Organocatalytic Regio- and Stereoselective Michael Reactions *via* Di- and Trienolate Intermediates

DOCTORAL THESIS

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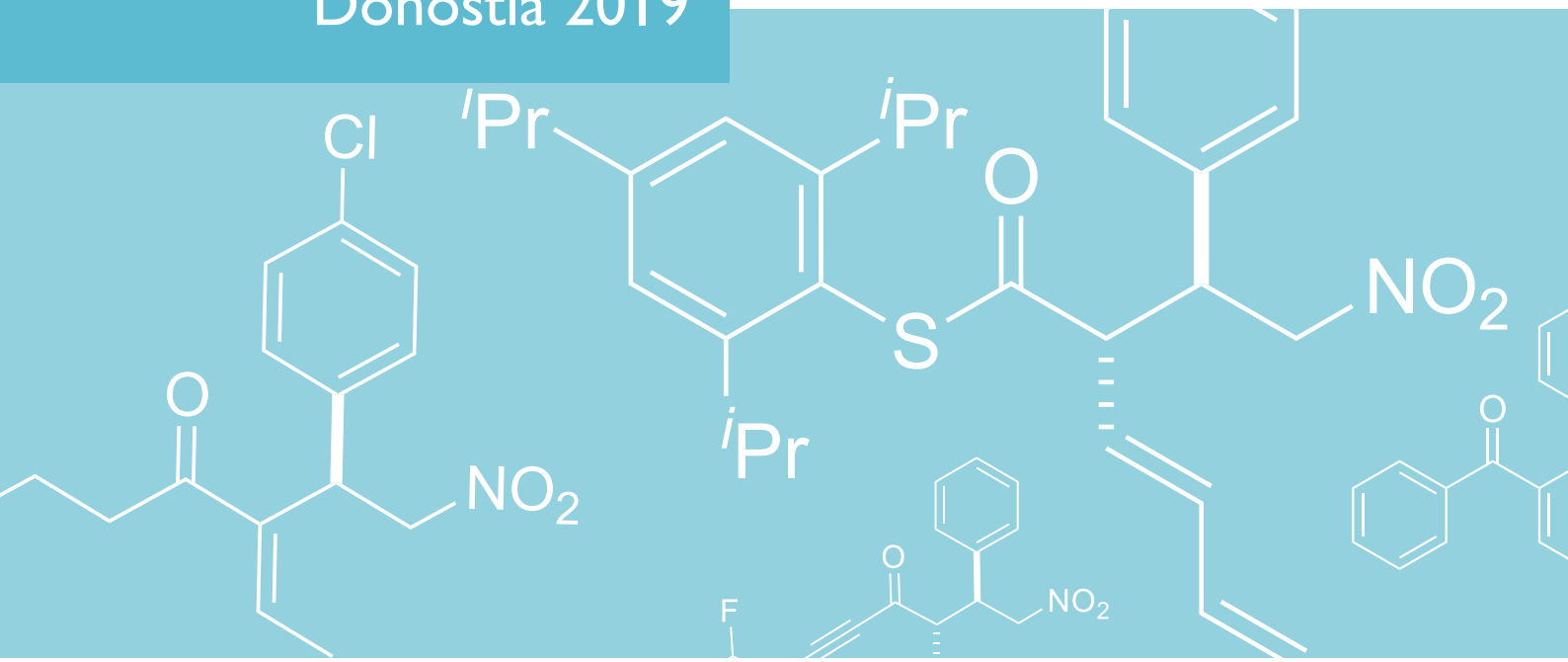
Donostia 2019



eman ta zabal zazu

Universidad del País Vasco
Euskal Herriko Unibertsitatea

Eskerrak

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Química de Donostia, Universidad del País Vasco (UPV/EHU), bajo la dirección del Dr. Claudio Palomo Nicolau y del Dr. Iñaki Gamboa. Querría agradecer sobre todo a Claudio por su esfuerzo y paciencia hacia mi persona. También me gustaría agradecer al resto de profesores que forman parte del departamento, Aitor, Antonia, Mikel… por su implicación en mi trabajo.

I also want to thank Prof. Jonathan Clayden and his group for giving me the opportunity to do a short stay in his laboratory at the University of Bristol (United Kingdom) and participate in one of their research work. Thank you very much for your kindness and hospitality. También agradecer a Javi y a Yoli, por hacer mi estancia en Bristol y en la Hodgkin house inmemorable (sesiones de series y películas interminables, con poder absoluto del living room, clases de español y euskera en vez de inglés, domingos de donuts de one pound, etc.).

Por otro lado, agradecer al Departamento de Educación del Gobierno Vasco por la beca predoctoral concedida, así como la ayuda para la realización de estancias predoctorales en centros distintos al de aplicación para el personal investigador en formación. Este trabajo tampoco habría podido ser realizado sin la financiación del MINECO y del Gobierno Vasco.

Labokideei ere eskerrak, joan (Amaiur, Iñaki B., Eider, Haizea, Iurre…) eta hemen zaudetenei (Julen, Iñaki U., Joseba…). Bide zail honetan laguntza behar nuenean eman didazuelako, muxu truk. Eskerrak batez ere, Xandrari, nire lehen lagun españolari eta nire bide osoan batera egon garen laukoteari. Nahiz eta “exagerada” bat naizela esateyazuen, beti altxatzen lagunduyazuelako: Odeiek bere goxotasunakin, Igorrek bere koerentzia ta frikadekin ta Anak bere erotasunakin. Ta bai, nik eskerrak in ditut ta berriro baita, nearrez ai naiz. Daukaun hau ez dezagun galdu, mesedez.

Azkenik, 28 urte hauetan nere benetako familiari. Ni sufritzen ikusi didatenean nirekin sufritu duteneei: Aitai, anaiai, Itziarri, izebeei ta bateze amatxoi. Nere kuadrillakoei, nahiz eta ez ulertu, batzutan ulertzen saiatze zialako eta triste neonen gaiaz aldatu ta animatzen ziatelako. Eta azken urte honetan, ezagutu dudan pertsona berezi horri ere bai, nere dei amaigabeak entzuteagatik, eta kontsolatzen saiatzeagatik (portadan diseinuangatik ere bai).

Kontun hartuz nere muxuk oso galestik diala, MUXU bana denoi! Eta ESKERRIK ASKO!

Summary

Molecules containing carbonyl groups with an adjacent stereocenter are structural motifs in numerous bioactive compounds and drugs (Figure A).

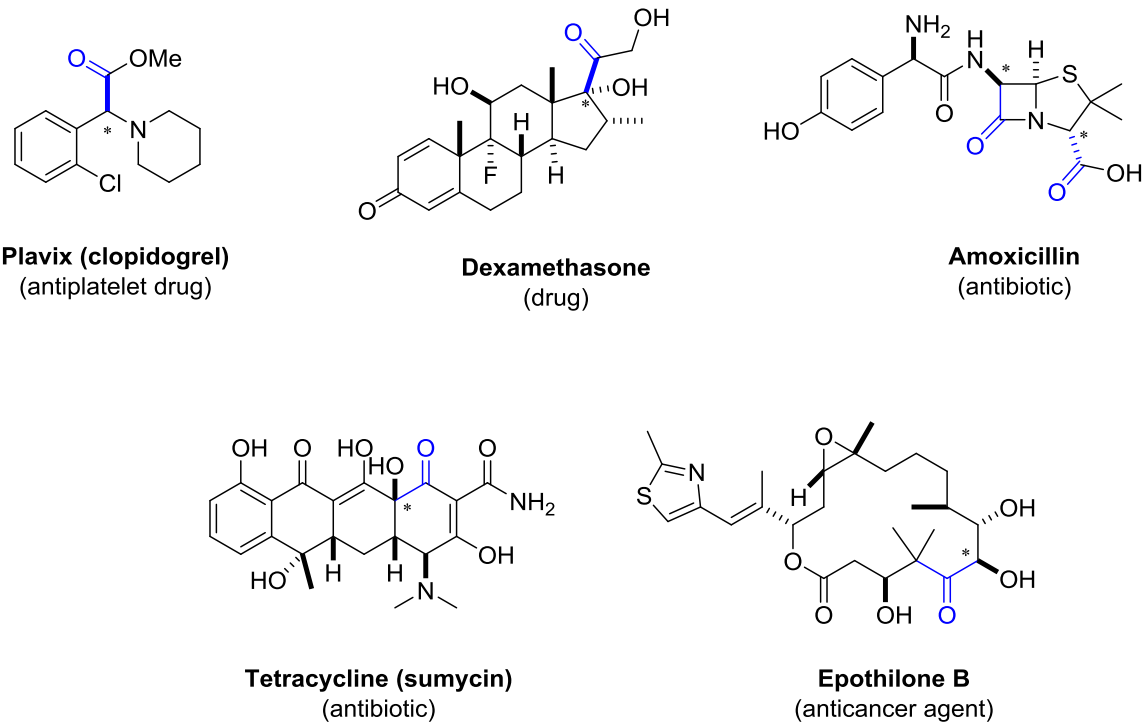
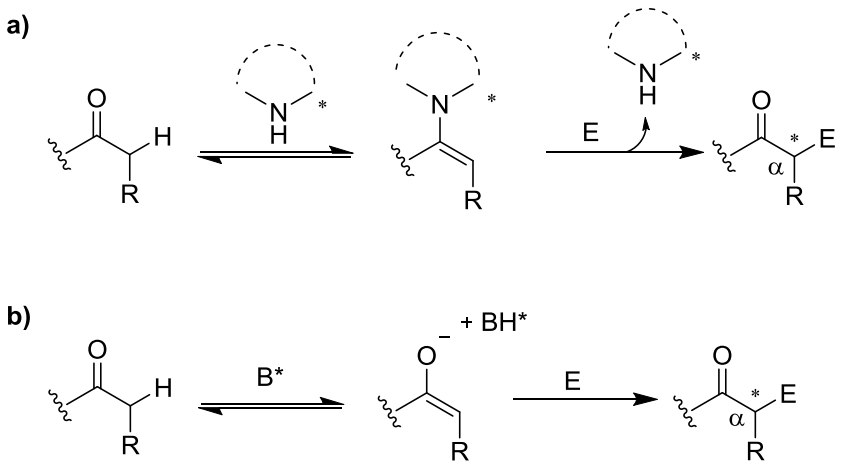


Figure A. Representative examples of bioactive compounds and drugs containing at least one carbonyl group with an adjacent stereocenter.

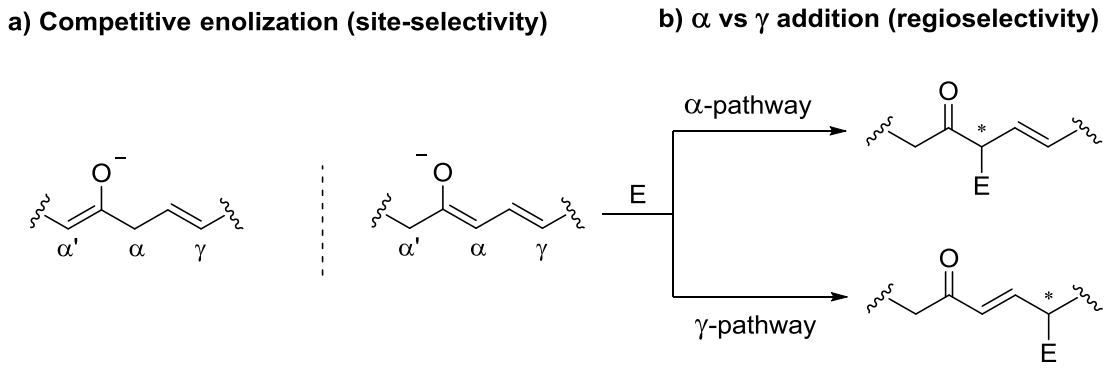
Several methodologies are known for the stereoselective construction of a stereogenic center at the Cα (sp^3) of a carbonyl compound. Even so, the most commonly used strategy is the reaction of an electrophile with an enamine (Scheme Aa) or enolate anion (Scheme Ab).



Scheme A. Most common strategies for the stereoselective formation of a stereogenic center at the α-position of a carbonyl compound.

Contrary to enamine- and iminium ion-mediated organocatalytic processes which are only suitable for aldehyde and ketones, Brønsted base (BB) activation can, in principle, be applied not only to the latter, but also to carboxylic acids and derivatives.

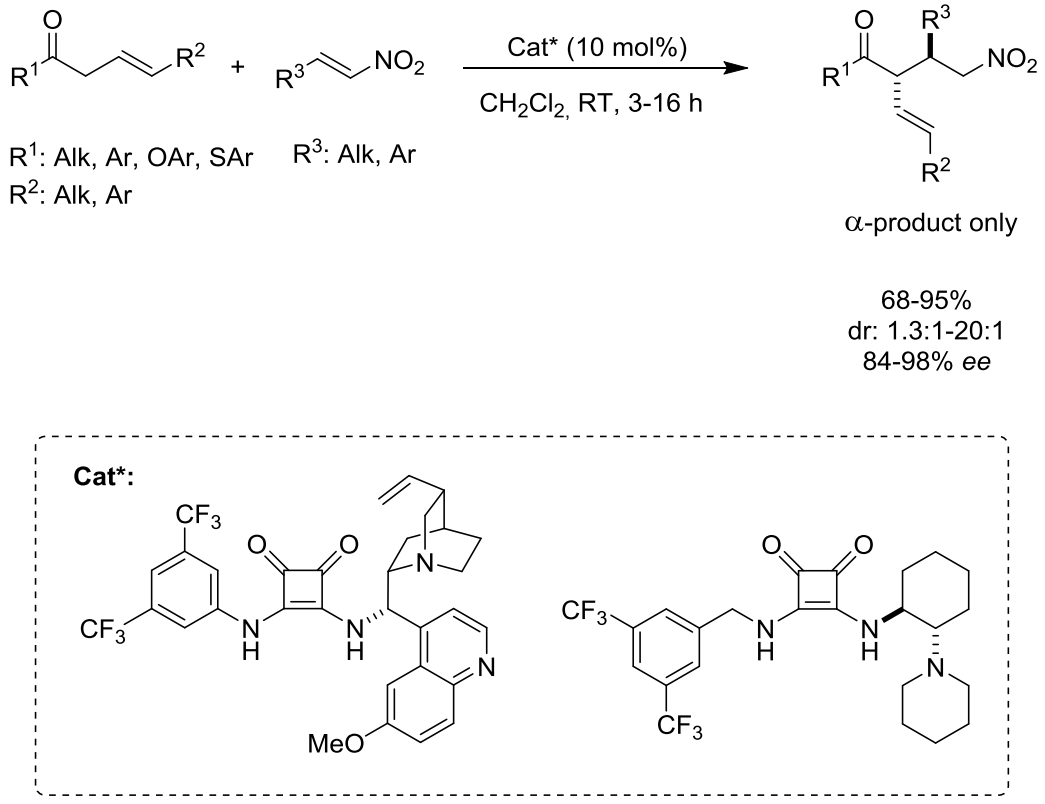
Direct organocatalytic methods based on Brønsted base catalysis have a functional pK_a barrier for nucleophile activation that lies between pK_a values of 16 and 17. Thus, the identification or design of enolizable carbonyl compounds with appropriate pK_a values (< 17) for ready deprotonation with weak Brønsted bases is crucial. Whereas this goal has been mainly achieved through the incorporation of electron withdrawing groups (EWG) in appropriate sites of the inactive carbonyl compound, the incorporation of a vinyl or styryl group can also increase the reactivity of the starting material, enabling generation of an enolate stabilized by conjugation. These β,γ-unsaturated carbonyl compounds have two potentially reactive sites (α *vs* γ), three if the starting material is a β,γ-unsaturated alkyl ketone (α´) (Scheme B).



Scheme B. Competitive α, γ and α´ addition.

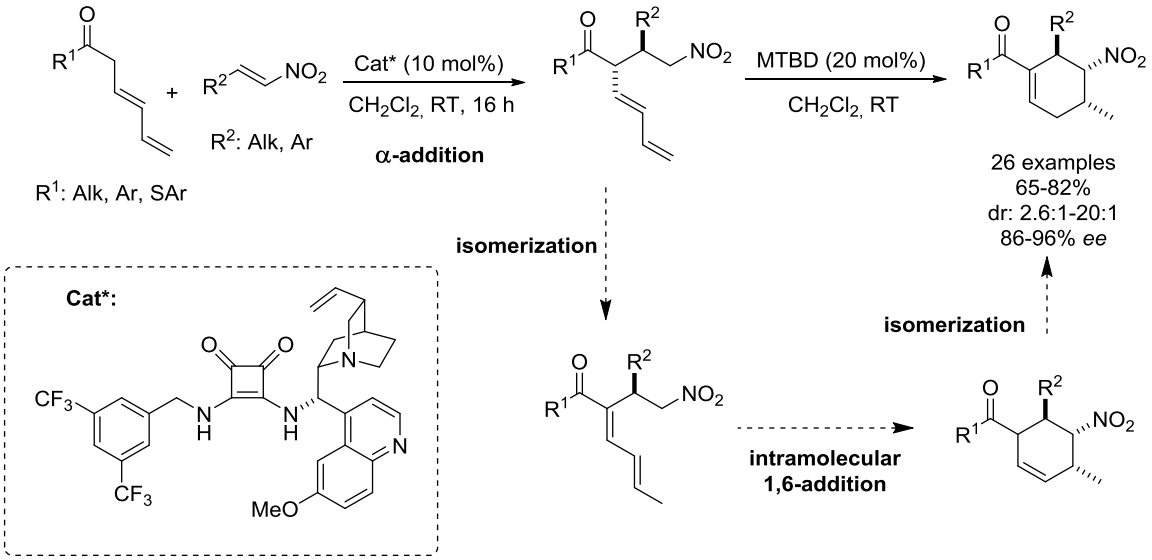
In contrast to the majority of asymmetric reactions involving vinylogous enolate equivalents which proceed from the γ-carbon, we have developed a Michael addition of β,γ-unsaturated ketones to nitroolefins, that proceeds *via* attack throuh the α-site of the

intermediate dienolate. The reaction is enabled by Brønsted base/hydrogen-bonding bifunctional catalysis (Scheme C) and the method was demonstrated to be robust, admitting both β,γ-unsaturated ketones with different side chains (alkynyl, alkyl, alkenyl etc.) and (thio)esters.



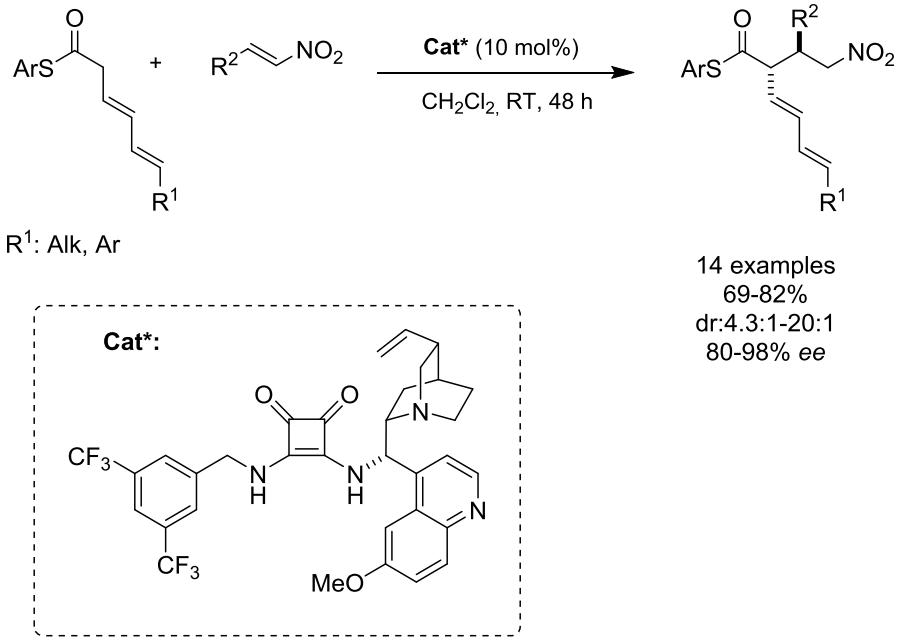
Scheme C. Regio-, diastereo- and enantioselective direct Michael addition of β,γ-unsaturated ketones and (thio)esters to nitroolefins (*Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864).

The vinylogous enolate concept has been extended to reactions involving transiently generated trienolate intermediates. In this manner, we have developed a catalyst driven one-pot reaction sequence for the enantio- and diastereoselective synthesis of tetrasubstituted cyclohexenes from simple unsaturated ketones and thioesters. The method involves a tertiary amine/squaramide-catalyzed α-selective addition of *in situ* generate trienolates to nitroolefins, subsequent base-catalyzed double bond isomerization, and an intramolecular 1,6-addition reaction that proceeds with essentially perfect stereocontrol (Scheme D).



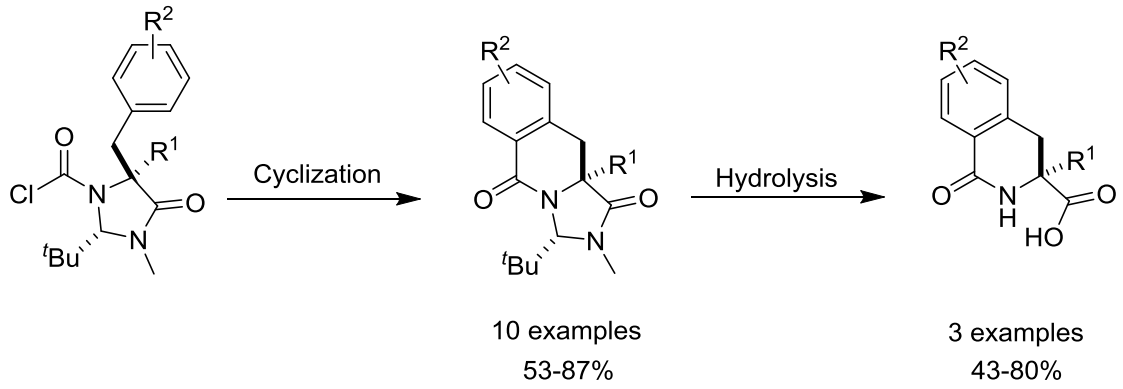
Scheme D. Catalyst driven one-pot reaction sequence for the enantio- and diastereoselective synthesis of tetrasubstituted cyclohexenes (*Angew. Chem. Int. Ed.* **2019**, *58*, 14250–14254).

Moreover, to explore the effectiveness of the novel regio-, diastereo- and enantioselective reaction in construction of tetrasubstituted cyclohexenes, polyunsaturated ε-substituted ($R^1 \neq H$) thioesters have been studied under the same reaction conditions. Although to date the desired cycle is not achieved regardless the base, we have described the first direct reaction where *in situ* generated trienolates are intermediates in a regio- and stereoselective Michael addition assisted by a Brønsted base catalyst (Scheme E).



Scheme E. Trienolates in α-Michael addition reactions.

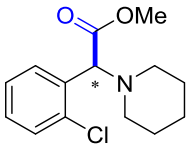
Finally, during a short stay at the School of Chemistry of the University of Bristol (United Kingdom), under the supervision of Prof. Jonathan Clayden, a cyclization of quaternary aryl imidazolidinone derivatives has been developed, describing a novel metal-free strategy for the stereoselective synthesis of 3,4-dihydroisoquinolones. The project has been completed by the hydrolysis of the imidizadolidinone ring to afford enantioenriched quaternary α-amino acid derivatives (Scheme F).



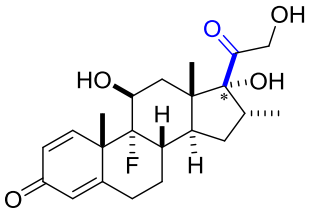
Scheme F. General procedure for the synthesis of 3,4-dihydroisoquinolones (*Org. Lett.* **2019**, *21*, 1908–1911).

Resumen

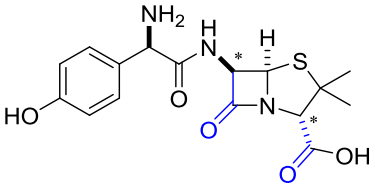
Las moléculas portadoras de grupos carbonilo con un estereocentro adyacente son elementos estructurales de numerosos compuestos bioactivos y fármacos (Figura A).



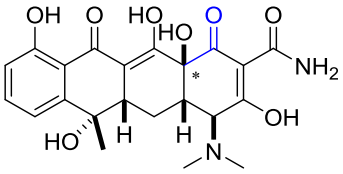
Plavix
(antiagregantes plaquetario)



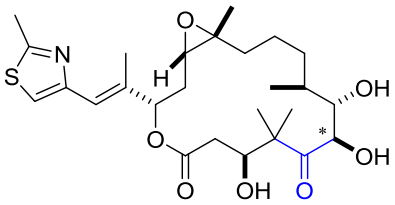
Dexamethasone
(fármaco)



Amoxicilina
(antibiótico)



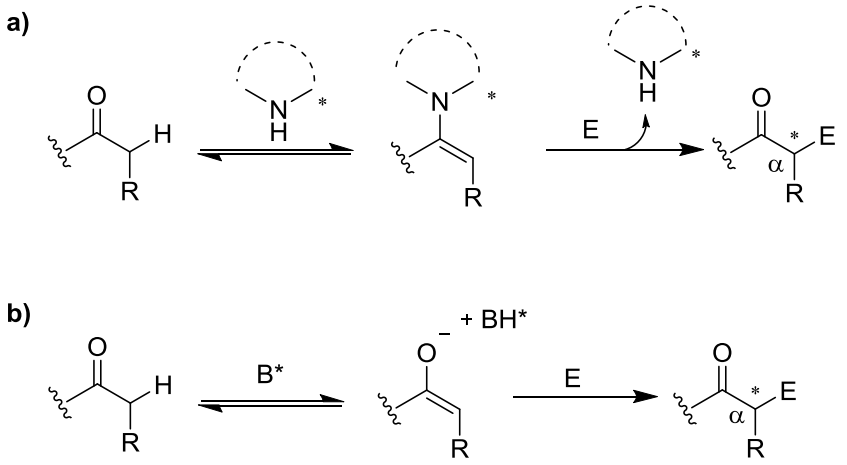
Tetraciclina
(antibiótico)



Epotilona B
(medicamento anticancerígeno)

Figura A. Ejemplos representativos de compuestos bioactivos y fármacos que contienen al menos un grupo carbonilo con un estereocentro adyacente.

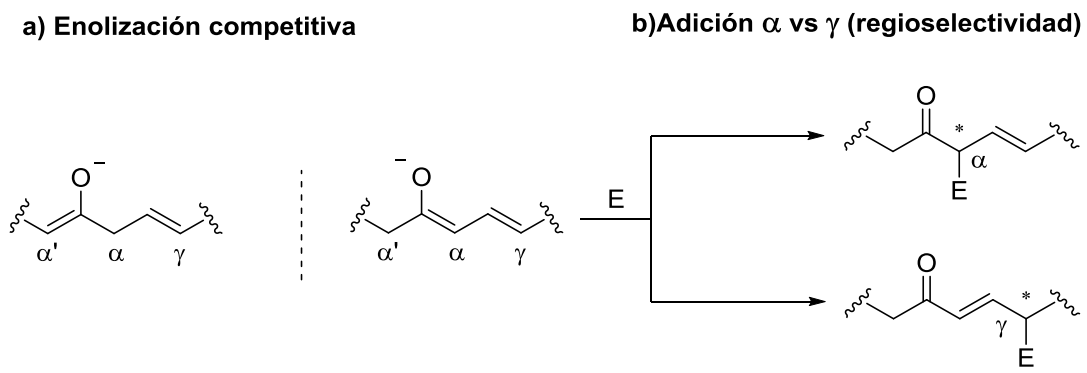
Aunque, se han descrito varias metodologías para la construcción estereoselectiva de un centro estereogénico en el carbono α de un compuesto carbonílico, la estrategia más empleada consiste en la reacción de un electrófilo con una enamina (Esquema Aa) o un anión enolato (Esquema Ab) en condiciones de transferencia de protones.



Esquema A. Estrategias más comúnes para la formación estereoselectiva de un centro estereogénico en la posición α de un compuesto carbonílico.

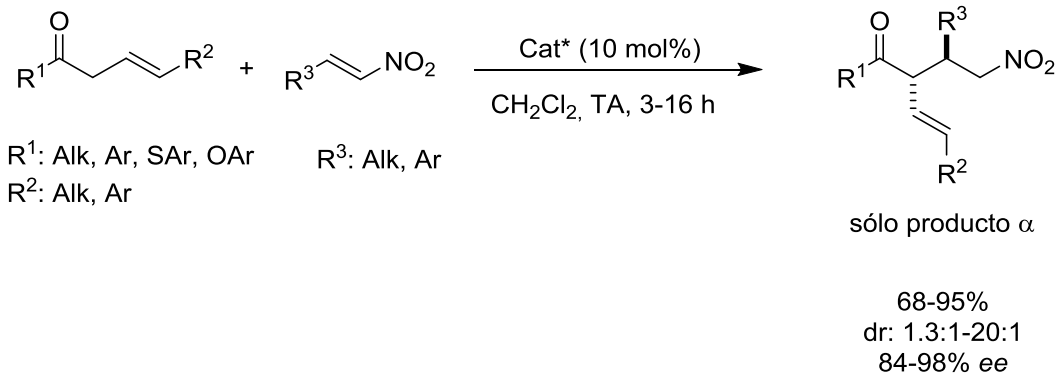
A diferencia de los procesos organocatalíticos mediados por iones iminio o enamina, que sólo son adecuados para aldehídos y cetonas, el protocolo de activación mediante bases de Brønsted puede, en principio, aplicarse no sólo a cetonas, sino también a compuestos carboxílicos y derivados.

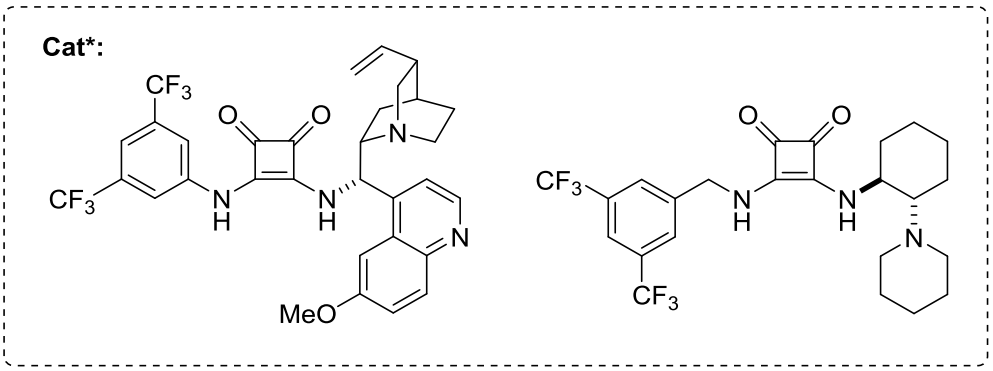
Los métodos organocatalíticos directos asistidos por bases de Brønsted, tienen una barrera funcional de pK_a para la activación de nucleófilos que se encuentra entre los valores de pK_a de 16 y 17. Por lo tanto, es crucial la identificación o diseño de compuestos carbonílicos enolizables con valores de pK_a apropiados (<17) para su desprotonación. Este objetivo ha sido logrado principalmente mediante la incorporación de grupos electroatrayentes en posiciones C_{ipso} y/o C_α del compuesto carbonílico. Hemos observado que la incorporación de un grupo vinilo o estirilo también puede aumentar la reactividad del compuesto de partida, permitiendo la formación de un enolato que está estabilizado por conjugación. Estos compuestos carbonílicos β,γ-insaturados tienen dos carbonos potencialmente nucleofílicos (α vs γ), tres si el material de partida es una alquil cetona β,γ-insaturada (α´) (Esquema B).



Esquema B. α, γ y α´adiciones en competencia.

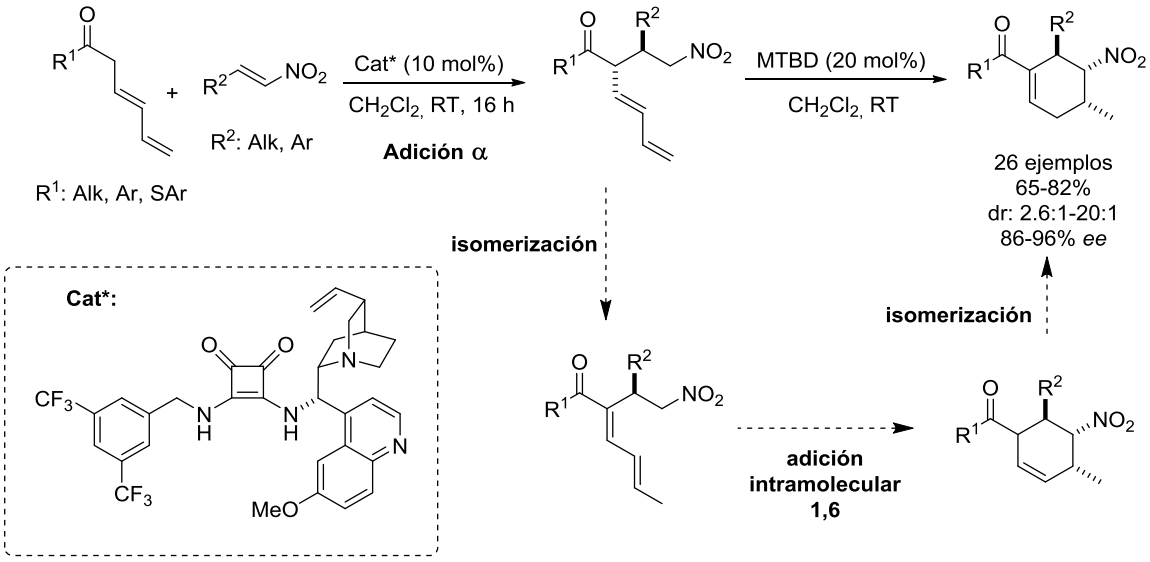
La mayoría de las reacciones catalíticas que involucran enolatos vinílicos proceden a través de la posición γ. En este contexto, hemos demostrado que los catalizadores bifuncionales de amina terciaria/escuaramida favorecen la adición de dienolatos de cetonas y (thio)ésteres β,γ-insaturados a nitroolefinas no solo con muy buen enantio- y diastereocontrol, sino que también con excelente regioselectividad (únicamente se consigue el aducto α) (Esquema C).





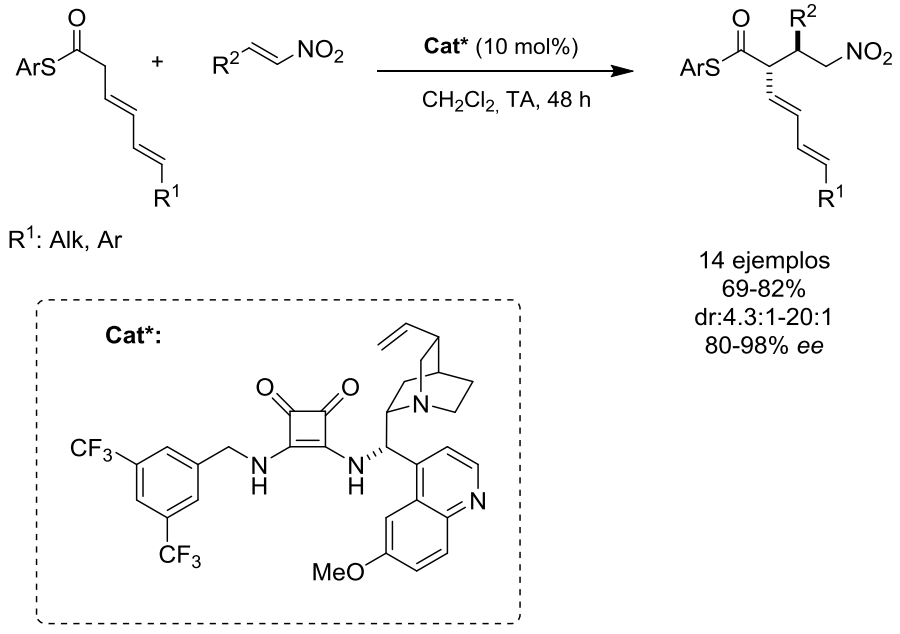
Esquema C. Adición regio-, diastereo- y enantioselectiva de cetonas β,γ-insaturadas a nitroolefinas (*Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864).

El concepto de enolato vinílogo se ha extendido a reacciones que involucran intermedios de trienolatos. De esta manera, hemos desarrollado una síntesis enantio- y diastereoselectiva de ciclohexenos tetrasustituidos a partir de cetonas y tioésteres terminales β, γ- δ, ε-insaturados con nitroolefinas, la cual es promovida por un catalizador bifuncional. El método implica una adición α-selectiva de trienolatos a nitroolefinas, posterior isomerización del doble enlace catalizada por una base aquiral y una reacción intramolecular de adición 1,6 como paso de carbociclación (Esquema D).



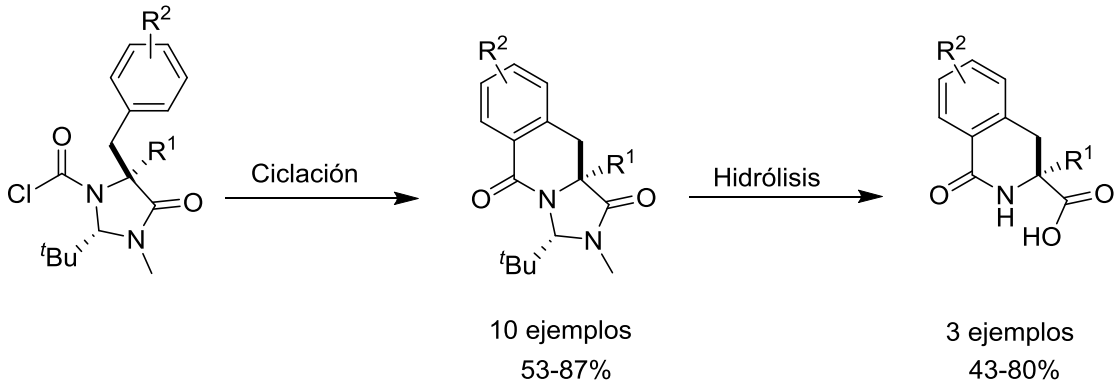
Esquema D. Síntesis diastero- y enenatioselectiva de ciclohexenos tetrasubstituidos (*Angew. Chem. Int. Ed.* **2019**, *58*, 14250–14254).

Además, con el fin de explorar la efectividad de la nueva metodología para la construcción regio-, diastereo- y enantioselectiva de ciclohexenos tetrasustituidos, se ha estudiado la misma reacción con tioésteres sustituidos en el carbono ε. Aunque no se consigue el ciclo final independientemente de la base que se emplea para la ciclación, hemos demostrado que, al igual que con los dienolatos, los catalizadores bifuncionales de amina terciaria/escuaramida favorecen la adición de trienolatos de tíoesteres β,γ-δ,ε-insaturados a nitroolefinas no solo con muy buen enantiocontrol, sino que también con excelente diastereocontrol y regioselectividad (en este caso también se consigue únicamente el aducto α) (Esquema E).



Esquema E. Trienolatos en adiciones de Michael.

Finalmente, durante una corta estancia en la Facultad de Química de la Universidad de Bristol (Reino Unido), bajo la supervisión del profesor Jonathan Clayden, se ha desarrollado una ciclación de derivados de aril imidazolidinonas cuaternarias. Gracias a esta metodología, se consiguen aductos derivados de las 3,4-dihidroisoquinolonas con buenos rendimientos. Los resultados de este proyecto se han completado con la síntesis de aminoácidos cuaternarios, obtenidos mediante la hidrólisis del anillo de la imidizadolidinona (Esquema F).



Esquema F. Procedimiento general para la síntesis de 3,4-dihidroisoquinolonas (*Org. Lett.* **2019**, *21*, 1908–1911).

Abbreviations and Acronyms

Standard abbreviations and acronyms have been used as recommended in "Guidelines for authors" (*J. Org. Chem.*, January 2017). Additionally, the following abbreviations and acronyms have been employed:

Alk	Alkyl
B	Base
BA	Brønsted acid
BB	Brønsted base
Cat	Catalyst
Conv.	Conversion
CPME	Cyclopentyl methyl ether
DA	Diels-Alder
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
E	Electrophile
EDC·HCl	*N*-(3-Dimethylaminopropyl)-*N*´-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EPC	Enantiomerically pure compound
EWG	Electron withdrawing group
Hal	Halogen
His	Histidine
HOBt	1-Hydroxybenzotriazole
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
KHMDS	Potassium bis(trimethylsilyl)amide
LG	Leaving group
LiHMDS	Lithium bis(trimethylsilyl)amide
m-	meta-
MBH	Morita-Baylis-Hillman
µW	Microwave
MS	Molecular sieves
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Napht	Naphtyl
ND	Not determined
NMM	*N*-methyl morpholine
n.r.	No reaction
o-	ortho-
*o*FBA	*o*-Fluorobenzoic acid
ORTEP	Oak ridge thermal ellipsoid plot
p-	para-
Phe	Phenylalanine
PTC	Phase transfer catalysis
Quin	Quinoline
rac	Racemic
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
Ref.	Reference
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

TMB	1,1,3,3-tetramethylbutyl
Tol	Toluene
Trp	Tryptophan
Tyr	Tyrosine
VT	Variable Temperature
X_c	Chiral auxiliary

Chapter 1

Introduction

1. Introduction

1.1. α-Functionalization of carbonyl compounds

Molecules containing carbonyl groups with an adjacent stereogenic center are common motifs found in numerous bioactive compounds and drugs. Some of these compounds are shown in Figure 1.[1]

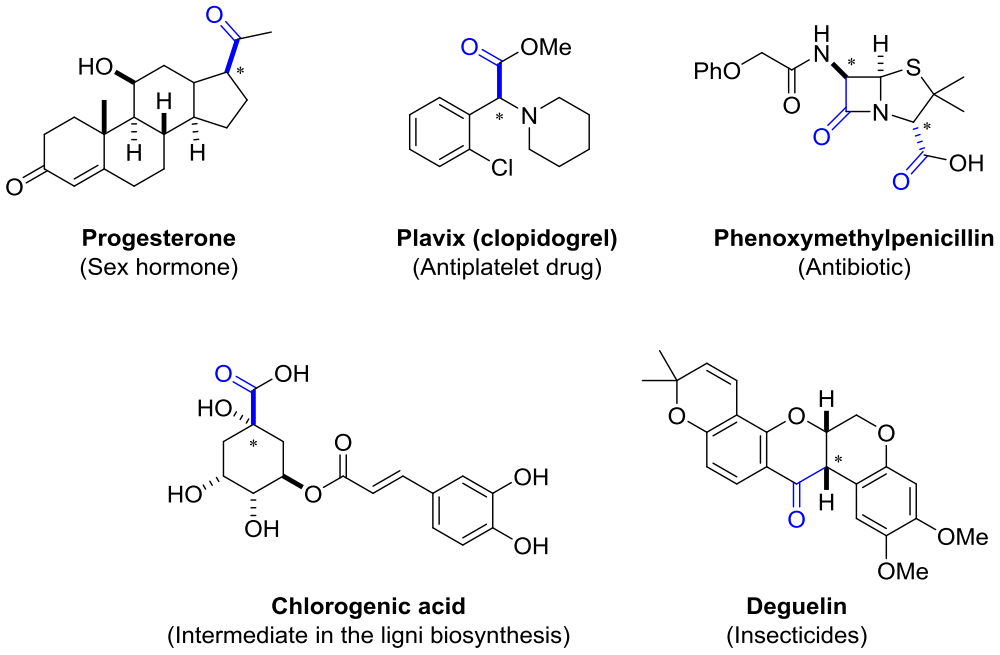
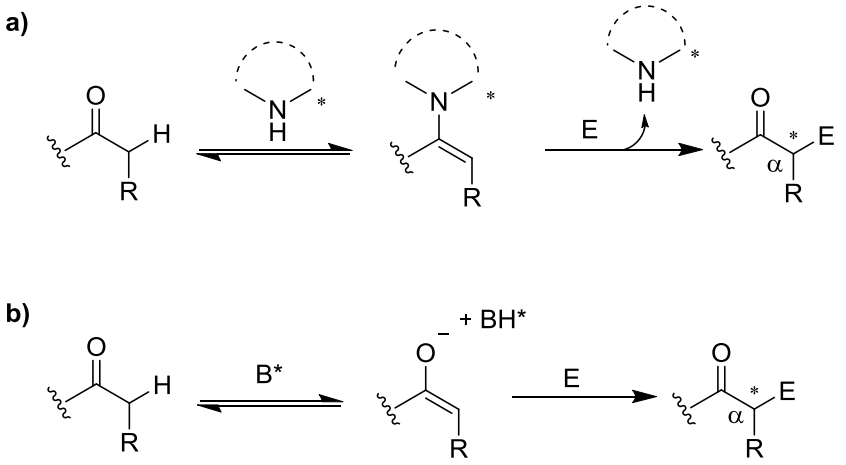


Figure 1. Examples of molecules containing at least one carbonyl group with an adjacent stereocenter.

At present, there is more than one methodology for the stereoselective formation of a stereogenic center at the Cα (sp^3) of a carbonyl compound. Even so, the most commonly used strategy is the reaction of an electrophile with an enamine (Scheme 1a) or enolate anion (Scheme 1b) under proton transfer conditions, which will be discussed later.

[1] For more information about Progesterone, see: a) W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, L. A. Dolak, *J. Am. Chem. Soc.* **1968**, *90*, 2994–2996. For more information about Clopidogrel, see: b) A. Saeed, D. Shahzad, M. Faisal, F. A. Larik, H. R. El-Seedi, P. A. Channar, *Chirality* **2017**, *29*, 684–707. For more information about Phenoxymethylpenicillin, see: c) J. Colloway, A. Couch, F. Foster, W. Hunter, V. Knight, A. C. White, *Antibiotics. Annu.* **1995**, *3*, 490–501. For more information about Chlorogenic acid, see: d) W. Boerjan, J. Ralph, M. Baucher, *Annu. Rev. Plant. Biol.* **2003**, *54*, 519–546. For more information about Deguelin, see: e) S. Xu, G. Wang, F. Xu, W. Li, A. Lin, H. Yao, J. Xu, *J. Nat. Prod.* **2018**, *81*, 1055–1059.



Scheme 1. Enamines and enolates of carbonyl compounds.

Since the tragedy of thalidomide,[2] the demand of enantiomerically pure compounds (EPC) has growth considerably in the pharmaceutical and agricultural industries. Due to this reason, the search of new methods capable of accessing enantiopure α-functionalized carbonyl compounds in a selective manner has reached great importance. In general, three main strategies have been developed for this goal: (i) resolution of racemates, (ii) the "chiral pool" approach, and (iii) asymmetric synthesis (Figure 2).

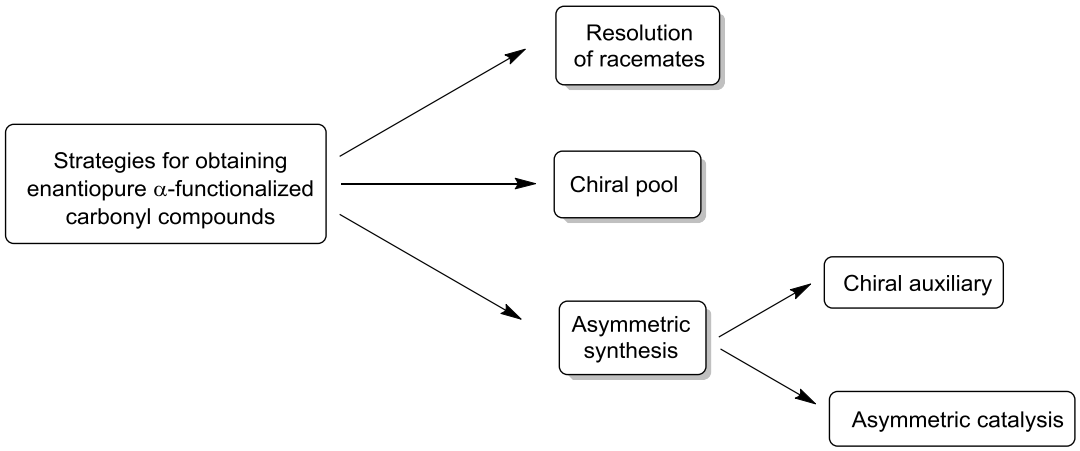


Figure 2. Strategies for obtaining enantiopure α-functionalized carbonyl compounds.

To date, the most used strategy in industry to obtain enantiopure compounds is the resolution of racemates.[3] The enantiopure compound is separated from an initial racemic mixture by crystallization, chromatographical resolution, kinetic resolution

[2] For more information about Thalidomide tragedy, see: a) J. H. Kim, A. R. Scialli, *Toxicol. Sci.* **2011**, *122*, 1–6. b) T. Stephens, R. Brynner, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine,* Perseus, Cambridge, MA, **2001**.

[3] M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

and/or dynamic kinetic resolution. As a general limitation, the total yield of the process can be at most 50%, having to discard the unwanted enantiomer except in the case of dynamic kinetic resolution.[4]

The chiral pool strategy, which consists of generating the desired enantiopure products through stereoselective transformations starting from a stock of readily available enantiopure substances, constitutes another option.[5] Therefore, for using this approach it is necessary to find in nature a compound with the appropriate chiral structure as a single enantiomer, which may be difficult.

The third strategy for obtaining enantiopure α-functionalized carbonyl compounds is asymmetric synthesis, where an achiral substrate is transformed into a chiral one with generation of at least one new stereogenic element. The asymmetric induction may come from a chiral auxiliary, from a chiral reagent or from a chiral catalyst. In the first case, the chiral auxiliary[6] is attached to the prochiral starting material (usually in high yield and under mild conditions) generally a carboxylic acid, although ketones have also been employed. Chiral auxiliaries were first introduced by E. J. Corey in 1975,[7] using chiral 8-phenylmenthol. Following this pioneering work, many other chiral auxiliaries were reported in the following years. Among them, Evans oxazolidinone auxiliaries, Oppolzer´s camphorsultam, the SAMP (RAMP) hydrazines of Enders and Myers amino alcohol (Scheme 2) have contributed significantly to the advancement of asymmetric synthesis.[8]

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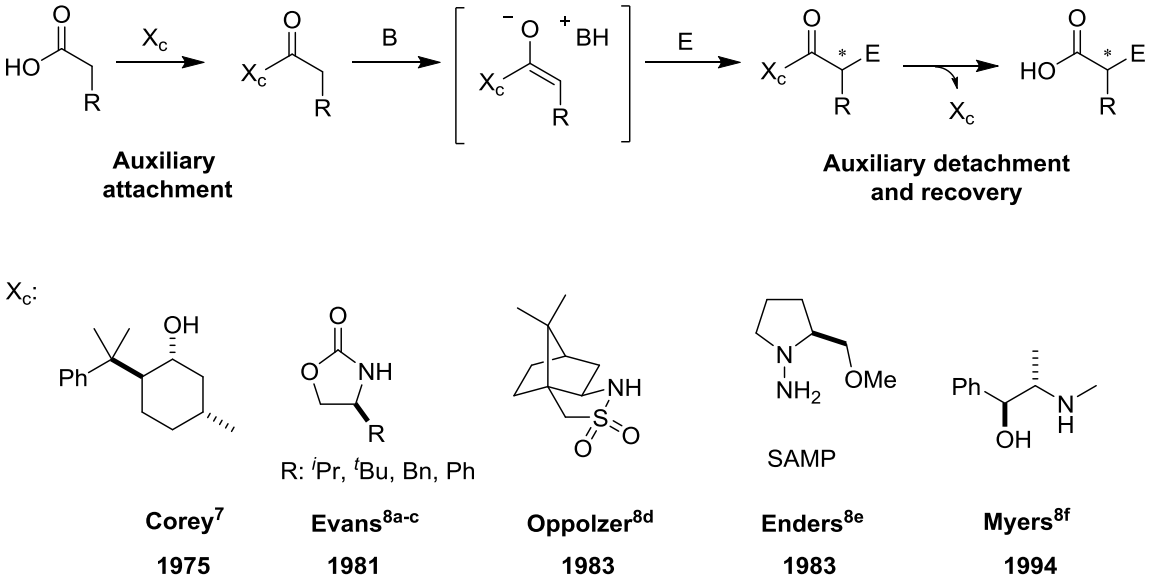
[4] Dynamic kinetic resolution allows *in situ* epimerization of the substrate prior to the reaction, obtaining quantitative conversion of the starting material into a single stereoisomer of the product. For more information about dynamic kinetic resolution, see: a) H. Pellissier, *Tetrahedron* **2011**, *67*, 3769–3802. b) F. F. Huerta, A. B. E. Minidis, J. -E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331. c) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.

[5] For more information about chiral pool strategy, see: a) Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753–11795. b) K. C. Nicolaou, S. A. Spyder, *Classics in Total Synthesis II,* Wiley-VCH, Weinheim, **2003**. c) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis I,* Wiley-VCH, Weinheim, **1996**. d) S. Hanessian, *Pure Appl. Chem.* **1993**, *65,* 1189–1204. e) H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935–952. f) S. Hanessian, J. Franco, B. Larouche, *Pure Appl. Chem.* **1990**, *62*, 1887–1910.

[6] For more information about chiral auxiliaries, see: a) G. Roos, *Key Chiral Auxiliary Applications*, Academic Press, New York, **2014**. b) L. A. Paquette, *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis,* Willey, New York, **2013**. c) F. Glorious, Y. Gnass, *Synthesis* **2006**, *12*, 1899–1930. d) G. Roos, *Compendium of Chiral Auxiliary Applications*, Academic Press, New York, **2002**.

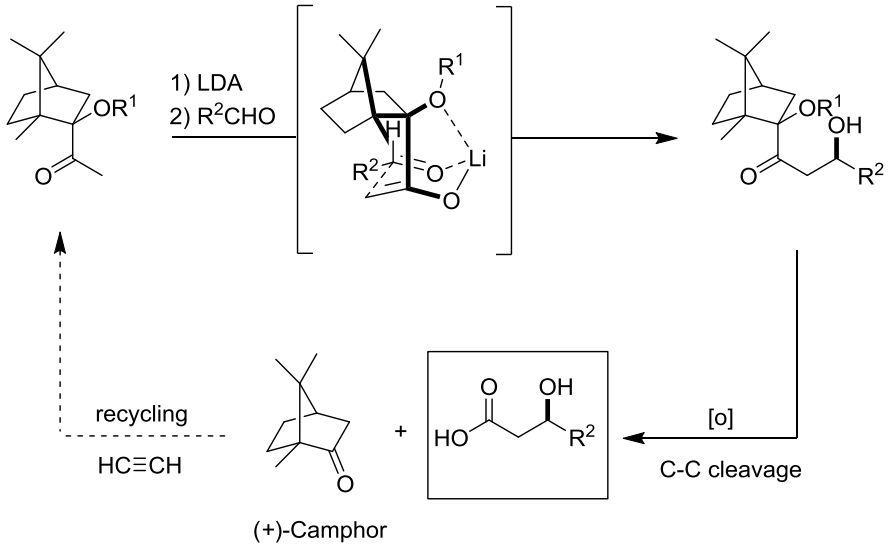
[7] E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.

[8] For general reviews on the use of Evan´s oxazolidinones as chiral auxiliaries, see: a) V. Zadsirjan, M. M. Heravi, *Current Organic Synthesis* **2018**, *15*, 3–20. b) M. M. Heravi, V. Zadsirjan, B. Farajpour, *RSC Adv.* **2016**, *6*, 30498–30551. c) M. M. Heravi, V. Zadsirjan, *Tetrahedron:Asymmetry* **2013**, *24*, 1149–1188. For a general review on the use of Oppolzer´s camphorsultams as chiral auxiliaries, see: d) M. M. Heravi, V. Zadrirjan, *Tetrahedron: Asymmetry* **2014**, *25*, 1061–1090. For a general review on the use of Enders´hydrazines as chiral auxiliaries, see: e) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329. For the first example of the use of Myers amino alcohol, see: f) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362.



Scheme 2. The chiral auxiliary strategy and some representative examples of chiral auxiliaries.

In this context, our group documented the utility of camphor-based ketones to carry out highly diastereoselective reactions.[9] In particular, the corresponding methyl ketone (Scheme 3) readily prepared from (1*R*)-(*+*)-camphor and acetylene, two raw materials available in bulk, successfully addresses the problem of the insufficient stereoselectivity often encountered in the diastereoselective "acetate" aldol reaction[10] with the auxiliaries noted above.



Scheme 3. Diastereoselective "acetate" aldol reaction and the Zimmerman-Traxler model accounting for stereocontrol.

[9] C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2012**, *41*, 4150–4164.
[10] C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodriguez, A. Linden, *Angew. Chem. Int. Ed.* **1998**, *37*, 180–182.

Although the use of chiral auxiliaries has been found successful in the total synthesis of several bioactive compounds,[11] it is not the method of choice nowadays as stoichiometric amount of homochiral auxiliary and additional steps for the attachment, detachment and recovery of the auxiliary are required.

Due to the convenient view of atom economy and simplicity, asymmetric catalytic procedures, in which a substoichiometric amount of a chiral inductor is enough to accomplish the reaction with high chemo-, regio- and stereoselectivity, have gained in importance. Depending on the catalyst used, three areas are distinguished: biocatalysis,[12] organometallic catalysis[13] and organocatalysis[14] (Figure 3).

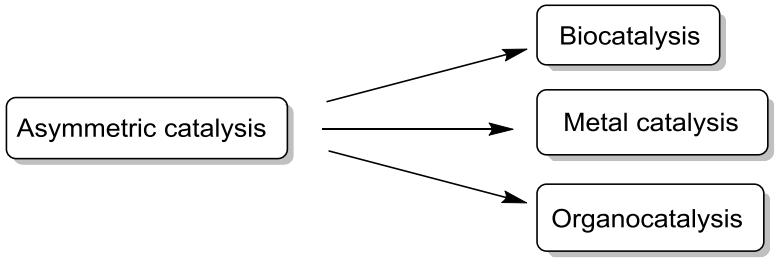


Figure 3. Asymmetric catalysis.

Biocatalysis is mainly based on high regio-, chemo- and stereoselective enzymatic processes which are commonly limited to certain substrates and reaction categories. However, organometallic catalysis and organocatalysis are more compatible with the development of numerous asymmetric transformations with a great variety of structurally different substrates. In this context, organocatalytic methods have attracted much interest in the last two decades. Organocatalysts tend to be i) air- and moisture-stable, ii) may work under mild conditions and high concentrations thus avoiding the use

[11] For general reviews on the use of chiral auxiliaries in total synthesis, see: a) S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Org. Biomol. Chem.* **2019**, *17*, 1322–1335. b) ref. 8a-b.

[12] For more information about biocatalysis, see: a) J. Albarrán, D. González, V. Gotor, *Biocatal. Biotransform.* **2018**, *36*, 102–130. b) U. T. Bornscheur, G. W. Huisman, R. J. Kazlauskas, S. Lutz, J. C. Moore, K. Robins, *Nature* **2012**, *485*, 185–194. c) J. Hernando, P. A. J. De Witte, E. M. H. P. Van Dijk, J. Korterik, R. J. M. Nolte, A. E. Nolte, A. E. Rowan, M. F. García-Parajo, N. F. Van Hulst, *Angew. Chem. Int. Ed.* **2004**, *43*, 4075–4078.

[13] For a general review on activation of C-H bonds *via* metal catalysis, see: a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452. For a general review on α-hetereofunctionalization of carbonyl compounds *via* metal catalysis, see: b) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637–1656. For a general review on fluoration *via* metal catalysis, see: c) C. Chen, L. Fu, P. Chen, G. Liu, *Chin. J. Chem.* **2017**, *17*, 1781–1788. For a general review on C-H bond cleavage *via* metal catalysis, see: d) C. G. Newton, S. -G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976.

[14] a) P. I. Dalko, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications,* Wiley-VCH, Weinheim, Vol. 1–3, **2013**. b) B. List, *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*, Thieme, Stuttgart, **2012**. c) K. Maruoka, *Brønsted Base and Acid Catalysts, and Additional Topics*, Thieme, Stuttgart, **2012**.

of undesired large amounts of solvents, iii) are low- or non-toxic, and iv) many are available in both enantiomers from nature, or can be obtained through simple chemical reactions.[15]

1.2. Direct organocatalytic asymmetric α-functionalitation of carbonyl compounds

Depending on how the organocatalyst activates the substrate, two types of organocatalysis can be differentiated: covalent catalysis and non-covalent catalysis.[16] In the first case, the catalyst and the substrate react through covalent interactions to afford a reactive intermediate, whereas, in non-covalent organocatalysis, which will be outlined later, reactions are accelerated and controlled by weak interactions such as hydrogen bonds between the substrate and the catalyst or the formation of ion pairs.

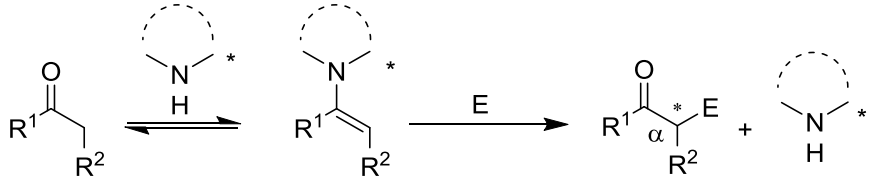
1.2.1. Covalent activation *via* aminocatalysis

Aminocatalysis constitutes one of the most employed method for asymmetric functionalization of carbonyl compounds (i.e. aldehydes and ketones) via formation of enamine and iminium ion as reactive covalent adducts. In this regard, HOMO (enamine, dienamine and trienamine),[17] LUMO (iminium ion)[18] and SOMO activation[19] strategies are used to activate aldehydes and ketones.

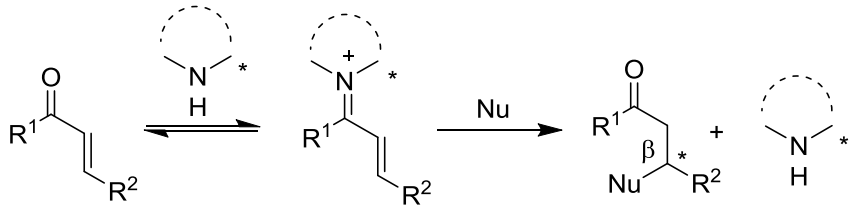
The enamine activation is based on the reversible generation of chiral enamine intermediates from a primary or secondary amine and an enolizable aldehyde or ketone substrate. Reaction of these intermediates with a suitable electrophile leads to the α-functionalization of such compounds (Scheme 4a). On the other hand, iminium activation strategy enables the β-functionalization of carbonyl compounds (Scheme 4b). It is worth of noting that this activation may also be combined with enamine catalysis for the consecutive formation of multiple stereocenters. Thus iminium ion/enamine cascade catalysis may proceed through the conjugate addition of a nucleophile to the iminium ion, followed by functionalization at the α-position of the transiently generated enamine intermediate (Scheme 4c).

[15] D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.
[16] For a classification of generic mechanisms of organocatalytic reactivity, see: M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41–49.
[17] For general reviews on enamine-mediated catalysis, see: a) Fu, N.; Zhang, L.; Luo, S. *Org. Biomol. Chem.* **2018**, *16*, 510–520. b) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[18] For general reviews on iminium ion-mediated catalysis, see: a) G. Bartoli, P. Melchiorre, *Synlett*, **2008**, *12*, 1759–1772. b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
[19] For general reviews on SOMO catalysis, see: a) M. Meciarová, P. Tisovský, R. Sebesta, *New J. Chem.* **2016**, *40*, 4855–4864. b) T. D. Beeson, A. Mastracchio, J. -B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582–585.

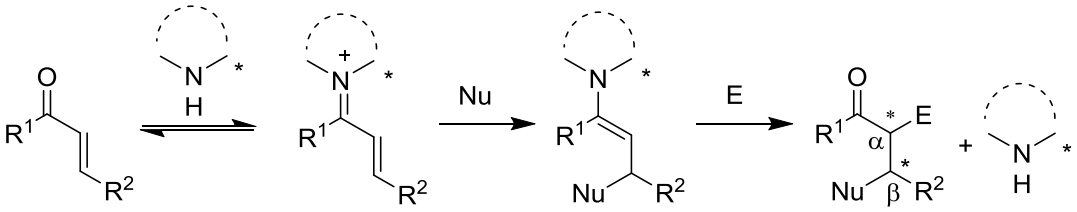
a) Enamine activation: α-functionalization



b) Iminium ion activation: β-functionalization



c) Iminium ion/enamine activation: α, β-functionalization



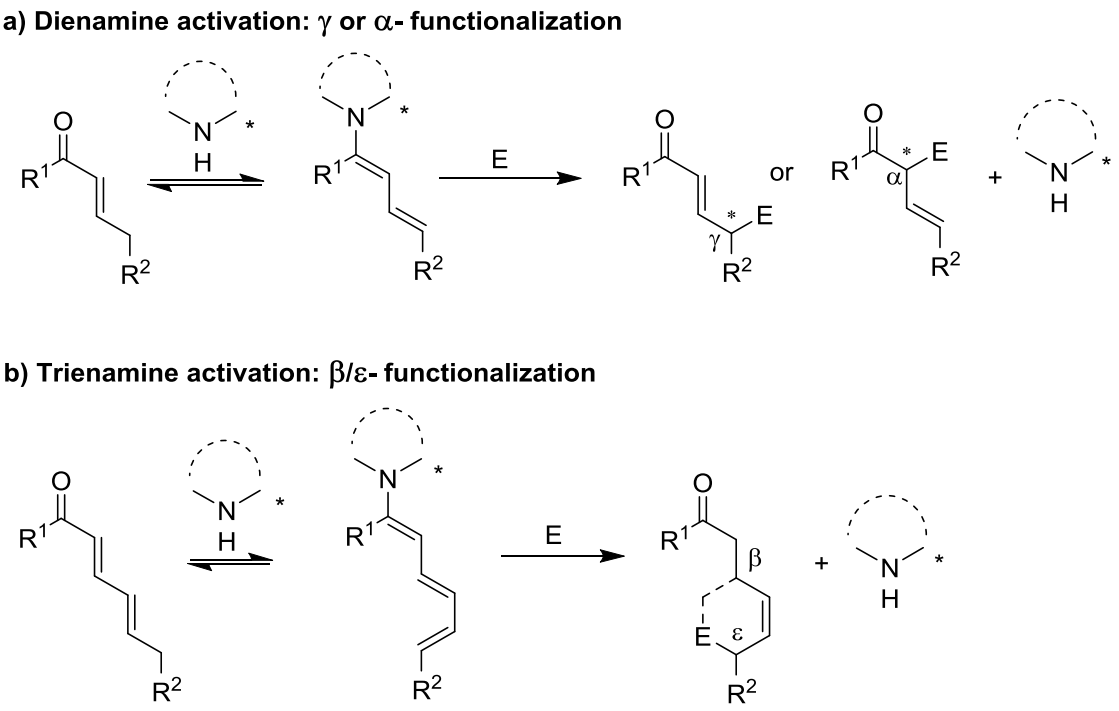
Scheme 4. Enamine, iminium ion and iminium ion/enamine activations for the functionalization of carbonyl compounds.

This HOMO-activation concept[20] was extended to the use of α,β-unsaturated aldehydes or ketones, which after condensation with a chiral amine generate a dienamine species capable of undergoing stereoselective α or γ-functionalization (Scheme 5a).[21] In 2011, the HOMO-activation strategy was expanded to trienamines, which are formed upon the condensation of an amine catalyst with dienals or dienones. These generated trienamines usually react at β,ε-positions leading to functionalized cyclohexenes (Scheme 5b).[22]

[20] E. Arceo, P. Melchiorre, *Angew. Chem. Int. Ed.* **2002**, *51*, 5290–5292.

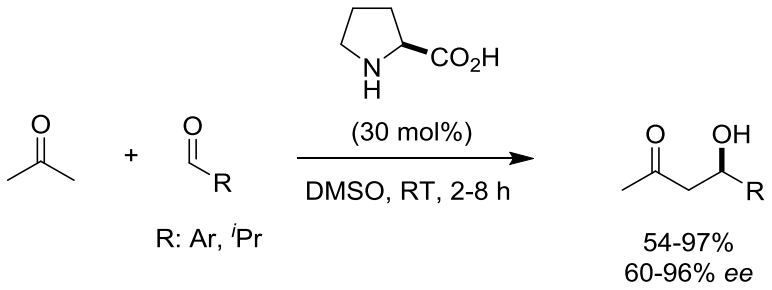
[21] For the first example of dienamine catalysis, see: S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

[22] For the first example of trienamine catalysis, see: Z. -J. Jia, H. Jiang, J. -L. Li, B. Gschwend, Q. -Z. Li, X. Yin, J. Grouleff, Y. C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.



Scheme 5. Dienamine and trienamine activations for the functionalization of carbonyl compounds.

Although the first asymmetric enamine catalysis was described in 1974,[17c] until the beginning of this century, the asymmetric enamine catalysis was limited to a narrow history. A revival of this chemistry was initiated by the discovery of the (*S*)-proline catalyzed direct asymmetric intermolecular aldol reaction, which was described by List, Lerner and Barbas III in 2000 (Scheme 6).[23]



Scheme 6. (*S*)-Proline-catalyzed first direct asymmetric intermolecular aldol reaction. List, Lerner and Barbas III, 2000.

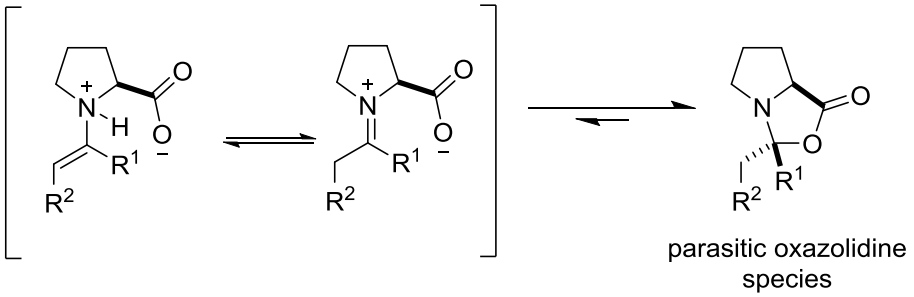
Since then, proline-catalyzed enantioselective intermolecular aldol,[24] Mannich,[25] and Michael reactions[26] have been reported, as well as other highly enantioselective α-

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

[24] For representative examples about the use of proline in asymmetric aldol reactions see: a) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575. b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387. For the first direct enantioselective cross-aldol reaction, see: c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

functionalizations of enolizable aldehydes and ketones, such as aminations,[27] hydroxylations,[28] alkylations[29] and halogenations.[30]

Given the poor solubility of proline in most organic solvents and the formation of a parasitic oxazolidine species (Scheme 7) which may lead to the entrapment of the catalyst,[31] new amino catalysts have been designed modifying the structure of the proline. The substitution of the carboxylic acid of the proline for other functional groups resulted in an increase of solubility, among other advantages.



Scheme 7. Parasitic oxazolidine species of proline.

Although proline emerged as fairly general and efficient organocatalyst, MacMillan's imidazolidinones,[32] protected prolinol derivatives, particularly α,α-

[25] For representative examples about the use of proline as a catalyst in Mannich reactions involving preformed imines, see: a) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* **2005**, *44,* 4079–4083. b) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem. Int. Ed.* **2003**, *42,* 3677–3680. c) Y. Hayasi, W. Tsuboi, M. Shoji, N. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 11208–11209. d) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337. e) B. List, P. Pojarliev, W. T. Biller, H. J. Martin *J. Am. Chem. Soc.* **2002**, *124*, 827–833. For examples about the use of proline in Mannich reactions involving imines, see: f) A. Cordova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, *J. Am. Chem. Soc*. **2002**, *124*, 1842–1843. g) A. Cordova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867.

[26] For representative examples about the use of proline as a catalyst in Michael reactions, see: a) D. Enders, A. Seki, *Synlett.* **2002**, *1*, 26–28. b) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.

[27] For representative examples about the use of proline in amination reactions, see: a) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657. b) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen*, J. Am. Chem. Soc.* **2002**, *124*, 6254–6255. c) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.

[28] For representative examples about the use of proline as a catalyst in hydroxylation reactions, see: a) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1115. b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan*, J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. c) G. Zhongm, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250.

[29] For example about the use of proline as a catalyst in intramolecular alkylation reaction, see: R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8707–8710.

[30] For a example about the use of proline as a catalyst in fluorination reaction, see: D. Enders, M. R. M. Hüttl, *Synlett.* **2005**, *6*, 991–993.

[31] D. A. Bock, C. W. Lehmann, B. List, *PNAS* **2010**, *107*, 20636–20641.

[32] For selected examples: For Diels-Alder reaction, see: a) K. A. Ahrendt, C. J. Borths, D. W. C. McMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243–4244. For α-fluorination, see: b) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828. For Michael reaction, see: c) M. H. Fonseca, B. List, *Angew. Chem. Int. Ed.* **2004**, *43*, 3958–3960. For α-chlorination, see: d) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am.*

diarylprolinol silyl ethers[33] and chiral primary amines[34] (including α-amino acid other than proline) have also shown high catalytic performance in several transformations (Figure 4).

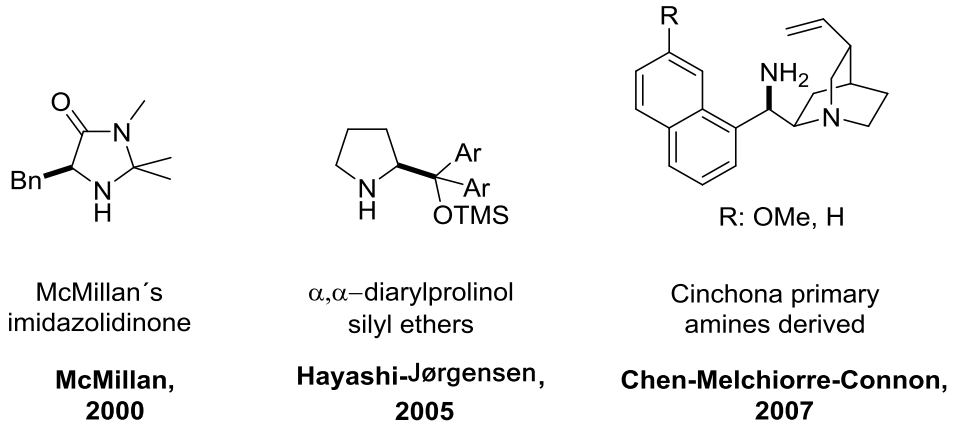
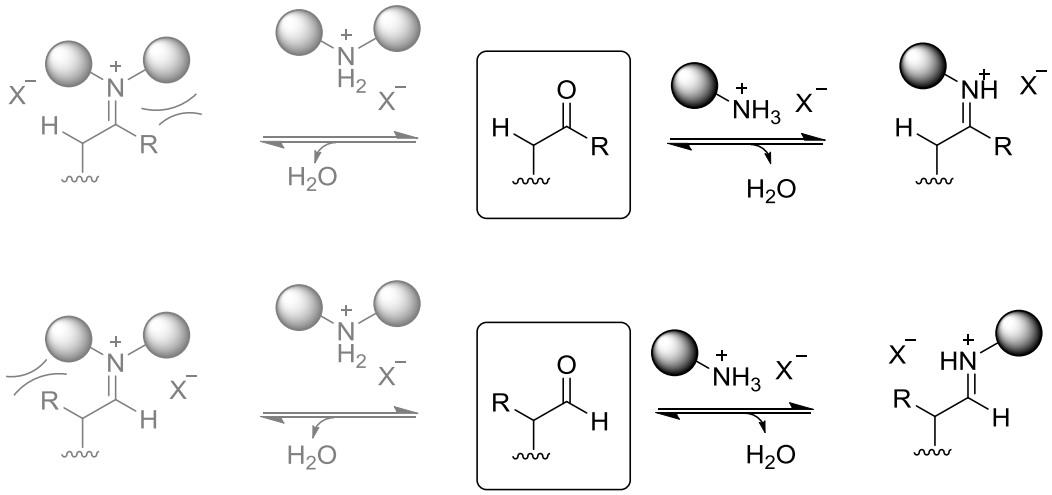


Figure 4. Most representative aminocatalysts: McMillan catalyst, α,α-diarylprolinol silyl ethers and cinchona based primary amines.

While primary chiral amines, in comparison with secondary amines, suffer from reduced nucleophilicity and unfavourable imine/enamine equilibrium,[35] they allow easier condensation with ketones and α-branched aldehydes (Scheme 8).[34b]



Scheme 8. Secondary and primary amine catalysis in the iminium activation of ketones and α-branched aldehydes.

Chem. Soc. **2004**, *126*, 4108–4109. For Friedel-Crafts alkylation, see: e) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4379–4371. For 1,3-dipolar cycloaddition, see: f) W. Jen, J. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2000**, *122*, 9874–9875.

[33] For a general review, see: a) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264. b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922-948. c) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880.

[34] For general reviews on primary amines as catalysts, see: a) L. Zhang, N. Fu, S. Luo*, Acc. Chem. Res*. **2015**, *48*, 986–997. b) P. Melchiore, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770.

[35] R. A. Clark, D. C. Parker, *J. Am. Chem. Soc*. **1971**, *93*, 7257–7261.

Since 2000, aminocatalysis has grown at a dizzying pace establishing itself as a powerful methodology for asymmetric synthesis.[14] Although essentially all types of ketones and aldehydes have been used, still the use of sterically hindered ketones remains challenging. Moreover, unsymmetrical ketones have been scarcely used mainly due to the difficulties in controlling regioselectivity.

1.2.2. Non-covalent activation *via* base promoted enolization

As mentioned before, non-covalent activation is based on the cooperation of several weak attractive interactions between a basic functional group of the substrate and the catalyst. Although the catalyst-substrate interactions are generally weaker and less directional compared with covalent substrate-catalyst interactions, high degree of enantioselectivity may also be obtained.[16] Hydrogen-bonding activation,[36] phase transfer catalysis (PTC),[37] anion binding activation,[38] Brønsted acid catalysis[39] and Brønsted base catalysis[40] all rely on non covalent interaction between the substrate and the catalyst. More specifically, Børnsted base catalysis enable several types of C-C and C-heteroatom bond forming reactions mediated by transiently generated enolate intermediates. However, a general problem with Brønsted base catalysis is the functional pK_a barrier of most catalysts that compromises their efficiency when less acidic carbon pronucleophiles are involved. Because of that, easily enolizable compounds, typically bearing an EWG at the α-carbon, are used.[40b]

The catalytic cycle in BB-trigged processes is initiated *via* deprotonation of the pronucleophile by the basic catalyst, forming a chiral ionic pair, which reacts with the corresponding electrophile in a stereoselective way to provide the product and liberation of free chiral basic catalyst, which could re-enter again the catalytic cycle (Scheme 9).

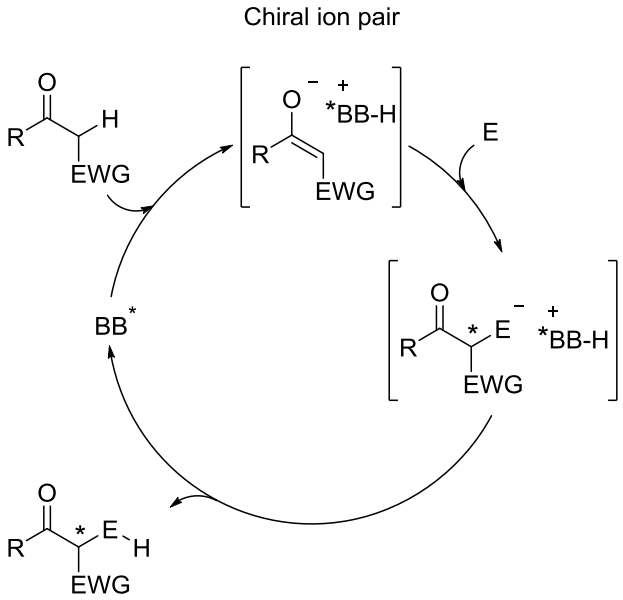
[36] For general reviews on hydrogen-bonding catalysis, see: a) Y. Nishikawa, *Tetrahedron Lett.* **2018**, *59*, 216–223. b) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem*. **2014**, 2633–2646.

[37] For general reviews on phase transfer catalysis, see: a) S. Kaneko, Y. Kumatabara, S. Shirakawa, *Org. Biomol. Chem.* **2016**, *14*, 5367–5376. b) J. Tan, N. Yasuda, *Org. Process Res. Dev.* **2015**, *19*, 1731–1746.

[38] For general reviews on anion-binding activation, see: a) M. D. Visco, J. Attard, Y. Guan, A. E. Mattson *Tetrahedron Lett.* **2017**, *58*, 2623–2628. b) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. c) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.

[39] For a general review on Brønsted acid catalysis, see: a) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153.

[40] For general reviews on Brønsted base catalysis, see: a) B. Teng, W. C. Lim, C. H. Tan, *Synlett.* **2017**, *28*, 1272–1277. b) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632–653.



Scheme 9. Catalytic cycle promoted by a chiral Brønsted base.

Tertiary amines, guanidines[41] amidines[42] and imidazoles[43] are the most prominent nitrogen-containing functionalities used for the design of chiral Brønsted base catalysts (Figure 5a). In this context, alkaloids, particularly those of the cinchona family, constitute a very popular source of enantiopure Brønsted base catalysts (Figure 5b).

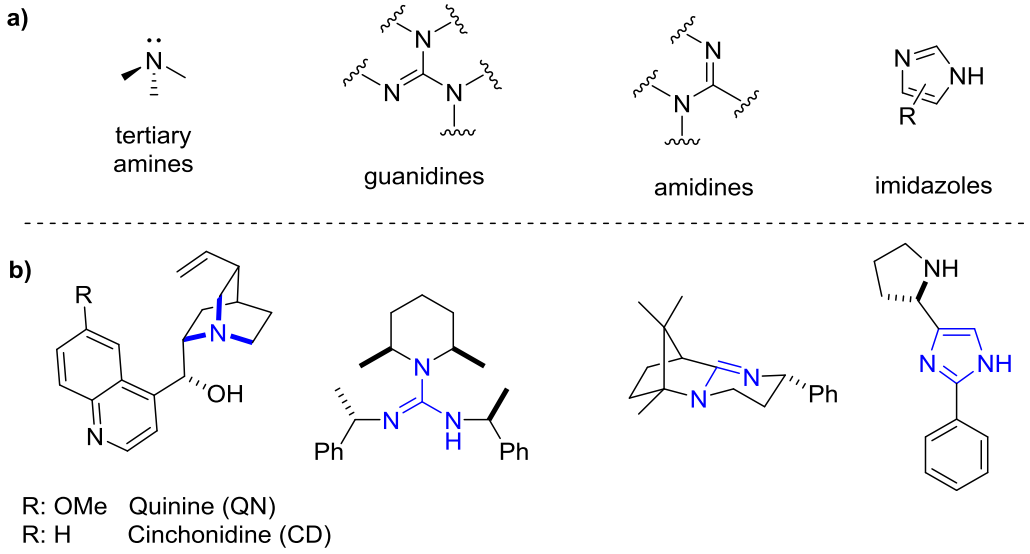


Figure 5. a) Core functions of Brønsted base catalysts. b) Some representative examples.

[41] For general reviews on chiral guanidines, see: a) S. Dong, X. Feng, X. Liu, *Chem. Soc. Rev.* **2018**, *47*, 8525–8540. b) P. Selig, *Synthesis* **2013**, *45*, 703–718.
[42] For more information about amidines, see: a) N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2004**, *43*, 478–482. b) W. ten Hoeve, H. Wynberg, *Synthetic communications* **1994**, *24*, 2215–2221.
[43] For more information about imidazoles, see: F. Bures, J. Kulhánek, *Tetrahedron: Asymmetry* **2005**, *16*, 1347–1354.

With the aim of emulating the efficiency and selectivity of enzymes, many efforts have focused on bifunctional catalysts, which include two different reacting functional sites.[44] In general, bifunctional catalysts possess either Lewis or Brønsted basic functionality and a hydrogen-bond donor group suitably positioned over a chiral scaffold and thus can simultaneously bind and activate the pronucleophile and the electrophile (Figure 6).

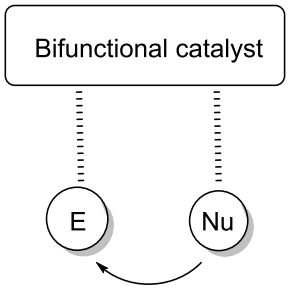


Figure 6. General activation mode of bifunctional catalysts.

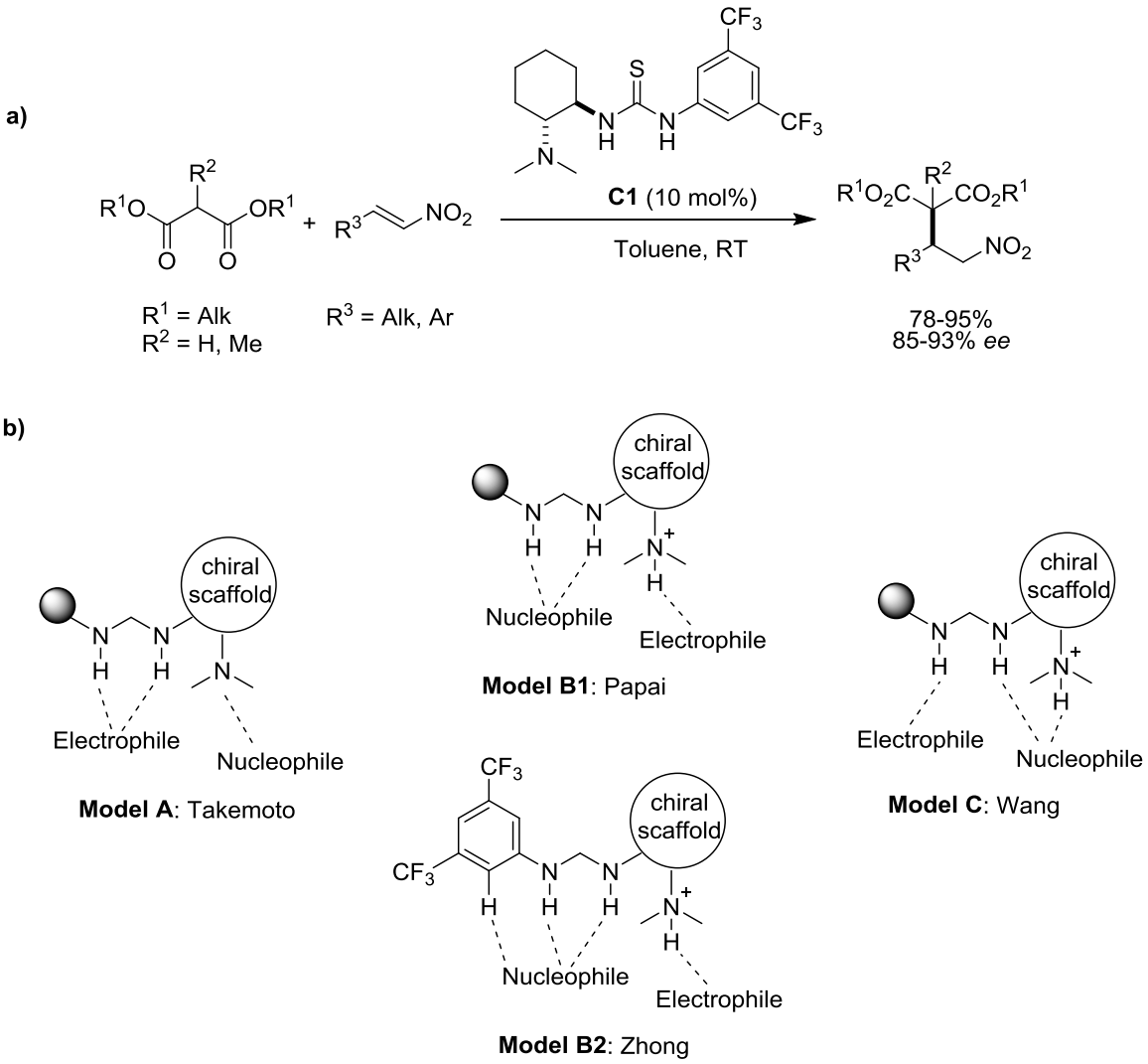
The concept of bifunctional organocatalysis was anticipated by Wynberg[45] and established, several years later, by Takemoto, who developed cyclohexyldiamine derived thiourea catalyst **C1** for the enantioselective Michael addition of dimethylmalonates to nitroolefins (Scheme 10a).[46] According to the authors proposal, the electrophile would be activated by the thiourea while the tertiary amine would deprotonate the pronucleophile. However, different mechanistic proposals have recently appeared, that support alternative activation modes (Scheme 10b).[47]

[44] For general reviews on bifunctional catalysis, see: a) X. Fang, C. -J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197. b) L. -Q. Lu, X. -L. An, J. -R. Chen, W. -J. Xiao, *Synlett.* **2012**, 23, 490–508.

[45] Wynberg published the first example of Brønsted base catalyzed reaction in which a cinchona alkaloid operated as bifunctional catalyst in enantioselective addition of α-ketoesters to vinyl ketones. For more information, see: H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4060.

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

[47] For example, Pápai found through computational studies that the malonate is coordinated by the thiourea moiety, whereas the electrophile is activated by the protonated tertiary amine. For more information, see: a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160. For more information on Zhong´s proposal (the proton in ortho position of the aromatic ring also participates in the activation of the nucleophile), see: b) B. Tan, Y. Lu, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682–2685. For more information on Wang´s proposal (the protonated amine and one N-H of the thiourea moiety activate simultaneously the nucleophile, whereas the other N-H of the thiourea moiety activates the electrophile), see: c) J. -L. Zhu, Y. Zhang, C. Liu, A. -M. Zheng, W. Wang, *J. Org. Chem.* **2012**, *77*, 9813–9825.



Scheme 10. a) Enantioselective Michael addition catalyzed by bifunctional organocatalyst **C1**. Takemoto, 2003. b) Three alternative substrate-catalyst combinations.

In view of the precedent set by Takemoto´s bifunctional catalyst, thiourea-substituted cinchona alkaloid catalysts were developed by Soós,[48] Connon[49] and Dixon[50] independently (Figure 7). To date, a large number of thiourea-tertiary amine catalysts have appeared and reviewed several times.[51]

[48] B. Vakulya, S. Varga, A. Csámpai, T. Sóos, *Org. Lett.* **2005**, *7*, 1967–1969.
[49] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.
[50] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.
[51] For more information about chincona alkaloids, see: a) E. M. O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron* **2011**, *67*, 1725–1762. b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279. c) C. E. Song, *Cinchona Alkaloids in Synthesis and Catalysis*, Wiley-VCH, **2009**. For general reviews on thiourea catalysts, see: d) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051–7071. e) S. J. Connon, *Chem. Commun.* **2008**, 2499–2509.

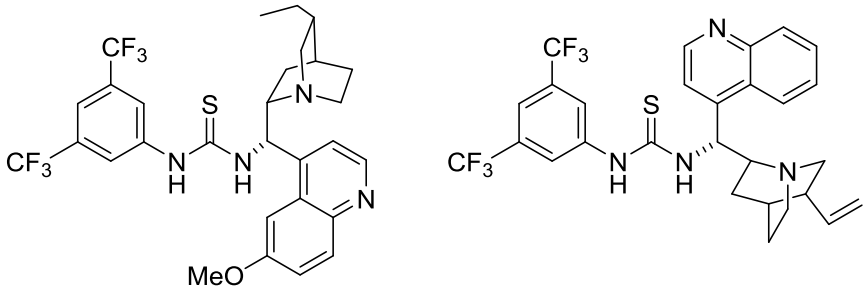
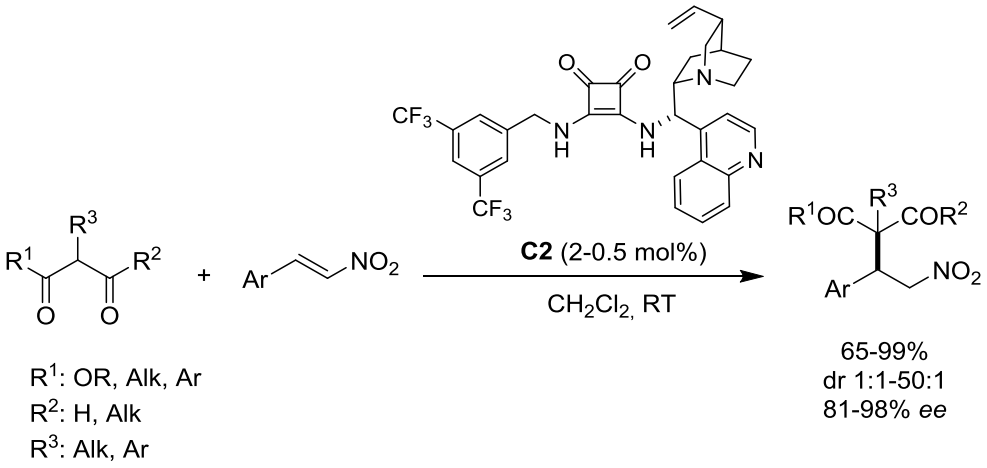


Figure 7. Bifunctional thiourea-tertiary amine catalysts.

In 2008 Rawal´s group demonstrated the capacity of the squaramide/tertiary amine conjugated to act as bifunctional catalysts (Scheme 11),[52] and since a number of studies concerning this class of catalyst have been realized.[53]



Scheme 11. Chiral squaramide/BB catalyst **C2** as excellent hydrogen bond donor in Michael addition. Rawal, 2008.

Although both families of catalysts are commonly employed, squaramides are more acidic than thioureas and hydrogen bond interactions with the substrate are usually stronger (Figure 8a).[54] The additional advantage compared to thioureas is the rapid and facile preparation of squaramides from easily available starting materials, squaric esters and amines (Figure 8b). Moreover, in many cases, once the catalyst is formed, it precipitates from the reaction mixture, making chromatographic purification unnecessary.

[52] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14418.
[53] For general reviews on squaramide based catalysts, see: a) B. -L. Zhao, J. -H. Li, D. -M. Du, *Chem. Rev.* **2017**, *17*, 994–1018. b) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906.
[54] For more information, see: a) B. -L. Zhao, J. -H. Li, D. -M. Du, *Chem. Rec.* **2017**, *17*, 994–1018. b) X. Ni, X. Li, Z. Wang, J. P. Cheng, *Org. Lett.* **2014**, *16*, 1786–1789. c) S. Tomàs, R. Prohens, M. Mega, M. C. Rotger, P. M. Deyá, P. Ballester, A. Costa, *J. Org. Chem.* **1996**, *61*, 9394–9401.

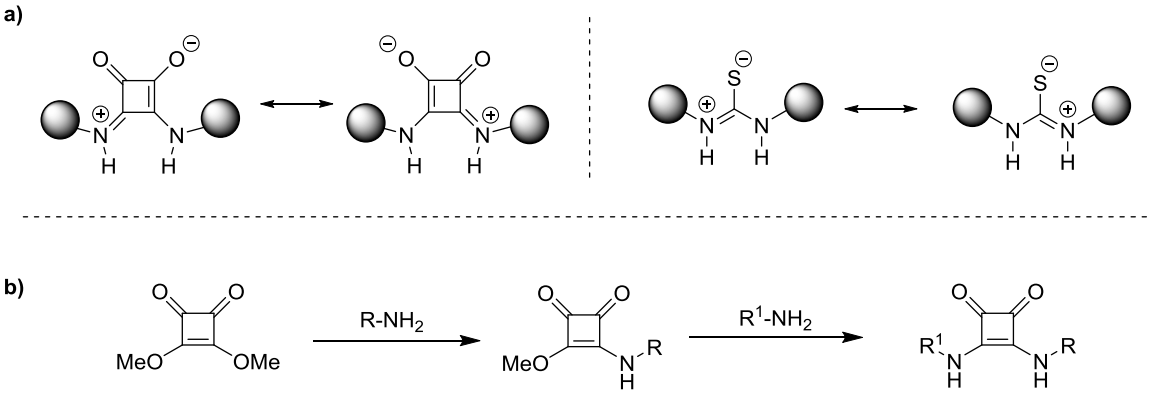


Figure 8. a) Comparison of zwitterionic forms of the thiourea and squaramide skeletons. b) General procedure for the synthesis of squaramide catalysts.

As mentioned above, a general problem with Brønsted base catalysis is the functional pK_a barrier of most catalysts that compromises their efficiency with less acidic carbon pronucleophiles.[40b] In the following section, some strategies to solve this limitation are described.

1.3. Less reactive carbonyl compounds in Brønsted base activation

Contrary to enamine- and iminium ion-mediated organocatalytic processes, which are suitable for aldehydes and ketones only, Brønsted base activation protocol can, in principle, be applied not only to the latter, but also to carboxylic acid derivatives and even non-carbonyl substrates with an acidic CH.

Any enolizable carbonyl compound may be activated as donor component by proton abstraction with a Brønsted base catalyst to react with an electrophilic species. Considerable progress has been made in enantioselective reactions of carbonyl and related compounds using these approaches; however simple monofunctional carbonyl compounds are often poorly reactive as nucleophile, and require an additional activation in order to get sufficient reactivity (Figure 9).

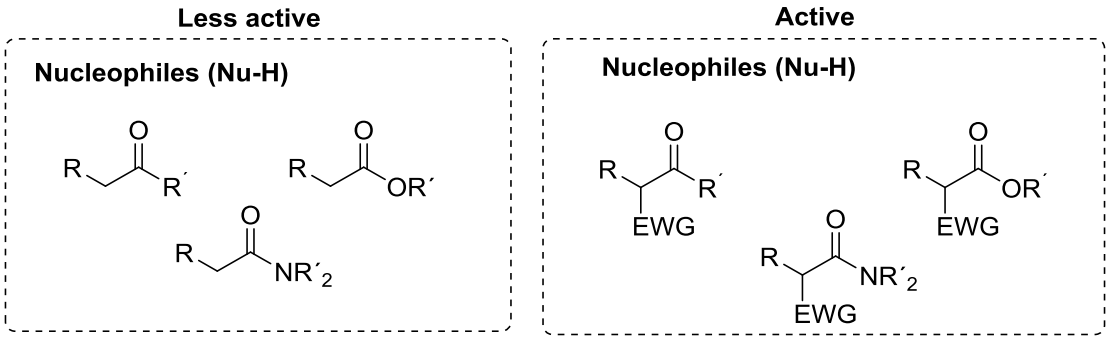
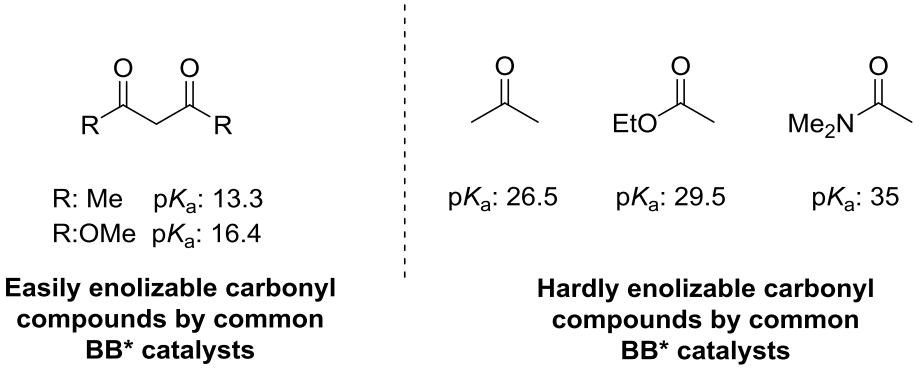


Figure 9. Examples of active and less active nucleophiles.

1.3.1. Activation of nucleophiles

When employing enolizable carbonyl compounds as nucleophiles, the acidity of the α-carbon is of great importance. This factor determines the aptitude of the compound to generate the corresponding enolate. Unactivated or less reactive carbonyl compounds display high pK_a values, thus they are challenging starting materials for their α-functionalization in the presence of weak Brønsted base catalysts (pK_a values of 16 and 17).[55] Some classes of carbonyl compounds are depicted in Scheme 12 with their pK_a values.



Scheme 12. pK_a values of some carbonyl compounds in DMSO.[56]

Previously reported data in the literature and our own observations in the context of asymmetric organocatalysis indicate that both reactivity and selectivity of catalytic organic transformations may be strongly influenced by tiny modifications on the structure of nucleophiles.

A solution for the efficient α-functionalization of less reactive carbonyl compounds is the incorporation of electron withdrawing groups in appropriate sites of the carbonyl compound (at the C_{ipso} position or at the α-carbon) (Figure 10). Up to date, the most used strategy consists of the incorporation of electron withdrawing groups (e. g. -COR,-CHO, -CO_2H, -CN, -NO_2, etc.) at the α-carbon of the respective carbonyl compound leading to a more acidic substrate. These kind of nucleophiles have been widely used in several transformations, which have been reviewed in more than one occasion.[57]

[55] J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett*. **2016**, *18*, 2648–2651.

[56] For a compilation of pKa values of representative organic compounds (Bordwell pK_a data), see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

[57] For a general review on enantioselective organocatalyzed transformations of β-ketoester and its derivatives, see: a) T. Govender, P. I. Arvidsson, G. E. M. Maguire, H. G. Kruger, T. Naicker, *Chem. Rev.* **2016**, *116*, 9375–9437. For a review on 1,3-dicarbonyl compounds in stereoselective domino and multicomponent reactions, see: b) D. Bonne, Y. Coquerel, T. Constantieux, J. Rodriguez, *Tetrahedron: Asymmetry* **2010**, *21*, 1085–1109. For a general review on enantioselective α-functionalization of

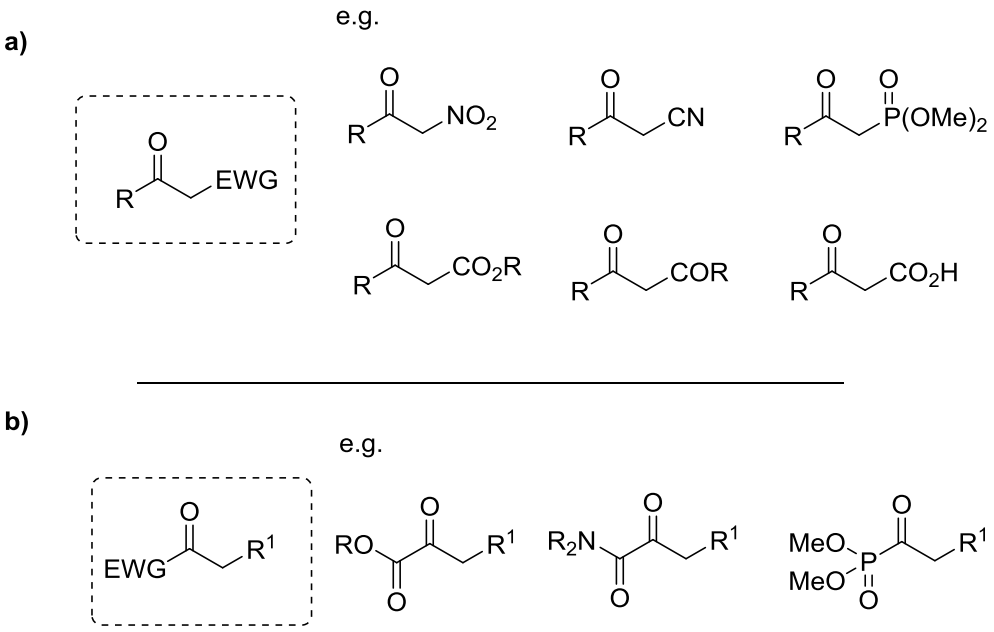
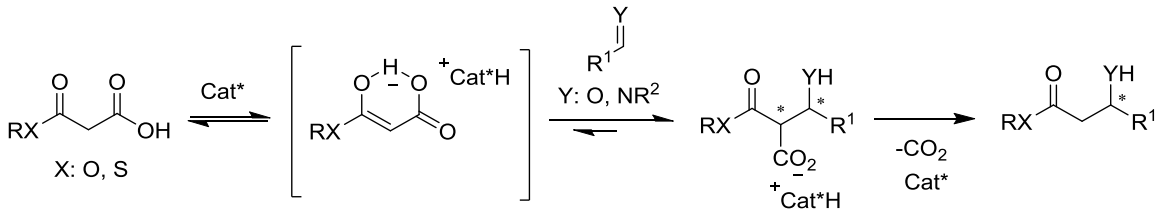


Figure 10. Active carbonyl compounds for BB-catalyzed α-functionalization incorporating an EWG at a) the α-carbon or b) the C_{ipso}.

One attractive example, inspired by the naturally occurring enzymatic polyketide biosynthesis, is the use of malonic acid half (thio)esters as (thio)ester enolate surrogates.[58] Although the reaction pathway is still under discussion, DFT studies support the reaction mechanism shown in Scheme 13 (a fast and possibly addition of the enolate intermediate is followed by a slow, irreversible decarboxylative step).[59]



Scheme 13. BB-catalyzed reactions of malonic acid half (thio)esters *via* (thio)ester enolate intermediates.

While in the above cases the electron withdrawing group is incorporated at the α carbon of the carbonyl compound, another possibility is to install the EWG at the C_{ipso} position. In this context, several groups have demonstrated that acyl phosponates[60] and

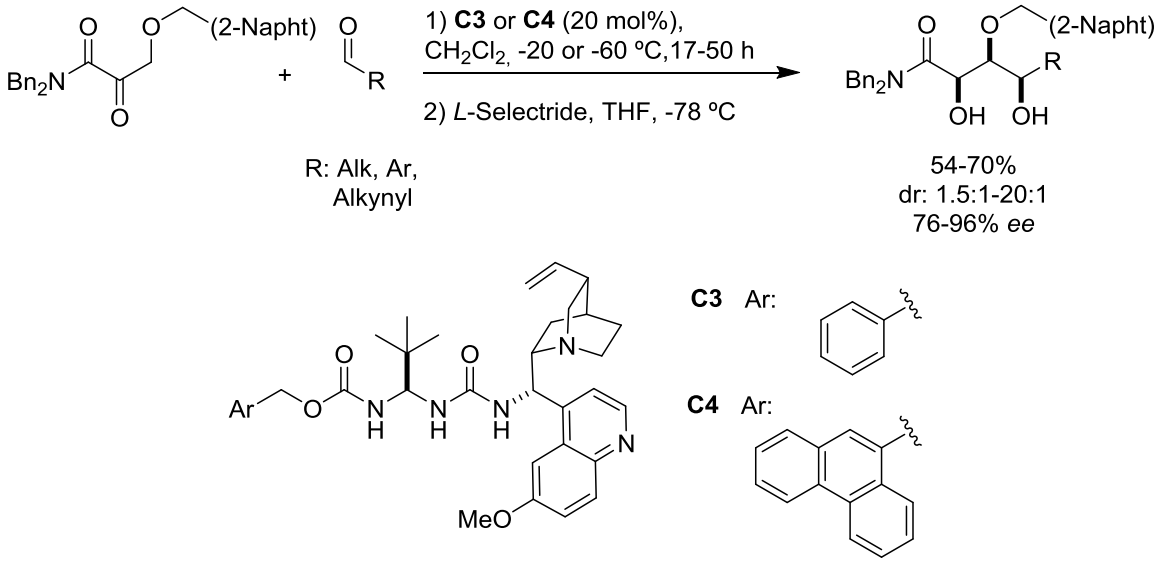
cyanoacetates, see: c) M. D. Díaz-de-Villegas, J. A. Gálvez, R. Badirrey, P. López-Ram-de-Víu, *Adv. Synth. Catal.* **2014**, *356*, 3261–3288.

[58] For general reviews on catalytic enantioselective decarboxylative reactions using organocatalysts, see: a) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394–405. b) Z. -L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745–2755. c) L. Benerdi, M. Fochi, M. Comer Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, *10*, 2911–2922.

[59] For further information on this subject, see: 58b

[60] For acyl phosponates in Michael additions, see: a) M. L. Zhang, L. Chen, Y. You, Z. -H. Wang, D. -F. Yue, X. -M. Zhang, X. -Y. Xu, W. -C. Yuan, *Tetrahedron* **2016**, *72*, 2677–2682. b) J. Guang, J. C. -G. Zhao,

α-keto esteres[61] or α-keto amides[62] are successful substrate donors in several organocatalytic carbon-carbon bond forming reactions.[63] For example, our group developed the first direct catalytic asymmetric cross-aldol reaction of α-ketoamides promoted by Brønsted base catalysts (**C3** and **C4**), affording aldol adducts in good yield, moderate diastereoselectivity and very good enantioselectivity (Scheme 14).[62b]



Scheme 14. α-Ketoamides in aldol reactions. Palomo, 2016.

Another strategy to increase the α-carbon acidity regarding enolizable carboxylic acid derivatives consist of using active thioesters. The α-carbon acidity of a thiophenol ester is about 2 pK_a units lower than that of the parent phenol ester. Based on this principle, 2,2,2-trifluoroethanethiol have been used as prone to enolize carboxylic acid derivatives (Figure 11).[64]

Tetrahedron Lett. **2013**, *54*, 5703–5706. For acyl phosponates in aldol reaction, see: c) J. Guang, Q. Guo, J. C. -G. Zhao, *Org. Lett*. **2012**, *14*, 3174–3177. For acyl phosponates in Michael addition/Lactonization reaction, see: d) M. L. Zhang, Z. J. Wu, J. -Q. Zhao, Y. Luo, X. -Y. Xu, X. -M. Zhang, W .-C. Yuan, *Org. Lett.* **2016**, *18*, 5110–5113.

[61] For α-keto esteres in aldol reaction, see: a) W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu, C. Li, *Chem. Eur. J.* **2014**, *20*, 8545–8550. For α-keto esteres in Michael addition, see: b) W. Raimondi, O. Baslø, T. Constantieux, D. Bonne, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 563–568. For α-keto esteres in amination reaction, see: c) M. Terada, K. Amagai, K. Ando, E. Kwon, H. Ube, *Chem. Eur. J.* **2011**, *17*, 9037–9041.

[62] For α-keto amides in Mannich reaction, see: a) H. Echave, I. Bastida, R. López, C. Palomo, *Chem. Eur. J.* **2018**, *24*, 11554–11558. For α-keto amides in aldol reaction, see: b) H. Echave, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2016**, *128*, 3425–3429.

[63] For general reviews on 1,2-dicarbonyl compounds, see: a) W. Raimondi, D. Bonne, J. Rodriguez, *Chem. Commun.* **2018**, *48*, 6763–6775. b) E. Raimondi, D. Bonne, J. Rodriguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 40–42. For a general review on α-oxoesteres, see: c) B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151–264. For a general review on α-keto amides, see: d) A. Muthukumar, S. Sangeetha, G. Sekar, *Org. Biomol. Chem.* **2018**, *16*, 7068–7083.

[64] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591.

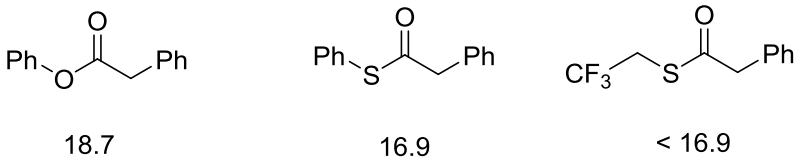
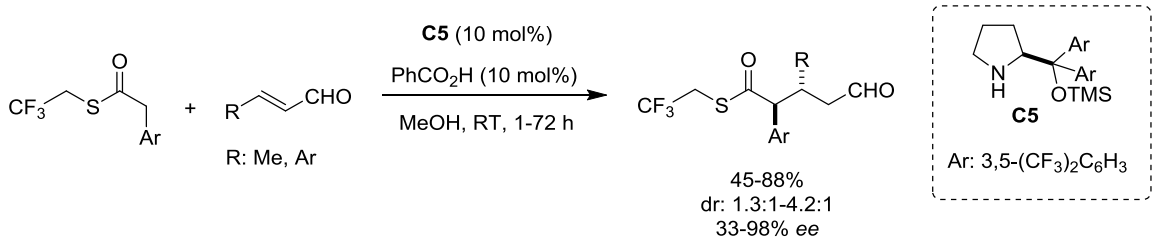


Figure 11. pK_a values of the α-carbons of some pronucleophiles in DSMO.

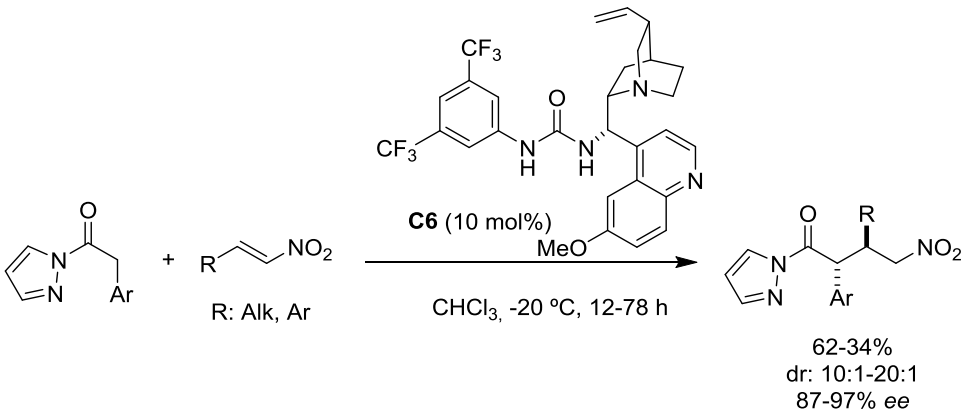
Thus, Barbas III and co-workers[64] developed the first direct catalytic asymmetric Michael addition of trifluoroethyl thioesters to α,β-unsaturated aldehydes (Scheme 15). The trialkylsilyl-protected diaryprolinol catalyst **C5** together with benzoic acid as co-catalyst provided the Michael adducts in good yield, moderate diastereoselectivity and good enantioselectivity.



Scheme 15. Trifluoroethyl thioesters in Michael additions. Barbas III, 2008.

The α-functionalization of amides promoted by Brønsted base catalysts is limited due to the low carbon acidity of amides (pK_a in DMSO ≈ 35). One exception is the case of pyrazoleamides,[65] which are considered active amides. Barbas III documented the use of pyrazoleamides for the first time as amide nucleophiles for the Michael reaction with nitroolefins catalyzed by the quinine derived bifunctional urea **C6** (Scheme 16).[65d] The authors hypothesized that the aromatic properties of the pyrazoleamide ring would provide a relatively low pK_a value, facilitating the enolization with relatively weak Brønsted bases. Moreover, this moiety serves as directing group trough hydrogen bonding to the catalyst for enhancing stereocontrol, as well as a good leaving group for further transformations.

[65] For pyrazoleamides in Diels-Alder reaction, see: a) J. Qin, Y. Zhang, C. Liu, J. Zhou, R. Zhan, W. Chen, *Org. Lett.* **2019**, *21*, 7337–7341. For pyrazoleamides in a one-pot Michael-cyclization with α,β-unsaturated aldehydes to afford δ-lactones, see: b) S. Agrawal, N. Molleti, V. Singh, *Chem. Commun*. **2015**, *51*, 9793–9796. For pyrazoleamides in Mannich reaction, see: c) T. -Z. Li, X. -B. Wang, F. Sha, X. -Y. Wu, *J. Org. Chem.* **2014**, *79*, 4332–4339. For pyrazoleamides in Michael reaction, see: d) B. Tan, G. Hernández-Torres, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2012**, *51*, 5381–5385.



Scheme 16. Pyrazoleamides in Michael additions to nitroolefins. Barbas III, 2012.

Another activation strategy for less reactive carbonyl compounds is the incorporation of a chemical auxiliary, which can activate the starting materials *via* intramolecular hydrogen-bonding. To the best of our knowledge, built on this activation principle, only *o*-hydroxyacetophenones,[66] *o*-hydroxybenzophenone imine of glycine esters[67] and α-hydroxy ketones[68] have been used as donor components in organocatalysis (Figure 12). The former ketones proved to be successful in enantioselective cross-aldol reactions with trifluoromethyl ketones; whereas diaryl ketimines of glycine esters and α-hydroxy ketones proved to be effective in enantioselective Michael additions to nitroolefins.

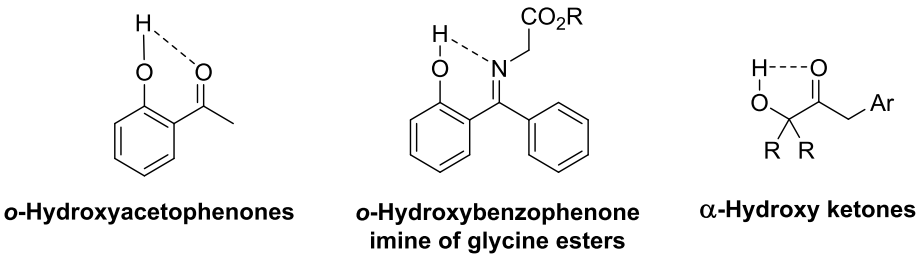
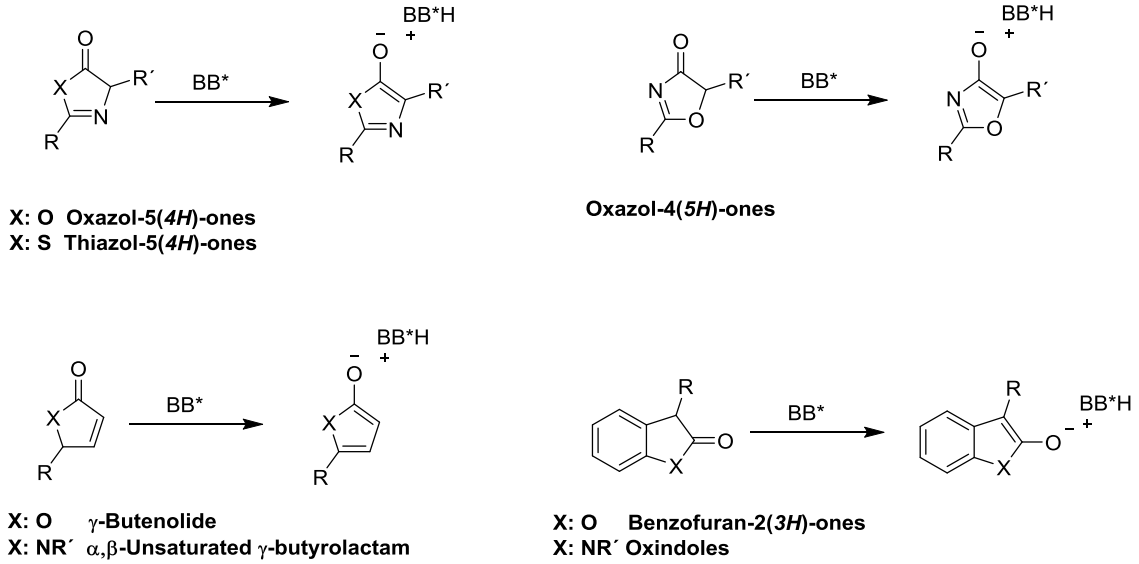


Figure 12. Intramolecular hydrogen-bonding activation of pronucleophiles in asymmetric organocatalysis.

Another type of active carbonyl compounds are the heterocycles shown in Scheme 17. These compounds upon exposure to bifunctional Brønsted base catalysts are efficiently deprotonated to give aromatic enolate ion-pairs stabilized by charge

[66] P. Wang, H. -F. Li, J. -Z. Zhao, Z. -H. Du, C. -S. Da, *Org. Lett.* **2017**, *19*, 2634–2637.
[67] A. Guerrero-Corella, F. Esteban, M. Iniesta, A. Martin-Somer, M. Parra, S. Díaz-Tendero, A. Fraile, J. Alemán, *Angew. Chem. Int. Ed.* **2018**, *57*, 5350–5354.
[68] I. Olaizola, T. E. Campano, I. Iriarte, S. Vera, A. Mielgo, J. M. García, J. M. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2018**, *24*, 3893–3901.

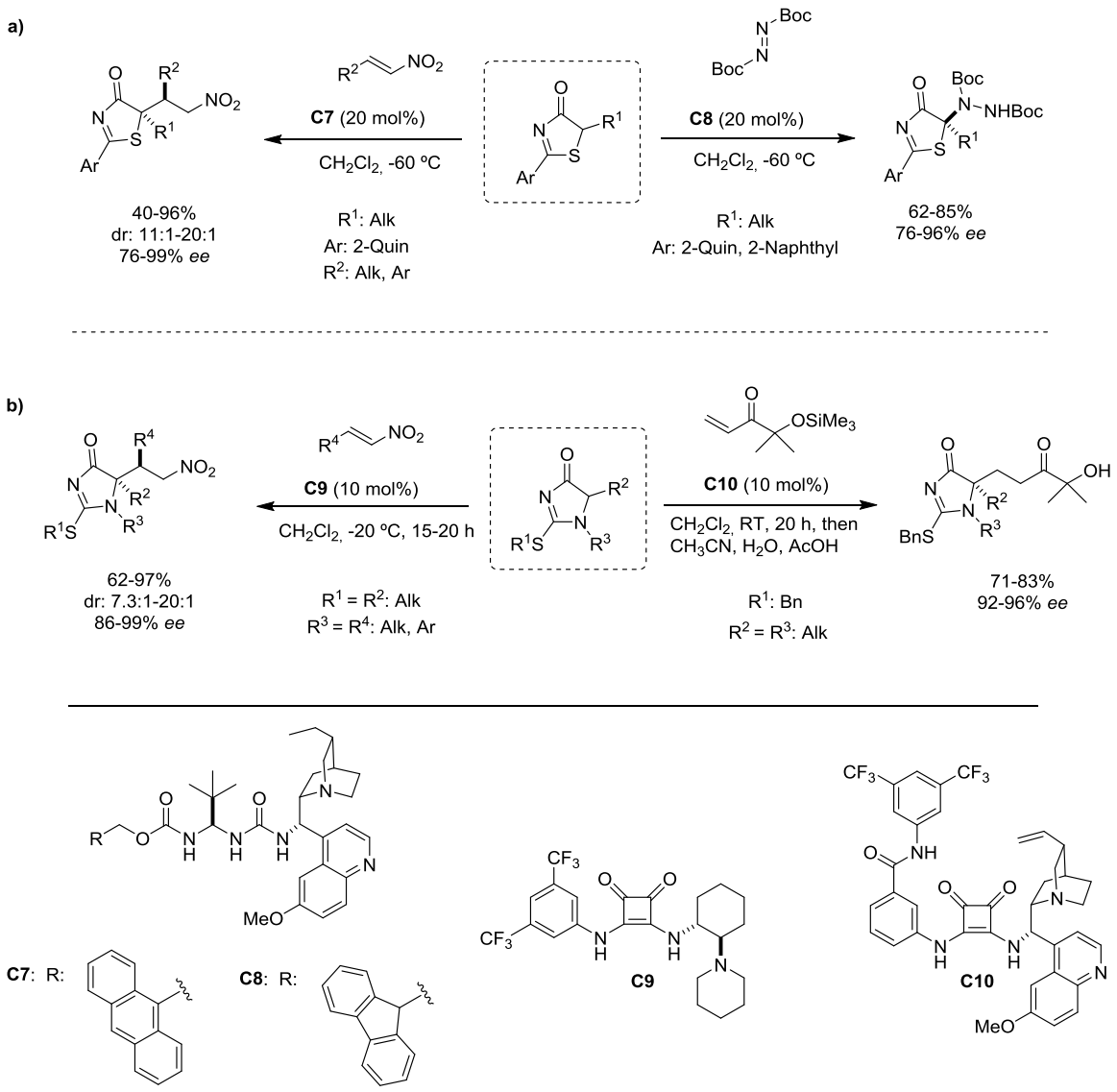
delocalization.[69] In this way, these heterocyclic compounds have been widely used as pronucleophiles in a number of reactions that have been reviewed several times.[70]



Scheme 17. Efficient deprotonation of enolizable heterocycles leading to aromatic enolates.

More recently, two further heterocycles of this type have been documented by our group. On the one hand, thiazolones[71] which have been demonstrated to be suitable pronucleophiles in conjugate additions to nitroolefins and in the amination reaction with ^{t}butyl azodicarboxylate in the presence of ureidopeptide-like catalysts **C7** and **C8** (Scheme 18a); and on the other hand, imidazolones[72] which have also been used in Michael additions promoted by bifunctional squaramide organocatalysts **C9** and **C10** (Scheme 18b).

[69] A. Mielgo, C. Palomo, *Bielstein J. Org. Chem.* **2016**, *12*, 918–936.
[70] For recent general reviews on catalytic asymmetric reactions with azlactones, see: a) I. F. S. Marra, P. P. de Castro, G. W. Amarante, *Eur. J. Org. Chem.* **2019**, 5830–5855. b) P. P. de Castro, A. G. Carpanez, G. W. Amarante, *Chem. Eur. J.* **2016**, *22*, 10294–10318. For a general review on catalytic asymmetric reactions with benzofuranones, see: c) Y. Li, X. Li, J. -P. Cheng, *Adv. Synth. Catal*. **2014**, *356*, 1172–1198. For general reviews on catalytic asymmetric reactions with oxindoles, see: d) P. Chauhan, S. S. Chimni, *Tetrahedron: Asymmetry* **2013**, *24*, 343–356. e) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. For a general review on catalytic asymmetric reactions with α,β-unsaturated γ-butyrolactams and γ-butenolides, see: f) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595–2615.
[71] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.
[72] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.



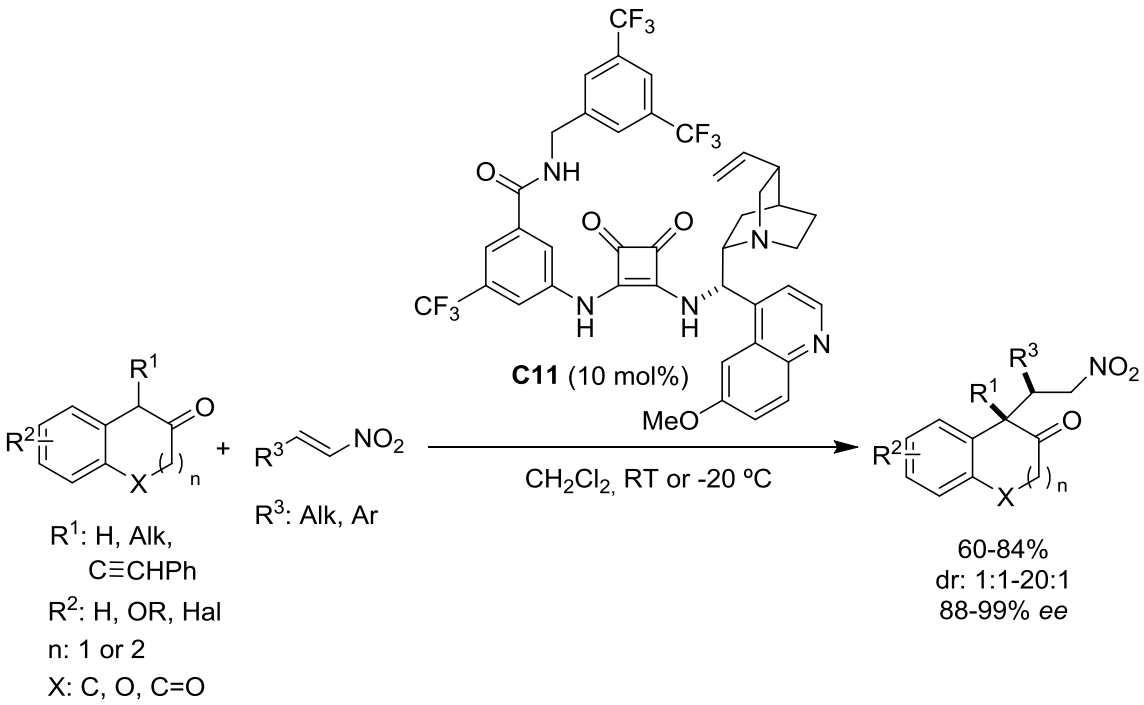
Scheme 18. a) Thiazolones in Michael addition to nitroolefins and in α-amination reaction. Palomo, 2013. b) Imidazolones in Michael additions to nitroolefins and α´-silyloxy enones. Palomo, 2015.

Despite the fact that there are several satisfying procedures for the α-functionalization of carbonyl compounds using Brønsted base catalysis, most of the direct methods are still limited to the use of easily enolizable specific nucleophiles bearing an EWG heterofunctional group (-CN, -CO_2R, COR, -NO_2, etc.) at the α-position or partially unsaturated heterocycles that upon deprotonation lead to aromatization as the driving force.

1.4. Objetives

As mentioned in the introduction, a general problem with Brønsted base catalysis is the functional pK_a barrier of most catalysts that compromises their efficiency with less acidic carbon pronucleophiles. Because of that, easily enolizable compounds typically bearing an EWG, such as -CO_2R, -COR, -CN, -NO_2 etc., at the α-carbon are used.

At the beginning of this thesis, I. Urruzuno and O. Mugica from this laboratory[73] described a regio-, diastereo- and enantioselective α-alkylation of β-tetralones and related aromatic-ring-fused cycloalkanones catalyzed by a bifunctional Brønsted base catalyst **C11** (Scheme 19).



Scheme 19. Regio- and stereoselective α-alkylation of β-tetralones and related aromatic-ring-fused cycloalkanones by Brønsted base catalysis. Palomo, 2017.

These observations prompted us to quest whether simple acyclic ketones incorporating a β,γ-unsaturation may mimic such reactivity pattern thus considerably expanding the pool of enantioenriched ketone products available (Figure 13).

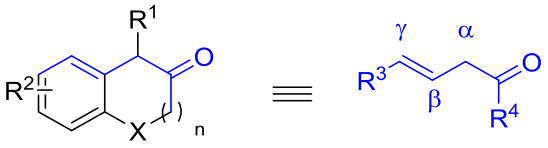


Figure 13. New family of nucleophiles.

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

The realization of this idea would face several selectivity issues, beyond the usual problem of enantio-and diastereocontrol. First, having two flanks for enolization, site-selective enolization is required (Figure 14a); second, and assuming α-enolization is dominant because of the presence of the double bond which would lower the p*K*a value of the α-position, the resulting dienolate may react through either Cα or Cγ (Figure 14b).

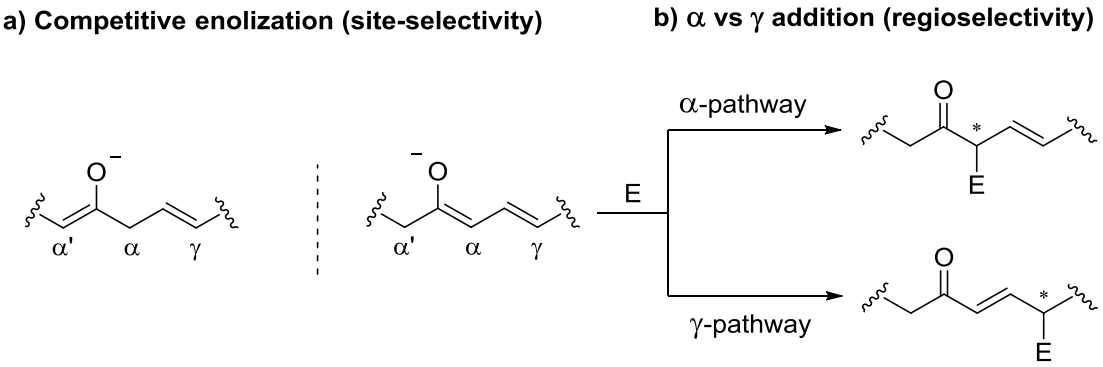
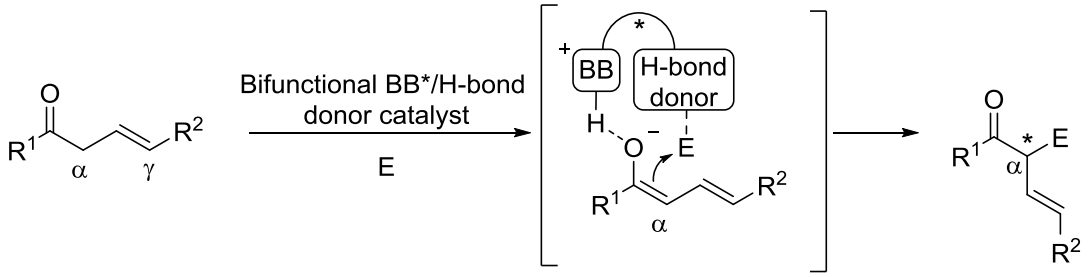


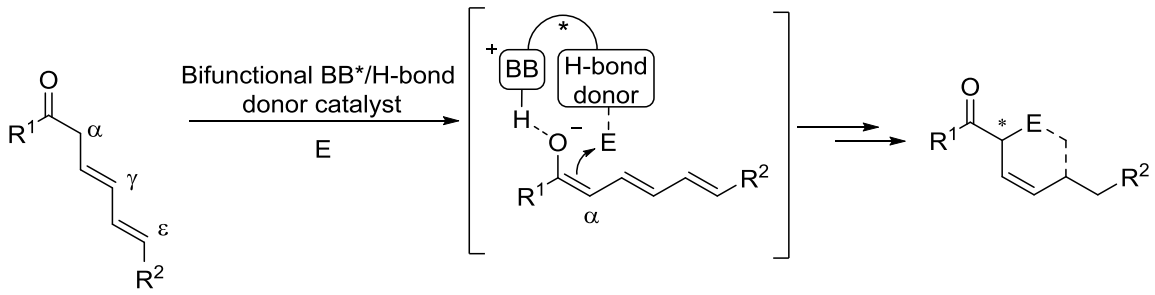
Figure 14. Competitive α´, α and γ addition.

Our hypothesis was that a bifunctional Brønsted base/H-bond donor catalyst might control the approach of the electrophile through the α-carbon of the *in situ* generated vinylogous enolate favoring reaction at the α-site (Scheme 20).



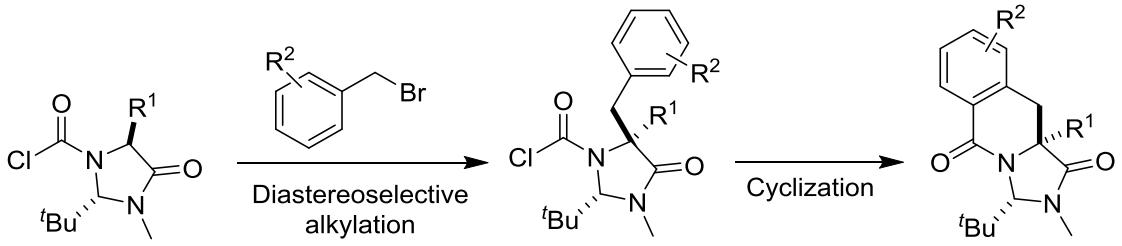
Scheme 20. α-Functionalization of β,γ-unsaturated ketones *via* selective addition of ambivalent vinylogous enolates.

In a variation of this idea, it was purposed to expand the study to transiently generated trienolate systems. It was thought that by adding an additional double bond, a bifunctional Brønsted base catalyst would generate a trienolate intermediate which would be able to react with electrophiles. Eventually, this study resulted in a new strategy for the synthesis of stereodefined six-member carbocycles (Scheme 21).



Scheme 21. Proposal for the synthesis of six-member carbocycles.

In the last part of this doctoral research period, a three months stay was carried out at the lab of Prof. Jonathan Clayden of the University of Bristol in the United Kingdom. The research project was focused on the Friedel-Crafts type cyclization of quaternary aryl imidazolidinone derivatives as a mean to access 3,4-dihydroisoquinolones stereoselectively (Scheme 22).



Scheme 22. Proposal for the synthesis of 3,4-dihydroisoquinolones.

Chapter 2

Controlling the α/γ-reactivity of dienolate intermediates in organocatalytic stereoselective Michael reactions

2. Controlling the α/γ-reactivity of dienolate intermediates in organocatalytic stereoselective Michael reactions

2.1. Introduction

Enamine and enolate based reactions are one of the cornerstones in organic synthesis, very useful for the production of highly functionalized products.[74] In recent years advances in the field have led to the development of dienamine and dienolate based reactions[75] in which these intermediates are formed *in situ* and can react with a broad range of electrophiles at the γ- and/or α-positions (Figure 15).

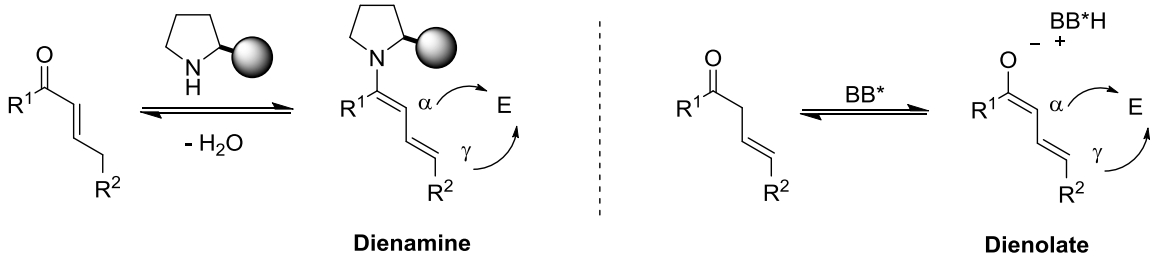


Figure 15. Vinilogous activation.

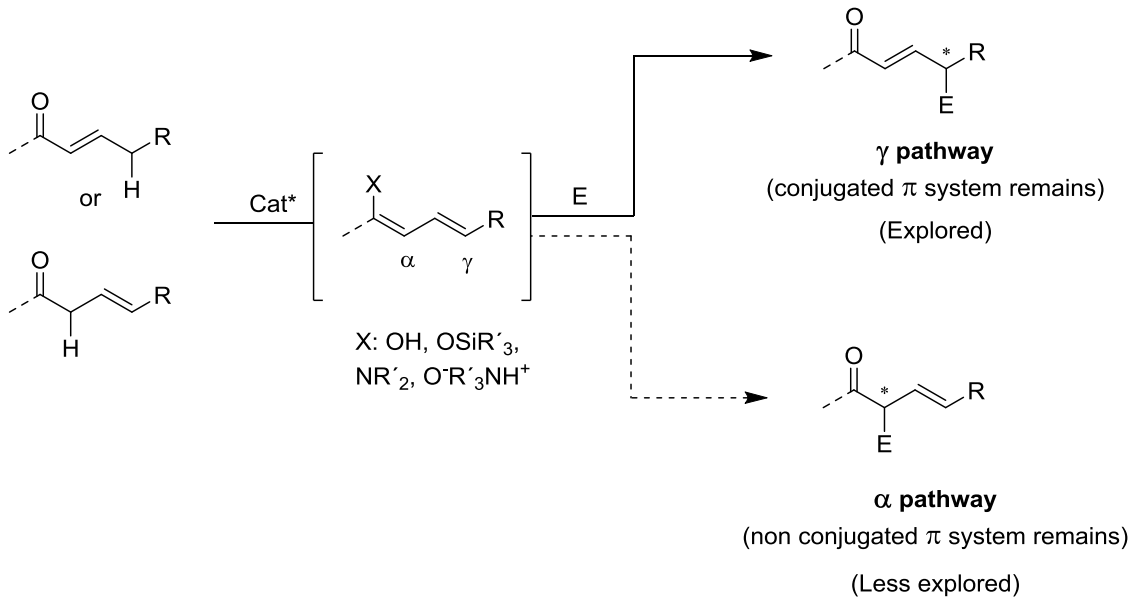
2.1.1. Reactions proceeding through Cγ of dienamine/dienolate intermediates

The overwhelming majority of catalytic reactions involving vinylogous enolate equivalents (both dienolates and dienamines) proceed at the γ-carbon of the unsaturated carbonyl compound. The reason for that lies in the preservation of the π-conjugation along the reaction (Scheme 23). This reactivity pattern is well illustrated in the literature for a broad range of enolizable substrate families using either metallic catalysis or organocatalysis.[76,74]

[74] C. Schneider, F. Abels, *Org. Biomol. Chem*. **2014**, *12*, 3531–3543.

[75] For more information about the principle of vinylogy, see: a) S. K. Krishramurthy, *J. Chem. Educ.* **1982**, *59*, 543–547. b) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1–27.

[76] For general reviews on vinylogous reactions, see: Only γ-product: a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076–3154. b) S. E. Demmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760–4777. c) S. F. Martin, *Acc. Chem. Res.* **2002**, *35*, 895–904. For a general review on asymmetric reactions of butenolides and butyrolactones (α and γ product), see: d) B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.* **2017**, *117*, 10502–10566.



Scheme 23. Divergent reaction pathways of dienolates and equivalents.

Performed acyclic and cyclic silicon dienolates have been extensively explored in a number of catalytic stereoselective vinylogous Mukaiyama type aldol,[77] Mannich[78] or Michael reactions.[79] However, direct addition reactions of dienolate equivalents generated *in situ* would be operationally simple and more atom economic.

Direct methods to trigger the γ-functionalization of unsaturated carbonyl compounds *via* organocatalytic activation have been developed. Some representative substrates are shown in (Figure 16).[80]

[77] For selected examples of γ-regioselective aldol reactions, see: a) L. V. Heumann, G. E. Keck, *Org. Lett.* **2007**, *9*, 4275–4278. b) S. Simsek, M. Horzella, M. Kalesse, *Org. Lett.* **2007**, *9*, 5637–5639. c) S. E. Denmark, J. R. Heemstra, *J. Am. Chem. Soc.* **2006**, *128*, 1038–1039.

[78] For selected examples of γ-regioselective Mannich reactions, see: a) Q. Zhang, Y. Hui, X. Zhou, L. Lin, X. Liu, X. Feng, *Adv. Synth. Catal.* **2010**, *352*, 976–980. b) M. Sickert, C. Schneider, *Angew. Chem. Int. Ed*. **2008**, *47*, 3631–3634. c) E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2006**, *45*, 7230–7233.

[79] For selected examples of γ-regioselective Michael additions, see: a) X. Jusseau, P. Retailleau, L. Chabaud, C. Guillou, *J. Org.Chem.* **2013**, *78*, 2289–2300. b) Q. Zhang, X. Xiao, L. Lin, X. Liu, X. Feng, *Org. Biomol. Chem.* **2011**, *9*, 5748–5754. c) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.

[80] For selected examples, see: For Michael reaction, see: a) Z.-L. Jia, Y. Wang, C.-G. Zhao, X.-H. Zhang, P.-F. Xu, *Org. Lett.* **2017**, *19*, 2130−2133. b) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479. c) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem. Int. Ed*. **2012**, *51*, 6200–6204. d) G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642–20647 (correction *PNAS* **2013**, *110*, 4852–4853). e) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem.* **2006**, *4*, 63–70. For aldol reaction, see: f) K. Kumar, M. K. Jaiswal, R. P. Singh, *Adv. Synth. Catal.* **2017**, *359*, 4136–4140. For [4+2] cycloaddition, see: g) J. Bojanowsky, A. Skrzynska, A. Albrecht, *Asian J. Org. Chem*. **2019**, *8*, 844–848. h) C.-Q. Duan, X.-L. He, W. Du, Y.-C. Chen, *Org. Chem. Front.* **2018**, *5*, 2057–2060.

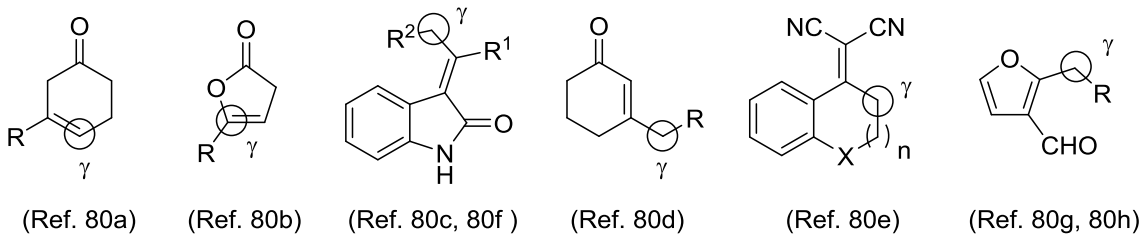
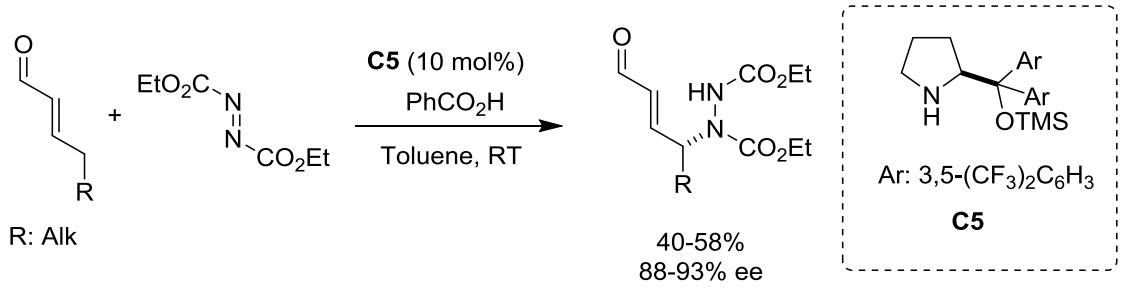


Figure 16. Representative substrates in direct organocatalytic vinylogous addition reactions.

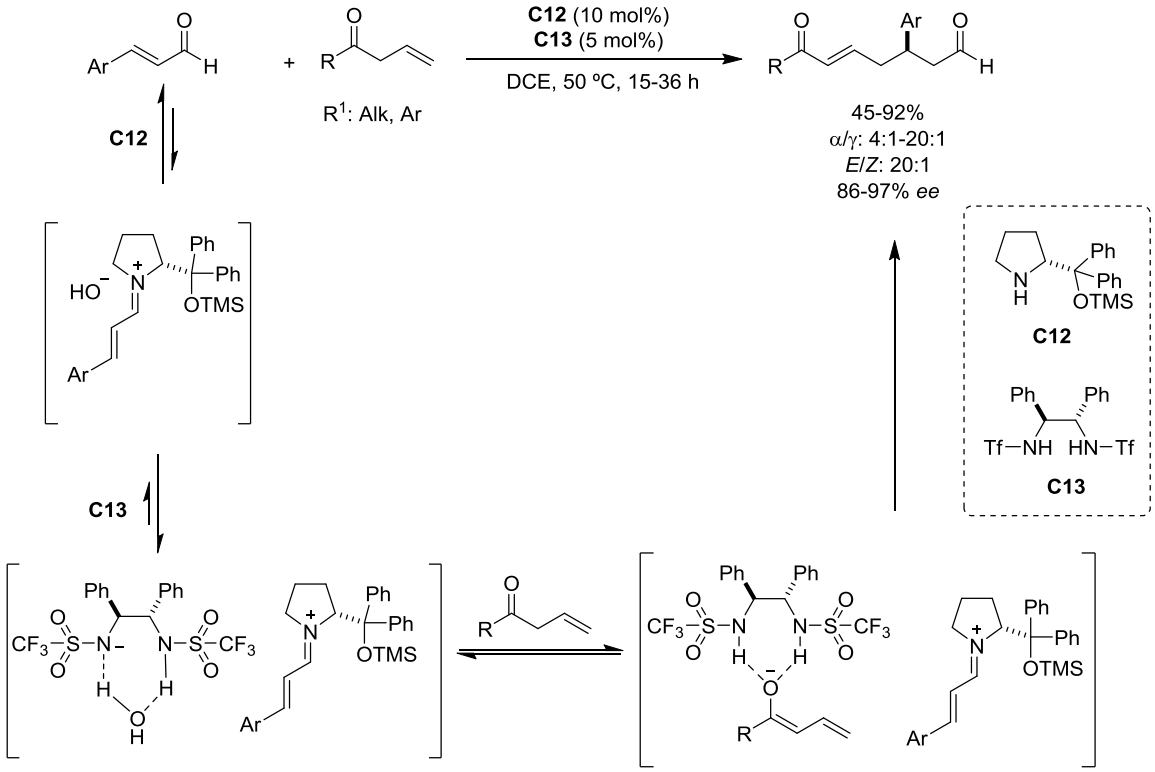
Among them, dienamine mediated activation has emerged as a powerful tool. In this context, in 2006, Jørgensen and co-workers described the first γ-regioselective amination of aliphatic α,β-unsaturated aldehydes (Scheme 24) with high enantioselectivities.[81] Since then, dienamine catalysis has been deeply investigated not only for γ-heterofunctionalization of carbonyl compounds, but also for new carbon-carbon bond construction generally at the γ-site.[82]



Scheme 24. γ-Amination of aliphatic α,β-unsaturated aldehydes. Jørgensen, 2006.

Catalytically generated dienolates from β,γ-unsaturated carbonyl compounds, have been found to react with a suitable acceptor to afford the corresponding γ-addition adduct. In this manner, in 2014, Xu and co-workers reported the direct vinylogous Michael addition of unmodified linear β,γ-unsaturated ketones to α,β-unsaturated aldehydes.[83] The α,β-unsaturated aldehydes are activated *via* iminium ion catalysis, while vinylogous substrates are activated by anion-binding interaction, with the reactions leading to the γ-adduct exclusively in good chemical yields and high enantioselectivities (Scheme 25). The authors suggested that catalyst **C12** could control enantioselectivity while the anion-binding catalyst **C13** could govern regioselectivity by shielding the α position of the vinylogous dienolate.

[81] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.
[82] For general reviews, see: a) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun*. **2013**, *49*, 4869– 4883. b) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832. For Michael reaction, see: d) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett*. **2016**, *18*, 2628–2631. For [4+2] cycloaddition, see: e) G.-Y. Ran, M. Gong, J.-F. Yue, X.-X. Yang, S.-L. Zhou, W. Du, Y.-C. Chen, *Org. Lett.* **2017**, *19*, 1874−1877.
[83] Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem. Int. Ed*. **2014**, *53*, 14128–14131.

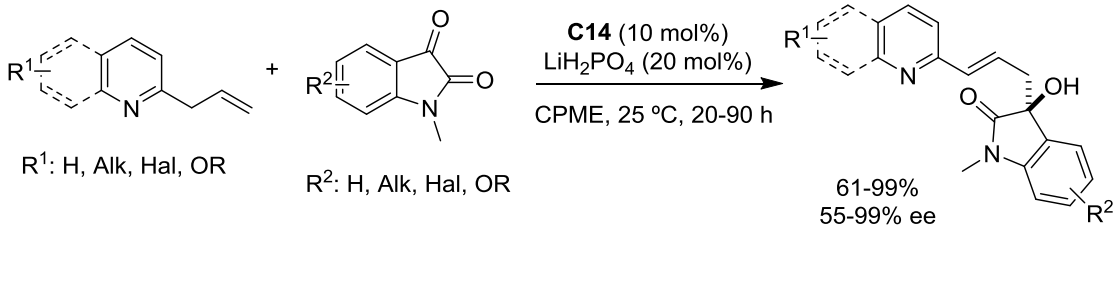


Scheme 25. Direct approach for a vinylogous Michael addition. Xu, 2014.

Despite this striking example, the most common approach to access dienolates consists of deprotonation of α-deconjugated carbonyl compounds, particularly aryl allyl ketones, although one example of allylazaarene derivatives has also been recently reported. Nevertheless, as Scheme 26 illustrates, few examples involving transiently generated dienolates have hitherto been described and the field still needs to be developed.[84]

[84] For aldol reaction, see: a) X. Bai, G. Zeng, T. Shao, Z. Jiang, *Angew. Chem. Int. Ed*. **2017**, *56*, 3684–3688. b) Z. Jing, X. Bai, W. Chen, G. Zhang, B. Zhu, Z. Jiang, *Org. Lett.* **2016**, *18*, 260–263. c) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed*. **2013**, *52*, 6666–6670. For amination reaction, see: d) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed*. **2012**, *51*, 2382–2386. For [4+2] cycloaddition, see: e) X. Li, X. Kong, S. Yang, M. Meng, X. Zhan, M. Zeng, X. Fang, *Org. Lett.* **2019**, *21*, 1979–1983. f) J. Qin, Y. Zhang, C. Liu, J. Zhou, R. Zhan, W. Chen, H. Haung, *Org. Lett.* **2019**, *21*, 7337–7341.

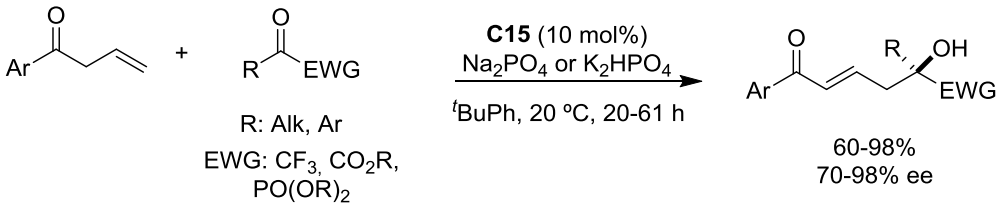
a)



R^1: H, Alk, Hal, OR

R^2: H, Alk, Hal, OR

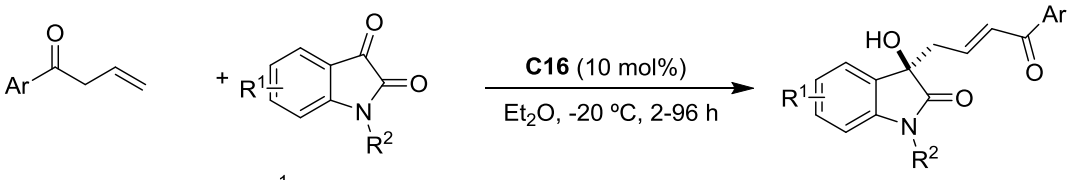
61-99%
55-99% ee



R: Alk, Ar

EWG: CF_3, CO_2R, $PO(OR)_2$

60-98%
70-98% ee



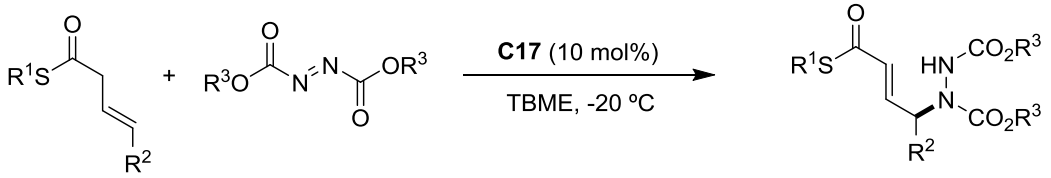
R^1: H, Alk, Hal

R^2: H, Alk

57-98%
E/Z: 13:1-99:1
88-99% ee

---

b)



R^1: Alk, Ar

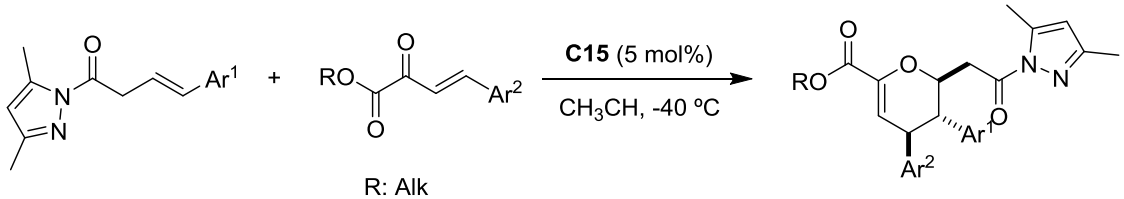
R^2: Alk

R^3: Alk

30-90%
50-96% ee

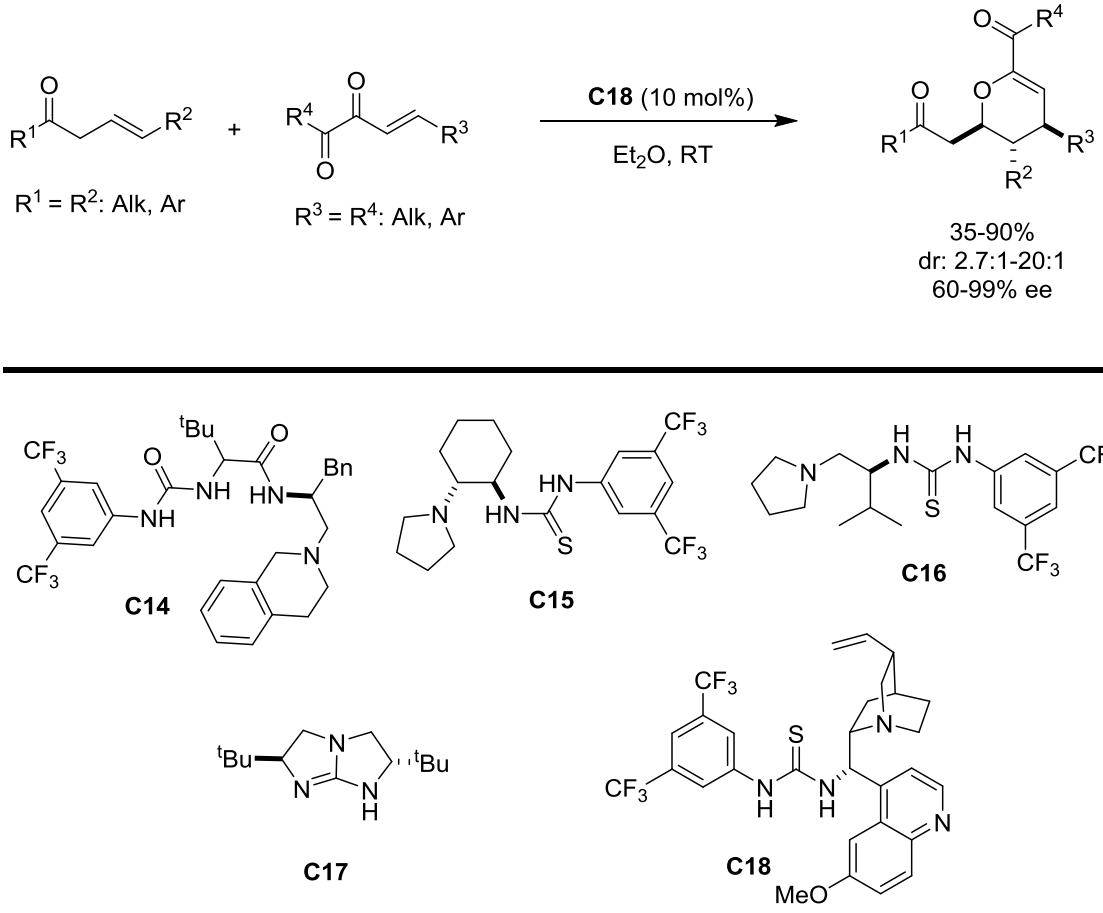
---

c)



R: Alk

61-99%
dr: 3.2:1-20:1
99% *ee*



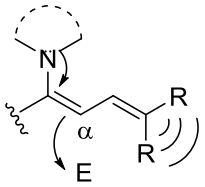
Scheme 26. a) γ-Aldol, b) γ-amination and c) [4+2] cycloaddition reactions of allyl ketone, thioesters, pyrazoleamides and allylazaarene derivatives promoted by Brønsted bases.

2.1.2. Reactions proceeding through Cα of dienamine/dienolate intermediates

Whereas the γ-reaction pathway implies the conservation of π-conjugation, the alternative α-approach implies disruption of the π-conjugation at some point of the reaction. Not surprisingly, changing the reactivity from the most usual γ- to α-carbon has resulted troublesome, with only few direct enantioselective approaches reported.

One of the strategies for the α-regioselective asymmetric addition is the use of γ-substituted nucleophiles wherein γ-carbon is sterically shielded (Figure 17).[85]

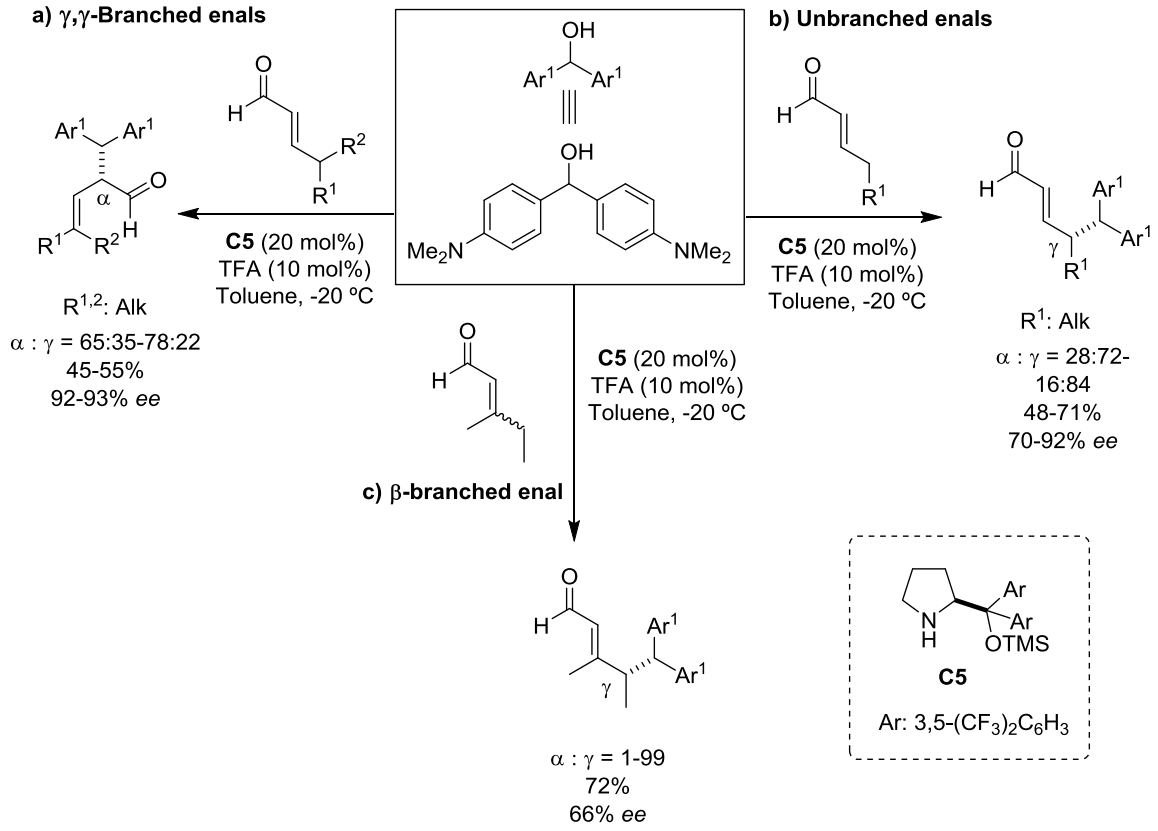
[85] a) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70–73. b) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian. J.* **2011**, *6*, 2255–2259. c) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660–4663.



Dienamine
intermediate

Figure 17. Strategy for the α-regioselective asymmetric addition: Congested γ-site.

With this idea, Christmann and co-workers performed alkylation reactions of various enals, including unbranched, α-, β- and γ-branched enals with diarylmethanols using a secondary chiral amine **C5** as catalyst.[85a] As shown in Scheme 27, the substitution type in the enal can affect the reaction outcome, and while a γ,γ-disubstituted enal (Scheme 27a) react through Cα preferentially, unbranched or β-branched enals proceeded through Cγ (Scheme 27b,c).

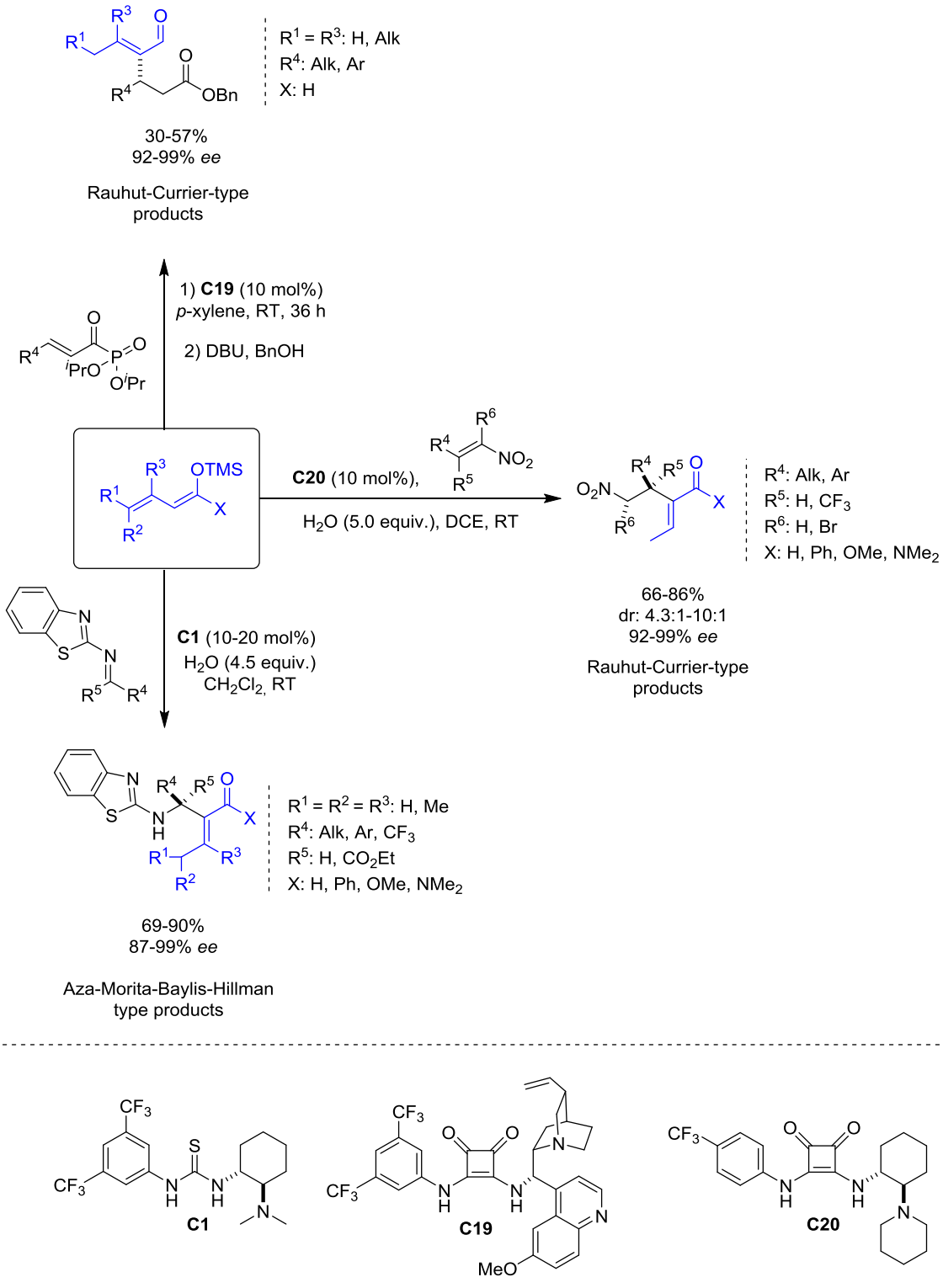


Scheme 27. Systematic studies of dienamine catalysis with enals as pronucleophiles. Christmann, 2011.

Other type of exceptions to the γ-selectivity consists of the concomitant isomerization of the C=C double bond. However, in this instance the initially formed adducts isomerized to the more stable Morita-Baylis-Hilman type conjugated adducts.[86] These MBH-adducts can be readily obtained using preformed silyl dienol ethers. In this way, during the development of the present work, the group of Alemán reported the α-selective functionalization of these performed silyl dienol ethers with different electrophiles under bifunctional Brønsted base catalysis (Scheme 28).[87]

[86] For a barium alkoxide catalyzed Mannich reaction of β,γ-unsaturated benzyl esters (Aza-Morita-Baylis-Hillman type products), see: a) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387–3390. For proline catalyzed Mannich reaction of β,γ-unsaturated aldehydes (Aza-Morita-Baylis-Hillman type products), see: b) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas, *Angew. Chem. Int. Ed*. **2007**, *46*, 1878–1880.

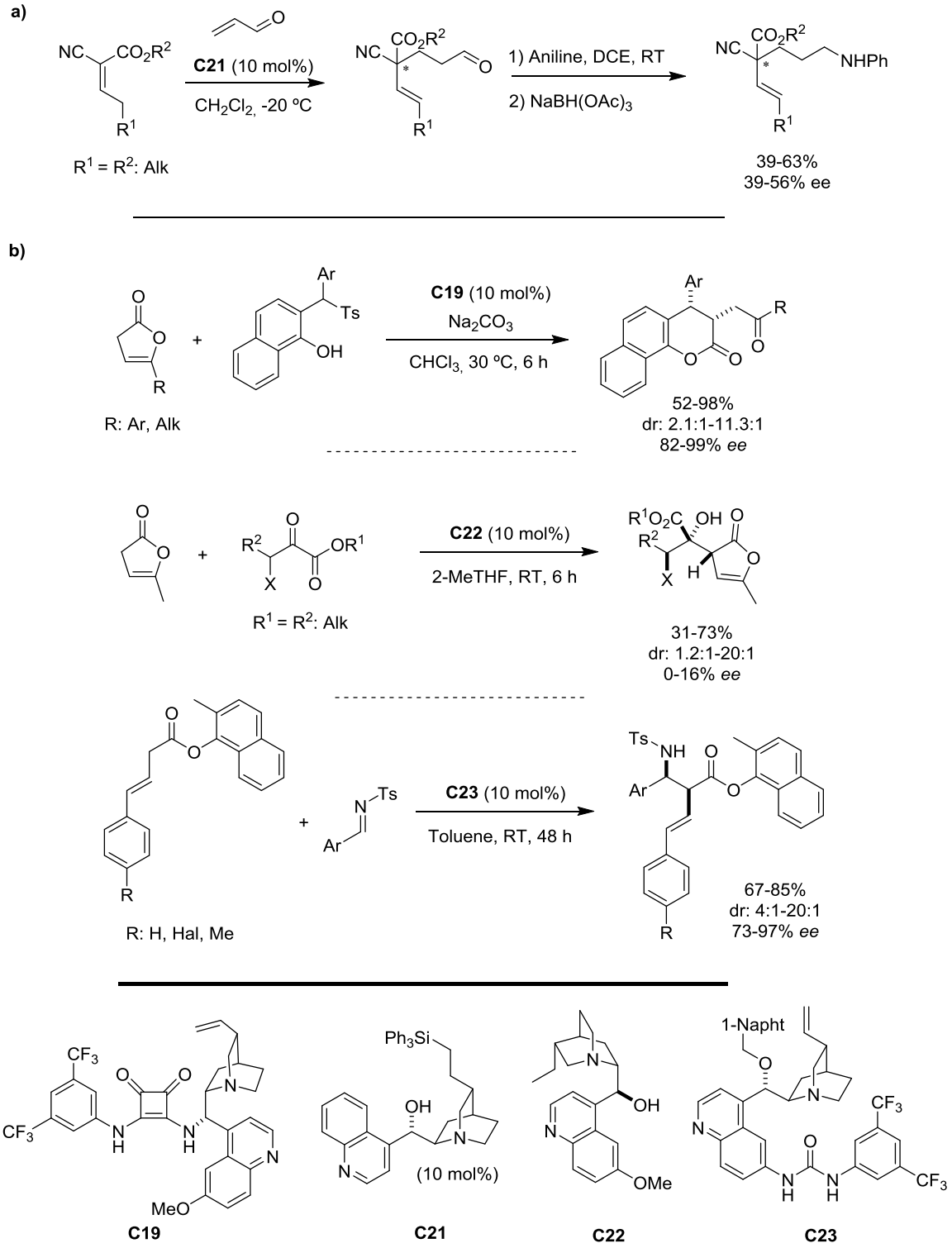
[87] For Mannich reaction *via* Brønsted base catalysis (Aza-Morita-Baylis-Hillman type products), see: a) M. Frías, A. M. Carrasco, A. Fraile, J. Alemán, *Chem. Eur. J.* **2018**, *24*, 3117–3121. For Michael addition to acylphosphonates *via* Brønsted base catalysis (Rauhut-Currier type products), see: b) V. Laina-Martín, R. del Rio-Rodríguez, S. Díaz-Tendero, J. A. Fernández-Salas, J. Alemán, *Chem. Commun.* **2018**, *54*, 13941–13944. For Michael addition to nitroolefins *via* Brønsted base catalysis (Rauhut-Currier type products), see: c) M. Frías, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, J. *Am. Soc.* **2017**, *139*, 672–679.



Scheme 28. Reactions of silyl dienol ethers with different electrophiles under Brønsted base catalysis. Alemán, 2017-2018.

Apart from the examples mentioned above, few additional Brønsted base-catalyzed α-site functionalizations of vinylogous enolic intermediates can be found in the literature. However, the reported examples lead to moderate enantioselectivity[88] (39-56% *ee*) (Scheme 29a) or are applied to very restricted substrate categories, two examples with deconjugated butenolides[89] and another with α-styryl acetates[90] (Scheme 29b).

[88] M. Bell, K. Frisch, K. A. Jørgensen, *J. Org. Chem*. **2006**, *71*, 5407–5410.
[89] a) B. Wu, Z. Yu, X. Gao, Y. Lan, Y. -G. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 4006–4010. b) J. A. Griswold, M. A. Horwitz, L. V. Leiva, J. S. Johnson, *J. Org. Chem.* **2017**, *82*, 2276–2280.
[90] J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett*. **2016**, *18*, 2648–2651.



Scheme 29. Brønsted bases catalyzed α-functionalization of vinylogous enolic intermediates. Examples with a) moderate enantioselectivity and b) restricted substrate categories.

2.2. Working hypothesis

Despite the great importance of chiral ketones, the direct asymmetric α-functionalization of enolizable ketones remains challenging, specially when non-symmetrical unactivated ketones[91] are used, which have two sites for deprotonation. Although α-functionalization of non-symmetrical ketones involving the use of stoichiometric chiral auxiliaries[92] as well as catalytic amount of metal catalysts,[93] primary or secondary amine catalysts[94] or Brønsted acid catalysts[95] have been extensively studied, few examples of the regio- and stereoselective functionalization of non-symmetrical unactivated ketones by Brønsted base catalysis can be found in the literature.[96]

As mentioned in the introduction (section 1.4), I. Urruzuno and O. Mugica from this laboratory[96a] have described a regio-, diastereo- and enantioselective α-alkylation of β-tetralones and related aromatic-ring-fused cycloalkanones catalyzed by the bifunctional Brønsted base catalyst **C11** (Scheme 30).

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

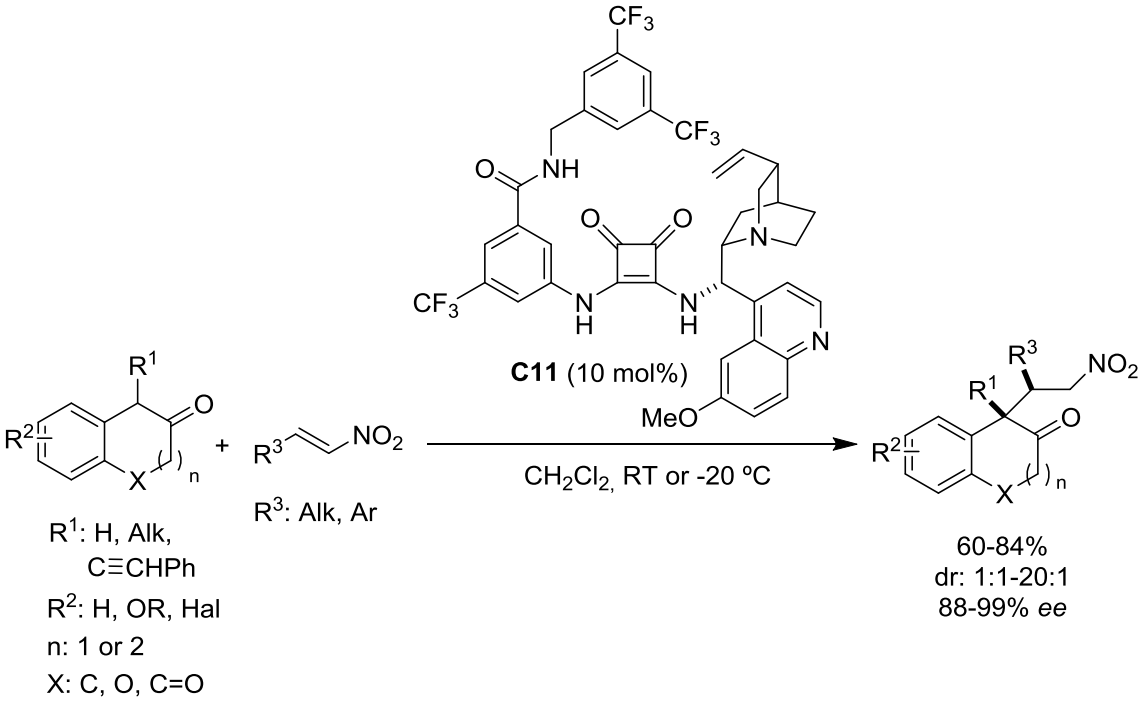
[92] For selective examples, see: a)S. E. Wengryniuk, D. Lim, D. M. Coltart, *J. Am. Chem. Soc.* **2011**, *133*, 8714–8720. b) D. Lim, D. M. Coltart, *Angew. Chem. Int. Ed.* **2008**, *47*, 5207–5210. c) A. Job, C. F. Janeck, W. Bettray, R. Petters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329. d) C. Palomo, M. Oiarbide, A. Mielgo, A. Gonzalez, J. M. Garcia, C. Landa, A. Lecumberri, A. Linden, *Org. Lett.* **2001**, *3*, 3249–3252.

[93] For general reviews on metal catalysis, see: For α-arylations, 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. c) D. A. Culkin, J. F. Hartwig, **2003**, *36*, 234–245. For α-alkylation, see: ref. 91

[94] For selective examples of the use of primary or secondary amines, see: a) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H. -Y. Cheong, R. G. Carter, *J. Org. Chem.* **2016**, 81, 3629–3637. b) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457–4463. c) J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178–3181.

[95] For selective examples of the use of Brønsted acid catalysts, see: a) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653–2656. b) G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed.* **2016**, *55*, 6099–6102. c) X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205–3208. d) G. A. Shevchenko, G. Pupo, B. List, *Synlett.* **2015**, *26*, 1413–1416. e) I. Felker, G. Pupo, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 1960–1964. f) X. Yang, R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5225–5228. g) L. Song, Q. -X. Guo, X. -C. Li, J. Tian, Y. -G. Peng, *Angew. Chem. Int. Ed.* **2012**, *51*, 1899–1902.

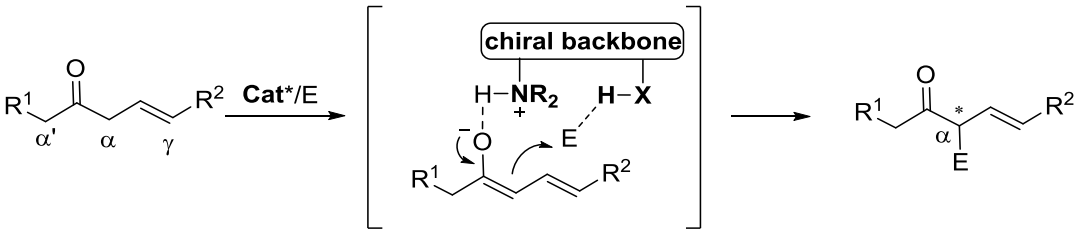
[96] a) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063. b) X. -Q. Dong, H. -L. Teng, M. -C. Tong, H. Huang, H. -Y. Tao, C. -J. Wang, *Chem. Commun*. **2010**, *46*, 6840–6842.



Scheme 30. Regio- and stereoselective α-alkylation of β-tetralones and related aromatic-ring-fused cycloalkanones, by Brønsted base catalysis. Palomo, 2017.

On this basis, we considered that a suitable bifunctional Brønsted base catalyst should also be effective in controlling α vs α´-reactivity of acyclic β,γ-unsaturated enones. What at this stage remained unclear was whether the allegedly formed dienolate intermediate would react preferentially through the Cα or the Cγ nucleophilic carbon.

As mentioned above, it seems that α- vs γ-selectivity problem appears to be multivariable. Our hypothesis was that a bifunctional Brønsted base/H-bonding catalyst might anchor both the *in situ* generated dienolate and the electrophile in a way favoring the α-reaction pathway (Scheme 31).

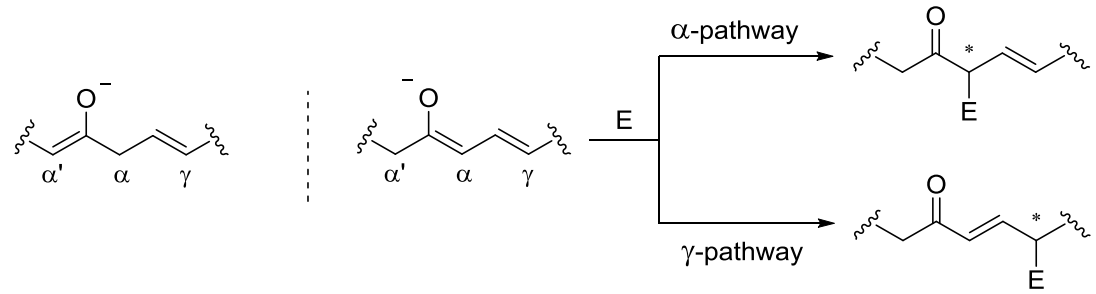


Scheme 31. Brønsted base bifunctional catalyst in α-functionalization of β,γ-unsaturated carbonyl compounds.

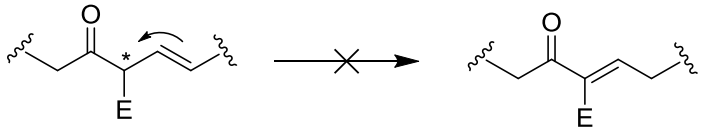
We envisaged the development of a general asymmetric bifunctional Brønsted base catalyzed Michael addition of transiently generated vinylogous enolates to nitroolefins, where the catalyst could control the site- and regioselectivity (α´- vs α- vs γ-selectivity) (Scheme 32a), stereoselectivity (diastereo- and enantioselectivity) and

prevent the isomerization pathway (Scheme 32b) which would lead to a loss of the generated α-stereocenter.

a) Competitive α´, α vs γ addition



b) Avoidance of the C=C double bond isomerization



Scheme 32. a) Competitive reactions. b) Avoidance of the C=C double bond isomerization.

2.3. Michael addition of β,γ-unsaturated carbonyl compounds

For this exploration alkynyl, aryl, alkenyl and alkyl allyl ketones were considered whose structure is shown in Figure 18.

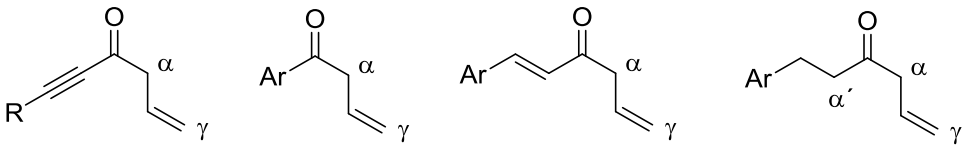


Figure 18. β,γ-Unsaturated ketones as pronucleophiles.

2.3.1. Allyl ynones as pronucleophiles

The initial study was carried out using alkynyl allyl ketones as pronucleophiles. Using this kind of pronucleophiles the α´-attack should not be taken into account, concentrating our efforts on avoiding the reaction at the γ-site and the isomerization of the C=C double bond.

Alkynyl ketones are excellent building-blocks for organic synthesis, due to the presence of both the C-C triple bond and the carbonyl group, however ynones have not been used in catalytic approaches extensively, perharps because their tendency to act as Michael acceptors, rather than donors.[97] Some direct asymmetric aldol[98] and Mannich[99] reactions of enolizable ynones *via* bifunctional metal catalysis[98a-e,99] and enamine activation[98f] are known. Due to the fact that ynones can play as Michael acceptors, in some cases the reaction cannot stop in the addition step, and adducts undergo intramolecular cyclization.

To the best of our knowledge, only one example on asymmetric Brønsted base catalyzed α-additions of enolizable ynones has been reported.[100] In this case, the ynone

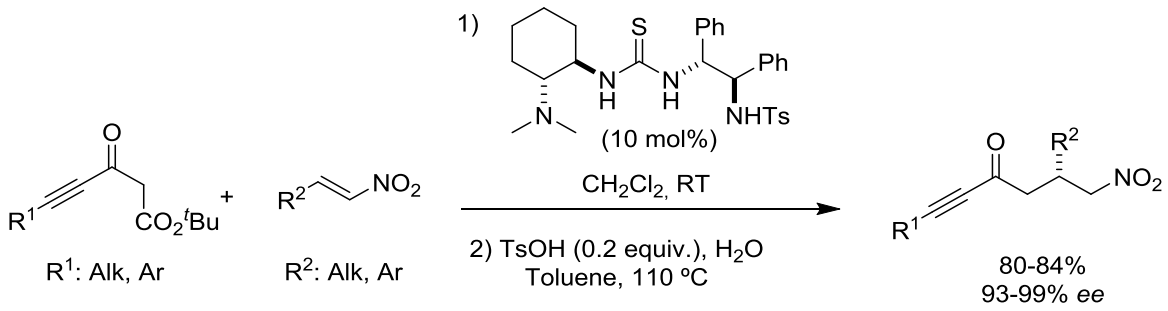
[97] For general reviews, see: a) R. E. Whittaker, A. Dermenci, G. Dong *Synthesis* **2016**, *48*, 161–183. b) R. Salvio, M. Moliterno, M. Bella, *Asian J. Org. Chem.* **2014**, *3*, 340–351. c) A. Fraile, A. Parra, M. Tortosa, J. Alemán *Tetrahedron* **2014**, *70*, 9145–9173.

[98] For aldol reactions catalyzed by bifunctional metal catalysis, see: a) S. L. Shi, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 3932–3935. b) F. Silva, M. Reiter, R. Mills-Webb, M. Sawicki, D. Klär, N. Bensel, A. Wagner, V. Gouverneur, *J. Org. Chem.* **2006**, *71*, 8390–8394. c) K. Maki, R. Moloki, K. Fuji, M. Kanai, T. Kobayashi, S. Tamura, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 17111–17117. d) B. M. Trost, A. Fetters, B. T. Shireman, *J. Am. Chem. Soc.* **2004**, *126*, 2660–2661. e) K. Fujii, K. Maki, M. Kanai, M. Shibasaki, *Org. Lett*. **2003**, *5*, 733–736. For aldol reactions catalyzed by enamine catalysis, see: f) F. Silva, M. Sawicki, V. Gouverner, *Org. Lett.* **2006**, *8*, 5417–5419.

[99] For an example of a Mannich reaction catalyzed by bifunctional metal catalysis, see: B. M. Trost, C. I. Hung, *J. Am. Chem. Soc.* **2015**, *137*, 15940–15946.

[100] W. Liu, L. Zou, B. Fu, X. Wang, K. Wang, Z. Sun, F. Peng, W. Wang, Z. Shao, *J. Org. Chem.* **2016**, *81*, 8296–8305.

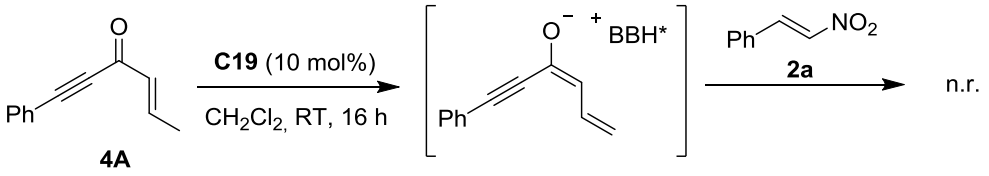
substrates bearing an ester group at the α-carbon are employed, requiring a final decarboxylation step, which promotes the loss of the α-stereocenter (Scheme 33).



Scheme 33. Ynones in Michael additions. Shao, 2016.

For initial studies, the model reaction of alkynyl allyl ketone **1A** with nitroolefin **2a** in the presence of several bifunctional Brønsted base catalysts **C6**-**C7, C18**-**C19** and **C24**-**C27**, was investigated (Table 1). To our delight, in all cases the α-addition adduct was formed exclusively within two hours of reaction. Unfortunately, the evolved adduct proved to be quite sensitive towards double bond isomerization, and product **3Aa** was obtained directly (Rauhut–Currier type product), even if low temperatures were used. This observation indicates that the initially formed α-adduct isomerizes spontaneously, losing one of the newly created stereocenters. Moreover, the isomerization of the starting allyl ynone **1A** to the most stable vinyl ynone **4A** was observed, regardless the reaction temperature.

A control experiment was carried out with the isolated enone **4A** and under the same reaction conditions, we observed that the addition reaction of enone **4A** did not take place due to the inability of catalyst **C19** to abstrat the γ-proton. Therefore, the corresponding dienolate is not generated (Scheme 34). In order to minimize the impact of the formation of ketone **4A** in the catalytic process, two equivalents of the starting ketone **1A** were systematically employed.

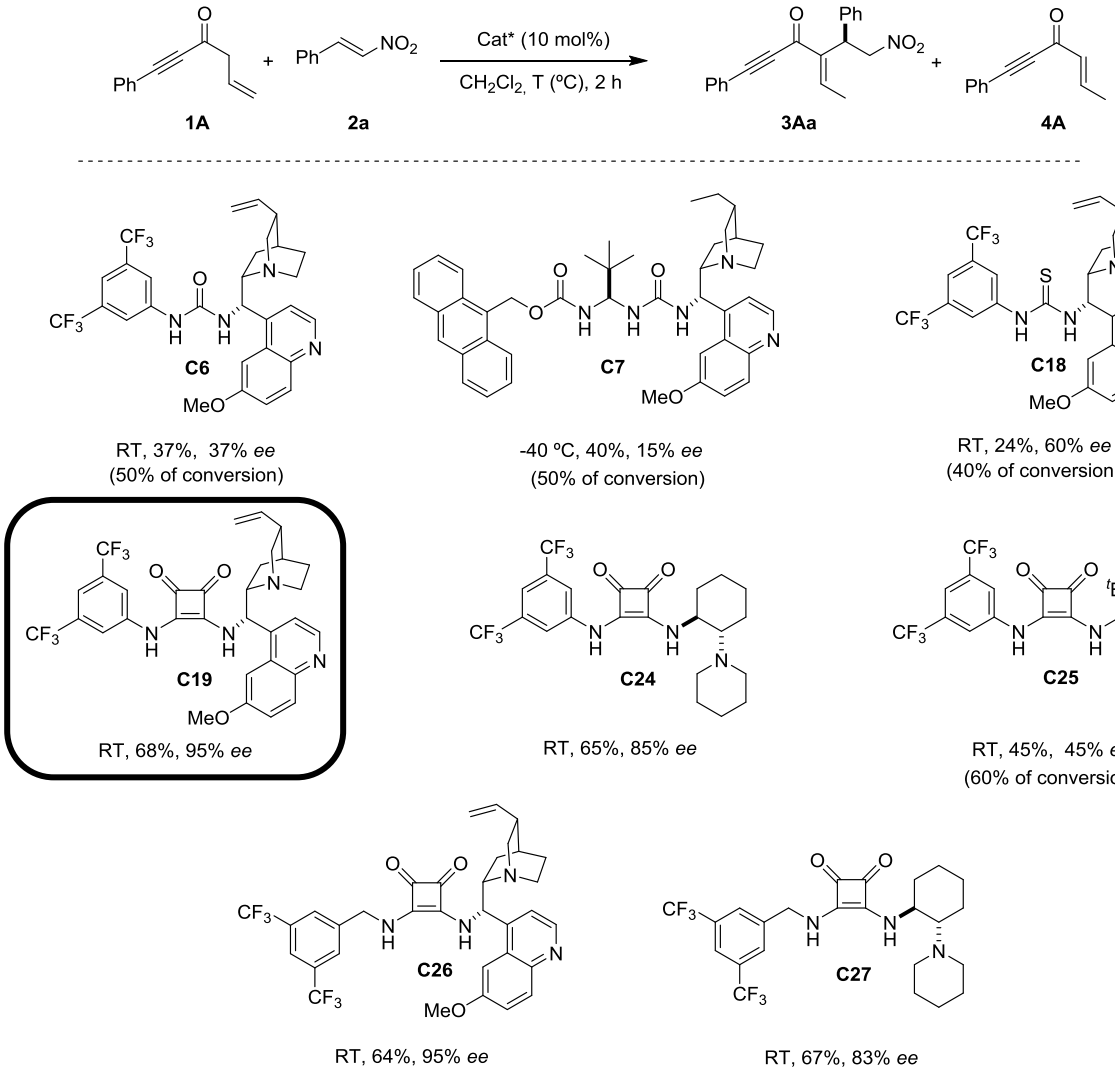


Scheme 34. Control experiment.

Among the catalysts screened, we found that squaramide catalysts **C19**, **C24**, **C26**-**C27** were better than the rest of catalysts in terms of yields and enantioselectivities (only 20% of isomerized material **4A** was observed). Although catalysts **C19** and **C26**

gave very similar results, we chose as optimal catalyst **C19**, since it provided a slightly higher yield.

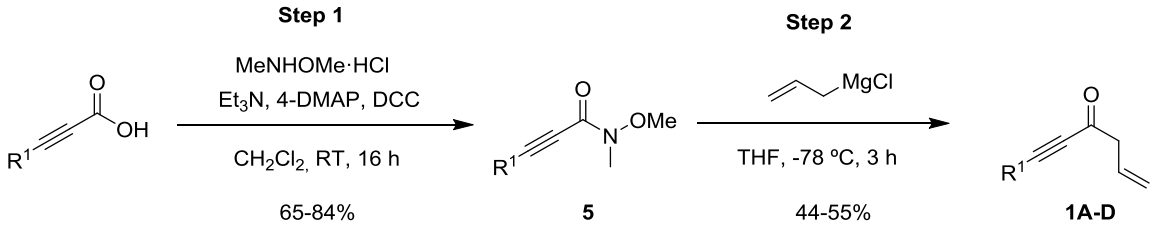
Table 1. Catalyst screening for the reaction of **1A** with **2a**.[a]



[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of alkynyl allyl ketone **1A** and 10 mol% of catalyst in 0.2 mL CH_2Cl_2 at the corresponding temperature for 2 h. Variable amounts of isomerized starting material were observed in all entries. The **4A**/**3Aa** ratio was determined on the crude material by ^{1}H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography. The enantioselectivity was determined by chiral HPLC.

Given the good results obtained with **1A**, we next studied the scope of the reaction with an array of alkynyl allyl ketones. Preparation of these ynones involved formation of the Weinreb amide **5** from the corresponding carboxylic acid, followed by subsequent treatment with a Grignard reagent (Scheme 35). The first step proceeded with good yield (65-84%), but the yield plummeted in the second step. This decrease may be due to the isomerization of the allyl ynone **1** to more stable conjugated enone **4**

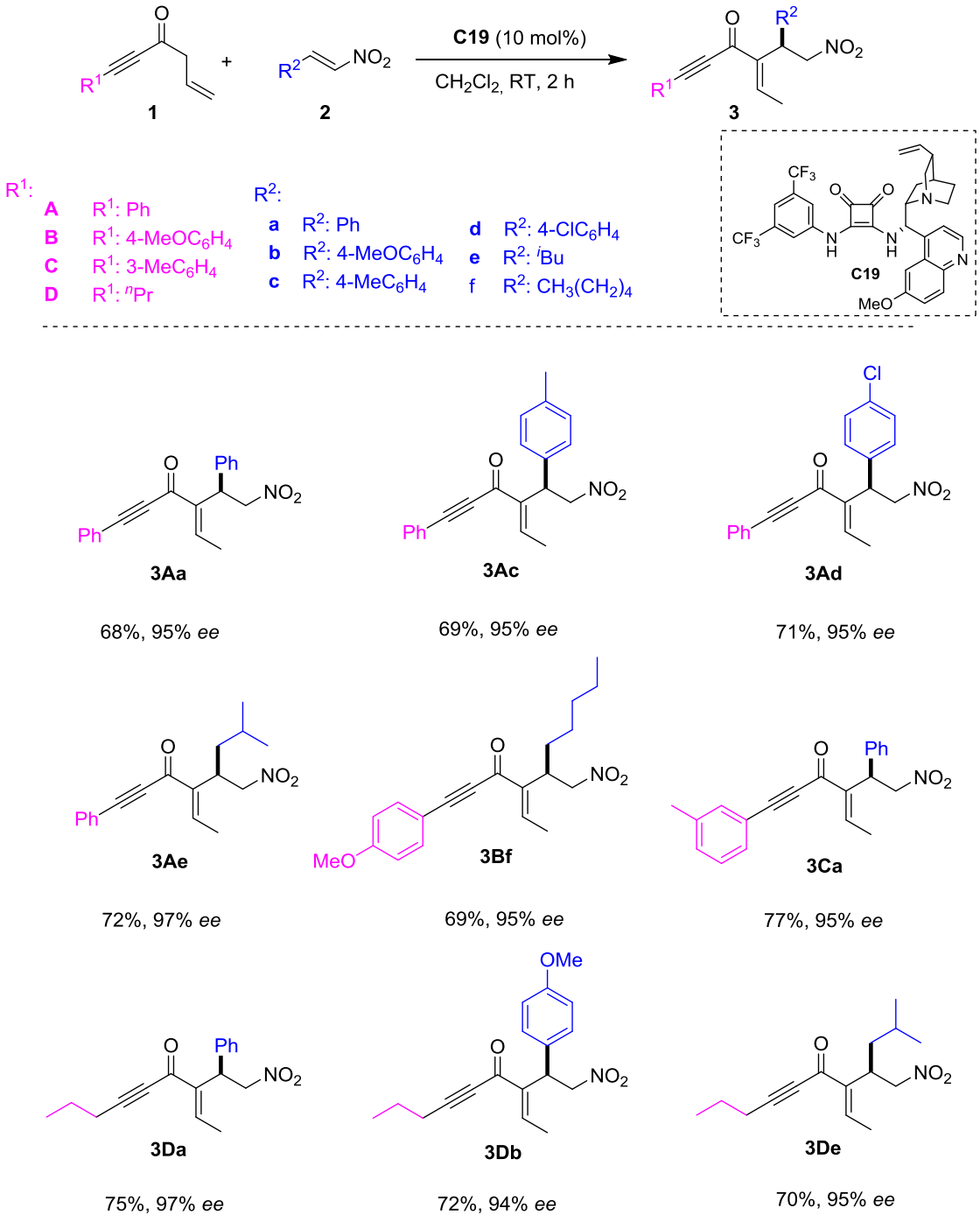
during isolation. Consistently acceptable yields were obtained using diethyl ether as solvent during the work-up and isolation of the products.



Scheme 35. Reaction sequence for ynone formation.

Once the reaction conditions had been optimized, various alkynyl allyl ketones **1A**-**D** and nitroolefins **2** were examined (Table 2). All the reactions proceeded smoothly to give the corresponding α-adducts in good yields and with excellent enantioselectivities. The reaction tolerated a variety of aromatic and aliphatic alkynyl allyl ketones and nitroolefins bearing electron-rich *p*-substituents (MeO- and Me-), and electron-poor *p*-substituent (Cl-) (adducts **3Ac**, **3Ad** and **3Db**). It is worth of noting that the less reactive β-alkyl nitroolefins **2e** and **2f** were also competent partners for this reaction, affording adducts **3Ae**, **3Bf** and **3De** in good yields and excellent enantioselectivities. Moreover, good results were obtained when pronucleophiles with other aromatic or alkyl substituents at the alkynyl moiety were employed (adducts **3Bf**, **3Ca**, **3Da**, **3Db** and **3De**).

Table 2. Catalytic enantioselective addition of alkynyl allyl ketones **1A**-**D** to nitroolefins **2**.[a]



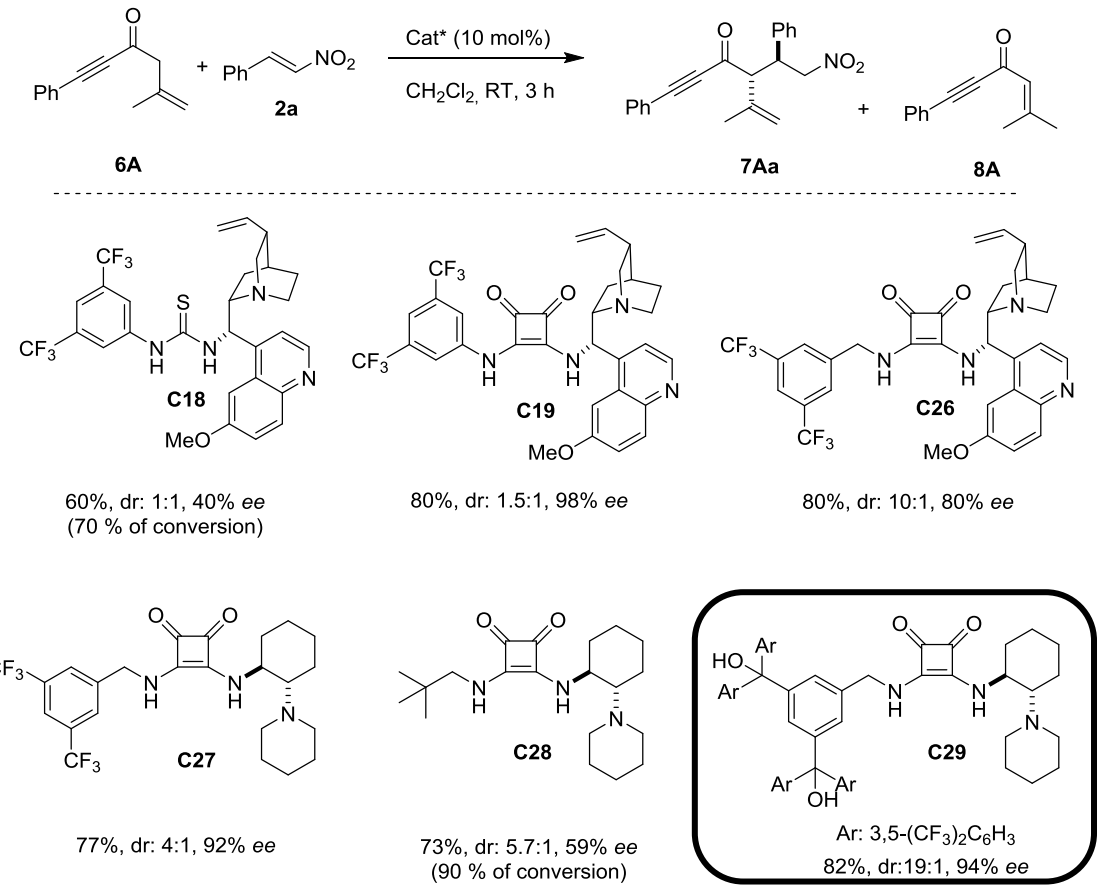
[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of alkynyl allyl ketone **1A**-**D** and 10 mol% of catalyst **C19** in 0.2 mL CH_2Cl_2 at room temperature for 2 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. The enone **4**/product **3** ratio was determined on the crude material by ^1H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography. The enantioselectivity was determined by chiral HPLC.

As menthioned before, the initially formed α-adduct isomerized spontaneously, with one of the newly created stereocenters being ultimately lost. Thus, our next task was to check whether this isomerization bias is general for other allylic systems. In this context, we synthesized the β-methyl alkynyl allyl ketone **6A**.[101] Fortunately, the experiment involving ynone **6A** and nitrostyrene **2a** in the presence of the bifunctional catalyst **C19** showed that, the resulting α-adduct **7Aa** resisted isomerization. For instance, after 3 h of stirring at room temperature with 10 mol% of catalyst **C19**, adduct **7Aa** was obtained in 80% isolated yield and with excellent 98% *ee* for the major diastereomer, although a nearly equimolar mixture of diastereomers was produced (dr: 1.5:1) (Table 3).

Owing to this result, the model reaction of ynone **6A** with nitroolefin **2a** in presence of several bifunctional Brønsted base catalysts **C18-C19** and **C26-C29** was investigated next (Table 3). With the *N*-benzyl analog **C26** diastereoselectivity was improved at the expense of enantioselectivity (80% *ee*), while the related cyclohexyldiamine-derived squaramide catalyst **C27** afforded the α-adduct **7Aa** with high *ee*, but yet suboptimal diastereoselectivity (dr: 4:1, 92% *ee*). Additional screening showed that thiourea catalyst **C18** was inferior in reactivity and selectivity, thus we decided to check cyclohexyldiamine-derived squaramide catalysts (**C28** and **C29**) Surprisingly, we found that the reaction in the presence of the newly developed bulky catalyst **C29**[102] afforded the desired adduct **7Aa** in 82% yield, a remarkable 19:1 dr and 94% *ee.*

[101] This pronucleophile was prepared following the same general procedure used for the synthesis of alkynyl allyl ketones, but in this case a freshly prepared solution of 2-methylallylmagnesium chloride was used. For more information, see experiemental section (pages 176–182).
[102] For more information about the synthesis of the catalyst, see experimental section (pages 172–175).

Table 3. Catalyst screening for the reaction of **6A** with **2a**.[a]



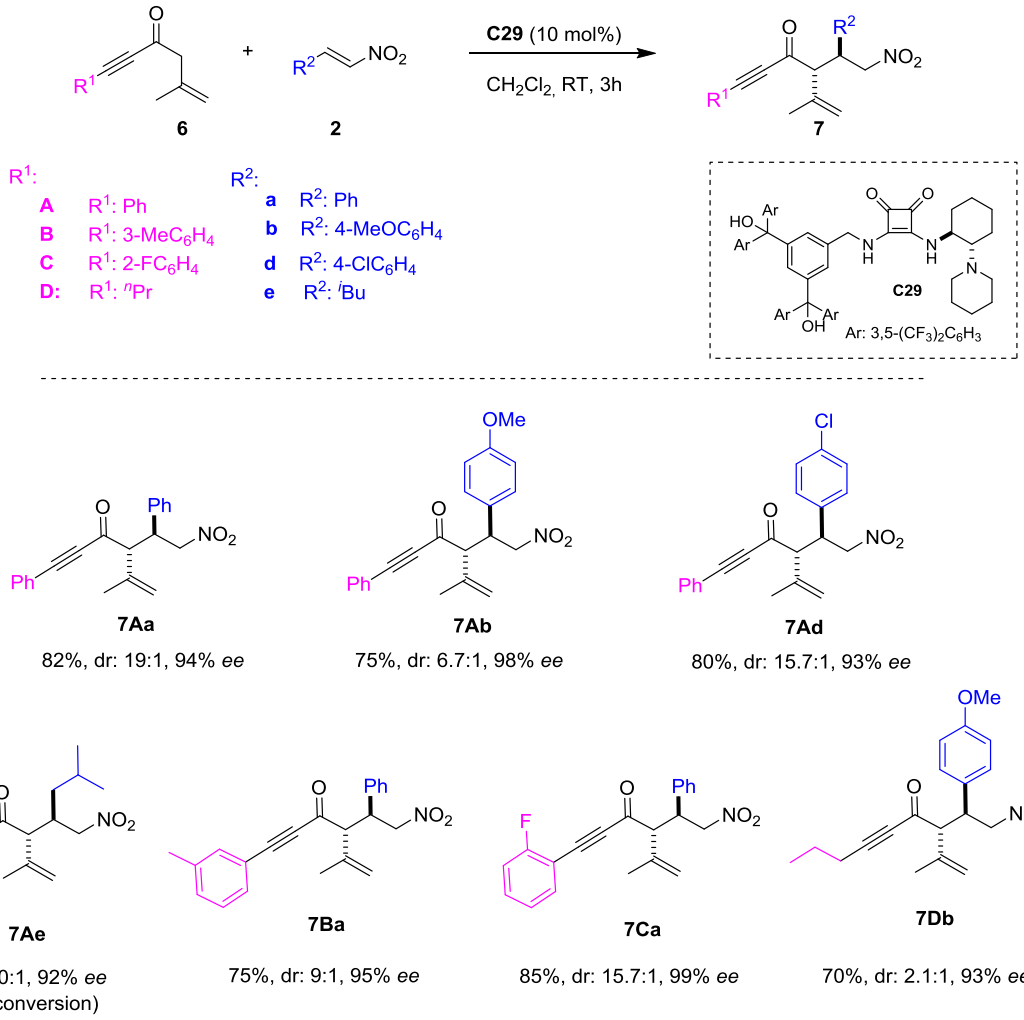
[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ynone **6A** and 10 mol% of catalyst in 0.2 mL CH_2Cl_2 at room temperature for 3 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. The enone **8**/product **7** ratio was determined on the crude material by ^{1}H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography. The diastereoselectivity and the enantioselectivity of the major diastereomer **7Aa** were determined on the crude material by chiral HPLC.

Once the reaction catalyst had been chosen, various β,γ-unsaturated ynones **6A**-**D** and nitroolefins **2** were examined (Table 4). The catalytic addition of **6A** to aromatic nitroolefins **2b** and **2d** worked well and adducts **7Ab** and **7Ad** were obtained in good yields and high selectivities. The reaction also tolerated the less reactive β-alkyl substituted nitroolefin **2e**, although, as expected, progressed more slowly (44% conversion after 3 h).[103] Good results were obtained when ynones with other aromatic substituents at the alkynyl moiety (adducts **7Ba** and **7Ca**) or even with alkyl substituent (**7Db**) were employed. These results constitute the first evidence of the efficiency of bifunctional Brønsted base catalysis in Michael additions of β,γ-unsaturated ynones that generate two adjacent tertiary stereocenters affording the Michael adducts in high

[103] The reaction stopped due to the isomerization of the rest of the starting material to the enone **8**, which did not take part in the reaction. However, in all the other cases, and under the same conditions, the impact of this process on the reaction yield was negligible.

enantio- and diastereoselectivity and with excellent regiocontrol (γ-adduct was not observed in any case).

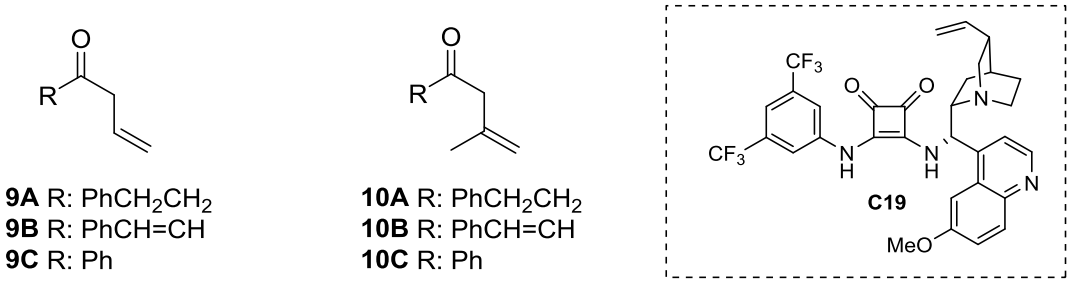
Table 4. Catalytic stereoselective addition of alkynyl allyl ketones **6A-D** to nitroolefins **2**.[a]



[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ynone **6A-D** and 10 mol% of catalyst **C29** in 0.2 mL CH_2Cl_2 at room temperature for 3 h. Variable amounts (~20%) of isomerized starting material **8** were observed in all entries. The enone **8**/product **7** ratio was determined on the crude material by ^1H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography. The diastereoselectivity and the enantioselectivity of the major diastereomer **7** were determined on the crude material by chiral HPLC.

2.3.2. Extension to allyl ketones witk alkyl, aryl and alkenyl side chain

After the study of the behavior of enolizable alkynyl allyl ketones, our next step was to investigate if the reaction could accept other kind of allyl ketones bearing alkyl, alkenyl and aryl side chains (Figure 19).



9A R: $PhCH_2CH_2$
9B R: PhCH=CH
9C R: Ph

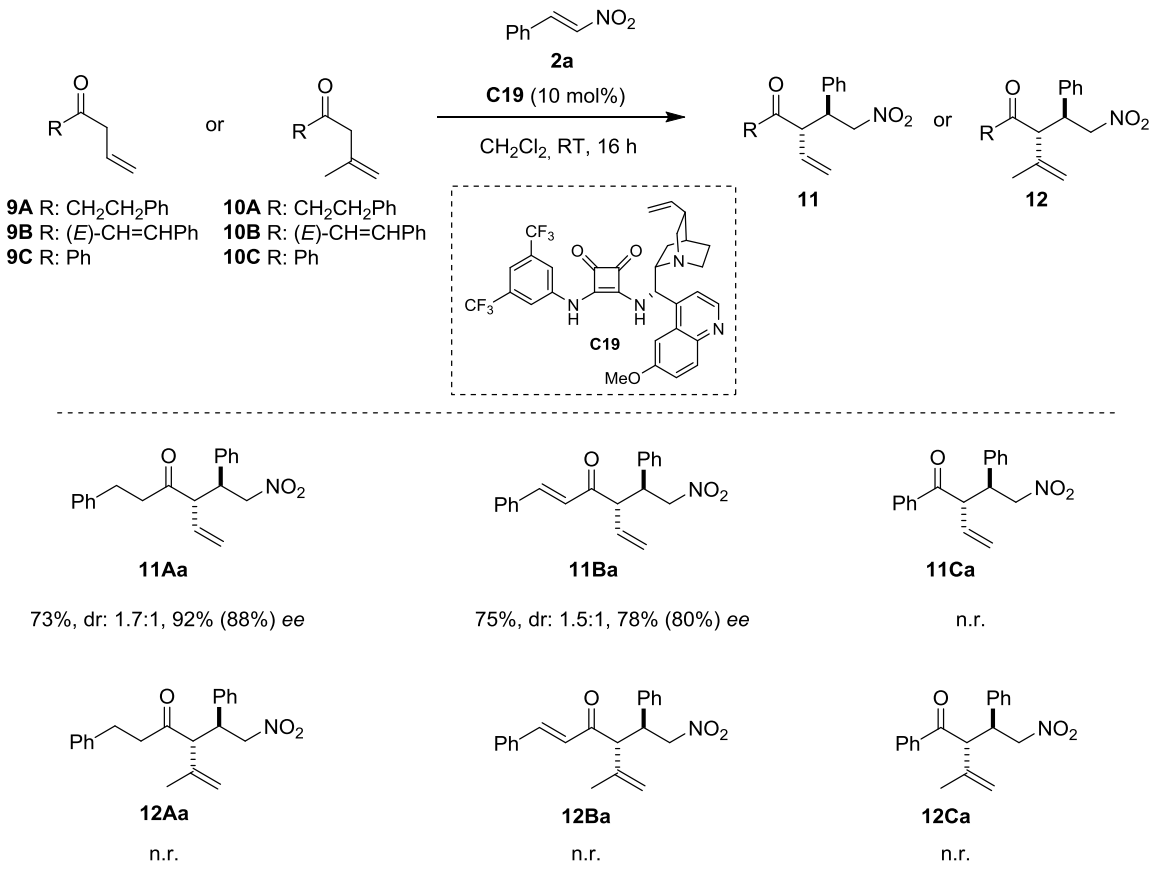
10A R: $PhCH_2CH_2$
10B R: PhCH=CH
10C R: Ph

Figure 19. Selected pronucleophiles for the study using catalyst **C19**.

First of all, we studied how the nature of the side chain and the β-substituent could affect the selectivity of the reaction in presence of catalyst **C19**.[104] The corresponding results are shown in Table 5 and reveal that this reaction tolerates few variations. Among the substrates **9** and **10** examined, only **9A** and **9B** were able to undergo the asymmetric addition to nitroolefin **2a** (adducts **11Aa** and **11Ba**). However, in both cases, the addition proceeded at the α-carbon and no isomerization of the C=C double bond nor α´- or γ-reaction were observed. When other pronucleophiles were used (**9C** and **10A**-**C**), the isomerization of the starting materials to their corresponding more stable enones was faster, comparing with the addition reaction, regardless the reaction temperature.

[104] These pronucleophiles were prepared following the same general procedure used for the synthesis of alkynyl allyl ketones and β-methyl alkynyl allyl ketones. For more information, see experiemental section (pages 178–184).

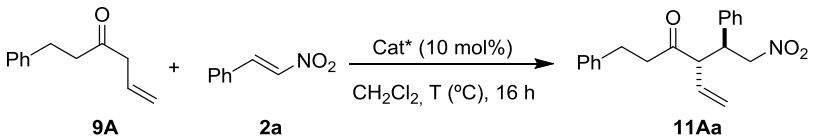
Table 5. Substrate optimization for the Michael addition of ketones **9A-C** and **10A-C** to nitrostyrene **2a**.[a]



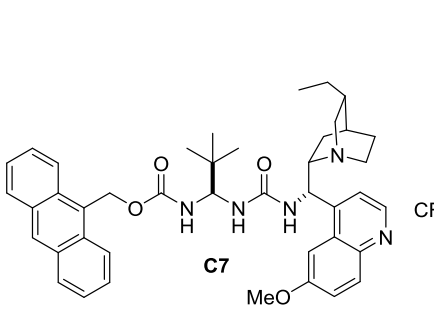
[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ketones **9**-**10** and 10 mol% of catalyst **C19** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. The enone/product ratio was determined on the crude material by ^{1}H NMR (300 MHz) analysis. The diastereoselectivity and the enantioselectivity were determined on crude material by chiral HPLC. The *ee* values of the minor diastereomers are given in parentheses. The conversion was determined by ^{1}H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography. n.r.: no reaction.

Owing to the poor selectivity obtained with **C19**, a range of bifunctional Brønsted base/H-bonding catalysts were tested in order to improve the reaction outcome. Gratifyingly, all the reactions carried out in presence of catalysts **C7**, **C11**, **C18**-**C19**, **C25**-**C27** and **C30** led to the α-Michael adduct **11Aa**, although selectivities varied. As the data in Table 6 show, in the presence of the known thiourea catalyst **C18** moderate stereoselectivities were obtained (dr: 1.5:1, *ee* for major/minor diastereomer 76%/70% *ee*). Then, the squaramide type catalysts **C11**, **C19** and **C25**-**C27** were checked, in order to improve the stereoselectivity. Catalysts **C11** and **C25** provided the lowest values of diastereoselectivity (**C11** dr: 1:1 and **C25** dr: 1.3:1). The Rawal´s catalyst **C26** gave moderate diastereoselectivity (dr: 1.9:1), which was improved when the equivalent cyclohexyldiamine-derived squaramide catalyst **C27** was used (dr: 4:1, 94%/99% *ee*). And finally, ureidopeptide type catalysts were screened; although **C7** and **C30** afforded excellent diastereoselectivities, the *ee* values were inferior.

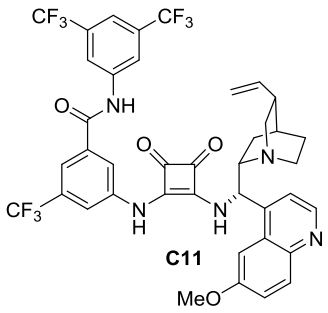
Table 6. Catalyst screening for the Michael reaction of **9A** with **2a**.[a]



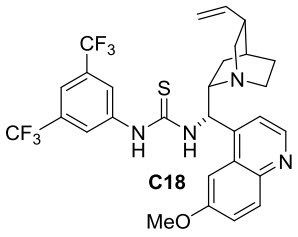
9A **2a** **11Aa**



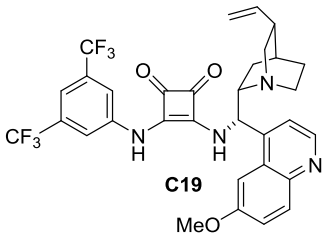
-40 ºC, 67%, dr: >20:1, -60% *ee*



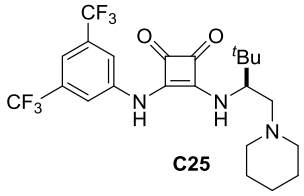
-20 ºC, 67%, dr: 1:1, 85% (54%) *ee*



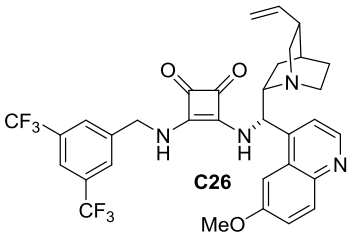
RT, 69%, dr: 1.5:1, 76% (70%) *ee*



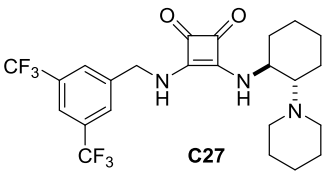
RT, 73%, dr: 1.7:1, 92% (88%) *ee*



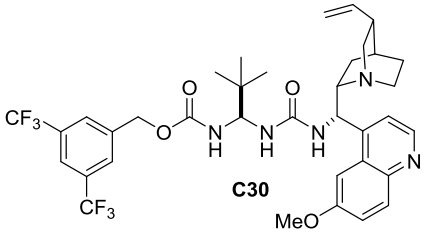
RT, 67%, dr: 1.3:1, 96% (83%) *ee*



-20 ºC, 65%, dr: 1.9:1, 90% (85%) *ee*
(90 % of conversion)



RT, 73%, dr: 4:1, 94% (99%) *ee*



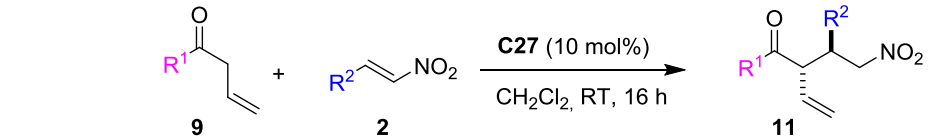
-40 ºC, 49%, dr: >20:1, -44% *ee*
(70 % of conversion)

[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ketones **9A** and 10 mol% of catalyst in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. The enone/product ratio was determined on the crude material by ^{1}H NMR (300 MHz) analysis. The diastereoselectivity and the enantioselectivity were determined on crude material by chiral HPLC. The *ee* values of the minor diastereomers are given in parentheses. The conversion was determined by ^{1}H NMR (300 MHz) analysis. Yield after isolation of the product after chromatography.

After choosing catalyst **C27** as optimum, alkyl and alkenyl allyl ketones **9A** and **9B** were examined in their reaction with nitroolefins **2** (Table 7). All the reactions proceeded smoothly to give the corresponding α-adducts **11** in good yields, but poor

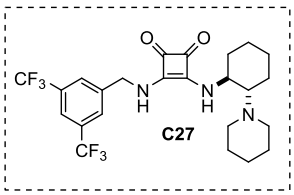
diastereomeric ratios were obtained in all adducts (**11Aa-d**, **11Ba**), whereas enantioselectivities were consistently high.[105]

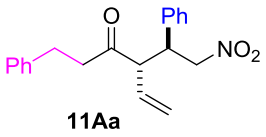
Table 7. Catalytic stereoselective addition of allyl ketones **9A** and **9B** to nitroolefins **2**.[a]



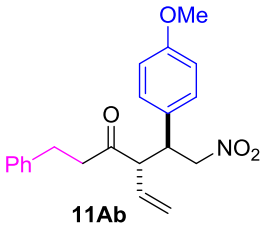
R^1:
A R^1: CH_2CH_2Ph
B R^1: (*E*)-CH=CHPh

R^2:
a R^2: Ph
b R^2: 4-$MeOC_6H_4$
c R^2: 4-MeC_6H_4
d R^2: 4-ClC_6H_4

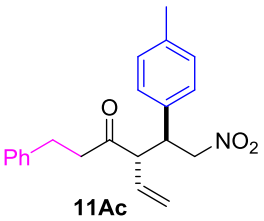




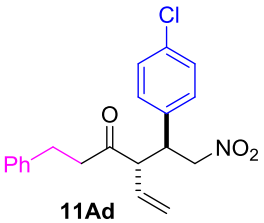
73%, dr: 4:1, 94% (99%) *ee*



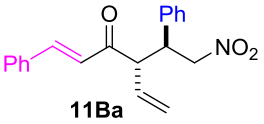
72%, dr: 2.2:1, 91% (97%) *ee*



70%, dr: 5.7:1, 97% (90%) *ee*



75%, dr: 5.3:1, 93% (98%) *ee*



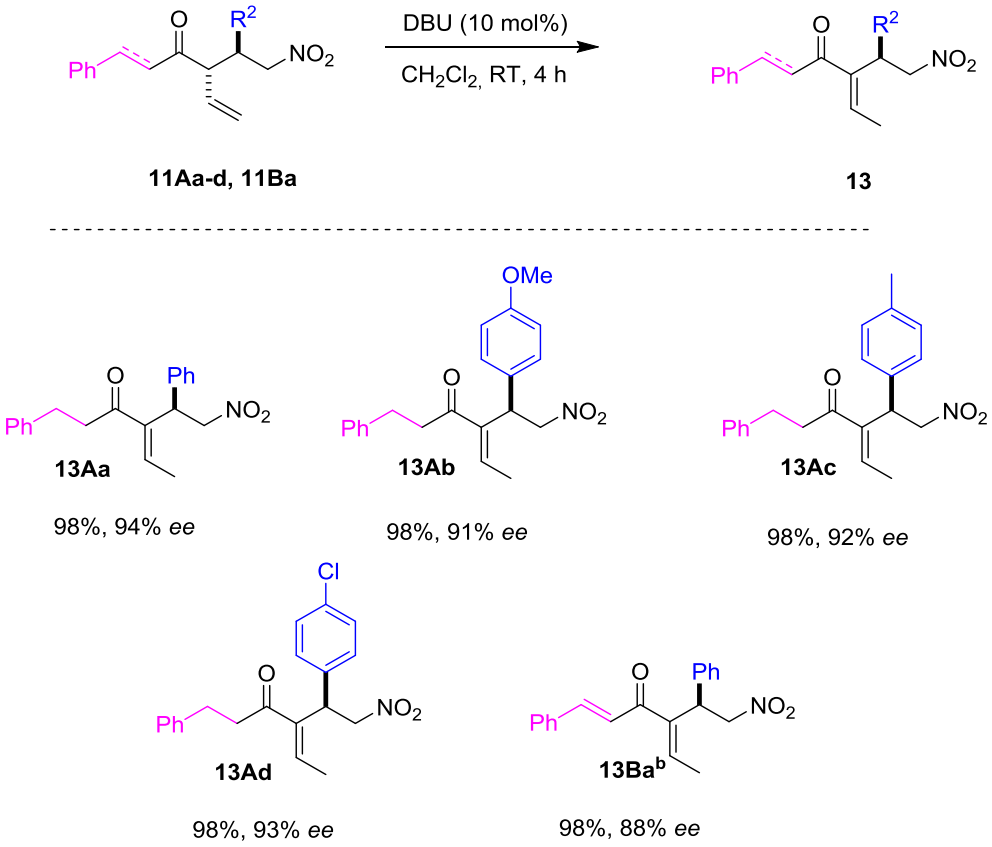
81%, dr: 1.3:1, 84% (90%) *ee*

[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of ketones **9A** or **9B** and 10 mol% of catalyst **C27** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. The enone/product **11** ratio was determined on the crude material by ^{1}H NMR (300 MHz) analysis. The diastereoselectivity and the enantioselectivity were determined on crude material by chiral HPLC. The *ee* values of the minor diastereomers are given in parentheses. Yield after isolation of the product after chromatography.

If desired, adducts from the above catalytic reactions, such as **11Aa-d** and **11Ba**, can be isomerized to the corresponding α,β-enone product **13Aa-d** and **13Ba** (Rauhut-Currier type products) almost quantitatively, and retaining the *ee* values, by exposure to 10 mol% DBU at RT in CH_2Cl_2 (Table 8).

[105] The starting ketones **9A** and **9B** underwent partial (about 20%) isomerization to the respective α,β-enones during the reaction. However, this circumstance did not affect the reaction outcome provided that two equivalents of the starting materials were employed.

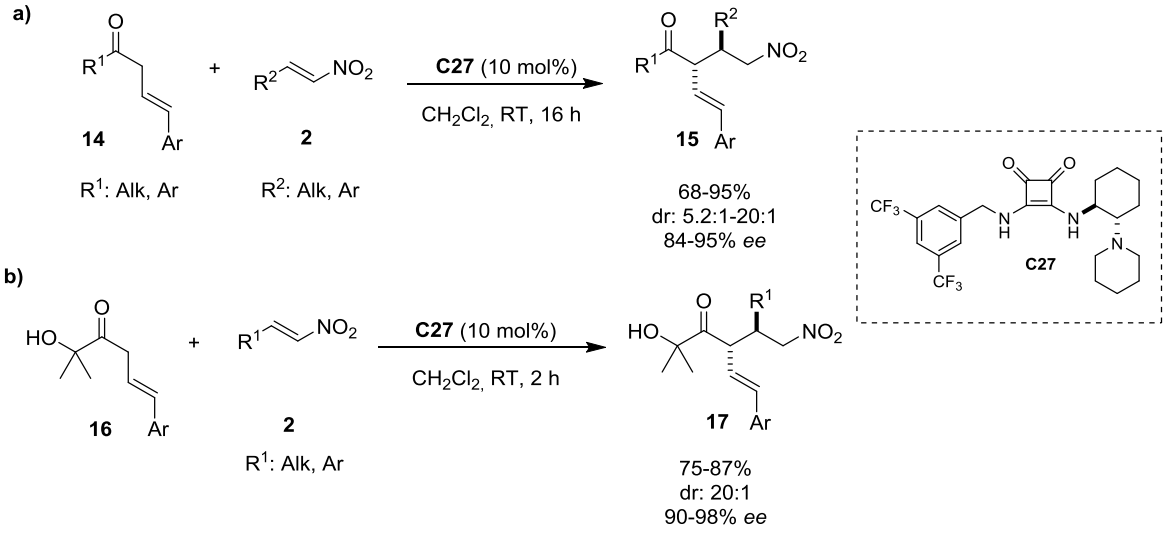
Table 8. Isomerization of the C=C double bond in adducts **11Aa-d** and **11Ba**.[a]



[a] Reactions carried out at 0.1 mmol scale, using 10 mol% of DBU in 0.1 mL CH_2Cl_2 at room temperature for 4 h. The enantioselectivity was determined by chiral HPLC. Yield after isolation of the product after chromatography. [b] **11Ba** was isomerized by treatment with Et_3N overnight.

In parallel to this work, I. Iriarte in our laboratory found that γ-substituted allyl ketones **14** with aryl and alkyl side chains (Scheme 36a) and hydroxyalkyl β,γ-unsaturated ketones **16** (Scheme 36b) are also suitable donor substrates for the Michael addition to nitroolefins **2**, futher illustrating the scope of the reaction.[106]

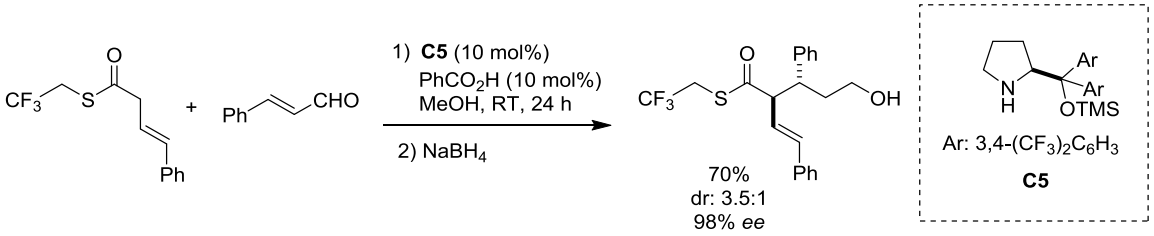
[106] For more information, see: I. Iriarte, O. Olaizola, S. Vera, I. Gamboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.



Scheme 36. a) β,γ-Unsaturated ketones **14** in Michael α-additions to nitroolefins **2**. b) Hydroxyalkyl β,γ-unsaturated ketones **16** in Michael α-additions to nitroolefins **2**.

2.3.3. β,γ-Unsaturated esters/thioesters as pronucleophiles

As mentioned before (chapter 2, Scheme 29b, page 45), β,γ-unsaturated esters are able to react with *N*-tosyl imines in a direct Mannich reaction to afford adducts with ee´s up to 97%.[90] In this context, a single example concerning the use of β,γ-unsaturated thioesters as pronucleophile in Michael reactions has been documented (Scheme 37).[107]



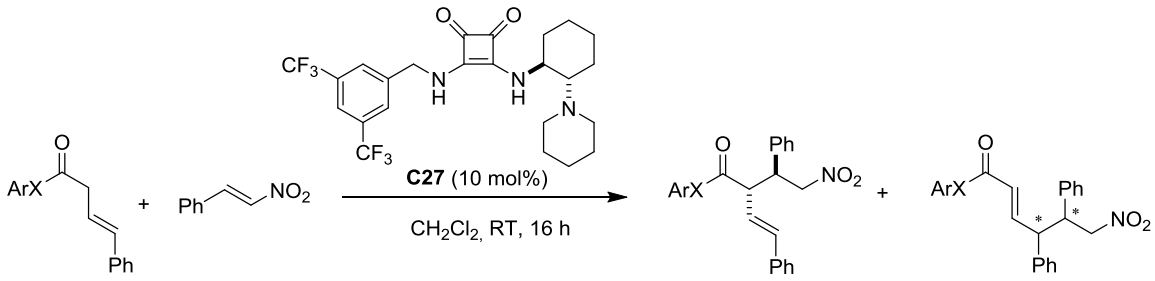
Scheme 37. α-Selective Michael addition of β,γ-unsaturated thioester to cinnamaldehyde. Barbas III, 2008.

On this basis, the Michael reaction of β,γ-unsaturated esters/thioesters **18** with *trans*-β-nitrostyrene **2a** was investigated in the presence of catalyst **C27**. The corresponding results are collected in Table 9 and illustrate that the reactions produced a mixture of α- and γ-addition products **19** and **20**, respectively. However, no isomerization of the starting material to the corresponding α,β-unsaturated ester or thioester was observed. Thioesters resulted more reactive and selective than the parent esters, regardless the nature of the *S*-substituent. However, while the minor γ-adducts

[107] D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591.

were obtained as essentially single diastereomer in all cases (adducts **20Aa**-**Ea**), the respective major α-adduct was obtained with diastereo- and enantioselectivities from low to moderate (adducts **19Aa**-**Ea**).

Table 9. Asymmetric Michael additions of β,γ-unsaturated (thio)esters **18** to nitroolefin **2a**.[a]



18A-E **2a** **19Aa-Ea** α-adduct **20Aa-Ea** γ-adduct

Entry	ArX	Nucleophile	Combined yields (%)	19/20	19		20	
				α/γ	dr	% *ee*	dr	% *ee*
1	PhO-	**18A**	91	2.3:1	2.7:1	63(50)	20:1	63
2[b]	PhS-	**18B**	92	4:1	4:1	89(80)	20:1	91
3	2-NaphO-	**18C**	88	2:1	3:1	62(54)	20:1	54
4	2-NaphS-	**18D**	87	2.1:1	4.4:1	84(81)	20:1	64
5	2,6-$Me_2C_6H_3S$-	**18E**	92	2.7:1	7.1:1	58(10)	20:1	56

[a] Reactions carried out at 0.2 mmol scale, using 2.0 equiv. of β,γ-unsaturated (thio)esters **18** and 10 mol% of catalyst **C27** in 0.2 mL CH_2Cl_2 at room temperature for 16 h. The **19**/**20** ratio determined by ^1H NMR (300 MHz) analysis. The diastereoselectivity and enantioselectivity were determined by chiral HPLC. [b] Reaction was finished after 6 h.

2.3.4. Determination of the adducts configuration

The absolute configuration of adduct **21** was established by X-ray analysis[108] and for remaining adducts **3**, **7**, **11** and **19** was assigned by analogy and by assuming a uniform reaction mechanism (Figure 20).

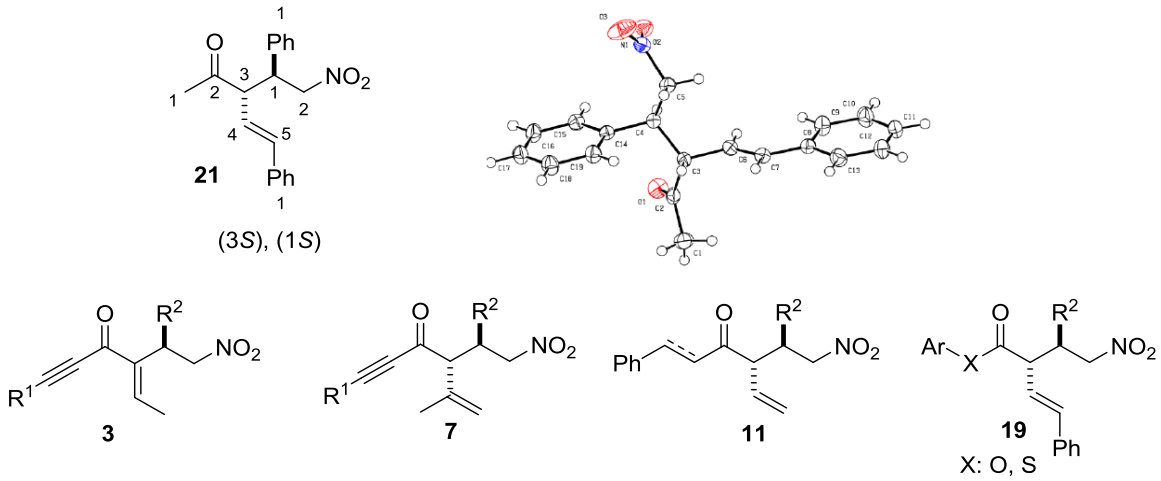


Figure 20. ORTEP diagram of compound **21**.

When it comes to the minor stereoisomer of compound **11**, its configuration was not established by X-ray analysis. As the results shown in Table 8 demostrate, the high *ee* values of products **13** formed upon isomerization of the diastereomeric mixtures of **11** could prove that the minor isomer should be epimeric at Cα (stereolabile center) with respect to the major isomer **11** (Figure 21).

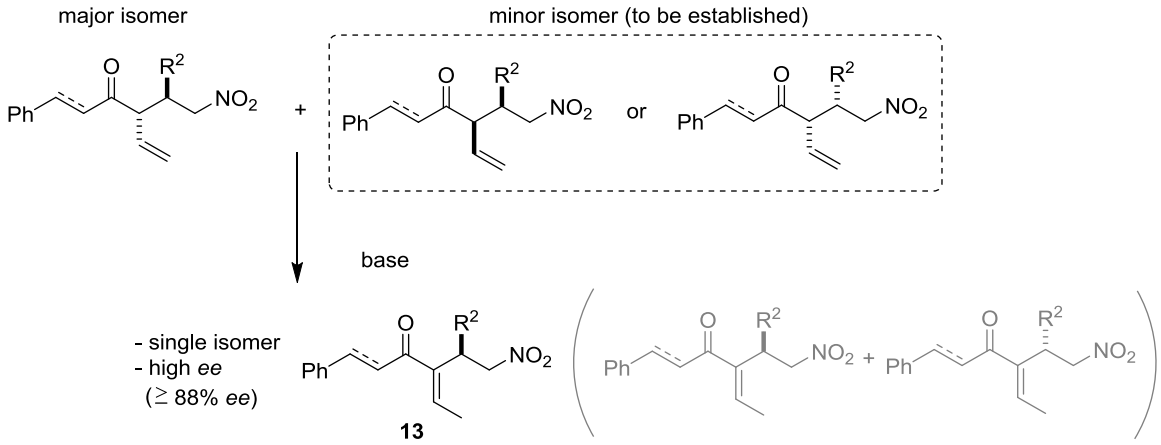


Figure 21. Major/minor isomers of compounds **11**.

[108] Compound **21** (CCDC-1542032) was prepared by Iriarte from this laboratory following the same methodology as described herein. For more details, see: I. Iriarte, doctoral thesis, *Brønsted Base Catalyzed Asymmetric C-C Bond-Forming Reactions with Unsaturated Ketones.* EHU/UPV, **2019** (https://www.ehu.eus/es/web/gicas/tesiak).

Moreover, the *E*/*Z* configuration of the C=C double bond of compounds **3** and **13** were established by a NOESY analysis using compound **3Ca** as reference. Irradiation at 2.19 ppm (H^b) (Figure 22) revealed the proximity of H^c, indicating that the protons are on the same side of the double bond. To confirm the proposed structure, the NOESY experiment was repeated, but in this case the irradiation was performed at 7.65 ppm (H^a) (Figure 23). No signals were detected, suggesting that the configuration of the double bond is *E* and not *Z*.

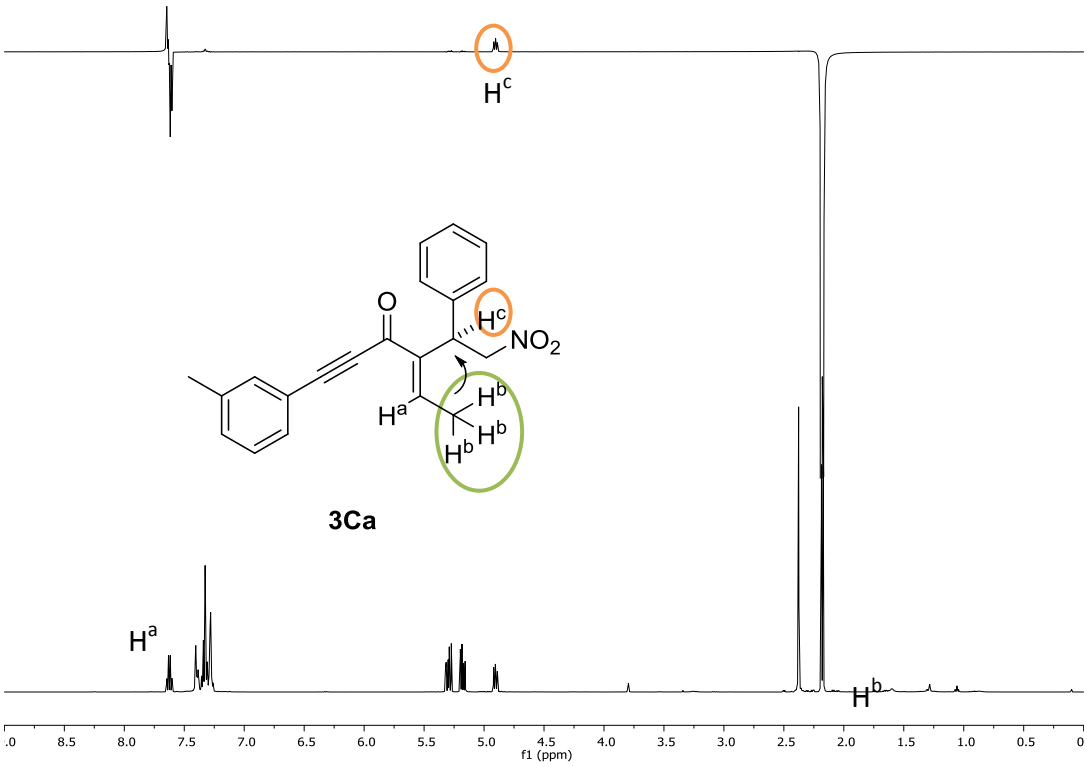


Figure 22. NOESY NMR spectrum for product **3Ca**.

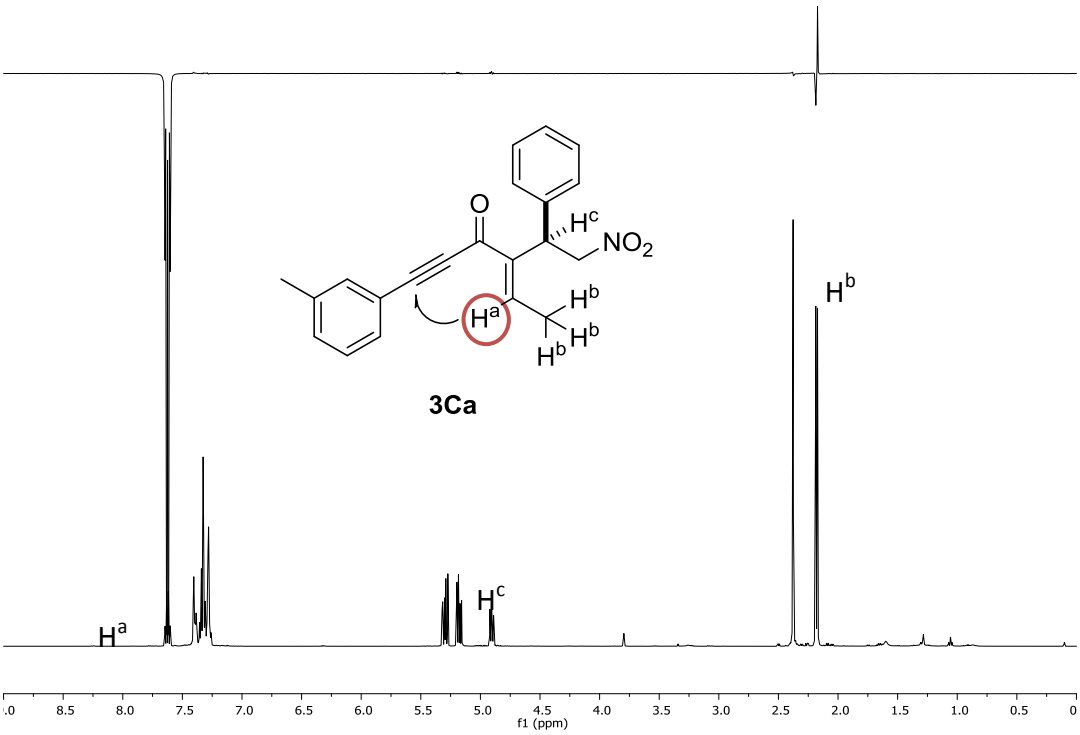


Figure 23. NOESY NMR spectrum for product **3Ca**.

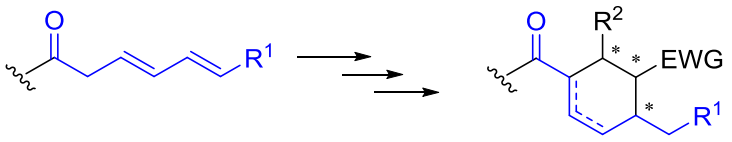
Chapter 3

Brønsted base catalyzed one-pot synthesis of stereodefined six-member carbocycles

3. Brønsted base catalyzed one-pot synthesis of stereodefined six-member carbocycles

3.1. Introduction

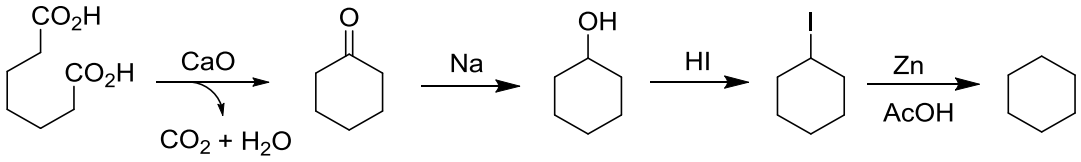
Having established an efficient methodology for direct α-functionalization of carbonyl compounds through trialkylammonium dienolates, we next focused on trienolates with the hope that their chemistry might open a way for construction of six-member carbocycles as will be discussed later (Scheme 38).



Scheme 38. α-Functionalization of trienolates intermediates.

3.1.1. Six-member carbocycles from functionalized compounds

Since the first synthesis of cyclohexane by Baeyer starting from pimelic acid in 1894 (Scheme 39),[109] the number of novel stereoselective synthetic methods for the construction of substituted cyclohexane derivatives has grown exponentially. The main reason is that six-member carbocycles are ubiquitous structural motifs in a great variety of natural products and bioactive substances.



Scheme 39. Baeyer´s synthesis of cyclohexane. Baeyer, 1894.

There are three classical ways in which a substituted cyclohexane can be prepared: i) by cycloaddition reactions[110] (intra- and intermolecular Diels-Alder

[109] a) A. Baeyer, *Ann*. **1894**, *278*, 111. b) E. W. Warnhoff, *J. Chem. Educ.* **1996**, *73*, 494–497.

[110] For general reviews on asymmetric Diels-Alder reactions, see: a) B. Yang, S. Gao, *Chem. Soc. Rev.* **2018**, *47*, 7926–7953. b) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491–1500. c) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* **2010**, 1–26. d) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698. For leading books about cycloaddition reactions, see: e) S. Kobayashi, K. A. Jørgansen, *Cycloaddition Reactions in Organic Synthesis,* Wiley-VCH Verlag GmbH, **2001**.

reactions), ii) by ring modifications (ring expansions[111] and ring contractions[112]) and iii) by ring closure reactions (Figure 24).

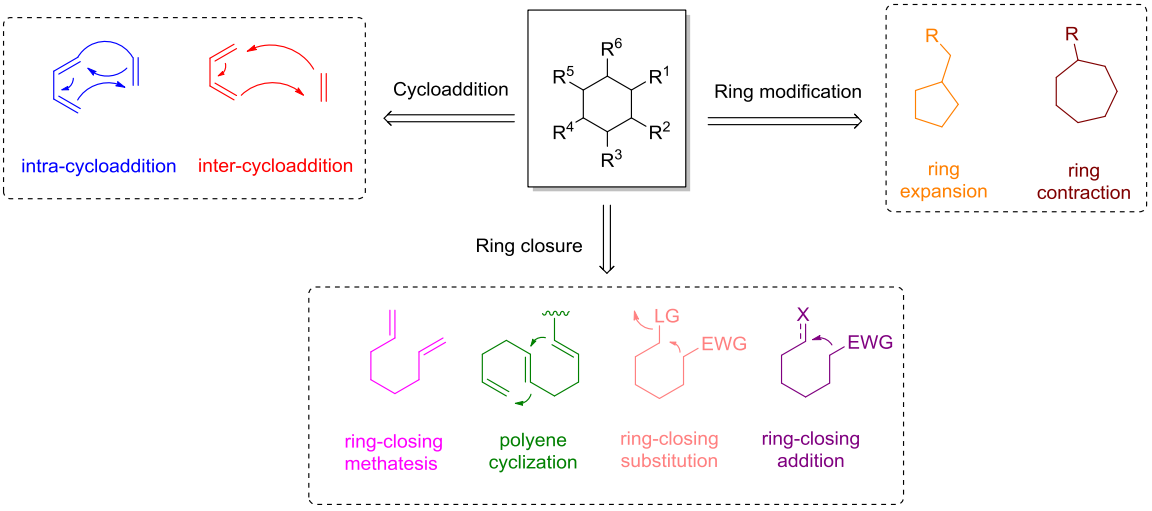


Figure 24. Strategies for the construction of six-member rings.

Although during the last decade the Diels-Alder cycloaddition (DA) has been the most employed approach to substituted cyclohexanes, great efforts have also been made to expand the ring-closing methodology. The ring-closing step can be achieved through different approaches, such as: i) ring-closing methatesis,[113] ii) polyene cyclizations,[114] iii) ring-closing substitutions[115] and iv) ring-closing additions. The latter is usually achieved by using substrates bearing carefully selected and strategically positioned donor and acceptor reaction sites. Depending on the position of the acceptor, three major approaches have been implemented for the key ring-closing addition step: the intramolecular 1,2-, 1,4- (*exo* and *endo*) and 1,6-additions (Figure 25). Examples of these approaches are outlined in the next sections.

[111] For selected recent examples of ring expansions, see: a) Y. J. Kim, D. Y. Kim, *Org. Lett.* **2019**, *21*, 1021–1025. b) N. Jeedimalla, C. Jacquet, D. Bahneva, J. -J. Y. Tendoung, S. P. Roche, *J. Org. Chem.* **2018**, *83*, 12357–12373.

[112] For selected examples of ring contractions, see: a) M. J. Mitcheltree, Z. A. Konst, S. B. Herzon, *Tetrahedron* **2013**, *69*, 5634–5639. b) R. S. Varma, D. Kumar, *Synthesis* **1999**, *8*, 1288–1290.

[113] For general reviews on ring-closing metathesis reactions, see: a) O. M. Ogba, N. C. Warner, D. J. O´Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510–4544. b) S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, *109*, 3783–3816. c) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452.

[114] For general reviews about polyene cyclization reactions, see: a) A. G. M. Barrett, T. -K. Ma, T. Mles, *Synthesis* **2019**, *51*, 67–82. b).C. N. Ungarean, E. H. Southgate, D. Sarlah, *Org. Biomol. Chem.* **2016**, *14*, 5454–5467. c) R. A. Yoder, J. N. Johnson, *Chem. Rev.* **2005**, *105*, 4730–4756.

[115] For examples about ring closure reactions through intramolecular substitution, see: a) M. Z. Blajet, R. Kowalczyk, J. Skarzewski, *Tetrahedron* **2005**, *61*, 5235–5240. b) M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, *Chem. Eur. J.* **2004**, *10*, 1752–1764.

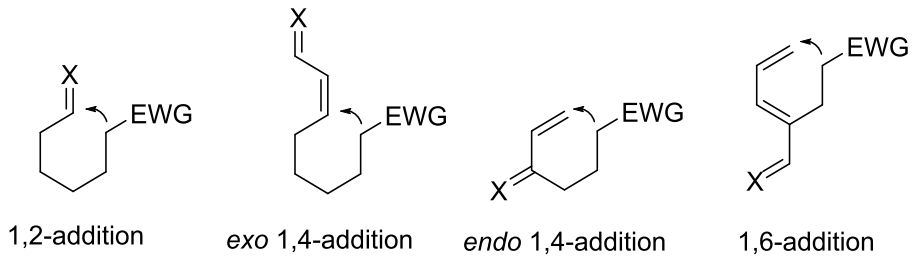
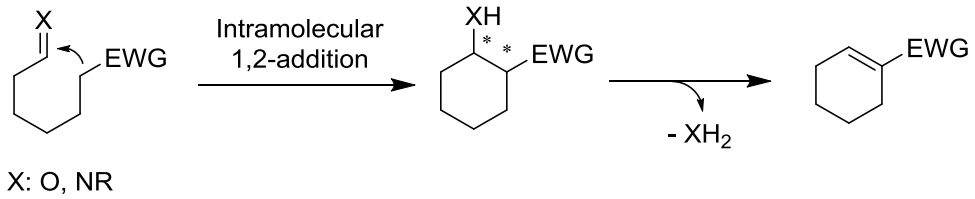


Figure 25. Three major approaches for the ring-closing addition step.

3.1.1.1. *Intramolecular 1,2-addition*

The intramolecular ring-closing 1,2-addition strategy is the most explored approach to substituted cyclohexanes. In general, all cyclizations that end up in an intramolecular 1,2-addition are based on an aldol or Mannich addition, with an additional elimination step in some cases (Scheme 40).



Scheme 40. The intramolecular ring-closing 1,2-addition strategy.

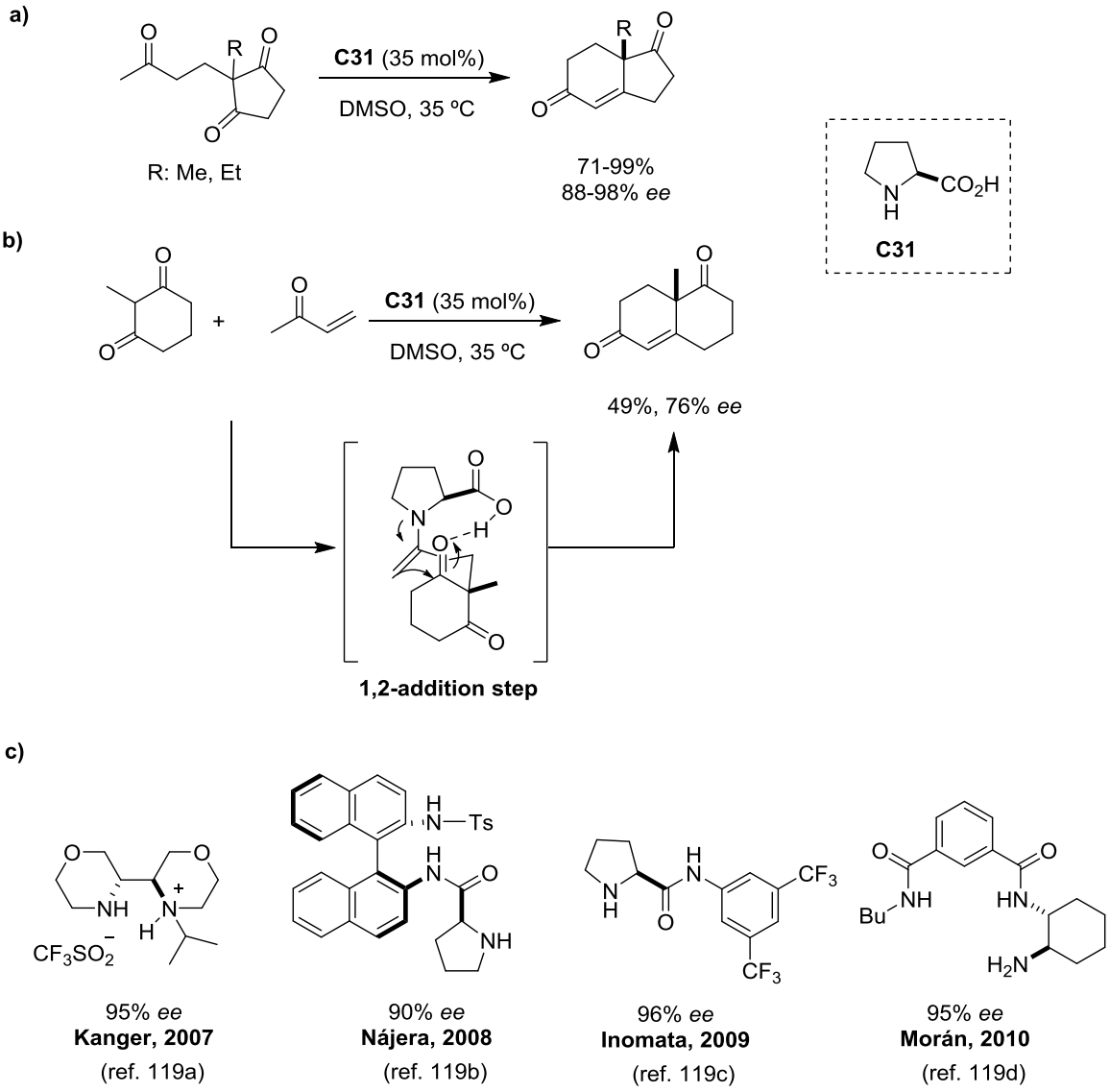
The first catalytic asymmetric direct reaction, in which a cyclohexene was formed by an intramolecular 1,2-addition, was described by Hajos and Parrish in 1974.[116] It was found that (*S*)-proline **C31** catalyzes an asymmetric aldol cyclization to afford optically active Robinson annulation type products (Scheme 41a). Due to the relevance of this kind of products as building blocks of a number of natural products and bioactive targets,[117] in 2000, Bui and Barbas III reported the (*S*)-proline catalyzed synthesis of the Wieland-Miescher (W. M.) ketone in a one-pot procedure starting from methyl vinyl ketone and 2-methyl-1,3-cyclohexanedione (Scheme 41b).[118] Later on, better enantiomeric excesses have been achieved by means of other catalysts,[119] such as those depicted in the Scheme 41c.

[116] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

[117] For general reviews on enantioselective access to Robinson annulation type products, see: a) F. Gallier, A. Martel, G. Dujardin, *Angew. Chem. Int. Ed.* **2017**, *56*, 12424–12458. b) B. Bradshaw, J. Bonjoch, *Synlett*. **2012**, *23*, 337–356.

[118] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951–6954.

[119] a) T. Kanger, K. Kriis, M. Laars, T. Kailas, A. Müürisepp, T. Pehk, M. Lopp, *J. Org. Chem.* **2007**, *72*, 5168–5173. b) G. Guillena, C. Nájera, S. F. Viózquez, *Synlett*. **2008**, 3031–3035. c) Y. Akahane, K. Inomata, Y. Endo, *Heterocycles* **2009**, *77*, 1065–1078. d) L. Fuentes de Arriba, D. G. Seisdedos, L. Simón, V. Alcázar, C. Raposo, J. R. Morán, *J. Org. Chem.* **2010**, *75*, 8303–8306.



Scheme 41. a) (*S*)-Proline catalyzed synthesis of Hajos–Parrish ketones. Hajos and Parrish, 1974. b) (*S*)-Proline catalyzed one pot synthesis of Wieland-Miescher ketone. Barbas III, 2000. c) Representative organocatalysts employed for the enantioselective synthesis of Wieland-Miescher ketone.

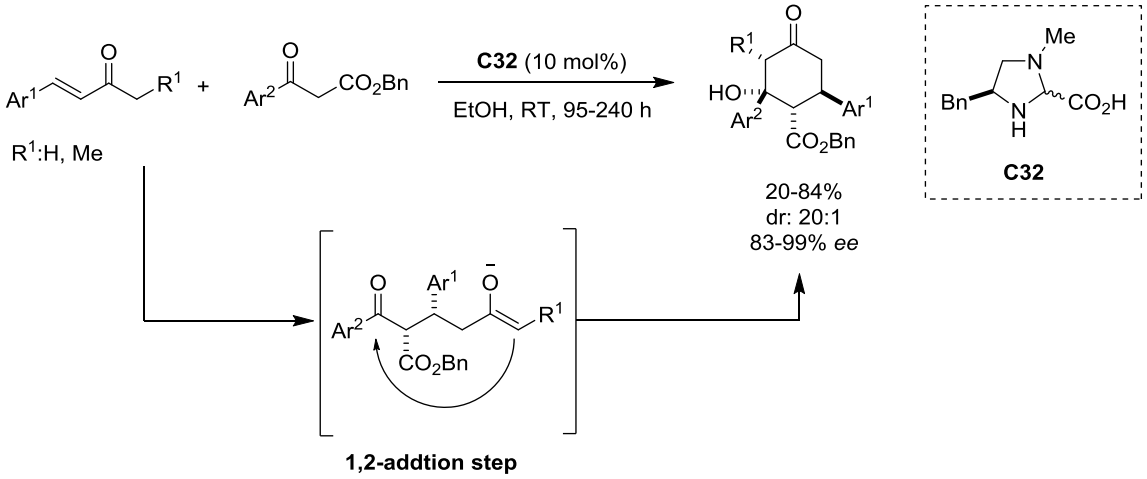
It is worth mentioning that the number of scientific reports containing the key word "one-pot reaction" that appeared each year increased significantly during the period 1980–2010,[120] which quickly became a gold mine for chemists in the following years. Although metal-catalyzed domino reactions can be found in the literature,[121] organocatalyzed cascade reactions have emerged as a powerful tool in the last

[120] L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492–8509.

[121] For general reviews on enantioselective metal-catalyzed domino reactions, see: a) H. Pellissier, *Adv. Synth. Catal.* **2019**, *361*, 1733–1755. b) H. Pellissier, *Adv. Synth. Catal.* **2016**, *358*, 2194–2259. c) A. de Meijere, P. von Zezschwitz, S. Brase, *Acc. Chem. Res.* **2005**, *38*, 413–422. d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.

decade.[122] Within this context, the field is dominated by the use of secondary chiral amines owing to their ability to activate α,β-unsaturated aldehydes and ketones through transient iminium ion formation and enolizable aldehydes and ketones through transient enamine generation.

In this respect, Robinson annulations are one of the most used cascade approaches for the construction of cyclohexenyl frameworks. Although the majority of the examples that can be found in the literature involve cyclic ketones, there are examples where acyclic ketones are also used. One of the earliest examples was described by Jørgensen and co-workers,[123] starting from styryl methyl ketones and acyclic β-ketoesters. These substrates react in the presence of imidazolidine catalyst **C32** to afford an intermediate product that undergoes an intramolecular aldol addition to give the depicted cyclohexanone product with excellent diastereoselectivity and enantioselectivity (Scheme 42).



