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Brønsted Base Catalysed Asymmetric C–C Bond-Forming Reactions with Unsaturated Ketones

DOCTORAL THESIS

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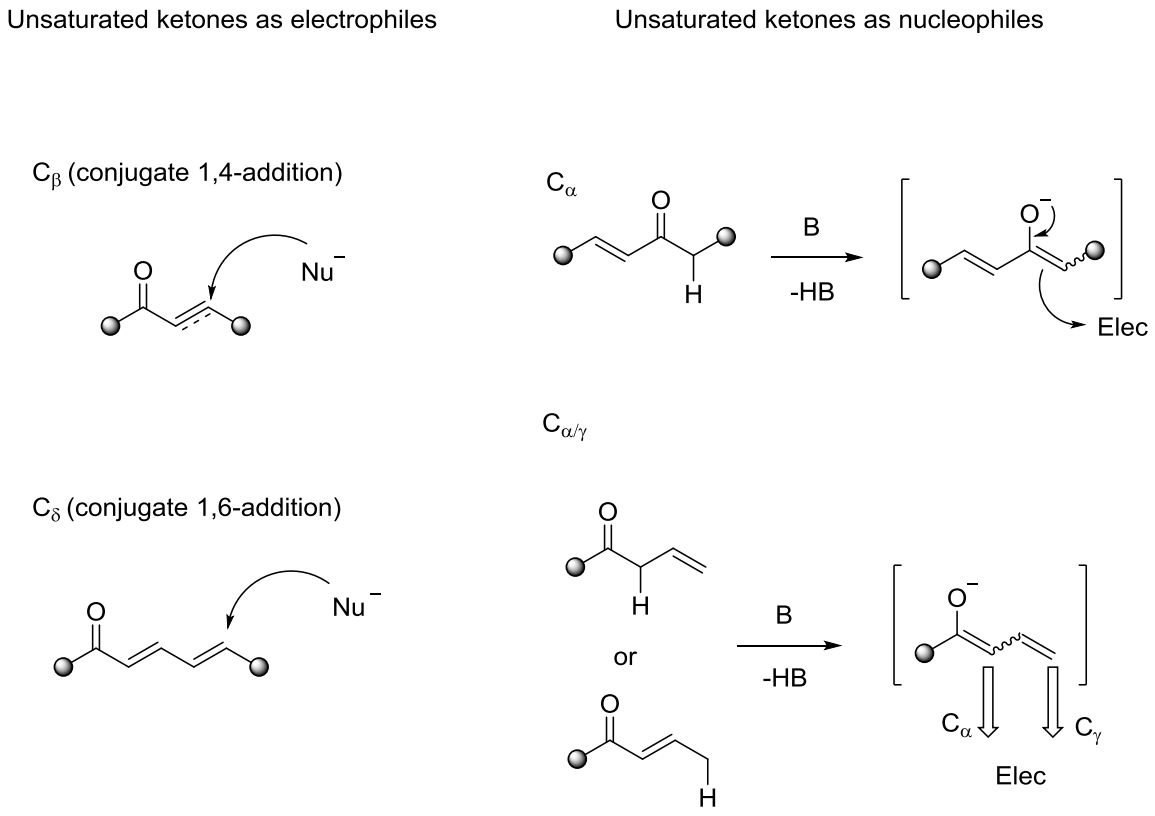
Summary

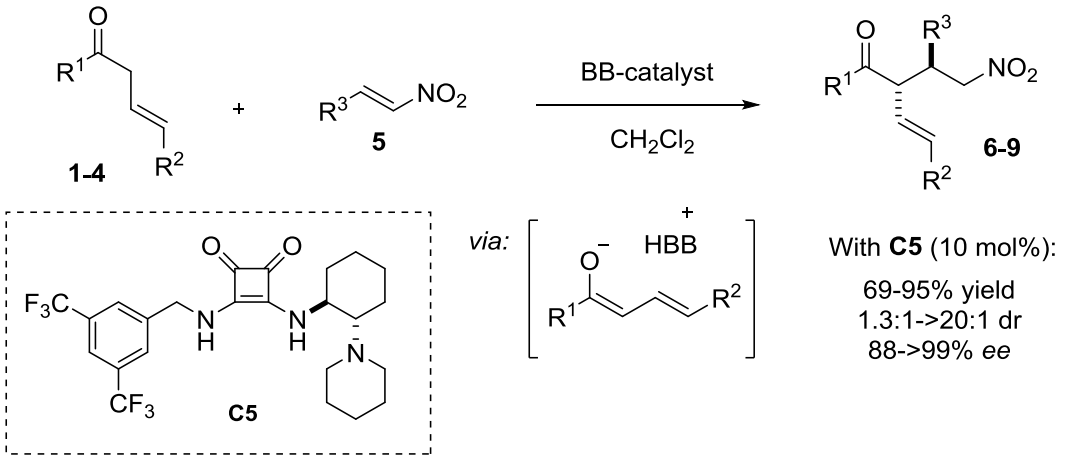
Ketone functional group is widespread among natural products and biologically active molecules. The asymmetric synthesis of ketones with increasingly complex carbon architectures through C–functionalization of easily available simple ketones is therefore a much sought after goal. In this endeavour, ketones can be used as either nucheophilic reagents (via the corresponding enolate or equivalent) or electrophilic reagents. However, the introduction of an unsaturation (C=C or C≡C) in the vicinity of the ketone carbonyl group can vary their electronic properties and, therefore, their reactivity, expanding the possibilities of synthesis because of the concept of vinylogy (Scheme A). For instance, α,β-unsaturated ketones (enones and ynones) can act as electrophiles through C_β, while deprotonation of enones, either conjugated or deconjugated, would give π extended enolates (allylic enolates, dienolates) with very interesting chemistry, allowing the construction of complex molecules. However, important aspects of this chemistry remain poorly addressed yet, especially in what direct asymmetric methodologies concern. In this Thesis, new advances for the Brønsted base catalysed asymmetric functionalization of unsaturated ketones are described.



Scheme A. Main routes for the functionalization of unsaturated ketones.

Summary

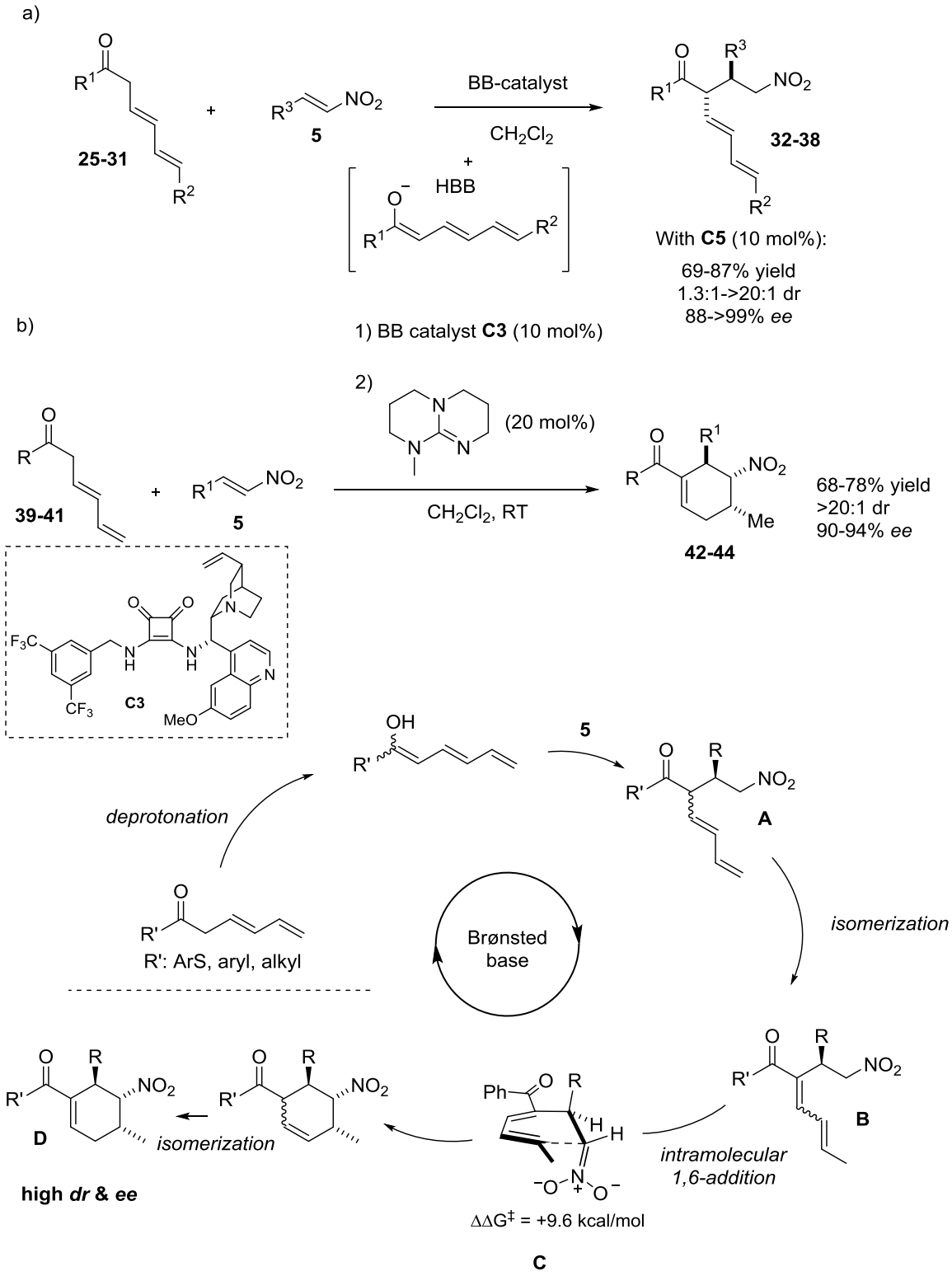
In the first part of the Thesis, we have demonstrated that tertiary amine/squaramide bifunctional catalysts can promote the addition of transiently generated dienolates from skipped enones **1**-**4** to nitroolefins **5** not only with very good enantio- and diastereocontrol, but also exclusive α-site selectivity to afford adducts **6**-**9** in generaly good yield (Scheme B). Interestingly, this reaction pathway is in contrast to the main reactivity of in situ generated dienamines, which have been reported to react predominantly from the γ-carbon.



Scheme B. Brønsted base-catalysed selective α-addition of β,γ-unsaturated ketones to nitroolefins.

Under similar catalytic conditions, the transiently generated trienolates from doubly unsaturated ketones **25**-**31** reacted with nitroolefins **5** affording, again, the α-adducts **32**-**38** exclusively (Scheme Ca). This reactivity pattern is divergent from the reported [4+2] cycloaddition pathways dominant in trienamine-mediated proceses.

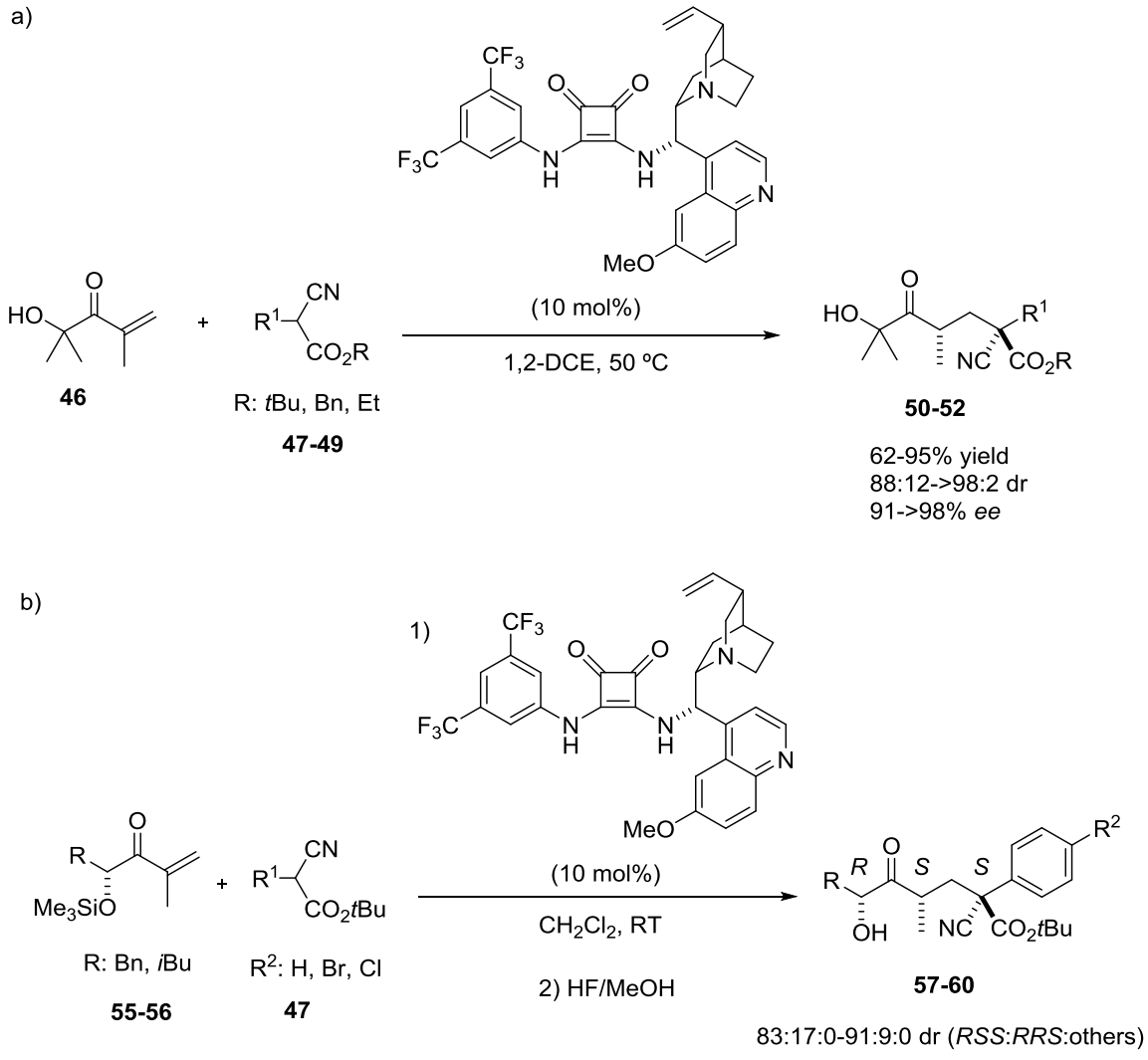
Most important, this reactivity could be coupled with a one-pot base-catalysed isomerization intramolecular 1,6-addition process leading to tetrasubstituted cyclohexenes in fully enantio- (90-94% *ee*) and diastereoselective (dr >20:1) fashion (Scheme Cb).



Scheme C. a) Trienolate mediated α-functionalization of dienones. b) Implementation of a one-pot diastereo- and enantioselective synthesis of cyclohexenes.

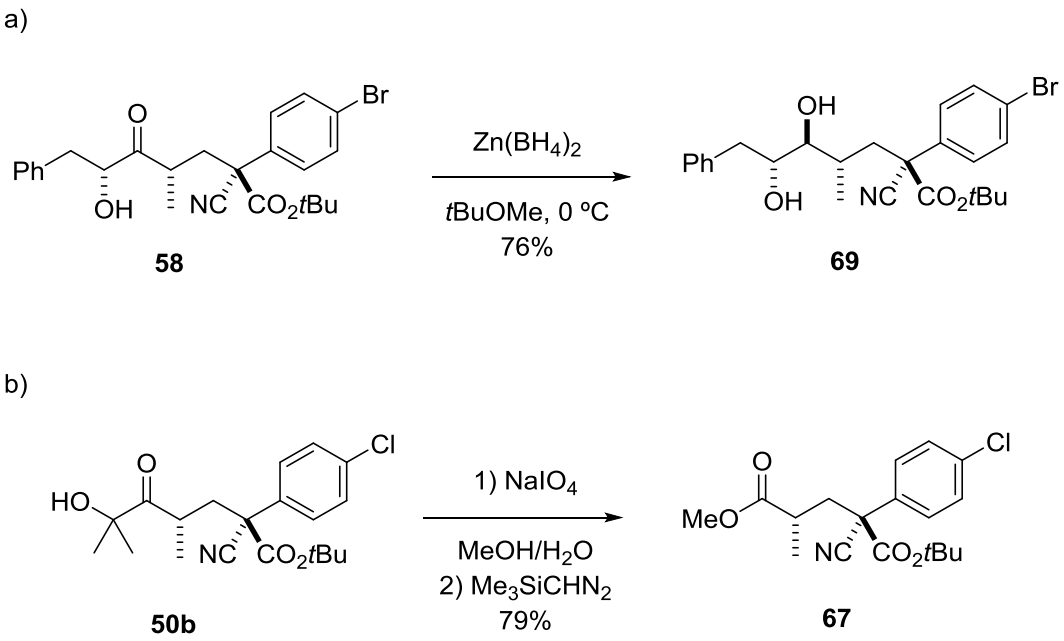
In the second part of the Thesis, the utility of α′-oxy enones as acceptor components in Brønsted base-catalysed C–C bond-forming reactions has been expanded. Based on the

previous work carried out in our laboratory, in which α-oxy enones were used as acrylate equivalents, now we have demonstrated that the α-substituted α´-oxy enones may act as efficient methacrylate equivalents under similar conditions. Thus, Brønsted base/squaramide-type bifunctional catalysts are able to promote the Michael addition of α-cyanoacetates to these enones in highly stereocontrolled manner (Scheme D, a). The process involves first the catalyst controlled Michael addition of α-cyanoacetates **47**-**49** followed by substrate-controlled highly diastereoselective α-protonation. This cascade reaction constitutes a direct method for the construction of acyclic carbonyl compounds with non-adjacent tertiary/quaternary all-carbon stereocenters with high diastereo- and enantioselectivity. This method has been extended to chiral α´-silyloxy enones **55**-**56** which afforded the corresponding adducts **57**-**60** in high dr upon using matching combination of substrate and catalyst (Scheme D, b).



Scheme D. Tandem Michael/α-protonation reaction using α-methyl α´-oxy enones as Michael acceptors.

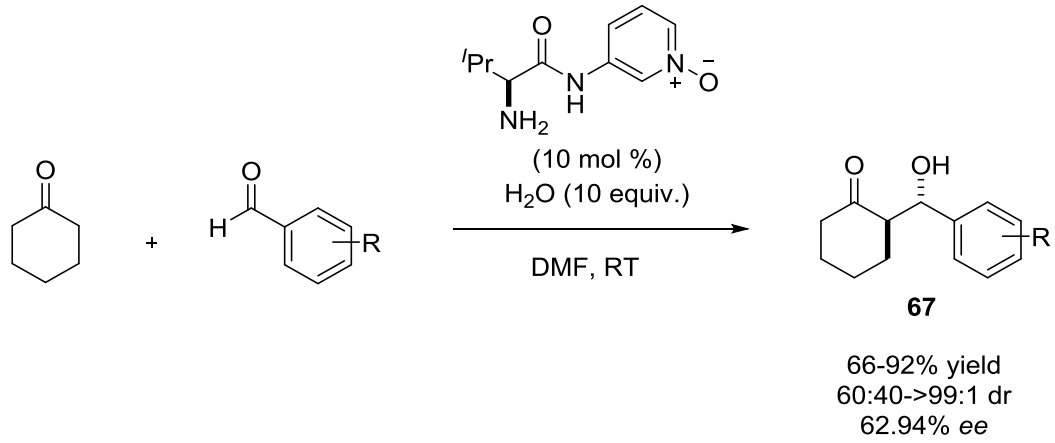
The practical utility of the above catalytic methodology is demonstrated by the easy transformations of adducts into useful building-blocks. For example, the diastereoselective reduction of the ketone **58** results in diol **69** with three tertiary adjacent stereocenters and a quaternary stereocenter (Scheme E, a). On the other hand, the adducts can be easily transformed into the corresponding methyl esters by oxidative cleavage and subsequent esterification of the resulting carboxylic acid (Scheme E, b).



Scheme E. a) Diastereoselective reduction of ketone group to yield *anti*-1,2-diols. b) Oxydative cleavage to obtain the corresponding methyl esters.

Finally, as a result of an international stay in the laboratory of Prof. Keiji Maruoka at the Kyoto University, a valine derived, easily accesible aminoamide-type catalyst (N-phenyl-L-valinamide) has been developed which is capable of promoting the asymmetric aldol reaction between cyclohexanone and aromatic aldehydes. Thus, this pyridine N-oxide-derived α-amino amide catalyst further expands the pool of primary amine catalysts available for enamine-mediated asymmetric transformations.

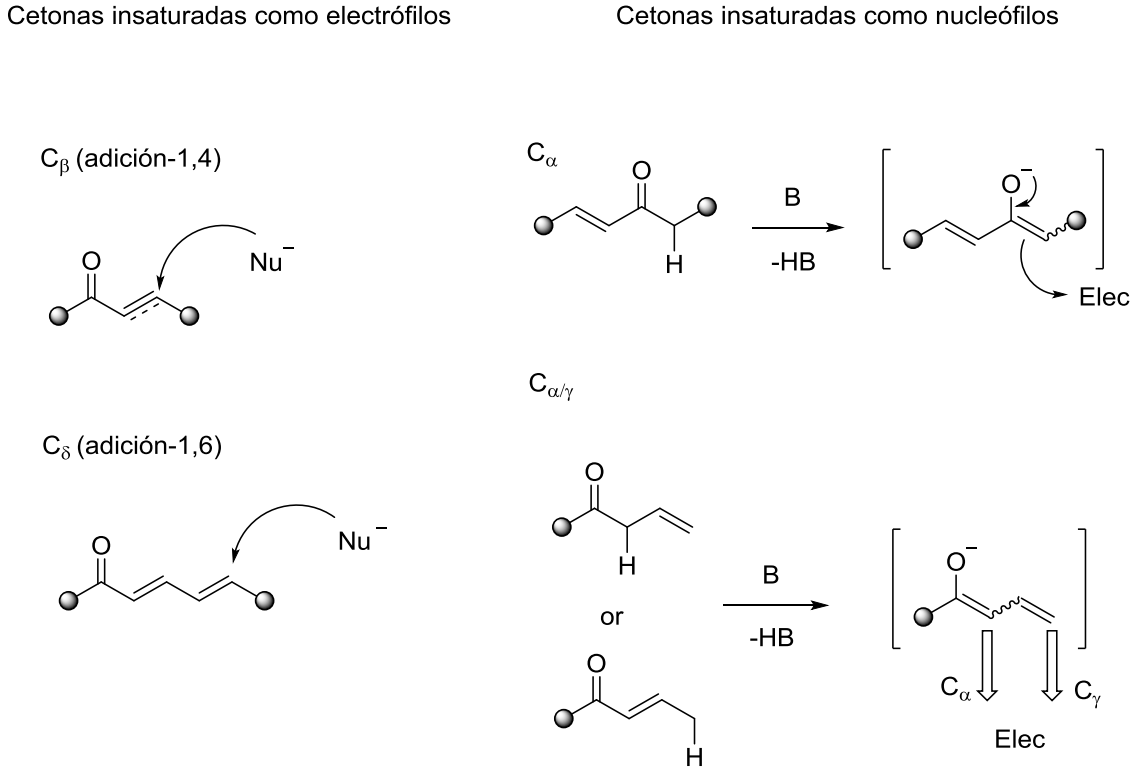
Summary



Scheme F. Aldol reaction between cyclohexanone and aromatic aldehydes promoted by N-phenyl-L-valinamide.

Resumen

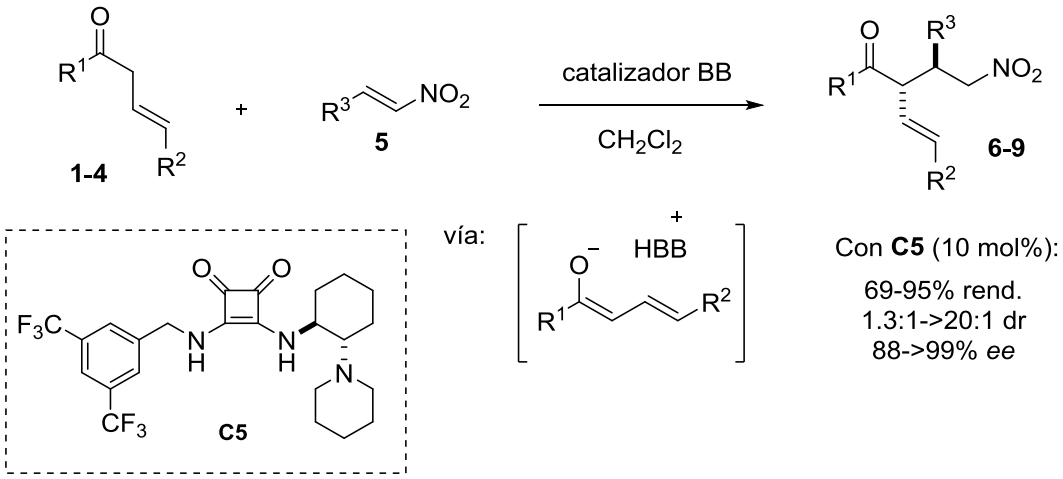
El grupo funcional cetona está muy extendido entre los productos naturales y las moléculas biológicamente activas. Las cetonas pueden actuar como nucleófilos (via enolato o equivalentes) o como electrófilos. Sin embargo, la introducción de una insaturación (C=C o C≡C) en la proximidad del grupo carbonilo de la cetona puede variar de manera decisiva sus propiedades electrónicas y, por lo tanto, su reactividad, ampliando las posibilidades de síntesis debido al concepto de vinilogía (Esquema A). Por ejemplo, las cetonas α,β-insaturadas (enonas e inonas) pueden actuar como electrófilos a través del C_β, mientras que la desprotonación de las enonas conjugadas y no conjugadas conduce a enolatos con un sistema π-extendido, que pueden presentar una química muy interesante, permitiendo la construcción de moléculas complejas. No obstante, varios aspectos importantes de las metodologías asimétricas directas de funcionalización de cetonas insaturadas aún no han sido abordados en la literatura. En esta Tesis, se describen nuevos avances para la funcionalización asimétrica de cetonas insaturadas catalizada por bases Brønsted.



Esquema A. Principales rutas para la funcionalización de cetonas insaturadas.

En la primera parte de esta Tesis, se muestra cómo los catalizadores bifuncionales de tipo amina terciaria/escuaramida pueden promover la adición de cetonas β,γ-

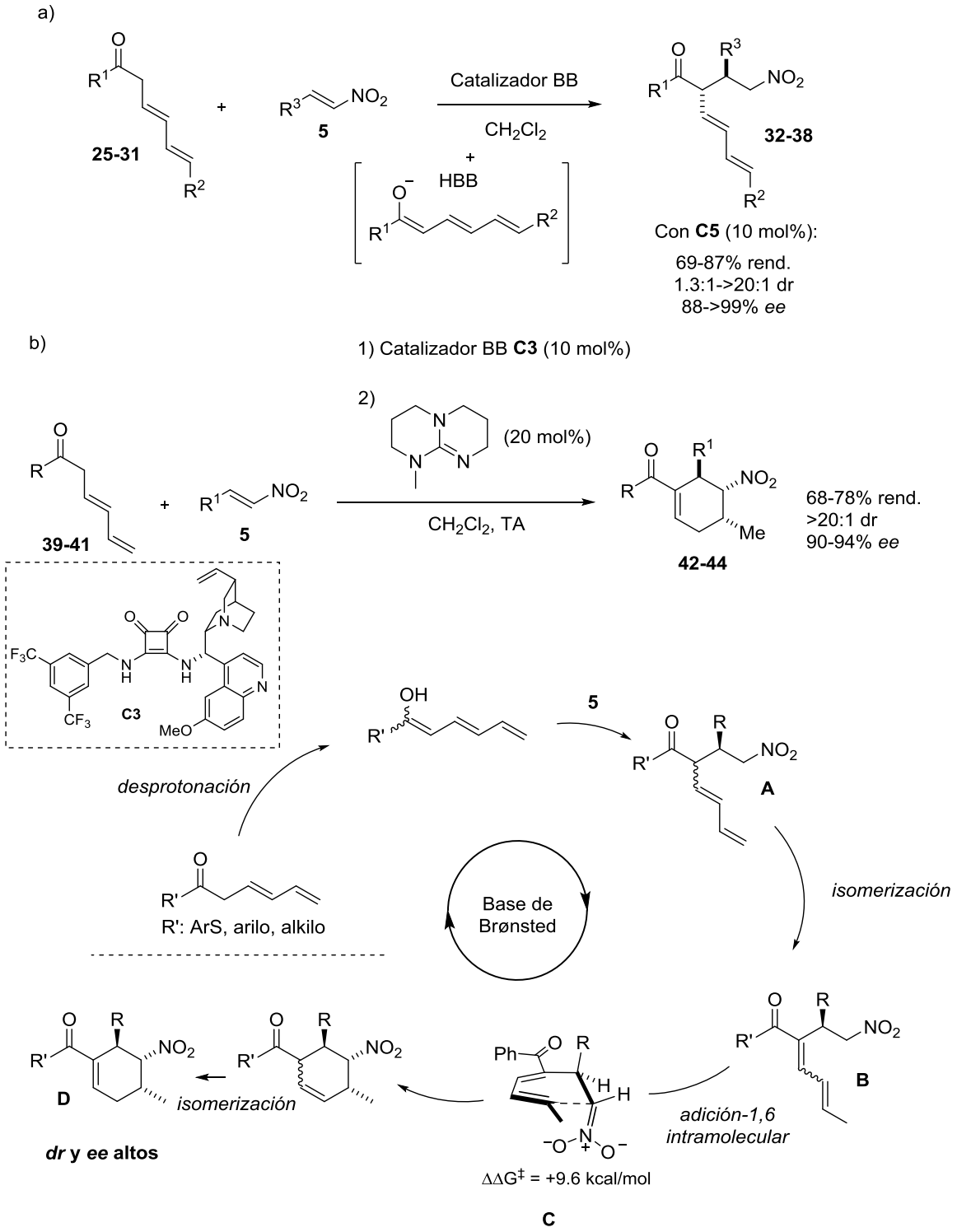
insaturadas **1**-**4** a nitroolefinas **5** vía los correspondientes dienolatos, un proceso que transcurre no solo con muy buen enantio- y diastereocontrol, sino también con total regioselectividad α (Esquema B). Este comportamiento difiere del previamente descrito para las dienaminas, que reaccionan principalmente por el carbono γ.



Esquema B. Adición α-selectiva de cetonas β,γ-insaturadas a nitroolefinas.

Bajo unas condiciones catalíticas similares, los trienolatos generados transitoriamente a partir de las cetonas doblemente insaturadas **25**-**31** reaccionan con nitroolefinas **5** dando lugar a los α-aductos **32**-**38** exclusivamente (Esquema Ca). Nuevamente, la regioselectividad observada difiere de la mostrada por las trienaminas, que generalmente actúan como dienos en cicloadiciones [4+2].

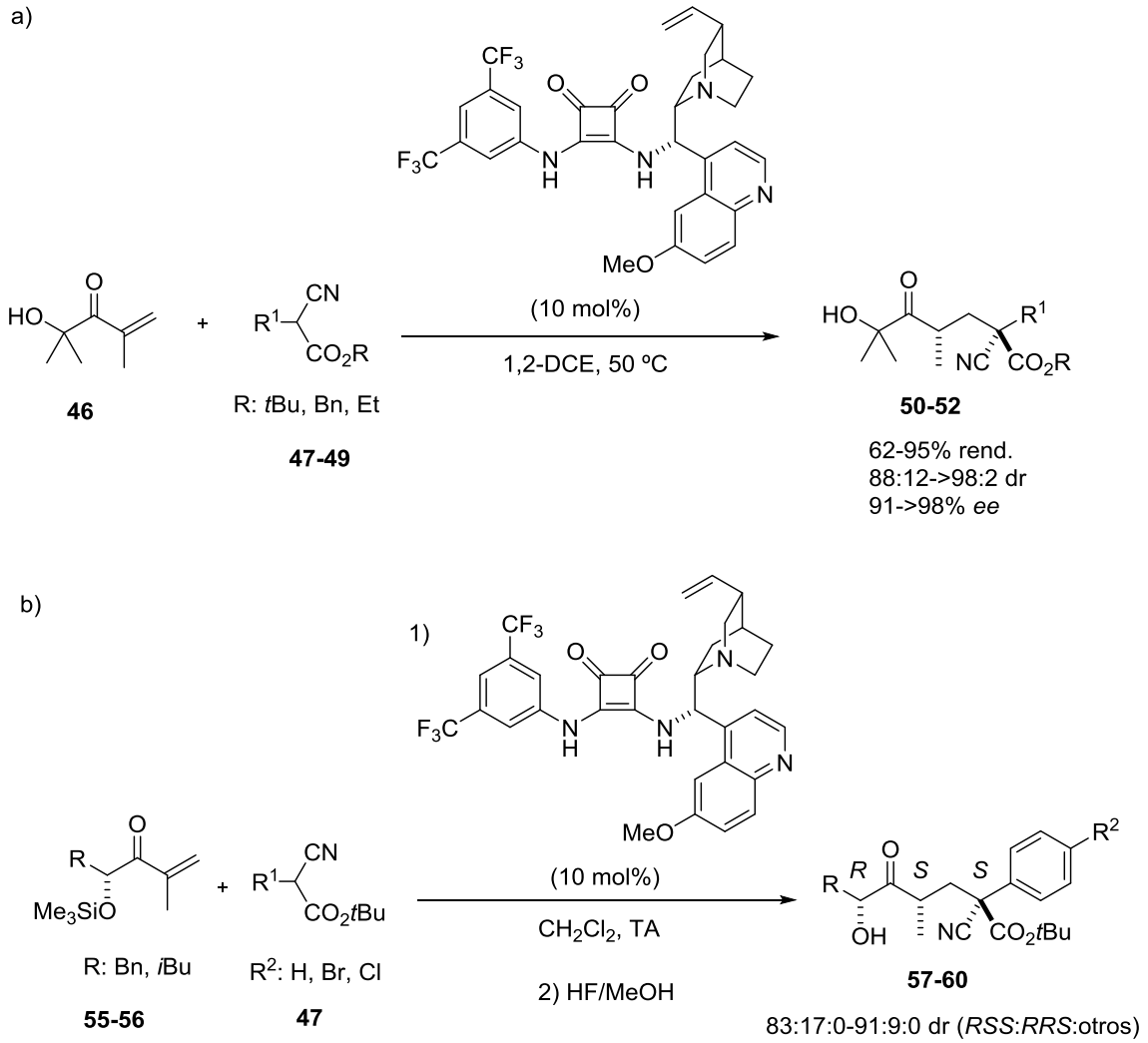
En este sentido, es destacable que la reacción de trienolatos terminales provenientes de cetonas β, γ, δ, ε-insaturadas con nitroolefinas, puede acoplarse en un proceso *one-pot* con una adición 1,6-intramolecular para proporcionar ciclohexenos tetrasustituidos. Este patrón de reactividad diverge con respecto al mostrado por las trienaminas generadas *in situ*, que conducen de forma dominante a cicloadiciones [4+2], y por lo tanto con los resultados presentes se ofrece una ruta complementaria a sistemas de ciclohexilo (Esquema Cb).



Esquema C. a) α-Funcionalización de dienonas vía trienolatos. b) Síntesis de ciclohexenos mediante un proceso one-pot entre cetonas β, γ, δ, ε-insaturadas y nitroolefinas.

En el segundo capítulo de la Tesis, basándonos en el trabajo previo realizado en nuestro laboratorio, en el que se emplearon α-oxi enonas como equivalentes de acrilato, se ha demostrado la utilidad de la 2,4-dimetil-4-hidroxipenten-3-ona **46** como equivalente de

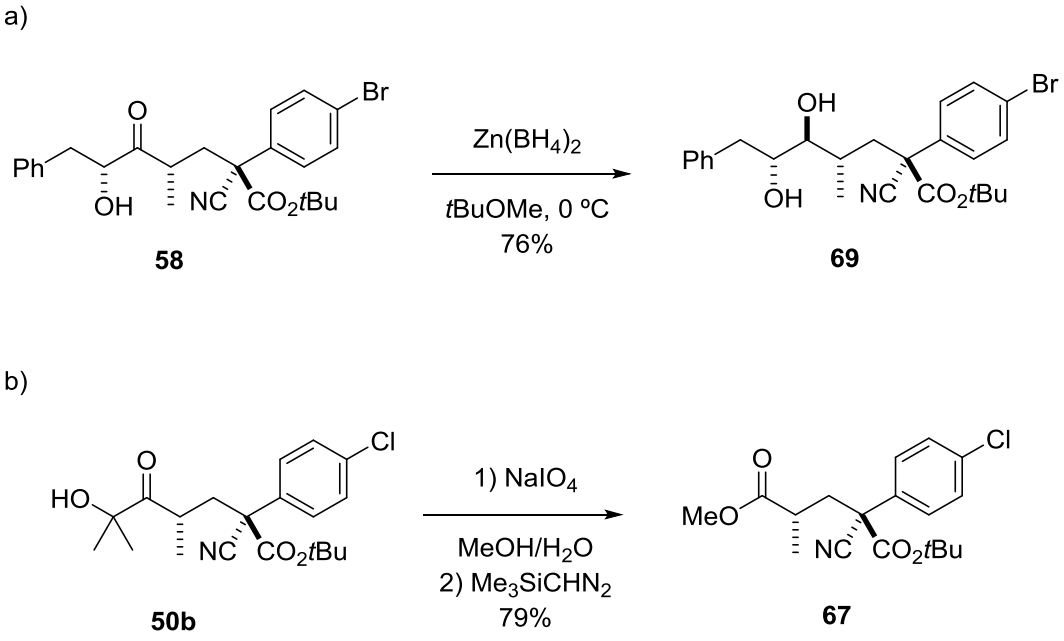
metacrilato, en una adición de Michael promovida por un catalizador bifuncional tipo base de Brønsted/esquaramida, seguida de una α-protonación asimétrica (Esquema D, a). Esta reacción en cascada supone un método directo para la construcción de compuestos carbonílicos acíclicos con estereocentros de carbono terciario/cuaternario no adyacentes con alta diastereo- y enantioselectividad. Esta metodología también ha sido extendida a α-sililoxi enonas quirales **55**-**56** obteniendo los aductos **57**-**60** con alta diastereoselectividad (Esquema D, b).



Esquema D. Proceso tándem de reacción de Michael/α-protonación utilizando α-metil α´-oxi enonas como equivalentes sintéticos del metacrilato como aceptores de Michael.

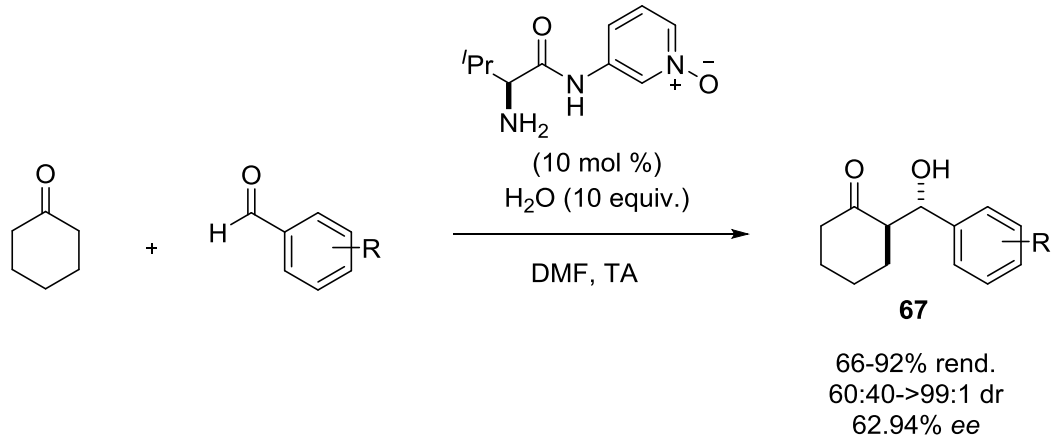
Para demostrar la versatilidad de estas estructuras se han realizado varias transformaciones, que dan lugar a grupos funcionales de utilidad. Por un lado, se sintetizó el diol **69** con tres estereocentros terciarios adyacentes y un estereocentro cuaternario mediante la reducción diastereoselectiva de la cetona **58** (Esquema E, a). Por otro lado, los aductos pueden ser fácilmente transformados a los correspondientes

ésteres metílicos mediante una escisión oxidativa y subsiguiente esterificación del ácido carboxílico resultante (Esquema E, b).



Esquema E. Ejemplos de la utilidad de los aductos obtenidos en síntesis. a) Reducción diastereoselectiva de la cetona para dar lugar a dioles con tres estereocentros terciarios adyacentes y un estereocentro cuaternario. b) Escisión oxidativa de los aductos de Michael para obtener los correspondientes ésteres metílicos.

Finalmente, como parte de una estancia internacional en el laboratio del Prof. Keiji Maruoka en la Universidad de Kyoto, se ha descrito un catalizador de tipo aminoamida fácilmente accesible, la N-fenil-L-valinamida, capaz de promover la reacción aldólica entre la ciclohexanona y aldehídos aromáticos, con lo que se contribuye a aumentar la variedad de catalizadores de amina primaria disponibles (Esquema F).



Esquema F. N-Fenil-L-valinamida como nuevo catalizador capaz de promover la reacción aldólica entre la ciclohexanona y aldehídos aromáticos.

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 used:

B	Base
BB*	Chiral Brønsted base
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
cat	Catalyst
conv.	Conversion
$(DHQD)_2PYR$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
E	Electrophile
ee	Enantiomeric excess
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
L	Ligand
LA	Lewis acid
LG	Leaving group
M	Metal
Me	Methyl
M.S.	Molecular sieve
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Naph	Naphthyl
n. d.	Not determined
NDC	Nicotinium dichromate
n. r.	No reaction
o. n.	Overnight
ORTEP	Oak ridge thermal ellipsoid plot
Phth	Phthalimide

Abbreviations and acronyms

pyr	Pyridine
quant.	Quantitative
Rac.	Racemic
Ref.	Reference
RT	Room temperature
t_R	Retention time
TBDMS	tert-butyldimethylsilyl
TEA	Triethylamine
*p*TSA	*para*-toluenesulfonic acid
X_c	Chiral auxiliary

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Chapter 1

Introduction

1. Introduction

1.1. Asymmetric Synthesis

Life is sustained in many chiral entities and chiral recognition events. For instance chiral enzymes and receptors interact differently with each enantiomer of a biologically active chiral compound. In 2006, more than 80% of the drugs approved by the FDA were enantiomerically pure.[1] Therefore, asymmetric synthesis, that is, formation of new bonds in a diastereo- and enantiocontrolled manner, has been a field of tremendous interest.

Traditionally, asymmetric synthesis has relied on the use of stoichiometric chiral inductors, either *auxiliaries*,[2] or *chiral stoichiometric ligands.*[3] *Chiral auxiliaries* are enantiomerically pure compounds or chemical units that are covalently linked to a substrate and influence the stereochemical course of a reaction (Figure 1).[4] The auxiliary is then removed and recycled. These additional synthetic steps of auxiliary attachment and removal, and the cost of stoichiometric amounts of the source of chirality compromise atom and step economy.

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[1] Thayler, A. N. *Chem. Eng. News* **2007**, *9*, 105−110.

[2] For general reviews on chiral auxiliaries, see: a) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. b) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials*, **2007**, Wiley-VCH, New York. c) Glorious, F.; Gnass, Y. *Synthesis* **2006**, *12*, 1899–1930. d) Roos, G. *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York. e) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. *Houben–Weyl Methods in Organic Chemistry, Stereoselective Synthesis*, **1995**, Thieme-Verlag, Stuttgart. f) Seyden-Penne, *J. Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, **1995**, Willey, New York.

[3] For general reviews on chiral ligands, see: a) *Privileged chiral ligands and catalyst*, Ed. Zhou, Q. L., **2011**, Wiley-VCH, Weinheim. b) Schütz, T. *Synlett* **2003**, *6*, 901–902.

[4] Representative examples: a) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767−2772. b) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095−3098. c) Myers, A. G.; Yang, B. H.; Chem. H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. d) Evans, D. A.; Morressey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346−4348. e) Casper D. M.; Burgenson, J. R.; Esken, J. M.; Ferrence, G. M.; Hitchock, S. R. *Org. Lett.* **2002**, *4*, 3739−3742.

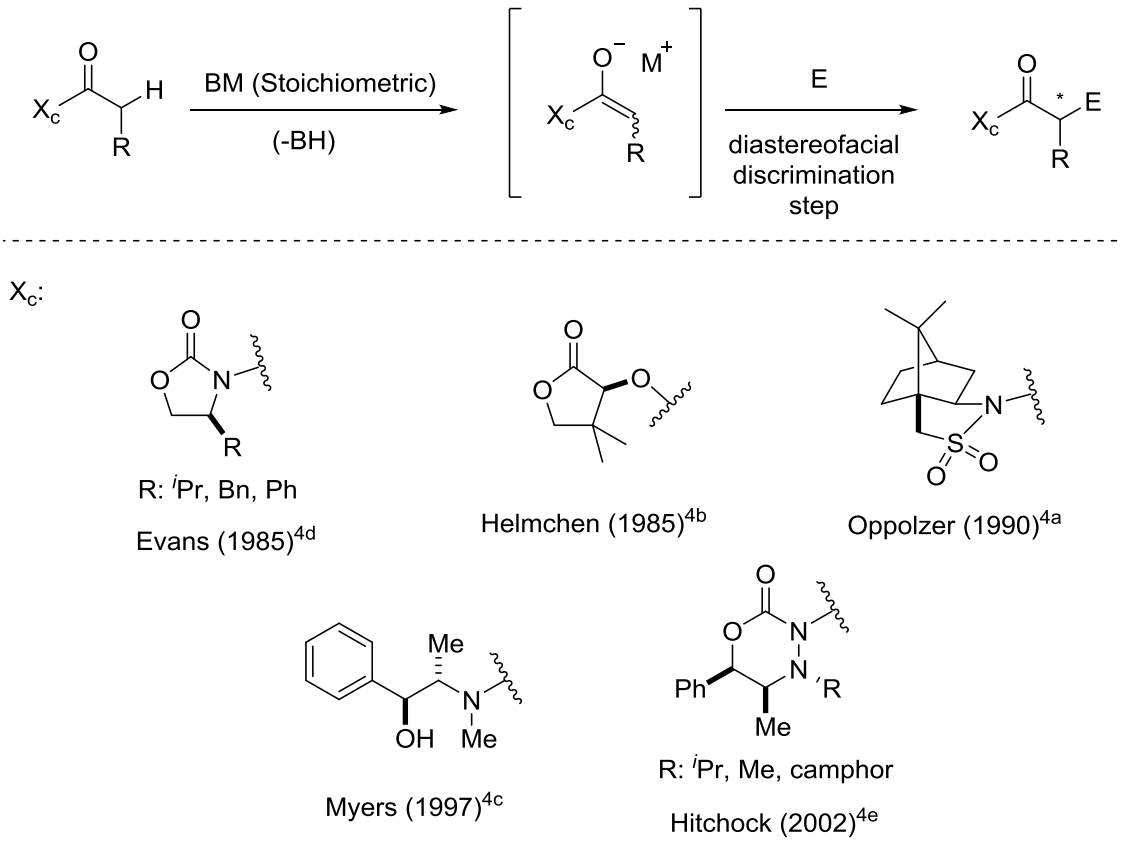

Figure 1. Representative examples of chiral auxiliaries for enolate mediated α-functionalization of carboxylic acid derivatives.

Chiral stoichiometric ligands[5] are enantiopure compounds capable of (Figure 2) interacting with a metallic center through quelation to generate a chiral reagent that used stoichiometrically transfers the chiral information to the product.

[5] Representative examples: a) Paterson, I.; Lister, M. S.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4748−4790. b) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279−8281. c) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932−7934. d) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062−4066. e) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129−3131.

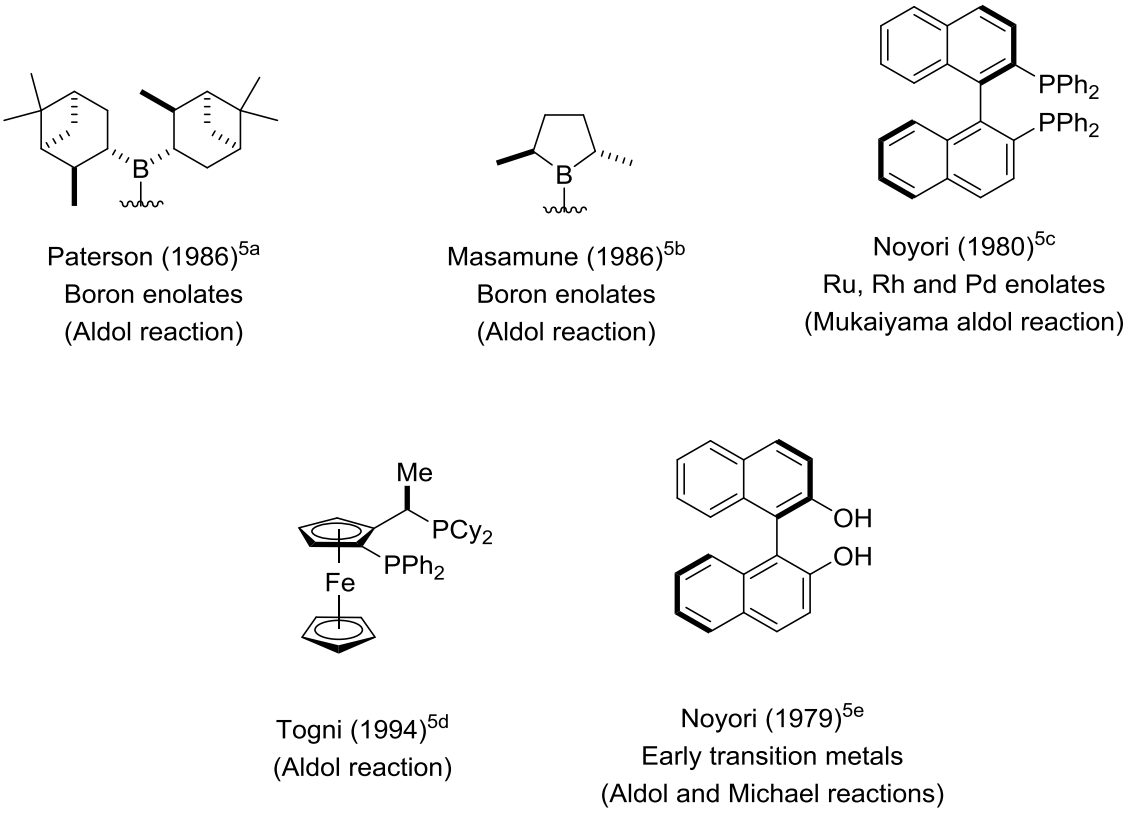

Figure 2. Representative examples of chiral ligands used in stoichiometric quantities for asymmetric reactions.

In contrast to methods that require stoichiometric amount of the source of chirality, *asymmetric catalysis*[6] constitutes an atom- and step-economic process with obvious advantages. In *asymmetric catalysis* a substoichiometric amount of an enantiopure chiral substance not only does speed up the reaction, but it also controls the stereochemistry of the process to yield enantioenriched products. In this field, three different strategies can be distinguished: *biocatalysis*, *metalic catalysis* and *organocatalysis*.

In this context, enolate-mediated C–C and C–X bond formation accounts as one of the most powerful and versatile bond-forming operations in organic synthesis. Not surprisingly, important efforts in the three types of asymmetric catalysis noted above have been devoted to develop new enolate (or enolate equivalent) mediated processes.

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[6] For general reviews on chiral catalysts, see: a) *Catalytic Asymmetric Synthesis* 3rd Edition, Ed. Ojima, I., **2013**, John Wily & Sons, Hoboken, New Jersey. b) *Catalytic Methods in Asymmetric Synthesis: Advanced materials, techniques and applications*, Eds. Gruttadauria, M. Giacalone, F. **2011**, John Wily & Sons, Hoboken, New Jersey. c) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weinhelm. d) Trost, B. M. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5348–5355.

These methods can be classified as either *directed* or *direct*. Procedures based on the use of preformed enolates or enolate equivalents (silyl enol ethers, enamines), are named *directed* methods, and have been studied in depth. The Mukaiyama aldol reaction (the addition of silyl enol ethers to carbonyl compounds) is a representative example of the potential of the directed methods for the formation of new C−C bonds in a stereocontrolled manner.[7] The preparation of the silyl enol ethers in a previous and irreversible synthetic operation employing stoichiometric quantities of reagents constitutes an important drawback. In contrast, *direct* methods in which the unmodified carbonyl compounds can react with the corresponding electrophiles are particularly attractive, and ketones are salient substrates for that purpose as ketone compounds can act as either nucleophiles (donor component) or electrophiles (acceptor component).

1.2. Unsaturated Ketones in C−C Bond Formation: Reactivity and Selectivity Issues

Since this Thesis work deals with catalytic asymmetric transformations involving ketones, and particularly unsaturated ketones, some general aspects related to the ketone´s reactivity are presented next.

The ketone functional group is widespread within natural products and bioactive molecules. It is also a versatile site for further chemical elaboration with the capacity to behave as electrophile (ipso position), or nucleophile (α-carbon) upon deprotonation with base (Figure 3a). This “dual” reactivity makes ketones very attractive for C−C bond forming transformations and generation of molecular complexity.

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

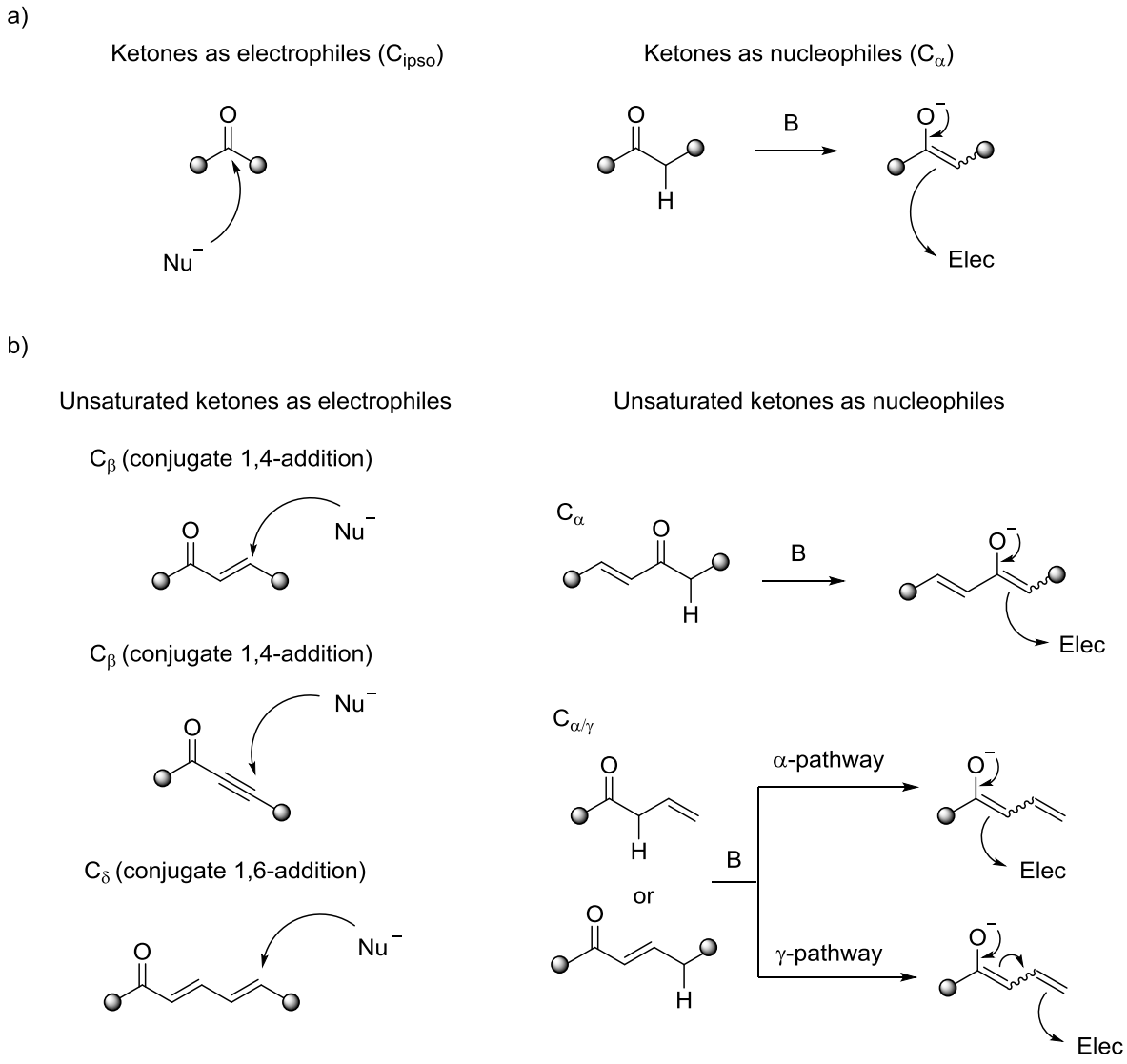


Figure 3. Functionalization of saturated and unsaturated ketones.

Introduction of an insaturation (C=C or C≡C) in the ketone carbonyl proximity may vary or tune decisively the electronic properties of ketones, and thus their reactivity profiles, expanding the possibilities in synthesis (Figure 3b). Thus, α,β-unsaturated ketones (enones and ynones) may act as electrophiles through C_β, while deprotonation of conjugate and nonconjugate enones would give π-extended enolate systems with very interesting chemistry, allowing the construction of complex molecules. For example, γ-functionalization of dienolates produces γ-substituted α,β-unsaturated adducts, that could act as Michael acceptors for further chemical elaboration.

Unsaturated ketones may also be activated as either nucleophile or electrophile upon formation of the corresponding enamine and unsaturated iminium ion species, respectively (Figure 4).

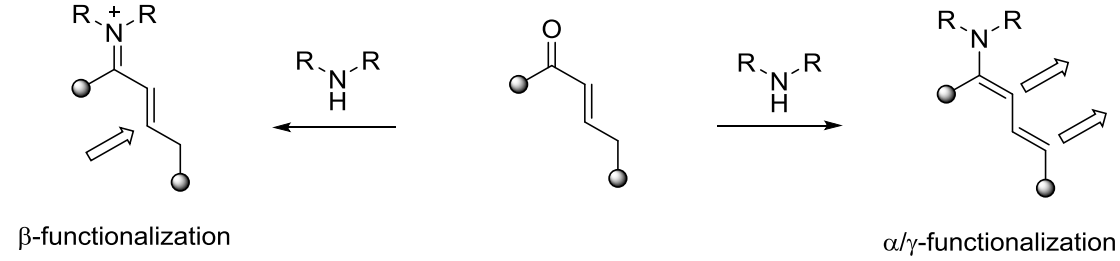


Figure 4. Activation of unsaturated ketones via enamine and iminium ion.

The rich and versatile chemistry of ketones, in general, and of unsaturated ketones, in particular, is associated to important reactivity and selectivity issues that require stringent control.

a) Reactivity: simple ketones can be deprotonated by strong bases, but the use of such bases in catalytic processes is problematic due to the difficult turnover of the base once protonated. Reversible proton transfer is most conveniently achievable when bases involved are weak (pK_a values of conjugated acid: 9−14), but then the concentration of formed enolate may be too low for the subsequent reaction with the electrophile to proceed. As a consequence, the majority of methods for the catalyst-promoted α-functionalization of ketones are limited to compounds bearing an EWG such as NO_2, CO_2R, COR or CN attached to the α-carbon, making the pronucleophile acidic enough for enolization (pK_a values: 10−17). α,β-Unsaturated ketones have been widely explored as Michael acceptors. However, the examples of Michael reactions involving α-substituted enones as acceptors are very limited due to their attenuated reactivity.
b) Site-selectivity: One problem with ketones is that they may possess two flanks for enolization (α/α´). So two different reactive sites (α/α´) and, thus, two different regioisomeric products might be formed unless they are symmetric (Figure 5a). Control of such regioselectivity is not trivial and the majority of methods deal with either symmetrical simple ketones (i.e. acetone, cycloalkanone) or those with an additional α-EWG (or those with α´ blocked).
c) Regioselectivity: di- or trienolates and di- or trienamines are species with multiple nucleophilic centers. As shown in Figure 5b, the α-attack implies disruption of the π-conjugation of the double bonds. Not surprisingly, the majority of examples involving dienolates and dienamines proceed through the

γ-carbon. Few of the extended enolate and enamine mediated reactions described in the literature proceed through the α-carbon selectively.

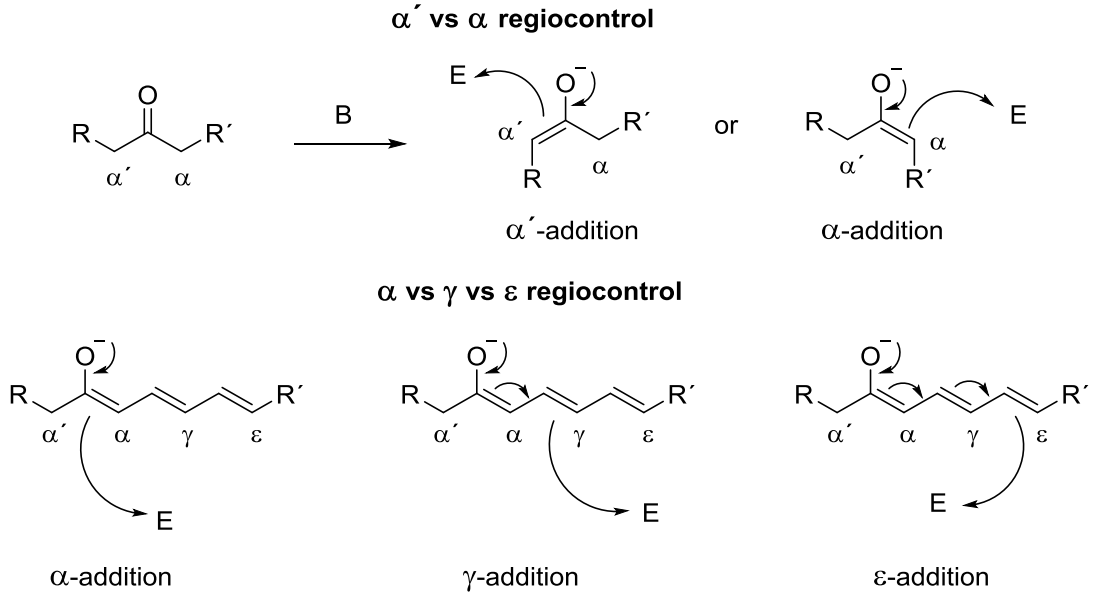


Figure 5. Regioselectivity issues in ketone reactions.

d) Stereoselectivity: A common aspect to address in asymmetric catalysis is the efficient control of the stereochemistry and thus the configuration, both absolute and relative, of the products formed. In this regard, the stereocontrol of the asymmetric reaction has some limitations:

   i) Effective and general methods for the enantioselective construction of quaternary stereocenters remain challenging, which prevents their implementation in drug discovery.

   ii) In reactions involving the construction of tertiary stereocenters in an enolizable position, racemization of the stereocenter may occur under reaction conditions.

   iii) Many methods for the synthesis of acyclic carbonyl compounds with contiguous stereocenters at α,β- or β,γ-positions have been described, while the construction of non-adjacent stereocenters, for example α,γ-branched acyclic carbonyl compounds, is less common (Figure 6).

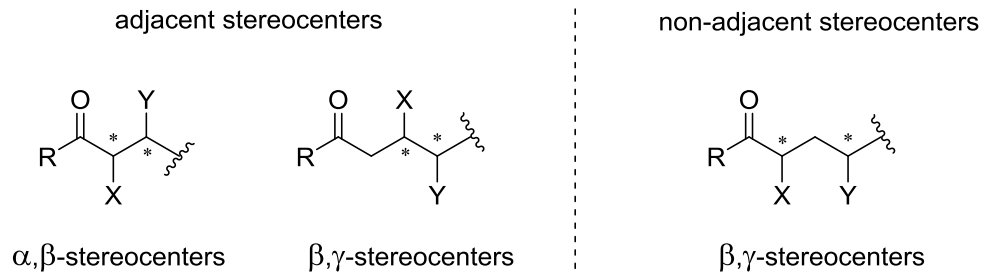


Figure 6. Acyclic carbonyl compounds with different stereoarrays.

1.3. Catalytic Asymmetric Functionalization of Ketones

Biocatalysis[8] or enzymatic catalysis refers to the use of enzymes or whole-cell systems to catalyse chemical transformations on organic compounds. Enzymes often activate both the donor and acceptor components in highly efficient and selective reactions. Following this dual substrate activation, laboratory designed catalysts capable of promoting the functionalization of carbonyl compounds have been developed. The most representative advances in this field are briefly described next according to two categories: metal-based methods and organocatalyst-based methods.

1.3.1. Methods based on metalic catalysis

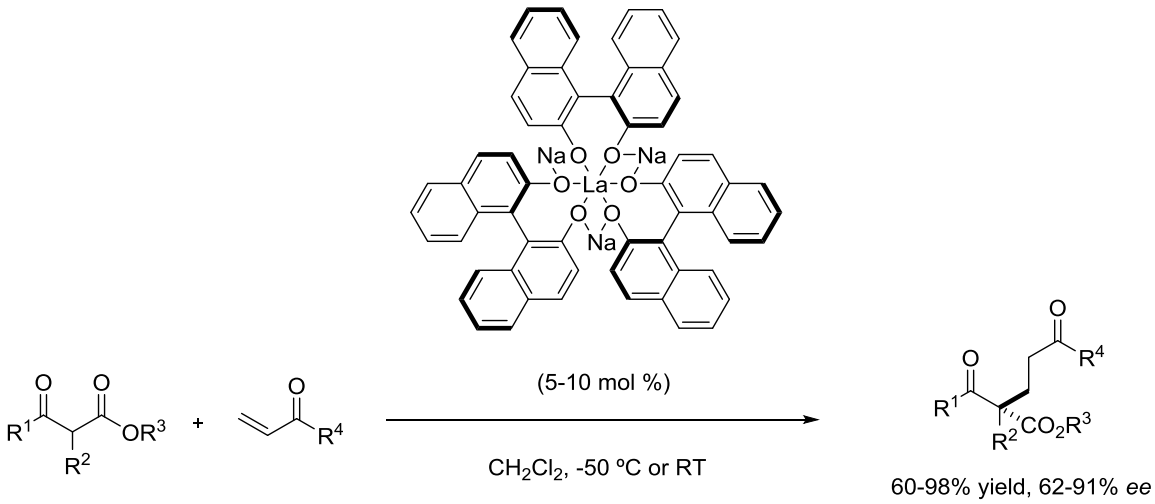
In 1966, Nozaky and Noyori reported a salen-copper complex-catalysed asymmetric cyclopropanation of alkenes resulting in adducts that did not surpass 6% *ee*.[9] Despite the low enantioselectivity of the process, this work marked the introduction of *organometallic catalysis*.[10] Since then, chemists have developed chiral organometallic catalysts capable of carrying out many enantioselective transformations of ketones.

A significant development in this area came from the groups of Shibasaki and Trost, who independently developed new bifunctional Lewis acid/Brønsted base metal complexes capable of catalysing some fundamental C–C bond formations.[11]

In 1996, the group of Shibasaki demonstrated that the Michael addition of cyclic β-ketoesters to methyl vinyl ketone and acrylates could be catalysed by a bifunctional heterobimetallic catalyst obtaining moderate to very good enantioselectivities (Scheme 1).[12] The main concept of these catalysts is that they contain a basic site (RO^- Na^+) which

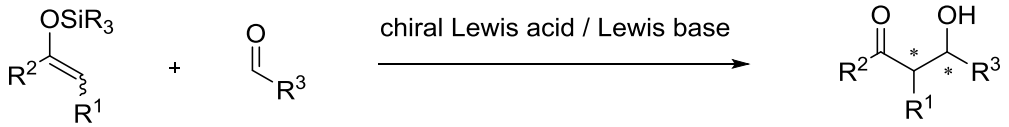
[8] a) *Enzyme Biocatalysis: Principles and Applications*, Ed. Illanes, A. **2008**, Springer, New York. b) Bommarius, A. S.; Riebel, B. R. *Biocatalysis: Fundamentals and Applications*, **2007**, Wiley-VCH. c) Pollard, D.J.; Woodley, J. M. *Trends Biotechnol.* **2007**, *25*, 66−73.
[9] Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *43*, 5239−5244.
[10] *Fundamentals of Organometallic Catalysis* (Steinborn, D. ed., Wiley-VCH Verlag GmbH & Co. KGaA) **2011**.
[11] For the concept of bifunctional metal complexes, see: a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393−406. b) Shibasaki, M.; Kanai, M.; Matsunaga, S. *Acc. Chem. Res.* **2009**, *42*, 1117−1127. c) Ito, J.; Nishimaya, H. *Bifunctional Molecular Catalysis. Topics in organometallic Chemistry*, Ed. Springer, Berlin, **2011**, vol. 37.
[12] Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561−5564.

triggers enolate formation, and a Lewis acid site (La (III)) which activates the acceptor of the reaction simultaneously.



Scheme 1. Direct Michael addition promoted by a bifunctional heterobimetallic catalyst.

The catalytic asymmetric aldol reaction has proven to be a powerful tool for the formation of new carbon−carbon bonds. However, in all of the examples reported before 1997, pre-formation of the enolate or equivalent silyl enol ether was needed (Mukaiyama aldol reaction, Scheme 2).[13]



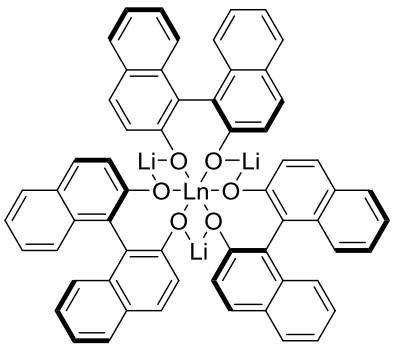
Scheme 2. General scheme of the Mukaiyama aldol reaction.

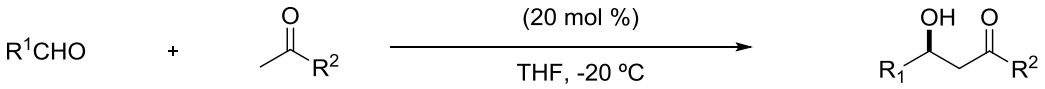
In 1997, Shibasaki and co-workers succeeded in carrying out the first direct catalytic asymmetric aldol reaction by using a heterobimetallic bifunctional catalyst (Scheme 3).[14] The lanthanum atom functions as a Lewis acid while the lithium binaphthoxide moiety works as a Brønsted base that facilitates α-CH deprotonation. It should be noted that the enantioselectivity of the process is low when aliphatic aldehydes are used as acceptors (R^1= Cy, *i*Pr, $Ph(CH_2)_2$), and low yields are observed due to self-condensation

[13] For selected examples, see the following papers and the references cited therein: a) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761−1772. b) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. c) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K. T. *J. Am. Chem. Soc.* **1996**, *118*, 7404−7405.

[14] Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1871−1873.

when the enolizable aldehyde contains a methylene group in the α-position (28% yield; R^1= $Ph(CH_2)_2$).





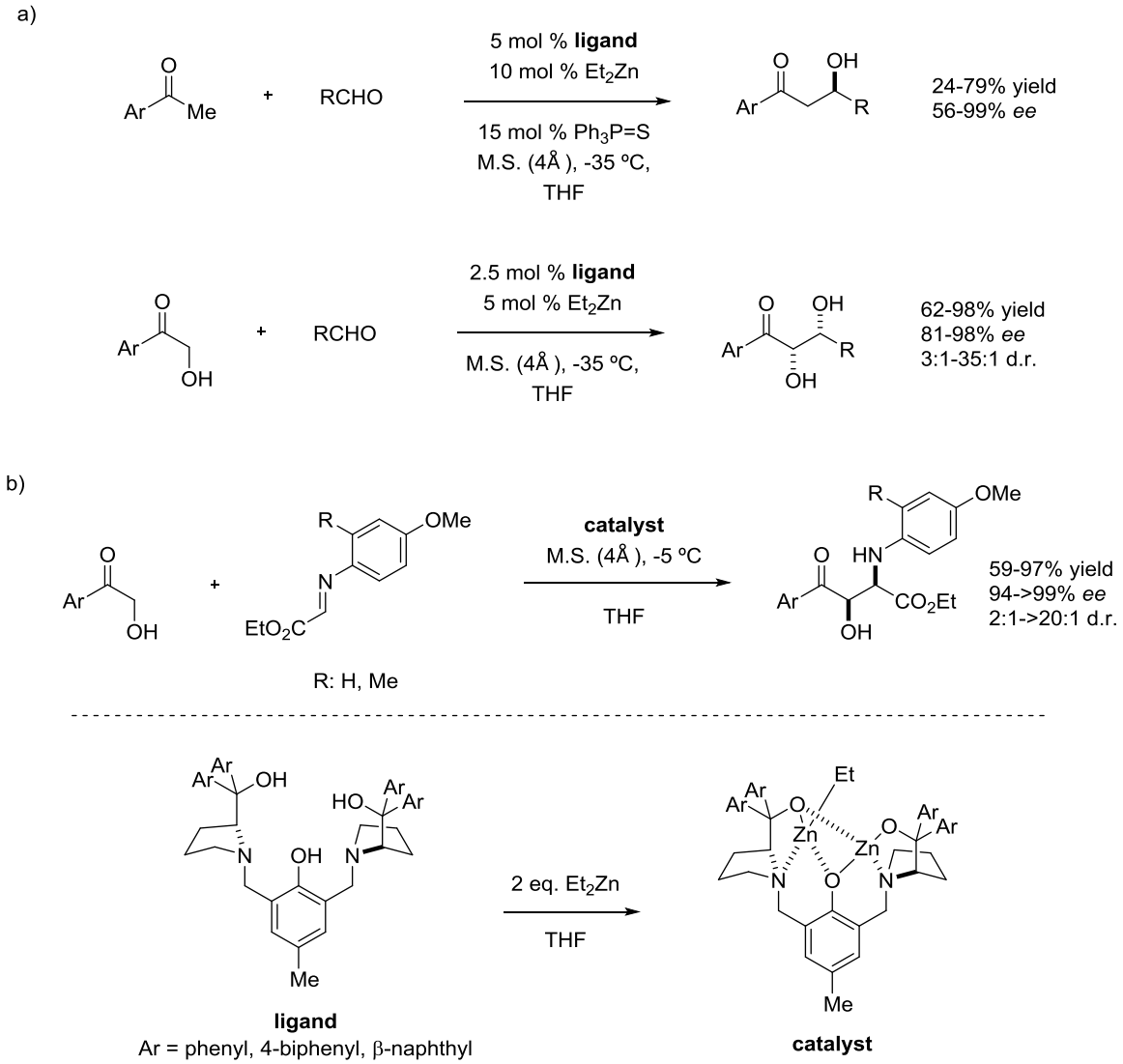
28% - 90% yield, 44% - 94% *ee*

R^1 = *t*Bu, $PhCH_2C(CH_3)_2$, Cy, *i*Pr, $Ph(CH_2)_2$
R^2 = Ph, 1-naphthyl, CH_3, Et

Scheme 3. First direct catalytic asymmetric aldol reaction performed by laboratory-designed catalyst.

Trost, in 2000, introduced a novel type of double-activation catalyst, the dinuclear zinc complex shown in Scheme 4, which was successfully applied in enantioselective direct aldol reactions (Scheme 4a) with both aromatic and aliphatic aldehydes.[15] This catalyst could be later applied to a related Mannich reaction (Scheme 4b).[16]

[15] a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368.
[16] Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338−339.



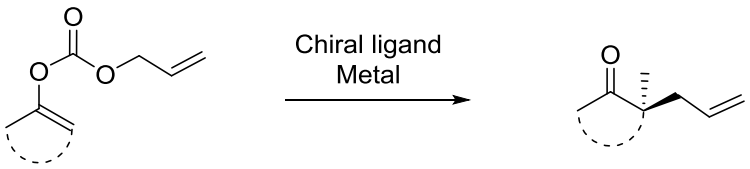
Scheme 4. Dinuclear zinc complex promoted aldol and Mannich reactions.

These pioneering examples paved the way for the study of the functionalization of enolizable carbonyl donors based on bifunctional metallic asymmetric catalysis.[17] However, the majority of these direct procedures are still limited to carbonyl compounds bearing an electron withdrawing group at the α-position or in some instance having an aryl group.

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

Transition-metal catalysed asymmetric allylic alkylation of ketones is one of the most studied α-functionalization reaction and provides useful building blocks.[18] Two main reactions can be differentiated in this field: the Tsuji-Trost reaction, and the decarboxylative allylation.

In the Tsuji-Trost reaction, an allylic acetate or carbonate reacts with palladium catalyst by displacement of the leaving group to give π-allyl palladium intermediate that can undergo substitution by a preformed ketone enolate, such as silyl enol ether,[19] tin and boron enolate, zinc enolate,[20] lithium and magnesium enolate.[21] Preformation of these enolates requires highly basic conditions, and a stoichiometric amount of metal source. As a solution to this problems, Stoltz and Trost introduced allyl enol carbonates, which can act as suitable enolate precursors in decarboxylative intramolecular allylations, typically catalysed by palladium complexes, where CO_2 is the only by-product.[22]



Scheme 5. General scheme for asymmetric decarboxylative allylations.

Although great advances in asymmetric catalytic functionalization of carbonyl compounds have been achieved by metal catalysed reactions, many of the asymmetric procedures are highly sensitive to water or oxygen and rely on the use of toxic metals of limited availability.

1.3.2. Organocatalytic methods

Organocatalysis, refers to the acceleration of chemical reactions by substoichiometric amount of organic molecules in metal-free processes. Although first examples of

[18] a) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395−422. b) Trost, B. T.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. c) Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952−6955. d) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. d) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708−5733.

[19] Trost, B. M. *Tetrahedron Lett.* **1980**, 21, 2591−2594.

[20] Moorlag, H; de Vries, J. G.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 129.

[21] Braun, M.; Laicher, F.; Meier, T. *Angew Chem. Int. Ed.* **2000**, *39*, 3494−3497.

[22] a) Behenna, D. C.; Stolz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045; b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846−2847.

organocatalysis were reported long time ago, its current development blossomed more recently, with many examples dealing with functionalization of carbonyl compounds. The renaissance of organocatalysis gave access to new methods for the functionalization of carbonyl compounds.[23] Organocatalytic methods may be distinguished according to the covalent or non-covalent nature of the substrate-catalyst interaction during substrate activation.

1.3.2.1. *Covalent catalysis*

The activation of a carbonyl compound through covalent interactions with primary or secondary amines forms *enamine* (donor) or *iminium ion* (acceptor) intermediates.

Enamines are enolate equivalents formed by the condensation of primary or secondary amines with aldehydes or ketones in a reversible manner. Key to enamine formation is the LUMO lowering effect and the dramatic increase in C−H acidity upon initial conversion of the carbonyl compound into an iminium ion. The enamine intermediate formed after deprotonation, if chiral, may then react with an electrophile, giving rise to new C−C bond enantioselectively. Eventually, the hydrolysis of the newly resulting iminium species may result in the α-functionalized carbonyl product and the regeneration of the chiral amine catalyst, which can take part in a new catalytic cycle.[24]

Two general models of stereocontrol are represented in Figure 7. i) H-bond mediated control: the hydrogen-bond donor group of the catalyst directs the approach of the electrophile towards one of the two diastereotopic faces of the enamine, and ii) steric control: the bulky substituents of the catalyst shields one of the faces forcing the electrophile to approach the enamine from the opposite side.

---

[23] For general reviews on asymmetric organocatalysis, see: a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138−5175. b) Pellissier, H. *Tetrahedron*. **2007**, *63*, 9267−9331. c) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638−4660. d) Pellissier, *Recent Developments in Asymmetric Organocatalysis*, ACS Publishing, Cambridge **2010**. e) List, B.; Maruoka, K. *Sience of Synthesis: Asymmetric Organocatalysis 1: Lewis base and acid catalysts*, Ed. Thieme, Stuttgart **2012**. f) List, B.; Maruoka, K. *Sience of Synthesis: Asymmetric Organocatalysis 2: Brønsted base and acid catalysts, and additional topics*, Ed. Thieme, Stuttgart **2012**.

[24] Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569.

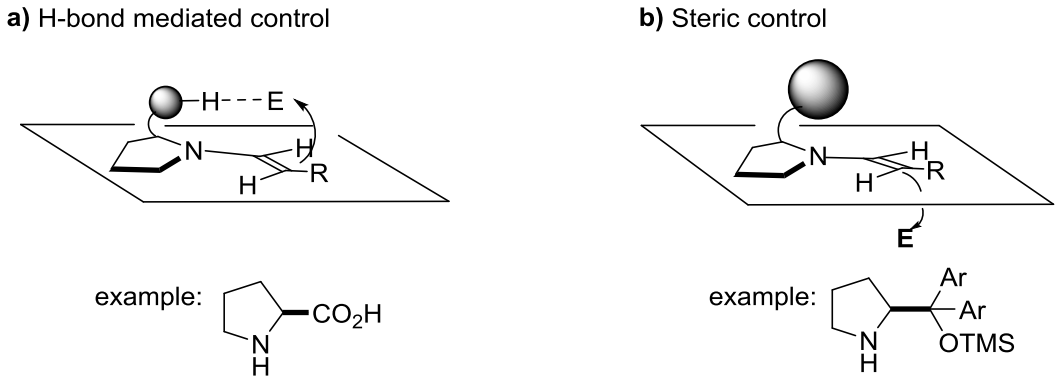
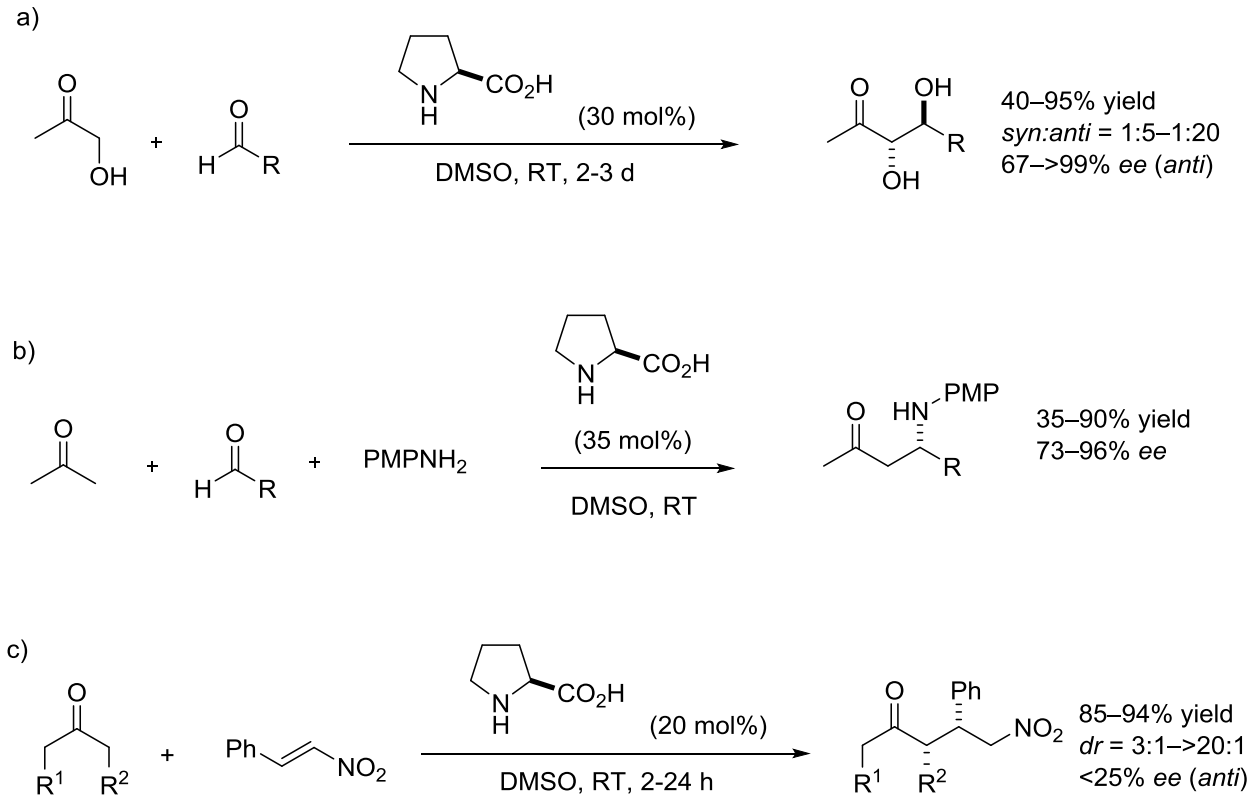


Figure 7. Two different mechanisms for enamine face-discrimination.

Following pioneering developments by Hajos and Parrish involving intramolecular reactions,[25] List and Barbas developed the first amine-catalysed asymmetric direct intermolecular aldol reaction in 2000 using proline as a catalyst.[26] Since that discovery, the field of asymmetric enamine mediated catalysis has experienced a tremendous growth.[27] Notz and List, using α-hydroxyacetone as the donor compound, reported the first example of enamine-mediated asymmetric aldol reaction of a pro-stereogenic ketone, affording the *anti*-aldol products in variable yields and diastereoselectivity, but in an overall excellent enantioselectivity (Scheme 6a).[28] In the same year, List´s group developed the first efficient proline-catalysed asymmetric three-component Mannich reaction of different ketones with *p*-anisidine and aldehydes in DMSO (Scheme 6b).[29] List, in 2001, was the first to report the proline-catalysed Michael reaction of pro-stereogenic ketone, even though the enantioselectivity obtained was very low (Scheme 6c).[30]

[25] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621.
[26] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
[27] For reviews on aminocatalysis see: a) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. b) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. d) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632–649. e) Paz, B. M.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2015**, *21*, 1846–1853.
[28] Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387.
[29] List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.
[30] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425.



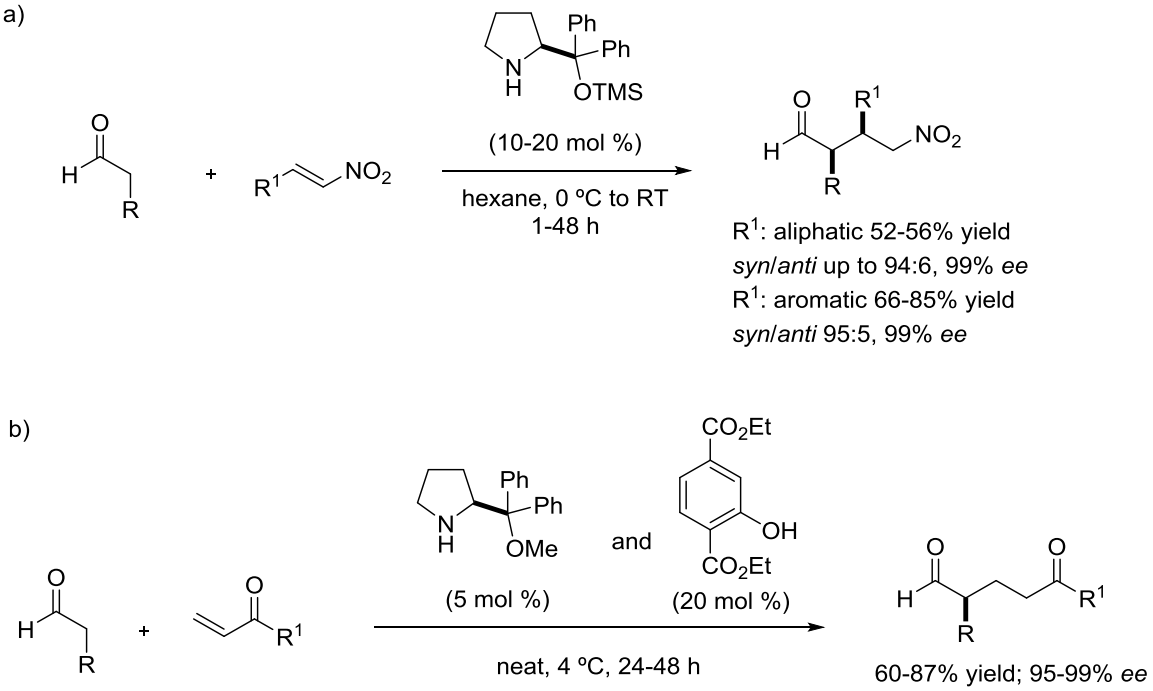
Scheme 6. Pioneering examples of the use of proline in aldol, Mannich and Michael reactions.

Generally, proline is inefficient for the direct catalytic asymmetric three-component Mannich reaction when electron-rich aldehydes are used,[31] and proline-catalysed Michael reactions seem to be less enantioselective than Mannich or aldol reactions (Scheme 6c).[30] Given this limitations, other catalysts besides proline have also been investigated. The first approaches were modifications of the proline structure. The carboxylic acid of proline was substituted for other functional groups, which resulted in more efficient catalysts. Prolinol silyl ethers have demonstrated the most versatile and general.[32] With these catalysts the configuration of the final adduct is controlled by steric hindrance of the substituent α to the pyrrolidine nitrogen as shown in Figure 7b, thus obtaining products of opposite configuration compared to those obtained with L-proline as catalyst.

[31] Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208−11209.

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

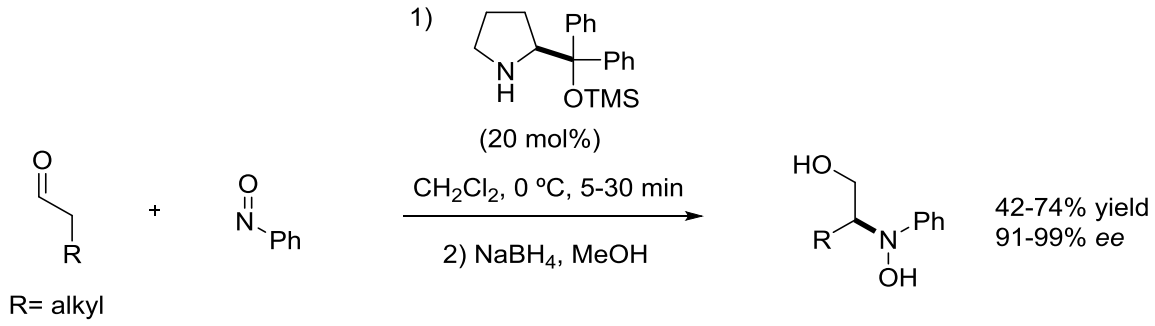
Hayashi et al.[33] developed the Michael addition of aldehydes to nitroalkenes catalysed by a diarylprolinol silyl ether (Scheme 7a), which is more effective with nitrostyrenes, while with β-alkyl-substituted nitroalkenes moderate yields are obtained. Gellman and co-workers[34] demonstrated the utility of diphenylprolinol methyl ether (Scheme 7b) in the Michael addition between aldehydes and vinyl ketones. The enone acceptors were activated by hydrogen-bond donation from a catechol derivative employed as a cocatalyst.



Scheme 7. Representative examples of Michael additions catalysed by diarylprolinol ethers.

