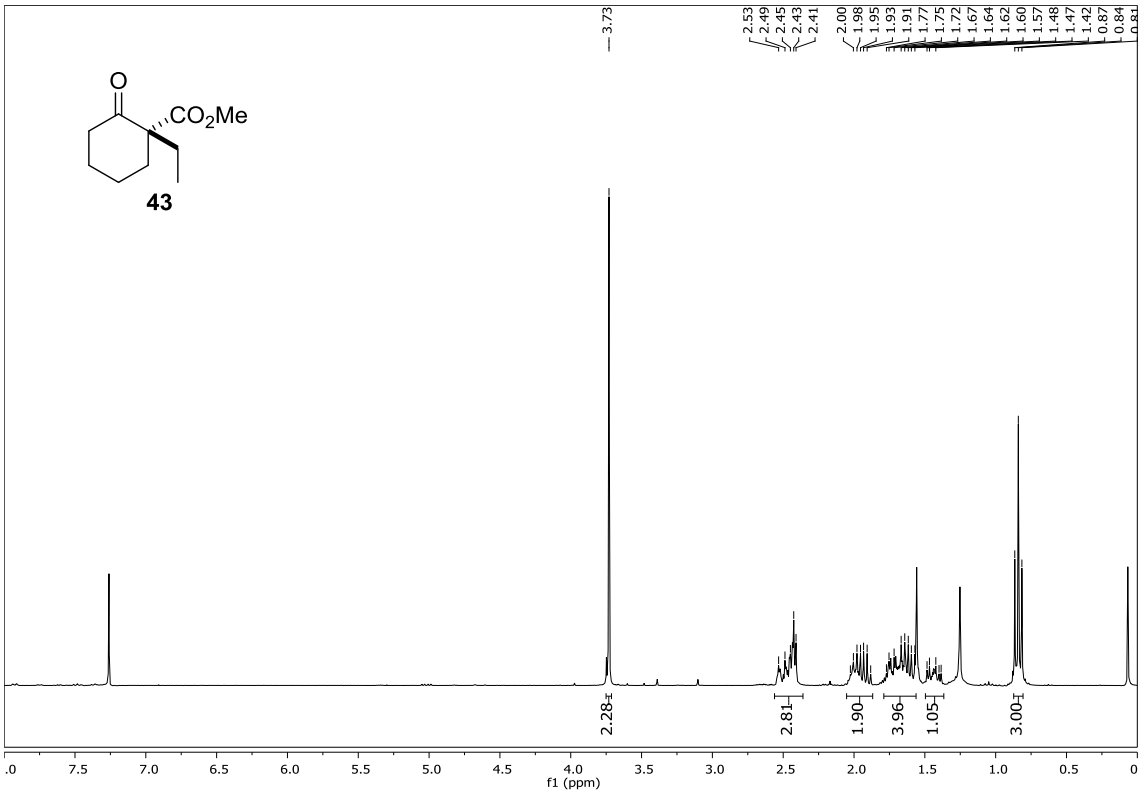
28.74
27.93
22.68
20.64
18.76
8.71
f1 (ppm)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1.91
1.77
1.75
1.72
1.67
1.64
1.62
1.60
1.57
1.48
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1.42
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0.84
0.81
2.28
2.81
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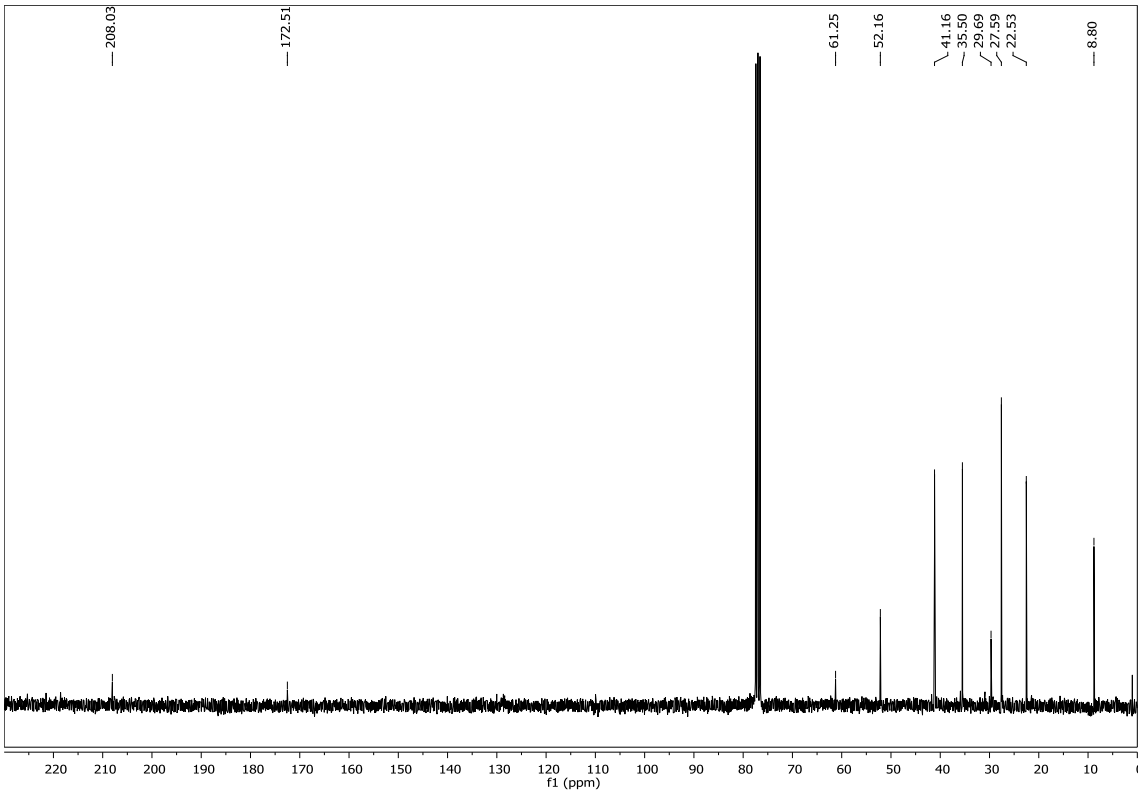
3.96
1.05
3.00
f1 (ppm)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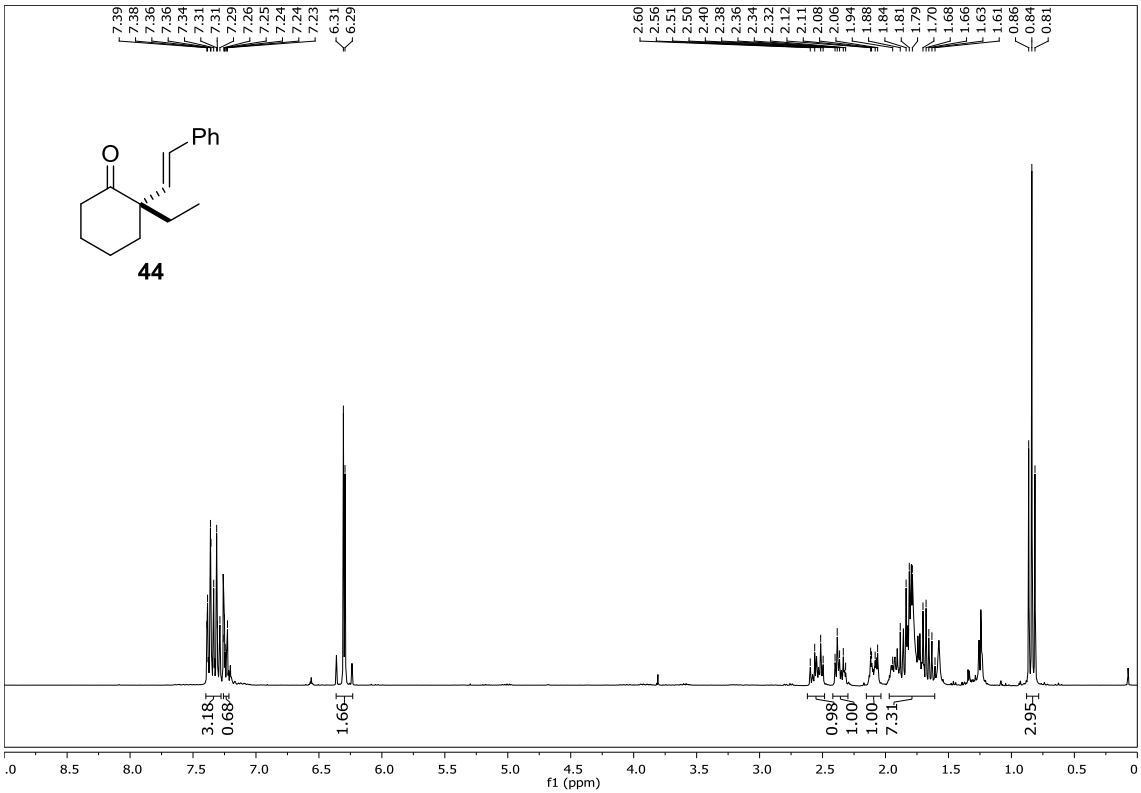
f1 (ppm)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7.23
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6.29
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2.56
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2.50
2.40
2.38
2.36
2.34
2.32
2.12
2.11
2.08
2.06
1.94
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0.84
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Ph
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1.00
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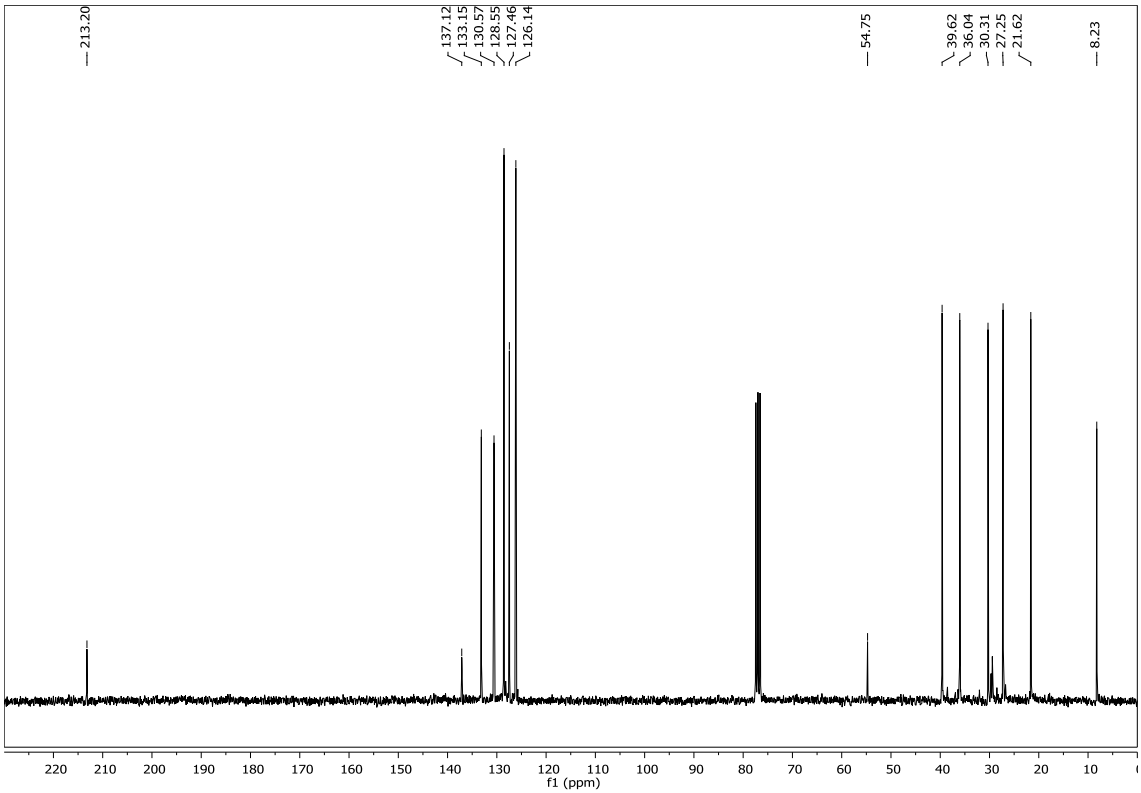
2.95
f1 (ppm)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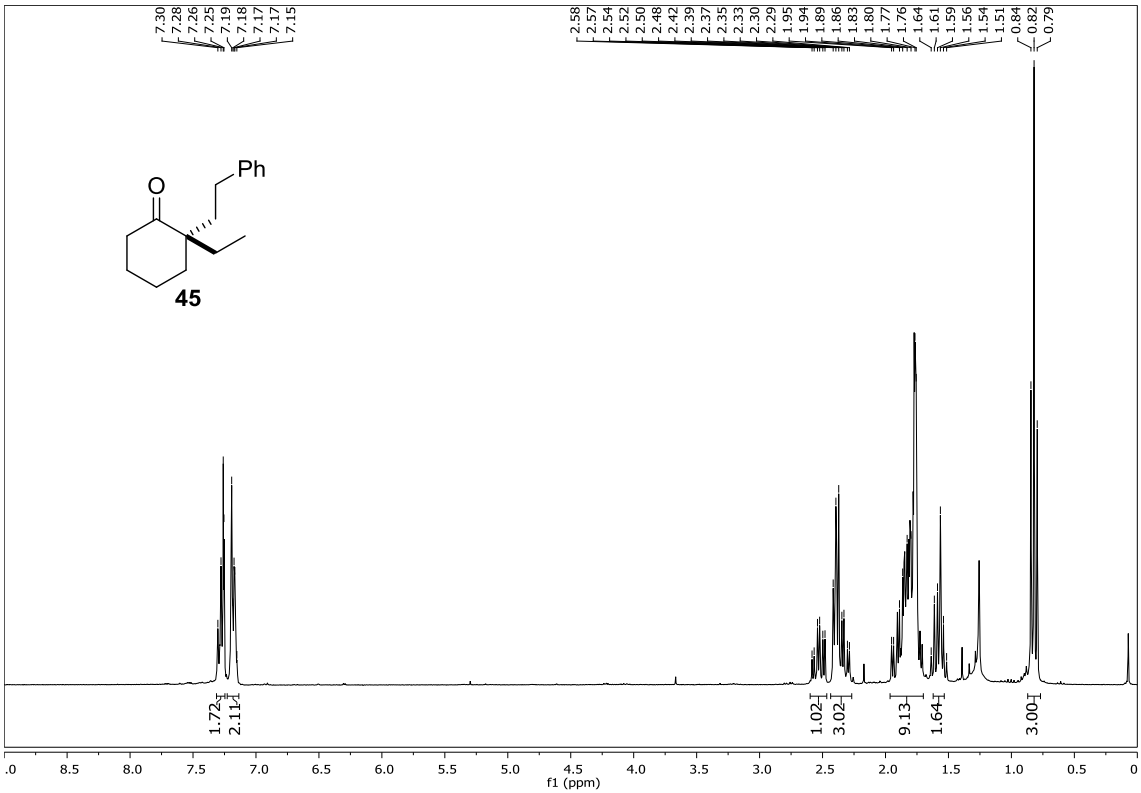
54.75
39.62
36.04
30.31
27.25
21.62
8.23
f1 (ppm)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Ph
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1.02
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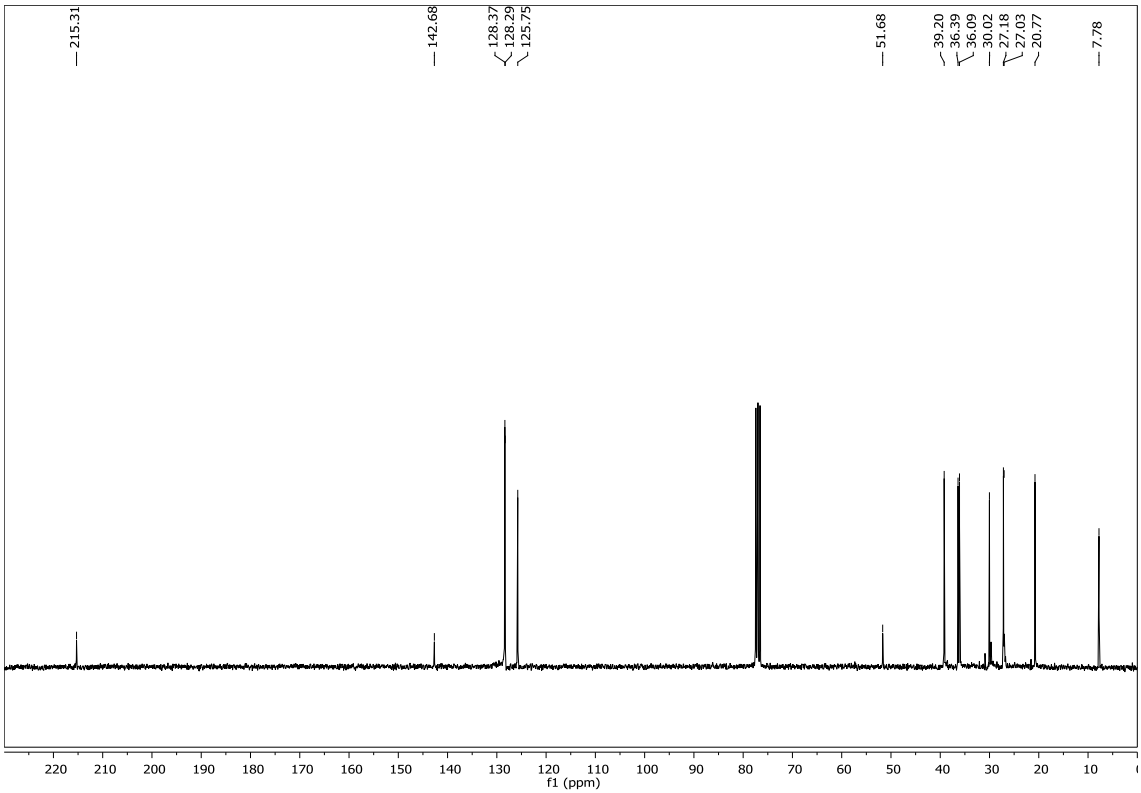
f1 (ppm)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27.18
27.03
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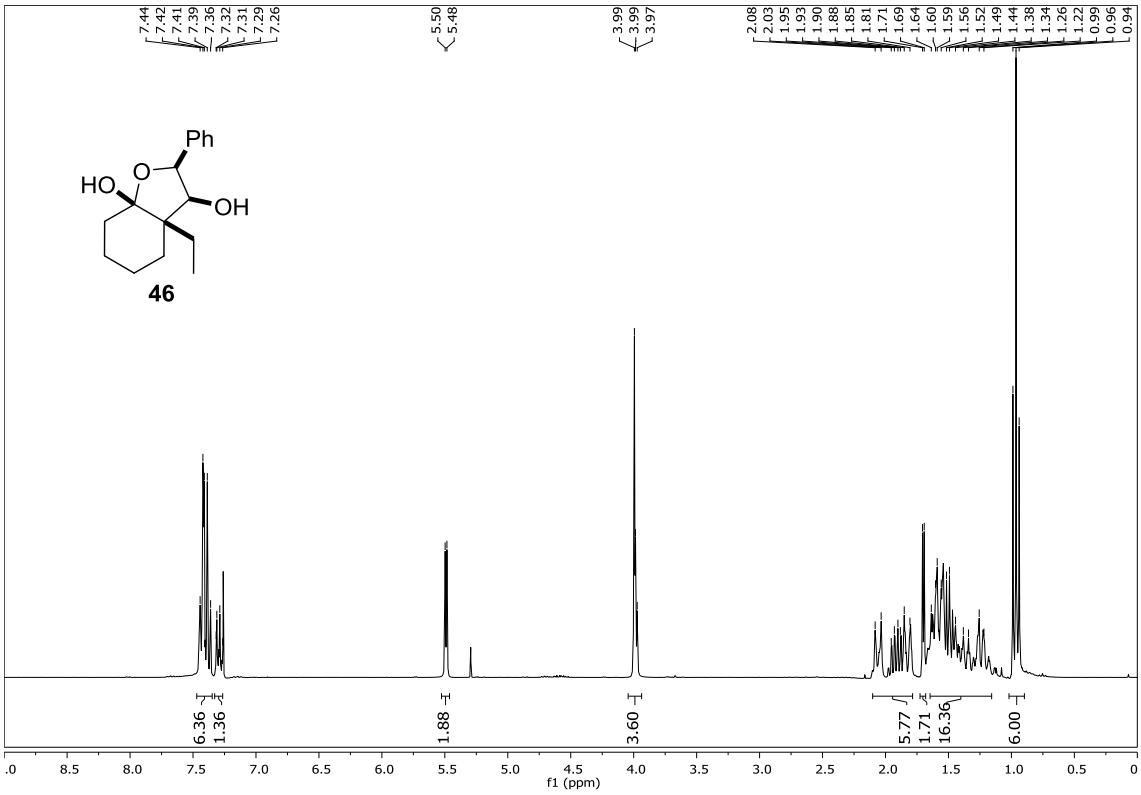
7.78
f1 (ppm)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1.44
1.38
1.34
1.26
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0.96
0.94
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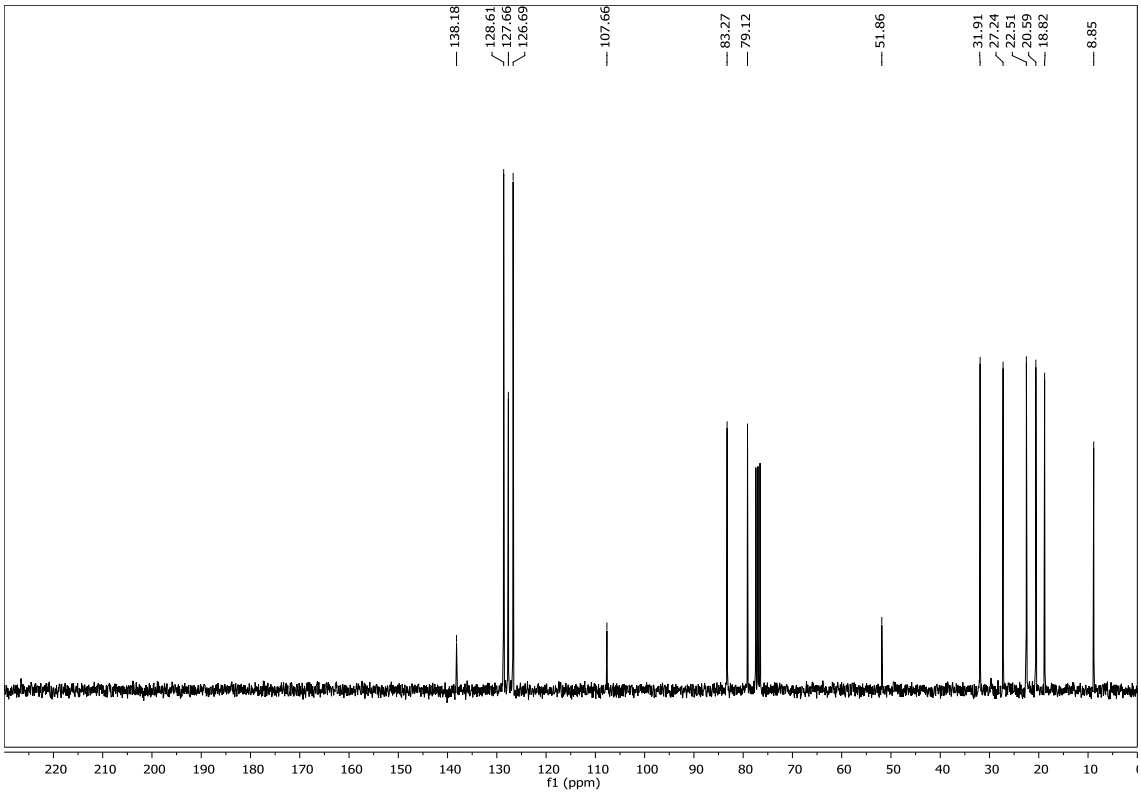
6.00
f1 (ppm)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27.24
22.51
20.59
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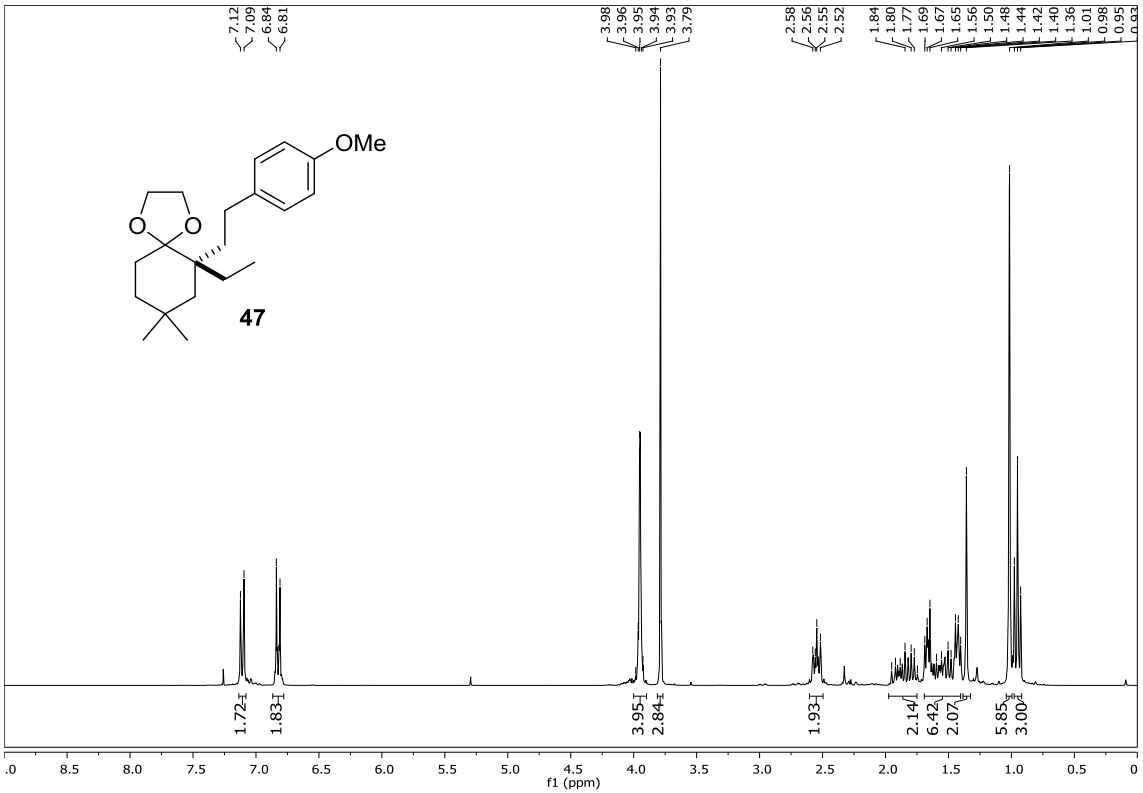
8.85
f1 (ppm)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3.79
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2.55
2.52
1.84
1.80
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1.69
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1.50
1.48
1.44
1.42
1.40
1.36
1.01
0.98
0.95
OMe
O
O
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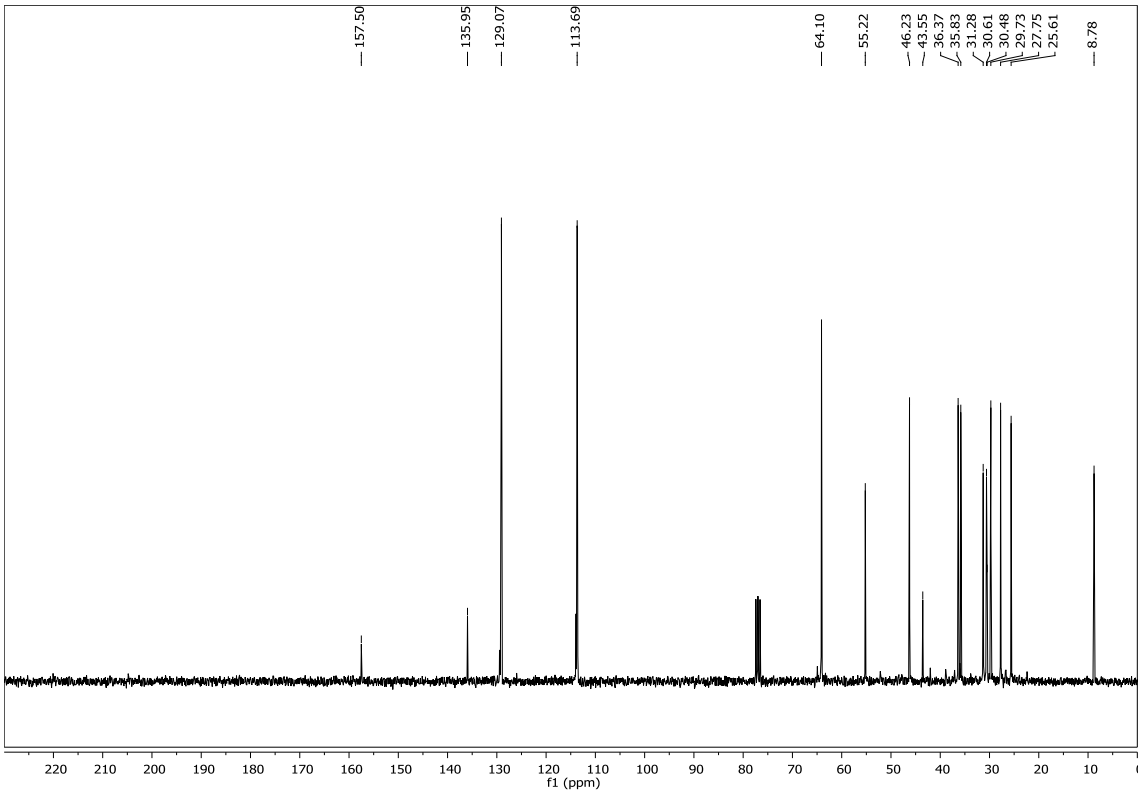
1.93
2.14
6.42
2.07
5.85
3.00
f1 (ppm)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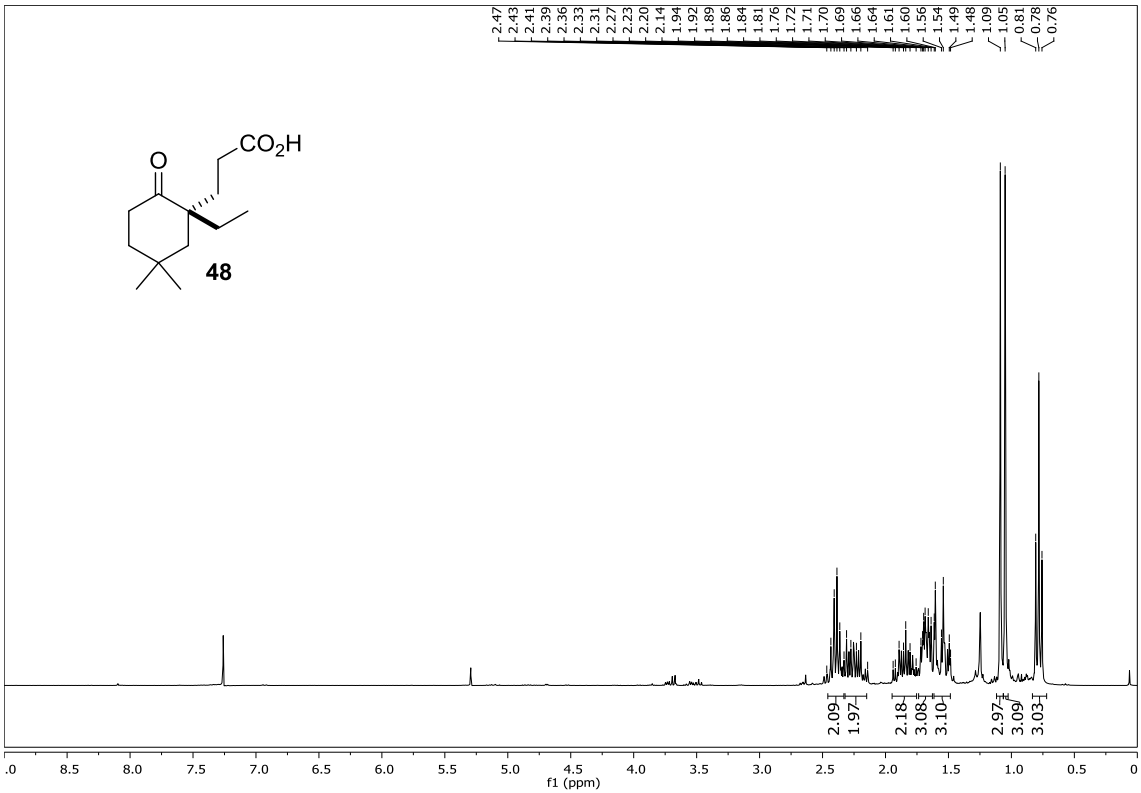
8.78
f1 (ppm)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1.61
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1.54
1.49
1.48
1.09
1.05
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0.78
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CO2H
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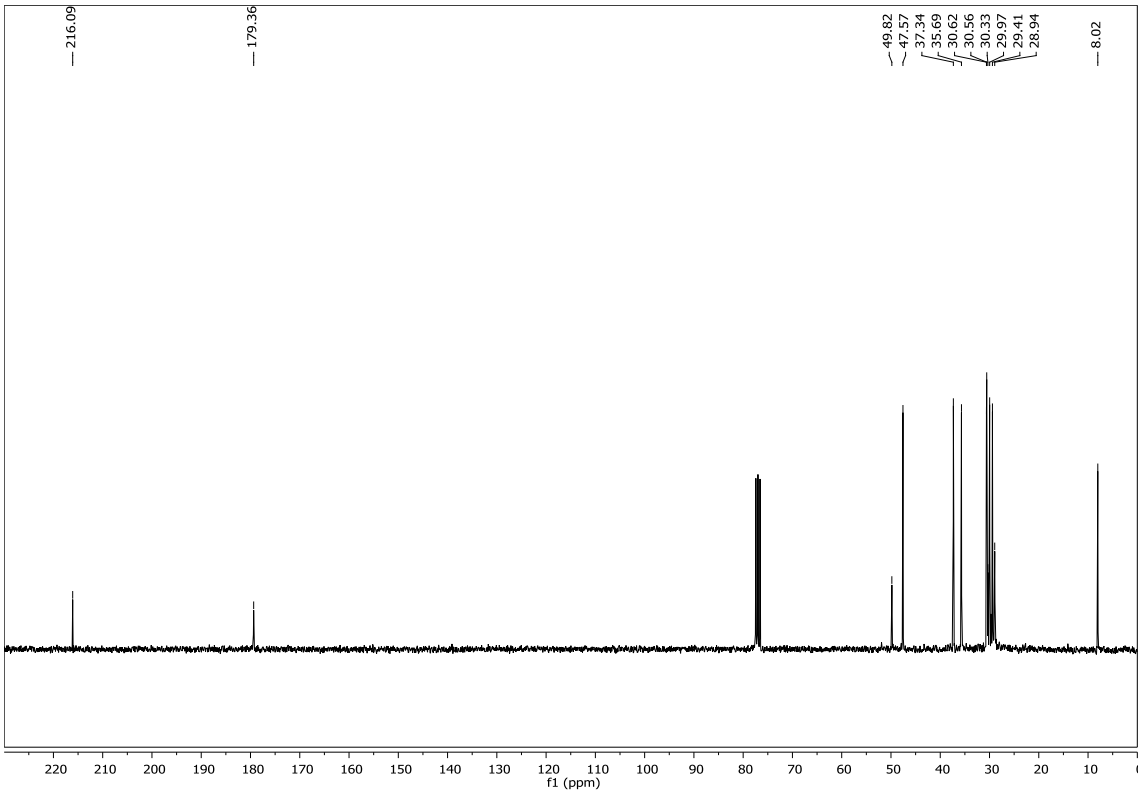
1.97
2.18
3.08
3.10
2.97
3.09
3.03
f1 (ppm)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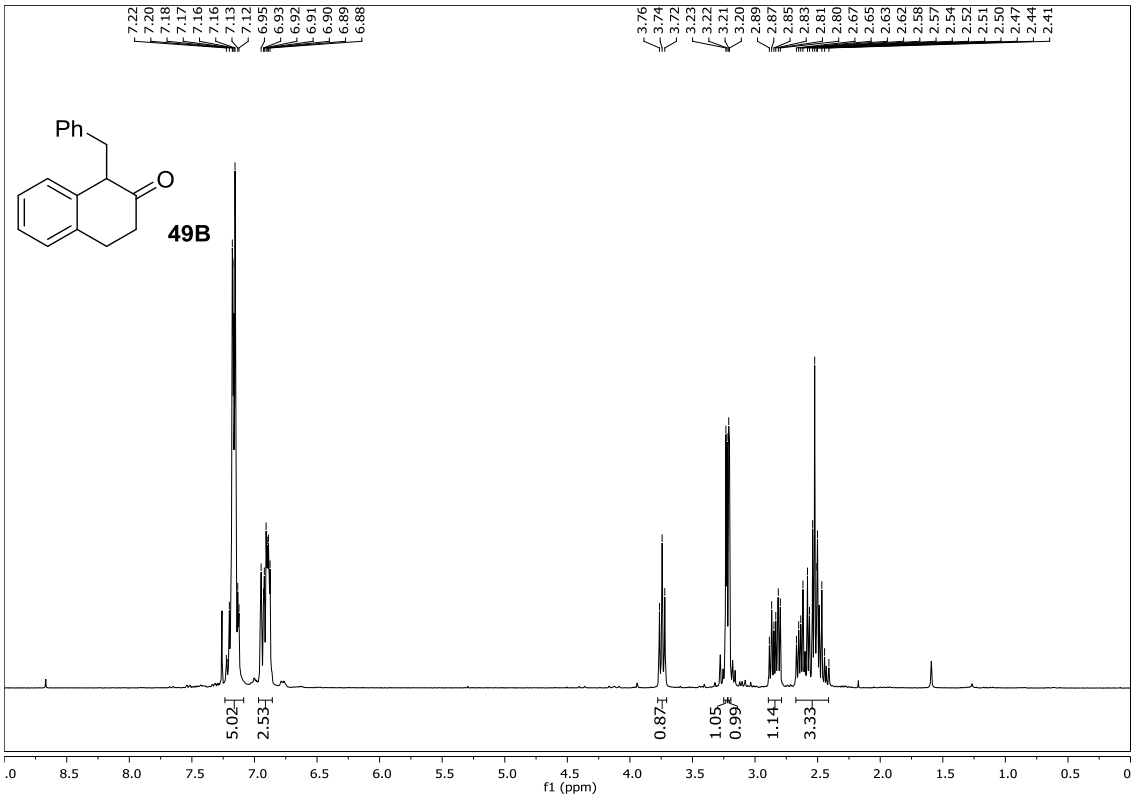
29.97
29.41
28.94
8.02
f1 (ppm)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6.93
6.92
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6.90
6.89
6.88
3.76
3.74
3.72
3.23
3.22
3.21
3.20
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2.81
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2.57
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2.52
2.51
2.50
2.47
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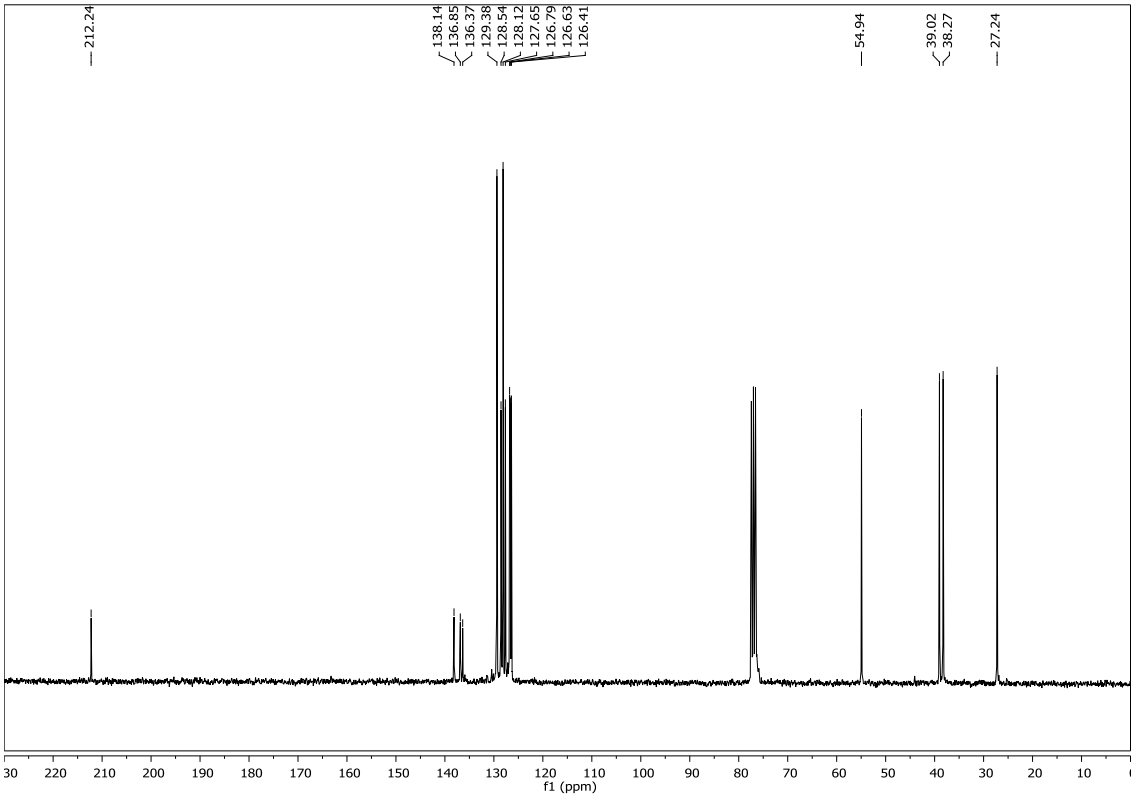
3.33
f1 (ppm)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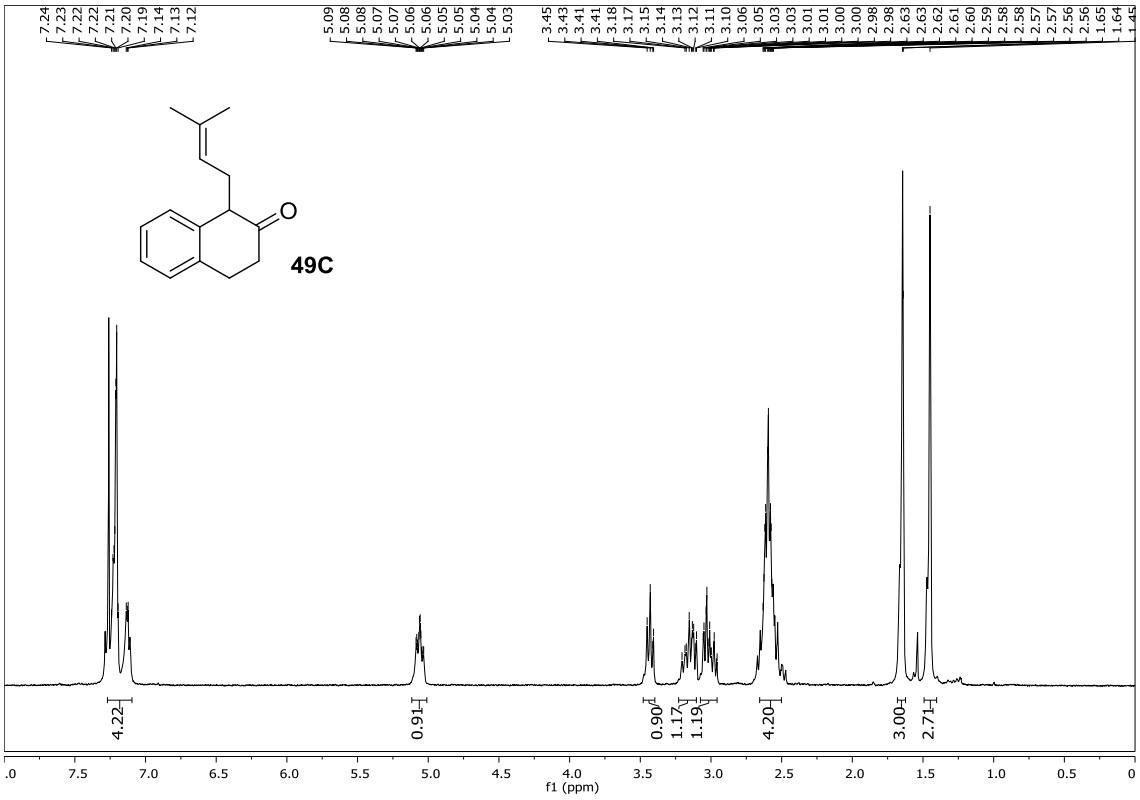
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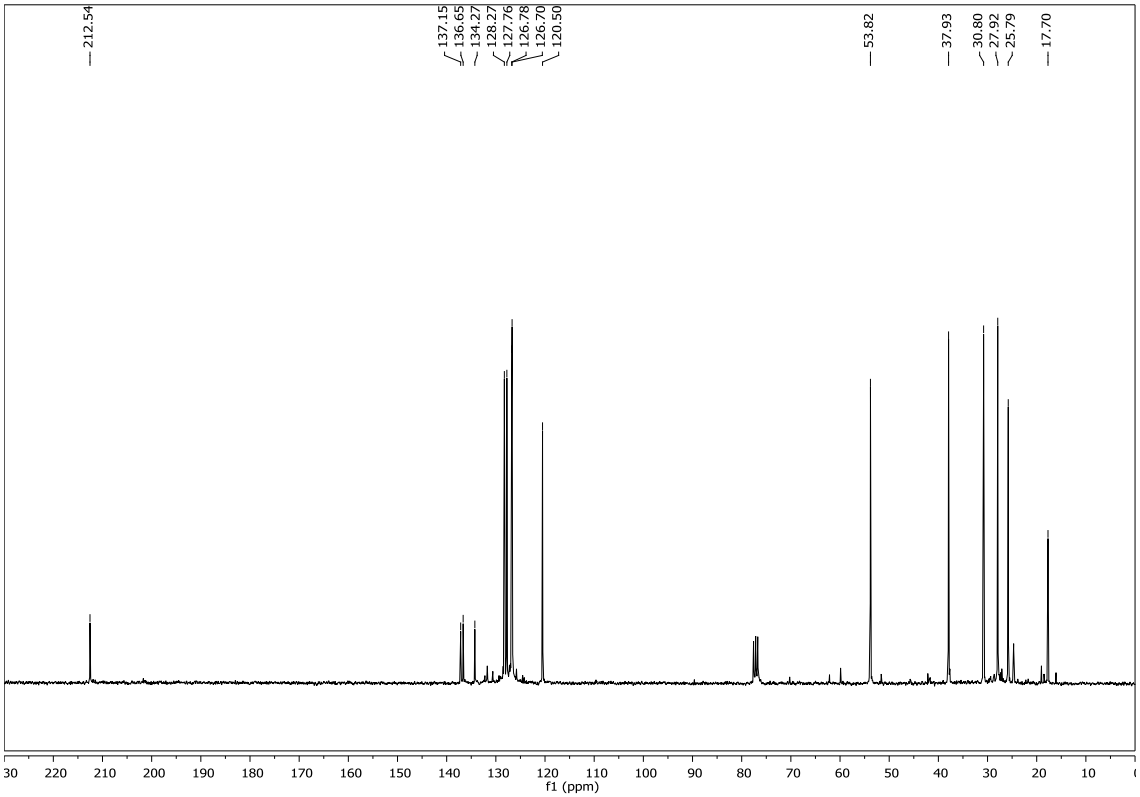
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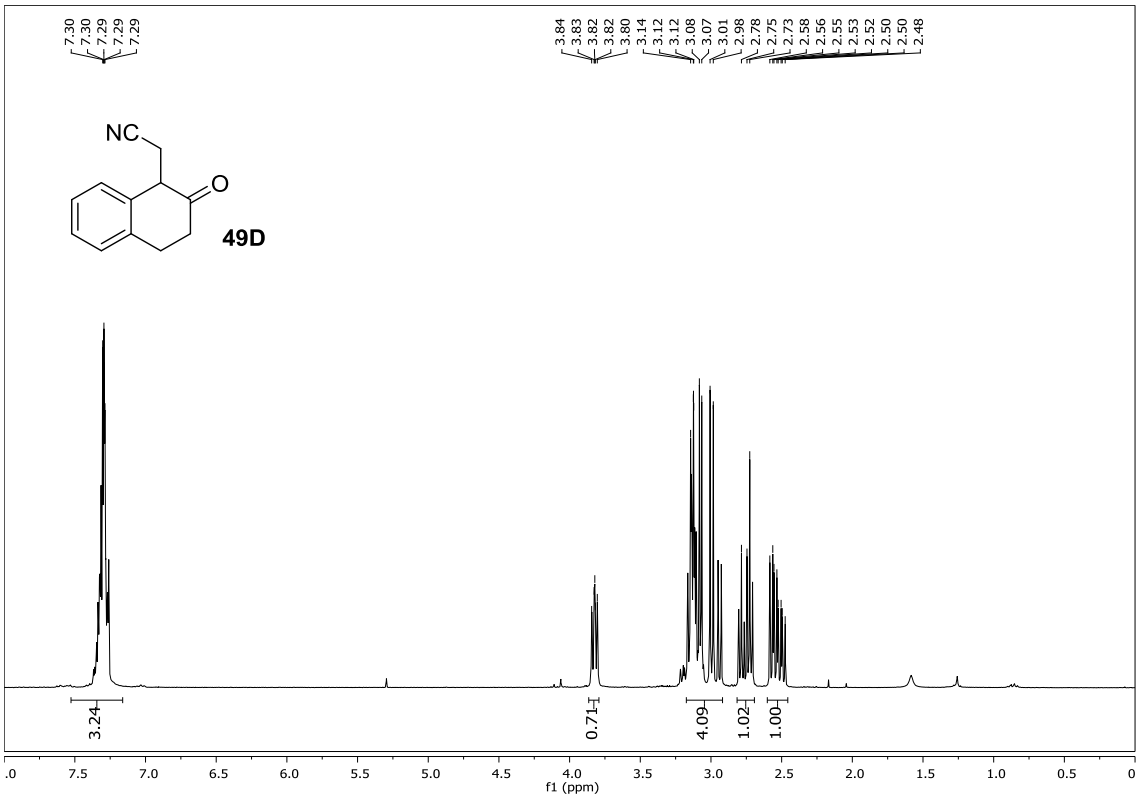
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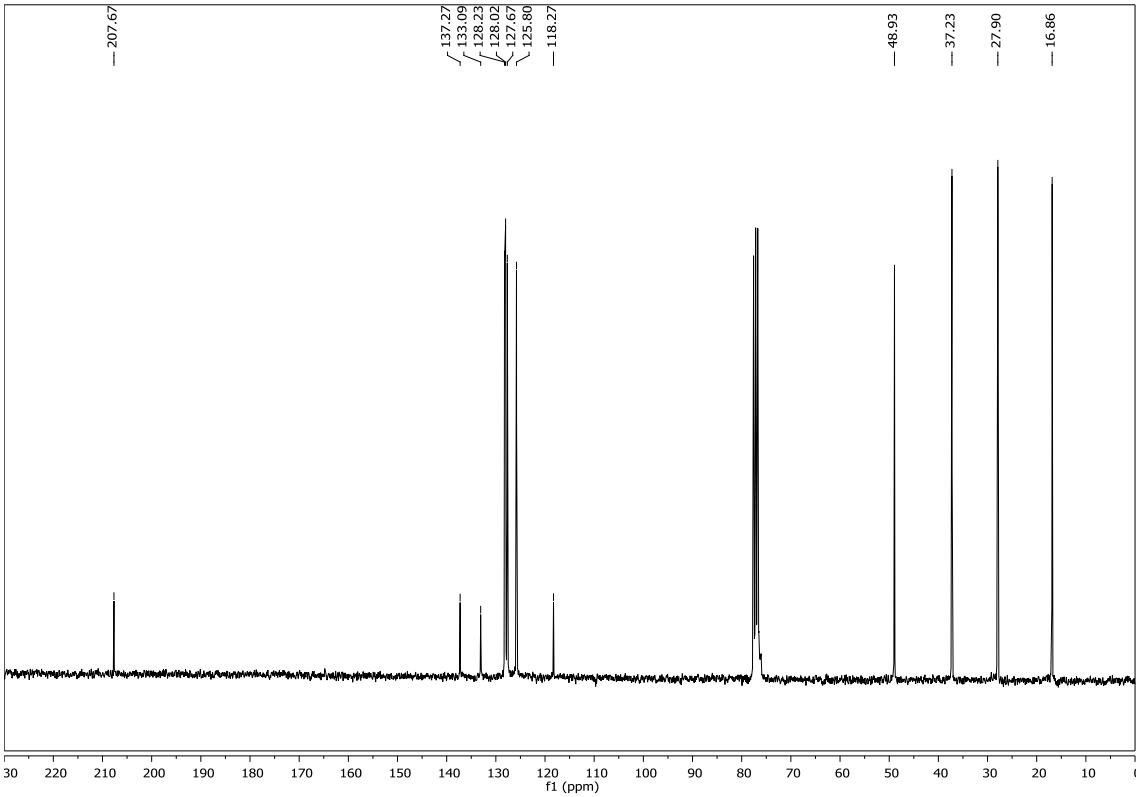
f1 (ppm)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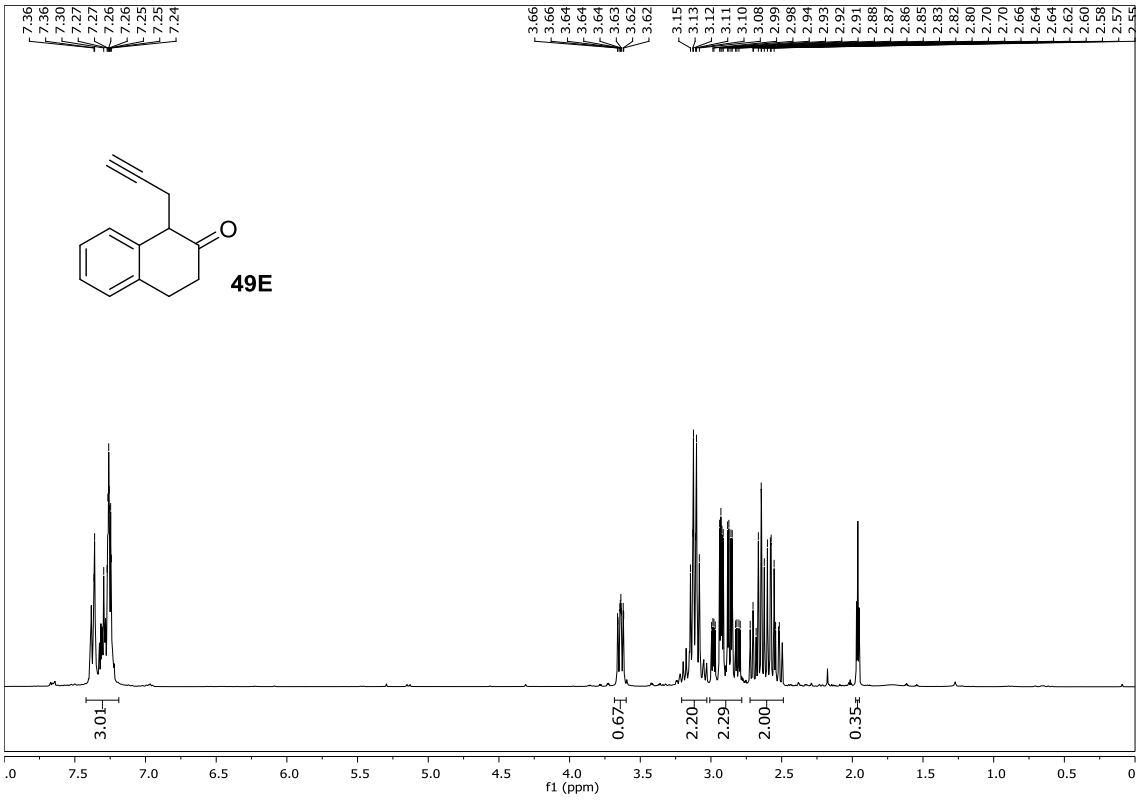
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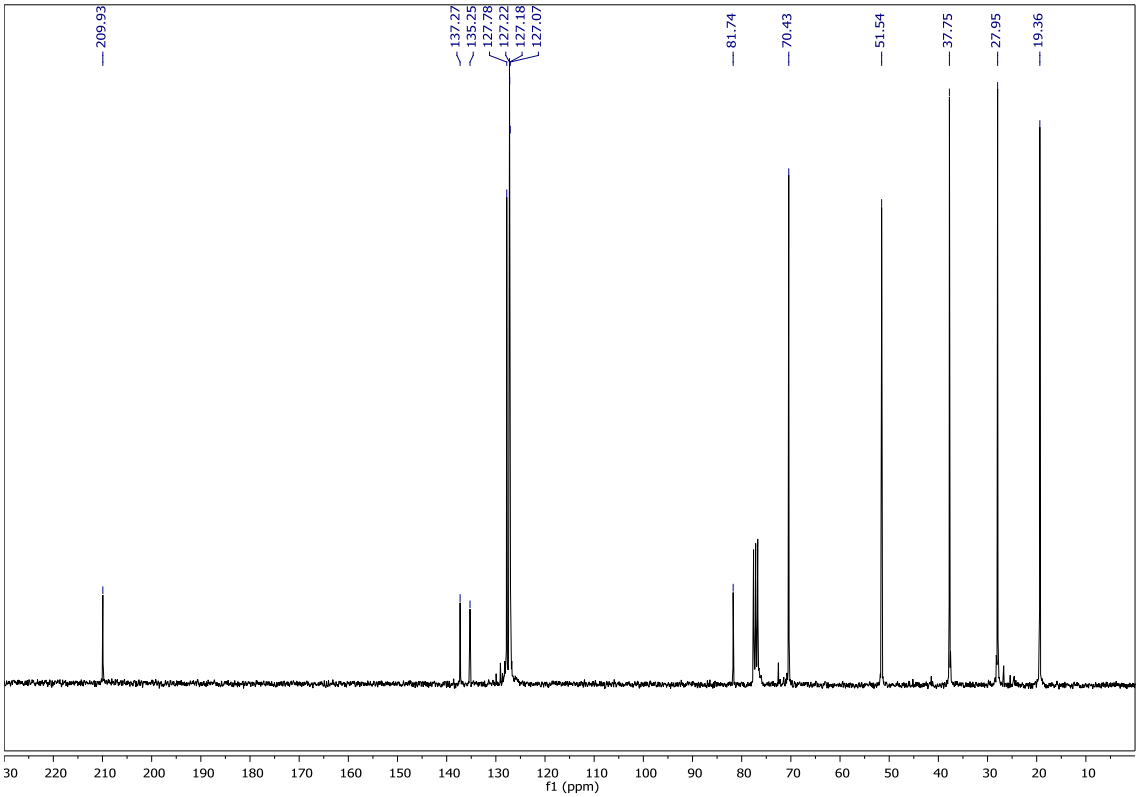
f1 (ppm)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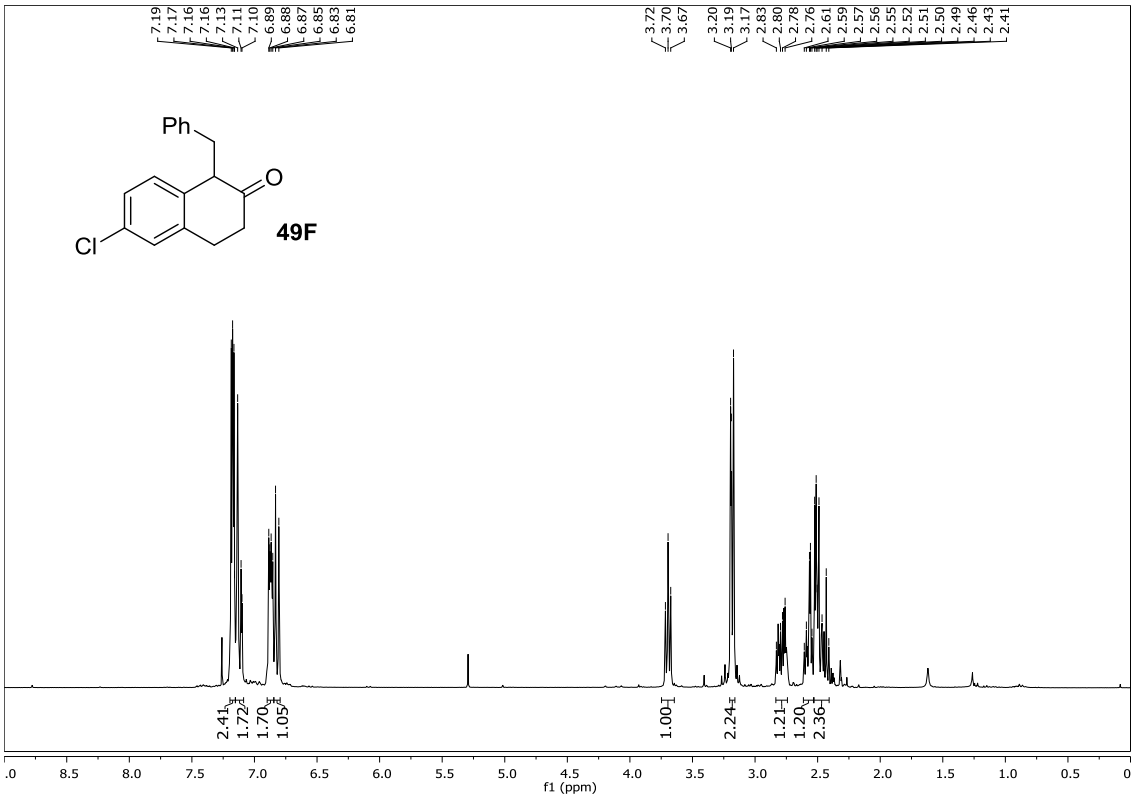
19.36
f1 (ppm)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6.81
3.72
3.70
3.67
3.20
3.19
3.17
2.83
2.80
2.78
2.76
2.61
2.59
2.57
2.56
2.55
2.52
2.51
2.50
2.49
2.46
2.43
2.41
Ph
O
Cl
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1.70
1.05
1.00
2.24
1.21
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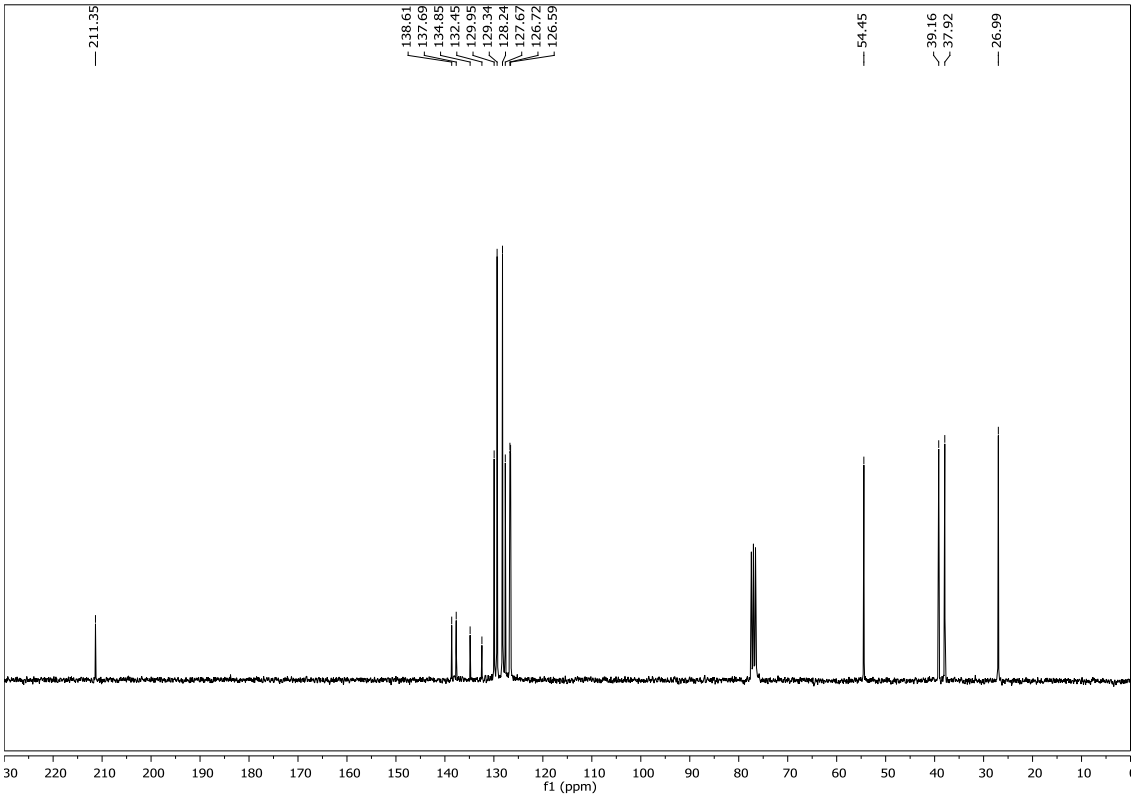
2.36
f1 (ppm)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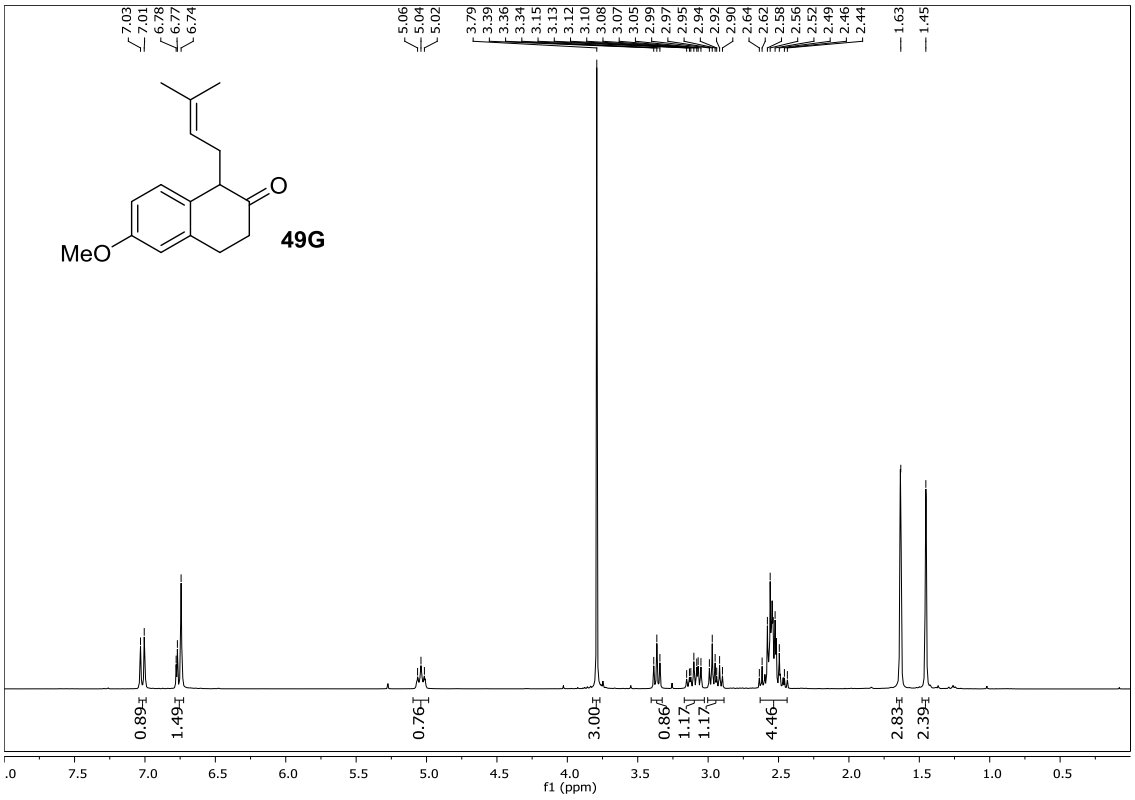
54.45
39.16
37.92
26.99
f1 (ppm)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3.08
3.07
3.05
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2.97
2.95
2.94
2.92
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2.64
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2.58
2.56
2.52
2.49
2.46
2.44
1.63
1.45
O
MeO
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4.46
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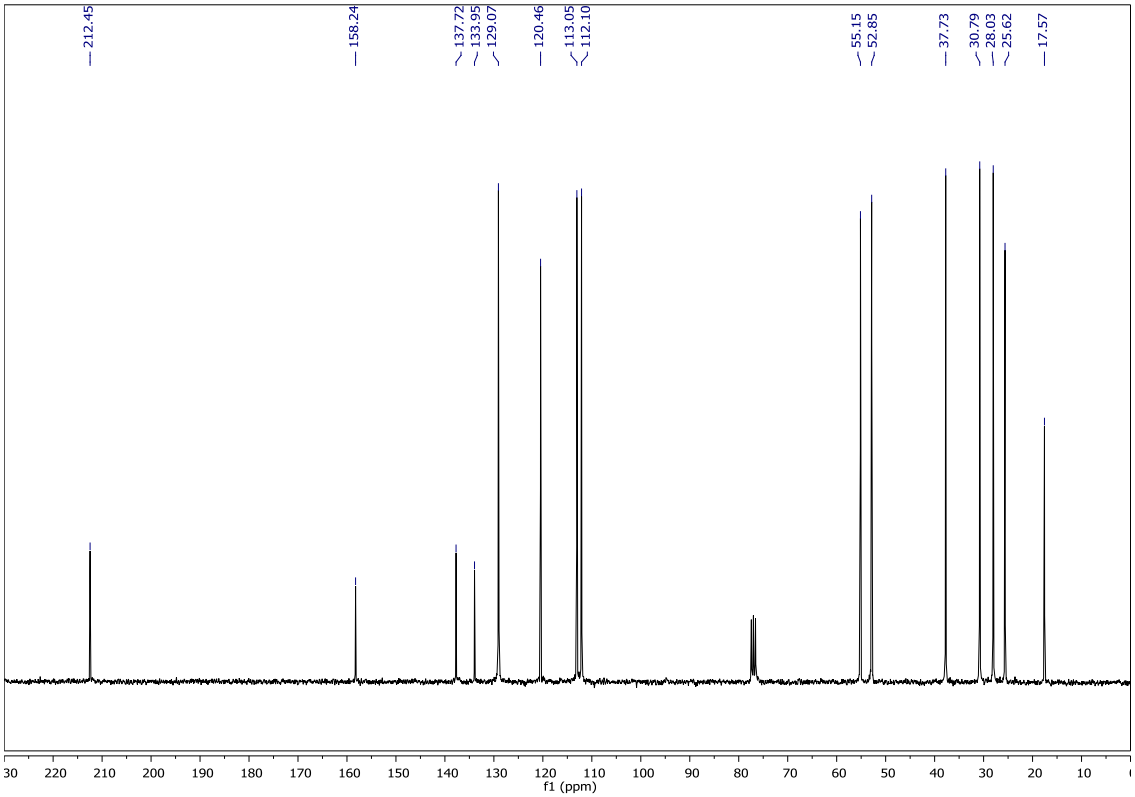
f1 (ppm)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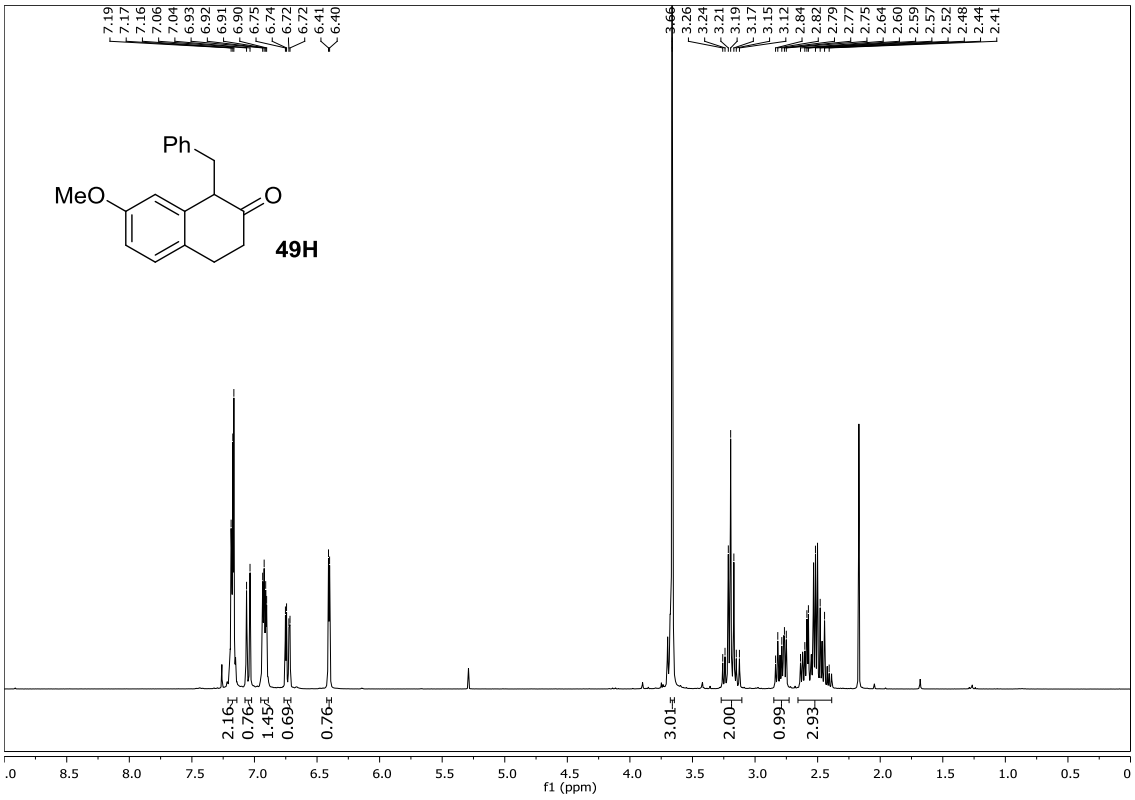
17.57
f1 (ppm)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2.59
2.57
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2.48
2.44
2.41
Ph
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2.00
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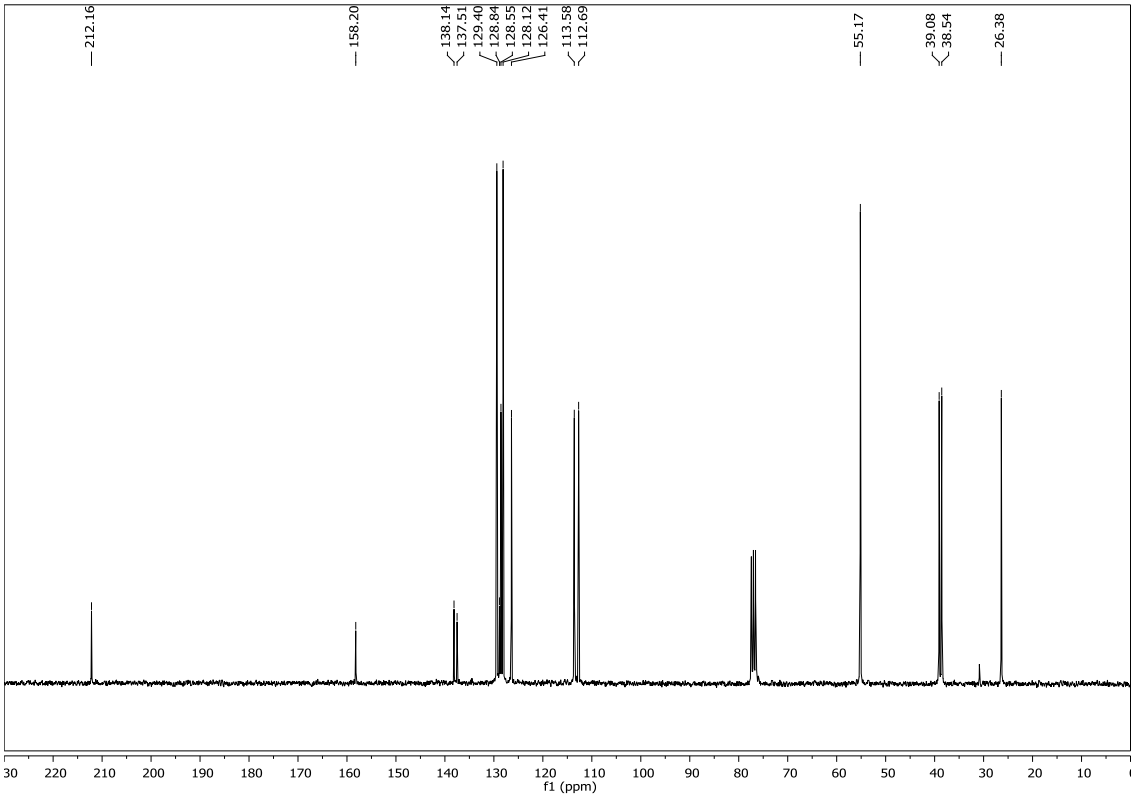
2.93
f1 (ppm)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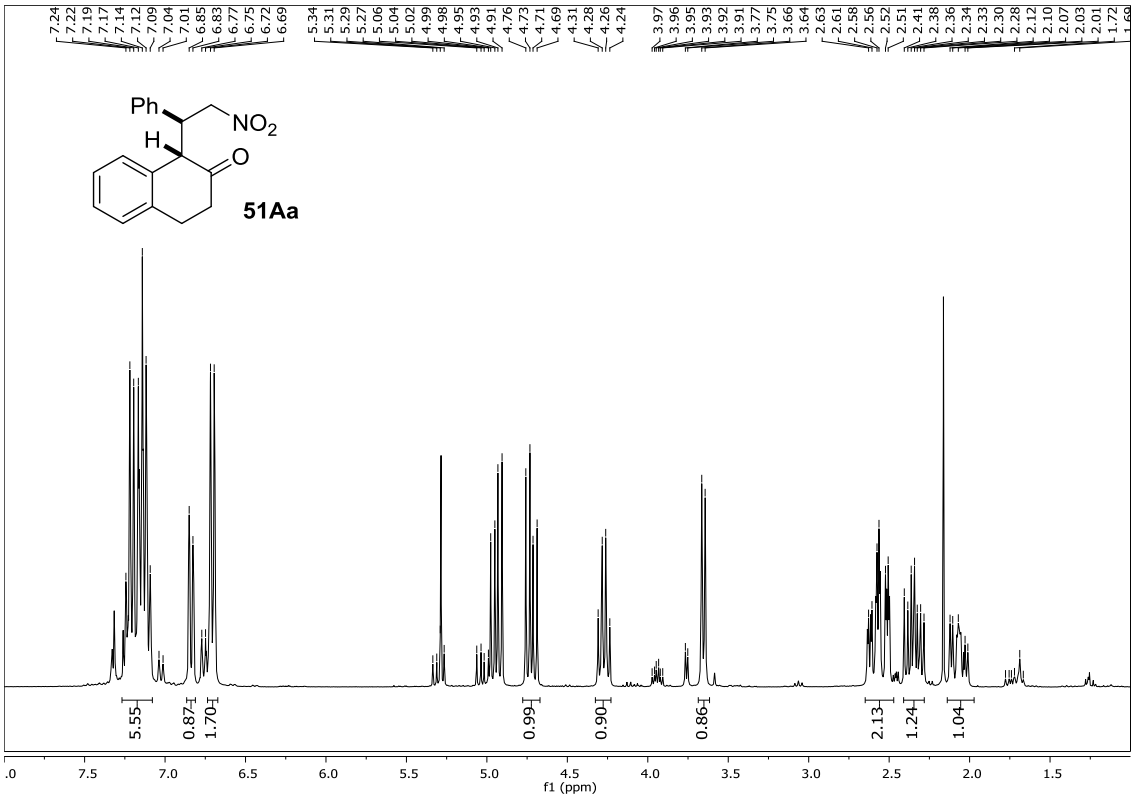
112.69
55.17
39.08
38.54
26.38
f1 (ppm)