Scheme 42. Imidazolidine catalyst **C32** in an intramolecular 1,2-addition reaction providing chiral cyclohexanones. Jørgensen, 2004.

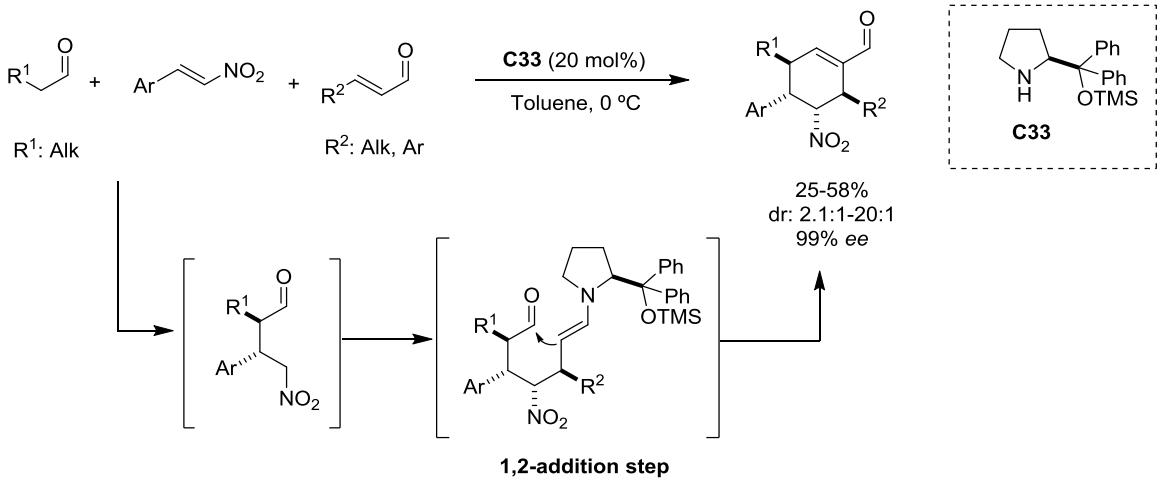
Two years later, in 2006, Enders *et al.* described the first triple organocatalytic cascade reaction,[124] which opened up a simple and flexible methodology for construction of polyfunctional cyclohexene building blocks. A readily available α,α-diarylprolinol organocatalyst **C33** is employed for the chemo-, diastereo- and enantioselective reaction, leading to cyclohexene carboxaldehydes in moderate yields

[122] For a general review on aminocatalyzed domino reactions, see: a) P. Chauhan, S. Mahajan, D. Enders *Acc. Chem. Res.* **2017**, *50*, 2809–2821. For general reviews on organocatalyzed domino reactions, see: b) Y. Wang, H. Lu, P. -F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832−1844. c) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431. d) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909−1930. e) H. Pellissier, *Adv. Synth. Catal*. **2012**, *354*, 237−294. f) D. Enders, C. Grondal, M. R. Hüttl, *Angew. Chem. Int. Ed*. **2007**, *46*, 1570−1581.

[123] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272–1277.

[124] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863.

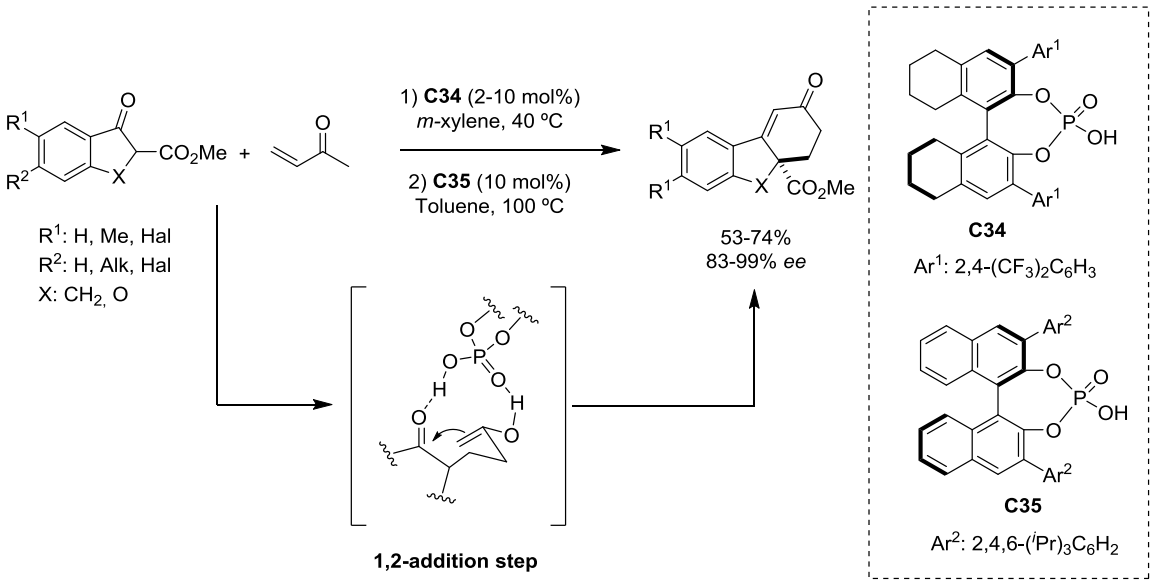
and most significantly with four contiguous stereogenic centers generated in one-pot procedure (Scheme 43).



Scheme 43. α,α-Diarylprolinol organocatalyst in an intramolecular 1,2-addition reaction. Enders, 2006.

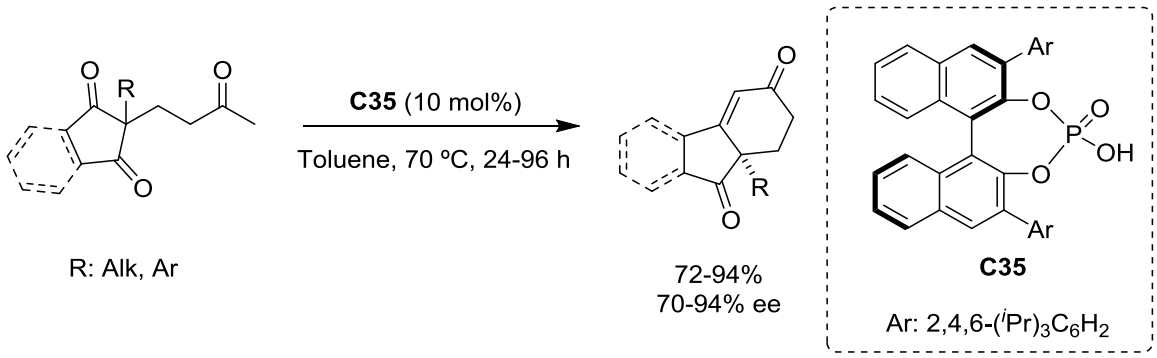
After these remarkable contributions a plethora of organocatalytic cascade reactions that proceed through enamine and/or iminium pathways have been developed and reviewed several times.[122] Besides secondary chiral amines, Brønsted acids have also been used as catalysts for construction of cyclohexanes. For example, Akiyama and co-workers[125] developed the first enantioselective Michael addition followed by an intramolecular 1,2-addition reaction catalyzed by two phosphoric acids **C34** and **C35**, which enables the synthesis of cyclohexenone derivatives with excellent enantioselectivities (Scheme 44). The authors observed that the first Brønsted acid **C34** catalyzes the enantioselective Michael addition reaction of α-alkyl-β-keto esters with methyl vinyl ketone, whereas the second one, **C35**, catalyzes a kinetic resolution in the intramolecular aldol reaction followed by dehydration. Brønsted acid **C34** is not effective in the second Michael addition as the treatment of the Michael adduct with 10 mol% of **C34** provides the final cyclohexenone in 13% yield and in 48% *ee*.

[125] T. Akiyama, T. Katoh, K. Mori, *Angew. Chem. Int. Ed.* **2009**, *48*, 4226–4228.



Scheme 44. Chiral Brønsted acid in an intramolecular 1,2-addition reaction. Akiyama, 2009.

The same group reported the asymmetric synthesis of Wieland–Miescher and Hajos–Parrish ketones catalyzed by chiral phosphoric acid **C35** *via* desymmetrization of meso-1,3-diones with good chemical yields and enantioselectivities (Scheme 45).[126] To the best of our knowledge, only one more example has been reported in which a Brønsted acid is used to promote the construction of six-member cycles through intramolecular 1,2-addition reaction.[127] These examples provide the basis for future advances.

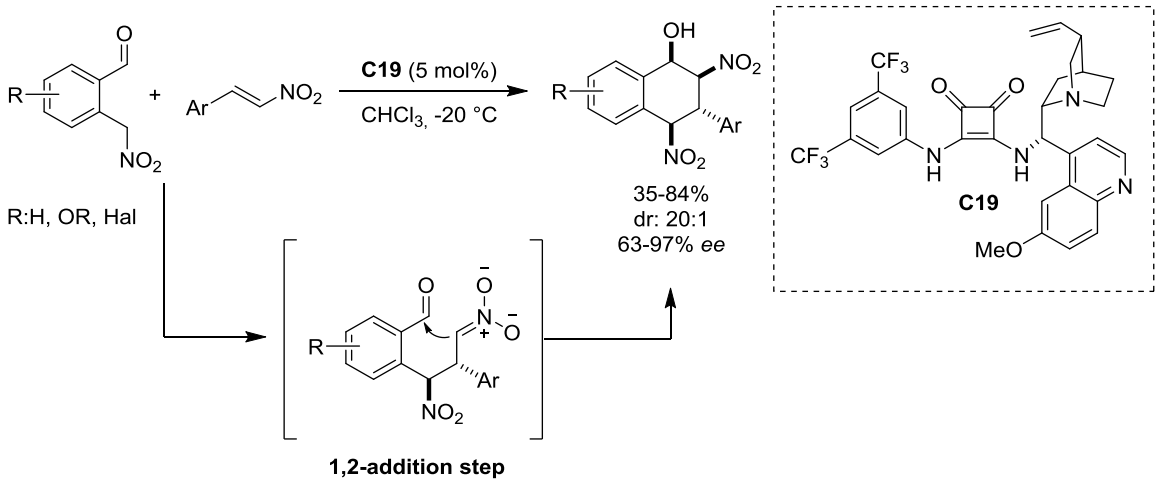


Scheme 45. Asymmetric synthesis of Hajos–Parrish ketones using a chiral phosphoric acid. Akiyama, 2009.

Similarly, Brønted bases, especially bifunctional squaramide catalysts,[128] have also contributed to this issue. One of the earliest examples for the construction of

[126] K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem. Int. Ed.* **2009**, *48*, 9652–9654.
[127] L. Clot-Almenara, C. Rodríguez-Escrich, M. A. Pericás, *RSC Adv.* **2018**, *8*, 6910–6914.
[128] For a general review on the use of squaramide catalysts in domino reactions, see: P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281.

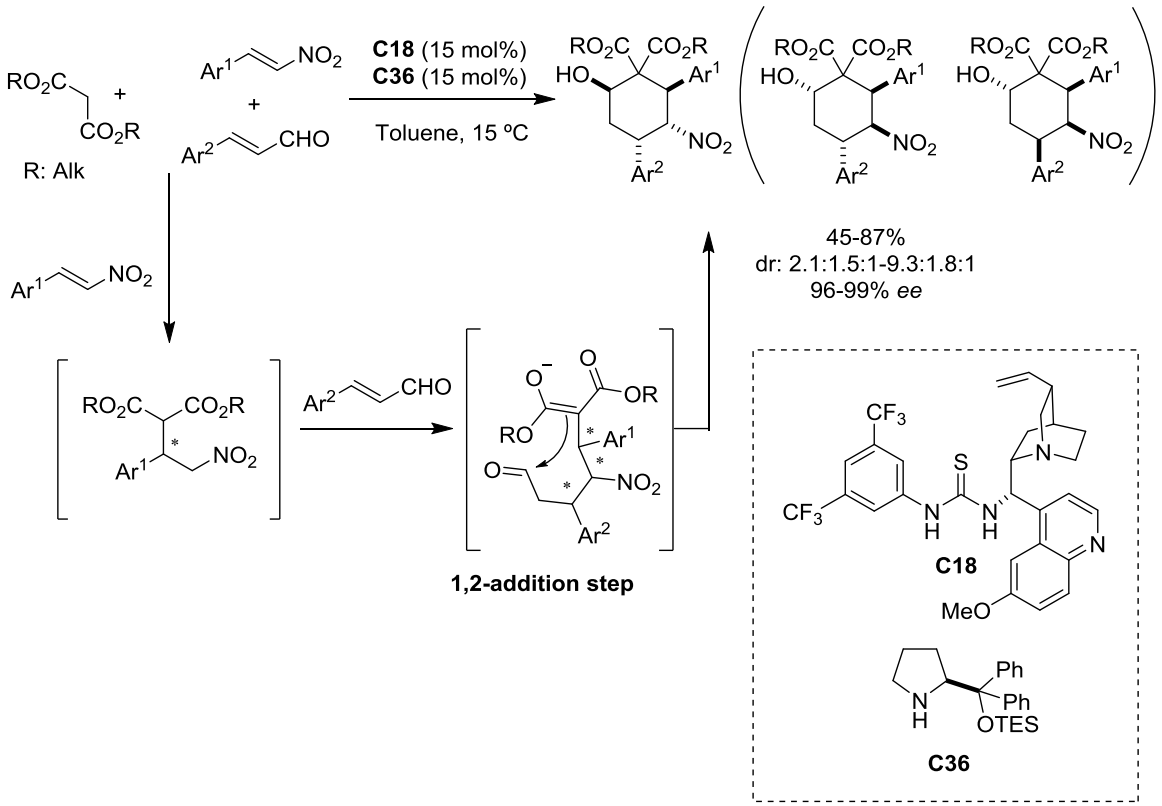
cyclohexanols bearing four contiguous stereocenters was described by Enders and co-workers using the cinchona-squaramide catalyst **C19** (Scheme 46).[129] The authors developed an organocatalytic Michael/Henry reaction starting from different *o*-nitromethyl benzaldehydes and nitroolefins to afford benzo-fused cyclohexanols with four contiguous stereogenic centers.



Scheme 46. Squaramides in an intramolecular 1,2-addition reaction. Enders, 2013.

In the majority of the above described one-pot reactions, only one catalyst is used for the course of the process. Even so, the use of two catalysts with different activation modes can provide greater reaction diversity. On this basis, in 2009, a collaborative work between the groups of Xu and Dixon[130] demonstrated the compatibility of two organocatalysts to perform a triple Michael/Michael/aldol cascade reaction. The authors suggested that the bifunctional thiourea-tertiary amine catalyst **C18** activates the malonate ester and the nitroolefin simultaneously, thus promoting the Michael addition with high chemo- and stereoselectivity. Next, the resulting Michael adduct participates directly in the second catalytic cycle as a nucleophile in a regioselective nitro-Michael reaction to α,β-unsaturated aldehydes under iminium ion activation with the secondary amine catalyst **C36**. And finally, the resulting Michael adduct undergoes a base-promoted intramolecular 1,2-addition to the aldehyde function to generate the desired cyclohexane with excellent enantioselectivity (Scheme 47).

[129] D. Enders, R. Hahn, I. Atoiresei, *Adv. Synth. Catal.* **2013**, *355*, 1126–1136.
[130] Y. Wang, R. -G. Han, Y. -L. Zhao, S. Yang, P. -F. Xu, D. J. Dixon, *Angew. Chem. Int. Ed.* **2009**, *48*, 9834–9838.



Scheme 47. Two different organocatalysts in an intramolecular 1,2-addition reaction. Xu and Dixon, 2009.

Recently, chiral isothiourea activation of α,β-unsaturated anhydrides or α,β-unsaturated acyl halides through formation of acylammonium salts has been examined.[131] These α,β-unsaturated acylammonium salts contain electrophilic centers at the C1 and C3 positions, and a latent nucleophilic center at C2, providing new opportunities for reaction design to target previously inaccessible product architectures (Figure 26).

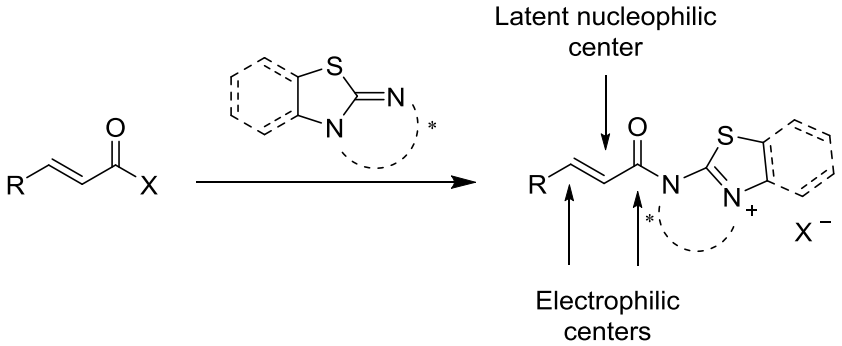
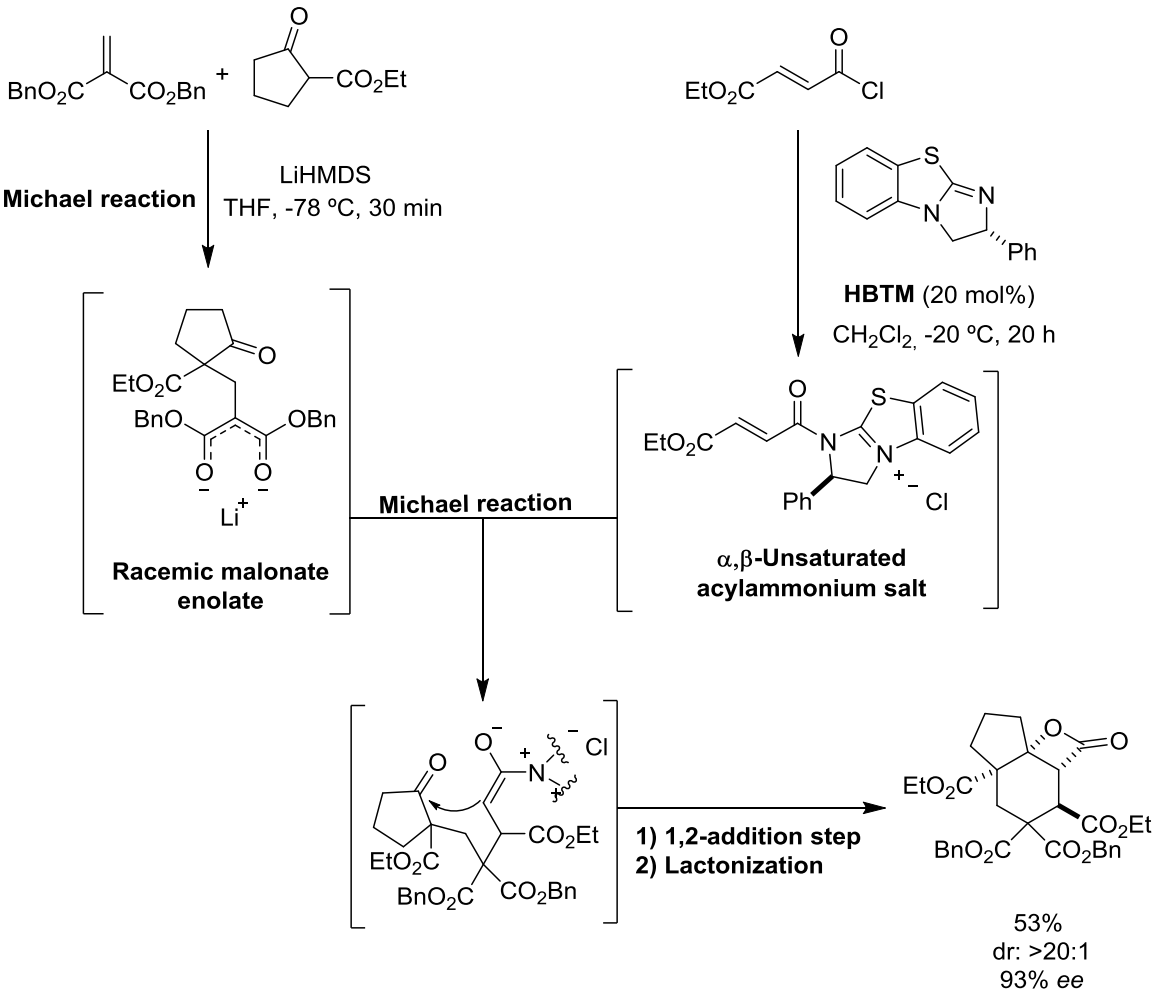


Figure 26. α,β-Unsaturated acylammonium salts as intermediates in chiral isothiourea catalysis.

[131] For general reviews on asymmetric organocatalytic reactions involving α,β-unsaturated acylammonium salts, see: a) J. Merad, J. -M. Pons, O. Chuzel, C. Bressy, *Eur. J. Org. Chem.* **2016**, 5589–5610. b) S. Vellalath, D. Romo, *Angew. Chem. Int. Ed.* **2016**, *55*, 13934–13943.

Employing this approach Romo and co-workers reported a rapid assembly of complex cycles involving the commercially available chiral isothiourea homobenzotetramisole (HBTM) as key element.[132] The authors observed that the initial Michael adduct from the reaction between β-ketoester and dibenzyl methylenemalonate depicted in Scheme 48 engages in a nucleophile-catalyzed Michael-aldol-lactonization sequence with an α,β-unsaturated acylammonium salt to give a highly functionalized cyclohexane fused tricyclic product. Although, this reaction features a kinetic resolution of the *in situ* generated racemic malonate enolate, no other examples were reported to confirm the generality of these observations.



Scheme 48. α,β-Unsaturated acylammonium salt in an intramolecular 1,2-addition reaction. Romo, 2013.

As shown in the described examples, the most employed catalytic systems for the construction of polyfunctionalized six-member carbocycles through intramolecular 1,2-addition are enamine and Brønsted base or acid catalysis (Figure 27).[122d]

[132] G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin, D. Romo, *Nat. Chem.* **2013**, *5*, 1049–1057.

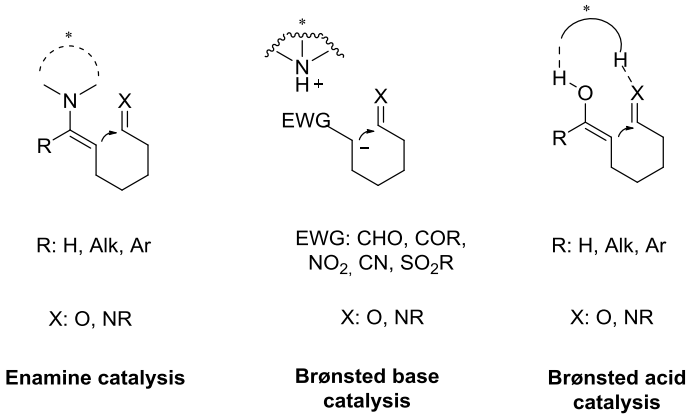
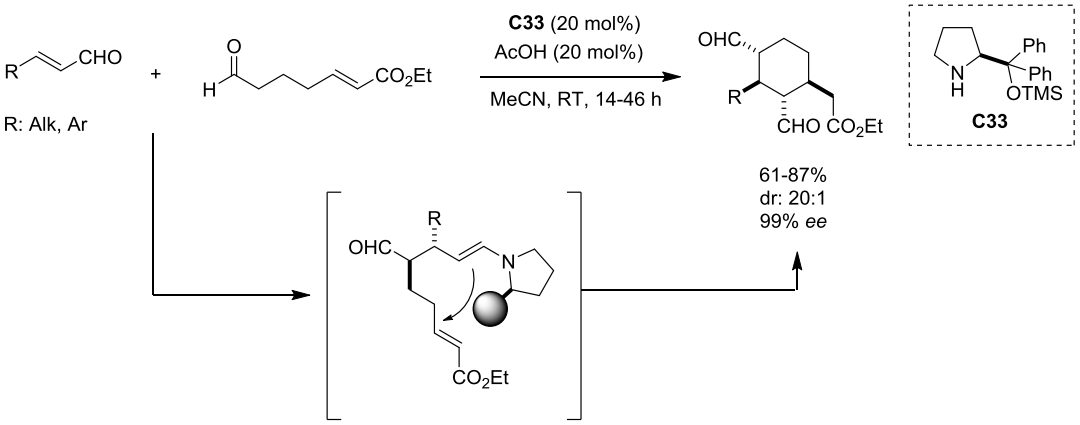


Figure 27. The most employed catalytic strategies in intramolecular 1,2-addition reactions.

3.1.1.2. *Intramolecular 1,4-addition*

The intramolecular ring-closing 1,4-addition approach has not been used as much as the 1,2-addition strategy. Although this ring-closing approach has been achieved *via* metal catalysis[121], organocatalyzed Michael/Michael reactions have also emerged in the field with great vigour.[122] In general, two distinct α,β-unsaturated systems with different reactivities are required to react in a sequential way. The reactivity of one of the systems should be low enough to no compete with the second system in the first Michael reaction and high enough to be able to undergo the second Michael addition.[122a]

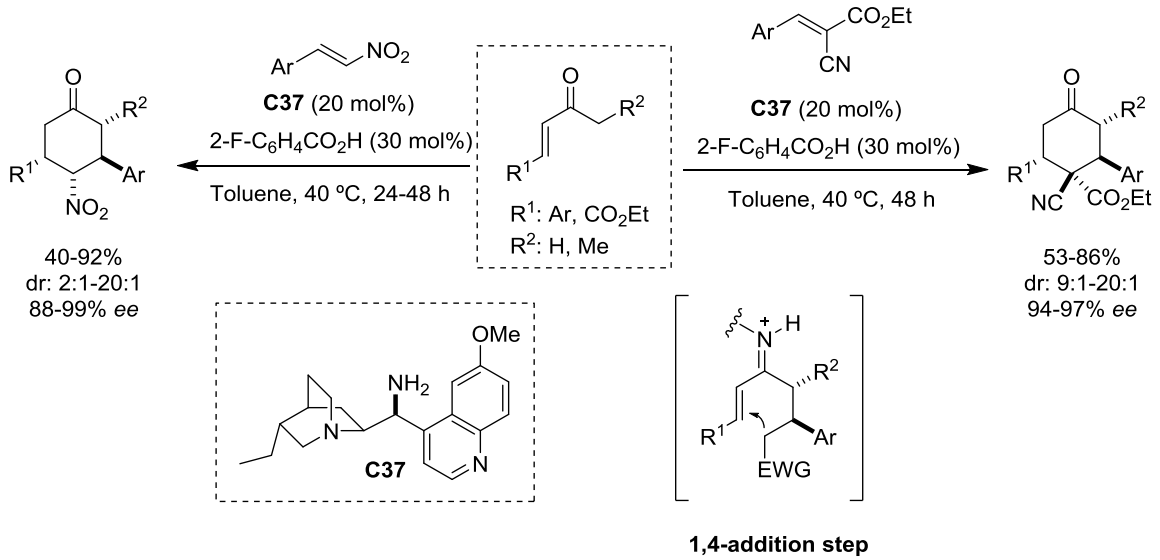
As in the ring-closing 1,2-addition strategy, the most employed organocatalysts are also proline derivatives.[122a] Hong and co-workers described one of the earliest examples of a diphenyl prolinol silyl ether catalyzed Michael/Michael cascade reaction (Scheme 49).[133] This approach provides cyclohexane carboxaldehydes with four contiguous stereogenic centers with excellent diastereoselectivities and enantioselectivities.



Scheme 49. α,α-Diarylprolinol ether organocatalyst in an intramolecular 1,4-addition reaction. Hong, 2011.

[133] B. -C. Hong, A. A. Sadani, R. Y. Roshan, N. S. Dange, G. -H. Leeb, *Synthesis* **2011**, *12*, 1887–1895.

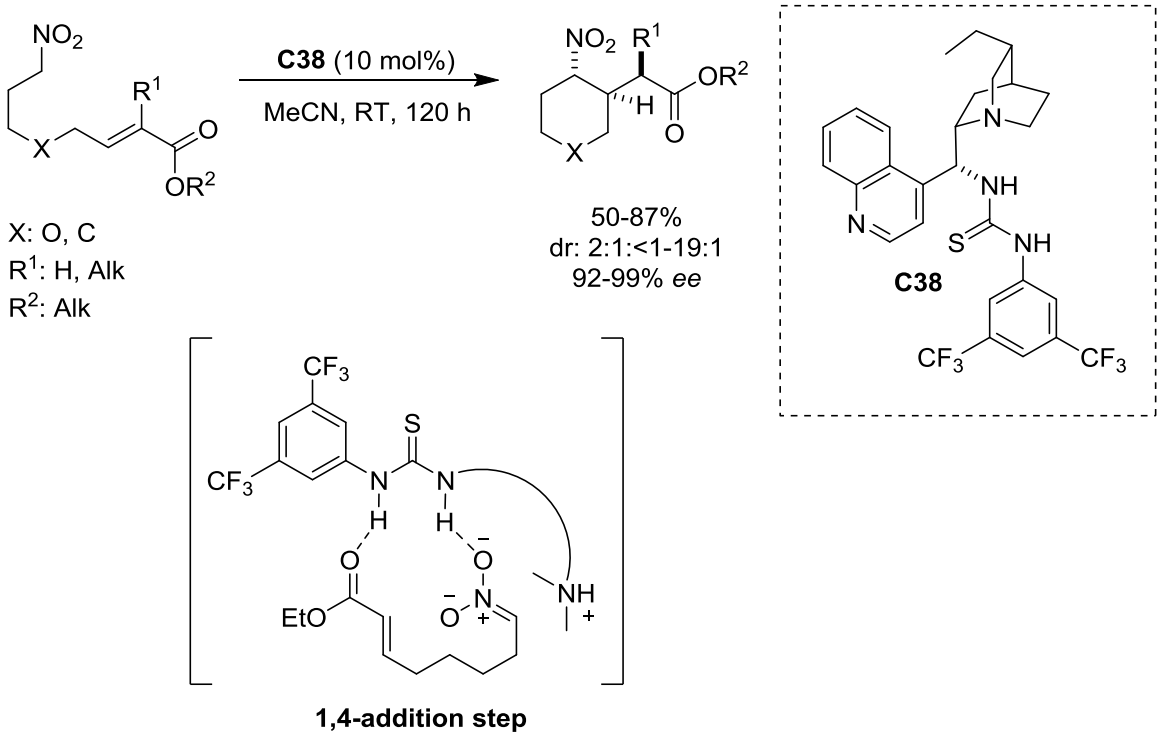
In 2009, Melchiorre and co-workers[134] introduced a cinchona-based primary amine as a versatile catalyst for the construction of cyclohexanones. In the presence of amine **C37** and 2-fluorobenzoic acid as co-catalyst, α´-alkylenones undergo an organocascade reaction with olefins such as (*E*)-α-cyanocinnamates or nitroolefins to afford cyclohexanones with excellent stereocontrol (Scheme 50).



Scheme 50. Primary amine catalyst in an intramolecular 1,4-addition reaction. Melchiorre, 2009.

Although this strategy has found wide applicability in the realm of asymmetric synthesis of cyclohexanones and related cyclic systems,[122] these enamine or iminium ion strategies cannot be employed when substrates are not aldehydes or ketones. In that case, Brønsted base activation can, in principle, be applied. For example, Cobb *et al.*[135] described the first enantioselective intramolecular Michael addition of nitronates onto conjugated esters employing the bifunctional organocatalyst **C38**, affording cyclohexanes with poor chemical yields and moderate diastereoselectivity but with high enantioselectivity (Scheme 51). Furthermore, the same group described two more examples of construction of nitrocyclohexanes employing thiourea based bifunctional catalysts through organocascade approaches.[136]

[134] L. -Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199.
[135] W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016–16017.
[136] a) S. Rajkumar, K. Shankland, J. M. Goodman, A. J. A. Cobb, *Org. Lett.* **2013**, *15*, 1386–1389. b) S. Rajkumar, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Sci.* **2012**, *3*, 584–588.



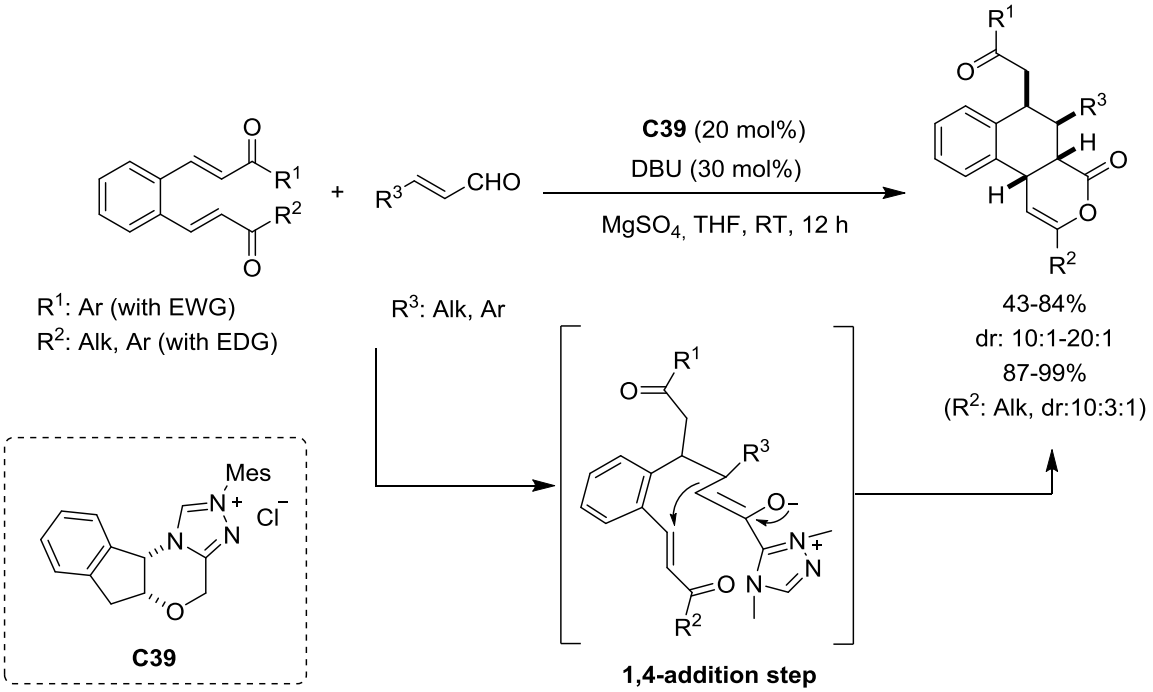
Scheme 51. A bifunctional thiourea-tertiary amine catalyst in an intramolecular 1,4-addition reaction. Cobb, 2009.

In order to open new horizons for the construction of polyfunctionalized six-member rings, in 2011 Chi and co-workers[137] employed *N*-heterocyclic carbene catalysis (NHCs).[138] This strategy proceeds *via* a unique activation mode that results in the umpolung of the carbonyl group, which behaves as an acyl anion equivalent. When enals are used, the nucleophilic properties are transferred to the β position and the activated intermediates are termed as homoenolates.[139] In this way, Chi *et al.*[137] combined β-(hetero)aryl-substituted enals with benzodienones in the presence of a chiral aminoindanol-derived triazolium catalyst **C39** (Scheme 52). The domino sequence consisted of an initial Michael addition of the homoenolate to one branch of the dienone and subsequent intramolecular 1,4-addition of the enal α-carbon atom to the other branch of the dienone, followed by the lactamization with release of the NHC catalyst.

[137] X. Fang, K. Jiang, C. Xing, L. Hao, Y. R. Chi, *Angew. Chem. Int. Ed.* **2011**, *50*, 1910–1913.

[138] For selected reviews on *N*-heterocyclic carbenes activation mode, see: a) R. S. Menon, A. T. BIJU, V. Nair, *Bellstein J. Org. Chem.* **2016**, *12*, 444–451. b) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040–5052. c) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorious, *Nature* **2014**, *519*, 485–496. d) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511–3522. e) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77–144. f) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.

[139] For a general review about carbon-carbon bond-forming reactions involving homoenolates, see: V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691–2698.



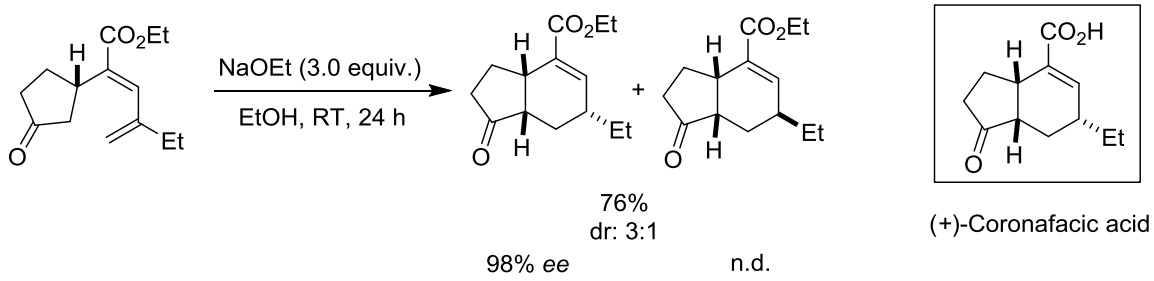
Scheme 52. *N*-Heterocyclic carbene catalysis in an intramolecular 1,4-addition reaction. Chi, 2011.

In general, the construction of cyclohexanes through intramolecular 1,4-addition reactions *via* enamine or Brønsted base catalysis has been widely studied and this is well illustrated in the literature.[122d] On the contrary, intramolecular ring-closing 1,6-addition approaches have been scarcely investigated.

3.1.1.3. *Intramolecular 1,6-addition*

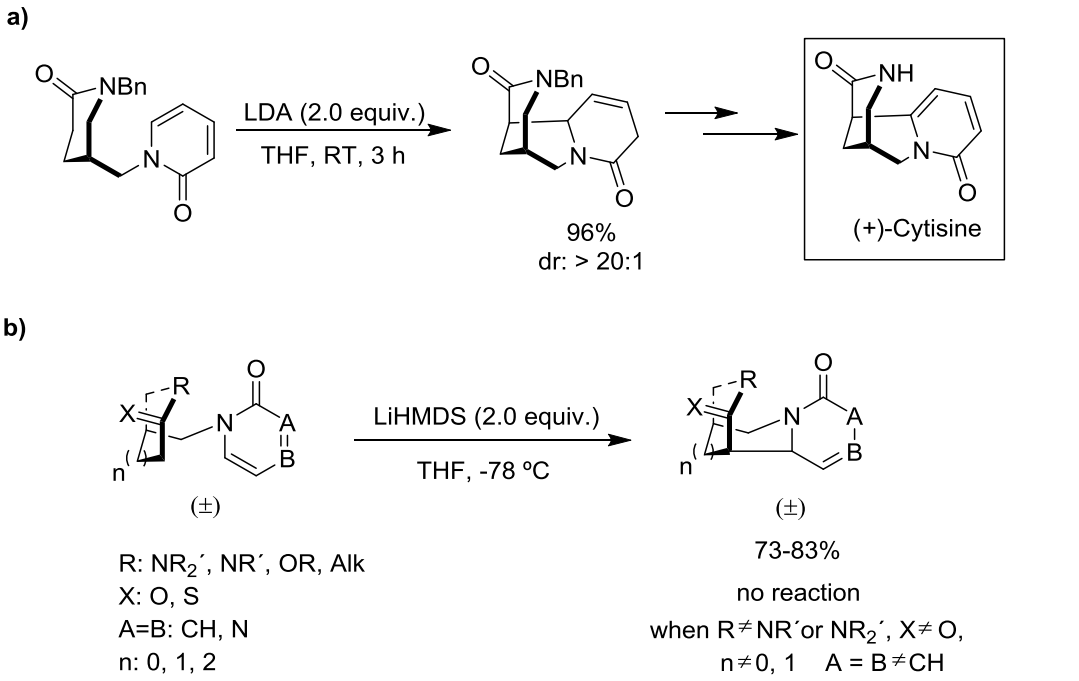
Although intermolecular 1,6-additions of nucleophiles have been widely investigated,[140] few examples of the intramolecular version are found in the literature. In 1997, Toshima and Ichihara developed an asymmetric total synthesis of (*+*)-Coronafacic acid *via* intramolecular 1,6-conjugate addition starting from chiral non racemic α,β-γ,δ-unsaturated ester using three equivalents of NaOEt (Scheme 53).[141] Although the conjugate addition occurs with essentially perfect enantioselectivity, the diastereoselectivity of the reaction is poor (dr: 3:1).

[140] For selected reviews on intermolecular conjugate 1,6-additions, see: For general, see: a) E. M. P. Silva, A. M. S. Silva, *Synthesis* **2012**, *44*, 3109–3128. b) A. G. Csáky, G. Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080–4102. For Organocatalytic, see: c) P. Chauhan, U. Kaya, D. Enders, *Adv. Synth. Catal.* **2017**, *359*, 888–912. d) A. T. Biju, *Chem. Cat. Chem* **2011**, *3*, 1847–1849.
[141] S. Nara, H. Toshima, A. Ichihara, *Tetrahedron* **1997**, *53*, 9509–9524.



Scheme 53. Total synthesis of (+)-Coronafacic acid using 3.0 equiv. of NaOEt. Toshima and Ichihara, 1997.

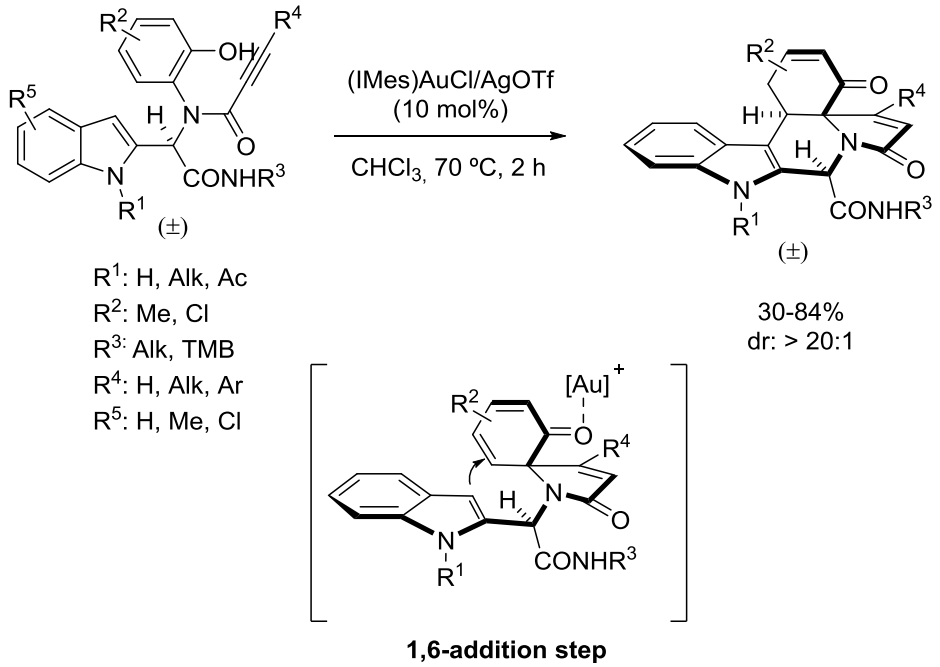
Using the same strategy, in 2006, Gallagher described the total synthesis of (+)-Cytisine, from the non racemic amide shown in Scheme 54a as the starting material.[142] The reaction is sensitive to the temperature, as the cyclization at lower temperatures affords mixture of diastereomeric adducts. Four years later, the same group, in order to explore the scope of this intramolecular 1,6-enolate addition, studied the variation of the nucleophilic component, ring size and heterocyclic acceptor. The authors observed that the methodology was limited to specific substrate (lactams), and only the construction of five or six-member ring was possible (Scheme 54b).[143]



Scheme 54. a) Total synthesis of (+)-Cytisine using 2.0 equiv. of LDA. Gallaher, 2006. b) Scope of the intramolecular 1,6-enolate addition. Gallaher, 2010.

[142] D. Gray, T. Gallargher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419–2423.
[143] T. Gallargher, I. Derrick, P. M. Durkin, C. A. Haseler, C. Hirschhäuser, P. Magrone, *J. Org. Chem.* **2010**, *75*, 3766–3774.

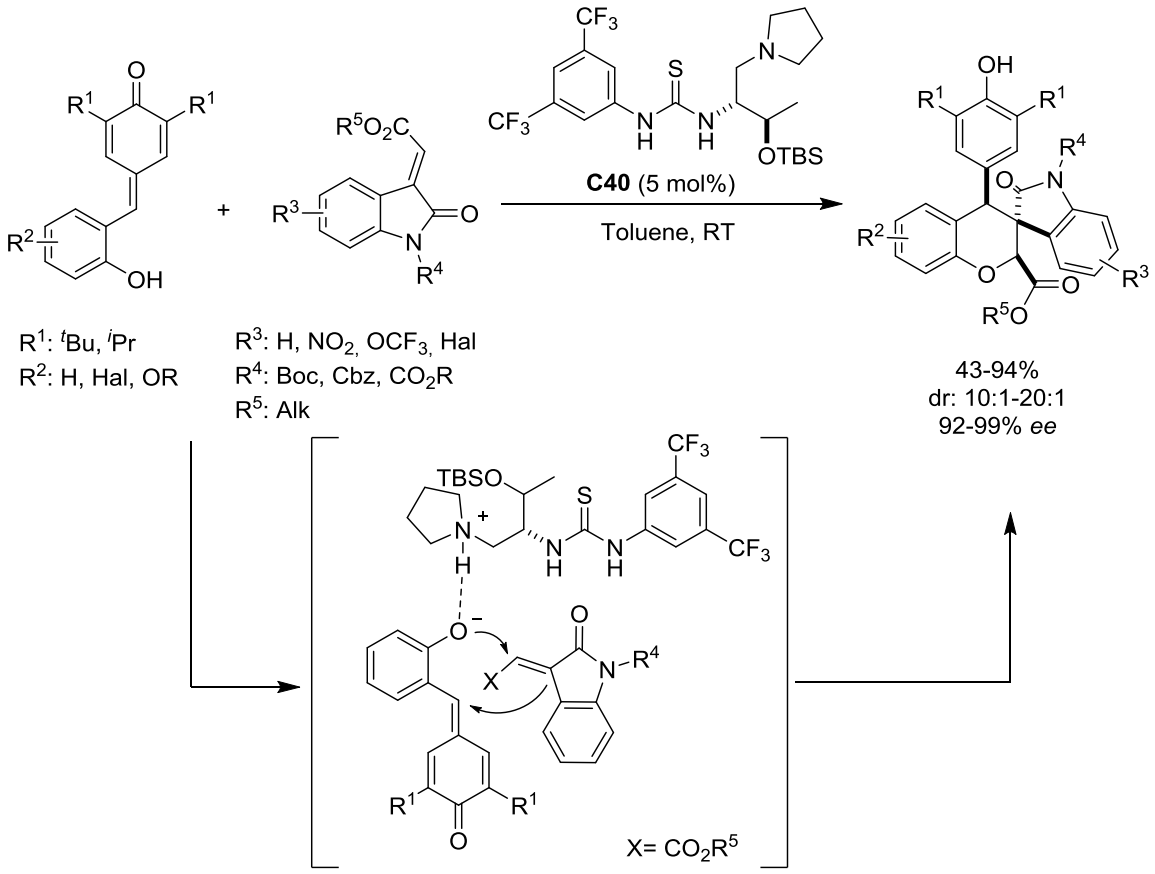
Few examples of catalytic intramolecular 1,6-additions have been described. An example involving a 1,6-conjugate addition has been recently described by Van der Eycken using a gold catalyst to give fused polyheterocyclic scaffolds albeit in racemic form (Scheme 55).[144]



Scheme 55. Construction of diverse polyheterocyclic scaffolds *via* a gold-catalyzed cascade reaction. Van der Eycken, 2019.

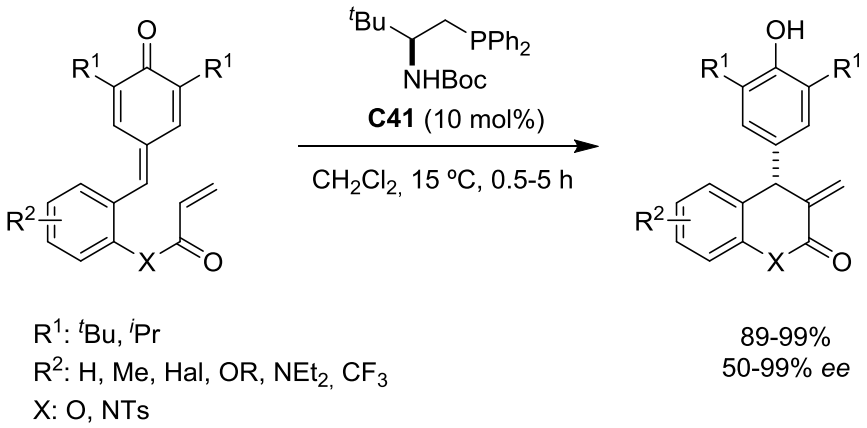
A couple asymmetric variations involving *p*-quinone methides are known. In this context, the first of asymmetric organocatalytic intramolecular 1,6-addition reaction has been reported quite recently by Enders and co-workers.[145] In the presence of 5 mol% of the bifunctional thiourea organocatalyst **C40**, this scalable oxa-Michael/1,6-addition domino reaction affords 4-phenyl-substituted chromans in good to excellent yields and with very high stereoselectivities (Scheme 56).

[144] Y. He, D. Wu, Z. Li, K. Robeyns, L. Van Meerveldt, E. V. Van der Eycken, *Org. Biomol. Chem.* **2019**, *17,* 6284–6292.
[145] K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *128*, 12104–12108.



Scheme 56. Asymmetric organocatalytic oxa-Michael/1,6-addition. Enders, 2016.

Using the same type of substrates, Fan and co-workers developed a catalytic enantioselective 1,6-conjugate addition as key step for the synthesis of heterocycles in high yields and enantioselectivities (Scheme 57).[146]



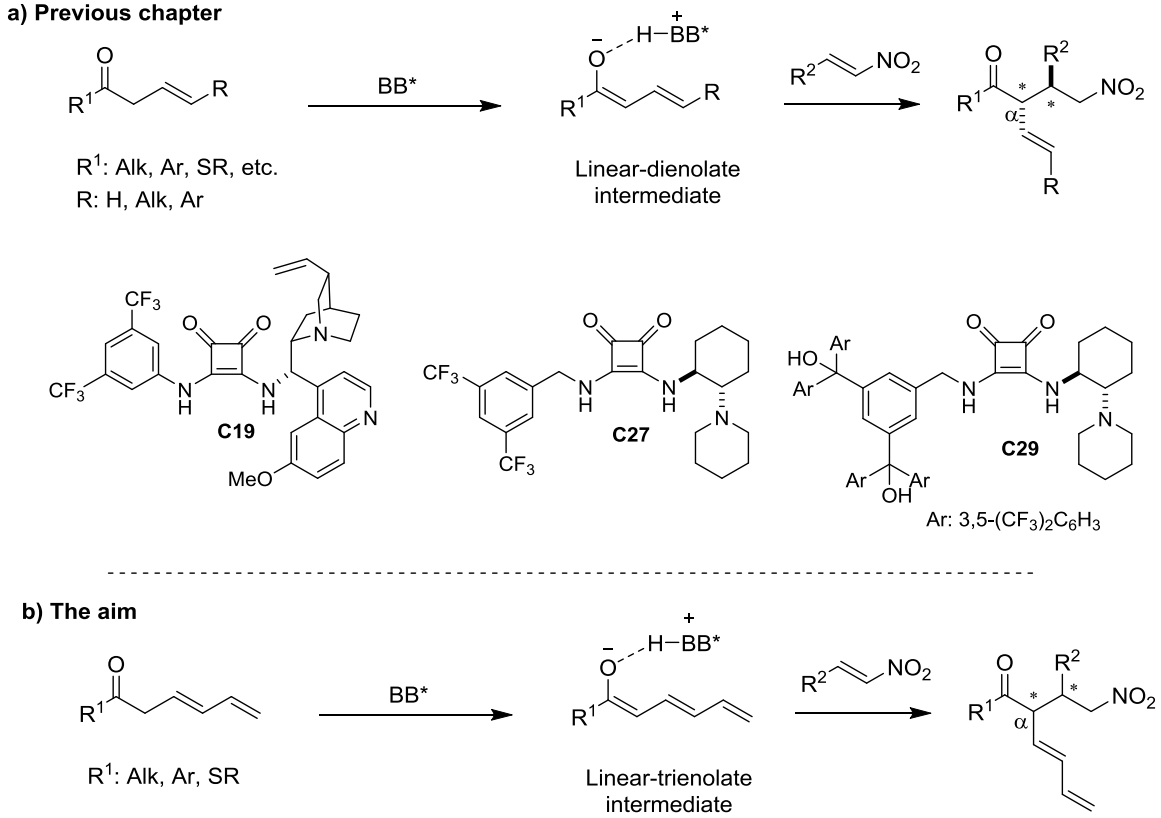
Scheme 57. Enantioselective intramolecular vinylogous Rauhut-Currier reaction. Fan, 2017.

[146] X. -Z. Zhang, K. -J. Gan, X. -X. Liu, Y. -H. Deng, F. -X. Wang, K. -Y. Yu, J. Zhang, C. -A. Fan, *Org. Lett.* **2017**, *19*, 3207–3210.

Given these precedents, we considered the development of a new methodology for the construction of six-member carbocycles in an organocatalytic, enantio- and diastereoselective manner that ends up with an intramolecular 1,6-addition. The corresponding plan and results are outlined in the next section.

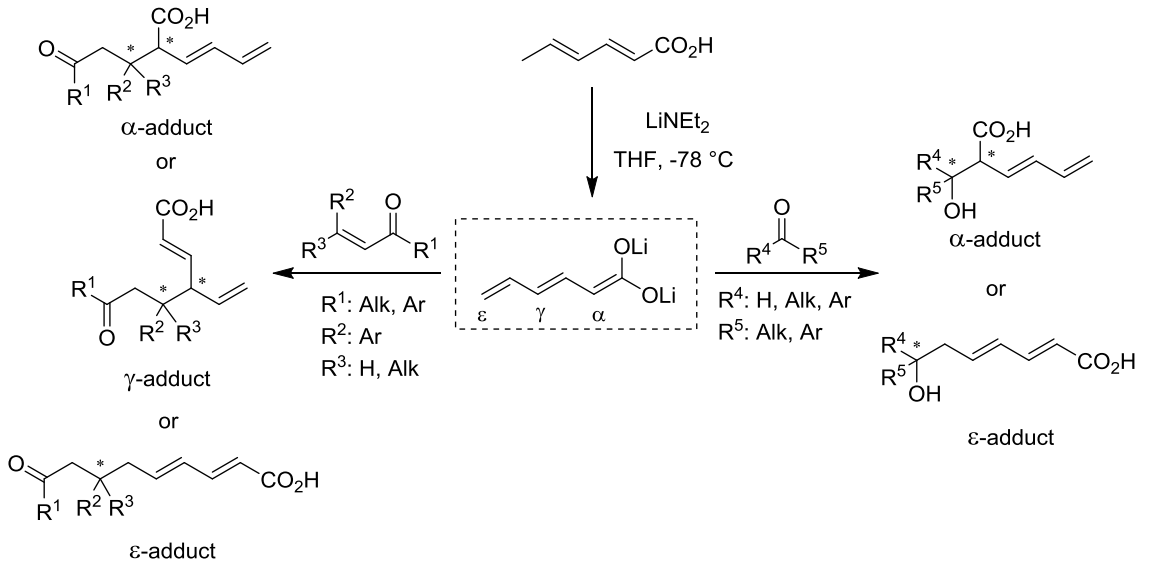
3.2. Working hypothesis

Previous studies (chapter 2) concerning the addition reaction of β,γ-unsaturated ketones and (thio)esters to nitroolefins showed that squaramide catalysts **C19**, **C27** and **C29** provided the corresponding adducts with good chemical yields and optimum diasteo- and enantioselectivities. Significantly, in each case exclusively α-site selectivity was observed (Scheme 58a). It was thought that incorporating an additional double bond, a bifunctional Brønsted base catalyst would generate a trienolate intermediate which would be able to react with Michael acceptors such as nitroolefins, in a similar way that in the previous work (Scheme 58b). These intermediates, upon isomerization of the double bonds, should be good candidates for 1,6-conjugate additions leading to the corresponding cyclohexane products.



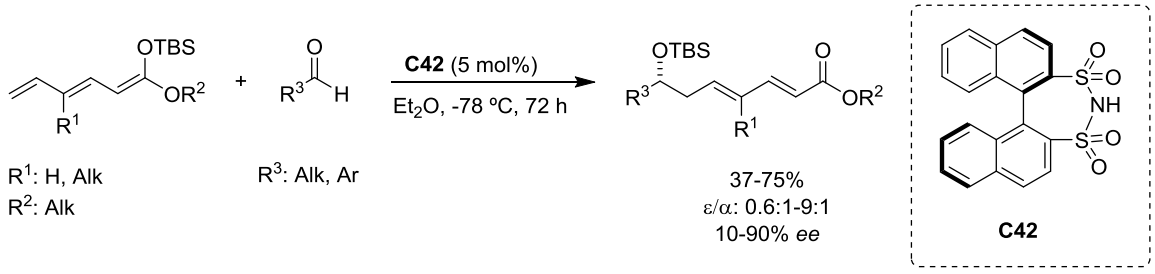
Scheme 58. a) Previously studied Michael addition of dienolate intermediates. b) Proposed Michael addition of trienolate intermediates.

Trienolate intermediates have been rarely used in carbon-carbon bond forming reactions. Mestres and co-workers[147] reported aldol and Michael addition reactions of lithium trienolates which lead to the corresponding aldol or Michael adducts with poor regiocontrol (Scheme 59). The reaction at α, γ or ε positions appears to be dependent upon the aldehyde and Michael acceptor employed.



Scheme 59. Lithium trienolates in aldol and Michael reactions. Mestres, 1985 and 1988.

More recently, List *et al.*[148] described an asymmetric bisvinylogous Mukaiyama aldol reaction promoted by the Lewis acid disulfonimide-catalyst **C42**, but, again, variable levels of regioselectivity were obtained (Scheme 60).



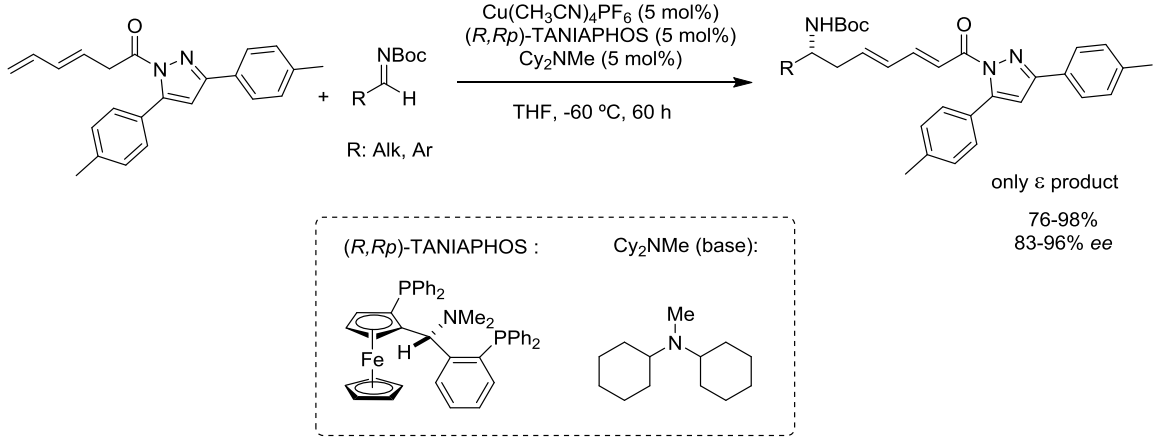
Scheme 60. Disulfonimide-catalyzed bisvinylogous Mukaiyama aldol reaction. List, 2011.

While in the above examples the trienolate intermediate is formed in a separate step, the first and unique direct asymmetric reaction where trienolate intermediates are generated *in situ* (Scheme 61) was documented by Ying and co-workers using a copper

[147] For examples of lithium trienolates in different transformations, see: a) P. Ballester, A. Costa, A. García-Raso, R. Mestres, *J. Chem. Soc. Perkin Trans. I* **1988**, 2797–2803. b) P. Ballester, A. Costa, A. García-Raso, A. Gómez-Solivellas, R. Mestres *Tetrahedron Lett.* **1985**, *26*, 3625–3628.

[148] L. Ratjen, P. García-García, F. Lay, M. E. Beck, B. List, *Angew. Chem. Int. Ed*. **2011**, *50*, 754–758.

(I) complex as catalyst and Cy_2NMe as base.[149] The transiently generated trienolates react with *N*-Boc imines to form the ε-amino adducts as essentially sole products in high enantioselectivities.



Scheme 61. Catalytic asymmetric bisvinylogous ε-Mannich reaction catalyzed by a copper (I) complex. Ying, 2017.

Similar nucleophiles, such as 2,4-hexadienals have been employed in trienamine catalysis.[150] The first realization of trienamine catalysis was established collectively by the groups of Chen and Jørgensen,[151] when they documented the Diels–Alder reaction of various dienophiles, such as 3-olefinic oxindoles (Scheme 62a) and olefinic cyanoacetates (Scheme 62b), with polyenals in presence of optically active secondary amines. In this manner, this pioneering work opened up new possibilities of trienamine catalyzed cycloadditions[152] and organocascade reactions,[153] offering an alternative entry to cyclohexene synthesis.

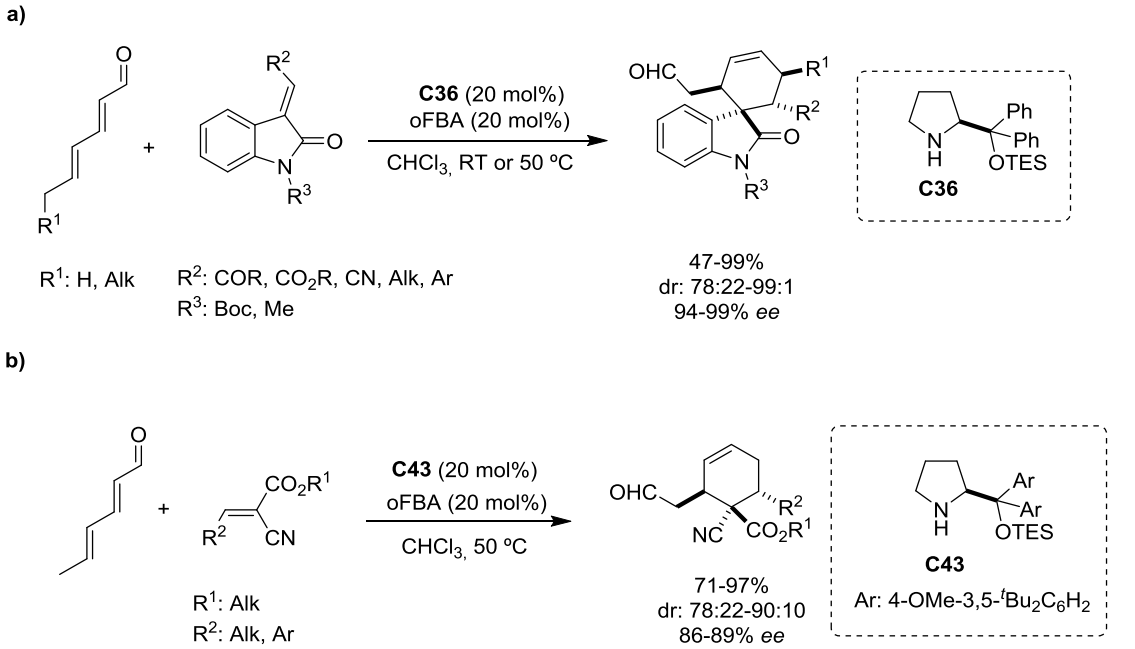
[149] H. -J. Zhang, C. -Y. Shi, F. Zhong, L. Ying, *J. Am. Chem. Soc.* **2017**, *139*, 2196–2199.

[150] For selected reviews on trienamine catalysis, see: a) L. Klier, F. Tur, P. H. Poulsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2017**, *46*, 1080–1102. b) J. L. Vicario, *Synlett.* **2016**, *27*, 1006–1021. c) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709–716. d) E. Arceo, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 5290–5292.

[151] Z. -J. Jia, H. Jiang, J. -L. Li, B. Gschwend, Q. -Z. Li, X. Yin, J. Grouleff, Y. C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.

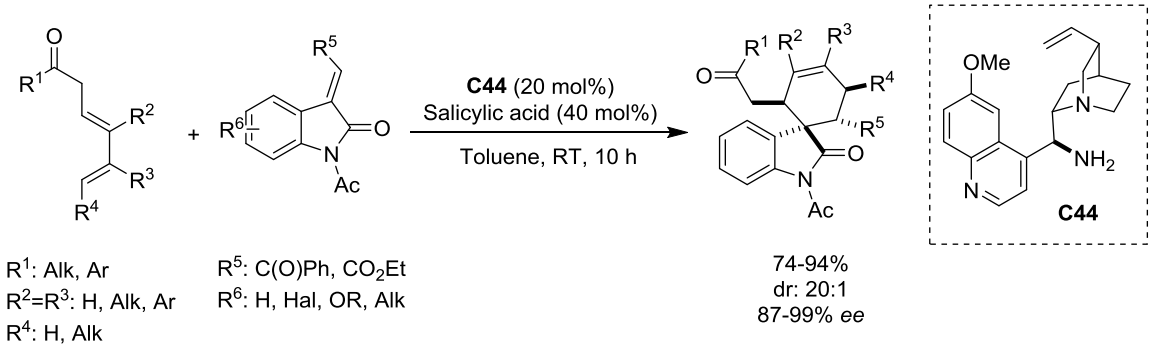
[152] For other reaction pathways of trienamine catalysis, see: For the first ε-functionalization, see: a) J. -L. Li, C. -Z. Yue, P. -Q. Chen, Y. -C. Xiao, Y. -C. Chen, *Angew. Chem. Int. Ed.* **2014**, *53*, 5449–5452. For the first example of cross trienamine catalysis, see: b) K. S. Halskov, T. K. Johasen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943–12946.

[153] a) J. Gu, B. -X. Xiao, Y. -R. Chen, W. Du, Y. -C. Chen, *Adv. Synth, Catal.* **2016**, *358*, 296–302. b) C. V. Gómez, D. C. Cruz, R. Mose, K. A. Jørgensen, *Chem. Commun.* **2014**, *50*, 6035–6038. c) D. C. Cruz, R. Mose, C. V. Gómez, S. V. Torbensen, M. S. Larsen, K. A. Jørgensen, *Chem. Eur. J.* **2014**, *20*, 11331–11335.



Scheme 62. 2,4-Dienals as trienamine precursor for Diels-Alder reactions. Jørgensen, 2011.

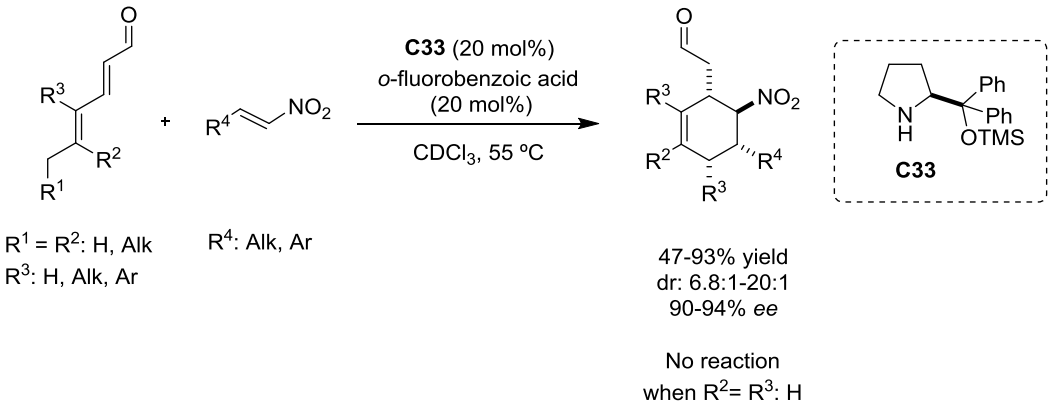
It is interesting to know that the same products may be obtained starting from linear deconjugated 3,5-dienones. One example has been provided by Chen and co-workers for the synthesis of spirocyclic oxindoles as shown in Scheme 63.[154]



Scheme 63. Linear deconjugated 3,5-dienones in trienamine catalysis. Chen, 2014.

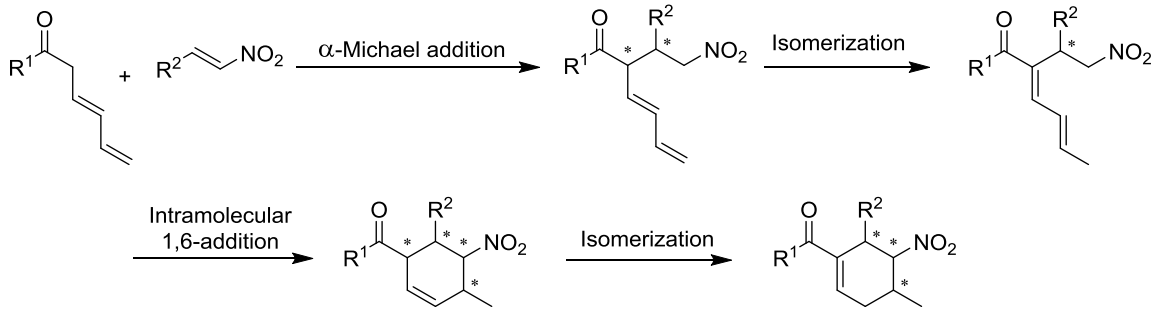
The same group extended the scope of trienamine catalysis for asymmetric Diels-Alder reactions with nitroolefins as dienophiles for the first time.[155] Interestingly, the introduction of electron-donating alkyl substituents at C4 and C5 positions of the 2,4-dienals was found to be necessary for the raising of the HOMO energy level of the trienamine intermediates, and for the Diels-Alder reaction to take place (Scheme 64).

[154] P. -Q. Chen, Y. -C. Xiao, C. -Z. Yue, Y. C. Chen, *Org. Chem. Front.* **2014**, *1*, 490−493.
[155] Z. J. Jia, Q. Zhou, Q. Q. Zhou, P. Q. Chen, Y. C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8638−8641.



Scheme 64. Trienamine mediated Diels-Alder reaction between 2,4-dienals and nitroolefins. Chen, 2011.

With these precedents in mind, we hypothesized that a trienolate intermediate would be able to react with a nitroolefin in the presence of a bifunctional Brønsted base catalyst. If this was the case, the double bond isomerization and subsequent intramolecular 1,6-addition reaction would lead to a six-member carbocycle, which most probably should isomerize to the final conjugated cyclohexanone shown in the Scheme 65. Most significantly, cyclohexane products different from that of the above trienamine based approach could be produced.



Scheme 65. Proposed catalytic one-pot construction of six-member carbocycles.

3.3. Results and catalyst screening

The study was initiated with the reaction between polyunsaturated thioester **22A** and nitrostyrene **2a** in dichloromethane in the presence of 10 mol% of several amine bases (Table 10).[156]

[156] In parallel experiments, the parent ester resulted totally unreactive under similar catalytic conditions. Sarting materials were isolated unchanged.

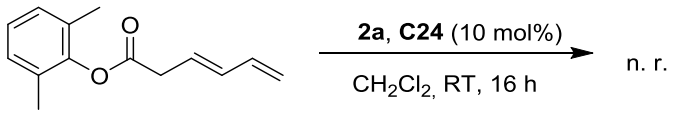
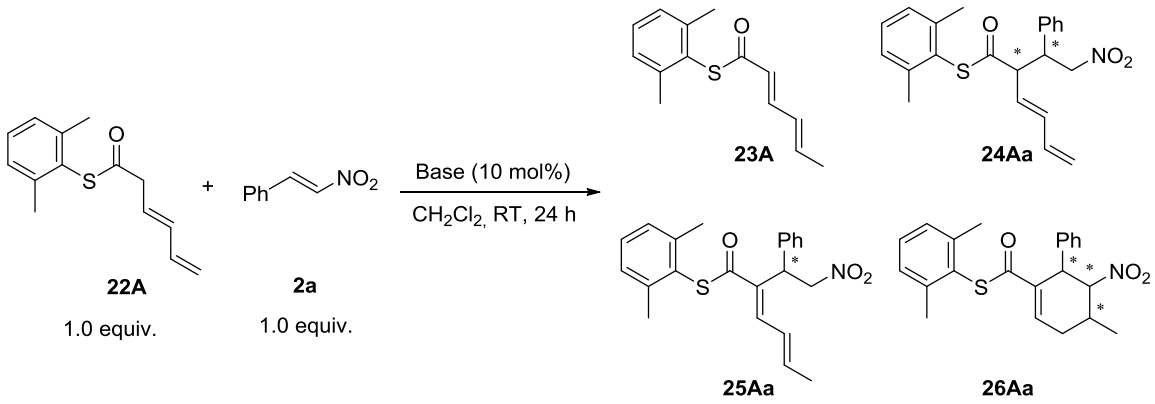
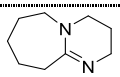
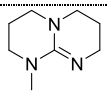
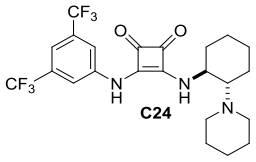


Table 10. Base dependent product distribution in the reaction of polyunsaturated thioester **22A** with nitrostyrene **2a**.[a]



Entry	Base	T (°C)	23A	24Aa (dr)	25Aa	26Aa(dr, %*ee*)
1	Et_3N	RT	83%	17% (>20:1)	---	---
2	$^{i}Pr_2EtN$	RT	45%	55% (1.4:1)	---	---
3		RT	70%	---	---	30% (>20:1)
4		0	58%	---	18%	24% (>20:1)
5[b]	DBU	0	58%	---	---	42% (>20:1)
6		RT	100%	---	---	---
7		0	100%	---	---	---
8	MTBD	-10	100%	---	---	---
9		RT	20%	80% (>20:1)[d]	---	---
10		0	40%	60% (>20:1)[d]	---	---
11[c]		80	35%	65% (>20:1)[d]	---	---
12[e]	C24	RT	22%	---	---	65%[g] (dr >20:1, 81% *ee*)
13[f]		RT	20%	---	---	60%[g] (dr >20:1, 81% *ee*)

[a] Reactions carried out at 0.1 mmol scale, using 1.0 equiv. of each reagents **22A** and **2a** and 10 mol% of base in 0.1 mL CH_2Cl_2 at the corresponding temperature for 16 h. The ratios of products **23A**/**24Aa**/**25Aa**/**26Aa** formed correspond to ^{1}H NMR integration. Data in parenthesis corresponds to dr. [b] Reaction run for 40 h. [c] Reaction carried out using 1,2-dichloroethane as solvent. [d] The *ee* was not determined. [e] Co-catalyst MTBD (20 mol%) was added after 16 h and stirring kept for additional 24 h. [f] Co-catalyst DBU (20 mol%) was added after 16 h and stirring kept for additional 24 h. [g] Yield after isolation of product by column chromatography. 1.5 equiv. of **22A** were used. The diastereoselectivity was determined by ^{1}H NMR (300 MHz) analysis. The enantioselectivity was determined by chiral HPLC.

As data in Table 10 show, the reaction progressed to essentially full conversion upon 16 hours at the corresponding temperature regardless the base used, although product distribution varied considerably. With simple tertiary amines as triethylamine isomerization to the more stable conjugated diene **23A**[157] occurred along with minor formation of the α-addition adduct **24Aa** (entry 1). Although the **23A**/**24Aa** (conjugated diene/α-addition adduct) ratio increased notably with $^{i}Pr_2EtN$, which is a sterically

[157] Conjugated diene **23A** was completely unreactive under the catalytic reaction conditions.

bulkier amine, the diastereoselectivity decreased (entry 2). Using stronger amine bases such as DBU caused the isomerization of the starting material to the conjugated thioester **23A**. However, in this case cycloadduct **26Aa** was observed for the first time with essentially perfect diastereoselectivity (dr >20:1) (entry 3). We presumed that this cycloadduct **26Aa** might be formed *via* cyclization of acyclic precursor **25Aa**. To proof this assumption the same reaction was carried out at lower temperature (entry 4) affording a mixture of the conjugated diene **23A**, the isomerized α-adduct **25Aa**, and cycloadduct **26Aa**. When this mixture was allowed to stir for longer time at 0 °C, a mixture of the conjugated diene **23A** (58%) and cycloadduct **26Aa** (42%) was obtained (entry 5), indicating that indeed acyclic precursor **25Aa** is an intermediate in the formation of cycloadduct **26Aa**. The use of even stronger guanidine base MTBD was disappointing and fully isomerized thioester **23A** was the only detected product regardless the reaction temperature (entries 6-8).

Then, hoping to reduce the amount of isomerized **23A**, we thought that a bifunctional Brønsted base/H-bonding catalyst **C24** would be able to ease the C–C bond forming event by simultaneous activation of the electrophile and the pronucleophile (entry 9). Gratifyingly, the reaction carried out in the presence of this catalyst led to α-addition adducts **24Aa** with the highest ratio so far (80%) along with 20% of the isomerized material **23A**. The same reaction was carried out at lower and higher temperatures (entries 10-11); however, mixtures of **23A**/**24Aa** with lower ratios were observed.

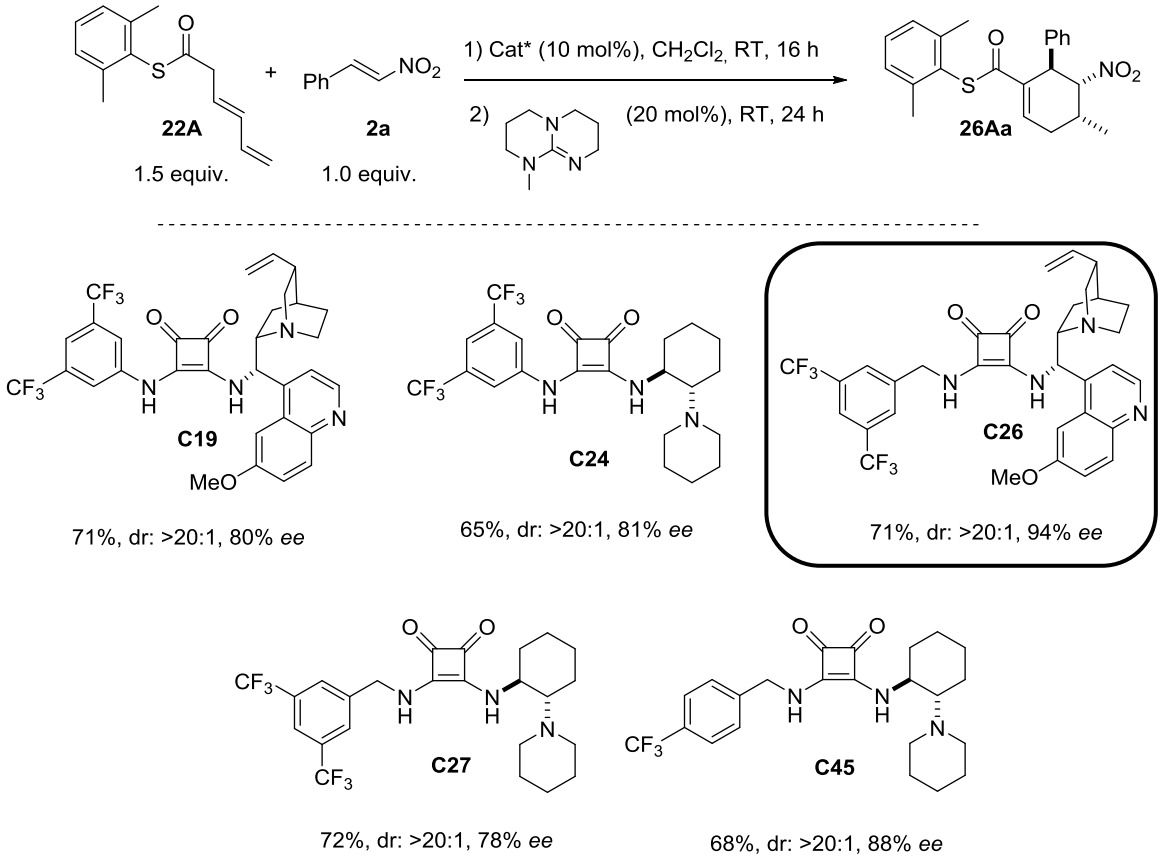
With these results in hand, we expected that the overall transformation could be performed in one-pot operation. So, once the α-Michael addition was completed in presence of chiral catalyst **C24**,[158] this mixture was stirred for additional 24 h in presence of 20 mol% MTBD or DBU (strong bases) (entries 12-13). In this way, total conversion of the α-Michael addition adduct **24Aa** into the cyclization product **26Aa** was observed. Although the *ee* values are moderate in both cases (81% *ee*), in terms of yields the best result was obtained using MTBD as achiral strong base.

Next a set of bifunctional chiral Brønsted base/H-bonding catalysts were screened in order to improve enantioselectivity (Table 11). Gratifyingly, all the one-pot two-step transformations (chiral bifunctional catalyst + MTBD) carried out in presence of squaramides (**C19, C24**, **C26**, **C27** and **C45**) led to cycloadduct **26Aa** as a single diastereomer. For this one-pot two-step transformation, the structurally related amine-squaramide catalysts **C24**, **C27** and **C45** resulted equally effective, affording cycloadduct **26Aa** as a single diastereomer in 65%, 72% and 68% yields and 81%, 78% and 88% *ee*´s, respectively. In order to improve the *ee*, the quinine-derived catalysts **C19** and **C26** were

[158] 1.5 equiv. of polyunsaturated thioester **22Aa** were used; in this way, the isomerization of the nucleophile did not affect the reaction outcome.

tested. The results indicate that catalyst **C26** was more effective than **C19** in terms of enantioselectivity (**C19**: 80% *ee* vs **C26**: 94% *ee*).

Table 11. Catalyst screening for the reaction of **22A** with **2a**.[a]



[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of thioester **22A** and 10 mol% of catalyst in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Then, 20 mol% of MTBD was added and stirred for additional 24 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. Yield after isolation of the product by chromatography. The diastereoselectivity was determined by ^{1}H NMR (300 MHz) analysis. The enantioselectivity was determined by chiral HPLC.

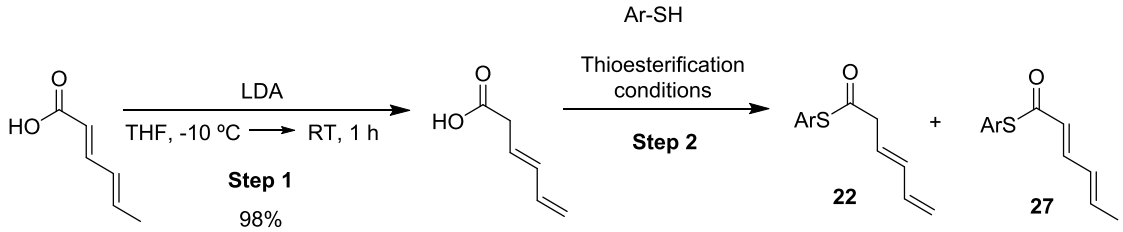
3.4. Scope of the reaction

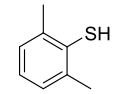
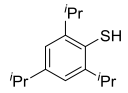
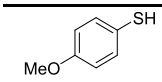
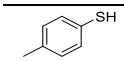
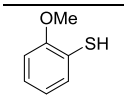
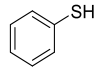
3.4.1. Polyunsaturated thioesters as pronucleophiles

First of all, we studied how the nature of the *S*-substituent could affect the selectivity of the reaction. Thus, we first focused our efforts on the development of an efficient methodology to prepare a variety of polyunsaturated thioesters (Table 12). These thioesters were prepared through sorbic acid deconjugation, followed by a coupling reaction with the respective thiol. Several coupling conditions were investigated for the synthesis of the 2,6-dimethyl thiophenol derivative (entries 1-4);[159] however the most suitable protocol for the preparation of thioesters in terms of yield was the thioesterification from the carboxylic acid and thiol in presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (entry 4).[159d] Although these thioesterification conditions were extended to other thiols with substituents in *ortho*- and/or *para*- positions (entries 5-8) achieving moderate yields, the simplest phenyl thioester could not be obtained due to the formation of a byproduct (entry 9). This byproduct, which was not characterized, might allegedly come from the addition reaction of the thiophenol to the α,β-γ,δ-unsaturated thioester **27**. This product, in its turn, came from isomerization of **22.**

[159] a) N. Ichiishi, C. A. Malapit, L. Wozniak, M. S. Sanford, *Org. Lett.* **2018**, *20*, 44–47. b) H. J. Zhang, C. Y. Shi, F. Zhong, L. Yin, *J. Am. Chem. Soc.* **2017**, *139*, 2196–2199. c) E.C. Garnier-Amblard, S.G. Mays, R.F. Arrendale, M.T. Baillie, A.S. Bushnev, D.G. Culver, T.J. Evers, J.J. Holt, R.B. Howard, L. S. Liebeskind, D.S. Menaldin, M.G. Natchus, J.A. Petros, H. Ramaraju, G.P. Reddy, D.C. Liotta, *Medd. Chem. Lett.* **2011**, *2*, 438–443. d) B. Movassagh, S. Balalaie, P. Shaygan, *ARKIVOC* **2007**, *13*, 47–52.

Table 12. Conditions for the thioesterification step.[a]



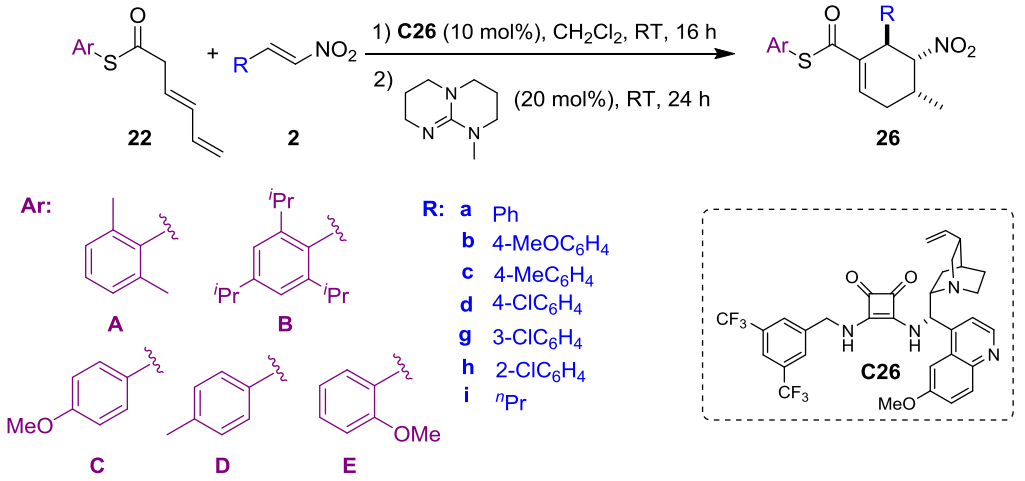
Entry	Thiol (ArSH)	Thioesterification conditions	Yield	Product	Ref.
1		1. Oxalyl chloride, CH_2Cl_2, RT, 16 h 2. Ar-SH, CH_2Cl_2, RT, 16 h	Messy crude	---	159a
2		Ar-SH, EDC·HCl, 4-DMAP, CH_2Cl_2, RT, 16 h	16%[b]	**22A**	159b
3		Ar-SH, HOBt, DCC, EtOAc, RT, 16 h	55%	**22A**	159c
4		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	70%	**22A**	159d
5		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	70%	**22B**	159d
6		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	30%[b]	**22C**	159d
7		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	70%	**22D**	159d
8		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	45%[b]	**22E**	159d
9		Ar-SH, TBTU, DIPEA, EtOAc, RT, 3 h	---	---	159d

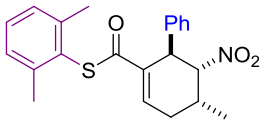
[a] Reactions carried out at 1.0 mmol scale. Yield after isolation of the product by chromatography. [b] The enone **27** was also isolated.

With the catalyst **C26** and MTBD selected as optimum bases, the substrate scope of the catalytic reaction was studied. As shown in Table 13, this two-step process tolerated well variations at both donor and acceptor reaction component. Gratifyingly, all the reactions carried out in the presence of squaramide **C26** led to cycloadduct **26** as single diastereomer (γ or ε-Michael adducts were not detected in any case). Thus, the reaction with nitrostyrenes bearing electron-reach MeO- and Me- *para*-substituents (adducts **26Ab** and **26Ac**) or electron-poor *p*-substituent Cl (adduct **26Ad**) all proceeded with good yields, excellent diastereoselectivity and enantioselectivity of 90% *ee* or higher. The position of the substitution (*ortho*- or *meta*-) did not affect the reaction efficiency as demonstrated by the good yields and high selectivities obtained (adducts **26Ag** and **26Ah**). Nevertheless, this reaction did not tolerate aliphatic nitroolefins as electrophiles (adduct **26Ai**). Regarding the substitution pattern of the thioester aromatic group, thioesters with *o*- and *p*- triisopropyl substituted phenyl groups (adducts **26Ba**-

26Bc) worked equally well, as did *o*- or *p*- monosubstituted phenyls (adducts **26Ca–26Ea**).

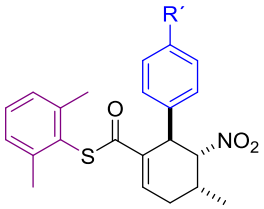
Table 13. Catalytic stereoselective reaction of polyunsaturated thioesters **22** with nitroolefins **2** to afford tetrasubstituted cyclohexenes **26**.[a]



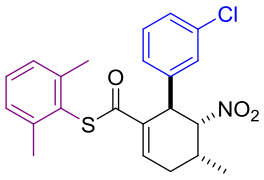


26Aa

65%, dr: >20:1, 94% *ee*

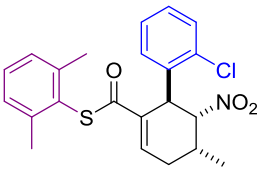


26Ab R′: OMe 65%, dr: >20:1, 92% *ee*
26Ac R′: Me 67%, dr: >20:1, 94% *ee*
26Ad R′: Cl 68%, dr: >20:1, 90% *ee*



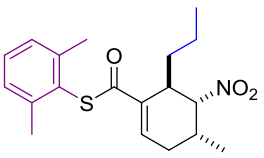
26Ag

65%, dr: >20:1, 94% *ee*



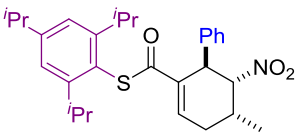
26Ah

73%, dr: >20:1, 95% *ee*



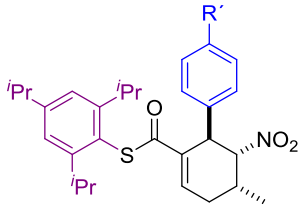
26Ai

n.r.

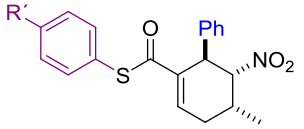


26Ba

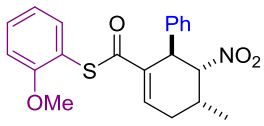
67%, dr: >20:1, 95% *ee*



26Bb R′: OMe 67%, dr: >20:1, 94% *ee*
26Bc R′: Me 65%, dr: >20:1, 92% *ee*



26Ca R′: OMe 65%, dr: >20:1, 88% *ee*
26Da R′: Me 66%, dr: >20:1, 91% *ee*



26Ea

70%, dr: >20:1, 90% *ee*

[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of thioester **22** and 10 mol% of catalyst **C26** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Then, 20 mol% of MTBD was added and the mixture was stirred for additional 24 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. Yield after isolation of the product by chromatography. The diastereoselectivity was determined by ^{1}H NMR (300 MHz) analysis. The enantioselectivity was determined by chiral HPLC. n.r.:no reaction.

The absolute configuration of adduct **26Ba** was determined by a single-crystal X-ray analysis (Figure 28). Configuration of the remaining adducts was assigned by analogy and by assuming a uniform reaction mechanism.

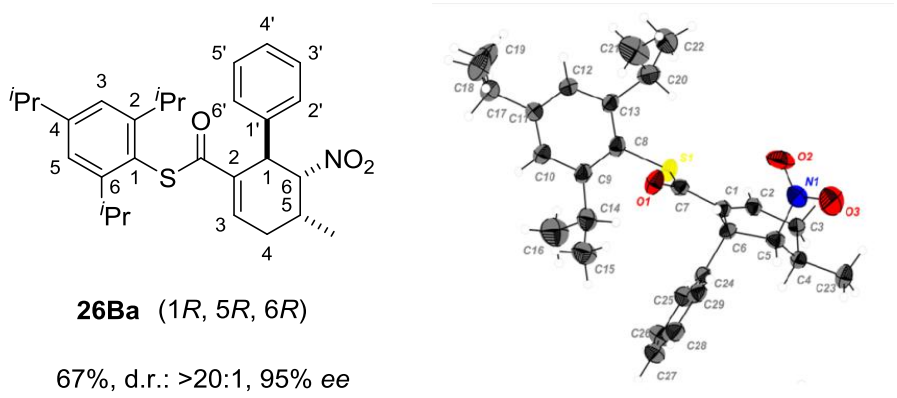
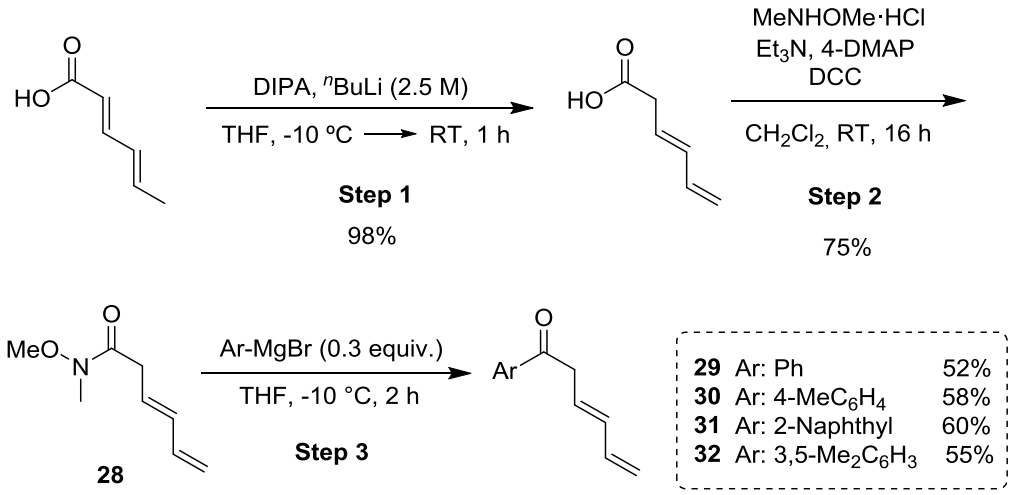


Figure 28. ORTEP diagram of compound **26Ba**.

3.4.2. Polyunsaturated ketones as pronucleophiles

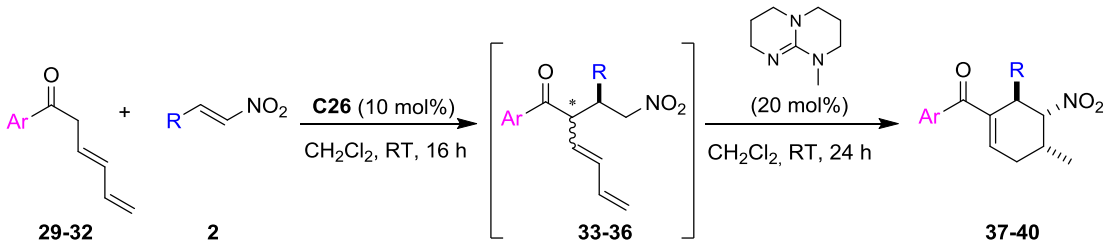
The expansion of this new methodology for obtaining cyclohexenes was next examined employing polyunsaturated aromatic ketones. As in the previous case, we first focused our efforts on the development of an efficient methodology to prepare a variety of polyunsaturated ketones. We performed the deconjugation of sorbic acid, followed by the formation of the Weinreb amide **28**. Subsequent treatment of this amide **28** with Grignard reagents led to the corresponding ketone products **29-32** in acceptable yields (Scheme 66).



Scheme 66. New methodology to prepare a variety of polyunsaturated ketones **29**-**32**.

As shown in Table 14, the reaction of unsaturated ketones **29**-**32** with nitroolefins **2** in the presence of 10 mol% catalyst **C26** cleanly afforded α-addition adducts **33**-**36** as mixtures of diastereomers. Most gratifyingly, one-pot treatment of the α-alkylated adducts **33**-**36** with catalytic base (MTBD) led to the formation of the respective cycloadducts **37**-**40** as a single diastereomer in each case, and with high enantiomeric excess. Thus, phenyl ketone **29** upon reaction with nitrostyrenes **2a**-**2c** and **2g**-**2h** afforded adducts **37a**-**37c** and **37g**-**37h** with isolated yields in the range 73-82%, diastereomeric ratios >20:1, and enantiomeric excesses higher than 86%. The reaction with the aliphatic nitroolefin **2i** did also proceed successfully to give **37i**, but in this instance a 2.6:1 mixture of diastereomers was formed. Other unsaturated enolizable ketones with aryl side chains (**30**, **31**, **32**) were also tolerated, affording the corresponding adducts **38**-**40** in good yields (77-81%) and very high diastereo- (dr: >20:1) and enantioselectivities (90-92% *ee*).

Table 14. Catalytic stereoselective reaction of polyunsaturated ketones **29**-**32** with nitroolefins **2** to afford tetrasubstituted cyclohexenes **37**-**40**.[a]

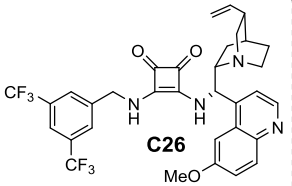


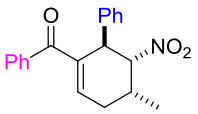
Ar: **29** Ph
30 4-MeC_6H_4
31 2-Naphthyl
32 3,5-$Me_2C_6H_3$

R: **a** Ph
b 4-$MeOC_6H_4$
c 4-MeC_6H_4
g 3-ClC_6H_4
h 2-ClC_6H_4
i ^{n}Pr

33 Ar: Ph
34 Ar: 4-MeC_6H_4
35 Ar: 2-Naphthyl
36 Ar: 3,5-$Me_2C_6H_3$

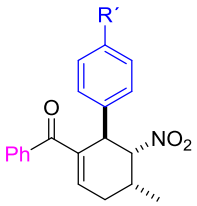
33a dr: 2.4:1	**33i** dr: 2.3:1
33b dr: 2.3:1	**34a** dr: 2.1:1
33c dr: 2.1:1	**35b** dr: 2.5:1
33g dr: 2.5:1	**35h** dr: 2.1:1
33h dr: 2.4:1	**36a** dr: 2.5:1



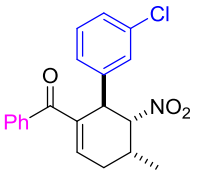


37a

80%, dr >20:1, 93% *ee*

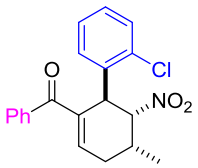


37b R´: MeO 78%, dr >20:1, 93% *ee*
37c R´: Me 82%, dr >20:1, 96% *ee*



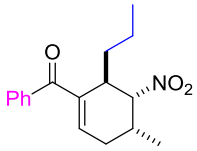
37g

77%, dr >20:1, 86% *ee*



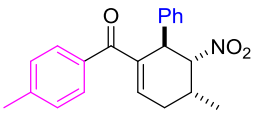
37h

73%, dr >20:1, 95% *ee*



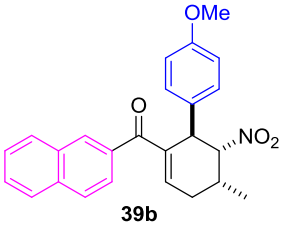
37i

74%, dr 2.6:1, 94% *ee*



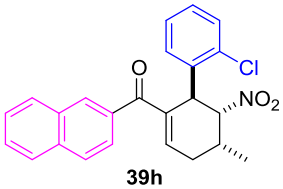
38a

77%, dr >20:1, 91% *ee*



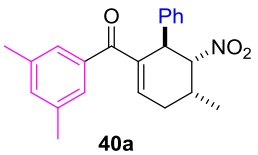
39b

70%, dr >20:1, 91% *ee*



39h

81%, dr >20:1, 90% *ee*

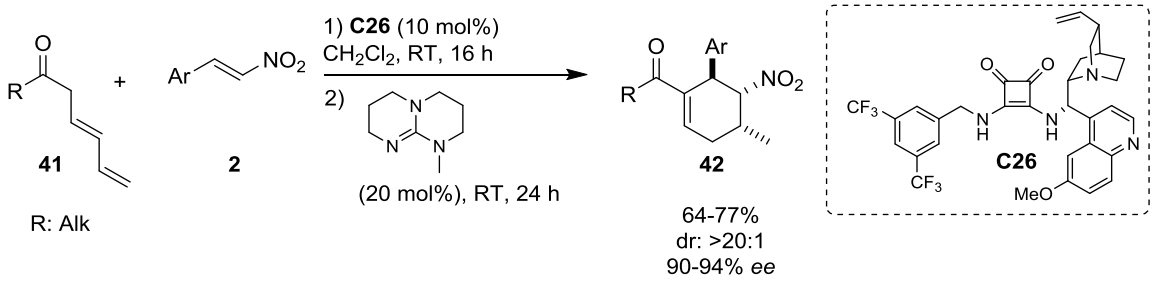


40a

72%, dr >20:1, 92% *ee*

[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of ketones **29**-**32** and 10 mol% of catalyst **C26** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. The diastereoselectivity of the α-alkylated adducts was determined by ^{1}H NMR (300 MHz) analysis on the reaction mixture. Then, 20 mol% of MTBD was added and the mixture was stirred for additional 24 h. Variable amounts (~20%) of isomerized starting material were observed in all entries. Yield after isolation of the product by chromatography. The diastereoselectivity of the final products was determined by ^{1}H NMR (300 MHz) analysis on the crude reaction. The enantioselectivity was determined by chiral HPLC.

It should be noted that, as demonstrated by Iriarte from this laboratory, the replacement of the aryl moiety in dienones **29**-**32** by an alkyl group, the resultant dienones **41** are equally effective leading to the corresponding cyclohexane products with essentially perfect diastereoselectivity and enantiomeric excesses within the 90-94% range (Scheme 67).[160]



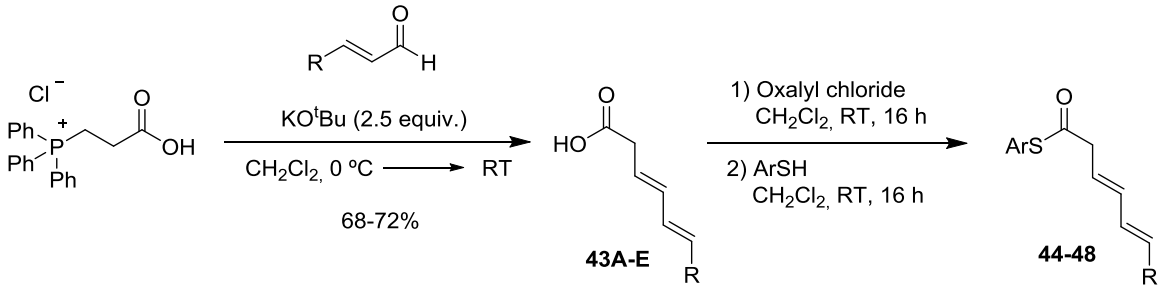
Scheme 67. Catalytic stereoselective reaction of polyunsaturated alkyl ketones **41** with nitroolefins **2** to afford tetrasubstituted cyclohexenes **42**.

3.4.3. Polyunsaturated ε-substituted thioesters as pronucleophiles

Due to the good results obtained with the polyunsaturated ε-unsubtituted thioesters **22** and ketones **29**-**32**, the behaviour of polyunsaturated ε-substituted thioesters in such a Michael reaction with nitroolefins was also investigated. The starting thioesters **44-48** were prepared by thioesterification of the carboxylic acids **43A-E**,[159a] which, in their turn, were prepared according to the method described by Davies and co-workers (Table 15).[161]

[160] For more details, see: I. Iriarte, doctoral thesis, *Brønsted Base Catalyzed Asymmetric C-C Bond-Forming Reactions with Unsaturated Ketones.* EHU/UPV, **2019** (https://www.ehu.eus/es/web/gicas/tesiak).
[161] D. M. Guptill, C. M. Cohen, H. M. L. Davies, *Org. Lett.* **2013**, *24*, 6120–6123.

Table 15. Synthesis of starting polyunsaturated ε-substituted thioesters **44**-**48**.[a]

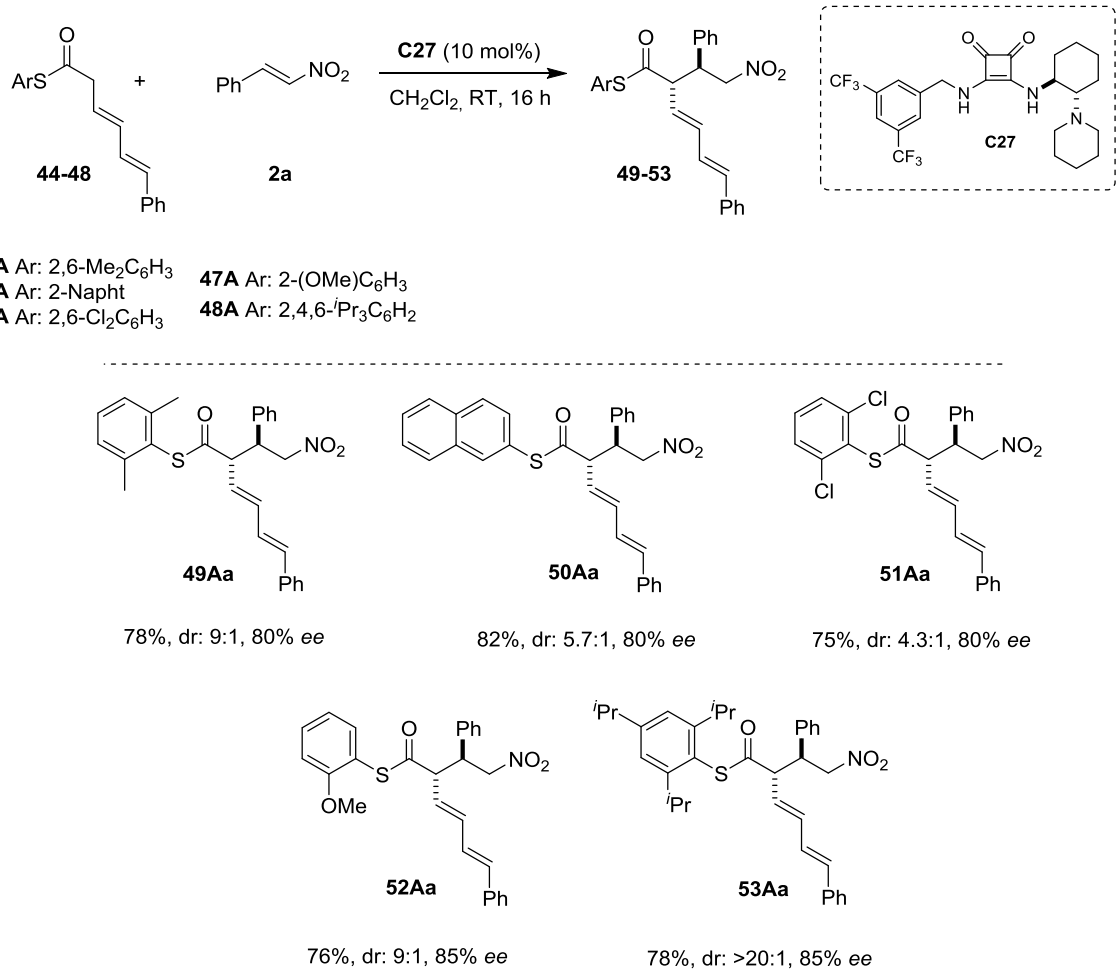


Entry	R	Ar	Product	Yield (%)
1	Ph	2,6-$(CH_3)_2C_6H_3$	**44A**	76%
2	Ph	2-Napht	**45A**	74%
3	Ph	2,6-$Cl_2C_6H_3$	**46A**	79%
4	Ph	2-$(OCH_3)C_6H_4$	**47A**	81%
5	Ph	2,4,6-(^{i}Pr)$_3C_6H_2$	**48A**	69%
6	4-$MeOC_6H_4$		**48B**	73%
7	4-BrC_6H_4		**48C**	65%
8	3-MeC_6H_4		**48D**	68%
9	^{n}Pr		**48E**	75%

[a] Reactions carried out at 1.0 mmol scale. Yield of the isolated product after chromatography.

In a first instance, we explored the influence of the nature of the *S*-substituent in the selectivity of the reaction in presence of catalyst **C27**, which was available at that moment in the laboratory and assuming that it possesses the same behaviour as catalyst **C26**. As shown in Table 16, this reaction tolerates well variations at the sulfur group, however in terms of diastereoselectivity different pattern was observed. While with thioesters **44A**-**47A** a mixture of diastereomers were obtained, the reaction between the thioester **48A** and nitrostyrene **2a** proceeded with essentially perfect diastereocontrol, obtaining the adduct **53Aa** as a single diastereomer.

Table 16. Substrate optimization for the Michael addition.[a]



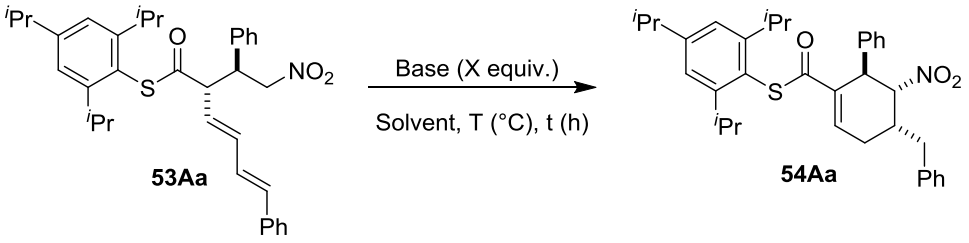
[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of thioesters **44-48** and 10 mol% of catalyst **C27** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Yield after isolation of the product by chromatography. The diastereoselectivity was determined by ^{1}H NMR (300 MHz) analysis. The enantioselectivity was determined by chiral HPLC.

To establish the effectiveness of the novel one-pot synthesis of six-member carbocycles described before with these ε-substituted thioesters, α-Michael adduct **53Aa** was stirred for an additional 24 h in presence of 20 mol% MTBD (Table 17, entry 1). Unfortunately, analysis of the crude mixture showed that the reaction did not work, recovering the starting material. In order to force the cyclization step, a set of different bases, amounts, solvents and temperatures were tested. For example, increasing the amount of base up to 2.0 equiv. (entries 2-4), no reaction was observed and the starting materials were recovered unchanged. Then, stronger organic bases (Figure 29)[162] were examined (entries 5-6) affording in all cases complex mixtures in which the expected

[162] a) K. Kaupmees, A. Trummal, I. Leito, *Croat. Chem. Acta* **2014**, *87*, 385–395. b) J. D. Rawn, R. J. Ouellette, *Organic Chemistry: Structure, Mechanism, Synthesis,* Elsevier, **2014**.

cyclized product was not observed. On the other hand, using inorganic bases similar results were obtained (entries 7-11).

Table 17. Attempts of cyclization step optimization employing different bases.[a]



Entry	Base (X equiv.)	Solvent	T (°C)	t (h)	Product
1[b]	MTBD (0.2 equiv.)	CH_2Cl_2	RT	16 h	---
2[b]	MTBD (0.5 equiv.)	Toluene	40 °C	48 h	---
3[b]	DBU (1.0 equiv.)	CH_2Cl_2	RT	16 h	---
4[b]	Et_3N (2.0 equiv.)	CH_2Cl_2	RT	16 h	---
5[c]	LDA (1.0 equiv.)	THF	-78 °C	5 h	---
6[c]	P4 ^{t}Bu (1.0 equiv.)	CH_3CN	RT	16 h	---
7[c]	NaOH (40%, 1.0 equiv.)	MeOH	RT	16 h	---
8[c]	LiOH (5.0 equiv.)	Dioxane/H_2O	RT	5 h	---
9[c]	NaH (1.0 equiv.)	THF	RT	5 h	---
10[c]	NaOMe (1.0 equiv.)	MeOH	60 °C	16 h	---
11[c]	KO^{t}Bu (1.0 equiv.)	DMSO	RT	2 h	---

[a] Reactions conducted on 0.1 mmol scale, using X equiv. of base in the corresponding solvent at the corresponding temperature for 2-48 h. Isomerized or saponification product was not observed in any cases. [b] Starting material was recovered unchanged. [c] Decomposition of the starting material was observed.

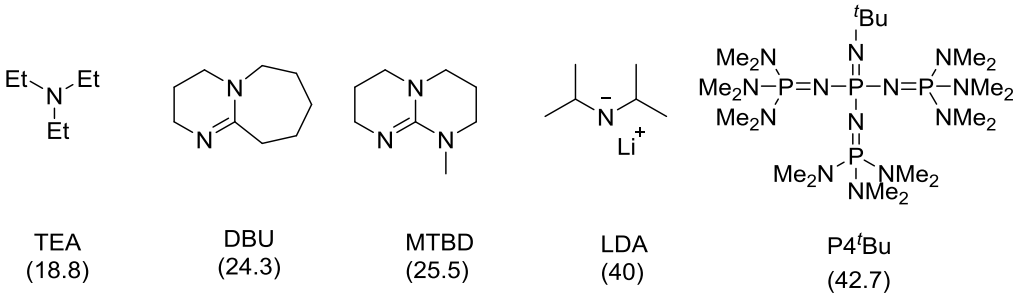
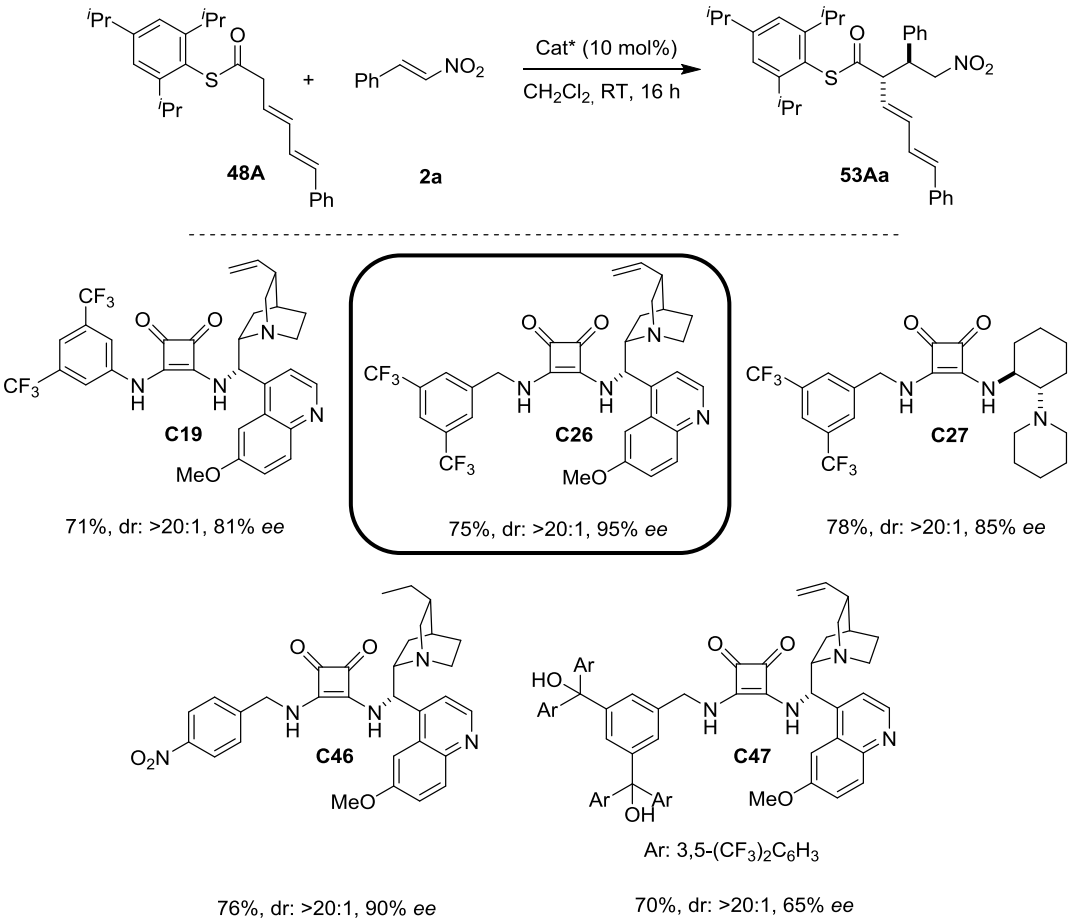


Figure 29. Organic bases and the pK_a values of their conjugated acids in acetonitrile.[162]

Screening of a set of bifunctional Brønsted base/H-bonding catalysts (Table 18), with the aim of improving the stereoselectivity obtained with **C27**, revealed, once again, that **C26** was the best, giving product **53Aa** essentially as a single diastereomer in 95% *ee*.

Table 18. Catalyst screening for the reaction of **48A** with **2a**.[a]

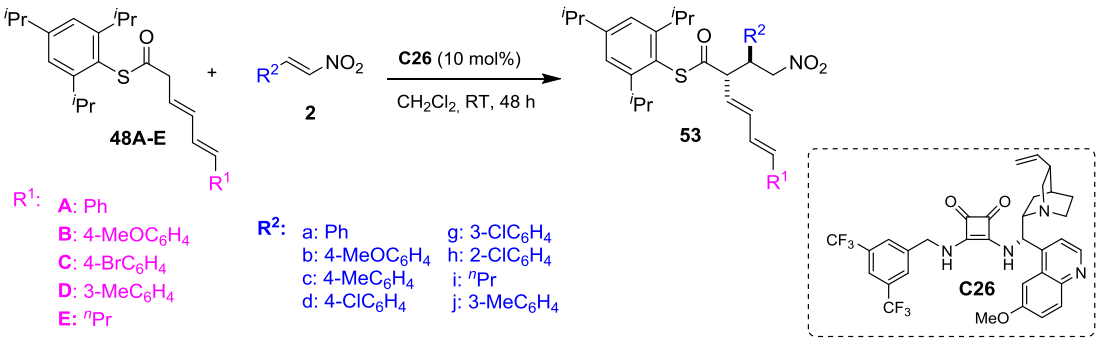


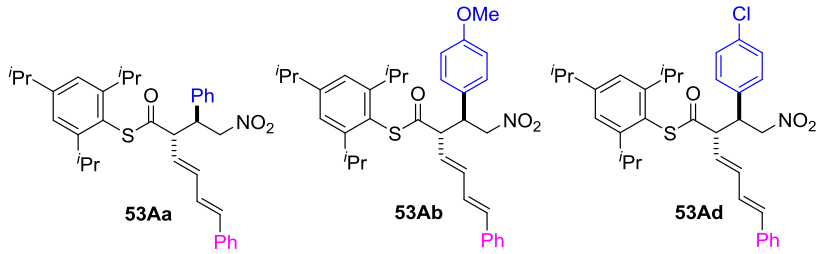
[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of thioester **48A** and 10 mol% of catalyst in 0.1 mL CH_2Cl_2 at room temperature for 16 h. Yield after isolation of the product by chromatography. The diastereoselectivity was determined by ^{1}H NMR (300 MHz) analysis. The enantioselectivity was determined by chiral HPLC.

With the best catalyst **C26** in hand the scope of the reaction was explored next. Experiment with an array of substrates revealed the suitability of various β-aryl substituted nitroolefins **2** and thioester **48** combinations (Table 19). The reaction of thioester **48A** with several β-aryl substituted nitroolefins (*meta*- and *para*-), provided the corresponding adducts **53Ab**, **53Ad**, **53Ag** and **53Aj** in good yields and perfect stereoselectivities. However, with 2-chloronitrostyrene **2h**, a 3.8:1 mixture of diastereomers was achieved in moderate enantioselectivity. Apparently, this reaction did not tolerate aliphatic nitroolefins as the result with **2i** shows (adduct **53Ai**). Variations of the R^1 substituent did not affect either yield or selectivity, and adducts

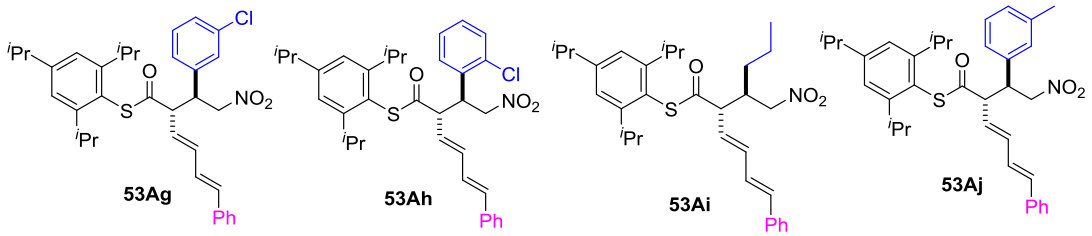
such as **53Ba**, **53Cc**, **53Da** and **53Eb** were obtained in good yields, perfect diastereoselectivities and *ee´*s in the range from 91% to 98%.

Table 19. Catalytic stereoselective reaction of thioesters **48A-E** with nitroolefins **2** to afford α-Michael adducts **53**.[a]

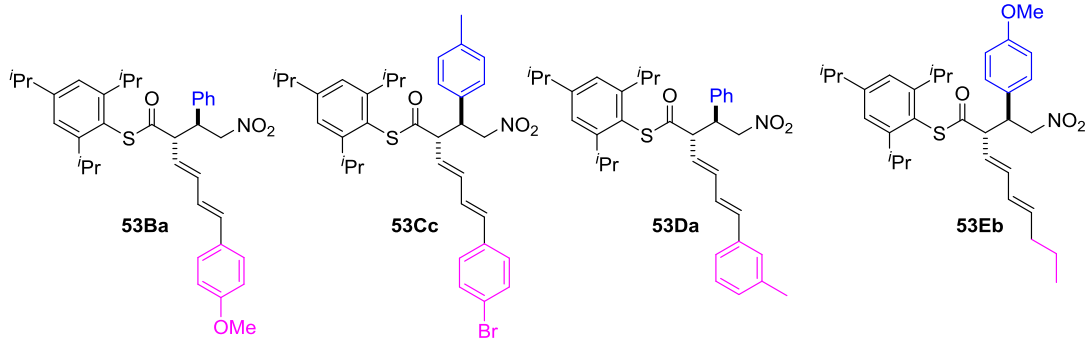




75%, dr: >20:1, 95% *ee* | 78%, dr: >20:1, 95% *ee* | 82%, dr: >20:1, 93% *ee*



74%, dr: >20:1, 90% ee | 74%, dr: 3.8:1, 80(55)% *ee* | n.r. | 74%, dr: >20:1, 81% *ee*



75%, dr: >20:1, 94% *ee* | 75%, dr: >20:1, 91% *ee* | 73%, dr: >20:2, 97 % *ee* | 69%, dr: >20:1, 98% *ee*

[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of thioesters **48** and 10 mol% of catalyst **C26** in 0.1 mL CH_2Cl_2 at room temperature for 16 h. The diastereoselectivity and enantioselectivity were determined by chiral HPLC. n.r.: no reaction.

The absolute configuration of the adducts was established by a single-crystal X-ray analysis of adduct **55**[163] and assuming a uniform reaction mechanism (Figure 30).

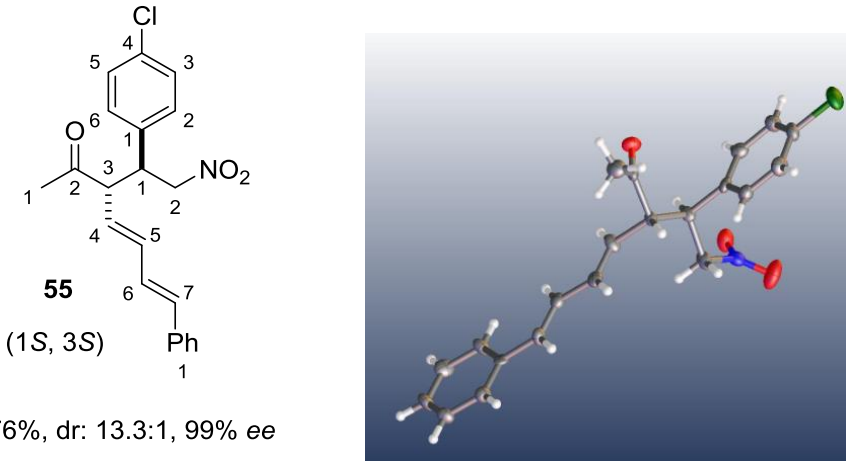


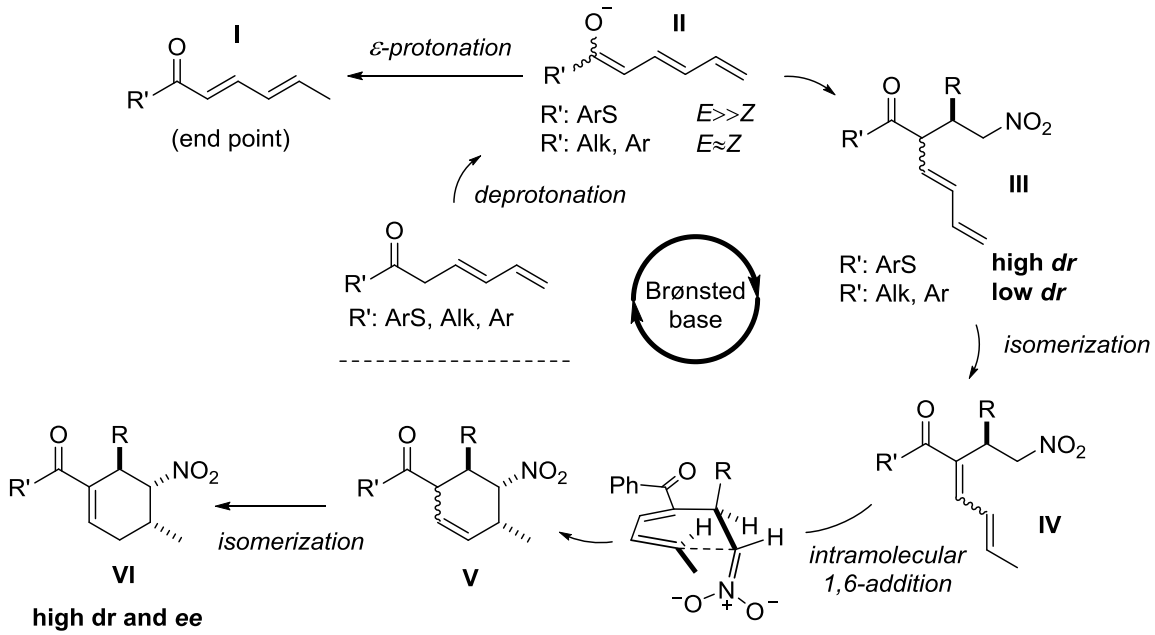
Figure 30. ORTEP diagram of compound **55**.

3.4.4. Plausible mechanism of the one-pot catalytic process

A rationale for the above experimental observations is proposed in Scheme 68, with Brønsted base catalysis as the unified mode of activation. As can be seen, the reaction would start with the asymmetric α-addition of the trienolate intermediate (**II**) in presence of the bifunctional catalyst. However, more or less 20 mol% of nucleophile is isomerized to the corresponding conjugated product (**I**), which is completely unreactive under the reaction conditions. Next, the addition of an external Brønsted base (20 mol% MTBD) promotes the isomerization of the α-Michael adduct (**III**)[164] to the isomerized dienone (**IV**), which makes the actual configuration of Cα stereocenter in **III** irrelevant. Then, after formation of the nitronate, intramolecular 1,6-addition occurs to obtain the cycloadduct (**VI**) with excellent stereoselectivity, which is isolated after isomerization of **V**.

[163] This compound was prepared by I. Iriarte from this laboratory following the same methodology as described herein. For more details, see: I. Iriarte, doctoral thesis, *Brønsted Base Catalyzed Asymmetric C-C Bond-Forming Reactions with Unsaturated Ketones.* EHU/UPV, **2019** (https://www.ehu.eus/es/web/gicas/tesiak).

[164] The low diastereoselectivies observed for the initial α-addition reaction of doubly unsaturated ketones to nitroolefins could be attributed to their tendency to form variable mixtures of *E* and *Z* enolates. However, the high diastereoselectivity attained with unsaturated thioesters would correlate with the relatively higher energy difference between thioester *Z* and *E* enolate, owing to the large aryl-*S* group.



Scheme 68. Plausible course of the one-pot reactions sequence.

In order to know how the electrophile and the pronucleophile interact with the chiral catalyst during the C-C bond formation, the possible transition state (TS) energies and geometries between trienolate, which comes from **41A**, and nitrostyrene **2a** in presence of catalyst **C27** were calculated by G. Zanella and E. Gómez-Bengoa.[165] Each of the reactant orientations leading to the four possible stereoisomers were investigated considering the two most commonly accepted modes of activation, namely Takemoto and Pápai models, respectively.[166,167] After several calculations carried out on this model reaction, G. Zanella and E. Gómez-Bengoa predicted the formation of α-Michael adduct featuring an (*R*)-configured β-carbon due to its lowest activation barrier in comparison with the others (Figure 31).[168]

[165] Given that **C27** induced the same sense of enantioselectivity as **C26**, the catalyst **C27** was selected for calculation due to computational simplicity and reliability.

[166] a) C. Trujillo, I. Rozas, A. Botte, S. J. Connon, *Chem. Commun.* **2017**, *53*, 8874–8877.b) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631–5639.

[167] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125. b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[168] For more information about these transient state energies, see experimental part: O. Olaizola, I. Iriarte, G. Zanella, E. Gómez-Bengoa, I. Gamboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2019**, *58*, 14250–14254.

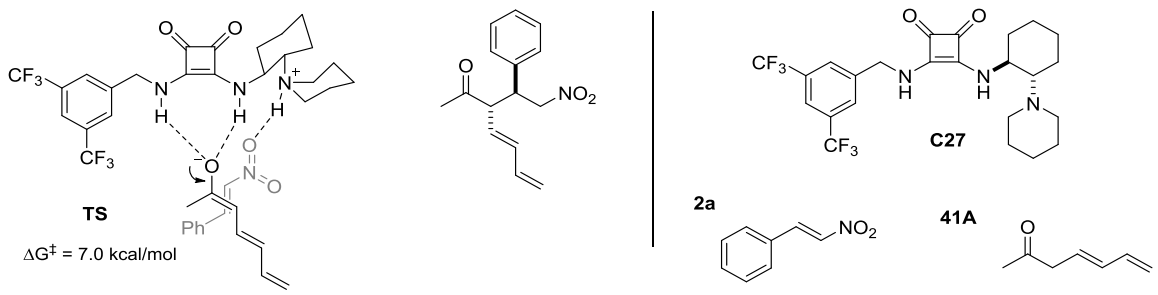


Figure 31. Proposed activation mode for the α-addition of polyunsaturated ketone **41A** to nitrostyrene **2a**.

Moreover, to support the almost perfect stereocontrol of the reaction the energies of the transition states for the carbocyclization step in its four possible nitronate-dienone face combinations were calculated by G. Zanella and E. Gómez-Bengoa.[168] The energy barrier for the *re*,*re* approach was found to be 9.6 kcal/mol, that is, about 2 kcal/mol lower than any of the other three possible approaches, which nicely explains the essentially perfect stereoinduction observed in all but one case (adduct **37i**) (Figure 32).

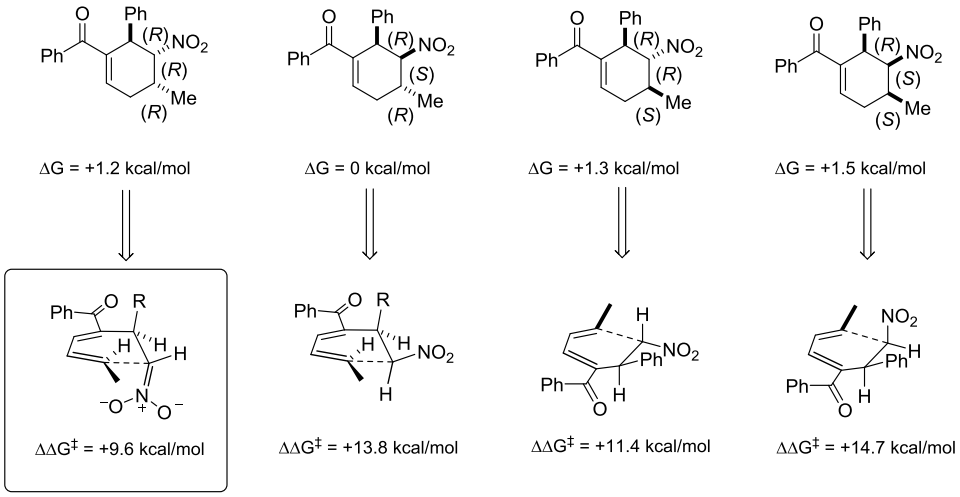
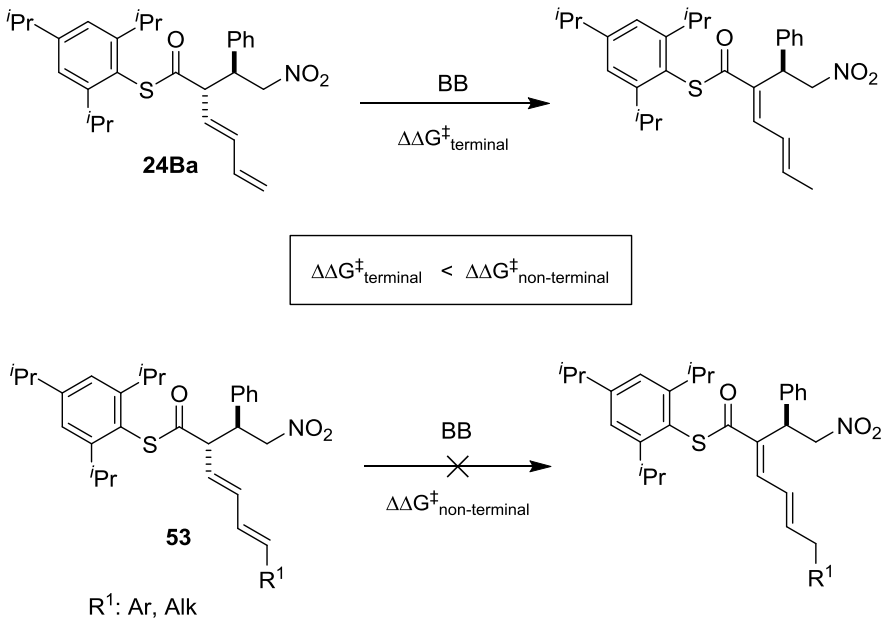


Figure 32. Free energies of products and transition states.

It is worth mentioning that isomerization and posterior cyclization of the ε-substituted thioester adducts **53** did not occur under the same reaction conditions employed for adducts **24**. We hypothesized that due to the larger substitution (higher stability) of the diene of adducts **53**, the energy barrier for the isomerization could be higher when compared to the terminal diene in **24** (Scheme 69). Nonetheless, to support this assumption, further theoretical work must be realized.



Scheme 69. Behavior of terminal unsaturated (**24Ba**) and substituted (**53**) dienes in the isomerization reaction promoted by Brønsted base (BB).

3.5. Elaboration of adducts

Having developed a catalytic one-pot process to assemble stereodefined tetrasubstituted six-member carbocycles from terminal polyunsaturated thioesters and ketones, the potential of the resulting enantioenriched adducts in synthesis was briefly explored.

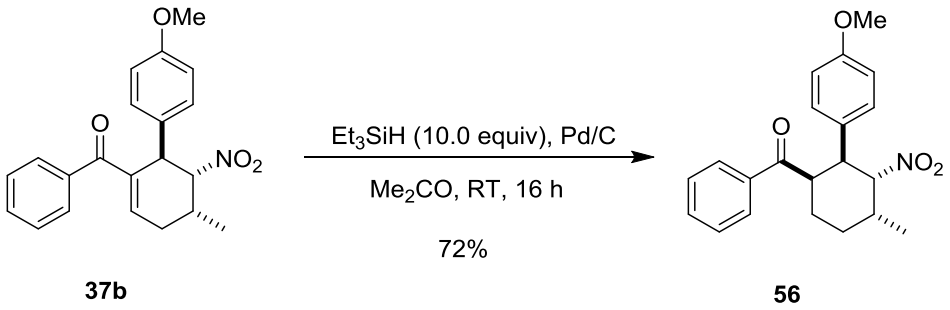
3.5.1. Selective reduction of the C=C double bond

As mentioned before, six-member carbocycles are ubiquitous structural motifs in natural products. Because of that, we suggest that the transformation of these tetrasubstituted cyclohexenes into tetrasubstituted cyclohexanes is easily conceivable through reduction of the C=C double bond.

Based on this idea, exposure of adduct **37b** to molecular hydrogen, which is generated *in situ* by addition of triethylsilane to palladium,[169] gave product **56** in good yield and as a single diastereomer without affecting the carbonyl and nitro groups (Scheme 70).[170]

[169] P. K. Mandal, J. S. McMurray, *J. Org. Chem.* **2007**, *72*, 6599–6601.

[170] For more information about the strategy used for facile reduction of thioesters to aldehydes, see: a) Y. Arakawa, S. P. Fritz, H. Wennemers, *J. Org. Chem*. **2014**, *79*, 3937–3945. b) T. Fukuyama, S. -C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.



37b **56**

Scheme 70. Selective reduction of the C=C double bond of enone **37b**.

The relative configuration of compound **56** was established by a NOESY experiment.[171] Irradiation at 5.06 ppm (H^f) (Figure 33) revealed the proximity of H^e and H^g, indicating that the protons are on the same side of the ring and that H^b is in the opposite side of the ring (no interaction between H^f and H^b was detected). This means that *syn* hydrogen addition occurs from the least hindered face (opposite side of the aromatic ring of the nitroolefin).

[171] First of all, proton assignment for compound **56** employing a COSY experiment was done. See experimental section (page 378).

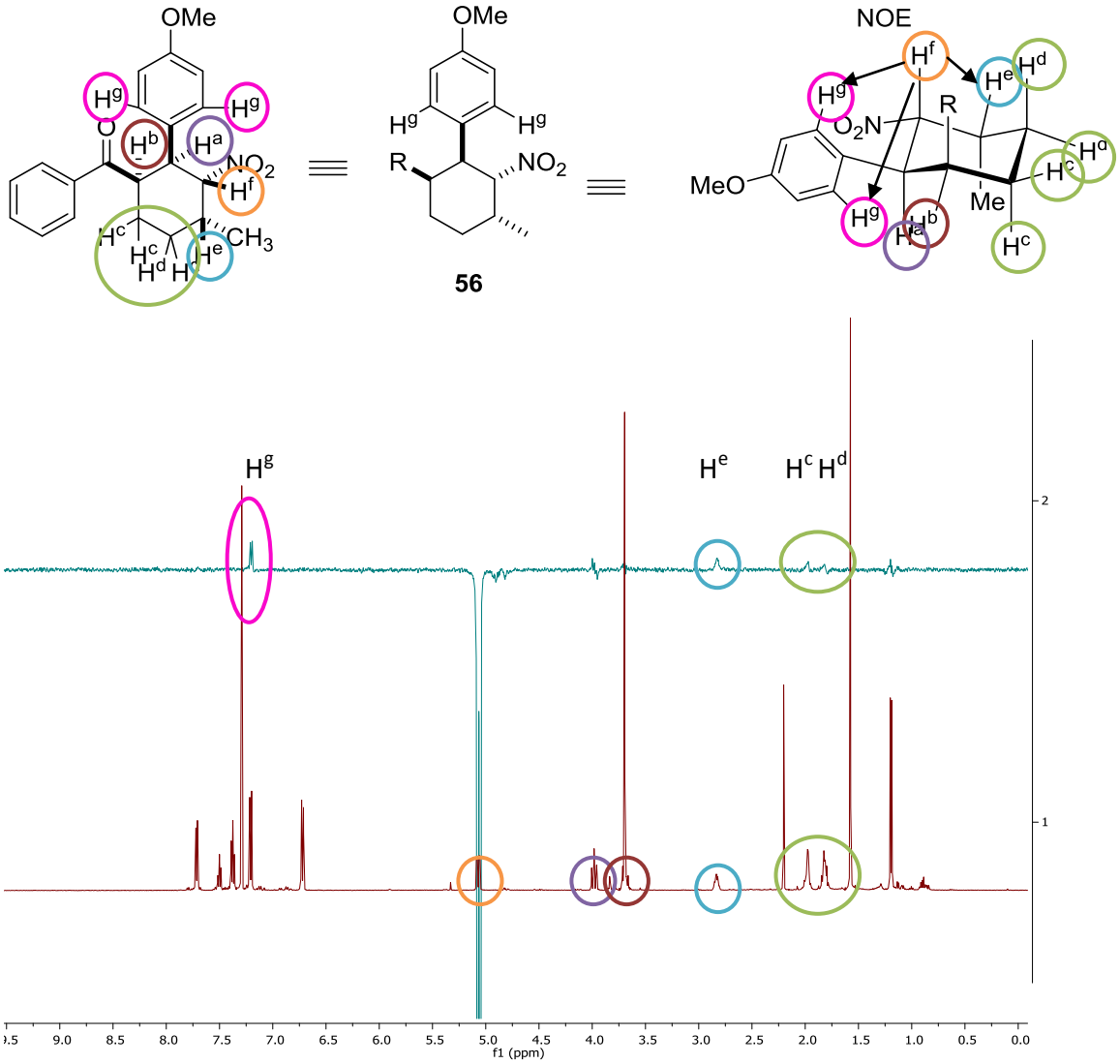
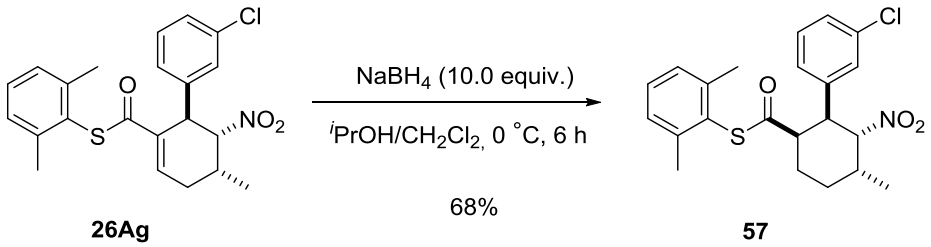


Figure 33. NOESY NMR spectrum for product **56**.

The same methodology was next employed for the selective reduction of the C=C double bond in thioester **26Ag**. However, starting material was recovered unchanged. After several attempts, it was found that $NaBH_4$ gave the reduction product **57** and significantly without reduction of the thioester group[172] with good yield and essentially as a single diastereomer (Scheme 71).

[172] For more information about the strategy used for reduction of thioester group, see: a) R. J. Alfie, N. Truong, J. M. Yost, D. M. Coltart, *Tetrahedron Lett.* **2017**, *58*, 185–189. b) A. G. M. Barrett, D. J. Rys, *J. Chem. Perkin Trans.* **1995**, *1*, 1009–1017.



Scheme 71. Selective reduction of the C=C double bond of thioester **26Ag**.

The configuration of compound **57** was also established by a NOESY analysis.[173] Irradiation at 5.90 ppm (H^f) (Figure 34) revealed the proximity of $H^{g+g'}$ and H^e, indicating that the protons are on the same side of the ring and that H^b is in the opposite side of the ring (no interaction between H^f and H^b were detected).

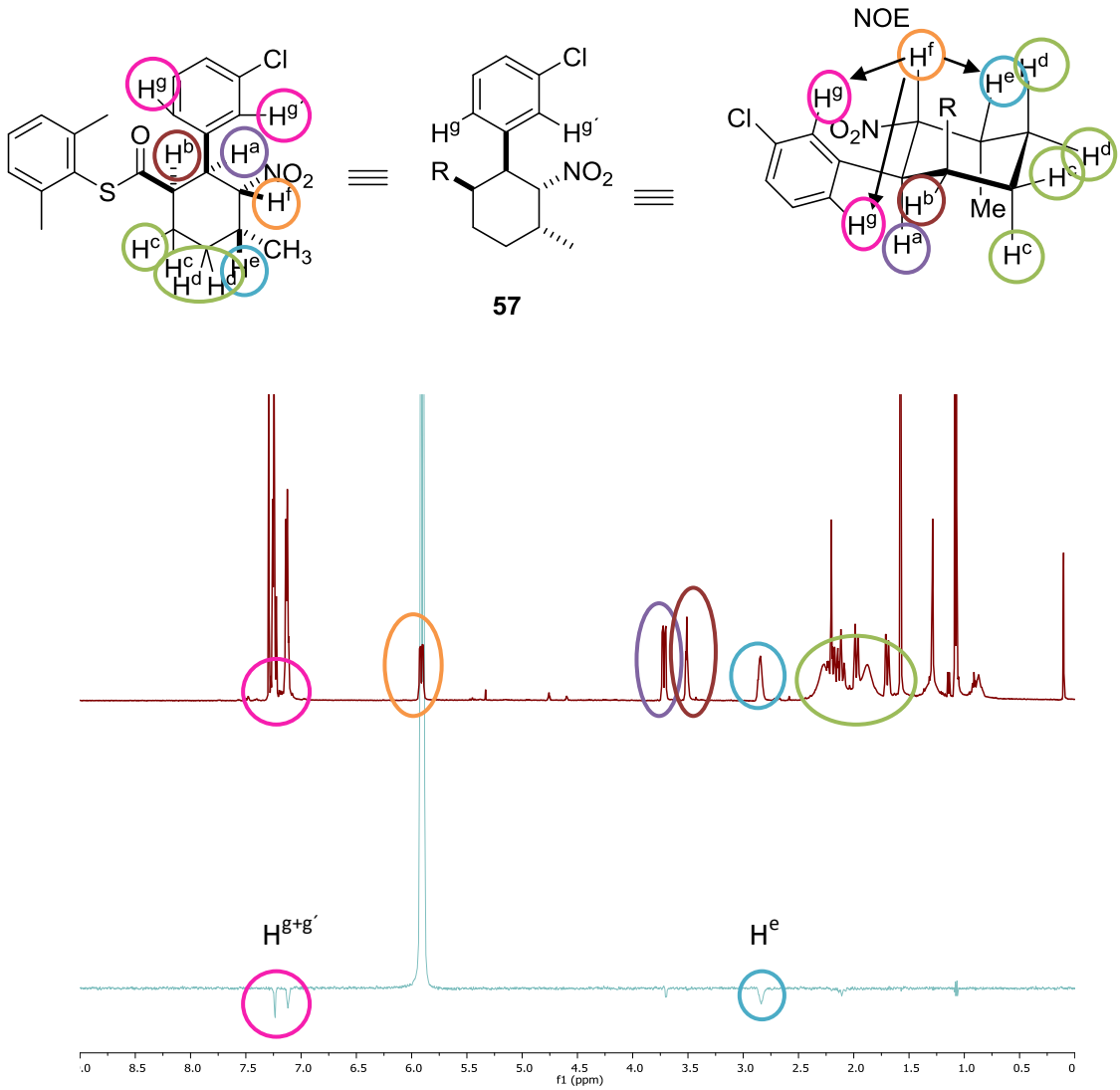


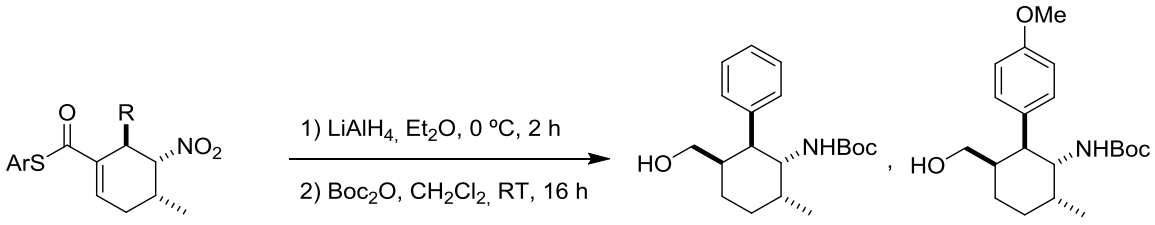
Figure 34. NOESY NMR spectrum for product **57**.

[173] First of all, proton assignment for compound **57** employing a COSY experiment was done. For more information, see experimental section (page 381).

3.5.2. Reduction of the thioester group

Having as reference that $NaBH_4$ reduced the C=C double bond of a α,β-unsaturated thioester, $LiAlH_4$,[174] which is a harder nucleophile, was employed as reducing agent for the reduction of the thioester group. However, starting from thioester adducts **26Aa** and **26Bb**, the reduction proceeded with concomitant reduction of the C=C double bond and nitro group as well. For better isolation of the final product, the amine group was protected with the *tert*-butyloxycarbonyl group, leading to products **58** and **59** in 50% and 60% yields, respectively (Table 20). Despite the fact that the reduction procedure was unselective, only one single diastereomer of the final products **58** and **59** was produced.

Table 20. Reduction of the thioester group.[a]

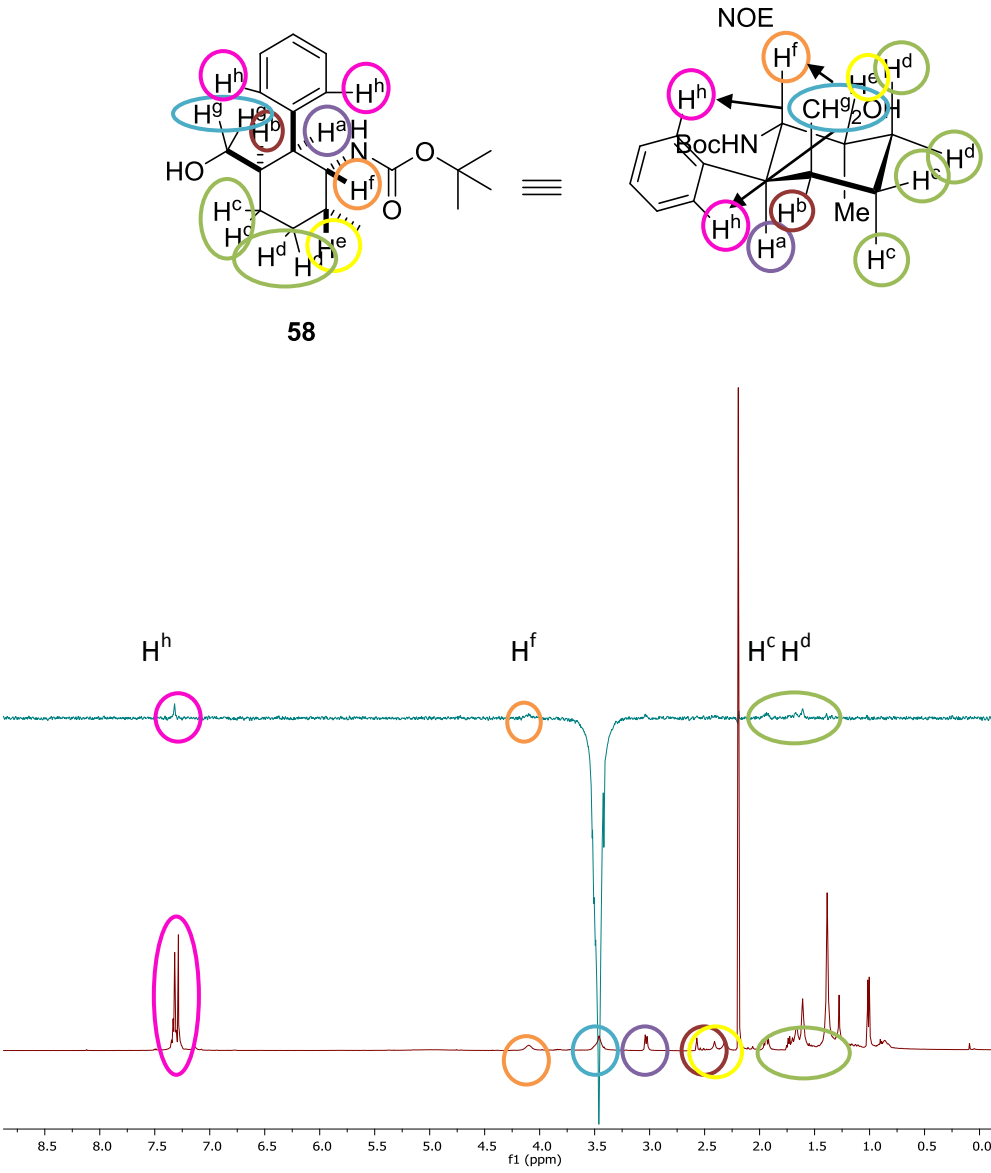


26Aa Ar: 2,6-$Me_2C_6H_3$, R: Ph
26Bb Ar: 2,4,6-$^{i}Pr_3C_6H_2$ R: 4-$MeOC_6H_4$

[a] Reactions carried out at 0.1 mmol scale, using 3.0 equiv. of $LiAlH_4$ in 1.0 mL Et_2O at 0 °C for 2 h. Then, 1.2 equiv. of Boc_2O was added to the mixture of the crude in 1.0 mL CH_2Cl_2 at room temperature for 16 h.

The configuration of compound **58** was established by a NOESY analysis, and that of product **59** was assumed based on a uniform reaction mechanism. Although the signals are very weak, irradiation at 3.47 ppm (H^g) (Figure 35) revealed the proximity of H^h, H^f, H^c and H^d, indicating that the protons are on the same side of the ring, thus confirming the final configuration of the adduct.

[174] J. Guang, A. J. Larson, J. C. -G. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 523–529.



58

Figure 35. NOESY NMR spectrum for product **58**.

3.5.3. Nazarov cyclization

The hydrofluorenone core exists in numerous biological compounds.[175] Some of these active compounds are shown in Figure 36.[176] The Nazarov reaction is one of the most effective strategies for the construction of the cyclopentenone core.[177] Typically in this method, divinyl ketones or derivatives are treated with Lewis or Brønsted acids (one or more equivalents of acid are normally necessary). Even so, photo-Nazarov reactions can be found in the literature.[175,178]

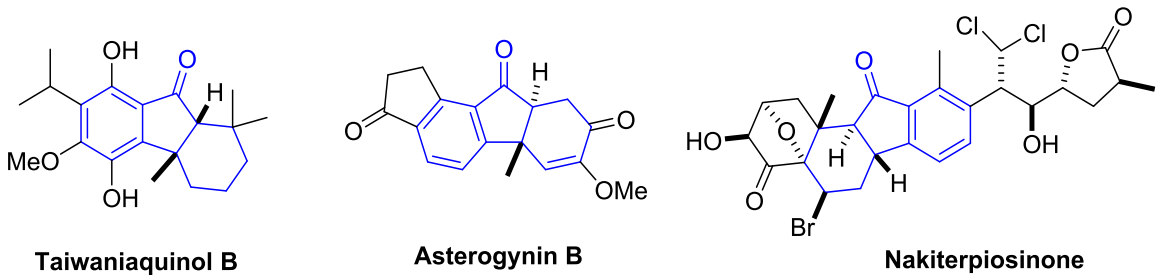


Figure 36. Hydrofluorenone-containing natural products.

In this context, enantioenriched aromatic ketone adducts **37**-**40,** which possess an aromatic vinyl ketone core inside their structures, are potential substrates for the Nazarov reaction. After several attempts, we observed that only adducts with electron rich aromatic groups (**39b**, **39h** and **40a**) were able to undergo cyclization,[179] whereas the simplest phenyl group was not suitable for the reaction. Moreover, we found that electron-donating groups at the *meta*-positions of the aryl group were crucial for the substrate to undergo Nazarov cyclization effectively. These products were isolated in good yields and as essentially single diastereomers (Table 21).

[175] S. Cai, Z. Xiao, Y. Shi, S. Gao, *Chem. Eur. J.* **2014**, *20*, 8677–8681.

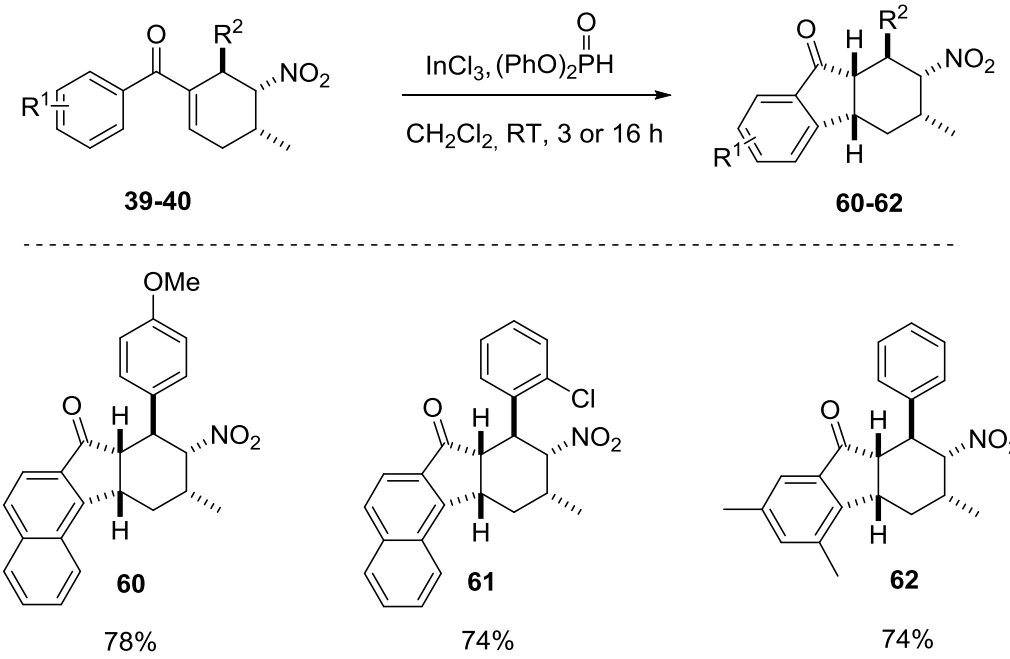
[176] For more information about the synthesis of Taiwaniaquinols, see: a) J. Deng, R. Li, Y. Luo, J. Li, S. Zhou, Y. Li, J. Hu, A. Li, *Org. Lett.* **2013**, *15*, 2022–2025. For more information about Asterogynin B, see: b) S. Cao, L. Ross, G. Tamayo, J. Clardy, *Org. Lett.* **2010**, *12*, 4661–4663. For more information about Nakiterpiosinone, see: c) S. Gao, Q. Wang, L. Lum, C. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 371–383.

[177] For general reviews of Nazarov reaction, see: a) N. Shimada, C. Stewart, M. A. Tius, *Tetrahedron* **2011**, *67*, 5851–5870. b) T. Vaidya, R. Eisenberg, A. J. Frontier, *Chem. Cat. Chem.* **2011**, *3*, 1531–1548.

[178] For more examples about photo-Nazarov reactions, see: a) W. L. Ashley, E. L. Timpy, T. C. Coombs, *J. Org. Chem.* **2018**, *83*, 2516–2529. b) J. Leitich, I. Heise, J. Rust, K. Schaffner, *Eur. J. Org. Chem.* **2001**, 2719–2726. c) J. Leitich, I. Heise, S. Werner, C. Krüger, K. Schaffner, *J. Photochem. Photobiol. A* **1991**, *57*, 127–151.

[179] Adapted from: a) Z. -G. Xi, L. Zhu, S. Luo, J. -P. Cheng, *J. Org. Chem.* **2013**, *78*, 606–613. b) L. H. Phun, D. V. Patil, M. A. Cavitt, S. France, *Org. Lett.* **2011**, *13*, 1952–1955.

Table 21. Nazarov cyclization to products **60**-**62**.[a]



[a] Reactions carried out at 0.1 mmol scale, using 0.3 equiv. of diphenyl phosphate and 30 mol% of $InCl_3$ in 0.1 mL CH_2Cl_2 at room temperature for 3 h. 16 h were needed for the synthesis of **62**. n.r.:no reaction.

The configuration of compound **60** was established by a NOESY analysis,[180] and that of products **61**-**62** was assumed based on a uniform reaction mechanism. Irradiation at 4.41 ppm (H^b) (Figure 37) revealed the proximity of H^a, H^c, H^d and H^e, indicating that the protons are on the same side of the ring. To confirm the proposed structure, the NOESY experiment was repeated irradiating H^a. In this case, irradiation at 3.20 ppm (H^a) revealed the proximity of H^b and H^d (Figure 23).

[180] First of all, proton assignment for compound **60** employing a COSY experiment was done. For more information, see experimental section (page 387).

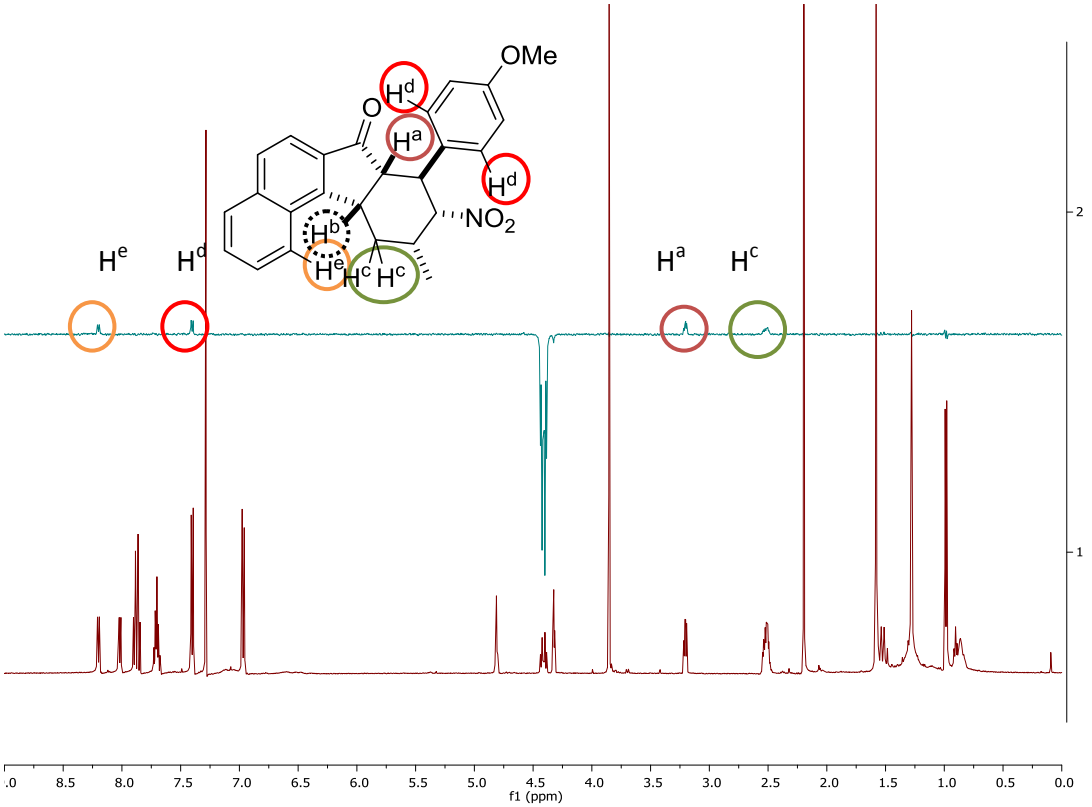


Figure 37. NOESY NMR spectrum for product **60**.

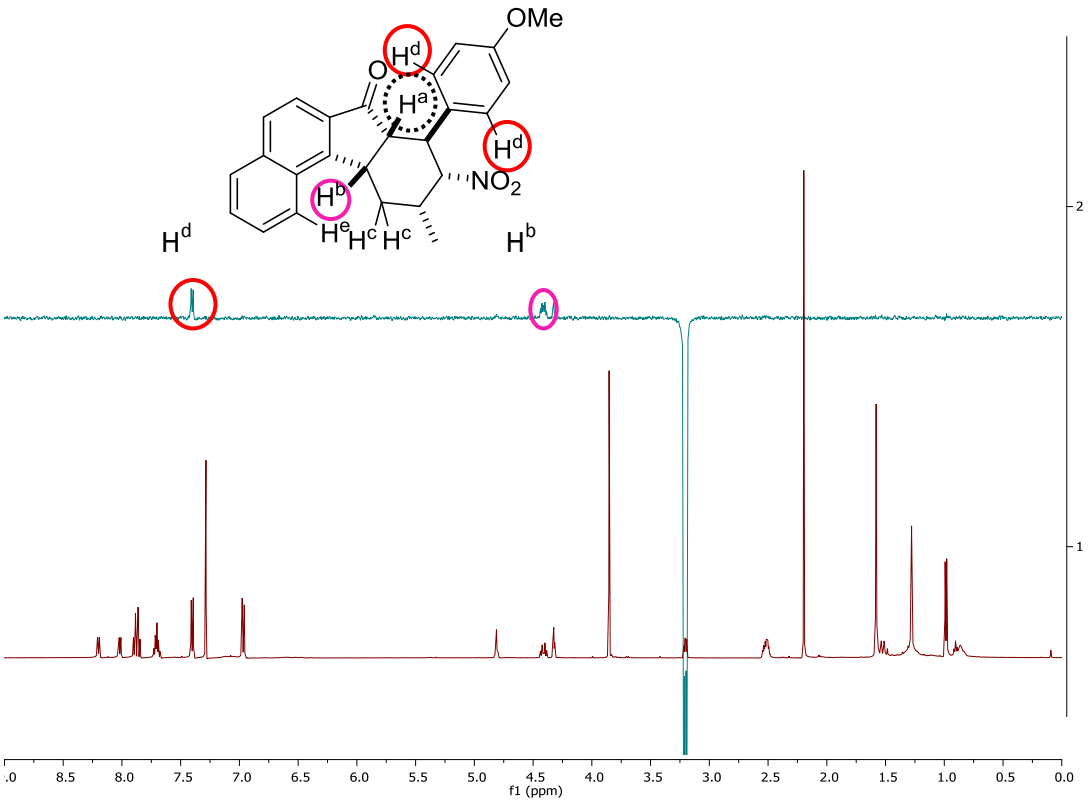


Figure 38. NOESY NMR spectrum for product **60**.

A subsequent X-ray single crystal structure analysis of compound **61** (Figure 39) served to confirm the configuration of the new two stereocenters, which were predicted before with NOESY experiments for the compound **60**.

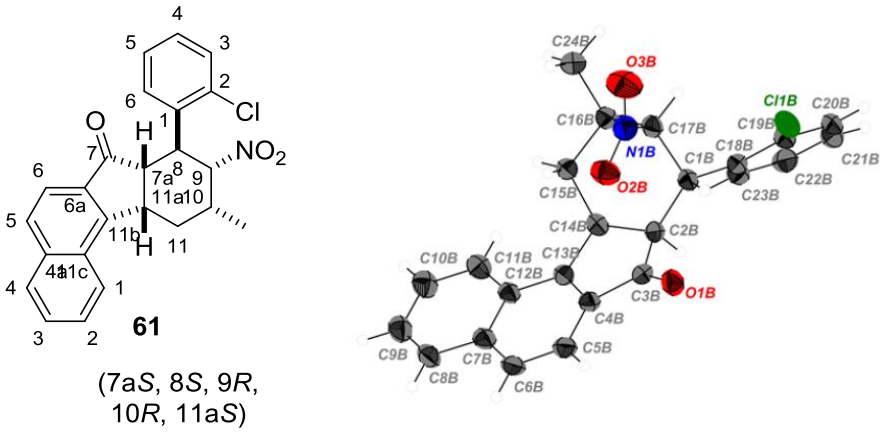


Figure 39. ORTEP diagram of compound **61**.

Chapter 4

Synthesis of 3,4-dihydroisoquinolones from *N*-chloroformylimidazolidinone enolates

4. Synthesis of 3,4-dihydroisoquinolones from *N*-chloroformylimidazolidinone enolates

4.1. Introduction

The work described in this chapter was carried out during three months stay at the laboratory of Prof. Clayden at the University of Bristol.

The 3,4-dihydroisoquinolone ring, which is a basic framework of many biologically active compounds and pharmaceutical products, attracts the attention of many researchers owing to their biological and pharmacological activity. [181] Some of these compounds are shown in Figure 40.[182]

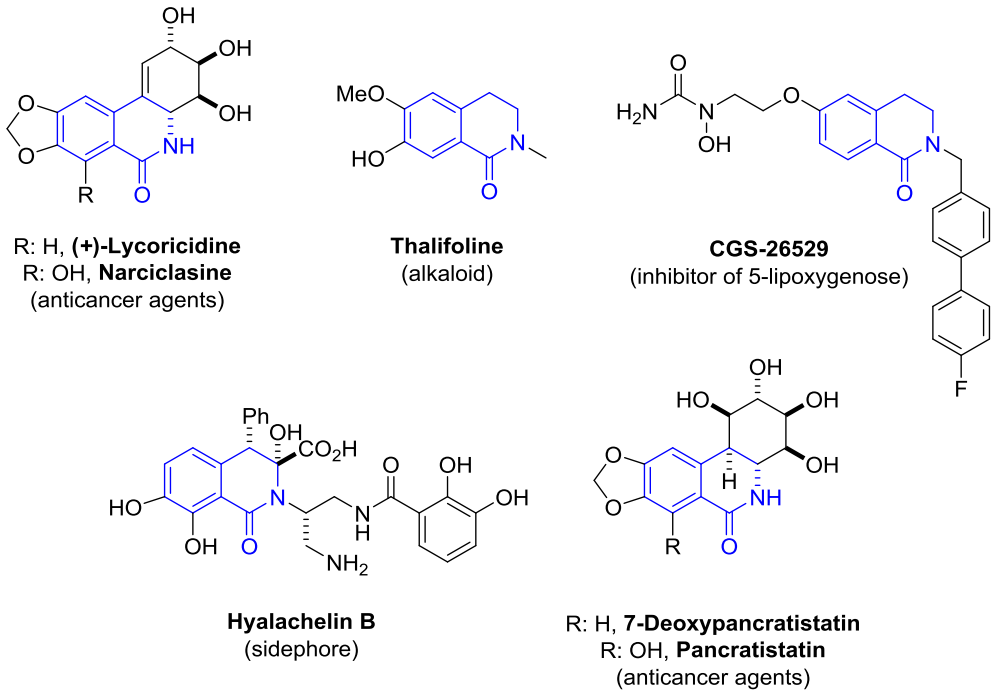


Figure 40. Pharmaceutical and biological active compounds containing the dihydroisoquinolone skeleton.

[181] V. A. Glushkov, Y. V. Shklyaev, *Chem. Heterocycl. Comp.* **2001**, *37*, 663–687.

[182] For more information about (+)-Lycoricidine, see: a) P. Saidhareddy, A. K. Shaw, *Tetrahedron* **2017**, *73*, 6773–6779. For more information about Narciclasine, see: b) R. Fürst, *Planta Med.* **2016,** *82*, 1389–1394. For more information about Thalifoline, see: c) R. W. Doskotch, P. L. Schiff, J. L. Beal, *Tetrahedron* **1969**, *25*, 469–475. For more information about CGS-26529, see: d) E. Kimble, T. Kowalski, D. White, A. Raychauduri, G. Pastor, H. Chertock, W Lee, R. Neale, A. Hamdan, J. Wasley, *Agents and Actions* **1991**, *34*, 125–128. For more information about Hyalachelin B, see: e) S. Nadmid, A. Plaza, G. Lauro, R. Garcia, G. Bifulco, *Org. Lett.* **2014**, *16*, 4130–4133. For more information about 7-Deoxypancratistatin, see: f) G. E. Keck, S. F. McHardy, J. A. Murry, *J. Am. Chem. Soc.* **1995**, *117*, 7289–7290. For more information about Pancratistatin, see: g) A. McLachlan, N. Kekre, J. McNulty, S. Pandey, *Apoptosis* **2005**, *10*, 619–630.

Given this relevance as well as their low natural abundance, these metabolites, especially Isocarbostyril alkaloids[183] (Narciclasine, Pancratistatin, (+)-Lycoricidine, etc.) have attracted significant interest in the synthetic community, resulting in numerous synthetic studies and several dozen total syntheses reported to date.[184]

The traditional synthetic methods for the preparation of this 3,4-dihydroisoquinolone core usually involve metal catalysis. For example, aromatic amides or their derivatives as hydroxamic acids among others, give 3,4-dihydroisoquinolones by metal catalyzed C-H activation with alkenes, alkynes or allenes *via* intermolecular cyclization (Scheme 72a)[185]. Another strategy for the synthesis of these useful skeletons is the cyclocarbonylation of amines by palladium catalysis (Scheme 72b).[186] Furthermore, Friedel–Crafts reactions (Scheme 72c),[187] which need powerful activating agents or strong Lewis acids, and substitution reactions[188] (Scheme 72d) are other alternatives for the synthesis of these scaffolds.

[183] For reviews on the synthesis of Isocarbostyril alkaloids, see: a) M. Ghavre, J. Froese, M. Pour, T. Hudlicky, *Angew. Chem. Int. Ed.* **2016**, *55*, 5642–5691. b) Z. Jin, *Nat. Prod. Rep.* **2009**, *26*, 363–381.

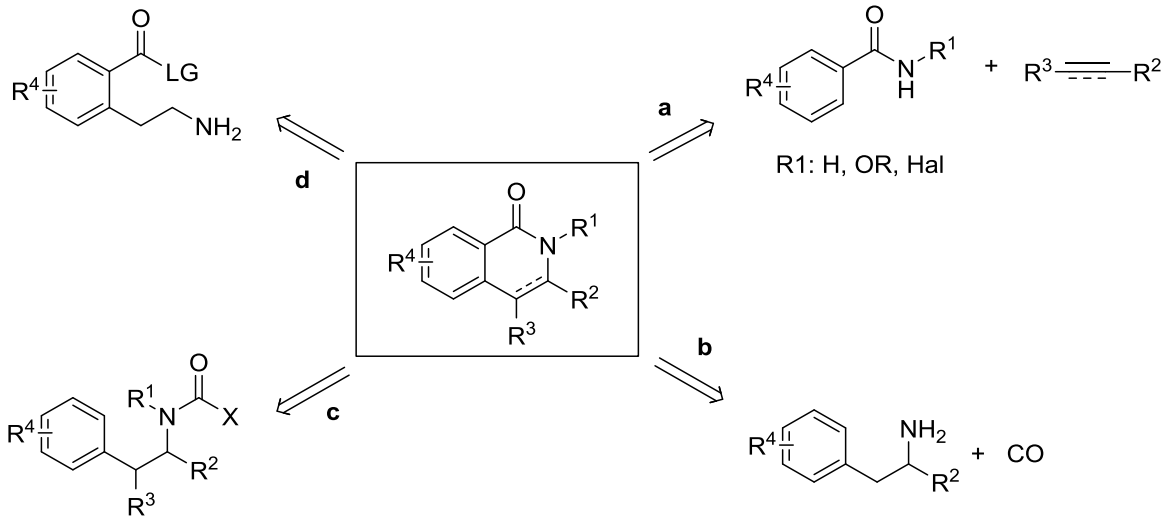
[184] For examples about total synthesis, see: a) H. -J. Lo, Y. -K. Chang, B. Ananthan, Y. -H. Lih, K. -S. Liu, T. -H. Yang, *J. Org. Chem.* **2019**, *84*, 10065–10075. b) E. H. Southgate, D. R. Holycross, D. Sarlah, *Angew. Chem. Int. Ed.* **2017**, *56*, 15049–15052. c) J. S. Yadav, G. Satheesh, C. V. S. R. Murthy, *Org. Lett.* **2010**, *12*, 2544–2547. d) M. Matveenko, M. G. Banwell, A. C. Willis, *Tetrahedron,* **2008**, *64*, 4817–4826. e) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570–2582. f) T. Hudlicky, A. J. Thorpe, *Chem. Commun.* **1996**, 1993–2000. g) B. M. Trost, S. R. Pulley, *J. Am. Chem. Soc.* **1995**, *117*, 10143–10144. h) T. Hudlicky, H. F. Olivo, B. McKibben, *J. Am. Chem. Soc.* **1994**, *116*, 5108–5115. i) M. C. Mcintosh, S. M. Weinreb, *J. Org. Chem.* **1993**, *58*, 4823–4832. j) N. Chida, M. Ohtsuka, S. Ogawa, *J. Org. Chem.* **1993**, *58*, 4441–4447. k) T. Hudlicky, H. F. Olivo, *J. Am. Chem. Soc.* **1992**, *114*, 9694–9696. l) N. Chida, M. Ohtsuka, S. Ogawa, *Tetrahedron Lett.* **1991**, *32*, 4525–4528.

[185] For selected examples about C-H activation, see: a) E. A. Trifonova, N. M. Ankudinov, A. A. Mikhaylov, A. A. Chusov, Y. V. Nelyubina, D. S. Perekalin, *Angew. Chem. Int. Ed.* **2018**, *57*, 7714–7718. b) X. Yu, K. Chen, Q. Wing, W. Zhang, J. Zhu, *Org. Chem. Front.* **2018***, 5,* 994–997. c) T. K. Hyster, D. M. Dalton, T. Rovis, *Chem. Sci*. **2015**, *6*, 254–258. d) N. J. Webb, S. P. Marsden, S. A. Raw, *Org. Lett.* **2014**, *16*, 4718–4721. e) M. D. Wodrich, B. Ye, J. F. Gonthier, C. Corminboueuf, N. Cramer, *Chem. Eur. J.* **2014**, *20*, 15409–15418. f) J. R. Huckins, E. A. Bercot, O. R. Thiel, T. -L. Hwang, M. M. Bio, *J. Am. Chem. Soc.* **2013**, *135*, 14492–14495. g) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science* **2012**, 338, 500–503. h) B. Ye, N. Cramer, *Science* **2012**, *338*, 504–506. i) H. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 7318–7322. j) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353. k) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457.

[186] For examples about cyclocarbonylation of amines by palladium catalysis, see: a) J. Albert, X. Ariza, T. Calvet, M. Font Bardia, J. Garcia, J.Granell, A. Lamela, B. López, M. Martinez, L. Ortega, A. Rodriguez, D. Santos, *Organometallics* **2013**, *32*, 649–659. b) B. López, A. Rodriguez, D. Santos, J. Albert, X. Ariza, J. Garcia, J. Granell, *Chem. Commun.* **2011**, *47*, 1054–1056.

[187] For examples about Friedel-Crafts reactions, see: a) R. Murashige, Y. Ohtsuka, K. Sagisawa, M. Shiraishi, *Tetrahedron Lett.* **2015**, *56*, 3410–3412. b) S. R. Angle, J. P. Boyce, *Tetrahedron Lett*. **1995**, *36*, 6185–6188. c) J. F. Stambach, L. Jung, *Tetrahedron* **1985**, *41*, 169–172.

[188] For examples about substitutions reactions, see: a) Q. He, N. Chatani, *J. Org. Chem.* **2018**, *83*, 13587–13594. b) B. Müjde, S. Özcan, M. Balci, *Phytochemistry Letters* **2011**, *4*, 407–410.

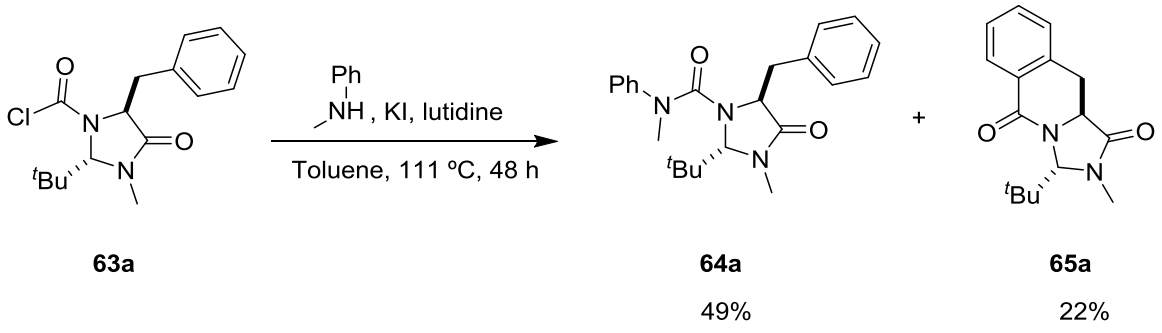


Scheme 72. Synthesis of 3,4-dihydroisoquinolones.

Although radical cyclization has emerged as a powerful method for the construction of this kind of heterocycles,[189] the majority of the examples need powerful activating agents or Lewis acids.

4.2. Group precedents and limitations

Previous work in the Clayden group in the context of general synthesis of enantiomerically enriched α-arylated quaternary amino acids explored the coupling of phenylalanine derived carbamoyl chloride **63a** with *N*-methyl aniline to form the corresponding urea **64a**.[190] However, an unusual tricyclic byproduct **65a** was observed, which appears to be the result of an intramolecular Friedel-Crafts-type acylation (Scheme 73).



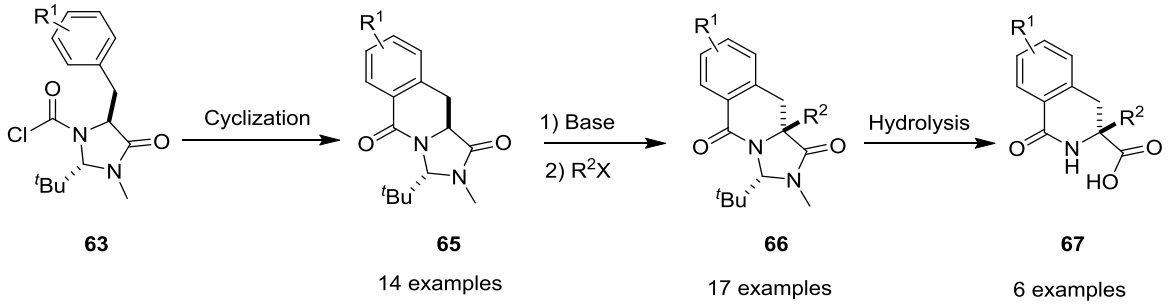
63a **64a** 49% **65a** 22%

Scheme 73. Reaction of carbamoyl chloride **63a**.

[189] For radical cyclizations, see: a) S. Zou, S, Geng, L. Chen, H. Wang, F. Huang, *Org. Biomol. Chem.* **2019**, *17*, 380–387. b) W. Zhou, S. Ni, H. Mei, J. Han, Y. Pan, *Org. Lett.* **2015**, *17*, 2724–2727. c) N. Cholleton, S. Z. Zard, *Tetrahedron Lett.* **1998**, *39*, 7295–7298.
[190] D. J. Leonard, J. W. Ward, J. Clayden, *Nature* **2018**, *562*, 105–109.

The generation of the lactam **65a** under these conditions seemed quite remarkable as similar Friedel-Crafts cyclizations of unactivated arenes typically require the use of strong and often highly toxic Lewis acids.[187] In an attempt to maximize the yield of the tricyclic byproduct **65a**, the reaction was performed in the absence of the competing nucleophile *N*-methylaniline, obtaining the target product **65a** in good yields (88%) as a single diastereomer.

This new methodology has been exploited in the Clayden group over recent years. In such a way, in 2018, they reported an intramolecular KI-promoted Friedel-Crafts cyclization of *N*-chloroformylimidazolidinones derived from aromatic amino acids, such as *L*-phenylalanine, which provides an efficient synthesis of certain substituted 3,4-dihydroisoquinolones (Scheme 74).[191]



Scheme 74. General procedure for the synthesis of 3,4-dihydroisoquinolones. Clayden, 2018.

This methodology was highly tolerant of a wide range of functional groups. However, for cyclization to proceed using this protocol, commercial amino acids already containing an aryl moiety are required. As far as it is known, only four of the twenty one proteinogenic amino acids can be used for this kind of cyclization (Figure 41a). However, there are other unnatural commercial amino acids, such as phenylglycine (Figure 41b) which can be used, although the price can be an inconvenience. In light of this limitation, alternative synthetic pathway was proposed to circumvent this limitation.

[191] M. M. Amer, A. C. Carrasco, D. J. Leonard, J. W. Ward, J. Clayden, *Org. Lett.* **2018**, *20*, 7977–7981.

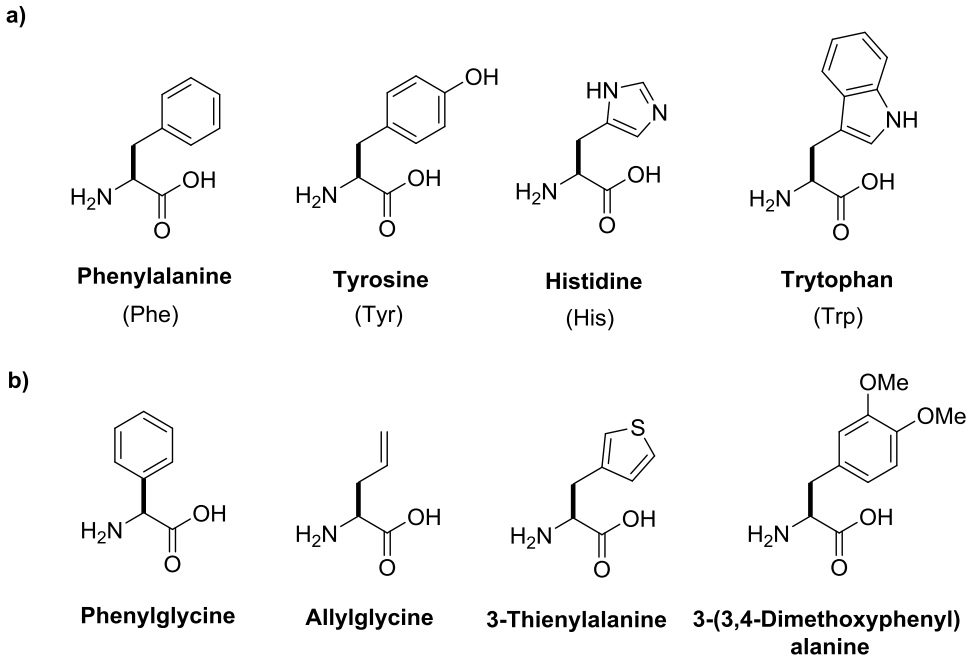
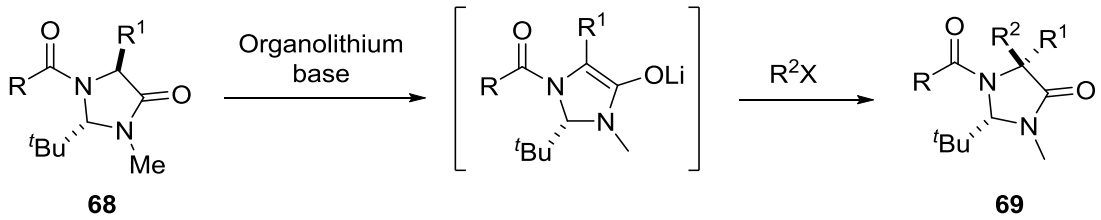


Figure 41. a) Proteinogenic aromatic amino acids. b) Some examples of unnatural but commercial amino acids.

4.3. Synthetic plan

According to the 'Self-Regeneration of Stereocenters' (SRS) principle developed by Dieter Seebach in the mid 1990s,[192] imidazolidinone motifs such as **68** can be deprotonated using organolithium bases such as LDA, to give non-racemic enolates which can undergo stereoselective alkylation when reacted with a wide range of commercial electrophiles, such as alkyl halides or allylic halides, to give quaternary amino acid derivatives **69** (Scheme 75).

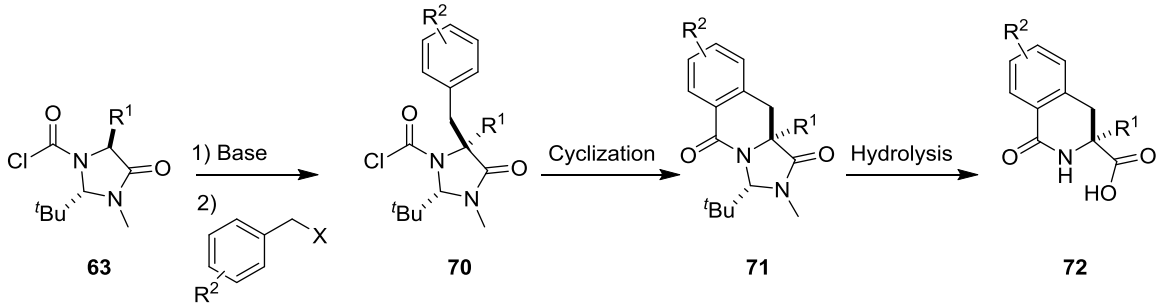


Scheme 75. Seebach´s "Self-Regeneration of Stereocenters" principle *via* chiral imidazolidinone intermediates.

It was envisaged that structures such as **63** may also be stereoselectively alkylated in a similar fashion. Moreover, these kind of adducts are potential substrates to form isoquinolone derivatives by intramolecular Friedel-Crafts cyclization. Adding the different benzyl components, which allow the cyclization step, we would be able to synthesize much wider range of lactams. Furthermore, these imidazolidinones, which

[192] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748.

play no further role in the synthesis, can be hydrolyzed to provide substituted 3,4-dihydroisoquinolones (Scheme 76).



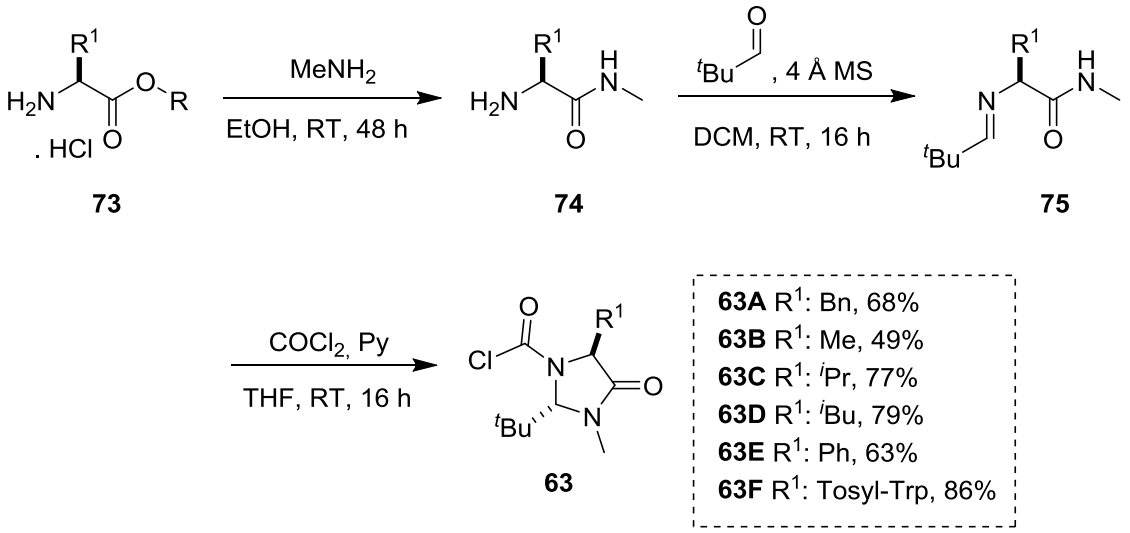
Scheme 76. General procedure for the synthesis of quaternary amino acid derivatives employing the alternative methodology.

Using this modified protocol would allow the preparation of quaternary amino acid derivatives **72** that could not be accessible by the other route described above.[191] Besides that, this synthetic route opens the possibility of accessing the opposite enantiomer of the quaternary amino acid (**67** vs. **72**).

4.4. Scope of diastereoselective alkylation

The *trans*-*N*-chloroformylimidazolidinone derivatives **63** were readily formed from the corresponding commercial amino ester hydrochloride salts **73**, following a three steps protocol, which has been optimized during the last two years to give only the *trans*-isomer **63** in excellent yields (Scheme 77).[193] The first step involves the formation of *N*-methylamide **74** upon treatment of commercial optically pure amino ester hydrochloride **73** with methyl amine.[194] After isolating this compound without further purification, the synthesis of the imine **75** was carried out in anhydrous medium. And finally, once the imine **75** had been formed, the desired *trans*-*N*-chloroformylimidazolidinone **63** was achieved in good yields (49-86%) *via* a phosgenation/ring closure reaction. This methodology was highly tolerant of a wide range of commercial amino acids.

[193] M. M. Amer, H. Abas, D. J. Leonard, J. W. Ward, J. Clayden, *J. Org. Chem.* **2019**, *84*, 7199–7206.
[194] L. Samulis, N. C. O. Tomkinson, *Tetrahedron* **2011**, *67*, 4263–4267.



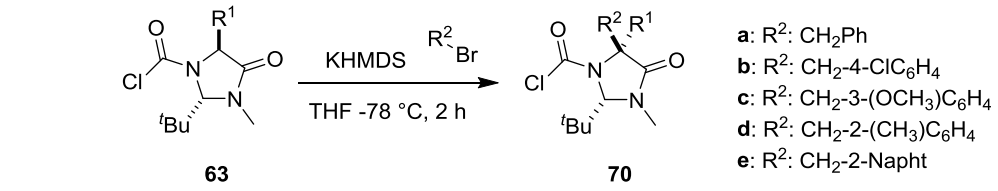
73 **74** **75** **63**

Scheme 77. General procedure for the synthesis of *trans*-*N*-chloroformylimidazolidinones **63**.

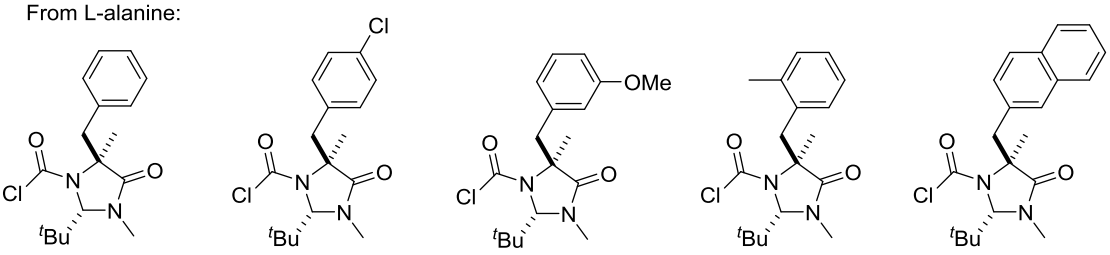
The preliminary studies within the Clayden group[191] had established the optimal conditions for the alkylation. Treatment of the *trans*-*N*-chloroformylimidazolidinones **63** with KHMDS and the corresponding benzyl bromide at -78 °C resulted in clean and stereoselective alkylation. The products were always isolated as single diastereomers. Satisfactorily, the alkylation of the alanine derivative **63B** with different benzyl bromide derivatives were universally successful (Table 22). Good yields (46-66%) were observed in each case irrespective of the nature of the electrophiles used. Electron-neutral (compounds **70Ba**) and electron-rich aryl rings (compounds **70Bc** and **70Bd**) were well tolerated. Moreover, alkylation with 4-chlorobenzyl bromide and 2-(bromomethyl)naphthalene also proceeded satisfactorily (compounds **70Bb** and **70Be**).

In order to investigate the scope further, extension of the strategy to derivatives of other proteinogenic and commercial amino acids was undertaken. Fortunately, the existing method was found to be directly transferable to these substrates (compounds **70Aa**, **70Ca**, and **70Ea**), affording the corresponding quaternary *trans*-*N*-chloroformylimidazolidinone derivatives in good yields (54-80%). However, the alkylation of *trans*-*N*-chloroformylimidazolidinone derivatives of leucine **63D** and tryptophan **63F** were unsuccessful using the previous conditions (Table 23, entry 1 and entry 4).

Table 22. Compounds obtained by alkylation of *trans-N*-chloroformylimidazolidinones **63**.[a]

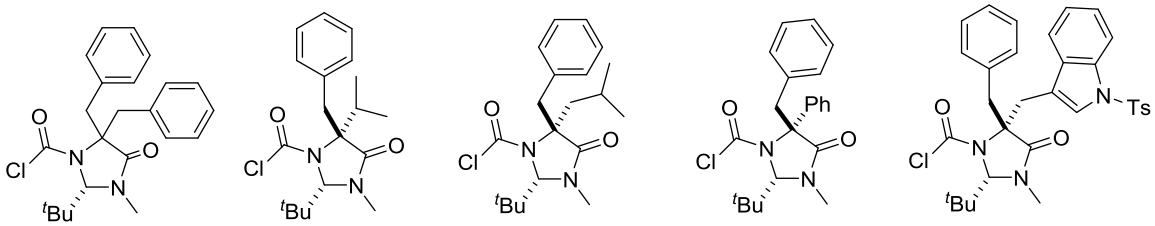


From L-alanine:



70Ba	**70Bb**	**70Bc**	**70Bd**	**70Be**
65%	74%	46%	59%	65%

From other L-amino acids:



70Aa	**70Ca**	**70Da**	**70Ea**	**70Fa**
84%	54%	no desired product	80%	no desired product

[a] Reactions carried out at 0.1 mmol scale, using 1.1 equiv. of KHMDS and the corresponding benzyl bromide at -78 °C. Yield after isolation of the product after chromatography.

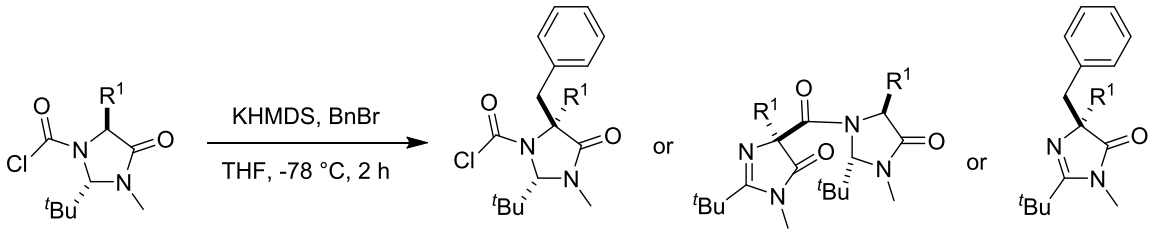
The result of the reaction with the leucine derivative **63D** was something unexpected given that the valine derivative worked well and provided the product **70Ca** in good yield (54%). In the first attempt, the desired product was not detected, and instead the dimmer **76** was isolated, which was formed after the *in situ* generated enolate reacted with another molecule of the starting material, followed by the loss of the carbonyl chloride moiety (Table 23, entry 1).[195] In order to ensure complete enolization of the starting material, **63D** was left in the presence of 2.0 equiv. of KHMDS for a prolonged time of 30 minutes, instead of the typical 5 minutes. However, once again the desired product was not detected, and in this occasion oxidative product **77**

[195] This structure was confirmed using 2D NMR experiments and mass spectroscopy analysis.

was detected (entry 2). Next, the reaction was conducted with the addition of the benzyl bromide before the addition of KHMDS, in order to promote the reaction of the enolate with the benzyl bromide and not with another molecule of starting material. Pleasingly, the desired product was isolated in excellent yield (90%, entry 3).

Preliminary experiment with the tryptophan derivative **63F** showed decomposition of the starting material, which may be related to the instability of the tosyl protecting group under the reaction conditions (entry 4). In order to study the importance of the protecting group, cleavage of the tosyl group using magnesium was attempted. However, no promising results were obtained, due to the decomposition of compound **63F**. In view of the success of the leucine derivative, the benzyl bromide was similarly added before the base, and once again we were delighted to obtain the desired product in excellent yield (87%, entry 5).

Table 23. Optimization of the alkylation of tryptophan and leucine derivatives (**63D**-**63F**).



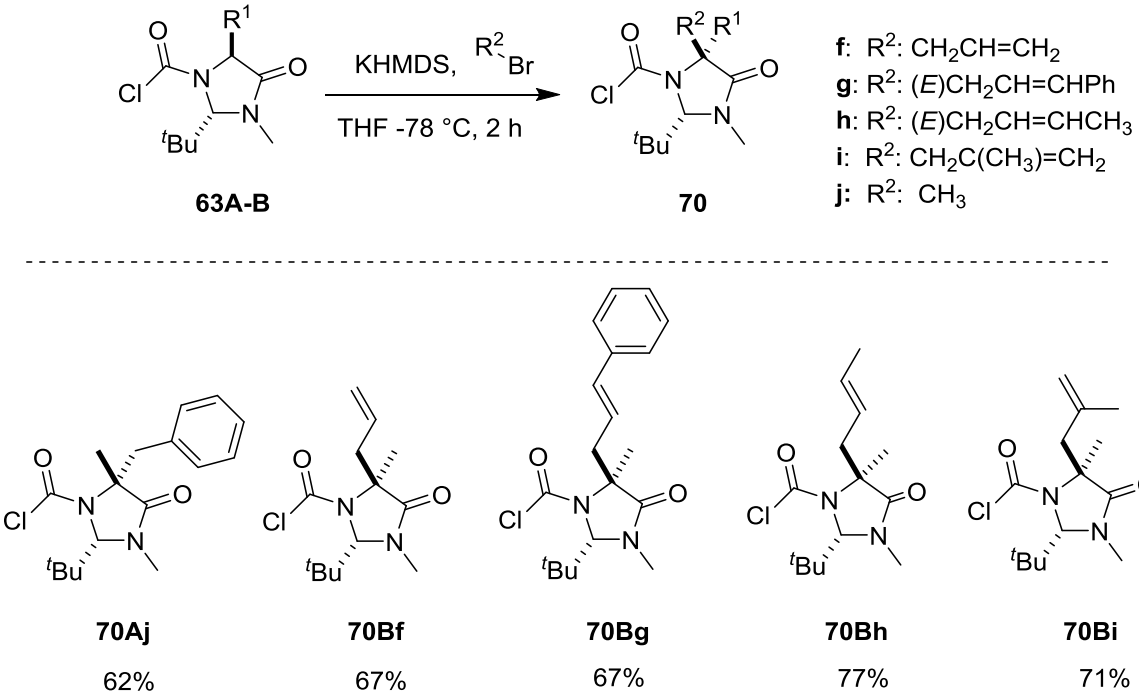
63D, **63F** **70** **76** **77**

Entry	Starting material (R^1)	Time allowed for the formation of enolate	Product[d] (%) (**70**/**76**/**77**)
1[a]	**63D (*i*Bu)**	5 min	--/53/--
2[b]	**63D (*i*Bu)**	30 min	--/--/73
3[c]	**63D (*i*Bu)**	---	90/--/--
4[a]	**63F (Tosyl-Trp)**	5 min	--/--/--
5[c]	**63F (Tosyl-Trp)**	---	87/--/--

[a] Reactions carried out at 0.1 mmol scale, using 1.1 equiv. of KHMDS and benzyl bromide at -78 °C. [b] 2.0 equiv. of KHMDS was added. [c] The benzyl bromide was added before addition of the base. [d] Yield after isolation of the product after chromatography.

The reaction scope using **63A** and **63B** was then explored with an array of allyl halides, including methyl iodide. As illustrated in Table 24, the results were good in all cases.

Table 24. Compounds obtained by alkylation of *trans*-*N*-chloroformylimidazolidinones **63A** and **63B**.[a]



[a] Reactions carried out at 0.1 mmol scale, using 1.1 equiv. of KHMDS and the corresponding allyl bromide at -78 °C. Yield after isolation of the product after chromatography.

It is worth mentioning that both the starting material imidazolidinone **63** and the alkylated quaternary derivatives **70** displayed hindered rotation about the amide bond leading to broad rotameric signals in ^{1}H and ^{13}C spectra at room temperature. To confirm this, VT NMR experiments (variable temperature nuclear magnetic resonance experiments) were carried out. ^{1}H NMR spectrum of **70Ba** in deuterated toluene was obtained at elevated temperatures (Figure 42). The two singlet signals that appear at 4.3 ppm at room temperature, which corresponds to the aminal proton (H^{1}), coalesce at 100 °C, indicating that we have a mixture of two rotamers (due to the hindered rotation) and not a *cis*-/*trans*- diastereomeric mixture of the two imidazolidinones.

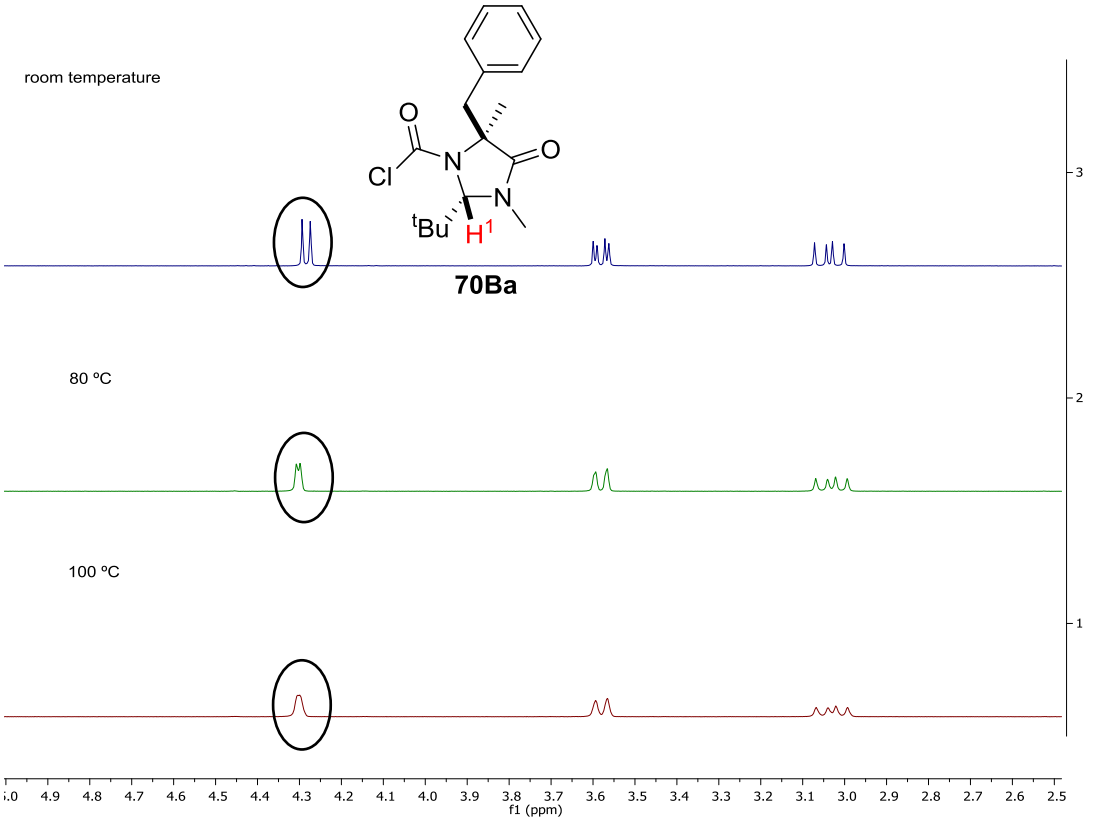
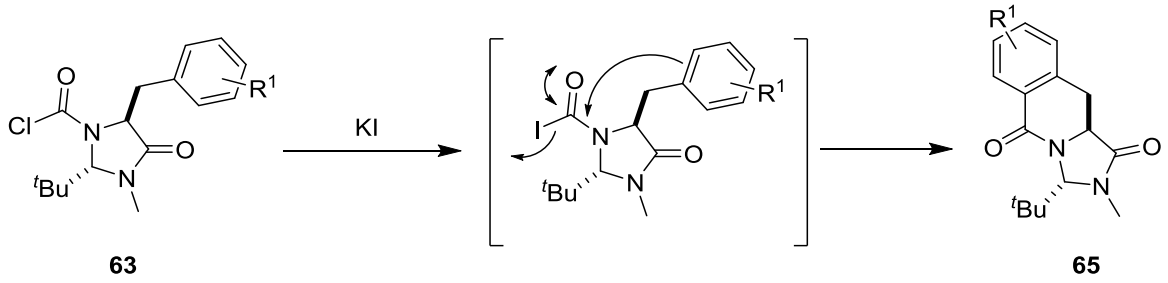


Figure 42. ^{1}H NMR spectrum at different temperatures of compound **70Ba**.

4.5. Cyclocarbonylation of quaternary imidazolidinones

Preliminary studies within the Clayden group[191] had established the optimal conditions for the cyclization of suitable tertiary *trans*-*N*-chloroformylimidazolidinone derivatives **63** (Scheme 78). Thus, the same conditions were employed on quaternary *trans*-*N*-chloroformylimidazolidinone derivatives **70**. It was known that KI[196] had a crucial role in the cyclization. It has been suggested that nucleophilic addition of I^- into carbonyl occurs to give the transient carbamoyl iodide thus increasing the rate of the acylation. The base, the temperature and the solvent have also important roles in the cyclization. For example, it was shown that the base acted to sequester the acid generated (HI and HCl) during the reaction, thereby driving the reaction forward. Moreover, the use of microwave conditions reduced reaction times significantly by allowing the use of temperatures above the boiling point of the solvent employed (boiling point of acetonitrile: 81-81 °C).

[196] R. J. Wakeham, J. E. Taylor, S. D. Bull, J. A. Morris, J. M. J. Williams, *Org. Lett.* **2013**, *15*, 702–705.

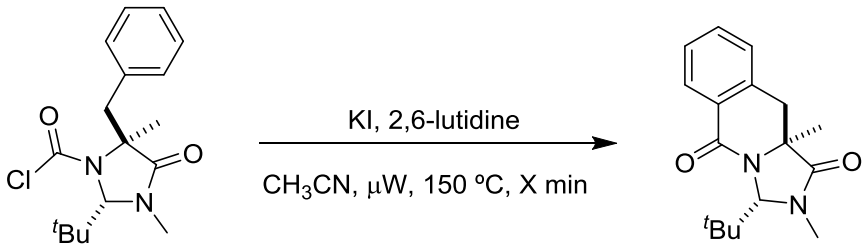


Scheme 78. Proposed mechanism for the cyclization.

4.5.1. Cyclization of quaternary aryl imidazolidinone derivatives

The study began with the alanine derived imidazolidinone **70Ba**. Although the first attempt showed only 18% conversion, the result was promising since the desired product **71Ba** was detected under these conditions (Table 25, entry 1). The reaction was attempted for a longer period of time. The cyclization was almost complete over 90 minutes (entry 3) giving the product in 85% yield. However, after two hours complete conversion was observed albeit the yield of isolated product was only slightly better (entry 4).

Table 25. Optimization of the cyclization of compound **70Ba**.[a]



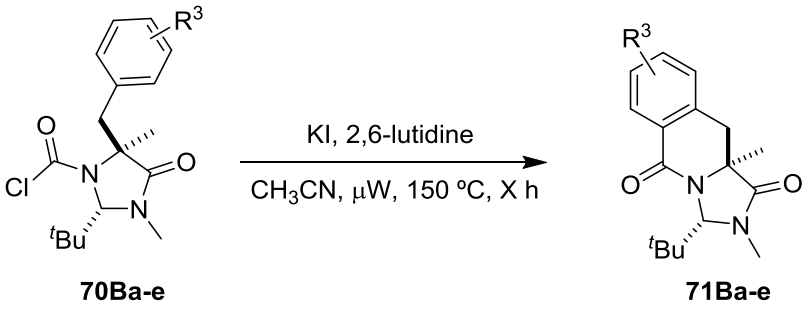
Entry	T (min)	Conv. (%)[b]	Yield[c]
1	5	18	12
2	60	91	83
3	90	>95	85
4	120	>99	87

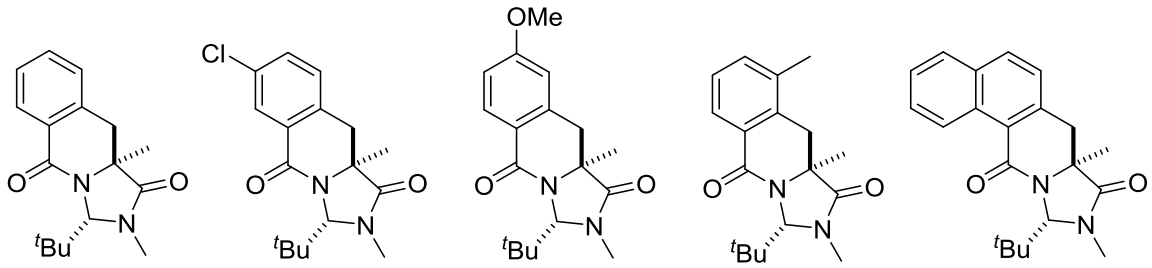
[a] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for X min. [b] Conversion detected by ^1H NMR analysis of the crude reaction mixture. [c] Yield after isolation of the product after chromatography.

In light of this result, the scope of the reaction was then explored employing the conditions described in entry 4 (Table 25). The study involved the reaction of quaternary *trans*-imidazolidinone derived from alanine **70B** using the optimized reaction conditions

(Table 26). It is known that the nature of the substitution on the aryl ring has an effect on the reactivity and regioselectivity of the acylation. Whilst activating groups in the aromatic ring increase reactivity, the electron deactivating groups have the adverse effect. In most cases, the activating groups are *ortho*- and *para*- directing, whereas deactivating groups are *meta*- directing.

Table 26. Scope of the cyclization of quaternary *trans*-imidazolidinones derived from alanine **70B**.



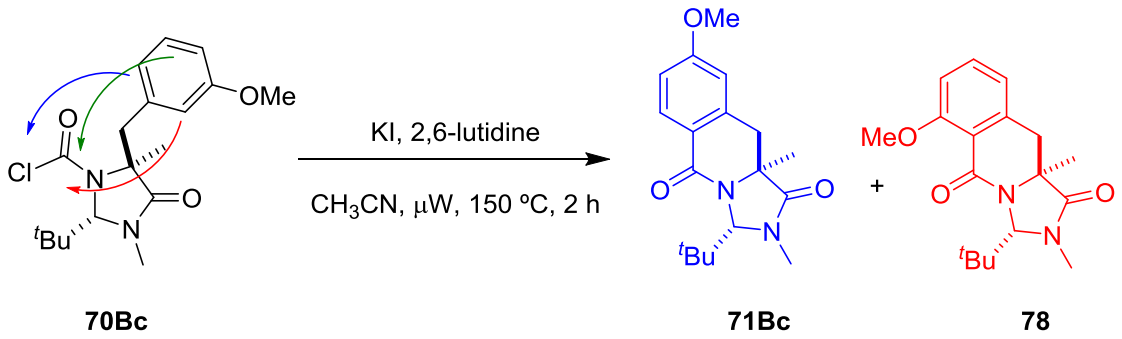


71Ba	**71Bb**	**71Bc**	**71Bd**	**71Be**
2 h, 87%	4 h, 54%	2 h, 76%	4 h, 89%	2 h, 87%

[a] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for 2-4 h. Yield after isolation of the product after chromatography.

Cyclization of compound **70Bc** highlights the effect the substituent can have. Thus, cyclization of compound **70Bc** can potentially occur at three different positions (two-*ortho* and one-*para*) (Scheme 79). However, only two products (**71Bc** and **78**, 88/12) were obtained.[197] Reaction at the *para*- position to the alkyl chain does not occur as this would provide the less thermodynamically stable eight-member ring lactam. Moreover, due to the steric constraints exerted by the methoxy group, the reaction forming compound **71Bc** was more favorable, giving the product in 76% yield.

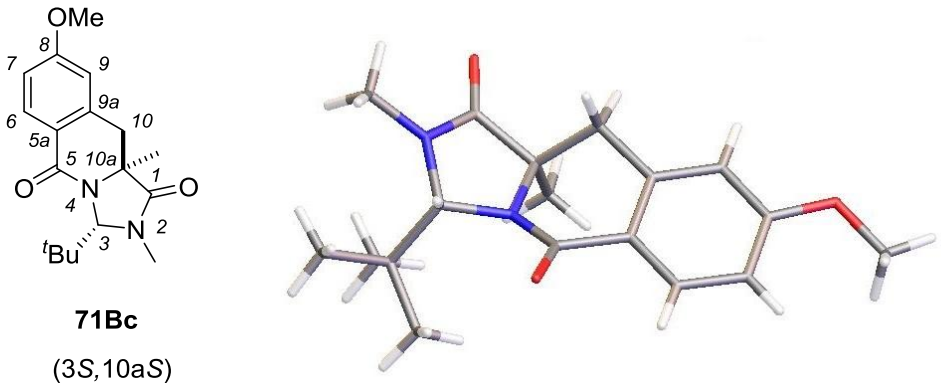
[197] Ratio measured in the ^{1}H NMR of the crude reaction mixture.



70Bc **71Bc** **78**

Scheme 79. Cyclization of compound **70Bc**.

The stereochemistry of the cyclic product **71Bc** was confirmed by X-ray crystallography (Figure 43). The X-ray crystal structure clearly shows that the methyl and the ^{t}butyl group are on the same face. Configuration of remaining compounds was assigned by analogy and by assuming a uniform reaction mechanism.



71Bc

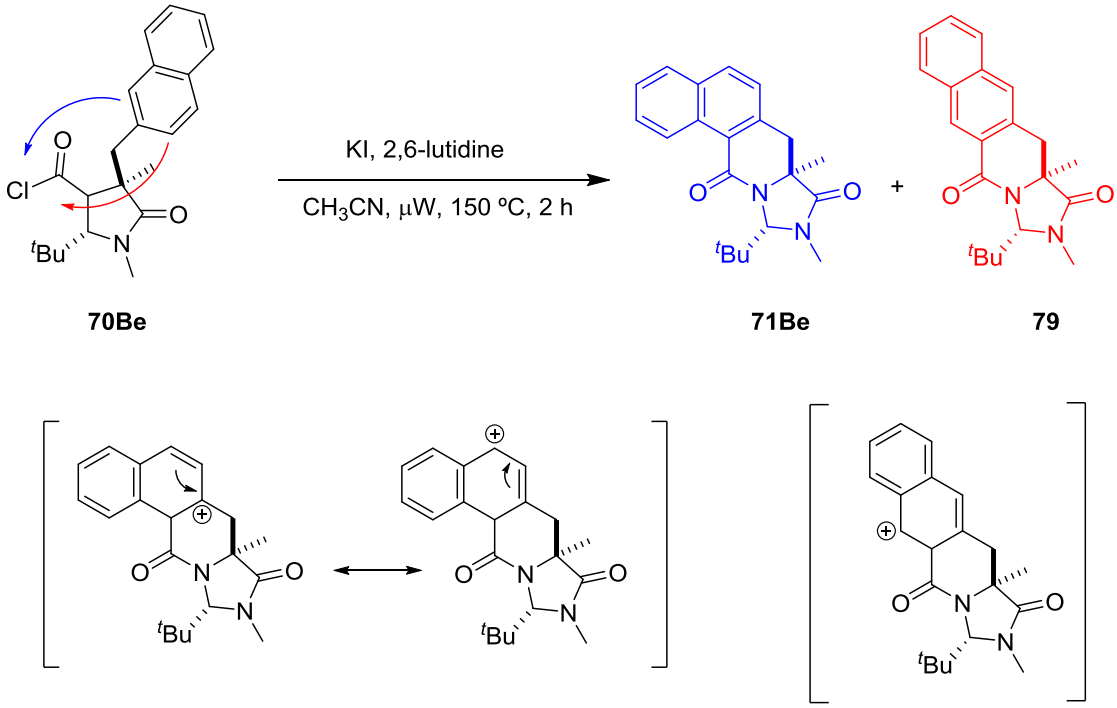
(3*S*,10a*S*)

Figure 43. ORTEP diagram of compound **71Bc**.

Other representative examples include lactams **71Bb** and **71Bd**, involving a chloro and methyl groups respectively, both of which are *ortho*- and *para*- directors, but the products obtained were those from reaction at the *meta*- position. This clearly highlights that the formation of the more stable six-member ring overrides the inherent reactivity of the aryl ring in the acylation step. Due to the fact that the halogens are weakly deactivating groups, prolonged reaction times were needed to reach full conversion of **71Bb**. Similarly lengthened reaction times were required for the *ortho*-methyl derivative **70Bd**, in this case, the reason for the longer reaction time could be related to the steric effect of the methyl group.

Another interesting example was the formation of compound **71Be**. Here, two possible six-member cyclic products could be formed (**71Be** and **79**); however only product **71Be** was isolated. Probably the main reason that justifies this result is the different stability of the corresponding intermediates leading to both products. The

most favorable resonance structures for either intermediate are those that have one fully aromatic ring. As shown in Scheme 80, **71Be** was more favorable because the positive charge can be distributed over two positions, leaving one aromatic ring unchanged; whereas only one resonance structure was possible for the other product **79**, without disruption of the second aryl ring.



Scheme 80. Two possible products of the cyclization of quaternary imidazolidinone **70Be**.

The structure of the product **71Be** was confirmed using COSY 2-D NMR experiments. In the case of **71Be**, one might expect to see a COSY correlation between the aromatic protons H-5 and H-6 (Figure 44), which would not be present for compound **79**, and instead there would be two single peaks corresponding to H-15 and H-18. Although it might seem possible that H-15 and H-18 can be coupled to H-19 or H-22 respectively, however, examples of similar compounds have been found in the literature and it is clear that they exist as singlets.[198] The COSY spectrum (Figure 45) revealed that there was correlation between H-5 and H-6 indicating that the product of the reaction was compound **71Be** and not **79**.

[198] For proton spectra of similar compounds, see: Z. Zhang, R. Sangaiah, A. Gold, L. M. Ball, *Org. Biomol. Chem.* **2011**, *9*, 5431–5435. To see similar proton spectra of compound **71Be**, see: Figure S29 (experimental section). To see similar proton spectra of compound **79**, see: Figure S47 (experimental section).

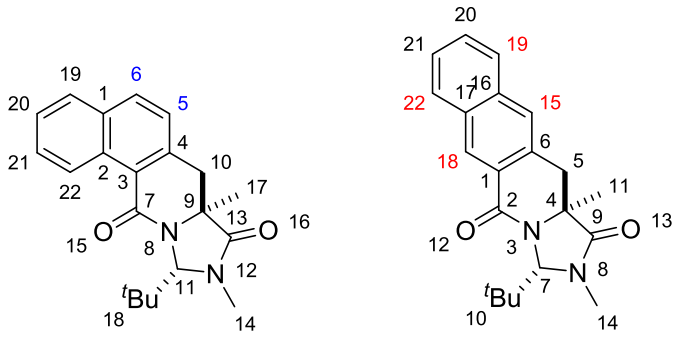


Figure 44. Proposed structures for naphthalene cyclic product.

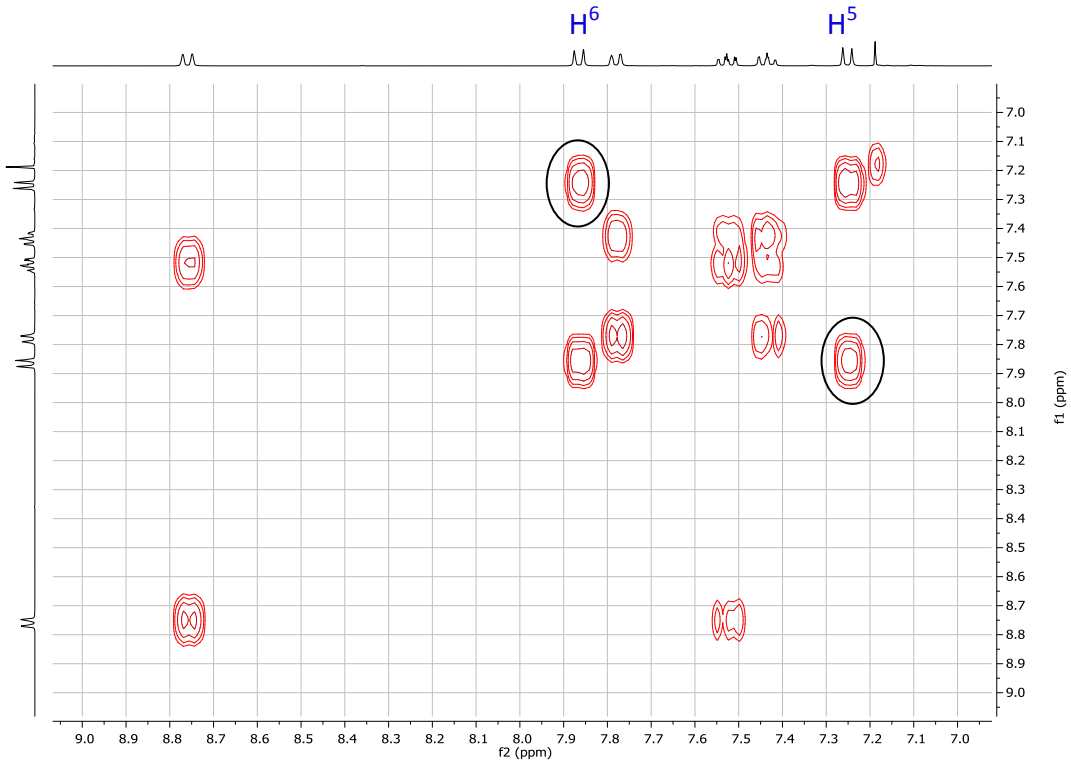
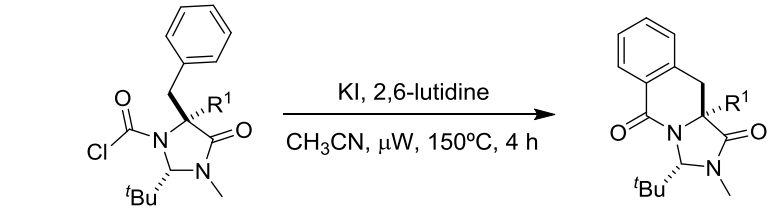


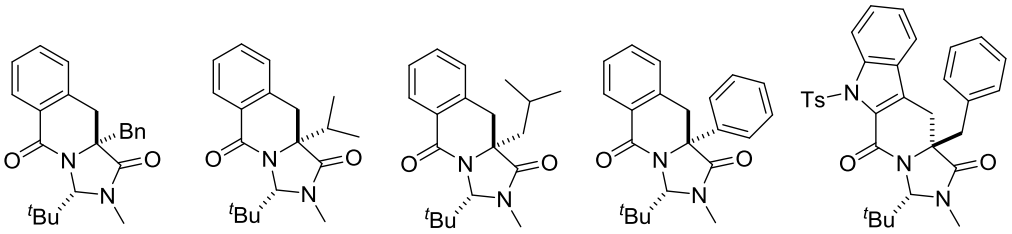
Figure 45. COSY NMR spectrum for naphthalene cyclic product.

When the cyclizations were performed with bulkier groups on the same face as the *tert*-butyl group, longer reaction times were necessary (Table 27). The reactions were carried out in good yields with phenylalanine (63%, compound **71Aa**), as well as the more hindered branched structure derived from valine (64%, compound **71Ca**), leucine (84%, compound **71Da**) or phenylglycine (71%, compound **71Ea**), although the yields are slightly lower than the alanine derivatives. Moreover, in the case of the tryptophan derived *N*-chloroformylimidazolidinone **70Fa**, cyclization of the more reactive indole ring was observed, even though this ring is oriented in the most hindered face.

Table 27. Scope of the cyclization of quaternary *trans*-imidazolidinones derived from amino acids other than alanine.



70 **71**

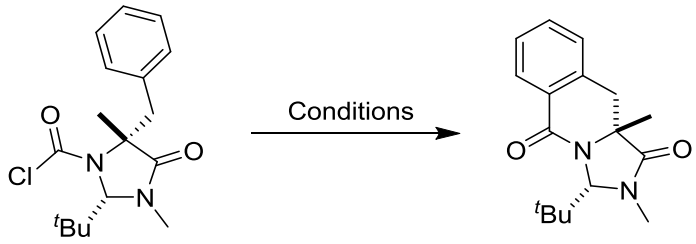


71Aa	**71Ca**	**71Da**	**71Ea**	**71Fa**
71%	64 %	84%	63%	53%

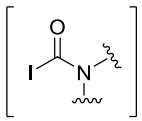
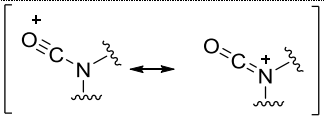
[a] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for 4 h. Yield after isolation of the product after chromatography.

Next, we wished to explore whether the *trans* relationship between the ^{t}butyl group and the aryl ring was necessary for the cyclization to occur. Thus, the cyclization of the quaternary imidazolidinone **70Aj** was investigated. No cyclization occurred and the desired product was not detected. It was observed that when the reaction times were long, the starting material decomposed to give a complex mixture (Table 28, entry 1), whereas if short reaction times were used, there was no conversion (entry 2). After finishing my stay, Dr. Hossay Abas, in terms of comparison, performed the same cyclization using the more forcing conditions ($AlCl_3$ in hot dichloroethane). In this way, satisfactory results were obtained (entry 3, 83% yield). These differences in reactivity suggest that different intermediates are generated. Thus, we propose that KI leads to transient carbamoyl iodide,[196] whereas $AlCl_3$ promotes formation of an *N*-acyllium ion, with the carbamoyl iodide being more sensitive to the geometry of imidazolidinone substituents.

Table 28. Cyclization of *cis*-imidazolidinone **70Aj**.



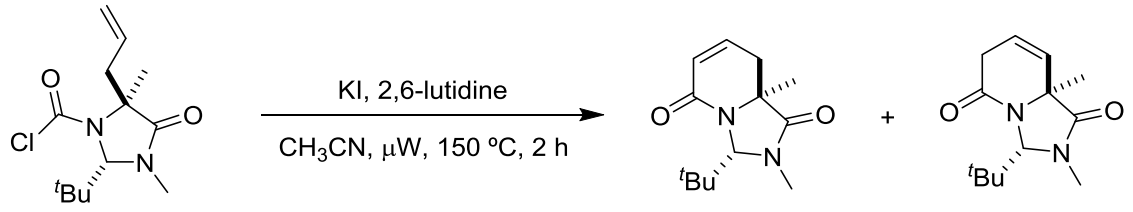
70Aj **81**

Entry	Conditions	Intermediates	Yield of isolated product[c]
1[a]	KI, 2,6-lutidine, μW, CH_3CN, 120 min		Complex mixture
2[a]	KI, 2,6-lutidine, μW, CH_3CN, 5 min		Starting material
3[b]	$AlCl_3$, 1,2-DCE, 80 °C, 18 h		83%

[a] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for X min. [b] Reaction carried out at 0.15 mmol scale, using 3.0 equiv. of $AlCl_3$ in 1.5 mL of 1,2-DCE at 80 °C for 18 h. [c] Yield after isolation of the product after chromatography.

4.5.2. Cyclization of quaternary allyl imidazolidinone derivatives

In order to further investigate the scope of the methodology, it was suggested to explore the cyclization using an allyl group instead of the aryl group. The cyclization reaction was attempted with compound **70Bf** using the optimized microwave conditions for two hours. This afforded two major products, the desired product **71Bf** and its isomer **82** (Scheme 81).

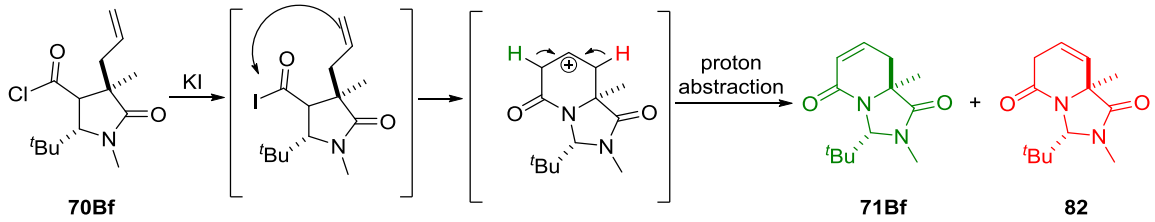


70Bf **71Bf** 39% **82** 50%

Scheme 81. Products obtained by cyclization of quaternary *trans*-carbamoyl chloride **70Bf**.

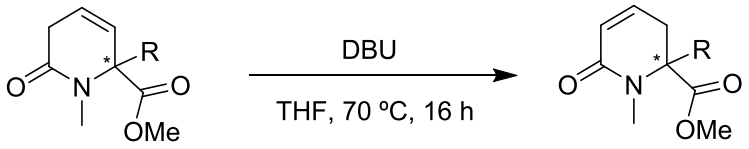
After nucleophilic attack of the double bond to the carbamoyl group a carbocation is generated which can form either of the two observed isomers depending on which proton is removed (Scheme 82). The ratio of the two compounds in the crude

reaction was about 45:55 conjugated **71Bf**/unconjugated **82**,[199] suggesting that the formation of compound **82** was slightly favored under the reaction conditions. Alternatively, it might be the case that the compound undergoes isomerization under the reaction conditions after the cyclization step.



Scheme 82. Cyclization reaction of quaternary *trans*-carbamoyl chloride **70Bf**.

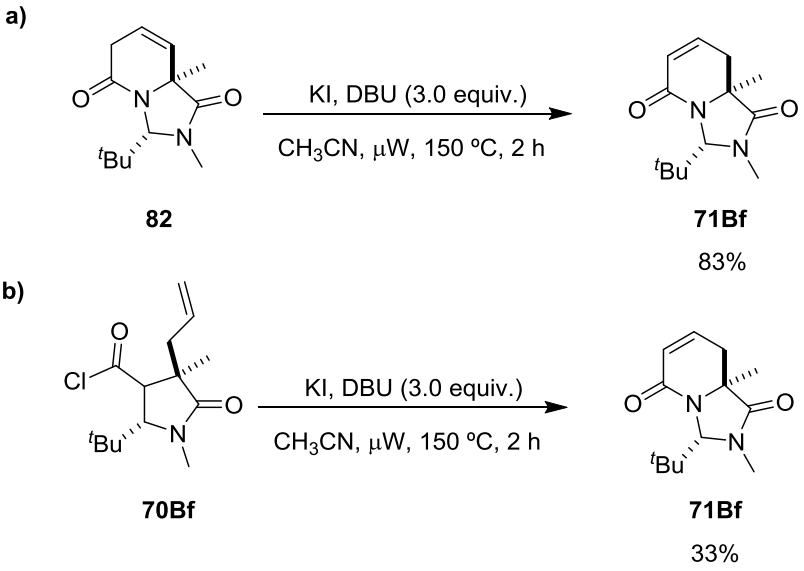
However, it may be possible to obtain exclusively the desired product, employing DBU as base to isomerize the C=C double bond, as Waltn *et al.* described in a very similar compound (Scheme 83).[200]



Scheme 83. Isomerization step for the synthesis of α,β-unsaturated carbonyl compound **84**.

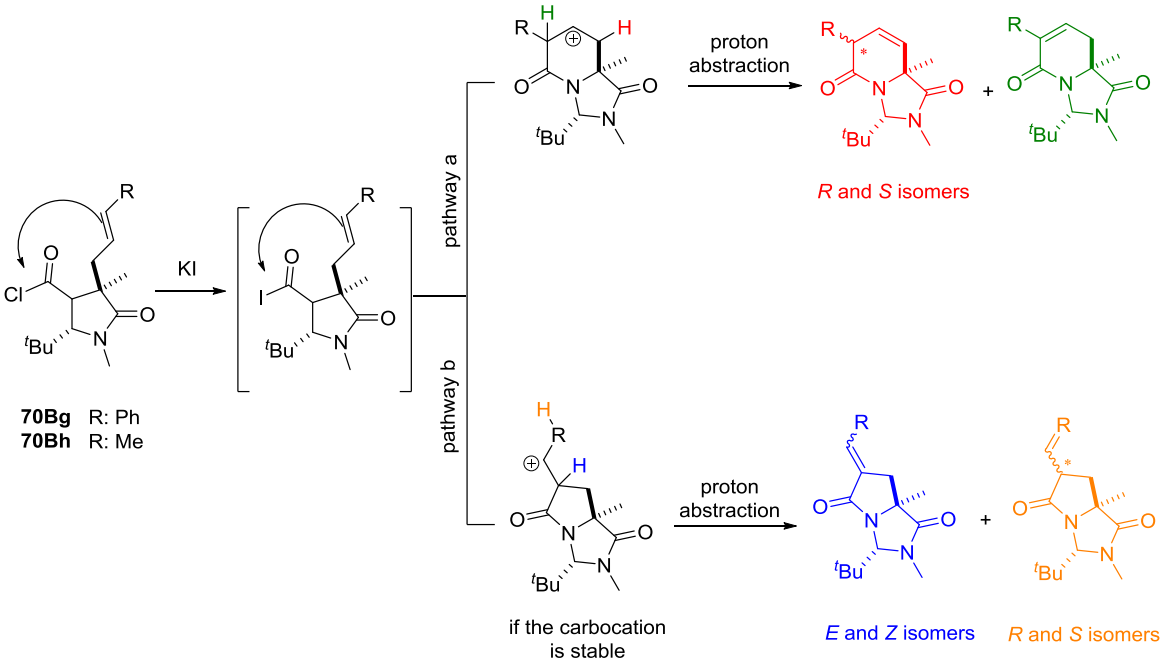
Several experiments were performed with the objective of increasing the yield of the desired product **71Bf**. In a first experiment, to establish whether the isomerization could be successfully achieved, the isomerization of the isolated compound **82** was carried out in presence of 3.0 equiv. of DBU. Heating the unconjugated isomer **82** in the microwave in CH_3CN at 150 °C in presence of DBU resulted in total conversion to desired isomer **71Bf** (Scheme 84a). We then wondered whether DBU could be used from the beginning to promote the cyclization as well as the subsequent isomerization to afford the desired product in one step (Scheme 84b). Surprisingly, the yield plummeted, due to the formation of a byproduct, which could not be identified. This decrease in the value of the yield might be due to the instability of the starting material in the presence of DBU, which is a stronger base than 2,6-lutidine.

[199] The ratio was detected by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture.
[200] T. J. Donohoe, M. J. Connolly, L. Walton, *Org. Lett.* **2009**, *11*, 5562–5565.



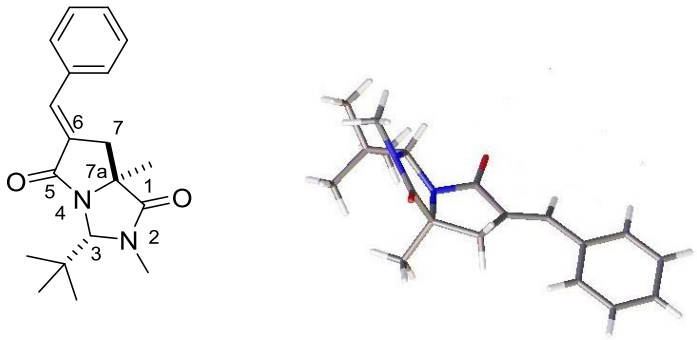
Scheme 84. Optimization of the formation of compound **71Bf**.

In light of the successful cyclization of the allyl group, we then looked to investigate more substituted allyl derivatives (compounds **70Bg** and **70Bh**) to explore the reactivity and regioselectivity of the reaction. Exposure of quaternary imidazoldinones to cyclization conditions revealed a new competitive reaction (Scheme 85, pathway b), the formation of the carbocation on the adjacent carbon, which forms a five-member ring upon loss of proton. Moreover, in this case, there were two possible products, depending on which proton was removed.



Scheme 85. Proposed pathways for the synthesis of all possible products.

The first experiment was conducted on compound **70Bg** containing a Ph group. Here, two products **85**/**86** were detected (in a 70/30 ratio which was detected by ^{1}H NMR analysis of the crude reaction mixture), which were separable by column chromatography. Identification of the structures of the two compounds proved challenging using NMR analysis alone. Fortunately, an X-ray crystal structure was obtained for the major product **85**, which allowed us to assign it as the five-member lactam with *E*-alkene configuration (Figure 39).

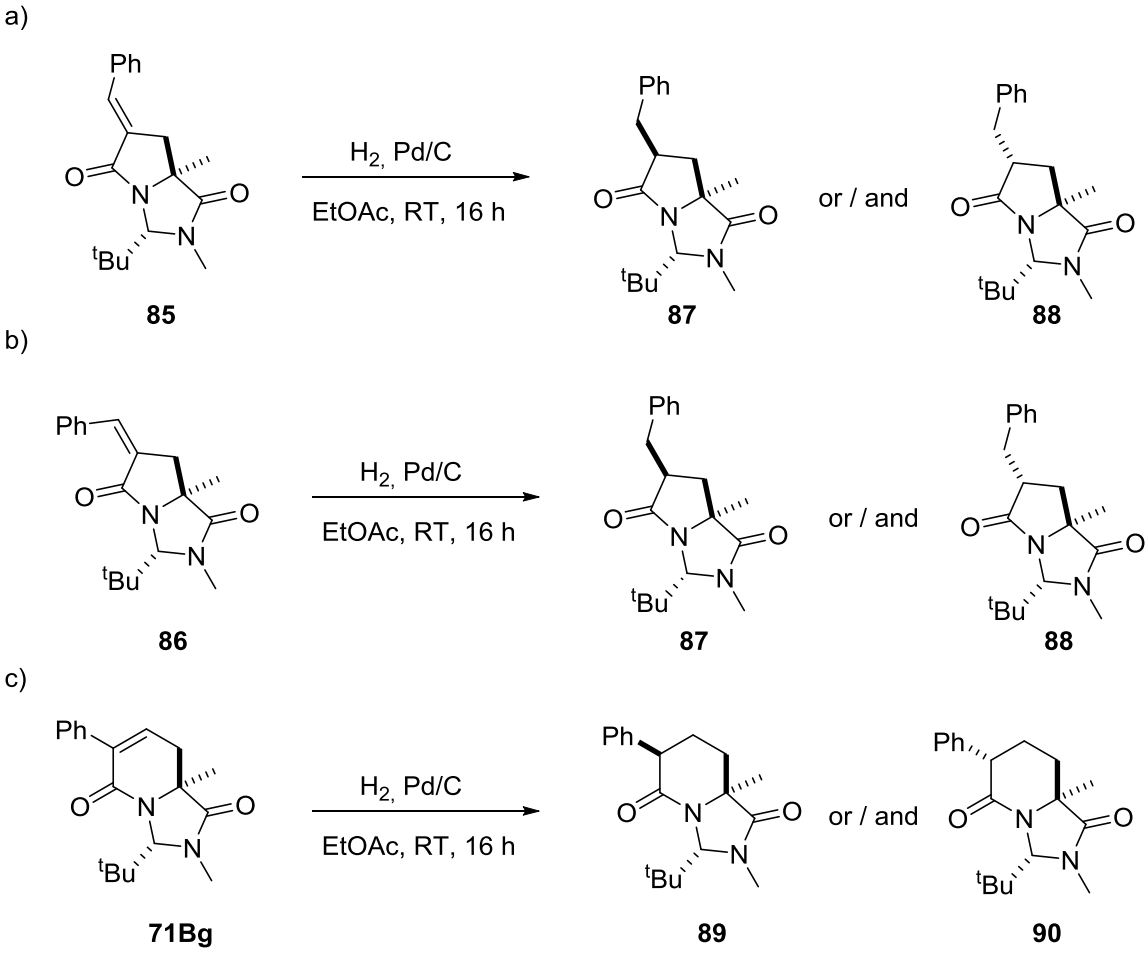


85

(3*S*, 6*E*, 7a*S*)

Figure 46. ORTEP diagram of compound **85**.

Having identified the structure of the major compound **85**, the next objective was to elucidate the structure of the other product **86**. Given the similarity in the NMR spectra (proton, carbon, COSY, DEPT, HSQC and HMBC) it was believed that **86** might be the five-member lactam with *Z*-alkene configuration. To confirm this, we decided to hydrogenate both, the known **85** and the unknown **86** and compare the results (Scheme 86 a and b). If **86** is indeed the *Z*-isomer, one might expect to get the same diastereomeric mixture of reduced products (compounds **87** and **88**) obtained in the hydrogenation of compound **85**. However, if the product was the six-member lactam **71Bg**, it would lead to two differed reduced compounds (compounds **89** and **90**), and should easily be identified by a COSY experiment (Scheme 86c).



Scheme 86. Proposed hydrogenation to identify the unknown product **86**.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture of the hydrogenation experiment confirmed that **86** is indeed the five-member lactam containing *Z*-alkene geometry. However, the diastereoselectivity of the hydrogenation was different for both isomers (Figure 47).

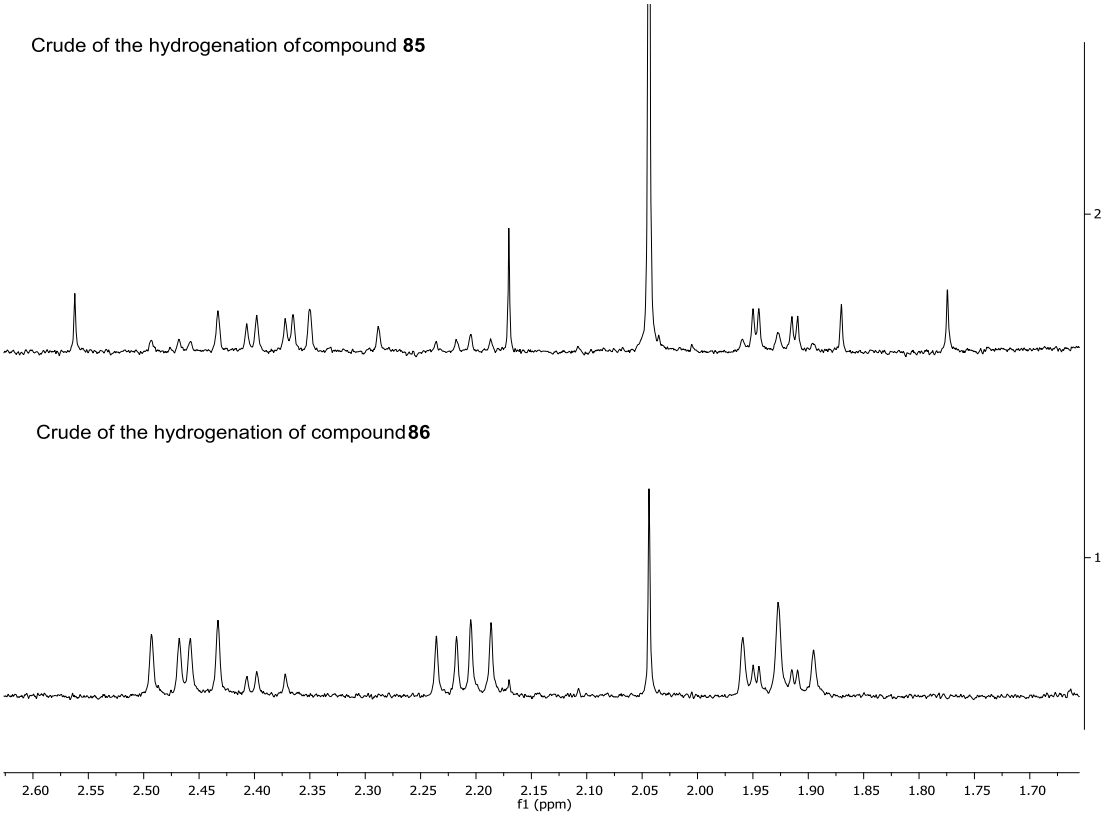
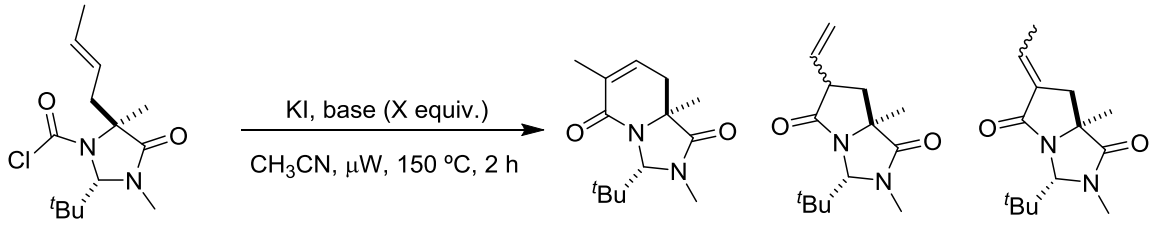


Figure 47. ^{1}H NMR spectra for the hydrogenations of compounds **85** and **86**.

In light of the results obtained, it is clear that the phenyl group at the terminal end of the double bond favors formation of the five-member cycle instead of six-member one. This is perhaps unsurprising as formation of the five-member lactam proceeds *via* a more stabilized benzylic carbocation intermediate.

On the other hand, the cyclization of compound **70Bh**, bearing the methyl group instead of phenyl (**70Bg**) in the terminal position of the allyl moiety, was not as clean as expected, and three different products were formed. Although two of the products could not be separated, using 2D NMR experiments we could deduce the structure of all three products: **71Bh**, **91** and **92** (29/23/48 ratio detected by ^{1}H NMR analysis of the crude reaction mixture) (Table 29, entry 1). It is necessary to mention that the products **91** and **92** were isolated as a single diastereomer. Once again, the role of the DBU was explored to see if it could promote formation of compound **71Bh**. As such, the reaction was carried out employing 3.0 equiv. of DBU as base (entry 2). Although, there was no increase in the proportion of the desired product **71Bh**, it was seen that the C=C double bond of unconjugated compound **91** was isomerized completely to give conjugated product **92**. Therefore, DBU clearly play an important role in the isomerization reaction of the C=C double bond, and furthermore, appears to favor the formation of five-member ring.

Table 29. Optimization of the cyclization of compound **70Bh**.

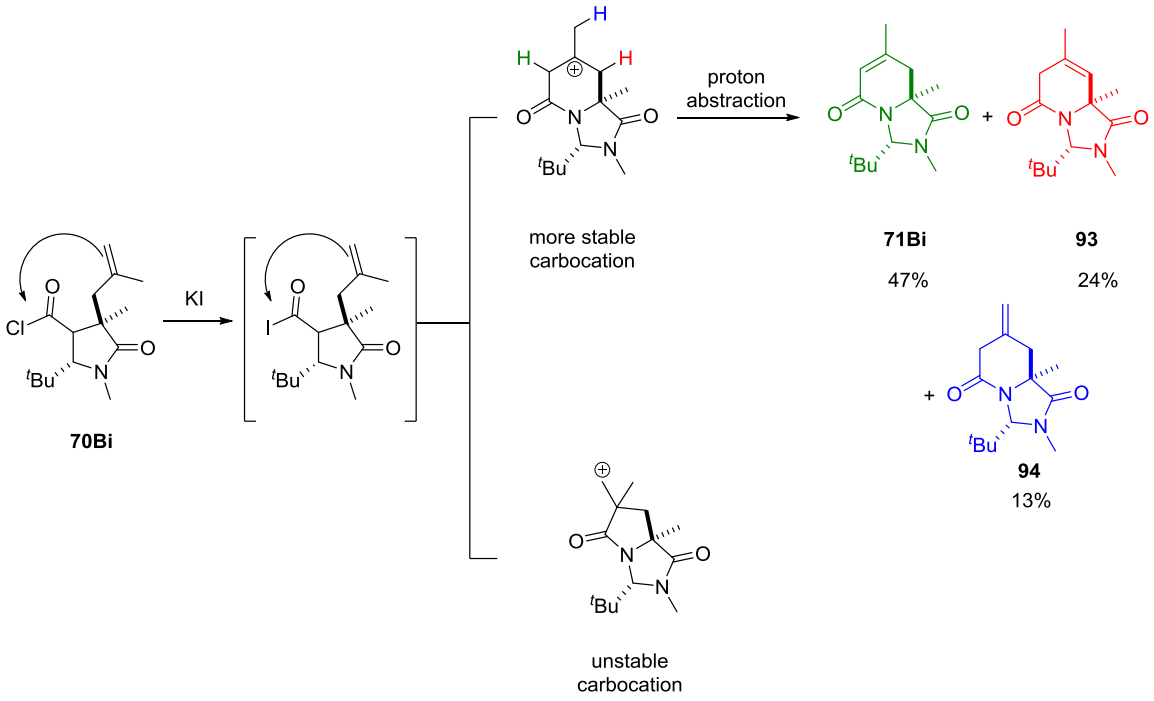


70Bh **71Bh** **91** **92**

Entry	Base (equiv.)	Crude ratio:[c] 71Bh/91/92	Yields: 71Bh+91/92
1[a]	2,6-lutidine (1.1 equiv.)	29/23/48	47%/36%[d]
2[b]	DBU (3.0 equiv.)	10/0/90	---[e]

[a] Reaction carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for 2 h. [b] Reaction carried out at 0.15 mmol scale, using 1.1 equiv. of KI and 3.0 equiv. of DBU in 1.5 mL of CH_3CN in μW at 150 °C for 2 h. [c] **71Bh**/**91**/**92** ratio detected by ^{1}H NMR analysis of the crude reaction mixture. [d] Yield after isolation of the product after chromatography. [e] Products were not isolated.

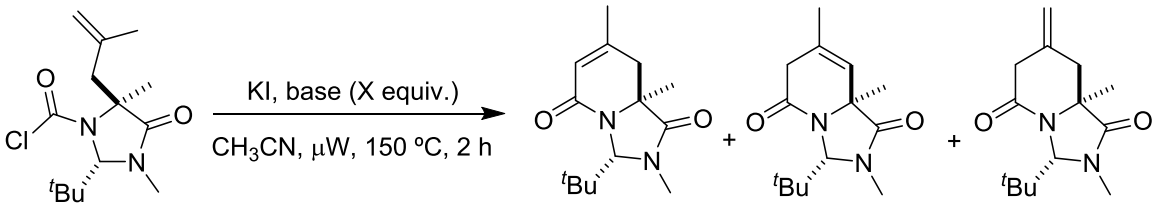
Next we wondered whether substitution at the internal carbon of the allyl group has some effect on the reaction outcome. To this end, the quaternary *trans*-*N*-chloroformylimidazolidinone **70Bi** was employed. We anticipated that this compound should mainly generated the six-member lactam as the intermediate carbocation would be more stable than that leading to the five-member ring (tertiary vs primary carbocation). Subjection of compound **70Bi** to the cyclization conditions yielded three possible products: **71Bi**, **93** and **94**, all of which are formed *via* the six-member carbocation intermediate (Scheme 87), as expected.



Scheme 87. Products generated by cyclization of compound **70Bi**.

Increasing the amount of base in the reaction yielded the desired product **71Bi** in greater quantity (Table 30, entry 2). In light of the results obtained, it was thought that DBU may induce the isomerization of the C=C double bond to form the most stable α,β-unsaturated carbonyl compound **71Bi**. Pleasingly, in this occasion replacing 2,6-lutidine by DBU worked well (entry 3), and increasing the amount of DBU up to 3.0 equivalents gave the best results (78%, entry 4).

Table 30. Optimization of the cyclization of compound **70Bi**.



70Bi **71Bi** **93** **94**

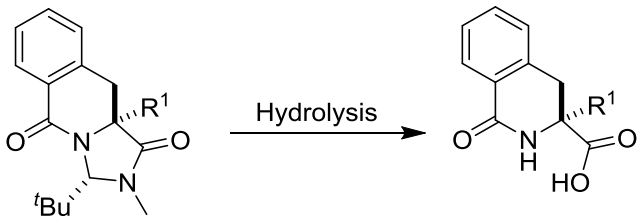
Entry	Base (equiv.)	Crude ratio:[c] 71Bi/93/94	Isolated yields:[d] 71Bi/93/94
1[a]	2,6-lutidine (1.1 equiv.)	27/50/23	24%/47%/13%
2[a]	2,6-lutidine (2.2 equiv.)	37/48/15	--[e]
3[b]	DBU (2.2 equiv.)	88/8/4	--[e]
4[b]	DBU (3.0 equiv.)	92/8/-	78%/---/---

[a] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and X equiv. of 2,6-lutidine in 1.5 mL of CH_3CN in μW at 150 °C for 2 h. [b] Reactions carried out at 0.15 mmol scale, using 1.1 equiv. of KI and X equiv. of DBU in 1.5 mL of CH_3CN in μW at 150 °C for 2 h. [c] **71Bi**/**93**/**94** ratio detected by ^{1}H NMR analysis of the crude reaction mixture. [d] Yield after isolation of the product after chromatography. [e] Products were not isolated.

As shown in above data, the substitution at the allyl group of *N*-chloroformylimidazolidinones (**70Bg**, **70Bh** and **70Bi**) has a dramatic effect on the regioselectivity of the cyclization reaction (five vs six-member lactam). In this context, further studies are being carried out at the laboratory.

4.6. Hydrolysis of imidizadolidinone ring

In order to complete the aim of the project, and demonstrate the versatility and potential of the new methodology, hydrolysis of the imidizadolidinone ring, which plays no further role in the synthesis, may be performed to reveal a masked carboxylic acid under acidic conditions (Scheme 88).

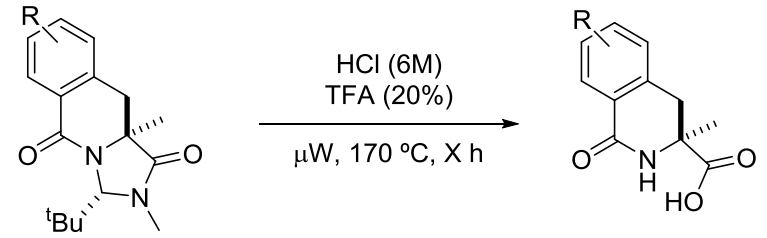


71 **72**

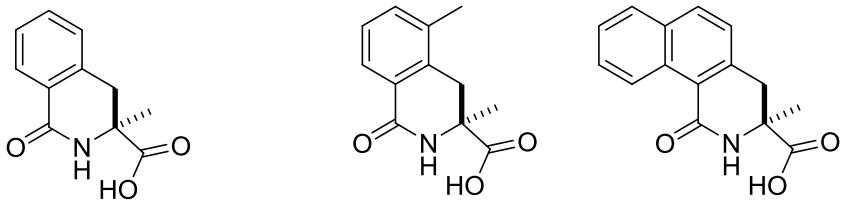
Scheme 88. Hydrolysis of α,α-disubstituted imidazolidinones **71** to the corresponding quaternary amino acids **72**.

It is known that α,α-disubstituted imidazolidinones can undergo hydrolysis by heating in the presence of 6.0 M aqueous HCl. These conditions were employed on compound **71Ba**, however analysis of the crude mixture showed that the reaction did not work, recovering the starting material. After several attempts at exploring the hydrolysis of related compounds, M. M. Amer,[191] a member of the Clayden´s group, found that heating the lactams **66** in the presence of HCl/TFA effected the hydrolysis to the corresponding quaternary amino acids in good yields. These conditions were therefore attempted on substrates **71Ba**, **71Bd** and **71Bf**. Pleasingly, the presence of TFA did effect hydrolysis and dihydroisoquinolones were obtained in good yields (Table 31). It is worth mentioning that in the case of **71Bd** and **71Bf**, the reaction times were extended to 8 hours, however we were hesitant about increasing the time further or indeed the temperature so as to avoid unwanted decarboxylation of the final product which has been observed in related compounds.

Table 31. Hydrolysis of imidazolidinones **71** to give dihydroisoquinolinones **72**.[a]



71 **72**



72Ba	**72Bd**	**72Bf**
6 h, 80%	8 h, 68%	8 h, 43%

[a] Reactions carried out at 0.10 mmol scale, using 1.6 mL of HCl (6.0 M) and 0.4 mL of TFA in μW at 170 °C for 6 h. Yield after isolation of the product after chromatography.

Chapter 5

Conclusions

5. Conclusions

Two new Brønsted base catalyzed methodologies have been developed for the synthesis of enantiomerically enriched α-functionalized carbonyl compounds.

First, we have demonstrated that tertiary amine/squaramide bifunctional catalysts promote the addition of β,γ-unsaturated carbonyl compounds to nitroolefins not only with very good enantio- and diastereocontrol, but also exclusive α-site selectivity, although (thio)esters showed inferior selectivity in the same reaction conditions. In addition, with the synthesis of β-methyl alkynyl allyl ketones we have provided a remedy to prevent the formation of Rauhut-Currier type products, thus obtaining adducts with two consecutive tertiary stereocenters in a highly diastereo- and enantioselective fashion.

Second, a catalytic one-pot process to assemble stereodefined tetrasubstituted six-member carbocycles from polyunsaturated thioesters and ketones was developed. This new methodology features a highly enantioselective α-addition of transiently generated trienolates to nitroolefins and a catalytic intramolecular 1,6-addition that proceeds with essentially perfect stereocontrol.

Finally, it has been shown that mild carbonylative cyclization of aromatic amino acids may be achieved by intramolecular Friedel–Crafts acylation of quaternary aryl *N*-chloroformylimidazolidinones, promoted by potassium iodide. Furthermore, successful hydrolysis of the imidazolidinone moiety provided a route towards unusual enantiomerically enriched quaternary amino acids in good yields.

Chapter 6

Experimental Section

6. Experimental section

6.1. Material and techniques

6.1.1. Reagents and solvents

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

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

In Bristol, anhydrous tetrahydrofuran, diethyl ether and dichloromethane were obtained from a purification column composed of activated alumina (A-2). Acetonitrile, methanol and ethanol were purchased from Acros as extra dry solvent over 3Å molecular sieves.

6.1.2. General experimental

All non-aqueous reactions were performed 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 sand or oil baths 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 MgSO4 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

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

solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (~0.5 mmHg) was employed.

6.1.3. 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, hexane/diethyl ether or dichloromethane/methanol) as eluent.

In Bristol, Flash chromatography was performed on an automated Biotage IsoleraTM Spektra Four using gradient elutions on pre-packed silica gel Biotage® SNAP Ultra/ZIP Sphere columns.

6.1.4. Optical rotation

Optical rotations were recorded using a Jasco P-2000 polarimeter, whereas in Bristol using a Bellingham and Stanley Ltd. ADP220 polarimeter; specific rotation (SR) ($[\alpha]_D^T$) 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).

6.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected. Whereas in Bristol, the melting points were measured on a Stuart Scientific melting point SMP 10 apparatus and were uncorrected.

6.1.6. 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) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Whereas the ^{1}H and ^{13}C NMR spectra of Bristol were recorded on Jeol ECS (400 MHz), Varian VNMR (400 MHz or 500 MHz) or Bruker Ultrashield (400 MHz or 500 MHz) spectrometers.

Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak: Chloroform-*d*, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0); Methanol-d_4, ^{1}H (δ = 3.31) and ^{13}C (δ = 49.0); DMSO-d_6, ^{1}H (δ = 2.50) and ^{13}C (δ = 39.52) .The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *br*s, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

6.1.7. 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. In Bristol, the high resolution mass spectra were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI) with only molecular ions $[M+H]^+$ and $[M+Na]^+$ reported. 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.

6.1.8. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. In Bristol, FT-IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer, using a Universal ATR sampling accessory. Only strong and relevant absorptions are reported.