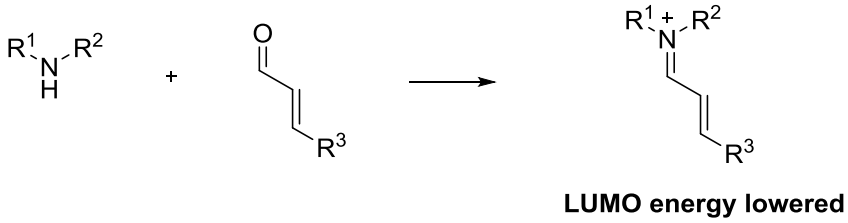
In 2007, our group demonstrated that simple diarylprolinol silyl ethers could promote the direct and regioselective oxyamination reaction of aldehydes with nitrosobenzene to afford the oxyaminated compounds in good yields and with excellent regio- and enantioselectivities (Scheme 8).[35]

[33] Hayashi, Y.; Gotoh, H.; Hayasi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212−4215.
[34] Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253−4256.
[35] Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054−8056.



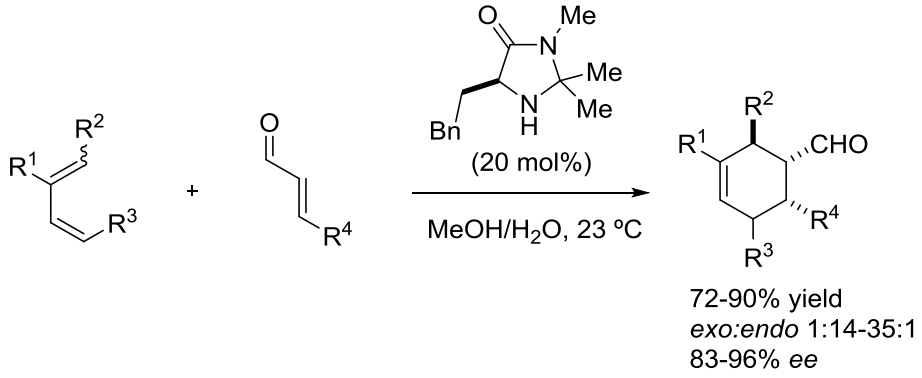
Scheme 8. Oxyamination reaction of aldehydes catalysed by α,α-diphenylprolinol trimethylsilyl ether.

Amine catalysts can also activate α,β-unsaturated carbonyl compounds via *iminium-ion*, which is formed by a condensation between the amine catalyst and the α,β-unsaturated carbonyl compound (Scheme 9).



Scheme 9. Activation of α,β-unsaturated aldehydes by iminium-ion formation.

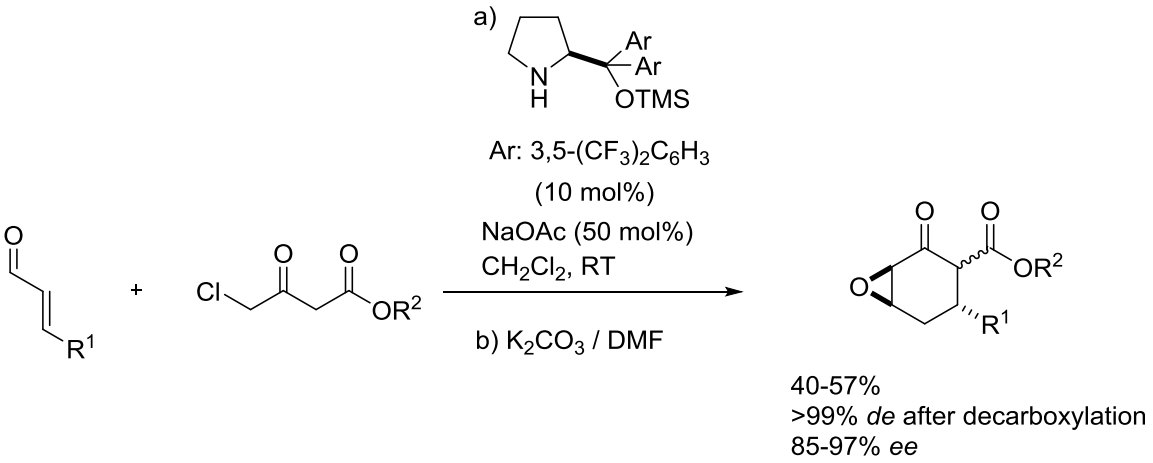
In 2000, MacMillan an co-workers, developed for the first time a iminium-ion mediated highly enantioselective Diels–Alder reaction between α,β-unsaturated aldehydes and various dienes (Scheme 10).[36]



Scheme 10. First highly enantioselective amine-catalysed Diels-Alder reaction.

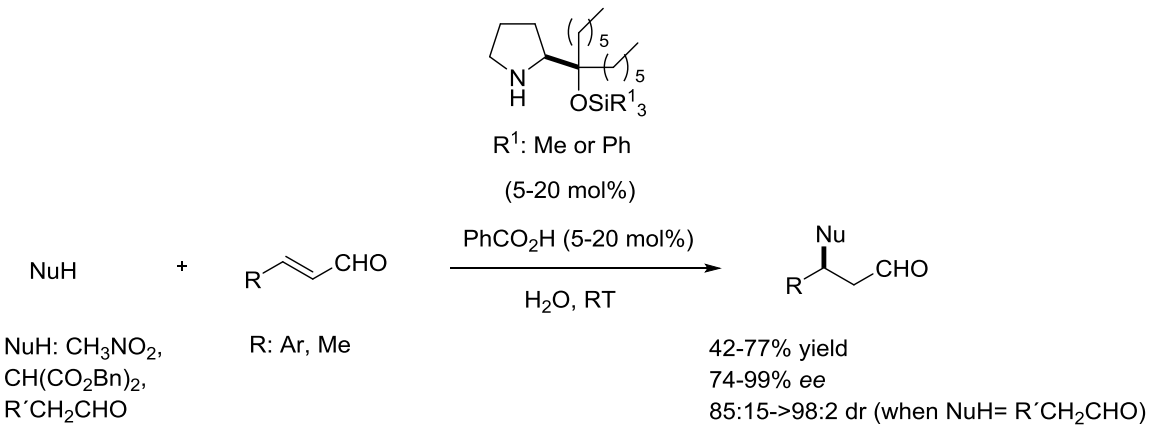
[36] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

In 2006, Jørgensen reported the one-pot Michael addition/aldol/S_N2 reaction of α,β-unsaturated aldehydes and γ-chloro-β-ketoesters.[37] In this process, iminium-ion and enamine activations are successively combined to afford epoxycyclohexanones in very good diastereo- and enantiomeric ratios (Scheme 11).



Scheme 11. One-pot Michael addition/aldol/S_N2 reaction of α,β-unsaturated aldehydes and γ-chloro-β-ketoesters.

In 2007, our group designed a new family of pyrrolidine catalysts that enable iminium-type catalysis of enals in water (Scheme 12). The Michael addition of nitrometane, benzyl malonate and aliphatic aldehydes proved the versatility and the potential of this family of catalysts in an aqueous environment.



Scheme 12. Michael additions of carbon-centered nucleophiles with enals via water-compatible iminium activation.

[37] Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475−5479.

In the initial report on proline-catalysed intermolecular aldol reactions in 2000,[26] it was shown that primary amino acids, such as phenylalanine and valine, were poor catalysts under the reaction conditions investigated. This seems to be reasonable as it is well accepted that a secondary enamine is better stabilized than its primary counterpart by hyperconjugation. However, the fact that primary amines were good catalysts in the intramolecular aldol reactions simply indicates that effective formation of the enamine from a primary amine is feasible.

The past two decades have witnessed the rapid development of chiral primary amine-based organocatalysts.[38] These catalysts can be classified as the following: 1) natural primary amino acids and their derivatives (Figure 8a); 2) primary amines derived from various chiral diamines (Figure 8b); 3) catalysts based on *Cinchona* alkaloids (Figure 8c); 4) primary amine catalysts containing chiral counter ions (Figure 8d).

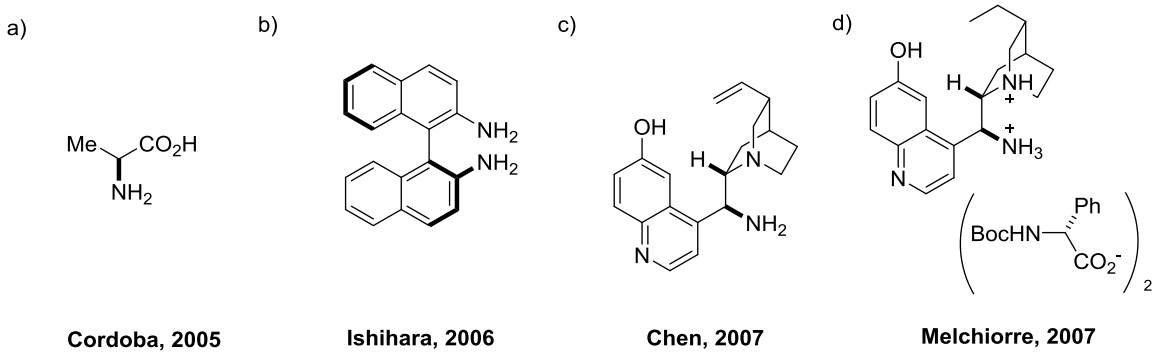


Figure 8. Chiral primary amine-based organocatalysts.

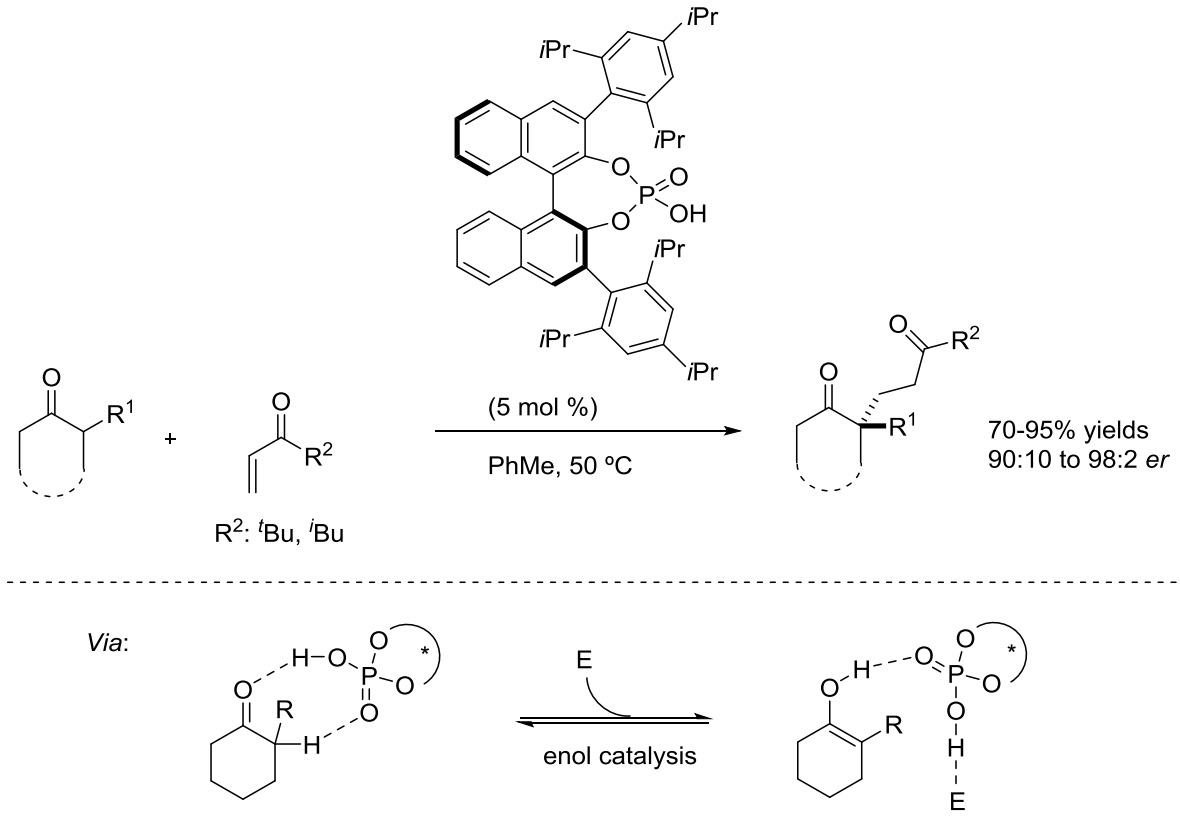
Although impressive progress has been done in the development of enamine-based catalytic functionalisation of carbonyl compounds, the procedures described so far are limited to aldehydes and symmetrical ketone donors, or those bearing an EWG at Cα. The use of sterically hindered ketones remains challenging due to their lower tendency towards formation of enamines.

1.3.2.2. *Non-covalent catalysis*

Enolizable carbonyl compounds can be non-convalently activated by *Brønsted acid* (enol) or *Brønsted bases* (enolates) catalysts.

[38] For a review on chiral primary amine-based organocatalysis, see: Xu, L. W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807−1821.

Although *Brønsted acids*[39] can catalyse the tautomerization of carbonyl compounds, only few examples of Brønsted acid-catalysed enolizations were reported in the context of asymmetric α-functionalization of ketones. In 2015, List and co-workers addressed for the first time the α functionalization of α-branched ketones via Brønsted acid catalysis reporting the enantioselective conjugate addition of α-branched cyclic ketones to enones (Scheme 13).[40] Remarkably, in the presence of a chiral phosphoric acid only the higher substituted enol was formed giving access to the α,α-disubstituted ketones. The authors suggested that the Brønsted-acidic P−OH and basic P=O moieties of the chiral phosphoric acid not only accelerated the enolization but also activated both reaction partners *via* hydrogen bonding. An important limitation of this methodology is that enones with a bulky R^2 (*t*Bu and *i*Bu) are needed to obtain high enantioselectivities.

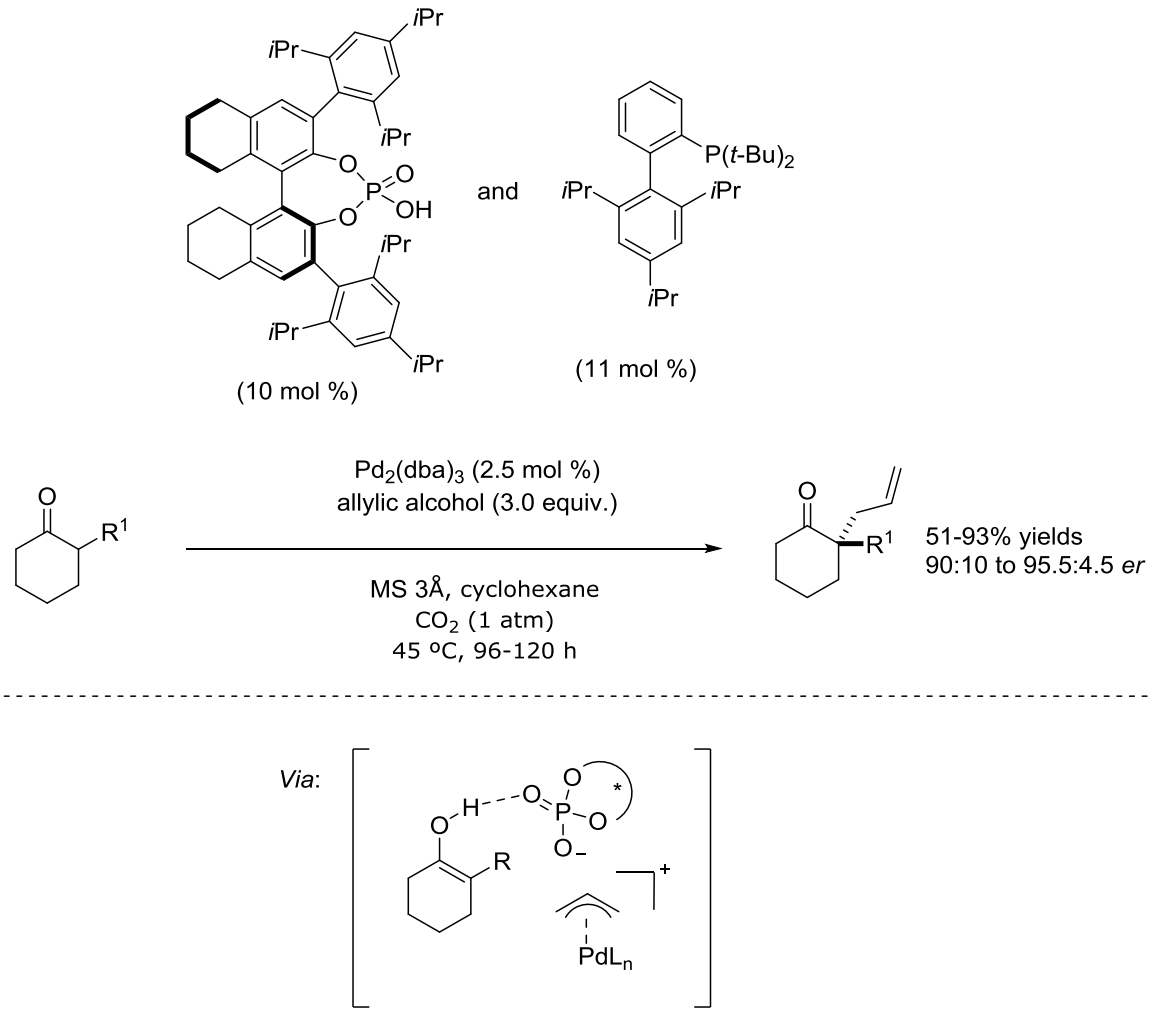


Scheme 13. Phosphoric acid catalysed addition of α-branched ketones to enones.

[39] For reviews on Brønsted acid catalysis, see: a) Schreiner, P. R.; *Chem. Soc. Rev.* **2003**, *32*, 289−296. b) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062−2064. c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 1758−1763. d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520−1543. e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713−5743. f) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G. *Chem. Eur. J.* **2018**, *24*, 3925−3943.

[40] Felker, I.; Pupo, G.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 1960−1964.

Recently, the List group achieved the direct allylation of α-branched cyclic ketones *via enol catalysis* in combination of Pd catalysis for electrophile activation (Scheme 14).[41] The targeted ketones, bearing a quaternary stereocenter were obtained in good to excellent yields and enantioselectivities.

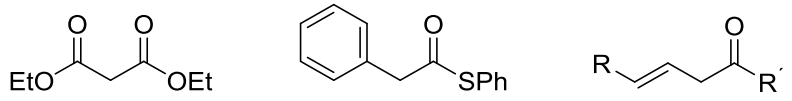


Scheme 14. Direct allylation of α-branched ketones.

The preferable substrates for *Brønsted base* catalysis are enolizable carbonyl compounds with relatively small (10−17) pK_a values. For instance, diethyl malonate **I** (Figure 9) with pK_a of 16.4[42a] has been extensively applied as a pronucleophile in Brønsted base catalysed reactions, whereas phenylthioester **II** with a pK_a of 16.9[42b] has

[41] Pupo, G.; Properzi, R.; List, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 6099−6102.
[42] a) Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299−3305. b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218−4223.

been less employed in Brønsted base promoted reactions.[43] As it will be described later, we envisaged that β,γ-unsaturated carbonyl compounds **III**, which have been poorly explored in this context, may become another subgroup of suitable substrates for direct Brønsted base catalysed reactions. In sharp contrast, simple ketones, aldehydes, esters and other carboxylic acid derivatives remain elusive substrates due to the insufficient acidity of the C−H group adjacent to the carbonyl group. Instead, the acidity of the C−H group is optimal when it is flanked by another electron withdrawing group (i.e. Figure 9, compound **I**). With this type of substrates, mainly Mannich-type and Michael-type reactions have been developed in the field of Brønsted base catalysis.[44]



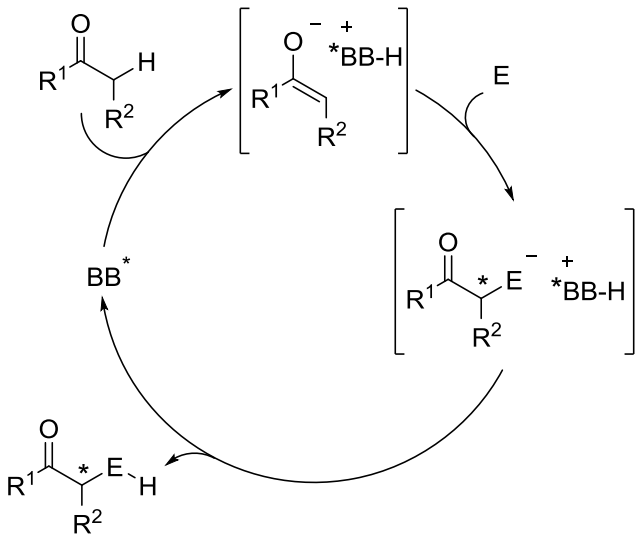
I (pK_a 16.4) **II** (pK_a 16.9) **III** (pK_a ?)

Figure 9. pK_a values of the α-protons of some pronucleophiles on DMSO.

Scheme 15 shows a simplified catalytic cycle for Brønsted base-catalysed reactions. The process is initiated *via* deprotonation of the pro-nucleophile by the basic catalyst, forming a chiral ionic pair. This anionic species reacts subsequently with the corresponding electrophile in an enantioselective manner to provide a Nu−E adduct as the ultimate reaction product and liberation of the free base catalyst.

[43] For a discussion on thioesters as nucleophiles in Brønsted base promoted reactions, see: a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588−4591. b) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376−3379.

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



Scheme 15. General catalytic cycle for Brønsted Base-catalysed reactions.

Chirality transfer during the new bond formation occurs in a chiral ion-pair system. In this sense, catalysts bearing a hydrogen-bond donor moiety along with the basic site can anchor both nucleophilic and electrophilic components in the transition state. As a result, these bifuctional Brønsted base/H-bond donor catalysts[45] are more active, and a higher degree of stereochemical order is achieved due to the more rigid transition states (Figure 10).

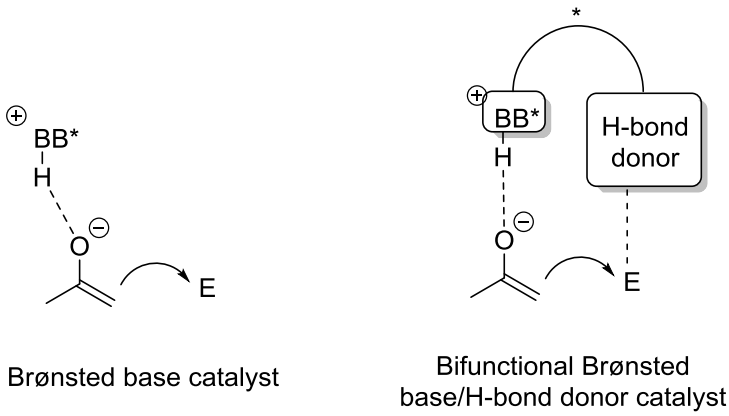


Figure 10. Transition states of Brønsted base catalysts vs. bifunctional Brønsted base/H-bond donor catalysts.

Among the nitrogen-containing functionalities that have been used for the design of chiral Brønsted base catalysts are: tertiary amines, guanidines, amidines and imidazoles

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

(Figure 11a). Phosphazenes have also been studied recently in an attempt to gather less acidic substrates.[46] For the preparation of chiral enantiopure Brønsted base catalysts, alcaloids, particularly those of the cinchona family, constitute a primary source of chiral amine starting materials (Figure 11b).[47] Non-natural sources, such as 1,2-diamines and binaphthyl amines, have also been employed as enantiopure precursors of Brønsted base catalysts (Figure 11b).

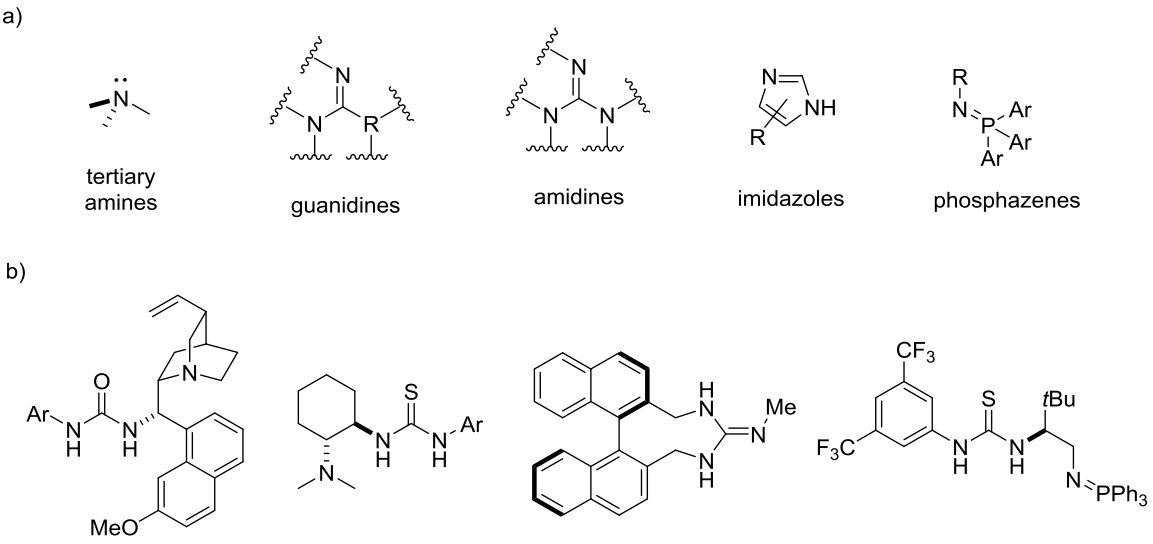


Figure 11. a) Basic moieties in chiral Brønsted base catalysts. b) Some representative chiral Brønsted base catalysts.

Takemoto developed the first chiral thiourea-tertiary amine bifunctional catalyst that promoted the Michael reaction of malonates to various nitroolefins with high enantioselectivities (Scheme 16a).[48] Following this work, Connon (Scheme 16b),[49] and Dixon[50] demonstrated that the same reaction could also be catalysed by urea/thiourea-substituted cinchona alkaloids, which have proven to be excellent bifunctional Brønsted base catalysts for several transformations.[51] Since then this type of bifunctional catalysts

[46] a) Nuñez, M.G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348−16351. b) Goldys, A. M.; Núñez, M. G.; Dixon, D. J. *Org. Lett.* **2014**, *16*, 6294−6297. c) Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992−15995.

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

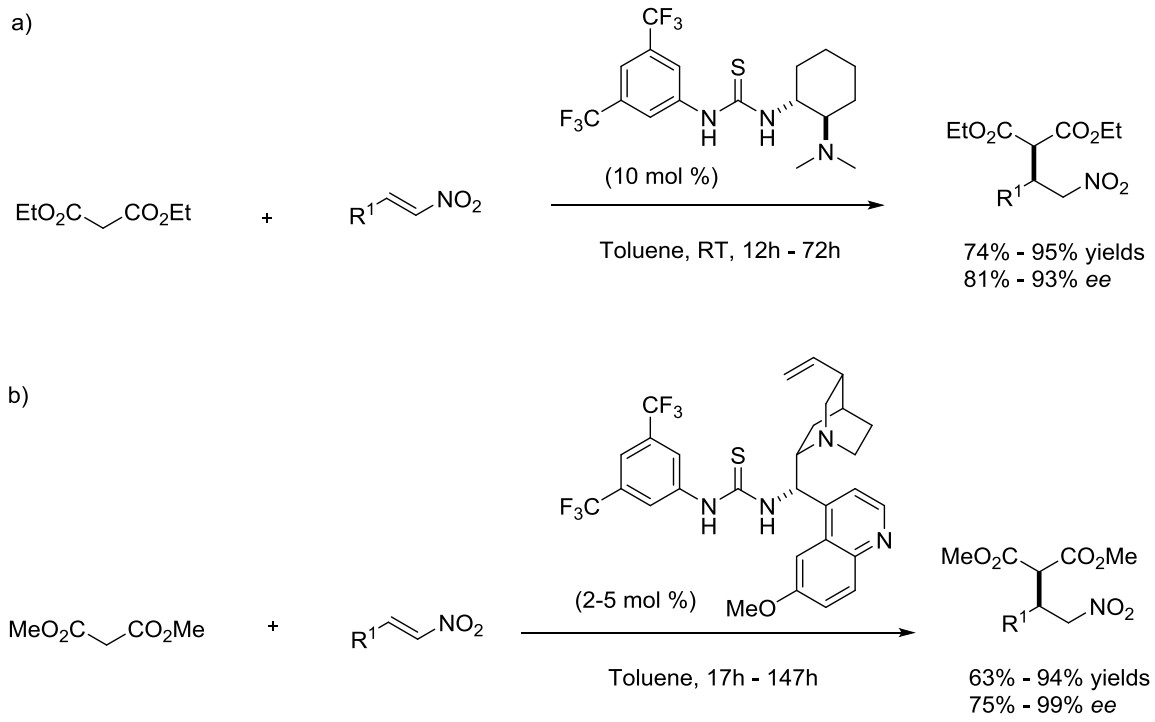
[48] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673.

[49] McCooey, H.; Connon, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367−6370.

[50] Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483.

[51] For recent reviews on (thio)urea-tertiary amines, see: a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418−5427. b) Siau, W. Y.; Wang, J. *J. Catal. Sci. Technol.* **2011**, *1*, 1298-1310. c) see ref. 44d.

have been proven useful for the α-functionalization of some carbonyl compounds. For example, Ellman and co-workers introduced the enantio- and diastereoselective addition of cyclohexyl Meldrum´s acid to nitroalkenes *via* an *N*-sulfinyl urea-tertiary amine catalyst.[52] Benzimidazole-tertiary amine[53] and quinazolone-tertiary amine[54] type catalysts have also been reported to catalyse the α-alkylation of carbonylic compounds.



Scheme 16. First thiourea-Brønsted base catalysed addition of malonates to nitroolefines.

Schreiner and co-workers[55] suggested that the success of (thio)urea Brønsted base catalysts that contain the 3,5-bis(trifluoromethyl)phenyl group may be attributed to the participation of both N–H bonds of the (thio)urea unit and the *ortho* C–H bond of the aryl group during substrate activation. With this in mind, our group reported ureidopeptide-based bifunctional H-bonding/Brønsted bases (Figure 12).[56] These

[52] Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121−125.
[53] a) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 6163−6168. b) Zhang, L.; Lee, M.; Lee, S.; Lee, J.; Cheng, M.; Jeong, B.; Park, H.; Jew, S. *Adv. Synth. Catal.* **2009**, *351*, 3063−3066.
[54] Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 10470−10477.
[55] Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919−5927.
[56] a) Diosdado, D.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846−11851. b) Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526−6531. c) Echae, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364−3368. d) Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 13332−13336. e) Lapuerta, I.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2016**, *22*, 7229−7237.

catalysts are readily accessible from the corresponding α-amino acid derived isocyanates and amino cinchona alkaloids and have proved to be very effective for the conjugate addition reaction of 5*H*-thiazol-4-ones to nitroolefins,[56a] the synthesis of β-amino nitriles from (arylsulfonyl)acetonitriles,[56b] the direct aldol reaction of α-keto amides,[56c] and the α-functionalization of 2-azaaryl acetates with N-Boc imines.[56d] Achiral ureidopeptide-based catalysts have also been used as cocatalysts in the *syn*-selective Mannich reaction of aldehydes with propargylic imines promoted by dual catalysis.[56e]

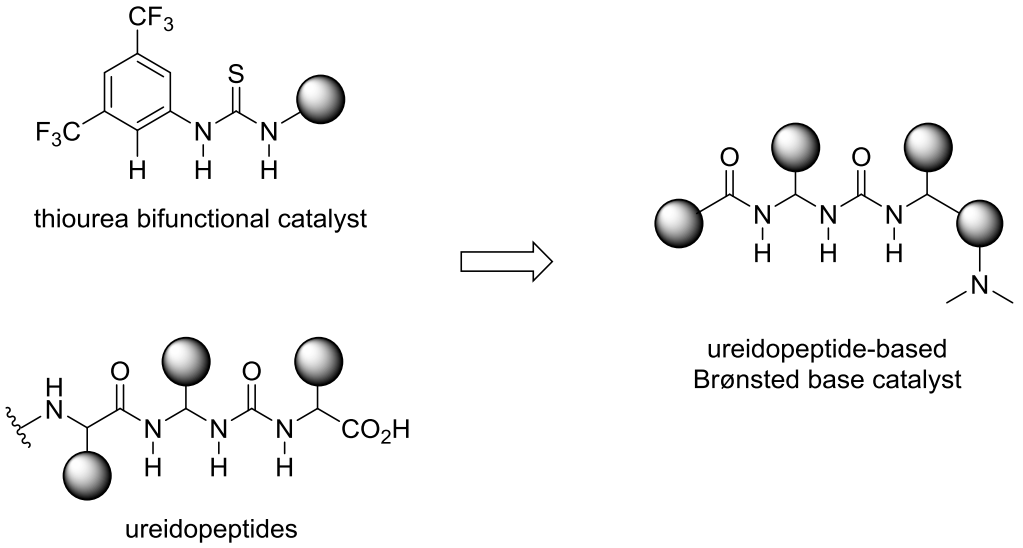


Figure 12. Desing of ureidopeptide-based Brønsted base catalysts.

In 2008, Rawal and co-workers[57] introduced the squaramide moiety as an efficient double H-bond donor site in asymmetric catalysis. Both (thio)urea and squaramides are structurally rigid, but some main differences can be highlighted: i) squaramides contain two hydrogen-bond donors (N−H) and two carbonyl acceptors (C=O) (one more acceptor than thioureas) ii) the cyclobutenedione ring induces a convergent orientation of the N−H groups, and the distance between them is estimated to be larger (2.71 Å)[57] than in the case of thioureas (2.13 Å) (Figure 13a)[58] iii) the squaramides have the possibility for further lone pair delocalization through the cyclobutenedione system (Figure 13b)[59] which makes the N−H acidity of the squaramide catalysts higher compared to the

[57] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417.
[58] Okino, T.; Hoashi, Y.; Fukurawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2008**, *127*, 119−125.
[59] Tomàs, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deyá, P. M.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394−9401.

thiourea analogs (0.1−2 pK_a gap units).[60] Thus, squaramides are capable of forming stronger hydrogen bonds.

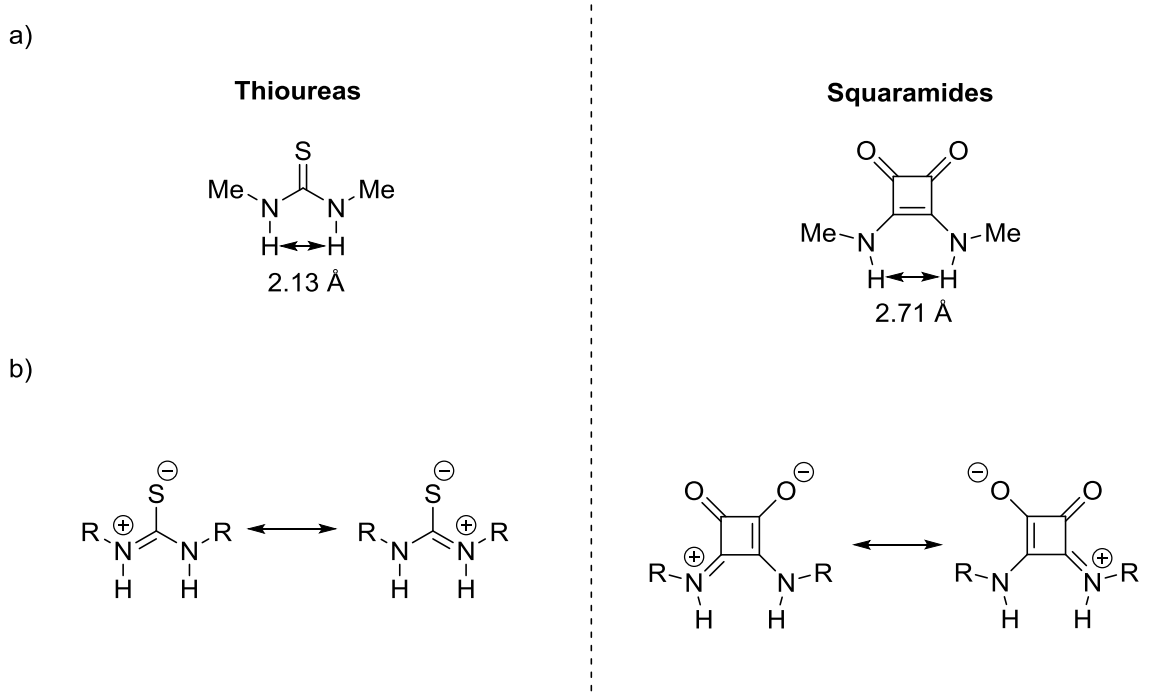
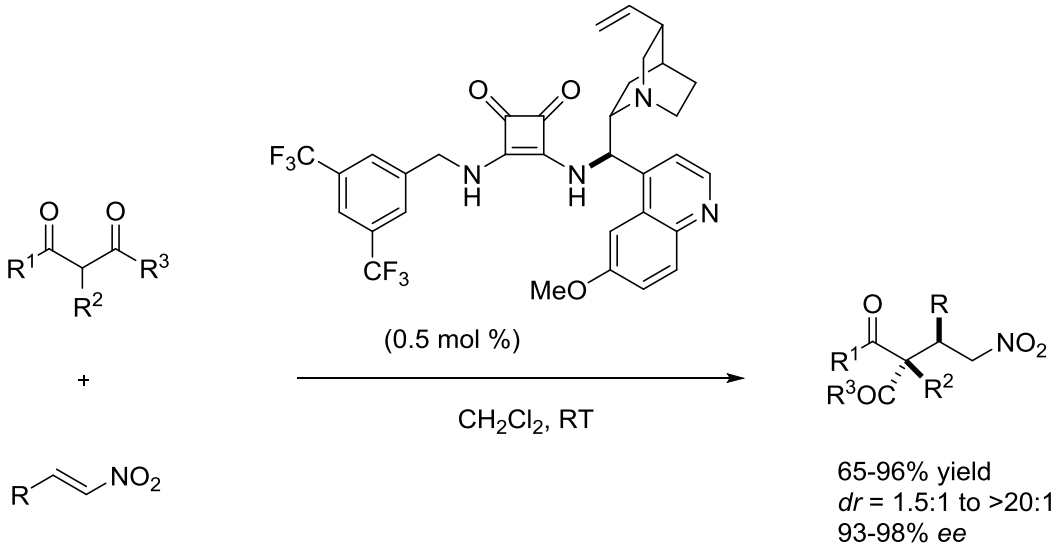


Figure 13. N−H group distance and lone pair delocalization in thioureas and squaramides.

Rawal demonstrated that cinchona derivatives bearing a squaramide group are effective catalysts for the conjugate addition reaction of 1,3-dicarbonyl compounds to nitroolefins (Scheme 17).[57] The most remarkable aspect of this reaction is the low catalyst loading needed for effective stereocontrol.

[60] Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Chem.* **2014**, *16*, 1786−1789.



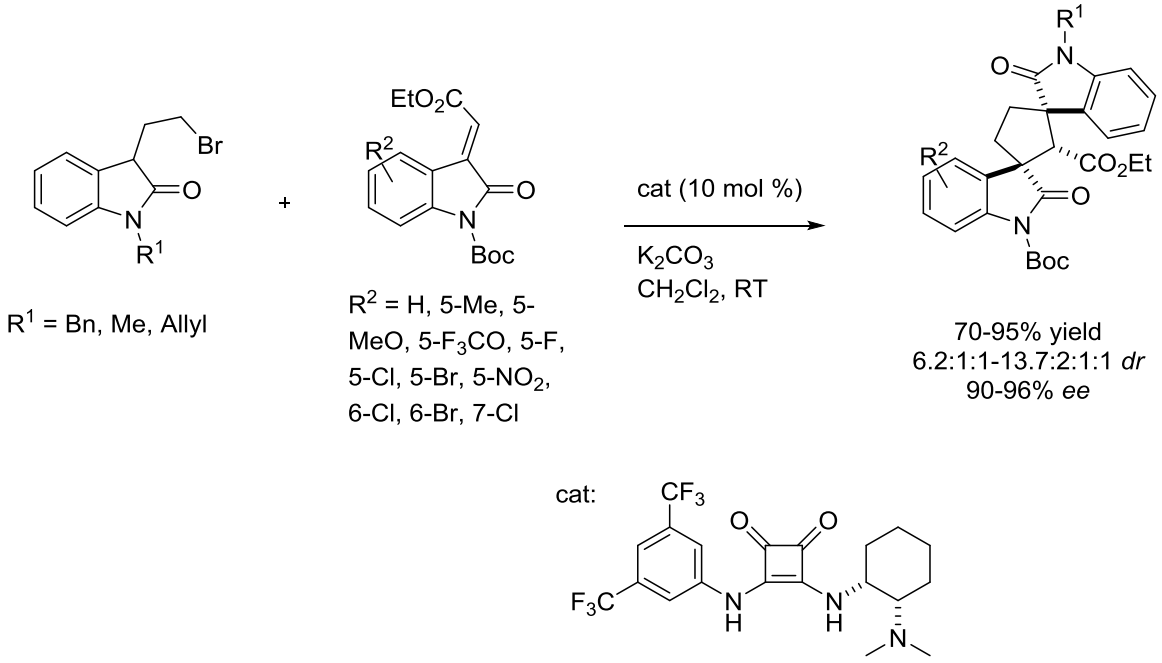
Scheme 17. First squaramide derivative catalysed Michael reaction between 1,3-dicarbonyl compounds and nitroolefins.

After Rawal´s pioneering work, many new squaramide catalysts were employed in different reactions.[61] These catalysts demonstrated to be efficient in many domino and tandem processes[62] where more complex molecules can be synthesized. Example of this is the Michael addition/alkylation sequence of 3-substituted oxindoles with 3-ylideneoxindoles to provide bispiro-oxindoles bearing three contiguous stereocenters, including two spiro quaternary carbons in good to high yields, acceptable *dr* and high *ee* (Scheme 18).[63]

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

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

[63] Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. *Chem. Eur. J.* **2012**, *18*, 6737−6741.



Scheme 18. Domino Michael addition/alkylation reaction of 3-subtituted oxindoles with 3-ylideneoxindoles.

Our group, in collaboration with Guichard´s lab in Bordeaux, have also demonstrated that the combination of a simple achiral amine base (i.e. Et_3N, DIPEA) with a chiral oligourea foldamer cocatalyst in very low loading (down to 0.01 mol%) is able to promote the addition of 1,3-dicarbonyl substrates to nitroalkenes in high yield and enantioselectivity.[64]

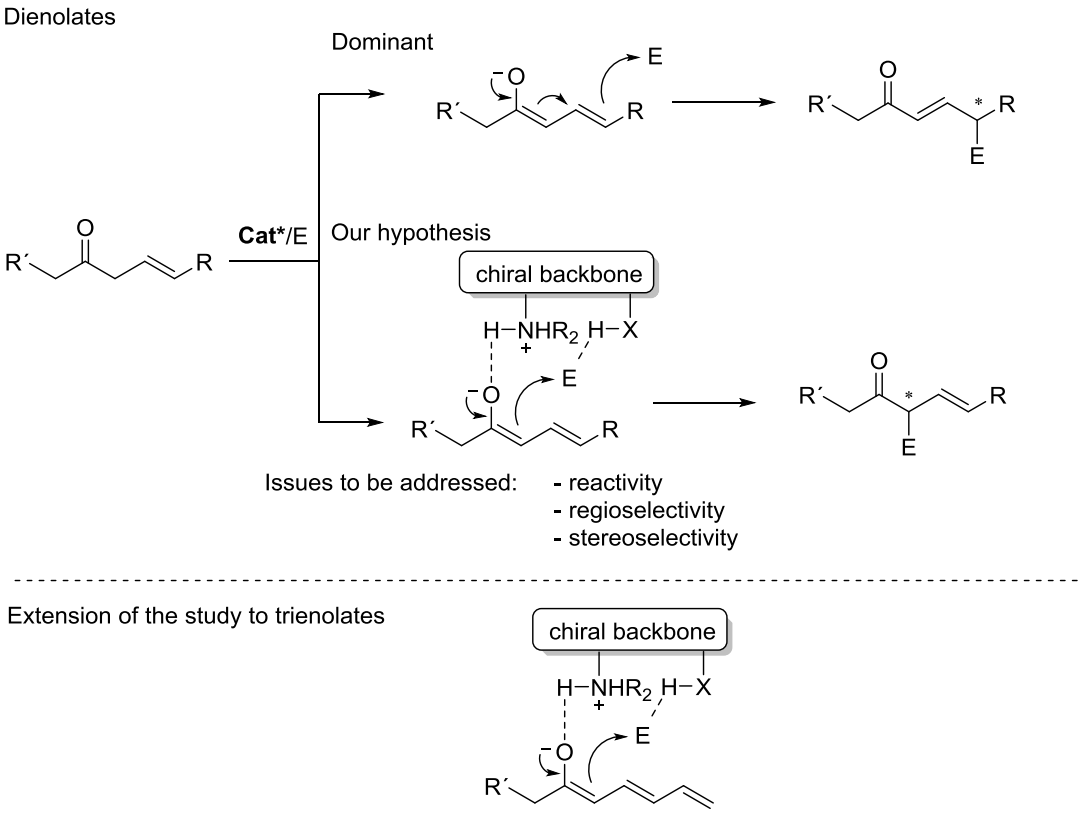
Most of the methods of carbonyl compound functionalization via asymmetric enolate formation using Brønsted base catalysts are restricted to easily enolizable pronucleophiles typically bearing an EWG at the α-position. Furthermore, the regioselectivity in reactions involving conjugated dienolates remains challenging, as most of the reactions proceed from the γ-carbon. On the other hand, the enones used as acceptors in Michael reactions are very rarely α-substituted due to reactivity and stereoselectivity issues.

[64] Bécart, D.; Diemer, V.; Salaün, A.; Oiarbide, M.; Nelli, Y. R.; Kauffmann, B.; Fischer, L.; Palomo, C.; Guichard, G. *J. Am. Chem. Soc.* **2017**, *139*, 12524−12532.

1.4. Objectives

a) Study of the reactivity trends of transiently generated di- and trienolate species.

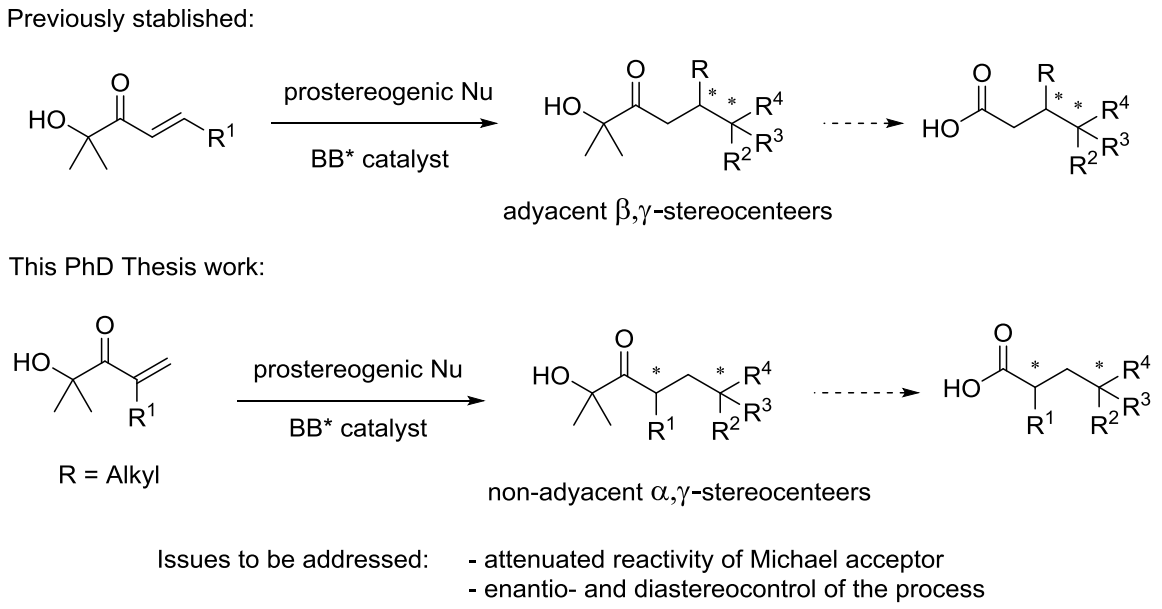
While di- and trienamine mediated catalysis is well studied in the recent years, the chemistry of transiently generated di- and trienolates remains poorly explored. The majority of catalytic reactions involving dienamines proceed through the γ-carbon atom of the unsaturated carbonyl substrate, and the chemistry of transiently generated trienamines is dominated by [4+2] cycloaddition pathways. In turn, dienolates tend to react through γ-carbon in most of the examples described in the literature, thus preserving the π-conjugation along the reaction coordinate. Our hypothesis was that bifunctional H-bond donor/Brønsted base catalysts may be able to direct the electrophile towards the α-carbon of di- and trienolates, as shown in Scheme 19, thus, complementing the currently described chemistry.



Scheme 19. Working hypothesis for the selective α-functionalization of di- and trienolates.

b) Study of α-substituted α´-hydroxy enones as methacrylate equivalent in Brønsted base-catalysed Michael reactions.

Previously, our group revealed that achiral α´-hydroxy enones are excellent acrylate equivalents in Brønsted base catalysed enantioselective conjugate additions.[65] While many methods have been described to obtain Michael adducts with two adjacent stereocenters, the formation of two non-adjacent α,γ-stereocenters remains challenging due to the attenuated reactivity of α-substituted Michael acceptors, and to the difficulty of the stereocontrol in the simultaneous formation of two stereocenters, including an α-protonation step. We hypothesized that α-substituted α´-hydroxy enones may act as efficient methacrylate equivalents in Michael reactions, which could be an entry to α,γ-branched Michael adducts bearing tertiary-quaternary non-adyacent stereocenters (Scheme 20).

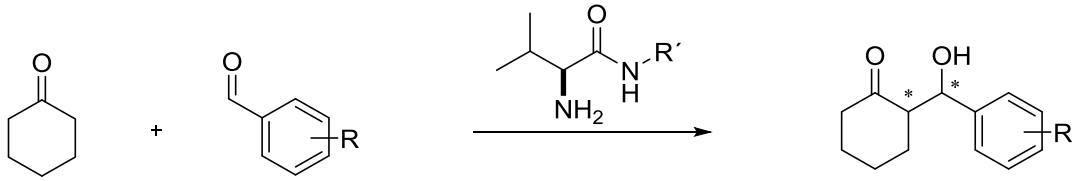


Scheme 20. Tandem Michael addition/protonation reaction for the asymmetric assembly of α,γ-nonadjacent stereocenters.

c) In the last part of my Doctoral research period, a short stay was carried out under the supervision of Prof. Keiji Maruoka in the Graduate School of Science of the Kyoto University in Japan. The research project was focused on the design of a novel *N*-aryl-L-valinamide to catalyse the aldol reaction between cyclohexanone and aromatic aldehydes (Scheme 21). Among the available α-amino acids, L-valine or L-valine derivatives are used less often than proline derivatives as catalysts due

[65] Badiola, B.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881.

to its flexibility, however, L-valine derived organocatalysts are small, simple, and relatively inexpensive.



Scheme 21. *N*-aryl-L-valinamide catalysed aldol reaction.

Chapter 2

Controlling the α/γ/ε-Reactivity of Di- and Trienolates in Organocatalytic Enantioselective Michael Reactions

2. Controlling the α/γ/ε-Reactivity of Transiently Generated Di- and Trienolates in Organocatalytic Enantioselective Michael Reactions

2.1. Introduction

2.1.1. Di- and trienamine mediated catalysis

Enolizable carbonyl compounds are useful pro-nucleophiles in synthesis for both C–C and C–X bond-forming reactions. The HOMO raising of aldehyde and ketone substrates has long been used as a mean to enhance the nucleophilicity of these substrates and induce asymmetry. First important advances in this area came with the use of stoichiometric chiral primary and secondary amines and the formation of the corresponding enamine intermediate in a separate previous operation. With the advent of catalytic versions, initially in intramolecular form[66] and then, in intermolecular fashion,[67] enamine catalysis has become one of the most versatile options for the α-functionalization of aldehydes and ketones.

Since 2000, within a short span of time, the HOMO raising strategy has advanced from *enamines* to *dienamines*, and to higher level of *trienamines*/*cross-trienamines* (Figure 14). These advances allow synthetic chemists to functionalize carbonyl compounds at more remote carbons as the γ- and ε-carbons, as will be briefly described in the following section.

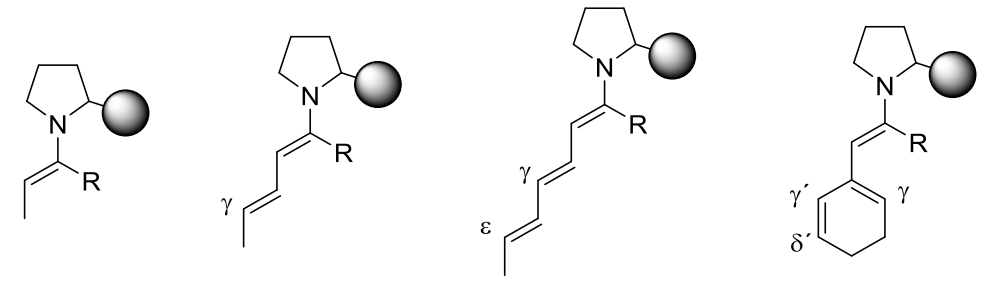


Figure 14. Progress of amine catalysis through HOMO-raising activation strategy.

[66] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
[67] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

2.1.1.1. *Dienamine mediated catalysis*

Dienamines are usually prepared from α,β-unsaturated aldehydes or ketones and a secondary or primary amine catalyst under conditions analogous to those used for preparation of the simple enamines. Dienamines differ from simple enamines in an additional nucleophilic site at the γ-position of the carbonyl compound. Due to the three types of reactivity modes (enamine reactivity, vinylogous reactivity and diene reactivity) and the novel properties of these species, dienamine chemistry has become an important field of study in organic chemistry.[68]

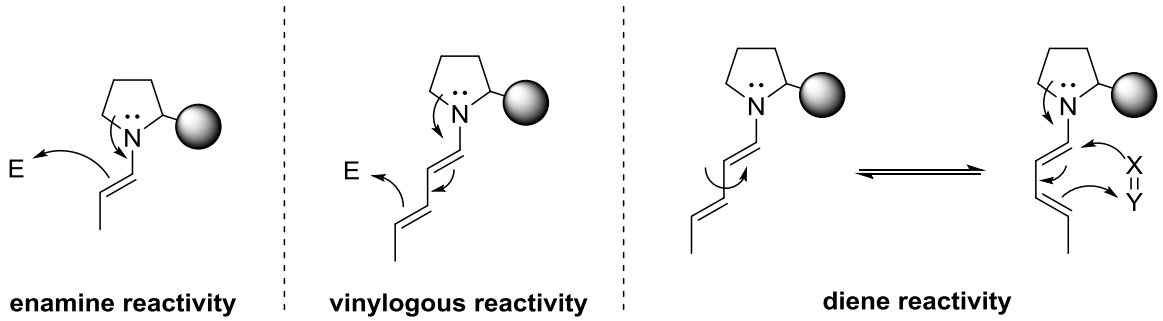
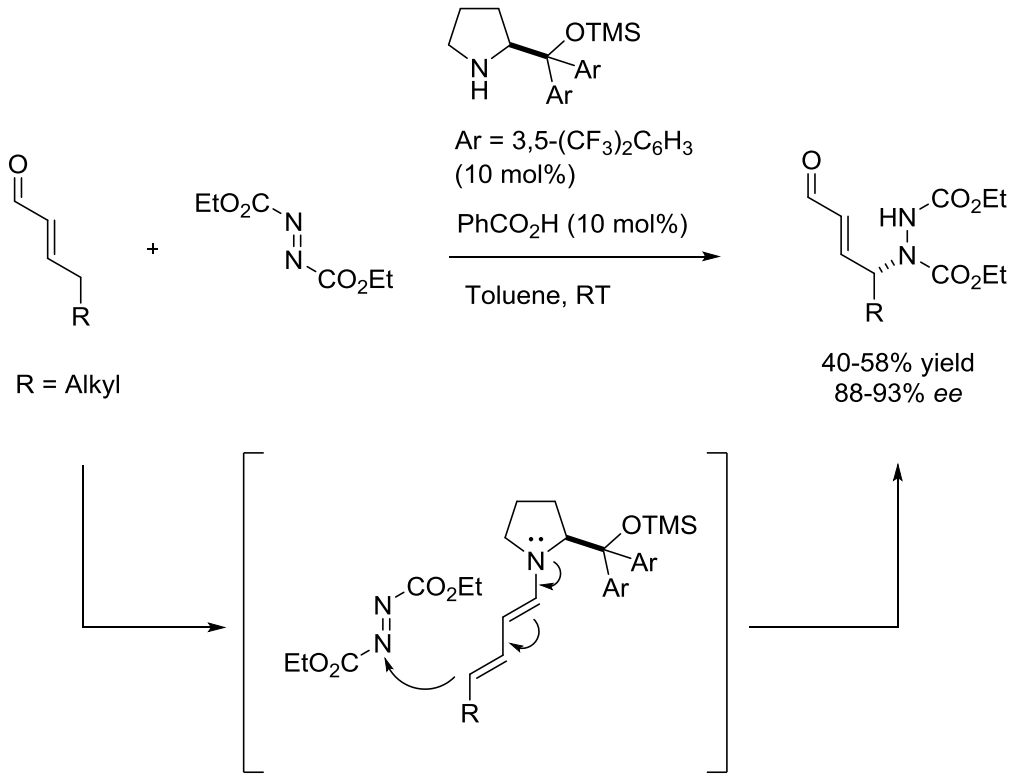


Figure 15. Reactivity modes of dienamines.

In 2006, Jørgensen and co-workers introduced the first direct γ-functionalization of α,β-unsaturated carbonyl compounds catalysed by proline derivatives,[69] by describing the reaction between α,β-unsaturated aldehydes and azodicarboxylates (Scheme 22). This methodology showed perfect site-selectivity with the reactions proceeding through the γ-position, and no detection of the potential α-amination product.

[68] For reviews on dienamine mediated reactions, see: a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865−887. b) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531−3543. c) Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812−6832. d) Hepburn, H. B.; Dell´Amico, L; Melchiorre, P. *Chem. Rec.* **2016**, *16*, 1787−1806.

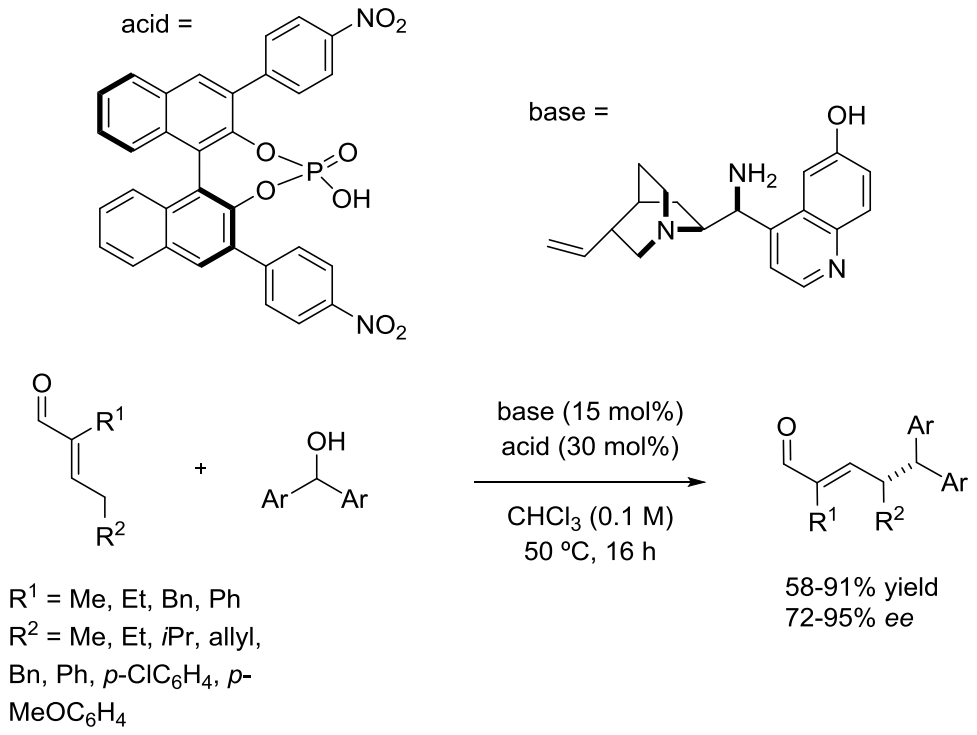
[69] Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973−12980.



Scheme 22. First dienamine mediated direct γ-functionalization of an α,β-unsaturated carbonyl compound.

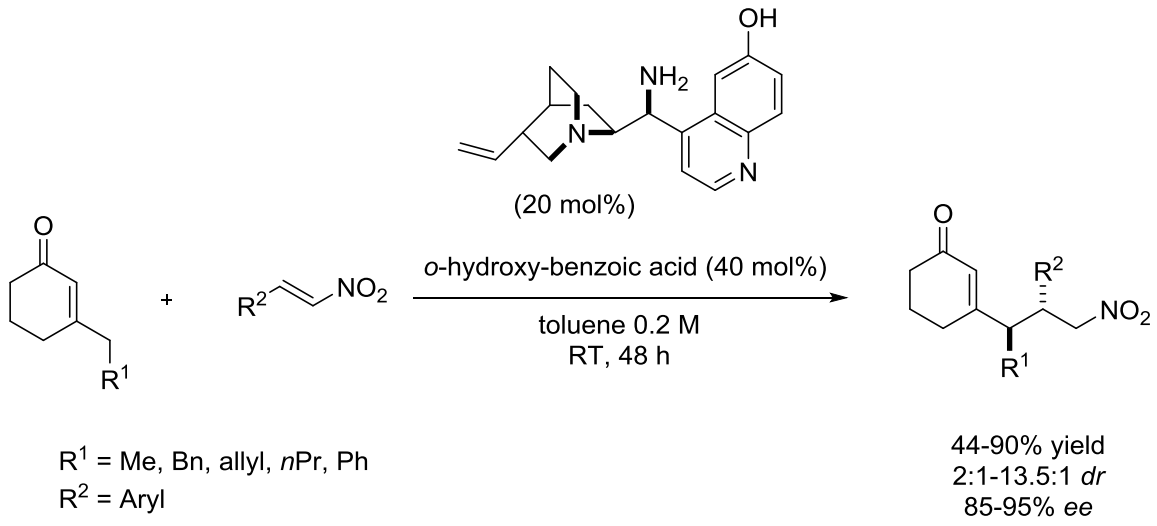
Melchiorre and co-workers, in 2010, reported a dienamine-mediated vinylogous nucleophilic substitution of in situ generated stable carbocations (Scheme 23).[70] This γ-site-selective alkylation represents the first example of a catalytic asymmetric vinylogous substitution reaction of unmodified carbonyl compounds.

[70] Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew, Chem. Int. Ed.* **2010**, *49*, 9685−9688.



Scheme 23. Catalytic asymmetric vinylogous substitution reaction of unmodified carbonyl compounds.

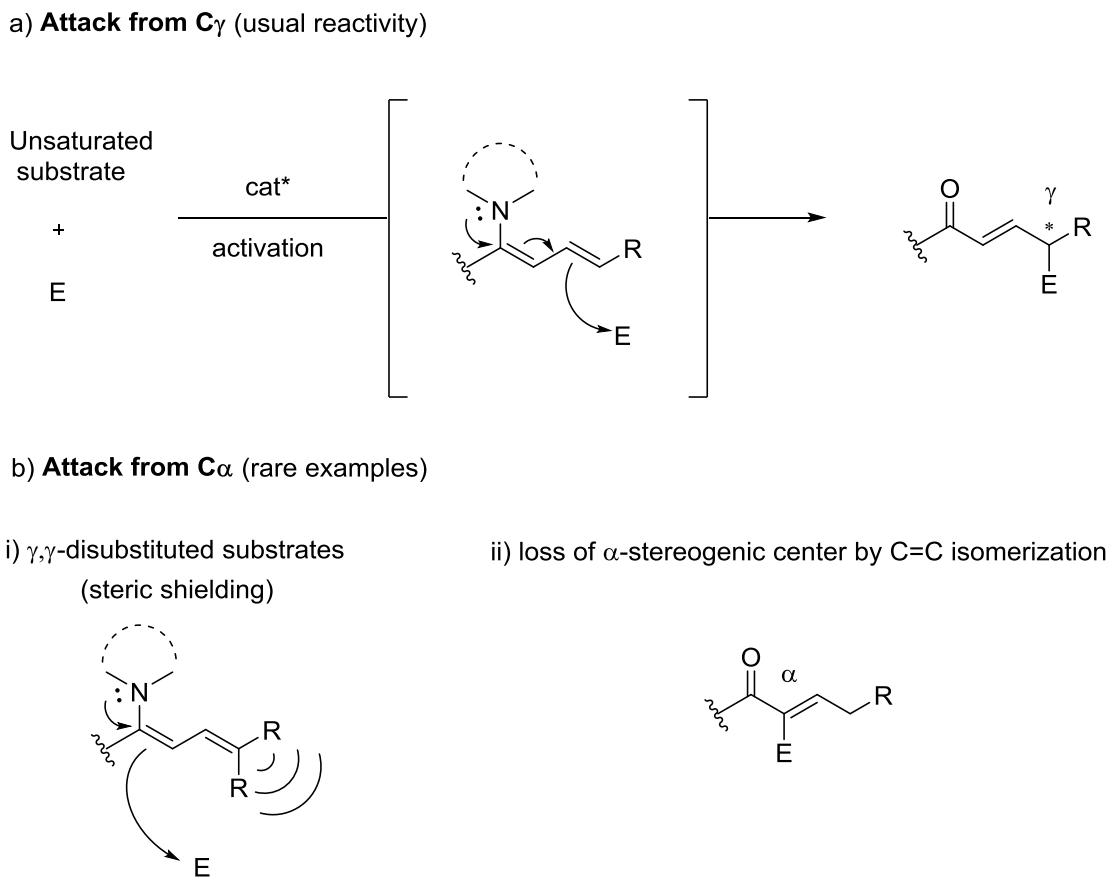
In the same year, Melchiorre described the asymmetric Michael addition of cyclic enones to nitroalkenes based on extended *exo* dienamine catalysis.[71] The process is γ-site-selective, and is catalysed by the primary amine shown in Scheme 24.



Scheme 24. Direct asymmetric Michael addition of cyclic enones to nitroalkenes via dienamine catalysis.

[71] Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642−20647. Correction: *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 4852−4853.

The majority of catalytic reactions involving vinylogous enolates or equivalents proceed from the γ-position of the carbonyl compound, which preserves π-conjugation as shown in Scheme 25a. In contrast, the alternative α-reaction pathway implies disruption of the π-conjugation along the reaction coordinate. Only few α-site-selective functionalization processes of dienamines have been reported. A strategy that has been used in the literature for switching the regioselectivity to the α-carbon is to sterically shield the γ-carbon by using γ,γ-disubstituted carbonyl compounds (Scheme 25bi). In addition, few α-selective dienamine mediated reactions have also been reported, but ulterior C=C isomerization occurs to give the Morita-Baylis-Hillman-type adducts and so the α-stereogenic center does not survive (Scheme 25cii).

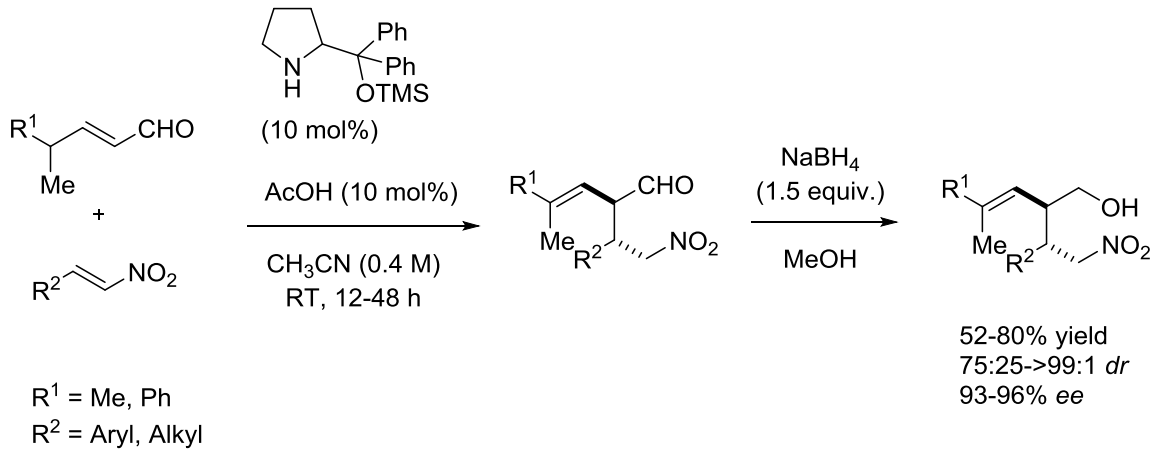


Scheme 25. α-site-selective and γ-site-selective reaction pathways in dienamine mediated reactions.

In 2009, Chen and co-workers used the γ-carbon shielding strategy to report the first direct chemo-, regio-, and enantioselective dienamine mediated Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins (Scheme 26).[72] The Michael

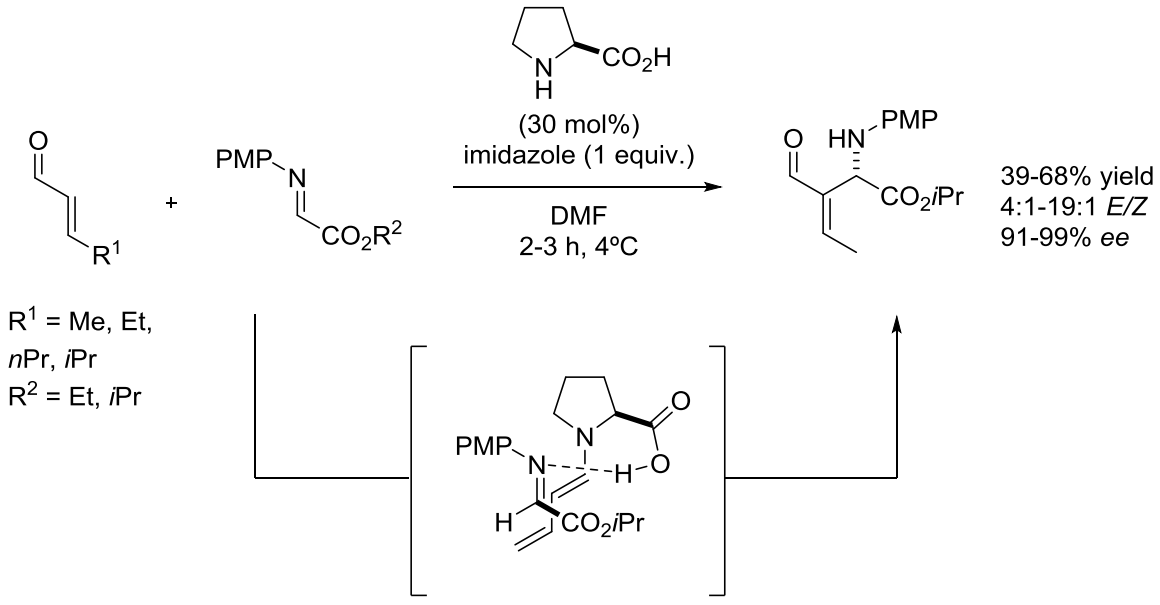
[72] Han, B.; Xiao, Y. C.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2009**, *11*, 4660−4663.

adduct was obtained in an α-regioselective process, in yields from moderate to good and excellent enantioselectivity.



Scheme 26. α-selective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins.

Barbas and co-workers,[73] in 2007, reported the Mannich reaction between β-substituted enals and *N*-PMP-protected isopropyl α-iminoglyoxylate catalysed by L-proline. The α-site-selective reaction transcurred via dienamine (Scheme 27) to obtain, upon isomerization of the C=C bond, aza-Morita-Baylis-Hillman-type products in variable yields and stereoselectivity.



Scheme 27. Dienamine mediated synthesis of aza-Morita-Baylis-Hillman-type products.

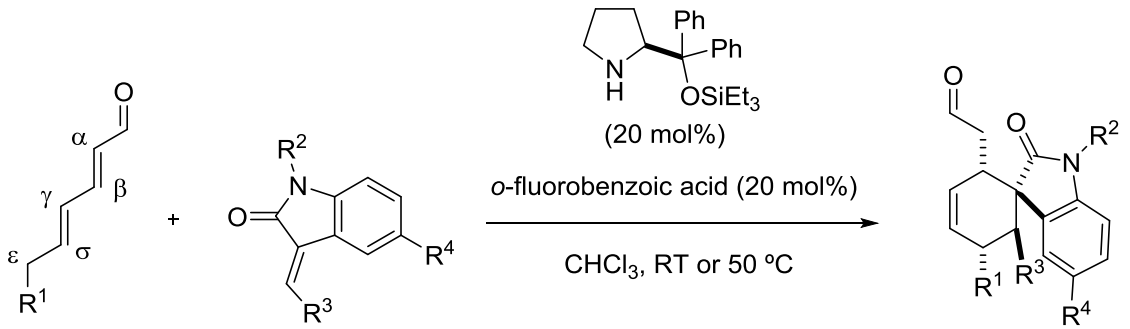
[73] Utsumi, N.; Zhang, H.; Tanaka, F. Barbas III, C. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1878−1880.

2.1.1.2. *Trienamine mediated catalysis*

Trienamine catalysis provides an opportunity for synthesizing complex molecules with high stereocontrol.[74] Two type of trienamine intermediates have been described in the literature: *linear trienamines* and *cross-trienamines*.

2.1.1.2.1. *Linear-trienamine mediated catalysis*

The groups of Chen and Jørgensen documented collectively the first trienamine catalysed Diels-Alder reaction between 2,4-dienals and electron defficient dienophiles,[75] with ε-site-selectivity and high stereoselectivity (Scheme 28).



Scheme 28. First trienamine mediated catalytic Diels-Alder reaction.

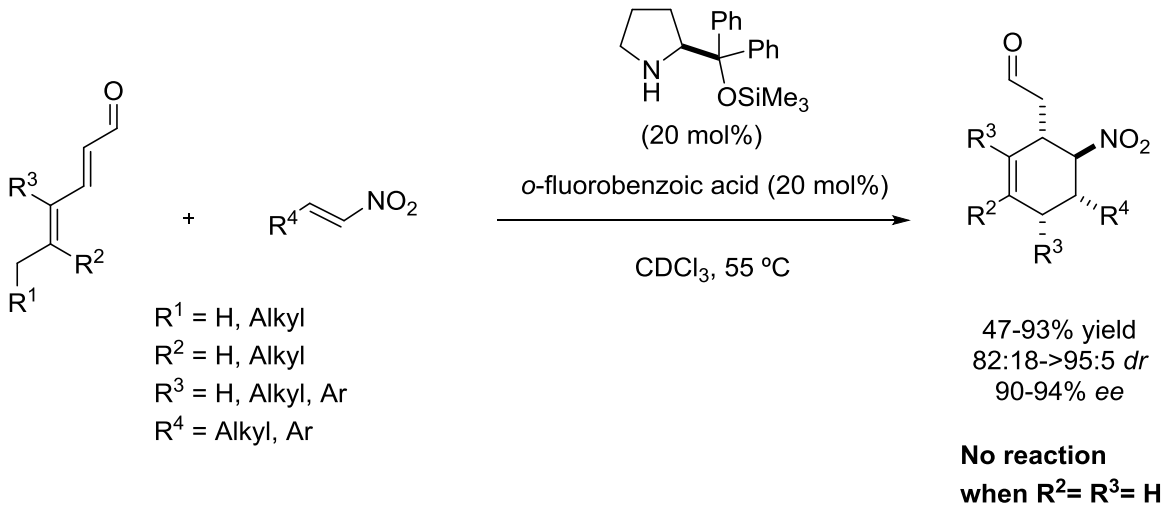
Soon after, Chen and co-workers further extended the scope of trienamine catalysis for asymmetric Diels-Alder reactions with nitroalkenes as dienophiles for the first time.[76] Interestingly, the introduction of electron-donating alkyl substituents at C4 and C5 positions of the 2,4-dienals was found 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 29).

---

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

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

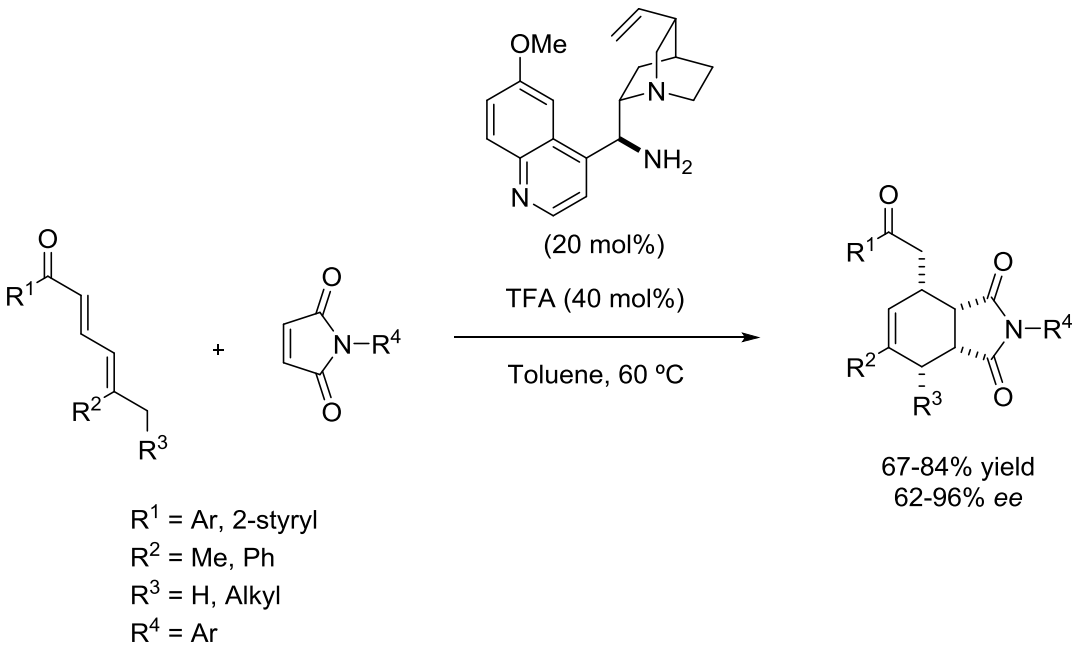
[76] Jia, Z. J.; Zhou, Q.; Zhou, Q. Q.; Chen, P. Q.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638−8641.



Scheme 29. Trienamine mediated Diels-Alder reaction between 2,4-dienals and nitroalkenes.

Chen and co-workers[77] have also established the suitability of substituted 2,4-dienones as precursors for trienamine catalysis, and demonstrated their applicability in the highly selective asymmetric Diels–Alder reaction. The trienamine specie is generated in the reaction by condensation between α´-non enolizable 2,4-dienones and cinchona alkaloid derived primary amine catalyst. To avoid the 2,4-dienones to act as dienes in a noncatalysed cycloaddition reaction, δ,δ-disubtituted 2,4-dienones had to be used (Scheme 30).

[77] Xiong, X. F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T. Y.; Chen, Y. C. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4401–4404.

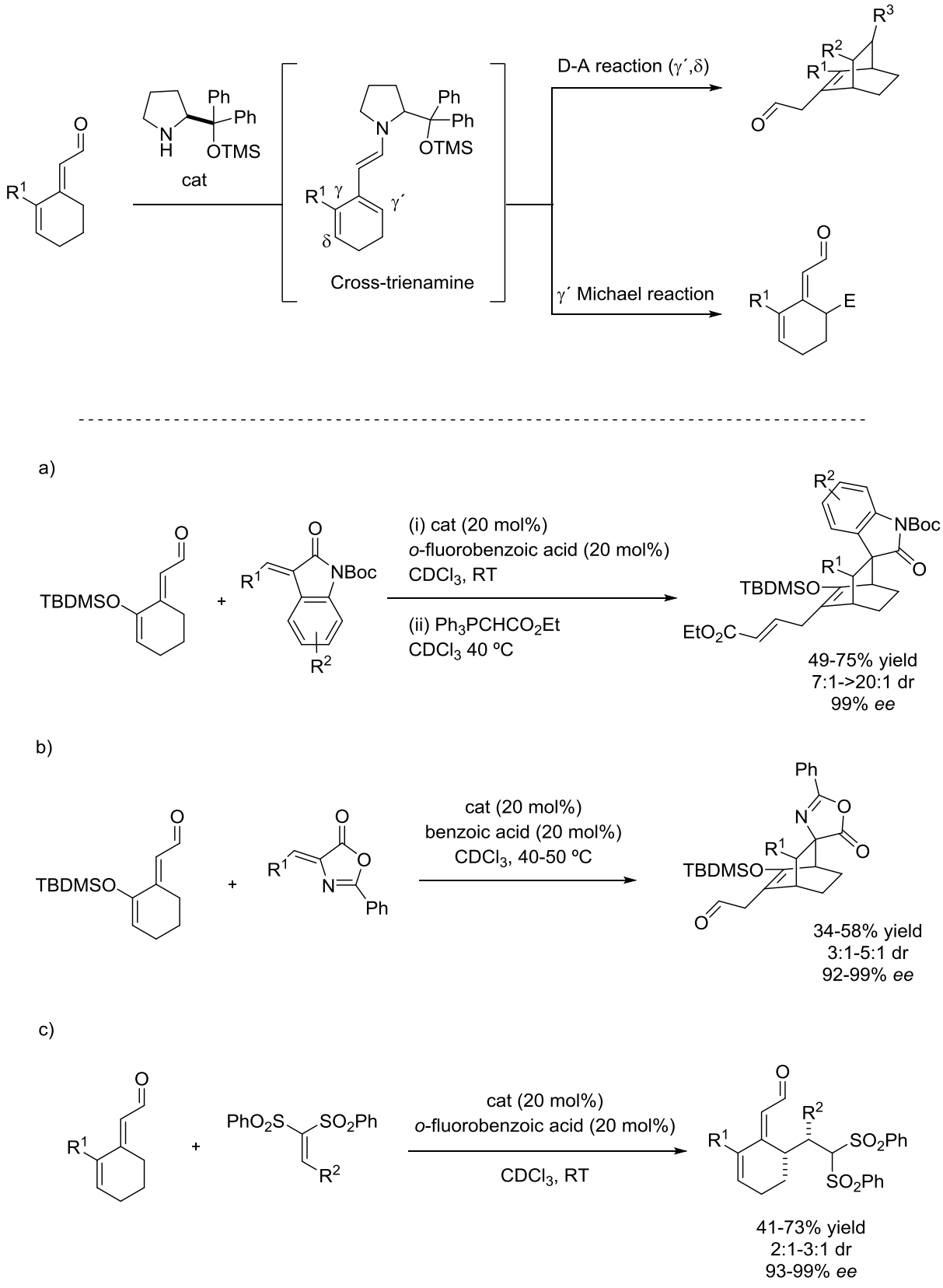


Scheme 30. Diels–Alder cycloaddition of δ,δ-disubstituted 2,4-dienones via trienamine catalysis.

2.1.1.2.2. *Cross-trienamine mediated catalysis*

In 2012, Jørgensen and co-workers introduced a new variant on trienamine activation by using β-branched dienals as starting material.[78] The in situ formed cross-trienamine intermediates undergo highly enantioselective Diels–Alder reactions with 3-olefinic oxindoles (Scheme 31a) and 5-olefinic azlactones (Scheme 31b), providing a path to important bicyclic structures although yields were occasionally moderate or low.

[78] Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943–12946.



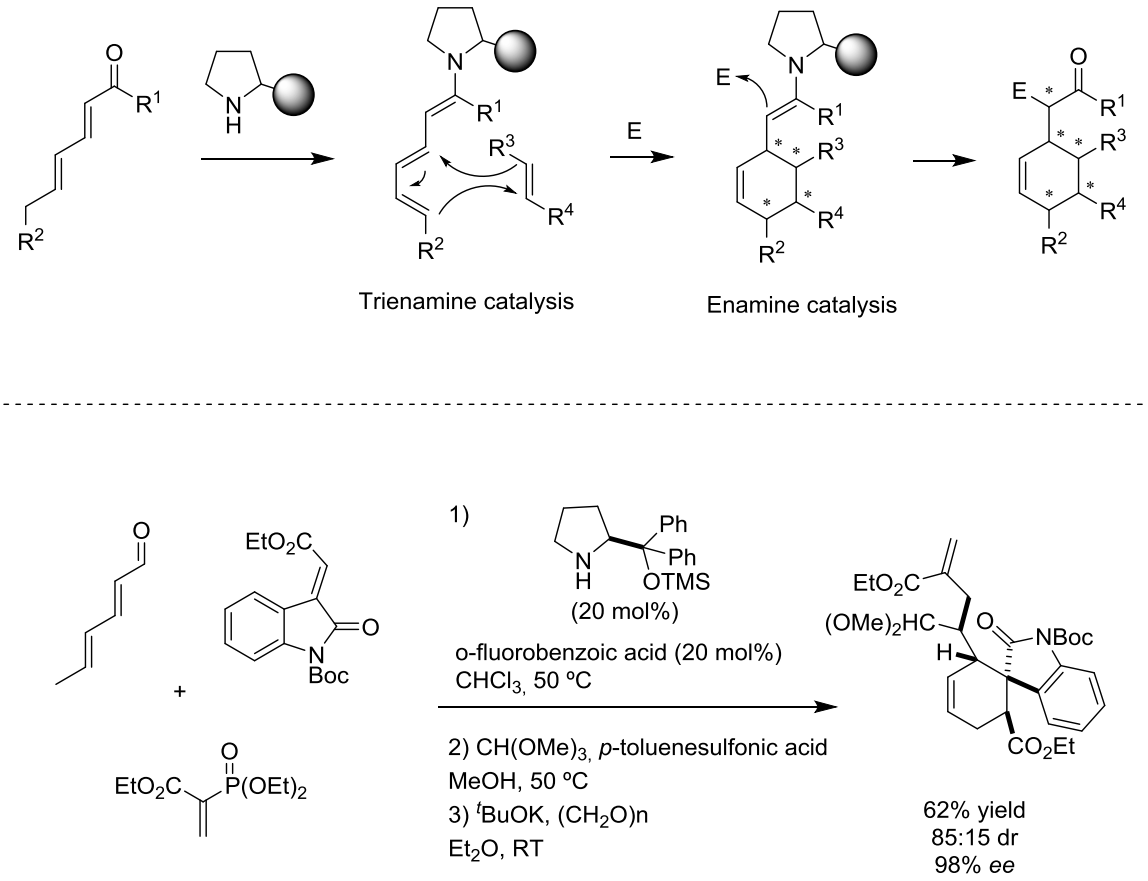
Scheme 31. Cross-trienamine mediated Diels–Alder and Michael reactions.

Although generally the concept of trienamine catalysis has been applied in the context of the Diels–Alder reaction, cross-conjugated trienamines may also react through Michael type addition selectively at the γ´-position. Thus, reaction of cyclic 2,4-dienals with vinyl bis-sulfones proceed through the γ´-carbon with high yields and excellent enantioselectivities (Scheme 31c).

Organocatalytic cascade or tandem reactions involving two or more selective transformations using single/multiple catalysis, allow the quick construction of complex structures in a one pot operation. This allows the design of simple synthetic routes for complex molecular structures with high yields and selectivities.[79]

The groups of Chen and Jørgensen reported the first trienamine-enamine tandem reaction in 2011.[75] In this process, the trienamine catalysed Diels-Alder reaction between a 2,4-dienal the oxindole takes place first, before the enamine promoted α-functionalization of the aldehyde using ethyl 2-(diethoxyphosphoryl)acrylate as the electrophile (Scheme 32).

[79] For reviews on organocatalytic cascade reactions, see: a) C. R. V. Volla, L. Atodiresei, M. Ruepin, *Chem. Rev.* **2014**, *114*, 2390–2431. b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178. c) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993–3009.



Scheme 32. Organocatalytic trienamine-enamine multicomponent tandem reaction.

2.1.2. Di- and trienolate mediated catalysis

While the di- and trienamine strategy is limited to enolizable aldehydes and ketones, di- and trienolates may be also applied to other enolizable substrates such as carboxylic acid derivatives or non-carbonyl compounds. However, the chemistry of di- and trienolates is poorly explored, in comparison to di- and trienamines.

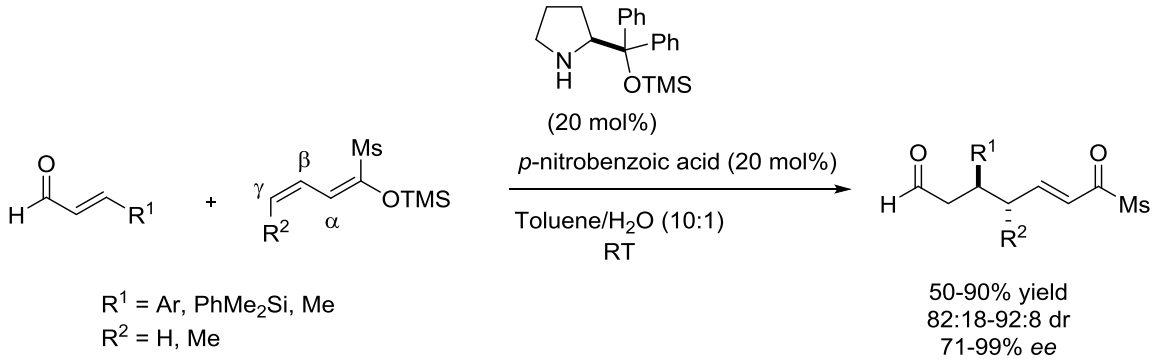
2.1.2.1. *Dienolate mediated catalysis*

Enolate-based reactions are the pillars of synthetic organic chemistry. Adding a conjugated double bond to the enolate moiety extends the reactivity of the new dienolate, which can react with a broad range of electrophiles from the α- or γ-position.

Carbon−carbon bond forming processes of dienolates have become highly attractive in synthetic chemistry as they are able to assemble complex organic molecules.[80]

As in dienamine catalysis, the majority of the examples of reactions involving dienolates proceed through the γ-carbon. In this context, the indirect Mukaiyama type additions have been explored, with both linear and cyclic silicon dienolates.