Ph
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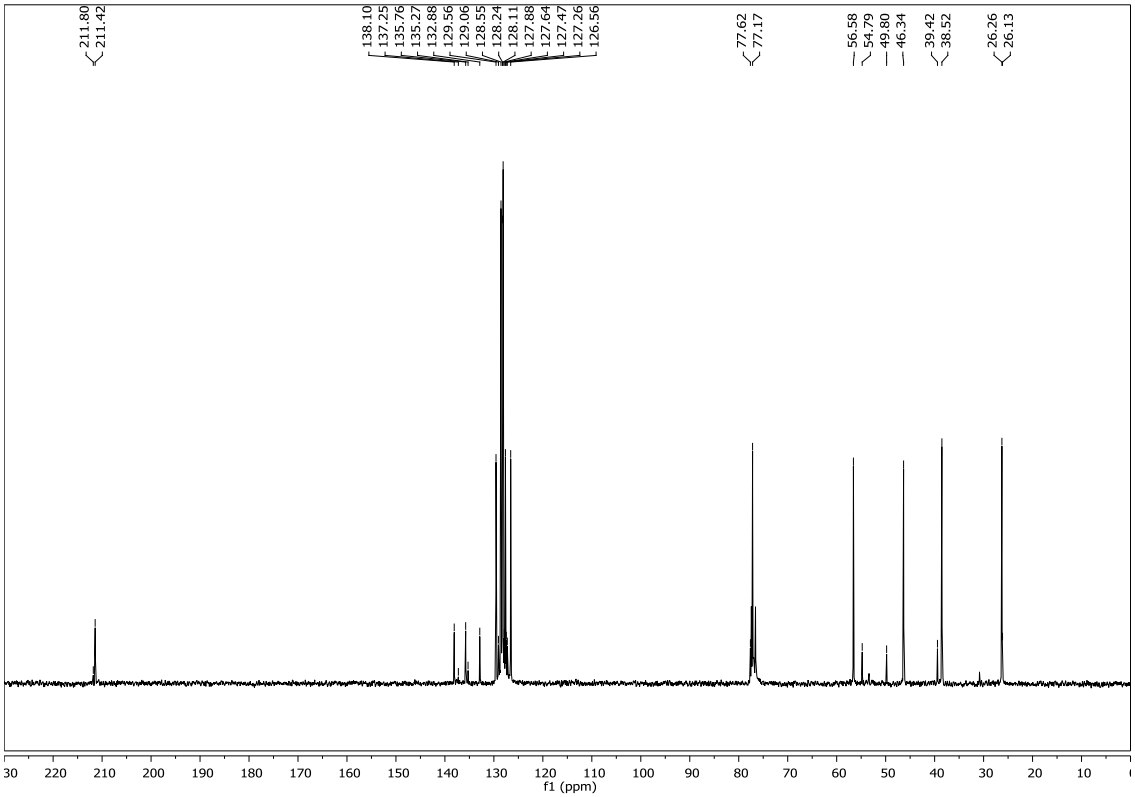
H
O
51Aa
f1 (ppm)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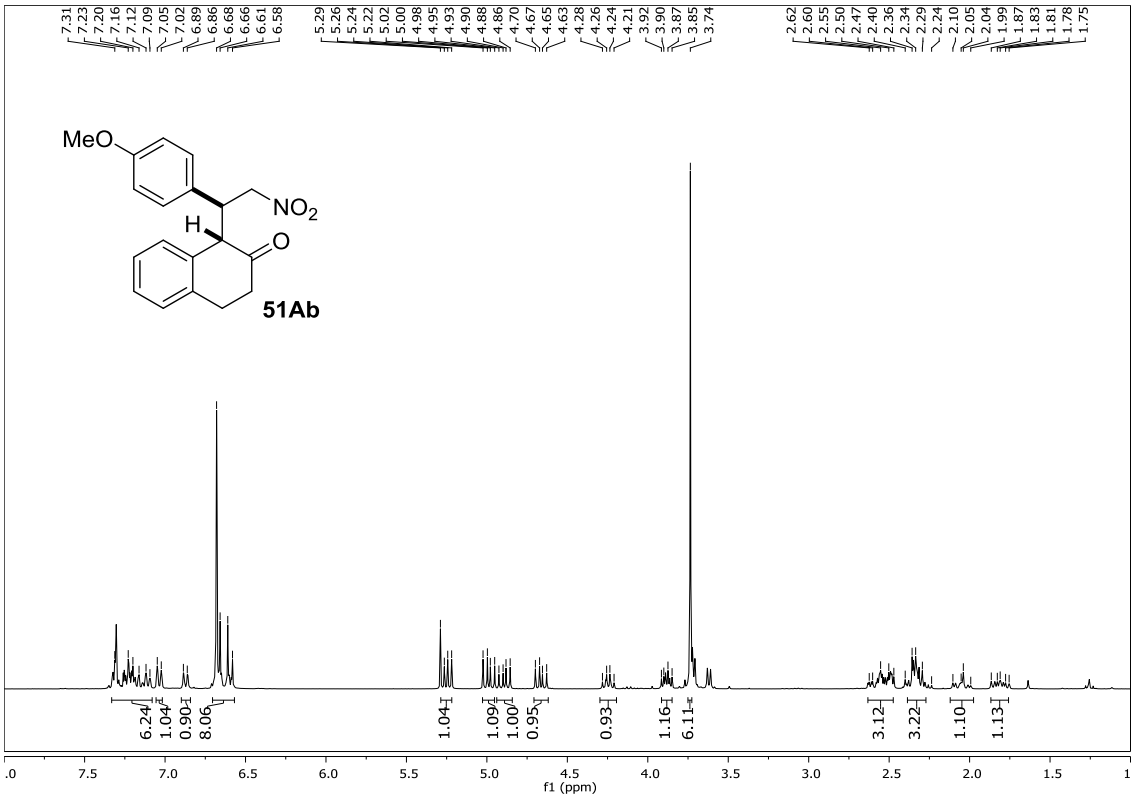
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NO2
H
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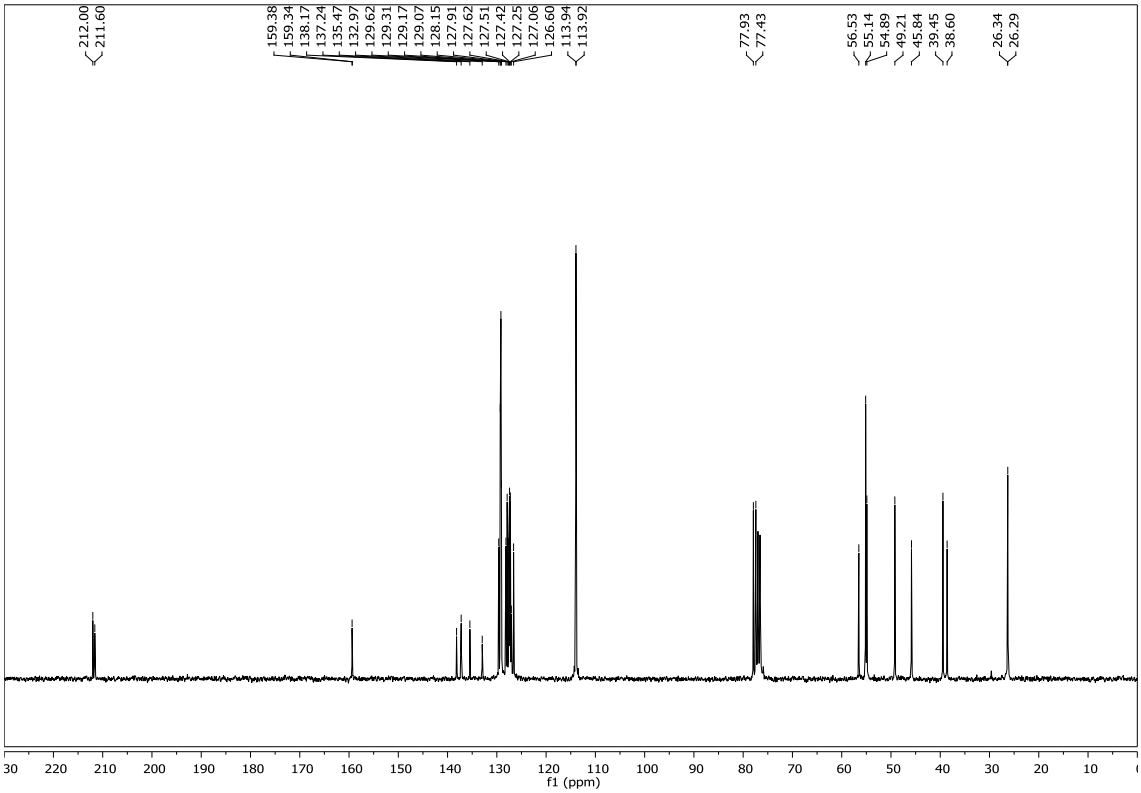
f1 (ppm)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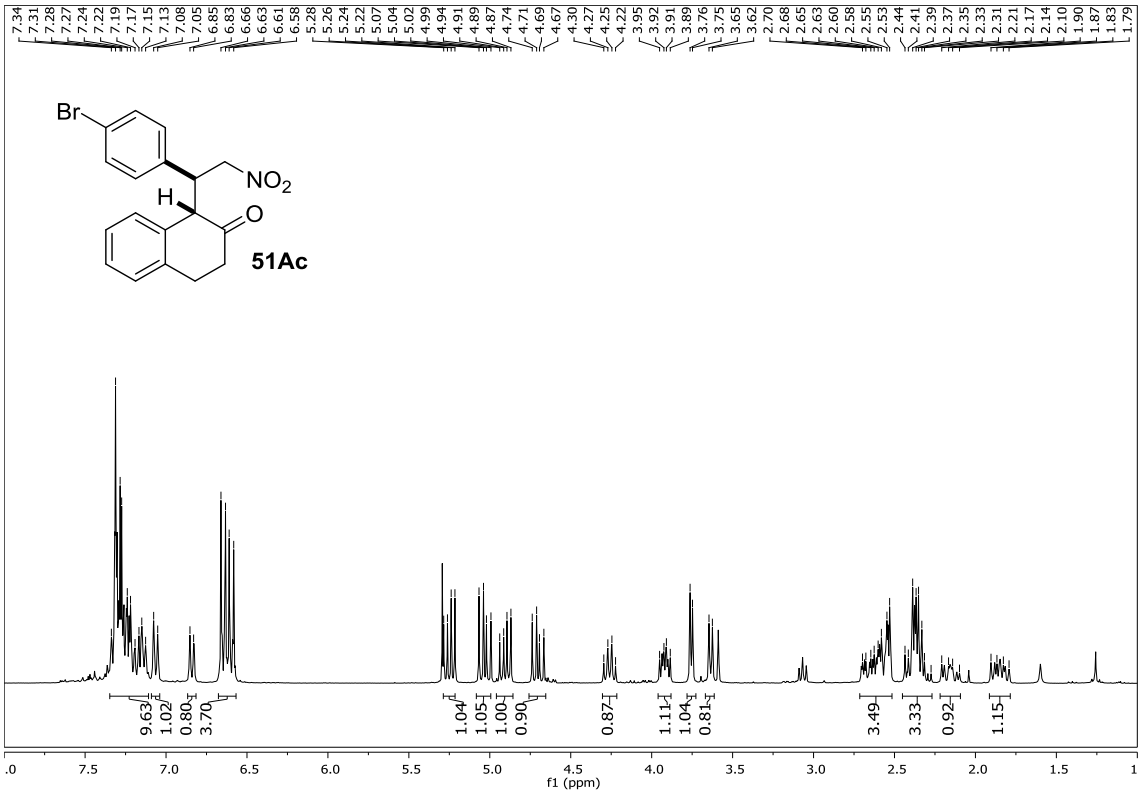
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NO2
H
O
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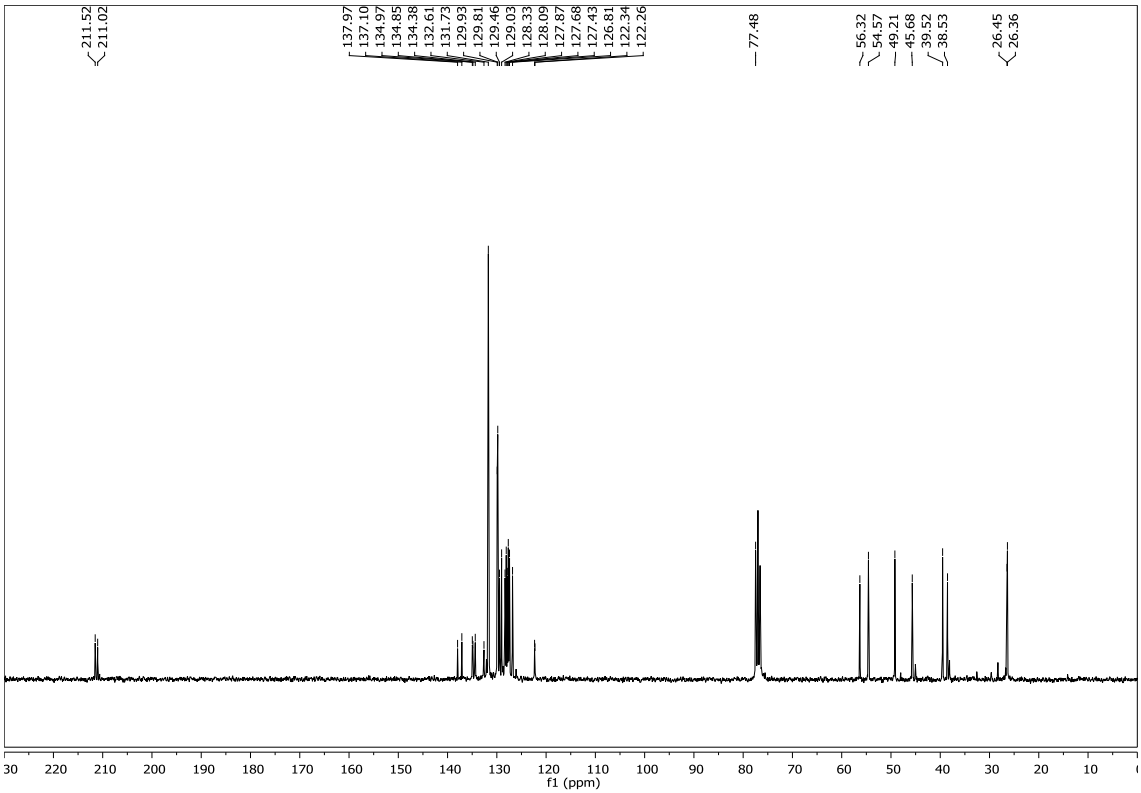
f1 (ppm)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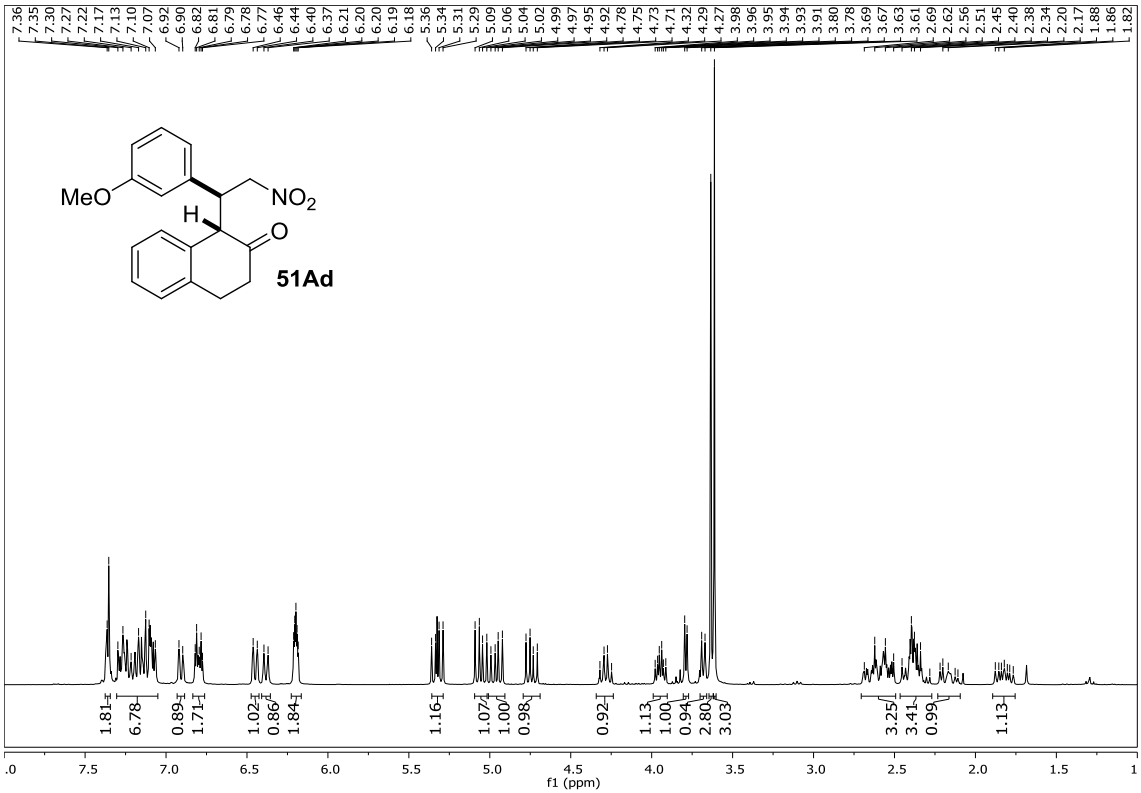
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O
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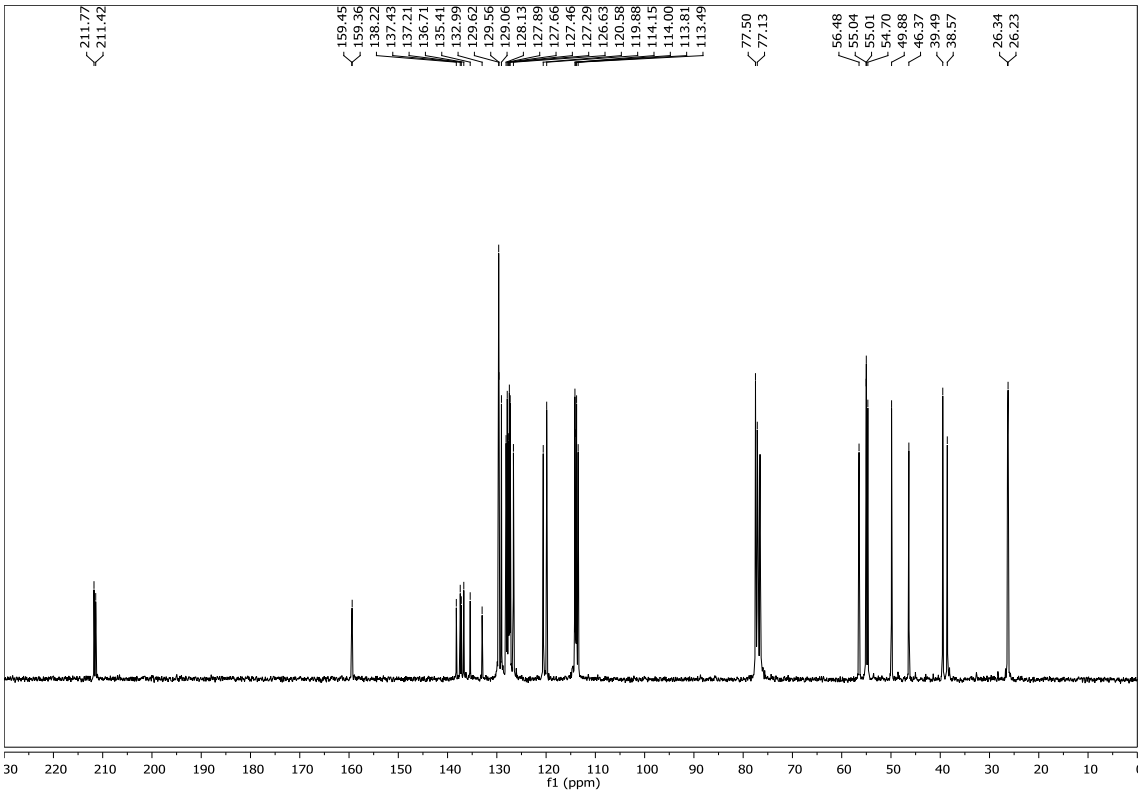
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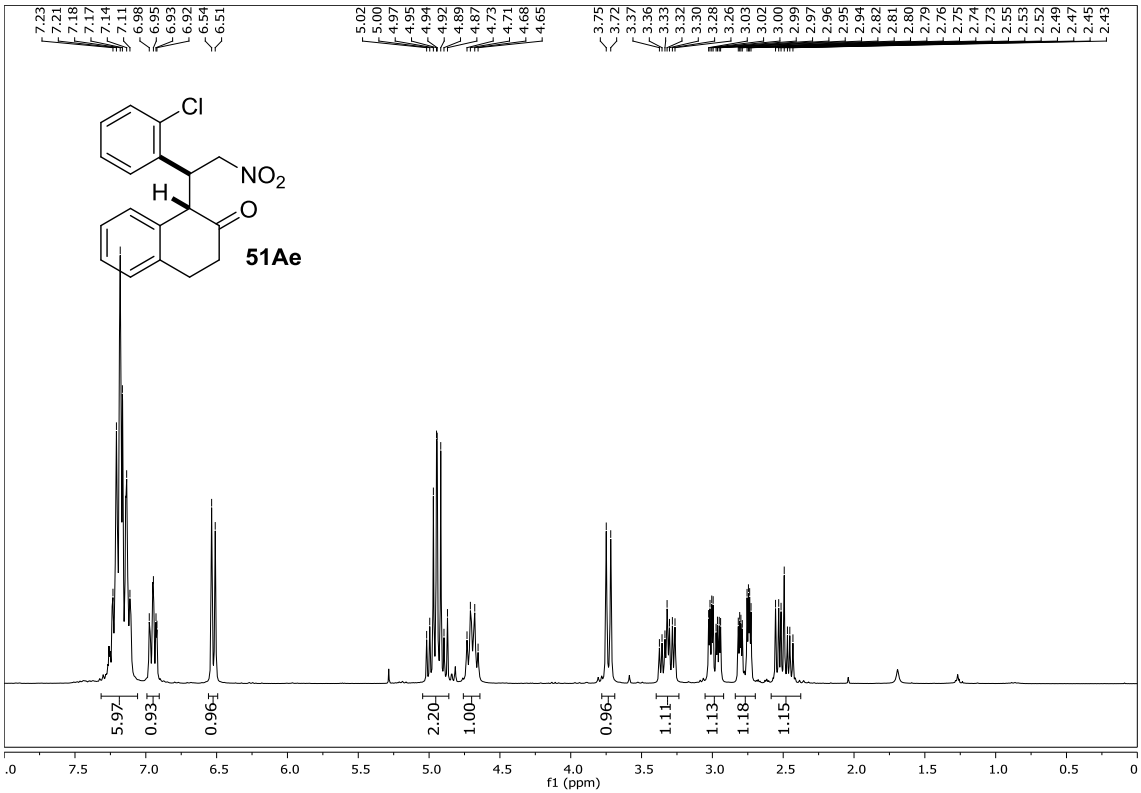
Cl
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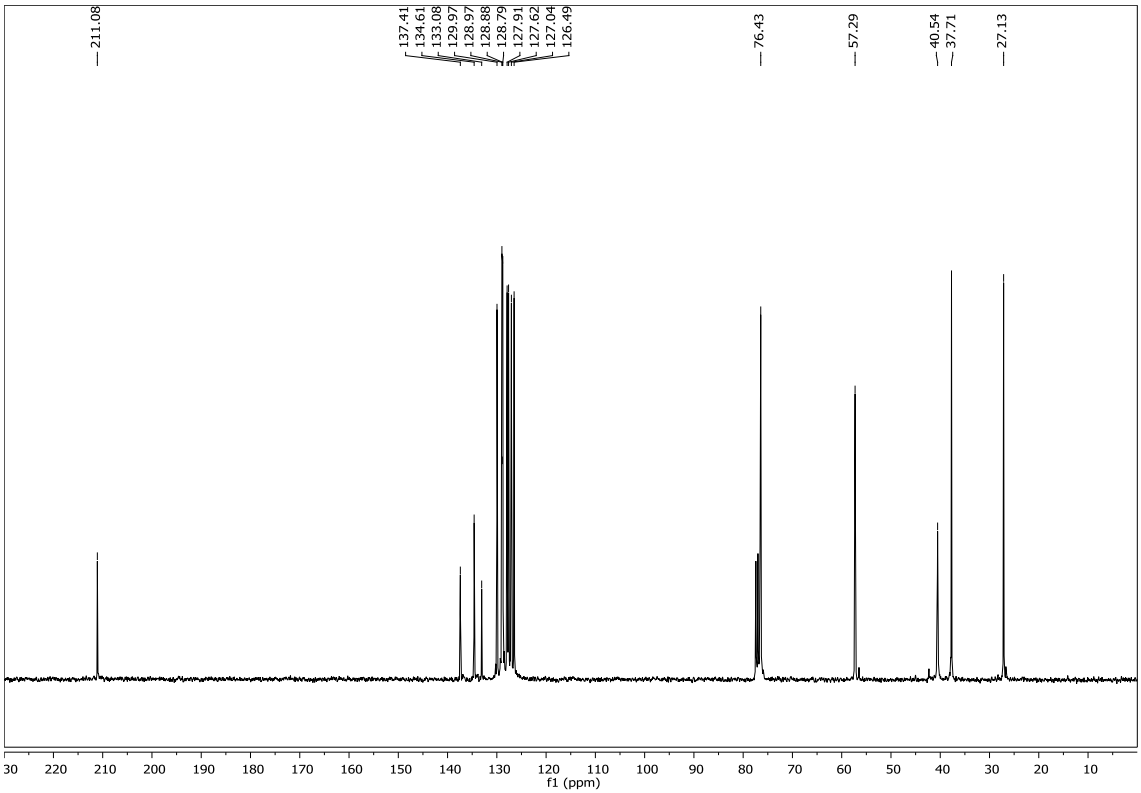
f1 (ppm)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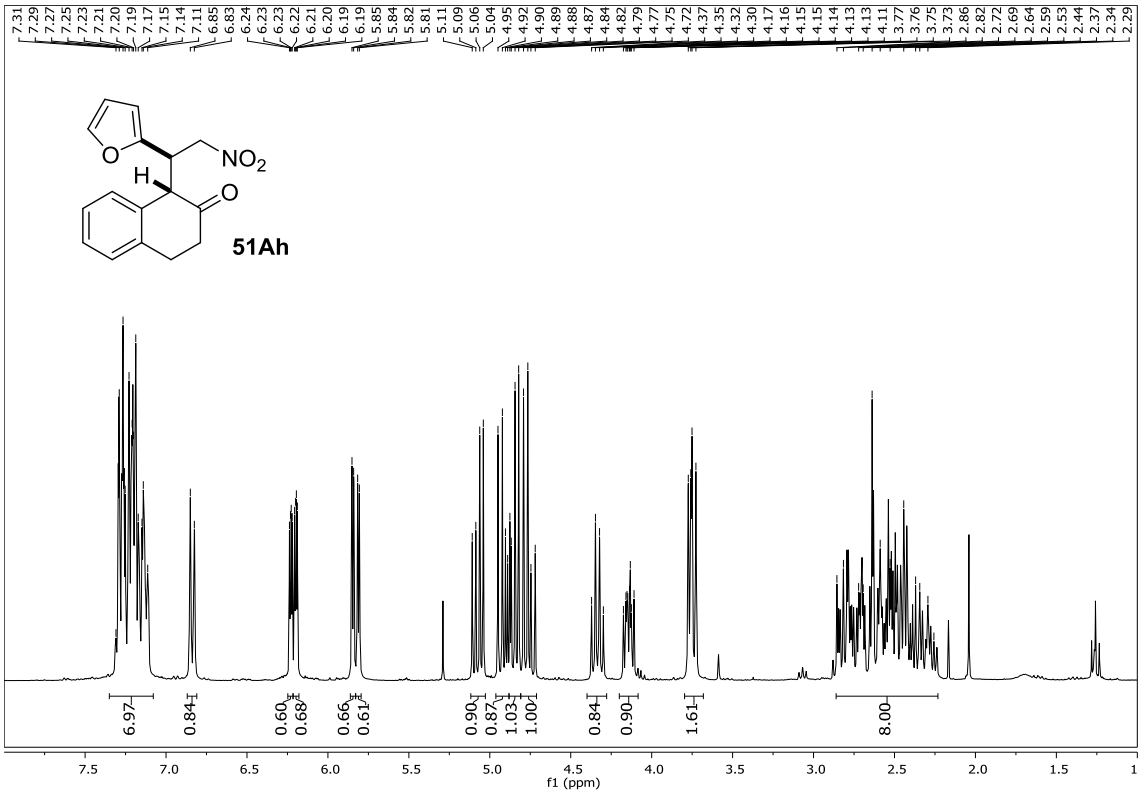
40.54
37.71
27.13
f1 (ppm)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O
H
NO2
O
51Ah
6.97
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0.60
0.68
0.66
0.61
0.90
0.87
1.03
1.00
0.84
0.90
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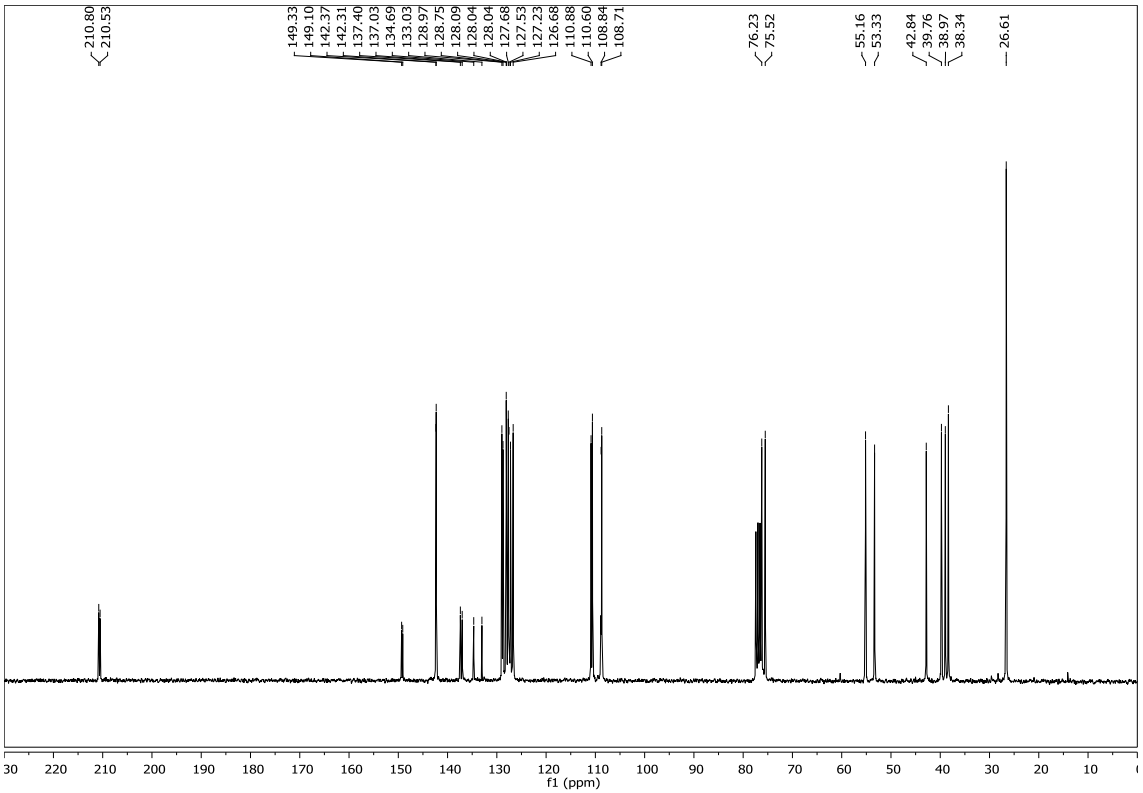
f1 (ppm)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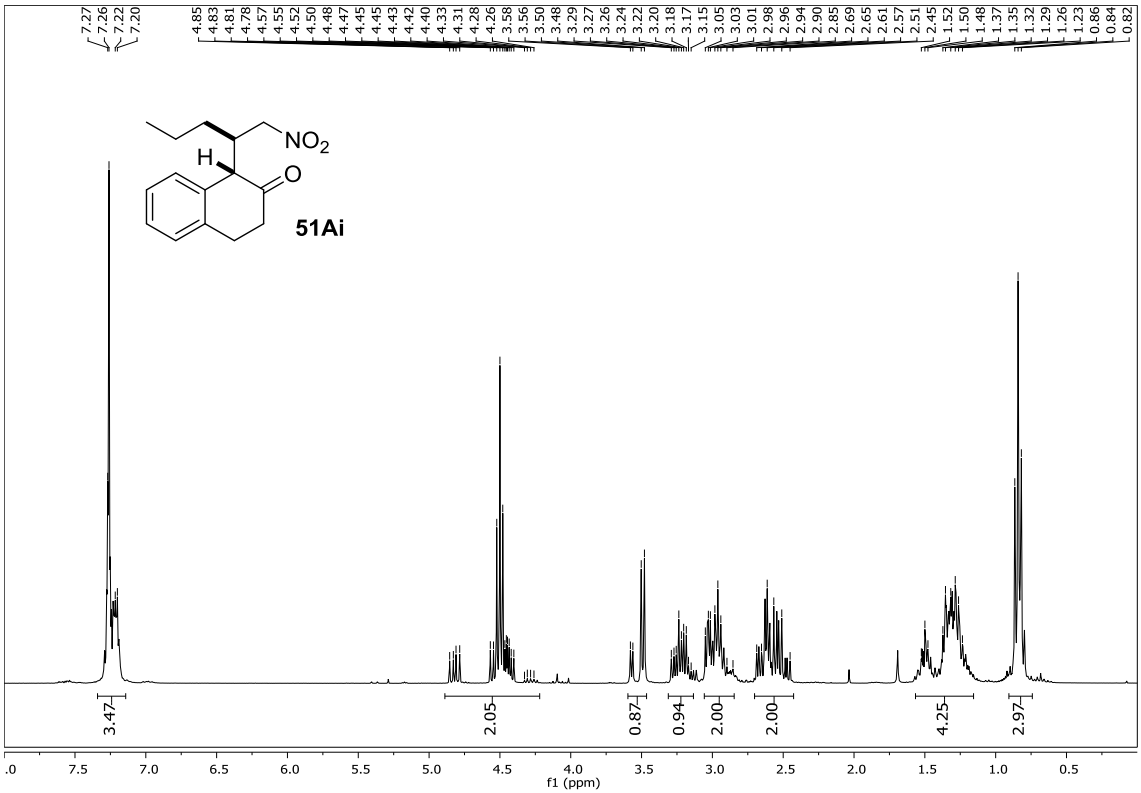
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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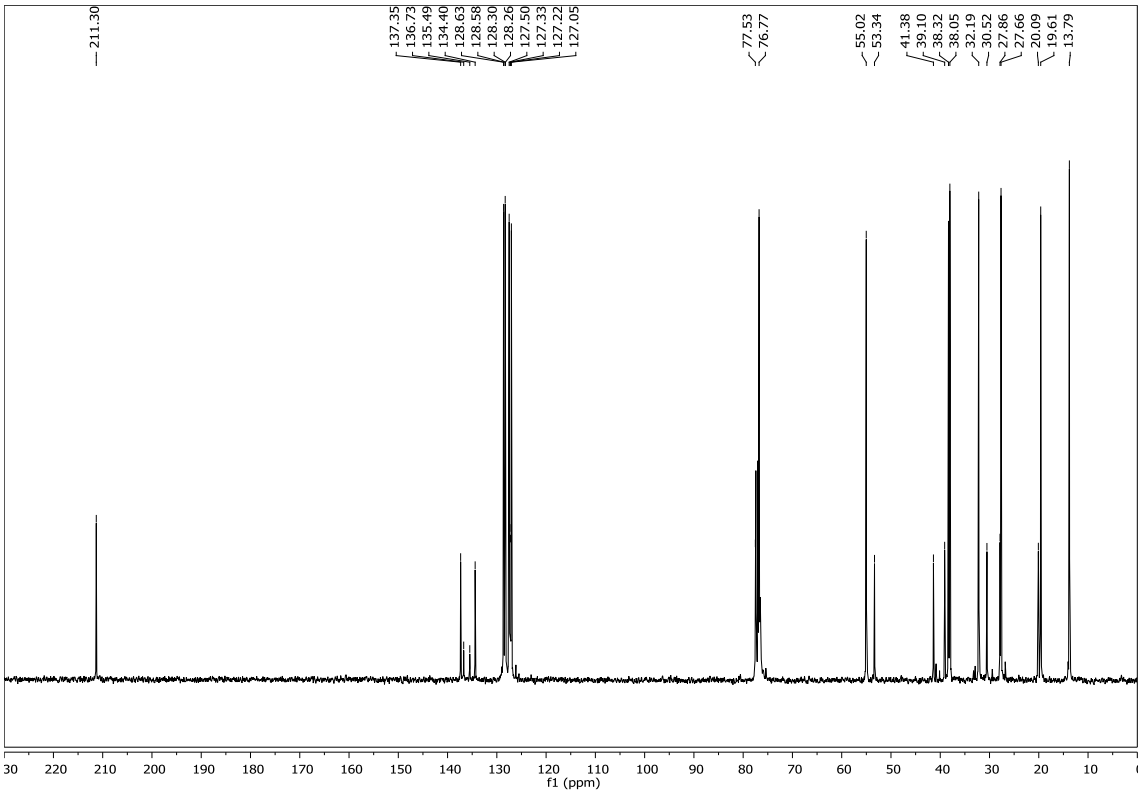
H
O
51Ai
f1 (ppm)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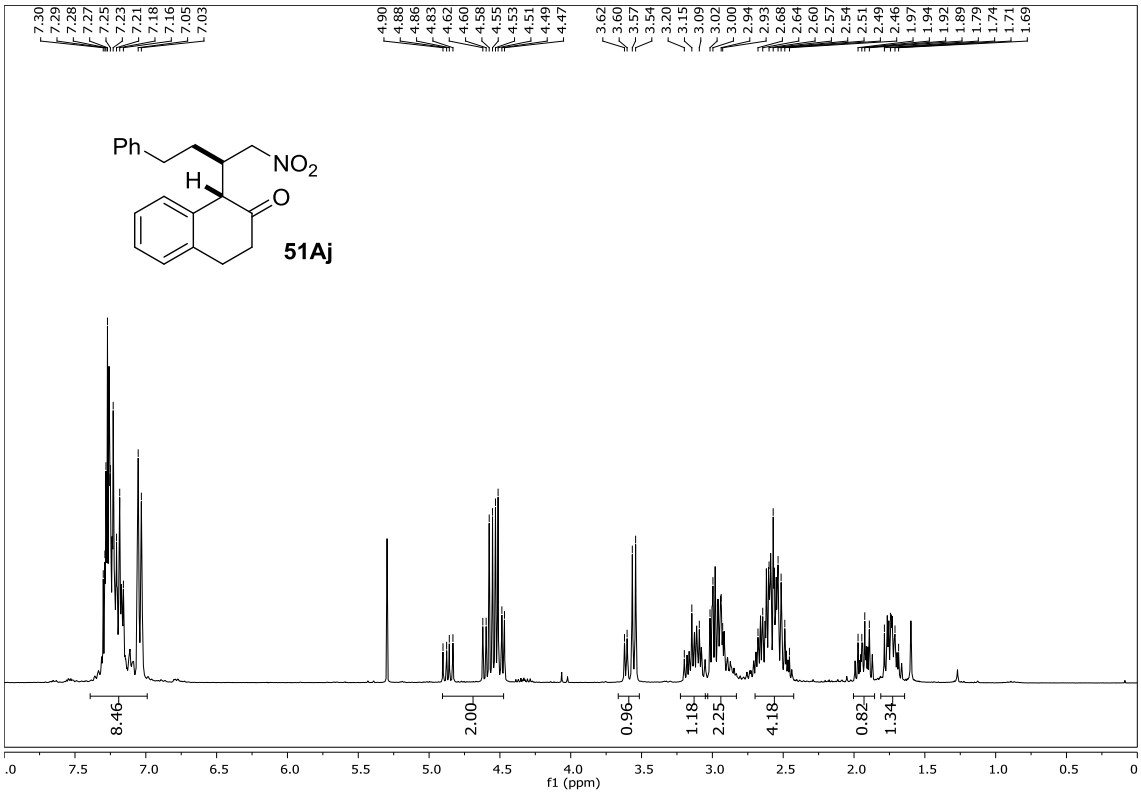
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4.62
4.60
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4.51
4.49
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3.60
3.57
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3.09
3.02
3.00
2.94
2.93
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2.54
2.51
2.49
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1.97
1.94
1.92
1.89
1.79
1.74
1.71
1.69
Ph
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H
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4.18
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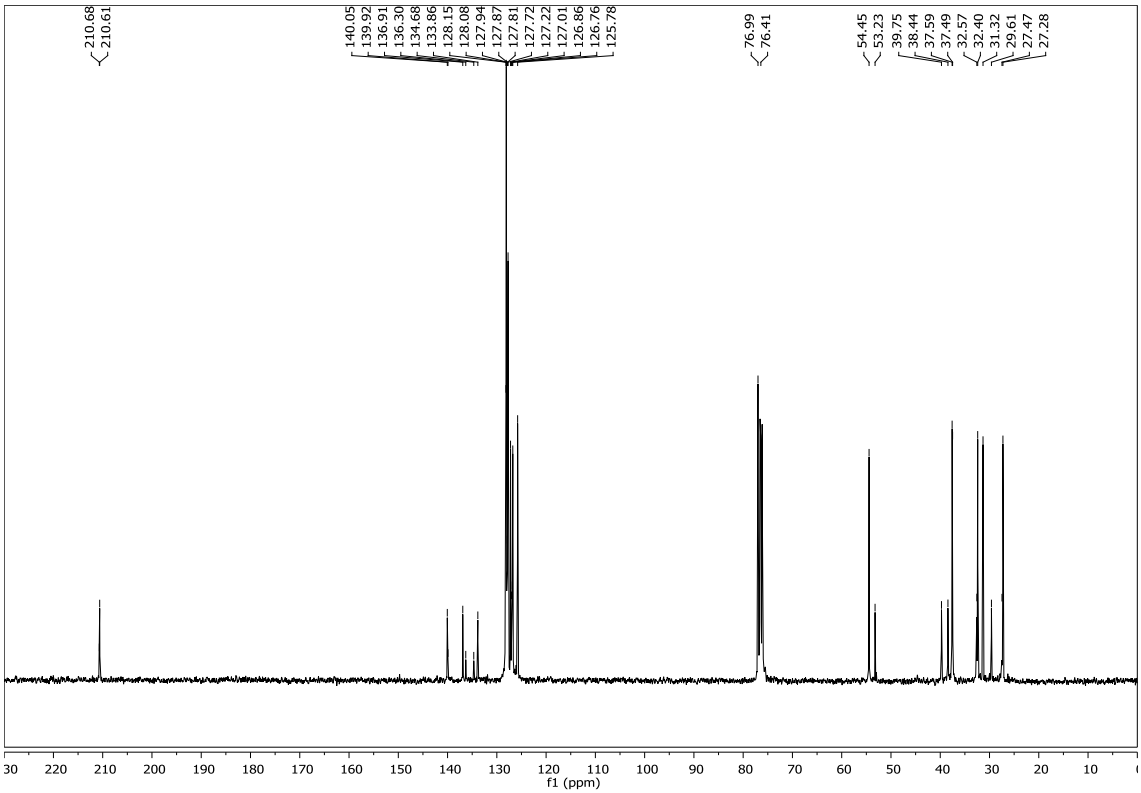
1.34
f1 (ppm)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127.81
127.72
127.22
127.01
126.86
126.76
125.78
76.99
76.41
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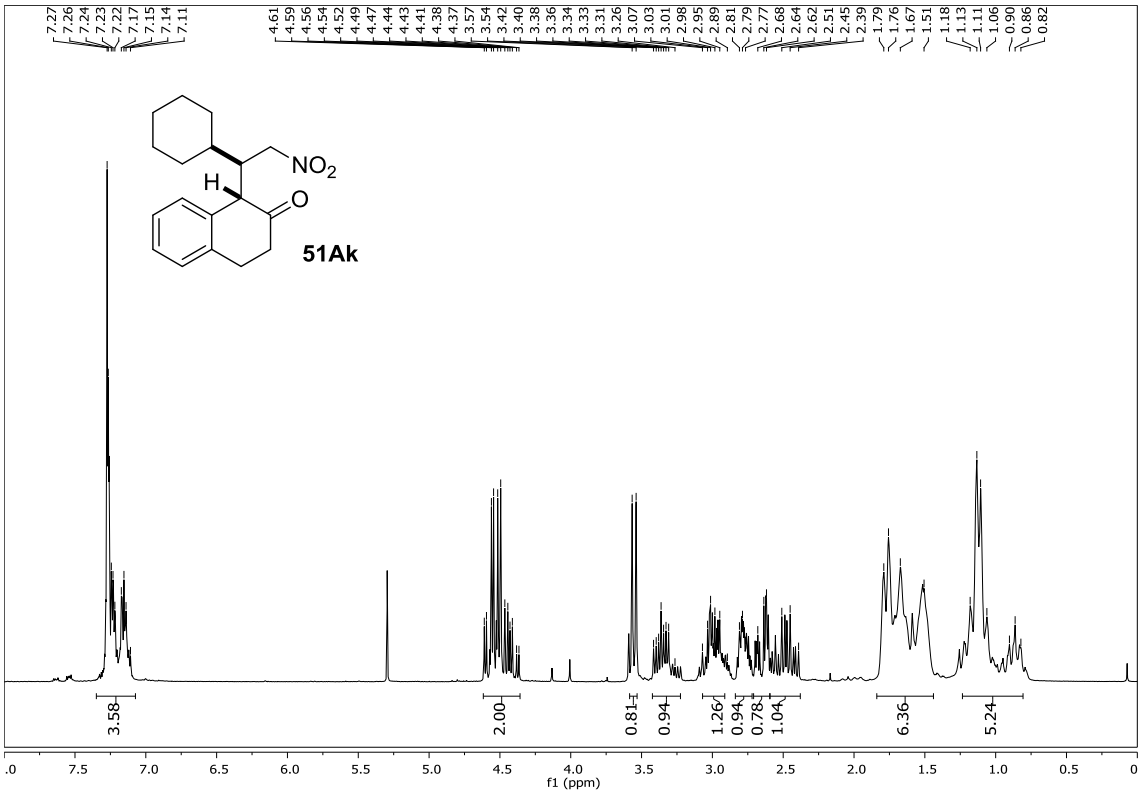
27.28
f1 (ppm)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O
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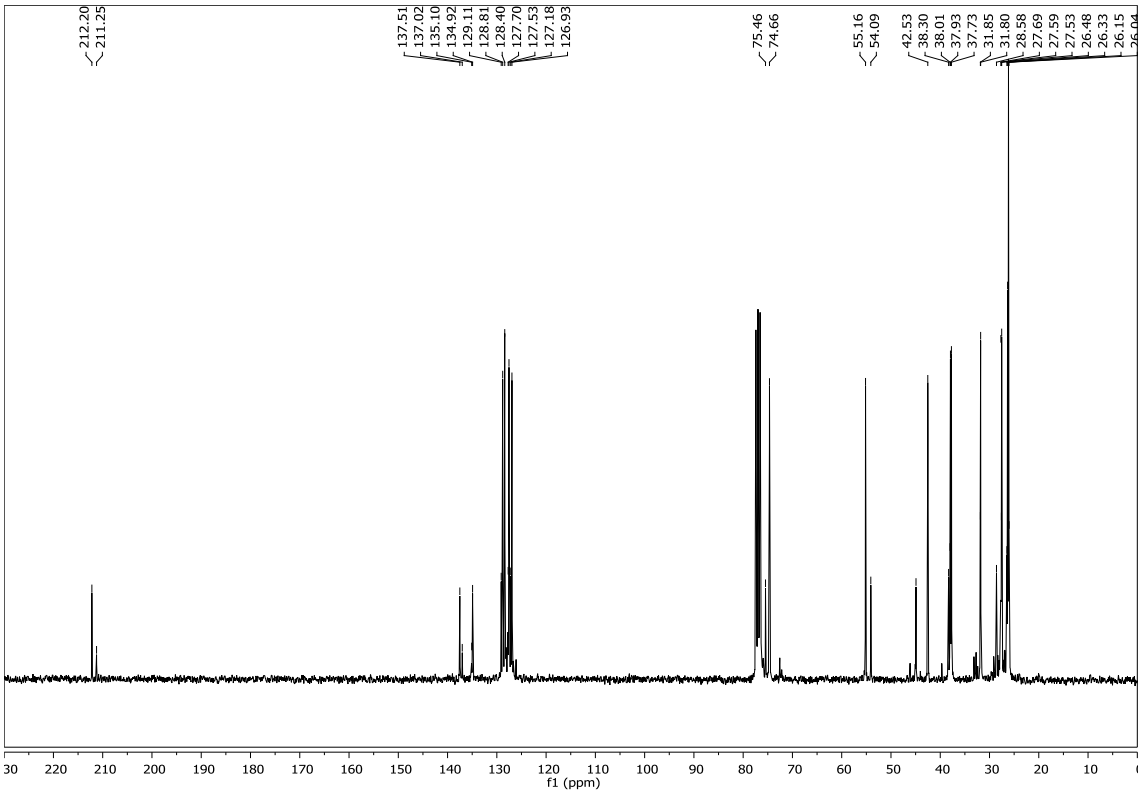
0.94
0.78
1.04
6.36
5.24
f1 (ppm)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74.66
55.16
54.09
42.53
38.30
38.01
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27.53
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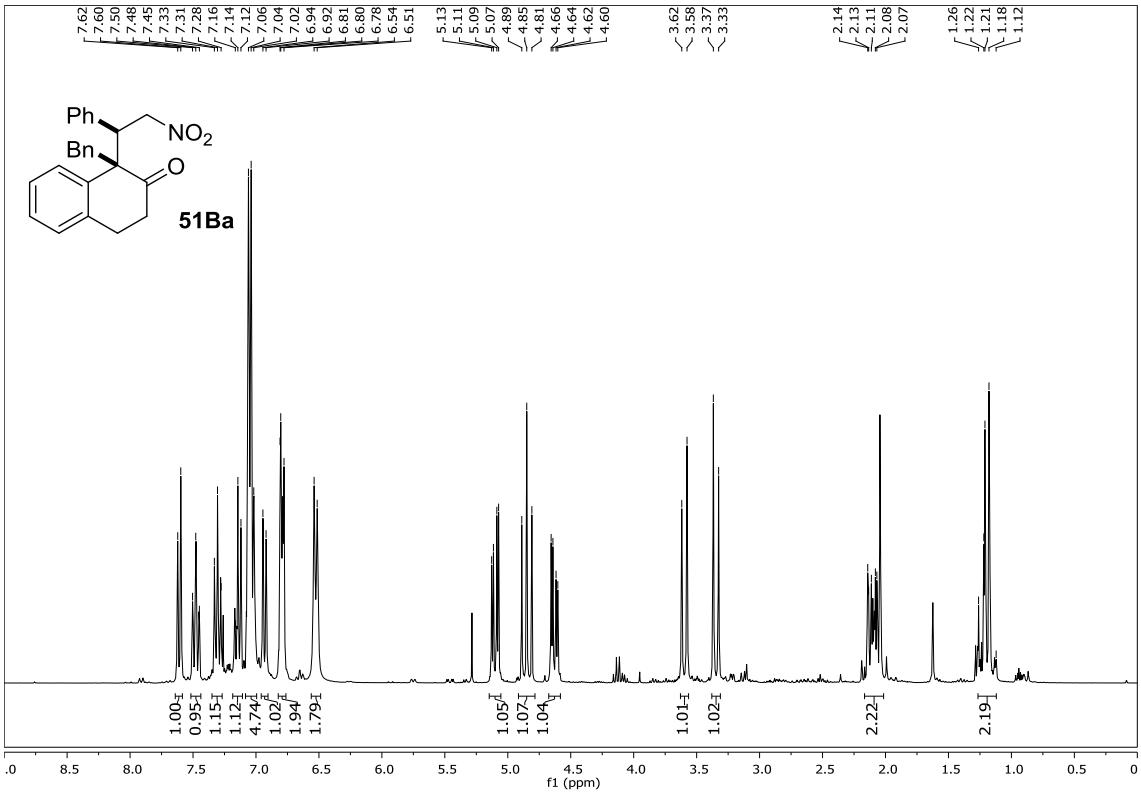
26.15
f1 (ppm)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O
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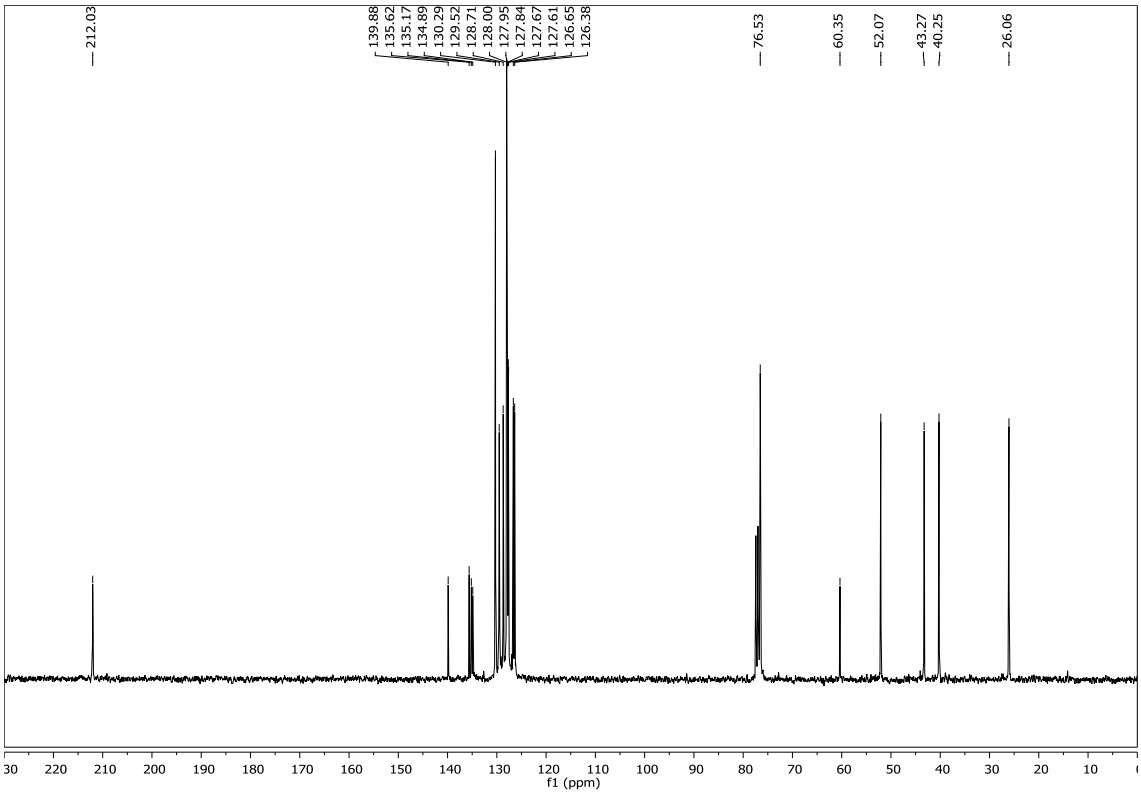
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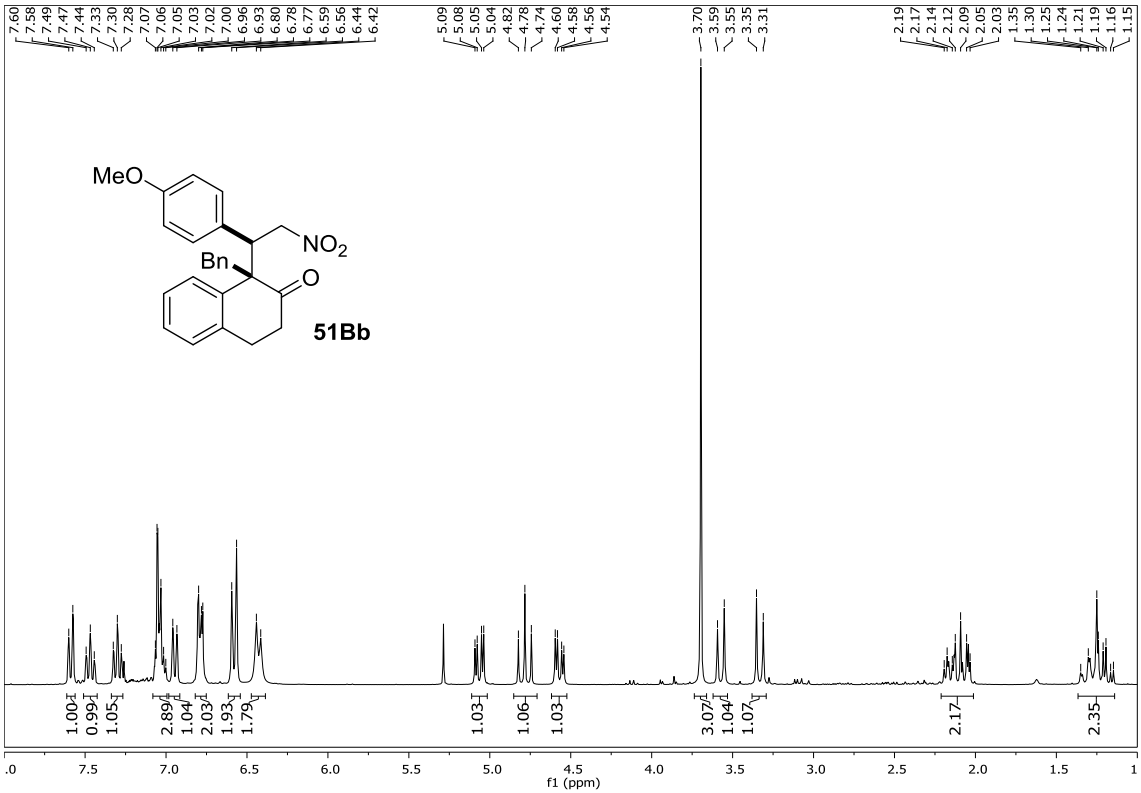
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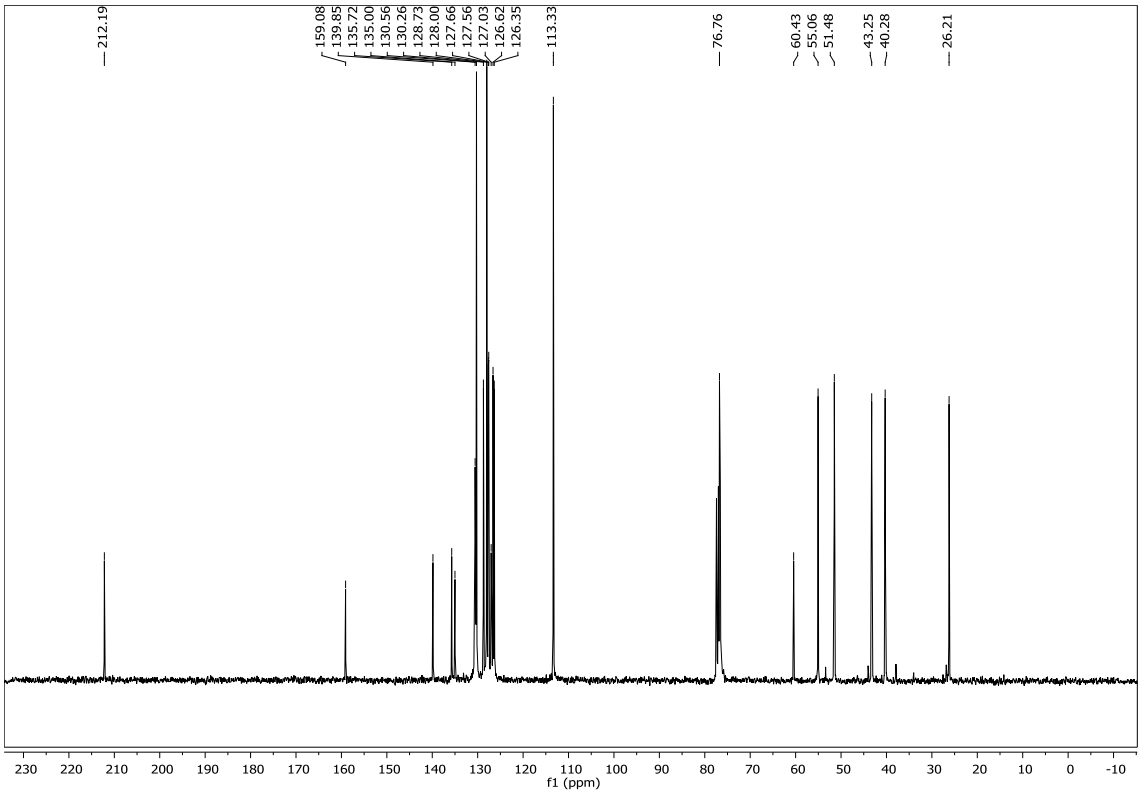
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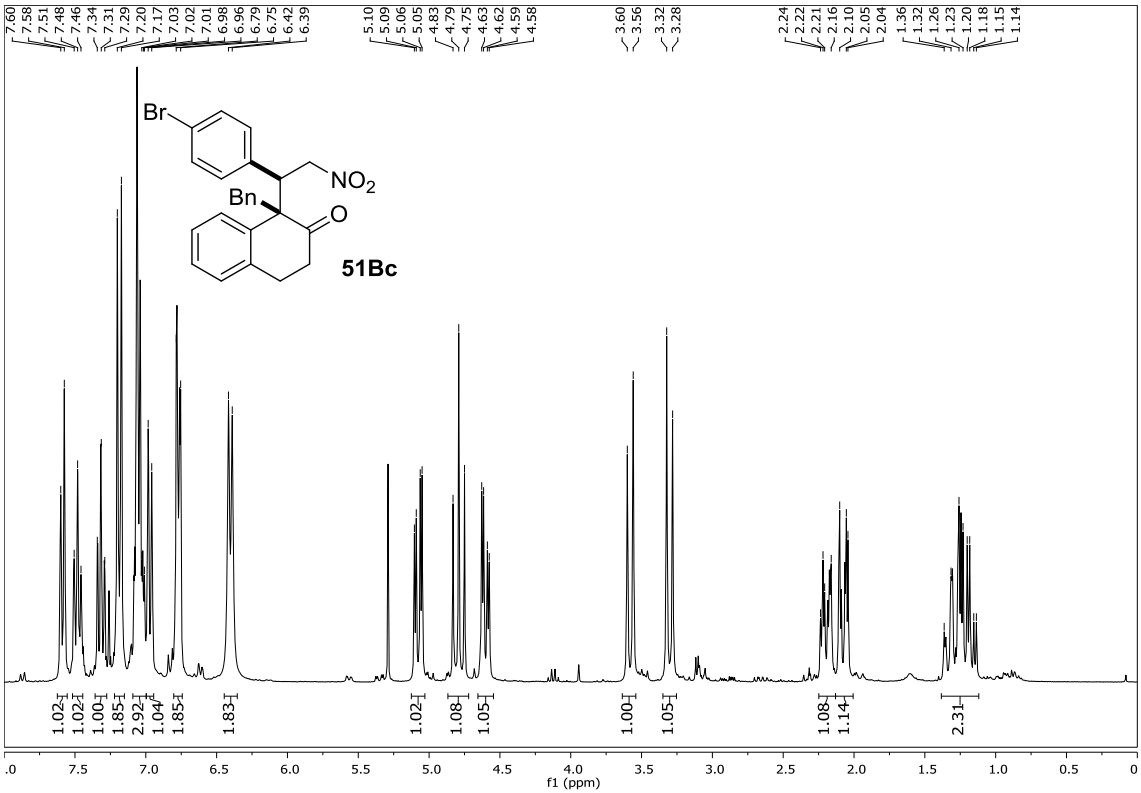
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O
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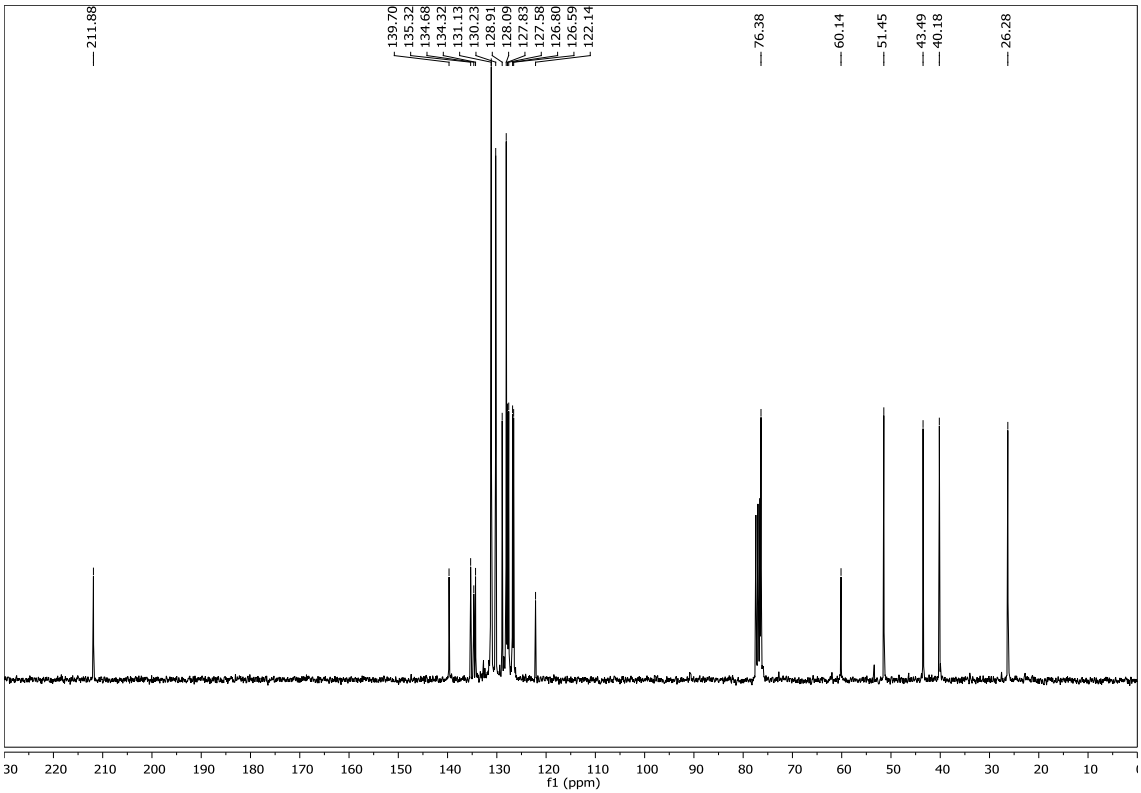
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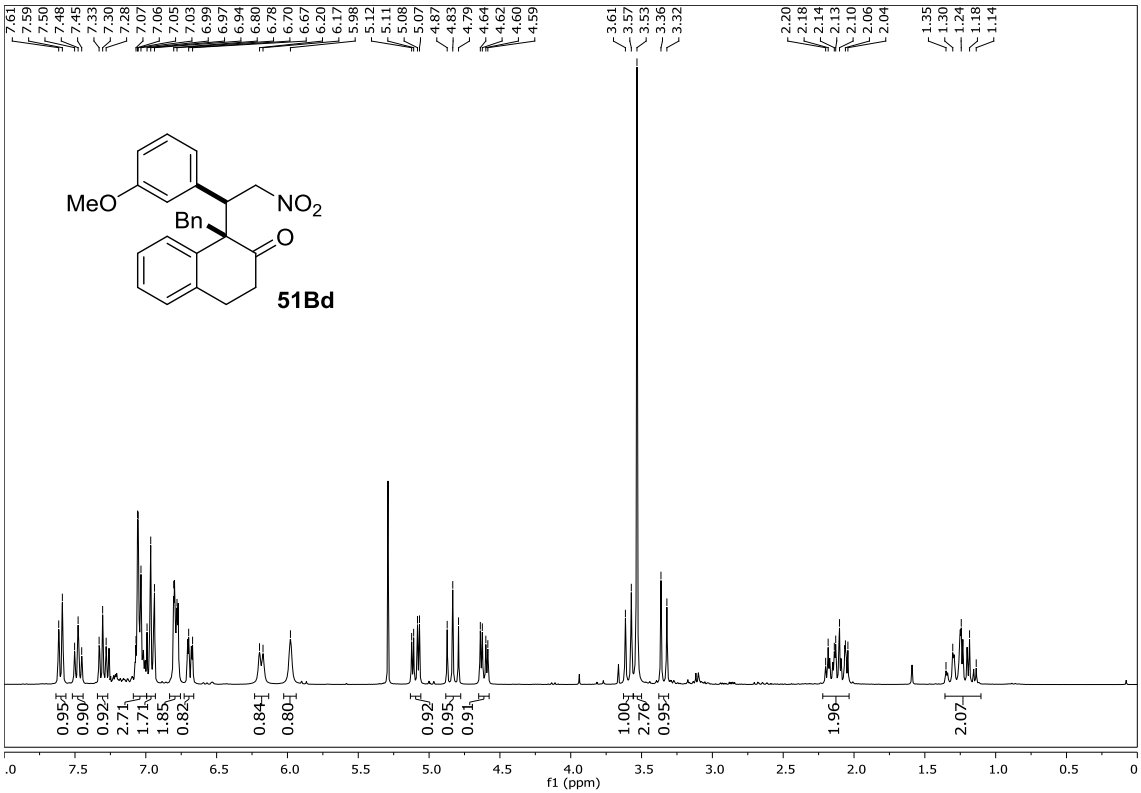
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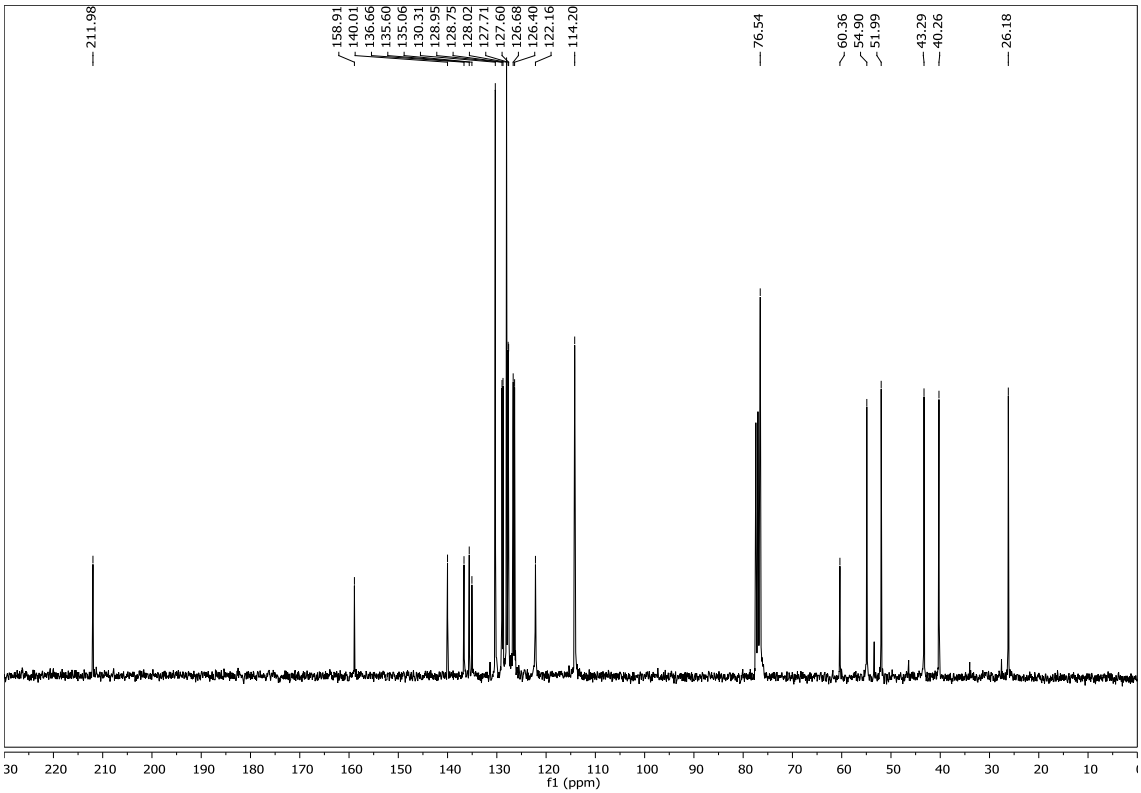
f1 (ppm)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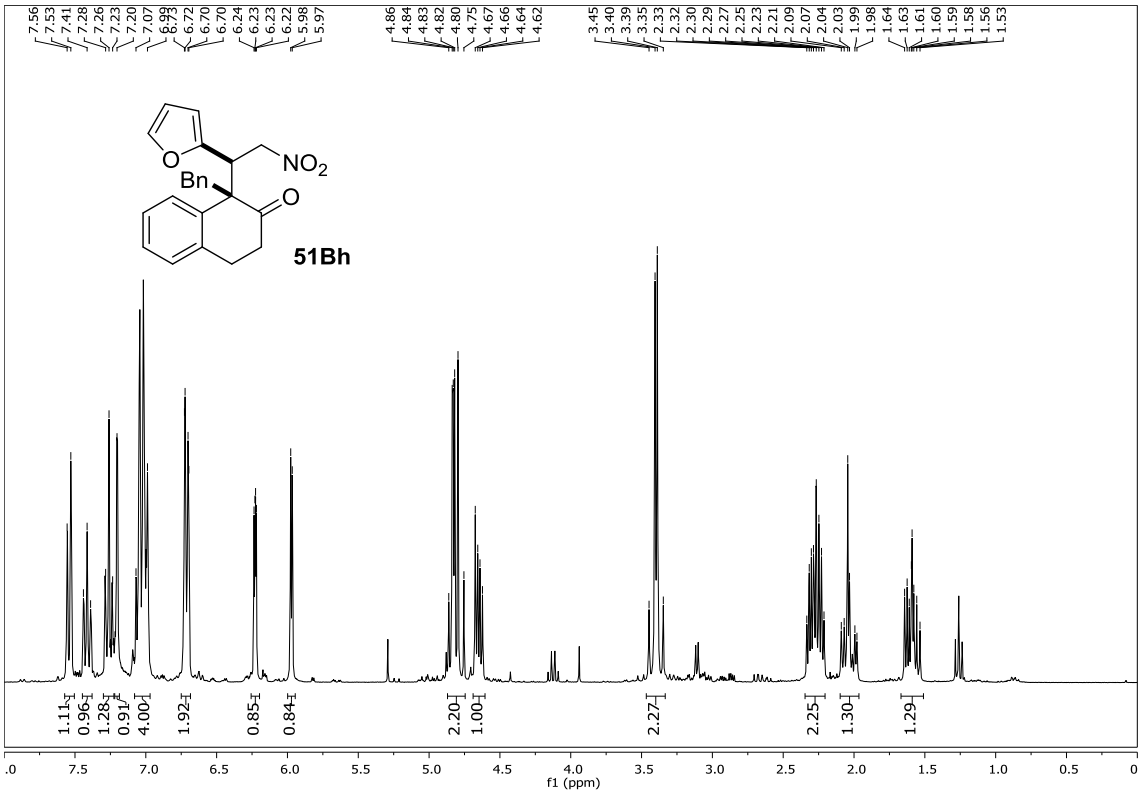
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6.23
6.23
6.22
5.98
5.97
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4.84
4.83
4.82
4.80
4.75
4.67
4.66
4.64
4.62
3.45
3.40
3.39
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2.33
2.32
2.30
2.29
2.27
2.25
2.23
2.21
2.09
2.07
2.04
2.03
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1.63
1.61
1.60
1.59
1.58
1.56
1.53
O
Bn
NO2
O
51Bh
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1.28
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1.00
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2.25
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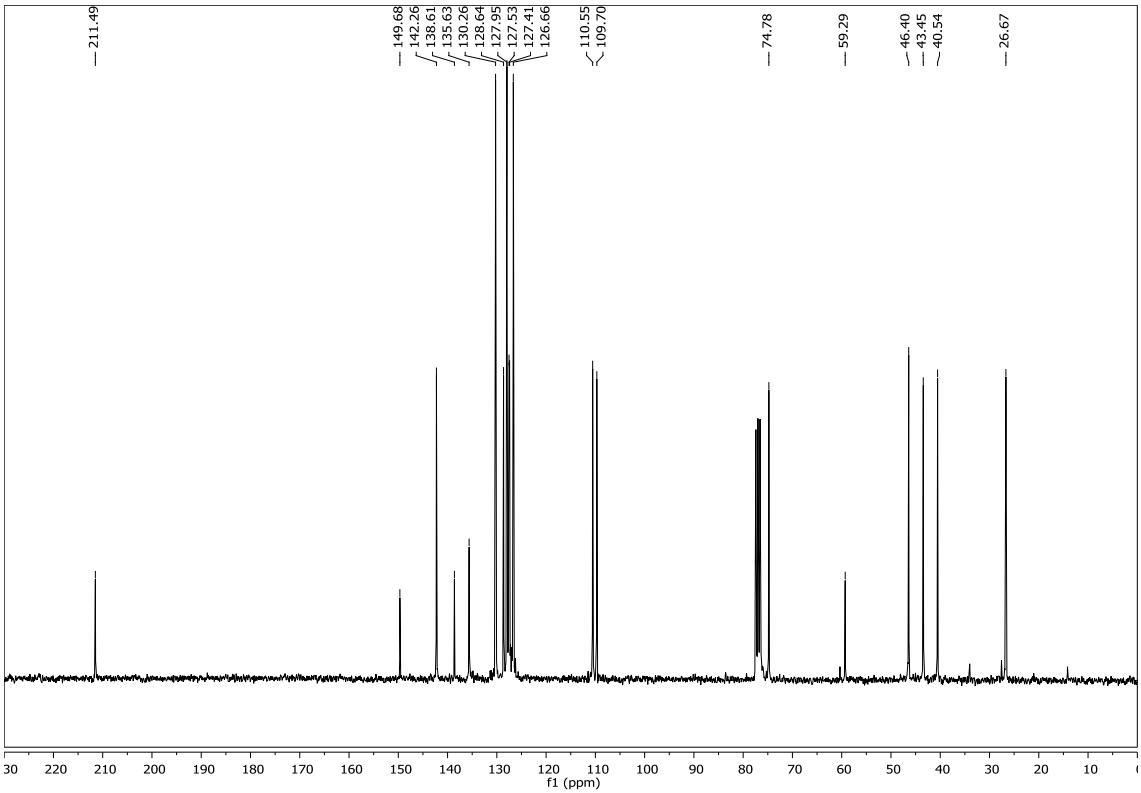
1.29
f1 (ppm)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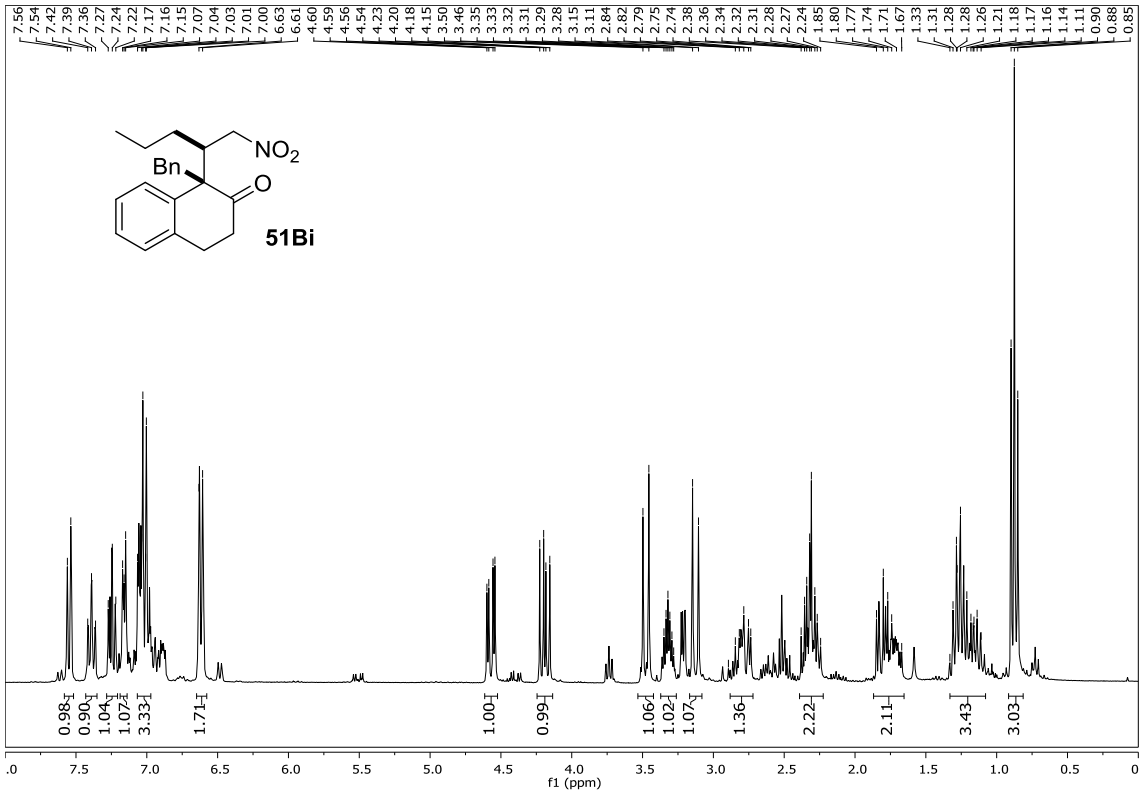
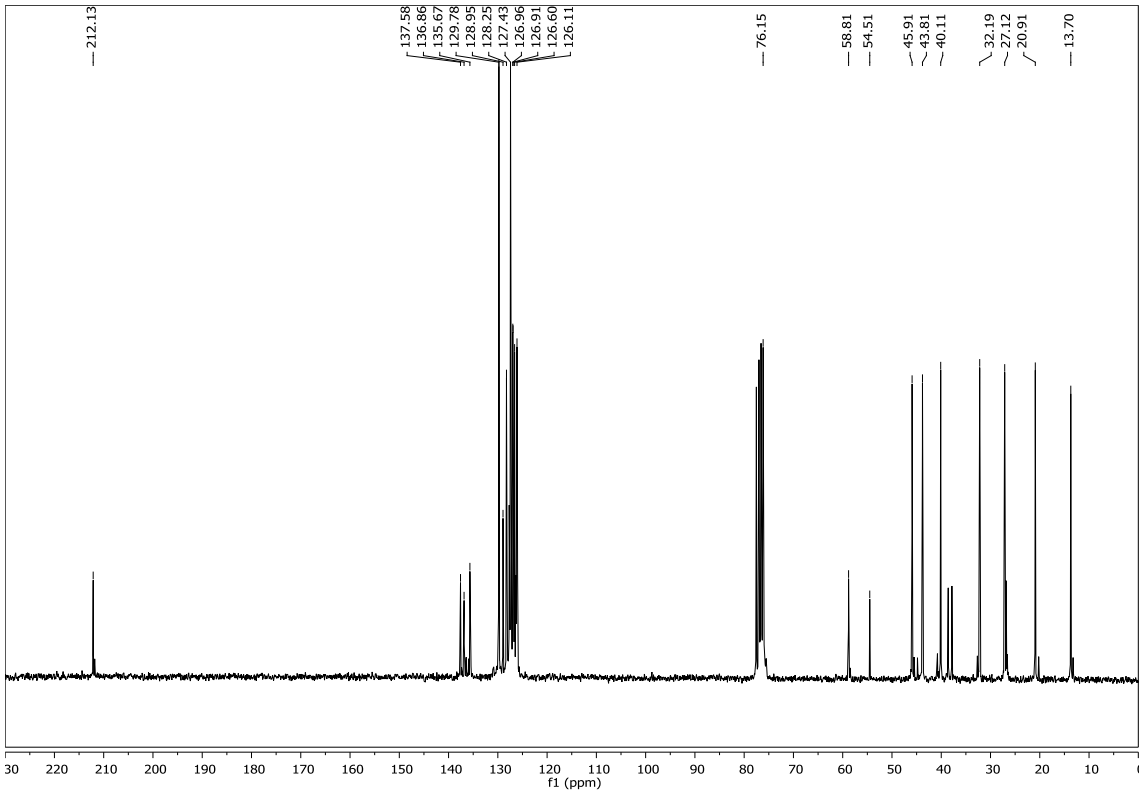
46.40
43.45
40.54
26.67
f1 (ppm)


NO2
Bn
O
51Bi
f1 (ppm)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126.60
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32.19
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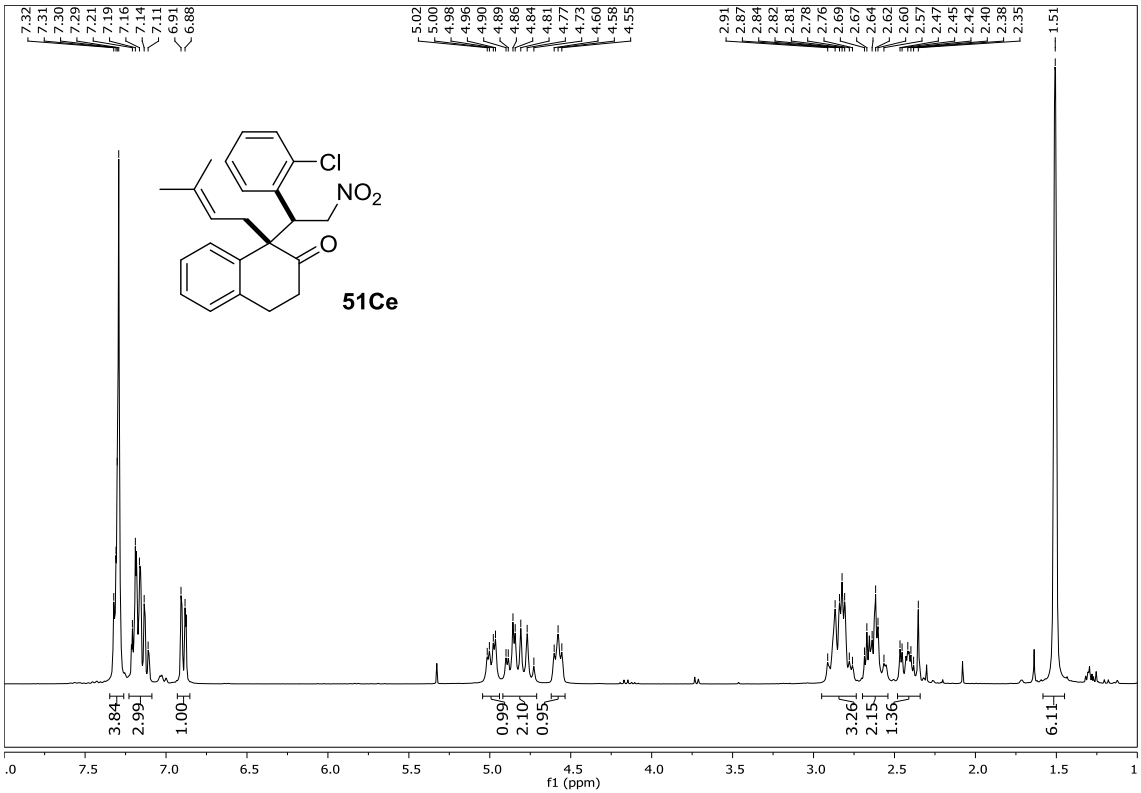
20.91
13.70
f1 (ppm)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7.14
7.11
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6.88
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2.64
2.62
2.60
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2.47
2.45
2.42
2.40
2.38
2.35
1.51
Cl
NO2
O
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1.00
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0.95
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2.15
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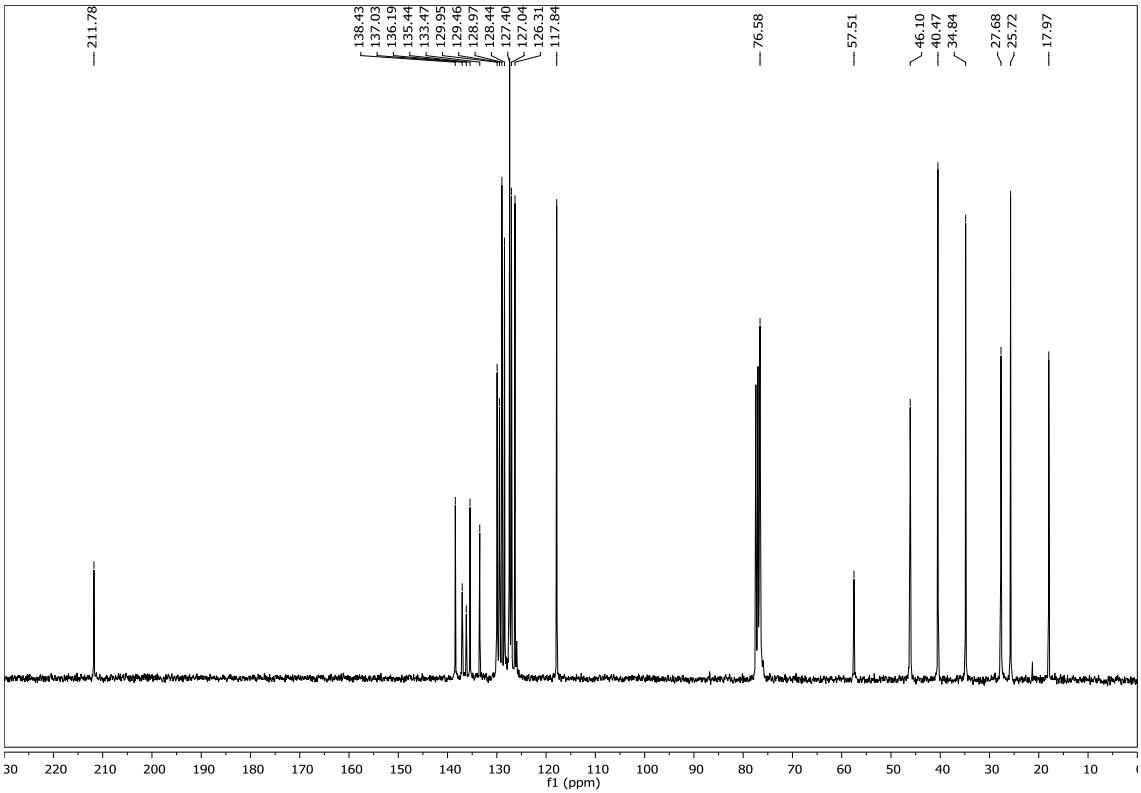
6.11
f1 (ppm)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128.97
128.44
127.40
127.04
126.31
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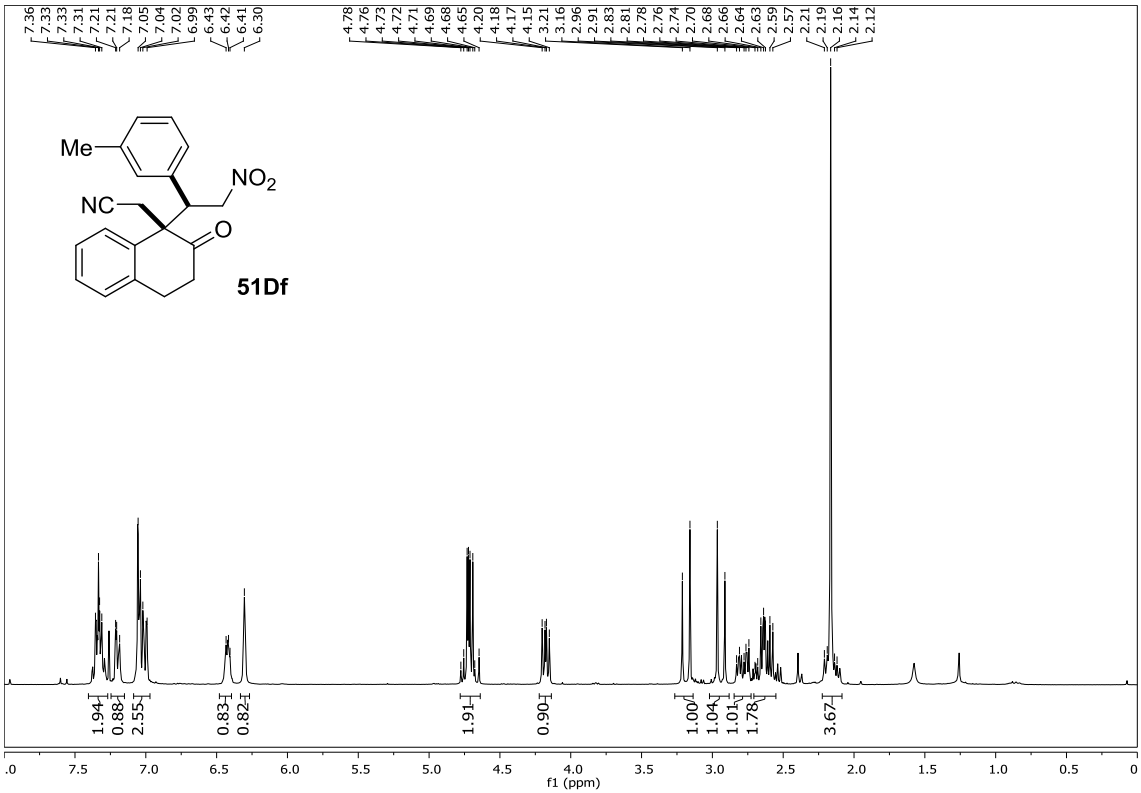
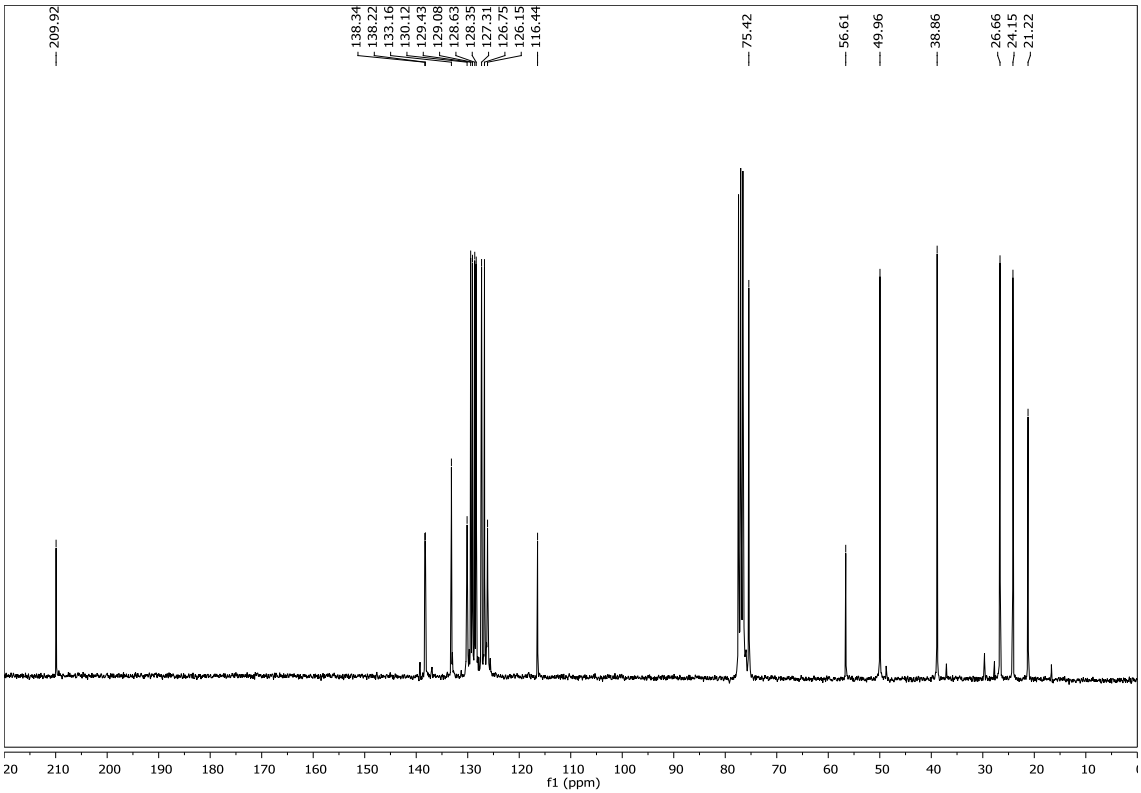
76.58
57.51
46.10
40.47
34.84
27.68
25.72
17.97
f1 (ppm)


Me
NO2
NC
O
51Df
f1 (ppm)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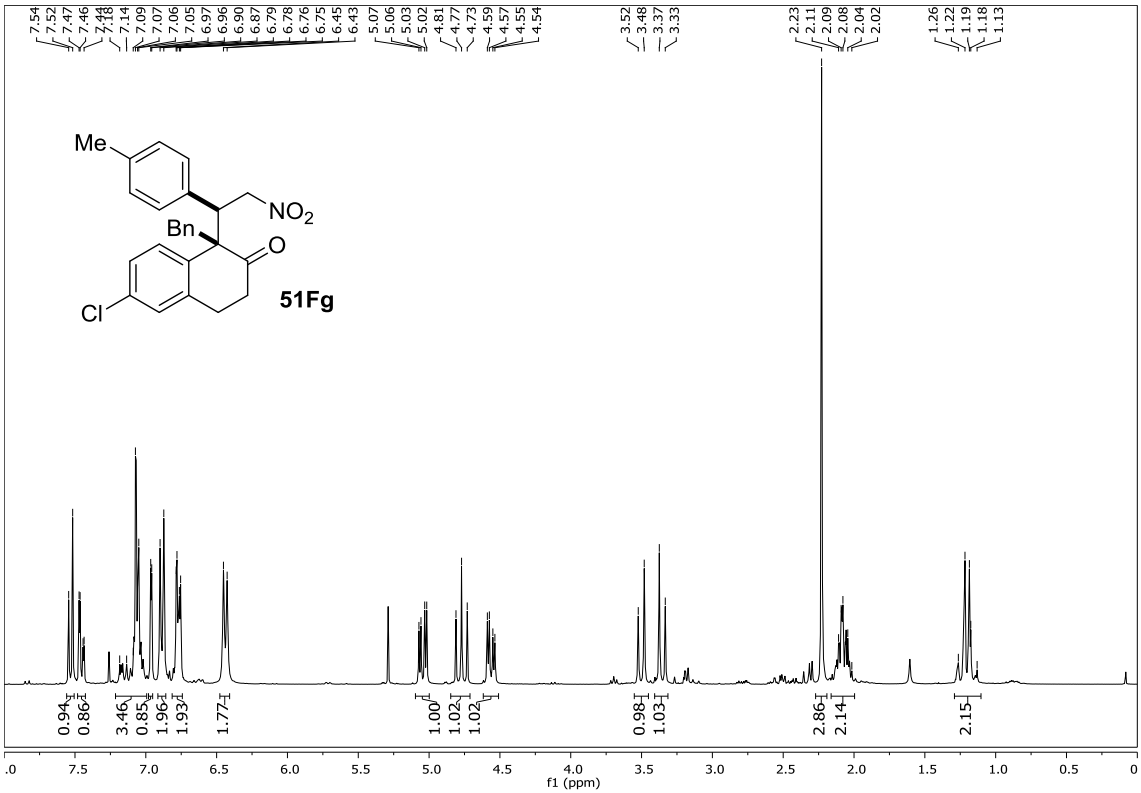
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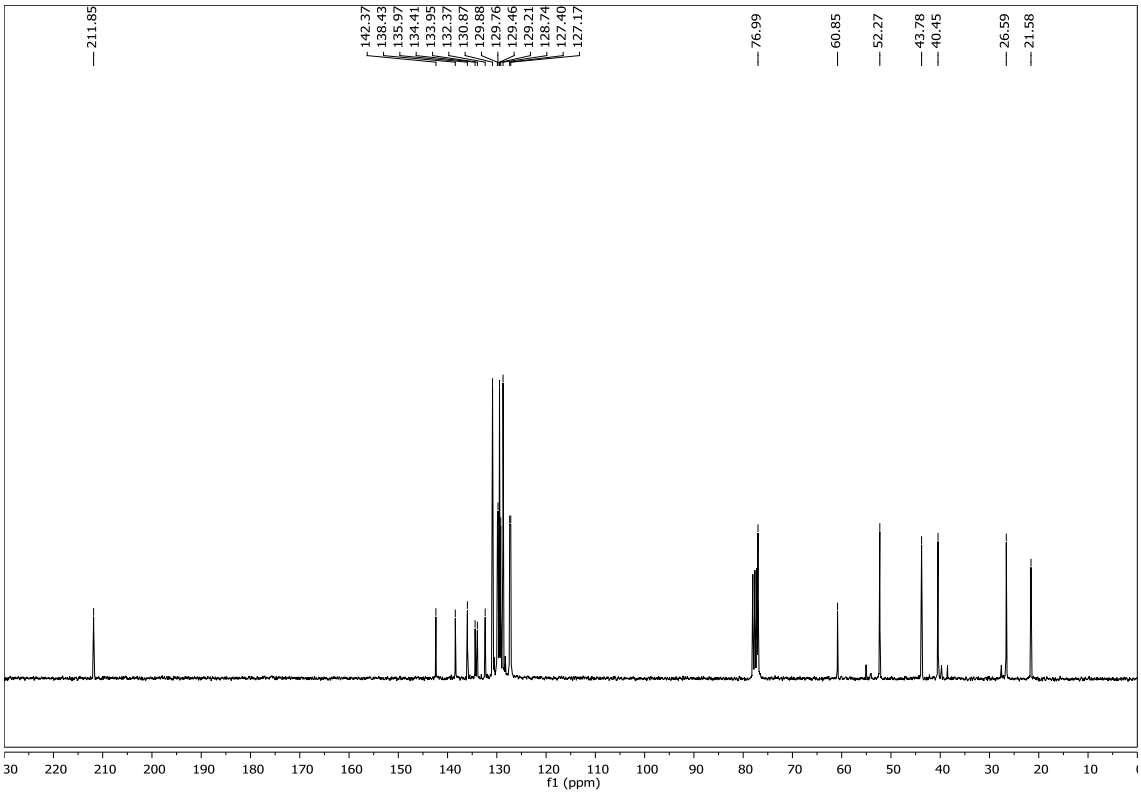
Bn
O
Cl
51Fg
f1 (ppm)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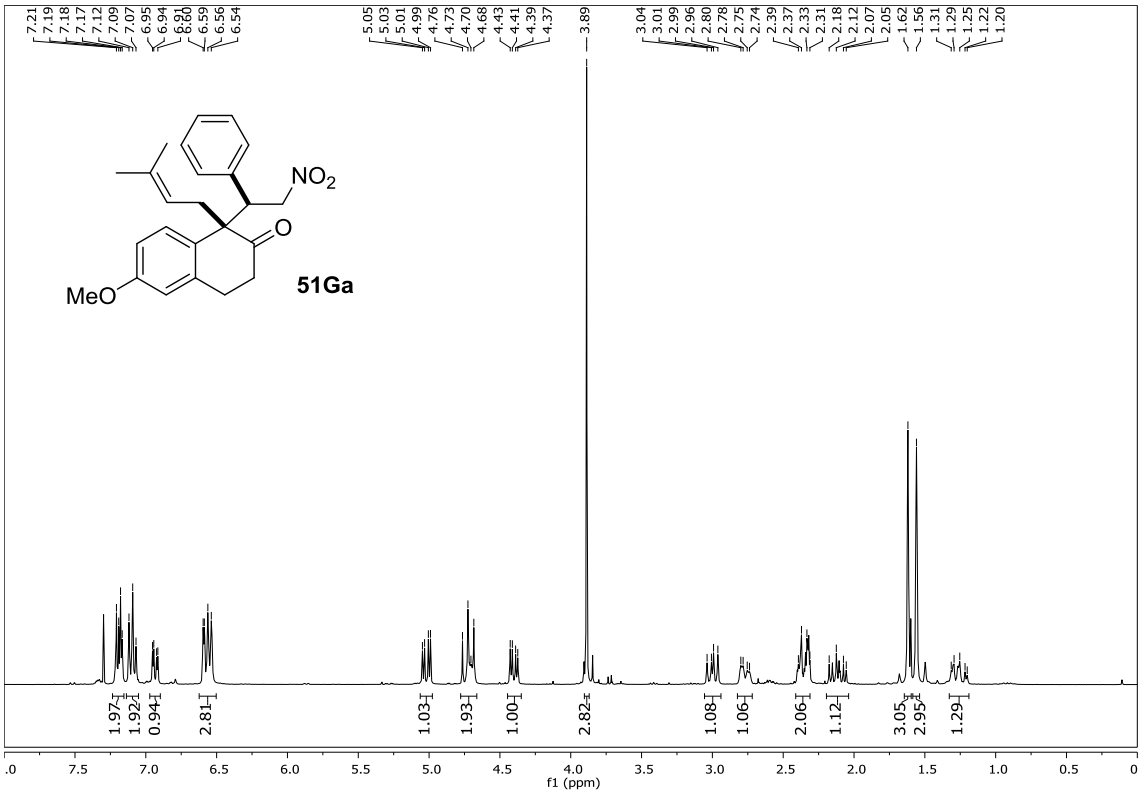
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6.56
6.54
5.05
5.03
5.01
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4.76
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4.68
4.43
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4.39
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3.04
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2.18
2.12
2.07
2.05
1.62
1.56
1.31
1.29
1.25
1.22
1.20
NO2
O
MeO
51Ga
1.97
1.92
0.94
2.81
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1.06
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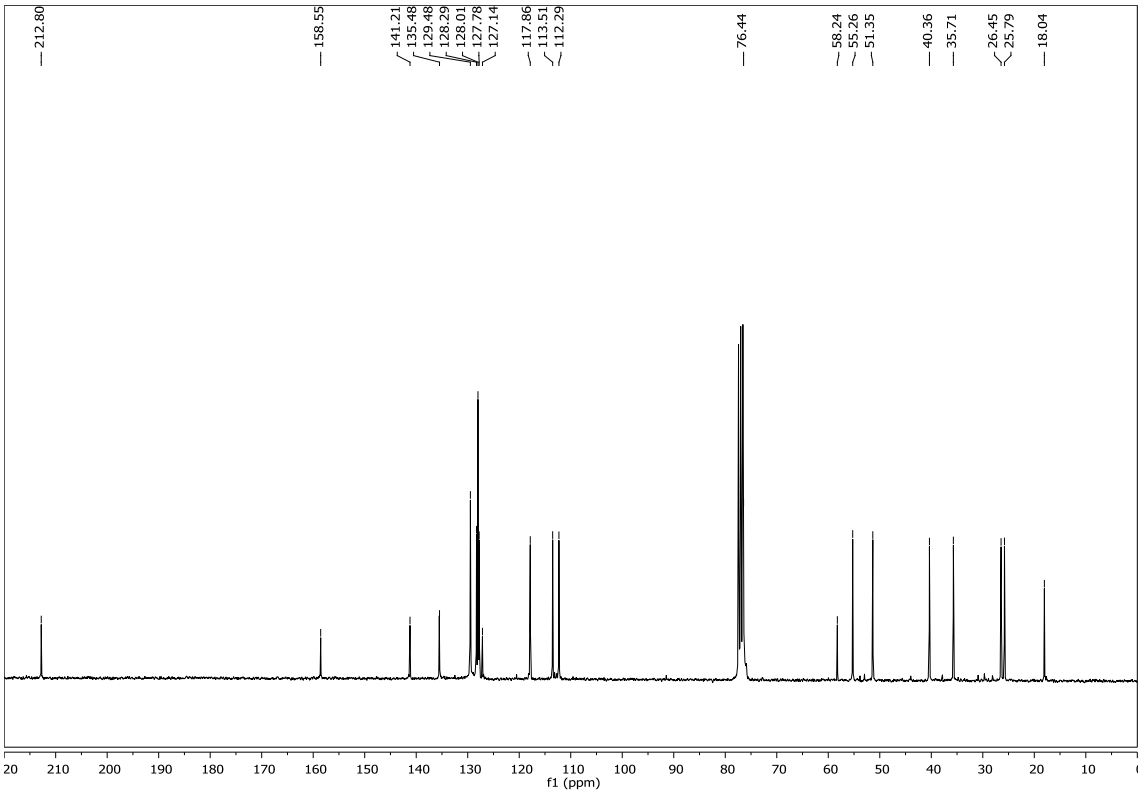
1.29
f1 (ppm)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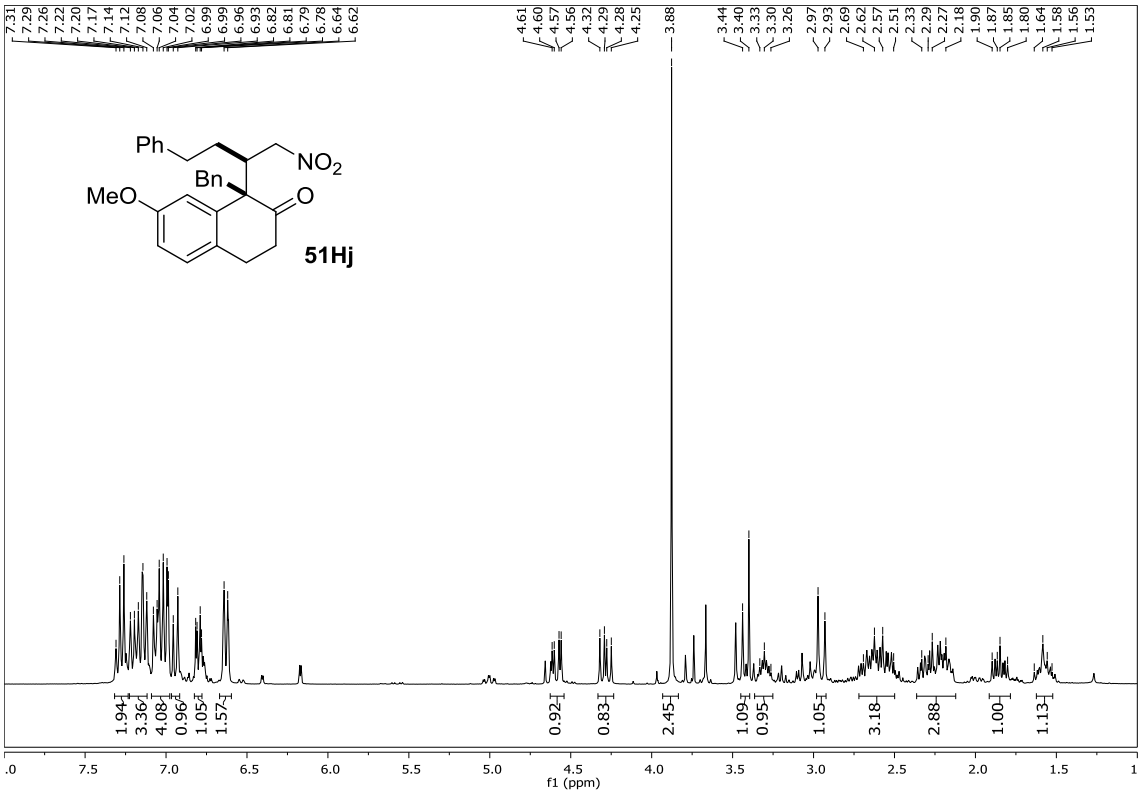
26.45
25.79
18.04
f1 (ppm)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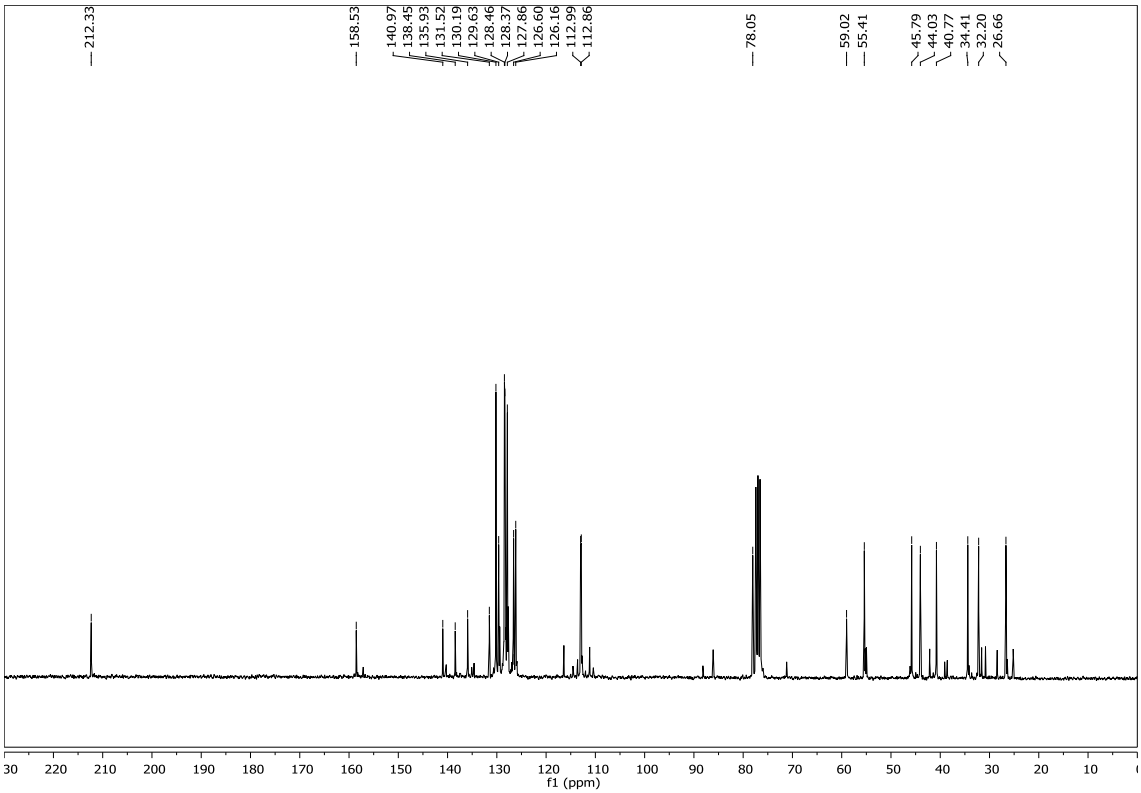
Bn
MeO
O
51Hj
f1 (ppm)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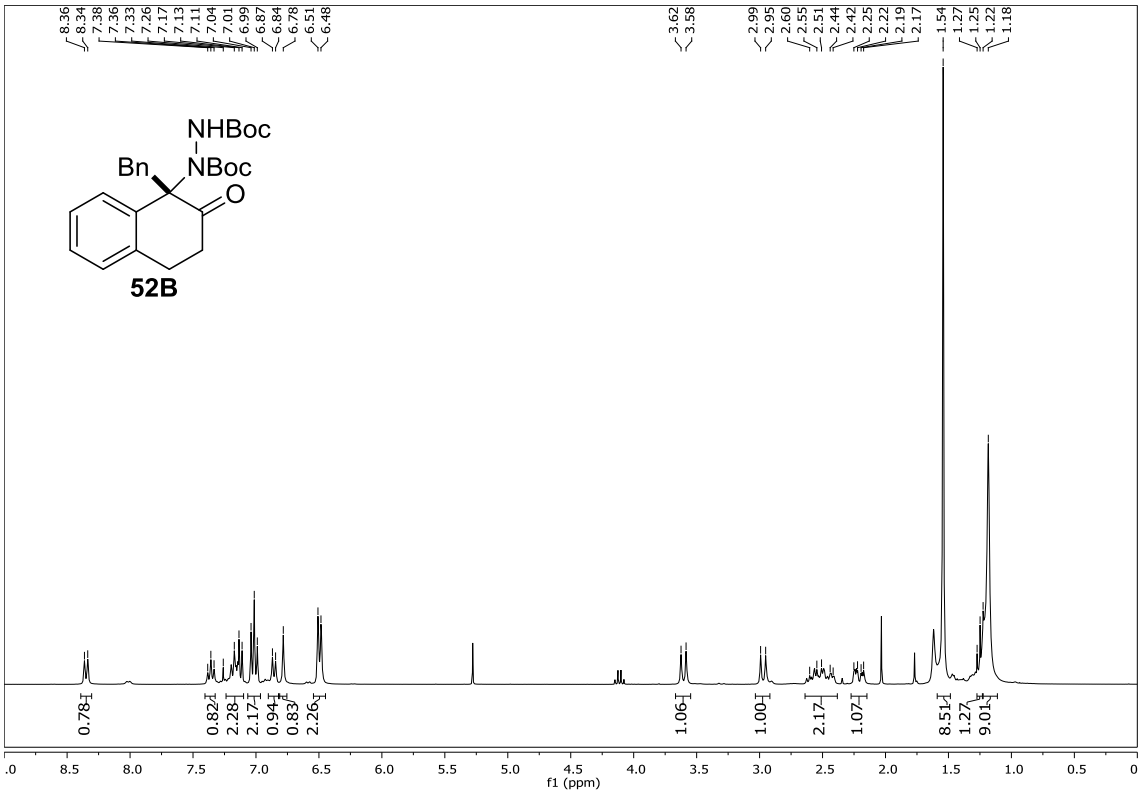
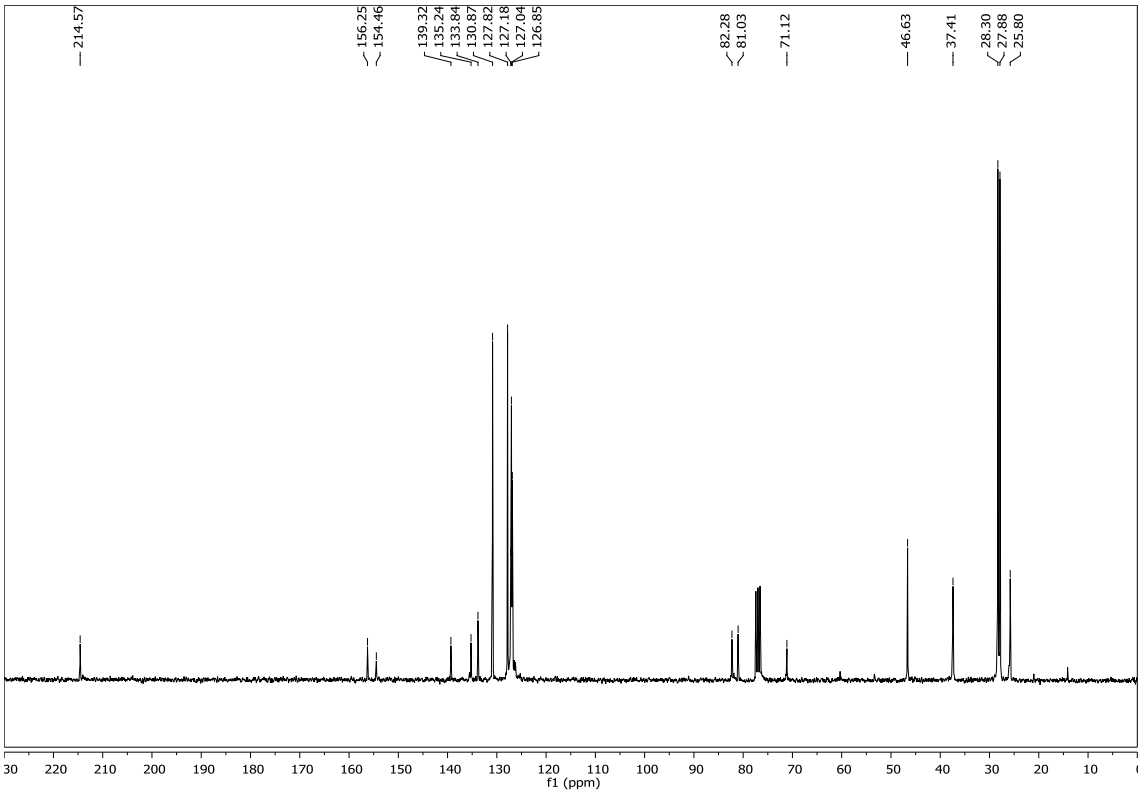