6.1.9. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters-600E (equipped with 2996 and 2998 photodiode array UV detector). The used columns were AY-H, AD-H, IA, IB, IC, ID and phenomenex Lu xi-Amylose-1 and flow/solvent conditions are given for each compound.

6.1.10. 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.

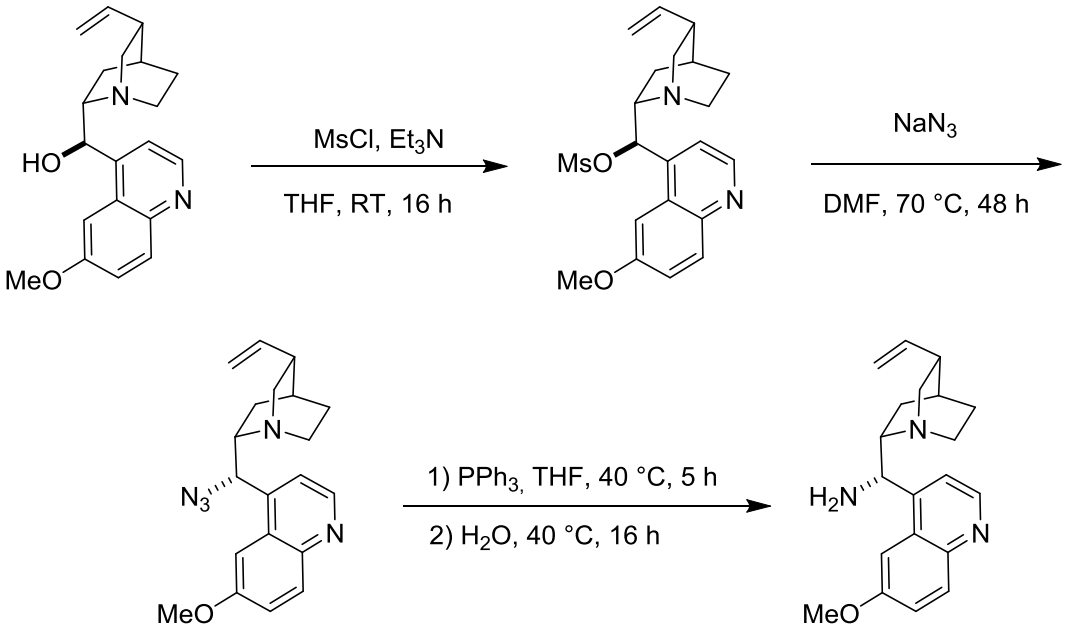
6.2. General procedure for the synthesis of catalysts

Catalysts **C6**[202], **C7**,[203] **C11**,[204] **C18**,[205] **C19**,[206] **C24**,[207] **C25**,[208] **C26**[209] and **C30**[210] were prepared following the procedures described in the literature.

6.2.1. Preparation of chiral amines

6.2.1.1. *Preparation of 9-epi cinchona-based amines*

6.2.1.1.1. *Preparation of 9-amino-(9-deoxy)-epiquinine*[211]



1st step:[212] A mixture of quinine (16.2 g, 50.0 mmol, 1.0 equiv.) and triethylamine (25.1 mL, 180.0 mmol, 3.6 equiv.) in dry THF (250.0 mL) was cooled to 0 °C and then, methanesulfonyl chloride (7.0 mL, 90.0 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with

[202] K. Greenaway, P. Dambruoso, A. Ferrali, A. J. Hazelwood, F. Sladojevich, D. J. Dixon, *Synthesis* **2011**, *12*, 1880–1886.
[203] H. Echave, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.
[204] E. Badiola, I. Olaizola, A.; Vázquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185–8195.
[205] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.
[206] W. Yang, D.-M. Du, *Org. Lett*. **2010**, *12*, 5450–5453.
[207] W. Yang, D. M. Du, *Adv*. *Synth. Catal.* **2011**, *353*, 1241–1246.
[208] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.
[209] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14418.
[210] I. Bastida, M. San Segundo, R. López, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 13332–13336.
[211] Adapted from: H. Brunner, J. Büegler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.
[212] Adapted from: M. Zielinska-Blajet, M. Kucharska, J. Skarzewski, *Synthesis* **2006**, *7*, 4383–4387.

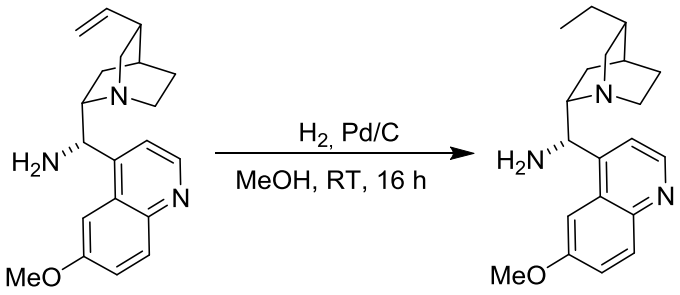
water (40.0 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40.0 mL) and washed with water (30.0 mL) and saturated sodium bicarbonate (30.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under reduced pressure to afford the crude product (19.3 g, 48.0 mmol, 97%), which was used in the next step without further purification. All spectroscopy data were coincident with those previously reported.

2nd step:[213] The previous crude product (19.3 g, 48.0 mmol, 1.0 equiv.) was dissolved in DMF (150.0 mL). The solution was cooled to 0 °C and NaN_3 (6.2 g, 96.0 mmol, 2.0 equiv.) was added portionwise. The mixture was stirred at 70 °C for 16 h and after this time the reaction was quenched with water (80.0 mL) and then ethyl acetate (150.0 mL) was added. The organic layer was separated and washed with saturated NaCl (5 x 60.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain the crude product (16.7 g, 48.0 mmol, > 99%), which was used in the next step without further purification. All spectroscopy data were coincident with those previously reported.

3rd step:[213] The previous crude product (16.7 g, 48.0 mmol, 1.0 equiv.) was dissolved in THF (250.0 mL) and PPh_3 (12.6 g, 48.0 mmol, 1.0 equiv.) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (6 h more or less). Then, H_2O (8.0 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (150.0 mL). HCl 6M (250.0 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100.0 mL). Then, the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150.0 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil (13.9 g, 43.2 mmol, 90%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) 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).

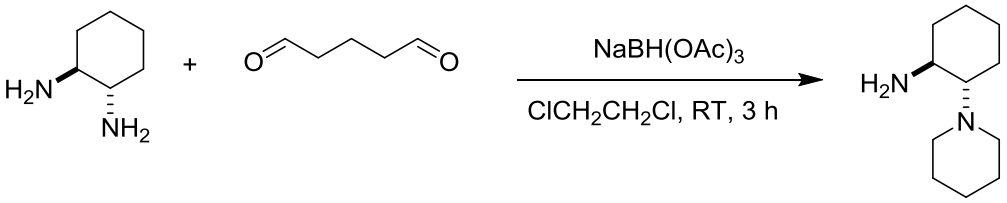
[213] Adapted from: U. Sudermeier, C. Döbler, G. M. Mehltretter, W. Baumann, M. Beller, *Chirality* **2003**, *15*, 127–134.

6.2.1.1.2. *Preparation of 9-amino-(9-deoxy)-epihydroquinine* [214]



10% Palladium on carbon (0.32 g, 10% w/w) was added to a solution of 9-amino-(9-deoxy)*epi*quinine (3.2 g, 10.0 mmol, 1.0 equiv.) in methanol (10.0 mL). The reaction mixture was stirred overnight under H_2 atmosphere, and then was filtered over celite and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*hydroquinine as a yellow viscous oil (3.0 g, 9.2 mmol, 92%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Methanol-d_4) δ 8.69 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.69 (*br*s, 1H), 7.61 (d, *J* = 4.7 Hz, 1H), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.36–3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H), 3.16 (q, *J* = 10.7 Hz, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 1.62–1.58 (m, 1H), 1.60 (dd, *J*= 13.3, 10.4 Hz, 1H), 1.58–1.47 (m, 4H), 1.37–1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

6.2.1.2. *Preparation of (1S,2S)-2-(piperidin-1-yl)cyclohexan-1-amine*[215]



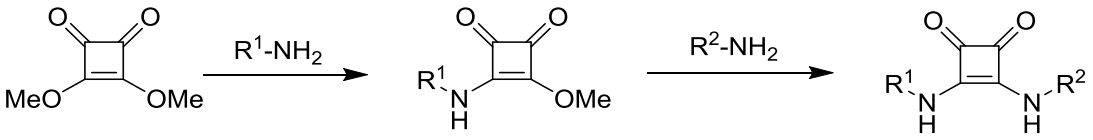
Glutaraldehyde (50 wt% H_2O, 0.93 mL, 5.1 mmol, 1.05 equiv.) was added dropwise into a mixture of (1*S*,2*S*)-(*+*)-1,2-diaminocyclohexane (560 mg, 4.9 mmol, 1.0 equiv.) and $NaBH(OAc)_3$ (4.16 g, 19.6 mmol, 4.0 equiv.) in $ClCH_2CH_2Cl$ (30.0 mL) at room temperature. The mixture was stirred at room temperature for 3 h, and quenched with NaOH 6.0 M (15.0 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice (2 x 15.0 mL). The organic layers were washed with brine (15.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the product as brown oil (715 mg, 3.92 mmol, 80%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 2.76 –

[214] Adapted from: B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.
[215] Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

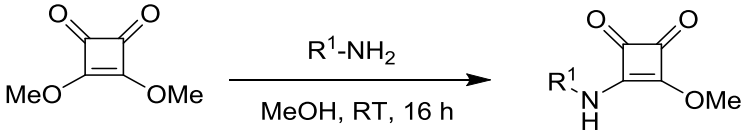
2.57 (m, 3H), 2.48 – 2.26 (m, 2H), 2.09 – 1.91 (m, 2H), 1.89 – 1.35 (m, 9H), 1.31 – 1.03 (m, 4H).

6.2.2. Squaramide-based Brønsted base catalysts

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

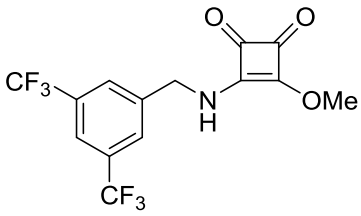


6.2.2.1. Preparation of squaric ester monoamide intermediate[209]



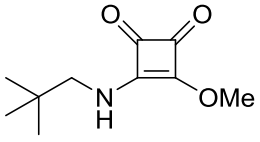
To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (142 mg, 0.9 mmol, 0.9 equiv.) in MeOH (2.0 mL), the corresponding commercial amine (1.0 mmol, 1.0 equiv.) was added and the mixture was stirred at room temperature for 16 h. Then, the solvent was evaporated under reduced pressure and the oil residue was purified by silica gel column chromatography (hexane/ethyl acetate 40/60) to give the desired product.

3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione[209]



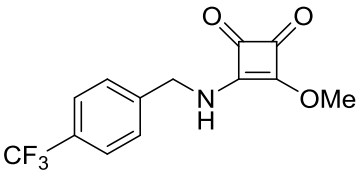
Prepared according to the general procedure starting from 3,5-bis(trifluoromethyl)benzylamine (243 mg, 1.0 mmol, 1.0 equiv.). Yellow solid (317 mg, 0.9 mmol, 86%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.82 (s, 2H), 7.71 (s, 1H), 4.71 (*br*s, 2H), 4.36 (s, 3H).

3-Methoxy-4-(neopentylamino)cyclobut-3-ene-1,2-dione



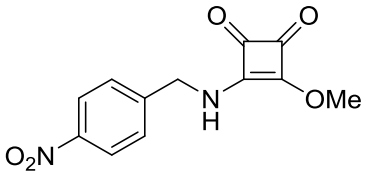
Prepared according to the general procedure starting from neopentylamine (88 mg, 1.0 mmol, 1.0 equiv.). Yellow solid (158 mg, 0.8 mmol, 80%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 5.94 (*br*s, 1H), 4.44 (s, 2H), 3.20 (s, 3H), 0.97 (s, 9H).

3-Methoxy-4-((4-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione



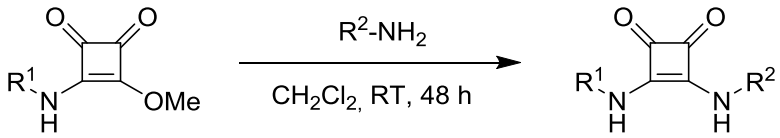
Prepared according to the general procedure starting from (4-(trifluoromethyl)phenylmethanamine (0.16 mL, 1.0 mmol, 1.0 equiv.). White solid (0.20 g, 0.7 mmol, 77%). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 4.67 (d, *J* = 63.3 Hz, 2H), 4.28 (s, 3H).

3-Methoxy-4-((4-nitrobenzyl)amino)cyclobut-3-ene-1,2-dione



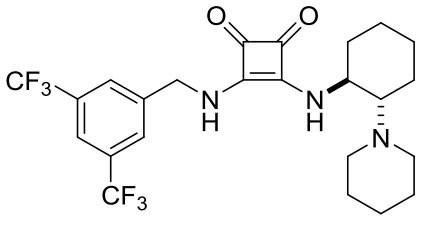
Prepared according to the general procedure starting from 4-nitrobenzylamine hydrochloride (189 mg, 1.0 mmol, 1.0 equiv.) and Et_3N (0.17 mL, 1.2 mmol, 1.2 equiv.). Orange solid (222 mg, 0.85 mmol, 95%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 4.80 (*br*s, 2H), 4.44 (s, 3H).

6.2.2.2. Preparation of catalysts C27, C45, and C46



To a suspension of the squaric ester monoamide intermediate obtained above (0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL), chiral amine (0.67 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the oil residue was purified by silica gel column chromatography (CH_2Cl_2/methanol 95/5) to give the pure catalyst.

3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (C27)[216]

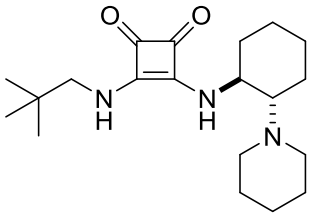


Prepared according to the general procedure starting from 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (158 mg, 0.45 mmol, 1.0 equiv.) and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (122 mg, 0.67 mmol, 1.5 equiv.). Yellow solid (163 mg, 0.32 mmol, 72%). **M.p.:** 253–255 °C. **$[\alpha]_D^{22}$** = +19.01°

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

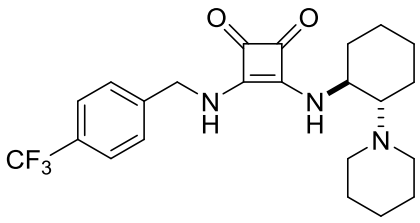
(*c*=0.33, DMSO). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.07 (s, 3H), 7.50 (s, 1H), 4.92 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 1H), 2.56 (d, *J* = 9.6 Hz, 2H), 2.22 (dd, *J* = 10.7, 5.0 Hz, 3H), 2.07 – 1.91 (m, 1H), 1.84 – 1.58 (m, 4H), 1.19 (d, *J* = 22.1 Hz, 10H). **^{13}C NMR** (101 MHz, DMSO-*d*6) δ 182.9, 182.1, 169.1, 143.0, 130.4 (q, *J* = 33.0 Hz), 128.4, 124.6, 121.9, 121.1, 68.4, 54.0, 49.3, 45.6, 33.9, 30.7, 26.2, 24.8, 24.4, 23.6. **UPLC-DAD-QTOF:** $C_{24}H_{28}N_3O_2F_6$ $[M+H]^+$ calcd.: 504.2080, found: 504.2086.

3-(Neopentylamino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione(C28)



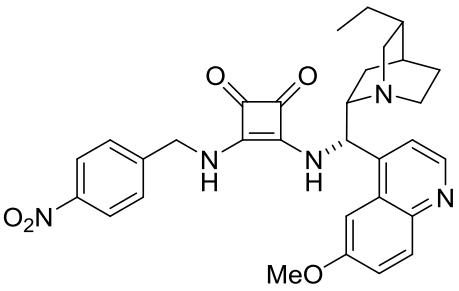
Prepared according to the general procedure starting from 3-methoxy-4-(neopentylamino)cyclobut-3-ene-1,2-dione (89 mg, 0.45 mmol, 1.0 equiv.) and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (122 mg, 0.67 mmol, 1.5 equiv.). White solid (101 mg, 0.3 mmol, 65%). **M.p.:** decompose at 171 °C. **$[\alpha]_D^{22}$** = +59.1° (*c*=0.5, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 – 7.22 (m, 0H), 3.97 – 3.78 (*br*m, 1H), 3.53 – 3.28 (m, 1H), 2.68 – 2.58 (m, 2H), 2.39 – 2.24 (m, 2H), 2.11 – 1.21 (m, 14H), 1.01 – 0.22 (m, 10H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 182.3, 168.1, 68.4, 54.5, 54.4, 53.7, 49.3, 34.3, 32.4, 32.3, 26.5, 26.3, 24.8, 24.6, 24.5, 23.7.

3-(((1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexyl)amino)-4-((4-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione (C45)



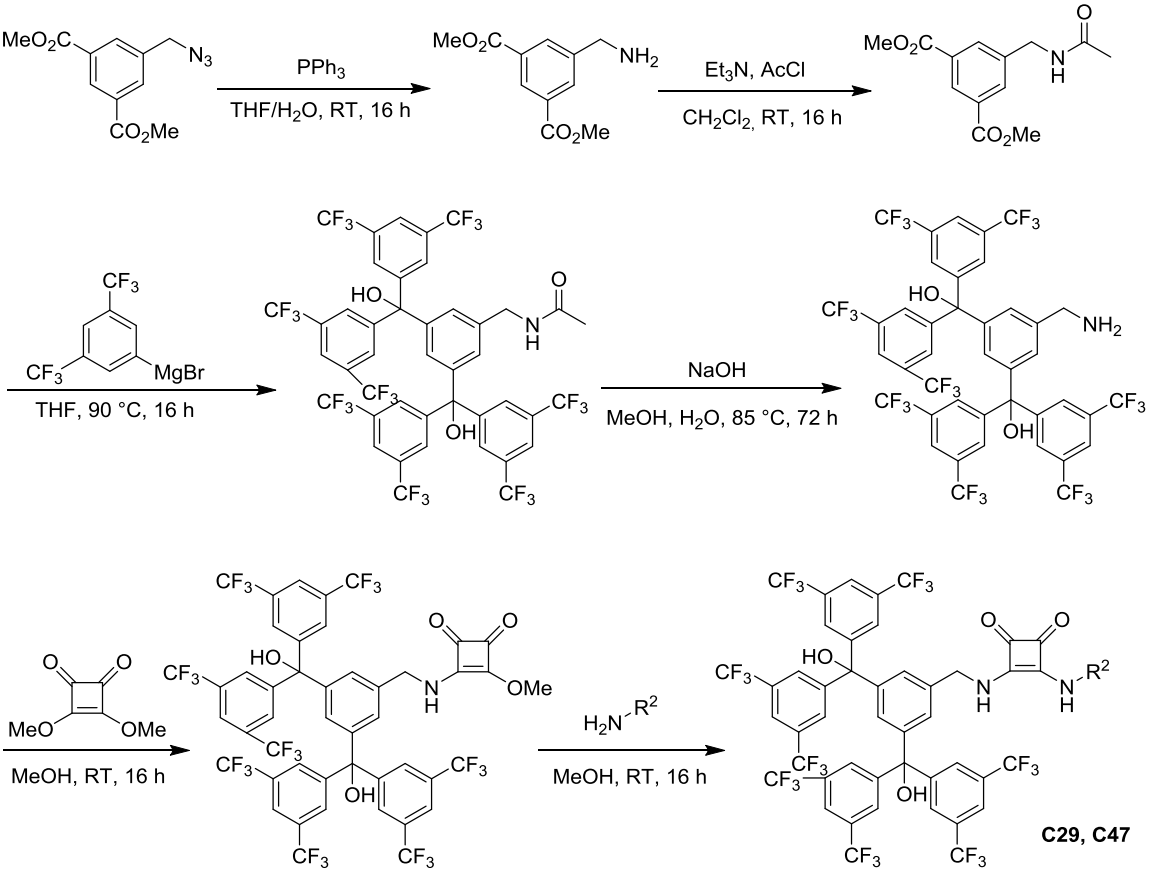
Prepared according to the general procedure starting from 3-methoxy-4-((4-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione (118 mg, 0.45 mmol, 1.0 equiv.) and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (122 mg, 0.67 mmol, 1.5 equiv.). Yellow solid (122 mg, 0.28 mmol, 64%). **M.p.**= decompose at 180 °C. **$[\alpha]_D^{22}$** = –25.9° (*c*=0.5, DMSO). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 4.81 (*br*s, 2H), 3.79 (*br*s, 1H), 2.65 – 2.50 (m, 2H), 2.28 – 1.92 (m, 4H), 1.87 – 1.53 (m, 4H), 1.39 – 1.02 (m, 10H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 182.8, 182.0, 168.7, 144.1, 143.8, 128.1, 128.0, 125.5, 125.4, 68.3, 53.9, 49.3, 46.2, 34.1, 26.2, 24.8, 24.5, 23.5. **UPLC-DAD-QTOF:** $C_{23}H_{29}N_3O_2F_3$ $[M+H]^+$ calcd.: 436.2212, found: 436.2211.

3-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)-4-((4-nitrobenzyl)amino)cyclobut-3-ene-1,2-dione (C46)



Prepared according to the general procedure starting from 3-methoxy-4-((4-nitrobenzyl)amino)cyclobut-3-ene-1,2-dione (118 mg, 0.45 mmol, 1.0 equiv.) and 9-amino-(9-deoxy)*epi*hydroquinine (217 g, 0.67 mmol, 1.5 equiv.). Yellow solid (157 mg, 0.28 mmol, 63%). **M.p.:** 219–235 °C. **$[\alpha]_D^{25}$**= −16.38° (*c*=1.0, CH_2Cl_2). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.38 (s, 1H), 8.10 (*br*s, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 2.6 Hz, 1H), 7.69 (d, *J* = 4.7 Hz, 1H), 7.55 – 7.25 (m, 3H), 6.05 (s, 1H), 4.95 – 4.64 (m, 2H), 3.94 (s, 3H), 3.34 (m, 2H), 3.17 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.65 (m, 1H), 2.52 – 2.29 (m, 2H), 1.68 – 1.06 (m, 7H), 0.74 (t, *J* = 7.2 Hz, 3H), 0.58 (d, *J* = 12.9 Hz, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 182.7, 181.9, 167.5, 166.8, 157.8, 147.7, 146.6, 146.4, 144.2, 143.5, 131.4, 128.5, 127.4, 123.6, 121.9, 101.5, 58.8, 56.9, 55.6, 54.9, 46.1, 36.4, 27.6, 26.6, 25.5, 24.9, 11.8. **UPLC-DAD-QTOF:** $C_{31}H_{34}N_5O_5$ $[M+H]^+$ calcd.: 556.2560, found: 556.2556.

6.2.2.3. *Preparation of catalysts C29 and C47*



1st step:[217] To a solution of dimethyl 5-(azidomethyl) isophthalate[218] (4.16 g, 16.8 mmol, 1.0 equiv.) in THF (80.0 mL) was added water (16.0 mL) and triphenylphosphine (4.88 g, 18.4 mmol, 1.1 equiv.), and the resulting clear solution was stirred at room temperature for 16 h. The solvent was removed and the crude material was purified by silica gel column chromatography (CH_2Cl_2/methanol 90/10) to give the desired product as a white solid (3.12 g, 14.0 mmol, 83%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.57 (t, *J* = 1.6 Hz, 1H), 8.20 (dd, *J* = 1.6, 0.7 Hz, 2H), 3.99 (d, *J* = 0.7 Hz, 2H), 3.95 (s, 6H).

2nd step:[219] To a solution of the previous amine (2.49 g, 11.1 mmol, 1.0 equiv.) and Et_3N (1.56 mL, 11.1 mmol, 1.0 equiv.) in CH_2Cl_2 (60.0 mL), acetic chloride (0.81 mL, 11.7 mmol, 1.05 equiv.) was added dropwise at 0 °C. After 16 h at room temperature, the reaction mixture was washed with water (60.0 mL) and brine (60.0 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired product as a white solid (2.5 g, 9.6 mmol, 86%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 8.18 (dd, *J* = 1.5, 0.7 Hz, 2H), 5.87 (s, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 3.99 (s, 6H), 2.11 (s, 3H).

3rd step:[219] To a solution of the crude material of the previous reaction (2.64 g, 10.0 mmol, 1.0 equiv.) in THF (20.0 mL), a solution of 3,5-bis(trifluoromethyl)-phenyl magnesium bromide (0.5M in THF, 160.0 mL, 80.0 mmol, 8.0 equiv.) was added dropwise at 0 °C. The mixture was stirred at reflux overnight. The reaction was quenched with NH_4Cl saturated solution (20.0 mL), the solvent was evaporated under reduced pressure and diluted with water (40.0 mL). The mixture was extracted with CH_2Cl_2 (3 × 20.0 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate 50/50) to give the product as brown solid (9.8 g, 9.3 mmol, 93%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.86 (s, 4H), 7.67 (d, *J* = 1.6 Hz, 8H), 7.27 (d, *J* = 1.8 Hz, 2H), 6.70 (t, *J* = 1.8 Hz, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 1.88 (s, 3H).

4th step:[219] NaOH (6.2 g, 154.4 mmol, 20.0 equiv.) was added to a solution of the amide product obtained above (8.02 g, 7.6 mmol, 1.0 equiv.) in MeOH (60.0 mL) and water (7.6 mL). The mixture was heated at 85 °C for 72 h. The reaction mixture was neutralized by adding dropwise HCl 1.0 M until pH 7 and then, extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/methanol 95/5) to give the product as brown solid (6.18 g, 7.1

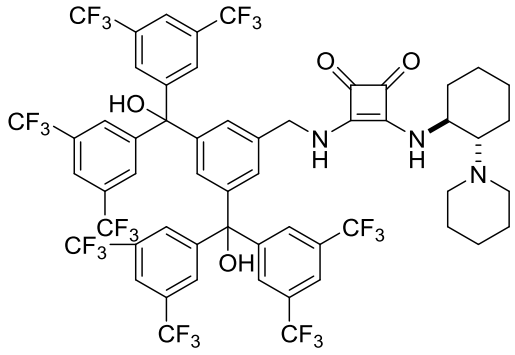
[217] Adapted from: U. Sudermeier, C. Döbler, G. M. Mehltretter, W. Baumann, *Chirality* **2003**, *15*, 127–134.
[218] S. M. Dimick, S. C. Powell, S. A. McMahon, D. N. Moothoo, J. H. Naismith, E. J. Toone, *J. Am. Chem. Soc.* **1999**, *121*, 10286-10296.
[219] Adapted from: A. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 12758-12762.

mmol, 80%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.00 (*br*s, 2H), 7.83 (s, 4H), 7.60 (d, *J* = 1.8 Hz, 8H), 6.49 (s, 1H), 4.61 (*br*s, 2H), 4.06 (s, 2H).

5th step:[220] To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (130 mg, 0.9 mmol, 0.9 equiv.) in MeOH (4.0 mL) was added the free amine product obtained above (1.01 g, 1.0 mmol, 1.0 equiv.) and the mixture was stirred at room temperature for 16 h. Then, the solvent was evaporated under reduced pressure and the oily residue was purified by silica gel column chromatography (hexane/ethyl acetate 70/30) to give the title compound as a white solid (894 mg, 0.8 mmol, 90%). **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.92 (s, 4H), 7.77 – 7.55 (m, 8H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 30.8 Hz, 1H), 4.66 (d, *J* = 48.8 Hz, 2H), 4.25 (d, *J* = 44.5 Hz, 3H).

6th step:[220] To a suspension of the hemisquaramide obtained above (563 mg, 0.5 mmol, 1.0 equiv.) in MeOH (2.0 mL), the corresponding chiral amine (0.55 mmol, 1.1 equiv.) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the oily residue was purified by silica gel column chromatography (CH_2Cl_2/methanol 97/3) to give the pure catalyst.

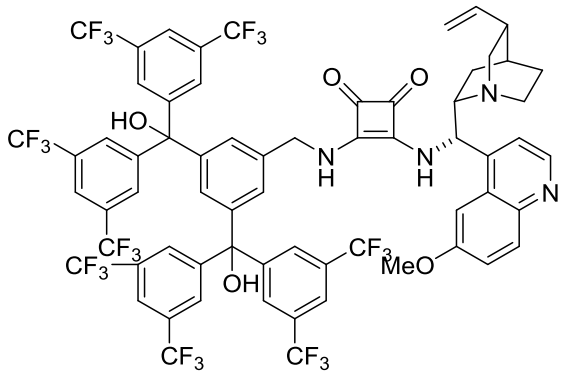
3-((3,5-Bis(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)benzyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (C29)



Prepared according to the general procedure starting from (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (100 mg, 0.55 mmol, 1.1 equiv.). Yellow solid (408.3 mg, 0.32 mmol, 64%). **M.p.:** 156.0–161.0 °C. **$[\alpha]_D^{22}$** = –9.35° (*c*=1.0, MeOH). **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.91 (t, *J* = 1.7 Hz, 4H), 7.68 (d, *J* = 1.6 Hz, 8H), 7.62 (d, *J* = 1.7 Hz, 2H), 6.57 (t, *J* = 1.7 Hz, 1H), 4.85 (s, 2H), 4.00 (*br*s, 1H), 2.93 (s, 2H), 2.59 (s, 2H), 2.16 – 1.07 (m, 16H). **^{13}C NMR** (75 MHz, Methanol-d_4) δ 183.6, 183.5, 169.4, 169.2, 150.2, 146.9, 142.1, 132.8 (q, *J* = 33.6 Hz), 129.9, 129.5, 128.0, 127.8, 126.3, 122.7, 119.0, 81.4, 70.0, 55.1, 50.9, 48.1, 35.7, 26.5, 26.0, 25.6, 24.8. **UPLC-DAD-QTOF:** $C_{56}H_{42}N_3O_4F_{24}$ $[M-H]^+$ calcd.: 1276.2792, found: 1276.2790.

[220] Addapted from: see ref. 209

3-((3,5-Bis(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)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 (C47)



Prepared according to the general procedure starting from 9-amino-(9-deoxy)*epi*quinine (179 mg, 0.55 mmol, 1.1 equiv.). Yellow solid (639 mg, 0.45 mmol, 90%). **M.p.:** 178–182 °C. **$[\alpha]_D^{22}$** = –10.32° (*c*=1.0, MeOH). **^{1}H NMR** (300 MHz, Methanol-d_4) δ 8.69 (d, *J* = 4.7 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H), 7.85 (dt, *J* = 3.6, 1.6 Hz, 4H), 7.66 (d, *J* = 1.7 Hz, 8H), 7.56 (d, *J* = 4.8 Hz, 2H), 7.41 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.52 (t, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 10.8 Hz, 1H), 5.90 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1H), 5.12 – 4.96 (m, 2H), 4.79 (s, 2H), 3.98 (s, 3H), 3.58 (d, *J* = 9.8 Hz, 2H), 2.98 – 2.72 (m, 2H), 2.44 (d, *J* = 10.9 Hz, 1H), 1.68 (t, *J* = 7.1 Hz, 4H), 0.74 (dd, *J* = 13.0, 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, Methanol-d_4) δ 183.6, 169.2, 168.3, 160.5, 150.1, 148.2, 146.9, 145.4, 142.0, 141.8, 132.7 (q, *J* = 33.6 Hz), 131.6, 129.8, 129.5, 128.9, 128.0, 127.8, 126.2, 124.4, 122.8, 122.6, 120.2, 119.0, 115.4, 102.1, 81.4, 61.1, 56.8, 56.7, 41.8, 40.3, 28.7, 28.0, 27.1. **UPLC-DAD-QTOF:** $C_{65}H_{45}N_4O_5F_{24}$ $[M-H]^+$ calcd.: 1417.2977, found: 1417.2979.

6.3. Experimental section of chapter 2

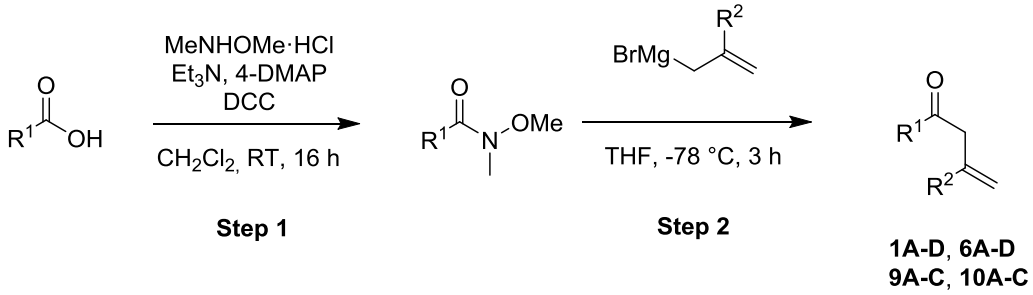
6.3.1. Synthesis of nitroolefins

Nitroolefins **2a**, **2b**, **2c**, **2g** and **2h** are commercially available. Compounds **2d-f** and **2i-j** were prepared according to the literature.[221]

[221] Aliphatic nitroolefins **2e-f** and **2i**: a) B. M. Trost, C. Muller, *J. Am. Chem. Soc.* **2008**, *130*, 2438–2439. Aromatic nitroolefins **2d** and **2j**: b) J. Bourguignon, G. Le Nard, G. Queguiner, *Can. J. Chem.* **1985**, *63*, 2354– 2361.

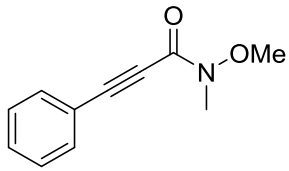
6.3.2. Synthesis of β,γ-unsaturated carbonyl compounds

6.3.2.1. *Synthesis of β,γ-unsaturated ketones (1A-D, 6A-D, 9A-C, 10A-C)*



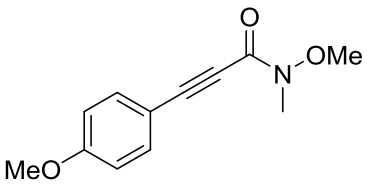
1st step:[222] To a stirred solution of the corresponding carboxylic acid (5.0 mmol, 1.0 equiv.) and *N*,*O*-dimethylhydroxyamine hydrochloride (501 mg, 5.2 mmol, 1.05 equiv.) in CH_2Cl_2 (15.0 mL) at 0 °C, Et_3N (1.4 mL, 10.0 mmol, 2.0 equiv.), *N*,*N*-dimethylpyridin-4-amine (4-DMAP) (30 mg, 0.25 mmol, 0.05 equiv.) and *N*,*N'*-methanetetraylbis[cyclohexanamine] (DCC) (1.09 g, 5.2 mmol, 1.05 equiv.) were added. The reaction mixture was allowed to stir overnight while warming to room temperature. The mixture was diluted with CH_2Cl_2 (10.0 mL) and quenched with water (30.0 mL). The layers were separated and the aqueous layer was extracted once with CH_2Cl_2 (30.0 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50.0 mL), water (50.0 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 80/20) to obtain the corresponding *N*-methoxy-*N*-methylamide.

***N*-Methoxy-*N*-methyl-3-phenylpropiolamide**



Prepared according to the general procedure starting from 3-phenylpropiolic acid (730 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (751 mg, 4.0 mmol, 80%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.65 – 7.51 (m, 2H), 7.51 – 7.29 (m, 3H), 3.85 (s, 3H), 3.31 (*br*s, 3H).

***N*-Methoxy-3-(4-methoxyphenyl)-*N*-methylpropiolamide**

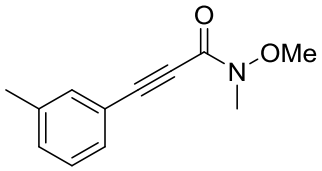


Prepared according to the general procedure starting from 3-(4-methoxyphenyl)propiolic acid[223] (880 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (731 mg, 3.3 mmol, 67%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.52 (d, *J*

[222] Adapted from: A. Dermenci, R.E. Whittaker, G. Dong, *Org.Lett.* **2013**, *15*, 2242–2245.
[223] F.-W. Li, Q.-L. Suo, H.-L. Hong, N. Zhu, Y.-Q. Wang, L.-M. Han, *Tetrahedron Lett.* **2014**, *55*, 3878–3880.

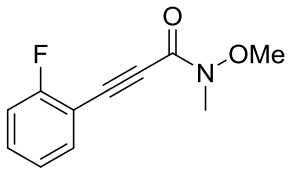
= 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 6H), 3.31 (*br*s, 3H).

_N_-Methoxy-_N_-methyl-3-(_m_-tolyl)propiolamide



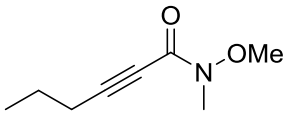
Prepared according to the general procedure starting from 3-(*m*-tolyl)propiolic acid[223] (800 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (662 mg, 3.3 mmol, 65%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.38 (m, 2H), 7.29 – 7.20 (m, 2H), 3.85 (s, 3H), 3.31 (*br*s, 3H), 2.35 (s, 3H).

3-(2-Fluorophenyl)-_N_-methoxy-_N_-methylpropiolamide



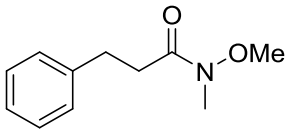
Prepared according to the general procedure starting from 3-(2-fluorophenyl)propiolic acid[223] (823 mg, 5.0 mmol, 1.0 equiv.). Yellow oil (576 mg, 2.7 mmol, 55%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.60 (td, *J* = 7.3, 1.8 Hz, 1H), 7.45 (dddd, *J* = 8.3, 7.3, 5.3, 1.8 Hz, 1H), 7.24 – 7.10 (m, 2H), 3.88 (s, 3H), 3.32 (s, 3H).

_N_-Methoxy-_N_-methylhex-2-ynamide



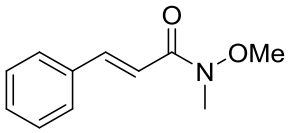
Prepared according to the general procedure starting from 2-hexynoic acid (560 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (652 mg, 4.2 mmol, 84%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 3.77 (s, 3H), 3.24 (*br*s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.62 (q, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).

_N_-Methoxy-_N_-methyl-3-phenylpropanamide



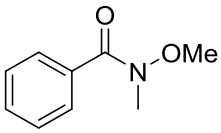
Prepared according to the general procedure starting from hydrocinnamic acid (753 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (775 mg, 4.0 mmol, 80%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.48 – 7.07 (m, 5H), 3.61 (s, 3H), 3.18 (s, 3H), 2.96 (dd, *J* = 9.0, 6.8 Hz, 2H), 2.80 – 2.69 (m, 2H).

_N_-Methoxy-_N_-methylcinnamamide:



Prepared according to the general procedure starting from *trans*-cinnamic acid (740 mg, 5.0 mmol, 1.0 equiv.). Colourless oil (792 mg, 4.2 mmol, 83%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 15.9 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.44 – 7.31 (m, 3H), 7.04 (d, *J* = 15.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H).

_N_-Methoxy-_N_-methylbenzamide:

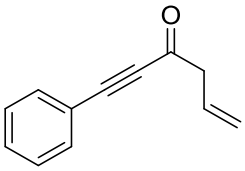


Prepared according to the general procedure starting from benzoic acid (1.22 g, 5.0 mmol, 1.0 equiv.). Colourless oil (735 mg, 4.5 mmol, 89%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.78 – 7.62 (m, 2H), 7.54 – 7.36 (m, 3H), 3.60 (s, 3H), 3.40 (s, 3H).

2nd step: To a mixture of magnesium powder (0.83 g, 35.0 mmol, 14.0 equiv) and $HgCl_2$ (27 mg, 0.1 mmol, 0.04 equiv.) in anhydrous Et_2O (2.5 mL), a solution of the corresponding bromide (10.0 mmol, 4.0 equiv.) in anhydrous Et_2O (7.5 mL) was added and stirred at room temperature for 3 h.

Then, the corresponding amount of freshly prepared magnesium bromide solution (3.0 mL, 3.0 mmol, 1.2 equiv., 1.0 M in Et_2O) was added dropwise to a solution of the corresponding *N*-methoxy-*N*-methylamide (2.5 mmol, 1.0 equiv.) obtained in the previous step at -78 °C. The reaction mixture was stirred at -78 °C until completion of the reaction (monitored by TLC). The reaction was quenched with saturated NH_4Cl (25.0 mL) at -78 °C and extracted with Et_2O (3 x 10.0 mL). The combined organic phases were washed with brine (10.0 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/diethyl ether 98/2) to obtain the desired product.

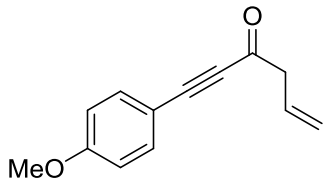
1-Phenylhex-5-en-1-yn-3-one (1A)[224]



Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-phenylpropiolamide (473 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.87 mL, 10.0 mmol, 4.0 equiv.). Yellow oil (234 mg, 1.35 mmol, 55%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.64 – 7.54 (m, 2H), 7.51 – 7.33 (m, 3H), 6.03 (ddt, *J* = 17.2, 10.4, 6.9 Hz, 1H), 5.33 – 5.19 (m, 2H), 3.44 (dt, *J* = 7.0, 1.4 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.4, 133.2, 130.9, 129.5, 128.7, 119.8, 92.0, 87.7, 50.0. **UPLC-DAD-QTOF:** $C_{11}H_1O$ $[M-H]^+$ calcd.: 171.0810, found: 171.0820.

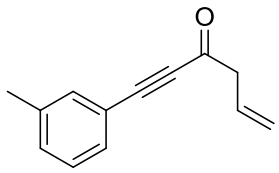
[224] A.R. Katritzky, K.N.B. Le, L. Khelashvili, P.P. Mohapatra, *J. Org. Chem.* **2006**, *71*, 9861–9864.

1-(4-Methoxyphenyl)hex-5-en-1-yn-3-one (1B)



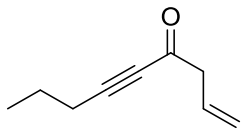
Prepared according to the general procedure starting from *N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropiolamide (550 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.83mL, 10.0 mmol, 4.0 equiv.). Yellow oil (220 mg, 1.1 mmol, 44%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.03 (ddt, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.31 – 5.18 (m, 2H), 3.85 (s, 3H), 3.41 (dt, *J* = 7.0, 1.4 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 186.4, 162.8, 136.3, 130.7, 120.6, 117.1, 115.5, 94.2, 88.7, 56.5, 50.9. **UPLC-DAD-QTOF:** $C_{13}H_3O_2$ $[M-H]^+$ calcd.: 201.0916, found: 201.0918.

1-(*m*-Tolyl)hex-5-en-1-yn-3-one (1C)



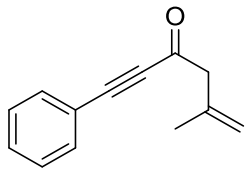
Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-(*m*-tolyl)propiolamide (550 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.83 mL, 10.0 mmol, 4.0 equiv.). Yellow oil (225 mg, 1.2 mmol, 49%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.45 – 7.34 (m, 2H), 7.27 (dd, *J* = 4.9, 1.2 Hz, 2H), 6.03 (ddt, *J* = 17.2, 10.4, 7.0 Hz, 1H), 5.32 – 5.15 (m, 2H), 3.42 (dt, *J* = 6.9, 1.4 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.4, 138.6, 133.7, 131.9, 130.4, 129.6, 128.76, 119.8, 92.4, 87.5, 50.1, 21.3. **UPLC-DAD-QTOF:** $C_{13}H_{13}O$ $[M-H]^+$ calcd.: 185.0966, found: 185.0970.

Non-1-en-5-yn-4-one (1D)



Prepared according to the general procedure starting from *N*-methoxy-*N*-methylhex-2-ynamide (387 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.83 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (170 mg, 1.25 mmol, 50%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 5.95 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.29 – 5.08 (m, 2H), 3.29 (dt, *J* = 7.0, 1.4 Hz, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 1.61 (h, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.5, 129.6, 119.4, 95.4, 80.9, 50.0, 21.3, 20.9, 13.4. **UPLC-DAD-QTOF:** $C_9H_{13}O$ $[M-H]^+$ calcd.: 137.0966, found: 137.0966.

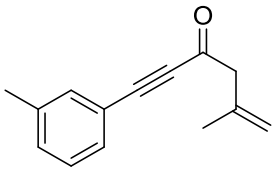
5-Methyl-1-phenylhex-5-en-1-yn-3-one (6A)



Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-phenylpropiolamide (473 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (437 mg, 2.37 mmol, 95%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.63 – 7.51 (m, 2H), 7.52 – 7.27 (m, 3H), 5.04 (d, *J* = 1.6 Hz, 1H), 4.97 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.36 (d, *J* = 1.1 Hz, 2H), 1.85 (t, *J* = 1.2 Hz,

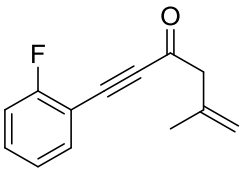
3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.1, 137.8, 132.9, 130.6, 128.4, 119.7, 115.8, 91.1, 87.5, 54.1, 22.4. **UPLC-DAD-QTOF:** $C_{13}H_{13}O$ $[M-H]^+$ calcd.: 185.0966, found: 185.0968.

5-Methyl-1-(*m*-tolyl)hex-5-en-1-yn-3-one (6B)



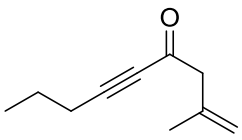
Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-(*m*-tolyl)propiolamide (505 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (446 mg, 2.25 mmol, 90%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 1.2 Hz, 2H), 7.28 (dd, *J* = 4.5, 1.6 Hz, 2H), 5.05 (s, 1H), 4.99 – 4.94 (m, 1H), 3.37 (d, *J* = 1.0 Hz, 2H), 2.36 (s, 3H), 1.86 (dd, *J* = 1.5, 0.9 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 186.5, 139.5, 139.1, 134.6, 132.7, 131.3, 129.5, 120.8, 117.1, 92.8, 88.5, 55.4, 23.7, 22.2. **UPLC-DAD-QTOF:** $C_{14}H_{15}O$ $[M-H]^+$ calcd.: 199.1123, found: 199.1122.

1-(2-Fluorophenyl)-5-methylhex-5-en-1-yn-3-one (6C)



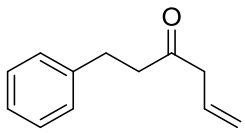
Prepared according to the general procedure starting from 3-(2-fluorophenyl)-*N*-methoxy-*N*-methylpropiolamide (502 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Yellow oil (465 mg, 2.3 mmol, 92%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.67 – 7.36 (m, 2H), 7.29 – 6.97 (m, 2H), 5.10 – 5.00 (m, 1H), 4.95 (dd, *J* = 2.1, 1.1 Hz, 1H), 3.50 – 3.30 (m, 2H), 1.83 (dd, *J* = 2.2, 1.2 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.6, 165.8, 138.2, 135.2, 133.4, 124.9, 116.8, 116.5, 116.3, 92.5, 85.1, 54.8, 23.2. **UPLC-DAD-QTOF:** $C_{13}H_{12}OF$ $[M-H]^+$ calcd.: 203.0872, found: 203.0869.

2-Methylnon-1-en-5-yn-4-one (6D)



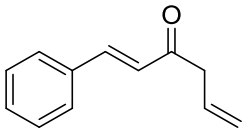
Prepared according to the general procedure starting from *N*-methoxy-*N*-methylhex-2-ynamide (388 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (348 mg, 2.32 mmol, 93%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.91 (q, *J* = 1.7 Hz, 1H), 4.81 (s, 1H), 3.16 (d, *J* = 1.3 Hz, 2H), 2.28 (dd, *J* = 7.8, 6.2 Hz, 2H), 1.73 (s, 3H), 1.54 (qd, *J* = 7.2, 1.6 Hz, 2H), 0.95 (td, *J* = 7.4, 1.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 183.0, 135.5, 113.1, 92.3, 78.3, 51.7, 19.9, 18.6, 18.3, 10.8. **UPLC-DAD-QTOF:** $C_{10}H_{15}O$ $[M-H]^+$ calcd.: 151.1123, found: 151.1125.

1-Phenylhex-5-en-3-one (9A)[225]



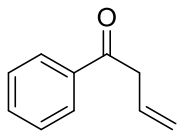
Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-phenylpropanamide (485 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.87 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (352 mg, 2.02 mmol, 81%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.36 – 7.09 (m, 5H), 5.93 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.31 – 4.96 (m, 2H), 3.16 (dt, *J* = 7.0, 1.4 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.83 – 2.73 (m, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 207.6, 142.0, 130.5, 128.5, 128.3, 126.1, 118.9, 47.9, 43.8, 29.7. **UPLC-DAD-QTOF:** $C_{12}H_{15}O$ $[M-H]^+$ calcd.: 175.1122, found: 175.1125.

(*E*)-1-Phenylhexa-1,5-dien-3-one (9B)



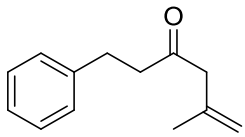
Prepared according to the general procedure starting from *N*-methoxy-*N*-methylcinnamamide (476 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.87 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (323 mg, 1.88 mmol, 75%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.66 – 7.48 (m, 4H), 7.39-7.36 (m, 3H), 6.76 (d, *J* = 16.1 Hz, 1H), 6.02 (ddt, *J* = 16.6, 10.7, 6.8 Hz, 1H), 5.37 – 4.81 (m, 2H), 3.43 (dt, *J* = 6.8, 1.4 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-d) δ 197.7, 143.1, 134.4, 130.9, 130.6, 129.0, 128.3, 125.5, 118.8, 45.9. **UPLC-DAD-QTOF:** $C_{12}H_{13}O$ $[M-H]^+$ calcd.: 173.0966, found: 173.0969.

1-Phenylbut-3-en-1-one (9C)[225]



Prepared according to the general procedure starting from *N*-methoxy-*N*-methylbenzamide (442 mg, 2.5 mmol, 1.0 equiv.) and allyl bromide (0.87mL, 10.0 mmol, 4.0 equiv.). Colourless oil (310 mg, 2.13 mmol, 85%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.13 – 6.06 (m, 1H), 5.25 – 5.19 (m, 2H), 3.76 (dd, *J* = 6.8, 1.2 Hz, 2H).

5-Methyl-1-phenylhex-5-en-3-one (10A)

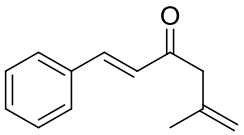


Prepared according to the general procedure starting from *N*-methoxy-*N*-methyl-3-phenylpropanamide (476 mg, 2.5mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (319 mg, 1.7 mmol, 68%). **^{1}H NMR** (300 MHz,

[225] G. Zhan, Q. He, X. Yuan, Y.C. Chen, *Org. Lett.* **2014**, *16*, 6000–6003.

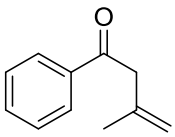
Chloroform-*d*) δ 7.34 – 7.26 (m, 2H), 7.25 – 7.12 (m, 3H), 4.97 – 4.91 (m, 1H), 4.82 (dd, *J* = 1.9, 1.0 Hz, 1H), 3.10 (d, *J* = 1.0 Hz, 2H), 2.92 (ddd, *J* = 8.3, 7.0, 1.7 Hz, 2H), 2.80 (ddd, *J* = 8.5, 6.9, 1.7 Hz, 2H), 1.74 (t, *J* = 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 207.7, 141.0, 139.1, 128.5, 128.4, 126.1, 115.1, 52.4, 43.3, 29.8, 22.6. **UPLC-DAD-QTOF:** $C_{13}H_{17}O$ $[M-H]^+$ calcd.: 189.1279, found: 189.1288.

(*E*)-5-Methyl-1-phenylhexa-1,5-dien-3-one (10B)



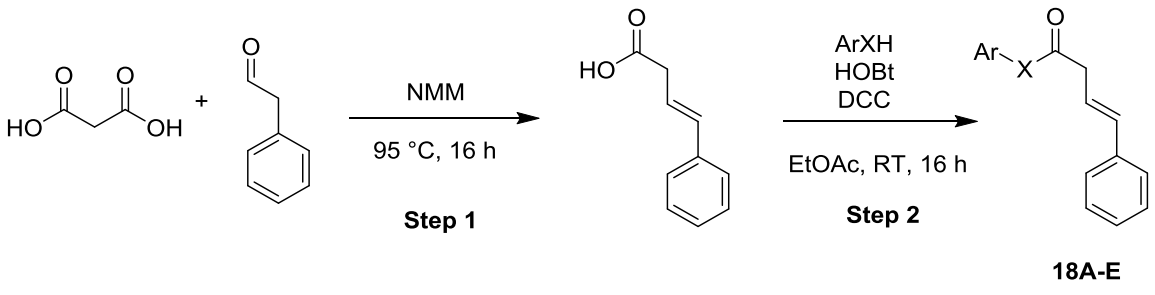
Prepared according to the general procedure starting from *N*-methoxy-*N*-methylcinnamamide (476 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (428 mg, 2.3 mmol, 92%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.72 – 7.48 (m, 3H), 7.40 (ddd, *J* = 3.4, 2.5, 1.4 Hz, 3H), 6.82 (d, *J* = 16.2 Hz, 1H), 4.99 (t, *J* = 1.6 Hz, 1H), 4.93 – 4.82 (m, 1H), 3.36 (d, *J* = 1.2 Hz, 2H), 1.80 (t, *J* = 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 196.6, 142.1, 138.9, 133.8, 129.8, 128.2, 127.7, 124.6, 114.3, 49.7, 22.0. **UPLC-DAD-QTOF**: $C_{13}H_{15}O$ $[M-H]^+$ calcd.: 187.1123, found: 187.1130.

3-Methyl-1-phenylbut-3-en-1-one (10C)



Prepared according to the general procedure starting from *N*-methoxy-*N*-methylbenzamide (413 mg, 2.5 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (1.0 mL, 10.0 mmol, 4.0 equiv.). Colourless oil (360 mg, 2.25 mmol, 90%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.05 – 7.94 (m, 2H), 7.70 – 7.55 (m, 1H), 7.55 – 7.42 (m, 2H), 5.03 (td, *J* = 1.5, 0.8 Hz, 1H), 4.90 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.78 – 3.57 (m, 2H), 1.86 (t, *J* = 1.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 197.2, 139.5, 136.5, 132.7, 128.1, 114.5, 47.2, 22.4. **UPLC-DAD-QTOF:** $C_{11}H_{13}O$ $[M-H]^+$ calcd.: 161.0966, found: 161.0960.

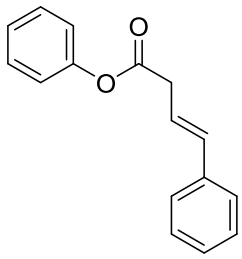
6.3.2.2. *Synthesis of β.γ-unsaturated esters/thioesters (18A-E)*



1st Step: [226] Phenylacetaldehyde (5.80 mL, 50.0 mmol, 1.0 equiv.) was added to a mixture of malonic acid (5.7 g, 55.0 mmol, 1.1 equiv.) and *N*-methylmorpholine (NMM) (5.6 g, 55.0 mmol, 1.1. equiv.). The reaction mixture was heated at 95 °C for 16 h. Then, the mixture was cooled to room temperature, and 11% H_2SO_4 (25.0 mL) was added with continuous stirring for 30 min. The mixture was extracted with CH_2Cl_2 (2 x 20.0 mL), washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 90/10) to obtain the acid as a yellow oil (6.89 g, 42.5 mmol, 85%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.18 (m, 5H), 6.61 – 6.48 (m, 1H), 6.32 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.33 (dd, *J* = 7.1, 1.4 Hz, 2H).

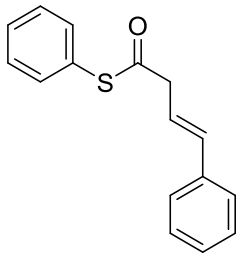
2nd Step:[227] To a solution of (*E*)-4-phenylbut-3-enoic acid (811 mg, 5.0 mmol, 1.0 equiv.) and 1-hydroxibenzotriazole (HOBt) (676 mg, 5.0 mmol, 1.0 equiv.) in dry EtOAc (50.0 mL) at 0 °C, the corresponding alcohol or thiol (10.0 mmol, 2.0 equiv.) was added. After 5 min, 1,3-dicyclohexylcarbodiimide (DCC) (1.08 g, 5.5 mmol, 1.1 equiv.) was added by portions. After stirring overnight at room temperature, the mixture was filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 98/2) to obtain the desired product **18**.

Phenyl (*E*)-4-phenylbut-3-enoate (18A)



Prepared according to the general procedure starting from phenol (940 mg, 10.0 mmol, 2.0 equiv.). White solid (835 mg, 3.5 mmol, 70%). **M. p.:** 76–78 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.19 (m, 8H), 7.16 – 7.08 (m, 2H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.40 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.50 (dd, *J* = 7.1, 1.4 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.6, 150.5, 136.5, 133.8, 129.2, 128.4, 127.5, 126.1, 125.6, 121.3, 120.8, 38.1. **UPLC-DAD-QTOF:** $C_{16}H_{15}O_2$ $[M-H]^+$ calcd.: 239.1072, found: 239.1069.

***S*-Phenyl (*E*)-4-phenylbut-3-enethioate (18B)**



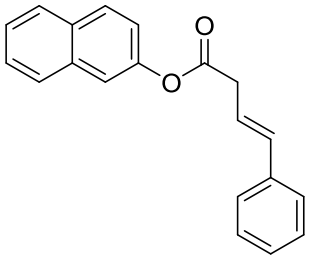
Prepared according to the general procedure starting from tiophenol (1.05 mL, 10.0 mmol, 2.0 equiv.). Colourless oil (826 mg, 3.25 mmol, 65%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.56 – 7.13 (m, 10H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.36 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.58 (dd, *J* = 7.2, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.7,

[226] S. -J. Zhang, W. -X. Hu, *Synthetic Communications* **2010**, *40*, 3093–3100.

[227] Adapted from: E. C. Garnier-Amblard, S. G. Mays, R. F. Arrendale, M. T. Baillie, A. S. Bushnev, D. G. Culver, T. J. Evers, J. J. Holt, R. B. Howard, L. S. Liebeskind, D. S. Menaldin, M. G. Natchus, J. A. Petros, H. Ramaraju, G. P. Reddy, D. C. Liotta, *Medd.Chem.Lett.* **2011**, *2*, 438–443.

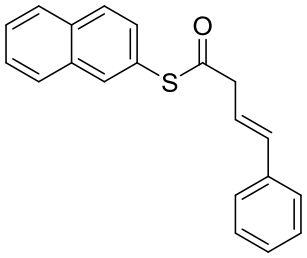
138.6, 137.1, 135.6, 134.9, 133.2, 129.7, 129.1, 128.3, 126.9, 121.2, 47.9. **UPLC-DAD-QTOF:** $C_{16}H_{15}OS$ $[M-H]^+$ calcd.: 255.0844, found: 255.0859.

Naphthalen-2-yl (*E*)-4-phenylbut-3-enoate (18C)



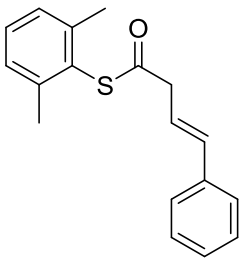
Prepared according to the general procedure starting from 2-naphthol (1.44 g, 10.0 mmol, 2.0 equiv.). White solid (1.04 g, 3.6 mmol, 72%). **M.p.:** 87–89 °C. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.97 – 7.76 (m, 3H), 7.64 – 7.57 (m, 1H), 7.54 – 7.40 (m, 4H), 7.41 – 7.19 (m, 4H), 6.66 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.46 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.57 (dd, *J* = 7.0, 1.4 Hz, 2H). **^{13}C NMR (**75 MHz, Chloroform-*d*) δ 170.3, 148.4, 136.8, 134.3, 133.9, 131.6, 129.6, 128.7, 127.9, 127.9, 127.8, 126.7, 126.5, 125.9, 121.2, 121.1, 118.6, 38.6. **UPLC-DAD-QTOF:** $C_{20}H_{17}O_2$ $[M-H]^+$ calcd.: 289.1229, found: 289.1225.

***S*-(Naphthalen-2-yl) (*E*)-4-phenylbut-3-enethioate (18D)**



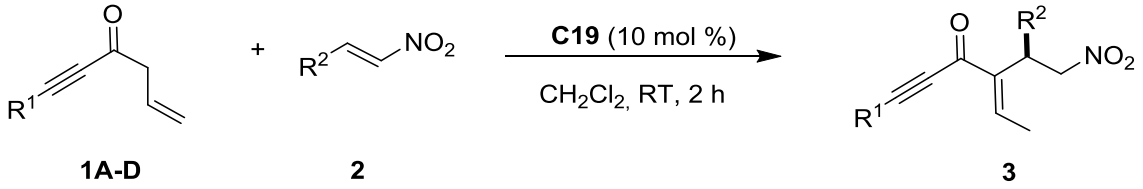
Prepared according to the general procedure starting from 2-naphthalenethiol (1.60 g, 10.0 mmol, 2.0 equiv.). Yellow solid (1.05 g, 3.45 mmol, 69%). **M.p.:** 91–93 °C. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.04 – 7.95 (m, 1H), 7.89 – 7.71 (m, 3H), 7.64 – 7.17 (m, 8H), 6.64 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.38 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.60 (dd, *J* = 7.2, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.3, 137.3, 135.8, 135.1, 134.2, 134.0, 131.5, 129.5, 129.3, 128.6, 128.5, 128.4, 127.8, 127.2, 127.1, 121.4, 48.2. **UPLC-DAD-QTOF:** $C_{20}H_{17}OS$ $[M-H]^+$ calcd.: 305.1000, found: 305.1003.

***S*-(2,6-Dimethylphenyl) (*E*)-4-phenylbut-3-enethioate (18E)**



Prepared according to the general procedure starting from 2,6-dimethylbenzenethiol (1.38 g, 10.0 mmol, 2.0 equiv.). Yellow oil (916 mg, 3.25 mmol, 65%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.22 (m, 2H), 7.17 (s, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.55 – 6.23 (m, 1H), 3.58 (dd, *J* = 7.1, 1.5 Hz, 2H), 2.40 (d, *J* = 1.8 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 194.7, 142.9, 136.9, 135.1, 130.1, 128.8, 128.5, 128.0, 126.7, 121.3, 47.8, 21.9. **UPLC-DAD-QTOF:** $C_{18}H_{19}OS$ $[M-H]^+$ calcd.: 283.1157, found: 238.1155.

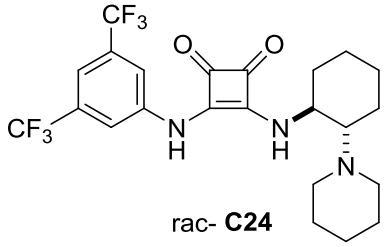
6.3.3. General procedure for the catalytic conjugate addition of allyl ynones 1A-D to nitroolefins 2



1A-D **2** **3**

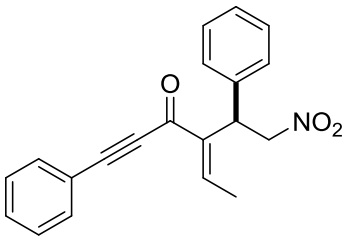
General procedure: To a solution of the corresponding ynone **1A-D** (0.4 mmol, 2.0 equiv.) and nitroolefin **2** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL), catalyst **C19** (13 mg, 0.02 mmol, 10 mol%) was added at room temperature and the resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 97/3) to obtain the desired Michael adducts **3**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

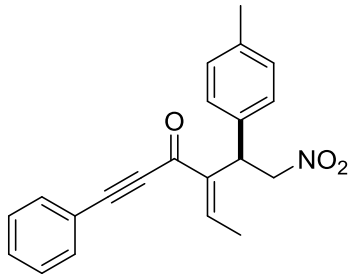
(*R*,*E*)-4-(2-Nitro-1-phenylethyl)-1-phenylhex-4-en-1-yn-3-one (3Aa)



Prepared according to the general procedure starting from allyl ketone **1A** (68 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (43 mg, 0.14 mmol, 68%). $[\alpha]_D^{25}$ = +42.7° (*c*=1.0, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.67 – 7.52 (m, 3H), 7.48 – 7.21 (m, 8H), 5.28 (dd, *J* = 13.0, 8.5 Hz, 1H), 5.15 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.88 (dd, *J* = 8.5, 6.7 Hz, 1H), 2.16 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.4, 150.3, 141.3, 137.9, 132.9, 130.7, 129.0, 128.7, 127.8, 127.6, 120.1, 92.1, 86.1, 77.0, 41.5, 15.5. **UPLC-DAD-QTOF:** $C_{20}H_{18}NO_3$ $[M-H]^+$ calcd.: 320.1287, found: 320.1288.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min). Retention times: 19.4 min (minor) and 31.0 min (major).

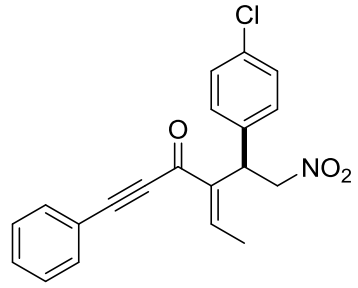
(*R*,*E*)-4-(2-Nitro-1-(*p*-tolyl)ethyl)-1-phenylhex-4-en-1-yn-3-one (3Ac)



Prepared according to the general procedure starting from allyl ketone **1A** (68 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2c** (32 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (46 mg, 0.14 mmol, 69%). **$[\alpha]_D^{25}$** = +54.9° (*c*=1.0, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.64 – 7.50 (m, 2H), 7.48 – 7.32 (m, 3H), 7.20 – 7.08 (m, 5H), 5.30 – 5.20 (m, 1H), 5.12 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.87 – 4.72 (m, 1H), 2.31 (s, 3H), 2.15 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.0, 149.7, 141.0, 136.9, 134.5, 132.4, 130.3, 129.2, 128.3, 127.3, 119.7, 91.5, 85.7, 76.9, 40.8, 20.7, 15.1. **UPLC-DAD-QTOF:** $C_{21}H_{20}NO_3$ $[M-H]^+$ calcd.: 334.1443, found: 334.1448.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min). Retention times: 19.6 min (minor) and 37.5 min (major).

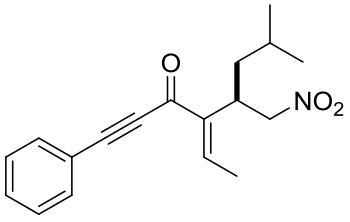
(*R*,*E*)-4-(1-(4-Chlorophenyl)-2-nitroethyl)-1-phenylhex-4-en-1-yn-3-one (3Ad)



Prepared according to the general procedure starting from allyl ketone **1A** (68 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2d** (36 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (48 mg, 0.14 mmol, 71%). **$[\alpha]_D^{25}$** = +38.0° (*c*=1.1, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.67 – 7.53 (m, 3H), 7.50 – 7.35 (m, 3H), 7.28 (q, *J* = 8.5 Hz, 4H), 5.35 – 5.04 (m, 2H), 4.86 (t, *J* = 7.6 Hz, 1H), 2.18 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 180.2, 151.4, 141.9, 137.4, 134.5, 133.9, 131.8, 130.2, 130.1, 129.7, 120.9, 93.4, 86.9, 41.9, 16.5. **UPLC-DAD-QTOF:** $C_{20}H_{17}NO_3$ $[M-H]^+$ calcd.: 354.0897, found: 354.0894.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 70/30, flow rate= 0.5 mL/min). Retention times: 24.3 min (minor) and 47.1 min (major).

(*R*,*E*)-4-Ethylidene-7-methyl-5-(nitromethyl)-1-phenyloct-1-yn-3-one (3Ae)

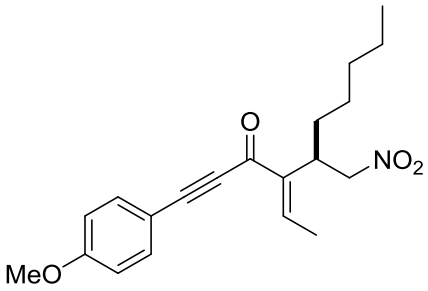


Prepared according to the general procedure starting from allyl ketone **1A** (68 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2e** (26 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (43 mg, 0.14 mmol, 72%). **$[\alpha]_D^{25}$** = −39.9° (*c*=0.7, 97% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.70 – 7.54 (m,

3H), 7.52 – 7.34 (m, 3H), 4.90 (dd, *J* = 12.2, 9.4 Hz, 1H), 4.58 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.66 (tt, *J* = 9.3, 5.5 Hz, 1H), 2.09 (d, *J* = 7.2 Hz, 3H), 1.91 – 1.76 (m, 1H), 1.55 – 1.33 (m, 2H), 0.95 (dd, *J* = 6.3, 2.3 Hz, 6H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.5, 150.4, 140.4, 132.7, 130.5, 128.6, 120.1, 91.4, 86.0, 78.1, 38.9, 35.1, 25.9, 23.1, 21.9, 15.2. **UPLC-DAD-QTOF:** $C_{18}H_{22}NO_3$ $[M-H]^+$ calcd.: 300.1600, found: 300.1609.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min). Retention times: 15.4 min (minor) and 16.7 min (major).

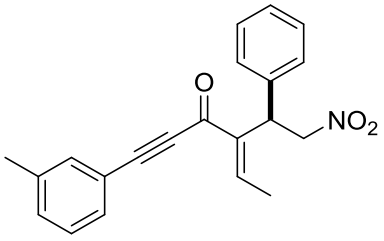
(*R*,*E*)-4-Ethylidene-1-(4-methoxyphenyl)-5-(nitromethyl)dec-1-yn-3-one (3Bf)



Prepared according to the general procedure starting from allyl ketone **1B** (80 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2f** (29 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (47 mg, 0.14 mmol, 69%). **$[\alpha]_D^{25}$** = −27.1° (*c*=0.5, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.65 – 7.48 (m, 3H), 6.95 – 6.72 (m, 2H), 4.86 (dd, *J* = 12.4, 9.0 Hz, 1H), 4.59 (dd, *J* = 12.4, 5.8 Hz, 1H), 3.84 (s, 3H), 3.51 (tt, *J* = 9.4, 5.6 Hz, 1H), 2.03 (d, *J* = 7.1 Hz, 3H), 1.89 – 1.72 (m, 1H), 1.69 – 1.46 (m, 1H), 1.34 – 1.14 (m, 6H), 0.86 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.6, 161.6, 150.1, 148.9, 140.5, 134.9, 134.1, 114.5, 112.1, 92.5, 86.0, 78.2, 55.6, 37.4, 31.7, 30.3, 27.3, 22.6, 15.3, 14.1. **UPLC-DAD-QTOF:** $C_{20}H_{26}NO_4$ $[M-H]^+$ calcd.: 334.1862, found: 334.1872.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min). Retention times: 16.2 min (major) and 23.6 min (minor).

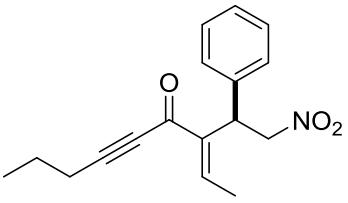
(*R*,*E*)-4-(2-Nitro-1-phenylethyl)-1-(*m*-tolyl)hex-4-en-1-yn-3-one (3Ca)



Prepared according to the general procedure starting from allyl ketone **1C** (74 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (51 mg, 0.15 mmol, 77%). **$[\alpha]_D^{25}$** = +22.9° (*c*=0.7, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.71 – 7.55 (m, 1H), 7.48 – 7.26 (m, 9H), 5.31 (dd, *J* = 13.0, 8.5 Hz, 1H), 5.19 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.92 (dd, *J* = 8.4, 6.7 Hz, 1H), 2.38 (s, 3H), 2.19 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.8, 150.7, 141.7, 139.0, 138.4, 133.8, 132.1, 130.5, 129.4, 129.1, 128.3, 128.1, 120.4, 92.9, 77.7, 42.0, 21.8, 16.0. **UPLC-DAD-QTOF:** $C_{21}H_{20}NO_3$ $[M-H]^+$ calcd.: 334.1443, found: 334.1454.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min). Retention times: 38.2 min (minor) and 63.0 min (major).

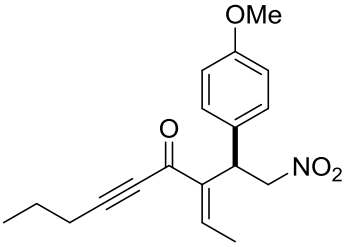
(*R*,*E*)-3-(2-Nitro-1-phenyleth yl)non-2-en-5-yn-4-one (3Da)



Prepared according to the general procedure starting from allyl ketone **1D** (54 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (43 mg, 0.15 mmol, 75%). **$[\alpha]_D^{25}$** = +36.5° (*c*=0.8, 97% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.52 (q, *J* = 7.2 Hz, 1H), 7.39 – 7.19 (m, 5H), 5.26 (dd, *J* = 13.0, 8.4 Hz, 1H), 5.15 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.86 (dd, *J* = 8.4, 6.7 Hz, 1H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.14 (d, *J* = 7.1 Hz, 3H), 1.73 – 1.56 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.5, 149.9, 141.1, 138.1, 128.9, 127.8, 127.5, 95.4, 79.0, 77.2, 41.4, 21.4, 21.1, 15.4, 13.7. **UPLC-DAD-QTOF:** $C_{17}H_{20}NO_3$ $[M-H]^+$ calcd.: 286.1443, found: 286.1451.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min). Retention times: 24.5 min (minor) and 41.7 min (major).

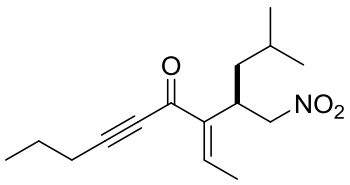
(*R*,*E*)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)non-2-en-5-yn-4-one (3Db)



Prepared according to the general procedure starting from allyl ketone **1D** (54 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2b** (36 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (45 mg, 0.14 mmol, 72%). **$[\alpha]_D^{25}$** = +41.6° (*c*=1.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) 7.44 (q, *J* = 7.2 Hz, 1H), 7.25 – 7.13 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.17 (dd, *J* = 12.9, 8.3 Hz, 1H), 5.06 (dd, *J* = 12.9, 6.9 Hz, 1H), 4.79 – 4.70 (m, 1H), 3.76 (s, 3H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.08 (d, *J* = 7.2 Hz, 3H), 1.61 (q, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 179.2, 158.4, 149.1, 140.9, 129.6, 128.5, 113.7, 94.8, 78.5, 77.0, 54.8, 40.4, 20.9, 20.6, 14.8, 13.2. **UPLC-DAD-QTOF:** $C_{18}H_{22}NO_4$ $[M-H]^+$ calcd.: 316.1549, found: 316.1553.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min). Retention times: 27.9 min (minor) and 52.0 min (major).

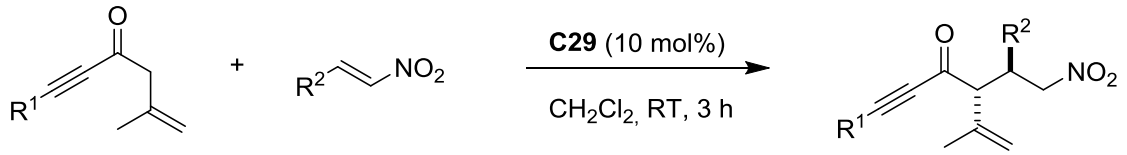
(*R*,*E*)-7-Ethylidene-10-methyl-8-(nitromethyl)undec-4-yn-6-one (3De)



Prepared according to the general procedure starting from allyl ketone **1D** (54 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2e** (26 mg, 0.2 mmol, 1.0 equiv.). Colourless oil (37 mg, 0.14 mmol, 70%). $[\alpha]_D^{25}$ = −13.1° (*c*=0.4, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42 (q, *J* = 7.2 Hz, 1H), 4.80 (dd, *J* = 12.2, 9.3 Hz, 1H), 4.50 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.56 (tt, *J* = 9.2, 5.4 Hz, 1H), 2.37 (t, *J* = 7.1 Hz, 2H), 2.00 (d, *J* = 7.1 Hz, 3H), 1.75 (ddd, *J* = 12.7, 9.1, 4.7 Hz, 1H), 1.63 (q, *J* = 7.2 Hz, 2H), 1.43 – 1.24 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.88 (dd, *J* = 6.3, 3.8 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 179.7, 149.9, 140.3, 94.7, 78.9, 78.2, 39.0, 35.1, 25.9, 23.1, 21.9, 21.3, 20.9, 15.1, 13.6. **UPLC-DAD-QTOF:** $C_{15}H_{24}NO_3$ $[M-H]^+$ calcd.: 266.1782, found: 266.1788.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 98/2, flow rate= 1.0 mL/min). Retention times: 14.5 min (minor) and 17.5 min (major).

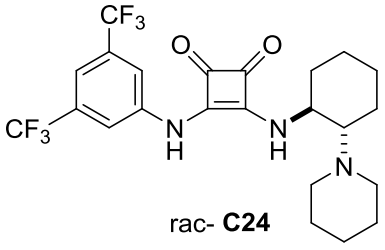
6.3.4. General procedure for the catalytic conjugate addition of ynones 6A-D to nitroolefin 2



6A-D **2** **7**

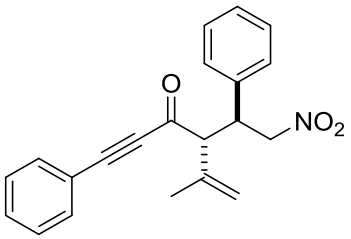
General Procedure: To a solution of ynone **6A-D** (0.4 mmol, 2.0 equiv.) and nitroolefin **2** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL) at RT, the catalyst **C29** (26 mg, 0.02 mmol, 10 mol%) was added at RT. The resulting mixture was stirred at the same temperature for 3 h. The crude was submitted to a flash column chromatography (hexane/ethyl acetate 97/3) to obtain the desired Michael adducts **7**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

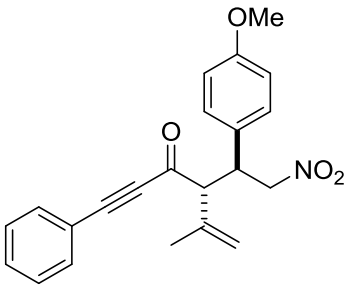
(*R*)-5-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenylhex-5-en-1-yn-3-one (7Aa)



Prepared according to the general procedure starting from ynone **6A** (74 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (55 mg, 0.16 mmol, 82%). **M.p.:** 126.7–129.9 °C. $[\alpha]_D^{24}$ = –70.6° (*c*=1.0, 94% *ee*, CH_2Cl_2).**^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.60 – 7.18 (m, 10H), 5.36 (q, *J* = 0.9 Hz, 1H), 5.31 (t, *J* = 1.4 Hz, 1H), 4.66 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.57 (dd, *J* = 12.6, 10.1 Hz, 1H), 4.23 (ddd, *J* = 11.8, 10.0, 4.4 Hz, 1H), 3.93 (d, *J* = 11.8 Hz, 1H), 1.93 (dd, *J* = 1.6, 0.8 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 184.0, 139.3, 137.8, 133.8, 131.7, 129.6, 129.3, 128.8, 128.8, 119.9, 110.7, 93.0, 87.9, 79.7, 65.9, 43.5, 20.8. **UPLC-DAD-QTOF:** $C_{21}H_{20}NO_3$ $[M-H]^+$ calcd.: 334.1443, found: 334.1443.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 11.3 min (major) and 13.0 min (minor) and for minor diastereomer: 18.8 min (major) and 24.0 min (minor).

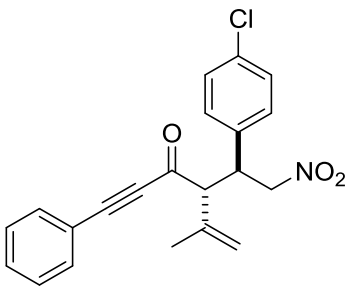
(*R*)-4-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-5-methyl-1-phenylhex-5-en-1-yn-3-one (7Ab)



Prepared according to the general procedure starting from ynone **6A** (74 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2b** (36 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (54 mg, 0.15 mmol, 75%). **M.p.:** 122.7–124.1 °C. $[\alpha]_D^{25}$ = –116.0° (*c*=1.0, 98% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.58 – 7.34 (m, 5H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.38 – 5.32 (m, 1H), 5.30 (m, 1H), 4.63 (dd, *J* = 12.4, 4.3 Hz, 1H), 4.52 (dd, *J* = 12.4, 10.2 Hz, 1H), 4.18 (ddd, *J* = 11.9, 10.2, 4.3 Hz, 1H), 3.87 (d, *J* = 11.8 Hz, 1H), 3.77 (s, 3H), 1.93 (dd, *J* = 1.5, 0.8 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 182.1, 157.8, 137.2, 131.6, 129.5, 127.8, 127.5, 127.2, 118.2, 117.6, 112.9, 90.9, 85.8, 77.7, 64.0, 53.7, 40.8, 18.7. **UPLC-DAD-QTOF:** $C_{22}H_{22}NO_4$ $[M-H]^+$ calcd.: 364.1549, found: 364.1546.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 22.3 min (major) and 25.9 min (minor) and for minor diastereomer: 33.8 min (major) and 46.4 min (minor).

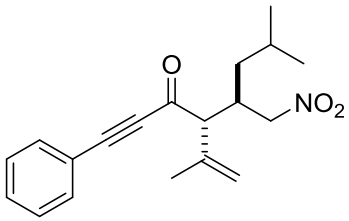
(*R*)-4-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-5-methyl-1-phenylhex-5-en-1-yn-3-one (7Ad)



Prepared according to the general procedure starting from ynone **6A** (74 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2d** (37 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (58 mg, 0.16 mmol, 80%). **M.p.:** 112.4–116.0 °C. **$[\alpha]_D^{25}$** = –102.5° (*c*=1.0, 93% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.83 – 7.12 (m, 9H), 5.37 – 5.34 (m, 1H), 5.33 – 5.31 (m, 1H), 4.64 (dd, *J* = 12.7, 4.4 Hz, 1H), 4.53 (dd, *J* = 12.7, 10.3 Hz, 1H), 4.20 (ddd, *J* = 11.8, 10.2, 4.3 Hz, 1H), 3.88 (d, *J* = 11.8 Hz, 1H), 1.92 (dd, *J* = 1.5, 0.8 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 182.0, 137.3, 134.8, 132.9, 132.1, 130.1, 128.6, 128.5, 128.1, 127.7, 118.5, 91.2, 86.2, 77.7, 64.2, 41.1, 19.0. **UPLC-DAD-QTOF:** $C_{21}H_{19}ClNO_3$ $[M-H]^+$ calcd.: 368.1053, found: 368.053.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min). Retention times for the major diastereomer: 12.0 min (major) and 14.8 min (minor) and for minor diastereomer: 21.3 min (major) and 34.2 min (minor)

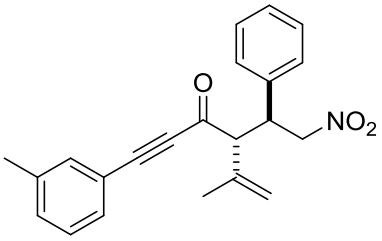
(4*R*,5*R*)-7-Methyl-5-(nitromethyl)-1-phenyl-4-(prop-1-en-2-yl)oct-1-yn-3-one (7Ae)



Prepared according to the general procedure starting from ynone **6A** (74 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2e** (26 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. 44% of conversion. Yellow oil (18.8 mg, 0.06 mmol, 30%). **$[\alpha]_D^{25}$** = –22.6° (*c*=0.5, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.63 – 7.53 (m, 2H), 7.52 – 7.38 (m, 3H), 5.25 (s, 1H), 5.21 – 5.14 (m, 1H), 4.55 (dd, *J* = 13.0, 4.4 Hz, 1H), 4.40 (dd, *J* = 13.0, 5.0 Hz, 1H), 3.59 (d, *J* = 10.6 Hz, 1H), 2.94 (tq, *J* = 9.3, 4.5 Hz, 1H), 1.85 (dd, *J* = 1.5, 0.9 Hz, 3H), 1.79 – 1.63 (m, 1H), 1.45 – 1.32 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 185.9, 139.8, 133.8, 131.7, 129.4, 126.9, 119.6, 92.7, 88.2, 77.1, 65.5, 40.5, 35.2, 26.1, 24.3, 22.0, 21.7. **UPLC-DAD-QTOF:** $C_{19}H_{24}NO_3$ $[M-H]^+$ calcd.: 314.1756, found: 314.1762.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 99/1, flow rate= 1 mL/min). Retention times: 18.7 min (major) and 23.7 min (minor).

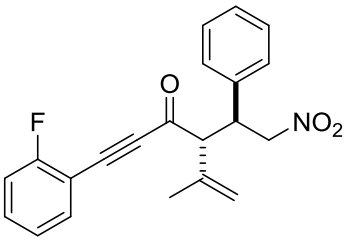
(*R*)-5-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-(m-tolyl)hex-5-en-1-yn-3-one (7Ba)



Prepared according to the general procedure starting from ynone **6B** (79 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (53 mg, 0.15 mmol, 75%). **M.p.:** 105.1–107.3 °C. $[\alpha]_D^{25}$ = –56.7° (*c*=1.0, 95% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.45 – 7.10 (m, 9H), 5.36 (d, *J* = 0.8 Hz, 1H), 5.31 (d, *J* = 2.8 Hz, 1H), 4.66 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.57 (dd, *J* = 12.6, 10.0 Hz, 1H), 4.23 (ddd, *J* = 11.8, 10.0, 4.4 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 1.93 (dd, *J* = 1.5, 0.8 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 184.0, 139.3, 137.9, 134.2, 132.6, 130.9, 130.1, 130.1, 129.6, 129.2, 128.8, 128.7, 128.2, 119.8, 93.5, 87.7, 79.7, 65.9, 43.5, 21.8, 20.8. **UPLC-DAD-QTOF:** $C_{22}H_{22}NO_3$ $[M-H]^+$ calcd.: 348.1600, found: 348.1599.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min). Retention times for the major diastereomer: 12.3 min (major) and 14.3 min (minor) and for minor diastereomer: 23.1 min (major) and 28.8 min (minor).

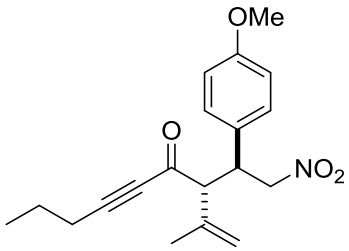
(*R*)-1-(2-Fluorophenyl)-5-methyl-4-((S)-2-nitro-1-phenylethyl)hex-5-en-1-yn-3-one (7Ca)



Prepared according to the general procedure starting from ynone **6C** (81 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (59 mg, 0.17 mmol, 85%). **M.p.:** 142.8–146.7 °C. $[\alpha]_D^{25}$ = –112.9° (*c*=1.0, 99% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.52 – 7.42 (m, 2H), 7.38 – 7.23 (m, 5H), 7.22 – 7.08 (m, 2H), 5.41 – 5.35 (m, 1H), 5.32 (s, 1H), 4.67 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.57 (dd, *J* = 12.6, 10.1 Hz, 1H), 4.26 (ddd, *J* = 11.9, 10.1, 4.4 Hz, 1H), 3.93 (d, *J* = 11.9 Hz, 1H), 1.94 (d, *J* = 0.6 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 181.8, 164.1, 137.0, 135.8, 133.5, 131.9, 131.7, 127.7, 126.9, 126.8, 123.1, 123.1, 118.1, 114.8, 114.5, 90.2, 84.4, 77.7, 63.8, 41.6, 19.0. **UPLC-DAD-QTOF:** $C_{21}H_{22}NO_3F$ $[M-H]^+$ calcd.: 352.1349, found: 352.1351.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 13.3 min (major) and 15.5 min (minor) and for minor diastereomer: 22.9 min (major) and 32.1 min (minor).

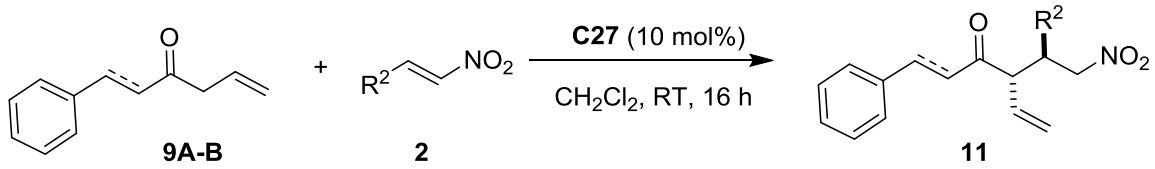
(*R*)-3-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-2-methylnon-1-en-5-yn-4-one (7Db)



Prepared according to the general procedure starting from ynone **6D** (60 mg, 0.4 mmol. 2.0 equiv.) and nitroolefin **2b** (36 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (46 mg, 0.14 mmol, 70%). **M.p.:** 97.3–99.1 °C. **$[\alpha]_D^{25}$** = –57.3° (*c*=0.5, 93% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.18 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.25 (s, 1H), 5.24 (s, 1H), 4.59 (dd, *J* = 12.4, 4.3 Hz, 1H), 4.47 (dd, *J* = 12.4, 10.3 Hz, 1H), 4.10 (ddd, *J* = 11.8, 10.3, 4.3 Hz, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 11.9 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.87 (dd, *J* = 1.5, 0.9 Hz, 3H), 1.64 – 1.54 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 184.4, 159.8, 139.4, 129.9, 119.4, 115.0, 96.7, 81.1, 79.8, 66.0, 55.8, 42.8, 21.8, 21.6, 20.7, 14.1. **UPLC-DAD-QTOF:** $C_{19}H_{24}NO_4$ $[M-H]^+$ calcd.: 330.1705, found: 330.1709.

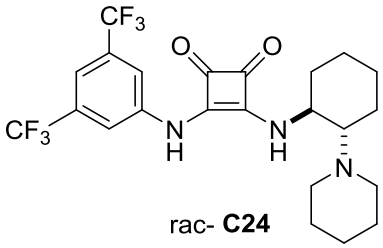
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 18.6 min (major) and 20.6 min (minor) and for minor diastereomer: 22.8 min (major) and 32.7 min (minor).

6.3.5. General procedure for the catalytic conjugate addition of allyl ketones 9A-B to nitroolefins 2



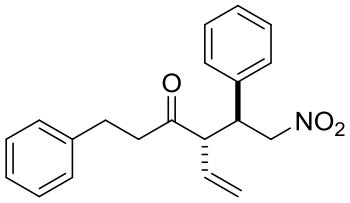
General procedure: To a mixture of the allyl ketone **9A-B** (0.4 mmol, 2.0 equiv.) and the corresponding nitroolefin **2** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL), the catalyst **C27** (10 mg, 0.02 mmol, 10 mol%) was added at room temperature. The resulting mixture was stirred at the same temperature for 16 h. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 97/3) to obtain the desired Michael adducts **11**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

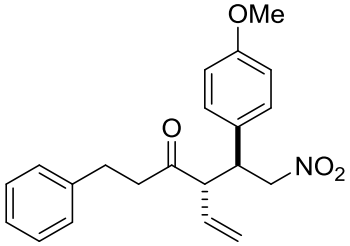
(*S*)-4-((*S*)-2-Nitro-1-phenylethyl)-1-phenylhex-5-en-3-one (11Aa)



Prepared according to the general procedure starting from allyl ketone **9A** (70 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr:17:1). Colourless oil (47 mg, 0.15 mmol, 73%). $[\alpha]_D^{25}$ = −55.8° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-d) δ 7.36 – 7.04 (m, 10H), 5.73 (dt, J = 17.2, 9.7 Hz, 1H), 5.37 – 5.28 (m, 2H), 4.70 (dd, J = 12.9, 5.0 Hz, 1H), 4.65 – 4.46 (m, 1H), 3.96 (td, J = 10.4, 5.1 Hz, 1H), 3.56 (t, *J* = 10.1 Hz, 1H), 2.93 – 2.52 (m, 3H), 2.33 – 2.30 (m, 1H) . **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 206.2, 139.8, 136.7, 135.1, 132.5, 131.2, 128.9, 128.6, 128.3, 127.7, 127.4, 127.2, 126.5, 125.3, 120.9, 92.7, 77.7, 60.5, 43.9, 43.8, 28.2. **UPLC-DAD-QTOF:** $C_{20}H_{22}NO_3$ $[M-H]^+$ calcd.: 324.1600, found: 324.1609.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 99/1, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 18.6 min (major) and 20.5 min (minor) and for minor diastereomer: 15.6 min (major) and 19.6 min (minor).

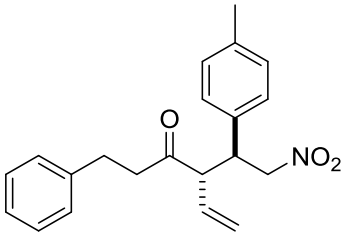
(*S*)-4-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1-phenylhex-5-en-3-one (11Ab)



Prepared according to the general procedure starting from allyl ketone **9A** (70 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2b** (36 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 18:1). Colourless oil (51 mg, 0.14 mmol, 72%). $[\alpha]_D^{25}$ = −51.7° (*c*=0.6, 91% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.39 – 7.02 (m, 5H), 7.02 – 6.89 (m, 2H), 6.91 – 6.78 (m, 2H), 5.72 (dt, *J* = 17.2, 9.8 Hz, 1H), 5.37 – 5.26 (m, 2H), 4.67 (dd, *J* = 12.7, 4.9 Hz, 1H), 4.57 – 4.39 (m, 1H), 3.90 (td, *J* = 10.3, 4.9 Hz, 1H), 3.78 (s, 3H), 3.53 (t, *J* = 10.1 Hz, 1H), 2.87 – 2.54 (m, 3H), 2.39 – 2.18 (m, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 207.5, 159.6, 140.9, 133.8, 129.7, 129.3, 128.8, 128.5, 126.4, 121.9, 114.8, 79.0, 61.8, 55.6, 44.9, 44.4, 29.3. **UPLC-DAD-QTOF:** $C_{21}H_{24}NO_4$ $[M-H]^+$ calcd.: 354.1705, found: 354.1699.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 99/1, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 34.2 min (major) and 44.9 min (minor) and for minor diastereomer: 28.9 min (major) and 38.0 min (minor).

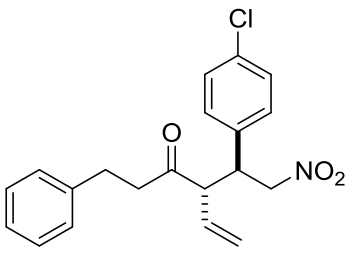
(*S*)-4-((*S*)-2-Nitro-1-(*p*-tolyl)ethyl)-1-phenylhex-5-en-3-one (11Ac)



Prepared according to the general procedure starting from allyl ketone **9A** (70 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2c** (32 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 17:1). Colourless oil (47 mg, 0.14 mmol, 70%). $\mathbf{[\alpha]_D^{25}}$ = −59.6° (*c*=0.8, 97% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.41 – 6.76 (m, 9H), 5.77 (dt, *J* = 17.2, 9.8 Hz, 1H), 5.41 – 5.32 (m, 2H), 4.72 (dd, *J* = 12.8, 5.0 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.01 – 3.89 (m, 1H), 3.58 (t, *J* = 10.1 Hz, 1H), 2.93 – 2.53 (m, 3H), 2.35 (s, 3H), 2.32 – 2.23 (m, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 207.4, 140.9, 138.1, 134.6, 133.8, 130.7, 130.1, 128.5, 128.1, 126.4, 121.9, 78.9, 61.7, 44.9, 44.8, 29.3, 21.5. **UPLC-DAD-QTOF:** $C_{21}H_{24}NO_3$ $[M-H]^+$ calcd.: 338.1756, found: 338.1760.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 21.3 min (major) and 30.8 min (minor) and for minor diastereomer: 25.2 min (minor) and 47.2 min (major).

(*S*)-4-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-1-phenylhex-5-en-3-one (11Ad)

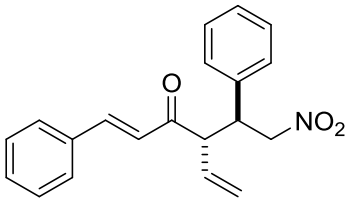


Prepared according to the general procedure starting from allyl ketone **9A** (70 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2d** (36 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 15:1). Colourless oil (51 mg, 0.15 mmol, 75%). $\mathbf{[\alpha]_D^{25}}$ = −32.9° (*c*=0.5, 93% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.41 – 6.87 (m, 9H), 5.68 (ddd, *J* = 17.2, 10.6, 8.7 Hz, 1H), 5.42 – 5.25 (m, 2H), 4.68 (dd, *J* = 13.0, 4.8 Hz, 1H), 4.59 – 4.44 (m, 1H), 4.03 – 3.85 (m, 1H), 3.63 – 3.37 (m, 1H), 2.95 – 2.53 (m, 3H), 2.30 (ddd, *J* = 16.8, 8.0, 5.9 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 207.2, 141.1, 136.6, 135.9, 134.6, 133.5, 130.3, 129.9,

129.9, 129.7, 129.2, 129.1, 128.8, 126.8, 122.8, 78.9, 61.7, 45.0, 44.6, 29.6. **UPLC-DAD-QTOF:** $C_{20}H_{21}NO_3Cl$ $[M-H]^+$ calcd.: 358.1210, found: 358.1212.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 99/1, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 31.0 min (major) and 60.6 min (minor) and for minor diastereomer: 27.8 min (major) and 41.9 min (minor).

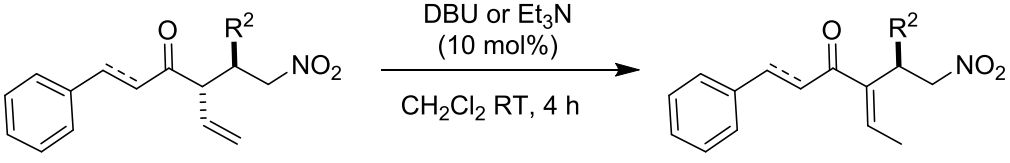
(*S*,*E*)-4-((*S*)-2-Nitro-1-phenylethyl)-1-phenylhexa-1,5-dien-3-one (11Ba)



Prepared according to the general procedure starting from allyl ketone **9B** (70 mg, 0.4 mmol, 2.0 equiv.) and nitroolefin **2a** (30 mg, 0.2 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 18:1). Colourless oil (52 mg, 0.16 mmol, 81%). $[\alpha]_D^{25}$ = −7.7° (*c*=0.5, 84% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.51 – 7.12 (m, 11H), 6.58 (d, *J* = 16.0 Hz, 1H), 5.86 (dt, *J* = 17.1, 9.7 Hz, 1H), 5.56 – 5.40 (m, 2H), 4.81 (dd, *J* = 12.9, 4.8 Hz, 1H), 4.66 (dd, *J* = 12.8, 9.7 Hz, 1H), 4.10 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.91 (t, *J* = 9.7 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 197.2, 144.5, 141.7, 138.3, 134.8, 134.1, 131.5, 129.6, 129.5, 129.1, 128.6, 125.2, 122.6, 79.2, 60.0, 45.2. **UPLC-DAD-QTOF:** $C_{20}H_{20}NO_3$ $[M-H]^+$ calcd.: 322.1443, found: 322.1450.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 85/15, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 27.9 min (major) and 68.1 min (minor) and for minor diastereomer: 45.7 min (minor) and 54.1 min (major).

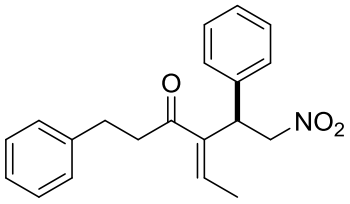
6.3.6. Isomerization of adducts 11 to α,β-enones 13



11 **13**

General procedure: DBU or Et_3N (0.01 mmol, 10 mol%) was added at room temperature to a solution of diastereomeric mixture of the corresponding adduct **11** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL) and the resulting mixture was stirred at the same temperature for 4 h. The reaction mixture was directly submitted to flash column chromatography (hexane/ethyl acetate 97/3) to obtain the desired adducts **13**.

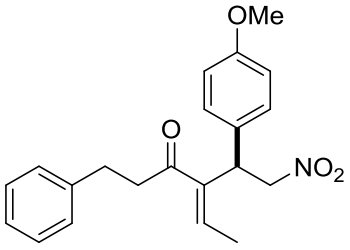
(*R*,*E*)-4-(2-Nitro-1-phenylethyl)-1-phenylhex-4-en-3-one (13Aa)



Prepared according to the general procedure starting from the adduct **11Aa** (31 mg, 0.1 mmol, 1.0 equiv.) and employing DBU (1.5 µL, 0.02 mmol, 10 mol%) as base. Colourless oil (31 mg, 0.10 mmol, 98%). $[\alpha]_D^{25}$ = −12.3° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.40 – 7.11 (m, 10H), 6.94 (q, *J* = 7.0 Hz, 1H), 5.26 (dd, *J* = 12.7, 8.7 Hz, 1H), 5.13 (dd, *J* = 12.7, 6.5 Hz, 1H), 4.82 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.10 – 2.81 (m, 4H), 2.04 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 200.6, 142.0, 141.1, 140.7, 138.5, 128.9, 128.6, 128.4, 127.7, 127.4, 126.2, 77.6, 42.0, 40.1, 30.5, 14.9. **UPLC-DAD-QTOF:** $C_{20}H_{22}NO_3$ $[M-H]^+$ calcd.: 324.1600, found: 324.1608.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 12.6 min (minor) and 14.6 min (major).

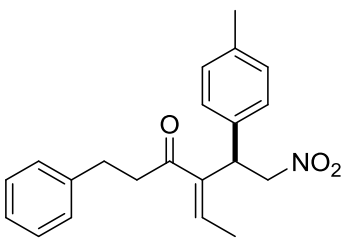
(*R*,*E*)-4-(1-(4-Methoxyphenyl)-2-nitroethyl)-1-phenylhex-4-en-3-one (13Ab)



Prepared according to the general procedure starting from the adduct **11Ab** (33 mg, 0.1 mmol, 1.0 equiv.) and employing DBU (1.5 µL, 0.01 mmol, 10 mol%) as base. Colourless oil (33 mg, 0.10 mmol, 98%). $[\alpha]_D^{25}$ = −18.1° (*c*=0.7, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.35 – 7.05 (m, 7H), 6.94 – 6.70 (m, 3H), 5.18 (dd, *J* = 12.6, 8.6 Hz, 1H), 5.04 (dd, *J* = 12.6, 6.7 Hz, 1H), 4.72 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.78 (s, 3H), 3.05 – 2.72 (m, 4H), 1.99 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 200.8, 158.8, 141.6, 141.2, 140.9, 130.5, 128.9, 128.6, 128.4, 126.2, 114.2, 77.9, 55.4, 41.5, 40.1, 30.5, 14.8. **UPLC-DAD-QTOF:** $C_{21}H_{24}NO_4$ $[M-H]^+$ calcd.: 354.1705, found: 354.1698.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 20.3 min (minor) and 39.4 min (major).

(*R*,*E*)-4-(2-Nitro-1-(p-tolyl)ethyl)-1-phenylhex-4-en-3-one (13Ac)

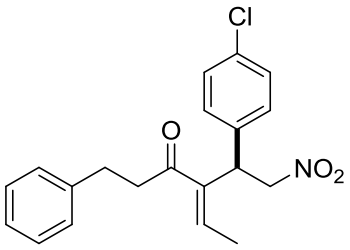


Prepared according to the general procedure starting from the adduct **11Ac** (34 mg, 0.1 mmol, 1.0 equiv.) and employing DBU (1.5 µL, 0.01 mmol, 10 mol%) as base. Colourless oil (67 mg, 0.1 mmol, 98%). $[\alpha]_D^{25}$ = −27.3° (*c*=0.5, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.31 – 7.00 (m, 9H), 6.88 (q, *J* = 7.0 Hz, 1H), 5.20 (dd, *J* = 12.7, 8.7 Hz, 1H), 5.06 (dd, *J* = 12.7, 6.6 Hz, 1H), 4.74 (dd, *J* = 8.7, 6.6 Hz, 1H), 3.09 – 2.69

(m, 4H), 2.31 (s, 3H), 1.99 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 201.1, 142.2, 141.6, 141.3, 137.5, 135.9, 130.0, 129.0, 128.9, 128.0, 126.6, 78.2, 42.1, 40.5, 21.6, 15.3. **UPLC-DAD-QTOF:** $C_{21}H_{24}NO_3$ $[M-H]^+$ calcd.: 338.1756, found: 338.1757.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 19.5 min (minor) and 26.1 min (major).

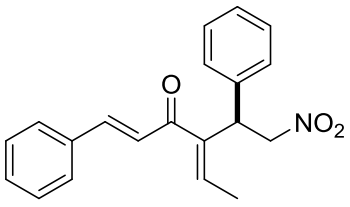
(*R*,*E*)-4-(1-(4-Chlorophenyl)-2-nitroethyl)-1-phenylhex-4-en-3-one (13Ad)



Prepared according to the general procedure starting from the adduct **11Ad** (35 mg, 0.1 mmol, 1.0 equiv.) and employing DBU (1.5 µL, 0.01 mmol, 10 mol%) as base. Colourless oil (35 mg, 0.1 mmol, 98%). **$[\alpha]_D^{25}$** = −17.9° (*c*=0.5, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.43 – 7.13 (m, 9H), 6.94 (q, *J* = 7.1 Hz, 1H), 5.22 – 5.02 (m, 2H), 4.77 (t, *J* = 7.5 Hz, 1H), 3.04 – 2.73 (m, 4H), 2.04 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 201.1, 148.1, 142.8, 141.0, 137.5, 129.7, 129.5, 129.2, 128.9, 126.8, 110.7, 77.9, 42.0, 40.5, 30.9, 15.5. **UPLC-DAD-QTOF:** $C_{20}H_{21}NO_3Cl$ $[M-H]^+$ calcd.: 358.1210, found: 358.1213.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 19.7 min (minor) and 22.7 min (major).

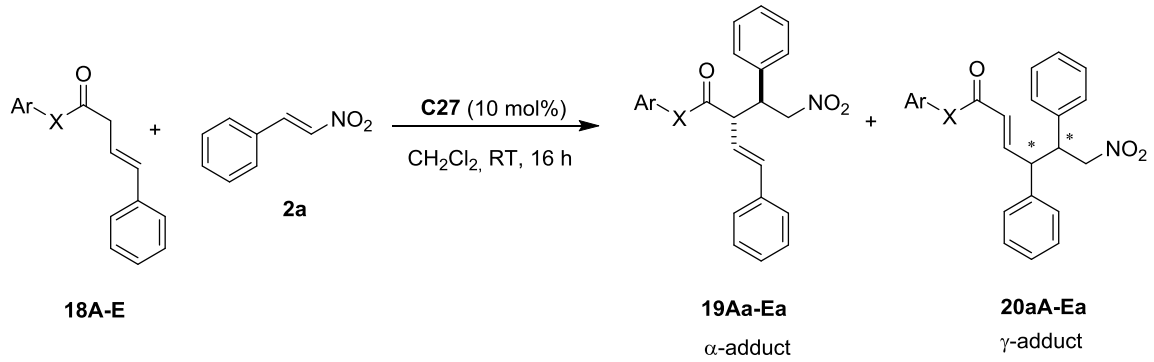
(1*E*,4*E*)-4-((*R*)-2-Nitro-1-phenylethyl)-1-phenylhexa-1,4-dien-3-one (13Ba)



Prepared according to the general procedure starting from the adduct **11Ba** (32 mg, 0.1 mmol, 1.0 equiv.) and employing Et_3N (1.4 µL, 0.02 mmol, 10 mol%) as base. Colourless oil (32 mg, 0.1 mmol, 98%). **$[\alpha]_D^{25}$** = −21.1° (*c*=0.5, 88% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.61 – 7.47 (m, 3H), 7.47 – 7.24 (m, 8H), 7.17 (d, *J* = 15.7 Hz, 1H), 6.97 (q, *J* = 7.0 Hz, 1H), 5.32 (dd, *J* = 13.0, 8.4 Hz, 1H), 5.17 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.89 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.08 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 191.9, 144.1, 141.1, 138.3, 134.7, 130.4, 128.8, 128.8, 128.2, 127.7, 127.3, 122.6, 77.6, 42.4, 14.6. **UPLC-DAD-QTOF:** $C_{20}H_{20}NO_3$ $[M-H]^+$ calcd.: 322.1443, found: 322.1449.

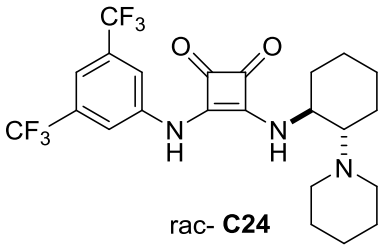
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 18.7 min (minor) and 29.8 min (major).

6.3.7. General procedure for the catalytic conjugate addition of β,γ-unsaturated esters/thioesters 18 to nitrostyrene 2a



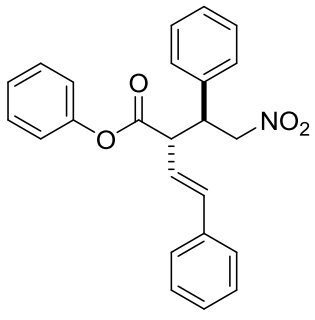
General procedure: To a mixture of the β,γ-unsaturated esters/thioesters **18** (0.4 mmol, 2.0 equiv.) and nitrostyrene **2a** (30 mg, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL), the catalyst **C27** (10 mg, 0.02 mmol, 10 mol%) was added at room temperature. The resulting mixture was stirred at the same temperature for 16 h. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 98/2) to afford **19** and (hexane/ethyl acetate 97/3) to afford **20**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

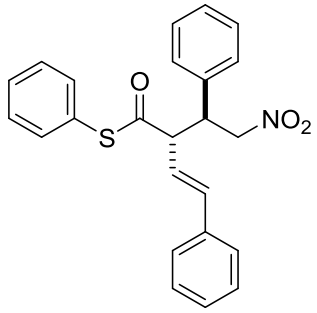
Phenyl (*S*,*E*)-2-((*S*)-2-nitro-1-phenylethyl)-4-phenylbut-3-enoate (19Aa)



Prepared according to the general procedure starting from β,γ-unsaturated ester **18A** (95 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 3:1). Colourless oil (50 mg, 0.13 mmol, 65%). $[\alpha]_D^{22}$ = −15.5° (*c*=0.5, 63% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (400 MHz, Chloroform-*d*) δ 7.65 – 7.04 (m, 15H), 6.83 (d, *J* = 15.9 Hz, 1H), 6.38 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.87 (dd, *J* = 12.9, 5.0 Hz, 1H), 4.73 (dd, *J* = 12.9, 9.6 Hz, 1H), 4.11 (td, *J* = 10.3, 5.0 Hz, 1H), 3.84 (t, *J* = 10.3 Hz, 1H). **^{13}C NMR** major isomer (101 MHz, Chloroform-*d*) δ 170.0, 150.4, 136.8, 135.8, 129.8, 129.6, 129.4, 129.1, 129.0, 128.8, 128.5, 127.0, 126.4, 123.5, 121.4, 78.7, 54.4, 46.8. **UPLC-DAD-QTOF:** $C_{24}H_{22}NO_4$ $[M-H]^+$ calcd.: 388.1549, found: 388.1552.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times for the major diastereomer: 38.9 min (minor) and 66.7 min (major) and for minor diastereomer: 22.0 min (major) and 29.2 min (minor).

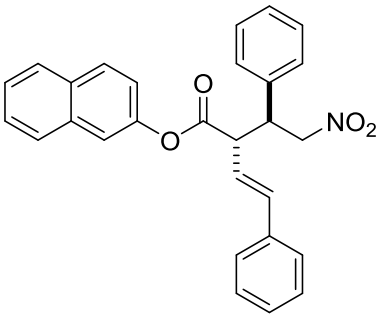
_S_-Phenyl (_S_,_E_)-2-((_S_)-2-nitro-1-phenylethyl)-4-phenylbut-3-enethioate (19Ba)



Prepared according to the general procedure starting from β,γ-unsaturated thioester **18B** (102 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 19:1). Colourless oil (61 mg, 0.15 mmol, 76%). **$[\alpha]_D^{22}$** = −26.7° (*c*=1.4, 89% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (400 MHz, Chloroform-*d*) δ 7.46 – 7.06 (m, 15H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.22 (dd, *J* = 15.7, 9.7 Hz, 1H), 4.87 – 4.76 (m, 1H), 4.70 (dd, *J* = 13.0, 9.8 Hz, 1H), 4.10 (td, *J* = 9.9, 5.1 Hz, 1H), 3.83 (t, *J* = 9.8 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 197.2, 137.9, 137.5, 136.7, 135.5, 130.7, 130.3, 130.0, 129.9, 129.7, 129.4, 129.4, 127.8, 124.2, 111.1, 79.2, 62.6, 47.4. **UPLC-DAD-QTOF:** $C_{24}H_{22}NO_3S$ $[M-H]^+$ calcd.: 404.1320, found: 404.1326.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times for the major diastereomer: 23.4 min (minor) and 40.0 min (major) and for minor diastereomer: 14.2 min (major) and 20.9 min (minor).

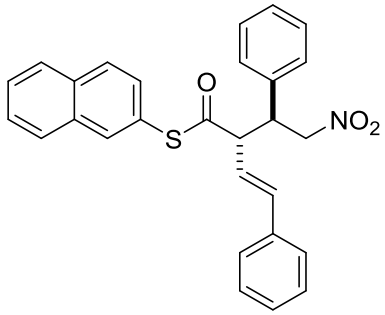
Naphth-2-yl (_S_,_E_)-2-((_S_)-2-nitro-1-phenylethyl)-4-phenylbut-3-enoate (19Ca)



Prepared according to the general procedure starting from β,γ-unsaturated ester **18C** (115 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 3:1). White solid (52 mg, 0.12 mmol, 60%). **M.p.:** 149–151 °C. **$[\alpha]_D^{22}$** = −13.3° (*c*=0.6, 62% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.93 – 7.65 (m, 3H), 7.57 – 7.24 (m, 13H), 7.16 – 7.00 (m, 1H), 6.86 (d, *J* = 15.8 Hz, 1H), 6.43 (dd, *J* = 15.8, 9.7 Hz, 1H), 4.98 – 4.81 (m, 1H), 4.75 (dd, *J* = 12.9, 9.5 Hz, 1H), 4.15 (td, *J* = 10.2, 4.9 Hz, 1H), 3.91 (q, *J* = 10.5, 9.8 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 170.1, 136.7, 135.7, 133.7, 131.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.5, 127.8, 127.7, 126.9, 126.7, 125.9, 123.3, 120.6, 118.4, 78.6, 54.3, 46.7. **UPLC-DAD-QTOF:** $C_{28}H_{24}NO_4$ $[M-H]^+$ calcd.: 438.1705, found: 438.1709.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 98/2, flow rate= 1 mL/min). Retention times for the major diastereomer: 51.8 min (minor) and 86.1 min (major) and for minor diastereomer: 36.9 min (major) and 41.2 min (minor).

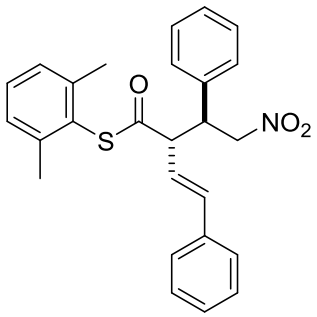
_S_-(Naphth-2-yl) (_S_,_E_)-2-((_S_)-2-nitro-1-phenylethyl)-4-phenylbut-3-enethioate (19Da)



Prepared according to the general procedure starting from β,γ-unsaturated thioester **18D** (122 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 4.4:1). White solid (54 mg. 0.12 mmol, 60%). **M.p.:** 168–170 °C. **$[\alpha]_D^{22}$ =** −27.3° (*c*=0.6, 84% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.98 – 7.73 (m, 4H), 7.69 – 7.10 (m, 13H), 6.77 (d, *J* = 15.7 Hz, 1H), 6.27 (dd, *J* = 15.8, 9.7 Hz, 1H), 4.92 – 4.67 (m, 2H), 4.15 (td, *J* = 9.7, 5.2 Hz, 1H), 3.90 (t, *J* = 9.8 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 196.5, 137.0, 134.6, 130.7, 129.1, 128.9, 128.8, 128.5, 128.4, 128.1, 127.9, 127.4, 126.9, 126.7, 123.2, 78.2, 61.7, 46.4. **UPLC-DAD-QTOF:** $C_{28}H_{24}NO_3S$ $[M-H]^+$ calcd.: 454.1477, found: 454.1481.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times for the major diastereomer: 38.2 min (major) and 51.4 min (minor) and for minor diastereomer: 27.3 min (minor) and 33.8 min (major).

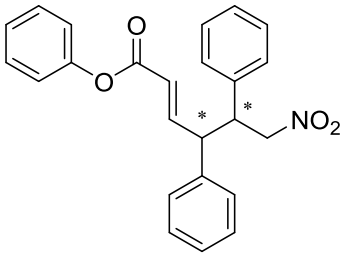
_S_-(2,6-Dimethylphenyl) (_S_,_E_)-2-((_S_)-2-nitro-1-phenylethyl)-4-phenylbut-3-enethioate (19Ea)



Prepared according to the general procedure starting from β,γ-unsaturated thioester **18E** (113 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 7.3:1). Yellow oil (59 mg, 0.14 mmol, 68%). **$[\alpha]_D^{22}$ =** −9.2° (*c*=0.7, 58% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.65 – 6.96 (m, 13H), 6.84 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 15.8, 9.4 Hz, 1H), 4.79 (dd, *J* = 12.9, 5.0 Hz, 1H), 4.67 (dd, *J* = 12.9, 9.4 Hz, 1H), 4.09 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 2.38 – 1.65 (*br*s, 6H). **^{13}C NMR** major isomer (101 MHz, Chloroform-*d*) δ 194.2, 142.3, 136.4, 135.4, 129.7, 128.7, 128.5, 128.3, 128.1, 127.8, 126.4, 123.3, 78.4, 60.9, 45.75, 20.8. **UPLC-DAD-QTOF:** $C_{26}H_{26}NO_3S$ $[M-H]^+$ calcd.: 432.1633, found: 432.1638.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1 mL/min). Retention times for the major diastereomer: 21.7 min (minor) and 43.6 min (major) and for minor diastereomer: 10.8 min (minor) and 13.2 min (major).

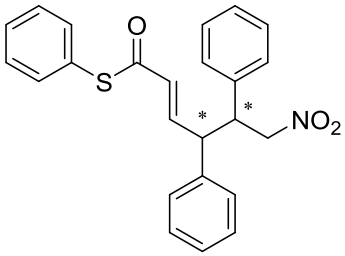
Phenyl (*E*)-6-nitro-4,5-diphenylhex-2-enoate (20Aa)



Prepared according to the general procedure starting from β,γ-unsaturated ester **18A** (95 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (20 mg, 0.05 mmol, 26%). **$[\alpha]_D^{22}$ =** −38.4° (*c*=0.8, 63% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 – 6.88 (m, 16H), 6.23 (d, *J* = 15.5 Hz, 1H), 4.85 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.74 (dd, *J* = 12.9, 9.5 Hz, 1H), 4.03 (td, *J* = 9.6, 5.5 Hz, 1H), 3.86 (t, *J* = 9.8 Hz, 1H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 164.8, 151.2, 138.9, 137.1, 130.1, 129.5, 129.3, 128.9, 128.8, 128.5, 128.2, 126.6, 123.5, 122.2, 110.7, 79.4, 53.3, 49.2. **UPLC-DAD-QTOF:** $C_{24}H_{22}NO_4$ $[M-H]^+$ calcd.: 388.1549, found: 388.1552.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 1 mL/min). Retention times: 17.6 min (minor) and 35.2 min (major).

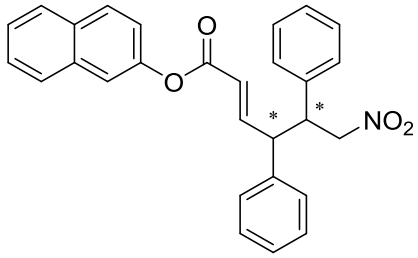
***S*-Phenyl (*E*)-6-nitro-4,5-diphenylhex-2-enethioate (20Ba)**



Prepared according to the general procedure starting from β,γ-unsaturated thioester **18B** (102 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a single diastereomer. Colourless oil (13 mg, 0.03 mmol, 16%). **$[\alpha]_D^{22}$ =** −75.7° (*c*=0.8, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.46 (s, 4H), 7.39 – 7.14 (m, 8H), 7.05 – 6.96 (m, 4H), 6.35 (d, *J* = 15.3 Hz, 1H), 4.80 (dd, *J* = 12.9, 5.7 Hz, 1H), 4.71 (dd, *J* = 12.9, 9.4 Hz, 1H), 4.00 (td, *J* = 9.5, 5.6 Hz, 1H), 3.78 (t, *J* = 9.7 Hz, 1H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 187.7, 144.2, 138.4, 136.5, 134.8, 129.9, 129.5, 129.5, 129.0, 128.8, 128.4, 128.4, 128.1, 127.7, 127.4, 127.0, 78.8, 52.7, 48.9. **UPLC-DAD-QTOF:** $C_{24}H_{22}NO_3S$ $[M-H]^+$ calcd.: 404.1320, found: 404.1328.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 1 mL/min). Retention times: 20.9 min (minor) and 40.8 min (major).

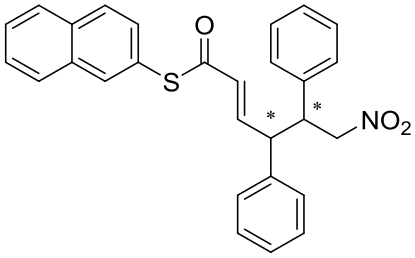
Naphth-2-yl (*E*)-6-nitro-4,5-diphenylhex-2-enoate (20Ca)



Prepared according to the general procedure starting from β,γ-unsaturated ester **18C** (115 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (24 mg, 0.06 mmol, 28%). **$[\alpha]_D^{22}$ =** −44.9° (*c*=0.5, 54% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.93 – 7.74 (m, 3H), 7.61 – 7.36 (m, 5H), 7.37 – 7.16 (m, 6H), 7.12 – 6.86 (m, 4H), 6.28 (d, *J* = 15.5 Hz, 1H), 4.87 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.76 (dd, *J* = 12.9, 9.5 Hz, 1H), 4.05 (td, *J* = 9.6, 5.4 Hz, 1H), 3.88 (t, *J* = 9.8 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 164.3, 149.4, 148.1, 138.2, 136.4, 133.7, 131.5, 129.4, 128.8, 128.7, 128.2, 127.8, 127.6, 127.5, 126.6, 125.7, 122.7, 120.9, 118.5, 78.7, 52.6, 48.5. **UPLC-DAD-QTOF:** $C_{28}H_{24}NO_4$ $[M-H]^+$ calcd.: 438.1705, found: 438.1706.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1 mL/min). Retention times: 25.6 min (minor) and 50.9 min (major).

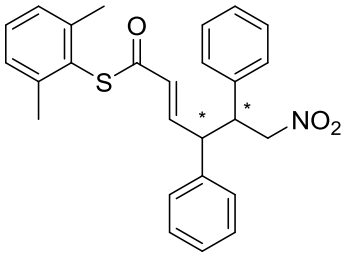
***S*-(Naphth-2-yl) (*E*)-6-nitro-4,5-diphenylhex-2-enethioate (20Da)**



Prepared according to the general procedure starting from β,γ-unsaturated thioester **18D** (122 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (24 mg, 0.05 mmol, 27%). **$[\alpha]_D^{22}$ =** −50.2° (*c*=0.6, 64% *ee*, CH_2Cl_2). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.07 – 7.73 (m, 4H), 7.66 – 7.08 (m, 10H), 7.04 – 6.93 (m, 4H), 6.39 (d, *J* = 15.3 Hz, 1H), 4.81 (dd, *J* = 12.9, 5.6 Hz, 1H), 4.72 (dd, *J* = 12.9, 9.4 Hz, 1H), 4.01 (td, *J* = 9.5, 5.6 Hz, 1H), 3.79 (t, *J* = 9.7 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.7, 144.1, 138.1, 134.5, 133.5, 130.8, 129.3, 128.8, 128.8, 128.6, 128.2, 128.2, 128.0, 127.8, 127.5, 127.2, 126.6, 78.6, 52.4, 48.6. **UPLC-DAD-QTOF:** $C_{28}H_{24}NO_3S$ $[M-H]^+$ calcd.: 454.1477, found: 454.1479.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1 mL/min). Retention times: 41.6 min (major) and 72.8 min (minor).

***S*-(2,6-Dimethylphenyl) (*E*)-6-nitro-4,5-diphenylhex-2-enethioate (20Ea)**



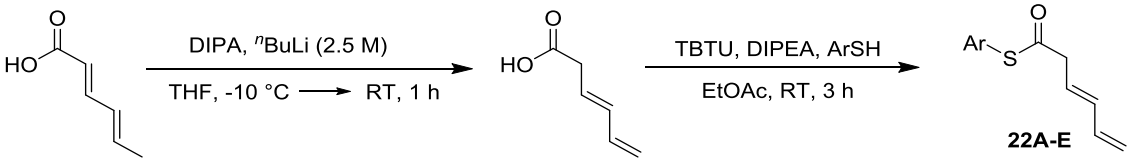
Prepared according to the general procedure starting from β,γ-unsaturated thioester **18E** (113 mg, 0.4 mmol, 2.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (21 mg, 0.05 mmol, 24%). **$[\alpha]_D^{22}$ =** −34.9° (*c*=0.6, 56% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.62 – 6.92 (m, 14H), 6.38 (d, *J* = 15.3 Hz, 1H), 4.75 (qd, *J* = 12.9, 7.5 Hz, 2H), 4.00 (td, *J* = 9.3, 5.9 Hz, 1H), 3.84 – 3.67 (m, 1H), 2.37 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 186.6, 143.9, 143.4, 142.9, 138.2, 136.3, 130.0, 129.5, 129.1, 128.7, 128.6, 128.3, 128.2, 127.8, 127.5, 78.6, 52.5, 48.7, 21.7. **UPLC-DAD-QTOF:** $C_{26}H_{26}NO_3S$ $[M-H]^+$ calcd.: 432.1633, found: 432.1637.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 16.9 min (minor) and 20.1 min (major).

6.4. Experimental section of chapter 3

6.4.1. Synthesis of polyunsaturated carbonyl compounds

6.4.1.1. *Synthesis of polyunsaturated thioesters (22A-E)*



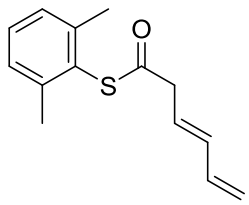
1st Step:[228] ^{n}BuLi (8.0 mL, 20.0 mmol, 2.0 equiv., 2.5 M in hexane) was added to a solution of diisopropyl amine (DIPA) (2.8 mL, 20.0 mmol, 2.0 equiv.) in dry THF (20.0 mL) at -10 °C. The reaction was allowed to stir at -10 °C for 30 min at which time a solution of sorbic acid (1.12 g, 10.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) was added dropwise. The reaction was warmed to room temperature and held there for one hour. The reaction was quenched by addition of HCl (20.0 mL, 3.0 M) at 0 °C. The compound was extracted with Et_2O (3 x 20.0 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain the desired product, which was used without any further purification in the next step (1.09 g, 9.8 mmol, 98%). All

[228] M. A. Brodney, J. P. O´Leary, J. A. Hansen, R. J. Giguere, *Synth. Commun.*, **1995**, *25*, 521–531.

spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 10.10 (*br*s, 1H), 6.44 – 6.11 (m, 2H), 5.89 – 5.72 (m, 1H), 5.26 – 5.17 (m, 1H), 5.14 – 5.06 (m, 1H), 3.20 (dd, *J* = 7.2, 1.3 Hz, 2H).

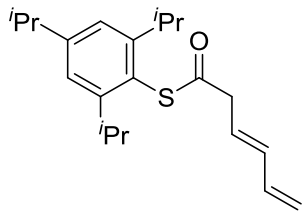
2nd Step: [229] To a solution of (*E*)-hexa-3,5-dienoic acid (224 mg, 2.0 mmol, 1.0 equiv.) in EtOAc (70.0 mL), TBTU (706 mg, 2.2 mmol, 1.1 equiv.) and DIPEA (0.54 mL, 3.0 mmol, 1.5 equiv.) were added. After 30 min, the corresponding thiol (2.0 mmol, 1.0 equiv.) was added and the mixture was stirred for 3 h. The solvent was removed under reduced pressure and the resulting crude material was purified by silica gel column chromatography (hexane/ethyl acetate 95/5).

S-(2,6-Dimethylphenyl) (*E*)-hexa-3,5-dienethioate (22A)



Prepared according to the general procedure starting from 2,6-dimethylbenzenethiol (0.26 mL, 2.0 mmol, 1.0 equiv.). Yellow oil (162 mg, 1.4 mmol, 70%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.23 – 7.10 (m, 3H), 6.48 – 6.13 (m, 2H), 5.94 – 5.80 (m, 1H), 5.25 (dd, *J* = 16.3, 1.5 Hz, 1H), 5.15 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.45 (dd, *J* = 7.3, 1.3 Hz, 2H), 2.37 (s, 6H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.3, 142.7, 137.2, 136.7, 130.9, 129.3, 129.3, 125.9, 118.6, 48.2, 22.7. **UPLC-DAD-QTOF:** $C_{14}H_{16}OSNa$ $[M+Na]^+$ calcd.: 255.0820, found: 255.0822.

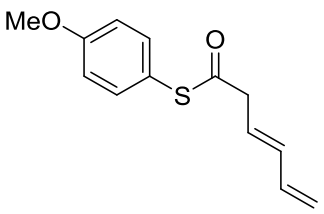
S-(2,4,6-Triisopropylphenyl) (*E*)-hexa-3,5-dienethioate (22B)



Prepared according to the general procedure starting from 2,4,6-triisopropylbenzenethiol[230] (552 mg, 2.0 mmol, 1.0 equiv.). Yellow oil (492 mg, 1.5 mmol, 75%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 6.8 Hz, 2H), 6.65 – 6.11 (m, 2H), 6.00 – 5.75 (m, 1H), 5.32 – 5.21 (m, 1H), 5.16 (dq, *J* = 9.4, 0.7 Hz, 1H), 3.62 – 3.23 (m, 4H), 2.95 (pd, *J* = 6.9, 2.5 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.9, 153.5, 152.2, 137.4, 136.5, 126.2, 123.4, 123.1, 118.5, 48.0, 35.4, 33.0, 24.9. **UPLC-DAD-QTOF:** $C_{21}H_{31}OS$ $[M+H]^+$ calcd.: 331.2096, found: 331.2099.

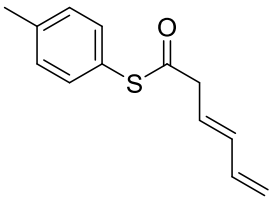
[229] B. Movassagh, S. Balalaie, P. Shaygan, *ARKIVOC* **2007**, *13*, 47–52.
[230] A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727–730.

S-(4-Methoxyphenyl) (E)-hexa-3,5-dienethioate (22C)



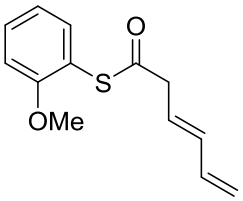
Prepared according to the general procedure starting from 4-methoxythiophenol (0.24 mL, 2.0 mmol, 1.0 equiv.). Colourless oil (140 mg, 0.6 mmol, 30%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.52 – 6.08 (m, 2H), 5.93 – 5.75 (m, 1H), 5.26 (ddd, *J* = 16.3, 1.4, 0.6 Hz, 1H), 5.15 (ddt, *J* = 9.9, 1.6, 0.6 Hz, 1H), 3.80 (s, 3H), 3.46 – 3.40 (m, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.7, 161.2, 142.1, 136.6, 136.3, 133.1, 125.3, 118.2, 115.4, 55.8, 47.3. **UPLC-DAD-QTOF:** $C_{13}H_{14}O_2S$ $[M+H]^+$ calcd.: 235.0793, found: 235.0790.

S-(p-Tolyl) (E)-hexa-3,5-dienethioate (22D)



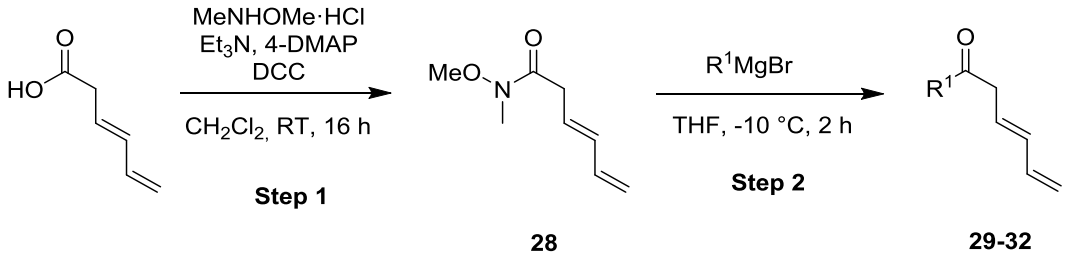
Prepared according to the general procedure starting from 4-methylbenzenethiol (248 mg, 2.0 mmol, 1.0 equiv.). Colourless oil (305 mg, 1.4 mmol, 70%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.35 – 7.03 (m, 4H), 6.53 – 6.05 (m, 2H), 5.85 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.42 – 5.20 (m, 1H), 5.16 (dd, *J* = 9.3, 1.2 Hz, 1H), 3.44 (dd, *J* = 7.3, 1.3 Hz, 2H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.4, 142.1, 140.3, 136.8, 136.4, 135.1, 130.7, 125.4, 118.3, 47.6, 22.0. **UPLC-DAD-QTOF:** $C_{13}H_{15}OS$ $[M+H]^+$ calcd.: 219.0844, found: 219.0845.

S-(2-Methoxyphenyl) (E)-hexa-3,5-dienethioate (22E)



Prepared according to the general procedure starting from 2-methoxythiophenol (0.24 mL, 2.0 mmol, 1.0 equiv.). Colourless oil (94 mg, 0.4 mmol, 20%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.54 – 7.24 (m, 2H), 7.11 – 6.80 (m, 2H), 6.53 – 6.12 (m, 2H), 6.02 – 5.77 (m, 1H), 5.28 – 5.19 (m, 1H), 5.17 – 5.10 (m, 1H), 3.86 (s, 3H), 3.51 – 3.41 (m, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.6, 160.3, 137.8, 137.3, 136.7, 132.7, 128.6, 126.0, 122.1, 118.6, 112.6, 57.0, 47.9. **UPLC-DAD-QTOF:** $C_{13}H_{14}O_2SNa$ $[M+Na]^+$ calcd.: 257.0612, found: 257.0599.

6.4.1.2. *Synthesis of polyunsaturated aromatic ketones (29-32)*



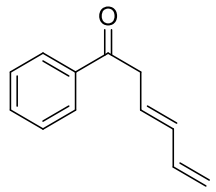
1st Step: [231] To a stirring solution of (*E*)-hexa-3,5-dienoic acid (1.12 g, 10.0 mmol, 1.0 equiv.) and *N*,*O*-dimethylhydroxyamine hydrochloride (1.03g, 10.5 mmol, 1.05 equiv.) in CH_2Cl_2 (30.0 mL) at 0 °C, Et_3N (2.8 mL, 20.0 mmol, 2.0 equiv.), 4-DMAP (61 mg, 0.5 mmol, 0.05 equiv.) and DCC (2.18 g, 10.5 mmol, 1.05 equiv.) were added. The reaction was allowed to stir overnight while warming to room temperature. The reaction was diluted with CH_2Cl_2 (30.0 mL) and quenched with water (40.0 mL). The layers were separated and the aqueous layer was extracted once with CH_2Cl_2 (50.0 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50.0 mL), water (50.0 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 70/30) to obtain the desired product **28**. Yellow oil (1.16 g, 7.5 mmol, 75%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.45 – 6.29 (m, 1H), 6.26 – 6.06 (m, 1H), 5.99 – 5.64 (m, 1H), 5.17 (ddt, *J* = 16.9, 1.7, 0.7 Hz, 1H), 5.06 (ddt, *J* = 10.0, 1.6, 0.7 Hz, 1H), 3.72 (s, 3H), 3.28 (d, *J* = 7.2 Hz, 2H), 3.21 (s, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 144.4, 137.2, 134.7, 127.3, 117.1, 62.0, 36.6, 32.9. **UPLC-DAD-QTOF:** $C_8H_{14}NO_2$ $[M+H]^+$ calcd.: 156.1025, found: 156.1027.

2nd Step: To a mixture of magnesium powder (135 mg, 5.5 mmol, 1.1 equiv) in anhydrous THF (25.0 mL), the corresponding bromide (5.0 mmol, 1.0 equiv.) was added and stirred at reflux for 3 h.

The corresponding amount of freshly prepared magnesium bromide solution (25.0 mL, 5.0 mmol, 1.0 equiv., 0.2 M in THF) was added dropwise to a solution of *N*-methoxy-*N*-methylamide (2.32 g, 15.0 mmol, 3.0 equiv.) in 10.0 mL THF at -10 °C. The reaction mixture was stirred at -10 °C for additional 2 h. The reaction was quenched with saturated NH_4Cl at -10 °C and extracted with Et_2O (3 x 20.0 mL). The combined organic phases were washed with brine (20.0 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/diethyl ether 98/2) to obtain the desired product. The unreacted weinreb amide was recovered and reused.

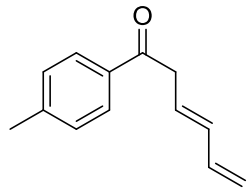
[231] See ref. 222

(*E*)-1-Phenylhexa-3,5-dien-1-one (29)



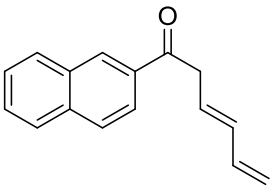
Prepared according to the general procedure starting from bromobenzene (0.53 mL, 5.0 mmol, 1.0 equiv.). Colourless oil (447 mg, 2.6 mmol, 52%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.24 – 7.78 (m, 2H), 7.66 – 7.56 (m, 1H), 7.54 – 7.40 (m, 2H), 6.40 (dt, *J* = 16.8, 10.2 Hz, 1H), 6.30 – 6.16 (m, 1H), 6.06 – 5.77 (m, 1H), 5.30 – 5.15 (m, 1H), 5.09 (ddt, *J* = 10.0, 1.5, 0.7 Hz, 1H), 3.82 (dd, *J* = 6.9, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 198.9, 137.7, 135.7, 134.3, 129.8, 129.4, 127.5, 117.8, 111.1, 43.4. **UPLC-DAD-QTOF:** $C_{12}H_{13}O$ $[M+H]^+$ calcd.: 173.0966, found: 173.0968.

(*E*)-1-(*p*-Tolyl)hexa-3,5-dien-1-one (30)



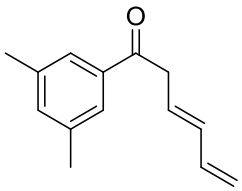
Prepared according to the general procedure starting from 4-bromotoluene (0.61 mL, 5.0 mmol, 1.0 equiv.). Colourless oil (539 mg, 2.9 mmol, 58%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4, 2H), 6.40 (dt, *J* = 16.8, 10.1 Hz, 1H), 6.29 – 6.16 (m, 1H), 6.07 – 5.73 (m, 1H), 5.32 – 5.14 (m, 1H), 5.08 (ddd, *J* = 9.9, 1.5, 0.7 Hz, 1H), 3.79 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 198.5, 145.1, 137.7, 135.5, 130.4, 129.5, 127.9, 127.8, 117.7, 43.3, 22.7. **UPLC-DAD-QTOF:** $C_{13}H_{15}O$ $[M+H]^+$ calcd.: 187.1123, found: 187.1125.

(*E*)-1-(Naphthalen-2-yl)hexa-3,5-dien-1-one (31)



Prepared according to the general procedure starting from 2-bromonaphthalene (1.03 g, 5.0 mmol, 1.0 equiv.). White solid (666 mg, 3.0 mmol, 60%). **M.p.:** 66.9-73.8 °C. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 8.15 – 7.77 (m, 4H), 7.67 – 7.51 (m, 2H), 6.51 – 6.15 (m, 2H), 6.05 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.27 – 5.17 (m, 1H), 5.10 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.94 (dd, *J* = 6.9, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 198.8, 137.6, 136.7, 135.6, 134.9, 133.6, 131.1, 130.6, 129.6, 128.8, 127.9, 127.6, 127.1, 125.0, 117.8, 43.4. **UPLC-DAD-QTOF:** $C_{14}H_{17}O$ $[M+H]^+$ calcd.: 223.1123, found: 223.1127.

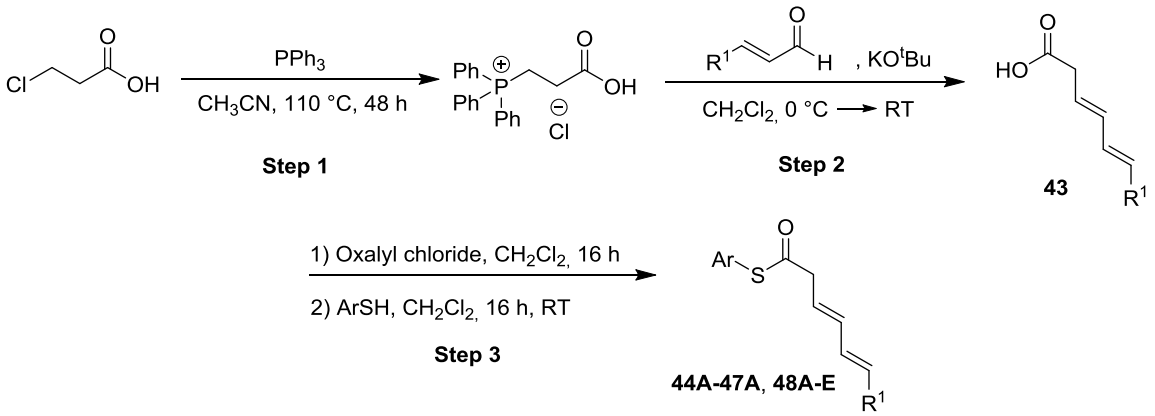
(*E*)-1-(3,5-Dimethylphenyl)hexa-3,5-dien-1-one (32)



Prepared according to the general procedure starting from 1-bromo-3,5-dimethylbenzene (0.68 mL, 5.0 mmol, 1.0 equiv.). Orange oil (550 mg, 2.75 mmol, 55%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.81 – 7.47 (m, 2H), 7.36 – 7.17 (m, 1H), 6.40 (dt, *J* = 16.8, 10.1 Hz, 1H), 6.28 – 6.10 (m, 1H), 5.99 (dt, *J* = 15.2, 6.9 Hz, 1H), 5.19 (dd, *J* = 16.9, 1.6 Hz, 1H), 5.08 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.78 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.40 (s, 6H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 198.8, 138.9, 137.3, 135.5, 134.9,

127.4, 126.7, 125.7, 117.2, 42.9, 21.9. **UPLC-DAD-QTOF:** $C_{14}H_{17}O$ $[M+H]^+$ calcd.: 201.1279, found: 201.1281.

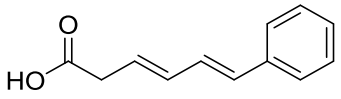
6.4.1.3. *Synthesis of polyunsaturated ε-substituted thioesters (44A-47A, 48A-E)*



1st Step:[232] To a stirring solution of 3-chloropropionic acid (1.08 g, 10.0 mmol, 1.0 equiv.) in CH_3CN (10.0 mL), PPh_3 (2.25 g, 10.0 mmol, 1.0 equiv.) was added and stirred at reflux for 48 h. The resulting colourless solution was cooled to room temperature and then Et_2O (30.0 mL) was added. After keeping at -20 °C for 4 h, the formed precipitate was filtered, washed with Et_2O (3 x 5.0 mL) and dried *in vacuo* to afford the desired product as a white solid (3.7 g, 10.0 mmol, > 99%). All spectroscopy data were coincident with those previously reported.

2nd Step:[233] To a stirring solution of (carboxymethyl)triphenylphosphonium chloride (3.17 g, 9.45 mmol, 1.2 equiv.) and the corresponding aldehyde (7.87 mmol, 1.0 equiv.) in CH_2Cl_2 (10.0 mL), KO^tBu (2.21 g, 19.7 mmol, 2.5 equiv.) was added at 0 °C. The reaction was allowed to stir overnight while warming to room temperature. The solution was quenched by the addition of H_2O (10.0 mL). The aqueous layer was acidified to pH = 1.0 with concentrated HCl and extracted with Et_2O (2 x 20.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 70/30) to obtain the desired acid **43**.

(3*E*,5*E*)-6-Phenylhexa-3,5-dienoic acid (43A)[233]

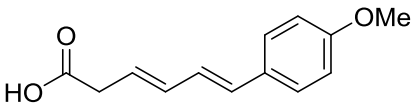


Prepared according to the general procedure starting from *trans*-cinnamaldehyde (0.99 mL, 7.87 mmol, 1.0 equiv.). Yellow solid (1.03 g, 5.5 mmol, 70%). All

[232] X. Liu, R. Zhang, J. Luo, X. Zhao, *Angew. Chem. Int. Ed.* **2016**, *55*, 5846–5850.
[233] Adapted from: D. M. Guptill, C. M. Cohen, H. M. L. Davies, *Org. Lett.* **2013**, *24*, 6120–6123.

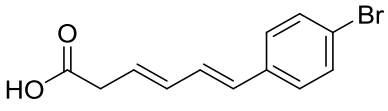
spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.51 – 7.12 (m, 5H), 6.81 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.36 (ddt, *J* = 15.2, 10.2, 1.5 Hz, 1H), 5.91 (dt, *J* = 14.9, 7.2 Hz, 1H), 3.27 (dd, *J* = 7.2, 1.4 Hz, 2H).

(3*E*,5*E*)-6-(4-Methoxyphenyl)hexa-3,5-dienoic acid (43B)



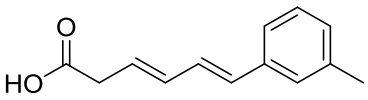
Prepared according to the general procedure starting from *trans*-*p*-methoxycinnamaldehyde (1.27 g, 7.87 mmol, 1.0 equiv.). Orange solid (1.22 g, 5.6 mmol, 72%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.68 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.39 – 6.27 (m, 1H), 5.85 (dt, *J* = 14.9, 7.2 Hz, 1H), 3.84 (s, 3H), 3.26 (dd, *J* = 7.2, 1.4 Hz, 2H).

(3*E*,5*E*)-6-(4-Bromophenyl)hexa-3,5-dienoic acid (43C)[234]



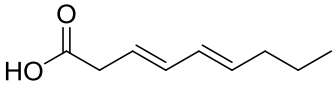
Prepared according to the general procedure starting from *trans*-*p*-bromocinnamaldehyde (1.66 g, 7.87 mmol, 1.0 equiv.). Orange solid (1.42 g, 5.35 mmol, 68%). All spectroscopy data were coincident with those previously reported. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H), 7.28 – 7.41 (m, 2H), 6.79 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 5.93 (dt, *J* = 15.0, 7.2 Hz, 1H), 3.27 (dd, *J* = 7.3, 1.4 Hz, 2H).

(3*E*,5*E*)-6-(*m*-Tolyl)hexa-3,5-dienoic acid (43D)



Prepared according to the general procedure starting from *trans*-*m*-methylcinnamaldehyde (1.15 g, 7.87 mmol, 1.0 equiv.). Yellow solid (1.11 g, 5.5 mmol, 70%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.44 – 7.17 (m, 3H), 7.11 – 7.04 (m, 1H), 6.87 – 6.72 (m, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.46 – 6.29 (m, 1H), 5.97 – 5.82 (m, 1H), 3.28 (dd, *J* = 7.2, 1.4 Hz, 2H), 2.38 (s, 3H).

(3*E*,5*E*)-Nona-3,5-dienoic acid (43E)

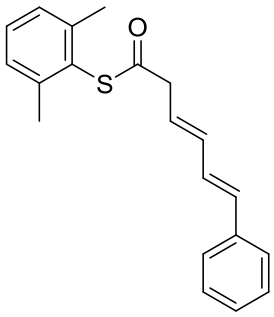


Prepared according to the general procedure starting from *trans*-2-hexen-1-al (0.91 mL, 7.87 mmol, 1.0 equiv.). Yellow oil (909 mg, 5.9 mmol, 75%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.25 – 6.01 (m, 2H), 5.75 – 5.57 (m, 2H), 3.19 – 3.13 (m, 2H), 2.14 – 1.99 (m, 2H), 1.51 – 1.37 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

[234] T. Sawano, H. Yamamoto, *ACS Catal.* **2019**, *9*, 3384–3388.

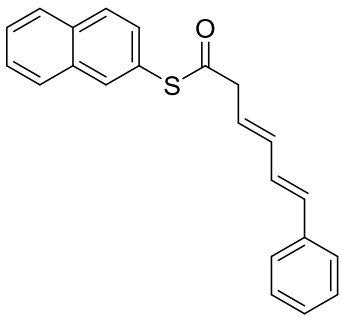
3rd step:[235] To a solution of the corresponding acid **43** (2.5 mmol, 1.0 equiv.) in dry CH_2Cl_2 (10.0 mL) at 0 °C, oxalyl chloride (0.41 mL, 4.47 mmol, 1.75 equiv.) was added. After stirring overnight at room temperature, the mixture was concentrated under reduced pressure. The crude material was redisolved in CH_2Cl_2 (7.0 mL) and the corresponding thiol (2.12 mmol, 0.85 equiv.), triethylamine (0.3 mL, 2.12 mmol, 0.85 equiv.) and 4-DMAP (27 mg, 0.22 mmol, 10 mol%) were added at 0 °C. After stirring overnight at room temperature, the solution was quenched by the addition of H_2O (10.0 mL). The organic layer was extracted with H_2O (2 x 10.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 95/5) to obtain the desired thioester.

_S_-(2,6-Dimethylphenyl) (3_E_,5_E_)-6-phenylhexa-3,5-dienethioate (44A)



Prepared according to the general procedure starting from (3*E*,5*E*)-6-phenylhexa-3,5-dienoic acid **43A** (470 mg, 2.5 mmol, 1.0 equiv.) and 2,6-dimethylthiophenol (0.29 mL, 2.12 mmol, 0.85 equiv.). Yellow oil (496 mg, 1.62 mmol, 76%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.54 – 7.13 (m, 8H), 6.91 – 6.73 (m, 1H), 6.59 (d, *J* = 15.7 Hz, 1H), 6.49 – 6.37 (m, 1H), 6.04 – 5.90 (m, 1H), 3.51 (dd, *J* = 7.4, 1.3 Hz, 2H), 2.38 (s, 6H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 194.8, 143.2, 137.5, 135.8, 133.3, 130.4, 129.1, 128.8, 128.6, 128.2, 127.1, 126.9, 125.3, 47.9, 22.2. **UPLC-DAD-QTOF**: $C_{20}H_{21}OS$ $[M+H]^+$ calcd.: 309.1313, found: 309.1316.

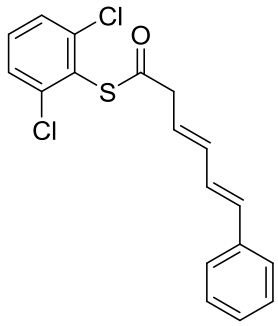
_S_-(Naphthalen-2-yl) (3_E_,5_E_)-6-phenylhexa-3,5-dienethioate (45A)



Prepared according to the general procedure starting from (3*E*,5*E*)-6-phenylhexa-3,5-dienoic acid **43A** (470 mg, 2.5 mmol, 1.0 equiv.) and 2-naphthalenethiol (340 mg, 2.12 mmol, 0.85 equiv.). Yellow oil (517 mg, 1.56 mmol, 74%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.99 – 7.77 (m, 4H), 7.63 – 7.29 (m, 8H), 6.97 – 6.75 (m, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.51 – 6.38 (m, 1H), 6.00 (ddd, *J* = 15.0, 7.8, 7.0 Hz, 1H), 3.57 (dd, *J* = 7.4, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.2, 145.2, 142.3, 136.3, 135.1, 133.6, 131.5, 129.5, 129.3, 128.7, 128.6, 128.4, 128.4, 127.8, 127.2, 127.1, 125.1, 48.0. **UPLC-DAD-QTOF:** $C_{22}H_{19}OS$ $[M+H]^+$ calcd.: 331.1157, found: 331.1151.

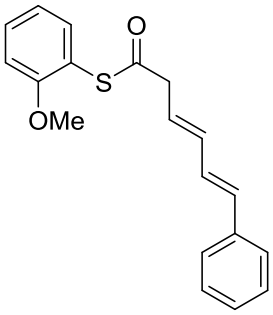
[235] N. Ichiishi, C. A. Malapit, L. Wozniak, M. S. Sanford, *Org. Lett.* **2018**, *20*, 44–47.

_S_-(2,6-Dichlorophenyl) (3_E_,5_E_)-6-phenylhexa-3,5-dienethioate (46A)



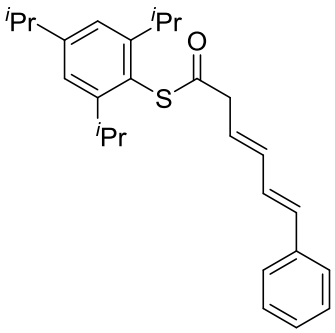
Prepared according to the general procedure starting from (3*E*,5*E*)-6-phenylhexa-3,5-dienoic acid **43A** (470 mg, 2.5 mmol, 1.0 equiv.) and 2,6-dichlorobenzenethiol (380 mg, 2.12 mmol, 0.85 equiv.). Yellow oil (583 mg, 1.67 mmol, 79%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.54 – 7.42 (m, 4H), 7.40 – 7.24 (m, 4H), 6.92 – 6.79 (m, 1H), 6.61 (d, *J* = 15.7 Hz, 1H), 6.56 – 6.41 (m, 1H), 5.98 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.56 (dd, *J* = 7.3, 1.3 Hz, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 192.9, 143.7, 141.9, 137.2, 134.2, 132.5, 132.0, 130.1, 129.7, 129.0, 128.8, 127.5, 124.7, 48.3. **UPLC-DAD-QTOF**: $C_{18}H_{15}OSCl_2$ $[M+H]^+$ calcd.: 349.0221, found: 349.0224.

_S_-(2-Methoxyphenyl) (3_E_,5_E_)-6-phenylhexa-3,5-dienethioate (47A)



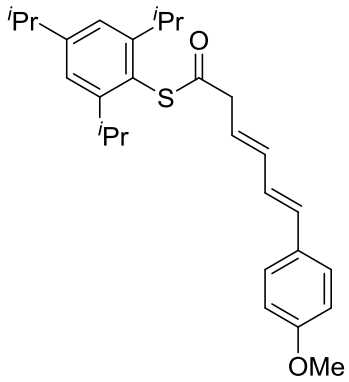
Prepared according to the general procedure starting from (3*E*,5*E*)-6-phenylhexa-3,5-dienoic acid **43A** (470 mg, 2.5 mmol, 1.0 equiv.) and 2-methoxythiophenol (0.26 mL, 2.12 mmol, 0.85 equiv.). Yellow oil (532 mg, 1.71 mmol, 81%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.54 – 7.20 (m, 7H), 7.12 – 6.94 (m, 2H), 6.96 – 6.73 (m, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.49 – 6.38 (m, 1H), 6.00 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.89 (s, 3H), 3.65 – 3.46 (m, 2H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.6, 160.2, 137.7, 136.4, 133.7, 132.7, 129.6, 129.2, 128.6, 127.4, 125.8, 122.1, 112.6, 57.0, 48.1. **UPLC-DAD-QTOF:** $C_{19}H_{19}O_2S$ $[M+H]^+$ calcd.: 311.1106, found: 311.1100.

_S_-(2,4,6-Triisopropylphenyl) (3_E_,5_E_)-6-phenylhexa-3,5-dienethioate (48A)



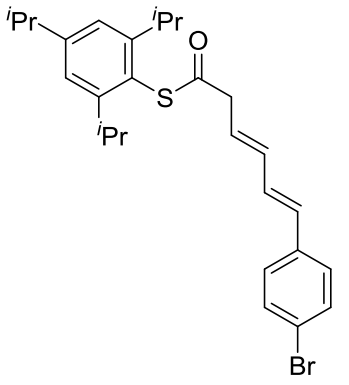
Prepared according to the general procedure starting from (3*E*,5*E*)-6-phenylhexa-3,5-dienoic acid **43A** (470 mg, 2.5 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenethiol[230] (585 mg, 2.12 mmol, 0.85 equiv.). Orange oil (656 mg, 1.47 mmol, 69%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.52 – 7.19 (m, 5H), 7.08 (s, 2H), 6.82 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.42 (dd, *J* = 14.9, 10.4 Hz, 1H), 5.96 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.49 (dd, *J* = 7.4, 1.3 Hz, 2H), 3.40 (p, *J* = 6.8 Hz, 2H), 2.90 (p, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.9, 152.5, 151.2, 137.2, 135.2, 132.7, 128.7, 128.3, 127.7, 126.7, 126.5, 125.1, 122.1, 47.4, 34.4, 32.0, 24.0. **UPLC-DAD-QTOF:** $C_{27}H_{35}OS$ $[M+H]^+$ calcd.: 407.2409, found: 407.2407.

_S_-(2,4,6-Triisopropylphenyl) (3_E_,5_E_)-6-(4-methoxyphenyl)hexa-3,5-dienethioate (48B)



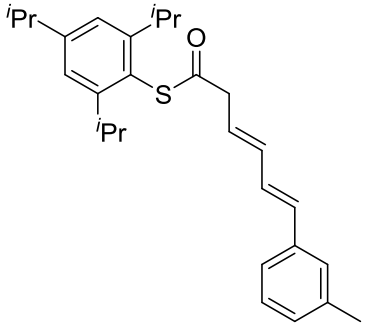
Prepared according to the general procedure starting from (3*E*,5*E*)-6-(4-methoxyphenyl)hexa-3,5-dienoic acid **43B** (547 mg, 2.5 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenethiol[230] (585 mg, 2.12 mmol, 0.85 equiv.). Orange oil (674 mg, 1.54 mmol, 73%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 3.2 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.76 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.51 – 6.28 (m, 1H), 5.96 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.86 (s, 3H), 3.53 (dd, *J* = 7.3, 1.3 Hz, 2H), 3.47 (p, *J* = 6.8 Hz, 2H), 2.97 (dddt, *J* = 13.9, 9.8, 6.9, 3.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 7.0 Hz, 12H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 196.0, 159.3, 152.4, 151.0, 135.3, 134.1, 133.0, 132.1, 129.9, 127.8, 126.2, 123.7, 121.9, 114.0, 55.2, 47.3, 34.3, 31.8, 23.8. **UPLC-DAD-QTOF:** $C_{28}H_{37}O_2S$ $[M+H]^+$ calcd.: 437.2514, found: 437.2511.

_S_-(2,4,6-Triisopropylphenyl) (3_E_,5_E_)-6-(4-bromophenyl)hexa-3,5-dienethioate (48C)



Prepared according to the general procedure starting from (3*E*,5*E*)-6-(4-bromophenyl)hexa-3,5-dienoic acid **43C** (662 mg, 2.5 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenethiol[230] (585 mg, 2.12 mmol, 0.85 equiv.). Orange oil (668 mg, 1.38 mmol, 65%).**^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 6.7 Hz, 2H), 7.17 – 7.07 (m, 2H), 6.90 – 6.51 (m, 1H), 6.47 – 6.34 (m, 2H), 6.00 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.51 (dd, *J* = 7.2, 1.3 Hz, 2H), 3.48 – 3.30 (m, 2H), 3.00 – 2.84 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.4, 153.0, 151.8, 140.0, 136.7, 135.5, 132.4, 131.9, 130.4, 129.6, 128.5, 126.5, 122.7, 47.9, 35.0, 32.6, 24.5. **UPLC-DAD-QTOF:** $C_{27}H_{34}OSBr$ $[M+H]^+$ calcd.: 486.5320, found: 486.5316.

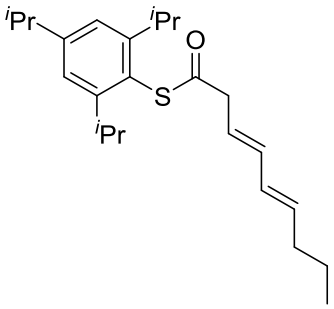
_S_-(2,4,6-Triisopropylphenyl) (3_E_,5_E_)-6-(*m*-tolyl)hexa-3,5-dienethioate (48D)



Prepared according to the general procedure starting from (3*E*,5*E*)-6-(*m*-tolyl)hexa-3,5-dienoic acid **43D** (505 mg, 2.5 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenethiol[230] (585 mg, 2.12 mmol, 0.85 equiv.). Orange oil (605 mg, 1.44 mmol, 68%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.35 – 7.24 (m, 3H), 7.19 – 7.08 (m, 3H), 6.87 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.54 – 6.42 (m, 1H), 6.00 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.54 (dd, *J* = 7.3, 1.3 Hz, 2H), 3.46 (p, *J* = 6.8 Hz, 2H), 2.96 (ddd, *J* = 10.8, 8.0, 5.4 Hz, 1H),

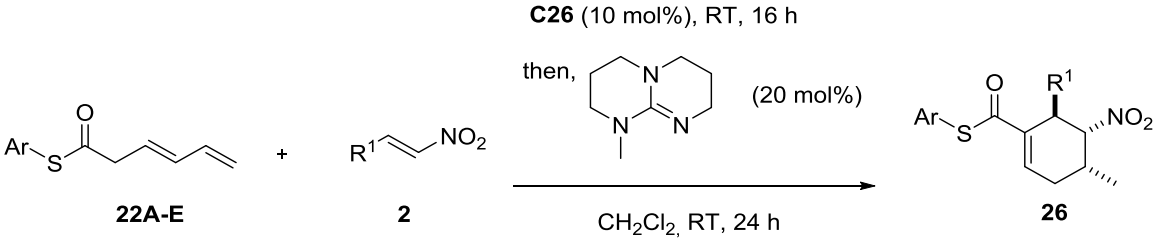
2.41 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.24 (d, *J* = 6.9 Hz, 12H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 195.9, 152.4, 151.1, 138.1, 137.0, 135.2, 132.7, 128.5, 128.0, 127.1, 124.8, 123.6, 122.0, 47.3, 34.3, 31.9, 23.8, 21.4. **UPLC-DAD-QTOF:** $C_{28}H_{37}OS$ $[M+H]^+$ calcd.: 421.2565, found: 421.2558.

***S*-(2,4,6-Triisopropylphenyl) (3*E*,5*E*)-nona-3,5-dienethioate (48E)**



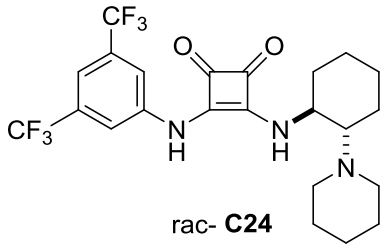
Prepared according to the general procedure starting from (3*E*,5*E*)-nona-3,5-dienoic acid **43E** (385 mg, 2.5 mmol, 1.0 equiv.) and 2,4,6-triisopropylbenzenethiol[230] (585 mg, 2.12 mmol, 0.85 equiv.). Yellow oil (591 mg, 1.59 mmol, 75 %). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.09 (s, 2H), 6.39 – 5.97 (m, 2H), 5.82 – 5.64 (m, 2H), 3.46 – 3.27 (m, 4H), 2.92 (p, *J* = 6.9 Hz, 1H), 2.19 – 2.00 (m, 2H), 1.53 – 1.36 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 12H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 189.4, 154.0, 153.2, 153.0, 151.9, 151.2, 122.7, 122.6, 122.4, 35.0, 32.7, 32.6, 32.0, 25.0, 24.5, 14.7. **UPLC-DAD-QTOF:** $C_{24}H_{37}OS$ $[M+H]^+$ calcd.: 373.2565, found: 373.2566.

6.4.2. General procedure for the catalytic enantioselective cyclization of thioesters 22A-E with nitroolefins 2



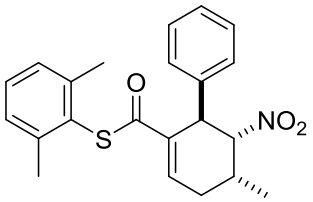
General Procedure: To a solution of the corresponding thioester **22A-E** (0.15 mmol, 1.5 equiv.) and nitroolefin **2** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.1 mL), catalyst **C26** (6 mg, 0.01 mmol, 10 mol%) was added at room temperature. After stirring the reaction mixture at room temperature for 16 h, MTBD (3.2 mg, 0.02 mmol, 20 mol%) was added and the reaction mixture was stirred for additional 24 h. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 95/5) to obtain the cyclohexene derivatives **26** as a single diastereomer.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

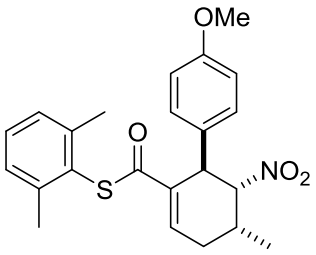
_S_-(2,6-Dimethylphenyl) (1_R_,5_R_,6_R_)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Aa)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.07 mmol, 71%). **M.p.:** 129.9–134.8 °C. **$[\alpha]_D^{19}$** = −13.5° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.56 – 6.71 (m, 9H), 4.78 (t, *J* = 3.2 Hz, 1H), 4.62 (d, *J* = 3.0 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.52 – 2.29 (m, 2H), 2.16 (*br*s, 6H), 1.12 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 189.7, 144.2, 140.3, 138.6, 137.8, 130.9, 130.0, 129.4, 129.3, 128.8, 111.1, 92.5, 45.2, 31.3, 28.1, 22.6, 17.8. **UPLC-DAD-QTOF:** $C_{22}H_{23}NO_3SNa$ $[M+Na]^+$ calcd.: 404.1296, found: 404.1296.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 14.3 min (major) and 27.3 min (minor).

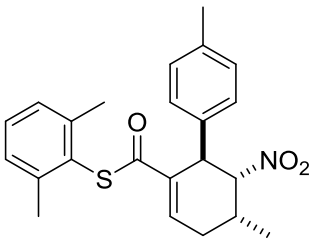
_S_-(2,6-Dimethylphenyl) (1_R_,5_R_,6_R_)-4'-methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ab)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.065 mmol, 65%). **M.p.:** 165.8–166.9 °C. **$[\alpha]_D^{19}$** = −10.6° (*c*=0.5, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.41 (ddd, *J* = 4.5, 3.0, 1.2 Hz, 1H), 7.23 – 7.11 (m, 3H), 7.11 – 7.04 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.74 (t, *J* = 3.2 Hz, 1H), 4.56 (*br*s, 1H), 3.56 (s, 3H), 2.88 – 2.44 (m, 1H), 2.36 – 2.31 (m, 2H), 2.18 (*br*s, 6H), 1.12 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 189.6, 144.2, 138.3, 138.0, 132.3, 130.9, 130.4, 129.3, 115.4, 111.1, 92.7, 56.4, 44.5, 31.3, 30.8, 28.0, 22.6, 17.8. **UPLC-DAD-QTOF:** $C_{23}H_{25}NO_4SNa$ $[M+Na]^+$ calcd.: 434.1402, found: 434.1399.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 1 mL/min). Retention times: 7.0 min (major) and 8.8 min (minor).

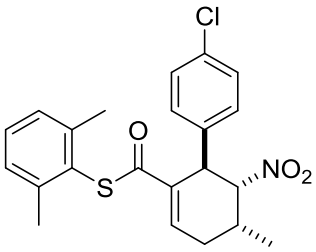
_S_-(2,6-Dimethylphenyl) (1_R_,5_R_,6_R_)-4',5-dimethyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ac)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2c** (16 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (26 mg, 0.07 mmol, 67%). **M.p.:** 134.8–136.7 °C. **$[\alpha]_D^{24}$** = −13.9° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.43 (ddd, *J* = 4.5, 3.0, 1.2 Hz, 1H), 7.12 (d, *J* = 15.0 Hz, 7H), 4.75 (*br*s, 1H), 4.57 (dd, *J* = 3.2, 1.6 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.51 – 2.37 (m, 2H), 2.33 (s, 3H), 2.16 (*br*s, 6H), 1.11 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 188.6, 143.1, 137.5, 137.4, 136.7, 136.2, 129.7, 129.6, 128.1, 128.1, 126.4, 91.5, 43.8, 30.2, 26.9, 21.5, 21.0, 16.8. **UPLC-DAD-QTOF:** $C_{23}H_{25}NO_3SNa$ $[M+Na]^+$ calcd.: 418.1453, found: 418.1441.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 22.6 min (minor) and 33.1 min (major).

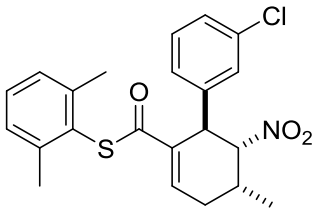
_S_-(2,6-Dimethylphenyl) (1_R_,5_R_,6_R_)-4'-chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ad)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2d** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (28 mg, 0.07 mmol, 68%). **M.p.:** 124.0–128.7 °C. **$[\alpha]_D^{24}$** = −17.3° (*c*=0.3, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.45 (ddd, *J* = 4.6, 3.2, 1.2 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.15 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 2H), 4.72 (t, *J* = 3.4 Hz, 1H), 4.66 – 4.38 (m, 1H), 2.68 (dtd, *J* = 19.0, 5.2, 1.5 Hz, 1H), 2.48 – 2.02 (m, 8H), 1.13 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 189.2, 143.7, 138.5, 137.2, 134.4, 130.6, 130.3, 129.8, 128.9, 126.8, 110.7, 91.9, 44.0, 31.0, 27.9, 22.2, 17.2. **UPLC-DAD-QTOF:** $C_{22}H_{22}NO_3SClNa$ $[M+Na]^+$ calcd.: 438.0907, found: 438.0909.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 12.3 min (major) and 13.1 min (minor).

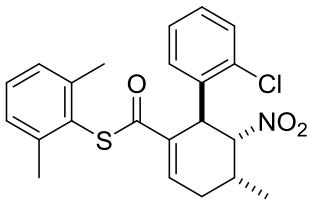
_S_-(2,6-Dimethylphenyl) (1_R_,5_R_,6_R_)-3'-chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ag)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2g** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.07 mmol, 65%). **M.p.:** 139.4–145.1 °C. **$[\alpha]_D^{24}$** = −12.4° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.47 (ddd, *J* = 4.6, 3.1, 1.2 Hz, 1H), 7.31 – 7.03 (m, 7H), 4.75 (t, *J* = 3.3 Hz, 1H), 4.62 – 4.58 (m, 1H), 2.78 – 2.57 (m, 1H), 2.45 (ddd, *J* = 9.0, 3.4, 2.0 Hz, 1H), 2.38 – 2.04 (m, 7H), 1.13 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 189.2, 143.8, 142.0, 138.8, 136.9, 135.6, 131.5, 130.9, 130.6, 128.9, 128.7, 127.4, 110.7, 91.8, 44.2, 30.9, 28.0, 22.1, 17.3. **UPLC-DAD-QTOF:** $C_{22}H_{22}NO_3SClNa$ $[M+Na]^+$ calcd.: 438.0907, found: 438.0900.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 1 mL/min). Retention times: 10.7 min (minor) and 13.5 min (major).

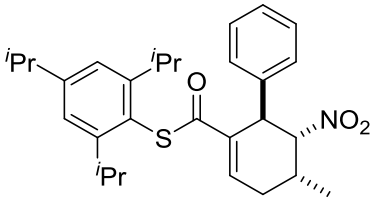
_S_-(2,6-Dimethylphenyl) (1_S_,5_R_,6_R_)-2'-chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ah)



Prepared according to the general procedure starting from thioester **22A** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2h** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (30 mg, 0.07 mmol, 73%). **M.p.:** 149.9–154.1 °C. **$[\alpha]_D^{24}$** = −9.6° (*c*=0.5, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.62 – 7.52 (m, 1H), 7.49 – 7.40 (m, 1H), 7.27 – 7.14 (m, 4H), 7.09 (d, *J* = 7.4 Hz, 2H), 5.18 – 4.93 (m, 1H), 4.79 (t, *J* = 2.4 Hz, 1H), 2.62 (dt, *J* = 19.6, 5.3 Hz, 1H), 2.44 – 2.06 (m, 8H), 1.14 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 188.6, 143.3, 139.6, 136.7, 136.2, 134.6, 130.6, 130.1, 129.4, 128.4, 127.1, 126.5, 88.6, 41.6, 30.0, 29.9, 21.8, 17.6. **UPLC-DAD-QTOF:** $C_{22}H_{22}NO_3SClNa$ $[M+Na]^+$ calcd.: 438.0907, found: 438.0901.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 6.2 min (minor) and 7.7 min (major).

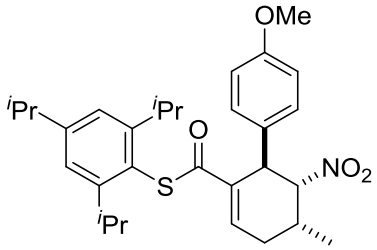
_S_-(2,4,6-Triisopropylphenyl) (1_R_,5_R_,6_R_)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ba)



Prepared according to the general procedure starting from thioester **22B** (50 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (31 mg, 0.07 mmol, 67%). **M.p.:** 126.9–128.1 °C. $[\alpha]_D^{23}$ = −26.8° (*c*=0.5, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.45 – 7.21 (m, 6H), 7.10 – 6.87 (m, 2H), 4.78 (t, *J* = 3.2 Hz, 1H), 4.62 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.22 (p, *J* = 6.8 Hz, 1H), 3.02 (p, *J* = 6.8 Hz, 1H), 2.86 (p, *J* = 6.9 Hz, 1H), 2.75 – 2.56 (m, 1H), 2.53 – 2.25 (m, 2H), 1.23 (dd, *J* = 6.9, 0.9 Hz, 6H), 1.14 – 1.09 (m, 12H), 0.75 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 190.8, 153.5, 153.3, 151.6, 140.0, 137.4, 131.5, 129.5, 129.0, 128.3, 122.7, 122.5, 92.1, 44.8, 35.0, 30.9, 27.8, 25.0, 24.9, 24.5, 24.4, 24.1, 23.9, 17.4. **UPLC-DAD-QTOF:** $C_{29}H_{37}NO_3SNa$ $[M+Na]^+$ calcd.: 502.2392, found: 502.2385.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 3.9 min (minor) and 5.2 min (major).

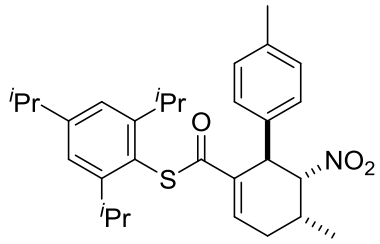
_S_-(2,4,6-Triisopropylphenyl) (1_R_,5_R_,6_R_)-4'-methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Bb)



Prepared according to the general procedure starting from thioester **22B** (50 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (34 mg, 0.07 mmol, 67%). **M.p.:** 116.7–118.7 °C. $[\alpha]_D^{23}$ = −30.2° (*c*=1.0, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.07 – 6.96 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.76 (t, *J* = 3.3 Hz, 1H), 4.56 (dd, *J* = 3.5, 1.6 Hz, 1H), 3.81 (s, 3H), 3.22 (p, *J* = 6.8 Hz, 1H), 3.02 (p, *J* = 6.8 Hz, 1H), 2.87 (p, *J* = 6.9 Hz, 1H), 2.72 – 2.57 (m, 1H), 2.53 – 2.29 (m, 2H), 1.24 (dd, *J* = 6.9, 0.8 Hz, 6H), 1.18 – 1.07 (m, 12H), 0.79 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 190.9, 159.7, 153.4, 153.3, 151.6, 137.8, 136.8, 131.9, 130.1, 122.7, 122.5, 114.9, 92.3, 56.0, 44.0, 35.0, 32.5, 32.4, 30.9, 27.9, 24.5, 17.3. **UPLC-DAD-QTOF:** $C_{30}H_{40}NO_4S$ $[M+H]^+$ calcd.: 510.2678, found: 510.2672.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 5.7 min (minor) and 6.4 min (major).

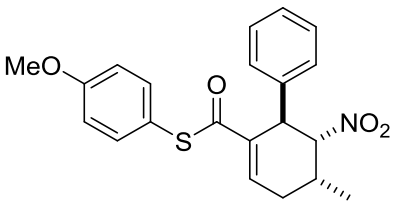
_S_-(2,4,6-Triisopropylphenyl) (1_R_,5_R_,6_R_)-4',5-dimethyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Bc)



Prepared according to the general procedure starting from thioester **22B** (50 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2c** (16 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (32 mg, 0.06 mmol, 65%). **M.p.:** 111.9–113.3 °C. **$[\alpha]_D^{23}$** = −33.8° (*c*=0.25, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, 1H), 7.18 – 7.06 (m, 4H), 7.04 – 6.89 (m, 2H), 4.74 (t, *J* = 3.2 Hz, 1H), 4.60 – 4.35 (m, 1H), 3.18 (p, *J* = 6.8 Hz, 1H), 2.99 (p, *J* = 7.0 Hz, 1H), 2.84 (p, *J* = 6.9 Hz, 1H), 2.72 – 2.55 (m, 1H), 2.47 – 2.26 (m, 5H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.12 – 0.99 (m, 12H), 0.74 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 190.8, 153.4, 153.3, 151.6, 138.0, 137.6, 137.0, 130.1, 128.9, 122.7, 122.5, 92.3, 44.4, 32.5, 32.4, 30.9, 27.9, 25.0, 24.9, 24.5, 24.5, 24.1, 23.8, 21.7, 17.3. **UPLC-DAD-QTOF:** $C_{30}H_{40}NO_3S$ $[M+H]^+$ calcd.: 494.2729, found: 494.2733.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 7.4 min (minor) and 8.2 min (major).

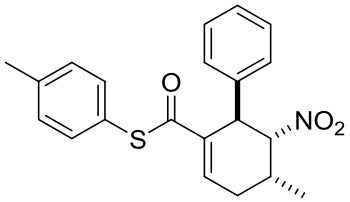
_S_-(4-Methoxyphenyl) (1_R_,5_R_,6_R_)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ca)



Prepared according to the general procedure starting from thioester **22C** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (26 mg, 0.07 mmol, 65%). **$[\alpha]_D^{24}$** = −16.7° (*c*=0.5, 88% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.47 (ddd, *J* = 4.5, 3.1, 1.0 Hz, 1H), 7.39 – 7.19 (m, 7H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.76 – 4.71 (m, 1H), 4.61 (*br*s, 1H), 3.80 (s, 3H), 2.73 – 2.55 (m, 1H), 2.48 – 2.21 (m, 2H), 1.11 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 190.8, 161.3, 139.9, 139.6, 137.2, 136.5, 129.7, 128.8, 128.4, 118.3, 115.5, 91.9, 56.0, 45.0, 30.9, 27.1, 17.7. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_4SNa$ $[M+Na]^+$ calcd.: 406.1089, found: 406.1088.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 11.7 min (major) and 19.4 min (minor).

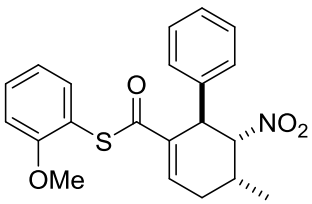
_S_-(_p_-Tolyl) (1_R_,5_R_,6_R_)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Da)



Prepared according to the general procedure starting from thioester **22D** (33 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **7a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (25 mg, 0.07 mmol, 66%). **M.p.:** 121.2–123.7 °C. **$[\alpha]_D^{23}$** = −34.9° (*c*=0.5, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.49 – 7.45 (m, 1H), 7.45 – 6.90 (m, 9H), 4.76 – 4.70 (m, 1H), 4.66 – 4.57 (m, 1H), 2.64 (dt, *J* = 19.5, 5.2 Hz, 1H), 2.47 – 2.21 (m, 5H), 1.10 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 189.9, 139.9, 139.4, 139.2, 136.1, 135.1, 130.1, 129.2, 128.4, 127.9, 123.7, 91.5, 44.6, 31.2, 26.6, 21.5, 17.3. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_3SNa$ $[M+Na]^+$ calcd.: 390.1140, found: 390.1145.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 10.5 min (major) and 16.7 min (minor).

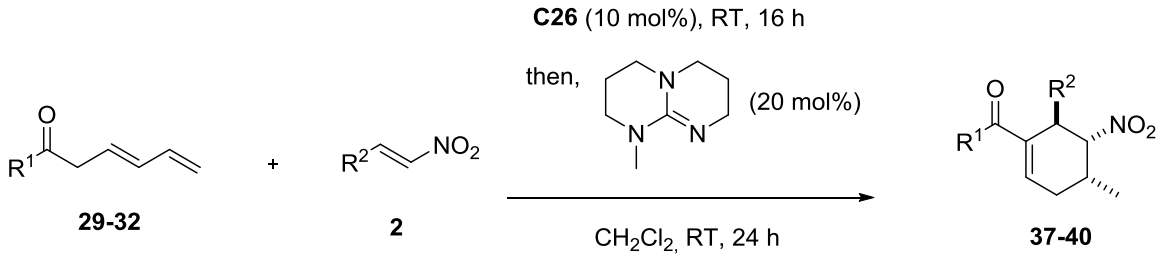
_S_-(2-Methoxyphenyl) (1_R_,5_R_,6_R_)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbothioate (26Ea)



Prepared according to the general procedure starting from thioester **22E** (35 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.07 mmol, 70%). **M.p.:** 161.8–164.5 °C. **$[\alpha]_D^{23}$** = −20.6° (*c*=0.5, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.57 – 7.20 (m, 8H), 7.01 – 6.86 (m, 2H), 4.74 (t, *J* = 3.0 Hz, 1H), 4.68 – 4.58 (m, 1H), 3.70 (s, 3H), 2.64 (dt, *J* = 19.5, 5.2 Hz, 1H), 2.47 – 2.24 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 188.6, 159.7, 139.6, 139.2, 137.2, 136.2, 131.8, 129.2, 128.4, 127.8, 121.2, 115.5, 111.8, 91.6, 56.1, 44.5, 30.4, 26.7, 17.2. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_4SNa$ $[M+Na]^+$ calcd.: 406.1089, found: 406.1085.

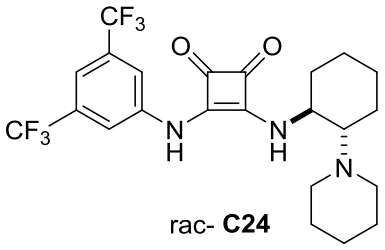
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 18.3 min (minor) and 22.5 min (major).

6.4.3. General procedure for the catalytic enantioselective cyclization of aromatic ketones 29-32 with nitroolefins 2

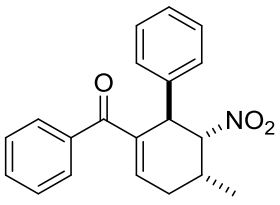


General procedure: To a mixture of the corresponding ketone **29**-**32** (0.15 mmol, 1.5 equiv.) and nitroolefin **2** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.1 mL), catalyst **C26** (6 mg, 0.01 mmol, 10 mol%) was added at room temperature. After stirring the reaction mixture at room temperature for 16 h, MTBD (3.2 mg, 0.02 mmol, 20 mol%) was added and the reaction mixture was stirred for additional 24 h at room temperature. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 95/5) to obtain only one diastereomer of cyclohexene derivatives **37**-**40**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



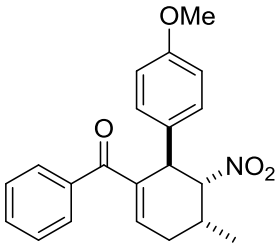
((1*R*,5*R*,6*R*)-5-Methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (37a)



Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (26 mg, 0.08 mmol, 80%). **M.p.:** 159.8–162.6 °C. $[\alpha]_D^{19}$ = −19.1° (*c*=0.5, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.74 – 7.63 (m, 2H), 7.60 – 7.41 (m, 3H), 7.38 – 7.20 (m, 5H), 6.98 – 6.63 (m, 1H), 4.96 – 4.82 (m, 2H), 2.70 (dt, *J* = 18.7, 4.6 Hz, 1H), 2.50 – 2.28 (m, 2H), 1.12 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.0, 142.4, 140.3, 138.5, 137.1, 132.6, 129.9, 129.6, 129.0, 128.9, 128.3, 92.2, 44.0, 31.3, 27.8, 17.3. **UPLC-DAD-QTOF:** $C_{20}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 344.1263, found: 344.1265.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 15.9 min (major) and 21.1 min (minor).

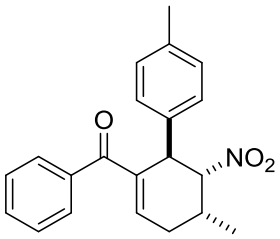
((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (37b)



Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.08 mmol, 78%). **M.p.:** 124.9–126.8 °C. **$[\alpha]_D^{19}$** = −45.3° (*c*=0.75, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.73 – 7.62 (m, 2H), 7.59 – 7.37 (m, 3H), 7.23 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.01 – 6.65 (m, 3H), 4.93 – 4.55 (m, 2H), 3.77 (s, 3H), 2.77 – 2.60 (m, 1H), 2.50 – 2.26 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.1, 159.7, 141.9, 138.5, 137.4, 132.6, 132.2, 130.0, 129.9, 128.9, 115.0, 92.3, 55.9, 43.3, 31.3, 27.8, 17.3. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_4Na$ $[M+Na]^+$ calcd.: 374.1368, found: 374.1369.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min). Retention times: 18.0 min (major) and 28.7 min (minor).

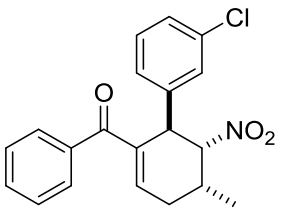
((1*R*,5*R*,6*R*)-4',5-Dimethyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (37c)



Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2c** (16 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (26 mg, 0.08 mmol, 82%). **M.p.:** 110.96–112.9 °C. **$[\alpha]_D^{19}$**= −9.1° (*c*=0.5, 96% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.74 – 7.65 (m, 2H), 7.56 – 7.39 (m, 3H), 7.23 – 7.08 (m, 4H), 6.84 (ddd, *J* = 4.2, 3.3, 1.1 Hz, 1H), 5.01 – 4.63 (m, 2H), 2.74 – 2.61 (m, 1H), 2.48 – 2.25 (m, 5H), 1.11 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 195.7, 141.7, 138.1, 137.6, 136.9, 136.8, 132.1, 129.9, 129.5, 128.4, 128.4, 91.8, 43.2, 30.9, 27.3, 21.2, 16.9. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 358.1419, found: 358.1421.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 18.1 min (major) and 20.8 min (minor).

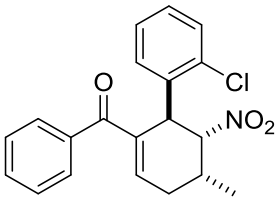
((1*R*,5*R*,6*R*)-3'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (37g)



Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2g** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (27 mg, 0.08 mmol, 77%). **M.p.:** 122.9–123.8 °C. **$[\alpha]_D^{19}$** = −54.3° (*c*=0.5, 86% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.59 – 7.40 (m, 3H), 7.36 – 7.08 (m, 4H), 6.99 – 6.81 (m, 1H), 5.01 – 4.52 (m, 2H), 2.78 – 2.65 (m, 1H), 2.48 – 2.30 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.8, 143.0, 142.4, 138.3, 136.6, 135.5, 134.3, 132.7, 130.9, 129.8, 129.0, 128.6, 127.3, 91.8, 43.6, 31.3, 28.0, 17.1. **UPLC-DAD-QTOF:** $C_{20}H_{18}NO_3ClNa$ $[M+Na]^+$ calcd.: 378.0873, found: 378.0871.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 80/20, flow rate= 1 mL/min). Retention times: 7.2 min (major) and 8.2 min (minor).

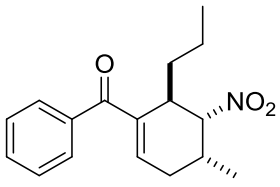
((1*S*,5*R*,6*R*)-2'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (37h)



Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2h** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (26 mg, 0.07 mmol, 71%). **M.p.:** 111.9–114.3 °C. **$[\alpha]_D^{19}$** = −41.5° (*c*=1.0, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.86 – 7.59 (m, 2H), 7.59 – 7.40 (m, 4H), 7.29 – 7.13 (m, 3H), 7.10 – 6.96 (m, 1H), 5.21 (dt, *J* = 2.2, 1.0 Hz, 1H), 4.90 (t, *J* = 2.6 Hz, 1H), 2.73 – 2.56 (m, 1H), 2.40 – 2.23 (m, 2H), 1.13 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.8, 144.4, 138.5, 137.5, 136.4, 134.9, 132.6, 131.1, 129.9, 129.7, 128.9, 127.7, 89.2, 41.4, 30.9, 27.5, 17.8. **UPLC-DAD-QTOF:** $C_{20}H_{18}NO_3ClNa$ $[M+Na]^+$ calcd.: 378.0873, found: 378.0867.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 11.4 min (minor) and 18.3 min (major).

((4*R*,5*R*,6*R*)-4-Methyl-5-nitro-6-propylcyclohex-1-en-1-yl)(phenyl)methanone (37i)

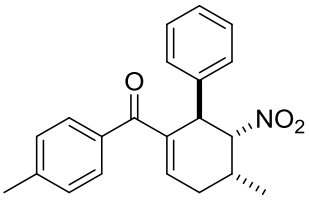


Prepared according to the general procedure starting from ketone **29** (26 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2i** (11 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a mixture of diastereomers (dr: 4:1). Yellow oil (21 mg, 0.07 mmol, 74%). **$[\alpha]_D^{19}$** = −6.9° (*c*=0.3, 94% *ee*, CH_2Cl_2). **^{1}H NMR** major

isomer (300 MHz, Chloroform-*d*) δ 7.75 – 7.64 (m, 2H), 7.64 – 7.51 (m, 1H), 7.51 – 7.39 (m, 2H), 6.57 (ddd, *J* = 4.3, 2.9, 0.9 Hz, 1H), 4.79 (dd, *J* = 3.3, 2.2 Hz, 1H), 3.55 (d, *J* = 8.1 Hz, 1H), 2.50 (dt, *J* = 18.1, 4.8 Hz, 1H), 2.38 – 2.20 (m, 2H), 1.53 – 1.32 (m, 4H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 197.3, 141.4, 139.8, 132.6, 130.2, 129.9, 128.9, 88.9, 38.4, 36.6, 30.9, 27.7, 21.3, 18.0, 14.5. **UPLC-DAD-QTOF:** $C_{17}H_{22}NO_3$ $[M+H]^+$ calcd.: 288.1600, found: 288.1603.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 17.3 min (major) and 20.3 min (minor), and for the minor diastereomer: 16.0 min (minor) and 21.8 min (major).

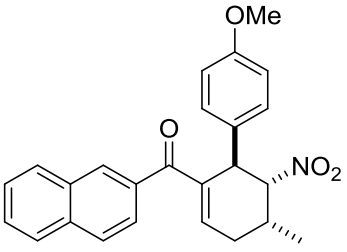
((1*R*,5*R*,6*R*)-5-Methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(*p*-tolyl)methanone (38a)



Prepared according to the general procedure starting from ketone **30** (27 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (26 mg, 0.08 mmol, 77%). **M.p.:** 123.9–124.3 °C. **$[\alpha]_D^{19}$** = −16.3° (*c*=0.5, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.63 (m, 2H), 7.48 – 7.07 (m, 7H), 6.98 – 6.77 (m, 1H), 4.85 (m, 2H), 2.76 – 2.64 (m, 1H), 2.50 – 2.28 (m, 5H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.77, 143.40, 141.40, 140.34, 137.16, 135.68, 130.14, 129.59, 129.37, 128.99, 128.26, 92.25, 44.05, 31.30, 27.99, 22.23, 17.23. **UPLC-DAD-QTOF:** $C_{21}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 358.1419, found: 358.1420.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 11.9 min (major) and 15.8 min (minor).

((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(naphthalen-2-yl)methanone (39b)

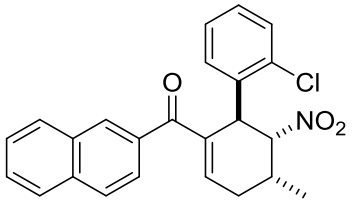


Prepared according to the general procedure starting from ketone **31** (34 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White foam (28 mg, 0.07 mmol, 69%). **$[\alpha]_D^{24}$** = −65.1° (*c*=0.5, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.19 (*br*s, 1H), 8.04 – 7.93 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.77 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.59 (tt, *J* = 6.8, 5.2 Hz, 2H), 7.34 – 7.14 (m, 2H), 6.96 – 6.66 (m, 3H), 4.89 – 4.77 (m, 2H), 3.77 (s,

3H), 2.99 – 2.60 (m, 1H), 2.54 – 2.25 (m, 2H), 1.14 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.1, 159.7, 141.7, 137.6, 135.7, 132.9, 132.2, 131.0, 130.0, 129.9, 129.7, 128.9, 128.7, 128.5, 127.4, 126.1, 115.1, 92.4, 55.9, 43.4, 31.4, 27.9, 17.3. **UPLC-DAD-QTOF:** $C_{25}H_{24}NO_4$ $[M+H]^+$ calcd.: 402.1705, found: 402.1701.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 32.6 min (major) and 57.1 min (minor).

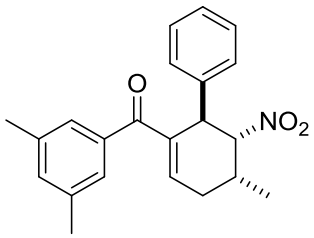
((1*S*,5*R*,6*R*)-2'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(naphthalen-2-yl)methanone (39h)



Prepared according to the general procedure starting from ketone **31** (34 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2h** (18 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White solid (33 mg, 0.08 mmol, 81%). **M.p.:** 170.5–171.4 °C. **$[\alpha]_D^{24}$** = −70.7° (*c*=1.0, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.23 (*br*s, 1H), 8.05 – 7.85 (m, 3H), 7.83 – 7.75 (m, 1H), 7.65 – 7.55 (m, 2H), 7.49 – 7.40 (m, 1H), 7.34 – 7.18 (m, 3H), 7.12 – 7.05 (m, 1H), 5.28 (s, 1H), 5.09 – 4.85 (m, 1H), 2.68 (td, *J* = 11.6, 9.8, 4.6 Hz, 1H), 2.36 (tdd, *J* = 10.1, 4.6, 2.3 Hz, 2H), 1.15 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 195.7, 144.3, 137.5, 136.6, 135.7, 135.6, 134.9, 132.9, 131.2, 130.9, 130.1, 129.9, 129.7, 129.0, 128.7, 128.5, 127.7, 127.5, 126.1, 89.3, 41.6, 31.0, 27.6, 17.9. **UPLC-DAD-QTOF:** $C_{24}H_{20}NO_3ClNa$ $[M+Na]^+$ calcd.: 428.1029, found: 428.1031.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1 mL/min). Retention times: 14.8 min (minor) and 31.2 min (major).

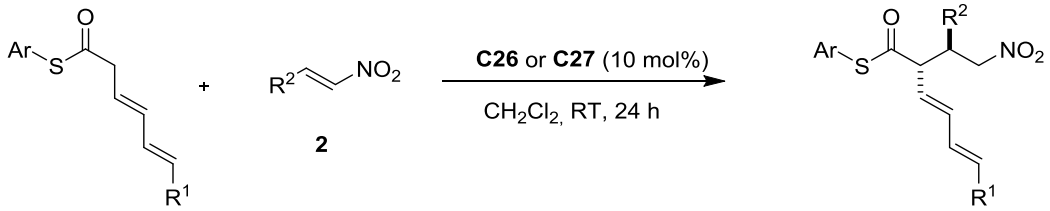
(3,5-Dimethylphenyl)((1*R*,5*R*,6*R*)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (40a)



Prepared according to the general procedure starting from ketone **32** (30 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. Yellow oil (25 mg, 0.08 mmol, 72%). **$[\alpha]_D^{24}$** = −23.3° (*c*=0.5, 92% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.45 – 7.15 (m, 8H), 6.86 (ddd, *J* = 4.1, 3.2, 1.0 Hz, 1H), 5.12 – 4.63 (m, 2H), 2.78 – 2.64 (m, 1H), 2.48 – 2.27 (m, 8H), 1.12 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.4, 142.3, 140.4, 138.5, 137.2, 134.2, 129.6, 129.0, 128.2, 127.5, 126.9, 92.2, 44.0, 31.3, 27.9, 21.9, 17.3. **UPLC-DAD-QTOF:** $C_{22}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 372.1576, found: 372.1574.

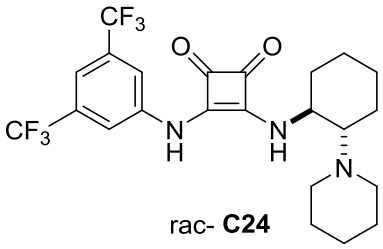
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min). Retention times: 9.1 min (major) and 13.4 min (minor).

6.4.4. General procedure for the Michael addition of substituted thioesters 44-48 to nitroolefins 2



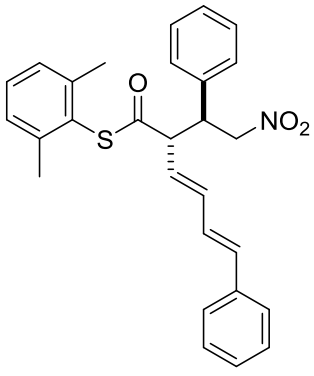
General procedure: To a solution of the corresponding substituted thioester **44**-**48** (0.15 mmol, 1.5 equiv.) and nitroolefin **2** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.1 mL), catalyst **C26** or **C27** (0.01 mmol, 10 mol%) was added at room temperature. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 95/5) to obtain the desired Michael adducts **49**-**53**.

The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C24** (20 mol%).



rac- **C24**

_S_-(2,6-Dimethylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dienethioate (49Aa)

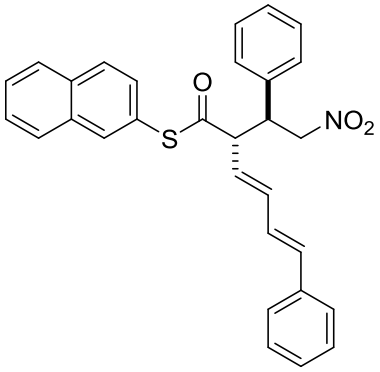


Prepared according to the general procedure starting from thioester **44A** (46 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C27** (5 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (36 mg, 0.08 mmol, 78%). **M.p.**: 131.2–132.4 °C. **$[\alpha]_D^{25}$** = −69.9° (*c*=0.5, 80% *ee*, CH_2Cl_2**).** **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.58 – 7.24 (m, 10H), 7.23 – 7.01 (m, 3H), 6.90 – 6.78 (m, 1H), 6.73 – 6.57 (m, 2H), 5.84 (dd, *J* = 14.9, 9.5 Hz, 1H), 4.78 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.66 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.05 (ddd, *J* =

10.8, 9.7, 4.9 Hz, 1H), 3.90 (dd, *J* = 10.8, 9.6 Hz, 1H), 2.34 – 1.64 (*br*s, 6H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 195.4, 143.8, 138.1, 138.0, 137.7, 137.7, 136.1, 135.8, 131.1, 130.1, 129.8, 129.5, 129.3, 129.2, 128.3, 128.1, 127.9, 127.7, 125.7, 123.4, 79.8, 62.1, 47.2, 22.2. **UPLC-DAD-QTOF**: $C_{28}H_{28}NO_3S$ $[M+H]^+$ calcd.: 458.1790, found: 458.1790.

The diastereomeric ratio was determined by ^{1}H NMR on crude material. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times for the major diastereomer: 26.9 min (minor) and 31.9 min (major).

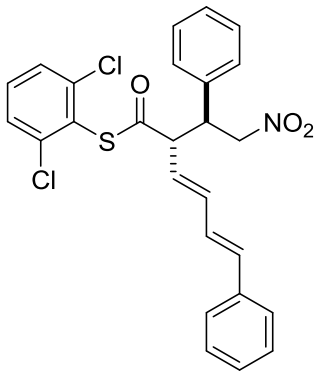
_S_-(Naphthalen-2-yl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dienethioate (50Aa)



Prepared according to the general procedure starting from thioester **45A** (50 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C27** (5 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a mixture of diastereomers (dr: 19:1). White solid (38 mg, 0.08 mmol, 82%). **M.p.:** 177.5–1778.1 °C. **$[\alpha]_D^{25}$** = −120° (*c*=0.5, 80% *ee*, CH_2Cl_2).**^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.88 – 7.72 (m, 3H), 7.56 – 7.19 (m, 13H), 7.11 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.84 (ddd, *J* = 15.6, 10.3, 0.7 Hz, 1H), 6.72 – 6.48 (m, 2H), 5.86 (dd, *J* = 15.0, 9.8 Hz, 1H), 4.91 – 4.58 (m, 2H), 4.09 (td, *J* = 9.8, 5.1 Hz, 1H), 3.88 – 3.72 (m, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 196.4, 137.5, 137.3, 136.8, 136.7, 135.1, 134.6, 133.6, 130.8, 129.2, 129.0, 129.0, 128.6, 128.5, 128.4, 128.2, 128.0, 127.5, 127.4, 127.1, 126.9, 126.9, 126.8, 78.4, 61.5, 46.5. **UPLC-DAD-QTOF:** $C_{30}H_{26}NO_3S$ $[M+H]^+$ calcd.: 480.1633, found: 480.1628.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 80/20, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 20.3 min (minor) and 38.3 min (major), and for the minor diastereomer: 9.3 min (minor) and 10.6 min (major).

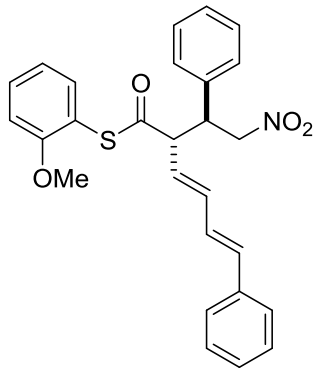
_S_-(2,6-Dichlorophenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dienethioate (51Aa)



Prepared according to the general procedure starting from thioester **46A** (52 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C27** (5 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a mixture of diastereomers (dr: 18:1). White solid (40 mg, 0.08 mmol, 75%). **M.p.:** 143.3–144.8 °C. **$[\alpha]_D^{23}$** = −55.1° (*c*=0.5, 80% *ee*, CH_2Cl_2).**^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.55 – 7.19 (m, 13H), 6.84 (dd, *J* = 15.4, 10.4 Hz, 1H), 6.73 – 6.50 (m, 2H), 5.82 (dd, *J* = 14.9, 9.6 Hz, 1H), 4.91 – 4.53 (m, 2H), 4.08 (td, *J* = 9.6, 4.9 Hz, 1H), 3.90 (t, *J* = 9.7 Hz, 1H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 193.3, 138.9, 136.1, 132.7, 130.5, 130.1, 129.8, 129.6, 129.4, 129.3, 128.2, 127.7, 126.9, 79.0, 61.9, 47.1. **UPLC-DAD-QTOF:** $C_{26}H_{22}NO_3SCl_2$ $[M+H]^+$ calcd.: 498.0697, found: 498.696.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 11.6 min (minor) and 13.3 min (major), and for the minor diastereomer: 9.7 min (major) and 10.4 min (minor).

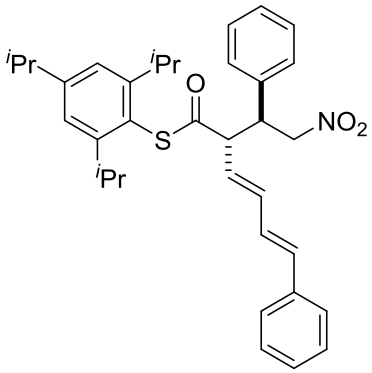
_S_-(2-Methoxyphenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dienethioate (52Aa)



Prepared according to the general procedure starting from thioester **47A** (46 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C27** (5 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a mixture of diastereomers (dr: 18:1). Yellow solid (35 mg, 0.08 mmol, 76%). **M.p.**: 145.7–145.9 °C. **$[\alpha]_D^{22}$** = −89.6° (*c*=0.5, 85% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.51 – 7.27 (m, 11H), 7.11 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.85 – 6.75 (m, 1H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.52 (dd, *J* = 15.1, 10.3 Hz, 1H), 5.83 (dd, *J* = 15.0, 9.7 Hz, 1H), 4.84 (dd, *J* = 12.9, 5.0 Hz, 1H), 4.71 (dd, *J* = 13.0, 9.9 Hz, 1H), 4.16 – 4.00 (m, 1H), 3.90 – 3.76 (m, 1H), 3.69 (s, 3H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 196.2, 160.2, 138.2, 137.8, 137.7, 137.5, 135.6, 133.0, 129.9, 129.8, 129.4, 129.2, 129.1, 128.4, 127.9, 127.7, 122.1, 112.6, 79.3, 61.8, 56.9, 47.3. **UPLC-DAD-QTOF:** $C_{27}H_{26}NO_4S$ $[M+H]^+$ calcd.: 460.1583, found: 460.1580.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 28.7 min (minor) and 34.3 min (major), and for the minor diastereomer: 15.4 min (major) and 19.4 min (minor).

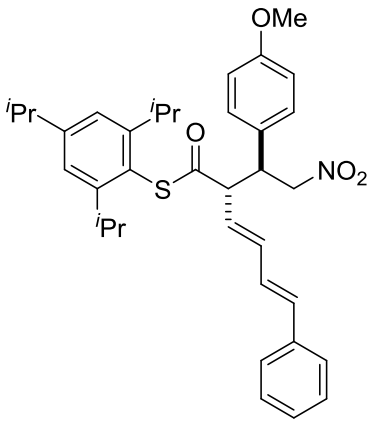
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dienethioate (53Aa)



Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (44 mg, 0.08 mmol, 78%). **M.p.:** 152.7–154.0 °C. **$[\alpha]_D^{24}$** = −145.7° (*c*=1.0, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.55 – 7.20 (m, 10H), 7.12 – 6.54 (m, 5H), 6.02 – 5.75 (m, 1H), 4.90 – 4.59 (m, 2H), 4.18 – 3.86 (m, 2H), 3.21 (*br*s, 1H), 2.98 – 2.82 (m, 1H), 2.43 (*br*s, 1H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.18 – 0.67 (m, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.3, 153.3, 153.0, 152.8, 151.9, 137.6, 137.4, 135.3, 129.6, 129.4, 128.9, 128.8, 128.0, 127.9, 127.3, 122.6, 79.6, 61.4, 46.8, 35.0, 32.1, 30.4, 24.5. **UPLC-DAD-QTOF:** $C_{35}H_{42}NO_3S$ $[M+H]^+$ calcd.: 556.2885, found: 556.2884.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 8.5 min (major) and 11.1 min (minor).

_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-1-(4-methoxyphenyl)-2-nitroethyl)-6-phenylhexa-3,5-dienethioate (53Ab)

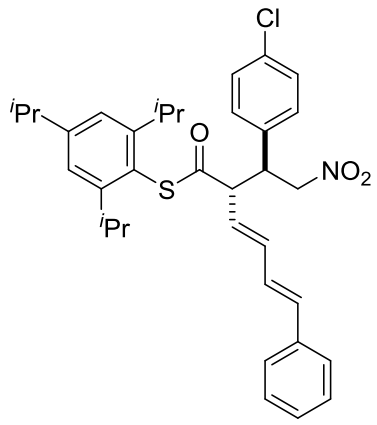


Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (47 mg, 0.08 mmol, 81%). **M.p.:** 168.2–169.7 °C. **$[\alpha]_D^{24}$** = −108.8° (*c*=0.5, 95% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.51 – 7.13 (m, 7H), 7.01-6.89 (m, 4H), 6.81 (d, *J* = 10.6 Hz, 1H), 6.73 – 6.43 (m, 2H), 5.83 (dd, *J* = 14.9, 8.9 Hz, 1H), 4.74 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.60 (dd, *J* = 12.5, 9.2 Hz, 1H), 4.07 – 3.86 (m, 2H), 3.83 (s, 3H), 3.20 (m, 1H), 2.86 (m, 1H), 2.50 – 2.37 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 6H), 0.98 (ddd, *J* = 54.0, 23.3, 6.8 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.3, 160.0, 153.2, 151.9, 137.4, 135.2, 130.0, 129.4, 128.8, 128.1,

127.9, 127.3, 122.6, 114.9, 79.8, 61.6, 55.8, 46.2, 35.0, 32.4, 32.1, 24.5. **UPLC-DAD-QTOF:** $C_{36}H_{44}NO_4S$ $[M+H]^+$ calcd.: 586.2991, found: 586.2995.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 9.9 min (major) and 17.4 min (minor).

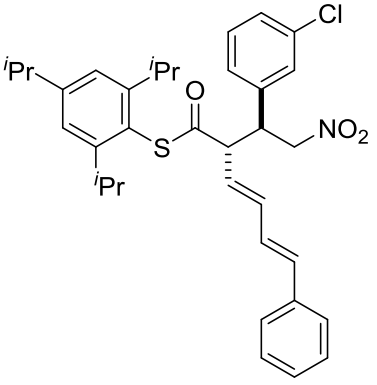
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-1-(4-chlorophenyl)-2-nitroethyl)-6-phenylhexa-3,5-dienethioate (53Ad)



Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2d** (16 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (47 mg, 0.08 mmol, 82%). **M.p.:** 153.3–155.0 °C. **$[\alpha]_D^{24}$** = −69.9° (*c*=0.5, 93% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.55 – 7.24 (m, 9H), 7.00 (d, *J* = 4.9 Hz, 2H), 6.89 – 6.55 (m, 3H), 5.82 (dd, *J* = 14.8, 9.3 Hz, 1H), 4.76 (dd, *J* = 12.8, 4.5 Hz, 1H), 4.62 (ddd, *J* = 12.8, 9.9, 3.9 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.90 (dd, *J* = 11.2, 9.3 Hz, 1H), 3.32 – 3.07 (m, 1H), 2.90 – 2.66 (m, 1H), 2.38 (dd, *J* = 11.2, 4.9 Hz, 1H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.00 (ddd, *J* = 48.8, 25.5, 6.8 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.5, 153.6, 153.2, 152.5, 138.3, 137.6, 136.4, 135.9, 135.2, 130.9, 130.8, 130.2, 129.8, 129.3, 128.1, 127.9, 127.7, 123.1, 79.7, 61.6, 46.6, 35.4, 32.8, 24.9. **UPLC-DAD-QTOF:** $C_{35}H_{41}NO_3SCl$ $[M+H]^+$ calcd.: 590.2496, found: 590.2499.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min. Retention times: 8.9 min (major) and 14.8 min (minor).

_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-1-(3-chlorophenyl)-2-nitroethyl)-6-phenylhexa-3,5-dienethioate (53Ag)

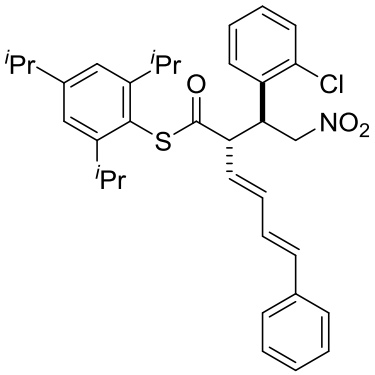


Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2g** (18 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (43 mg, 0.07 mmol, 74%). **M.p.:** 132.8–134.3 °C. **$[\alpha]_D^{25}$** = −77.5° (*c*=0.5, 90% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.58 – 7.19 (m, 9H), 7.00 (*brs*, 2H), 6.94 – 6.78 (m, 1H), 6.75 – 6.50 (m, 2H), 5.90 – 5.69 (m, 1H), 4.75 (ddd, *J* =

13.0, 4.5, 1.6 Hz, 1H), 4.66 – 4.51 (m, 1H), 4.12 – 3.87 (m, 2H), 3.28 – 3.10 (m, 1H), 2.99 – 2.82 (m, 1H), 2.48 (m, 1H), 1.23 (dd, *J* = 7.0, 1.7 Hz, 6H), 1.16 – 0.75 (m, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.0, 153.1, 153.0, 152.1, 139.6, 137.9, 135.6, 130.8, 129.5, 129.4, 129.1, 129.0, 128.9, 127.7, 127.5, 127.4, 127.3, 122.7, 79.3, 61.0, 46.3, 35.0, 32.4, 24.5. **UPLC-DAD-QTOF:** $C_{35}H_{41}NO_3SCl$ $[M+H]^+$ calcd.: 590.2496, found: 590.2501.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 10.3 min (major) and 13.0 min (minor).

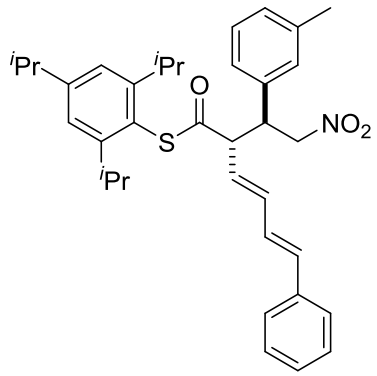
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-1-(2-chlorophenyl)-2-nitroethyl)-6-phenylhexa-3,5-dienethioate (53Ah)



Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2h** (18 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a mixture of diastereomers (dr: 18:1). White solid (32 mg, 0.06 mmol, 60%). **M.p.:** 177.2–178.0 °C. **$[\alpha]_D^{25}$** = −47.1° (*c*=0.5, 80% *ee*, CH_2Cl_2). **^{1}H NMR** major isomer (300 MHz, Chloroform-*d*) δ 7.51 – 7.20 (m, 9H), 7.00 (*br*s, 2H), 6.90 – 6.79 (m, 1H), 6.77 – 6.59 (m, 2H), 5.82 (dd, *J* = 14.8, 9.3 Hz, 1H), 4.76 (dd, *J* = 12.8, 4.5 Hz, 1H), 4.61 (dd, *J* = 12.8, 9.7 Hz, 1H), 4.02 (td, *J* = 10.3, 4.6 Hz, 1H), 3.90 (dd, *J* = 11.2, 9.2 Hz, 1H), 3.28 – 3.09 (m, 1H), 2.87 (p, *J* = 6.9 Hz, 1H), 2.46 – 2.33 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.17 – 0.80 (m, 12H). **^{13}C NMR** major isomer (75 MHz, Chloroform-*d*) δ 196.5, 153.6, 153.2, 152.5, 138.3, 137.6, 136.4, 135.9, 135.2, 130.8, 130.2, 129.8, 129.3, 128.1, 127.9, 127.7, 123.1, 79.7, 61.6, 46.6, 35.4, 32.8, 24.9. **UPLC-DAD-QTOF:** $C_{35}H_{41}NO_3SCl$ $[M+H]^+$ calcd.: 590.2496, found: 590.2503.

The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography. Retention times for the major diastereomer: 7.9 min (minor) and 10.3 min (major) and for minor diastereomer: 13.4 min (minor) and 18.3 min (major).

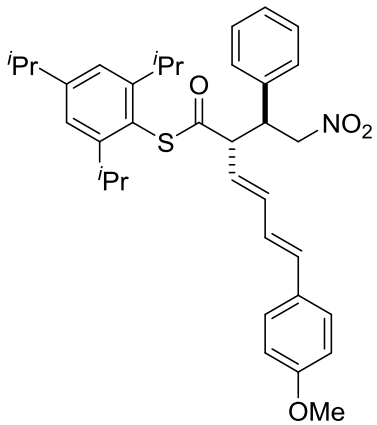
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-(m-tolyl)ethyl)-6-phenylhexa-3,5-dienethioate (53Aj)



Prepared according to the general procedure starting from thioester **48A** (61 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2j** (16 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (40 mg, 0.07 mmol, 74%). **M.p.:** 132.7–133.8 °C. **$[\alpha]_D^{24}$** = −80.9° (*c*=0.5, 81% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.58 – 7.24 (m, 6H), 7.22 – 7.07 (m, 3H), 7.00 (*br*s, 2H), 6.94 – 6.39 (m, 3H), 6.01 – 5.74 (m, 1H), 4.75 (dd, *J* = 12.6, 4.1 Hz, 1H), 4.71 – 4.53 (m, 1H), 4.16 – 3.87 (m, 2H), 3.34 – 3.08 (m, 1H), 2.95 – 2.76 (m, 1H), 2.64 – 2.28 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.18 – 0.73 (m, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 194.1, 151.2, 151.1, 150.7, 149.8, 137.1, 135.5, 135.2, 133.1, 127.7, 127.5, 127.3, 126.7, 126.1, 125.9, 125.4, 125.2, 123.8, 120.5, 77.7, 59.2, 44.7, 32.9, 30.2, 30.1, 22.4, 20.1. **UPLC-DAD-QTOF:** $C_{36}H_{44}NO_3S$ $[M+H]^+$ calcd.: 570.3042, found: 570.3051.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min). Retention times: 6.2 min (major) and 7.0 min (minor).

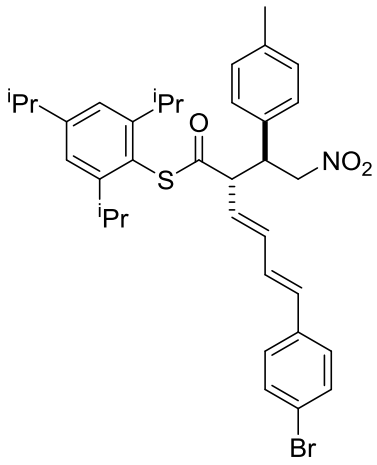
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-6-(4-methoxyphenyl)-2-((_S_)-2-nitro-1-phenylethyl)hexa-3,5-dienethioate (53Ba)



Prepared according to the general procedure starting from thioester **48B** (65 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (44 mg, 0.07 mmol, 75%). **M.p.:** 141.7–143.1 °C. **$[\alpha]_D^{24}$** = −120.7° (*c*=0.5, 94% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.44 – 7.26 (m, 7H), 7.03 – 6.98 (m, *J* = 7.6 Hz, 2H), 6.92 (*br*s, 2H), 6.80 – 6.54 (m, 3H), 5.77 (dd, *J* = 15.2, 9.2 Hz, 1H), 4.77 (dd, *J* = 12.7, 4.5 Hz, 1H), 4.63 (dd, *J* = 12.7, 9.5 Hz, 1H), 4.04 (ddd, *J* = 11.0, 9.4, 4.5 Hz, 1H), 3.94 (dd, *J* = 11.0, 9.2 Hz, 1H), 3.86 (s, 3H), 3.28 – 3.05 (m, 1H), 2.86 (p, *J* = 6.9 Hz, 1H), 2.45 – 2.34 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 6H), 0.97 (ddd, *J* = 63.9, 26.0, 6.8 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.7, 160.8, 153.7, 153.2, 152.3, 138.3, 137.9, 135.2, 130.5, 130.0, 129.4, 129.2, 129.0, 127.1, 126.3, 123.0, 115.3, 80.1, 61.9, 56.4, 47.2, 35.4, 32.7, 32.5, 24.9. **UPLC-DAD-QTOF:** $C_{36}H_{44}NO_4S$ $[M+H]^+$ calcd.: 586.2991, found: 586.3000.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min). Retention times: 8.7 min (major) and 12.1 min (minor).

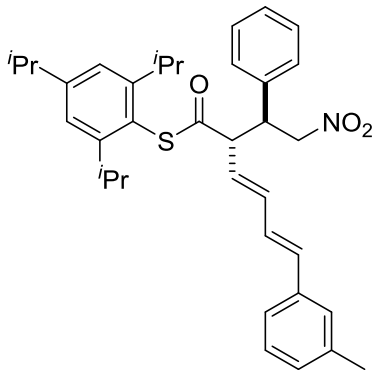
_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-6-(4-bromophenyl)-2-((_S_)-2-nitro-1-(_p_-tolyl)ethyl)hexa-3,5-dienethioate (53Cc)



Prepared according to the general procedure starting from thioester **48C** (73 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2c** (16 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (48 mg, 0.07 mmol, 75%). **M.p.:** 159.4–160.8 °C. **$[\alpha]_D^{25}$** = −117.8° (*c*=1.0, 91% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.09 (m, 6H), 6.99 (d, *J* = 6.0 Hz, 2H), 6.88 – 6.76 (m, 1H), 6.71 – 6.56 (m, 2H), 5.92 – 5.80 (m, 1H), 4.77 – 4.68 (m, 1H), 4.68 – 4.51 (m, 1H), 4.06 – 3.81 (m, 2H), 3.26 – 3.09 (m, 1H), 2.86 (p, *J* = 6.9 Hz, 1H), 2.37 (s, 4H), 1.23 (d, *J* = 6.9 Hz, 6H), 0.96 (ddt, *J* = 46.3, 24.1, 6.9 Hz, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.2, 153.3, 152.7, 151.9, 138.5, 137.1, 136.3, 135.1, 134.2, 133.8, 132.5, 130.3, 128.9, 128.8, 128.7, 128.6, 122.6, 79.7, 61.4, 46.5, 35.0, 32.4, 24.5, 21.8. **UPLC-DAD-QTOF:** $C_{36}H_{42}NO_3SBr$ $[M+H]^+$ calcd.: 548.2147, found: 548.2153.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 9.4 min (major) and 16.1 min (minor).

_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-2-nitro-1-phenylethyl)-6-(_m_-tolyl)hexa-3,5-dienethioate (53Da)

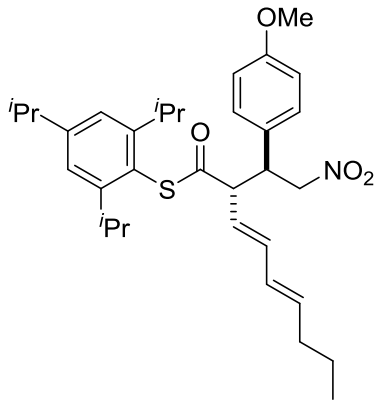


Prepared according to the general procedure starting from thioester **48D** (63 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2a** (15 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (41 mg, 0.07 mmol, 73%). **M.p.:** 142.3–144.9 °C. **$[\alpha]_D^{25}$** = −157.1° (*c*=1.5, 97% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.44 – 7.17 (m, 9H), 6.99 (d, *J* = 6.9 Hz, 2H), 6.91 – 6.79 (m, 1H), 6.73 – 6.53 (m, 2H), 5.83 (dd, *J* = 15.3, 9.1 Hz, 1H), 4.76 (dd, *J* = 12.7, 4.6 Hz, 1H), 4.64 (dd, *J* = 12.7, 9.3 Hz, 1H), 4.22 – 3.67 (m, 2H), 3.32 – 3.10 (m, 1H), 2.87 (dq, *J* = 13.8, 6.8 Hz, 1H), 2.47 – 2.27 (m, 4H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.15 – 0.69 (m, 12H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.2, 153.3, 152.8, 151.9, 139.0, 137.7, 137.4, 137.2, 135.4, 129.6, 129.6, 129.3, 129.0, 128.9, 128.8, 127.9, 127.7,

127.7, 124.5, 122.6, 79.6, 61.4, 46.8, 35.0, 32.4, 32.1, 24.4, 22.1. **UPLC-DAD-QTOF:** $C_{36}H_{44}NO_3S$ $[M+H]^+$ calcd.: 570.3042, found: 570.3054.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 7.1 min (major) and 9.3 min (minor).

_S_-(2,4,6-Triisopropylphenyl) (_S_,3_E_,5_E_)-2-((_S_)-1-(4-methoxyphenyl)-2-nitroethyl)nona-3,5-dienethioate (53Eb)



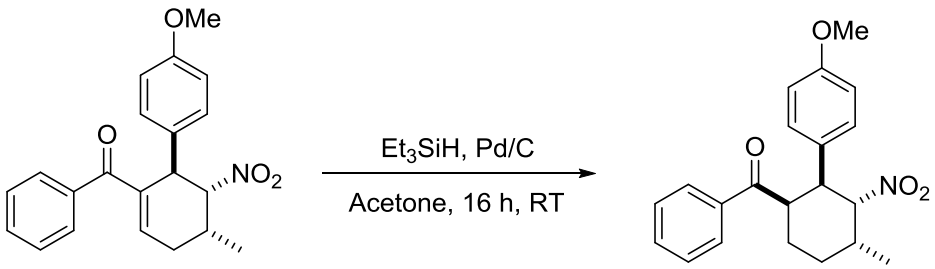
Prepared according to the general procedure starting from thioester **48E** (56 mg, 0.15 mmol, 1.5 equiv.) and nitroolefin **2b** (18 mg, 0.1 mmol, 1.0 equiv.) and **C26** (6 mg, 0.01 mmol, 10 mol%). The title compound was isolated as a single diastereomer. White solid (38 mg, 0.07 mmol, 69%). **M.p.:** 112.2–113.6 °C. **$[\alpha]_D^{25}$** = −38.1° (*c*=1.0, 98% *ee*, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.98 (*br*s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.44 (dd, *J* = 15.1, 10.3 Hz, 1H), 6.10 (dd, *J* = 15.2, 10.3 Hz, 1H), 5.84 (dt, *J* = 14.7, 7.0 Hz, 1H), 5.57 (dd, *J* = 15.1, 9.3 Hz, 1H), 4.71 (dd, *J* = 12.5, 4.6 Hz, 1H), 4.56 (dd, *J* = 12.5, 9.9 Hz, 1H), 4.02 – 3.69 (m, 5H), 3.26 – 3.08 (m, 1H), 2.86 (p, *J* = 7.0 Hz, 1H), 2.58 – 2.32 (m, 1H), 2.13 (q, *J* = 7.1, 6.7 Hz, 2H), 1.48 (q, *J* = 7.3 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.16 – 0.73 (m, 15H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 196.5, 159.9, 153.2, 151.8, 138.0, 137.7, 130.0, 129.7, 129.4, 125.2, 122.7, 122.5, 114.9, 79.8, 61.4, 55.8, 46.1, 35.4, 36.0, 32.2, 24.5, 23.0, 14.3. **UPLC-DAD-QTOF:** $C_{33}H_{46}NO_4S$ $[M+H]^+$ calcd.: 552.3148, found: 552.3154.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95/5, flow rate= 1 mL/min). Retention times: 6.2 min (major) and 10.3 min (minor).

6.4.5. Elaboration of adducts

6.4.5.1. *Selective reduction of the C=C double bond*

Reduction of ketone 37b to 56[236]

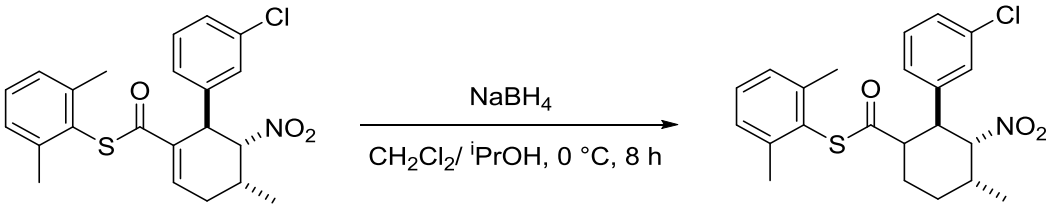


37b **56**

To a mixture of compound **37b** (35 mg, 0.1 mmol, 1.0 equiv.) and Pd/C (10 mg, 10 mol%, 10% in weight) in acetone (0.25 mL), triethylsilane (0.16 mL, 1.0 mmol, 10.0 equiv.) was added. The resulting mixture was stirred at room temperature for 16 h and filtered through celite rinsing with ethyl acetate. The organic layer was concentrated under reduced pressure and the resulting oily residue was purified by silica gel column chromatography (hexane/ethyl acetate 90/10) to yield compound **56** as a single diastereomer. White foam (27 mg, 0.07 mmol, 72%). $\mathbf{[\alpha]_D^{19}}$ **=** +8.3° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.55 – 7.42 (m, 1H), 7.37 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 5.06 (dd, *J* = 12.2, 4.8 Hz, 1H), 3.98 (t, *J* = 11.8 Hz, 1H), 3.84 – 3.57 (m, 4H), 2.83 (dq, *J* = 7.8, 3.7 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.81 (h, *J* = 4.3, 3.8 Hz, 2H), 1.19 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 200.9, 158.8, 136.7, 133.3, 130.9, 129.4, 128.8, 128.2, 114.2, 93.0, 55.3, 51.0, 41.1, 33.2, 24.6, 13.2. **UPLC-DAD-QTOF:** $C_{21}H_{23}NO_4Na[M+Na]^+$ calcd.: 376.1525, found: 376.1539.

[236] : a) Y. Arakawa, S. P. Fritz, H. Wennemers, *J. Org. Chem*. **2014**, *79*, 3937–3945. b) T. Fukuyama, S. -C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.

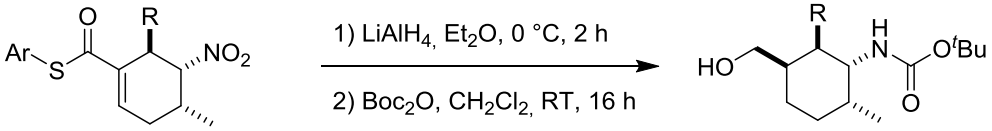
Reduction of thioester 26Ag to 57[237]



26Ag **57**

To a solution of thioester **26Ag** (42 mg, 0.1 mmol, 1.0 equiv.) in CH_2Cl_2/isopropanol (0.5/1.0 mL), $NaBH_4$ (46 mg, 1.0 mmol, 10.0 equiv.) was added at 0 °C. After being stirred for 8 h at 0 °C, the reaction mixture was poured into water (5.0 mL) and extracted with CH_2Cl_2 (3 x 5.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 90/10) to yield compound **57** as a single diastereomer. Yellow oil (28 mg, 0.07 mmol, 68%). **$[\alpha]_D^{19}$ =** +12.9° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.29 – 7.18 (m, 4H), 7.17 – 6.98 (m, 3H), 5.90 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.71 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.50 (td, *J* = 5.4, 2.1 Hz, 1H), 2.84 (ddd, *J* = 12.1, 6.3, 3.7 Hz, 1H), 2.39 – 2.07 (m, 5H), 1.99 – 1.79 (m, 4H), 1.69 (dd, *J* = 13.5, 3.2 Hz, 1H), 1.07 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 198.0, 140.9, 134.9, 130.4, 130.3, 128.6, 128.5, 128.1, 127.9, 126.7, 125.9, 86.5, 54.8, 41.5, 32.6, 29.9, 26.9, 23.5, 13.1. **UPLC-DAD-QTOF:** $C_{22}H_{24}NO_3SClNa$ $[M+Na]^+$ calcd.: 440.1063, found: 440.1065.

6.4.5.2. *Reduction of thioester group*



26Aa Ar: 2,6-$Me_2C_6H_3$ R:Ph **58**
26Bb Ar: 2,4,6-$^i Pr_3C_6H_2$ R: 4-$MeOC_6H_4$ **59**

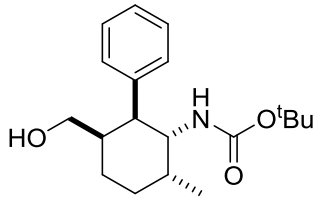
1st step:[238] To a suspension of $LiAlH_4$ (95 mg, 0.3 mmol, 3.0 equiv.) in diethyl ether (1.0 mL), the corresponding thioester **26Aa** or **26Bb** (0.1 mmol, 1.0 equiv.) was added dropwise at 0 °C. After being stirred for 2 h at 0 °C, the reaction was quenched by addition of H_2O (0.5 mL) and NaOH (1.0 mL, 20%) at 0 °C. The compound was extracted with Et_2O (3 x 5.0 mL). The organic layer was dried over $MgSO_4$, filtered and

[237] a) R. J. Alfie, N. Truong, J. M. Yost, D. M. Coltart, *Tetrahedron Lett.* **2017**, *58*, 185–189. b) A. G. M. Barrett, D. J. Rys, *J. Chem. Perkin Trans.* **1995**, *1*, 1009–1017.
[238] J. Guang, A. J. Larson, J. C. -G. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 523–529.

concentrated under reduced pressure to obtain the amine, which was used without any further purification in the next step.

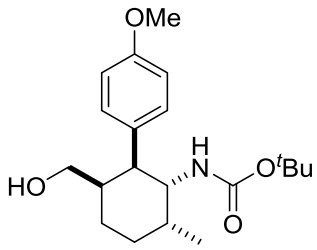
2nd step: To a solution of the previous synthesized amine (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL), Boc_2O (26 mg, 0.12 mmol, 1.2 equiv.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was directly submitted to a flash column chromatography (hexane/ethyl acetate 50/50) to obtain essentially pure protected amine **58** or **59**.

***tert*-Butyl ((1*R*,2*S*,3*R*,6*R*)-3-(hydroxymethyl)-6-methyl-2-phenylcyclohexyl)carbamate (58)**



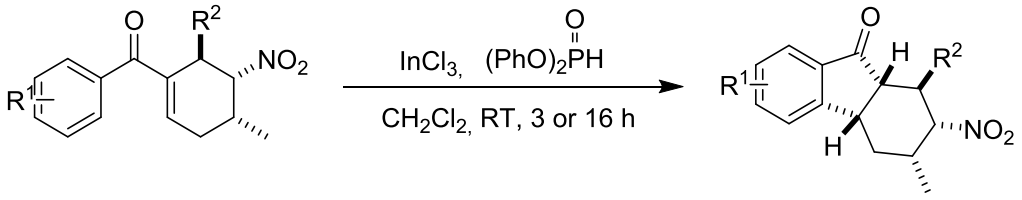
Prepared according to the general procedure starting from the compound **26Aa** (38 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White foam (16 mg, 0.05 mmol, 50%). **$[\alpha]_D^{24}$ =** −17.5° (*c*=0.3, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.43 – 7.17 (m, 5H), 4.20 – 3.93 (m, 1H), 3.47– 3.37 (m, 2H), 3.03 (d, *J* = 8.2 Hz, 1H), 2.45 – 2.24 (m, 2H), 2.02 – 1.85 (m, 1H), 1.76 – 1.59 (m, 3H), 1.39 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 155.4, 128.6, 128.5, 127.2, 79.0, 74.4, 53.4, 49.2, 33.9, 31.0, 29.7, 28.4, 25.6, 24.9, 14.1. **UPLC-DAD-QTOF:** $C_{19}H_{29}NO_3Na$ $[M+Na]^+$ calcd.: 342.2045, found: 342.2045.

***tert*-Butyl ((1*R*,2*S*,3*R*,6*R*)-3-(hydroxymethyl)-2-(4-methoxyphenyl)-6-methylcyclohexyl)carbamate (59)**



Prepared according to the general procedure starting from the compound **26Bb** (50 mg, 0.1 mmol, 1.0 equiv.). The title compound was isolated as a single diastereomer. White foam (20 mg, 0.06 mmol, 60%). **$[\alpha]_D^{24}$ =** −14.3° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.13 – 3.92 (m, 1H), 3.81 (s, 3H), 3.54 – 3.39 (m, 2H), 2.97 (d, *J* = 8.4 Hz, 1H), 2.42 – 2.25 (m, 2H), 1.97 – 1.84 (m, 1H), 1.74 – 1.57 (m, 3H), 1.39 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 158.9, 155.7, 130.8, 130.7, 114.1, 79.2, 74.7, 55.5, 52.7, 31.2, 29.9, 29.8, 28.6, 26.0, 14.3. **UPLC-DAD-QTOF:** $C_{20}H_{31}NO_4Na$ $[M+Na]^+$ calcd.: 372.2151, found: 372.2145.

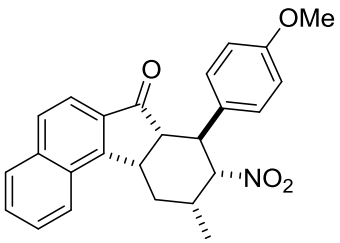
6.4.5.3. *Nazarov cyclization to products 60-62*[239]



39b, 39g, 40a **60-62**

To a suspension of $InCl_3$ (9 mg, 0.03 mmol, 0.3 equiv.) in CH_2Cl_2 (0.5 mL), the corresponding ketone **39**-**40** (0.1 mmol, 1.0 equiv.) and diphenyl phosphate (4 mg, 0.03 mmol, 0.3 equiv.) were added. The resulting mixture was stirred at room temperature for the corresponding time and the mixture was quenched by addition of a solution of saturated $NaHCO_3$ (5.0 mL). The compound was extracted with CH_2Cl_2 (2 x 5.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/ethyl acetate 70/30).

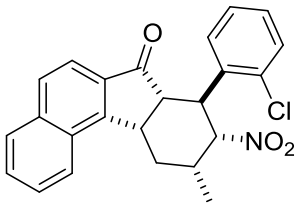
(7a*S*,8*S*,9*R*,10*R*,11a*S*)-8-(4-Methoxyphenyl)-10-methyl-9-nitro-7a,8,9,10,11,11a-hexahydro-7H-benzo[c]fluoren-7-one (60)



Prepared according to the general procedure starting from compound **39b** (40 mg, 0.1 mmol, 1.0 equiv.). The reaction was finished after 3 h. The title compound was isolated as a single diastereomer. White foam (31 mg, 0.08 mmol, 78%). **$[\alpha]_D^{24}$ =** −78.9° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.20 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.02 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.70 (dqd, *J* = 8.5, 6.9, 1.6 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.81 (t, *J* = 4.4 Hz, 1H), 4.41 (dt, *J* = 11.9, 7.1 Hz, 1H), 4.32 (t, *J* = 3.9 Hz, 1H), 3.85 (s, 3H), 3.20 (dd, *J* = 7.4, 3.8 Hz, 1H), 2.52 (ddt, *J* = 14.9, 8.9, 4.4 Hz, 2H), 1.54 – 1.50 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 203.4, 159.1, 157.3, 137.4, 134.2, 132.4, 129.8, 129.6, 129.5, 129.3, 129.2, 127.3, 124.7, 120.5, 114.7, 91.9, 55.6, 50.0, 41.5, 37.5, 33.1, 29.6, 18.1.**UPLC-DAD-QTOF:** $C_{25}H_{24}NO_4$ $[M+H]^+$ calcd.: 402.1705, found: 402.1709.

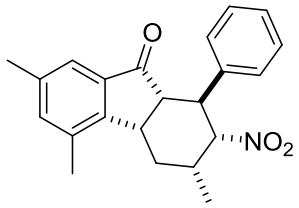
[239] Addapted from: Z. -G. Xi, L. Zhu, S. Luo, J. -P. Cheng, *J. Org. Chem.* **2013**, *78*, 606–613.

(7a*S*,8*S*,9*R*,10*R*,11a*S*)-8-(2-Chlorophenyl)-10-methyl-9-nitro-7a,8,9,10,11,11a-hexahydro-7H-benzo[c]fluoren-7-one (61)



Prepared according to the general procedure starting from compound **39h** (40 mg, 0.1 mmol, 1.0 equiv.). The reaction was finished after 3 h. The title compound was isolated as a single diastereomer. White foam (30 mg, 0.07 mmol, 74%). **$[\alpha]_D^{24}$ =** −65.3° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.33 – 8.08 (m, 1H), 8.06 – 7.98 (m, 1H), 7.94 – 7.80 (m, 2H), 7.76 – 7.64 (m, 2H), 7.53 (ddd, *J* = 7.4, 3.0, 1.8 Hz, 2H), 7.42 – 7.28 (m, 2H), 4.87 (*br*s, 2H), 4.46 (dt, *J* = 11.8, 7.3 Hz, 1H), 3.24 (d, *J* = 7.1 Hz, 1H), 2.60 – 2.30 (m, 2H), 1.56 – 1.40 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 157.6, 142.4, 137.8, 132.6, 131.2, 129.9, 129.7, 129.6, 129.0, 128.9, 128.0, 127.8, 125.1, 121.0, 110.7, 89.7, 49.7, 38.1, 33.3, 30.4, 18.6. **UPLC-DAD-QTOF:** $C_{24}H_{21}NO_3Cl$ $[M+H]^+$ calcd.: 406.1210, found: 406.1209.

(1*S*,2*R*,3*R*,4a*S*,9a*S*)-3,5,7-Trimethyl-2-nitro-1-phenyl-1,2,3,4,4a,9a-hexahydro-9H-fluoren-9-one (62)



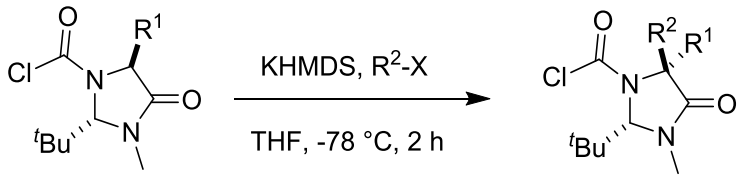
Prepared according to the general procedure starting from compound **40a** (35 mg, 0.1 mmol, 1.0 equiv.). The reaction was finished after 16 h. The title compound was isolated as a single diastereomer. White foam (30 mg, 0.07 mmol, 74%). **$[\alpha]_D^{24}$ =** −50.5° (*c*=0.5, CH_2Cl_2). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.51 (*br*s, 1H), 7.46 – 7.28 (m, 6H), 4.78 (t, *J* = 4.2 Hz, 1H), 4.30 (t, *J* = 3.7 Hz, 1H), 3.88 (dt, *J* = 11.8, 7.3 Hz, 1H), 3.05 (dd, *J* = 7.7, 3.7 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.33 – 2.16 (m, 2H), 1.45 – 1.33 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 203.5, 152.3, 142.0, 137.9, 137.2, 134.7, 134.4, 129.0, 128.2, 127.5, 122.2, 91.2, 49.7, 42.0, 37.3, 31.1, 29.3, 21.0, 18.0, 17.9. **UPLC-DAD-QTOF:** $C_{22}H_{24}NO_3$ $[M+H]^+$ calcd.: 350.1756, found: 350.1759.

6.5. Experimental section of chapter 4

6.5.1. Synthesis of *trans*-chloroformylimidazolidinones 63A-F

trans-Chloroformylimidazolidinones **63A**-**F** were prepared according to the literature.[240]

6.5.2. Synthesis of quaternary *trans*-imidazolinones 70



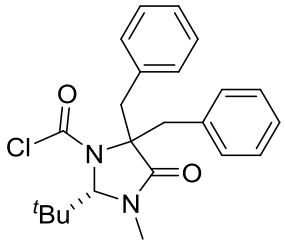
63 **70**

General procedure a: alkylation of carbamoyl chloride with addition of electrophile after KHMDS: To a solution of *trans*-carbamoyl chloride **63** (1.0 mmol, 1.0 equiv.) in dry THF (10.0 mL), KHMDS (1.1 mL, 1.1 mmol, 1.1 equiv., 1.0 M in toluene) was added at -78 °C dropwise and stirred for 5 minutes. Then, the electrophile (1.1 mmol, 1.1 equiv.) was added. After stirring for 2 h at -78 °C, the reaction was quenched with water (10.0 mL) and extracted with ethyl acetate (2 x 10.0 mL). The combined organic layers were washed with brine (2 x 10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/diethyl ether 80/20) to obtain the desired product **70**.

General procedure b: alkylation of carbamoyl chloride with addition of electrophile before KHMDS: To a solution of *trans*- carbamoyl chloride **63** (1.0 mmol, 1.0 equiv.) and the electrophile (1.1 mmol, 1.1 equiv.) in dry THF (10.0 mL), KHMDS (1.1 mL, 1.1 mmol, 1.1 equiv., 1.0 M in toluene) was added at -78 °C dropwise. After stirring for 2 h at -78 °C, the reaction was quenched with water (10.0 mL) and extracted with ethyl acetate (2 x 10.0 mL). The combined organic layers were washed with brine (2 x 10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/diethyl ether 80/20) to obtain the desired product **70**.

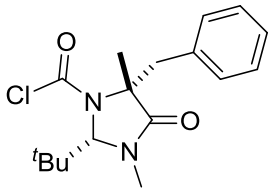
[240] For more information about the synthesis of carbamoyl chlorides **63**, see: a) H. Abas, J. Mas-Roselló, M. M. Amer, D. J. Durand, R. R. Groleau, N. Fey, J. Clayden, *Angew. Chem. Int. Ed.* **2019**, *58*, 2418–2422. b) M. M. Amer, A. C. Carrasco, D. J. Leonard, J. W. Ward, J. Clayden, *Org. Lett.* **2018**, 20, 7977–7981. c) D. J. Leonard, J. W. Ward, J. Clayden, *Nature* **2018**, *562*, 105–109.

(*S*)-5,5-Dibenzyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (70Aa)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-4-benzyl-2-(*tert*-butyl)-1-methyl-5-oxopyrrolidine-3-carbonyl chloride **63A** (308 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (334 mg, 0.84 mmol, 84%). $\mathbf{R_f}$ 0.60 (petroleum ether/diethyl ether 80/20). $\mathbf{[\alpha]_D^{26}}$ **=** −84° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2966 (C–H), 2927 (C–H), 1738 (C=O), 1711 (C=O). **^{1}H NMR** (500 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.51:0.49 ratio) δ 7.46 – 7.42 (m, 1H, rot. A + rot. B), 7.39 – 7.34 (m, 1H, rot. A + rot. B), 7.32 – 7.21 (m, 6H, rot. A + rot. B), 7.21 – 7.18 (m, 1H, rot. A + rot. B), 7.17 – 7.14 (m, 1H, rot. A + rot. B), 4.25 (s, 0.49H, rot. B), 4.07 (s, 0.51H, rot. A), 3.83 – 3.43 (m, 3H, rot. A + rot. B), 3.22 (d, *J* = 14.1 Hz, 0.51H, rot. A), 3.07 (d, *J* = 13.9 Hz, 0.49H, rot. B), 2.66 (s, 1.47H, rot. B), 2.59 (s, 1.53H, rot. A), 0.64 (s, 4.41H, rot. B), 0.38 (s, 4.59H, rot. A). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.9 (rot. B), 169.7 (rot. B), 149.3 (rot. A), 148.2 (rot. B), 135.8 (rot. A + rot. B), 134.5 (rot. A + rot. B), 134.2 (rot. A + rot. B), 131.4 (rot. A + rot. B), 131.3 (rot. A + rot. B), 130.5 (rot. A + rot. B), 130.3 (rot. A + rot. B), 128.7 (rot. A + rot. B), 128.5 (rot. A + rot. B), 128.3 (rot. A + rot. B), 128.2 (rot. A + rot. B), 127.8 (rot. A + rot. B), 127.6 (rot. A + rot. B), 127.5 (rot. A + rot. B), 127.5 (rot. A + rot. B), 82.8 (rot. A), 82.6 (rot. B), 75.8 (rot. B), 74.0 (rot. A), 44.0 (rot. A + rot. B), 42.0 (rot. A + rot. B), 41.3 (rot. A + rot. B), 40.7 (rot. A + rot. B), 38.3 (rot. A), 38.3 (rot. B), 31.3 (rot. A), 31.2 (rot. B), 27.3 (rot. A), 26.4 (rot. B). **HRMS** (ESI^+): $C_{23}H_{27}ClN_2O_2Na$ $[M + Na]^+$ calcd.: 421.1653, found: 421.1674.

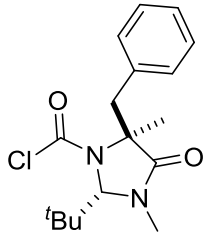
(2*S*,5*R*)-5-Benzyl-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Aj)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-4-benzyl-2-(*tert*-butyl)-1-methyl-5-oxopyrrolidine-3-carbonyl chloride **63A** (308 mg, 1.0 mmol, 1.0 equiv.) and methyl iodide (71 µL, 1.1 mmol, 1.1 equiv.). Colourless oil (199 mg, 0.62 mmol, 62%). $\mathbf{R_f}$ 0.50 (petroleum ether/diethyl ether 50/50). $\mathbf{[\alpha]_D^{26}}$ **=** −72° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2962 (C–H), 1737 (C=O), 1712 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.60:0.40 ratio) δ 7.45 – 7.14 (m, 5H, rot. A+B), 5.18 (s, 0.4H, rot. B), 5.12 (s, 0.6H, rot. A), 3.53 (d, *J* = 14.1 Hz, 0.6H, rot.A), 3.35 (d, *J* = 14.1 Hz, 0.6H, rot. A), 3.30 (s, 0.8H, rot. B), 3.02 (s, 1.2H, rot. B), 2.97 (s, 1.8H, rot. A), 1.72 (s, 1.8H, rot. A), 1.60 (s, 1.2H, rot. B), 0.90 (s, 3.6H, rot. B), 0.61 (s, 5.4H, rot. A). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.7 (rot. A + rot. B), 150.69 (rot. A), 147.5(rot. B), 136.0 (rot. A), 135.8 (rot. B), 131.2 (rot. A + rot. B), 131.1 (rot. A + rot. B), 128.6 (rot. A + rot. B), 128.4 (rot. A + rot. B), 127.5 (rot. A + rot. B), 127.3 (rot. A + rot. B), 82.7(rot. B), 82.0 (rot. A), 69.4(rot. B), 68.4(rot. A), 42.3(rot. B), 41.8(rot. A), 38.3 (rot. A + rot. B),

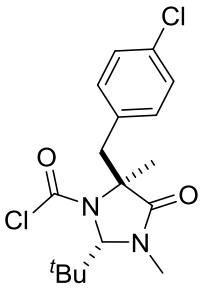
31.7 (rot. A + rot. B), 27.4 (rot. B), 27.0 (rot. A), 26.4 (rot. A), 23.8 (rot. B). **HRMS** (ESI^+): $C_{17}H_{23}ClN_2O_2Na$ $[M + Na]^+$ calcd.: 345.1340, found: 345.1352.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Ba)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (208 mg, 0.65 mmol, 65%). $\mathbf{R_f}$ 0.43 (petroleum ether/diethyl ether 80/20). $\mathbf{[\alpha]_D^{25}}$ **=** −40° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} = 2971 (C–H), 1738 (C=O), 1714 (C=O), 1241. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.54:0.46 ratio) δ 7.31 – 7.10 (m, 5H, rot. A+B), 4.54 (s, 0.54H, rot. A), 4.46 (s, 0.46H, rot. B), 3.75 (d, *J* = 14.2 Hz, 0.46H, rot. B), 3.61 (d, *J* = 13.9 Hz, 0.54H, rot. A), 3.15 (d, *J* = 14.1 Hz, 0.46H, rot. B), 3.07 (d, *J* = 13.9 Hz, 0.54H, rot. A), 2.76 (s, 1.62H, rot. A), 2.69 (s, 1.38H, rot. B), 1.83 (s, 1.38H, rot. B), 1.75 (s, 1.62H, rot. A), 1.02 (s, 4.86H, rot. A), 0.91 (s, 4.14H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.7 (rot. A + rot. B), 148.4 (rot. B), 146.9 (rot. A), 135.0 (rot. A), 134.8 (rot. B), 130.2 (rot. A), 130.0 (rot. B), 128.4 (rot. A + B), 128.3 (rot. A + B), 127.7 (rot. A + B), 127.4 (rot. A + B), 82.8 (rot. A), 82.7 (rot. B), 70.7 (rot. A), 68.5 (rot. B), 43.5 (rot. B), 41.0 (rot. A), 39.9 (rot. B), 39.5 (rot. A), 31.9 (rot. B), 31.5 (rot. A), 27.7 (rot. A), 27.0 (rot. B), 23.7 (rot. B), 22.7 (rot.B). **HRMS** (ESI^+): $C_{17}H_{23}ClN_2O_2Na$ $[M + Na]^+$ calcd.: 345.1340, found: 345.1356.

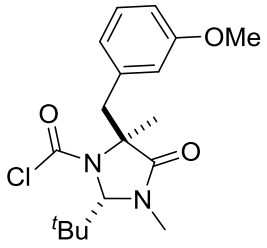
(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-chlorobenzyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Bb)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and 4-chlorobenzyl bromide (226 mg, 1.1 mmol, 1.1 equiv.). Colourless oil (264 mg, 0.74 mmol, 74%). $\mathbf{R_f}$ 0.23 (petroleum ether/diethyl ether 85/15). $\mathbf{[\alpha]_D^{23}}$ **=** −28° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2983 (C–H), 1736 (C=O), 1709 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.57:0.43 ratio) δ 7.22 (dd, *J* = 8.6, 2.3 Hz, 2H, rot. A + rot. B), 7.08 (t, *J* = 8.5 Hz, 2H, rot. A + rot. B), 4.59 (s, 0.57H, rot. A), 4.52 (s, 0.43H, rot. B), 3.72 (d, *J* = 14.2 Hz, 0.43H, rot. B), 3.59 (d, *J* = 14.0 Hz, 0.57H, rot. A), 3.11 (d, *J* = 14.2 Hz, 0.43H, rot. B), 3.02 (d, *J* = 14.0 Hz, 0.57H, rot. A), 2.78 (s, 1.71H, rot. A), 2.72 (s, 1.29H, rot. B), 1.81 (s, 1.29H, rot. B), 1.73 (s, 1.71H, rot. A), 1.02 (s, 5.13H, rot. A), 0.92 (s, 3.87H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.5 (rot. B), 171.5 (rot. A), 148.3 (rot. B), 146.9 (rot. A), 133.7 (rot. B), 133.5 (rot. A), 133.4 (rot. B), 133.3 (rot. B), 131.6 (rot. A), 131.3 (rot. B), 128.6 (rot. A), 128.4 (rot. A), 82.8 (rot. A), 82.7 (rot. B), 70.5 (rot. A), 68.3 (rot. B), 42.8 (rot. B), 40.2 (rot. A), 39.9 (rot.

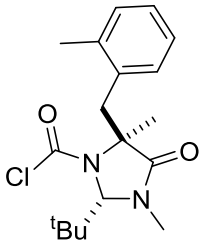
B), 39.4 (rot. A), 31.8 (rot. B), 31.5 (rot. A), 27.7 (rot. A), 26.9 (rot. B), 23.7 (rot. B), 22.7 (rot. A). **HRMS** (ESI+): $C_{17}H_{23}Cl_2N_2O_2Na$ $[M + Na]^+$ calcd.: 357.1131, found: 357.1143.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(3-methoxybenzyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Bc)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and 3-methoxybenzyl bromide (0.15 mL, 1.1 mmol, 1.1 equiv.). White solid (161 mg, 0.46 mmol, 46%). **M.p.:** 30–32 °C. $\mathbf{R_f}$ 0.50 (petroleum ether/diethyl ether 70/30). $\mathbf{[\alpha]_D^{23}}$ **=** −44° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2969 (C–H), 1737 (C=O), 1713 (C=O), 1264. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.55:0.45 ratio) δ 7.17 – 7.10 (m, 1H, rot. A + rot. B), 6.81 – 6.67 (m, 3H, rot. A + rot. B), 4.58 (s, 0.55H, rot. A), 4.49 (s, 0.45H, rot. B), 3.78 (s, 1.65H, rot. A), 3.76 (s, 1.35H, rot. B), 3.70 (d, *J* = 14.1 Hz, 0.45H, rot. B), 3.57 (d, *J* = 13.9 Hz, 0.55H, rot. A), 3.12 (d, *J* = 14.1 Hz, 0.45H, rot. B), 3.04 (d, *J* = 13.9 Hz, 0.55H, rot. A), 2.78 (s, 1.65H, rot. A), 2.71 (s, 1.35H, rot. B), 1.81 (s, 1.35H, rot. B), 1.73 (s, 1.65H, rot. A), 1.01 (s, 4.95H, rot. A), 0.91 (s, 4.05H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.6 (rot. B), 171.6 (rot. A), 159.5 (rot. B), 159.4 (rot. A), 148.2 (rot. A), 146.8 (rot. B), 136.3 (rot. A), 136.1 (rot. B), 129.1 (rot. B), 129.0 (rot. A), 122.3 (rot. A), 122.1 (rot. B), 114.9 (rot. A), 114.8 (rot. B), 113.6 (rot. B), 113.5 (rot. A), 82.7 (rot. A), 82.6 (rot. B), 70.5 (rot. A), 68.3 (rot. B), 55.2 (rot. A), 55.1 (rot. B), 43.3 (rot. B), 40.8 (rot. A), 39.8 (rot. B), 39.4 (rot. A), 31.8 (rot. B), 31.4 (rot. A), 27.6 (rot. A), 26.8 (rot. B), 23.6 (rot.B), 22.6 (rot.A). **HRMS** (ESI^+): $C_{18}H_{25}ClN_2O_3Na$ $[M + Na]^+$ calcd.: 375.1445, found: 375.1463.

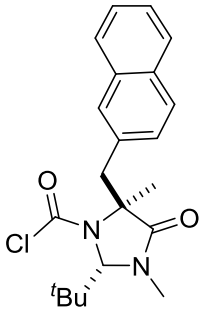
(2*S*,5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-5-(2-methylbenzyl)-4-oxoimidazolidine-1-carbonyl chloride (70Bd)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and 2-methylbenzyl bromide (0.15 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (198 mg, 0.59 mmol, 59%). $\mathbf{R_f}$ 0.43 (petroleum ether/diethyl ether 90/10). $\mathbf{[\alpha]_D^{23}}$ **=** −28° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2959 (C–H), 1738 (C=O), 1716 (C=O), 1241. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.55:0.45 ratio) δ 7.11 – 6.92 (m, 3H, rot. A + rot. B), 6.91 – 6.67 (m, 1H, rot. A + rot. B), 4.74 (s, 0.45H, rot. B), 4.70 (s, 0.55H, rot. A), 3.62 (d, *J* = 15.2 Hz, 0.45H, rot. B), 3.51 (d, *J* = 15.0 Hz, 0.55H, rot. A), 3.18 (d, *J* = 15.1 Hz, 0.45H, rot. B), 3.08 (d, *J* = 14.9 Hz, 0.55H, rot. A), 2.71 (s, 1.65H, rot. A), 2.49 (s, 1.35H, rot. B), 2.29 (s, 1.35H, rot. B), 2.28 (s, 1.65H, rot. A), 1.80 (s, 1.35H, rot. B), 1.70 (s, 1.65H, rot. A), 0.98 (s, 4.95H, rot. A), 0.89 (s, 4.05H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.1(rot. A), 171.8 (rot. B), 148.6 (rot. B), 146.6

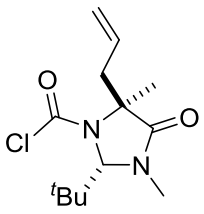
(rot. A), 138.2 (rot. A), 137.9 (rot. B), 133.8 (rot. A), 133.6 (rot. B), 131.0 (rot. B), 130.9 (rot. A), 128.5 (rot. B), 128.4 (rot. A), 127.0 (rot. B), 126.8 (rot. A), 125.6 (rot. B), 125.3 (rot. A), 82.9 (rot. B), 82.8 (rot. A), 69.8 (rot. A), 68.1 (rot. B), 40.1 (rot. B), 39.6 (rot. A), 39.4 (rot. B), 36.8 (rot. A), 31.7 (rot. A), 31.5 (rot. B), 27.6 (rot. A), 27.0(rot. B), 24.5 (rot. B), 23.4 (rot. A), 20.1 (rot. B), 19.9 (rot. A). **HRMS** (ESI^+): $C_{18}H_{26}ClN_2O_2$ $[M + H]^+$ calcd.: 337.1677, found: 337.1682.

(2*S*,5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-5-(naphthalen-2-ylmethyl)-4-oxoimidazolidine-1-carbonyl chloride (70Be)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and 2-(bromomethyl)naphthalene (243 mg, 1.1 mmol, 1.1 equiv.). Colourless oil (241 mg, 0.65 mmol, 65%). $\mathbf{R_f}$ 0.51 (petroleum ether/diethyl ether 80/20). $\mathbf{[\alpha]_D^{25}}$ **=** −44° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2971 (C–H), 1737 (C=O), 1712 (C=O), 1240. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.60:0.40 ratio) δ 7.75 – 7.67 (m, 2H, rot. A+B), 7.65 (m, 1H, rot. A+B), 7.57 (m, 1H, rot. A+B), 7.42 – 7.32 (m, 2H, rot. A+B), 7.18 (m, 1H, rot. A+B), 4.35 (s, 0.6H, rot. A), 4.29 (s, 0.4H, rot. B), 3.83 (d, *J* = 14.2 Hz, 0.4H, rot. B), 3.71 (d, *J* = 13.9 Hz, 0.6H, rot. A), 3.25 (d, *J* = 14.1 Hz, 0.4H, rot. B), 3.15 (d, *J* = 13.9 Hz, 0.6H, rot. A), 2.63 (s, 1.8H, rot. A), 2.56 (s, 1.2H, rot. B), 1.80 (s, 1.2H, rot. B), 1.73 (s, 1.8H, rot. A), 0.90 (s, 5.4H, rot. A), 0.80 (s, 3.6H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.6 (rot. A + rot. B), 148.2 (rot. B), 147.0 (rot. A), 133.3 (rot. A), 133.2 (rot. B), 132.6 (rot. B), 132.5 (rot. A), 132.4 (rot. A), 132.1 (rot. B), 129.3 (rot. A + rot. B), 129.0 (rot. A + rot. B), 127.9 (rot. A + rot. B), 127.9 (rot. A + rot. B), 127.8 (rot. A + rot. B), 127.7 (rot. A + rot. B), 127.7 (rot. A + rot. B), 127.5 (rot. A + rot. B), 127.5 (rot. A + rot. B), 126.2 (rot. A + rot. B), 126.0 (rot. A + rot. B), 125.9 (rot. A + rot. B), 125.8 (rot. A + rot. B), 82.6 (rot. A), 82.5 (rot. B), 70.8 (rot. A), 68.5 (rot. B), 43.5 (rot. B), 40.9 (rot. A), 39.8 (rot. B), 39.3 (rot. A), 31.8 (rot. B), 31.4 (rot. A), 27.5 (rot. A), 26.8 (rot. B), 23.7 (rot. B), 22.6 (rot. A). **HRMS** (ESI^+): $C_{21}H_{25}ClN_2O_2Na$ $[M + Na]^+$ calcd.: 395.1497, found: 395.1516.