Schneider and co-workers, in 2012, stablished the first catalytic, enantioselective vinylogous Mukaiyama-Michael reaction of acyclic dienol silyl ethers with α,β-unsaturated aldehydes, which are activated *via* iminium ion, obtaining valuable chiral 1,7-dioxo compounds in a γ-site selective process (Scheme 33).[81]



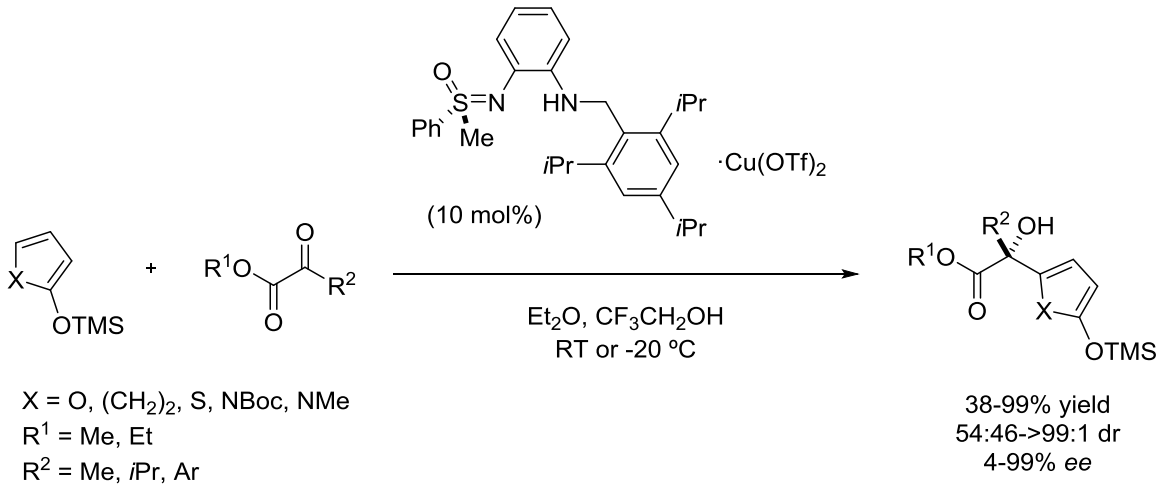
Scheme 33. Catalytic enantioselective Michael reaction with linear preformed dienolates.

Bolm and co-workers developed a vinylogous Mukaiyama aldol reaction between heterocyclic dienoxy silanes and α-keto esters catalysed by an amino sulfoximine copper complex. The γ-selective reaction leads to adducts bearing a quaternary stereogenic center (Scheme 34).[82]

[80] For reviews on dienolate mediated reactions, see: a) Casiraghi, G.; Battistine, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076−3154. b) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531−3543.

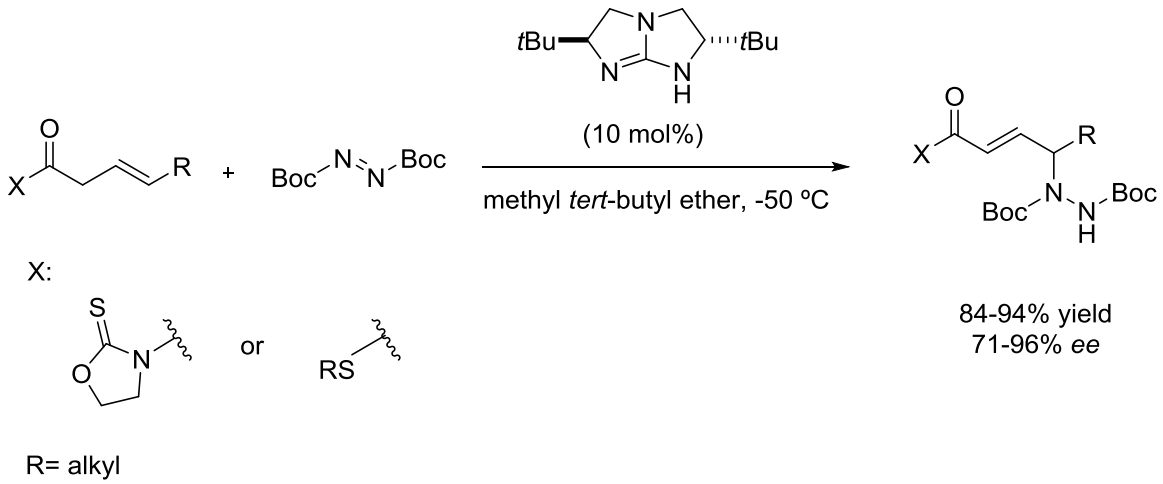
[81] Gupta, V.; Sudhir, A. V.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 12609−12612.

[82] a) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2007**, *10*, 917−920. b) Frings, M.; Atodiresei, I.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2009**, *15*, 1566−1569. c) Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577−4587.



Scheme 34. Catalytic enantioselective Michael reaction with cyclic preformed dienolates.

Direct dienolate mediated reactions have also been explored. In 2012, Tan and co-workers developed a guanidine catalysed asymmetric γ-selective allylic amination of β,γ-unsaturated thioesters and imides (Scheme 35).[83]

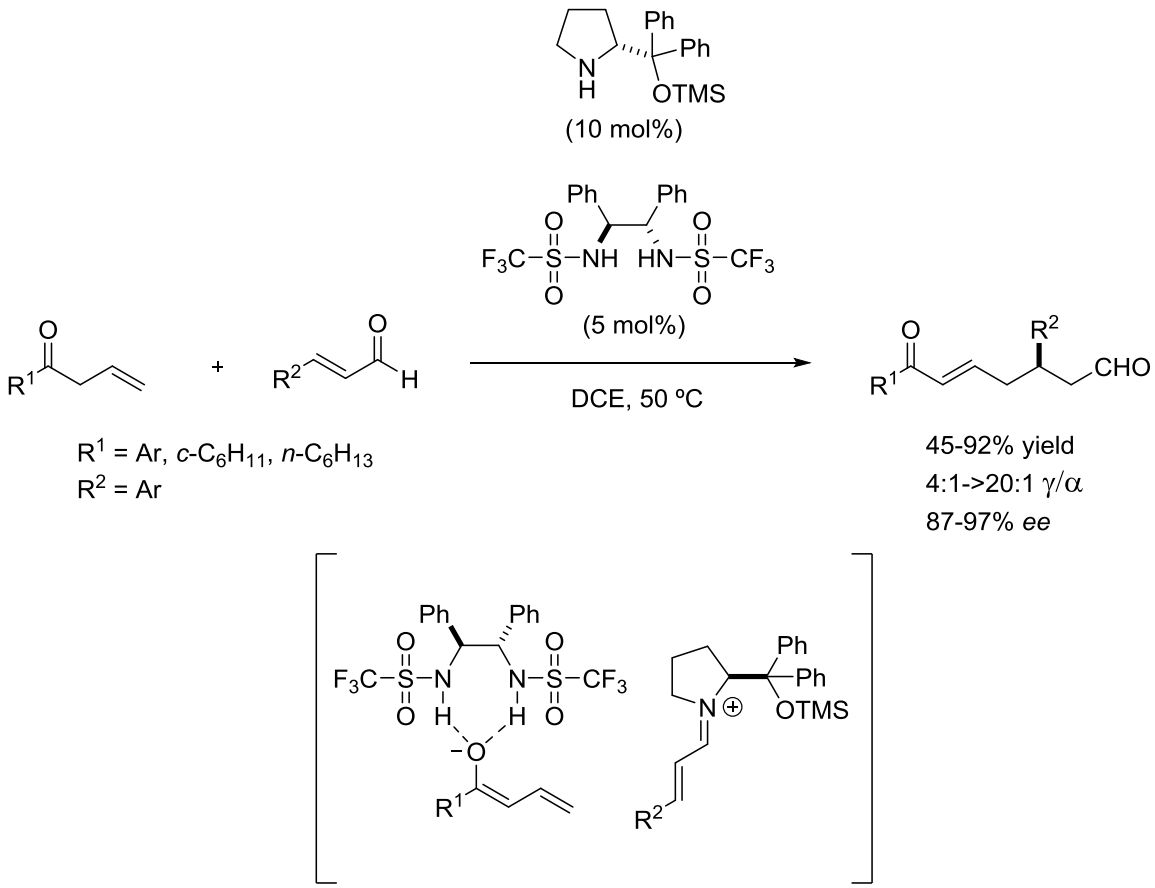


Scheme 35. γ-Selective asymmetric functionalization of β,γ-unsaturated thioesters and activated amides.

In 2014, Xu and co-workers reported the direct vinylogous Michael addition of unmodified linear β,γ-unsaturated ketones to α,β-unsaturated aldehydes.[84] The α,β-unsaturated aldehyde is activated *via* iminium ion, and the cocatalyst, activates the

[83] Wang, J.; Chen, J.; Kee, C. W.; Tan, C. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 2382−2386.
[84] Gu, Y.; Wang, Y.; Yu, T. Y.; Liang, Y. M.; Xu, P. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 14128−14131.

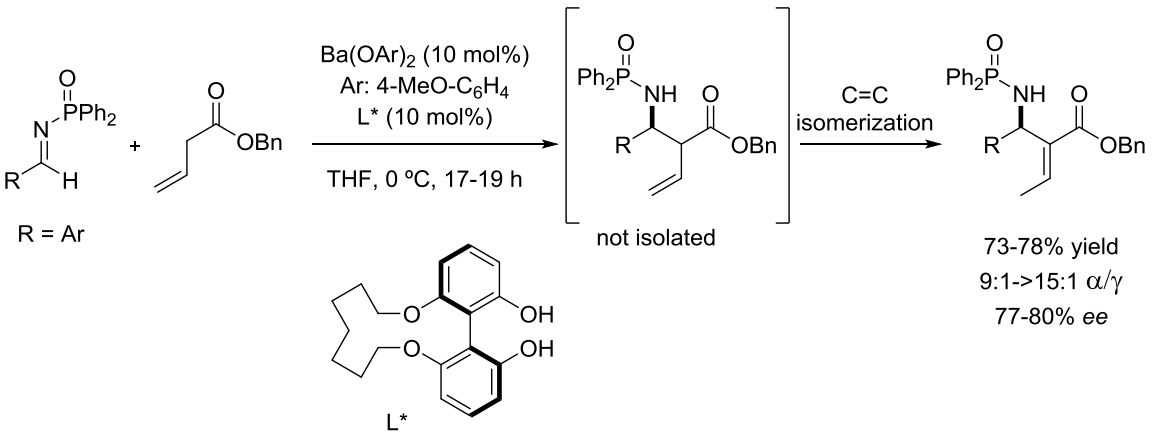
dienolate and shields the alpha carbon, obtaining the γ-adduct exclusively in good yields and excellent enantioselectivity (Scheme 36).



Scheme 36. β-selective vinylogous direct Michael addition of dienolates to α,β-unsaturated aldehydes.

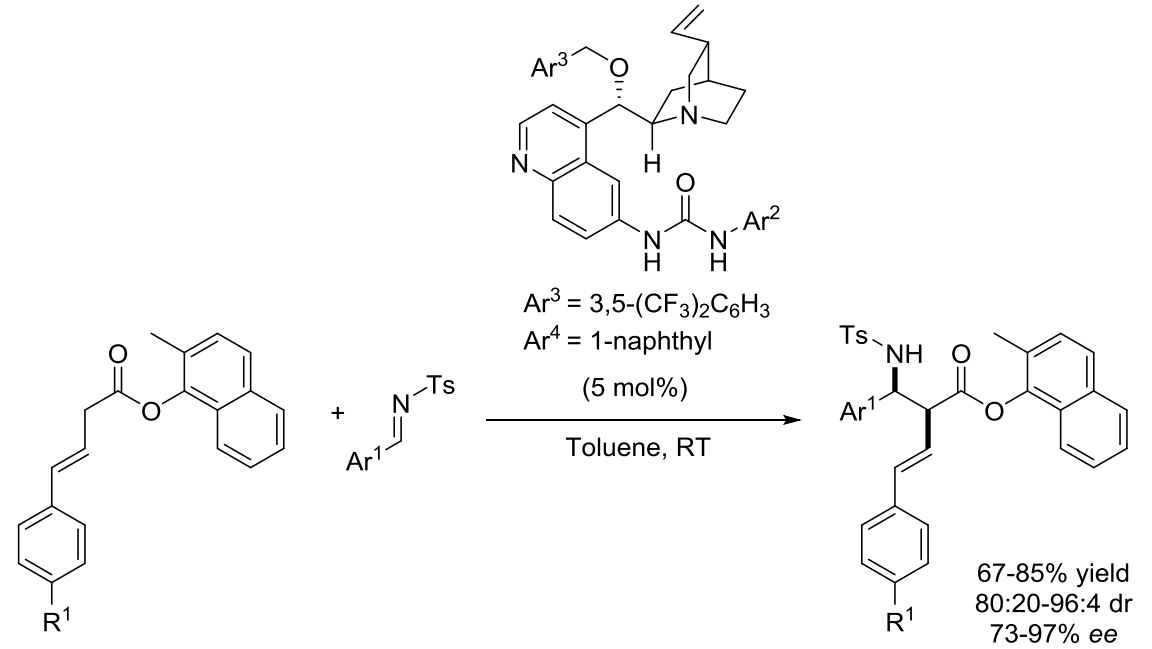
Examples of α-site selective dienolate mediated reactions are less common, as only a few enantioselective approaches have been reported. Shibasaki and co-workers described a barium alkoxide catalysed α-regioselective Mannich reaction of β,γ-unsaturated esters.[85] The C=C isomerization of the initially formed addition product provided the corresponding Morita-Baylis-Hillman-type products (Scheme 37).

[85] Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 3387−3390.



Scheme 37. Direct Mannich reaction/isomerization sequence to obtain Morita-Baylis-Hillman-type products.

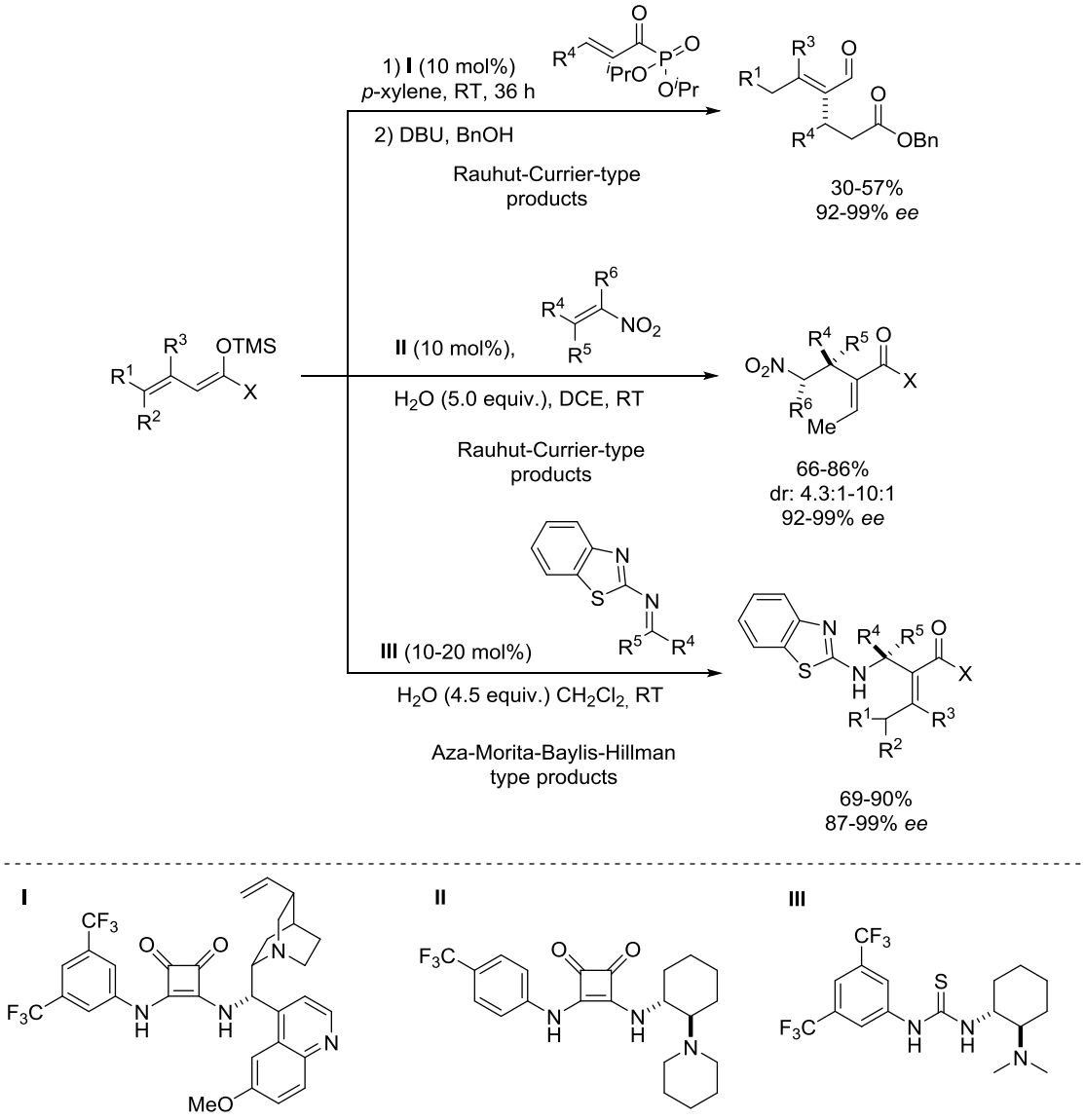
In 2016, Zhao and co-workers reported the direct α-selective Mannich reaction between aryl α-styrylacetates and *N*-tosyl imines promoted by a quinine-derived urea catalyst. Although the Mannich adducts are obtained with high yields and excellent enantioselectivities, the substrate scope is very limited (Scheme 38).[86]



Scheme 38. Organocatalysed enantioselective α-selective direct Mannich reaction of α-styrylacetates.

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

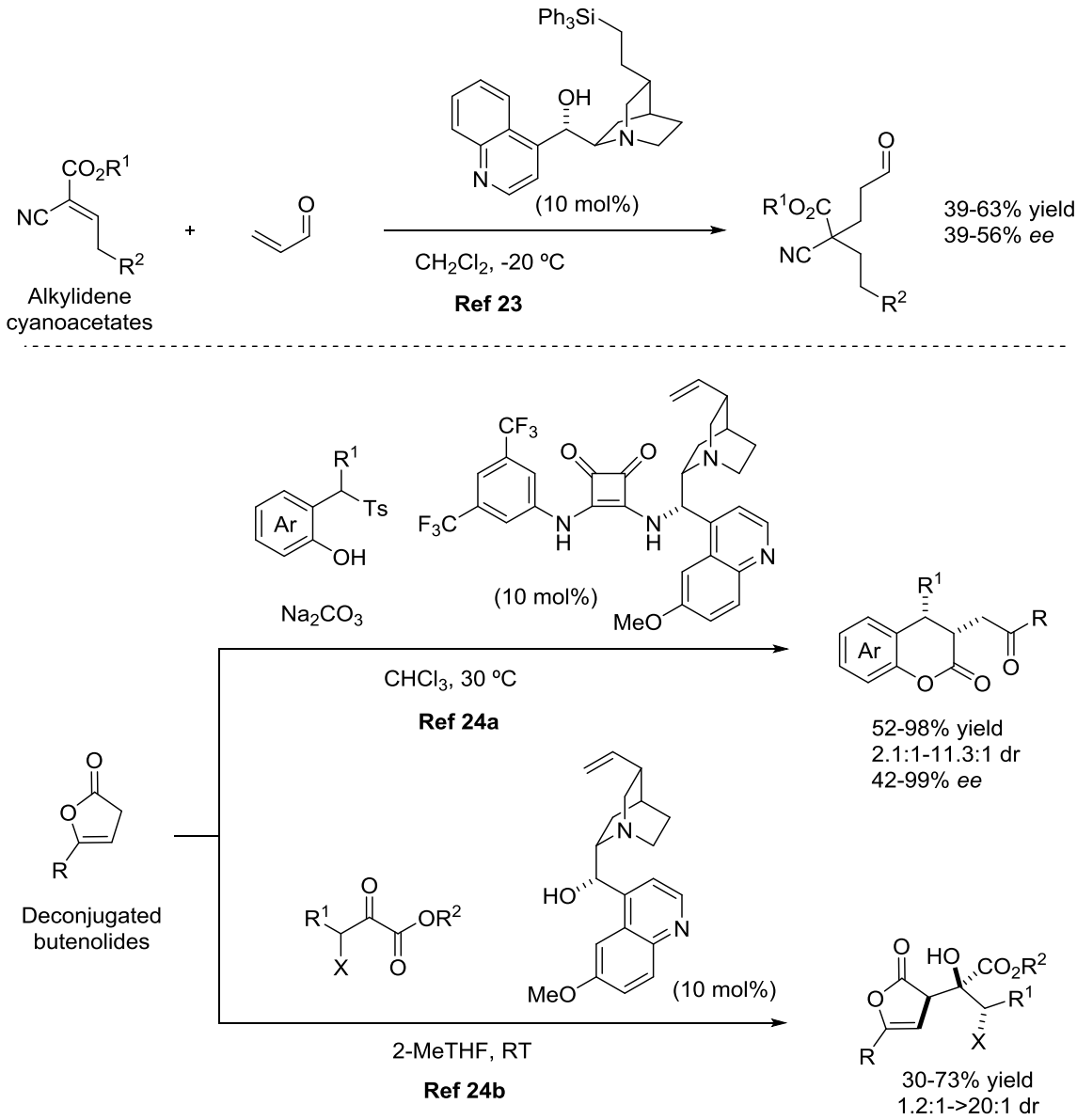
Once our work was in progress, the group of Alemán reported the Brønsted base catalysed α-regioselective functionalization of silyl dienol ethers to various acceptors to obtain the corresponding Rauhut-Currier and Morita-Baylis-Hillman-type products after the isomerization of the C=C double bond (Scheme 39).[87]



Scheme 39. Addition of silyl dienol ethers to various acceptors catalysed by bifunctional Brønsted base/H-bond donor catalyst to give Rauhut-Currier and Aza-Morita-Baylis-Hillman type adducts.

[87] a) Frias, M.; Mas-Ballesté, R.; Arias, S.; Alvarado, C.; Alemán, J. *J. Am. Chem. Soc.* **2017**, *139*, 672−679. b) Frias, M.; Carrasco, A. C.; Fraile, A.; Alemán, J. *Chem. Eur. J.* **2018**, *24*, 3117−3121. c) Laina-Martín, V.; del Río-Rodríguez, R.; Díaz-Tendero, S.; Fernández-Salas, J. A.; Alemán, J. *Chem. Commun.* **2018**, *54*, 13941−13944.

As shown in the examples above, the methodologies for α-functionalization of dienolates are rare, and the stereogenic center formed at the α-position is lost upon C=C isomerization. Only additional few Brønsted base catalysed α-site functionalizations of vinylogous enolates where posterior C=C isomerization is avoided have been reported, but these examples featured moderate enantioselectivities[88] or were restricted to specific substrates (Scheme 40).[89]



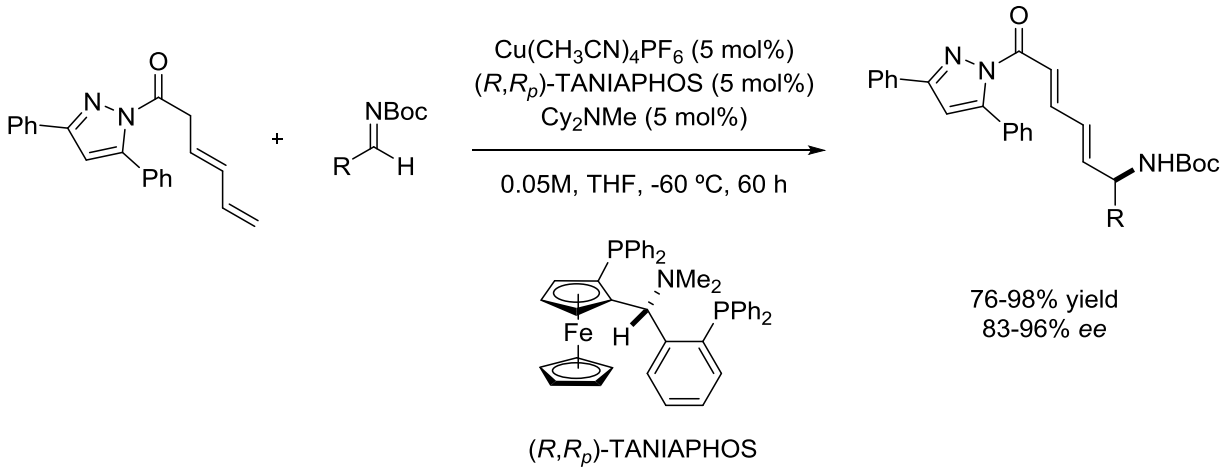
Scheme 40. Additional Brønsted base catalysed α-site functionalizations of vinylogous enolates.

[88] Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407−5410.
[89] a) Wu, B.; Yu, Z.; Gao, X.; Lan, Y.; Zhou, Y. G. *Angew. Chem. Int. Ed.* **2017**, *56*, 4006−4010. b) Griswold, J. A.; Horwitz, M. A.; Leiva, L. V.; Johnson, J. S. *J. Org. Chem.* **2017**, *82*, 2276−2280.

2.1.2.2. *Trienolate mediated catalysis*

Although trienamine mediated reactions have been widely explored, reactions involving trienolates remain, to the best of our knowledge, undeveloped, in spite of the chances for discovery of novel reaction pathways. Lithium trienolate formed from sorbic acid was documented as a donor in racemic additions to enones.[90] A mixture of regioisomeric products was obtained, which was dependant of the substituents of the acceptor.

To date, as far as we know, a single catalytic and asymmetric direct functionalization of transiently generated trienolates has been documented. During the period of this Doctoral Thesis, in 2017, Yin and co-workers developed an ε-selective catalytic asymmetric bisvinylogous Mannich reaction catalysed by a copper(I) complex (Scheme 41).[91]



Scheme 41. ε-selective direct asymmetric bisvinylogous Mannich-type reaction catalysed by a copper(I) complex.

2.1.3. Objectives

One of the aims of this Doctoral Thesis was to investigate the chemistry of transiently generated di- and trienolates. As the examples above show, there were only a few examples of α-selective functionalization of in situ generated dienolates with some

[90] a) Ballester, A.; Costa, A.; García-Raso, A.; Gómez-Solivellas, A.; Mestres, R. *Tetrahedron Lett.* **1985**, *26*, 3625−3628. b) Ballester, A.; Costa, A.; García-Raso, A.; Mestres, R. *J. Chem. Soc. Perkin Trans. I* **1988**, 2797−2803.

[91] Zhang, H. J.; Shi, C. Y.; Zhong, F.; Yin, L. *J. Am. Chem. Soc.* **2017**, *139*, 2196−2199.

important limitations, and there was virtually no precedent in trienolate mediated regioselective reactions.

Given the limitations in the α-selective functionalization methodologies of extended enolates, we decided to tackle this issue by using simple β,γ-unsaturated, and β,γ-δ,ε-unsaturated alkyl ketones (Figure 16) as pronucleophiles in Michael reactions. Parallel work from this laboratory has focused on the corresponding unsaturated carboxylic acid derivatives.[92]

Our efforts focussed on three main aspects:

- Controlling the α- vs (γ, ε or α´)- regioselectivity.
- Preventing isomerization of the C=C double bond once the initial Michael adduct is formed (Figure 16), thus preserving the α-stereocenter.
- Controlling the enantio- and diastereoselectivity of the process.

We hypothesized that a chiral bifunctional Brønsted base catalyst might anchor both the dienolate and the electrophilic reagent in a way favouring the α-reaction trajectory, while preventing isomerization of the adduct (Figure 16).

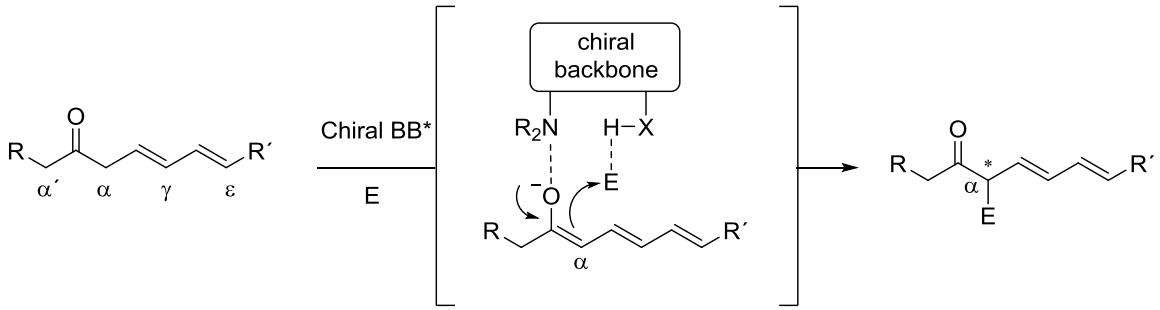


Figure 16. Working hypothesis.

2.2. Results and Discussion

2.2.1. Dienolates

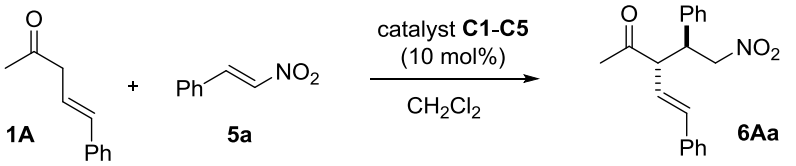
For the initial studies, the reaction of skipped enone **1A** with nitrostyrene **5a** in the presence of several bifunctional Brønsted base catalysts was investigated (Table 1). The

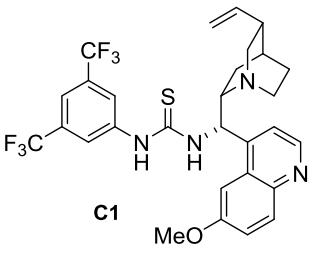
[92] Olatz Olaizola, Doctoral Thess: Dienolate and Trienolate Intermediates in Organocatalytic Regio- and Stereoselective Michael Reactions. UPV-EHU.

reaction was completed within a few hours, in a completely regioselective process that formed the α-addition product exclusively. However, the diastereo- and enantioselectivity were strongly catalyst-dependent. With cinchona-alkaloid-derived thiourea **C1**,[93] both the diastereo- and enantioselectivity were moderate. The enantioselectivity could be improved by using the squaramide catalysts pioneered by Rawal,[94] such as catalyst **C2**[95] and **C3**, and the cyclohexylamine-derived catalyst **C4**,[96] in particular, but the diastereoselectivity remained inadequate (d.r. <2:1). Additional screening showed that squaramide **C5** performed the best, affording product **6Aa** in complete conversion, 6.4:1 d.r., and 96% *ee* upon reaction at 0 °C.

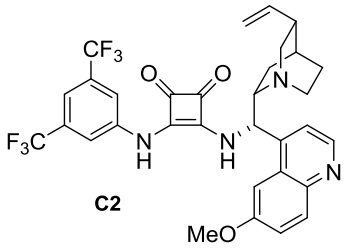
[93] a) McCooey, S. H.; Connon, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367−6370. b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. c) Vakulya, B.; Varga, S; Csampai, A.; Sojs, T. *Org. Lett.* **2005**, *7*, 1967−1969. d) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603−606.
[94] a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. b) Zhu, Y.; Malerich, J. P.; Rawal, V. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 153−156.
[95] Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953−957.
[96] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450−5453.

Table 1. Catalyst screening for the reaction of **1A** with **5a** to give **6Aa**.[a]

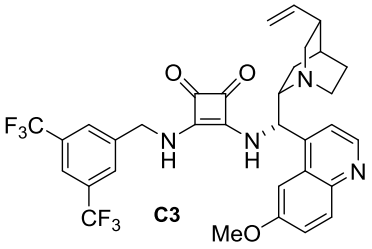




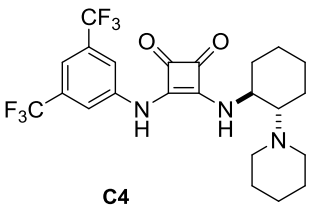
2 h, RT, 1.9:1 dr; 66 % *ee*
8 h, -20ºC, 2.4: 1 dr; 70% *ee*
64 h, -60ºC, 84% conv., 71: 29 dr; 70% *ee*



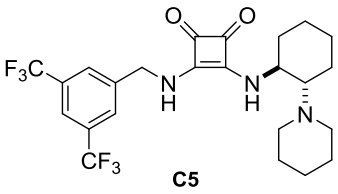
2 h, RT, 1:1.1 dr; 85% *ee*
6 h, -20ºC, 1:1.3, 93% *ee*



2 h, RT, 1.9:1 dr; 72% *ee*
6 h, -20ºC, 2.3:1; 86% *ee*



16 h, 0 ºC, 1.2:1; 97% *ee*



20 h, 0 ºC, 6.4:1; 96% *ee*

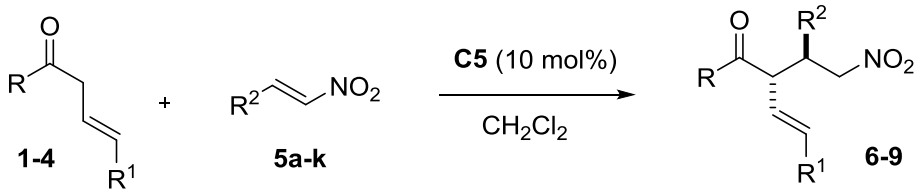
[a]Reactions carried out on 0.2 mmol scale, with **1A** (1.5 equiv.), **5a** (1 equiv.) and catalyst (10 mol%) in CH_2Cl_2. Diastereomeric ratio and *ee* values determined by HPLC analysis of crude material on a chiral stationary phase. *ee* values correspond to the major diastereomers.

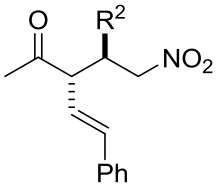
Once the reaction conditions had been optimized for the model reaction, various β,γ-unsaturated ketones and nitroolefins were examined. The reaction tolerates both aliphatic and aromatic β,γ-unsaturated ketones (**1**-**4**) and nitroolefins with either electron-rich, electron-neutral, or electron-poor aryl substituents at the β-carbon atom (Table 2). However, reactions involving aliphatic nitroolefins proceeded to lower conversions under the same reaction conditions (adducts **6Ah**, **6Ai** and **9Aj**). The corresponding adducts **6**-**9** were produced in diastereomeric ratios of 5:1 or higher and enantioselectivities of up to 98% *ee* for both the major and minor isomers.[97] In every

[97] Separation of diastereomers, while not systematic, was posible by column chromatography in some instances. See the experimental section for details.

case, the alkylation proceeded at the α-carbon atom of the unsaturated ketone, and no isomerization of the double bond in the adducts was observed.

Table 2. Scope of the reaction with ketones **1**-**4** and nitroalkenes **5**.[a]





6Aa R^2: Ph — 80%, dr 6.4 : 1, 96% *ee* (>99%)

6Ab R^2: 4-$MeOC_6H_4$ — 95%, dr 5.2 : 1, 98% *ee* (98%)

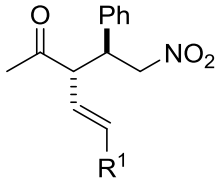
6Ac R^2: 4-MeC_6H_4 — 90%, dr 5.7 : 1, 97% *ee* (95%)

6Ad R^2: 3-MeC_6H_4 — 72%, dr 7.3 : 1, 96% *ee* (>99%)

6Ae R^2: 2-ClC_6H_4 — 72%, dr 6.7 : 1, 90% *ee* (60%)

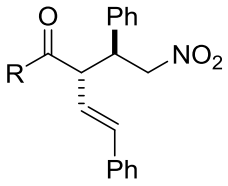
6Ah R^2: $CH_3(CH_2)_4$ — 30% conv after 24h

6Ai R^2: *i*Bu — 40% conv after 24h



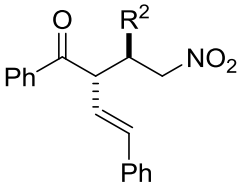
6Ba R^1: 4-ClC_6H_4

73%, dr 9.0 : 1, 92% *ee* (61%)



7Aa R: Et — 83%, dr 7.3 : 1, 95% *ee* (93%)

8Aa R: *t*Bu — 70% conv, dr >20:1, 84% *ee*



9Aa R^2: Ph — 75%, dr 6.7 : 1, 92% *ee* (90%)

9Ab R^2: 4-$MeOC_6H_4$ — 78%, dr 8.1 : 1, 94% *ee* (85%)

9Aj R^2: *i*Pr — No reaction

[a]All reactions were carried out on 0.2 mmol scale with 1.5 equiv. of the ketone and 10 mol% **C5** in CH_2Cl_2 (0.4 mL). Diastereomeric ratios determined by HPLC analysis. Yields of isolated products after column chromatography. The *ee* values of the minor diastereomers are given in parentheses.

The absolute configuration of **6Aa** was determined by X-ray analysis and for the remaining adducts was established by assuming a uniform reaction mechanism (Figure 17).

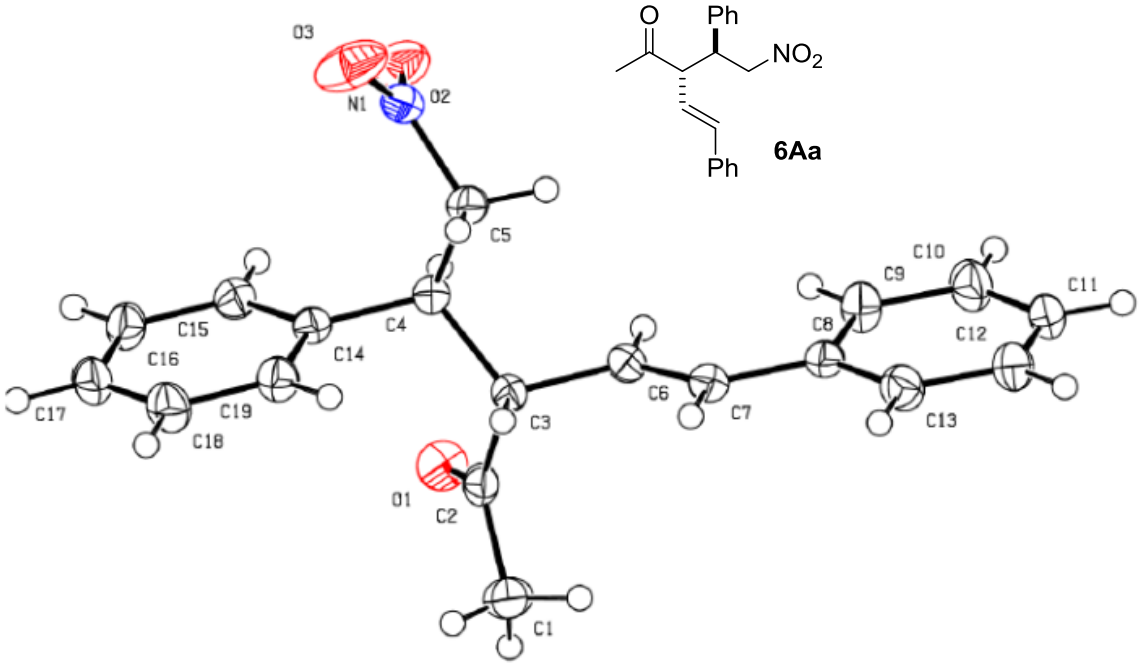


Figure 17. ORTEP diagram of compound **6Aa**.

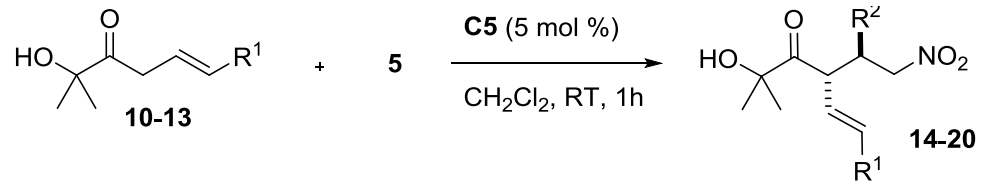
At this stage we decided to extend this method to β´,γ´-unsaturated α-hydroxy ketones **10**-**13**. α-Hydroxy ketones can be smoothly transformed into carboxylic acids through oxidative cleavage, and our group has developed a number of metal- and organocatalysed methodologies based on the use of α-hydroxy enones as acrylate surrogates.[98] Given these precedents, successful implementation of the present reaction to unsaturated hydroxyl ketones **10**-**13** would constitute a formal expansion of the methodology to carboxylic acids, which remain elusive substrates so far owing to their attenuated pK_a.

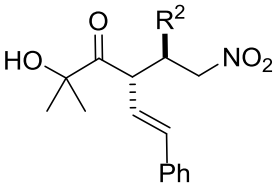
Gratifyingly, reactions of the unsaturated ketols **10**-**13** with nitroolefins **5** in the presence of **C5** led to the corresponding α-addition adducts **14**-**20** in high yield, essentially full diastereoselectivity, and enantioselectivities that were typically greater

[98] a) For a review on α´-hydroxy ketones as templates, see: Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150−4164. b) Badiola, B.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881. c) Palomo, C.; Oiarbide, M.; García, J. M. **2019**, 4-Hydroxy-4-methylpent-1-en-3-one. *Encyclopedia of Reagents for Organic Synthesis*.

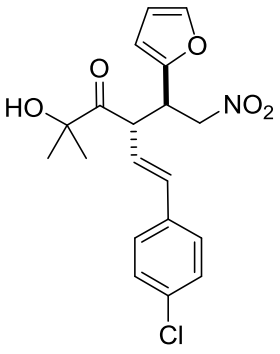
than 95% (Table 3). The use of the ketol moiety notably increases the reactivity of the process, as the reaction now tolerates aliphatic nitroolefins as acceptors (adduct **20**), and is completed in 1 h, with only 5 mol% catalyst. These results, especially the high diastereomeric ratios, might be related to the strong preference for *Z* enolate formation from these bulky ketols, as the corresponding *E* enolates would present destabilizing 1,3-allylic interactions (Scheme 42).

Table 3. Catalytic reactions with ketols **10**-**13**.

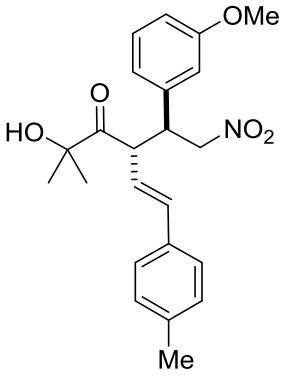




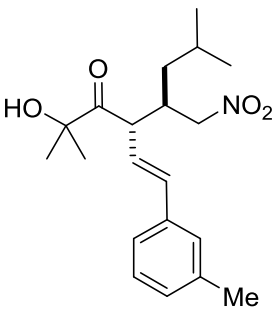
14 R_2: Ph 85%, dr >20:1, 97% *ee*
15 R_2: 4-MeC_6H_4 79%, dr >20:1, 96% *ee*
16 R_2: 4-ClC_6H_4 82%, dr >20:1, 95% *ee*
17 R_2: 4-$MeOC_6H_4$ 75%, dr >20:1, 94% *ee*



18 87%, dr >20:1, 98% *ee*

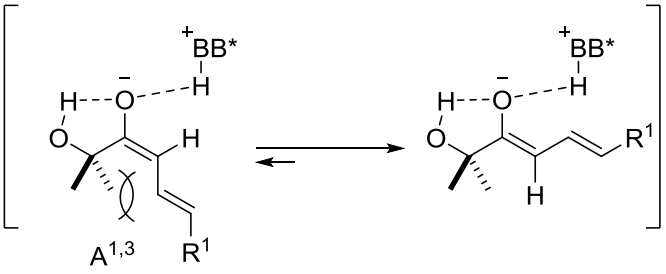


19 75%, dr >20:1, 90% *ee*



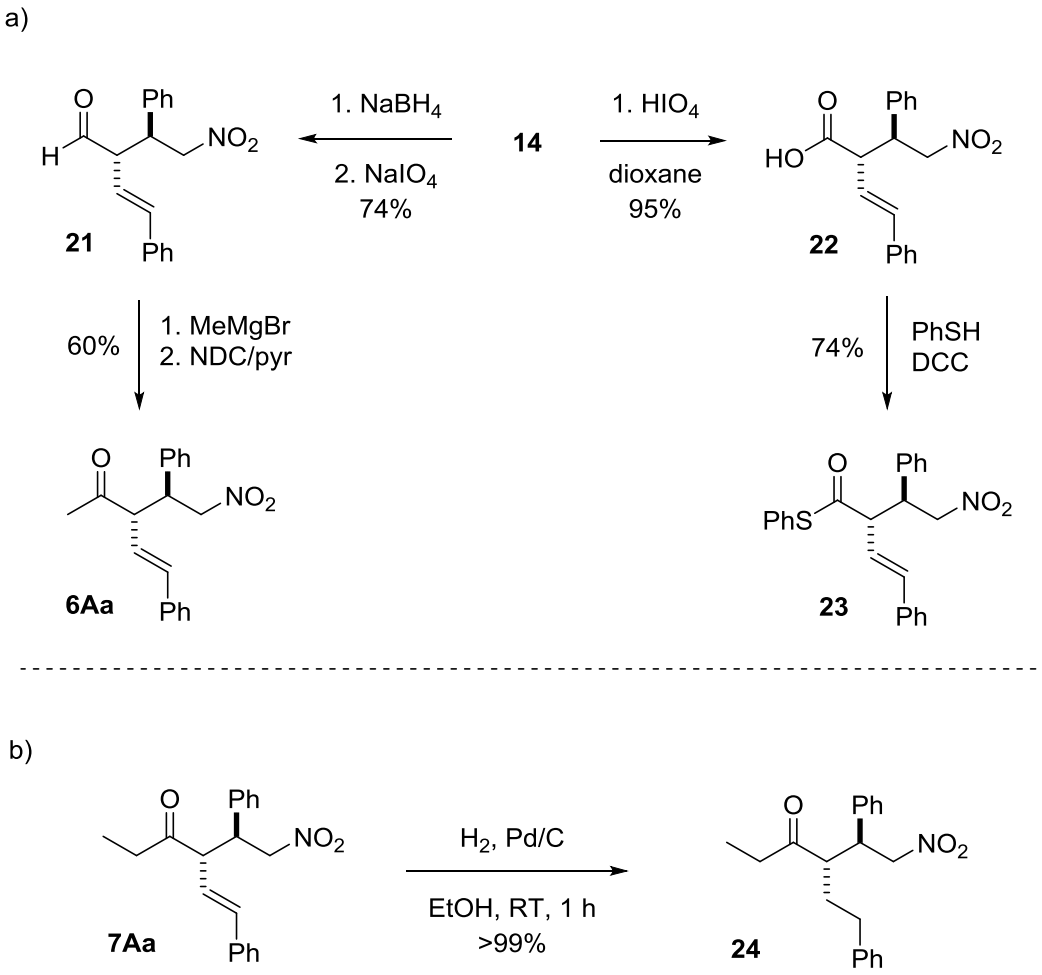
20 82%, dr >20:1, 98% *ee*[b]

[a]All reactions were carried out on 0.2 mmol scale with 1.1 equiv. of the nitroolefin and 5 mol% **C5** in CH_2Cl_2 (0.4 mL). Diastereomeric ratios determined by ^1H NMR analysis of crude samples. Yields of isolated products after column chromatography are given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b]After 16 h.



Scheme 42. Control over enolate *E*/*Z* geometry.

A few possible transformations of adducts were evaluated. On the one hand, adduct **14** was easily transformed, by reduction and subsequent diol oxidation, into aldehyde **21**, which was later converted into ketone **6Aa**, thus confirming the stereochemical assignment. Alternatively, **14** can also be converted into thioester **23** through oxidative cleavage of the α-ketol moiety and coupling of the resulting carboxylic acid **22** with thiophenol with acetone as the only organic sideproduct in the process. In every case, the reactions were clean and proceeded without double-bond isomerization or epimerization (Scheme 43a).



Scheme 43. Elaboration of the adducts.

On the other hand, the selective reduction of the double bond would provide products that are formally derived from the catalytic asymmetric α-functionalization of nonsymmetric aliphatic ketones, a yet unrealized transformation in direct fashion. For example, exposure of **7Aa** to H_2 over Pd on charcoal provided compound **24** almost quantitatively (Scheme 43b).

2.2.2. Trienolates

Given the promising results obtained with dienolates, and intrigued by the fact that no catalytic and asymmetric direct functionalization of trienolates is documented, we decided to explore the suitability of the methodology for trienolate mediated reactions.

For first assessment of the reactivity associated with trienolates we asked for assistance to theoretician Dr. Enrique Gómez-Bengoa, who in collaboration with PhD student Giovanna Zanella determined the charge distribution and Fukui nucleophilicity indexes (f-)[99] at the relevant carbon atoms of **I** and the corresponding trienamine **II** computationally.[100] As data in Figure 18 show, the largest (most negative) Fukui index corresponds to the α-carbon on both the trienolate **I** and tetramethylammonium salt **II**, suggesting a nucleophilicity decreasing in the order Cα > Cγ > Cε. This steady charge decay with increasing distance to the carbonyl center is not shown in the case of trienamine **III**, for which the highest calculated electronic charge corresponds to the γ-carbon. This last result would be in agreement with the γ- and γ,ε-reactivities observed experimentally for trienamines. At the same time, these data were encouraging in favour of a α-selectivity preference from trienolates.

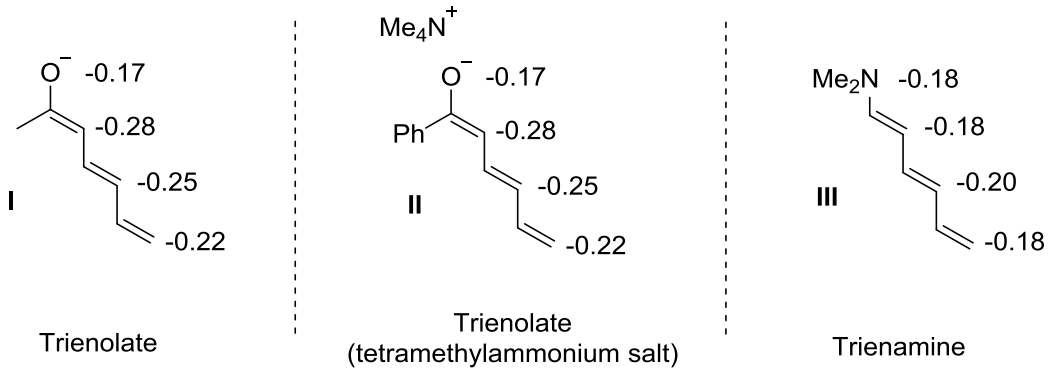


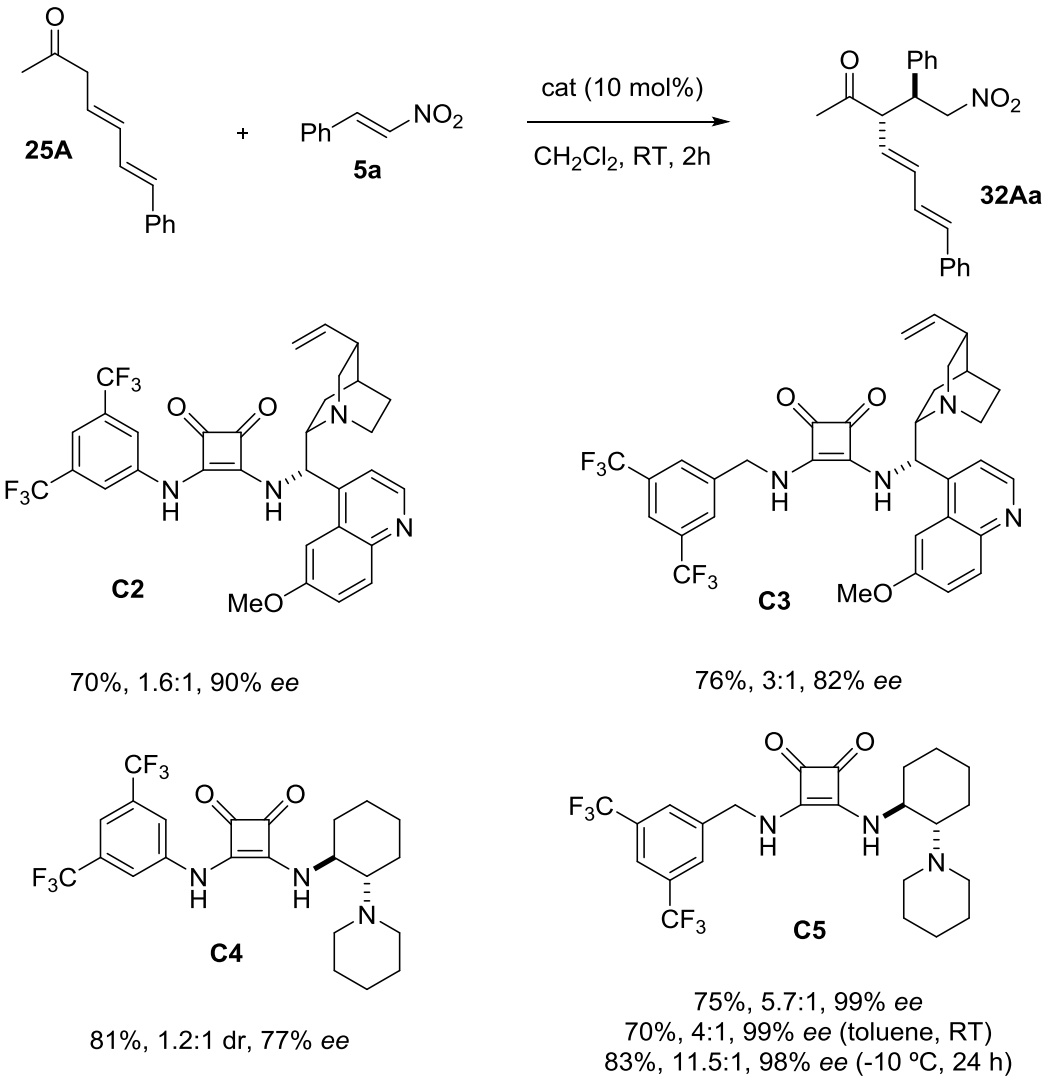
Figure 18. Fukui indices of relevant atoms in selected trienolate and trienamine systems.

We commenced the experimental study by evaluating several available bifunctional Brønsted base catalysts for the reaction between doubly unsaturated methyl ketone **25A** and nitrostyrene **5a**. Concordant with the above prediction, product **32Aa** arising from attack through Cα of the ketone was obtained exclusively, although with variable diastereo- and enantioselectivity. As indicated in Table 4, with 10 mol% **C4** as the catalyst the reaction proceeded smoothly affording a 1.2:1 mixture of diastereomers in moderate enantioselectivity. Both diastereo- and enantioselectivity increased significantly with catalyst **C5**, leading to product **32Aa** in 75% isolated yield, a diastereomeric ratio of 5.7:1 and 99% *ee* for the major diastereomer. Lowering the

[99] The Fukui functions were calculated from the NBO charge distribution a) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708−5711. b) Ayers, P. W., Yang, W.; Bartolotti, L. J. *The Fukui Function in Chemical Reactivity Theory: A Density Functional View,* Taylor & Francis: Boca Raton, FL, **2009**, pp 255−267.
[100] DFT calculations were carried out with the Gaussian16 set of programs and the M06-2X functional.

temperature to −10 °C improved the selectivity, affording very good yield (83%) and selectivity (dr 11.5:1, 98% *ee*). These figures were not surpassed with the corresponding cinchona-derived catalysts **C2** and **C3**, both providing yields and selectivities better than **C4**, but worse than **C5**.

Table 4. Catalyst screening for the addition of **25A** to **5a** leading to **31Aa**.[a]

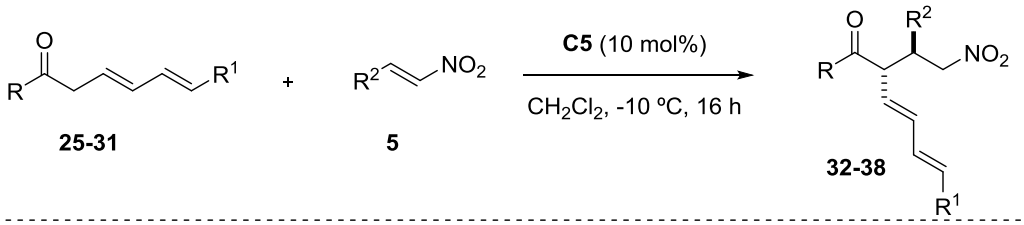


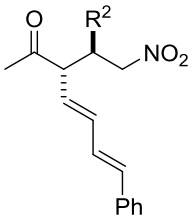
[a]Reactions carried out on 0.2 mmol scale, with **25** (1.5 equiv.) and catalyst (10 mol%) in CH_2Cl_2. Diastereomeric ratio and *ee* values determined by HPLC analysis on a chiral stationary phase. The *ee* values of the major diastereomers are given.

With **C5** selected as the best catalyst for the model reaction, a series of enolizable dienones were tested for the above reaction with nitroalkenes. As shown in Table 5, various nitroalkenes with electron rich (**5b** and **5d**) and poor β-aryl (**5k**) substituents reacted equally well with dienone **25A**. *o*-Chloronitrostyrene **5e** led to slightly

diminished diastereoselectivity and enantioselectivity (4.3:1 dr, 94% *ee*). The reaction tolerated β-alkyl substituted nitroalkenes as well, affording adducts **32Al** and **32Ai** as a mixture of diastereomers although with high enantioselectivity. Phenyl ketone **26**, or tolyl ketone **27** and **28** behaved uniformly well, affording adducts **33A**, **34Aa** and **35Aa** in good yield and high diastereo- (7.3:1-15.7:1 dr) and enantioselectivity (88->99% *ee*). As the results associated with products **33B** illustrate, aliphatic groups attached at the distal carbon are well tolerated too. Finally, high yields and selectivities were attained with the corresponding ethyl, phenethyl and cyclohexyl ketones **29**, **30** and **31**, which, once again, afforded the α-addition products exclusively, without detecting any α´-addition side product formation either. It could be expected that isomerization of the double bonds of adducts **32**-**38** would be possible under this reaction conditions, after deprotonation. However, adducts **32**-**38** are stable in the presence of 10 mol% of squaramide-type catalyst **C5**.

Table 5. Substrate scope of the **C5**-catalysed reaction between ketones **25**-**31** and nitroalkenes **5**.[a]





32Aa R^2: C_6H_5 83%, 11.5:1 dr, 98% *ee*

32Ab R^2: 4-$MeOC_6H_4$ 78%, 15.7:1 dr, 96% *ee*

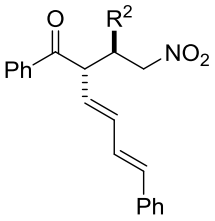
32Ak R^2: 4-ClC_6H_4 76%, 13.3:1 dr, > 99% *ee*

32Ad R^2: 3-MeC_6H_4 76%, >20:1 dr, 98% *ee*

32Ae R^2: 2-ClC_6H_4 70%, 4,3:1 dr, 94% *ee*

32Al R^2: $CH_3(CH_2)_2$ 83%, 1.3:1 dr, 95% *ee*

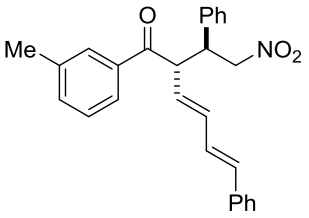
32Ai R^2: *i*Bu 72%, 1.4:1 dr, 94% *ee*



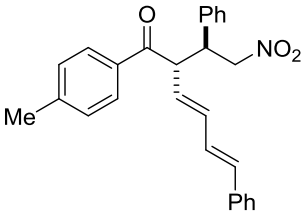
33Aa R^2: C_6H_5 80%, 9:1 dr, 90% *ee*[b]

33Ab R^2: 4-$MeOC_6H_4$ 75%, 10.1:1 dr, 92% *ee*[b]

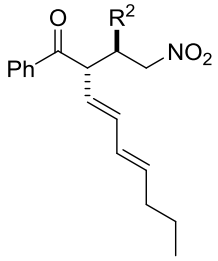
33Ad R^2: 3-MeC_6H_4 69%, 9:1 dr, 90% *ee*[b]



34Aa 76%, 13.3:1 dr, 96% *ee*[b]

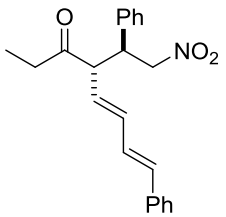


35Aa 87%, 10.1:1 dr, 92% *ee*[b]

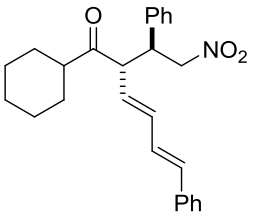


33Bb R^2: 4-$MeOC_6H_4$
82%, 15.7:1 dr, 96% *ee*

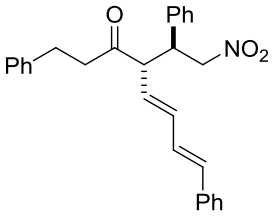
33Bd R^2: 3-MeC_6H_4
75%, 7.3:1 dr, 88% *ee*



36Aa 85%, 11.5:1 dr, > 99%



37Aa 85%, 9:1 dr, 94% *ee*



38Aa 74%, 5.7:1 dr, 96% *ee*

[a]Reactions carried out on 0.2 mmol scale, with 1.5 equiv. of **25**-**31** and 10 mol% of **C5** in 0.4 mL CH_2Cl_2. Diastereomeric ratio and *ee* values determined by HPLC analysis on a chiral stationary phase on the crude material. The *ee* values of the major diastereomers are given. Yields of isolated product. [b]Reactions carried out at -20 ºC.

The absolute configuration of adducts **32Ak** was determined by X-ray analysis and for the remaining adducts was established by assuming a uniform reaction mechanism (Figure 19).

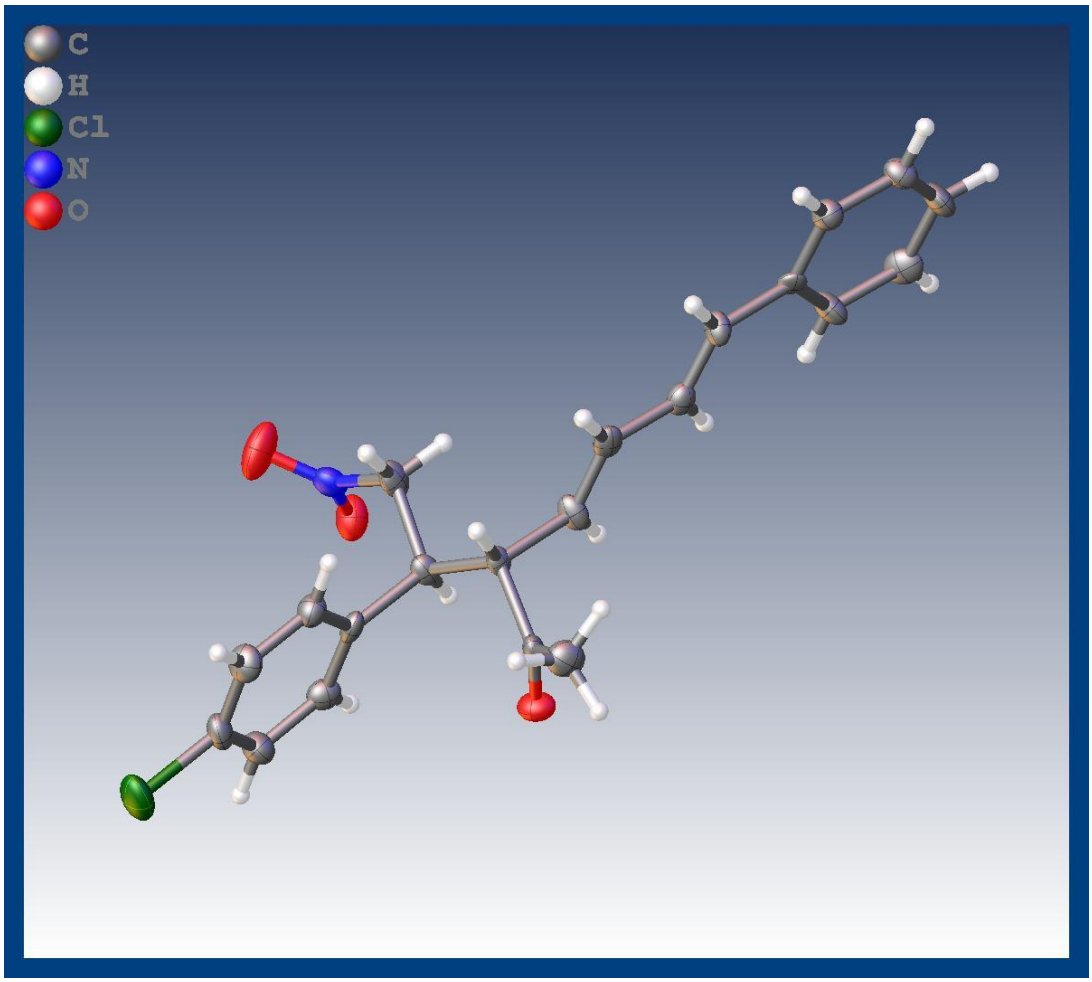


Figure 19. X-Ray image for compound **32Ak**.

2.2.3. Trienolate mediated synthesis of tetrasubstituted cyclohexenes

We hypothesized that the adducts obtained in these trienolate mediated Michael reactions could potentially be precursors of cyclohexenes upon base-catalysed isomerization of the double bonds and subsequent intramolecular 1,6-addition (Figure 20).

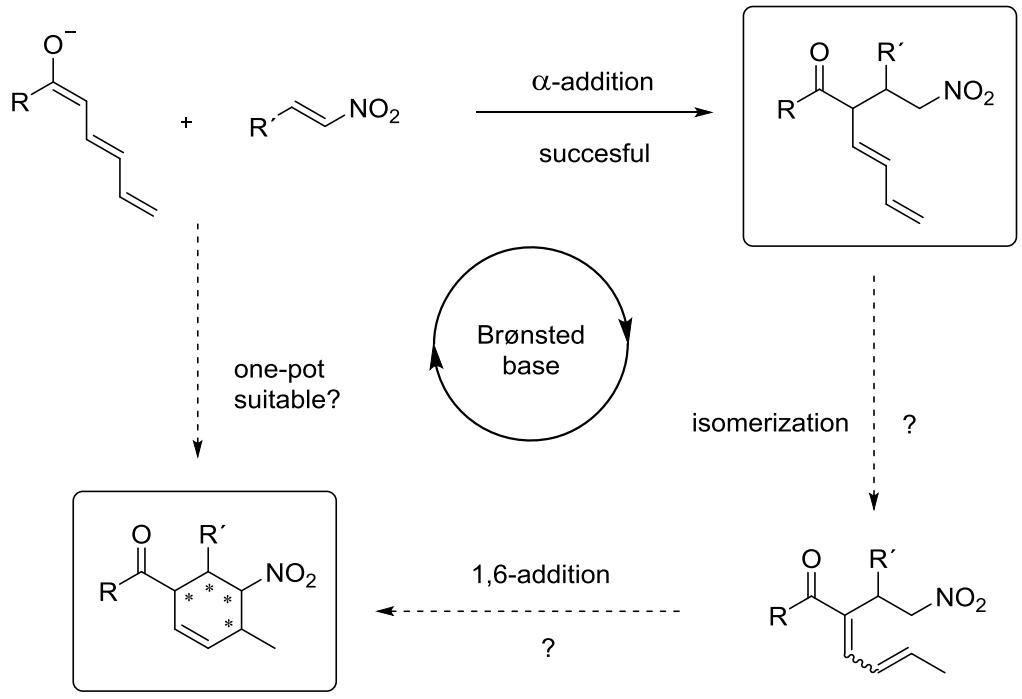
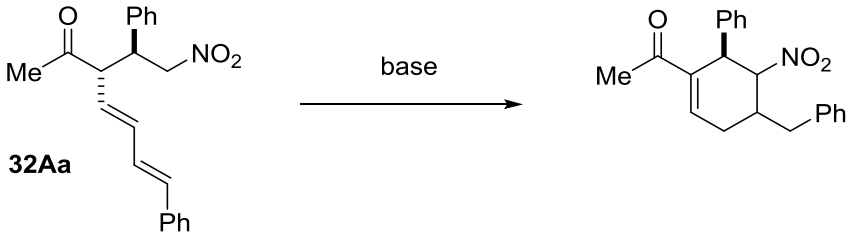
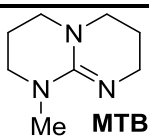
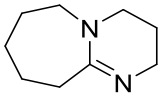


Figure 20. Working hypothesis for the trienolate mediated synthesis of cyclohexenes.

Although several bases were tested to evaluate the likelihood of this idea (Table 6), the isomerization of adduct **32Aa** and subsequent cyclization did not take place.

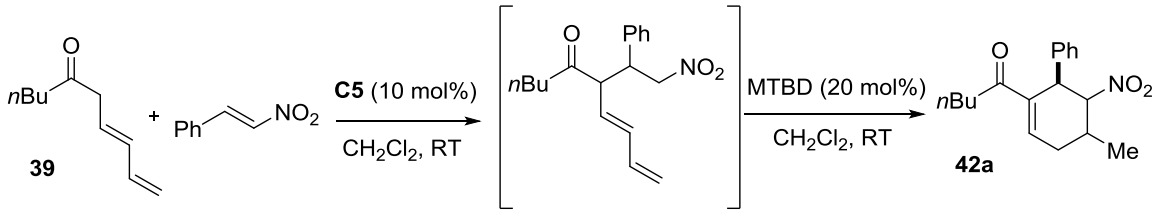
Table 6. Attempted base-promoted carbocyclization of adducts **32Aa** and **39**.



Base (mol %)		Solvent	T (ºC)	t (h)	Conv. (%)
 **MTBD**	(20 mol%)	CH_2Cl_2	RT	16	0[b]
	(50 mol%)	Toluene	40	24	0[b]
Et_3N **(1 equiv.)**		CH_2Cl_2	RT	16	0[b]
 **DBU**	(1 equiv.)	CH_2Cl_2	RT	16	0[b]
LDA **(20%)**		THF	-78	2	0[c]

[a]Reactions conducted on a 0.2 mmol scale. [b]Starting material was recovered. [c]Starting material decomposes.

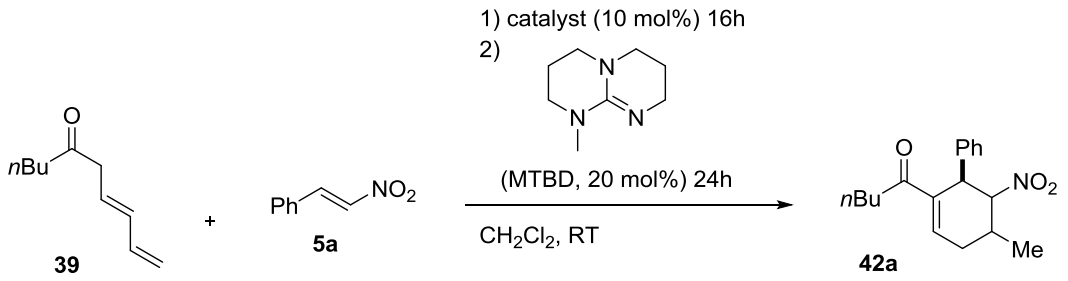
A different behaviour was found when dienone **39** was used. After α-functionalization using bifunctional Brønsted base/H-bond donor catalyst **C5**, isomerization of the adduct could be promoted by guanidine MTBD (20 mol%) to obtain cyclohexene **42a** (Scheme 44).

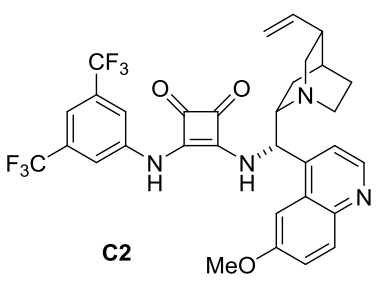


Scheme 44. Synthesis of cyclohexene **42a** via α-functionalization and posterior cyclization starting from dienone **39**.

As data in Table 7 show, catalysts **C2**-**C5** promoted the α-selective functionalization of **39** with nitroolefin **5a** in 16 h at room temperature. Next, MTBD was added to the reaction mixture to promote isomerization of the adduct, to obtain cyclohexene **42a** as an essentially single diastereomer. The enantioselectivity of the process was strongly dependent on the catalyst, and the best results were obtained with catalyst **C3**.

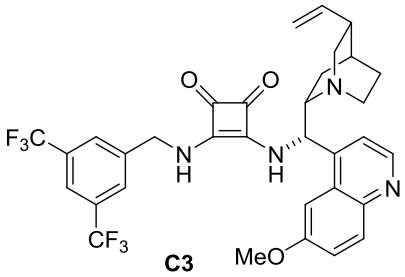
Table 7. Catalyst screening for the addition of **39** to **5a** leading to **42a**.[a]





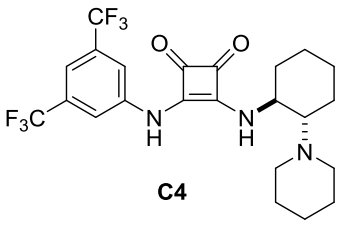
C2

79%, >20:1 dr, 80% *ee*



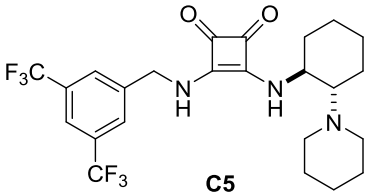
C3

71%, >20:1 dr, 93% *ee*



C4

76%, >20:1 dr, 72% *ee*



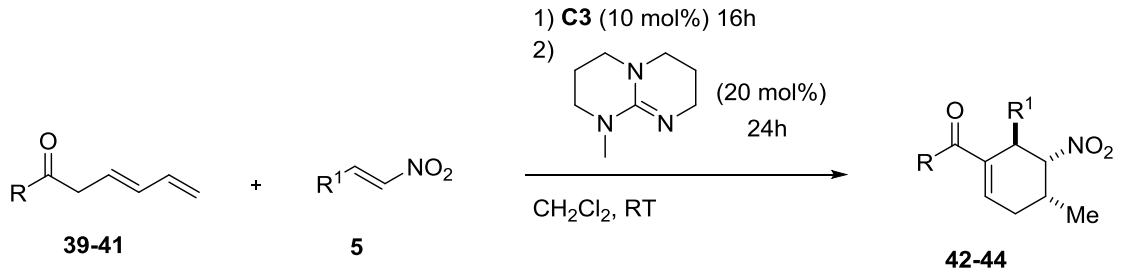
C5

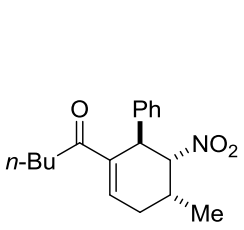
75%, >20:1 dr, 90% *ee*

[a]Reactions carried out on 0.2 mmol scale, with **39** (1.2 equiv.) in CH_2Cl_2 (0.2 mL). Diastereomeric ratio determined by ^1H NMR analysis and *ee* values determined by HPLC analysis on a chiral stationary phase.

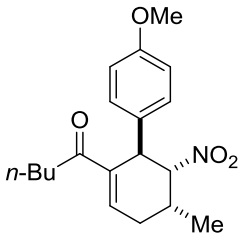
Next, we investigated the behaviour of ketones **39**-**41** under the above optimized conditions. As shown in Table 8, the reaction of unsaturated ketone **39**-**41** with nitrostyrenes **5** in the presence of 10 mol% catalyst **C3** was stirred for 16h to afford the α-substituted adducts, which were treated with 20 mol% MTBD for 20h, to afford adducts **42**-**44** as a single diastereomer in good yields and enantioselectivities. The regio- and stereochemical outcome of this catalytic reaction proved to be essentially independent of the length of the aliphatic R substituent in the ketone, and branched chains are also tolerated in the reaction as adduct **44a** was obtained in 68% yield and 92% *ee*.

Table 8. Substrate scope of the **C3** and MTBD catalysed reaction between ketones **39**-**41** and nitroalkenes **5**.[a]

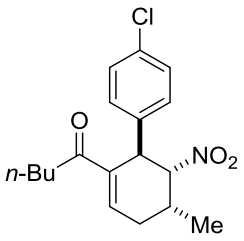




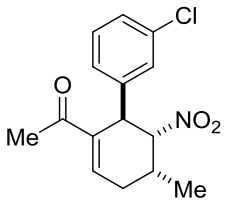
42a 71%, >20:1 dr, 93% *ee*



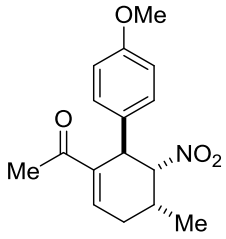
42b 77%, >20:1 dr, 90% *ee*



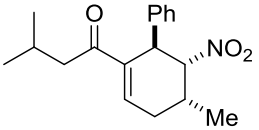
42k 75%, >20:1 dr, 94% *ee*



43m 69%, >20:1 dr, 90% *ee*



43b 78%, >20:1 dr, 93% *ee*



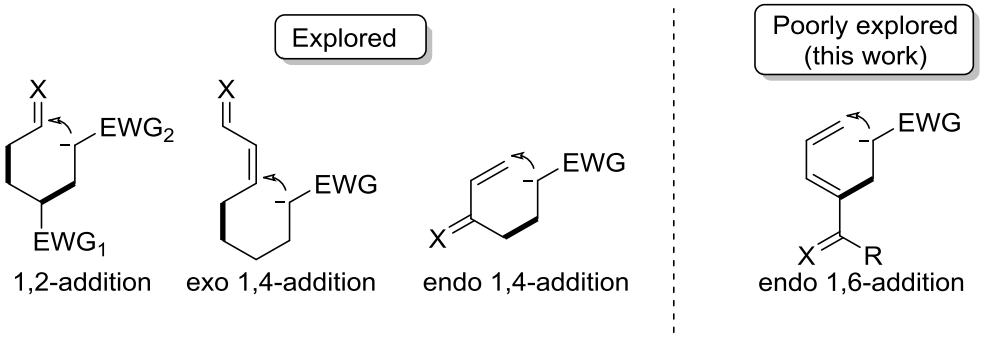
44a 68%, >20:1 dr, 92% *ee*

[a]Reactions carried out on 0.2 mmol scale, with **39**-**41** (1.2 equiv.), **C3** (10 mol%) and MTBD (20 mol%) in 0.4 mL CH_2Cl_2. Diastereomeric ratios determined by ^1H NMR analysis and *ee* values determined by HPLC analysis on a chiral stationary phase. Yields of isolated product.

This methodology constitutes of a catalytic and stereoselective one-pot construction of six-membered carbocycles that ends up with a rare[101] intramolecular 1,6-addition[102]

[101] A few carbocyclations through intramolecular 1,6-addition using stoichiometric base mainly, are known: a) Nara, S.; Toshima. H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6745−6748. b) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509−9524. c) Gray, D.; Gallager, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 2419−2423. d) Gallager, T.; Derrick, I.; Durkin, P. M.; Haseler, C. A.; Hirschhäuser, C.; Magrone, P. *J. Org. Chem.* **2010**, *75*, 3766−3774. e) He, Y.; Wu, D.; Li, Z.; Roebeyns, K.; Van Meerveltd, L.; Van der Eycken, E. V. *Org. Biomol. Chem.* **2019**, *17*, 6284−6292. Catalytic intramolecular 1,6-additions have been reported in the context of *o*- and *p*-quinone methides mainly: f) Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 12104−12108. g) Zhang, X. Z.; Gan, K. J.; Liu, X. X.; Deng, Y. H.;

step. Before this work, intramolecular nucleophilic ring-closing approaches relied on: the intramolecular 1,2-addition,[103] and the *exo* and *endo* variants of intramolecular 1,4-addition (Scheme 45).[104]



Scheme 45. Main ring-closing strategies for the construction of six-membered carbocycles and the actual work.

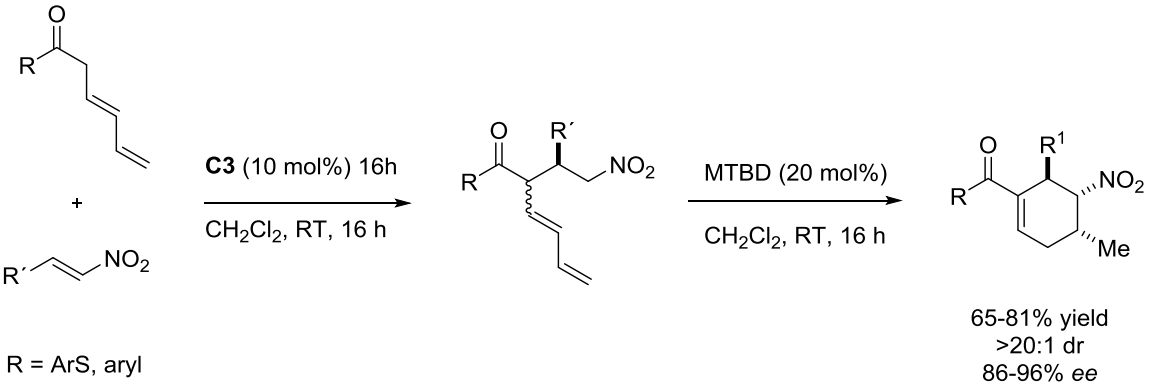
The suitability of this Brønsted base-catalysed one-pot access to cyclohexene systems *via* in-situ generated trienolates demonstrated to be not limited to doubly unsaturated alkyl ketones **39**-**41**, but also applicable to other unsaturated carbonyl compounds. In this regard, parallel experiments carried out by Olatz Olaizola[92] demonstrated that the reaction also tolerates thioesters and aryl ketones under similar conditions. As shown in Scheme 46 the desired cyclohexenes were obtained in very good yields and enantioselectivities, and essentially as a single diastereomer. The absolute configuration of the adducts was primarily established by X-ray analysis of thioester **45a** and by assuming a uniform reaction mechanism (Figure 21). Prior to the addition of MTBD to the reaction mixture, the α-addition product could be isolated (work done by Olatz Olaizola). This reinforces the hypothesis that the cycloadducts are formed through an intramolecular 1,6-addition.

Wang, F. X.; Yu, K. Y.; Zhang, J.; Fan, C. A. *Org. Lett.* **2017**, *19*, 3207−3210. h) Ye, Z.; Bai, L.; Bai, Y.; Gan, Z.; Zhou, H.; Pan, T.; Yu, Y.; Zhou, J. *Tetrahedron* **2019**, *75*, 682−687.

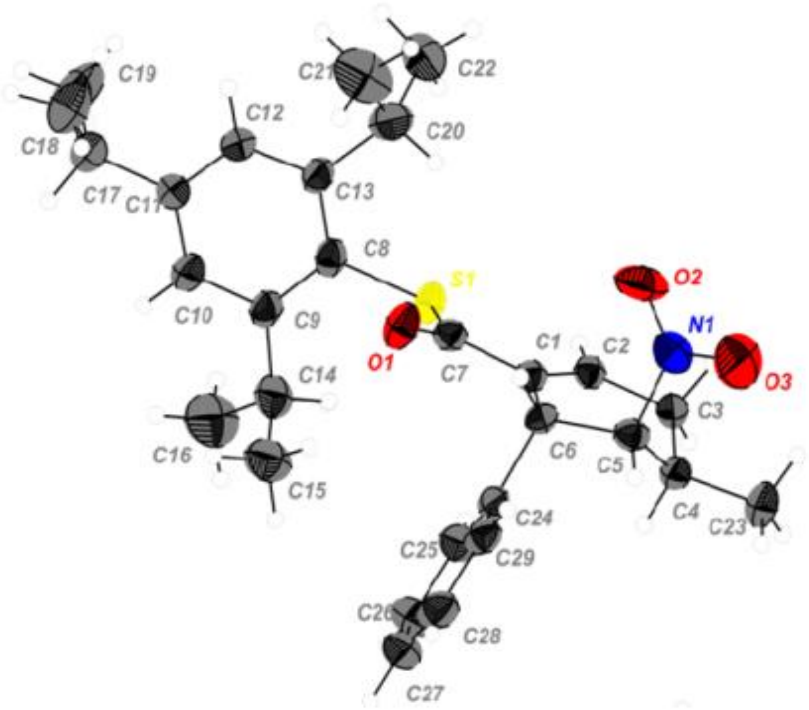
[102] Reviews on conjugate 1,6-additions: (General) a) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109−3128. b) Csáky, A. G.; Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080−4102. (Organocatalytic) c) Biju, A. T. *ChemCatChem* **2011**, *3*, 1847−1849.

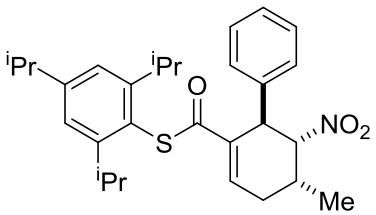
[103] Selected examples of formation of six-membered carbocycles with a 1,2-adition ring-closing step: a) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951–6954. b) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226–4228. c) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *44*, 861–863.

[104] Selected examples of formation of six-membered carbocycles with a 1,4-adition ring-closing step: (*exo*) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3732–3734. (*endo*) McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*, 6309–6319.



Scheme 46. Catalytic enantioselective one-pot synthesis of tetrasubstituted cyclohexane from thioesters and aryl ketone trienolates and nitroolefins.[92]



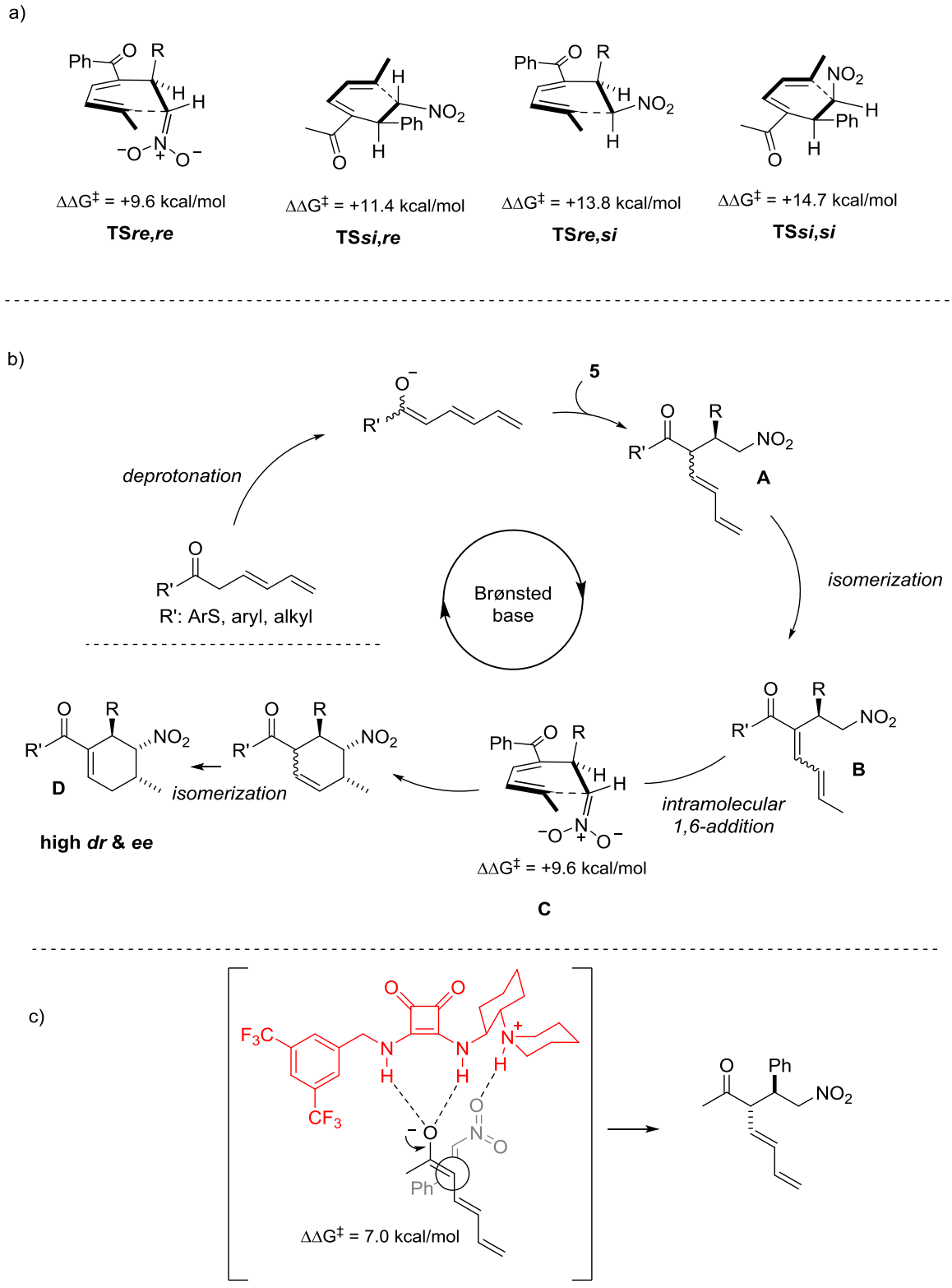


45a (1*R*, 5*R*, 6*R*)

67%, d.r.: >20:1, 95% *ee*

Figure 21. ORTEP diagram of compound **45a**.[92]

To get further insights about the factors that govern the high stereocontrol of the process, the energies of the TS for the carbocyclization step in its four possible nitronate-dienone approaching trajectories were calculated by Giovanna Zanella and Dr. Enrique Gómez-Bengoa. 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 other three possible approaches (Scheme 47a), in good agreement with the high diastereocontrol observed experimentally. Scheme 47b shows a plausible reaction sequence including two C−C bond forming events and two isomerizations that would account for the observed one-pot formation of tetrasubstituted cyclohexenes. First, the α-selective addition to the nitroolefin **5** is promoted by catalyst **C3** to obtain the Michael adduct **A.** Among the calculated transition states, the one showed in Scheme 47c has the lowest activation barrier, and correctly predicts the formation of *S*,*S*-product as major isomer.[100] Next, base-promoted isomerization of the double bonds would afford adduct **B** that would undergo intramolecular 1,6-addition through transition state **C** to obtain the ring-closing product which, in its turn, undergoes subsequent C=C double bond isomerization yielding the final α,β-unsaturated cyclohexenes **D**. It is noteworthy that the diastereomeric ratios are independent of the chiral catalyst used (Table 7), which could indicate that the diastereomeric outcome of the cyclisation process is substrate controlled.



Scheme 47. a) Activation energies of the transition states for the 1,6-intramolecular addition. b) Plausible course of the one-pot reaction sequence. c) Calculated Transition State for the addition of trienolates to nitroolefins.

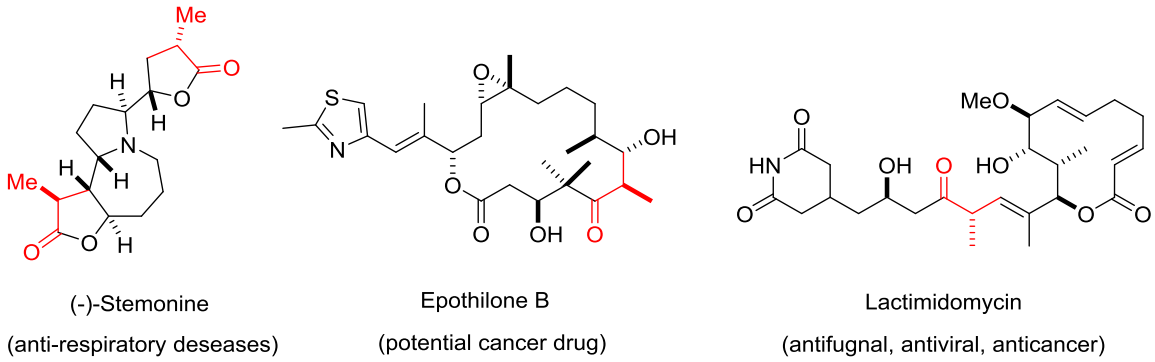
Chapter 3

α-Substituted α´-Oxyenones as Methacrylate Equivalents in Organocatalytic Asymmetric Michael Reactions

3. α-Substituted α´-Oxyenones as Methacrylate Equivalents in Organocatalytic Asymmetric Michael Reactions

3.1. Introduction

α-Branched aldehydes, ketones, and carboxylic acid, and derivatives are present in a number of natural products and biologically active compounds (Figure 22). In many cases such molecules are accessible from natural sources (Natural Products) directly; however, these sources rarely get sufficient for quantity, reliability or structural variation/optimization reasons. As a consequence, chemical synthesis becomes necessary and important efforts have been made for the construction of these moieties in an enantioselective manner.