NHBoc
Bn
NBoc
O
52B
f1 (ppm)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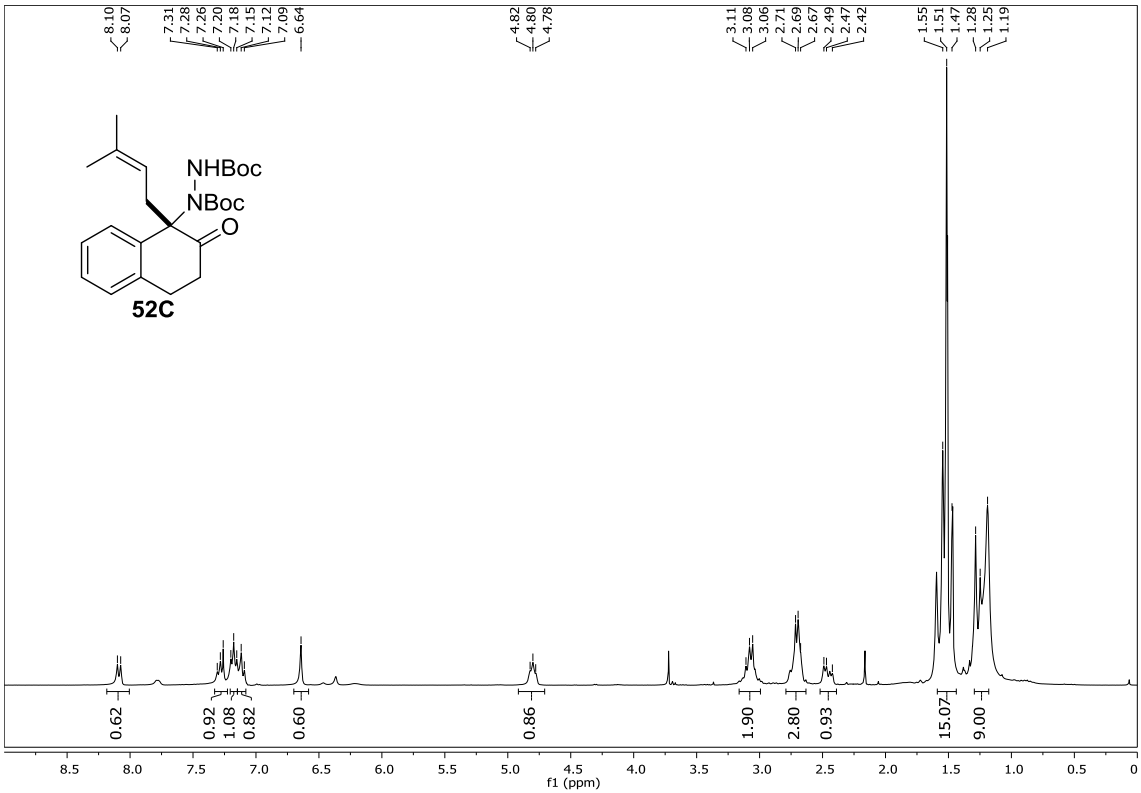
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7.09
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4.78
3.11
3.08
3.06
2.71
2.69
2.67
2.49
2.47
2.42
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1.51
1.47
1.28
1.25
1.19
NHBoc
NBoc
O
52C
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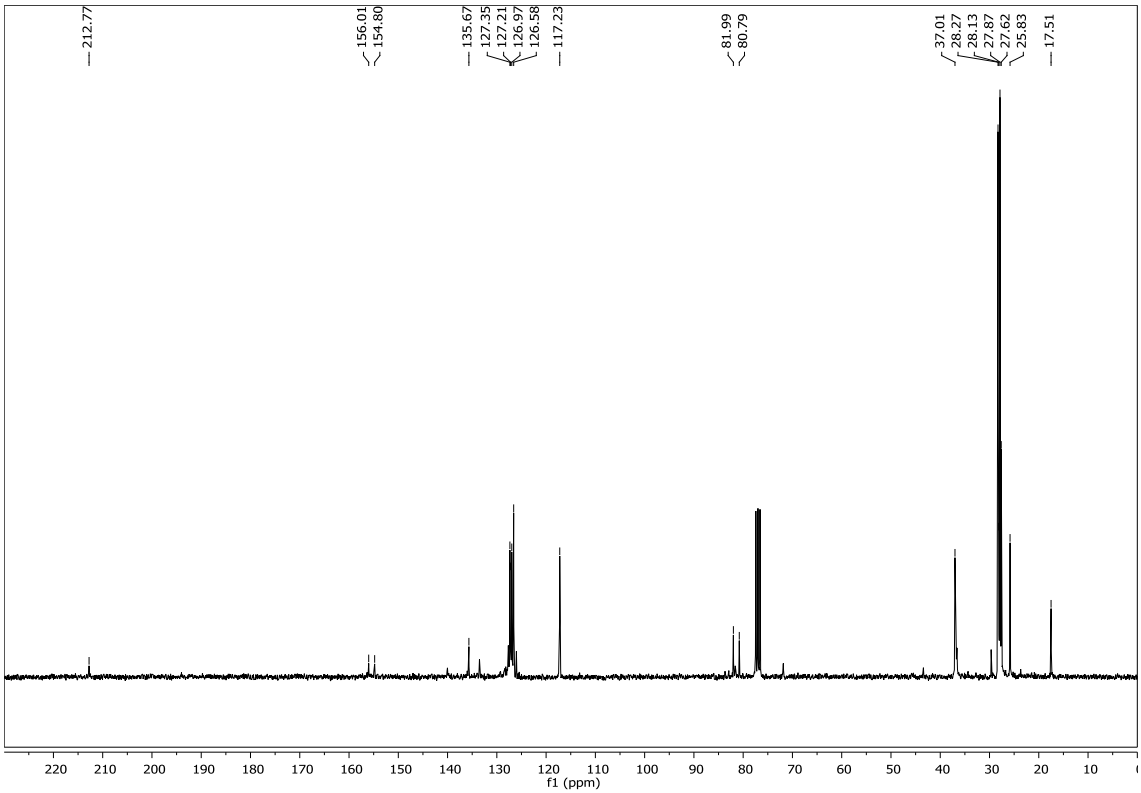
9.00
f1 (ppm)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27.62
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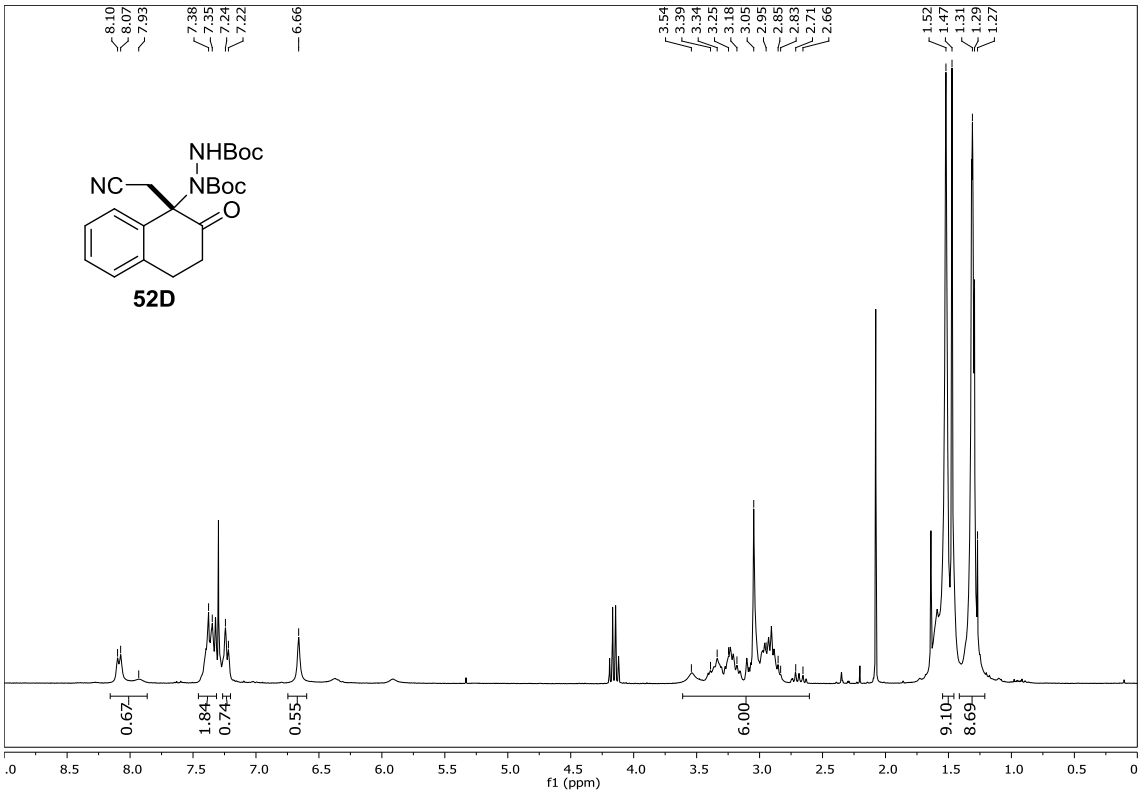
17.51
f1 (ppm)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3.34
3.25
3.18
3.05
2.95
2.85
2.83
2.71
2.66
1.52
1.47
1.31
1.29
1.27
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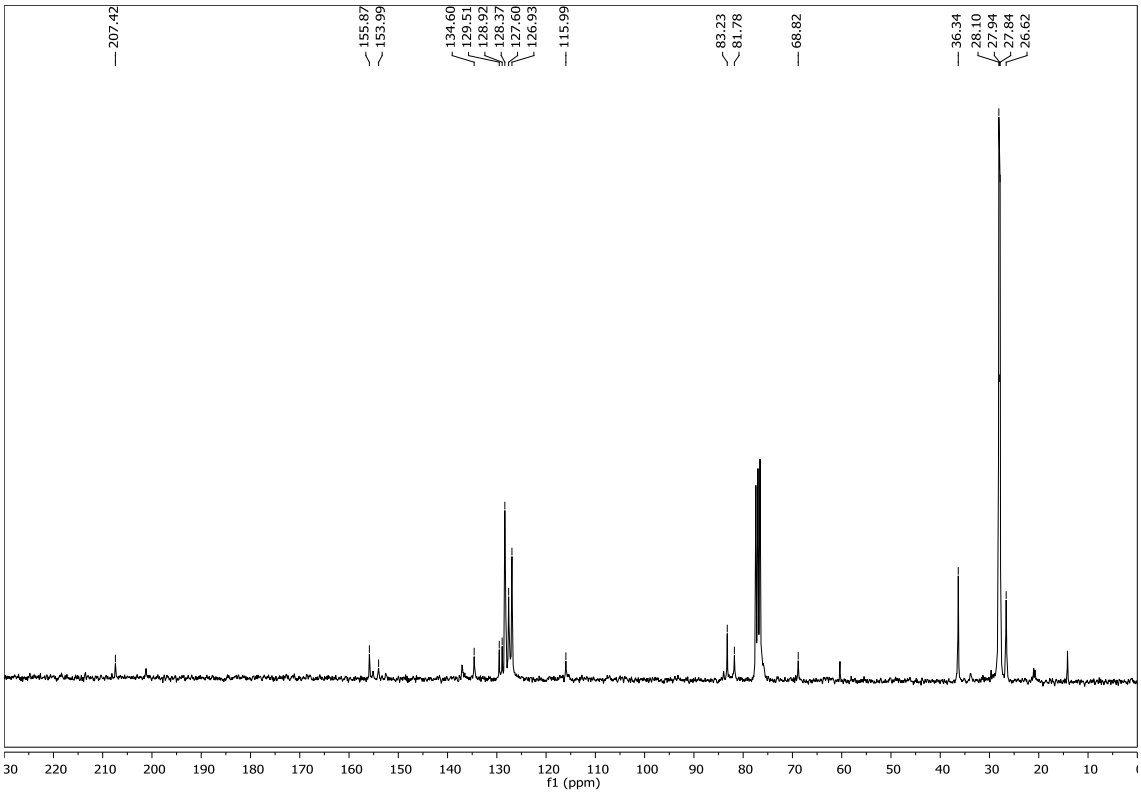
f1 (ppm)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128.92
128.37
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81.78
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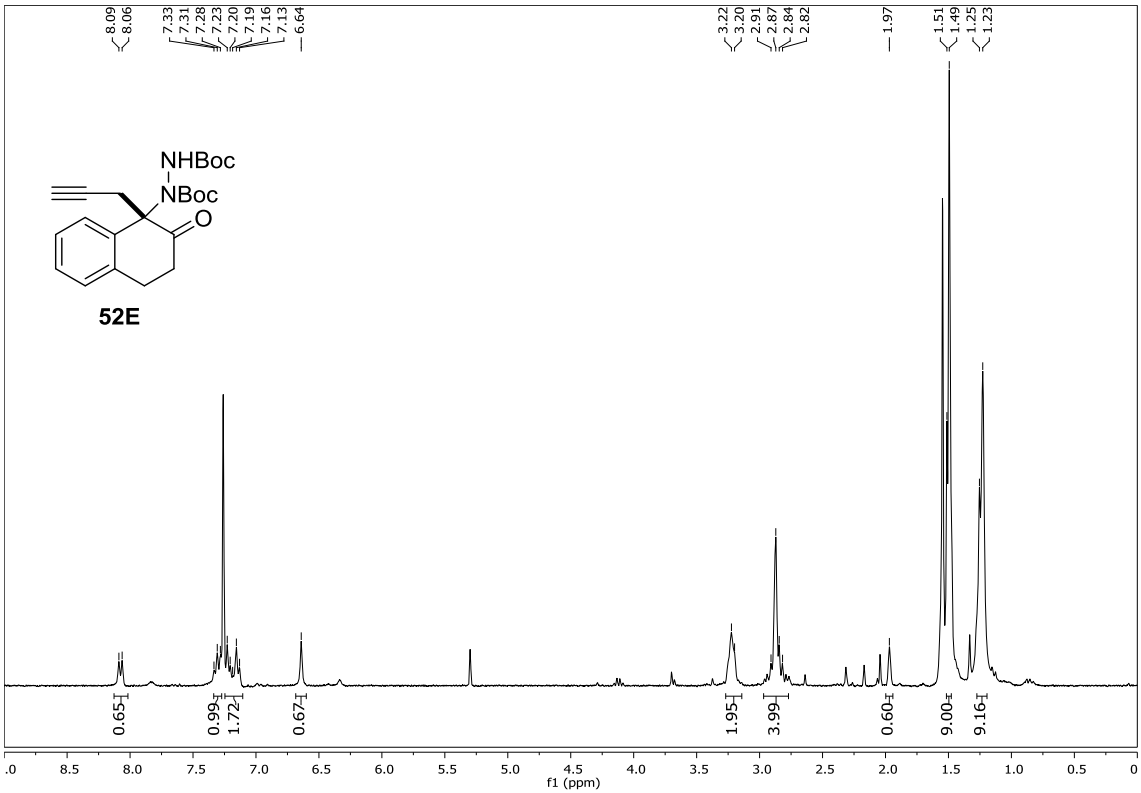
28.10
27.94
27.84
26.62
f1 (ppm)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2.87
2.84
2.82
1.97
1.51
1.49
1.25
1.23
NHBoc
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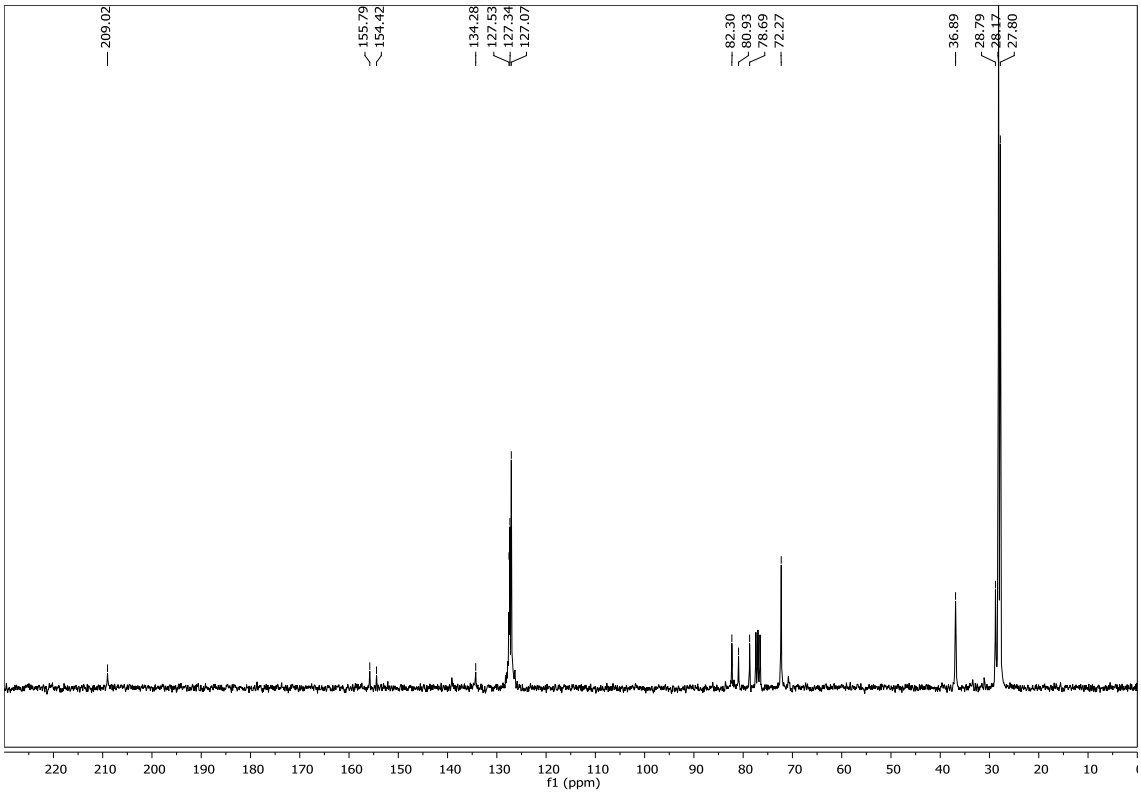
3.99
0.60
9.00
9.16
f1 (ppm)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72.27
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28.79
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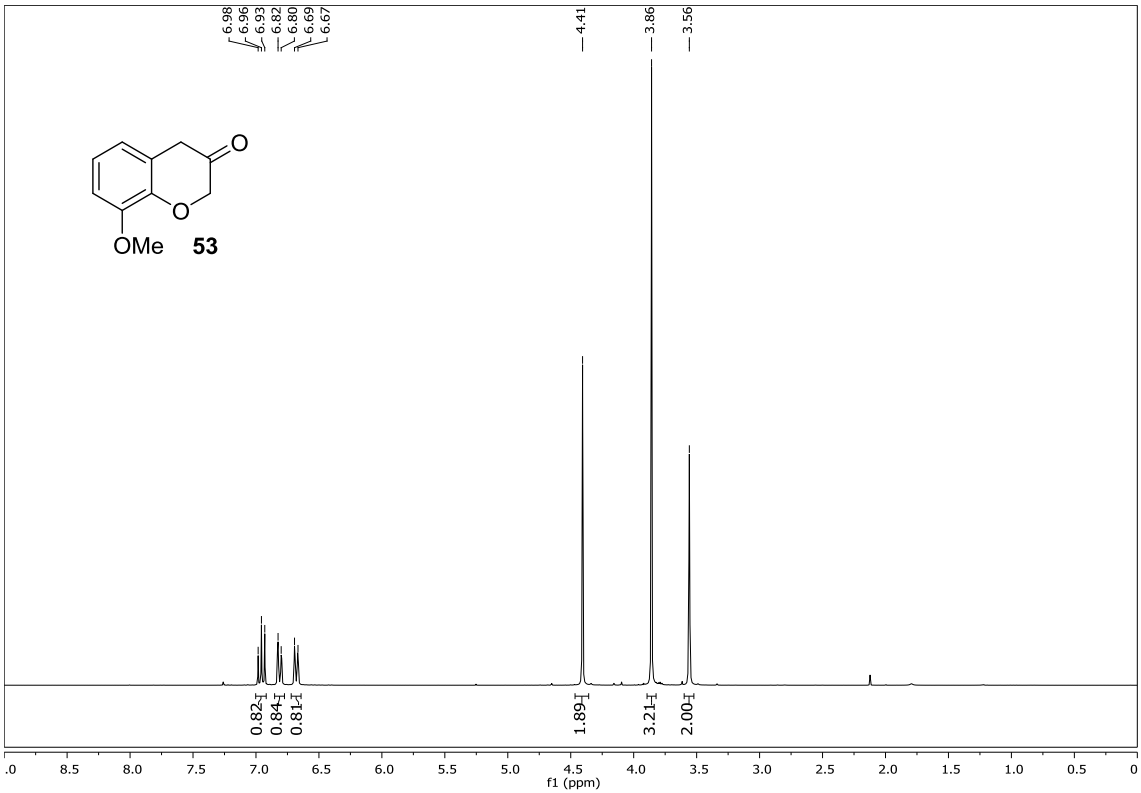
27.80
f1 (ppm)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O
OMe
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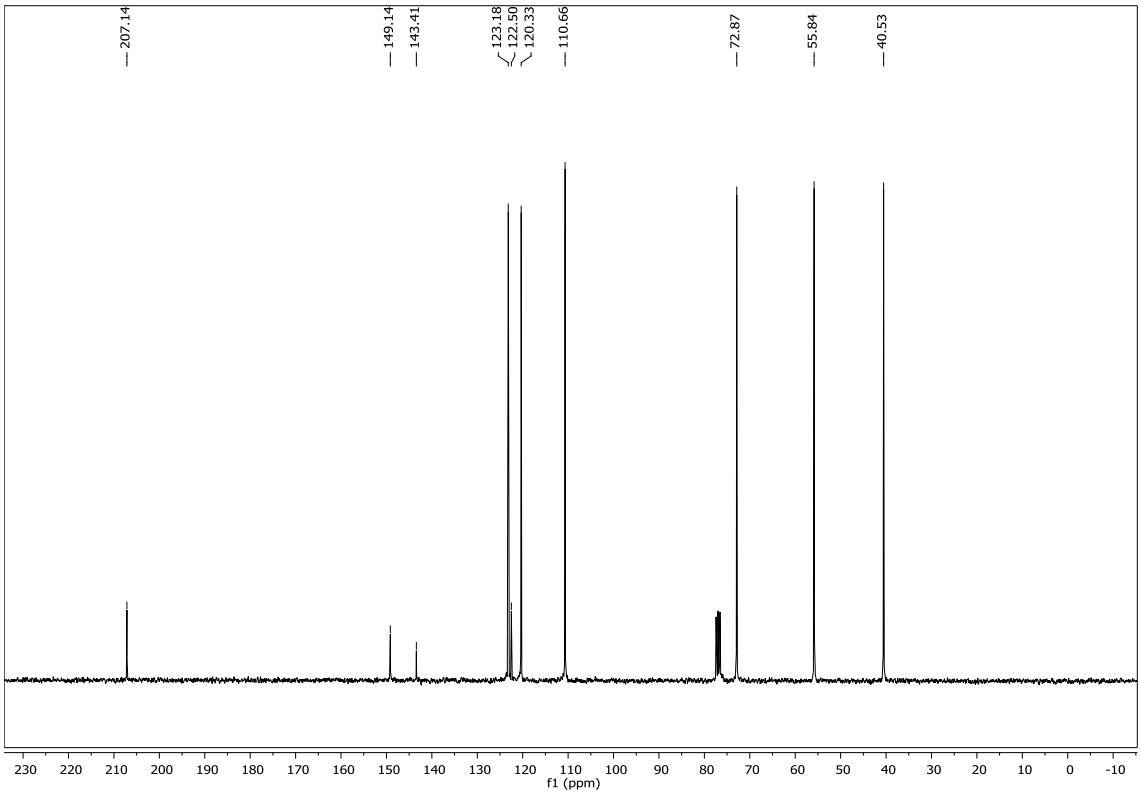
1.89
3.21
2.00
f1 (ppm)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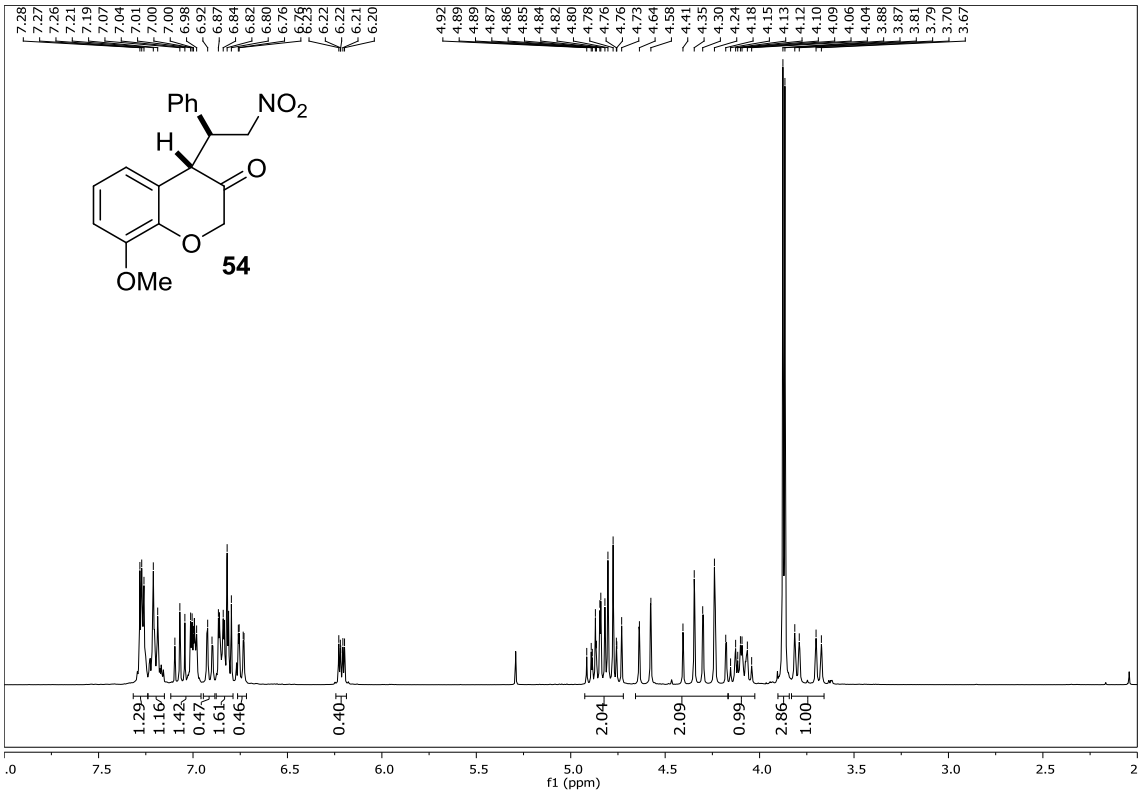
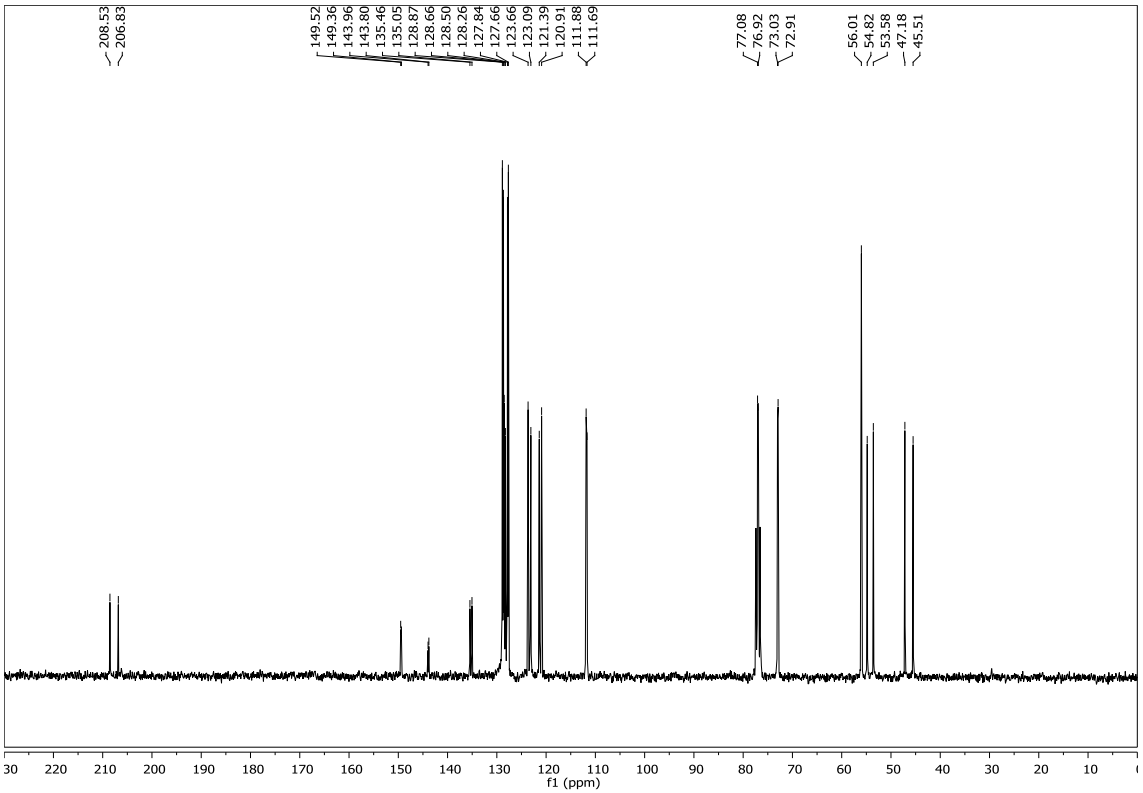
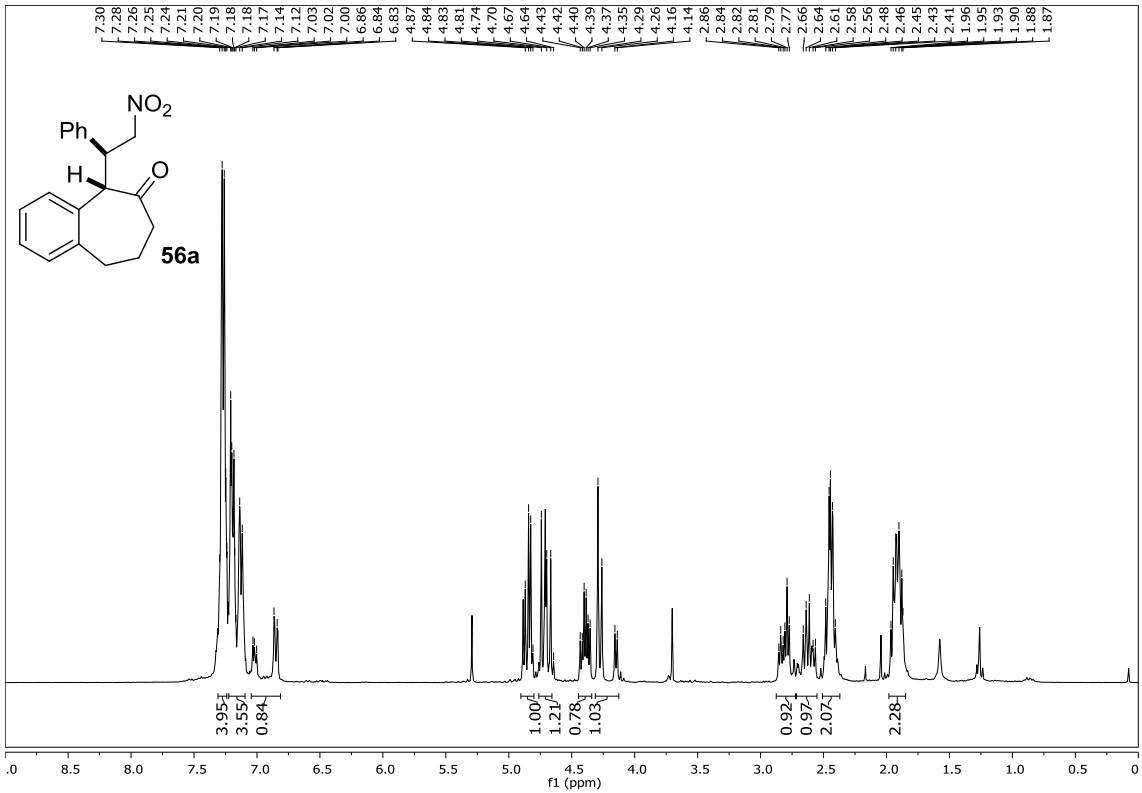
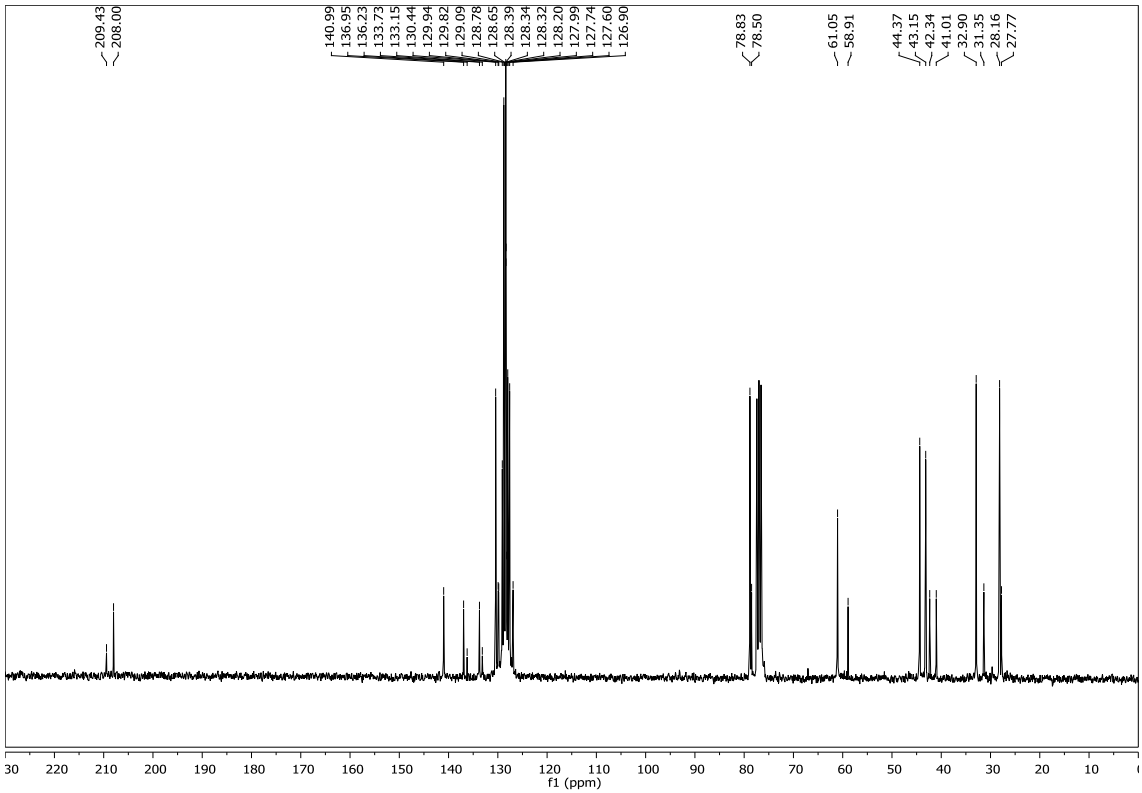
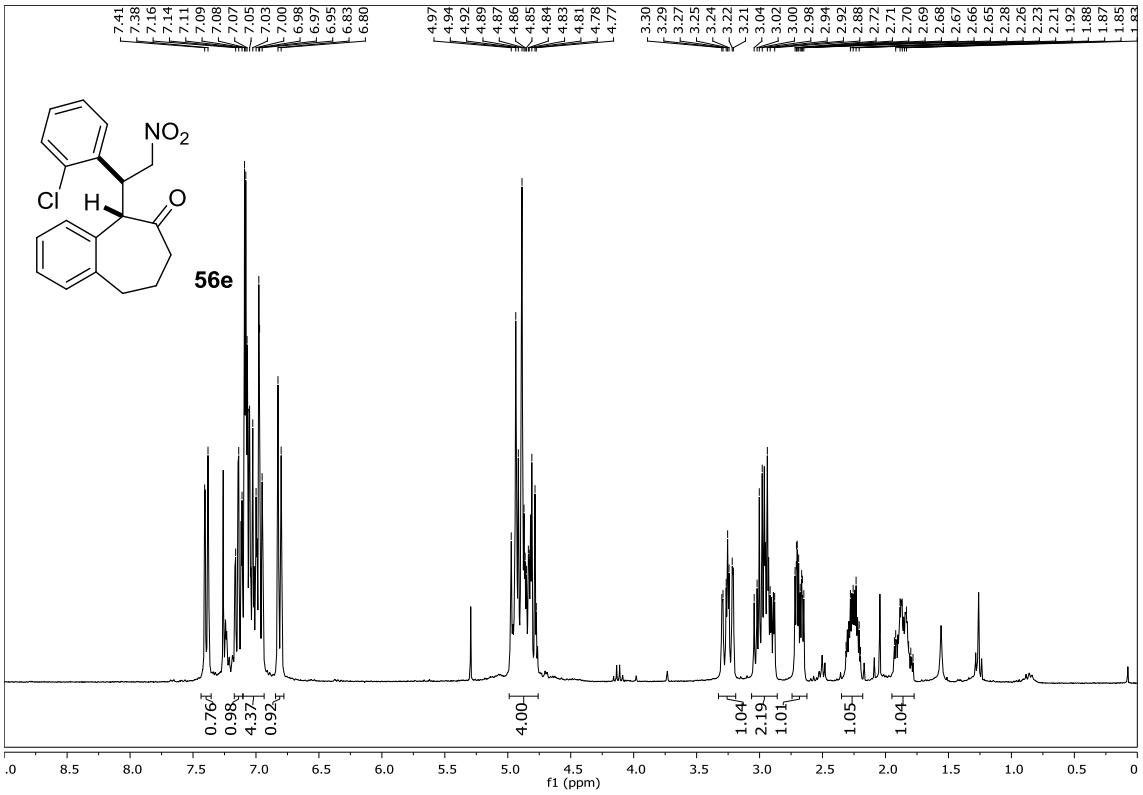
40.53
f1 (ppm)

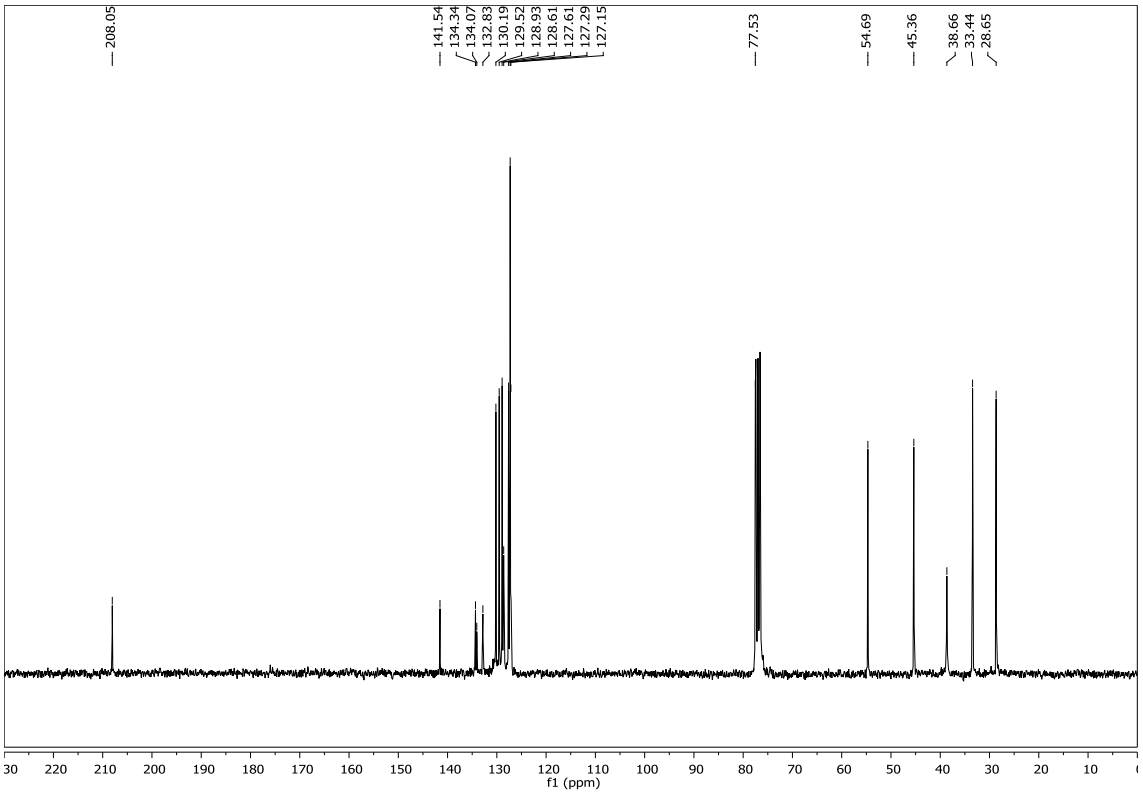

Ph
NO2
H
O
O
OMe
54
f1 (ppm)

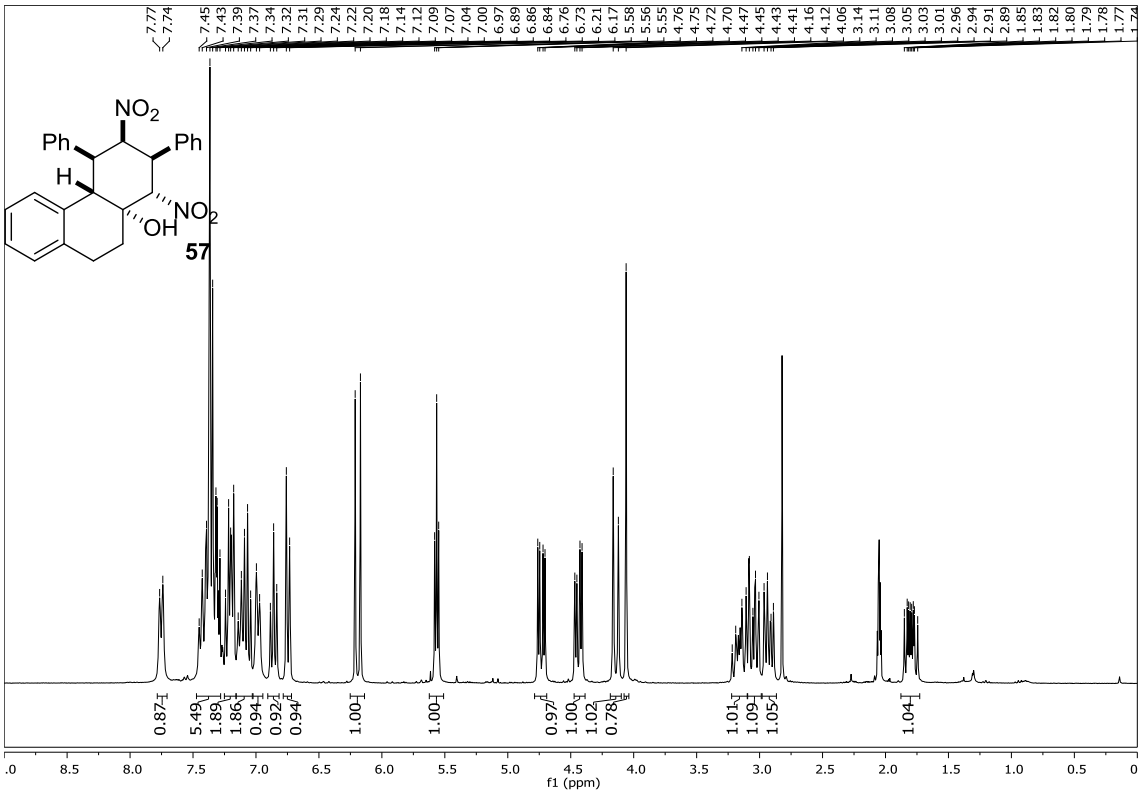

f1 (ppm)

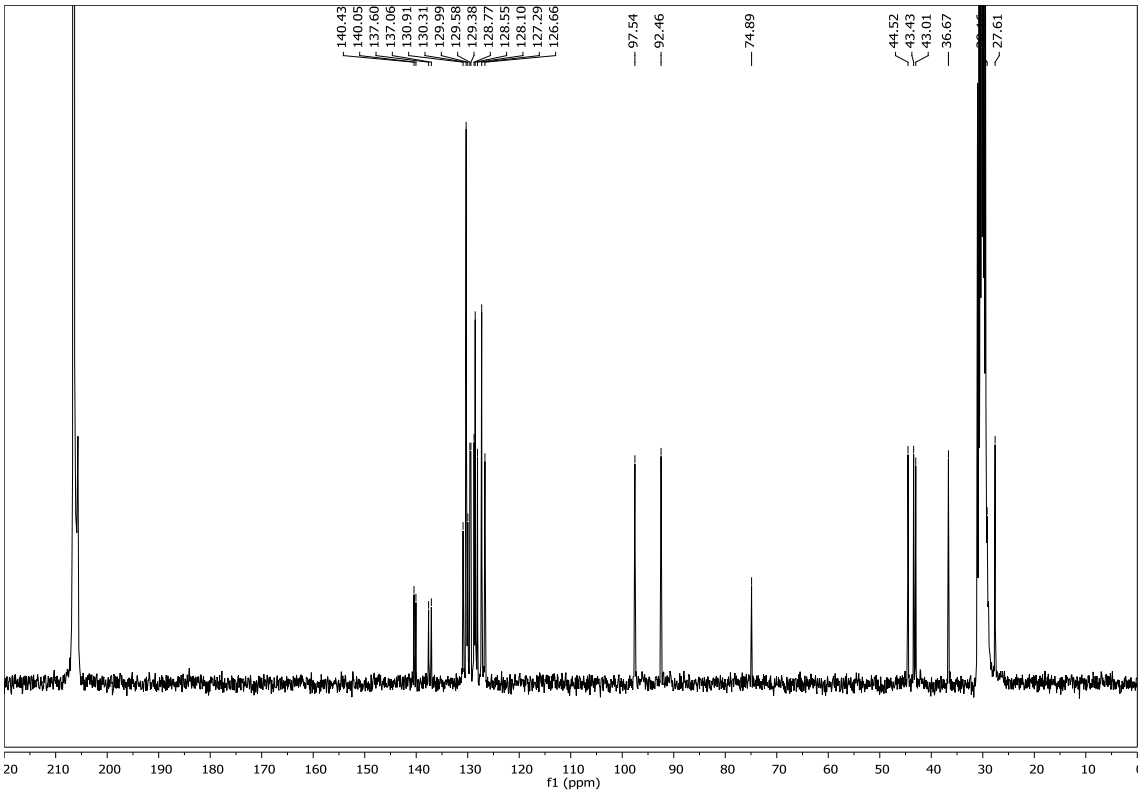

NO2
Ph
H
O
56a
f1 (ppm)

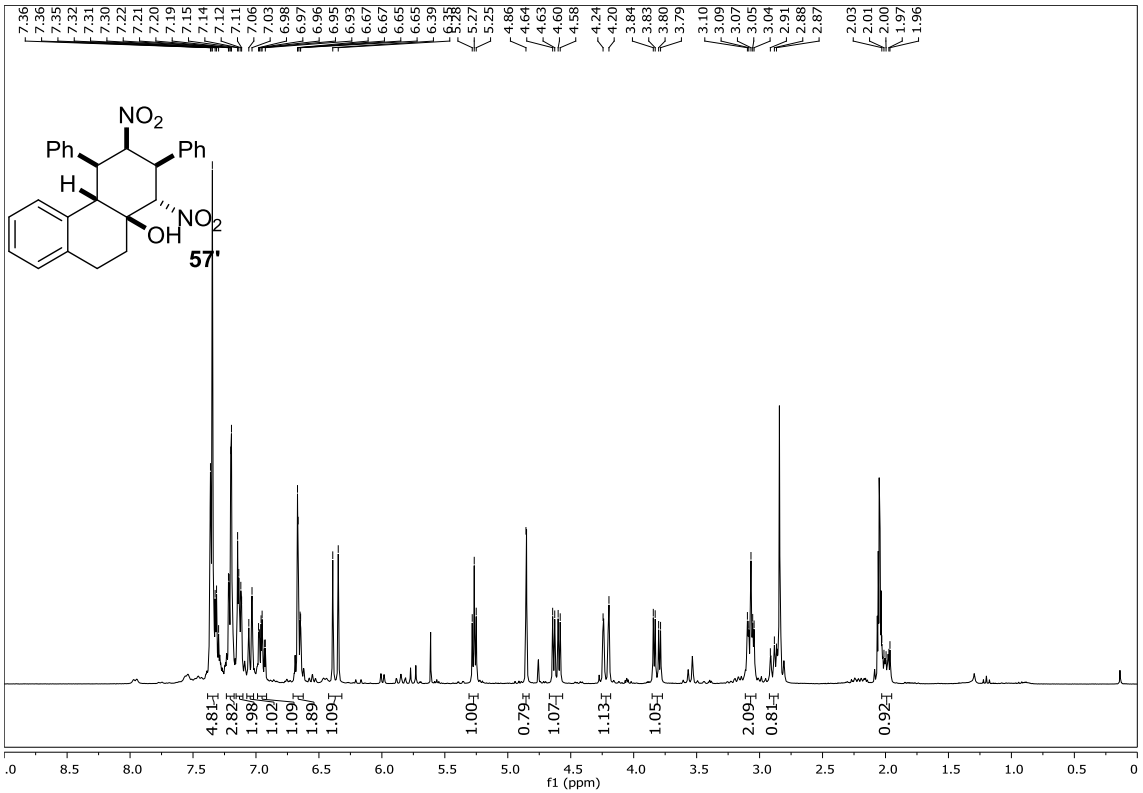

f1 (ppm)

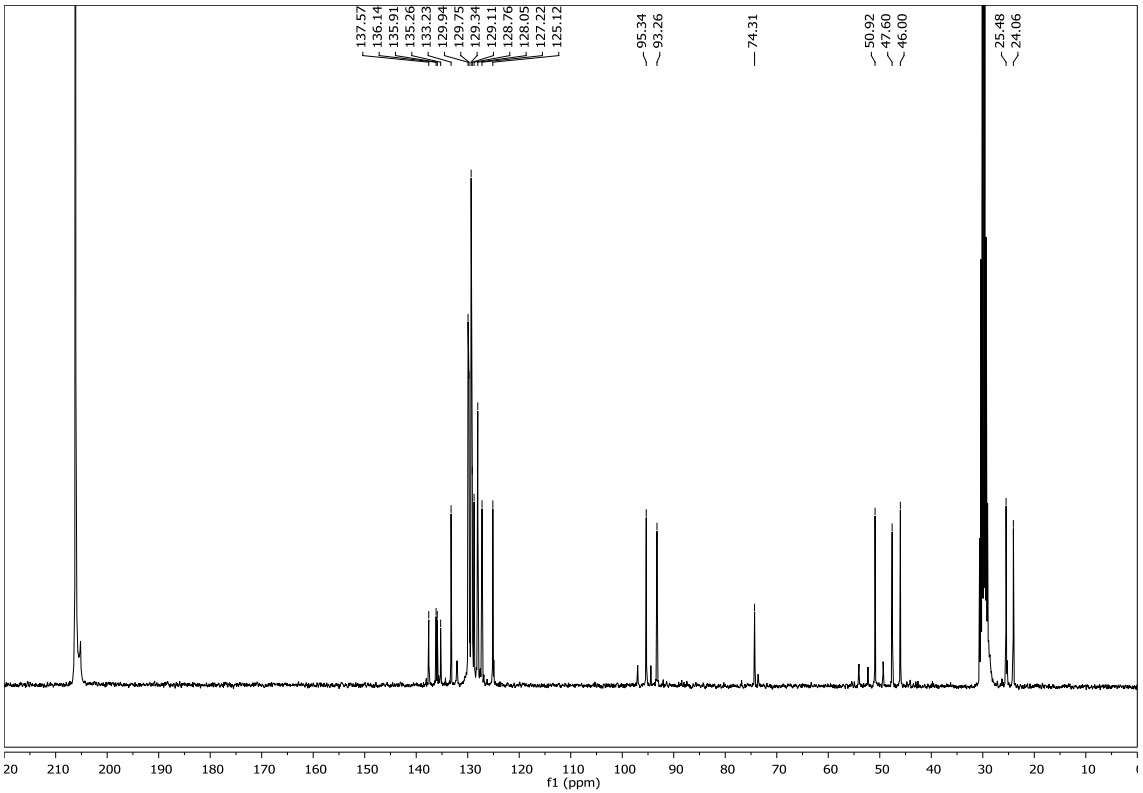

NO2
Cl
H
O
56e
f1 (ppm)


208.05
141.54
134.34
134.07
132.83
130.19
129.52
128.93
128.61
127.61
127.29
127.15
77.53
54.69
45.36
38.66
33.44
28.65
f1 (ppm)

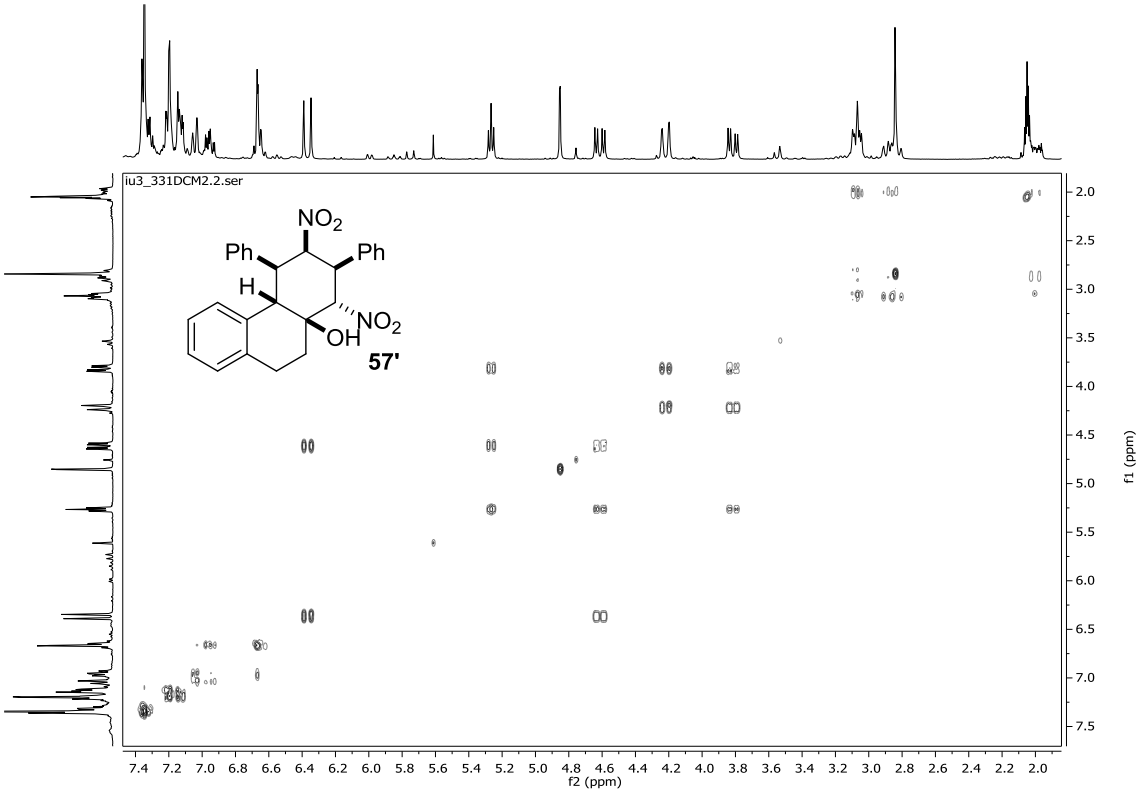

NO2
Ph
Ph
H
NO2
OH
57
f1 (ppm)


f1 (ppm)

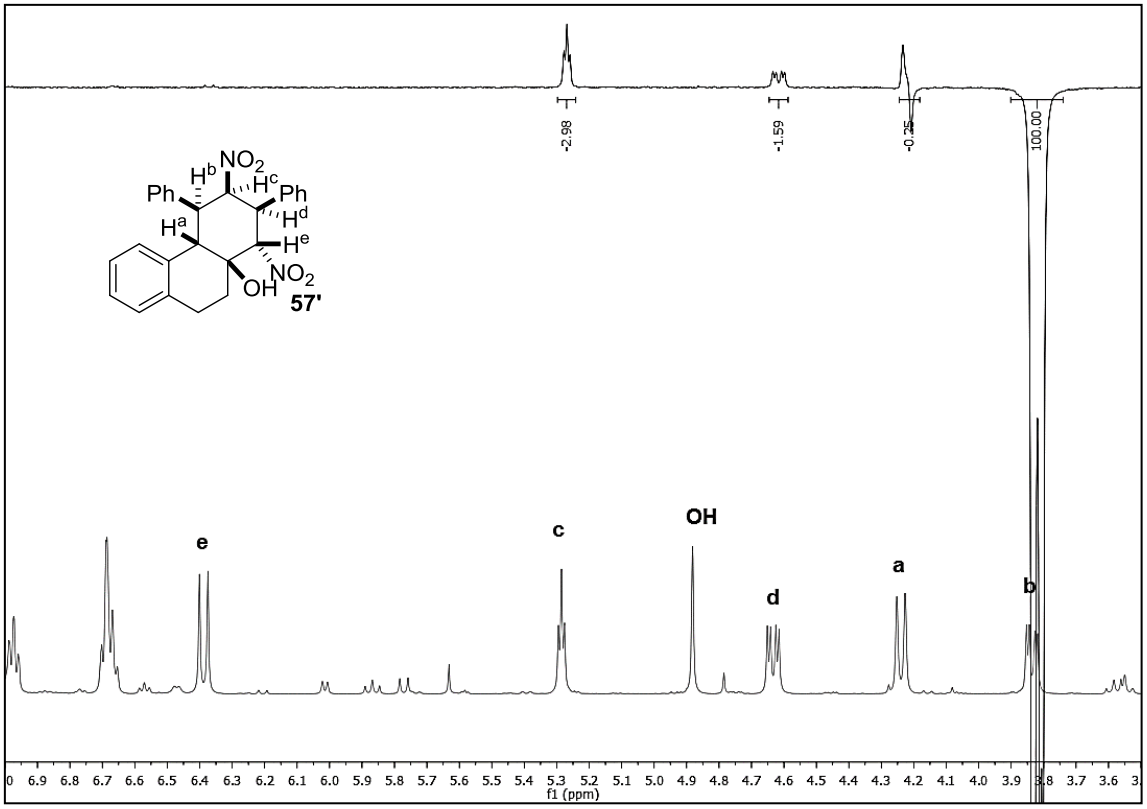

NO2
Ph
Ph
H
NO2
OH
57'
f1 (ppm)


f1 (ppm)

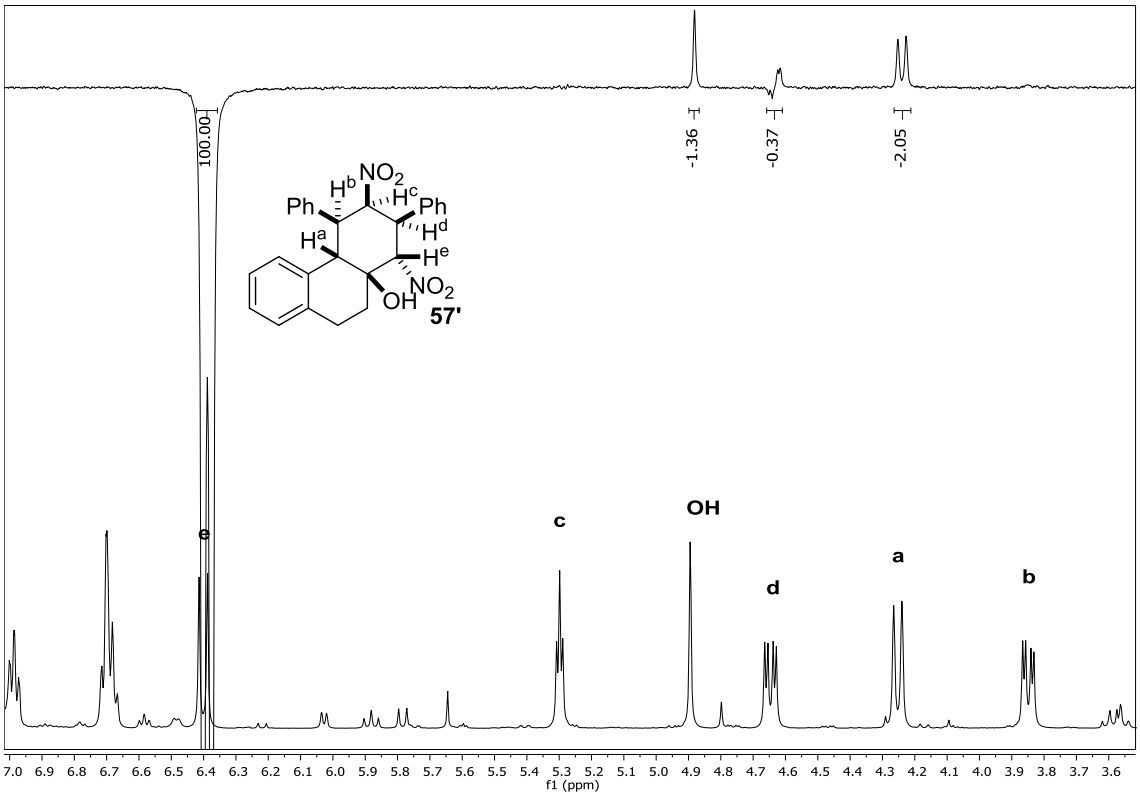
COSSY

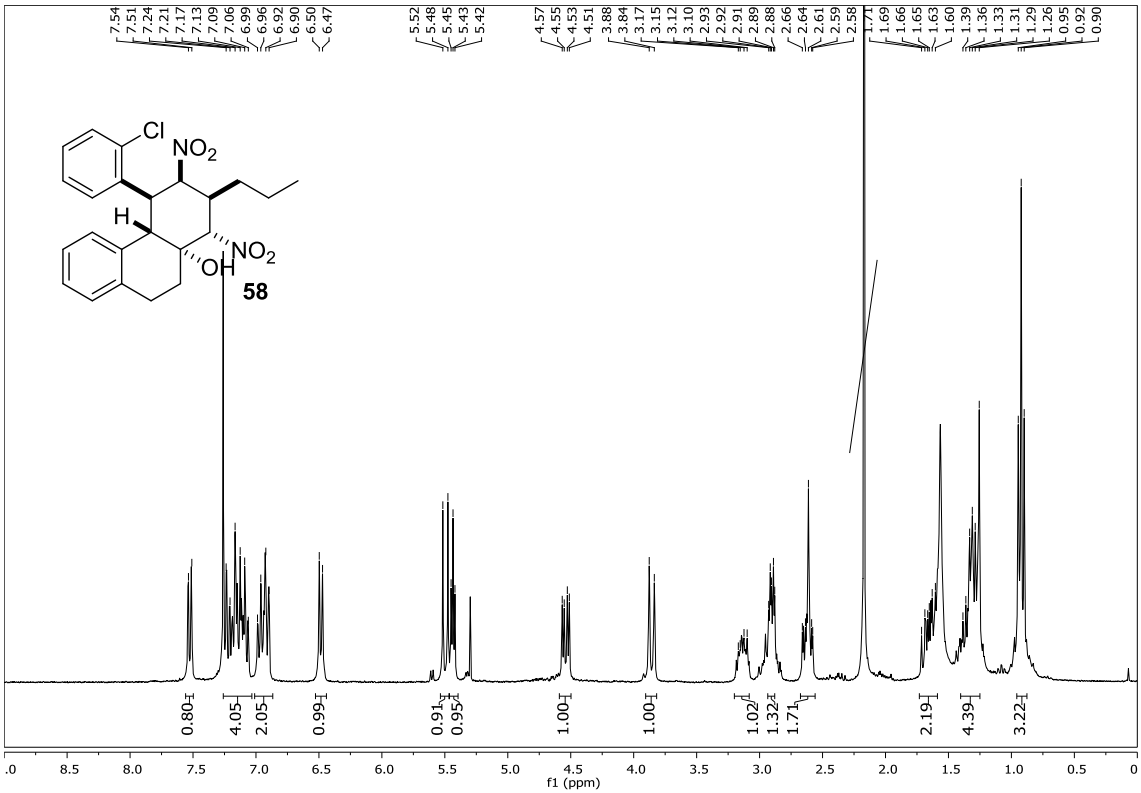


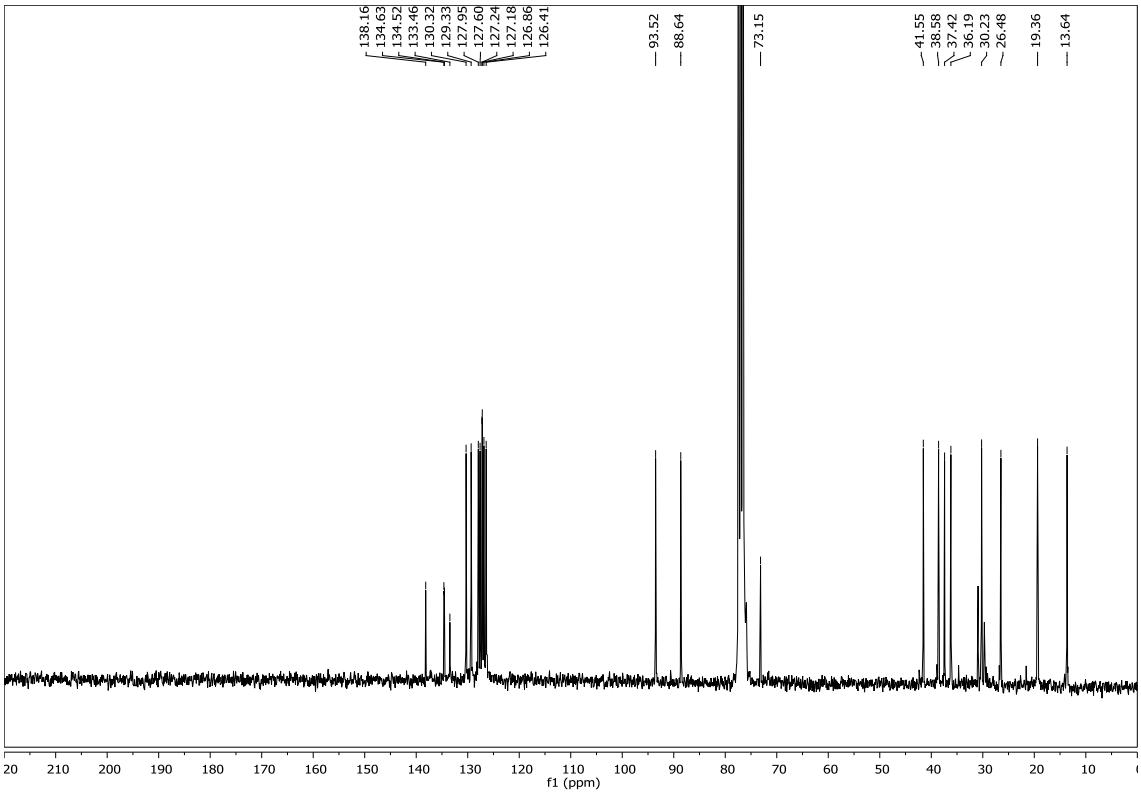
NOESY

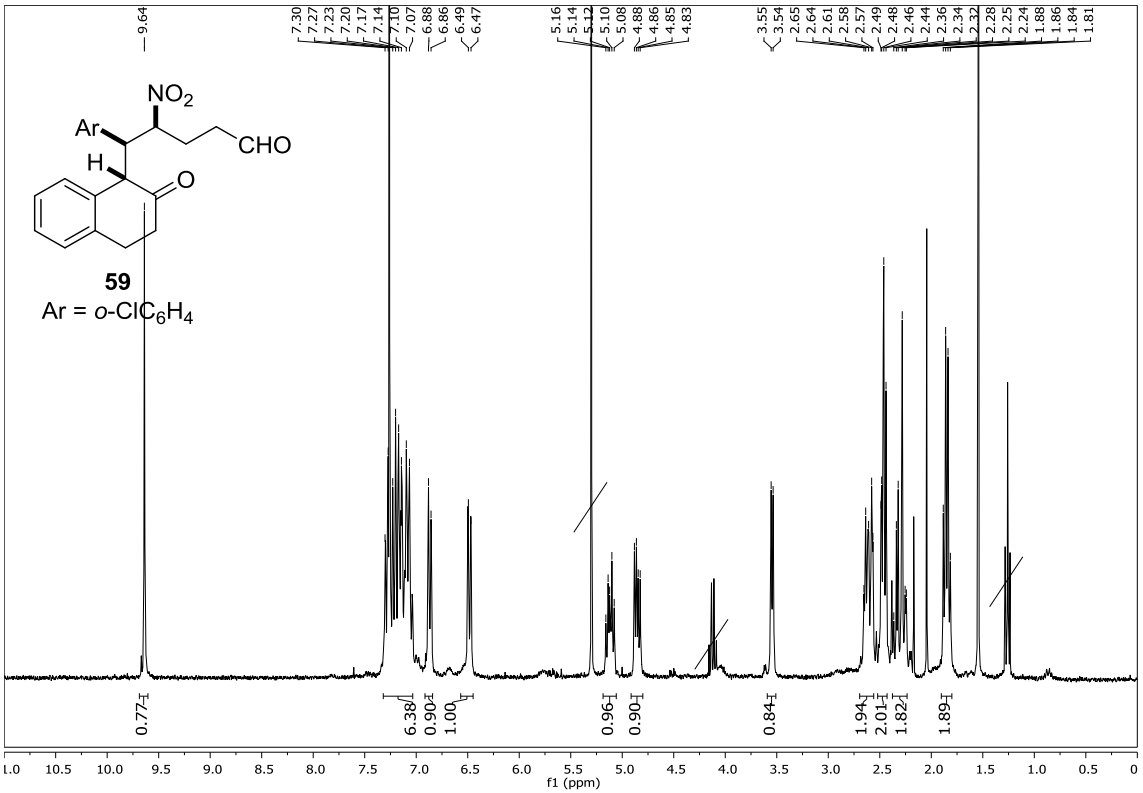

-2.98
-1.59
-0.25
100.00
NO2
Hb
Hc
Ph
Ph
Hd
Ha
He
NO2
OH
57'
e
c
OH
d
a
b
f1 (ppm)

NOESY

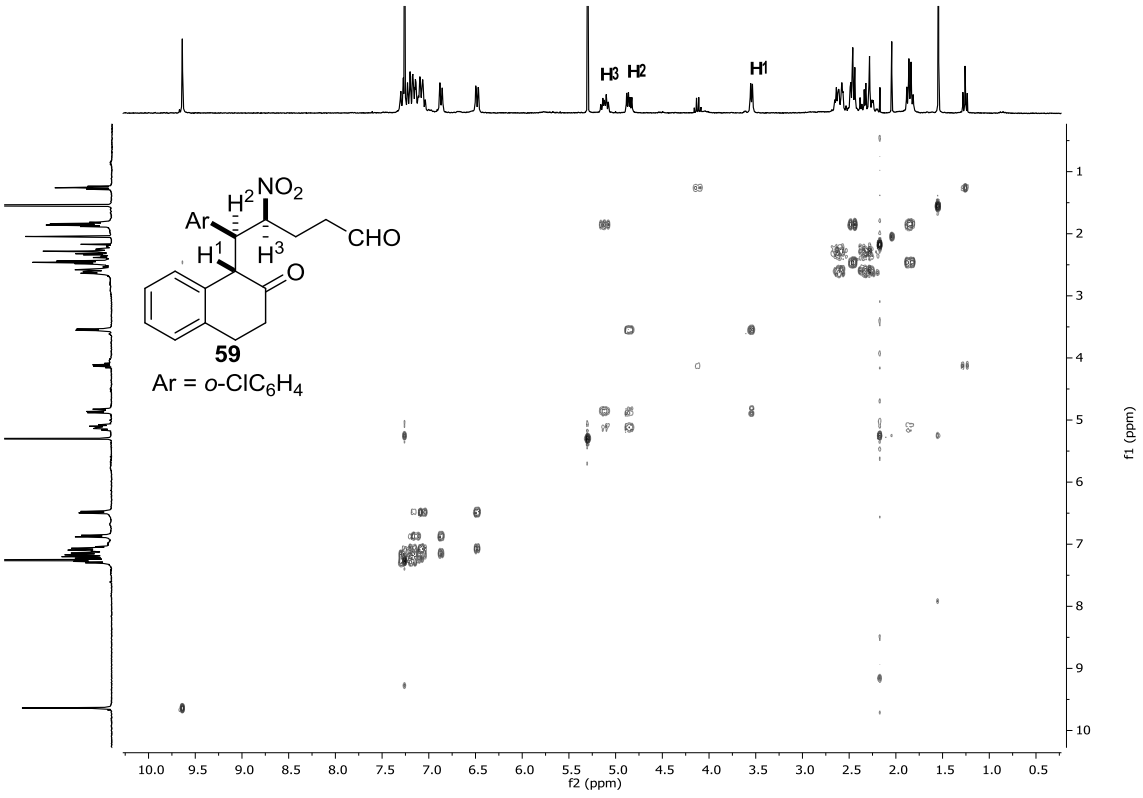

100.00
-1.36
-0.37
-2.05
NO2
Hb
Hc
Ph
Ph
Hd
Ha
He
NO2
OH
57'
e
c
OH
d
a
b
f1 (ppm)

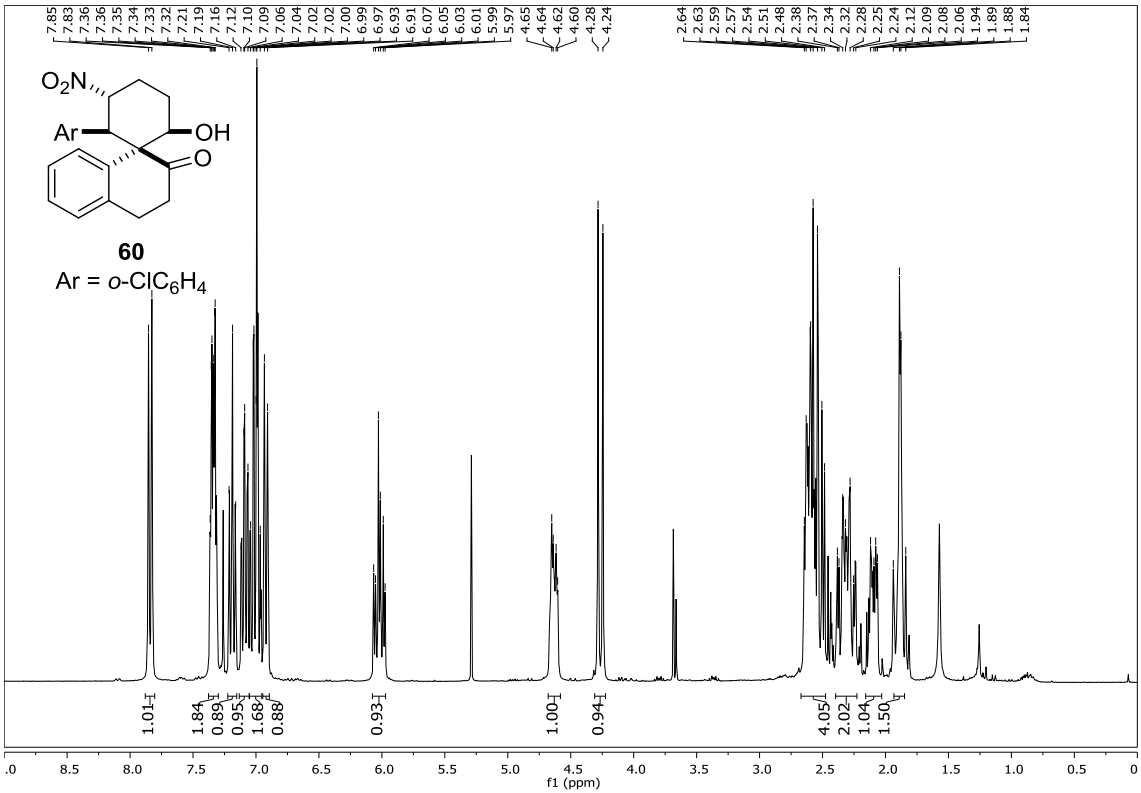

Cl
NO2
H
NO2
OH
58
f1 (ppm)

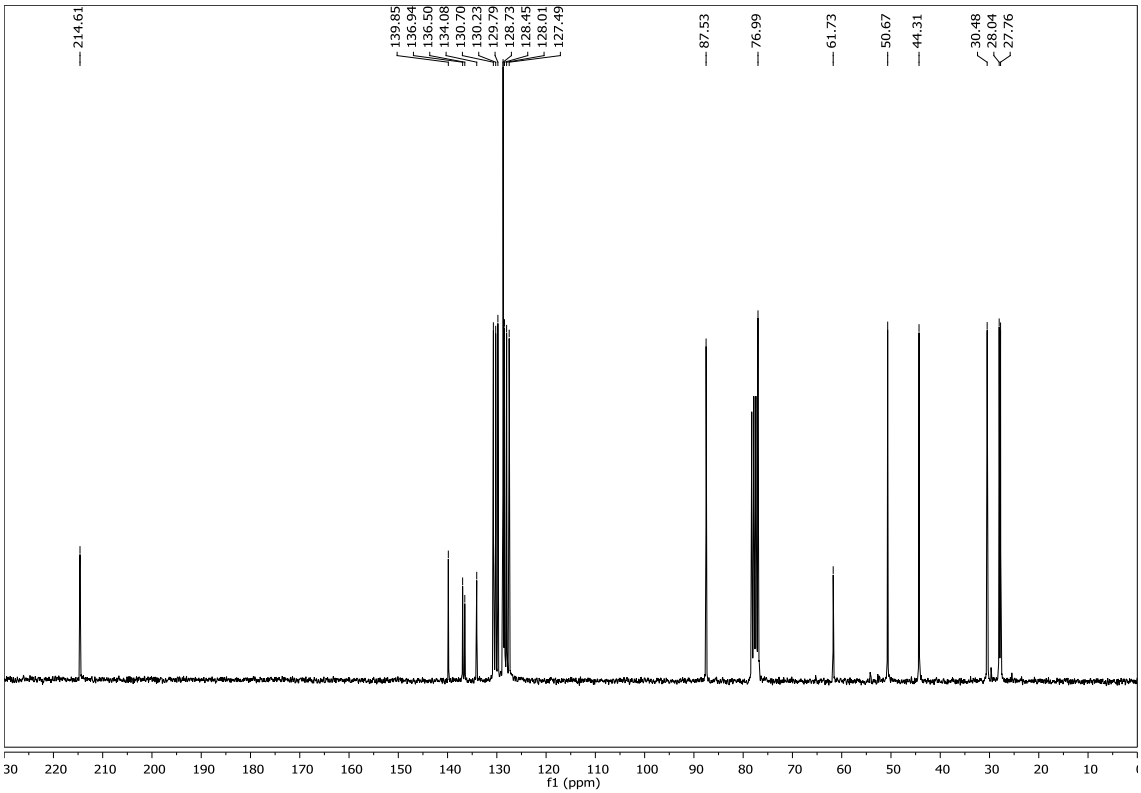

f1 (ppm)


9.64
7.30
7.27
7.23
7.20
7.17
7.14
7.10
7.07
6.88
6.86
6.49
6.47
5.16
5.14
5.12
5.10
5.08
4.88
4.86
4.85
4.83
3.55
3.54
2.65
2.64
2.61
2.58
2.57
2.49
2.48
2.46
2.44
2.36
2.34
2.32
2.28
2.25
2.24
1.88
1.86
1.84
1.81
NO2
Ar
H
CHO
O
59
Ar = o-ClC6H4
0.77
6.38
0.90
1.00
0.96
0.90
0.84
1.94
2.01
1.82
1.89
f1 (ppm)

COSSY


H3
H2
H1
NO2
H2
Ar
CHO
H1
H3
O
59
Ar = o-ClC6H4
f2 (ppm)
f1 (ppm)


O2N
Ar
OH
O
60
Ar = o-ClC6H4
f1 (ppm)


214.61
139.85
136.94
136.50
134.08
130.70
130.23
129.79
128.73
128.45
128.01
127.49
87.53
76.99
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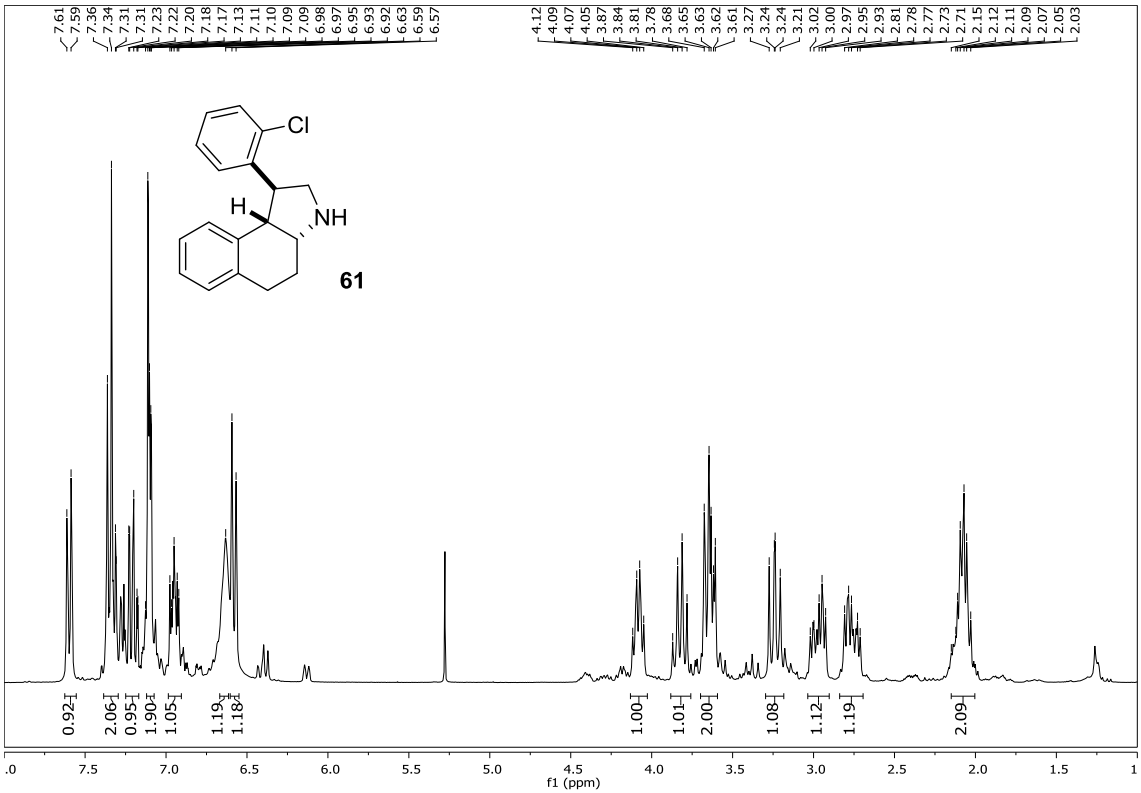
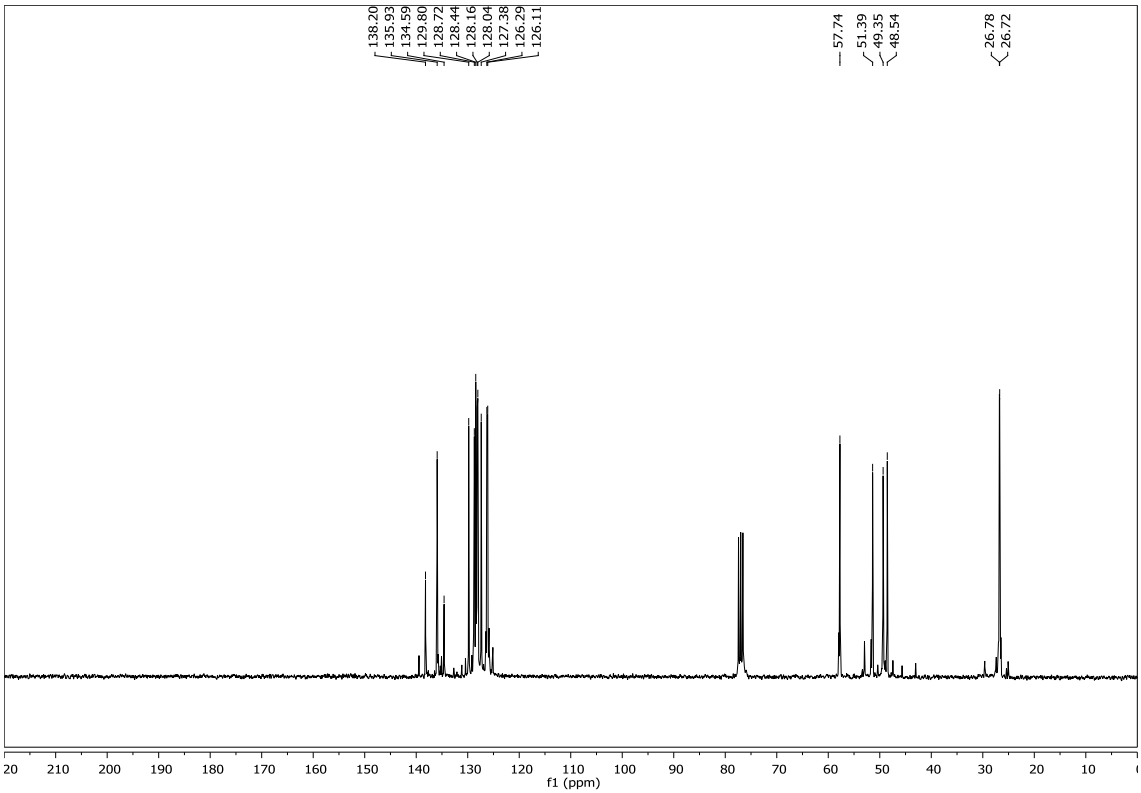
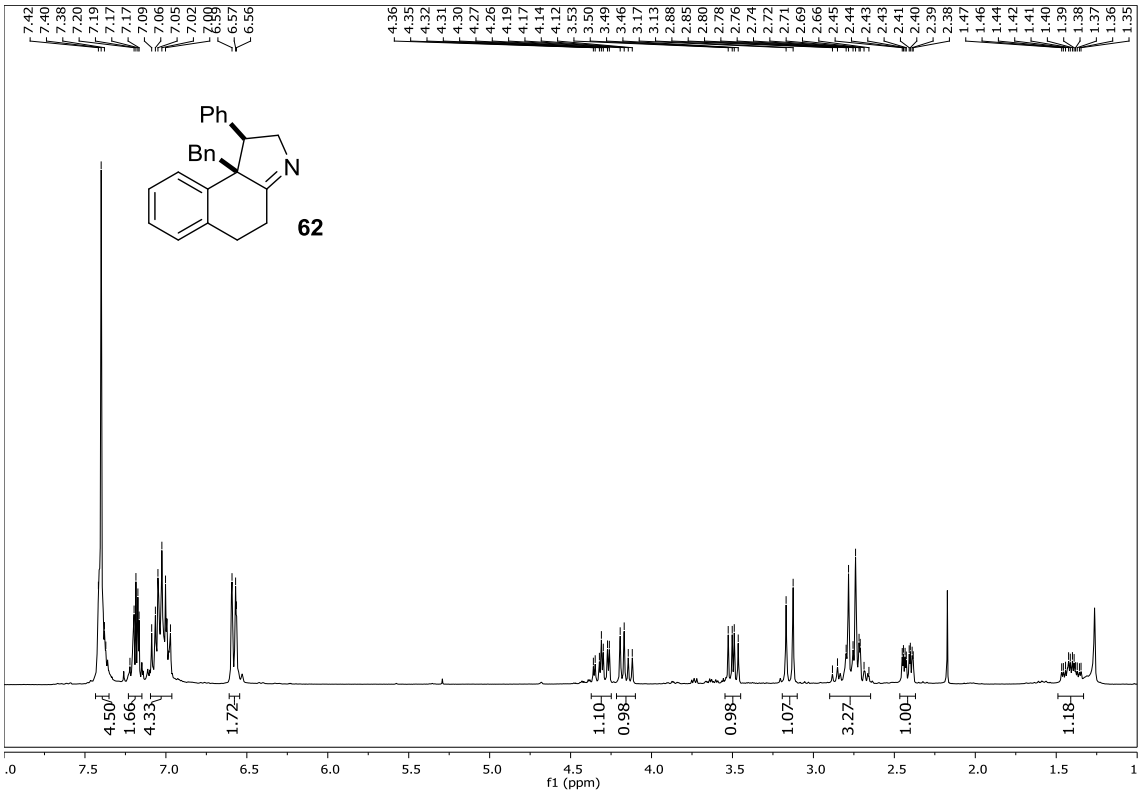
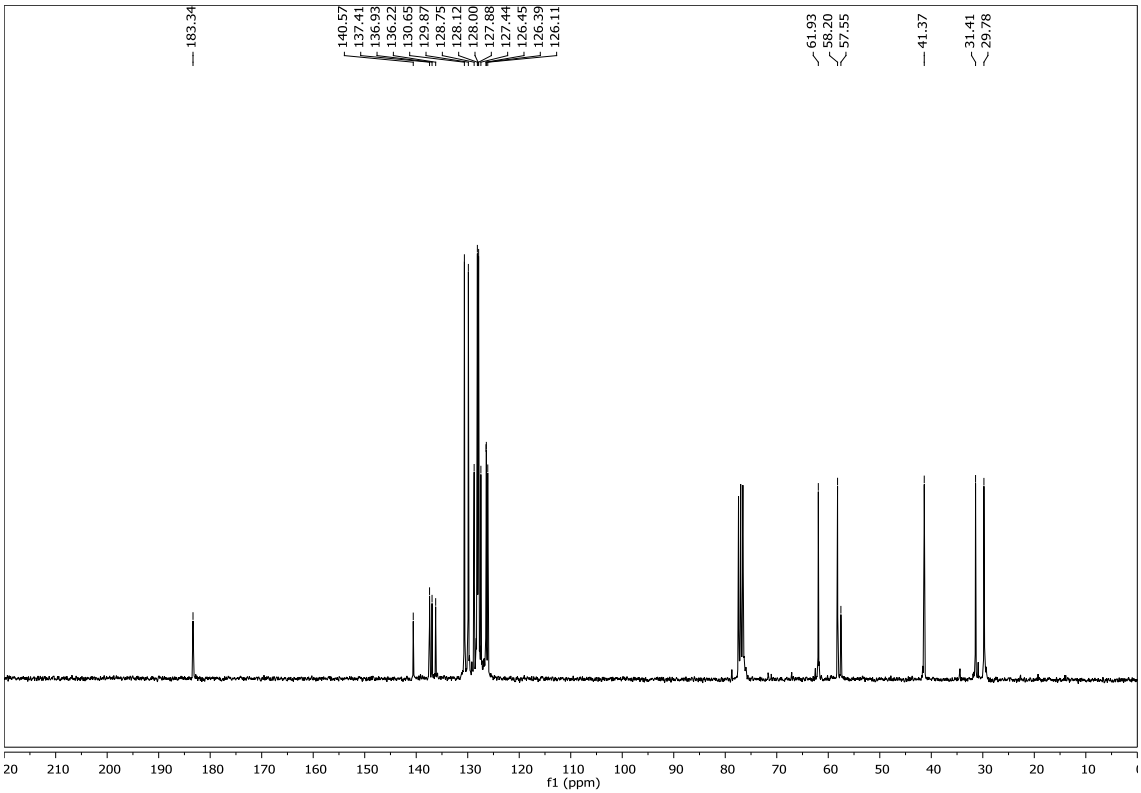
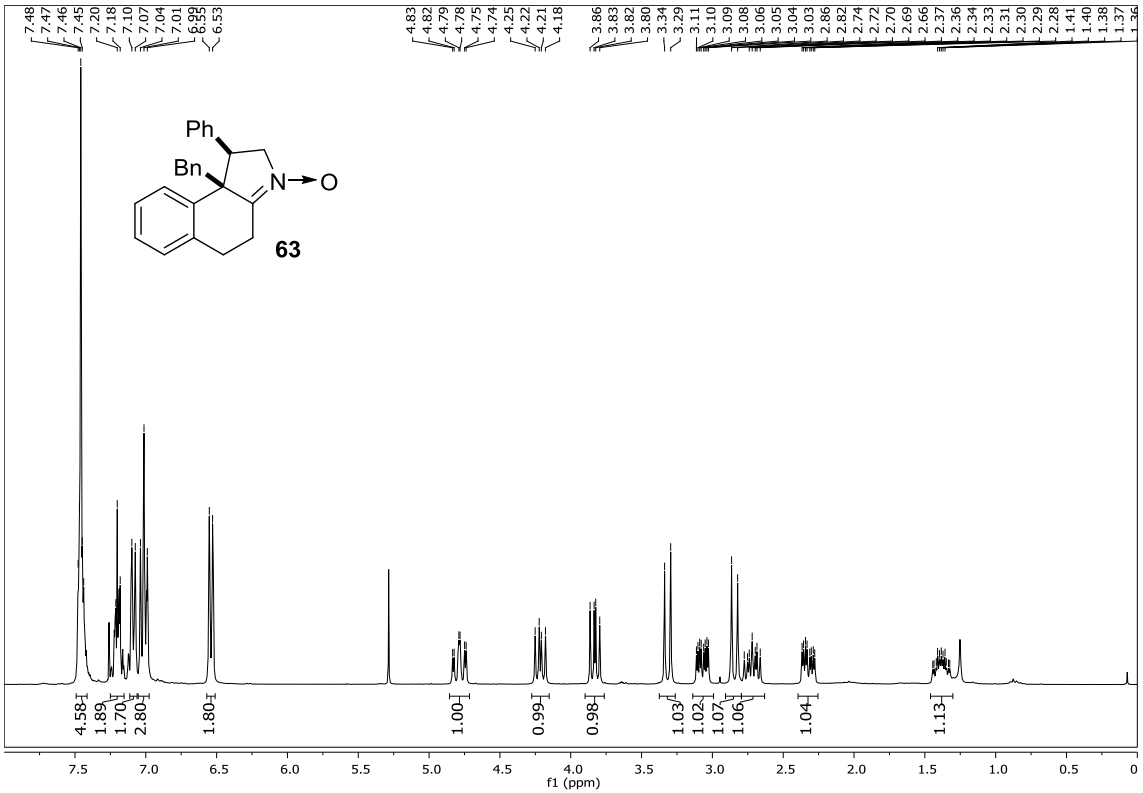
44.31
30.48
28.04
27.76
f1 (ppm)