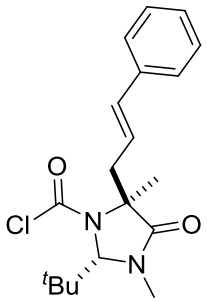
(2*S*,5*S*)-5-allyl-2-(*tert*-Butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Bf)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and allyl bromide (0.1 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (182 mg, 0.67 mmol, 67%). $\mathbf{R_f}$ 0.70 (petroleum ether/diethyl ether 70/30). $\mathbf{[\alpha]_D^{25}}$ **=** −84° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2974 (C–H), 1738 (C=O), 1713 (C=O), 1239. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.50:0.50 ratio) δ 5.13 (qdd, *J* = 10.3, 8.5, 5.0 Hz, 1H, rot. A + rot. B), 5.03 – 4.76 (m, 3H, rot. A + rot. B), 2.99 (dd, *J* = 14.4, 8.6 Hz,

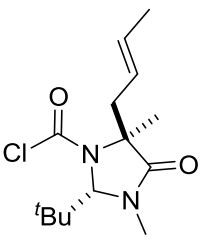
0.5H, rot. A), 2.91 – 2.83 (m, 0.5H, rot. B), 2.79 (s, 1.5H, rot. B), 2.77 (s, 1.5H, rot. A), 2.49 – 2.39 (m, 0.5H, rot. A), 2.25 (ddt, *J* = 14.1, 5.9, 1.3 Hz, 0.5H, rot. B), 1.44 (s, 1.5H, rot. A), 1.37 (s, 1.5H, rot. B), 0.86 (s, 4.5H, rot. B), 0.77 (s, 4.5H, rot. A). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.0 (rot. A), 171.8 (rot. B), 148.8 (rot. A), 146.3 (rot. B), 130.7 (rot. B), 130.3 (rot. A), 121.1 (rot. A), 120.9 (rot. B), 83.2 (rot. B), 82.8 (rot. A), 69.0 (rot. B), 66.7 (rot. A), 42.6 (rot. A), 39.7 (rot. B), 39.5 (rot. A), 39.0 (rot. B), 31.7 (rot. A), 31.4 (rot. B), 27.4 (rot. B), 26.8 (rot. A), 23.0 (rot. A), 22.3 (rot. B). **HRMS** (ESI$^+$): $C_{13}H_{21}ClN_2O_2Na$ [M + Na]$^+$ calcd.: 295.1183, found: 295.1152.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-cinnamyl-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Bg)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and cinnamyl bromide (0.16 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (234 mg, 0.67 mmol, 67%). **R_f** 0.45 (petroleum ether/diethyl ether 90/10). **$[\alpha]_D^{22}$ =** −20° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2972 (C–H), 1738 (C=O), 1718 (C=O), 1240. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.55:0.45 ratio) δ 7.26 – 6.86 (m, 5H, rot. A + rot. B), 6.37 (dd, *J* = 8.6, 1.2 Hz, 0.45H, rot. B), 6.33 (dd, *J* = 8.6, 1.1 Hz, 0.55H, rot. A), 5.71 – 5.44 (m, 1H, rot. A + rot. B), 4.91 (s, 0.45H, rot. B), 4.89 (s, 0.55H, rot. A), 3.23 (ddd, *J* = 14.3, 8.1, 1.1 Hz, 0.45H, rot. B), 3.09 (ddd, *J* = 14.0, 9.0, 1.0 Hz, 0.55H, rot. A), 2.83 (s, 1.65H, rot. A), 2.81 (s, 1.35H, rot. B), 2.64 (ddd, *J* = 14.3, 7.3, 1.3 Hz, 0.45H, rot. B), 2.49 (ddd, *J* = 14.0, 6.4, 1.4 Hz, 0.55H, rot. A), 1.58 (s, 1.35H, rot. B), 1.51 (s, 1.65H, rot. A), 0.92 (s, 4.95H, rot. A), 0.84 (s, 4.05H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.2 (rot. B), 171.9 (rot. A), 148.9 (rot. B), 146.7 (rot. A), 137.1 (rot. A), 136.8 (rot. B), 135.9 (rot. A + rot. B), 128.6 (rot. B), 128.5(rot. A), 127.7 (rot. B), 127.6 (rot. A), 126.3 (rot. B), 126.2 (rot. A), 122.0 (rot. A), 121.5 (rot. B), 83.2 (rot. A), 82.9 (rot. B), 69.7 (rot. A), 67.5 (rot. B), 41.8 (rot. B), 39.6 (rot. B), 39.1 (rot. A), 38.9 (rot. A), 31.9 (rot. A), 31.5 (rot. B), 27.4 (rot. A), 26.8 (rot. B), 23.0 (rot. B), 22.3 (rot. A). **HRMS** (ESI$^+$): $C_{19}H_{26}ClN_2O_2$ [M + H]$^+$ calcd.: 349.1677, found: 349.1675.

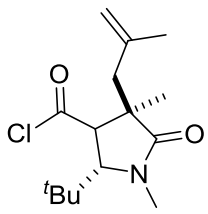
(2*S*,5*S*)-5-((*E*)-But-2-en-1-yl)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (70Bh)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and *trans*-1-bromo-2-butene (0.11 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (220 mg, 0.77 mmol, 77%). **R_f** 0.43 (petroleum ether/diethyl ether 70/30). **$[\alpha]_D^{24}$ =** −80° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2965 (C–H), 1738 (C=O), 1713 (C=O), 1239. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.62 – 5.41 (m, 1H, rot. A + rot. B), 5.03

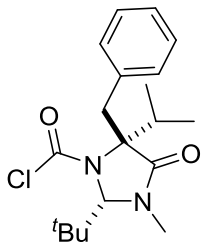
(s, 0.55H, rot. A), 5.02 (s, 0.45H, rot. B), 4.99 – 4.81 (m, 1H, rot. A + rot. B), 3.08 (ddt, *J* = 14.4, 8.6, 0.9 Hz, 0.55H, rot. A), 2.96 (s, 1.65H, rot. A), 2.94 (s, 1.85H, rot. B), 2.56 – 2.48 (m, 0.55H, rot. A), 2.36 (ddt, *J* = 14.2, 5.9, 1.4 Hz, 0.45H, rot. B), 1.59 (s, 1.65H, rot. A), 1.57 – 1.53 (m, 3H, rot. A + rot. B), 1.52 (s, 1.35H, rot. B), 1.02 (s, 4.05H, rot. B), 0.94 (s, 4.95H, rot. A). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.3 (rot. A), 172.1 (rot. B), 149.1 (rot. A), 146.5 (rot. B), 132.1 (rot. A), 132.0 (rot. B), 122.9 (rot. B), 122.6 (rot. A), 83.2 (rot. B), 82.8 (rot. A), 69.5 (rot. B), 67.1 (rot. A), 41.7 (rot. A), 39.5 (rot. A), 39.1 (rot. B), 38.9 (rot. B), 31.8 (rot. B), 31.4 (rot. A), 27.4 (rot. B), 26.8 (rot. A), 22.9 (rot. A), 22.2 (rot. B), 18.2 (rot. A or rot. B), 18.1 (rot. A or rot. B). **HRMS** (ESI$^+$): $C_{14}H_{24}ClN_2O_2$ $[M + H]^+$ calcd.: 287.1521, found: 287.1507.

(2*S*,4*R*)-2-(*tert*-Butyl)-1,4-dimethyl-4-(2-methylallyl)-5-oxopyrrolidine-3-carbonyl chloride (70Bi)



Prepared according to the general procedure **a** starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **63B** (231 mg, 1.0 mmol, 1.0 equiv.) and 3-bromo-2-methylpropene (0.11 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (202 mg, 0.71 mmol, 71%). **R_f** 0.50 (petroleum ether/diethyl ether 80/20). **$[\alpha]_D^{22}$ =** −76° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2970 (C–H), 1740 (C=O), 1716 (C=O), 1240. **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.50:0.50 ratio) δ 5.11 (s, 0.5H, rot. A), 5.10 (s, 0.5H, rot. B), 4.96 – 4.69 (m, 2H, rot. A + rot. B), 3.20 (dd, *J* = 14.8, 0.8 Hz, 0.5H, rot. A), 3.11 (dd, *J* = 14.5, 0.8 Hz, 0.5H, rot. B), 3.00 (s, 1.5H, rot. B), 2.98 (s, 1.5H, rot. A), 2.69 – 2.60 (m, 0.5H, rot. A), 2.51 – 2.32 (m, 0.5H, rot. B), 1.67 (s, 1.5H, rot. A), 1.59 (s, 1.5H, rot. B), 1.58 (s, 3H, rot. A + rot. B), 1.09 (s, 4.5H, rot. B), 1.01 (s, 4.5H, rot. A). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.1(rot. A), 171.9 (rot. B), 148.7 (rot. A), 146.3 (rot. B), 139.4 (rot. B), 139.1 (rot. A), 117.3 (rot. A), 116.9 (rot. B), 83.0 (rot. B), 82.8 (rot. A), 68.2 (rot. B), 65.9 (rot. A), 45.4 (rot. A), 42.8 (rot. B), 39.7 (rot. A), 39.2 (rot. B), 32.0 (rot. A), 31.6 (rot. B), 27.7 (rot. B), 27.0 (rot. A), 24.4 (rot. A), 23.4 (rot. B), 22.9 (rot. B), 22.7 (rot. A). **HRMS** (ESI$^+$): $C_{14}H_{23}ClN_2O_2Na$ $[M + Na]^+$ calcd.: 309.1340, found: 309.1349.

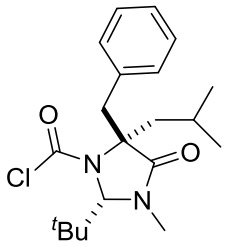
(2*S*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-isopropyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (70Ca)



Prepared according to the general procedure **a** starting from (2*R*,5*S*)-2-(*tert*-butyl)-5-isopropyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride **63C** (261 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). White solid (208 mg, 0.54 mmol, 54%). **M.p.:** 119–124 °C. **R_f** 0.37 (petroleum ether/diethyl ether 90/10). **$[\alpha]_D^{22}$ =** −48° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2957 (C–H), 1746 (C=O), 1705 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) only one rotamer was observed at room temperature δ 7.45 – 6.91 (m, 5H), 4.60 (s, 1H), 3.58 (d, *J* = 13.9 Hz,

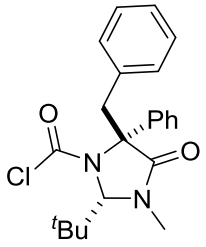
1H), 3.26 (d, *J* = 14.0 Hz, 1H), 2.85 (s, 3H), 2.40 (hept, *J* = 7.0 Hz, 1H), 1.27 (dd, *J* = 7.0, 4.7 Hz, 6H), 1.07 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 171.1, 148.0, 134.9, 130.6, 128.1, 127.0, 83.0, 76.6, 38.2, 36.2, 34.1, 31.2, 28.0, 19.6, 19.1. **HRMS** (ESI^+): $C_{19}H_{28}ClN_2O_2$ $[M + H]^+$ calcd.: 351.1834, found: 351.1848.

(2*S*,4*R*)-4-Benzyl-2-(*tert*-butyl)-4-isobutyl-1-methyl-5-oxopyrrolidine-3-carbonyl chloride (70Da)



Prepared according to the general procedure **b** starting from (2*S*,5*S*)-2-(*tert*-butyl)-5-isobutyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride **63D** (275 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). White solid (327 mg, 0.90 mmol, 90%). **M.p.:** 55−58 °C. **R_f** 0.69 (petroleum ether/diethyl ether 80/20). **$[\alpha]_D^{24}$ =** −32° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 2958 (C–H), 1741 (C=O), 1710 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.65:0.35 ratio) δ 7.28 – 6.98 (m, 5H, rot. A + rot. B), 4.46 (s, 0.65H, rot. A), 4.19 (s, 0.35H, rot. B), 3.58 (dd, *J* = 13.9, 6.8 Hz, 1H, rot. A + rot. B), 3.16 (dd, *J* = 13.9, 9.7 Hz, 1H, rot. A + rot. B), 2.69 (s, 1.95H, rot. A), 2.59 (s, 1.05H, rot. B), 2.33 – 2.19 (m, 1H, rot. A + rot. B), 2.21 – 2.02 (m, 1.35H, rot. A + rot. B), 1.88 (dd, *J* = 14.6, 5.2 Hz, 0.65H, rot. A), 1.10 – 0.91 (m, 11.85H, rot. A + rot, B), 0.86 (s, 3.15H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.8 (rot. A), 170.7 (rot. B), 149.0 (rot. B), 147.1 (rot. A), 134.9 (rot. A), 134.4 (rot. B), 130.3 (rot. A), 130.2 (rot. B), 128.2 (rot. B), 128.1 (rot. A), 127.5 (rot. B), 127.2 (rot. A), 82.8 (rot. B), 82.7 (rot. A), 73.4 (rot. A), 71.6 (rot. B), 46.3 (rot. A), 46.2 (rot. B), 43.0 (rot. B), 39.2 (rot. B), 38.9 (rot. A), 38.8 (rot. A), 31.5 (rot. B), 31.2 (rot. A), 27.8 (rot. A), 27.3 (rot. B), 25.1 (rot. A), 25.0 (rot. A), 24.8 (rot. B), 24.7 (rot. B), 23.7 (rot. B), 23.6 (rot. A). **HRMS** (ESI^+): $C_{20}H_{30}ClN_2O_2$ $[M + H]^+$ calcd.: 365.1996, found: 365.2008.

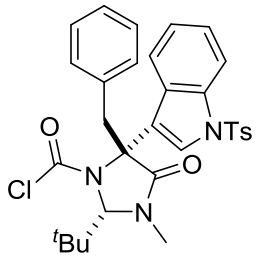
(2*S*,5*R*)-5-Benzyl-2-(*tert*-butyl)-3-methyl-4-oxo-5-phenylimidazolidine-1-carbonyl chloride (70Ea)



Prepared according to the general procedure **a** starting from (2*S*,5*S*)-2-(*tert*-butyl)-3-methyl-4-oxo-5-phenylimidazolidine-1-carbonyl chloride **63E** (294 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (307 mg, 0.80 mmol, 80%). **M.p.:** 119−121 °C. **R_f** 0.4 (petroleum ether/diethyl ether 85/15). **$[\alpha]_D^{24}$ =** +136° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 3006 (C–H), 2902 (C–H), 1738 (C=O), 1710 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) (mixture of rotamers A:B in a 0.82:0.18 ratio) δ 7.95 – 7.87 (m, 2H, rot. A + rot. B), 7.49 – 7.45 (m, 0.36H, rot. B), 7.44 – 7.39 (m, 1.64H, rot. A), 7.36 – 7.27 (m, 6H, rot. A + rot. B), 4.88 (s, 0.82H, rot. A), 4.64 (s, 0.18H, rot. B), 4.02 (d, *J* = 14.2 Hz, 0.18H, rot. B), 3.93 (d, *J* = 14.2 Hz, 0.18H, rot. B), 3.89 (d, *J* = 14.2 Hz, 0.82H, rot. A), 3.58 (d, *J* = 14.2 Hz, 0.82H, rot. A), 2.93 (s, 2.46H, rot. A), 2.81 (s, 0.54H, rot. B), 0.96 (s, 1.62H, rot. B), 0.89 (s, 7.38H, rot. A). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.8 (rot. A), 169.8 (rot. B), 150.1 (rot. B), 148.6 (rot. A), 139.0 (rot. A),

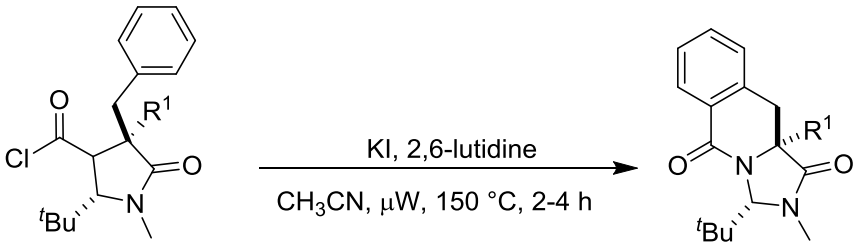
137.2 (rot. B), 134.7 (rot. A), 134.2 (rot. B), 130.7 (rot. A), 130.4 (rot. B), 128.5 (rot. B), 128.4 (rot. A), 128.4 (rot. A), 128.4 (rot. B), 128.0 (rot. A), 128.0 (rot. A), 128.0 (rot. A), 127.9 (rot. A), 127.5 (rot. A), 127.3 (rot. A), 126.5 (rot. A), 83.7 (rot. A), 82.8 (rot. B), 75.9 (rot. A), 73.6 (rot. B), 44.9 (rot. B), 43.9 (rot. A), 39.6 (rot. A), 39.1 (rot. B), 31.8 (rot. A), 31.8(rot. B), 27.2 (rot. B), 27.0 (rot. A). **HRMS** (ESI^+): $C_{22}H_{25}ClN_2O_2$ $[M + H]^+$ calcd.: 385.1677, found 385.1691.

(2*S*,5*R*)-5-Benzyl-2-(*tert*-butyl)-3-methyl-4-oxo-5-((1-tosyl-1H-indol-3-yl)methyl) imidazolidine-1-carbonyl chloride (70Fa)



Prepared according to the general procedure **b** starting from (2*S*,5*S*)-2-(*tert*-butyl)-3-methyl-4-oxo-5-((1-tosyl-1H-indol-3-yl)methyl)imidazolidine-1-carbonyl chloride **63F** (502 mg, 1.0 mmol, 1.0 equiv.) and benzyl bromide (0.14 mL, 1.1 mmol, 1.1 equiv.). Colourless oil (515 mg, 0.87 mmol, 87%). $\mathbf{R_f}$ 0.34 (petroleum ether/diethyl ether 80/20). $\mathbf{[\alpha]_D^{24}}$ **=** −32° (*c*=1.0, $CHCl_3$). **IR (neat, cm^{-1})** ν_{max} = 2925 (C–H), 1735 (C=O), 1709 (C=O), 1174, 671. **^{1}H NMR** (400 MHz, Chloroform-*d*)) (mixture of rotamers A:B in a 0.60:0.40 ratio) δ 7.99 – 7.95 (m, 1H, rot. A + rot. B), 7.87 – 7.69 (m, 3H, rot. A + rot. B), 7.64 (s, 0.4H, rot. B), 7.59 (s, 0.6H, rot. A), 7.37 – 7.05 (m, 9H, rot. A + rot. B), 4.30 (s, 0.6H, rot. A), 4.11 (s, 0.4H, rot. B), 3.83 – 3.37 (m, 3H, rot. A + rot. B), 3.16 (d, *J* = 14.1 Hz, 0.4H, rot. B), 2.92 (d, *J* = 13.9 Hz, 0.6H, rot.A), 2.67 (s, 1.8H, rot. A), 2.58 (s, 1.2H, rot. B), 2.31 (s, 1.2H, rot. B), 2.28 (s, 1.8H, rot. A), 0.67 (s, 5.4H, rot. A), 0.35 (s, 3.6H, rot. B). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.2 (rot. A), 170.1 (rot. B), 148.8 (rot. B), 148.2 (rot. A), 144.9 (rot. B), 144.8 (rot. A), 135.5 (rot. A or rot. B), 135.3 (rot. A or rot. B), 134.8 (rot. A or rot. B), 134.7 (rot. A or rot. B), 134.3 (rot. A or rot. B), 133.9 (rot. A or rot. B), 131.8 (rot. A or rot. B), 131.5 (rot. A or rot. B), 130.2 (rot. A or rot. B), 130.1 (rot. A or rot. B), 129.9 (rot. A or rot. B), 129.8 (rot. A or rot. B), 128.3 (rot. A or rot. B), 128.1 (rot. A or rot. B), 127.8 (rot. A or rot. B), 127.4 (rot. A or rot. B), 127.0 (rot. A or rot. B), 126.9 (rot. A or rot. B), 126.8 (rot. A), 126.7 (rot. B), 124.7(rot. A or rot. B), 124.7(rot. A or rot. B), 123.4(rot. A or rot. B), 123.3(rot. A or rot. B), 120.5(rot. A or rot. B), 120.3(rot. A or rot. B), 116.7(rot. A or rot. B), 116.5(rot. A or rot. B), 113.6(rot. A or rot. B), 113.4(rot. A or rot. B), 82.8 (rot. B), 82.6 (rot. A), 74.3(rot. A), 72.5 (rot. B), 43.1 (rot. B), 39.5 (rot. A), 38.4 (rot. A), 38.3 (rot. B), 31.4 (rot. B), 31.4 (rot. B), 31.3 (rot. A), 31.1 (rot. A), 27.2 (rot. A), 26.3(rot. B), 21.5 (rot. B), 21.4 (rot. A). **HRMS** (ESI^+): $C_{32}H_{35}ClN_3O_4S$ $[M + H]^+$ calcd.: 592.2031, found: 592.2016.

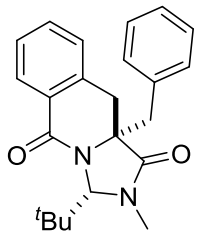
6.5.3. Cyclization of quaternary aryl imidazolidinone derivatives



70 **71**

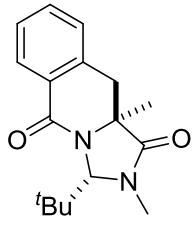
KI (28 mg, 0.16 mmol, 1.1 equiv.) and 2,6-lutidine (20 μL, 0.16 mmol, 1.1 equiv.) were added to a solution of the corresponding *trans*-*N*-chloroformylimidazolidinone **70** (0.15 mmol, 1.0 equiv.) in dry CH_3CN (1.5 mL). The solution was heated in μW at 150 °C for 2-4 h. The reaction was quenched with HCl (5.0 mL, 1.0 M). The desired compound was extracted with ethyl acetate (2 x 5.0 mL). The combined organic layers were washed with brine (2 x 5.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/diethyl ether 50/50) to obtain the desired cycle **71**.

(3*S*,10a*S*)-10a-Benzyl-3-(*tert*-butyl)-2-methyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Aa)



Prepared according to the general procedure starting from (2*S*)-4,4-dibenzyl-2-(*tert*-butyl)-1-methyl-5-oxopyrrolidine-3-carbonyl chloride **70Aa** (60 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. White solid (39 mg, 0.11 mmol, 71%). **M.p.:** 155–159 °C. $\mathbf{R_f}$ 0.28 (petroleum ether/ethyl acetate 70/30). $\mathbf{[\alpha]_D^{25}}$ **=** −172° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2960 (C–H), 1700 (C=O), 1661 (C=O), 1369. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.11– 7.02 (m, 5H), 6.95 – 6.92 (m, 1H), 5.43 (s, 1H), 3.23 (d, *J* = 14.0 Hz, 1H), 3.11 (m, 4H), 3.05 (d, *J* = 14.0 Hz, 1H), 2.90 (d, *J* = 15.8 Hz, 1H), 1.24 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.8, 165.1, 135.1, 134.7, 132.2, 130.5, 129.9, 127.9, 127.8, 127.6, 127.2, 127.0, 81.4, 63.2, 42.7, 37.8, 35.0, 31.4, 27.9. **HRMS** (ESI^+): *m/z* calcd. for $C_{23}H_{27}N_2O_2$ $[M + H]^+$363.2067, found 363.2078.

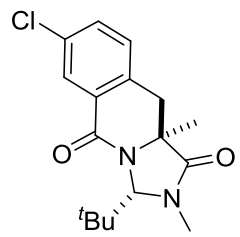
(3*S*,10a*S*)-3-(*tert*-Butyl)-2,10a-dimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Ba)



Prepared according to the general procedure starting from (2*S*,4*R*)-4-benzyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Ba** (50 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 2 h. Colourless oil (37 mg, 0.13 mmol, 87%). $\mathbf{R_f}$ 0.36 (petroleum ether/diethyl ether 60/40). $\mathbf{[\alpha]_D^{25}}$ **=** −248° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}):

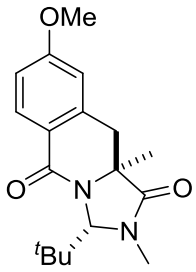
ν_{max} 2960 (C–H), 1705 (C=O), 1652 (C=O), 1354. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.25 – 7.18 (m, 1H), 5.39 (s, 1H), 3.09 (s, 3H), 3.00 (d, *J* = 1.8 Hz, 2H), 1.47 (s, 3H), 1.12 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.9, 164.6, 135.0, 132.4, 130.0, 128.1, 128.0, 127.8, 81.3, 61.2, 38.9, 38.1, 31.5, 27.7, 22.5. **HRMS** (ESI$^+$): $C_{17}H_{22}N_2O_2Na$ [M + Na]$^+$ calcd.: 309.1573, found: 309.1578.

(3*S*,10a*S*)-3-(*tert*-Butyl)-7-chloro-2,10a-dimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Bb)



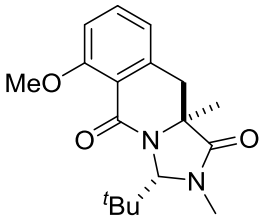
Prepared according to the general procedure starting from (2*S*,4*R*)-2-(*tert*-butyl)-4-(4-chlorobenzyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride chloride **70Bb** (53 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. Orange solid (26 mg, 0.09 mmol, 54%). **M.p.:** 101–103 °C. **R_f** 0.34 (petroleum ether/diethyl ether 70/30). **$[\alpha]_D^{24}$ =** −84° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2969 (C–H), 1706 (C=O), 1664 (C=O), 1421, 1358. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 5.36 (s, 1H), 3.08 (s, 3H), 3.01 – 2.87 (m, 2H), 1.45 (s, 3H), 1.11 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.3, 163.2, 133.8, 133.2, 132.2, 131.3, 129.3, 128.0, 81.2, 61.0, 38.2, 38.0, 31.4, 27.5, 22.3. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{17}H_{22}ClN_2O_2$ [M + H]$^+$ 321.1364 found 321.1381.

(3*S*,10a*S*)-3-(*tert*-Butyl)-8-methoxy-2,10a-dimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Bc)



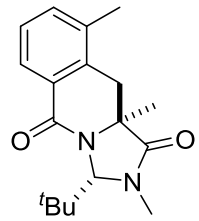
Prepared according to the general procedure starting from (2*S*,4*R*)-2-(*tert*-butyl)-4-(3-methoxybenzyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bc** (53 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 2 h. White solid (36 mg, 0.11 mmol, 76%). **M.p.:** 144–146 °C. **R_f** 0.29 (petroleum ether/diethyl ether 60/40). **$[\alpha]_D^{26}$ =** −232° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2960 (C–H), 1704 (C=O), 1657 (C=O), 1362, 1258. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.5 Hz, 1H), 6.86 (ddd, *J* = 8.6, 2.5, 0.8 Hz, 1H), 6.70 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.34 (s, 1H), 3.85 (s, 3H), 3.07 (s, 3H), 3.00 – 2.89 (m, 2H), 1.47 (s, 3H), 1.11 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.9, 164.3, 162.8, 137.1, 130.0, 122.6, 113.3, 113.0, 81.3, 61.0, 55.6, 39.1, 38.1, 31.5, 27.7, 22.5. **HRMS** (ESI$^+$): $C_{18}H_{25}N_2O_3$ [M + H]$^+$ calcd.: 317.1864, found: 317.1859.

(3S,10aS)-3-(*tert*-Butyl)-6-methoxy-2,10a-dimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (78)



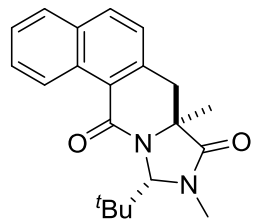
Prepared according to the general procedure starting from (2*S*,4*R*)-2-(*tert*-butyl)-4-(3-methoxybenzyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bc** (53 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 2 h. Colourless oil (5 mg, 0.01 mmol, 10%). $\mathbf{R_f}$ 0.16 (petroleum ether/diethyl ether 60/40). $\mathbf{[\alpha]_D^{26}}$ **=** −116° (*c*=1.0, $CHCl_3$). **IR (neat, cm^{-1}):** ν_{max} 2960 (C–H), 1703 (C=O), 1667 (C=O), 1477, 1357, 1259. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.5, 7.4 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 7.3, 0.9 Hz, 1H), 5.45 (s, 1H), 3.91 (s, 3H), 3.07 (s, 3H), 2.92 (s, 2H), 1.40 (s, 3H), 1.10 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 173.8, 163.2, 158.8, 137.3, 132.8, 120.2, 118.6, 111.3, 80.3, 61.4, 56.1, 39.9, 37.8, 31.5, 27.3, 21.6. **HRMS** (ESI^+): $C_{18}H_{24}N_2O_3Na[M + Na]^+$ calcd.: 339.1679, found: 339.1690.

(3*S*,10a*S*)-3-(*tert*-Butyl)-2,9,10a-trimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Bd)



Prepared according to the general procedure starting from (2*S*,5*S*)-2-(*tert*-butyl)-3,5-dimethyl-5-(2-methylbenzyl)-4-oxoimidazolidine-1-carbonyl chloride **70Bd** (51 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. Colourless oil (40 mg, 0.13 mmol, 89%).$\mathbf{R_f}$ 0.34 (petroleum ether/diethyl ether 60/40). $\mathbf{[\alpha]_D^{25}}$ **=** −192° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2972 (C–H), 1706 (C=O), 1669 (C=O), 1365. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 – 7.54 (m, 1H), 7.25 (ddd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.22 – 7.15 (m, 1H), 5.31 (s, 1H), 3.12 (dd, *J* = 15.5, 0.6 Hz, 1H), 3.02 (s, 3H), 2.68 (d, *J* = 15.4 Hz, 1H), 2.25 (s, 3H), 1.37 (s, 3H), 1.05 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.9, 164.8, 135.6, 133.7, 133.3, 129.9, 127.0, 125.6, 81.2, 60.8, 37.9, 35.3, 31.4, 27.5, 22.4, 19.2. **HRMS** (ESI^+): *m/z* calcd. for $C_{18}H_{25}N_2O_2$ $[M + H]^+$301.1910, found 301.1916.

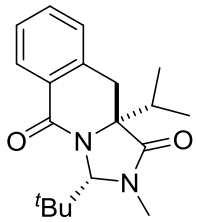
(7a*S*,10*S*)-10-(*tert*-Butyl)-7a,9-dimethyl-7,7a,9,10-tetrahydrobenzo[h]imidazo[1,5-b]isoquinoline-8,12-dione (71Be)



Prepared according to the general procedure starting from (2*S*,4*R*)-2-(*tert*-butyl)-1,4-dimethyl-4-(naphthalen-2-ylmethyl)-5-oxopyrrolidine-3-carbonyl chloride **70Be** (56 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 2 h. Colourless oil (44 mg, 0.13 mmol, 87%). $\mathbf{R_f}$ 0.47 (petroleum ether/diethyl ether 80/20). $\mathbf{[\alpha]_D^{24}}$ **=** −324° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2970 (C–H), 1705 (C=O), 1666 (C=O), 1248, 798. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.76 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.56 – 7.49 (m, 1H), 7.47 – 7.37 (m, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 5.49 (s, 1H), 3.14 (d, *J* = 15.3 Hz, 1H), 3.05 (s, 3H), 3.01 (d, *J* =

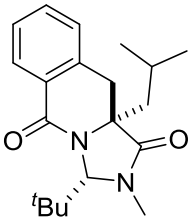
15.4 Hz, 1H), 1.37 (s, 3H), 1.09 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.8, 164.9, 134.7, 133.4, 132.6, 130.7, 128.3, 127.9, 126.0, 125.8, 125.7, 125.5, 80.5, 61.0, 40.0, 37.8, 31.5, 27.3, 21.8. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{21}H_{25}N_2O_2$ $[M + H]^+$ 337.1910 found 337.1901.

(3*S*,10a*R*)-3-(*tert*-Butyl)-10a-isopropyl-2-methyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Ca)



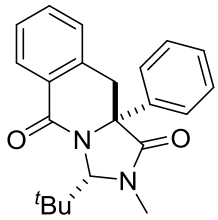
Prepared according to the general procedure starting from (2*S*,4*S*)-4-benzyl-2-(*tert*-butyl)-4-isopropyl-1-methyl-5-oxopyrrolidine-3-carbonyl chloride **70Ca** (52 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. White solid (30 mg, 0.10 mmol, 64%). **M.p.:** 68–73 °C. **R_f** 0.36 (petroleum ether/diethyl ether 60/40). **$[\alpha]_D^{24}$ =** −200° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2964 (C–H), 1703 (C=O), 1660 (C=O), 1377.**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.26 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.15 – 7.11 (m, 1H), 5.34 (s, 1H), 3.30 (d, *J* = 16.2 Hz, 1H), 2.98 (s, 3H), 2.82 (d, *J* = 16.2 Hz, 1H), 2.21 – 2.03 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 9H), 0.45 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.5, 165.9, 136.1, 132.5, 130.4, 127.5, 127.4, 126.4, 81.2, 65.3, 37.5, 35.1, 31.2, 31.1, 27.9, 19.2, 17.6. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{19}H_{27}N_2O_2$ $[M + H]^+$315.2067, found 315.2077.

(**3*S*,10a*S*)-3-(*tert*-Butyl)-10a-isobutyl-2-methyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Da)**



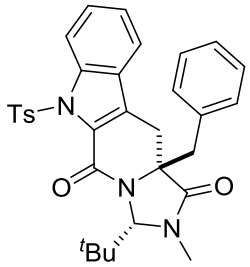
Prepared according to the general procedure starting from (2*S*,4*R*)-4-benzyl-2-(*tert*-butyl)-4-isobutyl-1-methyl-5-oxopyrrolidine-3-carbonyl chloride **70Da** (55 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. Colourless oil (41 mg, 0.13 mmol, 84%). **R_f** 0.42 (petroleum ether/diethyl ether 60/40). **$[\alpha]_D^{24}$ =** −208° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2957 (C–H), 1703 (C=O), 1660 (C=O), 1364.**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.23 – 7.18 (m, 1H), 5.36 (s, 1H), 3.24 (d, *J* = 15.7 Hz, 1H), 3.06 (s, 3H), 2.99 (dd, *J* = 15.7, 1.3 Hz, 1H), 1.93 (dtd, *J* = 13.2, 6.6, 4.9 Hz, 1H), 1.79 (ddd, *J* = 14.6, 4.9, 1.3 Hz, 1H), 1.67 (dd, *J* = 14.6, 6.3 Hz, 1H), 1.14 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.2, 164.5, 135.1, 132.4, 129.8, 127.8, 127.6, 127.5, 81.1, 63.0, 45.2, 37.5, 35.9, 31.2, 27.8, 24.8, 24.2, 23.9. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{20}H_{29}N_2O_2$ $[M + H]^+$ 329.2224 found 329.2234.

(3*S*,10a*R*)-3-(*tert*-Butyl)-2-methyl-10a-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione (71Ea)



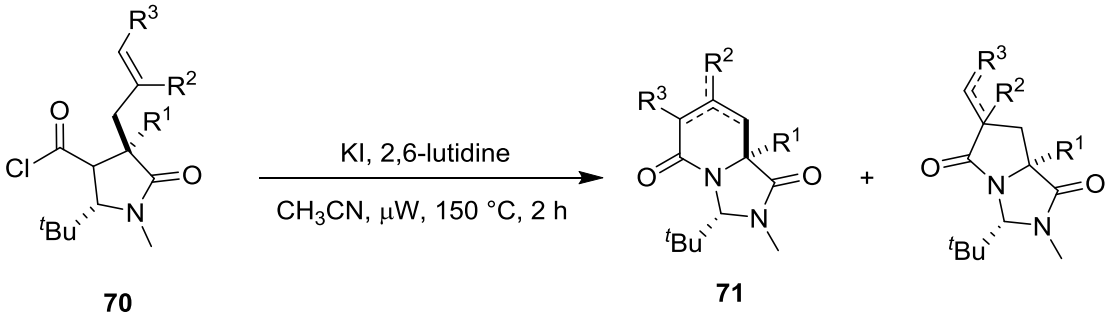
Prepared according to the general procedure starting from (2*S*,4*R*)-4-benzyl-2-(*tert*-butyl)-1-methyl-5-oxo-4-phenylpyrrolidine-3-carbonyl chloride **70Ea** (58 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. Colourless oil (33 mg, 0.09 mmol, 63%). $\mathbf{R_f}$ 0.42 (petroleum ether/diethyl ether 60/40). $\mathbf{[\alpha]_D^{24}}$ **=** −4° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2924 (C–H), 1704 (C=O), 1665 (C=O), 1354. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.35 – 7.20 (m, 2H), 7.14 – 7.01 (m, 3H), 6.86 (dt, *J* = 7.0, 1.4 Hz, 1H), 5.45 (s, 1H), 3.36 (d, *J* = 15.3 Hz, 1H), 3.22 (d, *J* = 15.3 Hz, 1H), 3.05 (s, 3H), 0.80 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.8, 165.3, 138.9, 133.6, 132.5, 130.0, 128.1, 127.9, 127.7, 127.7, 127.6, 125.6, 81.2, 65.4, 41.5, 38.0, 31.5, 26.9. **HRMS** (ESI^+): *m/z* calcd. for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1910 found 349.1905.

(3*S*,11a*R*)-11a-Benzyl-3-(*tert*-butyl)-2-methyl-6-tosyl-2,3,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,5(6H)-dione (71Fa)



Prepared according to the general procedure starting from (2*S*,5*R*)-5-benzyl-2-(*tert*-butyl)-3-methyl-4-oxo-5-((1-tosyl-1H-indol-3-yl)methyl)imidazolidine-1-carbonyl chloride **70Fa** (88 mg, 0.15 mmol, 1.0 equiv.). The reaction was finished after 4 h. Colourless oil (44 mg, 0.08 mmol, 53%). $\mathbf{R_f}$ 0.62 (petroleum ether/diethyl ether 90/10). $\mathbf{[\alpha]_D^{24}}$ **=** −108° (*c*=1.0, $CHCl_3$).). **IR** (neat, cm^{-1}): ν_{max} 2960 (C–H), 1708 (C=O), 1687 (C=O), 1368, 1174, 681. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.60 (m, 1H), 7.55 (ddd, *J* = 8.6, 7.2, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 1H), 7.25 (d, *J* = 6.3 Hz, 5H), 7.06 – 6.90 (m, 2H), 4.42 (s, 1H), 3.39 (d, *J* = 13.3 Hz, 1H), 3.29 (d, *J* = 1.0 Hz, 2H), 2.83 (d, *J* = 13.3 Hz, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 0.78 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 171.0, 156.7, 144.5, 140.1, 137.3, 134.7, 130.1, 129.9, 129.3, 128.3, 128.2, 128.1, 127.7, 127.2, 126.7, 124.0, 120.4, 116.4, 81.7, 68.0, 43.0, 40.6, 32.5, 28.9, 27.4, 21.6. **HRMS** (ESI^+): *m/z* calcd. for $C_{32}H_{33}N_3O_4SNa$ $[M + Na]^+$ 578.2084 found 578.2098.

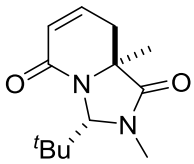
6.5.4. Cyclization of quaternary allyl imidazolidinone derivatives



70 **71**

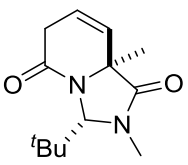
KI (28 mg, 0.16 mmol, 1.1 equiv.) and 2,6-lutidine (20 µL, 0.16 mmol, 1.1 equiv.) were added to a solution of the corresponding *trans*-*N*-chloroformylimidazolidinone **70** (0.15 mmol, 1.0 equiv.) in dry CH_3CN (1.5 mL). The solution was heated in µW at 150 °C for 2-4 h. The reaction was quenched with HCl (5.0 mL, 1.0 M). The desired compound was extracted with ethyl acetate (2 x 5.0 mL). The combined organic layers were washed with brine (2 x 5.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/diethyl ether 50/50) to obtain the desired product.

(3*S*,8a*S*)-3-(*tert*-Butyl)-2,8a-dimethyl-2,3,8,8a-tetrahydroimidazo[1,5-a]pyridine-1,5-dione (71Bf)



Prepared according to the general procedure starting from (2*S*,4*R*)-4-allyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bf** (41 mg, 0.15 mmol, 1.0 equiv.). White solid (13 mg, 0.06 mmol, 39%). **M.p.:** 103–107 °C. **R_f** 0.40 (petroleum ether/diethyl ether 40/60). **$[\alpha]_D^{23}$ =** −156° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2978 (C–H), 1704 (C=O), 1672 (C=O), 1389.**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.44 (ddd, *J* = 9.8, 6.4, 2.3 Hz, 1H), 5.95 (ddd, *J* = 9.8, 3.1, 0.6 Hz, 1H), 5.15 (s, 1H), 2.96 (s, 3H), 2.45 (ddd, *J* = 17.4, 6.4, 0.6 Hz, 1H), 2.31 (dddd, *J* = 17.4, 3.1, 2.3, 0.8 Hz, 1H), 1.51 (s, 3H), 1.02 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.7, 163.0, 136.3, 125.2, 80.9, 60.5, 37.8, 34.2, 31.2, 27.5, 22.8. **HRMS** (ESI^+): *m/z* calcd. for $C_{13}H_{20}N_2O_2Na$ $[M + Na]^+$ 259.1416, found 259.1409.

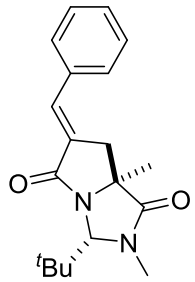
(3*S*,8a*S*)-3-(*tert*-Butyl)-2,8a-dimethyl-2,3,6,8a-tetrahydroimidazo[1,5-a]pyridine-1,5-dione (82)



Prepared according to the general procedure starting from (2*S*,4*R*)-4-allyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bf** (41 mg, 0.15 mmol, 1.0 equiv.). Colourless oil (17 mg, 0.07 mmol, 50%). **R_f** 0.70 (petroleum ether/diethyl ether 40/60). **$[\alpha]_D^{24}$ =** −28° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2978 (C–H), 1706 (C=O), 1677 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.11 (dd, *J* = 9.2, 3.5 Hz, 1H), 5.82 (ddd, *J* = 9.2, 6.0, 2.1 Hz, 1H), 5.13 (s, 1H), 3.03 – 2.79 (m, 5H), 1.48 (s, 3H), 1.02 (s, 9H). **^{13}C NMR** (101 MHz,

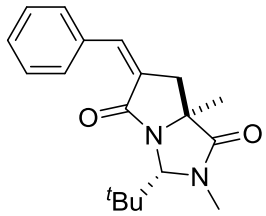
Chloroform-*d*) δ 171.4, 170.2, 131.1, 121.4, 80.8, 64.5, 37.2, 33.3, 31.3, 27.5, 24.8. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{13}H_{20}N_2O_2Na$ [M + Na]$^+$ 259.1416, found 259.1414.

(3*S*,7a*S*)-6-((*E*)-Benzylidene)-3-(*tert*-butyl)-2,7a-dimethyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,5(6H)-dione (85)



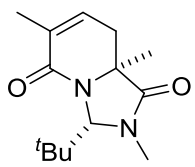
Prepared according to the general procedure starting from (2*S*,5*S*)-2-(*tert*-butyl)-5-cinnamyl-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride **70Bg** (52 mg, 0.15 mmol, 1.0 equiv.). White solid (30 mg, 0.1 mmol, 65%). **M.p.:** 99–107 °C. **R_f** 0.50 (petroleum ether/diethyl ether 70/30). **$[\alpha]_D^{23}$ =** +116° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2997 (C–H), 1699 (C=O), 1649 (C=O), 1334.**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.60 – 7.11 (m, 6H), 4.77 (s, 1H), 3.31 (dd, *J* = 17.6, 3.5 Hz, 1H), 3.03 (dd, *J* = 17.6, 2.2 Hz, 1H), 2.93 (s, 3H), 1.51 (s, 3H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 176.2, 174.8, 135.0, 133.5, 129.9, 129.8, 129.2, 128.8, 84.4, 63.5, 40.2, 36.4, 31.2, 27.3, 27.2. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{19}H_{24}N_2O_2Na$ [M + Na]$^+$ 335.1729, found 335.1740.

(3*S*,7a*S*)-6-((*Z*)-Benzylidene)-3-(*tert*-butyl)-2,7a-dimethyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,5(6H)-dione (86)



Prepared according to the general procedure starting from (2*S*,5*S*)-2-(*tert*-butyl)-5-cinnamyl-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride **70Bg** (52 mg, 0.15 mmol, 1.0 equiv.). White solid (13 mg, 0.04 mmol, 28%). **M.p.:** 105–113 °C. **R_f** 0.40 (petroleum ether/diethyl ether 70/30). **$[\alpha]_D^{23}$ =** −12° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2973 (C–H), 1697 (C=O), 1648 (C=O), 1256. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 – 7.63 (m, 2H), 7.46 – 7.13 (m, 3H), 6.68 (dd, *J* = 3.2, 1.2 Hz, 1H), 4.80 (s, 1H), 3.15 (dd, *J* = 15.7, 3.1 Hz, 1H), 2.93 (s, 3H), 2.79 (dd, *J* = 15.7, 1.4 Hz, 1H), 1.54 (s, 3H), 1.02 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 174.6, 172.6, 135.6, 134.2, 130.2, 130.0, 128.9, 128.2, 83.2, 62.4, 44.9, 36.5, 31.2, 27.0, 25.5. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{19}H_{24}N_2O_2Na$ [M + Na]$^+$ 335.1729, found 335.1718.

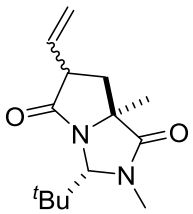
(3*S*,8a*S*)-3-(*tert*-Butyl)-2,6,8a-trimethyl-2,3,8,8a-tetrahydroimidazo[1,5-a]pyridine-1,5-dione (71Bh)



Prepared according to the general procedure starting from (2*S*,5*S*)-5-((*E*)-but-2-en-1-yl)-2-(tert-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride **70Bh** (43 mg, 0.15 mmol, 1.0 equiv.). Isolated as a mixture of products **71Bh/91**. Colourless oil (19 mg, 0.08 mmol, 47%). **R_f** 0.54 (petroleum ether/diethyl ether 50/50). **^{1}H NMR** 71Bh (400

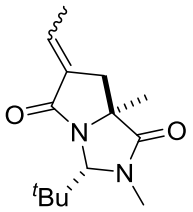
MHz, Chloroform-*d*) δ 5.96 (qdd, *J* = 7.3, 3.0, 1.4 Hz, 1H), 4.72 (s, 1H), 2.90 (m, 4H), 2.65 – 2.55 (m, 1H), 2.04 (m, 3H), 1.46 (s, 3H), 1.01 (s, 9H). **^{13}C NMR** 71Bh (101 MHz, Chloroform-*d*) δ 174.9, 174.3, 134.2, 129.9, 83.3, 62.5, 42.2, 36.4, 31.2, 27.0, 25.8, 13.9. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{14}H_{23}N_2O_2$ [M + H]$^+$ 251.1754, found 251.1754.

(3*S*,7a*S*)-3-(*tert*-Butyl)-2,7a-dimethyl-6-vinyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,5(6H)-dione (91)



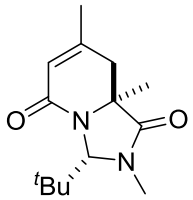
Prepared according to the general procedure starting from (2*S*,5*S*)-5-((*E*)-but-2-en-1-yl)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride **70Bh** (43 mg, 0.15 mmol, 1.0 equiv.). Isolated as a mixture of products **71Bh**/**91**. Colourless oil (19 mg, 0.08 mmol, 47%). **R_f** 0.54 (petroleum ether/diethyl ether 50/50). **^{1}H NMR** 91 (400 MHz, Chloroform-*d*) δ 5.83 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.3 Hz, 1H), 5.08 (dt, *J* = 17.3, 1.4 Hz, 1H), 4.71 (s, 1H), 3.48 (dddt, *J* = 13.4, 7.7, 6.3, 1.6 Hz, 1H), 2.90 (s, 3H), 2.33 (dd, *J* = 12.4, 7.4 Hz, 1H), 2.08 – 1.88 (m, 1H), 1.56 – 1.51 (s, 3H), 0.97 (s, 9H). **^{13}C NMR** 91 (101 MHz, Chloroform-*d*) δ 180.5, 174.6, 133.2, 118.1, 82.3, 63.2, 45.5, 41.4, 36.5, 31.1, 26.7, 23.8. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{14}H_{23}N_2O_2$ [M + H]$^+$ 251.1754, found 251.1754.

(3*S*,7a*S*)-3-(*tert*-Butyl)-6-ethylidene-2,7a-dimethyltetrahydro-1H-pyrrolo[1,2-c]imidazole-1,5(6H)-dione (92)



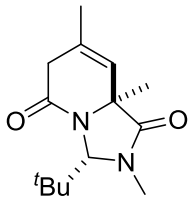
Prepared according to the general procedure starting from (2*S*,5*S*)-5-((*E*)-but-2-en-1-yl)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride **70Bh** (43 mg, 0.15 mmol, 1.0 equiv.). White solid (14 mg, 0.05 mmol, 36%). **M.p.:** 105–113 °C. **R_f** 0.43 (petroleum ether/diethyl ether 50/50). **$[\alpha]_D^{23}$ =** −28° (*c*= 1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2972 (C–H), 1696 (C=O), 1642 (C=O), 1246. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.52 (qdd, *J* = 7.1, 3.5, 2.2 Hz, 1H), 4.70 (s, 1H), 2.90 (s, 3H), 2.89 – 2.82 (m, 1H), 2.67 (ddq, *J* = 17.0, 2.7, 1.4 Hz, 1H), 1.72 (ddd, *J* = 7.2, 2.5, 1.3 Hz, 3H), 1.48 (s, 3H), 1.02 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.0, 174.9, 131.8, 131.7, 84.0, 63.0, 37.6, 36.3, 31.1, 27.1, 27.0, 15.1. **HRMS** (ESI$^+$): *m/z* calcd. for $C_{14}H_{23}N_2O_2$ [M + H]$^+$ 251.1754, found 251.1751.

(3*S*,8a*S*)-3-(*tert*-Butyl)-2,7,8a-trimethyl-2,3,8,8a-tetrahydroimidazo[1,5-a]pyridine-1,5-dione (71Bi)



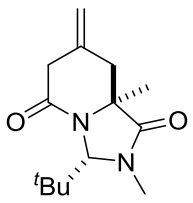
Prepared according to the general procedure starting from (2*S*,4*R*)-4-allyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bi** (43 mg, 0.15 mmol, 1.0 equiv.). White solid (9 mg, 0.04 mmol, 24%). **M.p.:** 134–139 °C. **R_f** 0.23 (petroleum ether/diethyl ether 40/60). **$[\alpha]_D^{23}$ =** −168° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2974 (C–H), 1705 (C=O), 1672 (C=O), 1380. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.78 (dd, *J* = 2.7, 1.4 Hz, 1H), 5.17 (s, 1H), 3.01 (s, 3H), 2.41 (d, *J* = 16.0 Hz, 1H), 2.29 (d, *J* = 16.9 Hz, 1H), 1.93 (t, *J* = 1.4 Hz, 3H), 1.54 (s, 3H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.8, 164.3, 147.7, 119.9, 80.9, 60.4, 39.5, 37.8, 31.2, 27.5, 23.2, 22.8. **HRMS** (ESI^+): *m/z* calcd. for $C_{14}H_{22}N_2O_2Na$ $[M + Na]^+$ 273.1573, found 273.1580.

(3*S*,8a*S*)-3-(*tert*-Butyl)-2,7,8a-trimethyl-2,3,6,8a-tetrahydroimidazo[1,5-a]pyridine-1,5-dione (93)



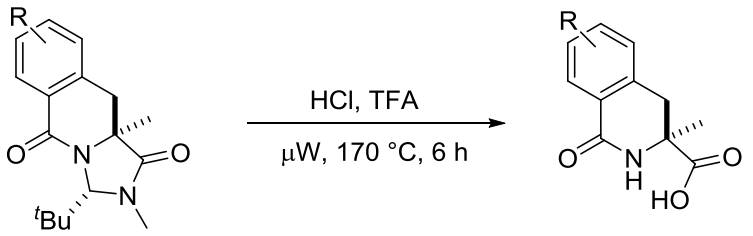
Prepared according to the general procedure starting from (2*S*,4*R*)-4-allyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bi** (43 mg, 0.15 mmol, 1.0 equiv.). White solid (18 mg, 0.07 mmol, 47%). **M.p.:** 90–94 °C. **R_f** 0.60 (petroleum ether/diethyl ether 40/60). **$[\alpha]_D^{23}$ =** −48° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} 2979 (C–H), 1705 (C=O), 1679 (C=O), 1264, 782, 768. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.84 (ddd, *J* = 3.3, 1.6, 0.6 Hz, 1H), 5.15 (s, 1H), 3.09 (ddd, *J* = 18.2, 3.3, 1.6 Hz, 1H), 2.98 (s, 3H), 2.72 (d, *J* = 18.2 Hz, 1H), 1.78 (t, *J* = 1.5 Hz, 3H), 1.50 (s, 3H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.0, 171.0, 130.5, 124.6, 80.8, 64.3, 38.2, 37.2, 31.2, 27.4, 24.9, 21.7. **HRMS** (ESI^+): *m/z* calcd. for $C_{14}H_{23}N_2O_2$ $[M + H]^+$ 251.1754, found 251.1758.

(3*S*,8a*S*)-3-(*tert*-Butyl)-2,8a-dimethyl-7-methylenehexahydroimidazo[1,5-a]pyridine-1,5-dione (94)



Prepared according to the general procedure starting from (2*S*,4*R*)-4-allyl-2-(*tert*-butyl)-1,4-dimethyl-5-oxopyrrolidine-3-carbonyl chloride **70Bi** (43 mg, 0.15 mmol, 1.0 equiv.). Colourless oil (5 mg, 0.02 mmol, 13%). **R_f** 0.45 (petroleum ether/diethyl ether 40/60). **$[\alpha]_D^{23}$ =** −52° (*c*=1.0, $CHCl_3$). I**R** (neat, cm^{-1}): ν_{max} 2961 (C–H), 1706 (C=O), 1674 (C=O), 1363. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.27 (s, 1H), 5.11 – 4.97 (m, 2H), 3.30 (dq, *J* = 20.2, 1.8 Hz, 1H), 3.20 (dq, *J* = 20.2, 2.1 Hz, 1H), 3.02 (s, 3H), 2.67 (d, *J* = 13.9 Hz, 1H), 2.18 (d, *J* = 13.9 Hz, 1H), 1.47 (s, 3H), 1.04 (s, 9H,). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.5, 170.7, 135.9, 113.9, 80.7, 61.4, 43.0, 38.4, 37.5, 31.2, 27.2, 22.6. **HRMS** (ESI^+): *m/z* calcd. for $C_{14}H_{22}N_2O_2Na$ $[M + Na]^+$ 273.1573, found 273.1573.

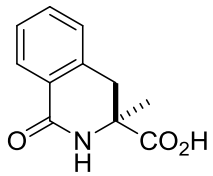
6.5.5. Hydrolysis to give dihydroisoquinolones 72



71 **72**

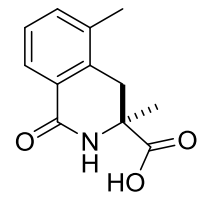
To a solution of the quaternary lactam **71** (0.10 mmol) HCl (1.6 mL of 6.0M solution) and TFA (0.4 mL) were added. The solution was heated in μW at 170 °C (10-12 Bar) for 8 h. The reaction mixture was concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/1% of formic acid in ethyl acetate 80/20) to obtain the desired dihydroisoquinolones **72**.

(*S*)-3-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (72Ba)



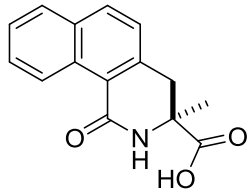
Prepared according to the general procedure starting from (3*S*,10a*S*)-3-(*tert*-butyl)-2,10a-dimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione **71Ba** (28 mg, 0.1 mmol, 1.0 equiv.). White foam (16.4 mg, 0.08 mmol, 80%). $\mathbf{R_f}$ 0.20 (petroleum ether/1% of formic acid in ethyl acetate 60/40). $\mathbf{[\alpha]_D^{22}}$ **=** −152° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 3269 (O-H), 2922 (C–H), 1704 (C=O), 1632 (C=O), 1401. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.64 (*br*s, 1H), 8.04 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.53 (td, *J* = 7.4, 1.4 Hz, 1H), 7.40 (tt, *J* = 7.6, 1.0 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 15.9 Hz, 1H), 3.20 (d, *J* = 15.9 Hz, 1H), 1.57 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 177.4, 166.6, 136.3, 133.3, 128.7, 128.0, 127.5, 127.0, 58.0, 36.2, 24.5. **HRMS** (ESI^+): *m/z* calcd. for $C_{11}H_{12}NO_3$ $[M + H]^+$ 206.0812, found 206.0808.

(*S*)-3,5-Dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (72Bd)



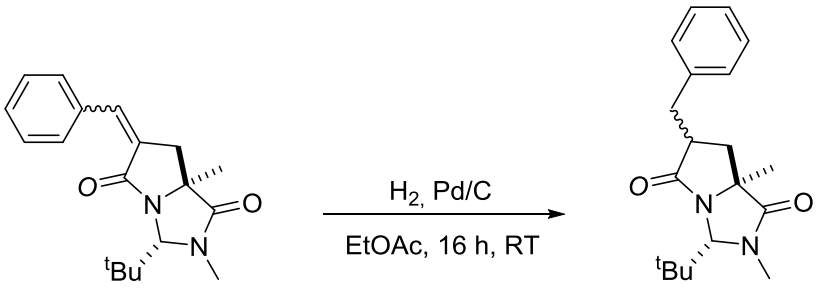
Prepared according to the general procedure starting from (3*S*,10a*S*)-3-(*tert*-butyl)-2,9,10a-trimethyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinoline-1,5-dione **71Bd** (30 mg, 0.1 mmol, 1.0 equiv.). Colourless oil (14.9 mg, 0.07 mmol, 68%). **M.p.:** decompose at 200–210 °C. $\mathbf{R_f}$ 0.17 (petroleum ether/1% of formic acid in ethyl acetate 60/ 40). $\mathbf{[\alpha]_D^{22}}$ **=** −276° (*c*= 1.0 in $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} = 3220 (O-H), 2920 (C–H), 1706 (C=O), 1622 (C=O), 749. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.74 (*br*s, 1H), 7.91 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 3.33 (d, *J* = 16.4 Hz, 1H), 3.17 (d, *J* = 16.3 Hz, 1H), 2.37 (s, 3H), 1.56 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 177.6, 167.0, 136.3, 134.9, 134.7, 127.0, 126.9, 125.8, 57.6, 32.9, 24.9, 19.3. **HRMS** (ESI^+): *m/z* calcd. for $C_{12}H_{14}NO_3$ $[M + H]^+$ 220.0968, found 220.0973.

(*S*)-3-Methyl-1-oxo-1,2,3,4-tetrahydrobenzo[h]isoquinoline-3-carboxylic acid (72Bf)



Prepared according to the general procedure starting from (7a*S*,10*S*)-10-(*tert*-butyl)-7a,9-dimethyl-7,7a,9,10-tetrahydrobenzo[h]imidazo[1,5-b]isoquinoline-8,12-dione **71Bf** (34 mg, 0.1 mmol, 1.0 equiv.). White solid (10.2 mg, 0.04 mmol, 43%). **M.p.:** decompose at 190–210 °C. $\mathbf{R_f}$ 0.18 (petroleum ether/1% of formic acid in ethyl acetate 60/40). $\mathbf{[\alpha]_D^{22}}$ **=** −120° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}) ν_{max} = 3258 (O-H), 2922 (C–H), 1704 (C=O), 1653 (C=O), 1440. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.69 (*br*s, 1H), 9.36 (dd, *J* = 8.7, 1.1 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.64 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 3.66 (d, *J* = 16.2 Hz, 1H), 3.32 (d, *J* = 17.9 Hz, 1H), 1.62 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 177.4, 167.7, 137.4, 134.1, 133.5, 131.4, 128.5, 128.2, 126.5, 126.4, 126.1, 122.0, 57.1, 38.1, 23.6. **HRMS** (ESI^+): *m/z* calcd. for $C_{15}H_{14}NO_3$ $[M + H]^+$ 256.0968, found 256.0976.

6.5.6. Hydrogenation of compounds 85 and 86[241]



85, 86 **87, 88**

To a solution of compound **85** or **86** (15 mg, 0.05 mmol, 1.0 equiv.) in ethyl acetate (1.1 mL) was added 10% Pd/C (6 mg, 0.005 mmol). Hydrogenation was carried out under a hydrogen atmosphere at room temperature for 16 h. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was purified by automated FC (petroleum ether/diethyl ether 80/20) to obtain the two diastereomers.

[241] P. V. Ramachndran, S. Madhi, L. Bland-Berry, M. V. R. Reddy, M. J. O´Donnell, *J. Am. Chem. Soc.* **2005**, *127*, 13450–13451.

Diastereomer A

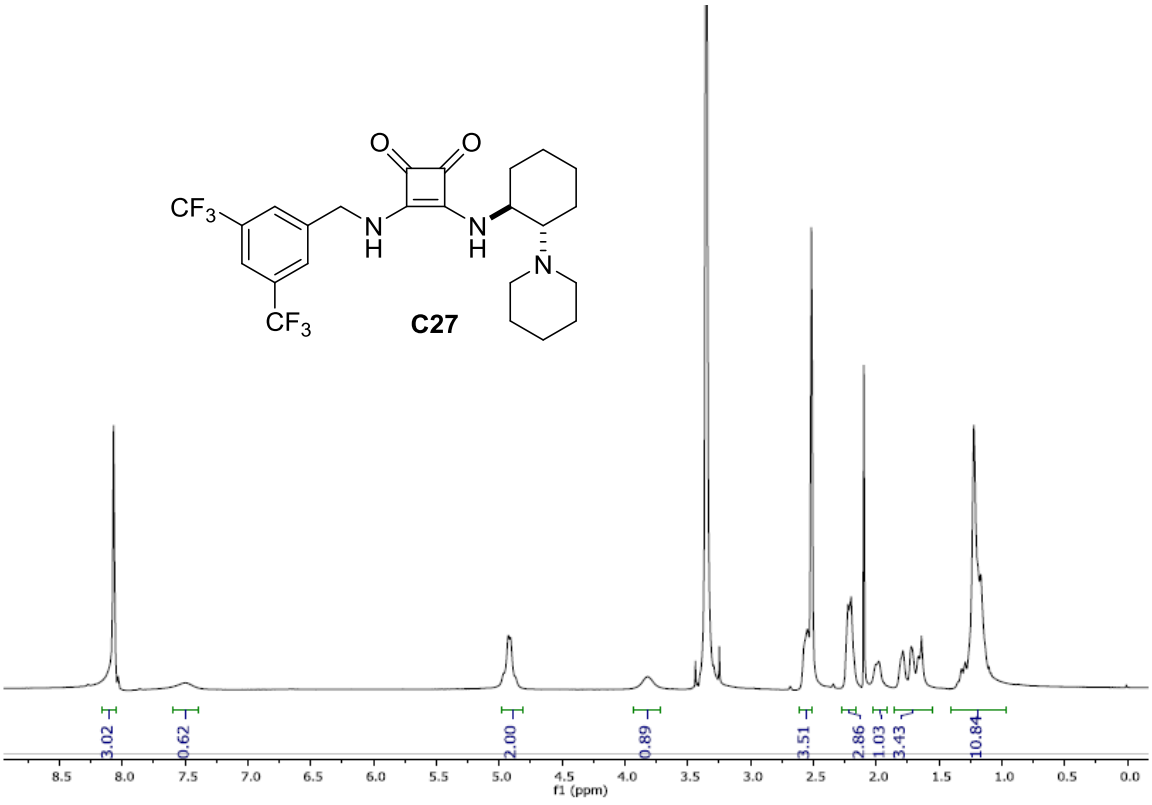
Prepared according to the general procedure. White solid (7 mg, 0.02 mmol, 45%). **M.p**.: 121–129 °C. **R_f** 0.55 (petroleum ether/ethyl acetate 60/40). **$[\alpha]_D^{22}$ =** +20° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} = 2923 (C–H), 1770 (C=O), 1704 (C=O). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.29 – 6.92 (m, 5H), 4.73 (s, 1H), 3.22 (dd, *J* = 13.9, 4.3 Hz, 1H), 3.00 (dddd, *J* = 13.1, 10.0, 7.3, 4.3 Hz, 1H), 2.90 (s, 3H), 2.39 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.14 (dd, *J* = 12.4, 7.3 Hz, 1H), 1.86 (t, *J* = 12.8 Hz, 1H), 1.43 (s, 3H), 0.98 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.6, 174.8, 139.2, 128.8, 128.6, 126.5, 82.2, 63.2, 43.9, 42.4, 36.5, 35.8, 31.1, 26.7, 23.7. **HRMS** (ESI^+): *m/z* calcd. for $C_{19}H_{26}N_2O_2Na$ $[M + Na]^+$ 337.1886, found 337.1896.

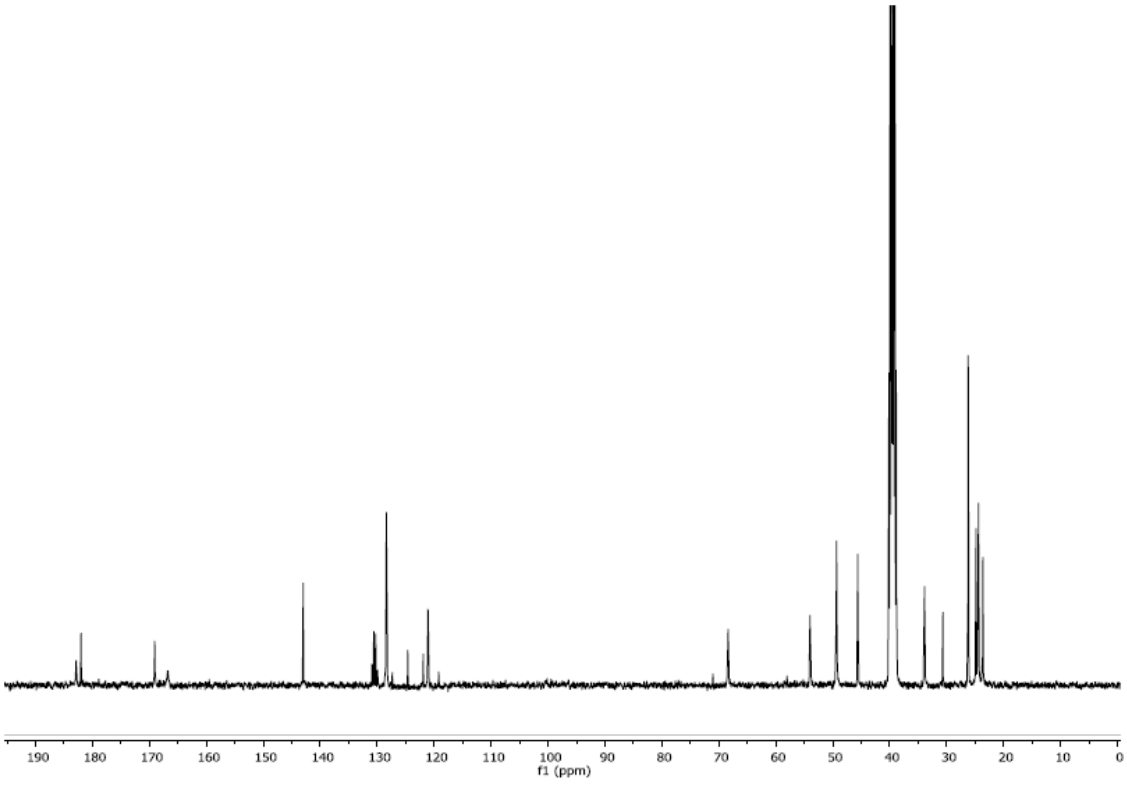
Diastereomer B

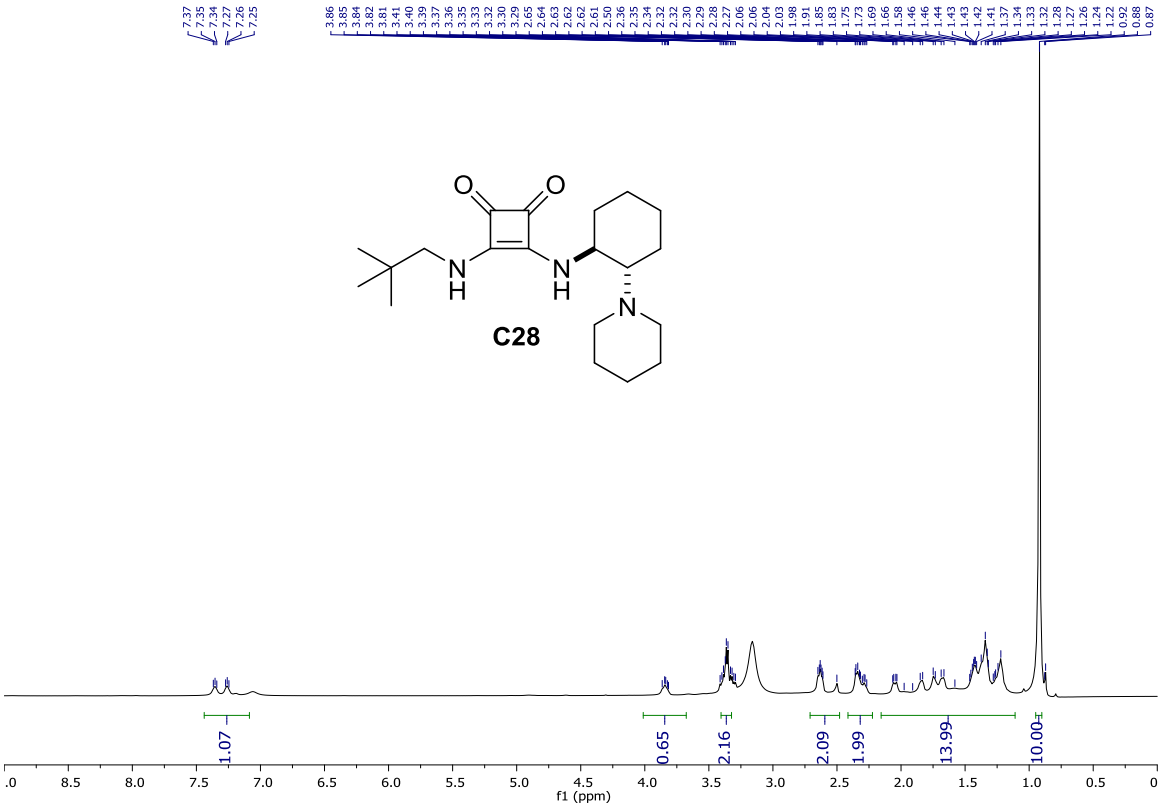
Prepared according to the general procedure. Colourless oil (3 mg, 0.009 mmol, 19%). **R_f** 0.25 (petroleum ether/ethyl acetate 60/40). **$[\alpha]_D^{22}$ =** +32° (*c*=1.0, $CHCl_3$). **IR** (neat, cm^{-1}): ν_{max} = 2955 (C–H), 1702 (C=O). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.34 – 7.22 (m, 5H), 4.80 (s, 1H), 3.15 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.96 (s, 4H), 2.85 (dddd, *J* = 10.4, 9.2, 5.2, 2.1 Hz, 1H), 2.42 (dd, *J* = 14.0, 10.4 Hz, 1H), 1.95 (dd, *J* = 13.9, 2.1 Hz, 1H), 1.36 (s, 3H), 1.08 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 183.9, 175.4, 138.3, 129.2, 128.6, 126.9, 83.1, 64.5, 46.0, 38.2, 36.7, 36.2, 30.9, 27.1. **HRMS** (ESI^+): *m/z* calcd. for $C_{19}H_{27}N_2O_2$ $[M + H]^+$ 315.2067, found 315.2066.

6.6. Representative NMR spectra

6.6.1. Catalysts






C28
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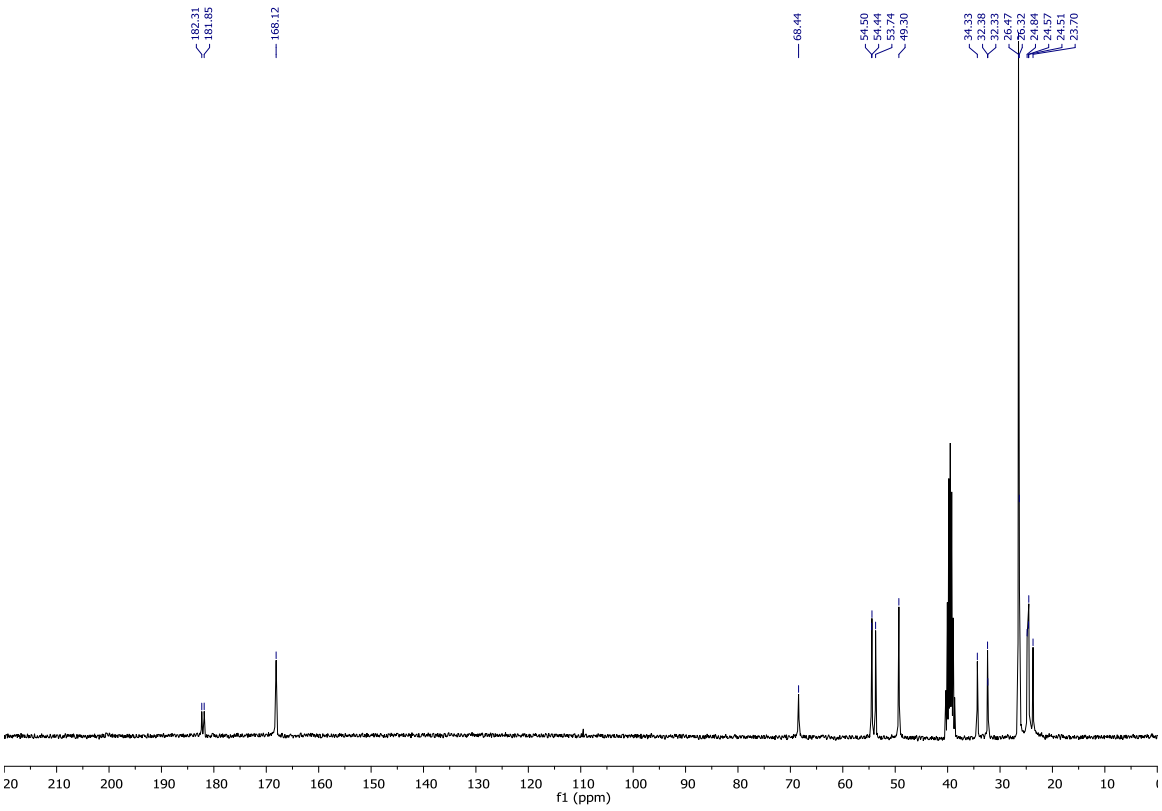
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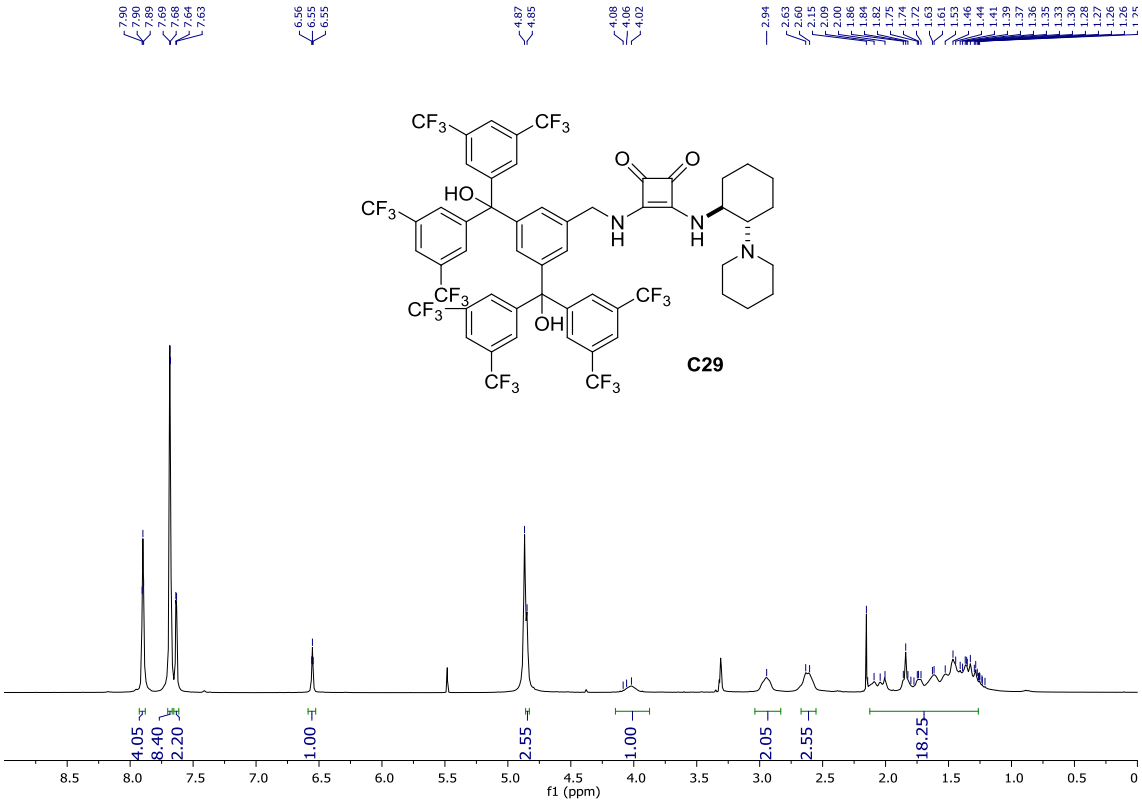
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4.06
4.02
2.94
2.63
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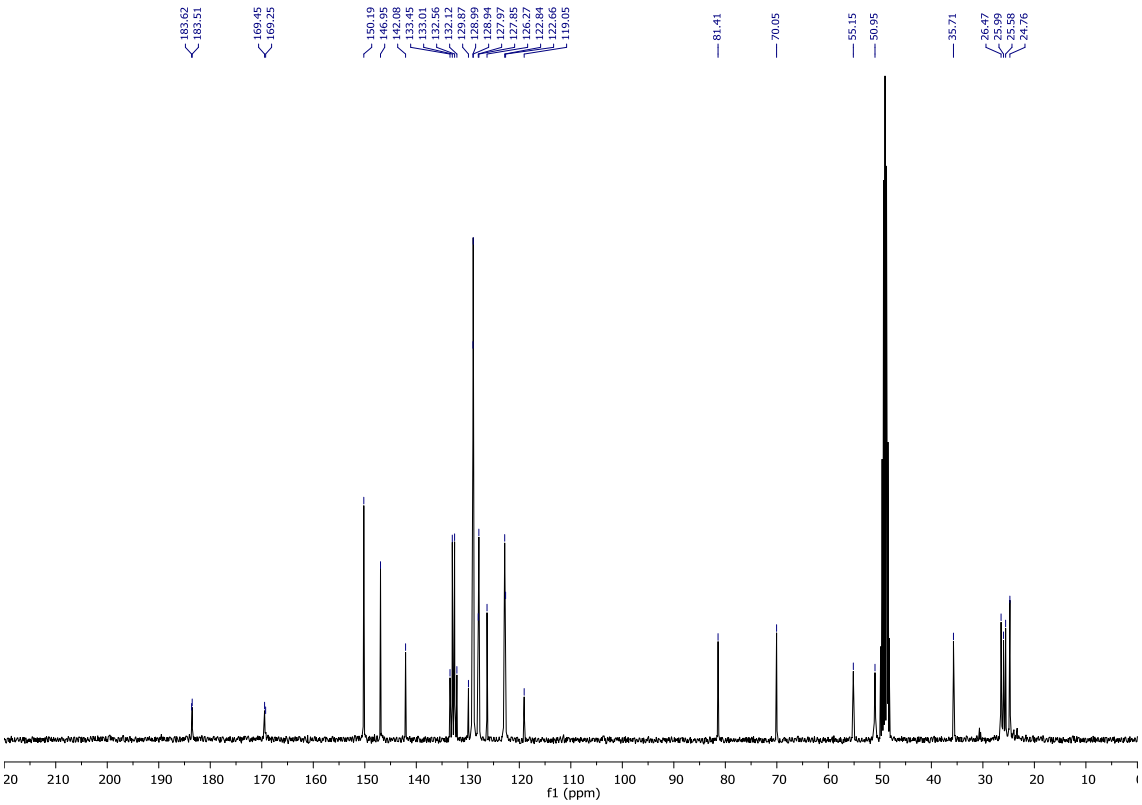
f1 (ppm)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119.05
81.41
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35.71
26.47
25.99
25.58
24.76
220
210
200
190
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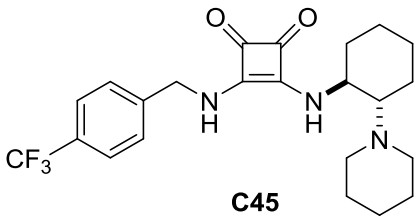
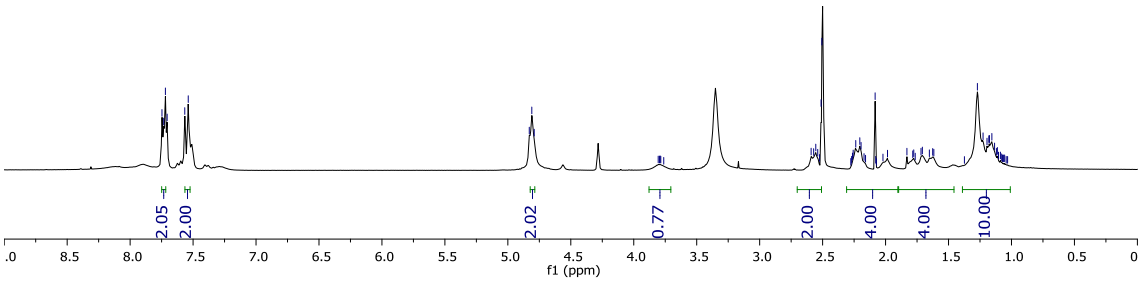
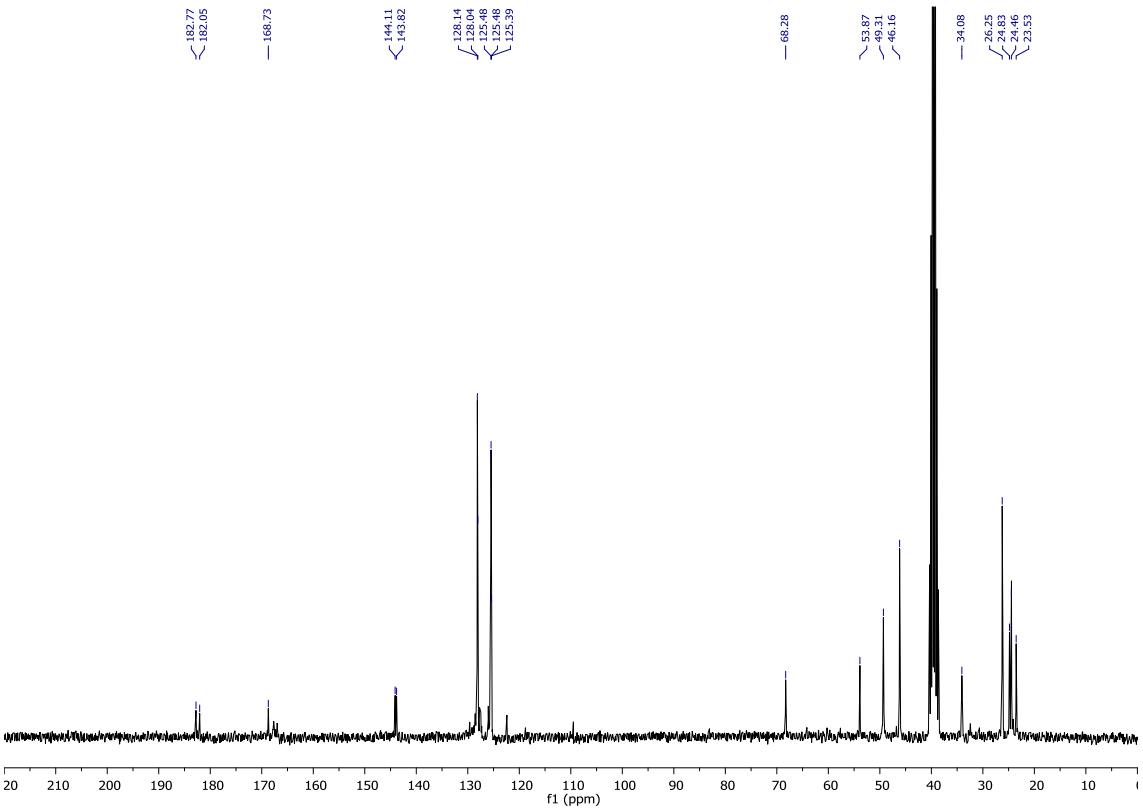
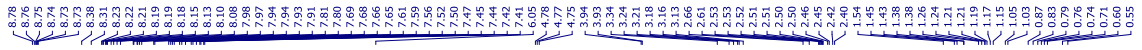
f1 (ppm)

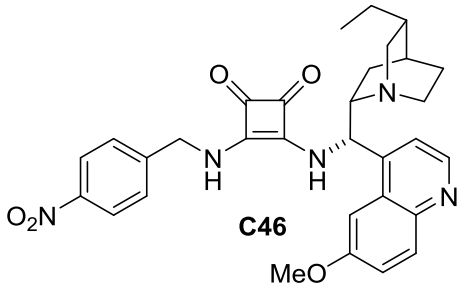


C45

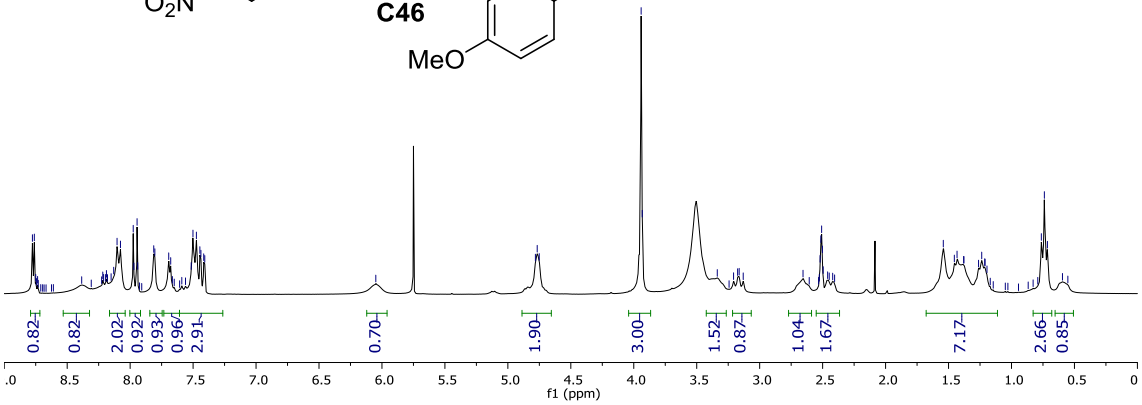


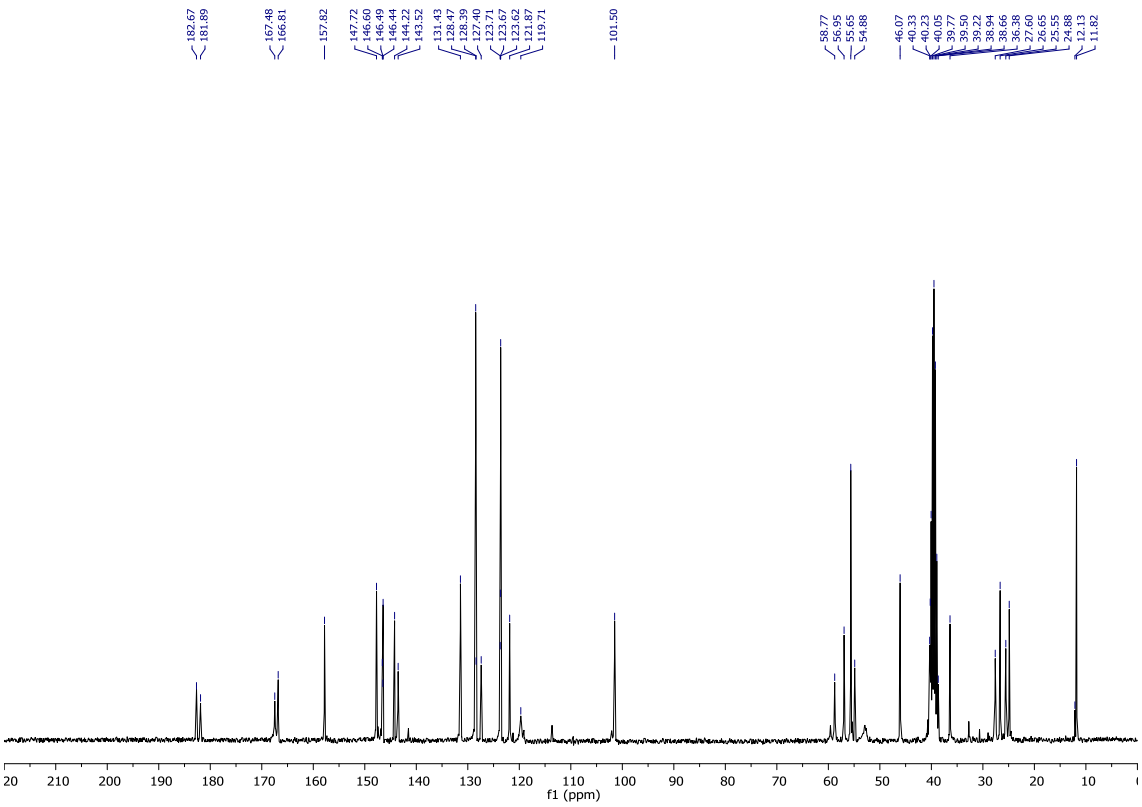


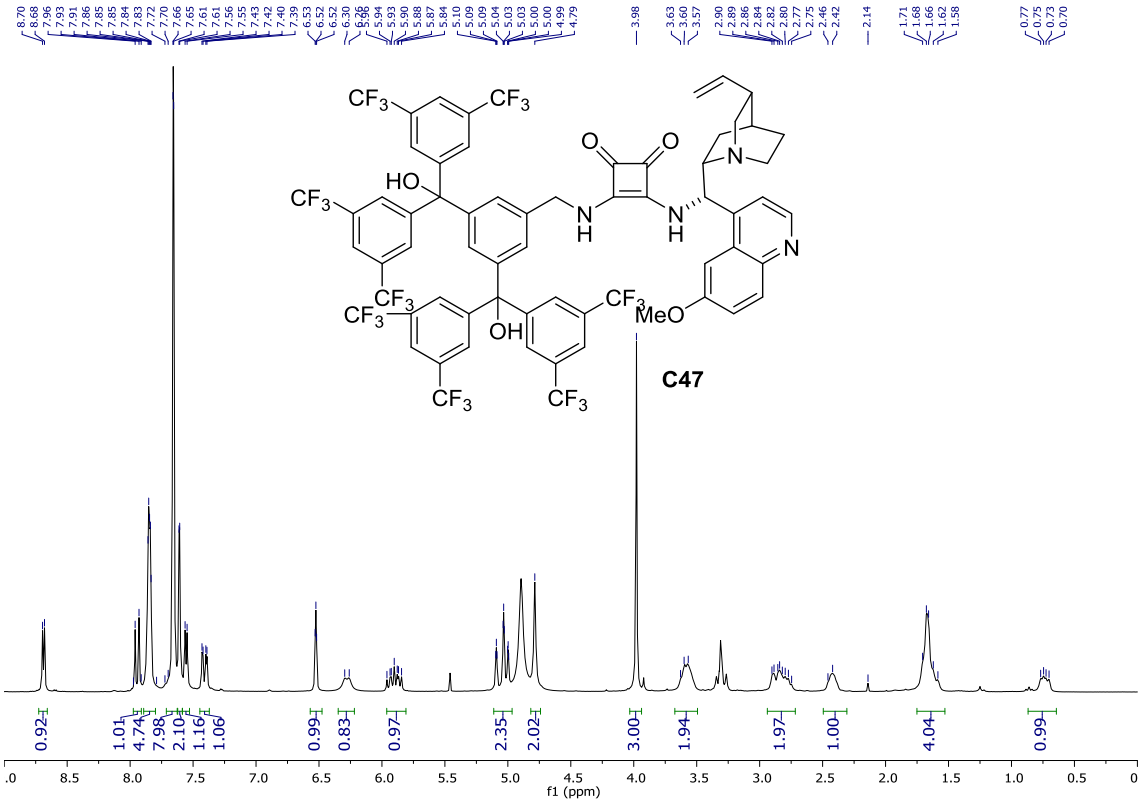


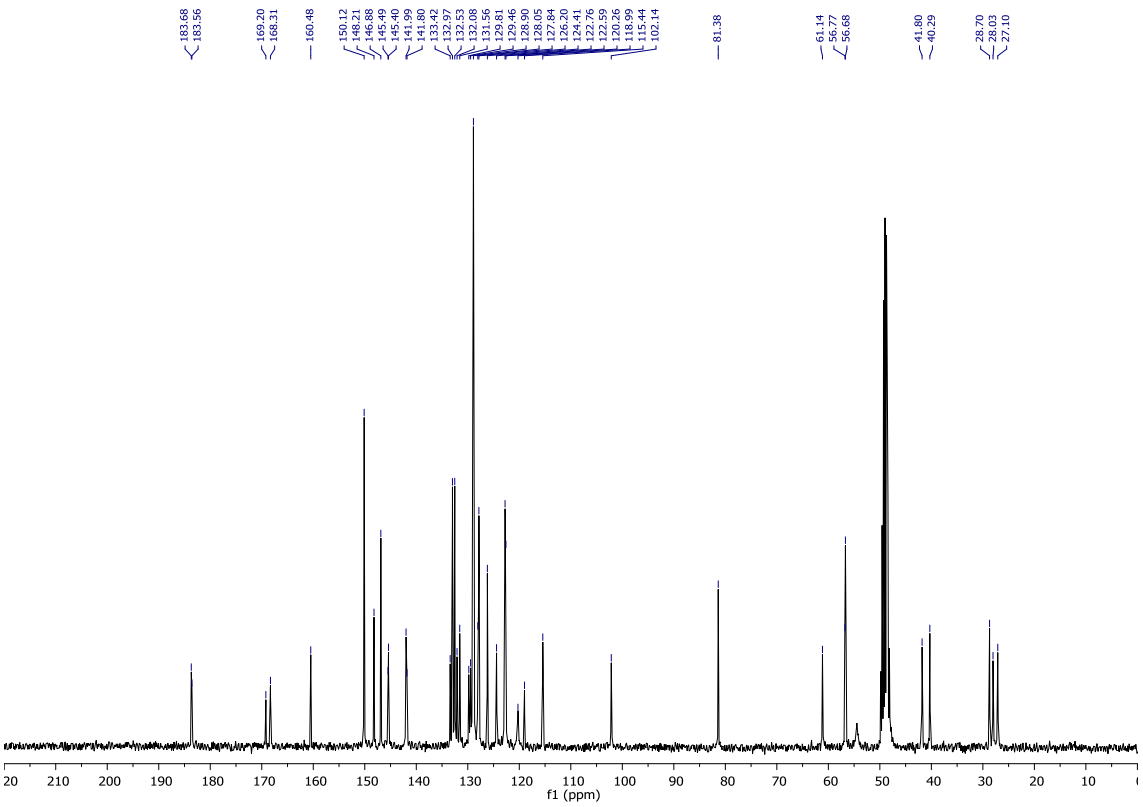

O
O
N
N
H
N
H
O_2N
N
MeO

C46

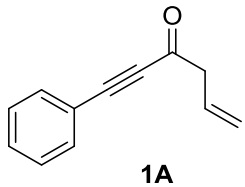

0.82
0.82
2.02
0.92
0.93
0.96
2.91
0.70
1.90
3.00
1.52
0.87
1.04
1.67
7.17
2.66
0.85
f1 (ppm)


f1 (ppm)

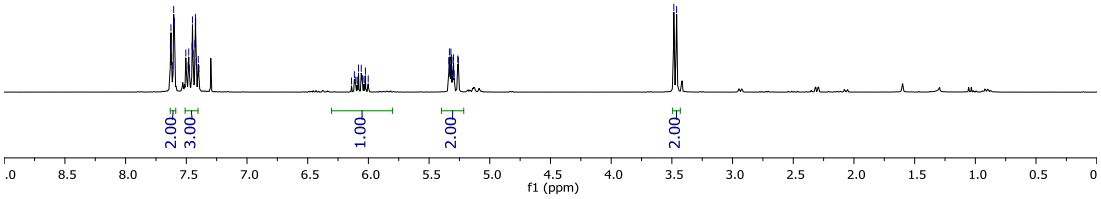

C47
f1 (ppm)

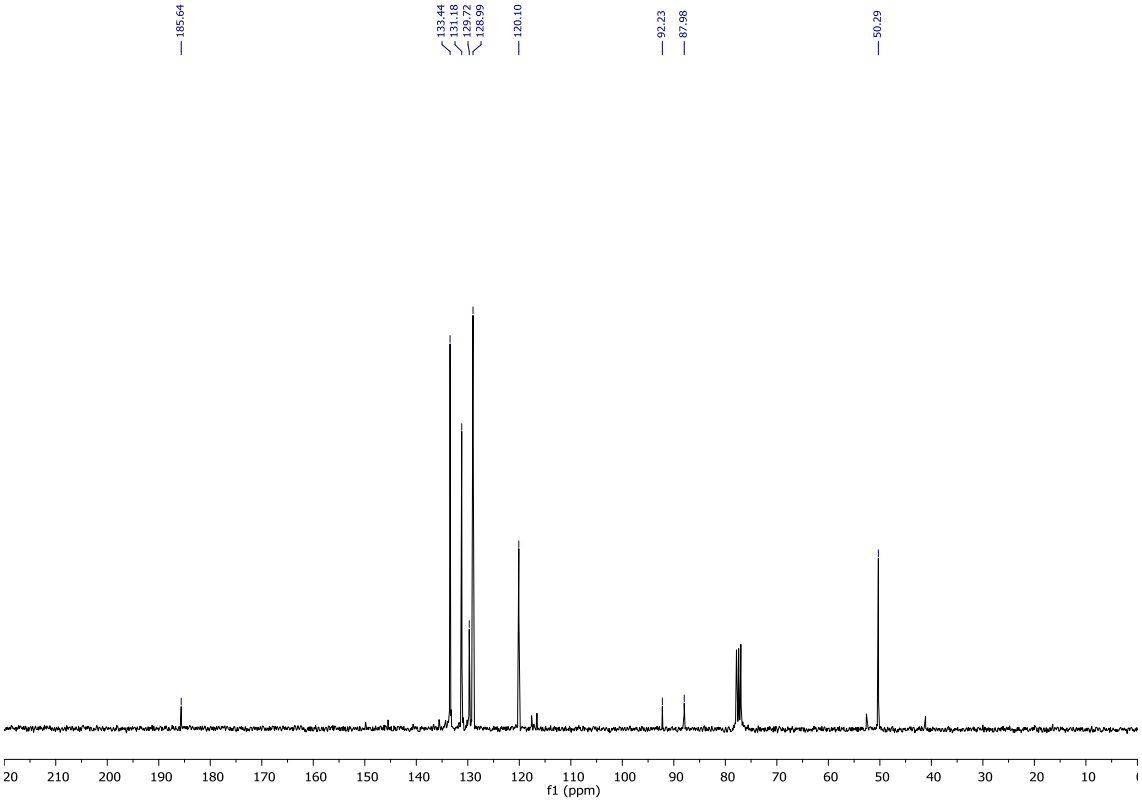

f1 (ppm)

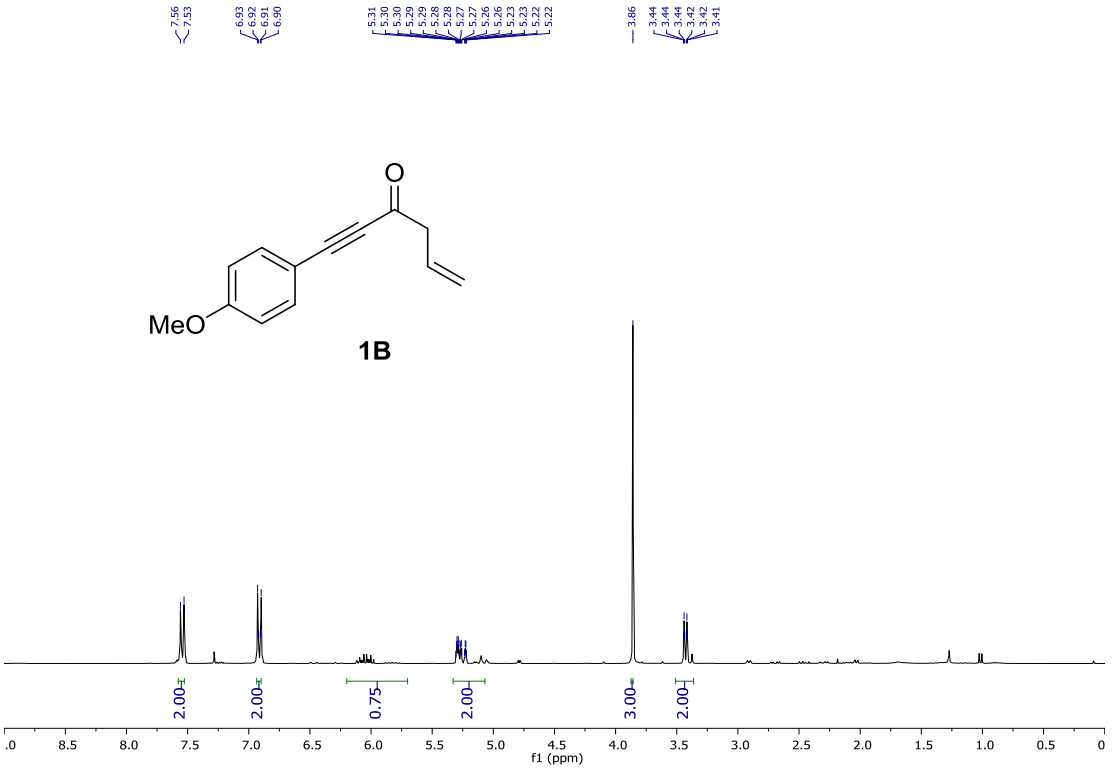
6.6.2. Chapter 2

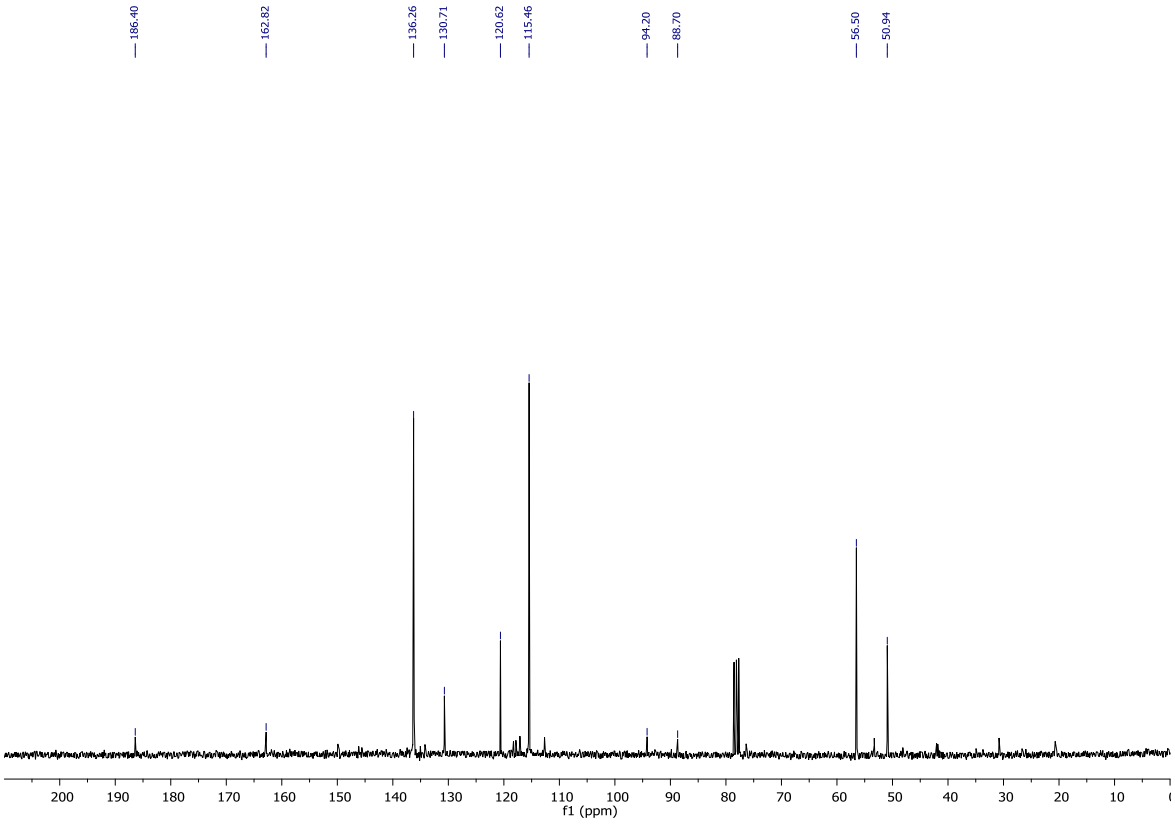


1A

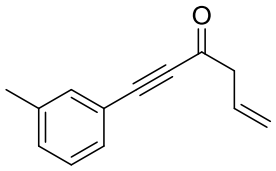




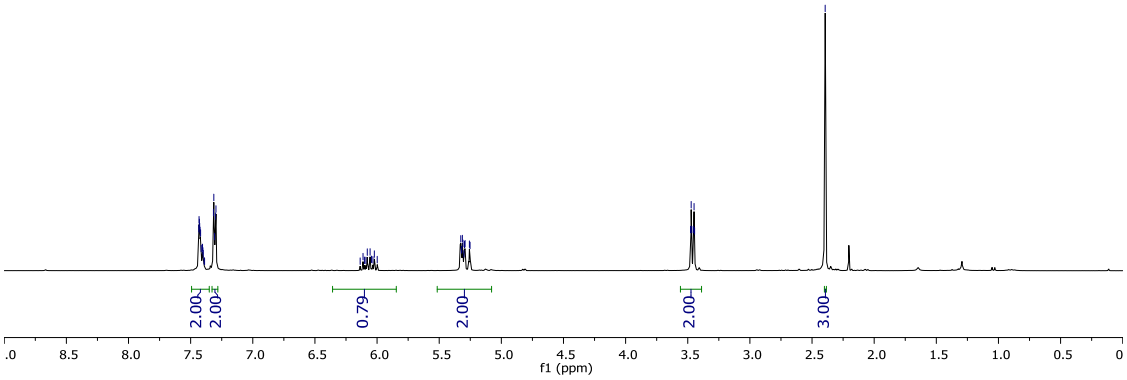

7.56
7.53
6.93
6.92
6.91
6.90
5.31
5.30
5.30
5.29
5.29
5.28
5.28
5.27
5.27
5.26
5.26
5.23
5.23
5.22
5.22
3.86
3.44
3.44
3.44
3.42
3.42
3.41
O
MeO
1B
2.00
2.00
0.75
2.00
3.00
2.00
f1 (ppm)

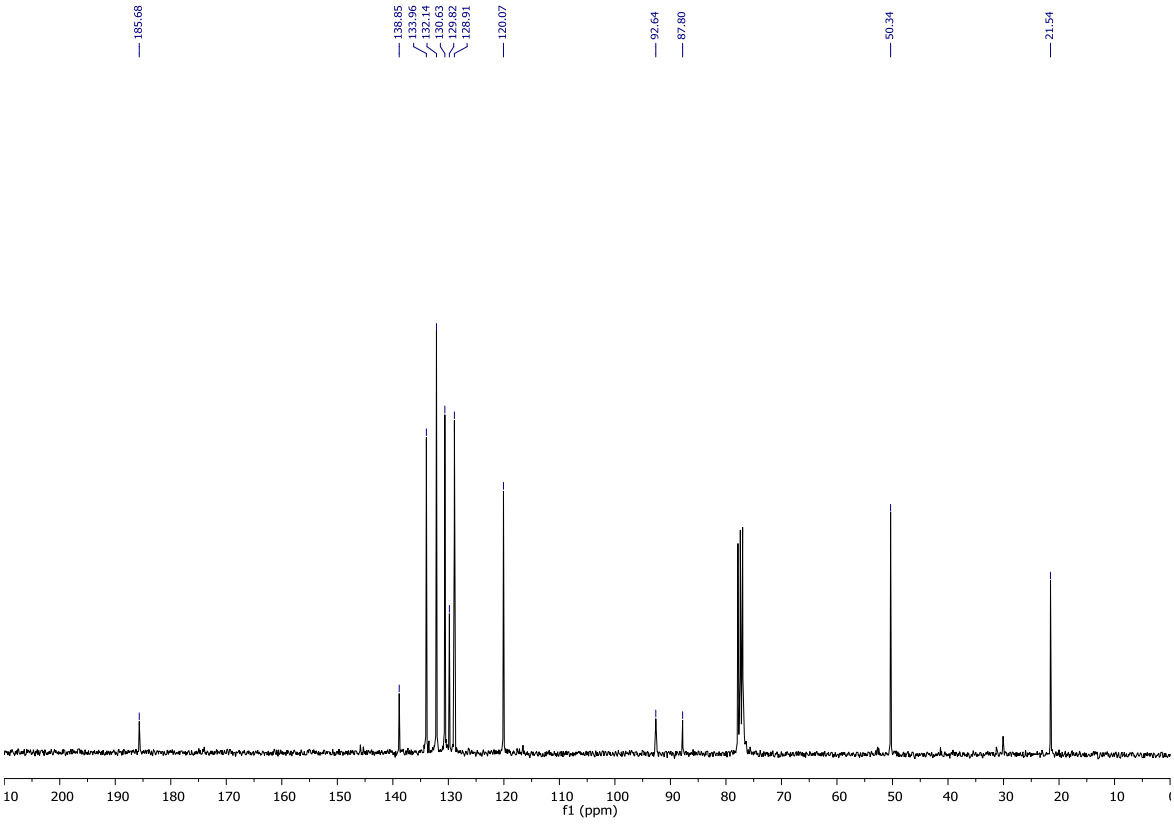

186.40
162.82
136.26
130.71
120.62
115.46
94.20
88.70
56.50
50.94
f1 (ppm)

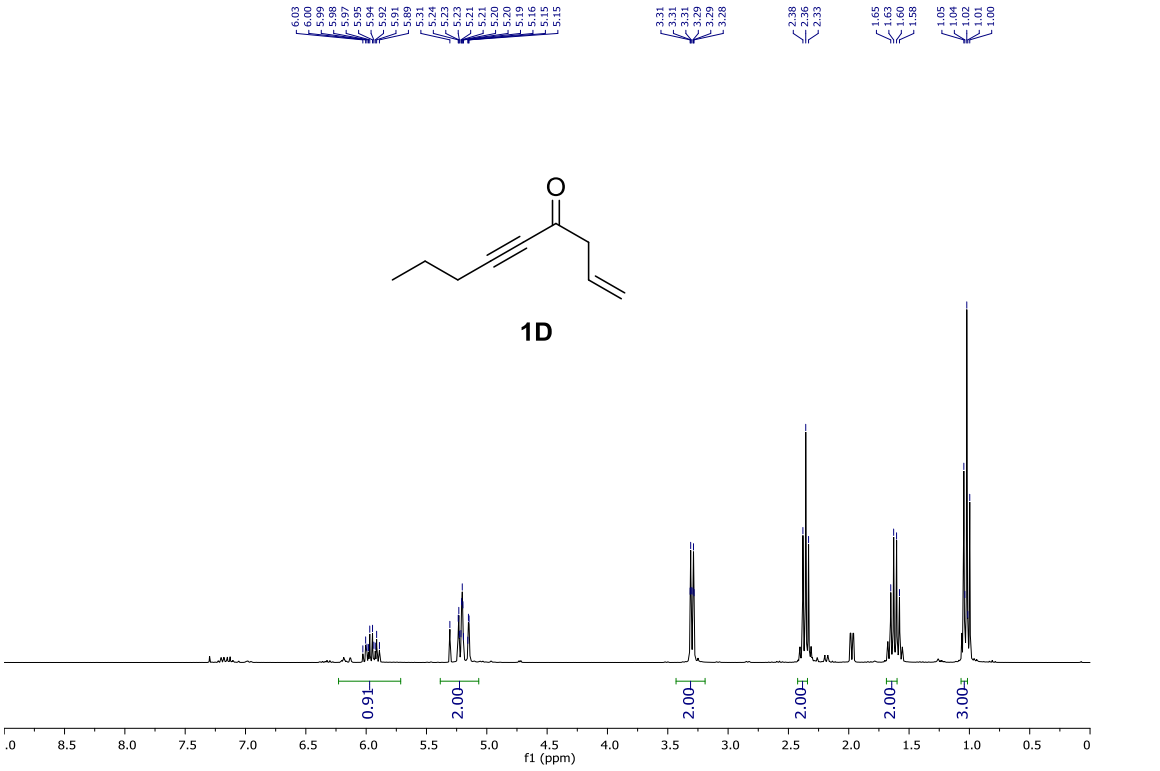

7.43
7.43
7.43
7.43
7.42
7.42
7.42
7.41
7.40
7.40
7.40
7.39
7.39
7.32
7.31
7.31
7.30
7.30
6.14
6.11
6.10
6.09
6.08
6.06
6.05
6.03
6.02
6.00
5.33
5.32
5.32
5.31
5.31
5.30
5.30
5.29
5.26
5.25
3.48
3.47
3.47
3.45
3.45
3.44
2.39

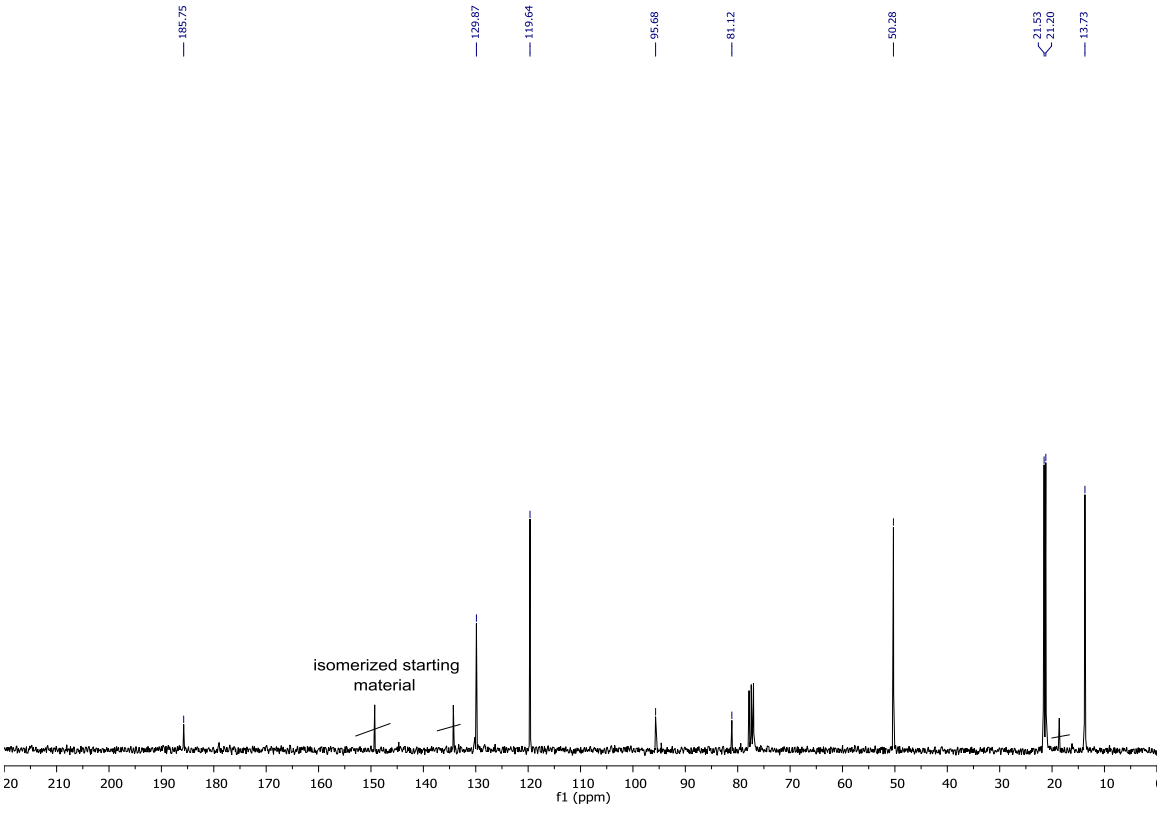

O

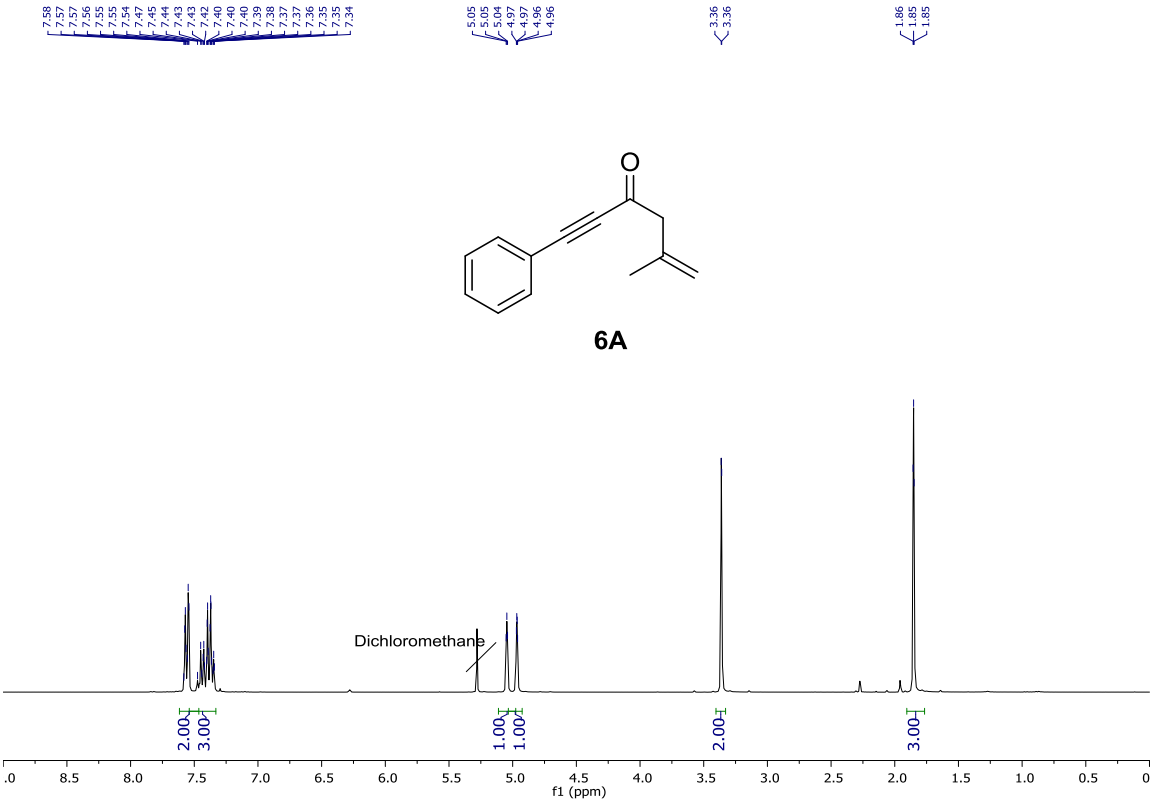
1C

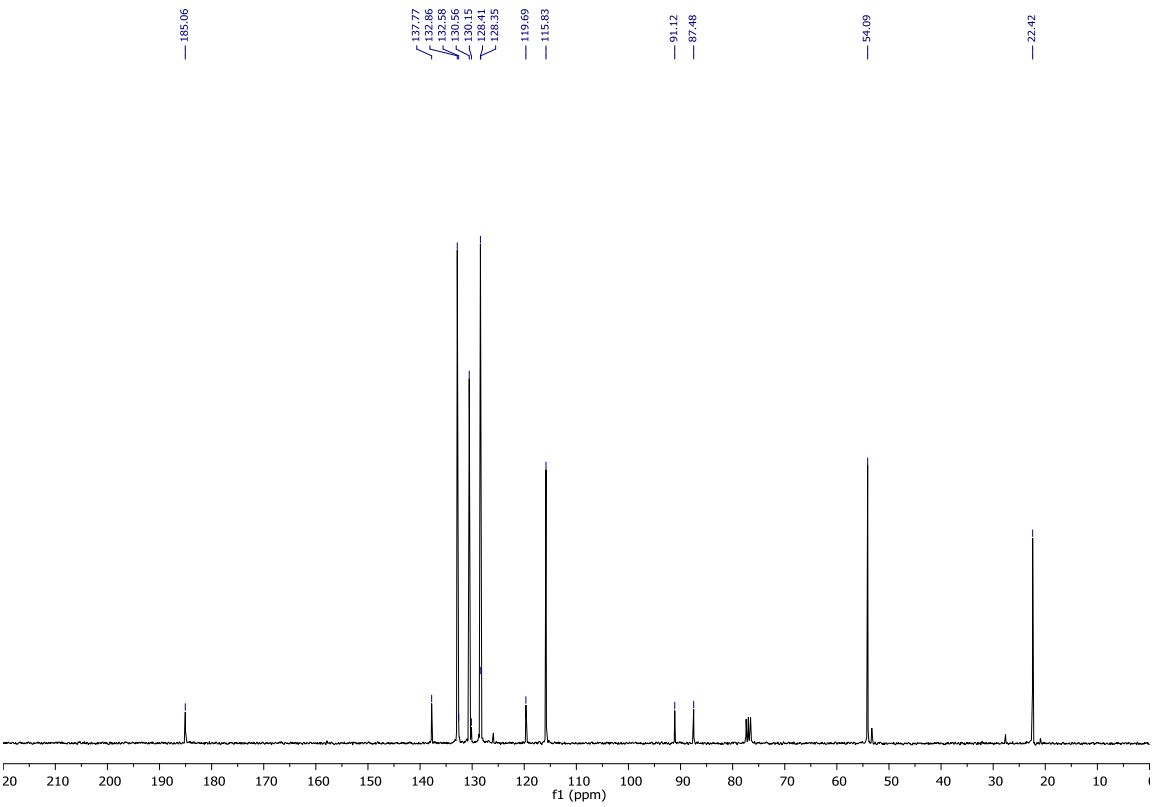

2.00
2.00
0.79
2.00
2.00
3.00
f1 (ppm)

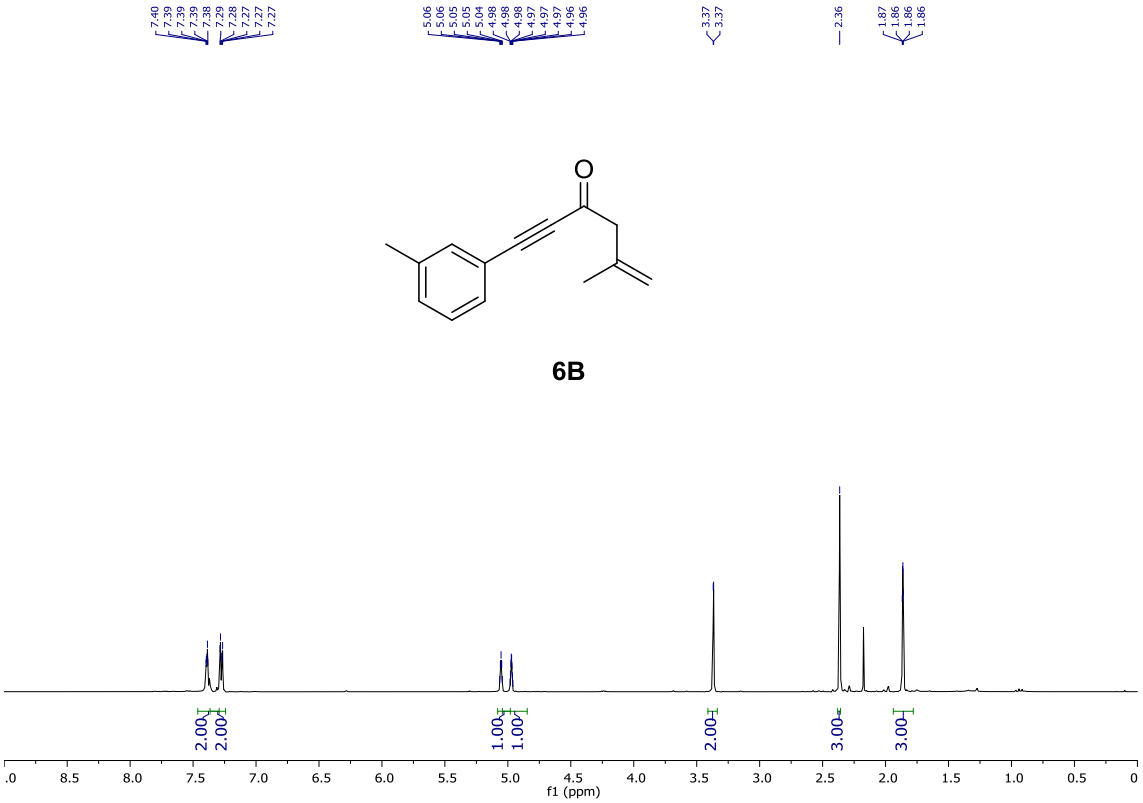

185.68
138.85
133.96
132.14
130.63
129.82
128.91
120.07
92.64
87.80
50.34
21.54
f1 (ppm)


6.03
6.00
5.99
5.98
5.97
5.95
5.94
5.92
5.91
5.89
5.31
5.24
5.23
5.23
5.21
5.21
5.20
5.20
5.19
5.16
5.15
5.15
3.31
3.31
3.31
3.29
3.29
3.28
2.38
2.36
2.33
1.65
1.63
1.60
1.58
1.05
1.04
1.02
1.01
1.00
O
1D
0.91
2.00
2.00
2.00
2.00
3.00
f1 (ppm)

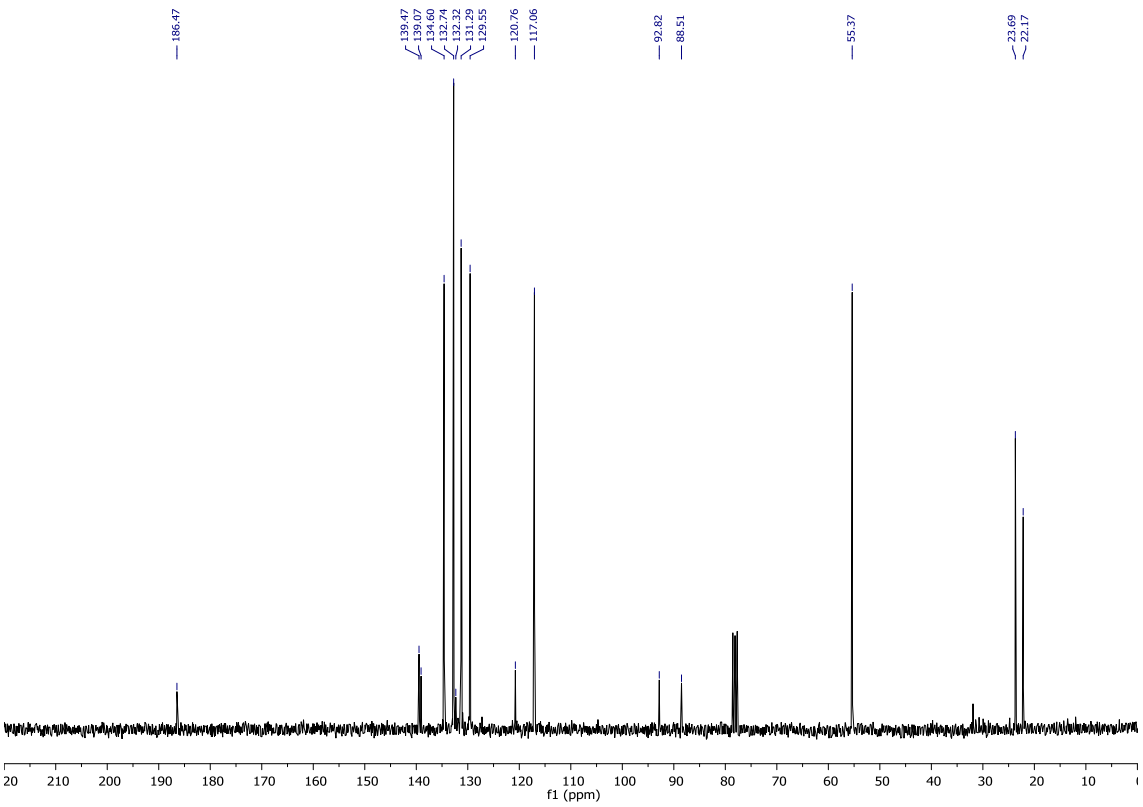

185.75
129.87
119.64
95.68
81.12
50.28
21.53
21.20
13.73
isomerized starting material
f1 (ppm)

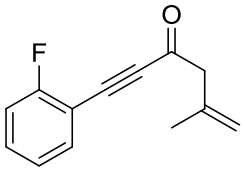

7.58
7.57
7.57
7.56
7.55
7.55
7.54
7.47
7.45
7.44
7.43
7.43
7.42
7.40
7.40
7.40
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.34
5.05
5.05
5.04
4.97
4.97
4.96
4.96
3.36
3.36
1.86
1.85
1.85
O
6A
Dichloromethane
2.00
3.00
1.00
1.00
2.00
3.00
f1 (ppm)


185.06
137.77
132.86
132.58
130.56
130.15
128.41
128.35
119.69
115.83
91.12
87.48
54.09
22.42
f1 (ppm)

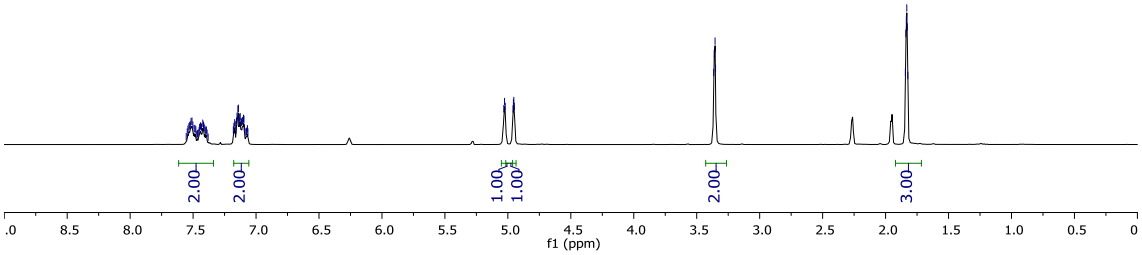

7.40
7.39
7.39
7.39
7.38
7.29
7.28
7.27
7.27
7.27
5.06
5.06
5.05
5.05
5.04
4.98
4.98
4.98
4.97
4.97
4.97
4.96
4.96
3.37
3.37
2.36
1.87
1.86
1.86
1.86
1.86
O
2.00
2.00
1.00
1.00
2.00
3.00
3.00
f1 (ppm)

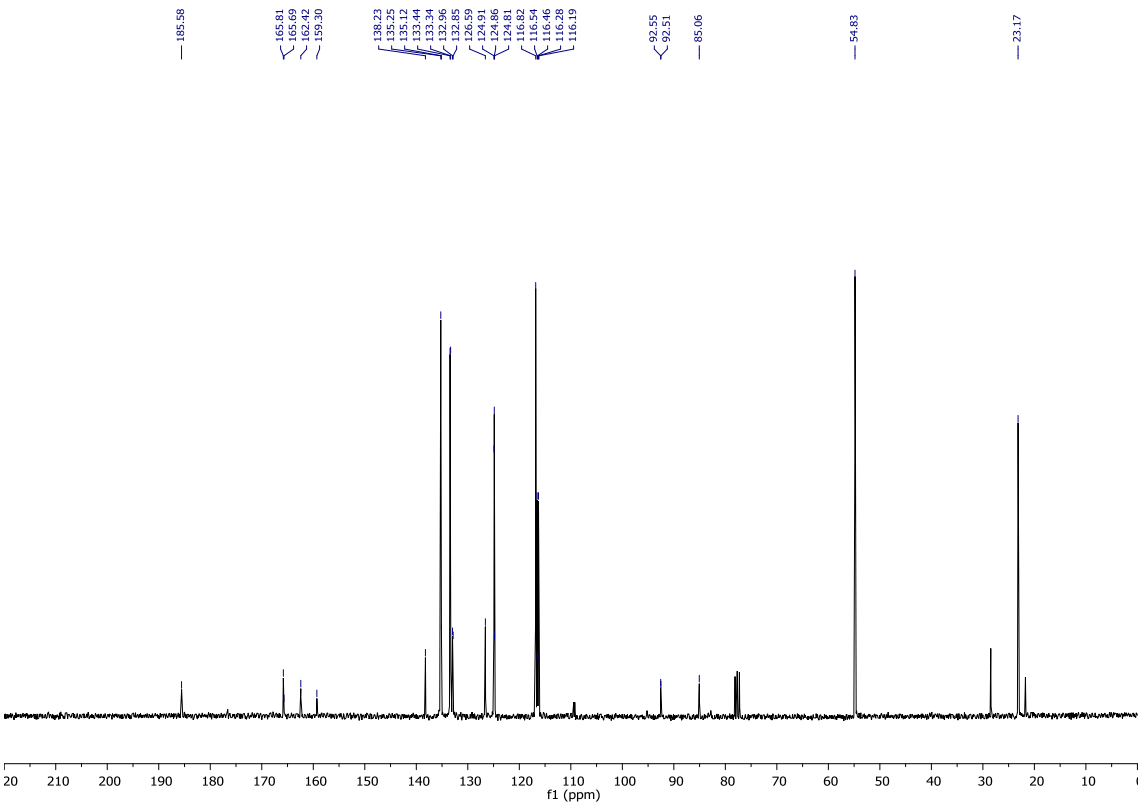
6B

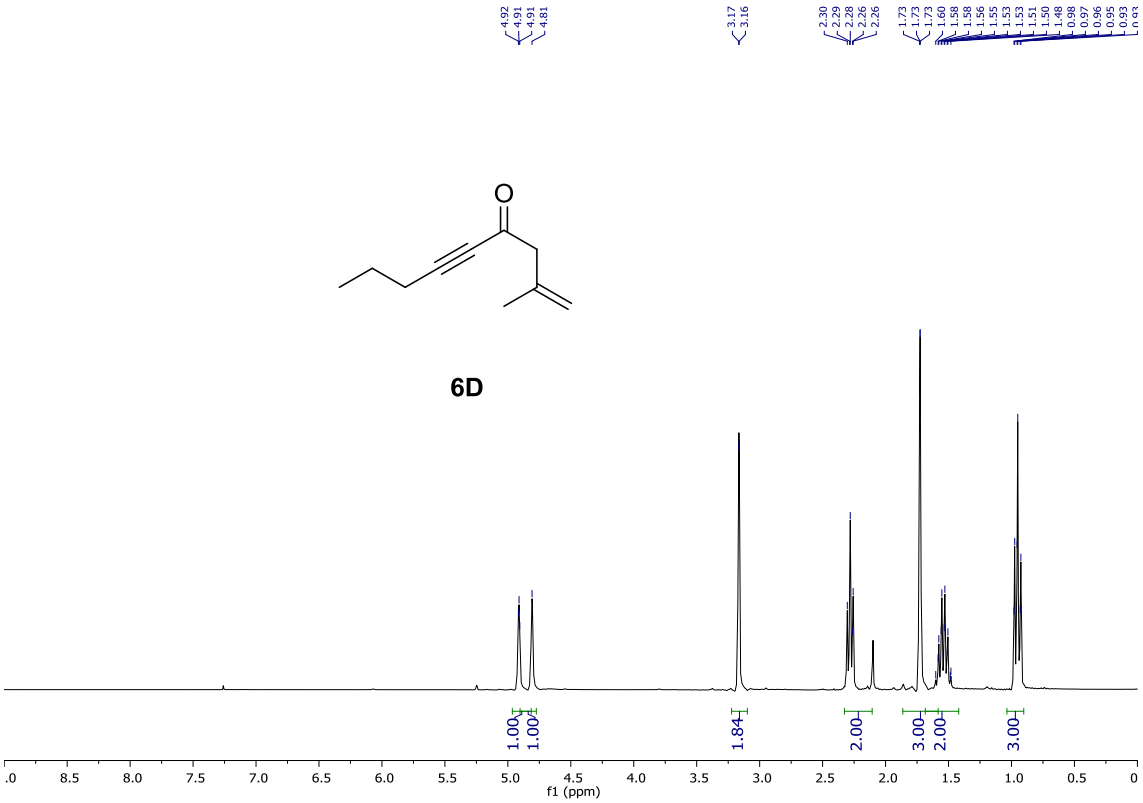

186.47
139.47
139.07
134.60
132.74
132.32
131.29
129.55
120.76
117.06
92.82
88.51
55.37
23.69
22.17
f1 (ppm)

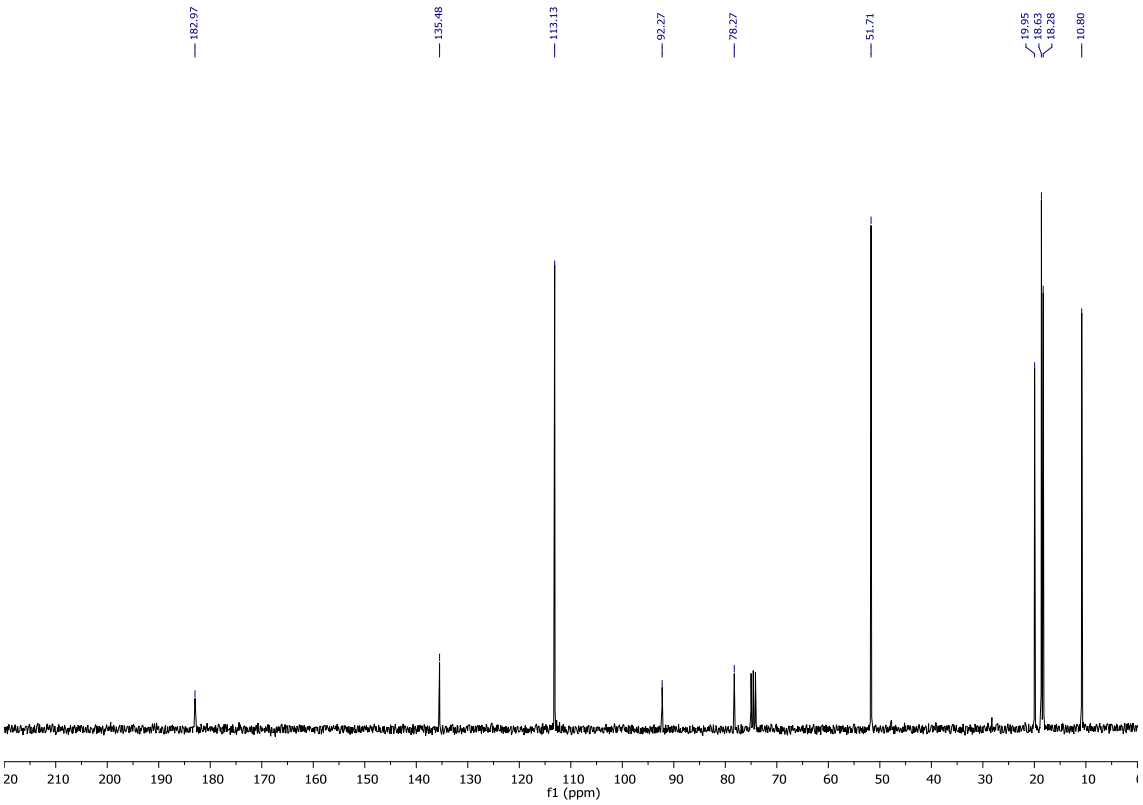

O
F

6C

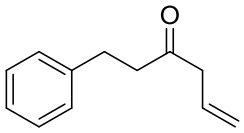

2.00
2.00
1.00
1.00
2.00
3.00
f1 (ppm)


185.58
165.81
165.69
162.42
159.30
138.23
135.25
135.12
133.44
133.34
132.96
132.85
126.59
124.91
124.86
124.81
116.82
116.54
116.46
116.28
116.19
92.55
92.51
85.06
54.83
23.17
f1 (ppm)

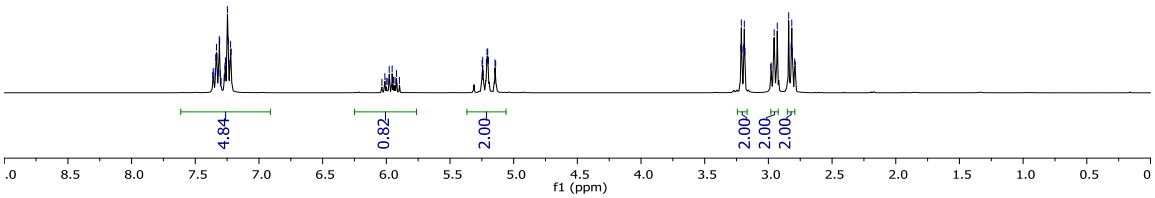

4.92
4.91
4.91
4.81
3.17
3.16
2.30
2.29
2.28
2.26
2.26
2.26
1.73
1.73
1.73
1.60
1.58
1.58
1.56
1.55
1.53
1.53
1.51
1.50
1.48
0.98
0.97
0.96
0.95
0.93
O
6D
1.00
1.00
1.84
2.00
3.00
2.00
3.00
f1 (ppm)

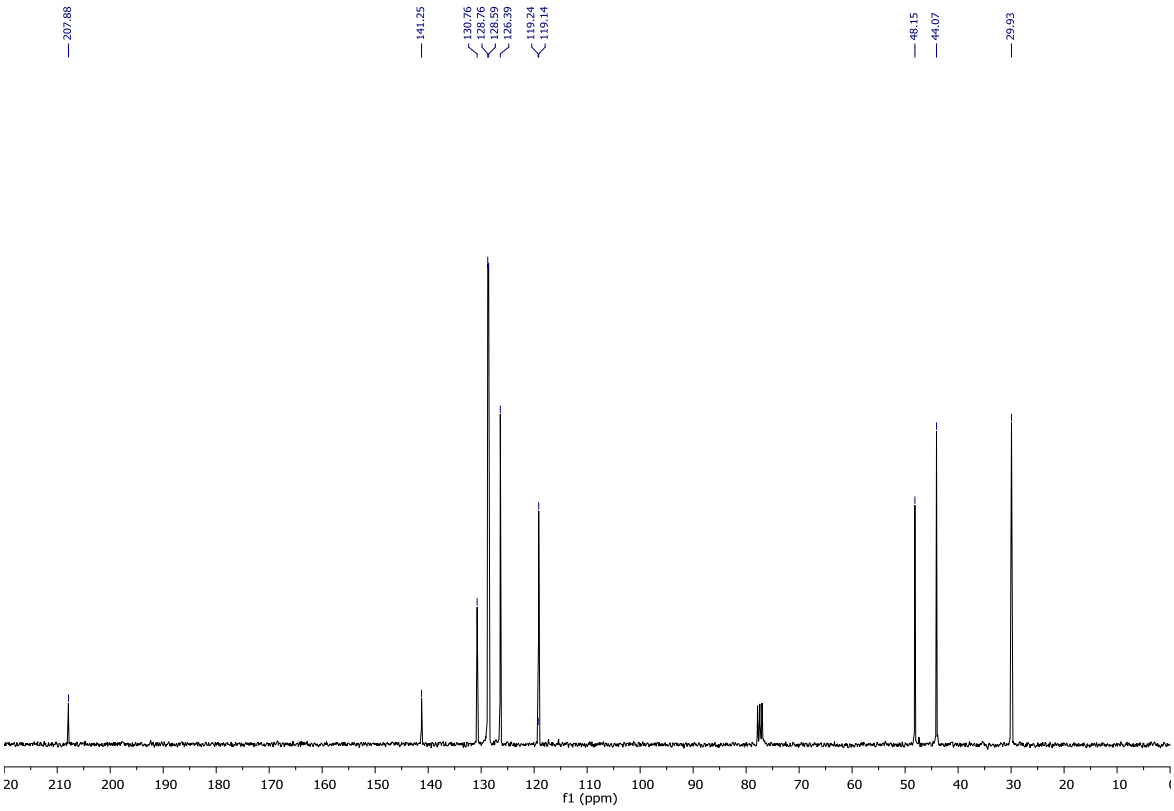

182.97
135.48
113.13
92.27
78.27
51.71
19.95
18.63
18.28
10.80
f1 (ppm)


7.36
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.27
7.27
7.26
7.25
7.24
7.23
7.22
7.22
6.03
6.01
6.00
5.99
5.98
5.95
5.94
5.93
5.92
5.90
5.25
5.24
5.24
5.21
5.21
5.20
5.20
5.15
5.14
3.22
3.21
3.21
3.19
3.19
3.18
2.98
2.98
2.95
2.93
2.84
2.82
2.82
2.81
2.79
2.79

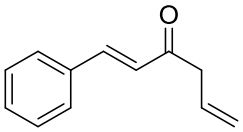

O

9A

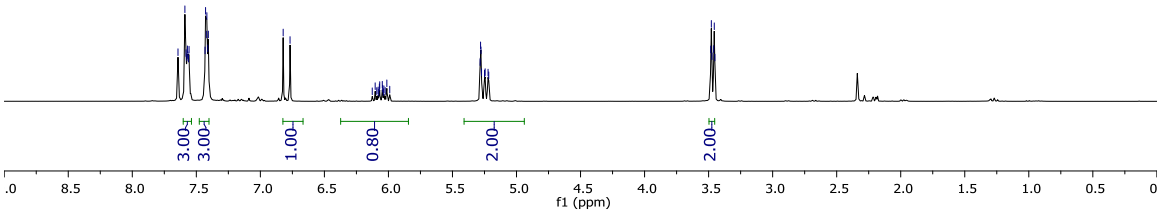

4.84
0.82
2.00
2.00
2.00
2.00
f1 (ppm)

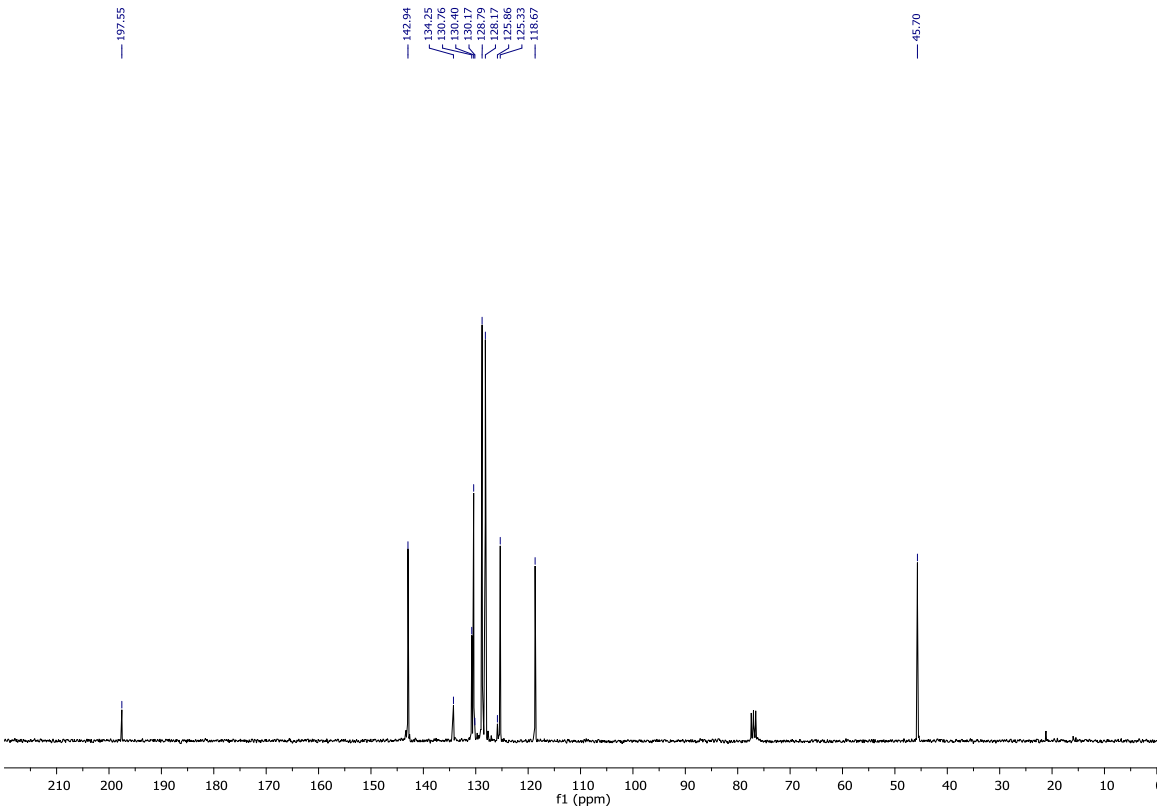

207.88
141.25
130.76
128.76
128.59
126.39
119.24
119.14
48.15
44.07
29.93
f1 (ppm)


7.64
7.59
7.58
7.57
7.57
7.57
7.56
7.56
7.43
7.43
7.42
7.42
7.41
7.41
6.82
6.77
6.13
6.10
6.09
6.08
6.08
6.07
6.07
6.05
6.04
6.04
6.04
6.03
6.01
5.99
5.28
5.28
5.28
5.27
5.25
5.24
5.22
5.22
3.48
3.48
3.47
3.46
3.46
3.45

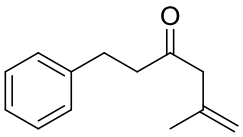

O

9B

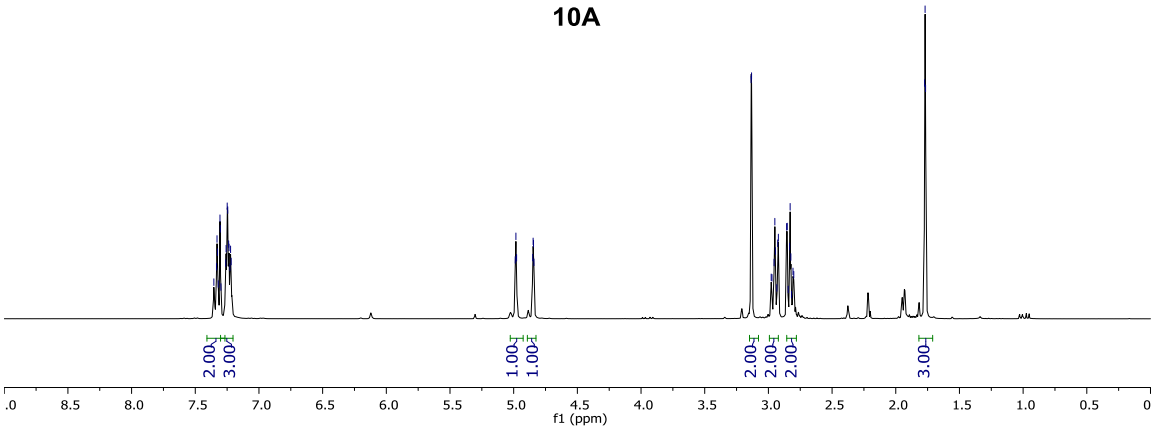

3.00
3.00
1.00
0.80
2.00
2.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

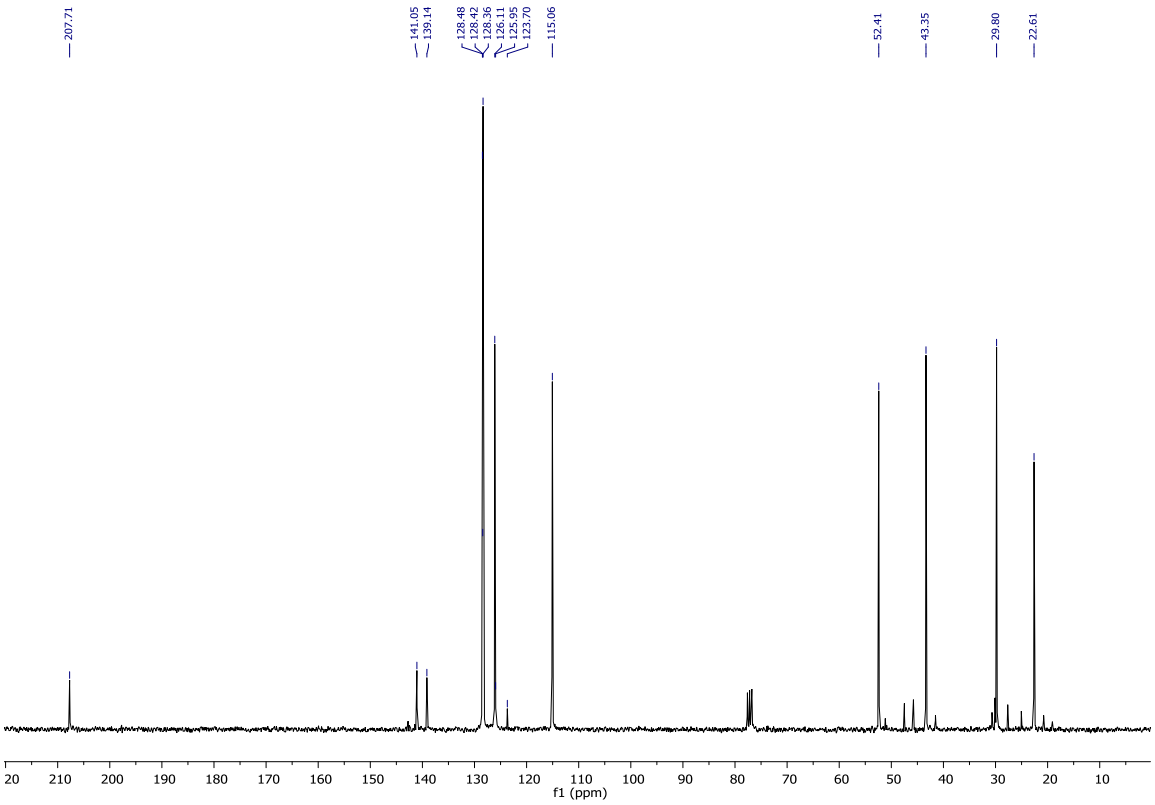

197.55
142.94
134.25
130.76
130.40
130.17
128.79
128.17
125.86
125.33
118.67
45.70
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

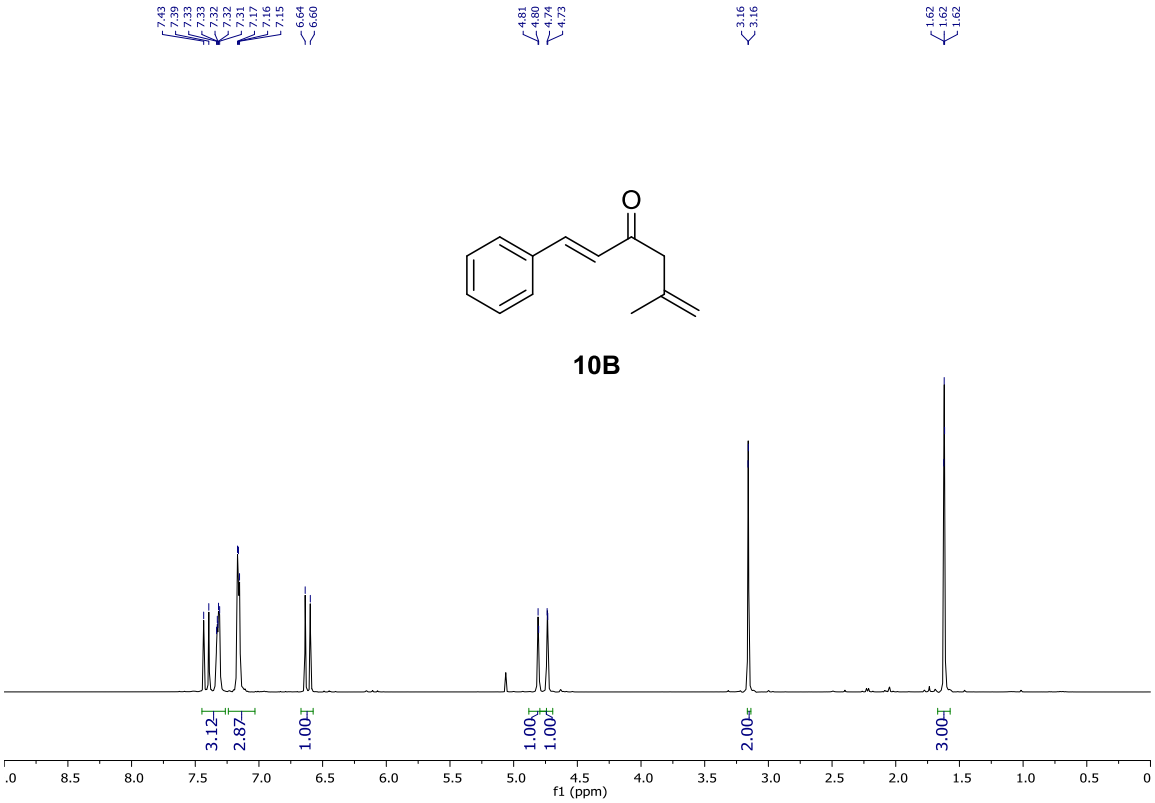

7.35
7.33
7.33
7.33
7.32
7.31
7.30
7.30
7.26
7.26
7.25
7.25
7.24
7.24
7.23
7.22
7.22
4.99
4.98
4.98
4.85
4.85
4.84
4.84
3.14
3.13
2.98
2.97
2.96
2.95
2.95
2.93
2.93
2.92
2.86
2.85
2.84
2.83
2.83
2.82
2.82
2.81
2.80
1.77
1.77
1.77

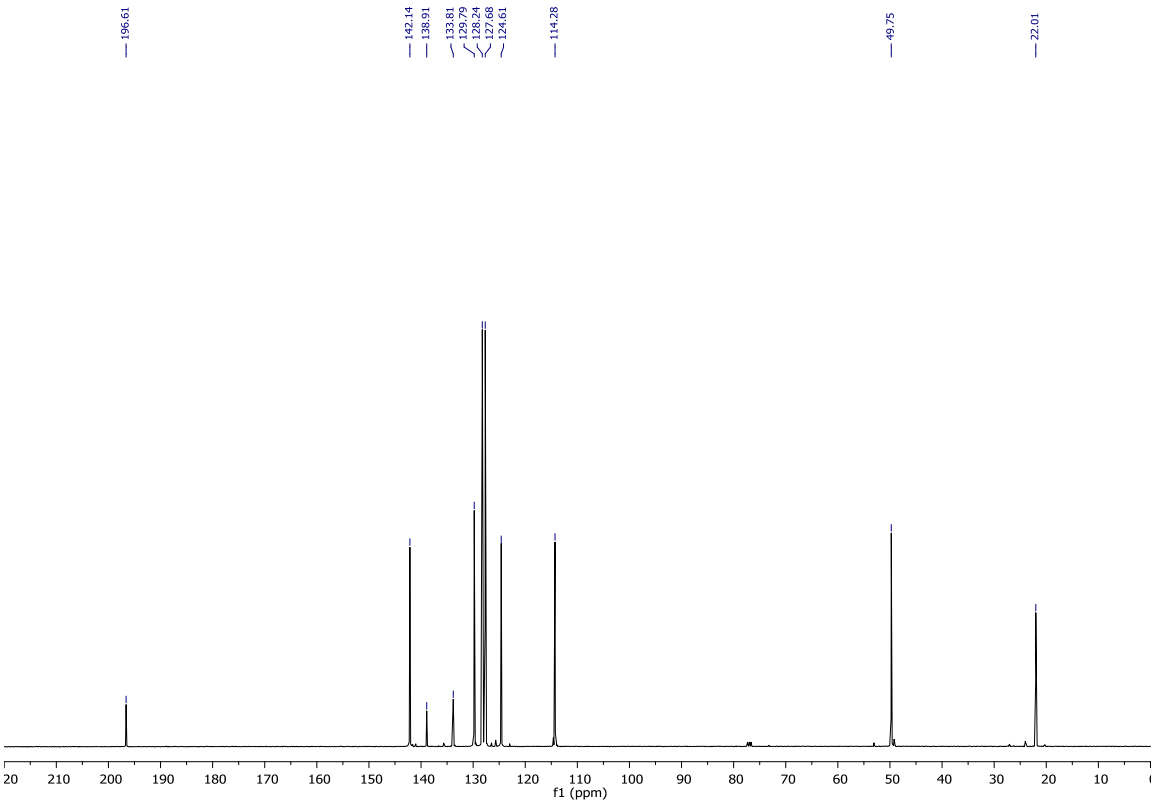

O

10A


2.00
3.00
1.00
1.00
2.00
2.00
2.00
3.00
.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
f1 (ppm)


207.71
141.05
139.14
128.48
128.42
128.36
126.11
125.95
123.70
115.06
52.41
43.35
29.80
22.61
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.43
7.39
7.33
7.32
7.32
7.31
7.17
7.16
7.15
6.64
6.60
4.81
4.80
4.74
4.73
3.16
3.16
1.62
1.62
1.62
O
10B
3.12
2.87
1.00
1.00
1.00
2.00
3.00
f1 (ppm)


196.61
142.14
138.91
133.81
129.79
128.24
127.68
124.61
114.28
49.75
22.01
f1 (ppm)


7.86
7.86
7.85
7.85
7.85
7.84
7.84
7.83
7.82
7.81
7.81
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.30
7.29
7.28
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7.26
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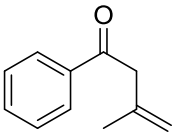
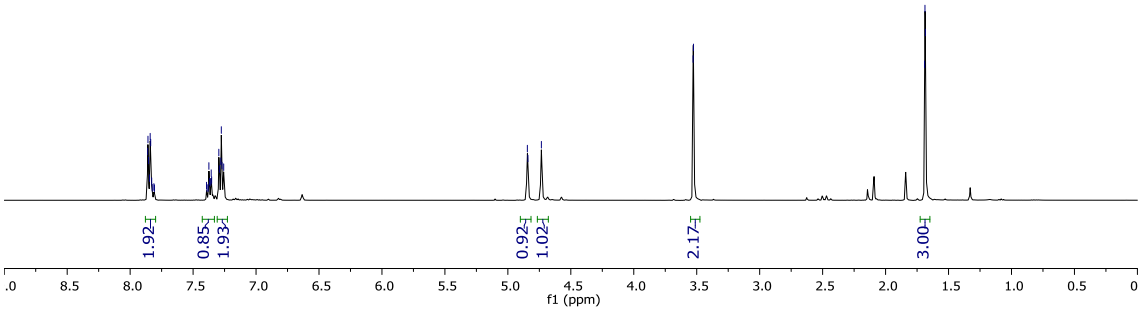
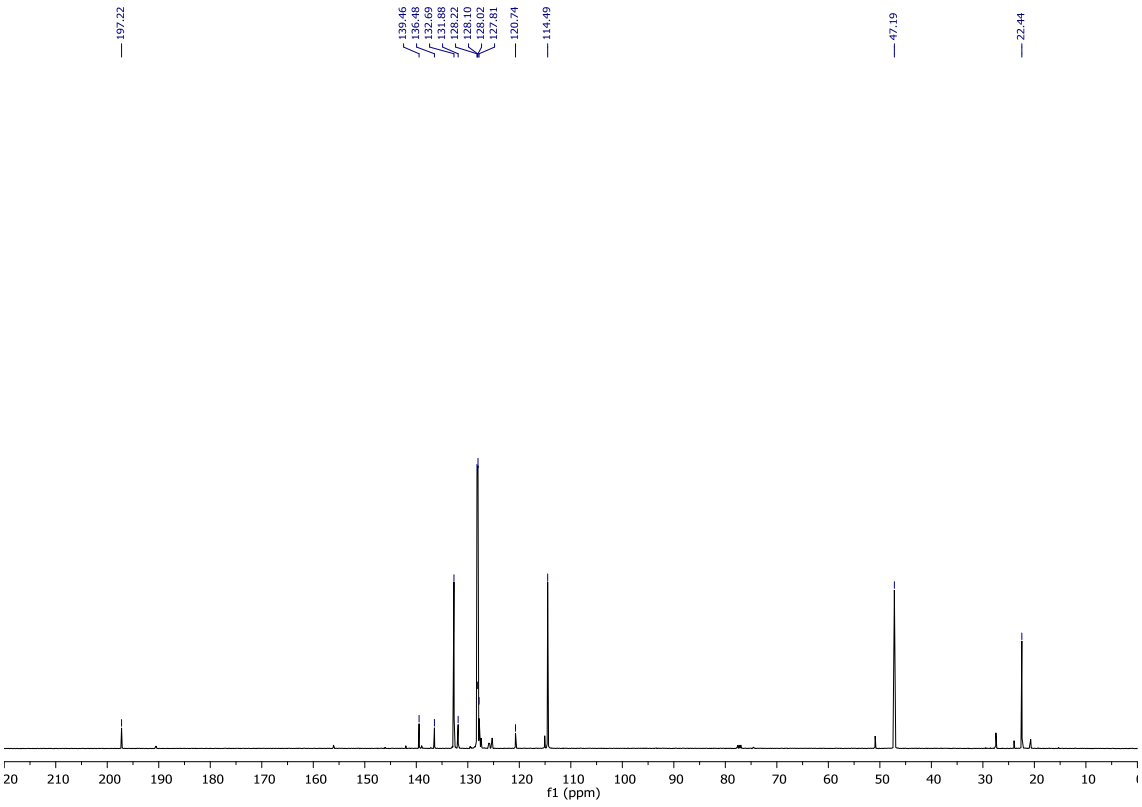
4.84
4.73
3.53
3.53
1.69
1.69
1.68


O

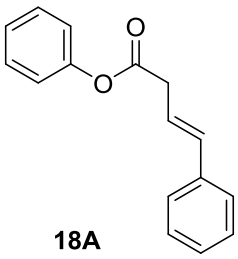
10C


1.92
0.85
1.93
0.92
1.02
2.17
3.00
f1 (ppm)

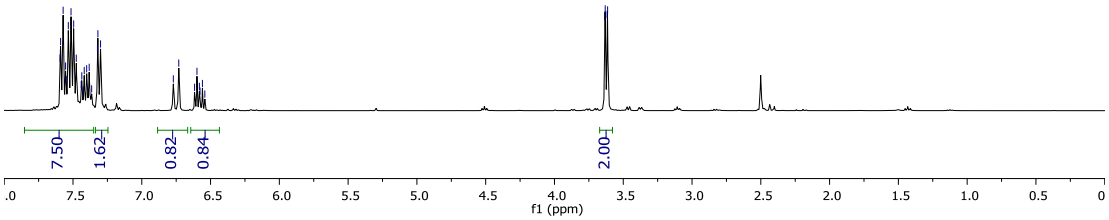

197.22
139.46
136.48
132.69
131.88
128.22
128.10
128.02
127.81
120.74
114.49
47.19
22.44
f1 (ppm)


7.59
7.59
7.57
7.57
7.55
7.55
7.53
7.51
7.50
7.48
7.44
7.44
7.42
7.42
7.40
7.38
7.36
7.32
7.32
7.30
6.77
6.73
6.62
6.60
6.58
6.58
6.56
6.54


3.63
3.63
3.62
3.61

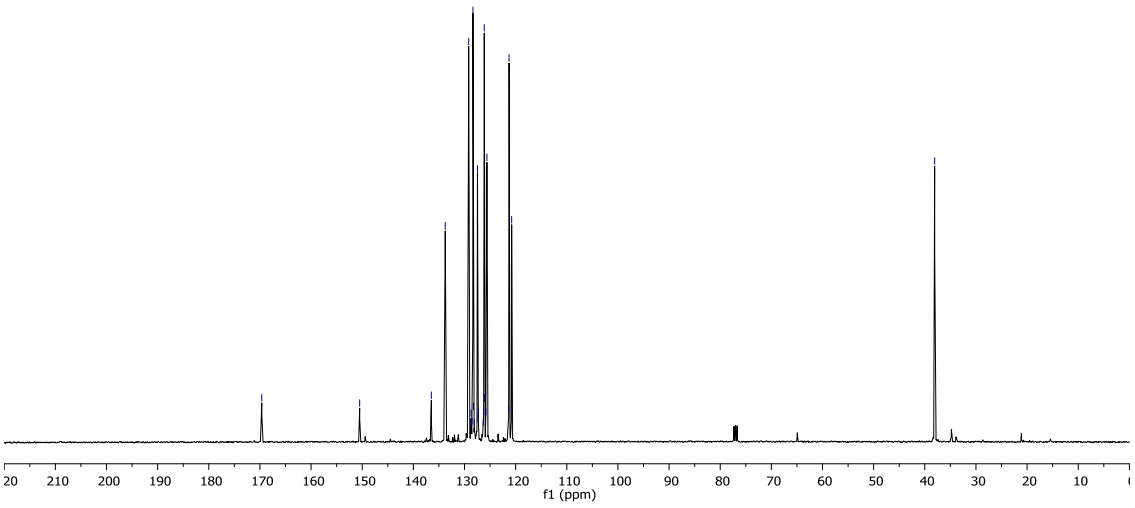

O
O

18A

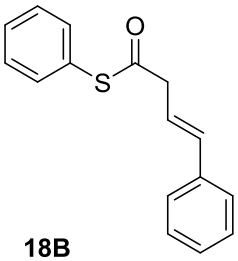

7.50
1.62
0.82
0.84
2.00
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


169.64
150.50
136.49
133.77
129.19
128.69
128.62
128.52
128.35
128.25
128.09
127.47
127.36
127.31
126.33
126.26
126.14
126.07
125.83
125.62
121.37
121.28
120.78

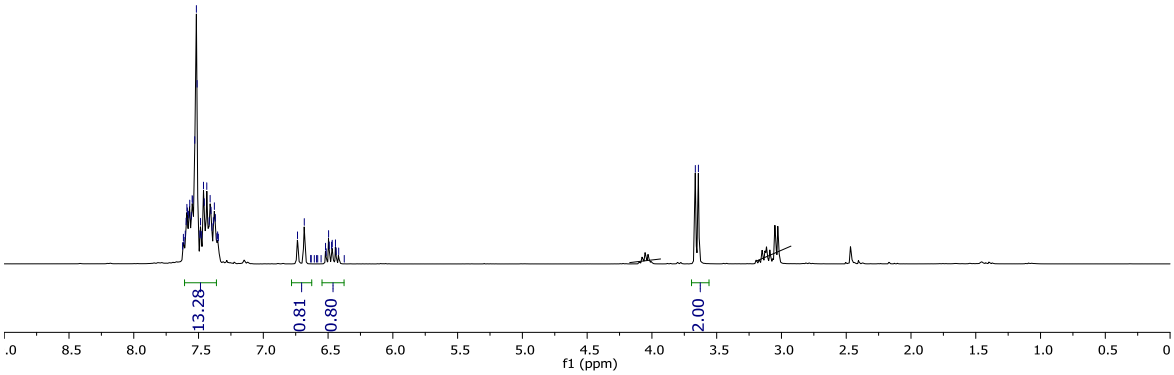
38.07

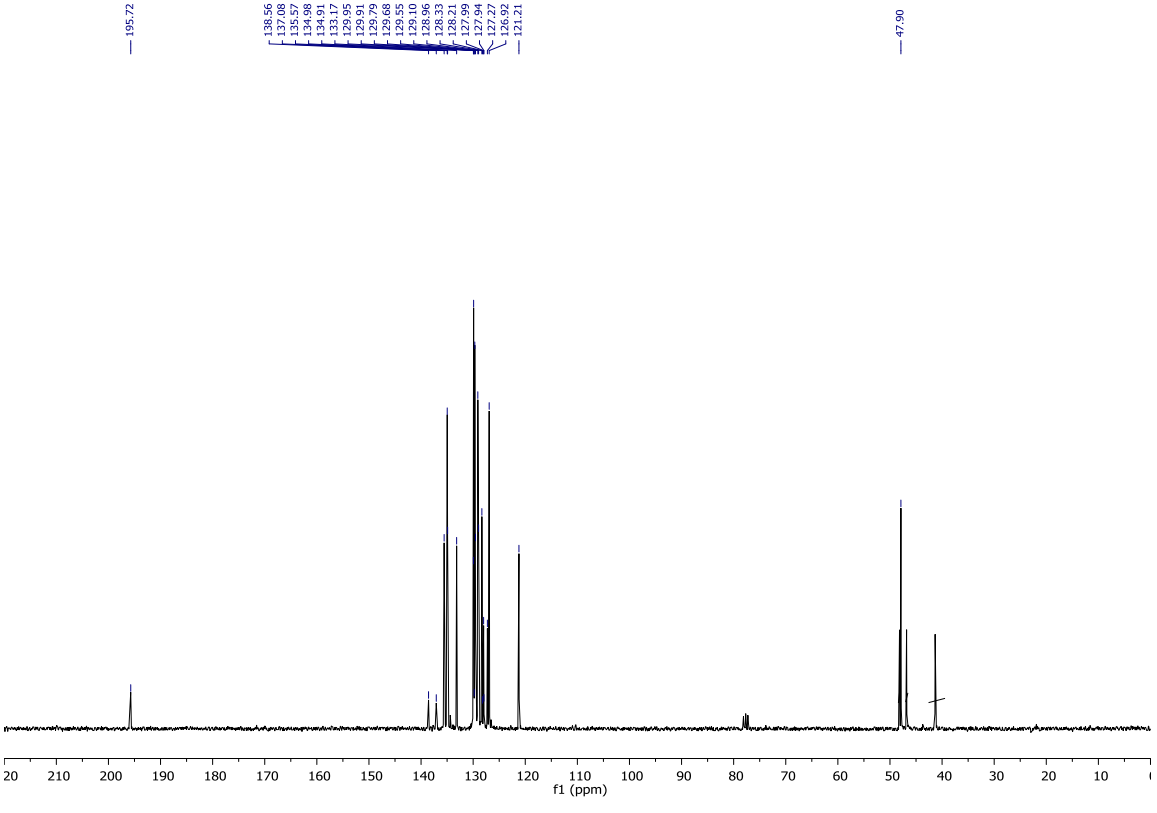

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

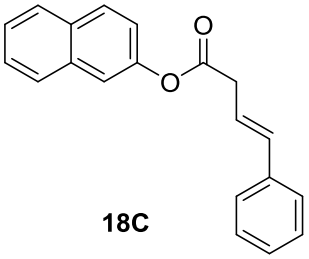

7.62
7.62
7.61
7.60
7.60
7.59
7.59
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.51
7.49
7.48
7.48
7.46
7.46
7.44
7.42
7.41
7.40
7.40
7.39
7.38
7.37
7.36
7.35
7.35
6.74
6.68
6.63
6.63
6.61
6.59
6.58
6.55
6.52
6.51
6.50
6.49
6.47
6.47
6.44
6.44
6.42
6.38
3.66
3.64


O
S

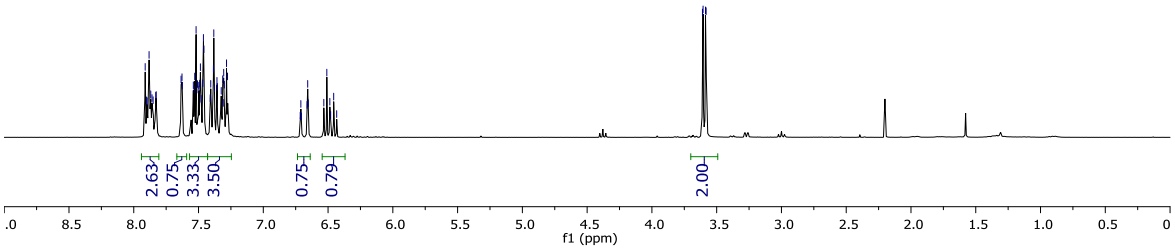
18B

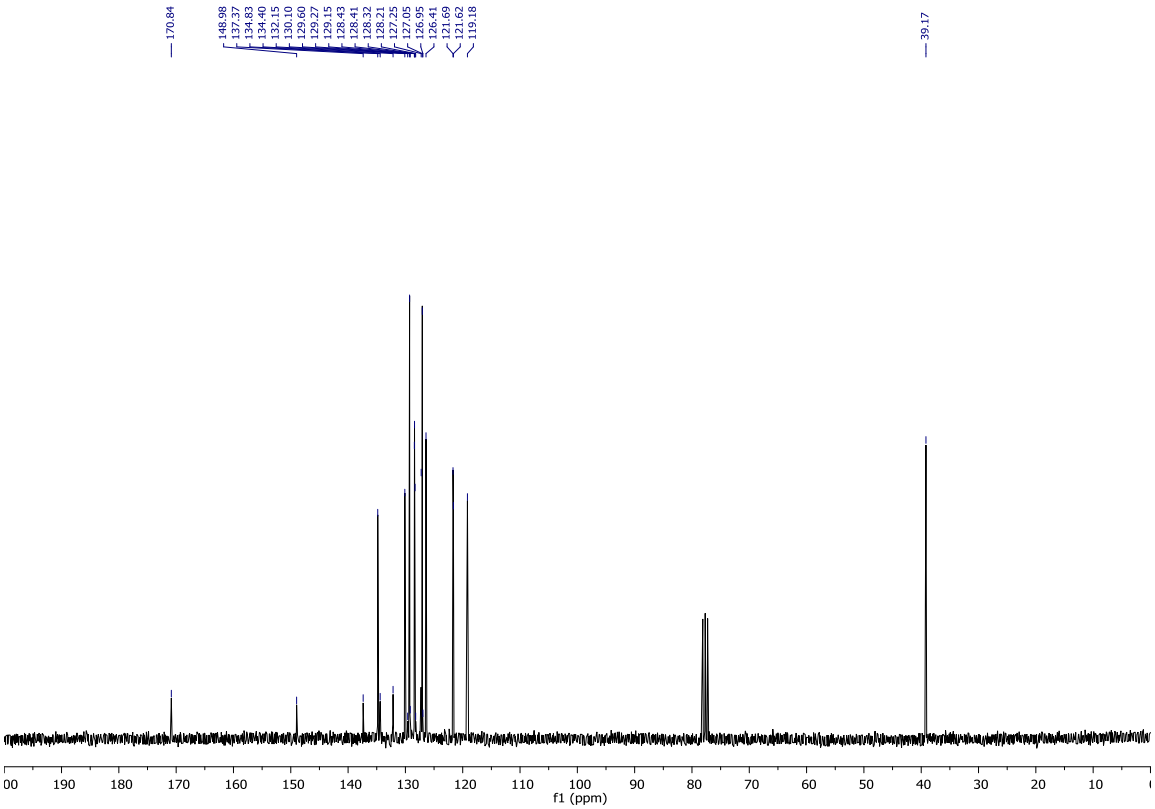

13.28
0.81
0.80
2.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


195.72
138.56
137.08
135.57
134.98
134.91
133.17
129.95
129.91
129.79
129.68
129.55
129.10
128.96
128.33
128.21
127.99
127.94
127.77
126.92
121.21
47.90
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

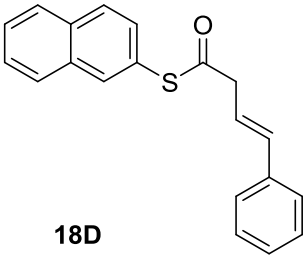


18C

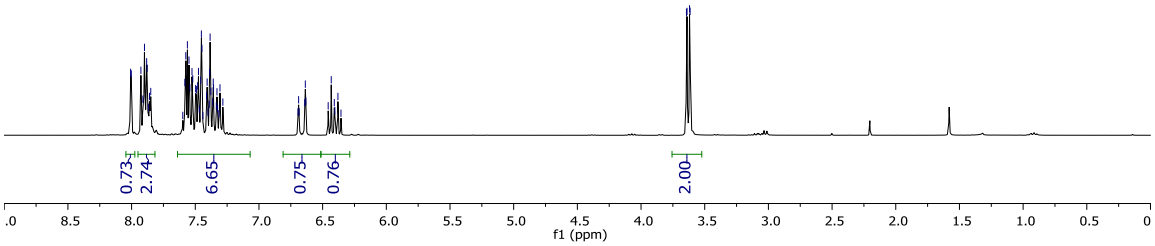

2.63
0.75
3.33
3.50
0.75
0.79
2.00
f1 (ppm)

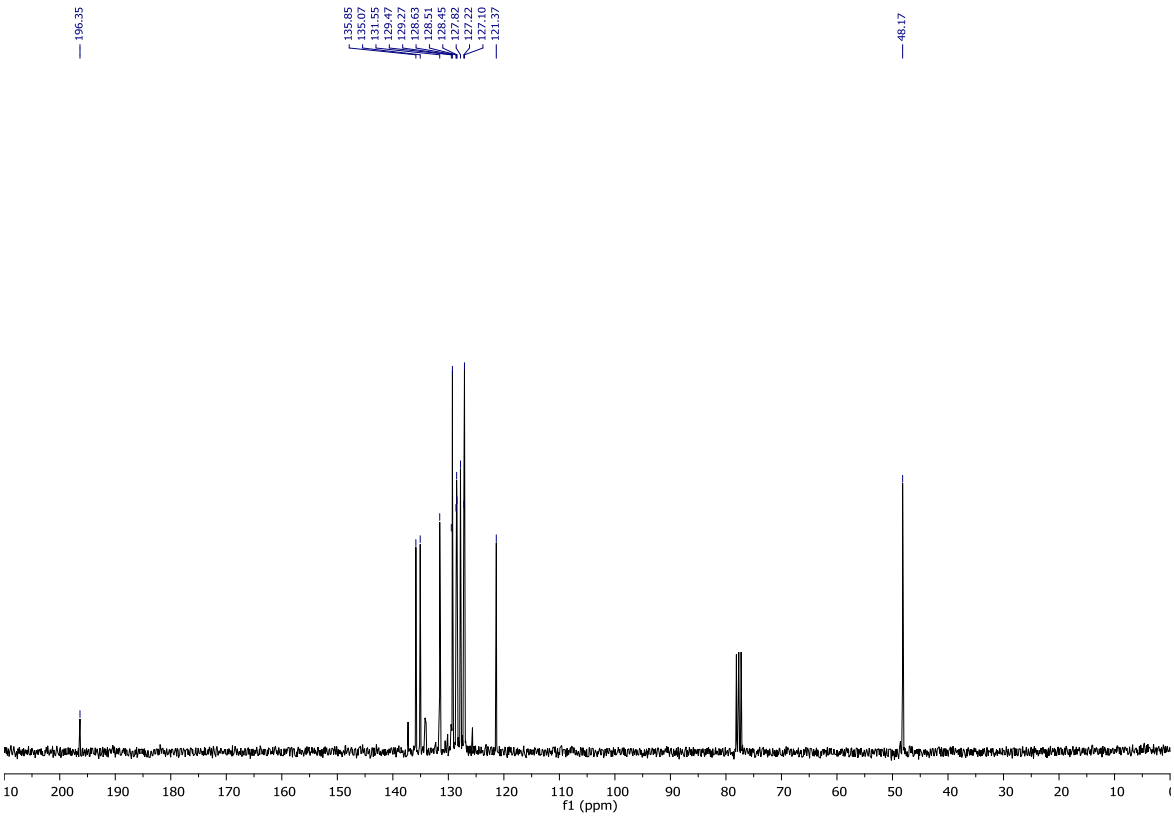

170.84
148.98
137.37
134.83
134.40
132.15
130.10
129.60
129.27
129.15
128.43
128.41
128.32
128.21
127.25
127.05
126.95
126.41
121.69
121.62
119.18
39.17
f1 (ppm)

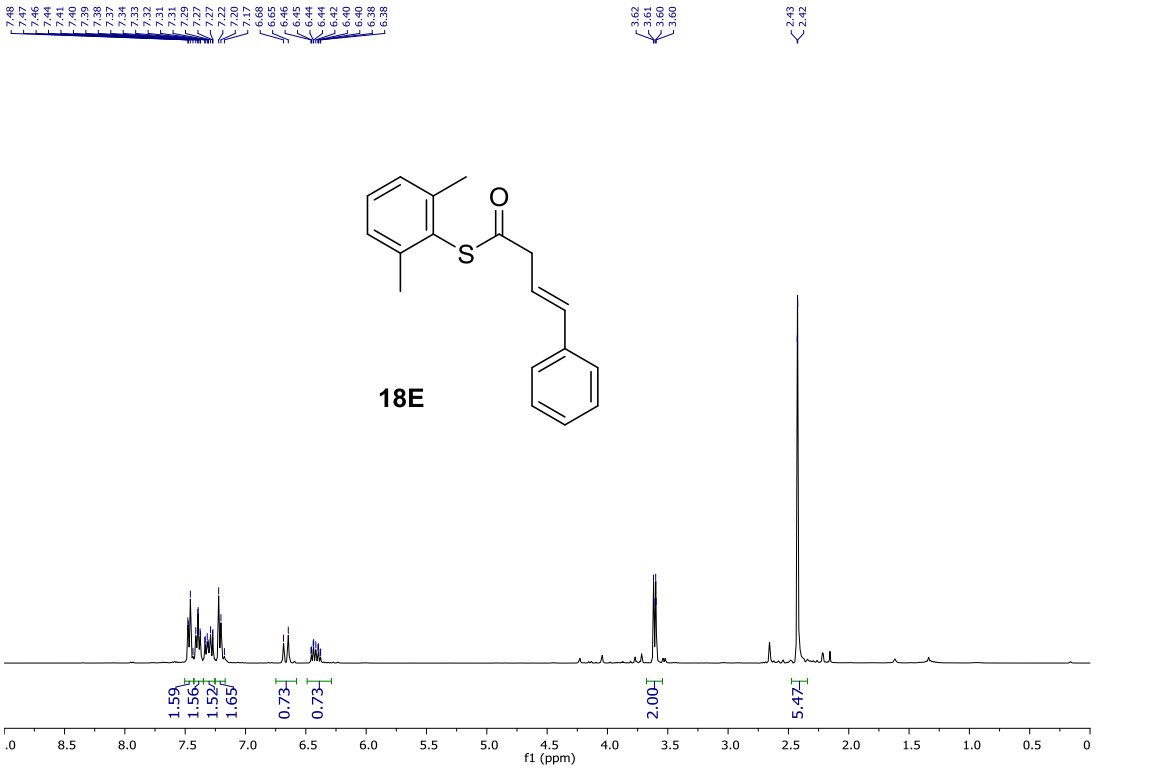

8.01
8.00
7.93
7.91
7.90
7.88
7.88
7.87
7.86
7.85
7.60
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.50
7.49
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.36
7.36
7.33
7.33
7.32
7.31
7.31
7.28
6.69
6.69
6.68
6.64
6.64
6.63
6.46
6.43
6.41
6.40
6.38
6.36
3.64
3.64
3.62
3.61

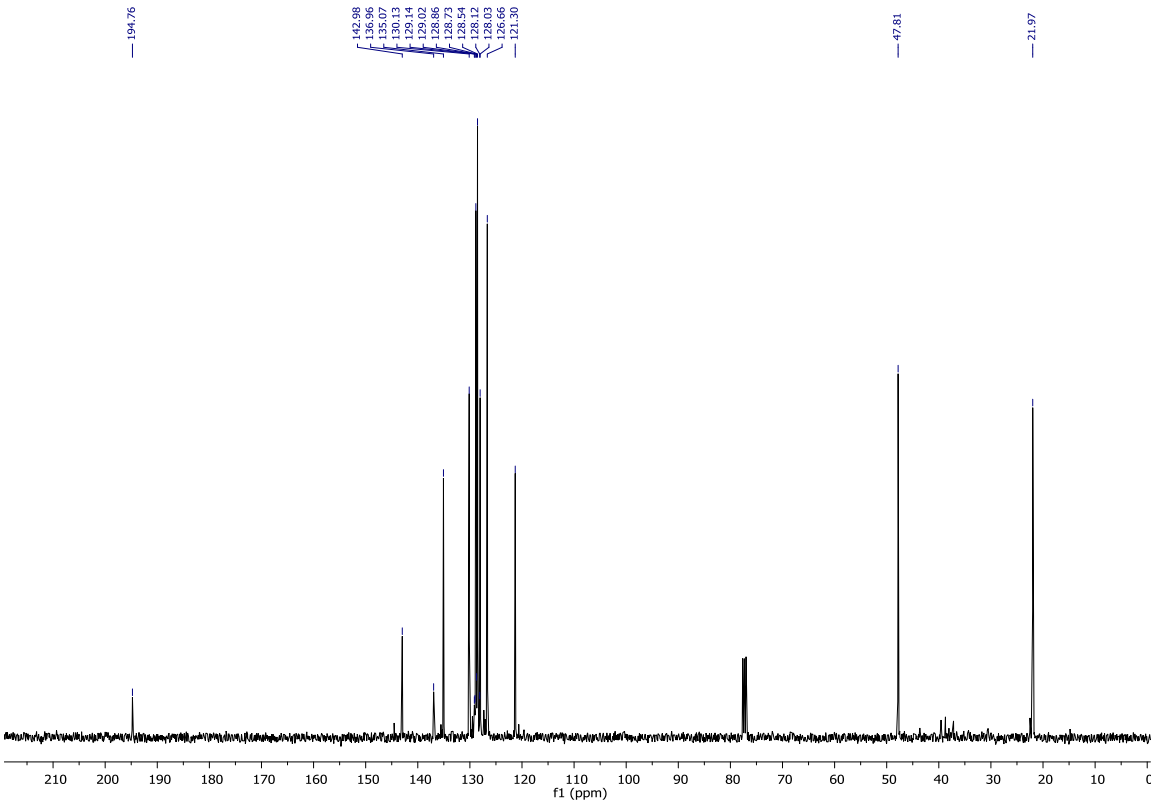

O
S

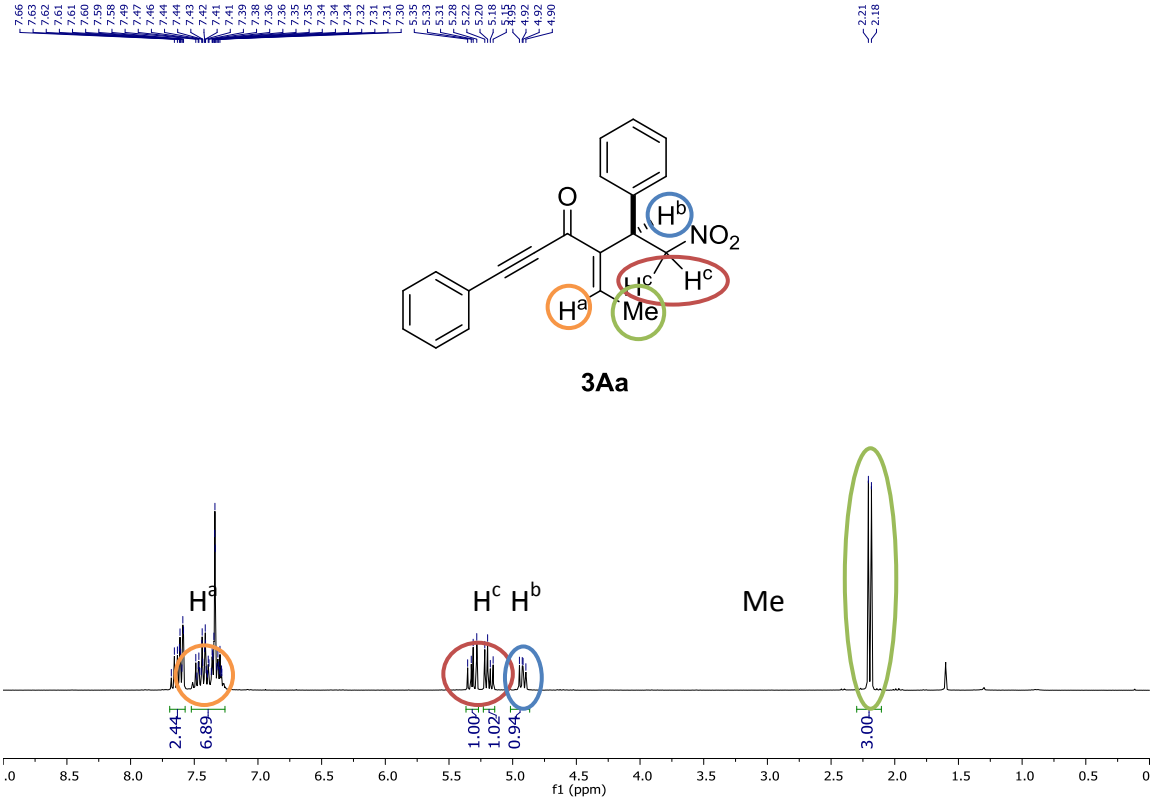
18D


0.73
2.74
6.65
0.75
0.76
2.00
.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
f1 (ppm)

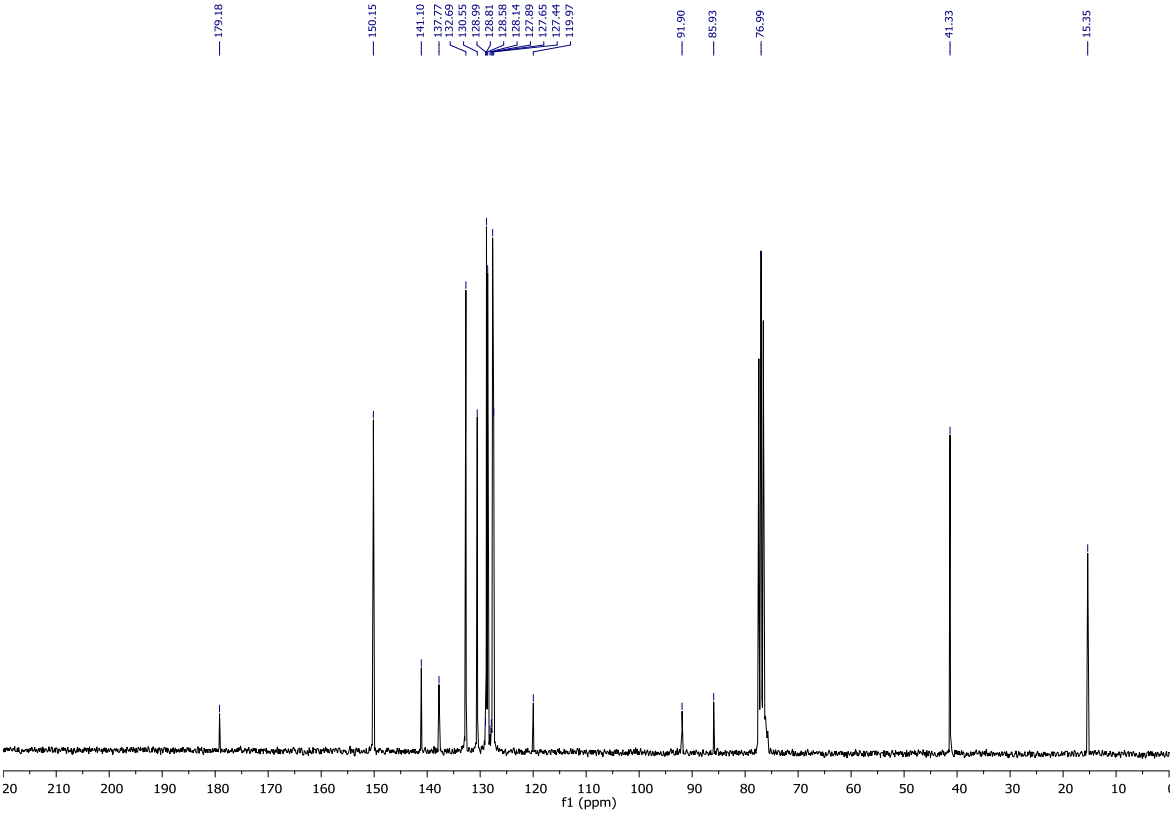

196.35
135.85
135.07
131.55
129.47
129.27
128.63
128.51
128.45
127.82
127.22
127.10
121.37
48.17
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

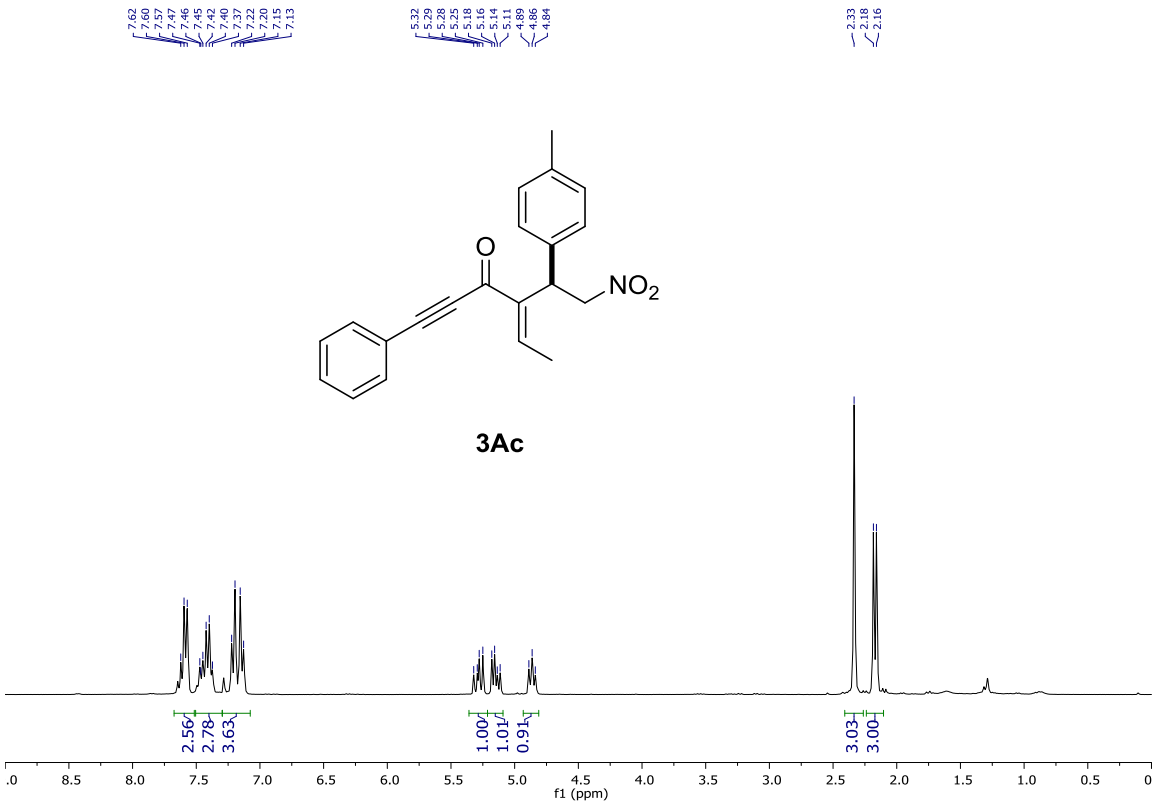

7.48
7.47
7.46
7.44
7.41
7.40
7.39
7.38
7.37
7.34
7.33
7.32
7.31
7.29
7.27
7.27
7.22
7.20
7.17
6.68
6.65
6.46
6.45
6.44
6.44
6.42
6.40
6.40
6.38
6.38
3.62
3.61
3.60
3.60
2.43
2.42
O
S
18E
1.59
1.56
1.52
1.65
0.73
0.73
2.00
5.47
f1 (ppm)


194.76
142.98
136.96
135.07
130.13
129.14
129.02
128.86
128.73
128.54
128.12
128.03
126.66
121.30
47.81
21.97
f1 (ppm)

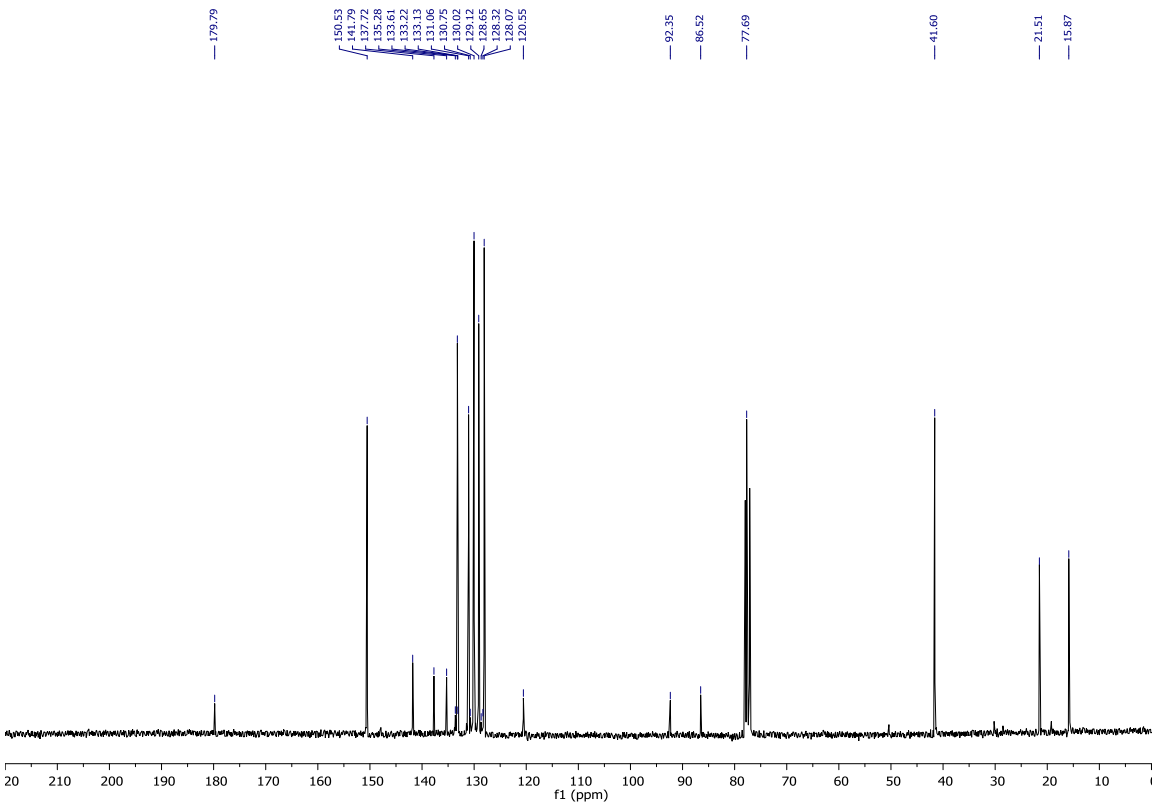

O
H^b
NO_2
H^c
H^c
H^a
Me
H^a
H^c H^b
Me
2.44
6.89
1.00
1.02
0.94
3.00
f1 (ppm)

3Aa

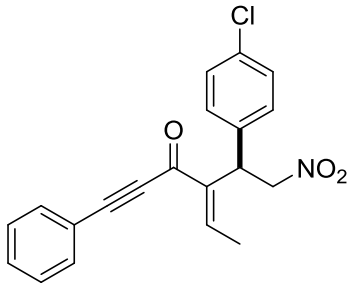

179.18
150.15
141.10
137.77
137.69
130.55
128.99
128.81
128.58
128.14
127.89
127.65
127.44
119.97
91.90
85.93
76.99
41.33
15.35
f1 (ppm)


7.62
7.60
7.57
7.47
7.46
7.45
7.42
7.40
7.37
7.22
7.20
7.15
7.13
5.32
5.29
5.28
5.25
5.18
5.16
5.14
5.11
4.89
4.86
4.84
2.33
2.18
2.16
O
NO2
2.56
2.78
3.63
1.00
1.01
0.91
3.03
3.00
f1 (ppm)

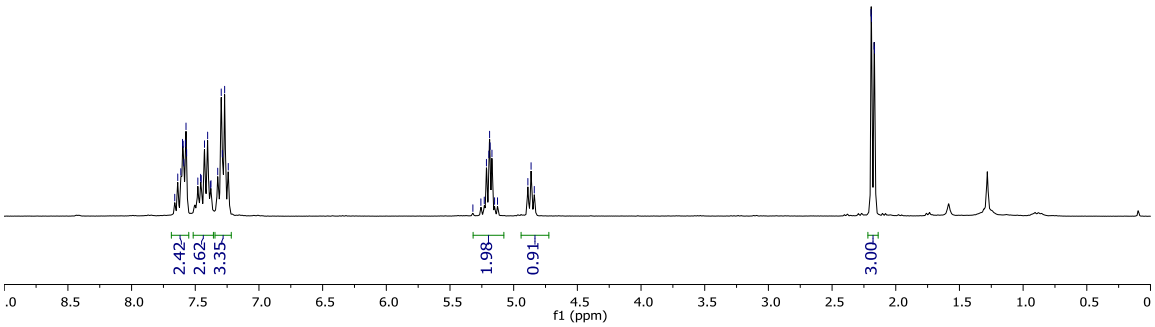
3Ac

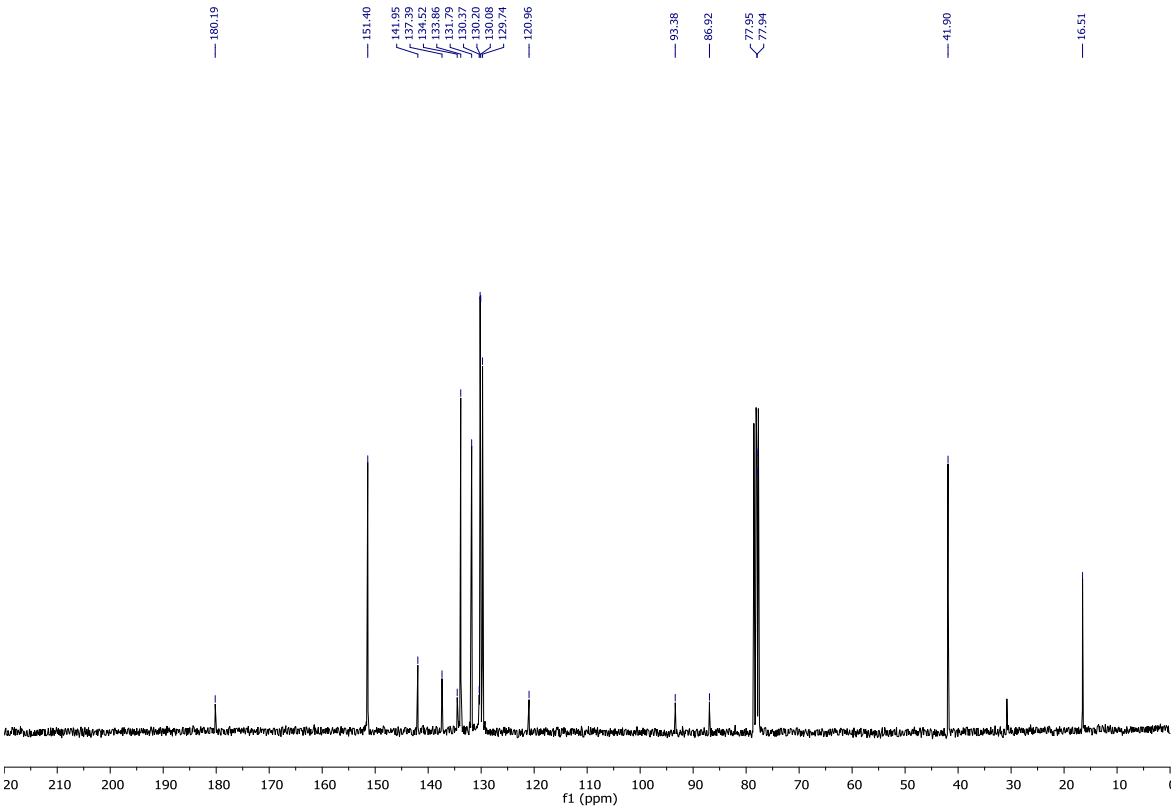

179.79
150.53
141.79
137.72
135.28
133.61
133.22
133.13
131.06
130.75
130.03
129.12
128.65
128.32
128.07
120.55
92.35
86.52
77.69
41.60
21.51
15.87
f1 (ppm)

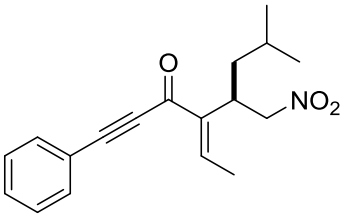

7.66
7.64
7.61
7.60
7.60
7.59
7.58
7.57
7.57
7.48
7.46
7.45
7.43
7.40
7.38
7.32
7.30
7.29
7.27
7.24
5.32
5.26
5.23
5.21
5.19
5.19
5.18
5.17
5.15
5.13
4.89
4.86
4.84
2.19
2.19
2.17
2.17


Cl
O
NO2

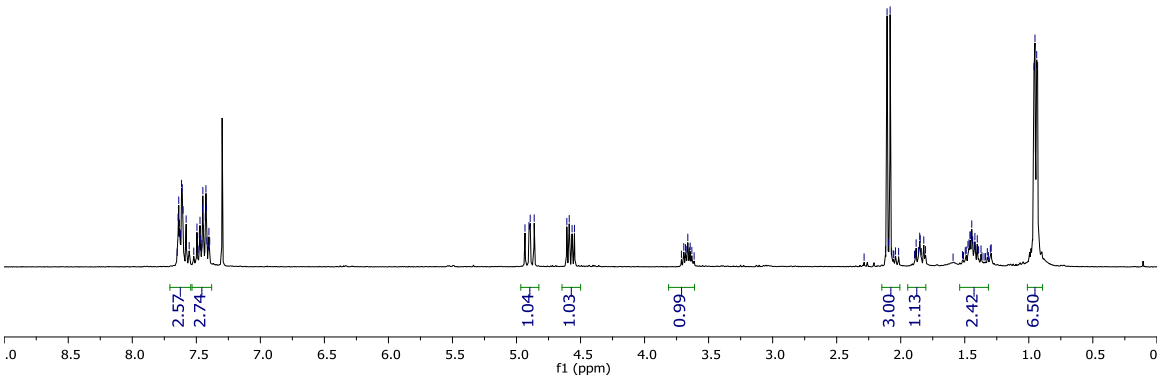
3Ad

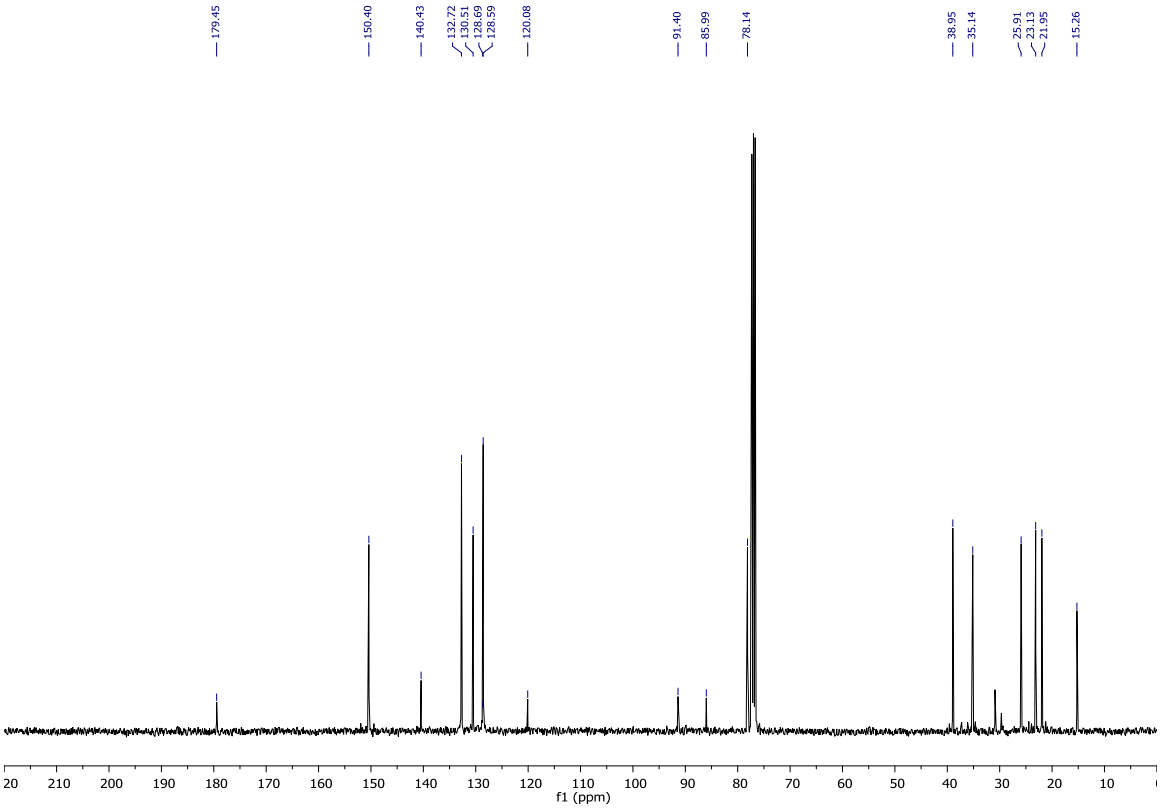

2.42
2.62
3.35
1.98
0.91
3.00
f1 (ppm)

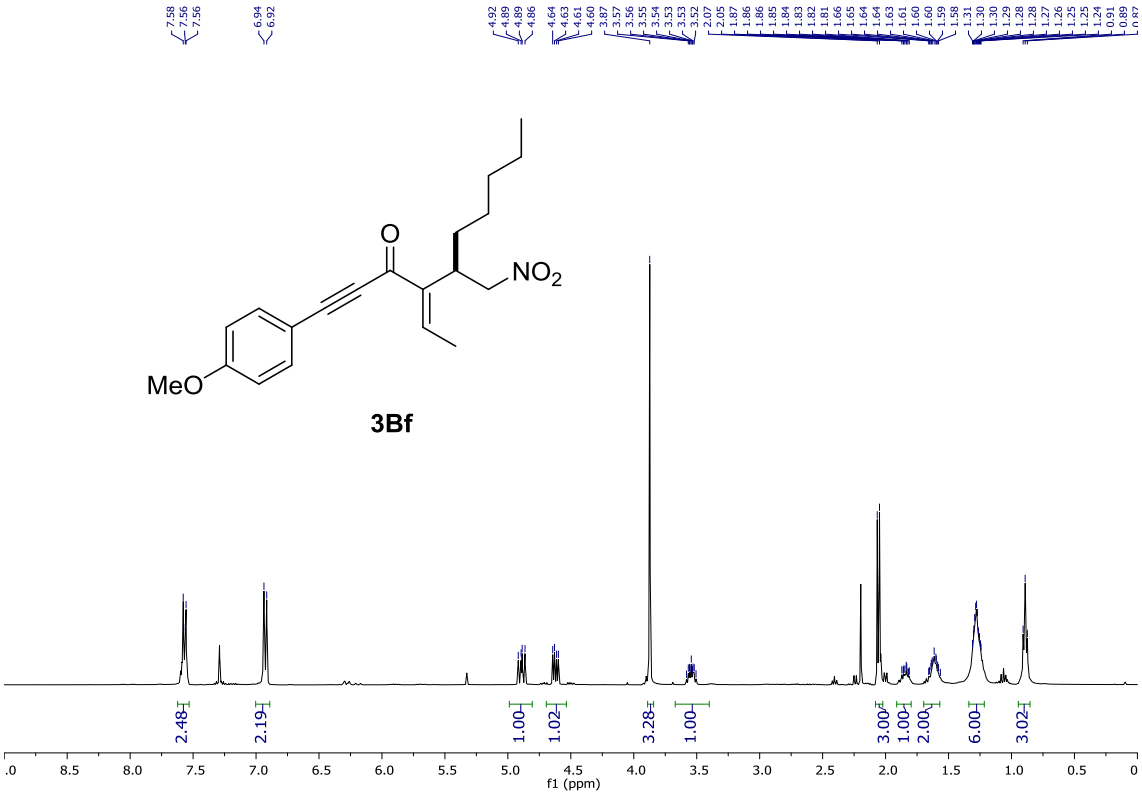

180.19
151.40
141.95
137.39
134.52
131.86
131.79
130.37
130.20
130.08
129.74
120.96
93.38
86.92
77.95
77.94
41.90
16.51
f1 (ppm)

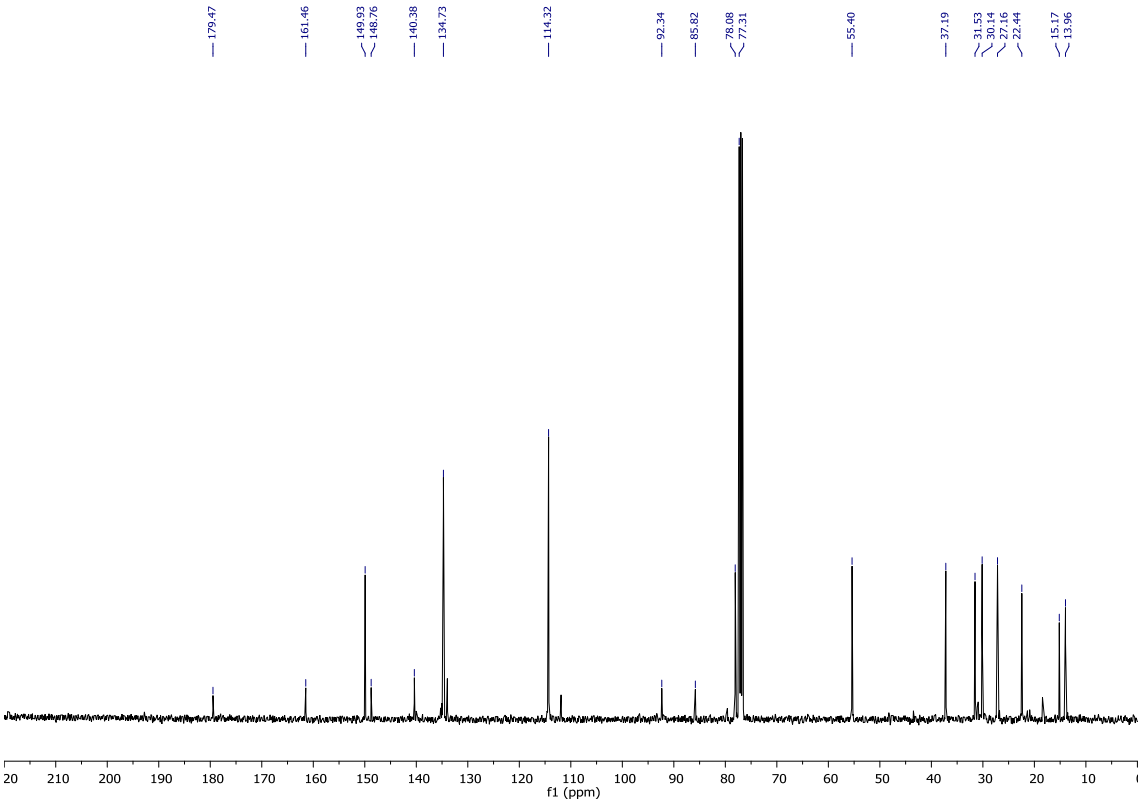

O
NO2

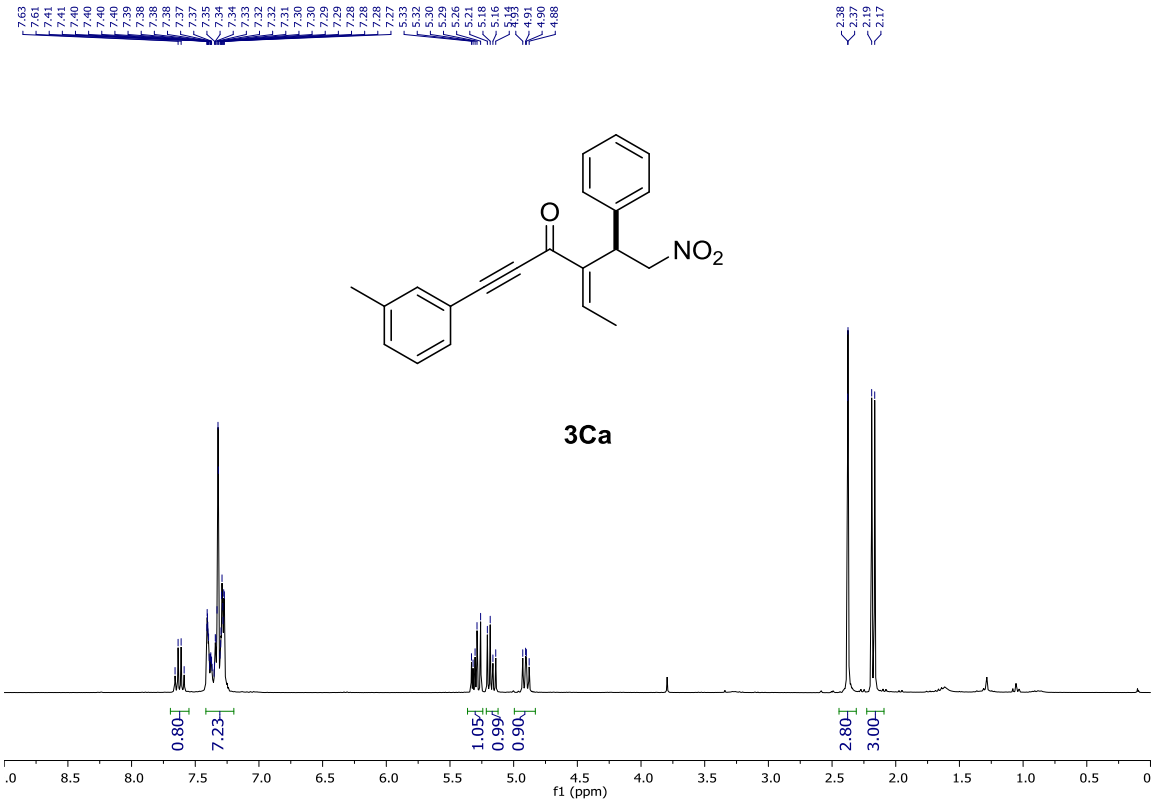
3Ae

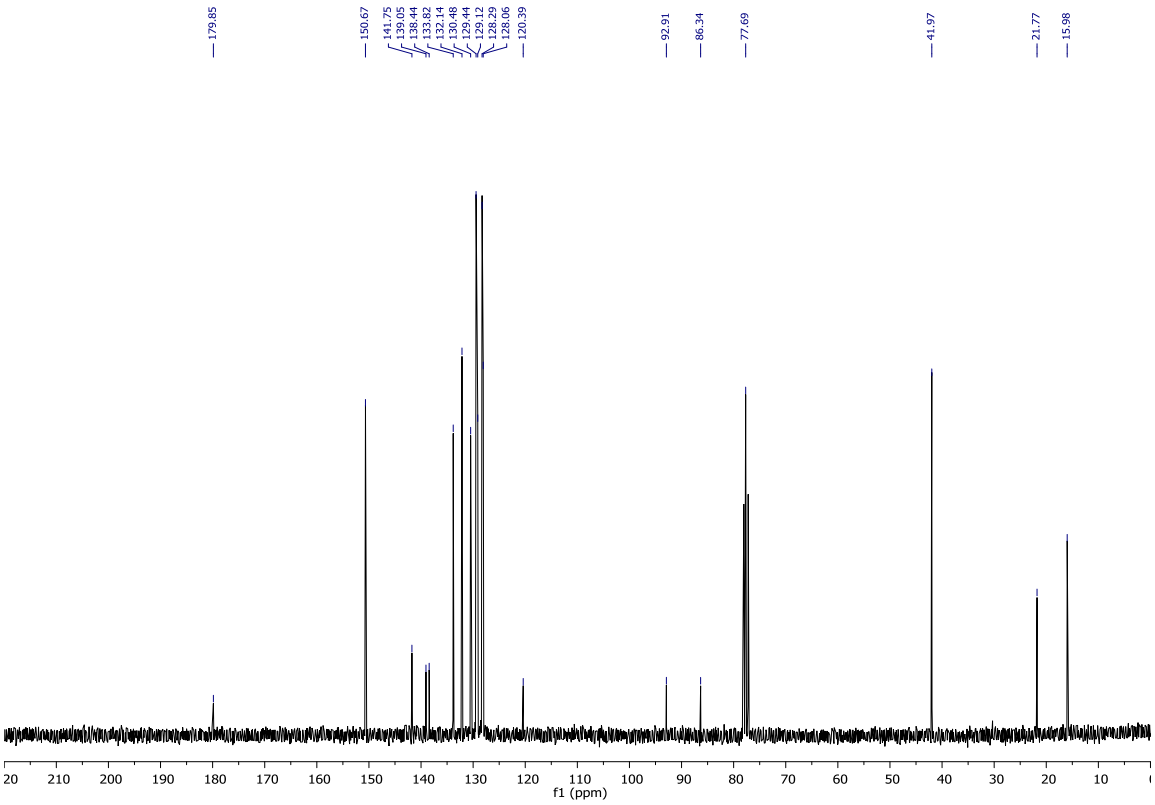

2.57
2.74
1.04
1.03
0.99
3.00
1.13
2.42
6.50
f1 (ppm)

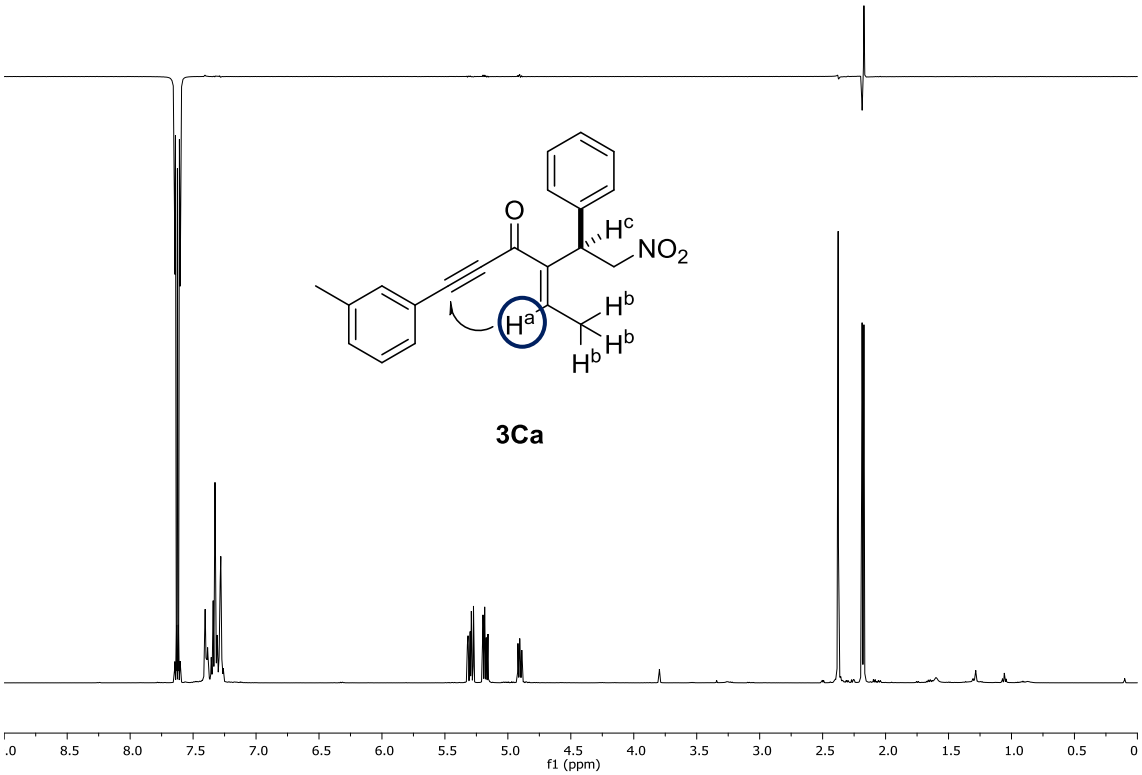

179.45
150.40
140.43
132.72
130.51
128.69
128.59
120.08
91.40
85.99
78.14
38.95
35.14
25.91
23.13
21.95
15.26
f1 (ppm)


O
NO2
MeO
3Bf
f1 (ppm)

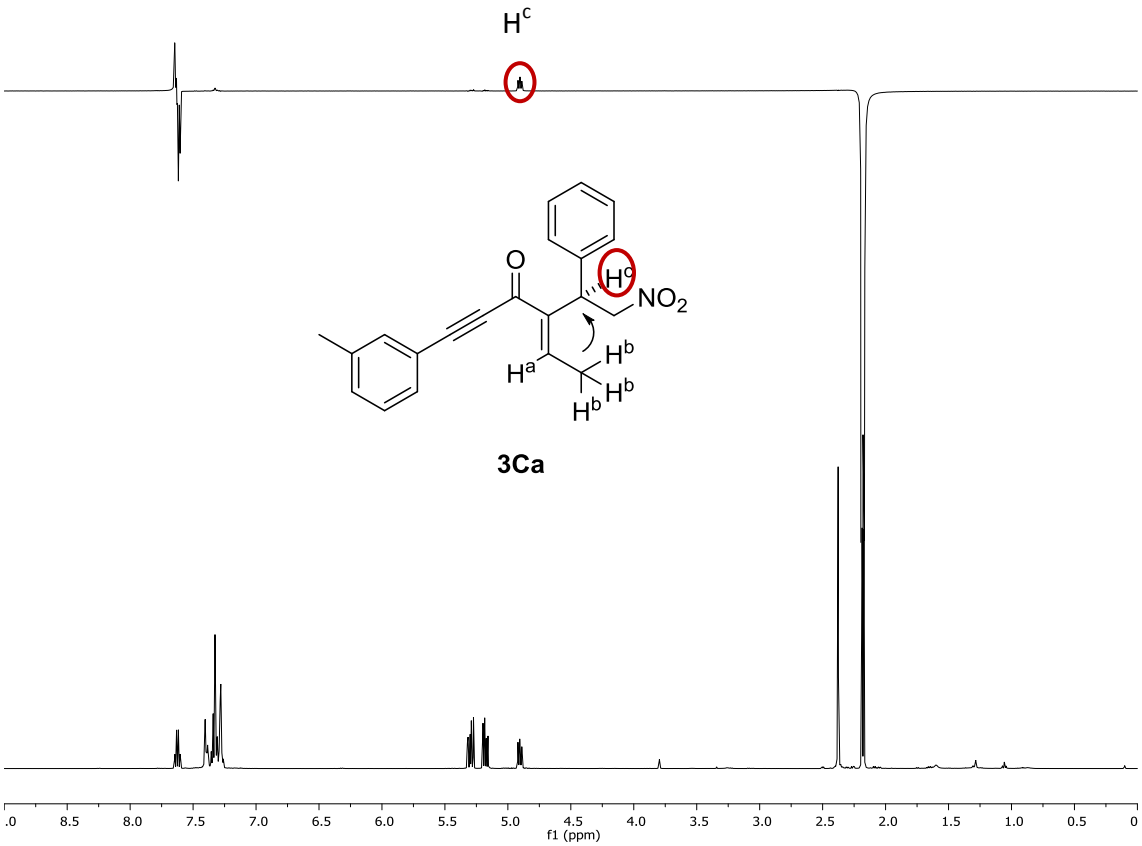

f1 (ppm)


O
NO2
3Ca
f1 (ppm)

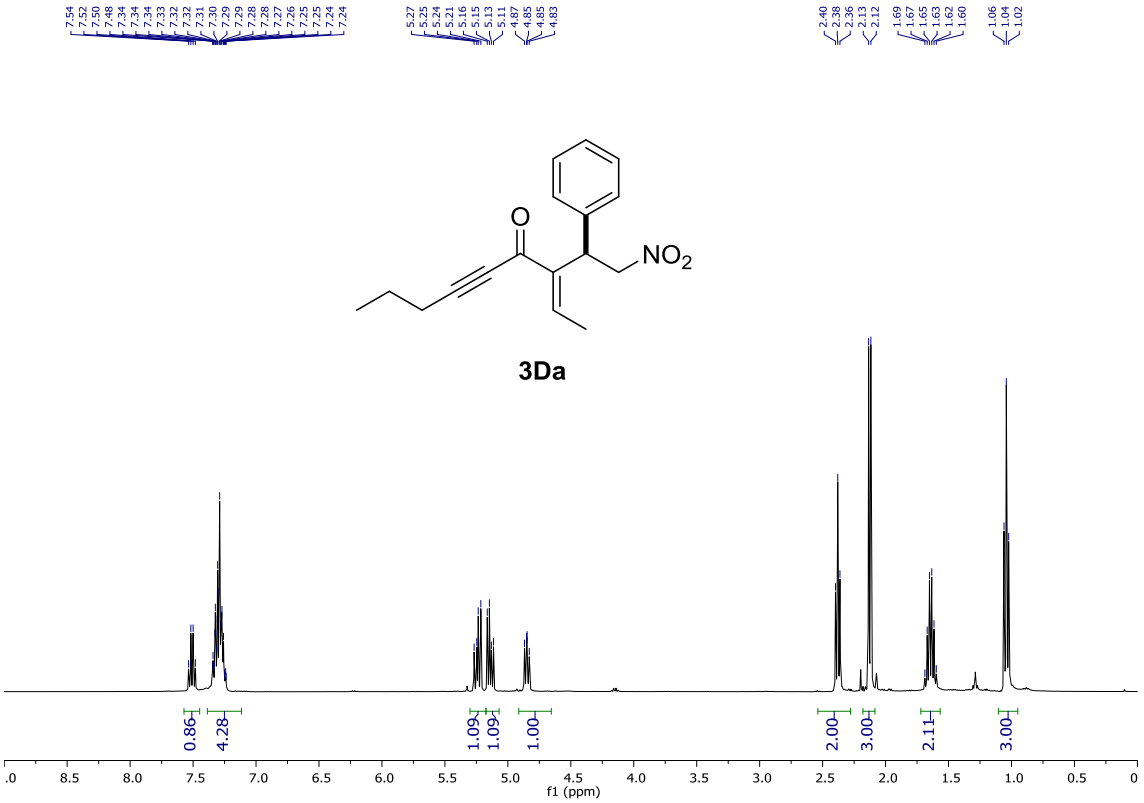

f1 (ppm)

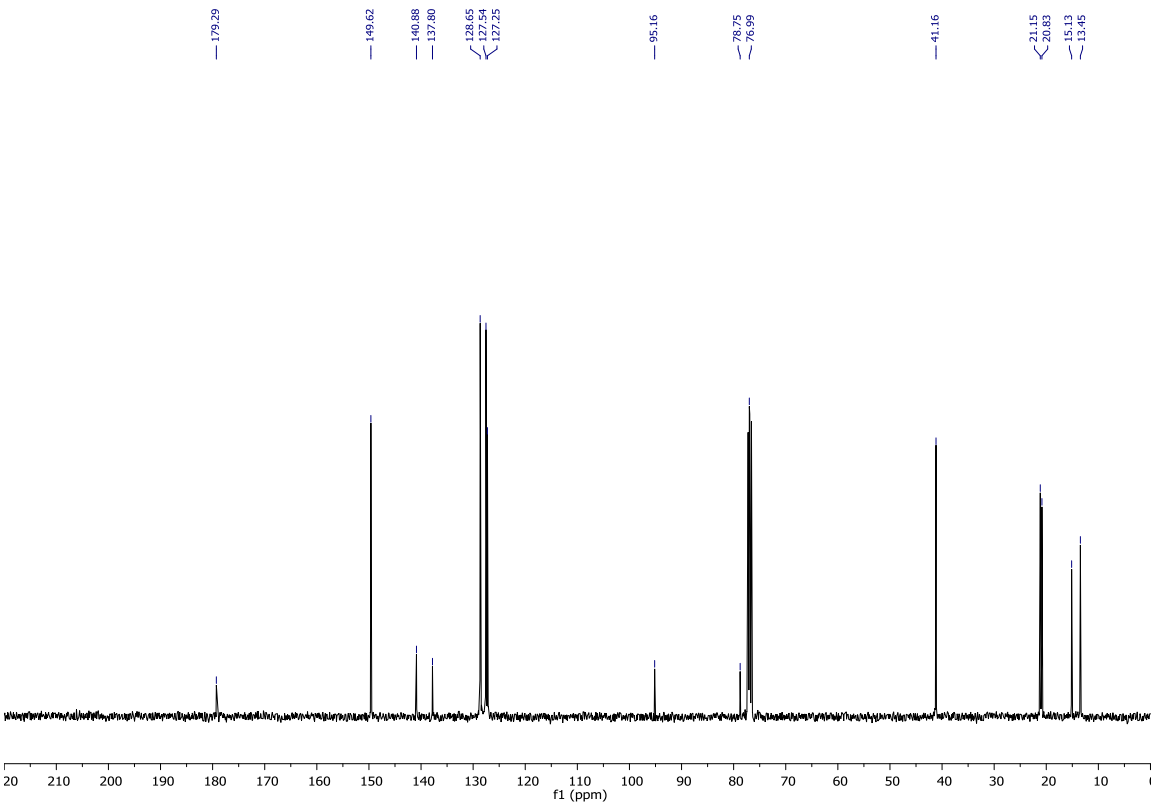


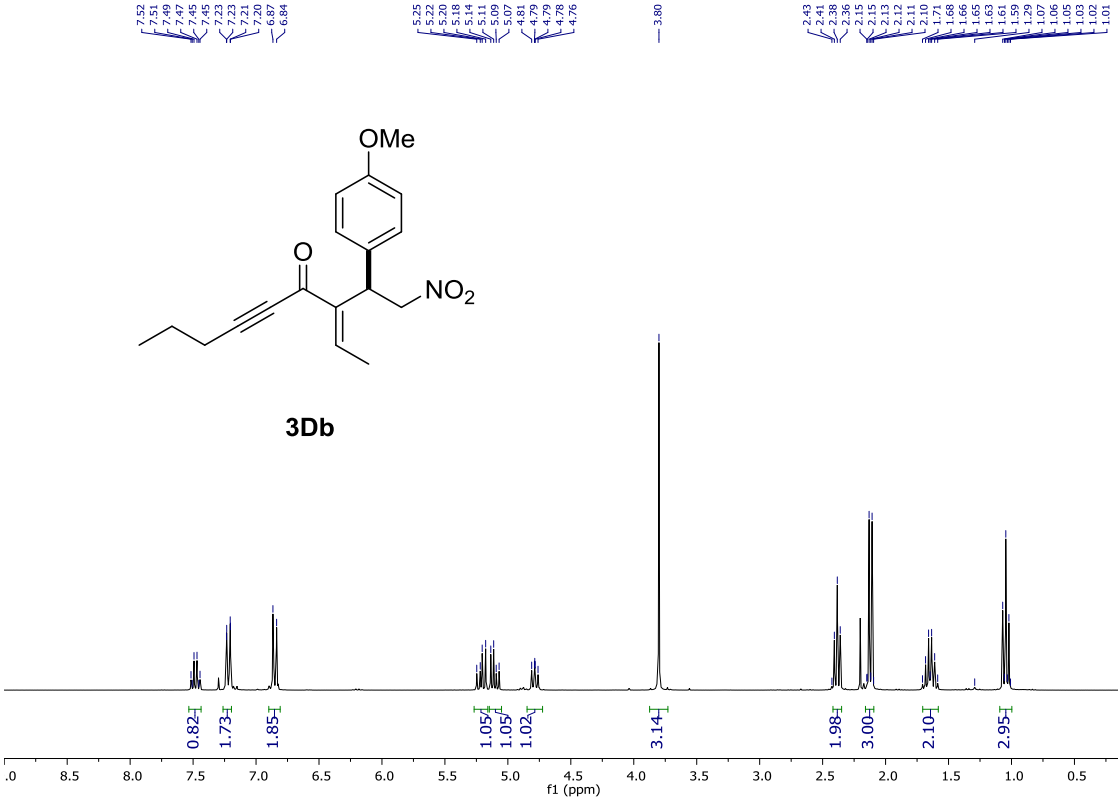
3Ca

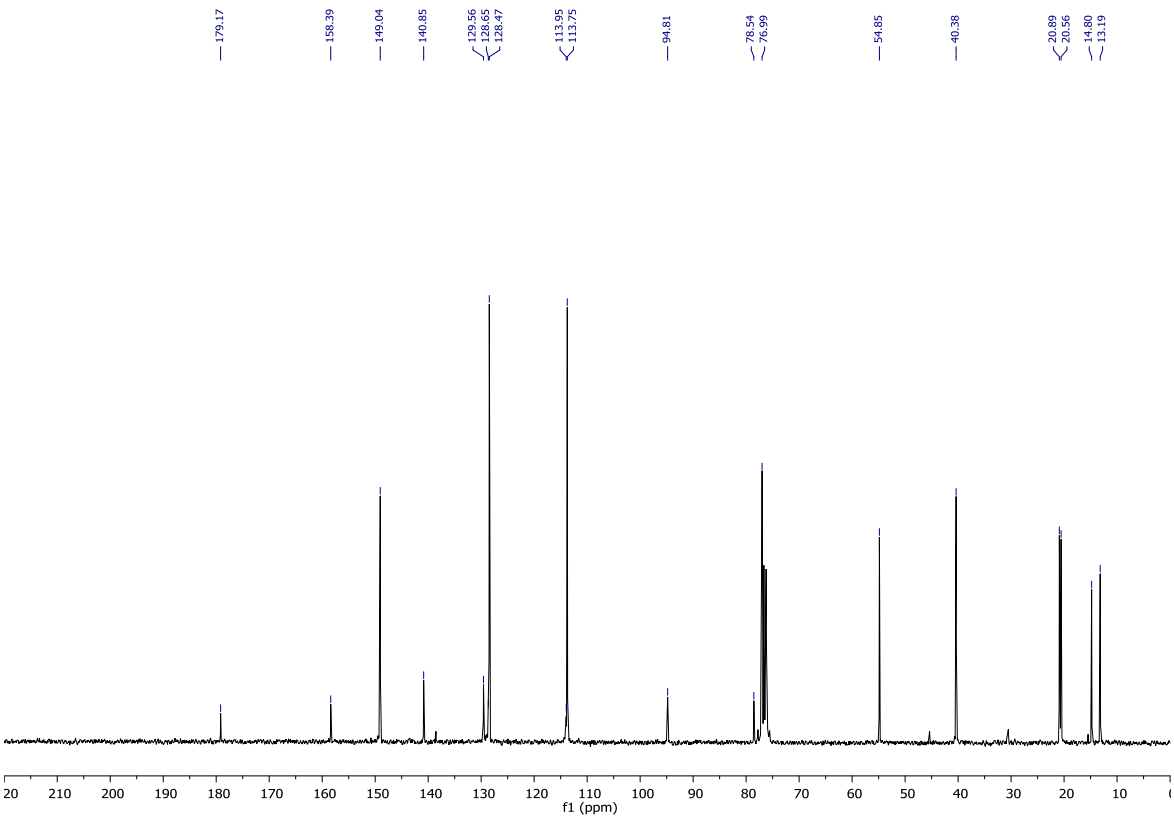


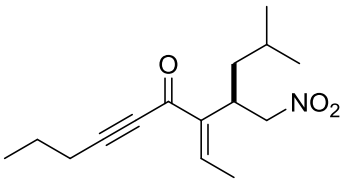
3Ca


7.54
7.52
7.50
7.48
7.34
7.34
7.34
7.33
7.32
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.25
7.24
7.24
5.27
5.25
5.24
5.21
5.16
5.15
5.13
5.11
4.87
4.85
4.85
4.83
2.40
2.38
2.36
2.13
2.12
1.69
1.67
1.65
1.63
1.62
1.60
1.06
1.04
1.02
O
NO2
3Da
0.86
4.28
1.09
1.09
1.00
2.00
3.00
2.11
3.00
f1 (ppm)


179.29
149.62
140.88
137.80
128.65
127.54
127.25
95.16
78.75
76.99
41.16
21.15
20.83
15.13
13.45
f1 (ppm)

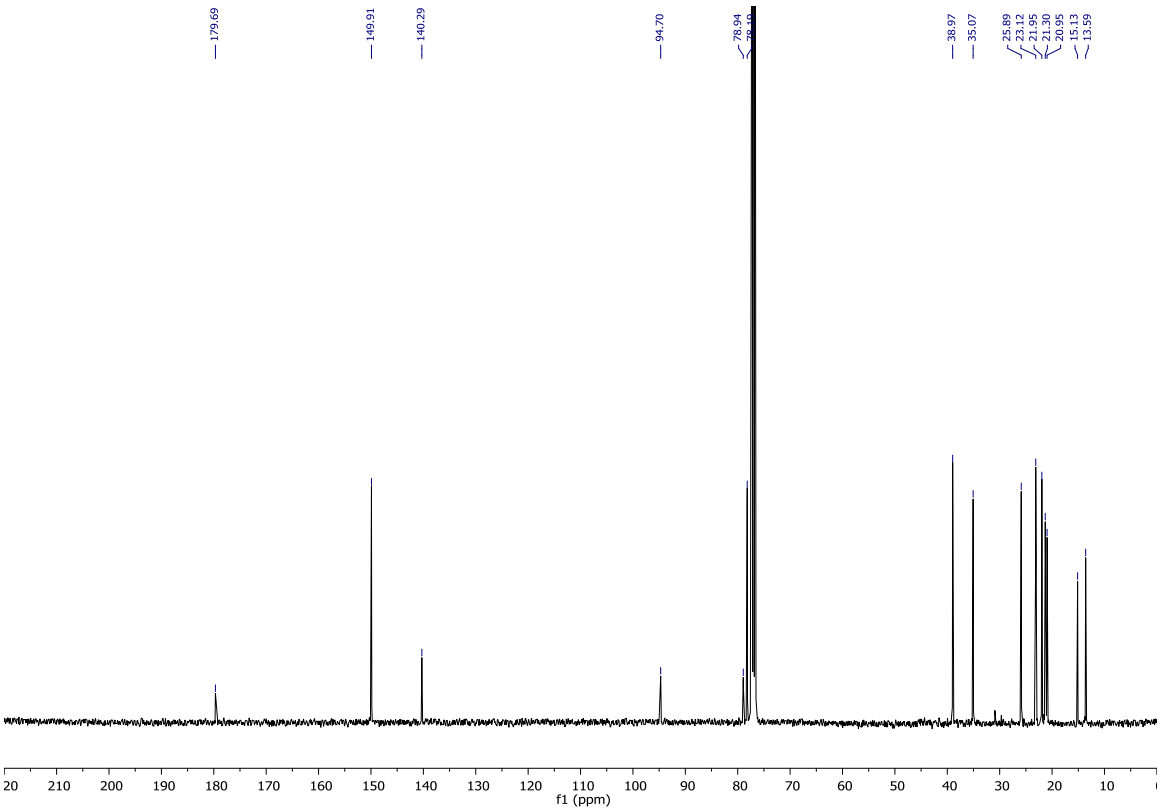

7.52
7.51
7.49
7.47
7.45
7.45
7.23
7.23
7.21
7.20
6.87
6.84
5.25
5.22
5.20
5.18
5.14
5.11
5.09
5.07
4.81
4.79
4.78
4.76
3.80
2.43
2.41
2.38
2.36
2.15
2.15
2.13
2.12
2.11
2.10
1.71
1.68
1.66
1.65
1.63
1.61
1.59
1.29
1.07
1.06
1.05
1.03
1.02
1.01
OMe
O
NO2
3Db
0.82
1.73
1.85
1.05
1.05
1.02
3.14
1.98
3.00
2.10
2.95
f1 (ppm)

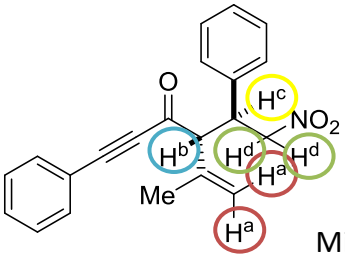

179.17
158.39
149.04
140.85
129.56
128.65
128.47
113.95
113.75
94.81
78.54
76.99
54.85
40.38
20.89
20.56
14.80
13.19
f1 (ppm)


O
NO2

3De

0.85
1.16
1.19
1.08
1.95
3.00
1.23
2.18
2.50
2.95
7.07
f1 (ppm)

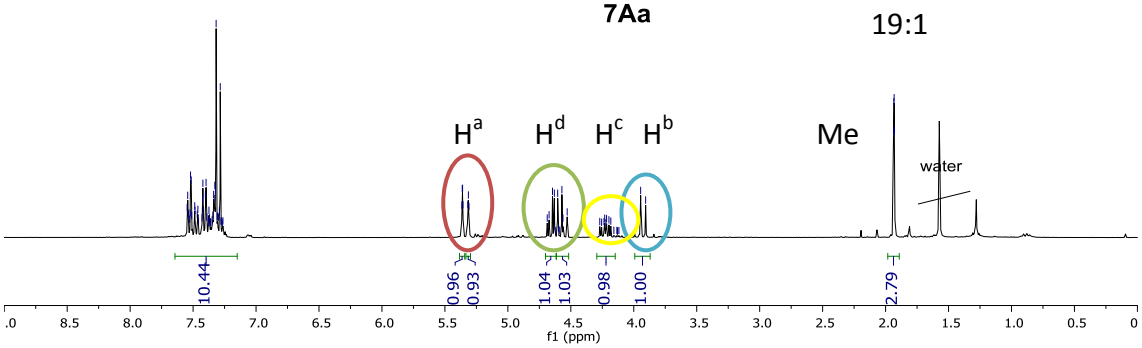

179.69
149.91
140.29
94.70
78.94
38.97
35.07
25.89
23.12
21.95
21.30
20.95
15.13
13.59
f1 (ppm)

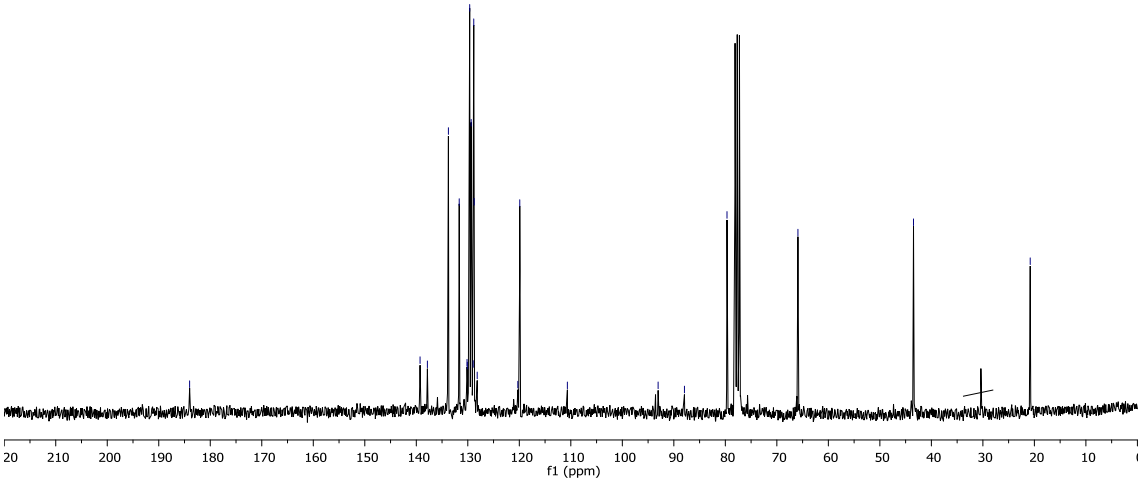


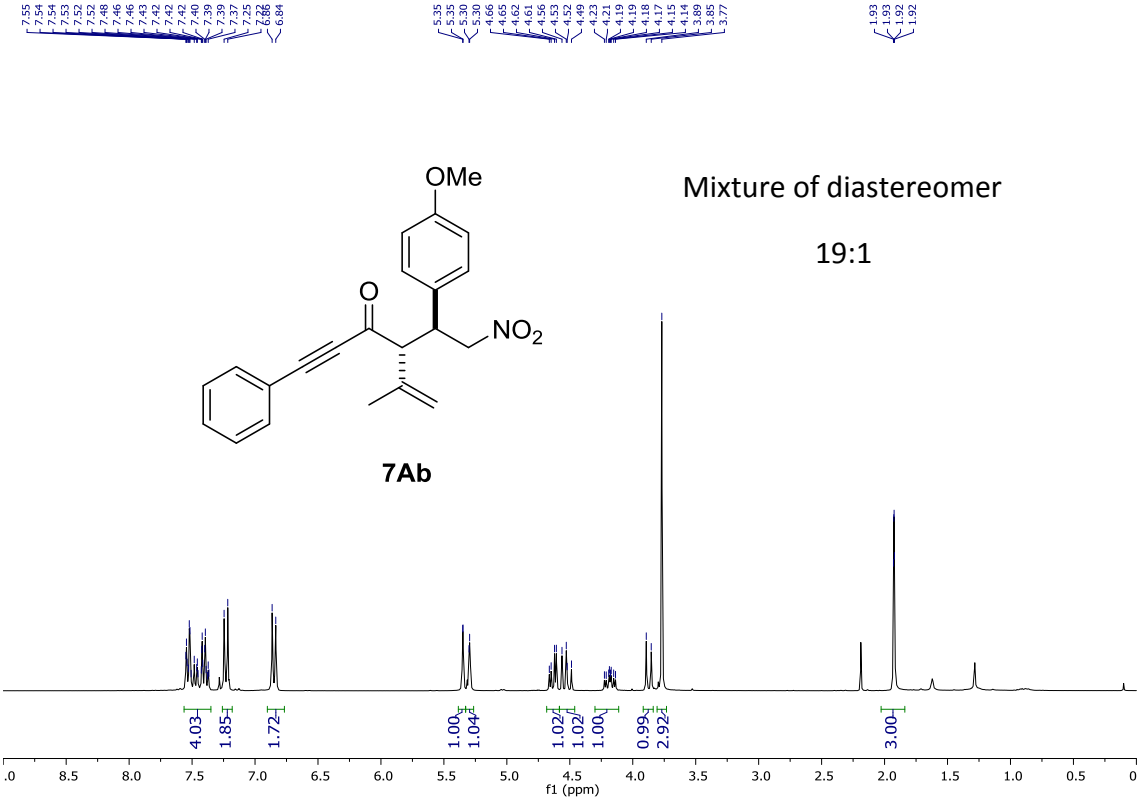
Mixture of diastereomer

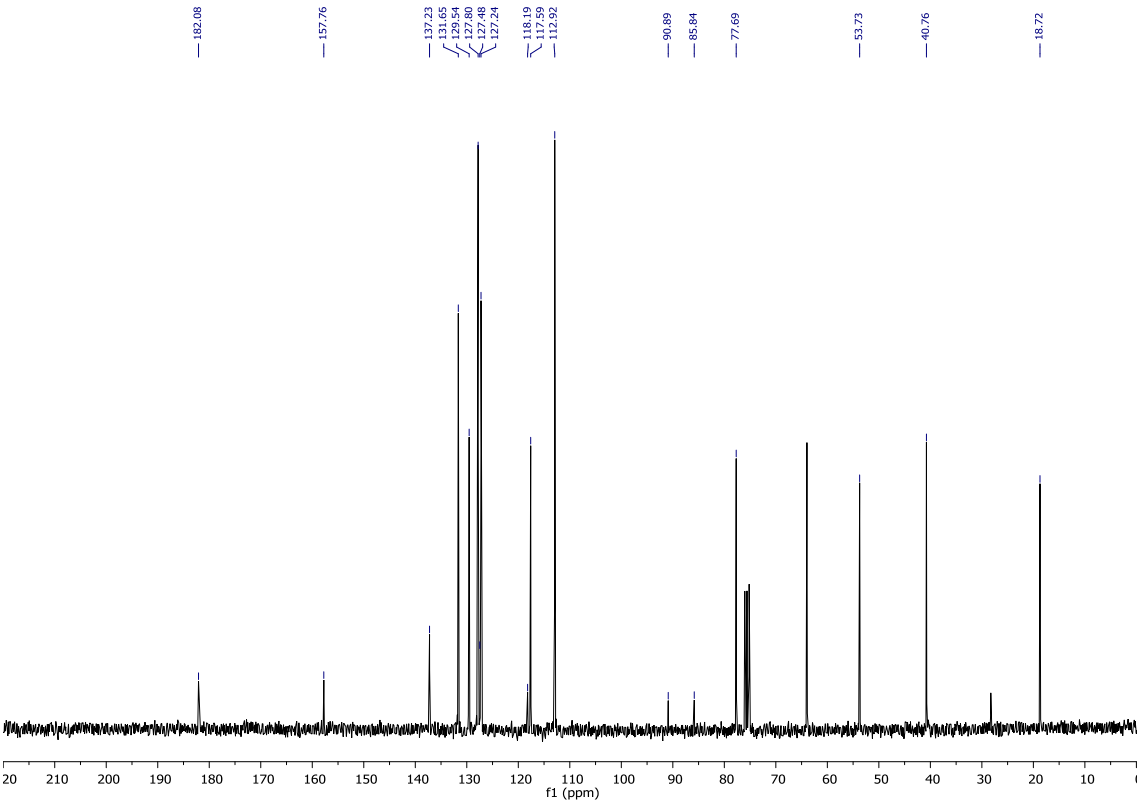
7Aa

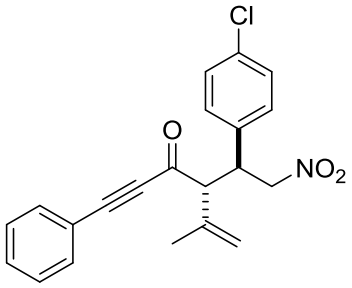
19:1






OMe
O
NO2
7Ab
Mixture of diastereomer
19:1
4.03
1.85
1.72
1.00
1.04
1.02
1.02
1.00
0.99
2.92
3.00
f1 (ppm)

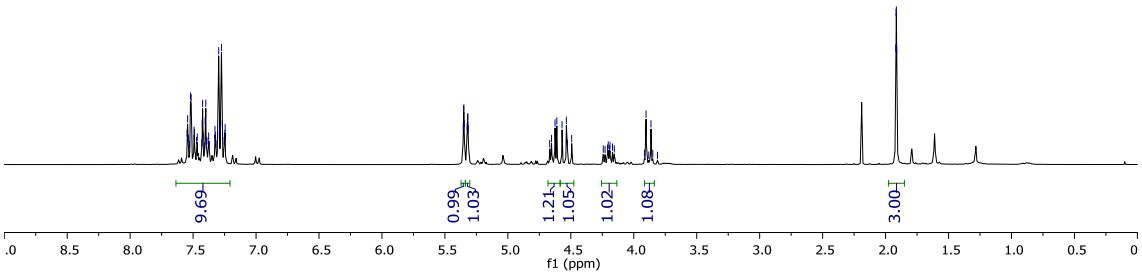

182.08
157.76
137.23
131.65
129.54
127.80
127.48
127.24
118.19
117.59
112.92
90.89
85.84
77.69
53.73
40.76
18.72
f1 (ppm)

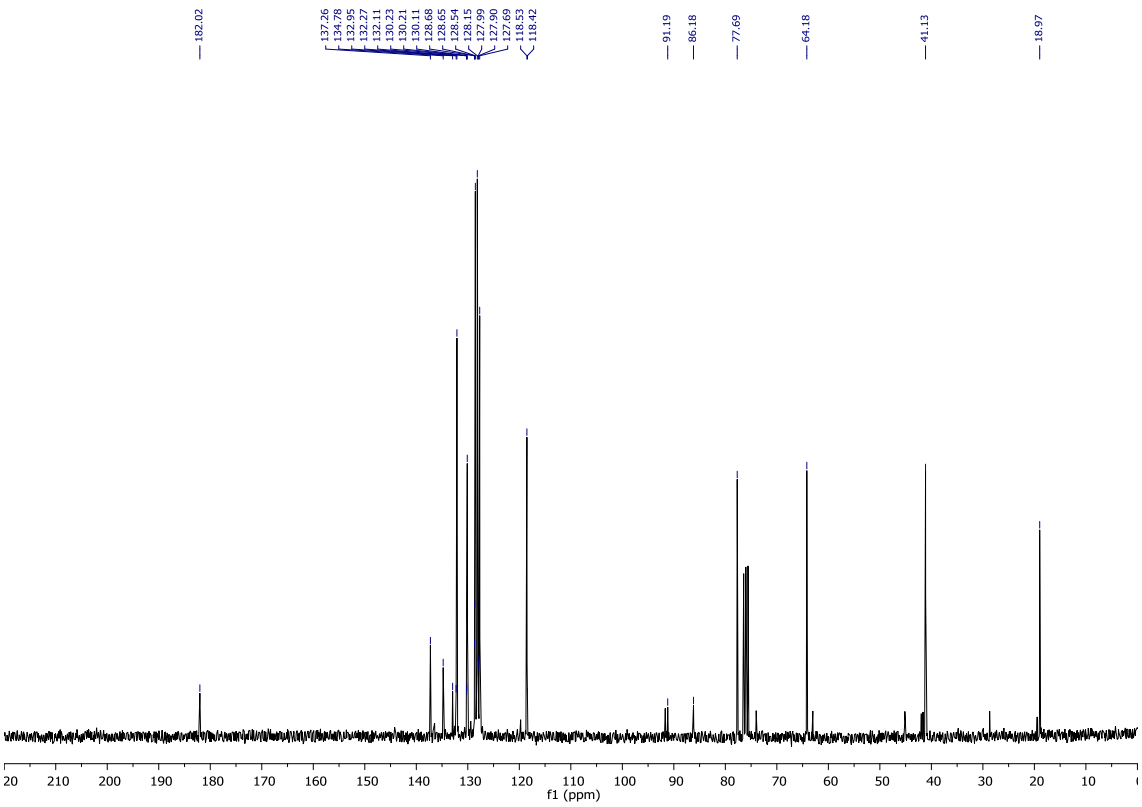


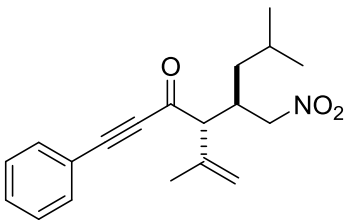
7Ad

Mixture of diastereomer

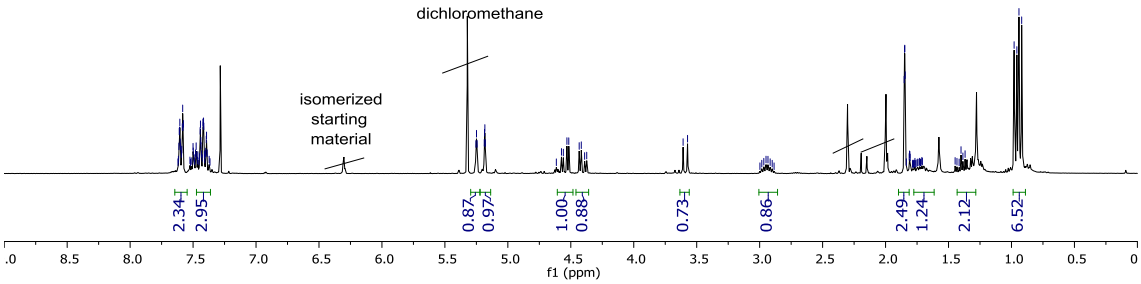
19:1

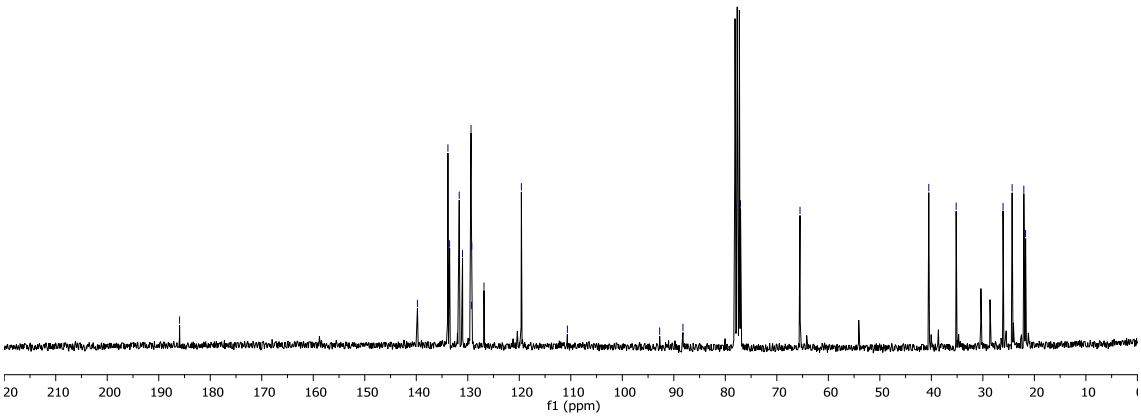


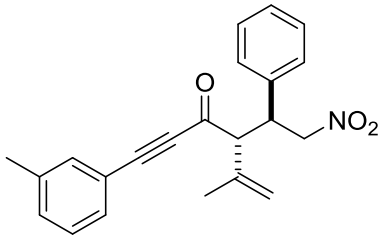



O
NO2

7Ae


dichloromethane
isomerized
starting
material
2.34
2.95
0.87
0.97
1.00
0.88
0.73
0.86
2.49
1.24
2.12
6.52
f1 (ppm)