(-)-Stemonine
(anti-respiratory deseases)

Epothilone B
(potential cancer drug)

Lactimidomycin
(antifugnal, antiviral, anticancer)

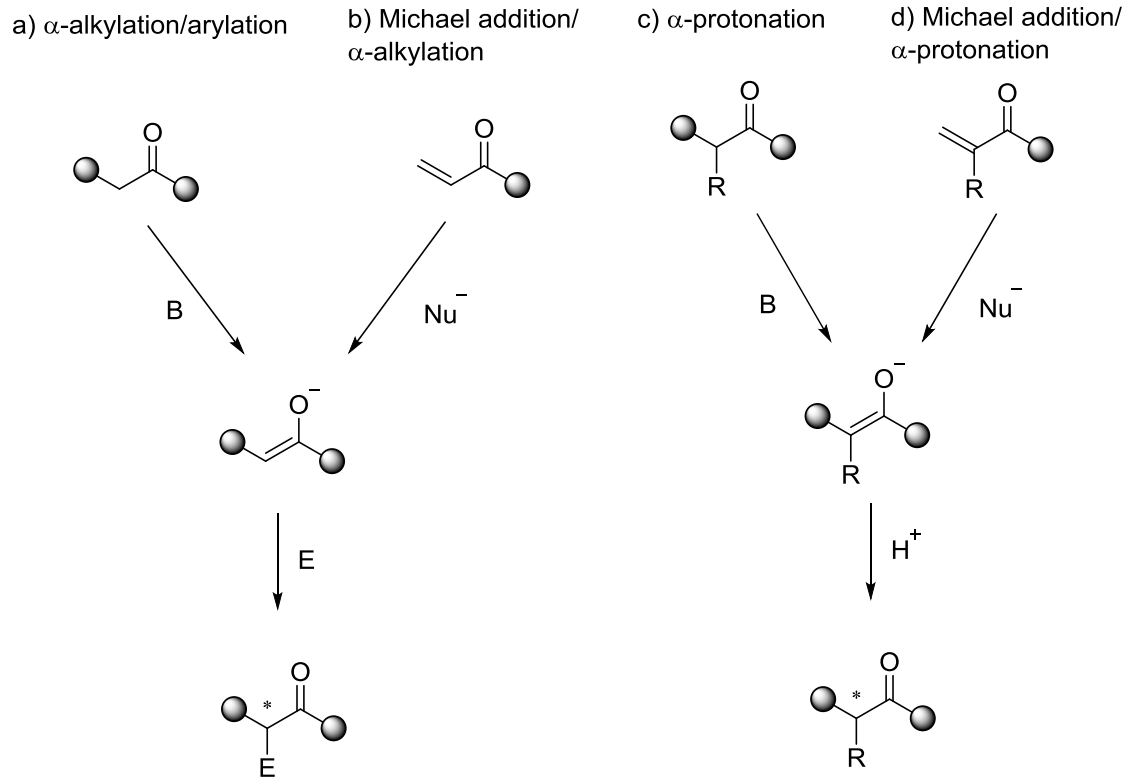
Figure 22. Representative examples of biologically active compounds bearing an α-alkylcarbonyl unit.

3.1.1. Organocatalytic asymmetric Michael addition/α-protonation processes for the construction of α-alkylcarbonyl units

Many possible synthetic routes can be proposed to target such structures. One of the most straightforward method to obtain α-alkylcarbonyl compounds involves intermediate enolate or equivalent species (Scheme 48). On the one hand, enolizable carbonyl compounds can be enantioselectively alkylated in the α-position after deprotonation under appropriate conditions (Scheme 48a). On the other hand, α-

alkylcarbonyl units can also be formed by stereoselective protonation of prostereogenic enolates (Scheme 48c).[105]

Intermediate enolates can also be generated through Michael addition of a nucleophile to an α,β-unsaturated carbonyl compound allowing a domino addition-enolate trapping process for the synthesis of more complex α-branched molecules containing multiple stereocenters (Scheme 48b and 1d).

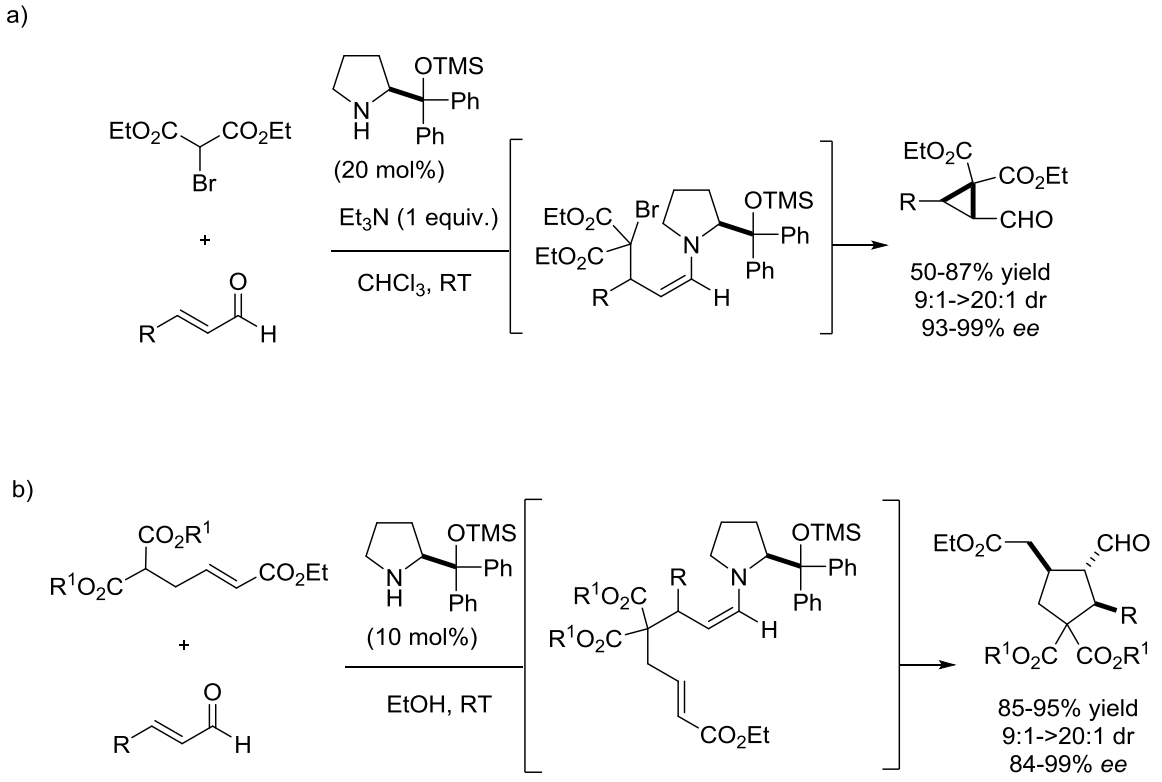


Scheme 48. Main synthetic routes for the construction of α-alkylcarbonyl units.

Many *organocatalytic Michael addition/α-alkylation* domino processes have been described in the literature. In particular, domino reactions where the α-alkylation involves a cyclization reaction have been mostly reported. For example, Córdova and co-workers developed a chiral amine catalysed enantioselective cyclopropanation reaction between α,β-unsaturated aldehydes and 2-bromomalonates involving intermediate

[105] For reviews on enantioselective protonation, see: a) Fehr, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2566−2587. b) Weerasooriya, N.; Eames, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1−24. c) Duhamel, L.; Duhamel, P.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653−3691. d) Levacher, V.; Oudeyer, S.; Brière, J. F. *Eur. J. Org. Chem.* **2014**, 6103–6119.

enamine species (Scheme 49a).[106] In 2007, Wang and co-workers reported an organocatalytic route to cyclopentanes based on asymmetric double Michael reactions (Scheme 49b).[107]



Scheme 49. Selected examples of cyclopropanation and cyclopentanation reactions via domino Michael/α-alkylation processes.

Conversely, organocatalyst-promoted *Michael addition/α-protonation* domino processes in which an α-stereocenter is generated are few. In 2011, Luo and co-workers described the first conjugate addition/enantioselective protonation cascade via enamine intermediates. The primary amine catalysed Friedel-Crafts reactions between α-substituted indoles, and α-substituted acroleins proceeded with moderate to excellent enantiocontrol (Scheme 50a).[108] In 2013, the same authors extended the method to both aliphatic and aromatic enones with excellent enantioselectivities (Scheme 50b).[109]

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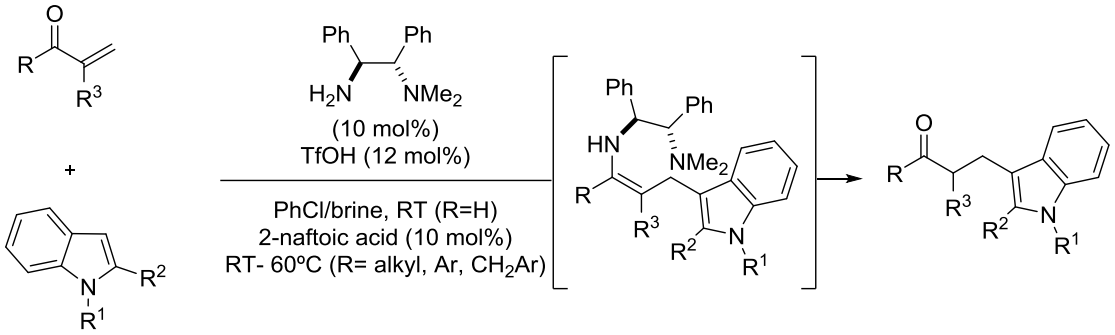
[106] Rios, R.; Sundén, H.; Vesely, J.; Zhao, G. L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Cat.* **2007**, *349*, 1028−1032. For a pioneering work of tandem Michael addition/α-alkylation processes, see: Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475−5479.
[107] Zu, L.; Hao, L.; Xie, H.; Wang, J.; Yang, Y.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3732−3734.
[108] Fu, N.; Zhang, L.; Li, J.; Cheng, J. P.; Luo, S. *Angew. Chem. Int. Ed.* **2011**, 50, 11451−11455.
[109] Fu, N.; Zhang, L.; Cheng, J. P.; Luo, S. *Chem. Eur. J.* **2013**, 19, 15669−15681.



(a)

R= H	R^1= H, Me, Bn R^2= H, alkyl, Ar R^3= Me, n-C_6H_{13}, n-C_7H_{15}, Cy, CH_2Ar, 1-oct-2-enyl	52-90% yield 68-90% *ee*

(b)

R= alkyl, Ar, $ArCH_2$	R^1= H R^2= Me R^3= Me, Et, *n*C_4H_9, $^i C_4H_9$, nC_7H_{15}, Ar, CH_2Ar	72-95% yield 84-91% *ee*

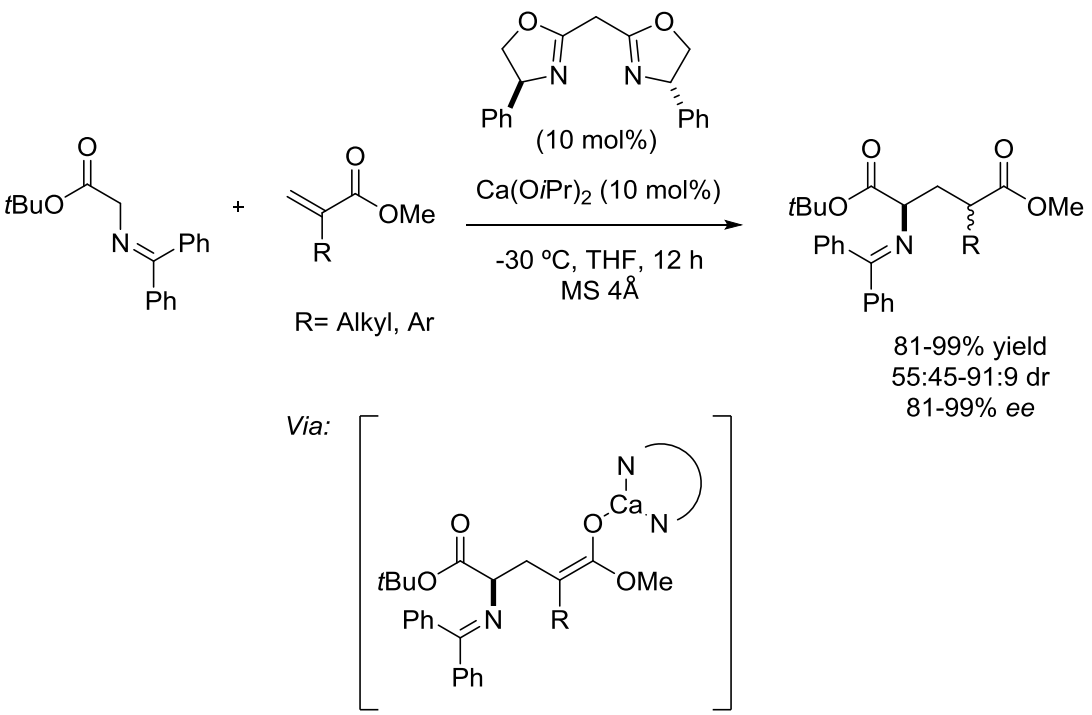
Scheme 50. Organocatalytic Michael addition/α-protonation reaction between α-substituted indoles and α-substituted acroleines.

Since then, some examples of *Michael addition/α-protonation* domino processes have been reported, where the nucleophiles are non-prostereogenic, thus, generating only one stereocenter in the α-position.[110] However, the use of prostereogenic nucleophiles in *Michael addition/α-protonation* domino processes, for the formation of two non-adjacent α,γ-stereocenters, remains less unexplored. Before this Doctoral Thesis, a metal-catalysed Michael addition of prostereogenic nucleophiles to α-carbon substituted enoyl acceptors for the formation of non-adjacent α,γ-stereocenters was reported.[111] Kobayashi described the *Michael addition/α-protonation* tandem reaction between glycine Schiff bases and α-substituted acrylic esters promoted by a chiral calcium complex leading to products in excellent yields and enantioselectivities in most

[110] For selected examples on *Michael addition/α-protonation* domino processes, see: a) Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Chem. Eur. J.* **2012**, *18*, 16297−16301. b) Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992−15995.

[111] Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321−13332.

of the cases. However, diastereomeric ratios were moderate as a consequence of poor stereocontrol during the protonation step (Scheme 51).



Scheme 51. Metal-catalysed Michael addition of proestereogenic nucleophiles to α-carbon substituted esters for the formation of non-adjacent α,γ-stereocenters

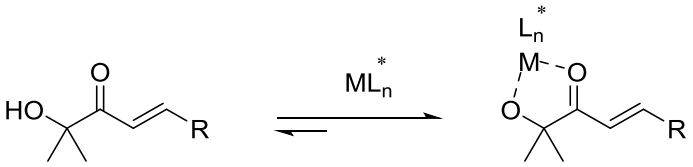
3.1.2. α´-Hydroxy enones as Michael acceptor templates

Selective protonation of prostereogenic enolates is a field of great interest. However, this process has demonstrated to be challenging due to the high reactivity of the smallest element of the Periodic Table, the proton, and the difficulty of controlling the geometry (*Z* or *E*) of the evolving enolate, which leads to bifurcate protonation, and so mixture of stereoisomers. An additional issue in the organocatalytic *Michael addition/α-protonation* processes is the attenuated reactivity of the α-substituted Michael acceptors compared to their α-non-substituted analogues. In this context, the design of an efficient Michael acceptor template, which is able to overcome all of these issues, would be of great interest.

Inspired in prior works by Heathcock[112] and Masamune[113] in the early 80´s, where α´-hydroxy enones were used as chiral auxiliaries in asymmetric C–C bond forming

[112] a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077−7079. b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.*

reactions, some time ago our group revealed that achiral α´-oxy ketones, and in particular α´-hydroxy enones, are efficient carboxylate acrylate surrogates and act as bidentate achiral templates in asymmetric catalysis [Eq. (1)].[114] Not only does this scaffold provide a rigid coordination with the chiral catalyst due to its bidentate nature, but it is also able to undergo cleavage of the C–C ketol/diol system releasing under suitable conditions the corresponding carboxylic acid, aldehyde or ketone product upon demand.



(1)

Our group described several metal catalysed asymmetric reactions involving α´-hydroxy enones, such as copper promoted cycloadditions[115] and 1,4-additions of different nucleophiles (carbamates,[116] pyrroles/indoles (Friedel-Crafts),[117] nitroalkanes[118] and β-ketoesters).[119] Other authors have further proved the validity of metal-catalysed reactions involving α´-hydroxy enones in Michael reactions with diethyl zinc[120] and *N*,*N*-dialkylhydrazones as source of acyl anions (umpolung) or cyanide equivalents have also been described.[121] Chiral NHC promoted catalytic asymmetric reactions[122] and Michael

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1981, *46*, 2290−2300. c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499−2506.

[113] a) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557−558. b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566−1568. c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521−5523.

[114] For a review on α´-hydroxy ketones as templates, see: Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150−4164.

[115] a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942−13943. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155.

[116] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189.

[117] a) See ref. 113b. For an efficient Friedel-Crafts alkylation of indoles with β-aryl α´-hydroxy enones, see: b) Yang, L.; Zhu, Q.; Guo, S.; Quian, B.; Xia, C.; Huang, H. *Chem. Eur. J.* **2010**, *16*, 1638−1645.

[118] Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M.; *Adv. Synth. Catal.* **2006**, *348*, 1161−1164.

[119] Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10*, 2637−2640.

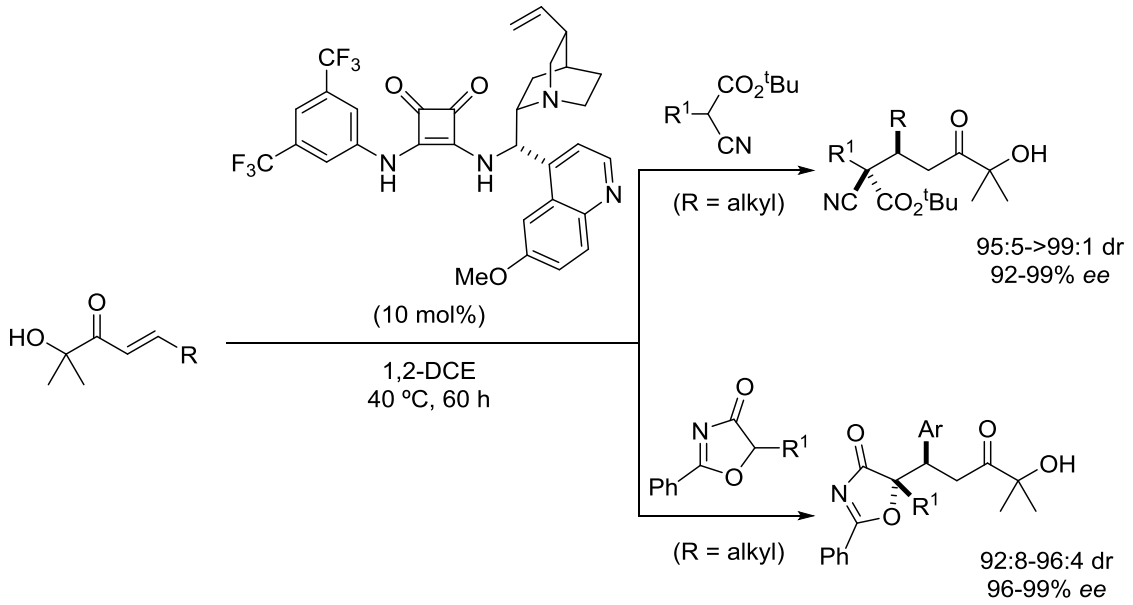
[120] García, J. M.; Gónzalez, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768−8771.

[121] Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 2867−2870.

[122] a) Chiang, P. C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714−8718. b) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378−5381. c) Chiang, P. C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566−4568. d)Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677−680.

additions following a radical pathway[123] involving α´-hydroxy enones have also been reported.

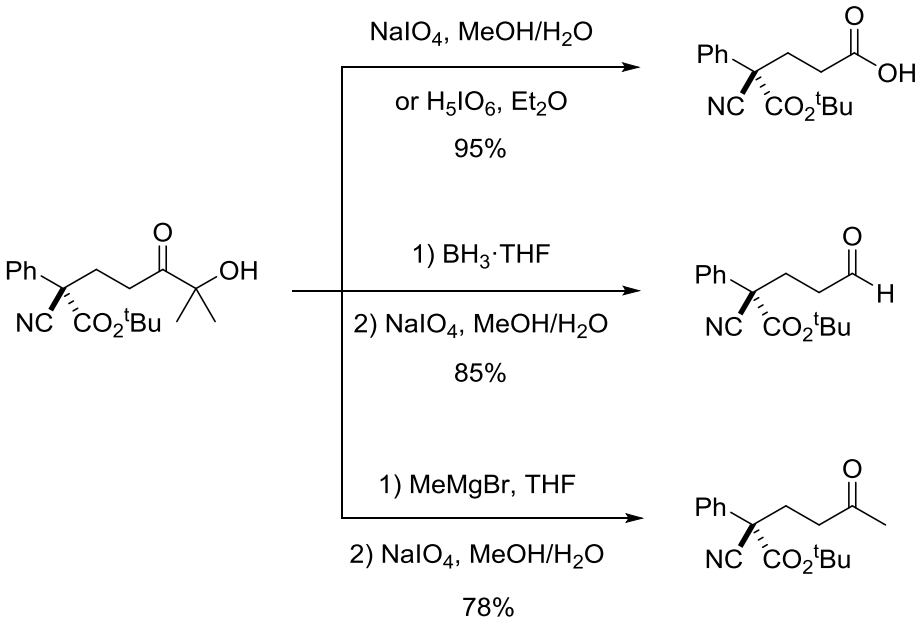
In 2014, our group further extended the utility of this template by describing the first organocatalytic (Brønsted base catalysis) enantioselective Michael reaction of various types of prostereogenic C–nucleophiles (3-substituted oxindoles, α-substituted cyanoacetates, 5H-thiazol-4-ones and 5H-oxazol-4-ones) to α´-oxy enones (Scheme 52). The resulting adducts bearing a γ-tetrasubstituted carbon were obtained with excellent diastereo- and enantioselectivities, including adducts with quaternary-tertiary adjacent stereocenters (Scheme 52).[124]



Scheme 52. Brønsted base-catalysed Michael addition of α-substituted cyanoacetates and oxazolones to β-substituted α´-hydroxy enones.

As mentioned before, some interesting products such as carboxylic acids, aldehydes and ketones can be obtained under smooth oxidative conditions from the Michael adducts bearing these templates (Scheme 53).

[123] Lee, S.; Lim, C. J.; Kim,S.; Subramaniam, R.; Zimmerman, J.; Sibi, M. P. *Org. Lett.* **2006**, *8*, 4311−4313.
[124] Badiola, B.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881.



Scheme 53. Transformation of the Michael adducts coming from the reaction with α,β-unsaturated α´-hydroxy enones.

3.1.3. Asymmetric assembly of all-carbon tertiary/quaternary nonadjacent stereocenters

As illustrated in the previous reaction, the stereoselective synthesis of carbonyl compounds bearing contiguous stereocenters at α,β- or β,γ-positions have been widely investigated (**A** and **B**, Figure 23) In addition, both stereocenters in **A** and **B** are usually stablished simultaneously during formation of the key C−C bond. In contrast, direct asymmetric entries to the α,γ-substituted analogues **C**, with two nonadjacent stereocenters, are less common,[125] and rarely involve construction of a quaternary stereocenter as in **D**.[126,127] Another distinction with respect to **A** and **B** is that most

[125] For selected examples of the synthesis of α,γ-branched Michael adducts, see: a) Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 9058−9061. b) Zheng, B.; Wang, H.; Han, Y.; Liu, C.; Peng, Y. *Chem. Commun.* **2013**, *49*, 4561−4563. c) Moorthy, N. V. G.; Dyapa, R.; Pensare, S. V. *Org. Lett.* **2015**, *17*, 5312−5315.

[126] For classic examples of multistep approaches to α,γ-substituted carbonyl patterns en route to erythromycins, see: a) Corey, E. J.; Hopkins, P. B.; Sung-eun, S. K.; Krishnan, Y.; Nambiar, P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131−7134. b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3215−3217. c) Stork, G.; Rychnovsky, D. R. *J. Am. Chem. Soc.* **1987**, *109*, 1565−1567. d) Mulzer, J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1452−1454. e) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101−103.

[127] For a racemic synthesis of a α,γ-substituted carbonyl pattern with all-carbon quaternary/tertiary nonadjacent stereocenters, see: Fan, J. H.; Wei, W. T.; Zhou, M. B.; Song, R. J.; Li, J. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 6650−6654.

conceivable routes toward **C**/**D** would stablish stereocenters α and β in two independent steps.

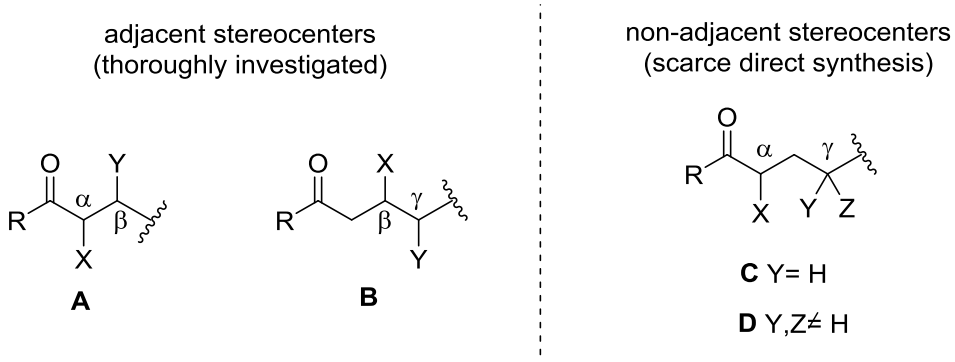


Figure 23. Acyclic carbonyl compounds with different stereoarrays.

Among the few precedents, Deng reported a cinchona derived Brønsted base/H-bond donor bifunctional catalyst promoted Michael addition/α-protonation domino process, which implies α-chloroacrylonitrile as the Michael acceptor (Figure 24a).[128] Later on the group of Chen and Xiao described[129] a similar domino reaction involving ethyl 2-phthalimidoacrylate or α-phosphonoacrylates as the doubly activated Michael acceptor (Figure 24b). Despite both methods are elegant, two aspects deserve comment. One is that in both cases, the electron-poor olefin is activated by two attached electron-withdrawing groups. On the other hand, none of these works constitutes a general method when it comes to diastereoselectivity, as the diastereomeric ratios are highly dependent on the substrate. Also, the extension of this methodology to inherently less reactive α-alkyl-substituted Michael acceptors, that is, methacrylates or equivalents, remains challenging, despite the fact that α-alkyl- and more specifically α-methylcarbonyl units are present in a number of natural products and bioactive targets (vide supra).

[128] a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928−3930. b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.*, **2007**, *129*, 768−769; for an extension of 2-oxindoles as pronucleophiles, see: c) Li, X.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2010**, *16*, 14290−14294.

[129] a) Duan, S. W.; An, J.; Chen, J. R.; Xiao, W. J. *Org. Lett.* **2011**, *13*, 2290−2293. b) Duan, S. W.; Liu, Y. Y.; Ding, W.; Li, T. R.; Shi, D. Q.; Chen, J. R.; Xiao, W. J. *Synthesis* **2013**, 1647−1653.

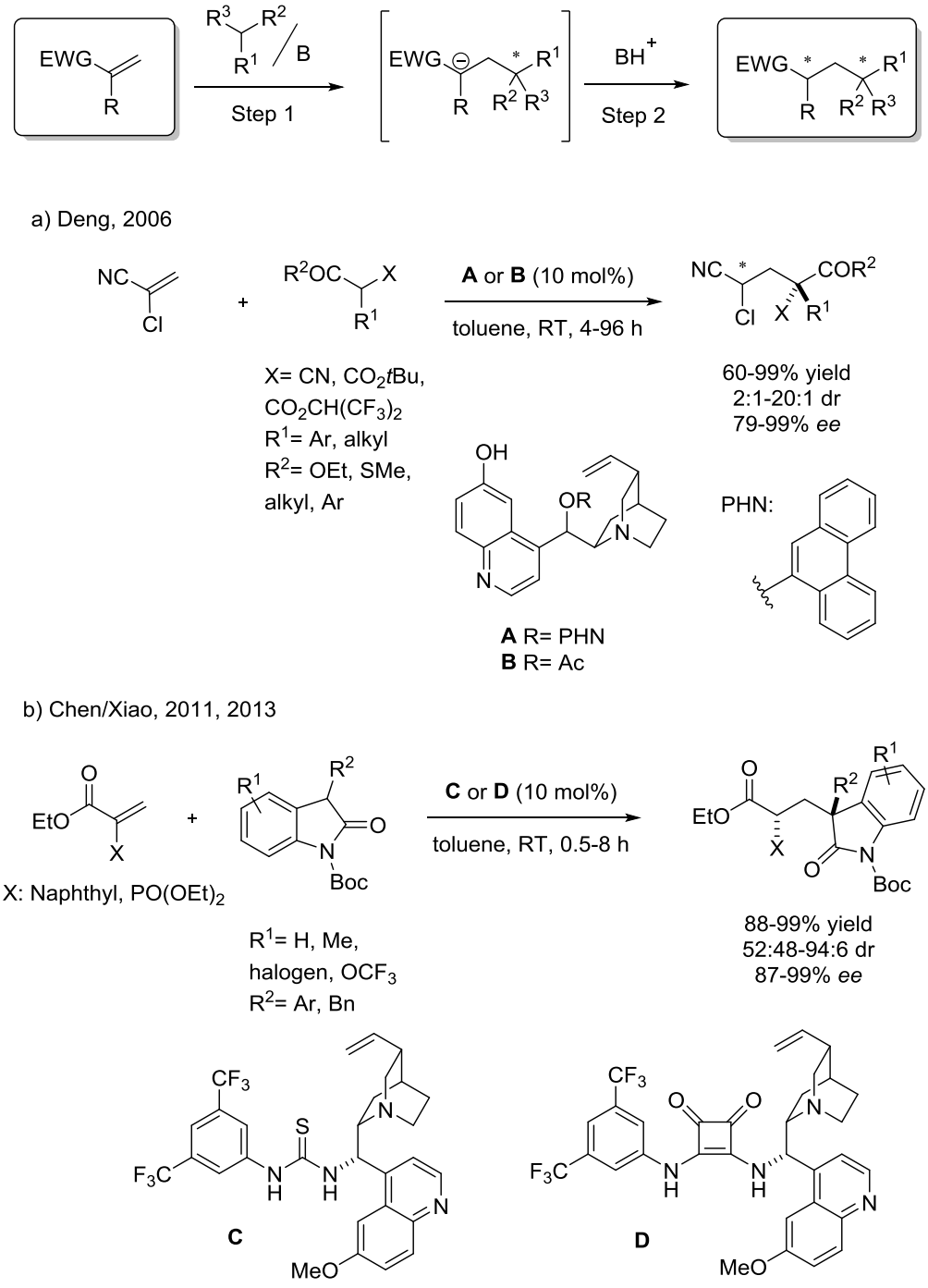
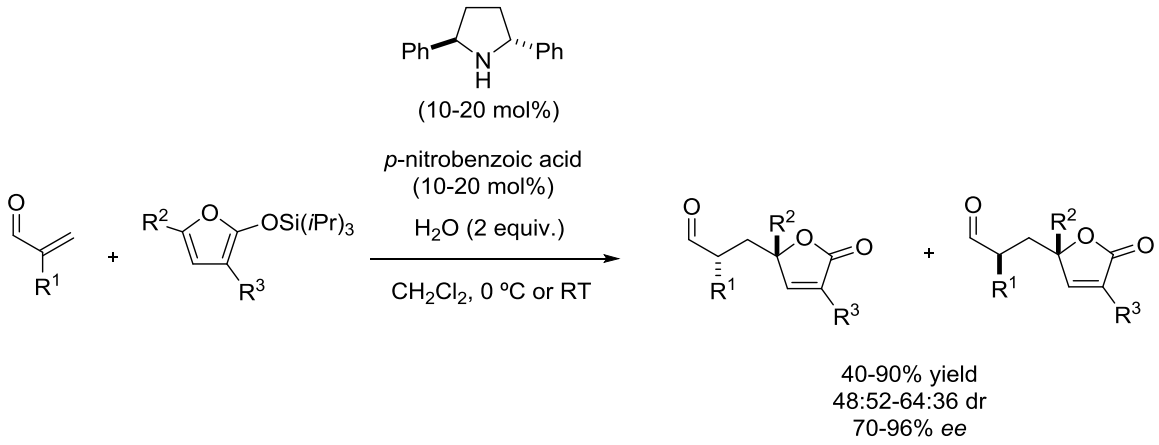


Figure 24. Advances in tandem Michael addition/protonation approaches for the asymmetric assembly of α,γ-nonadyacent stereocenters.

Pihko has described[130] the enantioselective Mukaiyama-Michael addition reaction of methacrolein through iminium ion activation mechanism; however, this reaction led to an approximately 1:1 mixture of the two possible diastereomers, revealing, once more, the difficulties in controlling the protonation step (Scheme 54).



Scheme 54. Mukaiyama−Michael reaction using α-substituted acroleins as acceptors.

As far as we know, before this thesis work, highly enantioselective Michael reactions involving methacrylates or equivalents to provide the corresponding carbonyl compounds with all-carbon tertiary/quaternary nonadjacent stereocenters had not been realized.

3.2. Hypothesis, Results and Discussion

3.2.1. α-Substituted α´-hydroxy enones as Michael acceptors: Hypothesis and working plan

Given the efficiency of β-substituted α´-hydroxy enones as acrylate equivalents in Brønsted base catalysed Michael reactions leading to quaternary-tertiary adjacent stereocenter, we hypothesized that the related α-substituted analogs might behave similarly. The hypothesis was that the unique capacity of these type of bidentate templates to act as both hydrogen-bond donor and acceptor, in cooperation with a proper Brønsted base catalyst, may also be translated to the key C−C bond formation

[130] a) Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. *Org. Lett.* **2012**, *14*, 1086−1089. b) Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza. A.; Kótai, B.; Pápai, I.; Pihko, P. M. *Chem. Eur. J.* **2014**, *20*, 5983−5993. c) Fu, N.; Zhang, L.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2013**, *19*, 15669−15681.

and the subsequent α-protonation (Figure 25). Two prerequisites for successful stereocontrol would be:

a) Efficient Nu-face selectivity (enantiocontrol) during the initial C–C bond-forming step (Step 1).
b) Efficient face selectivity (diastereocontrol) during α-protonation of the evolving chiral enolate intermediate (Step 2).

Our expectation was that given the precedents noted above,[124] requisite a) may be feasible. Regarding requisite b), our working hypothesis was that the evolved enolate from Step 1 would preferentially adopt a *Z* configuration because of unfavourable $A^{1,3}$ strain in the chelated *E* form (Figure 25). However, both chiral units, namely the protonated catalyst (BB*−H) and the newly generated stereocenter at γ, would have to work in concert in Step 2. In this respect, as far as we are aware, α-substituted α´-hydroxy enones have never been employed in catalytic asymmetric conjugate additions.

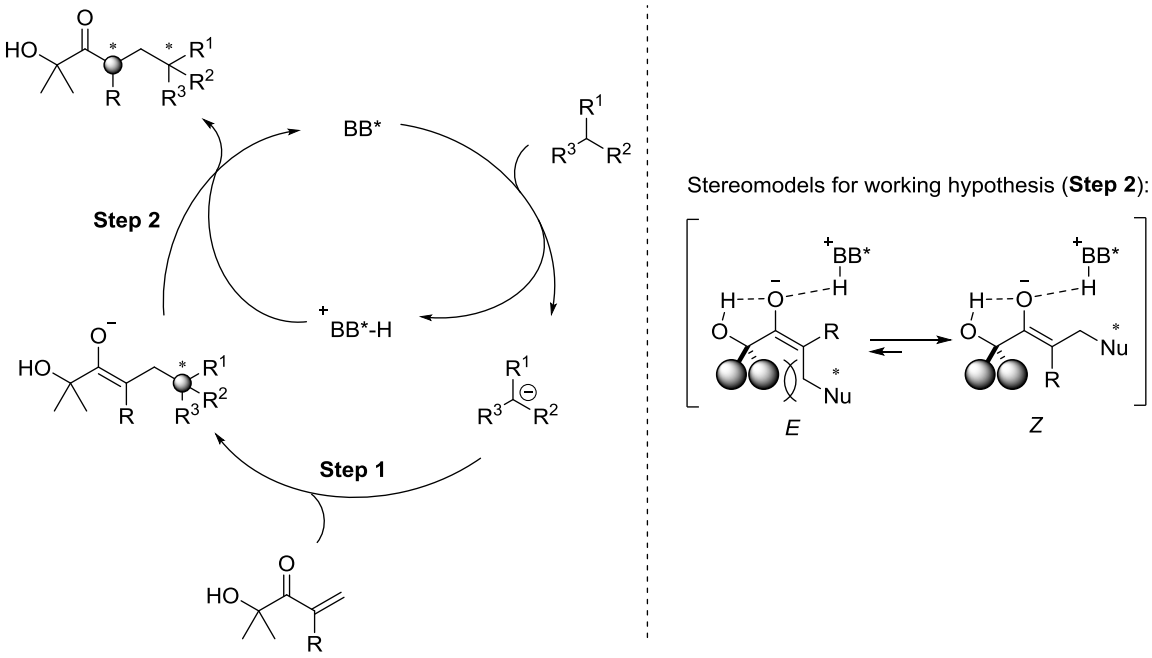
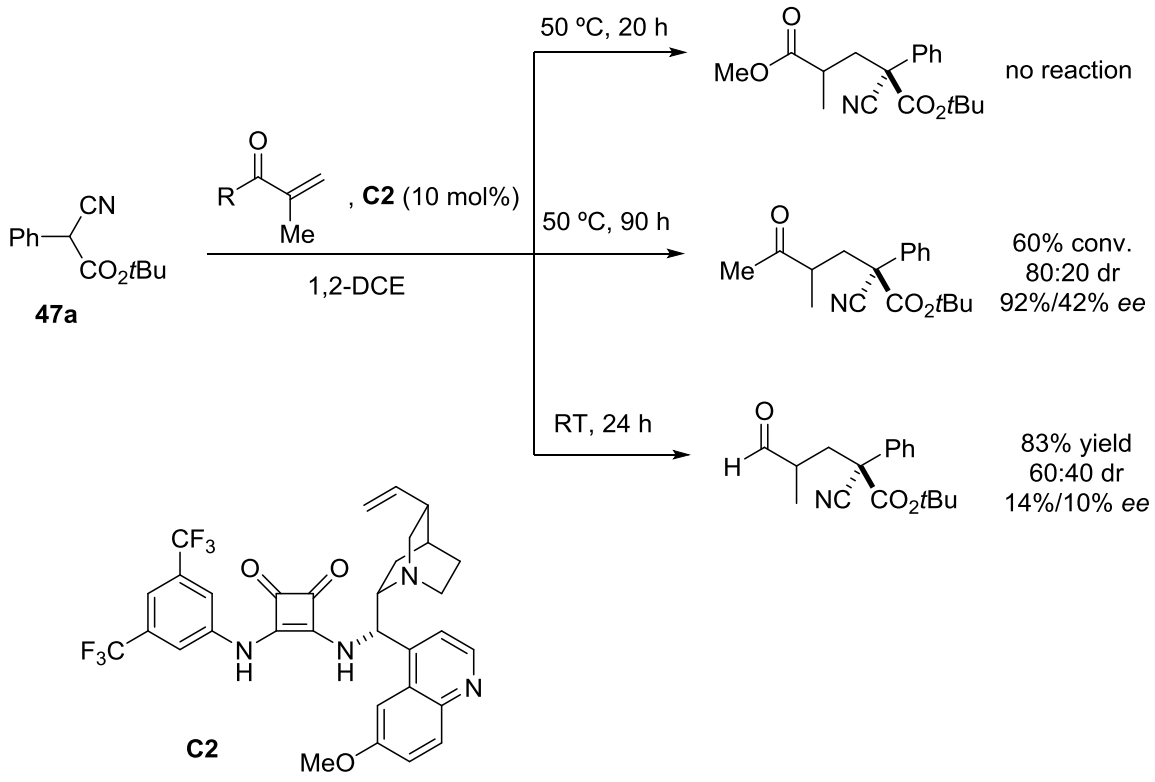


Figure 25. Construction of nonadjacent tertiary/quaternary stereocenters and working hypothesis for designed methacrylate equivalent.

3.2.2. Results and discussion

In order to demonstrate the attenuated reactivity and the difficulties in the stereocontrol of the process when using common Michael acceptors, preliminary studies where carried out by Dr. Eider Badiola involving the reaction of 2-phenyl α-cyanoacetate **47a** and some elementary α-substituted Michael acceptors revealed some serious difficulties. Thus, attempts to react **47a** with methyl methacrylate in the presence of

bifunctional Brønsted base catalyst **C2** led to recovery of unreacted material (Scheme 55). Under similar conditions, 3-methylbutenone resulted essentially unreactive at ambient temperature; 60% conversion was hardly achieved only after 90 h at 50 °C. Finally, methacrolein was more reactive, but led to unselective reaction.[130]



Scheme 55. Difficulties in the addition of α-cyanoester **47a** to α-methyl α,β-unsaturated ester, ketone or aldehyde under best reaction conditions.

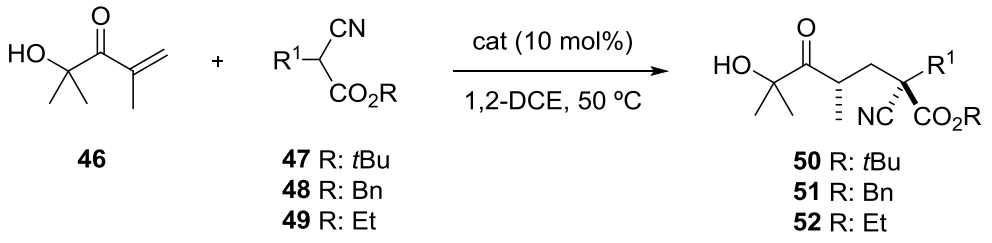
Next, the suitability of Brønsted base catalysts to trigger these Michael reactions was reassessed, but using α-alkyl α´-hydroxy enones as the Michael acceptor, with the hope to overcome the two main challenges in these reactions: a) the attenuated reactivity of α-alkyl-substituted enones as Michael acceptors and b) the stereocontrol during the key C–C bond formation (Figure 25, Step 1) and the subsequent α-protonation (Figure 25, Step 2).

3.2.3. Catalyst screening and reaction optimization

The optimization of the reaction was carried out by Dr. Badiola by studying the reaction of the α´-hydroxy enone **46** with α-substituted cyanoacetate **47a** in the presence of several bifunctional Brønsted bases (Table 9). Given the efficiency demonstrated by the α-cyanoacetates in the Michael reaction with α´-hydroxy enones,[124] we hypothesized

that these pronucleophiles may be well suited for the Michael addition to α-substituted α´-hydroxy enones. Commercially available **C6** and **C7**, thiourea derivative **C1** and squaramide-type catalysts **C8**, **C9** and **C2** were tested in the reaction model (Table 9). Using this catalyst **C2** the reaction between 2-phenyl α-cyanoacetate **47a** and **46** at ambient temperature afforded adduct **50a** with essentially perfect enantio- and diastereocontrol (>99:1 dr, 99% *ee*). Thus, both the initial addition and the subsequent α-protonation proceeded with remarkable face selectivity. The remaining catalysts all resulted inferior. Interestingly, the almost perfect chirality transfer obtained with catalyst **C2** was reproduced when the reaction was run at 50 °C (entry 3), which allowed attaining full reaction conversion at shorter time (24 h).

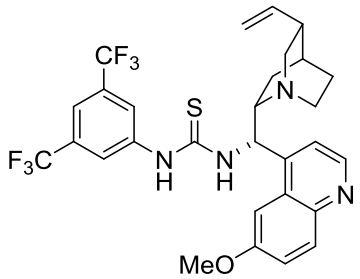
Table 9. Reaction of **46** with α-cyanoacetates **47**-**49** catalysed by chiral Brønsted bases. Catalyst screening for the reaction of **46** with **47a** (R^1 = Ph).[a]



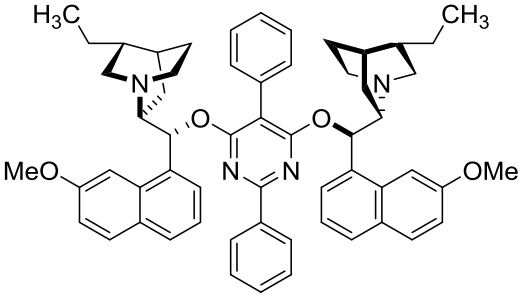
46

47 R: *t*Bu
48 R: Bn
49 R: Et

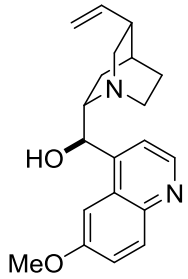
50 R: *t*Bu
51 R: Bn
52 R: Et



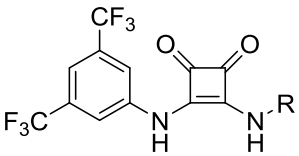
C1

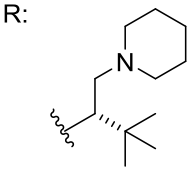


(DHQD)$_2$PYR, **C6**

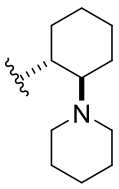


Quinine, **C7**

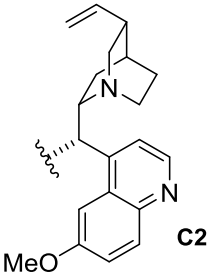




C8



C9



C2

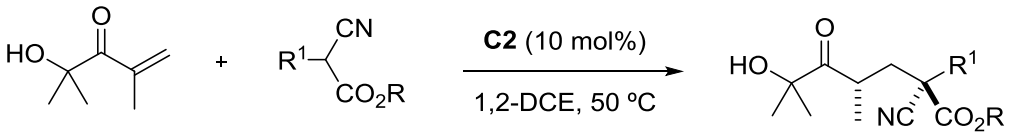
Catalyst	t (h)	Conv (%)	Yield (%)[b]	dr	*ee* (%)[c]
C1	72	70	46	80:20	68
C2[d]	96	n.d.	40	>99:1	99
C2	24	100	81	>99:1	98
C6	72	100	72	70:30	30
C7	72	65	49	75:25	16
C8	72	23	n.d.[e]	n.d.	n.d.
C9	40	100	75	75:25	−12

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C, using 1.5 equiv. of **47a** and 10 mol% catalyst. [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at room temperature. [e] n.d.: not determined.

3.2.4. Scope of the reaction

Next, the scope of the reaction was studied in collaboration with Dr. Badiola (entries 1-5 performed by Dr. Badiola) by evaluating a variety of α-substituted cyanoacetates under the optimized conditions (10 mol% **C2** in 1,2-DCE at 50 °C). Gratifyingly, the reaction of **46** worked equally well with an array of 2-aryl *tert*-butyl α-cyanoacetates **47** to afford the corresponding adducts **50** as essentially single diastereomer (dr ≥ 98:2) in yields within the range from 62% to 92% in most cases and very high enantioselectivity. As Table 10 shows, these results seem to be independent upon the meta/para substitution pattern of the aromatic ring or their electron donating/withdrawing character. Entry 6 was an exception probably because of steric constraints imposed by the *ortho* substituent. Using the less sterically demanding benzyl and ethyl cyano esters **48** and **49**, a slight loss of stereoselection was produced (entries 9 and 10), albeit it was still acceptable.

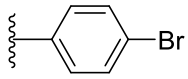
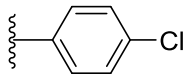
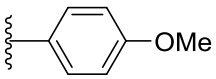
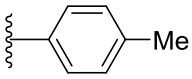
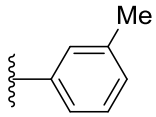
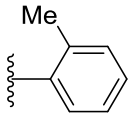
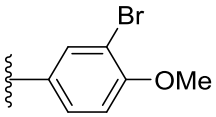
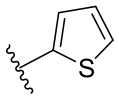
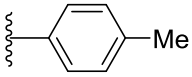
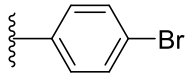
Table 10. Scope of the conjugate addition of α-cyanoacetates to **46**.



46

47 R: *t*Bu
48 R: Bn
49 R: Et

50 R: *t*Bu
51 R: Bn
52 R: Et

Entry	R^1	Product	t (h)	Yield (%)[b]	dr	*ee* (%)[c]
1		**50b**	24	69	98:2	98
2		**50c**	24	95	98:2	96
3		**50d**	40	70	>98:2	>98
4		**50e**	40	67	98:2	>98
5		**50f**	40	83	>98:2	97
6		**50g**	40	NR[d]	–	–
7		**50h**	16	62	97:3	96
8		**50i**	20	72	96:4	97
9		**51e**	24	76	90:10	92
10		**52b**	24	88	88:12	91

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C, using 1.5 equiv. of **47**, **48** and **49**. [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at room temperature. [e] NR: no reaction.

The configuration of adduct **50e** was determined by a single-crystal X-ray analysis (Figure 26) and the same configuration was assigned to the remaining adducts by assuming a

uniform reaction mechanism. Homochirality of the adducts was supported by the uniformly positive optical rotation values.

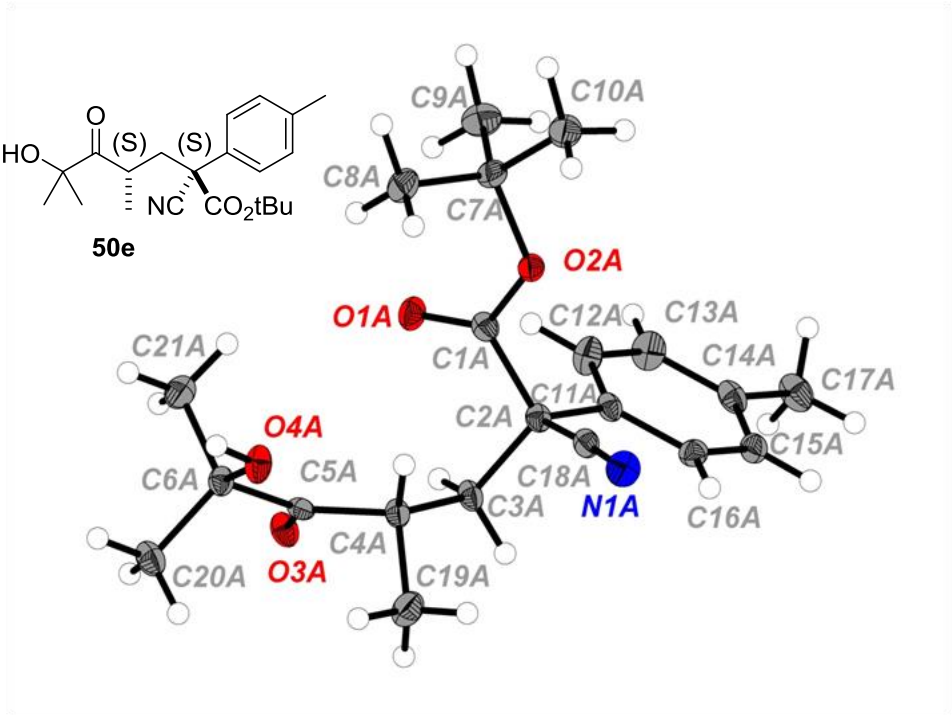


Figure 26. ORTEP diagram of compound **50e**.

3.2.5. Double asymmetric induction

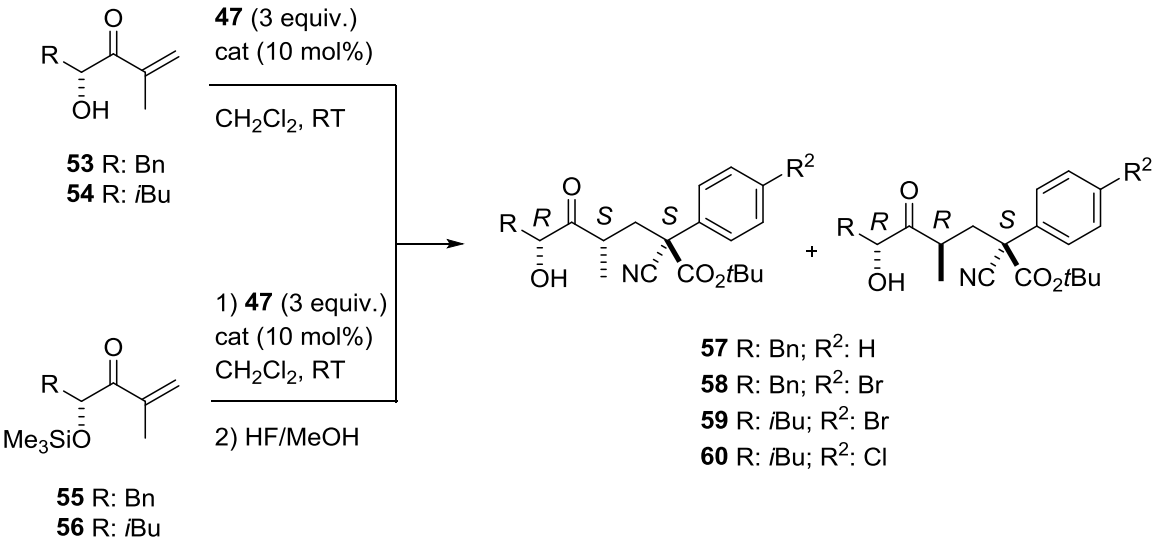
Double asymmetric induction refers to reactions in which a new stereocenter is generated under the influence of two or more chiral units. In our context, the addition reaction of α-cyanoacetates to *chiral* α´-oxy α-substituted enones catalysed by chiral Brønsted bases would be interesting as adducts bearing three stereocenters would become accessible. These latter, in their turn, would be precursors of complex 1,2-diols through carbonyl reduction.

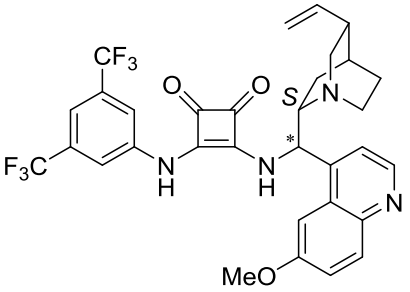
Given the paucity of methods for the construction of tertiary/quaternary nonadjacent stereocenters, this organocatalytic Michael reaction/protonation cascade was next extended to chiral α´-oxy enones **53**/**54** and **55**/**56**. At this stage, the main challenge was to find the right catalyst-substrate combination with both chiral inducers working in a *match* combination.

As the results in Table 11 show, the stereochemical outcome of the reactions varies notably depending on the catalyst used. The investigation was started with Et_3N as the only base (entries 1 and 8) and using the α´-hydroxy enones **53** (entry 1) and **55** (entry 8) as the only asymmetric promoters. Adducts **57** and **59** were produced with moderate

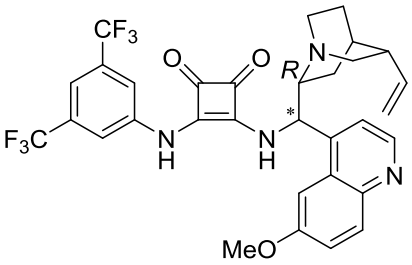
diastereoselectivity (ratio of *RSS*/other isomers 60:40 and 71:29, respectively), indicating that the stereoinduction capacity of the chiral substrate by its own is not sufficient, probably due to the fact that the inducing stereocenter is relatively far away from the newly generated stereocenter (relative 1,5-position). Then, double asymmetric induction was studied involving participation of chiral Brønsted base catalysts. The reaction between **53** (R= Bn) and **47a**, catalysed by **C2**, afforded products *RSS*/*RRS*-**57** in a 67:33 ratio and 70% yield (entry 2), while the use of the silylated analogue **55** improved the diastereoselectivity to 89:11 (entry 3). Next, catalysts **C10**, **C11** and **C12** were tested, and catalyst **C10** led to no reaction (entry 4), and **C11** and **C12** led to poor selectivity (entries 5 and 7). Under the same conditions as in entry 3, reactions between enone **56** (R= *i*Bu) and cyanoacetates **47c** and **47d** (entries 9 and 10) were also obtained in very good diastereomeric ratios (91:9 and 90:10) and yields (90% and 80%).

Table 11. Michael addition/protonation cascade involving chiral enones (double asymmetric induction).[a]





(*S*,*S**) **C2**
(*S*,*R**) **C10**

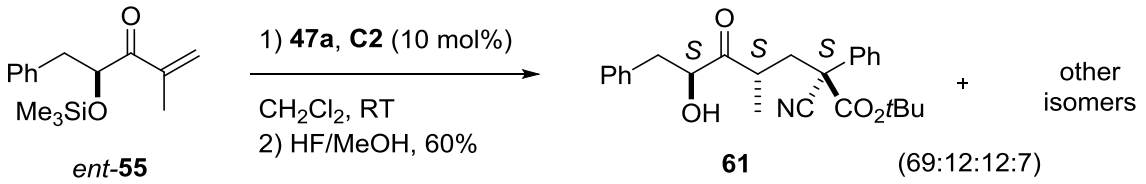


(*R*,*S**) **C11**
(*R*,*R**) **C12**

Entry	R	enone	cyanoester	catalyst	t (h)	product	Yield (%)	*RSS*:*RRS*:others
1	**Bn**	**53**	**47a**	Et_3N	24	**57**	75[b]	60:23:17:0
2		**53**	**47a**	**C2**	24	**57**	70[b]	67:33:0:0
3		**55**	**47a**	**C2**	60	**57**	73[b]	89:11:0:0
4		**55**	**47a**	**C10**	24	**57**	NR[d]	–
5		**55**	**47a**	**C11**	64	**57**	70[b]	49:41:10:0
6		**55**	**47b**	**C2**	72	**58**	75[b]	83:17:0:0
7		**55**	**47b**	**C12**	72	**58**	65[b,c]	22:21:57:0
8	***i*Bu**	**54**	**47b**	Et_3N	24	**59**	83[b]	71:29:0:0
9		**56**	**47b**	**C2**	72	**59**	90[b]	91:9:0:0
10		**56**	**47c**	**C2**	72	**60**	80[b]	90:10:0:0

[a] Reactions conducted on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 using 3 equiv. α-cyanoester **47a**-**c**. [b] Yields of isolated product (mixture of isomers). [c] Configuration of major isomer unknown. [d] NR: no reaction.

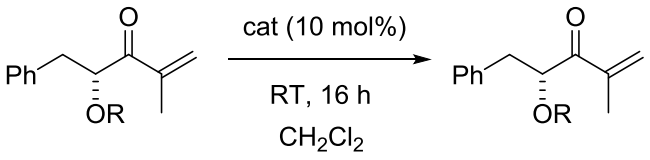
At this point it remained unclear whether the above substrate/catalyst combinations correspond to a matched stereochemical relationship. To answer that question, the reaction between **47a** and the (*S*)-configured ent-**55** was carried out in the presence of catalyst **C2**. As the data in Scheme 56 show, a 69:12:12:7 mixture of diastereomers was obtained, with (*S*,*S*,*S*)-**61** as the major product. By comparison with data in entry 3 of Table 11, it seems clear that the pair **55**/**C2**, with the configurations (*R*)-substrate/(*S*,*S*)-catalyst, corresponds to the matched combination.



Scheme 56. Reaction involving substrate/catalyst mismatched combination.

It is worth noting that in the above reactions (Table 11) *O*-silylated enones **55**/**56** behaved superior than hydroxy enones **53**/**54** as the results in entries 2/3 (d.r. of 67:33 and 89:11, respectively) and 8/9 (d.r. of 71:29 and 91:9, respectively) show. We questioned whether the better diastereomeric ratios obtained with the *O*-silylated enones compared to the parent hydroxy enones is caused by racemization of these latter in the presence of the basic catalyst. To assess this possibility, we carried out a study of the stability of enones **53** and **55** in the presence of different catalysts (Table 12). No racemization occurred when **53** and **55** were stirred in the presence of Et_3N, DBU or **C2**, and so the racemization hypothesis was ruled out.

Table 12. Configurational stability of chiral enones **53** and **55** in the presence of different bases (10 mol%).[a]



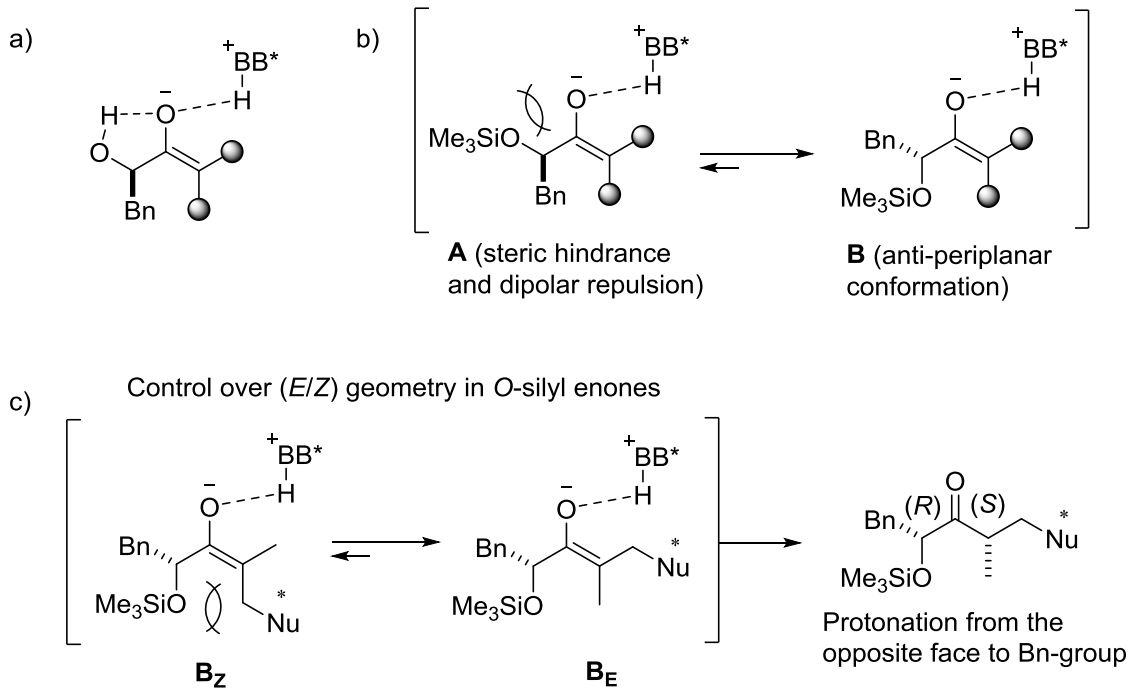
53 R= H
55 R= $SiMe_3$

ee %

Entry	enone	starting *ee* (%)[b]	catalyst	resulting *ee* (%)[b]
1	**53**	>99	**C2**	>99
2	**53**	>99	Et_3N	>99
3	**53**	>99	DBU	>99
4	**55**	>99	**C2**	>99
5	**55**	>99	**C2**	>99[c]
6	**55**	>99	Et_3N	>99
7	**55**	>99	DBU	>99

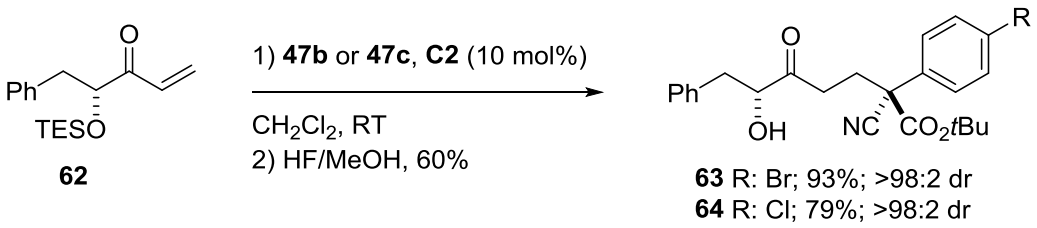
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.2 mL). [b] Determined by GC analysis. [c] *ee* measured by GC after 72 h.

The origin of the improved diastereoselectivity showed by the *O*-silylated enones **55**/**56** could tentatively be ascribed to the more efficient control of the enolate *E*/*Z* geometry as compared with the hydroxy analogues **53**/**54**. As shown in Scheme 57a, the hydroxy-group may form intramolecular *H*-bonds with the oxygen of the enolate, while in the *O*-silylated enones these intramolecular interactions would be cancelled, and instead both the oxygen atom from the enolate and the silyloxy-group would stay in an anti-periplanar conformation due to steric hindrance and dipolar repulsion (Scheme 57b). In this context, the enolate $\mathbf{B_E}$ would be the most stable, due to the allylic 1,3 interactions in $\mathbf{B_Z}$ (Scheme 57c). Therefore, the benzyl group in enolate $\mathbf{B_E}$ could direct the proton approach through the opposite face and explain the formation of (*S*) configured adducts. If the assumption is correct, the higher diastereoselectivity experimentally observed with *O*-silylated enones *vs.* hydroxy enones would be accounted for by a better control over *E*/*Z* geometry in *O*-silyl enones **55**/**56** than in hydroxy enones **53**/**54**.



Scheme 57. Allylic interactions of the enolate intermediates.

Given the absence of studies concerning double asymmetric induction in this field, we next examined briefly the reaction of chiral α´-hydroxy enones without substituents at Cα position. Under the above optimized conditions it was found that reaction of **62** with either **47b** or **47c** produced the corresponding adducts **63** and **64**, respectively¸essentially as single diastereomer (Scheme 58). The generation of the quaternary stereocenter proceeds with almost perfect asymmetric induction with catalyst **C2** for both α-substituted and unsubstituted enones.



Scheme 58. Generation of a quaternary γ-stereocenter in chiral α-unsubstituted α´-hydroxy ketones. TES:triethylsilyl.

The difference in diastereoselectivity between reactions involving α-substituted enone **55** and α-unsubstituted enone **62** is clear, which might indicate that the α-protonation step in reactions involving α-substituted enones is the limiting factor when it comes to the stereochemical outcome of the process. Once the γ-quaternary stereocenter is

formed, the stereochemical outcome of the next α-protonation event would be influenced by three stereoinductors (Figure 27): i) the α´-stereocenter (containing the *O*-silyl group), ii) the γ-quaternary stereocenter and iii) the Brønsted base catalyst. The fact that the stereoinduction comes from three different sites makes the α-protonation step a more challenging transformation.

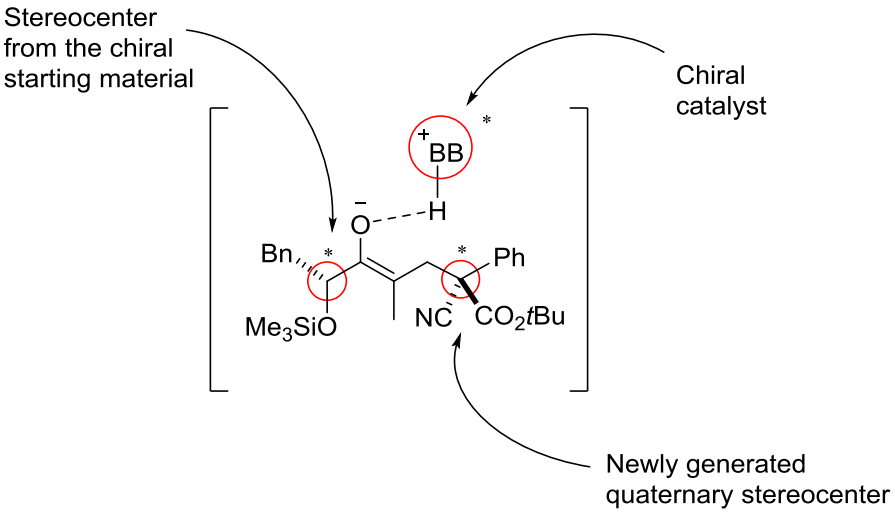


Figure 27. Transition state bearing three chiral inducers.

3.2.6. Proposed reaction models

The high fidelity with which chirality is transferred from the catalyst to the reaction products could be explained by the stereomodels depicted in Figure 28b. By analogy to previously calculated TS geometry for the related conjugate addition of cyanoesters to α-unsubstituted enone analog to **46** (Figure 28a),[124] Takemoto-type ternary complex **A** would account for the conjugate addition step, which would proceed with the catalyst interacting with both reaction components through several hydrogen bonds. Once the addition adduct is formed, the negative charge would no longer be located on the cyano ester moiety, but in the enolate site. This will weaken the hydrogen bond between the protonated quinuclidine and the cyano ester carbonyl. Finally, proton transfer, either directly from the protonated catalyst to the enolate or alternatively mediated by some proton−shuttle mechanism, would preferentially occur through the enolate *Re* face, as depicted in proposed model **B**.

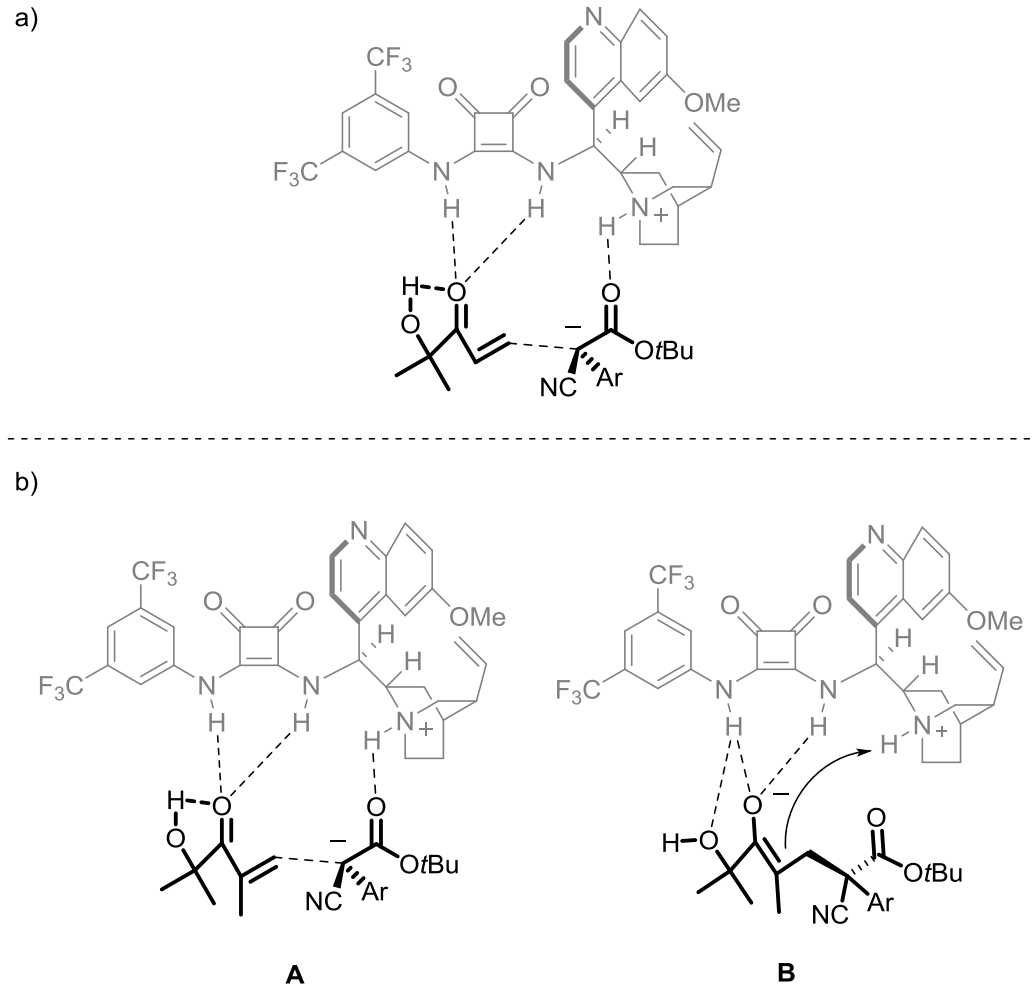


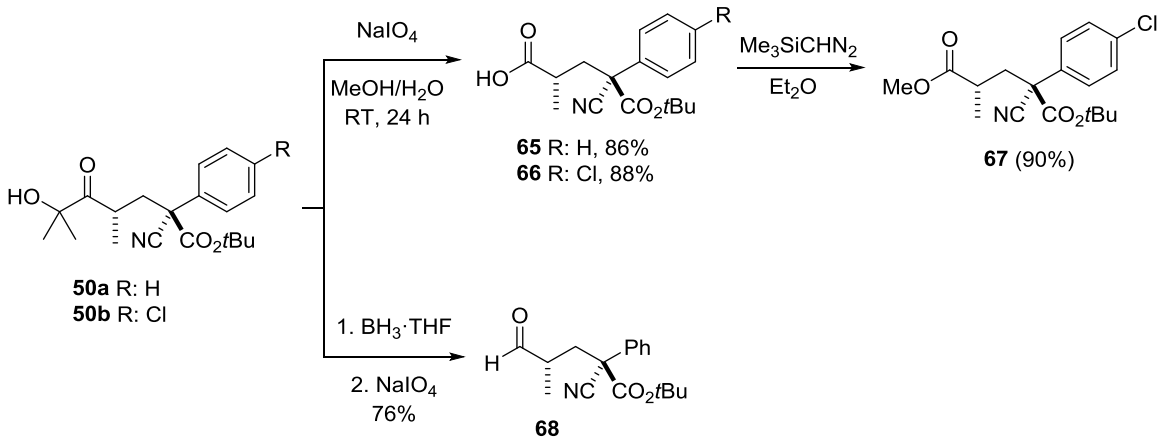
Figure 28. a) Transition State for the addition of α-cyanoacetates to α-unsubstituted α´-hydroxy enones. b) Proposed approaching models for the addition and protonation steps, respectively.

It should be concluded, however, that the above stereochemical arguments and explanations are, to a large extent, tentative, as the reactions described several dynamic, reversible interactions and are quite complex.

3.2.7. Elaboration of the adducts

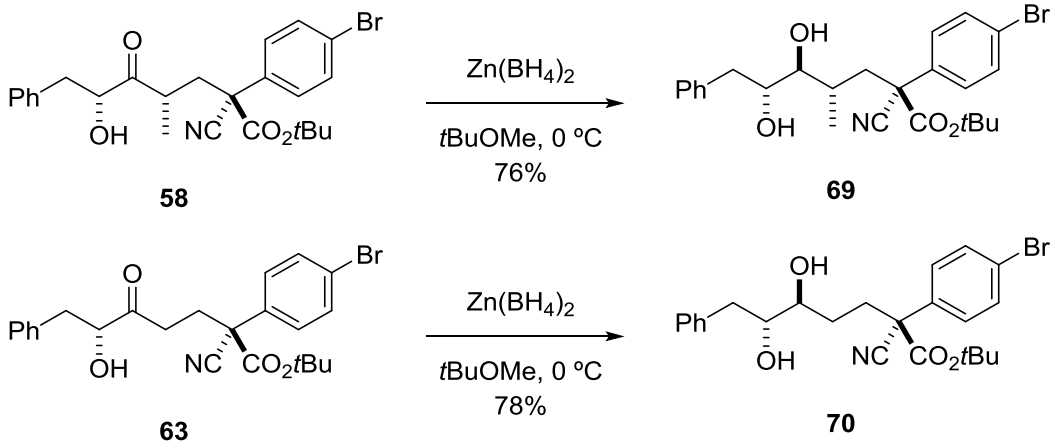
As mentioned before, the α´-ketol moiety is amenable for conversion into several functional groups of interest. Thus, in a variant, adducts **50a** and **50c** were treated with $NaIO_4$ in $MeOH/H_2O$ to provide the carboxylic acids **65** and **66** in 86% and 88% yield, respectively, with acetone being the only organic side product formed. Acid **66** was transformed into its methyl ester **67** for comparative purposes. Alternatively, reduction of the carbonyl group of **50a** with borane, followed by diol cleavage as above furnished aldehyde **68** in 76% yield over the two steps (Scheme 59). Thus, the lack of reactivity and

selectivity associated with methacrylate esters and methacrolein, respectively, may now be remediated with this new methacrylate equivalent.



Scheme 59. Conversion of ketol into carboxy and aldehyde functions.[131]

In addition to the above transformations, stereoarrays bearing up to four stereogenic centers (three contiguous tertiary stereocenters) may also be produced from this approach. Thus, diols **69** and **70** were obtained as essentially single *anti*-diol isomer and in good yield, through reduction of the respective α´-hydroxy ketone **58** and **63** with $Zn(BH_4)_2$ (Scheme 60). This outcome is not unexpected, as the stereochemistry of the reduction is presumed to be governed mainly by the stability of the chelated transition state (Figure 29).[132]



Scheme 60. Diastereoselective reduction of ketone group in adducts **58** and **63** to yield anti-1,2-diols.

[131] Experiments performed by Dr. Badiola.
[132] Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653−2656.

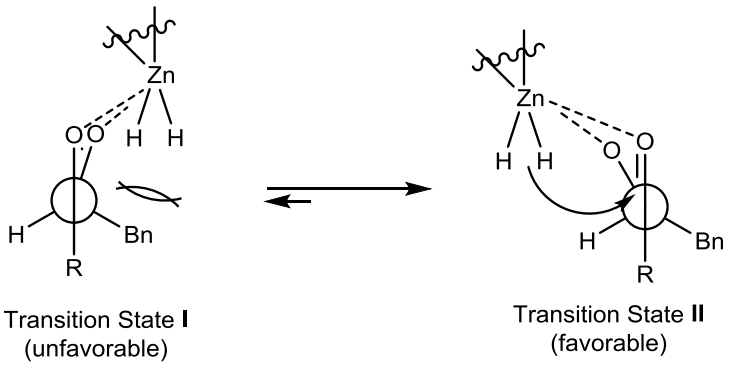
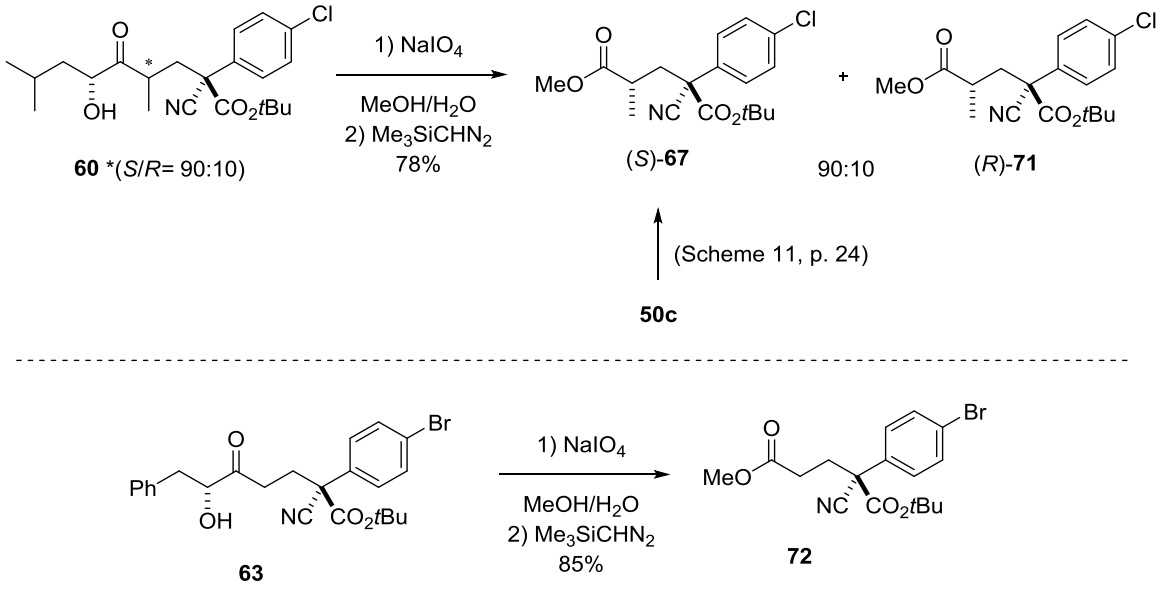


Figure 29. Transition state for the $Zn(BH_4)_2$ mediated diastereoselective reduction to yield anti-1,2-diols.

Finally, to confirm the stereochemical assignments, adduct **60** obtained through reaction involving double asymmetric induction (Table 11, 90:10 diastereomeric mixture), was subjected to oxidative cleavage and subsequent esterification, affording product **67** of identical spectroscopic and optical properties to that obtained from **50c**, along with the minor isomer **71** (Scheme 61). Similarly, **63** upon oxidative cleavage of ketol moiety as above and subsequent esterification of the resulting carboxylic acid provided the methyl ester **72**.



Scheme 61. Chemical correlations to confirm the stereochemical assignments: Oxydative cleavage of adducts **60** and **63** and esterification to obtain the corresponding esters.

Configurational identity of each isomer of adduct **60** was established by correlation of HPLC chromatograms of the corresponding methyl ester derivatives **67** obtained through either route, as follows:

Both racemic **rac-50c** and scalemic **50c** (configuration (*S*,*S*) determined by X-ray) were transformed into the methyl ester **67**, which afforded HPLC chromatograms of Figure 30. The peak at 17.1 min was assigned to compound **67** with (*S*,*S*) configuration.

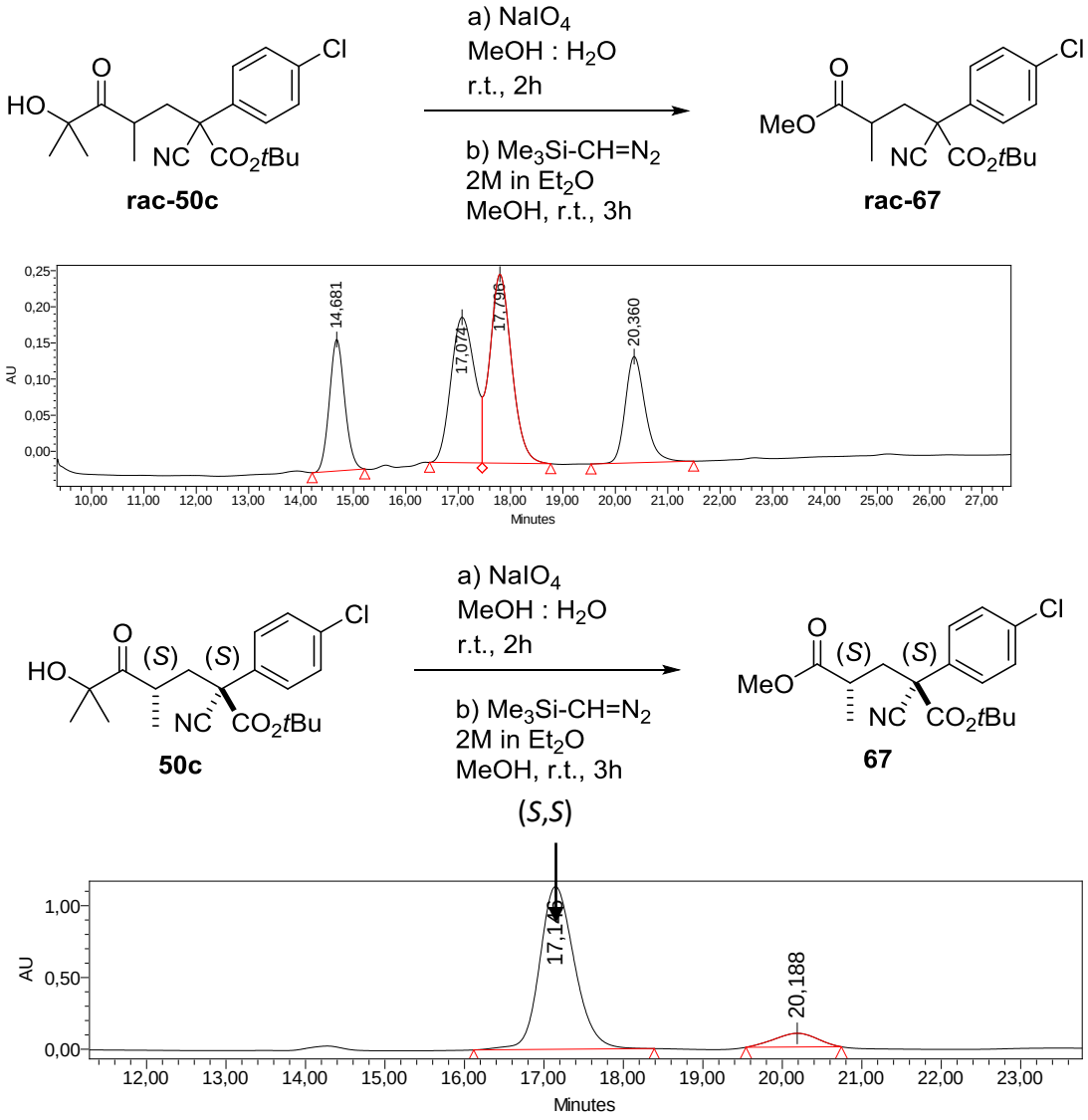


Figure 30. HPLC chromatogram of compound **67**.

Then, scalemic compound **50c** (configuration (*S*,*S*) determined by X-ray) was partially isomerized by treatement with DBU to obtain a 54:46 mixture of (*S*,*S*) and (*R*,*S*) epimers. Accordingly, peak 19.6 min was assigned to the (*R*,*S*) product (Figure 31a). Finally, compound **60** was transformed into ester **67** who´s absolute configuration (*S*,*S*) was stablished by the correlation of retention times (Figure 31b).

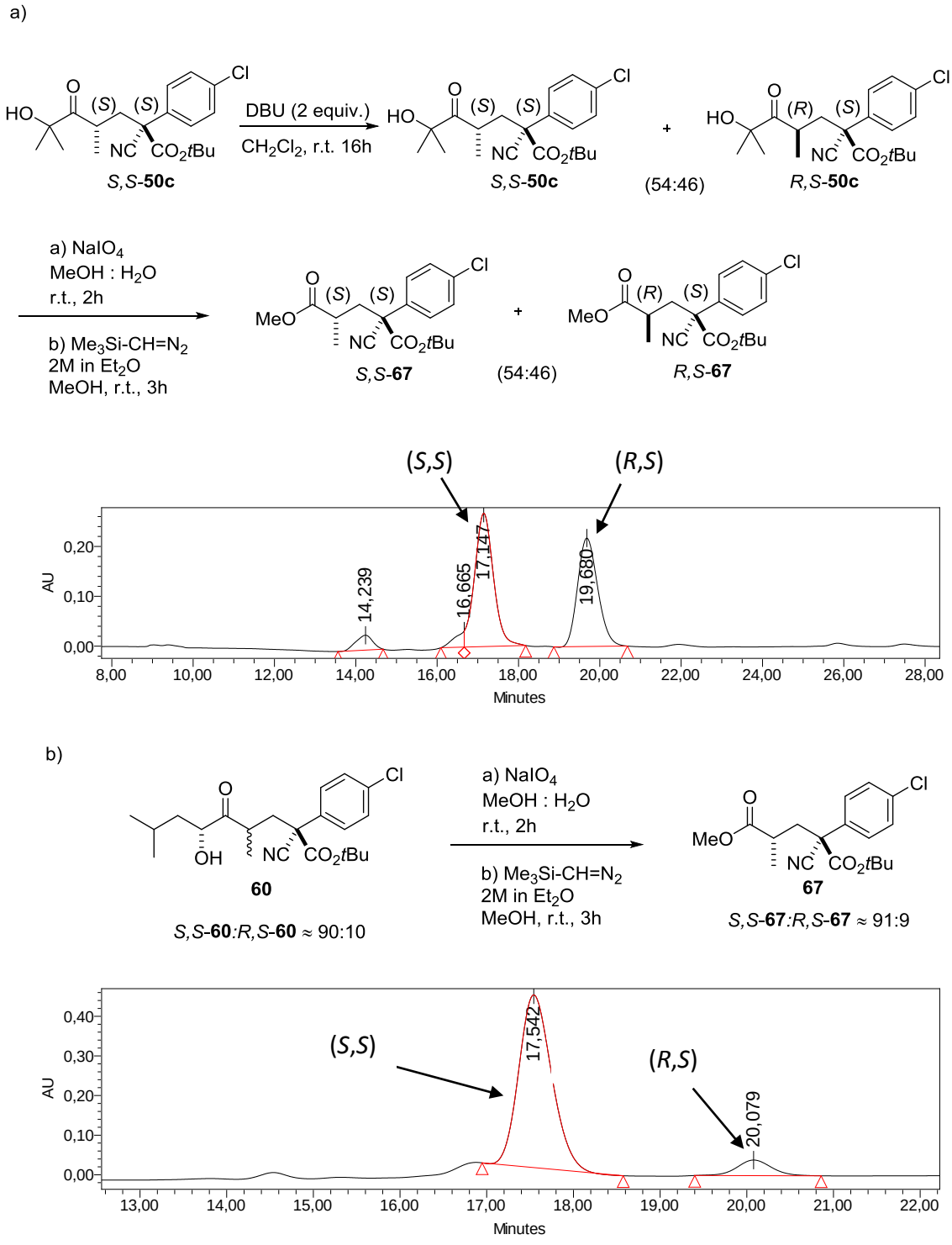


Figure 31. Determination of the absolute configuration of compound **67**.

Similarly, configurational identity of adduct **63** was established by correlation of HPLC chromatograms of the corresponding methyl ester derivatives **72** and comparison with ester products obtained from previously described adducts **73** and **rac-73**,[124] as follows:

Both racemic **rac-73** and scalemic **73** (configuration (*S*) determined by X-ray) were transformed into the methyl ester **72** and the following HPLC chromatograms were

obtained (Figure 32). The peak at minute 27.4 was stablished to be compound **72** with (*S*) configuration.