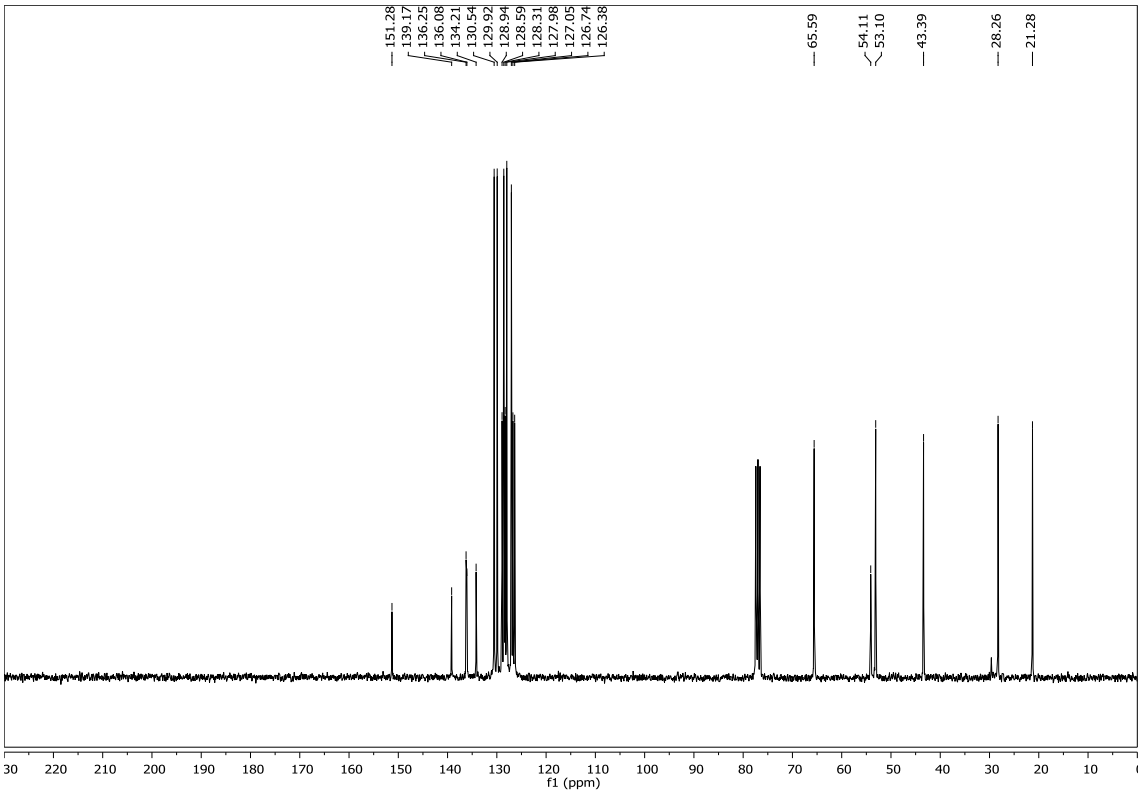

7.61
7.59
7.36
7.34
7.31
7.31
7.23
7.22
7.20
7.18
7.17
7.13
7.11
7.10
7.09
7.09
6.98
6.97
6.95
6.93
6.92
6.63
6.59
6.57
4.12
4.09
4.07
4.05
3.87
3.84
3.81
3.78
3.68
3.65
3.63
3.62
3.61
3.27
3.24
3.24
3.21
3.02
3.00
2.97
2.95
2.93
2.81
2.78
2.77
2.73
2.71
2.15
2.12
2.11
2.09
2.07
2.05
2.03
Cl
H
NH
61
0.92
2.06
0.95
1.90
1.05
1.19
1.18
1.00
1.01
2.00
1.08
1.12
1.19
2.09
f1 (ppm)

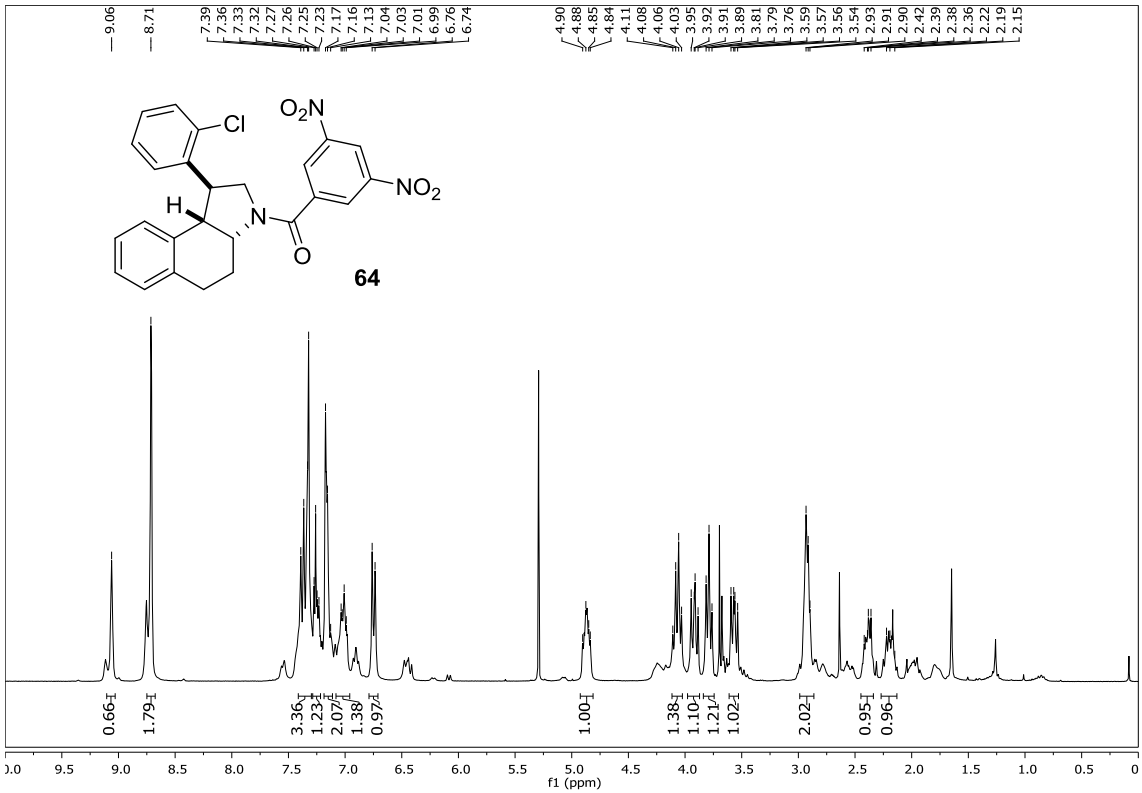

138.20
135.93
134.59
129.80
128.72
128.44
128.16
128.04
127.38
126.29
126.11
57.74
51.39
49.35
48.54
26.78
26.72
f1 (ppm)

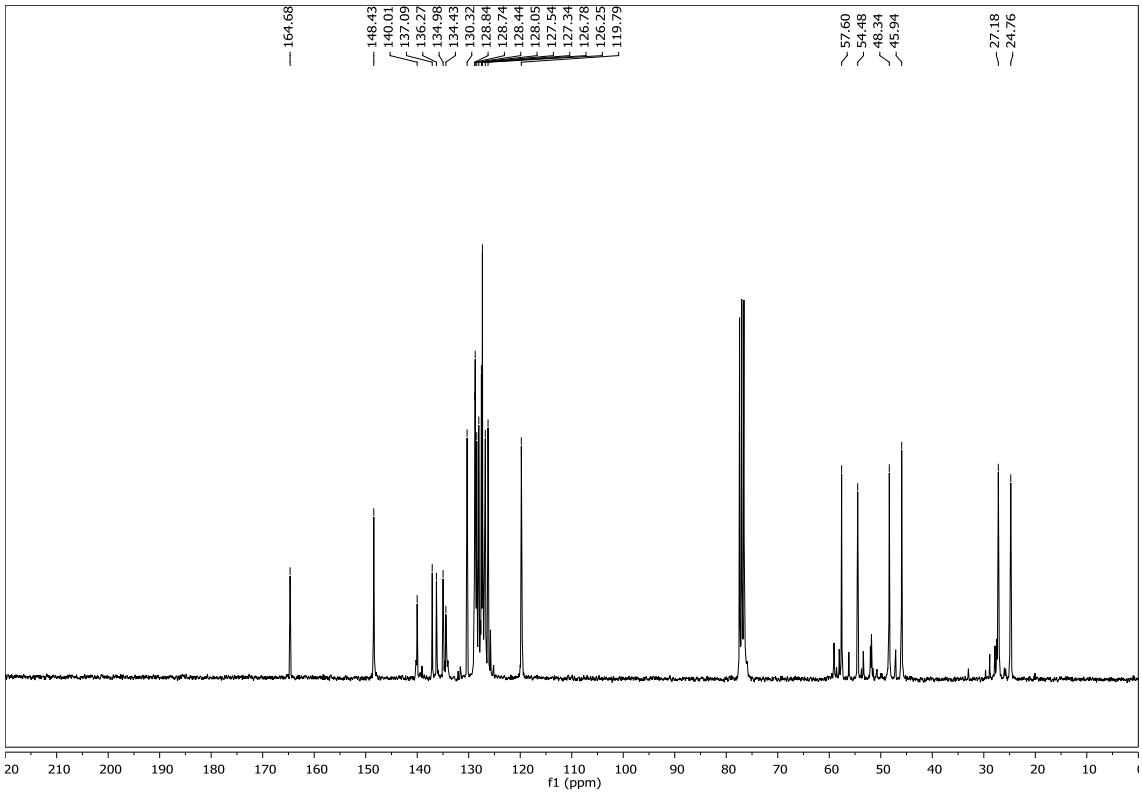

Ph
Bn
N
62
f1 (ppm)


f1 (ppm)

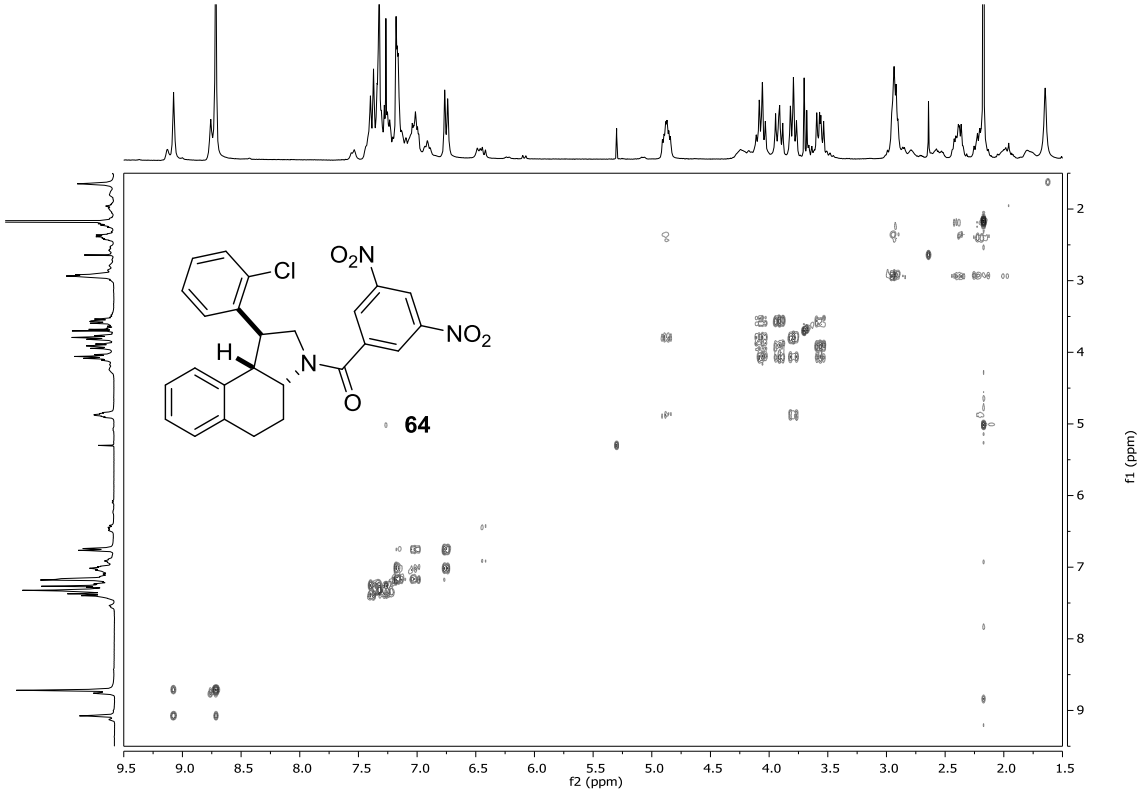

Ph
Bn
N→O
63
f1 (ppm)


f1 (ppm)

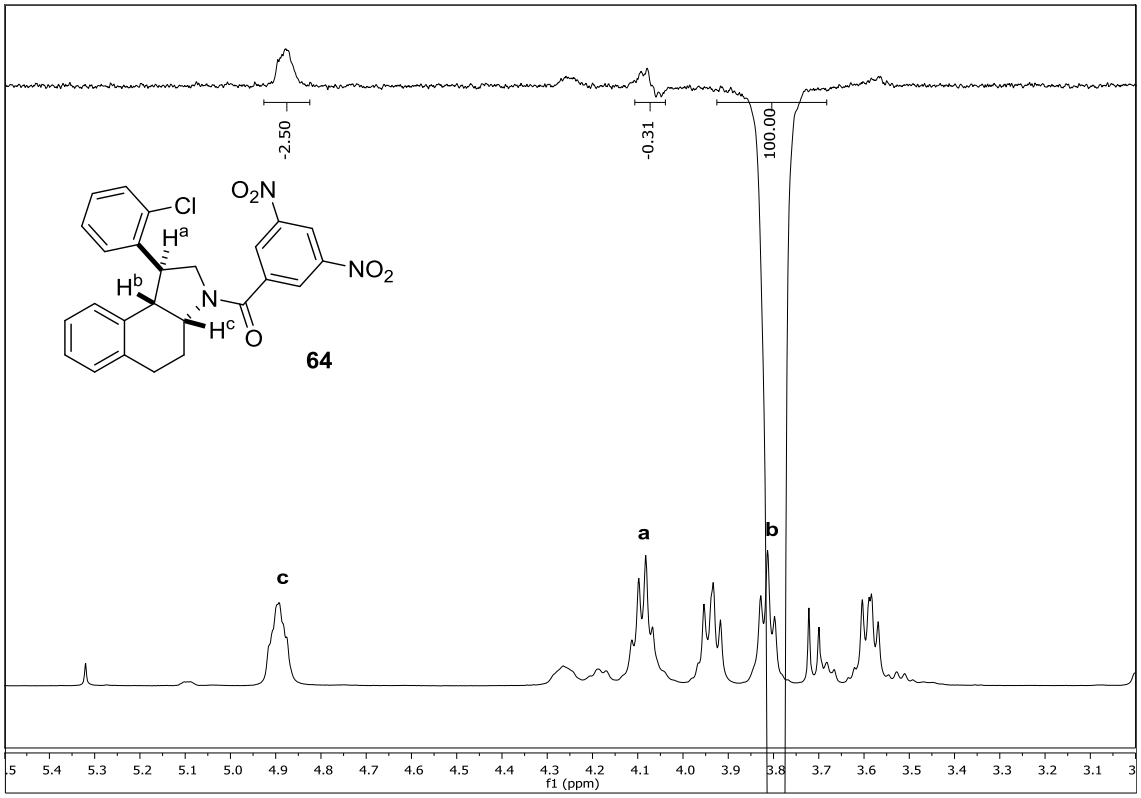

9.06
8.71
7.39
7.36
7.33
7.32
7.27
7.26
7.25
7.23
7.17
7.16
7.13
7.04
7.03
7.01
6.99
6.76
6.74
4.90
4.88
4.85
4.84
4.11
4.08
4.06
4.03
3.95
3.92
3.91
3.89
3.81
3.79
3.76
3.59
3.57
3.56
3.54
2.93
2.91
2.90
2.42
2.39
2.38
2.36
2.22
2.19
2.15
Cl
O2N
NO2
H
N
O
64
0.66
1.79
3.36
1.23
2.07
1.38
0.97
1.00
1.38
1.10
1.21
1.02
2.02
0.95
0.96
f1 (ppm)

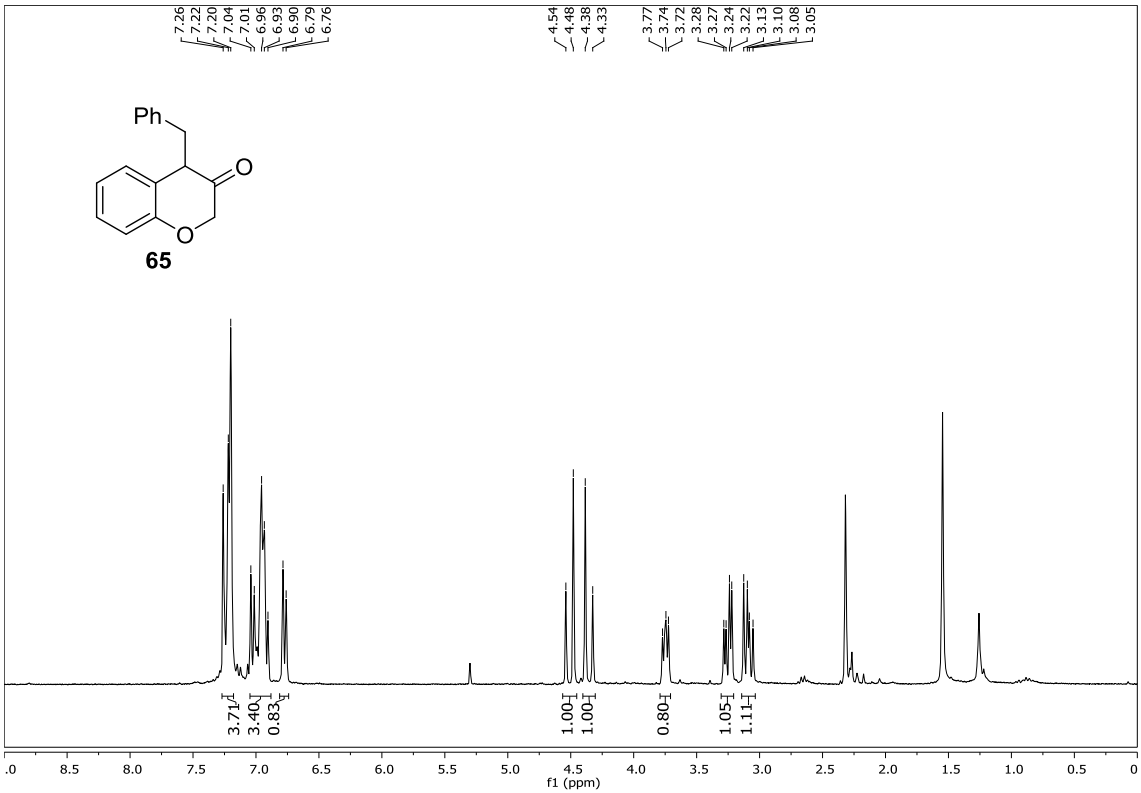

164.68
148.43
140.01
137.09
136.27
134.98
134.43
130.32
128.84
128.74
128.44
128.05
127.54
127.34
126.78
126.25
119.79
57.60
54.48
48.34
45.94
27.18
24.76
f1 (ppm)

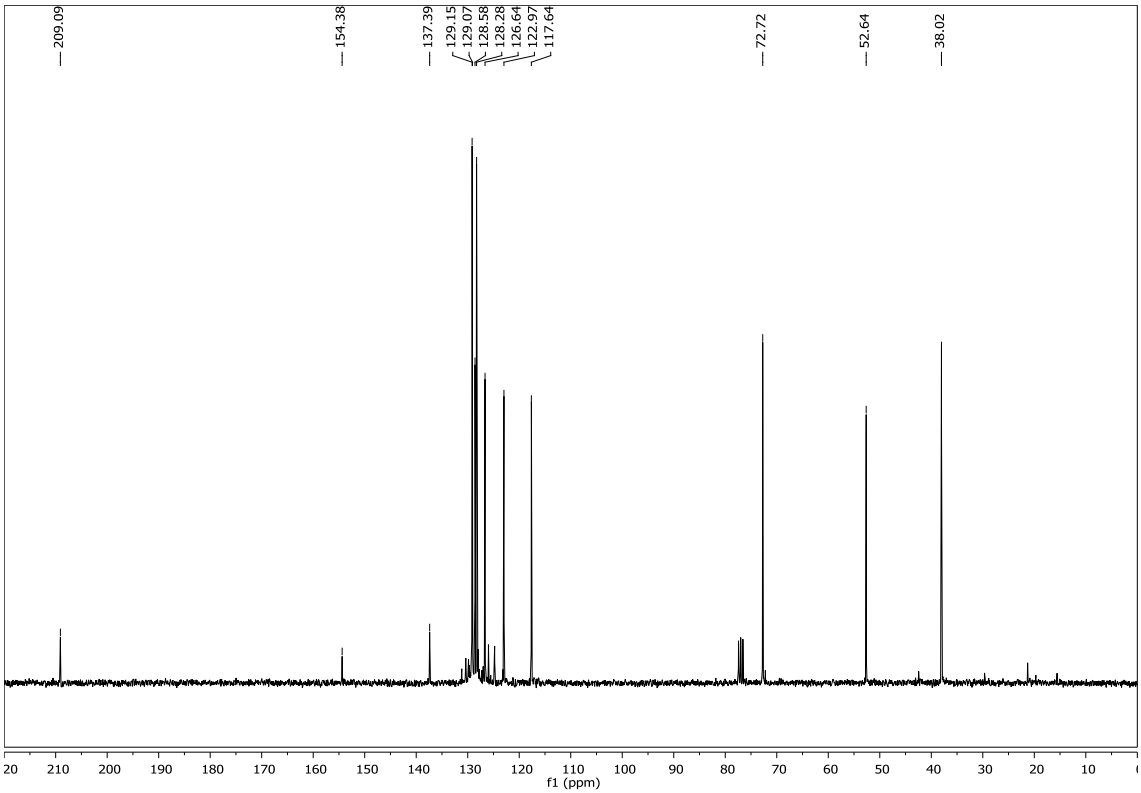
COSSY

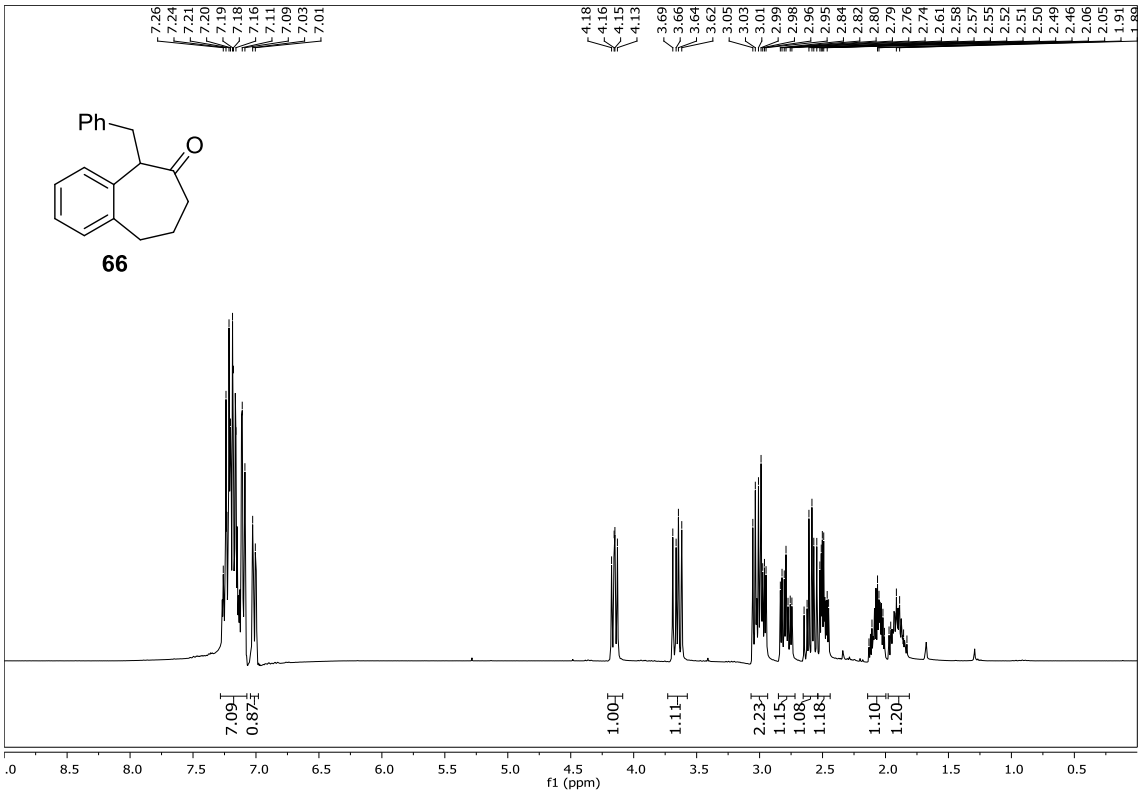

Cl
O_2N
NO_2
H
N
O
64
f2 (ppm)
f1 (ppm)

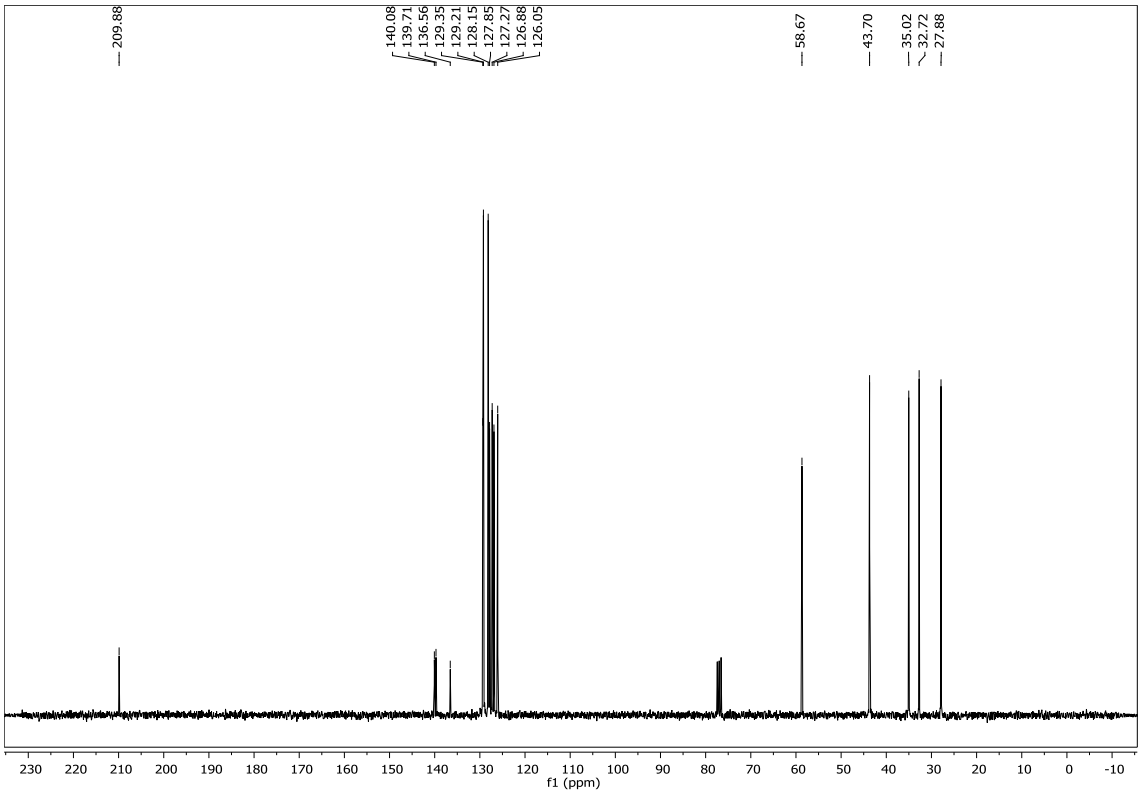
NOESY

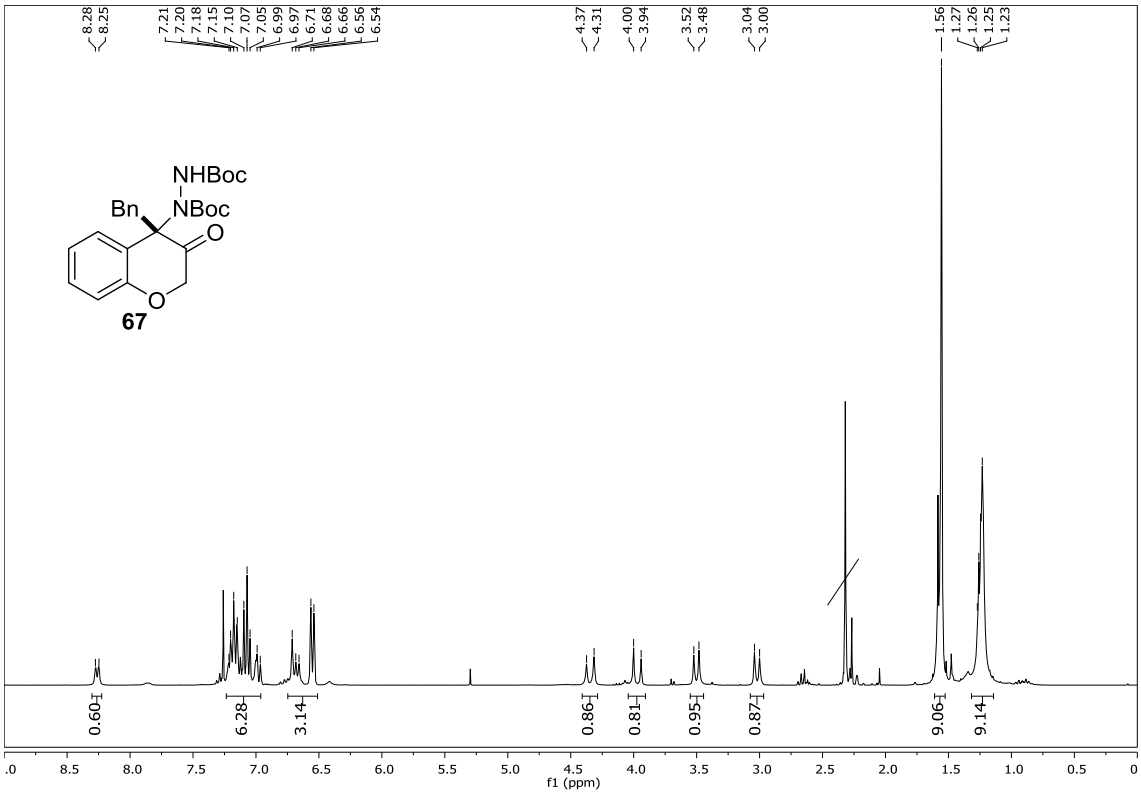

-2.50
-0.31
100.00
Cl
O_2N
NO_2
H^a
H^b
H^c
N
O
64
a
b
c
f1 (ppm)

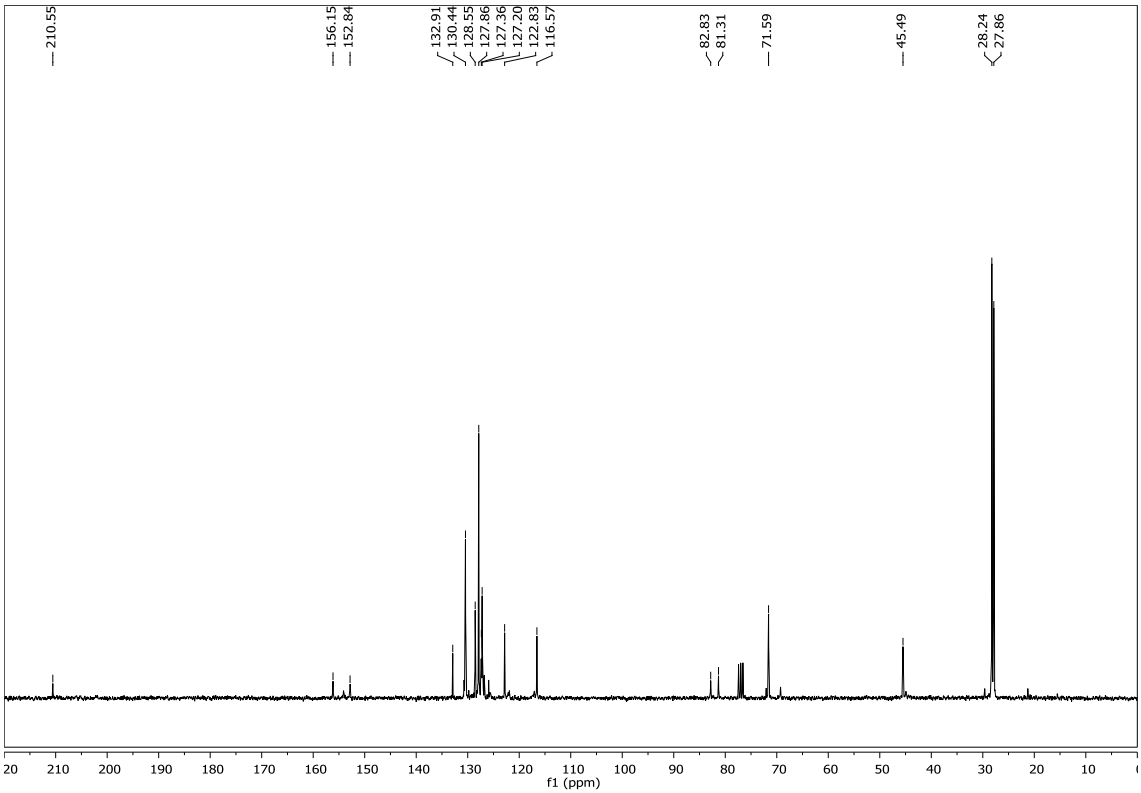

7.26
7.22
7.20
7.04
7.01
6.96
6.93
6.90
6.79
6.76
4.54
4.48
4.38
4.33
3.77
3.74
3.72
3.28
3.27
3.24
3.22
3.13
3.10
3.08
3.05
Ph
O
O
65
3.71
3.40
0.83
1.00
1.00
0.80
1.05
1.11
f1 (ppm)


209.09
154.38
137.39
129.15
129.07
128.58
128.28
126.64
122.97
117.64
72.72
52.64
38.02
f1 (ppm)


Ph
O
66
f1 (ppm)

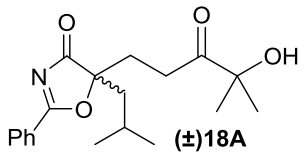

209.88
140.08
139.71
136.56
129.35
129.21
128.15
127.85
127.27
126.88
126.05
58.67
43.70
35.02
32.72
27.88
f1 (ppm)


8.28
8.25
7.21
7.20
7.18
7.15
7.10
7.07
7.05
6.99
6.97
6.71
6.68
6.66
6.56
6.54
4.37
4.31
4.00
3.94
3.52
3.48
3.04
3.00
1.56
1.27
1.26
1.25
1.23
NHBoc
Bn
NBoc
O
O
67
0.60
6.28
3.14
0.86
0.81
0.95
0.87
9.06
9.14
f1 (ppm)

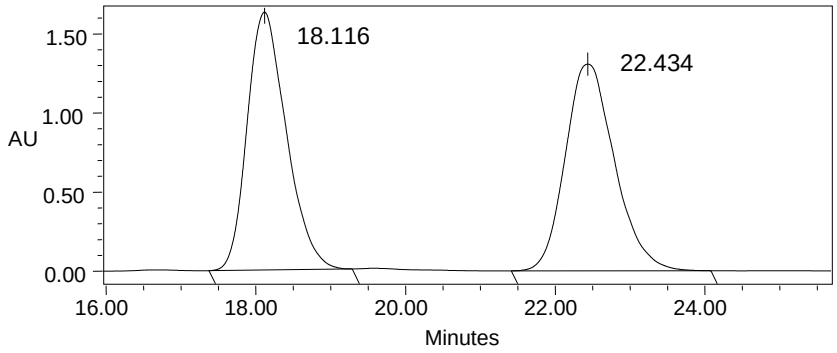

210.55
156.15
152.84
132.91
130.44
128.55
127.86
127.36
127.20
122.83
116.57
82.83
81.31
71.59
45.49
28.24
27.86
f1 (ppm)

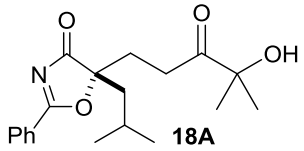
5.4.25. HPLC chromatograms

Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 260 nm

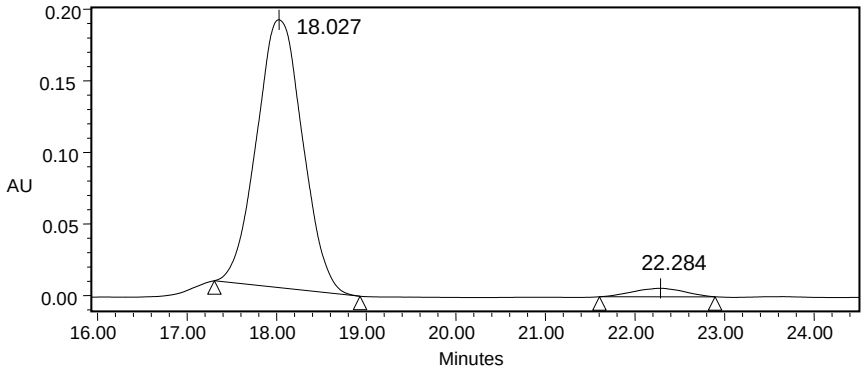


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.116	59260735	49.83	1629621
2	PDA 260.0 nm	22.434	59667978	50.17	1305917

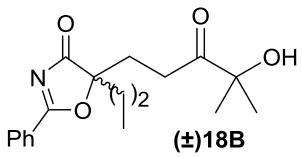




	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.027	6700761	96.59	187065
2	PDA 260.0 nm	22.284	236344	3.41	5894

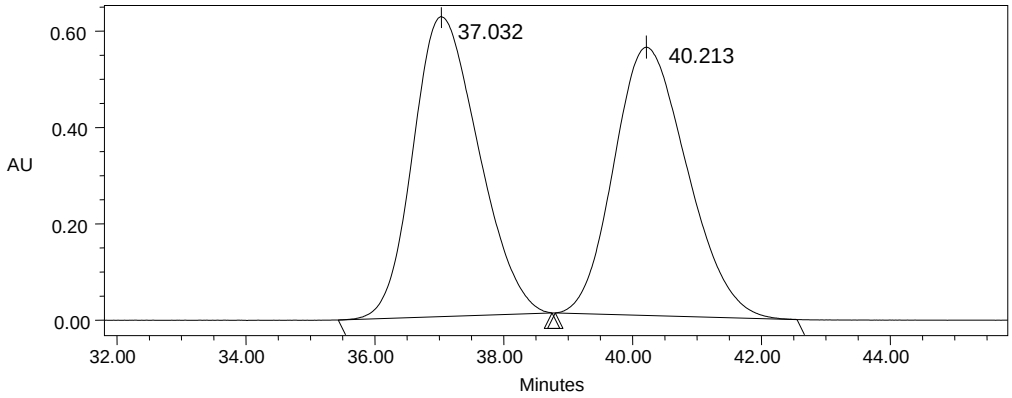


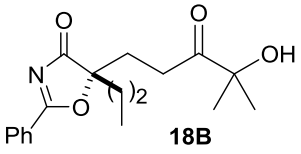
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 260 nm



(±)18B

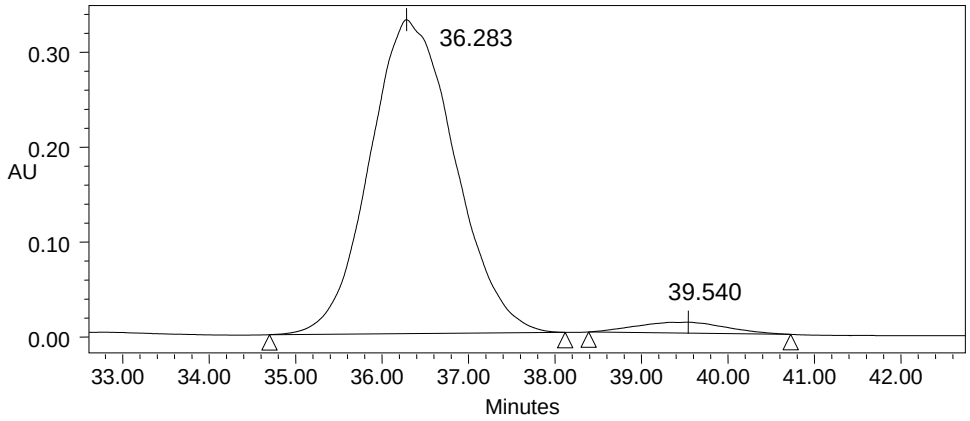
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	37.032	44049090	50.05	622372
2	PDA 260.0 nm	40.213	43956027	49.95	556604



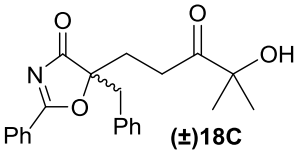


18B

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	36.283	22643618	96.48	330773
2	PDA 260.0 nm	39.540	826705	3.52	11595

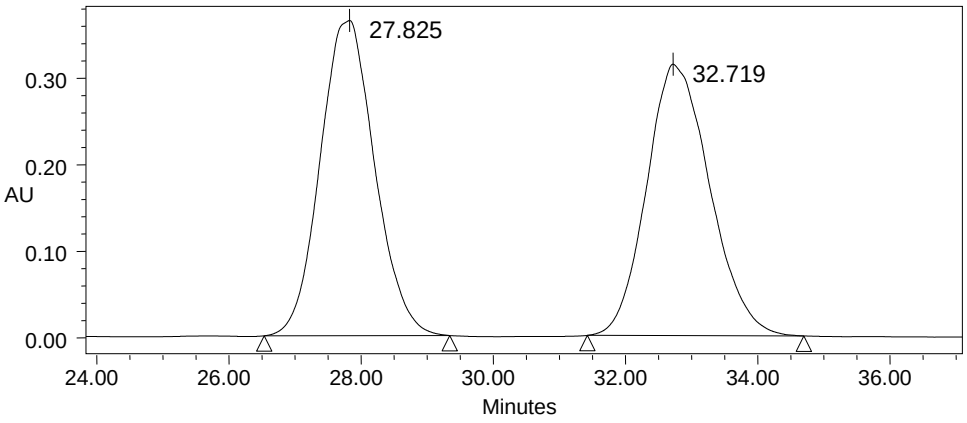


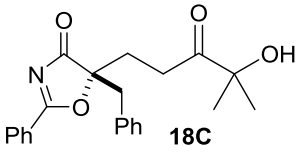
Chiralpack IC, 1 mL/min, hexane/isopropanol 85:15, λ = 260 nm



(±)18C

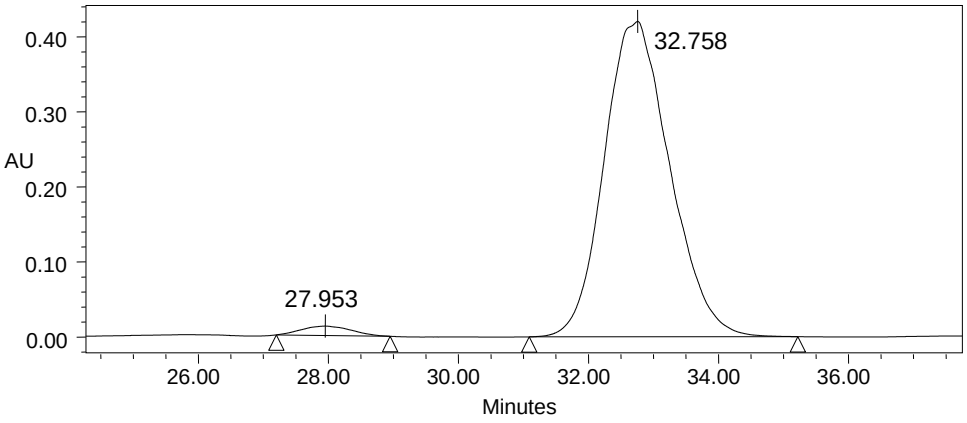
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	27.825	20941551	50.07	364212
2	PDA 260.0 nm	32.719	20880273	49.93	313597



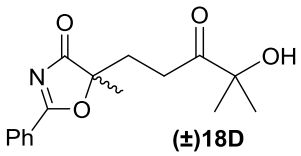


18C

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	27.953	660767	2.19	12549
2	PDA 260.0 nm	32.758	29507186	97.81	420246

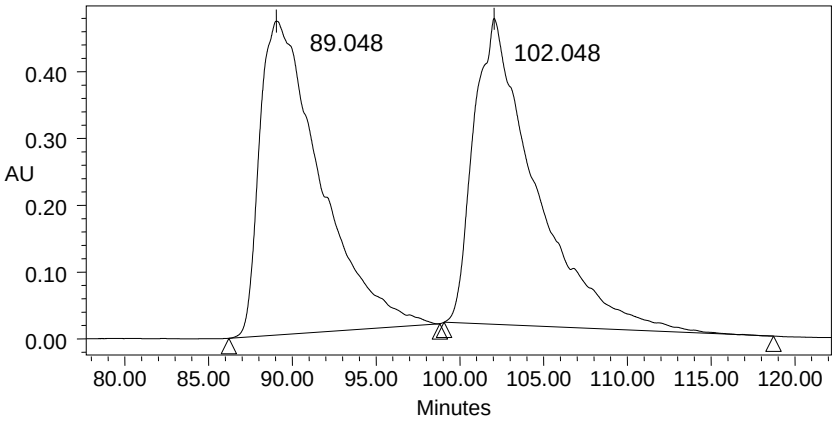


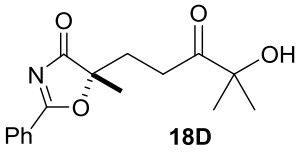
Chiralpack IA, 1 mL/min, hexane/isopropanol 98:2, λ = 260 nm



(±)18D

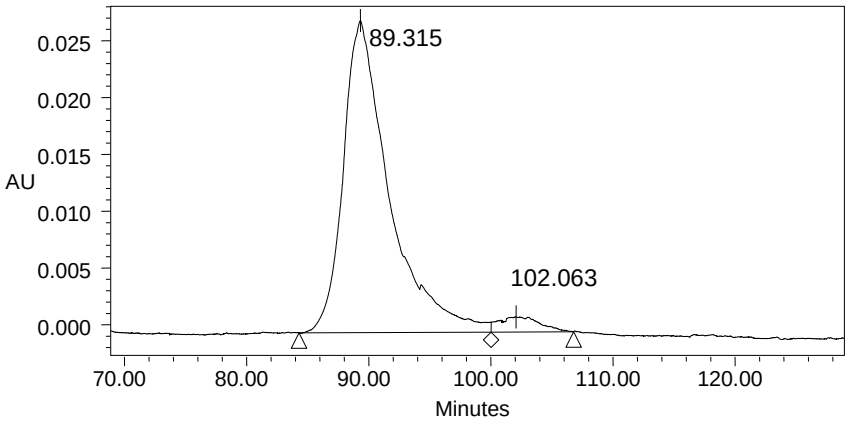
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	89.048	118497342	50.16	469984
2	PDA 260.0 nm	102.048	117740828	49.84	458109



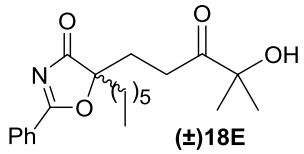


18D

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	89.315	7180567	95.79	27471
2	PDA 260.0 nm	102.063	315618	4.21	1329

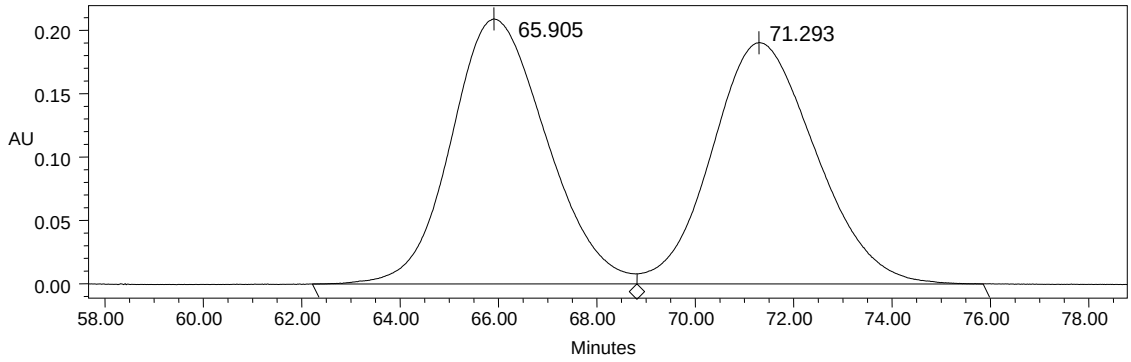


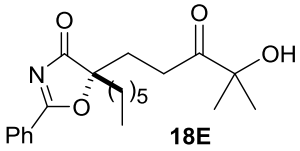
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 260 nm



(±)18E

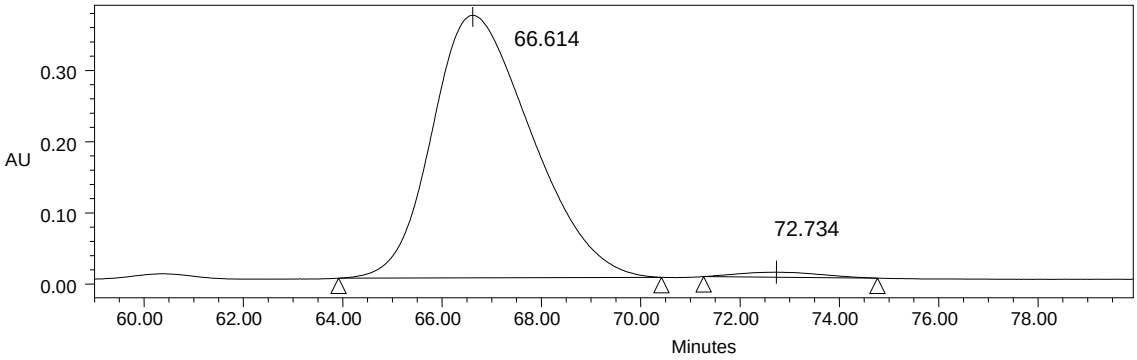
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	65.905	28191425	50.22	209121
2	PDA 260.0 nm	71.293	27942136	49.78	190342



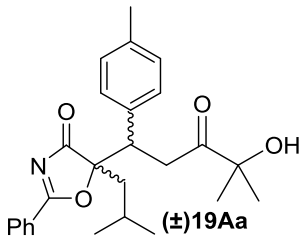


18E

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	66.614	51179803	98.42	368486
2	PDA 260.0 nm	72.734	820824	1.58	7110

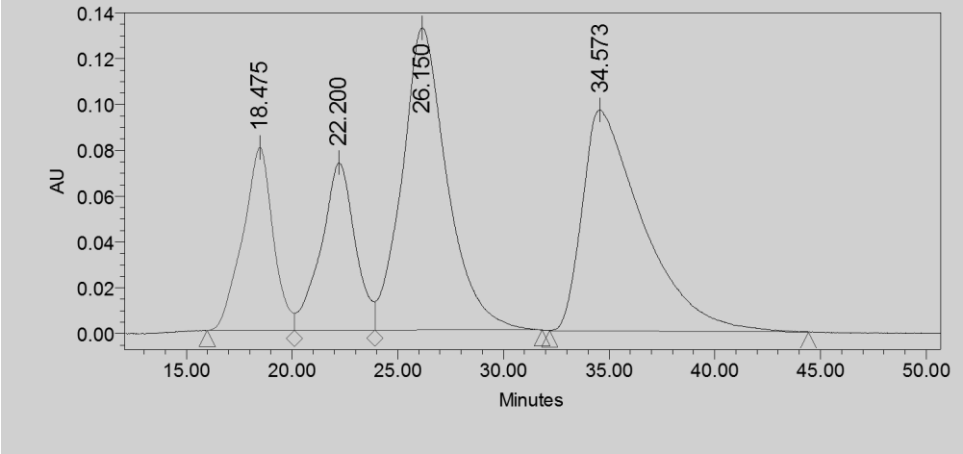


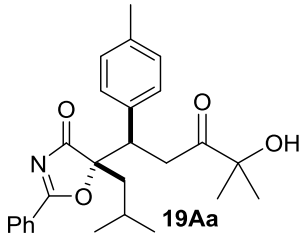
Chiralpack IB, 1 mL/min, hexane/isopropanol 98:2, λ = 260 nm



Processed Channel Descr.: PDA 260.0 nm

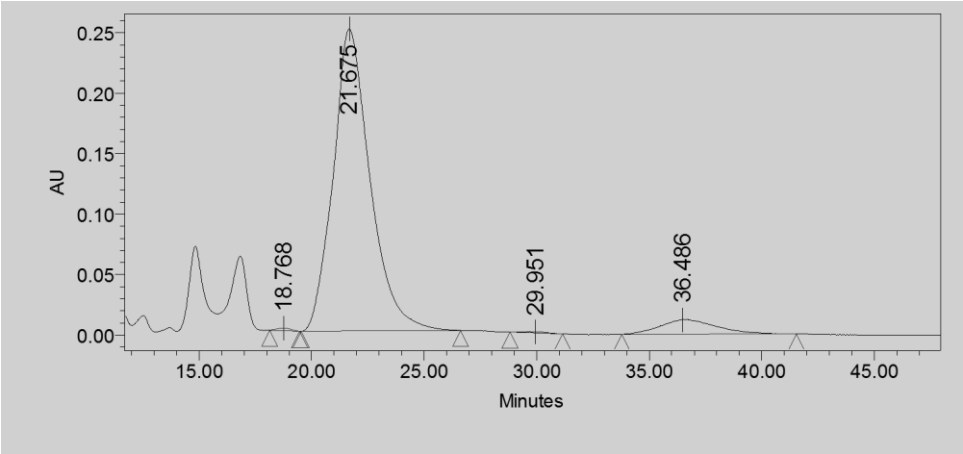
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.475	7978927	14.51	79920
2	PDA 260.0 nm	22.200	8161399	14.85	73067
3	PDA 260.0 nm	26.150	19563172	35.58	131901
4	PDA 260.0 nm	34.573	19272657	35.06	96637



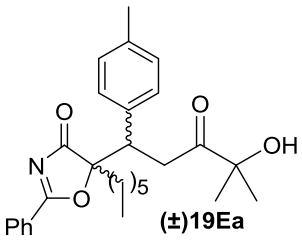


Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.768	95933	0.31	2270
2	PDA 250.0 nm	21.675	28488836	92.62	249852
3	PDA 250.0 nm	29.951	72674	0.24	1021
4	PDA 250.0 nm	36.486	2102577	6.84	12072

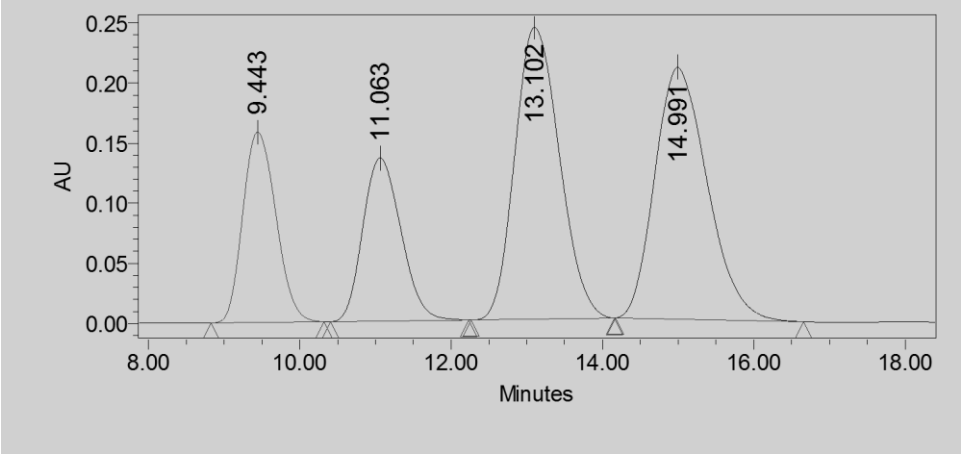


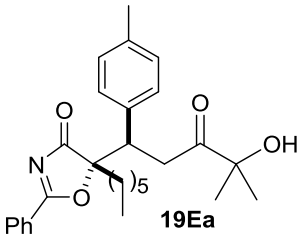
Chiralpack IC, 1 mL/min, hexane/isopropanol 80:20, λ = 260 nm



Processed Channel Descr.: PDA 260.0 nm

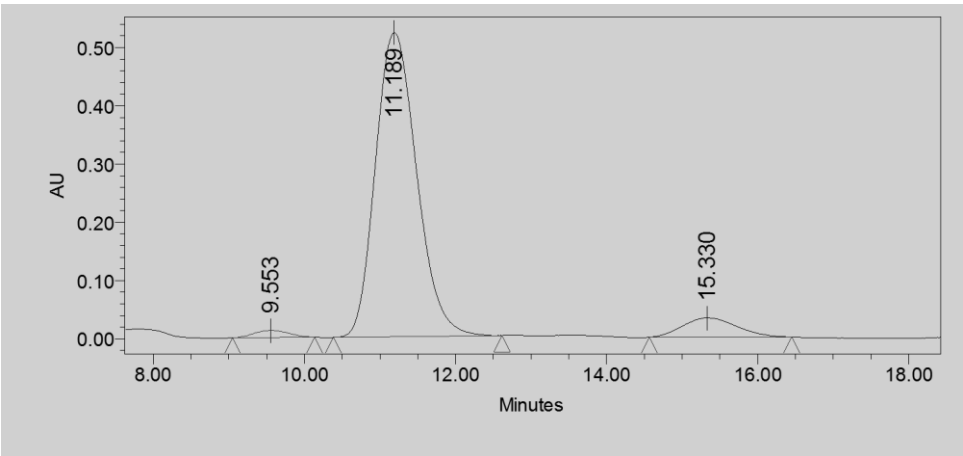
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	9.443	4821848	16.27	158449
2	PDA 260.0 nm	11.063	4762599	16.07	135827
3	PDA 260.0 nm	13.102	9941986	33.54	242748
4	PDA 260.0 nm	14.991	10115316	34.13	209634



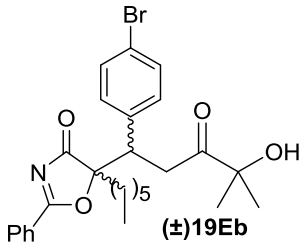


Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	9.553	393868	1.81	12294
2	PDA 260.0 nm	11.189	19794059	90.72	522490
3	PDA 260.0 nm	15.330	1631914	7.48	33016



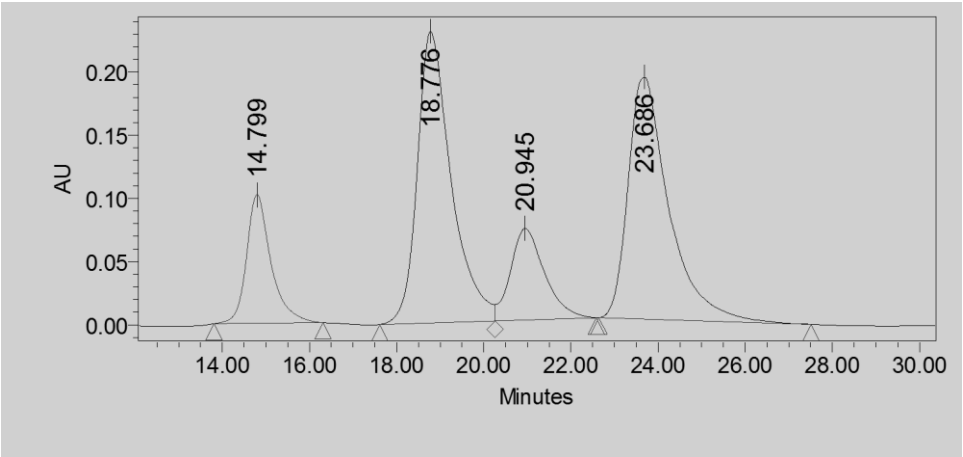
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm

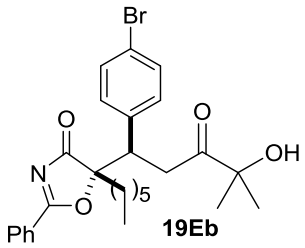


(±)19Eb

Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	14.799	3969749	12.11	101829
2	PDA 250.0 nm	18.776	12466053	38.02	230608
3	PDA 250.0 nm	20.945	3933109	12.00	72592
4	PDA 250.0 nm	23.686	12417080	37.87	191382

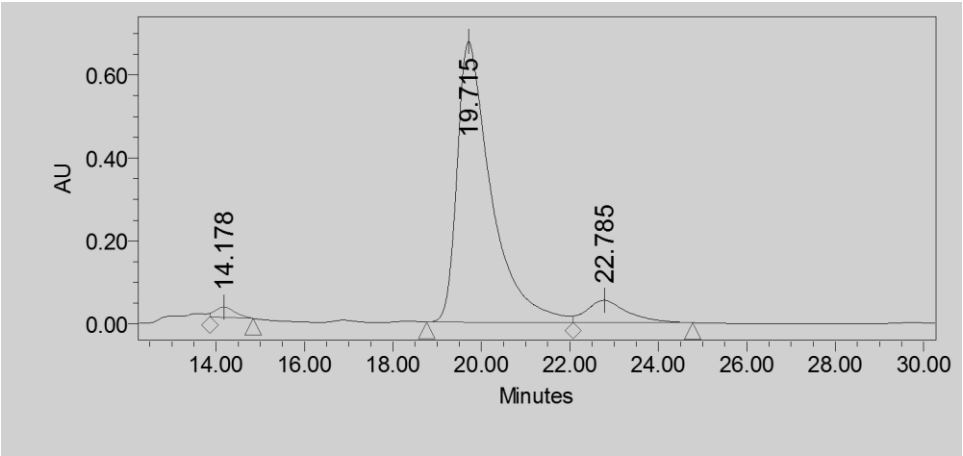




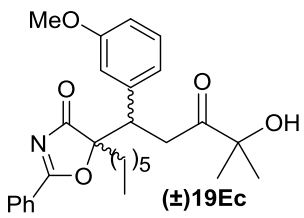
19Eb

Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	14.178	770917	1.91	24589
2	PDA 260.0 nm	19.715	36266603	89.65	676831
3	PDA 260.0 nm	22.785	3418193	8.45	53620

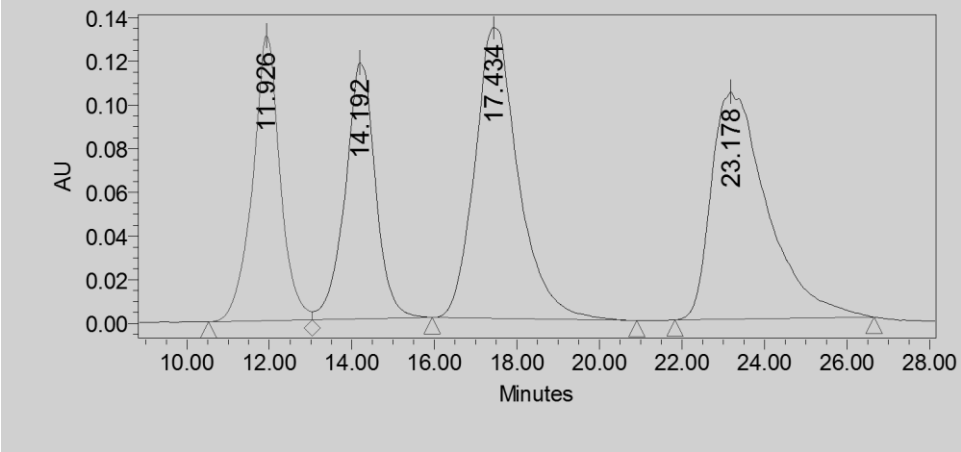


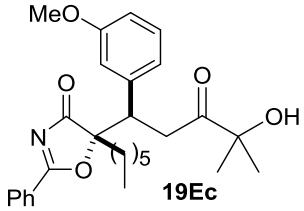
Chiralpack IB, 1 mL/min, hexane/isopropanol 95:5, λ = 250 nm



Processed Channel Descr.: PDA 250.0 nm

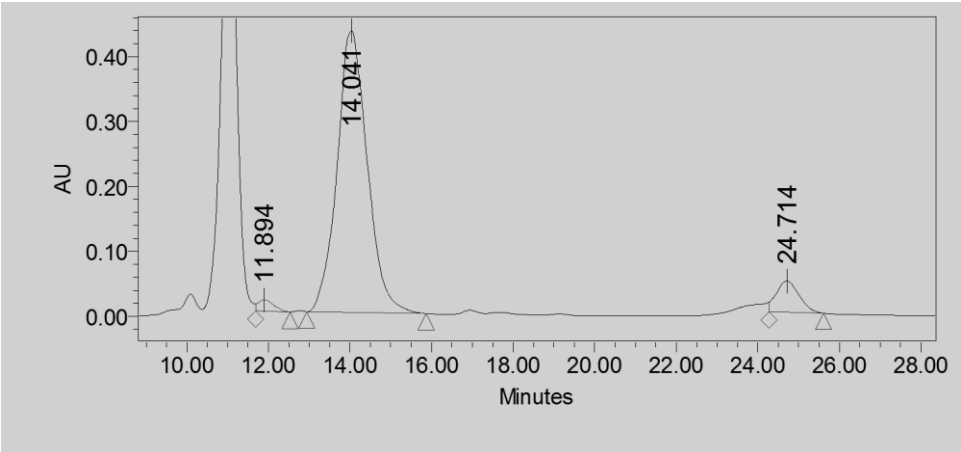
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	11.926	6047064	19.11	130505
2	PDA 250.0 nm	14.192	5984595	18.92	117190
3	PDA 250.0 nm	17.434	9791771	30.95	133192
4	PDA 250.0 nm	23.178	9812962	31.02	103965



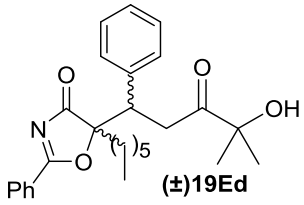


Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 255.0 nm	11.894	467820	1.89	17667
2	PDA 255.0 nm	14.041	22358074	90.56	433708
3	PDA 255.0 nm	24.714	1861859	7.54	47868

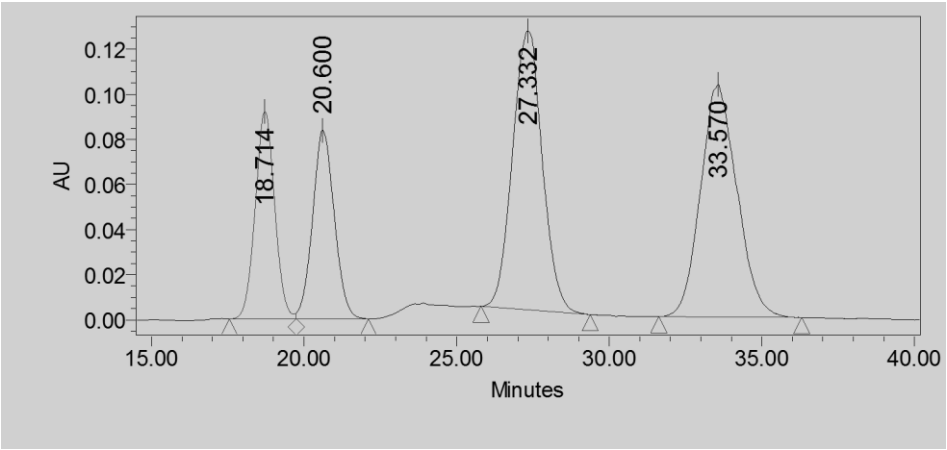


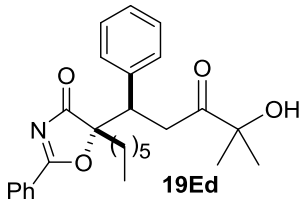
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 250 nm



Processed Channel Descr.: PDA 250.0 nm

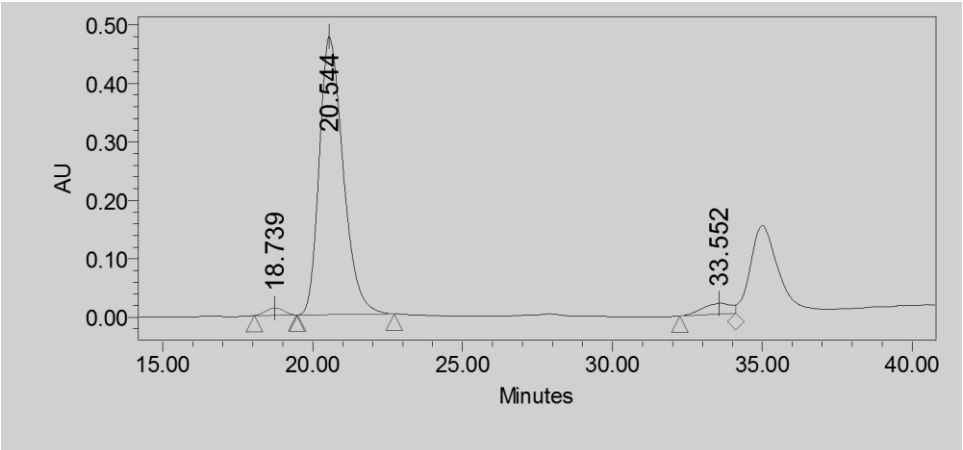
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.714	4063858	16.17	91873
2	PDA 250.0 nm	20.600	4126524	16.42	83675
3	PDA 250.0 nm	27.332	8387860	33.38	123623
4	PDA 250.0 nm	33.570	8553447	34.03	102997



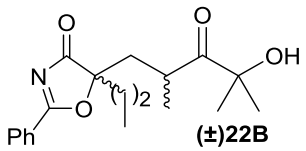


Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.739	525473	1.87	12484
2	PDA 250.0 nm	20.544	26371608	93.69	475634
3	PDA 250.0 nm	33.552	1251363	4.45	18581

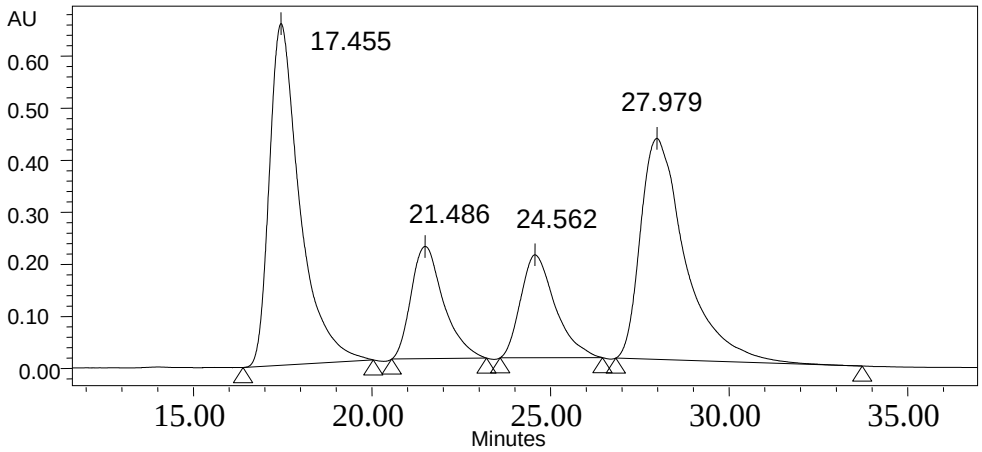


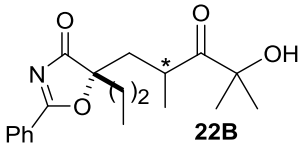
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 260 nm



(±)22B

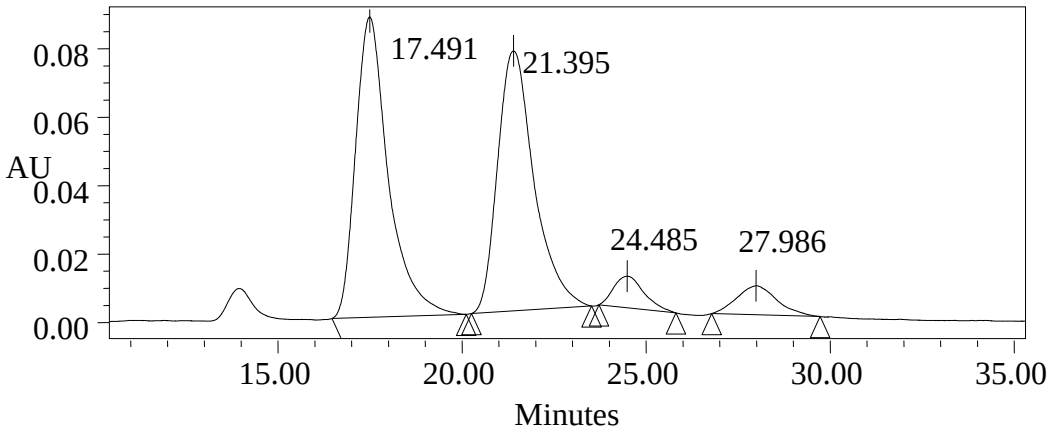
Retention Time	% Area
17.455	37.83
21.486	13.25
24.562	12.87
27.979	36.06



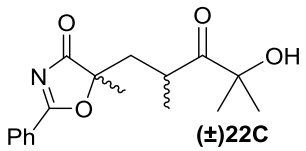


22B

Retention Time	% Area
17.491	45.97
21.395	44.22
24.485	4.74
27.986	5.07

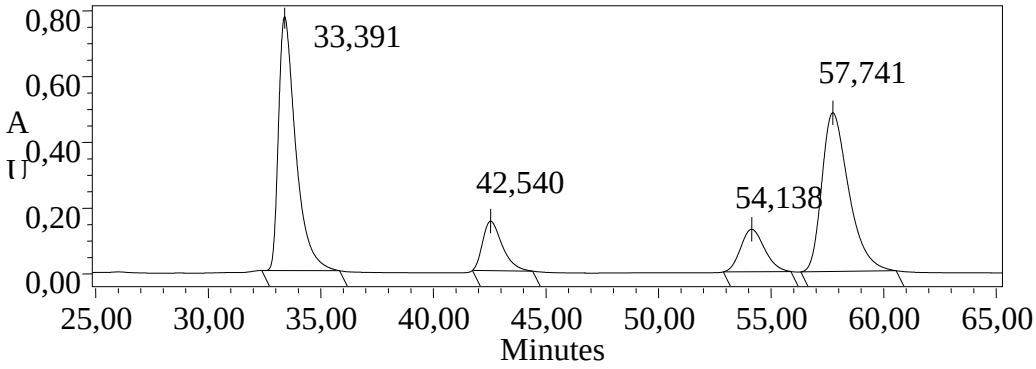


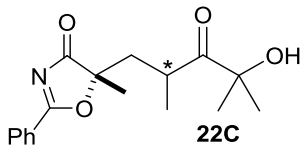
Chiralpack IA+AY-H, 0.5 mL/min, hexane/isopropanol 80:20, λ = 260 nm



(±)22C

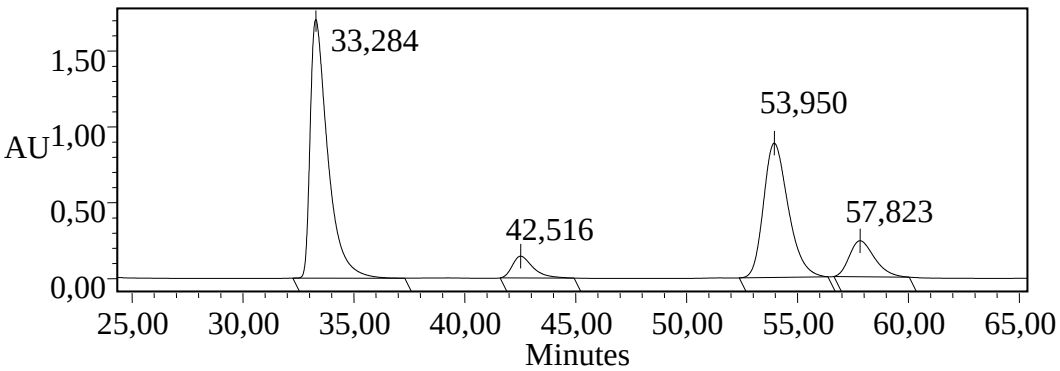
Retention Time	% Area
33,391	41,07
42,540	9,14
54,138	9,54
57,741	40,25



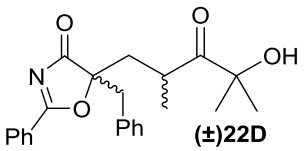


22C

Retention Time	% Area
33,284	50,35
42,516	4,22
53,950	36,27
57,823	9,16

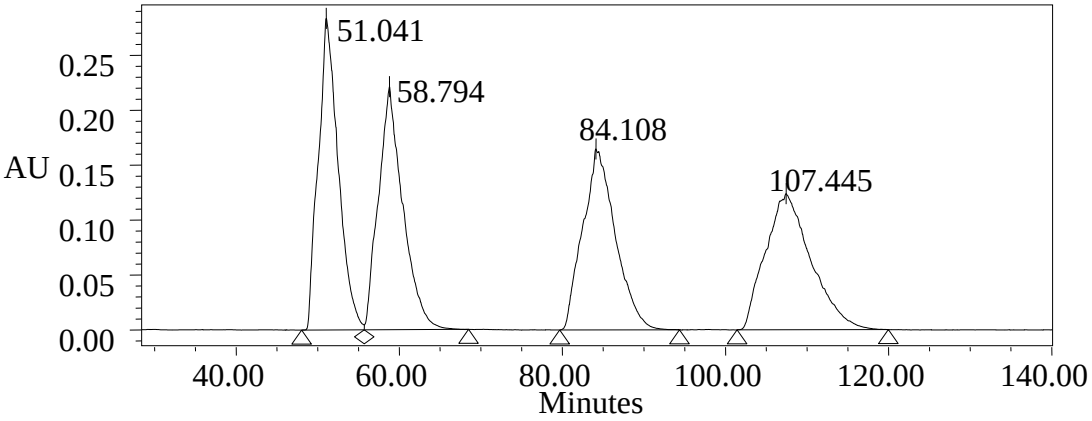


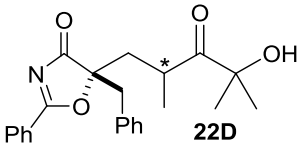
Chiralpack IA+AY-H, 0.5 mL/min, hexane/isopropanol 80:20, λ = 260 nm



(±)22D

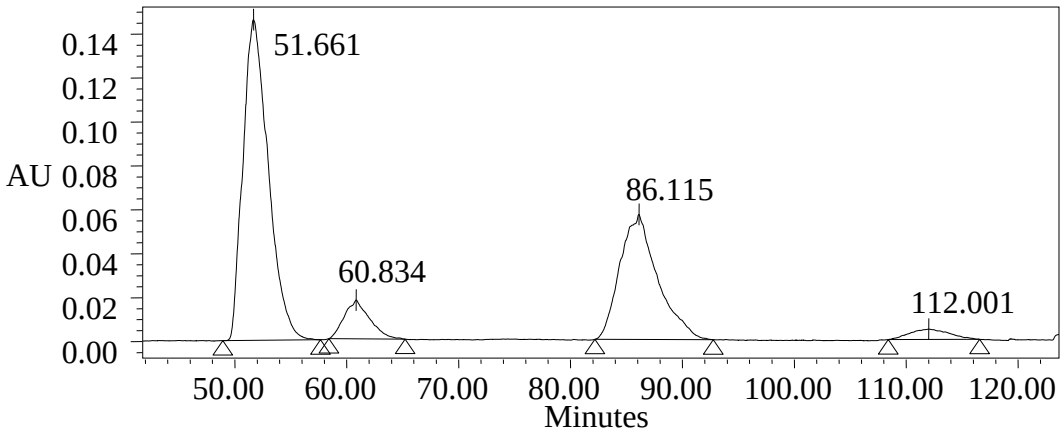
Retention Time	% Area
51.041	25.70
58.794	24.35
84.108	24.40
107.445	25.56



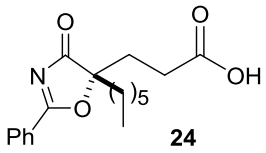


22D

Retention Time	% Area
51.661	57.16
60.834	6.86
86.115	33.10
112.001	2.88

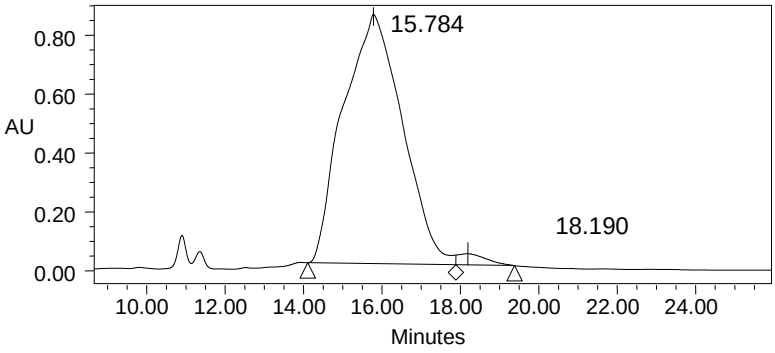


Chiralpack IC, 0.5 mL/min, hexane:ethanol 70:30, λ = 260 nm

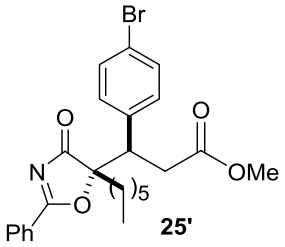


24

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	15.784	88764669	97.89	846380
2	PDA 260.0 nm	18.190	1910539	2.11	38140



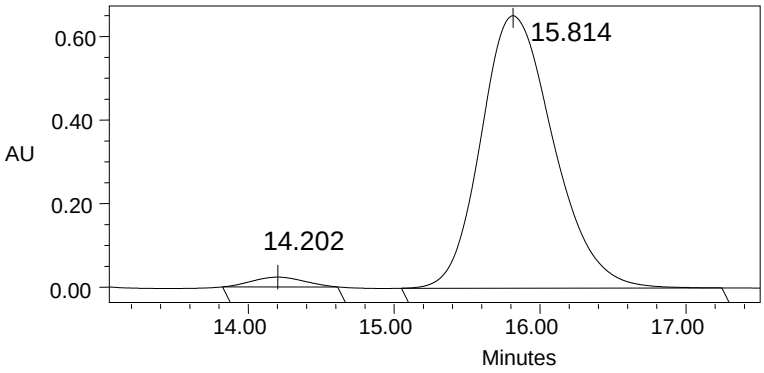
Chiralpack IC, 1 mL/min, hexane/isopropanol 80:20, λ = 260 nm



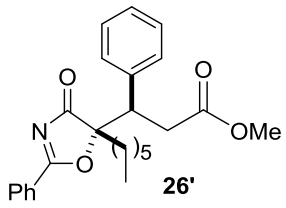
25'

Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	14.202	578170	2.50	23483
2	PDA 260.0 nm	15.814	22544216	97.50	651906



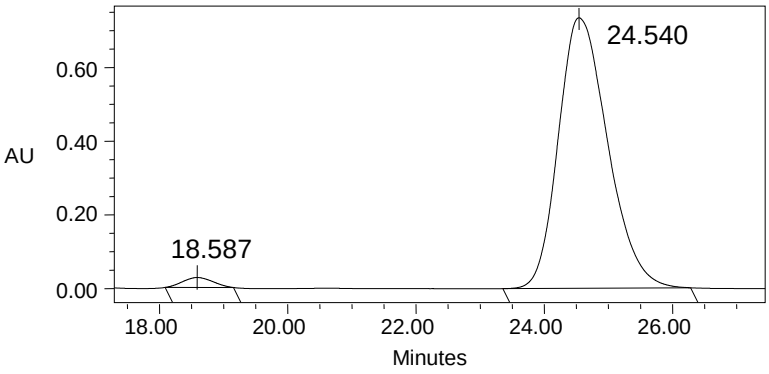
Chiralpack IC, 1 mL/min, hexane/isopropanol 80:20, λ = 260 nm



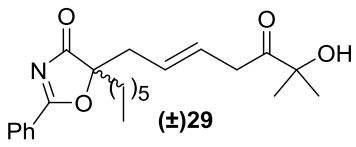
26'

Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.587	876506	2.18	27004
2	PDA 260.0 nm	24.540	39250164	97.82	734325

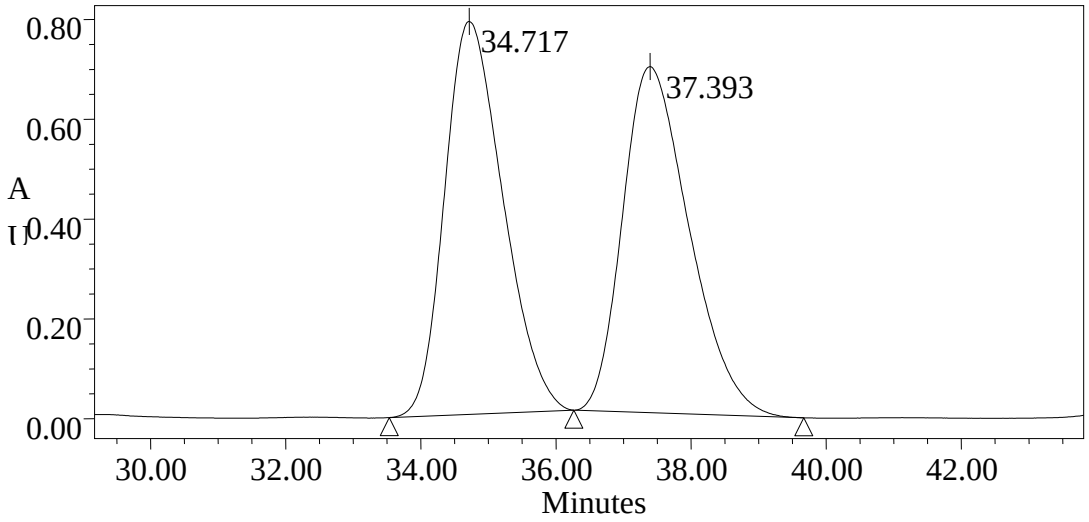


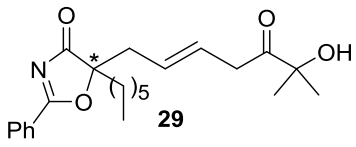
Chiralpack IC, 1 mL/min, hexane:etanol 95:5, λ = 260 nm



(±)29

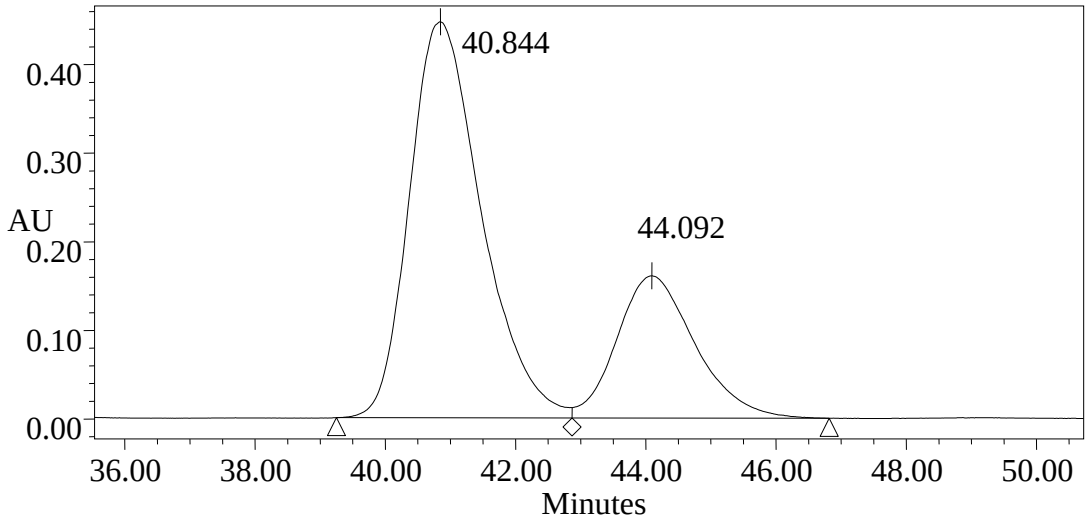
Retention Time	% Area
34.717	49.90
37.393	50.10



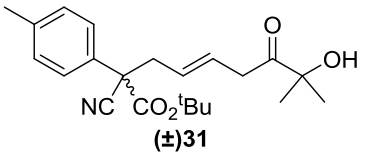


29

Retention Time	% Area
40.844	71.95
44.092	28.05

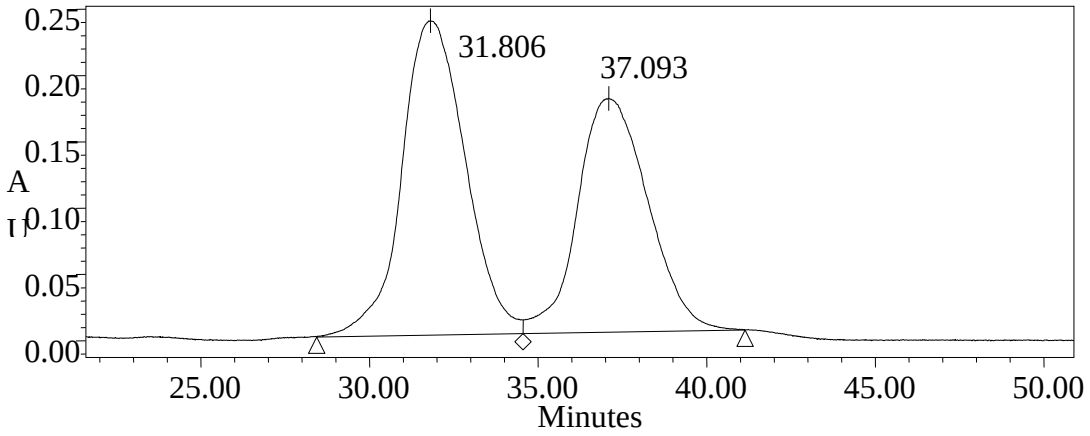


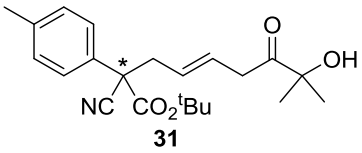
Chiralpack IC, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



(±)31

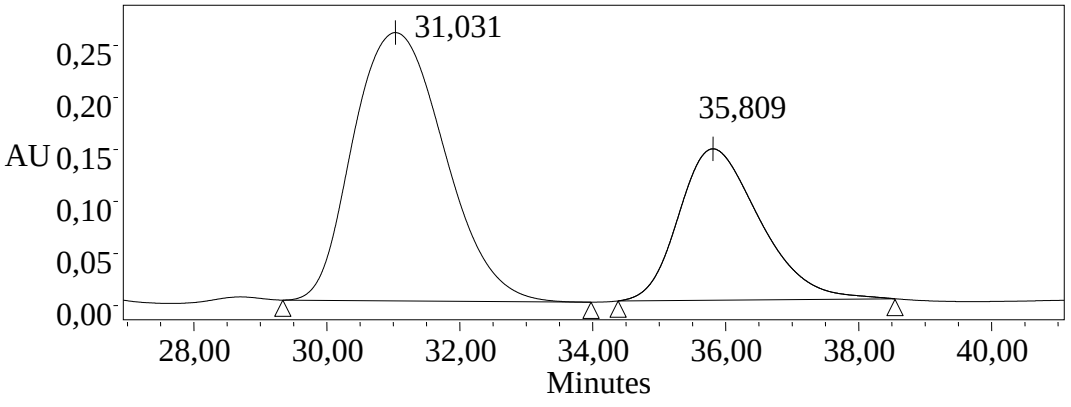
Retention Time	% Area
31.806	54.81
37.093	45.19



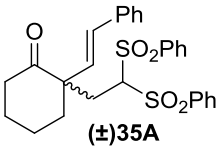


31

Retention Time	% Area
31.031	66.00
35.809	34.00

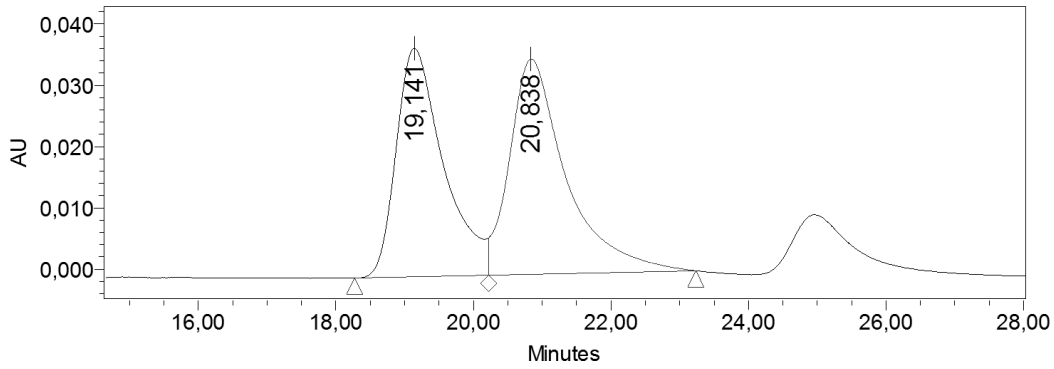


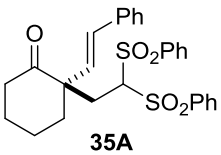
Chiralpack IA, 1 mL/min, hexane/isopropanol 70:30, λ = 250 nm



(±)35A

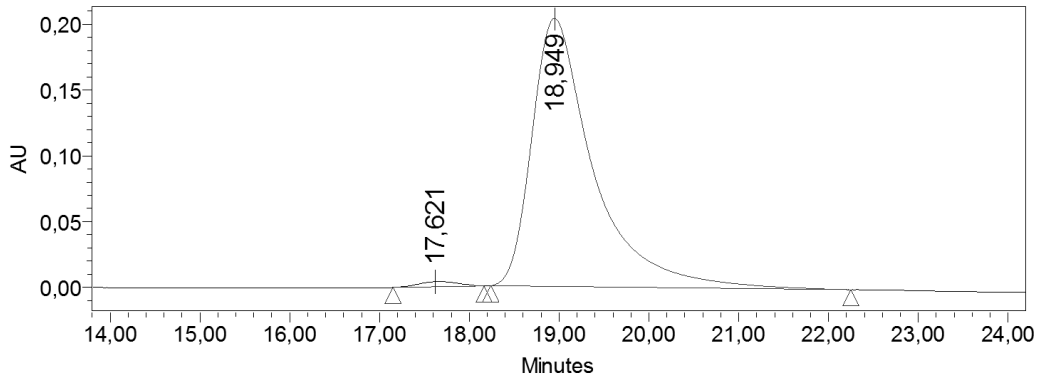
Retention Time	% Area
19,141	48,09
20,838	51,91



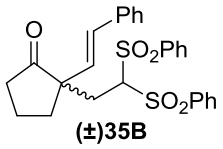


35A

Retention Time	% Area
17,621	1,21
18,949	98,79

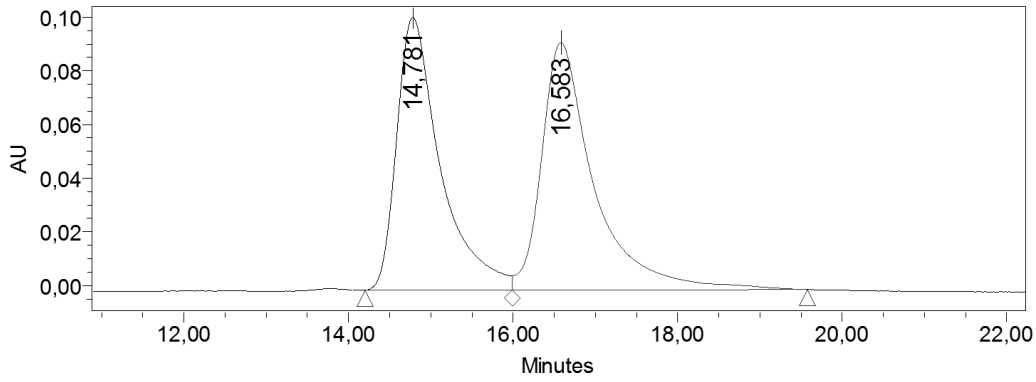


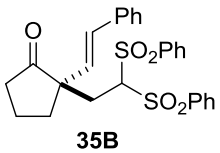
Chiralpack IA, 1 mL/min, hexane/isopropanol 70:30, λ = 260 nm



(±)35B

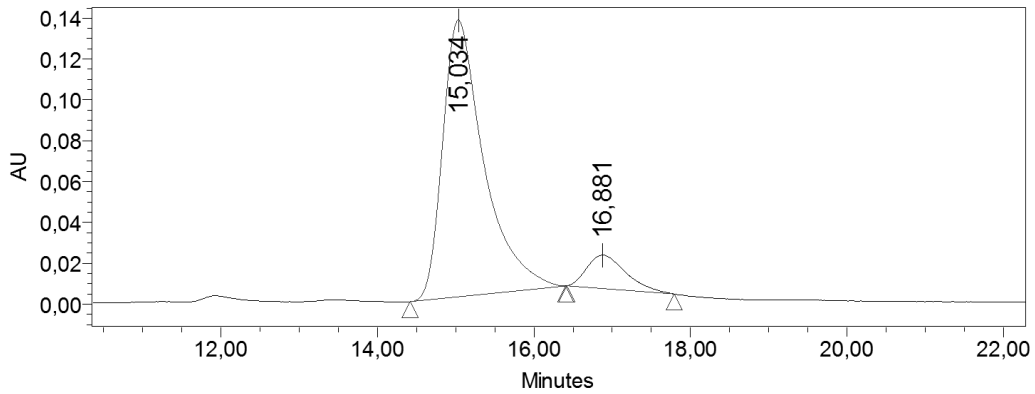
Retention Time	% Area
14,781	47,81
16,583	52,19



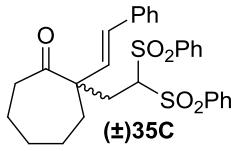


35B

Retention Time	% Area
15,034	89,78
16,881	10,22

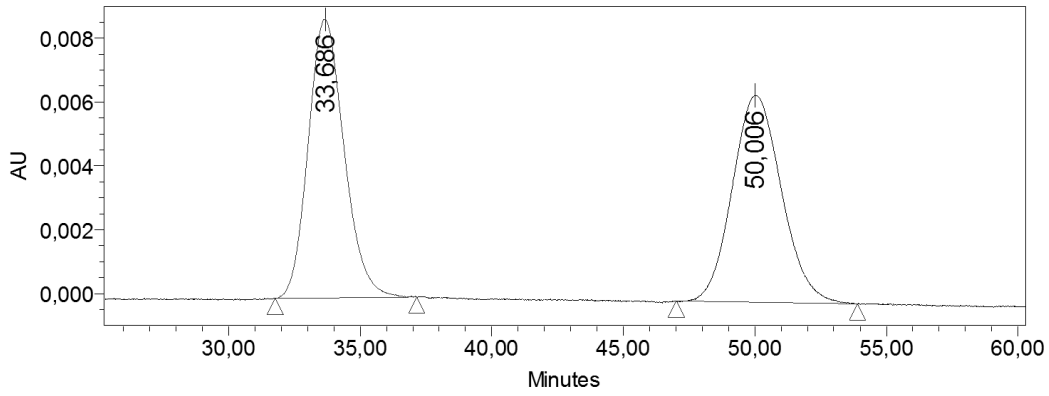


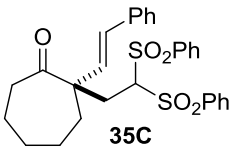
Chiralpack IC, 1 mL/min, hexane/isopropanol 50:50, λ = 250 nm