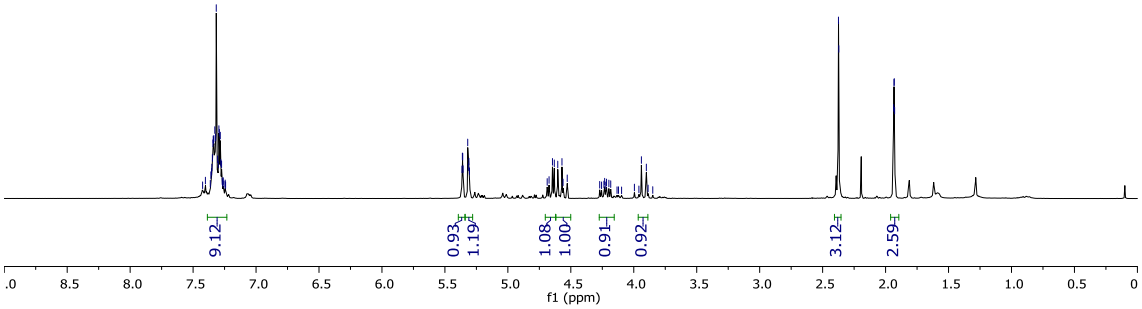

f1 (ppm)

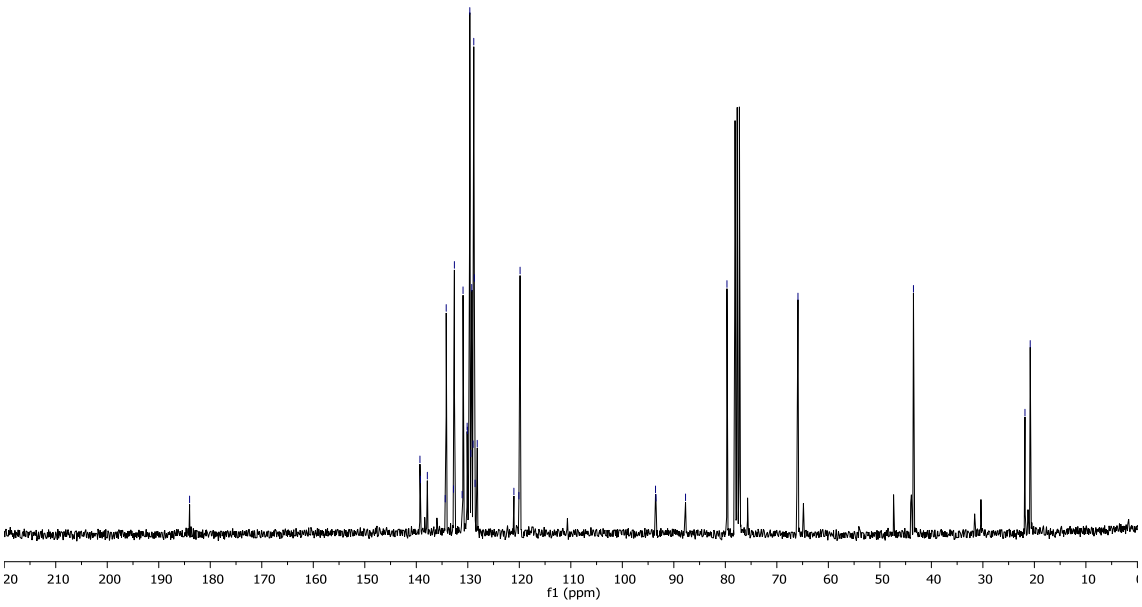


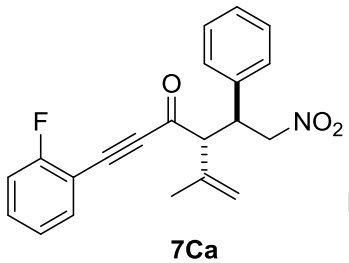
7Ba

Mixture of diastereomer

19:1



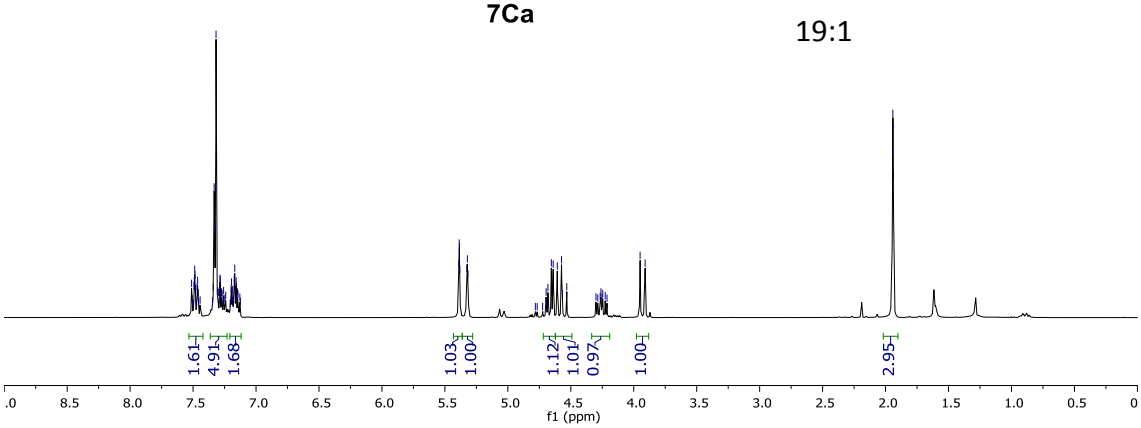


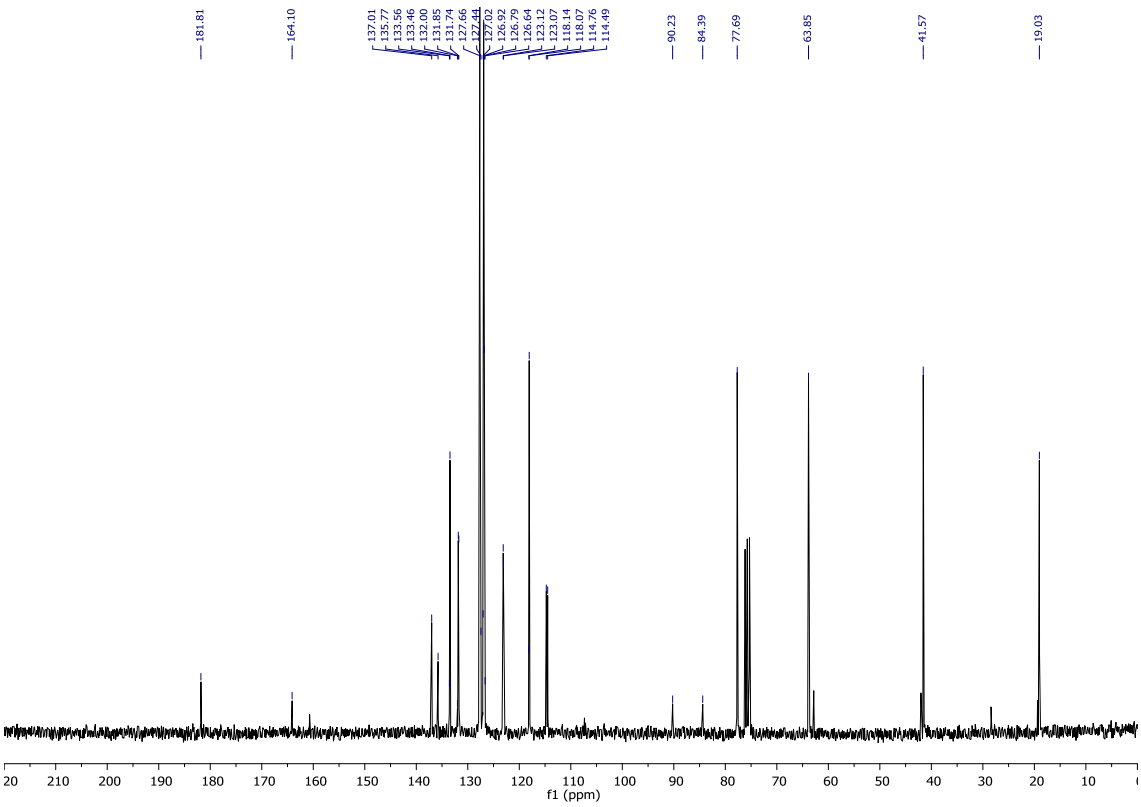


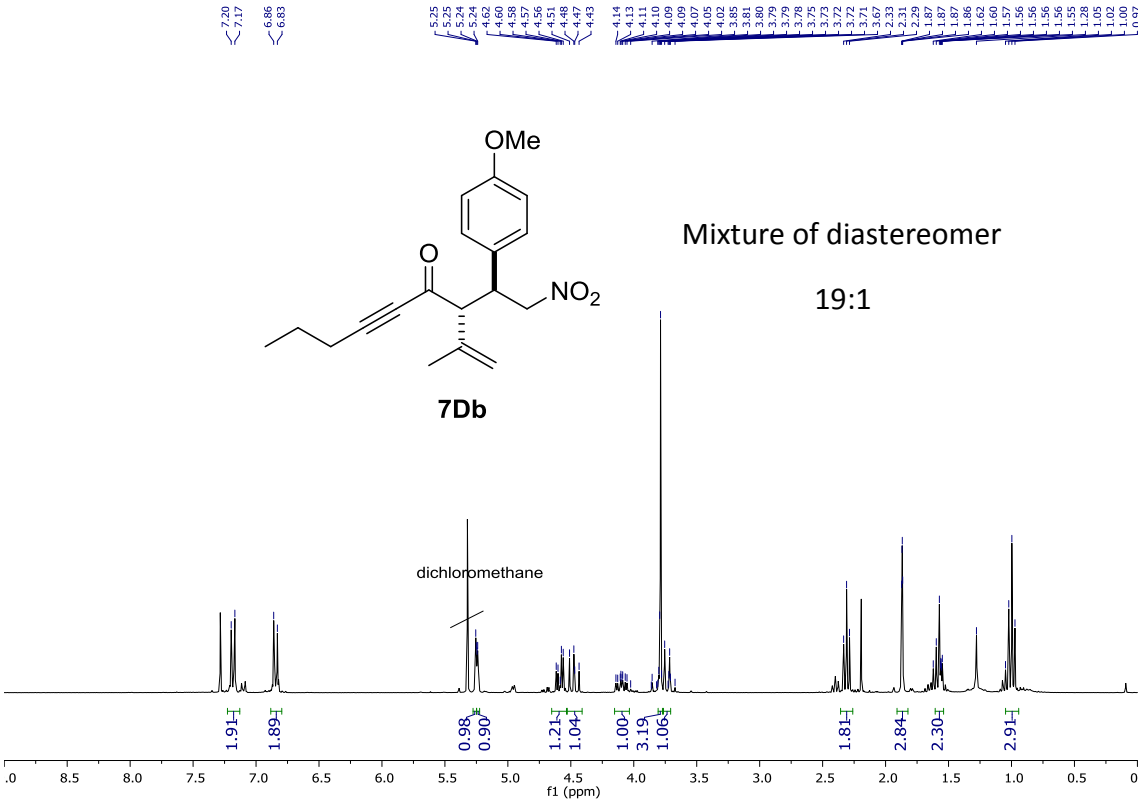
7Ca

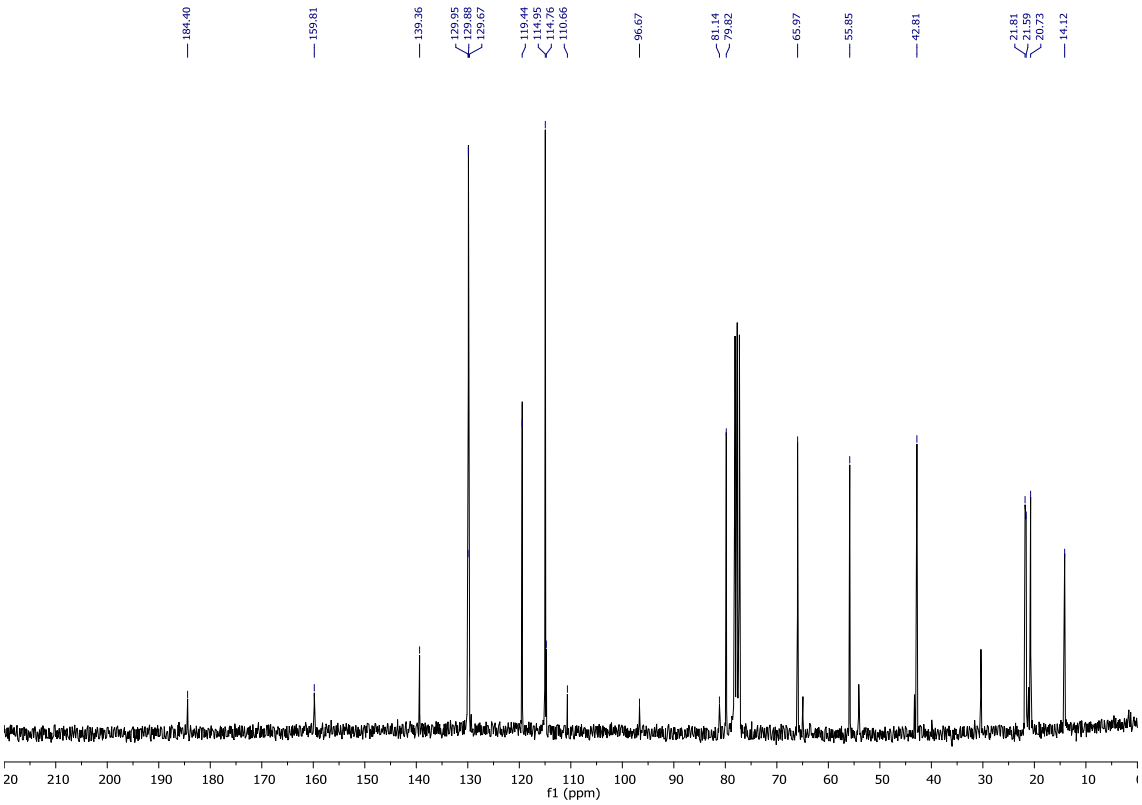
Mixture of diastereomer

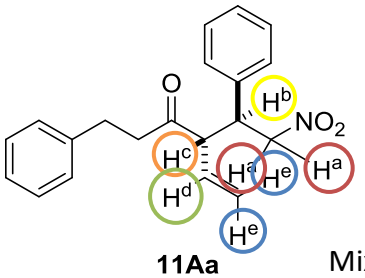
19:1






OMe
O
NO2
7Db
Mixture of diastereomer
19:1
dichloromethane
f1 (ppm)

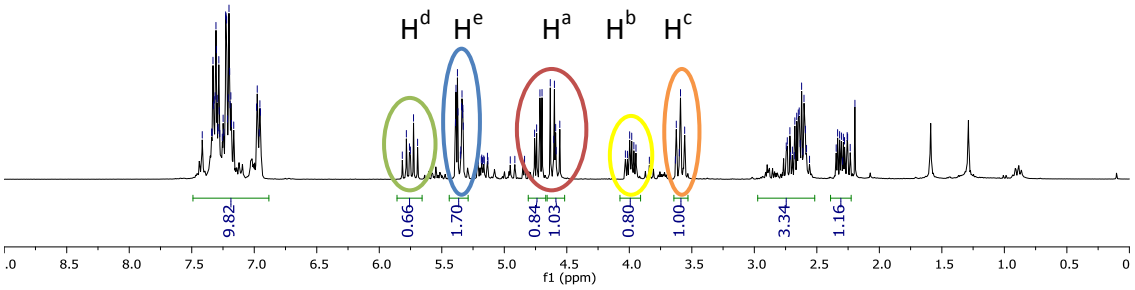

f1 (ppm)

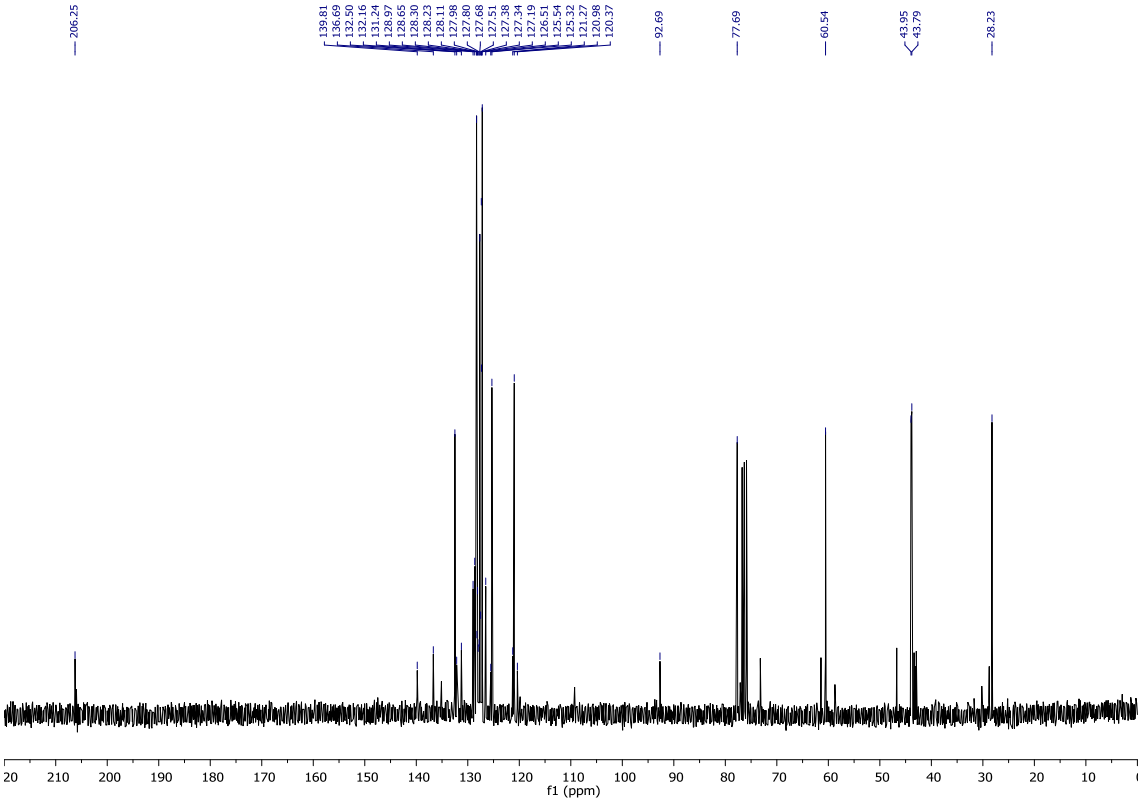


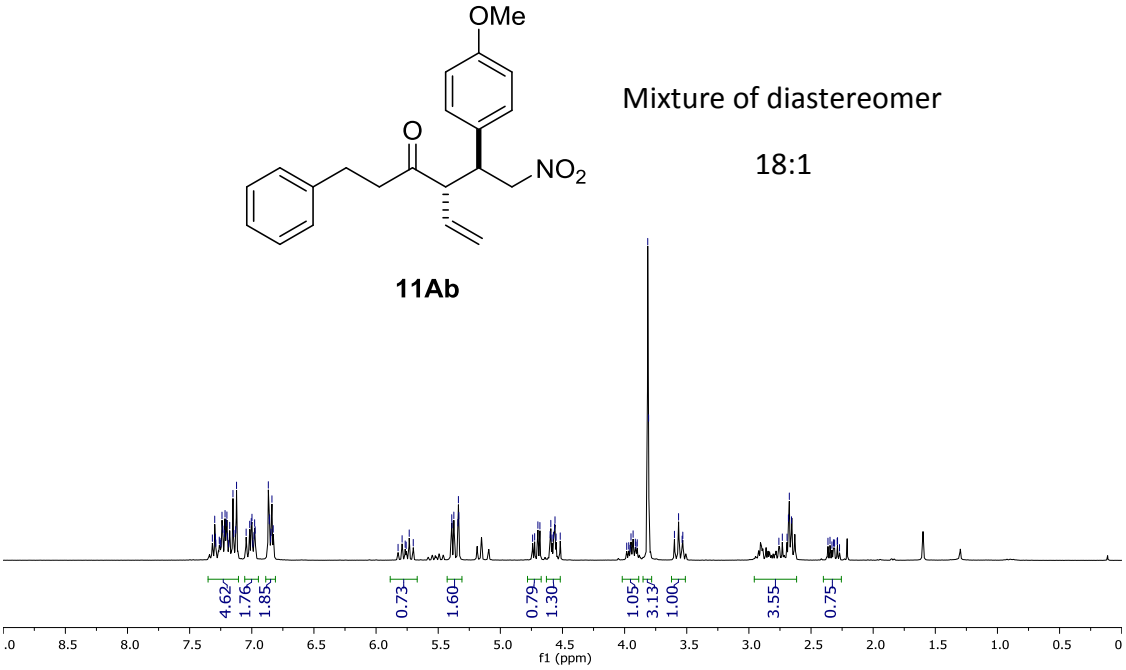
11Aa

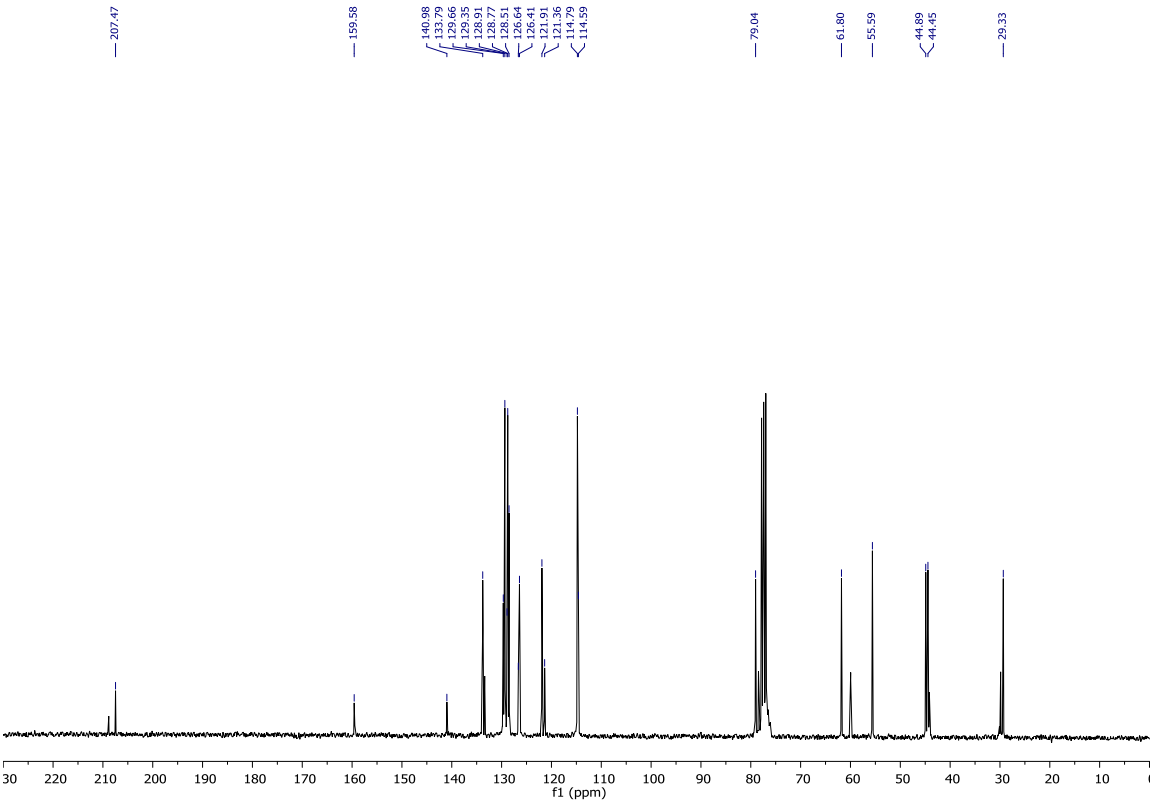
Mixture of diastereomer

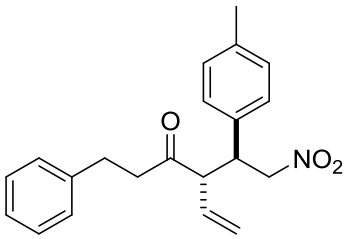
17:1






OMe
O
NO2
Mixture of diastereomer
18:1
11Ab
4.62
1.76
1.85
0.73
1.60
0.79
1.30
1.05
3.13
1.00
3.55
0.75
f1 (ppm)

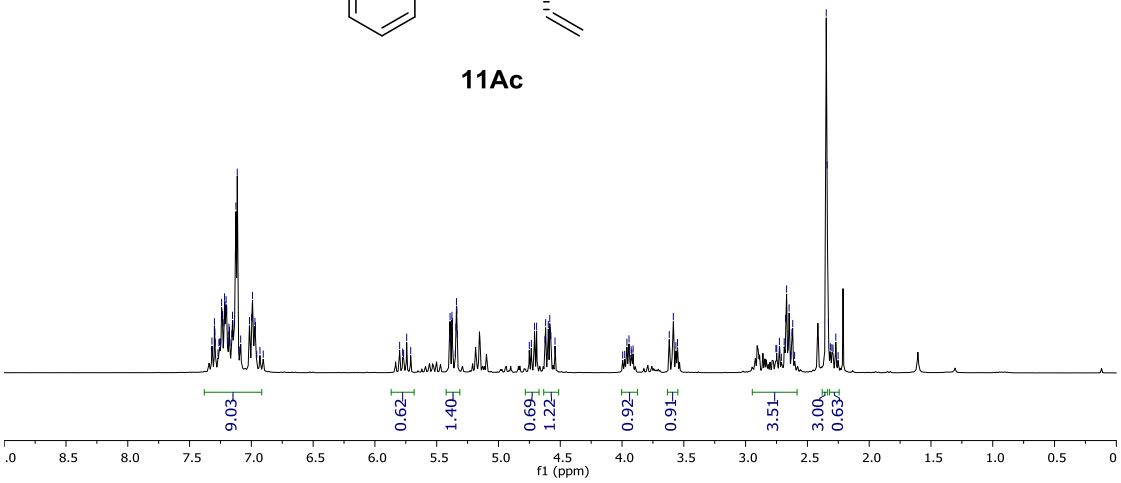

207.47
159.58
140.98
133.79
129.66
129.35
128.91
128.77
128.51
126.64
126.41
121.91
121.36
114.79
114.59
79.04
61.80
55.59
44.89
44.45
29.33
f1 (ppm)

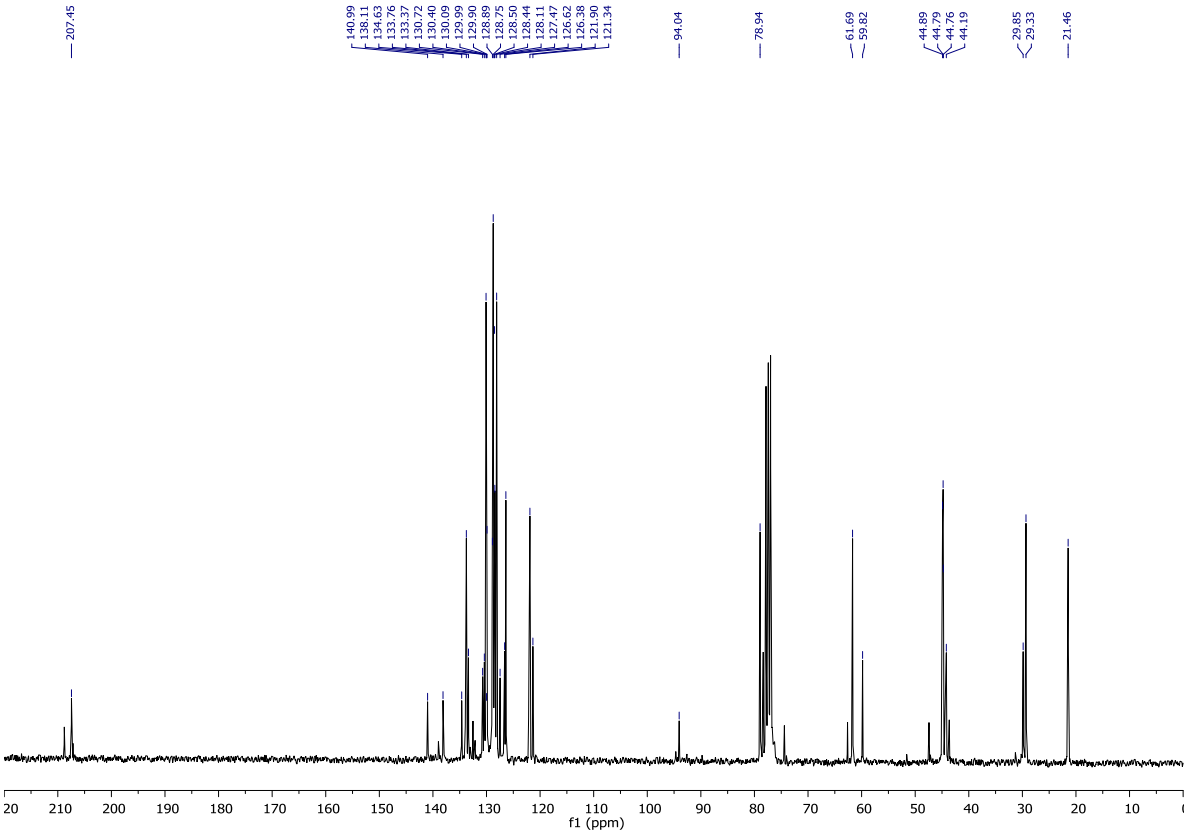


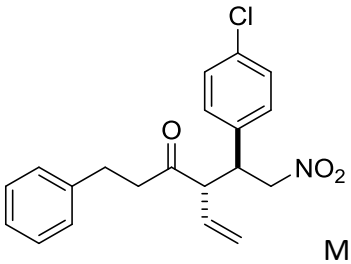
Mixture of diastereomer

17:1

11Ac



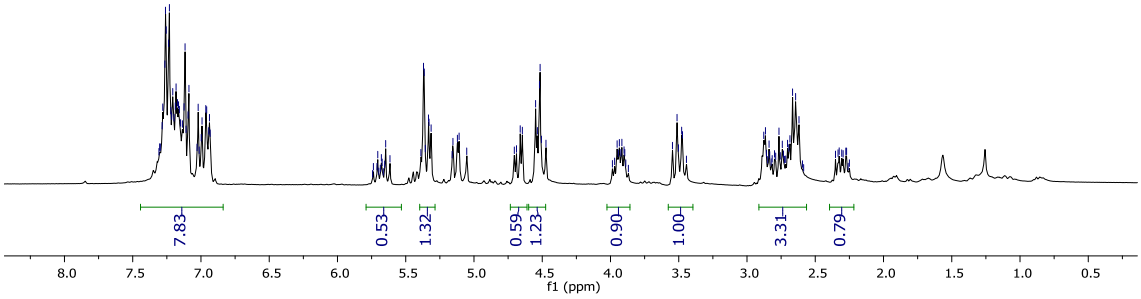


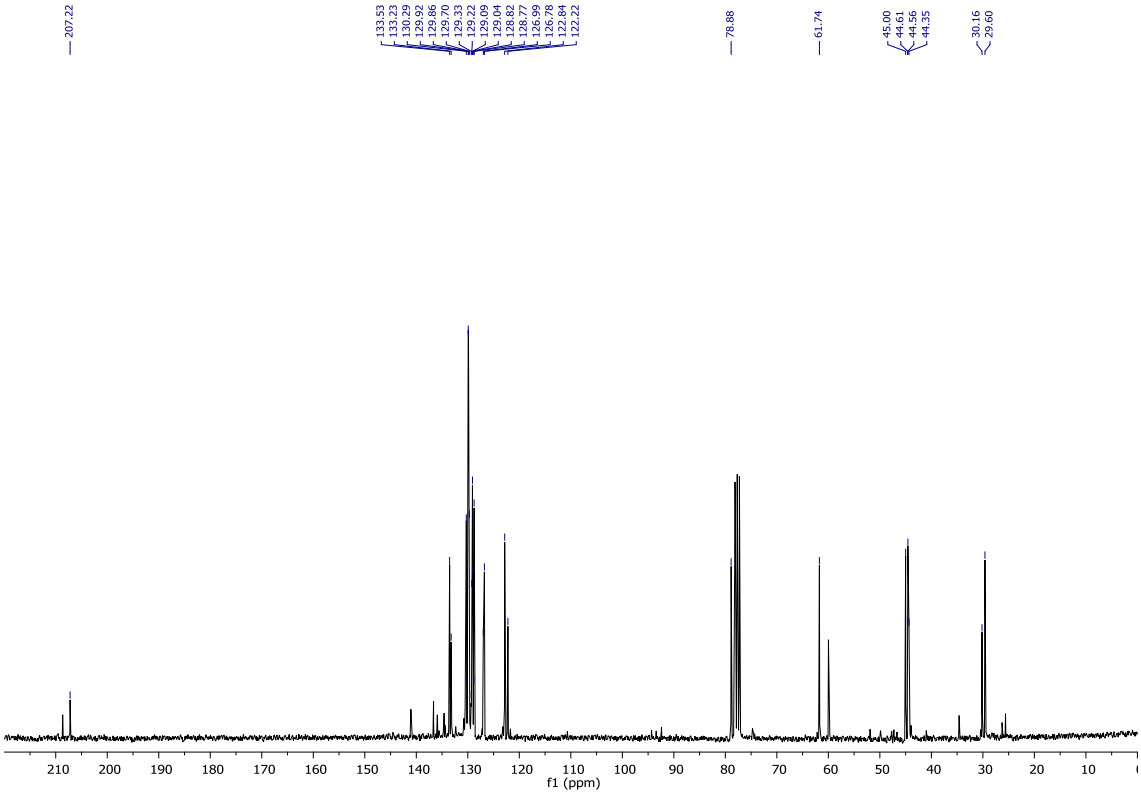


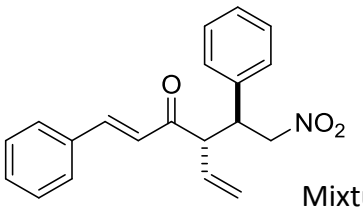
Mixture of diastereomer

11Ad

15:1

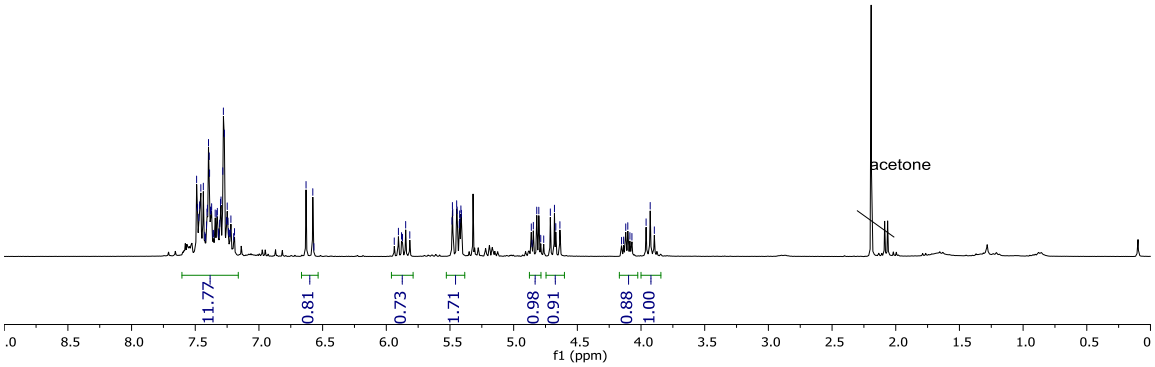


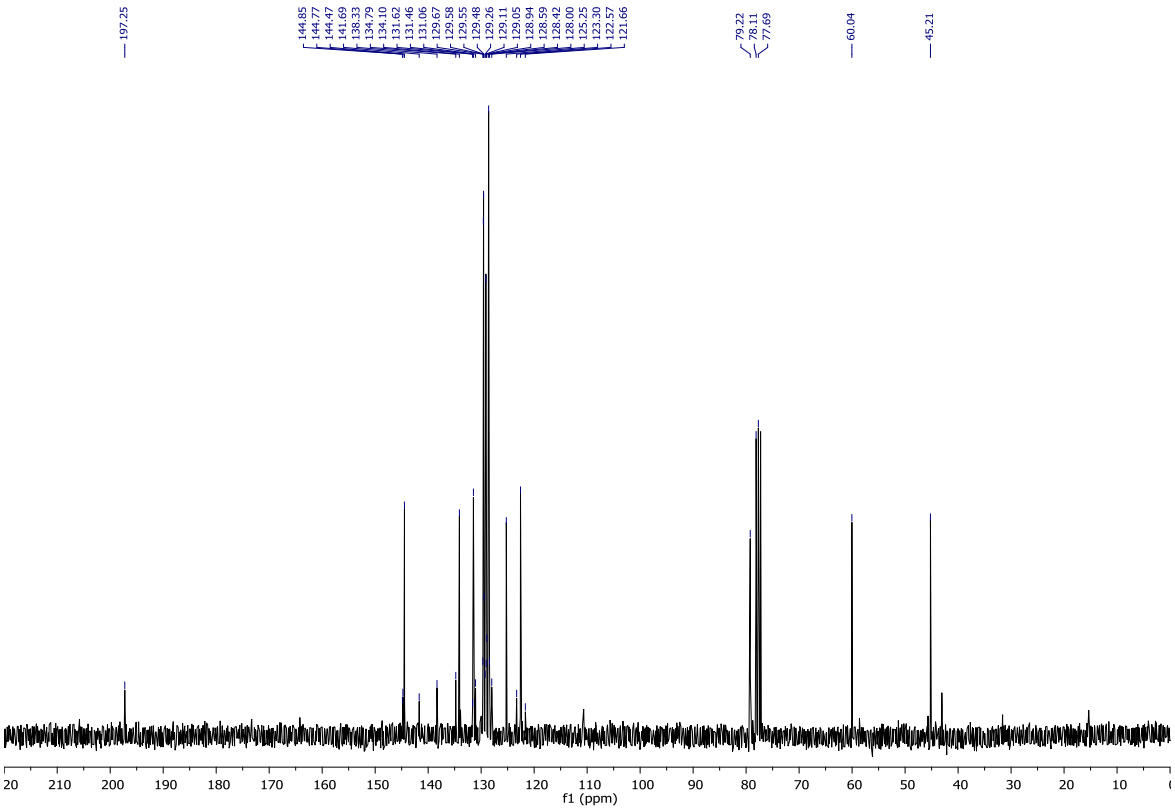


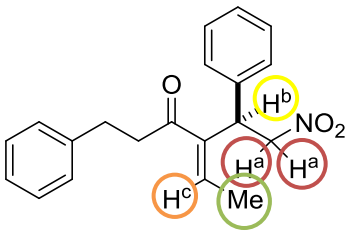


Mixture of diastereomer

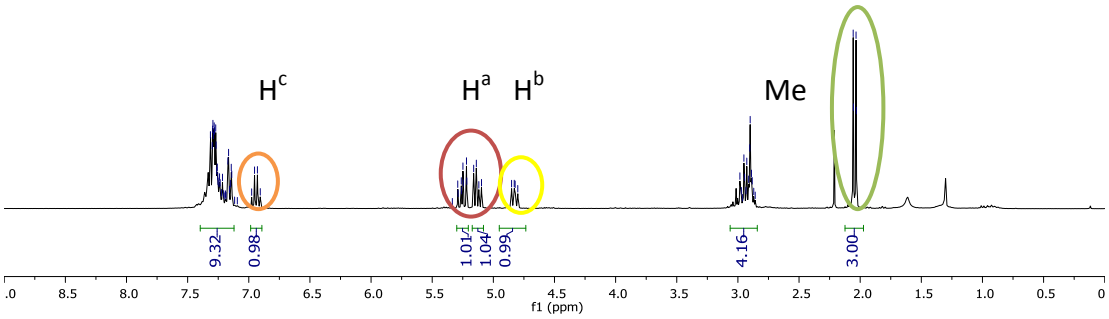
11Ba 18:1

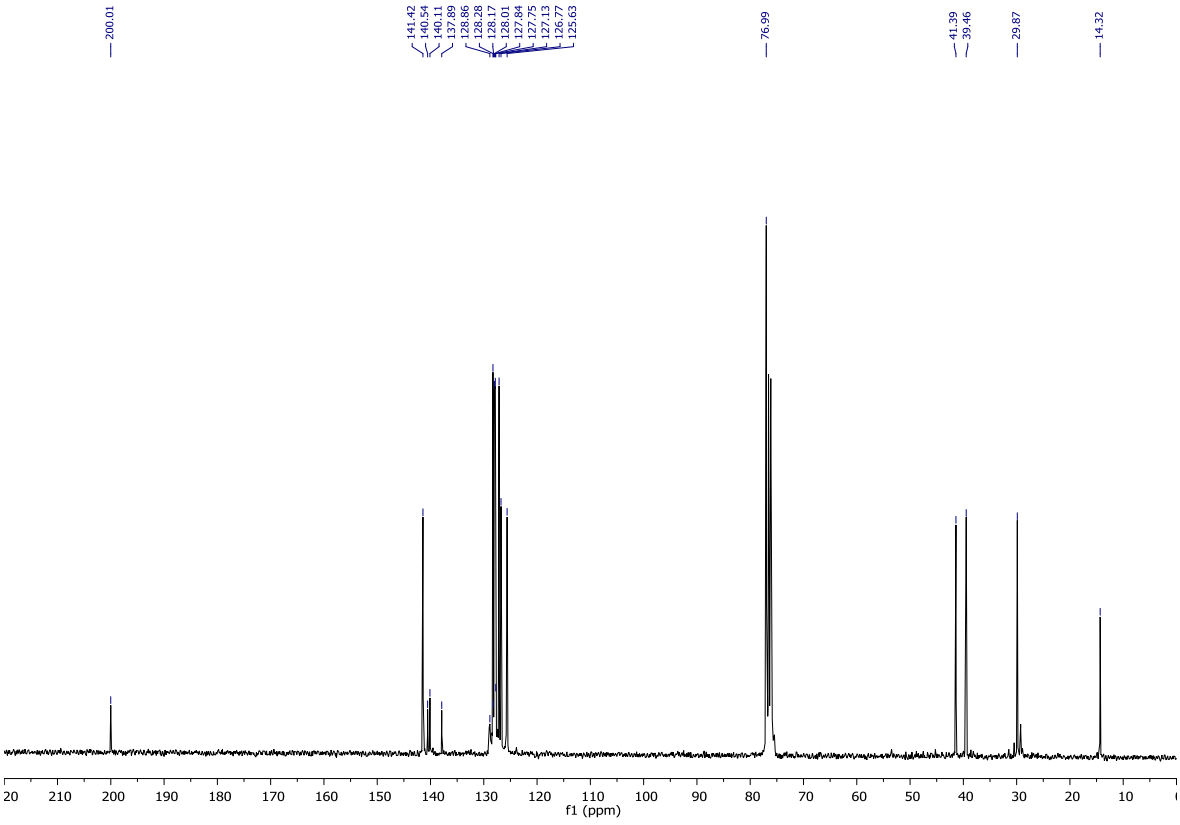


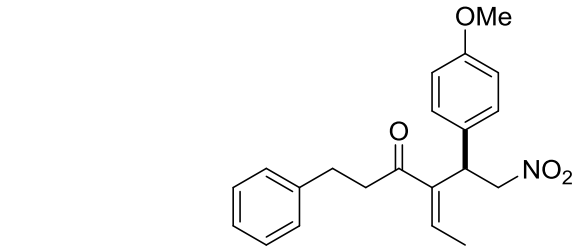



O
H^b
NO_2
H^a
H^a
H^c
Me

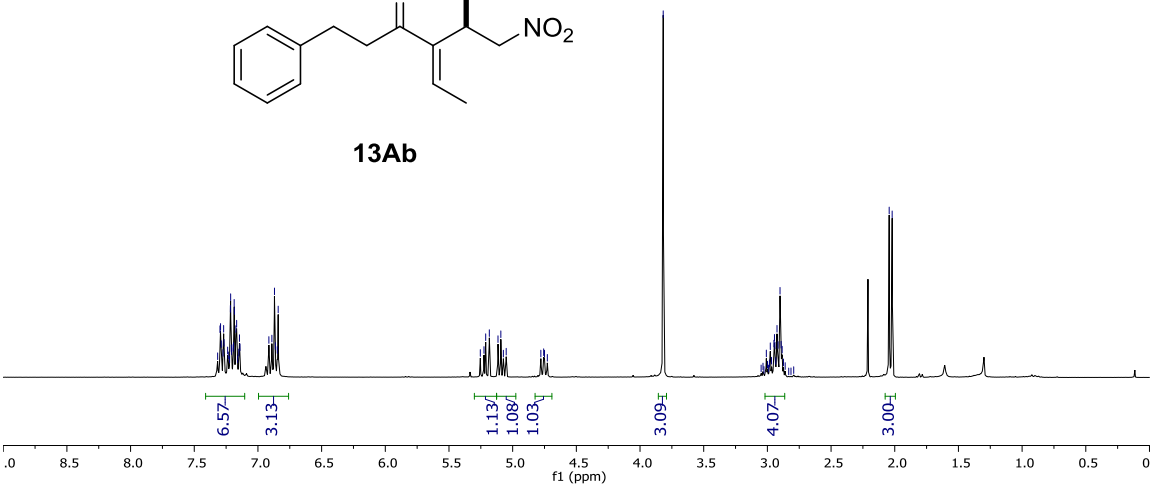
13Aa

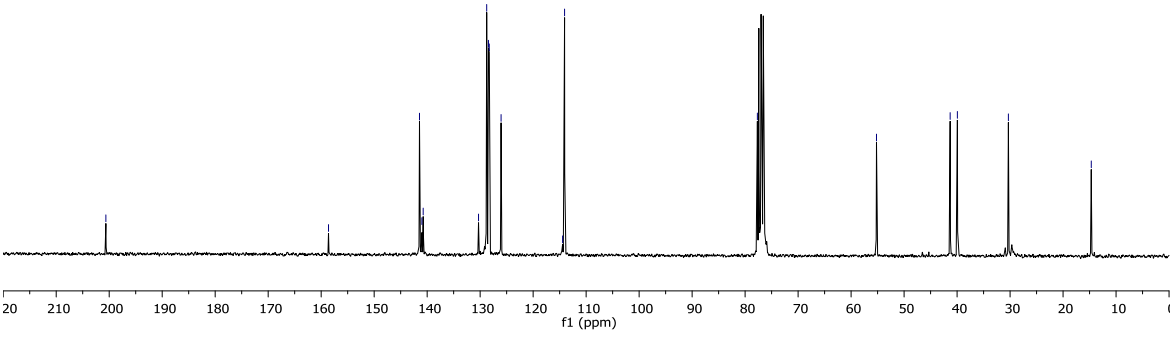

H^c
H^a H^b
Me
9.32
0.98
1.01
1.04
0.99
4.16
3.00
f1 (ppm)

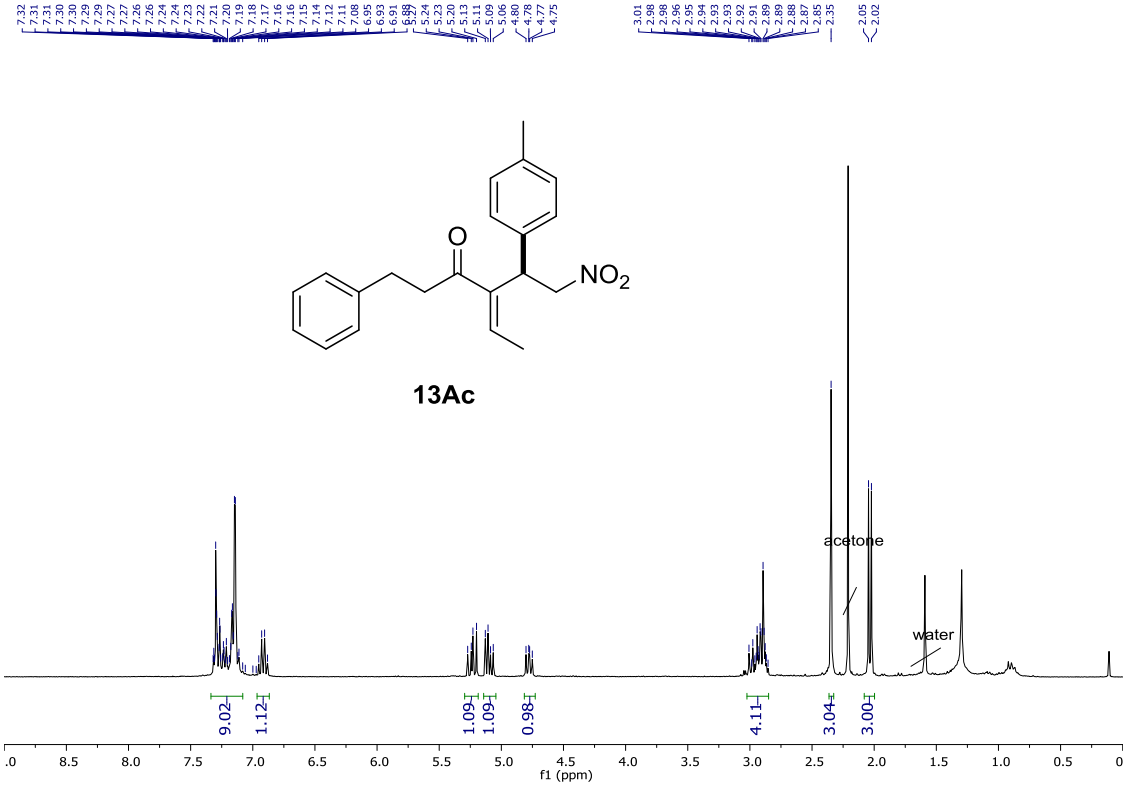

200.01
141.42
140.54
140.11
137.89
128.86
128.28
128.17
128.01
127.84
127.75
127.13
126.77
125.63
76.99
41.39
39.46
29.87
14.32
f1 (ppm)

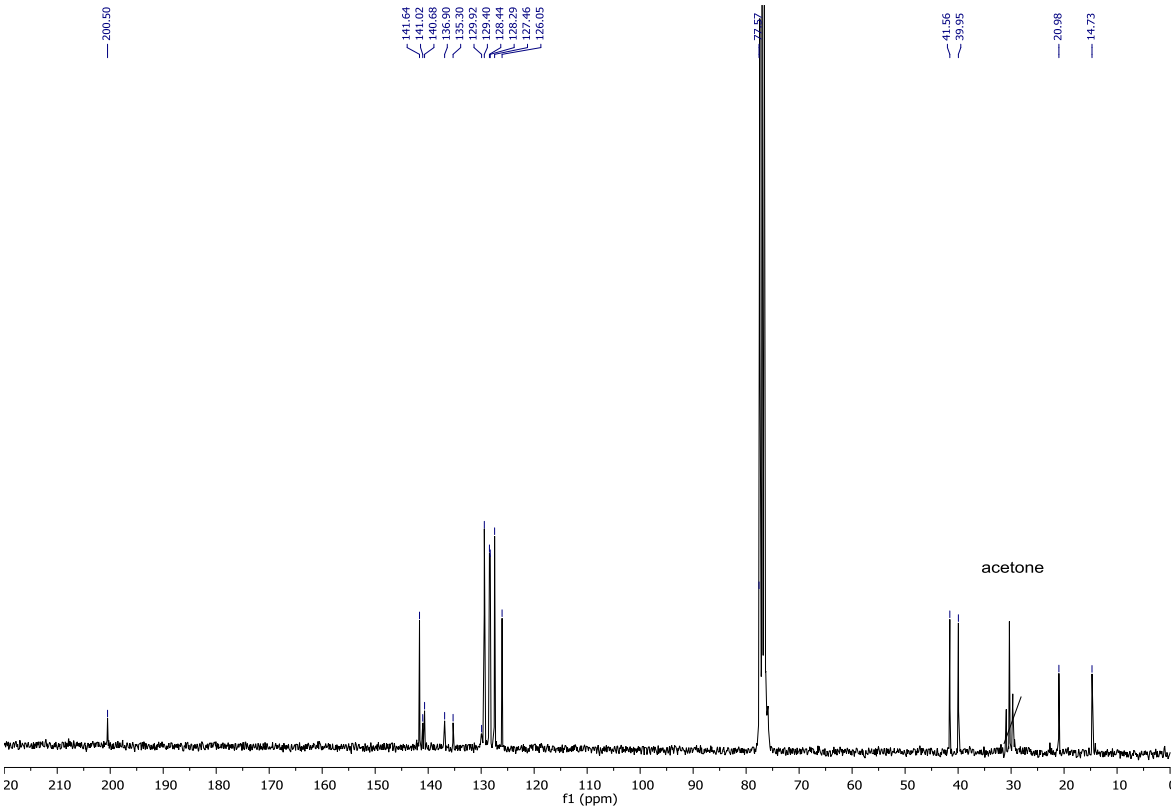


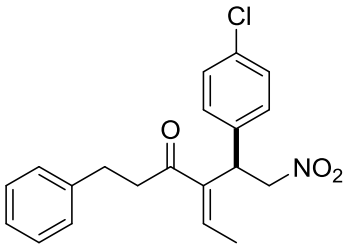
13Ab



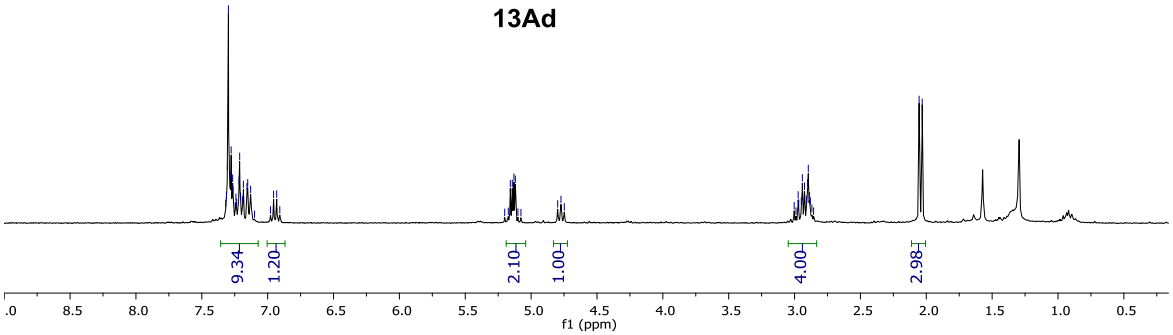


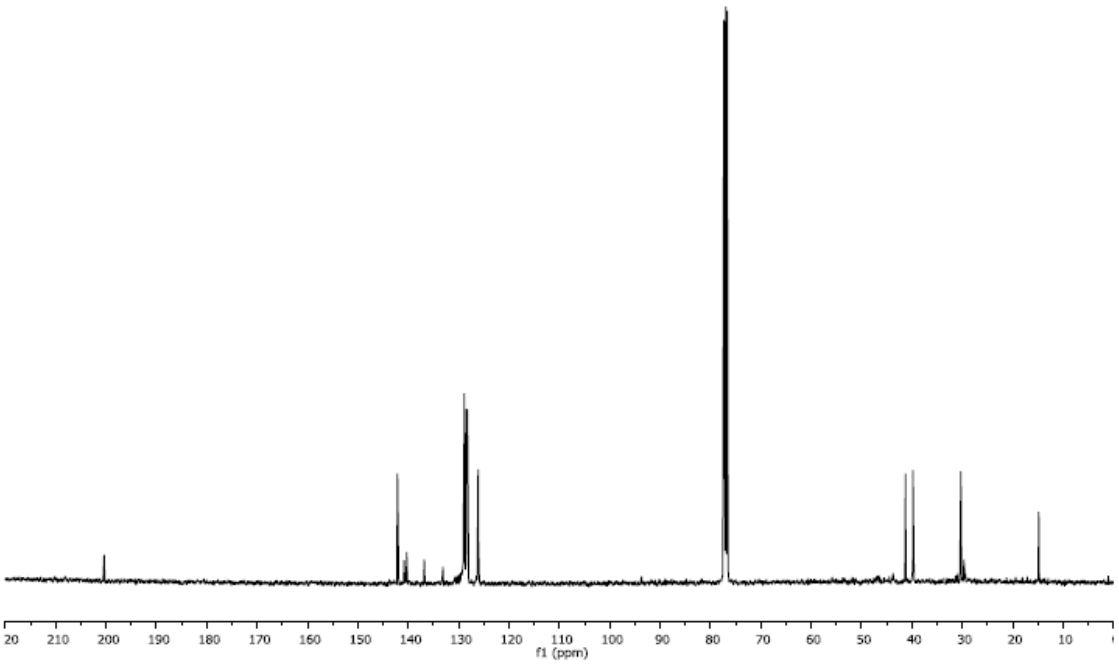

O
NO2
13Ac
acetone
water
9.02
1.12
1.09
1.09
0.98
4.11
3.04
3.00
f1 (ppm)


200.50
141.64
141.02
140.68
136.90
135.30
129.92
129.40
128.44
128.29
127.46
126.05
77.57
41.56
39.95
20.98
14.73
acetone
f1 (ppm)

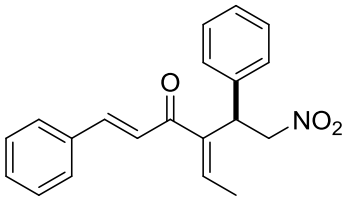


13Ad

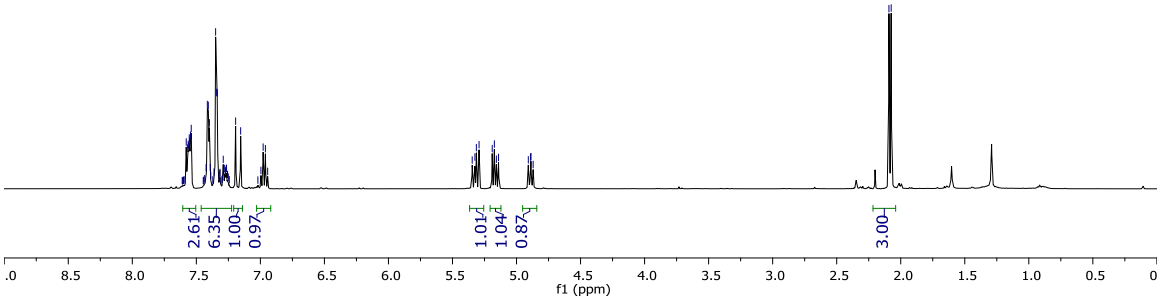


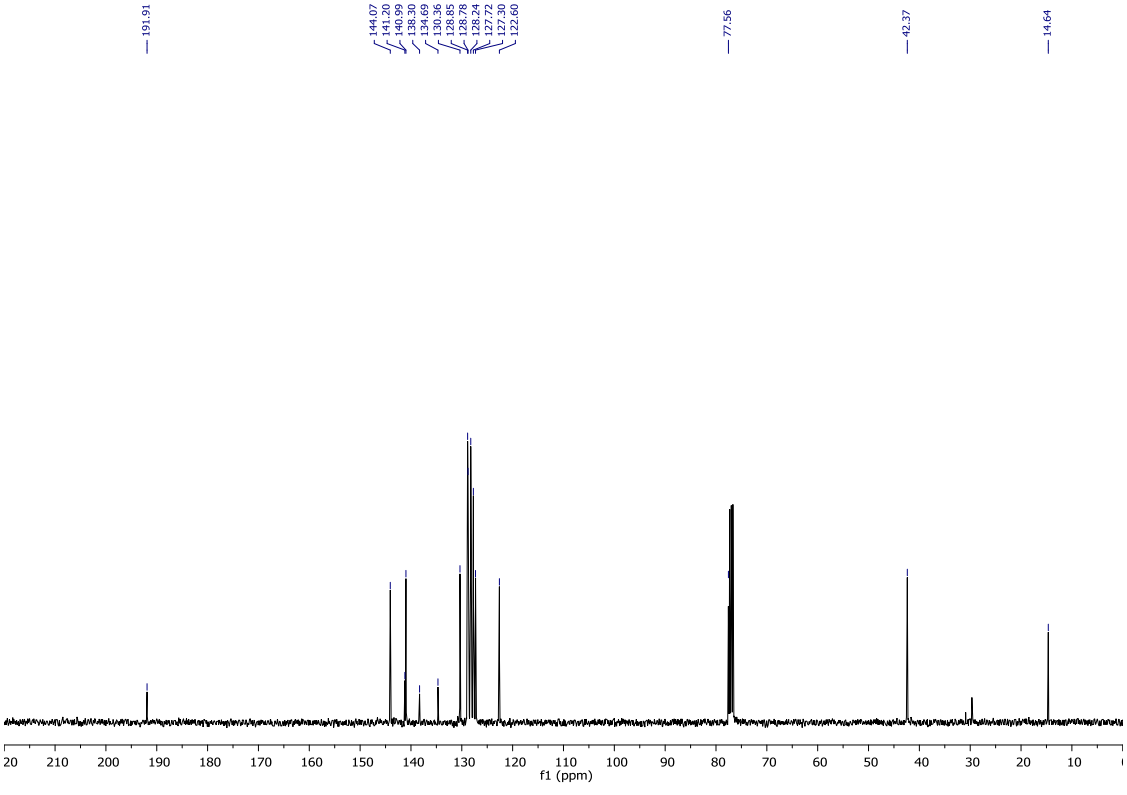



7.61
7.61
7.60
7.59
7.58
7.57
7.56
7.56
7.56
7.55
7.55
7.54
7.45
7.44
7.43
7.42
7.41
7.41
7.40
7.39
7.39
7.37
7.36
7.35
7.34
7.34
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.26
7.25
7.24
7.19
7.15
7.02
7.00
6.98
6.96
6.94
5.35
5.32
5.31
5.29
5.19
5.17
5.16
5.14
4.91
4.89
4.89
4.87
2.09
2.07


O
NO2

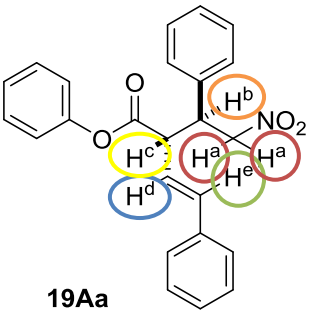
13Ba


2.61
6.35
1.00
0.97
1.01
1.04
0.87
3.00
f1 (ppm)

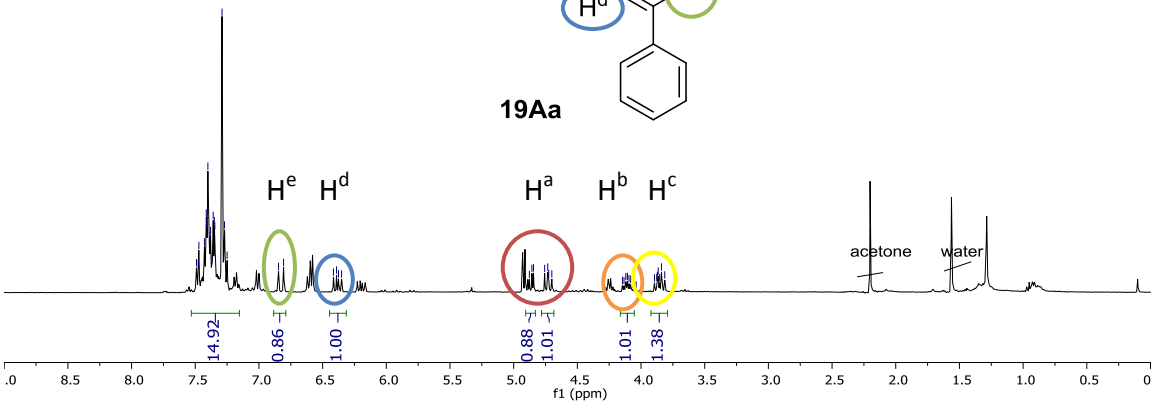

191.91
144.07
141.20
140.99
138.30
134.69
130.36
128.85
128.78
128.24
127.72
127.30
122.60
77.56
42.37
14.64
f1 (ppm)

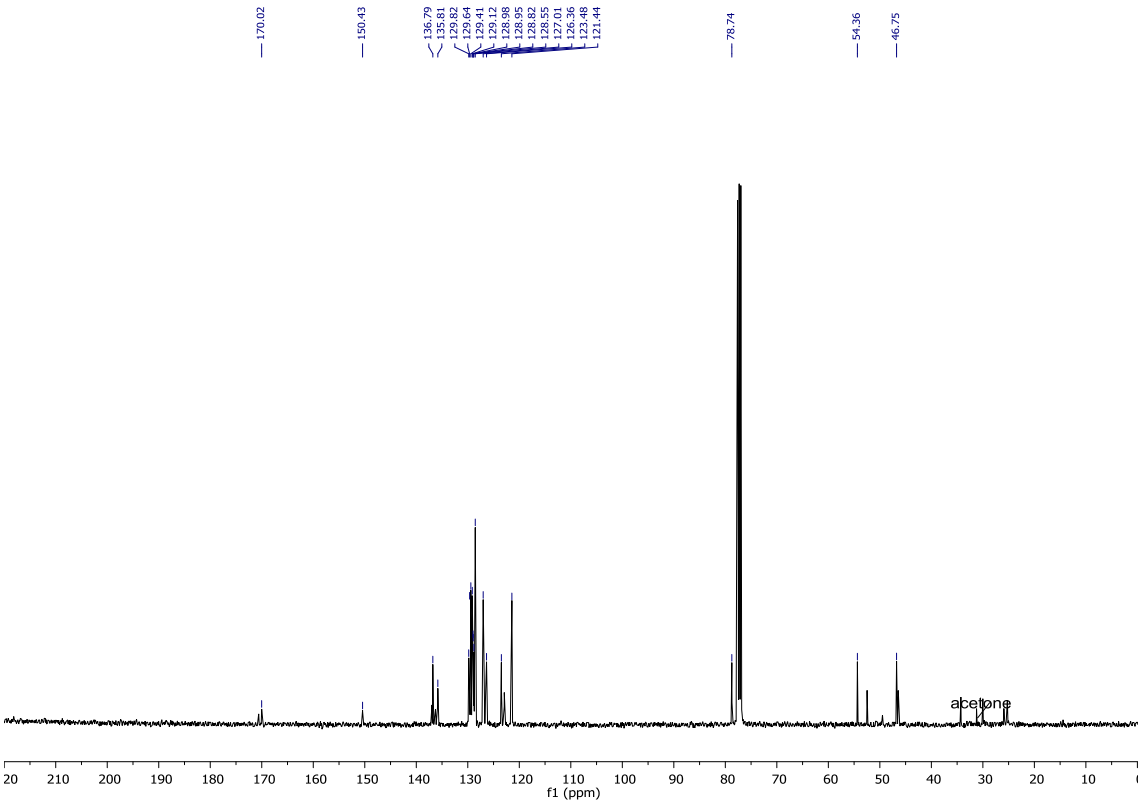
Mixture of diastereomer

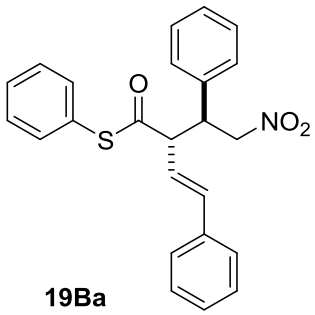
3:1



19Aa



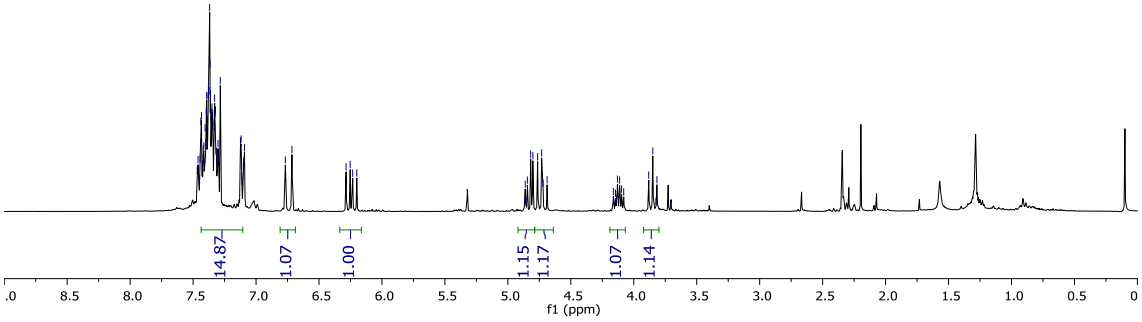


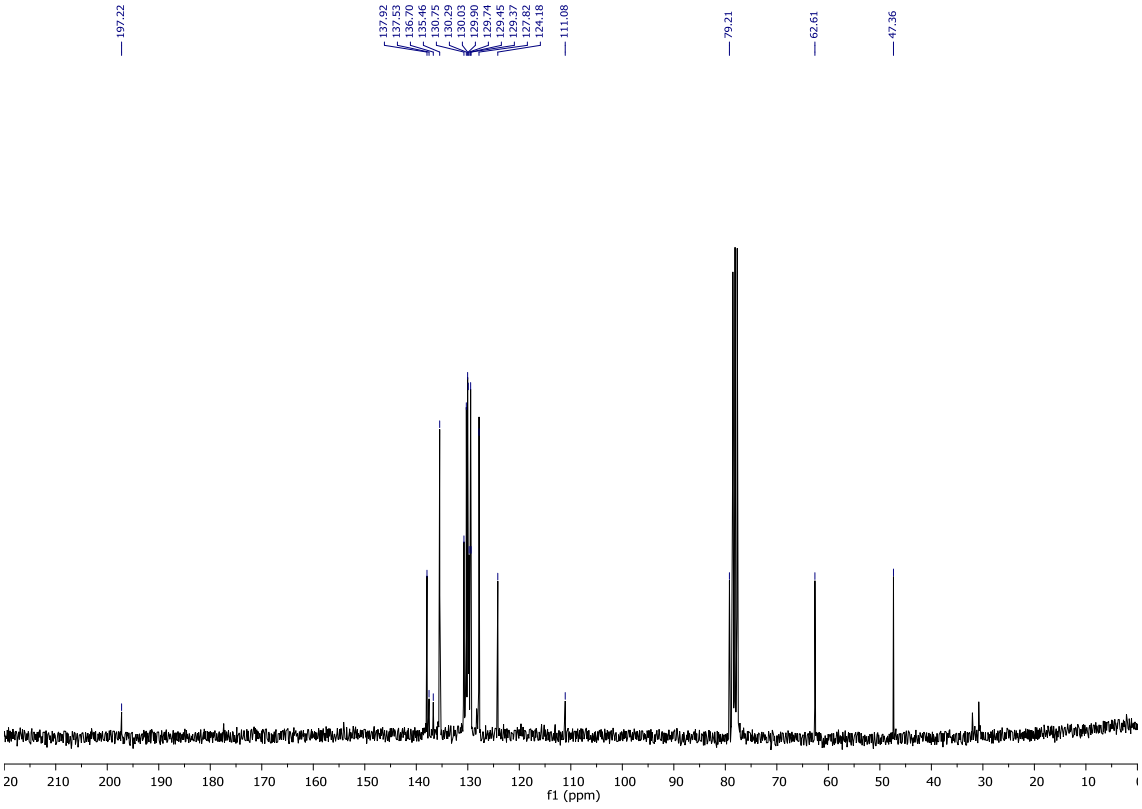


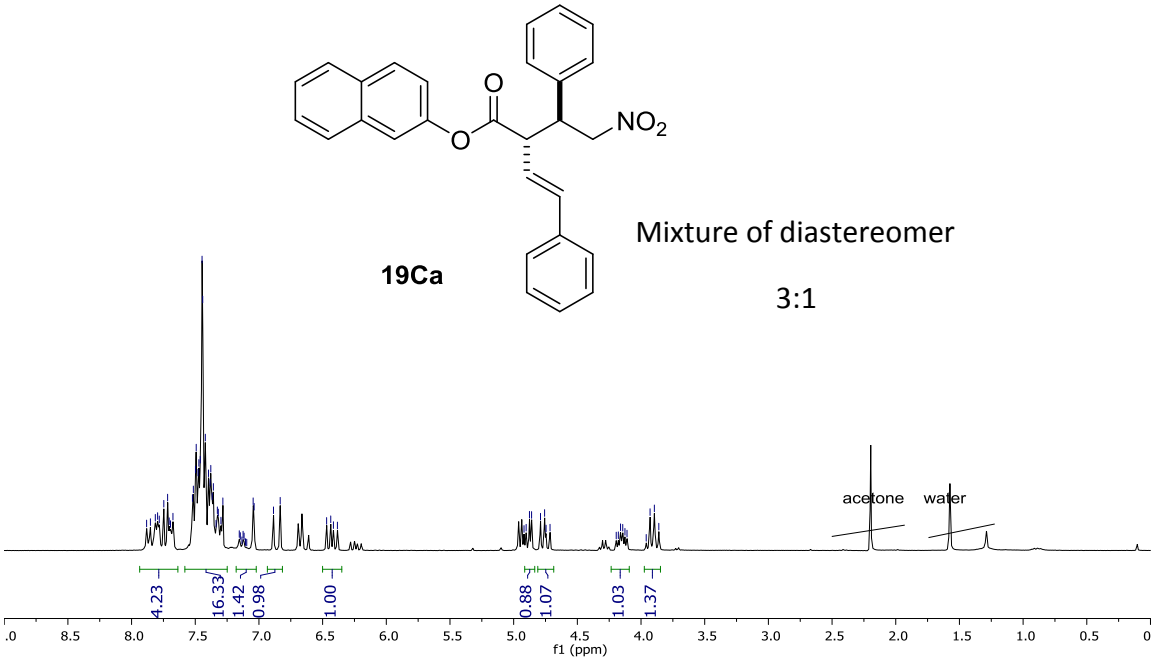
19Ba

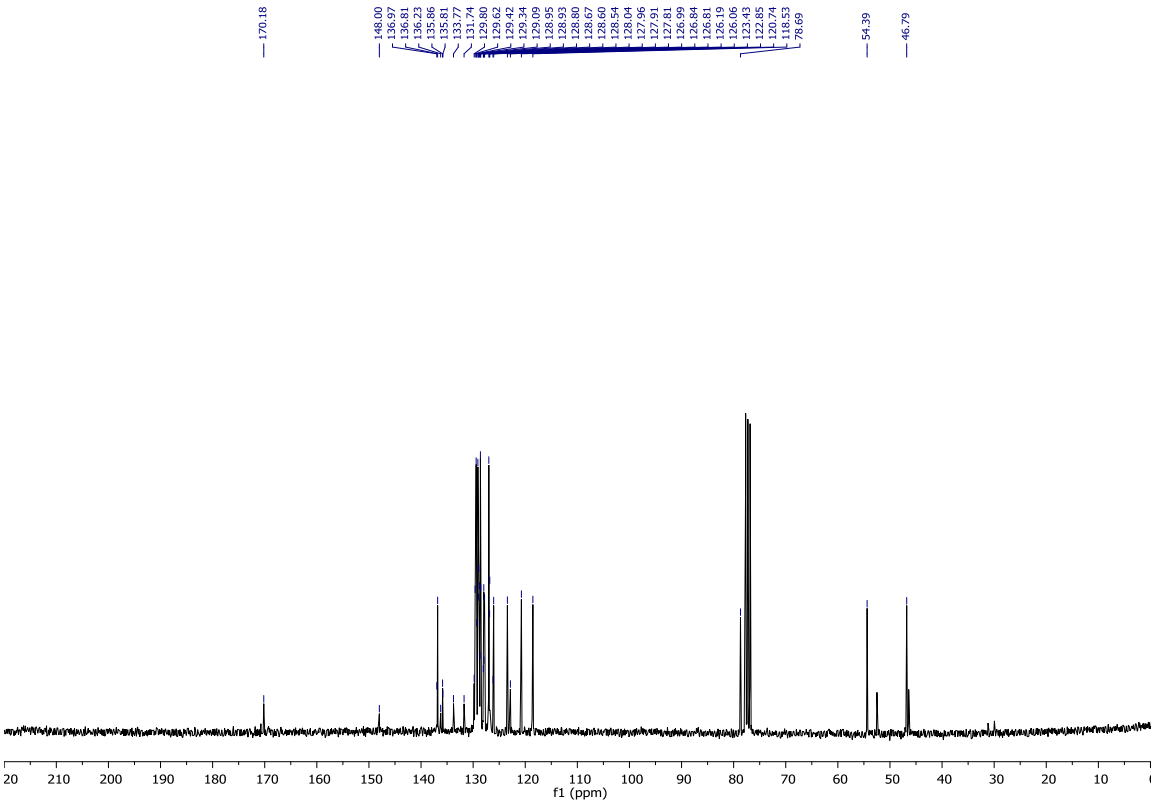
Mixture of diastereomer

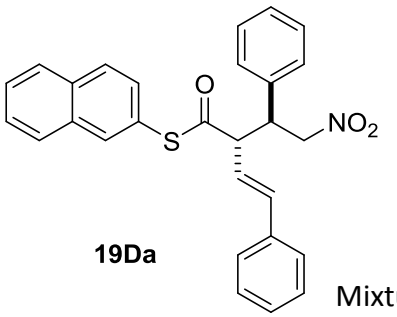
19:1






O
O
NO2
19Ca
Mixture of diastereomer
3:1
acetone
water
4.23
16.33
1.42
0.98
1.00
0.88
1.07
1.03
1.37
f1 (ppm)

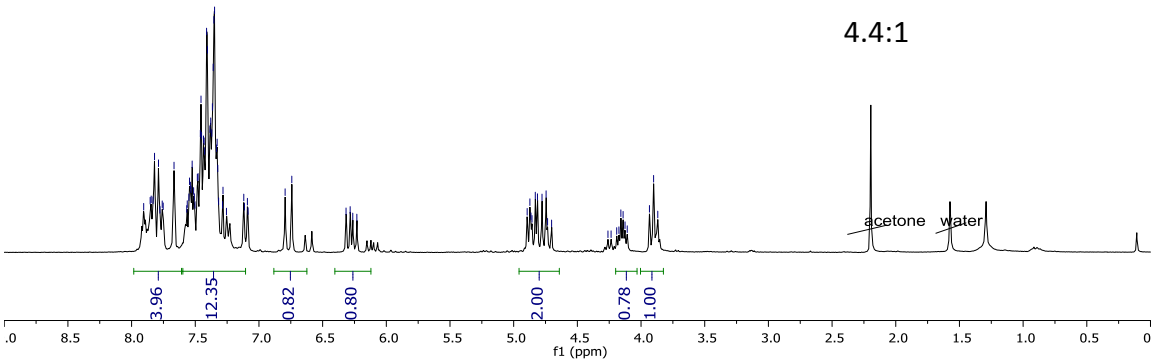

f1 (ppm)

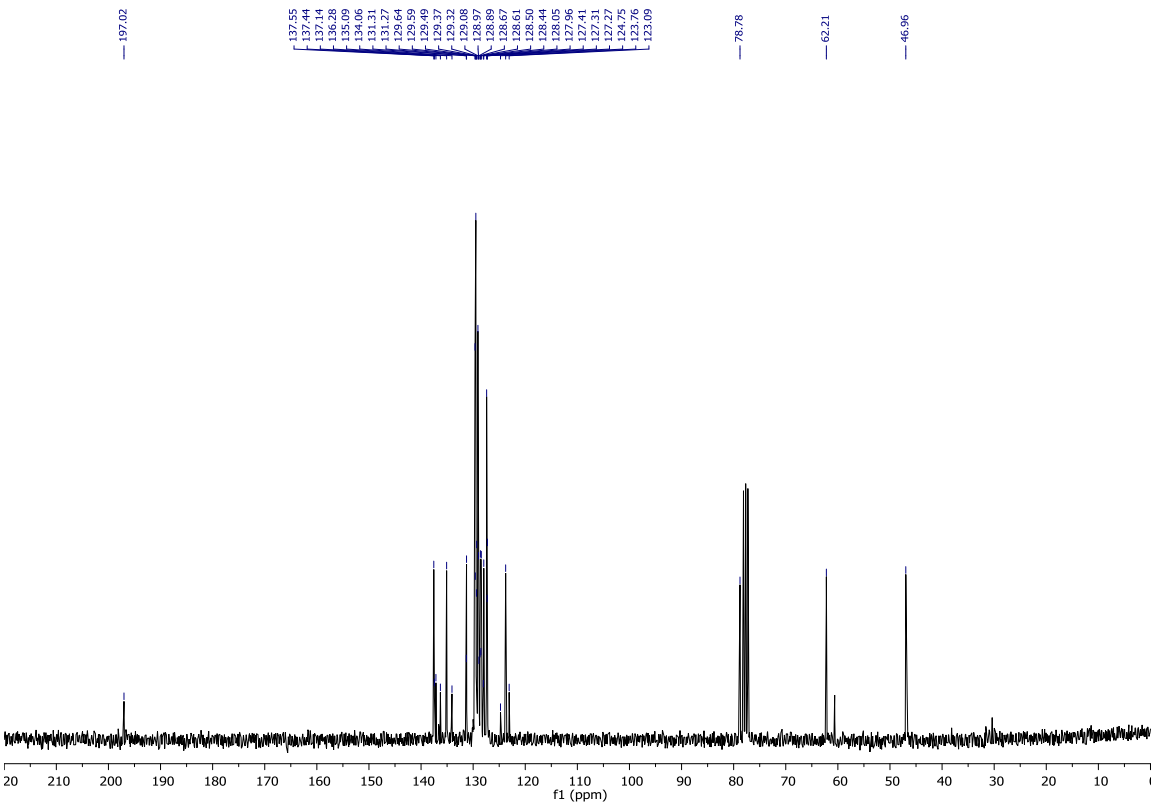


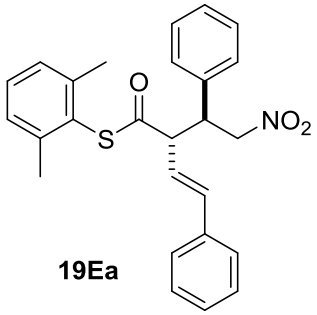
19Da

Mixture of diastereomer

4.4:1



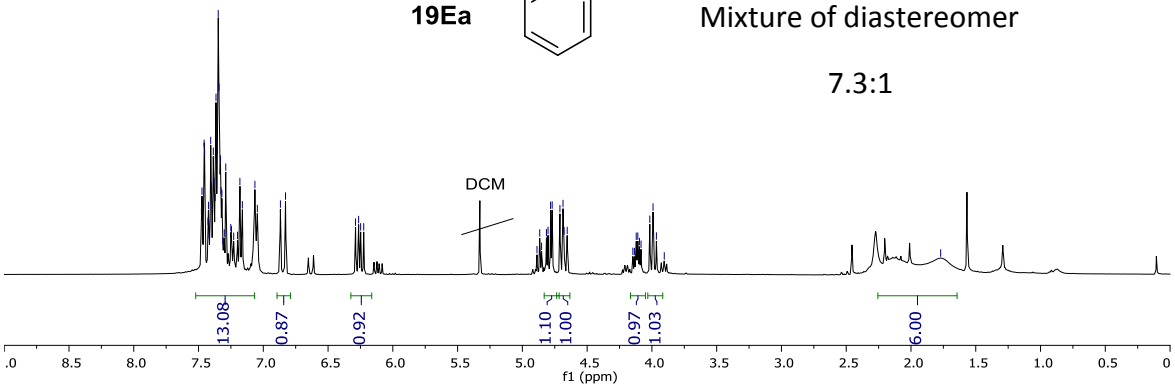


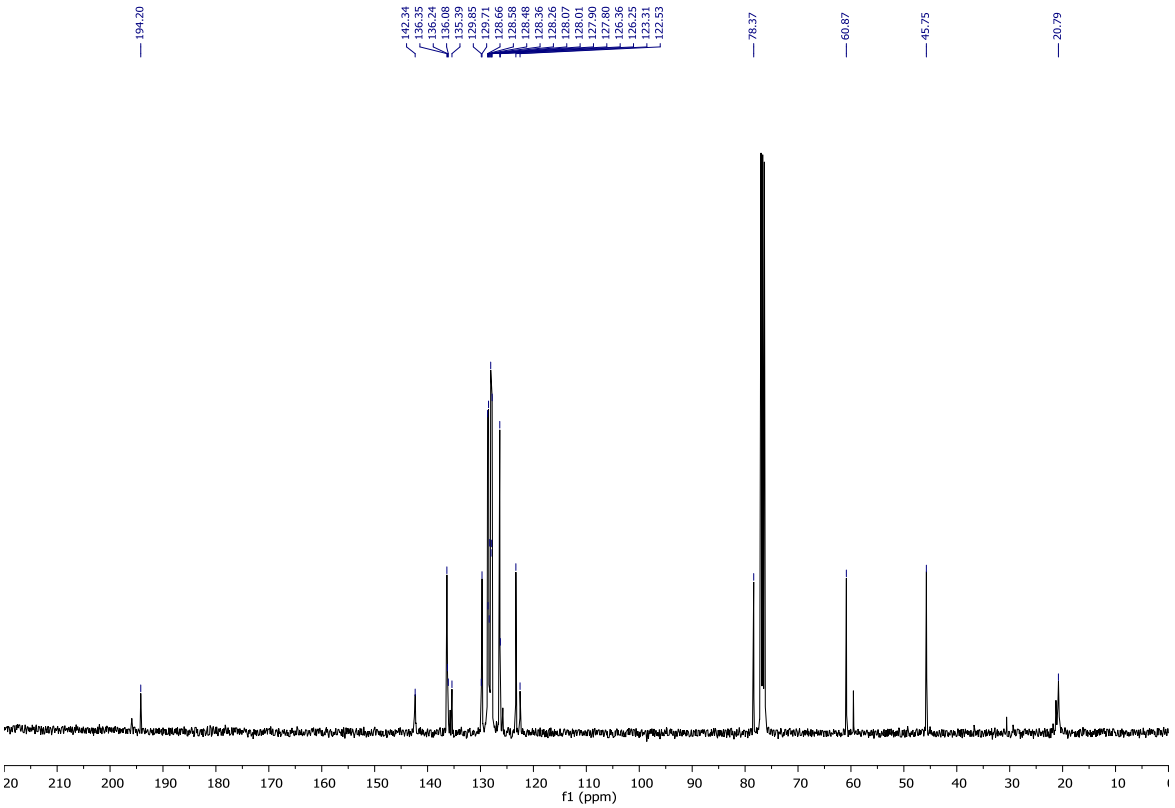


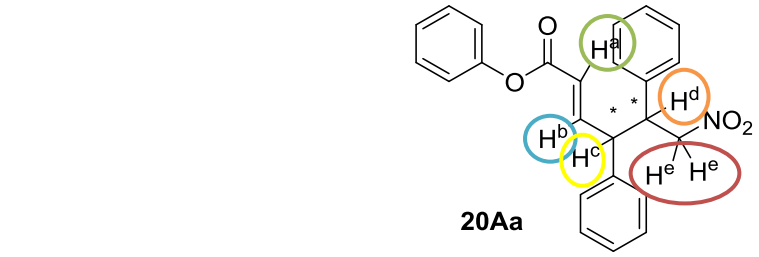
19Ea

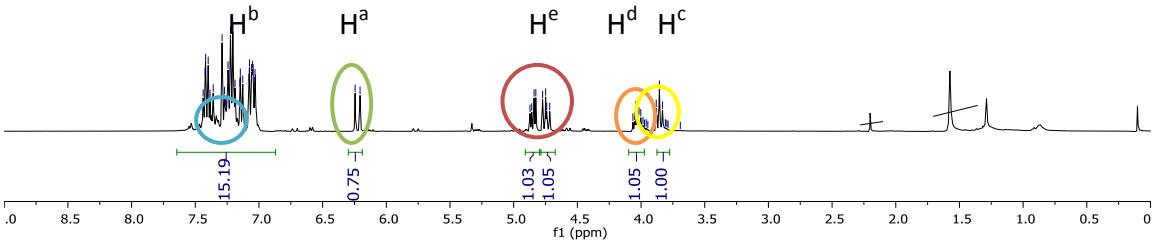
Mixture of diastereomer

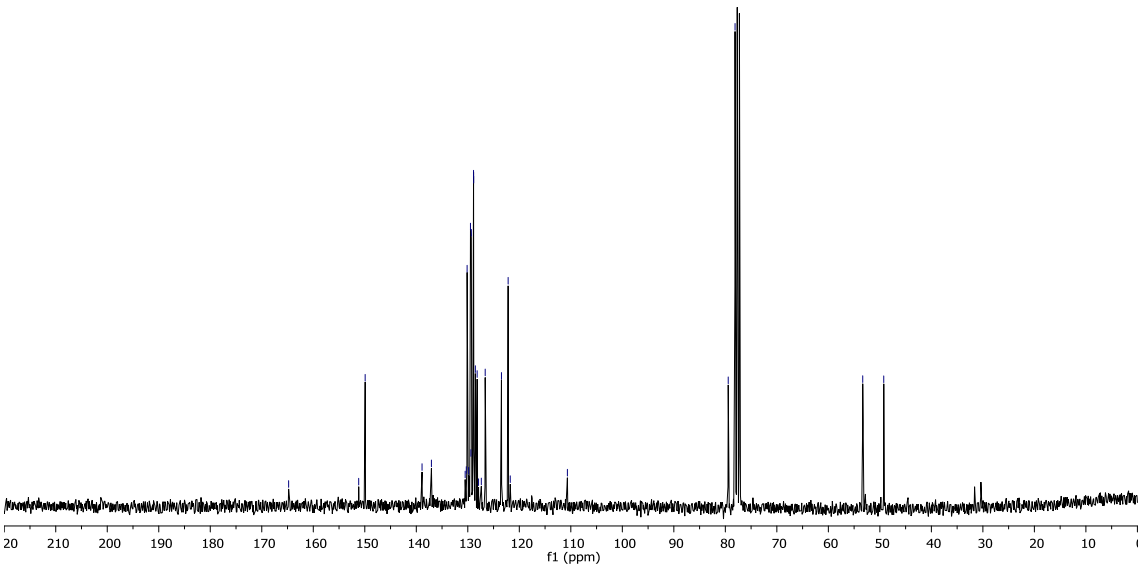
7.3:1

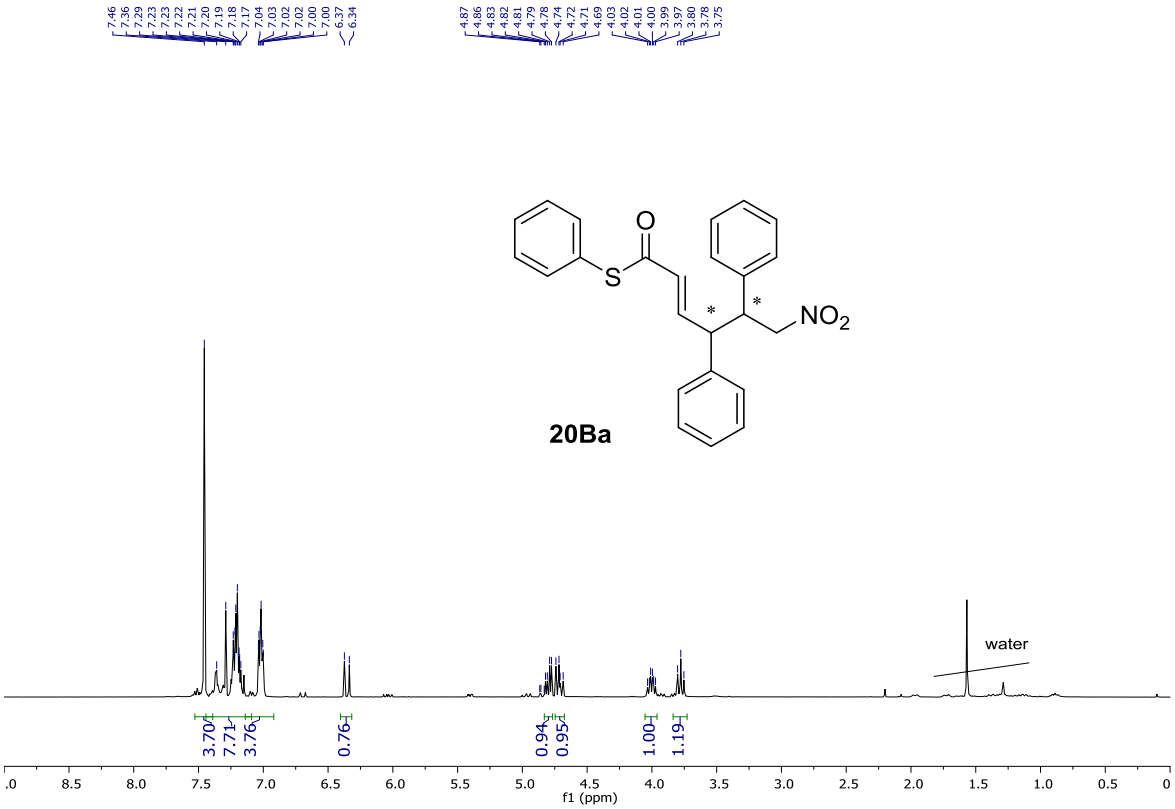


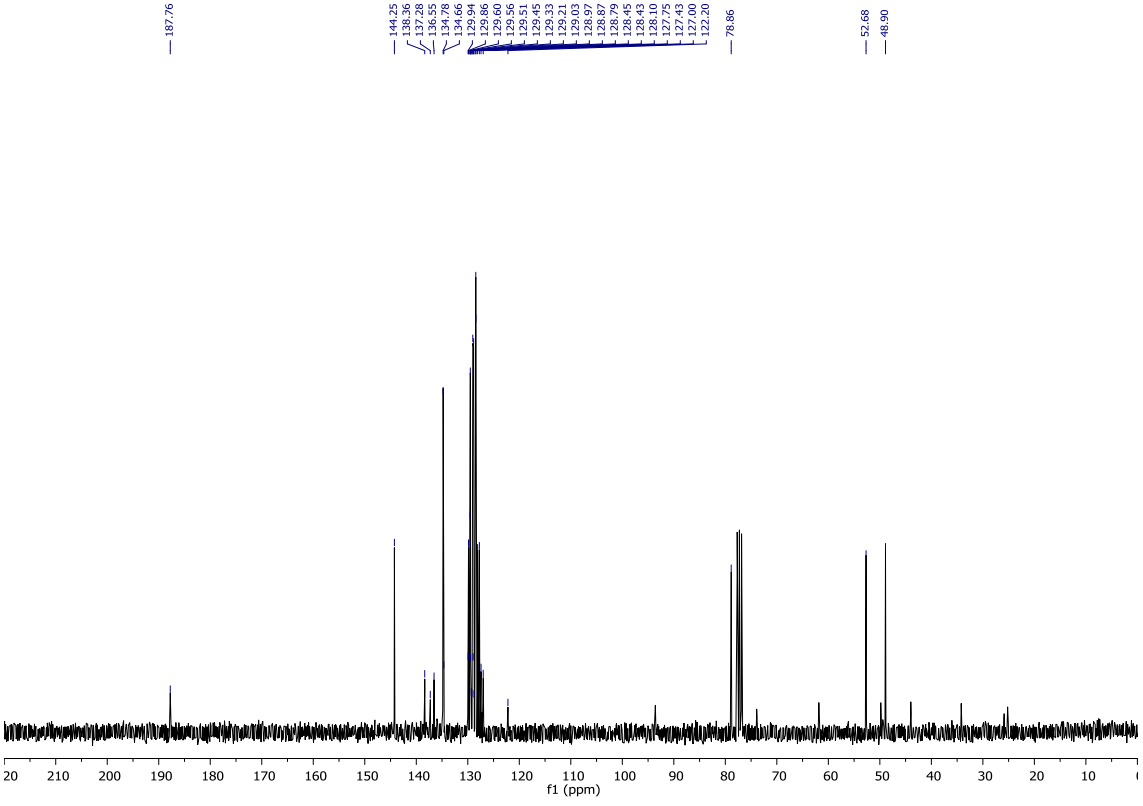


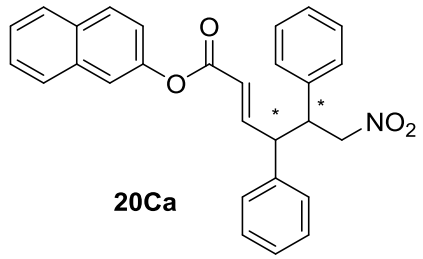

O
O
H^a
H^b
H^c
H^d
NO_2
H^e H^e
20Aa


H^b
H^a
H^e
H^d H^c
15.19
0.75
1.03
1.05
1.05
1.00
f1 (ppm)

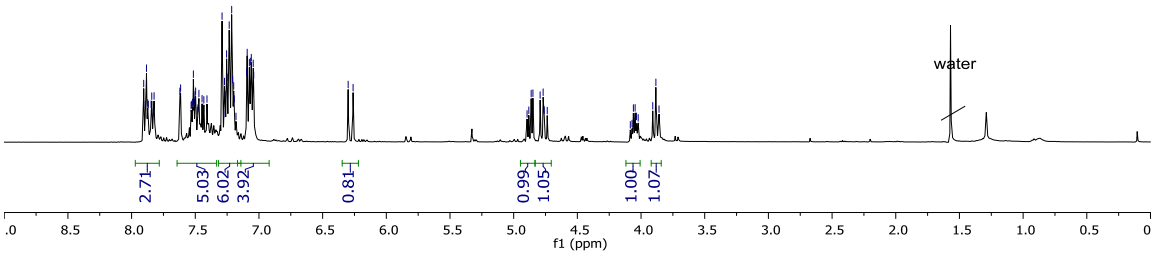

f1 (ppm)

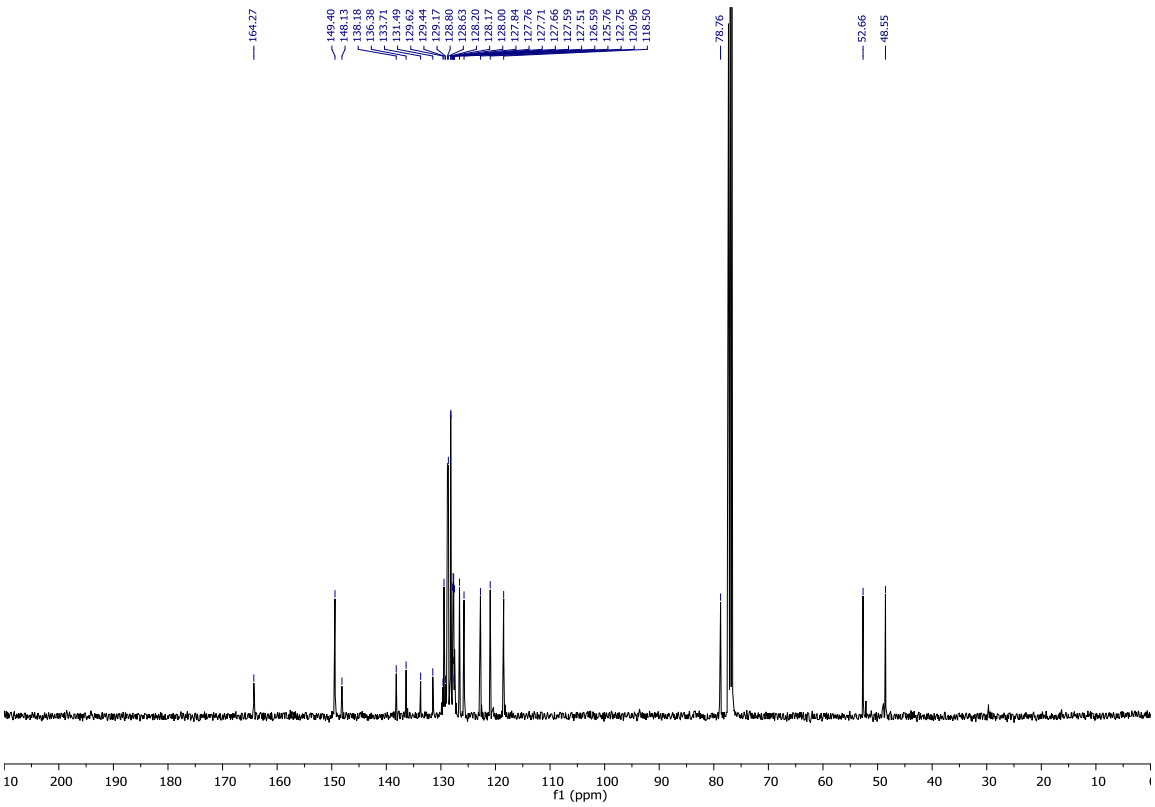

7.46
7.36
7.29
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.04
7.03
7.02
7.02
7.00
7.00
6.37
6.34
4.87
4.86
4.83
4.82
4.81
4.79
4.78
4.74
4.72
4.71
4.69
4.03
4.02
4.01
4.00
3.99
3.97
3.80
3.78
3.75
O
S
*
*
NO2
20Ba
water
3.70
7.71
3.76
0.76
0.94
0.95
1.00
1.19
f1 (ppm)

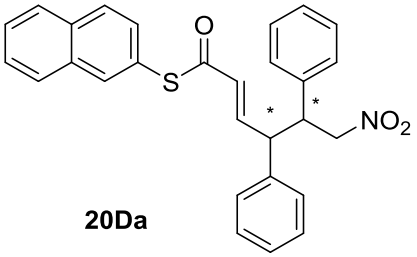

187.76
144.25
138.36
137.28
136.55
134.78
134.66
129.94
129.86
129.60
129.56
129.51
129.45
129.33
129.21
129.03
128.97
128.87
128.79
128.45
128.43
128.10
127.75
127.43
127.00
122.20
78.86
52.68
48.90
f1 (ppm)


O
O
*
*
NO2

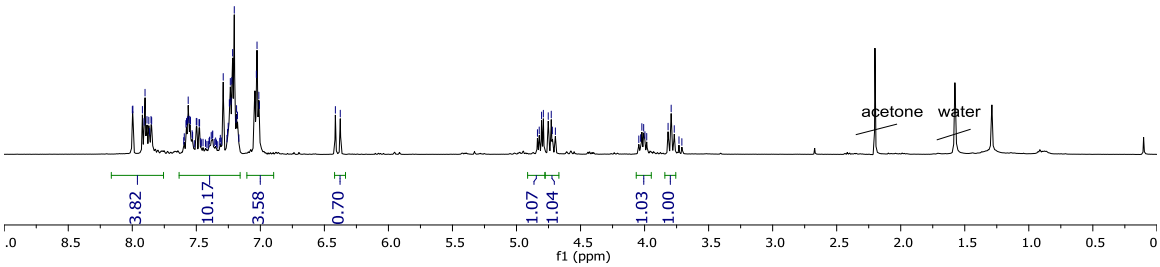
20Ca

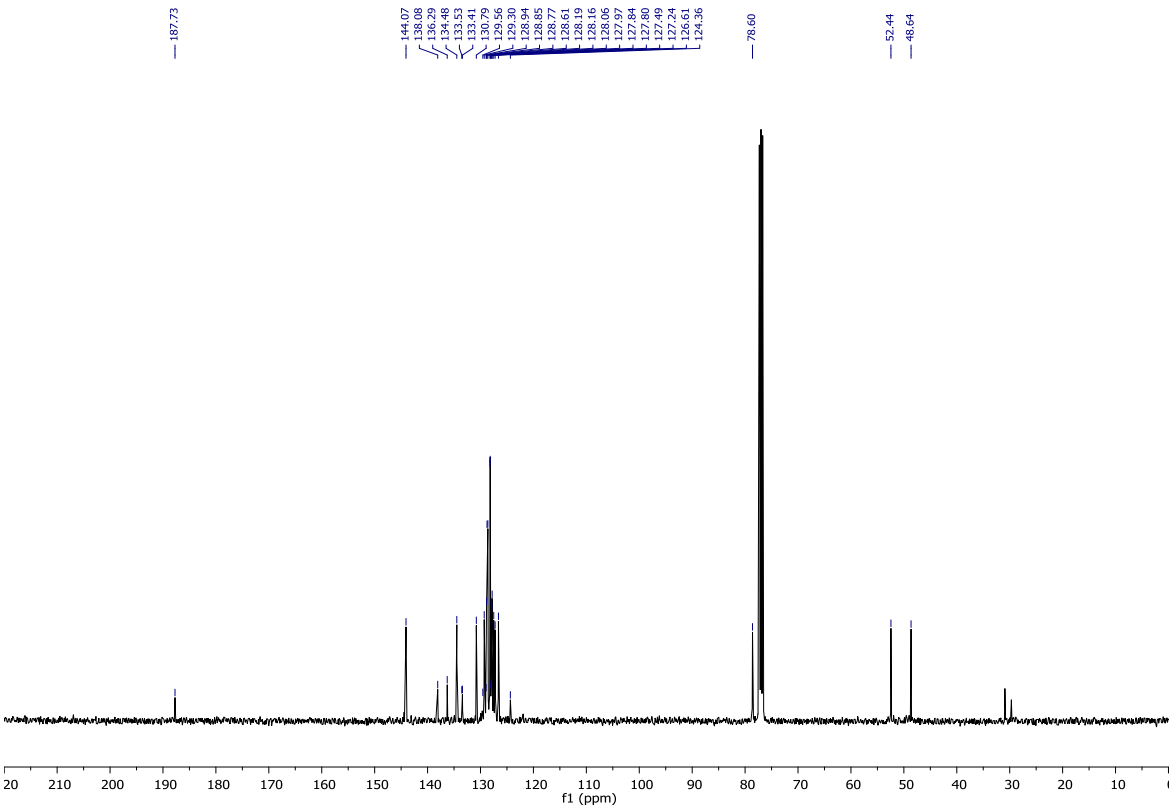

water
2.71
5.03
6.02
3.92
0.81
0.99
1.05
1.00
1.07
f1 (ppm)

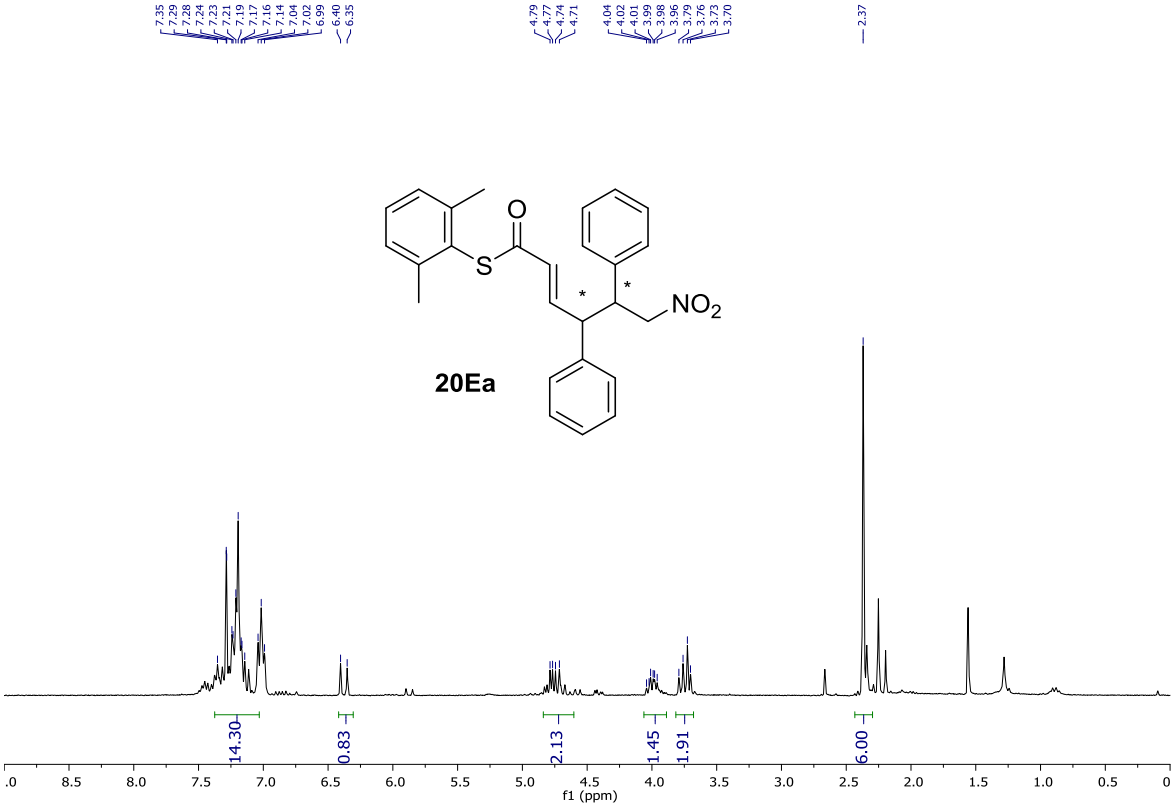

164.27
149.40
148.13
138.18
136.38
133.71
131.49
129.62
129.44
128.97
128.80
128.63
128.20
128.17
128.00
127.84
127.76
127.71
127.66
127.59
127.51
126.59
125.76
122.75
120.96
118.50
78.76
52.66
48.55
f1 (ppm)

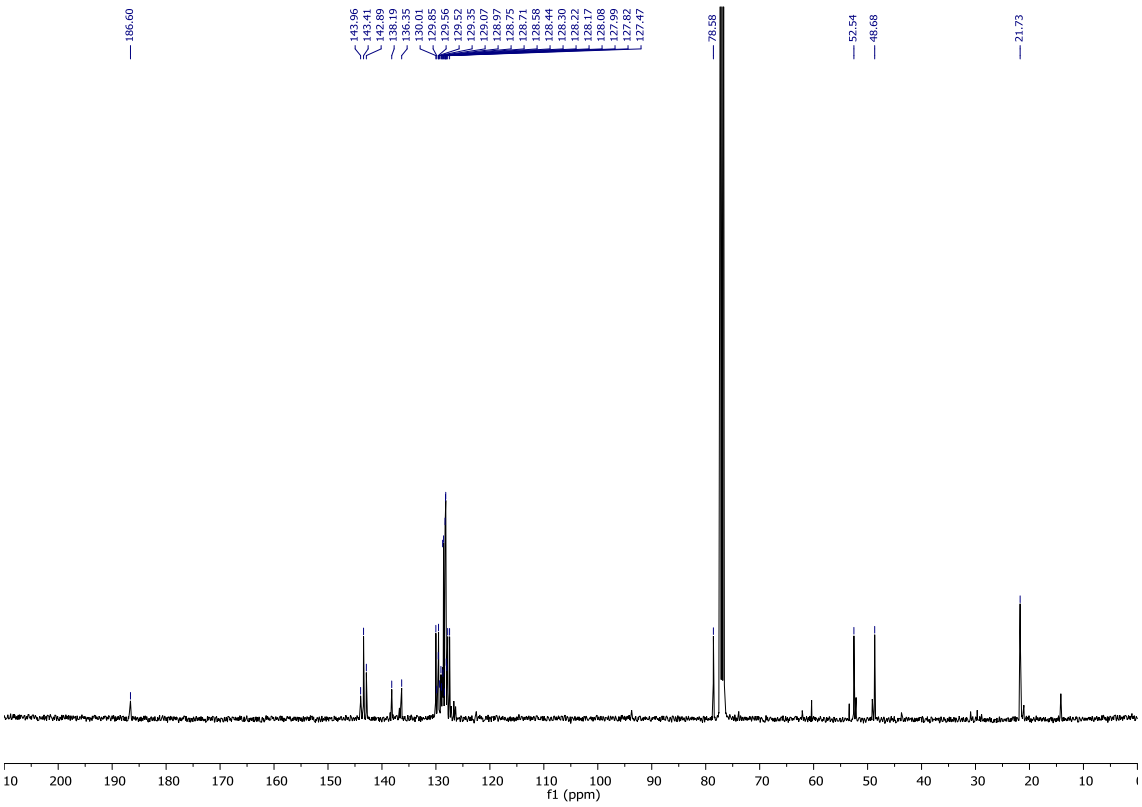

O
S
*
*
NO2

20Da

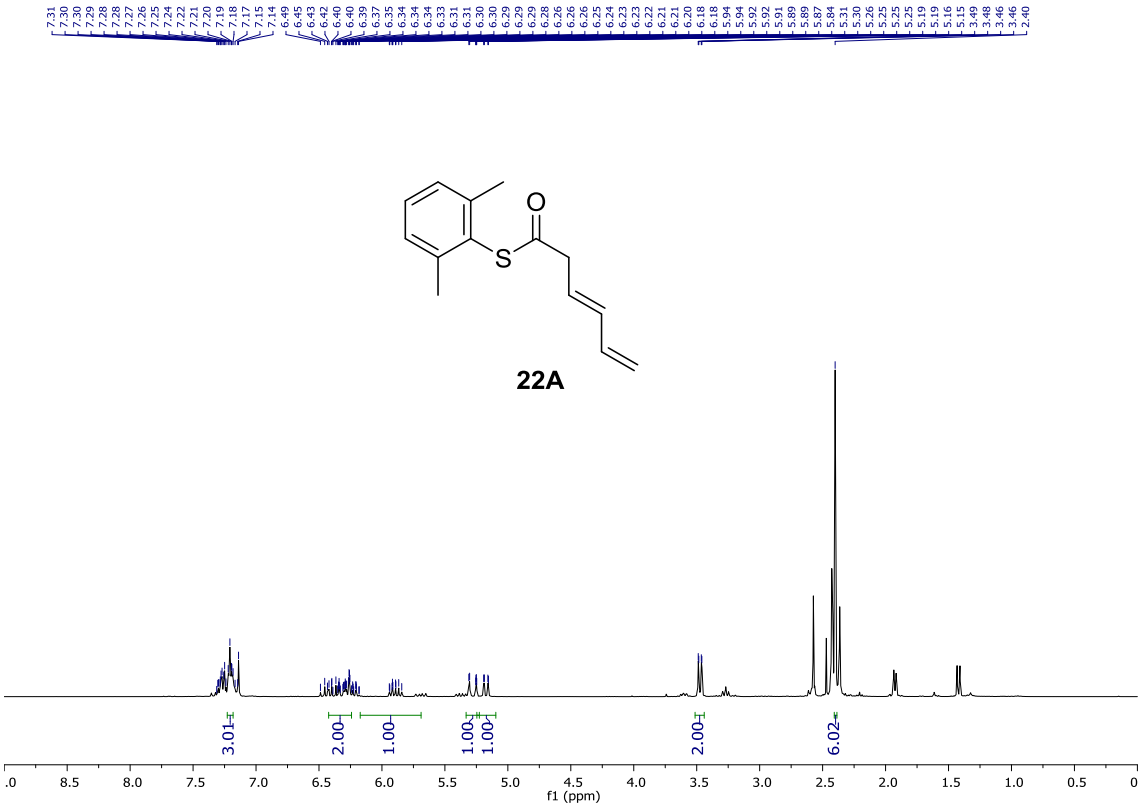

acetone
water
3.82
10.17
3.58
0.70
1.07
1.04
1.03
1.00
f1 (ppm)

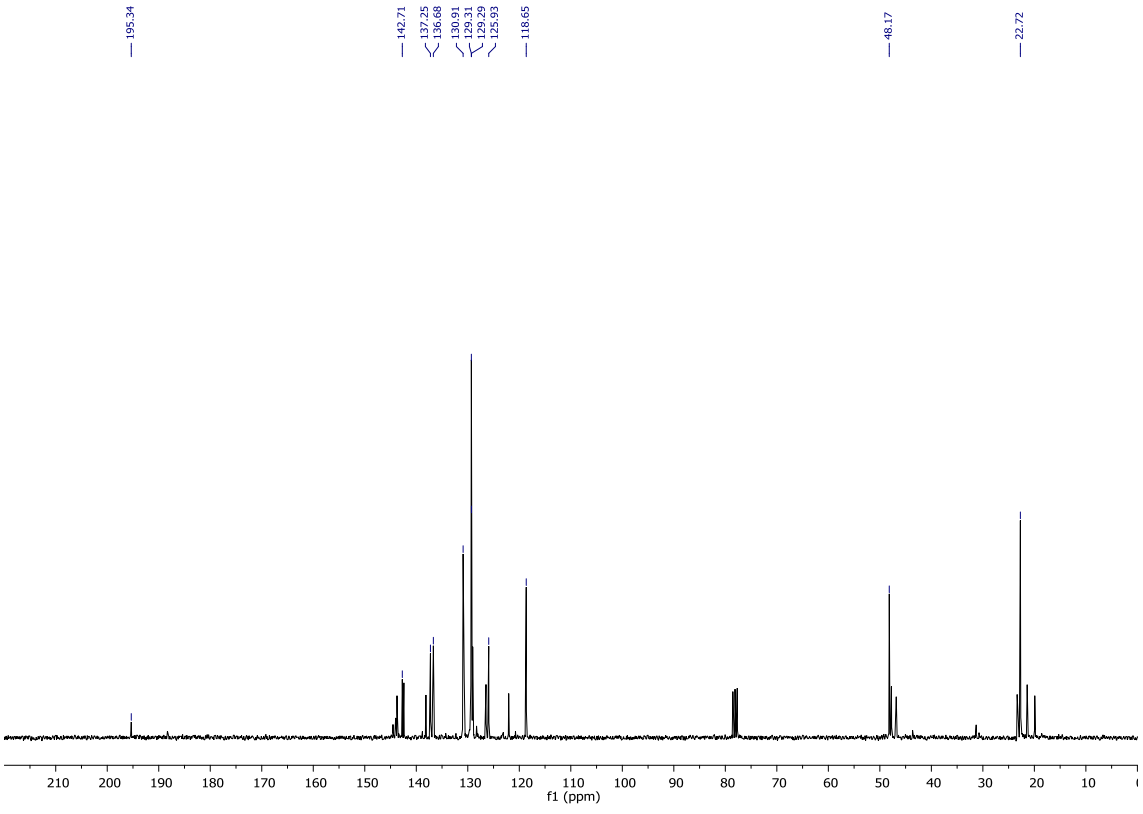

187.73
144.07
138.08
136.29
134.48
133.53
133.41
130.79
129.56
129.30
128.94
128.85
128.77
128.61
128.19
128.16
128.06
127.97
127.84
127.80
127.49
127.24
126.61
124.36
78.60
52.44
48.64
f1 (ppm)

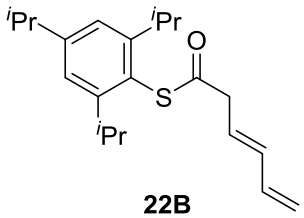

7.35
7.29
7.28
7.24
7.23
7.21
7.19
7.17
7.16
7.14
7.04
7.02
6.99
6.40
6.35
4.79
4.77
4.74
4.71
4.04
4.02
4.01
3.99
3.98
3.96
3.79
3.76
3.73
3.70
2.37
O
S
*
*
NO2
20Ea
14.30
0.83
2.13
1.45
1.91
6.00
f1 (ppm)


186.60
143.96
143.41
142.89
138.19
136.35
130.01
129.85
129.56
129.52
129.35
129.07
128.97
128.75
128.71
128.58
128.44
128.30
128.22
128.17
128.08
127.99
127.82
127.47
78.58
52.54
48.68
21.73
f1 (ppm)

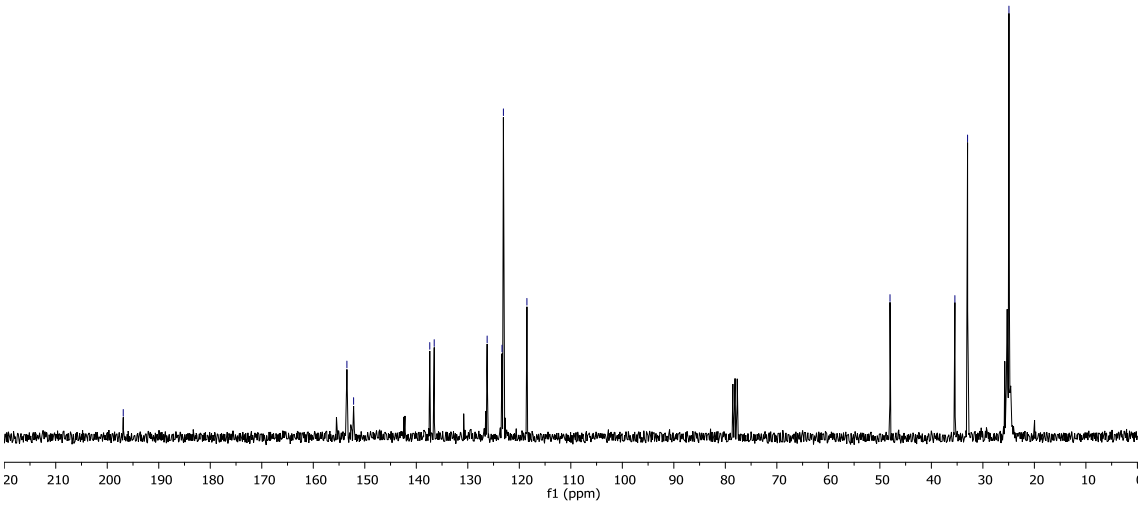
6.6.3. Chapter 3

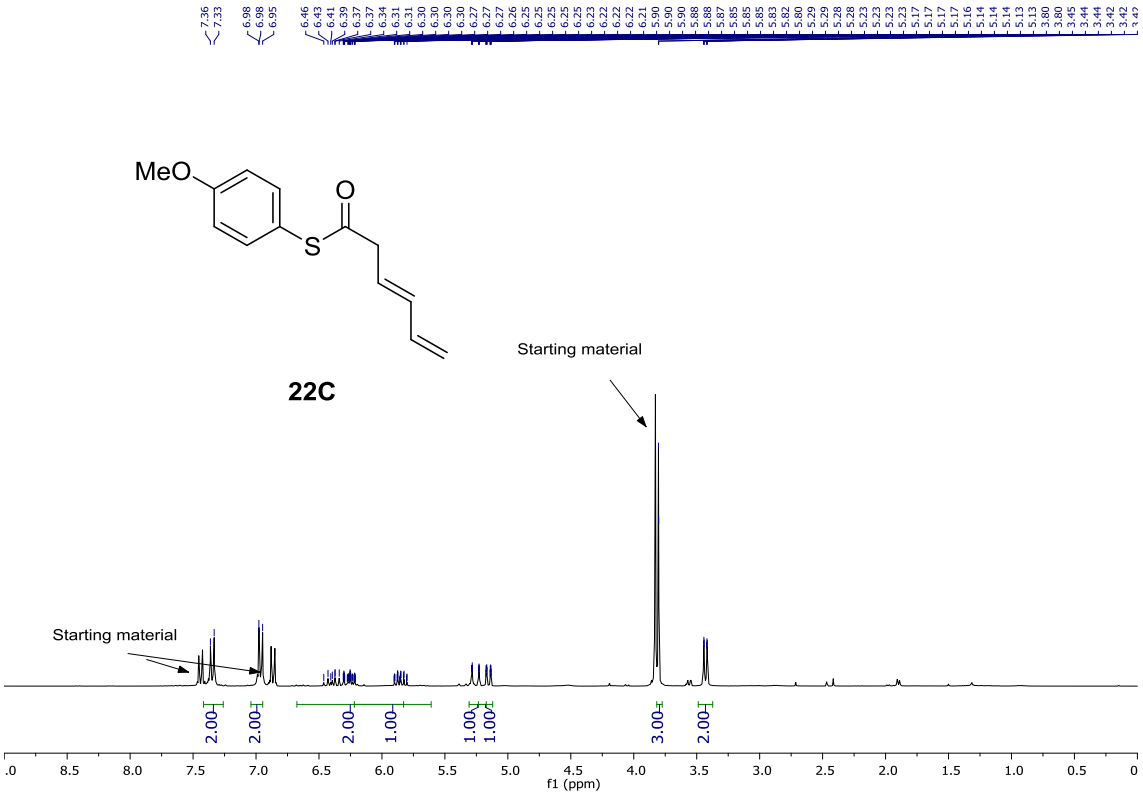


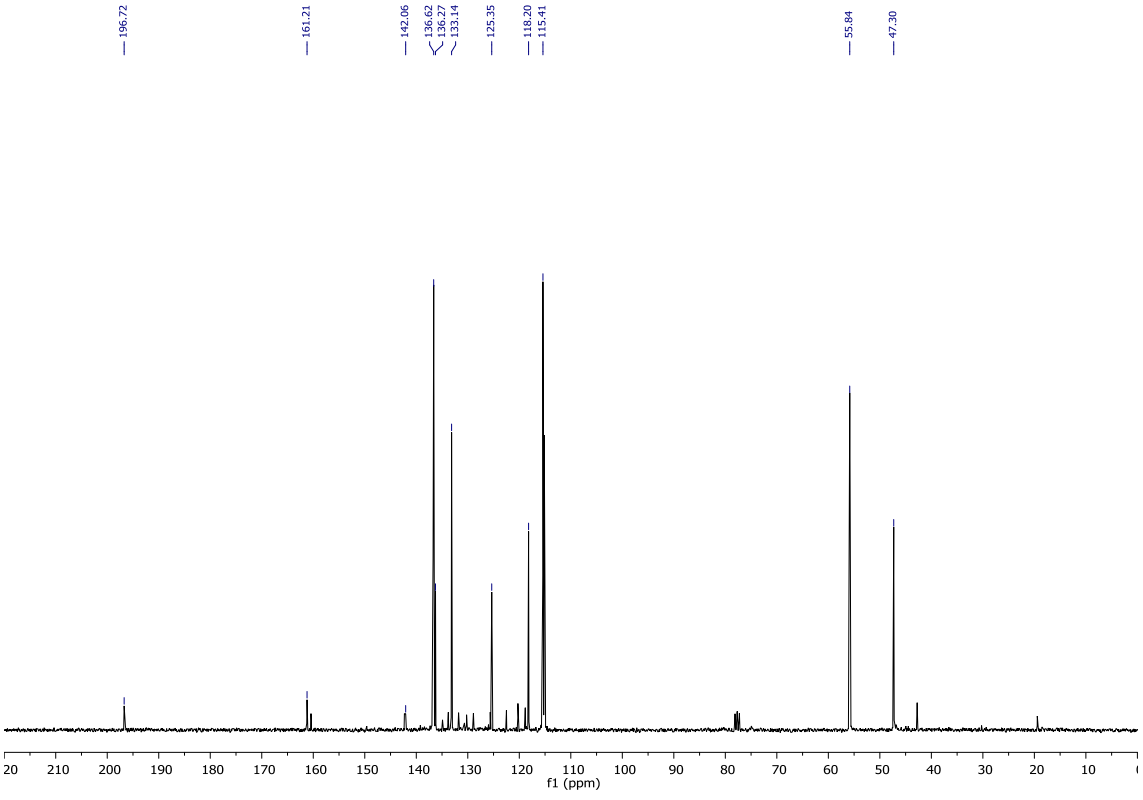


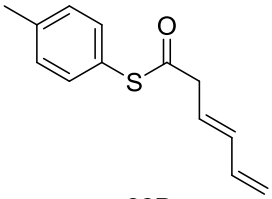


22B

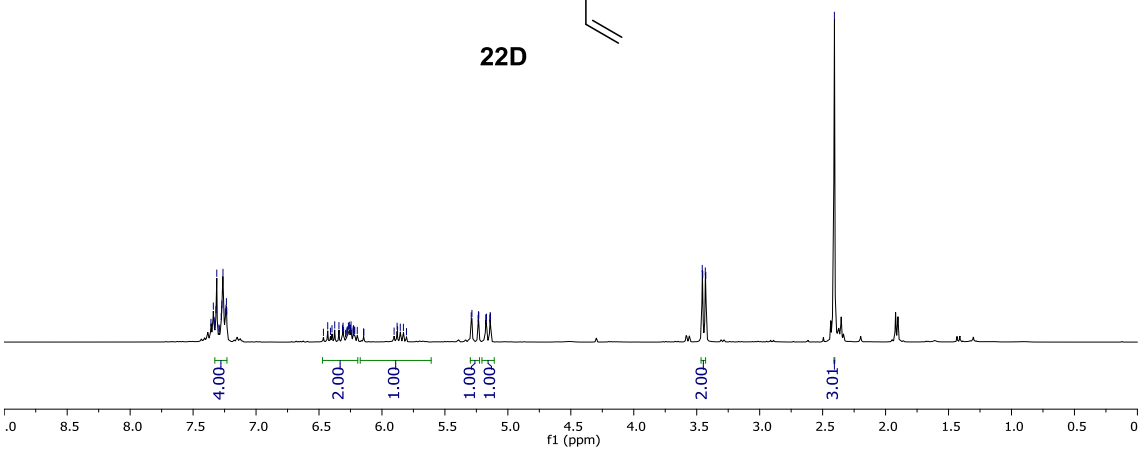


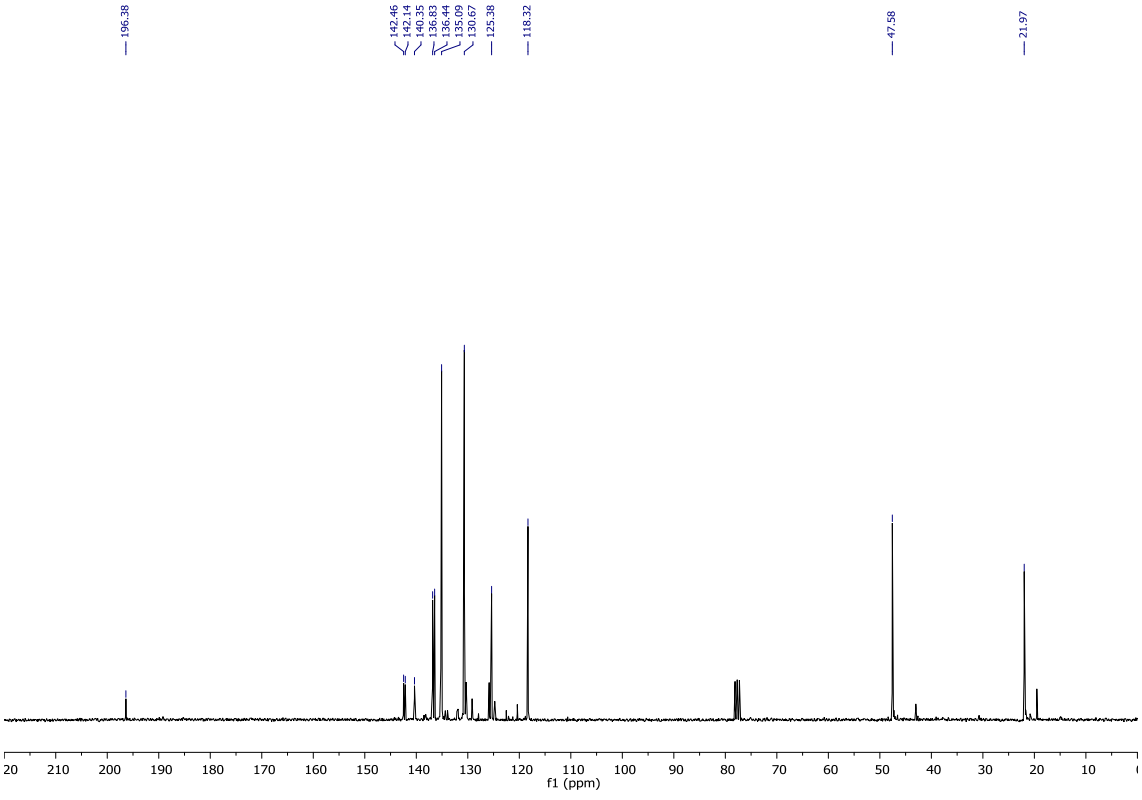

MeO
O
S
22C
Starting material
Starting material
2.00
2.00
2.00
1.00
1.00
1.00
3.00
2.00
f1 (ppm)

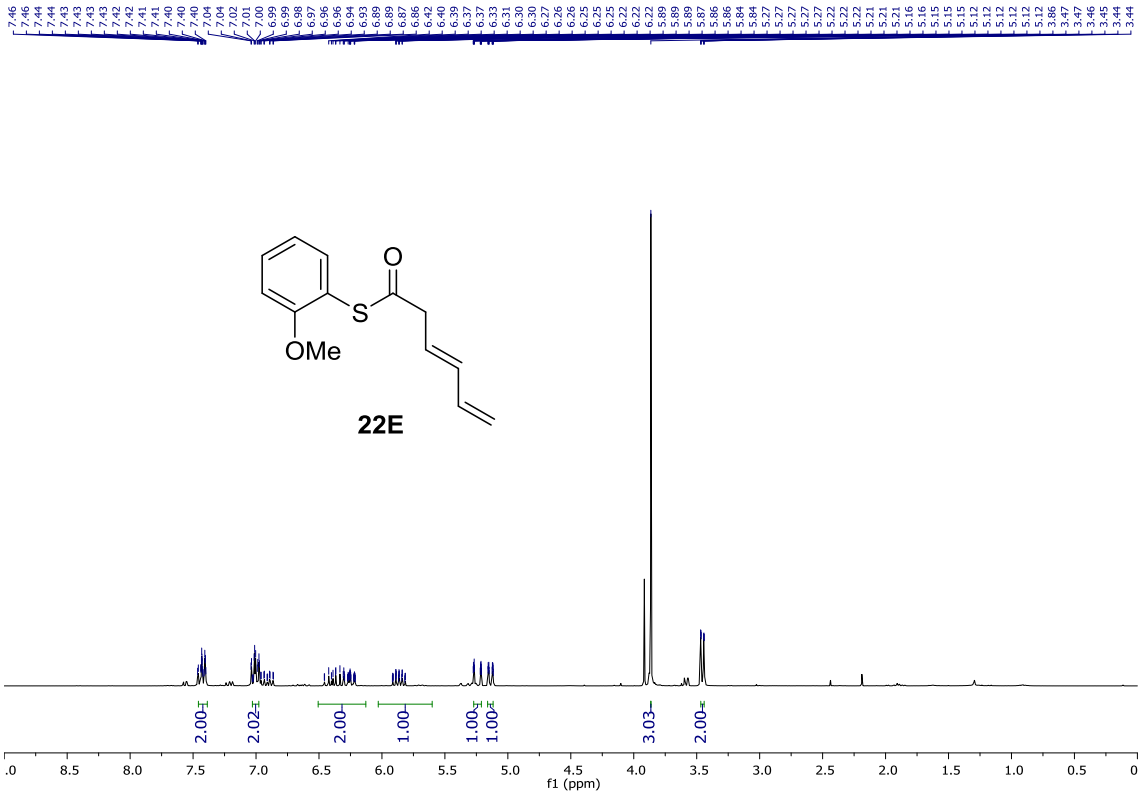

196.72
161.21
142.06
136.62
136.27
133.14
125.35
118.20
115.41
55.84
47.30
f1 (ppm)

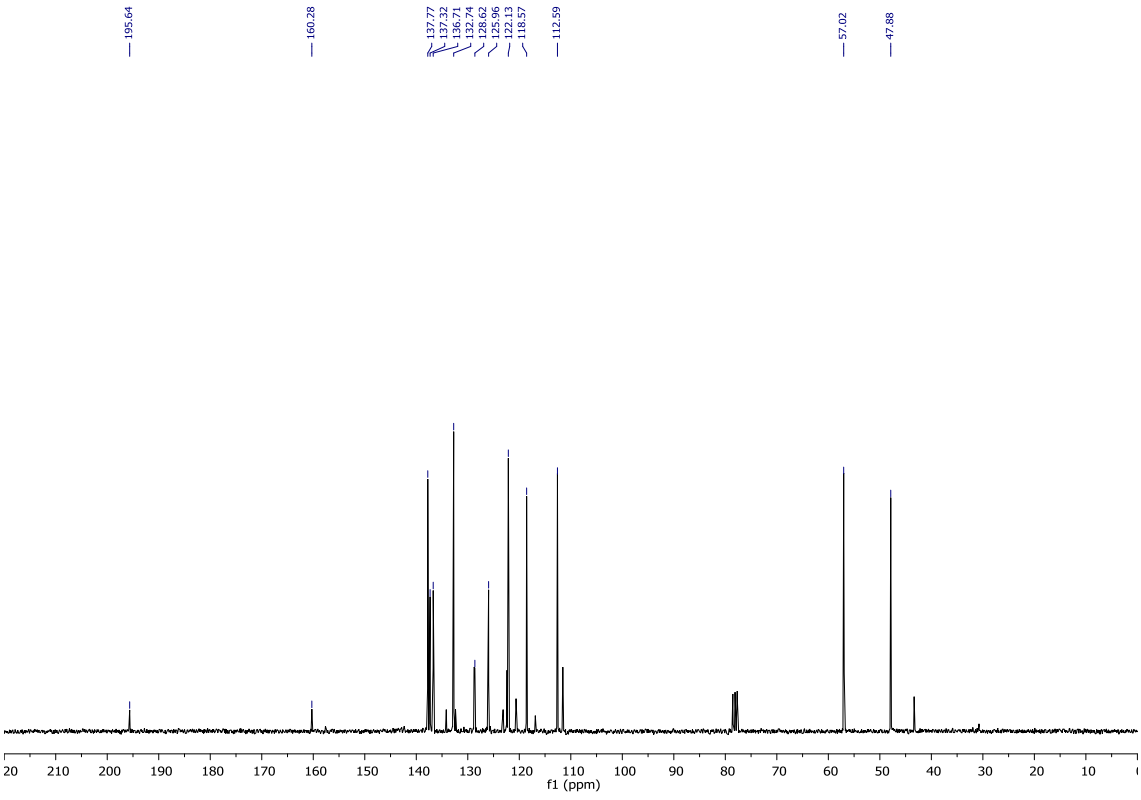


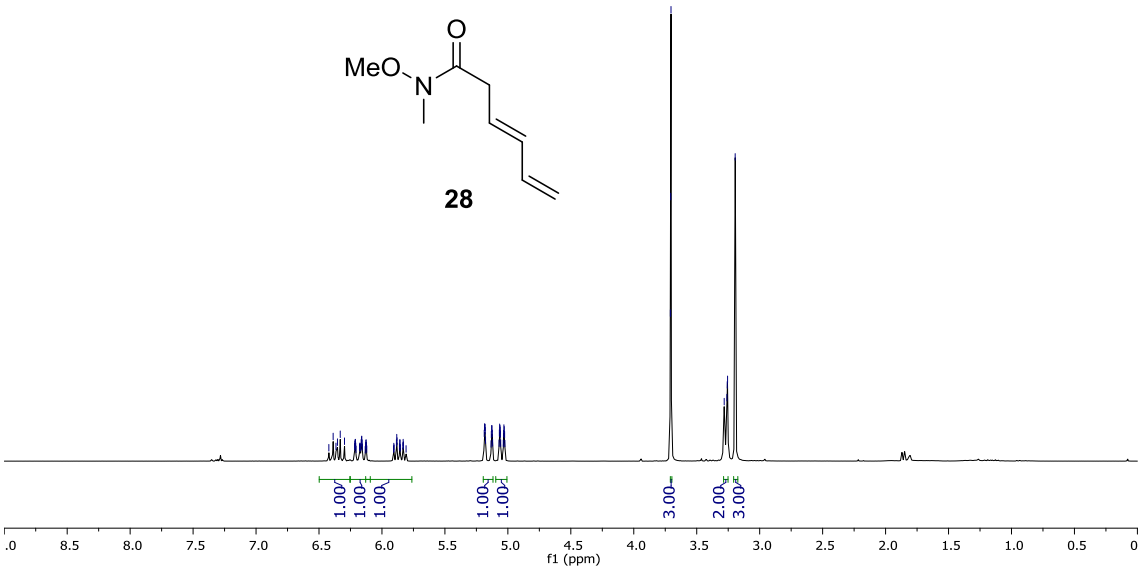
22D

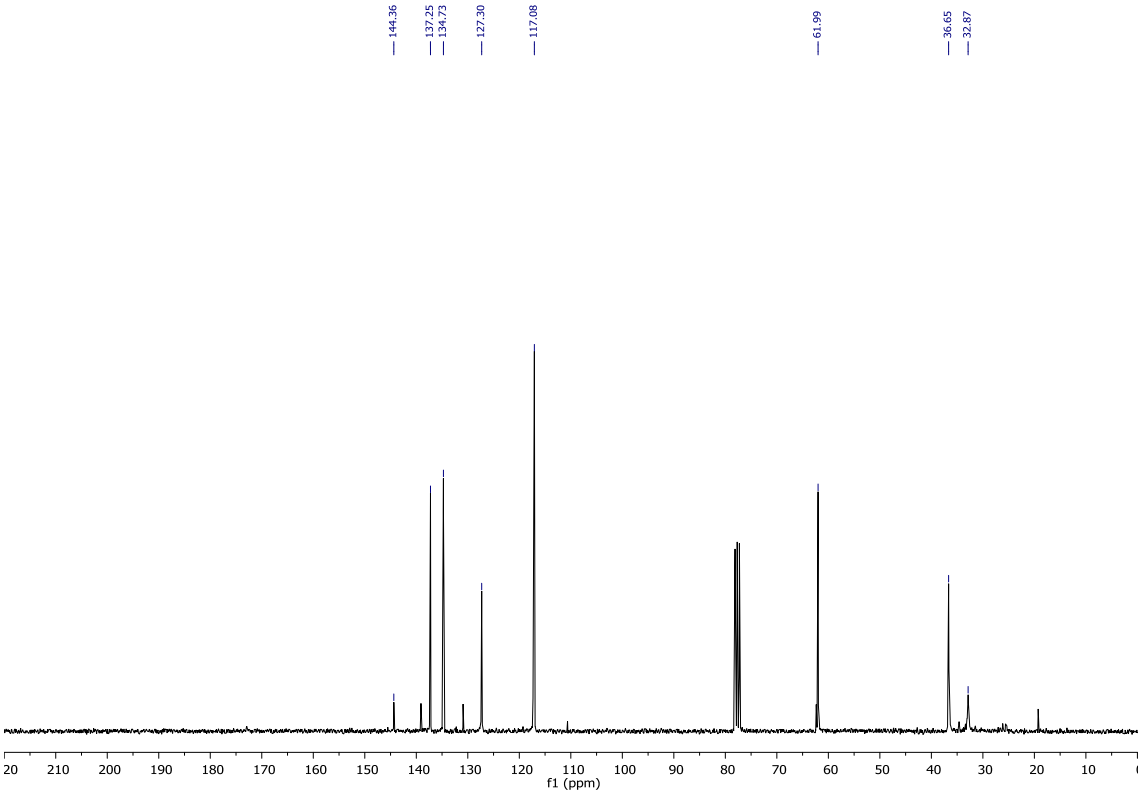

4.00
2.00
1.00
1.00
1.00
2.00
3.01
f1 (ppm)

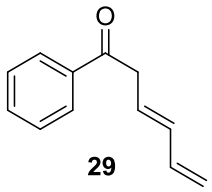

196.38
142.46
142.14
140.35
136.83
136.44
135.09
130.67
125.38
118.32
47.58
21.97
f1 (ppm)


O
S
OMe
22E
2.00
2.02
2.00
1.00
1.00
1.00
3.03
2.00
f1 (ppm)

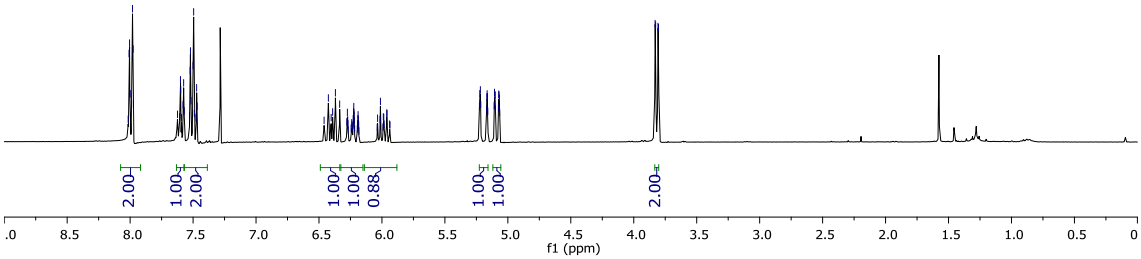

195.64
160.28
137.77
137.32
136.71
131.74
128.62
125.96
122.13
118.57
112.59
57.02
47.88
f1 (ppm)

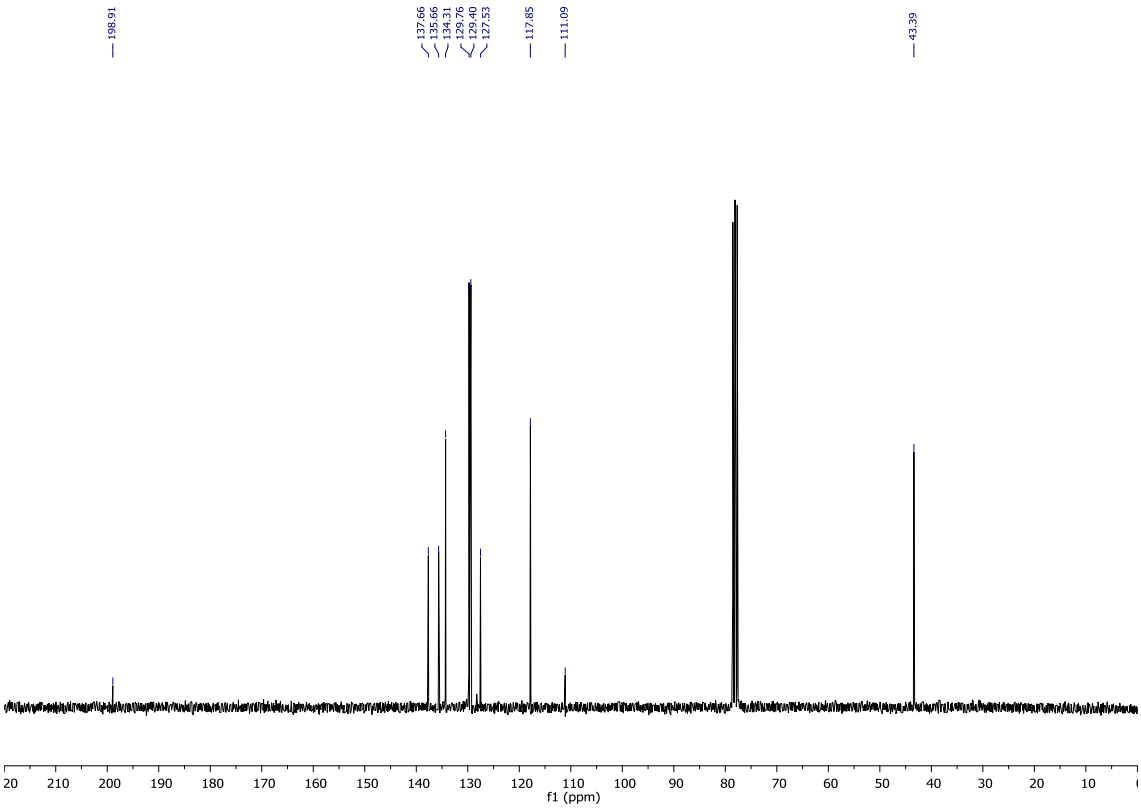

MeO
N
O
28
1.00
1.00
1.00
1.00
1.00
3.00
2.00
3.00
f1 (ppm)

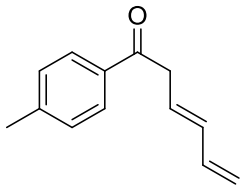

144.36
137.25
134.73
127.30
117.08
61.99
36.65
32.87
f1 (ppm)



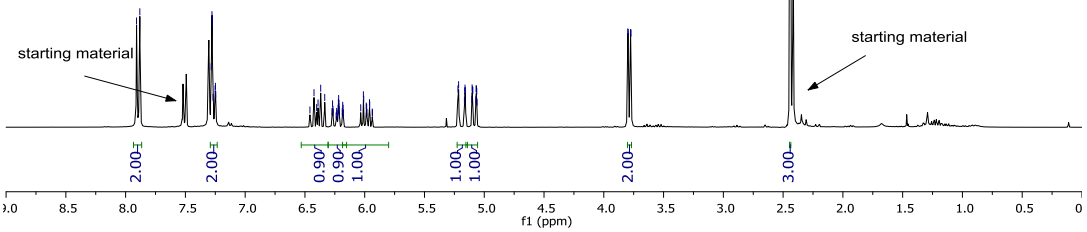
29

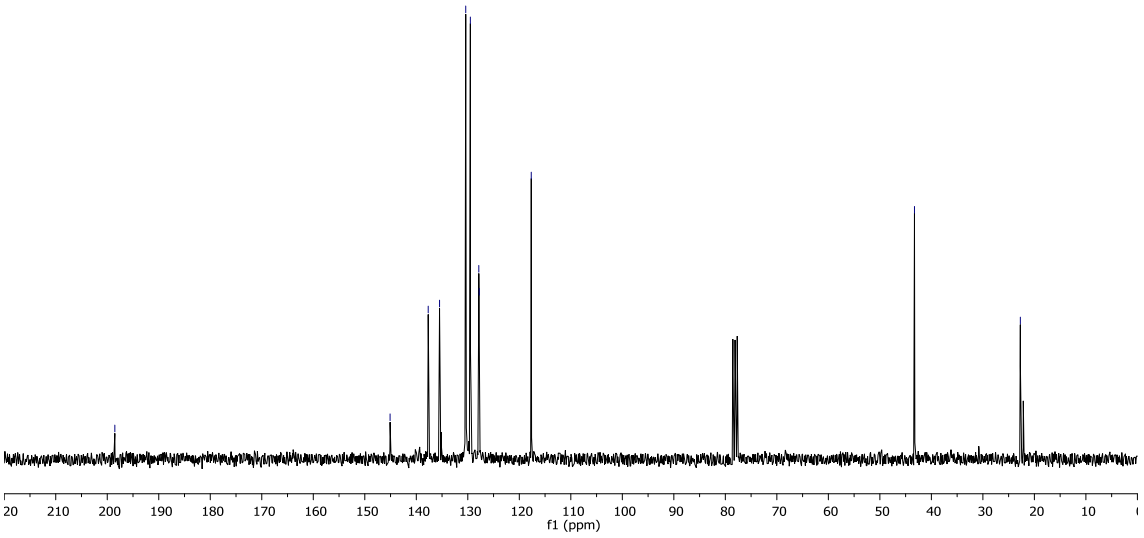

2.00
1.00
2.00
1.00
1.00
0.88
1.00
1.00
2.00
f1 (ppm)


198.91
137.66
135.66
134.31
129.76
129.40
127.53
117.85
111.09
43.39
f1 (ppm)

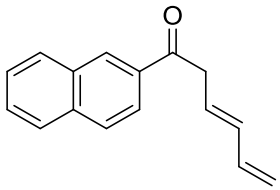


30

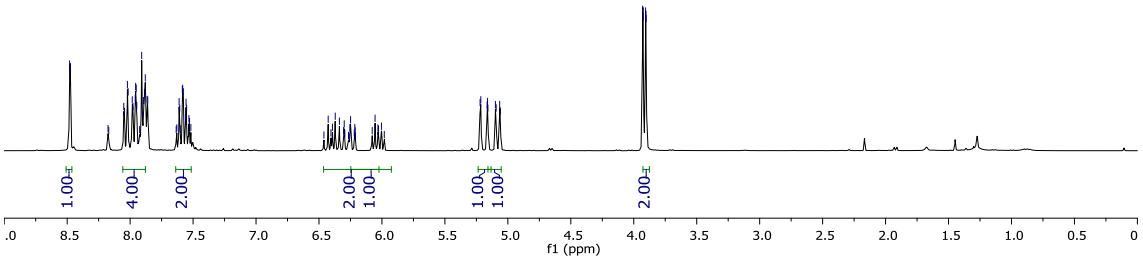

starting material
starting material
2.00
2.00
0.90
0.90
1.00
1.00
1.00
2.00
3.00
f1 (ppm)

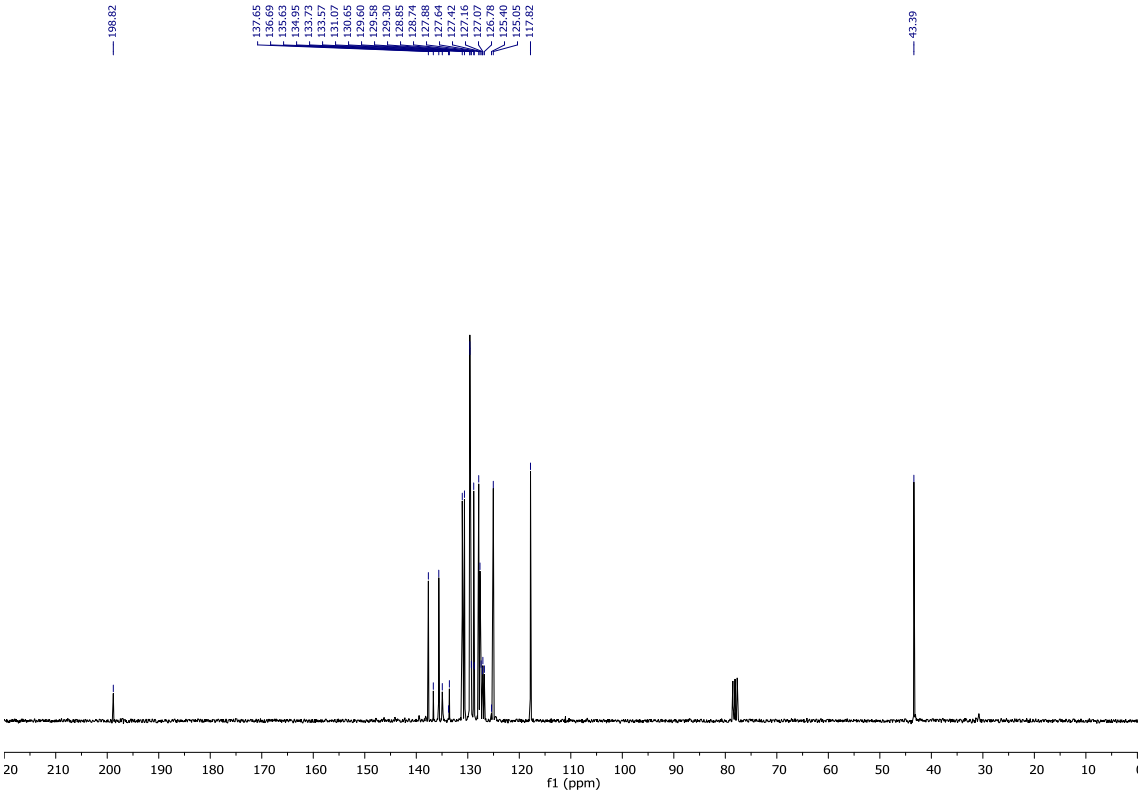

198.53
145.09
137.69
135.48
130.40
129.51
127.86
127.79
117.68
43.28
22.73
f1 (ppm)


8.48
8.47
8.18
8.17
8.05
8.04
8.02
8.02
7.98
7.98
7.96
7.96
7.95
7.95
7.92
7.91
7.90
7.89
7.89
7.88
7.87
7.86
7.63
7.63
7.61
7.61
7.60
7.59
7.58
7.58
7.56
7.56
7.55
7.53
7.53
7.52
6.46
6.43
6.40
6.39
6.37
6.34
6.30
6.30
6.27
6.26
6.25
6.25
6.22
6.22
6.21
6.21
6.08
6.05
6.03
6.03
6.00
5.98
5.22
5.21
5.16
5.16
5.10
5.09
5.06
5.06
3.93
3.92
3.91
3.90


O

31


1.00
4.00
2.00
2.00
1.00
1.00
1.00
2.00
.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
f1 (ppm)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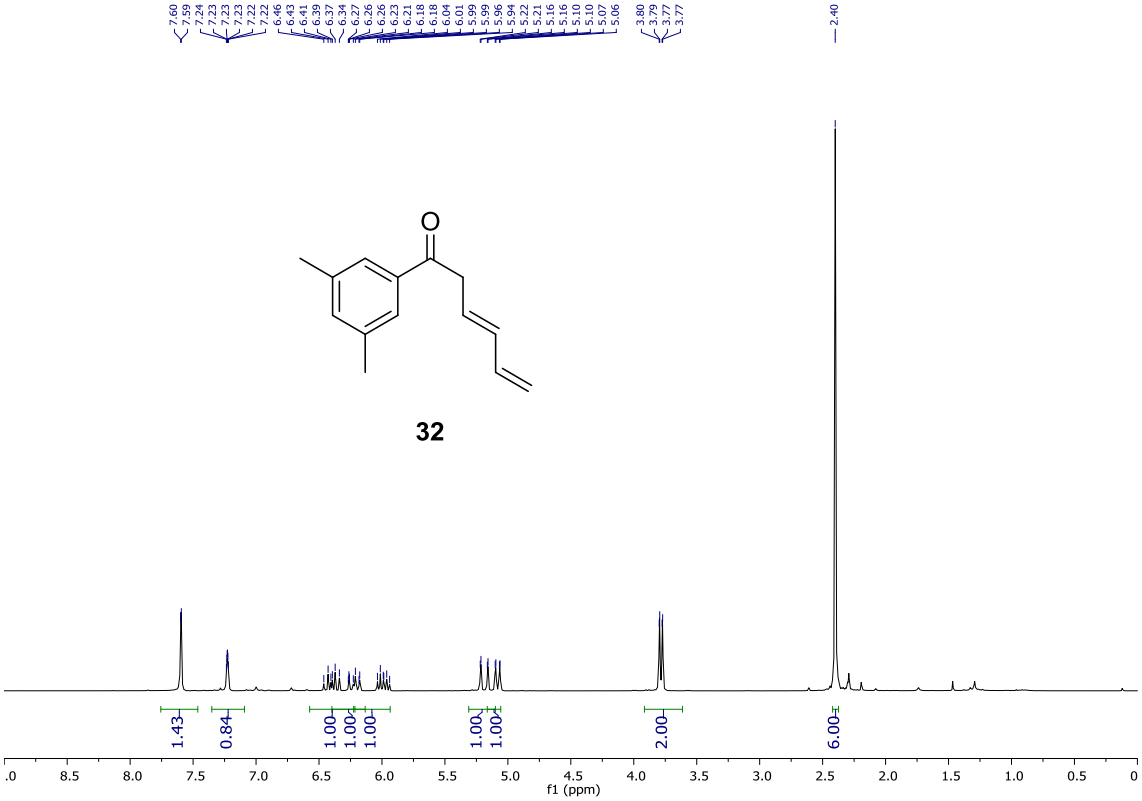
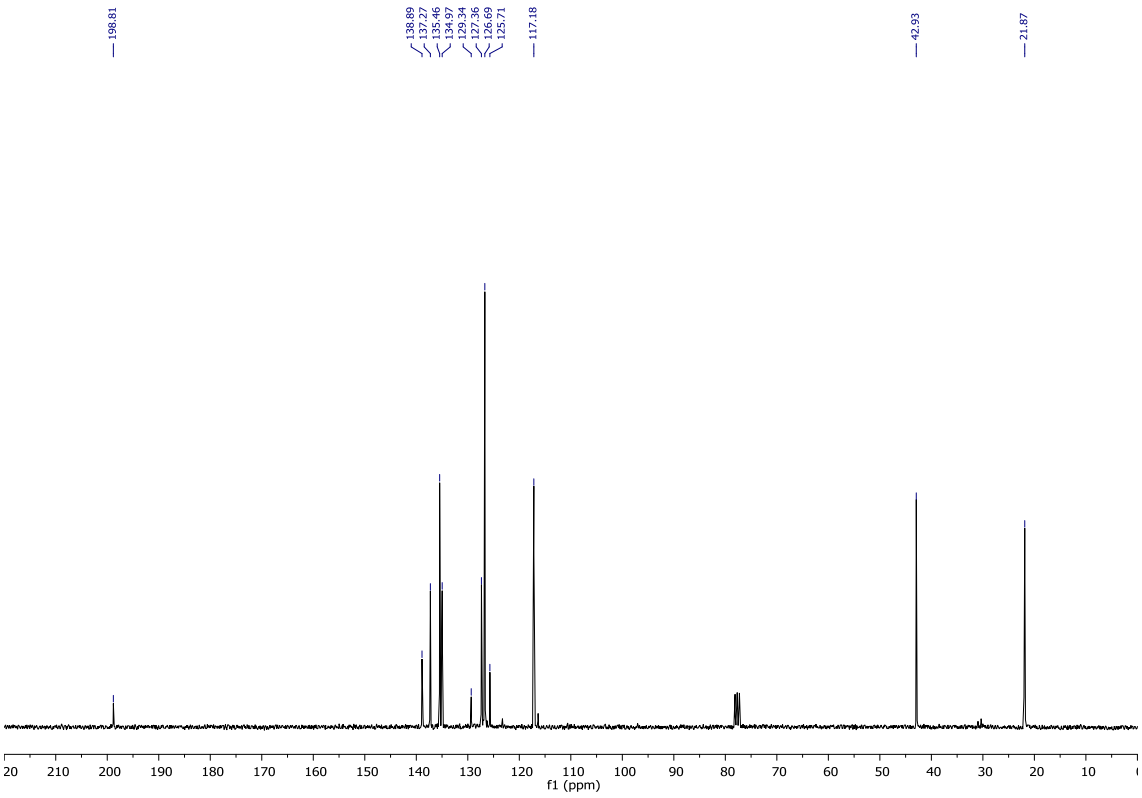
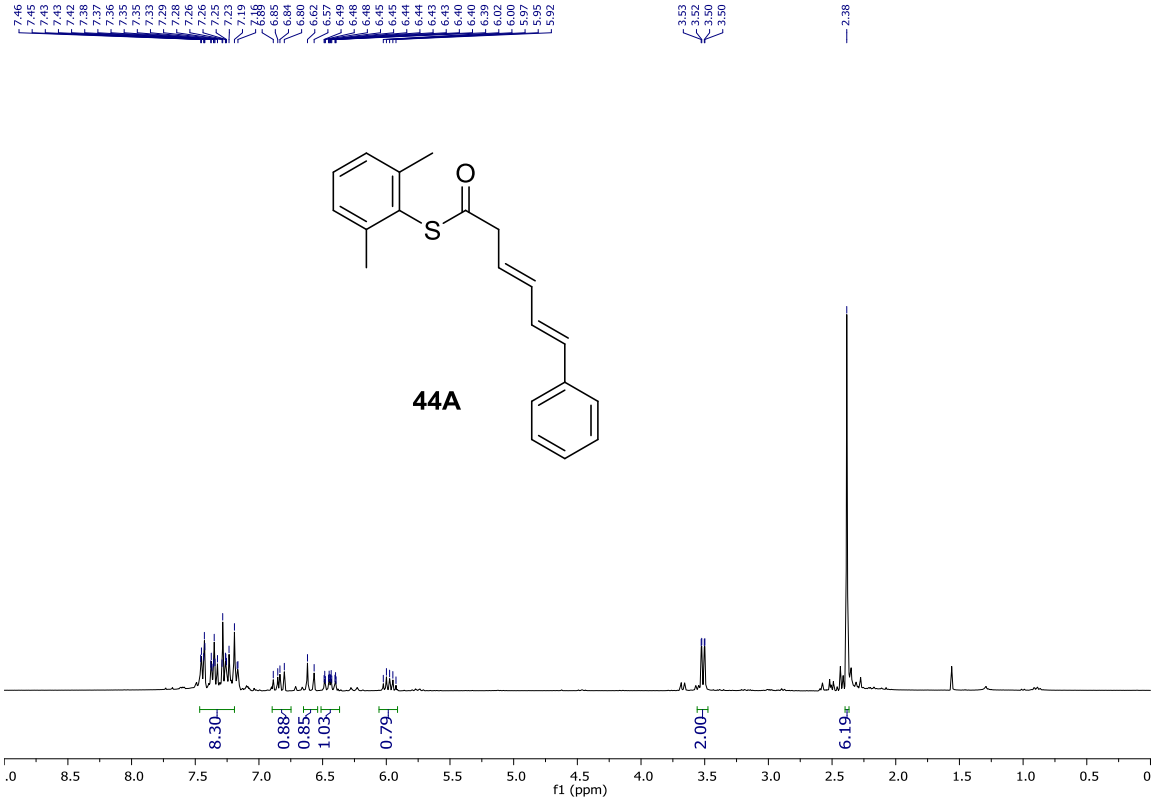
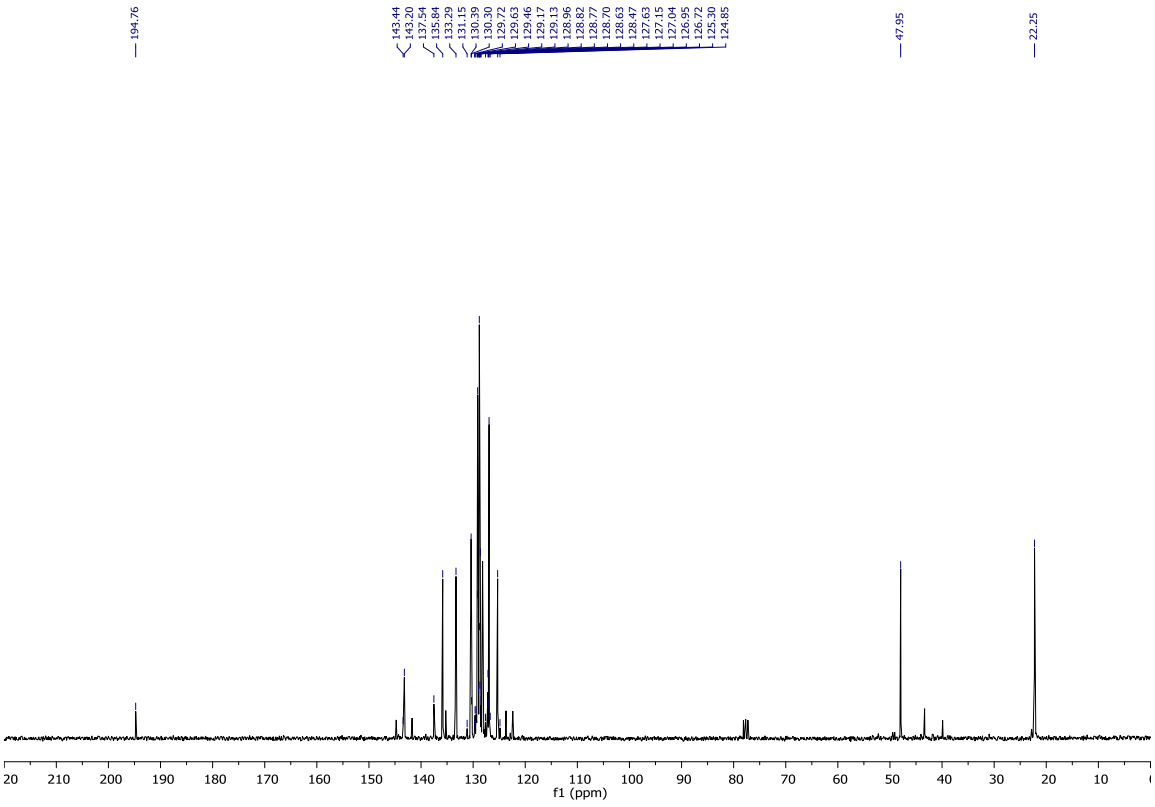
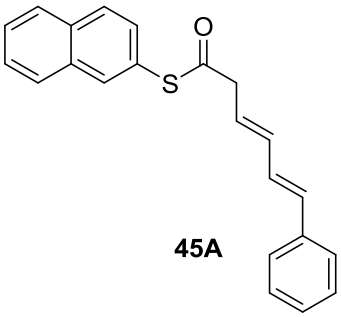
134.95
133.73
133.57
131.07
130.65
129.60
129.58
129.30
128.85
128.74
127.88
127.64
127.42
127.16
127.07
126.78
125.40
125.05
117.82
43.39
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.60
7.59
7.24
7.23
7.23
7.23
7.22
7.22
6.46
6.43
6.41
6.39
6.37
6.34
6.27
6.26
6.26
6.23
6.21
6.18
6.18
6.04
6.01
5.99
5.99
5.96
5.94
5.22
5.21
5.16
5.16
5.10
5.10
5.07
5.06
3.80
3.79
3.77
3.77
2.40
O
32
1.43
0.84
1.00
1.00
1.00
1.00
1.00
2.00
6.00
f1 (ppm)

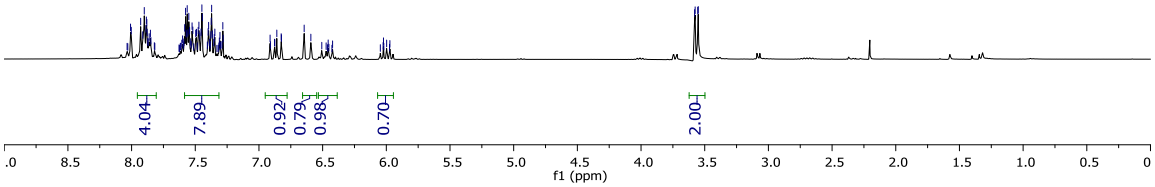

198.81
138.89
137.27
135.46
134.97
129.34
127.36
126.69
125.71
117.18
42.93
21.87
f1 (ppm)

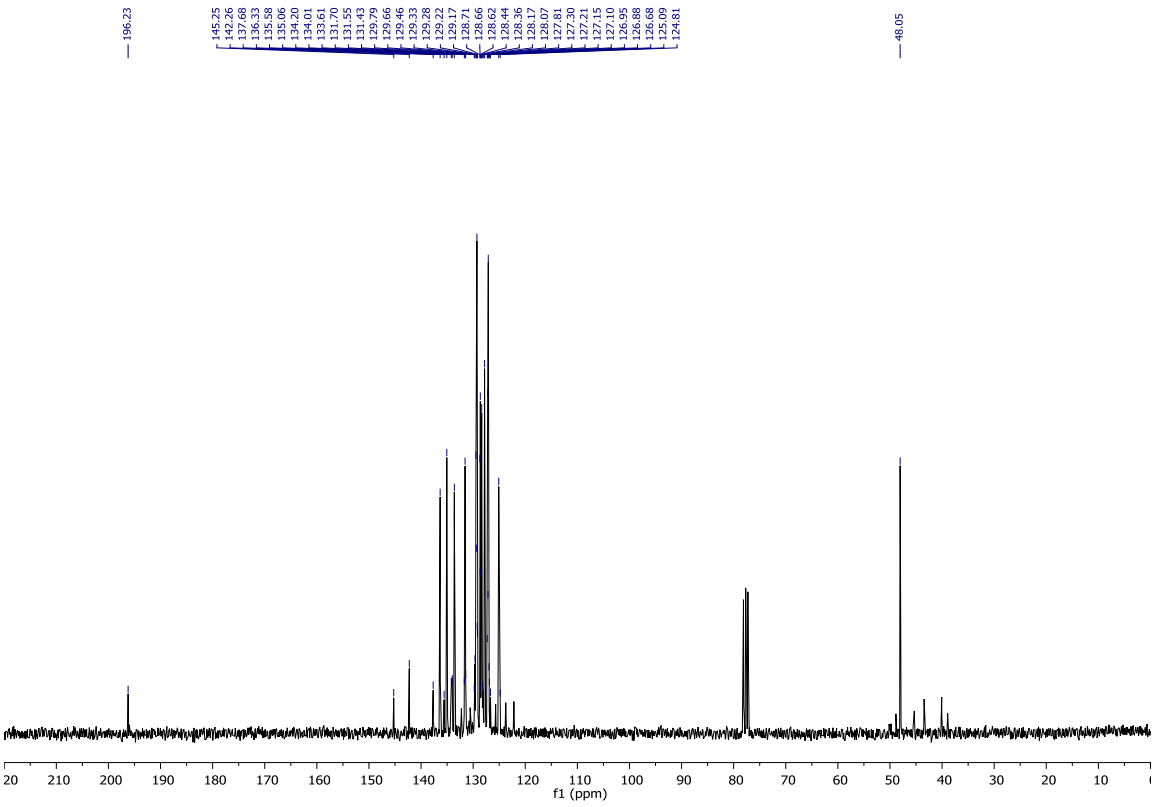

7.46
7.45
7.43
7.43
7.42
7.38
7.37
7.36
7.35
7.35
7.33
7.29
7.28
7.26
7.26
7.25
7.23
7.19
7.16
6.89
6.85
6.84
6.80
6.62
6.57
6.49
6.48
6.48
6.45
6.45
6.44
6.44
6.43
6.43
6.40
6.40
6.39
6.02
6.00
5.97
5.95
5.92
3.53
3.52
3.50
3.50
2.38
O
S
44A
8.30
0.88
0.85
1.03
0.79
2.00
6.19
f1 (ppm)


194.76
143.44
143.20
137.54
135.84
133.29
131.15
130.39
130.30
129.72
129.63
129.46
129.17
129.13
128.96
128.82
128.77
128.70
128.63
128.47
127.63
127.15
127.04
126.95
126.72
125.30
124.85
47.95
22.25
f1 (ppm)

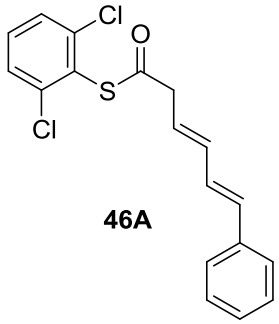


45A

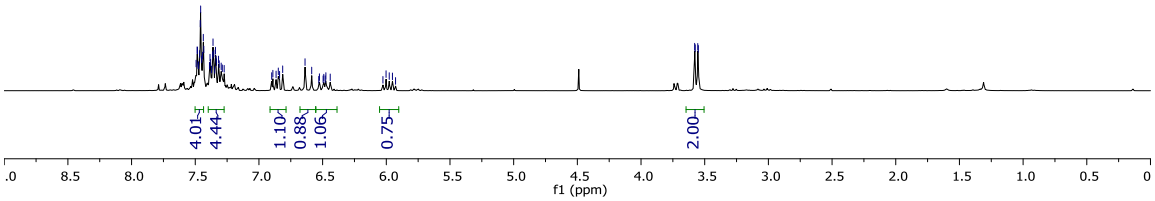


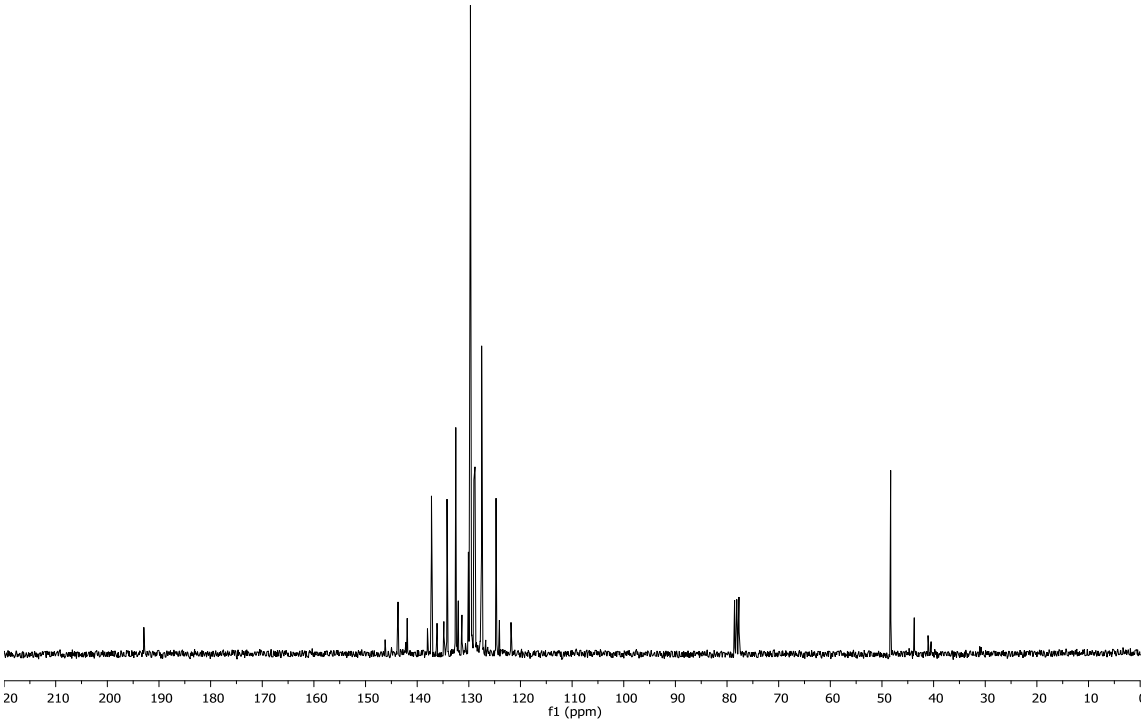


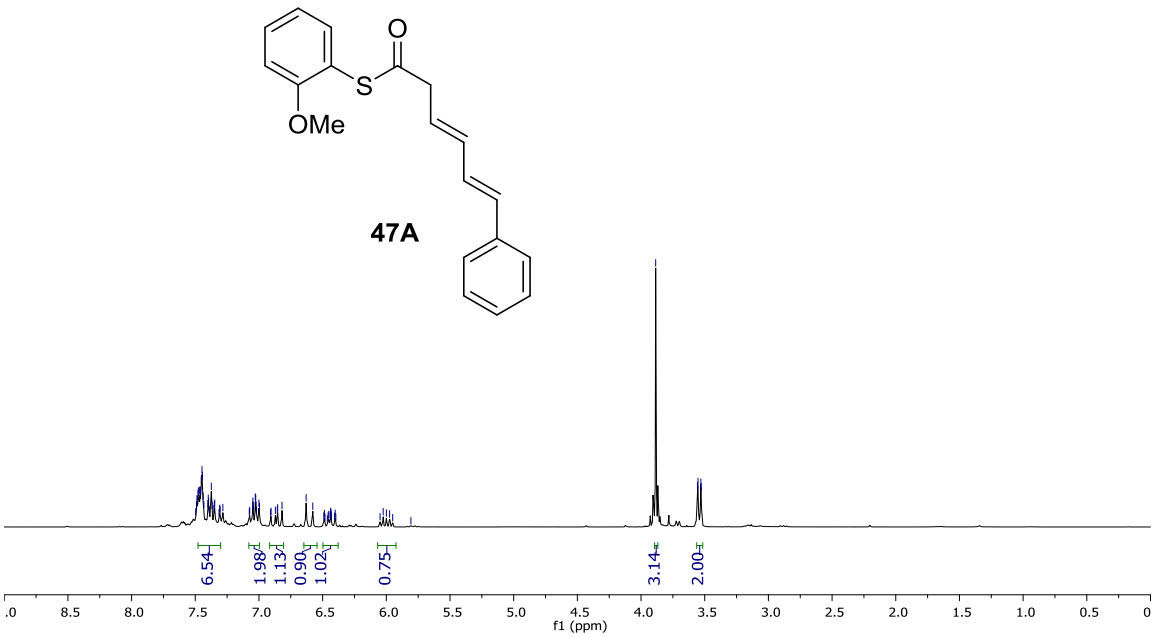

7.49
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.38
7.38
7.36
7.36
7.35
7.34
7.34
7.33
6.90
6.89
6.87
6.85
6.84
6.81
6.64
6.59
6.53
6.53
6.50
6.49
6.48
6.47
6.44
6.03
6.00
5.98
5.95
5.93
3.58
3.57
3.55
3.55


Cl
O
S
Cl

46A

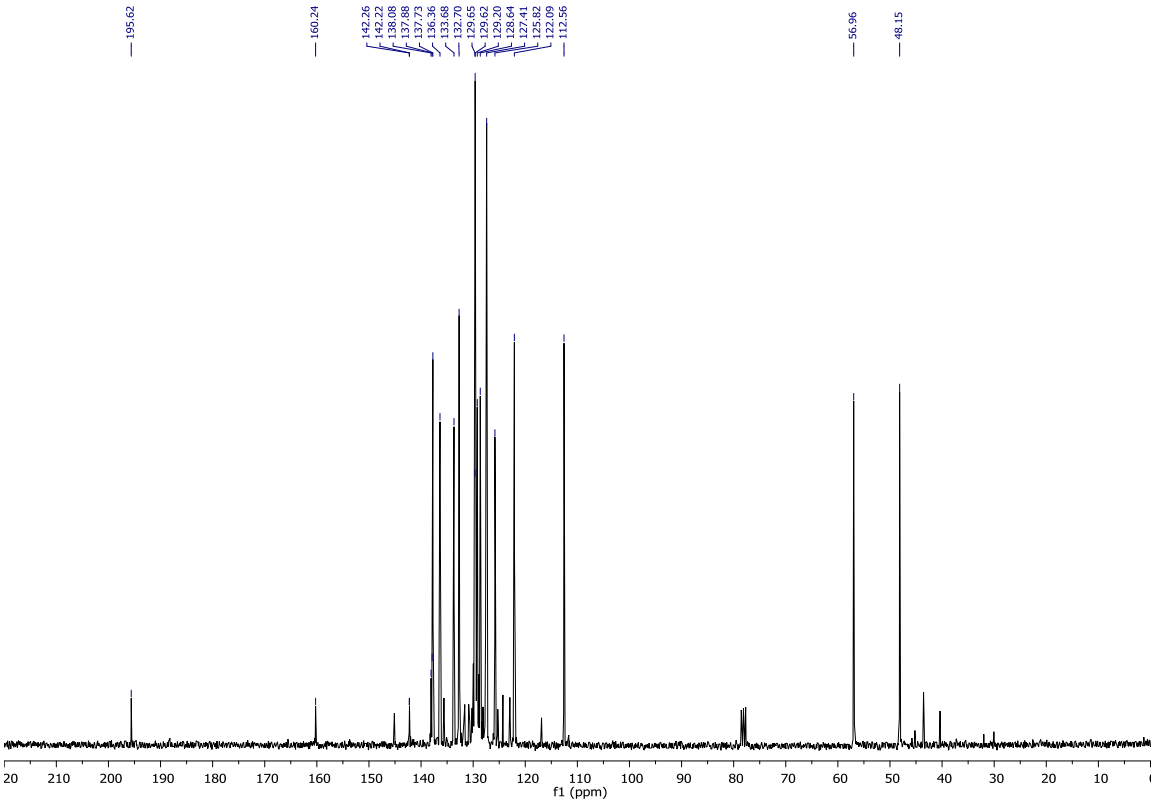

4.01
4.44
1.10
0.88
1.06
0.75
2.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

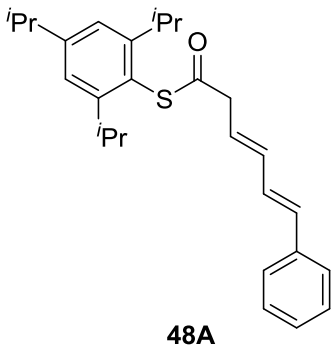

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
S
OMe

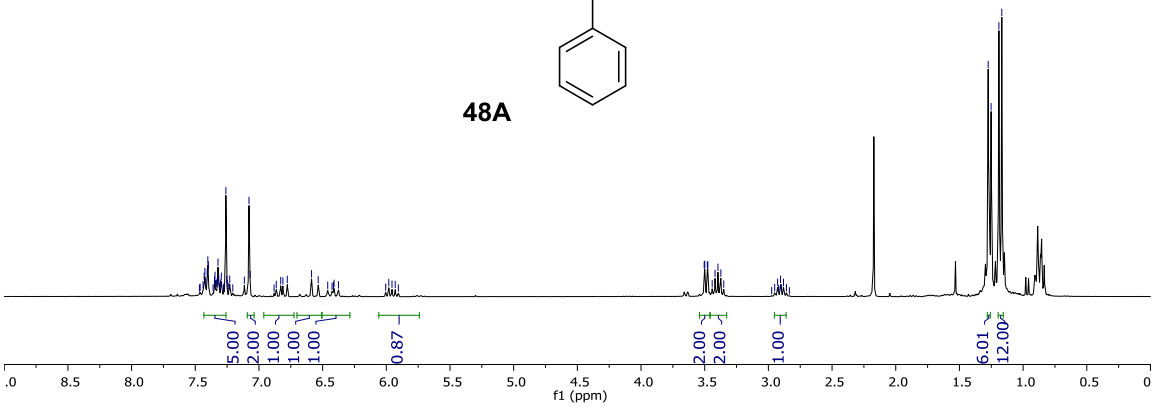
47A

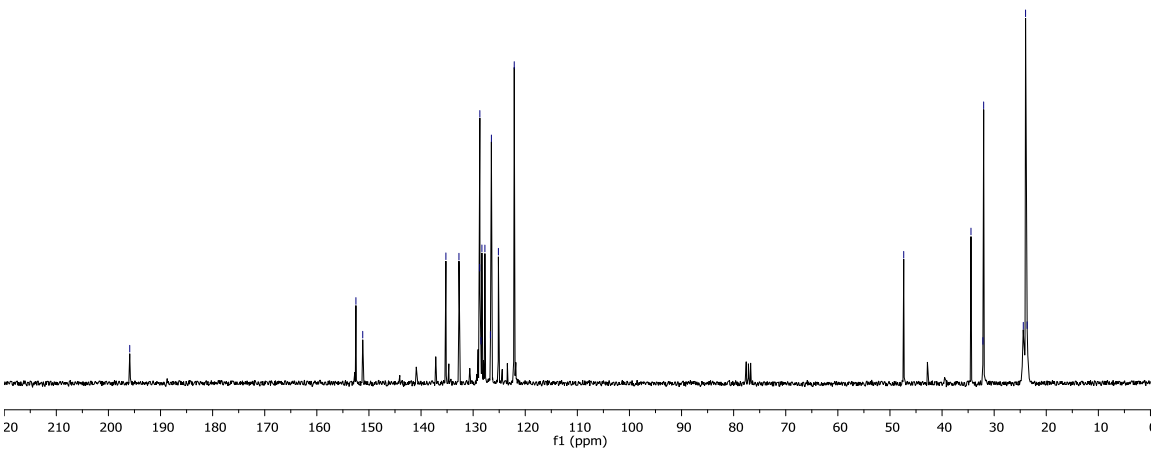
6.54
1.98
1.13
0.90
1.02
0.75
3.14
2.00
f1 (ppm)

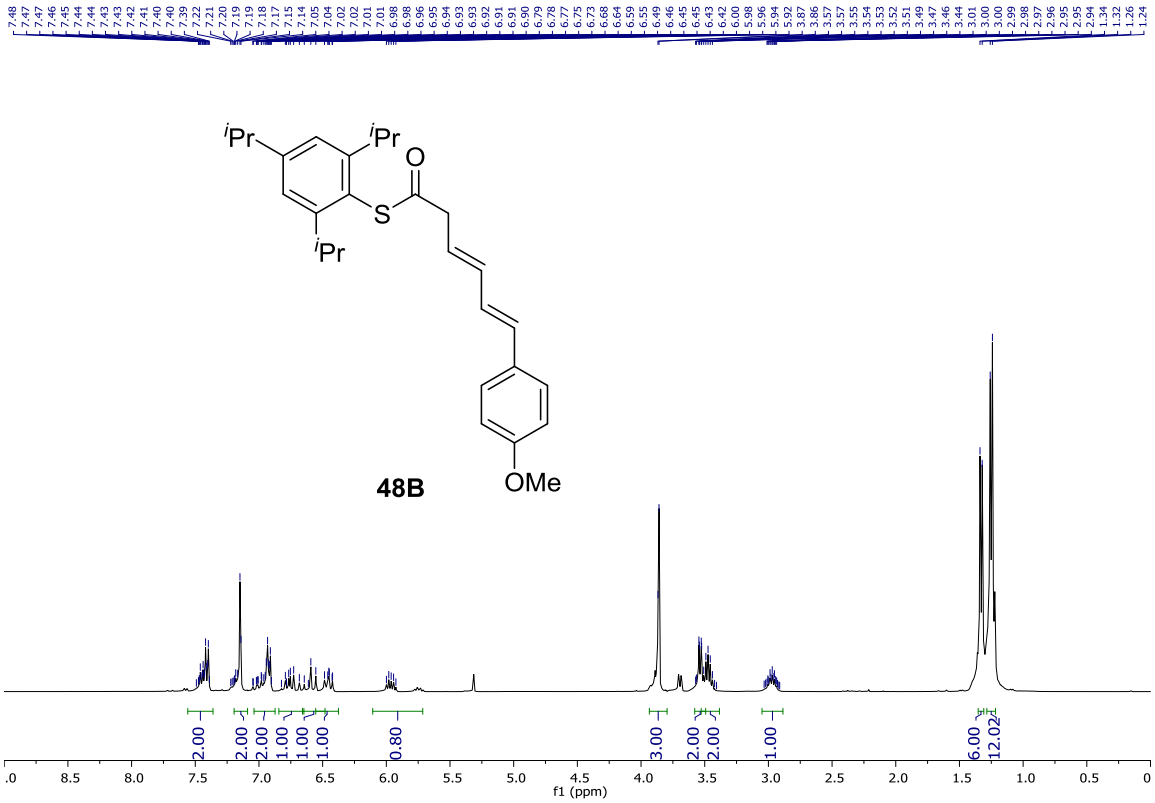

195.62
160.24
142.26
142.22
138.08
137.88
137.73
136.36
133.68
132.70
129.65
129.62
129.20
128.64
127.41
125.82
122.09
112.56
56.96
48.15
f1 (ppm)

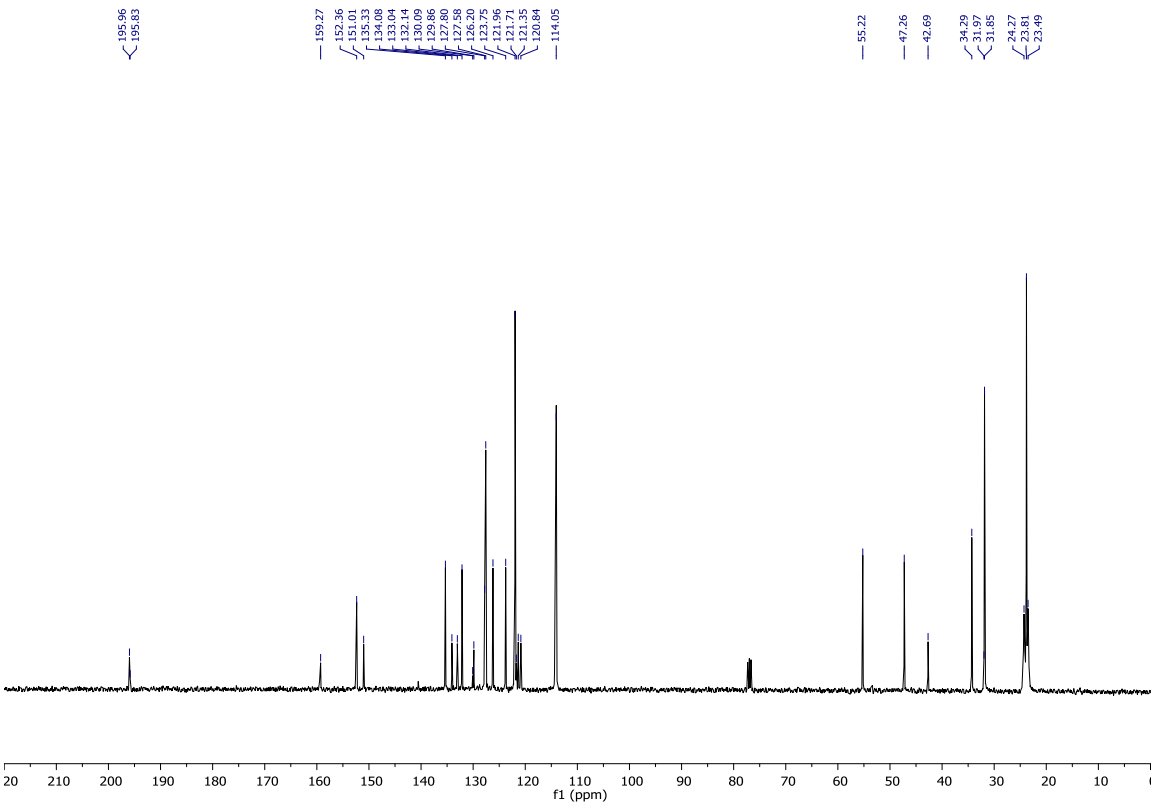


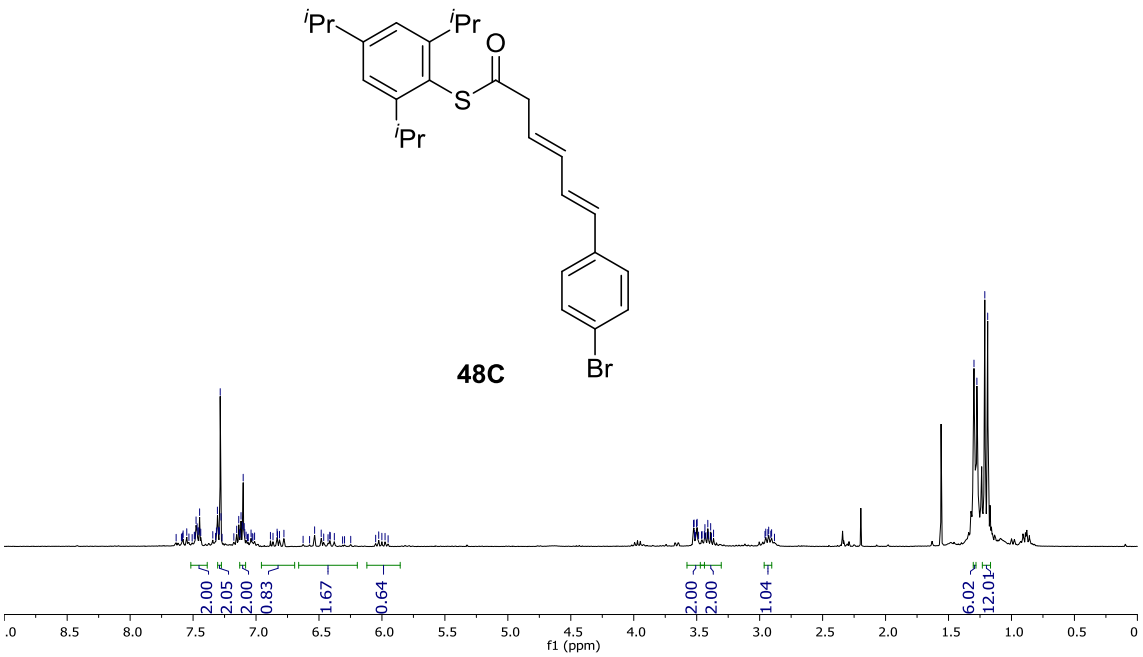
48A

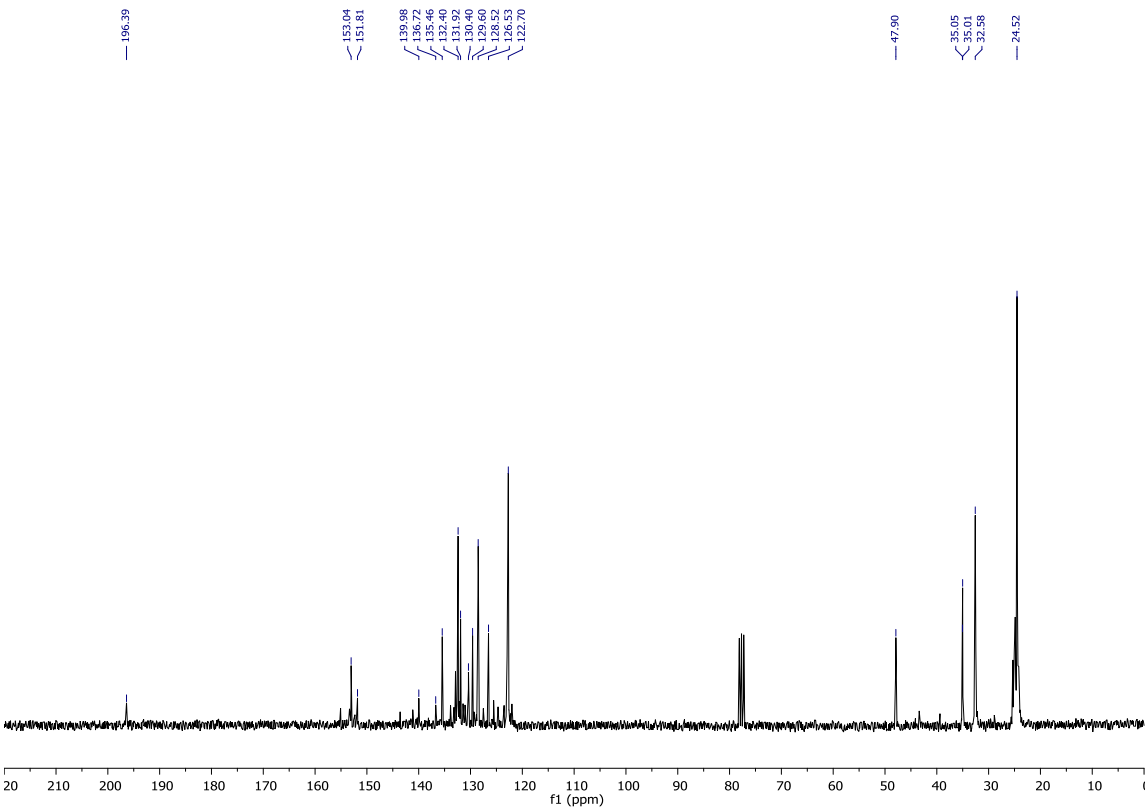


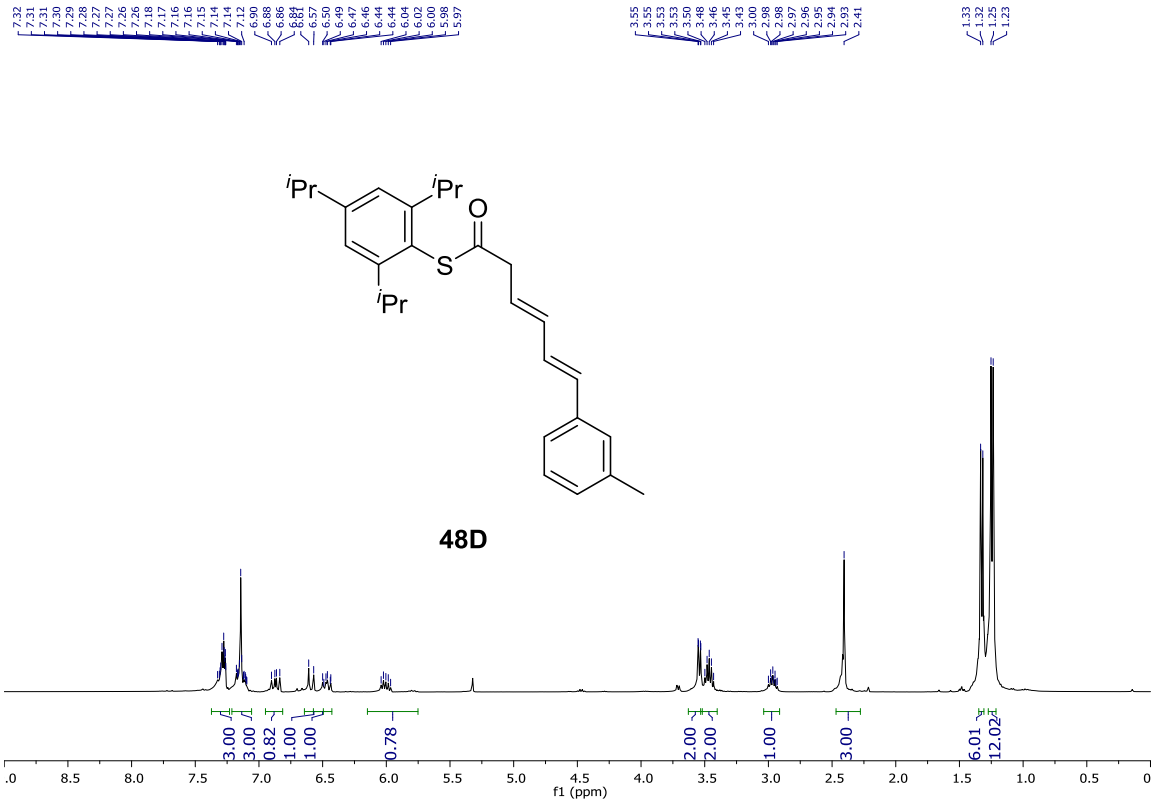


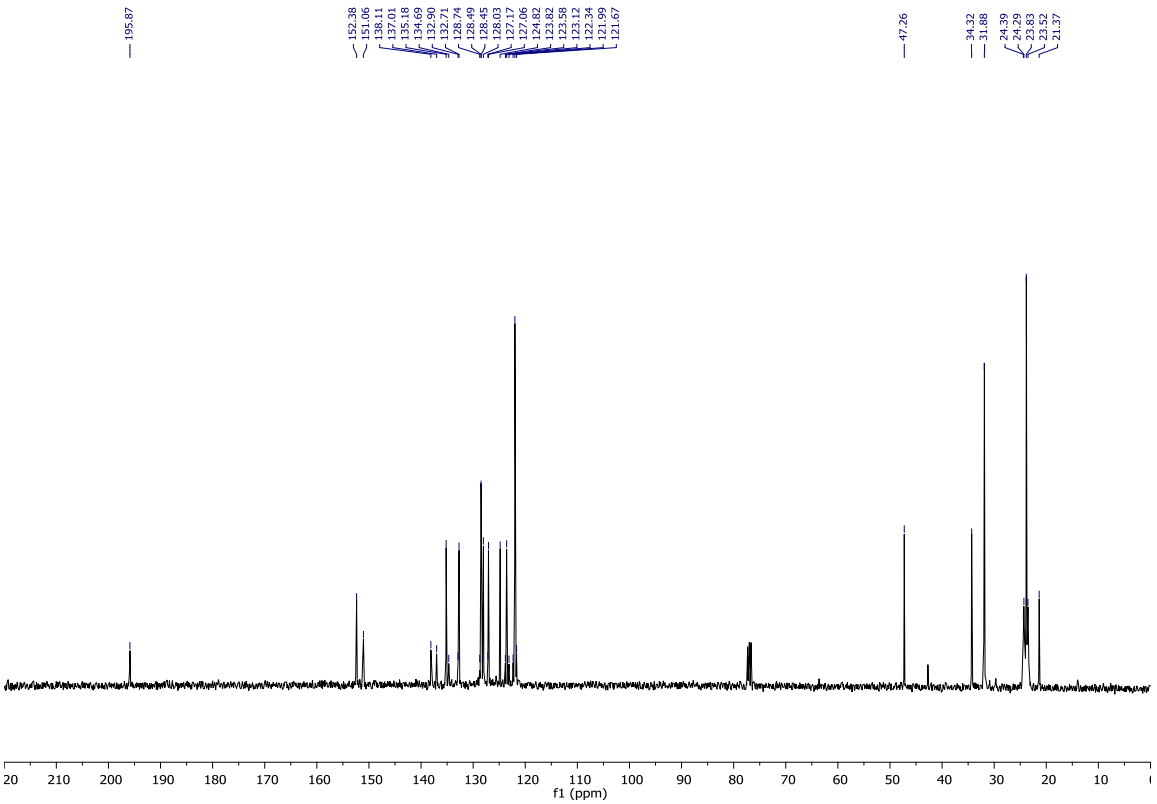

iPr
iPr
iPr
O
S
OMe
48B
2.00
2.00
2.00
1.00
1.00
0.80
3.00
2.00
2.00
1.00
6.00
12.02
f1 (ppm)

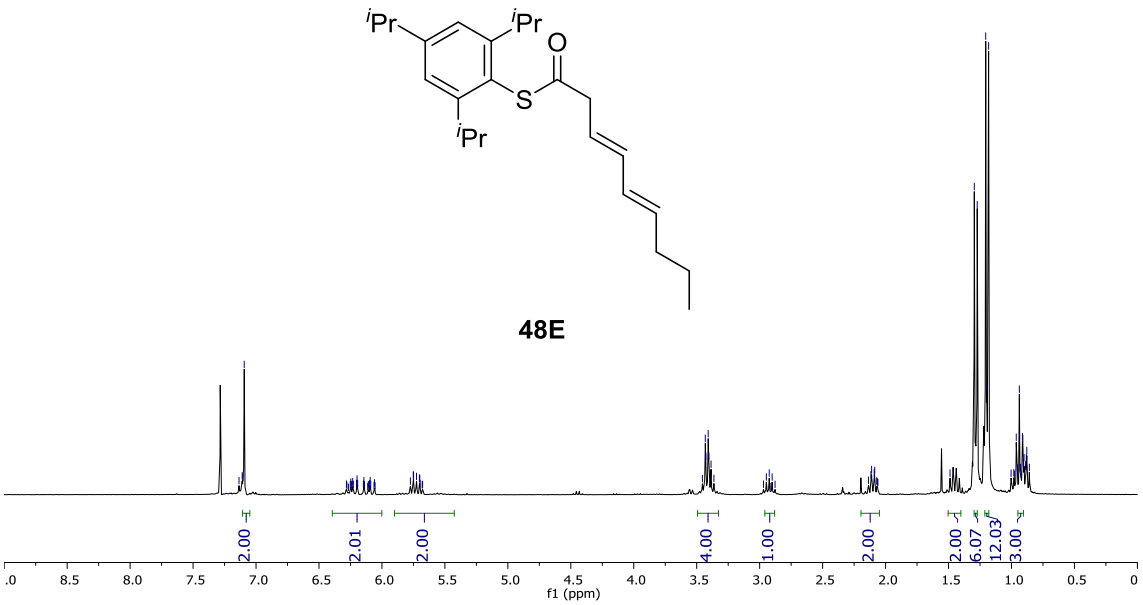

195.96
195.83
159.27
152.36
151.01
135.33
134.08
133.04
132.14
130.09
129.86
127.80
127.58
126.20
123.75
121.96
121.71
121.35
120.84
114.05
55.22
47.26
42.69
34.29
31.97
31.85
24.27
23.81
23.49
f1 (ppm)

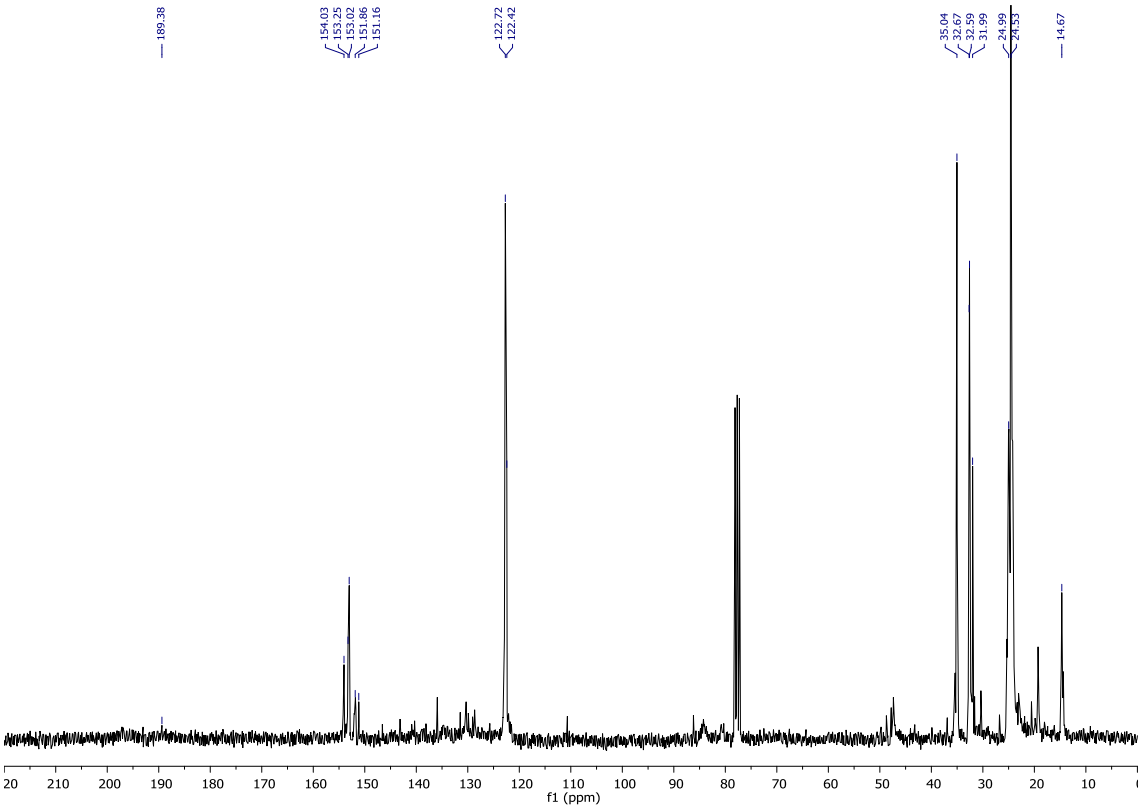

iPr
iPr
O
S
iPr
Br
48C
2.00
2.05
2.00
0.83
1.67
0.64
2.00
2.00
1.04
6.02
12.01
f1 (ppm)

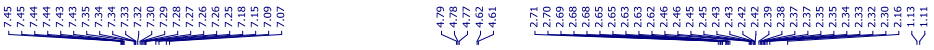

196.39
153.04
151.81
139.98
136.72
135.46
132.40
131.92
130.40
129.60
128.52
126.53
122.70
47.90
35.05
35.01
32.58
24.52
f1 (ppm)

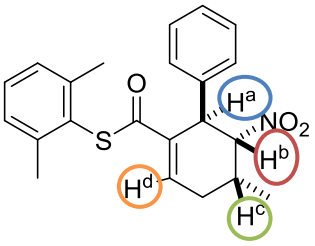

48D
f1 (ppm)


f1 (ppm)

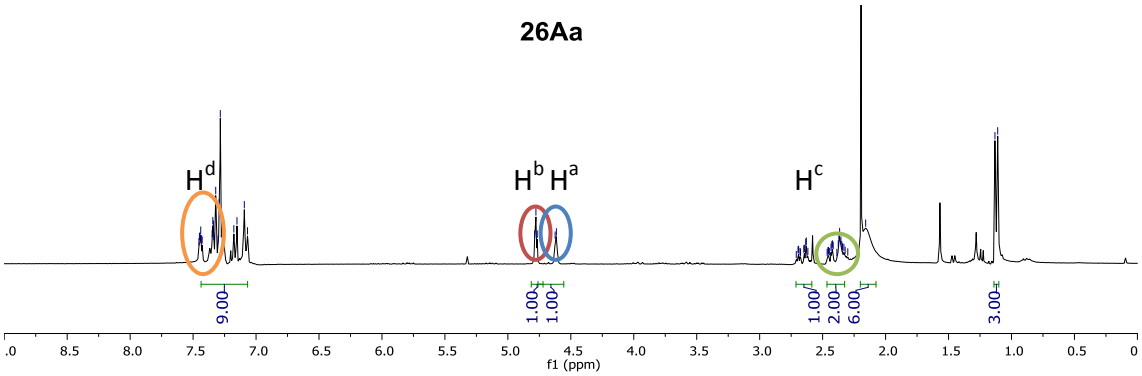

iPr
iPr
iPr
O
S
48E
2.00
2.01
2.00
4.00
1.00
2.00
2.00
6.07
12.03
3.00
f1 (ppm)

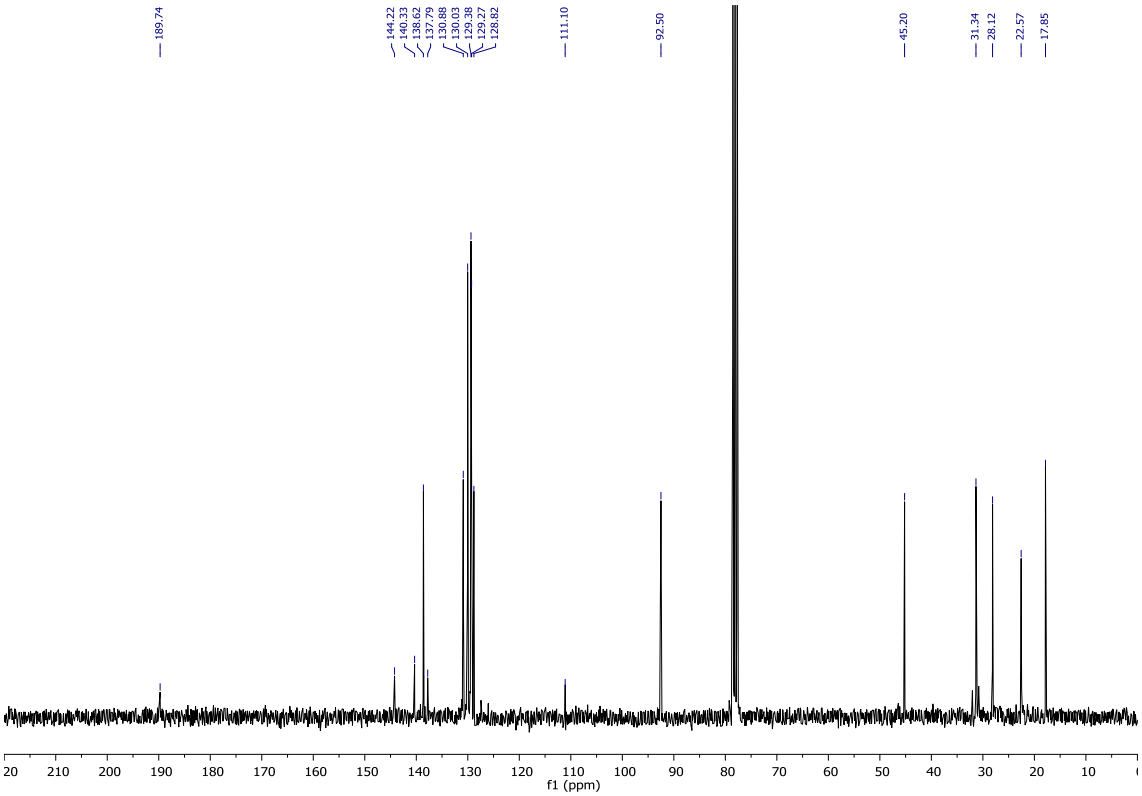

189.38
154.03
153.25
153.02
151.86
151.16
122.72
122.42
35.04
32.67
32.59
31.99
24.99
24.55
14.67
f1 (ppm)

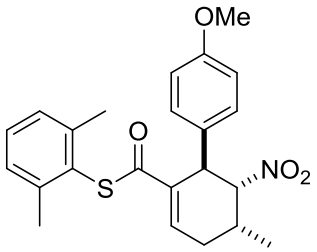



O
S
H^a
NO_2
H^b
H^d
H^c

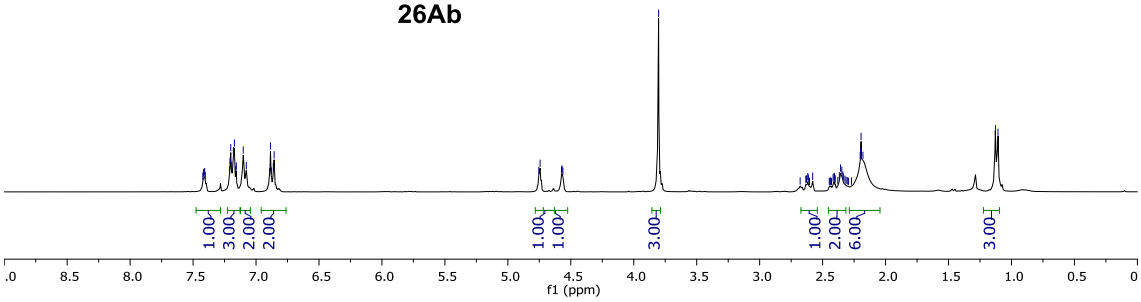
26Aa

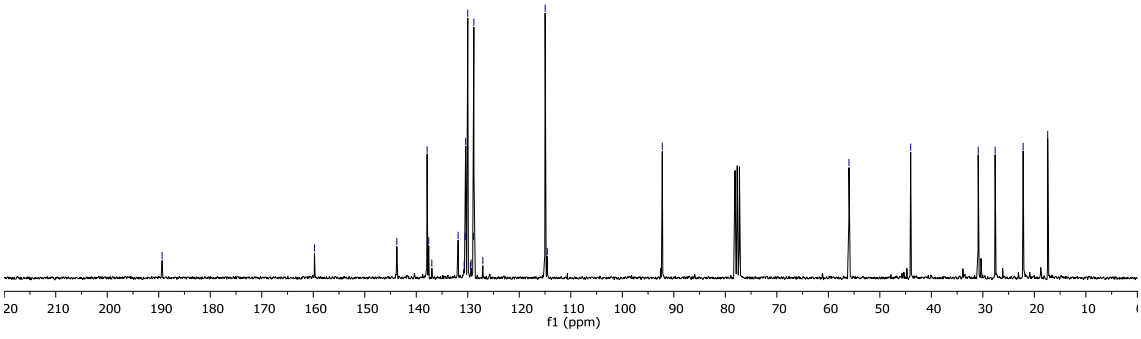

H^d
H^b H^a
H^c
9.00
1.00
1.00
1.00
2.00
6.00
3.00
f1 (ppm)


189.74
144.22
140.33
138.62
137.79
130.88
130.03
129.38
129.27
128.82
111.10
92.50
45.20
31.34
28.12
22.57
17.85
f1 (ppm)

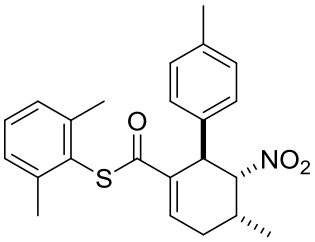

OMe
O
S
NO2

26Ab

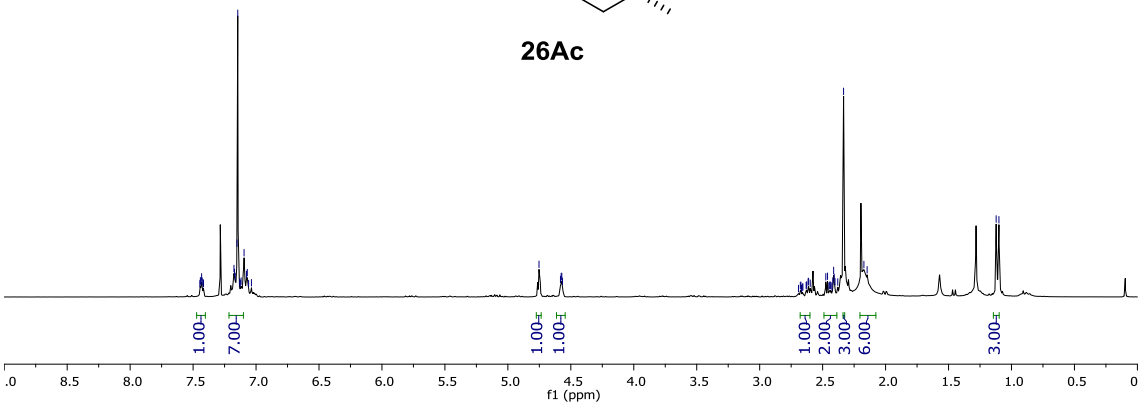

1.00
3.00
2.00
2.00
1.00
1.00
3.00
1.00
2.00
6.00
3.00
f1 (ppm)


f1 (ppm)

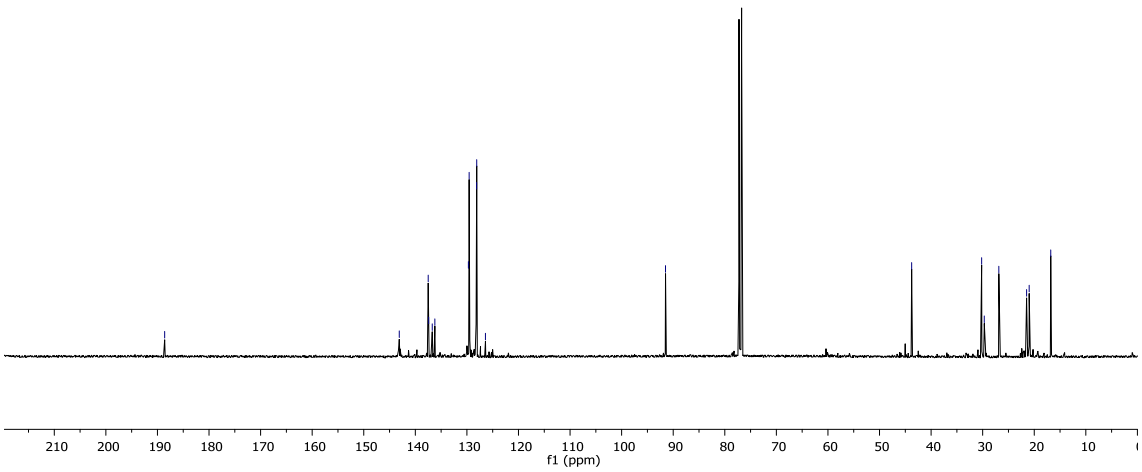

7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.18
7.17
7.17
7.15
7.15
7.13
7.12
7.12
7.10
7.08
7.07
7.06
7.04
4.75
4.58
4.58
4.57
4.57
2.69
2.68
2.67
2.67
2.66
2.66
2.63
2.63
2.62
2.61
2.60
2.47
2.46
2.45
2.44
2.44
2.43
2.42
2.42
2.41
2.41
2.40
2.38
2.33
2.17
2.15
1.12
1.10

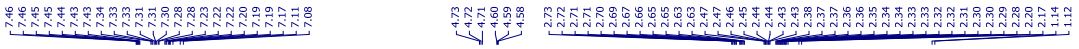

O
S
NO2

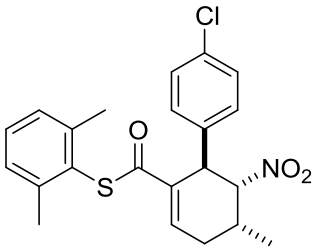
26Ac


1.00
7.00
1.00
1.00
1.00
2.00
3.00
6.00
3.00
.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
f1 (ppm)

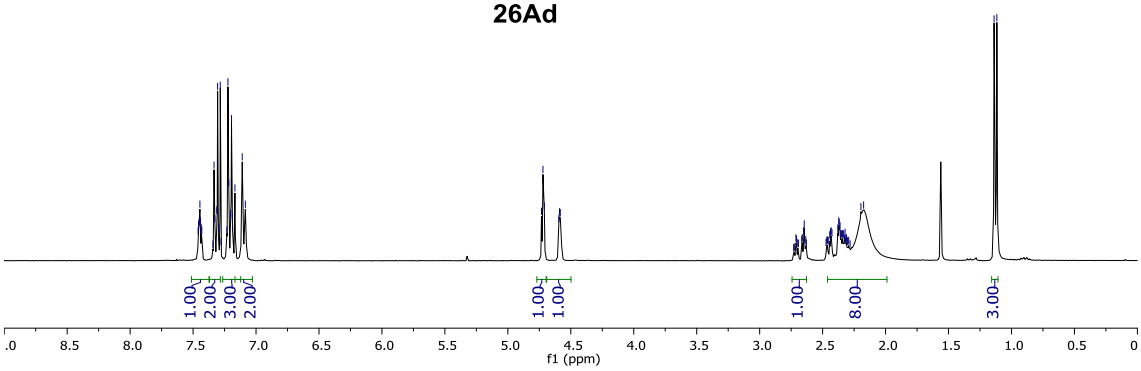

188.60
143.11
137.50
137.42
136.72
136.21
129.71
129.56
128.13
128.10
126.40
91.49
43.77
30.20
29.69
26.87
21.48
20.98
16.80

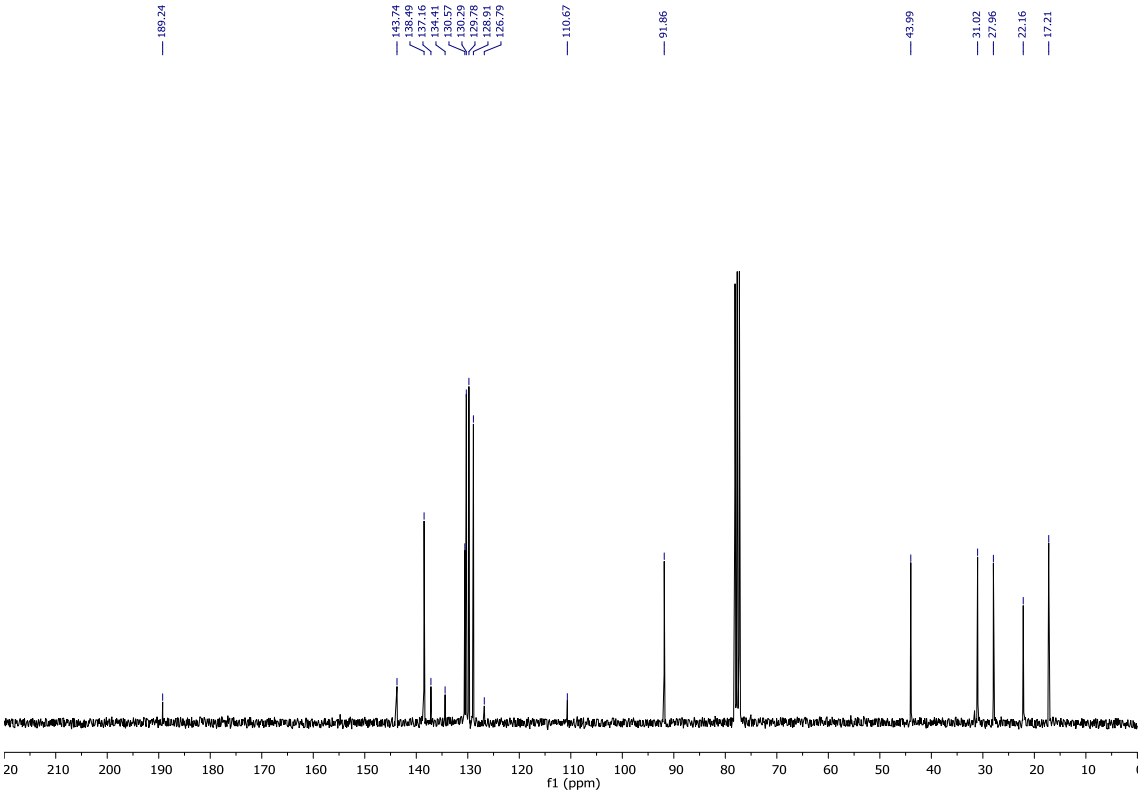

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

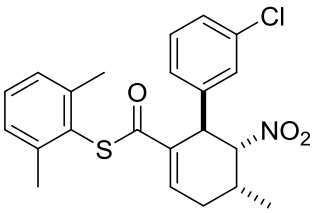



Cl
O
S
NO2

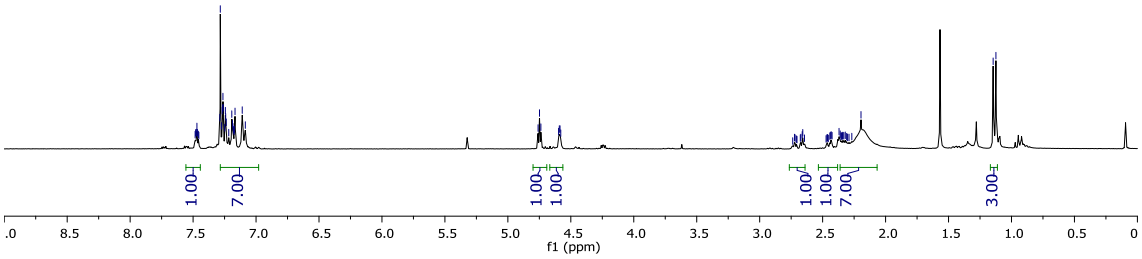
26Ad

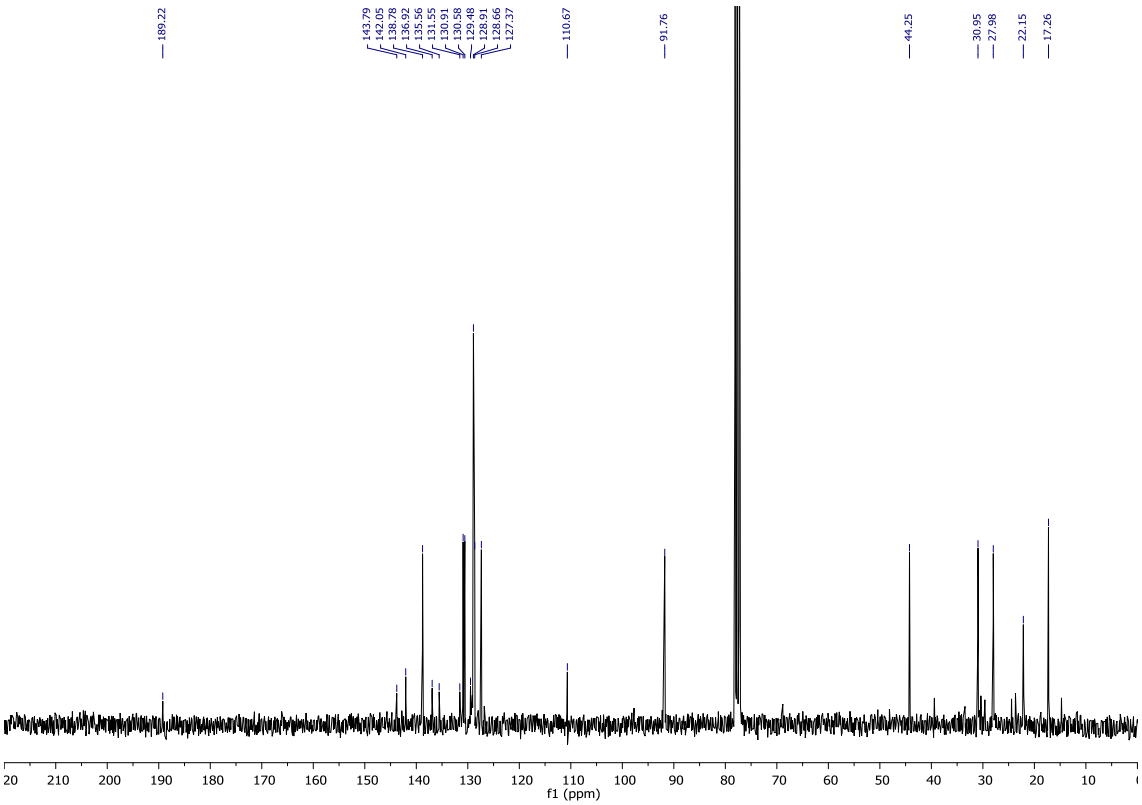

1.00
2.00
3.00
2.00
1.00
1.00
1.00
8.00
3.00
f1 (ppm)


189.24
143.74
138.49
137.16
134.41
130.57
130.29
129.78
128.91
126.79
110.67
91.86
43.99
31.02
27.96
22.16
17.21
f1 (ppm)

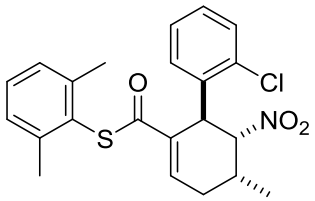

Cl
O
S
NO2

26Ag

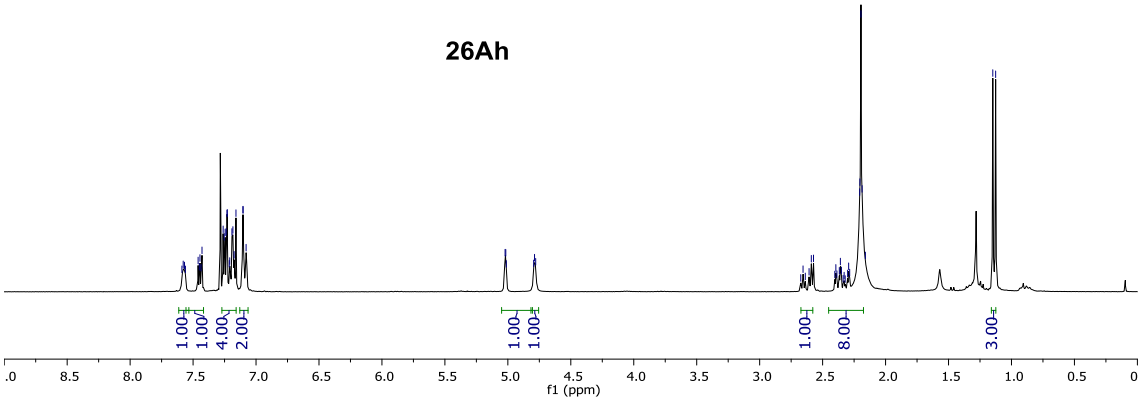

1.00
7.00
1.00
1.00
1.00
1.00
7.00
3.00
f1 (ppm)


189.22
143.79
142.05
138.78
136.92
135.56
131.55
130.91
130.58
129.48
128.91
128.66
127.37
110.67
91.76
44.25
30.95
27.98
22.15
17.26
f1 (ppm)

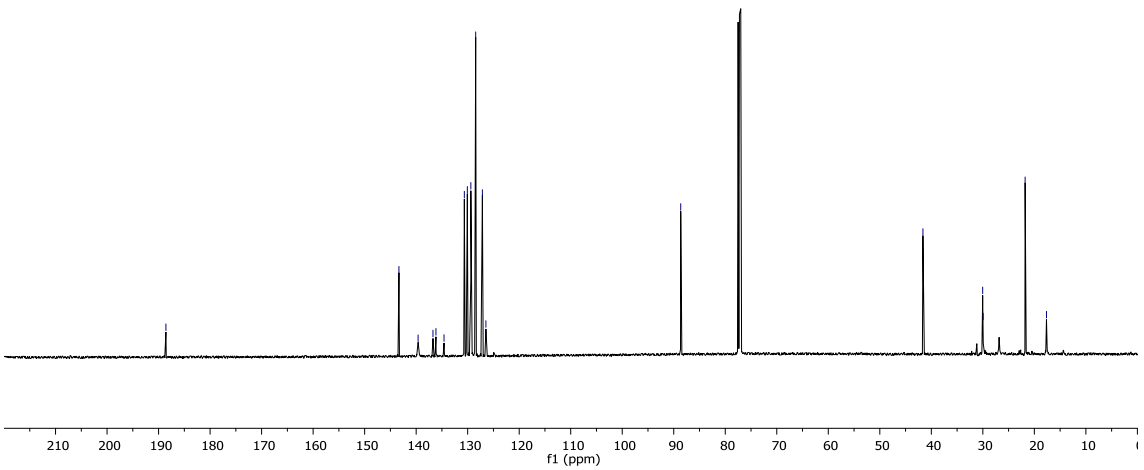

7.59
7.58
7.57
7.56
7.46
7.45
7.45
7.44
7.43
7.26
7.25
7.25
7.24
7.23
7.23
7.21
7.21
7.19
7.18
7.17
7.16
7.10
7.10
7.08
5.02
5.02
5.01
4.80
4.79
4.78
2.67
2.66
2.64
2.61
2.59
2.57
2.40
2.39
2.39
2.37
2.36
2.35
2.34
2.33
2.32
2.30
2.29
2.28
2.21
2.20
2.20
2.19
2.16
1.15
1.13

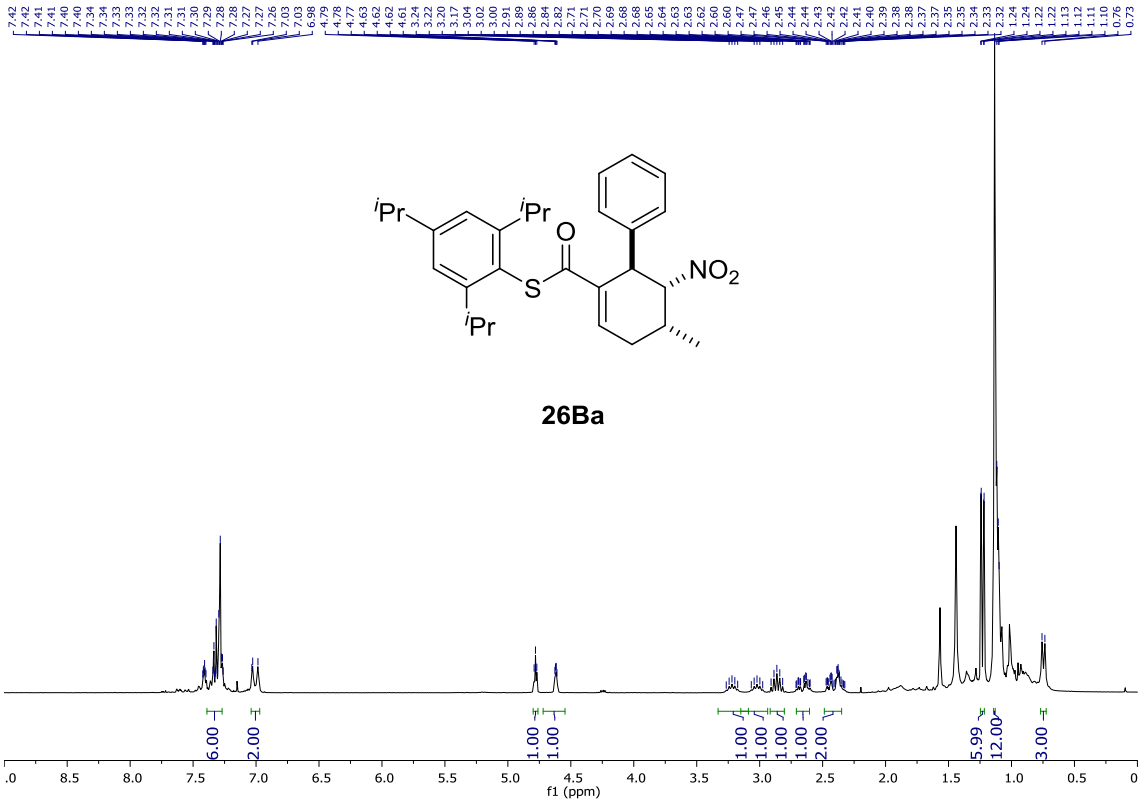

O
S
Cl
NO2

26Ah


1.00
1.00
4.00
2.00
1.00
1.00
1.00
8.00
3.00
f1 (ppm)

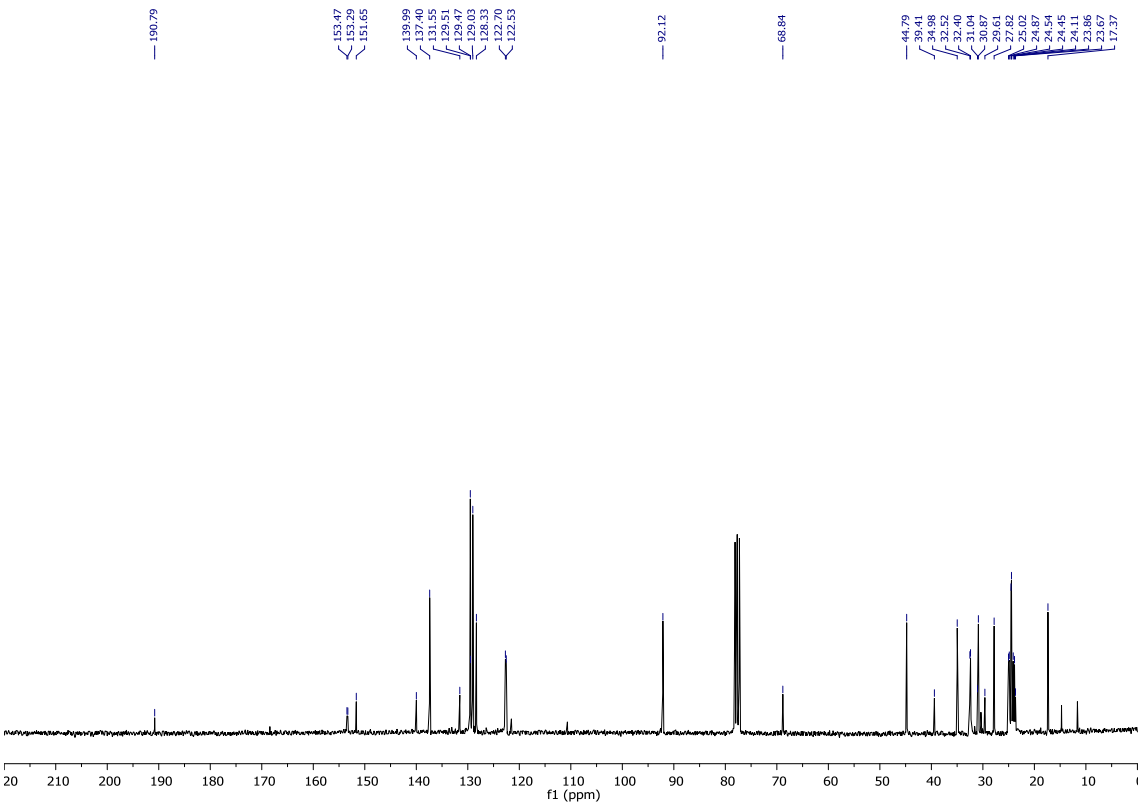

188.58
143.34
139.63
136.74
136.16
134.59
130.65
130.07
129.38
128.44
127.14
126.46
88.64
41.63
30.03
29.94
21.79
17.65

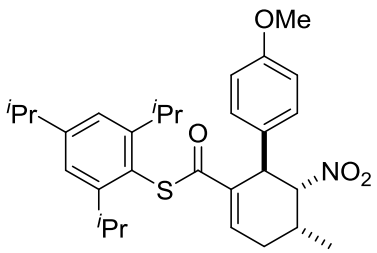

f1 (ppm)


iPr
iPr
iPr
O
S
NO2

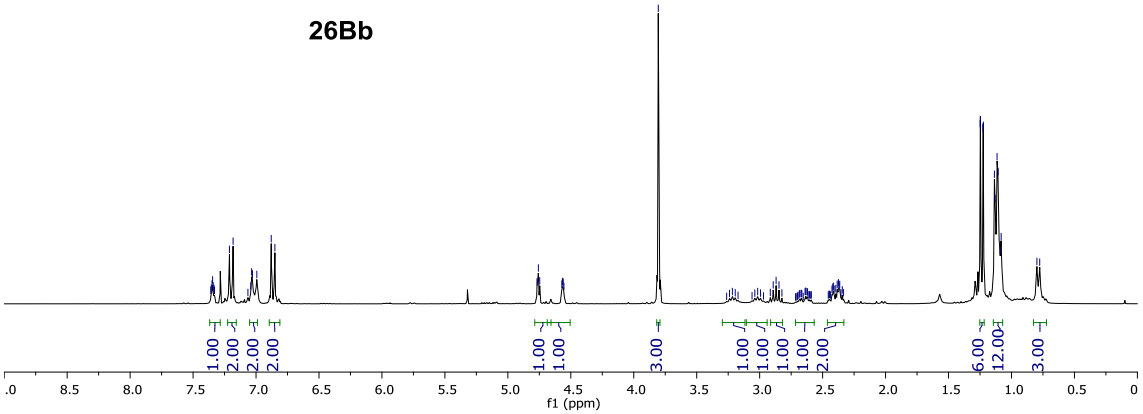
26Ba

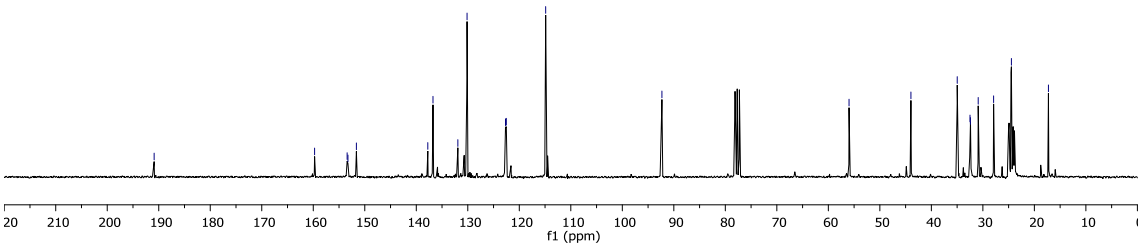
6.00
2.00
1.00
1.00
1.00
1.00
1.00
2.00
5.99
12.00
3.00
f1 (ppm)

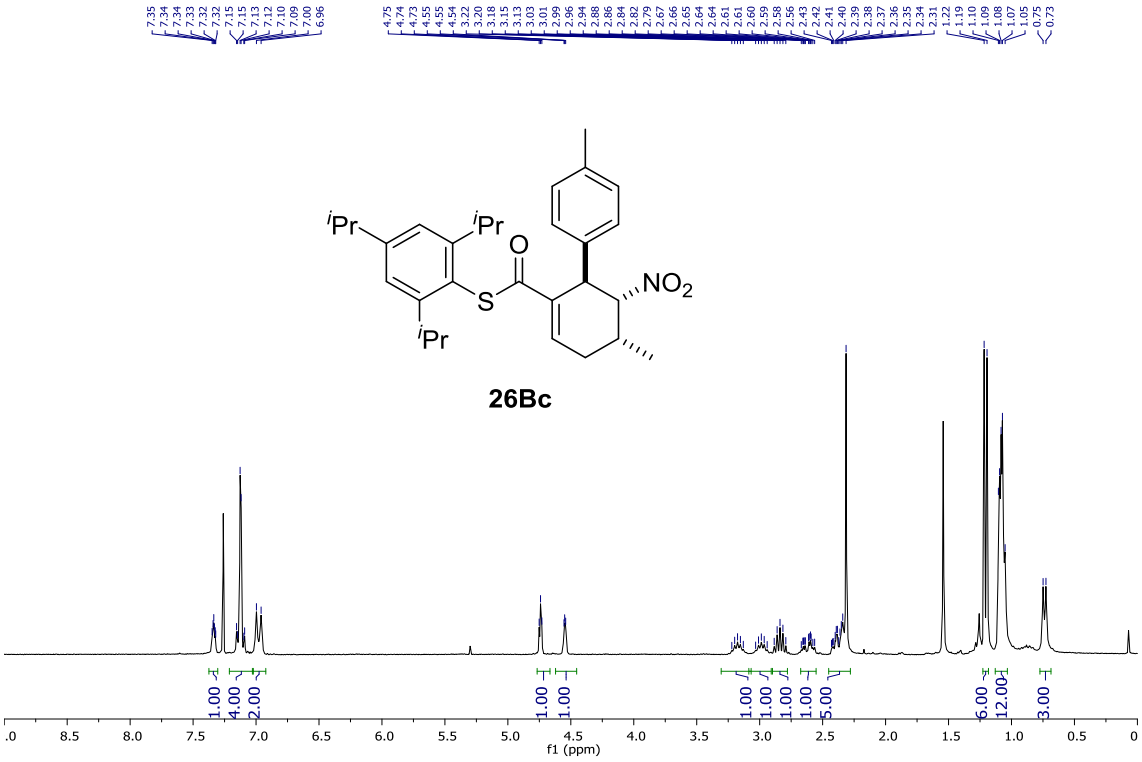

190.79
153.47
153.29
151.65
139.99
137.40
131.55
129.51
129.47
129.03
128.33
122.70
122.53
92.12
68.84
44.79
39.41
34.98
32.52
32.40
31.04
30.87
29.61
27.32
25.02
24.87
24.54
24.45
24.11
23.86
23.67
17.37
f1 (ppm)

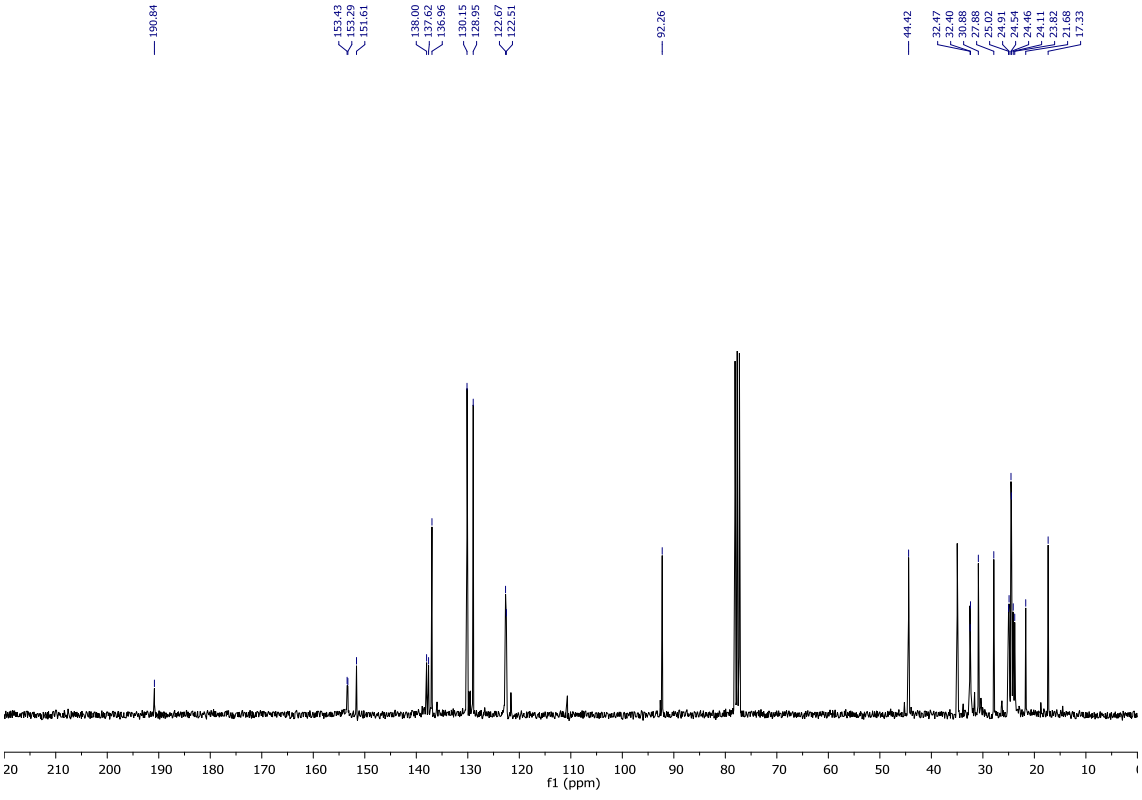

OMe
iPr
iPr
O
S
NO2
iPr

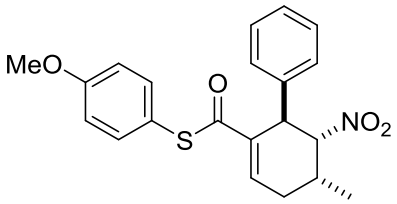
26Bb


1.00
2.00
2.00
2.00
1.00
1.00
3.00
1.00
1.00
1.00
2.00
6.00
12.00
3.00
f1 (ppm)

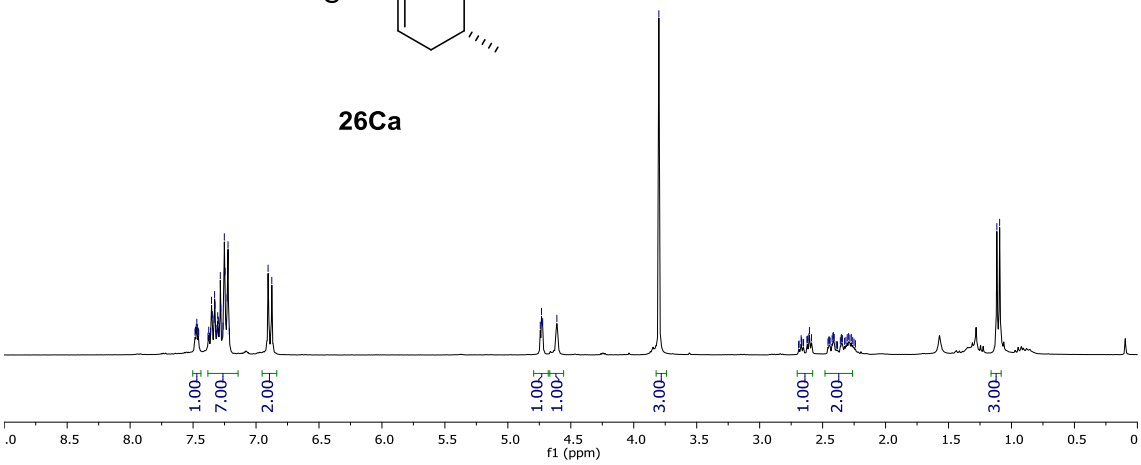

f1 (ppm)

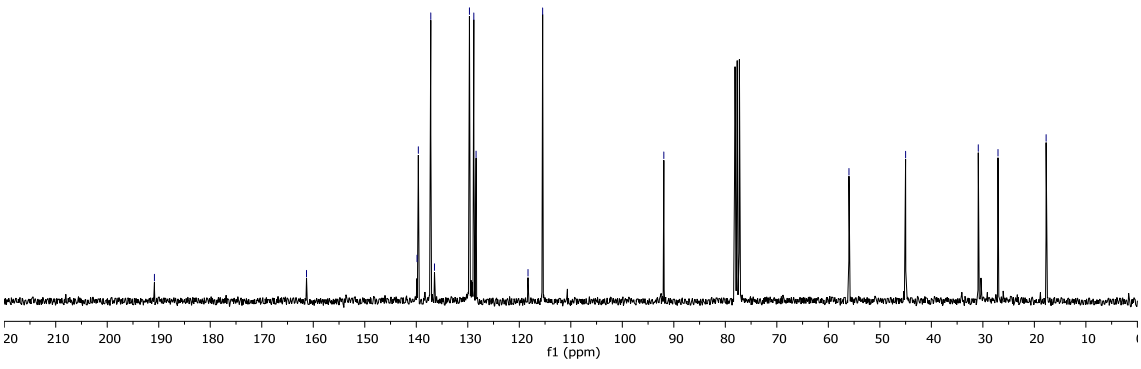

7.35
7.34
7.34
7.33
7.32
7.32
7.15
7.15
7.13
7.12
7.10
7.09
7.00
6.96
4.75
4.74
4.73
4.55
4.55
4.54
3.22
3.20
3.18
3.15
3.13
3.03
3.01
2.99
2.96
2.94
2.88
2.86
2.84
2.82
2.79
2.67
2.66
2.65
2.64
2.64
2.61
2.61
2.60
2.59
2.58
2.56
2.43
2.42
2.41
2.40
2.39
2.38
2.37
2.36
2.35
2.34
2.31
1.22
1.19
1.10
1.09
1.08
1.07
1.05
0.75
0.73
iPr
iPr
iPr
O
S
NO2
26Bc
1.00
4.00
2.00
1.00
1.00
1.00
1.00
1.00
5.00
6.00
12.00
3.00
f1 (ppm)

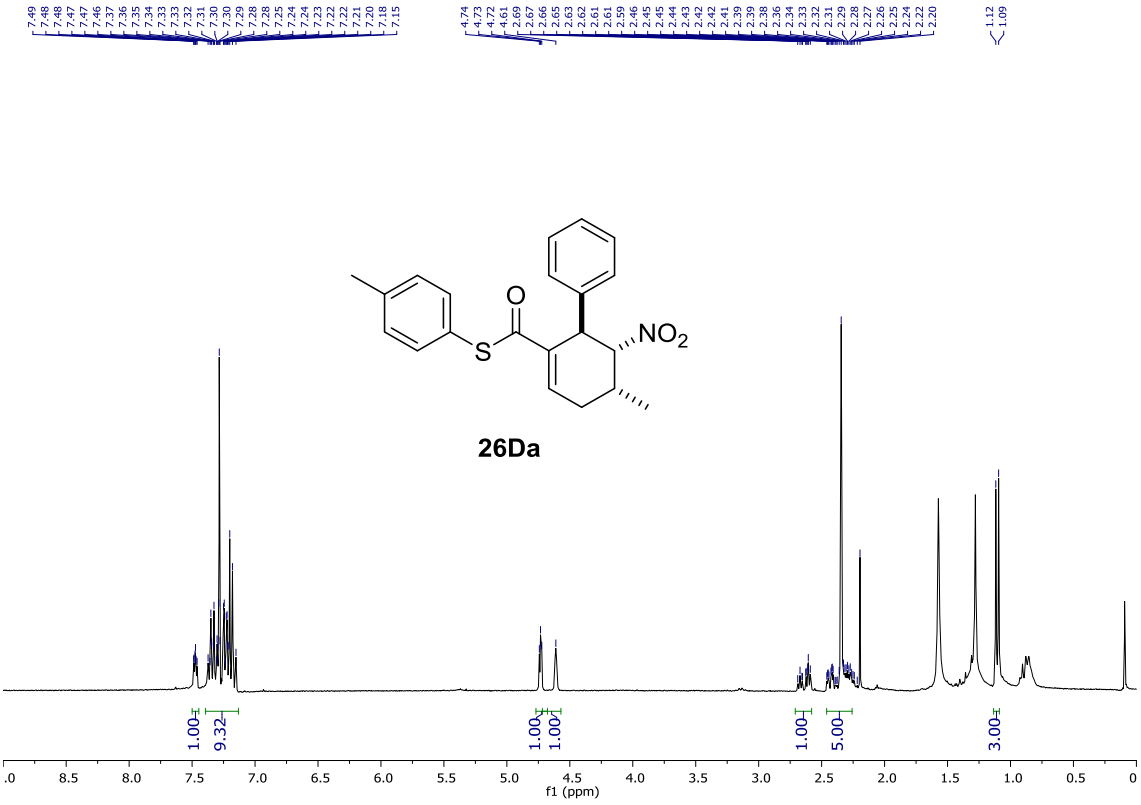

190.84
153.43
153.29
151.61
138.00
137.62
136.96
130.15
128.95
122.67
122.51
92.26
44.42
32.47
32.40
30.88
27.88
25.02
24.91
24.54
24.46
24.11
23.82
21.68
17.33
f1 (ppm)

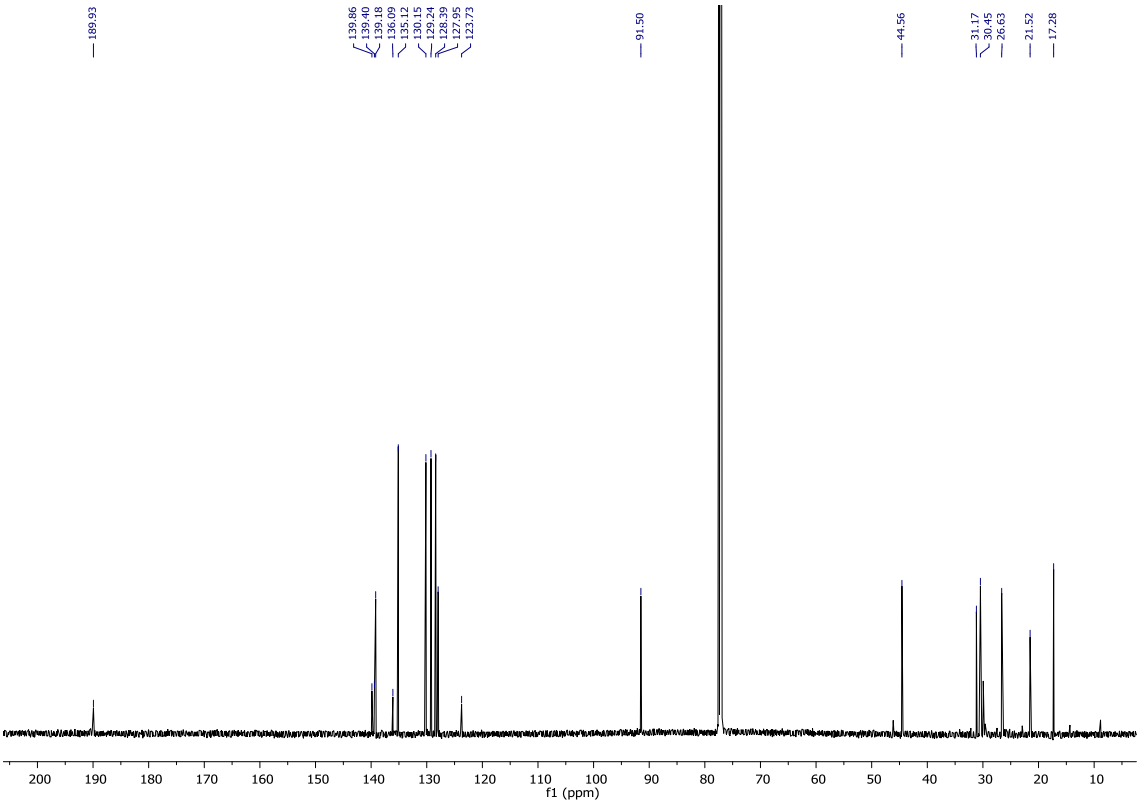


26Ca

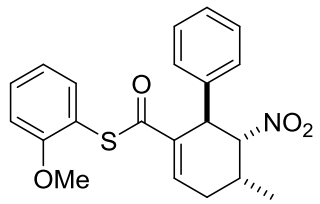




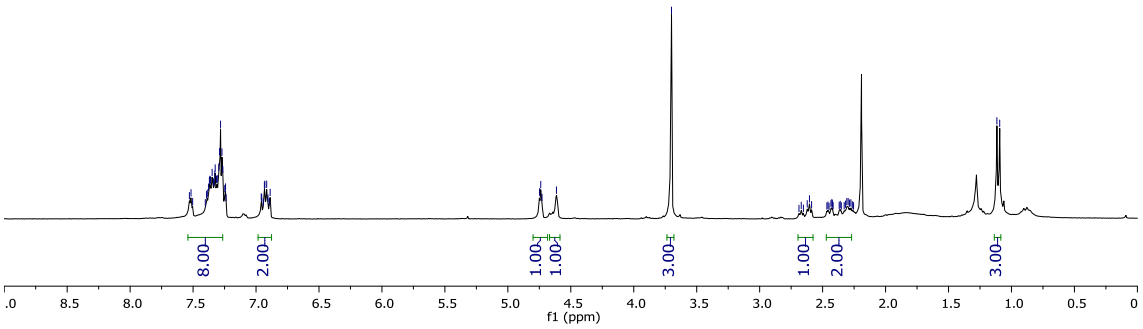

7.49 7.48 7.48 7.48 7.47 7.47 7.46 7.37 7.36 7.35 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.25 7.24 7.24 7.23 7.22 7.22 7.21 7.20 7.18 7.15
4.74 4.73 4.72 4.61 2.69 2.67 2.66 2.65 2.63 2.62 2.61 2.61 2.59 2.46 2.45 2.45 2.44 2.43 2.42 2.42 2.41 2.39 2.39 2.38 2.36 2.34 2.33 2.32 2.31 2.29 2.28 2.27 2.26 2.25 2.24 2.22 2.20
1.12 1.09
O
S
NO2
26Da
1.00 9.32 1.00 1.00 1.00 5.00 3.00
f1 (ppm)