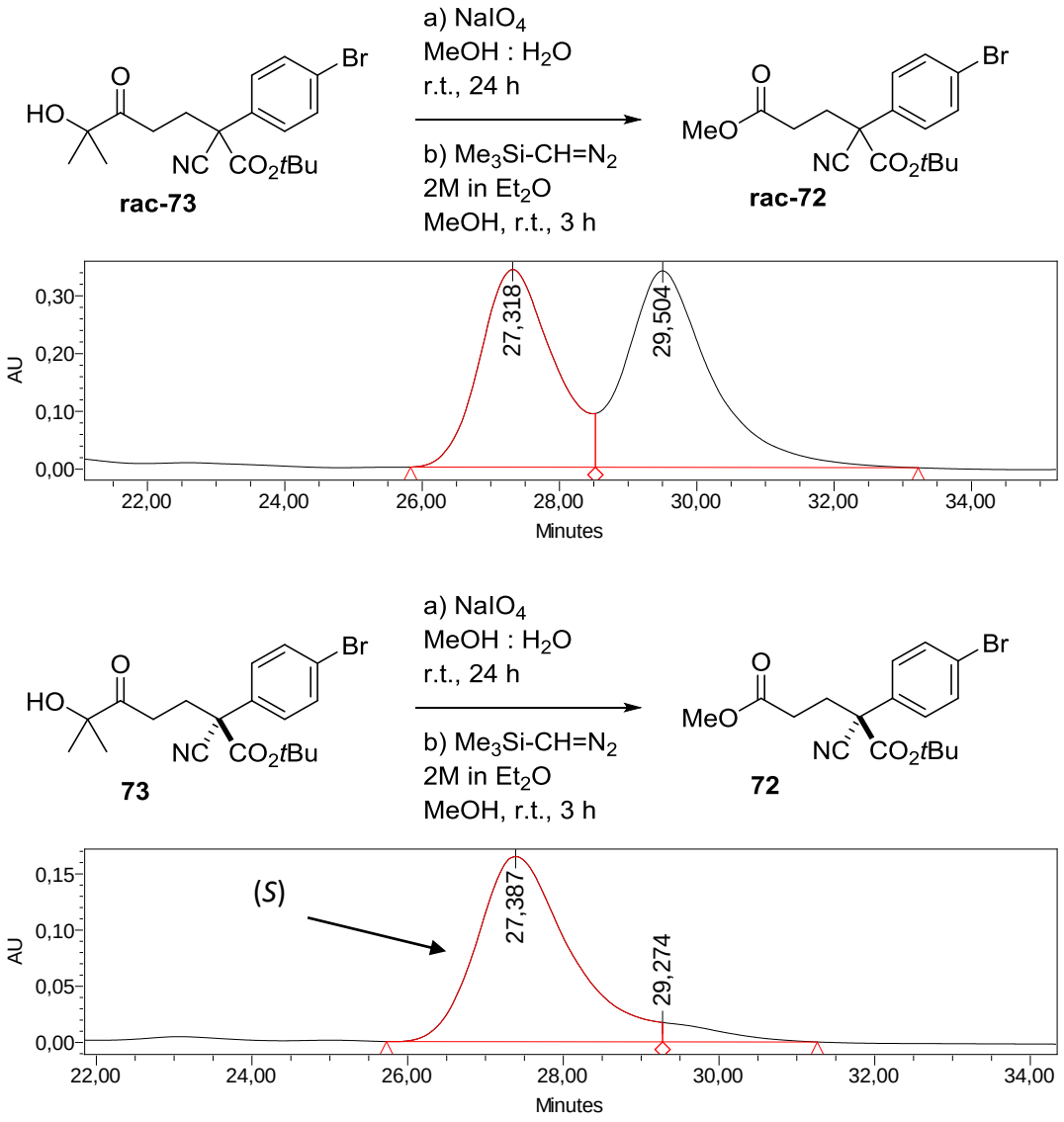


Figure 32. HPLC chromatogram of compound **72**.

Compound **63** was transformed into ester **72**, and by chemical correlation, absolute configuration of compound **63** was determined (Figure 33).

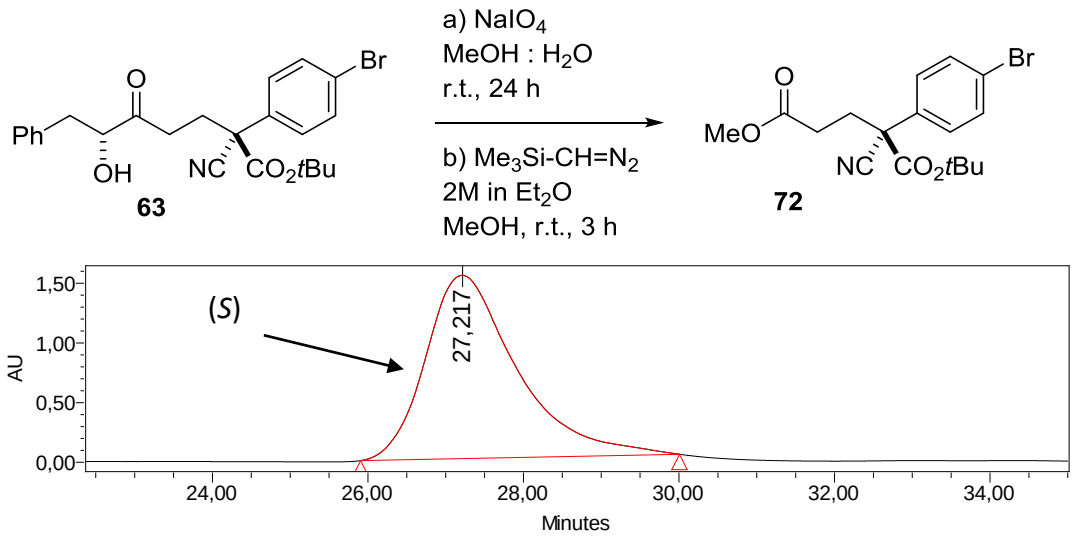


Figure 33. Determination of the absolute configuration of compound **63**.

Chapter 4

N-Phenyl-L-Valinamide as a New Bifunctional Catalyst for the Asymmetric Aldol Reaction

4. N-Phenyl-L-Valinamide as a New Bifunctional Catalyst for the Asymmetric Aldol Reaction

4.1. Introduction

The work described in this section was carried out during a 3 months stay at the laboratory of Prof. Keiji Maruoka at the Kyoto University.

4.1.1. Primary Amino Acids as Catalysts for the Asymmetric Aldol Reaction

Enzymes are highly efficient biocatalysts in living systems, and are able to promote asymmetric transformations with excellent stereocontrol. Developing small and simple organic molecules that can mimic enzymes represents a very useful and challenging task for organic chemists. Natural class **I** aldolases catalyse aldol reactions in water *via* the enamine mechanism, in which the enamine is formed at the lysine residue in the enzyme active site.[133] It has been demonstrated that the aldol reaction can be efficiently promoted by proline following a similar activation mechanism.[134]

In this context, it is quite surprising that only proline and its structural analogues have been intensively investigated in organocatalytic reactions, while the potential of primary amino acids as organocatalysts has been less studied.

4.1.2. Primary *versus* secondary amino acids in intermolecular condensations: mechanistic considerations

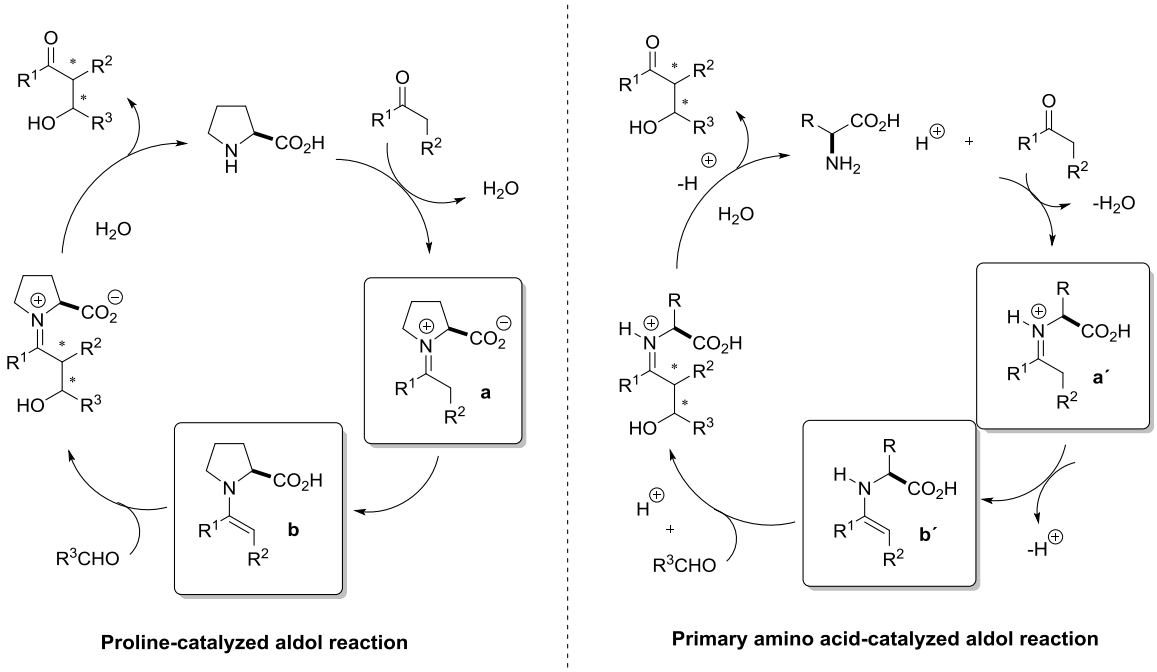
Aminocatalysis *via* enamine mechanism is one of the most important activation methods in asymmetric organocatalysis. The key of such activation is the transformation of the carbonyl group of an aldehyde or ketone into an enamine intermediate, which would increase the HOMO of the nucleophiles. In this context, proline and its structural analogues have been demonstrated to be powerful catalysts for a large variety of reactions, including aldol reactions. However, primary amino acid-promoted enamine catalysis is rather limited. In fact, in the initial report by List and Barbas on proline-

[133] Machajewski, T. D.; Wong, C. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352−1375.

[134] For reviews on catalytic asymmetric aldol reactions, see: a) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600−1632. Proline or proline derivatives catalysed aldol reactions: b) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580−591. c) Liu, J.; Wang, L. *Synthesis* **2017**, *49*, 960−972. Chiral primary amine-based aldol reactions: d) Xu, L. W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807−1821.

catalysed direct intermolecular asymmetric aldol reactions,[135] it was shown that primary amino acids, such as valine and phenylalanine, were poor catalysts for aldol reactions under the reaction conditions investigated. The catalytic cycles of enamine catalysis by proline and primary amino acids are compared in Scheme 62.[136] It has long been thought that secondary enamine is better stabilized by hyperconjugation, whereas a primary amine gives the predominant imine form. For primary amino acids to serve as efficient catalysts in enamine catalysis, effective tautomerization of their imine form (**a**´) to the enamine form (**b**´) is essential. Wong and co-workers[137] found that water molecules participated in a proton relay *via* a hydrogen-bonding network to effect the conversion of an imine formed between a lysine residue and acetaldehyde to the enamine form. Amedjkouh[138] subsequently demonstrated that the presence of water was crucial for the primary amino acid-mediated aldol reactions to take place. Tanaka and Barbas also showed that organic solvent (i.e. DMSO) with small amount of water as the additive facilitated enamine-based reactions involving primary amines.[139] Given these results, it is clear that it is certainly feasible to employ primary amino acids as potential catalysts in reactions involving enamine intermediates. In addition, the presence of an extra N−H in the enamine (**b**´) intermediate derived from the primary amino group may facilitate the control of the enamine structure, and direct the reaction to occur with specific reactivity and selectivity. Moreover, the ready availability of natural amino acids offers great flexibility in structural variation for the design of chiral organocatalysts. All these factors combined make primary amino acids interesting and promising catalysts in organocatalysis.

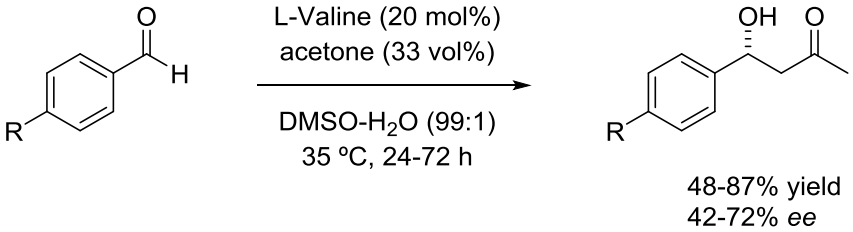
[135] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
[136] Xu, L. W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047−2053.
[137] Heine, A.; DeSantis, G.; Luz, L. G.; Mitchell, M.; Wong, C. H.; Wilson, I. A. *Science*, **2001**, *294*, 369−374.
[138] Amedjkouh, M. *Tetrahedron: Asymmetry*, **2005**, *16*, 1411−1414.
[139] Tanaka, F.; Thayumanavan, R.; Mase, N; Barbas III, C. F. *Tetrahedron Lett.* **2004**, *45*, 325−328.



Scheme 62. L-Proline and primary amino acid-promoted intermolecular aldol reaction *via* the enamine mechanism.

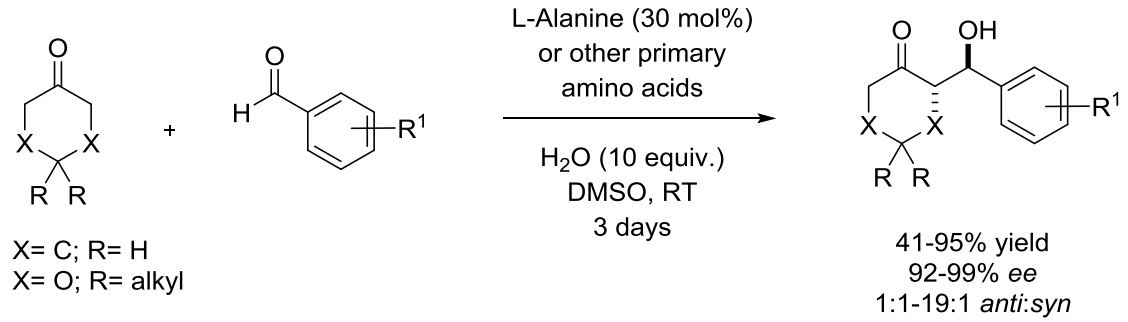
4.1.3. Intermolecular aldol reactions catalysed by primary amino acids and their derivatives

In 2005, Amedjkouh[138] found that L-valine was an effective catalyst in asymmetric direct aldol reactions between acetone and a variety of aromatic aldehydes, affording the aldol products in 48-83% yields and with moderate enantiomeric excesses (Scheme 63). The best results were obtained using either DMSO or DMF as solvent and the acetone (donor reagent) as cosolvent in the presence of one molar equivalent of water.



Scheme 63. L-Valine catalysed intermolecular aldol reaction.

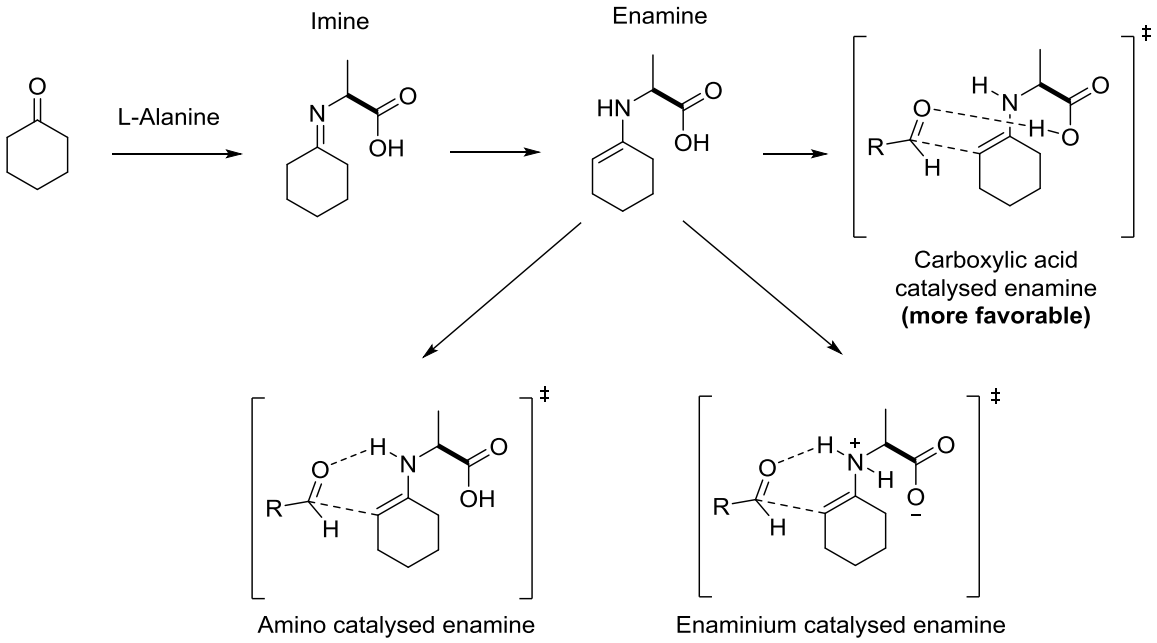
In the same year, Córdova and co-workers[140] reported that a number of primary amino acids could serve as excellent catalysts for direct asymmetric aldol reactions of cyclic ketones. For example, alanine, valine, leucine, isoleucine, serine, phenylalanine and threonine were all found to be excellent catalysts, furnishing the corresponding *anti*-selective-β-hydroxy ketones in high yields and with up to >99% *ee* (Scheme 64). Notably, the best results were obtained when the reactions were performed in wet polar solvents, *i.e.* with the addition of a small amount of water. The authors mentioned that the beneficial effect of water is due to improved catalytic turnover *via* rapid hydrolysis of the intermediates in the enamine catalytic cycle, as well as to suppression of catalyst inhibition.



Scheme 64. Intermolecular aldol reaction catalysed by a number of primary amino acids.

Córdoba and Himo next carried out computational studies to understand the origin of the observed stereoselectivity.[140c] DFT calculations on the alanine-catalysed aldol reaction were performed to provide a key understanding of the reaction mechanism. The carboxylic acid catalysed enamine mechanism is a more reasonable pathway, as it requires the lowest activation energy. The amino catalysed enamine mechanism, and the enaminium catalysed mechanism are less likely, as much higher activation energies are required (Scheme 65).

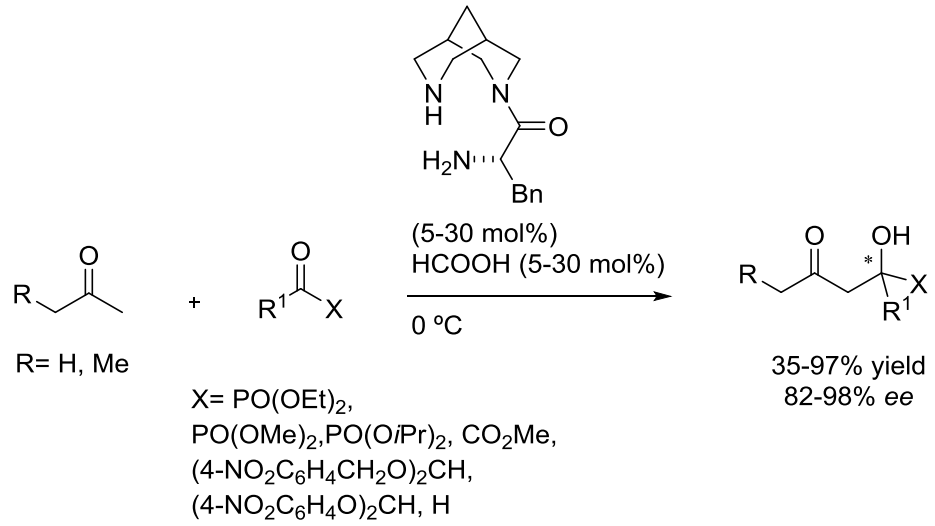
[140] a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W. W. *Chem. Commun.* **2005**, 3586–3588. b) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383–5397. c) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7028–7032.



Scheme 65. Possible mechanisms of L-alanine-catalysed aldol reactions.

The use of primary amino acid derivatives as catalysts can be extended to more challenging asymmetric aldol reactions. In 2008, Feng, Hu, and co-workers employed amino acids functionalized with a bicyclic bispidine framework as catalysts for the direct aldol reactions of functionalized α-ketones (Scheme 66).[141] They found that excellent yields and enantioselectivities were observed for the aldol reaction of acetone or 2-butanone with various activated ketones, such as α-keto esters, α,α-dialkoxy ketones, and α-keto phosphonates.

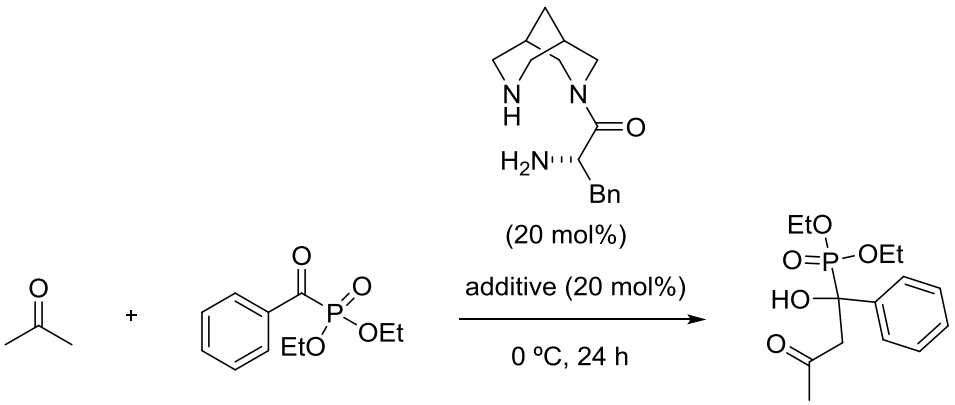
[141] Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654−5655.



Scheme 66. Bispidine-derived organocatalyst-catalysed asymmetric aldol reactions of functionalized ketones.

In this work, some acidic additives were tested, and it is shown that the reaction is strongly dependant on the acidity of the additive. As shown in Table 13, the weak acidic additives such as HCOOH were shown to be suitable for this reaction, affording the product with 95% yield and 96% *ee* (Table 13, entry 1), while stronger acids, such as TsOH and TFA (Table 13, entries 3, 4), made the reaction sluggish with only trace product.

Table 13. Effect of the acid additive in the intermolecular aldol reaction.



entry	additive	Yield (%)	*ee* (%)
1	HCOOH	95	96
2	CH_3COOH	92	88
3	PhCOOH	74	88
4	TsOH	trace	--
5	TFA	trace	--

4.1.4. Design of primary amino acid derived amino-amide organocatalysts for the aldol reaction

In the past years, various primary amines have been developed as bifunctional organocatalysts in asymmetric aldol transformations with high reactivity and stereoselectivities.[142] Even though these are highly efficient catalysts, many of these require long synthetic routes and have high molecular weight, which debases their value. In this context, the development of highly efficient primary amine bifunctional catalysts derived from simple commercially available compounds such as natural primary amino acids is a field of interest.

Several amino-amides, which are easily derived from natural amino acids, have been reported as bifunctional catalysts in asymmetric aldol transformations.[143] Modulating the amide group of the amino-amides to control the pK_a value of the Brønsted acid site of the catalyst has been identified as a key factor to properly design and create amino acid-derived bifunctional organocatalysts. For example, Yu and co-workers[144] designed several proline-derived catalysts for the Michael addition between cyclohexanone and nitrostyrene, and they calculated the pK_a values of approximate side chain of these catalysts (Figure 34a). The authors observed lower yields and enantioselectivities in the more acidic catalysts (lower pK_a values) which can be attributed to an intramolecular hydrogen bond, preventing it from coordinating with the acceptor (Figure 34b).

[142] a) Xu, L. W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807−1821. b) Mlynarski, J.; Bás, S. *Chem. Soc. Rev.* **2014**, *43*, 577−587.
[143] Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 6145−6158.
[144] Yu, C.; Qiu, J.; Zheng, F.; Zhong, W. *Tetrahedron Letters* **2011**, *52*, 3298−3302.

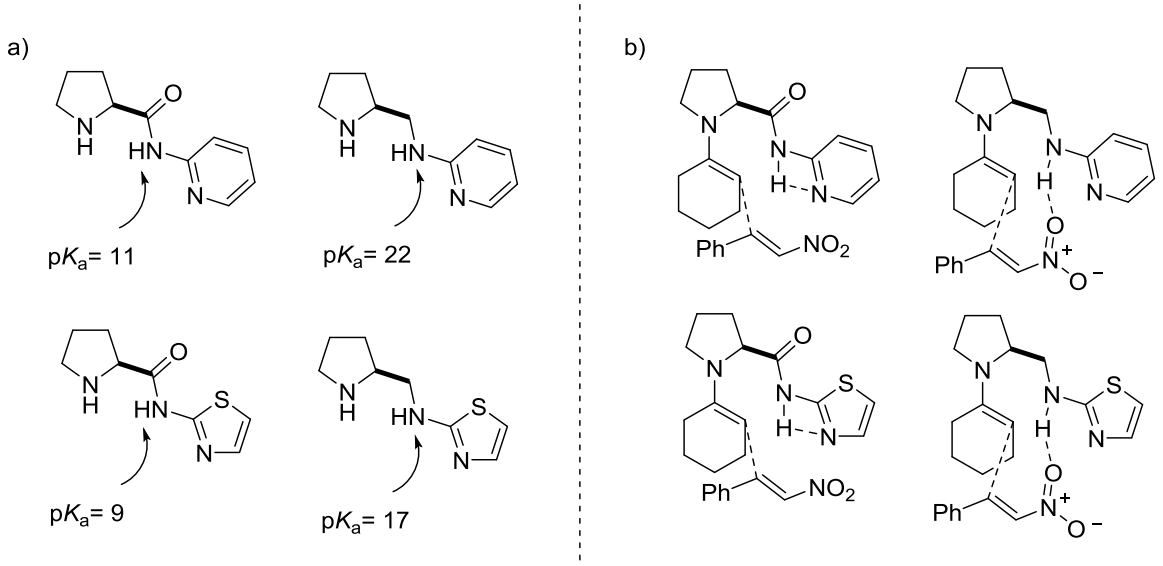
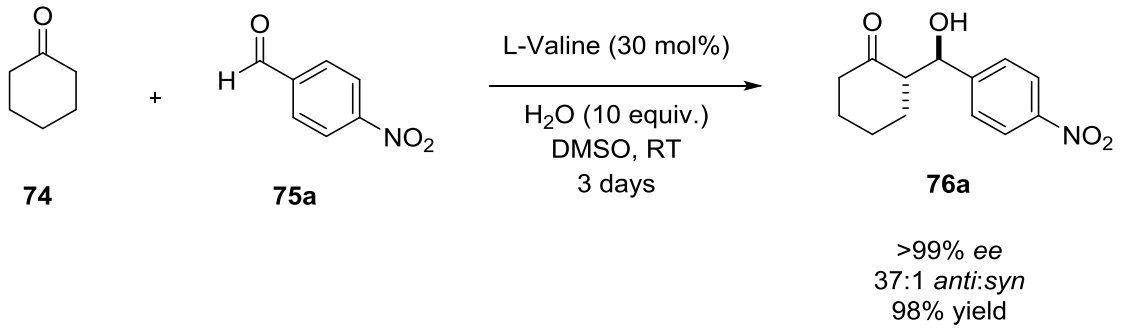


Figure 34. pK_a values and transition states for designed amino acid derived catalyst.

4.2. Results and discussion

In 2005, Córdova and co-workers screened several natural primary amino acids as catalysts in the asymmetric aldol reaction between **74** and **75a** and found that valine gave the best results with excellent yield and stereoselectivity in the selected conditions (Scheme 67). However, the reactivity of the process was insufficient (3 days at room temperature) and high catalyst loading (30 mol%) was necessary.

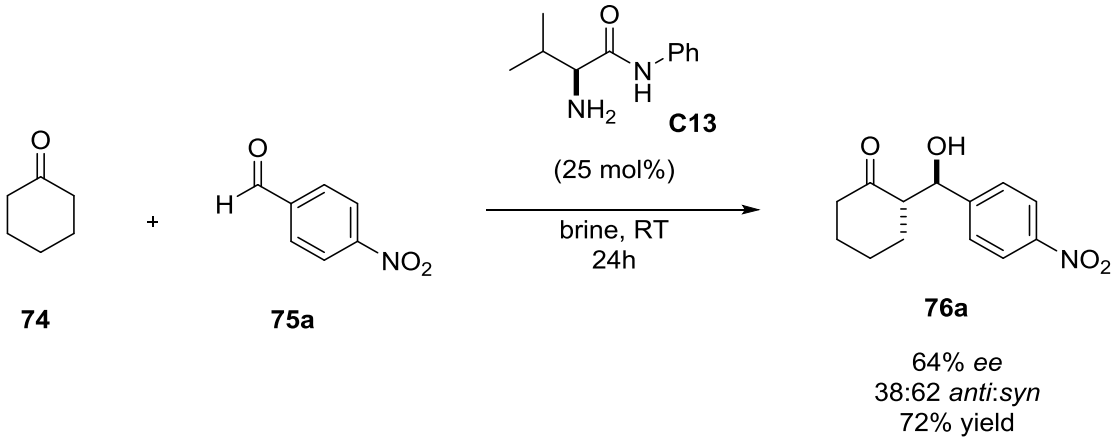


Scheme 67. L-valine promoted asymmetric aldol reaction between cyclohexanone **74** and aldehyde **75a**.

4.2.1. Design of the catalyst and optimization of the reaction conditions

Given the precedents, we hypothesized that valine derived amino-amides may be efficient catalysts for the asymmetric aldol reaction between cyclic enones and aromatic

aldehydes. In 2013, Ishimaru and co-workers[145] employed *N*-phenyl-L-valinamide **C13** as a catalyst in the reaction shown in Scheme 68, where both the diastereo- and enantioselectivity were moderate.

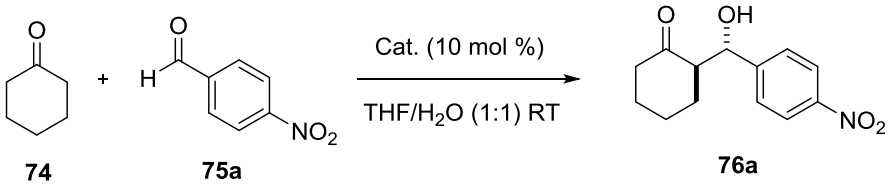


Scheme 68. *N*-phenyl-L-valinamide (**C13**) promoted asymmetric aldol reaction between cyclohexanone **74** and aldehyde **75a**.

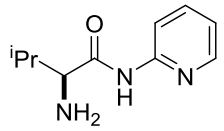
In order to increase the acidity of the amide group, in our laboratory, several *N*-pyridine-L-valinamide amino-amides prepared by my co-worker Dr. Hyo-Jun Lee where tested in the model reaction between cyclohexanone **74** and aldehyde **75a** (Table 14). The reaction did not proceed with pyridine derived catalyst **C14**, however, in the **C15** and **C16** promoted reactions complete conversion was obtained with a 10% catalyst loading, leading to enantioselectivities from poor to moderate. At this point, we decided to test the behaviour of the N-oxide analogues of catalysts **C14**, **C15** and **C16**, with a view to enhancing the acidity of the amide. The process remained essentially unreactive when promoted by **C17**, and the N-oxide catalyst **C18** performed just slightly better than its analogue **C15**. In contrast, catalyst **C19** showed to be considerably more efficient than its analogue **C16** in the model reaction, and was selected for further experiments. It is worth mentioning that with the more acidic triflate-substituted catalyst **C20**, only traces of the desired product were observed, which indicates the importance of controlling the acidity when it comes to designing amino-amide catalysts.

[145] Tanimura, Y.; Yasunaga, K.; Ishimaru, K. *Eur. J. Org. Chem.* **2013**, 6535−6539.

Table 14. Catalyst screening for the model reaction between **74** and **75a**.[a]

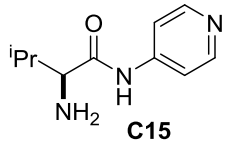


74 **75a** **76a**



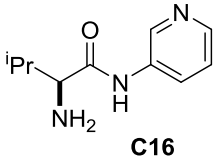
C14

THF/H_2O: 5 days, <5% conv.
dr: nd, 45% *ee*



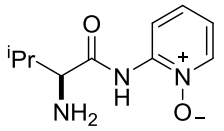
C15

THF/H_2O: 3 days, 100% conv.
78:22 dr, 86% *ee*



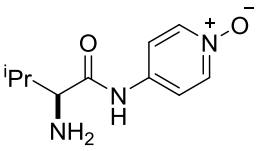
C16

THF/H_2O: 36 h, 100% conv.
77:23 dr, 37% *ee*



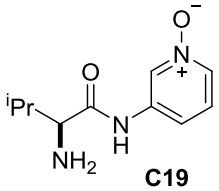
C17

THF/H_2O: 5 days, <5% conv.
dr: nd, 24% *ee*



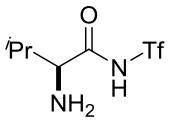
C18

THF/H_2O: 2 days, 100% conv.
78:22 dr, 89% *ee*



C19

THF/H_2O: 5 days, 100% conv.
85:15 dr, 90% *ee*



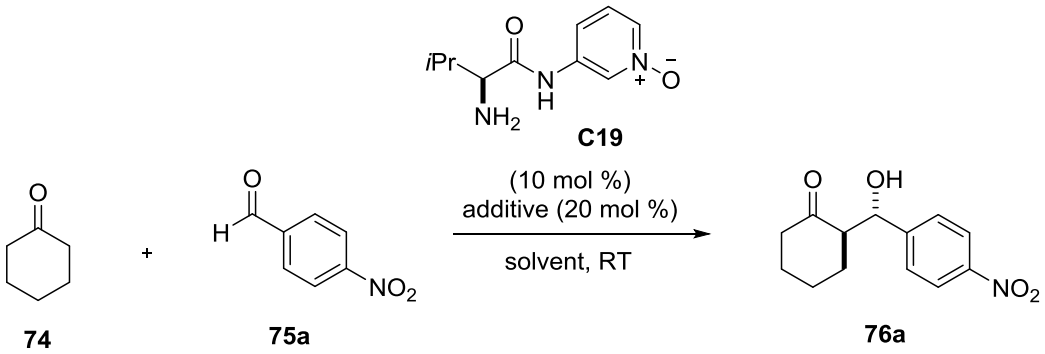
C20

THF/H_2O: 48 h, trace

[a]Reactions carried out on 0.1 mmol scale, with **74** (30 equiv.), catalyst (10 mol%) in 0.3 mL of THF/H_2O (1:1). Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. Conversion determined by ^1H NMR analysis.

Next, several co-solvents (1:1 with water) were screened (Table 15). DMF/H_2O (1:1 ratio) proved to be the only solvent comparable to THF/H_2O among the ones tested (entry 2), with an 86/14 *anti*/*syn* ratio, 91% *ee* and 100% conversion after 5 days. The addition of Brønsted acid additives could not improve the reaction leading to inferior results (compare entries 7-10 with 2).

Table 15. Solvent and additive screening of the reaction.[a]

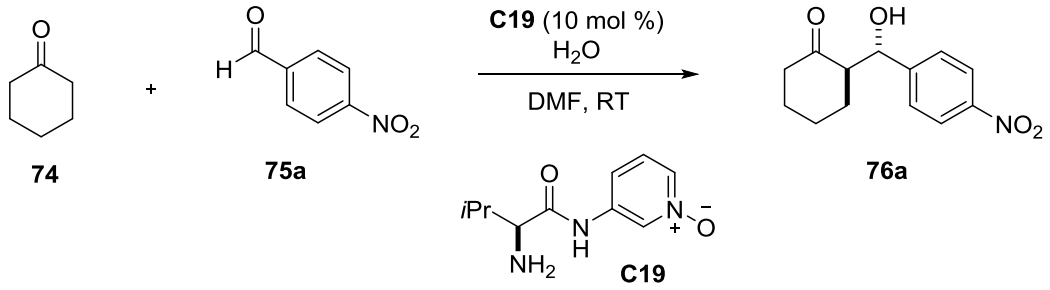


entry	solvent	additive	time	conv. (*anti*/*syn*)	*ee* (*anti*)
1	THF/H_2O	--	5 days	100% (85/15)	90%
2	DMF/H_2O	--	5 days	100% (86/14)	91%
3	MeCN/H_2O	--	6 days	90% (82/18)	43%
4	EtOH/H_2O	--	5 days	100% (85/15)	89%
5	Sat. NaCl	--	6 days	31% (84/16)	n.d.
6	neat	--	6 days	24% (74/26)	n.d.
7	DMF/H_2O	$PhCO_2H$	7 days	100% (80/20)	85%
8	DMF/H_2O	4-$NO_2C_6H_4CO_2H$	5 days	100% (82/18)	55%
9	DMF/H_2O	CF_3CO_2H	7 days	trace	n.d.
10	DMF/H_2O	HOAc	7 days	100% (86/14)	90%

[a]Reactions carried out on 0.1 mmol scale, with **74** (30 equiv.), catalyst (10 mol%) and additive (20 mol%) in 0.3 mL of solvent. Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. Conversion determined by ^{1}H NMR analysis.

Finally, we studied the effect of the amount of water in the reaction. As shown in Table 16, the absence of water in the medium makes the system essentially unreactive (entry 1, 13% conv.). Adding 5 equivalents of water to the reaction increases the reactivity, as 58% conversion is obtained in 72h (entry 2), and the best results are obtained with 10 equivalents of water (entry 3) in terms of conversion (95% in 72h) and stereoselectivity (91/9 *anti*/*syn*, 94% *ee*). Higher amounts of water decreased the reactivity (entries 4-6), which indicates that the optimal water equivalents for this system is around 10 (entry 3).

Table 16. Effect of the water in the aldol reaction between **74** and **75a** mediated by **C19**.[a]



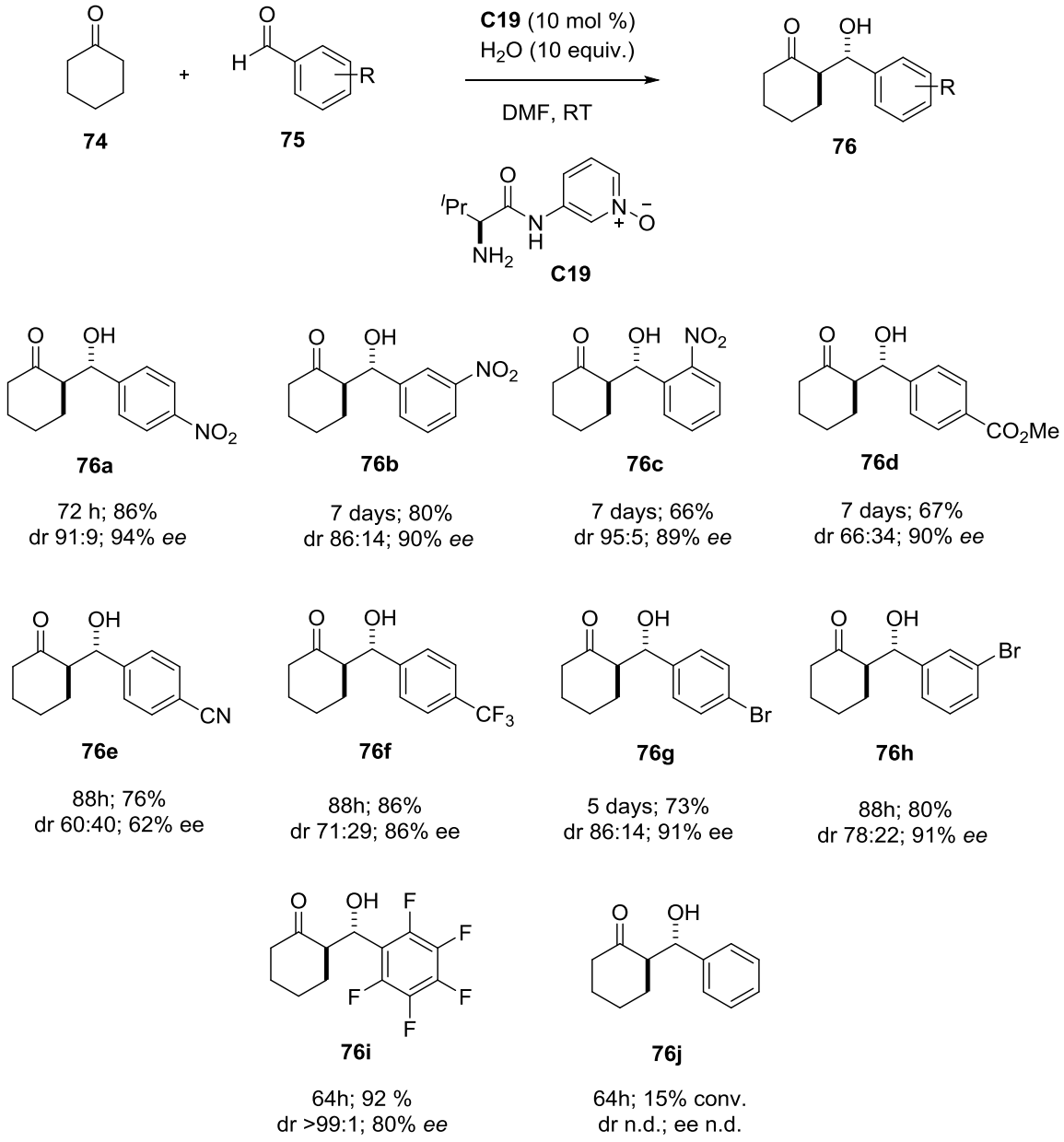
entry	solvent	additive	time	conv. (*anti*/*syn*)	*ee* (*anti*)
1	DMF	--	24h	13% (n.d.)	n.d.
2	DMF	H_2O (5 equiv.)	72h	58% (89/11)	88%
3	DMF	H_2O (10 equiv.)	72h	95% (91/9)	94%
4	DMF	H_2O (30 equiv.)	72h	76% (93/7)	88%
5	DMF	H_2O (50 equiv.)	72h	60% (90/10)	85%
6	DMF/H_2O (1:1)	--	72h	62% (86/14)	91%

[a]Reactions carried out on 0.1 mmol scale, with **74** (30 equiv.), catalyst (10 mol%) and water in 0.3 mL of DMF. Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. Conversion determined by ^{1}H NMR analysis.

4.2.2. Scope of the reaction

Under the optimized conditions (10 mol% **C19** and 10 equiv. of water in DMF at RT) we studied the scope of the reaction (Table 17). The reaction tolerated electron withdrawing substituents in the aromatic ring of the aldehyde, but the stereoselectivity of the process is substrate dependant. Although both enantio- and diastereoselectivities are high in most of the cases, low *anti*/*syn* selectivity is obtained when R = *p*-CO_2Me (**76d**) and R = *p*-CN. Moreover, **76e** is generated in moderate *ee* (62%). Unfortunately, the process seems to be limited to electron poor aldehydes, as 15% conversion was observed in 64h after the reaction with benzaldehyde to obtain **76j**.

Table 17. Scope of the reaction between **74** and **75** catalysed by **C19**.[a]



[a]Reactions carried out on 0.1 mmol scale, with **74** (30 equiv.), catalyst (10 mol%) and water (10 equiv.) in 0.3 mL of DMF. Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. Yields of isolated products after column chromatography are given.

Chapter 5

Conclusions

5. Conclusions

In summary, new catalytic methodologies have been described for the direct asymmetric functionalization of unsaturated ketones.

We have demonstrated that tertiary amine/squaramide bifunctional catalysts promote the addition of β,γ-unsaturated and β,γ,δ,ε-unsaturated ketones to nitroolefins through transiently generated di- and trienolates to afford the corresponding α-addition adducts exclusively with very good enantio- and diastereocontrol.

Specifically, the trienolate mediated α-selective reaction of β,γ,δ,ε-unsaturated ketones with nitroolefins can be coupled one-pot with a subsequent base-catalysed isomerization-intramolecular 1,6-addition domino process to afford tetrasubstituted cyclohexenes. The α-addition pathway observed for transiently generated trienolates is divergent from the [4+2] cycloaddition pathways dominant in trienamine mediated chemistry, thus providing a route to complementary cyclohexyl systems.

Next, we have described a bifunctional Brønsted base catalysed Michael addition/α-protonation cascade that involves 2,4-dimethyl-4-hydroxypenten-3-one as design methacrylate equivalent. This method enables a direct approach to the construction of acyclic carbonyl compounds with nonadjacent all carbon tertiary/quaternary stereocenters with high diastereo- and enantioselectivity. Implementation of this method to chiral α-substituted α´-silyloxy enones allows, upon subsequent diastereoselective carbonyl reduction, access to linear-chain stereoarrays with up to four stereogenic centers.

Finally, as a part of an international stay under the supervision of Prof. Keiji Maruoka at the Kyoto University, an easily accesible new amino-amide type catalyst has been described, *N*-phenyl-L-valinamide, which is able to promote the aldol reaction between cyclohexanone and aromatic aldehydes, thus increasing the pool of primary amine based catalyst.

Chapter 6

Experimental section

6. Experimental section

6.1. Materials and techniques

6.1.1. Reagents and solvents

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

Amine bases triethylamine, DBU, DIPA and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at –30 °C under nitrogen.

When anhydrous solvents were required, they were dried following established procedures.[146] Dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma Aldrich) columns.

$(DHQD)_2PYR$ (**C6**) and quinine (**C7**) were purchased from Alfa Aesar and catalysts **C1**,[147] **C2**,[148] **C3**,[149] **C4**,[150] **C8**,[151] **C9**,[150] **C10**,[148] **C11**[148] and **C12**[148] were prepared following the procedures described in the literature. Nitroalkenes were also prepared according to the literature.[152]

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

[147] a) McCooey, S. H.; Connon, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367−6370. b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. c) Vakulya, B.; Varga, S.; Csampai, A.; Sojs, T. *Org. Lett.* **2005**, *7*, 1967−1969. d) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603−606.

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

[149] a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. b) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153−156.

[150] a) Yang, W.; Du, D. M. *Adv. Synth. Catal.* **2011**, *353*, 1241−1246. b) Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450−5453.

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

[152] Aromatic nitroalkenes: a) J. Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem.* **1985**, *63*, 2354−2361. Aliphatic nitroalkenes: b) Trost, B. M.; Muller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438−2439.

6.1.2. General experimental

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

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

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

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

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, pentane/diethyl ether or dichloromethane/methanol) as eluent.

6.1.4. Optical rotation

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

6.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and are 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), JEOL JNM – FX400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) and JNM – ECA500 (500 MHz for ^{1}H, 150 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ= 7.26) and ^{13}C (δ= 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

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

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. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) or in the department of chemistry at the Kyoto University.

6.1.8. Infrared spectra

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

6.1.9. Gas chromatography

Performed using a Thermo Scientific Trace 1300 equipment with a FID. Chiral column HYDRODEX β-6TBDM, 25 m, 0.25 mm ID. Temperature gradient: 1) 100 °C for 1 min; 2) from 100 °C to 200 °C at a heating rate of 10 °C/min (11 min); 3) 200 °C for an additional 11 min.

6.1.10. Determination of enantiomeric excesses

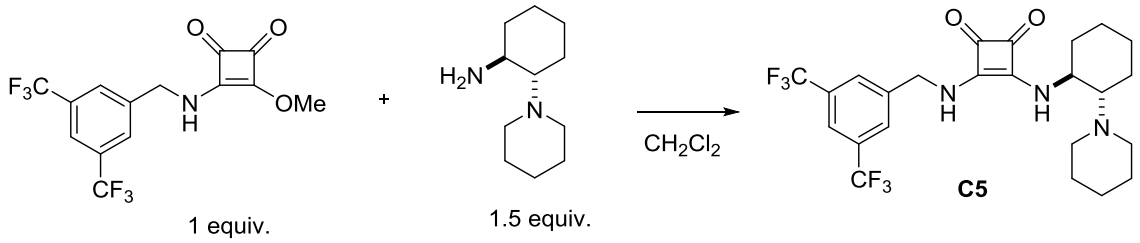
Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on either a Waters 600 (equipped with Photodiode Array Detector Waters 2996) or Shimadzu 20A instrument. The used columns were Chiralpack AS-H, AD-H, AY-H, IA, IB and IC; and flow/solvent conditions are given for each compound.

6.1.11. 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. Experimental section of Chapter 2

6.2.1. Preparation of catalyst C5[153]

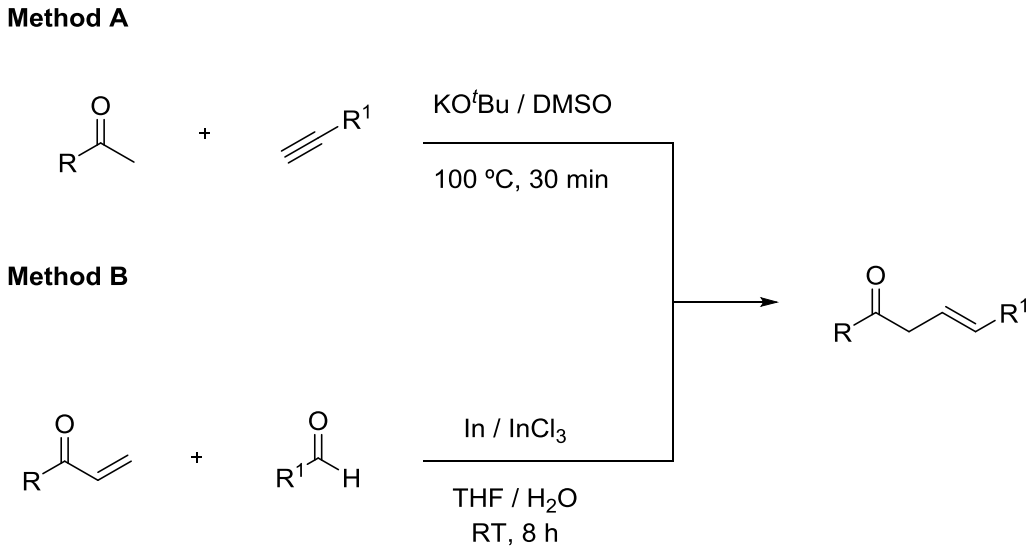


To a solution of (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine[154] (273 mg, 1.5 mmol, 1.5 equiv.) in CH_2Cl_2 O-methyl N-(3,5-trifluoromethylphenylmethyl) squaric acid hemiamide[155] (353 mg, 1 mmol, 1 equiv.) was added and the reaction mixture was stirred until consumption of the squarate (monitored by TLC, 48 h). The solvent was removed under reduced pressure and Et_2O was added to the crude product. The formed precipitate was filtered and washed with Et_2O to give title compound as a yellow solid (363 mg, 72%). $[\alpha]_D^{22}$= +19.01° (*c*= 0.33, DMSO). [Lit[6b] (**ent-C5**) $[\alpha]_D^{20}$= −4.81° (*c*= 0.31, DMSO)]. m. p.: 253–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ8.07 (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),

[153] **Ent-C5**: a) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028−2031. b) Baran, R.; Veverková, E.; Skvorcová, A.; Sebesta, R. *Org. Biomol. Chem.* **2013**, *11*, 7705−7711.
[154] Prepared as in: W. Yang, D. M. Du, *Adv. Synth. Catal.* **2011**, 353, 1241−1246.
[155] Prepared as in: J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, 130, 14416−14417.

1.84 –1.58 (m, 4H), 1.19 (d, J= 22.1 Hz, 10H). ^{13}C NMR (101 MHz, DMSO-d_6) δ182.9, 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.

6.2.2. General procedure for the preparation of allyl ketones 1-4



Method A:[156]

A mixture of the corresponding methyl ketone (5.0 mmol, 1 equiv.), alkyne (5.0 mmol, 1 equiv.) and KO^{t}Bu (561 mg, 5.0 mmol, 1 equiv.) in DMSO (12 mL) was heated to 100 °C and stirred for 30 min. The reaction mixture was cooled to room temperature and was diluted with H_2O (12 mL), neutralized with a saturated aqueous solution of NH_4Cl, and extracted with Et_2O (12 mL × 4). The organic extract was washed with H_2O (6 mL × 3) and dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 97/3).

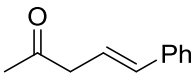
Method B:[157]

A mixture of the corresponding aldehyde (5.0 mmol, 1 equiv.), In powder (1.15 g, 10 mmol, 2 equiv.), $InCl_3$ (553 mg, 2.5 mmol, 0.5 equiv.) and the corresponding vinyl ketone

[156] B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem.* **2012**, 77, 6880–6886.
[157] S. Kang, T. S. Jang, G. Keum, S. B. Kang, S. Y. Han, Y. Kim, *Org. Lett.* **2000**, 2, 3615–3617.

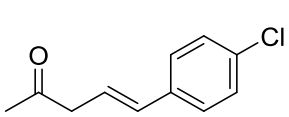
(15 mmol, 3 equiv.) in a mixture of THF and H_2O (1 : 1, 30 mL) was stirred at room temperature for 8 h. After the addition of 1 M HCl (15 mL), the reaction mixture was stirred for 30 min and extracted with ethyl acetate (50 mL × 4). The combined organic phases were washed with brine (100 mL) and dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 97/3).

(*E*)-5-Phenylpent-4-en-2-one (1A)



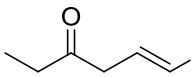
Prepared according to Method B starting from methyl vinyl ketone and benzaldehyde. The title compound was isolated as a colourless oil. Yield: 561 mg (70%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.20 (m, 5H), 6.52 (dt, *J* = 15.8, 1.3 Hz, 1H), 6.35 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.38 (dd, *J* = 7.0, 1.2 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 207.2, 137.4, 134.4, 129.2, 128.2, 126.8, 122.5, 48.3, 30.2. UPLC-DAD-QTOF: $C_{11}H_{12}O$ $[M+H]^+$ calcd.: 161.0966, found: 161.0969. ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 156.

(*E*)-5-(4-Chlorophenyl)pent-4-en-2-one (1B)



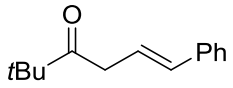
Prepared according to Method B starting from methyl vinyl ketone and 4-chlorobenzaldehyde. The title compound was isolated as a colourless oil. Yield: 730 mg (75%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 4H), 6.46 (dt, *J* = 15.9, 1.2 Hz, 1H), 6.33 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.38 (d, *J* = 6.4 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 205.9, 135.2, 132.8, 132.1, 128.4, 127.2, 122.5, 47.2, 29.4. UPLC-DAD-QTOF: $C_{11}H_{11}ClO$ $[M+H]^+$ calcd.: 195.0577, found: 195.0567.

(*E*)-6-Phenylhex-5-en-3-one (2A)



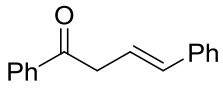
Prepared according to Method B starting from ethyl vinyl ketone and benzaldehyde. The title compound was isolated as a colourless oil. Yield: 793 mg (92%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.23 (m, 5H), 6.57 – 6.44 (m, 1H), 6.36 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.33 (d, *J* = 6.9 Hz, 2H), 2.53 (q, *J* = 7.3 Hz, 2H), 1.11 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 209.3, 137.2, 133.7, 128.8, 127.7, 126.4, 122.5, 46.7, 35.8, 7.9. UPLC-DAD-QTOF: $C_{12}H_{14}O$ $[M+H]^+$ calcd.: 175.1123, found: 175.1125.

(*E*)-2,2-Dimethyl-6-phenylhex-5-en-3-one (3A)



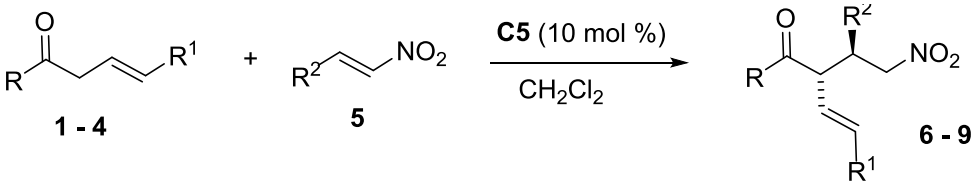
Prepared according to Method A starting from 3,3-dimethyl-2-butanone and phenylacetylene. The title compound was isolated as a brown oil. Yield: 860 mg (85%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.21 (m, 5H), 6.50 (d, *J* = 16.2 Hz, 1H), 6.46 – 6.35 (m, 1H), 3.48 (d, *J* = 6.1 Hz, 2H), 1.24 (s, 9H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 213.8, 133.1, 128.8, 127.6, 126.5, 123.7, 44.7, 40.9, 26.7. UPLC-DAD-QTOF: $C_{14}H_{18}O$ $[M+H]^+$ calcd.: 203.1436, found: 203.1438. ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 156.

(*E*)-1,4-Diphenylbut-3-en-1-one (4A)



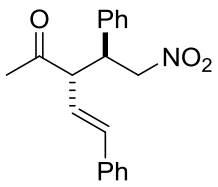
Prepared according to Method A starting from acetophenone and phenylacetylene. The title compound was isolated as a white solid. Yield: 889 mg (80 %). m. p.: 86 – 88 °C. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.13 – 8.02 (m, 2H), 7.69 – 7.21 (m, 8H), 6.61 (d, *J* = 16.1 Hz, 1H), 6.58 – 6.47 (m, 1H), 3.96 (d, *J* = 5.8 Hz, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 197.9, 136.9, 136.5, 133.5, 133.2, 128.6, 128.4, 128.2, 127.4, 126.2, 122.5, 42.6. UPLC-DAD-QTOF: $C_{16}H_{14}O$ $[M+H]^+$ calcd.: 223.1123, found: 223.1120. ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 156.

6.2.3. Catalytic conjugate addition of allyl ketones 1-4 to nitroalkenes 5



General procedure: To a mixture of the corresponding allyl ketone (0.3 mmol, 1.5 equiv.) and nitroalkene (0.2 mmol, 1 equiv.) in dichloromethane (0.4 mL), the catalyst (0.02 mmol, 10 mol %) was added at 0 °C. The resulting mixture was stirred at 0 °C for 16 h. The reaction mixture was directly submitted to a flash column chromatography (eluent hexane/ethyl acetate 95/5) to obtain essentially pure Michael adduct.

(*S*,*E*)-3-((*S*)-2-Nitro-1-phenylethyl)-5-phenylpent-4-en-2-one (6Aa)

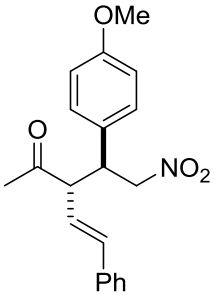


Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 51 mg (83%). m. p.: 131 – 133 °C. $[\alpha]_D^{25}$ = −47.6° (c=0.5, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.21 (m, 10H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.8, 9.8 Hz, 1H), 4.84 – 4.58 (m, 2H), 4.08 (td, *J* = 10.1, 5.0 Hz, 1H), 3.80 (t, *J* = 10.1 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (75

MHz, Chloroform-*d*) δ 206.4, 138.2, 137.1, 136.3, 129.7, 129.5, 129.2, 128.8, 128.6, 127.2, 124.4, 79.3, 61.4, 45.8, 30.9. UPLC-DAD-QTOF: $C_{19}H_{19}NO_3$ $[M+H]^+$ calcd.: 310.1443, found: 310.1443.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

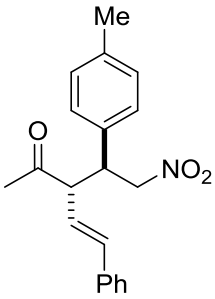
(*S*,*E*)-3-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ab)



Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5b**. The title compound was isolated as a mixture of diastereomers (dr 6.0:1) as a white solid. Yield: 64 mg (95%). ^{1}H NMR of major isomer (300 MHz, Chloroform-*d*) δ 7.49 – 7.24 (m, 6H), 7.22 – 7.17 (m, 2H), 6.91 – 6.86 (m, 2H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.8, 9.8 Hz, 1H), 4.84 – 4.52 (m, 2H), 4.02 (td, *J* = 10.0, 4.9 Hz, 1H), 3.81 (s, 4H), 1.99 (s, 3H). ^{13}C NMR major isomer (75 MHz, Chloroform-*d*) δ 204.1, 157.4, 134.4, 133.8, 127.4, 127.1, 126.9, 126.6, 124.7, 122.0, 112.6, 77.0, 59.0, 53.3, 42.7, 28.4. UPLC-DAD-QTOF: $C_{20}H_{21}NO_4$ $[M+H]^+$ calcd.: 340.1549, found: 340.1555.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

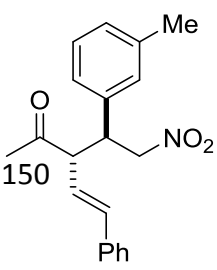
(*S*,*E*)-3-((*S*)-2-Nitro-1-(p-tolyl)ethyl)-5-phenylpent-4-en-2-one (6Ac)



Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5c**. The title compound was isolated as a mixture of diastereomers (dr 6.0:1) as a white solid. Yield: 52 mg (90%). ^{1}H NMR major isomer (300 MHz, Chloroform-*d*) δ 7.48 – 7.05 (m, 9H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.13 (dd, *J* = 15.8, 9.8 Hz, 1H), 4.81 – 4.54 (m, 2H), 4.12 – 3.99 (m, 1H), 3.80 (t, *J* = 10.1 Hz, 1H), 2.34 (d, *J* = 6.9 Hz, 3H), 2.00 (s, 3H). ^{13}C NMR major isomer (75 MHz, Chloroform-*d*) δ 204.1, 136.0, 134.5, 133.9, 132.6, 127.9, 127.0, 126.7, 125.9, 124.7, 122.1, 77.0, 58.9, 43.1, 28.4, 19.3. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 324.1600, found: 324.1605.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

(*S*,*E*)-3-((*S*)-1-(3-Methoxyphenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ad)

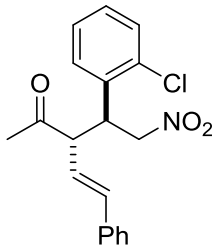


Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5d**. The title compound was isolated as a mixture of

diastereomers (dr 6.4:1) as a colourless oil. Yield: 49 mg (72%). ^{1}H NMR major isomer (300 MHz, Chloroform-*d*) δ 7.45 – 7.05 (m, 9H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.19 – 6.06 (m, 1H), 4.81 – 4.59 (m, 2H), 4.05 (td, *J* = 10.2, 5.1 Hz, 1H), 3.81 (t, *J* = 10.2 Hz, 1H), 2.37 (s, 3H), 2.00 (s, 3H). ^{13}C NMR major isomer (75 MHz, Chloroform-*d*) δ 204.1, 137.0, 135.7, 134.6, 134.0, 133.8, 127.1, 127.1, 126.8, 124.8, 122.9, 122.1, 77.0, 59.0, 43.4, 28.5, 19.7. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 324.1600, found: 324.1605.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

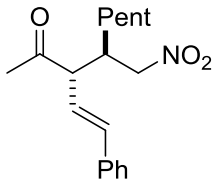
(*S*,*E*)-3-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ae)



Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5e**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 50 mg (72%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 – 7.15 (m, 9H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.11 (dd, *J* = 15.8, 9.8 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 2H), 4.55 (q, *J* = 7.3 Hz, 1H), 4.12 (t, *J* = 9.6 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 206.1, 137.6, 136.0, 135.3, 131.0, 129.6, 129.2, 129.0, 127.7, 127.0, 123.4, 76.8, 58.9, 30.1. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 344.1053, found: 344.1051.

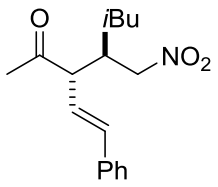
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

(3*S*,4*R*)-4-(Nitromethyl)-3-((*E*)-styryl)nonan-2-one (6Ah)



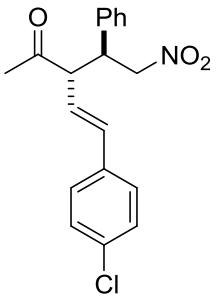
Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5h**. 30 % conversion was obtained after 24 h. The resulting mixture was not separated nor further analyzed.

(3*S*,4*R*)-6-Methyl-4-(nitromethyl)-3-((*E*)-styryl)heptan-2-one (6Ai)



Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5i**. 30 % conversion was obtained after 24 h. The resulting mixture was not separated nor further analyzed.

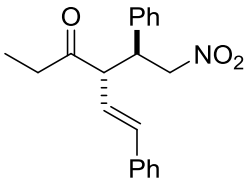
(*S*,*E*)-5-(4-Chlorophenyl)-3-((*S*)-2-nitro-1-phenylethyl)pent-4-en-2-one (6Ba)



Prepared according to the general procedure starting from allyl ketone **1B** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 50 mg (73%). m. p.: 120 – 122 °C. $[\alpha]_D^{25}$ = −88.0° (c=1, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.21 (m, 9H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.10 (dd, *J* = 15.8, 9.8 Hz, 1H), 4.89 – 4.56 (m, 2H), 4.17 – 4.02 (m, 1H), 3.91 – 3.71 (m, 1H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 206.0, 137.8, 135.5, 134.5, 129.5, 129.4, 128.6, 128.3, 128.2, 124.8, 79.0, 61.1, 45.6, 30.7. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 344.1053, found: 344.1053.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 98/2, flow rate= 1 mL/min.

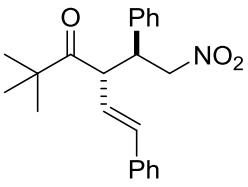
(*S*,*E*)-4-((*S*)-2-Nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (7Aa)



Prepared according to the general procedure starting from allyl ketone **2A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 54 mg (83 %). m. p.: 94 – 96 °C. $[\alpha]_D^{25}$ = −115.2° (c=0.4, 95% *ee*, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.23 (m, 11H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.13 (dd, *J* = 15.8, 9.9 Hz, 1H), 4.83 – 4.60 (m, 2H), 4.09 (td, *J* = 10.2, 5.0 Hz, 1H), 3.76 (t, *J* = 10.2 Hz, 1H), 2.52 – 2.40 (m, 1H), 2.02 (dq, *J* = 18.2, 7.3 Hz, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.5, 137.5, 136.0, 129.0, 128.8, 128.5, 128.0, 127.9, 126.5, 124.2, 78.6, 60.2, 45.3, 36.5, 7.2. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 324.1600, found: 324.1602.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

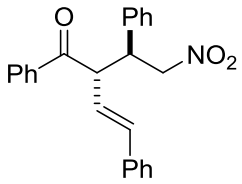
(*S*,*E*)-2,2-Dimethyl-4-((*S*)-2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (8Aa)



Prepared according to the general procedure starting from allyl ketone **3A** and nitroalkene **5a.** Reaction conducted at RT using 2 equiv. of ketone. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 48 mg (68%). $[\alpha]_D^{25}$ = − 55.5° (c=0.4, 84% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.17 (m, 10H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.07 (dd, *J* = 16.0, 9.3 Hz, 1H), 4.94 – 4.69 (m, 2H), 4.24 – 4.00 (m, 2H), 0.83 (s, 9H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 213.6, 138.9, 136.7, 129.9, 129.5, 129.5, 129.1, 127.6, 126.6, 79.2, 56.6, 46.9, 30.8, 27.1. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 352.1913, found: 352.1918.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

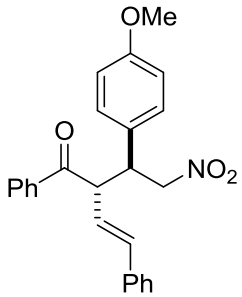
(*S*,*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-1,4-diphenylbut-3-en-1-one (9Aa)



Prepared according to the general procedure starting from allyl ketone 4A and nitroalkene 5a. The title compound was isolated as a single diastereomer as a white solid. Yield: 56 mg (75%). m. p.: 158 – 160 °C. $[\alpha]_D^{25}$ = −45.4° (c= 1, 95% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 – 7.78 (m, 2H), 7.59 – 7.17 (m, 13H), 6.75 (d, *J* = 15.9 Hz, 1H), 6.37 – 6.24 (m, 1H), 4.99 – 4.87 (m, 1H), 4.87 – 4.72 (m, 2H), 4.33 (td, *J* = 9.7, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 197.8, 137.7, 136.4, 135.7, 133.3, 128.9, 128.7, 128.6, 128.5, 128.2, 127.9, 126.5, 124.5, 78.6, 54.4, 45.6. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 372.1600, found: 372.1599.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

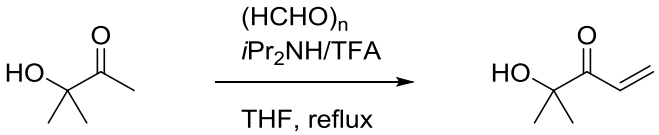
(*S*,*E*)-2-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,4-diphenylbut-3-en-1-one (9Ab)



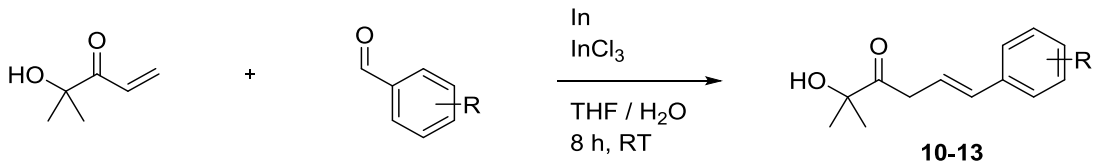
Prepared according to the general procedure starting from allyl ketone **4A** and nitroalkene **5a**. The title compound was isolated as a mixture of diastereomers (dr 8.1:1) as a colourless oil. Yield: 63 mg (78%). ^{1}H NMR major isomer (300 MHz, Chloroform-*d*) δ 7.95 – 7.76 (m, 2H), 7.63 – 7.09 (m, 9H), 6.85 – 6.69 (m, 3H), 6.27 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.99 – 4.58 (m, 4H), 4.29 (td, *J* = 9.9, 4.9 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR major isomer (75 MHz, Chloroform-*d*) δ 196.1, 157.1, 134.6, 134.4, 133.9, 131.4, 127.7, 127.4, 127.1, 126.8, 126.7, 126.4, 124.6, 122.8, 112.4, 77.0, 53.2, 52.7, 43.1. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3$ $[M+H]^+$ calcd.: 402.1705, found: 402.1709.

The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

6.2.4. Preparation of allylic hydroxyketones 10-13



2-Hydroxy 2-methyl pent-4-en-3-one:[158] Commercially available 3-hydroxy-3-methyl-2-butanone (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde (2 equiv., 3 g, 100 mmol) were added to a solution of *i*Pr_2NH (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure (230 mbar/ bath 40 °C). The residue was purified by flash column chromatography on silica gel (eluent: diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one as colorless oil which was obtained in sufficient purity to be used in the next step. Yield: 5.0 g, 44.5 mmol, 89%.



Allyl hydroxyketones 10-13.[159] A mixture of the corresponding benzaldehyde (3.0 mmol, 3 equiv.), In powder (230 mg, 2 mmol, 2 equiv.), $InCl_3$ (110 mg, 0.5 mmol, 0.5 equiv.) and 2-hydroxy 2-methyl pent-4-en-3-one (186 mg, 1 mmol, 1 equiv.) in a mixture of THF and H_2O (1 : 1, 16 mL) was stirred at room temperature for 8 h. After the addition of 1 M HCl (15 mL), the reaction mixture was stirred for 30 min and then extracted with ethyl acetate (15 mL × 4). The combined organic phases were washed with brine and dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10).

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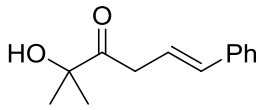
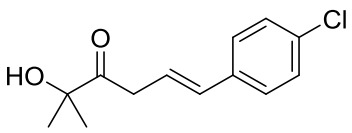
[158] a) Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun*. **2010**, *46*, 1715-1717. b) For an alternative method see: E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881.
[159] Adapted from: S. Kang, T. S. Jang, G. Keum, S. B. Kang, S. Y. Han, Y. Kim, *Org. Lett.* **2000**, 2, 3615–3617.

(*E*)-2-Hydroxy-2-methyl-6-phenylhex-5-en-3-one (10)



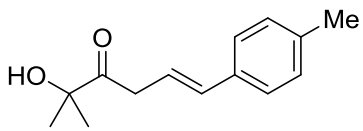
Prepared according to the general procedure starting from benzaldehyde. The title compound was isolated as a colourless oil. Yield: 129 mg (63%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.24 (m, 5H), 6.63 – 6.45 (m, 1H), 6.37 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.55 (dd, *J* = 6.7, 1.3 Hz, 2H), 1.47 (s, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 212.6, 137.1, 134.1, 128.9, 128.0, 126.6, 121.9, 76.8, 40.1, 26.9. UPLC-DAD-QTOF: $C_{13}H_{16}O_2$ $[M+H]^+$ calcd.: 205.1229, found: 205.1234.

(*E*)-6-(4-Chlorophenyl)-2-hydroxy-2-methylhex-5-en-3-one (11)



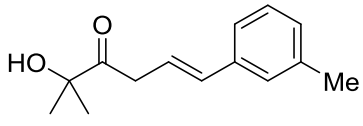
Prepared according to the general procedure starting from 4-chlorobenzaldehyde. The title compound was isolated as a yellow oil. Yield: 162 mg (68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.07 (m, 4H), 6.44 (dt, *J* = 15.9, 1.3 Hz, 1H), 6.34 (s, 1H), 3.52 (dd, *J* = 6.7, 1.3 Hz, 2H), 1.44 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.4, 135.5, 133.4, 132.7, 128.9, 127.7, 122.6, 76.7, 39.8, 26.7. UPLC-DAD-QTOF: $C_{13}H_{15}ClO_2$ $[M+H]^+$ calcd.: 239.0839, found: 239.0838.

(*E*)-2-Hydroxy-2-methyl-6-(p-tolyl)hex-5-en-3-one (12)



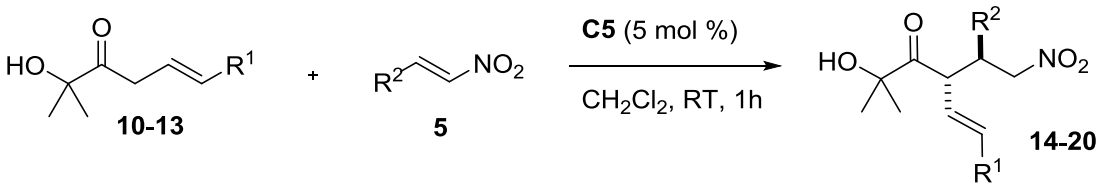
Prepared according to the general procedure starting from 4-methylbenzaldehyde. The title compound was isolated as a yellow oil. Yield: 157 mg (72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.33 (s, 1H), 3.53 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.36 (s, 3H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.9, 144.8, 137.9, 134.5, 134.1, 130.7, 129.8, 126.7, 121.0 , 77.0, 40.2, 27.0, 21.7. UPLC-DAD-QTOF: $C_{14}H_{18}O_2$ $[M+H]^+$ calcd.: 219.1385, found: 219.1389.

(*E*)-2-Hydroxy-2-methyl-6-(m-tolyl)hex-5-en-3-one (13)



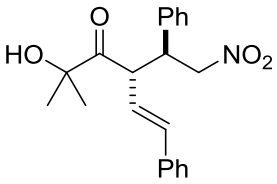
Prepared according to the general procedure starting from 3-methylbenzaldehyde. The title compound was isolated as a yellow oil. Yield: 157 mg (72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.15 (m, 4H), 6.58 – 6.44 (m, 1H), 6.37 (s, 1H), 3.53 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.38 (s, 3H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.9, 138.6, 137.2, 134.3, 131.4, 129.0, 128.9, 127.5, 124.0, 121.9, 77.0, 68.7, 40.2, 27.0, 21.9. UPLC-DAD-QTOF: $C_{14}H_{18}O_2$ $[M+H]^+$ calcd.: 219.1385, found: 219.1387.

6.2.5. Catalytic conjugate addition of allylic ketols 10-13 to nitroalkenes 5:



General procedure: To a solution of the corresponding allylic ketol (0.2 mmol, 1 equiv.) and nitroalkene **5** (0.22 mmol, 1.1 equiv.) in dichloromethane (0.4 mL), catalyst **C5** (0.01 mmol, 5 mol %) was added at 0 °C and the resulting homogeneous solution was stirred at RT for 2 h unless otherwise stated. The reaction mixture was directly submitted to flash column chromatography (eluent hexane/ethyl acetate 90/10).

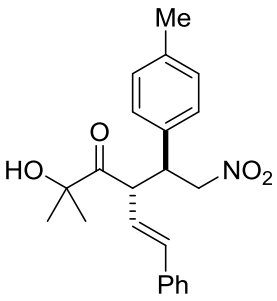
(*S*,*E*)-2-Hydroxy-2-methyl-4-((*S*)-2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (14)



Prepared according to the general procedure starting from allylic ketol **10** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 60 mg (85%). m. p.: 143 – 145 °C. $[\alpha]_D^{25}$ = −60.3° (c= 1, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.24 (m, 10H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.95 – 4.69 (m, 2H), 4.37 – 4.11 (m, 2H), 1.08 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 211.6, 128.9, 128.8, 128.6, 128.3, 126.5, 124.3, 78.0, 54.5, 45.7, 26.1, 25.9. UPLC-DAD-QTOF: $C_{21}H_{23}NO_4$ $[M+H]^+$ calcd.: 354.1705, found: 354.1707.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 90/10, flow rate= 1.0 mL/min.

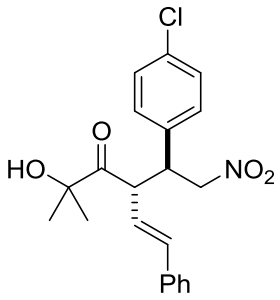
(*S*,*E*)-2-Hydroxy-2-methyl-4-((*S*)-2-nitro-1-(p-tolyl)ethyl)-6-phenylhex-5-en-3-one (15)



Prepared according to the general procedure starting from allylic ketol **10** and nitroalkene **5c**. The title compound was isolated as a single diastereomer as a white solid. Yield: 58 mg (79 %). m. p.: 146 – 148 °C. $[\alpha]_D^{25}$ = −80.5° (c= 1.5, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.19 (m, 4H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.10 (ddd, *J* = 15.9, 9.6, 0.9 Hz, 1H), 4.85 – 4.65 (m, 2H), 4.25 (d, *J* = 10.1 Hz, 1H), 4.16 (s, 1H), 2.33 (d, *J* = 7.9 Hz, 3H), 1.09 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 211.3, 137.5, 135.7, 135.0, 133.8, 129.1, 128.3, 128.1, 127.6, 126.0, 124.0, 77.7, 76.8, 54.0, 44.9, 25.7, 25.4, 20.6. UPLC-DAD-QTOF: $C_{22}H_{25}NO_4$ $[M+H]^+$ calcd.: 368.1862, found: 368.1860.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

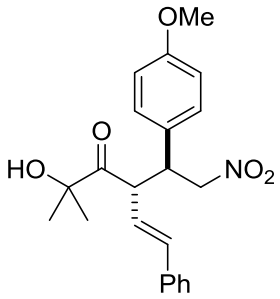
(*S*,*E*)-4-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (16)



Prepared according to the general procedure starting from allylic ketol **10** and nitroalkene **5f**. The title compound was isolated as a single diastereomer as a white solid. Yield: 64 mg (82%). m. p.: 166 – 168 °C. $[\alpha]_D^{25}$ = −102.6° (c= 0.5, 95% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.17 (m, 9H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.06 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.86 – 4.60 (m, 2H), 4.28 (dd, *J* = 10.8, 9.5 Hz, 1H), 4.18 (dd, *J* = 10.3, 4.8 Hz, 1H), 1.08 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 211.1, 136.5, 135.7, 135.1, 133.9, 129.4, 128.8, 128.6, 128.5, 126.3, 123.5, 77.7, 53.9, 44.7, 26.1, 26.0. UPLC-DAD-QTOF: $C_{21}H_{22}ClNO_4$ $[M+H]^+$ calcd.: 388.1316, found: 388.1323.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

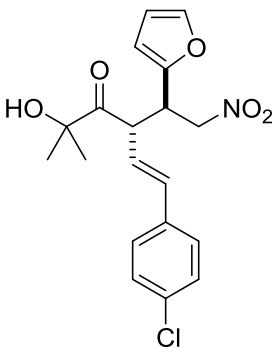
(*S*,*E*)-2-Hydroxy-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-methyl-6-phenylhex-5-en-3-one (17)



Prepared according to the general procedure starting from allylic ketol **10** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a white solid. Yield: 58 mg (75%). m. p.: 154 – 156 °C. $[\alpha]_D^{25}$ = −94.1° (c= 1.2, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.29 (m, 4H), 7.24 – 7.13 (m, 2H), 6.90 – 6.83 (m, 2H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.08 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.87 – 4.61 (m, 2H), 4.24 (dd, *J* = 10.8, 9.6 Hz, 1H), 4.12 (td, *J* = 10.4, 5.0 Hz, 1H), 3.79 (s, 3H), 1.00 (d, *J* = 53.0 Hz, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 212.4, 160.0, 136.9, 136.2, 130.0, 129.8, 129.5, 129.3, 127.2, 125.2, 115.0, 79.0, 55.9, 55.3, 45.7, 26.9, 26.7. UPLC-DAD-QTOF: $C_{22}H_{25}NO_5$ $[M+H]^+$ calcd.: 384.1811, found: 384.1807.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

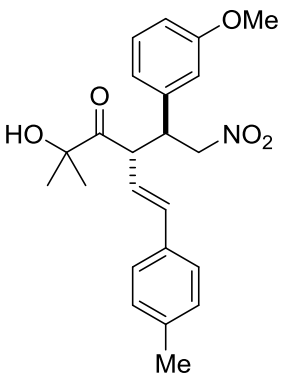
(*S*,*E*)-6-(4-Chlorophenyl)-4-((*R*)-1-(furan-2-yl)-2-nitroethyl)-2-hydroxy-2-methylhex-5-en-3-one (18)



Prepared according to the general procedure starting from allylic ketol **11** and nitroalkene **5g**. The title compound was isolated as a single diastereomer as a white solid. Yield: 66 mg (87%). m. p.: 130 – 132 °C. $[\alpha]_D^{25}$ = −77.7° (c= 0.5, 98% *ee*, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.24 (m, 7H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 6.02 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.79 – 4.68 (m, 2H), 4.45 – 4.25 (m, 2H), 1.23 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.4, 149.8, 142.5, 135.5, 134.5, 133.8, 129.0, 127.7, 124.4, 110.8, 109.5, 77.7, 75.9, 52.1, 39.7, 26.2, 25.6. UPLC-DAD-QTOF: $C_{19}H_{20}ClNO_5Na$ $[M+Na]^+$ calcd.: 400.0928, found: 400.0929.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

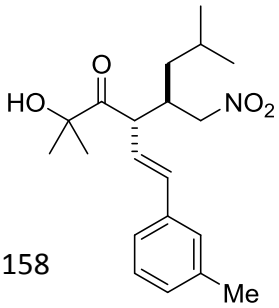
(*S*,*E*)-2-Hydroxy-4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-2-methyl-6-(p-tolyl)hex-5-en-3-one (19)



Prepared according to the general procedure starting from allylic ketol **12** and nitroalkene **5d**. The title compound was isolated as a colourless oil. Yield: 60 mg (75%). $[\alpha]_D^{25}$ = −128.9° (c= 0.1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.16 (m, 5H), 6.87 – 6.75 (m, 3H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.02 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.83 – 4.65 (m, 2H), 4.25 (t, *J* = 10.2 Hz, 1H), 4.15 (dt, *J* = 10.5, 5.2 Hz, 1H), 3.81 (s, 3H), 2.38 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.0, 160.2, 136.6, 133.0, 130.2, 129.8, 126.8, 123.5, 120.5, 114.9, 113.6, 78.4, 55.6, 54.8, 46.0, 26.6, 26.3, 21.5. UPLC-DAD-QTOF: $C_{23}H_{27}NO_5$ $[M+H]^+$ calcd.: 398.1967, found: 398.1968.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

(4*S*,5*R*)-2-Hydroxy-2,7-dimethyl-4-((*E*)-3-methylstyryl)-5-(nitromethyl)octan-3-one (20)



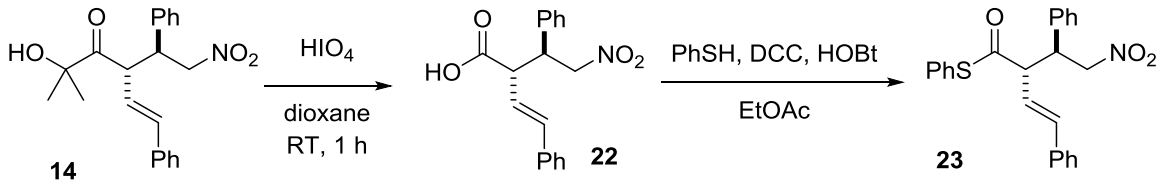
Prepared according to the general procedure starting from allylic ketol 1**3** and nitroalkene **5i** and running the reaction for 16 h. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 57 mg (82%). $[\alpha]_D^{25}$ = −162.9° (c= 1, 98% *ee*,

CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.09 (m, 4H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.00 (dd, *J* = 15.9, 9.7 Hz, 1H), 4.57 (ddd, *J* = 84.5, 13.0, 4.8 Hz, 2H), 4.08 (t, *J* = 9.1 Hz, 1H), 2.78 (dp, *J* = 13.8, 4.9 Hz, 1H), 1.80 – 1.68 (m, 1H), 1.43 (d, *J* = 17.2 Hz, 6H), 1.21 (dddd, *J* = 81.2, 14.0, 9.1, 5.1 Hz, 2H), 0.94 (dd, *J* = 6.5, 4.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 214.8, 139.5, 137.6, 136.9, 130.3, 129.8, 128.3, 125.1, 124.8, 77.0, 52.8, 40.6, 38.8, 28.1, 27.9, 26.4, 24.3, 22.6, 22.5. UPLC-DAD-QTOF: $C_{20}H_{29}NO_4$ $[M+H]^+$ calcd.: 348.2175, found: 348.2185.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 99/1, flow rate= 1.0 mL/min.

6.2.6. Elaboration of adducts

6.2.6.1. *Transformation of adduct 14 into acid 22 and thioesther 23*

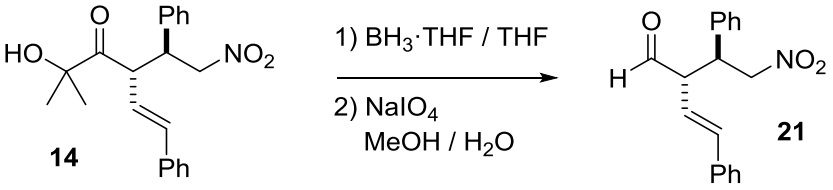


(*S*,*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-4-phenylbut-3-enoic acid (22): Procedure adapted from ref. 160. To a solution of the adduct **14** (106 mg, 0.3 mmol, 1 equiv.) in dioxane (1 mL), HIO_4 was added (410 mg, 1.8 mmol, 6 equiv.) at RT and the resulting mixture was stirred at the same temperature for 1 h. A saturated solution of NaCl (10 mL) was added and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20) to obtain the title compound as a yellow oil. Yield: 89 mg (95%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.19 (m, 14H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.8, 9.6 Hz, 1H), 4.88 – 4.57 (m, 2H), 4.01 (td, *J* = 9.9, 5.2 Hz, 1H), 3.63 (t, *J* = 10.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ172.3, 138.3, 136.0, 134.2, 128.6, 128.3, 128.2, 127.9, 127.7, 127.5, 126.5, 125.2, 78.4, 53.5, 45.6. UPLC-DAD-QTOF: $C_{18}H_{17}NO_4$ $[M+H]^+$ calcd.: 312,1236, found: 312,1237.

[160] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881.

S-phenyl (*S*,*E*)-2-((*S*)-2-nitro-1-phenylethyl)-4-phenylbut-3-enethioate (23): Procedure adapted from ref. 160. To a solution of (*S*,*E*)-2-((*S*)-2-nitro-1-phenylethyl)-4-phenylbut-3-enoic acid **22** (62 mg, 0.2 mmol, 1.0 equiv.) and 1-hydroxibenzotriazole HOBt (27 mg, 0.2 mmol, 1.0 equiv.) in dry EtOAc (2 mL) at 0°C, thiophenol (0.05 mL, 0.4 mmol, 2.0 equiv.) was added. After 5 min, 1,3-dicyclohexylcarbodiimide DCC (44 mg, 0.22 mmol, 1.1 equiv.) was added by portions. After for 2 h at room temperature, the mixture was filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (98:2/ Hexane: EtOAc) to obtain **23**. Yield: 59.7 mg (74 %). ^{1}H NMR (400 MHz, Chloroform-d) δ7.46 –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, S305.1 Hz, 1H), 3.83 (t, J= 9.8 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-d) δ197.2, 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.

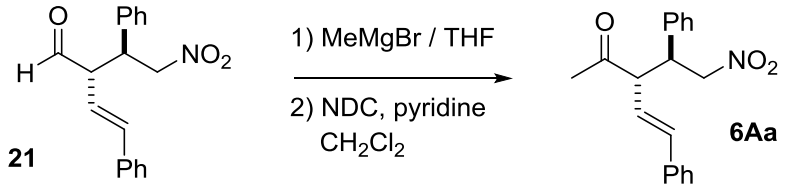
6.2.6.2. *Preparation of aldehyde 21 starting from adduct 14*[161]



Prepared as in reference 161, starting from 0.2 mmol of adduct **14**. The product was obtained starting from adduct **36** (106 mg, 0.3 mmol) and was isolated as a yellow solid. Yield: 66 mg (74%). m. p.: 85 – 87 °C. $[\alpha]_D^{25}$ = −84.4° (c= 1, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.52 (d, *J* = 2.2 Hz, 1H), 7.48 – 7.22 (m, 10H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.09 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.82 (dd, *J* = 12.9, 5.2 Hz, 1H), 4.76 – 4.64 (m, 1H), 4.13 (td, *J* = 9.6, 5.2 Hz, 1H), 3.70 (td, *J* = 9.5, 2.2 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.8, 138.2, 137.1, 135.9, 129.5, 129.1, 129.0, 128.6, 128.3, 126.9, 120.7, 78.6, 59.7, 44.1. UPLC-DAD-QTOF: $C_{18}H_{17}NO_3$ $[M+H]^+$ calcd.: 296,1287, found: 296,1292.

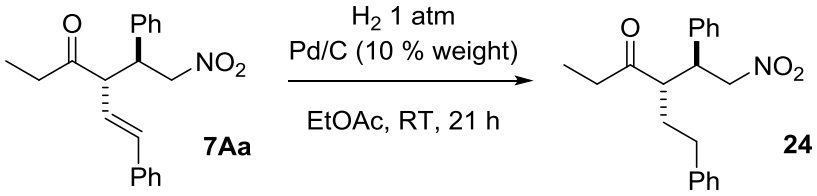
[161] Zhang, S. J.; Hu, W. X. *Synth. Commun.* **2010**, *40*, 3093−3100.

6.2.6.3. *Preparation of adduct 6Aa starting from adduct 21*



Procedure adapted from ref 160. To a cooled (−20 °C) solution of adduct **21** (59 mg, 0.2 mmol, 1 equiv.) in THF (1 mL), MeMgBr was added (3M, 0.07 mL, 0.2 mmol, 1 equiv.) at -20 °C and the resulting mixture was stirred at the same temperature for 20 min. A saturated solution of NH_4Cl (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. To a solution of the crude product in DCM (1.5 mL), NDC (232 mg, 0.5 mmol, 2.5 equiv.) and pyridine (0.32 mL, 0.4 mmol, 2 equiv.) were added at RT and the resulting mixture was stirred for 2 h at the same temperature. The reaction mixture was filtered through a short path of silica gel, diluted with DCM (10 mL) and washed with HCl (6M, 10 mL), water (10 mL) and a saturated solution of $NaHCO_3$ (10 mL). The organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (98:2/ Hexane: EtOAc) to afford compound **6Aa**. Yield: 60% (37 mg). ^1H and ^{13}C NMR spectra were identical to those obtained by the direct Michael addition of **1A** to **5a**.