(±)35C

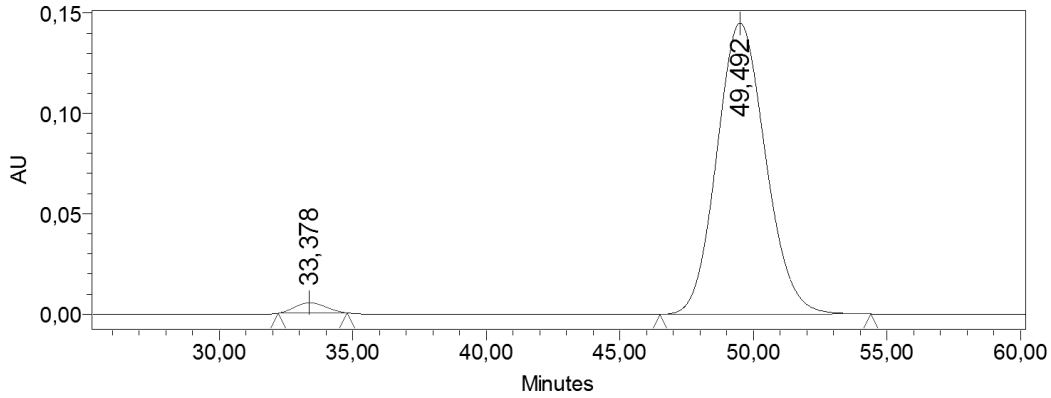
Retention Time	% Area
33,686	49,64
50,006	50,36



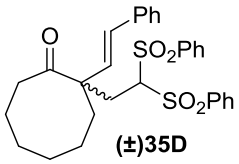


35C

Retention Time	% Area
33,378	2,19
49,492	97,81

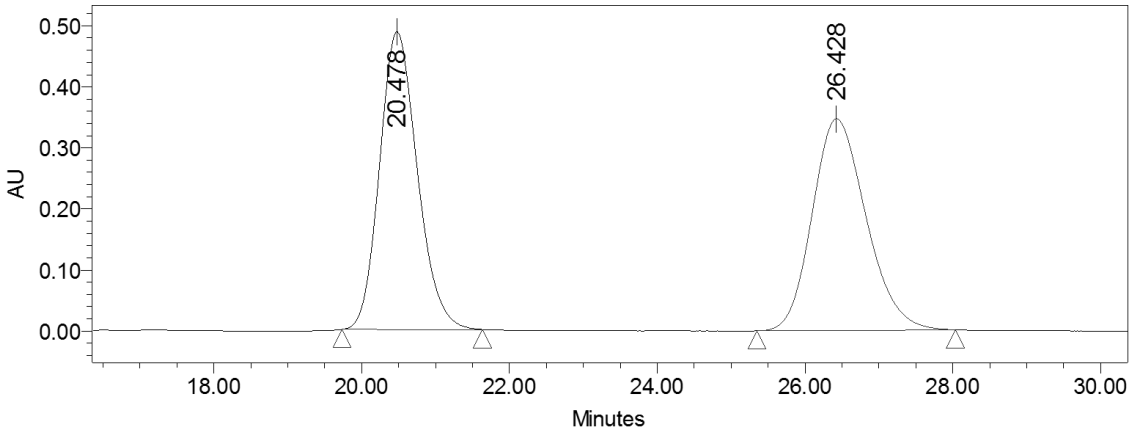


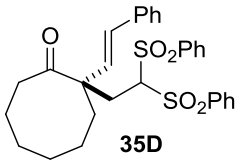
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 30:70, λ = 250 nm



(±)35D

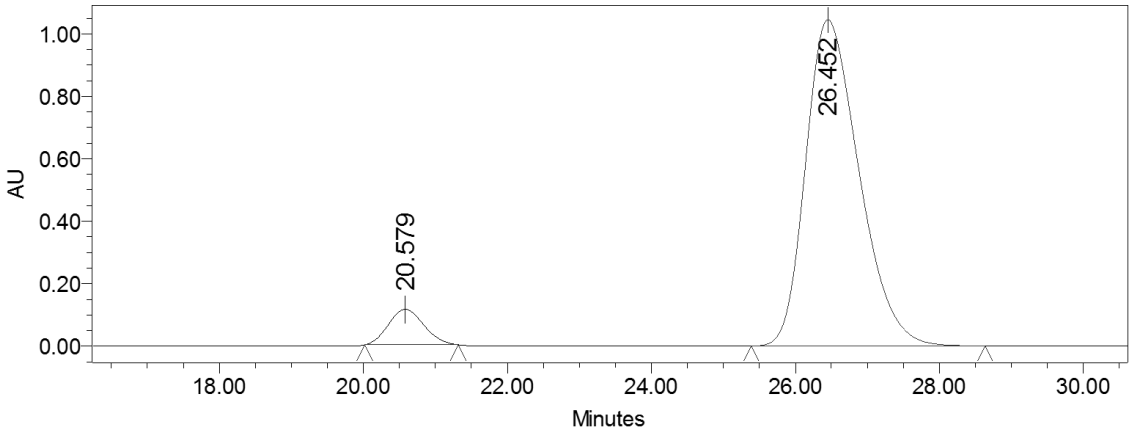
Retention Time	% Area
20.478	49.70
26.428	50.30



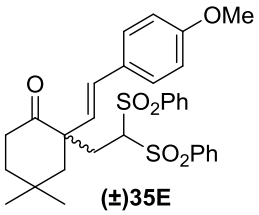


35D

Retention Time	% Area
20.579	6.07
26.452	93.93

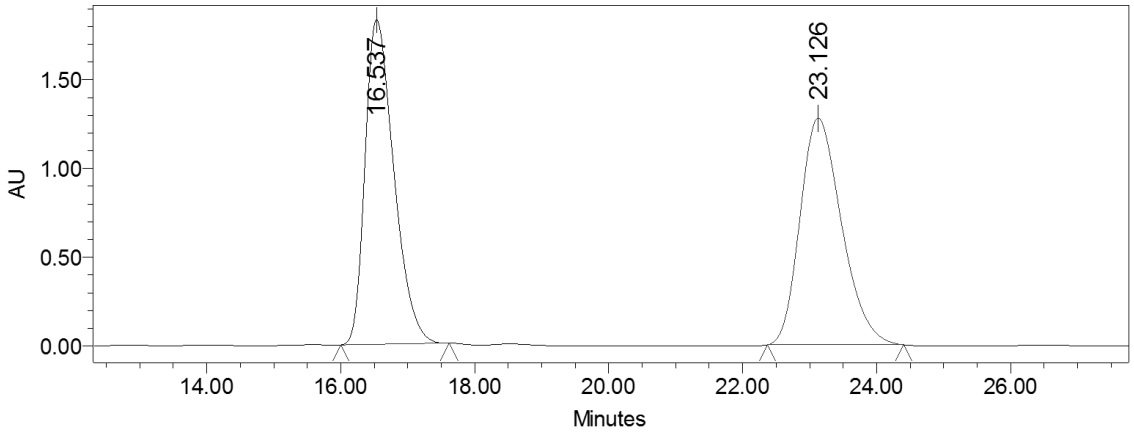


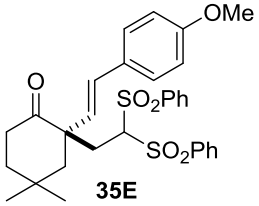
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 30:70, λ = 250 nm



(±)35E

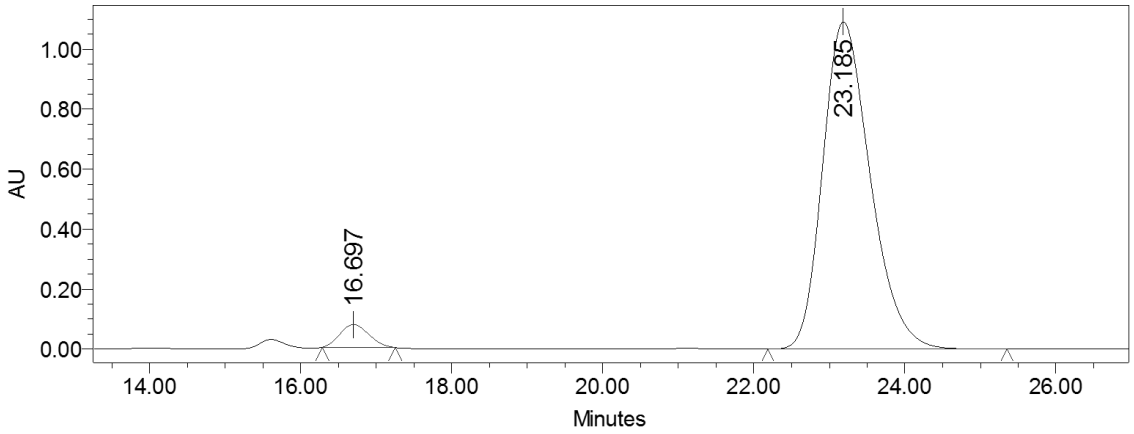
Retention Time	% Area
16.537	49.80
23.126	50.20



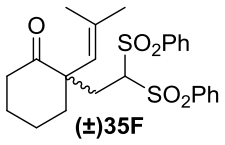


35E

Retention Time	% Area
16.697	4.09
23.185	95.91

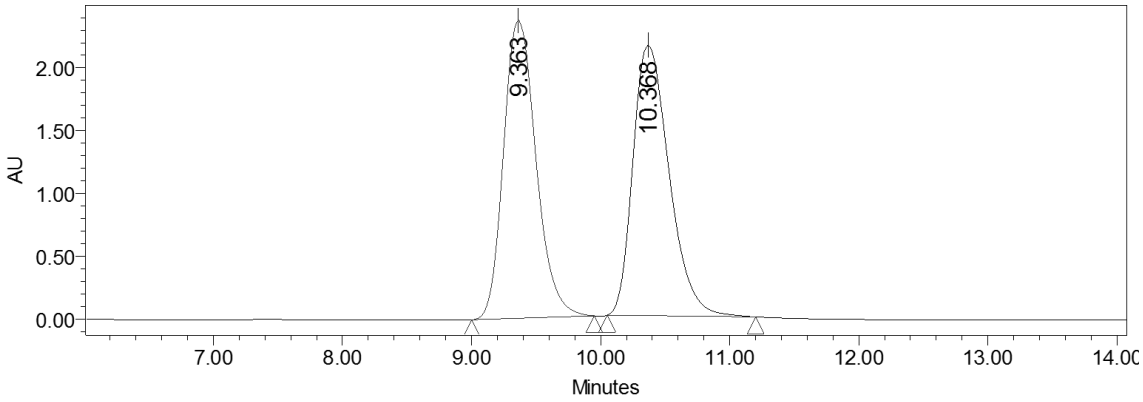


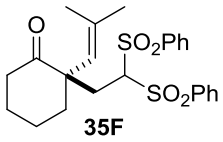
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 70:30, λ = 210 nm



(±)35F

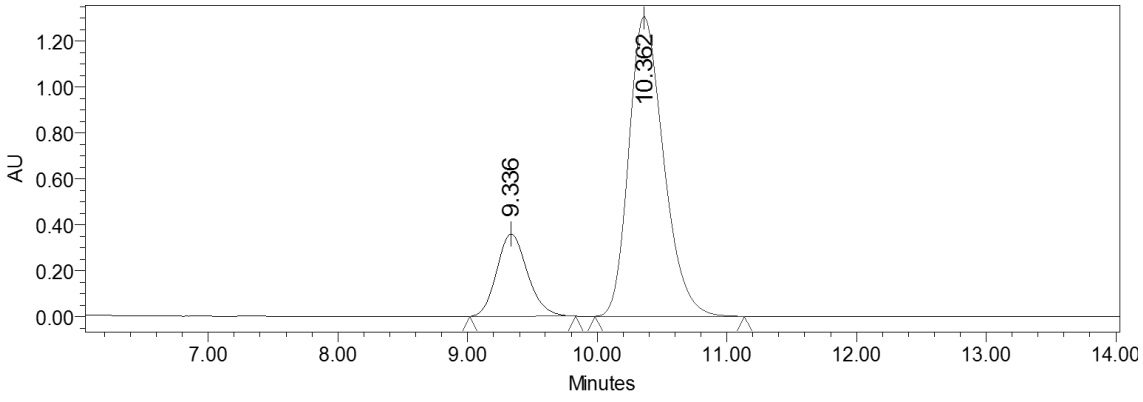
Retention Time	% Area
9.363	49.69
10.368	50.31



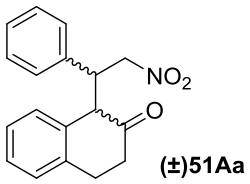


35F

Retention Time	% Area
9.336	19.50
10.362	80.50

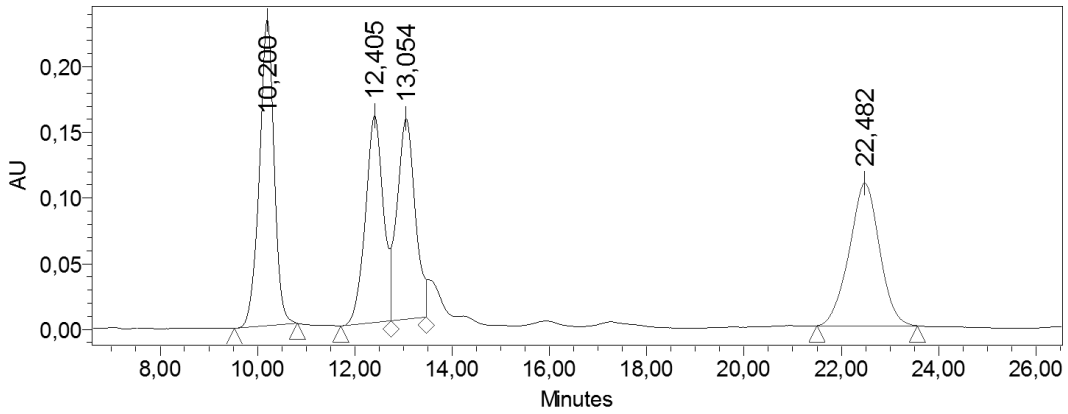


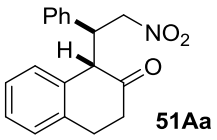
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



(±)51Aa

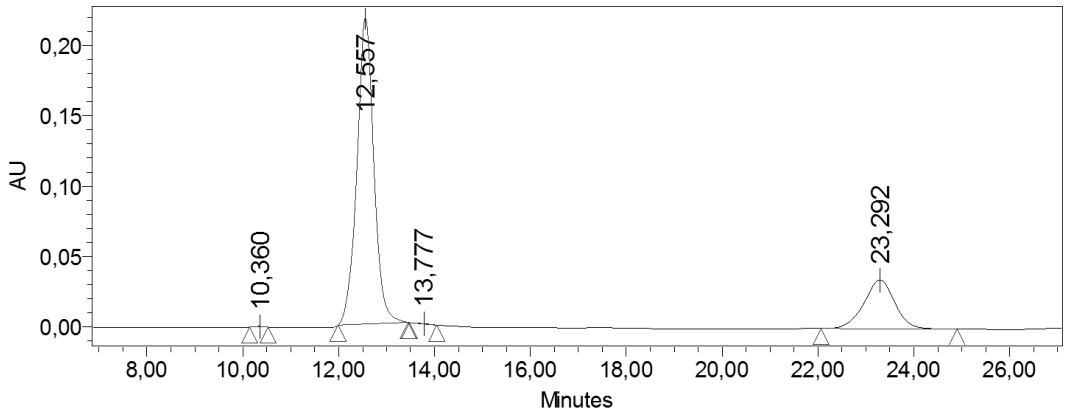
Retention Time	% Area
10,200	27,70
12,405	22,89
13,054	22,61
22,482	26,80



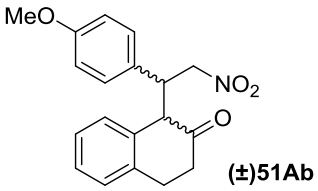


51Aa

Retention Time	% Area
10,360	0,09
12,557	77,43
13,777	0,07
23,292	22,41

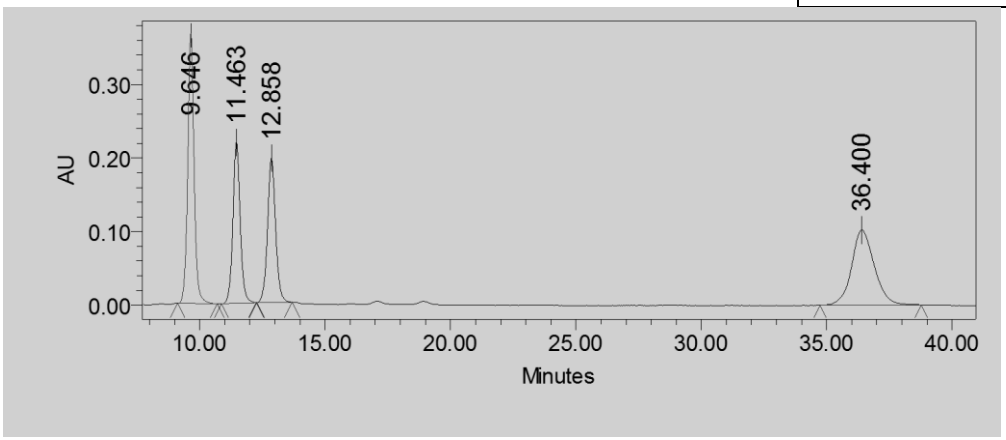


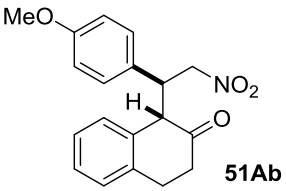
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 220 nm



(±)51Ab

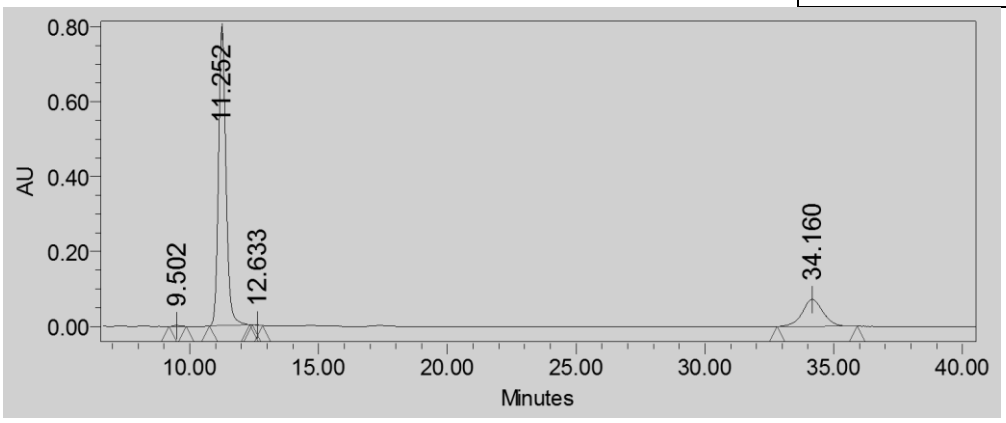
Retention Time	% Area
9.646	29.71
11.463	20.44
12.858	20.22
36.400	29.63



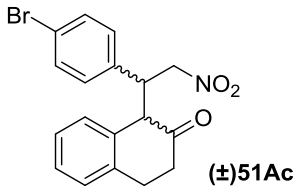


51Ab

Retention Time	% Area
9.502	0.23
11.252	79.64
12.633	0.07
34.160	20.05

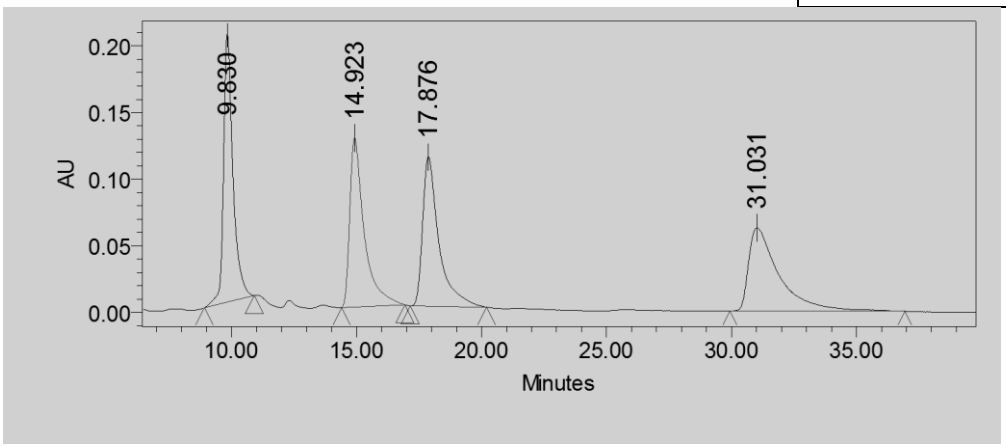


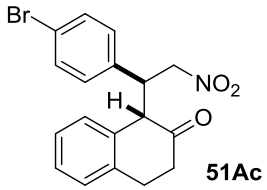
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 220 nm



(±)51Ac

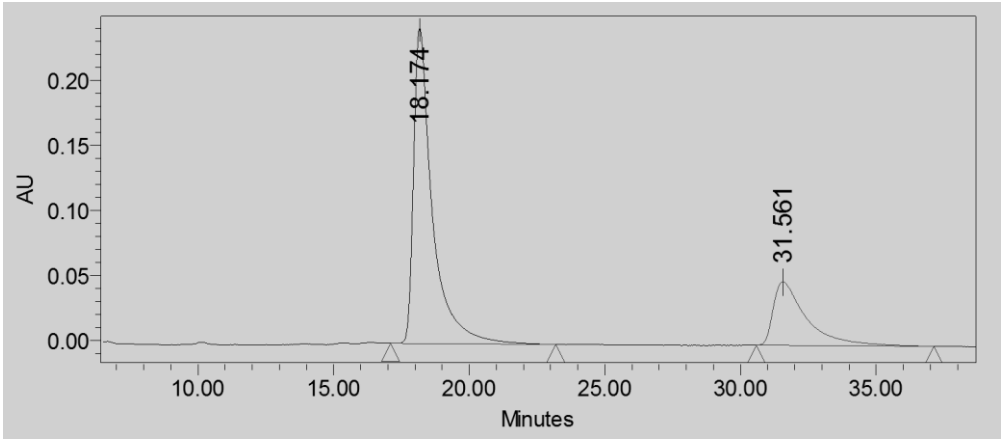
Retention Time	% Area
9.830	25.34
14.923	24.63
17.876	24.51
31.031	25.52



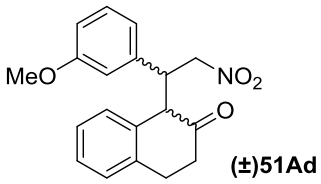


51Ac

Retention Time	% Area
18.174	73.87
31.561	26.13

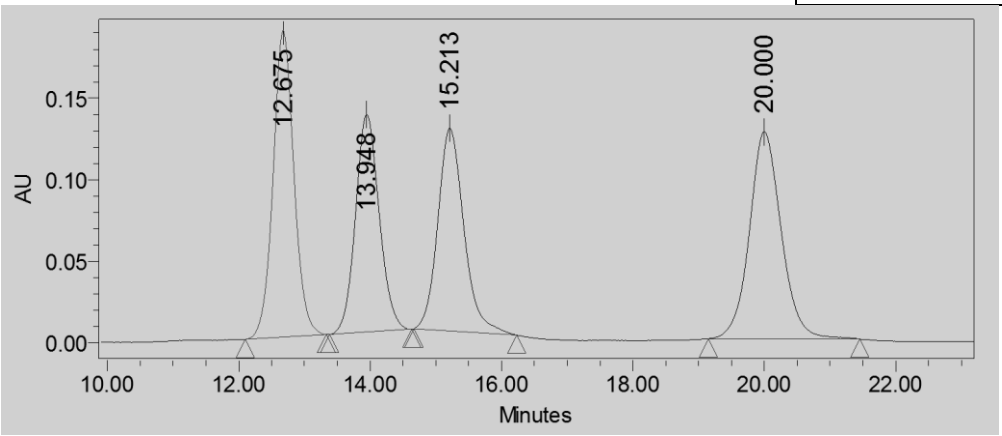


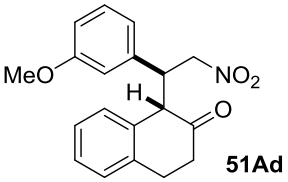
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



(±)51Ad

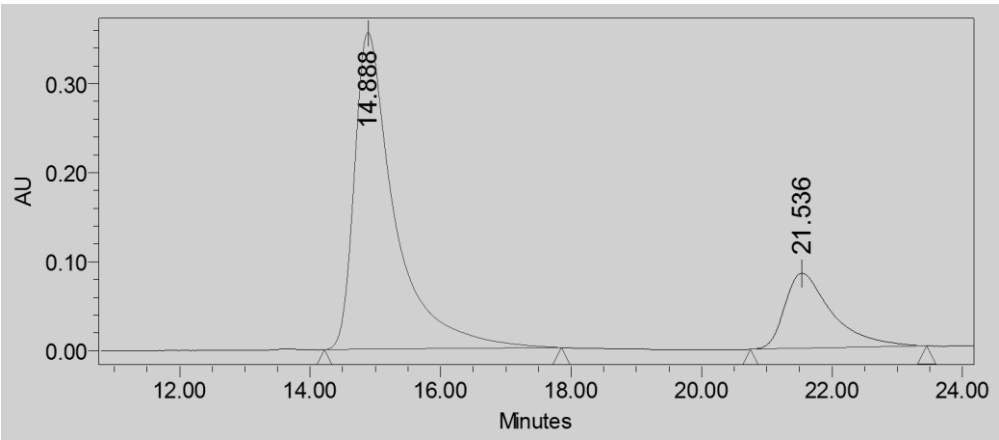
Retention Time	% Area
8.813	26.77
13.154	23.21
15.581	23.22
27.605	26.79



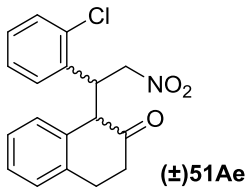


51Ad

Retention Time	% Area
14.888	78.39
21.536	21.61

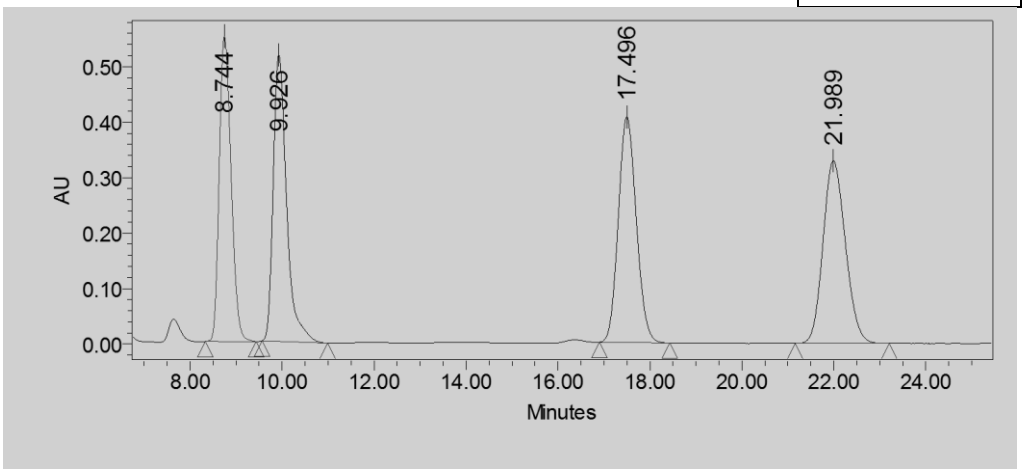


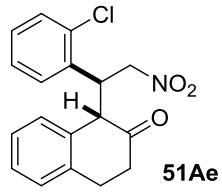
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Ae

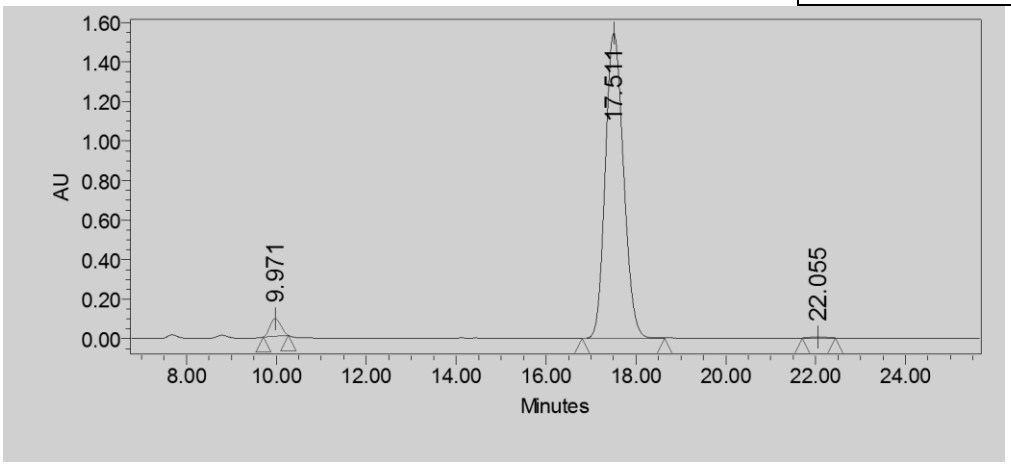
Retention Time	% Area
8.744	23.21
9.926	24.54
17.496	26.01
21.989	26.23



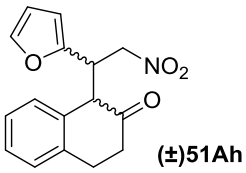


51Ae

Retention Time	% Area
9.971	3.31
17.511	96.32
22.055	0.37

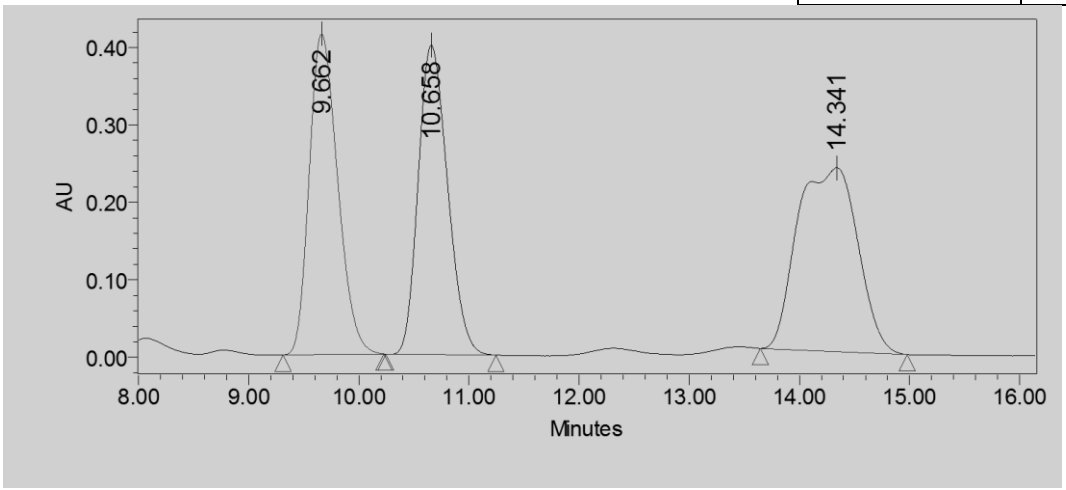


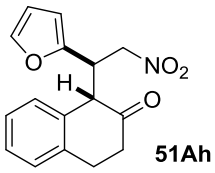
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Ah

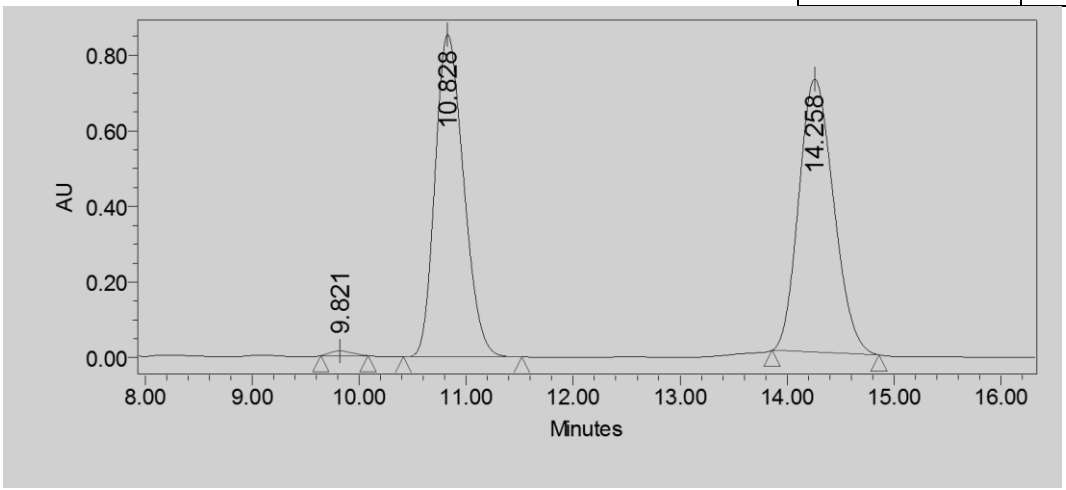
Retention Time	% Area
9.662	31.15
10.658	31.02
14.341	37.84



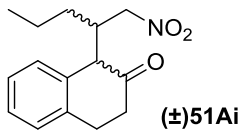


51Ah

Retention Time	% Area
9.821	0.54
10.828	48.92
14.258	50.55

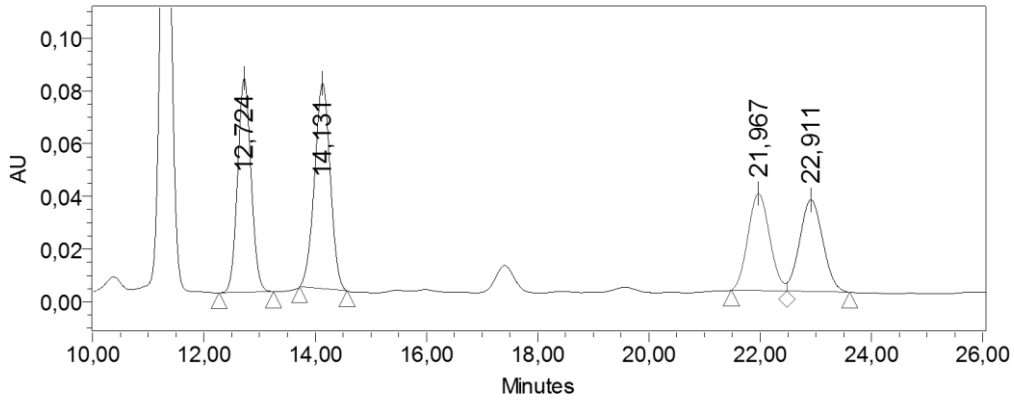


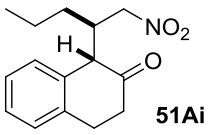
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 220 nm



(±)51Ai

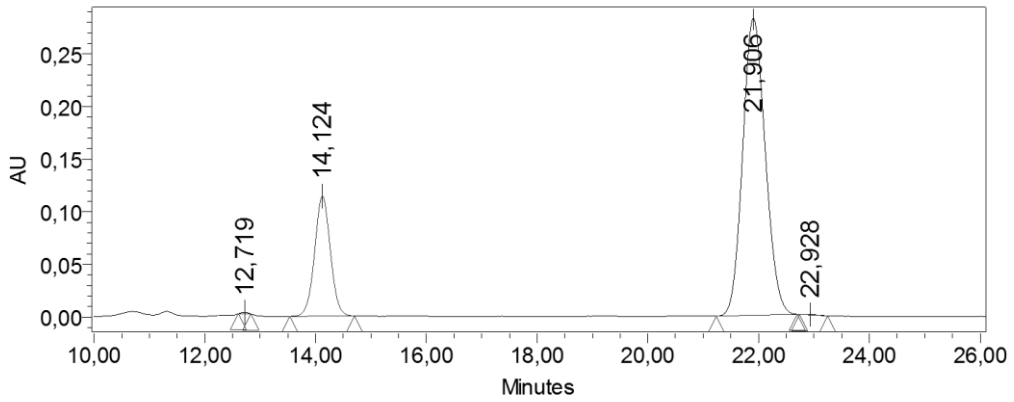
Retention Time	% Area
12,724	27,90
14,131	31,16
21,967	20,46
22,911	20,48



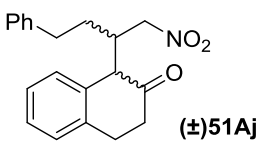


51Ai

Retention Time	% Area
12,719	0,12
14,124	22,02
21,906	77,78
22,928	0,07

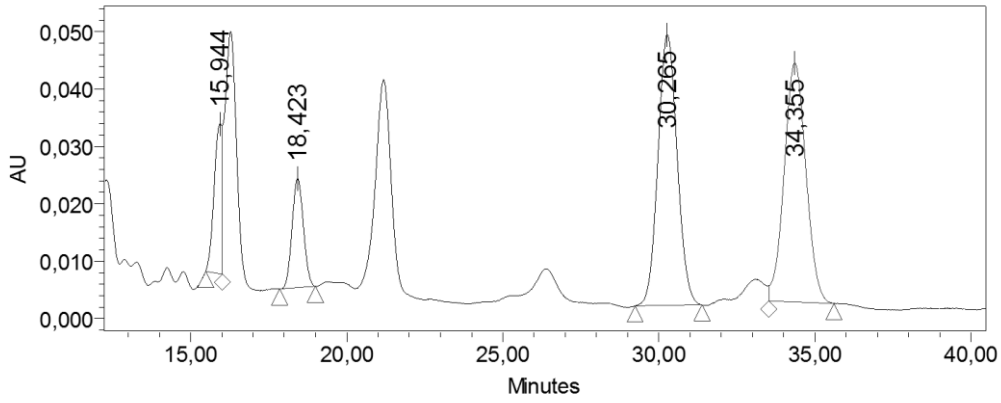


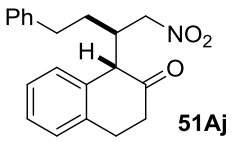
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Aj

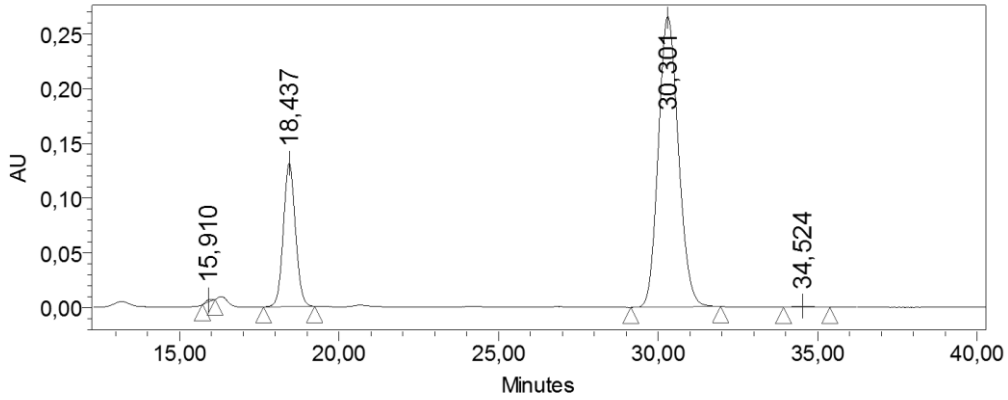
Retention Time	% Area
15,944	9,03
18,423	9,66
30,265	40,61
34,355	40,70



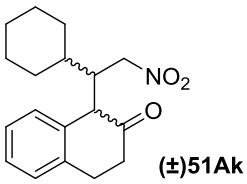


51Aj

Retention Time	% Area
15,910	0,19
18,437	22,81
30,301	76,72
34,524	0,28

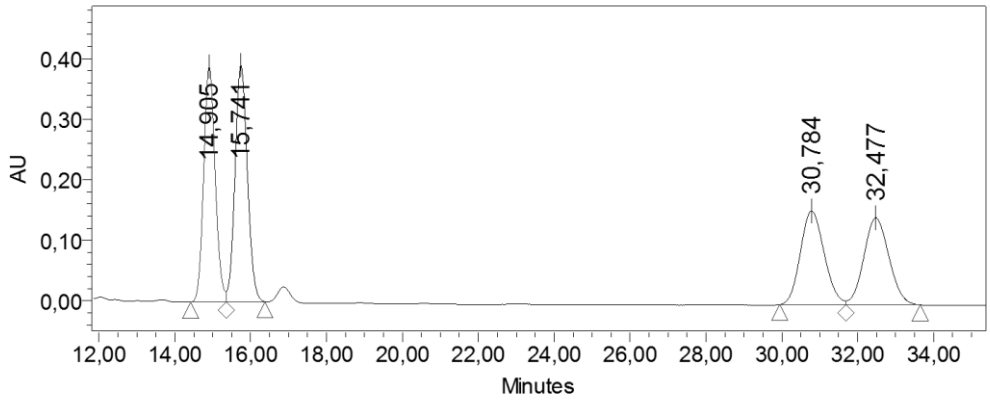


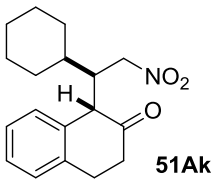
Chiralpack IC, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Ak

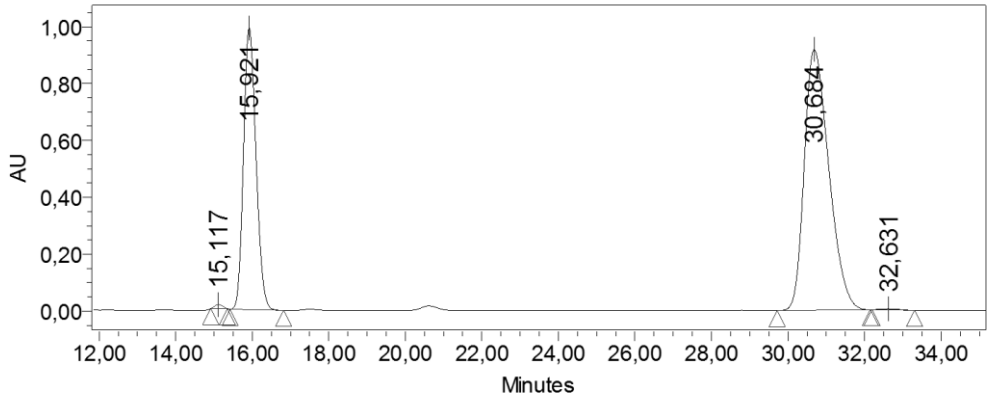
Retention Time	% Area
14,905	26,96
15,741	29,14
30,784	22,18
32,477	21,72



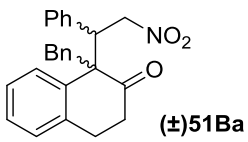


51Ak

Retention Time	% Area
15,117	0,25
15,921	35,27
30,684	64,26
32,631	0,23

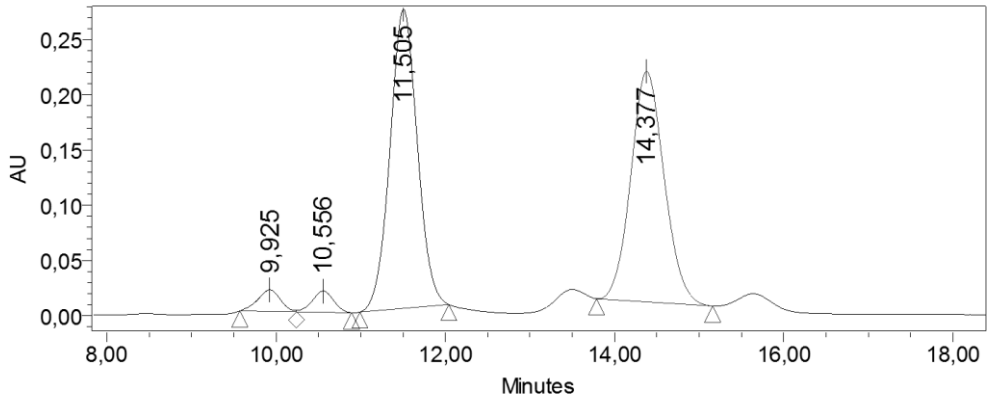


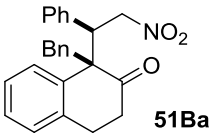
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 220 nm



(±)51Ba

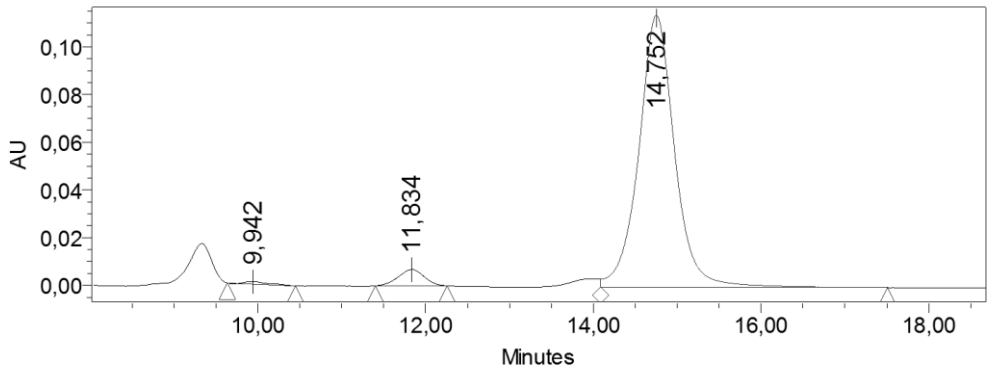
Retention Time	% Area
9,925	2,89
10,556	2,68
11,505	48,56
14,377	45,86



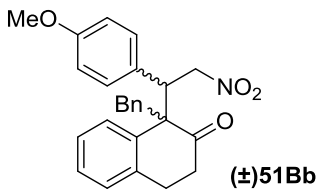


51Ba

Retention Time	% Area
9,942	0,64
11,834	4,14
14,752	95,22

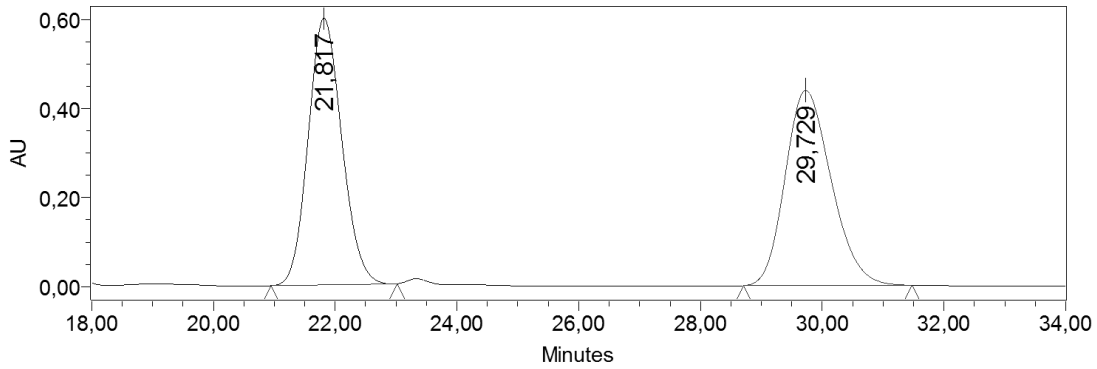


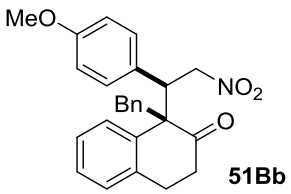
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Bb

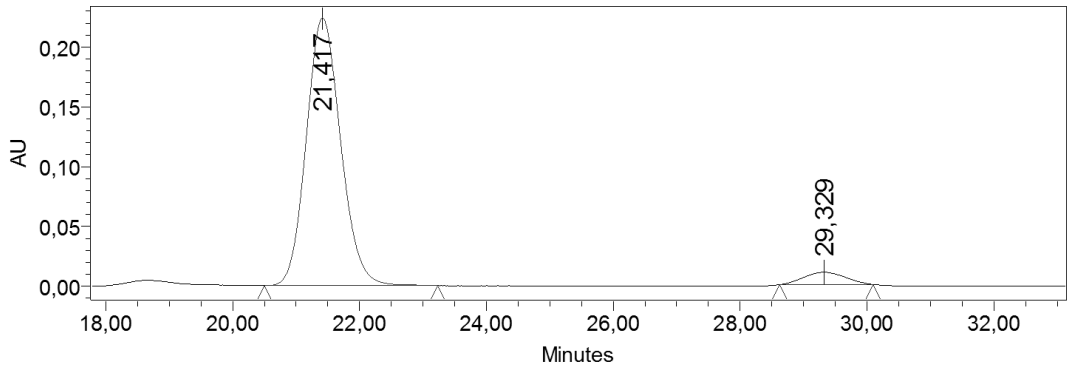
Retention Time	% Area
21,817	49,96
29,729	50,04



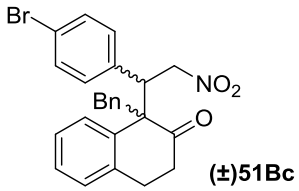


51Bb

Retention Time	% Area
21,417	94,76
29,329	5,24

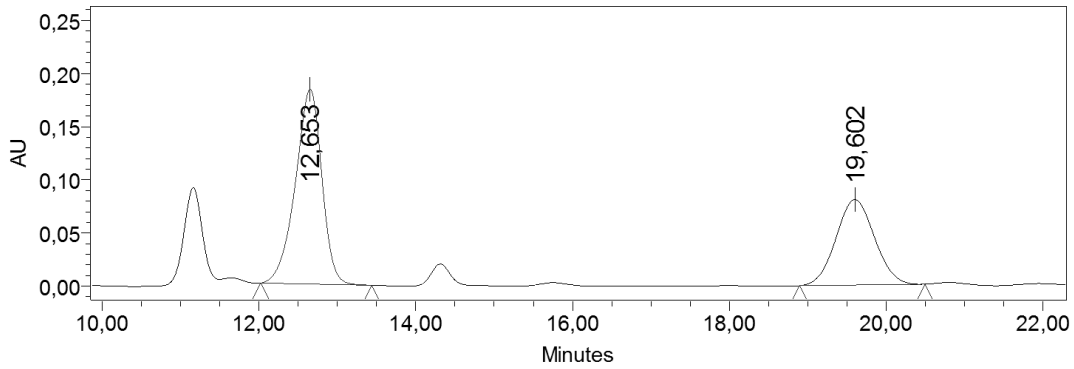


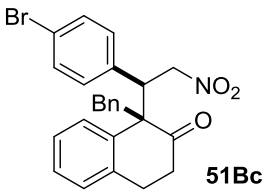
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Bc

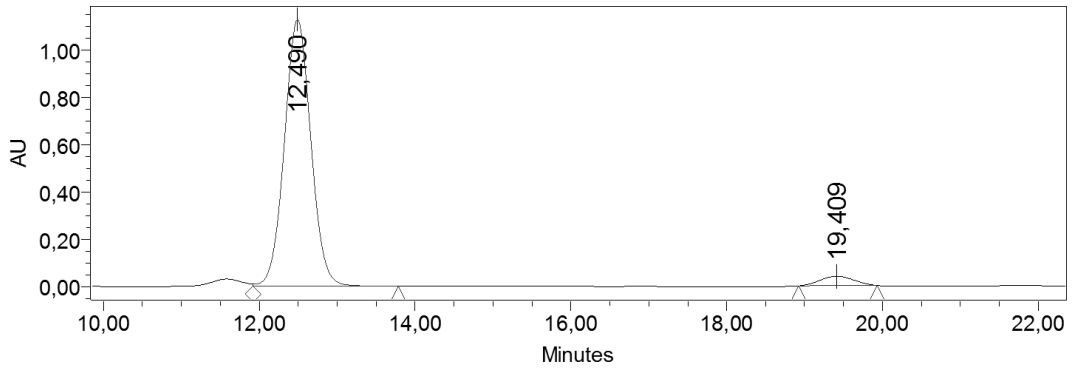
Retention Time	% Area
12,653	51,09
19,602	48,91



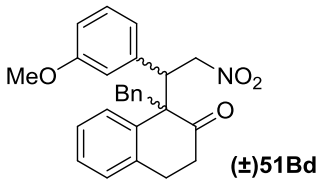


51Bc

Retention Time	% Area
12,490	95,70
19,409	4,30

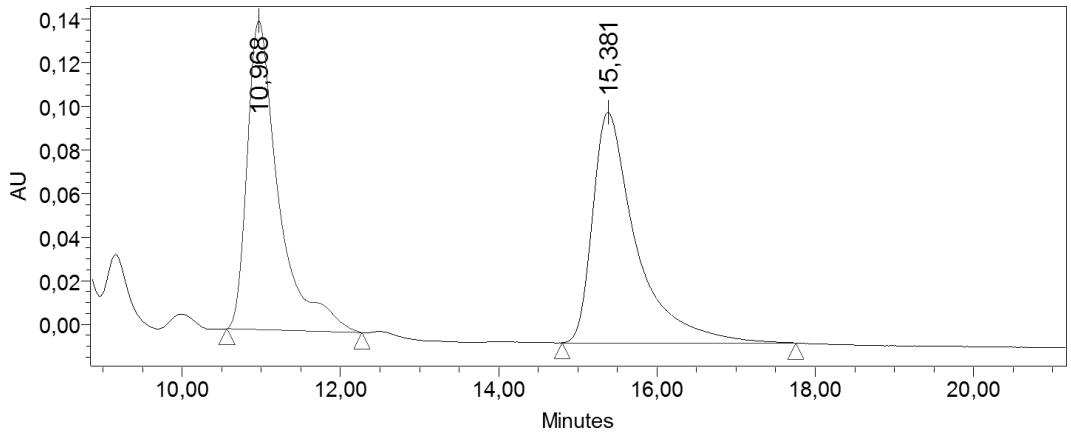


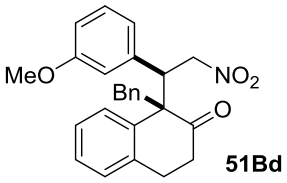
Chiralpack IA 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Bd

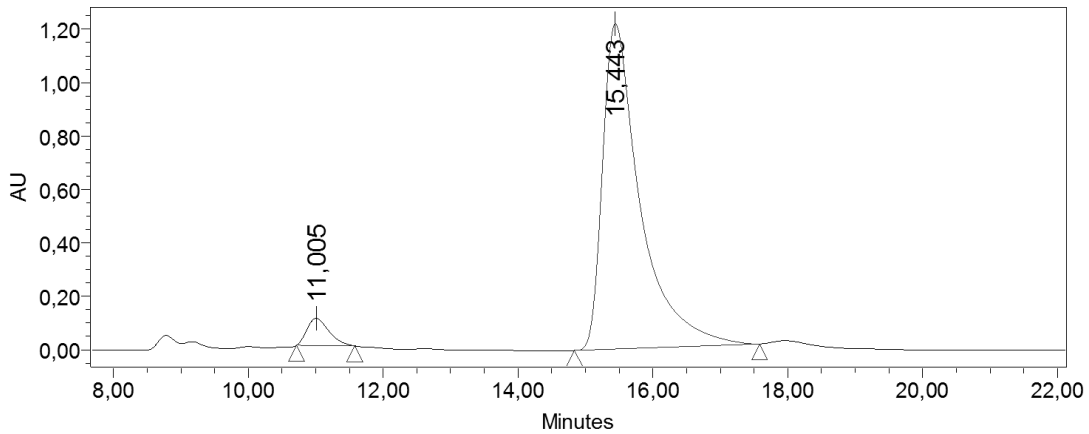
Retention Time	% Area
10,968	49,24
15,381	50,76



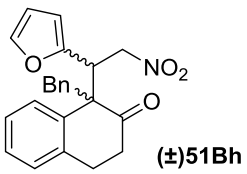


51Bd

Retention Time	% Area
11,005	4,64
15,443	95,36

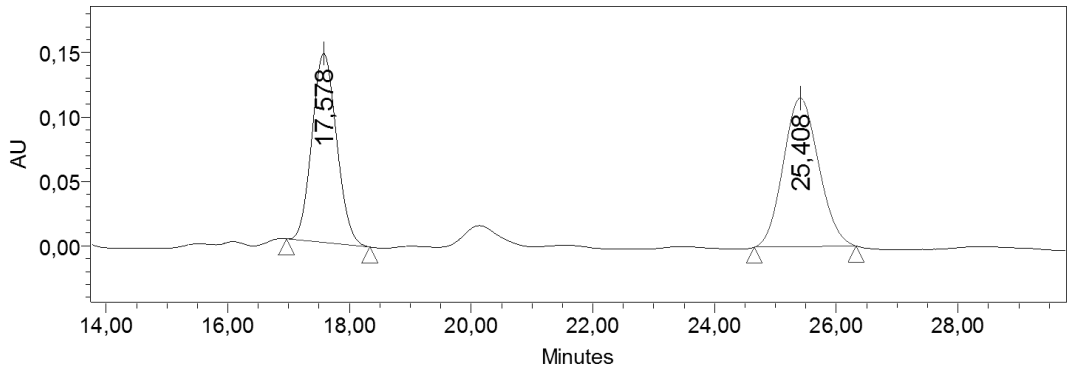


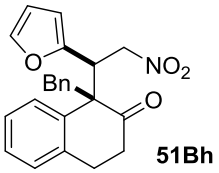
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Bh

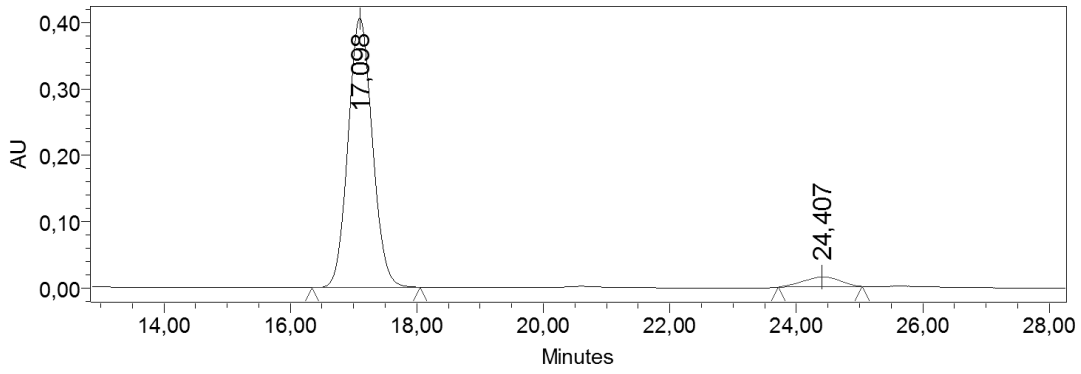
Retention Time	% Area
17,578	47,01
25,408	52,99



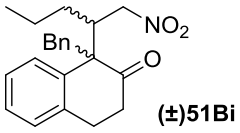


51Bh

Retention Time	% Area
17,098	94,82
24,407	5,18

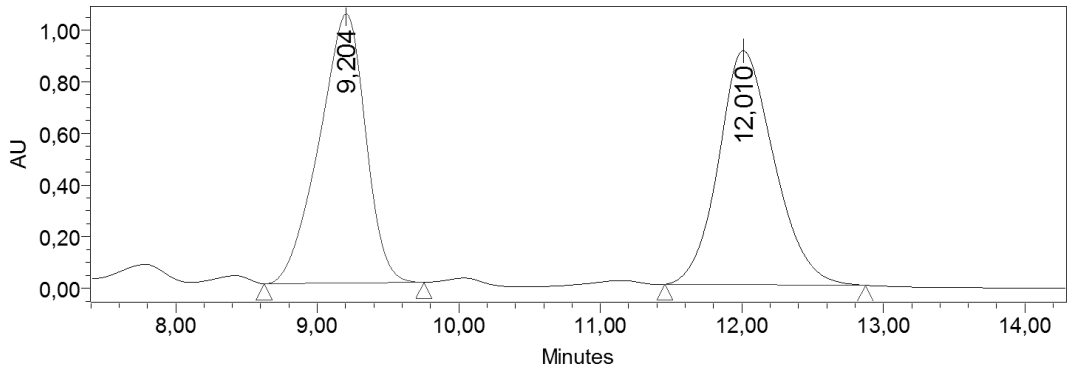


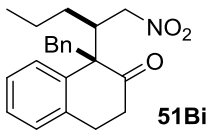
Chiralpack IA 1 mL/min, hexane/isopropanol 98:2, λ = 210 nm



(±)51Bi

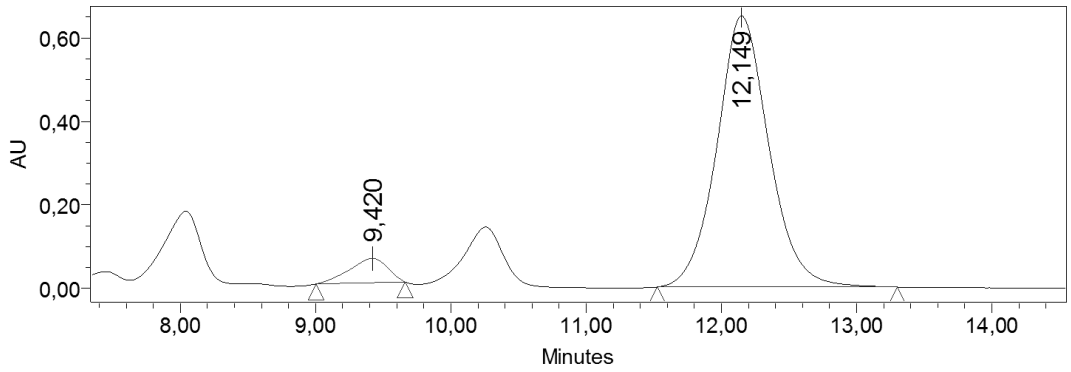
Retention Time	% Area
9,204	48,90
12,010	51,10



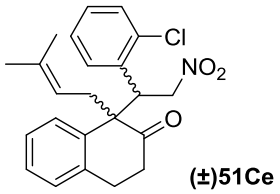


51Bi

Retention Time	% Area
9,420	6,16
12,149	93,84

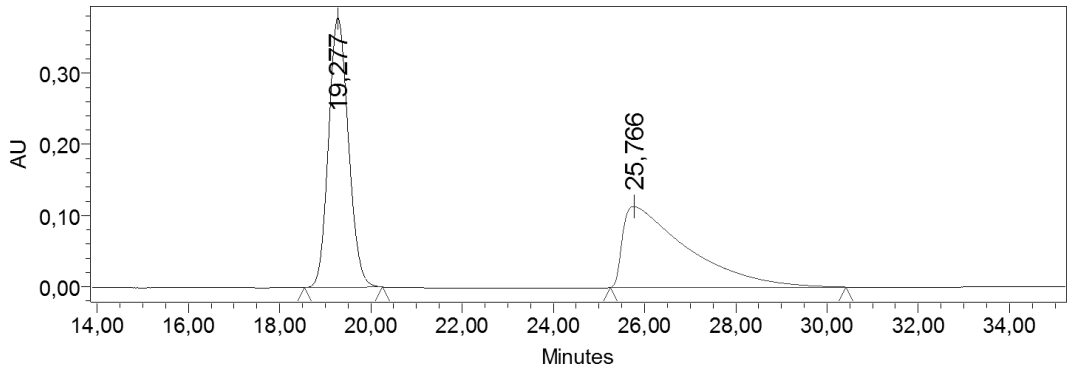


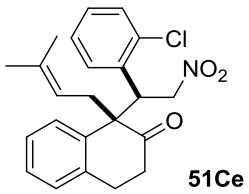
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Ce

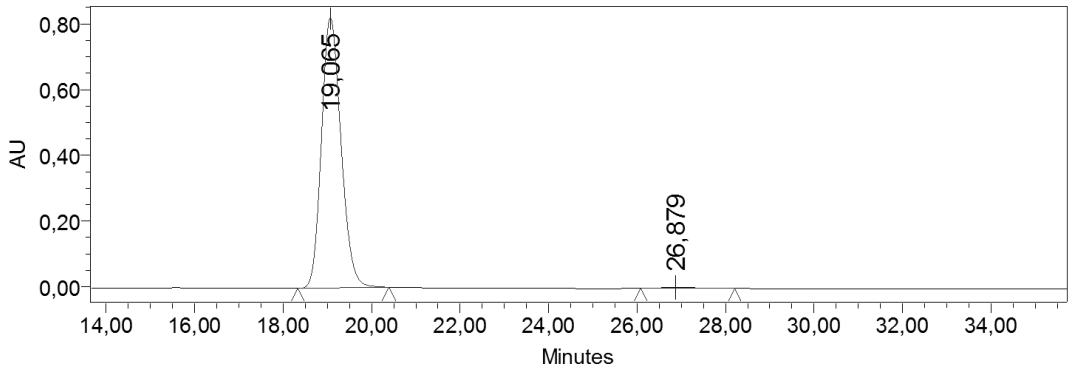
Retention Time	% Area
19,277	50,68
25,766	49,32



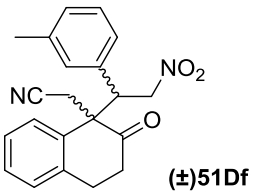


51Ce

Retention Time	% Area
19,065	99,39
26,879	0,61

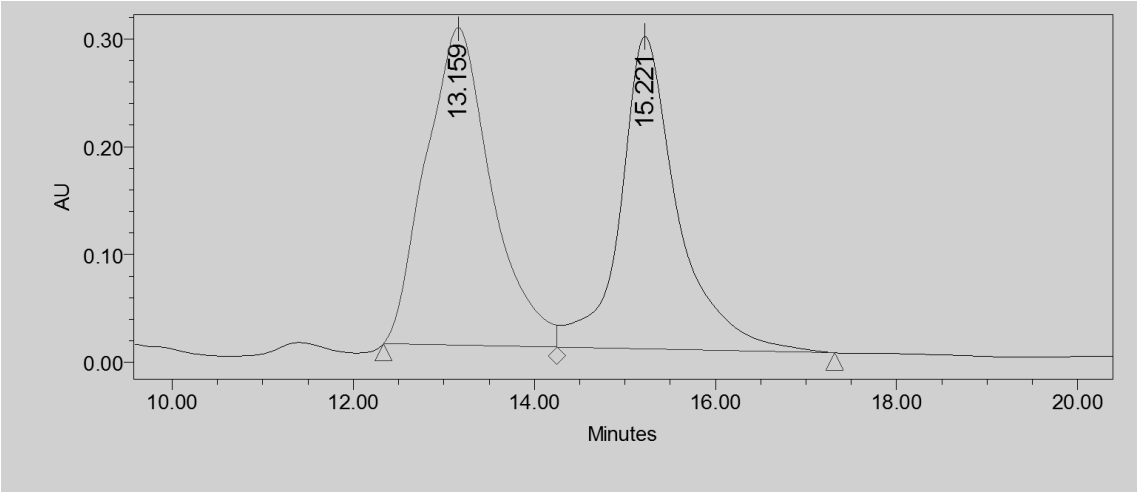


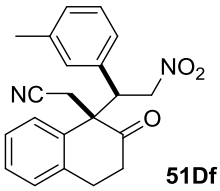
Chiralpack IA 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Df

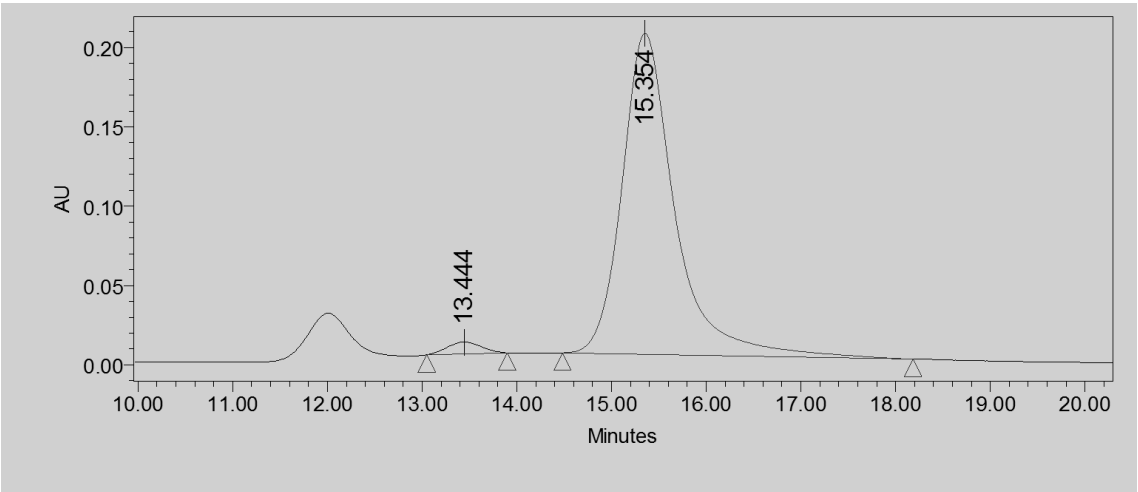
Retention Time	% Area
13.159	52.74
15.221	47.26



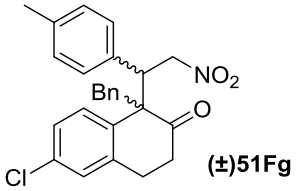


51Df

Retention Time	% Area
13.444	2.35
15.354	97.65

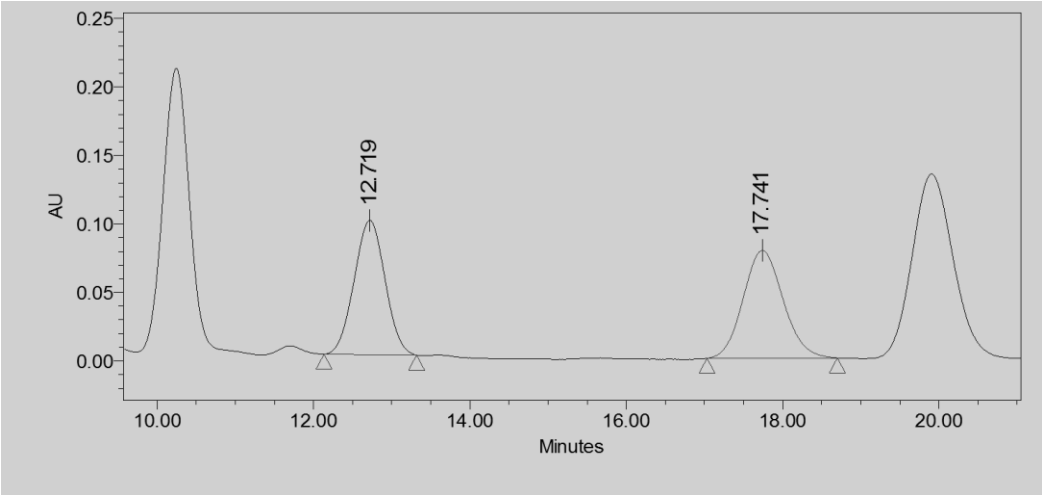


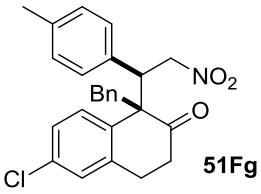
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Fg

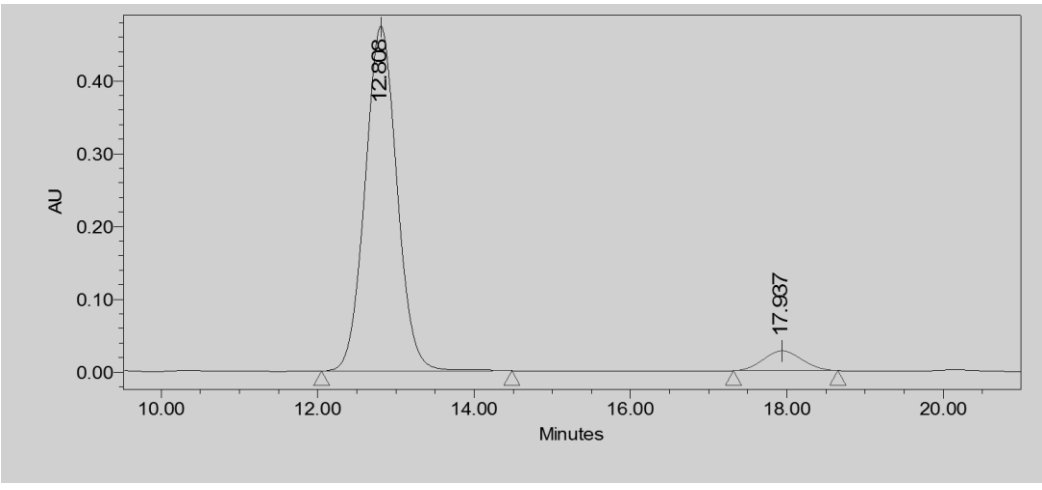
Retention Time	% Area
12.719	49.11
17.741	50.89



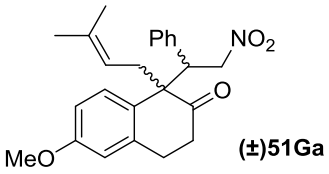


51Fg

Retention Time	% Area
12.808	94.81
17.937	5.19

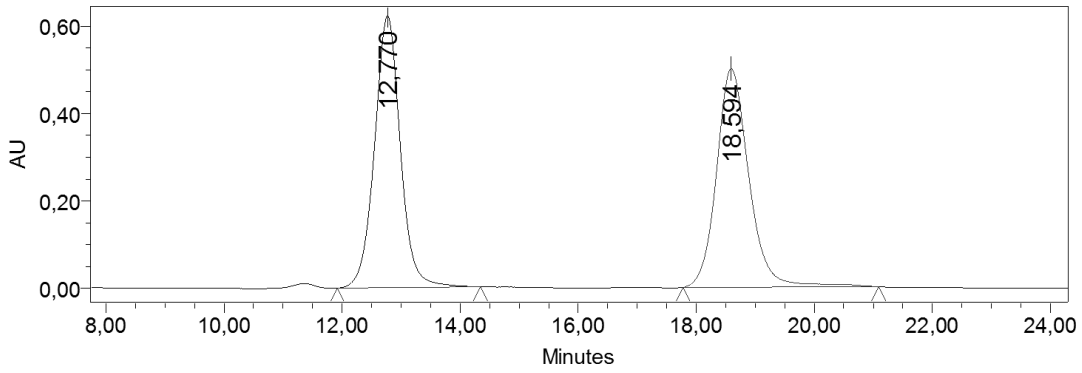


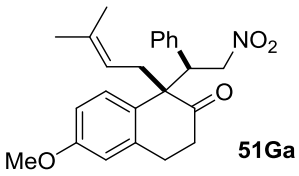
Chiralpack IC 1 mL/min, hexane/isopropanol 98:2, λ = 210 nm



(±)51Ga

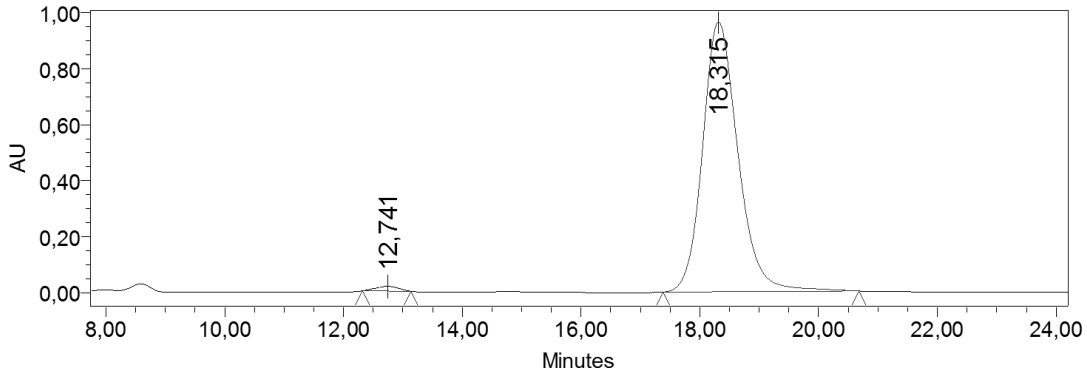
Retention Time	% Area
12,770	49,70
18,594	50,30



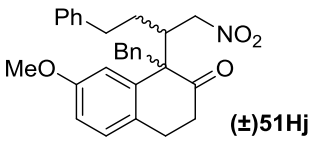


51Ga

Retention Time	% Area
12,741	1,09
18,315	98,91

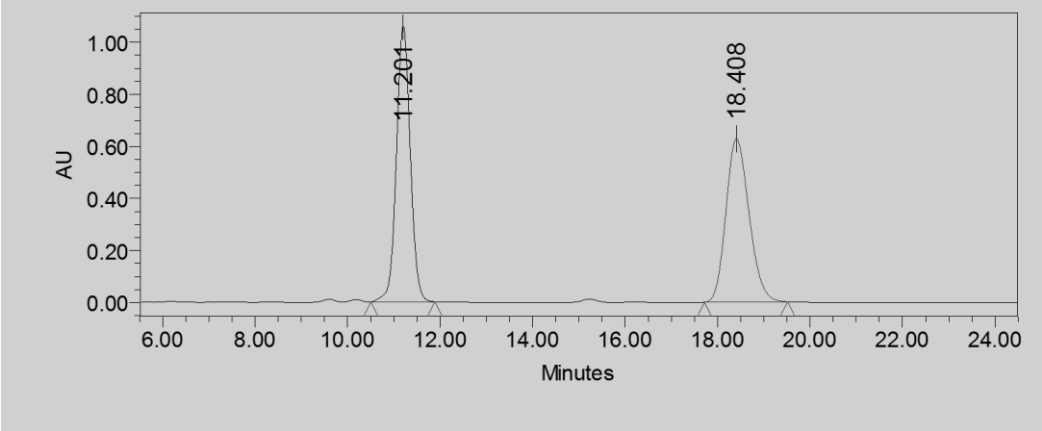


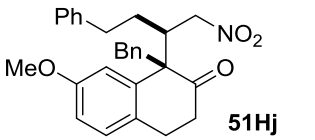
Chiralpack IC 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)51Hj

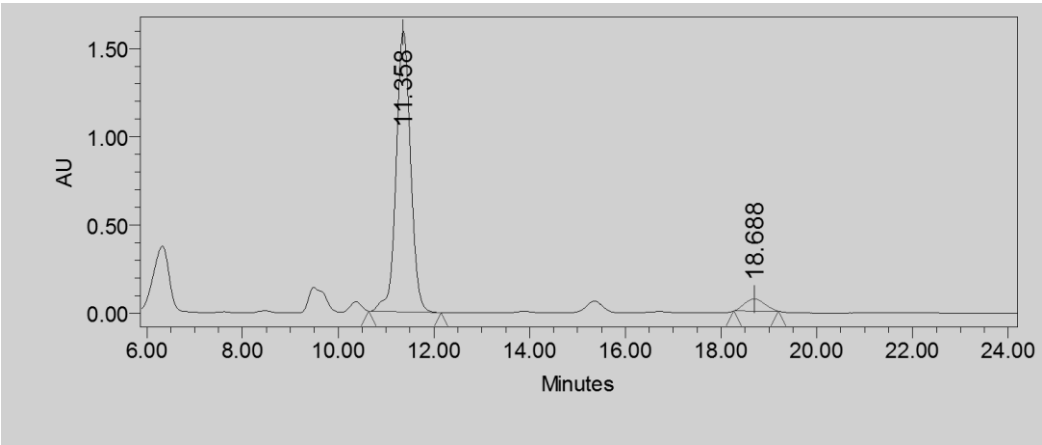
Retention Time	% Area
11.201	50.39
18.408	49.61



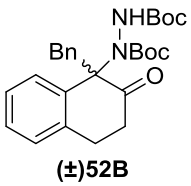


51Hj

Retention Time	% Area
11.358	94.29
18.688	5.71

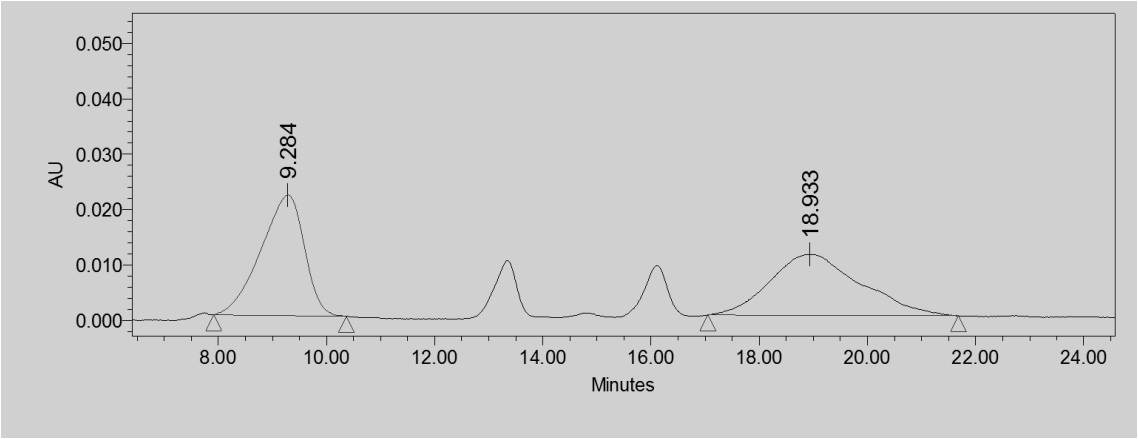


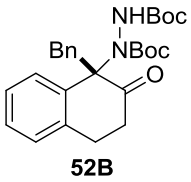
Chiralpack IC, 1 mL/min, hexane/isopropanol 98:2, λ = 210 nm



(±)52B

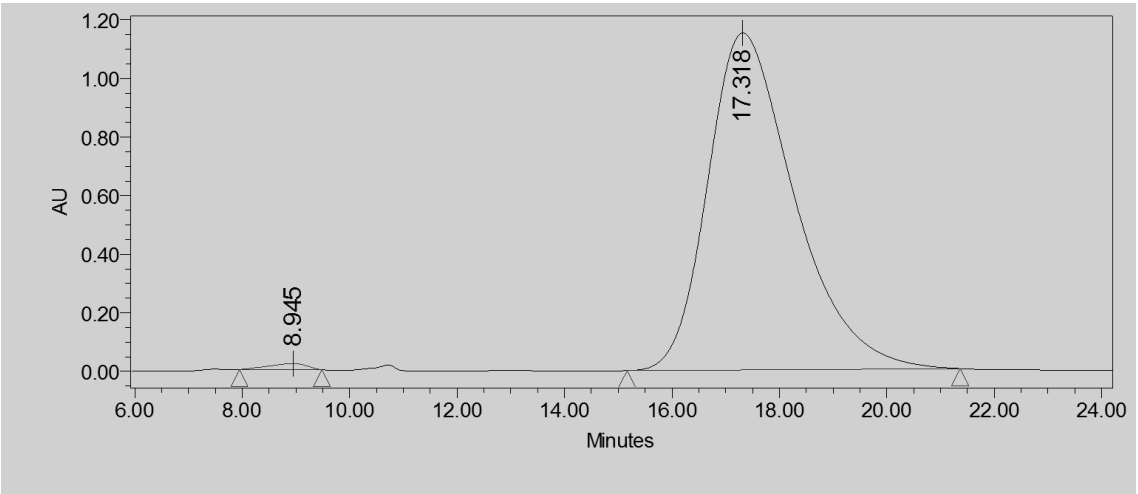
Retention Time	% Area
9.284	48.87
18.933	51.13



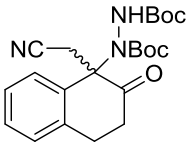


52B

Retention Time	% Area
9.284	48.87
18.933	51.13

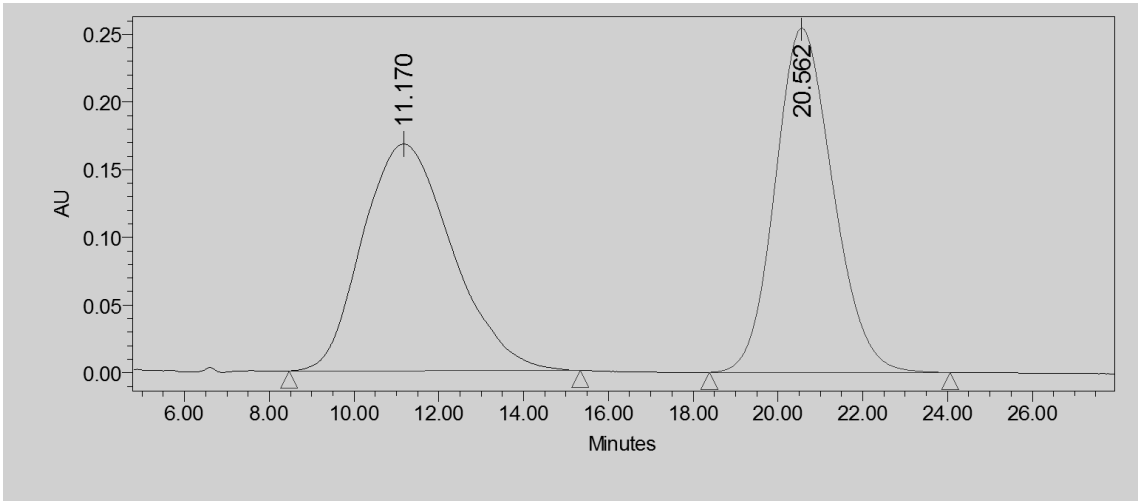


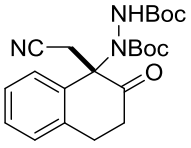
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)52D

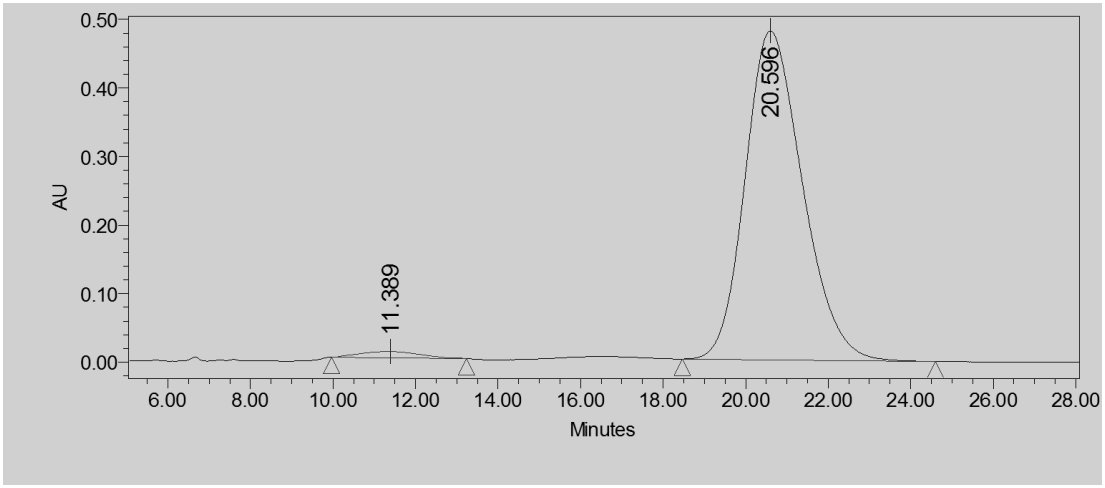
Retention Time	% Area
11.170	50.50
20.562	49.50



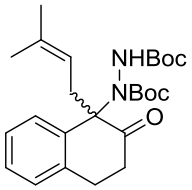


52D

Retention Time	% Area
11.389	1.97
20.596	98.03

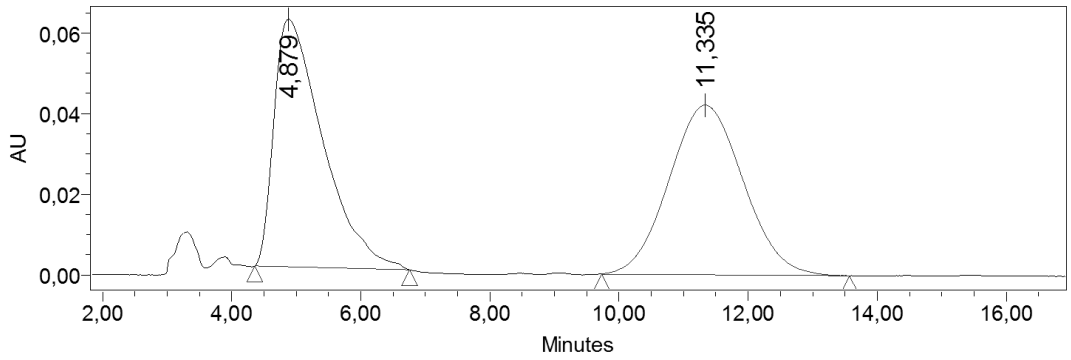


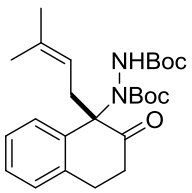
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)52C

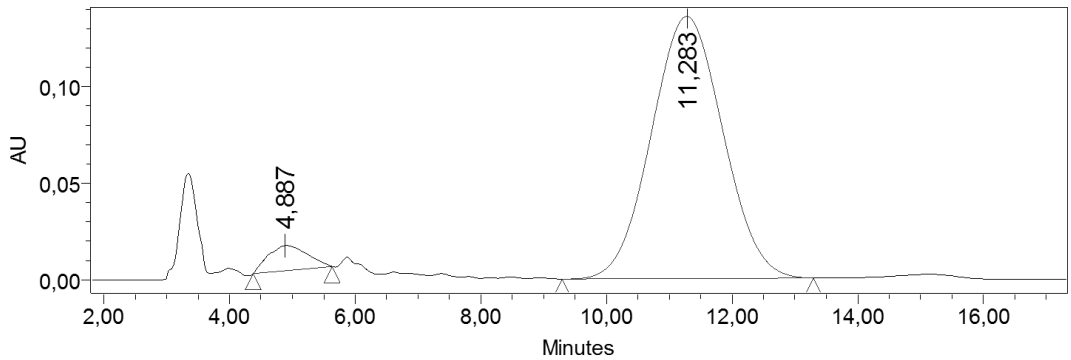
Retention Time	% Area
4,879	49,87
11,335	50,13



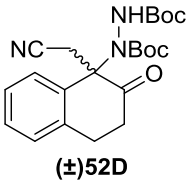


52C

Retention Time	% Area
4,887	4,96
11,283	95,04

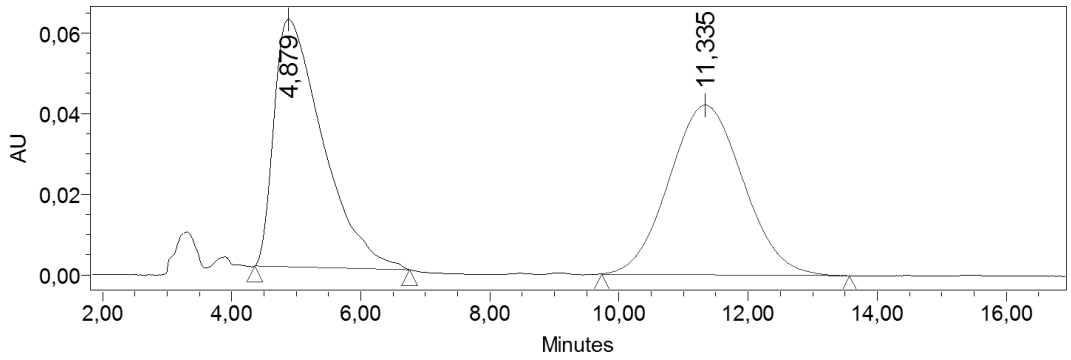


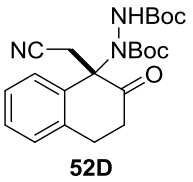
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)52D

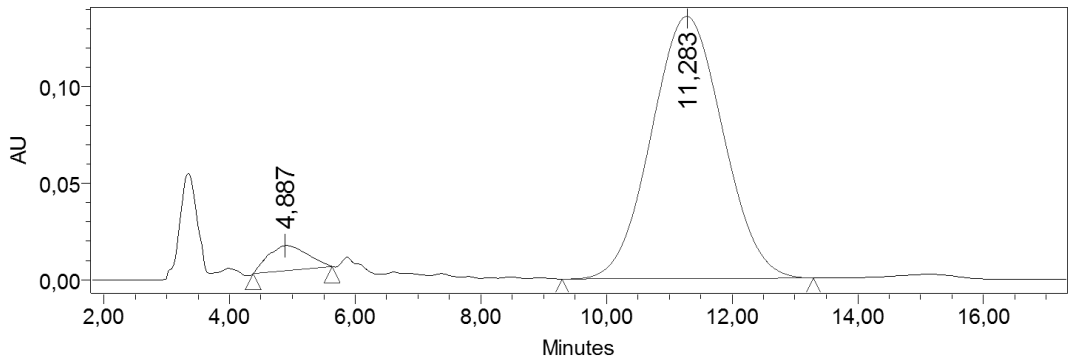
Retention Time	% Area
4,879	49,87
11,335	50,13



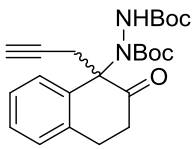


52D

Retention Time	% Area
4,887	4,96
11,283	95,04

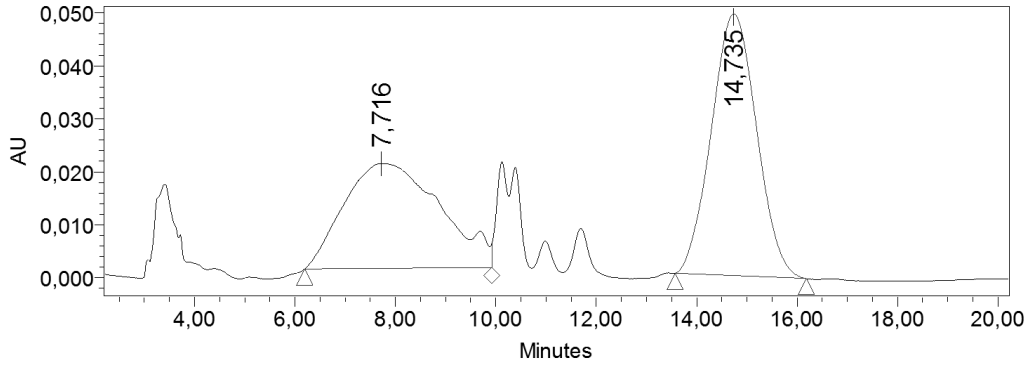


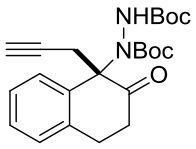
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 220 nm



(±)52E

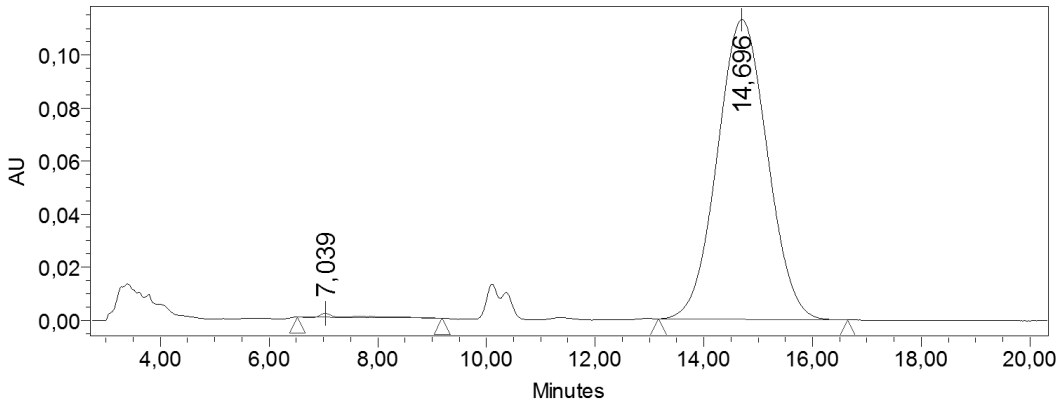
Retention Time	% Area
10,120	50,74
14,735	49,26



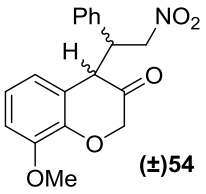


52E

Retention Time	% Area
7,039	0,63
14,696	99,37

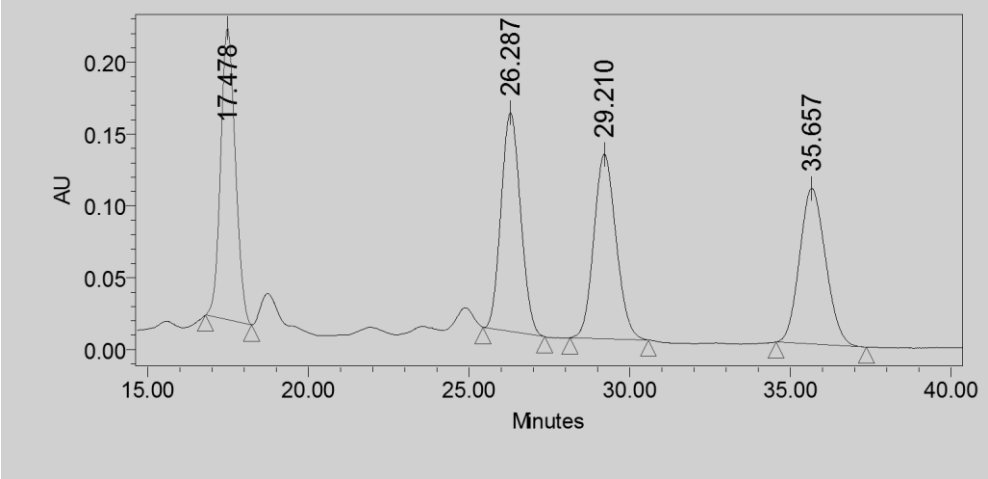


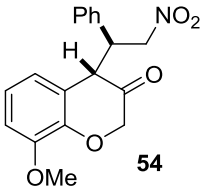
Chiralpack IC, 1 mL/min, hexane/isopropanol 80:20, λ = 210 nm



(±)54

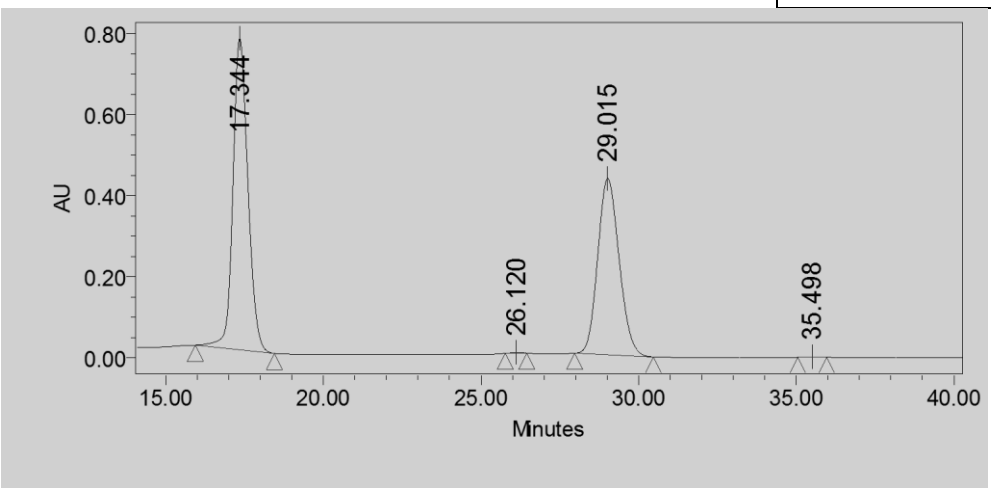
Retention Time	% Area
17.470	25.64
26.287	25.50
29.210	24.63
35.657	24.22



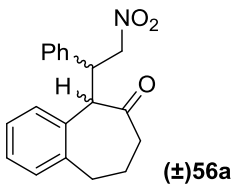


54

Retention Time	% Area
17.344	55.18
26.120	0.11
29.015	44.62
35.498	0.09

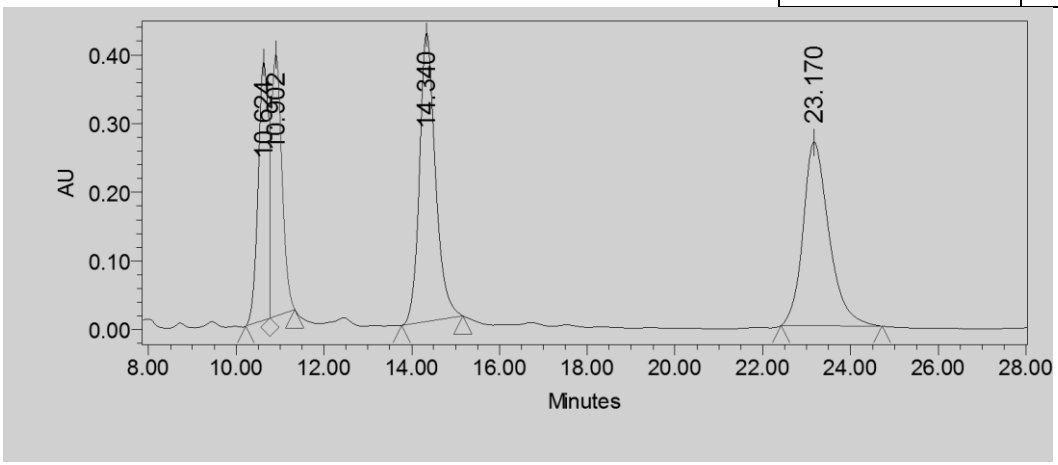


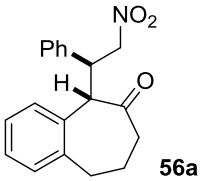
Chiralpack IA, 1 mL/min, hexane/isopropanol 95:5, λ = 210 nm



(±)56a

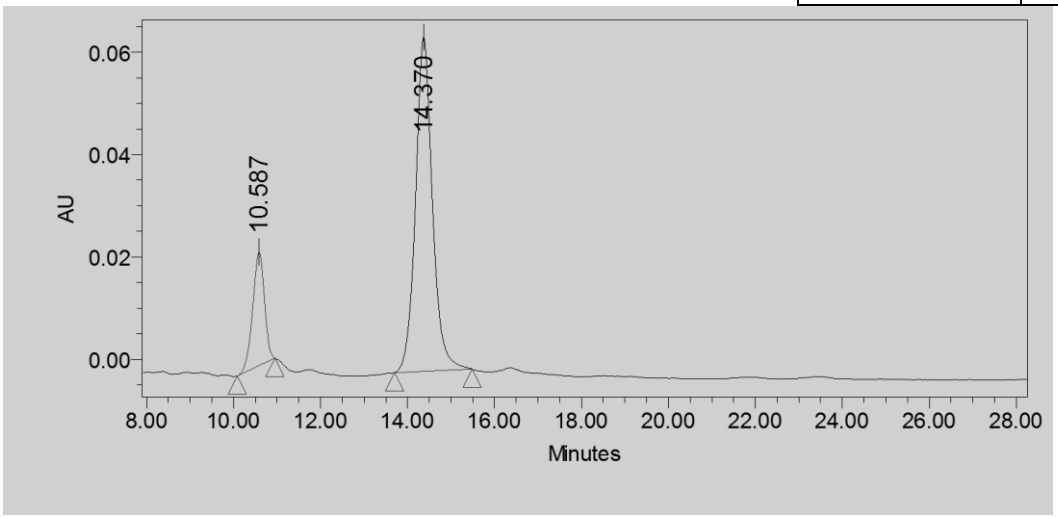
Retention Time	% Area
10.624	17.80
10.902	18.88
14.340	31.21
23.170	32.11



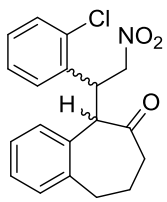


56a

Retention Time	% Area
10.587	19.05
14.370	80.95

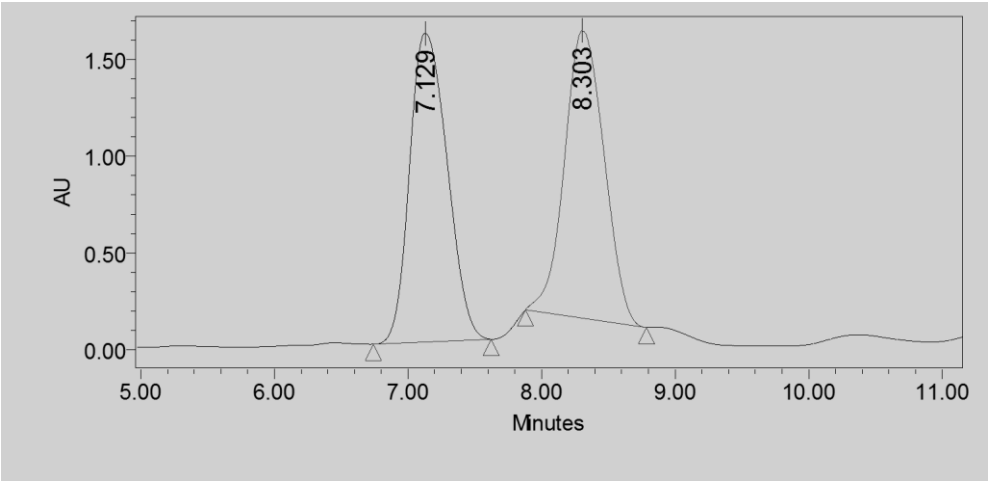


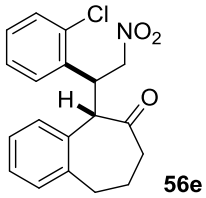
Chiralpack IA, 1 mL/min, hexane/isopropanol 90:10, λ = 210 nm



(±)56e

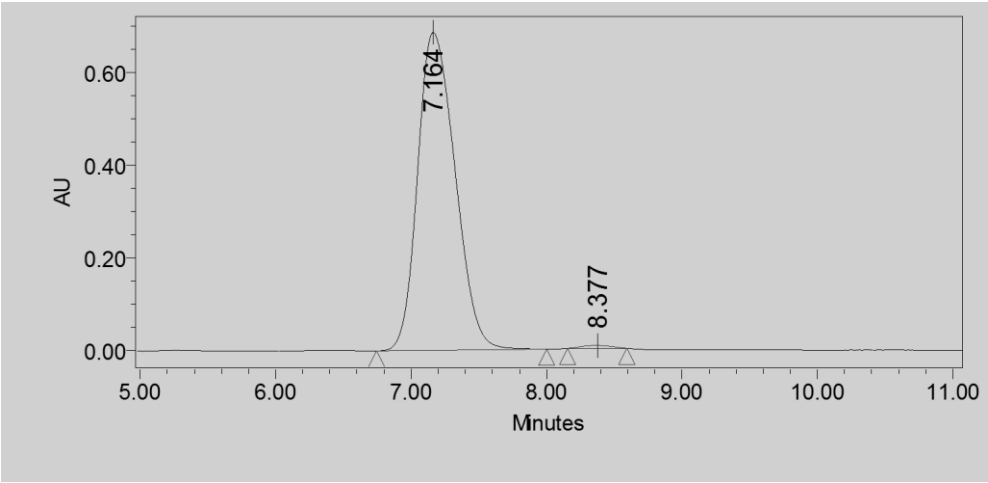
Retention Time	% Area
7.129	50.43
8.303	49.57



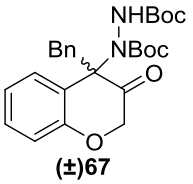


56e

Retention Time	% Area
7.164	99.29
8.377	0.71

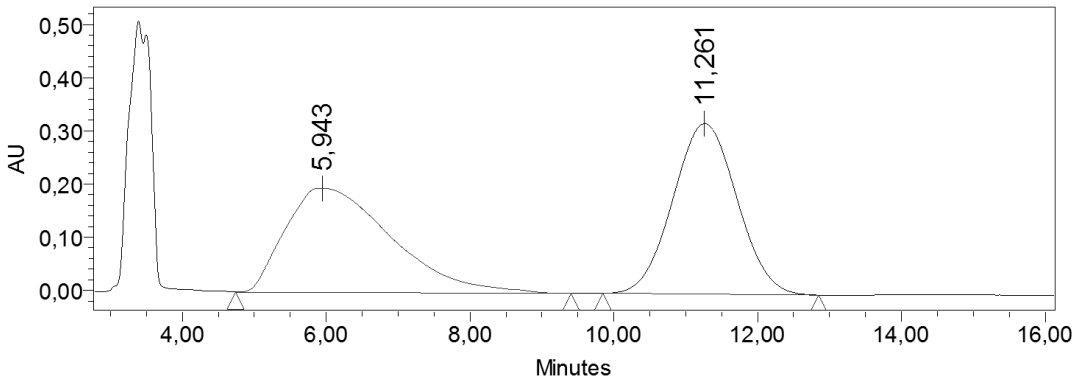


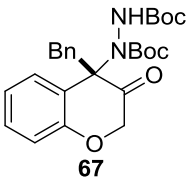
Chiralpack AD-H, 1 mL/min, hexane/isopropanol 90:10, λ = 220 nm



(±)67

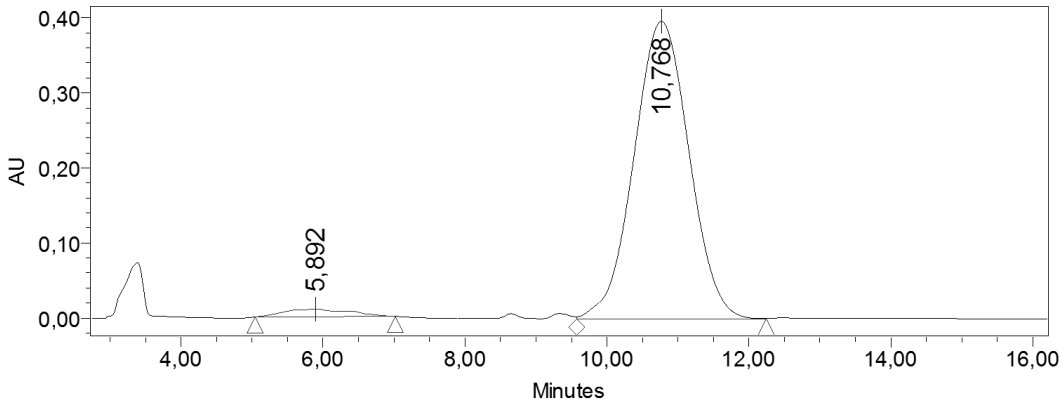
Retention Time	% Area
5,943	50,26
11,261	49,74





67

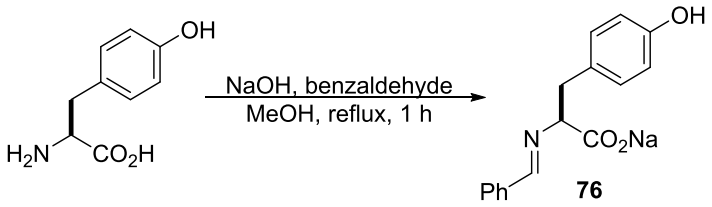
Retention Time	% Area
5,892	2,95
10,768	97,05



5.5. Experimental section of chapter 4

5.5.1. Oxazolidinone route

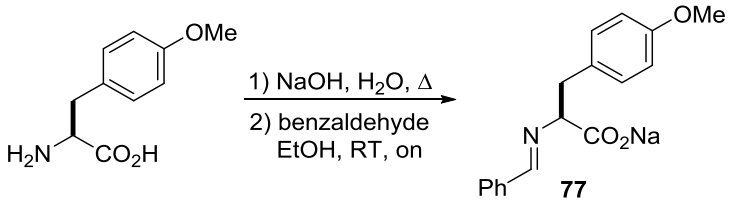
*5.5.1.1. Preparation of imine **76***[280]



L-Tyrosine (1.0 g, 5.5 mmol, 1 equiv.) and NaOH (220 mg, 5.5 mmol, 1 equiv.) were dissolved in dry methanol (20 mL) in a flame-dried round bottom flask gently warming the mixture and benzaldehyde (0.56 mL, 5.5 mmol, 1 equiv.) was added. The resulting solution was refluxed for 1 h, cooled to room temperature and isopropanol (20 mL was added so the product would precipitate. The resulting solid was filtrated, collected and stored in a vacuum oven at 50 ºC overnight affording compound **76** as a white solid. Yield: 96% (1.5 g, 5.3 mmol). **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.79 (s, 1H), 7.65 (dd, *J* = 7.3, 2.4 Hz, 2H), 7.41 – 7.30 (m, 3H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 3.90 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.26 – 3.20 (m, 1H), 2.94 (dd, *J* = 13.6, 9.7 Hz, 1H).