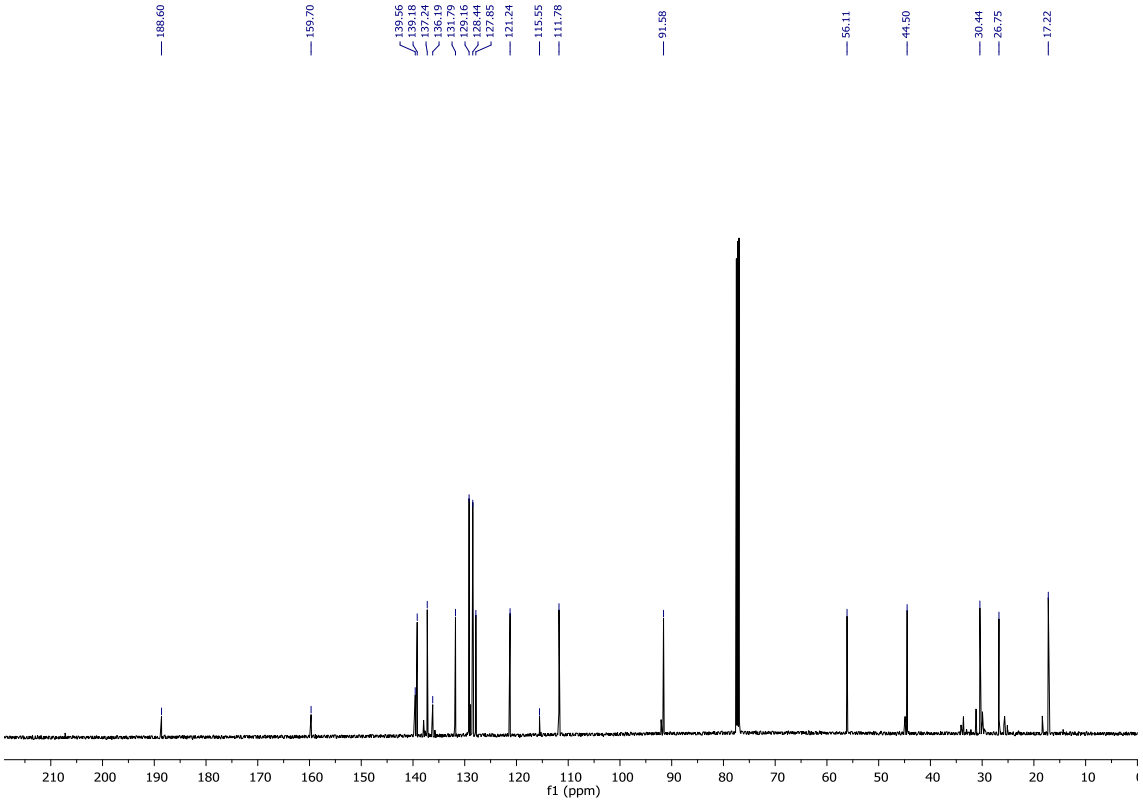

189.93
139.86 139.40 134.18 136.09 135.12 130.15 129.24 128.39 127.95 123.73
91.50
44.56
31.17 30.45 26.63
21.52
17.28
f1 (ppm)

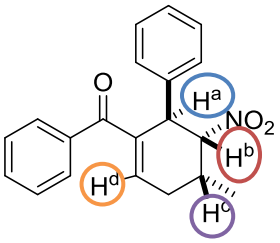

7.38
7.37
7.37
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
6.96
6.94
6.93
6.93
6.92
6.91
6.90
6.89
4.75
4.74
4.73
4.61
3.70
2.69
2.67
2.65
2.62
2.60
2.59
2.47
2.46
2.45
2.43
2.43
2.42
2.42
2.37
2.36
2.35
2.33
2.32
2.31
2.30
2.29
2.28
2.26
2.25
1.12
1.09


O
S
OMe
NO2

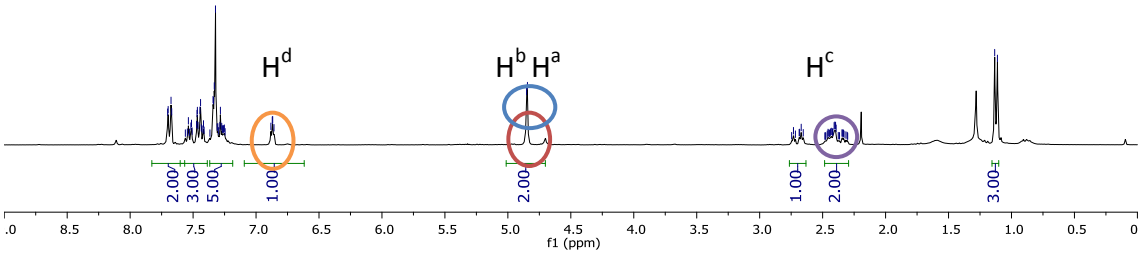
26Ea

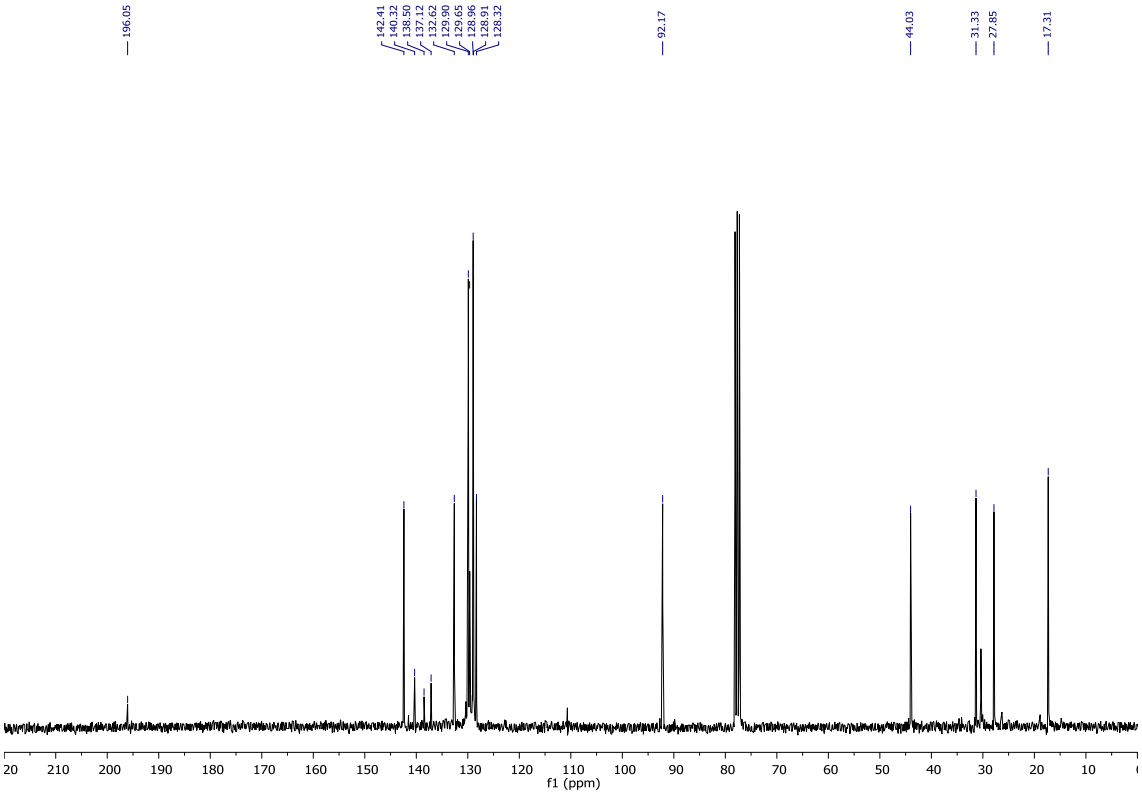

8.00
2.00
1.00
1.00
3.00
1.00
2.00
3.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

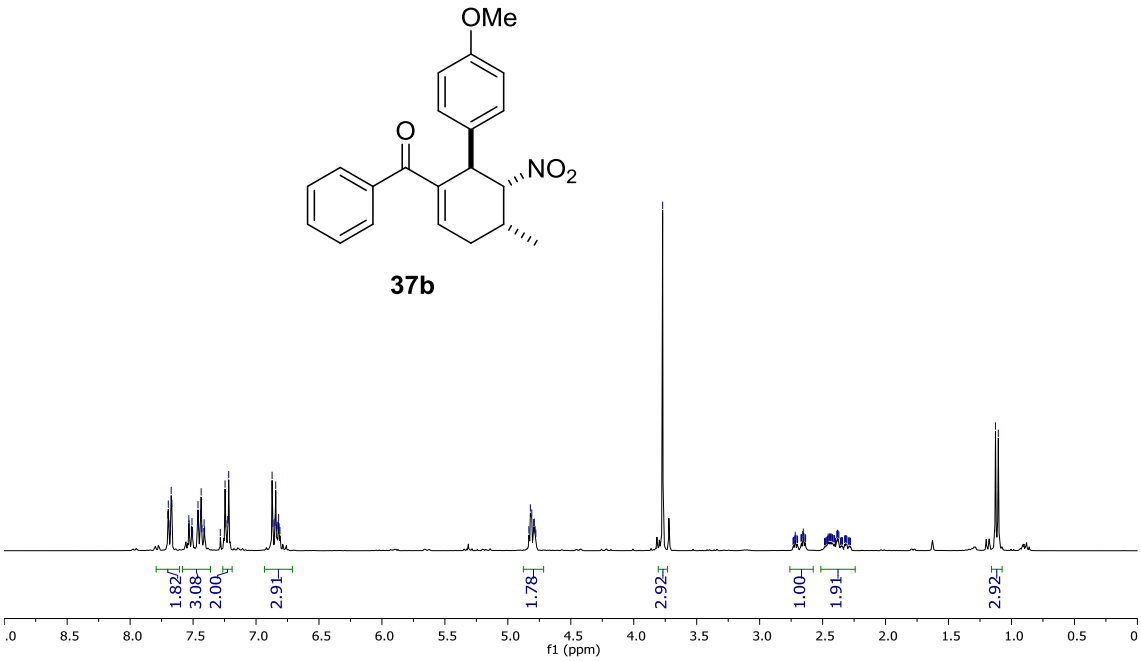

188.60
159.70
139.56
139.18
137.24
136.19
131.79
129.16
128.44
127.85
121.24
115.55
111.78
91.58
56.11
44.50
30.44
26.75
17.22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

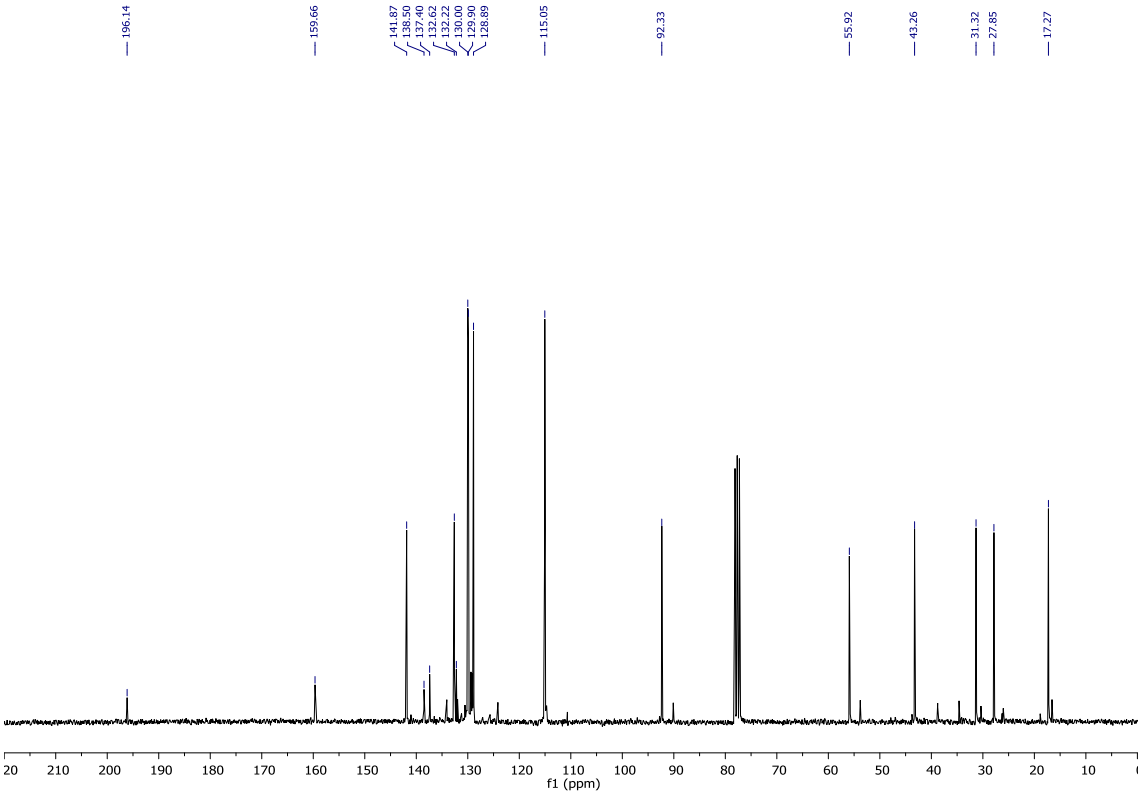

O
H^a
NO_2
H^b
H^d
H^c

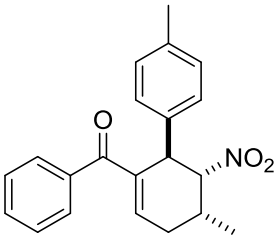
37a


H^d
H^b H^a
H^c
2.00
3.00
5.00
1.00
2.00
1.00
2.00
3.00
f1 (ppm)

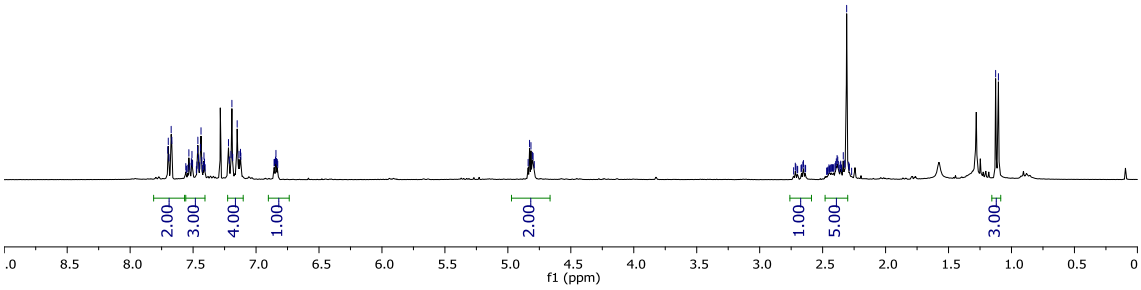

196.05
142.41
140.32
138.50
137.12
132.62
129.90
129.65
128.96
128.91
128.32
92.17
44.03
31.33
27.85
17.31
f1 (ppm)

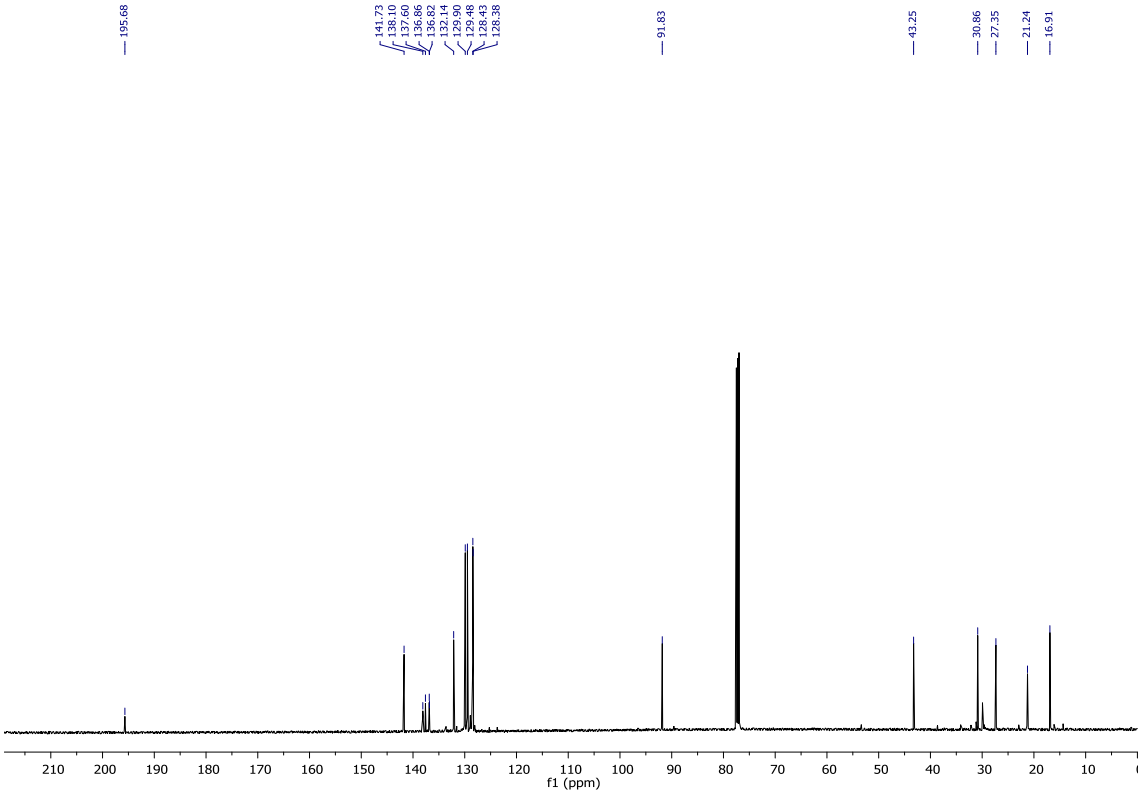

OMe
O
NO2
37b
1.82
3.08
2.00
2.91
1.78
2.92
1.00
1.91
2.92
f1 (ppm)

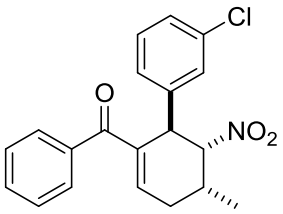

196.14
159.66
141.87
138.50
137.40
132.62
132.22
130.00
129.90
128.89
115.05
92.33
55.92
43.26
31.32
27.85
17.27
f1 (ppm)


O
NO2

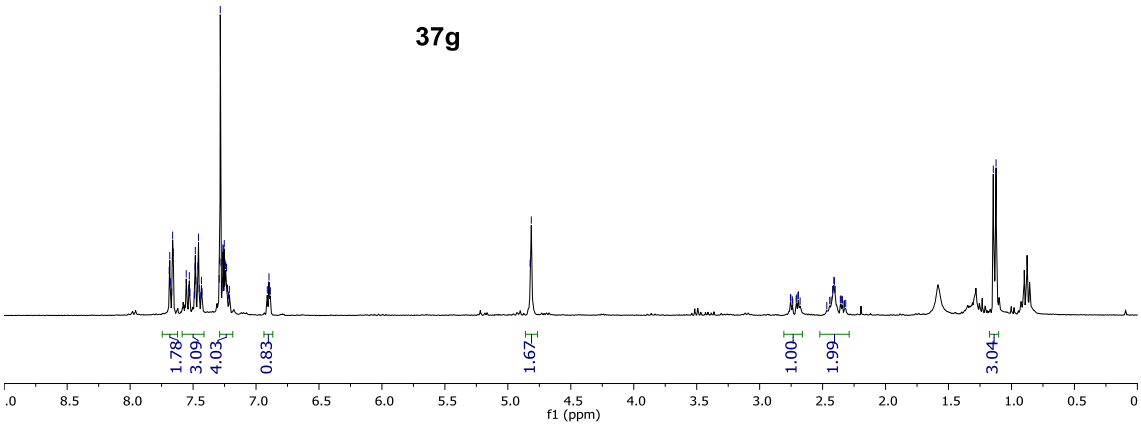
37c

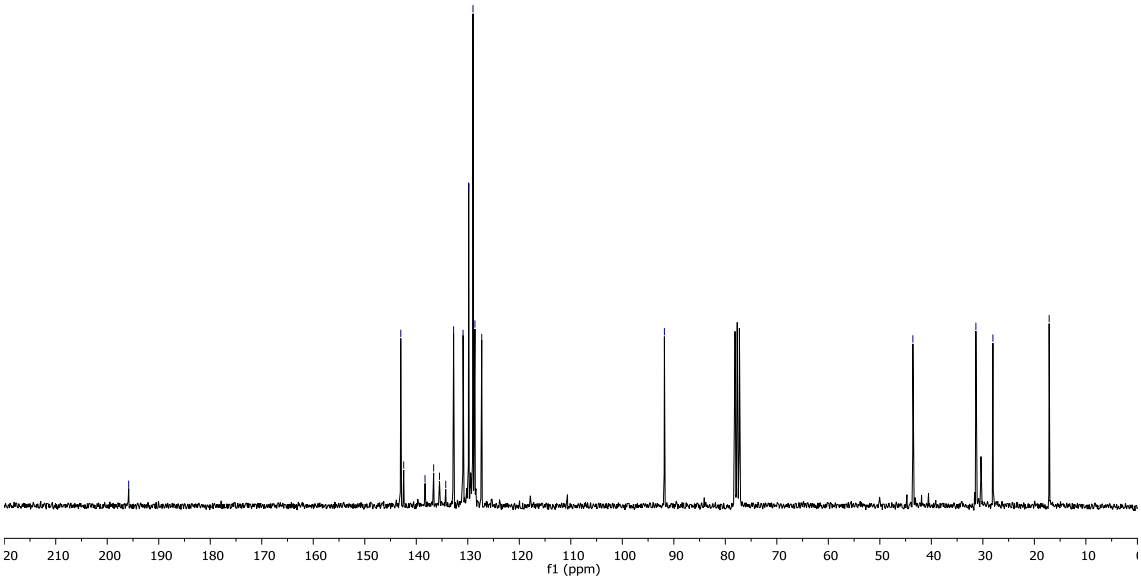

2.00
3.00
4.00
1.00
2.00
1.00
5.00
3.00
f1 (ppm)

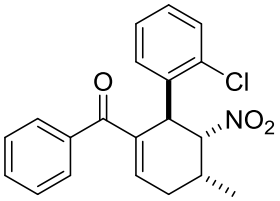

195.68
141.73
138.10
137.60
136.86
136.82
132.14
129.90
129.48
128.43
128.38
91.83
43.25
30.86
27.35
21.24
16.91
f1 (ppm)



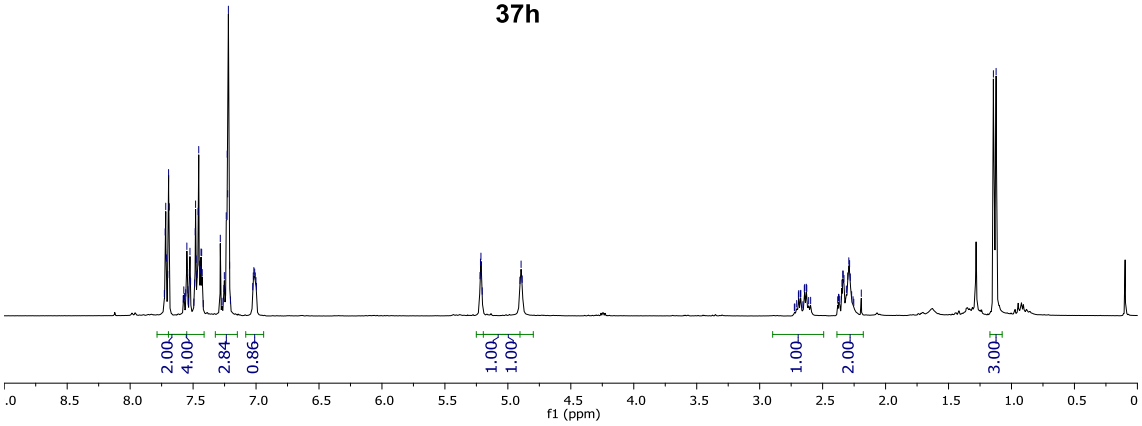
37g

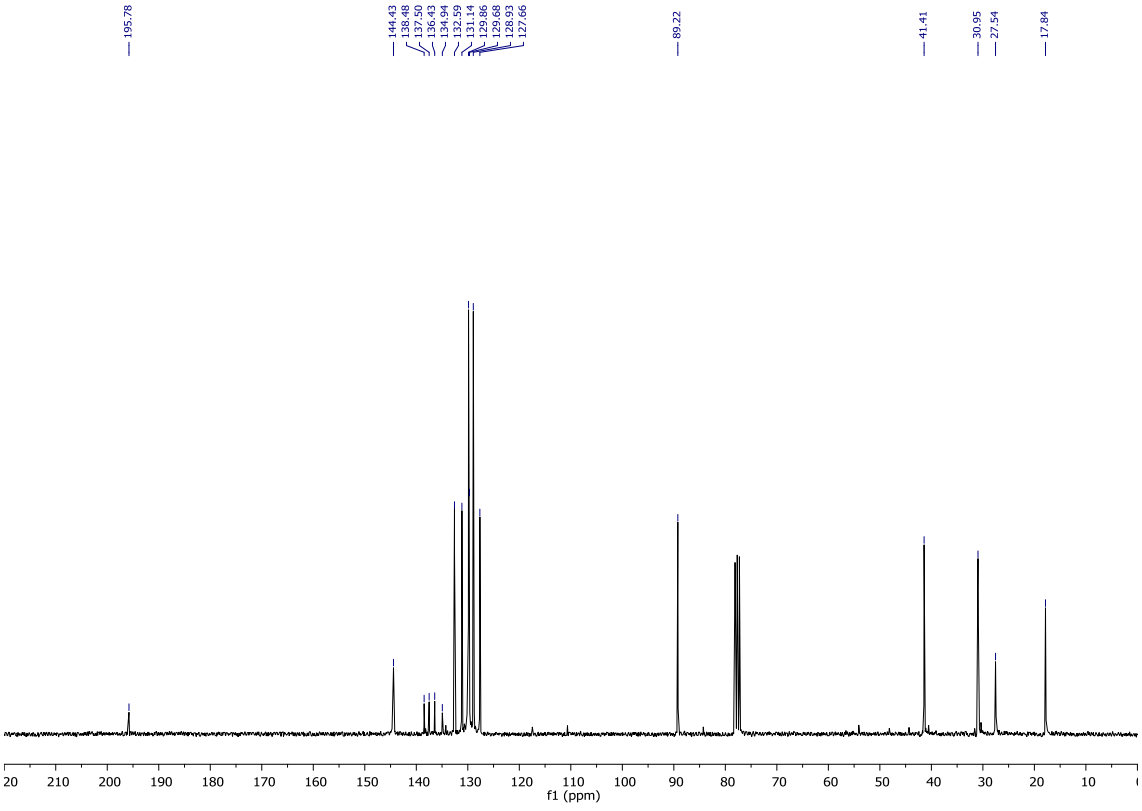


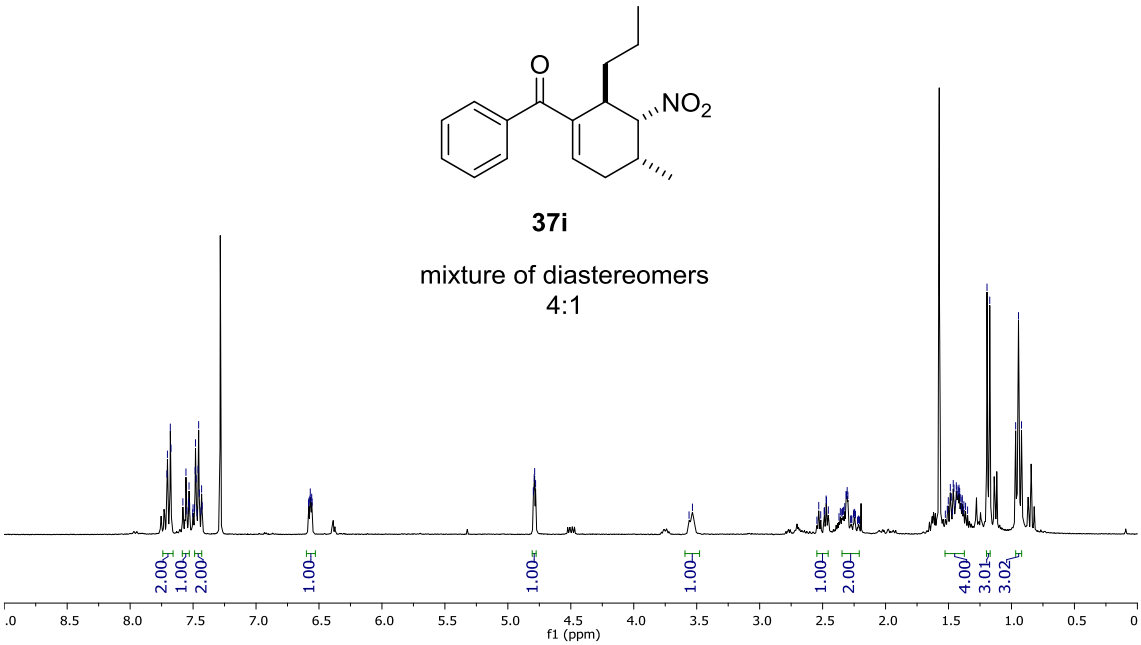


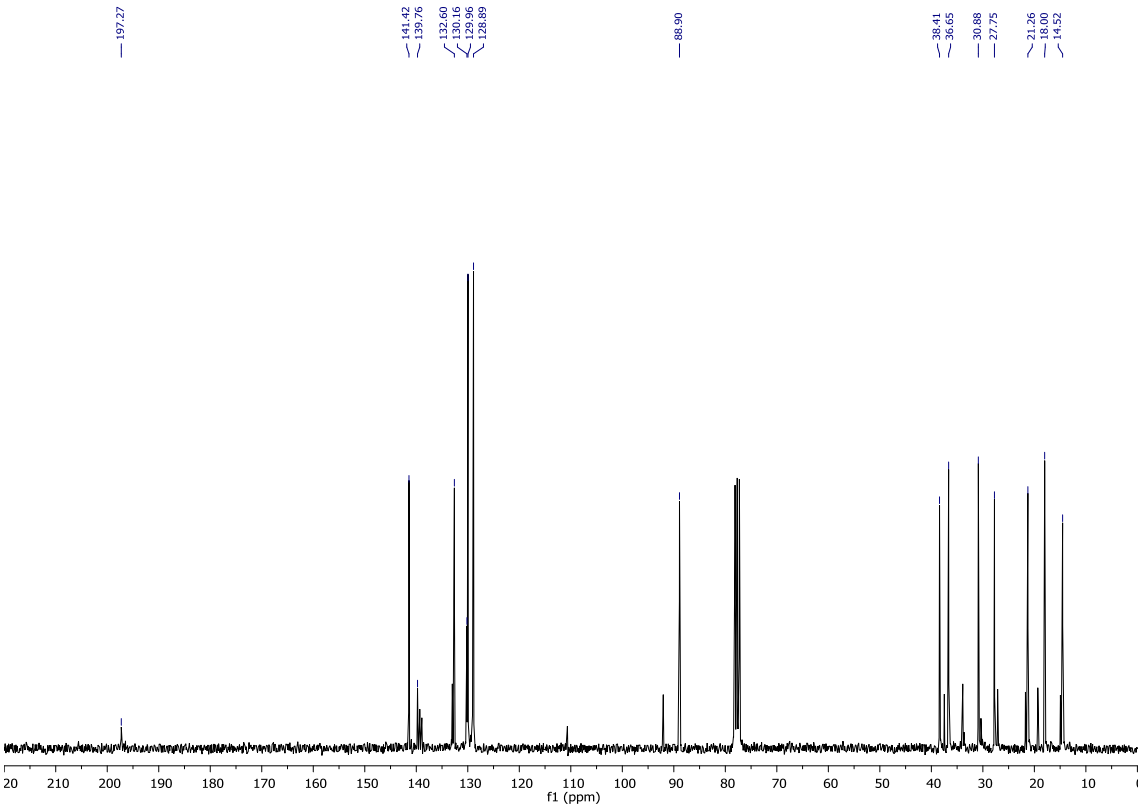

O
Cl
NO2

37h

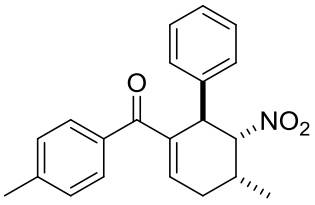

2.00
4.00
2.84
0.86
1.00
1.00
1.00
2.00
3.00
f1 (ppm)


195.78
144.43
138.48
137.50
136.43
134.94
132.59
131.14
129.86
129.68
128.93
127.66
89.22
41.41
30.95
27.54
17.84
f1 (ppm)

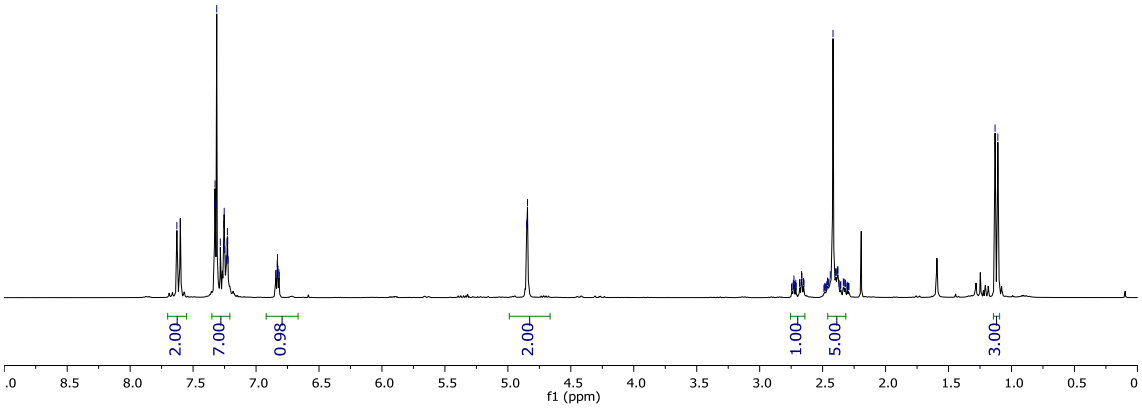

O
NO2
37i
mixture of diastereomers
4:1
2.00
1.00
2.00
1.00
1.00
1.00
1.00
2.00
4.00
3.01
3.02
f1 (ppm)

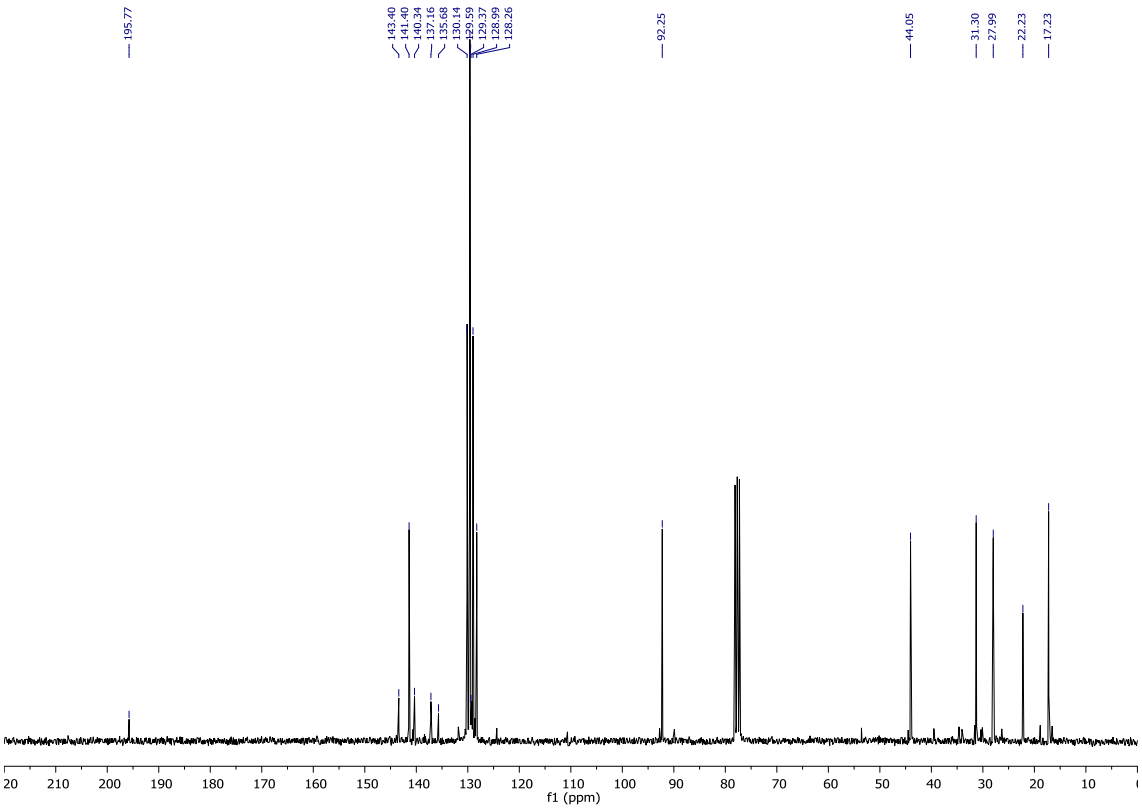

197.27
141.42
139.76
132.60
130.16
130.06
128.89
88.90
38.41
36.65
30.88
27.75
21.26
18.00
14.52
f1 (ppm)


7.63
7.33
7.33
7.32
7.31
7.28
7.26
7.25
7.24
7.23
7.23
7.23
7.22
6.84
6.84
6.83
6.83
6.82
6.82
4.85
4.84
2.75
2.74
2.73
2.73
2.72
2.72
2.71
2.71
2.68
2.68
2.67
2.66
2.65
2.65
2.49
2.48
2.48
2.47
2.47
2.46
2.45
2.44
2.42
2.40
2.39
2.39
2.38
2.38
2.37
2.36
2.36
2.34
2.33
2.32
2.31
2.30
2.30
2.29
2.29
1.13
1.11


O
NO2

38a


2.00
7.00
0.98
2.00
1.00
5.00
3.00
f1 (ppm)


195.77
143.40
141.40
140.34
137.16
135.68
130.14
129.59
129.37
128.99
128.26
92.25
44.05
31.30
27.99
22.23
17.23
f1 (ppm)


8.20
8.19
8.19
7.98
7.97
7.96
7.95
7.91
7.88
7.78
7.78
7.76
7.75
7.64
7.63
7.62
7.62
7.61
7.60
7.59
7.58
7.58
7.57
7.55
7.55
7.30
7.29
7.28
7.28
7.27
6.90
6.90
6.89
6.88
6.88
6.87
6.86
6.85
4.87
4.86
4.85
4.84


3.77
2.78
2.76
2.75
2.74
2.71
2.71
2.70
2.68
2.55
2.52
2.50
2.49
2.48
2.47
2.47
2.46
2.45
2.42
2.41
2.41
2.40
2.39
2.39
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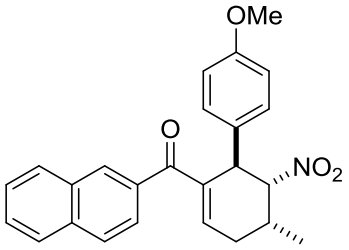
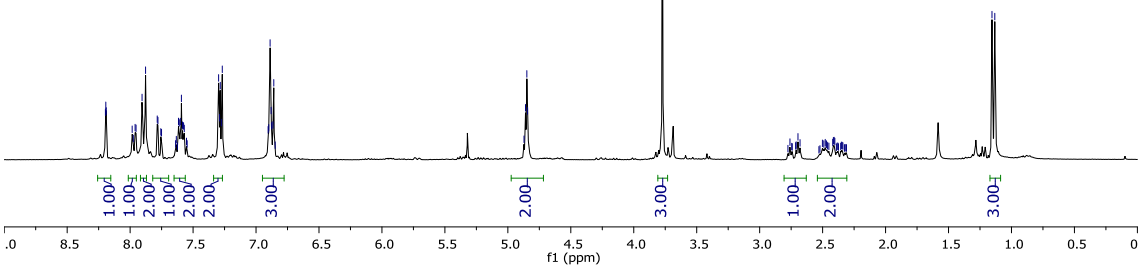
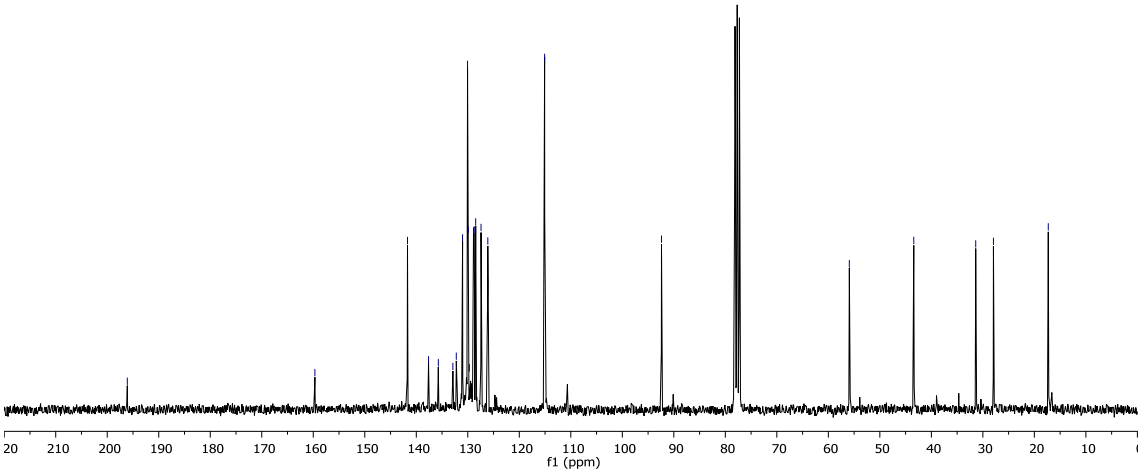
2.33
2.32
2.31
2.31
1.15
1.13

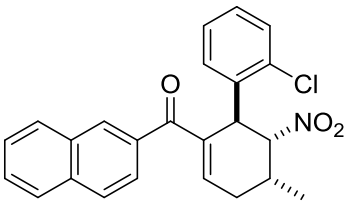

OMe
O
NO2

39b

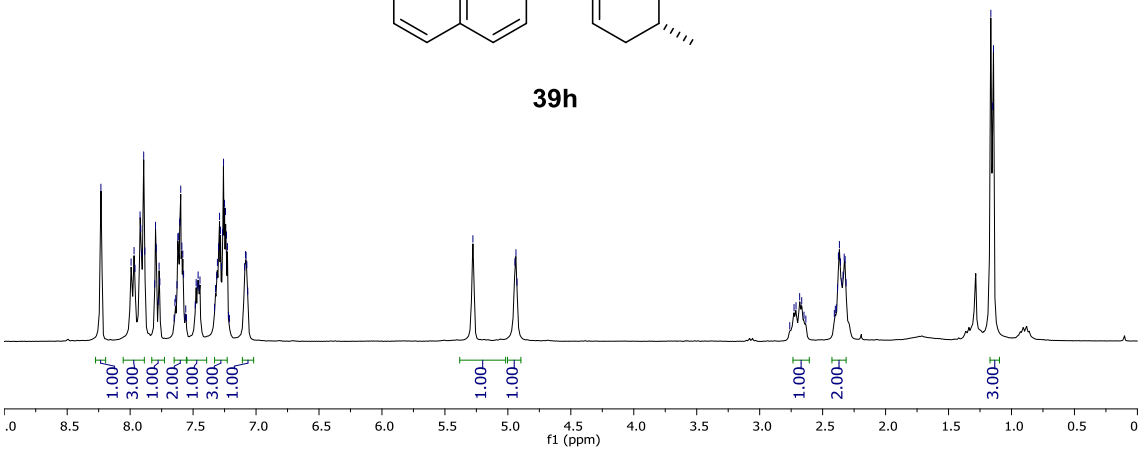

1.00
1.00
2.00
1.00
2.00
2.00
3.00
2.00
3.00
1.00
2.00
3.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

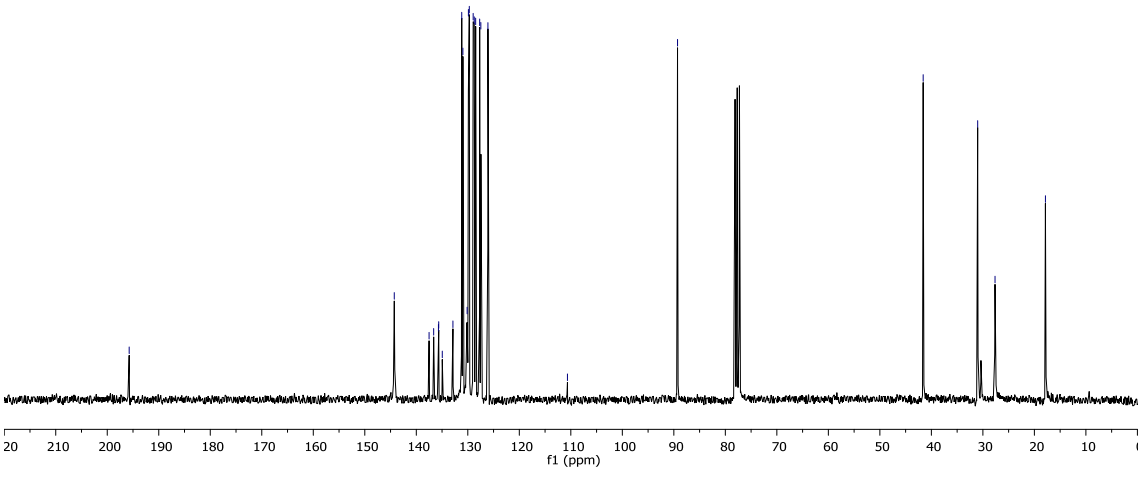

196.10
159.68
141.70
137.62
135.72
132.90
132.23
131.01
130.05
129.90
129.70
128.89
128.74
128.46
127.43
126.11
115.08
92.39
55.93
43.41
31.38
27.95
17.30

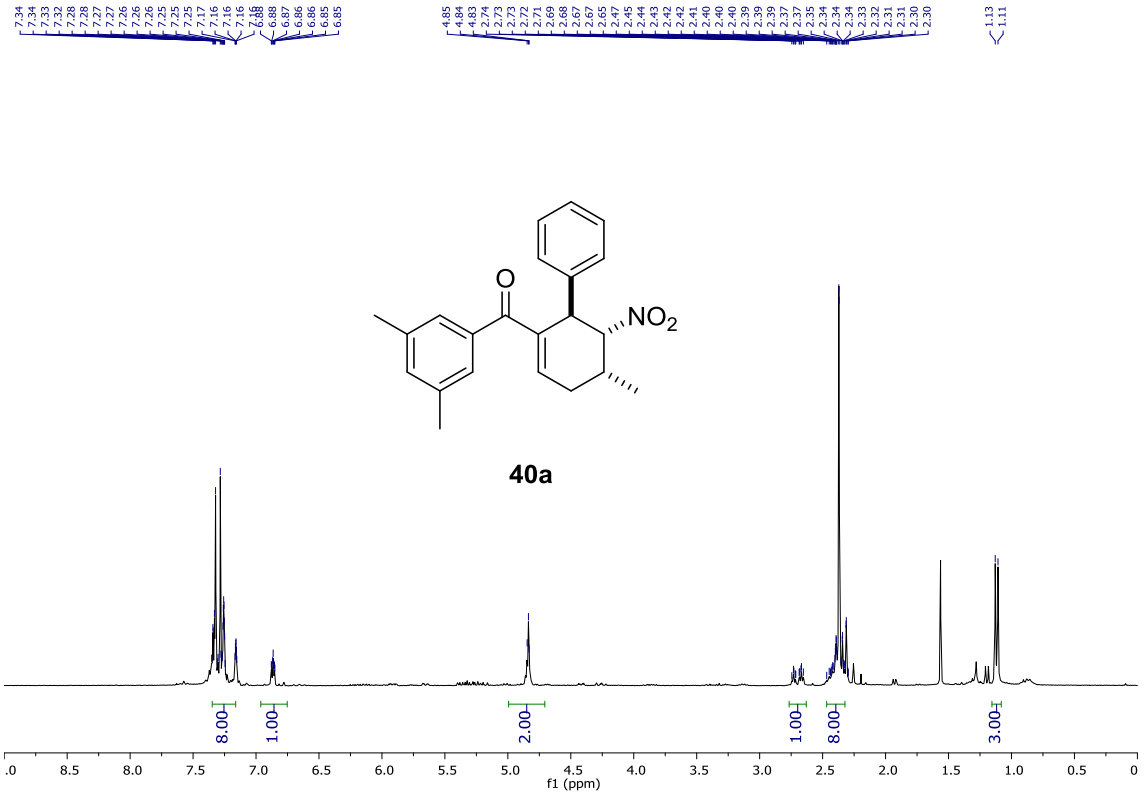

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

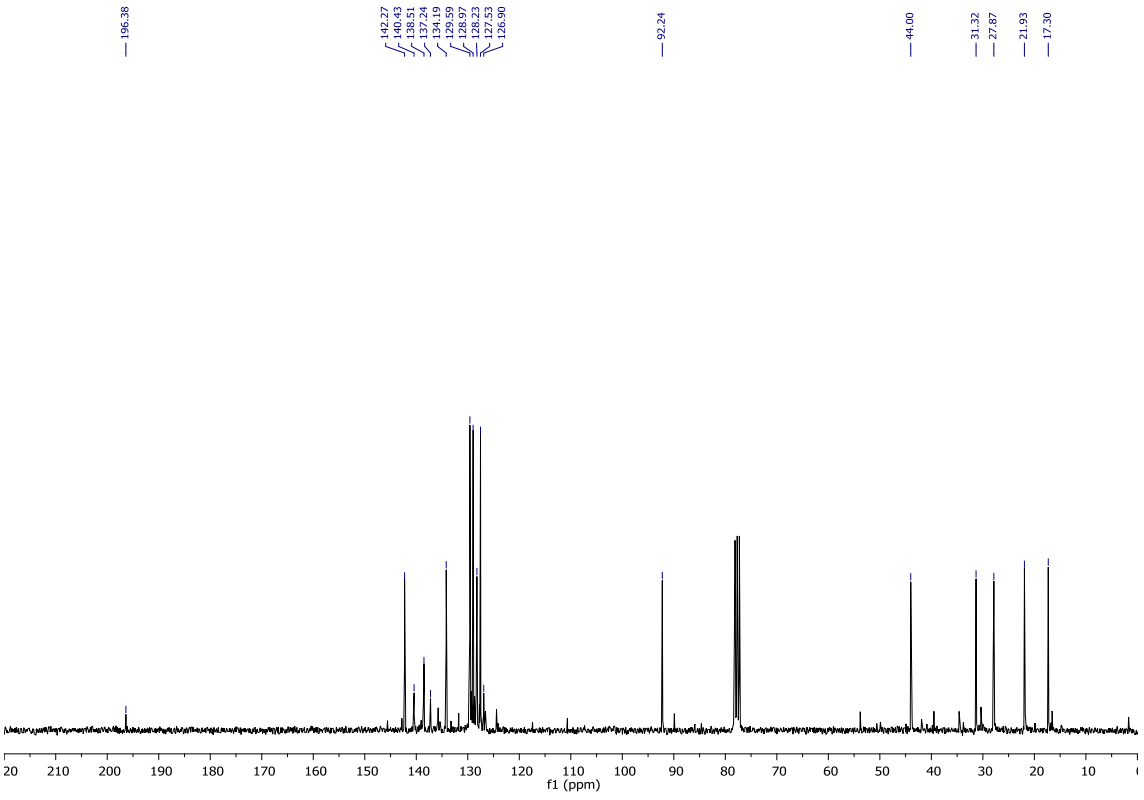


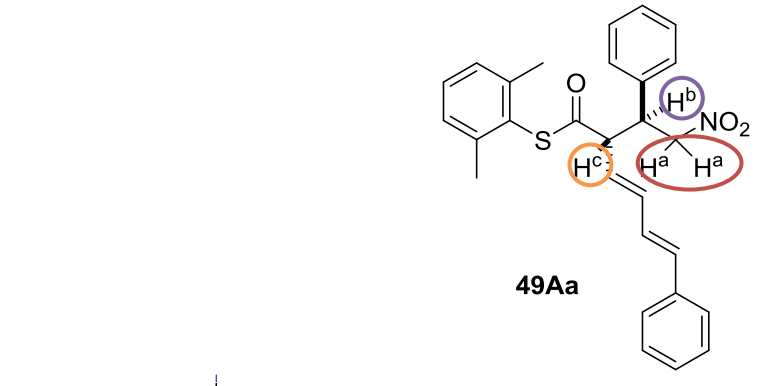
39h





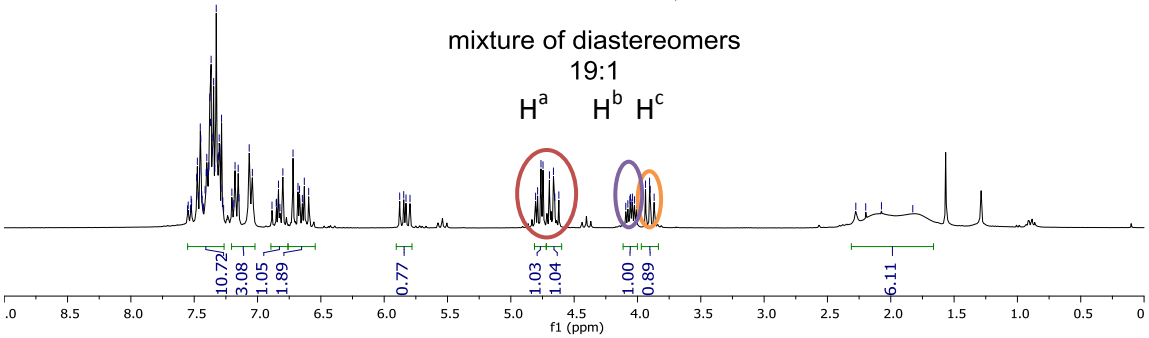

7.34
7.34
7.33
7.32
7.28
7.28
7.27
7.27
7.26
7.26
7.26
7.25
7.25
7.25
7.17
7.16
7.16
7.16
6.88
6.87
6.86
6.86
6.85
6.85
4.85
4.84
4.83
2.74
2.73
2.73
2.72
2.71
2.69
2.68
2.67
2.67
2.65
2.47
2.45
2.44
2.43
2.42
2.42
2.41
2.40
2.40
2.40
2.39
2.39
2.39
2.37
2.37
2.35
2.34
2.34
2.34
2.33
2.32
2.31
2.31
2.30
2.30
1.13
1.11
O
NO2
40a
8.00
1.00
2.00
1.00
8.00
3.00
f1 (ppm)

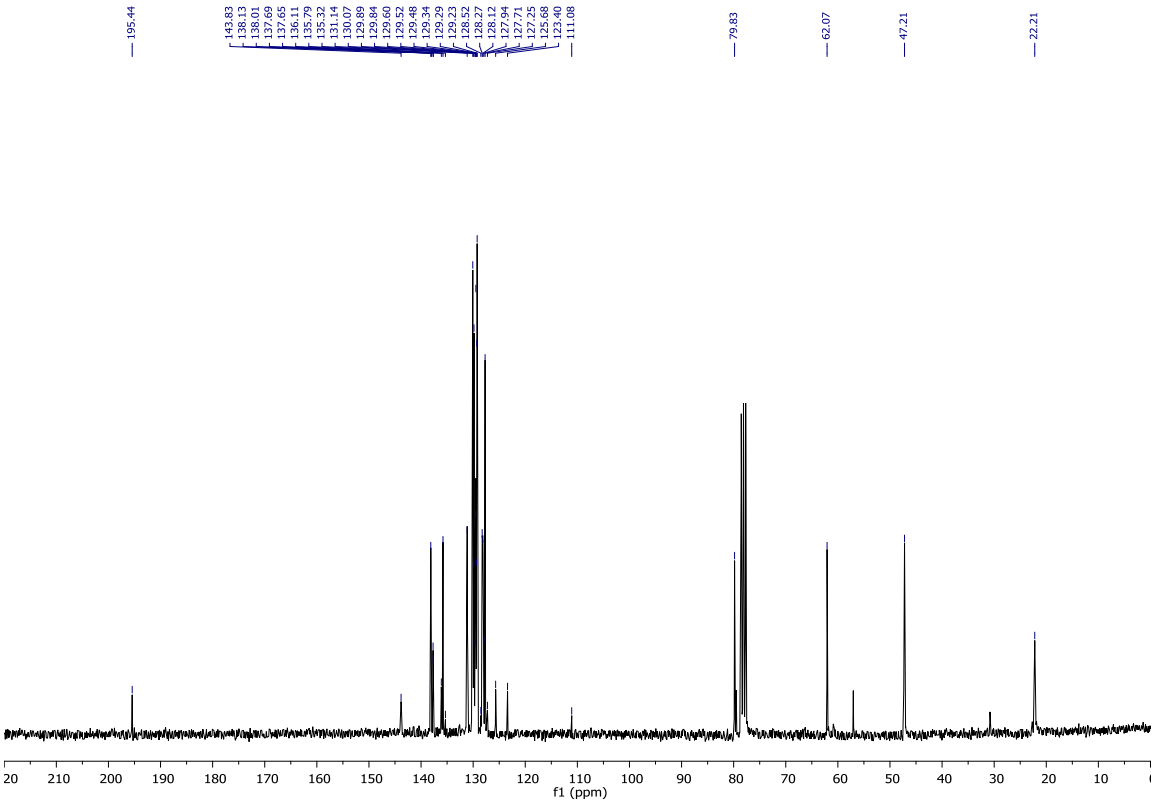

196.38
142.27
140.43
138.51
137.24
134.19
129.59
128.97
128.23
127.53
126.90
92.24
44.00
31.32
27.87
21.93
17.30
f1 (ppm)

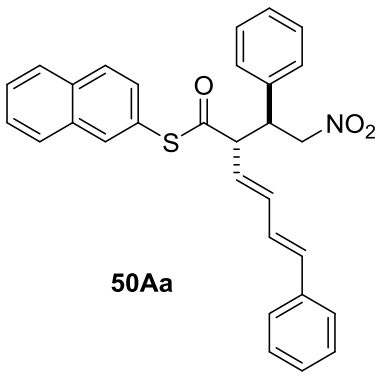


49Aa

mixture of diastereomers
19:1
H^a H^b H^c

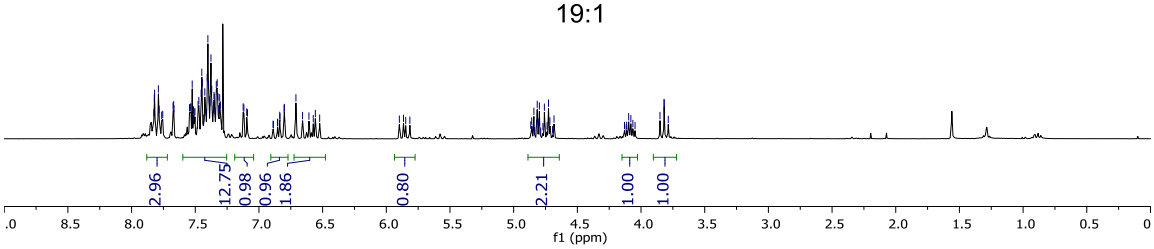


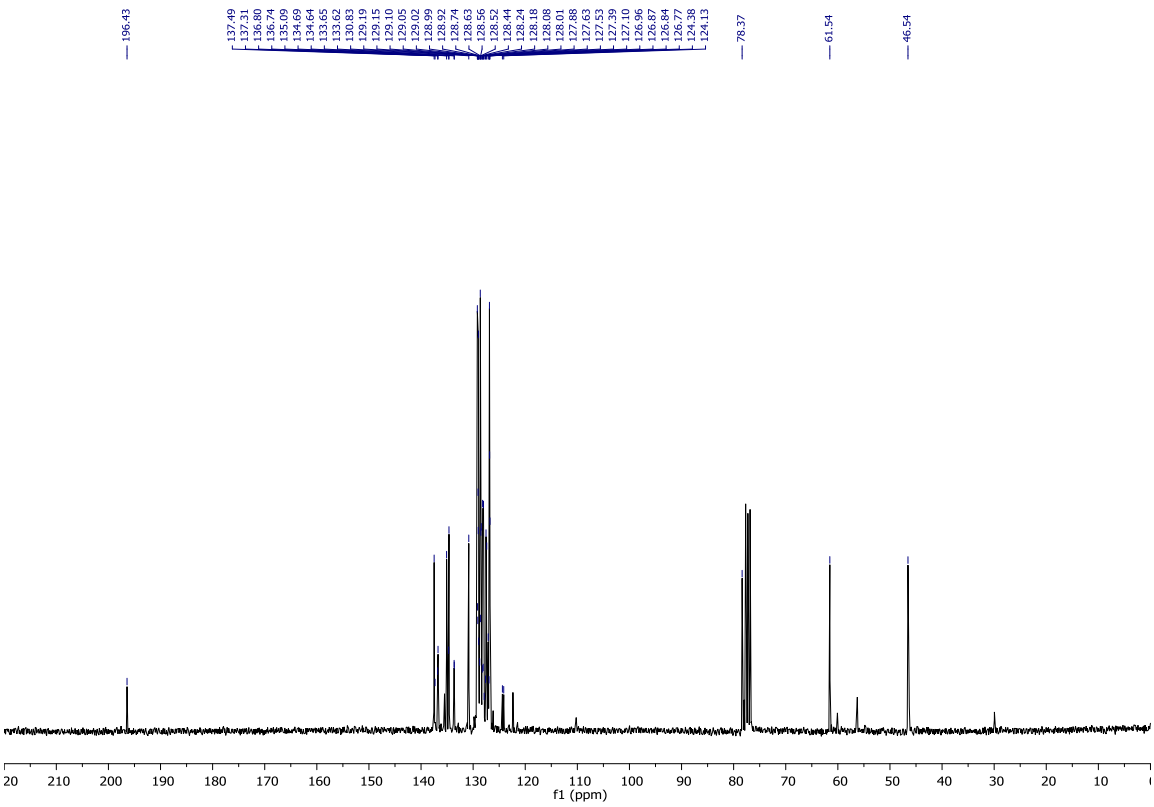


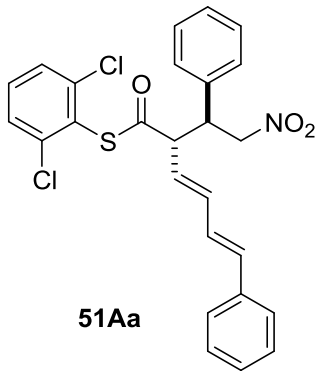


50Aa

mixture of diastereomers
19:1

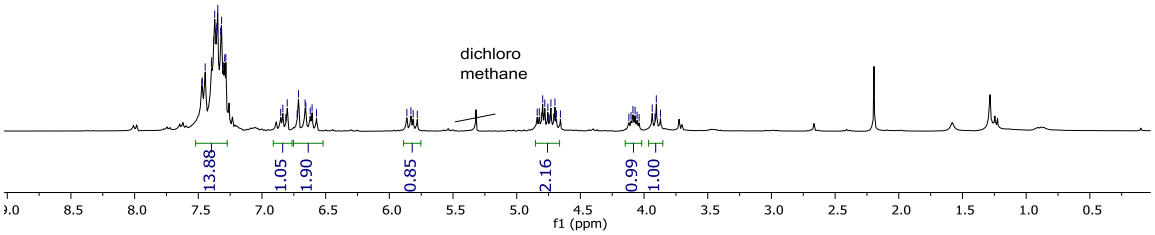


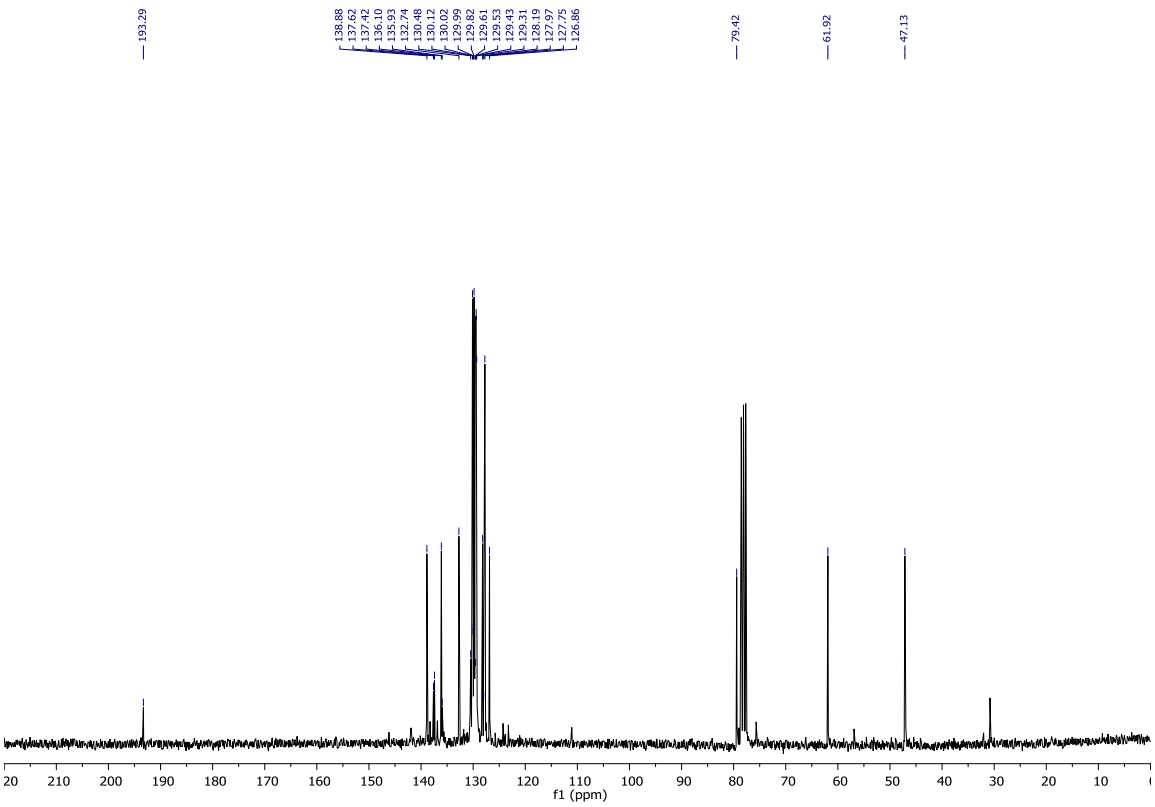


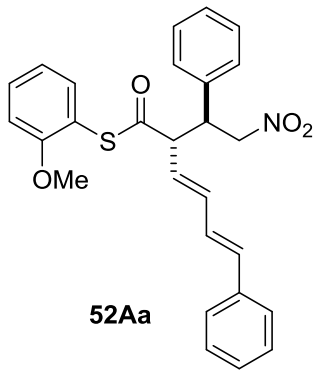


51Aa

mixture of diastereomers
18:1

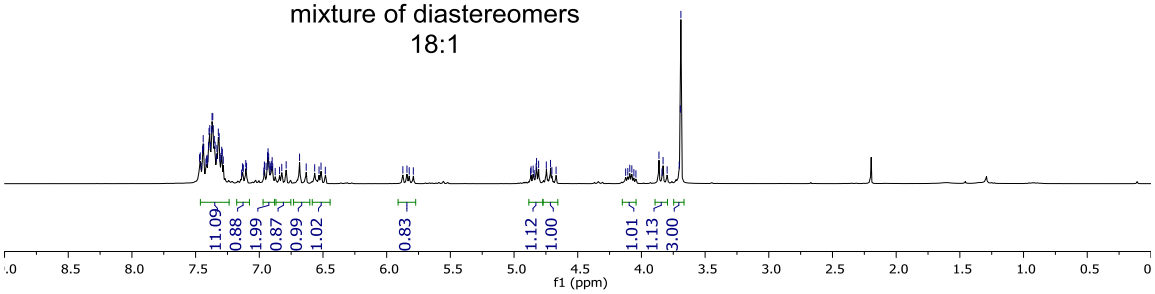


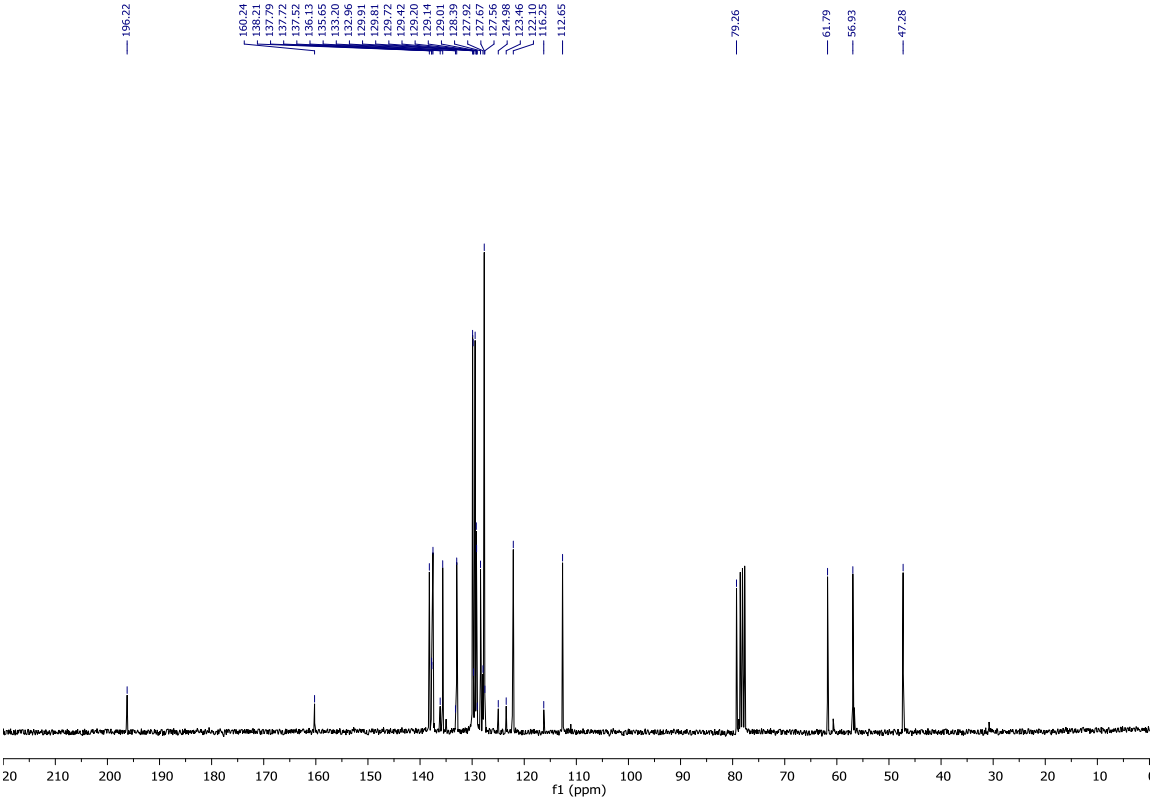


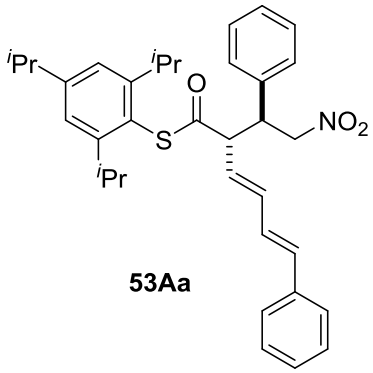


52Aa

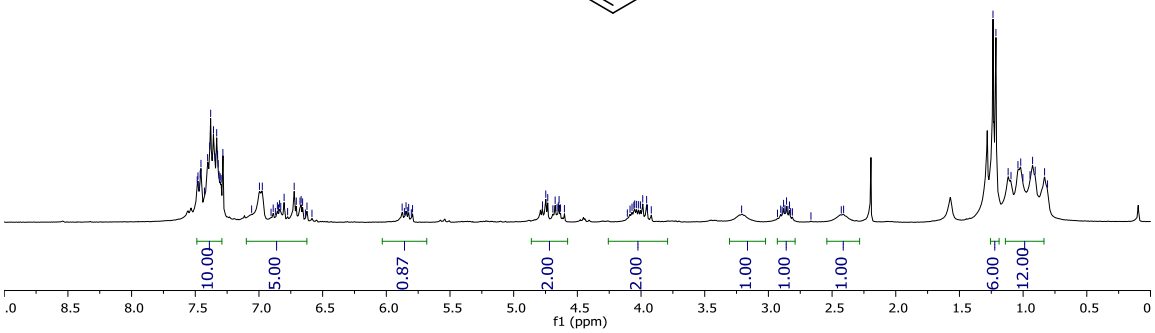
mixture of diastereomers
18:1

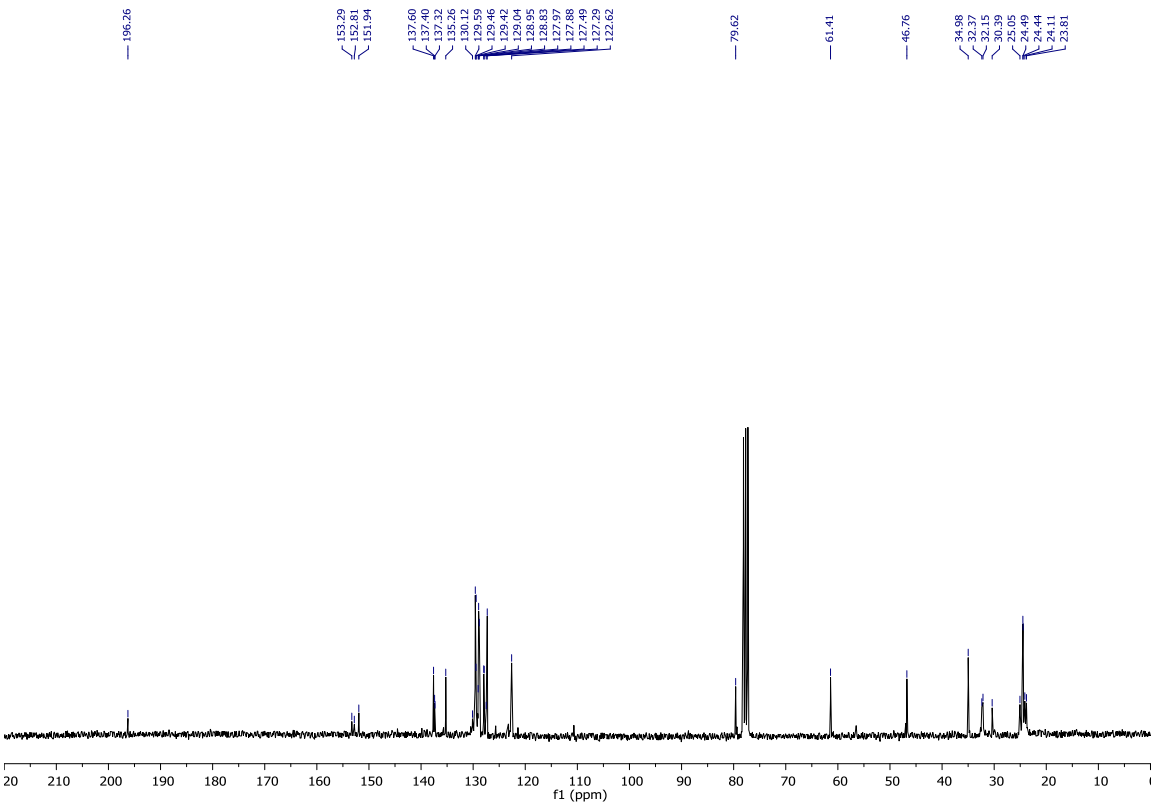


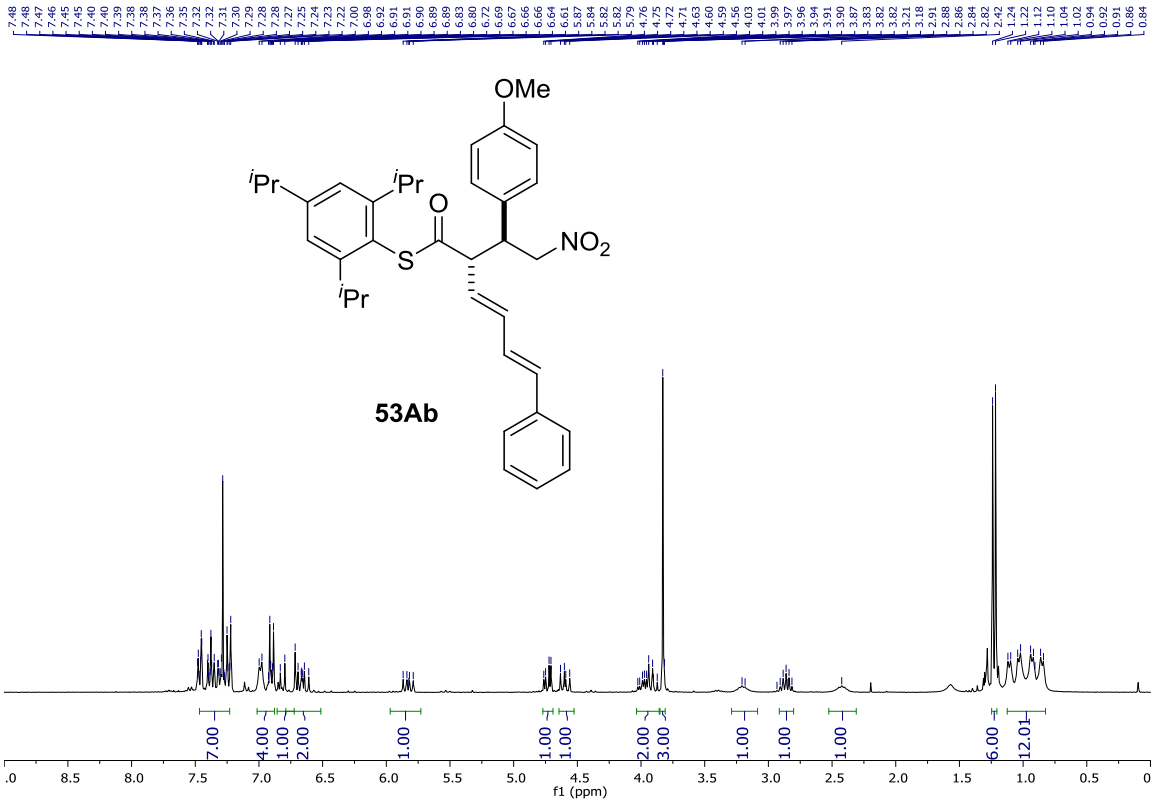


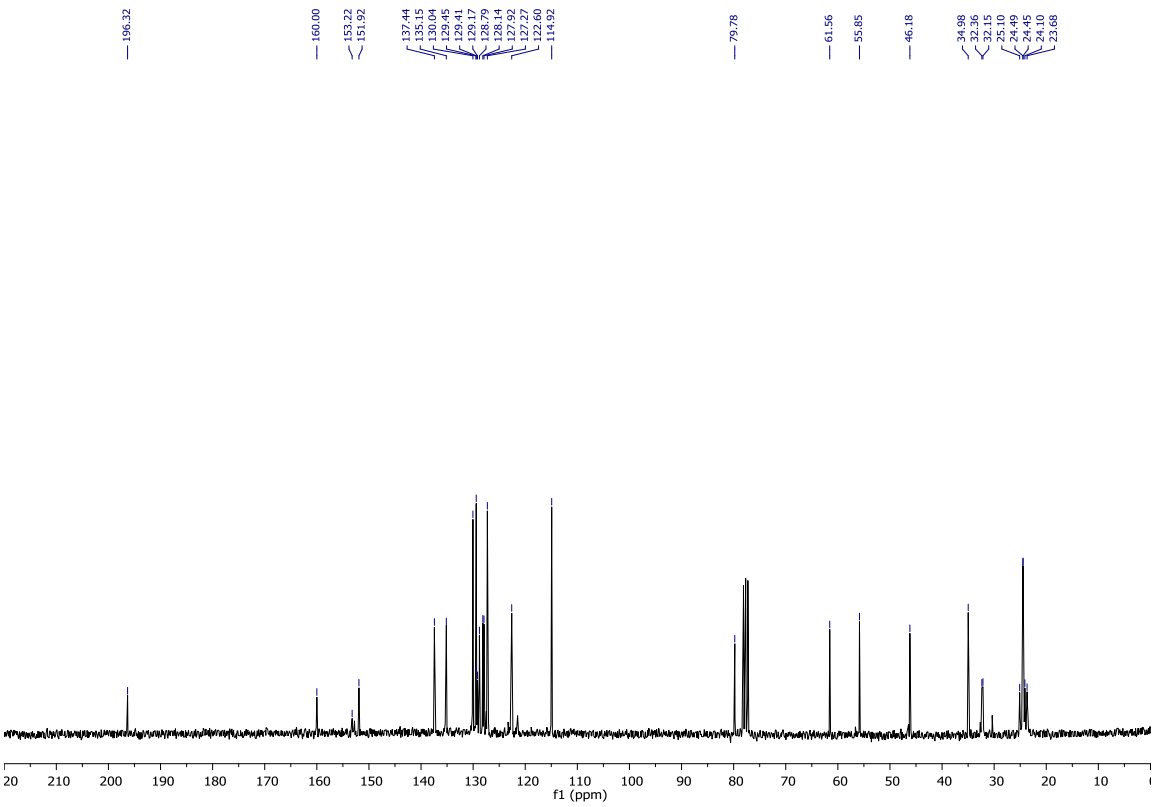

iPr
iPr
iPr
O
S
NO2

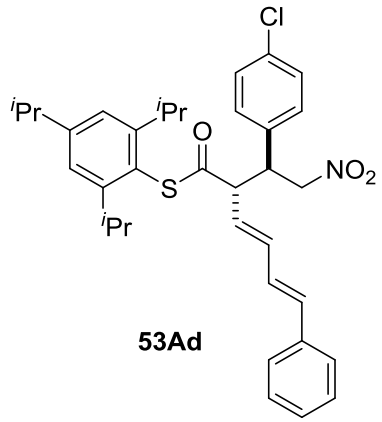
53Aa


10.00
5.00
0.87
2.00
2.00
1.00
1.00
1.00
6.00
12.00
f1 (ppm)

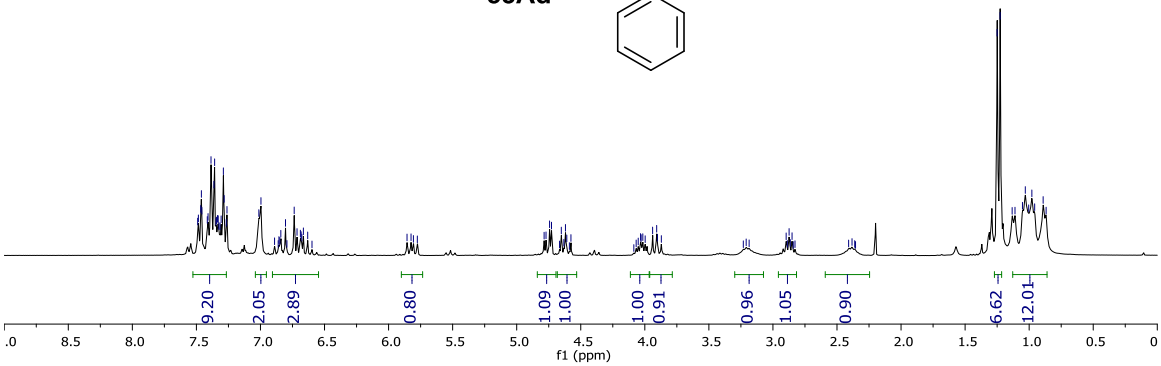

f1 (ppm)

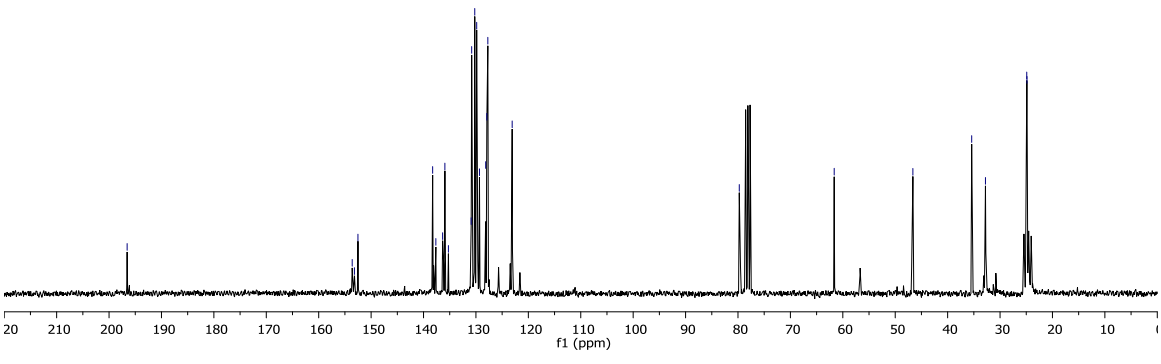

OMe
iPr
iPr
iPr
O
S
NO2
53Ab
f1 (ppm)

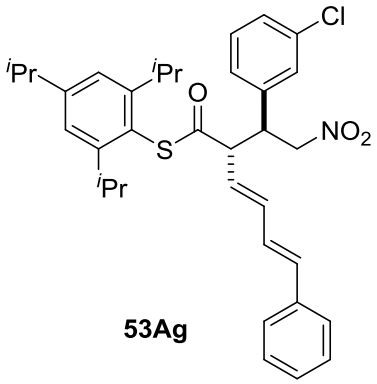

f1 (ppm)


Cl
iPr
iPr
O
S
NO2
iPr

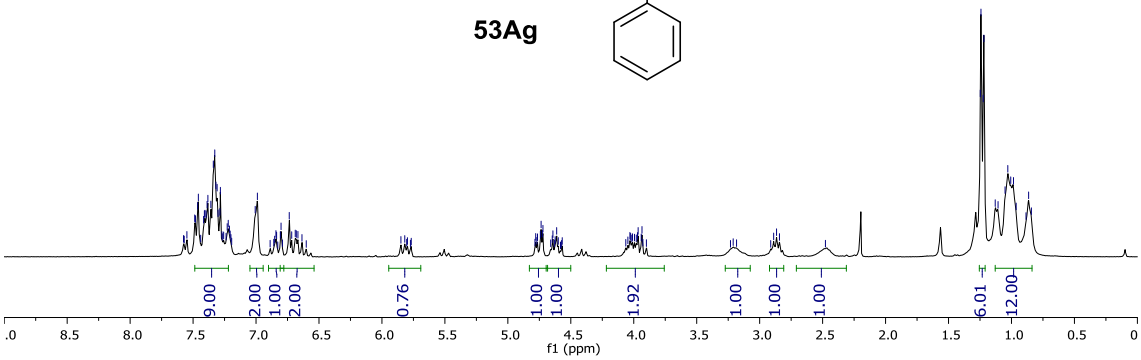
53Ad

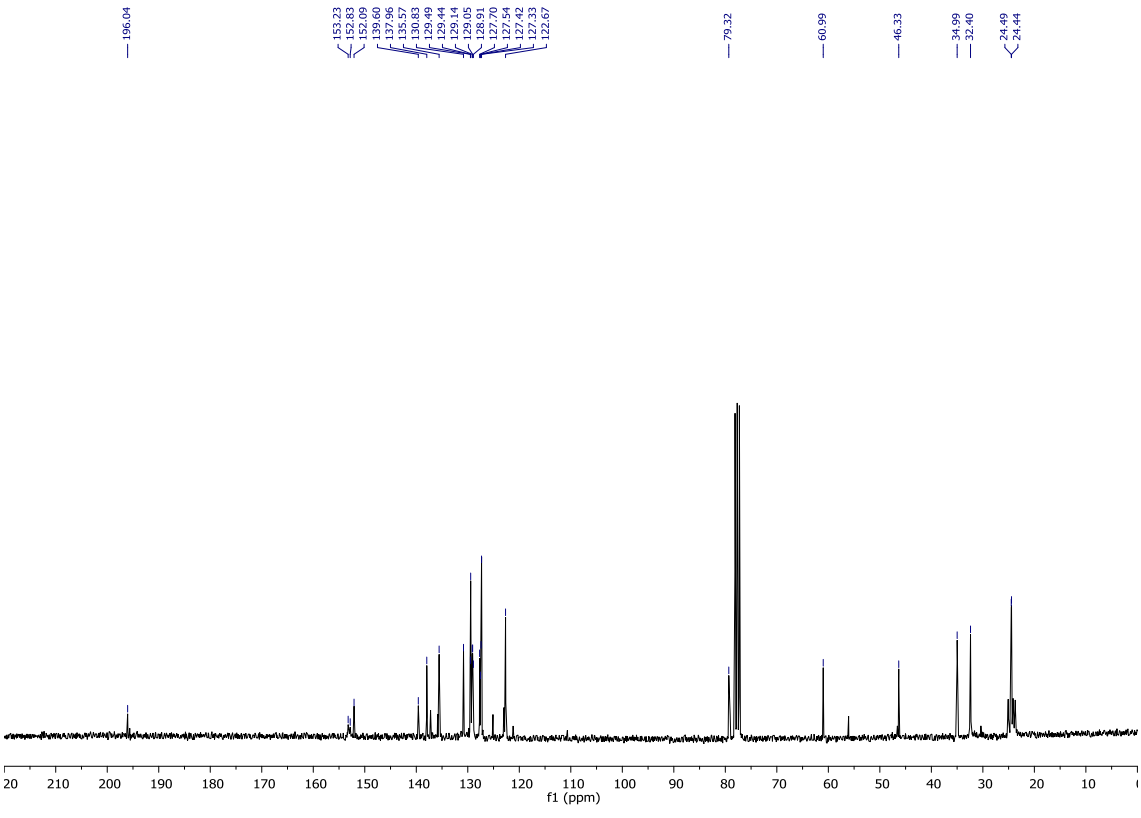

9.20
2.05
2.89
0.80
1.09
1.00
1.00
0.91
0.96
1.05
0.90
6.62
12.01
f1 (ppm)

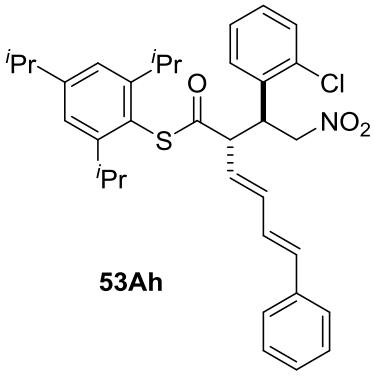

f1 (ppm)


Cl
iPr
iPr
O
NO2
S
iPr

53Ag

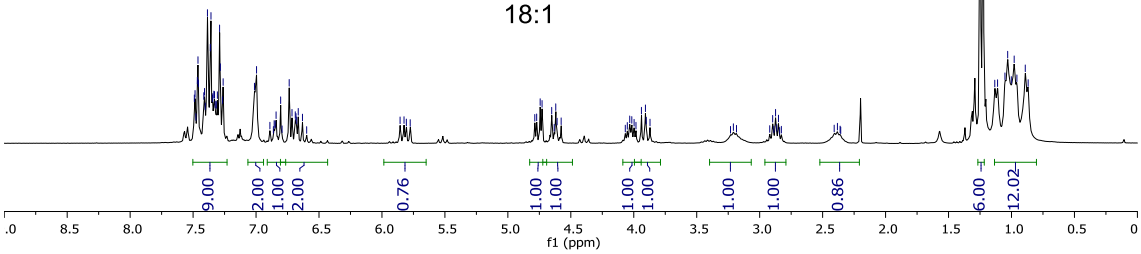

9.00
2.00
1.00
2.00
0.76
1.00
1.00
1.92
1.00
1.00
1.00
6.01
12.00
f1 (ppm)

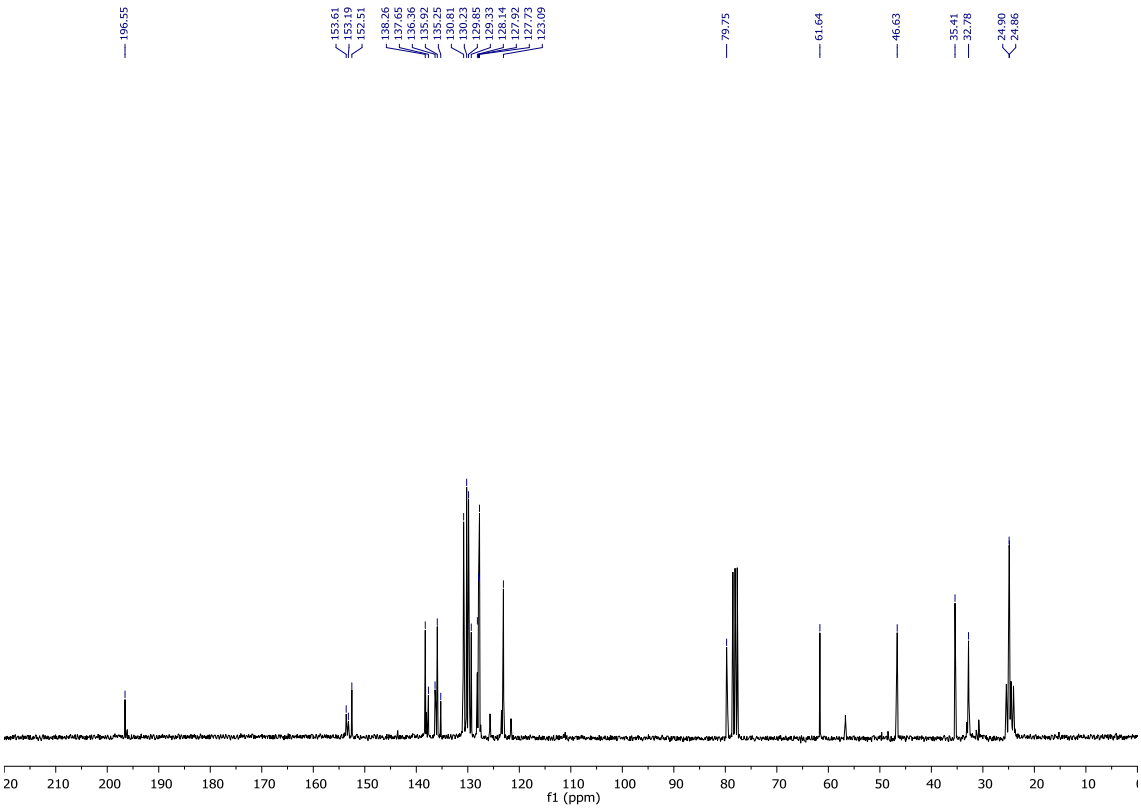

196.04
153.23
152.83
152.09
139.60
137.96
135.57
130.83
129.49
129.44
129.14
129.05
128.91
127.70
127.54
127.42
127.33
122.67
79.32
60.99
46.33
34.99
32.40
24.49
24.44
f1 (ppm)

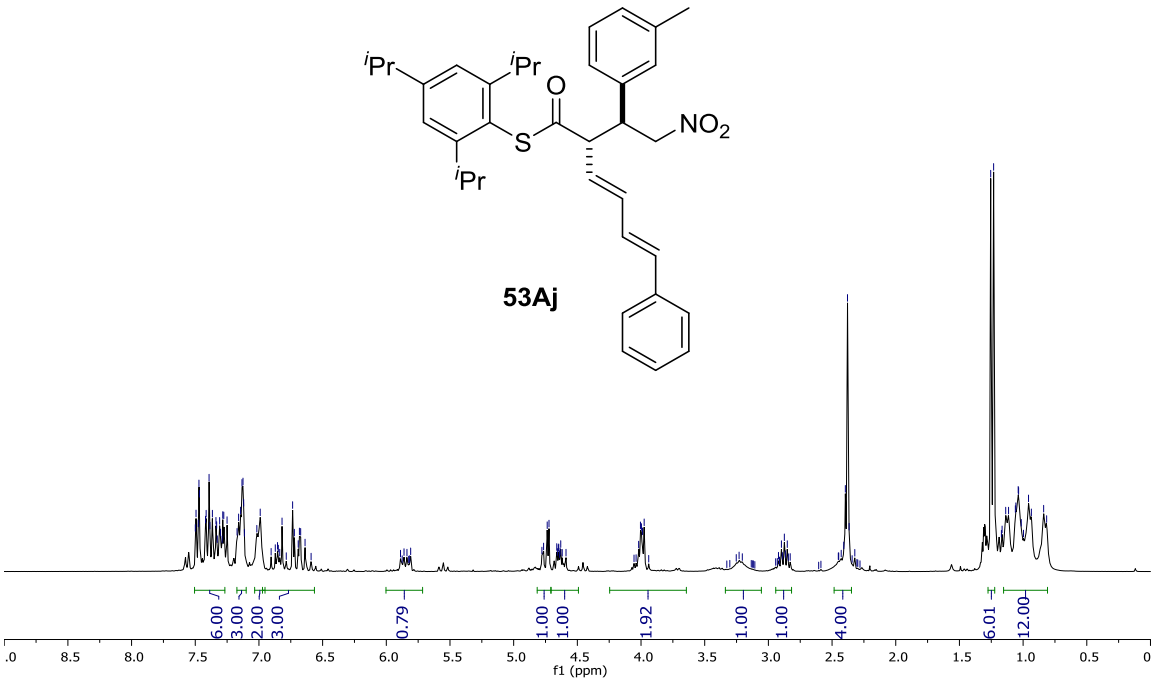


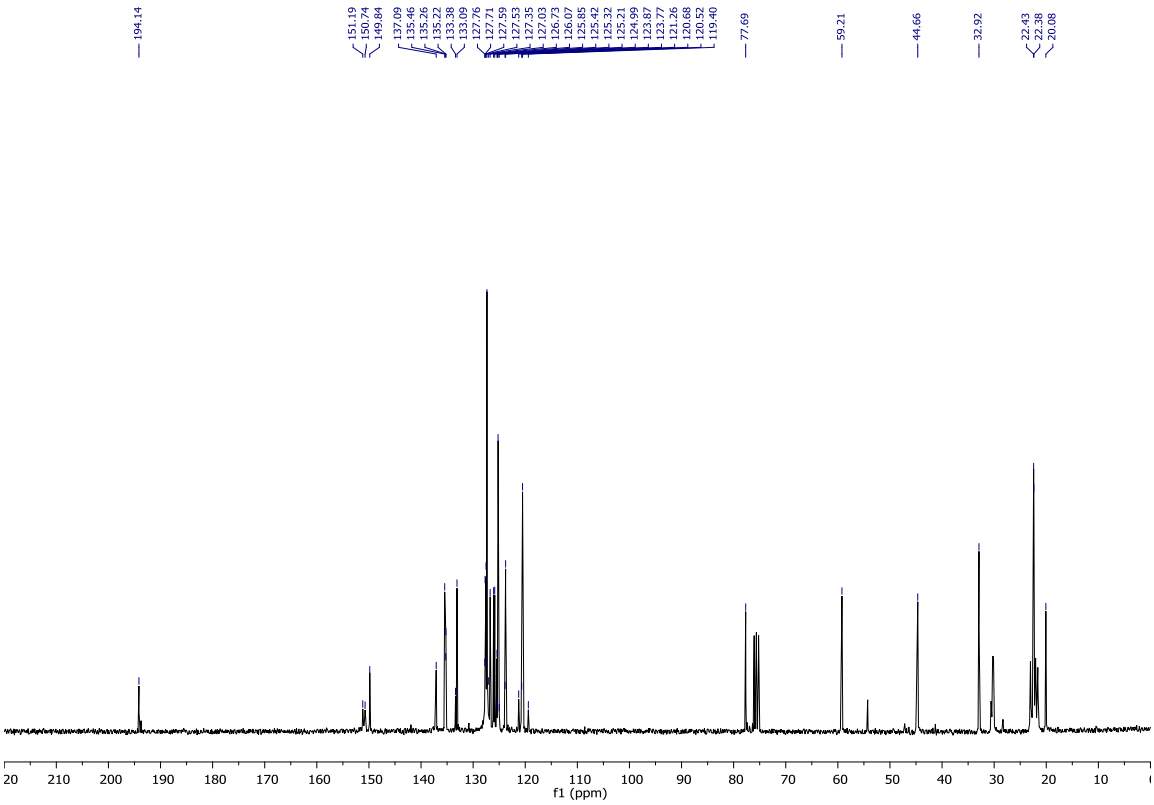
53Ah

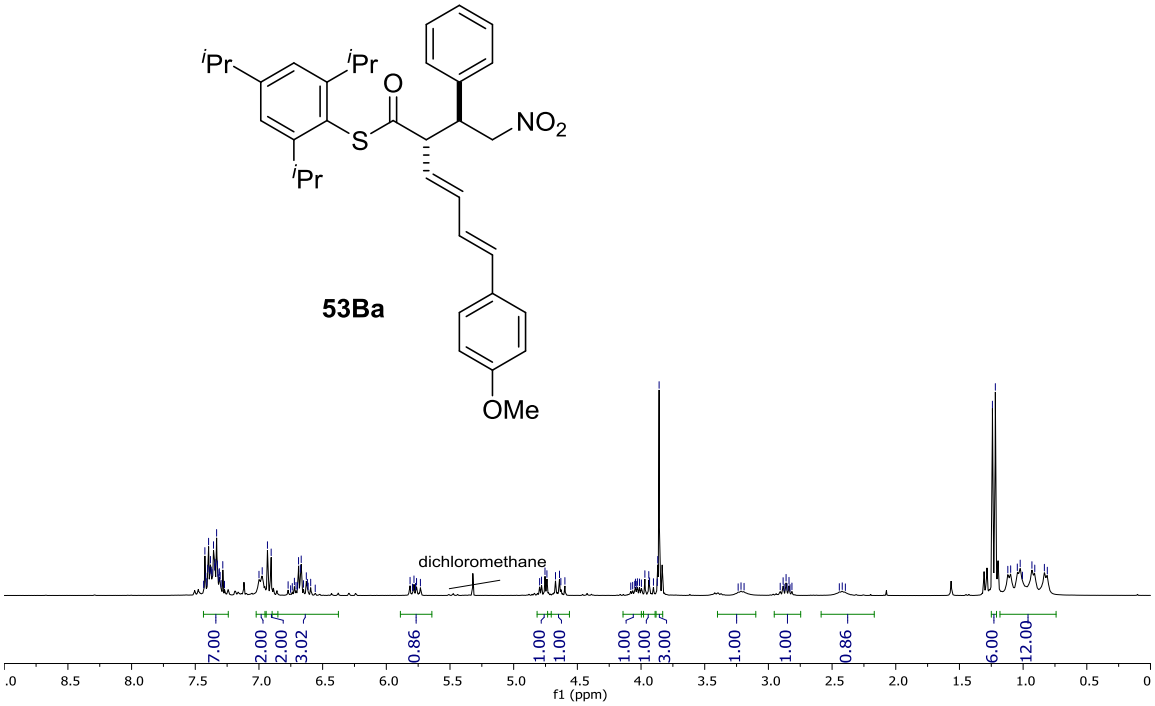
mixture of diastereomers
18:1

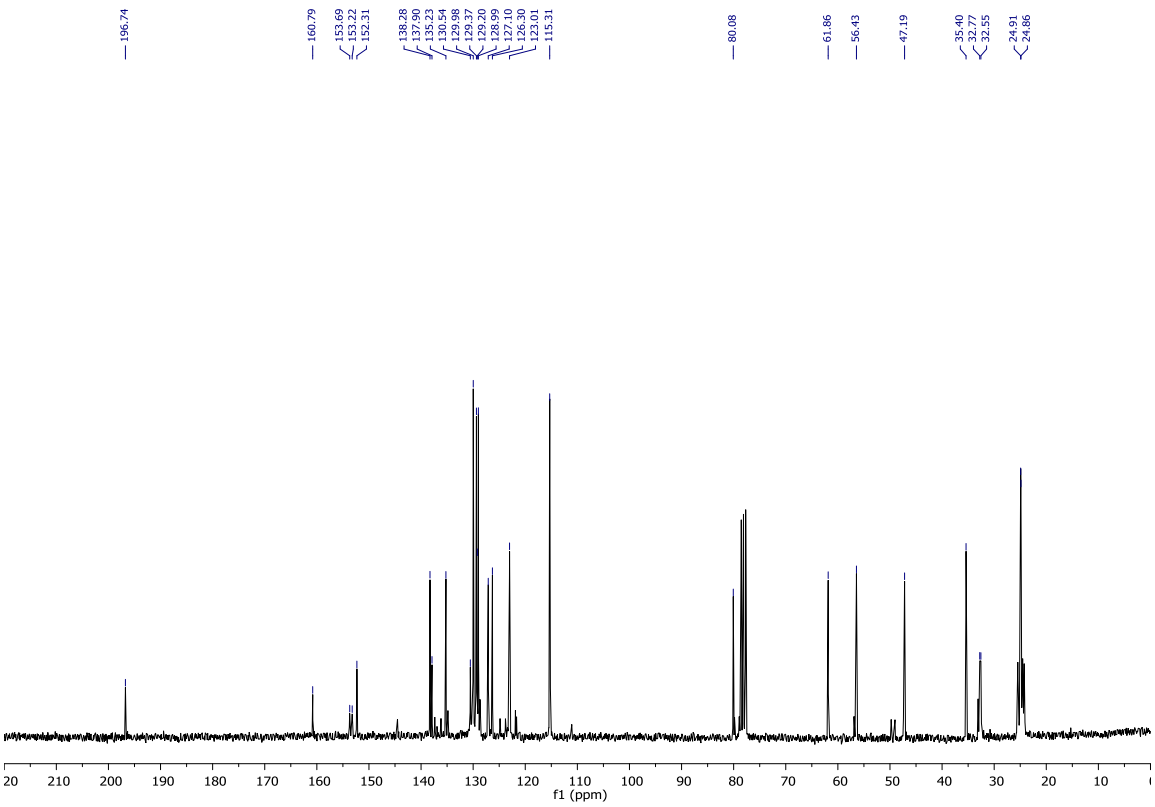


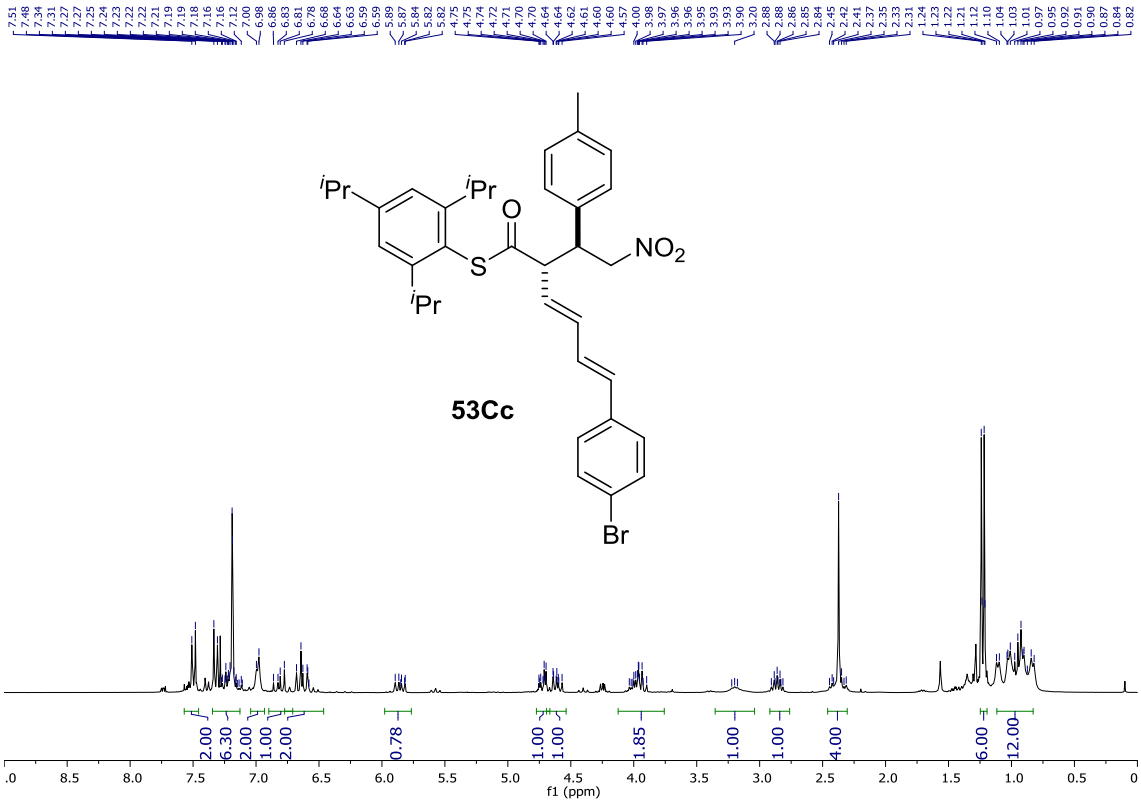


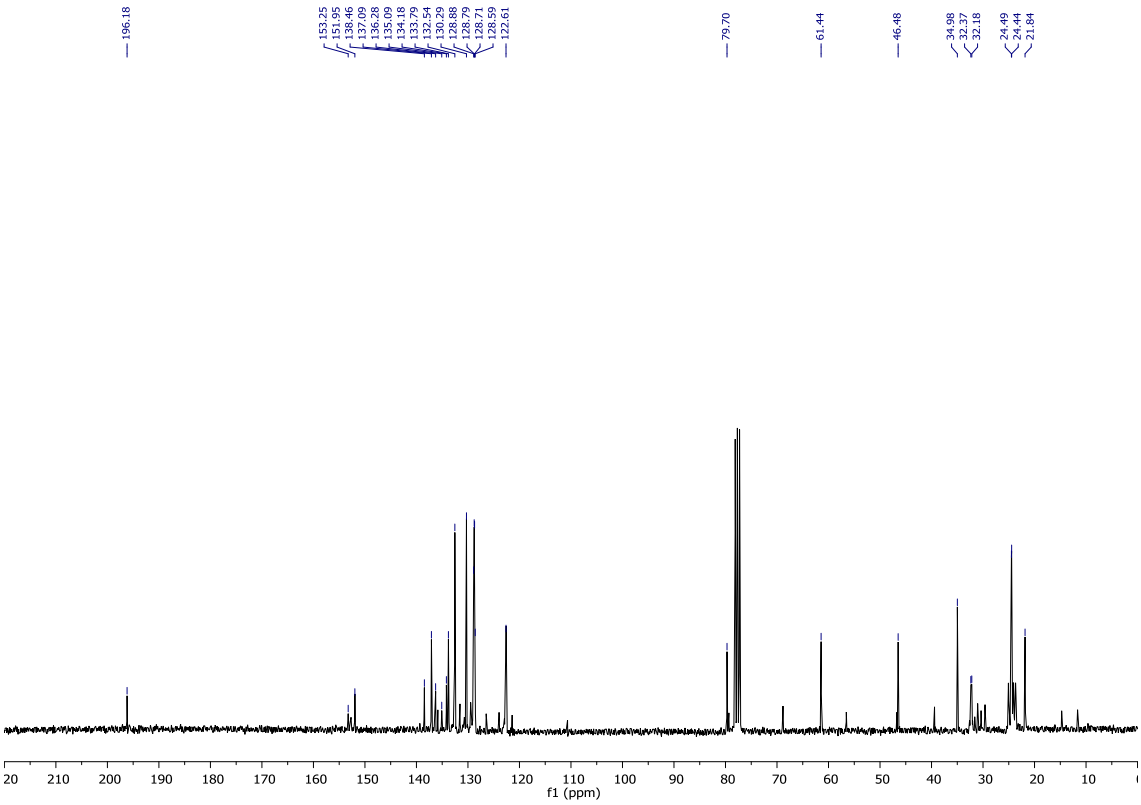

iPr
iPr
iPr
O
S
NO2
53Aj
6.00
3.00
2.00
3.00
0.79
1.00
1.00
1.92
1.00
1.00
4.00
6.01
12.00
f1 (ppm)

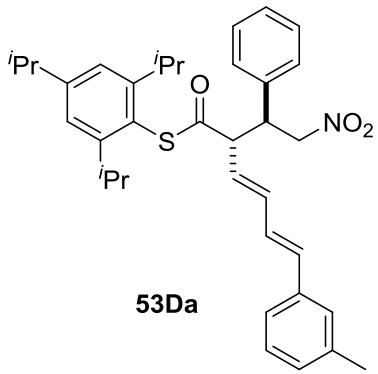

194.14
151.19
150.74
149.84
137.09
135.46
135.26
135.22
133.38
133.09
127.76
127.71
127.59
127.53
127.35
127.03
126.73
126.07
125.85
125.42
125.32
125.21
124.99
123.87
123.77
121.26
120.68
120.52
119.40
77.69
59.21
44.66
32.92
22.43
22.38
20.08
f1 (ppm)


iPr
iPr
iPr
O
S
NO2
OMe
53Ba
dichloromethane
7.00
2.00
2.00
3.02
0.86
1.00
1.00
1.00
1.00
3.00
1.00
1.00
0.86
6.00
12.00
f1 (ppm)

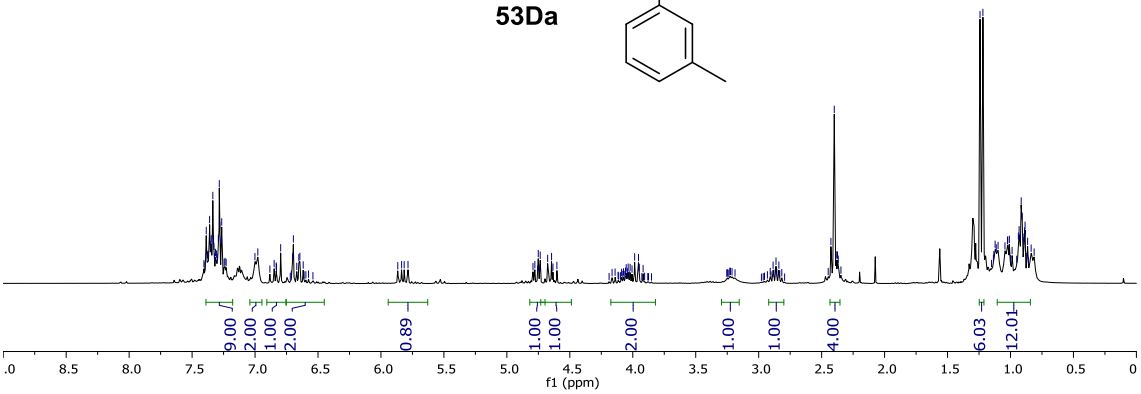

196.74
160.79
153.69
153.22
152.31
138.28
137.90
135.23
130.54
129.98
129.37
129.20
128.99
127.10
126.30
123.01
115.31
80.08
61.86
56.43
47.19
35.40
32.77
32.55
24.91
24.86
f1 (ppm)

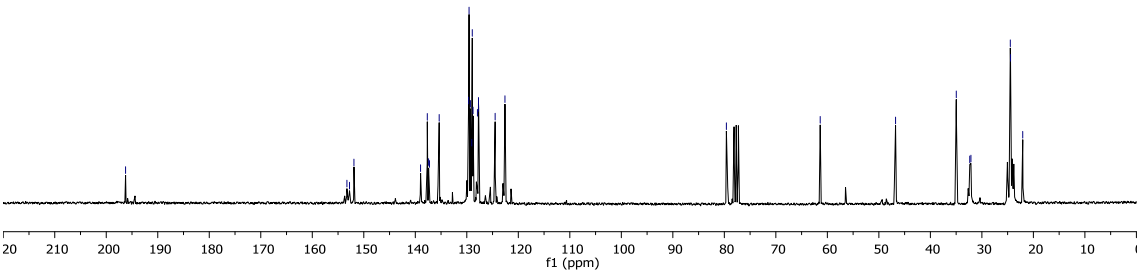

53Cc
Br
f1 (ppm)

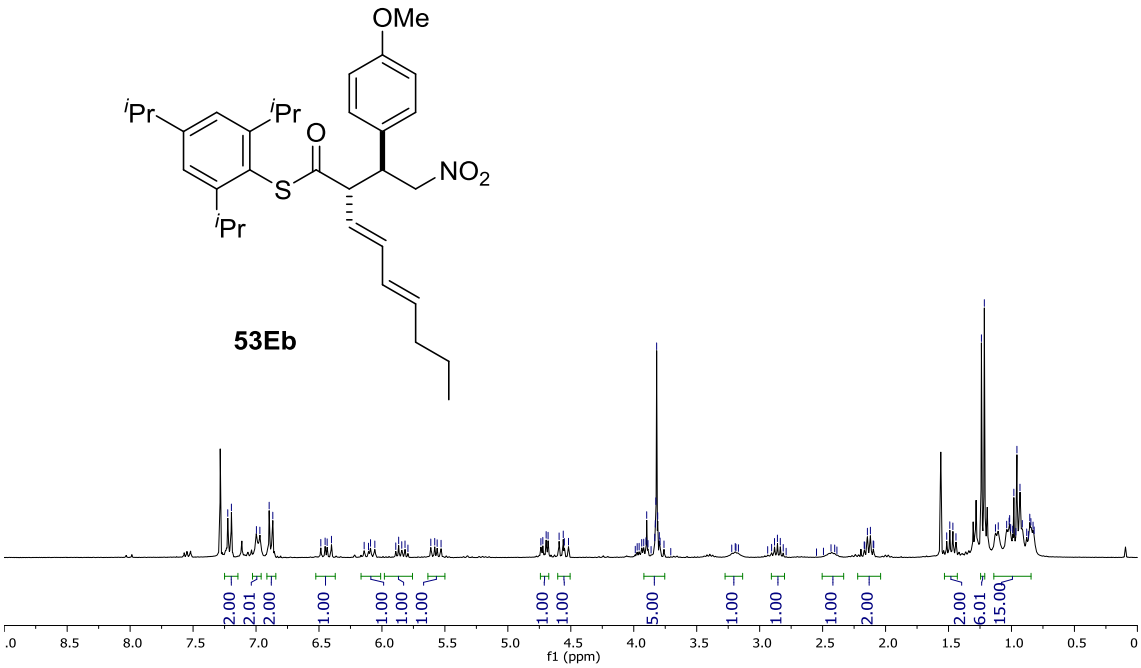

f1 (ppm)

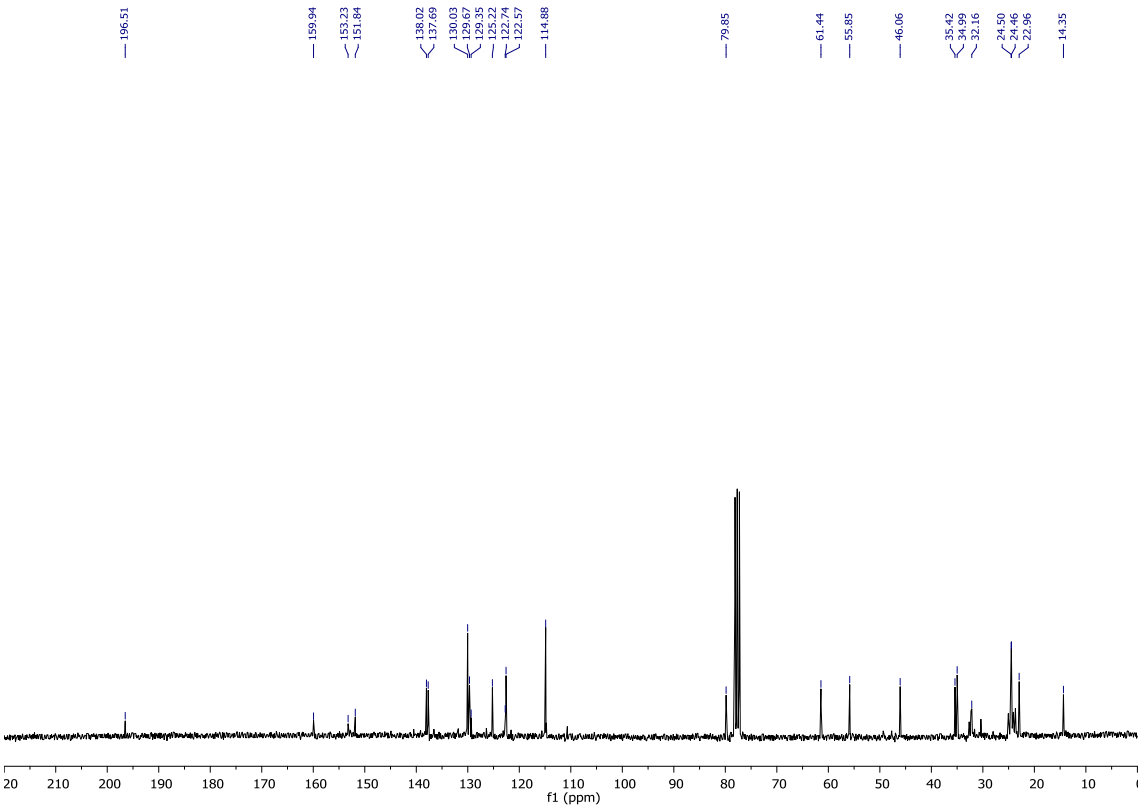

iPr
iPr
iPr
O
S
NO2

53Da


9.00
2.00
1.00
2.00
0.89
1.00
1.00
2.00
1.00
1.00
4.00
6.03
12.01
f1 (ppm)


f1 (ppm)


OMe
iPr
iPr
iPr
O
S
NO2
53Eb
2.00
2.01
2.00
1.00
1.00
1.00
1.00
1.00
1.00
5.00
1.00
1.00
1.00
2.00
2.00
6.01
15.00
f1 (ppm)


196.51
159.94
153.23
151.84
138.02
137.69
130.03
129.67
129.35
125.22
122.74
122.57
114.88
79.85
61.44
55.85
46.06
35.42
34.99
32.16
24.50
24.46
22.96
14.35
f1 (ppm)


7.72
7.72
7.70
7.69
7.52
7.51
7.50
7.49
7.49
7.47
7.47
7.47
7.39
7.39
7.37
7.37
7.34
7.34
7.21
7.19
6.73
6.70
5.09
5.08
5.05
5.04
4.01
3.98
3.94
3.83
3.78
3.73
3.71
3.70
3.69
3.67
3.66
3.64
2.86
2.85
2.83
2.82
2.81
2.79
2.00
1.99
1.97
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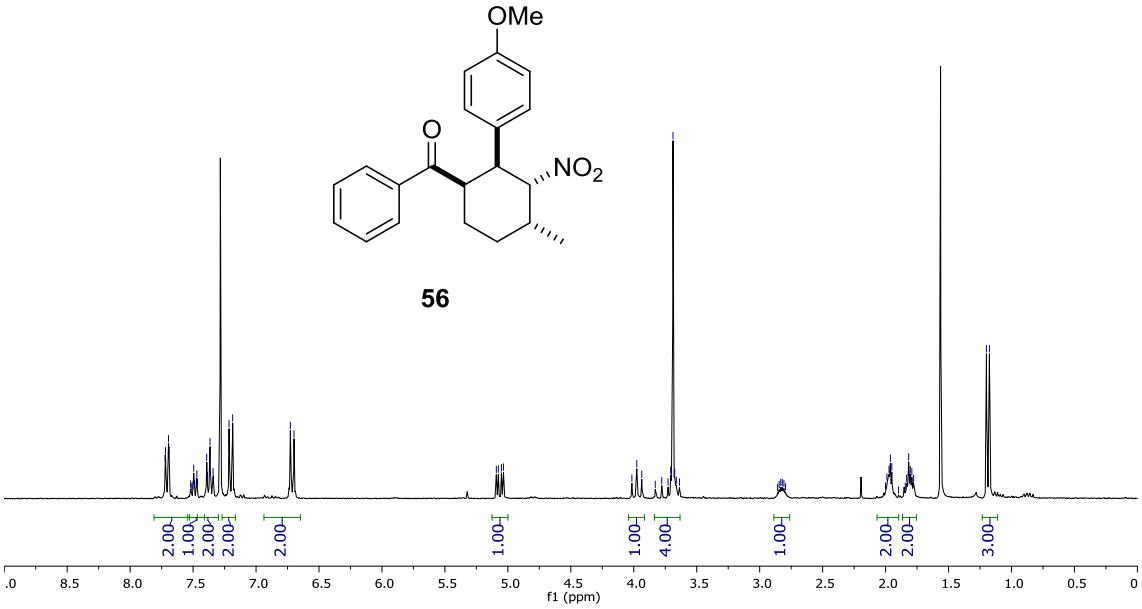
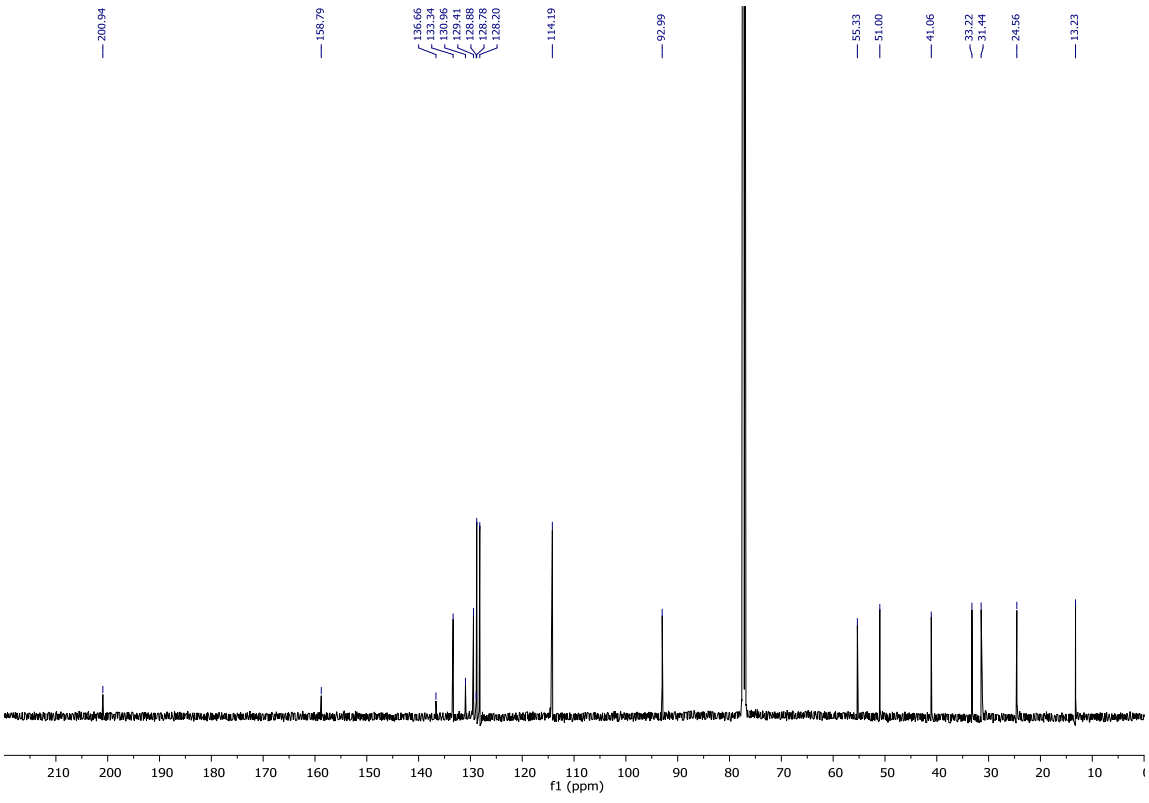
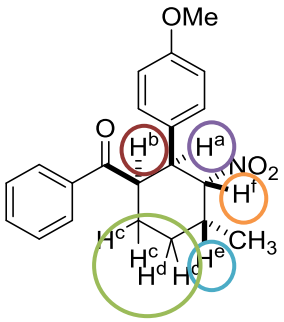
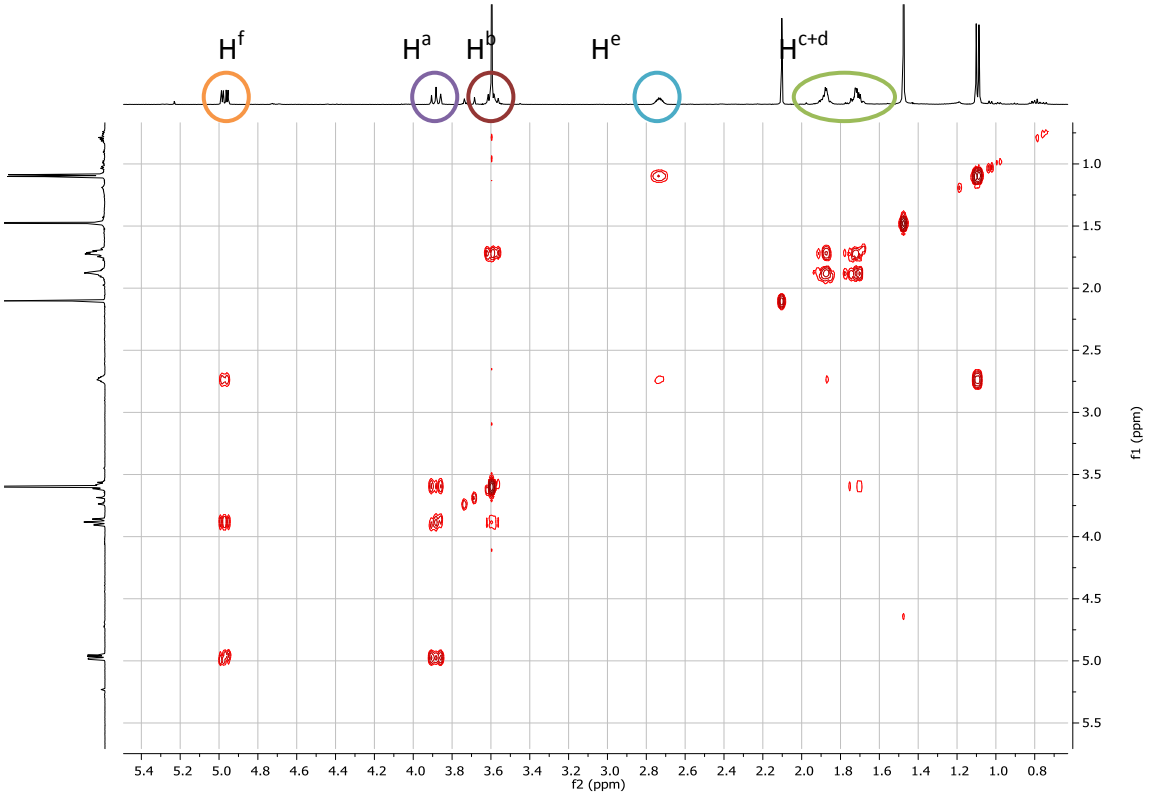
1.83
1.82
1.80
1.79
1.78
1.20
1.18


OMe
O
NO2
56
2.00
1.00
2.00
2.00
2.00
1.00
1.00
4.00
1.00
2.00
2.00
3.00
f1 (ppm)

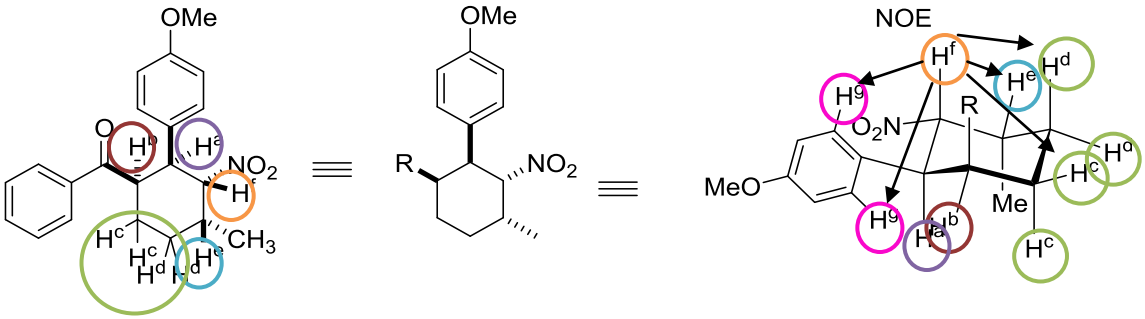

200.94
158.79
136.66
133.34
130.96
129.41
128.88
128.78
128.20
114.19
92.99
55.33
51.00
41.06
33.22
31.44
24.56
13.23
f1 (ppm)

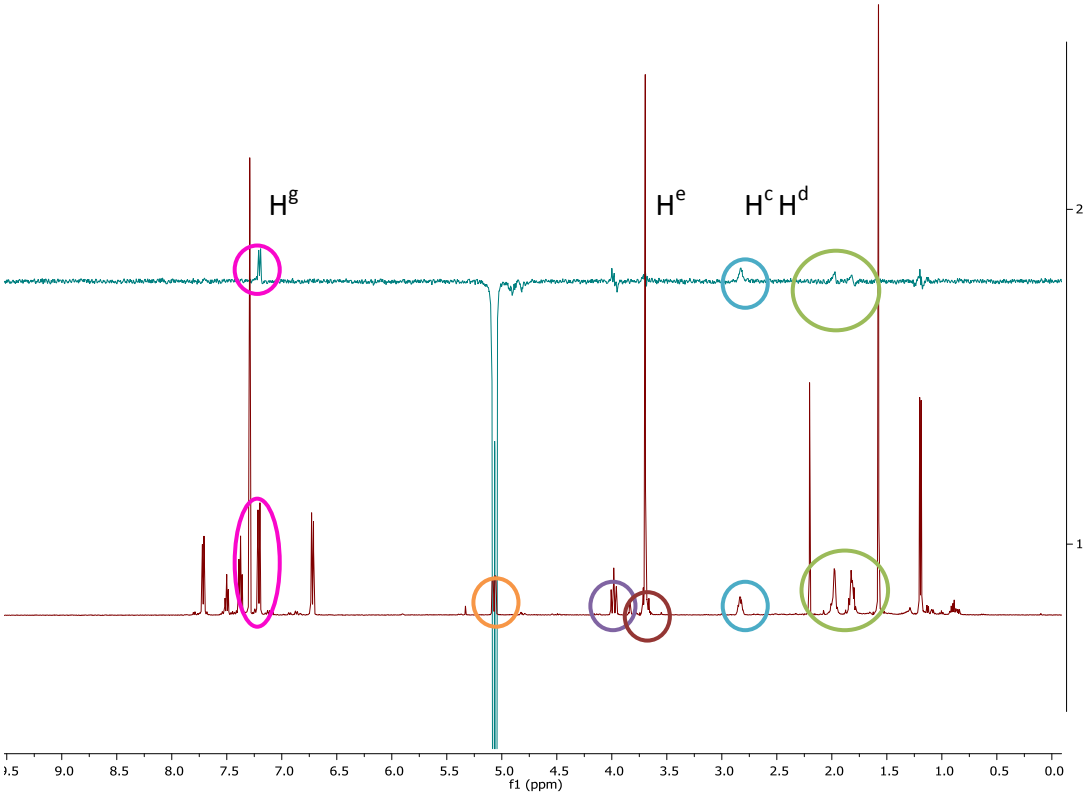
The proton assignment for the compound **56** employing a COSY experiment:

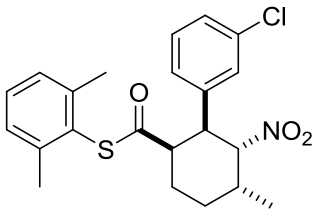




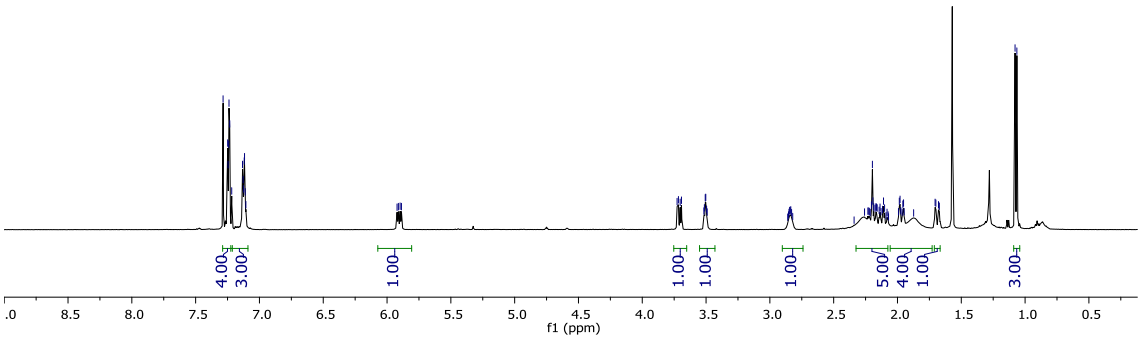
The relative stereochemistry of **56** was unambiguously established on the basis of NOE experiment, showing an interaction between protons H^f and $H^c + H^d + H^e + H^g$:

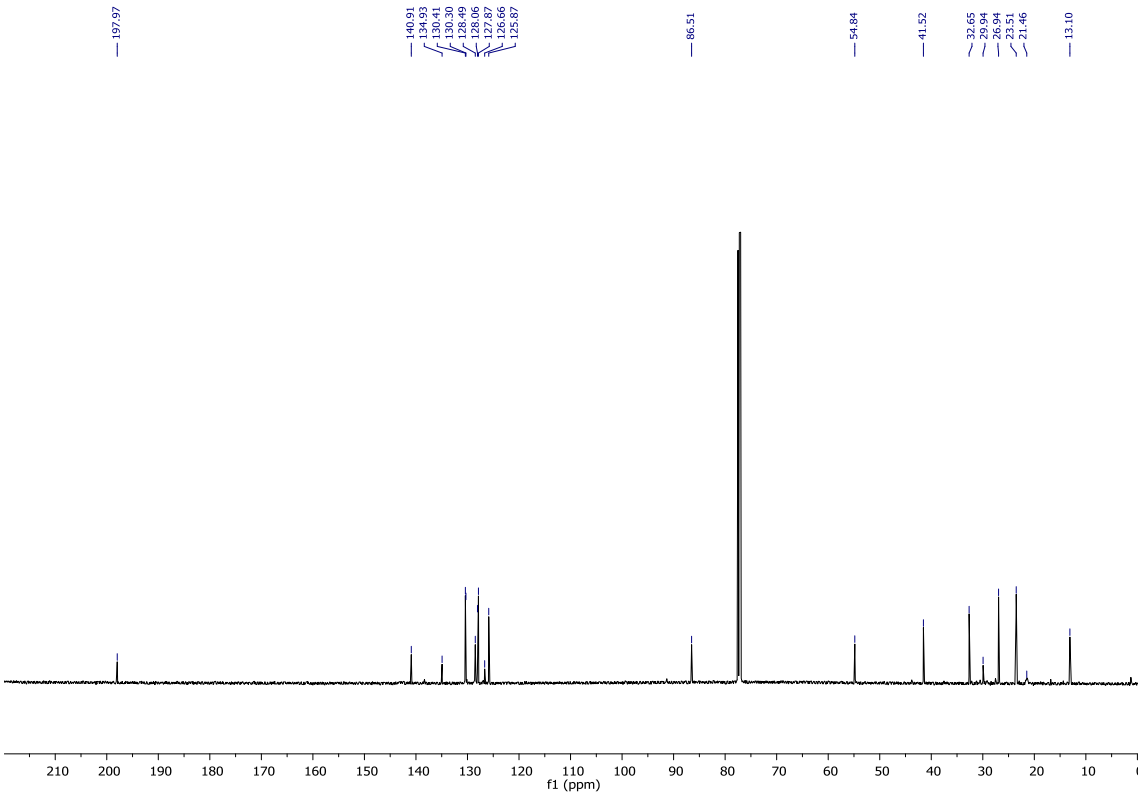




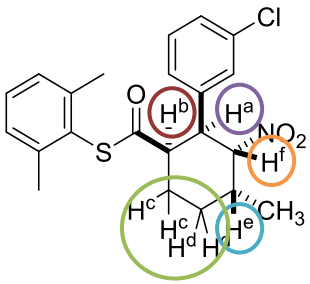

Cl
O
S
NO2

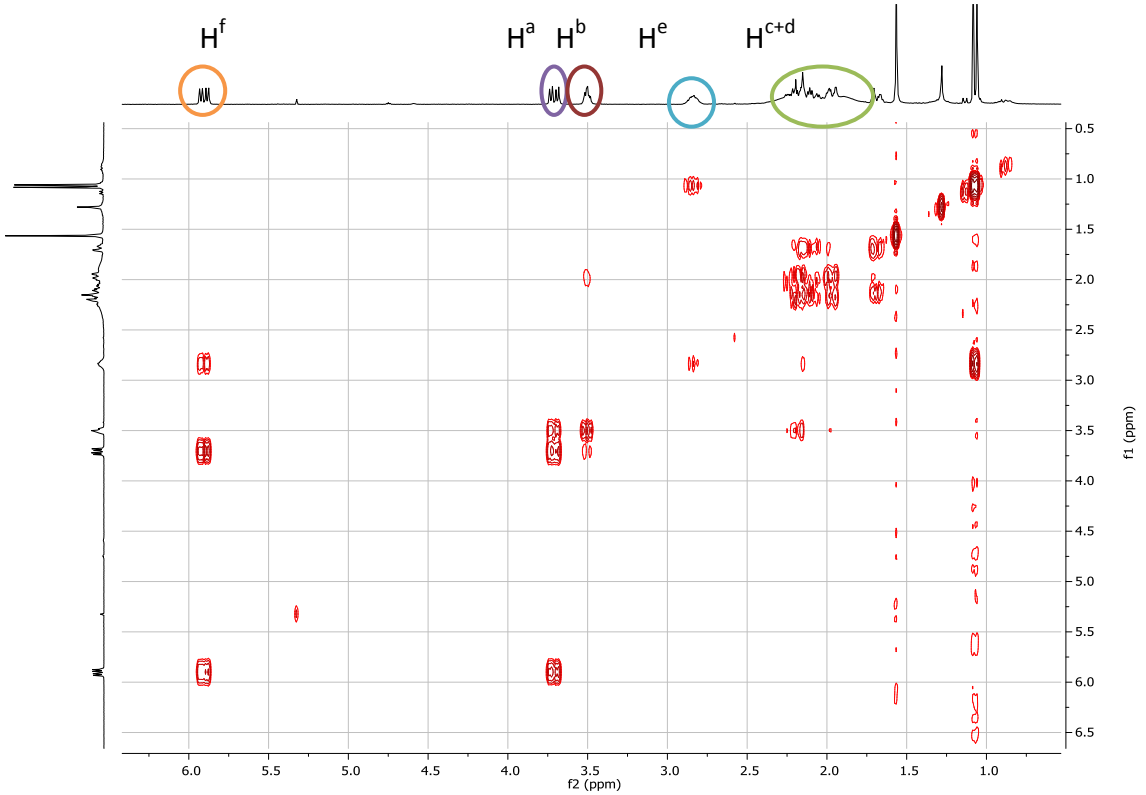
57


4.00
3.00
1.00
1.00
1.00
1.00
5.00
4.00
1.00
3.00
f1 (ppm)

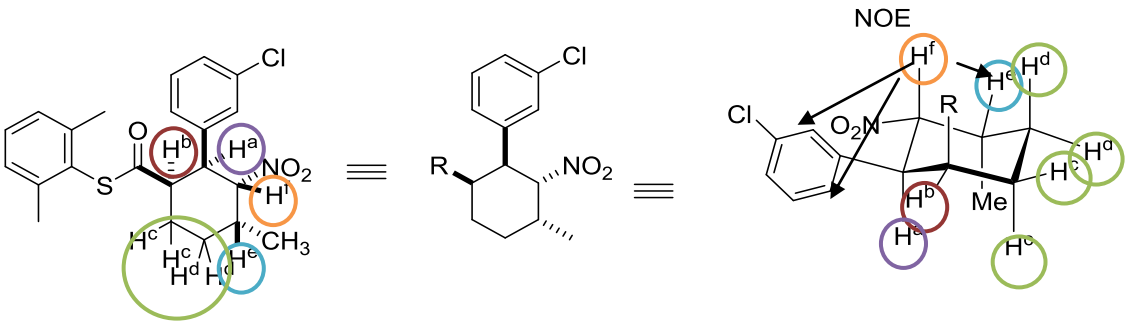

197.97
140.91
134.93
130.41
130.30
128.49
128.06
127.87
126.66
125.87
86.51
54.84
41.52
32.65
29.94
26.94
23.51
21.46
13.10
f1 (ppm)

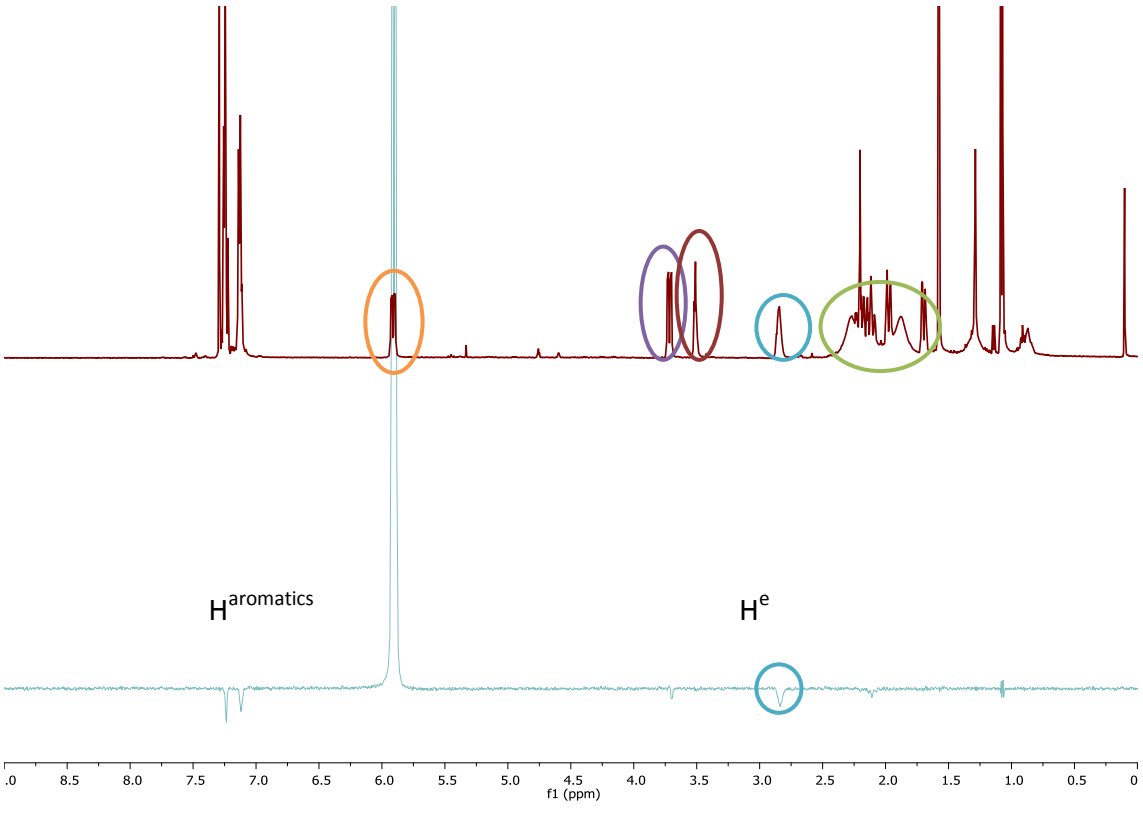
The proton assignment for the compound **57** employing a COSY experiment:

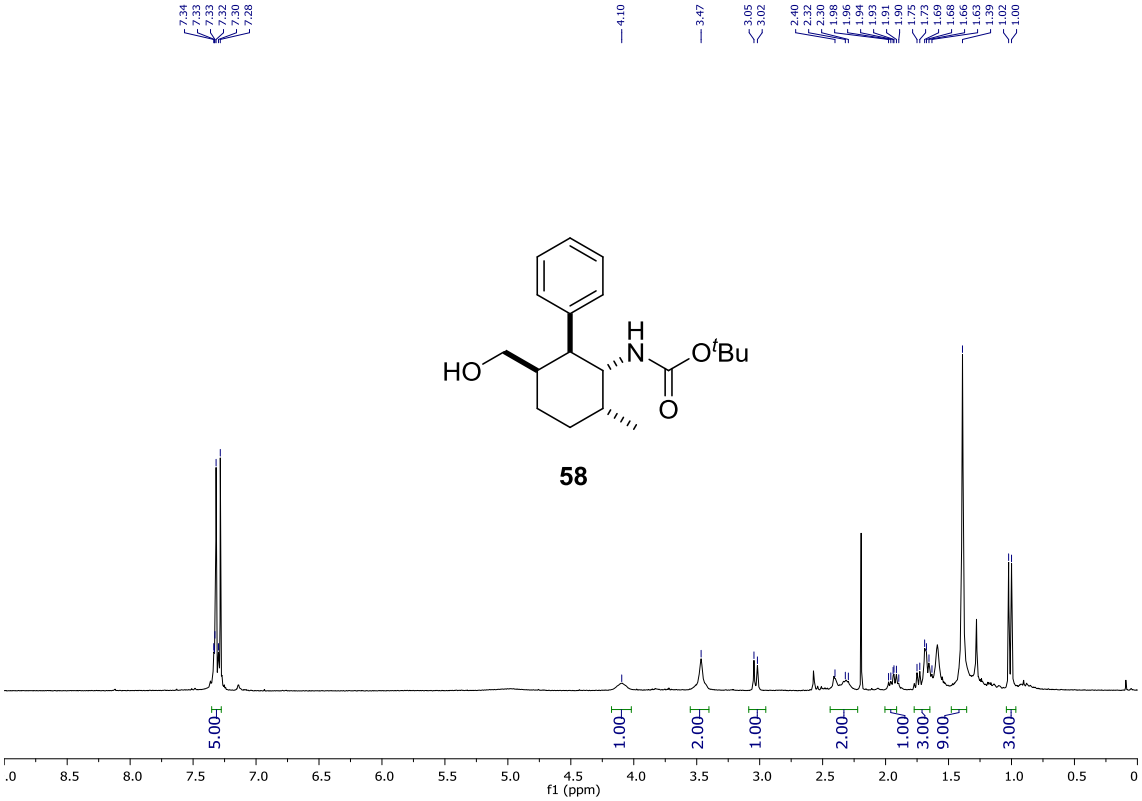


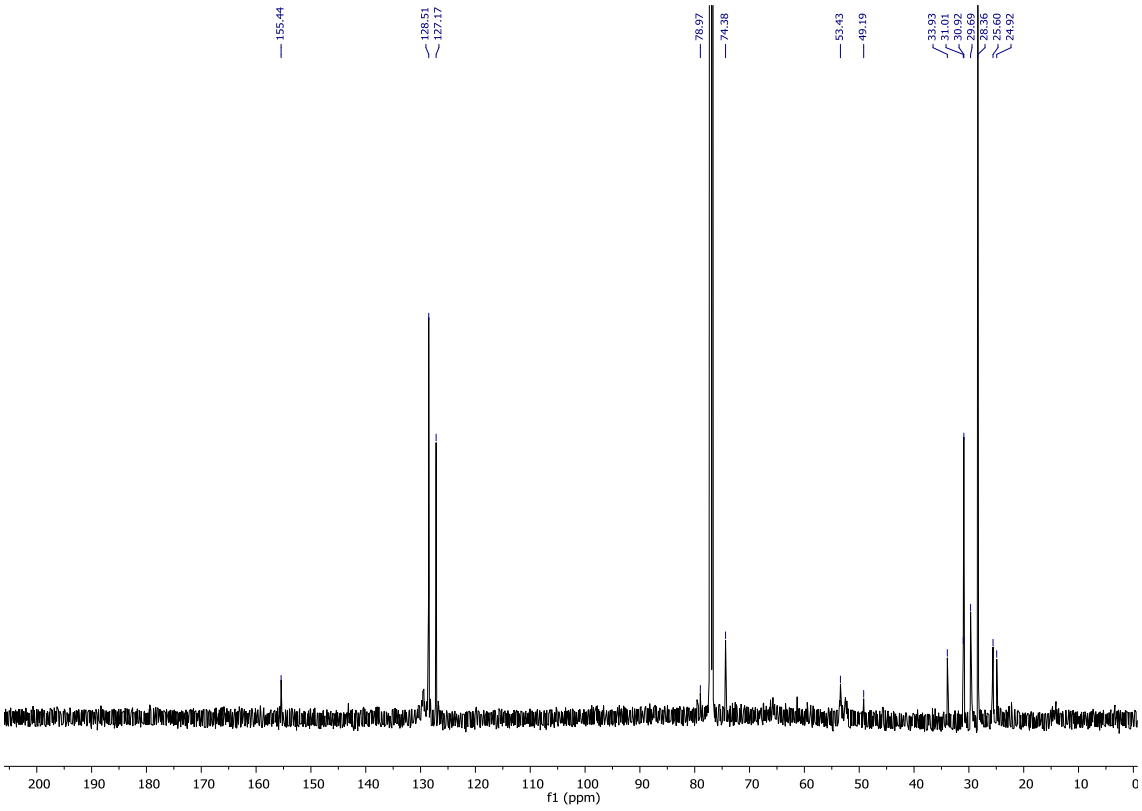


The relative stereochemistry of **57** was unambiguously established on the basis of NOE experiment, showing an interaction between protons H^f and H^e + $H^{aromatics}$:

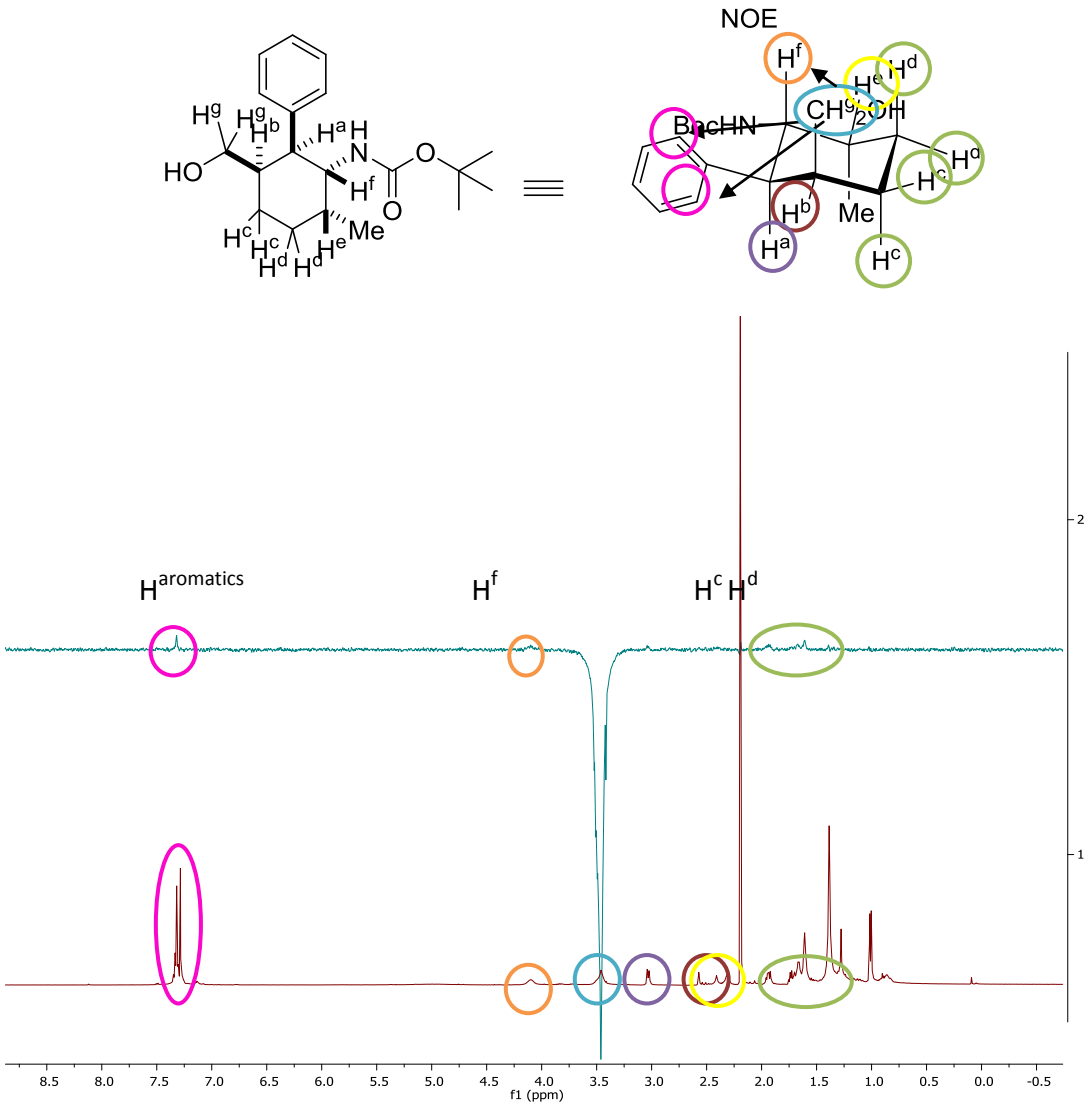


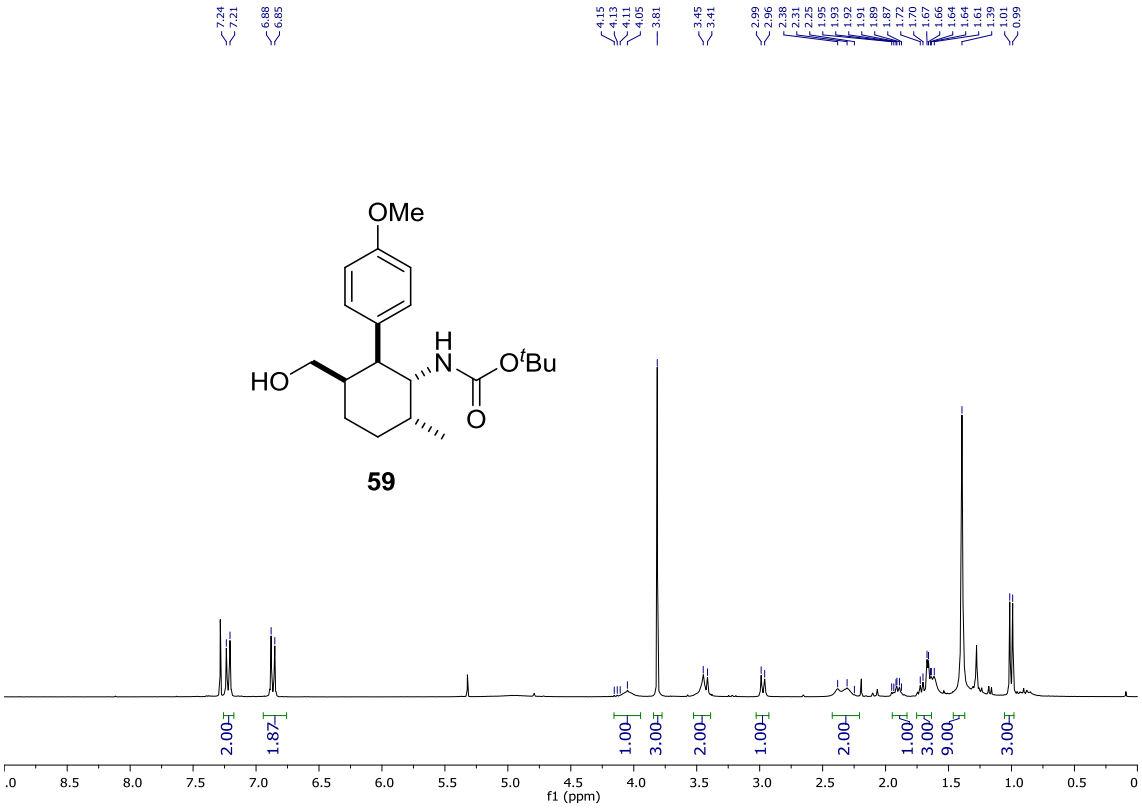


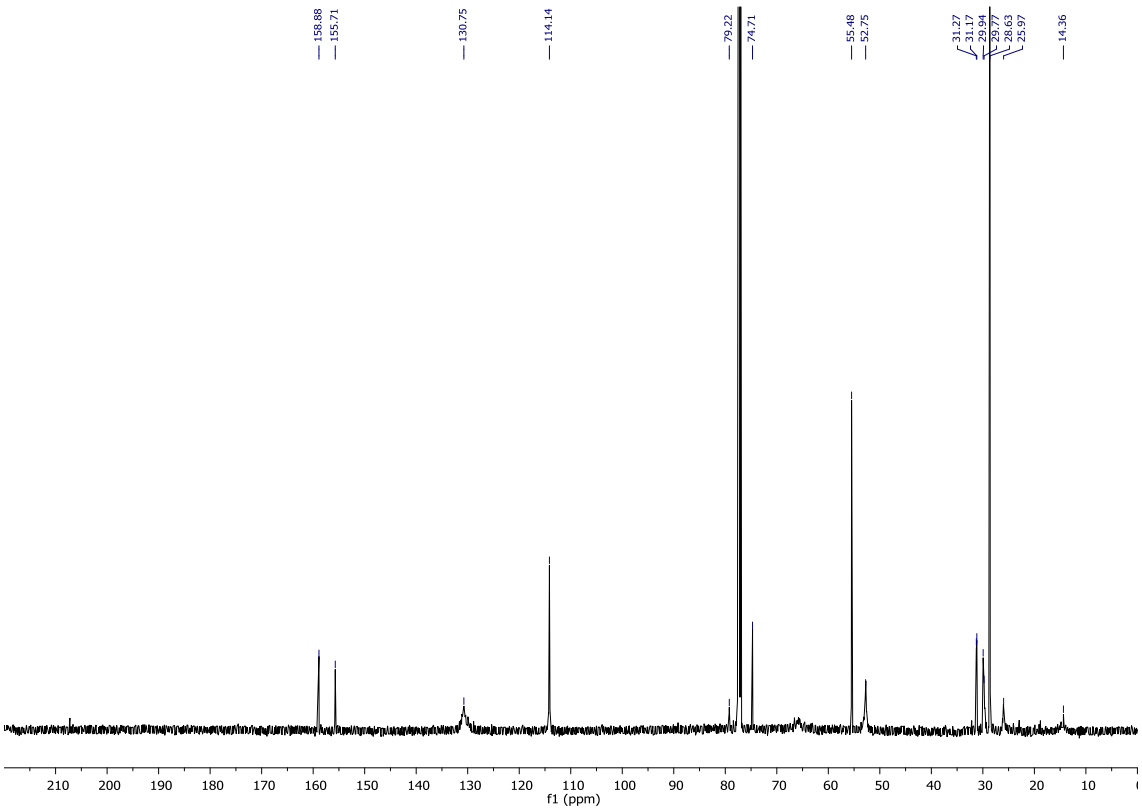

7.34
7.33
7.33
7.32
7.30
7.28
4.10
3.47
3.05
3.02
2.40
2.32
2.30
1.98
1.96
1.94
1.93
1.91
1.90
1.75
1.73
1.69
1.68
1.66
1.63
1.39
1.02
1.00
HO
H
N
O
O
tBu
58
5.00
1.00
2.00
1.00
2.00
1.00
3.00
9.00
3.00
f1 (ppm)

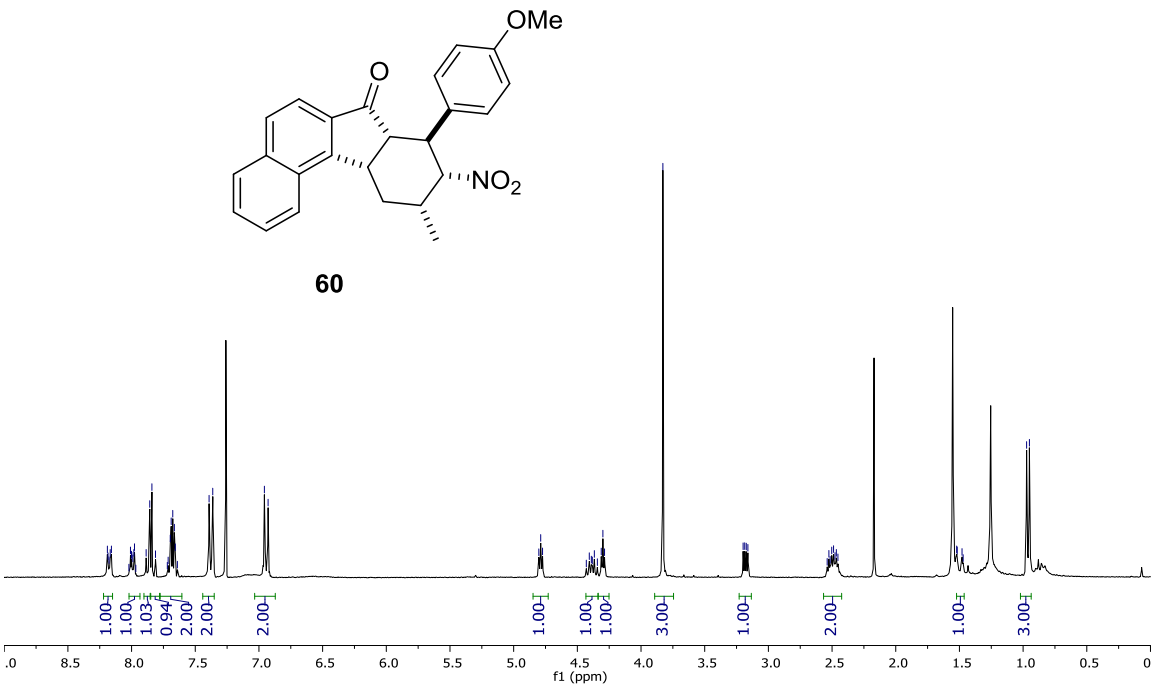

155.44
128.51
127.17
78.97
74.38
53.43
49.19
33.93
31.01
30.92
29.69
28.36
25.60
24.92
f1 (ppm)

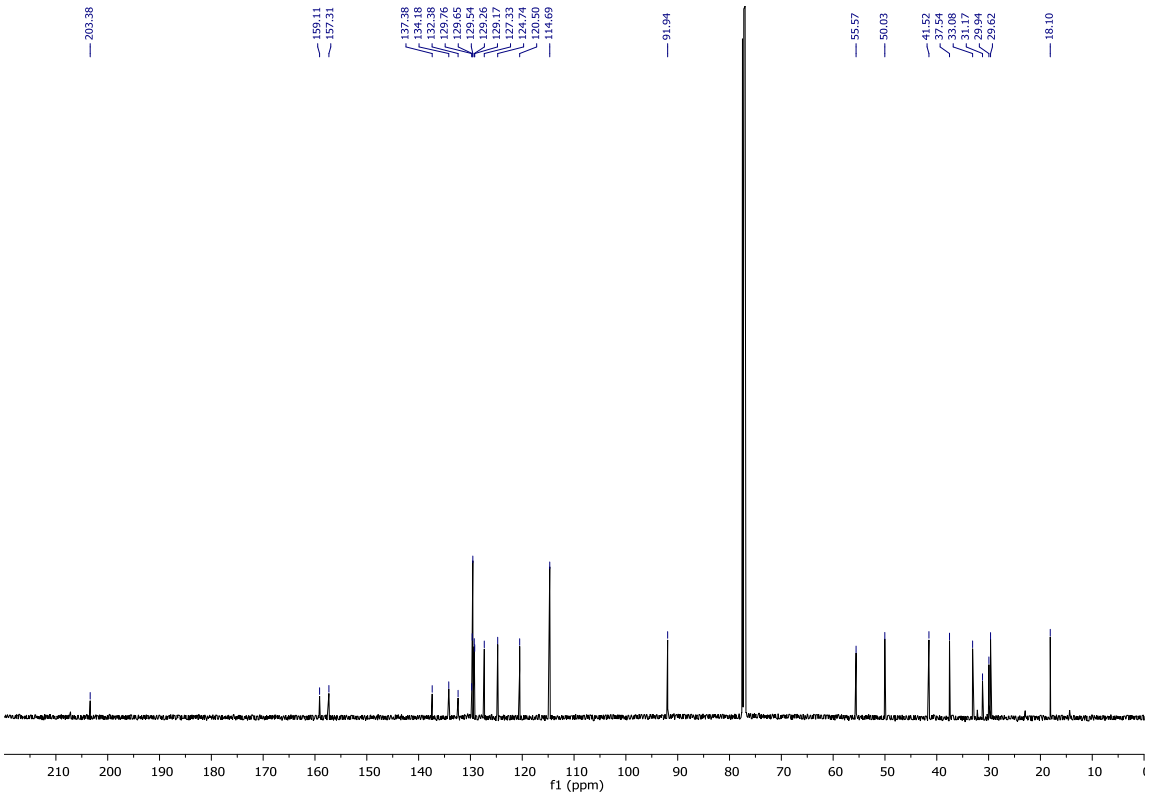
The relative stereochemistry of **58** was unambiguously established on the basis of NOE experiment, showing an interaction between protons H^g and H^e + $H^{aromatics}$:



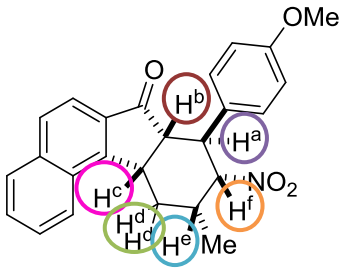

7.24
7.21
6.88
6.85
4.15
4.13
4.11
4.05
3.81
3.45
3.41
2.99
2.96
2.38
2.31
2.25
1.95
1.93
1.92
1.91
1.89
1.87
1.72
1.70
1.67
1.66
1.64
1.61
1.39
1.01
0.99
OMe
HO
H
N
O
O^{t}Bu
59
2.00
1.87
1.00
3.00
2.00
1.00
2.00
1.00
3.00
9.00
3.00
f1 (ppm)

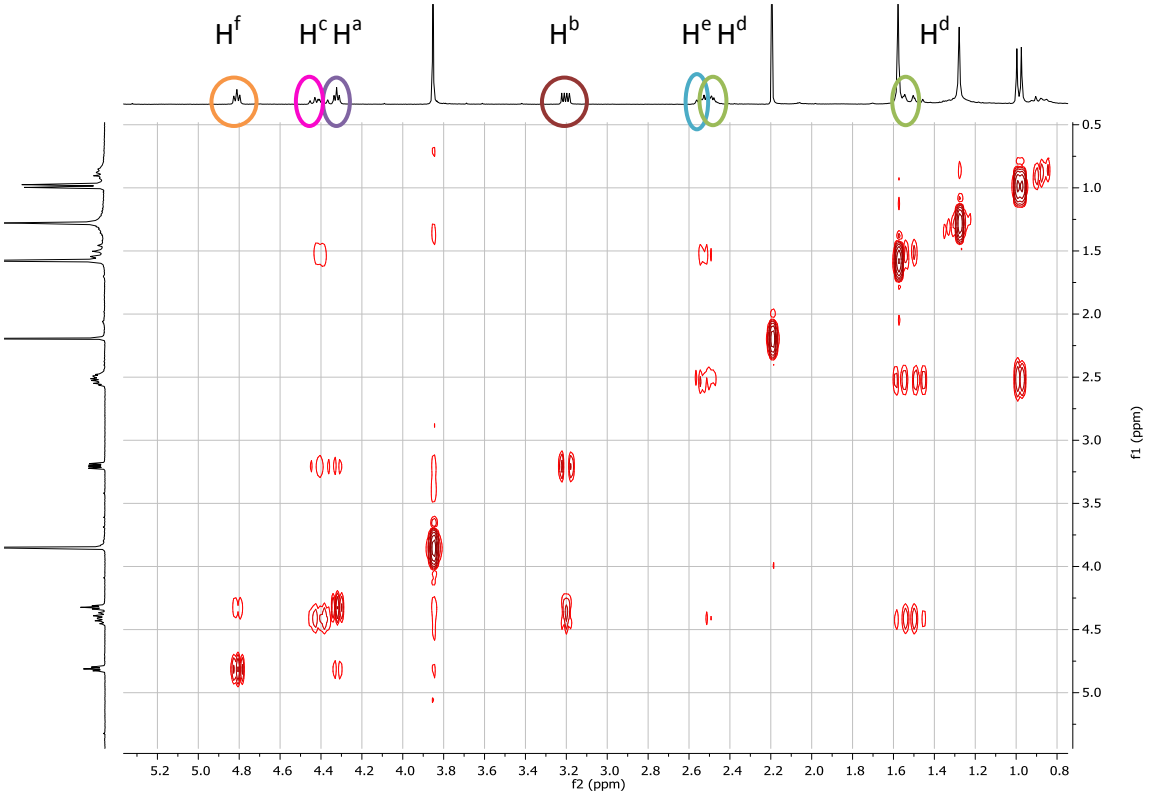

158.88
155.71
130.75
114.14
79.22
74.71
55.48
52.75
31.27
31.17
29.94
29.77
28.63
25.97
14.36
f1 (ppm)


OMe
O
NO2
60
1.00
1.00
1.03
0.94
2.00
2.00
2.00
1.00
1.00
1.00
3.00
1.00
2.00
1.00
3.00
f1 (ppm)

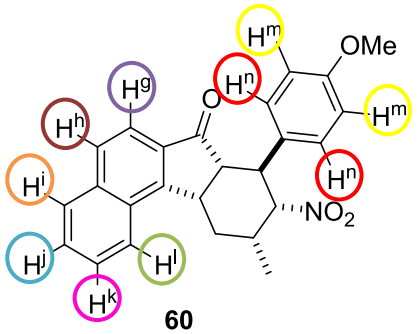

203.38
159.11
157.31
137.38
134.18
132.38
129.76
129.65
129.54
129.36
129.17
127.33
124.74
120.50
114.69
91.94
55.57
50.03
41.52
37.54
33.08
31.17
29.94
29.62
18.10
f1 (ppm)

The proton assignment for the compound **60** employing a COSY experiment:

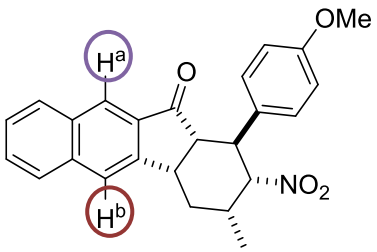




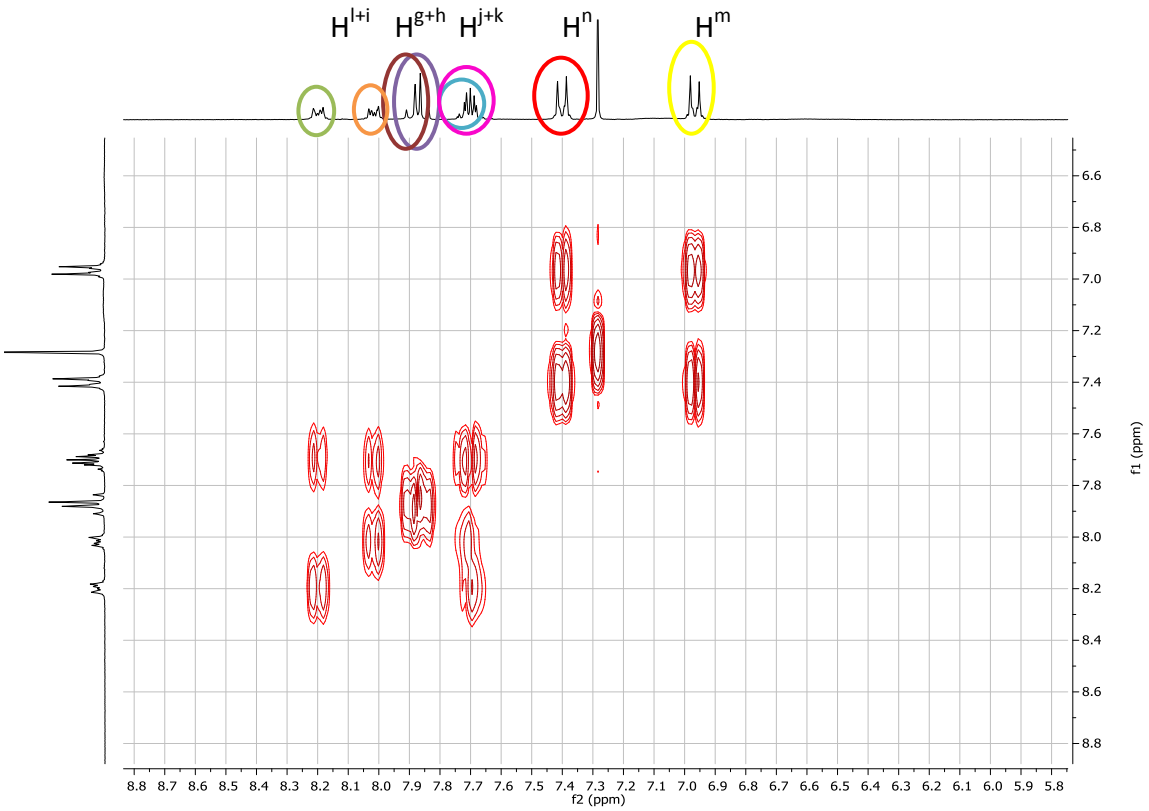
The structure of the product was confirmed using COSY 2-D NMR experiments, which reveal through bonded H-H correlations. In the case of compound **60**, one might expect to see a COSY correlation between the aromatic protons H^h and H^g. Whereas, if we have the other regioisomer, there would be two single peaks corresponding to H^a and H^b. The COSY spectra revealed that there was a correlation between H^h and H^g, indicating that the product of the reaction was compound **60.**



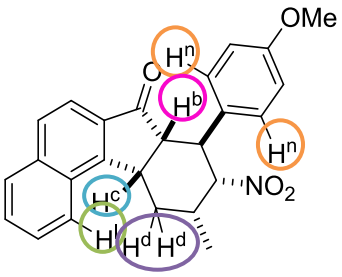
60

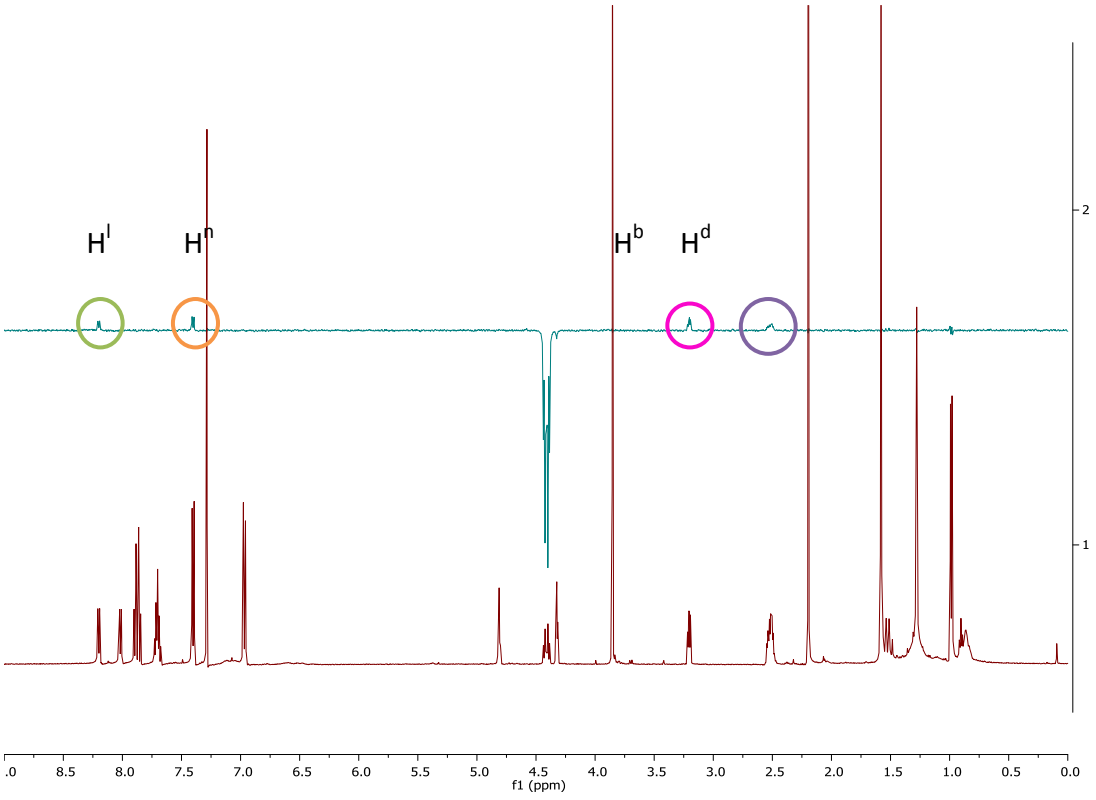


regioisomer of 60

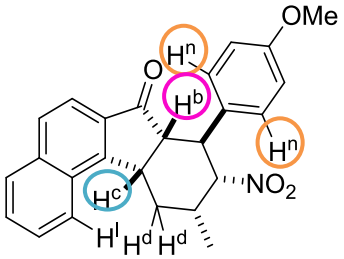


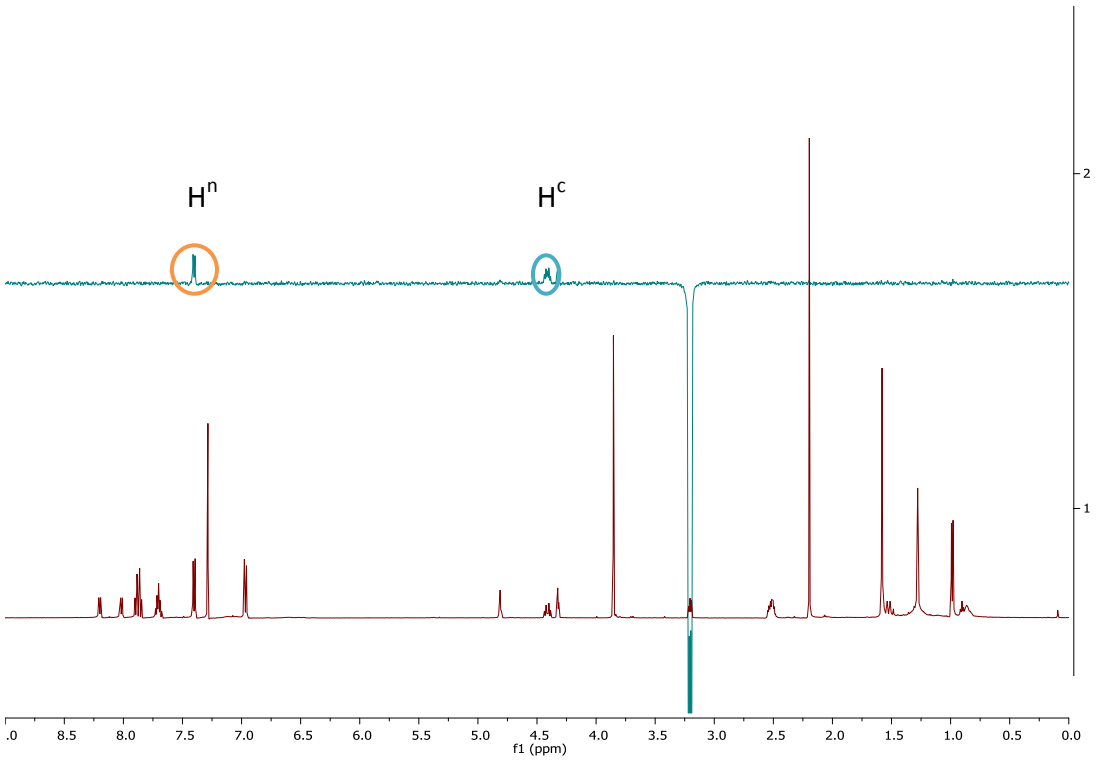
The relative stereochemistry of **60** was unambiguously established on the basis of NOE experiment, showing an interaction between protons H^c and $H^b + H^d + H^l + H^n$:

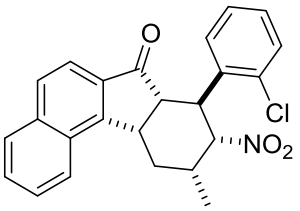




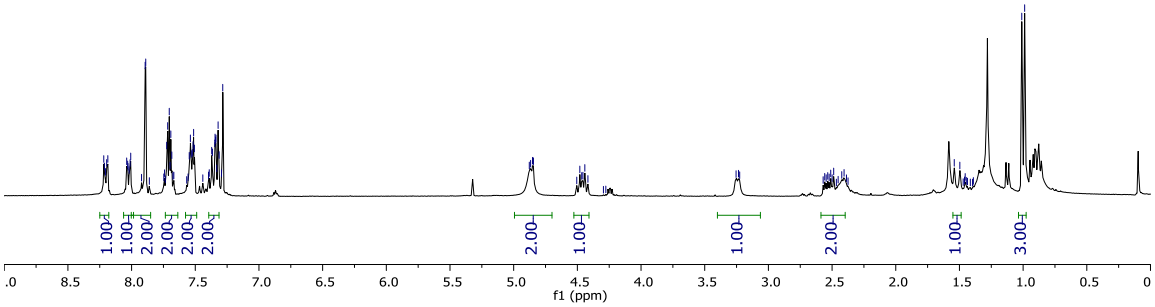
The relative stereochemistry of **60** was unambiguously established on the basis of NOE experiment, showing an interaction between protons H^b and H^c + H^n:






O
Cl
NO2

61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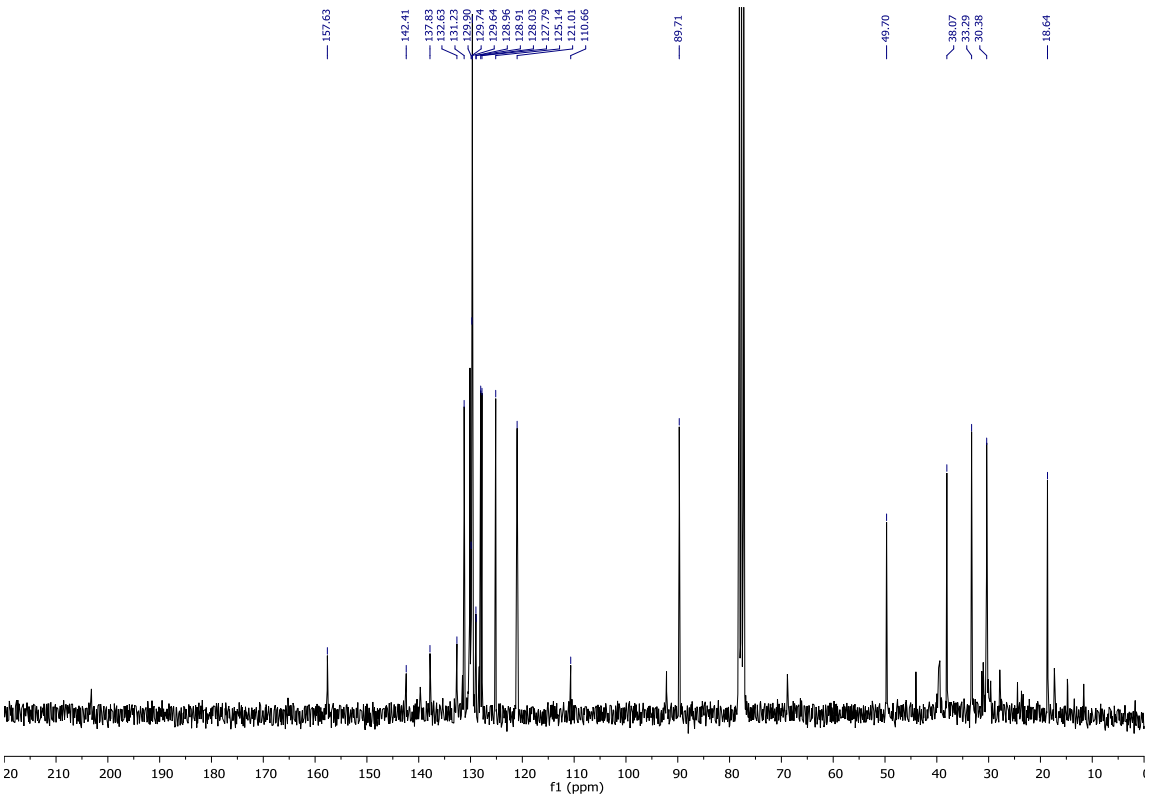
1.00
1.00
2.00
1.00
3.00
f1 (ppm)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142.41
137.83
132.63
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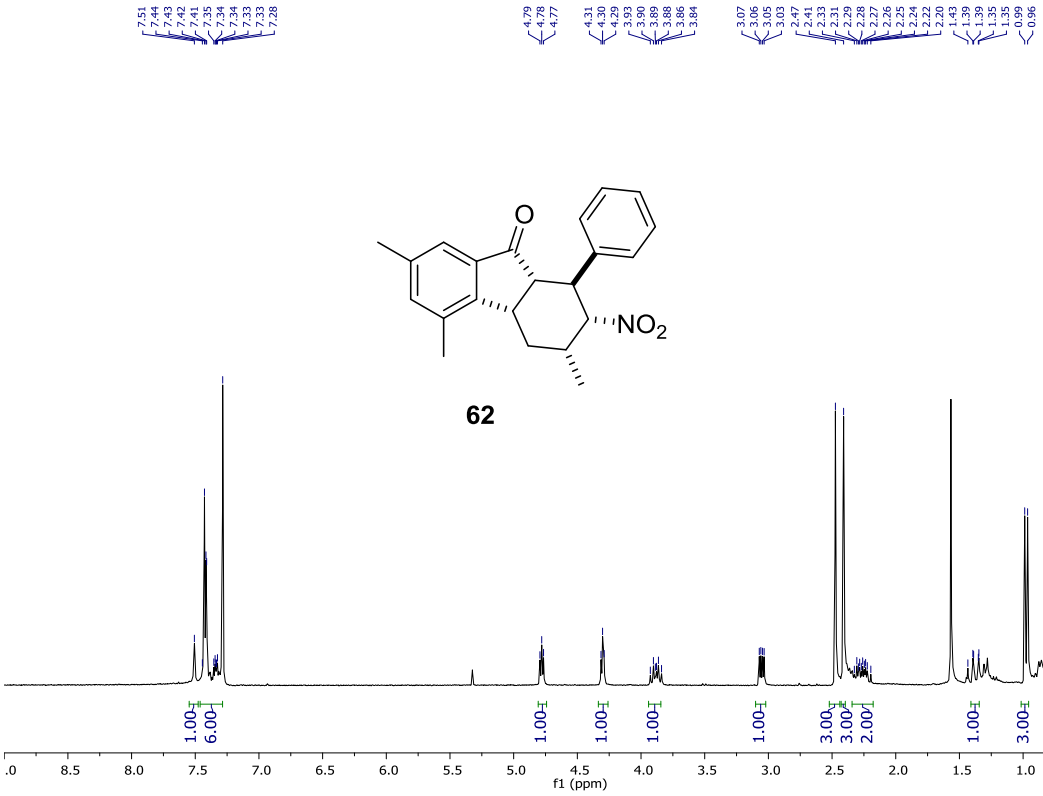
129.90
129.74
129.64
128.96
128.91
128.03
127.79
125.14
121.01
110.66
89.71
49.70
38.07
33.29
30.38
18.64
f1 (ppm)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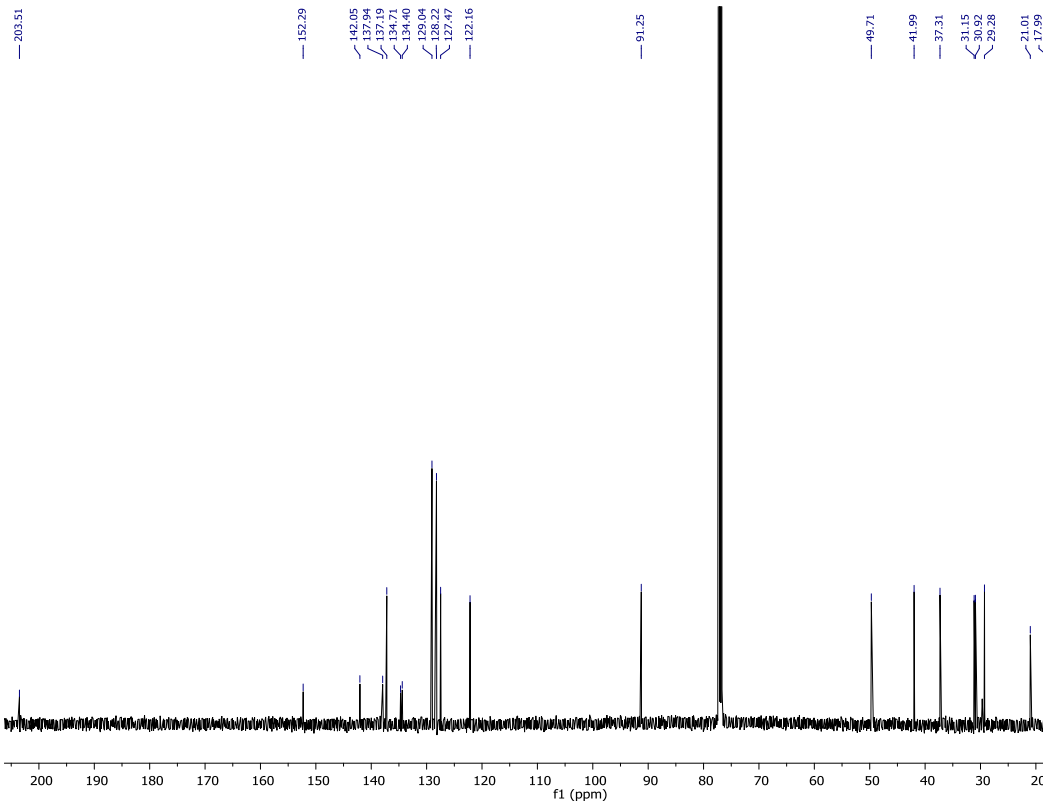
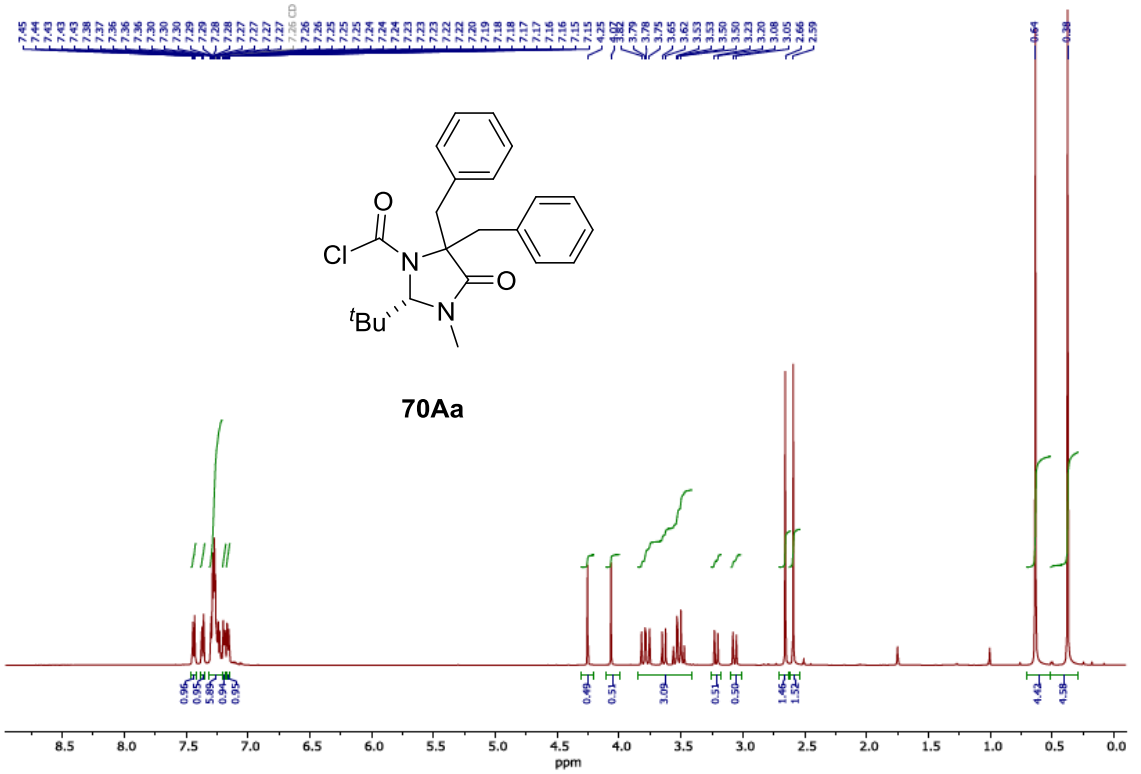
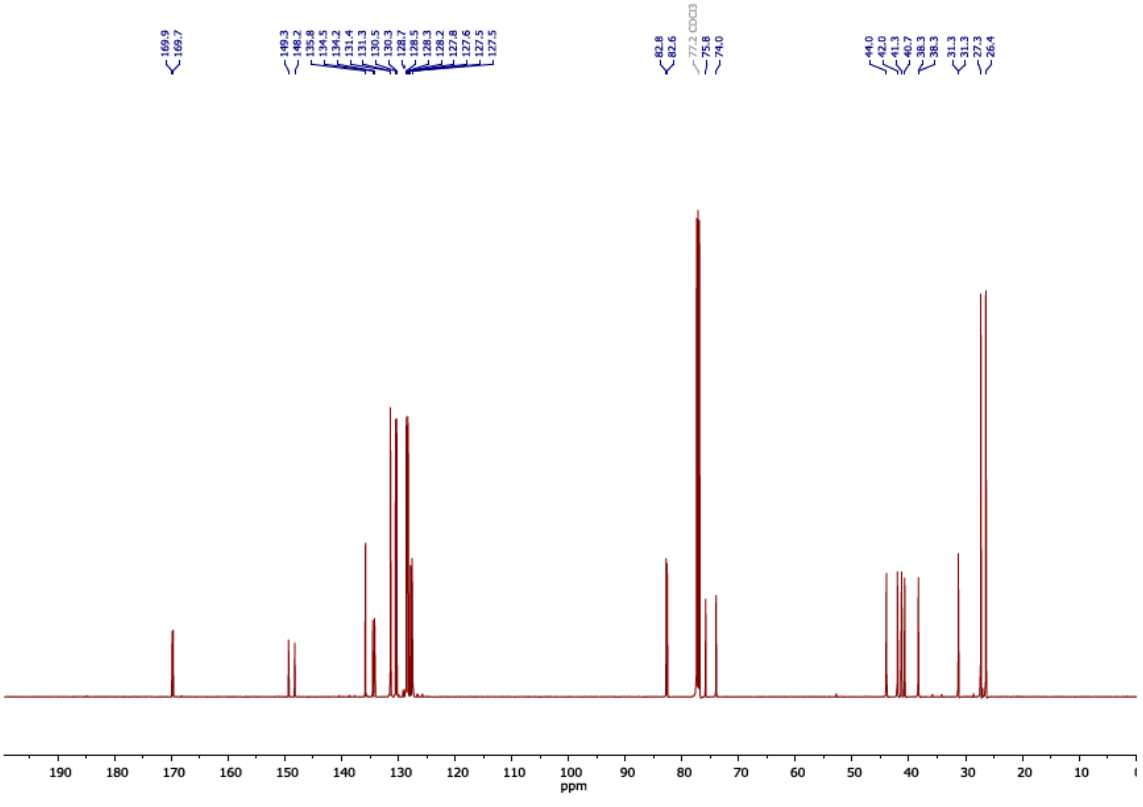
7.42
7.41
7.35
7.34
7.34
7.33
7.33
7.28
4.79
4.78
4.77
4.31
4.30
4.29
3.93
3.90
3.89
3.88
3.86
3.84
3.07
3.06
3.05
3.03
2.47
2.41
2.33
2.31
2.29
2.28
2.27
2.26
2.25
2.24
2.22
2.20
1.43
1.39
1.39
1.35
1.35
0.99
0.96
O
NO2
62
1.00
6.00
1.00
1.00
1.00
1.00
3.00
3.00
2.00
1.00
3.00
f1 (ppm)


203.51
152.29
142.05
137.94
137.19
134.71
134.40
129.04
128.22
127.47
122.16
91.25
49.71
41.99
37.31
31.15
30.92
29.28
21.01
17.99
17.86
f1 (ppm)

6.6.4. Chapter 4






7.37
7.36
7.36
7.35
7.34
7.34
7.34
7.29
7.28
7.27
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.19
5.18
5.12
3.55
3.52
3.37
3.34
3.30
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2.97
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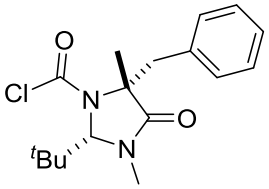
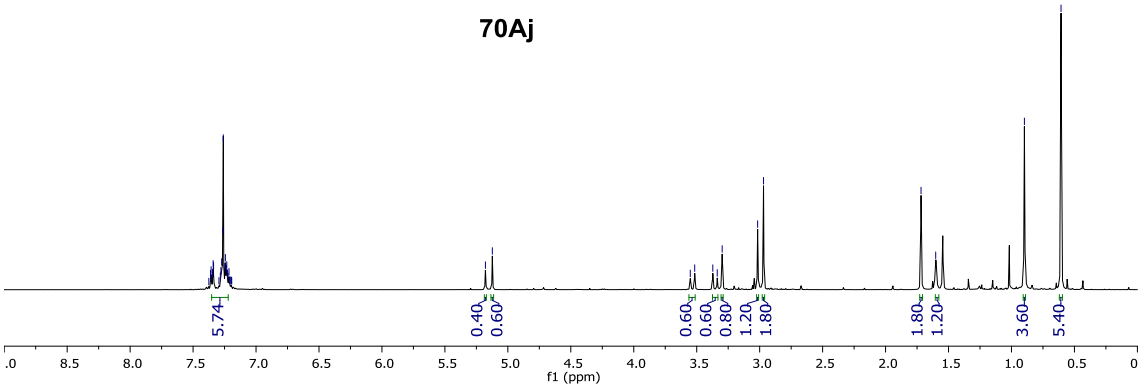
1.60
0.90
0.61


O
Cl
N
O
tBu
N

70Aj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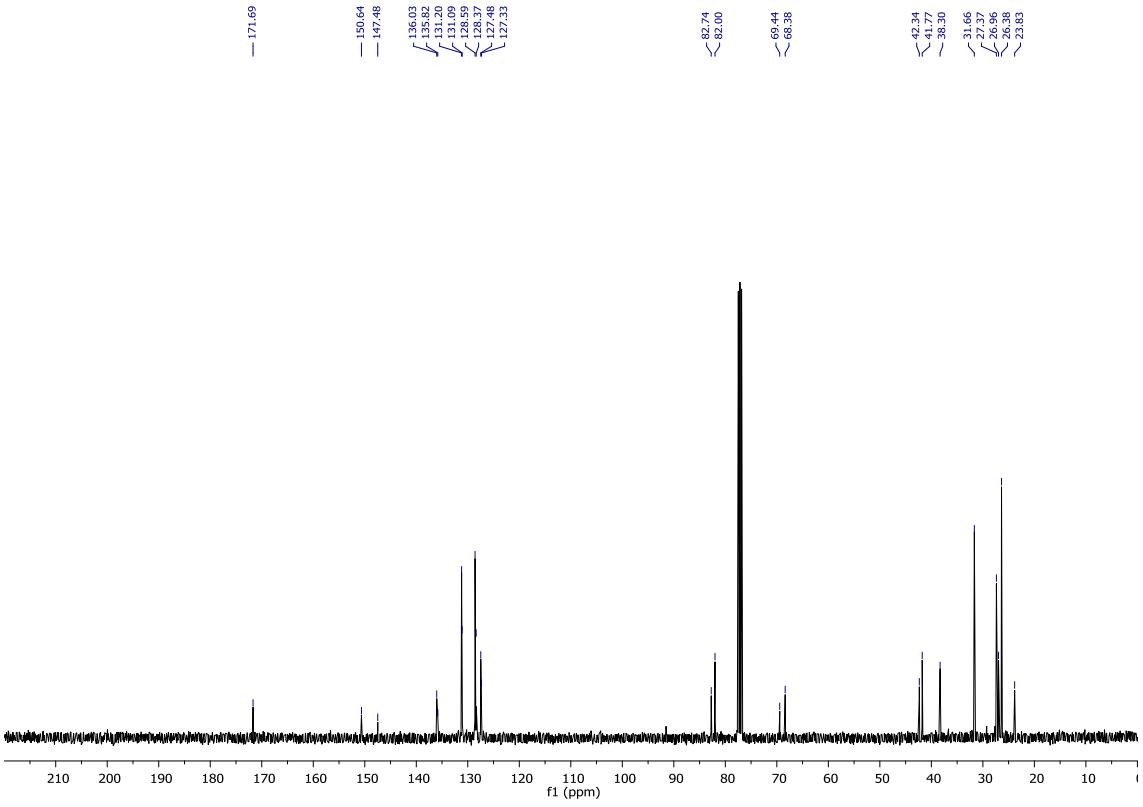
1.80
1.80
1.20
3.60
5.40
f1 (ppm)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136.03
135.82
131.20
131.09
128.59
128.37
127.48
127.33
82.74
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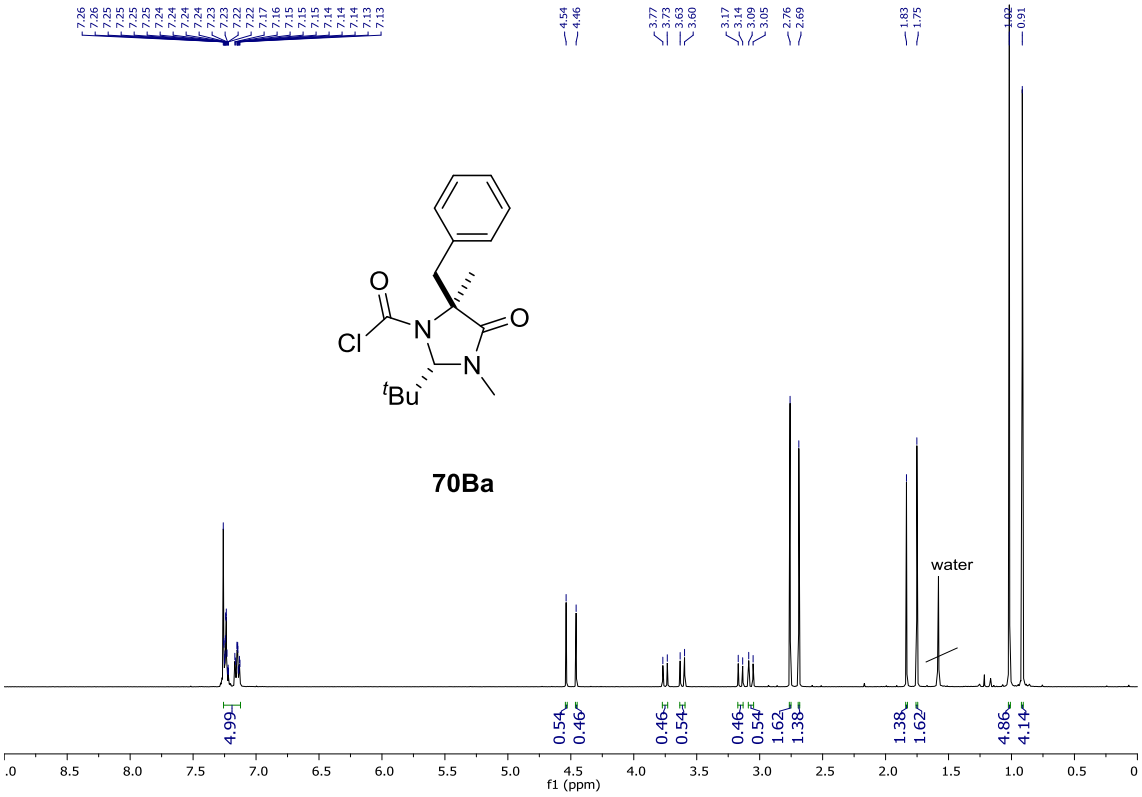
27.37
26.96
26.38
23.83
f1 (ppm)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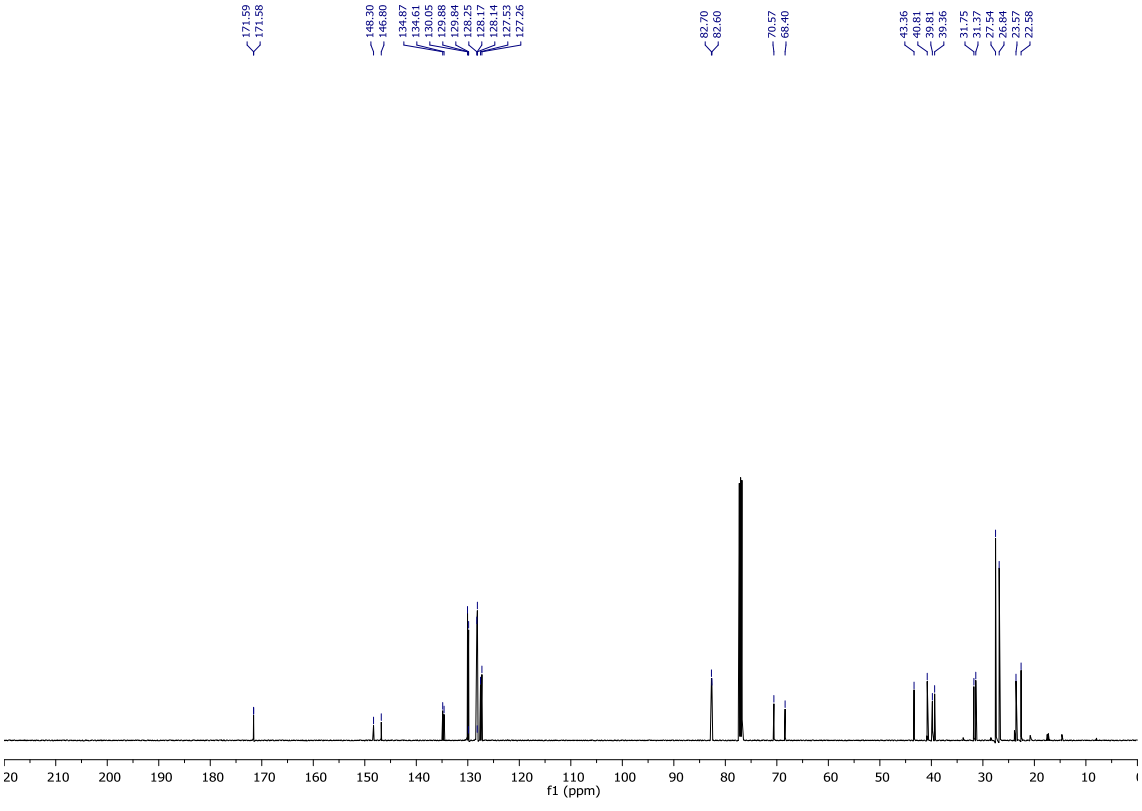
7.25
7.24
7.23
7.22
7.17
7.16
7.15
7.14
7.13
4.54
4.46
3.77
3.73
3.63
3.60
3.17
3.14
3.09
3.05
2.76
2.69
1.83
1.75
1.03
0.91
O
Cl
N
O
N
tBu
water
4.99
0.54
0.46
0.46
0.54
0.46
0.54
1.62
1.38
1.38
1.62
4.86
4.14
f1 (ppm)

70Ba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134.61
130.05
129.88
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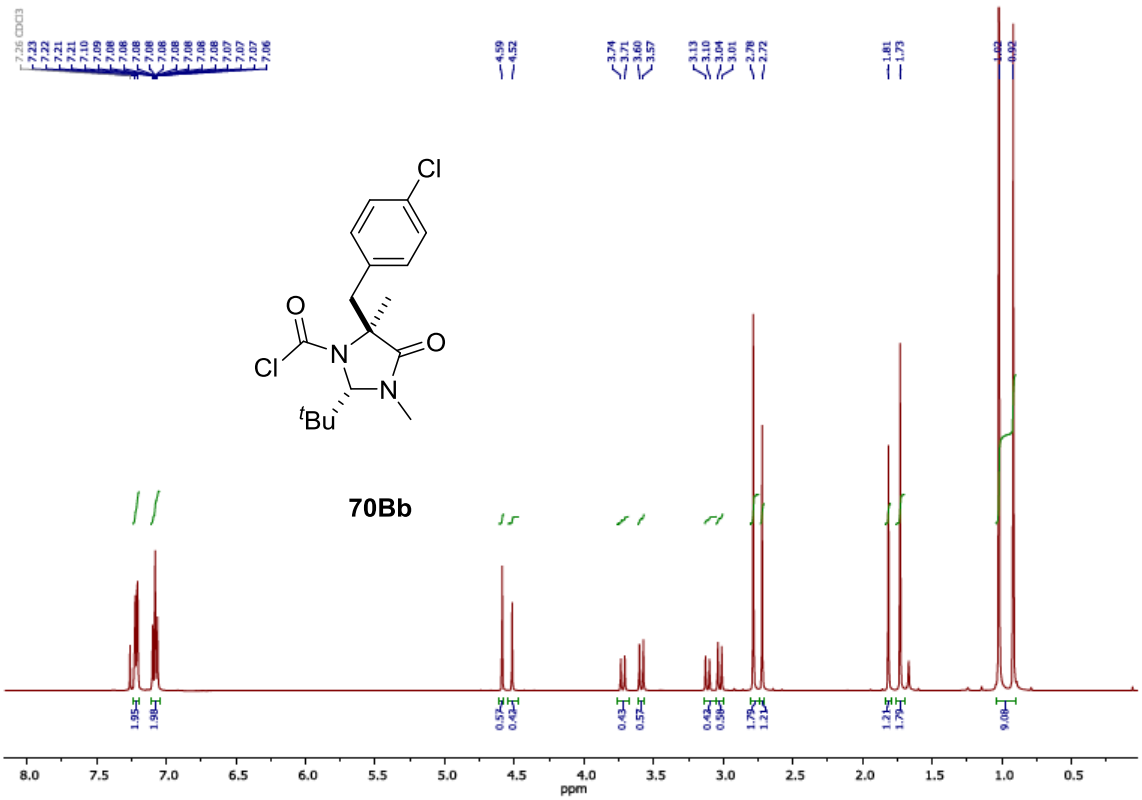
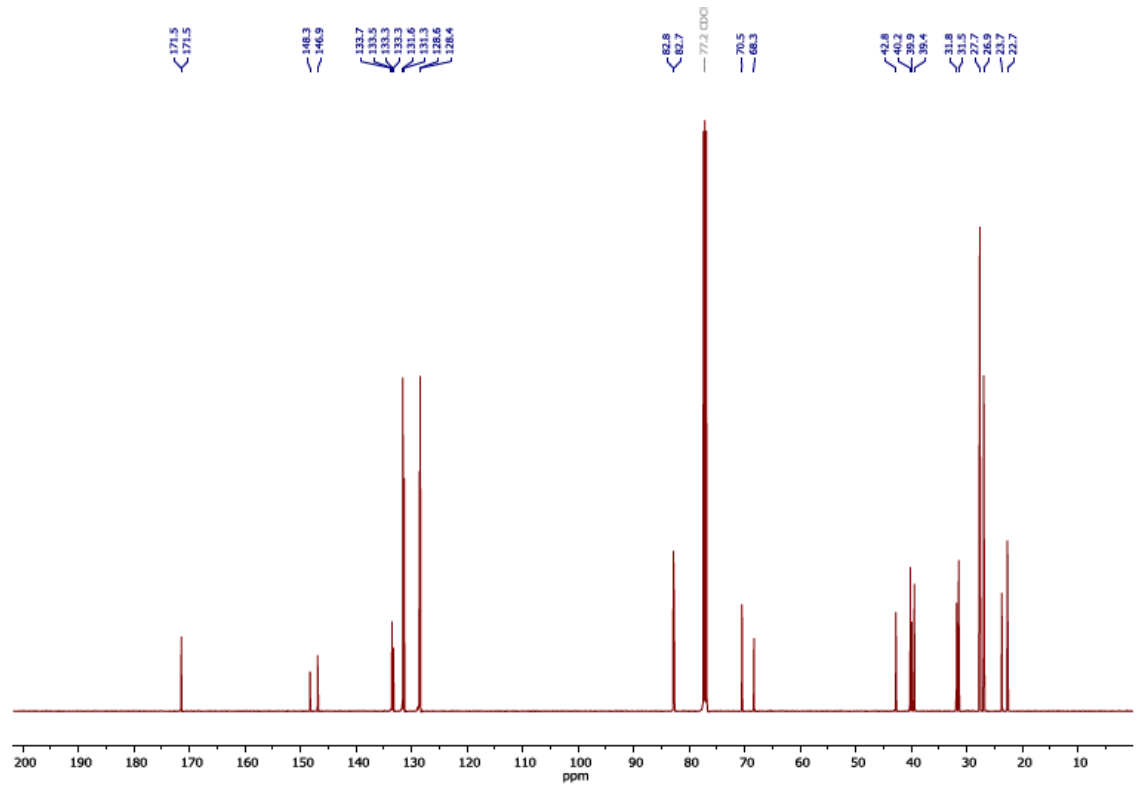
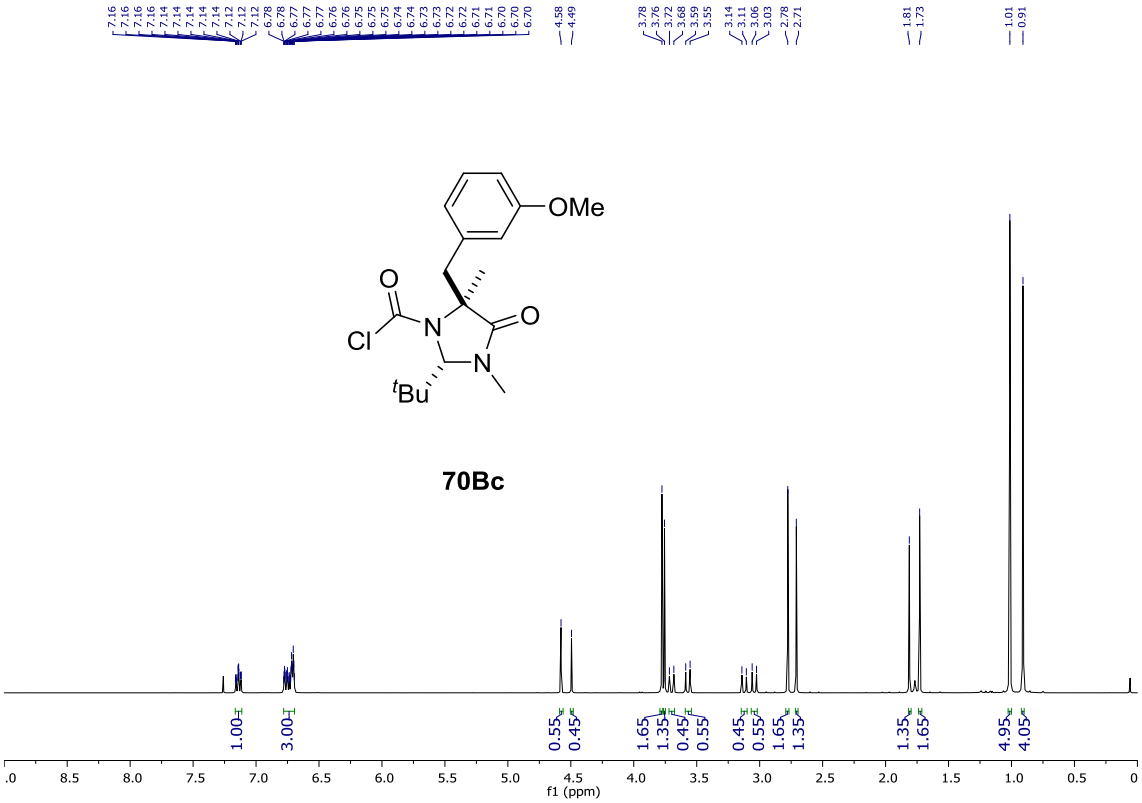
128.25
128.17
128.14
127.53
127.26
82.70
82.60
70.57
68.40
43.36
40.81
39.81
39.36
31.75
31.37
27.54
26.84
23.57
22.58
f1 (ppm)


Cl
O
Cl
N
O
N
tBu
70Bb
ppm


ppm


OMe
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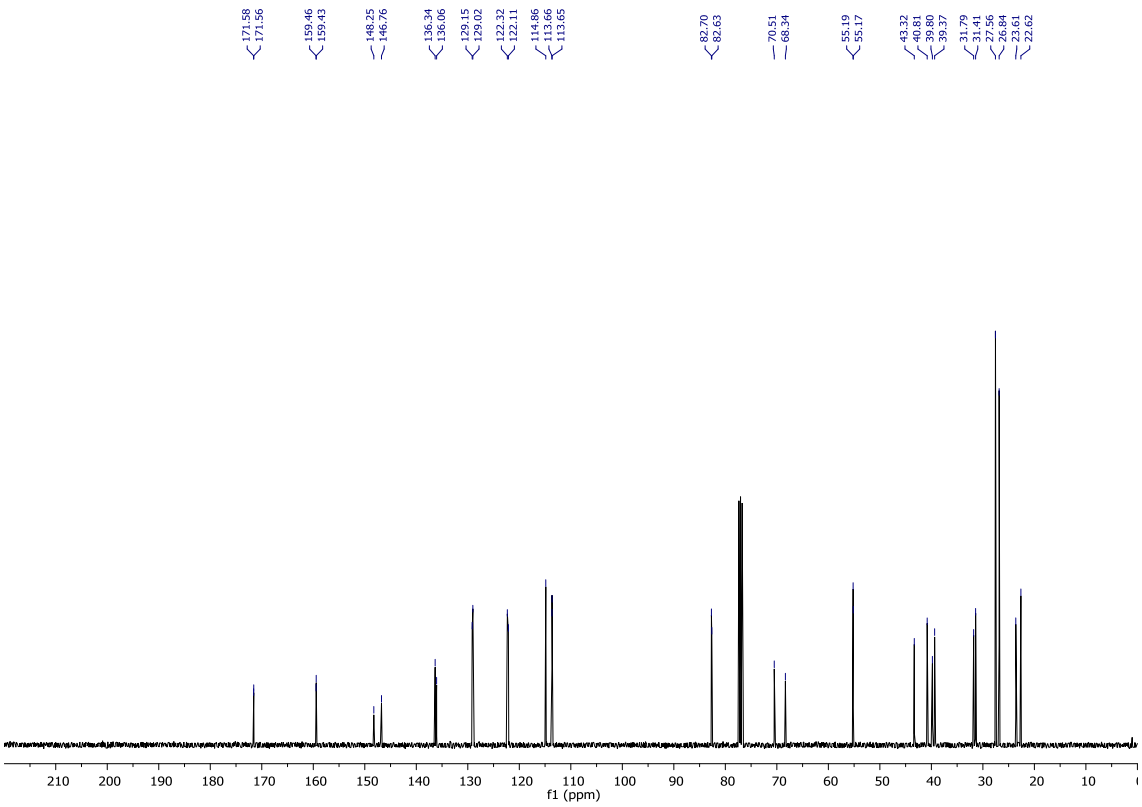
Cl
N
O
N
tBu
70Bc
f1 (ppm)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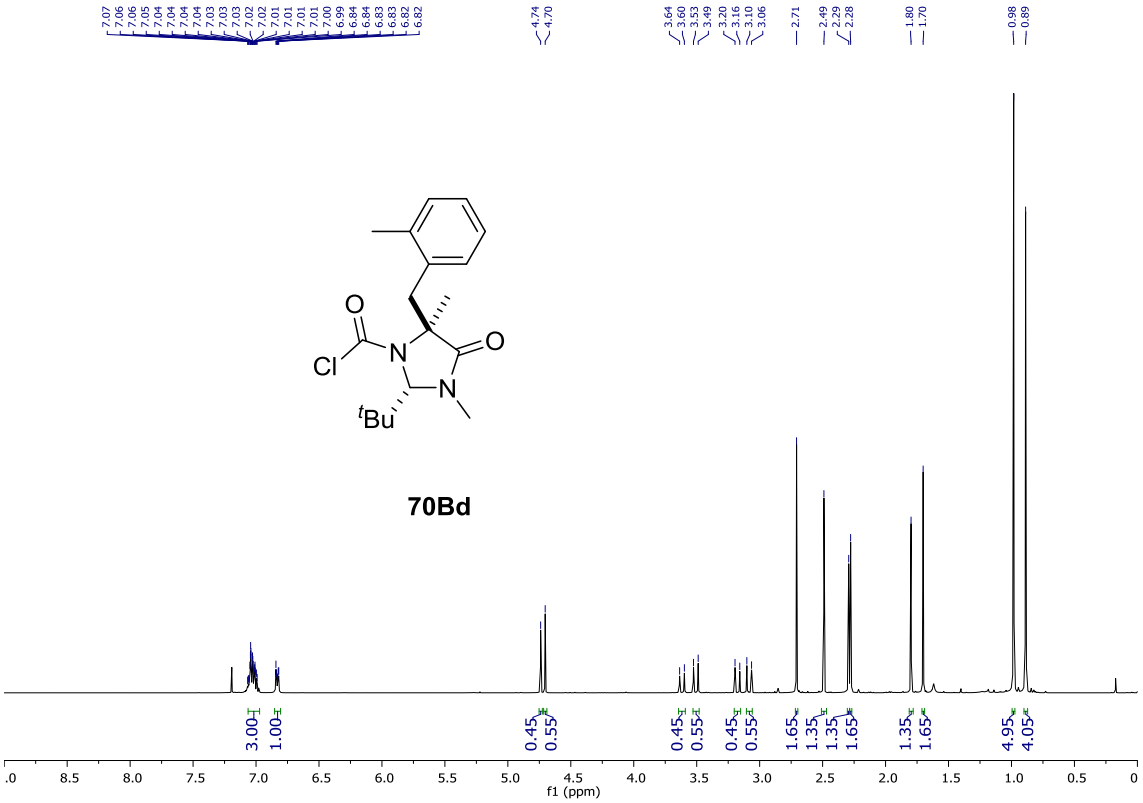
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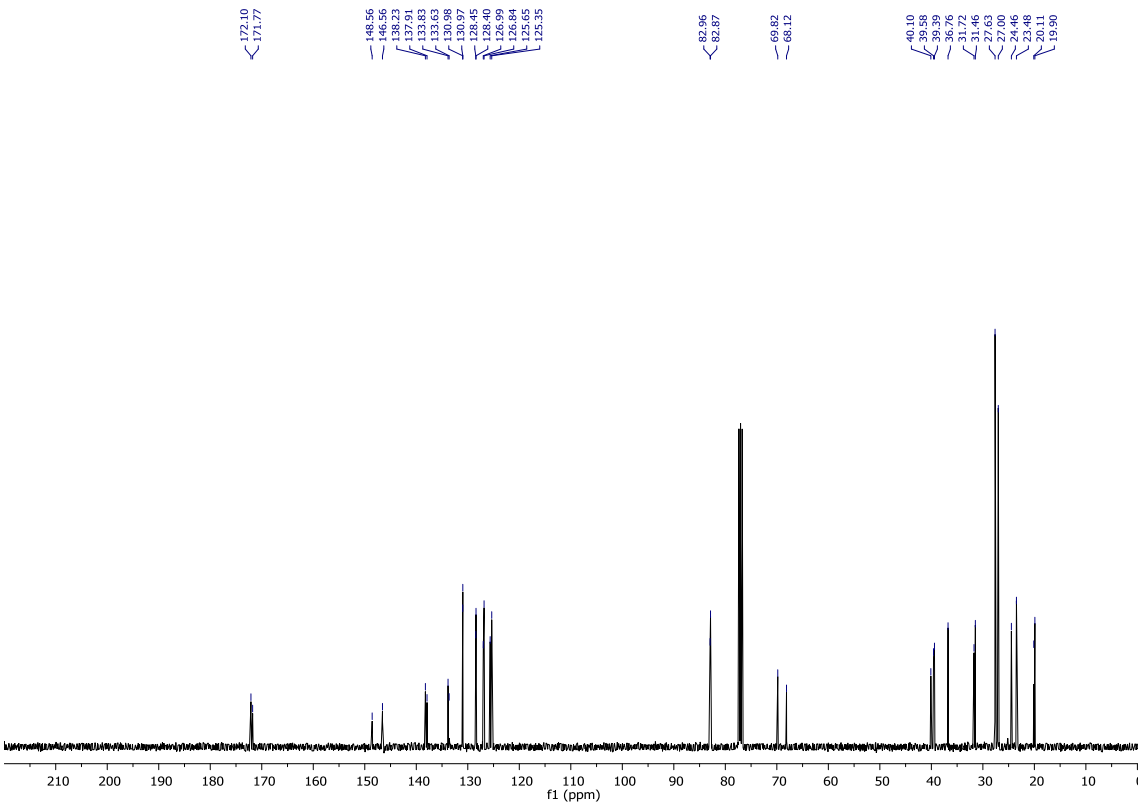
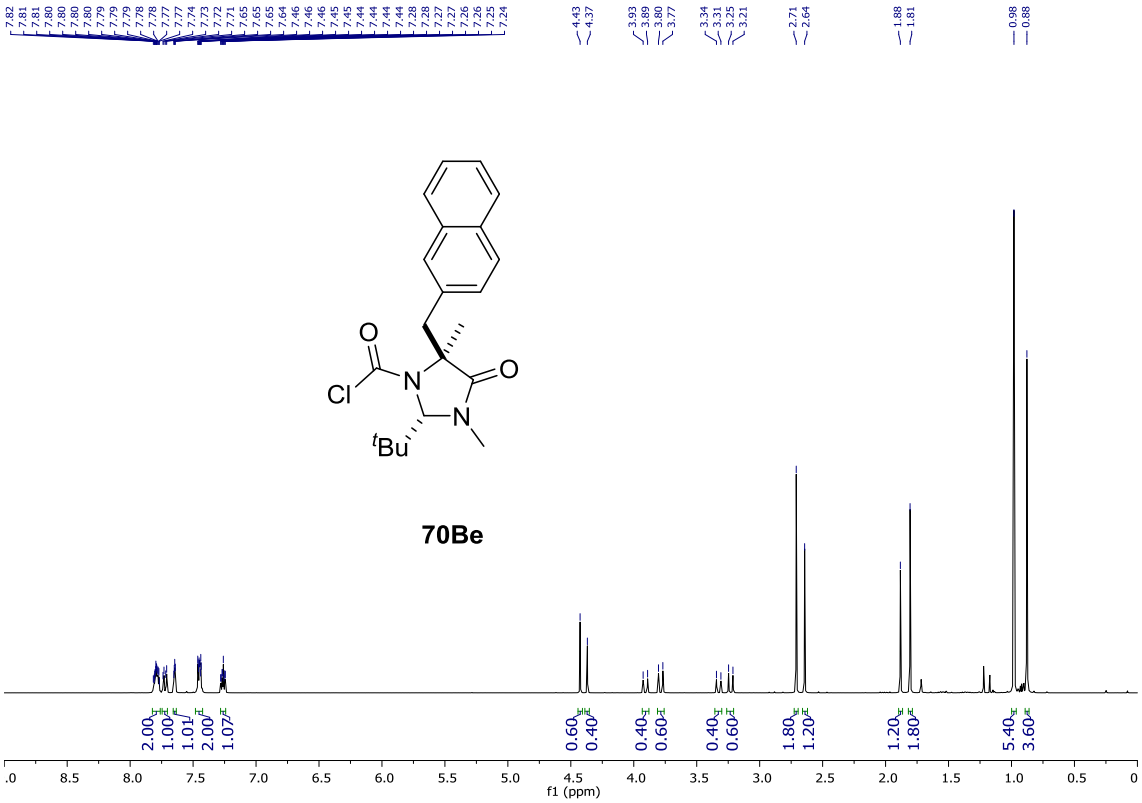
4.74 4.70
3.64 3.60 3.53 3.49 3.20 3.16 3.10 3.06
2.71
2.49 2.29 2.28
1.80 1.70
0.98 0.89
O
Cl
N
O
N
tBu
70Bd
3.00 1.00 0.45 0.55 0.45 0.55 0.45 0.55 1.65 1.35 1.35 1.65 1.35 1.65 4.95 4.05
f1 (ppm)


172.10 171.77
148.56 146.56 138.23 137.91 133.83 133.63 130.98 130.97 128.45 128.40 126.99 126.84 125.65 125.35
82.96 82.87
69.82 68.12
40.10 39.58 39.39 36.76 31.72 31.46 27.63 27.00 24.46 23.48 20.11 19.90
f1 (ppm)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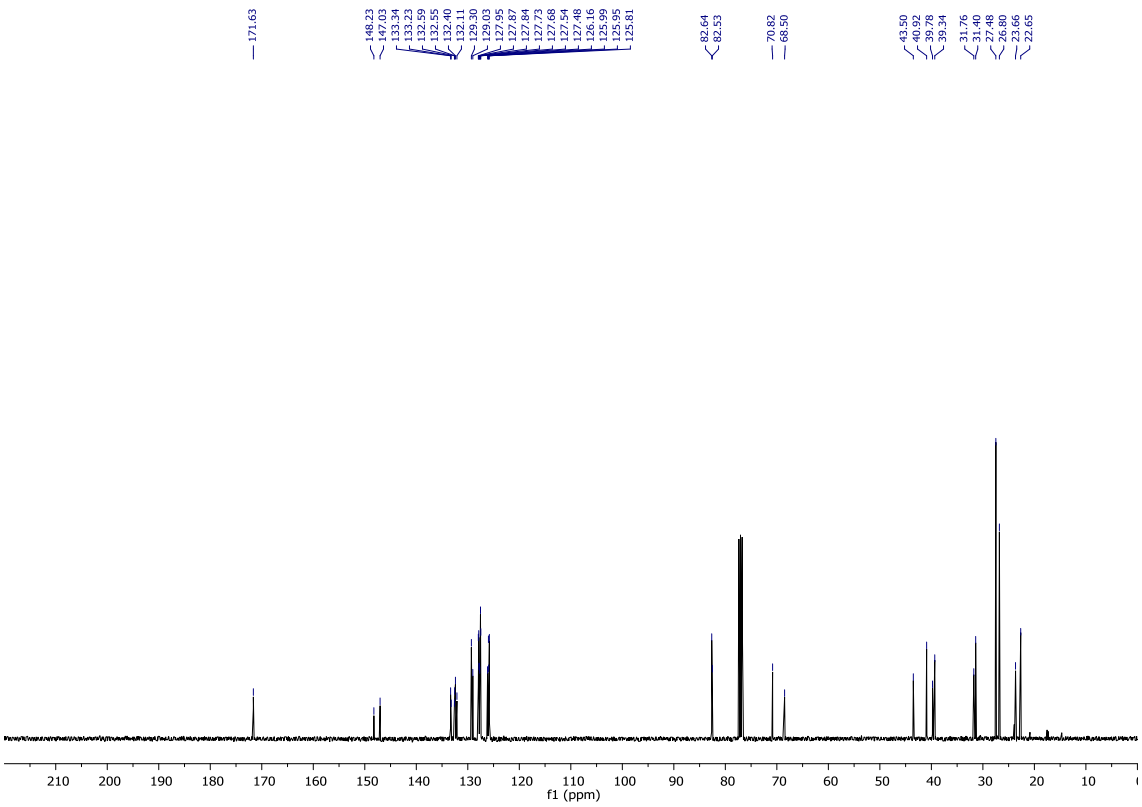
4.43 4.37
3.93 3.89 3.80 3.77
3.34 3.31 3.25 3.21
2.71 2.64
1.88 1.81
0.98 0.88
O
Cl
N
O
N
tBu
70Be
2.00 1.00 1.01 2.00 1.07
0.60 0.40
0.40 0.60
0.40 0.60
1.80 1.20
1.20 1.80
5.40 3.60
f1 (ppm)


171.63
148.23 147.03 133.34 133.23 132.99 132.55 132.40 132.11 129.30 129.03 127.95 127.87 127.84 127.73 127.68 127.54 127.48 126.46 125.99 125.95 125.81
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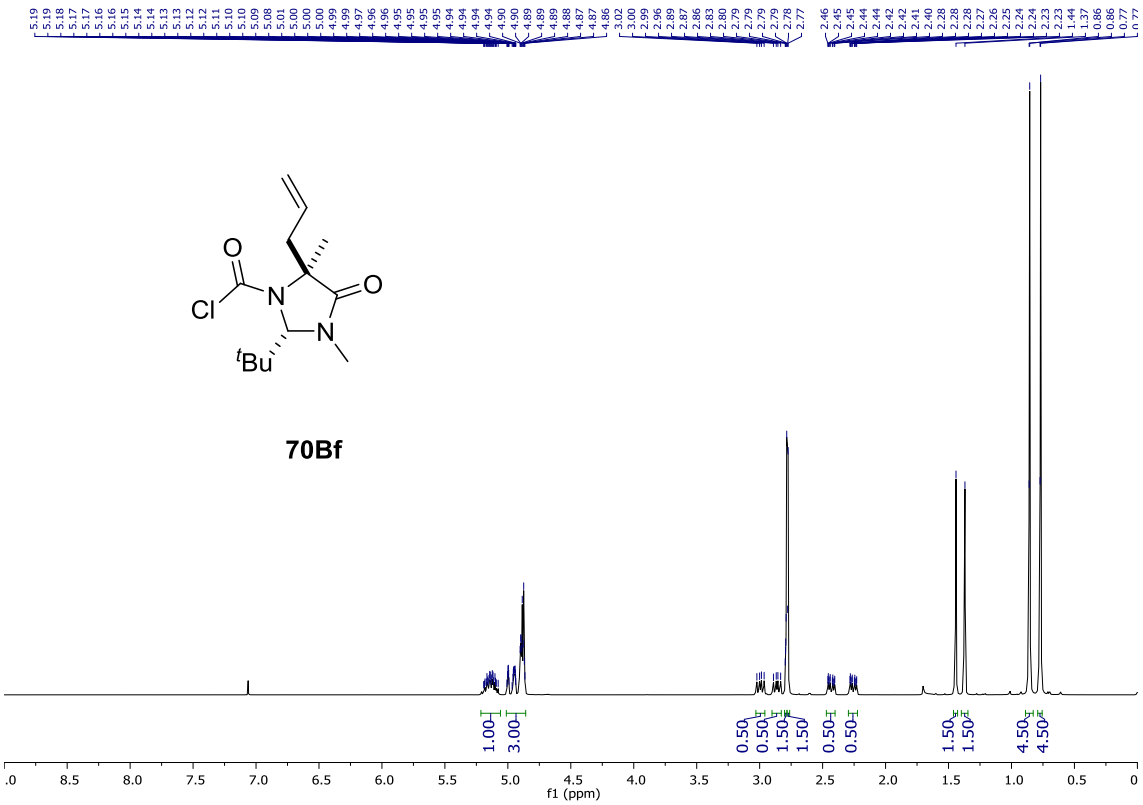
f1 (ppm)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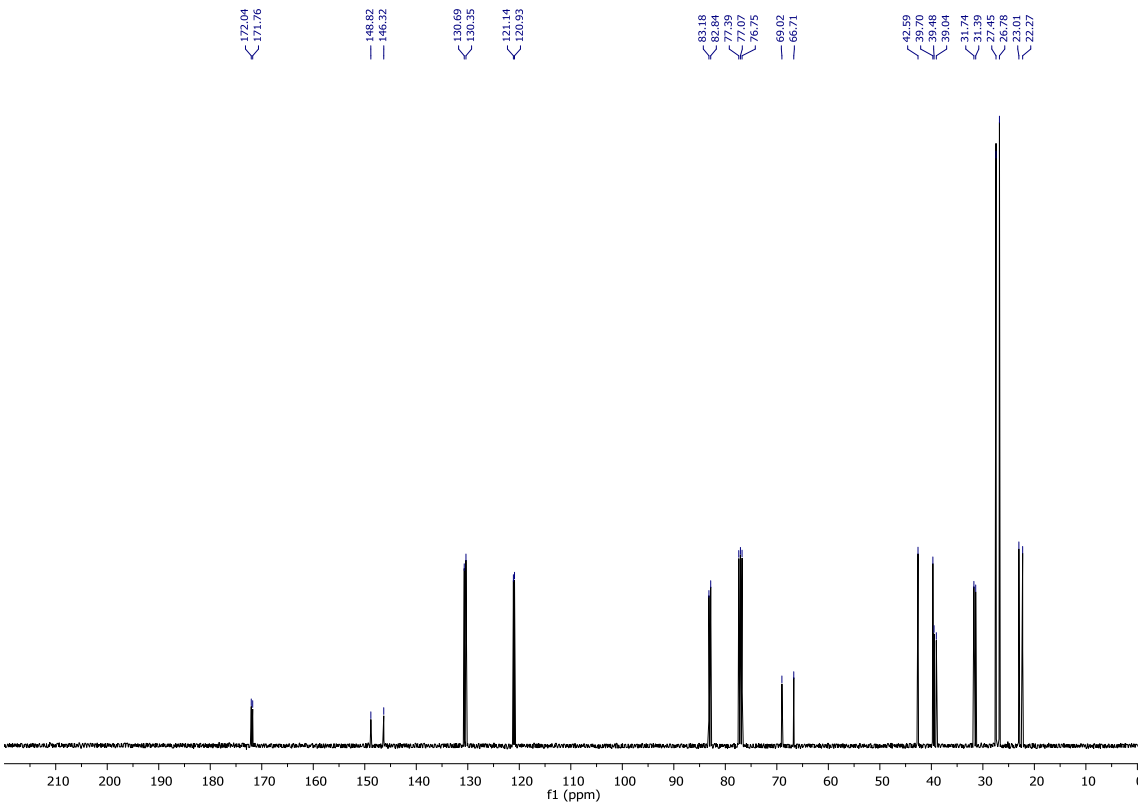
f1 (ppm)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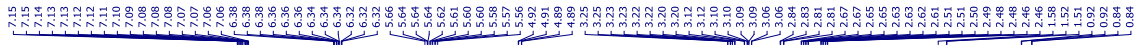
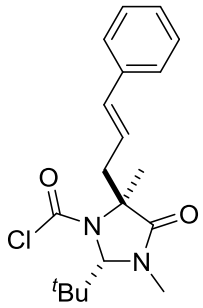
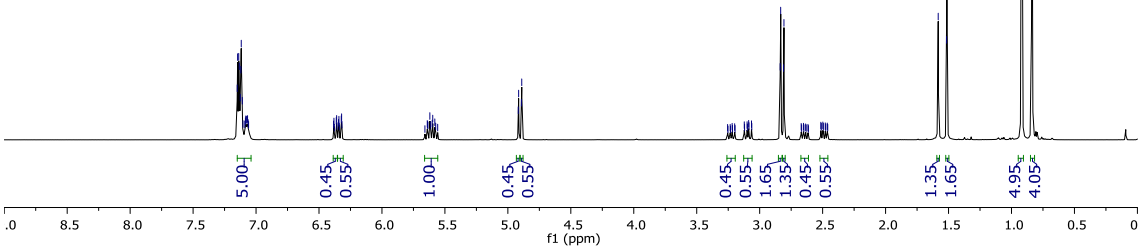



O
Cl
N
O
N
tBu

70Bg


5.00
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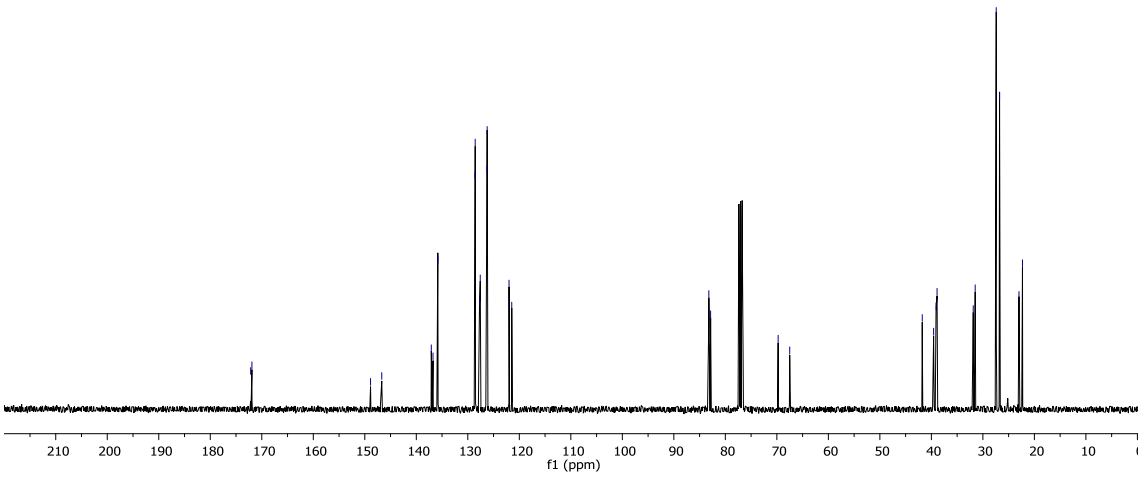
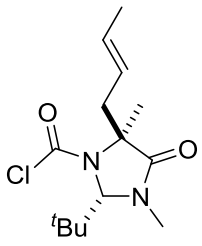
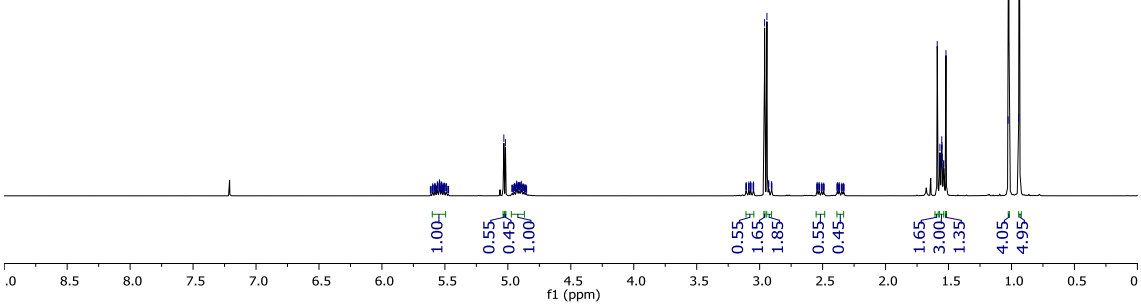
0.55
1.65
1.35
0.45
0.55
1.35
1.65
4.95
4.05
f1 (ppm)


f1 (ppm)