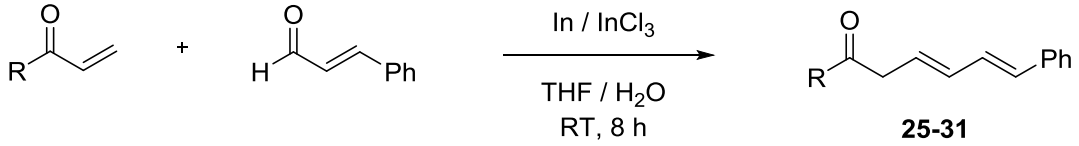
6.2.6.4. *Hydrogenation of 7Aa to obtain adduct 24*



(4*S*,5*S*)-6-Nitro-4-phenethyl-5-phenylhexan-3-one (24): 10% Palladium on carbon (7 mg) was added to a solution of **7Aa** (65 mg, 0.2 mmol) in EtOAc (2 mL) under a H_2 balloon (1 atm) atmosphere. The reaction mixture was stirred for 21 h at RT. The reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure to afford compound **24** as a colourless oil. Yield: 65 mg (quantitative). $[\alpha]_D^{25}$ = −15.6° (c= 1.5, CH_2Cl_2). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.09 (m, 10H), 4.75 (qd, *J* = 12.9, 7.5 Hz, 2H), 3.78 (dt, *J* = 9.4, 4.7 Hz, 1H), 2.98 (ddd, *J* = 10.1, 8.8, 3.7 Hz, 1H), 2.54 (dddd, *J* = 43.9, 13.8, 10.0, 5.9 Hz, 2H), 2.24 – 1.95 (m, 3H), 1.87 (dddd, *J* = 13.7, 10.2, 6.4, 3.8

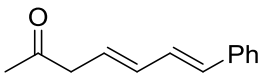
Hz, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.6, 140.6, 137.5, 131.4, 128.9, 128.6, 128.2, 128.2, 126.3, 77.4, 54.6, 45.6, 37.9, 33.4, 31.0, 7.1. UPLC-DAD-QTOF: $C_{20}H_{23}NO_3$ $[M+H]^+$ calcd.: 326,1756, found: 326,1750.

6.2.7. General procedure for the preparation of dienones 25-31



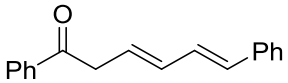
Procedure adapted from ref 157. A mixture of trans-cinnamaldehyde (5.0 mmol, 1 equiv.), In powder (1.15 g, 10 mmol, 2 equiv.), $InCl_3$ (553 mg, 2.5 mmol, 0.5 equiv.) and the corresponding vinyl ketone (15 mmol, 3 equiv.) in a mixture of THF and H_2O (1 : 1, 30 mL) was stirred at room temperature for 8 h. After the addition of 1 M HCl (15 mL), the reaction mixture was stirred for 30 min and extracted with ethyl acetate (50 mL × 4). The combined organic phases were washed with brine (100 mL) and dried with $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 97/3).

(4*E*,6*E*)-7-Phenylhepta-4,6-dien-2-one (25A)



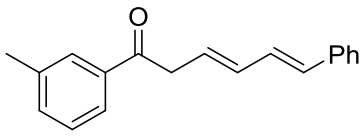
Prepared according to the general procedure starting from methyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a yellow oil. Yield: 605 mg (65%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.65 – 7.20 (m, 5H), 6.82 (dd, J = 15.6, 10.3 Hz, 1H), 6.55 (dd, J = 15.7, 5.5 Hz, 1H), 6.41 – 6.26 (m, 1H), 5.93 (dt, J = 14.9, 7.3 Hz, 1H), 3.30 (d, J = 7.2 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 193.9, 153.0, 134.6, 132.3, 129.3, 128.8, 127.8, 126.6, 126.1, 47.8, 29.8. UPLC-DAD-QTOF: $C_{13}H_{15}O$ $[M+H]^+$ calcd.: 187.1123 , found: 187.1120.

(3*E*,5*E*)-1,6-Diphenylhexa-3,5-dien-1-one (26A)



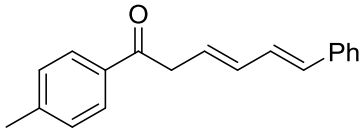
Prepared according to the general procedure starting from phenyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a yellow oil. Yield: 720 mg (58%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 – 7.94 (m, 2H), 7.69 – 7.17 (m, 8H), 6.85 (dd, J = 15.6, 10.3 Hz, 1H), 6.55 (d, J = 15.7 Hz, 1H), 6.40 (dd, J = 15.3, 10.3 Hz, 1H), 6.11 (dt, J = 14.8, 7.0 Hz, 1H), 3.89 (d, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 198.1, 137.5, 136.8, 134.4, 133.5, 132.2, 128.9, 128.9, 128.6, 127.8, 126.8, 126.6, 42.8. UPLC-DAD-QTOF: $C_{18}H_{17}O$ $[M+H]^+$ calcd.: 249.1279 , found: 249.1287.

(3*E*,5*E*)-6-Phenyl-1-(m-tolyl)hexa-3,5-dien-1-one (27A)



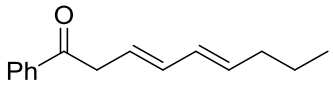
Prepared according to the general procedure starting from 1-(*m*-tolyl)prop-2-en-1-one and *trans*-cinnamaldehyde. The title compound was isolated as a white solid. Yield: 787 mg (60%). m. p.: 89 – 91 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 – 7.75 (m, 2H), 7.54 – 7.10 (m, 8H), 6.85 (dd, J = 15.7, 10.4 Hz, 1H), 6.55 (d, J = 15.6 Hz, 1H), 6.40 (dd, J = 15.3, 10.4 Hz, 1H), 6.11 (dt, J = 14.7, 7.0 Hz, 1H), 3.88 (d, J = 7.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 198.3, 138.7, 137.5, 136.9, 134.3, 134.2, 132.1, 129.0, 128.8, 127.7, 126.9, 126.6, 125.8, 42.9, 21.6. UPLC-DAD-QTOF: $C_{19}H_{19}O$ $[M+H]^+$ calcd.: 263.1436, found: 263.1432.

(3*E*,5*E*)-6-Phenyl-1-(p-tolyl)hexa-3,5-dien-1-one (28A)



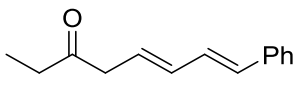
Prepared according to the general procedure starting from 1-(*p*-tolyl)prop-2-en-1-one and *trans*-cinnamaldehyde. The title compound was isolated as a white solid. Yield: 892 mg (68%). m. p.: 86 – 88 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, J = 7.9 Hz, 2H), 7.56 – 7.22 (m, 8H), 6.97 – 6.75 (m, 1H), 6.56 (d, J = 15.7 Hz, 1H), 6.40 (dd, J = 15.4, 10.3 Hz, 1H), 6.13 (dt, J = 14.8, 6.9 Hz, 1H), 3.85 (d, J = 7.1 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 197.4, 144.1, 137.4, 134.2, 134.1, 131.9, 129.4, 128.8, 128.7, 128.6, 127.6, 127.0, 126.4, 42.6, 21.8. UPLC-DAD-QTOF: $C_{19}H_{19}O$ $[M+H]^+$ calcd.: 263.1436, found: 263,1440.

(3*E*,5*E*)-1-Phenylnona-3,5-dien-1-one (26B)



Prepared according to the general procedure starting from phenyl vinyl ketone and *(E)*-hex-2-enal. The title compound was isolated as a yellow oil. Yield: 664 mg (62%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 – 7.96 (m, 2H), 7.65 – 7.45 (m, 3H), 6.14 (ddd, J = 41.7, 15.1, 10.3 Hz, 2H), 5.84 (dd, J = 14.7, 7.3 Hz, 1H), 5.69 (dd, J = 14.7, 7.2 Hz, 1H), 3.79 (d, J = 7.0 Hz, 2H), 2.08 (p, J = 7.2, 6.6 Hz, 2H), 1.43 (h, J = 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 198.1, 136.6, 134.4, 134.2, 133.1, 129.8, 128.6, 128.3, 123.1, 42.4, 34.6, 22.4, 13.7. UPLC-DAD-QTOF: $C_{15}H_{19}O$ $[M+H]^+$ calcd.: 215.1436, found: 215.1435.

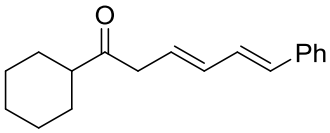
(5*E*,7*E*)-8-Phenylocta-5,7-dien-3-one (28)



Prepared according to the general procedure starting from ethyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a colourless oil. Yield: 551 mg (55%). ^{1}H NMR (400 MHz,

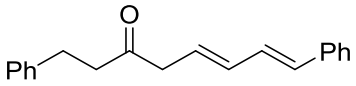
Chloroform-d) δ 7.66 – 7.22 (m, 5H), 6.88 – 6.76 (m, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.32 (dd, J = 15.3, 10.3 Hz, 1H), 5.94 (dt, J = 14.9, 7.3 Hz, 1H), 3.29 (d, J = 7.3 Hz, 2H), 2.53 (q, J = 7.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 194.0, 137.4, 134.4, 132.2, 128.9, 128.7, 127.8, 126.6, 126.4, 46.7, 35.9, 8.0. UPLC-DAD-QTOF: $C_{14}H_{17}O$ $[M+H]^+$ calcd.: 201.1279, found: 201.1285.

(3*E*,5*E*)-1-Cyclohexyl-6-phenylhexa-3,5-dien-1-one (30)



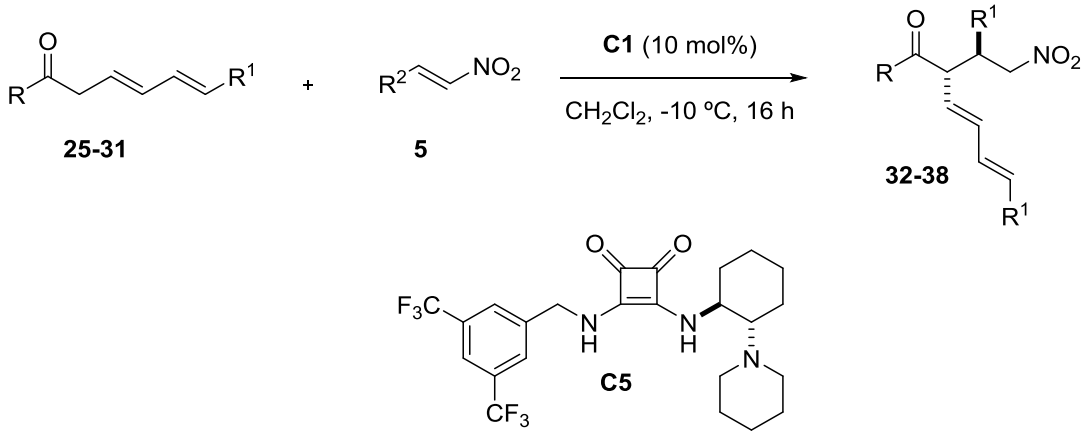
Prepared according to the general procedure starting from cyclohexyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a mixture of compound **6A** and an unidentified byproduct in a 1 : 1 ratio. Yield of the mixture: 1.02 g (80%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 – 7.21 (m, 5H), 6.81 (dd, J = 15.6, 10.4 Hz, 1H), 6.52 (d, J = 15.6 Hz, 1H), 6.29 (dd, J = 15.2, 10.3 Hz, 1H), 5.93 (dt, J = 14.9, 7.2 Hz, 1H), 3.33 (dd, J = 7.2, 1.3 Hz, 2H), 2.51 – 2.40 (m, 1H), 1.75 – 1.66 (m, 2H), 1.43 – 1.22 (m, 8H). ^{13}C NMR (101 MHz, Chloroform-d) δ 212.2, 137.2, 133.9, 131.7, 128.5, 127.4, 126.4, 126.2, 50.4, 44.6, 28.4, 25.8, 25.6. UPLC-DAD-QTOF: $C_{18}H_{23}O$ $[M+H]^+$ calcd.: 255.1749, found: 255.1747.

(5*E*,7*E*)-1,8-Diphenylocta-5,7-dien-3-one (31)



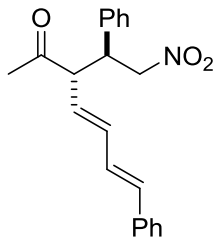
Prepared according to the general procedure starting from 5-phenylpent-1-en-3-one and *trans*-cinnamaldehyde. The title compound was isolated as a colourless oil. Yield: 954 mg (69%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.50 – 7.18 (m, 10H), 6.80 (dd, J = 15.7, 10.5 Hz, 1H), 6.53 (d, J = 15.6 Hz, 1H), 6.29 (dd, J = 15.2, 10.3 Hz, 1H), 5.90 (dt, J = 15.0, 7.3 Hz, 1H), 3.27 (d, J = 7.3 Hz, 2H), 3.03 – 2.78 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-d) δ 207.6, 152.7, 140.9, 137.1, 134.3, 132.0, 131.2, 129.1, 128.6, 128.5, 128.3, 128.3, 127.5, 126.3, 126.1, 125.7, 47.0, 43.9, 29.7. UPLC-DAD-QTOF: $C_{20}H_{21}O$ $[M+H]^+$ calcd.: 277.1592, found: 277.1596.

6.2.8. Catalytic conjugate addition of dienyl ketones to nitroolefins



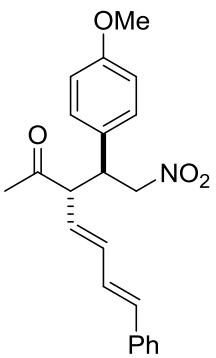
General procedure: To a mixture of the corresponding allyl ketone (0.3 mmol, 1.5 equiv.) and nitroalkene (0.2 mmol, 1 equiv.) in dichloromethane (0.4 mL), the catalyst (0.02 mmol, 10 mol%) was added at −10 °C unless otherwise stated. The resulting mixture was stirred at −10 °C unless otherwise stated for 16 h. The reaction mixture was directly submitted to a flash column chromatography (eluent hexane/ethyl acetate 95/5) to obtain essentially pure Michael adduct.

(*S*,4*E*,6*E*)-3-((*S*)-2-Nitro-1-phenylethyl)-7-phenylhepta-4,6-dien-2-one (32Aa)



Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 56 mg (83%). m. p.: 140 – 142 °C. $[\alpha]_D^{25}$ = −56.7° (c= 0.7, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 – 7.21 (m, 10H), 6.80 (dd, J = 15.6, 10.4 Hz, 1H), 6.65 (d, J = 15.6 Hz, 1H), 6.52 (dd, J = 15.0, 10.3 Hz, 1H), 5.70 (dd, J = 15.0, 9.9 Hz, 1H), 4.81 – 4.57 (m, 2H), 4.02 (td, J = 10.1, 4.8 Hz, 1H), 3.71 (t, J = 10.1 Hz, 1H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 205.5, 137.5, 136.8, 134.4, 129.0, 128.7, 128.1, 128.0, 127.8, 127.2, 126.5, 78.6, 60.5, 45.2, 30.1. UPLC-DAD-QTOF: $C_{21}H_{22}NO_3$ $[M+H]^+$ calcd.: 336.1600, found: 336.1603.

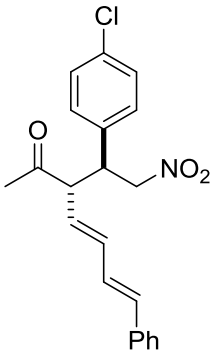
(*S*,4*E*,6*E*)-3-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-7-phenylhepta-4,6-dien-2-one (32Ab)



Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a white solid. Yield: 57 mg (78%). m. p.: 125 – 127 °C. $[\alpha]_D^{25}$ = −131.0° (c= 1, 96% *ee*, CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 – 7.27 (m, 5H), 7.23 – 7.14 (m, 2H), 6.90 – 6.86 (m, 2H), 6.86 – 6.74 (m, 1H), 6.64 (dd, J = 15.6, 2.0 Hz, 1H), 6.51 (ddd, J = 15.0, 10.3, 2.0 Hz, 1H), 5.69 (ddd, J = 15.1, 9.8, 2.0 Hz, 1H), 4.81 –

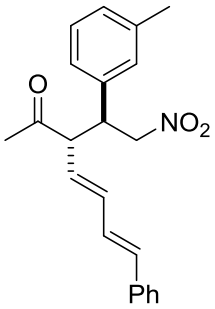
4.52 (m, 2H), 3.96 (dtd, J = 10.1, 5.6, 4.7, 1.9 Hz, 1H), 3.81 (d, J = 2.1 Hz, 3H), 3.67 (td, J = 10.2, 2.1 Hz, 1H), 1.98 (d, J = 2.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 205.7, 159.2, 136.6, 134.3, 129.2, 128.9, 128.7, 128.1, 127.4, 127.2, 126.5, 114.4, 78.8, 60.7, 55.2, 44.6, 30.1. UPLC-DAD-QTOF: $C_{22}H_{24}NO_4$ $[M+H]^+$ calcd.: 366.1705, found: 366,1701.

(*S*,4*E*,6*E*)-3-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-7-phenylhepta-4,6-dien-2-one (32Ak)



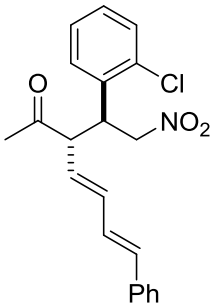
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5k**. The title compound was isolated as a single diastereomer as a white solid. Yield: 56 mg (76%). m. p.: 137 – 139 °C. $[\alpha]_D^{25}$ = −107° (c= 1, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.57 – 7.11 (m, 9H), 6.79 (ddd, J = 15.6, 10.2, 0.7 Hz, 1H), 6.65 (d, J = 15.6 Hz, 1H), 6.51 (dd, J = 15.1, 10.2 Hz, 1H), 5.64 (dd, J = 15.0, 9.9 Hz, 1H), 4.80 – 4.51 (m, 2H), 4.01 (td, J = 10.2, 4.8 Hz, 1H), 3.66 (t, J = 10.1 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 204.4, 136.5, 135.7, 135.5, 134.0, 133.2, 128.5, 128.5, 128.0, 127.5, 126.3, 125.9, 77.7, 59.6, 43.7, 29.3. UPLC-DAD-QTOF: $C_{21}H_{21}ClNO_3$ $[M+H]^+$ calcd.: 370.1210, found: 370.1207.

(*S*,4*E*,6*E*)-3-((*S*)-2-Nitro-1-(m-tolyl)ethyl)-7-phenylhepta-4,6-dien-2-one (32Ad)



Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a white solid. Yield: 53 mg (76%). m. p.: 106 – 108 °C. $[\alpha]_D^{25}$ = −95.3° (c= 1.2, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.53 – 6.99 (m, 9H), 6.88 – 6.45 (m, 3H), 5.69 (dd, J = 15.0, 9.9 Hz, 1H), 4.81 – 4.53 (m, 2H), 3.97 (td, J = 10.1, 4.9 Hz, 1H), 3.70 (t, J = 10.1 Hz, 1H), 2.35 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 204.6, 137.6, 136.4, 135.7, 135.5, 133.3, 127.8, 127.7, 127.7, 127.1, 126.3, 126.2, 125.5, 123.5, 77.7, 59.4, 44.1, 29.1, 20.4. UPLC-DAD-QTOF: $C_{22}H_{24}NO_3$ $[M+H]^+$ calcd.: 350.1756, found: 350.1763.

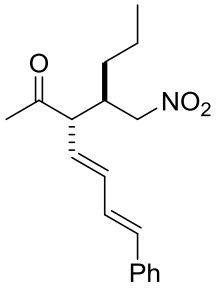
(*S*,4*E*,6*E*)-3-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-7-phenylhepta-4,6-dien-2-one (32Ae)



Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5e**. The title compound was isolated as a single diastereomer as a white solid. Yield: 52 mg (70%). m. p.: 84 – 86 °C. $[\alpha]_D^{25}$ = −109.3° (c= 1.5, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.50 – 7.18 (m, 9H), 6.80 (ddd, J = 15.5, 10.3, 0.7 Hz, 1H), 6.63 (d, J = 15.7 Hz, 1H), 6.49 (dd, J = 15.0, 10.2 Hz, 1H), 5.68 (dd, J = 15.1, 9.7 Hz, 1H), 4.80 (d, J = 6.4 Hz, 2H), 4.48 (q, J = 7.4 Hz, 1H), 4.02 (t, J = 9.7 Hz, 1H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ

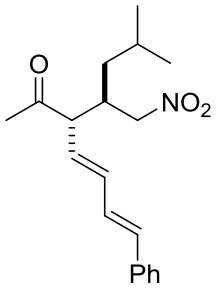
206.6, 138.6, 137.6, 135.7, 131.7, 130.3, 129.8, 129.3, 128.4, 128.2, 127.7, 127.5, 77.5, 59.5, 30.7. UPLC-DAD-QTOF: $C_{21}H_{21}ClNO_3$ $[M+H]^+$ calcd.: 370.1210, found: 370.1210.

(*S*,4*E*,6*E*)-3-((*R*)-1-Nitropentan-2-yl)-7-phenylhepta-4,6-dien-2-one (32Al)



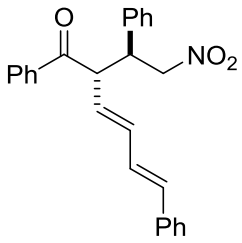
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5l**. The title compound was isolated as a mixture of diastereomers (dr 57 : 43) as a colourless oil. Yield: 50 mg (83%). ^{1}H NMR major diastereomer (300 MHz, Chloroform-d) δ 7.35 (s, 5H), 6.75 (ddd, J = 10.3, 7.9, 0.7 Hz, 1H), 6.61 (d, J = 13.4 Hz, 1H), 6.53 – 6.35 (m, 1H), 5.60 (dd, J = 13.7, 11.2 Hz, 1H), 4.63 – 4.30 (m, 2H), 3.50 – 3.29 (m, 1H), 2.79 – 2.58 (m, H), 2.25 (s, 3H), 1.52 – 1.21 (m, 4H), 0.98 – 0.91 (m, 3H). ^{13}C NMR major diastereomer (75 MHz, Chloroform-d) δ 207.8, 137.3, 134.7, 129.4, 128.7, 128.4, 128.2, 127.2, 77.2, 77.0, 59.2, 39.0, 32.8, 31.2, 20.6, 14.6. UPLC-DAD-QTOF: $C_{18}H_{24}NO_3$ $[M+H]^+$ calcd.: 302.1756, found: 302.1760.

(*S*,4*E*,6*E*)-3-((*R*)-4-Methyl-1-nitropentan-2-yl)-7-phenylhepta-4,6-dien-2-one (32Ai)



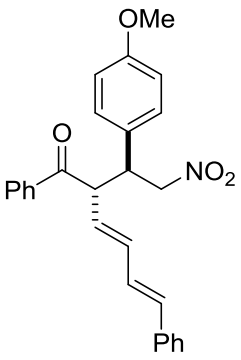
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5i**. The title compound was isolated as a mixture of diastereomers (dr 59 : 41) as a colourless oil. Yield: 45 mg (72%). ^{1}H NMR major diastereomer (300 MHz, Chloroform-d) δ 7.52 – 7.18 (m, 5H), 6.88 – 6.34 (m, 3H), 5.68 – 5.50 (m, 1H), 4.67 – 4.26 (m, 2H), 3.50 – 3.25 (m, 1H), 2.83 – 2.63 (m, 1H), 2.24 (s, 3H), 1.77 – 1.59 (m, 1H), 1.34 – 1.12 (m, 2H), 1.00 (s, 1H), 0.94 (ddd, J = 6.4, 4.5, 1.7 Hz, 6H). ^{13}C NMR major diastereomer (75 MHz, Chloroform-d) δ 208.4, 138.0, 135.0, 133.2, 129.8, 129.1, 128.6, 128.3, 127.6, 77.7, 59.9, 40.4, 37.5, 31.3, 26.3, 24.7, 22.9. UPLC-DAD-QTOF: $C_{19}H_{25}NO_3$ $[M+H]^+$ calcd.: 316.1913, found: 316.1913.

(*S*,3*E*,5*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-1,6-diphenylhexa-3,5-dien-1-one (33Aa)



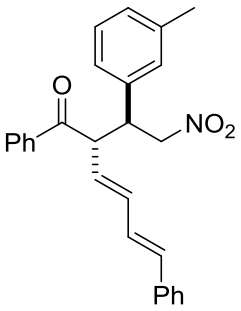
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 64 mg (80%). m. p.: 144 – 146 °C. $[\alpha]_D^{25}$ = −86.1° (c= 0.5, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.91 – 7.77 (m, 2H), 7.55 – 7.17 (m, 13H), 6.77 (dd, J = 15.5, 10.3 Hz, 1H), 6.60 (d, J = 15.4 Hz, 1H), 6.58 – 6.45 (m, 1H), 5.85 (dd, J = 15.1, 9.7 Hz, 1H), 5.00 – 4.63 (m, 3H), 4.28 (dd, J = 9.8, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-d) δ 196.6, 136.8, 135.8, 133.3, 132.3, 128.6, 128.2, 127.9, 127.7, 127.6, 127.2, 127.1, 127.0, 126.9, 126.8, 126.3, 125.5, 77.7, 53.2, 44.6. UPLC-DAD-QTOF: $C_{26}H_{24}NO_3$ $[M+H]^+$ calcd.: 398.1756, found: 398.1754.

(*S*,3*E*,5*E*)-2-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,6-diphenylhexa-3,5-dien-1-one (33Ab)



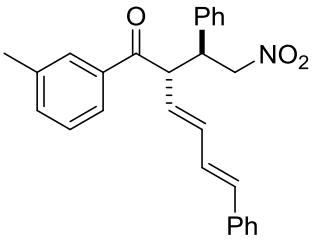
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a white solid. Yield: 64 mg (75%). m. p.: 133 – 135 °C. $[\alpha]_D^{25}$ = −13.4° (c= 0.2, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.91 – 7.77 (m, 2H), 7.56 – 7.14 (m, 12H), 6.84 – 6.75 (m, 2H), 6.66 – 6.49 (m, 2H), 5.93 – 5.77 (m, 1H), 4.97 – 4.59 (m, 3H), 4.23 (dd, J = 9.9, 4.8 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 196.5, 157.8, 135.4, 135.3, 135.2, 133.0, 132.1, 128.4, 127.7, 127.5, 127.4, 127.0, 126.8, 126.2, 125.3, 125.2, 113.0, 77.7, 53.9, 53.2, 43.8. UPLC-DAD-QTOF: $C_{27}H_{26}NO_4$ $[M+H]^+$ calcd.: 428.1862, found: 428.1859.

(*S*,3*E*,5*E*)-2-((*S*)-2-Nitro-1-(m-tolyl)ethyl)-1,6-diphenylhexa-3,5-dien-1-one (33Ad)



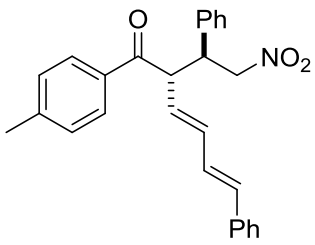
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a white solid. Yield: 57 mg (69%). m. p.: 130 – 132 °C. $[\alpha]_D^{25}$ = −28.0° (c= 1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.81 (dt, J = 7.3, 1.4 Hz, 2H), 7.35 (dtd, J = 30.9, 8.7, 8.1, 6.2 Hz, 8H), 7.19 – 6.95 (m, 5H), 6.76 (dd, J = 15.5, 10.3 Hz, 1H), 6.66 – 6.55 (m, 1H), 6.55 – 6.45 (m, 1H), 5.84 (dd, J = 15.2, 9.7 Hz, 1H), 4.93 – 4.58 (m, 3H), 4.20 (td, J = 9.8, 4.9 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 198.4, 144.5, 139.1, 138.4, 137.4, 134.9, 134.0, 130.3, 129.6, 129.4, 129.3, 129.3, 128.9, 128.9, 128.8, 128.0, 127.2, 125.2, 79.4, 54.9, 46.2, 22.1. UPLC-DAD-QTOF: $C_{27}H_{26}NO_3$ $[M+H]^+$ calcd.: 412.1913, found: 412.1914.

(*S*,3*E*,5*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-6-phenyl-1-(m-tolyl)hexa-3,5-dien-1-one (34Aa)



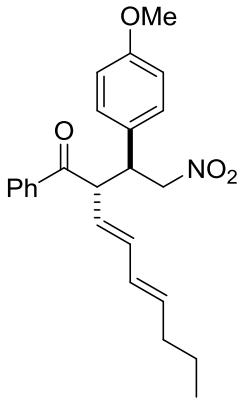
Prepared according to the general procedure starting from allyl ketone **27A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 62 mg (76%). m. p.: 145 – 147 °C. $[\alpha]_D^{25}$ = −125.6° (c= 1, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.62 (dd, J = 6.8, 1.7 Hz, 2H), 7.51 – 7.13 (m, 12H), 6.77 (dd, J = 15.7, 10.1 Hz, 1H), 6.65 – 6.55 (m, 1H), 6.56 – 6.48 (m, 1H), 5.85 (dd, J = 15.1, 9.6 Hz, 1H), 4.99 – 4.56 (m, 3H), 4.27 (dt, J = 9.8, 4.9 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 198.4, 139.2, 138.5, 137.4, 134.9, 134.8, 129.5, 129.5, 129.4, 129.1, 128.8, 128.7, 128.5, 128.5, 128.0, 127.2, 126.1, 79.4, 54.9, 46.3, 22.0. UPLC-DAD-QTOF: $C_{27}H_{26}NO_3$ $[M+H]^+$ calcd.: 412.1913, found: 412.1913.

(*S*,3*E*,5*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-6-phenyl-1-(p-tolyl)hexa-3,5-dien-1-one (35Aa)



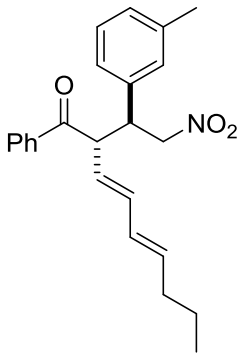
Prepared according to the general procedure starting from allyl ketone **28A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 71 mg (87%). m. p.: 133 – 135 °C. $[\alpha]_D^{25}$ = −38.0° (c= 0.4, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.78 – 7.67 (m, 2H), 7.43 – 7.17 (m, 12H), 6.82 – 6.43 (m, 3H), 5.84 (dd, J = 15.1, 9.6 Hz, 1H), 4.95 – 4.70 (m, 2H), 4.65 (t, J = 9.8 Hz, 1H), 4.26 (td, J = 9.8, 4.8 Hz, 1H), 2.38 (s, 3H). $_{13}$C NMR (75 MHz, Chloroform-d) δ 197.8, 145.0, 138.6, 137.3, 137.2, 134.8, 130.2, 130.0, 129.5, 129.4, 129.1, 129.0, 128.7, 128.5, 128.5, 128.1, 127.2, 79.4, 54.7, 46.2, 22.3. UPLC-DAD-QTOF: $C_{27}H_{26}NO_3$ $[M+H]^+$ calcd.: 412.1913, found: 412.1912.

(*S*,3*E*,5*E*)-2-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1-phenylnona-3,5-dien-1-one (33Bb)



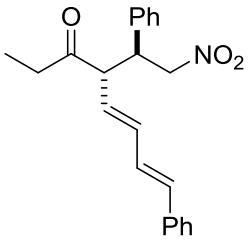
Prepared according to the general procedure starting from allyl ketone **26B** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 64 mg (82%). $[\alpha]_D^{25}$ = −139.9° (c= 1.2, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.88 – 7.69 (m, 2H), 7.57 – 7.48 (m, 1H), 7.39 (dd, J = 8.4, 7.0 Hz, 2H), 7.23 – 7.09 (m, 2H), 6.82 – 6.68 (m, 2H), 6.32 (dd, J = 15.3, 10.3 Hz, 1H), 6.03 (dd, J = 15.3, 10.5 Hz, 1H), 5.75 (dt, J = 14.8, 6.9 Hz, 1H), 5.57 (dd, J = 15.3, 9.6 Hz, 1H), 4.92 – 4.62 (m, 2H), 4.53 (t, J = 9.9 Hz, 1H), 4.15 (td, J = 10.1, 4.8 Hz, 1H), 3.72 (s, 3H), 2.13 – 2.00 (m, 2H), 1.42 (q, J = 7.4 Hz, 2H), 0.93 (dt, J = 9.1, 7.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 198.6, 159.6, 137.8, 137.6, 137.2, 133.9, 130.4, 129.7, 129.6, 129.2, 128.9, 126.0, 114.9, 79.7, 55.8, 54.9, 45.6, 35.4, 22.9, 14.4. UPLC-DAD-QTOF: $C_{24}H_{28}NO_4$ $[M+H]^+$ calcd.: 394.2018, found: 394.2022.

(*S*,3*E*,5*E*)-2-((*S*)-2-Nitro-1-(m-tolyl)ethyl)-1-phenylnona-3,5-dien-1-one (33Bd)



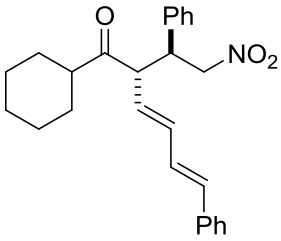
Prepared according to the general procedure starting from allyl ketone **26B** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 57 mg (75%). $[\alpha]_D^{25}$ = −43.5° (c= 0.4, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.78 (dt, J = 7.1, 1.4 Hz, 2H), 7.56 – 7.31 (m, 3H), 7.18 – 6.91 (m, 4H), 6.31 (dd, J = 15.3, 10.2 Hz, 1H), 6.11 – 5.97 (m, 1H), 5.75 (dt, J = 14.8, 6.9 Hz, 1H), 5.66 – 5.54 (m, 1H), 4.92 – 4.66 (m, 2H), 4.55 (t, J = 9.7 Hz, 1H), 4.15 (td, J = 9.9, 4.8 Hz, 1H), 2.25 (s, 3H), 2.11 – 2.03 (m, 2H), 1.44 (p, J = 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 199.0, 139.5, 138.9, 138.2, 138.0, 137.7, 137.3, 136.8, 134.2, 130.1, 130.0, 129.7, 129.6, 129.3, 126.4, 125.7, 80.0, 55.1, 46.6, 35.8, 23.3, 22.5, 14.8. UPLC-DAD-QTOF: $C_{24}H_{28}NO_3$ $[M+H]^+$ calcd.: 378.2069, found: 378.2071.

(*S*,5*E*,7*E*)-4-((*S*)-2-Nitro-1-phenylethyl)-8-phenylocta-5,7-dien-3-one (36Aa)



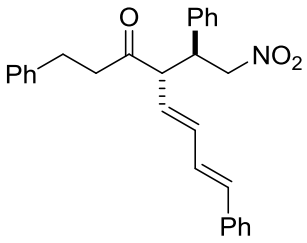
Prepared according to the general procedure starting from allyl ketone **29A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 60 mg (85%). m. p.: 113 – 115 °C. $[\alpha]_D^{25}$ = −92.8° (c= 1.5, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.16 (m, 10H), 6.79 (ddd, *J* = 15.6, 10.2, 0.7 Hz, 1H), 6.63 (d, *J* = 15.7 Hz, 1H), 6.49 (dd, *J* = 15.1, 10.3 Hz, 1H), 5.70 (dd, *J* = 15.0, 9.9 Hz, 1H), 4.83 – 4.56 (m, 2H), 4.04 (td, *J* = 10.2, 4.9 Hz, 1H), 3.68 (t, *J* = 10.2 Hz, 1H), 2.51 – 2.37 (m, 1H), 2.06 – 1.95 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 207.4, 136.7, 135.6, 135.5, 133.3, 128.0, 127.8, 127.2, 127.1, 127.0, 126.9, 126.3, 125.6, 77.7, 59.0, 44.4, 35.5, 30.7, 21.7, 13.2, 6.3. UPLC-DAD-QTOF: $C_{22}H_{24}NO_3$ $[M+H]^+$ calcd.: 350.1756, found: 350.1757.

(*S*,3*E*,5*E*)-1-Cyclohexyl-2-((*S*)-2-nitro-1-phenylethyl)-6-phenylhexa-3,5-dien-1-one (37Aa)



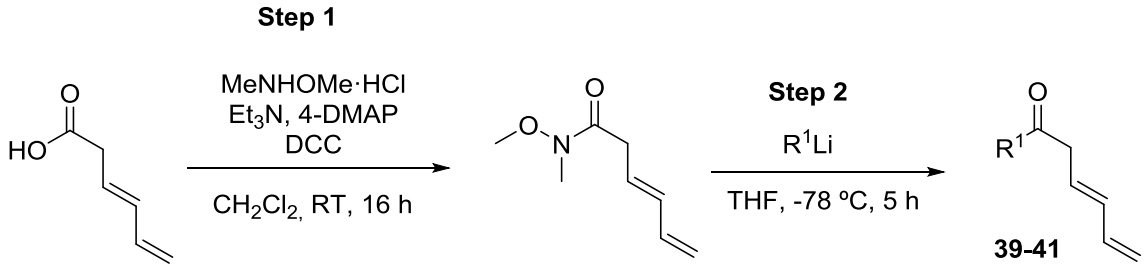
Prepared according to the general procedure starting from allyl ketone **30A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 68 mg (85%). $[\alpha]_D^{25}$ = −60.3° (c= 1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.20 (m, 10H), 6.78 (dd, *J* = 15.5, 10.1 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.48 (dd, *J* = 15.1, 10.1 Hz, 1H), 5.66 (dd, *J* = 15.1, 9.9 Hz, 1H), 4.81 – 4.60 (m, 2H), 4.04 (td, *J* = 10.4, 5.0 Hz, 1H), 3.78 (t, *J* = 10.2 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.32 – 0.67 (m, 10H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 210.2, 137.8, 136.6, 136.2, 134.1, 128.8, 128.7, 128.1, 127.9, 127.3, 126.5, 78.5, 59.0, 51.0, 45.3, 27.9, 27.4, 25.6, 25.4, 25.3, 1.0. UPLC-DAD-QTOF: $C_{26}H_{30}NO_3$ $[M+H]^+$ calcd.: 404.2226, found: 404.2220.

(*S*,5*E*,7*E*)-4-((*S*)-2-Nitro-1-phenylethyl)-1,8-diphenylocta-5,7-dien-3-one (38Aa)



Prepared according to the general procedure starting from allyl ketone **31A** and nitroalkene **5a**. The title compound was isolated as a mixture of diastereomers (dr 85 : 15) as a white solid. Yield: 63 mg (74 %). ^{1}H NMR major diastereomer (300 MHz, Chloroform-*d*) δ 7.54 – 7.08 (m, 13H), 7.03 – 6.91 (m, 2H), 6.82 – 6.36 (m, 3H), 5.64 (dd, *J* = 15.1, 9.9 Hz, 1H), 4.81 – 4.55 (m, 2H), 4.02 (qd, *J* = 9.5, 8.9, 5.3 Hz, 1H), 3.64 (q, *J* = 9.4, 8.7 Hz, 1H), 2.81 – 2.59 (m, 3H), 2.33 (ddd, *J* = 16.8, 8.2, 5.7 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 207.4, 141.2, 138.2, 137.3, 136.7, 135.0, 129.7, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 127.9, 127.9, 127.2, 126.7, 79.2, 60.9, 46.0, 45.3, 29.7. UPLC-DAD-QTOF: $C_{28}H_{28}NO_3$ $[M+H]^+$ calcd.: 426.2069, found: 426.2075.

6.2.9. General procedure for the preparation of dienones 39-41



Step 1. Preparation of (*E*)-N-methoxy-N-methylhexa-3,5-dienamide: [162]

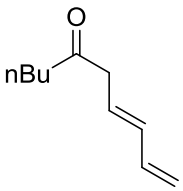
To a stirring solution of (*E*)-hexa-3,5-dienoic acid (1.12 g, 10.0 mmol, 1.0 equiv.) and N,O-dimethylhydroxyamine hydrochloride (1.03g, 10.5 mmol, 1.05 equiv.) in CH_2Cl_2 (30.0 mL) at 0 °C Et_3N (2.8 mL, 20.0 mmol, 2.0 equiv.), 4-DMAP (61 mg, 0.5 mmol, 0.05 equiv.) and DCC (2.18 g, 10.5 mmol, 1.05 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 via silica gel chromatography (Hexane/ EtOAc 70:30) to obtain the desired product. 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.

Step 2. Preparation of dienones 39-41:

The corresponding alkyllithium reagent (1 equiv.) was added to a solution of the Weinreb amide prepared as above (930 mg, 6.0 mmol, 3 equiv.) in dry THF (6.0 mL) at −40 °C. The reaction was stirred at −40 °C for 16 h and was then quenched with aqueous HCl (1M, 20 mL). The mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude material was purified via silica gel column chromatography (95:5 Hexane/EtOAc) to obtain a mixture of about 70:30 ratio of non-conjugated and conjugated isomers, which was used in the next step without a need for further purification.

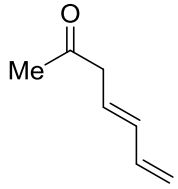
(*E*)-Deca-7,9-dien-5-one (39)

[162] Adapted from: A. Dermenci, R.E. Whittaker, G. Dong, *Org.Lett.* **2013**, *15*, 2242-2245.



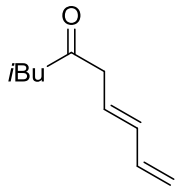
Prepared according to the general procedure for aliphatic ketones starting from *n*-buthyllithium. The title compound was isolated as a yellow oil as a mixture of isomers (desired product / isomerized product: 70/30). Yield: 182 mg (60%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.36 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.15 – 6.04 (m, 1H), 5.87 – 5.72 (m, 1H), 5.23 – 4.97 (m, 2H), 3.21 (dd, *J* = 7.2, 1.3 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.69 – 1.45 (m, 4H), 0.96 – 0.87 (m, 3H). UPLC-DAD-QTOF: $C_{10}H_{17}O$ $[M+H]^+$ calcd.: 153.1279, found: 153.1280.

(*E*)-Hepta-4,6-dien-2-one (40)



Prepared according to the general procedure for aliphatic ketones starting from methyllithium. The title compound was isolated as a yellow oil as a mixture of isomers (desired product / isomerized product: 76:24). Yield: 132 mg (60%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.45 – 6.23 (m, 1H), 6.16 – 6.00 (m, 1H), 5.91 – 5.67 (m, 1H), 5.23 – 5.02 (m, 2H), 3.22 (dd, *J* = 7.2, 1.3 Hz, 2H), 2.17 (s, 3H). UPLC-DAD-QTOF: $C_7H_{11}O$ $[M+H]^+$ calcd.: 111.0810, found: 111.0813.

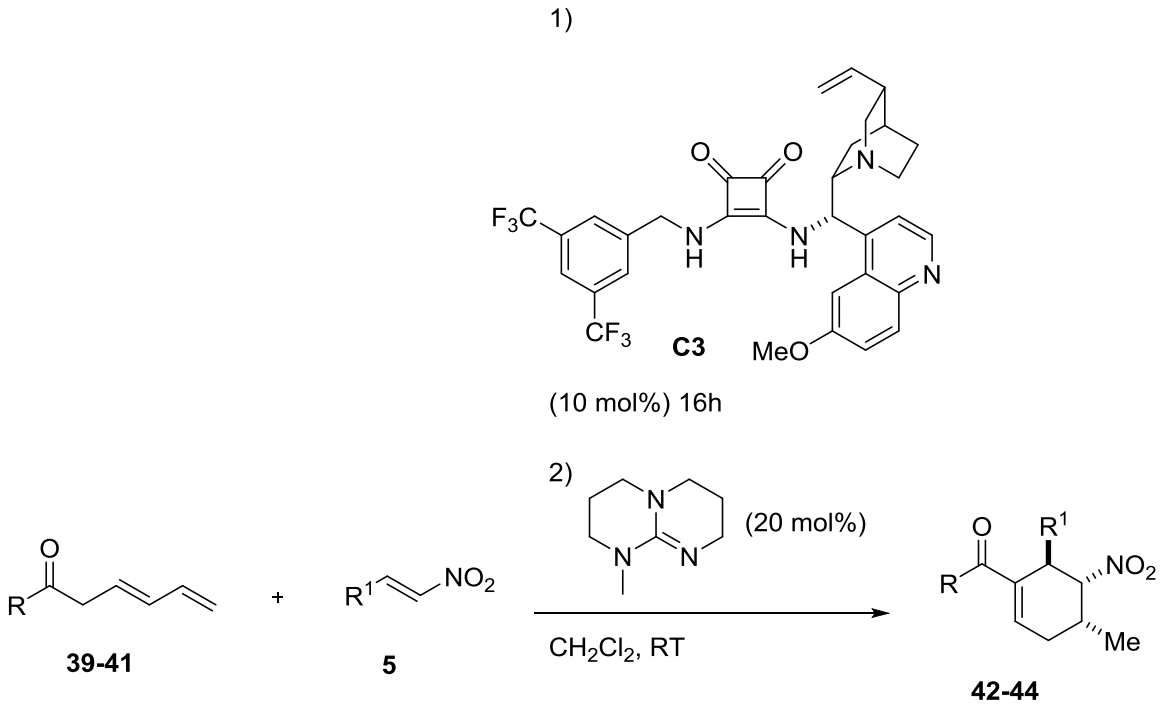
(*E*)-2-Methylnona-6,8-dien-4-one (41)



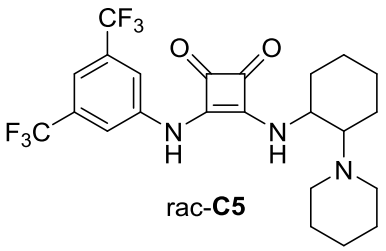
Prepared according to the general procedure for aliphatic ketones starting from isobuthyllithium. The title compound was isolated as a yellow oil as a mixture of isomers (desired product / isomerized product: 67/33). Yield: 100 mg (33%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.42 – 6.26 (m, 1H), 6.15 – 6.00 (m, 1H), 5.87 – 5.66 (m, 1H), 5.29 – 4.89 (m, 2H), 3.17 (dd, *J* = 7.4, 1.3 Hz, 2H), 2.32 (d, *J* = 6.9 Hz, 2H), 2.23 – 2.07 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). UPLC-DAD-QTOF: $C_{10}H_{17}O$ $[M+H]^+$ calcd.: 153.1279, found: 153.1279.

6.2.10. Addition-cyclisation reaction using ketones 39-41

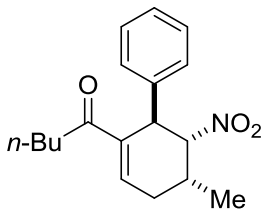
General procedure: To a mixture of the corresponding ketone **39-41** (0.12 mmol, 1.2 equiv.) and nitroalkene **5** (0.1 mmol, 1.0 equiv.) in dichloromethane (0.1 mL), catalyst **C3** (6 mg, 0.01 mmol, 10 mol %) was added at room temperature. After stirring the reaction mixture at room temperature for 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 (eluent hexane/ethyl acetate 95:5) to obtain essentially pure cyclohexene derivatives.



The corresponding racemic reaction was ran following the above procedure, but using as catalyst rac-**C5** (20 mol %).



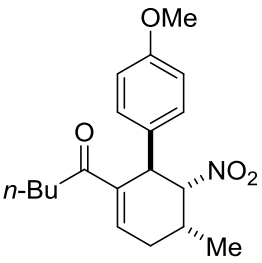
1-((1*R*,5*R*,6*R*)-5-Methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42a)



Prepared according to the general procedure starting from ketone **39** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 43 mg (71%). $[\alpha]_D^{25}$ = −27.5° (*c*= 1, 93% *ee*, CH_2Cl_2). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.13 (m, 6H), 4.72 (dd, *J* = 3.5, 2.4 Hz, 1H), 4.62 (s, 1H), 2.70 – 2.56 (m, 2H), 2.41 – 2.21 (m, 2H), 1.54 – 1.48 (m, 1H), 1.33 – 1.23 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 199.4, 140.2, 138.9, 136.6, 128.9, 128.0, 127.5, 91.4, 43.4, 37.3, 30.3, 29.7, 26.5, 26.1, 22.3, 17.1. UPLC-DAD-QTOF: $C_{18}H_{24}NO_3$ $[M+H]^+$ calcd.: 302.1756, found: 302.1760.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA) hexane/isopropanol 98:2, flow rate= 1 mL/min. Retention times: 18.1 min (major) and 26.5 min (min).

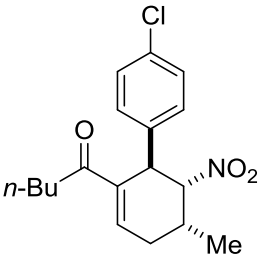
1-((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42b)



Prepared according to the general procedure starting from ketone **39** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 51 mg (77%). $[\alpha]_D^{25}$ = −4.0° (*c*= 2, 90% *ee*, CH_2Cl_2). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (t, *J* = 4.0 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.69 (dd, *J* = 3.4, 2.5 Hz, 1H), 4.57 (s, 1H), 3.80 (s, 3H), 2.69 – 2.53 (m, 2H), 2.41 – 2.29 (m, 2H), 1.54 – 1.50 (m, 1H), 1.40 – 1.32 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 199.8, 159.1, 138.8, 137.0, 132.4, 129.3, 114.6, 91.8, 55.5, 42.9, 37.6, 30.5, 29.9, 26.7, 26.3, 22.6, 17.4. UPLC-DAD-QTOF: $C_{19}H_{26}NO_4$ $[M+H]^+$ calcd.: 332.1862, found: 332.1866.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID) hexane/isopropanol 95:5, flow rate= 1 mL/min. Retention times: 14.6 min (min) and 16.2 min (major).

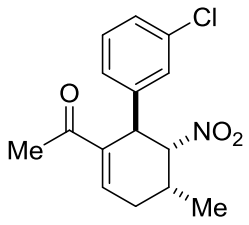
1-((1*R*,5*R*,6*R*)-4'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42k)



Prepared according to the general procedure starting from ketone **39** and nitroalkene **5k**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 50 mg (75%). $[\alpha]_D^{25}$ = −10.7° (*c*= 1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.04 (m, 5H), 4.66 (t, *J* = 3.0 Hz, 1H), 4.59 (s, 1H), 2.73 – 2.58 (m, 2H), 2.45 – 2.29 (m, 1H), 1.57 – 1.45 (m, 1H), 1.41 – 1.29 (m, 4H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.4, 140.4, 139.9, 137.5, 130.4, 130.2, 111.1, 92.3, 43.8, 38.3, 31.4, 30.8, 27.6, 27.4, 23.4, 18.1. UPLC-DAD-QTOF: $C_{18}H_{23}NO_3$ $[M+H]^+$ calcd.: 336.1366, found: 336.1365.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC) hexane/isopropanol 95:5, flow rate= 1 mL/min. Retention times: 18.3 min (major) and 20.9 min (min).

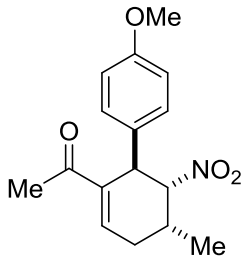
1-((1*R*,5*R*,6*R*)-3'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (43m)



Prepared according to the general procedure starting from ketone **40** and nitroalkene **5m**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 40 mg (69%). $[\alpha]_D^{25}$ = −28.2° (*c*= 1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 – 7.07 (m, 5H), 4.69 (dd, *J* = 3.5, 2.4 Hz, 1H), 4.59 (s, 1H), 2.61 (t, *J* = 5.4 Hz, 2H), 2.45 – 2.38 (m, 1H), 2.35 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 196.8, 142.2, 141.1, 139.9, 136.4, 130.2, 127.9, 127.8, 126.3, 90.9, 42.9, 30.2, 29.7, 26.1, 17.0. UPLC-DAD-QTOF: $C_{15}H_{17}ClNO_3$ $[M+H]^+$ calcd.: 294.0819, found: 294.0815.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC) hexane/isopropanol 95:5, flow rate= 1 mL/min. Retention times: 45.5 min (major) and 58.8 min (min).

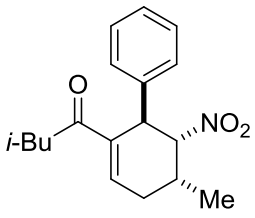
1-((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (43b)



Prepared according to the general procedure starting from ketone **40** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 45 mg (78%). $[\alpha]_D^{25}$ = −15.9° (*c*= 0.5, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 (t, *J* = 3.9 Hz, 1H), 7.17 – 7.05 (m, 2H), 6.92 – 6.78 (m, 2H), 4.72 – 4.63 (m, 1H), 4.55 (s, 1H), 3.79 (s, 3H), 2.60 (dt, *J* = 19.7, 5.4 Hz, 1H), 2.38 (t, *J* = 2.4 Hz, 1H), 2.31 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 197.9, 159.6, 140.9, 129.6, 128.6, 122.8, 115.0, 92.1, 61.4, 55.9, 43.2, 31.0, 26.5, 17.8. UPLC-DAD-QTOF: $C_{16}H_{20}ClNO_4$ $[M+H]^+$ calcd.: 290.1392, found: 290.1389.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC) hexane/isopropanol 95:5, flow rate= 1 mL/min. Retention times: 29.9 min (min) and 46.4 min (major).

3-Methyl-1-((1*R*,5*R*,6*R*)-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)butan-1-one (44a)



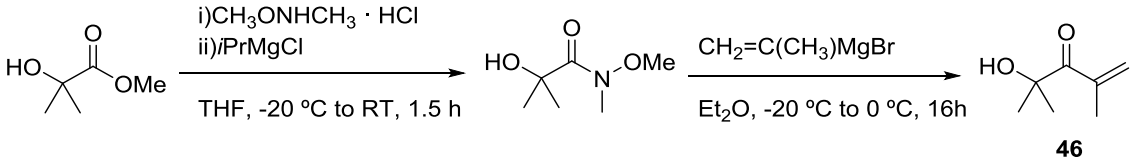
Prepared according to the general procedure starting from allyl ketone **41** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 41 mg (68%). $[\alpha]_D^{25}$ = −17.8° (*c*= 0.5, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.36 – 7.29 (m, 2H), 7.26 – 7.13 (m, 3H), 4.73 (dd, J = 3.4, 2.5 Hz, 1H), 4.63 (s, 1H), 2.70 – 2.55 (m, 1H), 2.52 (dd, J = 6.9, 3.5 Hz, 2H), 2.45 – 2.30 (m, 2H), 2.25 (dt, J = 6.5, 3.3 Hz, 1H), 1.08 (d, J = 6.7 Hz, 3H), 0.85 (dd, J = 6.6, 2.8 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 199.2, 140.2, 139.1, 137.1, 128.9, 128.0,

127.5, 91.4, 46.4, 43.4, 30.3, 29.7, 28.3, 26.2, 22.8. UPLC-DAD-QTOF: $C_{18}H_{24}NO_3$ $[M+H]^+$ calcd.: 302.1756, found: 302.1760.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA) hexane/isopropanol 95:5, flow rate= 1 mL/min. Retention times: 5.7 min (major) and 6.9 min (min).

6.3. Experimental section of Chapter 3

6.3.1. Preparation of α´-hydroxyenone 46



Step 1. 2-Hydroxy-N-methoxy-N,2-dimethylpropanamide: To a solution of the hydroxy ester (15 mmol, 1.77 g, 1 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride 22.5 mmol, 1.37 g, 1.5 equiv.) in THF (50 mL), a 2M solution of ^{i}PrMgCl in THF (60 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at room temperature. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20) to obtain the desired Weinreb amide as a colorless oil. Yield: 1.99 g (90%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[163]

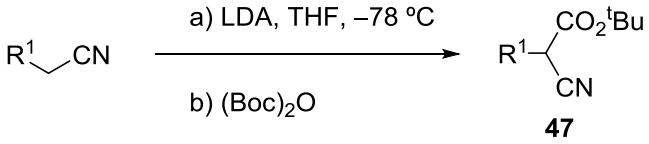
Step 2. 4-Hydroxy-2,4-dimethylpent-1-en-3-one (46): To a solution of thus obtained amide (10 mmol, 1.85 g, 1 equiv.) in Et_2O (20 mL), a solution of isopropenyl magnesium bromide (0.5 M, 60 mL, 3 equiv.) was added at −20 °C, and the resulting mixture was stirred at 0 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography

[163] F. Miege, B. M. Trost, *J. Am. Chem. Soc.,* **2014**, 136, 3016-3019.

(pentane/Et_2O 95/5) to obtain the desired product **46** as a colorless oil. Yield: 833 mg (65%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature[164]

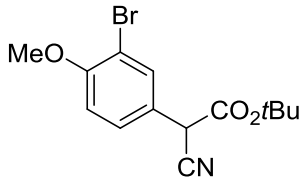
6.3.2. Preparation of α-cyanoesters 47-49

6.3.2.1. *General procedure for the preparation of tertbutyl α-cyanoesters 47*[165]



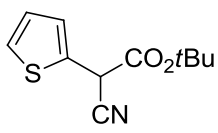
A solution of starting alkyl nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) previously cooled to −78 °C. The reaction mixture was allowed to stir at −78 °C for 45 min, and then at room temperature for an additional 45 min. The reaction mixture was then cooled to −78 °C and a solution of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at −78 ºC for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography (EtOAc:hexane 1:20) to yield the desired α-cyanoester **47**.

tert-Butyl 2-(3-bromo-4-methoxyphenyl)-2-cyanoacetate 47h



Yield: 213 mg (31%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 1H), 7.41 (ddd, *J* = 8.5, 2.4, 0.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.56 (s, 1H), 3.95 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 156.4, 132.7, 128.0, 123.6, 115.7, 112.2, 112.1, 84.8, 56.3, 43.5, 27.7. $C_{14}H_{16}NO_3Br$ $[M-H]^+$ calcd.: 326.0392, found:326.0396.

tert-Butyl 2-cyano-2-(thiophen-2-yl)acetate 47i

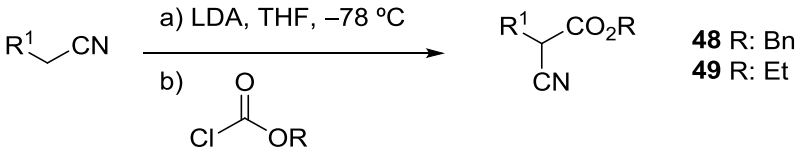


Yield: 679 mg (60%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 6.96 (m, 3H), 4.92 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 147.5,

[164] A. Basheer, M. Mishima, I. Marek, *Org. Lett.*, **2011**, 13, 4076-4079.
[165] B. M. Trost, J. R. Miller, C. M. Hoffman Jr., *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.

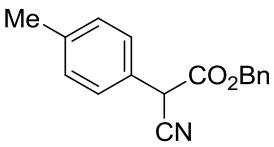
131.1, 127.9, 127.1, 115.2, 85.1, 40.1, 27.6. UPLC-DAD-QTOF: $C_{11}H_{14}NO_2S$ $[M]^+$ calcd.: 224.0746, found: 224.0745.

6.3.2.2. *General procedure for the preparation of α-cyanoesters 48 and 49*



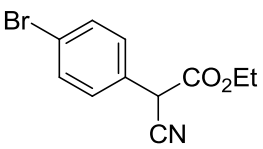
A solution of the corresponding nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to –78 °C. The reaction mixture was allowed to stir at –78 °C for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture was then cooled to –78 °C and a solution of the corresponding chloroformate (15 mmol, 1.5 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at –78 °C for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography to yield the desired cyanoester.

Benzyl 2-cyano-2-(p-tolyl)acetate (48e)



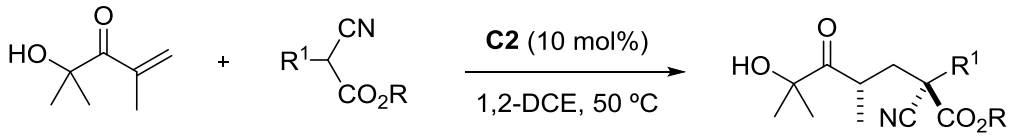
Yield: 886 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 9H), 5.23 (s, 2H), 4.78 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 139.3, 134.6, 130.0, 128.7, 128.2, 127.9, 127.0, 115.8, 68.5, 43.4, 21.1. UPLC-DAD-QTOF: $C_{17}H_{15}NO_2Na$ $[M+Na]^+$ calcd.: 288.1000, found: 288.1000.

Ethyl 2-(4-bromophenyl)-2-cyanoacetate (49b)



Yield: 1.24 g (92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.29 (m, 4H), 4.75 (s, 1H), 4.27 – 4.18 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 132.4, 129.7, 129.2, 123.4, 115.4, 63.5, 43.1, 13.8. UPLC-DAD-QTOF: $C_{11}H_9NO_2Br$ $[M-H]^-$ calcd.: 265.9850, found: 265.9817.

6.3.3. Catalytic conjugate addition of α-cyanoesters 47-49 to enone 46: General procedure and characterization data



46

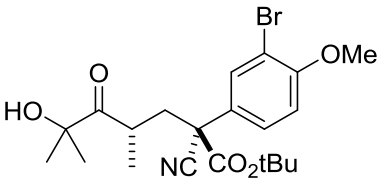
47 R: *t*Bu
48 R: Bn
49 R: Et

50 R: *t*Bu
51 R: Bn
52 R: Et

General Procedure: To a mixture of the corresponding α-cyanoacetate (0.3 mmol, 1.5 equiv.) and α-hydroxy enone **46** (26 mg, 0.2 mmol, 1 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C2** (13 mg, 0.02 mmol) was added. The resulting mixture was stirred at 50 °C unless otherwise stated until consumption of the enone (monitored by ^{1}H-NMR). The reaction was quenched with HCl 1N and the product was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product which was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5).

For the data of the adducts obtained in entries 1-5 see ref 166.

***tert*-Butyl (2S,4S)-2-(3-bromo-4-methoxyphenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (50h)**

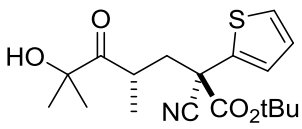


Prepared according to the general procedure starting from cyanoacetate **47h** (98 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 57 mg (62%).$[\alpha]_D^{25}$ = +7.8 (c=1, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.94 (s, 3H), 3.33 – 3.27 (m, 1H), 2.81 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.12 (dd, *J* = 14.6, 5.8 Hz, 1H), 1.50 – 1.40 (m, 15H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.4, 165.8, 156.2, 130.8, 128.1, 126.3, 118.3, 112.2, 111.9, 85.0, 56.3, 52.6, 40.4, 36.7, 27.5, 27.0, 19.8. UPLC-DAD-QTOF: $C_{21}H_{29}NO_5Br$ $[M+H]^+$ calcd.: 454.1229, found: 454.1233.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OJ-H hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: 54.8 min (major.) and 67.9 min (minor.). Processed Channel Descr.: PDA 210.0 nm).

[166] E. Badiola, Doctoral Thesis, α'-Oxy Enones and Pyrrolidin-2,3-diones as Efficient New Templates in Asymmetric Organocatalytic Michael Reactions, EHU/UPV, 2016.

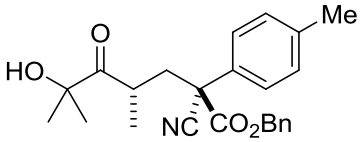
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(thiophen-2-yl)heptanoate (50i)



Prepared according to the general procedure starting from cyanoacetate **47i** (67 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 51 mg (72%). $[\alpha]_D^{25}$ = +4.0 (c=1, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 6.93 (m, 3H), 3.35 (dt, *J* = 7.0, 5.9 Hz, 1H), 2.88 (dd, *J* = 14.5, 6.1 Hz, 1H), 2.22 (dd, *J* = 14.4, 5.6 Hz, 1H), 1.49 (s, 9H), 1.44 (d, *J* = 3.1 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 165.3, 137.7, 126.8, 118.0, 85.4, 77.1, 50.8, 41.9, 36.7, 27.5, 27.1, 19.5. UPLC-DAD-QTOF: $C_{18}H_{25}NO_4SNa$ $[M+Na]^+$ calcd.: 374.1406, found: 374.1402.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 29.9 min (minor.) and 47.4 min (major.). Processed Channel Descr..: PDA 245.0 nm).

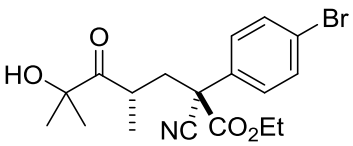
Benzyl (2S,4S)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(p-tolyl)heptanoate (51e)



Prepared according to the general procedure starting from cyanoacetate **48e** (80 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 60 mg (76%). $[\alpha]_D^{25}$ = +11.2 (c=1, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.14 (m, 9H), 5.19 (q, *J* = 12.3 Hz, 2H), 3.40 – 3.28 (m, 1H), 2.91 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.39 (s, 3H), 2.23 (dd, *J* = 14.6, 5.5 Hz, 1H), 1.39 (d, *J* = 5.9 Hz, 6H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.5, 167.2, 139.1, 134.5, 131.2, 129.9, 128.5, 128.5, 127.8, 125.9, 118.3, 68.6, 52.6, 40.6, 36.7, 26.9, 26.5, 21.0, 19.7. UPLC-DAD-QTOF: $C_{24}H_{28}NO_4$ $[M+H]^+$ calcd.: 394.2015, found: 394.2018.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC+AY-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 74.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm).

Ethyl (2S,4S)-2-(4-bromophenyl)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxoheptanoate (52b)



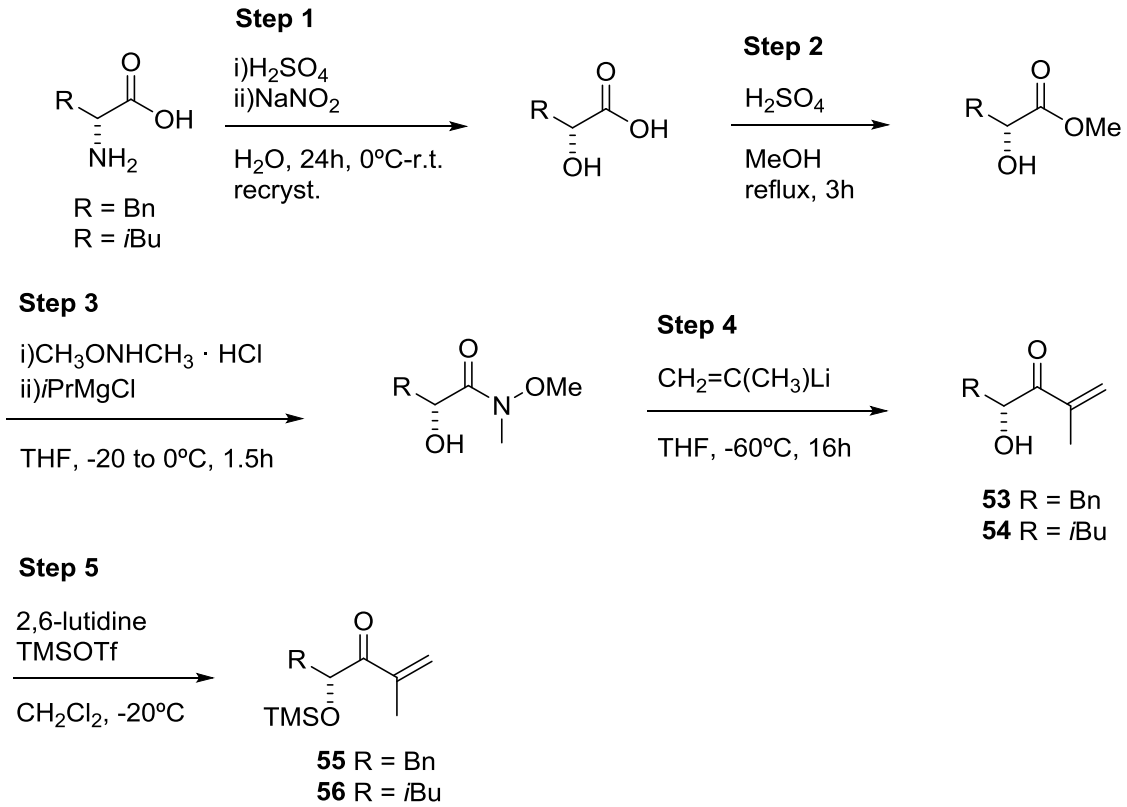
Prepared according to the general procedure starting from cyanoacetate **49b** (80 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 70 mg (88%). $[\alpha]_D^{25}$ = +12.5 (c=1, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.39 (m, 4H), 4.39 – 4.15 (m, 2H), 3.35 (qd, *J* = 6.8, 5.3 Hz, 1H), 2.93 (dd, *J* = 14.6, 6.4 Hz, 1H), 2.18 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.43 (d, *J* = 4.7 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3, 166.9, 133.5, 132.4, 127.8, 123.4, 117.9, 77.1, 63.7, 52.6, 40.6, 36.7, 27.0, 19.9, 13.7. UPLC-DAD-QTOF: $C_{18}H_{23}NO_4Br$ $[M+H]^+$ calcd.: 396.0810, found: 396.0811.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 97/3, flow rate= 0.6 mL/min, retention times: 43.9 min (major.) and 51.4 min (minor.). Processed Channel Descr..: PDA 235.0 nm).

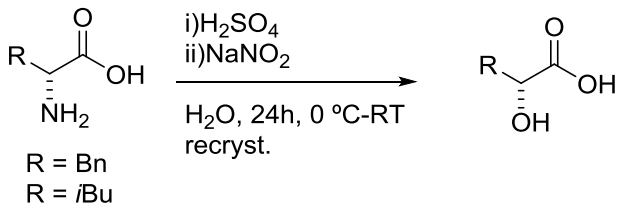
General procedure for the racemic reactions:

Racemic reactions were conducted following the above General Procedure, but using as catalyst DBU (20 mol%) and running the reaction at room temperature.

6.3.4. Preparation of chiral α´-oxyenones 53-56



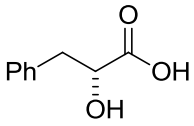
Step 1: Preparation of (*R*)-2-hydroxy acids:[167]



[167] A. Bodlenner; S. M. Glueck; B. M. Nestl; C; C.Gruber; N; Baudendistel; B. Hauer; W. Kroutil; K. Faber; *Tetrahedron*, **2009**, 65, 7752-7755.

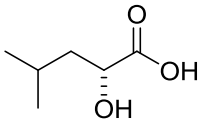
To a suspension of the corresponding amino acid (50 mmol) in water (27.5 mL), an aqueous solution of sulfuric acid (2N, 27.5 mL) was added dropwise at 0 °C. At the same temperature, an aqueous solution of sodium nitrite (2N, 27.5 mL) was also added dropwise. The reaction mixture was stirred at 0 °C for 3 h. The mixture was then warmed up to r.t. and was stirred for 24 h. The mixture was extracted with Et_2O (3 × 40 mL) and the combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by crystallization (ethyl acetate / hexane 1:1).

(*R*)-2-Hydroxy-3-phenylpropanoic acid



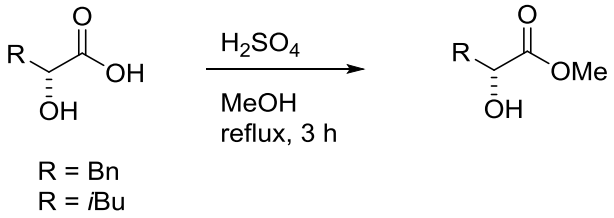
Prepared according to the general procedure starting from D-phenylalanine (50 mmol, 8.26 g). Product obtained as white crystals after recrystallization. Yield: 4.15 g (50%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[167]

(R)-2-Hydroxy-4-methylpentanoic acid



Prepared according to the general procedure starting from D-leucine (50 mmol, 6.55 g). Product obtained as white crystals after recrystallization. Yield: 3.18 g (43%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[167]

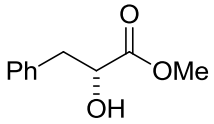
Step 2: Preparation of methyl-(*R*)-2-hydroxy esters:[168]



To a solution of the corresponding 2-hydroxy acid (40 mmol) in methanol (35 mL), an aqueous solution of sulfuric acid (96%, 0.93 mL) was added and the resulting mixture was heated to reflux and stirred for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in Et_2O (50 mL) and washed successively with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL) and NaCl (20 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting oil was used without further purification.

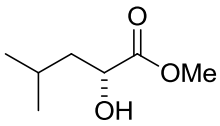
(*R*)-Methyl 2-hydroxy-3-phenylpropanoate

[168] M. Poterala; J. Plenkiewicz *Tetrahedron*, **2011**, 22, 294-299.



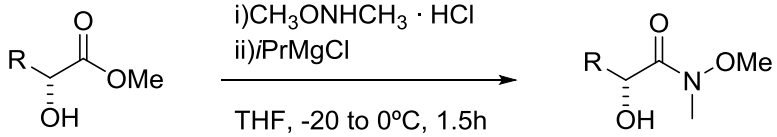
Product obtained as yellow oil. Yield: 7.28 g (100%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[168]

(*R*)-Methyl 2-hydroxy-4-methylpentanoate



Product obtained as colorless oil. Yield: 4.97 g (85%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature. [168]

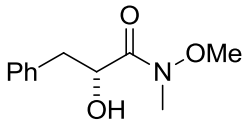
Step 3: Preparation of (*R*)-2-hydroxy-N-methoxy-N-methylamides:[169]



R = Bn
R = *i*Bu

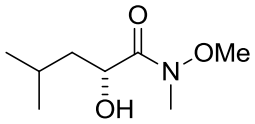
To a solution of the corresponding hydroxy ester (10 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv.) in THF (35 mL), a 2M solution of $^{i}PrMgCl$ in THF (40 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at 0°C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20).

(*R*)-2-Hydroxy-N-methoxy-N-methyl-3-phenylpropanamide



Product obtained as a white solid. Yield: 1.98 g (95%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[170]

(*R*)-2-Hydroxy-N-methoxy-N,4-dimethylpentanamide

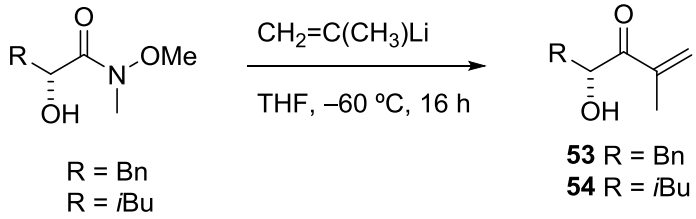


Product obtained as a colorless oil. Yield: 1.42 g (81%). $[\alpha]_D^{23}$= +28.3 (ee >99%, c=0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.74 (s, 3H), 3.26 (s, 3H), 1.95 (td, *J* = 13.4,

[169] Procedure adapted from: Miege, F.; Trost, B. M. *J. Am. Chem. Soc.,* **2014**, 136, 3016-3019.
[170] M. R. Aronoff, N. A. Bourjaily, K. A. Miller, *Tetrahedron*, **2010**, 51, 6375-6377.

6.7 Hz, 1H), 1.52 – 1.42 (m, 2H), 0.98 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 67.3, 61.2, 44.0, 24.6, 23.6, 21.3. UPLC-DAD-QTOF: $C_8H_{17}NO_3$ $[M]^+$ calcd.: 176.1287, found: 176.1289.

Step 4: Preparation of hydroxyenones 53 and 54:

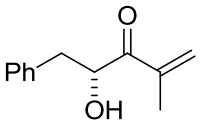


R = Bn
R = *i*Bu

53 R = Bn
54 R = *i*Bu

To a solution of 2-bromopropene (9 mmol, 0.79 mL, 3 equiv.) in Et_2O (5 mL), a *tert*-butyllithium solution (1.6M, 6.75 mL, 3.6 equiv.) was added at −78 °C, and the resulting mixture was stirred at the same temperature for 1 h. A solution of the corresponding Weinreb amide (3 mmol) in Et_2O (10 mL) was then added at −78 °C and the reaction mixture was stirred at −60 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5).

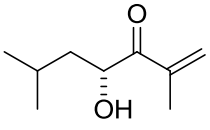
(*R*)-4-Hydroxy-2-methyl-5-phenylpent-1-en-3-one (53)



Product obtained as a yellow oil. Yield: 411 mg (72 %). $[\alpha]_D^{23}$= −49.5 (ee >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 5H), 6.07 – 5.95 (m, 2H), 5.11 (td, *J* = 7.0, 4.2 Hz, 1H), 3.52 (d, *J* = 7.1 Hz, 1H), 3.03 (ddd, *J* = 20.9, 14.0, 5.5 Hz, 2H), 1.96 (dd, *J* = 1.4, 0.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 142.0, 137.0, 129.8, 128.8, 127.2, 126.8, 73.4, 42.9, 18.2. UPLC-DAD-QTOF: $C_{12}H_{15}O_2$ $[M+Na]^+$ calcd.: 191.1062, found: 191.1072.

The enantiomeric purity was determined by HPLC analysis (Chiralpak column AS-H, 95:5 Hexane:*i*-PrOH, 0.5 mL/min, λ=210 nm).

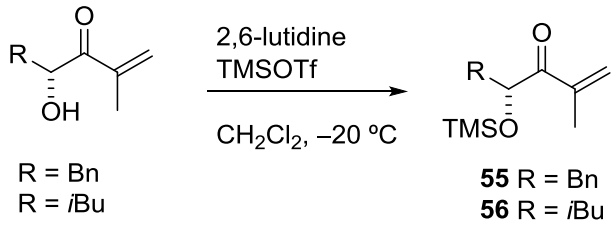
(*R*)-4-Hydroxy-2,6-dimethylhept-1-en-3-one (54)



Product obtained as a yellow oil. Yield: 214 mg (46%). $[\alpha]_D^{23}$= −32.7 (ee >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (d, *J* = 1.3 Hz, 2H), 4.89 – 4.77 (m, 1H), 3.41 (d, *J* = 7.0 Hz, 1H), 2.07 – 1.90 (m, 4H), 1.44 (dddd, *J* = 18.2, 14.1, 9.7, 3.5 Hz, 2H), 0.99 (dd, *J* = 25.0, 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 141.6, 126.4, 71.4, 45.9, 25.3, 24.0, 21.7, 18.3. UPLC-DAD-QTOF: $C_9H_{16}O_2$ $[M+Na]^+$ calcd.: 179.1048, found: 179.1051.

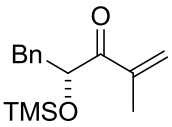
The enantiomeric purity was determined by GC analysis (Chiral column HYDRODEX β-6TBDM. Temperature gradient: 100ºC for 1 min., 10ºC/min. until minute 11, 200ºC until minute 22).

Step 5: Preparation of silyloxyenones 55 and 56:



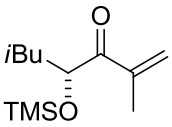
To a solution of the corresponding hydroxyenone (2 mmol) in CH_2Cl_2 (20 mL) cooled to −20°C, were added successively 2,6-lutidine (0.55 mL, 4.8 mmol, 2.4 equiv.) and TMSOTf (0.72 mL, 4 mmol, 2 equiv.). The mixture was stirred at −20 °C for 3 h and then EtOAc (40 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ (40 mL), $CuSO_4$ (3 x 40 mL), $NaHCO_3$ (2 x 40 mL) and NaCl (40 mL). The organic phase was 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 99/1).

(*R*)-2-Methyl-5-phenyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (55)



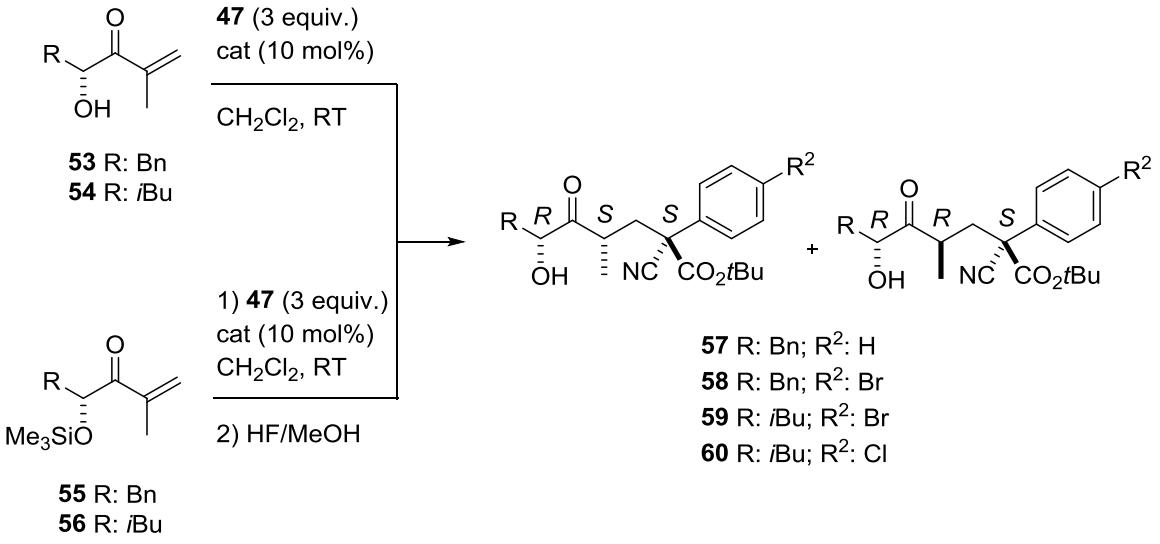
Product obtained as a yellow oil. Yield: 399 mg (72%). $[\alpha]_D^{23}$= -1.7 (c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 5H), 6.14 (s, 1H), 5.87 (dd, *J* = 1.4, 0.8 Hz, 1H), 4.84 (dd, *J* = 9.0, 4.0 Hz, 1H), 2.96 (ddd, *J* = 22.5, 13.5, 6.5 Hz, 2H), 1.93 (dd, *J* = 1.3, 0.9 Hz, 3H), -0.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 142.6, 137.9, 129.5, 128.2, 126.5, 125.5, 76.4, 42.1, 18.4, -0.4. UPLC-DAD-QTOF: $C_{15}H_{23}O_2Si$ $[M]^+$ calcd.: 263.1467, found: 263.1464.

(*R*)-2,6-Dimethyl-4-((trimethylsilyl)oxy)hept-1-en-3-one (56)



Product obtained as a yellow oil. Yield: 279 mg (61%). $[\alpha]_D^{23}$= +0.5 (c=0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.79 (dd, *J* = 1.4, 0.8 Hz, 1H), 4.75 (dd, *J* = 9.8, 3.4 Hz, 1H), 1.93 – 1.74 (m, 4H), 1.47 (dddd, *J* = 17.2, 13.7, 9.4, 4.4 Hz, 2H), 0.92 (dd, *J* = 6.6, 2.2 Hz, 6H), 0.11 – 0.05 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 142.3, 124.9, 73.6, 44.5, 24.4, 23.3, 21.2, 18.3, -0.1. [UPLC-DAD-QTOF: $C_{12}H_{25}O_2Si$ $[M]^+$ calcd.: 229.1620, found: 229.1624.

6.3.5. Catalytic addition of α-cyanoacetates 47 to quiral enones 53-56

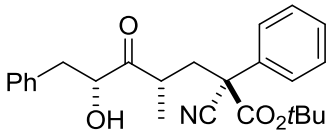


General Procedure: To a solution of the corresponding *tert*-butyl cyanoacetate **47** (0.6 mmol) and the corresponding α´-oxy enone **53-56** (0.2 mmol, 1 equiv.) in CH_2Cl_2 (0.4 mL), the Brønsted base catalyst (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α´-oxy enone (monitored by ^{1}H-NMR). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

Reactions from α´-hydroxy enone **53/54**: The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

Reactions from α´-silyloxy enone **55/56**: The resulting material was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH was added (10 mmol, 0.2 mL) and the resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was basified to pH 7 with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 4 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

(2*S*,4*S*,6*R*)-*tert*-Butyl 2-cyano-6-hydroxy-4-methyl-5-oxo-2,7-diphenylheptanoate (57)

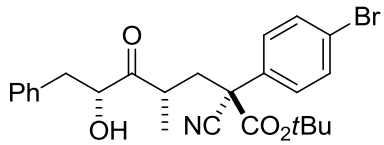


Prepared according to the general procedure starting from hydroxyenone **55** and cyanoacetate **47a**, and using catalyst **C2**. The title compound was isolated as an oil. Yield: 59 mg

(73%). $[\alpha]_D^{23}$ = +5.7 (c=0.3, dr: 89:11:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.71 – 7.18 (m, 10H), 4.54 (ddd, *J* = 9.3, 5.8, 3.6 Hz, 1H), 3.23 – 2.93 (m, 4H), 2.93 – 2.70 (m, 1H), 2.29 – 2.11 (m, 1H), 1.44 (s, 9H), 1.12 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 214.1, 166.1, 136.8, 134.4, 129.3, 129.2, 128.9, 128.6, 126.8, 126.0, 118.6, 84.7, 76.0, 53.7, 39.7, 38.8, 27.5, 19.0. UPLC-DAD-QTOF: $C_{25}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 430.1993, found: 430.1994. dr: 89:11:0:0.

The ratio of diastereomers was determined by ^{1}H NMR analysis.

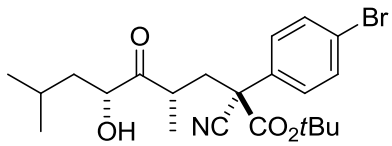
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4-methyl-5-oxo-7-phenylheptanoate (58)



Prepared according to the general procedure starting from hydroxyenone **55** and cyanoacetate **47b**, and using catalyst **C2**. The title compound was isolated as an oil. Yield: 73 mg (75%). $[\alpha]_D^{25}$ = +4.5 (c=1, dr: 83:17:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.64 – 7.19 (m, 9H), 4.59 – 4.47 (m, 1H), 3.19 – 2.94 (m, 3H), 2.83 (dt, *J* = 14.1, 9.3 Hz, 1H), 2.17 – 2.00 (m, 1H), 1.45 (s, 9H), 1.09 (d, *J* = 13.6 Hz, 3H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 212.8, 165.6, 137.0, 134.0, 132.3, 129.6, 129.3, 128.5, 127.7, 126.8, 85.1, 76.0, 54.1, 42.9, 40.6, 38.8, 27.5, 19.0. UPLC-DAD-QTOF: $C_{25}H_{29}NO_4Br$ $[M]^+$ calcd.: 486.1280, found: 486.1282. dr: 83:17:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

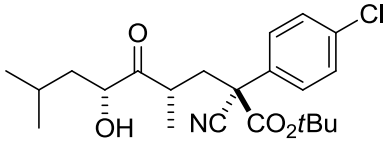
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (59)



Prepared according to the general procedure starting from hydroxyenone **56** and cyanoacetate **47b**, and using catalyst **C2**. The title compound was isolated as an oil. Yield: 81 mg (90 %). $[\alpha]_D^{23}$ = -1.2 (c=0.6, dr: 91:9:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.66 – 7.41 (m, 4H), 4.40 – 4.28 (m, 1H), 3.20 (d, *J* = 5.9 Hz, 1H), 3.14 – 2.84 (m, 2H), 2.14 – 1.90 (m, 2H), 1.45 (s, 9H), 1.44 – 1.24 (m, 2H), 1.19 (d, 3H), 1.08(d, 6H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 213.7, 165.5, 134.0, 131.7, 127.7, 123.3, 118.0, 85.1, 73.3, 42.8, 38.6, 38.5, 27.5, 24.8, 23.6, 21.0, 19.4. UPLC-DAD-QTOF: $C_{22}H_{31}NO_4Br$ $[M]^+$ calcd.: 452.1436, found: 452.1439. dr: 91:9:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

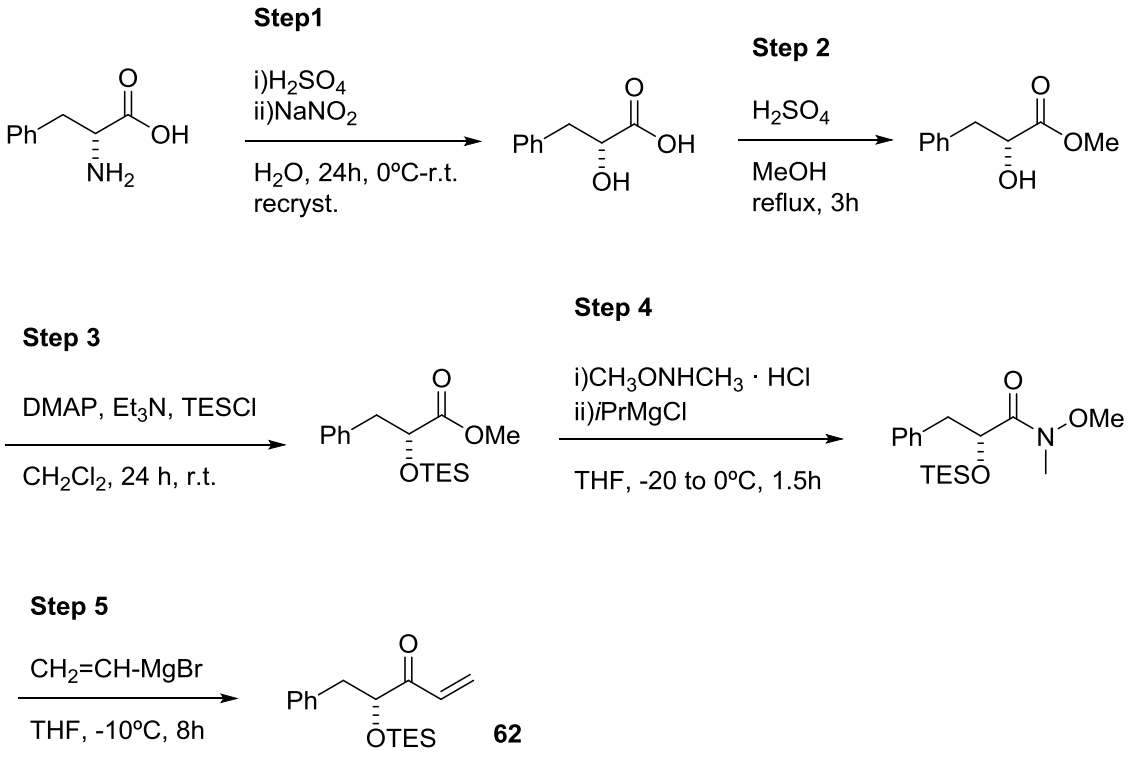
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-chlorophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (60)



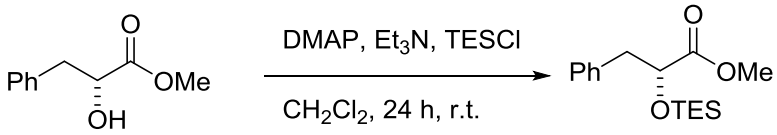
Prepared according to the general procedure starting from hydroxyenone **56** and cyanoacetate **47c**, and using catalyst **C2**. The title compound was isolated as an oil. Yield: 65 mg (80%). $[\alpha]_D^{23}$ = -0.8 (c=0.7, dr: 90:10:0:0, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.61 – 7.35 (m, 4H), 4.43 – 4.29 (m, 1H), 3.21 (d, *J* = 5.9 Hz, 1H), 3.06 (dt, *J* = 13.4, 6.7 Hz, 1H), 3.01 – 2.90 (m, 1H), 2.06 (dt, *J* = 12.5, 4.0 Hz, 1H), 1.96 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.62 – 1.40 (m, 11H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.04 – 0.98 (m, 6H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 214.4, 165.7, 135.1, 133.5, 129.4, 127.4, 118.4, 85.1, 73.4, 53.2, 42.8, 38.6, 27.5, 24.8, 23.8, 21.1, 19.6. UPLC-DAD-QTOF: $C_{22}H_{31}NO_4Cl$ $[M]^+$ calcd.: 408.1942, found: 408.1943. dr: 90:10:0:0.

The diastereomeric purity was determined by ^{1}H NMR analysis.