*5.5.1.2. Preparation of imine **77** and transformation into compounds **78-80***

Sodium (*S*,*E*)-2-(benzylideneamino)-3-(4-methoxyphenyl)propanoate (77)[281]



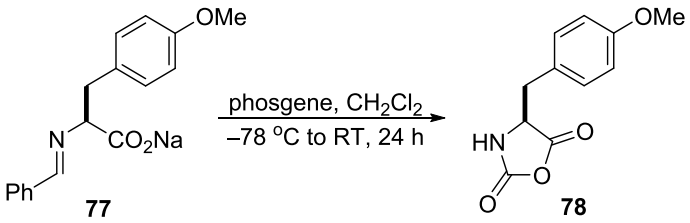
o-Methyl-*L*-tyrosine (1.0 g, 5.1mmol, 1 equiv.) was dissolved in a 1 M NaOH aqueous solution (5.1 mL, 5.1 mmol, 1 equiv.) stirring and gently heating. The water was then evaporated under reduced pressure and the residue was stored in a vacuum oven at 50 ºC overnight before being suspended in dry EtOH (10 mL) in a flame-dried

[280] Adapted from: R. Roy, M. C. Saha, P. S. Roy, *Transition Met. Chem.* **1990**, *15*, 51-57.

[281] F. Alonso, S. G. Davies, A. S. Elend, A. D. Smith, *Org. Biomol. Chem.* **2009**, 7, 518–526.

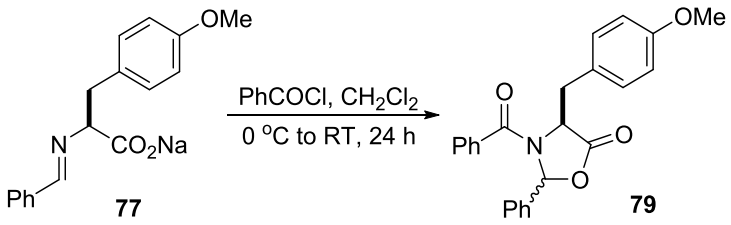
round bottom flask and adding benzaldehyde (0.55 mL, 5.4 mmol, 1.05 equiv.). The reaction mixture was stirred overnight, concentrated under reduced pressure, suspended in pentane and filtrated to obtain the desired imine as a white solid. Yield: 82% (1.3 g, 4.2 mmol). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.83 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 6.9 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.94 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, *J* = 4.1 Hz, 1H), 3.01 (dd, *J* = 13.5, 9.8 Hz, 1H).

(*S*)-4-(4-Methoxybenzyl)oxazolidine-2,5-dione (78)



The previously obtained imine **76** (200 mg, 0.66 mmol, 1 equiv.) was suspended in dry CH_2Cl_2 (5 mL) in a flame-dried round bottom flask and cooled to –78 ºC. Then phosgene (15% wt. in toluene) (2.4 mL, 3.3 mmol, 5 equiv.) was slowly added and the resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The crude of the reaction was concentrated under reduced pressure and was subjected to flash column chromatography (petrol ether/EtOAc 60:40) obtaining *N*-carboxyanhydride **78** as the major product. White solid. Yield: 31% (45 mg, 0.20 mmol). **^{1}H NMR** (500 MHz, Acetone-d_6) δ 8.00 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.79 (t, *J* = 5.3 Hz, 1H), 3.76 (s, 3H), 3.14 (dd, *J* = 14.3, 4.7 Hz, 1H), 3.08 (dd, *J* = 14.3, 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, Acetone-d_6) δ 171.2, 159.9, 152.5, 131.7, 127.5, 114.7, 59.6, 55.4, 36.8. **MS:** calculated for $C_{11}H_{11}NO_4Na$ (M + Na^+), 244.0580; found 244.0580.

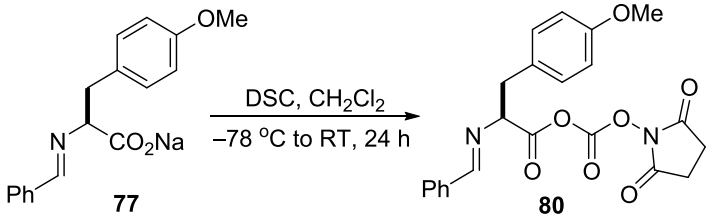
(*S*)-3-Benzoyl-4-(4-methoxybenzyl)-2-phenyloxazolidin-5-one (79)



The previously obtained imine **77** (200 mg, 0.66 mmol, 1 equiv.) was suspended in dry CH_2Cl_2 (5 mL) in a flame-dried round bottom flask and cooled to 0 ºC. Then

benzoyl chloride (0.76 mL, 6.6 mmol, 10 equiv.) was slowly added and the resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The crude of the reaction was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by flash column chromatography (petrol ether/EtOAc 80:20) obtaining the desired product **79** as a white solid in a 2:1 *dr*. Yield: 70% (180 mg, 0.46 mmol). Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 6.73 (m, 14H), 5.94 (s, 1H), 5.25 (b, 1H), 3.87 (s, 3H), 3.80 – 3.04 (b, 2H). Minor isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 6.73 (m, 15H), 5.08 (b, 1H), 3.82 (s, 3H), 3.80 – 3.04 (b, 2H). **MS:** calculated for $C_{24}H_{22}NO_4$ ($M + H^+$), 388.1543; found 388.1554.

2,5-Dioxopyrrolidin-1-yl (*S*)-4-(4-methoxybenzyl)-5-oxo-2-phenyloxazolidine-3-carboxylate (80)

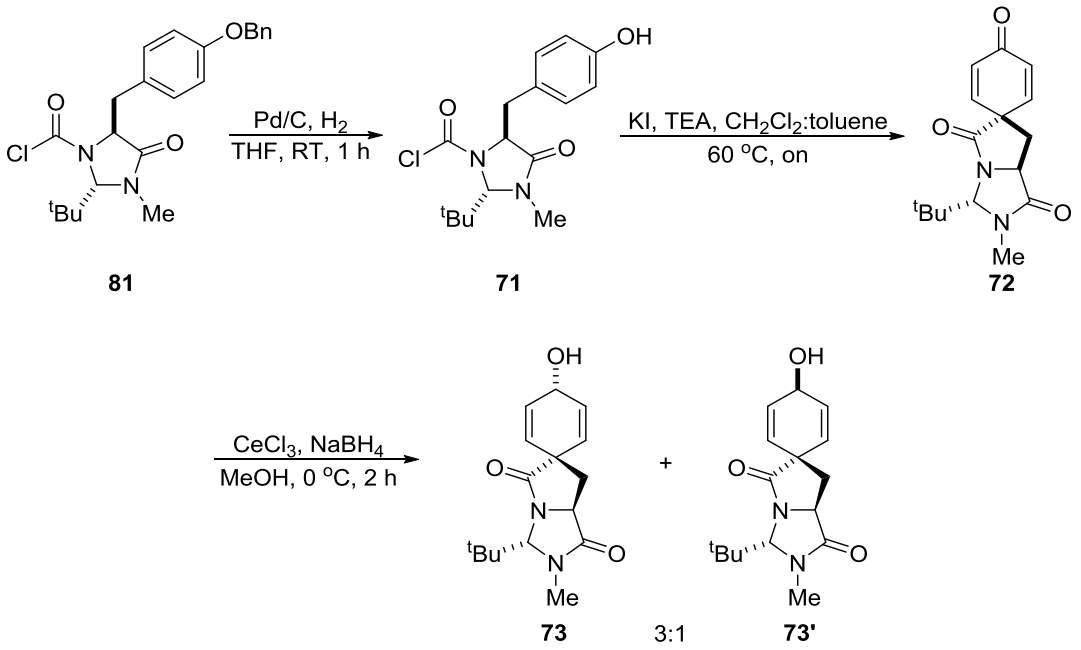


The previously obtained imine **77** (200 mg, 0.66 mmol, 1 equiv.) and *N*,*N*'-disuccinimidyl carbonate (DSC) (338 mg, 1.32 mmol, 2 equiv.) were cooled in a flame-dried round bottom flask to –78 ºC and dry CH_2Cl_2 (5 mL) was slowly added. The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The crude of the reaction was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by flash column chromatography (petrol ether/EtOAc 80:20) obtaining the desired product as a white solid, which showed low stability. Yield: 35% (98 mg, 0.23 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.70 (d, *J* = 6.7 Hz, 2H), 7.46 – 7.34 (m, 3H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.44 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.75 (s, 3H), 3.44 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.25 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.85 (s, 4H).

5.5.2. Imidazolidinone route

*5.5.2.1. Preparation of spirocyclic compound **73***

Imidazolidinone **73** was synthesised from intermediate **81** provided by L. Eagling according to the following synthetic sequence:[282]



1st step: Palladium on active carbon (10% wt.) (200 mg, 20% wt.) was added to a solution of the benzyl ether **81** (0.95 g, 2.3 mmol) in dry THF in a flame-dried round bottom flask and the mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The reaction mixture was filtered over a pad of celite and the solvent was eliminated under reduced pressure obtaining the desired alcohol **71** as a white solid. Yield: 83% (620 mg, 1.9 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.72 (bs, 2H), 4.86 (d, *J* = 36.8 Hz, 1H), 4.69 (d, *J* = 44.5 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 3.74 (dd, *J* = 54.3, 17.6 Hz, 1H), 3.24 (dd, *J* = 34.7, 14.3 Hz, 1H), 2.82 (d, *J* = 49.2 Hz, 3H), 0.97 (d, *J* = 28.3 Hz, 9H).

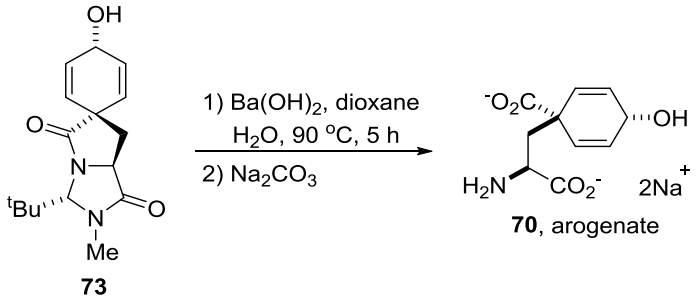
2nd step: Triethylamine (0.37 mL, 3.6 mmol, 2 equiv.) and potassium iodide (340 mg, 2.0 mmol, 1.1 equiv.) were added to a solution of the previously obtained phenol **71** (600 mg, 1.8 mmol, 1 equiv.) in a 4:1 mixture of CH_2Cl_2 and toluene (3.5 mL) in a flame-dried round bottom flask and the reaction mixture was stirred at 60 ºC for 72 h. The solvent was then eliminated under reduced pressure and the residue was dissolved in dihloromethane (5 mL), washed with water (3 x 5 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by flash

[282] Previously developed in the Clayden group.

column chromatography (petrol ether/EtOAc 70:30) obtaining the desired product **72** as a white solid. Yield: 81% (420 mg, 1.5 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 9.7 Hz, 1H), 6.72 (d, *J* = 9.7 Hz, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 6.41 (d, *J* = 10.1 Hz, 1H), 4.86 (s, 1H), 4.46 (t, *J* = 8.2 Hz, 1H), 3.04 (s, 3H), 2.62 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.47 (dd, *J* = 13.2, 9.2 Hz, 1H), 1.04 (s, 9H).

3rd step: Cerium chloride heptahydrate (780 mg, 2.1 mmol, 1.5 equiv.) and sodium borohydride (81 mg, 2.1 mmol, 1.5 equiv.) were added to a solution of the previously obtained spirocycle **72** (380 mg, 1.4 mmol, 1 equiv.) at 0 ºC in dry methanol in a flame-dried round bottom flask and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with water and diluted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The two diastereomers could be separated by flash column chromatography (CH_2Cl_2/MeOH 95:5) obtaining the product as a white solid in a 3:1 **73**/**73'** proportion. Total yield: 67% (270 mg, 0.94 mmol). Store under argon, slowly oxidizes back to the ketone with time. Major isomer (**74**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.21 (ddd, *J* = 10.0, 3.8, 1.4 Hz, 1H), 6.12 (ddd, *J* = 9.8, 3.8, 1.5 Hz, 1H), 5.92 (d, *J* = 9.4 Hz, 1H), 5.64 (d, *J* = 10.4 Hz, 1H), 4.79 (s, 1H), 4.47 (s, 1H), 4.36 (t, *J* = 8.2 Hz, 1H), 2.99 (s, 3H), 2.47 (dd, *J* = 13.2, 7.7 Hz, 1H), 2.15 (dd, *J* = 13.2, 8.8 Hz, 1H), 1.01 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.0, 172.3, 131.6, 130.8, 129.4, 128.1, 81.8, 61.4, 56.8, 50.5, 38.9, 38.3, 31.4, 25.8. Minor isomer (**74'**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 (d, *J* = 9.6 Hz, 1H), 6.05 (d, *J* = 10.8 Hz, 1H), 5.90 (d, *J* = 9.9 Hz, 1H), 5.61 (d, *J* = 10.0 Hz, 1H), 4.80 (s, 1H), 4.68 (s, 1H), 4.36 (t, *J* = 8.2 Hz, 1H), 3.00 (s, 3H), 2.53 – 2.45 (m, 1H), 2.25 – 2.16 (m, 1H), 1.60 (d, *J* = 8.9 Hz, 1H), 1.02 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.5, 172.3, 131.5, 129.8, 128.0, 126.3, 81.6, 61.8, 56.8, 50.2, 38.5, 38.3, 31.3, 25.8.

*5.5.2.2. Synthesis of disodium arogenate (**70**)*[283]

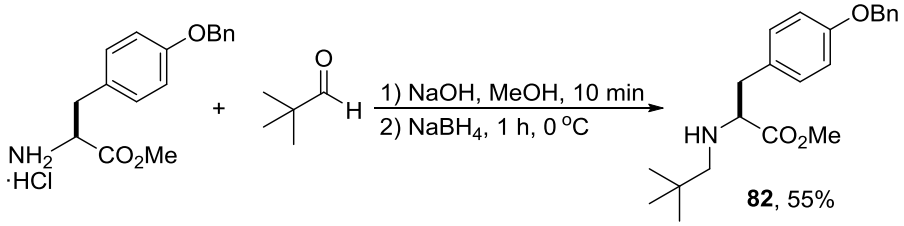


[283] Adapted from: W. H. Pirkle, R. Heire, M. H. Hyun, *Chirality.* **1992**, *4*, 302–307.

The major diastereomer of the above obtained alcohol (**73**) (50 mg, 0.17 mmol, 1 equiv.) was dissolved in a mixture of H_2O (0.75 mL) and dioxane (0.25 mL), and barium hydroxide (87 mg, 0.51 mmol, 3 equiv.) were added. The reaction mixture was stirred at 90 ºC for 4 h, after which the reaction mixture was cooled to room temperature and sodium carbonate anhydrous (110 mg, 1.0 mmol, 6 equiv.) and water (3 mL) were added. The resulting barium carbonate salt was separated by filtration and the aqueous layer was washed with CH_2Cl_2 (3 x 4 mL). The aqueous phase was concentrated under reduced pressure and the product was purified by reverse phase chromatography (0.1 M TFA/acetonitrile 99:1 to 0:100) being the last thing to exit the column. The spectroscopic data resulted coincidental with the one found in the literature.[284] **^{1}H NMR** (400 MHz, D_2O) δ 6.06 – 5.97 (m, 3H), 5.90 (d, *J* = 10.3 Hz, 1H), 4.63 – 4.52 (m, 1H), 3.14 – 3.08 (m, 1H), 2.23 – 2.07 (m, 1H), 1.89 (dd, *J* = 14.1, 7.4 Hz, 1H).

5.5.3. Acyclic route

*5.5.3.1. Preparation of ester intermediate **82***[285]



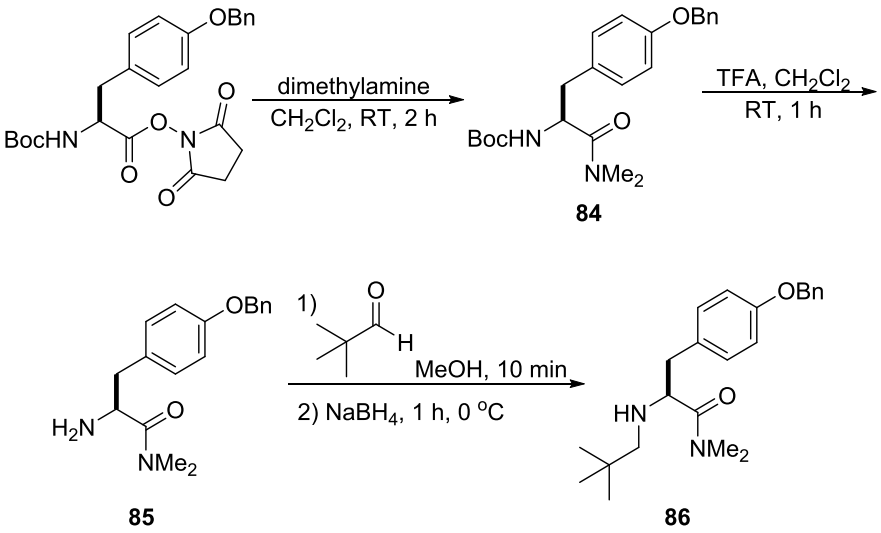
The commervially available *O*-benzyl methyltyrosinate hydrochloride (1.0 g, 3.1 mmol, 1 equiv.) was dissolved in dry MeOH (15 mL) and neutralised with sodium hydroxide powder (130 mg, 3.3 mmol, 1.05 equiv.). Trimethylacetaldehyde (0.47 mL, 4.34 mmol, 1.4 equiv.) was added and the solution was stirred at room temperature for 10 min before cooling it to 0 ºC and adding sodium borohydride (95 mg, 2.5 mmol, 0.8 equiv.). The resulting mixture was stirred at the same temperature for 1 h and the remaining sodium borohydride was treated adding water (5 mL). The methanol was eliminated under reduced pressure and EtOAc (15 mL) was added. The organic phase was separated, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (petrol ether/EtOAc 85:15) obtaining the desired compound **82** as a white solid. Yield: 55% (610 mg, 1.7 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 5H), 7.11 (d, *J* =

[284] S. Danishefsky, J. Morris, L. A. Clizbe, *J. Am. Chem. Soc.* **1981**, *103*, 1602-1604.

[285] G. Verardo, P. Geatti, E. Pol, A. G. Giumanini, *Can. J. Chem.* **2002**, *80*, 779-788.

8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.04 (s, 2H), 3.63 (s, 3H), 3.39 (t, *J* = 6.9 Hz, 1H), 2.88 (dd, *J* = 6.8, 2.5 Hz, 2H), 2.38 (d, *J* = 11.2 Hz, 1H), 2.11 (d, *J* = 11.2 Hz, 1H), 0.85 (s, 9H).

*5.5.3.2. Preparation of amide intermediate **86***



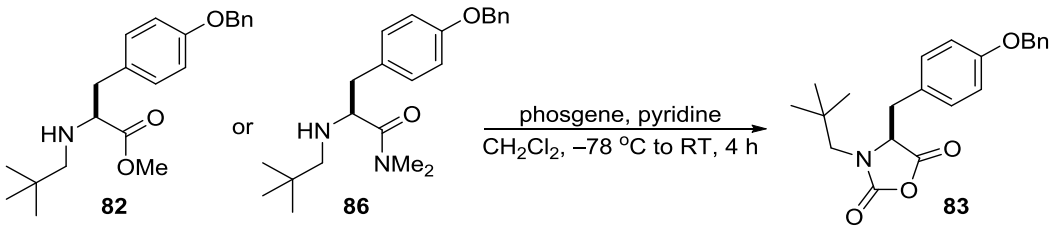
1st step:[286] Dimethylamine (2 M in THF) (0.55 mL, 1.1 mmol, 1.0 equiv.) was added to a solution of Boc-*O*-benzyl-*L*-tyrosine hydrosuccinimide ester (500 mg, 1.1 mmol, 1.0 equiv.) in dry dichloromethane (2 mL) and the resulting solution was stirred for 2 h. The mixture was concentrated under reduced pressure and product was purified by flash column chromatography (petrol ether/EtOAc 80:20) obtaining compound **84** as a colourless oil. Yield: Cuantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 5H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.39 (d, *J* = 8.6 Hz, 1H), 4.82 – 4.69 (m, 1H), 2.96 – 2.85 (m, 2H), 2.84 (s, 3H), 1.41 (s, 9H).

2nd step:[286] The above obtained Boc-protected amine **84** (400 mg, 1.0 mmol, 1.0 equiv.) was dissolved in a 1:1 mixture of CH_2Cl_2 and trifluoroacetic acd (5 mL) and was stirred at room temperature for 1 h. The solvent was eliminated under reduced pressure and the residue dissolved in CH_2Cl_2 (5 mL). The organic phase was washed with an aqueous solution of NaOH (1 M) (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure obtaining the desired compound **85** as a white solid. Yield: Cuantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 2H), 3.91 (t, *J* = 7.1 Hz, 1H), 2.90 (s, 3H), 2.92 – 2.84 (m, 1H), 2.73 (s, 3H), 2.76 – 2.69 (m, 1H), 1.82 (s, 2 H).

[286] L. Ribeiro, N. Silva, J. Iley, J. Rautio, T. Järvinen, H. Mota-Filipe, R. Moreira and E. Mendes, *Arch. Pharm. Chem.* **2007**, *340*, 32-40.

3rd step:[285] The previously obtained amine **85** (300 mg, 1.0 mmol, 1 equiv.) was dissolved in dry MeOH (15 mL) trimethylacetaldehyde (0.15 mL, 1.4 mmol, 1.4 equiv.) was added. The solution was stirred at room temperature for 10 min before cooling it to 0 ºC and adding sodium borohydride (30 mg, 0.8 mmol, 0.8 equiv.). The resulting mixture was stirred at the same temperature for 1 h and the remaining sodium borohydride was treated adding H_2O (2 mL). The methanol was eliminated under reduced pressure and EtOAc (5 mL) was added. The organic phase was separated, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (petrol ether/EtOAc 50:50) obtaining the desired amide **86** as a white solid. Yield: 62% (230 mg, 0.62 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.26 (m, 5H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.05 (s, 2H), 3.61 (dd, *J* = 8.5, 6.1 Hz, 1H), 2.90 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.85 (s, 3H), 2.71 (dd, *J* = 13.2, 8.5 Hz, 1H), 2.56 (s, 3H), 2.31 (d, *J* = 10.9 Hz, 1H), 2.03 (d, *J* = 10.9 Hz, 1H), 0.88 (s, 9H).

*5.5.3.3. Synthesis of NCA **83***

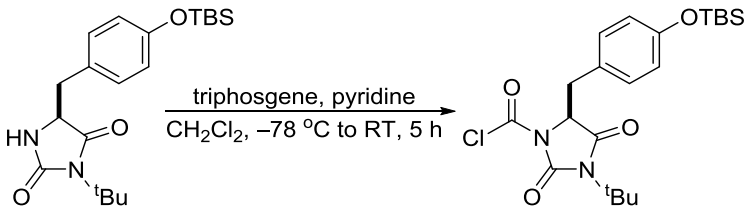


Pyridine (45 µL, 0.56 mmol, 1 equiv) and phosgene (15% wt. in toluene) (1.2 mL, 1.7 mmol, 3 equiv.) were added in this order to a solution of the previously obtained ester **82** or amide **86** (0.56 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at –78 ºC. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The solvent and the remaining phosgene were eliminated under reduced pressure and the product was purified by flash column chromatography (petrol ether/EtOAc 90:10) obtaining the pure NCA as a white solid. Yield from ester **82**: 65% (134 mg, 0.36 mmol). Yield from amide **86**: 40% (82 mg, 0.22 mmol). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 14.8, 7.2 Hz, 4H), 7.33 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.03 (s, 2H), 4.62 (t, *J* = 4.2 Hz, 1H), 3.60 (d, *J* = 14.4 Hz, 1H), 3.18 (d, *J* = 4.2 Hz, 2H), 2.87 (d, *J* = 14.4 Hz, 1H), 1.00 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.5, 158.6, 152.4, 136.7, 130.4, 128.6, 128.0, 127.5, 124.6, 115.4, 70.0, 62.4, 52.8, 34.1, 33.4, 28.0. **MS:** calculated for $C_{22}H_{25}NNaO_4$ (M + Na^+), 390.1676; found 390.1679.

5.5.4. Hydantoin route

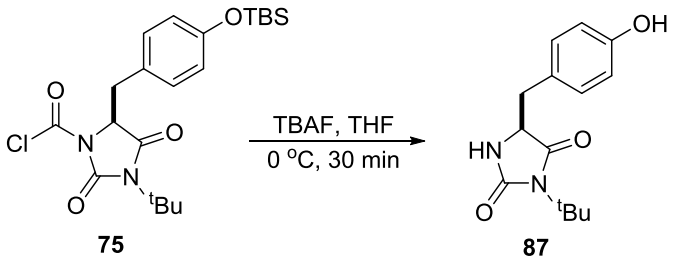
*5.5.4.1. Synthesis of hydantoins **87** and **88***

(*S*)-3-(tert-Butyl)-5-(4-((tert-butyldimethylsilyl)oxy)benzyl)-2,4-dioxoimidazolidine -1-carbonyl chloride (75)



Pyridine (64 µL, 0.80 mmol, 1.5 equiv.) was added to a triphosgene (80 mg, 0.27 mmol, 0.5 equiv.) solution in dry dichloromethane (3 mL) in a flame-dried round bottom flask at –78 ºC and the resulting solution was stirred at the same temperature for 10 min before adding hydantoin **74** provided by L. Eagling (200 mg, 1.53 mmol, 1 equiv.) in CH_2Cl_2 (2 mL). The resulting mixture was slowly warmed to room temperature and was stirred at that temperature for 5 h. The solvent was partially eliminated under reduced pressure and the product was purified by flash column chromatography (petrol ether/EtOAc 90:10) obtaining the desired product **75** as colourless oil. Yield: 63% (423 mg, 0.96 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.60 (dd, *J* = 4.7, 2.6 Hz, 1H), 3.46 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.21 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.36 (s, 9H), 0.96 (s, 9H), 0.15 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5, 155.5, 150.7, 143.6, 130.9, 124.9, 120.4, 61.1, 59.8, 34.2, 28.0, 25.6, 18.2, –4.5. **MS:** calculated for $C_{21}H_{31}ClN_2NaO_4Si$ (M + Na^+), 461.1639; found 461.1634.

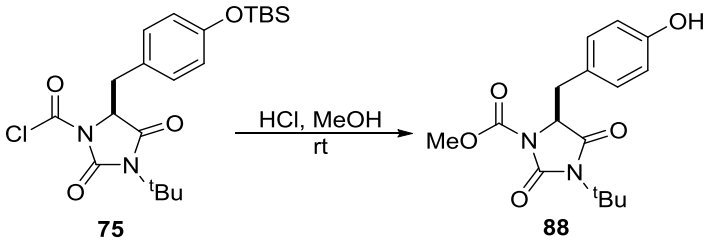
(*S*)-3-(tert-Butyl)-5-(4-hydroxybenzyl)imidazolidine-2,4-dione (87)[287]



[287] N. Casanova, A. Seoane, J. L. Mascareñas, M. Gulías, *Angew. Chem. Int. Ed.* **2015**, *54*, 2374-2377.

The above obtained compound **75** (45 mg, 0.1 mmol, 1 equiv.) was dissolved in dry THF (1 mL) and tetrabutylammonium fluoride (1 M in THF) (105 µL, 0.105 mmol, 1.05 equiv.) was added at 0 ºC. The resulting solution was stirred at the same temperature for 30 min before the reaction was quenched by adding brine and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (petrol ether/EtOAc 50:50) obtaining compound **87** as a white solid. Yield: 60% (16 mg, 0.060 mmol). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.00 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 4.3 Hz, 1H), 3.00 – 2.84 (m, 2H), 1.34 (s, 9H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 176.6, 173.0, 157.7, 132.2, 126.5, 116.0, 58.4, 37.4, 28.8, 20.9. **MS:** calculated for $C_{14}H_{18}NNaO_3$ ($M + Na^+$), 285.1215; found 185.12.

Methyl (*S*)-3-(tert-butyl)-5-(4-hydroxybenzyl)-2,4-dioxoimidazolidine-1-carboxylate (88)

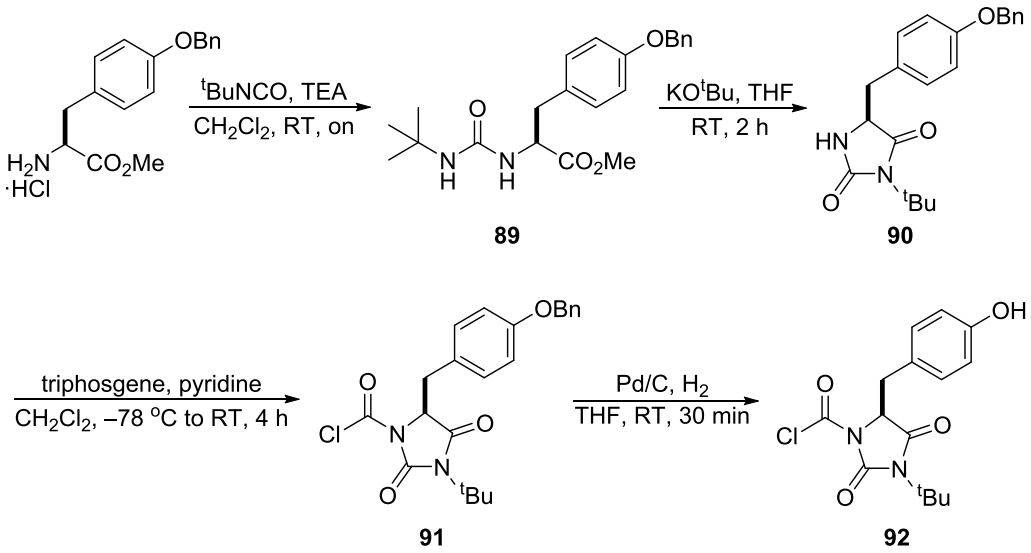


75 **88**

The carbonyl chloride above obtained (**75**) (45 mg, 0.1 mmol, 1 equiv.) was dissolved in dry MeOH (1 mL) in a flame-dried round bottom flask under nitrogen atmosphere and hydrogen chloride (1.25 M in MeOH) (0.2 mL, 0.25 mmol, 2.5 equiv.) was added. The resulting solution was stirred at room temperature for 16 h and the solvent was eliminated under reduced pressure obtaining the desired product as a white solid. Yield: 60% (19 mg, 0.060 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (d, J = 5.7 Hz, 2H), 6.74 (d, J = 5.8 Hz, 2H), 6.21 (s, 1H), 4.49 (s, 1H), 3.95 (s, 2H), 3.37 (d, J = 13.4 Hz, 1H), 3.15 (d, J = 13.6 Hz, 1H), 1.33 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.0, 155.8, 152.5, 150.8, 130.9, 124.4, 115.4, 59.4, 59.1, 54.0, 34.5, 28.1. **MS:** calculated for $C_{16}H_{20}N_2NaO_5$ ($M + Na^+$), 343.1264; found 343.1265.

*5.5.4.2. Synthesis of hydantoin **92***

Hydantoin **92** was prepared according to the following synthetic sequence:



1st step: *tert*-Butyl isocyanate (0.45 mL, 3.9 mmol, 1.1 equiv.) was added to a stirred solution of *O*-benzyl methyltyrosinate hydrochloride (1.1 g, 3.5 mmol, 1 equiv.) and triethylamine (1.4 mL, 10.5 mmol, 3 equiv.) in CH_2Cl_2 (15 mL) in a flame-dried round bottom flask under nitrogen atmosphere and the reaction mixture was stirred at room temperature overnight. The organic phase was washed with a saturated solution of NH_4Cl (3 x 10 mL), a saturated solution of $NaHCO_3$ (3 x 10 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent was eliminated under reduced pressure to afford the pure urea **89** as a white solid. Yield: Quantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.03 (s, 2H), 4.72 – 4.63 (m, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.20 (s, 1H), 3.71 (s, 3H), 3.10 – 2.94 (m, 2H), 1.30 (s, 9H).

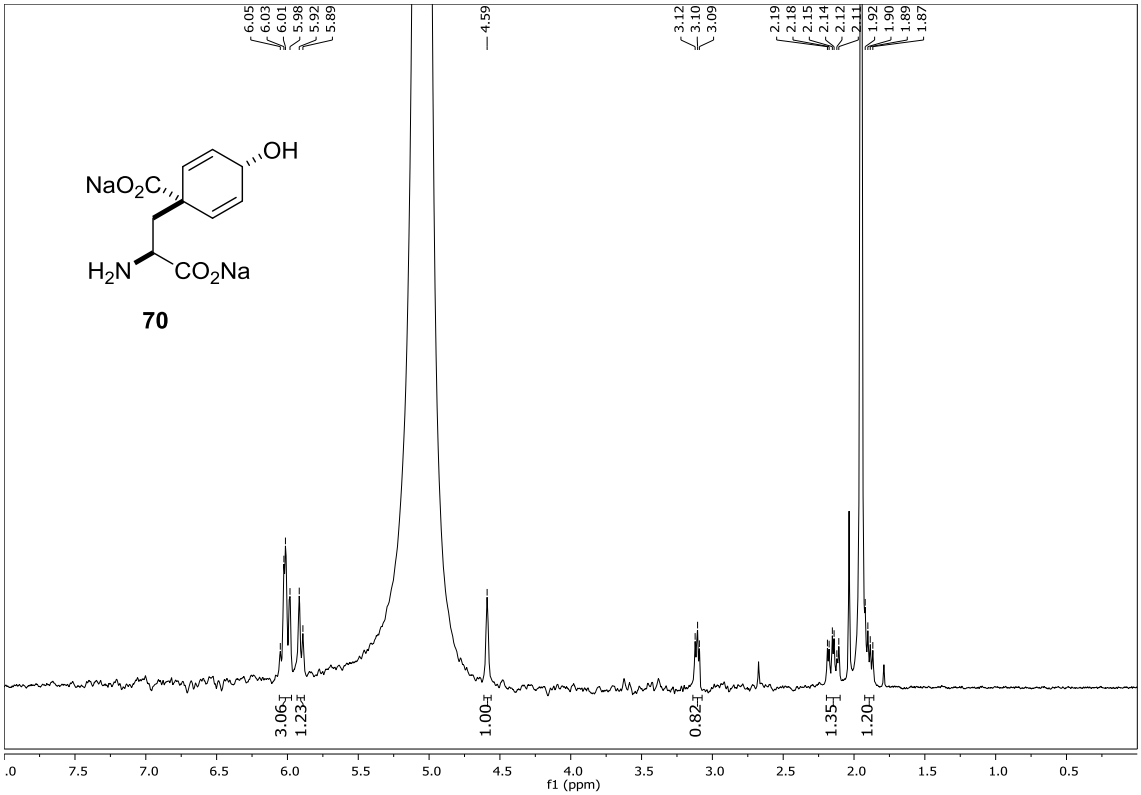
2nd step: Potassium *tert*-butoxyde (390 mg, 3.9 mmol, 1.1 equiv.) was added to a stirred solution of the urea **89** obtained in the previous step (1.3 g, 3.5 mmol, 1 equiv.) in THF (12 mL) in a flame-dried round bottom flask under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 2 h. The reaction was then quenched by adding a saturated solution of NH_4Cl (10 mL). The organic phase was separated and washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (petrol ether/EtOAc 70:30) obtaining the desired compound **90** as a white solid. Yield: 58% (512 mg, 2.0 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.47 (s, 1H), 5.04 (s, 2H), 4.02 (dd, *J* = 7.4, 3.3 Hz, 1H), 3.10 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.81 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.49 (s, 9H).

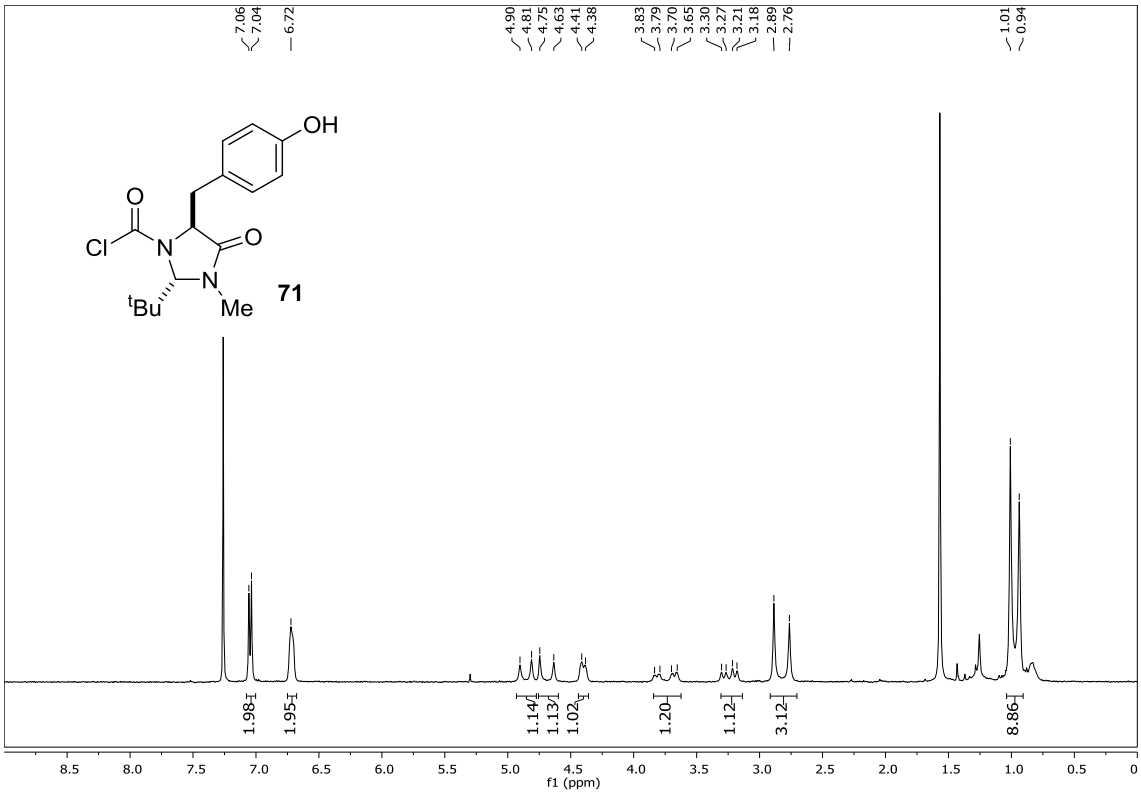
3rd step: Pyridine (0.24 mL, 3.0 mmol, 1.5 equiv.) was added to a triphosgene (297 mg, 1.0 mmol, 0.5 equiv.) solution in dry dichloromethane (15 mL) in a flame-dried round

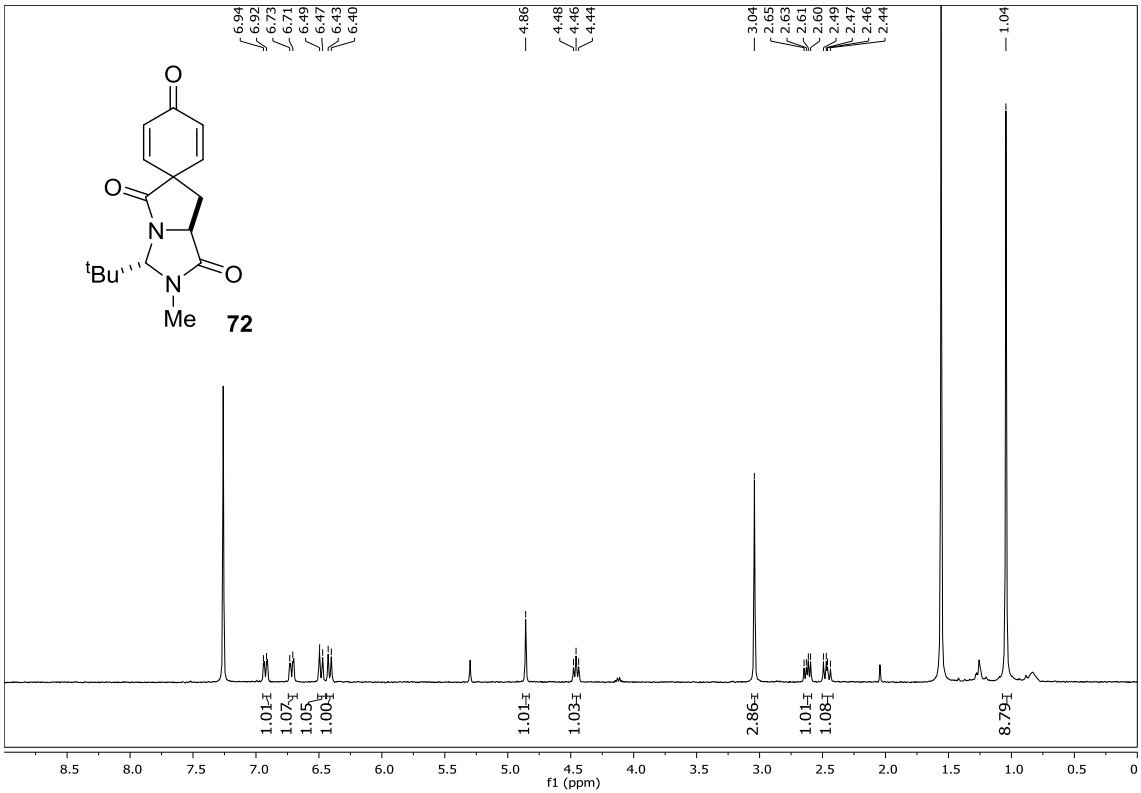
bottom flask at –78 ºC and the resulting solution was stirred at the same temperature for 10 min before adding the hydantoin **90** obtained in the previous step (715 mg, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL). The resulting mixture was slowly warmed to room temperature and was stirred at that temperature for further 4 h. The solvent was partially eliminated under reduced pressure and the product was purified by flash column chromatography (petrol ether/EtOAc 80:20) obtaining the desired compound **91** as colourless oil. Yield: 43% (360 mg, 0.86 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.60 (dd, *J* = 4.6, 2.6 Hz, 1H), 3.47 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.24 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.34 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5, 158.5, 150.7, 143.6, 136.7, 130.9, 128.6, 128.0, 127.3, 124.5, 115.2, 69.9, 61.1, 59.9, 34.2, 28.0. **MS:** calculated for $C_{22}H_{23}ClN_2NaO_4$ ($M + Na^+$), 437.1239; found 437.1243.

4th step: Palladium on active carbon (10% wt.) (2 mg, 20% wt.) was added to a solution of compound **91** above obtained (20 mg, 0.05 mmol) in dry THF in a flame-dried round bottom flask and the mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The reaction mixture was filtered over a pad of celite and the solvent was eliminated under reduced pressure obtaining the desired product **92** as a white solid. Yield: 50% (8.1 mg, 0.025 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.06 (s, 1H), 4.60 (dd, *J* = 4.7, 2.7 Hz, 1H), 3.46 (dd, *J* = 14.5, 4.8 Hz, 1H), 3.23 (dd, *J* = 14.5, 2.5 Hz, 1H), 1.37 (s, 9H). **MS:** calculated for $C_{15}H_{17}ClN_2NaO_4$ ($M + Na^+$), 347.0769; found 347.0767.

5.5.5. Representative NMR spectra



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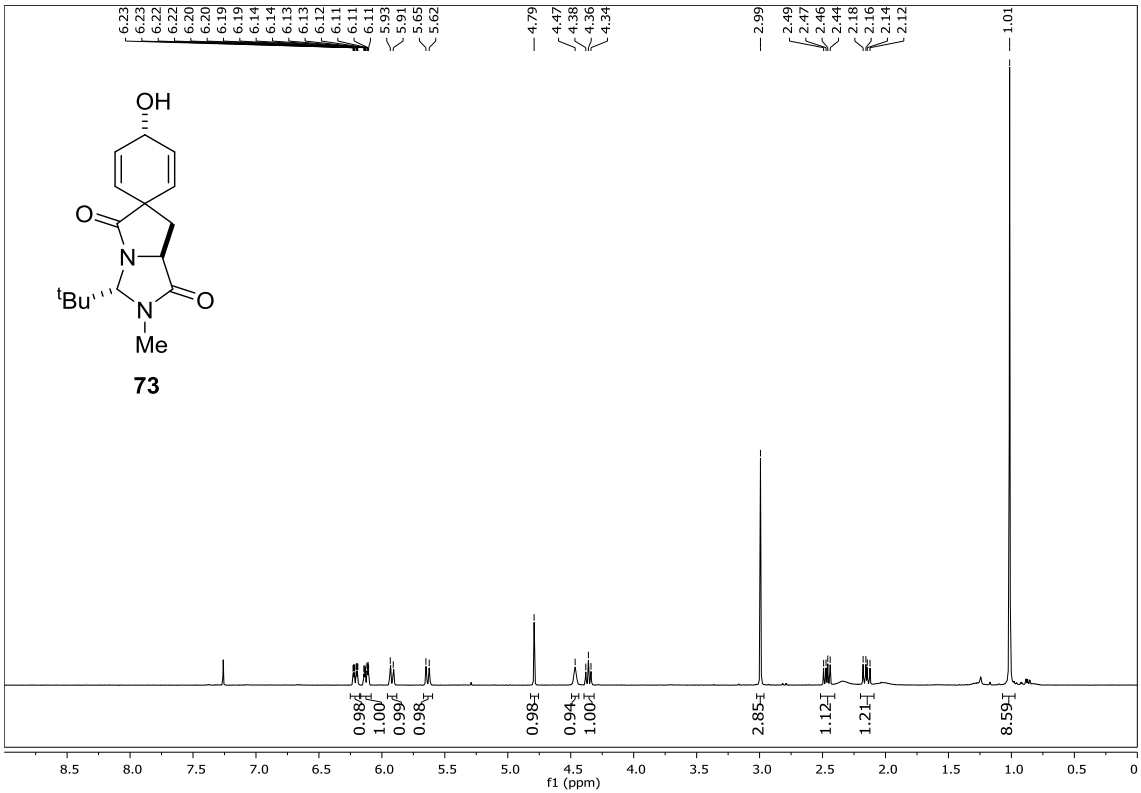
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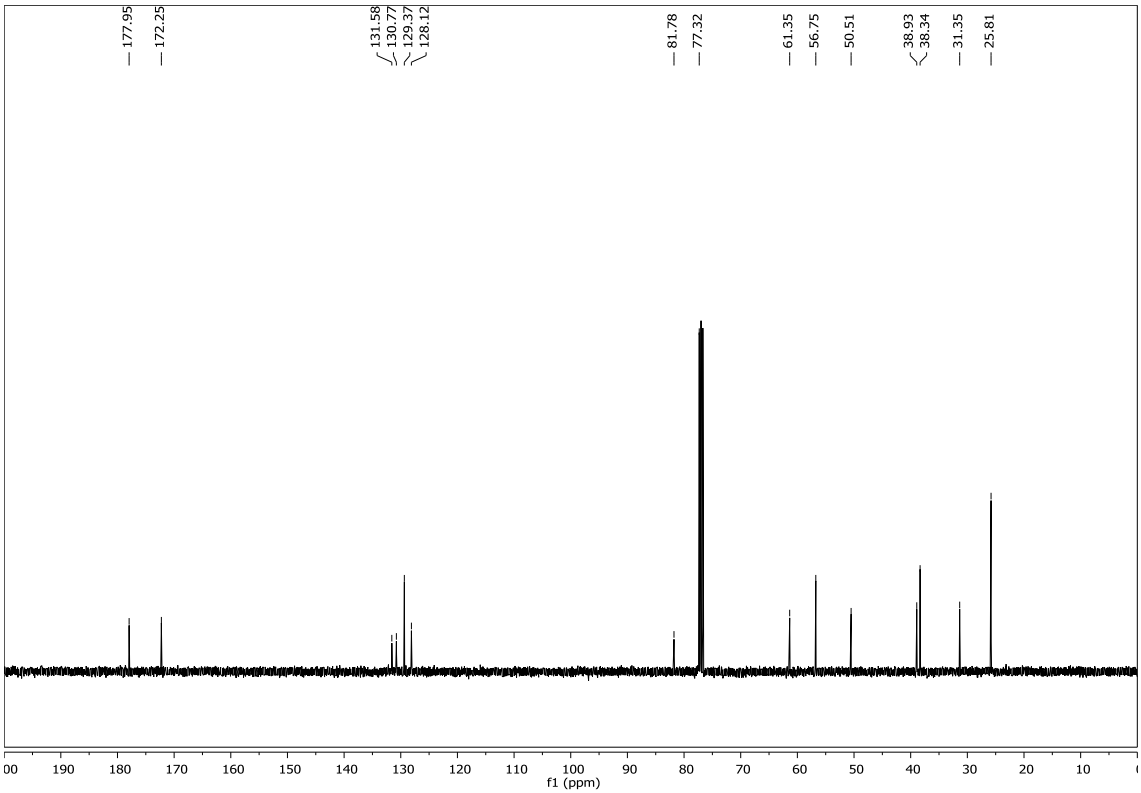
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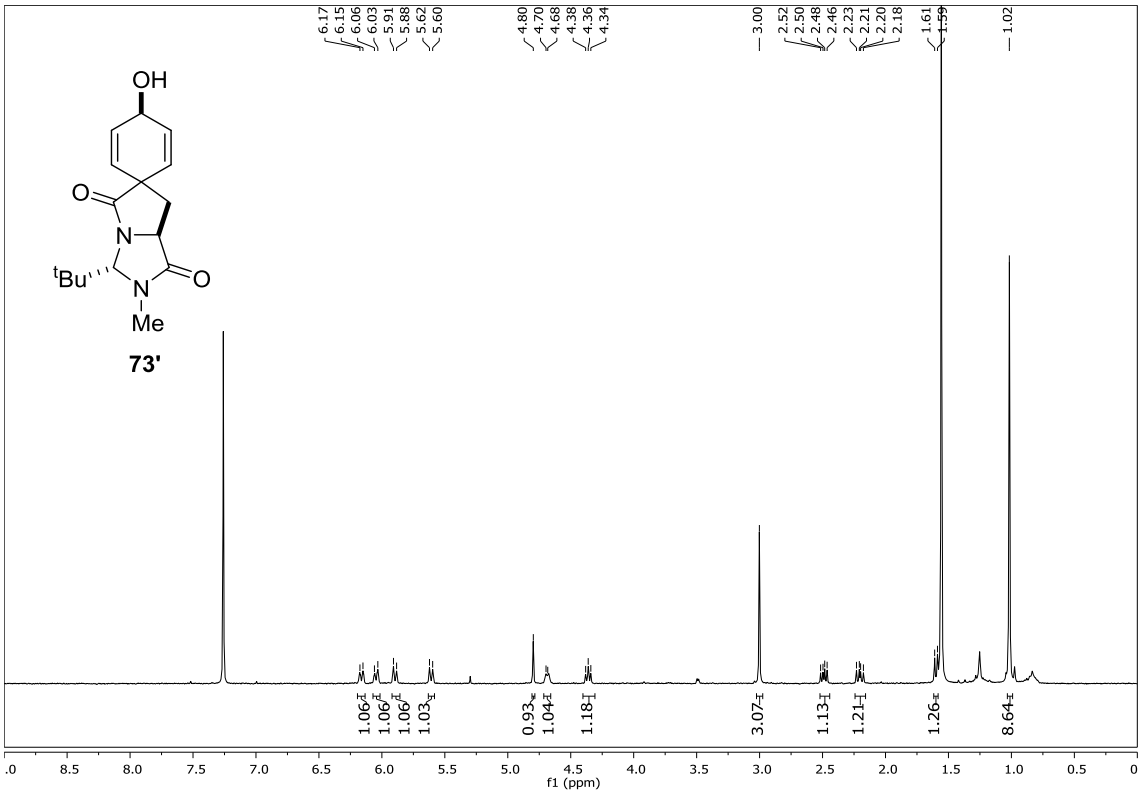
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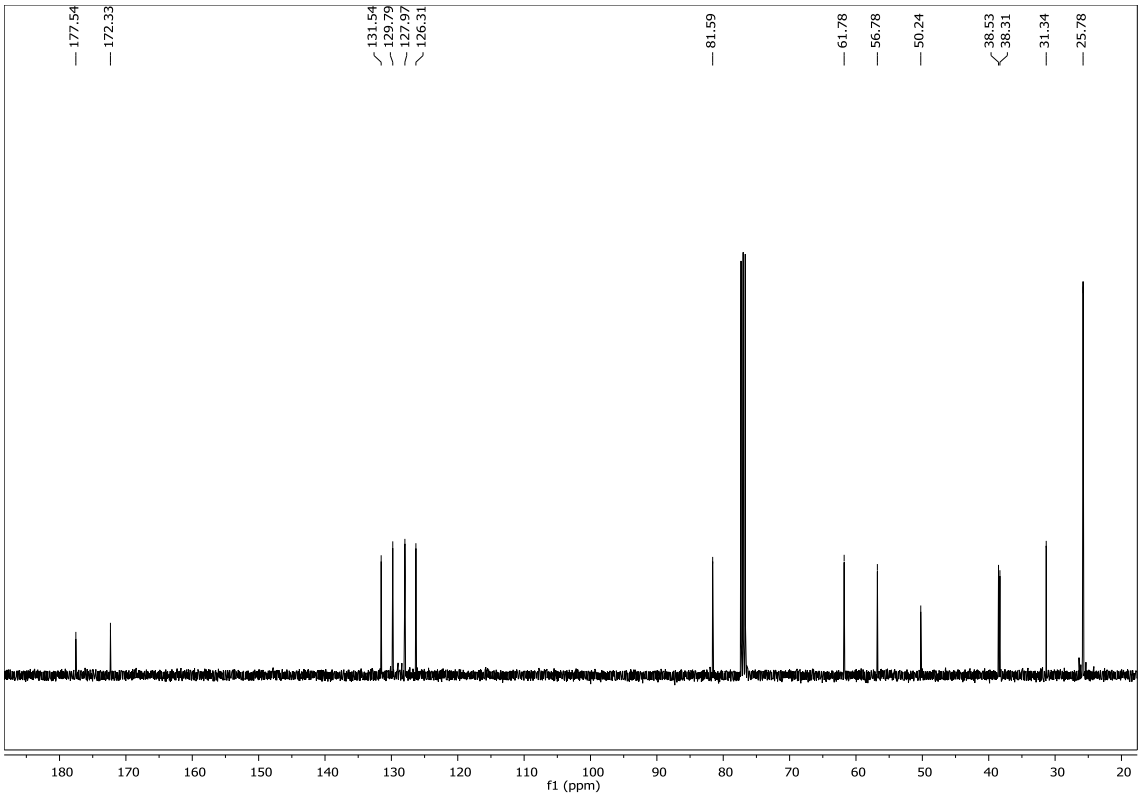
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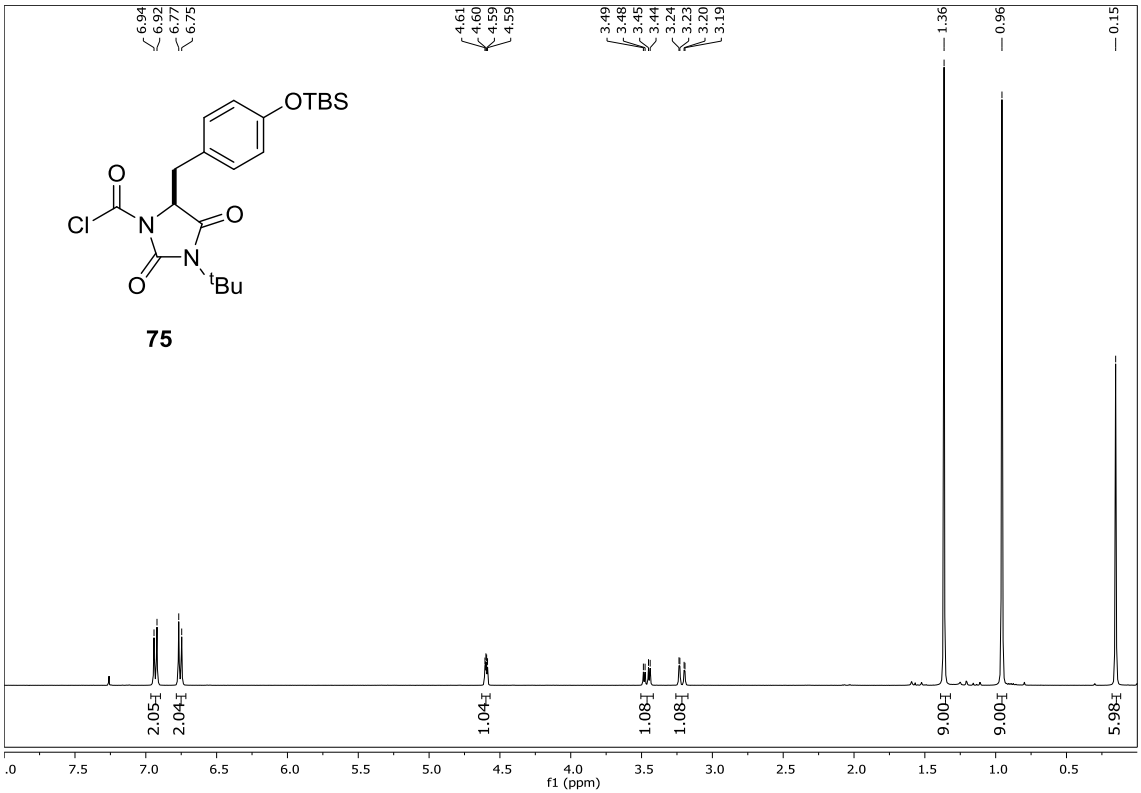
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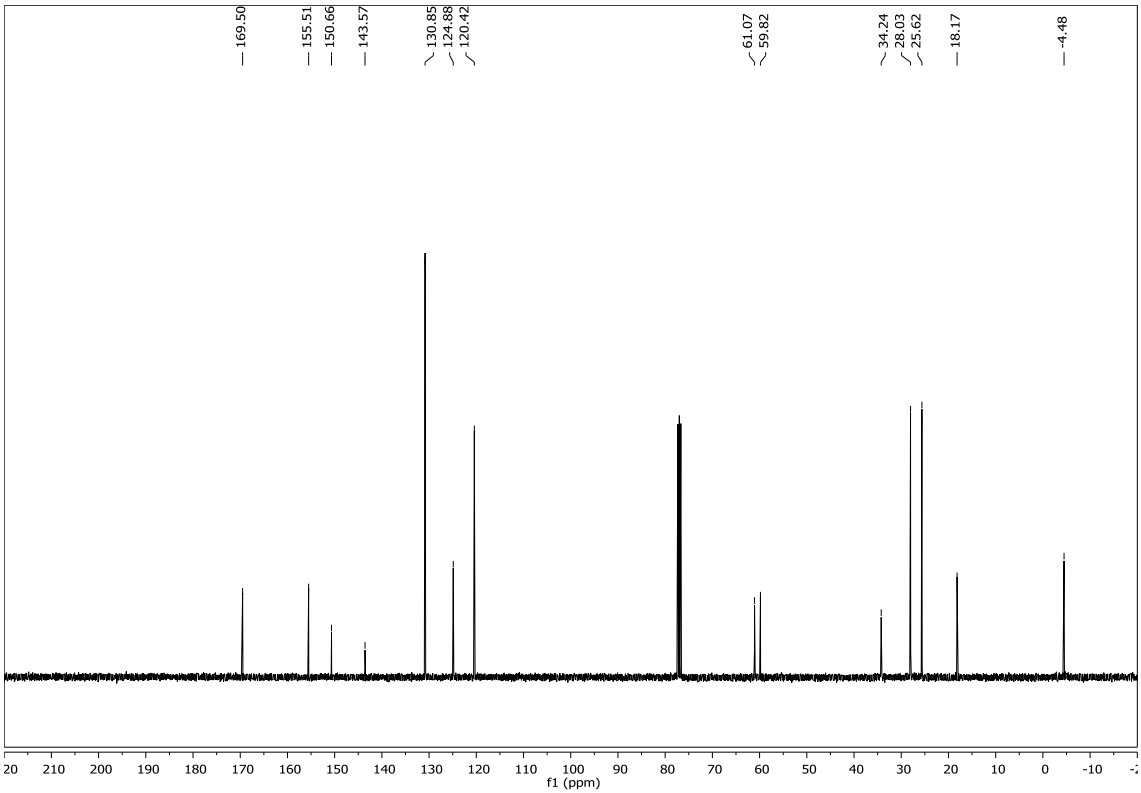
75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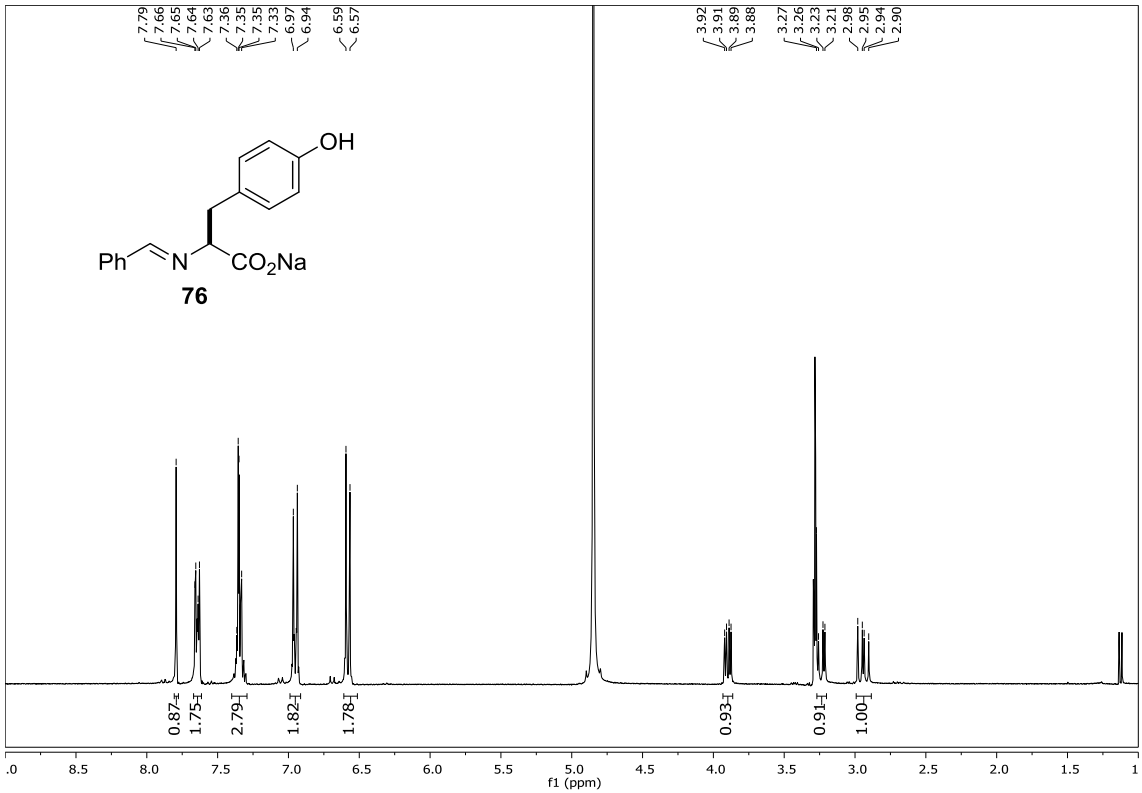
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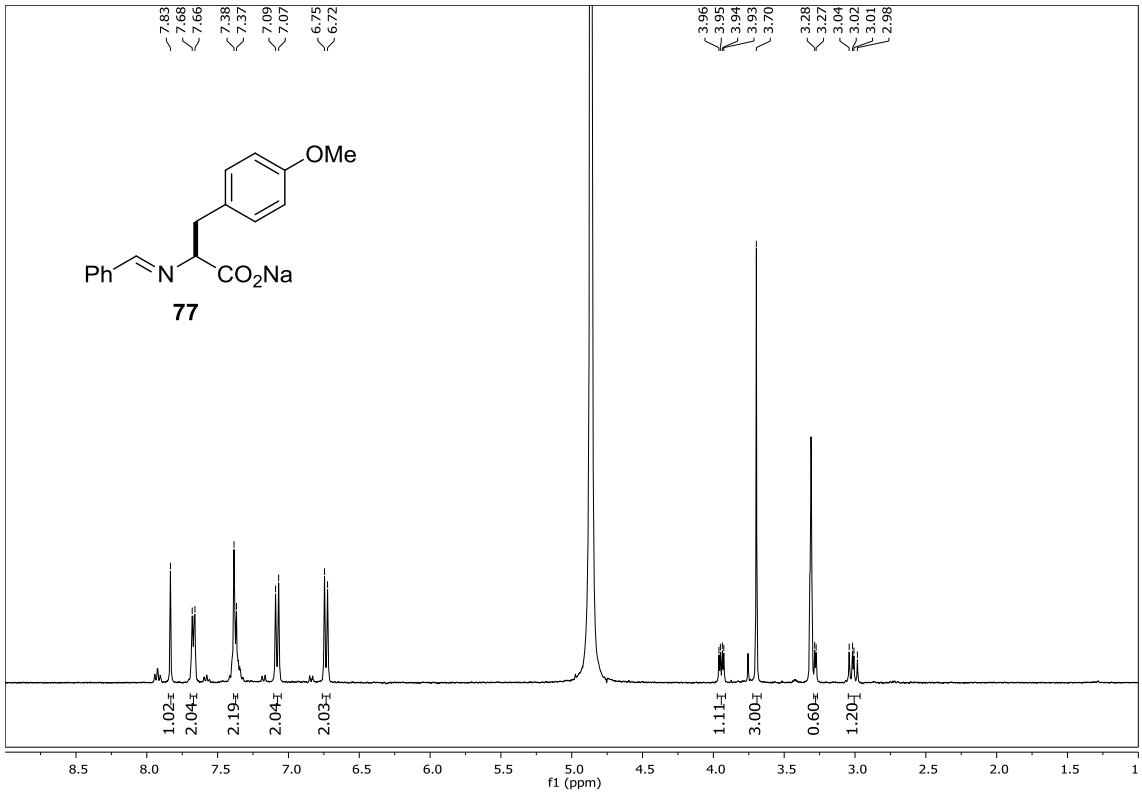
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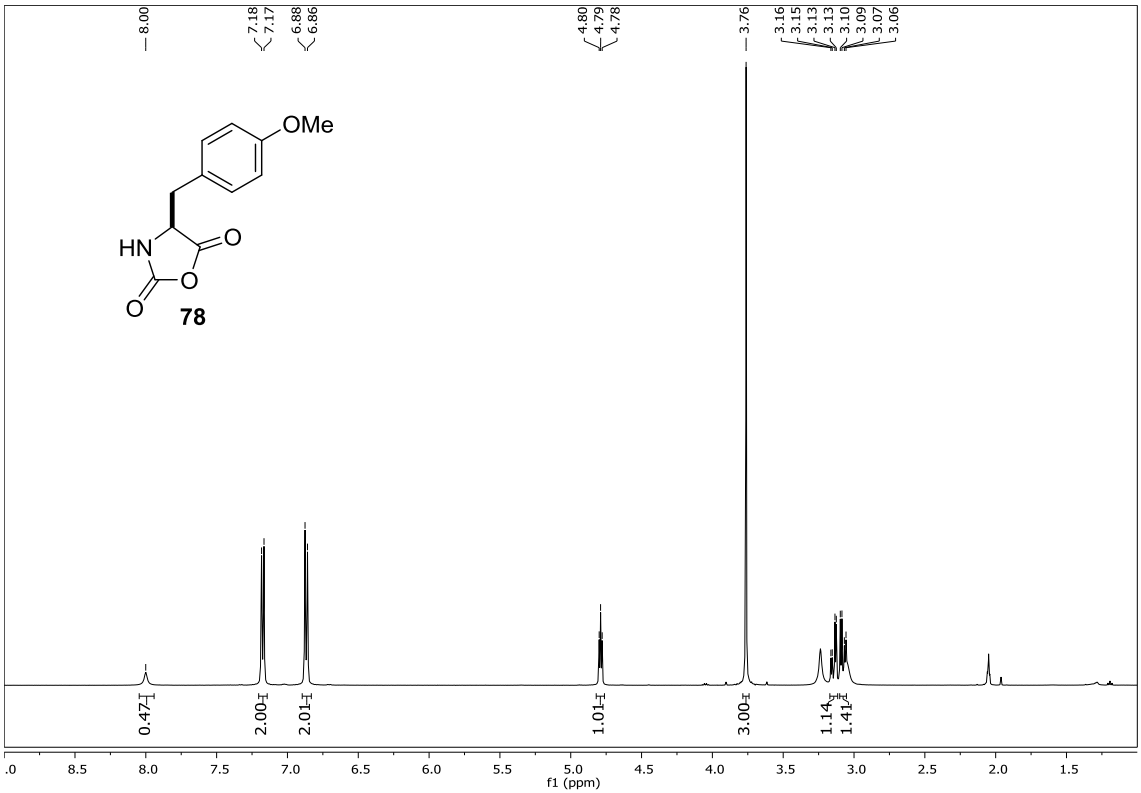
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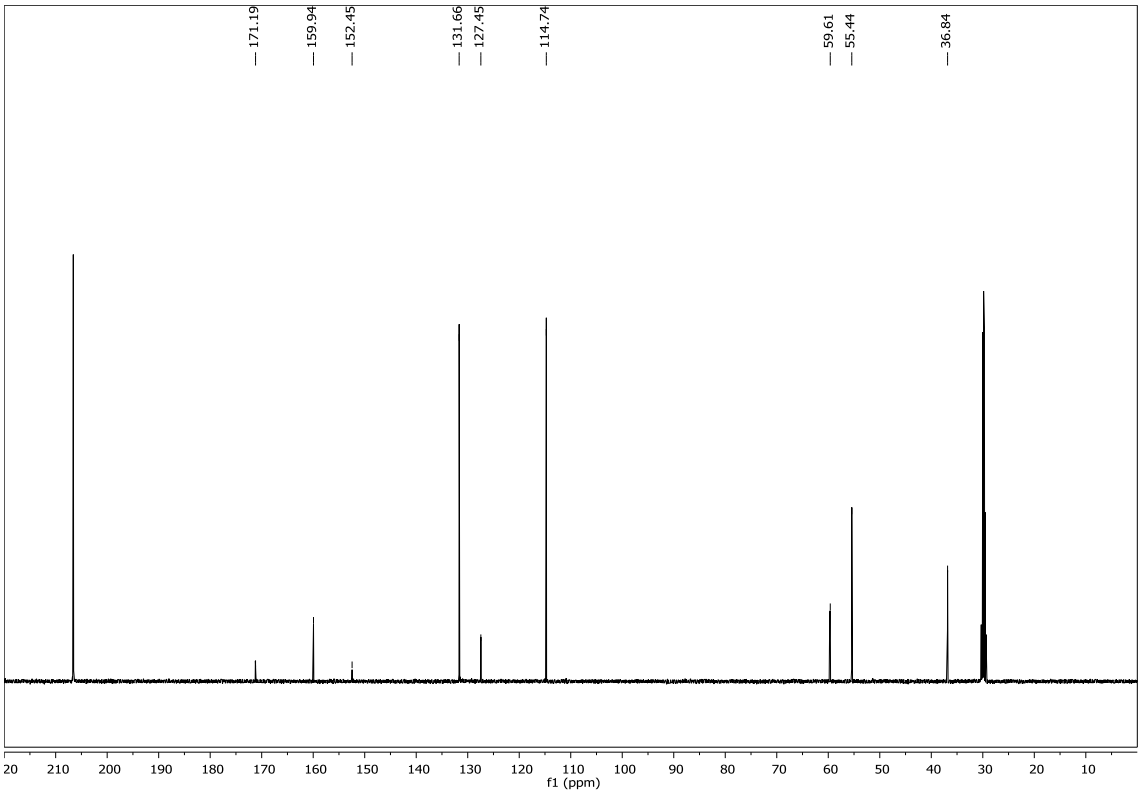
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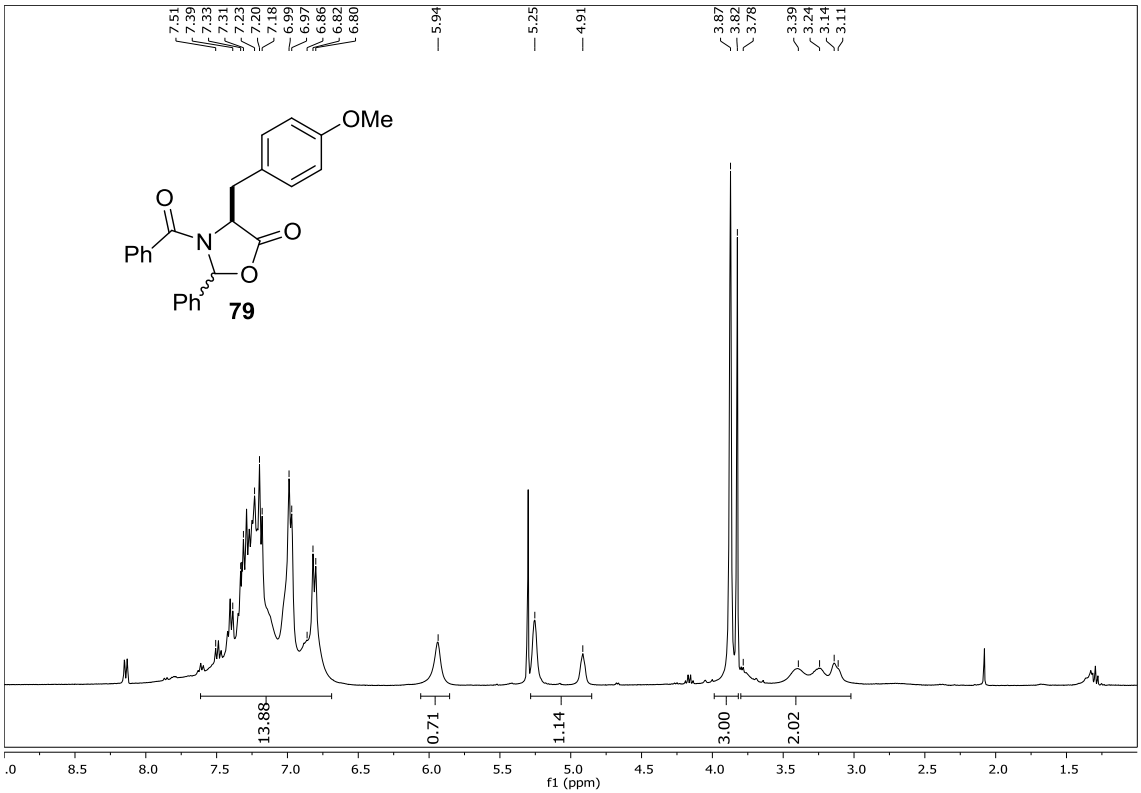
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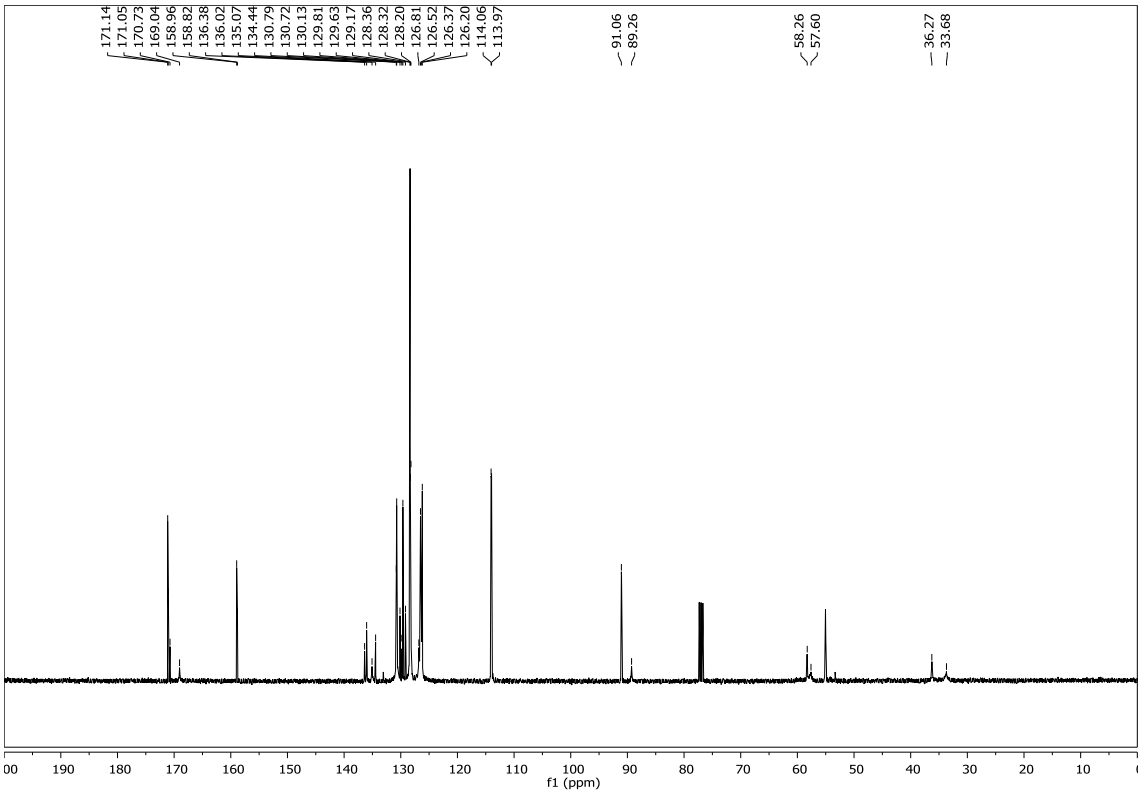
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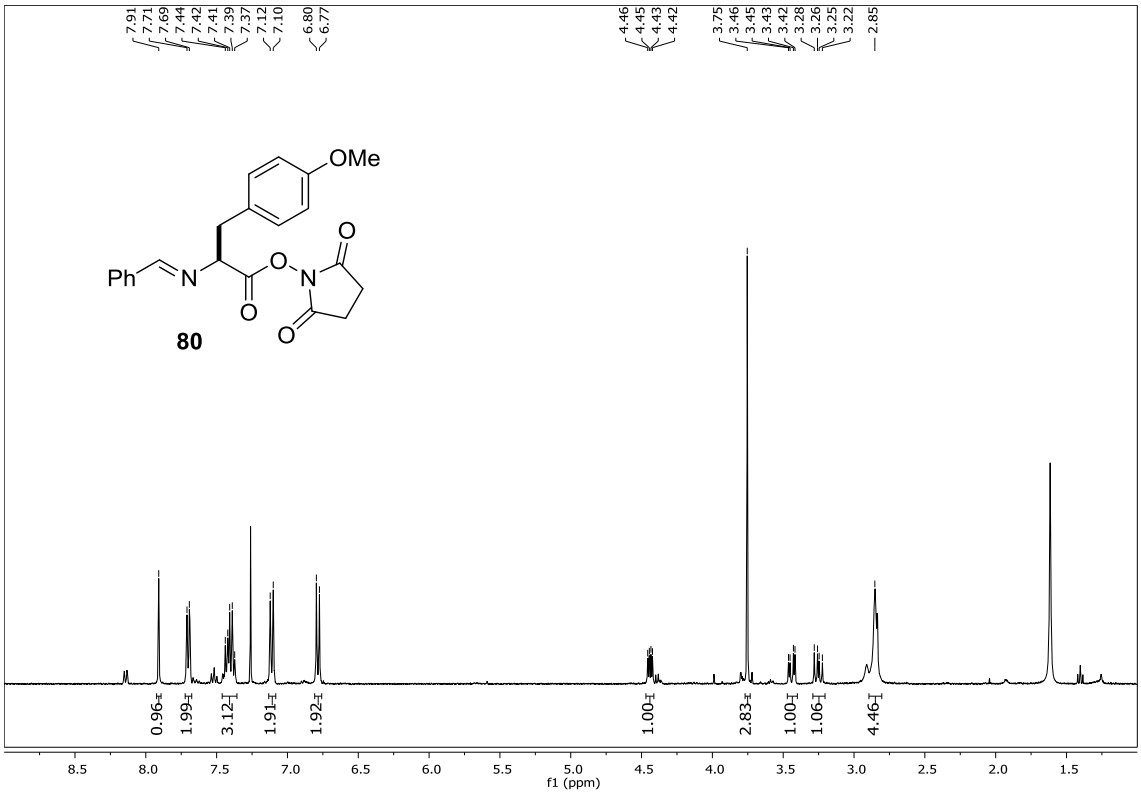
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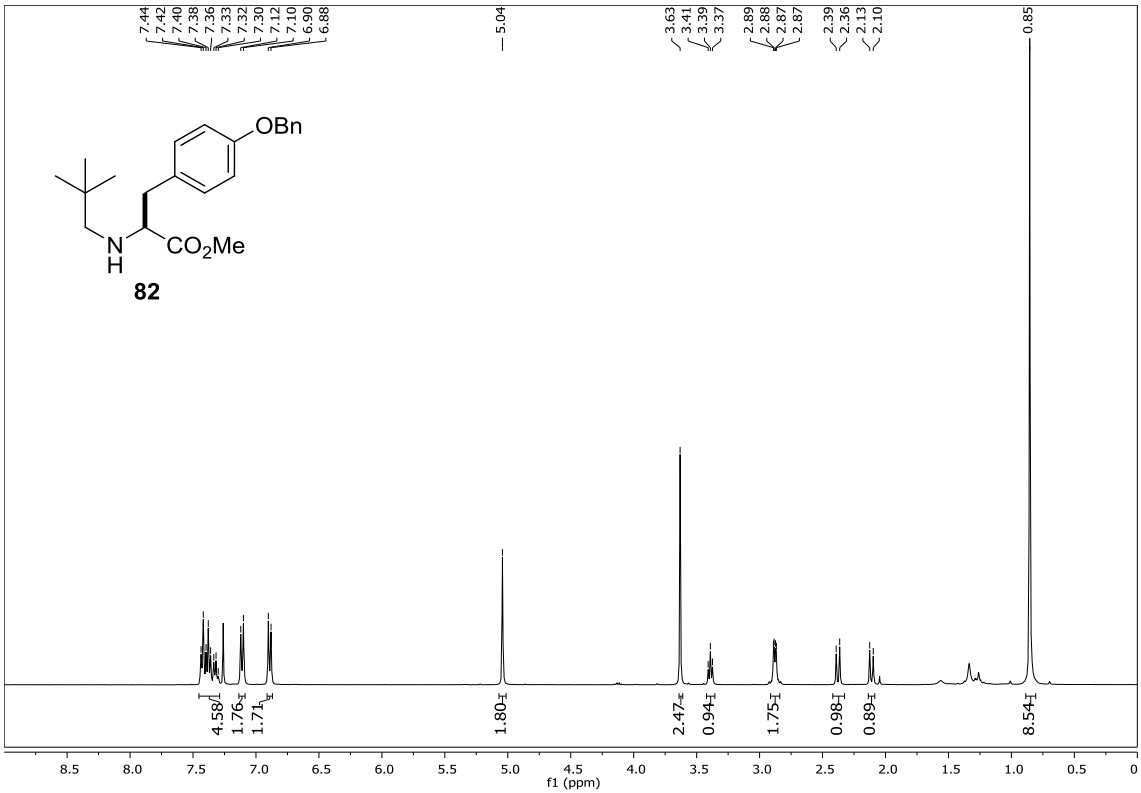
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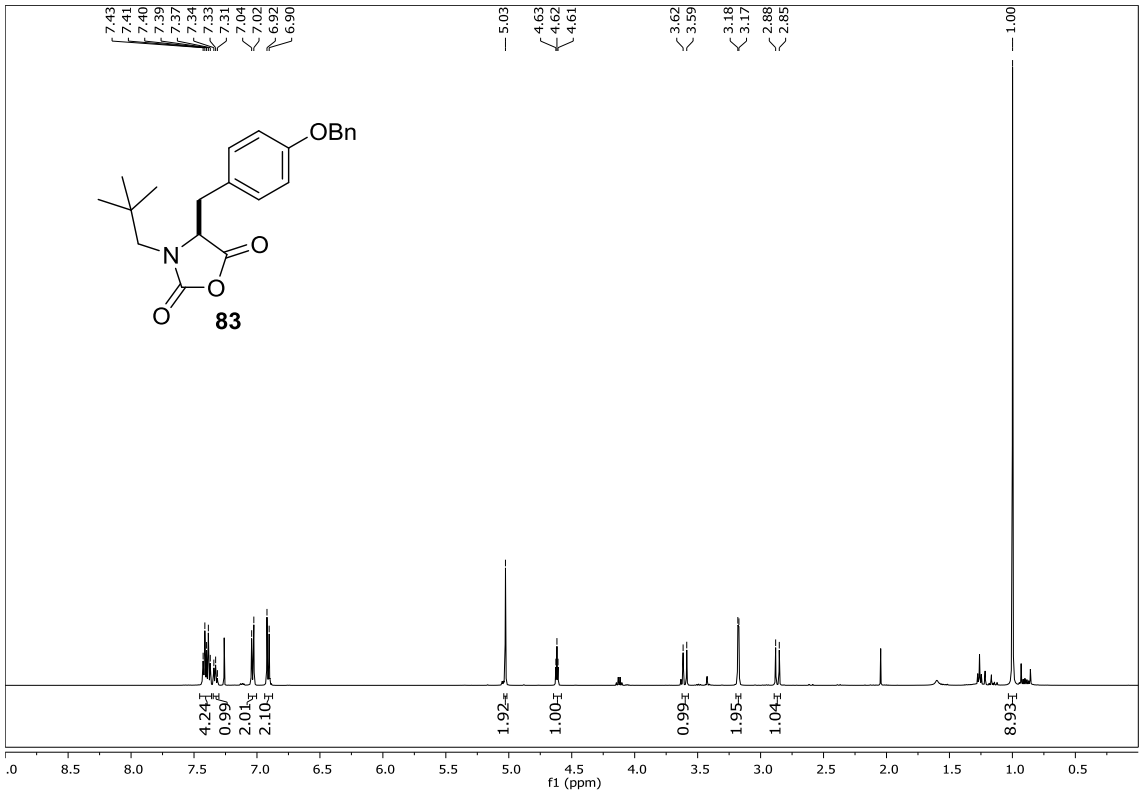
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1.04
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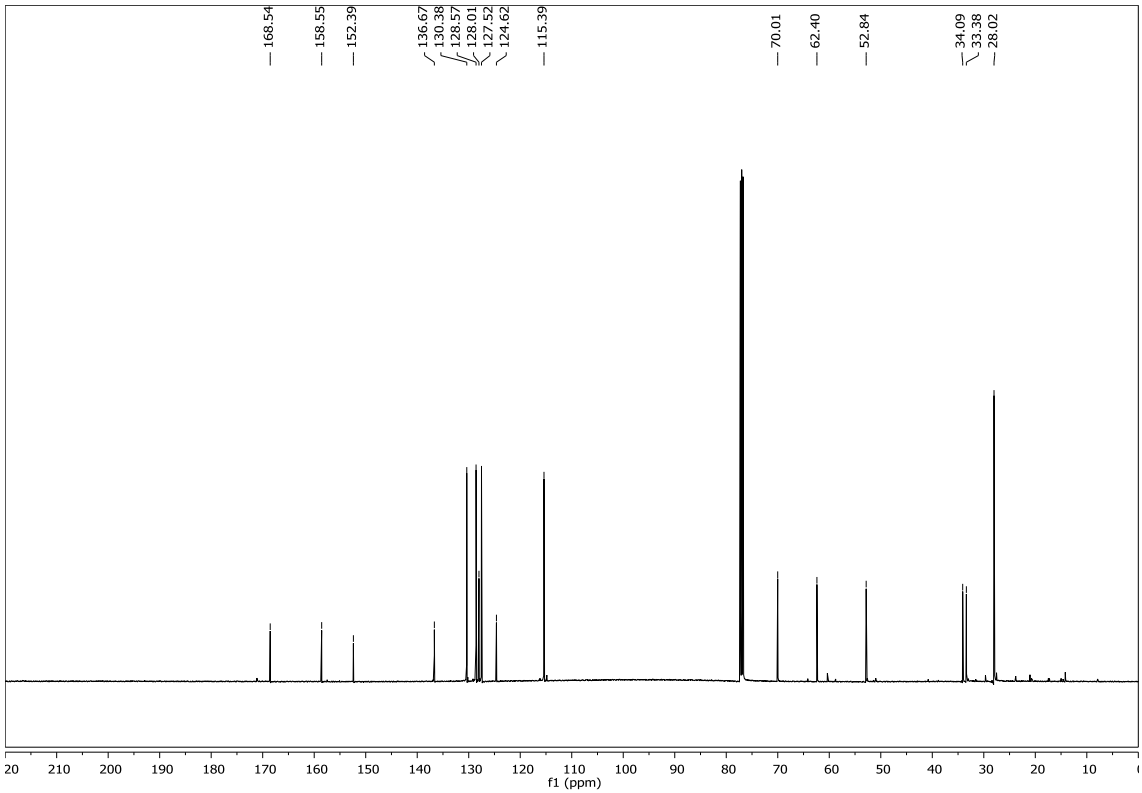
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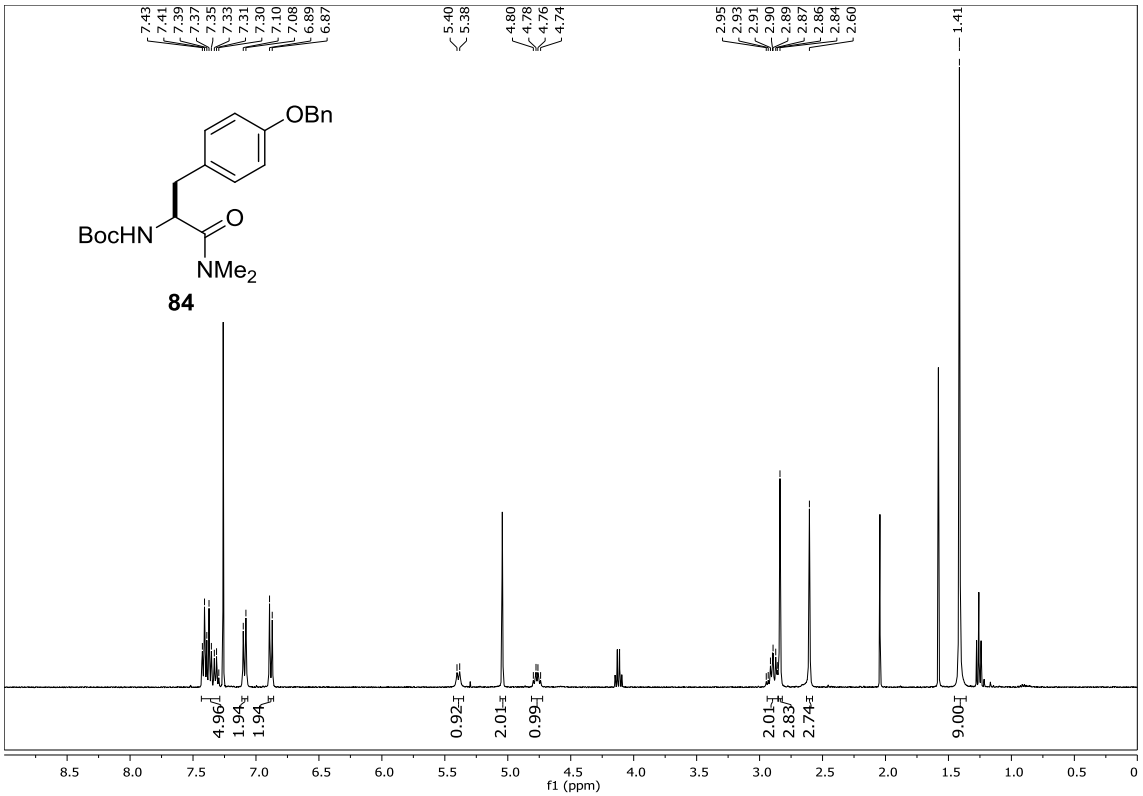
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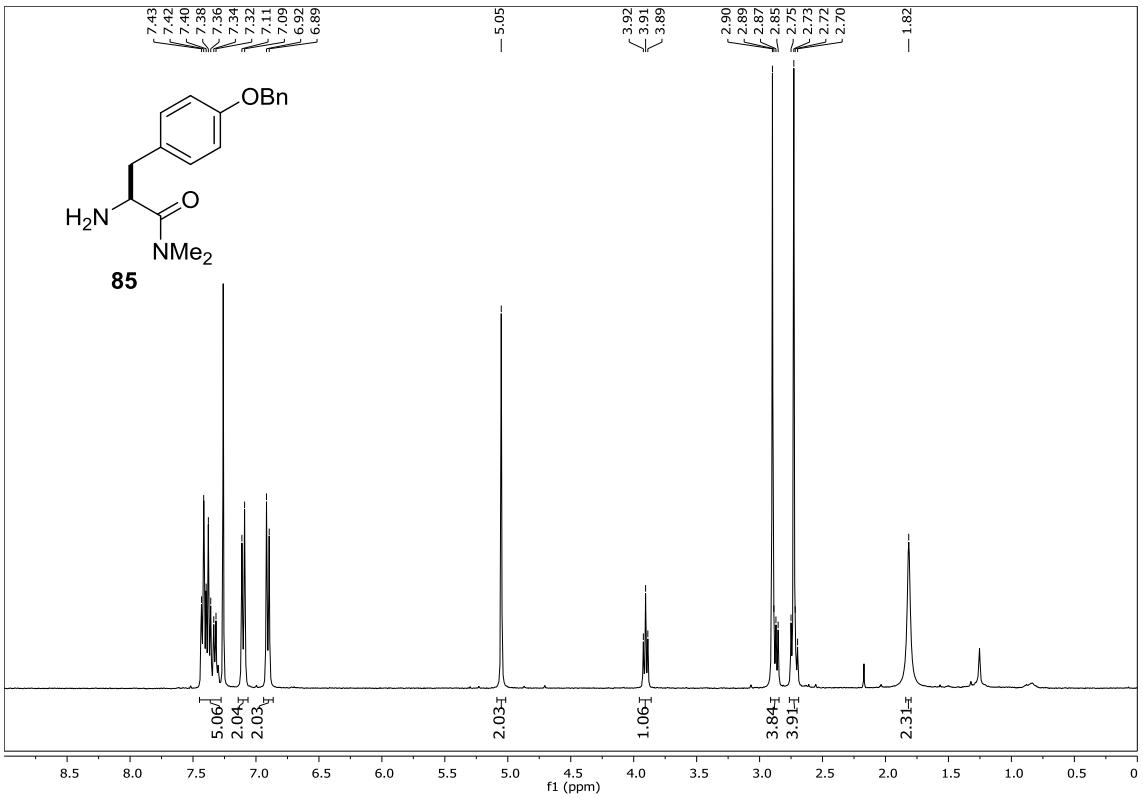
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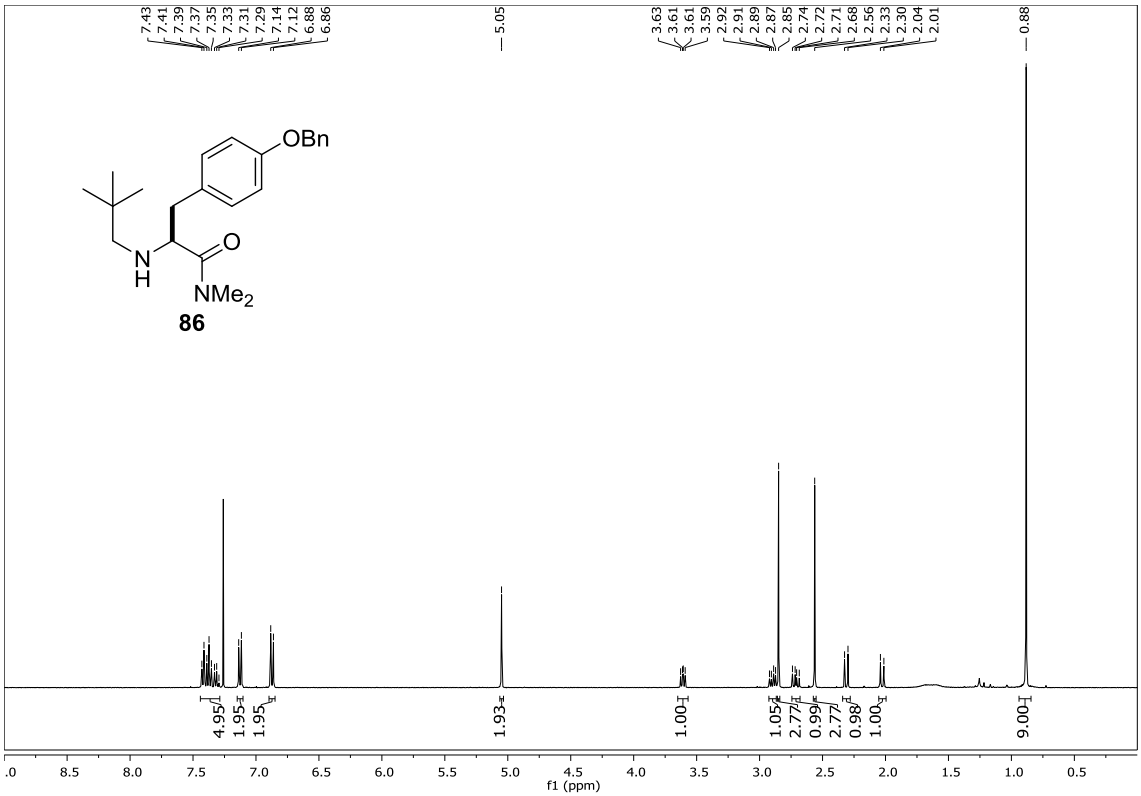
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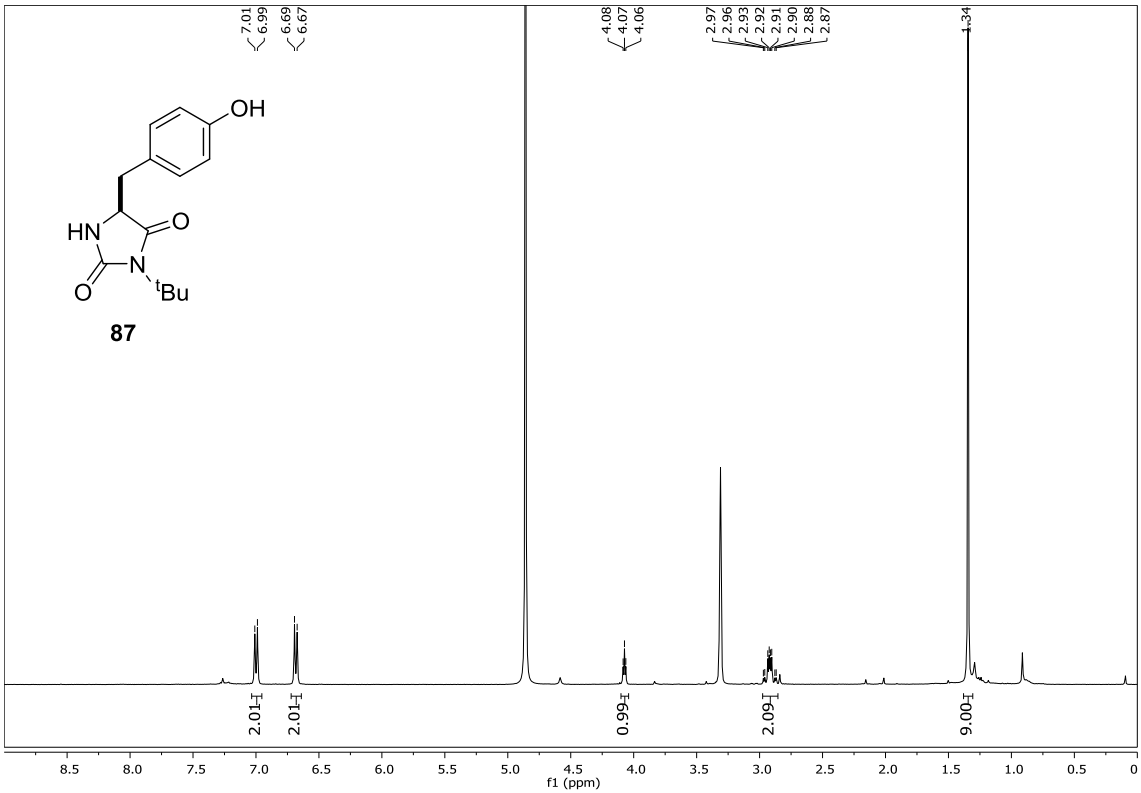
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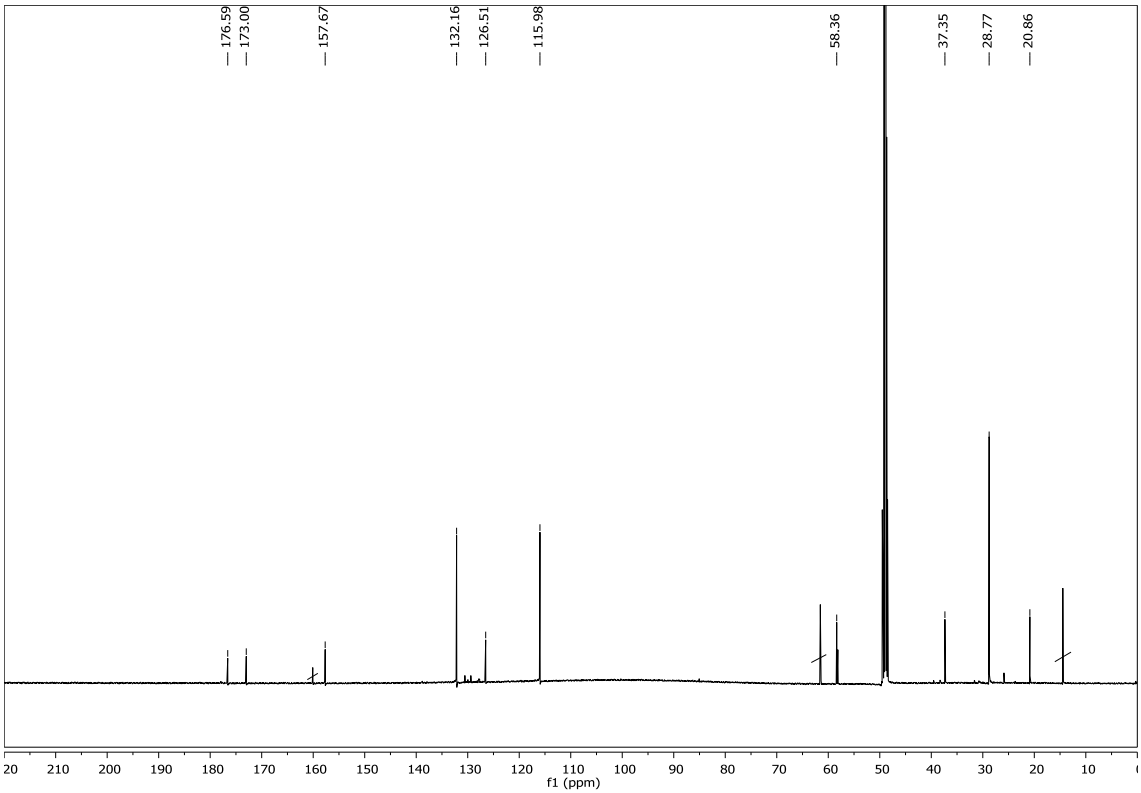
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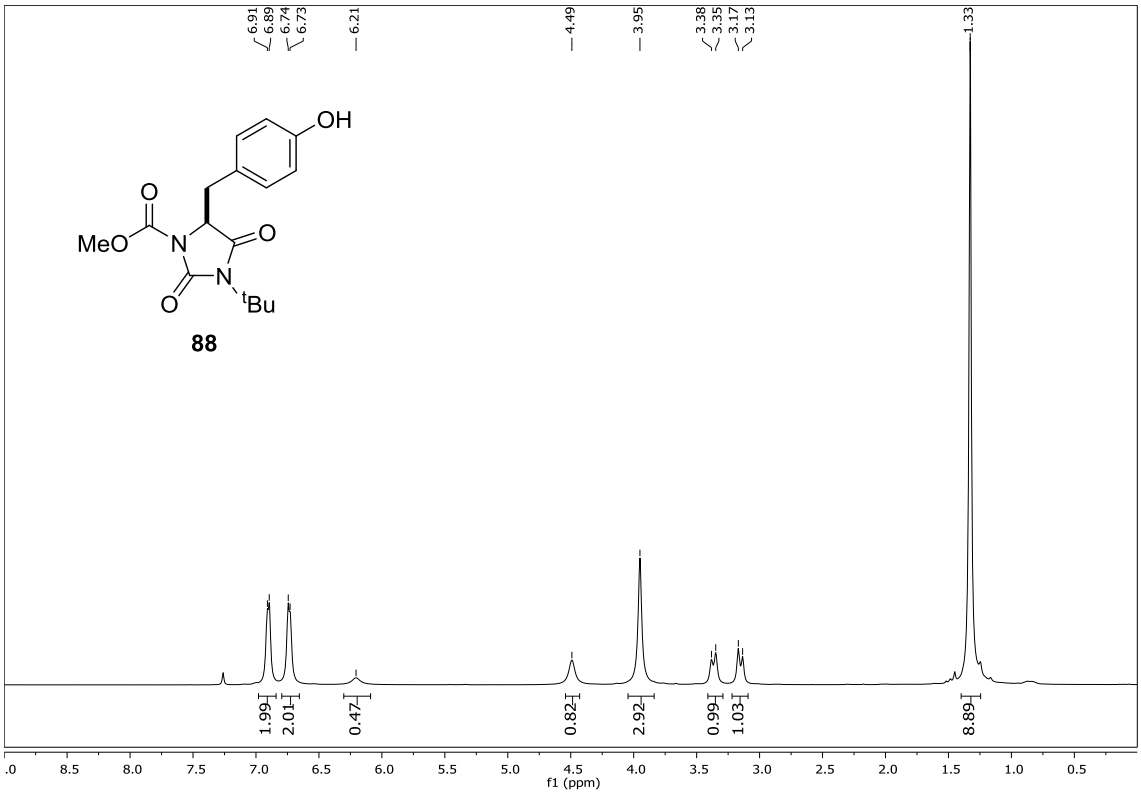
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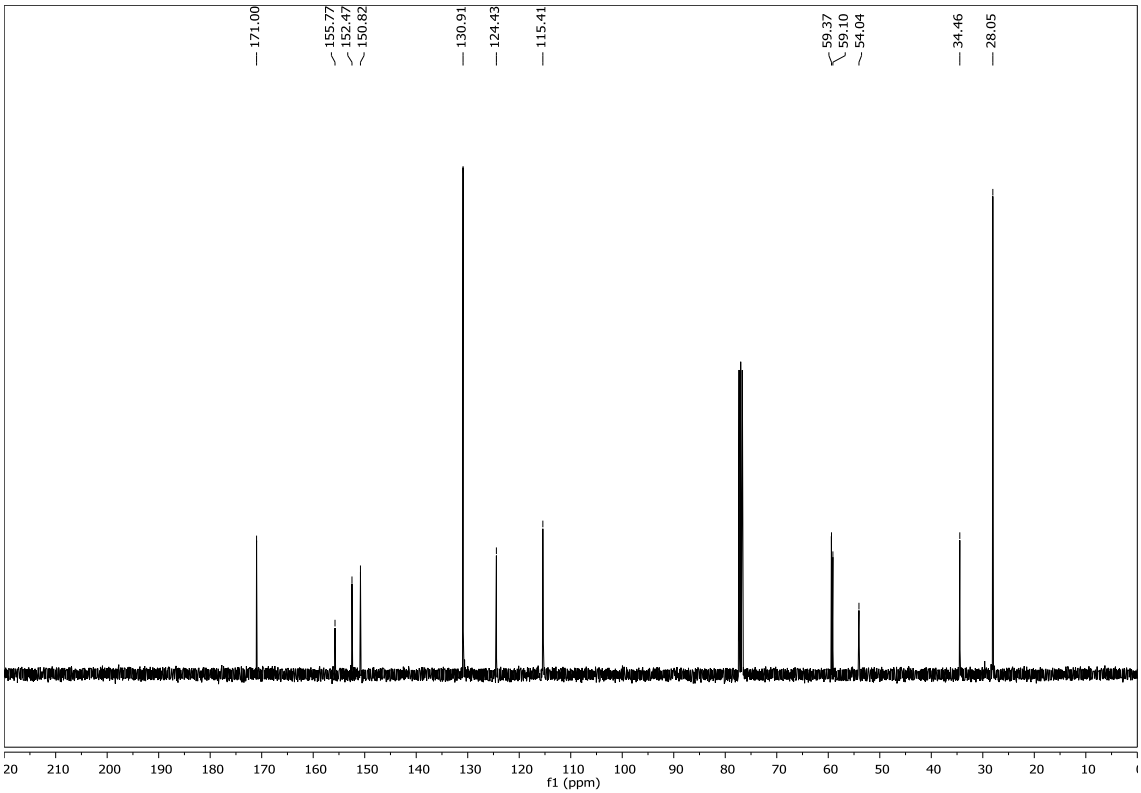
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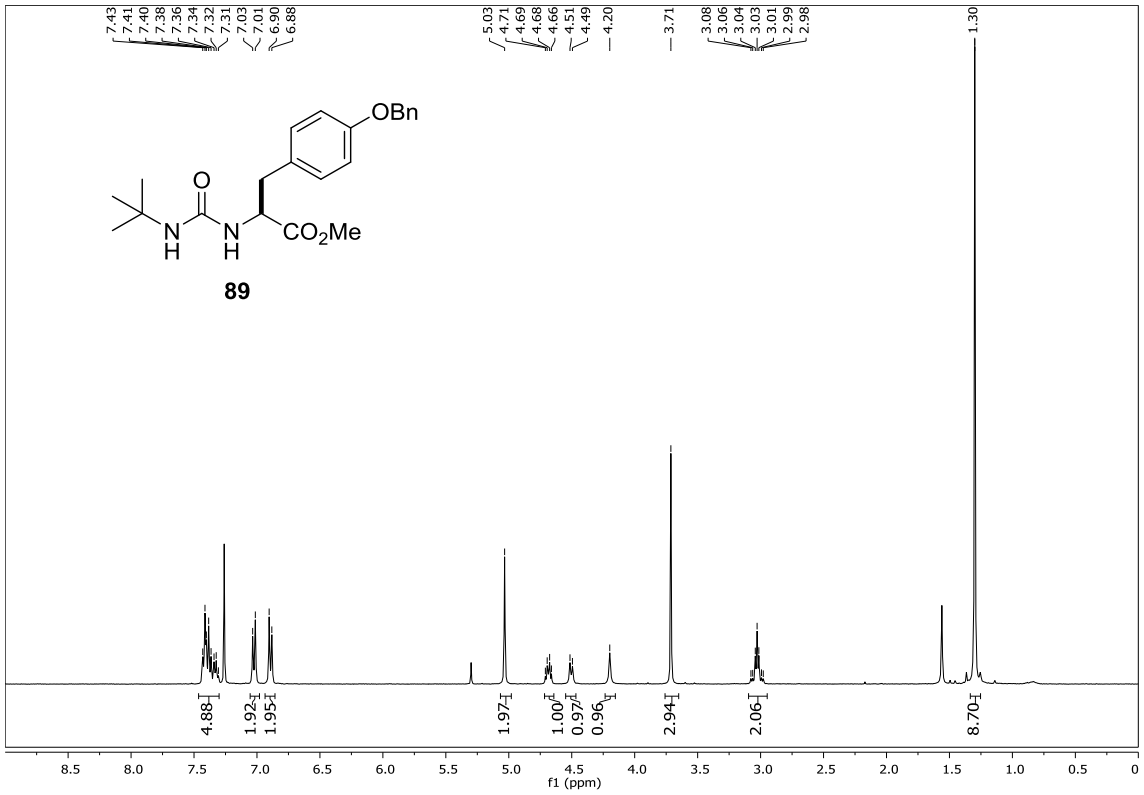
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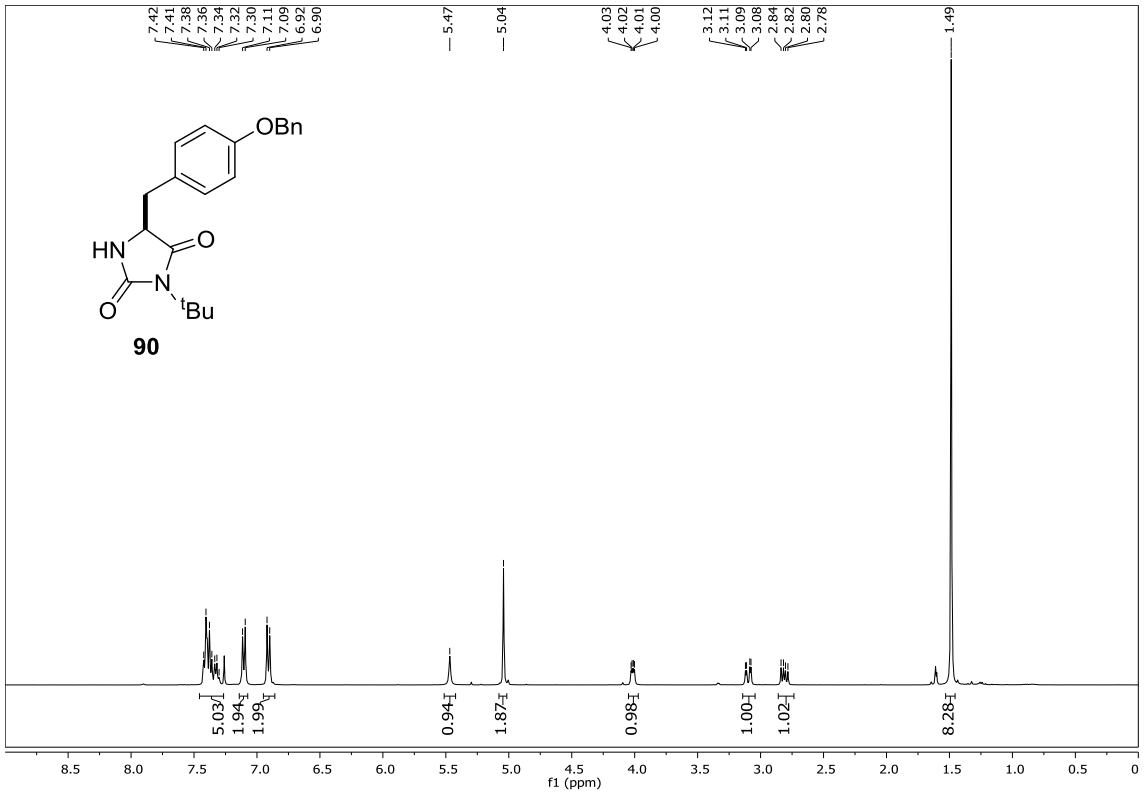
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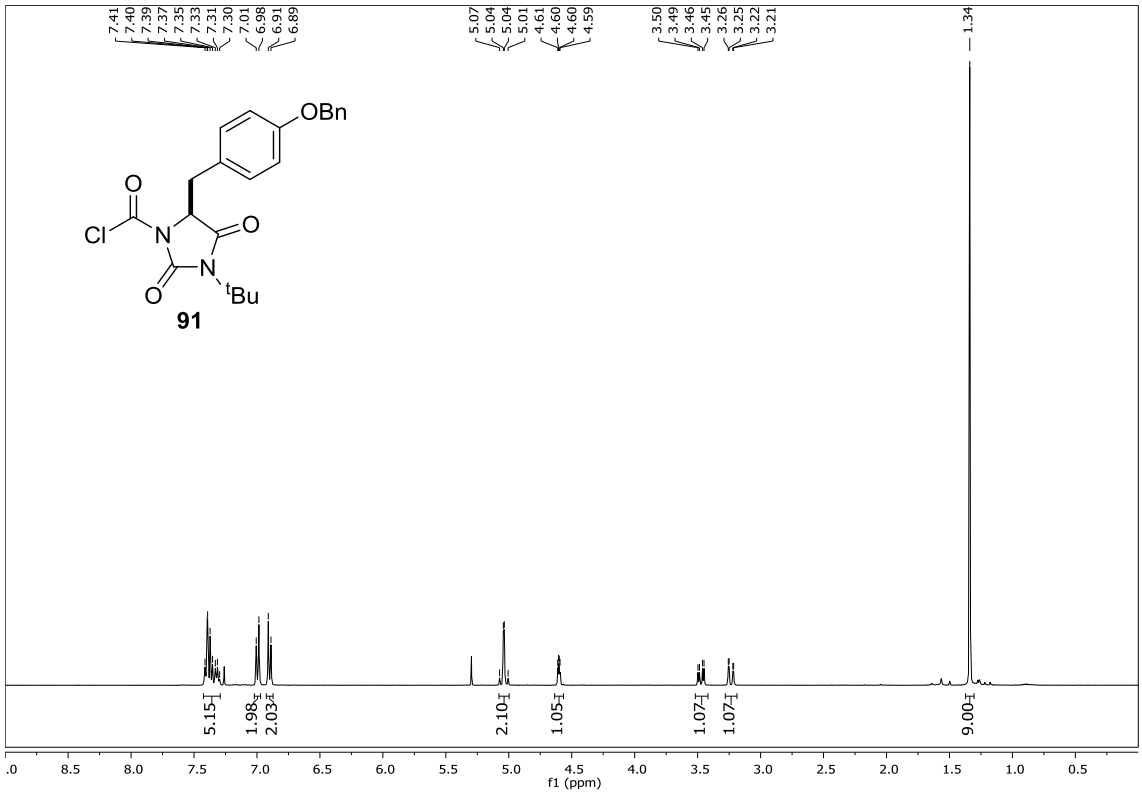
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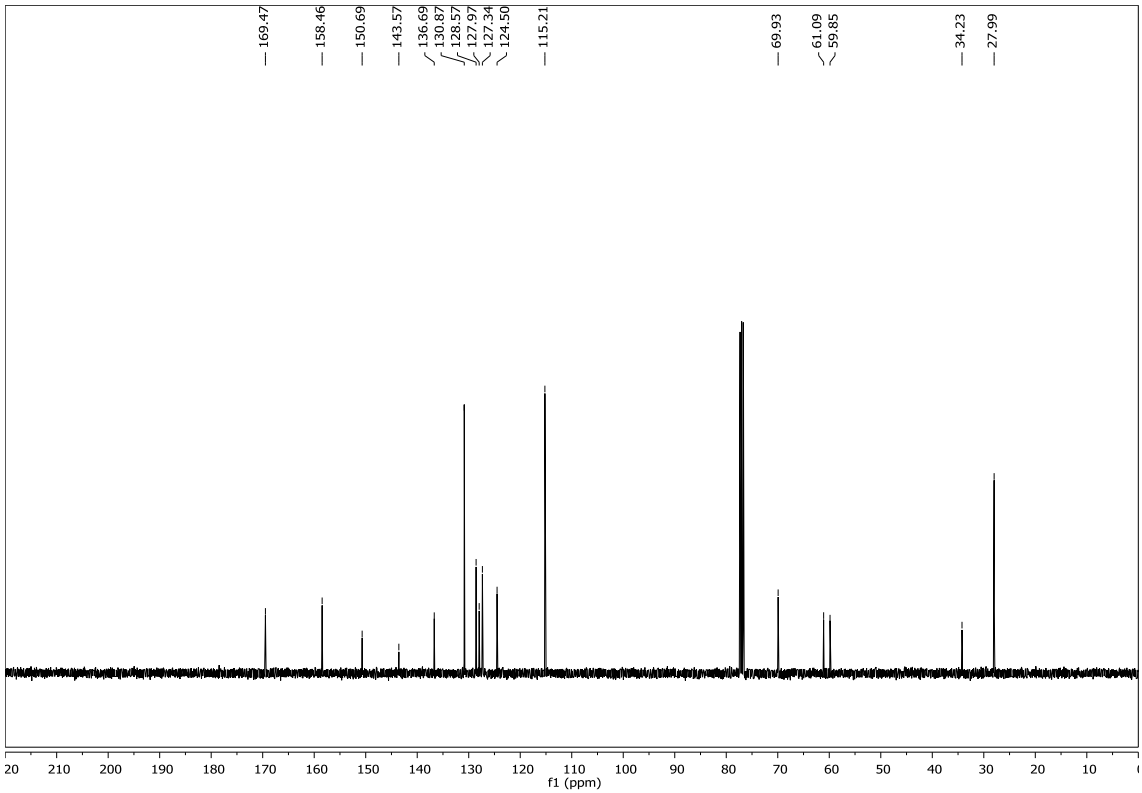
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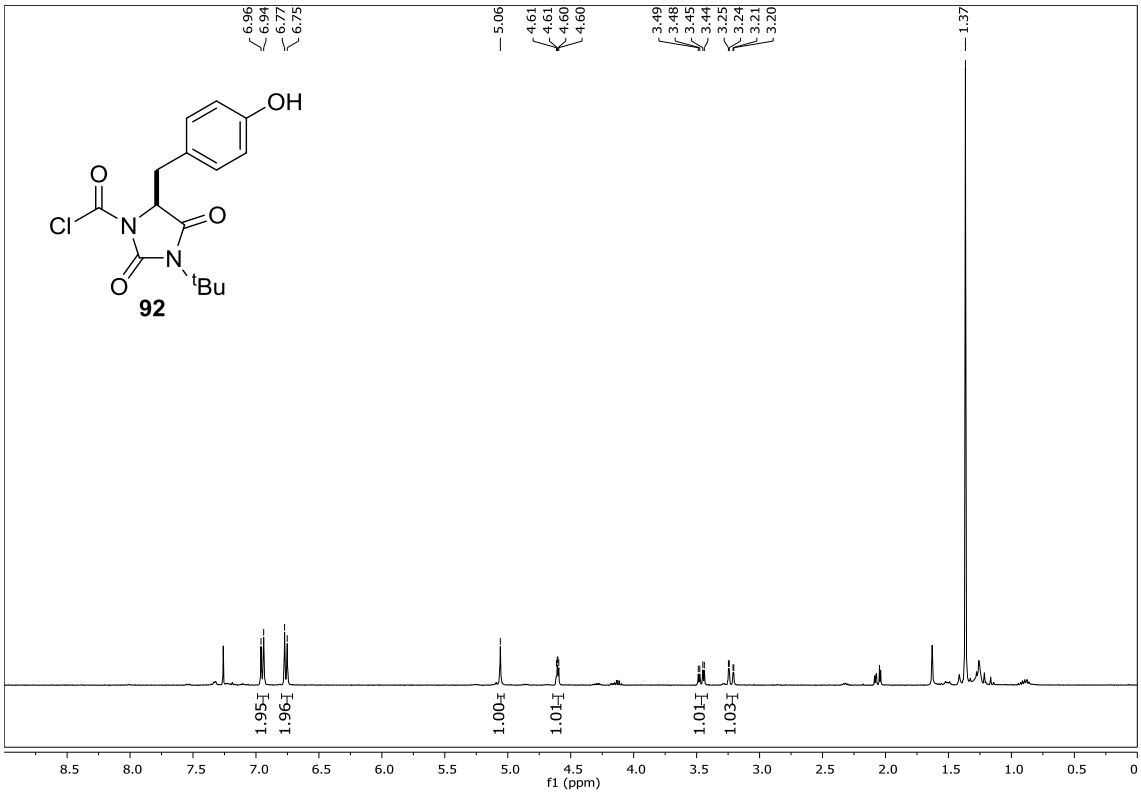
f1 (ppm)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f1 (ppm)