70Bh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1.00
0.55
1.65
1.85
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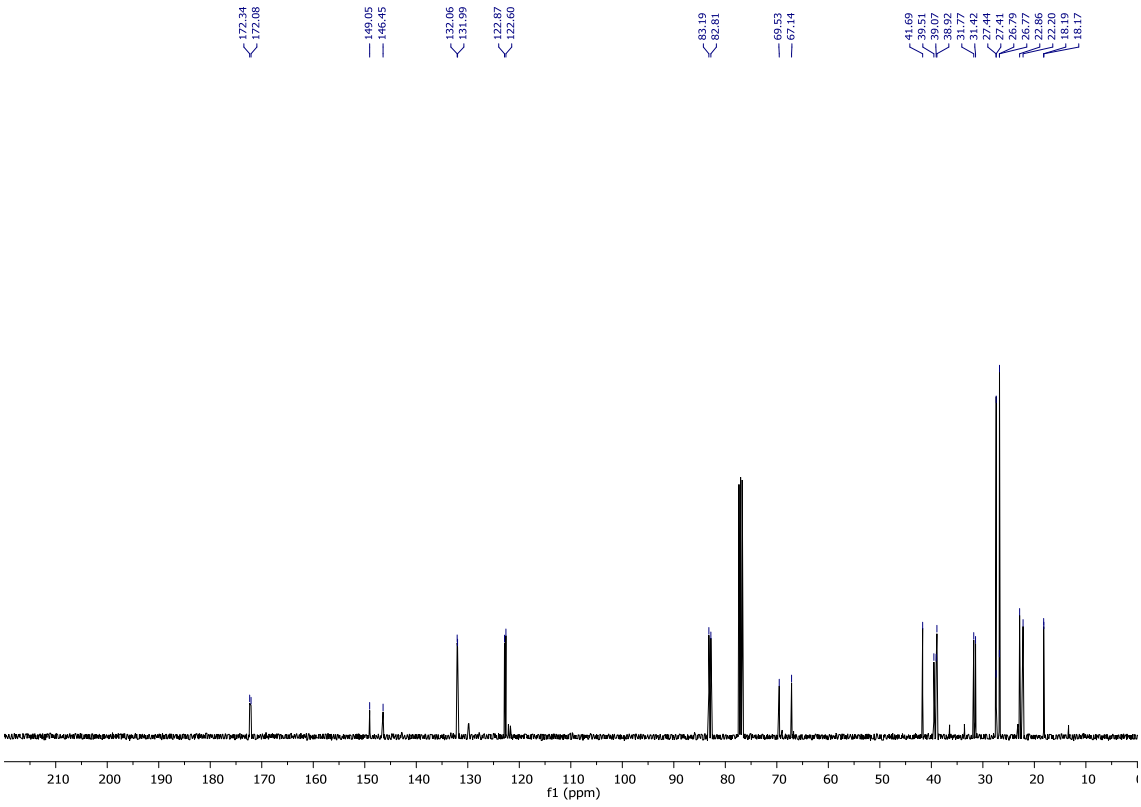
f1 (ppm)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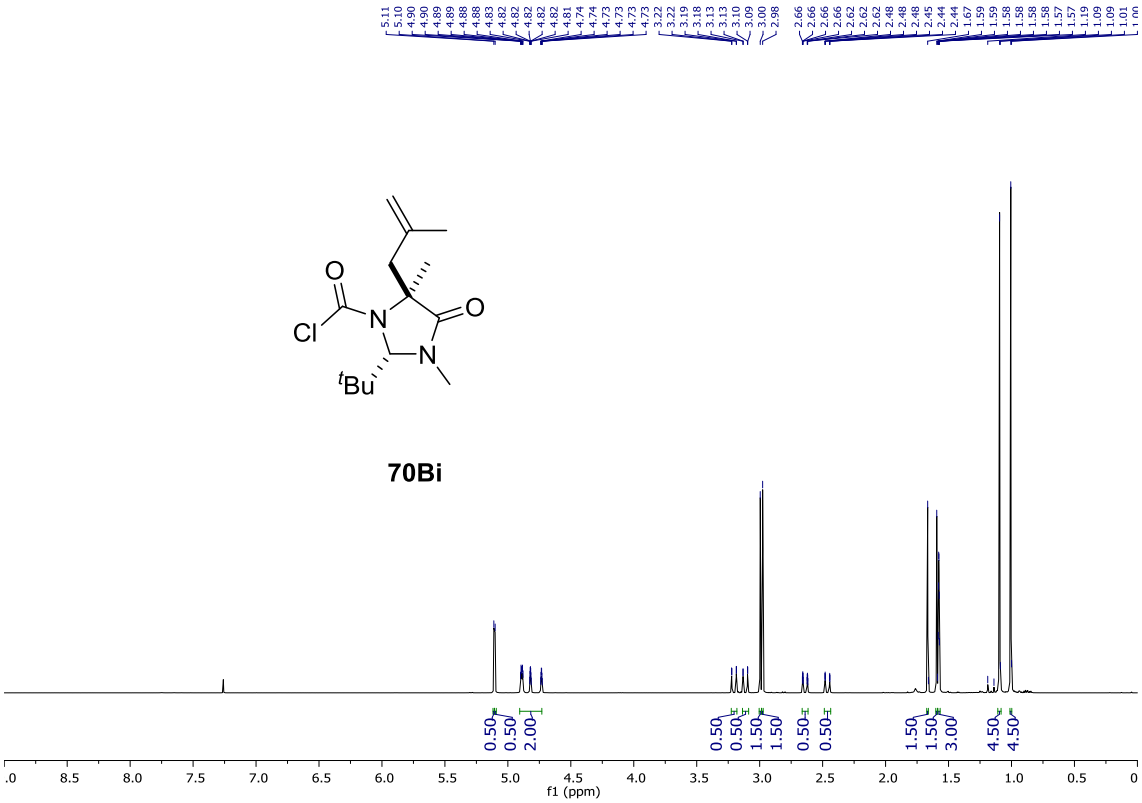
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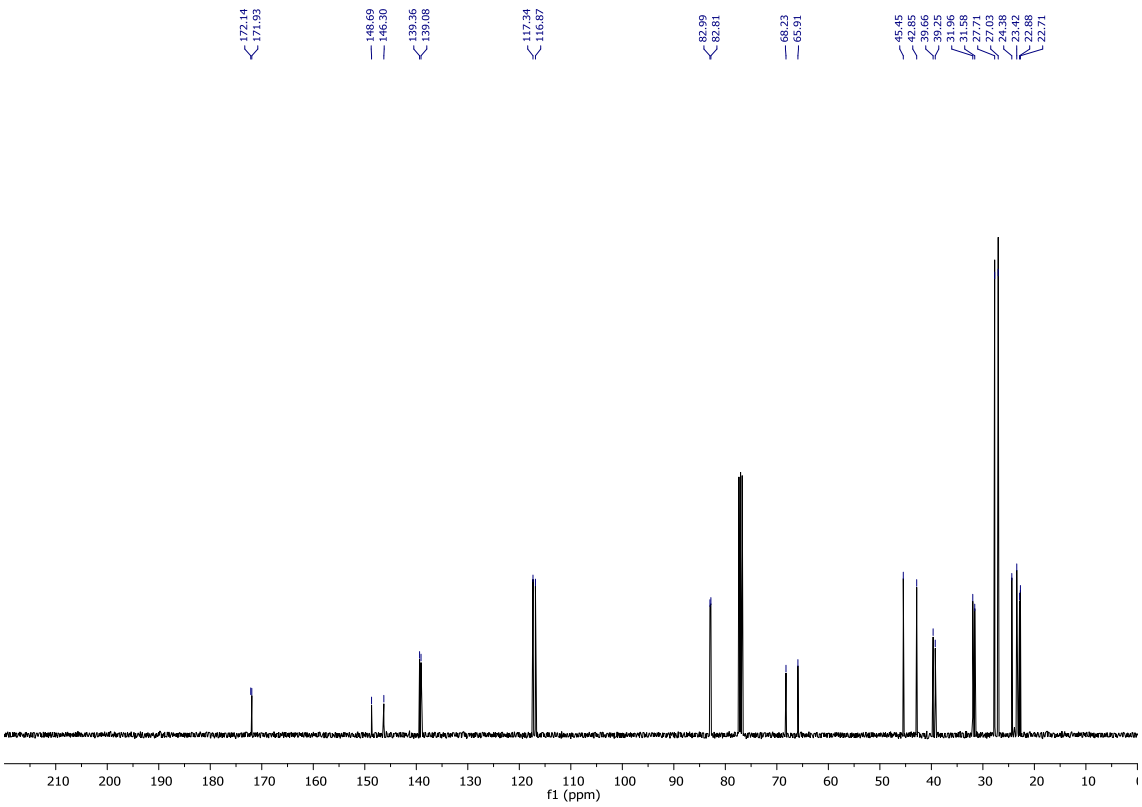
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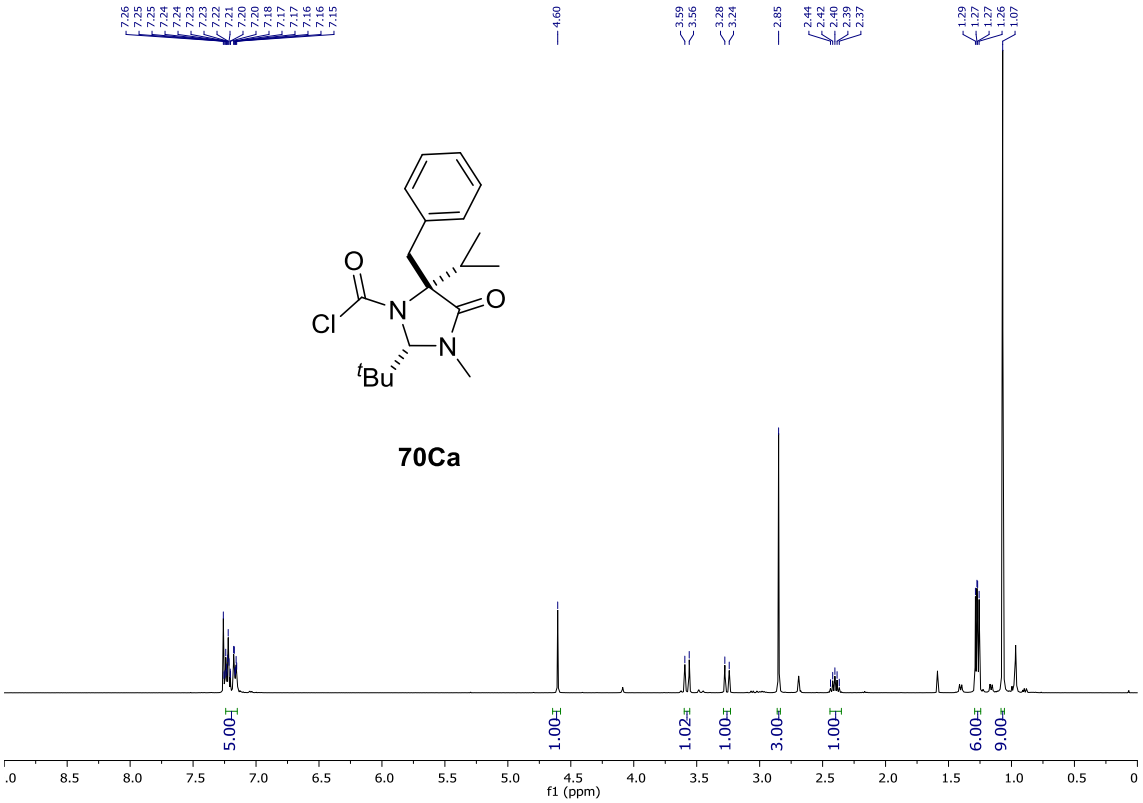
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7.17
7.16
7.16
7.15
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3.56
3.28
3.24
2.85
2.44
2.42
2.40
2.39
2.37
1.29
1.27
1.27
1.26
1.07
O
Cl
N
O
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1.02
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3.00
1.00
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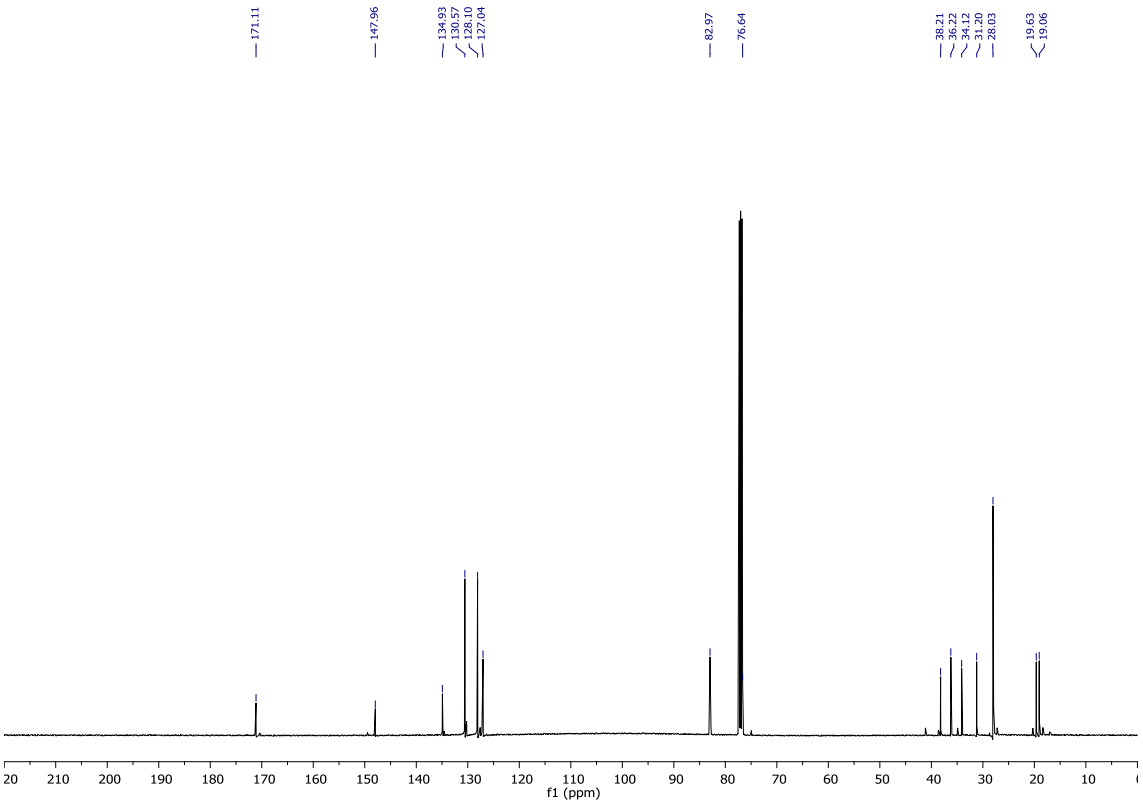
9.00
f1 (ppm)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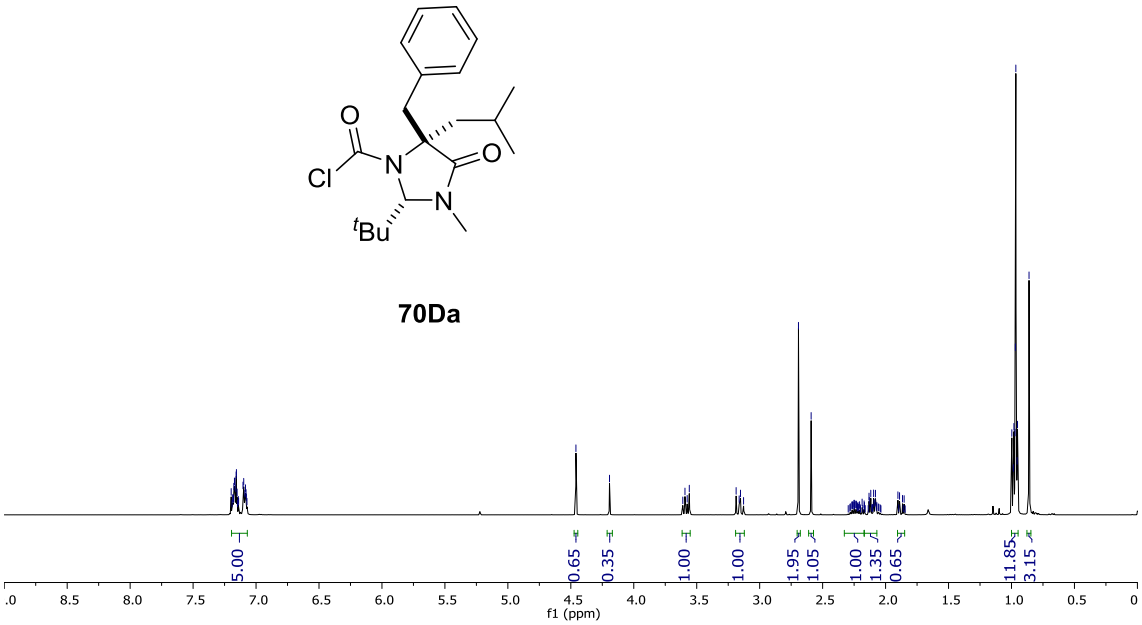
f1 (ppm)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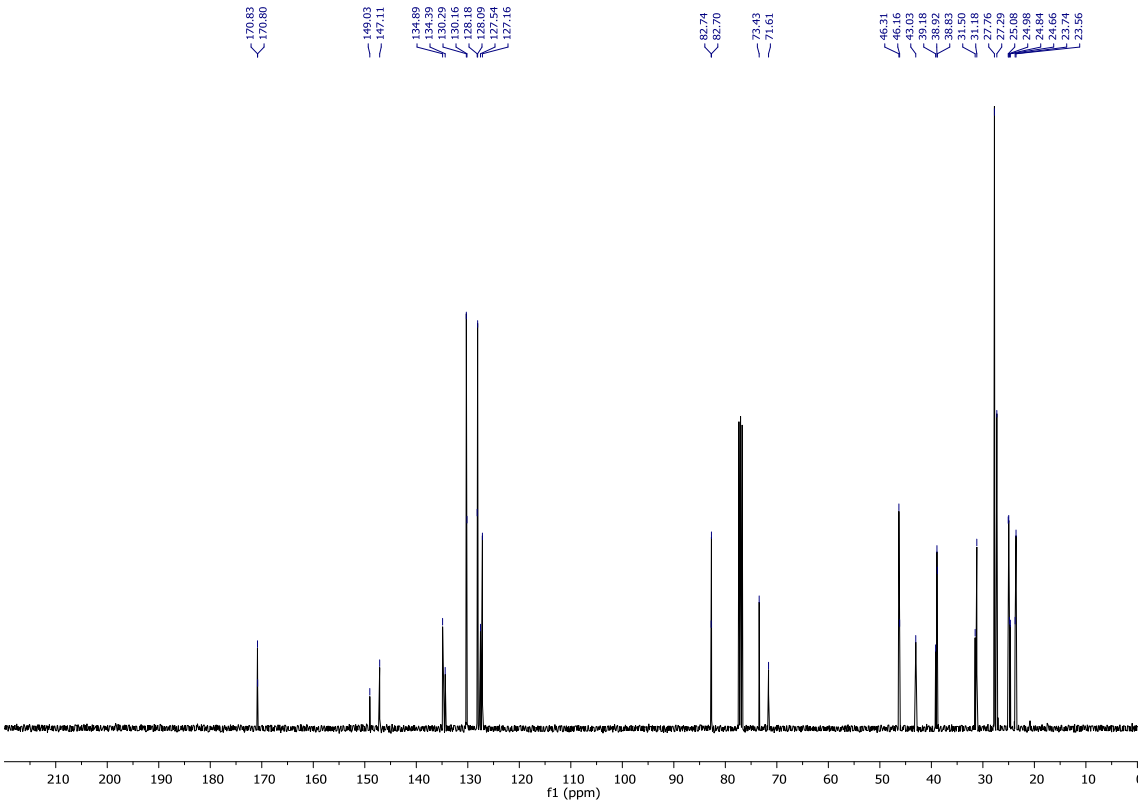
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73.43
71.61
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46.16
43.03
39.18
38.92
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24.84
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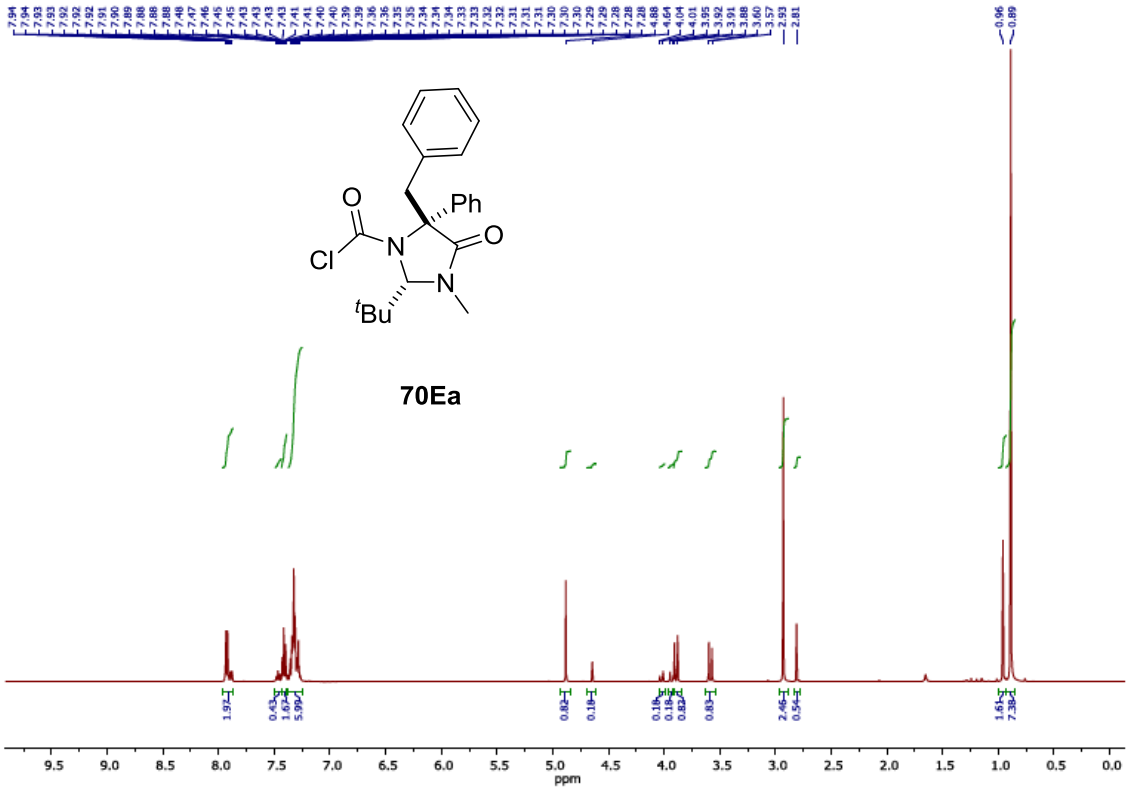
23.74
23.56
f1 (ppm)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O
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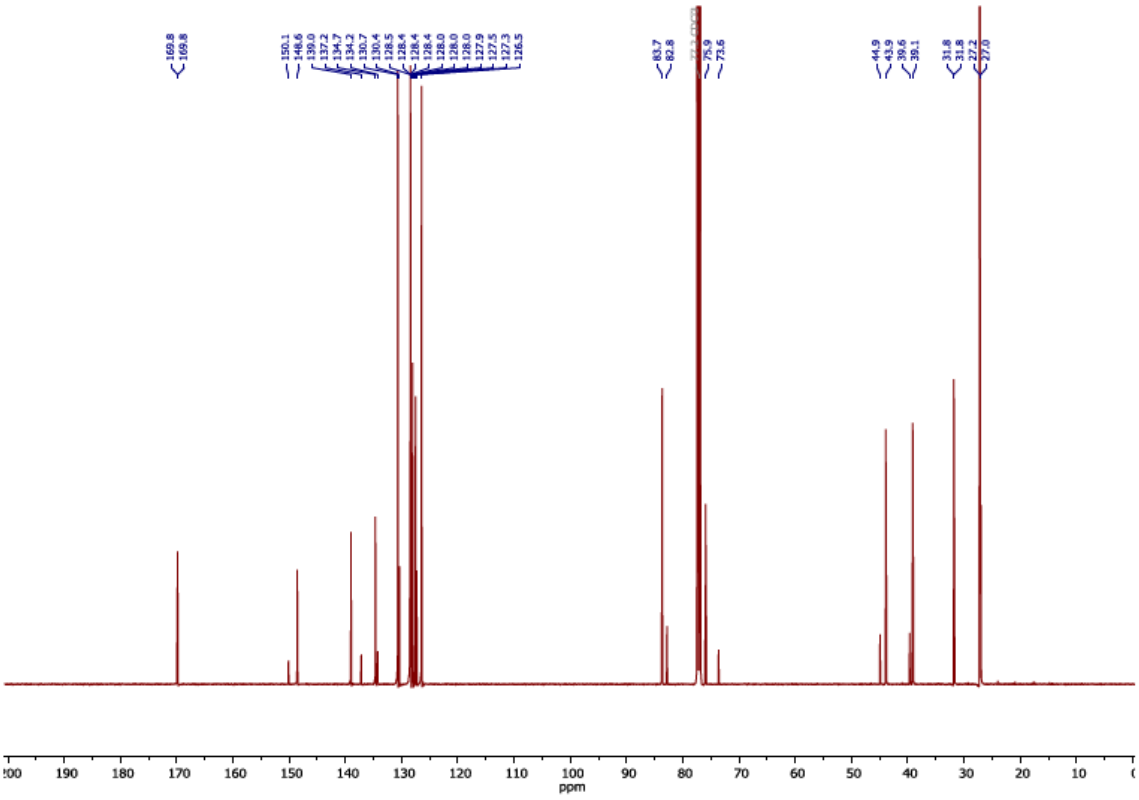
ppm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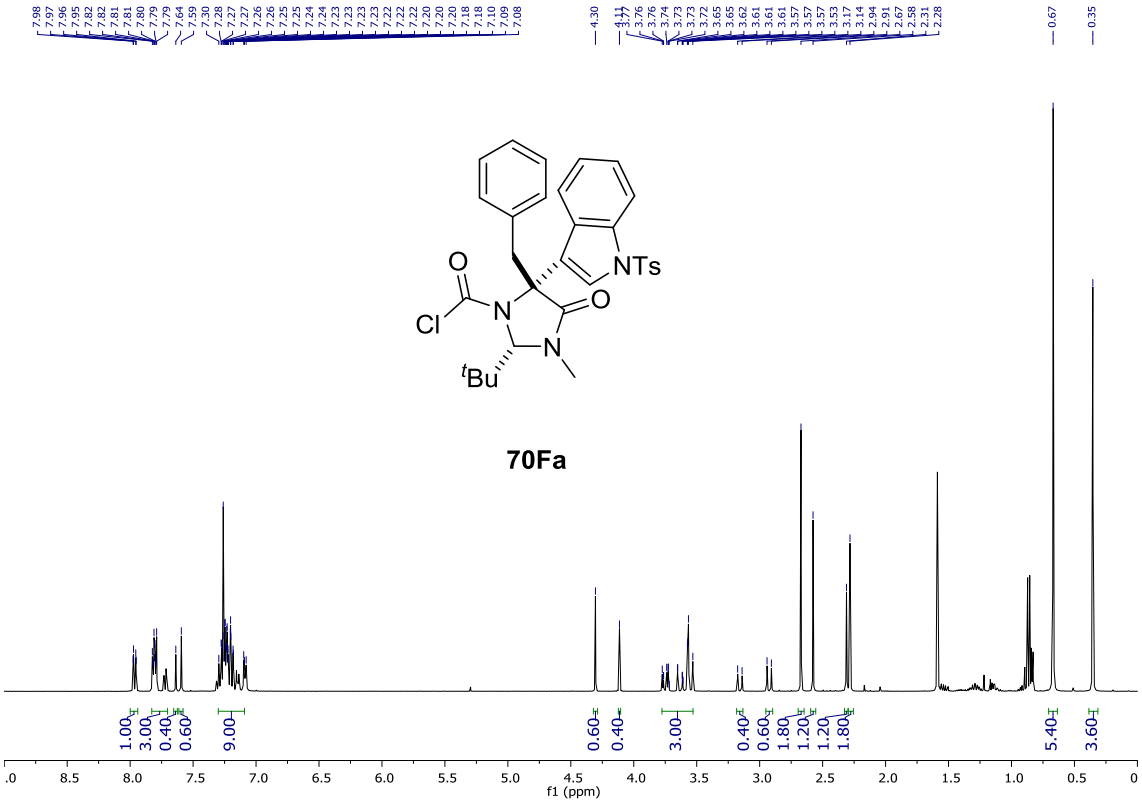
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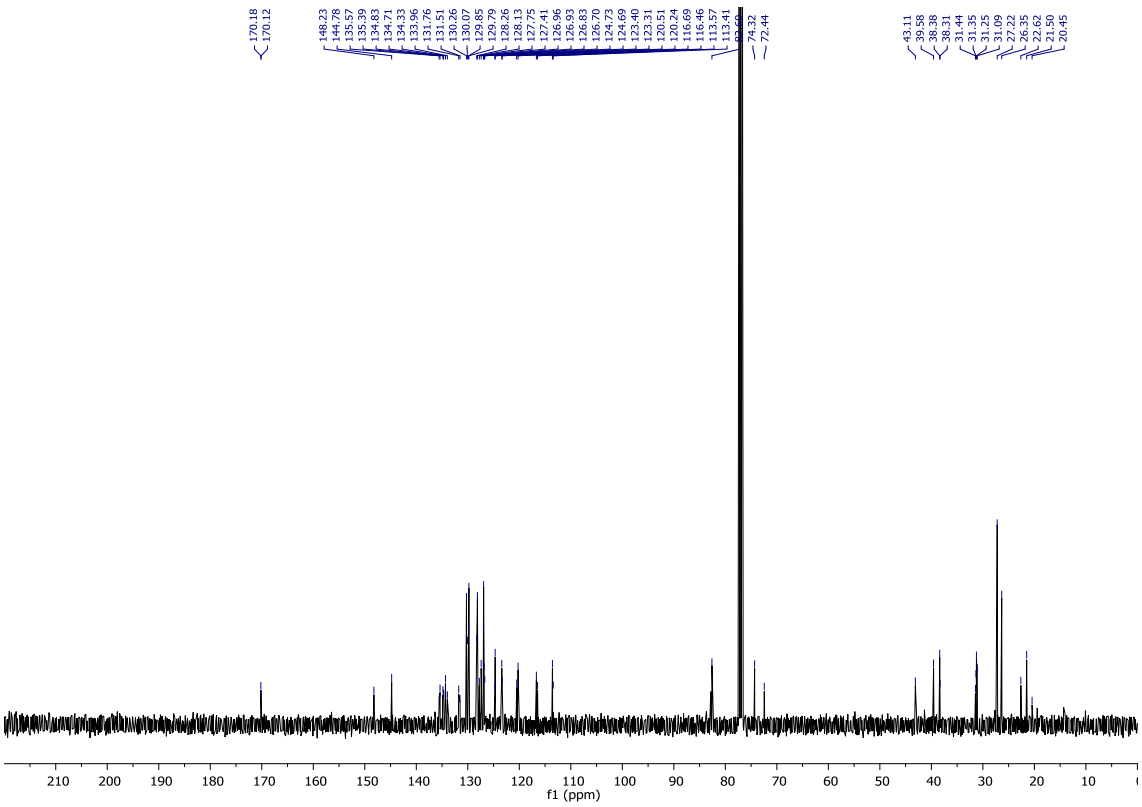
Cl
O
N
tBu
70Fa
f1 (ppm)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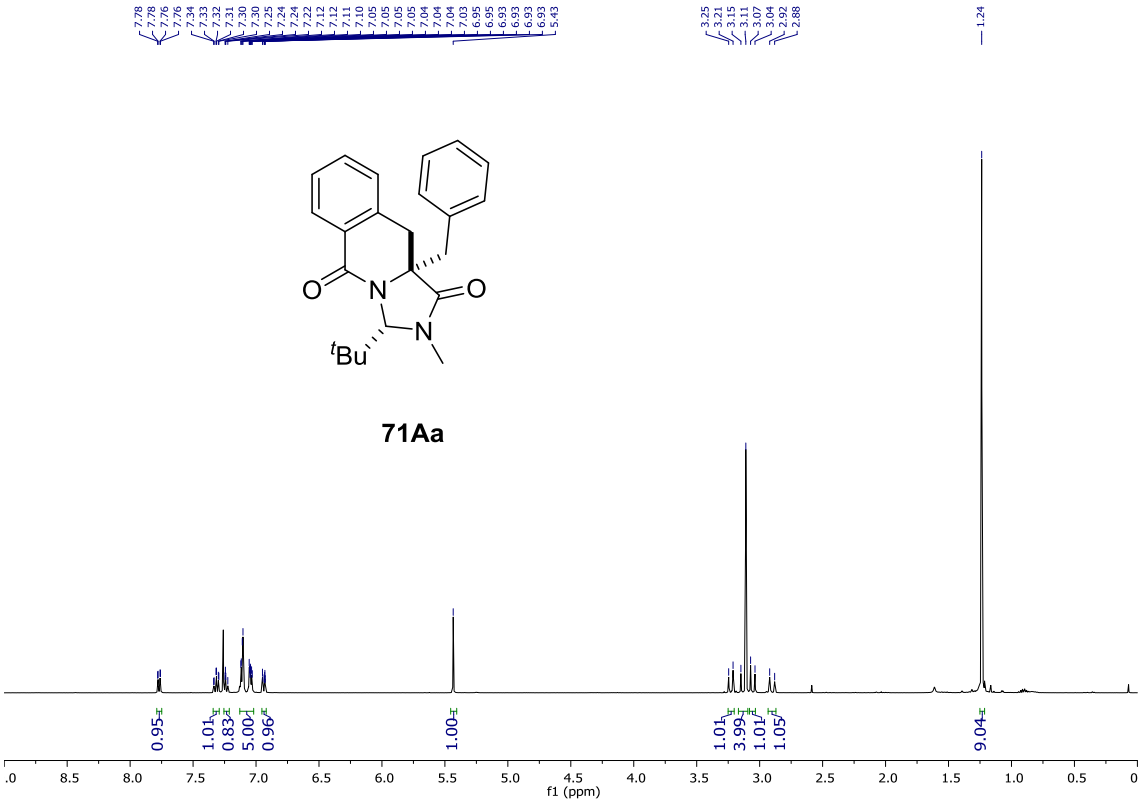
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7.12
7.11
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7.05
7.05
7.05
7.04
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7.04
7.03
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6.95
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6.93
6.93
6.93
5.45
3.25
3.21
3.15
3.11
3.07
3.04
2.92
2.88
1.24
O
N
O
N
tBu
71Aa
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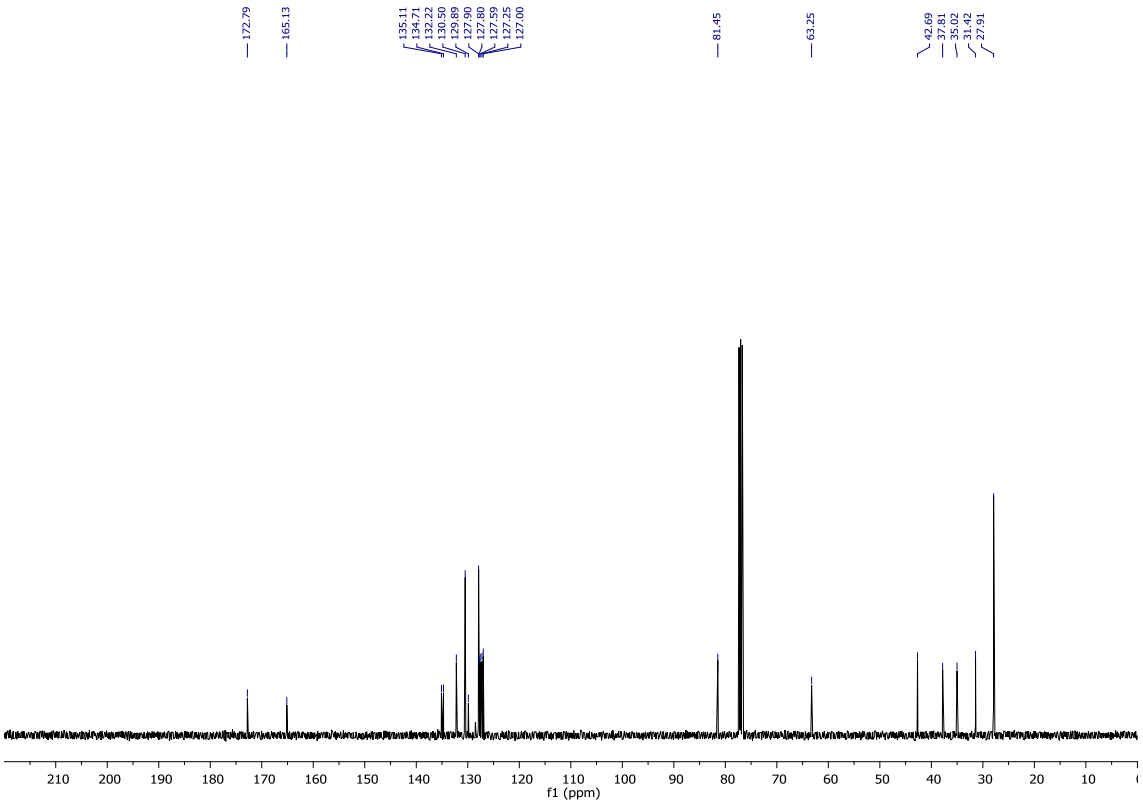
0.96
1.00
1.01
3.99
1.01
1.05
9.04
f1 (ppm)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129.89
127.90
127.80
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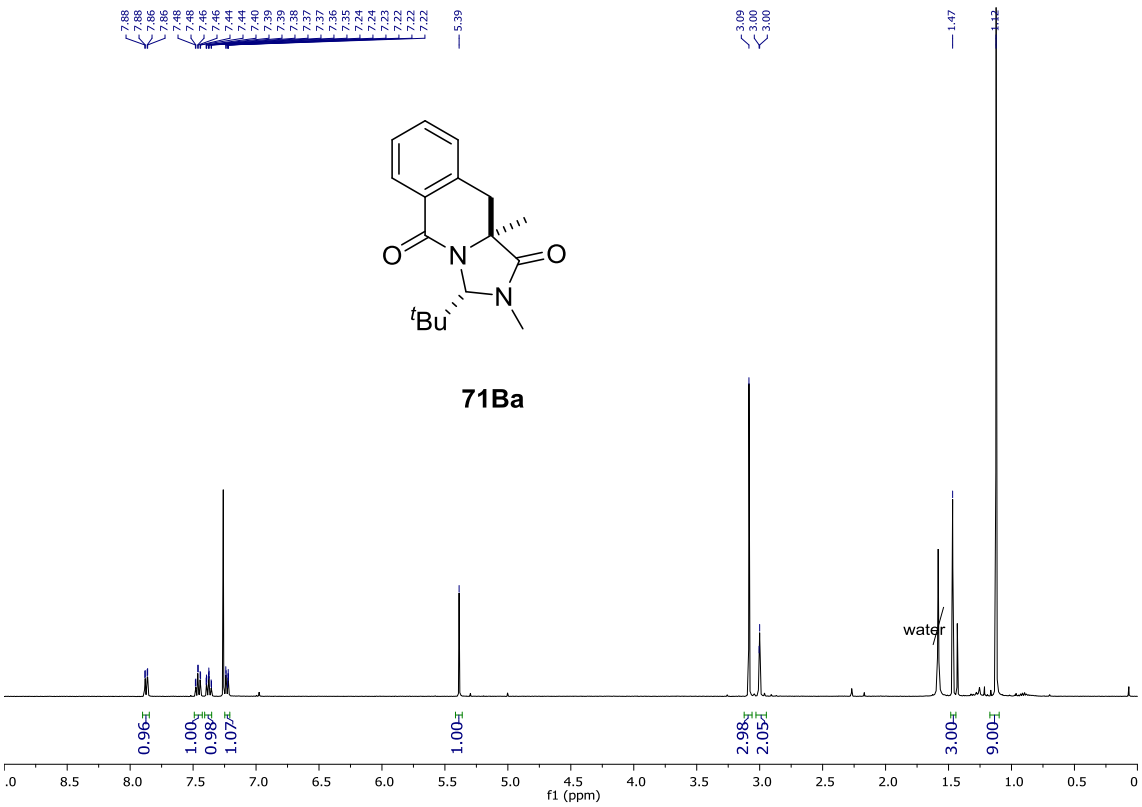
127.25
127.00
81.45
63.25
42.69
37.81
35.02
31.42
27.91
f1 (ppm)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7.46
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7.39
7.38
7.37
7.37
7.36
7.35
7.24
7.24
7.23
7.22
7.22
7.22
5.39
3.09
3.00
3.00
1.47
1.12
O
N
O
N
tBu
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1.00
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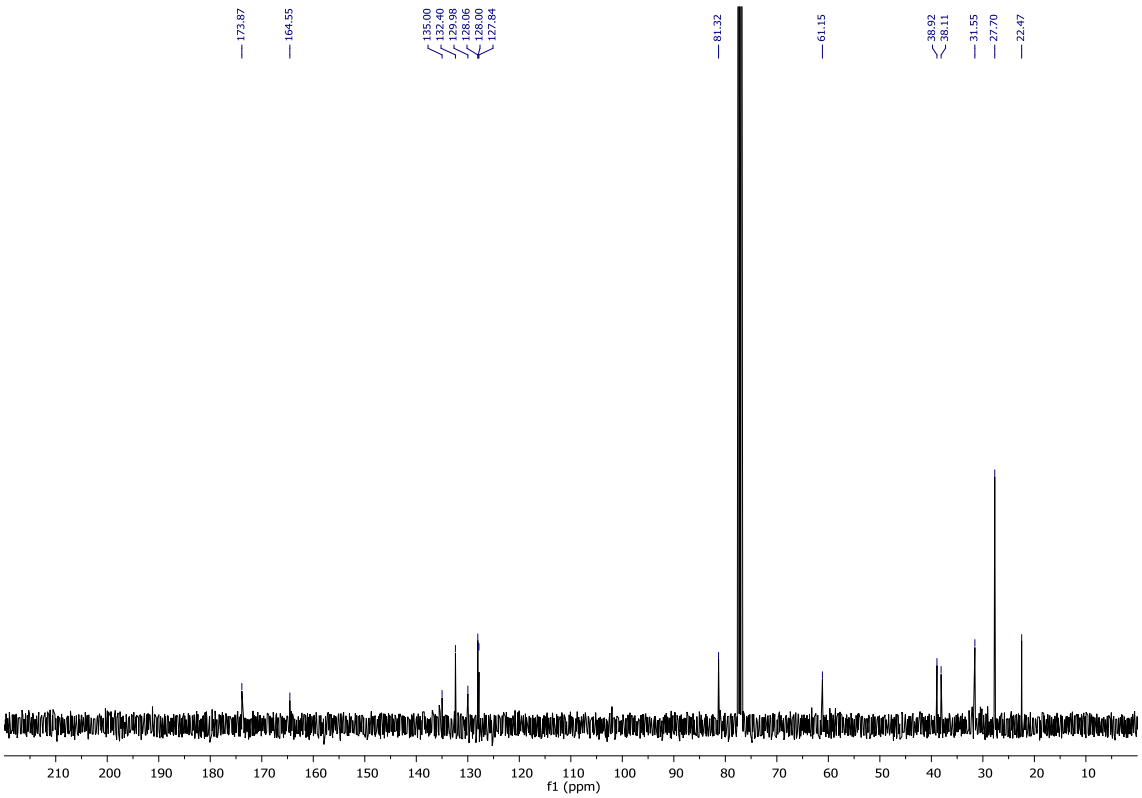
1.07
1.00
2.98
2.05
3.00
9.00
f1 (ppm)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31.55
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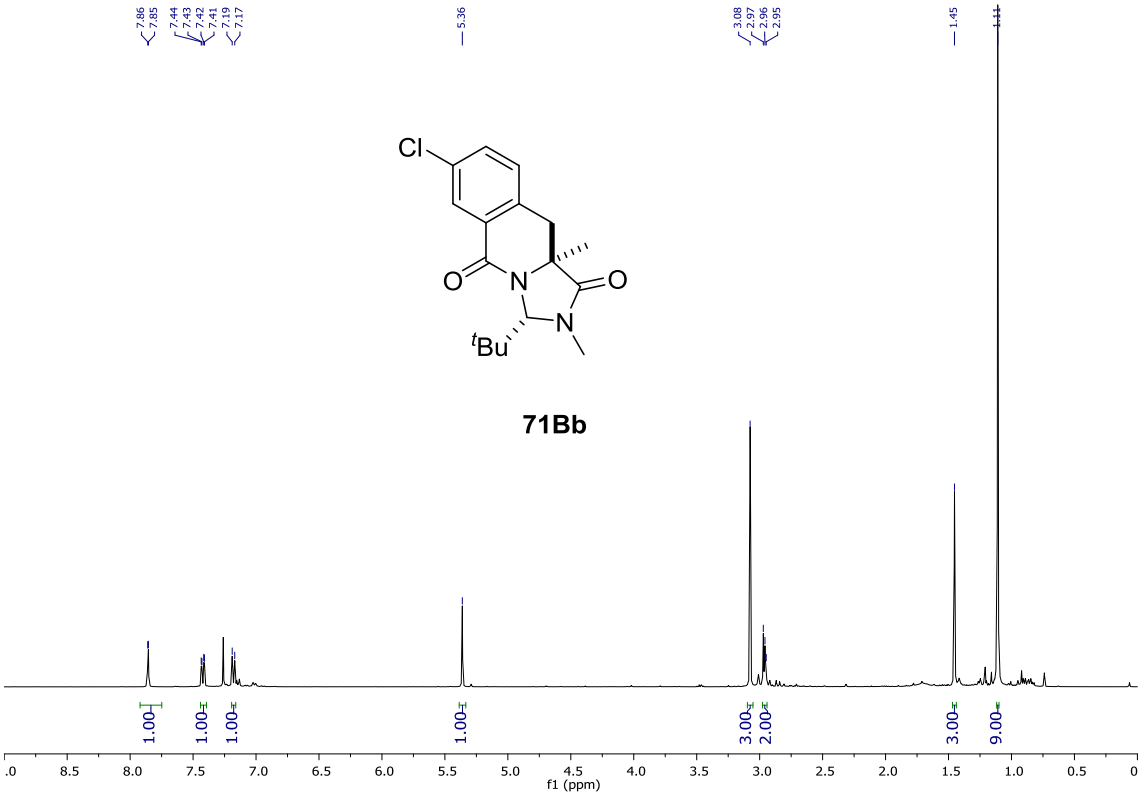
22.47
f1 (ppm)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3.08
2.97
2.96
2.95
1.45
1.11
Cl
O
N
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tBu
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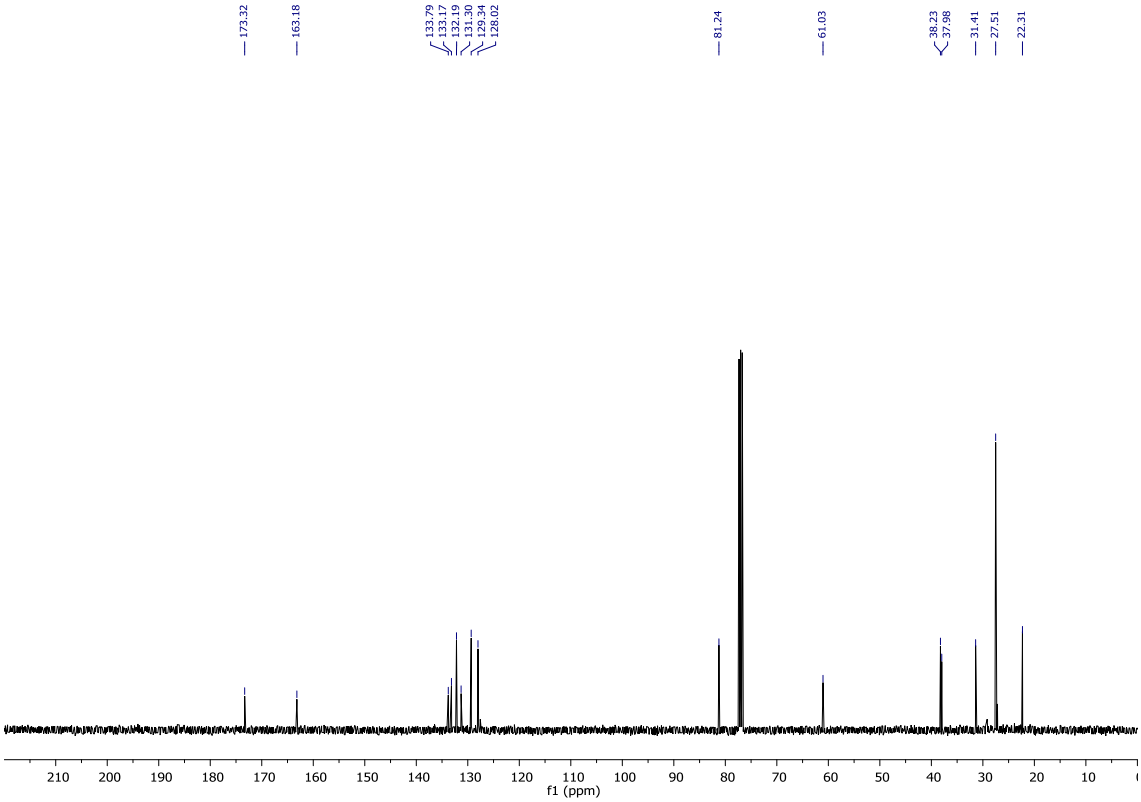
1.00
1.00
1.00
3.00
2.00
3.00
9.00
f1 (ppm)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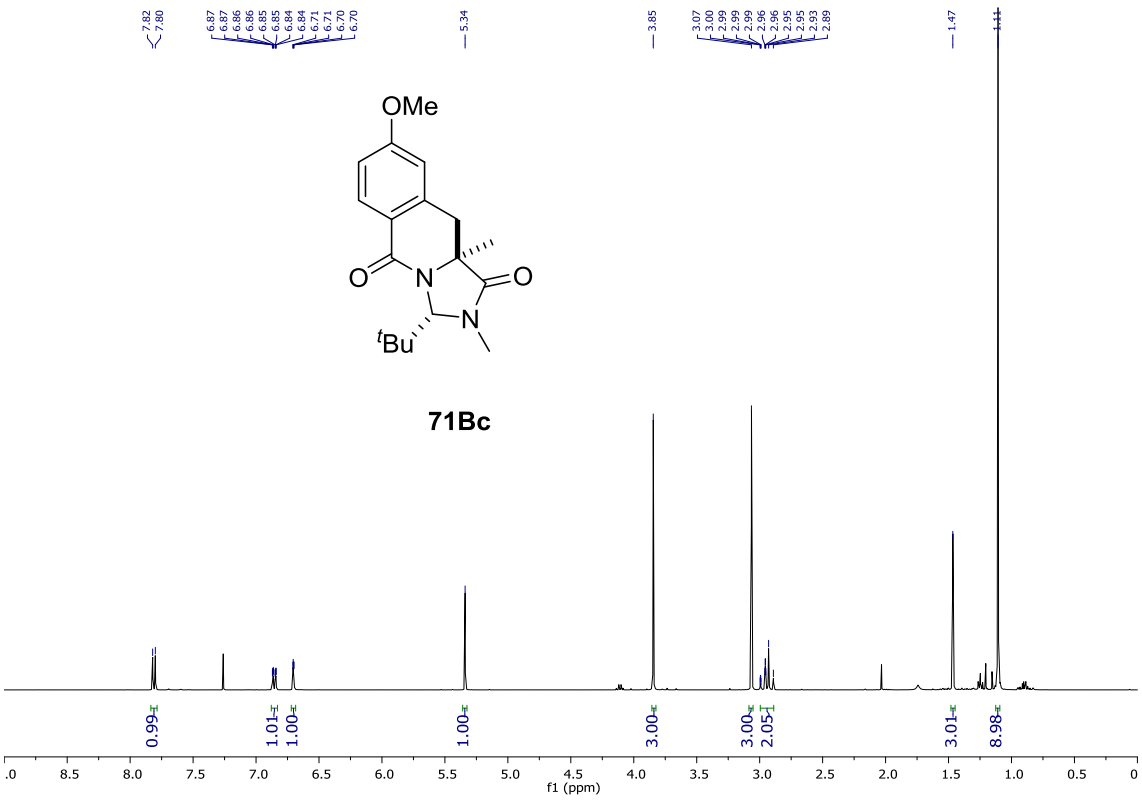
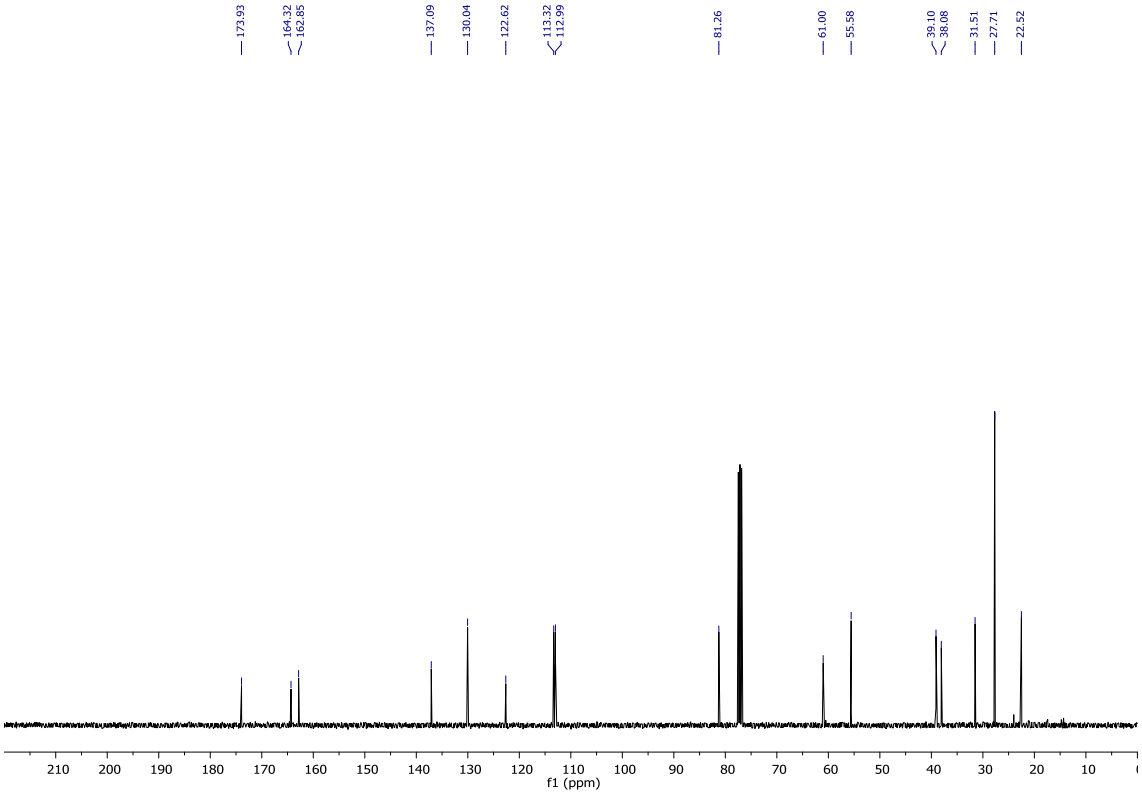
38.23
37.98
31.41
27.51
22.31
f1 (ppm)


OMe
O
N
O
N
tBu
71Bc
f1 (ppm)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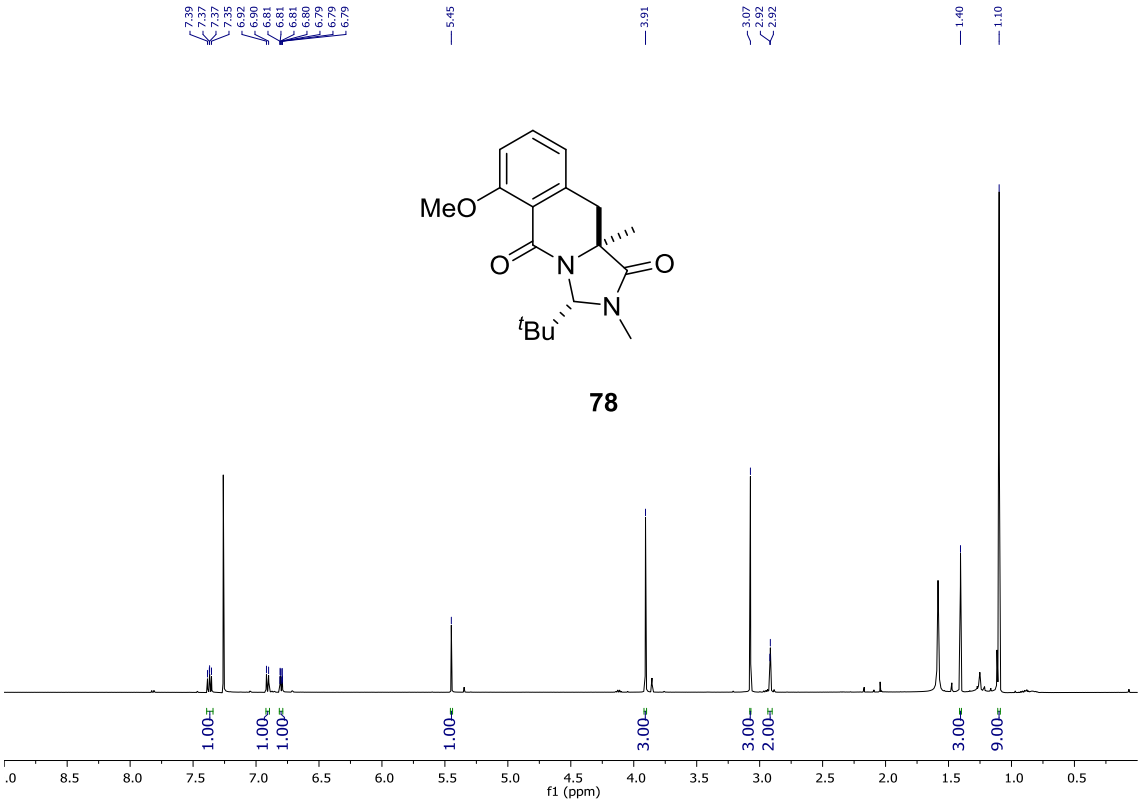
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6.90
6.81
6.81
6.81
6.80
6.79
6.79
6.79
5.45
3.91
3.07
2.92
2.92
1.40
1.10
MeO
O
N
O
N
tBu
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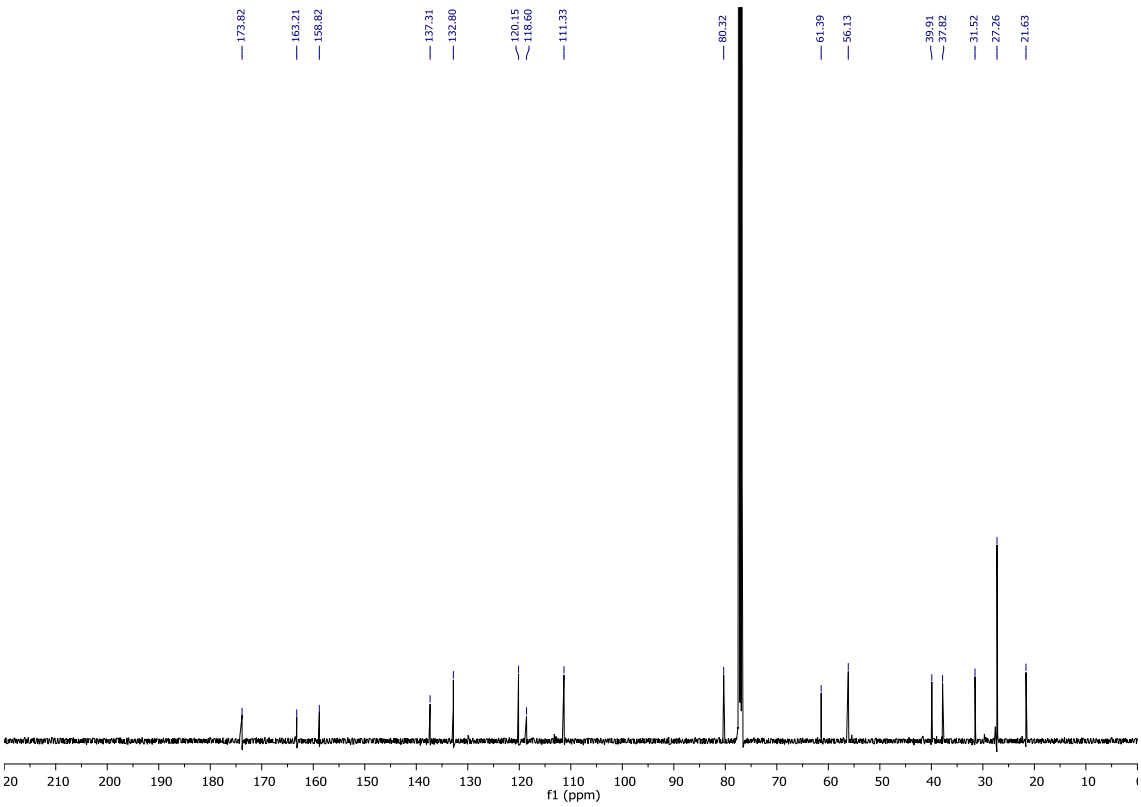
1.00
1.00
1.00
3.00
3.00
2.00
3.00
9.00
f1 (ppm)

78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137.31
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56.13
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31.52
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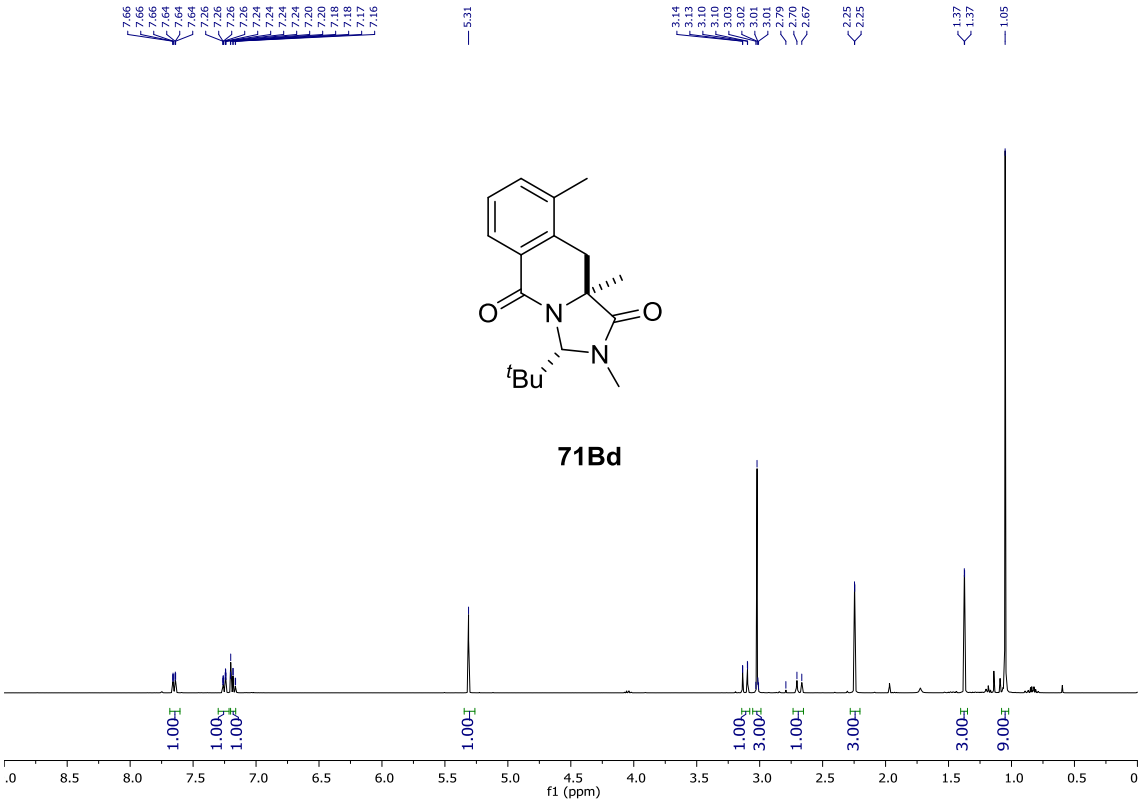
21.63
f1 (ppm)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7.17
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3.13
3.10
3.10
3.03
3.02
3.01
3.01
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2.25
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1.37
1.05
O
N
O
N
tBu
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1.00
3.00
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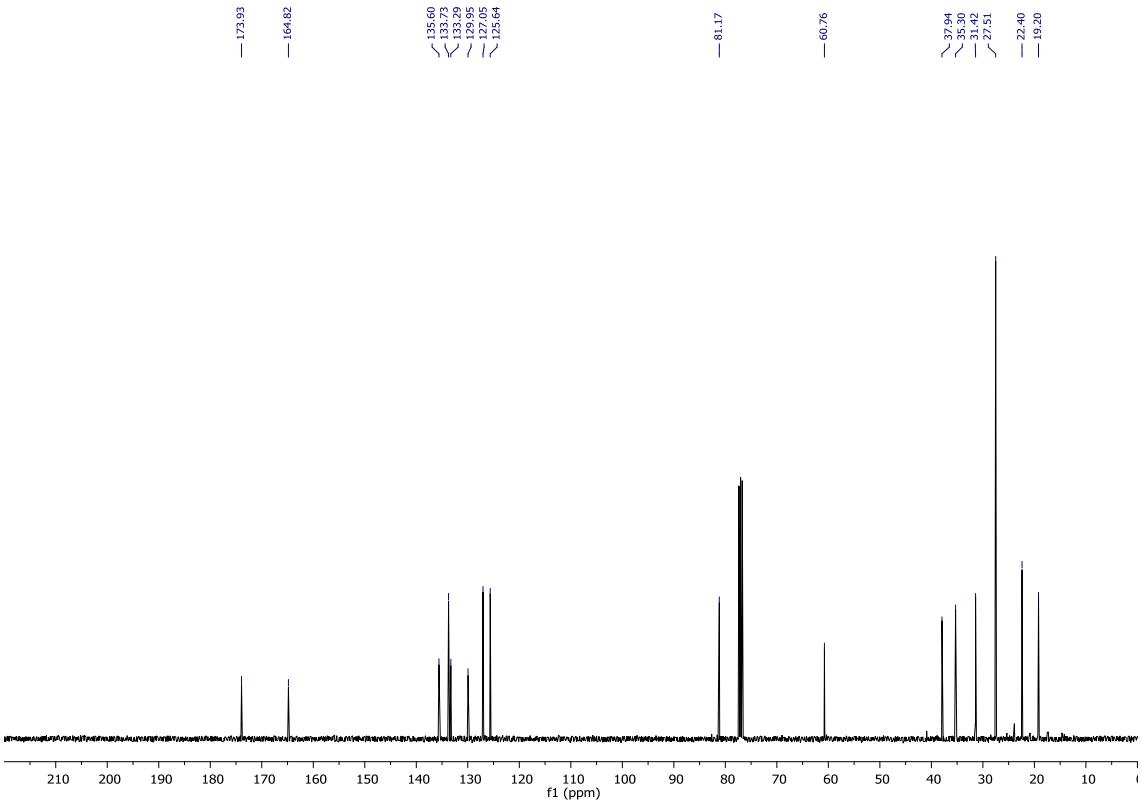
9.00
f1 (ppm)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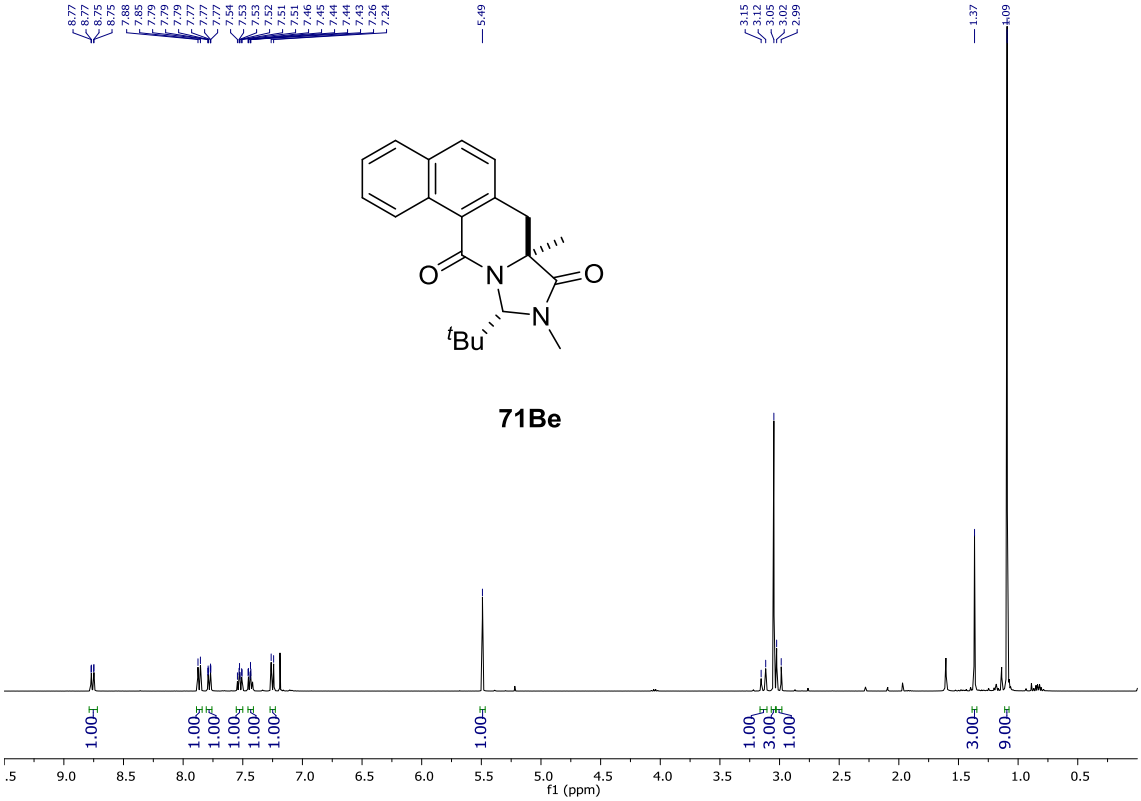
19.20
f1 (ppm)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7.24
5.49
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3.12
3.05
3.02
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1.09
O
N
O
N
tBu
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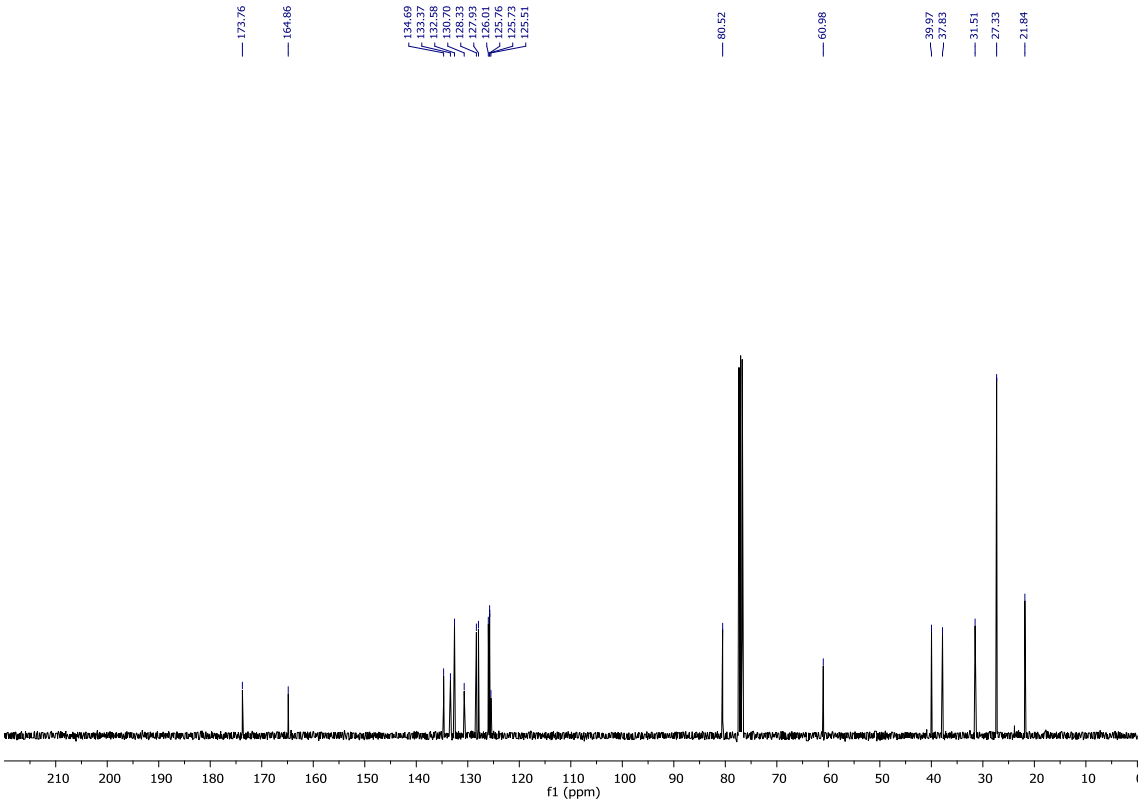
9.00
f1 (ppm)

71Be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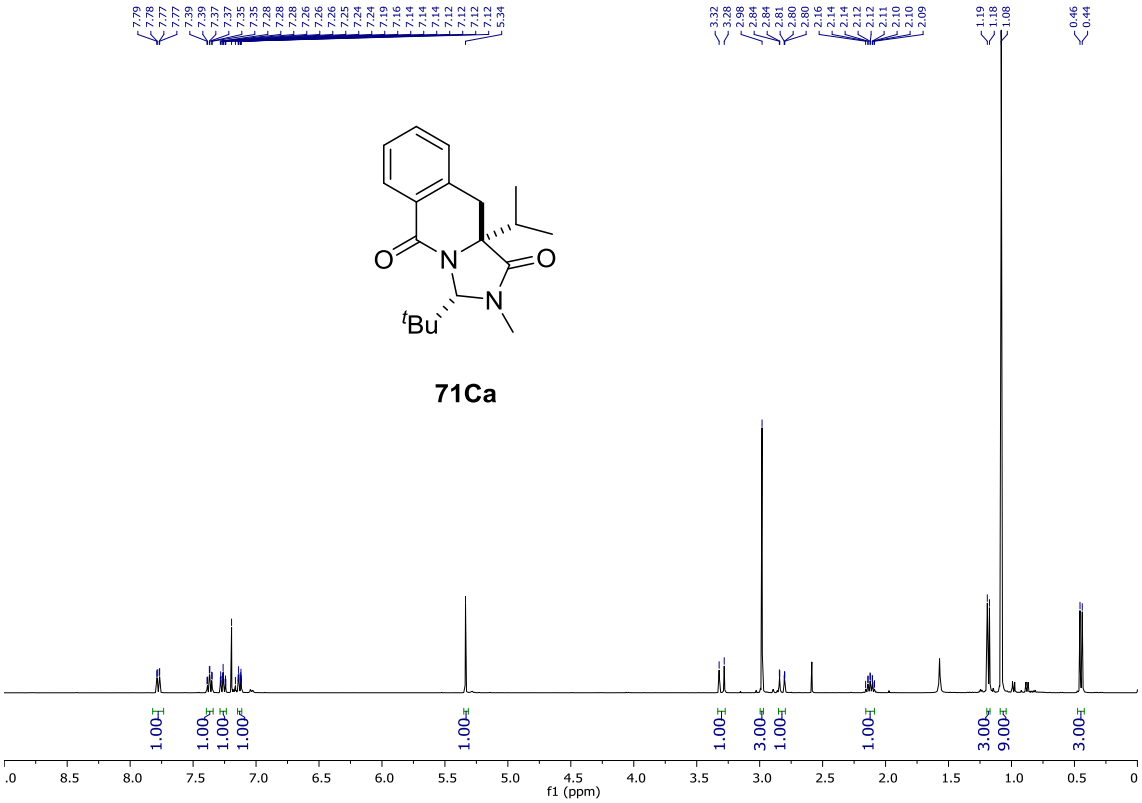
21.84
f1 (ppm)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2.84
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2.14
2.14
2.12
2.12
2.11
2.10
2.10
2.09
1.19
1.18
1.08
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O
N
O
N
tBu
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1.00
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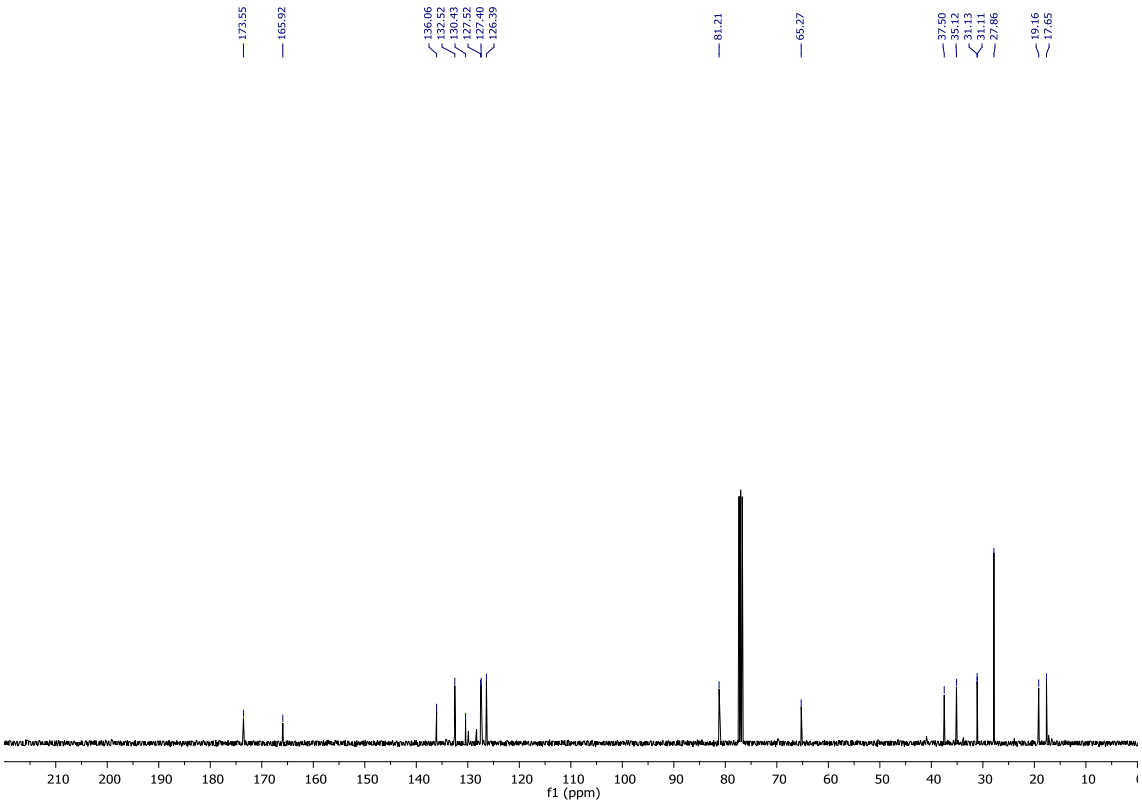
1.00
1.00
3.00
9.00
3.00
f1 (ppm)

71Ca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27.86
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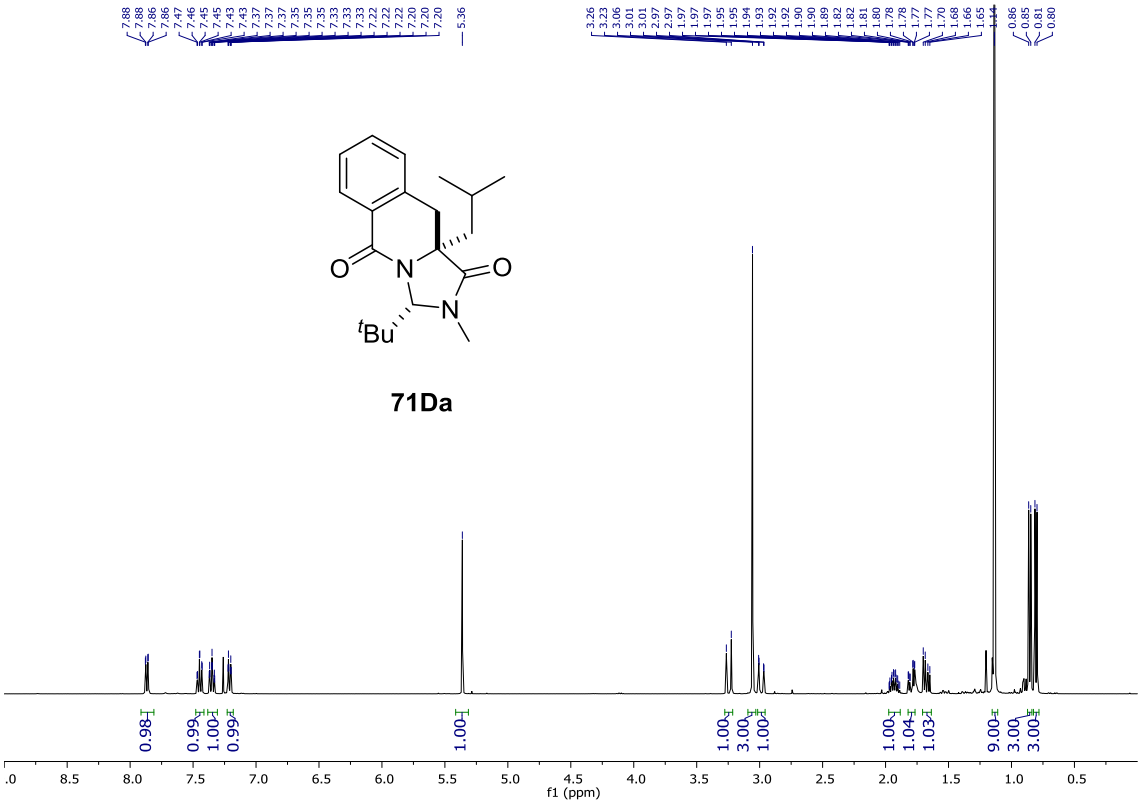
17.65
f1 (ppm)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3.06
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0.80
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71Da
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1.00
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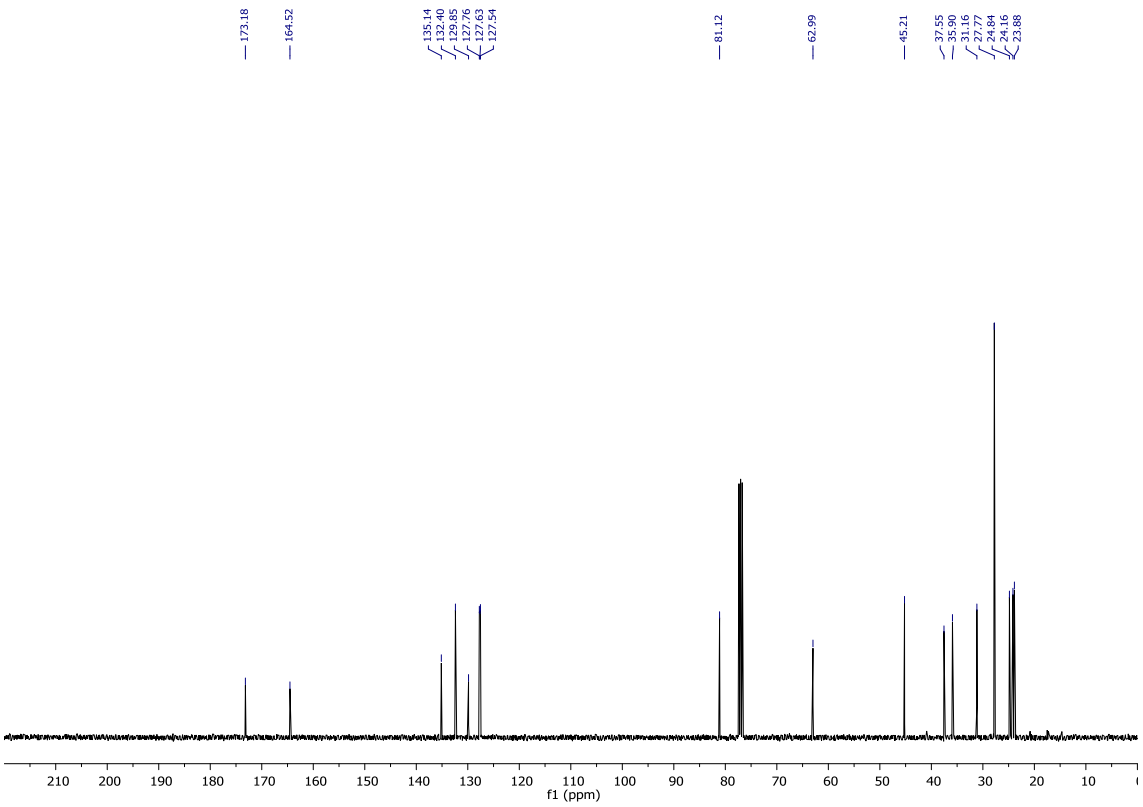
3.00
f1 (ppm)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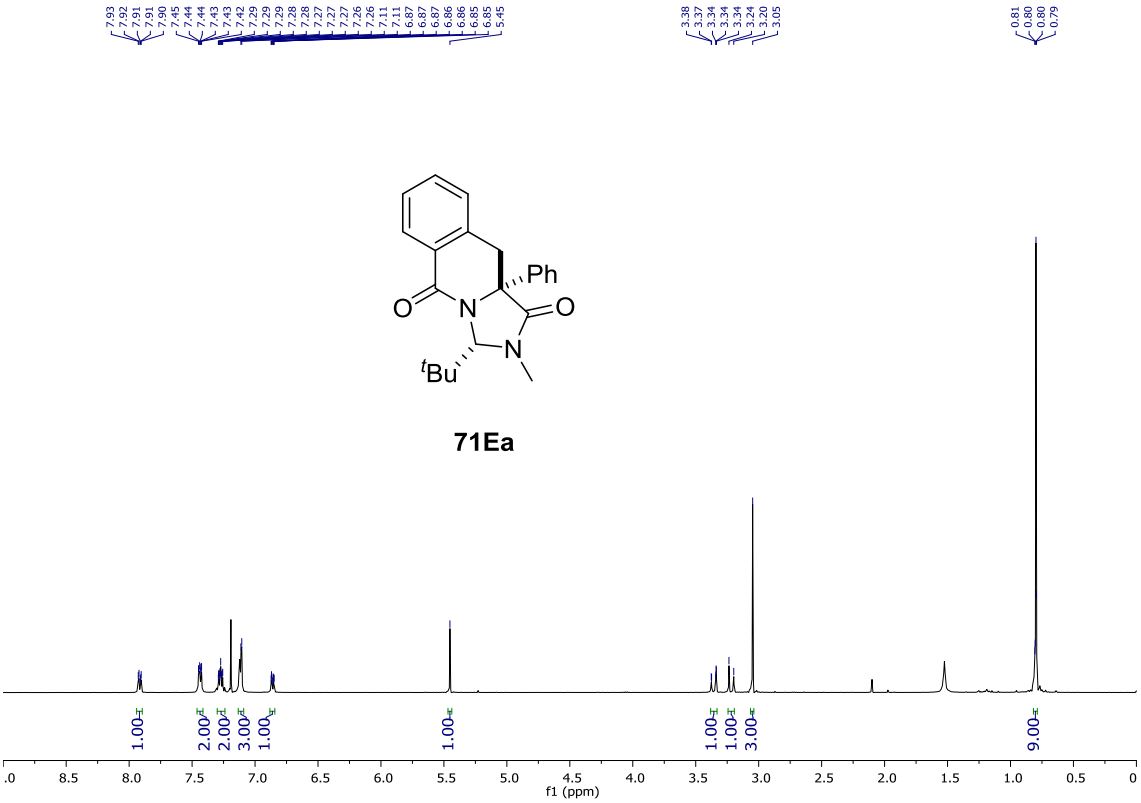
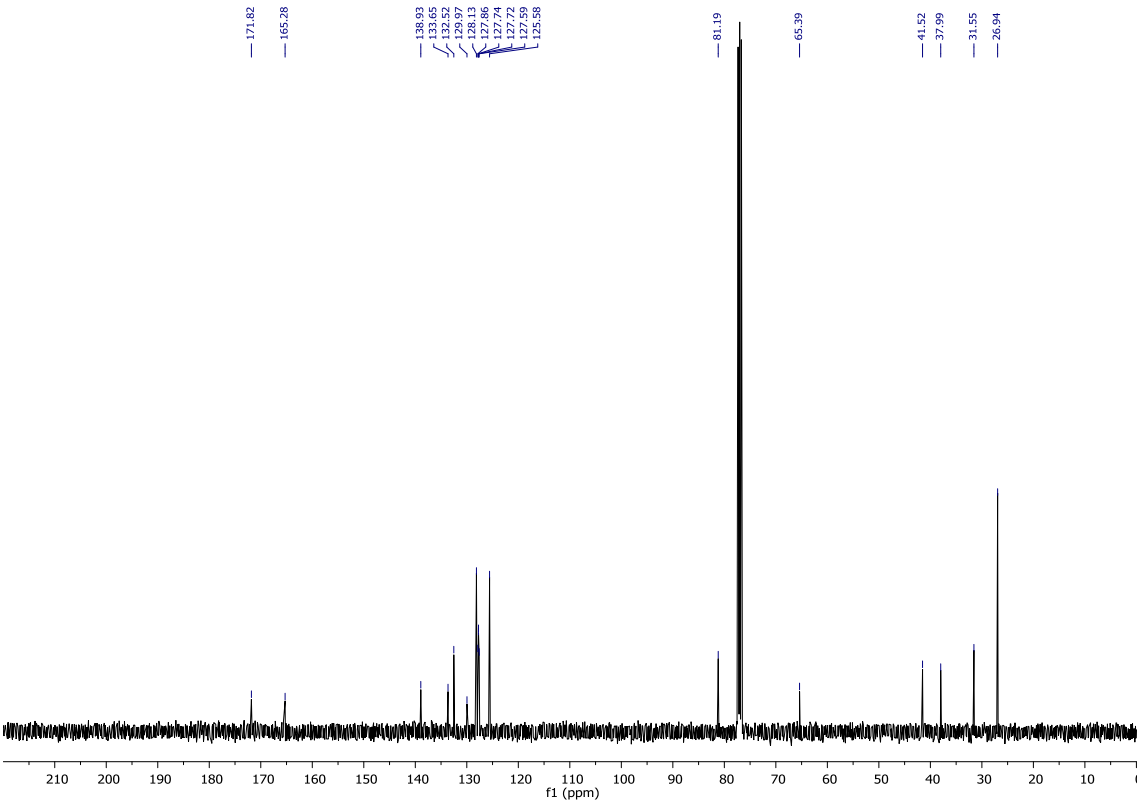
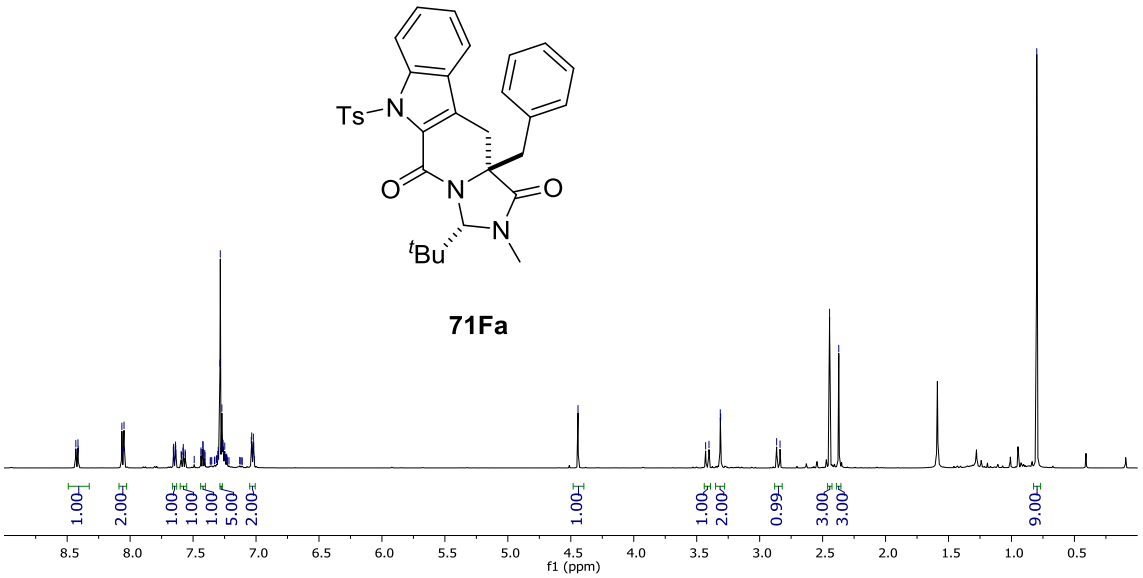
37.55
35.90
31.16
27.77
24.84
24.16
23.88
f1 (ppm)


7.93
7.92
7.91
7.91
7.90
7.45
7.44
7.44
7.43
7.43
7.42
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.11
6.87
6.87
6.87
6.86
6.86
6.85
6.85
5.45
3.38
3.37
3.34
3.34
3.34
3.24
3.20
3.05
0.81
0.80
0.80
0.79
Ph
O
N
O
N
tBu
1.00
2.00
2.00
3.00
1.00
1.00
1.00
3.00
9.00
f1 (ppm)

71Ea


171.82
165.28
138.93
133.65
132.52
129.97
128.13
127.86
127.74
127.72
127.59
125.58
81.19
65.39
41.52
37.99
31.55
26.94
f1 (ppm)


Ts
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O
N
O
N
tBu
71Fa
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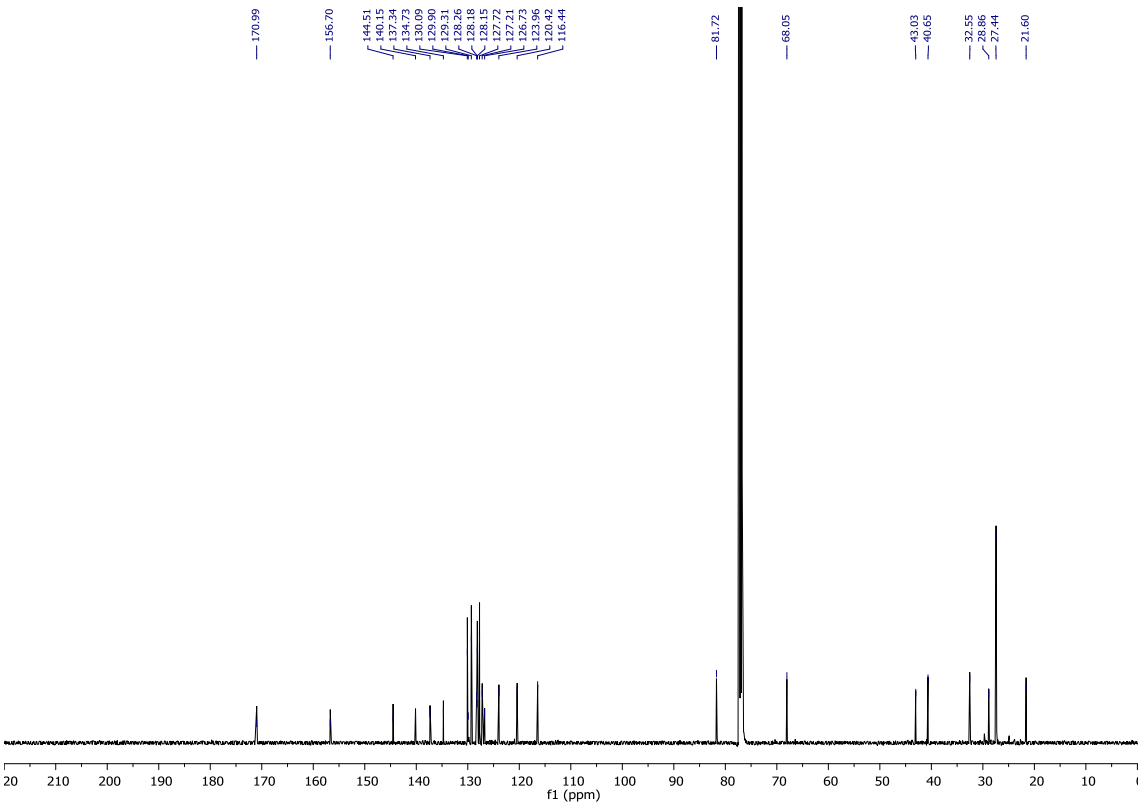
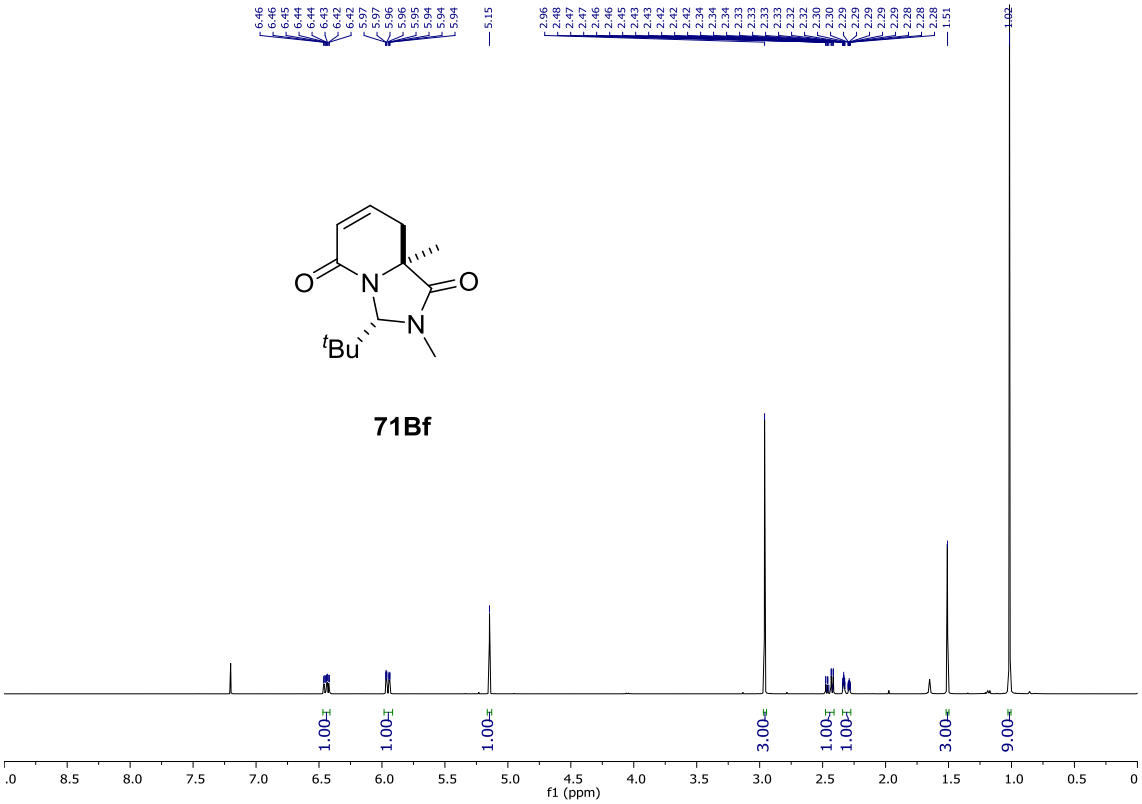
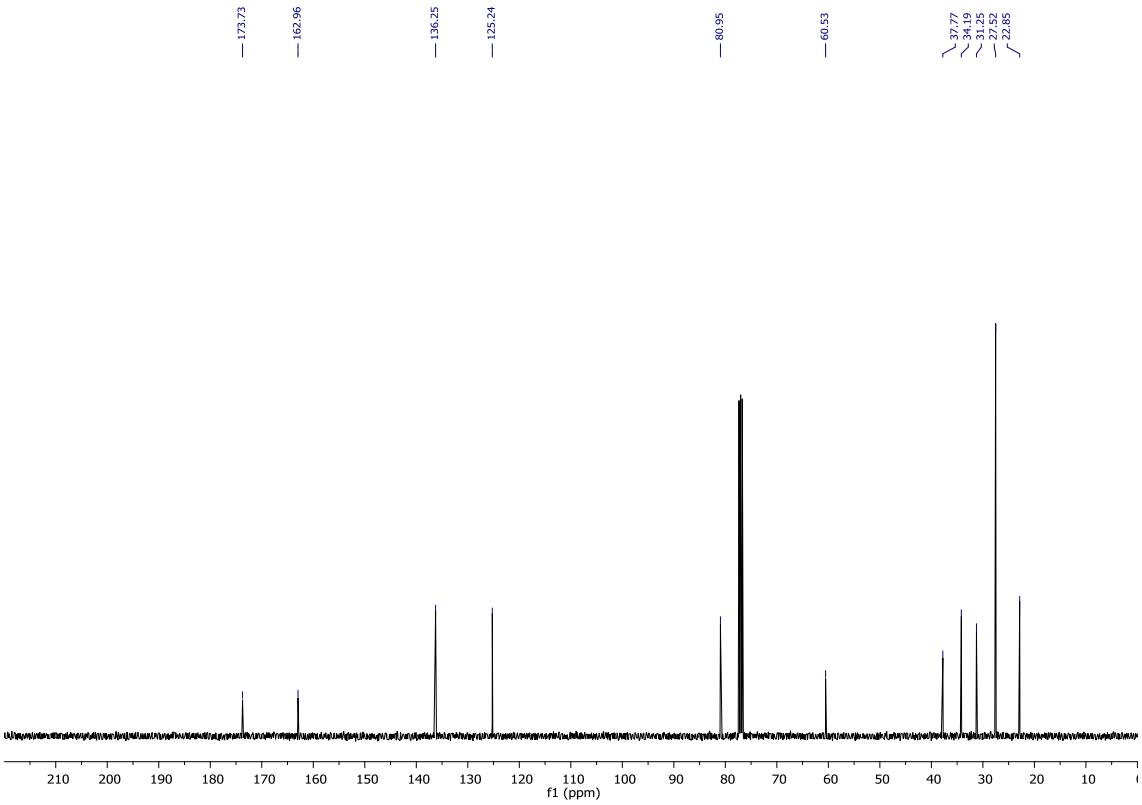
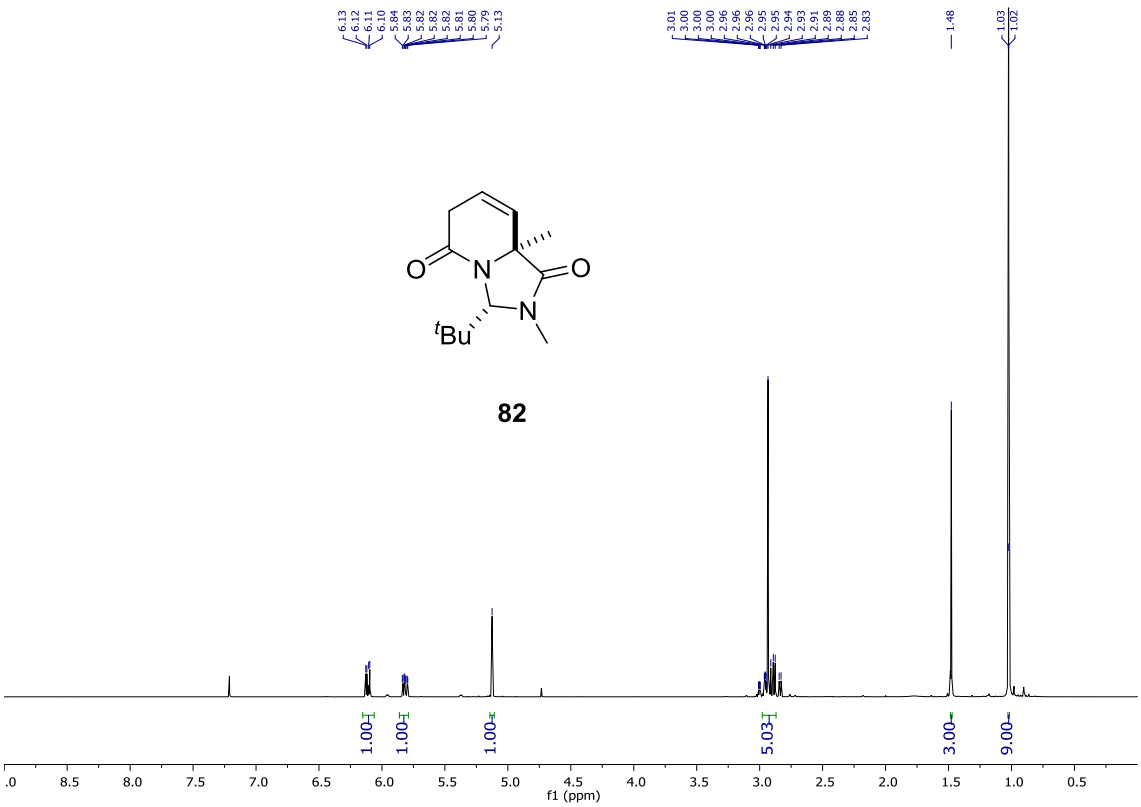
2.00
1.00
1.00
1.00
5.00
2.00
1.00
1.00
2.00
0.99
3.00
3.00
9.00
f1 (ppm)

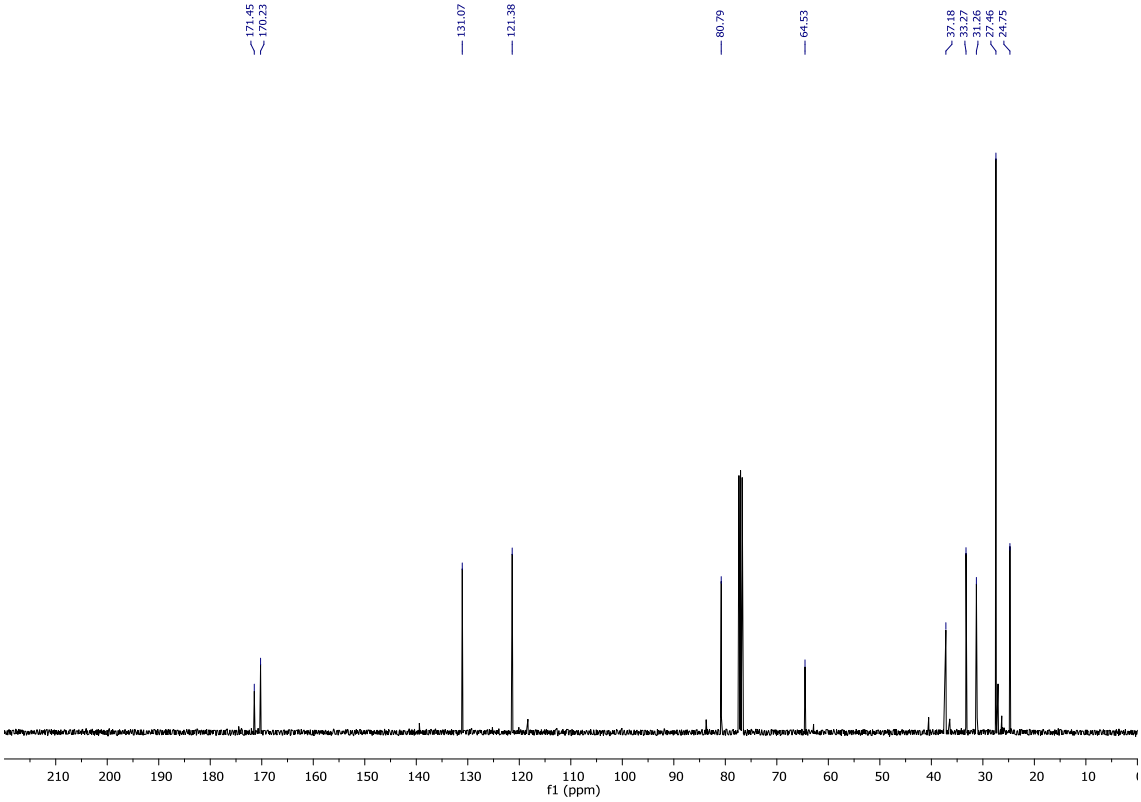

170.99
156.70
144.51
140.15
137.34
134.73
130.09
129.90
129.31
128.26
128.18
128.15
127.72
127.21
126.73
123.96
120.42
116.44
81.72
68.05
43.03
40.65
32.55
28.86
27.44
21.60
f1 (ppm)


71Bf
f1 (ppm)


f1 (ppm)


6.13
6.12
6.11
6.10
5.84
5.83
5.82
5.82
5.82
5.81
5.80
5.79
5.13
3.01
3.00
3.00
3.00
2.96
2.96
2.96
2.95
2.95
2.94
2.93
2.91
2.89
2.88
2.85
2.83
1.48
1.03
1.02
O
N
O
N
tBu
1.00
1.00
1.00
5.03
3.00
9.00
f1 (ppm)

82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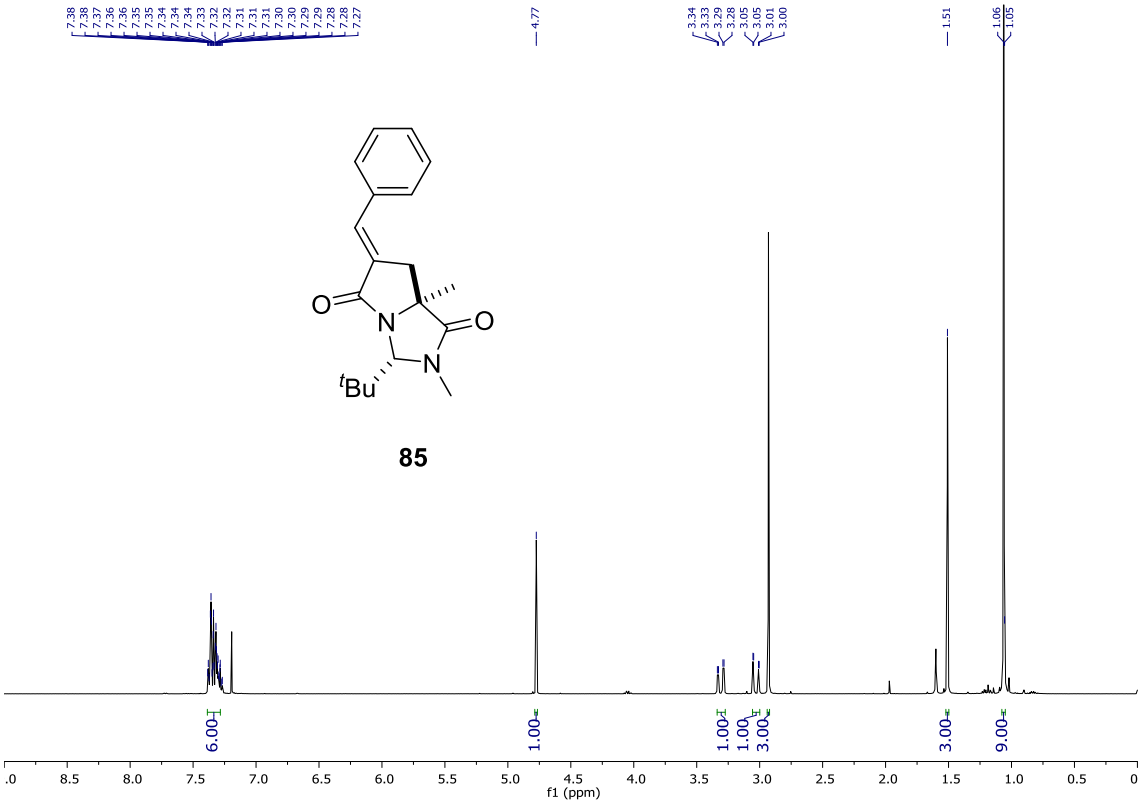
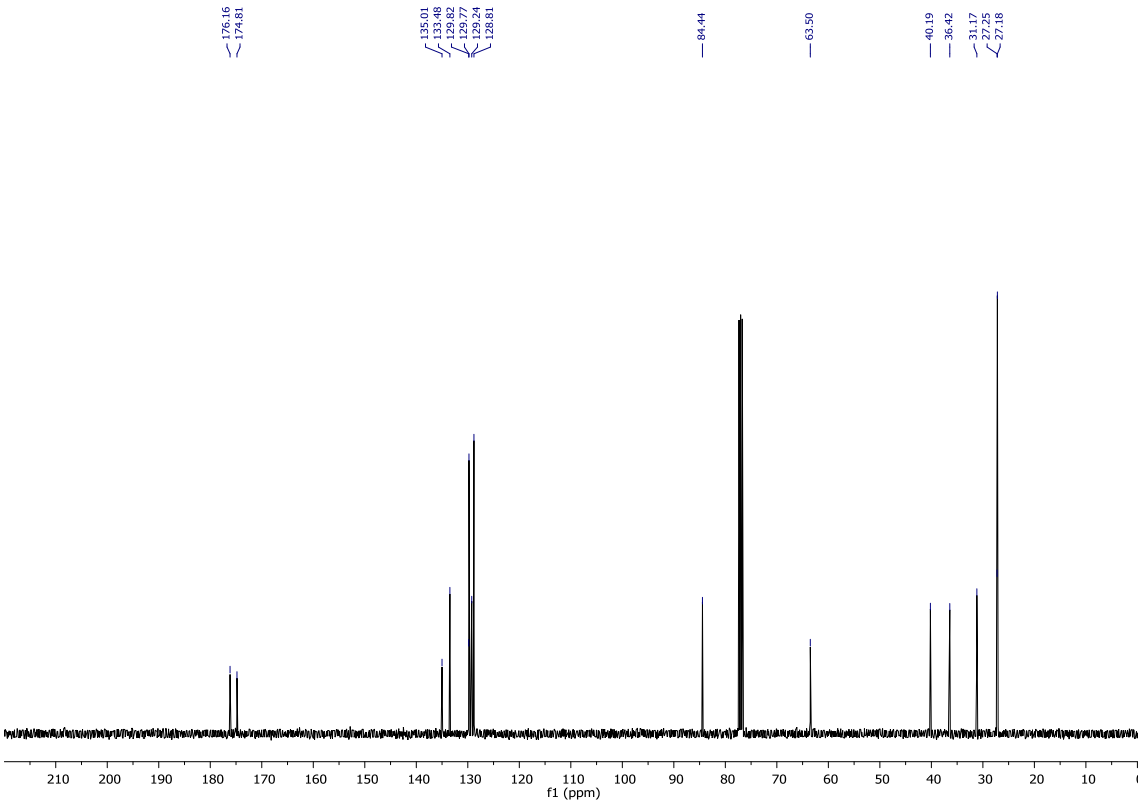
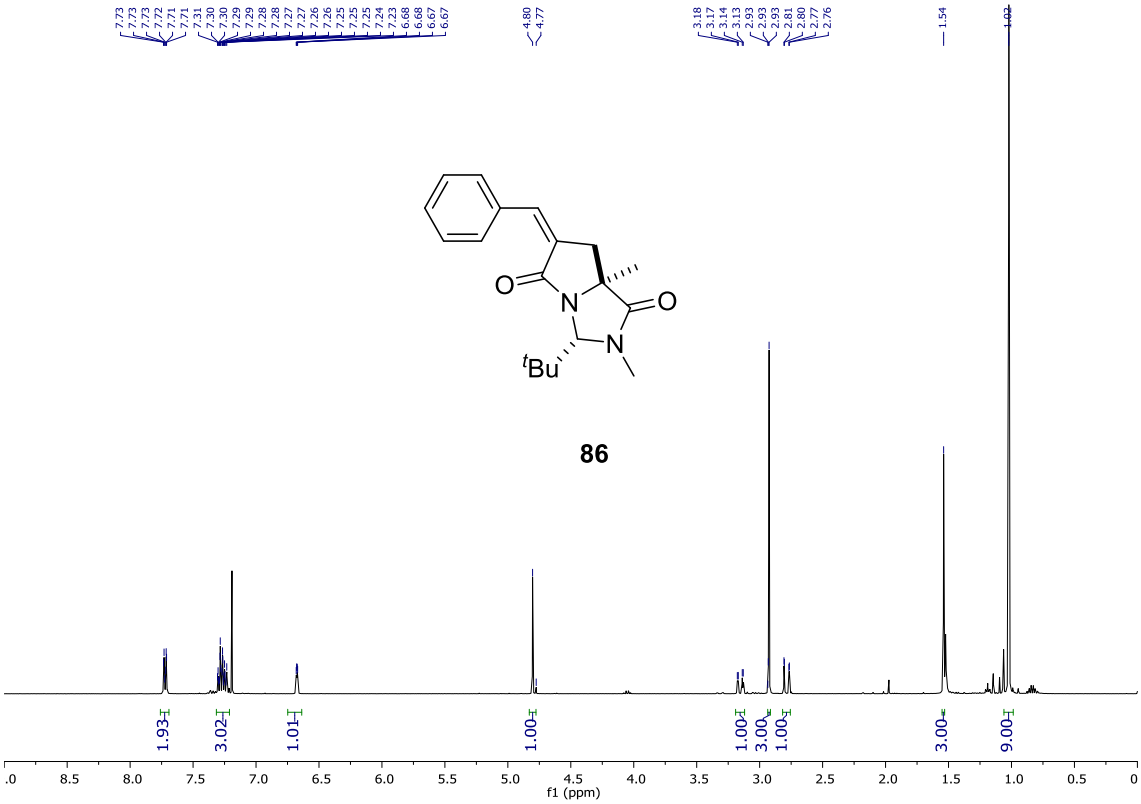
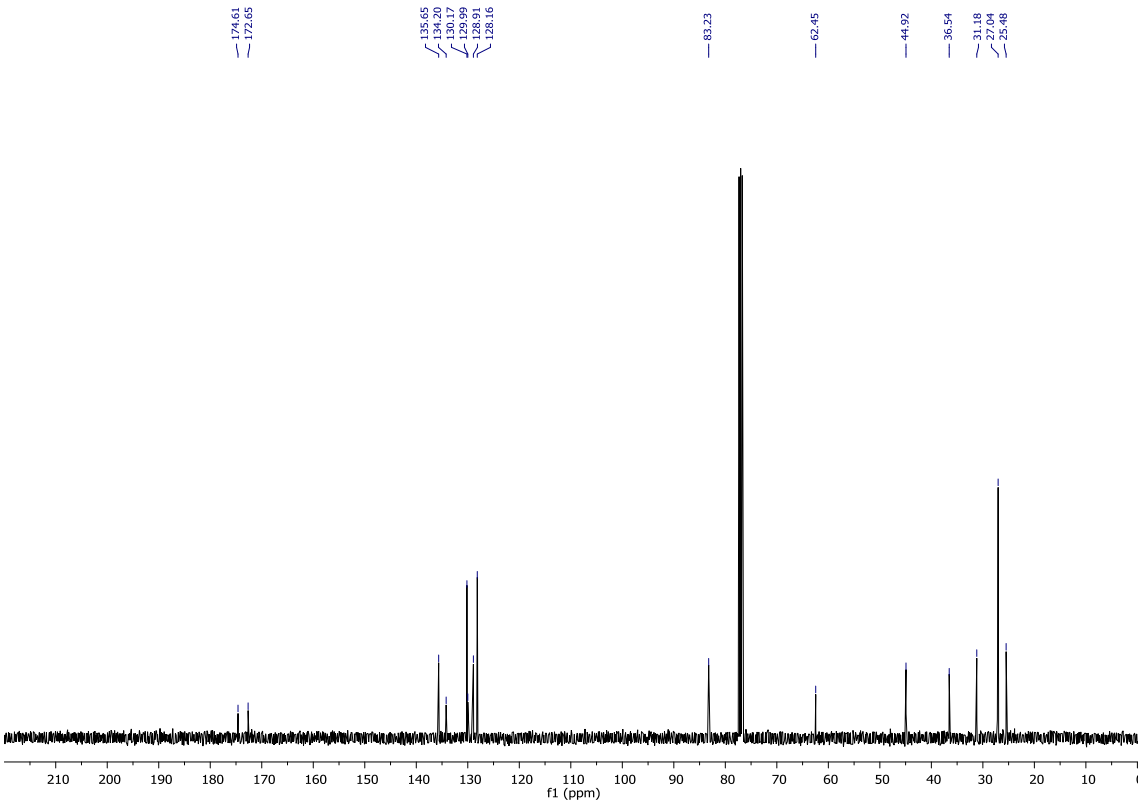
170.23
131.07
121.38
80.79
64.53
37.18
33.27
31.26
27.46
24.75
f1 (ppm)

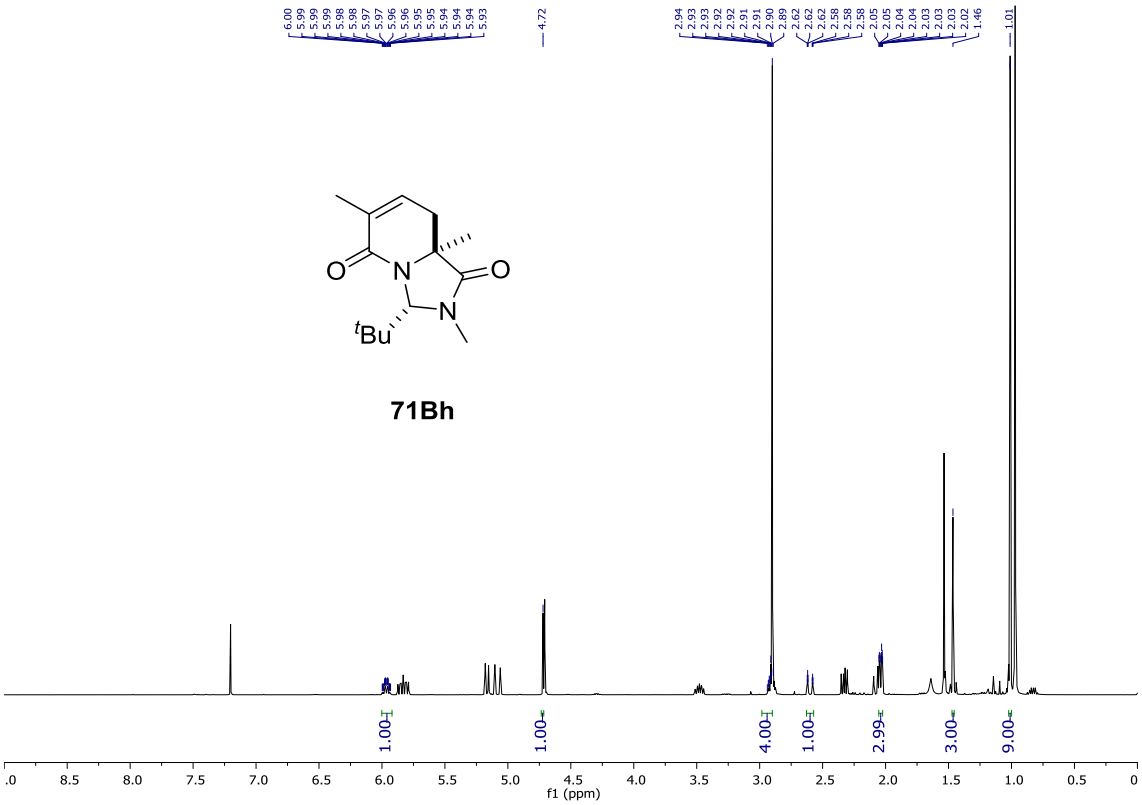

7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
4.77
3.34
3.33
3.29
3.28
3.05
3.05
3.01
3.00
1.51
1.06
1.05
O
N
O
N
tBu
6.00
1.00
1.00
1.00
3.00
3.00
9.00
f1 (ppm)

85


176.16
174.81
135.01
133.48
129.82
129.77
129.24
128.81
84.44
63.50
40.19
36.42
31.17
27.25
27.18
f1 (ppm)


7.73
7.73
7.73
7.72
7.71
7.71
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.23
6.68
6.68
6.67
6.67
4.80
4.77
3.18
3.17
3.14
3.13
2.93
2.93
2.81
2.80
2.77
2.76
1.54
1.02
O
N
O
N
tBu
86
1.93
3.02
1.01
1.00
1.00
3.00
1.00
3.00
9.00
f1 (ppm)


174.61
172.65
135.65
134.20
130.17
129.99
128.91
128.16
83.23
62.45
44.92
36.54
31.18
27.04
25.48
f1 (ppm)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5.99
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5.98
5.97
5.97
5.96
5.96
5.95
5.95
5.94
5.94
5.94
5.93
4.72
2.94
2.93
2.93
2.92
2.92
2.91
2.91
2.90
2.89
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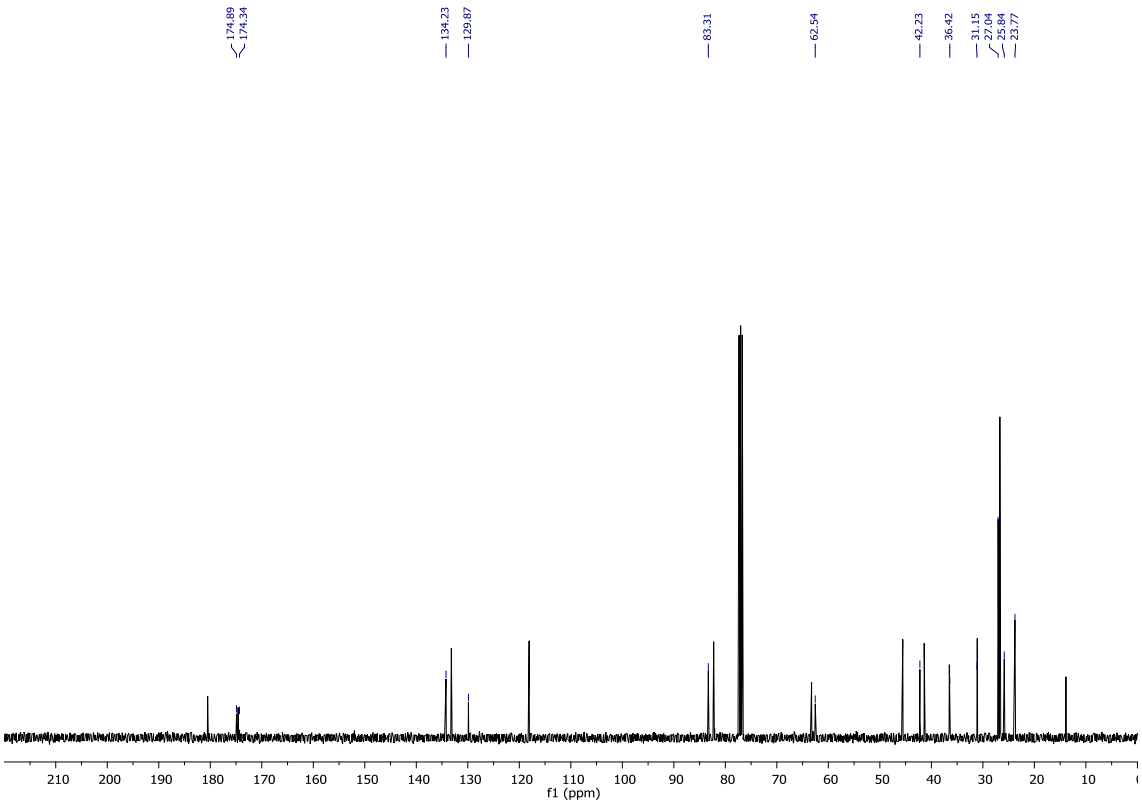
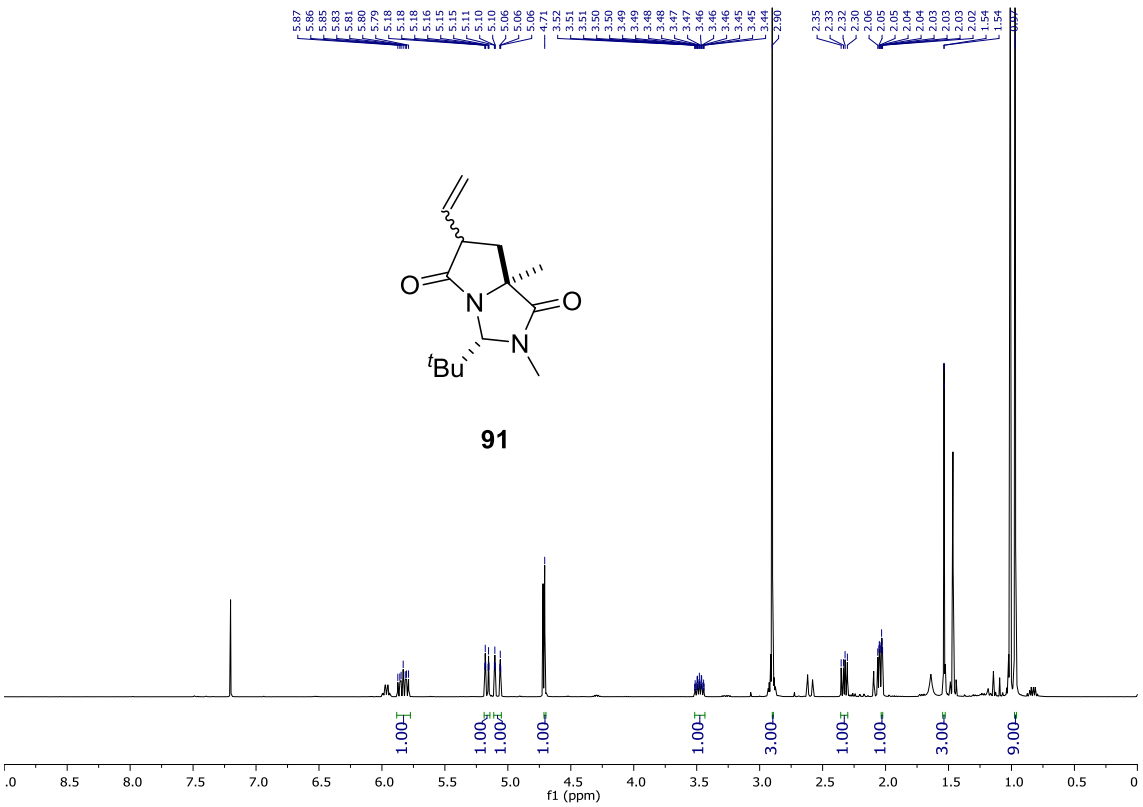
2.62
2.62
2.58
2.58
2.58
2.05
2.05
2.04
2.04
2.03
2.03
2.03
2.02
1.46
1.01
O
N
O
N
tBu
1.00
1.00
4.00
1.00
2.99
3.00
9.00
f1 (ppm)

71Bh


174.89
174.34
134.23
129.87
83.31
62.54
42.23
36.42
31.15
27.04
25.84
23.77
f1 (ppm)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5.86
5.85
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5.81
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5.79
5.18
5.18
5.18
5.16
5.15
5.15
5.11
5.10
5.10
5.06
5.06
5.06
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3.51
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3.47
3.47
3.46
3.46
3.46
3.45
3.45
3.44
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2.33
2.32
2.30
2.06
2.05
2.05
2.04
2.04
2.03
2.03
2.03
2.02
1.54
1.54
O
N
O
N
tBu
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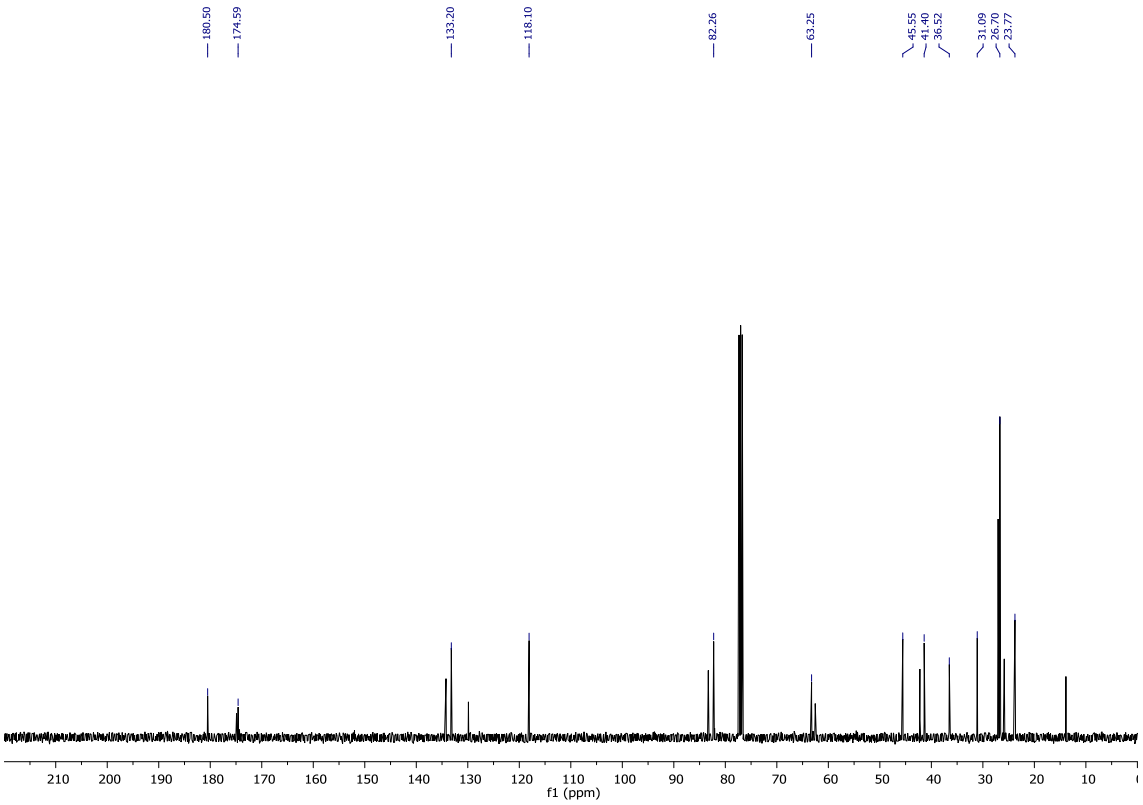
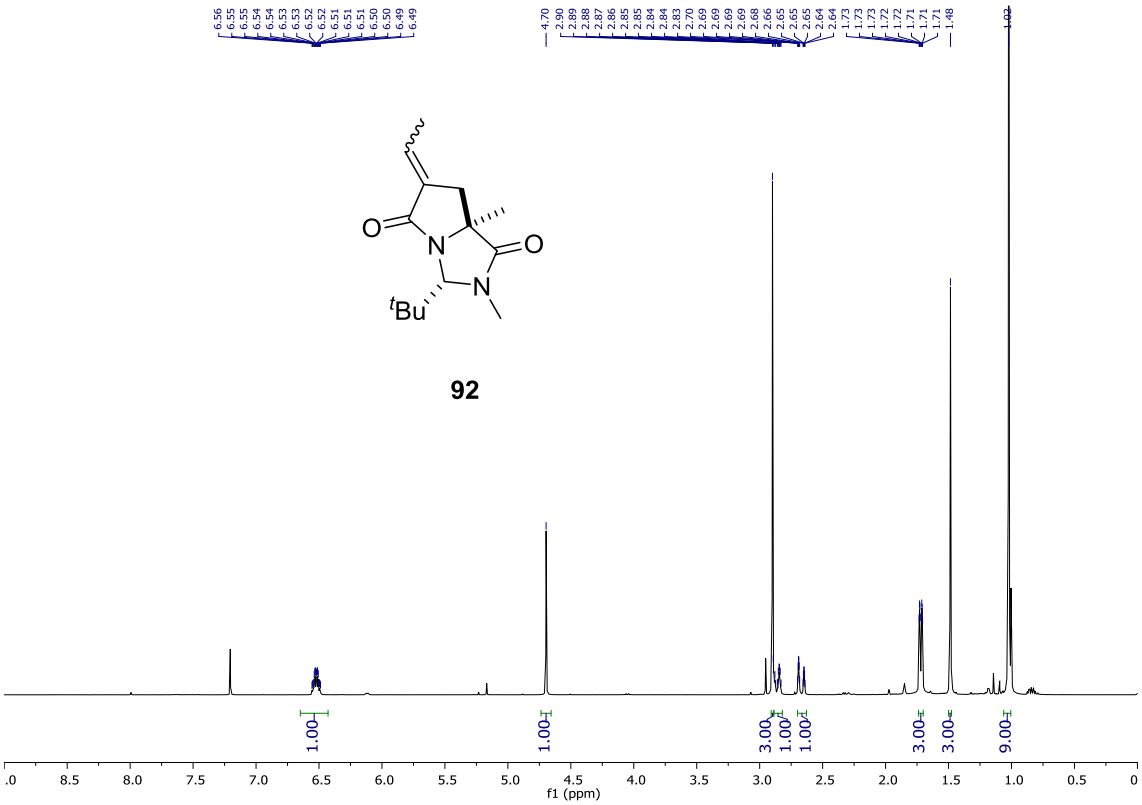
1.00
1.00
3.00
9.00
f1 (ppm)


180.50
174.59
133.20
118.10
82.26
63.25
45.55
41.40
36.52
31.09
26.70
23.77
f1 (ppm)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6.54
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6.53
6.52
6.52
6.51
6.51
6.51
6.50
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6.49
6.49
4.70
2.90
2.89
2.89
2.88
2.87
2.86
2.85
2.85
2.84
2.84
2.83
2.70
2.69
2.69
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2.68
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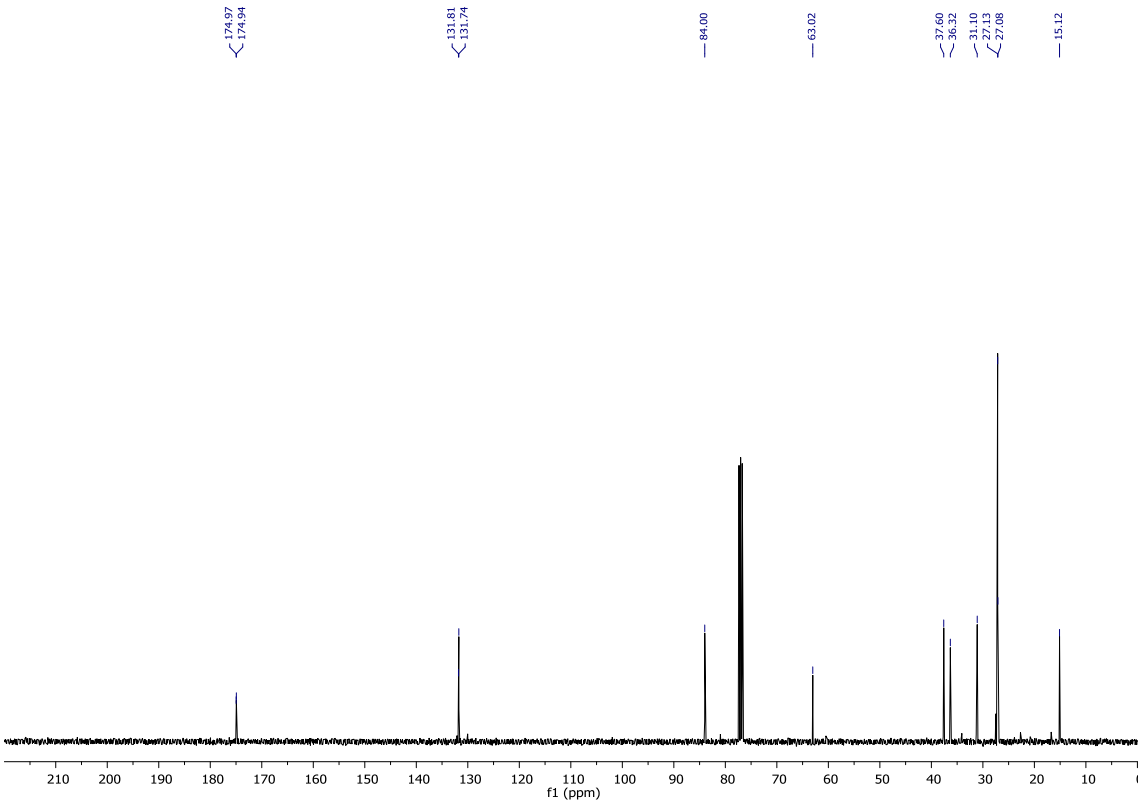
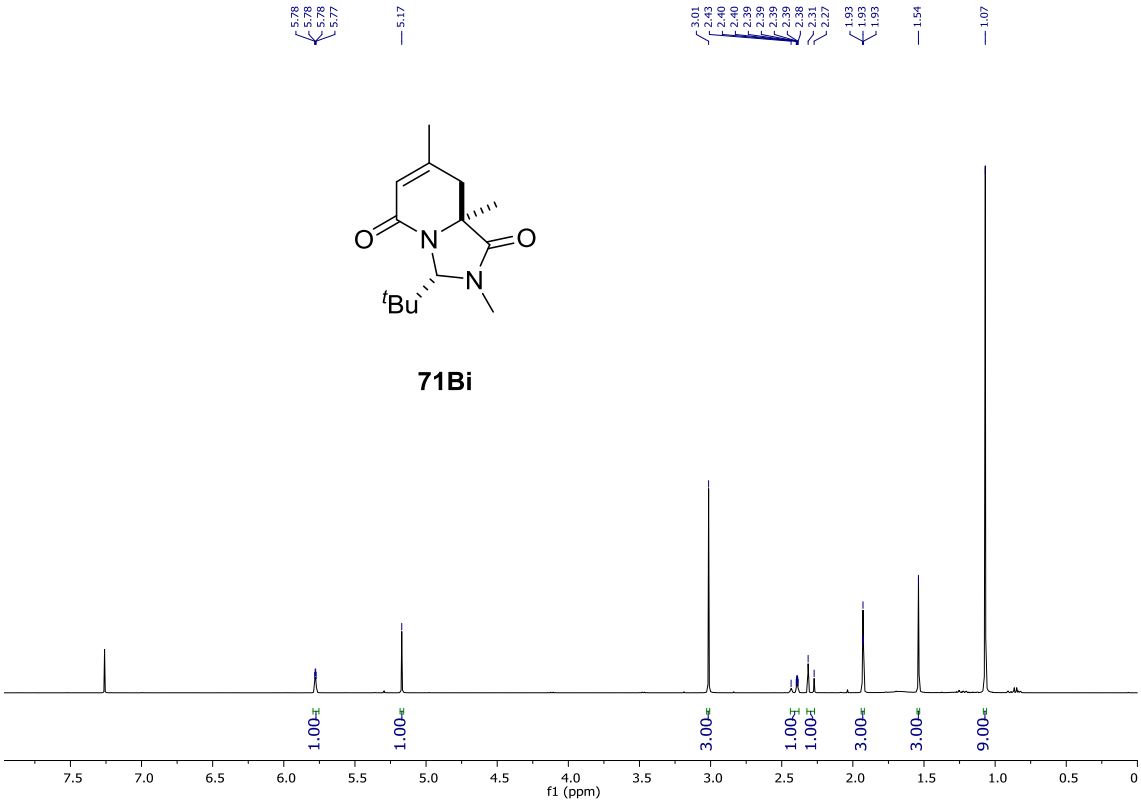
2.65
2.65
2.64
2.64
1.73
1.73
1.73
1.72
1.72
1.71
1.71
1.71
1.48
1.03
O
N
O
N
tBu
1.00
1.00
3.00
1.00
1.00
3.00
3.00
9.00
f1 (ppm)

92


174.97
174.94
131.81
131.74
84.00
63.02
37.60
36.32
31.10
27.13
27.08
15.12
f1 (ppm)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5.78
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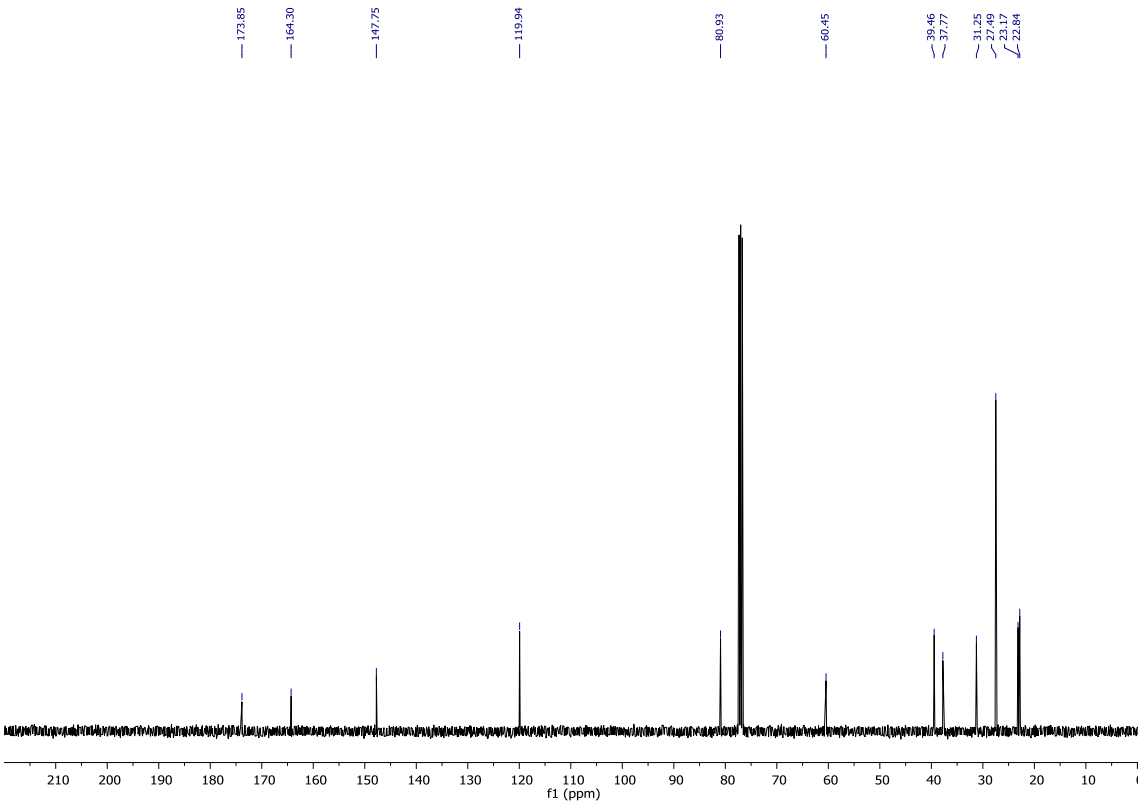
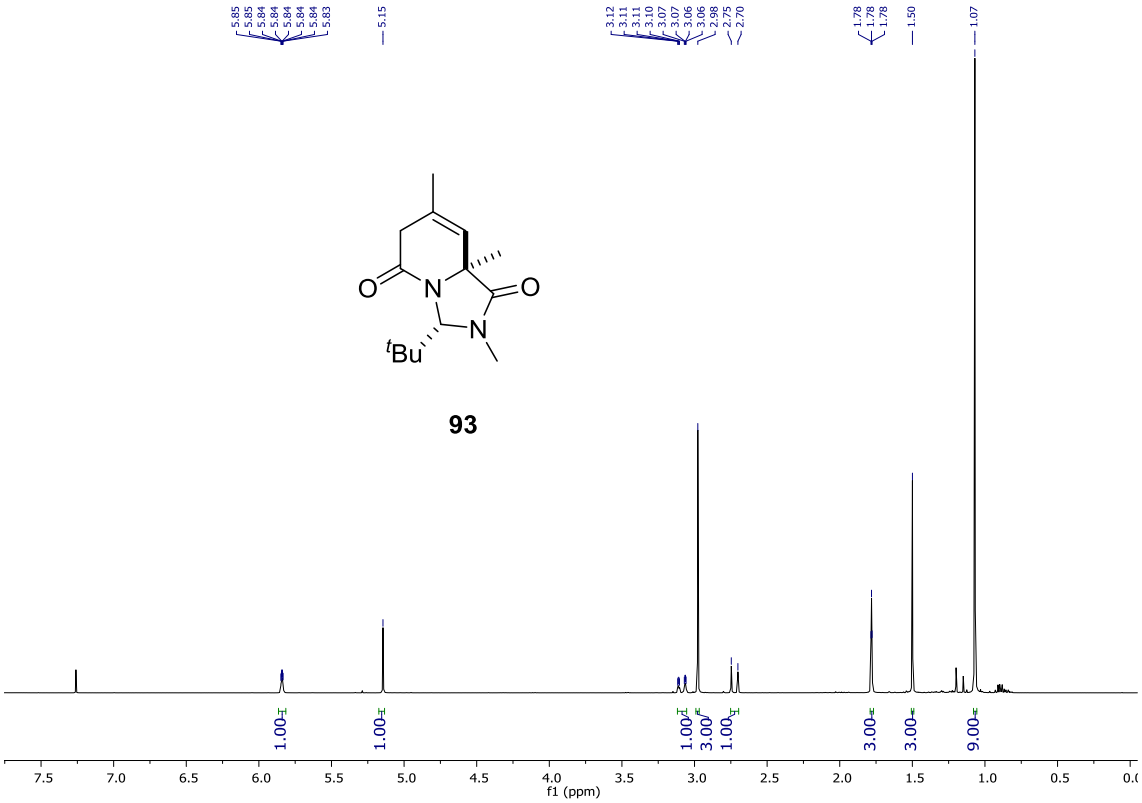
5.17
3.01
2.43
2.40
2.40
2.39
2.39
2.39
2.39
2.38
2.31
2.27
1.93
1.93
1.93
1.54
1.07
O
N
O
N
tBu
1.00
1.00
3.00
1.00
1.00
3.00
3.00
9.00
f1 (ppm)

71Bi


173.85
164.30
147.75
119.94
80.93
60.45
39.46
37.77
31.25
27.49
23.17
22.84
f1 (ppm)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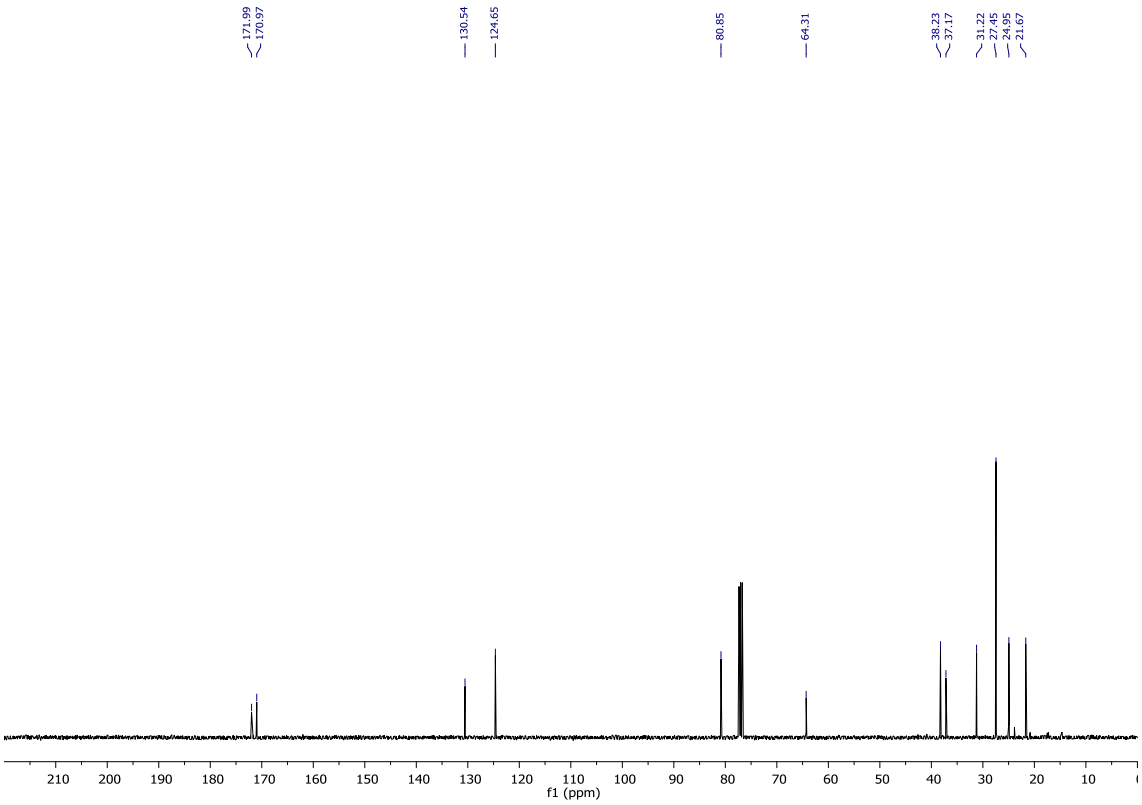
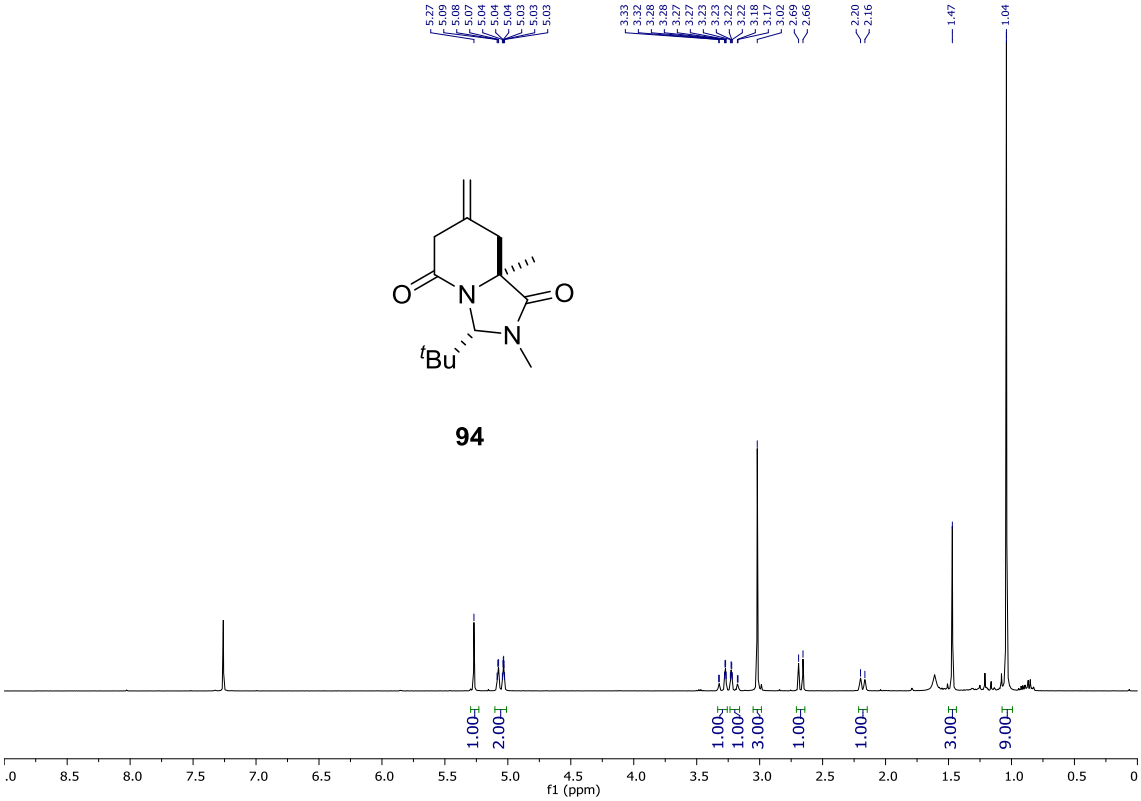
5.85
5.84
5.84
5.84
5.84
5.84
5.83
5.15
3.12
3.11
3.11
3.10
3.07
3.07
3.06
3.06
2.98
2.75
2.70
1.78
1.78
1.78
1.50
1.07
O
N
O
N
tBu
1.00
1.00
1.00
3.00
1.00
3.00
3.00
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

93


171.99
170.97
130.54
124.65
80.85
64.31
38.23
37.17
31.22
27.45
24.95
21.67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


5.27
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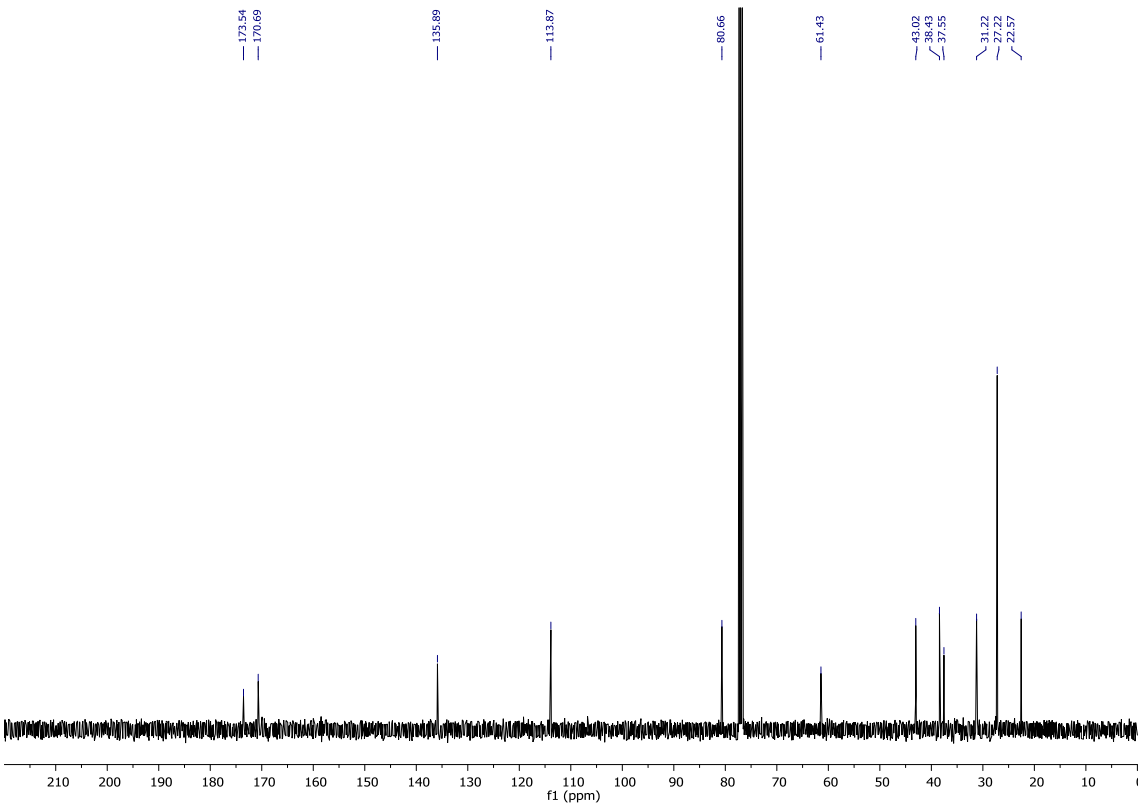
5.08
5.07
5.04
5.04
5.04
5.03
5.03
5.03
3.33
3.32
3.28
3.28
3.27
3.27
3.23
3.23
3.22
3.22
3.18
3.17
3.02
2.69
2.66
2.20
2.16
1.47
1.04
O
N
O
N
tBu
1.00
2.00
1.00
1.00
3.00
1.00
1.00
3.00
9.00
f1 (ppm)

94


173.54
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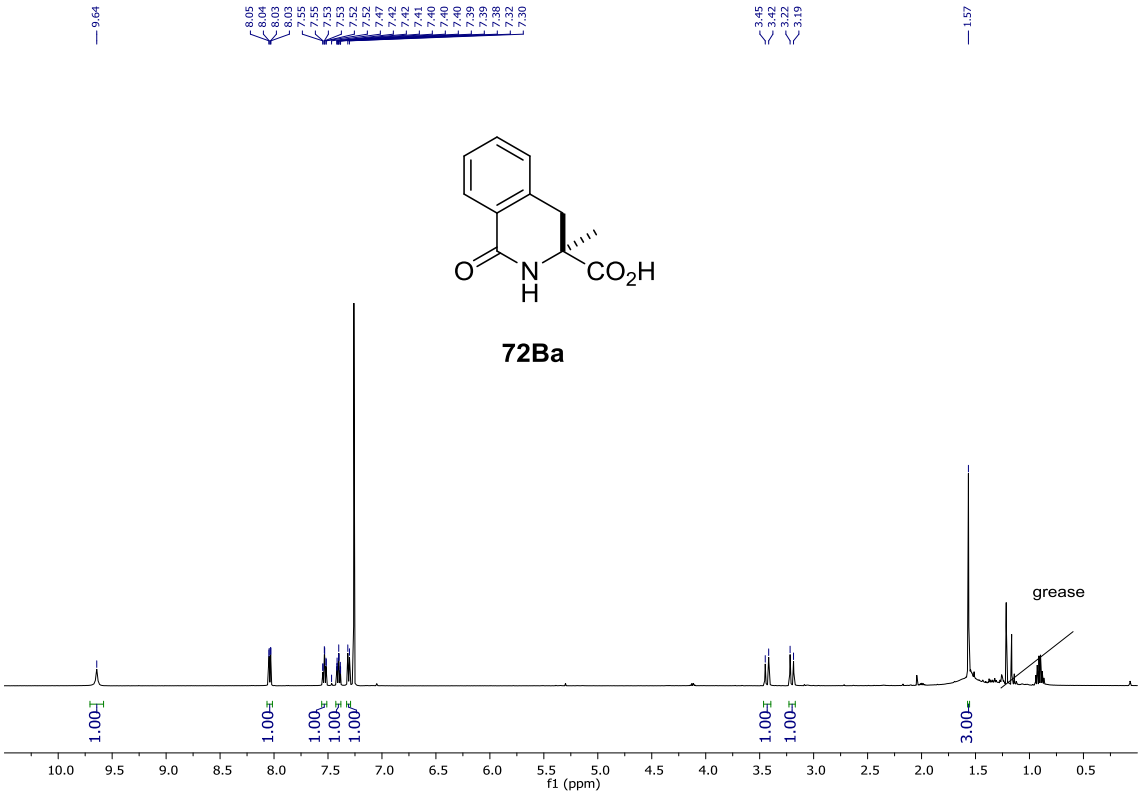
135.89
113.87
80.66
61.43
43.02
38.43
37.55
31.22
27.22
22.57
f1 (ppm)


9.64
8.05
8.04
8.03
7.55
7.53
7.52
7.47
7.42
7.41
7.40
7.39
7.38
7.32
7.30
3.45
3.42
3.22
3.19
1.57
O
N
H
CO2H
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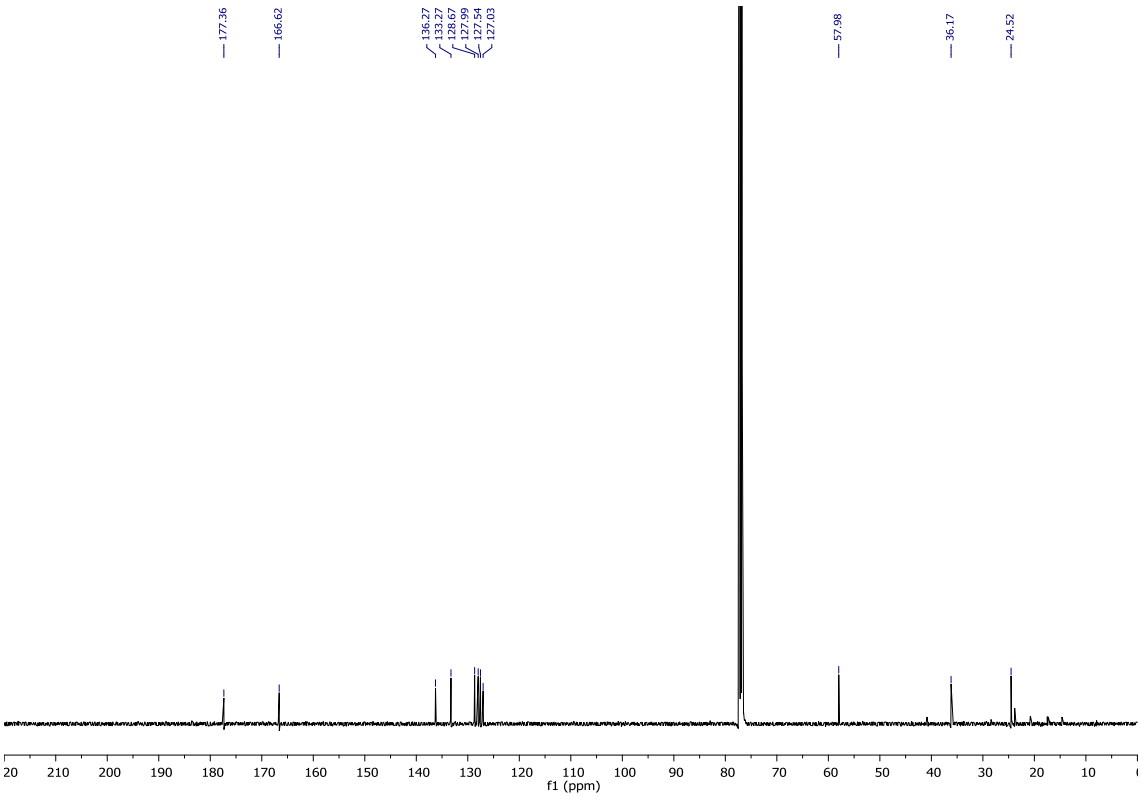
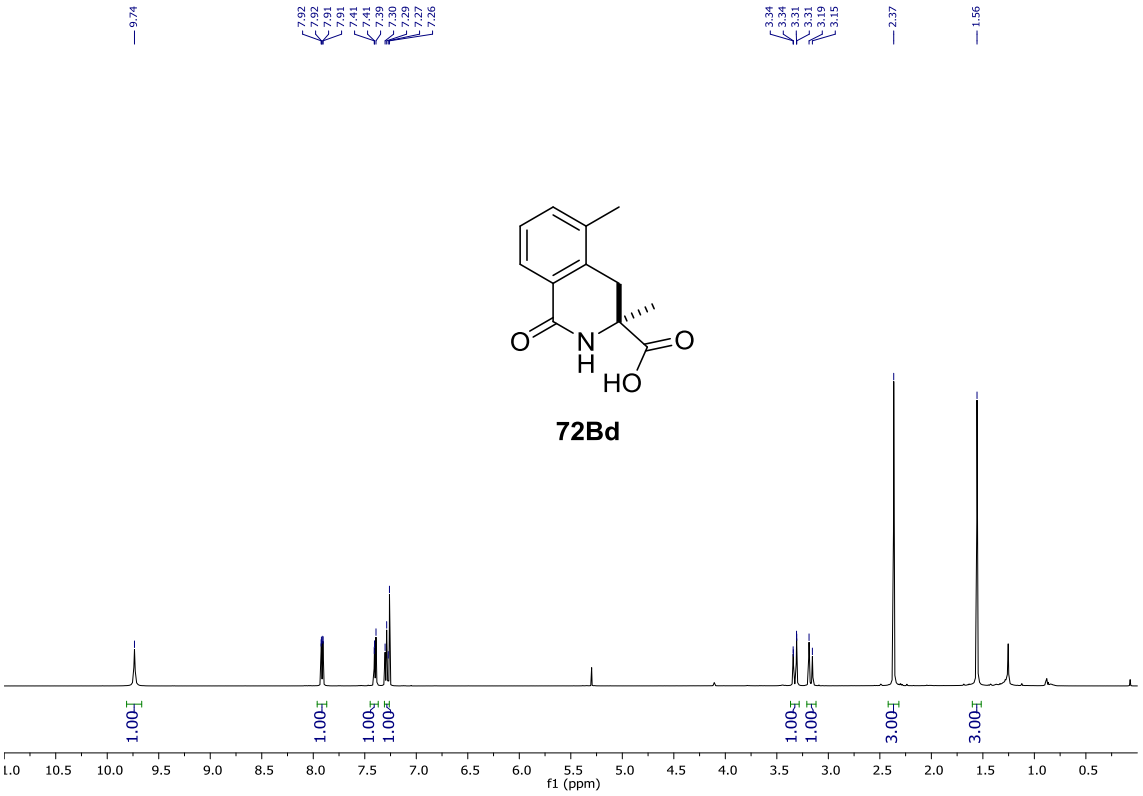
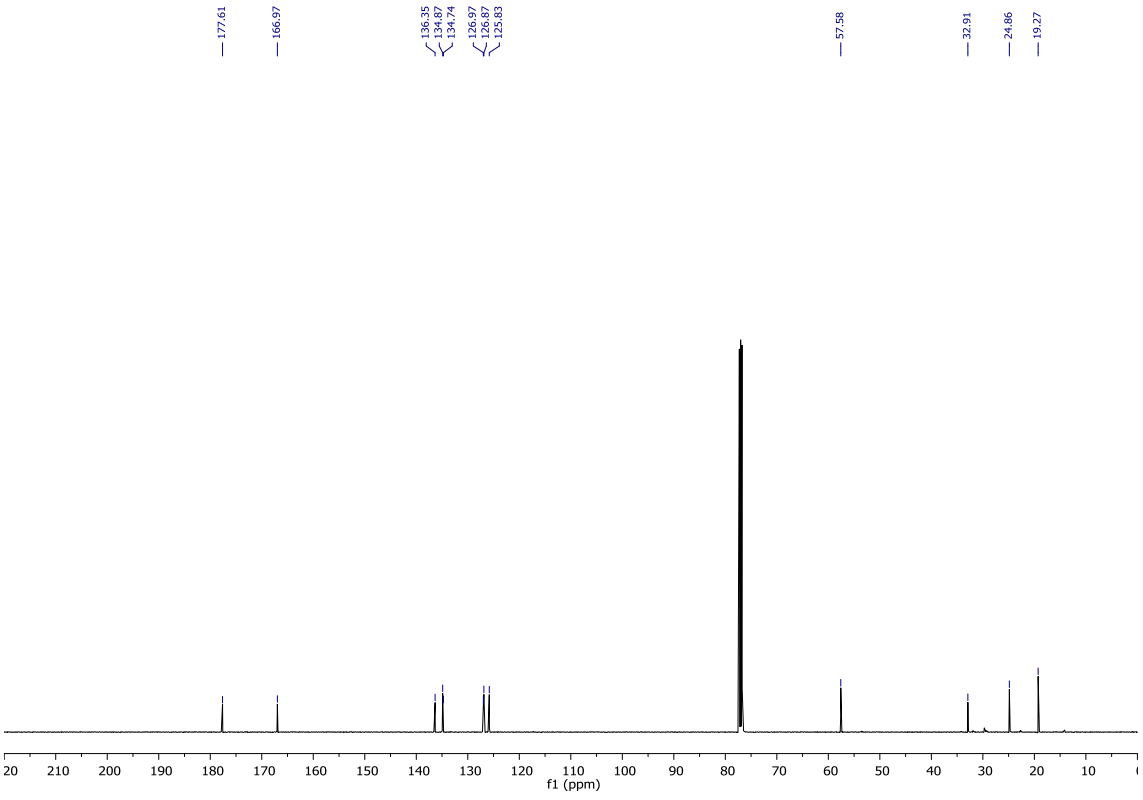
1.00
1.00
1.00
1.00
1.00
3.00
f1 (ppm)

72Ba


177.36
166.62
136.27
133.27
128.67
127.99
127.54
127.03
57.98
36.17
24.52
f1 (ppm)


9.74
7.92
7.92
7.91
7.91
7.41
7.41
7.39
7.30
7.29
7.27
7.26
3.34
3.34
3.31
3.31
3.19
3.15
2.37
1.56
O
N
H
HO
O
72Bd
1.00
1.00
1.00
1.00
1.00
1.00
3.00
3.00
f1 (ppm)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32.91
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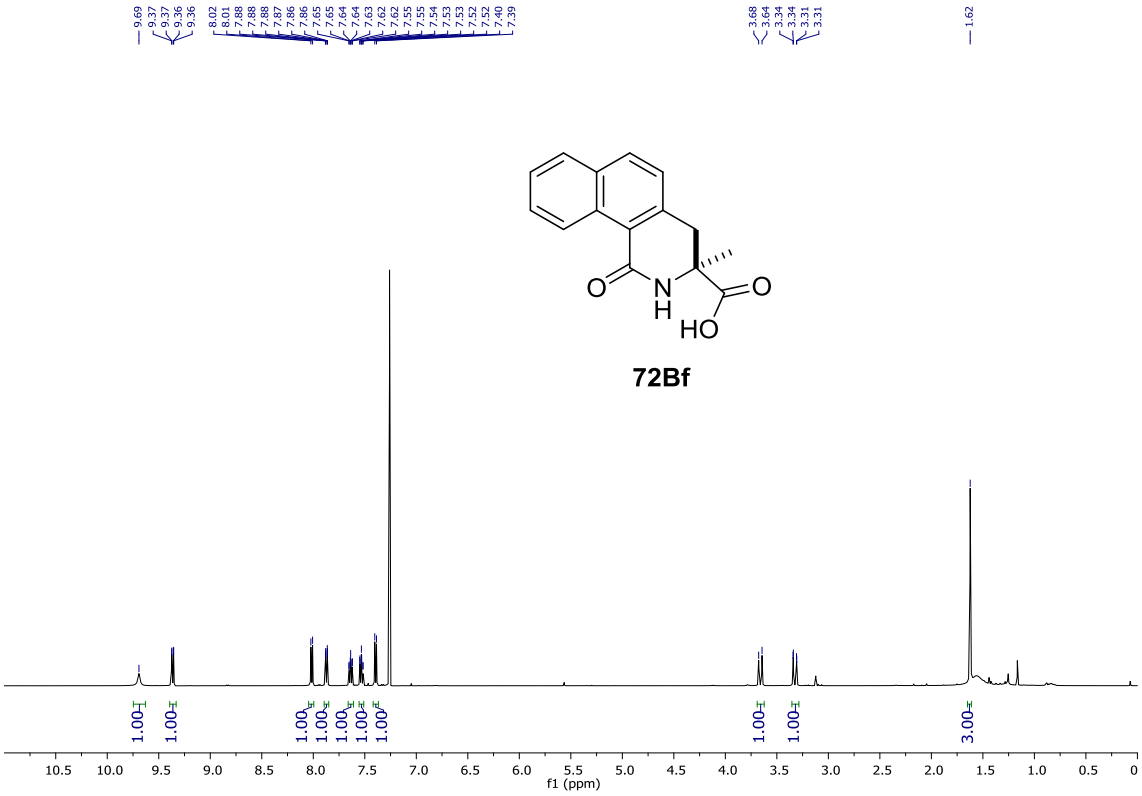
19.27
f1 (ppm)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9.36
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7.88
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7.88
7.87
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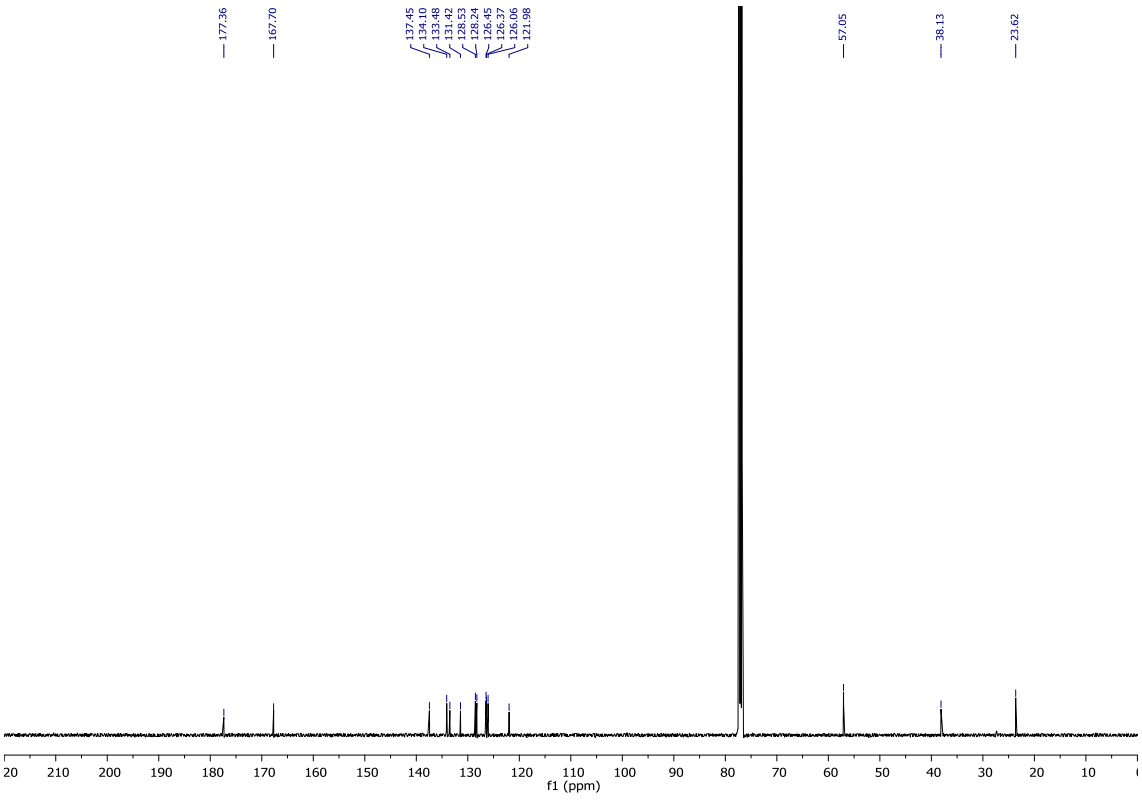
7.86
7.65
7.65
7.64
7.64
7.63
7.62
7.62
7.55
7.54
7.53
7.53
7.52
7.52
7.40
7.39
3.68
3.64
3.34
3.34
3.31
3.31
1.62
O
N
H
O
HO
1.00
1.00
1.00
1.00
1.00
1.00
1.00
1.00
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

72Bf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133.48
131.42
128.53
128.24
126.45
126.37
126.06
121.98
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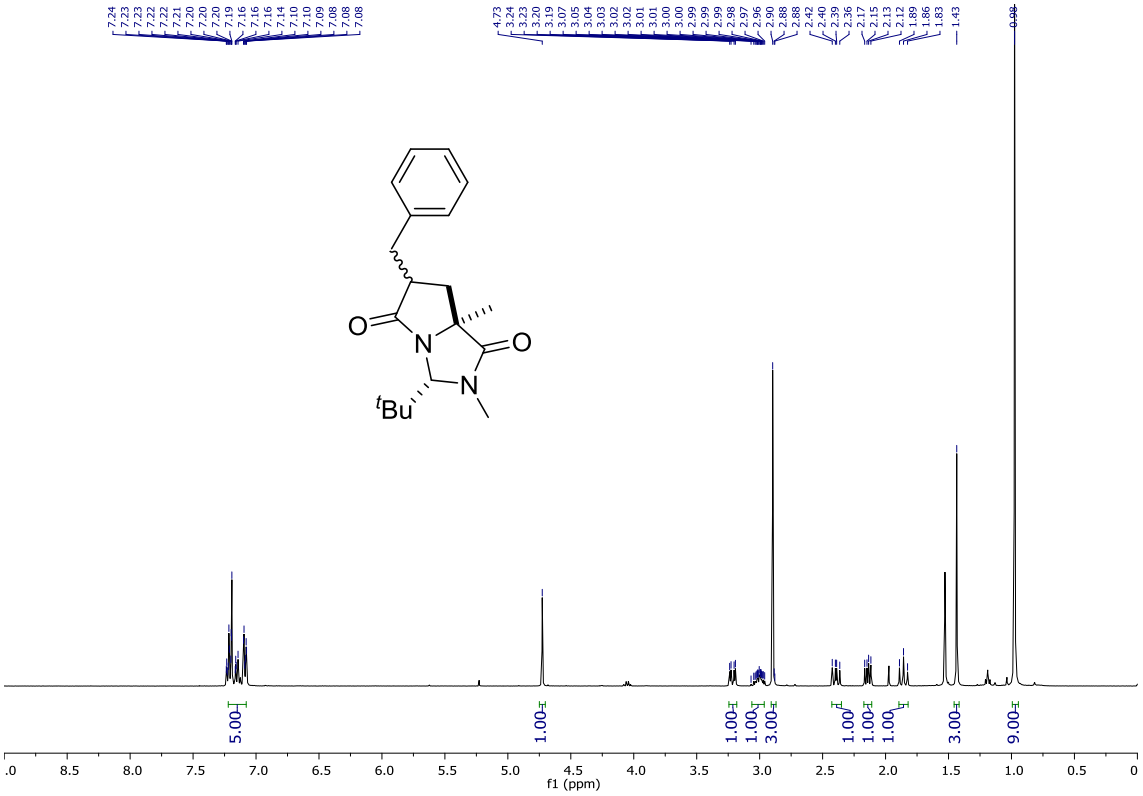
38.13
23.62
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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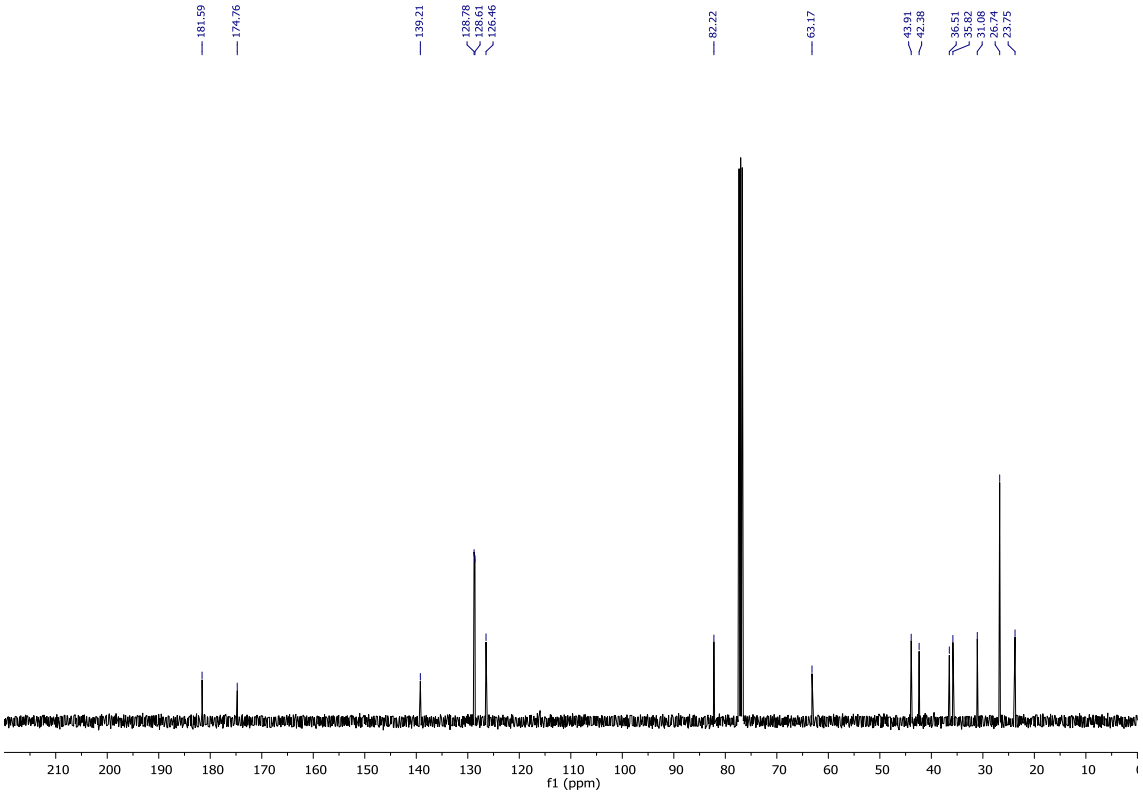
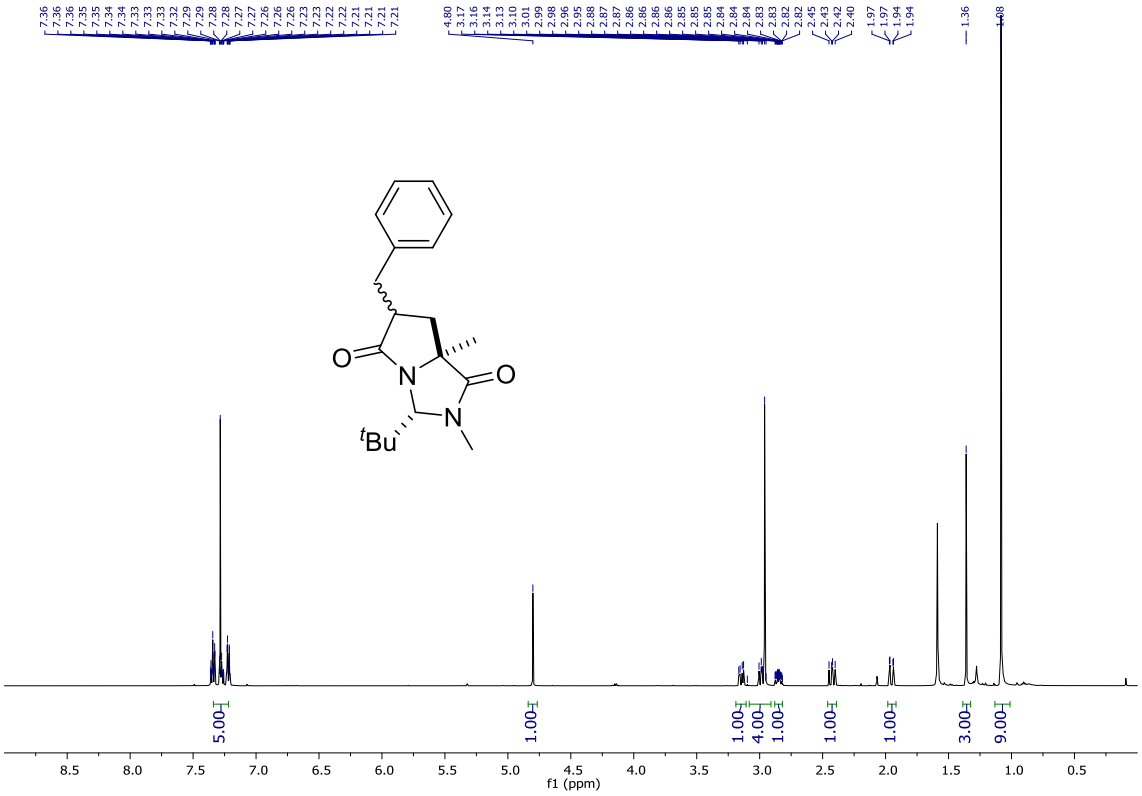
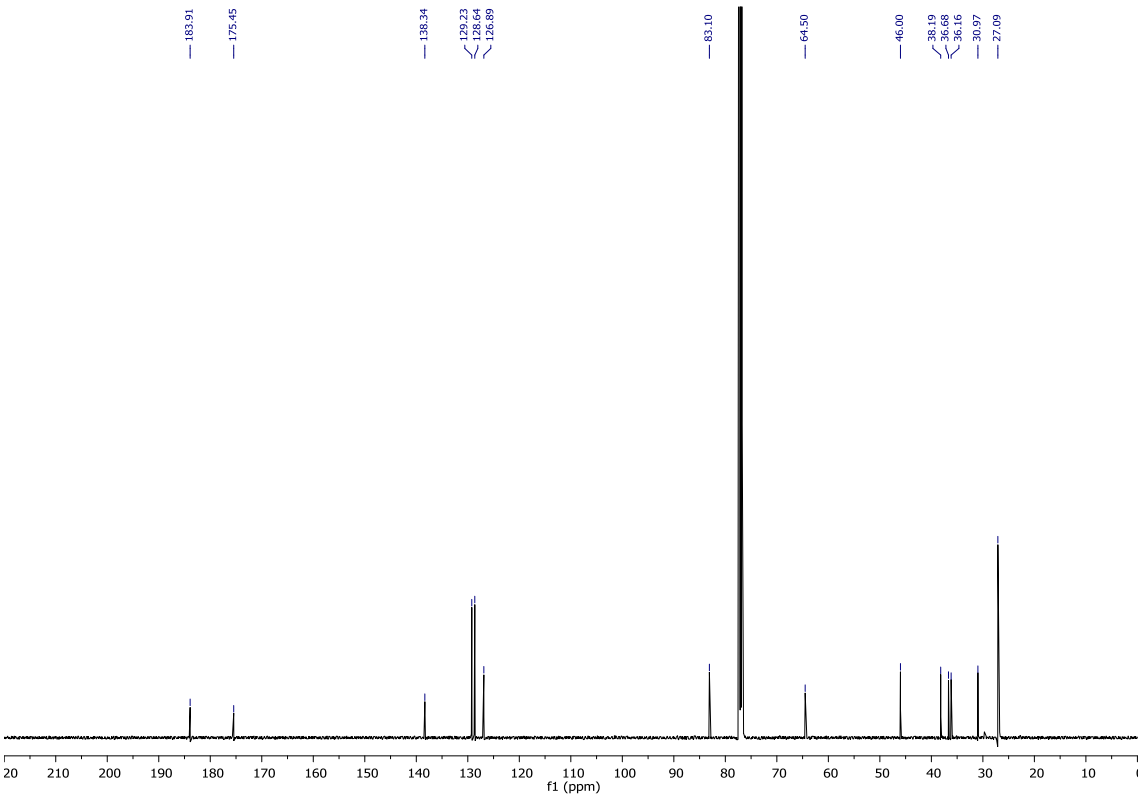
7.20
7.20
7.19
7.16
7.16
7.16
7.14
7.10
7.09
7.08
7.08
7.08
4.73
3.24
3.23
3.20
3.19
3.07
3.05
3.04
3.03
3.02
3.02
3.01
3.01
3.00
3.00
2.99
2.99
2.98
2.97
2.96
2.90
2.88
2.88
2.42
2.40
2.39
2.36
2.17
2.15
2.13
2.12
1.89
1.86
1.83
1.43
0.98
O
N
O
N
tBu
5.00
1.00
1.00
1.00
3.00
1.00
1.00
1.00
3.00
9.00
f1 (ppm)

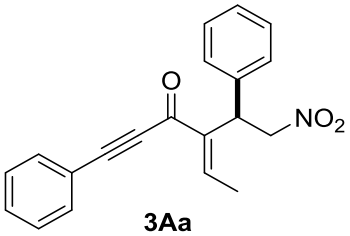

181.59
174.76
139.21
128.78
128.61
126.46
82.22
63.17
43.91
42.38
36.51
35.82
31.08
26.74
23.75
f1 (ppm)


O
N
O
N
tBu
f1 (ppm)


f1 (ppm)

6.7. HPLC chromatograms of representative compounds

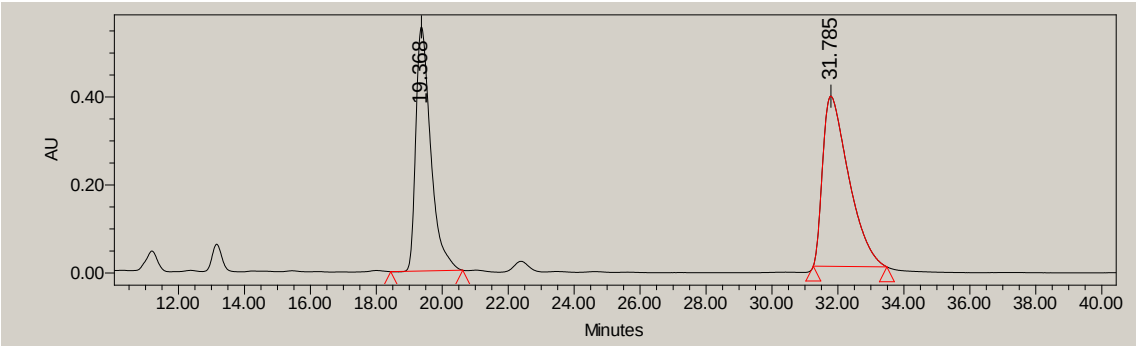
6.7.1. Chapter 2



3Aa

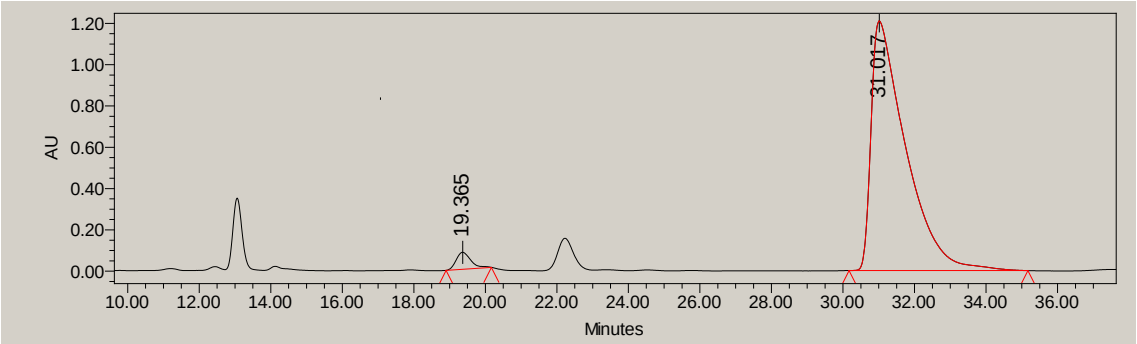
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min).

Rac-**3Aa**



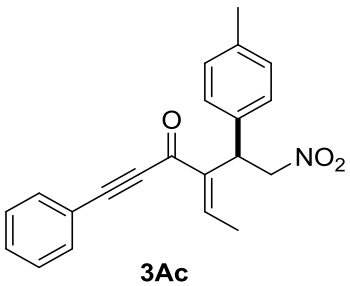
	Retention Time	% Area
	19.369	48.64
	31.785	51.36

Scalemic-**3Aa**



	Retention Time	% Area
	19.365	2.78
	31.017	97.22

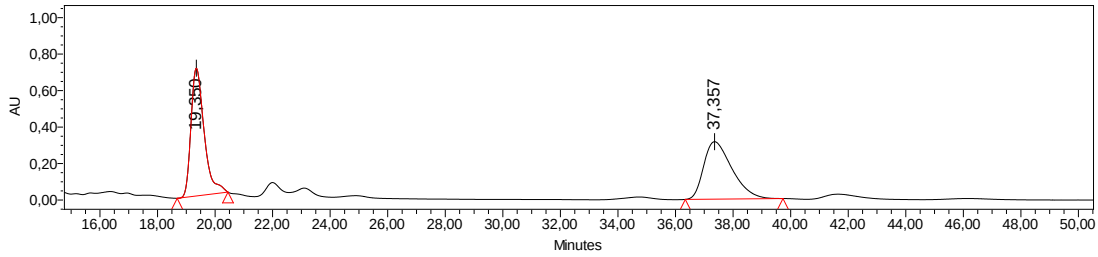
95% *ee*



3Ac

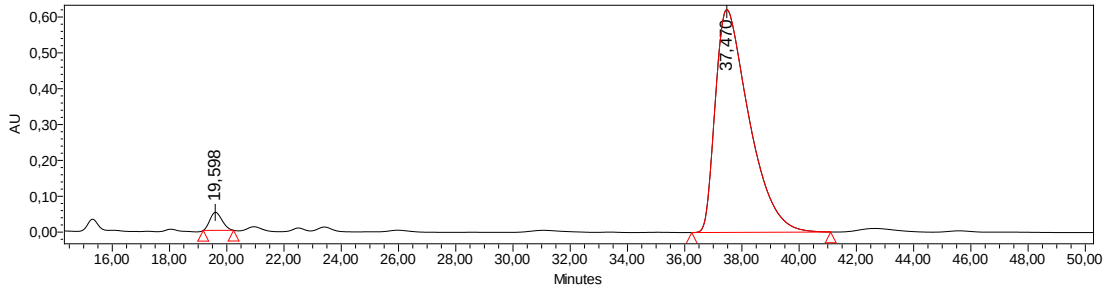
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min).

Rac-**3Ac**



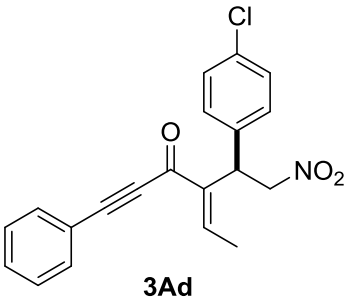
	Retention Time	% Area
	19,350	50,89
	37,357	49,11

Scalemic-**3Ac**



	Retention Time	% Area
	19,598	2,84
	37,470	97,16

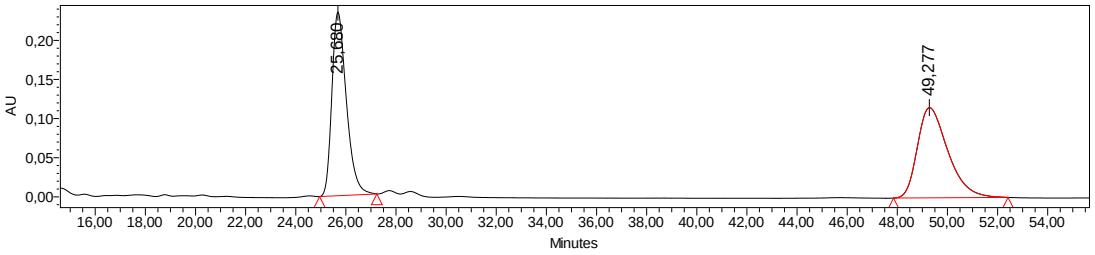
95% *ee*



3Ad

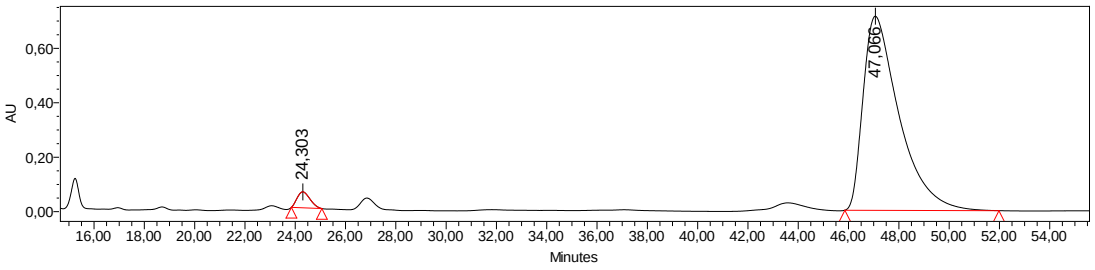
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 70/30, flow rate= 0.5 mL/min).

Rac-**3Ad**



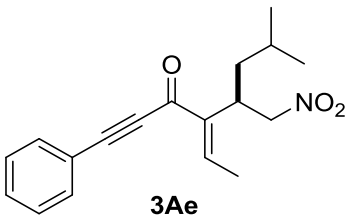
	Retention Time	% Area
	25,680	49,14
	49,277	50,86

Scalemic-**3Ad**



	Retention Time	% Area
	24,303	2,84
	47,066	97,16

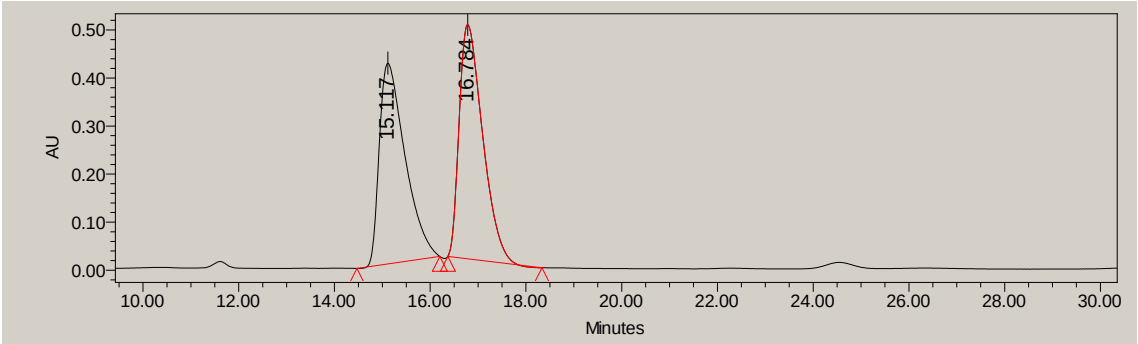
95% *ee*



3Ae

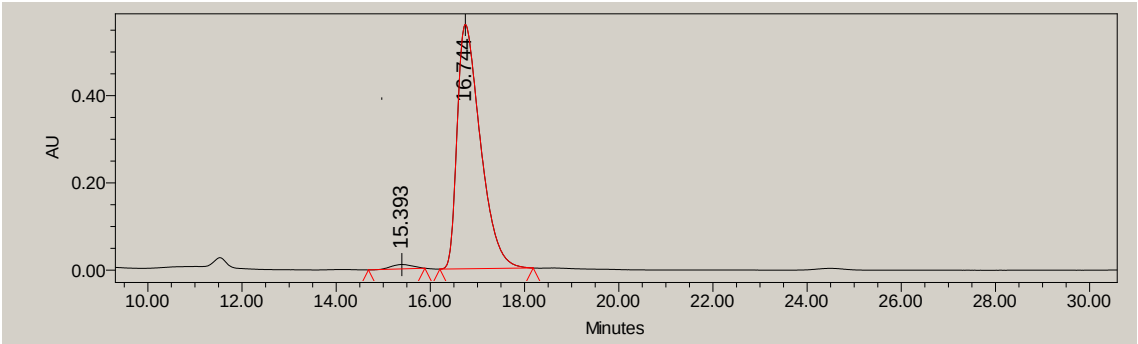
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min).

Rac-**3Ae**



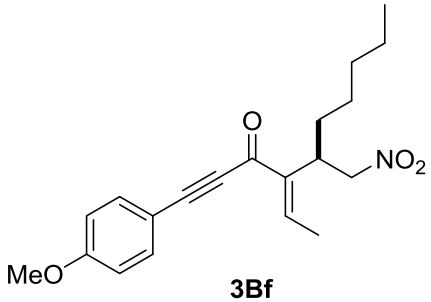
	Retention Time	% Area
	15.117	48.41
	16.784	51.59

Scalemic-**3Ae**



	Retention Time	% Area
	15.393	1.64
	16.744	98.36

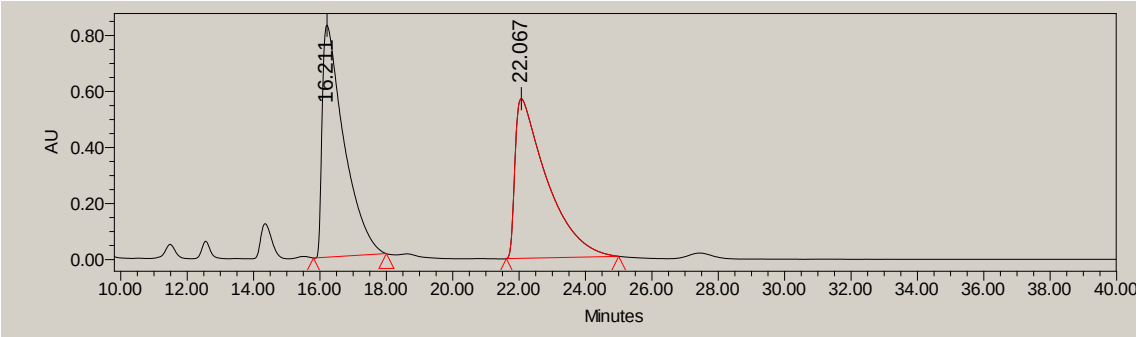
97% *ee*



3Bf

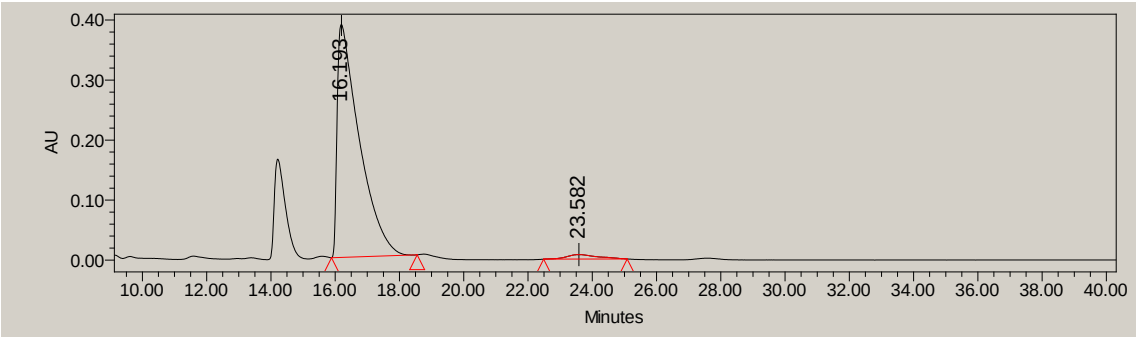
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min).

Rac-**3Bf**



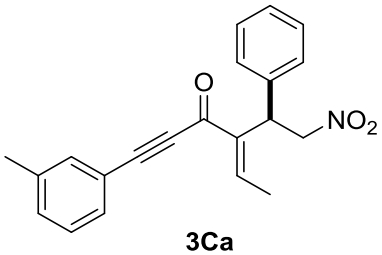
	Retention Time	% Area
	16.211	50.12
	22.067	49.88

Scalemic-**3Bf**



	Retention Time	% Area
	16.193	97.34
	23.582	2.66

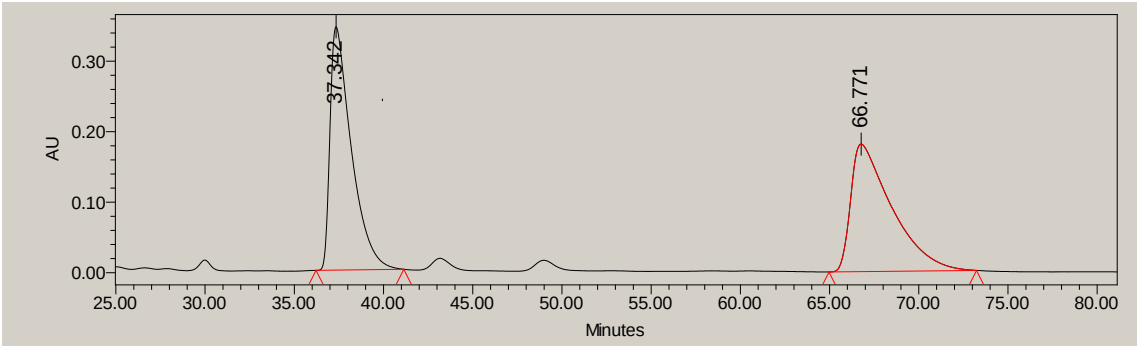
95% *ee*



3Ca

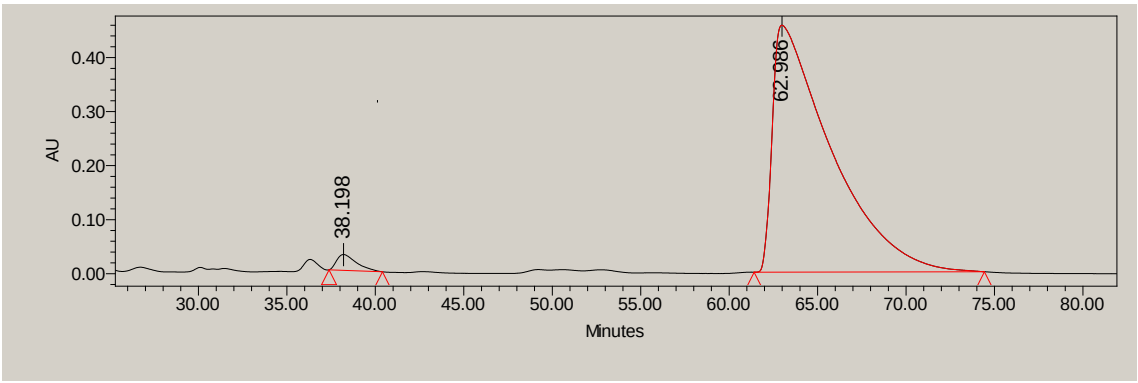
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**3Ca**



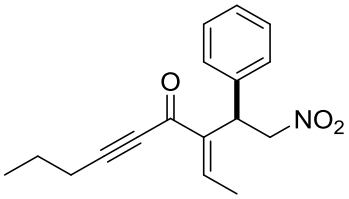
	Retention Time	% Area
	37.342	50.17
	66.771	49.83

Scalemic-**3Ca**



	Retention Time	% Area
	38.198	2.14
	62.986	97.86

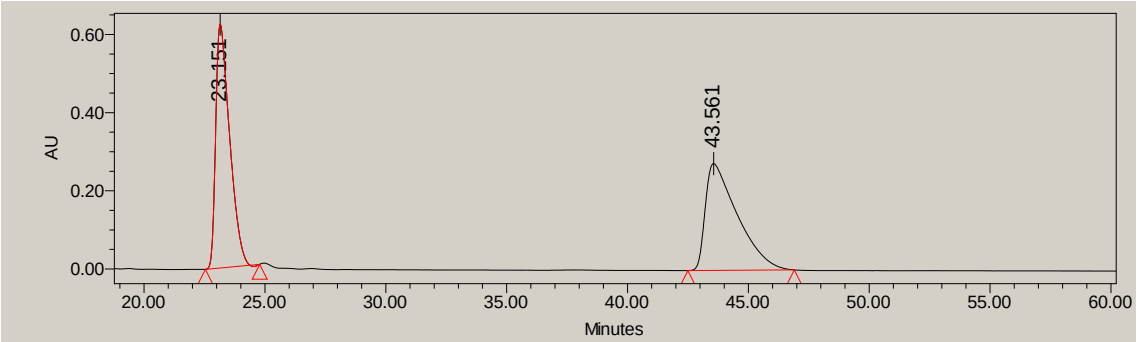
95% *ee*



3Da

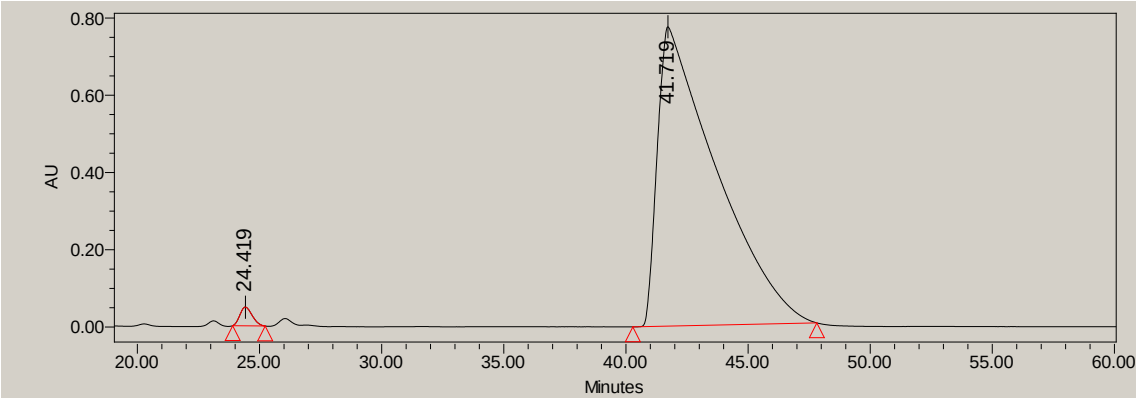
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**3Da**



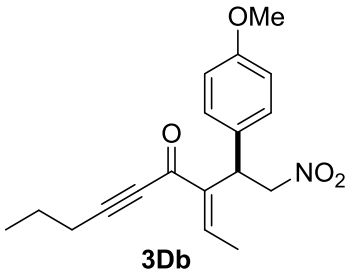
	Retention Time	% Area
	23.151	49.92
	43.561	50.08

Scalemic-**3Da**



	Retention Time	% Area
	24.419	1.29
	41.719	98.71

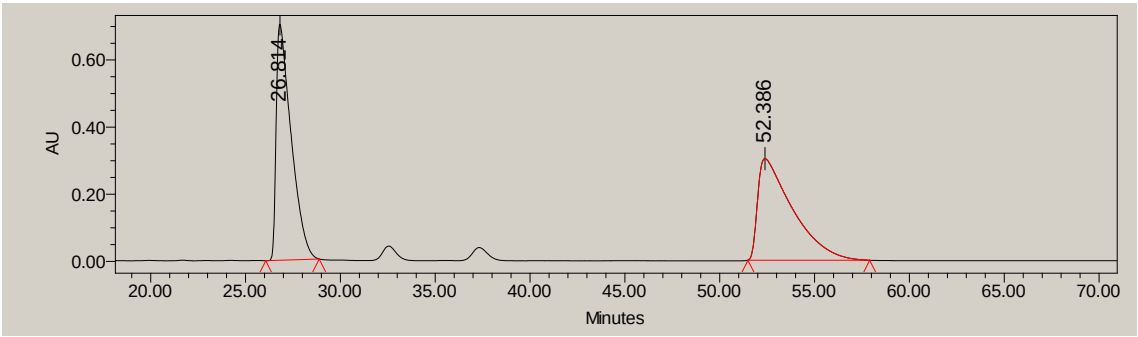
97% *ee*



3Db

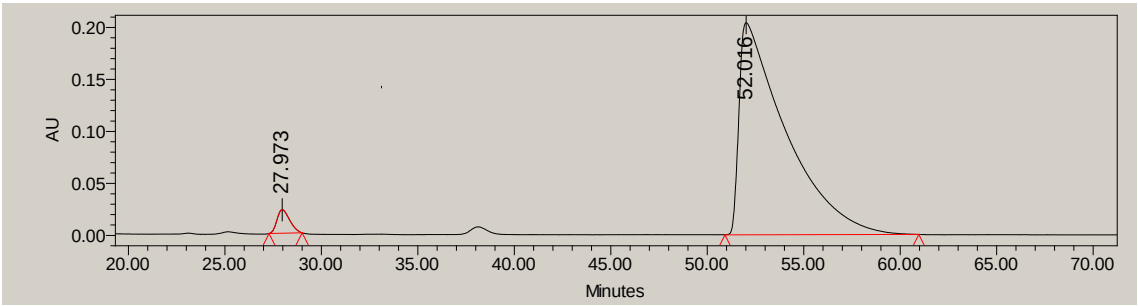
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min).

Rac-**3Db**



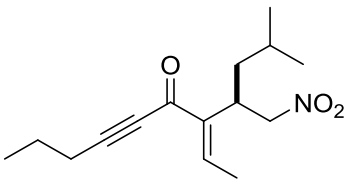
	Retention Time	% Area
	26.814	50.02
	52.386	49.98

Scalemic-**3Db**



	Retention Time	% Area
	27.973	2.93
	52.016	97.07

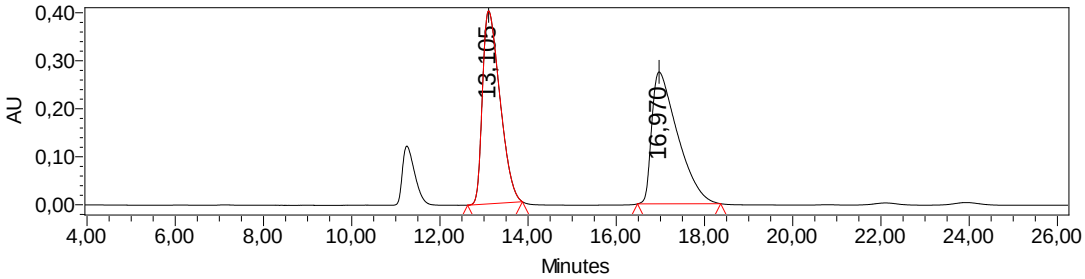
94% *ee*



3De

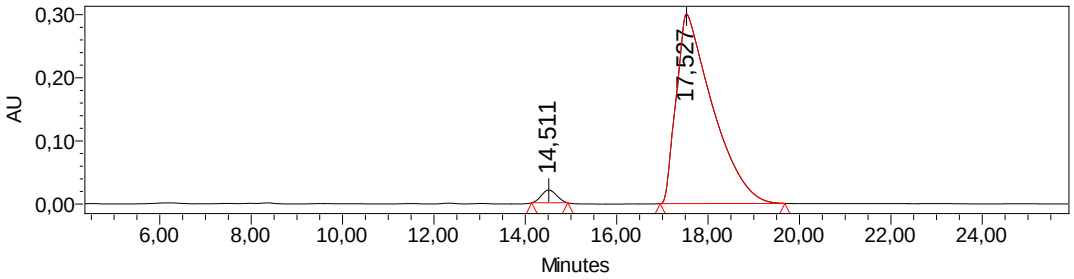
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 98/2, flow rate= 1.0 mL/min).

Rac-**3De**



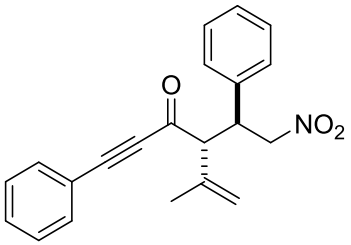
	Retention Time	% Area
	13,105	49,66
	16,970	50,34

Scalemic-**3De**



	Retention Time	% Area
	14,511	2,72
	17,527	97,28

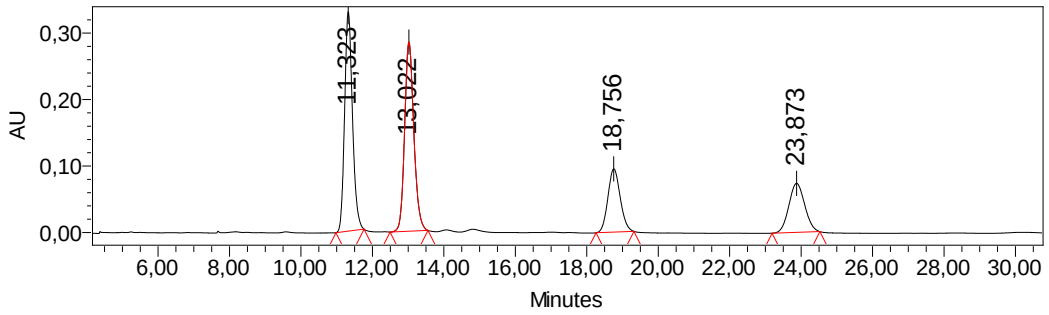
95% *ee*



7Aa

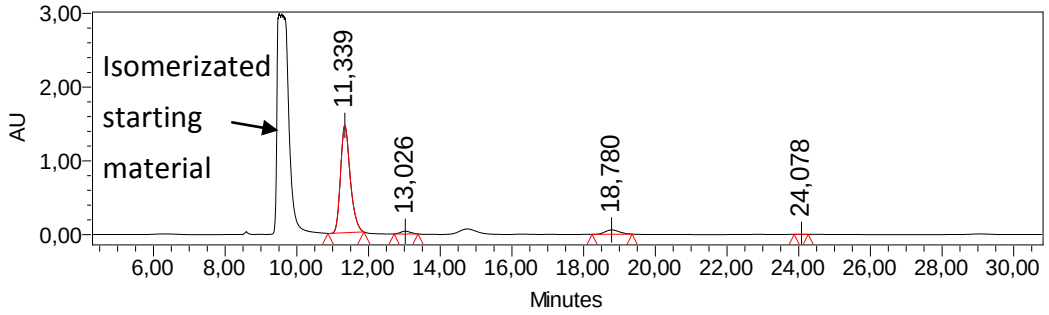
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography.

Rac- **7Aa**



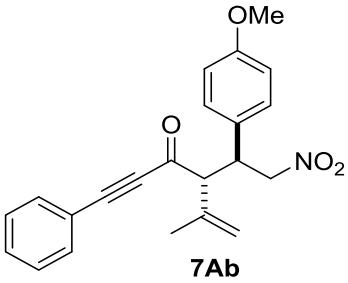
	Retention Time	% Area
	11.323	34.24
	13.022	34.75
	18.756	15.55
	23.873	15.46

Scalemic-**7Aa**



	Retention Time	% Area
	11.339	92.12
	13.026	2.40
	18.780	5.45
	24.078	0.03

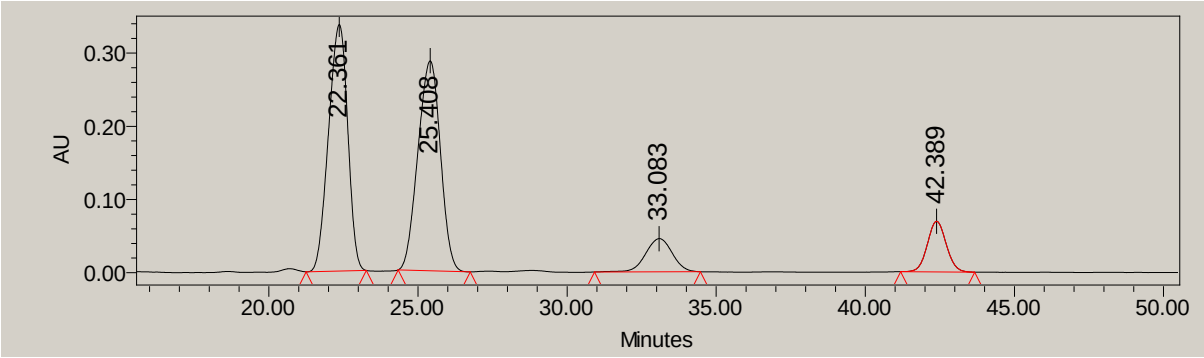
dr: 19:1, 94% *ee*



7Ab

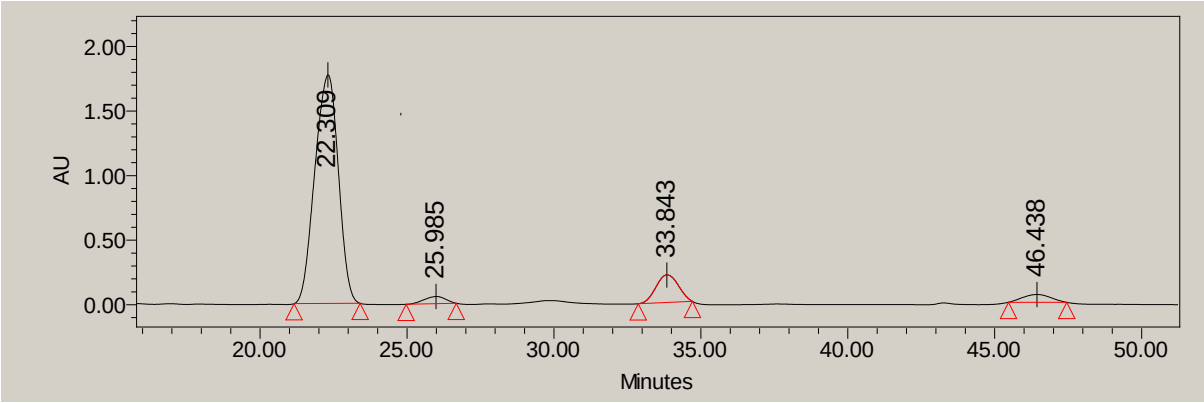
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography.

Rac- **7Ab**



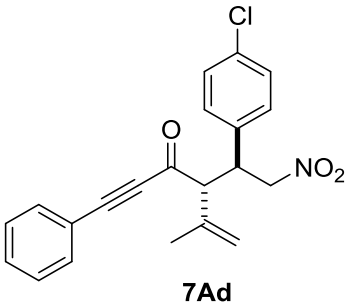
	Retention Time	% Area
	22.361	41.90
	25.408	41.75
	33.083	7.89
	42.389	8.46

Scalemic-**7Ab**



	Retention Time	% Area
	22.309	84.42
	25.985	2.44
	33.843	9.72
	46.438	3.42

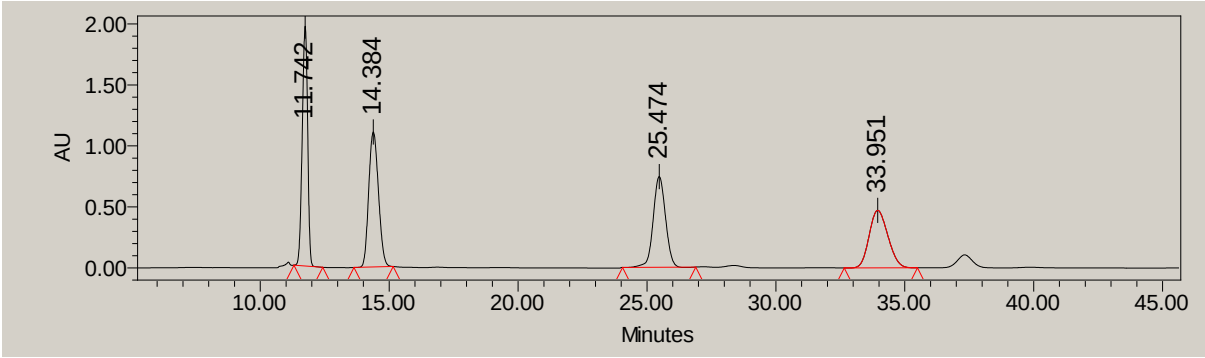
dr: 6.7:1, 98% *ee*



7Ad

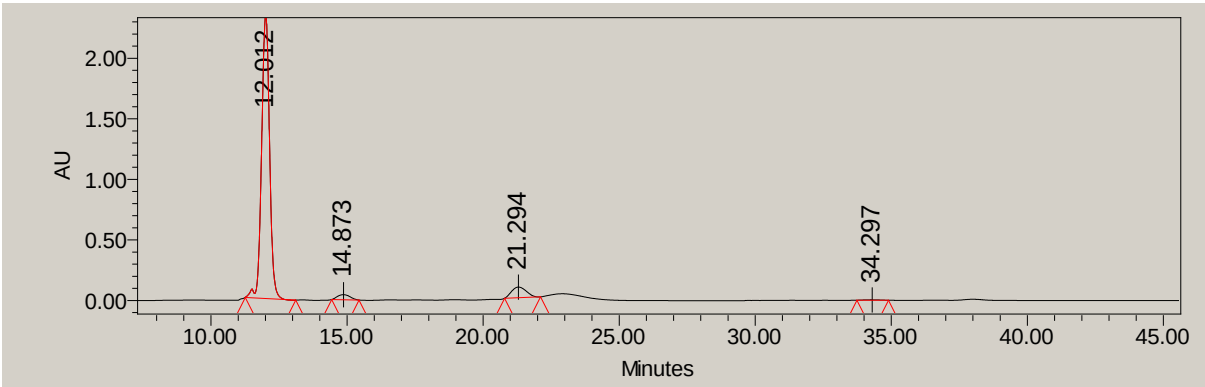
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min).

Rac- **7Ad**



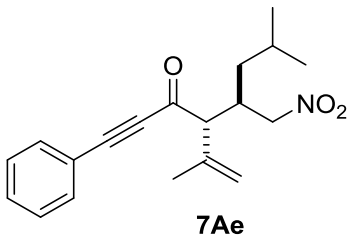
	Retention Time	% Area
	11.742	27.01
	14.384	27.30
	25.474	23.34
	33.951	22.35

Scalemic-**7Ad**



	Retention Time	% Area
	12.012	90.90
	14.873	2.59
	21.294	6.27
	34.297	0.24

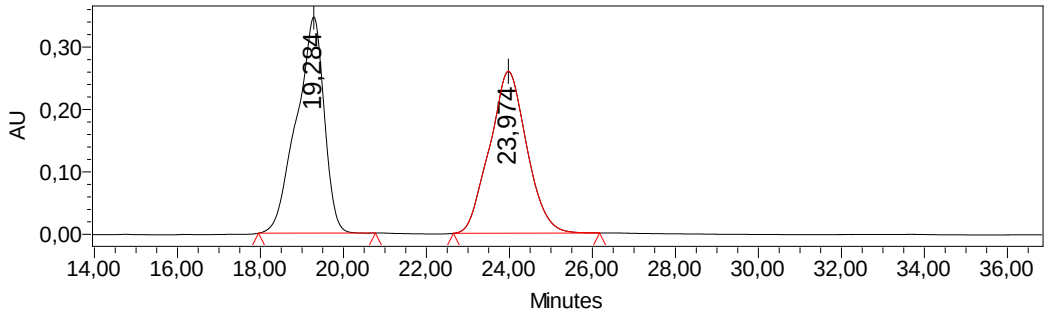
dr: 15.7:1, 93% *ee*



7Ae

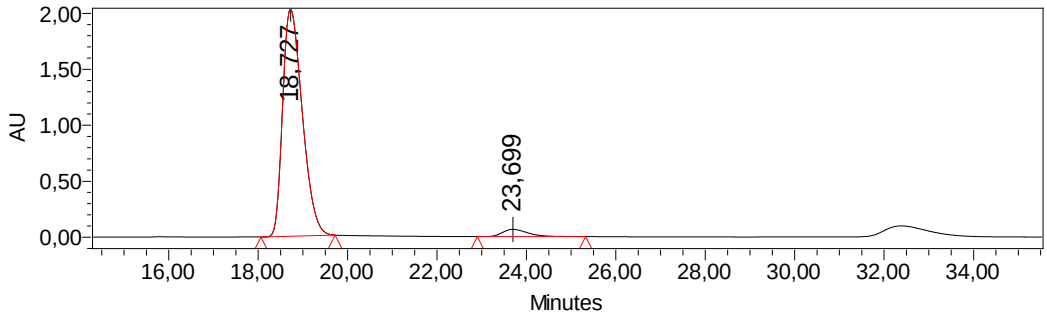
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 99/1, flow rate= 1 mL/min).

Rac- **7Ae**



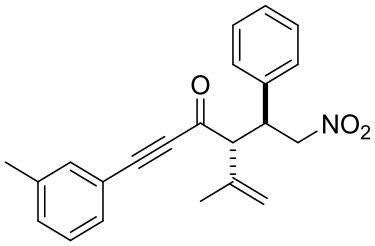
	Retention Time	% Area
	19.284	49.91
	23.974	50.09

Scalemic-**7Ae**



	Retention Time	% Area
	18.727	96.05
	23.699	3.95

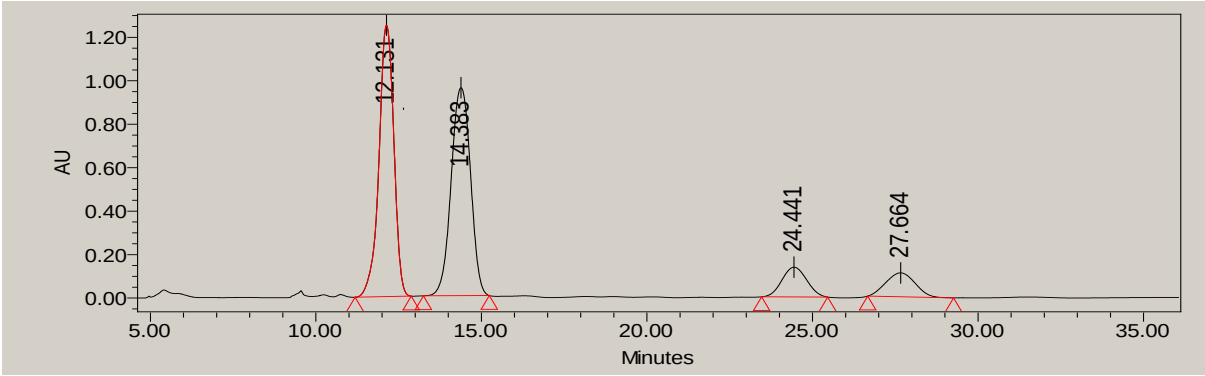
dr: 20:1, 92% *ee*



7Ba

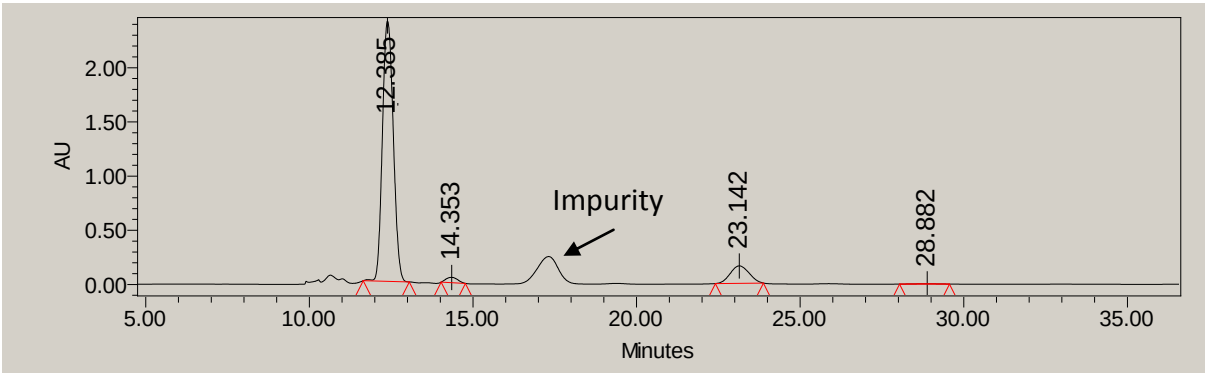
The enantiomeric and diastereomeric purity were determined on by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min).

Rac- **7Ba**



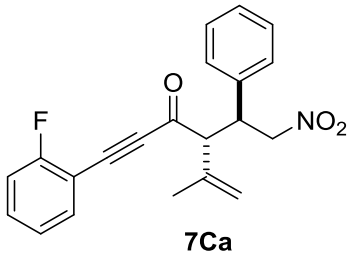
	Retention Time	% Area
	12.131	42.52
	14.383	42.40
	24.441	7.71
	27.664	7.37

Scalemic-**7Ba**



	Retention Time	% Area
	12.385	87.68
	14.353	1.92
	23.142	10.16
	28.882	0.24

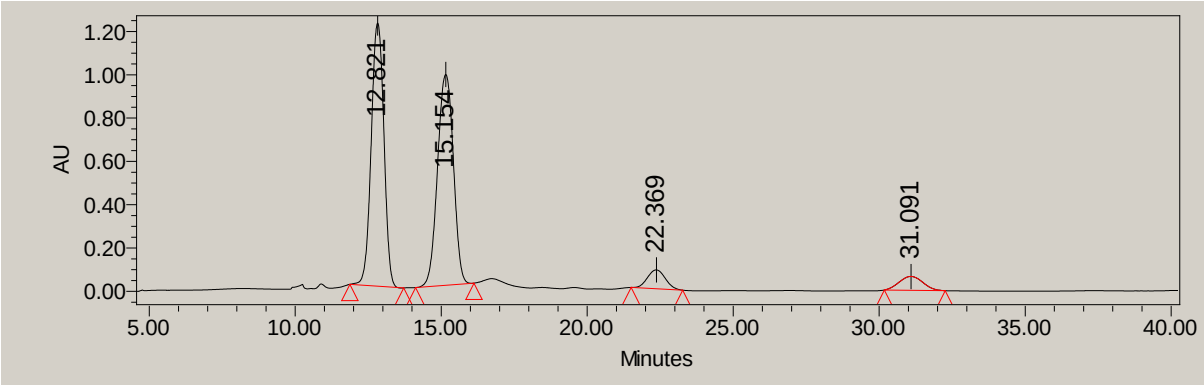
dr: 9:1, 95% *ee*



7Ca

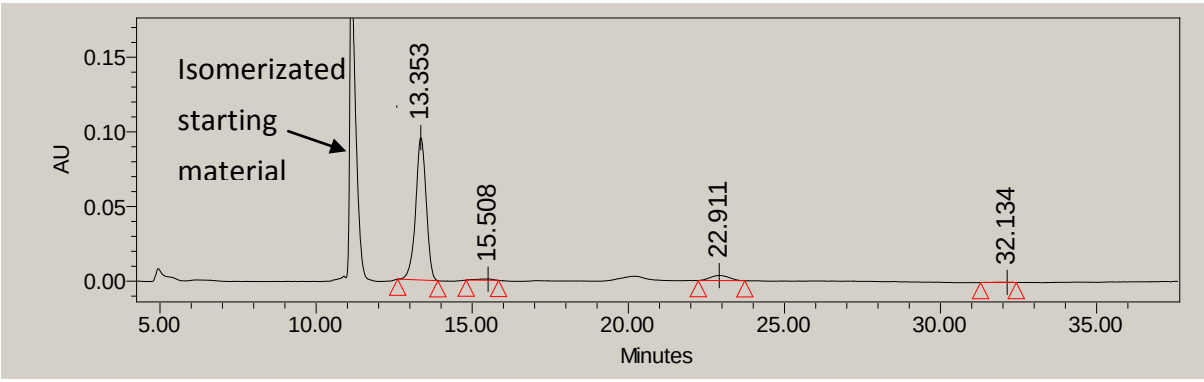
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography.

Rac- **7Ca**



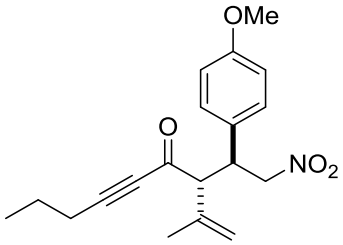
	Retention Time	% Area
	12.821	45.32
	15.154	45.60
	22.369	4.60
	31.091	4.47

Scalemic-**7Ca**



	Retention Time	% Area
	13.353	92.36
	15.508	1.40
	22.911	6.04
	32.134	0.19

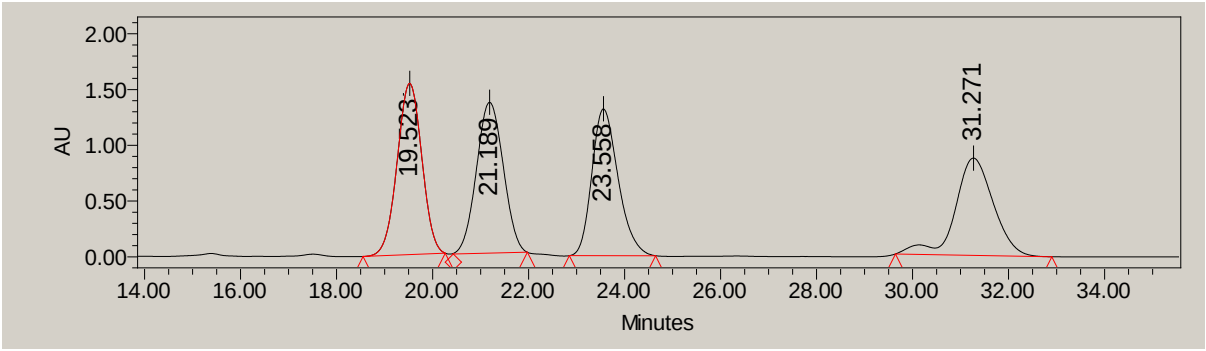
dr: 15.7:1, 99% *ee*



7Db

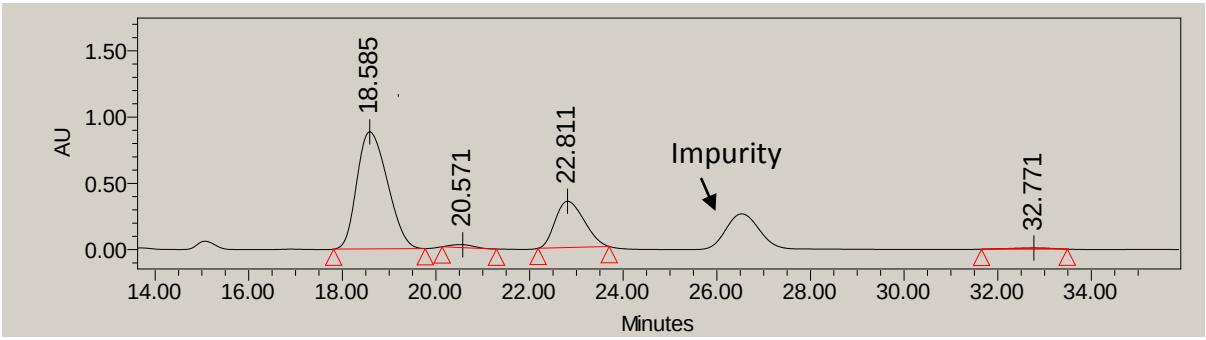
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 98/2, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**7Db**



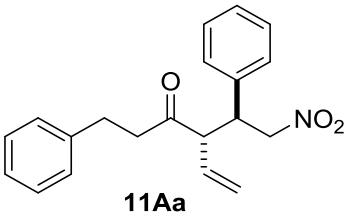
	Retention Time	% Area
	19.523	26.64
	21.189	25.56
	23.558	24.35
	31.271	23.46

Scalemic-**7Db**



	Retention Time	% Area
	18.585	65.77
	20.571	2.23
	22.811	30.89
	32.771	1.11

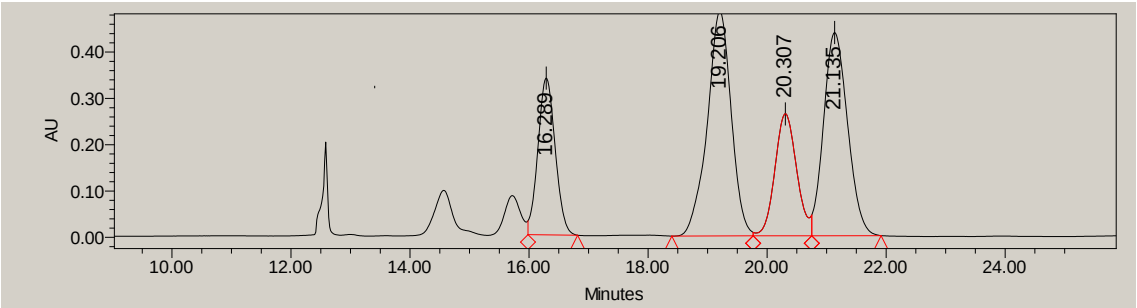
dr: 2.1:1, 93% *ee*



11Aa

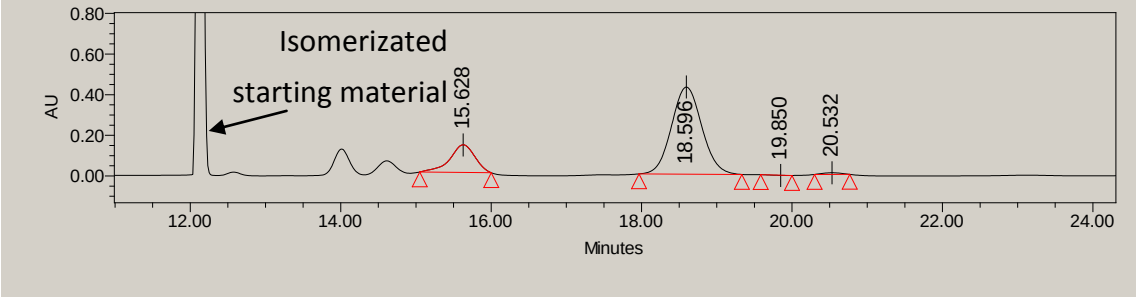
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 99/1, flow rate= 1.0 mL/min) on crude material before column chromatography.

Rac-**11Aa**



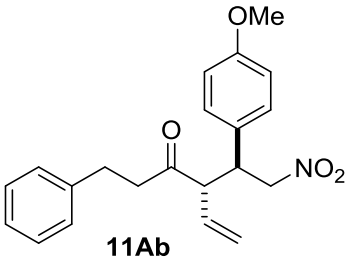
	Retention Time	% Area
	16.289	17.33
	19.206	34.37
	20.307	17.08
	21.135	31.22

Scalemic-**11Aa**



	Retention Time	% Area
	15.628	20.48
	18.596	78.53
	19.850	0.10
	20.532	0.90

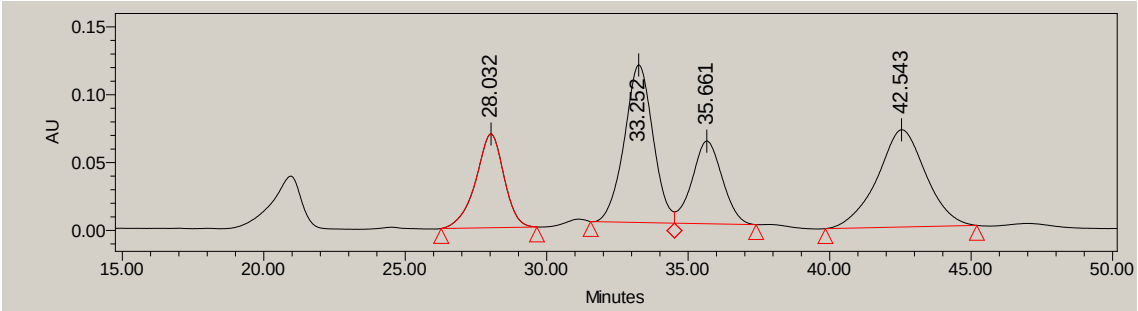
dr: 4:1, 94% (99%)*ee*



11Ab

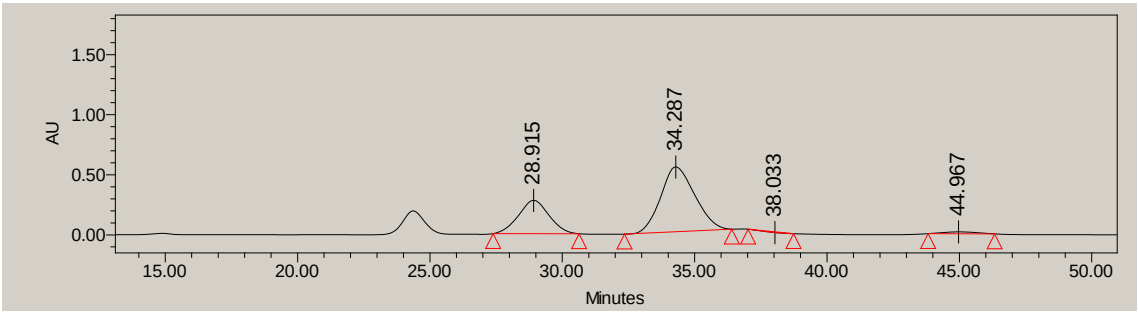
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 99/1, flow rate= 1.0 mL/min) on crude material before column chromatography.

Rac-**11Ab**



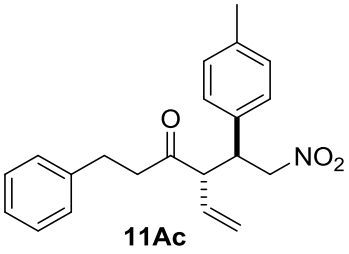
	Retention Time	% Area
	28.032	18.00
	33.252	31.99
	35.661	17.68
	42.543	32.32

Scalemic-**11Ab**



	Retention Time	% Area
	28.915	30.81
	34.287	66.79
	38.033	0.48
	44.967	1.92

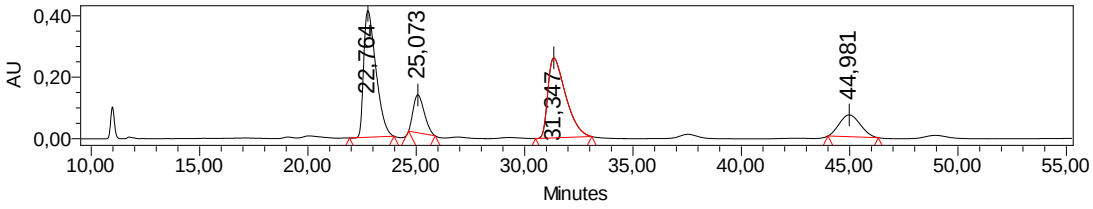
dr: 2.2:1, 91% (97%)*ee*



11Ac

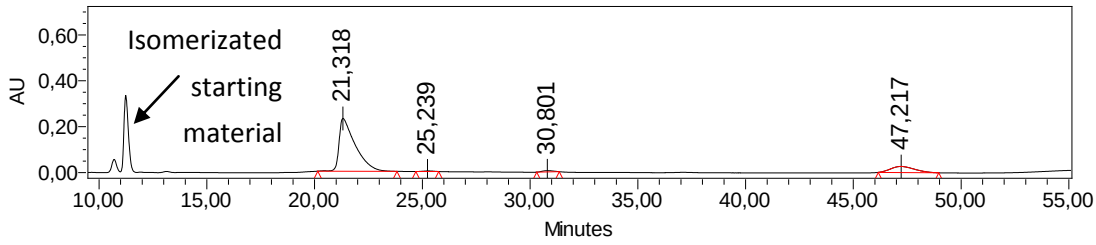
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min) on crude material before column chromatography.

Rac-**11Ac**



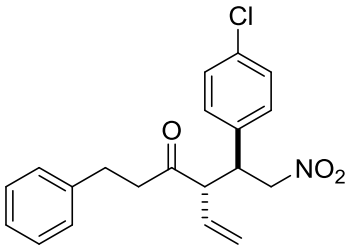
	Retention Time	% Area
	22,764	40,26
	25,073	10,90
	31,347	37,02
	44,981	11,82

Scalemic-**11Ac**



	Retention Time	% Area
	21,318	83,80
	25,239	0,57
	30,801	1,37
	47,217	14,27

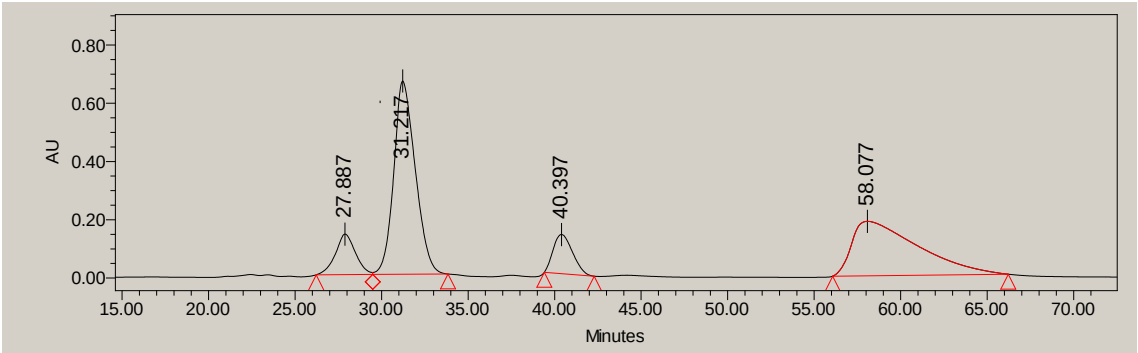
dr: 5.7:1, 97% (90%)*ee*



11Ad

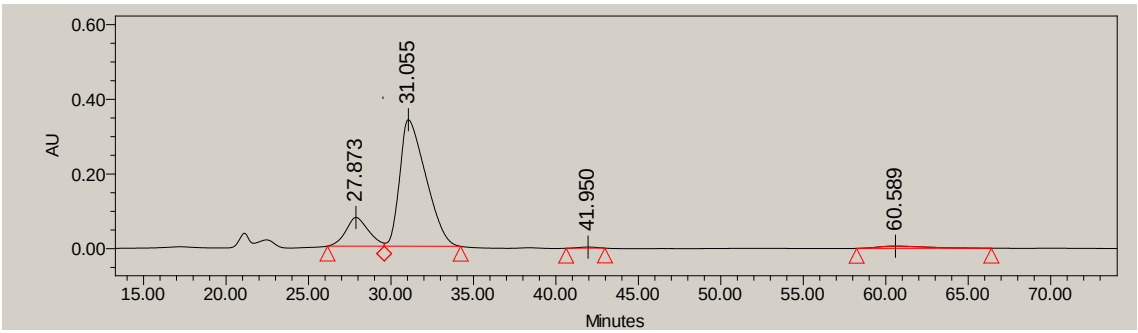
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ ethanol 99/1, flow rate= 1.0 mL/min) on crude material before column chromatography.

Rac-**11Ad**



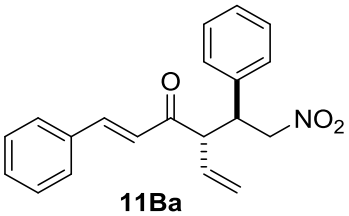
	Retention Time	% Area
	27.887	8.70
	40.397	44.54
	31.217	8.15
	58.077	38.61

Scalemic-**11Ad**



	Retention Time	% Area
	27.873	15.85
	31.055	80.91
	41.950	0.51
	60.589	2.73

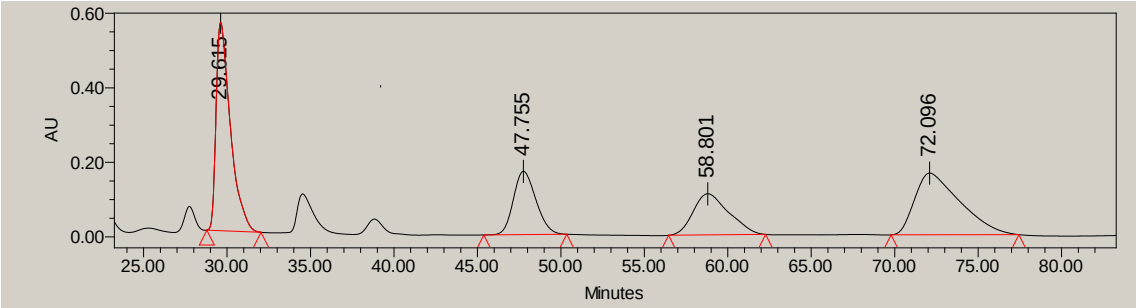
dr: 5.3:1, 93% (98%)*ee*



11Ba

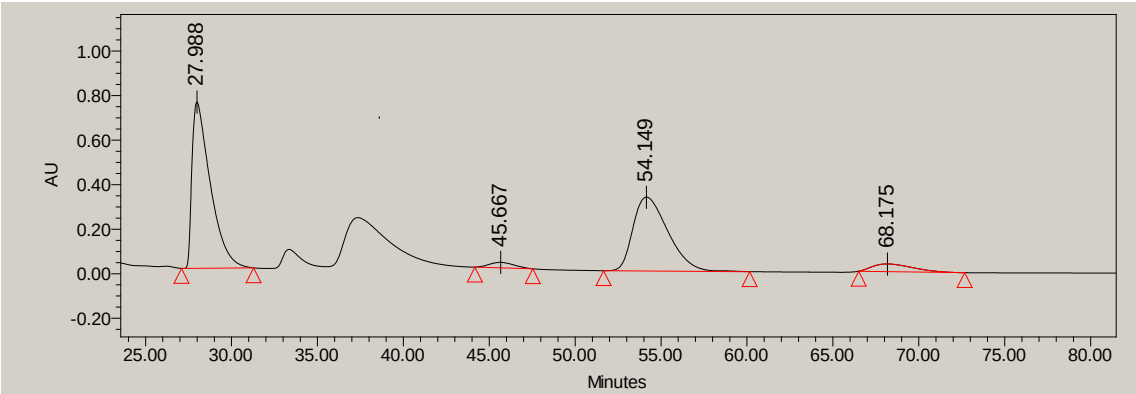
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 85/15, flow rate= 1.0 mL/min) on crude material before column chromatography.

Rac-**11Ba**



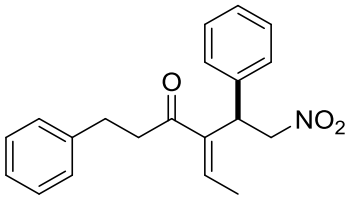
	Retention Time	% Area
	29.615	34.40
	47.755	16.52
	58.801	16.92
	72.096	32.16

Scalemic-**11Ba**



	Retention Time	% Area
	27.988	50.28
	45.667	2.23
	54.149	42.42
	68.175	5.08

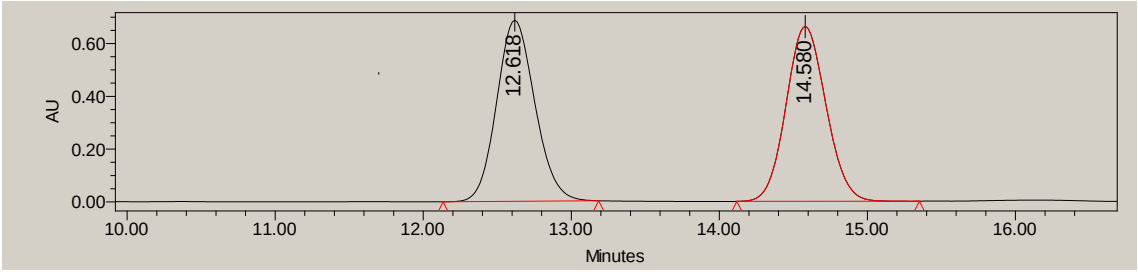
dr: 1.3:1, 84% (90%)*ee*



13Aa

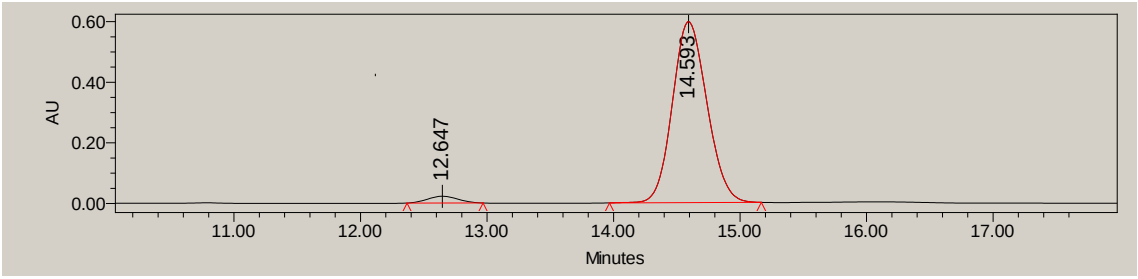
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**13Aa**



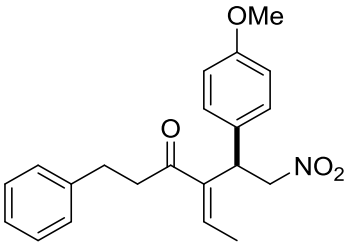
	Retention Time	% Area
	12.618	50.19
	14.580	49.81

Scalemic-**13Aa**



	Retention Time	% Area
	12.647	3.15
	14.593	96.85

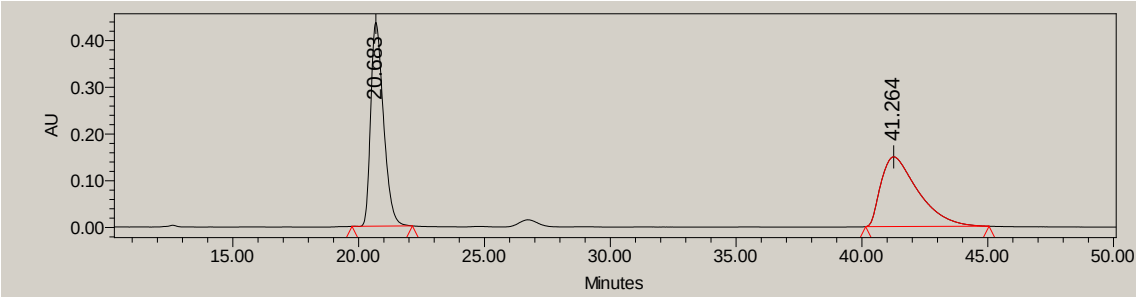
94% *ee*



13Ab

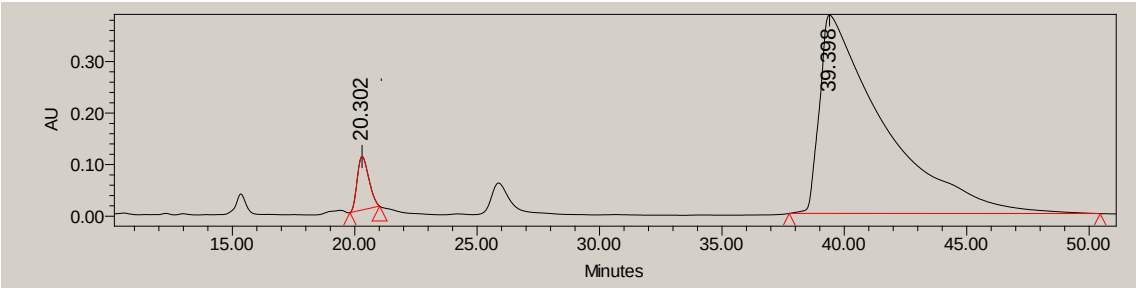
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min).

Rac-**13Ab**



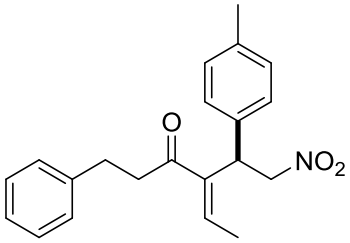
	Retention Time	% Area
	20.683	49.83
	41.264	50.17

Scalemic-**13Ab**



	Retention Time	% Area
	20.302	4.66
	39.398	95.34

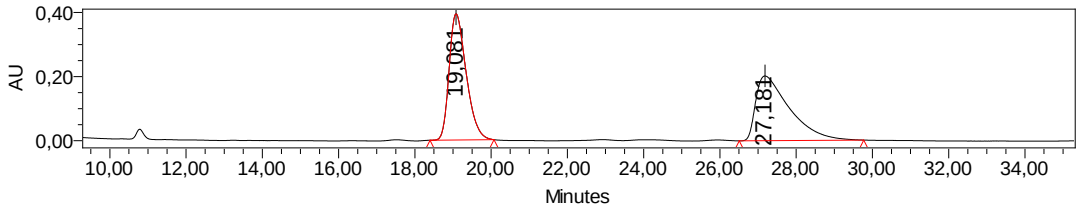
91% *ee*



13Ac

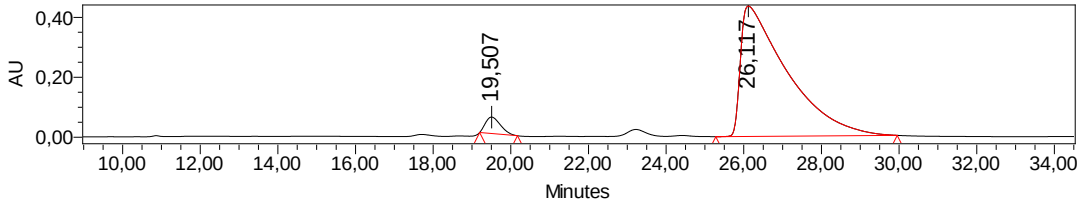
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**13Ac**



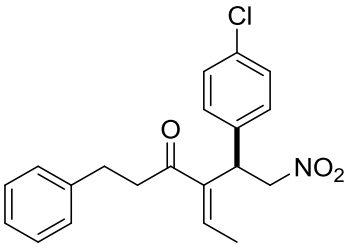
	Retention Time	% Area
	19,081	50,34
	27,181	49,66

Scalemic-**13Ac**



	Retention Time	% Area
	19,507	3,94
	26,117	96,06

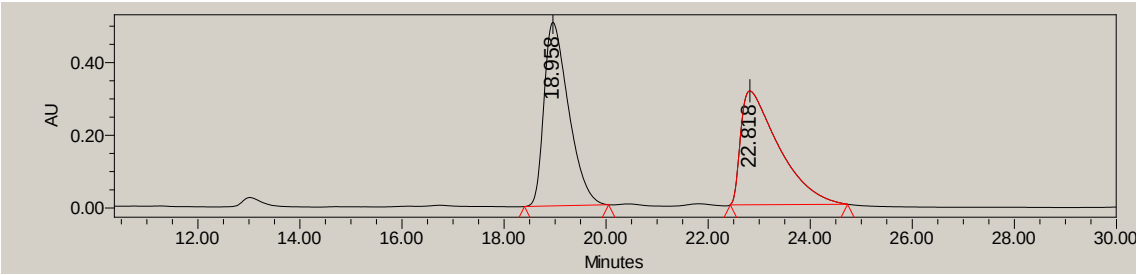
92% *ee*



13Ad

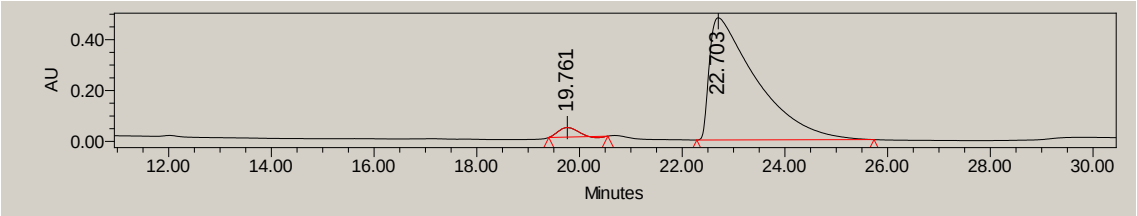
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**13Ad**



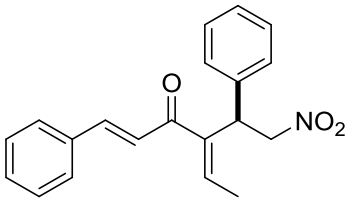
	Retention Time	% Area
	18.958	48.98
	22.818	51.02

Scalemic-**13Ad**



	Retention Time	% Area
	19.761	3.27
	22.703	96.73

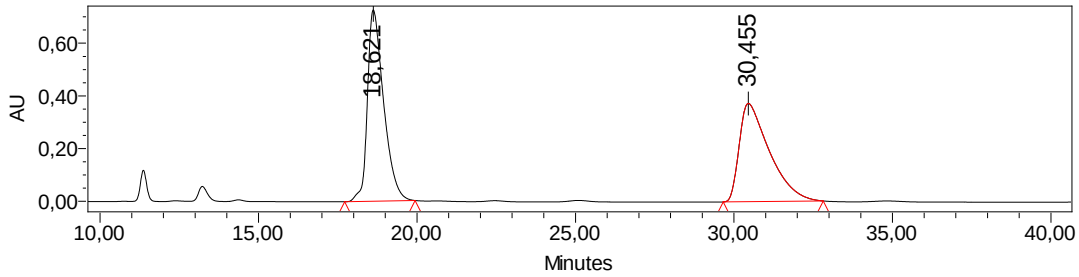
93% *ee*



13Ba

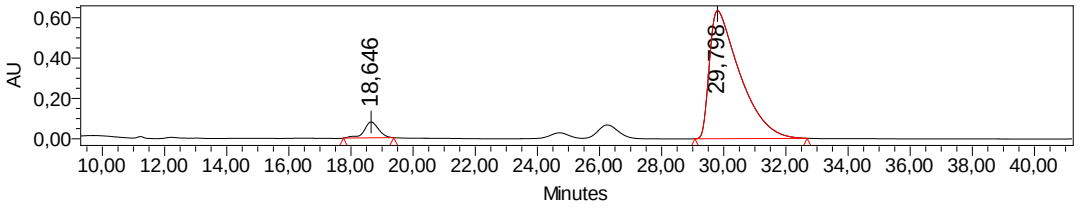
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**13Ba**



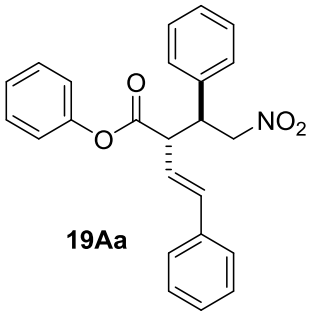
	Retention Time	% Area
	18,621	51,18
	30,455	48,82

Scalemic-**13Ba**



	Retention Time	% Area
	18,646	5,62
	29,798	94,38

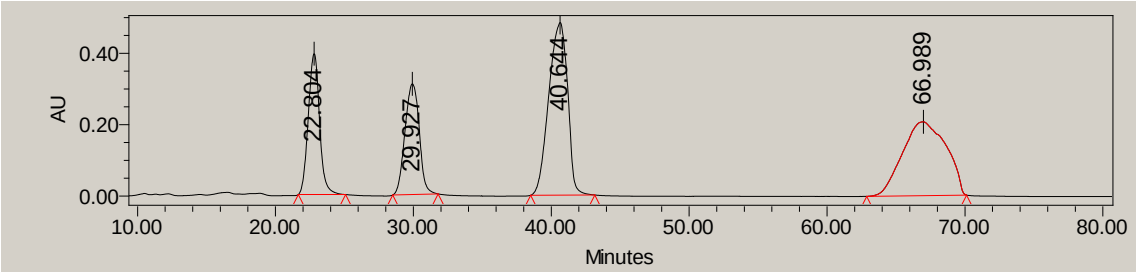
88% ee



19Aa

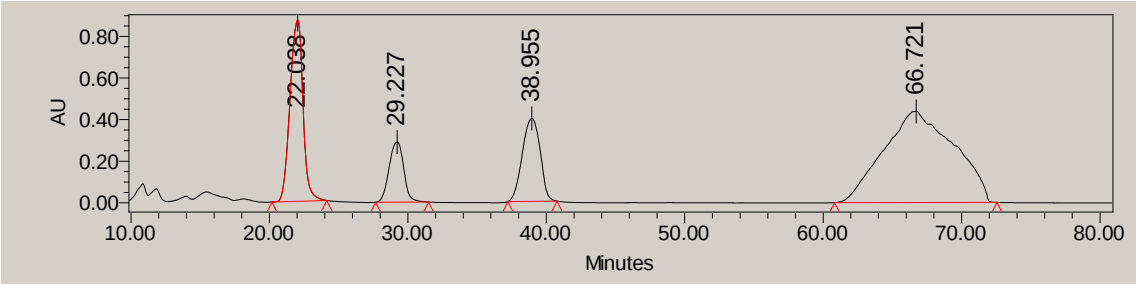
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**19Aa**



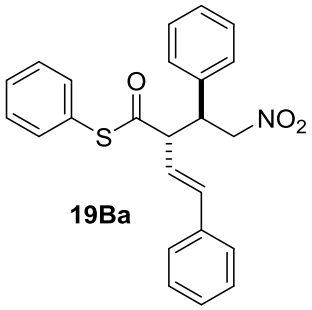
	Retention Time	% Area
	22.804	16.47
	29.927	16.38
	40.644	33.66
	66.989	33.49

Scalemic-**19Aa**



	Retention Time	% Area
	22.041	18.94
	29.227	6.68
	38.959	13.77
	66.737	60.60

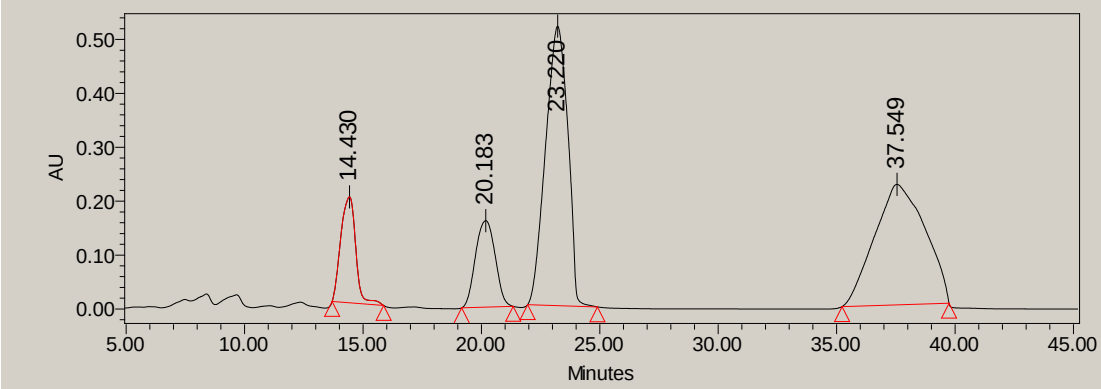
dr: 2.7:1, 63% (50%)*ee*



19Ba

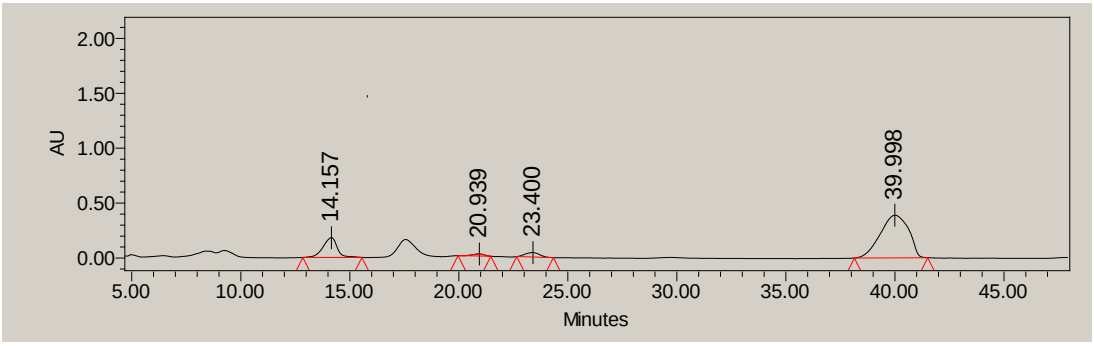
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**19Ba**



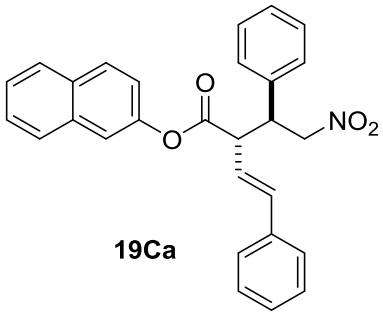
	Retention Time	% Area
	14.428	12.08
	20.177	12.73
	23.220	37.40
	37.556	37.79

Scalemic-**19Ba**



	Retention Time	% Area
	14.157	17.79
	20.939	1.54
	23.400	4.09
	39.998	76.58

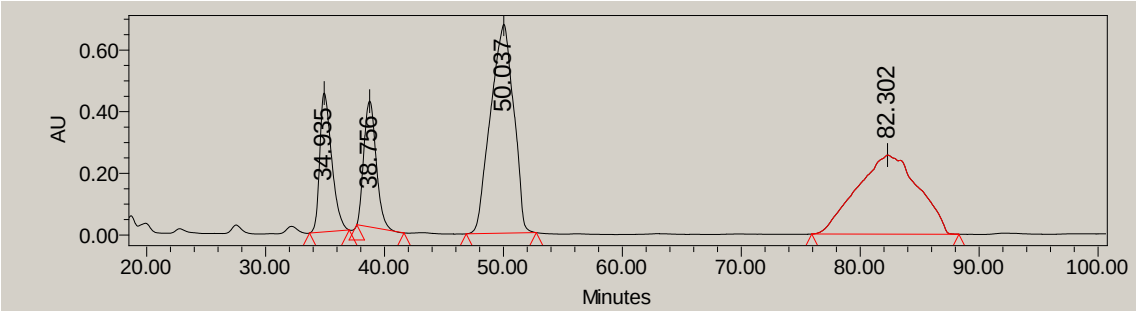
dr: 4:1, 89% (80%)*ee*



19Ca

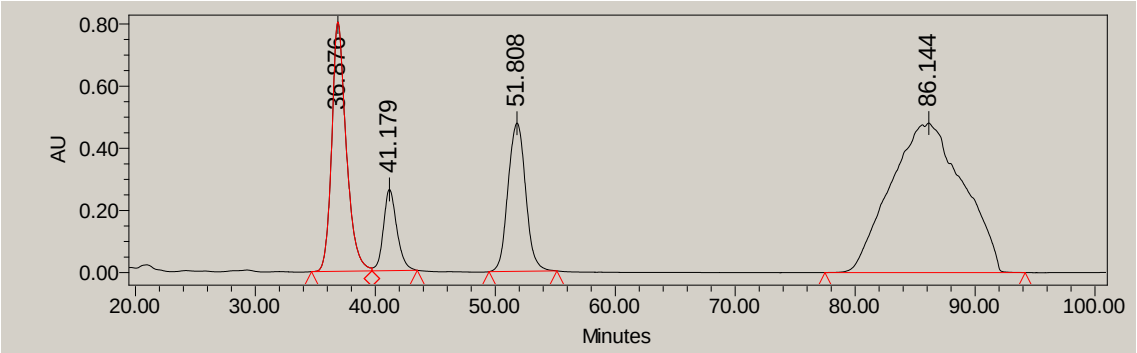
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 98/2, flow rate= 1.0 mL/min).

Rac-**19Ca**



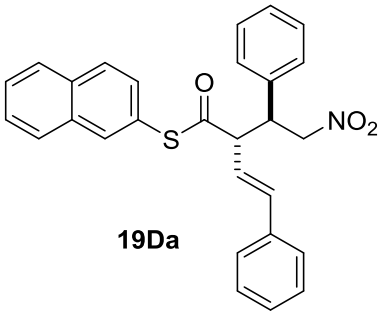
	Retention Time	% Area
	34.935	12.79
	38.756	12.04
	50.037	37.37
	82.302	37.80

Scalemic-**19Ca**



	Retention Time	% Area
	36.878	19.15
	41.180	5.34
	51.823	14.52
	86.144	60.99

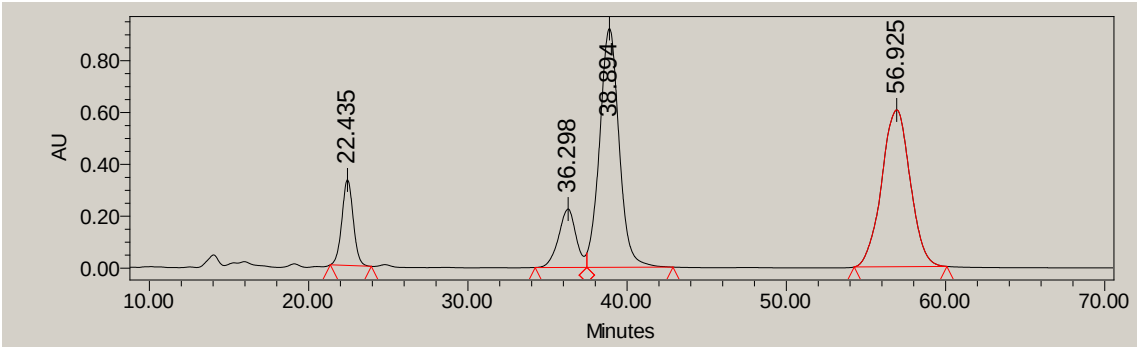
dr: 3:1, 62% (54%)*ee*



19Da

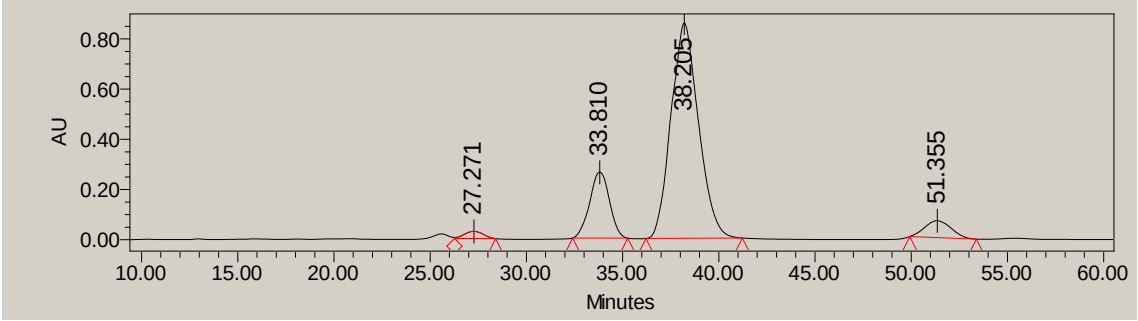
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1.0 mL/min).