6.3.6. Preparation of chiral α´-silyloxyenone 62

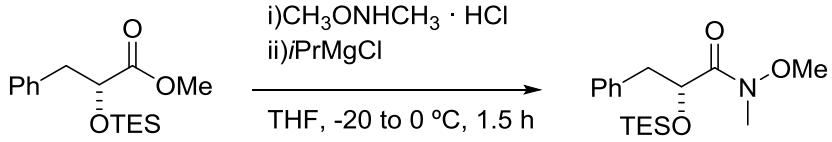


Step 3. Preparation of methyl (*R*)-3-phenyl-2-((triethylsilyl)oxy)propanoate[171]



To a solution of 4-dimethylamino pyridine (900 mg, 7.5 mmol), triethylamine (0.7 mL, 5 mmol), and triethylchlorosilane (1.27 mL, 7.5 mmol) in CH_2Cl_2 (7.5 mL), the methyl-2-hydroxy ester (901 mg, 5 mmol) was added and the reaction was stirred at room temperature for 24 h. After filtration over celite, the filtrate was diluted with diethyl ether (50 mL) and the resulting solution was washed with brine (1 × 25 mL), HCl 3M (3 × 50 mL), and water (1 × 25 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 20/1) to give the desired compound as a colorless oil (1.21 g, 82%). $[\alpha]_D^{23}$= + 47.4 (ee >99%, c=2.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 5H), 4.40 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.74 (s, 3H), 3.19 – 2.85 (m, 2H), 0.92 – 0.79 (m, 9H), 0.57 – 0.41 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 137.3, 129.6, 128.1, 126.6, 73.5, 51.8, 41.6, 6.4, 4.3. UPLC-DAD-QTOF: $C_{16}H_{27}O_3Si$ $[M+H]^+$ cald.: 295.1729, found: 295.1731.

Step 4. Preparation of (*R*)-N-methoxy-N-methyl-3-phenyl-2-((triethylsilyl)oxy)propanamide[172]

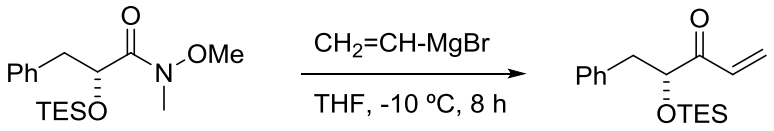


To a solution of the silyloxy ester (1.21 g, 4.1 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (601 mg, 6.2 mmol, 1.5 equiv.) in THF (14 mL), a 2M solution of ^{i}PrMgCl in THF (8.2 mL, 16.5 mmol, 4 equiv.) was added at −20 °C. The reaction mixture was stirred for 1.5 h at 0 °C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80/20) to obtain the desired product as a yellow oil (1.08 g, 3.3 mmol, 81%). $[\alpha]_D^{23}$= + 3.6 (ee >99%, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 5H), 4.72 (dd, *J* = 8.1, 4.9 Hz, 1H), 3.56 (s, 3H), 3.18 (s, 3H), 3.12 – 2.83 (m, 2H), 0.85

[171] Procedure adapted from: J. M. García, A. Gozalez, B. G. Kardak, J. M. Odriozola, M. Oiarbide, J. Razkin, C. Palomo, *Chem. Eur. J.*, **2008**, *14*, 8768−8771.
[172] Procedure adapted from: F. Miege, B. M. Trost, *J. Am. Chem. Soc.*, **2014**, *136*, 3016−3019.

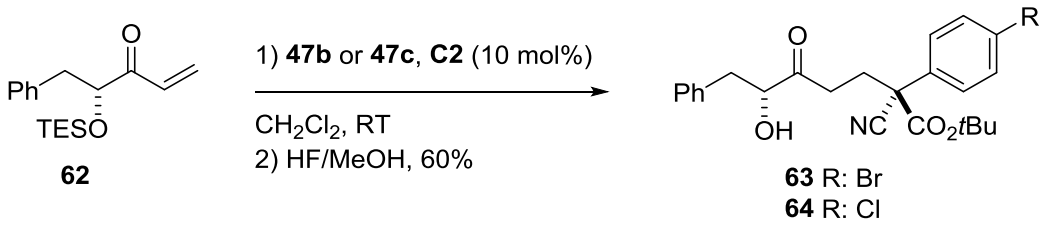
(t, *J* = 7.8 Hz, 9H), 0.60 – 0.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 137.7, 129.6, 128.1, 126.4, 70.8, 61.0, 41.2, 32.4, 6.4, 4.4. UPLC-DAD-QTOF: $C_{17}H_{30}NO_3Si$ $[M+H]^+$ cald.: 324.1995, found: 324.1999.

Step 5. Preparation of (*R*)-5-phenyl-4-((triethylsilyl)oxy)pent-1-en-3-one (62)



To a solution of the silyloxy amide (458 mg, 1.4 mmol) in dry THF (4 mL), a 0.7 M solution of vinylmagnesium bromide in THF was added at 0 °C. The reaction mixture was stirred for 24 h at 0 °C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried with $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95/5) to obtain the desired product as a colorless oil (159 mg, 0.6 mmol, 43%). $[\alpha]_D^{23}$= + 15.6 (ee >99%, c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 5H), 6.84 (ddd, *J* = 17.4, 10.5, 0.7 Hz, 1H), 6.42 (ddd, *J* = 17.5, 1.9, 0.7 Hz, 1H), 5.78 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.38 (ddd, *J* = 8.4, 4.5, 0.7 Hz, 1H), 3.03 – 2.81 (m, 2H), 0.85 (t, *J* = 7.9 Hz, 9H), 0.52 – 0.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 137.4, 131.4, 130.2, 129.8, 128.6, 127.0, 79.7, 41.9, 7.0, 4.9. UPLC-DAD-QTOF: $C_{17}H_{30}NO_3Si$ $[M+H]^+$ cald.: 291.1780, found: 291.1778.

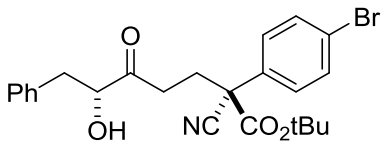
6.3.7. Catalytic addition of α-cyanoacetates 47b and 47c to chiral enone 62



General Procedure: To a solution of the corresponding *tert*-butyl cyanoacetate **47** (0.6 mmol) and α´-silyloxy enone **62** (0.2 mmol, 1 equiv.) in CH_2Cl_2 (0.4 mL), **C2** (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α´-oxy enone (monitored by ^{1}H-NMR). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting material was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH was added (10 mmol, 0.2 mL) and the resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was

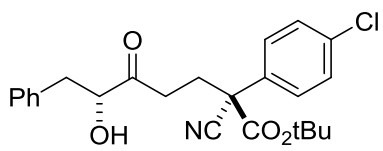
basified to pH 7 with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 4 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95/5).

tert-Butyl (2*S*,6*R*)-2-(4-bromophenyl)-2-cyano-6-hydroxy-5-oxo-7-phenylheptanoate (63)



Prepared according to the general procedure starting from α´-silyloxy enone **62** and cyanoacetate **47b**. The title compound was isolated as an oil. Yield: 88 mg (93%). $[\alpha]_D^{23}$= + 11.7 (dr: >95:5, c=2.3, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.19 (m, 9H), 4.48 – 4.34 (m, 1H), 3.13 (dd, *J* = 14.2, 4.8 Hz, 2H), 2.90 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.77 (ddd, *J* = 17.2, 12.2, 3.6 Hz, 1H), 2.62 – 2.36 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 165.0, 135.7, 132.9, 132.1, 128.9, 128.3, 127.3, 126.7, 123.0, 117.5, 84.8, 77.0, 53.1, 39.8, 34.3, 30.9, 27.2. UPLC-DAD-QTOF: $C_{24}H_{27}BrNO_4$ $[M+H]^+$ cald.: 472.1123, found: 472.1124.

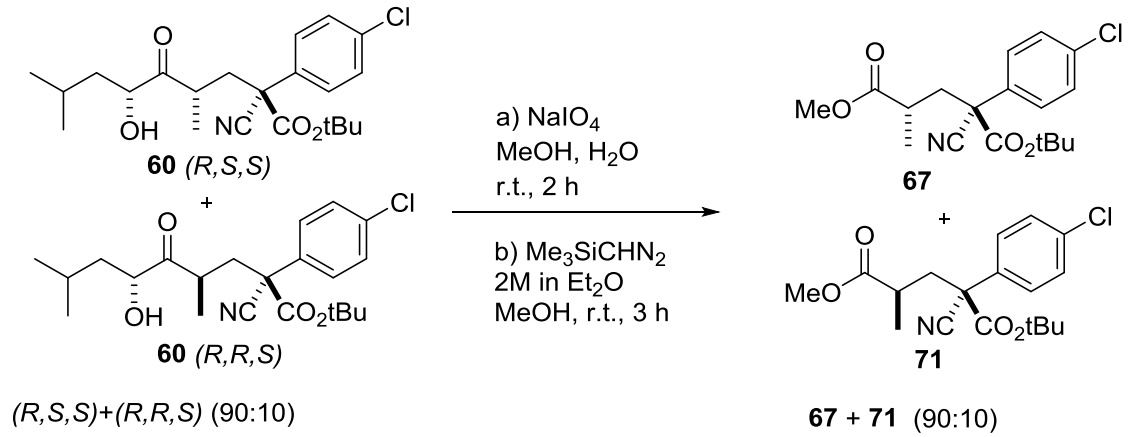
tert-Butyl (2S,6R)-2-(4-chlorophenyl)-2-cyano-6-hydroxy-5-oxo-7-phenylheptanoate (64)



Prepared according to the general procedure starting from α´-silyloxy enone **62** and cyanoacetate **47c**. The title compound was isolated as an oil. Yield: 68 mg (79%). $[\alpha]_D^{23}$= +7.8 (dr: > 95:5, c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.20 (m, 9H), 4.48 – 4.36 (m, 1H), 3.22 – 3.08 (m, 2H), 2.96 – 2.69 (m, 2H), 2.61 – 2.36 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 165.4, 136.0, 135.2, 132.7, 129.4, 129.2, 128.6, 127.3, 127.0, 117.8, 85.1, 77.3, 53.4, 40.2, 34.6, 31.2, 27.5. UPLC-DAD-QTOF: $C_{24}H_{27}ClNO_4$ $[M+H]^+$ cald.: 428.1629, found: 428.1633.

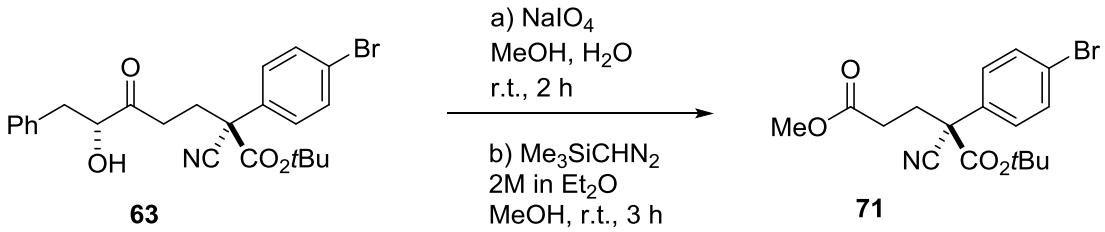
6.3.8. Chemical elaboration of adducts

6.3.8.1. *Scision of 60 and 63. Synthesis of methyl esters 67, 71 and 72*



1-tert-Butyl 5-methyl 2-(4-chlorophenyl)-2-cyano-4-methylpentanedioate 67/71

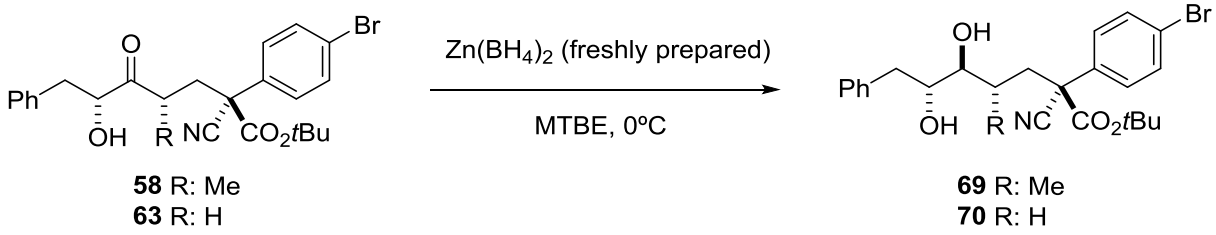
Procedure adapted from 160. A suspension of $NaIO_4$ (171 mg, 0.79 mmol) in water (0.38 mL) was added to a solution of adduct **60** (90:10 mixture of diastereomers, 65 mg, 0.16 mmol) in methanol (0.79 mL). The mixture was stirred at room temperature until the starting material dissapeared (monitored by TLC) and the solvent was removed under reduced pressure. Water (2.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. To a solution of the resulting residue (0.13 mmol, 44 mg) in MeOH (1 mL), a solution of Me_3SiCHN_2 (2M, 0.65 mmol, 0.33 mL, 5 equiv.) was added and the resulting mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10). Yield (two steps): 42 mg (90:10 mixture of diastereomers, 78%). $[\alpha]_D^{23}$ = +11.0 (c=0.5, CH_2Cl_2). ^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.57 – 7.34 (m, 4H), 3.74 (s, 3H), 2.90 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.12 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.45 (s, 9H), 1.21 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR major diastereomer (75 MHz, $CDCl_3$) δ 175.9, 166.0, 135.4, 133.8, 129.7, 127.9, 118.2, 85.3, 53.6, 52.4, 41.3, 37.1, 27.9, 19.3. UPLC-DAD-QTOF: $C_{18}H_{23}NO_4Cl$ $[M]^+$ calcd.: 352.1316, found: 352.1321.



1-(*tert*-Butyl) 5-methyl (*S*)-2-(4-bromophenyl)-2-cyanopentanedioate (71)

Procedure adapted from 160. A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of α-hydroxy ketone **63** (0.2 mmol) in methanol (1 mL) and water (0.8 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 24h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. To a solution of the resulting residue in MeOH (1 mL), a solution of $Me_3SiCH_2N_2$ (2M, 1 mmol, 0.5 mL, 5 equiv.) was added and the resulting mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 90/10). Yield (two steps): 65 mg (85%). $[\alpha]_D^{23}$= +0.7 (c=0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.37 (m, 4H), 3.70 (s, 3H), 2.74 – 2.35 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 165.8, 133.7, 132.8, 128.1, 123.7, 118.1, 85.5, 54.0, 52.4, 33.2, 30.5, 28.0. UPLC-DAD-QTOF: $C_{17}H_{21}BrNO_4$ $[M+H]^+$ cald.: 382.0654, found: 382.0656.

6.3.8.2. *Reduction of 58 and 63 to corresponding anti-diols 69 and 70*



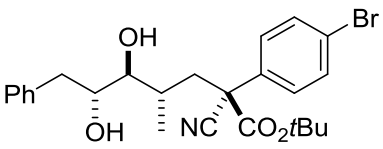
Preparation of zinc borohydride

A mixture of anhydrous zinc chloride (2 g, 14.5 mmol) with dry MTBE (25 mL) was refluxed until most of the solid had disolved. The mixture was allowed to stand, and the supernatant liquid was decanted from the insoluble material. The solution was added dropwise at room temperature to a stirred suspension of sodium borohydride (1.30 g,

34.5 mmol, 2.4 equiv.) in 75 mL of dry MTBE. The resulting mixture was stirred for 3 days at room temperature. The solids were allowed to settle, and the solution was directly used for the next reactions.

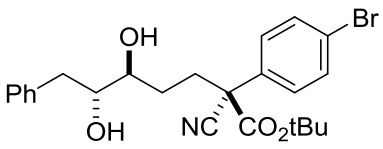
General procedure for the reduction of 69 and 70: To a solution the corresponding α´-hydroxy ketones (0.6 mmol, 290 mg) in dry MTBE (2 mL) a solution of zinc borohydride in MTBE was added at 0 °C (25 mL) and the mixture was stirred at 0 °C for 10-15 minutes. The reaction mixture was quenched with water and the layers were separated. The organic phase was 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).

***tert*-Butyl (2S,4S,6R)-2-(4-bromophenyl)-2-cyano-5,6-dihydroxy-4-methyl-7-phenylheptanoate 69**



Prepared according to the general procedure starting from adduct **58**. The title compound was isolated as a colorless oil. Yield 225 mg (76%). $[\alpha]_D^{25}$ = +29.9 (c=1, dr >95:5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.21 (m, 9H), 3.95 (dtd, *J* = 9.8, 4.9, 2.9 Hz, 1H), 3.55 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.00 (dd, *J* = 13.8, 2.9 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.37 – 2.19 (m, 2H), 2.10 (qd, *J* = 7.3, 3.3 Hz, 1H), 1.85 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.46 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 138.3, 135.3, 132.1, 129.5, 128.6, 127.6, 126.6, 122.9, 118.8, 85.5, 78.4, 72.7, 53.7, 40.9, 37.5, 33.2, 27.5, 17.7. UPLC-DAD-QTOF: $C_{25}H_{31}NO_4Br$ $[M]^+$ calcd.: 488.1436, found: 488.1440.

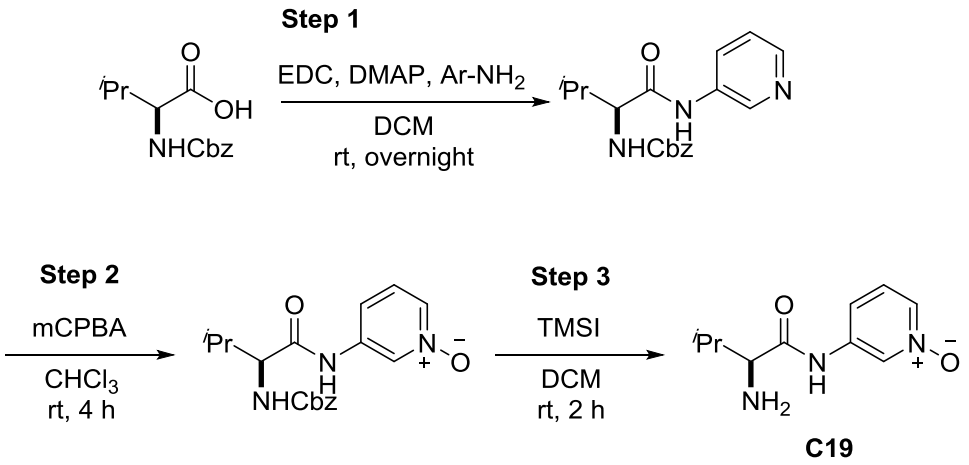
***tert*-Butyl (2S,5S,6R)-2-(4-bromophenyl)-2-cyano-5,6-dihydroxy-7-phenylheptanoate 70**



Prepared according to the general procedure starting from adduct **63**. The title compound was isolated as a white solid. Yield: 222 mg (78%). m. p.: 127 – 129 °C. $[\alpha]_D^{23}$= +6.7 (dr: > 95:5, c=0.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.38 (m, 4H), 7.41 – 7.14 (m, 5H), 4.63 (ddd, *J* = 8.9, 7.5, 5.2 Hz, 1H), 4.32 (ddd, *J* = 10.5, 7.5, 2.9 Hz, 1H), 2.94 – 2.67 (m, 2H), 2.16 – 1.86 (m, 2H), 1.47 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 137.6, 133.8, 132.2, 129.0, 128.5, 127.7, 126.5, 123.1, 118.1, 84.8, 79.3, 78.2, 54.3, 37.3, 34.9, 27.6, 25.2. UPLC-DAD-QTOF: $C_{24}H_{29}BrNO_4$ $[M+H]^+$ cald.: 474.1280, found: 474.1285.

6.4. Experimental section of Chapter 4

6.4.1. Preparation of catalyst C19



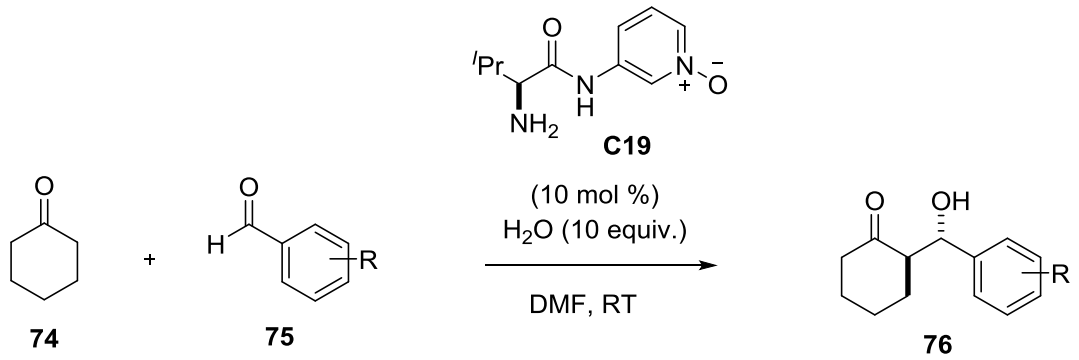
Step 1. To a stirring solution of N-Benzyloxycarbonyl-L-valine (2.51 g, 10.0 mmol, 1.0 equiv.) and 3-aminopyridina (1.41 g, 15 mmol, 1.5 equiv.) in CH_2Cl_2 (30.0 mL) at room temperature EDC (2.87, 15.0 mmol, 1.5 equiv.) and 4-DMAP (1.83 g, 15.0 mmol, 15.0 equiv.) were added. The reaction was allowed to stir overnight while at room temperature. The mixture 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 via silica gel chromatography (Hexane/ EtOAc 70:30) to obtain the desired product (1.73 g, 53%).

Step 2. To a solution of the previously obtained amino-amide (1.64 g, 5.0 mmol, 1 equiv.) in $CHCl_3$ (10 mL) m-CPBA (1.12 g, 6.5 mmol, 1.3 equiv.) was added and the resulting mixture was stirred for 4 h at room temperature. The organic layer was removed and the crude was purified via silica gel chromatography (Hexane/EtOAc 60:40) to obtain the desired product (1.41 g, 82%).

Step 3. To a solution of the previously obtained N-oxidated amino-amide (687 mg, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) TMSI (0.88 mL, 6 mmol, 3 equiv.) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with MeOH (5 mL) and the mixture was stirred for an additional 30 min. The resulting mixture was concentrated under reduced pressure was purified via silica gel chromatography (CH_2Cl_2/MeOH 85:15) to obtain catalyst **C19** as a colorless oil (377 mg, 90%). $[\alpha]_D^{24}$= +1.37° (*c*= 0.3, MeOH). ^{1}H NMR (495 MHz, Methanol-d_4) δ 9.03 (t, *J* = 1.9 Hz,

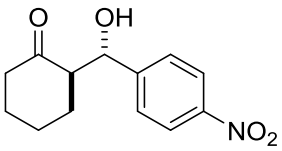
1H), 8.16 – 8.01 (m, 1H), 7.74 – 7.63 (m, 1H), 7.47 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.30 – 3.17 (m, 1H), 2.04 (pd, *J* = 6.9, 5.4 Hz, 1H), 0.97 (dd, *J* = 33.3, 6.9 Hz, 6H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 174.8, 138.6, 134.0, 130.9, 126.4, 120.1, 60.9, 32.2, 18.5. UPLC-DAD-QTOF: $C_{10}H_{16}N_3O_2$ $[M+H]^+$ calcd.: 210.1243, found: 210.1241.

6.4.2. General procedure for the aldol reaction between cyclohexanone 74 and aldehydes 75



To a mixture of catalyst **C19** (6 mg, 0.02 mmol, 10 mol%) and H_2O (4 µL, 0.02 mmol, 10 mol%) was added the aldehyde **75** (0.2 mmol) and cyclohexanone **74** (0.6 mL, 6.0 mmol). The resulting homogeneous mixture was stirred at room temperature for the appropriate time until the reaction was completed by TLC. Then, saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring. The residue was then purified by column chromatography on silica gel (mixture ethyl acetate/hexane) to give the corresponding aldol adducts. ^{1}H and ^{13}C NMR spectra of compounds **76a**-**76i** were identical to those reported in the literature.[173]

(*R*)-2-((*S*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (76a)

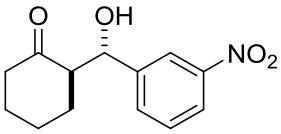


Prepared following the general procedure starting from cyclohexanone **74** and *p*-nitrobenzaldehyde **75a**. Yield: 86% (43 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 5/1, flow rate= 0.6 mL/min.

(*R*)-2-((*S*)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (76b)

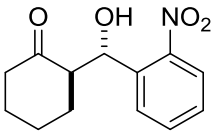
[173] a) Gryko, D.; Lipínski, R. *Eur. J. Org. Chem.* **2006**, 3864−3876. b) Suri, J. T.; Ramachary, D. B.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 1383−1385.



Prepared following the general procedure starting from cyclohexanone **74** and *m*-nitrobenzaldehyde **75b**. Yield: 80% (40 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack IA hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

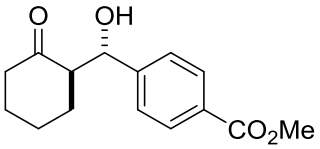
(*R*)-2-((*S*)-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (76c)



Prepared following the general procedure starting from cyclohexanone **74** and *o*-nitrobenzaldehyde **75c**. Yield: 66% (33 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

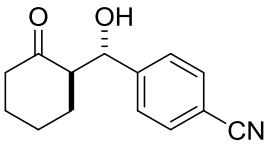
Methyl 4-((*S*)-hydroxy((*R*)-2-oxocyclohexyl)methyl)benzoate (76d)



Prepared following the general procedure starting from cyclohexanone **74** and methyl 4-formylbenzoate **75d**. Yield: 67% (35 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AS-H hexane/isopropanol 4/1, flow rate= 0.5 mL/min.

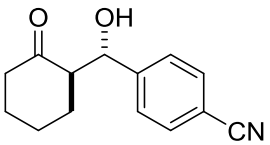
4-((*S*)-Hydroxy((*R*)-2-oxocyclohexyl)methyl)benzonitrile (76e)



Prepared following the general procedure starting from cyclohexanone **74** and 4-formylbenzonitrile **75e**. Yield: 76% (35 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 85/15, flow rate= 0.5 mL/min.

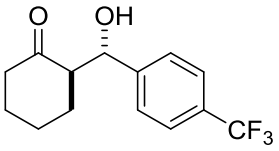
4-((*S*)-Hydroxy((*R*)-2-oxocyclohexyl)methyl)benzonitrile (76e)



Prepared following the general procedure starting from cyclohexanone **74** and 4-formylbenzonitrile **75e**. Yield: 76% (35 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 85/15, flow rate= 0.5 mL/min.

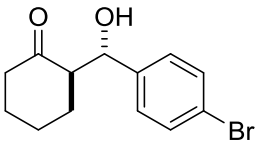
(*R*)-2-((*S*)-Hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (76f)



Prepared following the general procedure starting from cyclohexanone **74** and 4-(trifluoromethyl)benzaldehyde **75f**. Yield: 86% (46 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

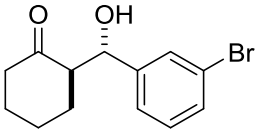
(*R*)-2-((*S*)-(4-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (76g)



Prepared following the general procedure starting from cyclohexanone **74** and *o*-bromobenzaldehyde **75g**. Yield: 73% (39 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 9/1, flow rate= 0.5 mL/min.

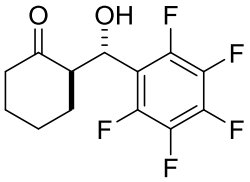
(*R*)-2-((*S*)-(3-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (76h)



Prepared following the general procedure starting from cyclohexanone **74** and *m*-bromobenzaldehyde **75h**. Yield: 80% (45 mg).

The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 9/1, flow rate= 0.5 mL/min.

(*R*)-2-((*S*)-Hydroxy(perfluorophenyl)methyl)cyclohexan-1-one (76i)

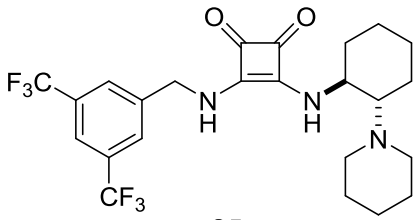


Prepared following the general procedure starting from cyclohexanone **74** and 2,3,4,5,6-pentafluorobenzaldehyde **75i**. Yield: 92% (55 mg).

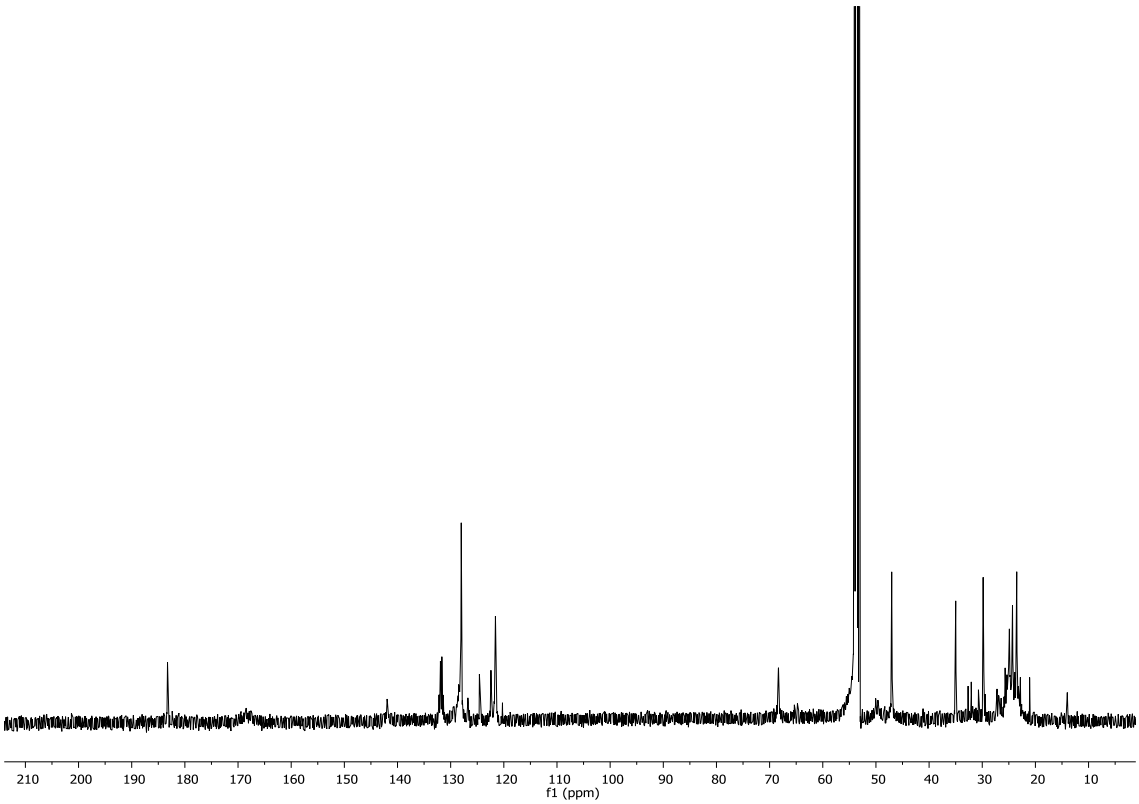
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

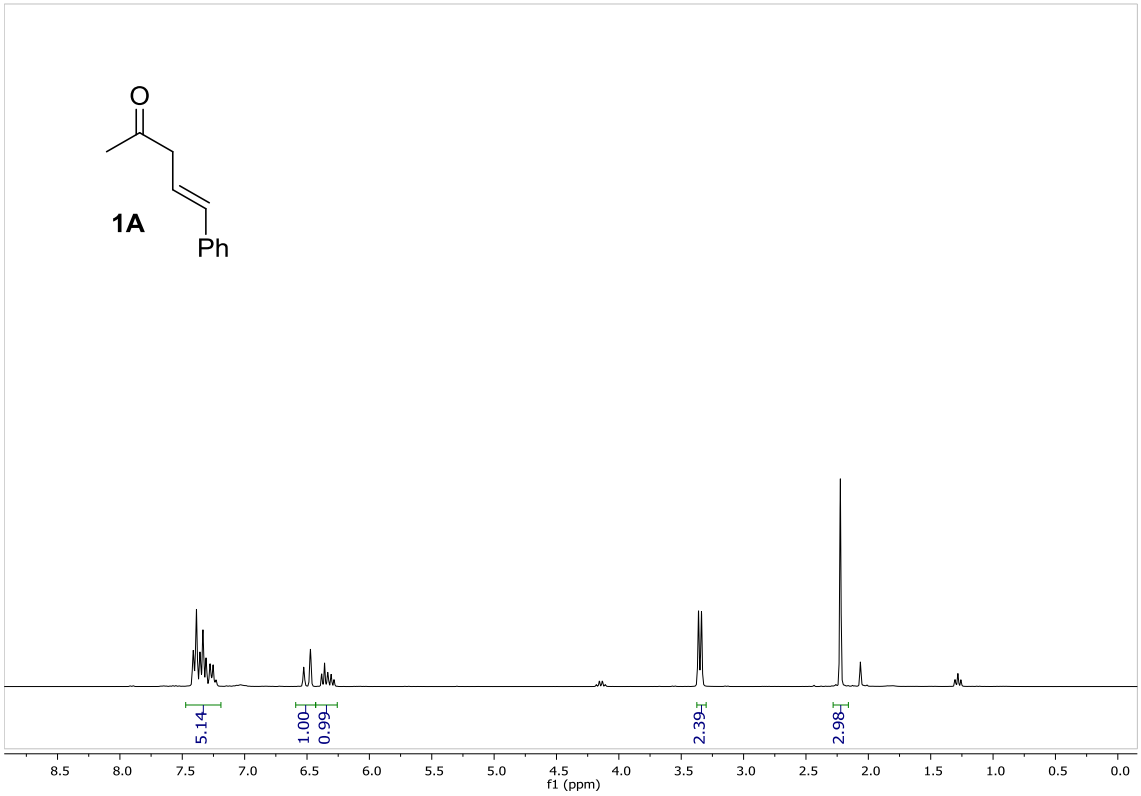
6.5. NMR spectra

6.5.1. NMR spectra of Chapter 2



C5

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1A
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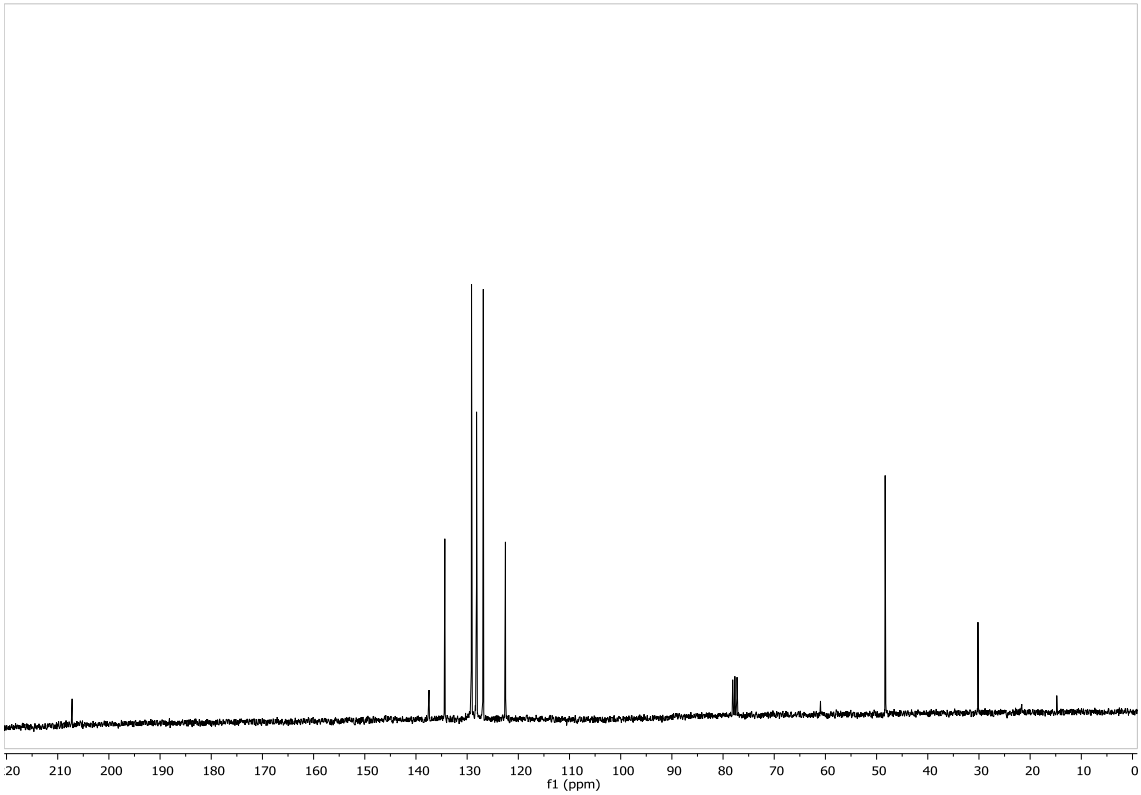
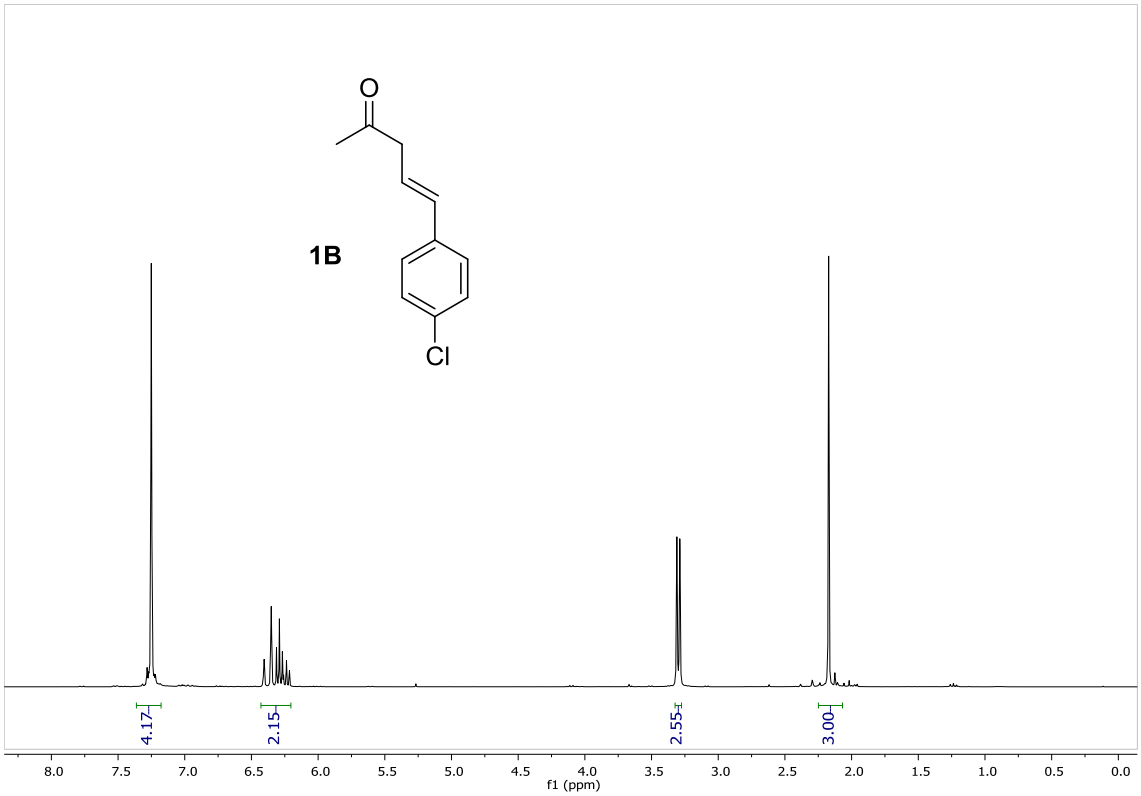
0.99
2.39
2.98
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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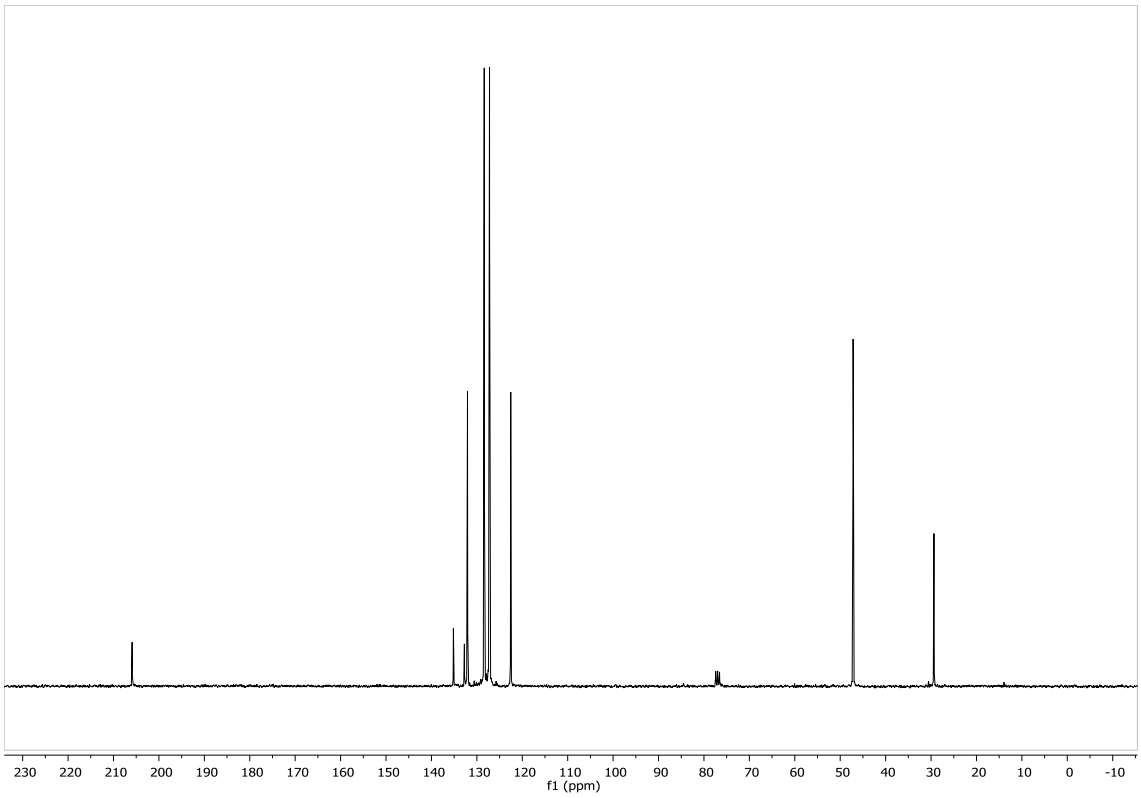
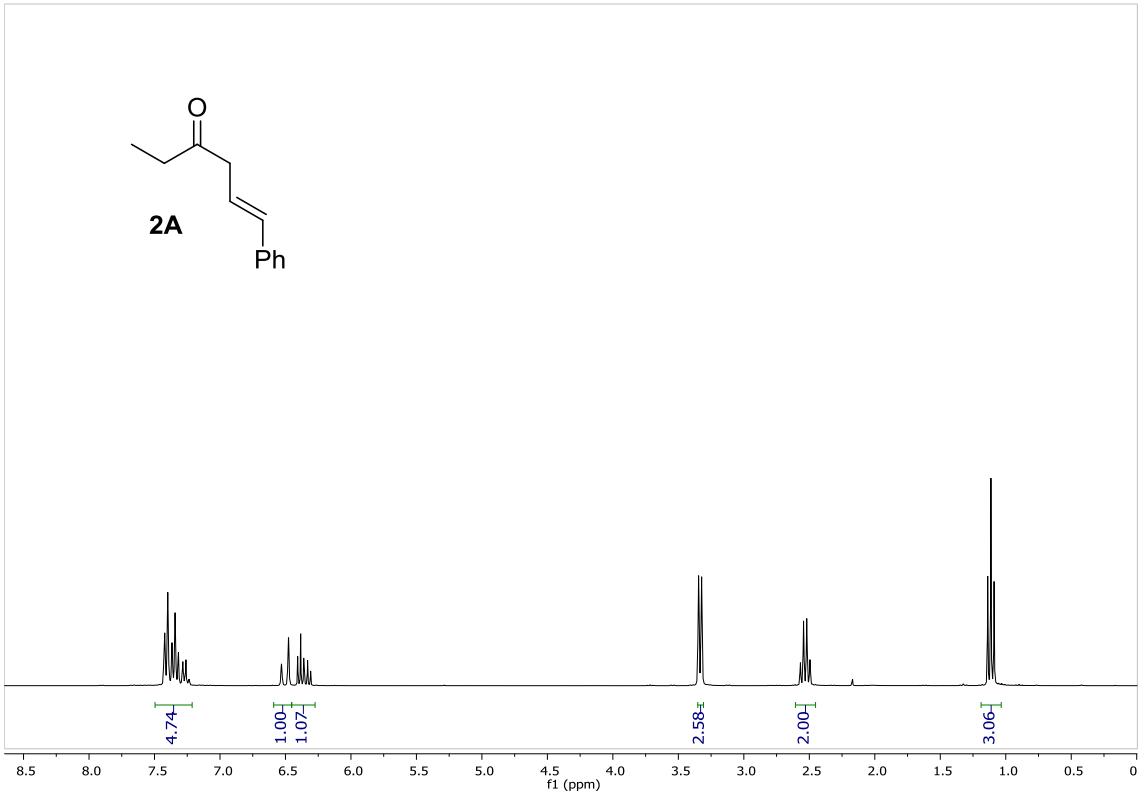
2.55
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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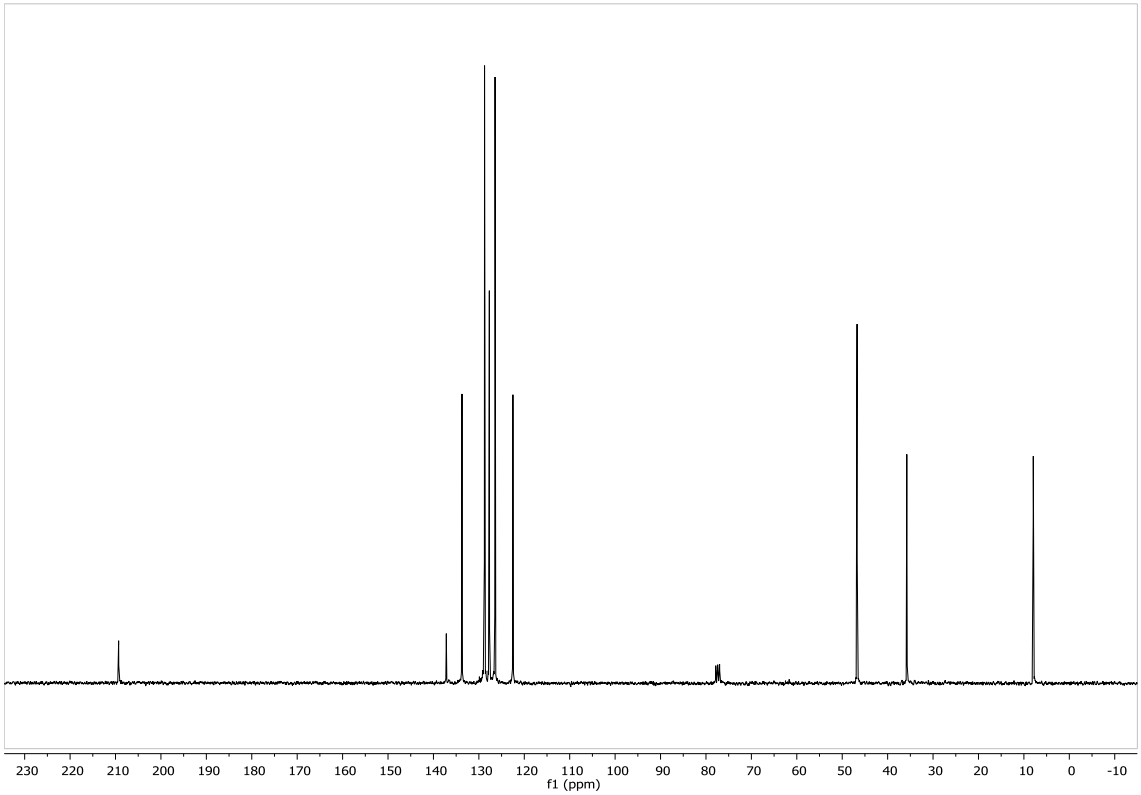
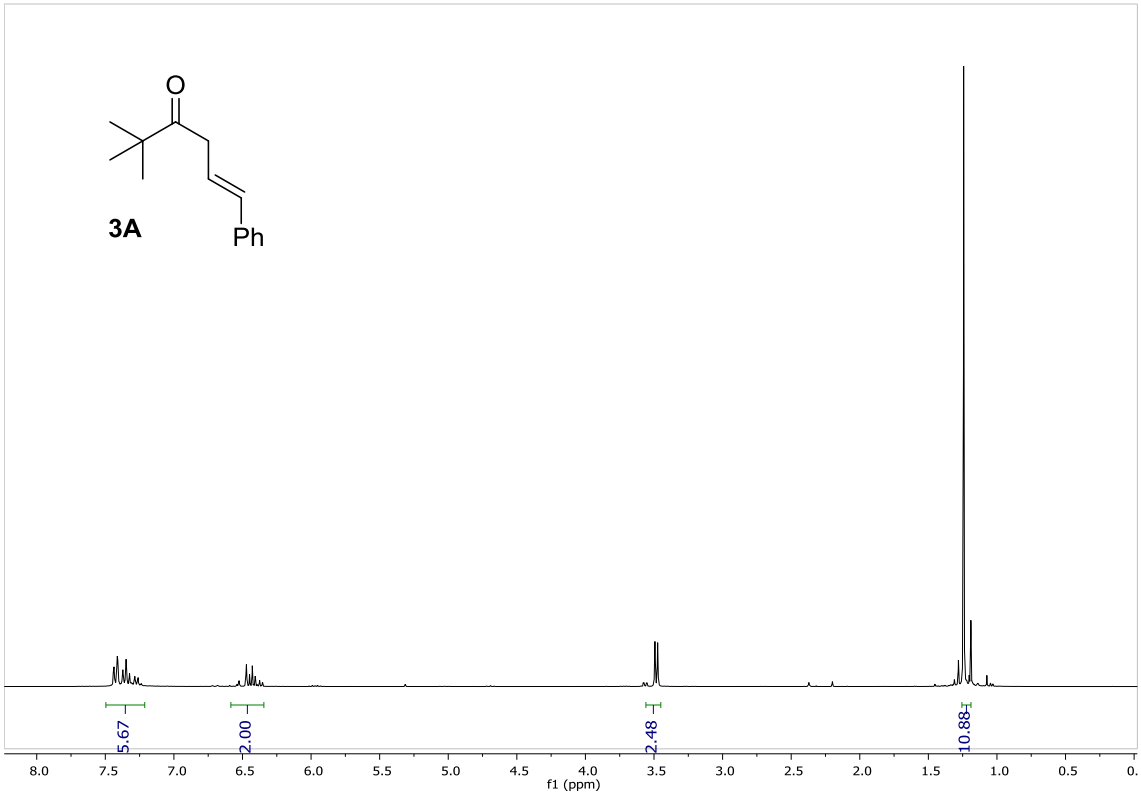
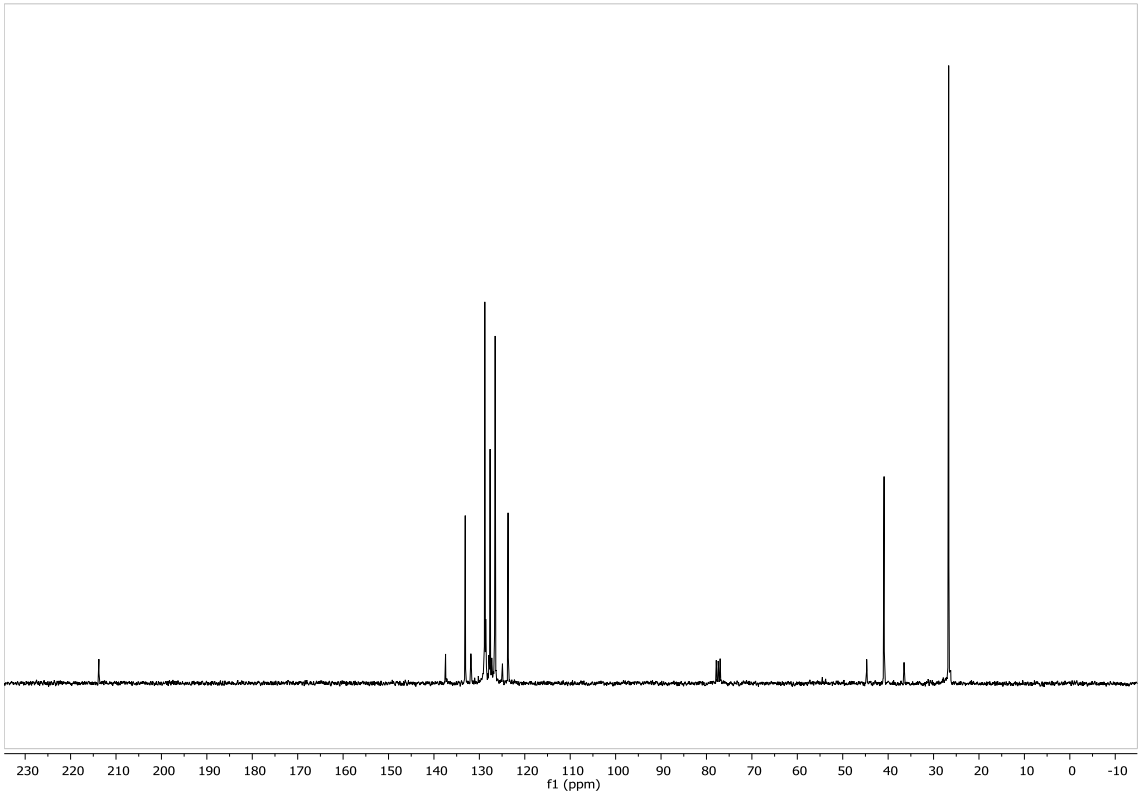
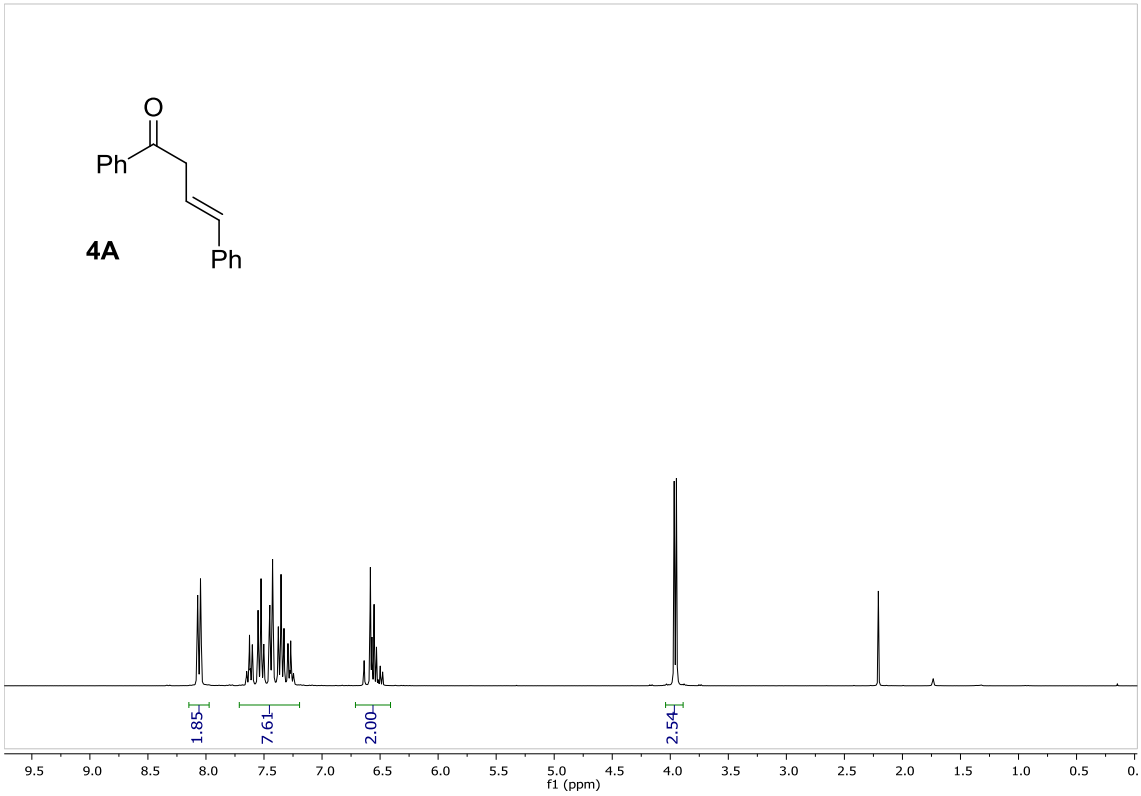
2.00
3.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
3A
Ph
5.67
2.00
2.48
10.88
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)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Ph
Ph
4A
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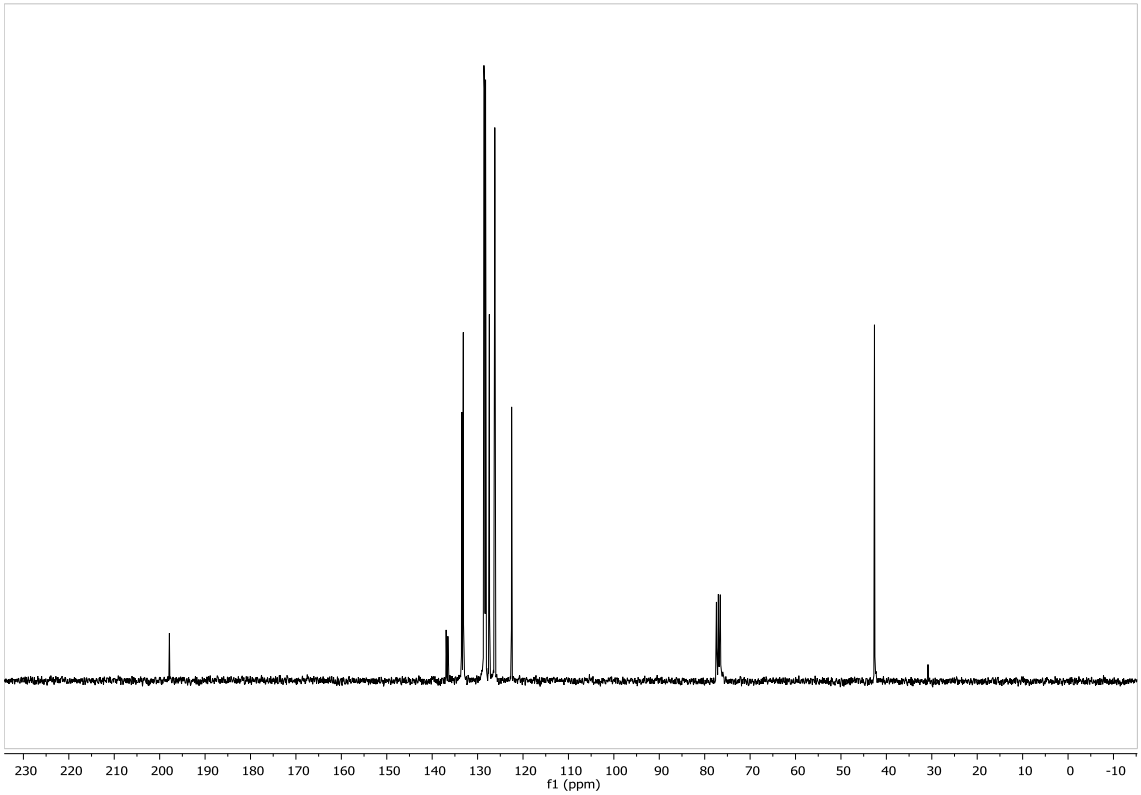
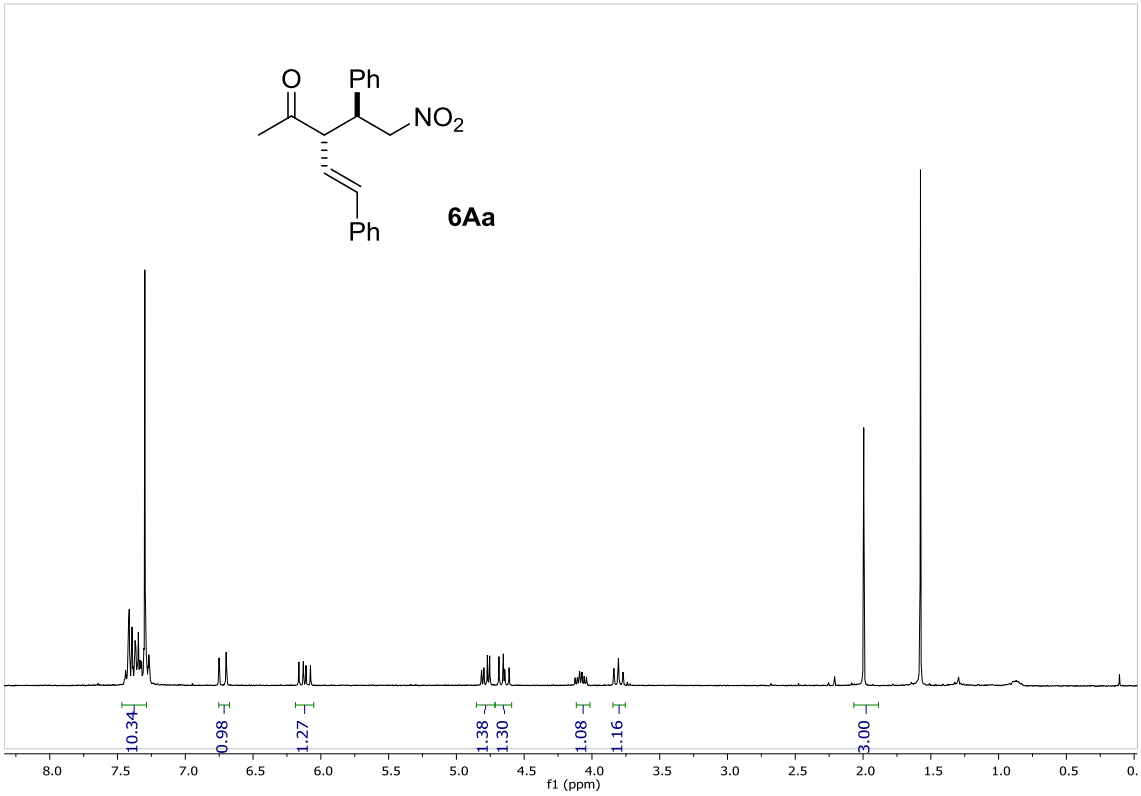
7.61
2.00
2.54
f1 (ppm)


f1 (ppm)


O
Ph
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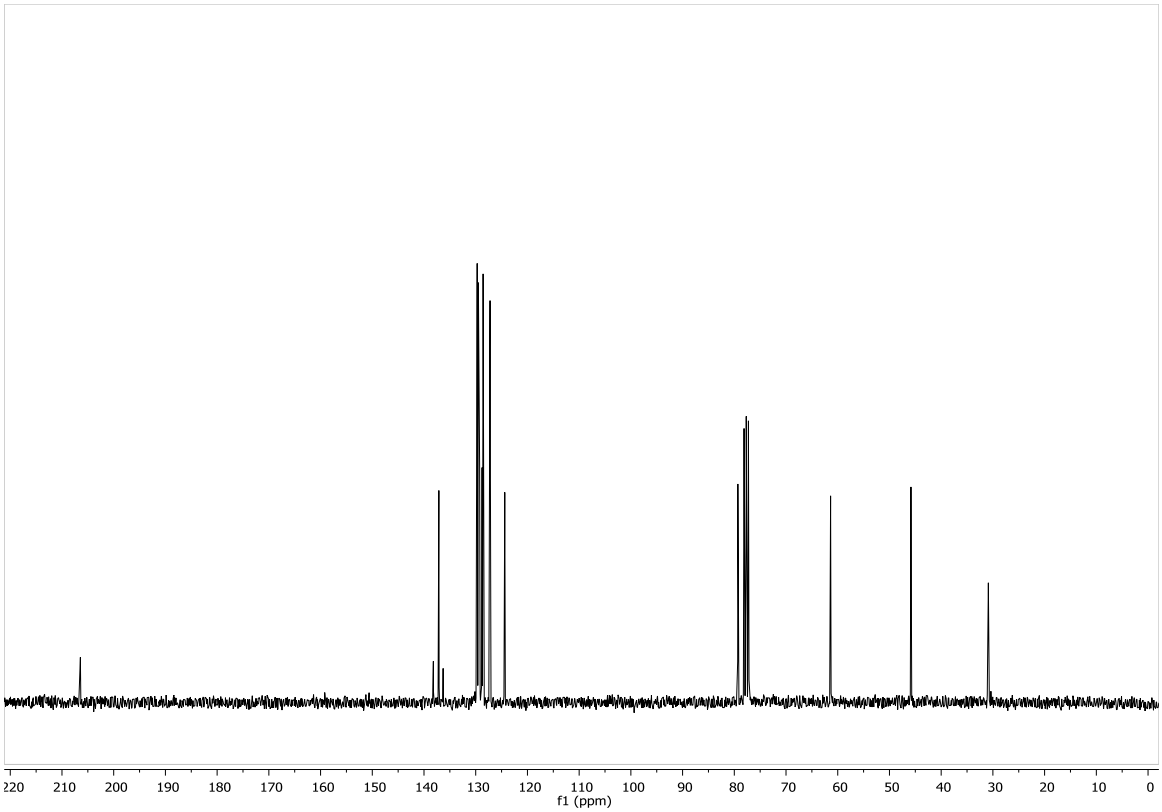
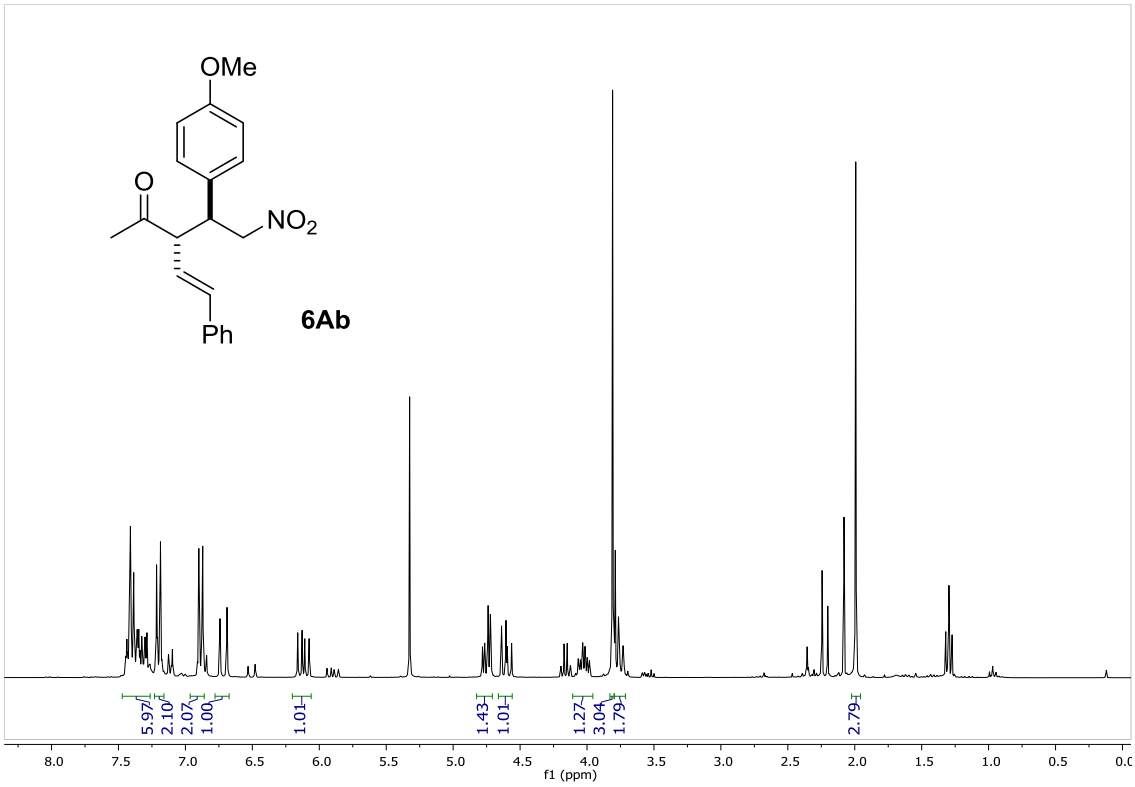
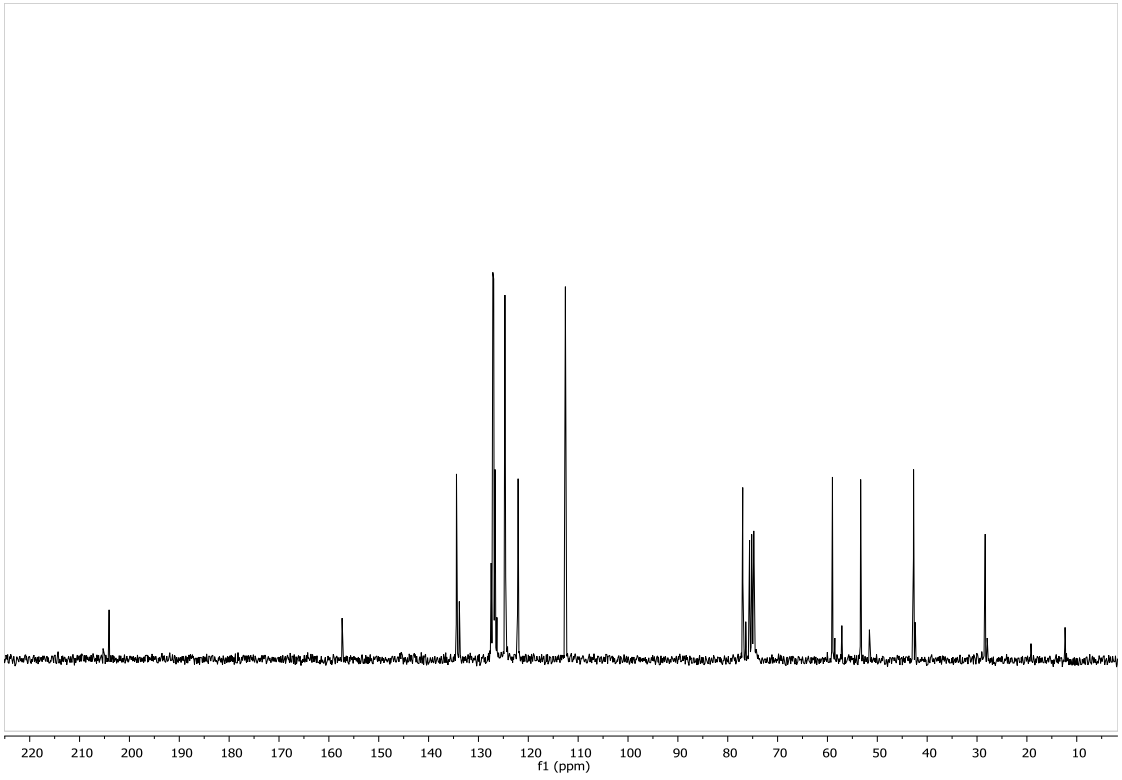
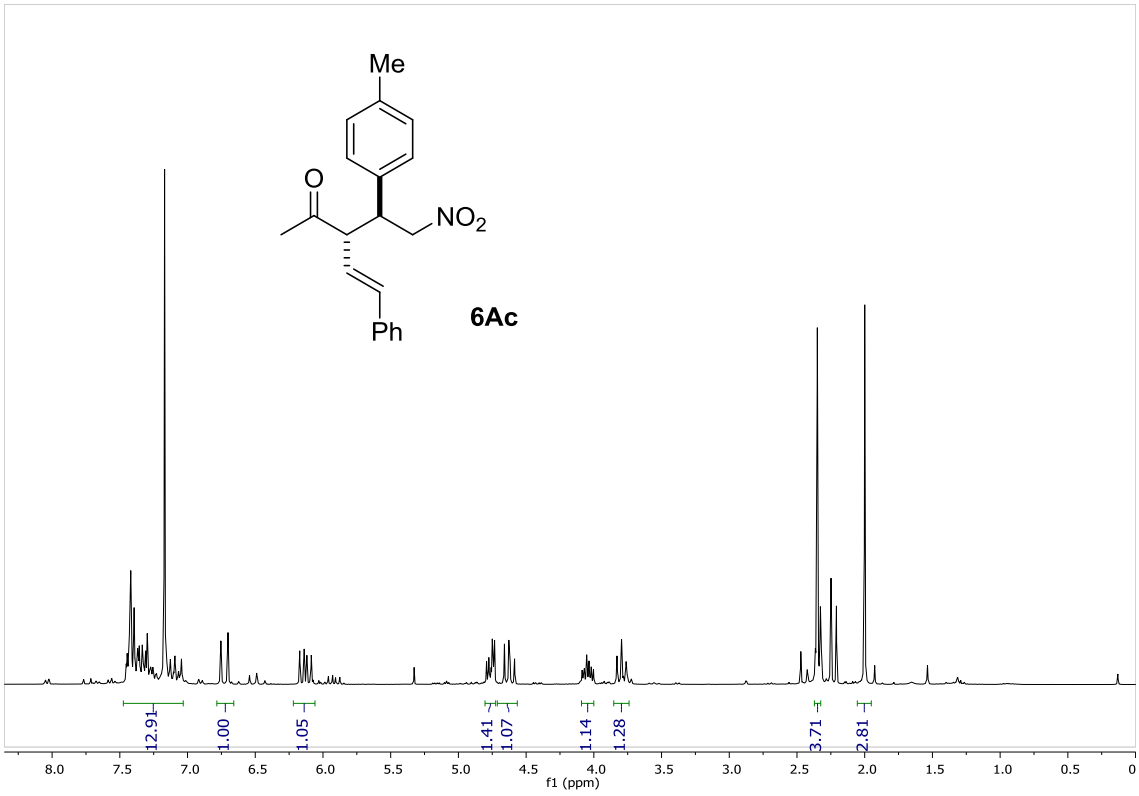
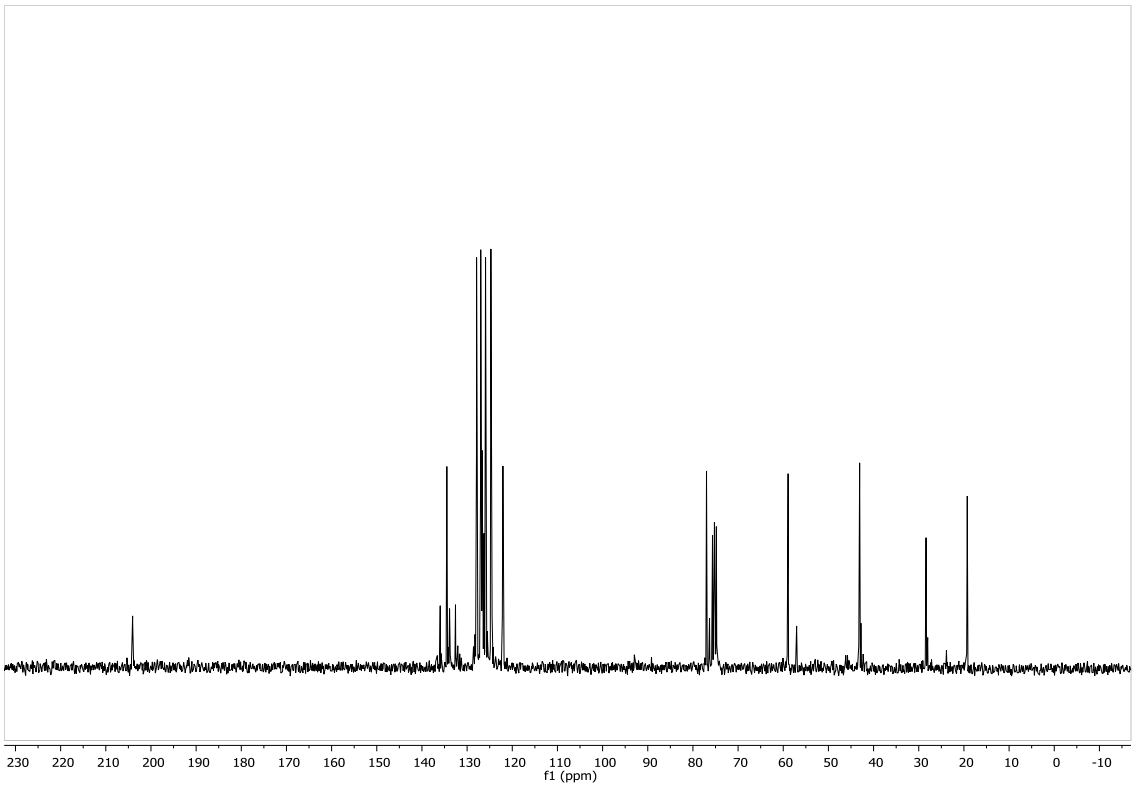
1.38
1.30
1.08
1.16
3.00
f1 (ppm)

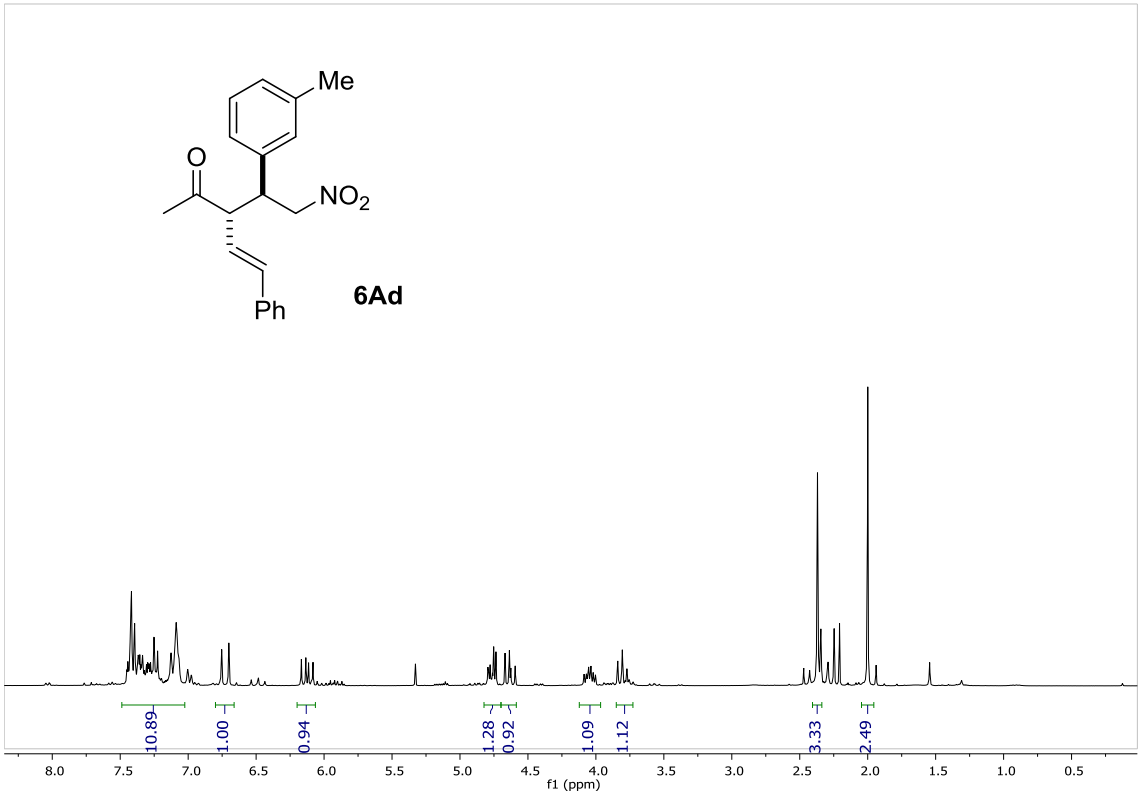

f1 (ppm)

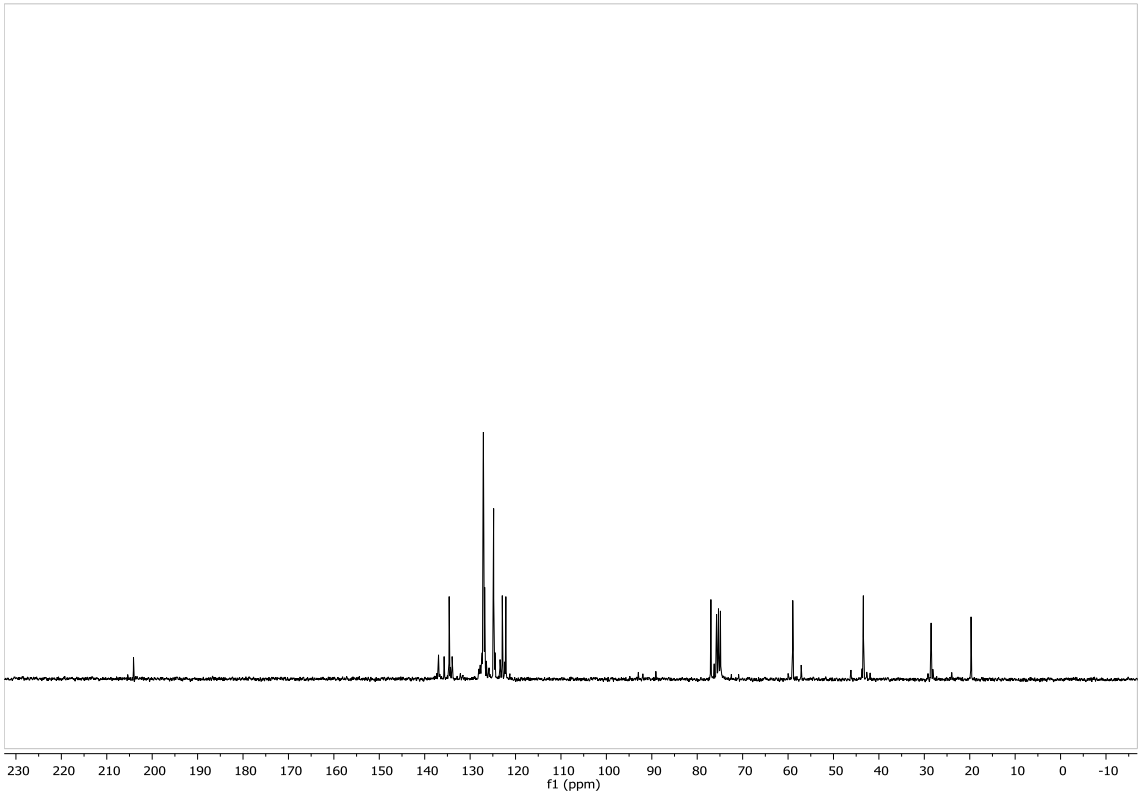

OMe
O
NO2
Ph
6Ab
5.97
2.10
2.07
1.00
1.01
1.43
1.01
1.27
3.04
1.79
2.79
f1 (ppm)

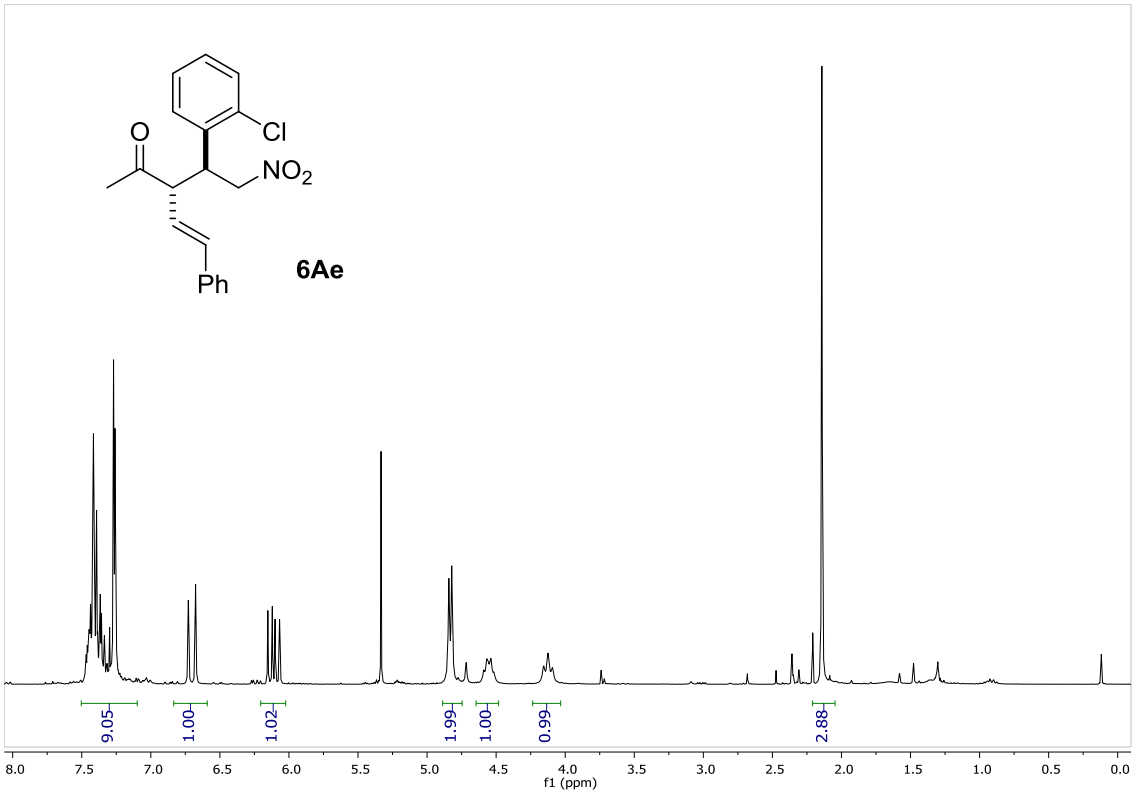

f1 (ppm)

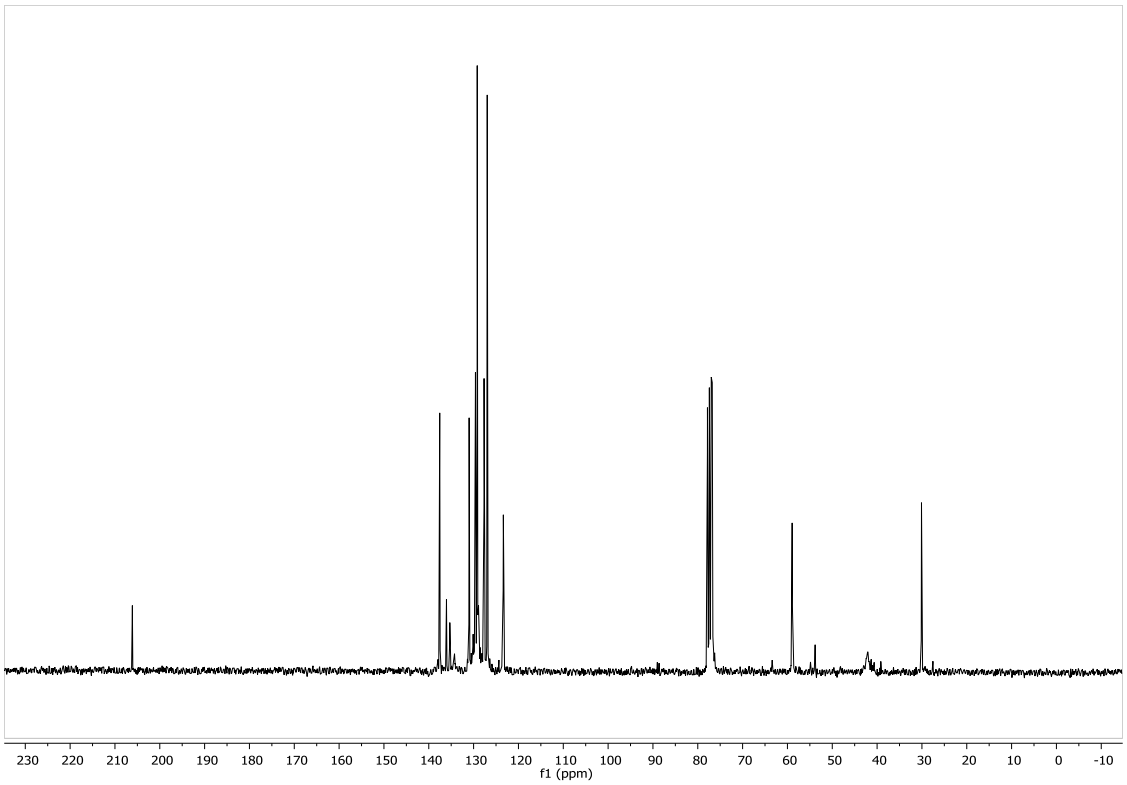

Me
O
NO2
Ph
6Ac
12.91
1.00
1.05
1.41
1.07
1.14
1.28
3.71
2.81
f1 (ppm)

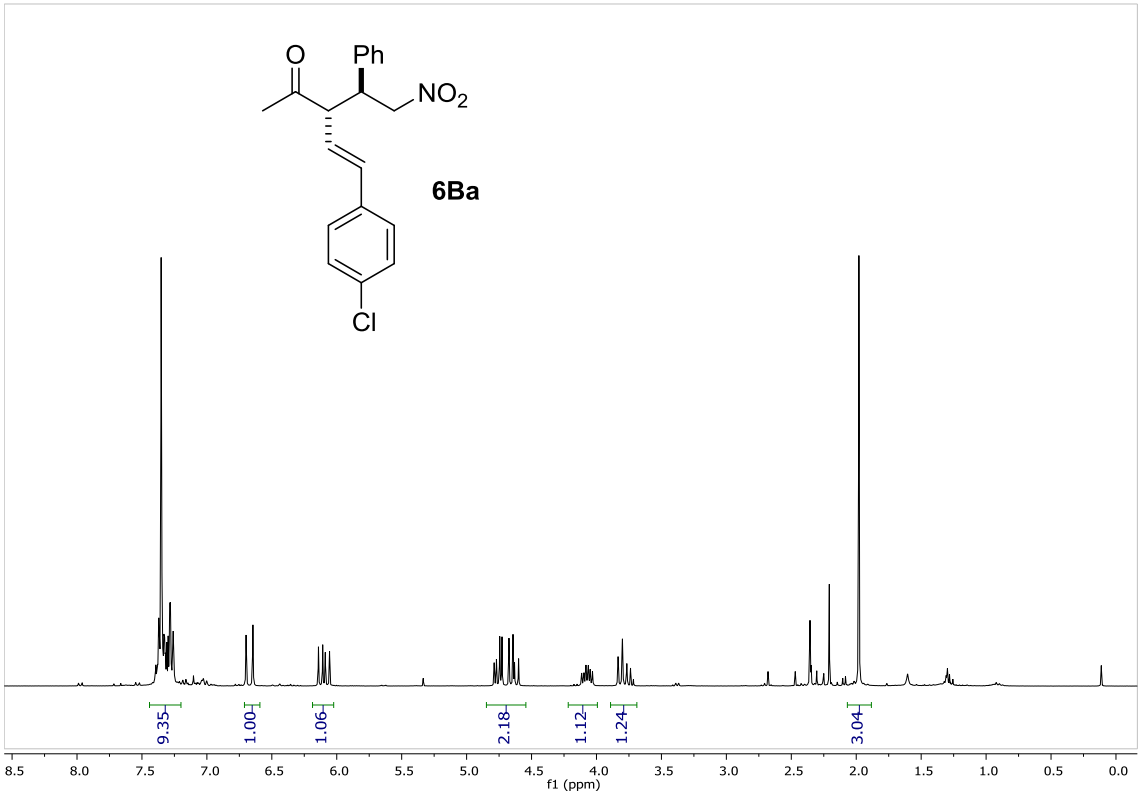

f1 (ppm)