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Organocatalysis

Catalytic Enantioselective Quick Route to Aldol-Tethered 1,6- and 1,7-Enynes from ω-Unsaturated Aldehydes

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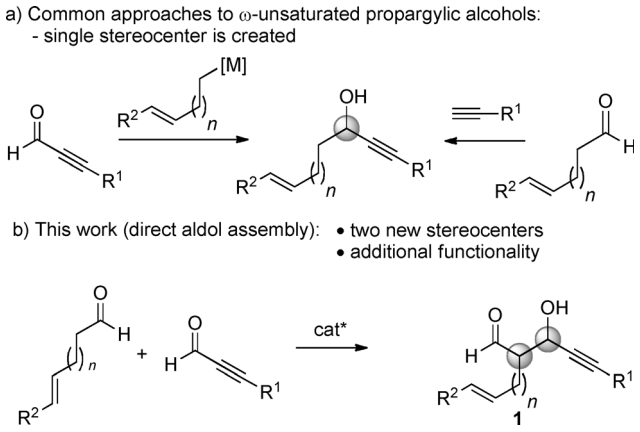
Abstract: An effective asymmetric route to functionalized 1,6- and 1,7-enynes has been developed based on a direct cross-aldol reaction between ω-unsaturated aldehydes and propargylic aldehydes (α,β-ynals) promoted by combined α,α-dialkylprolinol ether/Brønsted acid catalysis. This synergistic activation strategy is key to accessing the corresponding aldol adducts with high stereoselectivity, both enantio- and diastereoselectivity. The aldol reaction also proceeds well with propargylic ketones (α,β-ynones) thus enabling a stereocontrolled access to the corresponding tertiary alcohols. The utility of these adducts, which are difficult to prepare through standard methodology, is demonstrated by their transformation into trisubstituted bicyclic enones using standard Pauson–Khand conditions.

Introduction

A pivotal role in the construction of molecular complexity is usually played by relatively simple molecular building-blocks of stereodefined structure that present several sites amenable for chemical manipulations.[1] For example, oxygenated structure **1** ($n=1$ or 2, Scheme 1) exhibits a 1,6- or 1,7-enyne carbon backbone tethered by a central aldol unit and may serve as useful intermediate in synthesis.[2] Oxygenated 1,ω-enynes are immediate precursors of bicyclic [m.3.0] ring systems which are found in many natural sesquiterpene products.[3] In this context, [3.3.0]-octane and [4.3.0]-nonane skeletons, common to the family of picrotoxanes,[4] have conveniently been prepared from the corresponding 5-oxy-1,6-enynes[5] and 6-oxy-1,7-enynes.[6] Related bicyclic [5.3.0] and [6.3.0] ring systems can also be found in guaianolides and ophiobulins, respectively, as well as other related compounds.[3]



Scheme 1. Catalytic enantioselective approaches to oxygenated 1,ω-enynes.

These key oxygenated 1,ω-enyne intermediates share a propargylic alcohol structural unit. Main catalytic routes to synthesize propargylic alcohols stereoselectively are the reduction of the corresponding ynones, the nucleophilic alkylation of alkynyl aldehydes (α,β-ynals), and the addition of terminal alkynes to aldehydes.[7] Although these two latter approaches, wherein the new stereocenter and the C–C bond are created simultaneously, have been applied to the synthesis of oxygenated 1,ω-enyne structures successfully (Scheme 1a),[5,6d] they usually allow for the generation of a sole stereocenter; in addition, these methods are not easy to implement for concomitant introduction of additional functionality (i.e. that shown in **1**) due in part to difficulties in preparing the required reagents or limited functional group compatibility. Hence, there is a need to develop new methods, preferably direct and catalytic, for synthesizing propargylic alcohols stereoselectively, thus expanding the range of currently available propargylic systems and derivatives thereof.

Quite recently, we have communicated the first direct aldol addition of aldehydes to α,β-ynals promoted by a dialkylprolinol ether/transition metal/Brønsted acid cooperative catalysis system.[8] The preliminary experiments demonstrated some benefits of this novel approach to propargylic alcohols,[9] such as wide substrate tolerance and high stereoselectivity (both enantio- and *anti*/*syn* selectivity). Herein we describe the viabil-

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ity of this approach (Scheme 1) in the synthesis of enantioenriched 5- and 6-oxy-1,6-enynes bearing an additional carbonyl group, and the synthetic utility of these building-blocks in the preparation of oxygenated carbocycles.

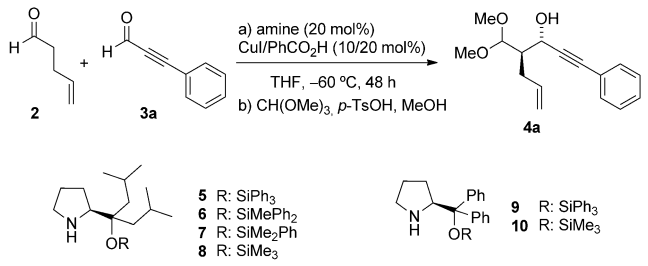
Results and Discussion

Background and catalyst screening

In contrast to the existing methods for the catalyst-promoted production of propargylic alcohols, one inherent advantage of the aldol reaction strategy involving α,β-ynals (Scheme 1b) is that the new carbon–carbon bond-forming event is concomitant with the generation of two contiguous stereogenic centers. Furthermore, a carbonyl group is also installed in the same synthetic operation which would allow for additional chemical manipulation if required, all under rather smooth reaction conditions. However, before our studies were carried out only few examples dealing with the aldol addition reaction of α,β-ynals had been reported and most of them evidenced difficulties in controlling either diastereoselectivity or enantioselectivity, or both.[10,11] In our preliminary study we identified the α,α-dialkylprolinol silyl ether/CuI/$PhCO_2H$ combination as effective catalyst system in promoting the reaction between simple aliphatic aldehydes and α,β-ynals. With a 20/10/20 mol% loading of each catalyst component, respectively, in THF at low (−60 °C) temperature, the corresponding aldol adducts were obtained in good yields (isolated as the corresponding alcohol or dimethyl acetal), *anti*/*syn* ratios usually above 10:1, and excellent enantioselectivity.[8] In those experiments, not only did each catalyst component appear to be crucial for successful reactivity and stereoselectivity, but also the substituent groups at the α position of the prolinol ether catalyst seemed to play a fundamental role in controlling reaction *anti*/*syn* selectivity. Thus, when the reactions were carried out using the parent α,α-diarylprolinol silyl ethers as the amine catalyst instead, under otherwise identical conditions, eroded *anti*/*syn* selectivity was attained.

According to these precedents, our study commenced by evaluating the influence of all these reaction parameters on the outcome of the target aldehyde–aldehyde cross-aldol reaction, exemplified by **2** + **3a** (Table 1). The reaction carried out under previously established conditions (catalyst combination: **5**/CuI/$PhCO_2H$; Table 1, entry 2) led, upon subsequent acetalization, to the desired adduct **4a** in good yield and very high diastereo- and enantioselectivity (*anti*/*syn* 11:1; 96% *ee*). The reaction in the absence of benzoic acid resulted sluggish or unpractical (less than 30% conversion after 48 h of reaction), thus corroborating the crucial role played by the Brønsted acid cocatalyst. However, the influence of CuI on both the reaction yield and stereoselectivity was less significant for this reaction (Table 1, entries 1/3 vs. 2/4). We next evaluated the influence of the amine catalyst structure by carrying out parallel reactions with catalysts **6**–**10**. Variation of the silyl group from $SiPh_3$ to $SiMePh_2$, $SiMe_2Ph$, and $SiMe_3$ indicated a correlation between the size of the alcohol protecting group of the catalyst and the reaction stereoselectivity. Thus, while similar yields and enantioselectivity levels were attained with either catalyst **5**, **6**, or **7**, both catalysts **6** and **7**, bearing $SiMePh_2$ and $SiMe_2Ph$ groups (Table 1, entries 3 and 5, respectively), led to lower *anti*/*syn* ratio of the aldol adducts compared with **5**. The same trend was observed with sterically less demanding catalyst **8**, which also led to somewhat lower enantioselectivity (Table 1, entry 6). On the other hand, a switch of the substituent groups at α-position of the prolinol ether from dialkyl to diaryl (catalysts **9** and **10**)[12] also eroded the *anti*/*syn* ratio (Table 1, entries 7 and 9 vs. 1). From these observations it was apparent that combined use of both amine and Brønsted acid catalyst components was crucial for the target reaction, while **5** was the optimum amine catalyst with variation on its structure at either the silyl group or the α-substituent affecting negatively the reaction *anti*/*syn* selectivity.

Table 1. Catalyst screening for the direct cross-aldol reaction between **2** and phenylpropynal **3a**.[a]



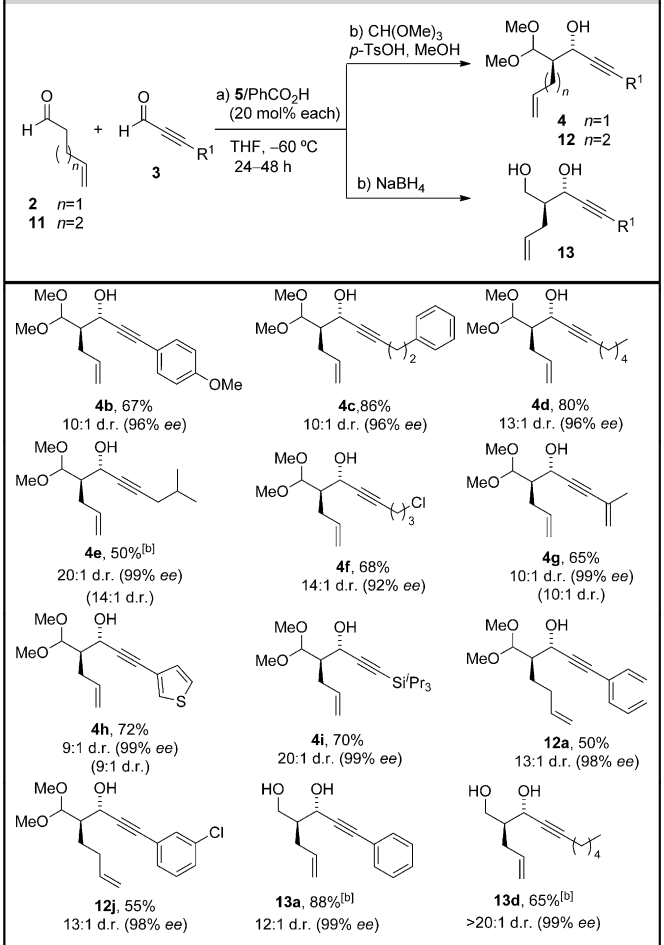
Entry	Amine	Metal	Conv. [%][b]	Yield [%][c]	*anti*/*syn*[d]	*ee* [%][e]
1	**5**	–	96	61	8:1	98
2	**5**	CuI	96	67	11:1	96
3	**6**	–	95	n.d.	4:1	96
4	**6**	CuI	79	n.d.	4:1	94
5	**7**	–	92	66	4:1	97
6	**8**	–	90	67	4:1	94
7	**9**	–	93	68	1:1	99
8	**9**	CuI	72	51	1.5:1	99
9	**10**	–	93	66	4:1	98
10	**10**	CuI	33	n.d.	6:1	91

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (**2**/**3a**/amine/$PhCO_2H$/CuI molar ratio = 1.5:1:0.2:0.2:0.1). [b] Determined by ^1H NMR spectroscopy on reaction aliquots before workup. [c] Combined yield of *anti*/*syn* adducts after chromatography; n.d. = not determined. [d] Determined by ^1H NMR spectroscopy and corroborated by HPLC. [e] Determined by chiral HPLC.

Reaction scope: α,β-ynals and α,β-ynones

Results from different aldehyde substrate combinations are shown in Table 2. In general, the reaction of 4-pentenal with a survey of α,β-ynals in the absence of any metal cocatalyst afforded the corresponding dimethyl acetals **4** in useful yields, with *anti*/*syn* ratios generally within the range 8:1 to 20:1, and excellent enantioselectivities for the major *anti* isomer. The reactions with β-aryl ynals usually proceed within 36–48 h, whereas β-alkyl ynals provided the product within 24 h of reaction. These reactions include propargylic aldehydes bearing aryl, heteroaryl, branched and unbranched alkyl, alkenyl, and chloroalkyl R^1 groups. Similarly, the reaction with 5-hexenal

Table 2. Oxygenated enynes from direct aldol reaction of unsaturated aldehydes with α,β-ynals.[a]

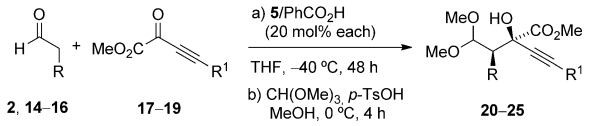


[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF (aldehyde/ynal//**5**/$PhCO_2H$ molar ratio = 1.5-1.2:1:0.2:0.2). d.r. values in parentheses correspond to reactions conducted in the presence of 10 mol% CuI. Combined yields of *anti*/*syn* adducts after chromatography. [b] Reaction run at 5 mmol scale.

(**11**) served well to afford the corresponding 6-oxy-1,7-enyne adducts **12** with satisfactory levels of chemical and stereochemical efficiency. Importantly, in all of these instances, separation of the major *anti* isomer from the diastereomeric mixture was easily accomplished by flash chromatography on silica gel. In a variation of the above method, aldol adducts could also be isolated as the corresponding diols such as **13a** and **13d** by in situ treatment with $NaBH_4$. Assignment of the configuration for thus-obtained adducts was made by correlation with previous data.[8] In general, the reactions were carried out at 0.5 mmol scale, but increasing the scale up to 5 mmol led to essentially same chemical and stereochemical results as determined for compounds **4e**, **13a**, and **13d**. On the other hand, it is important to note that for reactions leading to adducts **4e**, **4g**, **4h**, parallel experiments carried out in the presence of CuI (10 mol%) served to corroborate that, in contrast to our previous observations,[8] for these types of donor aldehydes the metal salt additive provokes essentially no change on the reactions' *anti*/*syn* selectivity and enantioselectivity. It thus seems that the α,α-dialkylprolinol ether catalyst is the main stereocontrol element of these reactions. In this respect, we confirmed that the active catalysts in the above reactions are the silylated prolinol derivatives and not the corresponding free prolinols that might eventually arise from hydrolysis. These latter species led, depending on the reaction conditions, to no reaction at all or to a different reaction outcome.[13] The crucial role of the amine catalyst structure was also evident in aldol reactions of α,β-ynals other than **3a**, where α,α-diarylprolinol ether catalysts **9** and **10** showed, once again, to be less efficient in terms of both reactivity and diastereoselectivity relative to catalyst **5**.[14] Although at present we do not have a rational explanation that correlates these changes in catalyst structure with the observed variations in reactivity and diastereoselectivity, our results indicate that the aryl to alkyl shift in the amine catalyst side chain is important and may, in certain situations, be highly effective.[15]

The present methodology could also be extended to the construction of chiral tertiary propargylic alcohols bearing an adjacent stereogenic center by aldol reaction with propargylic ketoesters.[16] In this context, although the aminocatalytic aldol reaction of ketones with α,β-ynones is known,[16a] examples of direct aldehyde–ynone aldol reactions remain elusive, likely because the occurrence of the competitive aldehyde self-aldol side reaction can not be avoided with common primary and secondary amine catalysts. Accordingly, it was gratifying that when using propargylic ketoesters **17**–**19** as the acceptor carbonyl under the above conditions (20 mol% of each cocatalyst amine and benzoic acid, −60 °C) high stereoselectivities were obtained, although the reactions progressed slowly (typically, 35% conversion after 20 h). The relatively lower solubility of these ynones as compared with the parent ynals may account for this result. However, practical reaction conversions could be obtained by carrying out the aldol reaction at −40 °C instead, under otherwise identical conditions, followed by subsequent acetalyzation. In this way, good yields and high diastereo- and enantioselectivies of the corresponding acetal products were obtained (Table 3). Thus, although this increase in reaction temperature caused homoaldolization of aldehyde **2** to occur to a limited extent (about 10% with respect to the cross-aldol process), adducts **20**, **21**, and **22** were isolated in yields of 74%, 77% and 65%, respectively, and *syn*/*anti* ratios typically from 5:1 to 8:1. In each case the major *syn* isomer was separated from the mixture by simple column chromatography and determined to possess an enantiomeric excess of 93–94% *ee*. Other aldehydes such as **14**, **15**, and **16** participated equally well in the reaction with ynone **17** giving the expected adducts **23**, **24**, and **25** in diastereomeric ratios (d.r.) up to 8:1. In each case the *syn*-aldol product was obtained in good enantioselectivity. Selection of the solvent proved to have some effect on the outcome of the above reactions. Thus, changing the solvent from THF to CH_2Cl_2 generally resulted in reactions becoming faster, with practical results attained even at −60 °C. For instance, the reaction of **2** with ynone **17** in CH_2Cl_2 led, after acetalyzation, to product **20** in 72% yield, *syn*/*anti* selectivity of 7:1 and 95% *ee* for the major *syn* isomer. Again, the successful realization of this catalytic

Table 3. Direct aldol reactions leading to tertiary propargylic alcohols.[a]



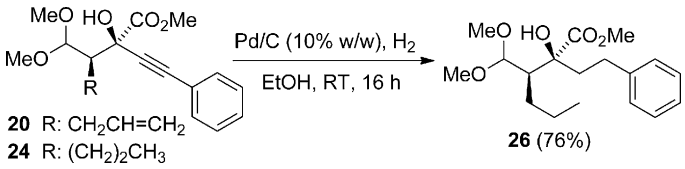
2, 14–16 17–19 20–25

Aldehyde	Ynone (R^1)	Product	Yield [%][b]	*syn/anti*[c]	*ee* [%][c]
	17	**20**	74	6:1	94
	17	**20**[d]	72	7:1	95
2	18	**21**	77	8:1	93
	19	**22**	65	5:1	94
14	17	**23**	83	5:1	93
15	17	**24**	65	8:1	93
16	17	**25**	70	5:1	95

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of THF with 1.5 equivalents of donor aldehyde. [b] Yield of combined *syn/anti* mixture of acetal product. [c] Determined by chiral HPLC analysis of the crude acetal. [d] Reaction carried out in CH_2Cl_2 at −60 °C for 48 h.

aldol assembly leading to tertiary alcohols is tightly bound to the use of our catalyst **5**. For example, the reaction of aldehyde **14** with **17** promoted by either α,α-diarylprolinol ether catalyst **9** or **10** provided the aldol adduct **23**, essentially as an equimolar mixture of diastereomers.

Configuration of the adducts was established by a single crystal X-ray analysis of compound **23** and by assuming a uniform reaction mechanism.[17] Further proof of stereochemical uniformity was obtained by correlation of both adducts **20** and **24** to the same reduction product **26** through simple hydrogenation over Pd on charcoal (Scheme 2). It is worth noting



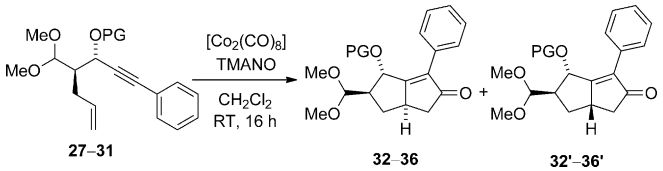
Scheme 2. Elaboration of adducts.

that **26** is the acetal form of the adduct formally derived from the cross-aldol reaction between two enolizable carbonyl compounds, pentanal acting as the ene component and methyl 2-oxo-4-phenylbutyrate, acting as the carbonyl component.

Pauson–Khand reaction

The suitability of thus-obtained enyne adducts for participating in an intramolecular Pauson–Khand cycloaddition reaction was investigated next.[18] In this respect, it has been previously noted that propargylic alcohol based enynes are not well suited substrates for Pauson–Khand reactions,[5c] presumably because inactivation of $Co_2(CO)_8$ occurs through interaction with the free hydroxyl group of the substrate. To remediate this deficiency, protection of the hydroxyl group as *tert*-butyldimethylsilyl (TBDMS) ether has been shown sufficient, providing the Pauson–Khand cycloadducts with variable diastereoselectivity that depends upon the nature of the substituent at the *C*-terminus of the alkyne moiety.[6a,d] By applying this same protecting protocol, we had observed that the Pauson–Khand reaction of *O*-TBDMS enyne **29** led to cycloadducts **34**/**34′** as a 3:1 mixture of diastereomers isolated in 67% yield. With the aim to control more effectively the diastereoselectivity of this reaction, several silyl protecting groups were screened, Table 4.

Table 4. Effect of silyl protecting group on Pauson–Khand reaction stereoselectivity.[a]



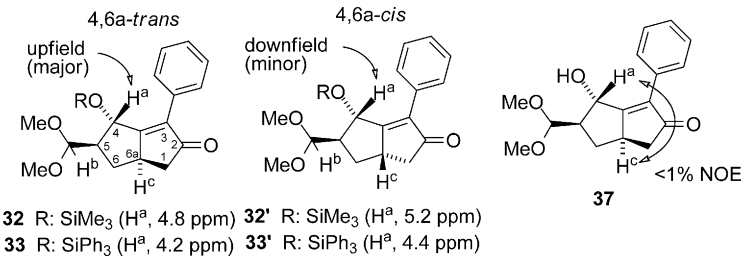
27–31 32–36 32′–36′

Enyne	PG	Product	Yield, [%][b]	Isomeric Ratio[c]
27	$SiMe_3$	**32**/**32′**	65	5:1
28	$SiPh_3$	**33**/**33′**	66	4:1
29	$SiMe_2tBu$	**34**/**34′**	67	3:1
30	$Si(SiMe_3)_3$	**35**/**35′**	60	>20:1
31	$SiiPr_3$	**36**/**36′**	65	>20:1

[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of CH_2Cl_2 at RT overnight. [b] Combined yield of diastereomers after chromatography. [c] Determined by ^1H NMR. PG = protecting group.

It turned out that the bulky tris(trimethylsilyl)silyl and triisopropylsilyl (TIPS) groups (compounds **30** and **31**) were far more efficient than TBDMS, and cycloadducts **35** and **36** were produced, from **30** and **31** respectively, essentially as single diastereomer.

The diastereomeric ratio of bicyclic products on the crude reaction mixtures was established by integrating the H^a and H^b signals on ^1H NMR spectra and the identity of each isomer was deduced by chemical shift correlation (Figure 1). Thus, it has been well established that, for these types of ring junctions with H^a and H^c in a *trans* relationship, H^a resonates more upfield than in the corresponding *cis* isomer.[19] Accordingly, for adducts **32**/**32′**, obtained from enyne **27** (R = $SiMe_3$), we assigned structure **32** to the major isomer, which shows H^a signal at 4.8 ppm, and **32′** to the minor isomer (H^a signal at 5.2 ppm). Eventually, we observed that the chemical shifts of proton H^b also follow same trend, appearing more upfield in the major isomer (5.1 ppm) as compared to the minor isomer



32 R: $SiMe_3$ (H^a, 4.8 ppm) **32'** R: $SiMe_3$ (H^a, 5.2 ppm)
33 R: $SiPh_3$ (H^a, 4.2 ppm) **33'** R: $SiPh_3$ (H^a, 4.4 ppm)

Figure 1. Configurative assignment for Pauson–Khand adducts.

(5.6 ppm). The same pattern was reproduced in the rest of cycloadducts **34**-**36**, as illustrated in the case of products **33**/**33**′ (H^a and H^b signals at 4.2 ppm and 3.8 ppm for major isomer; 4.4 ppm and 4.1 ppm for minor). The absence of any significant NOE effect between protons H^a and H^c in desilylated derivative **37** further supports these assignments.[20] Thus, the sense of stereoinduction in the above reactions is in accord with literature precedents for this type of Pauson–Khand transformation.[5,18,19]

With results of the above screening in hand, we decided to carry out the Pauson–Khand reaction of selected oxygenated enyne adducts **4** in their *O*-TIPS-protected forms.[21] The reactions could be easily monitored by TLC until disappearance of the initially formed Co complex, usually between 20 h and 24 h, and the adducts were isolated by column chromatography in yields within the range 55–85%. With one exception (see below), in all cases studied the reaction proceeded satisfactorily, leading to bicyclic products **38**-**45** as essentially single stereoisomer (Table 5). It thus seems that the high fidelity with which chirality is transferred during these intramolecular Pauson–Khand reactions is independent of the nature of the R substituent on the alkyne moiety. Similarly, 1,7-enyne **12j** provided the [4.3.0]-cycloadduct **45** in 54% yield, again as sole diastereomer. An exception to this general pattern was observed with the *O*-TIPS derivative of adduct **4i**, bearing a bulky iPr_3Si substituent on the alkyne, which, upon exposure to the same Pauson–Khand reaction conditions, did not lead to the expected cycloadduct.

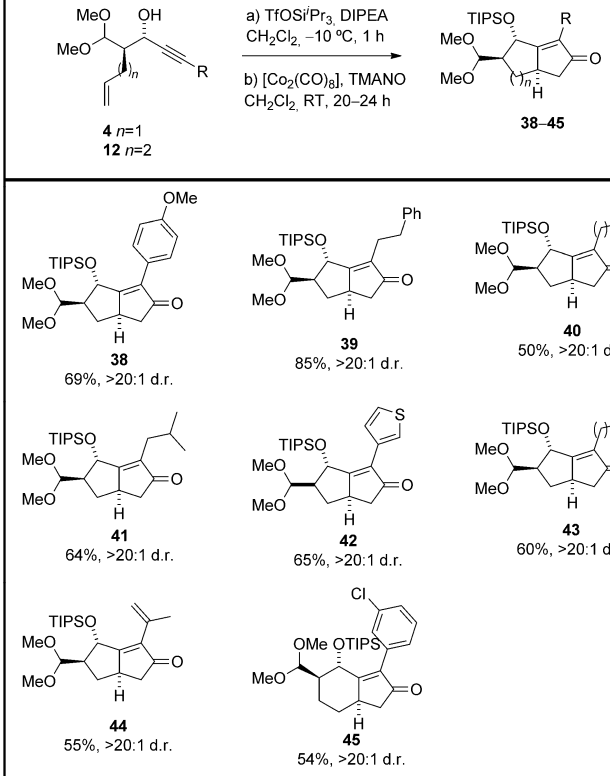
In contrast, the Pauson–Khand reaction of the TIPS ether derivative **13a**, under otherwise identical conditions, proceeded less selectively than for the parent acetal **31**, leading to a 5:1 diastereomeric mixture of adducts **46**/**46**′ isolated in 48% yield (Scheme 3). As expected, the Pauson–Khand reaction with tertiary propargylic alcohols was also found to be less selective. For example, submission of **20**-*O*-TMS (trimethylsilyl) ether[22] to the above reaction conditions provided the mixture of diastereomers **47**/**47**′ isolated in yields of 32% and 21%, respectively.

Finally, exposure of cycloadducts **36**, **42**, and **43** to Mori's conditions ($FeCl_3/SiO_2$)[23] in methylene chloride as solvent was found to provide the unprotected aldehydes **48**, **49**, and **50** (Scheme 4). Although hydrolysis was not complete under these conditions, the respective unreacted dimethyl acetal (20–35%) could be separated by column chromatography very easily and recycled, leading to the above aldehyde products, isolated in yields of 80%, 83%, and 87%, respectively, based on recovered acetal. Synthesis of aldehyde **48** by an alternative hydrolysis–oxidation sequence, starting from adduct **46**, served to corroborate the chemical identity and purity of thus-obtained aldehyde products.

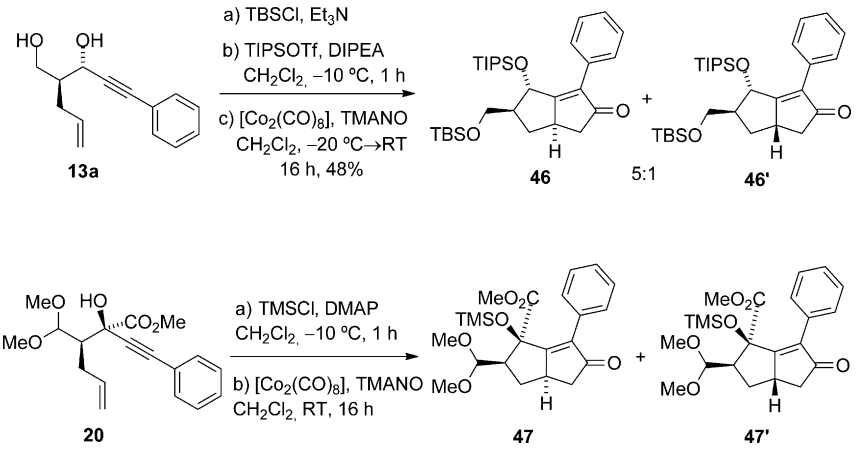
Conclusion

In summary, a direct and highly stereocontrolled route to 1,6- and 1,7-enynes with a central aldol core is demonstrated for the first time to be feasible by means of a catalytic cross-aldol reaction between ω-unsaturated aldehydes and propargylic aldehydes. Crucial for efficient control of the cross-aldol reaction diastereoselectivity is the use of an α,α-dialkylprolinol ether as the amine catalyst in cooperation with a Brønsted acid cocatalyst. The method is quite general with respect to the propargylic aldehyde substrate and can even be extended to propargylic ketoesters, giving rise to the corresponding tertiary alcohols in good yields and enantio- and diastereoselectivities. Transformation of the resulting 1,6- and 1,7-enyne structures to the corresponding trisubstituted [3.3.0] and [4.3.0] bicyclic enones with essentially perfect diastereoselectivity (d.r. > 20:1) has also been achieved, enabled by *O*-TIPS protection as key prior step for effective stereocontrol in the intramolecular Pauson–Khand reaction.

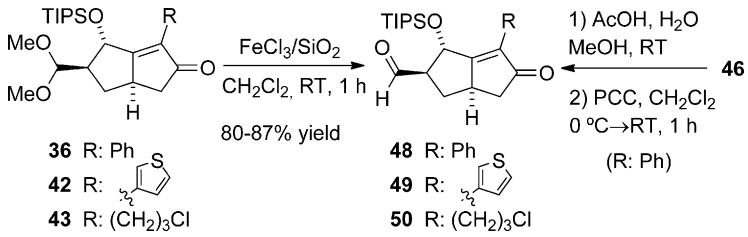
Table 5. Pauson–Khand cycloadducts from propargylic alcohol-based enynes.[a]



[a] Reactions conducted on a 0.5 mmol scale in 0.5 mL of CH_2Cl_2 at RT overnight. d.r. determined by ^{1}H NMR spectroscopy.



Scheme 3. Pauson–Khand reaction of enyne **13a** and tertiary alcohol **20**.



Scheme 4. Hydrolysis of the acetal moiety.

Experimental Section

General remarks: The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance-300 and 400, and are reported in ppm from an internal tetramethylsilane (TMS) standard. Analytical high-performance liquid chromatography (HPLC) was performed on a Waters 600E apparatus, equipped with 2996 and 2998 photodiode array UV detector, using Daicel Chiralpak AD-H, OD-H, AY-H, IC and IA columns. Optical rotations were recorded on a Jasco P-2000 polarimeter. MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model). Combustion analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyzer. All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. 4-Pentenal and 5-hexenal were distilled prior to use. Propargylic aldehydes were synthesized using previously described procedures,[8] except 2-octynal and phenyl propynal, which are commercially available. Preparation of 5-hexenal and propargylic ketoesters is reported in the Supporting Information.

General procedure for the catalytic direct cross-aldol reactions of α,β-ynals: To a solution of the amine catalyst **5** (47 mg, 0.1 mmol, 20 mol%) in THF (0.5 mL) at −60 °C were successively added the corresponding donor aldehyde (**2**, **11**, or **14**--**16**; 1.5 equiv), benzoic acid (12 mg, 0.1 mmol, 20 mol%) and the corresponding ynal **3** (0.5 mmol, 1 equiv). The resulting solution was stirred at −60 °C for 24–48 h and then treated according to two alternative protocols:

Method A (isolation of aldol as the 1,3-diol derivative **13**): To the above mixture, a suspension of $NaBH_4$ (4.5 mmol, 8 equiv) in EtOH (1 mL) was added dropwise at −60 °C, and after reaction completion monitored by ^{1}H NMR (typically 30–60 min), the mixture was quenched with brine (4 mL), and allowed to reach room temperature. After extraction with CH_2Cl_2 (3×6 mL), the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica gel.

Method B (isolation of aldol as the dimethyl acetal **4**/**12**): To the above mixture, MeOH (4.5 mL), trimethyl orthoformate (0.16 mL, 1.5 mmol) and *p*-toluenesulfonic acid (20.0 mg, 0.1 mmol, 20 mol%) were successively added at −60 °C. The mixture was allowed to reach 0 °C and, after 2 h of stirring, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (2×4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel, thus allowing in each case separation of *anti* (major) and *syn* (minor) aldol diastereomers. Data for major *anti* isomer:

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-phenylhept-6-en-1-yn-3-ol (4a): $[\alpha]_D^{24} = -8.2$ (*c* = 1.05, 98% *ee*, in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.31 (m, 5H), 5.94 (ddt, *J*(H,H) = 17.2, 10.1, 7.2 Hz, 1H), 5.27–5.07 (m, 2H), 4.80 (d, *J*(H,H) = 5.9 Hz, 1H), 4.64 (d, *J*(H,H) = 4.9 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 2.55–2.37 (m, 2H), 2.20 (ddd, *J*(H,H) = 10.7, 7.4, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1 36.5, 131.6, 128.3, 128.2, 122.4, 117.0, 106.7, 88.9, 85.7, 63.0, 55.9, 54.8, 46.3, 30.3; MS (ESI): *m*/*z* calcd for $C_{16}H_{21}O_3$: 261.1446 [M + H$^+$]; found: 261.1440. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material (Daicel Chiralpak AD-H, hexane/isopropanol 95/5, flow rate: 1 mL min^{-1}; retention times: 19.8 min (minor) and 22.0 min (major)).

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-(4-methoxyphenyl)hept-6-en-1-yn-3-ol (4b): $[\alpha]_D^{22} = +23.9$ (*c* = 1.00, 96% *ee*, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.33 (m, 2H), 6.83–6.79 (m, 2H), 5.88 (m, 1H), 5.14 (m, 1H), 5.05 (m, 1H), 4.73 (d, *J*(H,H) = 6 Hz, 1H), 4.57 (d, *J*(H,H) = 5.2 Hz, 1H), 3.77 (s, 3H), 3.43 (s, 3H), 3.42 (s, 3H), 2.46-2.33 (m, 2H), 2.16-2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 136.6, 133.0, 116.9, 114.8, 113.8, 106.6, 87.4, 85.6, 63.0, 55.8, 55.2, 54.7, 46.3, 30.2; elemental analysis calcd (%) for $C_{17}H_{22}O_4$ (290.36): C 70.32, H 7.65; found: C 70.01, H 7.58. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material (Daicel Chiralpak IC-3, hexane/isopropanol 92/8, flow rate: 1 mL min^{-1}, retention times: 20.02 min (major) and 21.70 min (minor)).

(4*R*,5*S*)-4-(Dimethoxymethyl)-9-phenylnon-1-en-6-yn-5-ol (4c): $[\alpha]_D^{22} = +10.4$ (*c* = 1.00, 96% *ee*, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 5H), 5.74 (m, 1H), 5.00 (d, *J*(H,H) = 17.2 Hz, 1H), 4.95 (d, *J*(H,H) = 10 Hz, 1H), 4.42 (brs, 1H), 4.33 (d, *J*(H,H) = 4.8 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 3.22 (m, 1H), 2.76 (t, *J*(H,H) = 7.4 Hz, 2H), 2.48 (dt, *J*(H,H) = 7.4, 1.6 Hz, 2H), 2.24–2.15 (m, 2H), 1.92-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 136.6, 128.3, 128.2, 126.2, 116.7, 106.4, 85.4, 80.4, 62.6, 55.6, 54.6, 46.1, 34.9, 30.1, 20.6; elemental analysis calcd (%) for $C_{18}H_{24}O_3$ (288.39): C 74.96, H 8.40; found: C 74.91, H 7.44. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material

(Daicel Chiralpak IA, hexane/isopropanol 98/2, flow rate: 0.7 mL min^{-1}, retention times: 20.21 min (major) and 22.35 min (minor)).

(4*R*,5*S*)-4-(Dimethoxymethyl)dodec-1-en-6-yn-5-ol (4d): $[\alpha]_D^{25} = +11.42$ ($c = 1.00$, 96% *ee*, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.81$ (m, 1H), 5.06 (m, 1H), 4.99 (m, 1H), 4.47 (d, J(H,H) = 4.8 Hz, 1H), 4.46–4.44 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 3.38–3.25 (m, 1H), 2.36–2.23 (m, 2H), 2.18 (dt, J(H,H) = 7.2, 2 Hz, 2H), 2.00–1.94 (m, 1H), 1.47 (q, J(H,H) = 7.2 Hz, 2H), 1.37–1.22 (m, 4H), 0.85 (t, J(H,H) = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.7$, 116.6, 106.6, 86.4, 79.7, 62.7, 55.6, 54.6, 46.2, 31.0, 30.1, 28.3, 22.1, 18.6, 13.9; elemental analysis calcd (%) for $C_{15}H_{26}O_3$ (254.37): C 70.82, H 10.32; found: C 70.78, H 10.27. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the corresponding *O*-benzoylated derivative (Daicel Chiralpak IC-3, hexane/isopropanol 99/1, flow rate: 1 mL min^{-1}, retention times: 6.04 min (major) and 7.16 min (minor)).

((4*R*,5*S*)-4-(dimetoxymethyl)-9-methyldec-1-en-6-yn-5-ol (4e): $[\alpha]_D^{25} = +14{,}3$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta =$ 6.14–5.70 (m, 1H), 5.18–4.95 (m, 2H), 4.62–4.44 (m, 2H), 3.43 (s, 3H), 3.41 (s, 3H), 2.47–2.25 (m, 2H), 2.13 (dd, J(H,H) = 6.5, 2.0 Hz, 2H), 2.08–1.97 (m, 1H), 1.82 (dt, J(H,H) = 13.2, 6.6 Hz, 1H), 0.98 (d, J(H,H) = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 135.71$, 115.80, 105.65, 84.37, 79.64, 61.82, 54.79, 53.64, 45.31, 29.18, 27.01, 26.95, 21.00; HRMS (ESI): m/z calcd for $C_{13}H_{21}O_2$: 209.1536 [$M-CH_3O$]; found: 209.1523. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the corresponding *O*-benzoylated derivative (Daicel Chiralpak IC, hexane/isopropanol 98/2, flow rate = 0.75 mL min^{-1}, retention times: 6.5 min (major) and 7.5 min (minor).

(4*R*,5*S*)-10-Chloro-4-(dimethoxymethyl)dec-1-en-6-yn-5-ol (4f): $[\alpha]_D^{22} = -3.85$ ($c = 1$, 92% *ee*, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 5.85 (d, J(H,H) = 7.3 Hz, 1H), 5.09 (dd, J(H,H) = 32.7, 13.0 Hz, 2H), 4.51 (d, J(H,H) = 4.7 Hz, 2H), 3.66 (t, J(H,H) = 6.3 Hz, 2H), 3.43 (d, J(H,H) = 8.9 Hz, 6H), 2.44 (d, J(H,H) = 5.0 Hz, 2H), 2.34 (d, J(H,H) = 11.0 Hz, 2H), 1.99 (dd, J(H,H) = 17.4, 10.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 136.6$, 117.2, 106.8, 84.4, 81.1, 62.9, 56.1, 54.9, 46.4, 43.8, 31.4, 30.57, 16.4; HRMS (ESI): m/z calcd for $C_{11}H_{14}ClO$: 197.0733 [M-$(CH_3O)_2$]; found: 197.0755. The enantiomeric purity of the major diastereomer was determined by chiral HPLC analysis of the corresponding *O*-benzoylated derivative (Daicel Chiralpak IC hexane/isopropanol 98/2, flow rate = 1 mL min^{-1}, retention times: 5.4 min (minor) and 6.8 min (major).

(5*S*,6*R*)-6-(Dimethoxymethyl)-2-methyl-1,8-dien-3-yn-5-ol (4g): $[\alpha]_D^{22} = +34.8$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 5.86 (ddd, J(H,H) = 17.1, 7.2, 2.9 Hz, 1H), 5.23 (p, J(H,H) = 1.6 Hz, 1H), 5.16 (q, J(H,H) = 1.5 Hz, 1H), 5.13–5.04 (m, 2H), 4.64 (t, J(H,H) = 6.0 Hz, 1H), 4.53 (d, J(H,H) = 4.9 Hz, 1H), 3.43 (d, J(H,H) = 4.1 Hz, 6H), 3.41–3.34 (m, 2H), 2.44–2.31 (m, 2H), 2.07 (ddd, J(H,H) = 8.8, 6.4, 4.8 Hz, 1H), 1.93–1.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 136.5, 122.1, 117.1, 106.7, 88.0, 87.1, 63.0, 56.0, 54.9, 46.3, 30.3, 23.5; HRMS (ESI): m/z calcd for $C_{12}H_{17}O_2$: 193.1223 [$M-CH_3O$]; found: 193.1229. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 98/2, flow rate = 0.5 mL min^{-1}, retention times: 31.2 min (major) and 37.2 min (minor).

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-(thiophen-3-yl)hept-6-en-1-yn-3-ol (4h): $[\alpha]_D^{25} = +21{,}6$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (s, 1H), 7.26 (s, 1H), 7.11 (d, J(H,H) = 3.9 Hz, 1H), 6.03–5.74 (m, 1H), 5.16 (d, J(H,H) = 16.0 Hz, 1H), 5.08 (d, J(H,H) = 9.6 Hz, 1H), 4.74 (s, 1H), 4.58 (d, J(H,H) = 4.7 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.48–2.33 (m, 2H), 2.15–1.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 136.5$, 131.6, 128.3, 128.2, 122.4, 117.0, 106.7, 88.9, 85.7, 63.0, 55.9, 54.8, 46.3, 30.3; HRMS (ESI): m/z calcd for $C_{13}H_{15}O_2S$: 235.0787 [$M-CH_3O$]; found: 235.0784. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 95/5, flow rate = 0.5 mL min^{-1}, retention times: 25.8 min (minor) and 28.7 min (major)).

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-(triisopropylsilyl)hept-6-en-1-yn-3-ol (4i): $[\alpha]_D^{25} = +11.9$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.90$ (d, J(H,H) = 7.6 Hz, 1H), 5.17 (d, J(H,H) = 17.0 Hz, 1H), 5.08 (d, J(H,H) = 10.0 Hz, 1H), 4.64 (d, J(H,H) = 4.8 Hz, 1H), 4.62–4.55 (m, 1H), 3.45 (d, J(H,H) = 1.4 Hz, 6H), 2.41 (d, J(H,H) = 7.4 Hz, 2H), 2.07 (s, 1H), 1.11 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 136.9$, 117.2, 107.6, 106.8, 63.1, 56.2, 54.9, 46.3, 29.7, 18.8, 11.4; HRMS (ESI): m/z calcd for $C_{17}H_{29}OSi$: 277.1988 [$M-(CH_3O)_2$]; found: 277.1999. The enantiomeric purity of the major diastereomer was determined by chiral HPLC analysis of its *O*-triphenylsilyl ether derivative (Daicel Chiralpak AY-H, hexane/isopropanol 98/2, flow rate = 0.5 mL min^{-1}, retention times: 4.9 min (major) and 15 min (minor)).

(3*S*,4*R*)-4-(Dimethoxymethyl)-1-phenyloct-7-en-1-yn-3-ol (12a): $[\alpha]_D^{22} = -9.8$ ($c = 1$, 98% *ee*, CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.47–7.41 (m, 2H), 7.34–7.28 (m, 3H), 5.83 (ddt, J(H,H) = 16.9, 10.2, 6.6 Hz, 1H), 5.12–4.96 (m, 2H), 4.75 (t, J(H,H) = 6.0 Hz, 1H), 4.65 (d, J(H,H) = 4.3 Hz, 1H), 3.47 (d, J(H,H) = 2.6 Hz, 6H), 2.34–2.02 (m, 4H), 1.78–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.66$, 131.80, 128.49, 128.43, 115.10, 107.60, 89.25, 85.62, 56.29, 55.47, 45.58, 31.73, 24.40; HRMS (ESI): m/z calcd for $C_{17}H_{22}O_3 + Na^+$: 297.1467 [$M + Na^+$]; found: 297.1473. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H hexane/isopropanol 98/2, flow rate = 0.5 mL min^{-1}, retention times: 22.2 min (minor) and 51.7 min (major)).

(3*S*,4*R*)-1-(3-Chlorophenyl)-4-(dimethoxymethyl)oct-7-en-1-yn-3-ol (12j): $[\alpha]_D^{22} = -69.9$ ($c = 1$, 98% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$ (t, J(H,H) = 1.5 Hz, 1H), 7.31 (tt, J(H,H) = 6.1, 1.6 Hz, 2H), 7.24 (s, 1H), 7.21 (s, 1H), 5.09 (q, J(H,H) = 1.6 Hz, 1H), 5.06–4.96 (m, 1H), 4.74 (t, J(H,H) = 5.9 Hz, 1H), 4.61 (d, J(H,H) = 4.3 Hz, 1H), 3.52–3.48 (m, 1H), 3.47 (d, J(H,H) = 1.1 Hz, 5H), 2.29–2.14 (m, 2H), 2.11–2.01 (m, 1H), 1.75–1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.5$, 134.1, 131.5, 129.8, 129.6, 128.6, 124.5, 115.0, 107.3, 90.5, 84.1, 63.1, 56.1, 55.3, 45.5, 31.7, 24.5; HRMS (ESI): m/z calcd for $C_{16}H_{18}ClO_2$: 277.0990 [MCH_3O]; found: 277.0993. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H hexane/isopropanol 98/2, flow rate = 0.5 mL min^{-1}, retention times: 16.5 min (minor) and 28.0 min (major)).

(2*S*,3*S*)-2-allyl-5-phenylpent-4-yne-1,3-diol (13a): $[\alpha]_D^{25} = -6.88$ ($c = 1$, 99% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, Chloroform-*d*) $\delta = 7.52$–7.39 (m, 2H), 7.38–7.28 (m, 3H), 5.98–5.75 (m, 1H), 5.23–5.02 (m, 2H), 4.74 (t, $J = 5.5$ Hz, 1H), 4.12–4.03 (m, 1H), 3.86–3.70 (m, 1H), 2.55–2.39 (m, 1H), 2.35–2.22 (m, 1H), 2.03–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 136.1$, 131.6, 128.4, 128.2, 117.1, 88.9, 85.9, 65.7, 63.6, 45.7, 32.4. HRMS (ESI): m/z calcd for $C_{14}H_{17}O_2$: 217.1237 [$M + H^+$]; found: 217.1229. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 98/2, flow rate: 1 mL min^{-1}, retention time 48.17 min (minor) and 84.87 min (major).

(2*S*,3*S*)-2-allyldec-4-yne-1,3-diol (13d): $[\alpha]_D^{25} = -11.57$(c=1, 99% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, Chloroform-*d*) $\delta = 5.95$–5.69 (m, 1H), 5.18–4.96 (m, 2H), 4.49 (d, $J = 5.7$ Hz, 1H), 3.98 (dd, $J = 11.1$, 3.3 Hz, 1H), 3.71 (dd, $J = 11.1$, 6.1 Hz, 1H), 2.47–2.30 (m, 1H), 2.20 (m, 3H), 1.91–1.76 (m, 1H), 1.62–1.44 (m, 2H), 1.44–1.22 (m, 4H), 0.90 (t, $J =$ 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 136.3$, 116.4, 86.2, 80.1, 65.2, 63.4, 45.9, 32.2, 30.9, 28.2, 21.9, 18.5, 13.7; HRMS (ESI): m/z

calcd for $C_{13}H_{23}O_2$: 211.177 [$M+H^+$]; found: 211.1608. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis of the corresponding *O*-silylated derivative (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate: 0.5 mL min^{-1}, retention times: 10.10 min (major) and 15.34 min (minor).

General Procedure for the catalytic Cross-Aldol reactions with α,β-ynones: To a solution of the amine catalyst **5** (47 mg, 0.1 mmol, 20 mol%), benzoic acid (12 mg, 0.1 mmol, 20 mol%) and the corresponding α,β-ynone **17–19** (0.5 mmol, 1 equiv) in THF (0.5 mL) at −40 °C was added the corresponding donor aldehyde (**2**, **14–16**) (0.6 mmol, 1.2 equiv). The resulting solution was stirred at −40 °C for 48 h and then 4.5 mL of MeOH, trimethyl orthoformate (0.16 mL, 1.5 mmol) and *p*-toluenesulfonic acid (20.0 mg, 0.1 mmol, 20 mol%) were successively added at −40 °C. The mixture was allowed to reach 0 °C and, after 2 h of stirring, the reaction was quenched with $NaHCO_3$ sat. (5 mL) and extracted with ethyl acetate (2×4 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/THF 92.5:7.5) thus allowing in each case separation of *syn* (major) and *anti* (minor) diastereomers. Data of *syn* isomer:

(2*R*,3*R*)-Methyl 3-(dimethoxymethyl)-2-hydroxy-2-(phenylethynyl)hex-5-enoate (20): $[\alpha]_D^{21}=-83.0$ ($c=1$, 94% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.50$–7.40 (m, 2H), 7.37–7.22 (m, 3H), 6.05 (td, J(H,H)=10.1, 5.0 Hz, 1H), 5.17–4.96 (m, 2H), 4.42 (d, J(H,H)=7.0 Hz, 1H), 4.04 (s, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.77–2.66 (m, 1H), 2.62–2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.14$, 137.53, 132.25, 129.14, 128.65, 122.46, 116.36, 106.32, 87.83, 86.14, 73.68, 57.35, 54.19, 53.77, 48.57, 32.24; HRMS (ESI): *m/z* calcd for $C_{16}H_{15}O_3$: 255.1021 [$M-(CH_3O)_2$, $-H^+$]; found: 255.1039. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 98/2, flow rate = 1 mL min^{-1}, retention times: 11.6 min (major) and 13.1 min (minor)).

(2*R*,3*R*)-Methyl 3-(dimethoxymethyl)-2-((4-fluorophenyl)ethynyl)-2-hydroxyhex-5-enoate (21): $[\alpha]_D^{21}=-80.9$ ($c=1$, 93% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.41$ (dd, J(H,H)=8.9, 5.4 Hz, 2H), 6.99 (t, J(H,H)=8.7 Hz, 2H), 6.15–5.90 (m, 1H), 5.15–4.99 (m, 2H), 4.39 (d, J(H,H)=6.9 Hz, 1H), 4.04 (s, 1H), 3.82 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.76–2.64 (m, 1H), 2.62–2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=172.61$, 164.36, 161.05, 137.04, 133.79, 133.68, 115.91, 115.67, 115.37, 105.83, 87.14, 84.60, 73.18, 56.89, 53.75, 53.31, 48.08, 31.73; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}FO_3$: 273.0927 [$M-(CH_3O)_2$,$-H^+$]; found: 273.0916. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 95/5, flow rate = 1 mL min^{-1}, retention times: 7.3 min (major) and 8.0 min (minor)).

(2*R*,3*R*)-Methyl 2-((3-chlorophenyl)ethynyl)-3-(dimethoxymethyl)-2-hydroxyhex-5-enoate (22): $[\alpha]_D^{21}=-18.31$ ($c=1$, 94% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$ (t, J(H,H)=1.8 Hz, 1H), 7.34–7.28 (m, 2H), 7.25–7.20 (m, 1H), 6.02 (td, J(H,H)=10.1, 5.0 Hz, 1H), 5.16–4.97 (m, 2H), 4.40 (d, J(H,H)=6.9 Hz, 1H), 4.05 (s, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 2.74–2.65 (m, 1H), 2.62–2.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=172.48$, 136.94, 134.11, 131.66, 129.95, 129.50, 129.04, 125.49, 116.06, 105.84, 88.64, 84.23, 73.22, 56.96, 53.83, 53.41, 48.07, 31.77; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}ClO_3$: 261.0318 [$M-(CH_3O)_2$,$-C_2H_5$]; found: 261.0763. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate = 1 mL min^{-1}, retention times: 9.5 min (major) and 11.5 min (minor)).

(*R*)-Methyl 2-((*R*)-1,1-dimethoxy-3-phenylpropan-2-yl)-2-hydroxy-4-phenylbut-3-ynoate (23): m.p. 123–127 °C; $[\alpha]_D^{25}=-69.5$ ($c=1$, 95% *ee*, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.41$–7.38 (m, 2H), 7.36–7.27 (m, 6H), 7.22–7.13 (m, 2H), 4.33 (d, J(H,H)=6.2 Hz, 1H), 3.81 (s, 3H), 3.52 (s, 1H), 3.41 (dd, J(H,H)=7.4, 6.1 Hz, 1H), 3.34 (s, 3H), 3.10 (s, 3H), 2.93 (dd, J(H,H)=14.4, 7.9 Hz, 1H), 2.89–2.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=172.56$, 140.84, 132.01, 131.92, 129.24, 129.15, 129.08, 128.71, 128.63, 128.49, 128.22, 128.18, 125.89, 106.21, 87.70, 85.88, 73.63, 56.73, 53.46, 53.21, 50.11, 33.31; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}O_3$: 305.1178 [$M-(CH_3O)_2$,$-H$]; found: 305.1189. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate = 0.5 mL min^{-1}, retention times: 20.2 min (major) and 27.5 min (minor)).

(2*R*,3*R*)-Methyl 3-(dimethoxymethyl)-2-hydroxy-2-(phenylethynyl)hexanoate (24): $[\alpha]_D^{23}=+21.0$ ($c=1$, 93% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.45$–7.40 (m, 2H), 7.34–7.27 (m, 3H), 4.39 (d, J(H,H)=7.4 Hz, 1H), 4.01 (d, J(H,H)=0.4 Hz, 1H), 3.83 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.45 (dt, J(H,H)=7.3, 4.8 Hz, 1H), 1.89 (ddd, J(H,H)=11.9, 8.4, 3.5 Hz, 1H), 1.73–1.50 (m, 3H), 0.96 (t, J(H,H)=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.40$, 132.19, 129.04, 128.62, 125.88, 122.56, 107.00, 88.10, 85.53, 73.92, 58.71–57.40, 54.31, 53.69, 48.50, 30.70, 30.00, 22.13, 14.95; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}O_4$: 289.1434 [$M-CH_3O$]; found: 289.1427. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA and Daicel Chiralpak IC hexane/isopropanol 95/5, flow rate = 0.5 mL min^{-1}, retention times: 29.7 min (major) and 34.6 min (minor)).

(2*R*,3*R*)-Methyl-3-(dimethoxymethyl)-2-hydroxy-4-methyl-2-(phenylethynyl) pentanoate (25): $[\alpha]_D^{21}=-33.4$ ($c=1$, 95% *ee*, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.46$–7.40 (m, 2H), 7.33–7.26 (m, 3H), 4.52 (d, J(H,H)=8.1 Hz, 1H), 3.98 (d, J(H,H)=0.7 Hz, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.68–2.56 (m, 1H), 2.47–2.40 (m, 1H), 1.16 (dd, J(H,H)=7.1, 3.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 173.32, 131.73, 129.01, 128.59, 128.24, 128.17, 105.16, 88.05, 85.74, 74.19, 57.13, 53.31, 53.23, 51.61, 27.70, 23.23, 19.06; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_3$: 257.1178 [$M-(CH_3O)_2$]; found: 257.1216. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate = 1 mL min^{-1}, retention times: 9.2 min (major) and 11.2 min (minor)).

Synthesis of (2*S*,3*R*)-Methyl 3-(dimethoxymethyl)-2-hydroxy-2-phenethylhexanoate (26) from 20/24: To a solution of **20** or **24** (0.2 mmol) in EtOH (0.8 mL) Pd 10% w/w on activated carbon (20 wt%) was added. The mixture was allowed to stir under H_2 atmosphere (1 atm) for 16 h. The mixture was then filtered over celite (2 cm) and the solvent was eliminated under vacuum yielding the desired product as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.31$–7.24 (m, 2H), 7.23–7.14 (m, 3H), 4.28 (d, J(H,H)=5.8 Hz, 1H), 3.75 (s, 3H), 3.73 (d, J(H,H)=0.8 Hz, 1H), 3.35 (s, 3H), 3.35 (s, 3H), 2.76 (td, J(H,H)=12.8, 4.6 Hz, 1H), 2.35–2.20 (m, 1H), 2.15–2.01 (m, 2H), 1.99–1.85 (m, 1H), 1.60–1.43 (m, 3H), 1.41–1.25 (m, 1H), 0.89 (t, J(H,H)=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 176.92, 141.82, 128.43, 128.35, 125.85, 78.29, 56.69, 54.62, 52.23, 47.62, 39.39, 29.74, 27.37, 22.18, 14.57; HRMS (ESI): *m/z* calcd for $C_{17}H_{25}O_4$: 293.1749 [$M-CH_3O$]; found: 293.1768.

Typical procedure for the silylation of adducts 4: To a solution of alcohol **4** (0.5 mmol) in CH_2Cl_2 (2 mL) at −10 °C were successively added diisopropylethylamine (DIPEA; 194 mg, 1.5 mmol, 3 equiv) and triisopropylsilyl trifluoromethanesulfonate (184 mg, 0.6 mmol, 1.2 equiv). The resulting mixture was stirred at −10 °C for 1 h, diluted with CH_2Cl_2 (15 mL), and the organic solution was washed with saturated NH_4Cl (2×10 mL) and saturated $NaHCO_3$ (2×10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting

with hexane/ethyl acetate 20:1) to isolate the pure silyl ether compound as a yellow oil.

General Procedure for the intramolecular Pauson–Khand reaction: $[Co_2(CO)_8]$ (341 mg, 1 mmol, 2 equiv) was added to a solution of the corresponding silylated propargylic alcohol (0.5 mmol) in CH_2Cl_2 (2 mL) at room temperature and was stirred for 30 min. Then trimethylamine *N*-oxide (TMANO) (226 mg, 3 mmol, 6 equiv) was added at −10 °C and the mixture was allowed to warm to room temperature and stirred at room temperature until the initially formed Co complex disappeared (20–24 h), at which time usually a purple precipitate had formed. The mixture was passed through a small plug of silica gel and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 20:1) to isolate the pure compound as a yellow oil.

(4*S*,5*R*,6a*R*)-5-(Dimethoxymethyl)-3-phenethyl-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (36): Prepared according to the General Procedure starting from silylated compound **31** (208 mg, 0.5 mmol). Yield: 144 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.31 (m, 5H), 5.08 (s, 1H), 4.12 (d, *J*(H,H) = 6.4 Hz, 1H), 3.37 (s, 3H), 3.36 (m, 1H, hidden), 3.35 (s, 3H), 2.88 (dd, *J*(H,H) = 18.3, 6.6 Hz, 1H), 2.75–2.69 (m, 1H), 2.47–2.39 (m, 1H), 2.27 (dd, *J*(H,H) = 18.3, 2.7 Hz, 1H), 1.30–1.16 (m, 1H), 0.98–0.93 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 180.3, 134.3, 131.5, 128.5, 128.3, 127.9, 106.3, 69.7, 54.9, 53.9, 53.3, 42.8, 39.1, 30.2, 17.9, 17.8, 12.3; elemental analysis calcd (%) for $C_{26}H_{40}O_4Si$ (444.68): C 70.23, H 9.07; found: C 70.28, H 9.12.

(4*S*,5*R*,6a*R*)-5-(dimethoxymethyl)-3-(4-methoxyphenyl)-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (38): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl derivative of **4b** (223 mg, 0.5 mmol). Yield: 164 mg (69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 2H), 6.90–6.83 (m, 2H), 5.02 (brs, 1H), 4.03 (d, *J*(H,H) = 6.8 Hz, 1H), 3.78 (s, 3H), 3.30 (s, 3H), 3.29 (s, 3H), 3.33–3.24 (m, 1H, hidden), 2.80 (dd, *J*(H,H) = 18.3, 6.6 Hz, 1H), 2.65 (m, 1H), 2.36 (m, 1H), 2.19 (dd, *J*(H,H) = 18.3, 2.6 Hz, 1H), 1.14 (m, 1H), 0.95–0.90 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 179.0, 159.4, 133.7, 129.6, 123.8, 113.7, 106.2, 69.9, 55.2, 54.8, 53.7, 53.3, 42.8, 38.9, 30.2, 17.9, 17.8, 12.3; elemental analysis calcd (%) for $C_{27}H_{42}O_5Si$ (474.70): C 68.31, H 8.92; found: C 68.36, H 8.89. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material (Phenomenex Lux 3μ Cellulose-4, hexane/isopropanol 93/7, flow rate: 1 mL min^{-1}, retention times: 10.07 min (minor) and 13.04 min (major)).