Rac-**19Da**



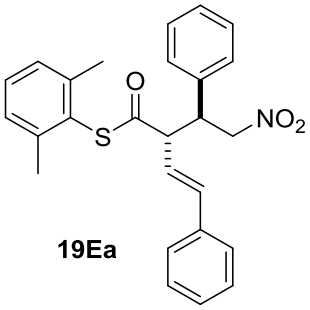
	Retention Time	% Area
	22.435	8.73
	36.298	9.27
	38.894	41.73
	56.925	40.27

Scalemic-**19Da**



	Retention Time	% Area
	27.271	1.76
	33.810	16.70
	38.205	75.82
	51.355	5.72

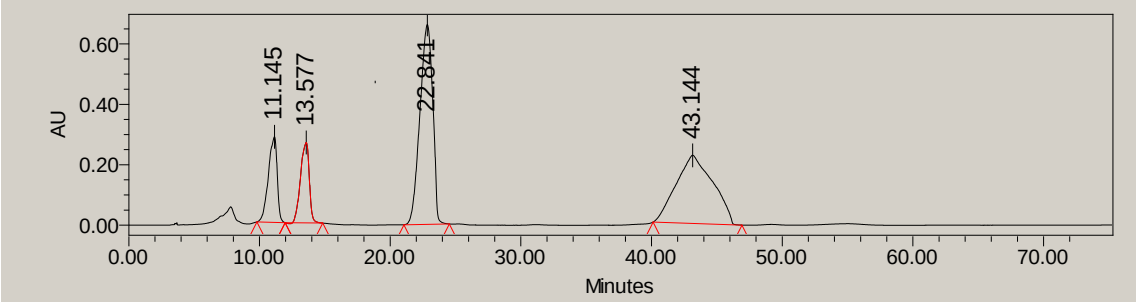
dr: 4.4:1, 84% (81%)*ee*



19Ea

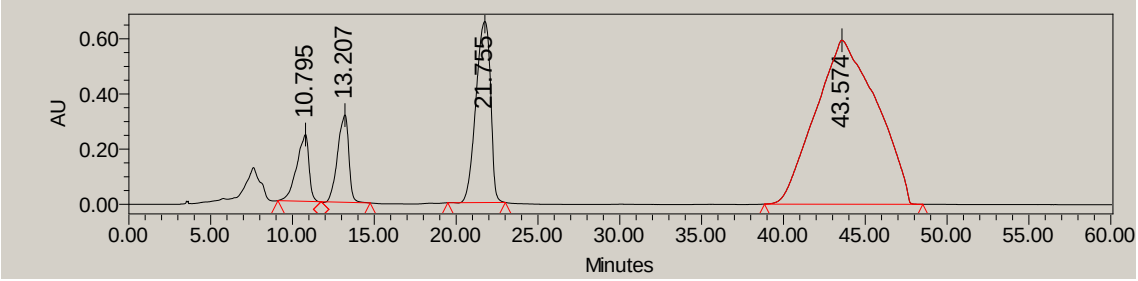
The diastereomeric and enantiomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1.0 mL/min).

Rac-**19Ea**



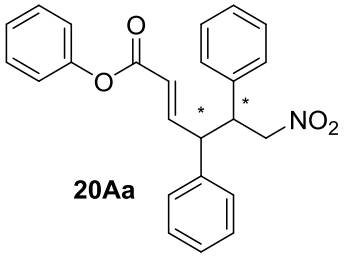
	Retention Time	% Area
	11.145	11.60
	13.577	10.87
	22.841	39.21
	43.144	38.32

Scalemic-**19Ea**



	Retention Time	% Area
	10.795	5.61
	13.207	6.73
	21.755	18.28
	43.574	69.38

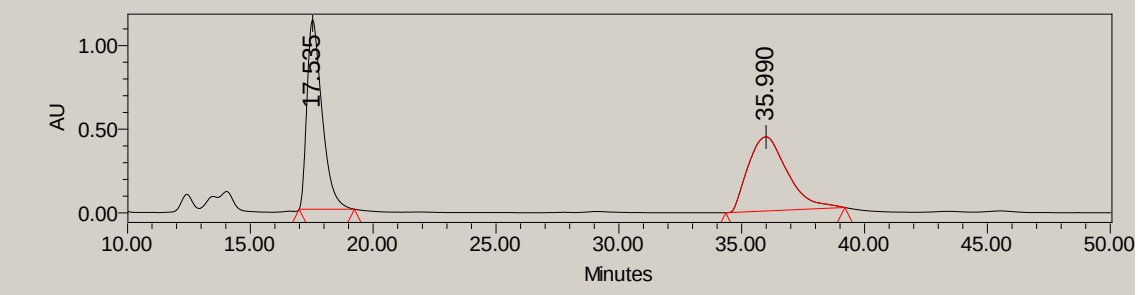
dr: 7.1:1, 58% (10%)*ee*



20Aa

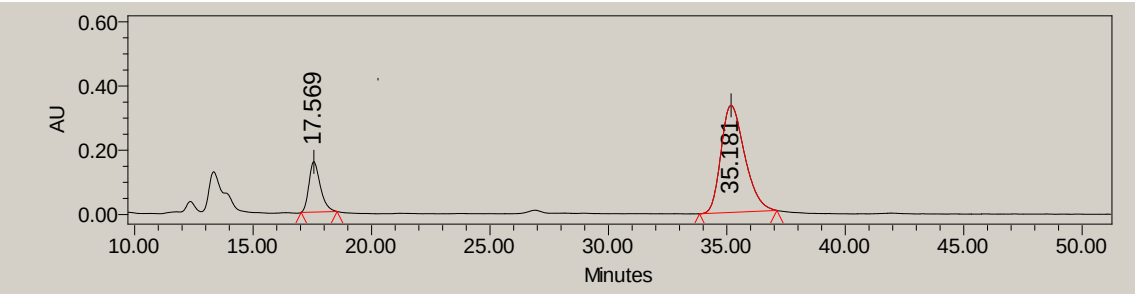
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 1.0 mL/min).

Rac-**20Aa**



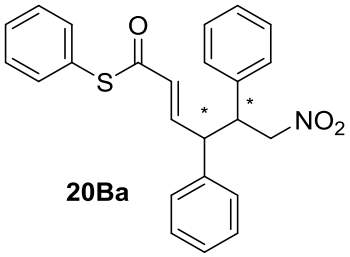
	Retention Time	% Area
	17.535	50.32
	35.990	49.68

Scalemic-**20Aa**



	Retention Time	% Area
	17.569	18.39
	35.181	81.61

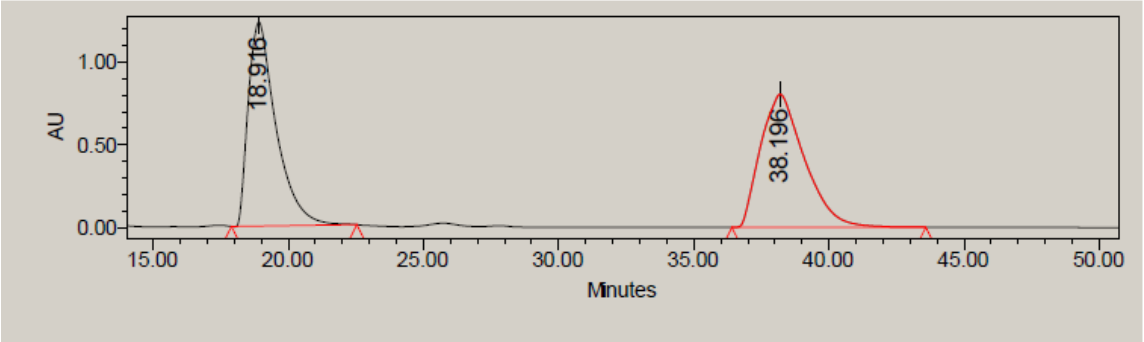
dr: >20:1, 63% *ee*



20Ba

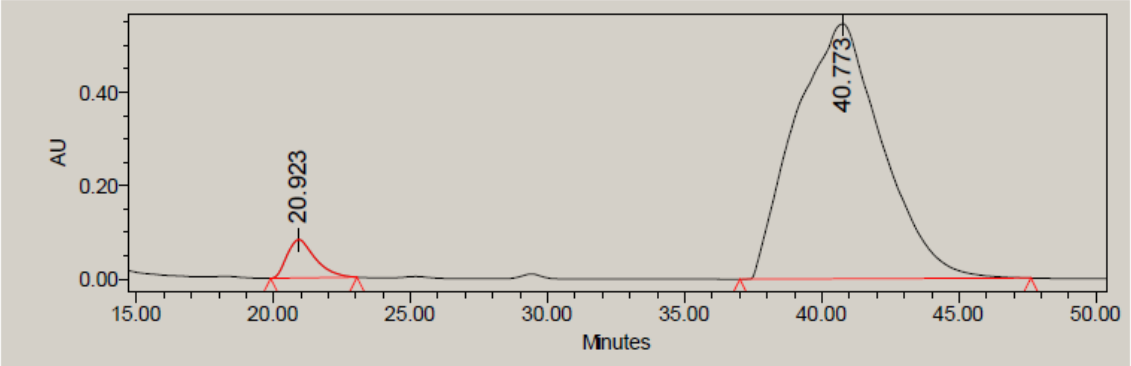
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 1.0 mL/min).

Rac-**20Ba**



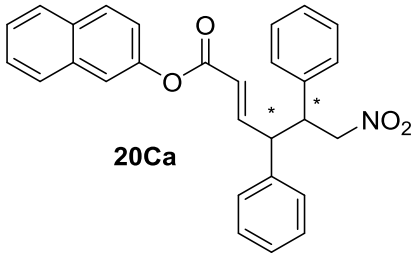
	Retention Time	% Area
	18.916	50.20
	38.196	49.80

Scalemic-**20Ba**



	Retention Time	% Area
	20.923	4.64
	40.773	95.36

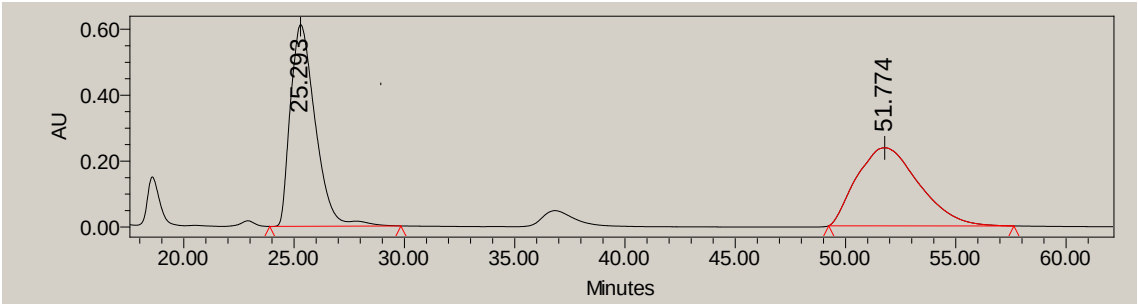
dr: >20:1, 91% *ee*



20Ca

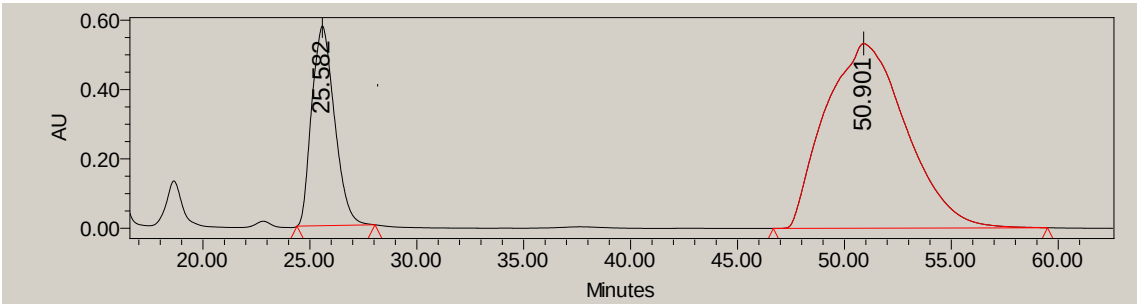
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1.0 mL/min).

Rac-**20Ca**



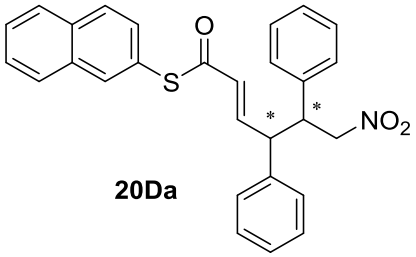
	Retention Time	% Area
	25.293	49.21
	51.774	50.79

Scalemic-**20Ca**



	Retention Time	% Area
	25.582	23.32
	50.901	76.68

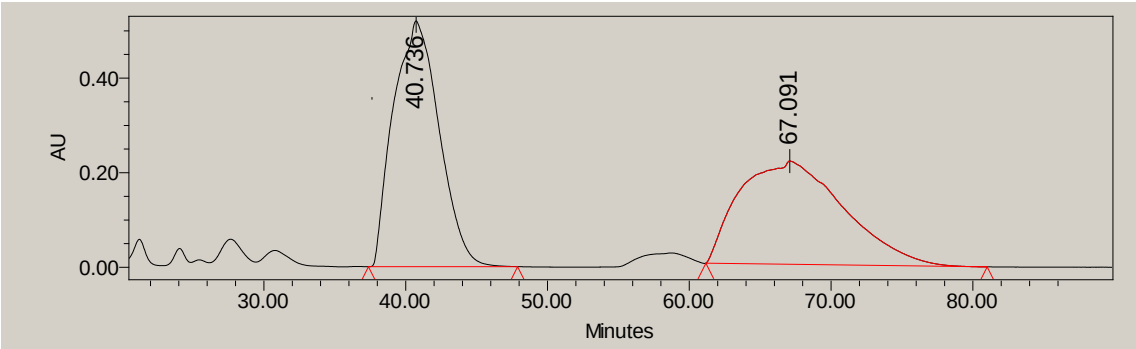
dr: >20:1, 54% *ee*



20Da

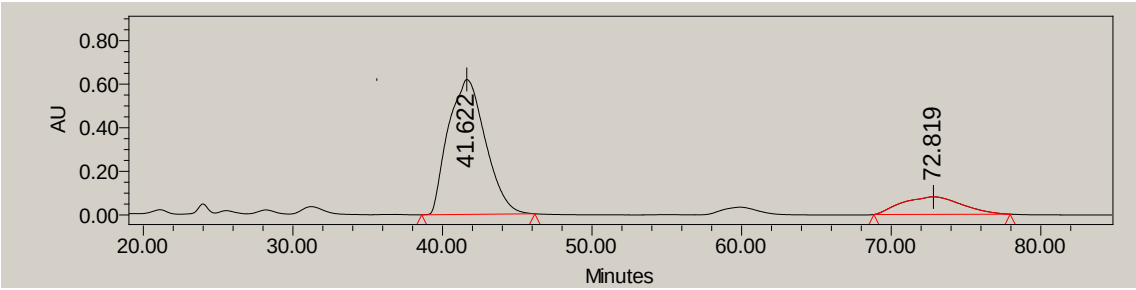
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 1.0 mL/min).

Rac-**20Da**



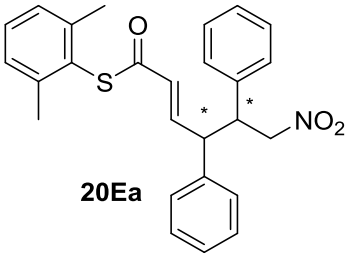
	Retention Time	% Area
	40.736	48.92
	67.091	51.08

Scalemic-**20Da**



	Retention Time	% Area
	41.630	82.16
	72.812	17.84

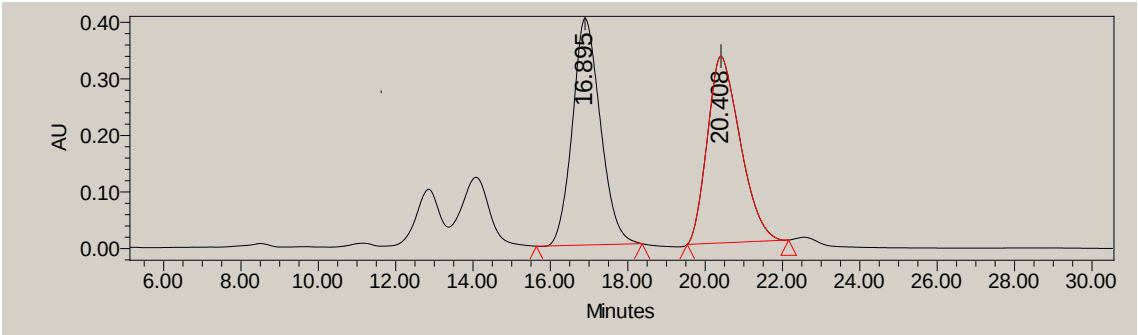
dr: >20:1, 64% *ee*



20Ea

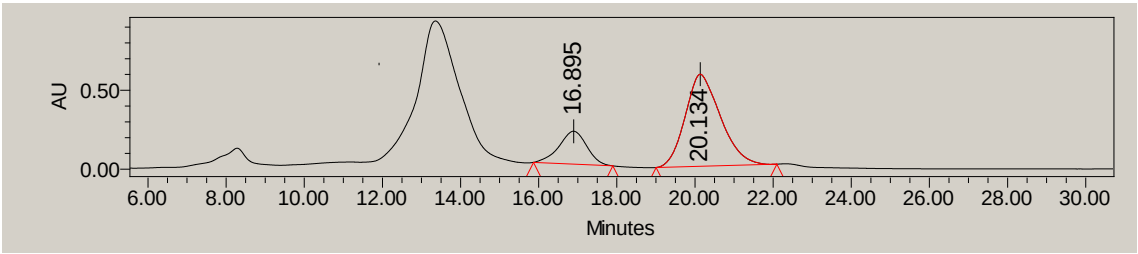
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90/10, flow rate= 1.0 mL/min).

Rac-**20Ea**



	Retention Time	% Area
	16.895	49.16
	20.408	50.84

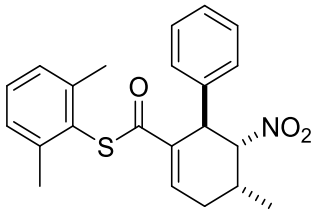
Scalemic-**20Ea**



	Retention Time	% Area
	16.895	22.04
	20.134	77.96

dr: >20:1, 56% *ee*

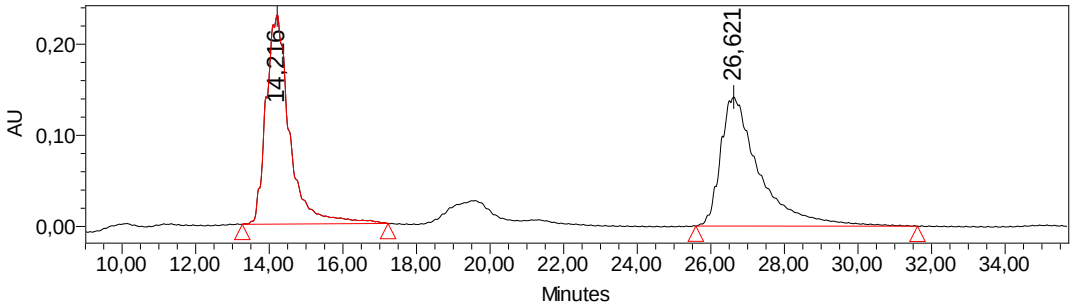
6.7.2. Chapter 3



26Aa

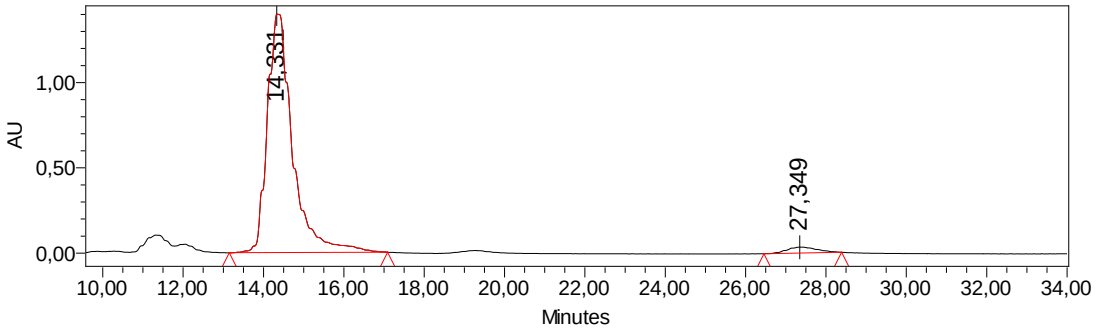
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**26Aa**



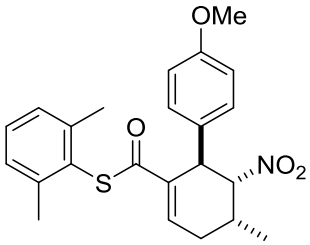
	Retention Time	% Area
	14,216	50,44
	26,621	49,56

Scalemic-**26Aa**



	Retention Time	% Area
	14,331	97,12
	27,349	2,88

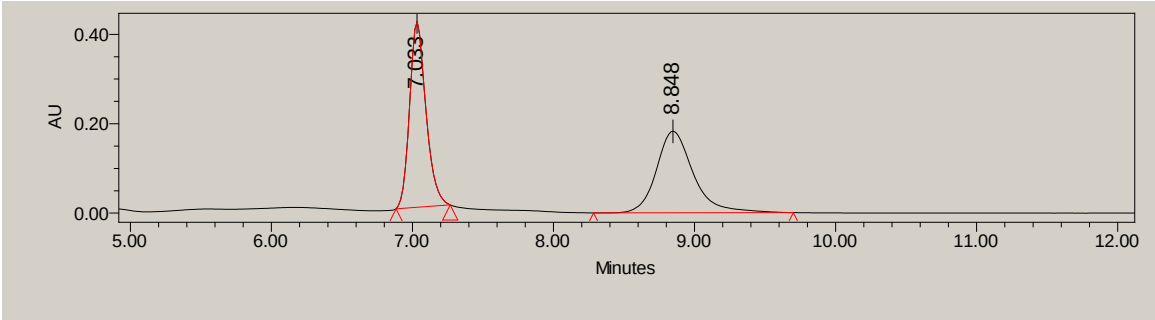
dr: >20:1, 94% *ee*



26Ab

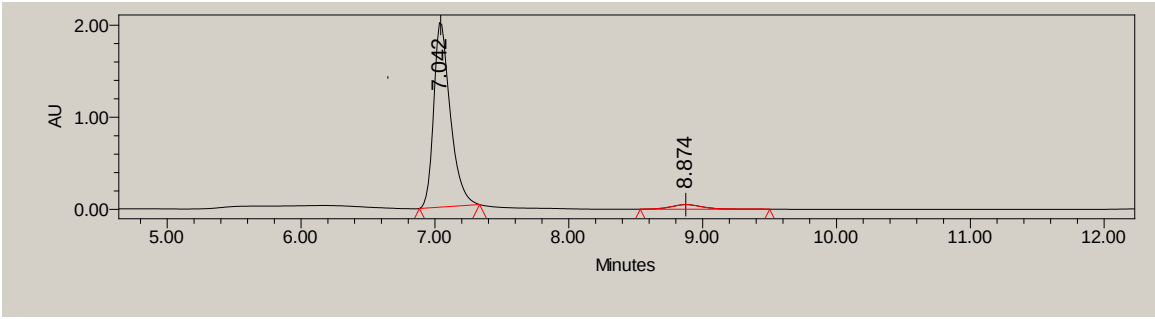
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 1 mL/min).

Rac-**26Ab**



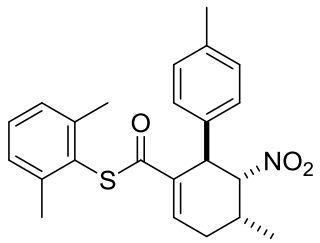
	Retention Time	% Area
	7.033	50.12
	8.848	49.88

Scalemic-**26Ab**



	Retention Time	% Area
	7.042	96.38
	8.874	3.62

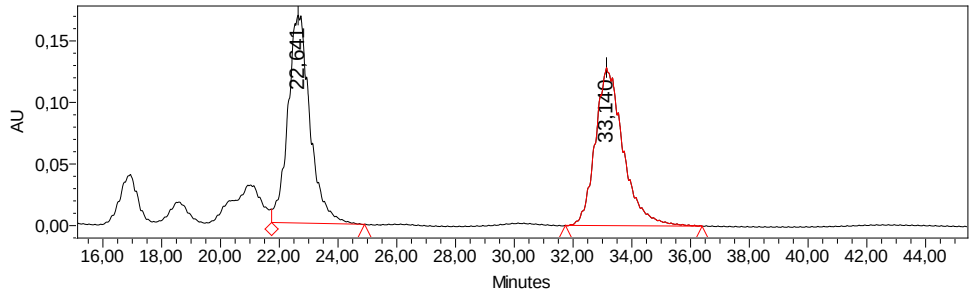
dr: >20:1, 92% *ee*



26Ac

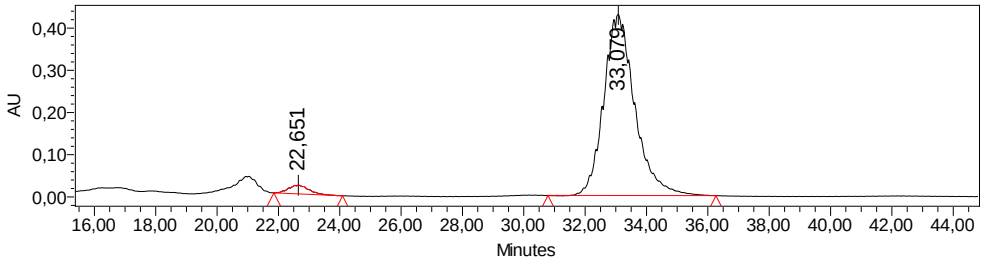
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**26Ac**



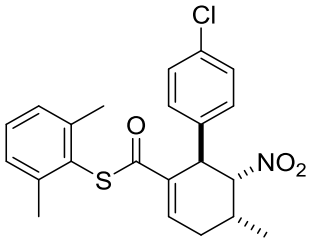
	Retention Time	% Area
	22,641	50,19
	33,140	49,81

Scalemic-**26Ac**



	Retention Time	% Area
	22,651	3,09
	33,079	96,91

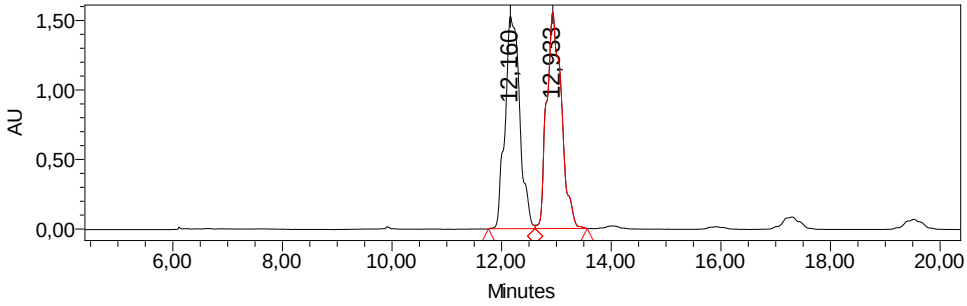
dr: >20:1, 94% *ee*



26Ad

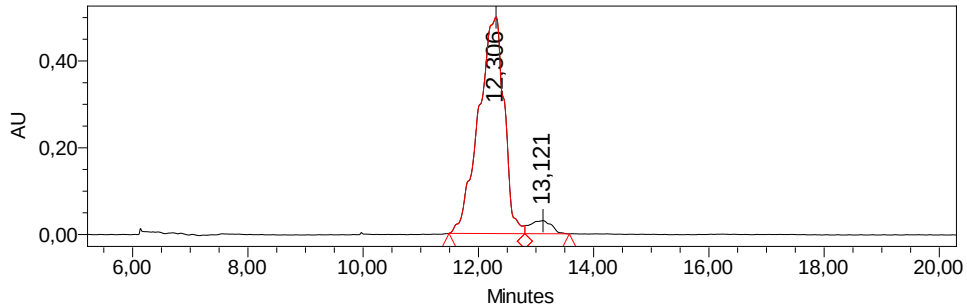
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1 mL/min).

Rac-**26Ad**



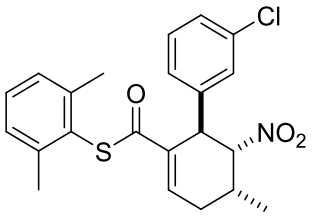
	Retention Time	% Area
	12,160	49,45
	12,933	50,55

Scalemic-**26Ad**



	Retention Time	% Area
	12,306	95,10
	13,121	4,90

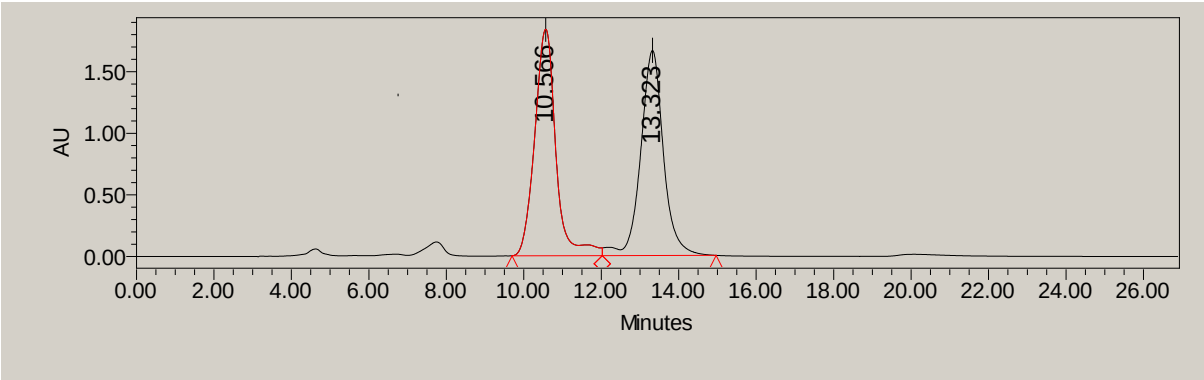
dr: >20:1, 90% *ee*



26Ag

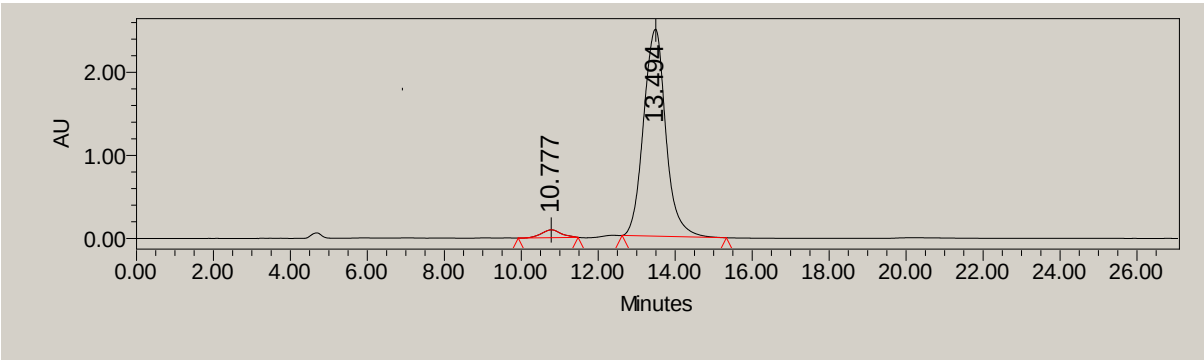
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 1 mL/min).

Rac-**26Ag**



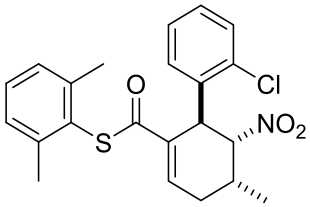
	Retention Time	% Area
	10.566	51.04
	13.323	48.96

Scalemic-**26Ag**



	Retention Time	% Area
	10.777	3.24
	13.494	96.76

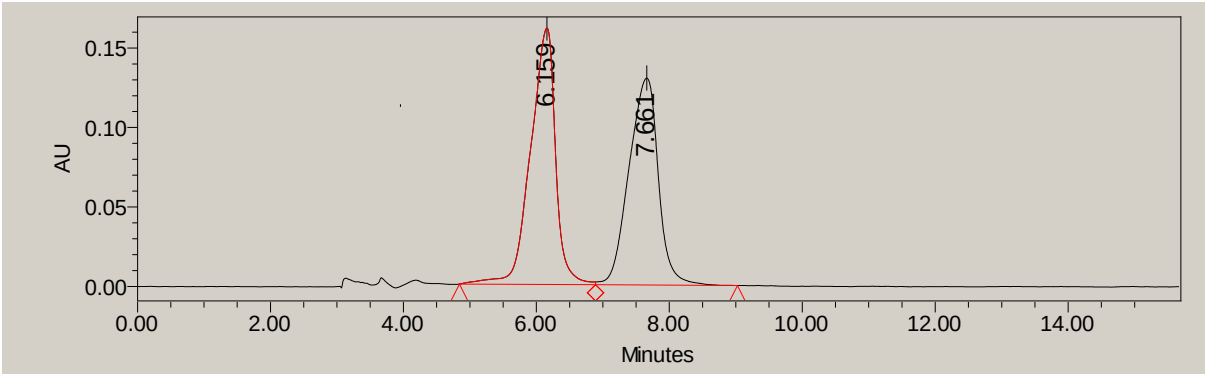
dr: >20:1, 94% *ee*



26Ah

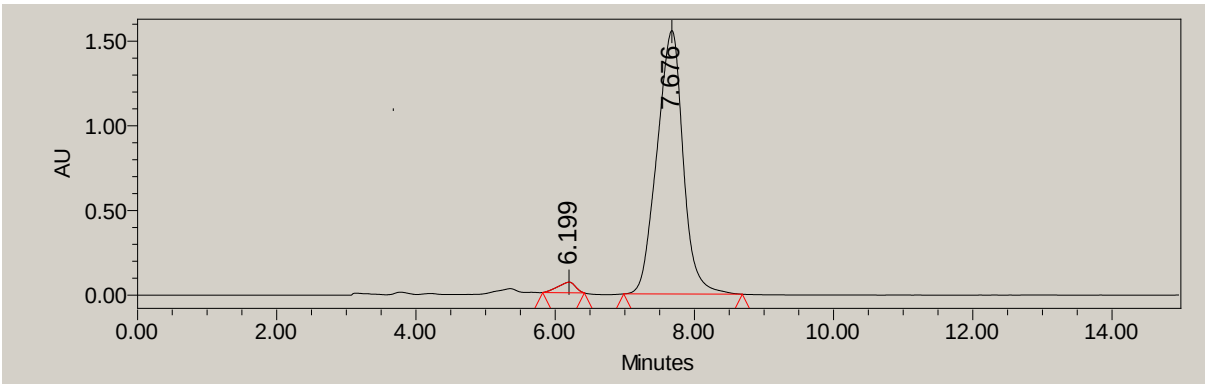
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**26Ah**



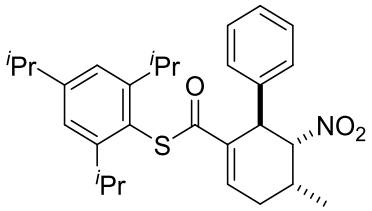
	Retention Time	% Area
	6.159	51.34
	7.661	48.66

Scalemic-**26Ah**



	Retention Time	% Area
	6.199	2.63
	7.676	97.37

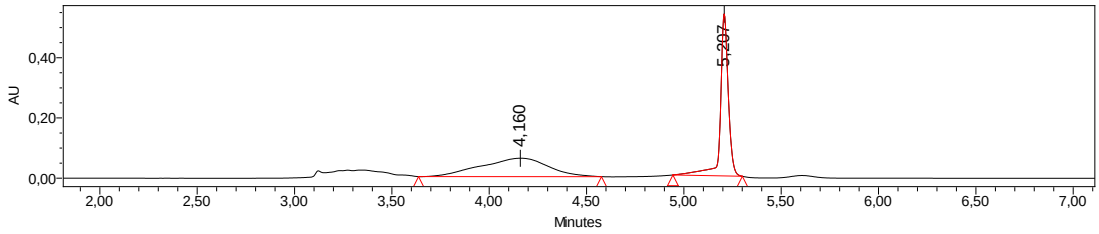
dr: >20:1, 95% *ee*



26Ba

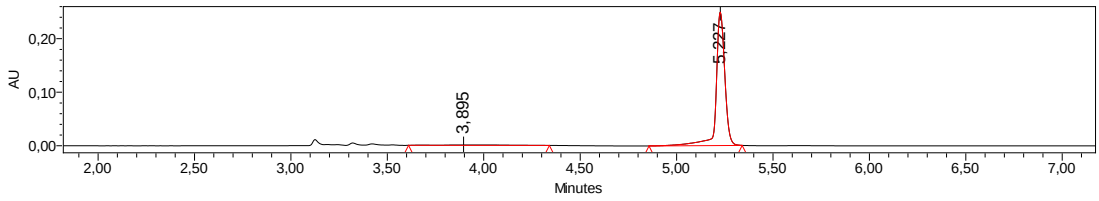
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**26Ba**



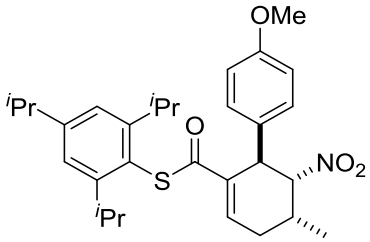
	Retention Time	% Area
	4,160	49,07
	5,207	50,93

Scalemic-**26Ba**



	Retention Time	% Area
	3,895	2,47
	5,227	97,53

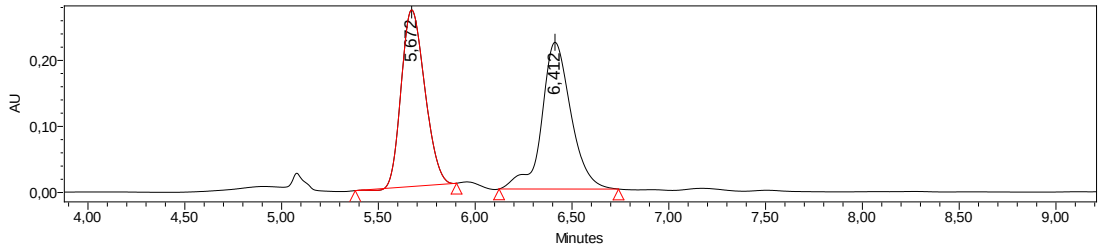
dr: >20:1, 95% *ee*



26Bb

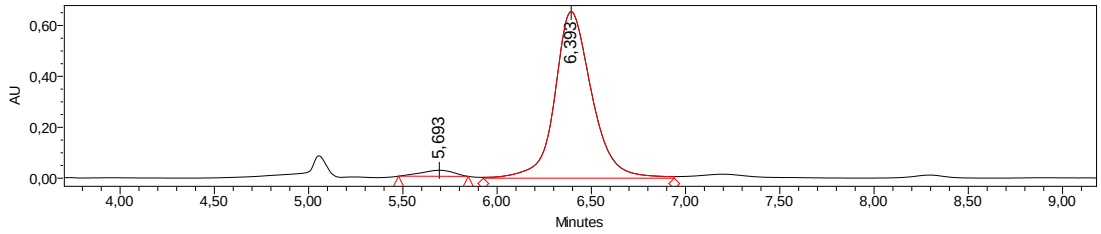
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**26Bb**



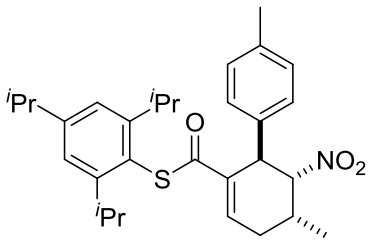
	Retention Time	% Area
	5,672	49,34
	6,412	50,66

Scalemic-**26Bb**



	Retention Time	% Area
	5,693	3,08
	6,393	96,92

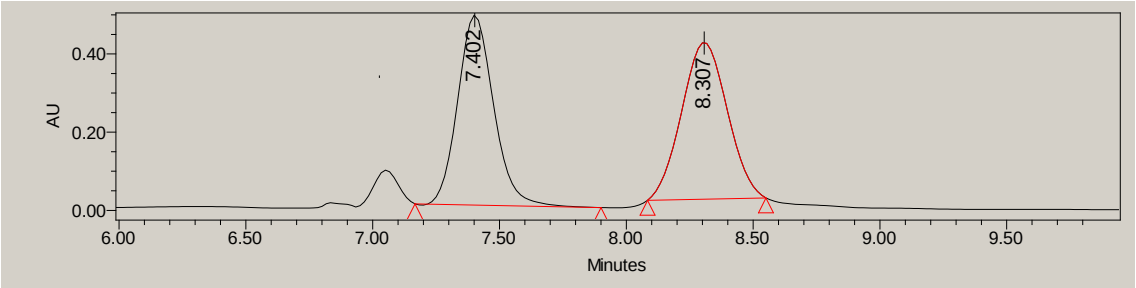
dr: >20:1, 94% *ee*



26Bc

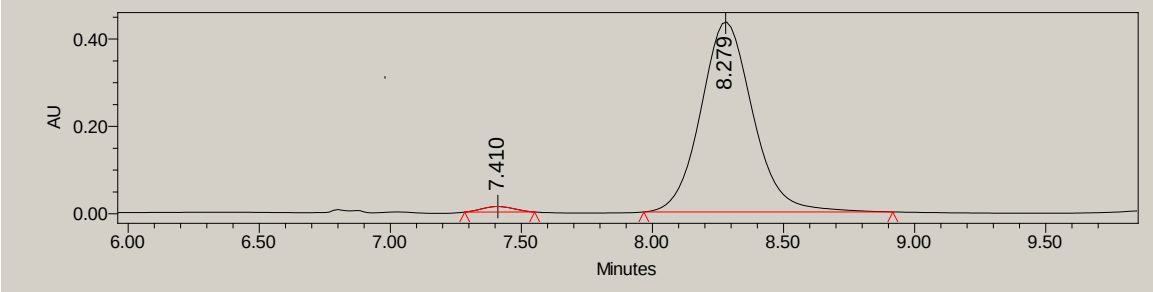
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**26Bc**



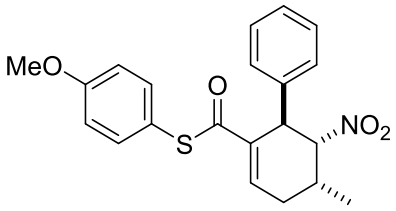
	Retention Time	% Area
	7.402	49.89
	8.307	50.11

Scalemic-**26Bc**



	Retention Time	% Area
	7.410	3.75
	8.279	96.25

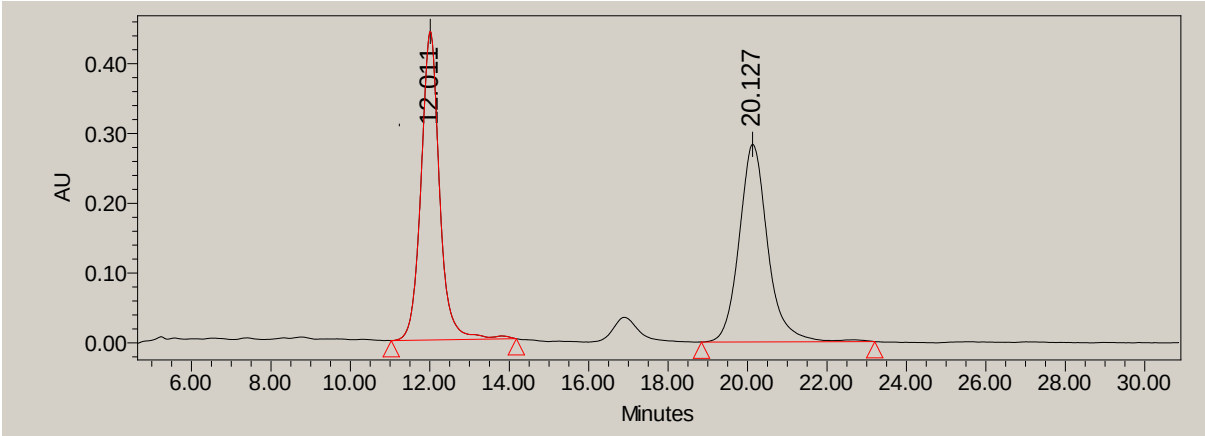
dr: >20:1, 92% *ee*



26Ca

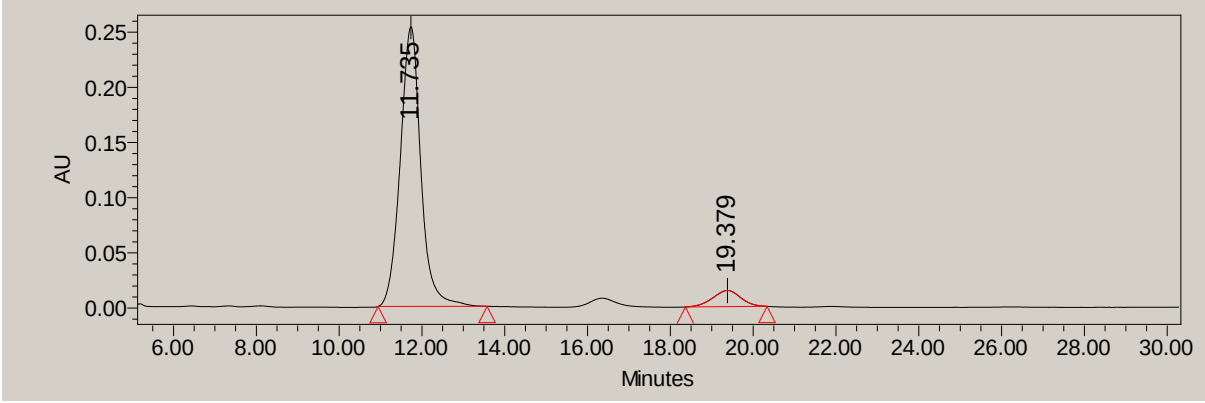
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min).

Rac-**26Ca**



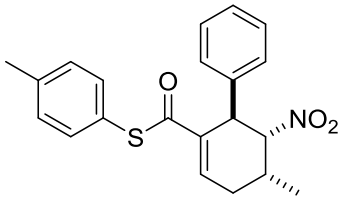
	Retention Time	% Area
	12.011	50.33
	20.127	49.67

Scalemic-**26Ca**



	Retention Time	% Area
	11.735	93.94
	19.379	6.06

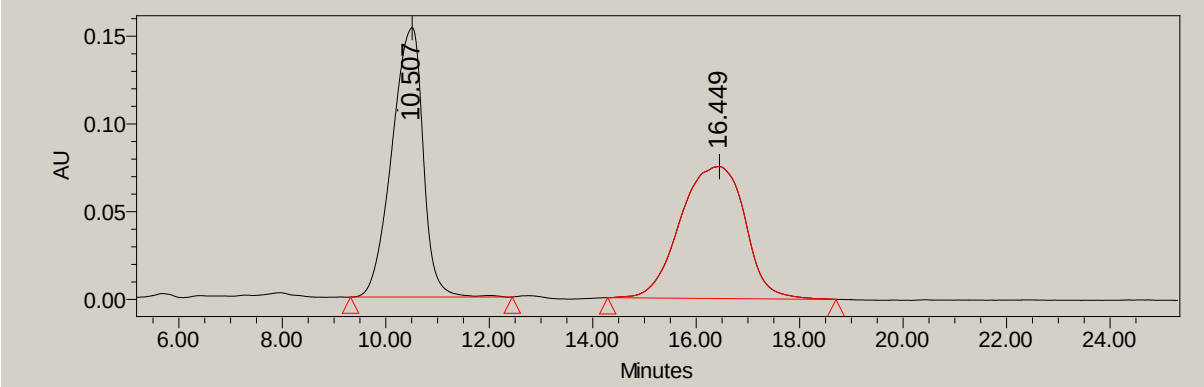
dr: >20:1, 88% *ee*



26Da

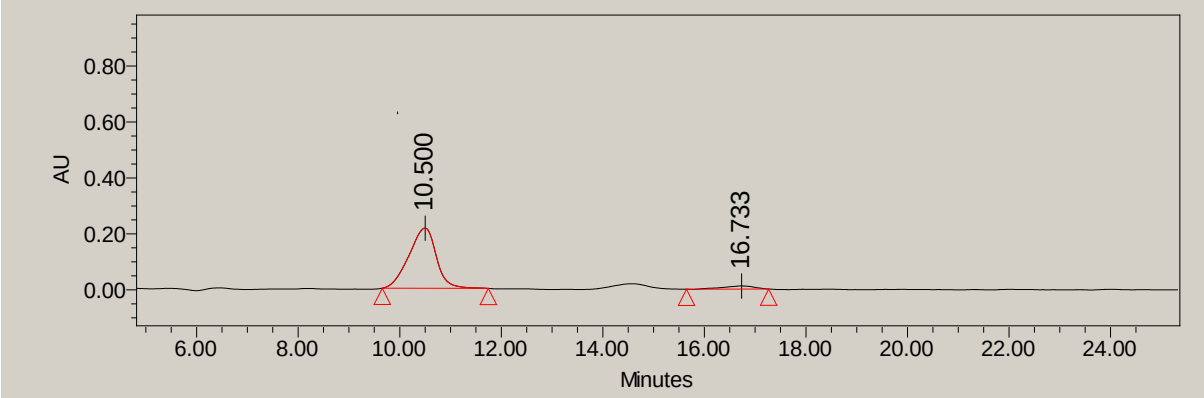
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min).

Rac-**26Da**



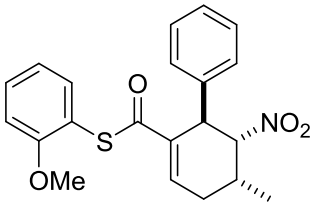
	Retention Time	% Area
	10.507	49.70
	16.449	50.30

Scalemic-**26Da**



	Retention Time	% Area
	10.500	95.26
	16.733	4.74

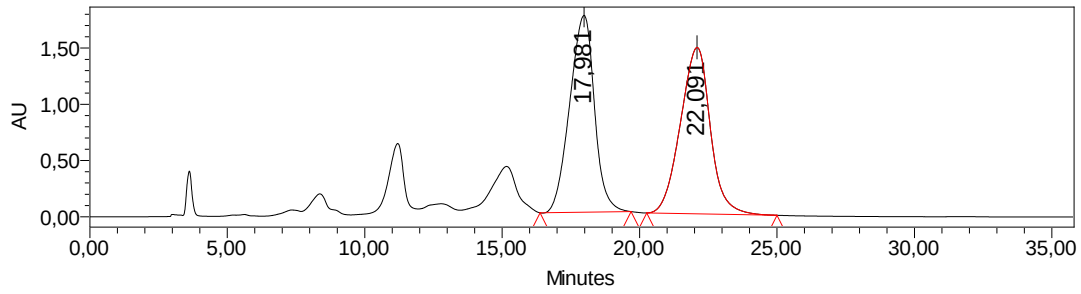
dr: >20:1, 91% *ee*



26Ea

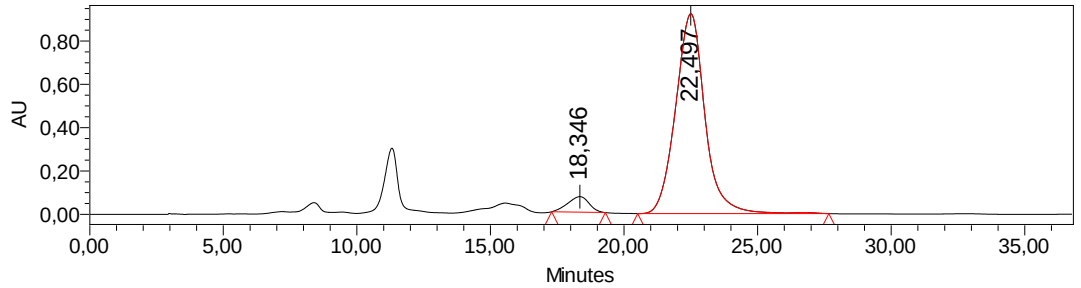
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min).

Rac-**26Ea**



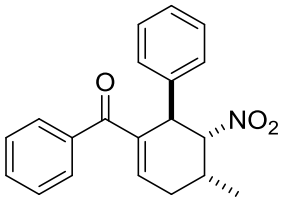
	Retention Time	% Area
	17,981	49,47
	22,091	50,53

Scalemic-**26Ea**



	Retention Time	% Area
	18,346	5,34
	22,497	94,66

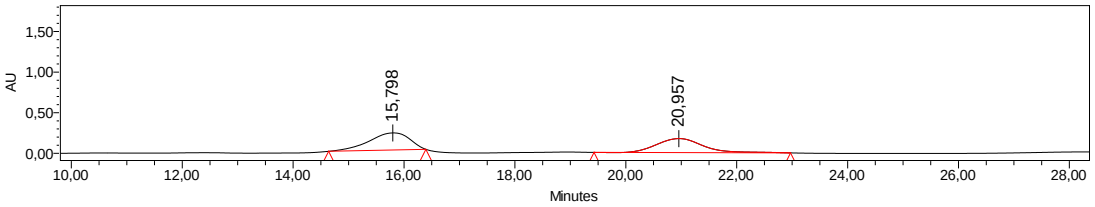
dr: >20:1, 90% *ee*



37a

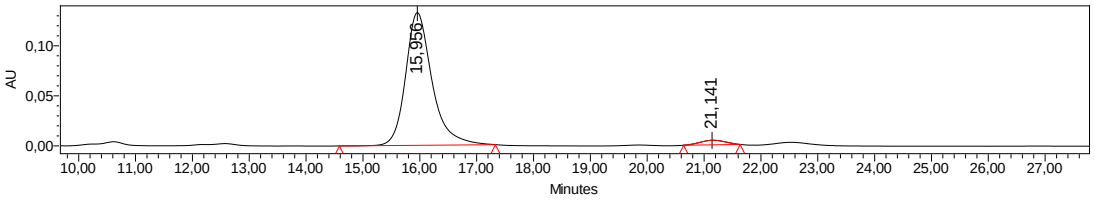
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**37a**



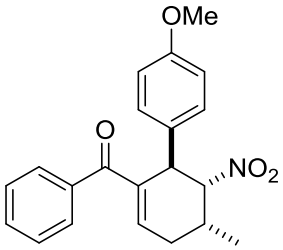
	Retention Time	% Area
	15,798	51,34
	20,957	48,66

Scalemic-**37a**



	Retention Time	% Area
	15,956	96,78
	21,141	3,22

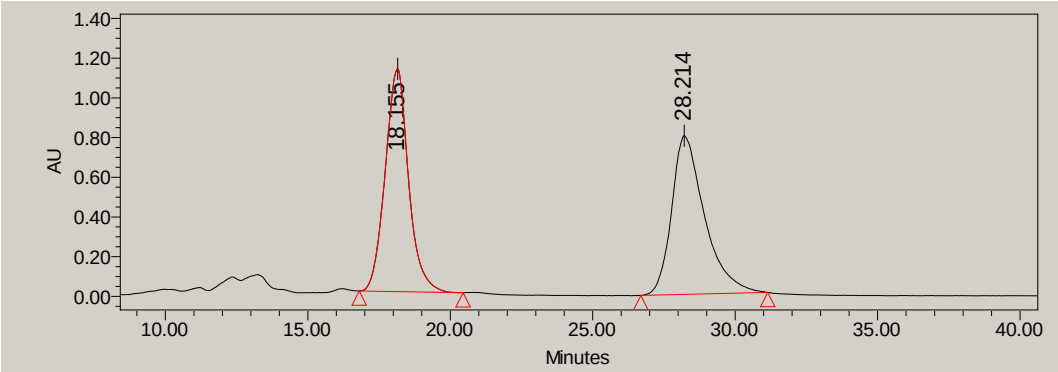
dr: >20:1, 93% *ee*



37b

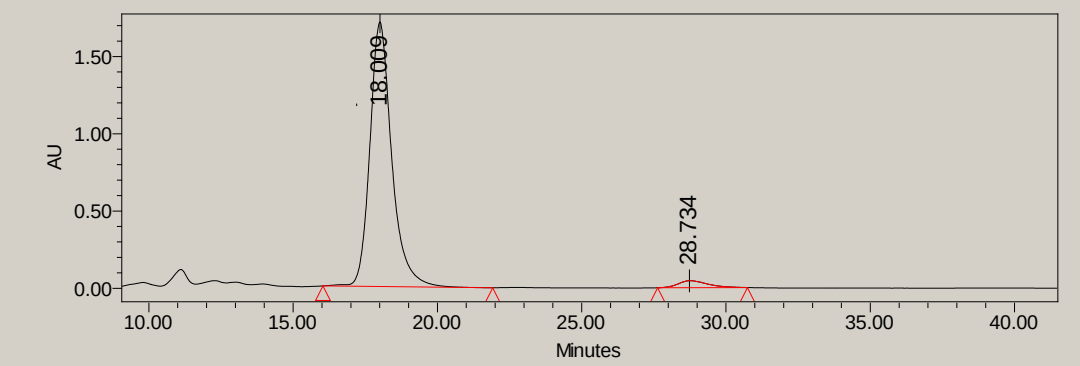
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min).

Rac-**37b**



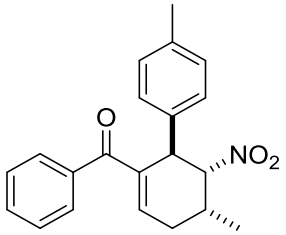
	Retention Time	% Area
	18.155	49.89
	28.214	50.11

Scalemic-**37b**



	Retention Time	% Area
	18.009	96.54
	28.734	3.46

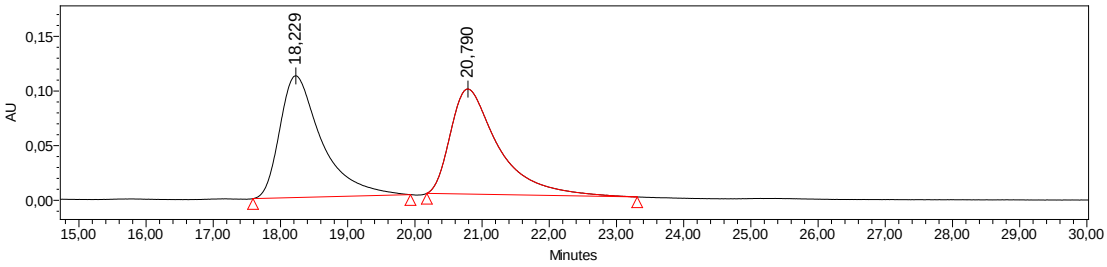
dr: >20:1, 93% *ee*



37c

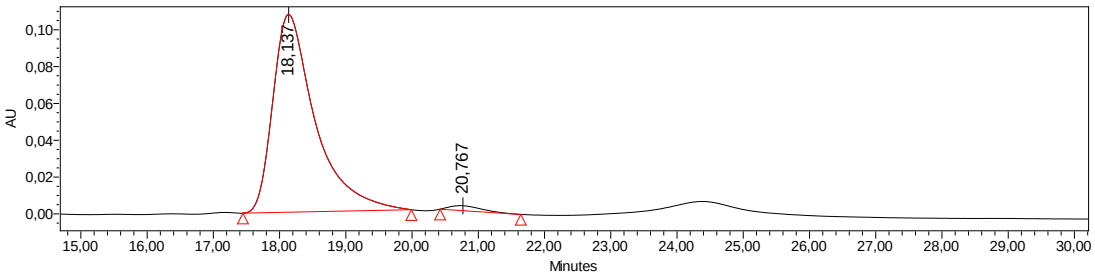
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**37c**



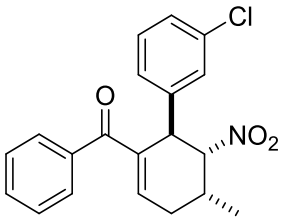
	Retention Time	% Area
	18,229	50,19
	20,790	49,81

Scalemic-**37c**



	Retention Time	% Area
	18,137	98,20
	20,767	1,80

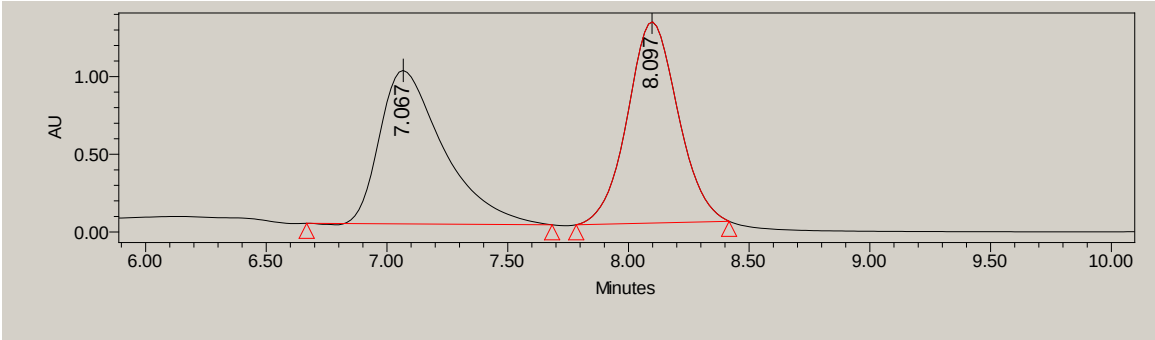
dr: >20:1, 96% *ee*



37g

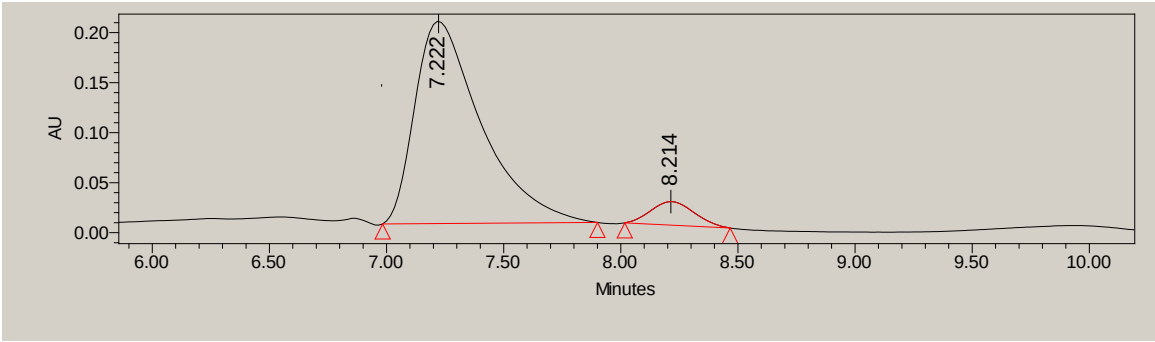
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 80/20, flow rate= 1 mL/min).

Rac-**37g**



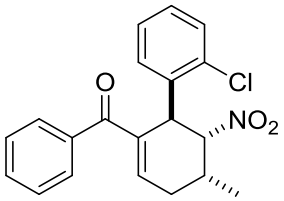
	Retention Time	% Area
	7.067	49.10
	8.097	50.90

Scalemic-**37g**



	Retention Time	% Area
	7.222	92.92
	8.214	7.08

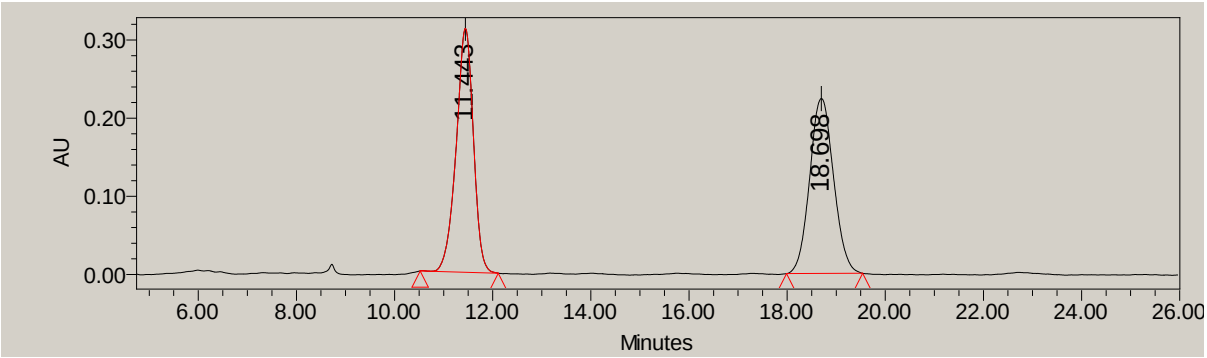
dr: >20:1, 86% *ee*



37h

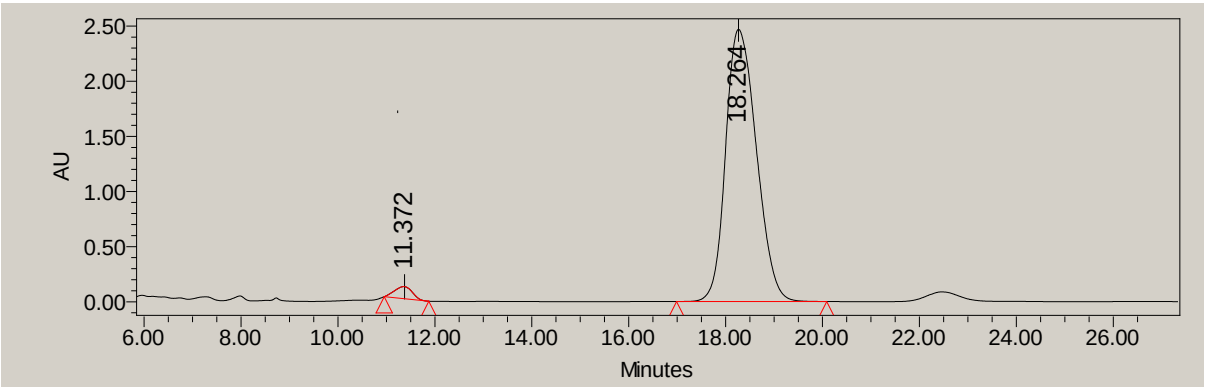
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**37h**



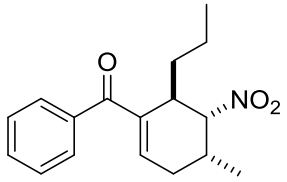
	Retention Time	% Area
	11.443	50.11
	18.698	49.89

Scalemic-**37h**



	Retention Time	% Area
	11.372	2.48
	18.264	97.52

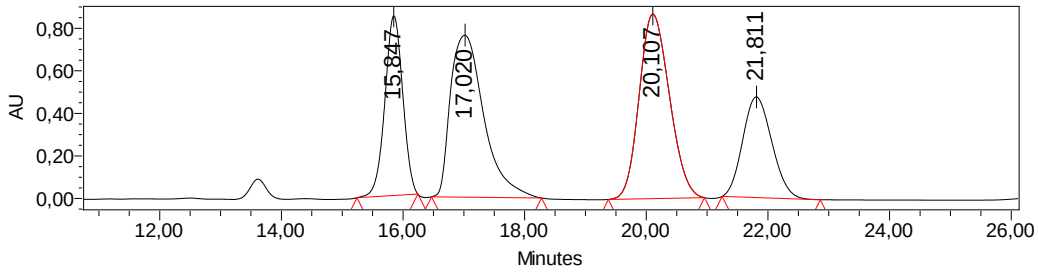
dr: >20:1, 95% *ee*



37i

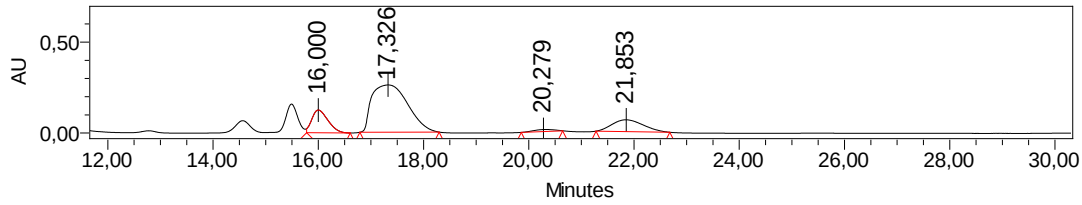
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**37i**



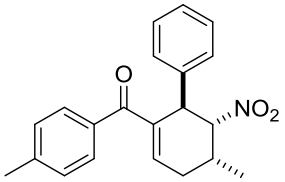
	Retention Time	% Area
	15,848	19,23
	17,011	30,38
	20,107	33,21
	21,807	17,18

Scalemic-**37i**



	Retention Time	% Area
	16,000	14,74
	17,326	68,74
	20,279	1,64
	21,853	14,88

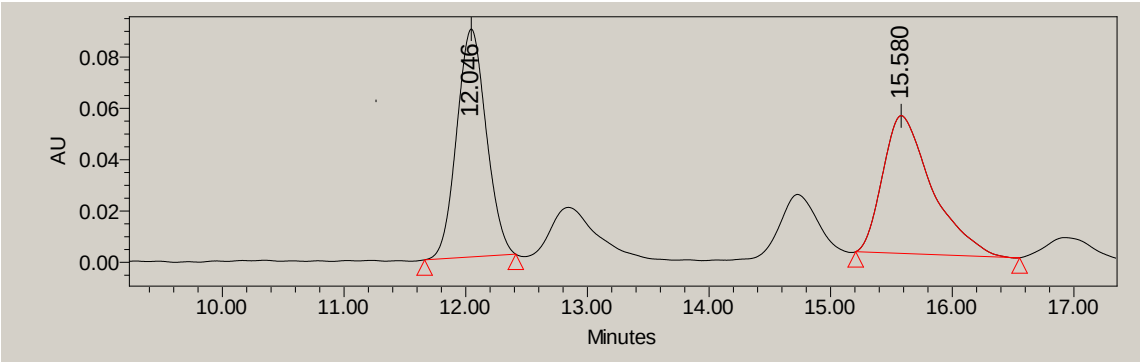
dr: 2.6:1, 94% *ee*



38a

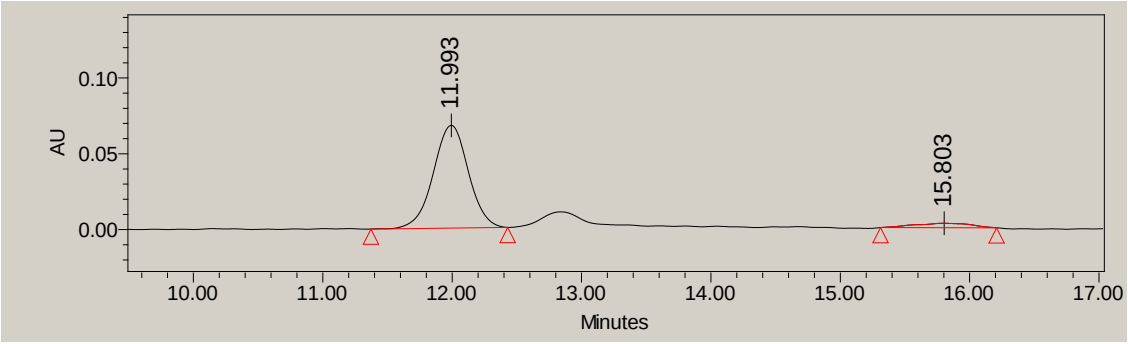
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**38a**



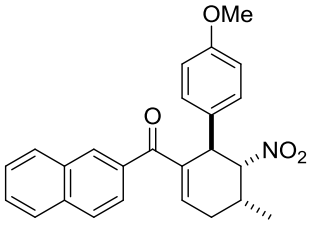
	Retention Time	% Area
	12.046	49.80
	15.580	50.20

Scalemic-**38a**



	Retention Time	% Area
	11.993	95.40
	15.803	4.60

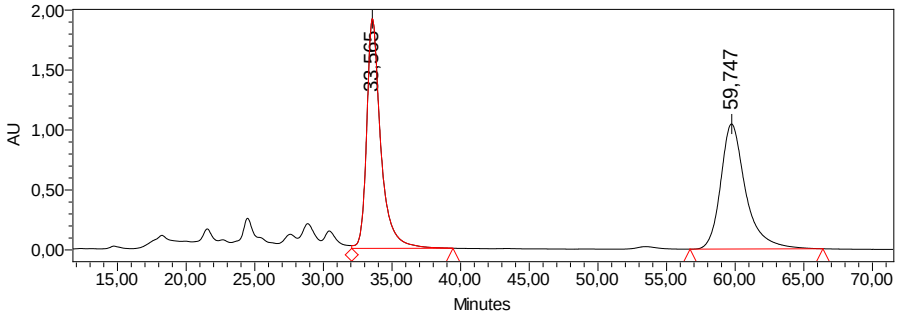
dr: >20:1, 91% *ee*



39b

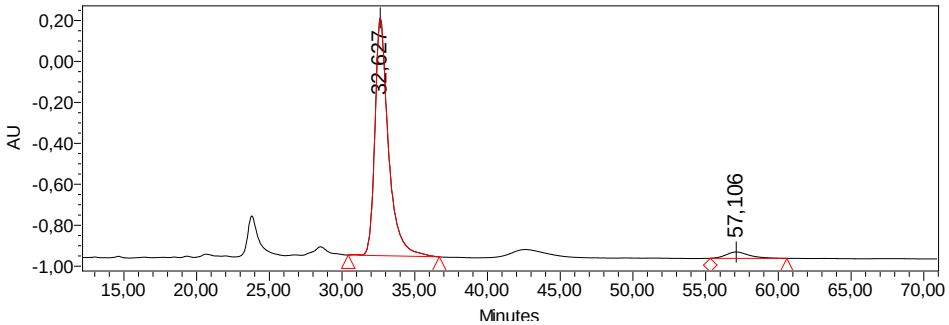
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**39b**



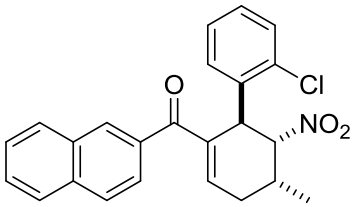
	Retention Time	% Area
	33,565	50,81
	59,747	49,19

Scalemic-**39b**



	Retention Time	% Area
	32,627	95,56
	57,106	4,44

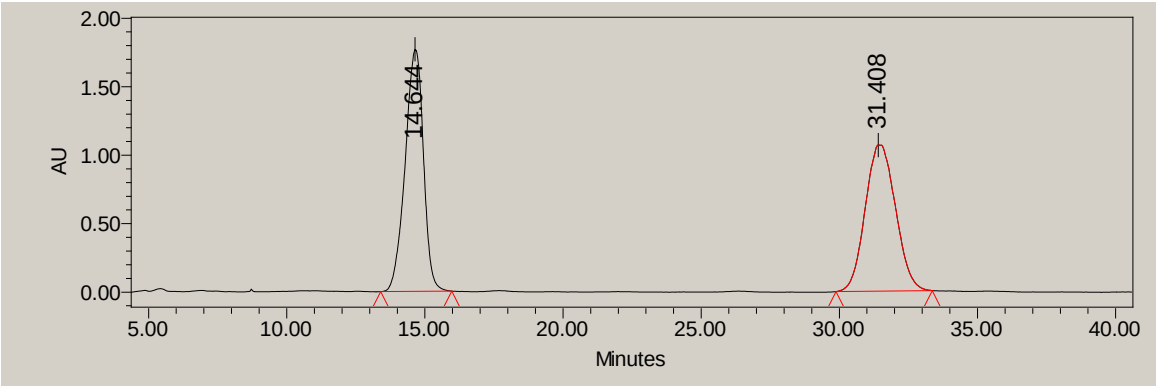
dr: >20:1, 91% *ee*



39h

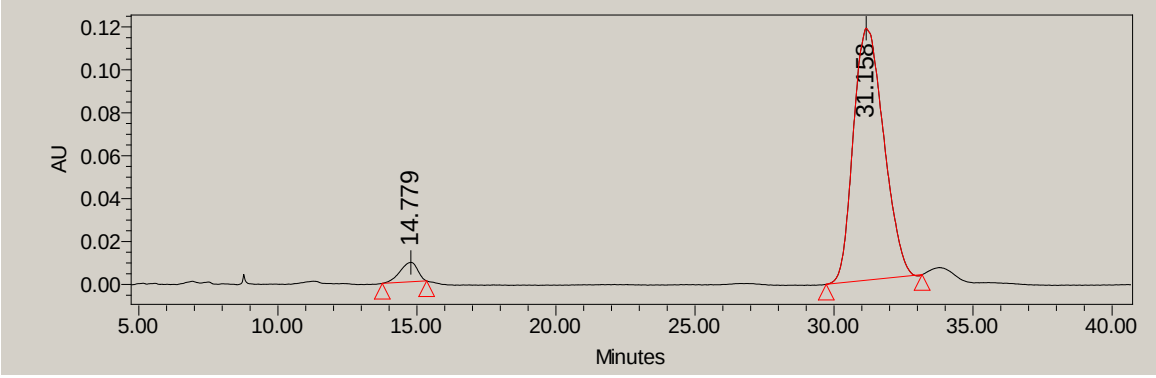
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1 mL/min).

Rac-**39h**



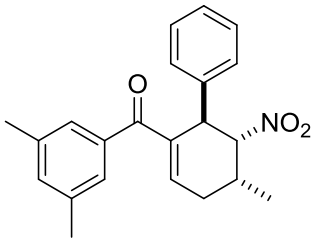
	Retention Time	% Area
	14.644	49.99
	31.408	50.01

Scalemic-**39h**



	Retention Time	% Area
	14.779	4.81
	31.158	95.19

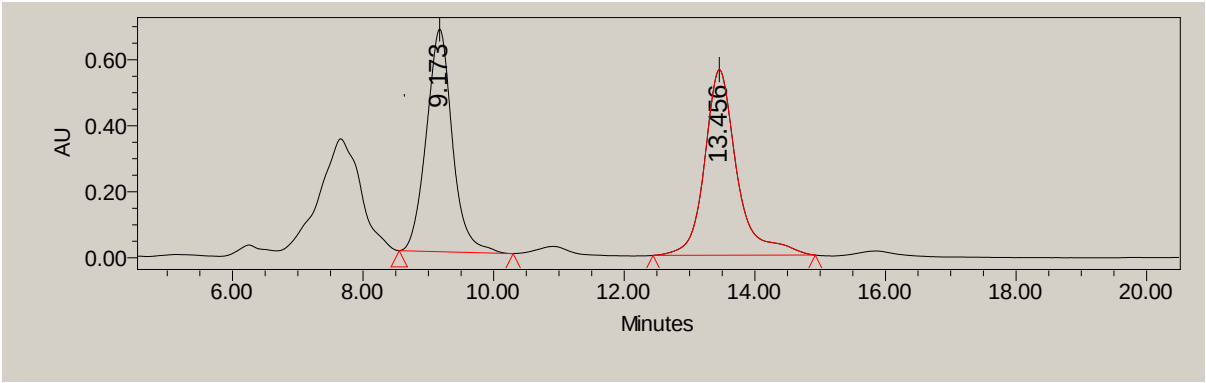
dr: >20:1, 90% *ee*



40a

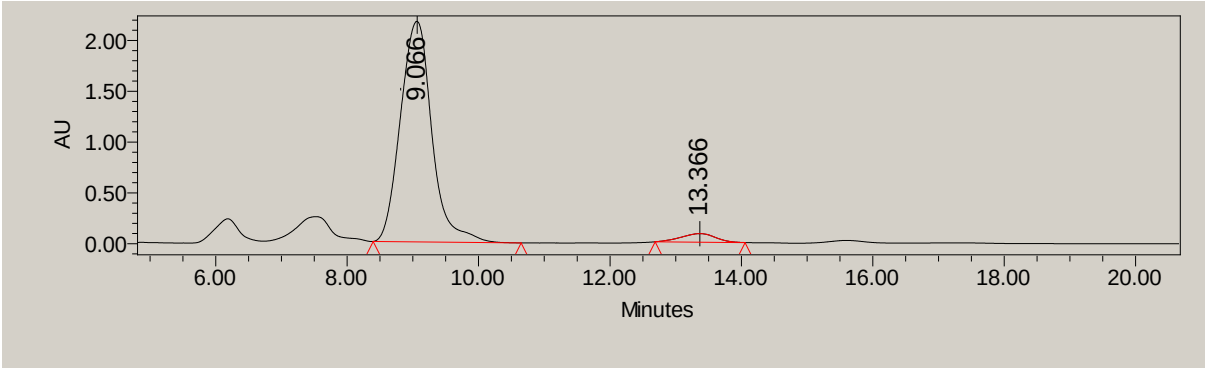
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 1 mL/min).

Rac-**40a**



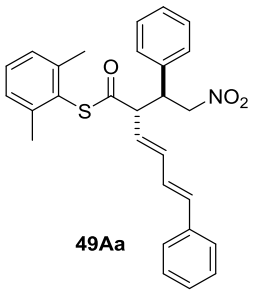
	Retention Time	% Area
	9.173	49.08
	13.456	50.92

Scalemic-**40a**



	Retention Time	% Area
	9.066	95.96
	13.366	4.04

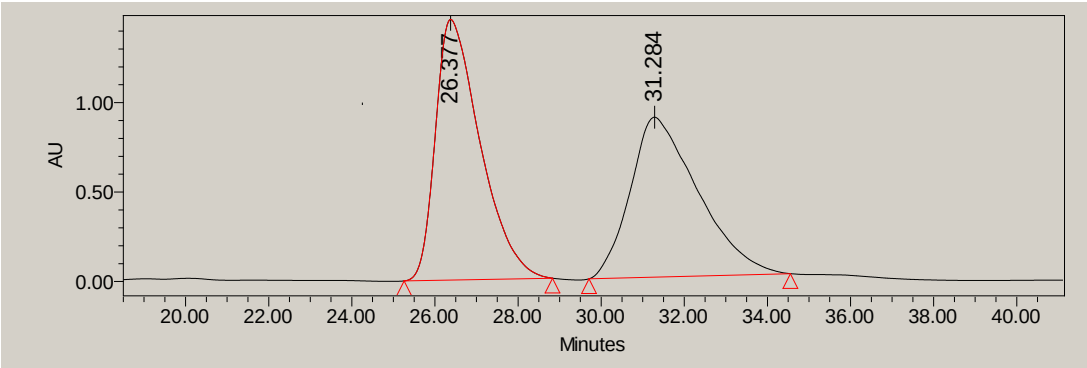
dr: >20:1, 92% *ee*



49Aa

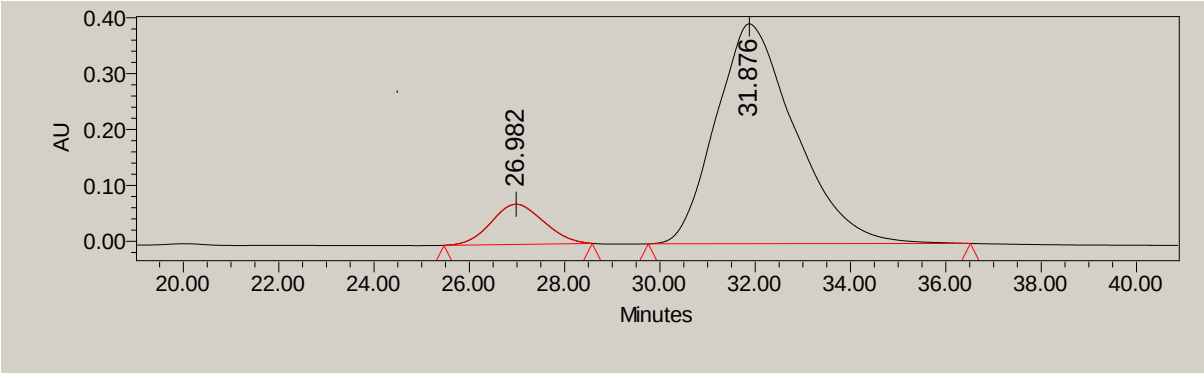
The diastereomeric ratio was determined by ^{1}H NMR analysis on crude material. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**49Aa**



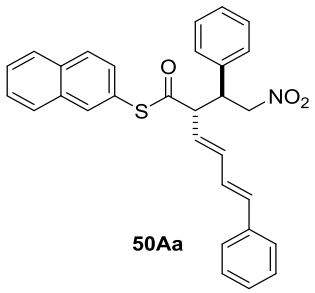
	Retention Time	% Area
	26.377	51.8
	31.284	48.12

Scalemic-**49Aa**



	Retention Time	% Area
	26.982	10.76
	31.876	89.24

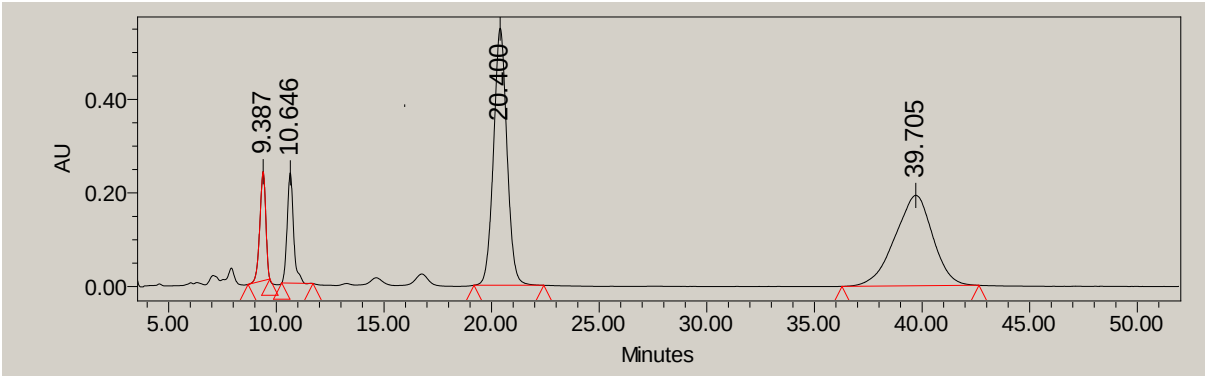
dr: 9:1, 80% *ee*



50Aa

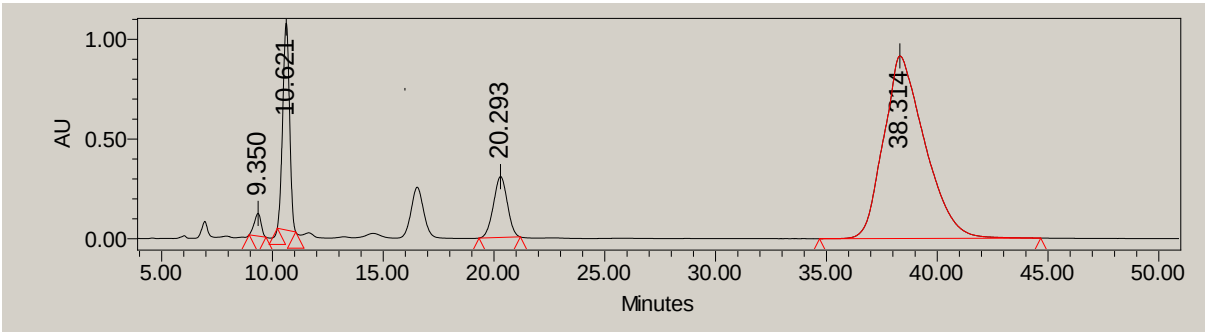
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 80/20, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**50Aa**



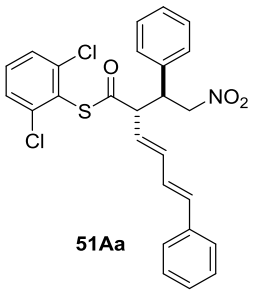
	Retention Time	% Area
	9.387	7.88
	10.646	8.56
	20.400	41.85
	39.705	41.72

Scalemic-**50Aa**



	Retention Time	% Area
	9.350	1.57
	10.621	14.11
	20.293	8.52
	38.314	75.80

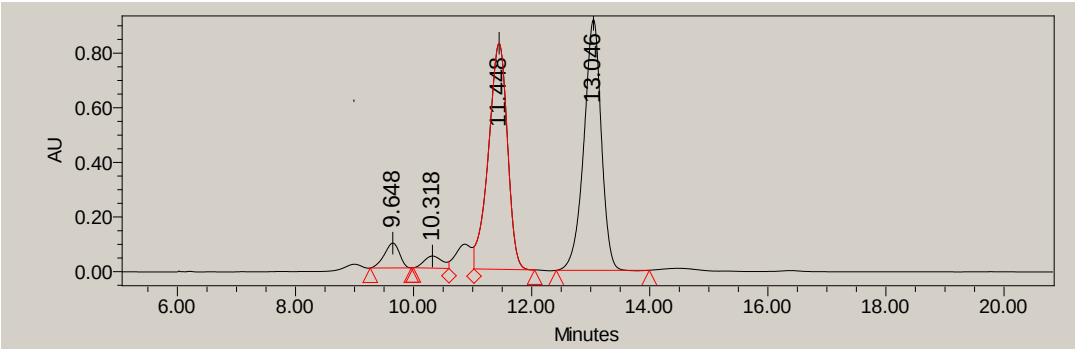
dr: 5.7:1, 80%(82%)*ee*



51Aa

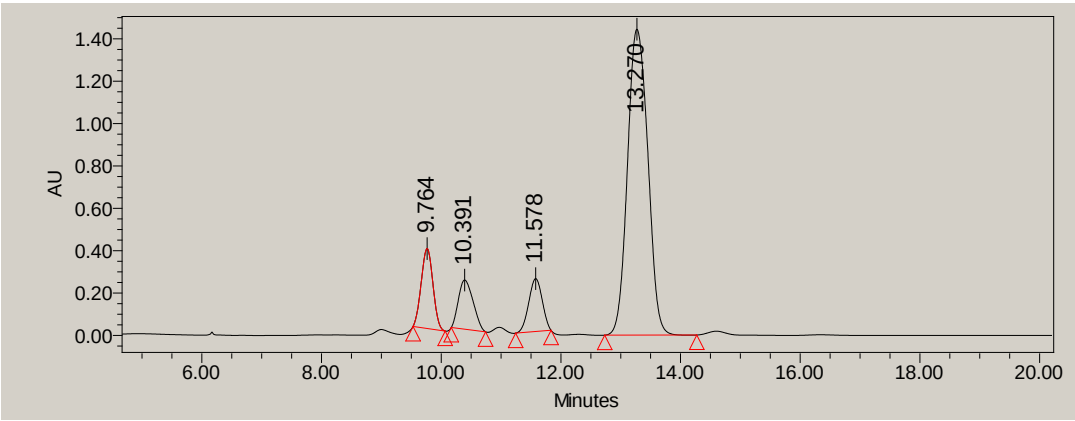
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**51Aa**



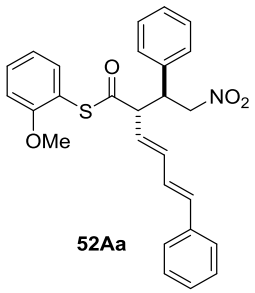
	Retention Time	% Area
	9.648	4.07
	10.318	2.41
	11.448	46.34
	13.046	47.17

Scalemic-**51Aa**



	Retention Time	% Area
	9.764	10.88
	10.391	8.38
	11.578	8.29
	13.270	72.45

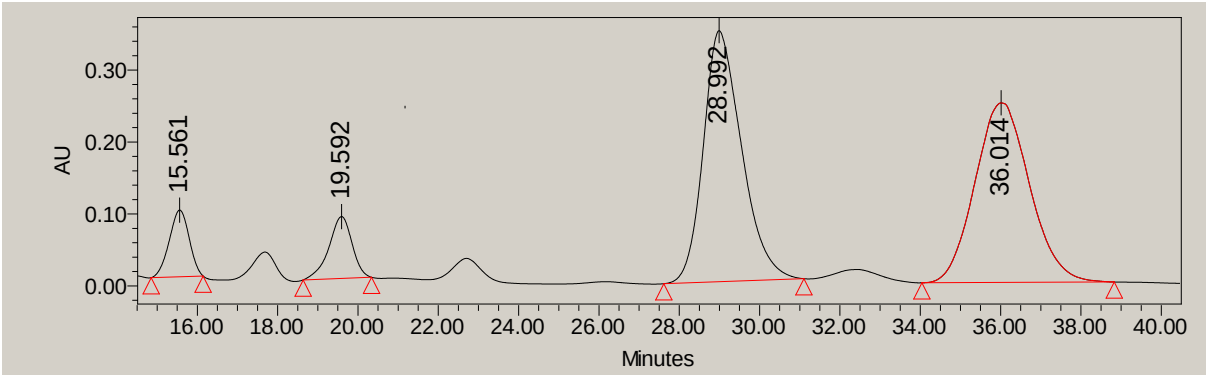
dr: 4.3:1, 80% (10%)*ee*



52Aa

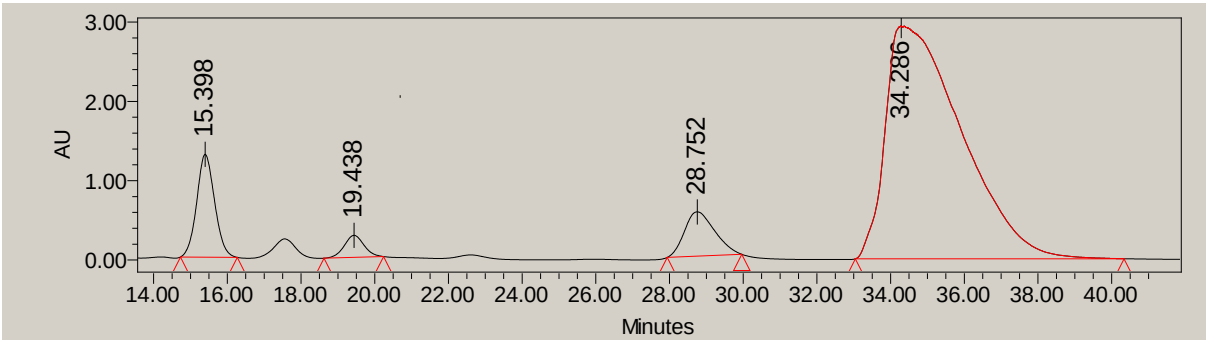
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**52Aa**



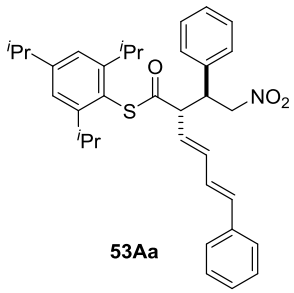
	Retention Time	% Area
	15.561	5.96
	19.592	6.48
	28.992	43.38
	36.014	44.18

Scalemic-**52Aa**



	Retention Time	% Area
	15.398	8.62
	19.438	2.05
	28.752	6.27
	34.286	83.07

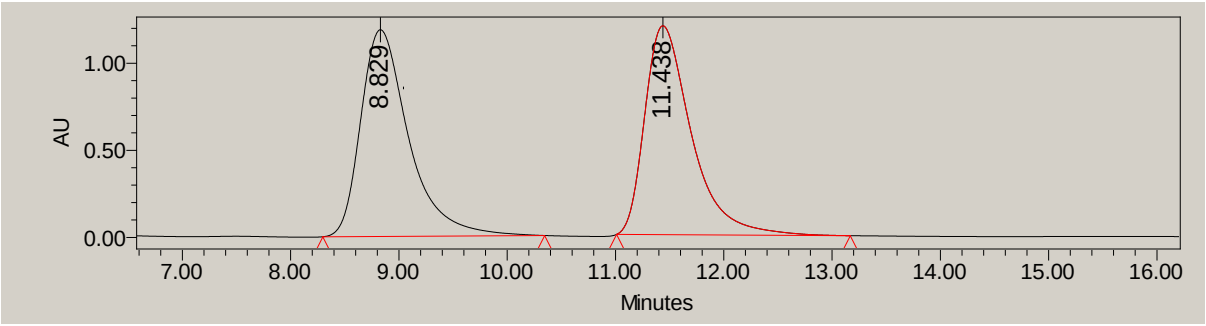
dr: 9:1, 85% (60%)*ee*



53Aa

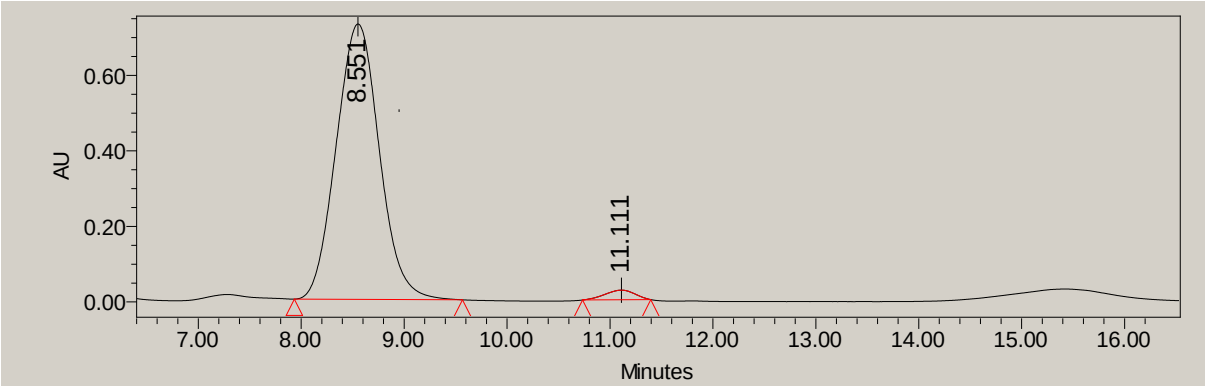
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Aa**



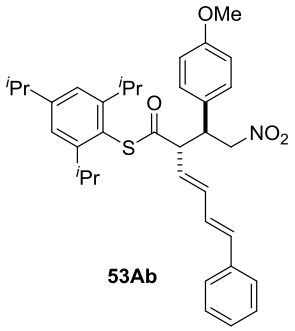
	Retention Time	% Area
	8.829	50.47
	11.438	49.53

Scalemic-**53Aa**



	Retention Time	% Area
	8.551	97.64
	11.111	2.36

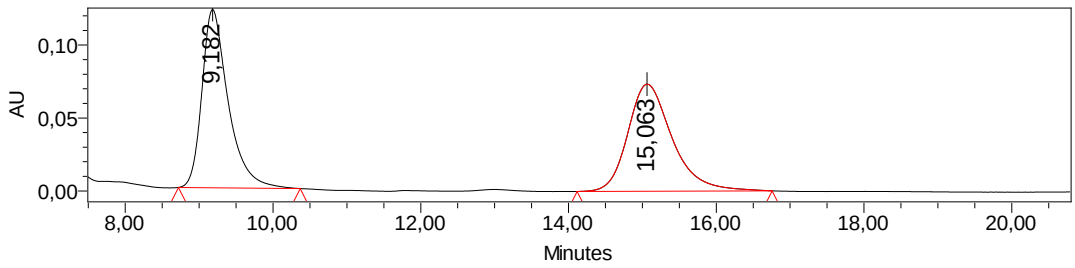
dr:>20:1, 95% *ee*



53Ab

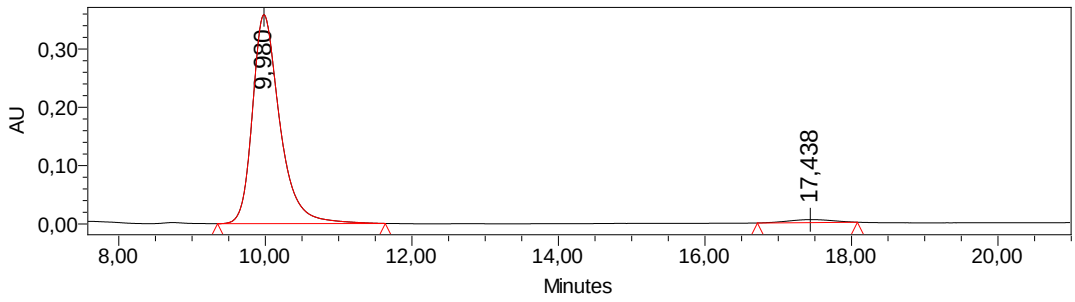
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Ab**



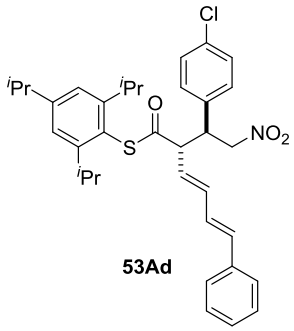
	Retention Time	% Area
	9,182	49,71
	15,063	50,29

Scalemic-**53Ab**



	Retention Time	% Area
	9,980	97,78
	17,438	2,22

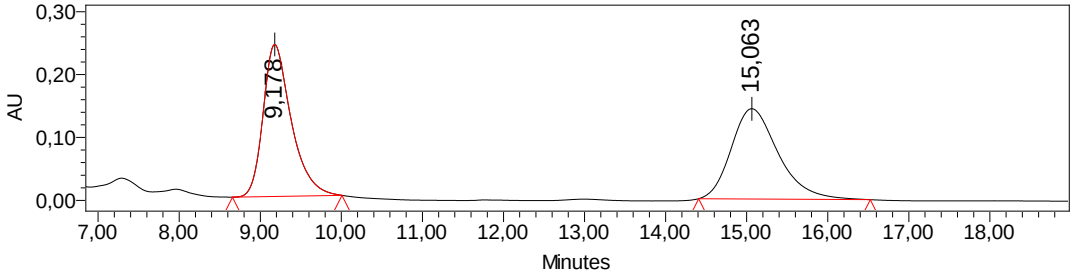
dr:>20:1, 95% *ee*



53Ad

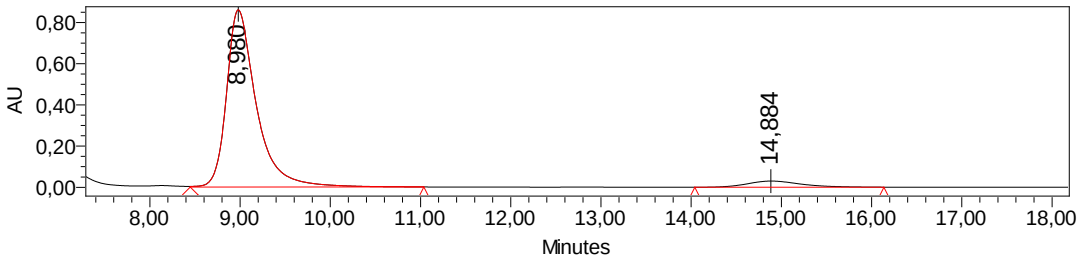
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Ad**



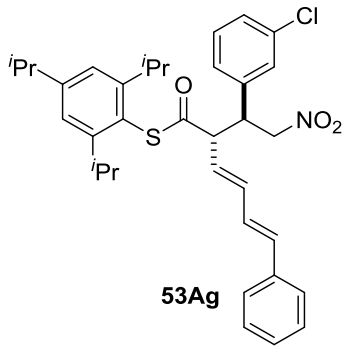
	Retention Time	% Area
	9,178	50,16
	15,063	49,84

Scalemic-**53Ad**



	Retention Time	% Area
	8,980	96,41
	14,884	3,59

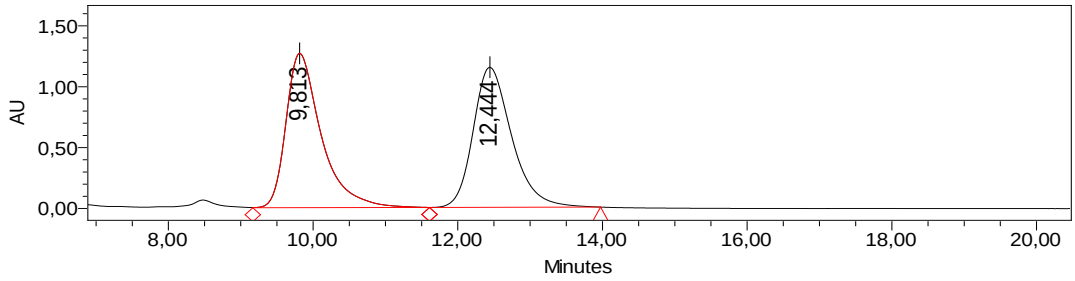
dr:>20:1, 93% *ee*



53Ag

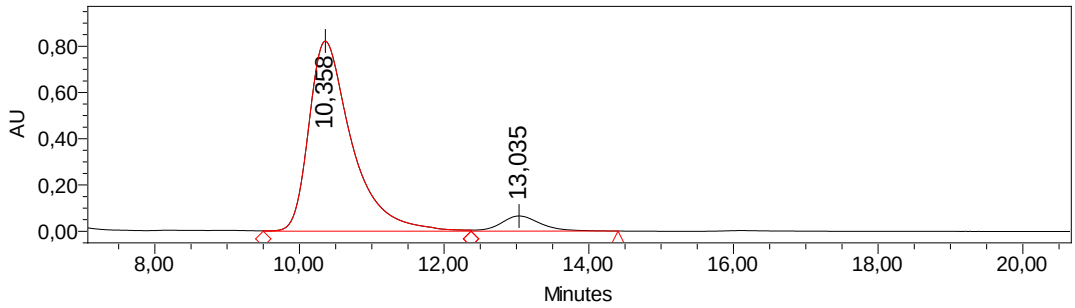
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Ag**



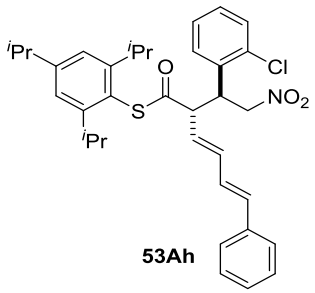
	Retention Time	% Area
	9,813	50,18
	12,444	49,82

Scalemic-**53Ag**



	Retention Time	% Area
	10,358	95,19
	13,035	4,81

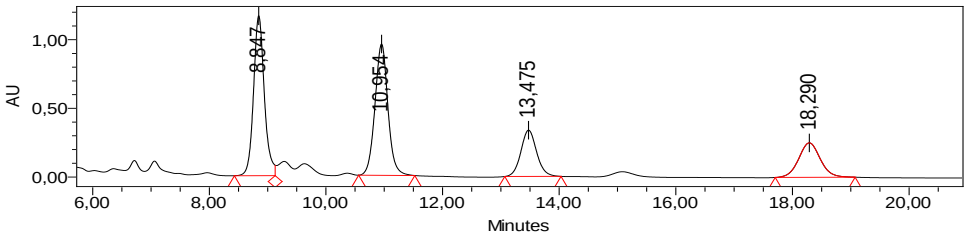
dr:>20:1, 90% *ee*



53Ah

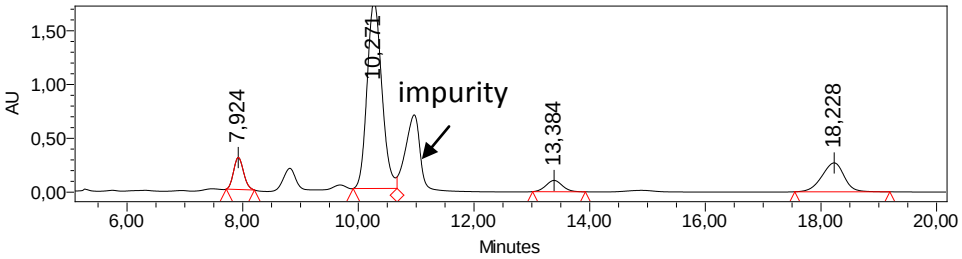
The enantiomeric and diastereomeric purity were determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min) on crude material before column chromatography.

Rac-**53Ah**



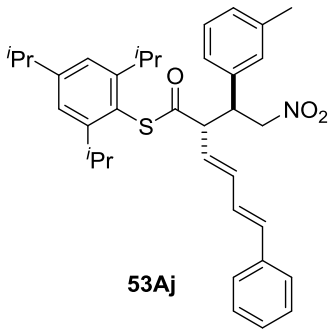
	Retention Time	% Area
	8,847	35,22
	10,954	34,71
	13,475	14,88
	18,290	15,19

Scalemic-**53Ah**



	Retention Time	% Area
	7,924	8,17
	10,271	70,63
	13,384	4,72
	18,228	16,48

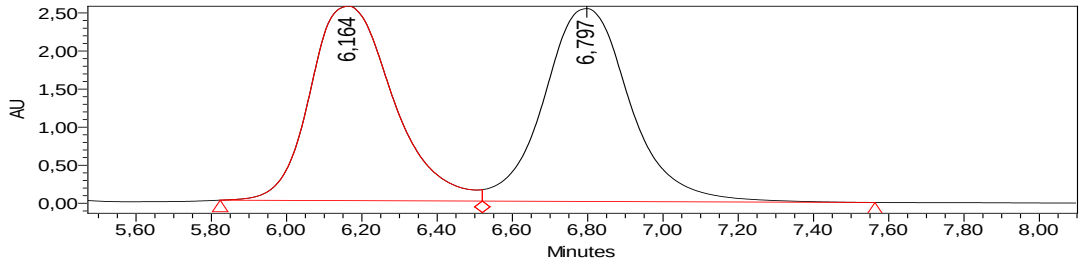
dr: 3.8:1, 80 (55)% *ee*



53Aj

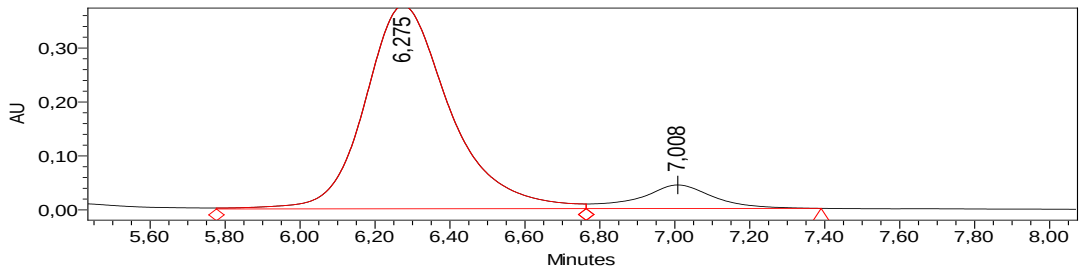
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min).

Rac-**53Aj**



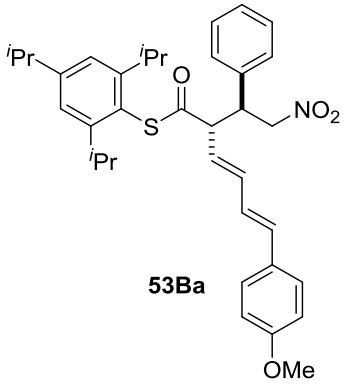
	Retention Time	% Area
	6,164	49,31
	6,797	50,69

Scalemic-**53Aj**



	Retention Time	% Area
	6,275	90,89
	7,008	9,11

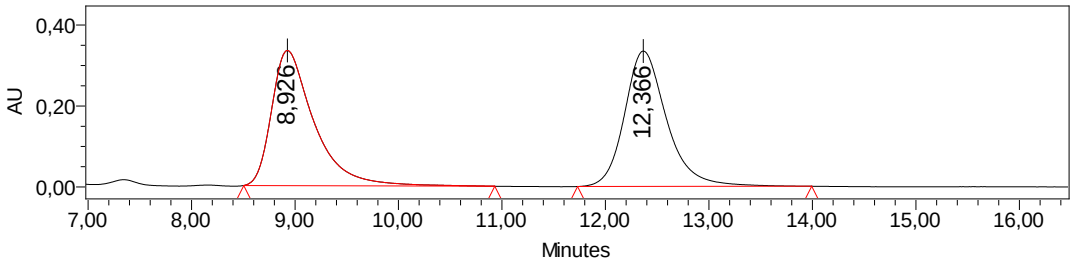
dr:>20:1, 81% *ee*



53Ba

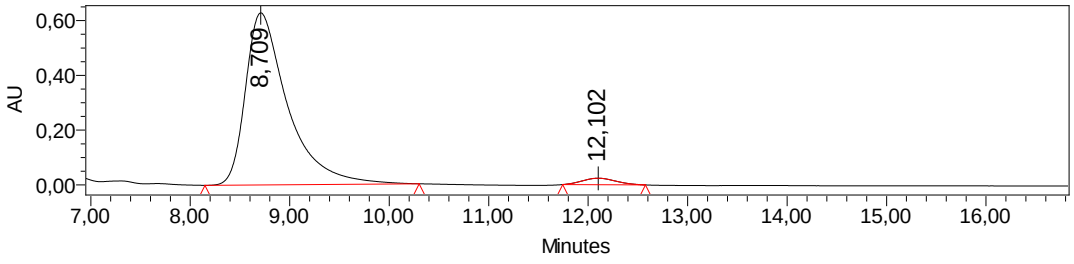
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 90/10, flow rate= 1 mL/min).

Rac-**53Ba**



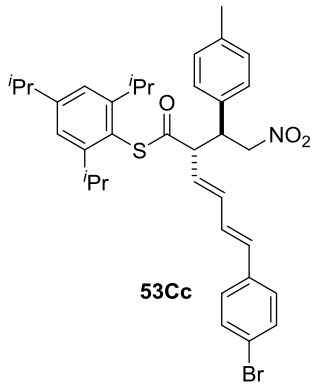
	Retention Time	% Area
	8,926	50,20
	12,366	49,80

Scalemic-**53Ba**



	Retention Time	% Area
	8,709	97,08
	12,102	2,92

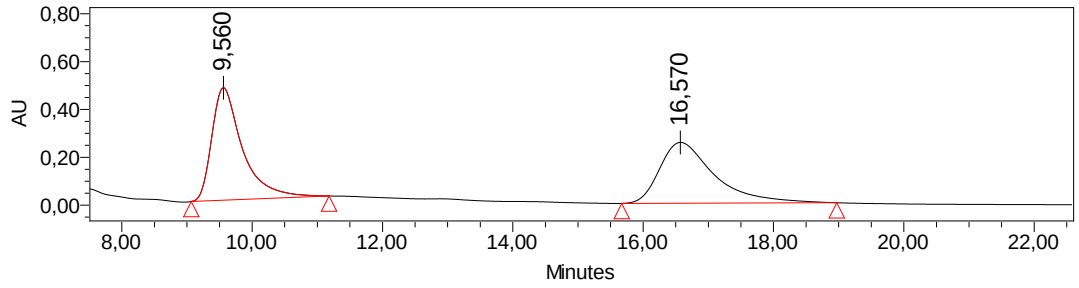
dr:>20:1, 94% *ee*



53Cc

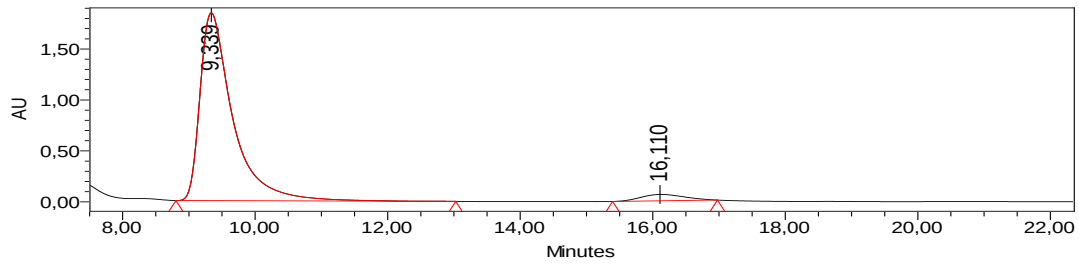
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Cc**



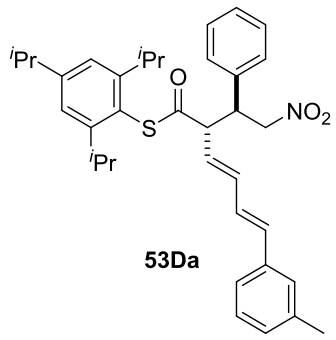
	Retention Time	% Area
	9,560	50,95
	16,570	49,05

Scalemic-**53Cc**



	Retention Time	% Area
	9,339	95,68
	16,110	4,32

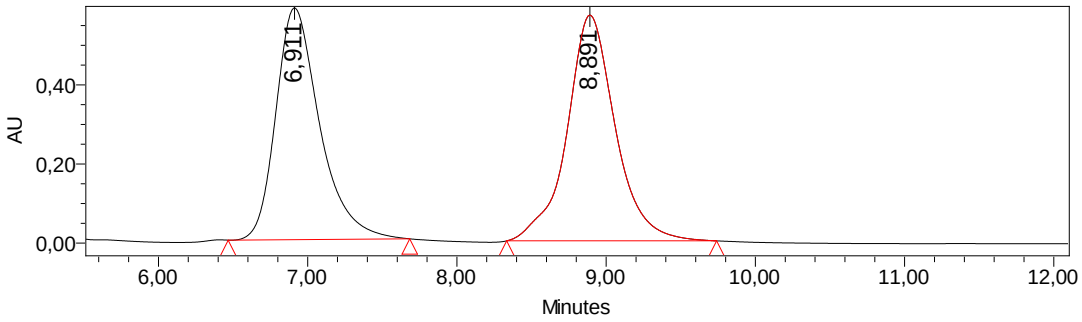
dr:>20:1, 91% *ee*



53Da

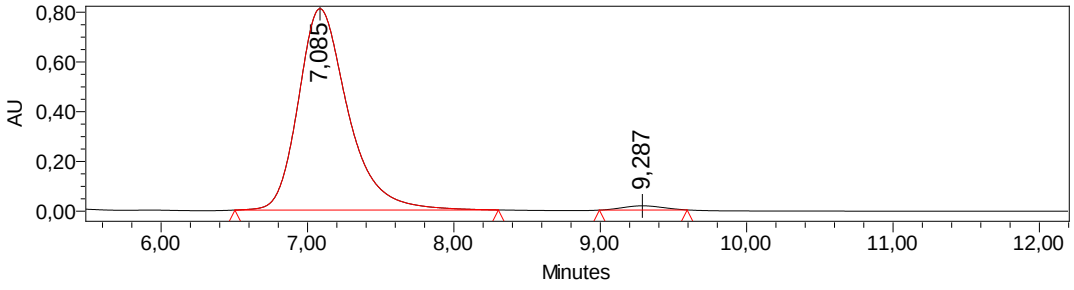
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate= 1 mL/min).

Rac-**53Da**



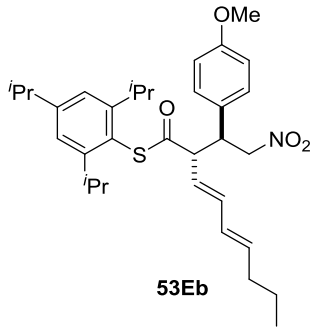
	Retention Time	% Area
	6,911	48,19
	8,891	51,81

Scalemic-**53Da**



	Retention Time	% Area
	7,085	98,36
	9,287	1,64

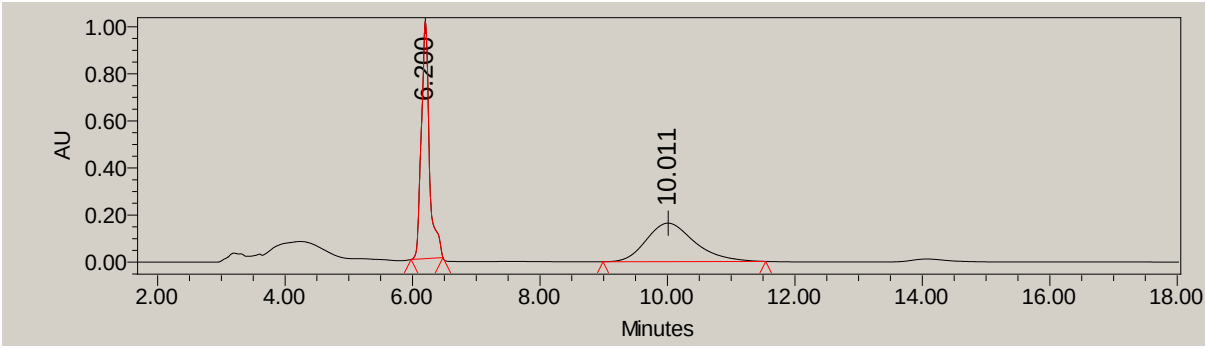
dr:>20:1, 97% *ee*



53Eb

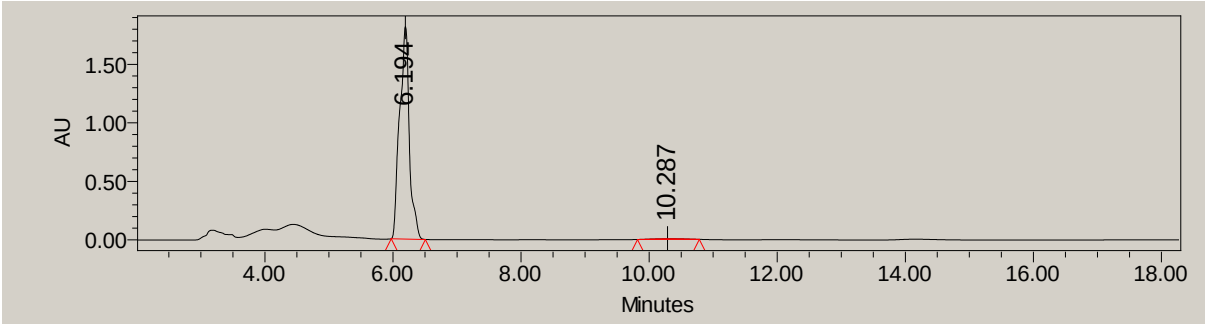
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95/5, flow rate= 1 mL/min.

Rac-**53Eb**



	Retention Time	% Area
	6.200	50.57
	10.011	49.43

Scalemic-**53Eb**



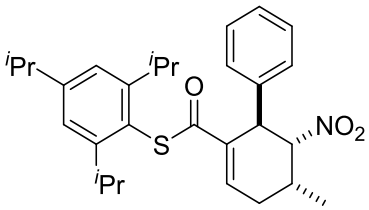
	Retention Time	% Area
	6.194	98.93
	10.287	1.07

dr:>20:1, 98% *ee*

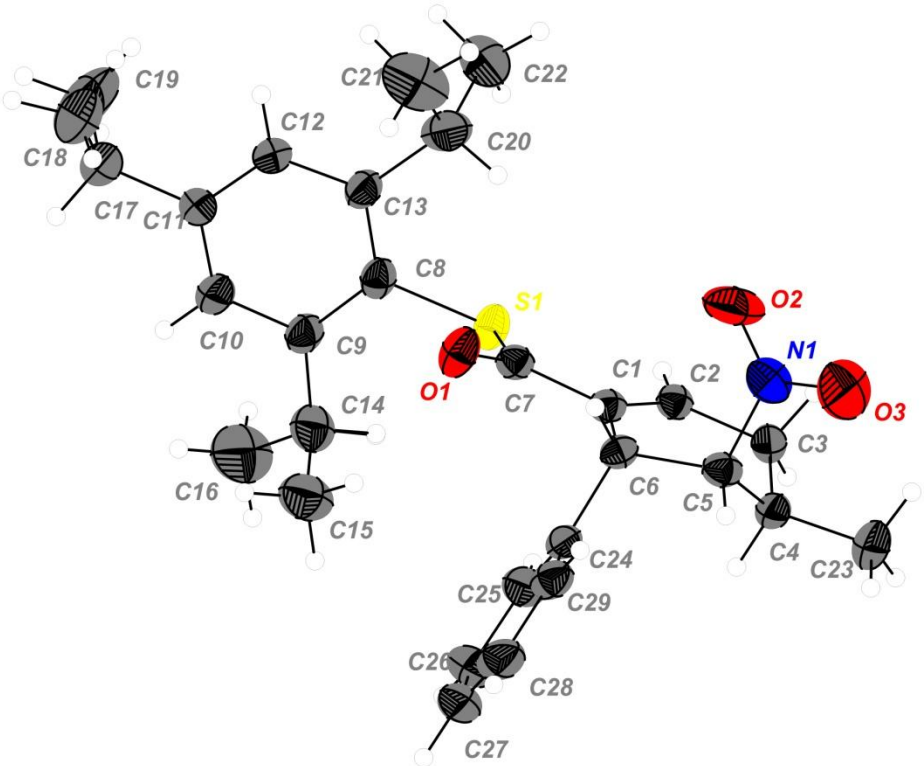
6.8. X-Ray analysis

6.8.1. ORTEP diagram of compound 26Ba

CCDC-1915882 contains the supplementary crystallographic data for the structural analysis of compound **26Ba**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via*: https://www.ccdc.cam.ac.uk/data_request/cif.

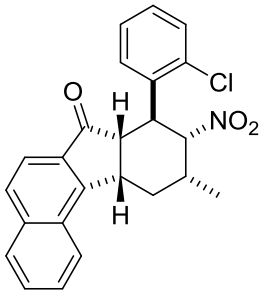


26Ba



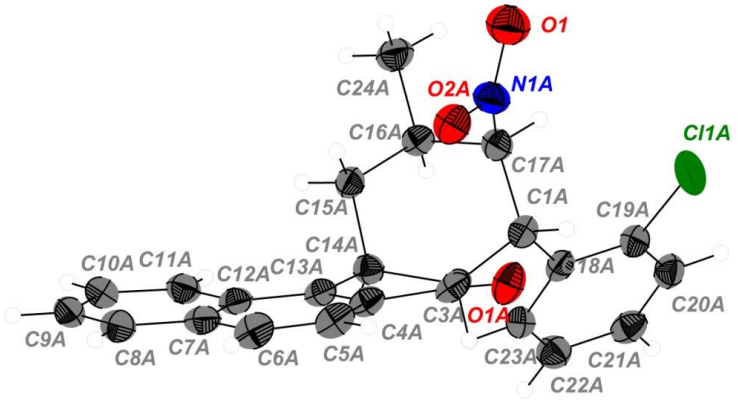
6.8.2. ORTEP diagram of compound 61

CCDC-915883 contains the supplementary crystallographic data for the structural analysis of compound **61**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via*: https://www.ccdc.cam.ac.uk/data_request/cif.

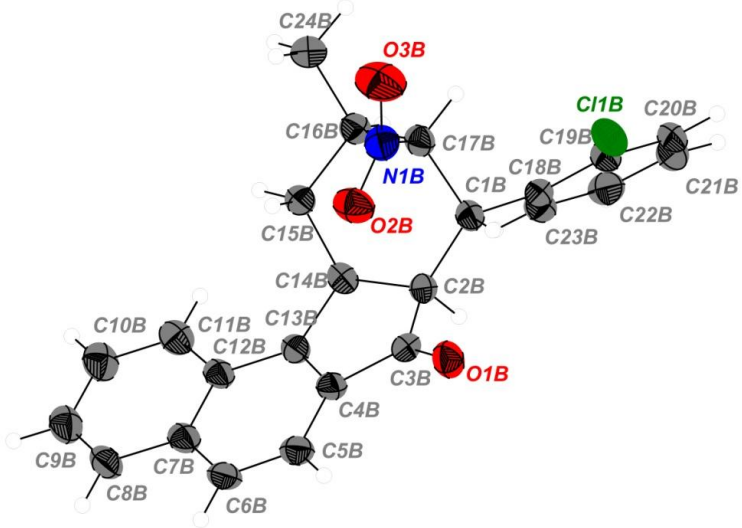


61

Molecule A

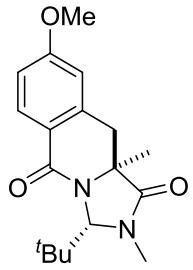


Molecule B

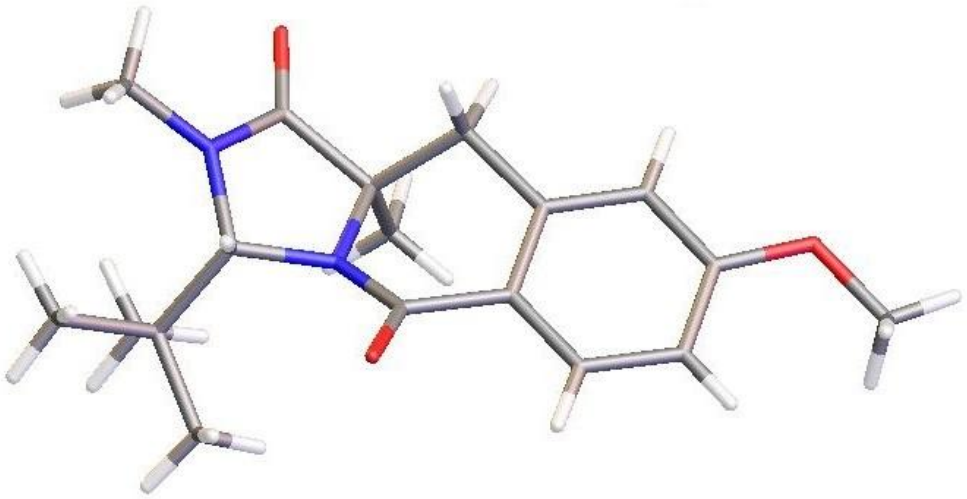


6.8.3. ORTEP diagram of compound 71Bc

CCDC 1895400 contains the supplementary crystallographic data for the structural analysis of compound **71Bc**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via*: https://www.ccdc.cam.ac.uk/data_request/cif.



71Bc



Publications

Organocatalysis

International Edition: DOI: 10.1002/anie.201703764
German Edition: DOI: 10.1002/ange.201703764

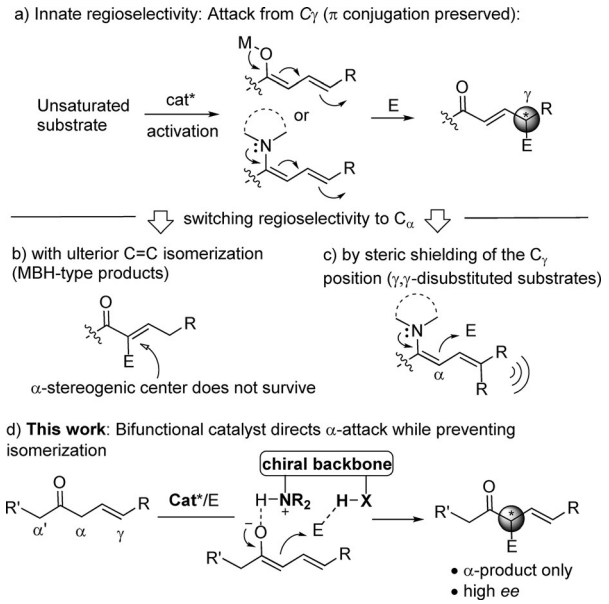
Controlling the α/γ-Reactivity of Vinylogous Ketone Enolates in Organocatalytic Enantioselective Michael Reactions

Igor Iriarte, Olatz Olaizola, Silvia Vera, Iñaki Gamboa, Mikel Oiarbide, and Claudio Palomo**

Abstract: *The first regio-, diastereo-, and enantioselective direct Michael reaction of β,γ-unsaturated ketones with nitroolefins is enabled by Brønsted base/hydrogen-bonding bifunctional catalysis. A squaramide-substituted tertiary amine catalyzes the reaction of a broad range of β,γ-unsaturated ketones to proceed at the α-site exclusively, giving rise to adducts with two consecutive tertiary carbon stereocenters in diastereomeric ratios of up to >20:1 and enantioselectivities generally in the 90–98% ee range.*

Catalyst-controlled reactions of in situ generated vinylogous nucleophiles are of great synthetic value.[1] The overwhelming majority of catalytic reactions involving vinylogous enolate equivalents proceed from the γ-carbon atom of the unsaturated carbonyl substrate, a process that preserves π-conjugation along the reaction coordinate (Scheme 1a). This reactivity pattern is well-illustrated in the literature for a broad range of enolizable substrate families with either metal catalysis[2] or different aminocatalysis approaches.[3–5]

In contrast, the alternative α-reaction pathway implies disruption of the π-conjugation at some point along the reaction coordinate. Not surprisingly, switching the reactivity from the most usual γ- to the α-carbon atom has been troublesome, and only few direct enantioselective approaches have been reported. Shibasaki and co-workers described a barium alkoxide catalyzed Mannich reaction of β,γ-unsaturated benzyl esters that provided the corresponding Morita–Baylis–Hillman-type adducts[6] upon C=C isomerization (Scheme 1b). On the other hand, γ,γ-disubstituted enals have been found to react through the α-carbon atom of the dienamine intermediate[7] because the disubstituted γ-carbon atom is sterically shielded (Scheme 1c).[8] A few Brønsted base catalyzed α-site functionalizations of vinylogous enolate intermediates have also been reported,[9] but these examples featured moderate enantioselectivities[9a] or were restricted to specific substrates.[9b–d] Notably, readily available β,γ-unsaturated alkyl ketones, with three potentially reactive sites (α, γ, and α′), have remained undeveloped pronucleophiles in this context.[10] Herein, we report the first Brønsted base catalyzed direct Michael reaction of β,γ-unsaturated alkyl ketones with nitroolefins that exclusively proceeds through the ketone α-carbon atom and features high diastereo- and enantioselectivity. During the preparation of this manuscript, an α-selective functionalization of preformed silyl dienol ethers with nitroolefins to give Rauhut–Currier-type products under bifunctional catalysis was also reported.[11]



Scheme 1. Site selectivity in the catalyst-driven functionalization of ambivalent vinylogous enolates.

Whereas the C_α/C_γ selectivity problem appeared to be multivariate,[12] we hypothesized that a bifunctional Brønsted base/hydrogen-bonding catalyst[13] might anchor both the dienolate and the electrophilic reagent in a way favoring the α-reaction trajectory (Scheme 1d). However, additional issues, namely 1) the α- vs. α′-selectivity, 2) the diastereo- and enantioselectivity, and 3) the potential loss of α-stereogenicity through C=C bond isomerization, also needed to be addressed.

For the initial assessment of these aspects, the model reaction of **1A** with **7a** in the presence of several bifunctional Brønsted base catalysts[14] was investigated (Scheme 2). To our delight, the α-addition adducts were formed exclusively within a few hours of reaction whereas product diastereo- and enantioselectivity were strongly catalyst-dependent (Table 1). With cinchona-alkaloid-derived thiourea **C1**,[15] both the diastereo- and enantioselectivity were only moderate. The enantioselectivity could be improved by using the squaramide catalysts pioneered by Rawal,[16] such as catalyst **C2**[17] and the cyclohexylamine-derived catalyst **C4**,[18] in particular, but the

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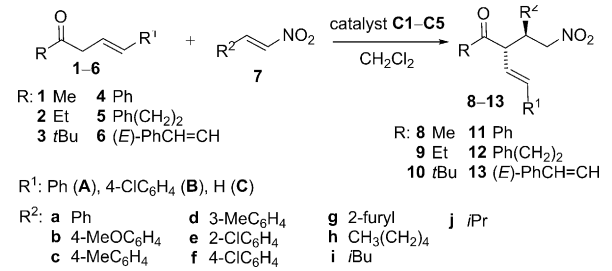
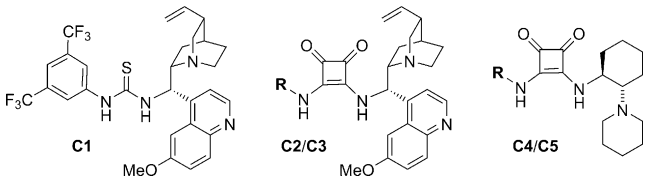


Scheme 2. Catalyst-controlled enantioselective direct reactions of β,γ-unsaturated ketones with nitroalkenes.

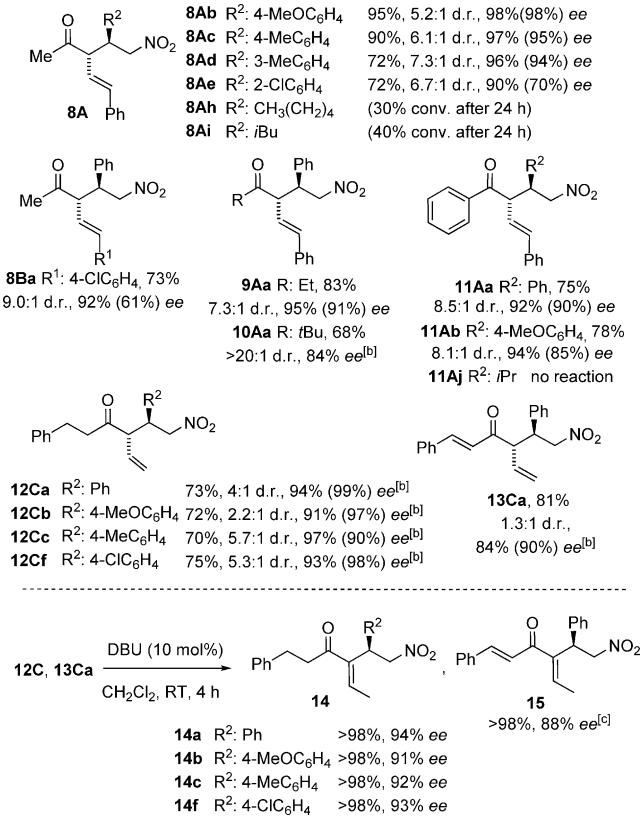
Table 1: Catalyst screening for the reaction of **1A** with **7a** to give **8Aa**.[a]



Catalyst	R	*T* [°C]	*t* [h]	d.r.	*ee* [%]
C1	n/a	RT	2	1.9:1	66
C1	n/a	−20	8	2.4:1	70
C1	n/a	−60	64	2.4:1	70[b]
C2	3,5-$(F_3C)_2C_6H_3$	RT	2	1:1.1	85
C2	3,5-$(F_3C)_2C_6H_3$	−20	6	1:1.3	93
C3	3,5-$(F_3C)_2C_6H_3CH_2$	RT	2	1.9:1	72
C3	3,5-$(F_3C)_2C_6H_3CH_2$	−20	6	2.3:1	86
C4	3,5-$(F_3C)_2C_6H_3$	0	16	1.2:1	97
C5	3,5-$(F_3C)_2C_6H_3CH_2$	0	20	6.4:1	96

[a] Reactions carried out on 0.2 mmol scale, with **1A** (1.5 equiv) and catalyst (10 mol%) in CH_2Cl_2 (0.4 mL). Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. The *ee* values of the major diastereomers are given. [b] 84% Conversion.

Table 2: Scope of the reaction with ketones **1–6** and nitroalkenes **7**.[a]



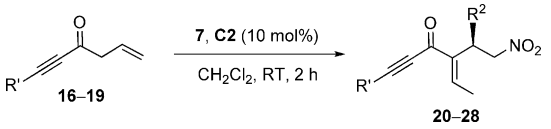
[a] Unless otherwise stated, all reactions were carried out on 0.2 mmol scale with 1.5 equiv of the ketone and 10 mol% **C5** at 0°C in CH_2Cl_2 (0.4 mL). Diastereomeric ratios determined by HPLC analysis. Yields of isolated products after column chromatography are given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. The *ee* values of the minor diastereomers are given in parentheses. [b] Reaction conducted at room temperature using 2 equiv of the ketone. [c] Isomerized upon treatment with Et_3N overnight.

diastereoselectivity remained inadequate (d.r. < 2:1). Additional screening showed that squaramide **C5** performed best, affording product **8Aa** in high yield, 6.4:1 d.r., and 96% *ee* for both isomers upon reaction at 0°C.

Once the reaction conditions had been optimized, various β,γ-unsaturated ketones and nitroolefins were examined.[19,20] The reaction tolerates a variety of β,γ-unsaturated ketones with alkyl and aryl side chains and nitroolefins with either electron-rich, electron-neutral, or electron-poor aryl substituents at the β-carbon atom (Table 2). The corresponding adducts **8–11** were produced in diastereomeric ratios of 5:1 or higher and enantioselectivities of up to 98% *ee* for both the major and minor isomers.[21] For the γ-unsubstituted allyl ketones **5C** and **6C**, the corresponding products **12C** and **13C** were formed in poor diastereomeric ratios whereas the enantioselectivities were consistently high. In every case, the alkylation proceeded at the α-carbon atom of the unsaturated ketone,[22] and no isomerization of the double bond was observed. Incidentally, the starting ketones **5C** and **6C** underwent partial (about 20%) isomerization to the respective α,β-enone during the reaction.[23] However, this circumstance did not affect the reaction outcome provided that two equivalents of the starting material **5C** or **6C** were employed. If desired, the adducts of the above catalytic reactions, such as **12** and **13**, can be isomerized to the corresponding α,β-enone products **14** and **15** almost quantitatively by exposure to 10 mol% DBU at room temperature in CH_2Cl_2.

On the other hand, alkynyl allyl ketones were also competent substrates (Table 3). The reactions of ketones **16–19** with nitroolefins **7** in the presence of quinine derivative **C2**, which was the best catalyst for these substrates, proceeded smoothly to give the corresponding products in good yields and with excellent enantioselectivity. However, unlike in the previous reactions, the evolved adducts proved to be quite sensitive towards double-bond isomerization, and products **20–28** were obtained directly. Once again, products from an eventual γ-attack were not observed. It is worth noting that the otherwise difficult β-alkyl-substituted nitroolefins **7h** and **7i** were competent partners for this reaction, affording adducts **23**, **25**, and **28** in good yields and excellent selectivity. The absolute configuration of the adducts was primarily established by X-ray analysis of compound **8Aa** and by assuming a uniform reaction mechanism.[24,25]

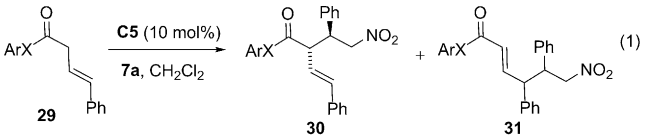
Table 3: Catalytic reactions with β′,γ′-unsaturated ynones **16–24**.[a]



Entry	Ynone	R′	R^2	Product	Yield [%][b]	*ee* [%][c]
1	**16**	Ph	Ph	**20**	68	95
2	**16**	Ph	4-MeC_6H_4	**21**	69	95
3[d]	**16**	Ph	4-MeC_6H_4	**21**	69	73
4	**16**	Ph	4-ClC_6H_4	**22**	71	95
5[d]	**16**	Ph	4-ClC_6H_4	**22**	68	66
6	**16**	Ph	*i*Bu	**23**	72	97
7	**17**	3-MeC_6H_4	Ph	**24**	77	95
8	**18**	4-$MeOC_6H_4$	$CH_3(CH_2)_4$	**25**	69	95
9	**19**	*n*Pr	Ph	**26**	75	97
10	**19**	*n*Pr	4-$MeOC_6H_4$	**27**	72	94
11	**19**	*n*Pr	*i*Bu	**28**	70	95

[a] Reactions carried out on 0.2 mmol scale, with 2.0 equiv of the ynone. [b] Yields of isolated products after chromatographic purification. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Using catalyst **C5**.

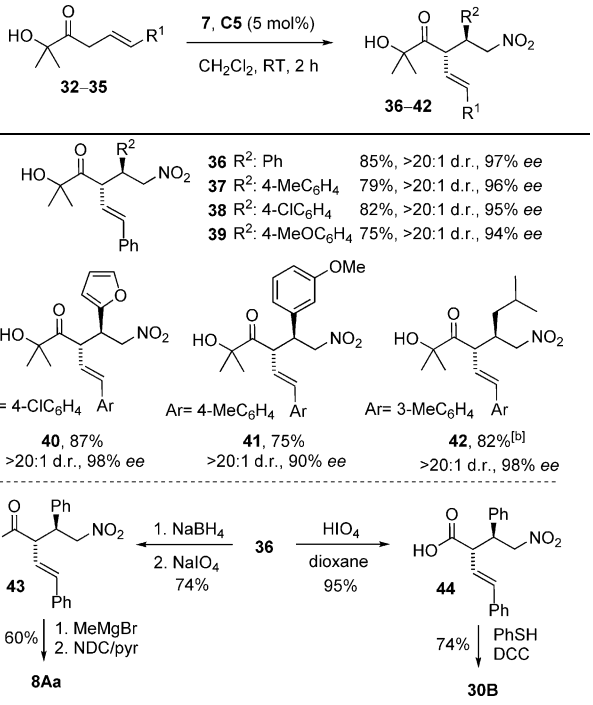
Attempts to translate the present conditions to simple β,γ-unsaturated esters and equivalents, a substrate category that, to the best of our knowledge, has never been employed in enantioselective direct conjugate additions,[26] revealed a divergent behavior. As illustrated in Equation (1), the **C5**-catalyzed reaction of β,γ-unsaturated esters/thioesters **29** with nitrostyrene produced a mixture of the α- and γ-addition products **30** and **31**. Thioesters were found to be more reactive and selective than the parent esters. However, while the minor γ-adducts were essentially obtained as single isomers in some cases,[27] the respective major α-adduct was obtained with low to moderate diastereo- and enantioselectivities.



ArX	conditions	30/31		
PhO (**A**)	RT, 16 h	70:30	2.7:1 d.r., 63/50% *ee*	>20:1 d.r., 63% *ee*
PhS (**B**)	0 °C, 6 h	80:20	4:1 d.r., 89/80% *ee*	>20:1 d.r., 91% *ee*

Given the observations noted above and owing to the facile conversion of the ketol moiety into diverse functional groups,[28] we decided to examine the suitability of β′,γ′-unsaturated ketols as equivalents of β,γ-unsaturated esters. Gratifyingly, reactions of the unsaturated ketols **32–35**[29] with nitroolefins **7** in the presence of 5 mol% **C5** led to the corresponding α-addition adduct **36–42** in high yield, essentially full diastereoselectivity, and enantioselectivities that were typically greater than 95% (Table 4). These results, especially the high diastereomeric ratios, might be related to the strong preference for *Z* enolate formation from these bulky ketols, as the corresponding *E* enolates would present destabilizing 1,3-allylic interactions. Adduct **36** was easily

Table 4: Catalytic reactions with ketols **32–35** and further elaboration.[a]

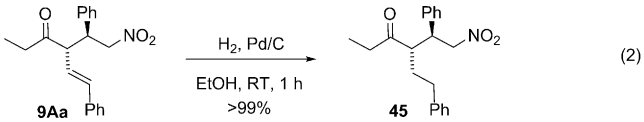


[a] Reactions carried out on 0.2 mmol scale, using 1.1 equiv of the nitroolefin and 5 mol% **C5** at room temperature, unless otherwise stated, in 0.4 mL CH_2Cl_2. Diastereomeric ratios determined by ^{1}H NMR analysis of crude samples. Yields of isolated products after chromatographic purification are given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] After 16 h. DCC = *N*,*N*′-dicyclohexylcarbodiimide, NDC = nicotinium dichromate.

transformed, by reduction and subsequent diol oxidation, into aldehyde **43**, which was later converted into ketone **8Aa**, thus confirming the stereochemical assignment. Alternatively, **36** can also be converted into thioester **30B** through oxidative cleavage and coupling of the resulting carboxylic acid **44** with thiophenol. In each case, the reactions were clean and proceeded without double-bond isomerization or epimerization.

Aside from these elaborations, the most obvious one is the selective reduction of the double bond to afford products that are formally derived from the α-alkylation of nonsymmetric aliphatic ketones, which is difficult to achieve regioselectively. For example, exposure of **9Aa** to H_2 over Pd on charcoal provided compound **45** almost quantitatively [Eq. (2)].

In conclusion, we have demonstrated that tertiary amine/squaramide bifunctional catalysts promote the addition of β,γ-unsaturated ketones to nitroolefins not only with very good enantio- and diastereocontrol, but also exclusive α-site selectivity. Different subsets of readily available β,γ-unsaturated ketones, including those with alkyl, aryl, alkynyl, and hydroxyalkyl side chains, all participated well, giving access to a variety of α-branched ketones with generally two vicinal



tertiary carbon stereocenters essentially as single isomers. Under similar catalytic conditions, β,γ-unsaturated (thio)esters showed inferior α/γ-site as well as stereoselectivity, but the use of β′,γ′-unsaturated ketols as superb equivalents can remedy this limitation. This study complements previous efforts[9–11] to switch from the innate γ-reactivity of most vinylogous enolate equivalents (conjugation preserved) to α-reactivity (conjugation disrupted), and sets the basis for further developments.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Brønsted bases · conjugate additions · ketones · organocatalysis · regioselectivity

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[1] For reviews on vinylogous addition reactions, see: a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076–3154; b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531–3543; c) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698; *Angew. Chem.* **2005**, *117*, 4760–4777.

[2] For selected leading examples, see: unsaturated γ-butenolides: a) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572–4573; b) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319–2322; c) L. Yin, H. Takada, N. Kumagai, M: Shibasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 7310–7313; *Angew. Chem.* **2013**, *125*, 7451–7454; for reviews, see: d) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595–2615; e) Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764–785; unsaturated γ-butyrolactams: f) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666–3667; alkylidene oxindoles: g) X. Xiao, H. Mei, Q. Chen, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Commun.* **2015**, *51*, 580–583; linear enones: h) D. Yang, L. Wang, F. Han, D. Zhao, B. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6739–6742; *Angew. Chem.* **2013**, *125*, 6871–6874.

[3] For reviews on such processes that proceed via dienamine intermediates, see: a) I. D. Jurberg, I. Chatterjee, R. Tannerta, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869–4883; b) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832; for selected examples, see: cyclic enones: c) G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642–20647 (correction: G. Bencivenni, P. Galzeranoa, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 4852–4853); allyl ketones: d) G. Zhan, Q. He, X. Yuan, Y.-C. Chen, *Org. Lett.* **2014**, *16*, 6000–6003; e) M.-L. Shi, G. Zhan, S.-L. Zhou, W. Du, Y.-C. Chen, *Org. Lett.* **2016**, *18*, 6480–6483.

[4] For examples of reactions that proceed by iminium activation, see: linear enones as donors: a) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett.* **2016**, *18*, 2628–2631; b) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 14128–14131; *Angew. Chem.* **2014**, *126*, 14352–14355; silyl dienol ethers: c) V. Gupta, S. V. Sudhir, T. Mandal, C. Schneider, *Angew. Chem. Int. Ed.* **2012**, *51*, 12609–12612; *Angew. Chem.* **2012**, *124*, 12778–12781; γ-butenolides: d) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479; alkylidene malononitriles: e) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107–11114.

[5] For examples of Brønsted base catalysis with allyl ketones, see: a) B. Zhu, W. Zhang, R. Lee, Z. Han, W. Yang, D. Tan, K.-W. Huang, Z. Jiang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6666–6670; *Angew. Chem.* **2013**, *125*, 6798–6802; b) T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha, X.-Y. Wu, *Chem. Commun.* **2014**, *50*, 10790–10792; c) Z. Jing, X. Bai, W. Chen, G. Zhang, B. Zhu, Z. Jiang, *Org. Lett.* **2016**, *18*, 260–263; with alkylidene malononitriles and oxindoles: d) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem.* **2006**, *4*, 63–70; e) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin, R. Wang, *Org. Lett.* **2014**, *16*, 1394–1397; f) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi, G. Casiraghi, *Angew. Chem. Int. Ed.* **2012**, *51*, 6200–6204; *Angew. Chem.* **2012**, *124*, 6304–6308; with α,β-unsaturated thioesters: g) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2012**, *51*, 2382–2386; *Angew. Chem.* **2012**, *124*, 2432–2436; with α,β-enals: h) J.-K. Xie, Y. Wang, J.-B. Lin, X.-R. Ren, P.-F. Xu, *Chem. Eur. J.* **2017**, *23*, 6752–6756.

[6] a) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387–3390; for a proline-catalyzed Mannich reaction leading to MBH-type aldehydes, see: b) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 1878–1880; *Angew. Chem.* **2007**, *119*, 1910–1912.

[7] For pioneering work on dienamine-mediated asymmetric reactions, see: S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

[8] a) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70–73; b) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, *Org. Lett.* **2009**, *11*, 4116–4119; c) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660–4663; d) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian J.* **2011**, *6*, 2255–2259; e) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474–5477; *Angew. Chem.* **2009**, *121*, 5582–5585; for a review, see Ref. [3b].

[9] For reactions with alkylidene cyanoacetates, see: a) M. Bell, K. Frisch, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 5407–5410; with α-styryl acetates: b) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648–2651; with α-angelica lactone: c) J. A. Griswold, M. A. Horwitz, L. V. Leiva, J. S. Johnson, *J. Org. Chem.* **2017**, *82*, 2276–2280; with deconjugated butenolides: d) B. Wu, Z. Yu, X. Gao, Y. Lan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 4006–4010; *Angew. Chem.* **2017**, *129*, 4064–4068.

[10] To the best of our knowledge, a sole report deals with allyl ketones and involves the allylic α-alkylation of aryl allyl ketones with Morita–Baylis–Hillman carbonates; see: a) G. Tong, B. Zhu, R. Lee, W. Yang, D. Tan, C. Yang, Z. Han, L. Yan, K.-W. Huang, Z. Jiang, *J. Org. Chem.* **2013**, *78*, 5067–5072; b) Ref. [4a] includes three examples of (essentially racemic) direct α-functionalization reactions of α,β-unsaturated ketones.

[11] a) M. Frias, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc.* **2017**, *139*, 672 – 679; for catalytic asymmetric reactions involving preformed silyl dienol ethers, see: b) Ref. [1c]; c) S. V. Pansare, E. K. Paul, *Chem. Eur. J.* **2011**, *17*, 8770 – 8779.
[12] a) R. Gompper, H. U. Wagner, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321 – 333; *Angew. Chem.* **1976**, *88*, 389 – 401; b) H. L. van Maanen, H. Kleijn, J. T. B. H. Jastrzebski, M. T. Lakin, A. L. Spek, G. van Koten, *J. Org. Chem.* **1994**, *59*, 7839 – 7848; c) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813 – 814.
[13] For selected reviews on dual or cooperative organocatalysis, see: a) L. Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, 490 – 508; b) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis* (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**.
[14] For reviews on Brønsted base catalysis, see: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics*: *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145 – 200.
[15] a) S. H. McCooey, S. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367 – 6370; *Angew. Chem.* **2005**, *117*, 6525 – 6528; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481 – 4483; c) B. Vakulya, S. Varga, A. Csampai, T. Sojs, *Org. Lett.* **2005**, *7*, 1967 – 1969; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603 – 606.
[16] a) J. P. Malerich, K. Hagihama, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153 – 156; *Angew. Chem.* **2010**, *122*, 157 – 160.
[17] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953 – 957.
[18] W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450 – 5453.
[19] For selected reviews on asymmetric organocatalytic conjugate additions, see: a) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselecive Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge, **2010**; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; c) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365.
[20] For selected reviews on conjugate additions to nitroalkenes, see: a) L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; b) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) L. S. Aitken, N. R. Arezki, A. Dell Isola, A. J. A. Cobb, *Synthesis* **2013**, 2627 – 2628.
[21] Separation of diastereomers, while not systematic, was possible by column chromatography in some instances. See the Supporting Information for details.
[22] Control experiments in which the bifunctional catalyst was replaced with Et_3N, an achiral squaramide, or a combination of both led to no reaction at all or variable amounts of the α- and γ-addition adducts. See the Supporting Information for details.
[23] Conjugated enones were completely unreactive under the present conditions.
[24] CCDC 1542032 (**8Aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[25] Although the configuration of the minor stereoisomer of compounds **8**–**13** (Table 2) was not determined, they should be epimeric at C_α (stereolabile center) with respect to the major isomer. This assumption would be in agreement with the essentially perfect nitroalkene facial selectivity observed in all examples in Tables 3 and 4 and, most importantly, with the high *ee* of products **14** and **15** formed upon isomerization of diastereomeric mixtures of **12** and **13**, respectively.
[26] For its use for direct γ-amination and α-Mannich reactions, see Ref. [5g] and [9b], respectively.
[27] For the full screen of β,γ-unsaturated (thio)esters, see the Supporting Information.
[28] a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2012**, *41*, 4150 – 4164; b) E. Badiola, B. Fiser, E. Gómez-Bengoa, 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.
[29] These β,γ-unsaturated ketones are readily prepared from commercially available 3-hydroxy-3-methylbutan-2-one in two steps. See the Supporting Information for details.

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Asymmetric Catalysis

Enantioselective Addition of Alkynyl Ketones to Nitroolefins Assisted by Brønsted Base/H-Bonding Catalysis

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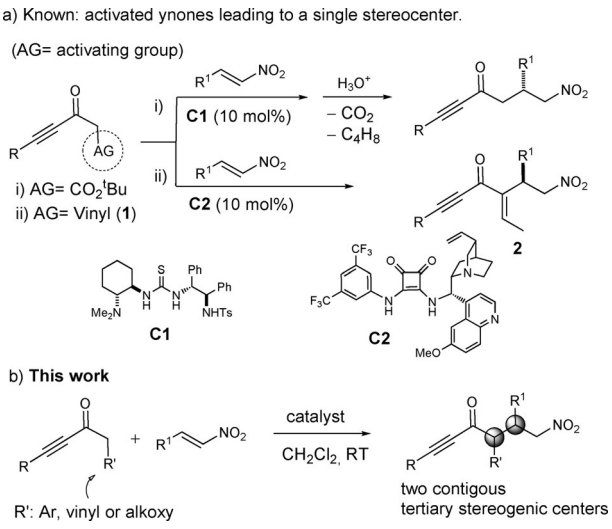
Abstract: Various sets of enolizable alkynyl ketones (including methyl ynones with α-aryl, α-alkenyl, and α-alkoxy groups) were able to react smoothly with nitroolefins with the assistance of bifunctional Brønsted base/H-bond catalysts to provide adducts with two consecutive tertiary stereocenters in a highly diastereo- and enantioselective fashion. Further transformation of the obtained adducts into optically active acyclic and polycyclic molecules, including some with intricate carbon skeletons, was also demonstrated.

Introduction

Given the rich chemistry of both the carbon–carbon triple bond[1] and the carbonyl function,[2] alkynyl ketones (α,β-ynones) are excellent building-blocks for organic synthesis.[3] Therefore, the development of catalytic methods for the proliferation of simple ynones through new C–C bond forming processes into configurationally defined, structurally and functionally more complex, ynone molecules is highly desirable. A logical approach would rely on the α-functionalization of enolizable ynones with electrophiles, but the implementation of catalytic asymmetric methodologies progresses very slowly. One problem relies on the tendency of α,β-ynones to act as Michael acceptors rather than donors.[4] In addition, useful methods would require exquisite control of the intervening ketone enolate geometry as well as the stereochemistry of the subsequent C–C bond forming reaction. Some direct asymmetric aldol[5] and Mannich[6] reactions of enolizable ynones acting as donor components promoted by bifunctional metal catalysts[5a–e,6] or enamine activation[5f–h] are known. In some instances, the enamine activation approach cannot stop at the acyclic addition adduct which undergoes intramolecular cyclization,[7] hence exemplifying the tendency of α,β-ynones to act as Michael acceptors.

As a complement to metal- and aminocatalytic activation strategies, Brønsted base catalysis bears great interest considering that it proceeds under proton-transfer conditions, with ideal atom economy and usually broad functional group tolerance.[8] However, a general problem with this type of activation is the functional pK_a barrier of most catalysts, which compromises their efficiency with less acidic carbon pronucleophiles.[9] To the best of our knowledge, there is a single report on asymmetric Brønsted-base-catalyzed α-additions of enolizable ynones, by Peng, Wang, and Shao (Scheme 1a, top).[10] Ynone substrates bearing an ester group at Cα have been used, requiring a final decarboxylation by acid treatment at 110 °C in toluene.



Scheme 1. Progress on bifunctional Brønsted-base-assisted direct Michael reactions of alkynyl ketones.

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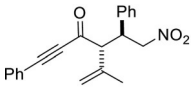
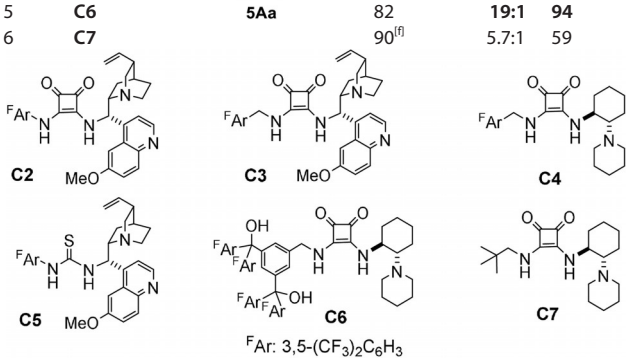
During recent studies on the catalyst-controlled reactivity of transiently generated vinylogous ketone enolates,[11] we have found that alkynyl allyl ketones are a suitable subset of allyl ketones for their reaction with nitroolefins in the presence of bifunctional Brønsted base/H-bond catalysts like **C2**[12] (Scheme 1a, down). Interestingly, these reactions proceeded with nearly perfect enantio- and α/γ-selectivity, but, unfortunately, the C=C double bond in adducts isomerizes spontaneously to the most stable α,β-position with loss of a stereocenter.[11] Therefore, both the above Brønsted-base-catalyzed methods afford products with a single new stereocenter. In the present investigation, we demonstrate that the Brønsted base activation of enolizable α,β-ynones can be applied beyond the above constrains and thus becomes a practical approach to synthetically useful building-blocks. Specifically, ynones bearing an arylmethyl, alkoxymethyl or α-alkenyl sidearm all resulted suitable substrates for direct, Brønsted base-catalyzed Michael reactions producing adducts with two contiguous stereogenic centers in high selectivity (Scheme 1b). Details of the substrate scope, catalyst requirements, and the utility of the obtained adducts for accessing stereochemically complex carbon skeletons are shown.

Table 1. Catalyst screening for the reaction of **3A** with **4a** to give **5Aa**[a] and catalysts described in these manuscript.

Entry	Catalyst	Product	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**C2**		80	1.5:1	98
2	**C3**		80	10:1	80
3	**C4**		77	4:1	92
4	**C5**		70[e]	1:1	40
5	**C6**		82	**19:1**	**94**
6	**C7**		90[f]	5.7:1	59

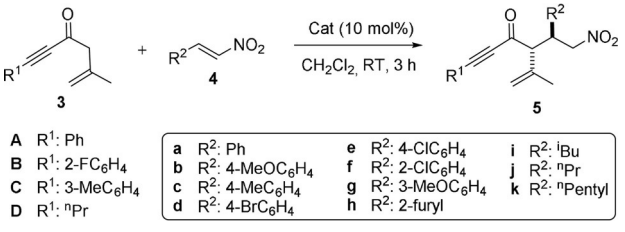


[a] Reactions performed on a 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3A**/**4a**/cat 2:1:0.1. [b] Combined yield of diastereomers after chromatography. [c] Determined by chiral HPLC after filtration through a short path of SiO_2. [d] *ee* of major diastereomer determined by chiral HPLC. [e] Reaction conversion. [f] Conversion after 3 h reaction; 73% isolated yield.

Results and Discussion

Alkenyl alkynyl ketones: background and reaction generality

In our preliminary study, allyl alkynyl ketones **1** were found to react with nitroolefins in the presence of catalyst **C2** to afford the Morita–Baylis–Hillmann-type products **2**.[11] These observations indicate that the initially formed adduct isomerizes spontaneously, with one of the newly created stereocenters being ultimately loosed (Scheme 1a). Our first task was to check whether this isomerization bias is general for other allylic systems. The experiments involving ynone **3A**, showing a 1,1-(*gem*)-disubstituted olefin, and nitrostyrene **4a** in the presence of several bifunctional Brønsted base catalysts[13] (Scheme 2 and Table 1) showed that, indeed, the β,γ-unsaturated adduct **5Aa** resists isomerization regardless the catalyst employed. For instance, after 3 h of stirring at room temperature with 10 mol% catalyst **C2**, adduct **5Aa** was obtained in 80% isolated yield and an excellent 98% *ee*, although a nearly equimolar mixture of diastereomers was produced (entry 1). With the N-benzyl analog **C3**[14] diastereoselectivity was improved at the expense of enantioselectivity (80% *ee*, entry 2), whereas the related cyclohexyldiamine-derived squaramide catalyst **C4**[15] afforded product **5Aa** with high *ee*, but yet suboptimal diastereoselectivity (*dr* 4:1, 92% *ee*, entry 3; *dr* = diastereomeric ratio). After additional screening that showed thiourea catalysts inferior in reactivity and selectivity (e.g., **C5**, entry 4), we finally found that the reaction in the presence of newly developed catalyst **C6**[16] afforded the desired product **5Aa** in 82% yield, a remarkable 19:1 *dr* and 94% *ee* (entry 5). Although the superior behavior of catalyst **C6** correlates well with previous observations,[16] it seems that its origin cannot be explained by steric congestion merely as the bulky neopentyl-derived catalyst **C7** was comparatively inferior (entry 6).



Scheme 2. Catalytic addition of alkenyl ynones **3** to nitroolefins and catalysts employed in this study.

As data in Figure 1 show, the catalytic addition of **3A** to aromatic nitroolefins **4b** and **4e** worked equally well and adducts **5Ab** and **5Ae** were obtained in good yield and high selectivity. The reaction was also very selective with the β-alkyl substituted nitroolefin **4i**, although, as expected, progressed more slowly (44% conversion after 3 h). Ynone substrates with other aromatic substituents at the alkynyl moiety (adducts **5Ba**, **5Ca**) or even alkyl substituents (**5Db**) were well tolerated too. These results constitute the first evidence of Brønsted base catalyzed Michael additions of α,β-ynones that generate two adjacent tertiary stereocenters in highly enantio- and diastereoselective manner. One feature of these reactions is that, although isomerization of the double bond on the newly formed adducts was not observed, the starting allyl ynones **3** isomerized to the respective vinyl ynones to some extent. However, the impact of this process on the reaction yield was negligible upon the use of two equivalents of the starting ynone. Some control experiments to assess the stability of products towards

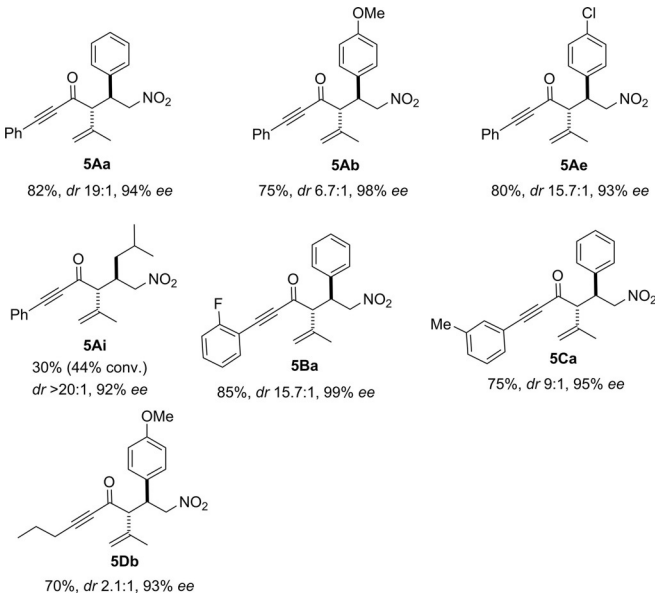
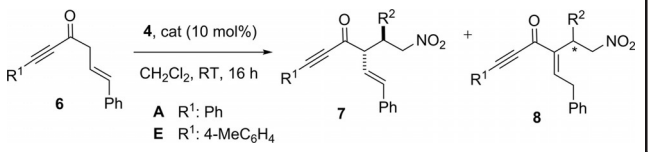


Figure 1. C6-catalyzed conjugate addition of alkenyl ynones **3** to nitroolefins **4**. Reactions performed on a 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3**/**4**/catalyst 2:1:0.1. Variable amounts of isomerized starting material were observed in most entries; yield of major diastereomer after chromatography, except for **5Db** (combined yield). The *dr* and *ee* values were determined by chiral HPLC analysis.

epimerization or double bond isomerization under the reaction conditions employed were carried out. For instance, when a solution of each adduct **5** was stirred at room temperature overnight in the presence of 10 mol% **C4** or **C6**, no change in the configurational integrity of adducts, nor appreciable isomerization, were observed.

We next studied the reaction outcome involving allyl ynones with a 1,2-disubstitution pattern on the olefin, which turned out to be strongly catalyst-dependent. Thus, as Table 2 shows, the reaction of **6A** with nitrostyrene **4a** in the presence of catalyst **C4** at room temperature overnight led to a mixture of adduct **7Aa** and its isomer **8Aa** in a 66:34 ratio (entry 1). In contrast, the same reaction promoted by catalyst **C6** cleanly led to **7Aa** as the only isolated product, which was obtained as a mixture of diastereomers each in very high enantioselectivity (entry 2). A similar trend was observed in the reactions of ynone **6A** with nitroolefins **4c** and **4f**, and of ynone **6E** with **4a**. Thus, exclusive formation of the α-addition products **7Ac**, **7Af** and **7Ea** was observed using catalyst **C6** (entries 4, 6, and 7), whereas with catalyst **C4** mixtures of products **7** and **8** were obtained in ratios of 83:17 and 81:19, respectively (entries 3 and 5). As before, control experiments with adducts **7** (unaltered material recovered after stirring a solution of the adduct in the presence of 10 mol% **C6** at room temperature overnight) demonstrated their stability towards double-bond isomerization or epimerization. Two general conclusions can be brought from these and the previous[11] results involving vinylogous alkynyl ketone enolates: 1) Brønsted-base-catalyzed additions of allyl alkynyl ketones proceed in all cases tested with high Cα selectively, and 2) the tendency of the allylic ynone products towards double-bond isomerization depends primarily on the alkene substitution pattern, but also the catalyst employed. Isomerization can be totally cancelled by choosing the right Brønsted base catalyst, for example, **C6**, providing adducts with two contiguous stereocenters in very high enantioselectivity and diastereomeric ratios from moderate to excellent.

Table 2. Reaction of allylic ynones **6**: no isomerization with catalyst **C6**.[a]

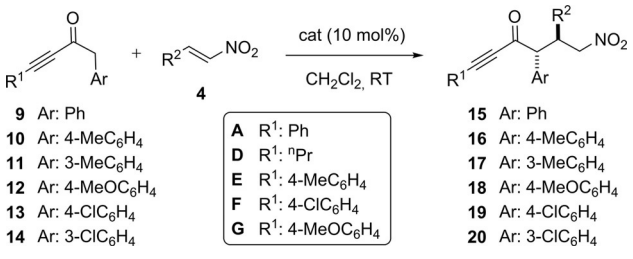


Entry	R^1	R^2	Catalyst	Ratio[b] **7**/**8**	Yield of **7** [%][c]	*dr*[b]	*ee* [%][d]
1	Ph	Ph	**C4**	66:34	38	1.3:1	88/90
2	Ph	Ph	**C6**	>95:5	56	1:1	94/>98
3	Ph	4-MeC_6H_4	**C4**	83:17	47	1.2:1	91/89
4	Ph	4-MeC_6H_4	**C6**	>95:5	62	1.4:1	95/85
5	Ph	2-ClC_6H_4	**C4**	81:19	46	1.2:1	96/93
6	Ph	2-ClC_6H_4	**C6**	>95:5	47	1:1	95/83
7	4-MeC_6H_4	Ph	**C6**	>95:5	58	1.4:1	94/79

[a] Reactions performed on a 0.2 mmol scale in 0.6 mL CH_2Cl_2; mol ratio of **6**/**4**/cat 2:1:0.1. [b] Determined by ^1H NMR. [c] Yield of pure **7** after chromatography. [d] The *ee* value of each diastereomer determined by chiral HPLC.

Benzylic alkynyl ketones as nucleophiles

Although the above results were encouraging, the question of whether this method is suitable for a broader range of ynone compounds remained unanswered so far. In particular, simple alkyl ynones, such as methyl ynones, have been previously shown unable to react with nitrostyrene in the presence of typical Brønsted base catalysts.[10] However, recent work by our own group has revealed some particularly active benzylic ketones to be amenable substrates for Brønsted-base-assisted activation.[15] Accordingly, benzylic ynones were envisioned as candidates for the evaluation of the method generality. A range of benzylic ynones **9**–**14** were easily accessible for the reaction screening which was initiated with ynone **9A** and β-aryl substituted nitroolefin **4b** in the presence of several bifunctional squaramide catalysts.[13] As data in Scheme 3 and Table 3 show, the reaction in the presence of **C2** took place in a few hours to give product **15Ab** in good yield, albeit with no diastereocontrol at all (entry 1). Diastereoselectivity was im-



Scheme 3. Catalytic reaction of benzylic ynones **9**–**14** and nitroolefins **4**.

Table 3. Catalyst screening for the reaction of ynone **9A** and nitroolefin **4b** to yield adduct **15Ab**.[a]

Entry	Catalyst	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][c]
1	**C2**	2.5	95	1:1	ND
2	**C3**	2.5	96	2.8:1	82 (92)
3	**C4**	4.5	99	3.3:1	91 (97)
4	**C6**	6	97	5.7:1	96 (99)
5	**C7**	6	90	1.5:1	–

[a] Reactions performed on a 0.1 mmol scale in 0.3 mL CH_2Cl_2; mol ratio of **9A**/**4b**/cat 1:1.2:0.1. [b] Combined yield of diastereomers after chromatography. [c] Determined by chiral HPLC before chromatography. In parentheses the *ee* of the minor isomer.

proved using catalyst **C3** (entry 2) and even more with **C4** (entry 3) that afforded product **15Ab** in 3.3:1 *dr* and 91 and 97% *ee*, respectively, for each isomer. Further screening showed catalyst **C6** the most selective once more (5.7:1 *dr*, 96% and 99% *ee*, entry 4), whereas its bis-*O*-trimethylsilyl analogue (see the Supporting Information) led to slightly lower diastereoselectivity (3.2:1 *dr*, 98% and 99% *ee*). For comparative purposes, the reaction with catalyst **C7**, which bears a bulky neopentyl group at the squaramide terminus, was carried out, but again led to an almost equimolar mixture of diastereomers. These results support the initial assumption that steric effects alone may not suffice to explain the salient performance of **C6**. This trend in catalyst behavior was confirmed along the exploration of the reaction scope with regard to the nitroolefin. As shown in Figure 2, when the reaction of **9A** with **4a** and **4e** was promoted by catalysts **C4** and **C6**, similar results were produced, although the latter provided somewhat better diastereoselectivity. β-Alkyl-substituted nitroolefins as well as a variety of electron-poor, and -rich, β-aryl substituted nitroolefins participate well in the reaction of alkynylketones **9**–**14** to afford adducts **15**–**20** in very high yield, good diastereoselectivity and nearly perfect enantioselectivity for most cases, independently of the substitution pattern of each reaction component. The absolute configuration of adduct **15Ab**

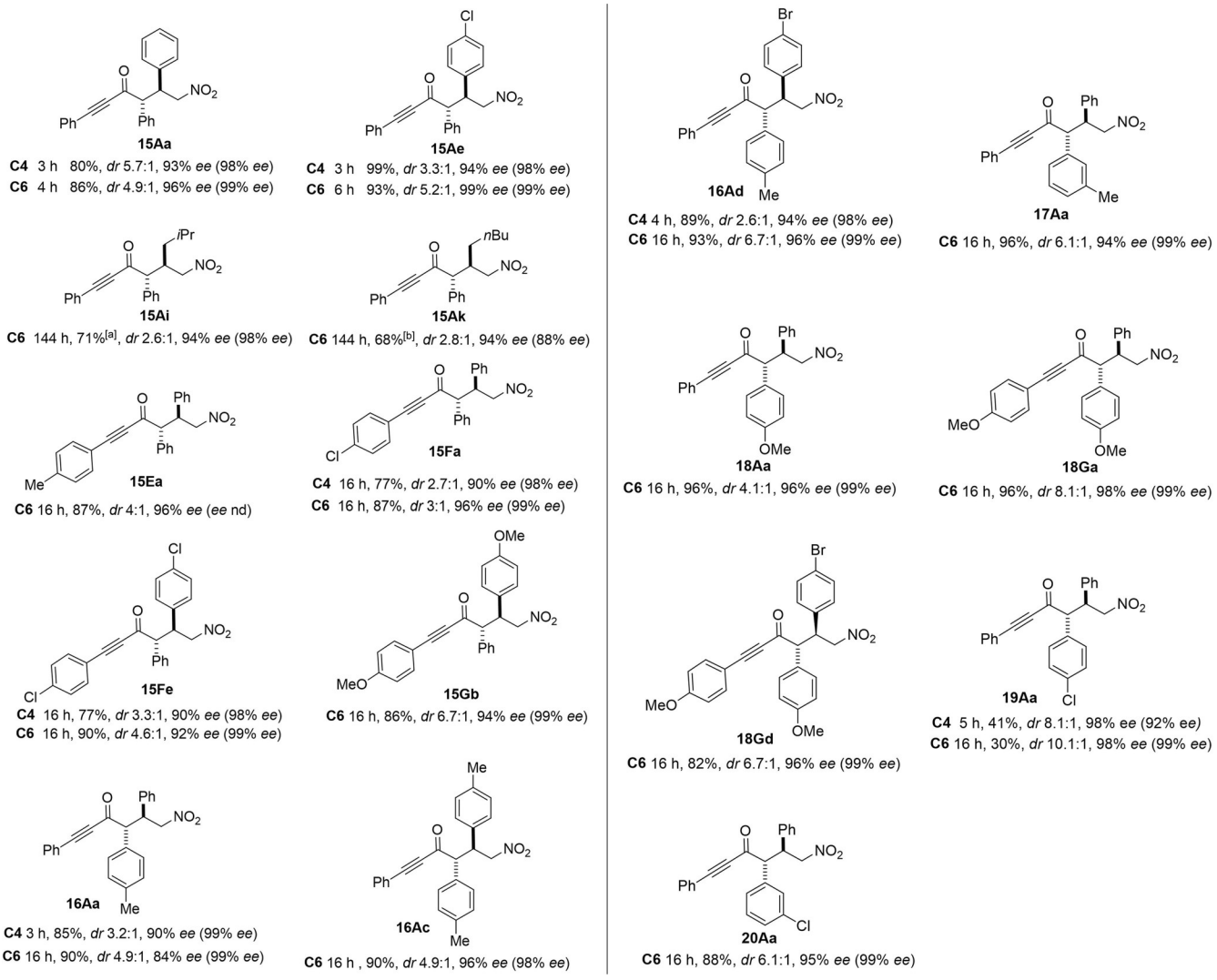


Figure 2. Scope of the catalytic, enantioselective addition of alkynyl ketones **9**–**14** to nitroolefins **4**. Reactions performed on a 0.1 mmol scale in 0.3 mL CH_2Cl_2; molar ratio of **9**–**14**/**4**/cat 1:1.2:0.1. Combined yield of diastereomers after chromatography; *dr* and *ee* determined by chiral HPLC. In parentheses the *ee* of minor isomer. [a] Conversion of 84%. [b] Conversion of 74%.

was established by single-crystal X-ray structure analysis[17] and for the remaining adducts was assumed by analogy on the basis of a uniform reaction mechanism.

Benzyloxymethyl alkynyl ketones as nucleophiles

In view of the successful reactivity of both benzyl and allyl ynones, the behavior of ynones with an alkoxymethyl side-chain was explored next. The heteroatom-substituted side-chain would render not only synthetically appealing adducts, but also increased acidity to substrates for Brønsted base catalyst activation. Concordant with our expectations, it was found that ynones **21**, bearing a benzyloxymethyl side arm, are indeed competent for the catalyzed reaction with nitroolefins. Among the catalysts examined for these reactions,[13] **C3** resulted superior. For example, as data in Figure 3 show, the reactions of **21A** with nitrostyrenes **4a**–**g** in the presence of 10 mol% **C3** afforded adducts **22Aa**–**g** in excellent diastereomeric ratio (typically greater than 10:1) and *ee* values up to 99% for the major diastereomer. The reaction with the β-heteroaromatic nitroolefin **4h**, or the most challenging alkyl nitroolefin **4j**, also provided the corresponding adducts **22Ah**, **22Aj** in very good yields, diastereomeric ratios of 10:1 and 6.7:1, and enantioselectivities of 99 and 96%, respectively. Similarly, the alkyl-substituted ynone **21D** reacted smoothly with either aromatic or aliphatic nitroolefins, giving access to adducts **22Da** and **22Dj** in nearly perfect stereoselectivity. Absolute configuration of adduct **22Ae** was established by single-crystal X-Ray structure analysis[17] and for the remaining adducts **22** was assumed by analogy on the bases of a uniform reaction mechanism.

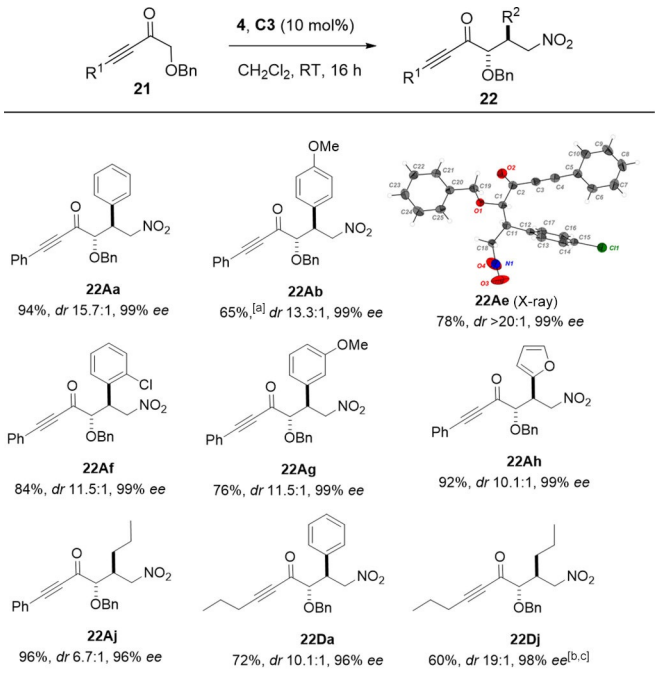
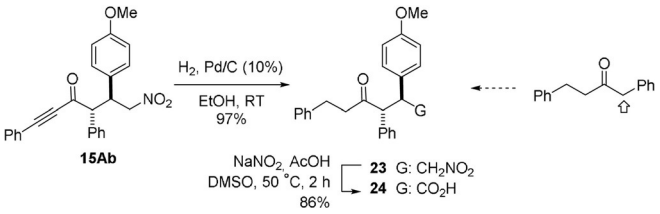


Figure 3. Catalytic, enantioselective reaction of benzyloxy ynones **21** with nitroolefins **4**. Reactions performed on 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **21**/**4**/catalyst 1:2:0.1. Yields of isolated product after chromatography; *ee* determined by chiral HPLC before chromatography. [a] 80% conversion after 72 h. [b] Reaction performed on a 0.2 mmol scale in 0.2 mL 1,2-DCE using 3 equiv of nitroolefin. 1,2-DCE = 1,2-dichloroethane. [c] 65% conversion after 48 h.

Elaboration of the adducts

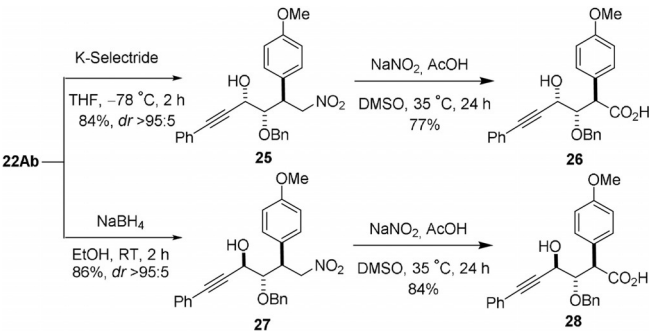
An interesting aspect of the above catalytic reactions is that adducts can be transformed into polyfunctionalized structures with two or more contiguous tertiary stereocenters by using simple chemical protocols. For instance, reduction of the alkynyl moiety in adducts provides dissymmetric alkyl alkyl ketone products with two tertiary stereocenters at α and β positions. For instance, catalytic hydrogenation of **15Ab** afforded **23** in 97% yield (Scheme 4), the α-branched ketone product formally derived from the yet-unrealized site- and stereoselective α-alkylation of the corresponding phenethyl ketone.



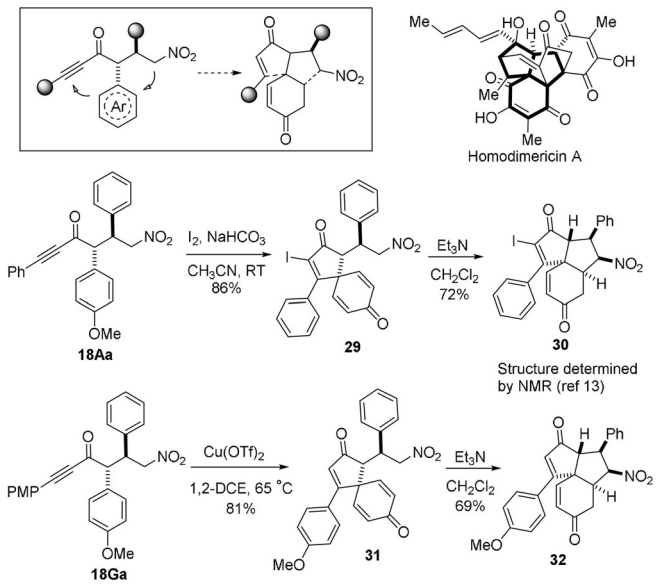
Scheme 4. Reduction of adducts to α-branched alkyl alkyl ketones.

Alternatively, substrate-controlled stereoselective reduction of the ketone carbonyl to carbinol was feasible according to two stereodivergent pathways (Scheme 5). On the one hand, reduction of **22Ab** with K-Selectride proceeded through a Felkin–Anh model[18] to afford *syn* alcohol **25** exclusively, whereas chelation-controlled reduction with $NaBH_4$ afforded the complementary *anti*-alcohol[19] **27**, in both cases with good isolated yields. The nitro group in these molecules is amenable for efficient transformation into a carboxylic acid function upon oxidation according to Mioskowski[20] conditions, as illustrated by the conversion of **23** to acid **24** (86%; Scheme 4), **25** to **26** (77%), and **27** to **28** (84%), respectively (Scheme 5).

Further synthetic interest of the present catalytic addition reactions is derivable from intramolecular carbofunctionalizations of the alkynyl moiety in adducts. As shown in Scheme 6, Lar-



Scheme 5. Diastereodivergent reduction of the ketone carbonyl to *syn*- and *anti*-diol units.



Scheme 6. Elaboration of the adducts into carbocycles of intricate structure.

ock's *ipso*-halocyclization[21] of adduct **18Aa** furnished spirocycle **29** in 86% yield, whereas heating adduct **18Ga** at 65 °C in the presence of Cu^{II}, according to the method of Taylor and Unsworth,[22] led to the spirocycle **31**. These spirocyclic quinones are easily converted into compounds **30** and **32**, respectively, which display a tricyclic carbon core similar to that present in homodimericin A,[23] a structurally intricate compound, the enantioselective chemical synthesis of which is still lacking.[24]

Conclusions

In summary, conjugate addition of enolizable α,β-ynones to nitroolefins is feasible in a highly selective fashion in the presence of tertiary amine/squaramide bifunctional catalysts, affording an atom-economic route to densely functionalized building-blocks. For the new C–C bond forming reaction not only allyl ynones, but also benzylic ynones and alkoxymethyl ynones are suitable ketone donors, thus complementing the few existing direct approaches for the α-functionalization of alkynyl ketones. Elaboration of the α-branched ynone adducts through simple protocols allows for the access to stereochemically complex structures, both acyclic and intricate tricyclic carbon skeletons, in optically pure form.

Experimental Section

General procedure for the Michael reaction

To a solution of the corresponding ynone (0.1 mmol, 1 equiv) and nitroalkene (0.12 mmol, 1.2 equiv) in CH_2Cl_2 (0.3 mL) at room temperature the catalyst (0.01 mmol, 10 mol%) was added and the resulting mixture was stirred at the same temperature for the time indicated in the tables. Then the mixture was directly submitted to a flash column chromatography (eluent hexane/ethyl acetate).

Compound 15Ab: The title compound was prepared from 1,4-diphenylbut-3-yn-2-one (**9A**) (22.0 mg, 0.1 mmol) according to the general procedure with catalyst **C6**, affording a 5.7:1 mixture of diastereomers. Yield: 38.6 mg, 97%. Crystallized from Et_2O. White solid. $[\alpha]_D^{25} = -62.9°$ ($c = 0.53$ in CH_2Cl_2, 96% *ee*); m.p. 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$–7.29 (m, 12H), 6.89 (d, $J =$ 8.7 Hz, 2H), 4.56–4.28 (m, 4H), 3.79 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 184.6$, 160.0, 134.8, 133.7, 131.6, 130.3, 129.9, 129.6, 129.5, 129.3, 120.2, 115.1, 110.7, 94.0, 88.1, 79.6, 64.5, 55.9, 45.5 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{25}H_{22}NO_4$: 400.1549$[M+H]^+$; found: 400.1550.

Compound 18Aa: Prepared from 1-(4-methoxyphenyl)-4-phenylbut-3-yn-2-one (**12A**) (25.0 mg, 0.1 mmol) according to the general procedure with catalyst **C6**, affording a 4.1:1 mixture of diastereomers. Yield: 38.34 mg, 96%. Crystallized from Et_2O. White solid. $[\alpha]_D^{25} = -55.5°$ ($c = 0.3$ in CH_2Cl_2, 96% *ee*); m.p. 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.52$–7.26 (m, 14H), 6.99 (d, $J = 8.7$ Hz, 2H), 4.53–4.32 (m, 4H), 3.85 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 182.7, 158.8, 136.1, 131.8, 129.7, 128.9, 127.8, 127.4, 127.0, 126.9, 124.6, 118.4, 113.9, 92.0, 86.3, 78.0, 61.5, 54.1, 44.3 ppm. UPLC-DAD-QTOF: *m/z* calcd for $C_{25}H_{22}NO_4$: 400.1549 $[M+H]^+$; found: 400.1551.

Compound 18Ga: Prepared from 1,4-bis(4-methoxyphenyl)but-3-yn-2-one (**12G**) (28.0 mg, 0.1 mmol) according to the general procedure with catalyst **C6**, affording an 8.1:1 mixture of diastereomers. Yield: 41.2 mg, 96%. Crystallized from Et_2O. White solid. $[\alpha]_D^{25} = -1.4°$ ($c = 0.2$, 98% *ee*, CH_2Cl_2); m.p. 142–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H), 7.38–7.29 (m, 5H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 4.51–4.30 (m, 4H), 3.85 (s, 3H), 3.85 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 184.6$, 160.6, 138.1, 135.8, 131.7, 130.7, 129.6, 128.8, 128.7, 128.2, 126.7, 115.7, 115.0, 110.7, 95.0, 88.3, 79.6, 63.3, 56.0, 46.3 ppm; UPLC-DAD-QTOF *m/z* calcd for $C_{26}H_{24}NO_5$: 430.1654 $[M+H]^+$; found: 430.1658; *m/z* calcd for $C_{26}H_{23}NO_5 + Na^+$: 452.1474 $[M+Na]^+$; found: 452.1470.

Compound 22Ab: Prepared starting from ynone **21A** (50 mg, 0.2 mmol) according to the general procedure with catalyst **C3**. Orange oil, yield: 56 mg (65%). $[\alpha]_D^{25} = +26.1°$ ($c = 1$ in CH_2Cl_2, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$–7.28 (m, 11H), 7.25–7.18 (m, 2H), 6.90–6.82 (m, 2H), 4.95–4.68 (m, 4H), 4.46 (d, $J =$ 11.3 Hz, 1H), 4.15 (ddd, $J = 9.3$, 7.0, 4.9 Hz, 1H), 3.78 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 187.5$, 160.6, 137.5, 134.5, 132.4, 131.4, 130.5, 129.8, 129.7, 129.4, 129.3, 128.2, 120.4, 115.5, 87.4, 87.2, 77.7, 74.2, 56.3, 46.6 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{26}H_{24}NO_5$: 430.1654 $[M+H]^+$; found: 430.1654.

Syn-selective reduction of 22Ab

To a solution of **22Ab** (0.2 mmol, 86 mg) in dry THF (0.5 mL) at −78 °C a solution of K-Selectride in THF (1 M, 3 equiv, 0.6 mmol, 0.6 mL) was added and the mixture was stirred at that temperature for 2 hours. Water (0.2 mL) and EtOH (0.4 mL) were successively added, and after 5 min of stirring H_2O_2 (30%, 0.4 mL) was added. The reaction mixture was allowed to rise to room temperature and the mixture was stirred for an additional 10 min. Then, it was diluted with EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3×5 mL), the organic layers were combined, and dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to afford compound **25** as a yellow oil ($dr > 95:5$). Yield: 70 mg (84%). $[\alpha]_D^{25} = +3.4°$ ($c = 0.1$ in CH_2Cl_2, from adduct of 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$–7.26 (m, 10H), 7.20–7.15 (m, 2H), 6.92–6.87 (m, 2H), 5.13 (d, $J = 10.9$ Hz, 1H), 4.91–4.84 (m, 1H), 4.84–4.79 (m, 1H), 4.62–4.49 (m, 1H), 4.39 (d, $J = 1.4$ Hz,

1H), 4.00–3.93 (m, 2H), 3.81 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 150.8, 138.1, 132.7, 131.2, 130.4, 129.9, 129.8, 129.6, 129.6, 129.5, 115.8, 89.6, 84.1, 78.8, 76.5, 63.1, 56.4, 46.4, 30.8 ppm; DAD-QTOF: *m/z* calcd for $C_{26}H_{26}NO_5$: 432.1811 $[M+H]^+$; found: 432.1814.

Anti-selective reduction of 22Ab

$NaBH_4$ (16 mg, 0.4 mmol, 2 equiv) was added to a stirred mixture of compound **22Ab** (0.2 mmol, 86 mg) in EtOH (1 mL) at room temperature. After 2 h the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), and dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to afford compound **27** as a colorless oil (*dr* > 95:5). Yield: 74 mg (86%). $[\alpha]_D^{25} = +18.3^\circ$ (*c* = 0.3 in CH_2Cl_2, from adduct of > 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.25 (m, 10H), 7.24–7.20 (m, 2H), 6.89–6.84 (m, 2H), 5.02 (dd, *J* = 12.9, 5.0 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.73–4.62 (m, 2H), 4.59 (d, *J* = 3.5 Hz, 1H), 4.03 (ddd, *J* = 9.8, 7.5, 5.1 Hz, 1H), 3.93 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.84–3.82 (m, 1H), 3.80 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 137.4, 131.8, 129.2, 129.0, 128.8, 128.7, 128.3, 128.2, 128.1, 122.0, 114.4, 83.3, 74.7, 64.7, 55.2, 45.2, 29.7 ppm. DAD-QTOF: *m/z* calcd for $C_{26}H_{26}NO_5$: 432.1811 $[M+H]^+$; found: 432.1810.

Procedure for the Nef oxidation of adducts 23, 25, and 27 (Mioskowski conditions)

A solution of the corresponding diol (1 equiv), sodium nitrite (3 equiv) and acetic acid (10 equiv) in DMSO (0.5 mL/0.2 mmol) was stirred at 35 or 50 °C for 24 h. After this period, the reaction mixture was quenched with HCl 1 N (5 mL) and the mixture was extracted with Et_2O (4×5 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography.

Compound 24: Prepared from compound **23** (65 mg, 0.16 mmol) according to the general procedure. White solid, yield 53.8 mg (86%). $[\alpha]_D^{25} = -129.6^\circ$ (*c* = 0.1 in CH_2Cl_2, from adduct of 96% *ee*); m.p. 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–6.80 (m, 14H), 4.53–4.33 (m, 2H), 3.82 (s, 3H), 2.77–2.32 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6, 177.6, 160.3, 141.6, 136.5, 133.4, 130.7, 130.0, 129.8, 129.4, 129.1, 129.0, 127,0, 115.3, 62.3, 56.3, 54.1, 45.4, 30.1 ppm. UPLC-DAD-QTOF: *m/z* calcd for $C_{25}H_{24}O_4Na$: 411.1572 $[M+Na]^+$, found:411.1570.

Compound 26: Prepared from compound **25** (86 mg, 0.2 mmol) according to the general procedure. Colorless oil, yield 64 mg (77%). $[\alpha]_D^{25} = +13.5^\circ$ (*c* = 0.3 in CH_2Cl_2, from adduct of 99% *ee*); IR: $\tilde{\nu}$ = 3356 (O–H), 1716 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.91 (m, 2H), 7.55–7.43 (m, 3H), 7.34–7.24 (m, 3H), 7.23–7.14 (m, 2H), 7.12–7.03 (m, 2H), 6.95–6.86 (m, 2H), 5.36 (d, *J* = 4.2 Hz, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.54 (dd, *J* = 6.6, 4.3 Hz, 1H), 4.48 (q, *J* = 11.7 Hz, 1H), 3.83 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.9, 164.4, 159.1, 137.6, 130.6, 130.5, 129.2, 128.6, 128.2, 128.1, 127.7, 127.4, 127.1, 117.9, 114.2, 94.1, 72.8, 72.7, 55.6, 53.7, 45.3, 29.9 ppm. DAD-QTOF: *m/z* calcd for $C_{26}H_{25}NO_5$: 417.1702 $[M+H]^+$; found: 417.1702.

Compound 28: Prepared from compound **27** (86 mg, 0.2 mmol) according to the general procedure. Yield: 70 mg (84%). $[\alpha]_D^{25} = +27.5^\circ$ (*c* = 0.4 in CH_2Cl_2, from adduct of 99% *ee*); IR: $\tilde{\nu}$ = 3500 (O–H), 1731 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–7.94 (m, 2H), 7.58–7.40 (m, 2H), 7.37 (d, *J* = 8.6 Hz, 5H), 7.32–7.25 (m, 2H), 7.12–7.06 (m, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.27 (dd, *J* = 7.5, 5.1 Hz, 1H), 4.66 (dd, *J* = 5.9, 5.1 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 1H), 4.35–4.21 (m, 2H), 3.85 (s, 3H), 3.13 ppm (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 165.1, 159.8, 137.4, 131.4, 130.9, 129.6, 129.2, 128.9, 128.9, 128.0, 128.0, 127.5, 120.2, 114.6, 88.9, 77.9, 74.6, 68.3, 56.0, 47.0, 30.4 ppm. DAD-QTOF: *m/z* calcd for $C_{26}H_{25}NO_5$: 417.1702 $[M+H]^+$, found: 417.1698.

Preparation of spirocycle 29

To a solution of adduct **18Aa** (1 equiv., 0.1 mmol, 40 mg.) in CH_3CN (0.3 mL) at room temperature was added I_2 (3 equiv., 0.3 mmol, 76 mg) and $NaHCO_3$ (2 equiv., 0.2 mmol, 17 mg). The reaction mixture was stirred at room temperature overnight, then it was diluted with Et_2O and washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the resulting product was crashed with hexane to afford a brown foam. Yield: 44 mg (86%). $[\alpha]_D^{25} = -11.8^\circ$ (*c* = 1.0 in CH_2Cl_2, from adduct of 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.21 (m, 9H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.79 (dd, *J* = 10.0, 2.6 Hz, 1H), 6.39 (dd, *J* = 10.0, 1.4 Hz, 1H), 6.27–6.16 (m, 2H), 5.22 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.89 (dd, *J* = 13.4, 7.6 Hz, 1H), 3.90–3.64 (m, 2H), 3.54 ppm (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 184.9, 175.8, 148.5, 147.7, 136.9, 134.4, 132.6, 132.5, 131.2, 130.6, 129.8, 129.3, 129.2, 127.5, 106.1, 78.8, 59.4, 57.31, 43.5, 30.5 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{24}H_{19}INO_4$: 512.0359 $[M+H]^+$; found: 512.0362; *m/z* calcd for $C_{24}H_{18}NO_4INa$: 534.0178 $[M+Na]^+$; found:534.0184.

Preparation of spirocycle 31

To a solution of adduct **18Ga** (1 equiv., 0.13 mmol, 55 mg) in 1,2-DCE (1 mL) was added $Cu(OTf)_2$ (1 equiv., 0.13 mmol, 47 mg). The reaction mixture was stirred at 65 °C for 3 h. Then the mixture was filtered, rinsed with CH_2Cl_2 and concentrated in vacuo to afford a brown foam. Yield: 44 mg (81%). $[\alpha]_D^{25} = -9.5^\circ$ (*c* = 1.5 in CH_2Cl_2, from adduct of 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.7 Hz, 3H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 6.56 (d, *J* = 10.1 Hz, 1H), 6.34–6.12 (m, 2H), 5.24 (dd, *J* = 13.2, 7.5 Hz, 1H), 5.02–4.84 (m, 1H), 3.81 (s, 3H), 3.65 (td, *J* = 7.2, 3.5 Hz, 1H), 3.32 ppm (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.2, 185.4, 173.1, 163.3, 151.4, 151.1, 137.4, 131.0, 130.1, 129.6, 128.9, 127.7, 125.6, 115.1, 94.1, 79.4, 73.8, 56.3, 56.1, 43.1, 30.3 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{25}H_{22}NO_5$: 416.1498 $[M+H]^+$; found: 416.1501; *m/z* calcd for $C_{25}H_{21}NO_5Na$: 438.1317 $[M+Na]^+$; found: 438.1314.

Preparation of tricycles 30 and 32

To a solution of the corresponding spirocyclic compound **29** or **31** (1 equiv, 0.1 mmol) in CH_2Cl_2 (0.6 mL) was added Et_3N (20 equiv, 2 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was directly submitted to a non-acidic silica gel column chromatography (eluent hexane/AcOEt 95:5 to 90:10).

Compound 30: Prepared from compound **29** (51.1 mg, 0.1 mmol) according to the general procedure. Brown foam, yield: 36.8 mg (72%). $[\alpha]_D^{25} = -35.1^\circ$ (*c* = 0.3 in CH_2Cl_2, from adduct of 96% *ee*); decomp. 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.23 (m, 10H), 6.81 (dd, *J* = 10.2, 1.6 Hz, 1H), 6.36 (dd, *J* = 10.2, 0.7 Hz, 1H), 5.00 (t, *J* = 11.2 Hz, 1H), 3.96–3.84 (m, 1H), 3.24 (d, *J* = 9.1 Hz, 1H), 3.21–3.11 (m, 1H), 2.37 (d, *J* = 17.7 Hz, 1H), 1.94 ppm (dd, *J* = 17.8, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 194.2, 176.7, 147.7,

136.8, 134.8, 131.3, 131.2, 130.1, 129.8, 129.2, 128.0, 127.6, 105.5, 94.7, 60.3, 50.7, 47.3, 35.7 ppm. UPLC-DAD-QTOF: *m/z* calcd for $C_{24}H_{18}NO_4INa$: 534.0175 $[M+Na]^+$; found: 534.0184.

Compound 32: Prepared from compound **31** (41.5 mg, 0.1 mmol) according to the general procedure. Brown solid, yield: 28.7 mg (69%). $[\alpha]_D^{25} = -9.0^\circ$ ($c = 0.4$ in CH_2Cl_2, from adduct of 98% *ee*); decomp. 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 8.9$ Hz, 2H), 7.46–7.24 (m, 5H), 7.05–6.90 (m, 3H), 6.45 (d, $J = 10.2$ Hz, 1H), 6.34 (s, 1H), 4.99 (t, $J = 11.1$ Hz, 1H), 3.89 (s, 3H), 3.84 (d, $J = 10.9$ Hz, 1H), 3.21–3.12 (m, 1H), 3.10 (d, $J = 9.5$ Hz, 1H), 2.61–2.56 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 203.9$, 195.0, 174.9, 163.0, 150.7, 137.0, 130.3, 129.1, 128.2, 128.1, 126.7, 115.4, 96.0, 63.9, 56.2, 51.2, 46.7, 36.8 ppm. UPLC-DAD-QTOF: *m/z* calcd for $C_{25}H_{22}NO_5$: 416.1498 $[M+H]^+$; found: 416.1500.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynyl ketones · asymmetric catalysis · Brønsted bases · Michael reaction · organocatalysis

[1] a) *Modern Acetylene Chemistry*, (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**; b) E. B. Bauer, *Synthesis* **2012**, *44*, 1131–1151.
[2] *Modern Carbonyl Chemistry*, (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**.
[3] Selected examples: a) (Cyathane diterpenes) P. A. Wender, F. C. Bi, M. A. Brodney, F. Gosselin, *Org. Lett.* **2001**, *3*, 2105–2108; b) (Oxcillatoxin D) Y. Nokura, Y. Araki, A. Nakazaki, T. Nishikawa, *Org. Lett.* **2017**, *19*, 5992–5995; c) (Azaspiracide-3) N. T. Kenton, D. Adu-Ampratwum, A. A. Okumu, Z. Zhang, Y. Chen, S. Nguyen, J. Xu, Y. Ding, P. McCarron, J. Kilcoyne, F. A. L. Wilkins, C. O. Miles, C. J. Forsyth, *Angew. Chem. Int. Ed.* **2018**, *57*, 810–813; *Angew. Chem.* **2018**, *130*, 818–821.
[4] For reviews, see: a) R. Salvio, M. Moliterno, M. Bella, *Asian J. Org. Chem.* **2014**, *3*, 340351; b) A. Fraile, A. Parra, M. Tortosa, J. Alemán, *Tetrahedron* **2014**, *70*, 9145–9173; c) R. E. Whittaker, A. Dermenci, G. Dong, *Synthesis* **2016**, *48*, 161–183.
[5] a) K. Fujii, K. Maki, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 733–736; b) K. Maki, R. Moloki, K. Fuji, M. Kanai, T. Kobayashi, S. Tamura, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 17111–17117; c) S. L. Shi, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 3932–3935; *Angew. Chem.* **2012**, *124*, 3998–4001; d) B. M. Trost, A. Fetters, B. T. Shireman, *J. Am. Chem. Soc.* **2004**, *126*, 2660–2661; e) B. M. Trost, M. U. Fredericksen, J. P. N. Papillon, P. E. Harrington, S. Shin, B. T. Shireman, *J. Am. Chem. Soc.* **2005**, *127*, 3666–3667; f) F. Silva, M. Sawicki, V. Gouverner, *Org. Lett.* **2006**, *8*, 5417–5419; g) G. Kang, J. Jiang, H. Liu, H. Wu, *J. Braz. Chem. Soc.* **2012**, *23*, 5–10; h) F. Silva, M. Reiter, R. Mills-Webb, M. Sawicki, D. Klär, N. Bensel, A. Wagner, V. Gouverneur, *J. Org. Chem.* **2006**, *71*, 8390–8394.
[6] a) B. M. Trost, C. I. Hung, *J. Am. Chem. Soc.* **2015**, *137*, 15940–15946; b) S.-L. Shi, X.-F. Wei, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2012**, *134*, 17019–17022.
[7] Domino cyclisation: a) D. B. Ramachary, C. Venkaiah, P. M. Krishna, *Chem. Commun.* **2012**, *48*, 2252–2254; b) D. B. Ramachary, C. Venkaiah, R. Nadhavachary, *Org. Lett.* **2013**, *15*, 3042–3045.
[8] Selected reviews on Brønsted-base-promoted asymmetric reactions: a) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; c) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2009**, *291*, 201–232; d) R. P. Singh, L. Deng in *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*, (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 41–118; e) H. B. Jang, J. S. Oh, C. E. Song in *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*, (Ed.: K. Maruoka), Thieme, Stuttgart, pp. 119–116.
[9] a) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591; *Angew. Chem.* **2008**, *120*, 4664–4667; b) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C. G. Zhao, *Org. Lett.* **2016**, *18*, 2648–2651.
[10] W. Liu, L. Zou, B. Fu, X. Wang, K. Wang, Z. Sun, F. Peng, W. Wang, Z. Shao, *J. Org. Chem.* **2016**, *81*, 8296–8305.
[11] I. Iriarte, O. Olaizola, S. Vera, I. Ganboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864; *Angew. Chem.* **2017**, *129*, 8986–8990.
[12] a) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137–2141; b) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453. For pioneering work on squaramides as catalysts, see: c) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; d) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156; *Angew. Chem.* **2010**, *122*, 157–160. For reviews, see: e) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346; f) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; g) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281.
[13] See the Supporting Information for details.
[14] H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783.
[15] I. Olaizola, T. E. Campano, I. Iriarte, S. Vera, A. Mielgo, J. M. García, J. M. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2018**, *24*, 3893–3901.
[16] A. Odriozola, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 12758–12762.
[17] CCDC 1858603 **15Ab**, and 1858826 **22Ae** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.. See the Supporting Information for details.
[18] a) N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61–70; b) T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, *24*, 2653–2656.
[19] T. Tokuyama, K. Shimada, M. Uemura, *Tetrahedron Lett.* **1982**, *23*, 2121–2124.
[20] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234–235.
[21] X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231.
[22] A. K. Clarke, J. T. R. Liddon, J. D. Cuthbertson, R. J. K. Taylor, N. P. Unsworth, *Org. Biomol. Chem.* **2017**, *15*, 233–245.
[23] A. E. Mevers, J. Sauri, Y. Liu, A. Moser, T. R. Ramadhar, M. Varlan, R. T. Williamson, G. E. Martin, J. Clardy, *J. Am. Chem. Soc.* **2016**, *138*, 12324–12327.
[24] Racemic synthesis of homodimericin A: J. Huang, Y. Gu, K. Guo, L. Zhu, Y. Lan, J. Gong, Z. Yang, *Angew. Chem. Int. Ed.* **2017**, *56*, 7890–7894; *Angew. Chem.* **2017**, *129*, 7998–8002.

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Brønsted Base Catalyzed One-Pot Synthesis of Stereodefined Six-Member Carbocycles Featuring Transient Trienolates and a Key Intramolecular 1,6-Addition

Olatz Olaizola, Igor Iriarte, Giovanna Zanella, Enrique Gómez-Bengoa, Iñaki Ganboa, Mikel Oiarbide, and Claudio Palomo**

Abstract: *A catalyst-driven one-pot reaction sequence is developed for the enantio- and diastereoselective synthesis of tetrasubstituted cyclohexenes from simple unsaturated ketones or thioesters. The method involves a tertiary amine/squaramide-catalyzed α-selective addition of transiently generated trienolates to nitroolefins, subsequent base-catalyzed double bond isomerization, and an intramolecular (vinylogous) 1,6-addition reaction, a rare key carbocyclization step that proceeded with essentially perfect stereocontrol.*

Six-membered carbocycles are ubiquitous structural motifs in natural products and bioactive substances, and their stereoselective synthesis has attracted great interest. This has traditionally relied on the Diels–Alder reaction, with several metal- and organocatalyzed variants being established already.[1] Catalytic, one-pot domino processes[2] are also valuable approaches, provided that each bond-forming step occurs with high site- and stereocontrol. This is usually achieved by using substrates bearing carefully selected, and strategically positioned, donor and acceptor reaction sites. In this context, covalent aminocatalysis has revealed extremely versatile owing to the complementary donor/acceptor character of the intervening enamine/iminium species, enabling the de novo construction of six-membered carbocycles from aldehyde and ketone substrates.[2,3] Common to these domino processes, the key ring-closing step is achieved through three major approaches: the intramolecular 1,2- and 1,4-addition reactions, the latter in its *endo* and *exo* variants (Figure 1 a). In sharp contrast, to the best of our knowledge, the catalytic intramolecular (vinylogous) 1,6-addition approach remains underdeveloped,[4] despite its simplicity and the minimal need of preinstalled functional groups. Herein we describe a catalytic, enantio- and diastereoselective one-pot construction of six-membered carbocycles that ends up with an unprecedented intramolecular 1,6-addition step. The new method requires Brønsted base catalysts[5] as the only reaction promoter and can equally start from simple unsaturated ketones or (thio)esters (Figure 1 b).

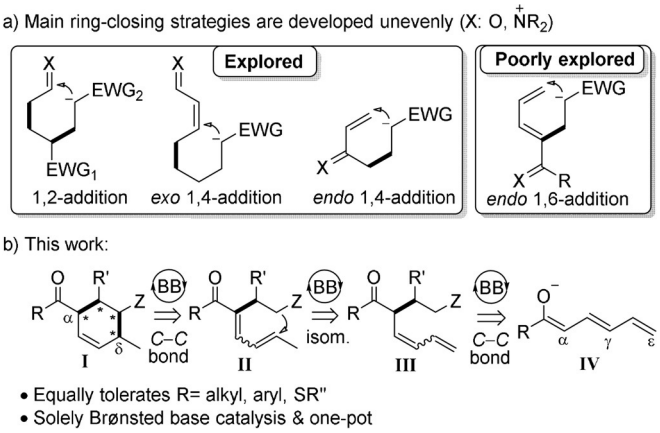

Figure 1. Catalytic one-pot construction of six-membered carbocycles.

In this conception conversion of **III** to **II** seemed conjugation-driven and feasible, but transformations of **II**→**I** and **IV**→**III** appeared most difficult and unpredictable. While stereocontrol of **II**→**I** may become an issue,[4,6] the catalytic Cα-alkylation of transiently generated trienolates **IV** to produce **III** remained unaddressed so far, posing obvious site- and stereoselectivity concerns.[7] Quite recently we have documented[8] that bifunctional Brønsted base/H-bonding catalysts successfully induce in situ formation of dienolates and their α-selective reaction, most likely through an anchoring effect. We hypothesized that the present setting might be a good platform to further prove the generality of the concept. At the outset, the reaction of deconjugated thioester **1A**[9] and nitrostyrene **2a**[10] in dichloromethane in the presence of 10–20 mol % of several amine bases was investigated. As the data in Table 1 show, the reaction progressed to essentially full conversion upon 24 hours at room temperature regardless of the base used, although product distribution varied considerably. With the simple tertiary amine Et_3N isomerization to the conjugated diene **3A** occurred along with formation of minor α-addition product **4Aa** (entry 1). With sterically bulkier amine *i*Pr_2EtN the **4Aa**/**3A** ratio increased notably, but at the expense of diastereoselectivity (entry 2). Similar product distribution was obtained using chiral, dimeric catalyst $(DHQD)_2PYR$, but the dr of product **4Aa** was high (>20:1, entry 3). Using stronger amine base DBU caused isomerization of the substrate to conjugated thioester **3A**. However, in this case

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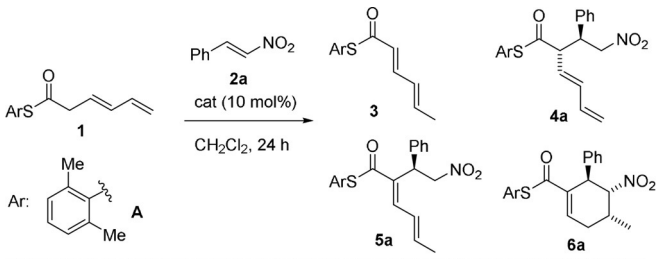
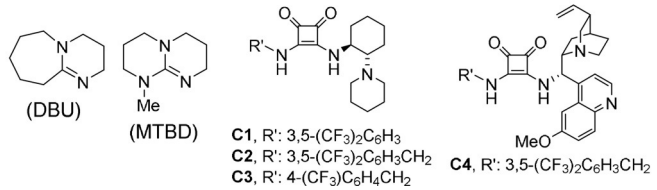
Table 1: Catalyst-dependent product distribution in the reaction of polyunsaturated thioester **1A** with nitrostyrene.[a]





Entry	Catalyst	3A	4Aa	5Aa	6Aa
1	Et_3N	83	17 (>20:1)	–	–
2	iPr_2EtN	45	55 (1.4:1)	–	–
3	$(DHQD)_2PYR$	45	55 (>20:1)[b]	–	–
4	DBU	70	–	–	30 (>20:1)
5	DBU (0°C)	58	–	18	24 (>20:1)
6	DBU (0°C, 40 h)	58	–	–	42 (>20:1)
7	MTBD (RT, 16 h)	100	–	–	–
8	MTBD (0°C, 16 h)	100	–	–	–
9	MTBD (−10°C, 16 h)	100	–	–	–
10	**C1**	20	80 (>20:1)[b]	–	–
11	**C1** + MTBD[c]	20	–	–	65[d] (>20:1, 81% *ee*)
12	**C2** + MTBD[c]	23	–	–	72[d] (>20:1, 78% *ee*)
13	**C3** + MTBD[c]	25	–	–	68[d] (>20:1, 88% *ee*)
14	**C4** + **MTBD**[c]	**18**	–	**–**	**71[d] (>20:1, 94% *ee*)**

[a] Reactions carried out at 0.1 mmol scale, using 1 equiv of each **1A** and **2a** and 10 mol% catalyst in 0.1 mL CH_2Cl_2 at room temperature. The ratios of products **3A**/**4Aa**/**5Aa**/**6Aa** formed correspond to ^{1}H NMR integration. Data in parenthesis correspond to dr and *ee*. [b] The *ee* was not determined. [c] Cocatalyst MTBD (20 mol%) was added after 16 h and stirring kept for additional 24 h. [d] Yield after isolation of product by column chromatography, 1.5 equiv of **1A** were used.

cycloadduct **6Aa** was produced for the first time and with high diastereoselectivity (dr > 20:1, entry 4).[11]

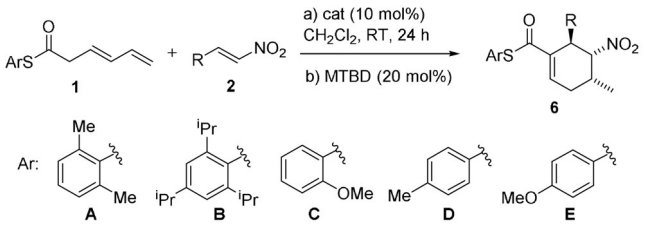
We presumed that this cycloadduct might be formed through cyclization of acyclic precursor **5Aa**, followed by double bond isomerization. To prove this assumption the same reaction was carried out at 0°C affording a mixture of **3A**, isomerized α-adduct **5Aa**, and **6Aa** (entry 5). When this mixture was allowed to stir for longer time at 0°C, a mixture of **3A** (58%) and **6Aa** (42%) was isolated (entry 6), indicating that indeed **5Aa** is an intermediate in the formation of **6Aa**. The use of even stronger guanidine base MTBD was disappointing, as isomerized thioester **3A**, probably a thermodynamic sink, was the only isolated product regardless of the reaction temperature (entries 7–9). Then, hoping to ease the C–C bond forming event by simultaneous activation of the electrophile, bifunctional Brønsted base/H-bonding catalysts were investigated. Gratifyingly, the reaction carried out in the presence of squaramide **C1**[12] led to α-addition adduct **4Aa** with the highest isolated yield so far (80%) along with 20% of isomerized material **3A** (entry 10). When this mixture was stirred for an additional 20 hours in the presence of 20 mol% DBU or MTBD, total conversion of **4Aa** into the cyclization product **6Aa** was observed, the latter obtained in 65% isolated yield as pure diastereomer and most significantly in 81% *ee* (entry 11). For this one-pot two-step transformation,[13] the structurally related amine-squaramide catalysts **C2** and **C3** behaved similarly to **C1**, affording cycloadduct **6Aa** as single diastereomer in yields of 72% and 68%, and *ee*'s of 78% and 88%, respectively (entries 12, 13). Finally, the quinine-derived catalyst **C4** led to improved 94% *ee* (entry 14).

Several thioesthers **1**, with variable aryl groups at sulfur, and nitroalkenes **2** were subjected to the optimized conditions, consisting of stirring the mixture in the presence of 10 mol% **C4** and then one-pot treatment with 20 mol% of either DBU or MTBD. As the results in Table 2 show, the reaction with nitrostyrenes bearing electron-rich MeO and Me *p*-substituents (adducts **6Ab**, **6Ac**) or electron-poor *p*-substituent Cl (adduct **6Ad**) all proceeded with good yields, perfect regio- and diastereoselectivity and enantioselectivity of 90% *ee* or higher. The position of the substitution did not affect the reaction efficiency, as demonstrated by the good yields and high selectivities obtained with the *m*- and *o*-substituted nitrostyrenes **2e** and **2f** (adducts **6Ae** and **6Af**). Thioesters with varying substitution patterns at the Ar–S group, such as *o*- and *p*-disubstituted thioester **1B**, and *o*- or *p*-monosubstituted substrates **1C–E**, worked equally well (adducts **6B–6E**). The relative and absolute configuration of compound **6Ba** was determined by X-ray single crystal structure analysis[14] and that of the remaining adducts was assumed based on a uniform reaction mechanism.

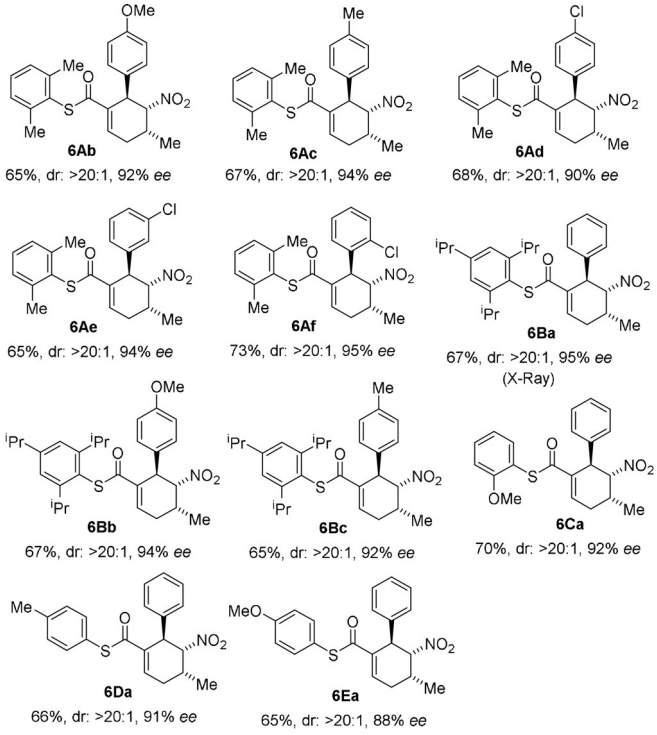
The validity of this new, one-pot, enantio- and diastereoselective carbocyclization approach was also tested with deconjugated dienones **7–12**. As shown in Table 3, the reaction of unsaturated ketone **7** with nitrostyrene **2a** in the presence of 10 mol% catalyst **C4** cleanly afforded α-addition adduct **13a** in 84% yield as a 2.4:1 mixture of diastereomers in 93% and 87% *ee*.

Similarly, the reaction with nitroolefin **2c** afforded adduct **13c** in 85% yield, 2.1:1 dr and 97%/90% *ee*. Both reaction regio- and stereoselectivity remained invariable when starting from *p*-tolyl dienone **8** (adduct **14a**, 82% yield, 2.1.1 dr and 95%/89% *ee*). Most gratifyingly, one-pot treatment of the α-alkylated adducts **13**/**14** with catalytic base (MTBD) led to formation of the corresponding cycloadducts **15**/**16** as a single diastereomer, in high enantioselectivity. Thus, reaction of phenyl ketone **7** with nitrostyrenes **2a–2f** provided adducts **15a–f** with isolated yields in the range 73–82%, diastereomeric ratios of >20:1, and enantioselectivity typically higher than 90%. The reaction with the aliphatic nitroalkene **2g** did also proceed efficiently to give **15g**, but as a 2.6:1 mixture of diastereomers. Other nonconjugated dienones with aryl (**8**, **9**, **10**) and alkyl (**11**, **12**) side chains were equally tolerated,

Table 2: Catalytic enantioselective reaction of thioesters **1** with nitroolefins to afford tetrasubstituted cyclohexenes **6**.[a]

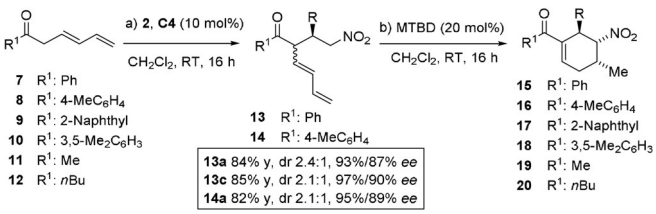


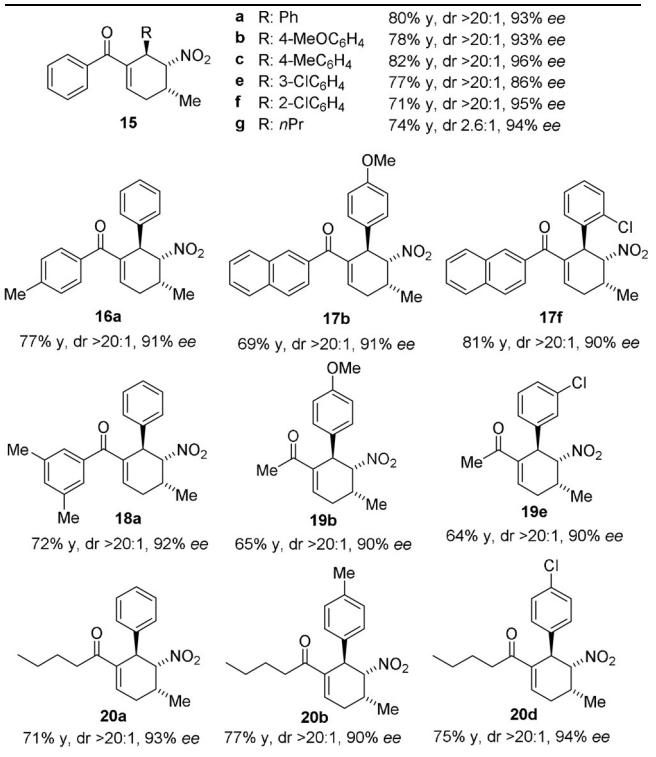
R= **a**: Ph; **b**: 4-$MeOC_6H_4$; **c**: 4-MeC_6H_4; **d**: 4-ClC_6H_4; **e**: 3-ClC_6H_4; **f**: 2-ClC_6H_4; **g**: *n*Pr



[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv of **1** and 10 mol% catalyst in 0.1 mL DCM at room temperature. Variable amounts (ca. 20%) of isomerized starting material were observed in most entries. Yield after chromatography. The dr determined by ^{1}H NMR (300 MHz). The *ee* determined by chiral HPLC.

Table 3: Catalytic enantioselective one-pot, two-step synthesis of tetrasubstituted cyclohexenes from ketone trienolates and nitroolefins.[a]

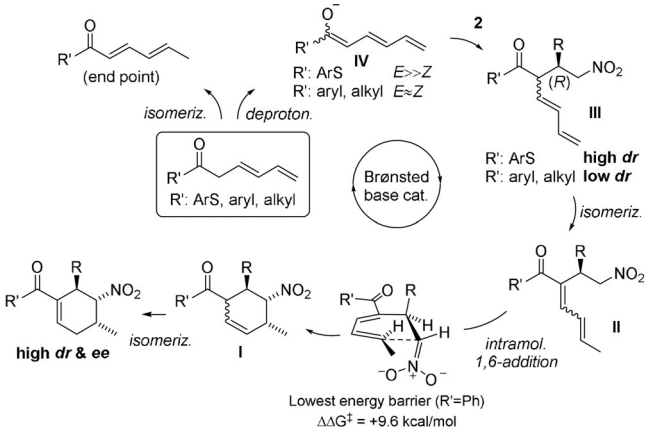




[a] Reactions carried out at 0.1 mmol scale, using 1.2 equiv of **7**–**12** and in 0.1 mL DCM at room temperature. Yield after chromatography. The dr values are determined by ^{1}H NMR (300 MHz). The *ee*s are determined by chiral HPLC.

affording the corresponding adducts **16**–**20** in good yields and high selectivities. These results overall underline the high enantio- and regiocontrol imparted by bifunctional Brønsted base/H-bonding catalysis during trienolates α-functionalization. Previously established activation modes using similar polyunsaturated substrates, particularly trienamine activation, becomes unsuitable due to its inability to activate (thio)esters and/or divergent reactivity patterns.[3h,15]

A rationale for the above experimental observations is proposed in Scheme 1, with Brønsted base catalysis as the unified mode of activation. The sequence would involve: 1) deprotonation of the unsaturated ketone/thioester to render trienolate intermediates **IV**, which would react with acceptor **2** through Cα preferentially;[16] 2) isomerization of the double bonds in **III** to lead to conjugate dienone/dienoate **II**; 3) base-promoted carbocyclization of adducts **II** through intramolecular 1,6-addition; and 4) base-catalyzed final reconjugation. Among the four possible isomeric products in step 1),

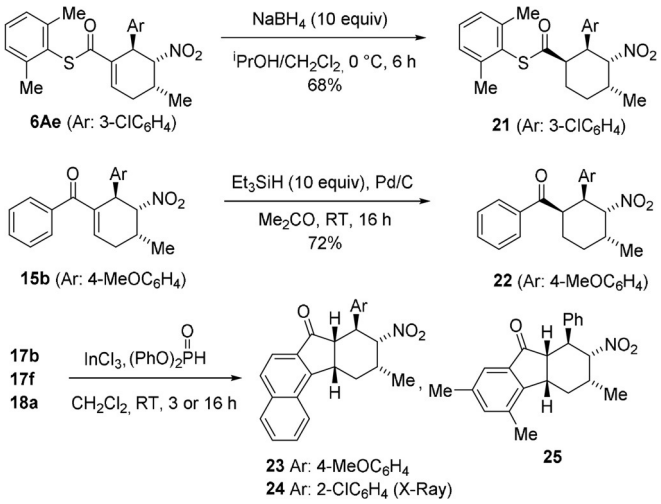


Scheme 1. Plausible course of the one-pot reactions sequence.

calculations carried out on a model reaction correctly predict formation of **III** featuring an (*R*)-configured β-carbon as major isomer.[17] It should be noted that isomerization of **III** to

II (step 2) makes the actual configuration of Cα stereocenter in **III** irrelevant. On the other hand, none of the chiral catalyst **C1**–**C4** by their own can promote the **III**→**II** isomerization nor the subsequent conversion of **II** to **I** (step 3) under the conditions tested. Instead, a stronger base catalyst, that is, amidine (DBU) or guanidine (MTBD), was necessary. Accordingly, the stereochemical outcome of this catalytic carbocyclization process appears to be fully substrate-controlled. In support of this assumption, the energies of the TS for the four possible nitronate-dienone face combinations were calculated. The energy barrier for the *re*,*re* approach was found to be 9.6 kcal mol^{-1} (about 2 kcal mol^{-1} lower than any of the other three possible approaches) which nicely explains the essentially perfect stereoinduction observed in all but one case (compound **15g**).

Several transformations of these polysubstituted cyclohexene adducts were explored (Scheme 2). Selective reduction of the C–C double bond in thioester **6Ae** was achieved by



Scheme 2. Elaboration of adducts through reduction and Nazarov cyclization.

simply using an excess of $NaBH_4$ in isopropyl alcohol and CH_2Cl_2 mixture, affording cyclohexane **21** as the only isomer in 68% isolated yield. In its turn, the reduction of enone **15b** to **22** could be achieved in 72% yield and without affecting the carbonyl group by using Et_3SiH in the presence of Pd/C.[18] Interestingly, these cyclohexene adducts were also well suited for expanding the Nazarov cyclization,[19] as demonstrated by the conversion of adducts **17b**, **17f**, and **18a** into products **23**–**25** in good yields and as a single diastereomer. The structures of these polycyclic products were established by NMR experiments and corroborated by X-ray analysis of **24**.[14]

In summary, a catalytic one-pot process to assemble stereodefined tetrasubstituted six membered carbocycles from polyunsaturated thioesthers or ketones is developed. The new method features: 1) A highly enantioselective α-addition of transiently generated trienolates to nitrolefins. 2) A catalytic intramolecular 1,6-addition that proceeds with essentially perfect stereocontrol and has almost no precedents. 3) Two intermediate C=C isomerizations, with Brønsted base catalysts as the only promoters. Importantly, the α-addition pathway observed for trienolates is divergent from the [4+2] cycloaddition pathways dominant in trienamine mediated chemistry,[3h,15] and provides a route to complementary cyclohexene systems and products derived thereof. Given that both proton transfer and H-bonding are general activation modes, new enantioselective reactions involving trienolate-like π-extended systems from carbonyl and non-carbonyl substrates might be predictable.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Brønsted bases · 1,6-conjugate additions · organocatalysis · synthetic methods · trienolates

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Angew. Chem. **2019**, *131*, 14388–14392

[1] Selected reviews: a) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; *Angew. Chem.* **2002**, *114*, 1724–1741; b) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* **2010**, 1–26; c) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491–1500; d) D. Carmona, M. P. Lamata, L. A. Oro, *Coord. Chem. Rev.* **2000**, *200–202*, 717–772.

[2] For reviews, see: a) D. Enders, C. Grondal, M. R. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; *Angew. Chem.* **2007**, *119*, 1590–1601; b) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237–294; c) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2461; d) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281; e) H. Pellissier, *Adv. Synth. Catal.* **2016**, *358*, 2194–2259.

[3] For reviews on organocatalytic cyclizations and cycloadditions, see: a) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; b) P. Chauhan, S. Mahajan, D. Enders, *Acc. Chem. Res.* **2017**, *50*, 2809–2821; c) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909–1930. From dienamines: d) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832; e) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865–887; f) H. B. Hepburn, L. Dell'Amico, P. Melchiorre, *Chem. Rec.* **2016**, *16*, 1787–1806; g) L. Klier, F. Tur, P. H. Poulsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2017**, *46*, 1080–1102. From trienamines: h) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709–716. From polyenamines: i) A. Przydacz, A. Skrzyńska, Ł. Albrecht, *Angew. Chem. Int. Ed.* **2019**, *58*, 63–73; *Angew. Chem.* **2019**, *131*, 64–75.

[4] A few carbocyclizations through intramolecular 1,6-addition using stoichiometric base mainly, are known: a) S. Nara, H.

Toshima, A. Ichihara, *Tetrahedron Lett.* **1996**, *37*, 6745 – 6748; b) S. Nara, H. Toshima, A. Ichihara, *Tetrahedron* **1997**, *53*, 9509 – 9524; c) D. Gray, T. Gallagher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419 – 2423; *Angew. Chem.* **2006**, *118*, 2479 – 2483; d) T. Gallagher, I. Derrick, P. M. Durkin, C. A. Haseler, C. Hirschhäuser, P. Magrone, *J. Org. Chem.* **2010**, *75*, 3766 – 3774; e) Y. He, D. Wu, Z. Li, K. Robeyns, L. Van Meerveltd, E. V. Van der Eycken, *Org. Biomol. Chem.* **2019**, *17*, 6284 – 6292. For reviews on conjugate 1,6-additions, see: (General) f) A. G. Csákÿ, G. Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080 – 4102; g) E. M. P. Silva, A. M. S. Silva, *Synthesis* **2012**, *44*, 3109 – 3128; (Organocatalytic) h) A. T. Biju, *ChemCatChem* **2011**, *3*, 1847 – 1849; i) P. Chauhan, U. Kaya, D. Enders, *Adv. Synth. Catal.* **2017**, *359*, 888 – 912.

[5] For selected reviews on Brønsted base catalysis, see: a) S.-K. Tian, Y. Chen, Y. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621 – 631; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; c) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145 – 200; d) "Cinchona Alkaloid Organocatalysts": R. P. Singh, L. Deng in *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 41 – 118; e) "Bifunctional Cinchona Alkaloid Organocatalysts": H. B. Jang, J. S. Oh, C. E. Song in *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 119 – 168.

[6] Catalytic intramolecular 1,6-additions have been reported in the context of *o*- and *p*-quinone methides mainly, see: a) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 12104 – 12108; *Angew. Chem.* **2016**, *128*, 12283 – 12287; b) X.-Z. Zhang, K.-J. Gan, X.-X. Liu, Y.-H. Deng, F.-X. Wang, K.-Y. Yu, J. Zhang, C.-A. Fan, *Org. Lett.* **2017**, *19*, 3207 – 3210; c) Z. Ye, L. Bai, Y. Bai, Z. Gan, H. Zhou, T. Pan, Y. Yu, J. Zhou, *Tetrahedron* **2019**, *75*, 682 – 687.

[7] Reactions of lithium trienolates with enones have been documented to afford a mixture of regioisomeric products depending on the substitution pattern of the trienolate and enone. See: a) P. Ballester, A. Costa, A. García-Raso, A. Gómez-Solivellas, R. Mestres, *Tetrahedron Lett.* **1985**, *26*, 3625 – 3628; b) P. Ballester, A. Costa, A. García-Raso, R. Mestres, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2797 – 2803.

[8] I. Iriarte, O. Olaizola, S. Vera, I. Ganboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860 – 8864; *Angew. Chem.* **2017**, *129*, 8986 – 8990.

[9] These thioesters were prepared through sorbic acid deconjugation and coupling with the respective thiol. The simplest phenyl thioester could not be prepared in practical yields for screening, because of concomitant thio-Michael addition. For details, see the Supporting Information.

[10] Reviews on conjugate additions to nitroolefins: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; b) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, *45*, 2627 – 2628. Nitroalkenes in the synthesis of carbocycles: d) A. Z. Halimehjani, I. N. N. Namboothiri, S. E. Hooshmanda, *RSC Adv.* **2014**, *4*, 31261 – 31299.

[11] For the first direct example of enantioselective synthesis of polysubstituted cyclohexyl systems, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863. For Reviews, see: b) ref. [3].

[12] a) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153 – 156; *Angew. Chem.* **2010**, *122*, 157 – 160. For selected reviews on squaramide catalysts, see: c) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330 – 2346; d) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890 – 6899.

[13] For selected reviews on organocatalytic one-pot reactions, see: a) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492 – 8509; *Angew. Chem.* **2011**, *123*, 8642 – 8660; b) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866 – 880.

[14] CCDC 1915882(**6Ba**), and 1915883 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[15] The groups of Jørgensen and Chen have shown that transiently generated trienamines tend to react through various distal carbons, but not through Cα. For leading references (dominant β,ε-additions), see: a) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053 – 5061; b) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8638 – 8641; *Angew. Chem.* **2011**, *123*, 8797 – 8800. For additional reactivity patterns involving crossed trienamines, see: c) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943 – 12946; d) W. Xiao, Q.-Q. Yang, Z. Chen, Q. Ouyang, W. Du, Y.-C. Chen, *Org. Lett.* **2018**, *20*, 236 – 239, and references therein.

[16] The predominant α-regioselectivity observed is in agreement with the calculated charge distributions (Fukui index) for ketone and thioester-derived trienolates. This same reactivity trend is inferred from the calculated energy barriers for the α-, γ-, and ε-reaction pathways, respectively. For details, see the Supporting Information.

[17] See the Supporting Information for details.

[18] a) Y. Arakawa, S. P. Fritz, H. Wennemers, *J. Org. Chem.* **2014**, *79*, 3937 – 3945; b) T. Fukuyama, S.-C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050 – 7051.

[19] Z.-G. Xi, L. Zhu, S. Luo, J.-P. Cheng, *J. Org. Chem.* **2013**, *78*, 606 – 613.

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N-Chloroformylimidazolidinone Enolates as 1,3-Dipolar Reagents for the Stereoselective Synthesis of 3,4-Dihydroisoquinolones

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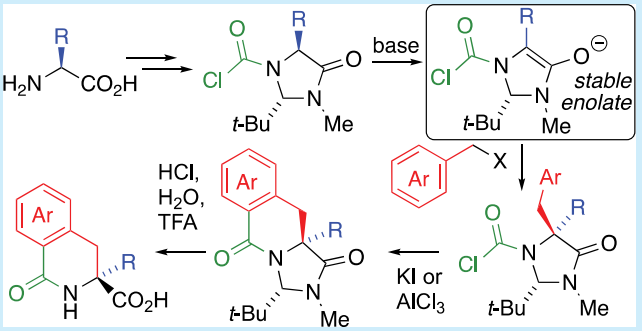
School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

Supporting Information

ABSTRACT: *N*-Chloroformyl imidazolidinone derivatives of enantiopure amino acids may be deprotonated to give remarkably well-behaved enolates with both nucleophilic and electrophilic character. The enolates undergo diastereoselective C-alkylation with benzylic halides. A Bischler–Napieralski-like cyclization reaction onto the chloroformyl group, induced by either nucleophilic (KI, 2,6-lutidine) or Lewis acid ($AlCl_3$) catalysis, gives substituted 3,4-dihydroisoquinolone derivatives in enantioenriched form. The reaction sequence constitutes a formal [3 + 3] route to the six-membered lactam ring of the dihydroisoquinolones.



The 3,4-dihydroisoquinolone[1−7] core represents an important structural motif found among a wide variety of natural products (Figure 1).[8−11] The dihydroisoquinolone skeleton also displays a range of biological activities,[12,13] including anti-inflammatory,[10] anticancer,[14] and antiangiogenic[15] characteristics.

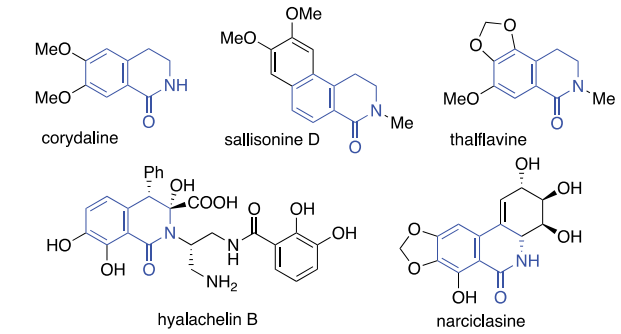
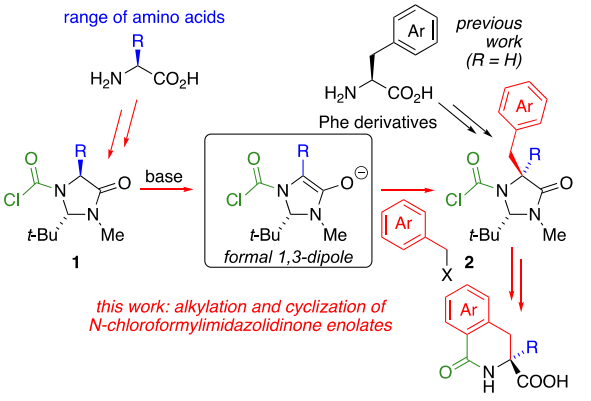


Figure 1. Natural products containing the dihydroisoquinolone skeleton.

We previously reported that an intramolecular KI-promoted Friedel–Crafts cyclization of *N*-chloroformylimidazolidinones derived from aromatic amino acids, such as L-phenylalanine, provides an efficient synthesis of certain substituted 3,4-dihydroisoquinolones (Scheme 1).[16]

The limitation of this work was the availability of suitable enantiopure amino acids bearing nucleophilic aromatic substituents. We now report a way to circumvent this limitation by exploiting the functionalization of a much wider range of *N*-chloroformylimidazolidinones **1** at the α-carbon. In this paper, we show that, remarkably, the enolate of the imidazolidinone **1** can be generated in the presence of the reactive, electrophilic chloroformyl group (Scheme 1). The enolate functions as a formal 1,3-dipole: alkylation of the nucleophilic enolate with benzylic electrophiles, followed by electrophilic cyclization of the *N*-chloroformylimidazolidinone **2**, provides a dihydroisoquinolone in a formal [3 + 3] annulation. Introducing the nucleophilic aromatic component of the cyclization after formation of the *N*-chloroformyl imidazolidinone enables the synthesis of a much wider range of cyclized products, leading to dihydroisoquinolones bearing a variety of functionality on the aryl ring.

Scheme 1. Dihydroisoquinolones by Cyclization of Amino Acid Derived *N*-Chloroformylimidazolidones



The *trans*-*N*-chloroformylimidazolidinones **1** were obtained in three simple steps from the commercially available amino acids using our previously reported conditions for the selective formation of the *trans* diastereoisomer.[16−18] Treatment of the

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N-chloroformylimidazolidinone **1** (R = Me) with KHMDS and benzyl bromide at −78 °C resulted in clean and stereoselective alkylation of the enolate, with the product **2a** formed as a single diastereoisomer. The relative stereochemistry of **2a** (and of its diastereoisomer **2u** described below) was established by NOE studies (see Supporting Information (SI)). As expected, the product is formed by the alkylating agent approaching *anti* to the bulky *tert*-butyl group.

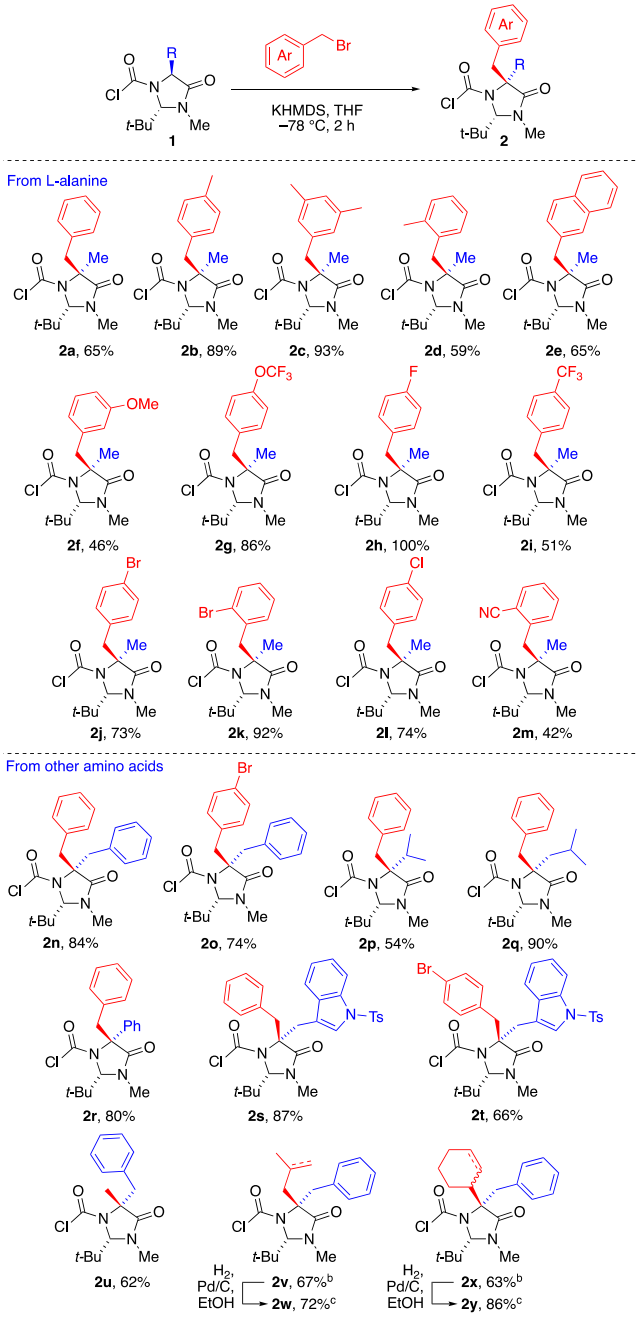
Scheme 2 shows the results of alkylating the enolate of **1** with a range of substituted benzyl halides. The enolate of the L-alanine derived *N*-chloroformylimidazolidinone **1** (R = Me) reacted successfully with benzyl bromides bearing a variety of functional groups and substitution patterns. Electron-neutral and electron-rich aryl rings were tolerated well, including those substituted with methyl (**2b**−**2d**), methoxy (**2f**), and trifluoromethoxy (**2g**) groups. Alkylation with halogenated benzyl bromides also proceeded well (giving **2h**−**2l**). Electron-deficient rings bearing a trifluoromethyl and a nitrile group (**2i** and **2m**) likewise underwent diastereoselective alkylation, though in slightly diminished yields.

N-Chloroformylimidazolidinones derived from amino acids other than L-alanine also reacted cleanly with benzylic electrophiles. Alkylated imidazolidinones derived from L-phenylalanine (giving **2n**, **2o**), L-valine (**2p**), L-leucine (**2q**), L-phenylglycine (**2r**), and L-tryptophan (**2s**, **2t**) were obtained in good yields. Wider reactivity toward alkylating agents was also demonstrated with the L-phenylalanine-derived *N*-chloroformylimidazolidinones **1** (R = Bn), whose enolate reacted with other electrophiles such as methyl iodide (**2u**), 3-bromo-2-methylpropene (**2v**), and 3-bromocyclohexene (**2x**) in moderate to good yields. This imidazolidinone enolate was unreactive toward more bulky simple (nonallylic) alkylating agents, but remarkably the carbamoyl chloride function was resistant to hydrogenolysis, so the alkene functions of **2v** and **2x** could be hydrogenated to give the alkylated products **2w** and **2y**.

N-Chloroformylimidazolidinones are potential substrates[16] for Bischler−Napieralski-like ring closure[19−21] to form isoquinolone derivatives by intramolecular Friedel−Crafts cyclization. This transformation was explored by subjecting imidazolidinone **2a** (in which an unsubstituted benzyl ring lies *trans* to the *tert*-butyl group) to nucleophilic catalysis by KI in our previously optimized cyclocarbonylation conditions (Table 1, entry 1: KI, 2,6-lutidine, μW, 150 °C). 12% of the dihydroisoquinolone **3a** was isolated after 5 min, increasing to full conversion after 2 h (87% isolated yield, entry 3). With the electron-deficient aryl ring of the *para*-bromo derivative **2j**, the starting material was completely consumed after 4 h, but only 15% of the isoquinolone product **3j** was isolated (entry 5). We therefore turned toward alternative promoters of Friedel−Crafts acylations. After some optimization of the reaction time and temperature (see SI for details), we found that $AlCl_3$ in 1,2-dichloroethane at 80 °C served as an efficient promoter of the cyclization. Under these optimized conditions, **2j** was converted into **3j** in excellent yield (entry 5).

The other diastereoisomer of **2a**, namely **2u**, was available from the methylation of the phenylalanine-derived imidazolidinone. In previous work, we found that only aryl substituents *trans* to the *tert*-butyl group would undergo clean cyclization onto the chloroformyl group. **2u** gave the opportunity to explore whether this was also the case when the α-carbon of the imidazolidinone is fully substituted. Treatment of **2u** (where the benzyl group and the *tert*-butyl group are in a *cis* relationship) with KI under the standard conditions led to decomposition of the starting material with loss of the chloroformyl group, and gave none of the tricyclic lactam. However, treating *cis*-imidazolidinone **2u** with $AlCl_3$ under the conditions optimized for **2j** promoted successful cyclization, and the tricyclic lactam **4u** was obtained in 83% yield. **4u** carries the *tert*-butyl group on the *endo* face of the bicyclic imidazolidinone, and its relative configuration was confirmed by NOE analysis (see SI). Using these two optimized methods for cyclization, we explored the scope of the cyclocarbonyla-

Scheme 2. Scope of Diastereoselective Alkylation[a]



[a]Isolated yields shown. *N*-Chloroformylimidazolidinone (1.0 equiv), THF (0.1 M), KHMDS (1−1.2 equiv, added dropwise), electrophile (1−1.5 equiv); the electrophile was added either before or 5 min after addition of KHMDS (see SI for further details). [b]Unsaturated product. [c]Saturated product

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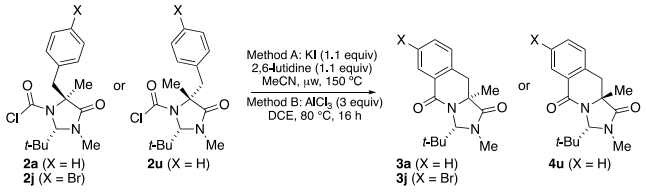
Table 1. Optimization of the Cyclocarbonylation



entry	SM	X	method	time	product	yield
1	**2a**	H	A	5 min	**3a**	12%
2	**2a**	H	A	1 h	**3a**	83%
3	**2a**	H	A	2 h	**3a**	87%
4	**2j**	Br	A	4 h	**3j**	15%
5	**2j**	Br	B	16 h	**3j**	93%
6	**2u**	H	A	4 h	[a]	–
7	**2u**	H	B	16 h	**4u**	83%

[a]A diastereoisomeric mixture of imidazolidinones lacking the chloroformyl group was recovered.

tion reaction with a range of quaternary *N*-chloroformyl-imidazolidinones **2** (Scheme 3).

Using the L-alanine derived chloroformylimidazolidinones **2a**–**2m**, good to excellent yields of imidazolidinone-fused dihydroisoquinolones **3a**–**f** were obtained by cyclization of electron-neutral and electron-rich rings bearing different substitution patterns using KI and 2,6-lutidine under the conditions of method A. X-ray crystallography confirmed the structure of **3f** (CCDC 1895400).

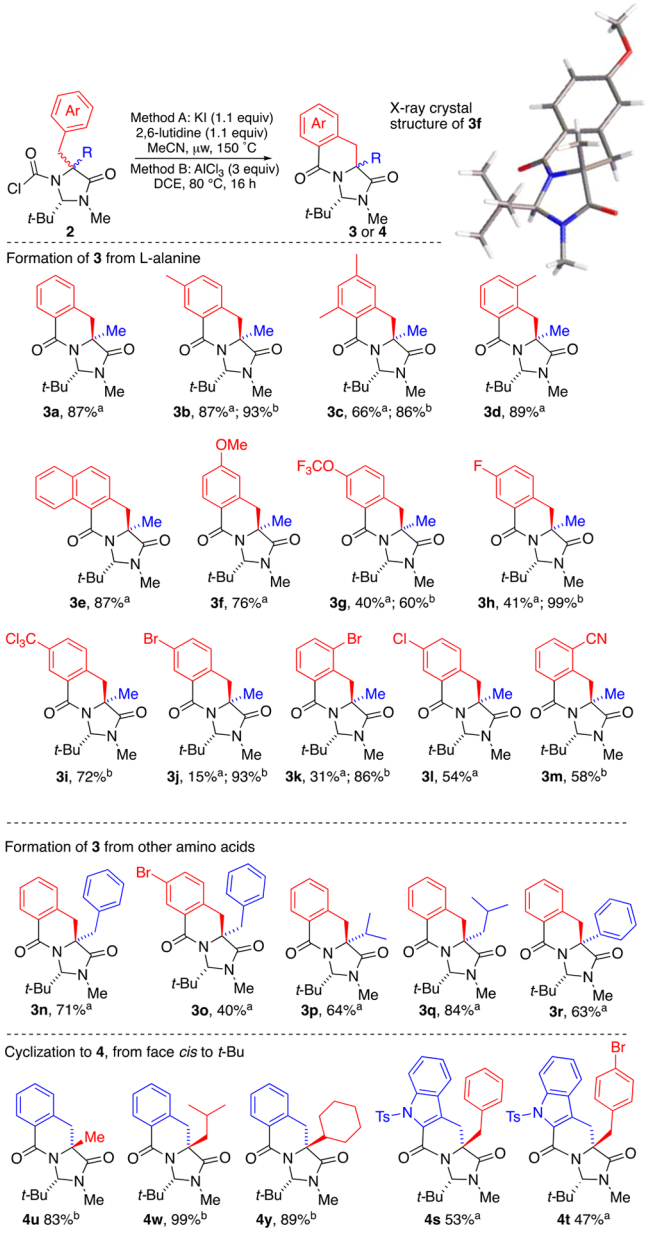
For comparison, some of these cyclizations were also carried out using the more forcing conditions of method B ($AlCl_3$ in hot dichloroethane). Yields were generally similar for the cyclization of electron-neutral rings (viz. 93% $AlCl_3$ vs 87% KI for the *para*-tolyl derivative **3b**). However, for substrates **2h**–**2m** bearing electron-withdrawing groups, $AlCl_3$ proved to be a far superior reagent for the formation of dihydroisoquinolones **3h**–**3m**. For chloroformylimidazolidinones **2j** and **2k** bearing an *ortho*-bromophenyl and *para*-bromophenyl rings, yields using KI were <35%, whereas with $AlCl_3$ yields were >85%. The electron-deficient *ortho*-cyano derivative **2m** did not cyclize with KI, but gave 58% dihydroisoquinolone **3m** with $AlCl_3$.

Cyclizations to dihydroisoquinolones were also successful using imidazolidinones derived from other amino acids, such as phenylalanine (giving **3n** and **3o**), as well as the more hindered branched structures derived from valine (**3p**), leucine (**3q**), and phenylglycine (**3r**).

In the case of the tryptophan-derived *N*-chloroformyl-imidazolidinones **2s** and **2t**, KI promoted cyclization of the more nucleophilic indole ring, even though this ring is orientated in the less reactive position (see Table 1) *cis* to the *tert*-butyl group. The products of the cyclization of **2s** and **2t** are thus **4s** and **4t**, in which the *tert*-butyl group is located on the *endo* face of the bicyclic imidazolidinone. It thus appears that sufficiently reactive, electron-rich rings can cyclize from the same face as the *tert*-butyl group even under the milder KI-promoted conditions.

Other imidazolidinones **2u**–**2y** formed by alkylation of the L-phenylalanine-derived imidazolidinone, and thus bearing benzyl groups *cis* to the *tert*-butyl, did not cyclize with KI. Nonetheless, with $AlCl_3$, excellent yields were obtained of the *endo* products **4u**, **4w**, and **4y**.[22] The differences in reactivity under the two sets of reaction conditions suggest that different

Scheme 3. Scope of the Cyclocarbonylation



[a]By method A. [b]By method B.

intermediates are generated. We propose that KI leads to a transient carbamoyl iodide,[16,23] whereas $AlCl_3$ promotes formation of an *N*-acylium ion, with the carbamoyl iodide being more sensitive to the geometry of imidazolidinone substituents.

The products **3** and **4** of the cyclofunctionalization contain a valuable dihydroisoquinolone core, fused to an imidizadolidinone which plays no further role in the synthesis. These imidazolidinones may be hydrolyzed to reveal a masked carboxylic acid under acidic conditions. 6 M HCl alone was ineffective, but we found that the addition of 20% TFA to 6 M HCl[16,24] resulted in clean hydrolysis to the dihydroisoquinolone products in good to excellent yields. Where **3** and **4** are diastereoisomeric (e.g., **3a** and **4u**), the hydrolysis provides either enantiomer of the same product (for example **5a**), both formed from an L-amino acid precursor (Scheme 4).

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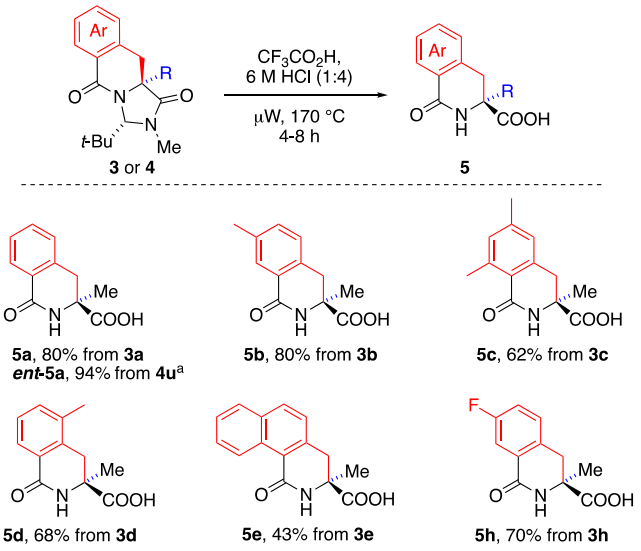
Scheme 4. Hydrolysis To Give Dihydroisoquinolones



[a]See ref 16.

Overall, this method is complementary to our previously reported synthesis of dihydroisoquinolones.[16] It expands the scope to a range of aromatic substituents by exploiting the remarkably clean nucleophilic reactivity of the *N*-chloroformylimidazolidinone enolate. Cyclization of this dipolar reagent by nucleophilic and then electrophilic addition to a benzylic halide provides a carbonylative route to the dihydroisoquinolone ring. Choice of route allows the synthesis of both enantiomers of the product 2-carboxydihydroisoquinolones **5** starting from naturally occurring L-amino acid precursors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00548.

Full experimental details and spectroscopic characterization of all new compounds (PDF)

Accession Codes

CCDC 1895400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ardizzoia, G. A.; Beccalli, E. M.; Borsini, E.; Brenna, S.; Broggini, G.; Rigamonti, M. *Eur. J. Org. Chem.* **2008**, *2008*, 5590.
(2) Müjde, B.; Özcan, S.; Balci, M. *Phytochem. Lett.* **2011**, *4* (4), 407.
(3) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14* (3), 736.
(4) Tang, Q.; Xia, D.; Jin, X.; Zhang, Q.; Sun, X.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 4628.
(5) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421.
(6) Abate, C.; Selivanova, S. V.; Müller, A.; Krämer, S. D.; Schibli, R.; Marottoli, R.; Perrone, R.; Berardi, F.; Niso, M.; Ametamey, S. M. *Eur. J. Med. Chem.* **2013**, *69*, 920.
(7) Kung, P.; Rui, E.; Bergqvist, S.; Bingham, P.; Braganza, J.; Collins, M.; Cui, M.; Diehl, W.; Dinh, D.; Fan, C.; Fantin, V. R.; Gukasyan, H. J.; Hu, W.; Huang, B.; Kephart, S.; Krivacic, C.; Kumpf, R. A.; Li, G.; Maegley, K. A.; Mcalpine, I.; Nguyen, L.; Ninkovic, S.; Ornelas, M.; Ryskin, M.; Scales, S.; Sutton, S.; Tatlock, J.; Verhelle, D.; Wang, F.; Wells, P.; Wythes, M.; Yamazaki, S.; Yip, B.; Yu, X.; Zehnder, L.; Zhang, W.; Rollins, R. A.; Edwards, M. *J. Med. Chem.* **2016**, *59*, 8306.
(8) Nadmid, S.; Plaza, A.; Lauro, G.; Garcia, R.; Bifulco, G.; Müller, R. *Org. Lett.* **2014**, *16*, 4130.
(9) Li, Y. H.; Li, H. M.; He, J.; Deng, X.; Peng, L. Y.; Gao, L. H.; Zhao, Q. S.; Li, R. T.; Wu, X. De. *Tetrahedron* **2014**, *70* (46), 8893.
(10) Furst, R. *Planta Med.* **2016**, *82*, 1389.
(11) He, Q.; Chatani, N. *J. Org. Chem.* **2018**, *83* (21), 13587.
(12) Fisher, M. J.; Gunn, B. P.; Harms, C. S.; Kline, A. D.; Mullaney, J. T.; Scarborough, R. M.; Skelton, M. A.; Um, S. L.; Utterback, B. G.; Jakubowski, J. A. *Bioorg. Med. Chem. Lett.* **1997**, *7* (19), 2537.
(13) Morgan, R. K.; Carter-O'Connell, I.; Cohen, M. S. *Bioorg. Med. Chem. Lett.* **2015**, *25* (21), 4770.
(14) Xi, B. M.; Ni, P. Z.; Jiang, Z. Z.; Wu, D. Q.; Zhang, S.-H.; Zhang, H.-B.; Wang, T.; Chen, W.-H. *Chem. Biol. Drug Des.* **2010**, *76* (6), 505.
(15) Leese, M. P.; Jourdan, F. L.; Major, M. R.; Dohle, W.; Thomas, M. P.; Hamel, E.; Ferrandis, E.; Mahon, M. F.; Newman, S. P.; Purohit, A.; Potter, B. V. L. *ChemMedChem* **2014**, *9* (4), 798.
(16) Amer, M. M.; Carrasco, A. C.; Leonard, D. J.; Ward, J. W.; Clayden, J. *Org. Lett.* **2018**, *20*, 7977.
(17) Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562* (7725), 105.
(18) Abas, H.; Mas-Roselló, J.; Amer, M. M.; Durand, D. J.; Groleau, R. R.; Fey, N.; Clayden, J. *Angew. Chem., Int. Ed.* **2019**, *58*, 2418.
(19) Stambach, J. F.; Jung, L. *Tetrahedron* **1985**, *41* (1), 169.
(20) Dou, D.; Viwanathan, P.; Li, Y.; He, G.; Alliston, K. R.; Lushington, G. H.; Brown-Clay, J. D.; Padmanabhan, R.; Groutas, W. C. *J. Comb. Chem.* **2010**, *12* (6), 836.
(21) Mengozzi, L.; Gualandi, A.; Cozzi, P. G. *Chem. Sci.* **2014**, *5* (10), 3915.
(22) Imidazolidinones bearing two benzylic substituents at the α-carbon of the imidazolidinone (such as **2n** and **2o**) did not cyclize cleanly with $AlCl_3$, and instead decomposed to complex mixtures.
(23) Wakeham, R. J.; Taylor, J. E.; Bull, S. D.; Morris, J. A.; Williams, J. M. *Org. Lett.* **2013**, *15* (3), 702.
(24) Tsugita, A.; Scheffler, J.-J. *Eur. J. Biochem.* **1982**, *124*, 585.

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