(4*S*,5*R*,6a*R*)-5-(Dimethoxymethyl)-3-phenethyl-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (39): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl derivative of **4c** (222 mg, 0.5 mmol). Yield: 201 mg (85%); $[\alpha]_D^{25} = +68.4$ (*c* = 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.08 (m, 5H), 4.56 (brs, 1H), 3.61 (d, *J*(H,H) = 8 Hz, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.17 (m, 1H), 2.86–2.53 (m, 5H), 2.47 (m, 1H), 2.25 (m, 1H), 2.06 (dd, *J*(H,H) = 18.4, 1.8 Hz, 1H), 1.12–1.04 (m, 21H), 0.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.3, 179.4, 141.7, 134.4, 128.5, 128.4, 126.0, 105.5, 69.6, 54.1, 53.4, 52.5, 42.3, 39.3, 33.5, 31.0, 26.6, 18.0, 17.9, 12.4; elemental analysis calcd (%) for $C_{28}H_{44}O_4Si$ (472.73): C 71.14, H 9.38; found: C 71.18, H 9.34. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material (Phenomenex Lux 3μ Cellulose-2, hexane/isopropanol 99/1, flow rate: 1 mL min^{-1}, retention times: 13.42 min (minor) and 15.53 min (major)).

(4*S*,5*R*,6a*R*)-5-(Dimethoxymethyl)-3-pentyl-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (40): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl ether derivative of **4d** (205 mg, 0.5 mmol). Yield: 110 mg (50%); $[\alpha]_D^{24} = +87.8$ (*c* = 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (brs, 1H), 3.93 (d, *J*(H,H) = 7.6 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 3.17 (m, 1H), 2.67–2.58 (m, 2H), 2.32–2.00 (m, 5H), 1.44–1.35 (m, 2H), 1.31–1.16 (m, 4H), 1.08–0.99 (m, 21H), 0.86 (d, *J*(H,H) = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.6, 178.5, 135.6, 105.9, 69.8, 54.5, 53.4, 53.0, 42.5, 39.0, 32.0, 30.5, 27.8, 24.2, 22.4, 18.0, 17.9, 14.0, 12.4; elemental analysis calcd (%) for $C_{25}H_{46}O_4Si$ (438.72): C 68.44, H 10.57; found: C 68.38, H 10.60. The enantiomeric purity of the major diastereomer was determined by HPLC analysis of the crude material (Phenomenex Lux 3μ Cellulose-1, hexane/isopropanol 99.9/0.1, flow rate: 1 mL min^{-1}, retention times: 16.56 min (minor) and 20.35 min (major)).

(4*S*,5*R*,6a*R*)-5-(Dimethoxymethyl)-3-isobutyl-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (41): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl ether derivative of **4e** (127 mg, 0.32 mmol). Yield: 87 mg (64%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.82 (s, 1H), 4.01 (d, *J*(H,H) = 7.4 Hz, 1H), 3.34 (s, 3H), 3.29 (s, 3H), 2.67 (dd, *J*(H,H) = 18.3, 6.4 Hz, 2H), 2.36–2.27 (m, 1H), 2.26–2.18 (m, 1H), 2.11–2.01 (m, 1H), 1.97 (d, *J*(H,H) = 13.1 Hz, 1H), 1.91–1.81 (m, 1H), 1.09–1.02 (m, 21H), 1.00–0.92 (m, 2H), 0.88 (d, *J*(H,H) = 6.5 Hz, 3H), 0.80 (d, *J*(H,H) = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 211.52, 179.21, 134.74, 105.89, 69.79, 54.49, 53.72, 52.93, 42.41, 39.36, 33.05, 30.83, 27.08, 22.88, 22.39, 18.04, 17.98, 12.46; HRMS (ESI): *m/z* calcd for $C_{24}H_{44}O_4Si + H^+$: 425.3087 [$M + H^+$]; found: 425.3053.

(4*S*,5*R*,6a*R*)-5-(Dimethoxymethyl)-3-(thiophen-3-yl)-4-(triisopropylsilyloxy)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (42): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl ether derivative of **4h** (76 mg, 0.18 mmol). Yield: 52 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 1H), 7.35–7.28 (m, 2H), 5.16 (s, 1H), 4.04 (d, *J*(H,H) = 6.5 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.83 (dd, *J*(H,H) = 18.3, 6.6 Hz, 1H), 2.70 (dd, *J*(H,H) = 14.8, 6.6 Hz, 1H), 2.46–2.33 (m, 1H), 2.21 (dd, *J*(H,H) = 18.3, 2.7 Hz, 1H), 1.23–1.10 (m, 2H), 1.03–0.90 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.23, 178.48, 126.99, 125.15, 124.31, 106.18, 70.14, 54.89, 53.80, 53.20, 42.84, 38.95, 30.14, 17.92, 17.84, 12.33; HRMS (ESI): *m/z* calcd for $C_{24}H_{38}O_4SSi + H^+$: 451,2338 [$M + H^+$]; found: 451,2318.

(4*S*,5*R*)-3-(3-Chloropropyl)-5-(dimethoxymethyl)-4-((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1H)-one (43): Prepared according to the General Procedure starting from the *O*-triisopropylsilyl ether derivative of **4f** (0.22 mmol). Yield: 53.6 mg (60%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.86 (s, 1H), 4.05 (d, *J*(H,H) = 6.6, 1H), 3.53 (d, *J*(H,H) = 5.9, 1H), 3.42 (s, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 2.68 (dd, *J*(H,H) = 18.4, 6.5 Hz, 2H), 2.34 (dd, *J*(H,H) = 24.2, 10.3 Hz, 3H), 2.00–1.88 (m, 3H), 1.09 (s, 11H), 1.04 (d, *J*(H,H) = 5.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.63, 180.43, 133.83, 106.28, 69.69, 55.16, 54.00, 53.69, 44.80, 42.55, 39.61, 30.53, 30.43, 21.70, 18.22, 12.62; HRMS (ESI): *m/z* calcd for $C_{23}H_{41}ClO_4Si + H^+$: 444. 2545 [$M + H^+$]; found: 445.2541.

(4*S*,5*R*)-5-(Dimethoxymethyl)-3-(prop-1-en-2-yl)-4-((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1H)-one (44): Prepared according to the General Procedure starting from *O*-triisopropylsilyl derivated of **4g** (0.2 mmol). Yield: 44 mg (55%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (s, 2H), 4.99 (s, 1H), 4.25–4.19 (m, 1H), 3.97 (d, *J*(H,H) = 7.0 Hz, 1H), 3.32 (d, *J*(H,H) = 10.1 Hz, 7H), 2.78–2.58 (m, 3H), 2.40–2.28 (m, 2H), 2.11 (d, *J*(H,H) = 18.4 Hz, 2H), 1.96 (s, 3H), 1.05 (d, *J*(H,H) = 7.4 Hz, 26H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.03, 131.03, 128.95, 117.03, 106.14, 70.17, 53.17, 43.04, 38.80, 30.02, 23.91, 22.06, 18.17; HRMS (ESI): *m/z* calcd for $C_{23}H_{41}O_4Si + H^+$: 409.2774 [$M + H^+$]; found: 409.2769.

(4*S*,5*R*)-3-(3-Chlorophenyl)-5-(dimethoxymethyl)-4-((triisopropylsilyl)oxy)-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one (45): Prepared according to the General Procedure starting from O-triisopropylsilyl derivated of **12j** (0.37 mmol).Yield: 98.2 mg (54%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J*(H,H) = 1.9 Hz, 1H), 7.36–7.24 (m, 3H), 5.13 (d, *J*(H,H) = 2.7 Hz, 1H), 4.29 (d, *J*(H,H) = 9.2 Hz, 1H), 3.32 (d, *J*(H,H) = 5.6 Hz, 6H), 3.29–3.19 (m, 1H), 2.74 (dd, *J*(H,H) = 19.1, 6.7 Hz, 1H), 2.43–2.34 (m, 1H), 2.25–2.03 (m, 3H), 1.78 (d, *J*(H,H) = 14.3 Hz, 1H), 1.39–1.24 (m, 2H), 0.89 (d, *J*(H,H) = 5.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.2, 132.8, 129.4, 129.1, 128.0, 127.3, 101.9, 65.0, 53.5, 52.2, 45.8, 41.8, 35.9, 31.0, 17.9, 12.2; HRMS (ESI): *m/z* calcd for $C_{27}H_{42}O_4ClSi + H^+$: 493.2541 [$M + H^+$]; found: 493.2530.

Pauson–Khand reaction from diol 13a: synthesis of (4S,5S,6aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-phenyl-4- ((triisopropylsilyl)oxy)-4,5,6,6a-tetrahydropentalen-2(1H)-one (46): To a solution of diol **13a** (0.5 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at 0 °C were successively added Et_3N (83.5 μL, 0.6 mmol, 1.2 equiv) and tert-butyldimethylsilyl chloride (90.4 mg, 0.6 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature and controlled by TLC. Then, DIPEA (0.26 ml, 1.5 mmol, 3 equiv) and triisopropylsilyl trifluoromethanesulfonate (18 mg, 0.6 mmol, 1.2 equiv) were added at −10 °C and the mixture was stirred at that temperature for 1h. It was diluted with CH_2Cl_2 (15ml) and the organic solution was washed with saturated NH_4Cl (2×10 ml) and saturated $NaHCO_3$ (2×10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 98:2) to isolate the pure disilylated compound as colorless oil. Yield: 97.3 mg (40%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.44–7.35 (m, 2H), 7.35–7.27 (m, 3H), 5.95–5.78 (m, 1H), 5.13–4.96 (m, 3H), 3.72 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.62 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.63–2.51 (m, 1H), 2.11–1.94 (m, 2H), 1.10 (dd, *J* = 15.7, 4.1 Hz, 21H), 0.91 (d, *J* = 9.1 Hz, 9H), 0.06 (d, *J* = 3.2 Hz, 6H).

The resulting disilylated compound was submitted to the general Pauson-Khan condiditions above (room temperature, 16 h) to afford **46**, after purification by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 20:1), as a 5:1 mixture of diastereomers. Combined yield: 49.4 mg (48%). Data for major isomer: ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.47–7.28 (m, 5H), 5.10 (s, 1H), 3.55 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.48–3.32 (m, 1H), 3.22 (dd, *J* = 10.2, 8.5 Hz, 1H), 2.88 (dd, *J* = 18.2, 6.7 Hz, 1H), 2.65–2.49 (m, 1H), 2.50–2.35 (m, 1H), 2.20 (dd, *J* = 18.3, 2.8 Hz, 1H), 1.03–0.80 (m, 31H), −0.03 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.7, 181.1, 135.4, 131.8, 128.9, 128.6, 128.4, 70.9, 65.0, 52.8, 43.9, 39.1, 31.4, 26.2, 18.4, 18.3, 12.7, −5.2. HRMS (ESI): *m/z* calcd for $C_{30}H_{51}O_3Si_2$: 515.3381 [$M + H^+$]; found: 515.3377.

Pauson–Khand reaction from tertiary alcohol 20: synthesis of (1*R*,2*R*,3a*R*)-Methyl-2-(dimethoxymethyl)-5-oxo-6-phenyl-1-(trimethylsilyloxy)-1,2,3,3a,4,5-hexahydropentalene-1-carboxylate (47): To a solution of tertiary alcohol 20 (0.5 mmol) in CH_2Cl_2 (2 mL) at −10 °C were successively added TEA (0.2 mL, 1.5 mmol, 3 equiv), DMAP (6.11 mg, 0.05 mmol, 0.1 equiv) and trimethylchlorosilane (134 μL, 1 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 4 h, diluted with CH_2Cl_2 (15 mL) and the organic solution was washed with saturated NH_4Cl (2×10 mL) and saturated $NaHCO_3$ (2×10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 20:1). The resulting silylated compound (colorless oil) was submitted to the general Pauson–Khand conditions above (room temperature, 16 h) to afford, after purification by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 19:1), a colorless oil consisting of a 1.5:1 mixture of diastereomers. Combined yield: 97 mg (53%). Data for major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (ddd, *J*(H,H) = 8.7, 7.8, 6.1 Hz, 3H), 7.26–7.16 (m, 2H), 4.54 (d, *J*(H,H) = 8.5 Hz, 1H), 3.54–3.43 (m, 1H), 3.30 (s, 3H), 3.30 (s, 3H), 3.07–2.89 (m, 2H), 2.86 (s, 3H), 2.36 (dd, *J*(H,H) = 18.0, 3.7 Hz, 1H), 2.16 (ddd, *J*(H,H) = 13.4, 11.4, 9.3 Hz, 1H), 1.72 (ddd, *J*(H,H) = 13.7, 10.2, 5.3 Hz, 1H), 0.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.46, 177.45, 171.07, 135.10, 130.31, 129.18, 128.24, 128.00, 104.78, 80.90, 55.52, 53.41, 52.04, 51.15, 44.69, 39.79, 29.02, 2.45; HRMS (ESI): *m/z* calcd for $C_{24}H_{44}O_4Si + H^+$: 419.1890 [$M + H^+$]; found: 419.1869.

Hydrolysis of the acetals 36, 42, 43: To a solution of acetal **36**, **42** or **43** (0.80 mmol) in CH_2Cl_2 (40 mL) 7.4 wt% $FeCl_3$ on SiO_2 (80 mg) was added, and the resulting suspension was stirred vigorously for 1 h. Then aqueous $NaHCO_3$ (1 mL) was added, and the organic phase was washed with brine, dried over $MgSO_4$ and concentrated. Flash column chromatography on silica gel of the residue afforded pure aldehyde **48**–**50**, with recovery of the unreacted starting material (20–35%).

(1S,2R,3aR)-5-oxo-6-phenyl-1-(triisopropylsilyloxy)-1,2,3,3a,4,5-hexahydropentalene-2-carbaldehyde (48): Flash column chromatography on silica gel (hexane:ethyl acetate, 95:5) of the residue afforded pure aldehyde **48** (yellow oil, 206 mg, 65%) along with recovery of unreacted starting material **36** (54 mg, 15%). Effective yield of isolated **48** based on recovered starting material: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.74 (d, *J*(H,H) = 1.1 Hz, 1H), 7.44–7.30 (m, 5H), 5.42 (s, 1H), 3.45 (ddd, *J*(H,H) = 16.2, 9.4, 2.8 Hz, 1H), 3.39–3.30 (m, 1H), 2.90 (dd, *J*(H,H) = 18.4, 6.6 Hz, 1H), 2.60 (dt, *J*(H,H) = 12.8, 9.1 Hz, 1H), 2.30 (dd, *J*(H,H) = 18.4, 2.8 Hz, 1H), 1.51 (ddd, *J*(H,H) = 12.9, 9.8, 7.5 Hz, 1H), 1.07–0.84 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.27, 199.58, 177.17, 135.67, 130.73, 128.58, 128.40, 128.26, 67.96, 62.93, 42.60, 39.27, 29.32, 17.95, 17.85, 12.29. HRMS (ESI): *m/z* calcd for $C_{24}H_{35}O_3Si$: 399.2355 [$M + H^+$]; found: 399.2328.

((1S,2R,3aR)-5-oxo-6-(thiophen-3-yl)-1-((triisopropylsilyl)oxy)-1,2,3,3a,4,5-hexahydropentalene-2-carbaldehyde (49): Flash column chromatography on silica gel (hexane/tetrahydrofuran, 95:5) of the residue afforded aldehyde **49** (colorless oil, 113.3 mg, 35%) along with recovery of unreacted starting material **42** (48%). Treatment of thus-recovered material under identical conditions afforded an additional 40.2 mg of **49**. Total yield of **49**: 153.5 mg (83% based on recovered starting material). ^{1}H NMR (300 MHz, chloroform-*d*) δ = 9.72 (s, 1H), 7.87–7.67 (m, 1H), 7.35 (d, *J* = 2.4 Hz, 2H), 5.53 (s, 1H), 3.57–3.22 (m, 2H), 2.88 (dd, *J* = 18.3, 6.6 Hz, 1H), 2.60 (dt, *J* = 12.8, 9.1 Hz, 1H), 2.27 (dd, *J* = 18.4, 2.9 Hz, 1H), 1.51–1.39 (m, 1H), 1.15–0.87 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.6, 200.0, 175.7, 131.2, 130.7, 127.5, 125.8, 125.5, 68.7, 63.2, 42.9, 39.7, 29.78, 18.4, 12.8. HRMS (ESI): *m/z* calcd for $C_{22}H_{33}O_3SSi$ [M + H] +: 405.1920 [$M + H^+$]; found: 405.1902.

(1S,2R,3aR)-6-(3-chloropropyl)-5-oxo-1-((triisopropylsilyl)oxy)-1,2,3,3a,4,5-hexahydropentalene-2-carbaldehyde (50): Flash column chromatography on silica gel (hexane:tetrahydrofuran, 95:5) of the residue afforded the aldehyde **50** (colorless oil, 134.1 mg, 42%) along with recovery of unreacted starting **43** (45%). Treatment of thus recovered material under identical conditions afforded an additional 67.5 mg of **50**. Total yield of **50** 201.6 mg (87% based on recovered starting material). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.75 (s, 1H), 5.30 (s, 1H), 3.53 (dt, *J* = 11.1, 5.6 Hz, 1H), 3.39–3.25 (m, 3H), 2.73 (dd, *J* = 18.4, 6.5 Hz, 1H), 2.53–2.33 (m, 3H), 2.13 (dd, *J* = 18.5, 2.6 Hz, 1H), 2.01–1.81 (m, 2H), 1.45 (ddd, *J* = 13.0, 9.6, 7.2 Hz, 1H), 1.07 (dd, *J* = 8.9, 5.8 Hz, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.8, 199.5, 178.3, 134.8, 70.7, 55.4, 44.6, 42.3, 39.6, 32.4, 30.0, 21.5, 18.0, 12.3. HRMS (ESI): *m/z* calcd for $C_{21}H_{36}O_3SiCl$ [M + H] +: 399.2122 [$M + H^+$]; found: 399.2140.

Sequential chemoselective deprotection of 46/oxidation to 48: Adduct **46** (1 mmol) was added to a solution of AcOH/MeOH/H_2O (v/v: 3.5:6:1.5; 11 ml) and the mixture was stirred at room temperature until disappearance of the starting material. MeOH was removed and CH_2Cl_2 was added. Then, the combined organic layers were washed by 1 M NaOH (2×10 ml), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 19:1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.49–7.30 (m, 5H), 5.03 (s, 1H), 3.60 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.42 (dd, *J* = 10.6, 7.7 Hz, 2H), 2.87 (dd, *J* = 18.3, 6.6 Hz, 1H), 2.58 (d, *J* = 7.3 Hz, 1H), 2.49 (dd, *J* = 12.4, 9.0 Hz, 1H), 2.22 (dd, *J* = 18.6, 3.1 Hz, 1H), 0.96 (d, 22H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.26, 180.23, 135.11, 131.28, 128.07, 70.55, 64.45, 52.58, 43.09, 39.07, 31.55, 17.98, 12.36. HRMS (ESI): *m/z* calcd for $C_{24}H_{37}O_3Si$ [M+H]+: 401.2512 [M+H$^+$]; found: 401.2495. To a solution of the resulting material (200 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added Molecular Sieves (0.4 mg) and the mixture was stirred at 0 °C for 5 min. Pyridinium chlorochromate (PCC, 185 mg, 0.85 mmol) was added in portions and after stirring the reaction mixture at room temperature for 4 h, diethyl ether (5 mL) was added and the mixture was stirred for an additional 30 min. The solid precipitate was filtered through a pad of silica gel and celite, washed several times with diethyl ether, dried over $MgSO_4$ and concentrated. The crude material was purified by silica gel chromatography to give aldehyde **48** with identical physical and spectroscopic data as the product obtained above from hydrolysis of **36**.

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Keywords: aldol reaction · enynes · organocatalysis · Pauson–Khand · propargylic alcohols

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Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Brønsted Base Catalyzed Michael Reactions: α′-Hydroxy Enones as Key Enoate Equivalent

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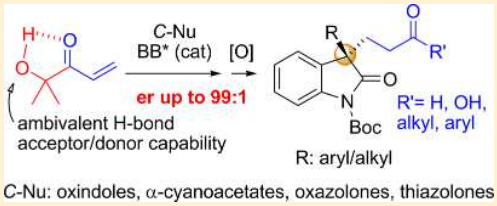
Supporting Information

ABSTRACT: Catalytic and asymmetric Michael reactions constitute very powerful tools for the construction of new C−C bonds in synthesis, but most of the reports claiming high selectivity are limited to some specific combinations of nucleophile/electrophile compound types, and only few successful methods deal with the generation of all-carbon quaternary stereocenters. A contribution to solve this gap is presented here based on chiral bifunctional Brønsted base (BB) catalysis and the use of α′-oxy enones as enabling Michael acceptors with ambivalent H-bond acceptor/donor character, a yet unreported design element for bidentate enoate equivalents. It is found that the Michael addition of a range of enolizable carbonyl compounds that have previously demonstrated challenging (i.e., α-substituted 2-oxindoles, cyanoesters, oxazolones, thiazolones, and azlactones) to α′-oxy enones can afford the corresponding tetrasubstituted carbon stereocenters in high diastereo- and enantioselectivity in the presence of standard BB catalysts. Experiments show that the α′-oxy ketone moiety plays a key role in the above realizations, as parallel reactions under identical conditions but using the parent α,β-unsaturated ketones or esters instead proceed sluggish and/or with poor stereoselectivity. A series of trivial chemical manipulations of the ketol moiety in adducts can produce the corresponding carboxy, aldehyde, and ketone compounds under very mild conditions, giving access to a variety of enantioenriched densely functionalized building blocks containing a fully substituted carbon stereocenter. A computational investigation to rationalize the mode of substrate activation and the reaction stereochemistry is also provided, and the proposed models are compared with related systems in the literature.



INTRODUCTION

Catalytic asymmetric conjugate addition reactions account as one of the most useful and atom economic approaches for the construction of new C−C and C−X bonds stereoselectively.[1] Major advances in the field have been triggered by the design and discovery of new chiral catalysts, both metal catalysts and organocatalysts, often in conjunction with the development of appropriate Michael acceptor templates.[2] The templates not only should provide gained chemical versatility to the resulting conjugate addition adducts, but also should contribute to attain optimal performance by the intervening catalyst in terms of reactivity and stereoselectivity. Ideally, strongly biased achiral templates may override otherwise observed substrate-dependent catalyst behavior, thus attenuating undesired fluctuations on the catalyst efficiency. This aid from properly design templates may result instrumental when difficult transformations, such as the enantioselective generation of tetrasubstituted carbon stereocenters, are pursued.

Among several categories of Michael acceptors, α,β-unsaturated carbonyl compounds are of prime synthetic significance. Adducts resulting from the conjugate addition of a nucleophilic reagent to α,β-unsaturated aldehydes, ketones, or carboxylic acid derivatives have all found a myriad of applications. In particular, certain carboxylic acid derivatives may afterward be converted into the corresponding aldehyde or ketone derivatives smoothly, making the former very versatile compounds. However, while both the addition reactions to α,β-unsaturated aldehydes and to ketones are well suited for iminium ion activation catalysis,[3] conjugate addition to the corresponding carboxylic acids and their derivatives is not. In this latter case, the most common activation mechanism relies upon coordination of the carbonyl group of the α,β-unsaturated carboxylic acid derivative to a Lewis acid (metal catalysis) or a H-bond donor species (organocatalysis). In this context, several two-point binding enoyl templates bearing an additional coordinating site (X, Figure 1a) tethered to the enoyl system have been developed. Compared with monodentate templates, which may lead to two degenerate C═O···metal complex geometries, thus complicating stereocontrol, bidentate templates can form chelates upon coordination to the metal as key organizational/activation element.[4] Similarly, bidentate enoyl

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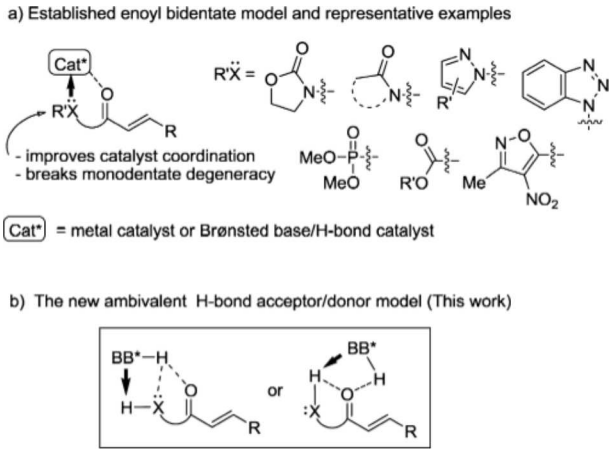


Figure 1. Bidentate enoyl templates for asymmetric catalysis: (a) previously established and (b) the new proposal. (BB* = chiral Brønsted base.)

templates may perform superiorly in conjugate addition reactions triggered by bifunctional Brønsted base–H-bond catalysts, because of the likely occurrence of double H-bond interactions between the substrate and the catalyst (Figure 1a).[1,5] This type of Brønsted base catalysis has emerged as very advantageous, not only because many Brønsted bases (BB) are commercially available and/or readily accessible, but also because the pronucleophilic reagent (NuH) does not generally need to be preactivated in a separate step.[6] However, successful BB-catalyzed enantioselective *C*–*C* bond forming conjugate addition reactions are often limited to certain inherently reactive nucleophiles (particularly 1,3-dicarbonyl compounds) and/or electrophiles (particularly nitroalkenes),[7] while in many other instances, α,β-unsaturated esters being a notable example, sluggish reactivity or poor enantiocontrol is achieved. This situation becomes more problematic when generation of all-carbon quaternary stereocenters is pursued.[8] Both reactivity attenuation by steric constraints and difficulties in controlling face selectivity in prostereogenic trisubstituted trigonal centers make this goal to be a hot topic yet.

In this study, we describe a new enoyl template model for asymmetric organocatalysis in which the bidentate substrate might engage as either H-bond donor or acceptor or both (ambivalency) during activation by the bifunctional catalyst (Figure 1b). As representatives of such a model, we show that α'-hydroxy enones perform exceedingly well in the Brønsted base-catalyzed asymmetric conjugate addition of a range of soft *C*-nucleophiles leading to tetrasubstituted carbon stereocenters in very high enantioselectivity. The chemical versatility of thus obtained adducts is also illustrated and a theoretical interpretation of the results provided.

■ RESULTS AND DISCUSSION

Background and Working Hypothesis. While being a prominent synthetic operation toward 1,5-dicarbonyl frameworks, successful catalytic and asymmetric methods for the constructive assembly of all-carbon quaternary centers from monodentate α,β-enones are usually restricted to 1,3-dicarbonyl substrates and related active pronucleophiles. In this context, metal-catalyzed[9] enantioselective conjugate addition of 1,3-diketones, β-ketoesters, and α-aryl cyanoesters to acrolein or vinyl ketones (mainly methyl vinyl ketone) as the Michael acceptor have been reported by the groups of Ito,[10] Shibasaki,[11] Sodeoka,[12] and Jacobsen,[13] among others.[9]

In concurrent efforts under metal-free conditions, chiral Brønsted base-catalyzed conjugate additions of enolizable carbonyl compounds have also been explored after the pioneering work by Wynberg and co-workers.[6,14] Deng and co-workers have reported conjugate additions of α-substituted β-dicarbonyl compounds and α-aryl cyanoacetates to acrolein or methyl vinyl ketone promoted by a bifunctional Cinchona based catalyst,[15,16] while Jørgensen and co-workers documented the reaction of cyclic β-keto esters with both acrolein and methyl vinyl ketone using a nonbiaryl atropisomeric Cinchona-based catalyst.[17] More recently, Rodriguez, Constantieux, and co-workers[18] extended the Brønsted base catalysis approach to cyclic β-ketoamides as nucleophiles against methyl vinyl ketone. Notwithstanding these achievements, the realization of BB-catalyzed asymmetric conjugate additions involving more reluctant substrate combinations, such as less reactive enolizable carbonyl compounds and acryloyl equivalents, remains challenging. Thus, while some ester surrogates have been applied to Brønsted base-catalyzed conjugate addition reactions,[5] to the best of our knowledge, only in three cases the generation of all-carbon quaternary centers has been documented. In a significant work, Dixon and Rigby[5m] described highly enantioselective conjugate additions of cyclic β-keto esters to naphthyl thioacrylate and *N*-acryloyl pyrrol, respectively, using a modified cinchona alkaloid as bifunctional Brønsted base catalyst. When acyclic keto esters were used as nucleophiles, yields and selectivity diminished, a limitation also noticed by Bartoli, Melchiorre and co-workers[5n] who used maleimides as competent Michael acceptors. Also, β,γ-unsaturated acyl phosphonates[5f] have been reported to be effective enoate surrogates against reactive pronucleophiles including azlactones and 1,3-dicarbonyl compounds.

In the early 1980s Heathcock and co-workers demonstrated that α'-hydroxy ketones are convenient enoate equivalents in the context of aldol addition reactions,[19] since oxidative cleavage of the ketol moiety in the corresponding aldol adducts affords β-hydroxy carboxylic acids. Focused on this observation, research from these laboratories has led to the development of metal-catalyzed conjugate addition and cycloaddition reactions of simple α'-hydroxy enones,[20] as well as Brønsted acid-catalyzed Diels–Alder reactions of chiral α'-hydroxy enones,[21,22] methods that provide, after cleavage of the ketol moiety, products in the carboxylic acid oxidation state. In these developments, the ability of the ketol moiety for both 1,4-metal and 1,4-proton binding (Figure 2a)[23] revealed to be critical for success. Based on these precedents, we hypothesized that the H-bonding ability of the ketol moiety in α'-hydroxy enones may decisively influence reactions initiated by a proton-transfer event, such as the BB-catalyzed Michael reactions (Figure 2b).[24] Specifically, the substrate α'-hydroxy enone might participate as a two-point H-bond donor/acceptor (DA-model) or acceptor/acceptor (AA-model) partner in the transition state, a diverting design element that is lacking in previous enoyl templates.[5] To the best of our knowledge, α'-hydroxy enones have not been studied within the context of organocatalytic asymmetric bond-construction processes.[25,26]

Preparation of α'-Hydroxy Enones. The α-oxy enones **1** and **3** were readily prepared[27] from the addition of lithium methoxyallene **6** to acetone and 1,3-diphenylacetone **8**, respectively, and subsequent smooth one-pot hydrolysis of the resulting intermediates, as shown in Scheme 1. Alter-

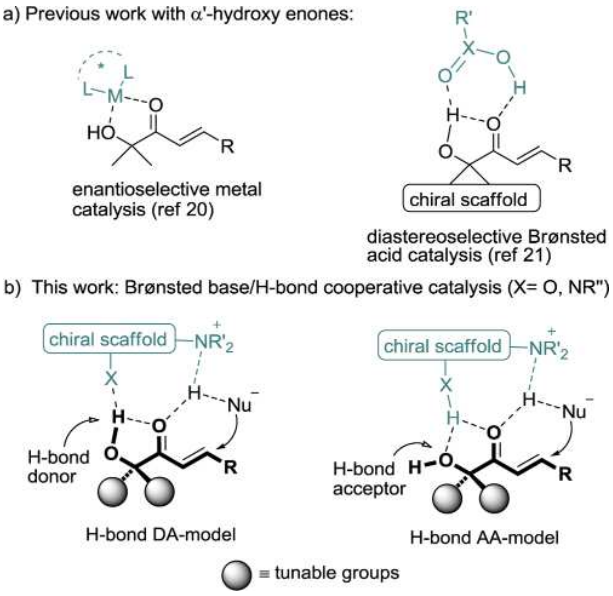
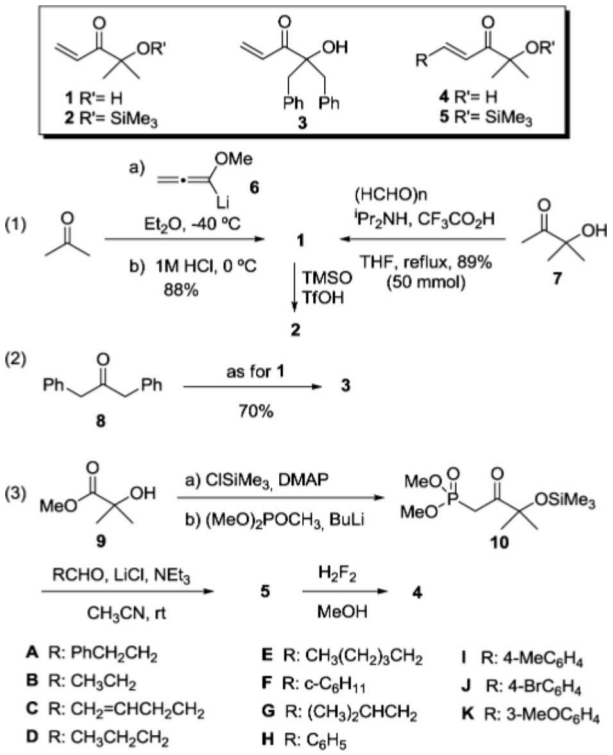


Figure 2. Two point binding α′-hydroxy enone templates for asymmetric catalysis.

Scheme 1. Preparation of α′-Hydroxy Enones[a]



[a]TMSO: *N*-(trimethylsilyl)-oxazolidin-**2**-one.

natively, enone **1** could also be prepared by the method of Connell et al.,[28] starting from the commercially available α-hydroxy ketone **7**. In both cases, compound **1** was obtained in yields between the range 80−90% at 50 mmol scale. Preparation of **2** from **1** is straightforward and quantitative by silylation with commercial *N*-trimethylsilyl oxazolidin-2-one (TMSO). For β-substituted enones **5**, the classical Horner−Wadsworth−Emmons olefination protocol from the β-keto phosphonate **10** was used. This phosphonate was in its turn prepared from commercial hydroxyester **9**.[29] Likewise, for β-aryl substituted α-hydroxy enones **4** (R = Ar), an aldol condensation of **7** with benzaldehydes may also be employed.[27]

Conjugate Additions of 3-Substituted Oxindoles. To assess the reactivity profile of these α′-hydroxy enones in Brønsted base catalysis, our study was initiated with the reaction of α′-hydroxy enone **1** and 3-substituted oxindoles. The oxindole structural motif is widely present within natural and synthetic bioactive molecules;[30] however, Brønsted base promoted reaction of 3-substituted oxindoles with alkyl vinyl ketones has met with limited success so far.[31,32] For example, it has been reported that methyl vinyl ketone (MVK),[31a,b] ethyl vinyl ketone,[31a] and phenyl vinyl ketone[31a] all provided enantiomeric excess (ee) values in the range of 60−70% in the reactions with 3-aryl oxindoles; the reactions with 3-methyl-, 3-isobutyl-, and 3-allyl oxindoles proceed with even lower ee's (of about 55%).[31c] In addressing these issues, and after screening several Brønsted base catalysts,[27] we found that the above addition reactions using **1**, conducted in the presence of 10 mol % $(DHQD)_2PYR$ (**C1**), afforded the corresponding adducts **12** in excellent yields and enantioselectivities. As the data in Table 1 show, under these conditions (−50 °C in $CHCl_3$ as solvent), oxindoles **11A−F** bearing 3-aryl substituents with either electron donating or electron withdrawing groups are tolerated with almost equal efficiency. Oxindoles with substitution at the aromatic ring also provided adducts with excellent chemical and stereochemical results. Likewise, the 3-methyl oxindoles **11Ga**, **11Gc**, and **11Gd**, which are valuable precursors of natural products, vide infra, were competent reaction partners to give the respective adducts **12Ga**, **12Gc**, and **12Gd** in good yields and enantioselectivities, typically 90% ee. Nevertheless, attempts to further expand this reaction to oxindoles bearing larger alkyl chains at the *C*3 position failed. Oxindoles **11H**, **11I**, **11J**, **11K**, and **11M** all provided the corresponding adducts **12** with poor enantioselectivity, typically 50% ee. While these results seem to be quite common for reactions involving 3-alkyl substituted oxindoles, very few attempts to address this deficiency have resulted with success.[32] In fact, few catalytic systems work well for both aryl- and alkyl-substituted oxindoles.[32d] Given the ready availability of α′-hydroxy enones, we focused on the α′-disubstitution pattern as an additional element for steric tuning. We were pleased to observe that the enantioselectivity was notably increased, typically from 50% ee up to 90% ee, by using α′-hydroxy enone **3**. As the results in Table 1 show, the reactions were tolerant with oxindoles bearing short, large, and ramified alkyl chains as well as alkyl chains with functional groups. These results are of special interest in that diverse functionality may be generated from a single common adduct. Thus, treatment of adducts **12Aa** and **12Gc** with $NaIO_4$ in $MeOH/H_2O$ provided the corresponding carboxylic acids **14** in yields of 98% and 94%, respectively, along with acetone as the only organic side product formed, Scheme 2. Alternatively, oxidative cleavage of adducts **13La** and **13Oa**, by treatment with periodic acid in this case, led to acids **14La** and **14Oa** in 87% and 90% yield, along with dibenzyl ketone which could be recovered and reused. On the other hand, the addition of the corresponding Grignard reagent or reduction of the carbonyl group followed by diol cleavage as above furnished the methyl and aryl ketones **15**/**16** and the aldehyde **17**, respectively, in good yields. Importantly, during the above manipulations, configurational integrity of

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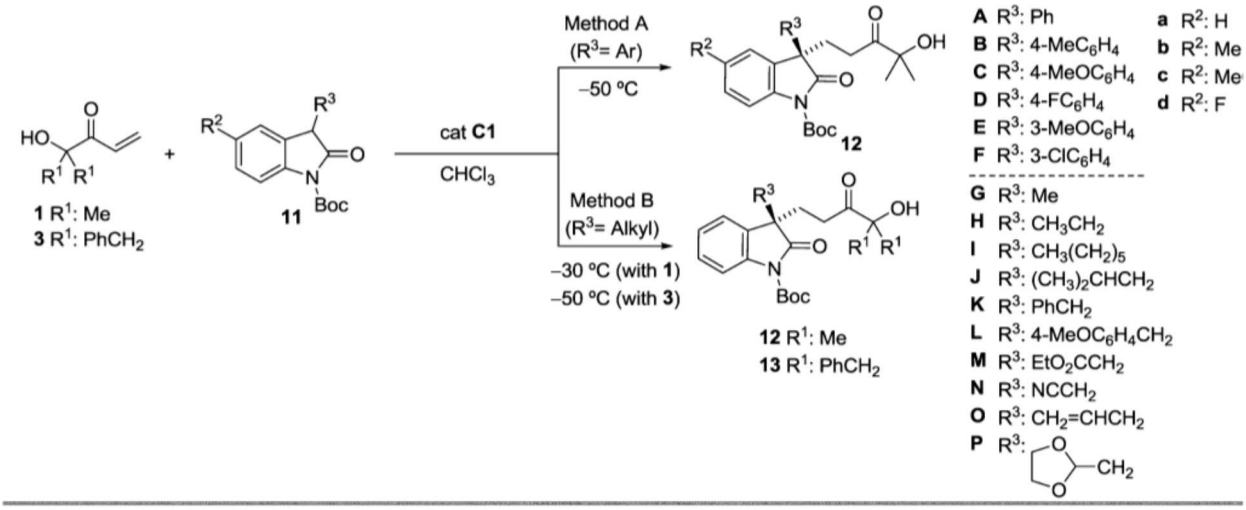
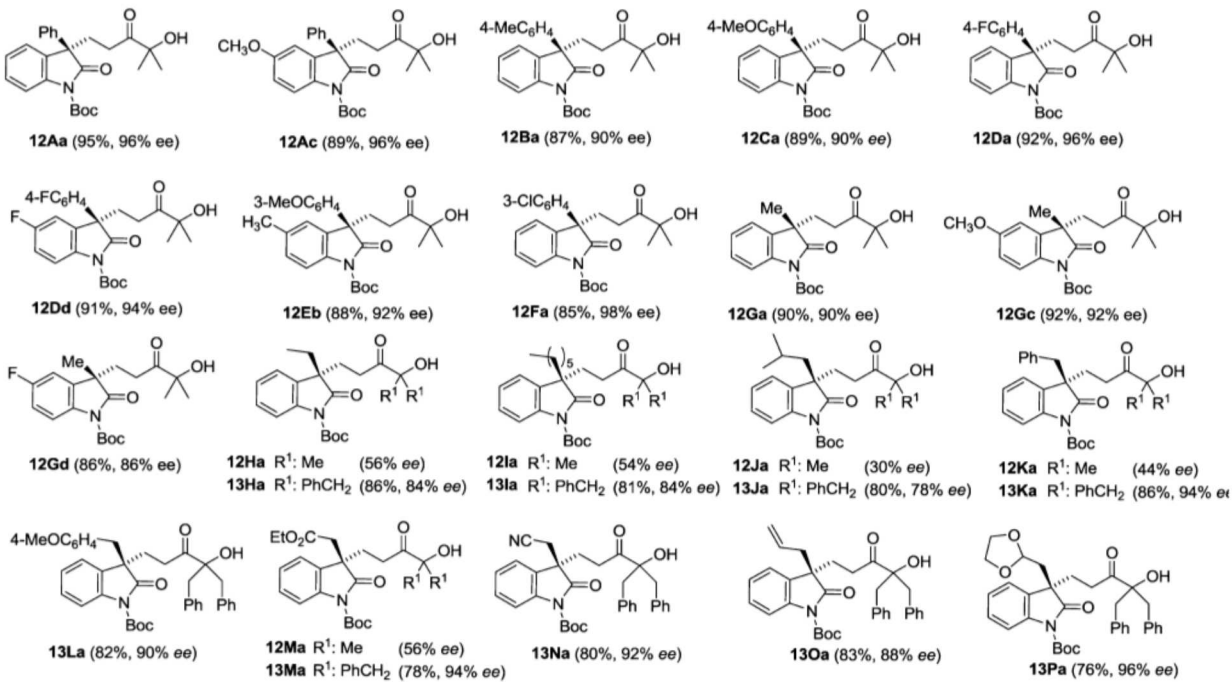
Table 1. Conjugate Additions of 3-Substituted Oxindoles to α'-Hydroxy Enones 1 and 3[a]





[a]The reactions were generally performed on a 0.30 mmol (for R^3 = Ar or Me) or 0.1 mmol (for R^3 = alkyl) scale in $CHCl_3$ (1.5 mL/mmol) using enone **1** (1.5 equiv) or **3** (3 equiv) and catalyst **C1** (10 mol % for **1**; 30 mol % for **3**). Yield of isolated product after chromatography. ee determined by HPLC analysis on chiral stationary phases.

newly generated tetrasubstituted stereogenic carbons in adducts was untouched as determined for aldehyde **17Aa** (94% ee) and acid **14Gc** (90% ee as determined in esermethole, vide infra). It is worth noting that the present method allows preparation of ketones such as **15Ga** and **16Ga**, formally derived from the less sterically demanding methyl-sustituted oxindoles, with enantioselectivities among the best reported until now.[31]

In addition, as far as we know, no asymmetric and catalytic conjugate addition of 3-substituted oxindoles to acrylate esters or their surrogates have been developed yet.[30,33] Our method may serve to remediate this deficiency by providing building blocks that can be easily transformed into biologically active compounds such as (−)-esermethole, Scheme 3,[34] an advanced intermediate for the synthesis of (−)-physostigmine.[35] Thus, Curtius rearrangement of carboxylic acid **14Gc** afforded carbamate **18**, which upon treatment with $LiAlH_4$ underwent reductive cyclization to (−)-esermethole of 90% ee.

The key role played by the $(CH_3)_2COH$ fragment of the template as a traceless activating group in the above reactions was clear from competitive experiments involving both **1** and methyl vinyl ketone (MVK), a simple enone lacking any group for additional H-bond coordination. Thus, when the reaction of oxindole **11Aa** was carried out with a 1:1 mixture of **1** and MVK in the presence of **C1** (10 mol %) at −50 °C, **12Aa** was the exclusive addition product obtained, without detecting any product from the addition reaction of **11Aa** to MVK. In

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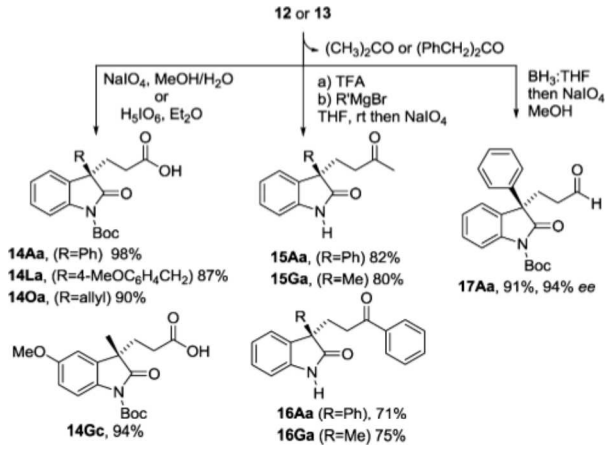
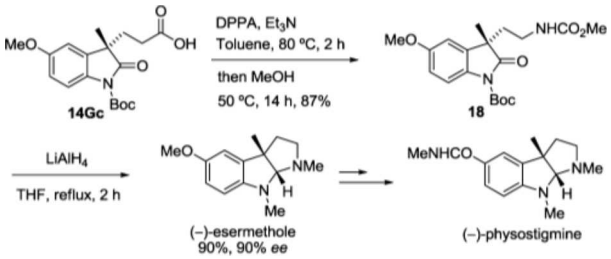
Scheme 2. Ketol Scission in Adducts 12



Scheme 3. Short Enantioselective Synthesis of (−)-Esermethole



another experiment, the reaction between oxindole **11Aa** and MVK run at −30 °C in the presence of **C1** led, after 48 h, to 35% conversion only, with an isolated product of 50% ee.

Conjugate Additions of Cyanoacetates. Encouraged by these results, we next investigated the reaction of α′-hydroxy enones with α-substituted cyanoacetates.[36,37] The problems experienced in achieving efficient chirality transfer in metal catalyzed conjugate additions with these pronucleophiles have been ascribed to the fact that cyanoacetates are incapable of two-point binding.[38] We reasoned that the capacity of α′-hydroxy enones for two-point binding (Figure 2) may ameliorate this deficiency. Indeed, we found that **1** was effective in the Brønsted base catalyzed reaction with not only α-aryl, but also α-alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates,[37] particularly against alkyl vinyl ketones.[37a] After evaluation of a survey of different Brønsted bases, including **C1**, the squaramide family of catalysts pioneered by Rawal and co-workers[39] probed the most effective in these instances. Among them, catalyst **C2**[40] (Figure 3) resulted optimal for the reaction between **1** and a range of both α-aryl and α-alkyl *tert*-butyl cyanoacetates **19**. In general, the reaction with α-aryl cyanoacetates **19a−d** was performed at room temperature using 3 equiv of enone **1** to afford, after 1 h, adducts **20a−d** with excellent yields independently of the nature of the aromatic ring substitution. In contrast, most α-alkyl cyanoacetates tested showed decreased reactivity with reaction times of about 120 h required for complete conversion under the above conditions. However, by using 3-fold excess of the latter and rising the temperature to about 50 °C, full conversions of products **19e−k** were attained within about 30 h

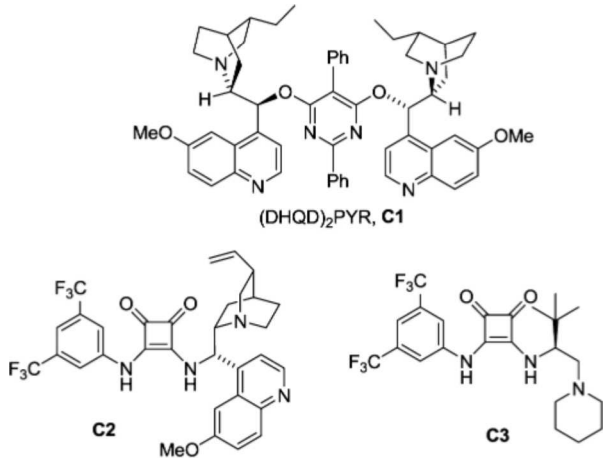


Figure 3. Catalysts employed within this work.

or less, with very high yields of isolated product and essentially perfect enantioselectivity obtained. Again, chemical manipulation of the ketol unit in adducts **20** using simple Grignard technology and/or reduction/oxidation protocols, as in Scheme 2, provided a straightforward entry to the corresponding carboxylic acids **21**, aldehydes **22**, and ketones **23**/**24**. Comparison of optical rotation value of product **23e** (see Table 2, footnote b) with literature data[10] served to set the configuration of the products and hence the stereochemical course of the above catalytic reactions. As noted above enantioselective synthesis of products like **21−24** through direct catalytic Michael reactions remains challenging. Once more, the design enone **1** demonstrated to be instrumental in achieving these levels of reactivity and selectivity. For example, when an equimolar mixture of cyanoacetate **19a**, enone **1**, and MVK was stirred at 20 °C for 30 min in the presence of 10 mol % **C2**, a 12:1 mixture of **20a** and the addition adduct from MVK, respectively, was obtained. Likewise, parallel reactions of other typical Michael acceptor templates, i.e. *N*-acryloyl oxazolidinone or *N*-acryloyl pyrazole, with cyanoacetate **19e** under the above conditions were sluggish (less than 55% conversion after 120 h at room temperature for the two cases).

Conjugate Additions of Heteroatom-Bearing Soft Carbon Nucleophiles. Besides all-carbon quaternary stereocenters, tetrasubstituted stereogenic carbons bearing a sulfur, oxygen or nitrogen heteroatom are also interesting yet difficult products to obtain as single enantiomers. Therefore, we decided to investigate the capacity of our template model to participate in Brønsted base-catalyzed conjugate additions of several heteroatom-bearing soft carbon nucleophiles. For this study 5*H*-thiazol-4-ones **25**[41] and 5*H*-oxazol-4-ones **26**[42,43] were initially selected and we found that reaction of thiazolone **25a** and oxazolone **26a** with α′-hydroxy enone **1** did proceed in the presence of several Brønsted bases, including **C1** and **C2**, but with very poor enantioselectivity. Further exploration led us to examine the modified enoyl template **2**, prepared by simple silylation of the hydroxyl group in enone **1**. To our pleasure, the reaction of 5*H*-thiazol-4-ones **25** and enone **2** catalyzed by **C2** in dichloromethane at −20 °C provided, after desilylation of the resulting intermediates, the corresponding addition products **27** in good yields and ee's up to 98%. The parent 5*H*-oxazol-4-ones **26** participated with equal chemical efficiency in the reaction with enone **2**. For example, under the above conditions, **26a** provided **28a** in 85% yield albeit in 73% ee.

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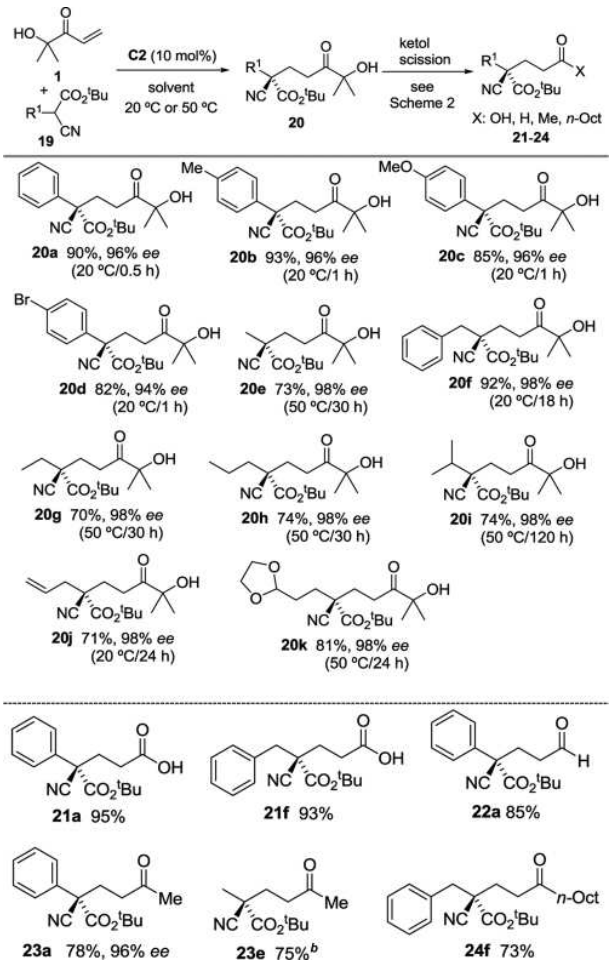
Table 2. Conjugate Addition of α-Substituted tert-Butyl Cyanoacetates 19 to α′-Hydroxy Enone 1 Promoted by C2[a]



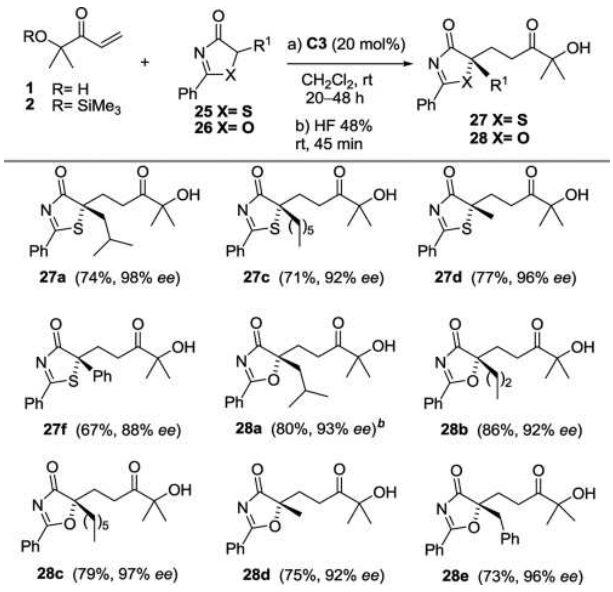
[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 at 20 °C or in $CHCl_3$ at 50 °C. Yield of isolated major isomer after chromatography. ee determined by HPLC. [b]$[\alpha]_D^{22}$ = +3.9 (*c* = 1, $CHCl_3$); lit.[10] $[\alpha]_D^{20}$= +2.7 (*c* = 5, $CHCl_3$, 81% ee).

This result was further improved by using catalyst **C3**[44] (Figure 3), and the reaction between **2** and oxazolone **26a** performed at room temperature afforded, after desilylation of the resulting intermediate, adduct **28a** in 80% yield and 93% ee.

In general, excellent yields and enantioselectivities were achieved for a survey of thiazolones and oxazolones bearing either short, large, or ramified alkyl chains at the heterocyclic ring (Table 3). While these reactions were typically carried out in the presence of 20 mol % of catalyst, the catalyst loading could be reduced to 10 mol % provided the reactions were carried out at higher temperature. For example, products **28a** and **28b** were obtained in essentially same chemical yields and stereoselectivities as above when the corresponding reactions were performed in $CHCl_3$ at 40 °C during 30−40 h. Clearly, these results show that the α′−hydroxy enone template may be easily modified to better adapt to different substrate/catalyst combinations.

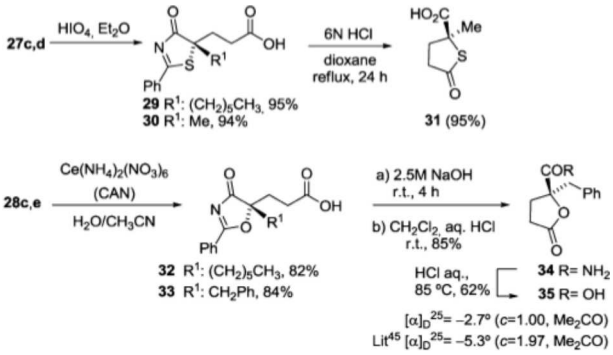
Transformation of adducts **27** and **28** into the corresponding carboxylic acids **29**, **30**, **32**, and **33**, Scheme 4, was easily achieved by treatment with periodic acid in the case of thiazolone adducts **27**, and with cerium ammonium nitrate

Table 3. Conjugate Addition of 5H-Thiazolones 25 and 5H-Oxazolones 26 to α′-Silyloxy Enone 2[a]



[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.9 mL) using 1.5 equiv of enone **2**. For thiazolones **25**, reactions were conducted at −20 °C and for oxazolones **26** at rt. Yields after chromatography. ee determined by HPLC. [b]73% ee from catalyst **C2**.

Scheme 4. Elaboration of Thiazolone and Oxazolone Adducts 27 and 28



(CAN) in the case of oxazolones **28**. Subsequent transformation of adduct **30** into the thiolactone **31**, as well as adduct **33** into the lactone derivative **34**, by simple ring opening under mild acid and/or basic conditions, illustrates the utility of the method. In addition, formation of known lactone **35**[45] from **34** served to establish the stereochemical course of the reactions. It should also be noted that both **25a** and **26a** upon treatment with either methyl acrylate or *tert*-butyl acrylate under the above conditions did not provided the corresponding Michael adducts.

Further exploration of the broad scope of α-silyloxy enone **2** showed that α-substituted azlactones, 4*H*-oxazol-5-ones, also fit well. For example, Table 4, the reaction between azlactones **36** and enone **2** in the presence of the catalyst **C2** or **C3** led, after desilylation of the intermediate adducts, to the corresponding products **37** with good yields and ee's. In each case, reactions proceeded with high site selectivity and no products from

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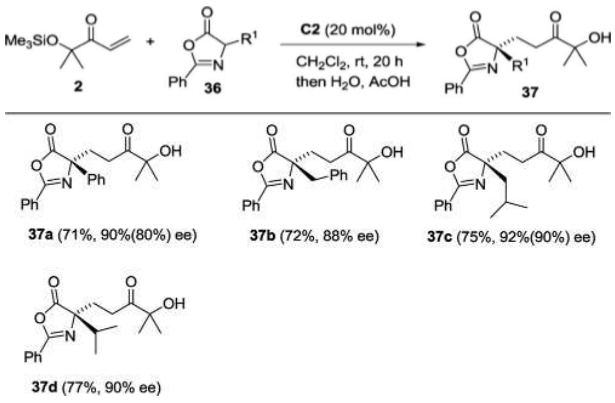
Table 4. Conjugate Addition of Azlactones[a]

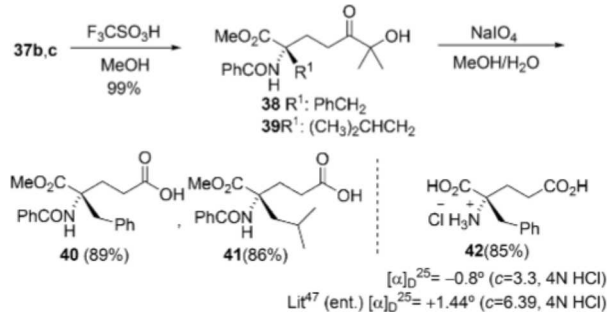


[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.6 mL) using 3.0 equiv of enone **2**. Yield of isolated products after chromatography. ee determined by HPLC. In parentheses are ee's from catalyst **C3** (10 mol %).

reaction at the C_2-position of the azlactone ring were observed.[46]

Elaboration of thus obtained azlactone adducts afforded useful building-blocks. For instance, Scheme 5, azlactone ring

Scheme 5. Elaboration of Adducts to α,α-Disubstituted Glutamic Acid Derivatives

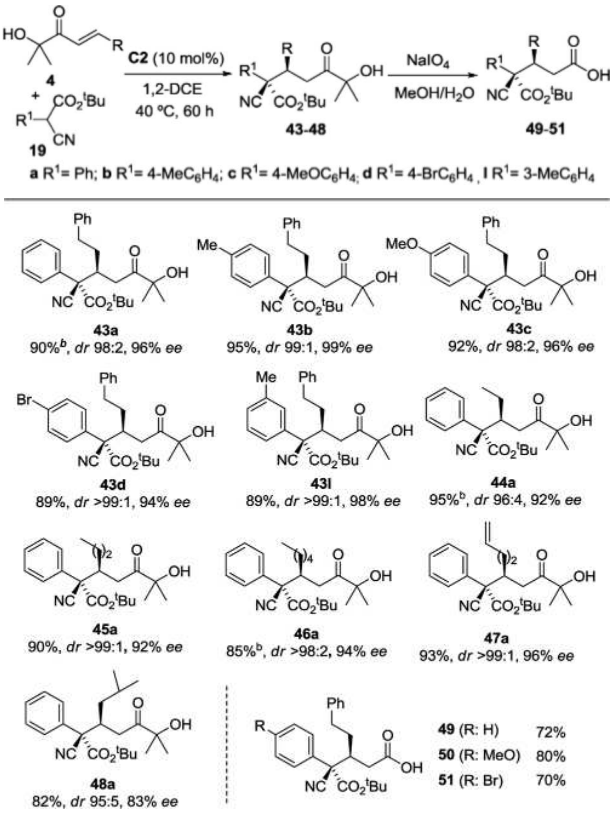


opening in **37b,c** to afford the corresponding compounds **38** and **39**, and subsequent ketol elaboration, provided acids **40** and **41**, respectively. The former was then transformed into the known glutamic acid derivative **42**[47] as a proof of the stereochemical course of the catalytic reaction.

Reactions with β-Substituted α-Oxy Enones: Generation of Adjacent Quaternary/Tertiary Stereocenters. Given the results attained with the α-oxy vinyl ketones **1** and **2**, we wondered whether this template model would be effective to generate a quaternary carbon adjacent to a tertiary stereogenic center, a synthetic task that generally presents added difficulties. To this end, we selected the reaction of α-substituted cyanoacetates owing to the inherent challenges associated with this kind of pronucleophiles, vide supra. In this context, Peters has recently addressed this issue and provided a solution to the case of reactions involving cyclic enones, that is, cyclohexenone, using metal catalysis.[38a] On the other hand, only one example of Michael reaction of α-substituted cyanoacetates with β-substituted alicyclic enones has been documented, based on salen complex catalysis.[38d]

It was gratifying to observe that α-aryl cyanoacetates **19a–d** and **19l** reacted with β-alkyl substituted α-hydroxy enones **4A–E** to furnish adducts **43–47** in good yields, Table 5. The reactions were carried out in 1,2-dichloroethane at 40 °C, and

Table 5. Conjugate Addition of Cyanoacetates to β-Substituted α-Hydroxy Enones[a]



[a]The reactions were performed on a 0.30 mmol scale in 1,2-DCE (1.2 mL) using 3.0 equiv of enone **4**, at 40 °C otherwise stated. Yield of isolated products after chromatography. ee determined by HPLC. dr determined by ^{1}H NMR or HPLC. [b]Reaction carried out at 50 °C.

generally essentially one diastereomer was produced in excellent enantiomeric excess. As exceptions, β-substituted enones **4F** and **4H**, bearing the cyclohexyl and phenyl groups, respectively, were ineffective under these conditions, while **4G** provided **48a** in good yield but diminished stereoselectivity. On the other hand, α-alkyl cyanoacetates were unreactive and did not provide the corresponding adducts. Despite these limitations, which, in their turn, confirm the difficulties associated with these problematic pronucleophiles, the method represents the first Michael addition of α-substituted cyanoacetates to β-alkyl enones catalyzed by a chiral Brønsted base, and confirms once more the excellent behavior of α'-hydroxy enones as Michael acceptors. In this respect, while no reaction was observed from **19a**, **19c**, and **19d** with methyl 5-phenylpent-2-enoate in the presence of **C2**, oxidative cleavage of **43a**, **43c**, and **43d** provided the desired carboxylic acids **49–51**. We also examined the **C2** catalyzed reaction between cyanoacetate **19a** and *trans*-3-nonen-2-one **52**, which lacks the α'-hydroxy group (Scheme 6). The reaction proceeded, but required 7 days to reach 95% of conversion and the product was formed as an 80:20 mixture of diastereomers with only modest enantioselectivity for the major isomer **53**. In sharp contrast, the reaction between **19a** and α'-hydroxy enone **4E**, as

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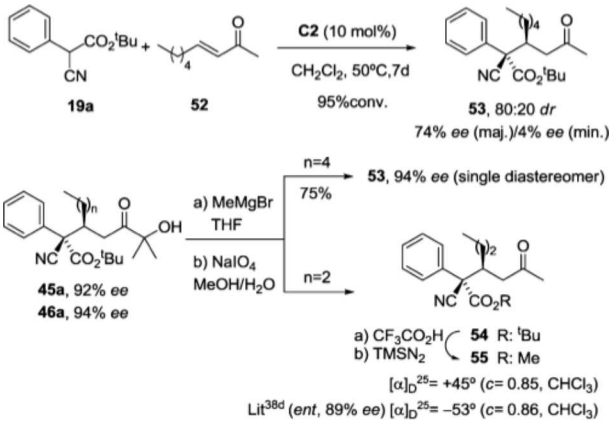
Scheme 6. Conjugate Addition of α-Substituted Cyanoacetates to Simple Enones and an Indirect Solution to the Low Inherent Stereoselectivity

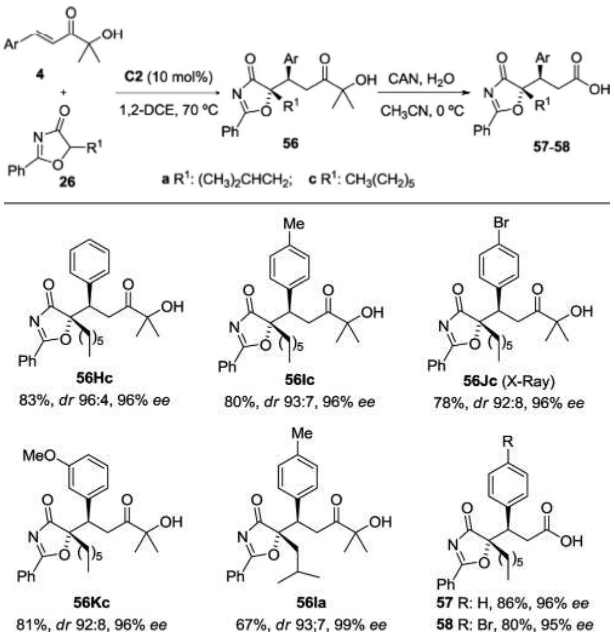


mentioned above, gave **46a** as essentially single diastereomer in 94% ee (Table 5), which enables an alternative and highly stereoselective entry to product **53** via usual alkylation and oxidative scission. Similarly, **45a** could be converted into the methyl ketone **54** and, upon subsequent transesterification, the corresponding methyl ester **55**, which exhibited essentially identical ^{1}H and ^{13}C NMR spectra to those reported in the literature,[38d] but opposite optical activity, thus confirming the stereochemical assignments for the adducts.

Oxazolones **26** also participated in the reaction with β-substituted enones **4** to give the corresponding α,α-disubstituted α-hydroxy acid precursors with an adjacent tertiary stereocenter, Table 6. However, in contrast to the case of cyanoacetates noted above, the reactions of oxazolones **26** worked well only with β-aryl enones to afford the corresponding addition products **56**. The reactions with β-alkyl enones were unproductive and the starting materials could be recovered unchanged. From these results, it is clear that for these types of substrate combinations leading to adjacent quaternary/tertiary stereocenters, there might be strong steric interactions that may justify the observed variability. Configuration of adduct **56Jc** was established by a single crystal X-ray analysis and that of the remaining adducts by assuming a uniform reaction mechanism. Additionally, conversion of **56** into the carboxylic acids **57** and **58** could be accomplished by using CAN as the optimum oxidant.

Computational Studies. With these experimental data in hand, it seemed clear that α'-oxy enones exhibit some unique reactivity as compared with ordinary enones, that is, MVK. Both higher reactivity and improved levels of enantioselectivity are observed in the BB-catalyzed reactions studied. Similarly, our experimental results indicate a distinct behavior of α'-oxy enones as compared with other typical enoyl templates previously reported for the BB-catalyzed enantioselective generation of quaternary stereogenic carbon centers. More specifically, the catalyst-controlled conjugate addition of α-substituted cyanoacetates is, as mentioned before, sluggish with the majority of Michael acceptors, while it works well with α'-oxy enones. With the aim to bring some light on such distinguishing behavior, we decided to study computationally[48] the case of the conjugate addition reactions of cyanoacetates. MVK and the two α'-oxy enones **1** and **59** were selected as the model Michael acceptors, and the relationship between their

Table 6. Conjugate Addition of Oxazolones to β-Substituted α-Hydroxy Enones[a]



[a]The reactions were performed at 70 °C on a 0.15 mmol scale in dichloroethane (0.45 mL) using 3.0 equiv of enone **4**. Yield of isolated products after chromatography. Diastereomeric ratios determined by ^{1}H NMR (300 MHz) on the crude reaction products and confirmed by HPLC. ee determined by HPLC analysis on chiral stationary phases (for compounds **57** and **58**, after derivatization to their methyl esters).

reactivity and structure was examined first. In agreement with our working hypothesis, calculations show that the intramolecular H-bond activation in **1** and **59** induces a change in a series of electronic parameters (Figure 4), explaining their higher reactivity in comparison with MVK. In particular, the electrophilicity index ω[49] for both **1**/**59** (2.0 eV) is higher than that for MVK (ω = 1.6 eV), which is consistent with the lower energy of LUMO for **1** and **59** (−1.9 eV) as compared with the LUMO of MVK (−1.5 eV), and also the more positive

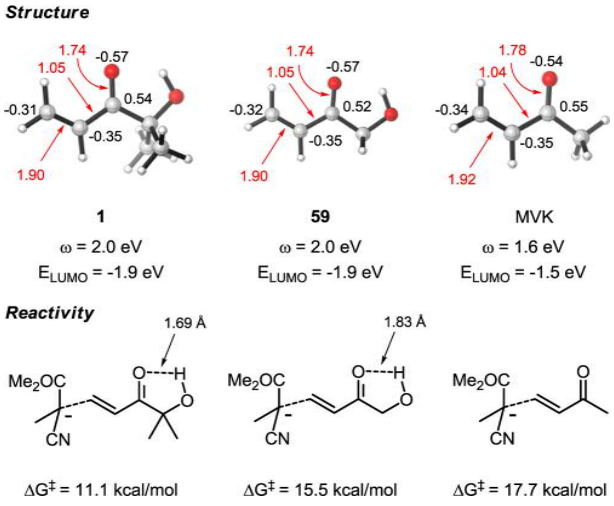


Figure 4. Structure−reactivity relationship.

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character of the β-carbon of **1** (NPA charge of −0.31) than the corresponding β-carbon of MVK (−0.34). These values correlate well with the Wiberg bond index for **1** (1.90) and MVK (1.92), respectively, indicating the diminished double bond character of the enone C═C bond in **1**.

Subsequently, the activation energy of the reaction of these three Michael acceptors with methyl α-methylcyanoacetate was computed. This barrier resulted significantly lower for α'-hydroxy enone **1** (11.1 kcal/mol) than for MVK (17.7 kcal/mol). On the other hand, although the electronic parameters of both α'-hydroxy enones **1** and **59** do not differ significantly from one another (see above), the reaction involving the latter presents an activation energy 4.4 kcal/mol higher than the reaction with **1**. This additional stabilization of the transition state (TS) for the reaction with **1** as compared with **59** is consistent with the shorter intramolecular hydrogen bond in the former case (1.69 vs 1.83 Å, Figure 1) and might be ascribed to a favorable Thorpe−Ingold effect[50] imparted by the two geminal methyl substituents in **1**.

The origin of the stereoselectivity in the **C2**-catalyzed reaction between hydroxy enone **1** and α-cyanoacetates was addressed next, and the first question to elucidate was the preferred H-bond pattern formed between the catalyst and both substrates in the TS corresponding to the *C*−*C* bond-forming step. In this respect, up to (at least) three different ternary complexes (**A**−**C**, Figure 5) have been proposed for

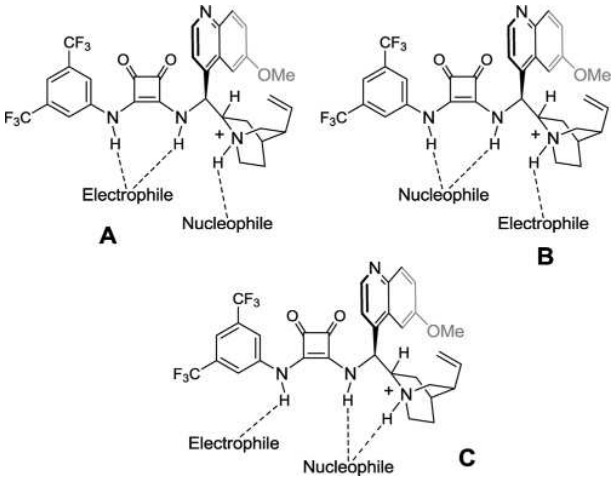

Figure 5. Three alternative substrate−catalyst combinations.

reactions involving noncovalent cooperative activation of the intervening nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)-tertiary amine catalyst.[51] Therefore, the question of whether or not a unified H-bond network model (**A**, **B**, **C**, other) could be applied to different reactions within this catalysis category seems to be still open and more data are desirable. In our case, we computed the reaction leading to adduct **20e** (Table 2), and despite much effort we were unable to find any plausible transition structure of type **B** among the several H-bond combinations studied.[52] From a look to the geometries of the resulting complexes, it seemed that once cyanoacetate is H-bonded to the catalyst there is not space available for the electrophile to interact with the same catalyst molecule. Thus, the structure closest to **B** we could find involves attack of the H-bonded cyanoacetate anion to the non complexed enone.[53] On the other hand, a single structure similar to model **C** was also found; however, it was predicted to be unrealistic due to its high activation energy.

In its turn, four feasible structures of type **A** (**TS-R$_1$**, **TS-S$_1$**, **TS-R$_2$**, **TS-S$_2$**, Figure 6) were located, in which the α'-hydroxy

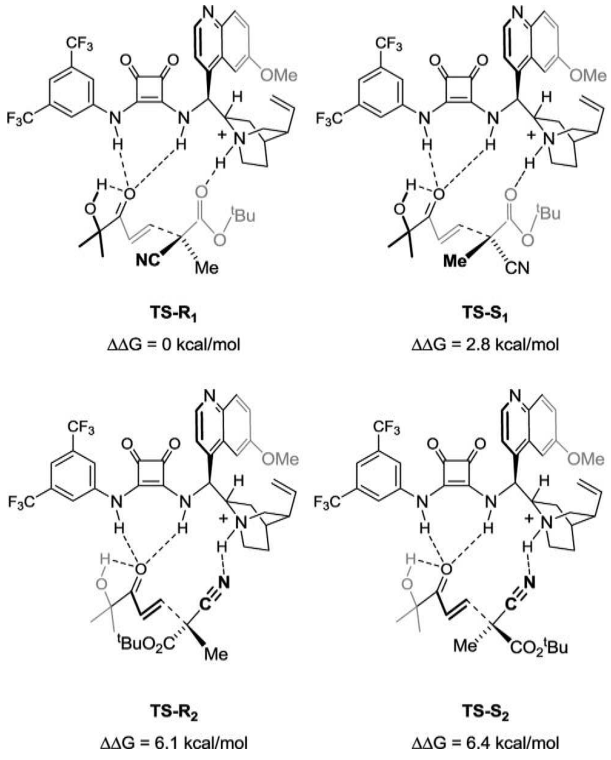

Figure 6. Located TSs for the catalytic addition reaction.

enone carbonyl is double H-bonded to the squaramide NH groups, while the protonated quinuclidine NH$^+$ might bind to either the CN or the ester group of the cyanoacetate moiety. **TS-R$_1$** is the lowest in energy and correctly explains the formation of the major isomer observed experimentally.[54] The next most feasible structure is **TS-S$_1$**. Interestingly, in both cases, the $CO_2{}^tBu$ is involved in H-bonding with the catalyst NH$^+$ moiety, while the methyl (**TS-S$_1$**) and the cyano group (**TS-R$_1$**) are, respectively, almost eclipsed with the enone double bond. The energy difference between these two structures is 2.8 kcal/mol at the M06-2X/6-311+G** computational level,[55] with the preference of **TS-R$_1$** being attributable to a larger destabilizing effect of pseudoeclipsed methyl (dihedral angle 21.9°) than pseudoeclipsed cyano (dihedral angle 33.5°). The remaining two structures, **TS-R$_2$** and **TS-S$_2$**, both involving a NH$^+$···NC interaction, lye 6.1 and 6.4 kcal/mol higher in energy than **TS-R$_1$**, respectively. From these results, some tentative conclusions may be drafted: (i) in the studied catalytic reactions, the ketol moiety of the acceptor α'-hydroxy enone plays a key role in both decreasing reaction energy barriers; (ii) among the several possible H-bond combinations for the ternary nucleophile−catalyst−electrophile complex, type **A**[51a−e] is preferred, with the squaramide group interacting with the α'-hydroxy enone (electrophile activation), and the protonated quinuclidine interacting with the cyanoacetate anion (nucleophile activation); (iii) given previous data in the literature in favor of models of type **B**[51f−k] and **C**[51l] for related catalytic reactions, we believe that a unified model cannot accommodate

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well for all reactions falling within this type of noncovalent bifunctional catalysis, and case to case analysis is required; (iv) calculations for our system confirms that H-bond with a nitrile group contributes poorly to TS stabilization as compared with H-bond to a ester group, probably due to the fact that linear arrangements, as in C≡N···HX, are more difficult to fit in the TS than angular arrangements, as in C═O···HX.[56] Eventually, the combination of these factors leads to the highly stereoselective formation of the new quaternary stereocenter in **20e**.

CONCLUSIONS

In summary, the highly stereoselective generation of tetrasubstituted carbons, including *C*−*N*, *C*−*O*, *C*−*S*, and all-carbon quaternary stereocenters, has been realized via bifunctional Brønsted base catalyzed Michael reaction of various types of hitherto challenging prostereogenic C-nucleophiles and α′-oxy enones as key enoate surrogates. Competitive and parallel experiments using simple enones (or esters) and the respective α′-oxy enones indicate that the α-oxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity. The ability of α′-hydroxy enones to engage in H-bond networks as either donor or acceptor component (or both) was unknown in previous bidentate enoyl templates, and may in the future be exploited as a new design element in other organocatalytic asymmetric transformations. An additional noteworthy aspect of this design is that the *gem*-dialkylcarbinol framework of the template can be easily modified at both the carbon and oxygen sites, thus enabling easy template tuning for optimal performance. The resulting α-oxy ketone adducts can smoothly be converted into the corresponding aldehyde, ketone, or carboxylic acid derivatives through simple oxidative cleavage of the ketol unit. The present methodology thus provides access to synthetically relevant building-blocks bearing a fully substituted stereogenic carbon atom which were hitherto difficult to prepare in enantioenriched form. Studies toward broadening this methodology are currently underway.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization of compounds including NMR spectra, HPLC chromatograms, and X-ray ORTEP, as well as Cartesian coordinates of all computed stationary points, relative and absolute activation energies for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(54) Extrapolation of this TS model to the case of the reaction between β-substituted enones **4** and cyanoacetates **19** would also correctly predict the (S,S) relative configuration of adducts obtained in Table S. In contrast, the structure closest to **B** we could find predicts products of wrong relative stereochemistry upon a similar extrapolation.

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(56) It seems that the preference of the nitrile versus the ester group to get coordinated to a metal center does not correlate with the ability of each group for engaging in H-bonding. Thus, most TS models invoked in the literature for the metal-catalyzed conjugate addition reactions of α-cyanoacetates consider metal-coordinated nitrile and uncoordinated ester groups, respectively (see refs 10, 38a, 38b, 38h, and 38i). In contrast, and in agreement with our own calculations, previously reported qualitative activation models for related reactions involving H-bond catalysis assume the preference of the ester group over the nitrile for H-bonding (see refs 37a, 37f, and 37i). To further illustrate this divergency, the structure of a cyanoacetate−metal catalyst complex has been elucidated (reference 38i) in which both the metal−CN and the ester−H-bond interactions are identified.

Organocatalysis

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Bifunctional Brønsted Base Catalyst Enables Regio-, Diastereo-, and Enantioselective C_α-Alkylation of β-Tetralones and Related Aromatic-Ring-Fused Cycloalkanones

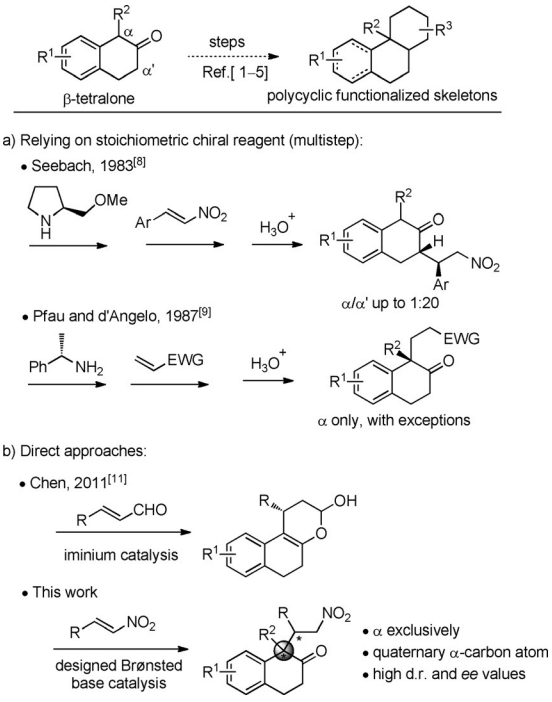
*Iñaki Urruzuno, Odei Mugica, Mikel Oiarbide, and Claudio Palomo**

In memory of José Barluenga

Abstract: *The catalytic asymmetric synthesis of both α-substituted and α,α-disubstituted (quaternary) β-tetralones through direct α-functionalization of the corresponding β-tetralone precursor remains elusive. A designed Brønsted base-squaramide bifunctional catalyst promotes the conjugate addition of either unsubstituted or α-monosubstituted β-tetralones to nitroalkenes. Under these reaction conditions, not only enolization, and thus functionalization, occurs at the α-carbon atom of the β-tetralone exclusively, but adducts including all-carbon quaternary centers are also formed in highly diastereo- and enantioselective manner.*

Syntheses of many bioactive compounds with polycyclic structures, including homoerythrina alkaloids,[1] morphan derivatives,[2] glucocorticoid receptors,[3] and stradiols,[4] among others,[5] have employed β-tetralones. However, this interest did not translate into a variety of approaches for the asymmetric synthesis of substituted β-tetralones. Most approaches for the α/α′-functionalization of β-tetralones so far documented exploit the idea of Stork et al.[6] which involves condensation with a chiral amine and subsequent C-alkylation of the resulting enamine, typically by addition to a Michael acceptor.[7] One complication, for any nonsymmetric cycloalkanone, is that enolization may occur at either the α or α′ site. In this context, Blarer and Seebach[8] reported that the reaction with nitrostyrenes of the enamine derived from (*S*)-2-methoxymethylpyrrolidine, and the respective β-tetralone produced in moderate yields the α′-adduct predominantly (α/α′ from 1:4 to 1:20) with generally good diastereo- and enantioselectivity after hydrolysis of the resulting iminium species (Scheme 1 a). Alternatively, the groups of Pfau and d'Angelo reported the condensation of β-tetralones with (*S*)-1-phenylethylamine and subsequent Michael reaction to afford the α-substituted adducts preferentially,[9] but with exceptions.[9a]

Apart from these stoichiometric multistep approaches, we are unaware of catalytic methods for the enantioselective α-functionalization of β-tetralones leading to an all-carbon quaternary stereocenter.[10] Chen and co-workers have reported direct reaction of β-tetralones with α,β-unsaturated aldehydes by iminium activation,[11] but stereogenicity at C_α is lost upon spontaneous hemiketal formation. Herein we report the direct site-, diastereo-, and enantioselective C_α-alkylation of β-tetralones by conjugate addition reaction enabled by newly designed Brønsted base catalysts. The new C–C bond is formed at the α-carbon atom exclusively, and adducts, including those with an α-quaternary center, are formed in a highly stereoselective manner.



Scheme 1. Enantioselective α/α′-functionalization of β-tetralones. EWG = electron-withdrawing group.

Our consideration was that the fused aromatic ring in β-tetralones might induce preferential enolization at C_α rather than C_α', and that in the presence of a Brønsted base relatively high concentrations of the enolic form would be expected, thus eventually driving the catalytic process forward. Nonetheless, this assumption was accompanied by a second significant challenge, namely the effective control of both the absolute and relative stereochemistry during con-

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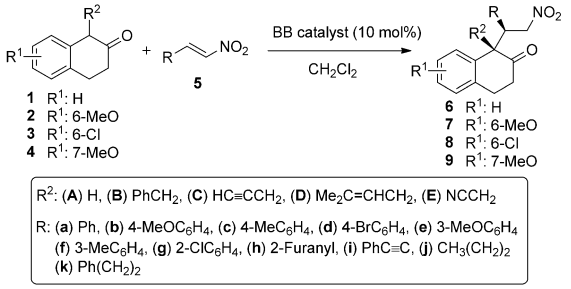
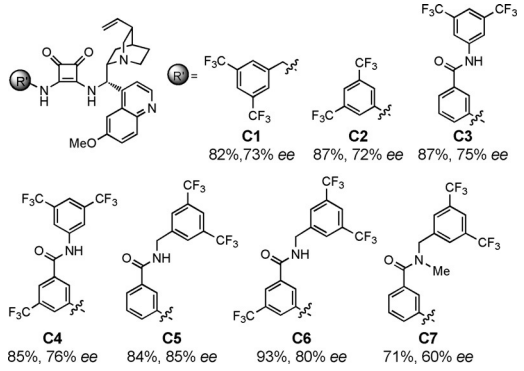
struction of the quaternary carbon stereocenter. In fact, while some success has been achieved in the enantioselective synthesis of α-quaternary carbonyl compounds by Brønsted base-catalyzed Michael reactions[12,13] of α-aryl cyclopentanones,[14a] the corresponding α-aryl cyclohexanones behaved sluggishly.[14,15] We started by screening a set of chiral bifunctional Brønsted base catalysts for the reaction of **1B** with the nitrostyrene **5a** (Scheme 2). It was found that while



Scheme 2. Catalytic addition of β-tetralones to nitroalkenes. BB = Brønsted base.

in each case the α,α-dialkyl β-tetralone **6Ba** was formed exclusively and with essentially perfect diastereoselectivity regardless of the chiral catalyst employed (Table 1),[16] the enantioselectivities were highly catalyst-dependent. The bifunctional squaramide-cinchona Brønsted base catalysts pioneered by Rawal and co-workers[17,18] were the most effective. Thus, by using the catalysts **C1**[17] and **C2**[19] the product **6Ba** was formed exclusively, albeit in moderate enantioselectivity (73 and 72% *ee*, respectively).

Table 1: Screening of catalysts for the reaction of **1B** with **5a**.[a]

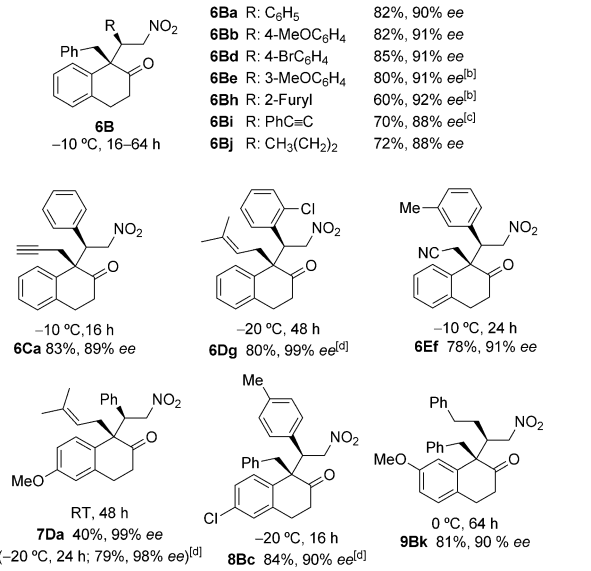


[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of **5a** and 10 mol% catalyst in 0.6 mL CH_2Cl_2 at room temperature. Yield is that of the isolated product **6Ba** after chromatography. The *ee* value was determined by chiral-phase HPLC.

Next we examined the catalysts **C3**[20]/**C4** bearing an amide unit, which would provide a site not only for catalyst fine tuning, but also for additional hydrogen bonding (Table 1).[21] Both **C3** and **C4** catalyzed the reaction of **1B** with **5a**, but produced no improvement in the *ee* value. After several variations of the amide group, we were delighted to find that acceptable selectivity was achieved with the new catalysts **C5** and **C6** (85 and 80% *ee*, respectively). In contrast, the N-methylated catalyst **C7** led to a moderate 60% *ee*, thus indicating that the amide NH in the former catalysts is important. Lowering the reaction temperature allowed further improvement in the selectivity (90% *ee* at −10 °C for **C6**), although **C5** behaved sluggishly at subzero temperatures because of limited solubility. The same trend in the behavior of **C1**–**C7** was observed for the reaction of **1B** with the nitroalkene **5b**.[16]

As Table 2 illustrates, results with differently β-substituted nitroalkenes[22] were uniformly good when using **C6**. Thus, the stereoselectivity of the reactions seems to be independent of the electronic properties of the nitroalkene, and products **6Ba**, **6Bb**, **6Bd**, and **6Be** were formed from the respective nitrostyrenes **5** in yields around 80% and with *ee* values in the range of 90–91%. Nitroalkenes having heteroaromatic or alkynyl β-substituents (**5h**, **5i**) also led to the corresponding products (**6Bh**, **6Bi**) with similarly good yield and enantioselectivity. Remarkably, even the less reactive β-alkyl-substituted nitroalkenes, such as **5j** and **5k**, afforded the corresponding addition adducts (**6Bj**, **9Bk**) with equally good yields and *ee* values. The stereochemical outcome of the reaction is also independent of the α-substituent of the β-tetralone employed. The tetralones **1C**, **1D**, and **1E** reacted with the respective nitroalkenes **5** to afford the adducts **6Ca**, **6Dg**, and **6Ef**, respectively, in good yields and with *ee* values of up to 99%. The reaction also tolerates the β-tetralones **2D**, **3B**, and **4B**, bearing, respectively the 6-methoxy-, 6-chloro-,

Table 2: Scope of the reaction with respect to the α-substituted β-tetralones **1**–**4** with nitroalkenes **5** catalyzed by **C6**.[a]

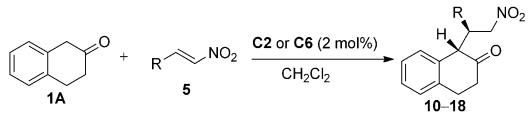


[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of *trans*-nitroalkene **5** and 10 mol% **C6**, unless otherwise stated, in 0.6 mL CH_2Cl_2. d.r. > 20:1 in all entries as determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. Yield is that of the product isolated after chromatographic purification. The *ee* value was determined by chiral-phase HPLC. [b] Reaction conducted at −20 °C. [c] Obtained as a 1.5:1 mixture of diastereomers (94% *ee* for minor isomer). [d] Using catalyst **C4**.

and 7-methoxy groups at the aromatic ring, which were equally efficient (adducts **7Da**, **8Bc**, and **9Bk**). In the case of **7Da**, **C4** produced the best reaction outcome. Importantly, in every case no traces of products from the reaction at the α′-carbon atom of the β-tetralone were formed.

Next, the behavior of the α-unsubstituted β-tetralone **1A** was investigated and the reactions under similar reaction conditions were found, again, to be completely regioselective (Table 3). The products **10**–**18** were obtained from both aryl-

Table 3: Reaction of the β-tetralone **1A** with nitroalkenes catalyzed by either **C2** or **C6**.[a]



Product, R	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
10, Ph	−20	8	83	4:1	99
11, 4-MeOC_6H_4	−20	8	85	8:1	99
12, 4-BrC_6H_4	−20	8	88	4:1	99
13, 3-MeOC_6H_4	−20	8	80	4:1	99
14, 2-ClC_6H_4	−20	8	86	>20:1	99
15, 2-furyl	−20	8	84	1:1	98
16, $CH_3(CH_2)_2$	RT	16	81	5:1	99
17, C_6H_{11}	RT	24	80	4:1	99
18, $Ph(CH_2)_2$	RT	16	83	5:1	99

[a] Reactions carried out at 0.30 mmol scale, using 1.2 equiv of *trans*-nitroalkene and 2 mol% of either **C2** or **C6** in 0.6 mL CH_2Cl_2. [b] Yield of product isolated after chromatographic purification. [c] Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [d] Both diastereomers obtained with the same *ee* value as determined by chiral-phase HPLC.

and alkyl-substituted nitroalkenes in yields in the 80–88% range and, importantly, no products from a sequential addition of two equivalents of nitroalkene, either at $C_{\alpha/\alpha'}$ of the ketone or at C_α of the nitro group, were detected. With the exception of the 2-furyl-substituted nitroalkene **5h** (product **15**), in all other cases diastereoselectivity was good (d.r. ≥ 4:1) and enantioselectivity essentially perfect for both diastereomers. For these reactions both **C2** and **C6** were found to be equally effective at a 2 mol% loading. It should be noted that the thus obtained α-monosubstituted β-tetralones were prone toward epimerization under basic conditions at room temperature. For example, the compound **14**, which was isolated essentially as a single diastereomer (d.r. > 20:1), led, after exposure to 5 mol% of **C2** at room temperature in methylene chloride for 3 hours, to an almost equimolar mixture of diastereomers. In the absence of base, however, no epimerization was observed after a prolonged time (20 h) even at 80 °C.

Eventually, the suitability of this highly site- and stereoselective α-functionalization strategy was also investigated for related ketone substrates. As results in Figure 1 show, aromatic ring-fused cycloalkanones with an oxygen heteroatom in the cycle, or larger seven-membered cycloalkanones, were equally competent substrates undergoing the corresponding addition reaction at C_α exclusively, and with very high stereoselectivity. In particular cases, the enolizable

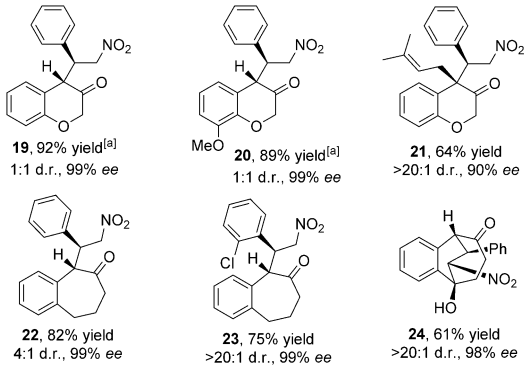
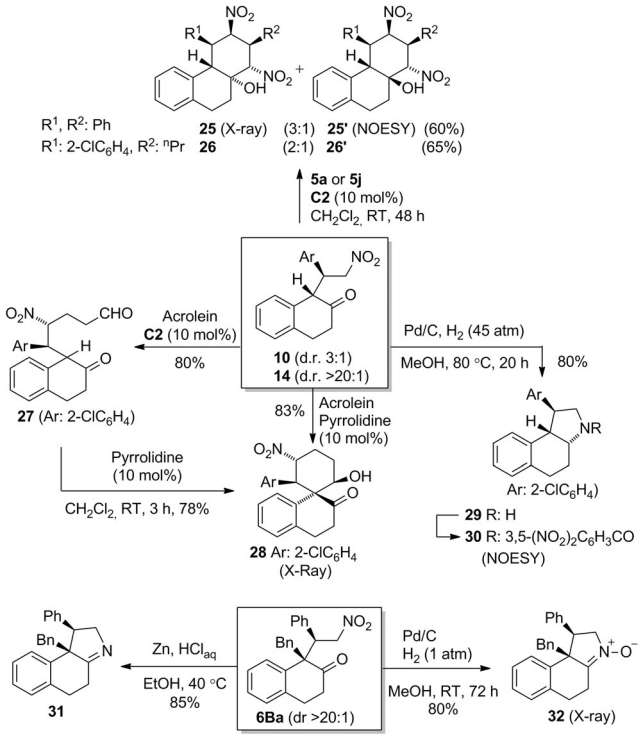


Figure 1. Adducts from the direct reaction of a survey of arene-fused cycloalkanones with nitroolefins in the presence of 10 mol% **C6** (for details, see the Supporting Information). [a] 2 mol% of catalyst **C2** used. Both diastereomers obtained with the same *ee* value.

compounds **19** and **20** were obtained as a mixture of two diastereomers, probably as a result of easy epimerization under the reaction conditions used. In contrast, in the case of employing a diketone substrate, the adduct **24** from a sequential Michael/intramolecular Henry reaction was obtained, again, as essentially a single diastereomer and very high enantioselectivity.

The excellent regio- and stereoselectivity achieved in the above reactions are of particular interest in that several options for further elaboration of the adducts are now made feasible. For instance (Scheme 3), the adduct **10** (3:1 ratio of diastereomers), upon treatment with **5a** in the presence of 10 mol% of **C2** provided the tricyclic systems **25**/**25′** in 60%



Scheme 3. Elaboration of adducts into a variety of polycyclic molecules.

combined yield. Remarkably, only two out of the possible 2^6 stereoisomers of **25** were formed.[23] An interesting aspect is that apparently no cyclization product derived from the minor isomer of **10** was detected. Moreover, the isomeric composition of isolated product **25**/**25′** was around 3:1 regardless of the initial mixture of starting **10** employed (3:1 in first run; 1:1 in second run). These results suggest that formation of the tricycles **25**/**25′** through a Michael/Henry cascade[24,25] not only proceeds in high stereoselectivity, but also involves some kinetic resolution process. Similarly, treatment of **14** (d.r. > 20:1) with **5j** in the presence of **C2** afforded the products **26**/**26′** in a 2:1 ratio. The absolute configuration of **25** was determined by single-crystal X-ray structure analysis,[26] and that of **25′** by NOESY experiments.[16] The configuration of **26**/**26′** was assigned by analogy. In a different example, when **14** was treated with acrolein in the presence of **C2** at room temperature, the Michael addition product **27** was isolated in 80% yield. The aldol-reaction-mediated cyclization of **27** to **28** could be carried out smoothly at room temperature by exposure to 10 mol% pyrrolidine. Alternatively, direct transformation of **14** into the spirocyclic aldol **28** was achieved by treatment with acrolein in the presence of 10 mol% pyrrolidine. In both cases **28** was produced as essentially a single diastereomer. The course of the above cascade reaction is quite surprising considering that cycloalkanones under similar reaction conditions are reported to furnish substituted decalins instead.[27] Importantly, as far as we know, no other catalytic enantioselective approach that allows regioselective production of tetralone-derived α-spirocycles are available until now.[5,28] In addition, hexahydro-benzo[*e*]indoles, heterocyclic cores present in various biologically active compounds,[29] could also be prepared. For example, reduction of the nitro group in adduct **6Ba** with either Zn/H^+ or H_2/Pd provided, respectively, **31** and **32**, whilst reduction of **14** led to **29**, all with good yields. The absolute configurations for the compounds **28** and **32** were determined by single-crystal X-ray structure analysis[26] and that of their precursor adducts was established by extrapolation.

In summary, we report the first examples of catalytic regio-, diastereo-, and enantioselective α-alkylation of both α-unsubstituted and α-substituted β-tetralones with Michael acceptors.[30] The synthetic utility of the method is demonstrated by easy conversion of adducts into diverse polycyclic compounds featuring up to six stereogenic centers or new spirocyclic system. This realization was feasible thanks to a readily available subclass of cinchona-alkaloid-derived bifunctional catalysts bearing a carboxamide group as an additional moiety for catalyst fine tuning. Importantly, the method proved to be applicable beyond β-tetralones, and the direct α-functionalization of other aromatic ring-fused cycloalkanones are equally affordable and selective. Investigations to further broadening the substrate scope of the approach are ongoing.

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Conflict of interest

The authors declare no conflict of interest.

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