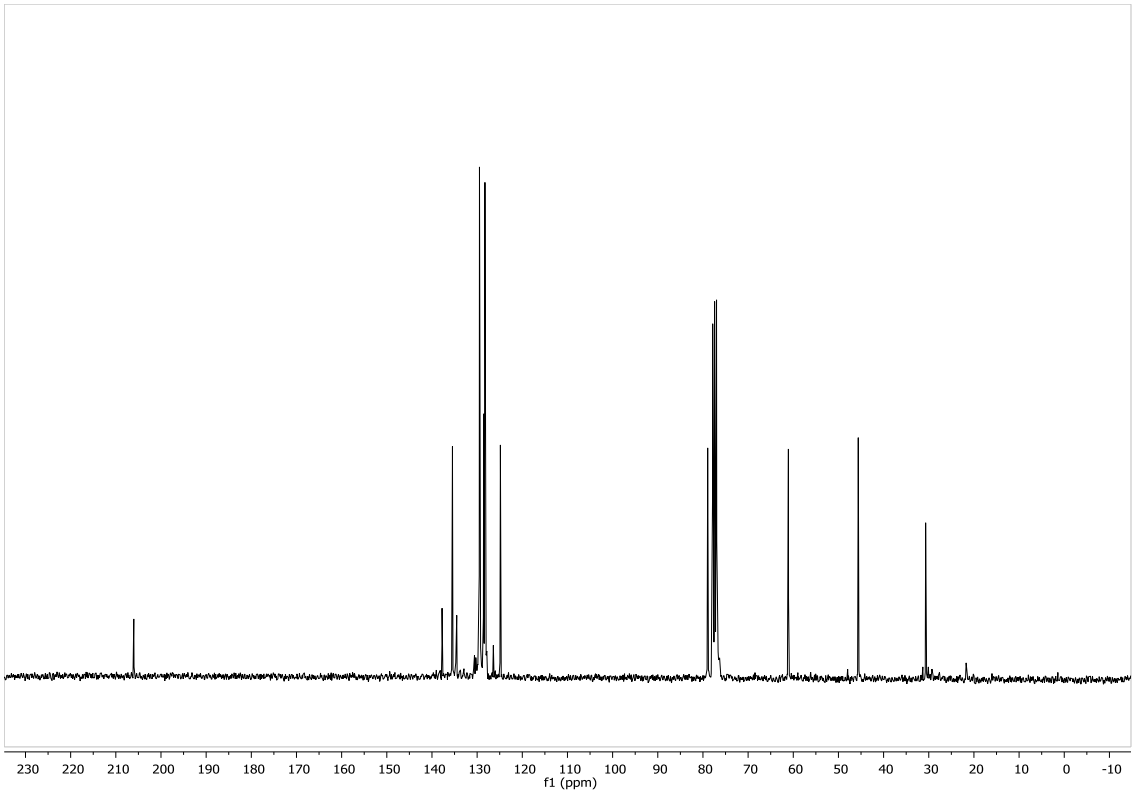

Me
O
NO2
Ph
6Ad
10.89
1.00
0.94
1.28
0.92
1.09
1.12
3.33
2.49
f1 (ppm)

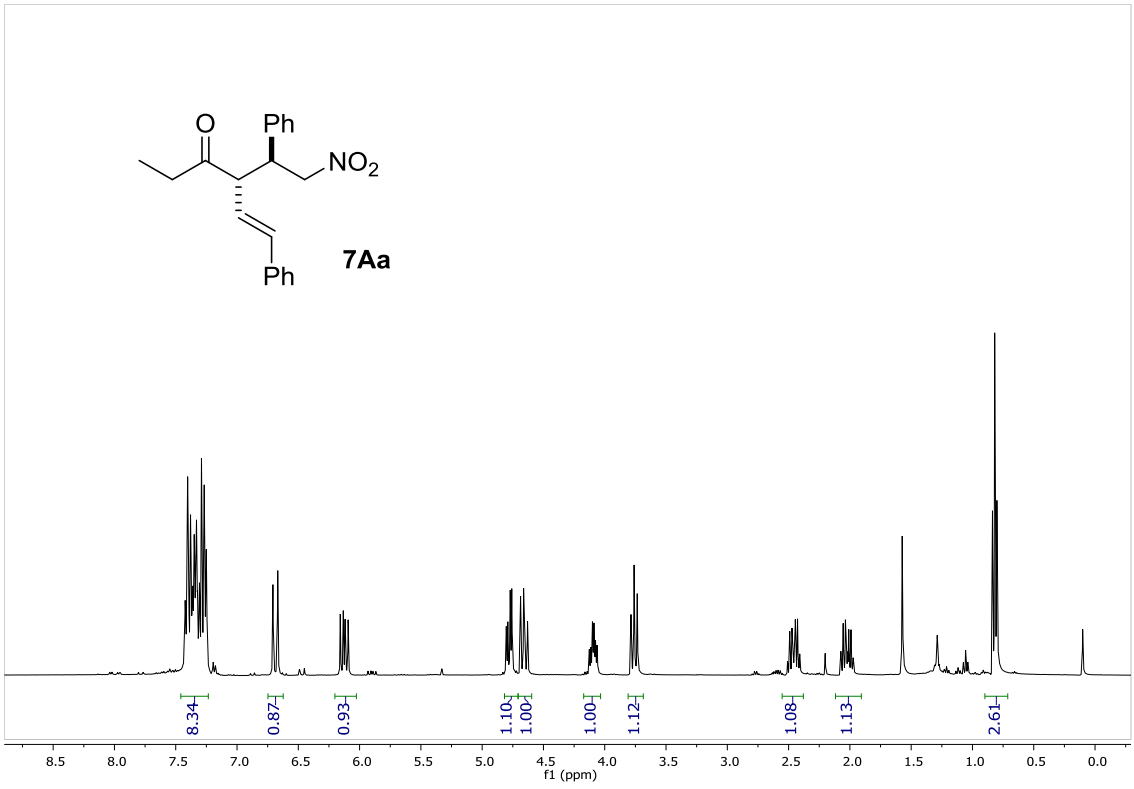

f1 (ppm)

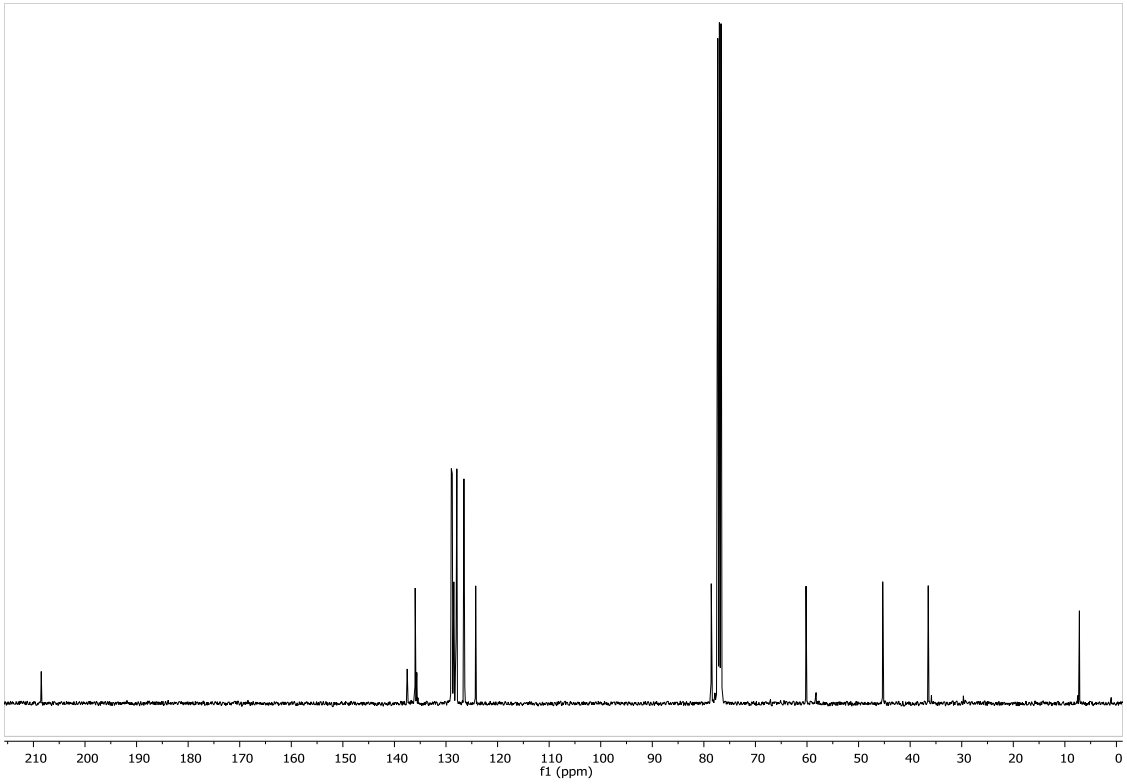

O
Cl
NO2
Ph
6Ae
9.05
1.00
1.02
1.99
1.00
0.99
2.88
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

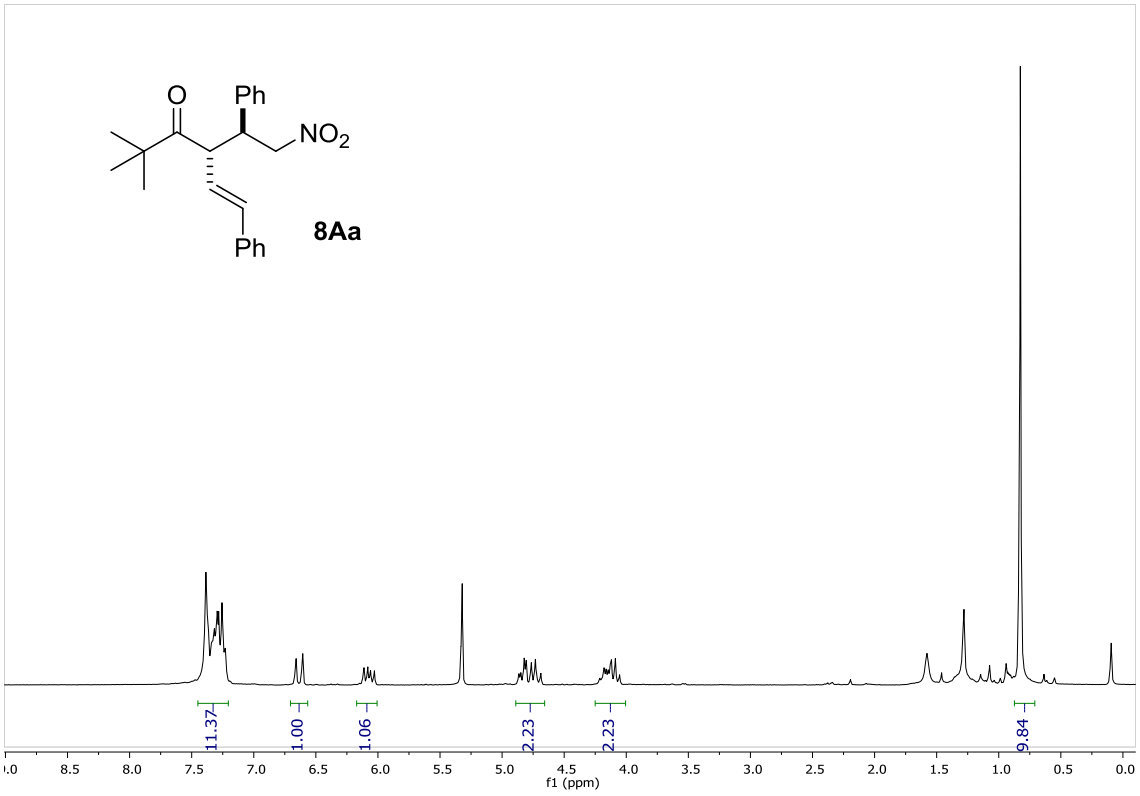

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

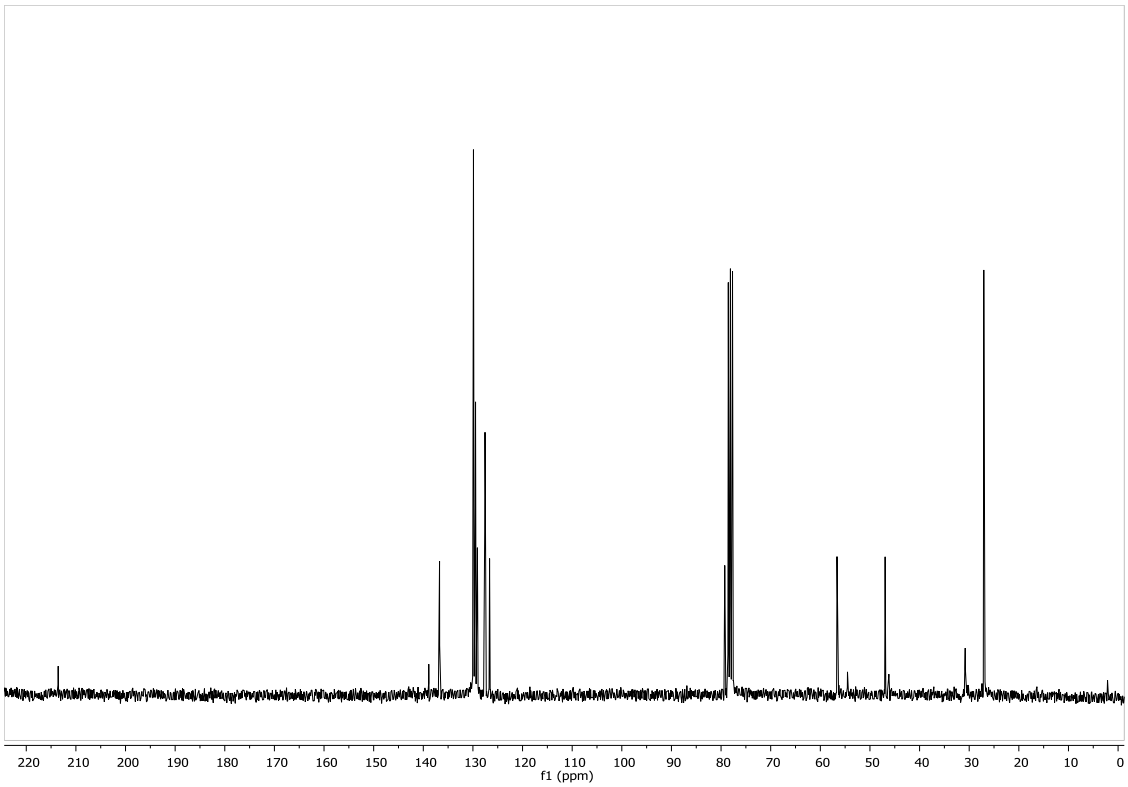

O
Ph
NO2
6Ba
Cl
9.35
1.00
1.06
2.18
1.12
1.24
3.04
f1 (ppm)

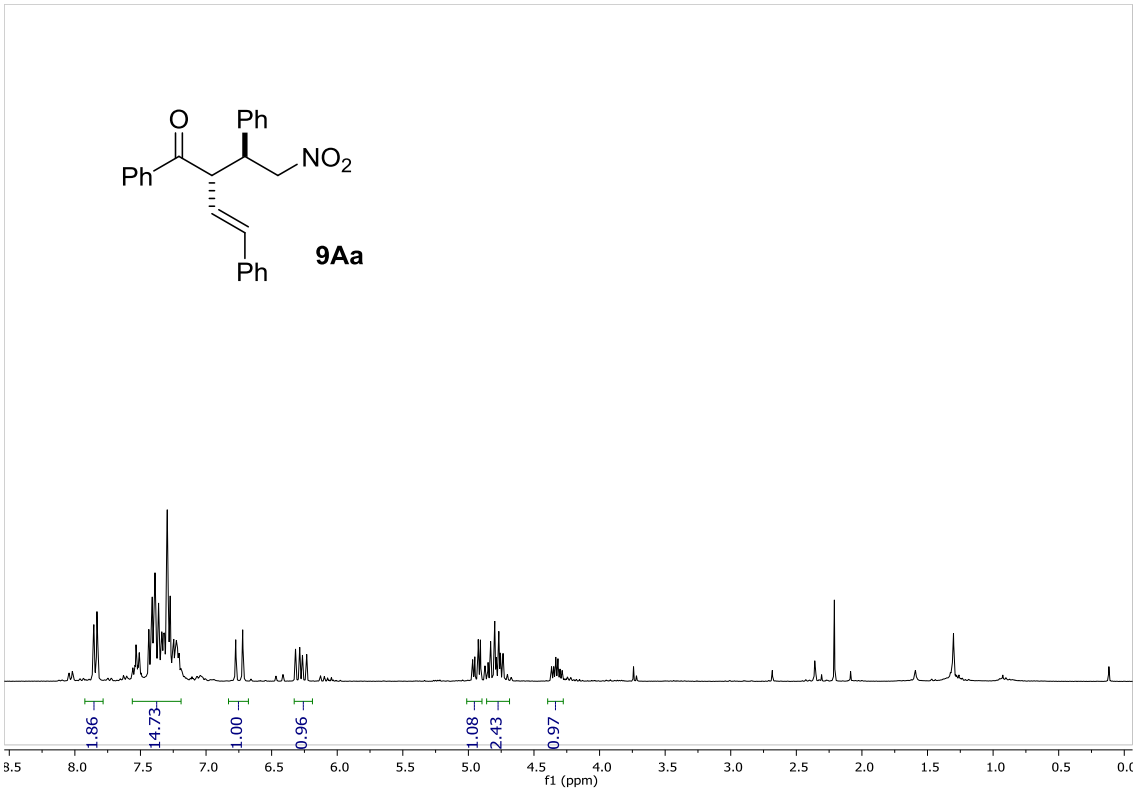

f1 (ppm)

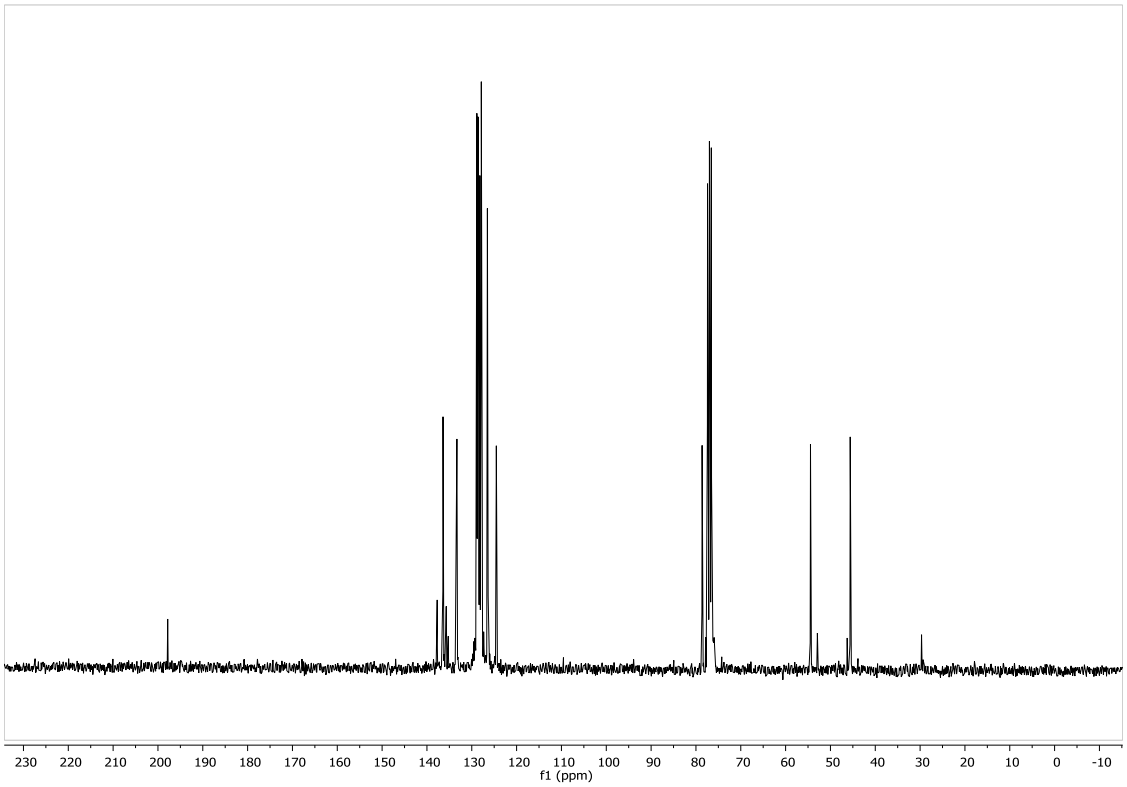

O
Ph
NO2
Ph
7Aa
8.34
0.87
0.93
1.10
1.00
1.00
1.12
1.08
1.13
2.61
f1 (ppm)

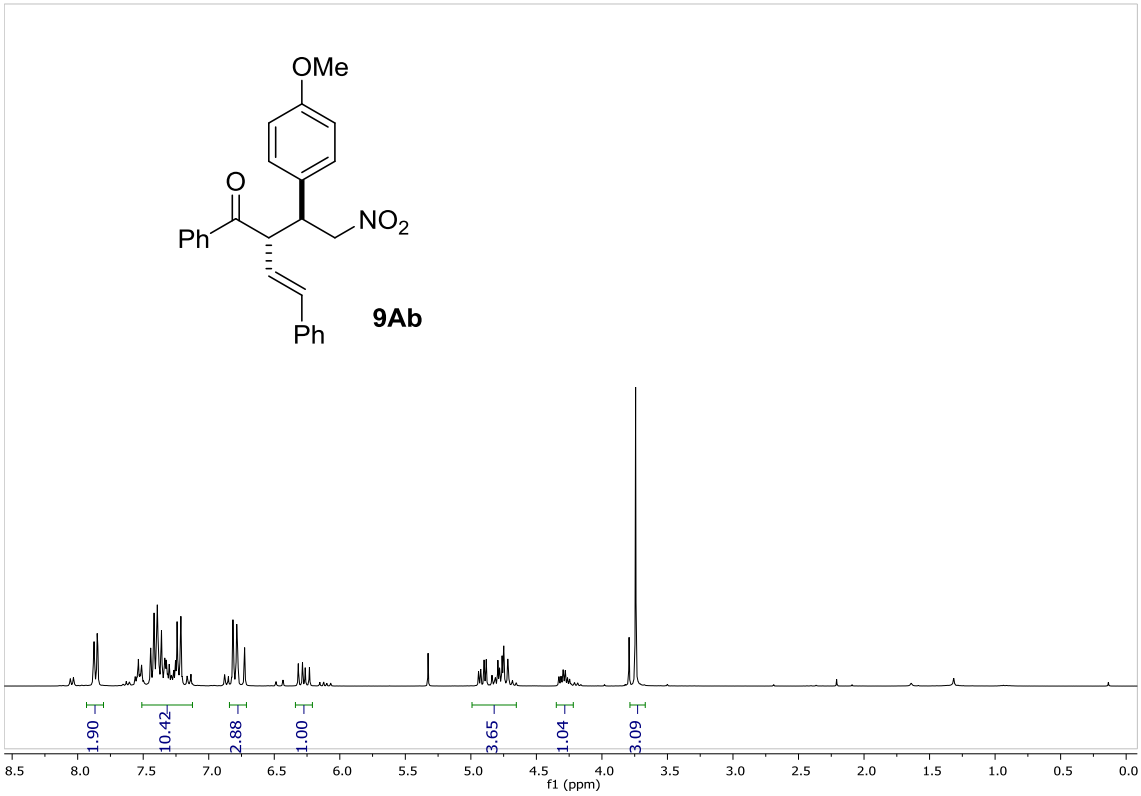

f1 (ppm)

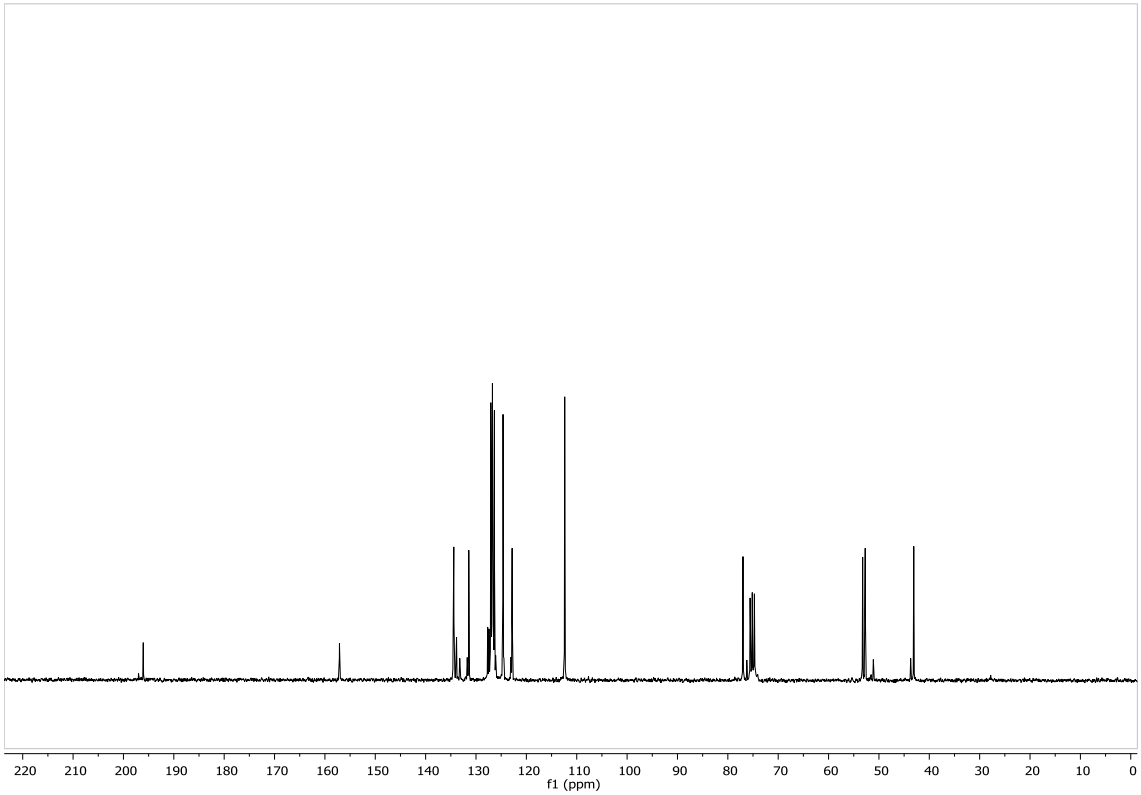

O
Ph
NO2
Ph
8Aa
11.37
1.00
1.06
2.23
2.23
9.84
f1 (ppm)

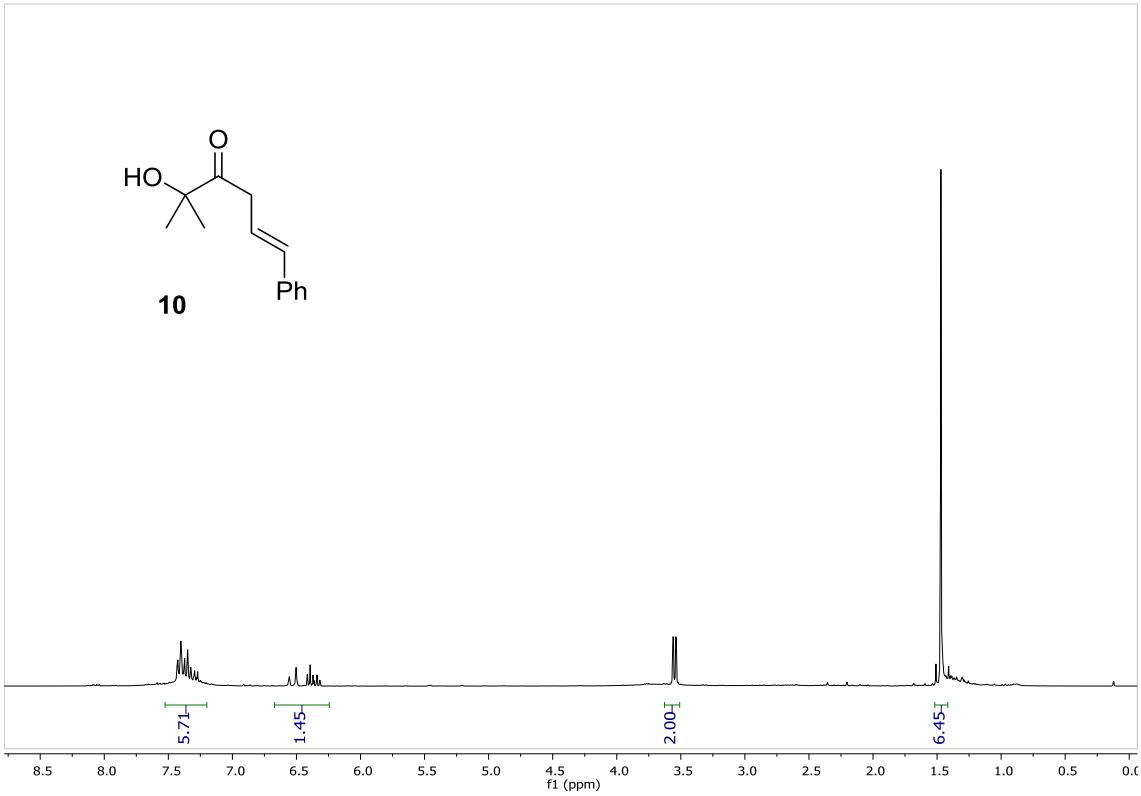

f1 (ppm)

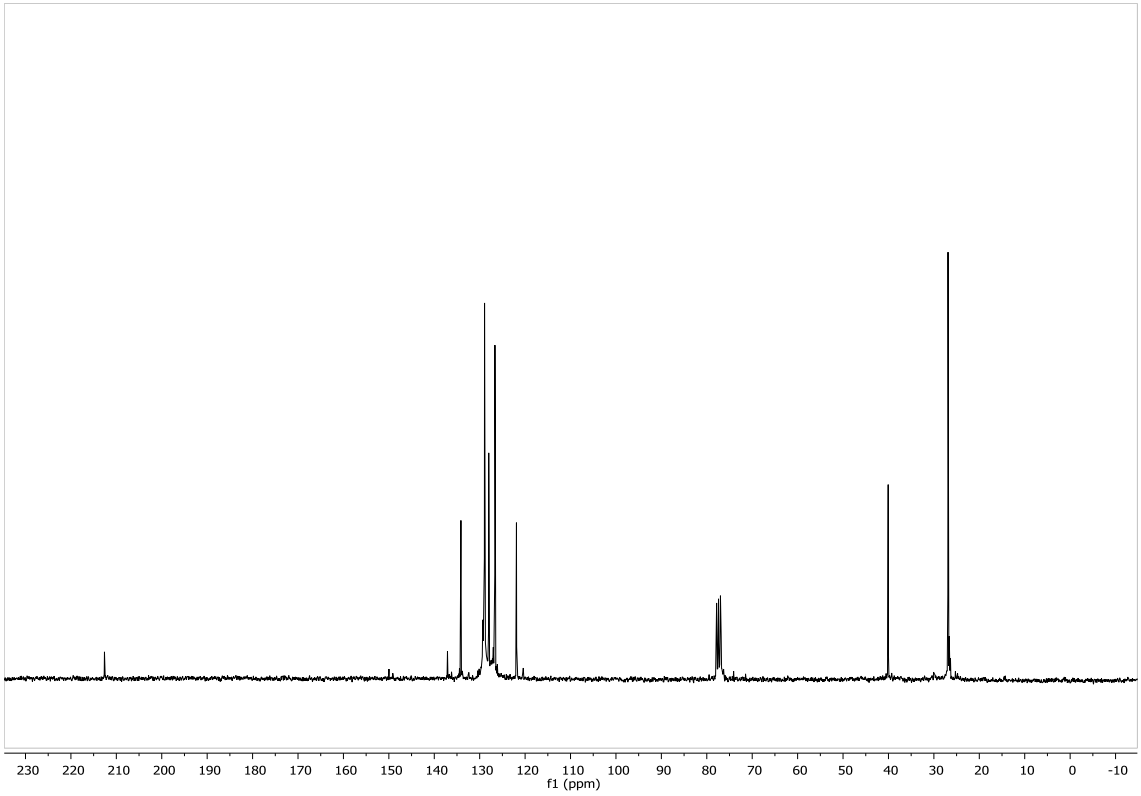

O
Ph
Ph
NO2
Ph
9Aa
1.86
14.73
1.00
0.96
1.08
2.43
0.97
f1 (ppm)

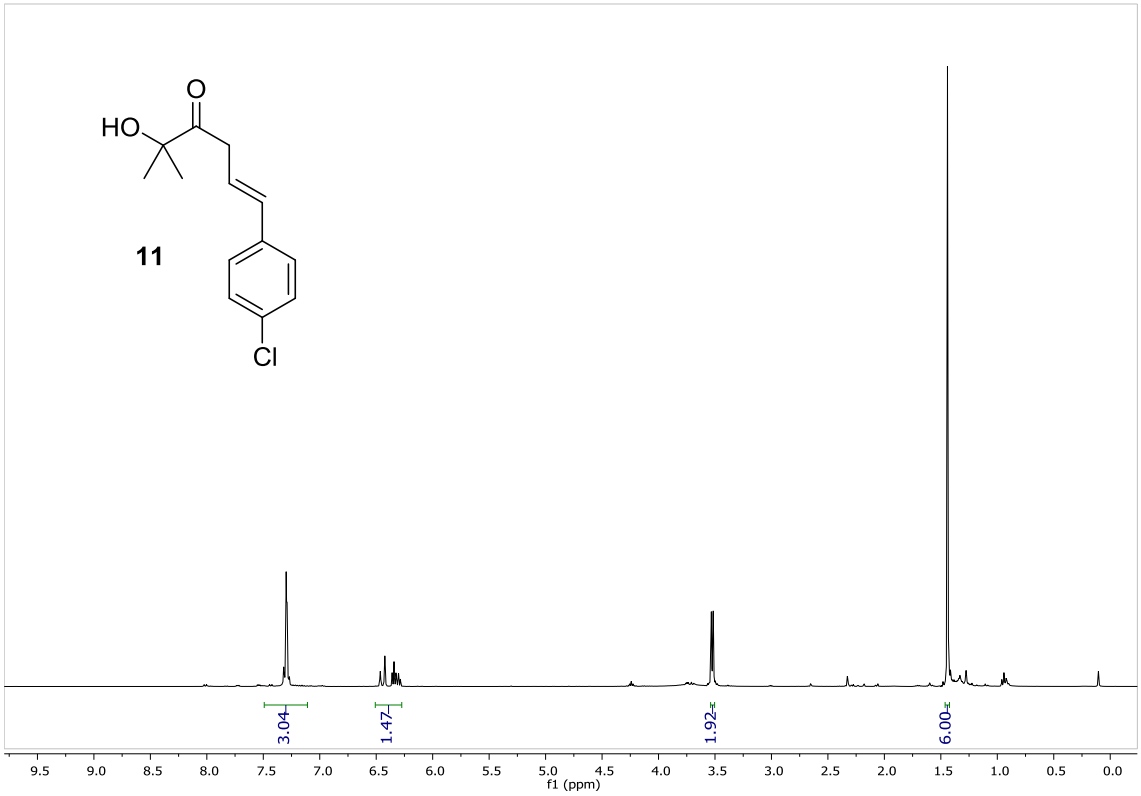

f1 (ppm)

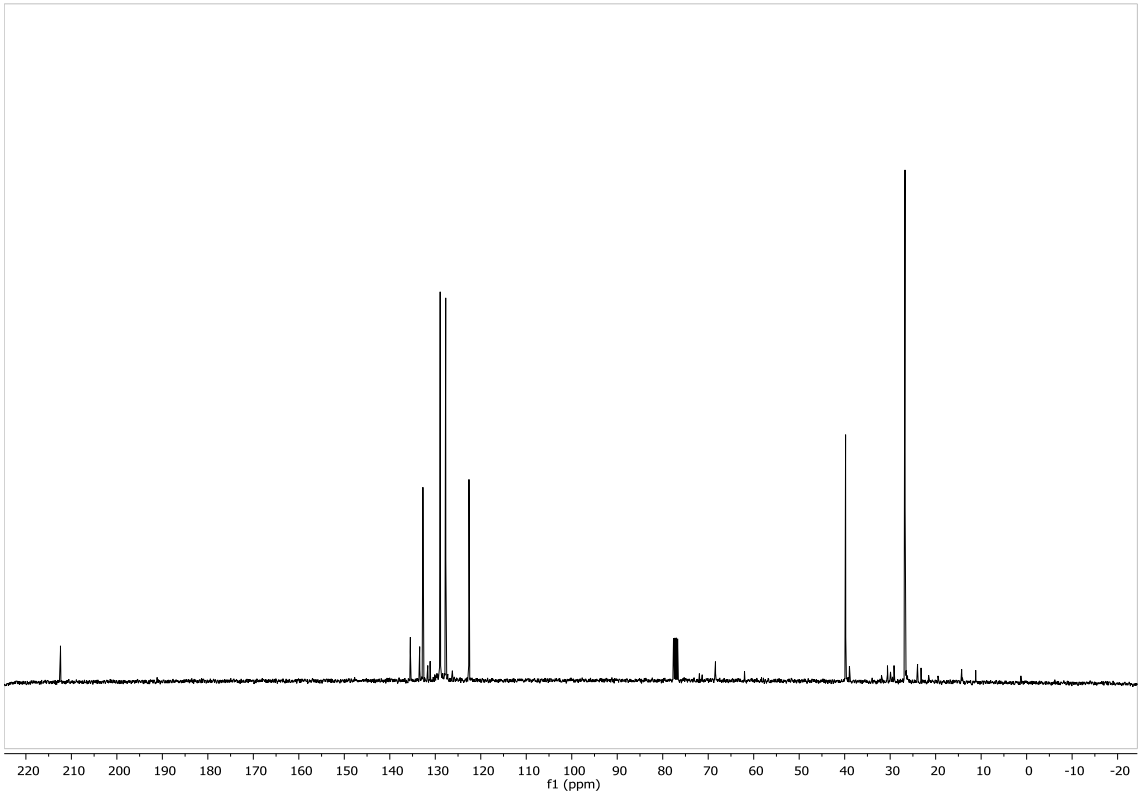

OMe
O
Ph
NO2
Ph
9Ab
1.90
10.42
2.88
1.00
3.65
1.04
3.09
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

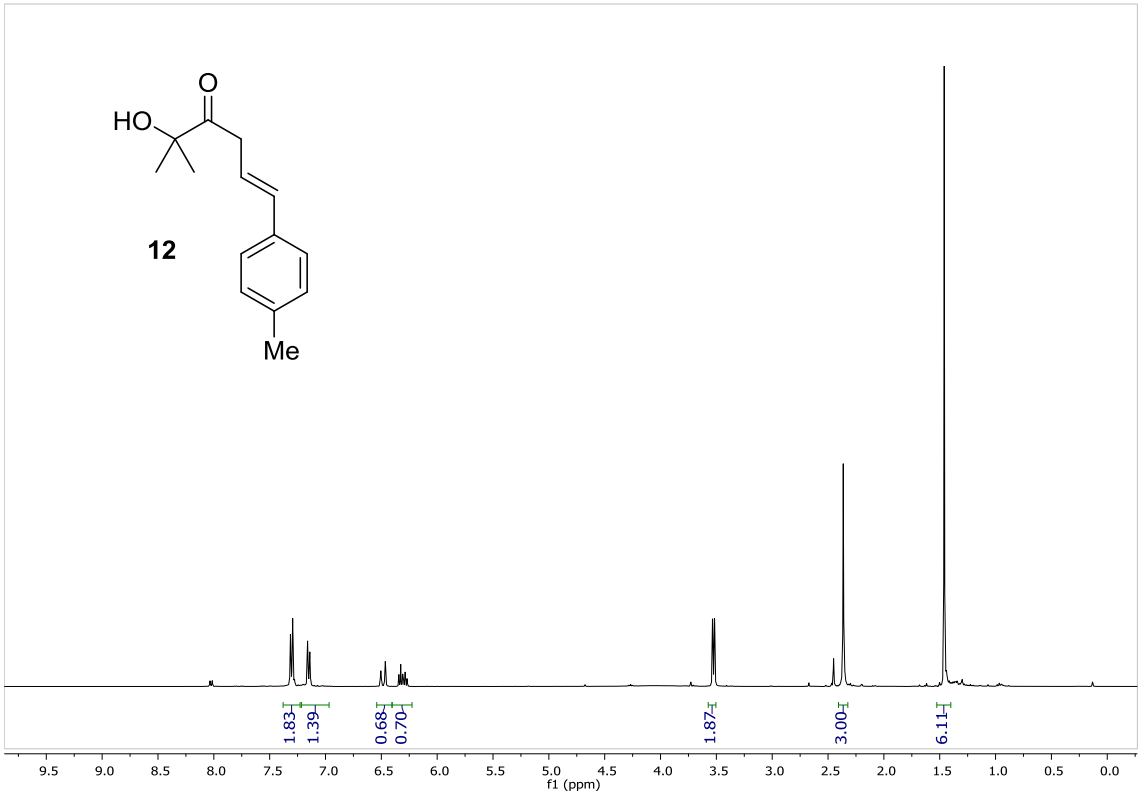

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

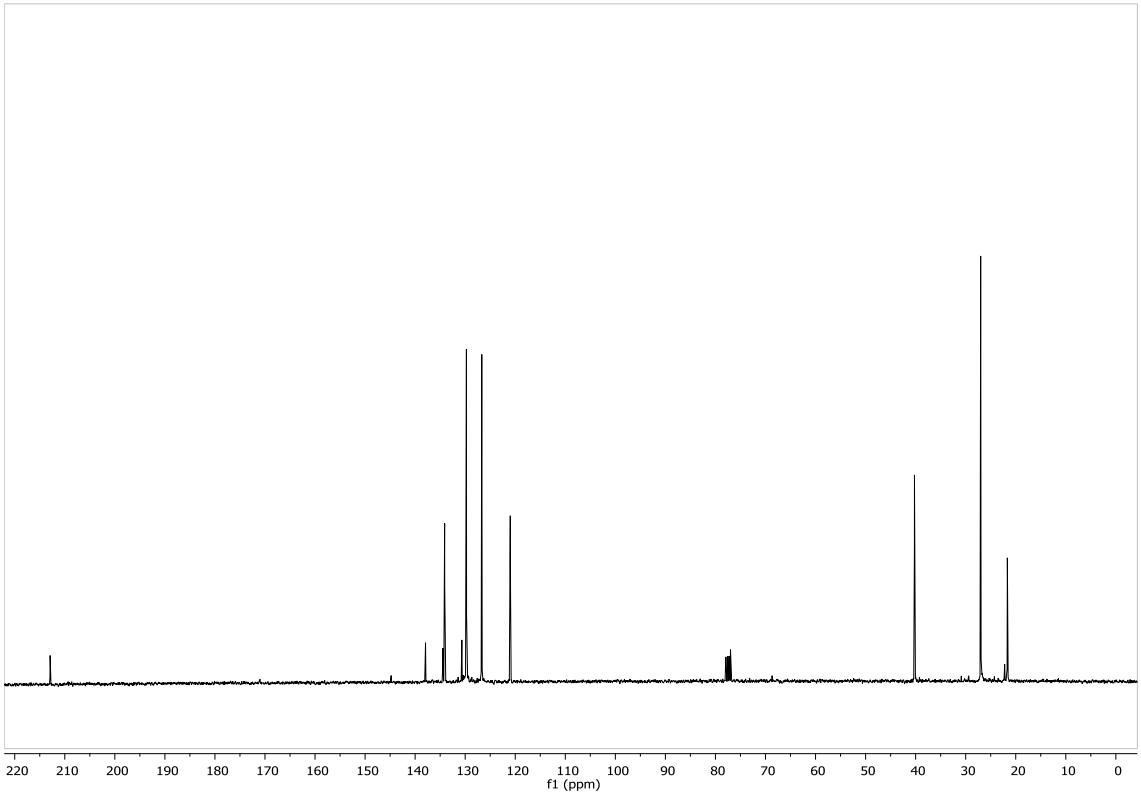

HO
O
Ph
10
5.71
1.45
2.00
6.45
f1 (ppm)

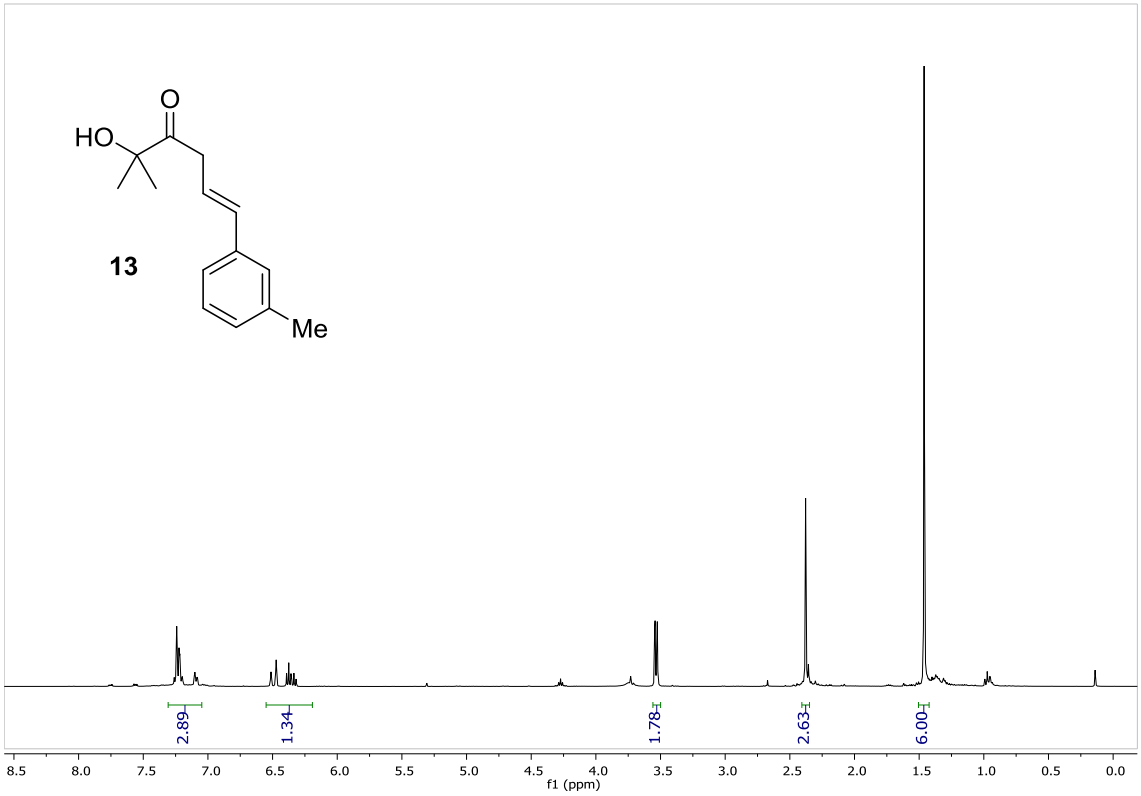

f1 (ppm)

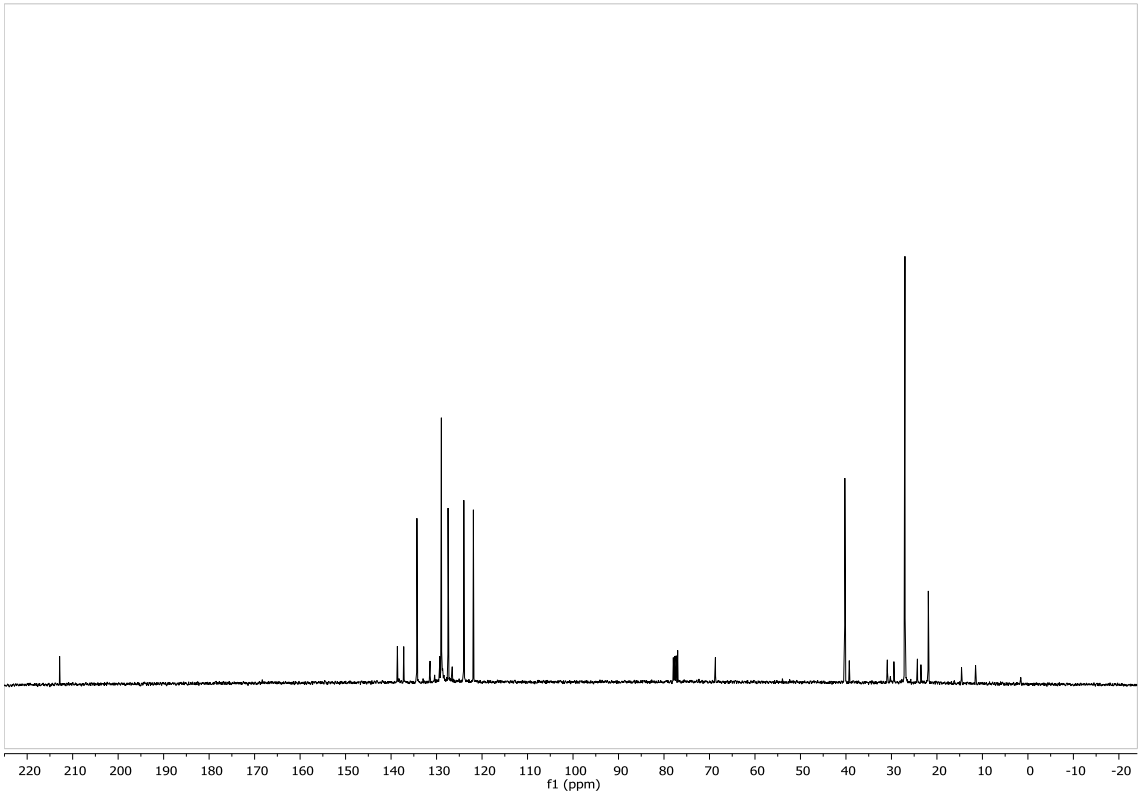

HO
O
Cl
11
3.04
1.47
1.92
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

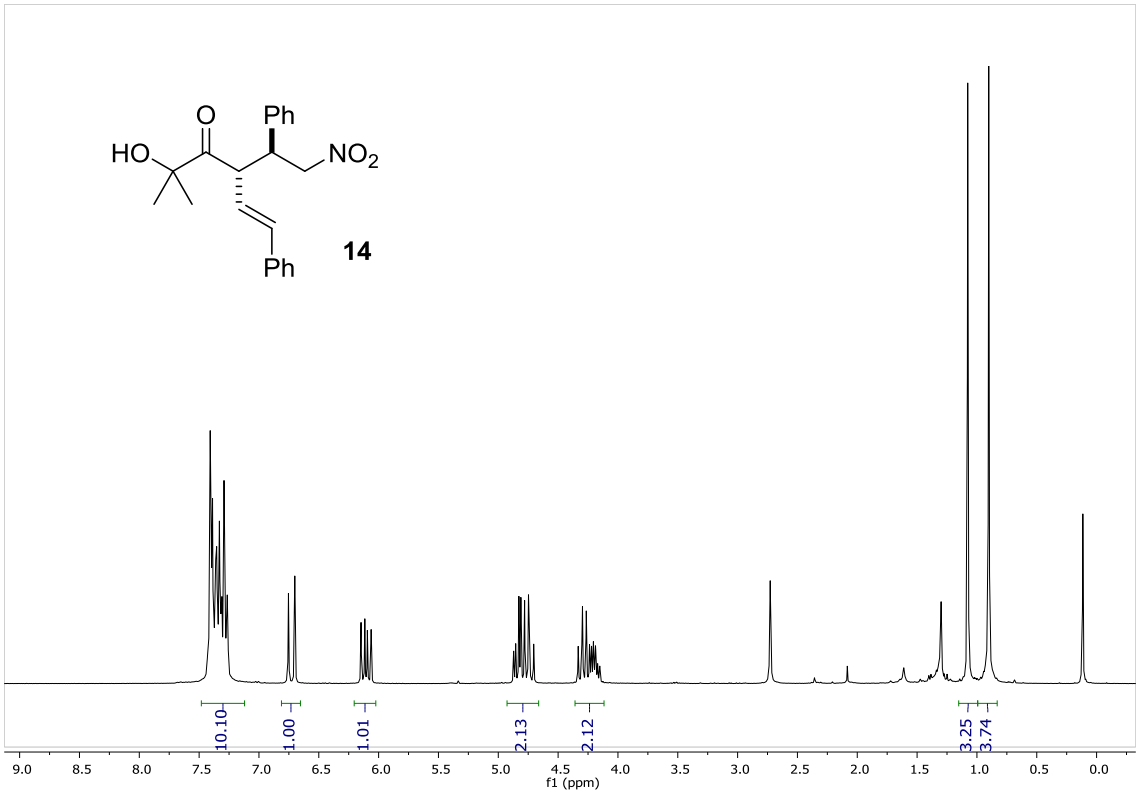

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

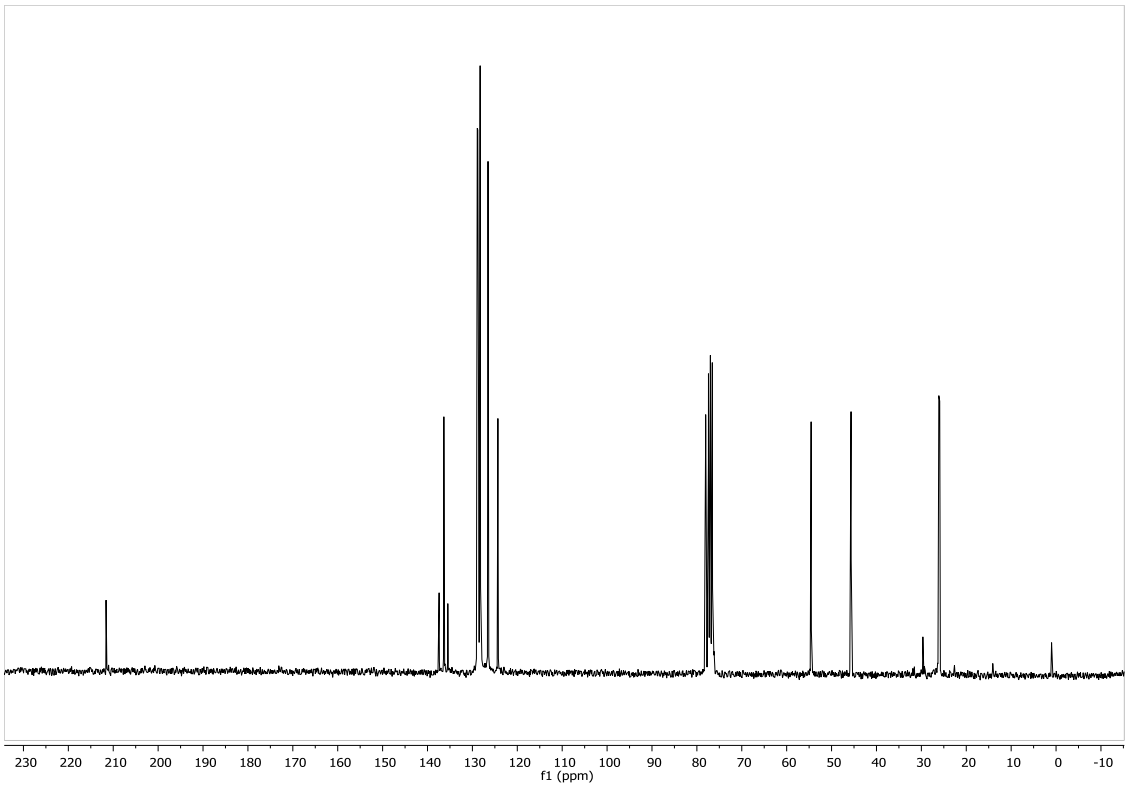

HO
O
12
Me
1.83
1.39
0.68
0.70
1.87
3.00
6.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

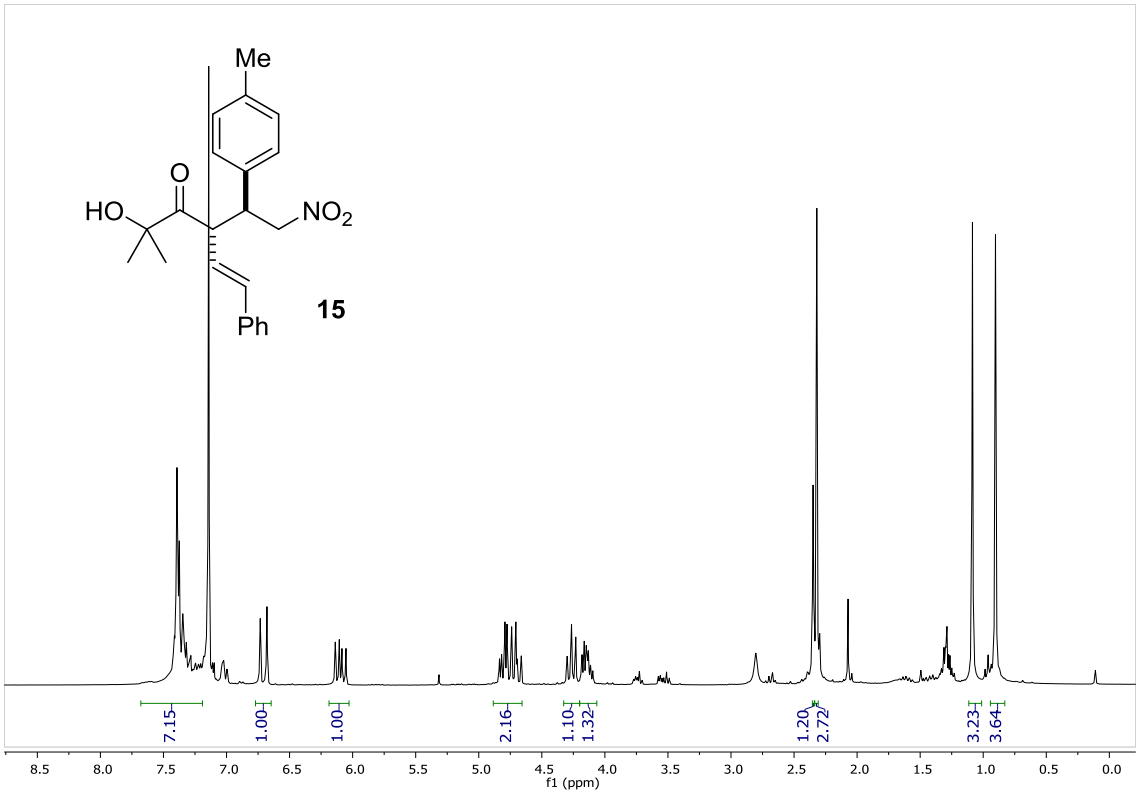

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

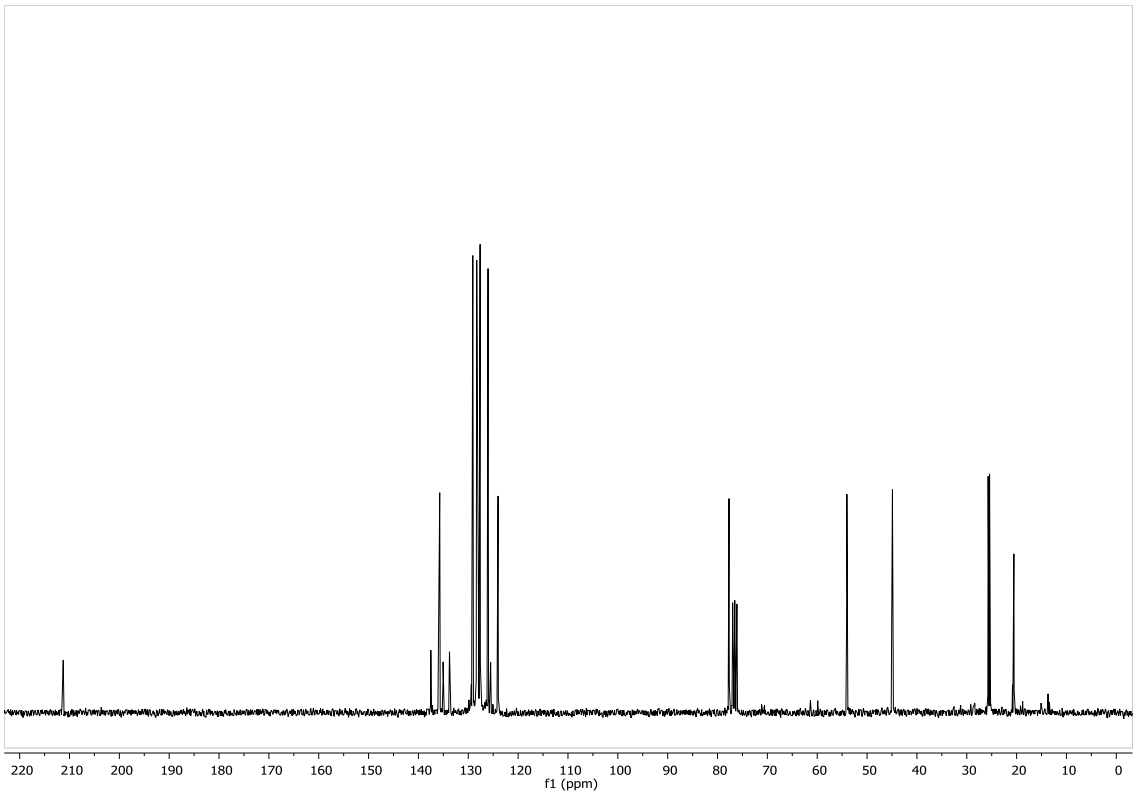

HO
O
13
Me
2.89
1.34
1.78
2.63
6.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

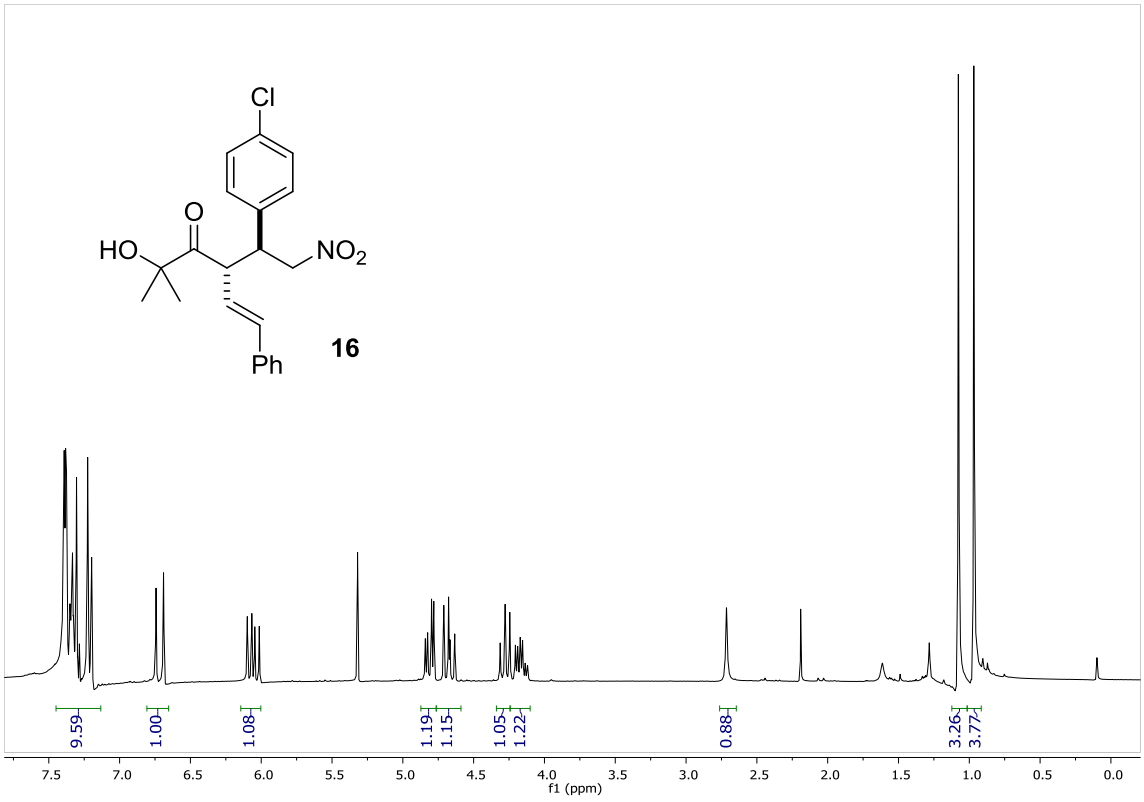

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

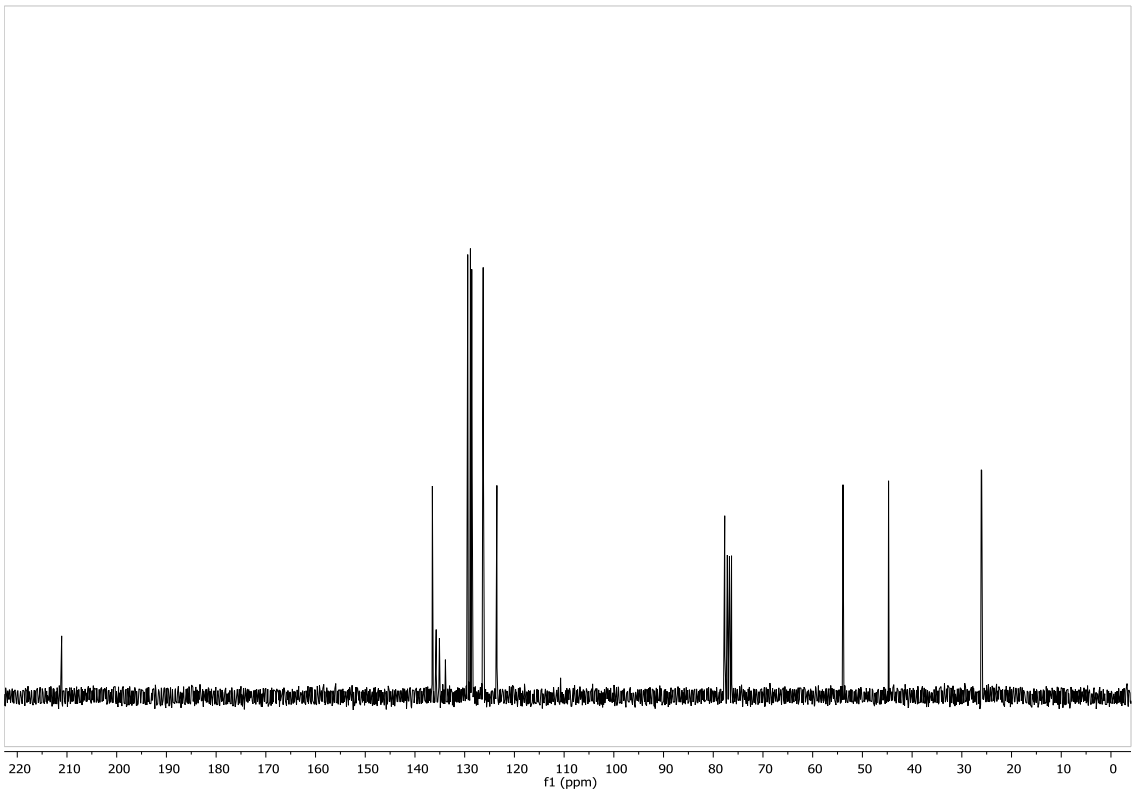

O
Ph
HO
NO2
Ph
14
10.10
1.00
1.01
2.13
2.12
3.25
3.74
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

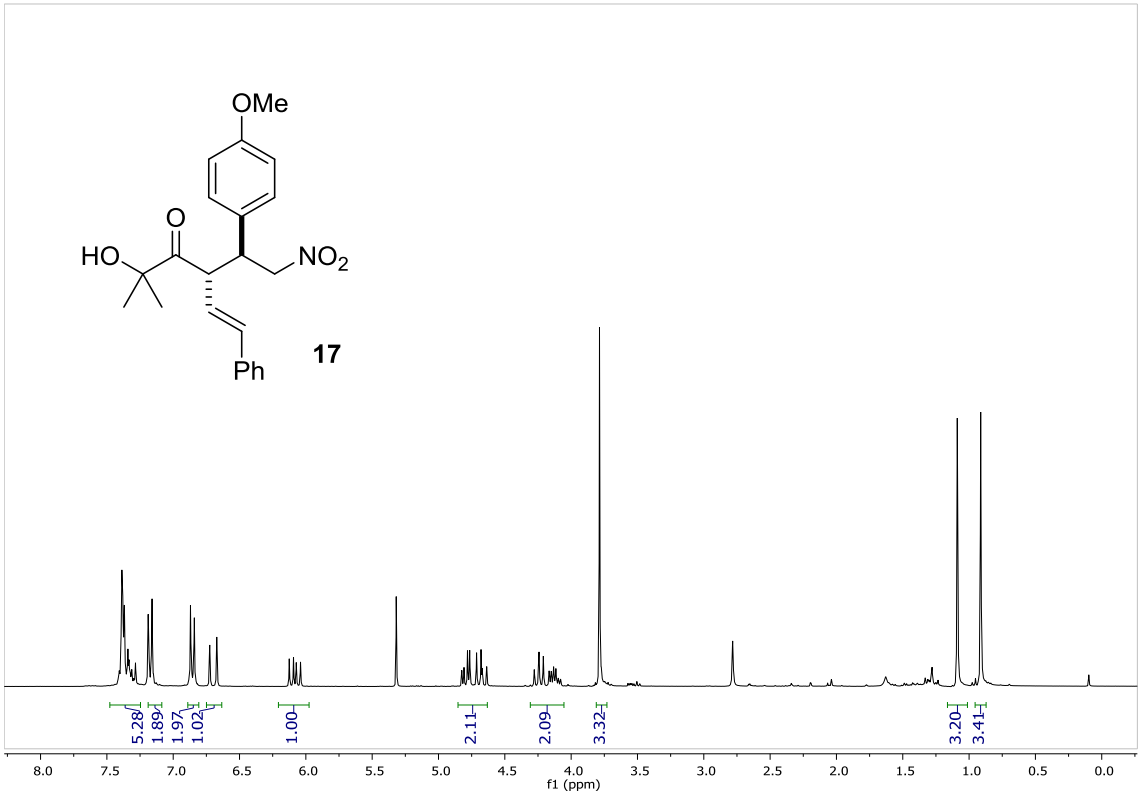

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

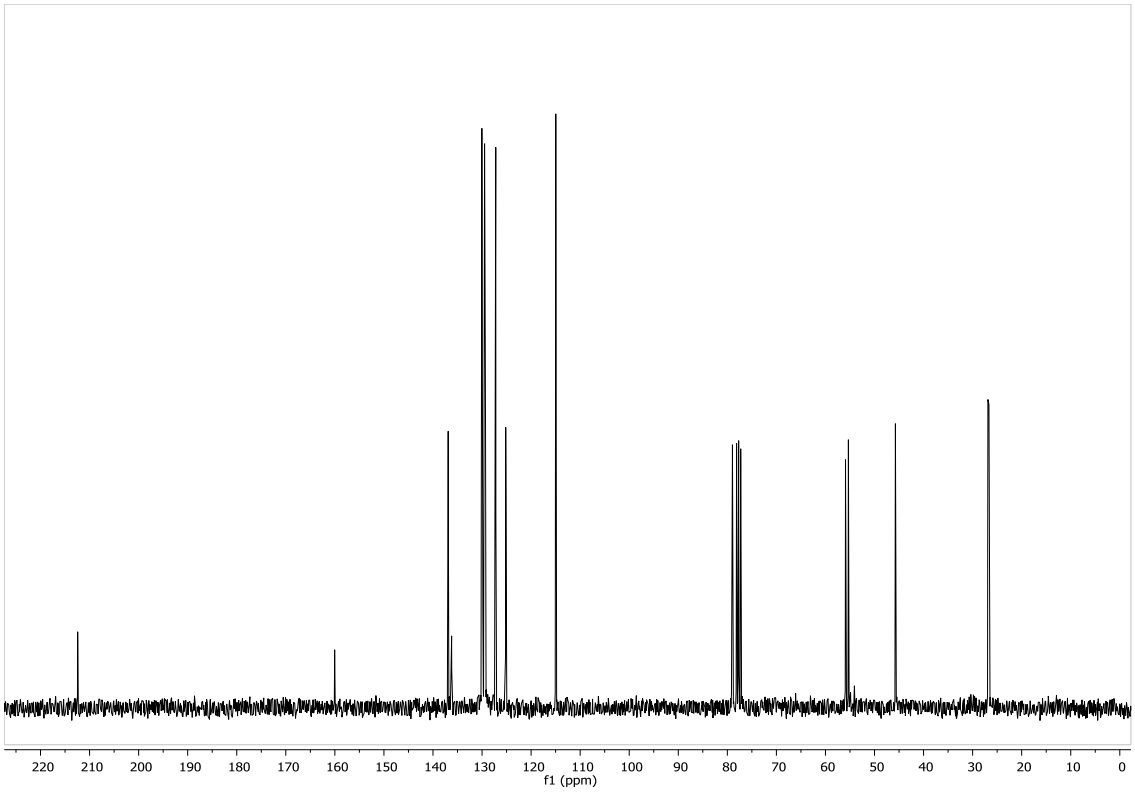

Me
O
HO
NO2
Ph
15
7.15
1.00
1.00
2.16
1.10
1.32
1.20
2.72
3.23
3.64
f1 (ppm)

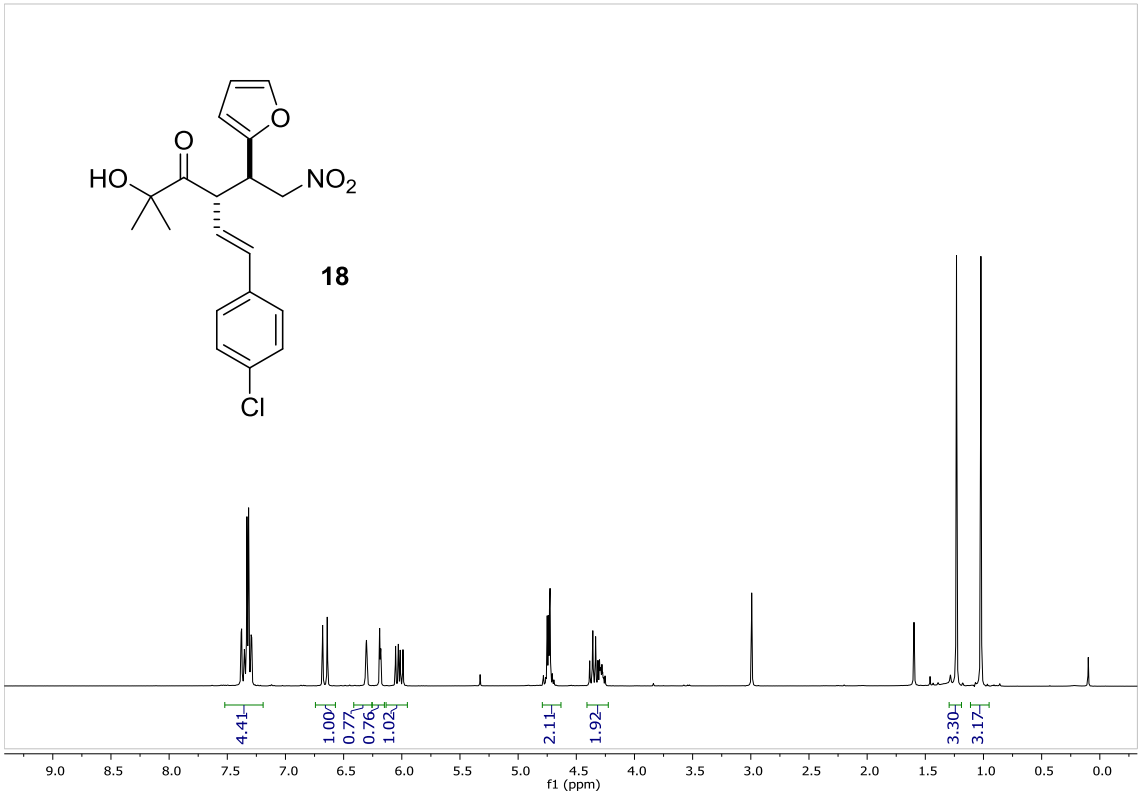

f1 (ppm)

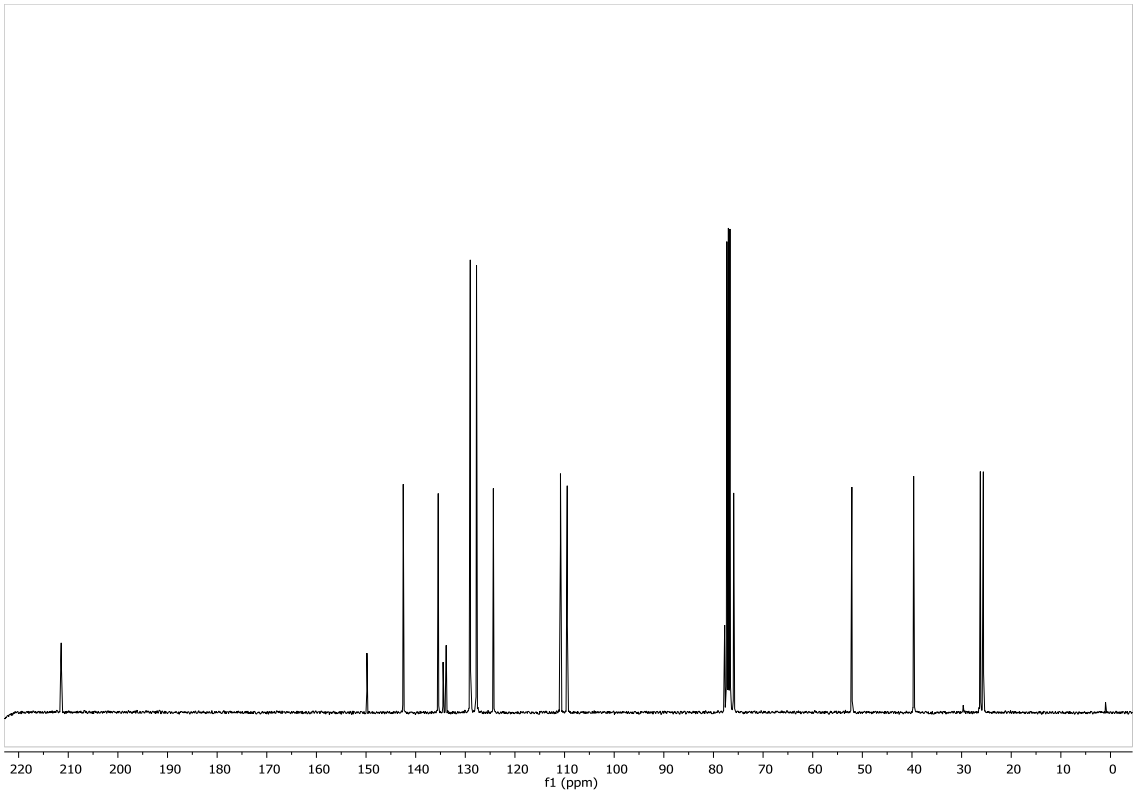

Cl
O
HO
NO2
Ph
16
9.59
1.00
1.08
1.19
1.15
1.05
1.22
0.88
3.26
3.77
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

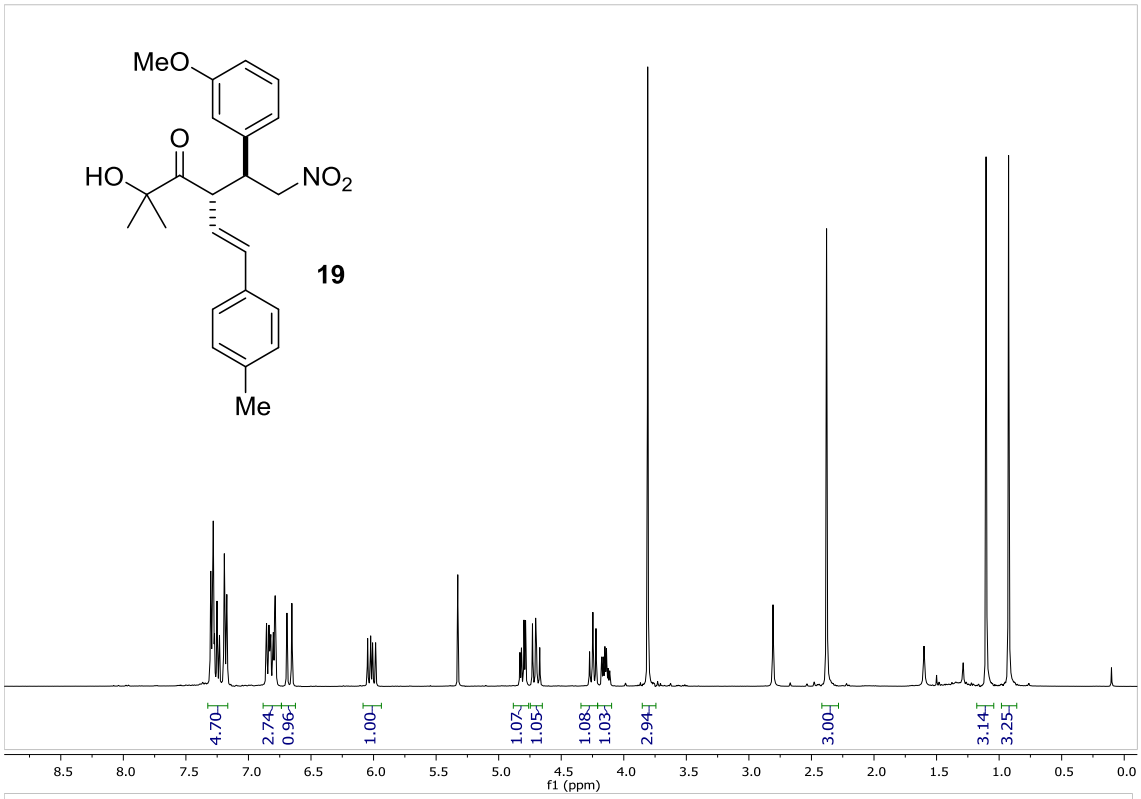

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

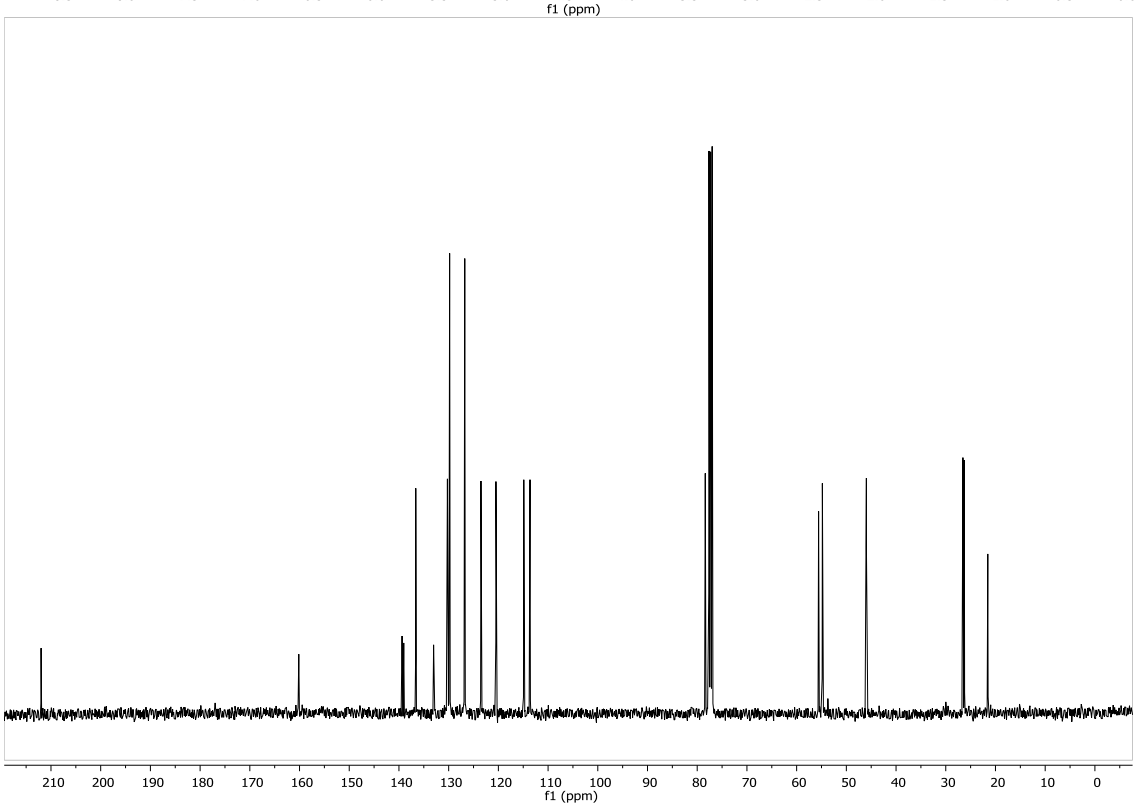

OMe
O
HO
NO2
Ph
17
5.28
1.89
1.97
1.02
1.00
2.11
2.09
3.32
3.20
3.41
f1 (ppm)

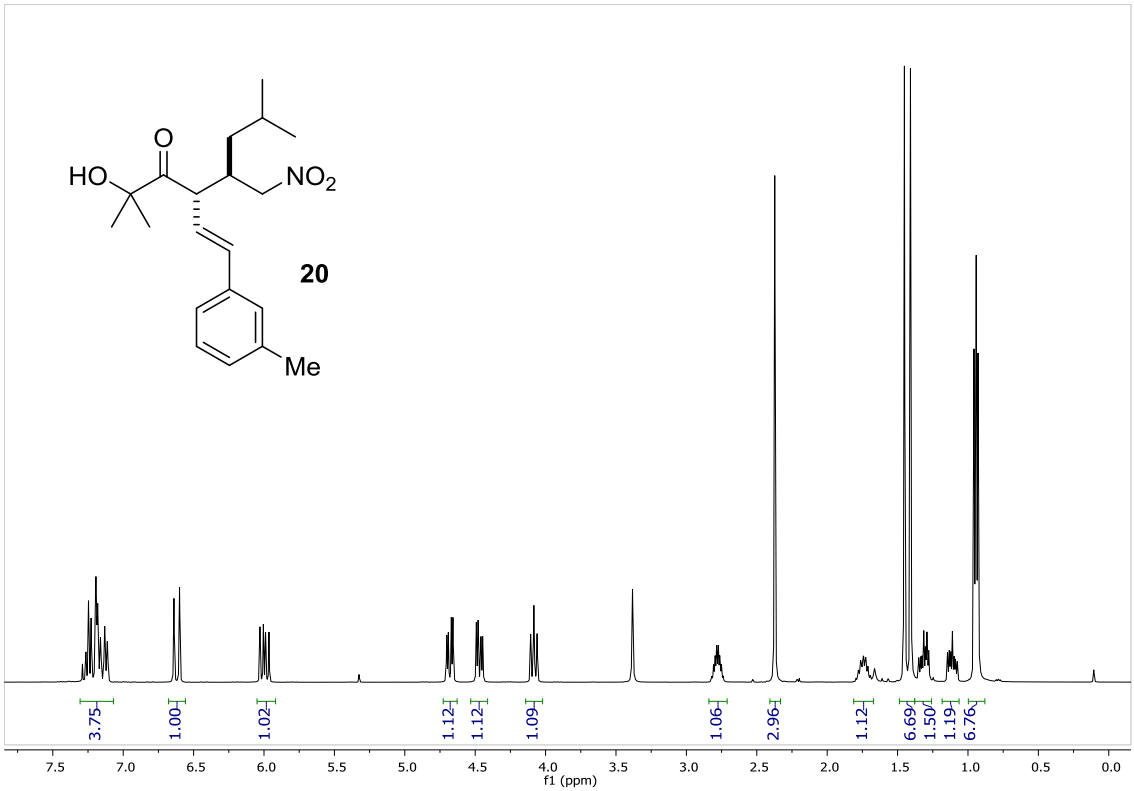

f1 (ppm)


HO
O
O
NO2
Cl
18
4.41
1.00
0.77
0.76
1.02
2.11
1.92
3.30
3.17
f1 (ppm)


f1 (ppm)


MeO
O
HO
NO2
19
Me
4.70
2.74
0.96
1.00
1.07
1.05
1.08
1.03
2.94
3.00
3.14
3.25
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
O
NO2
Me
20
3.75
1.00
1.02
1.12
1.12
1.09
1.06
2.96
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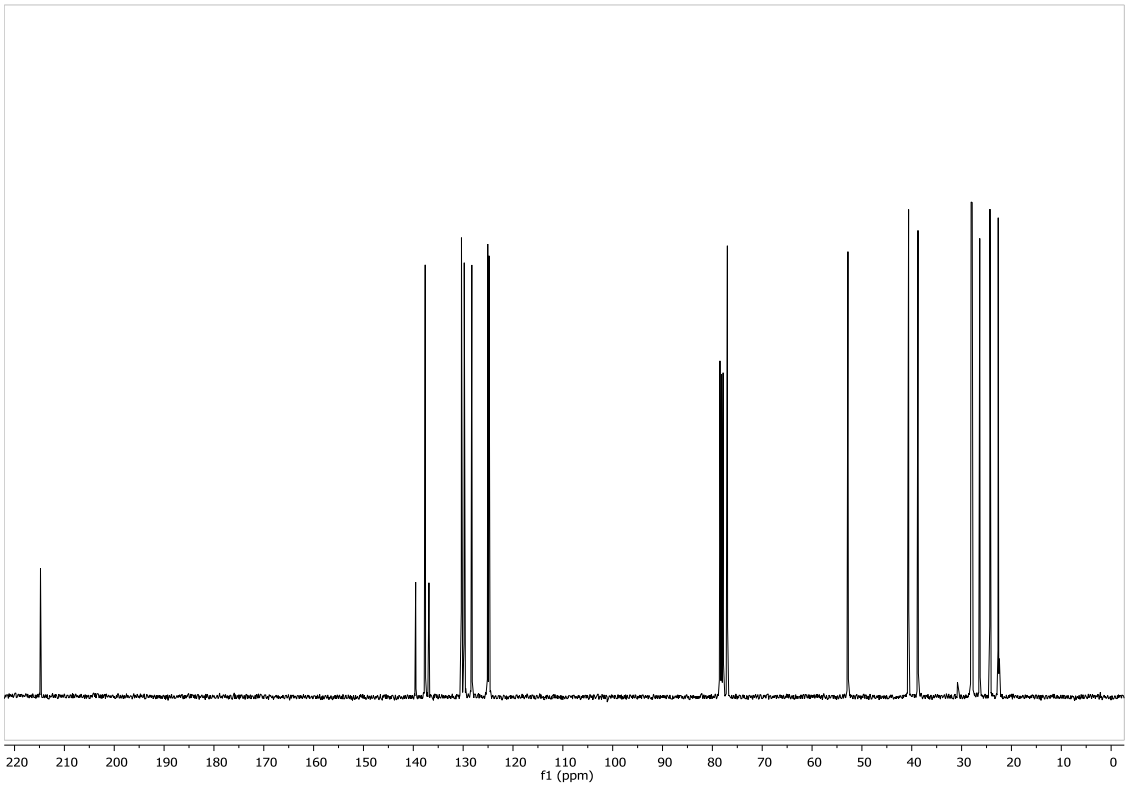
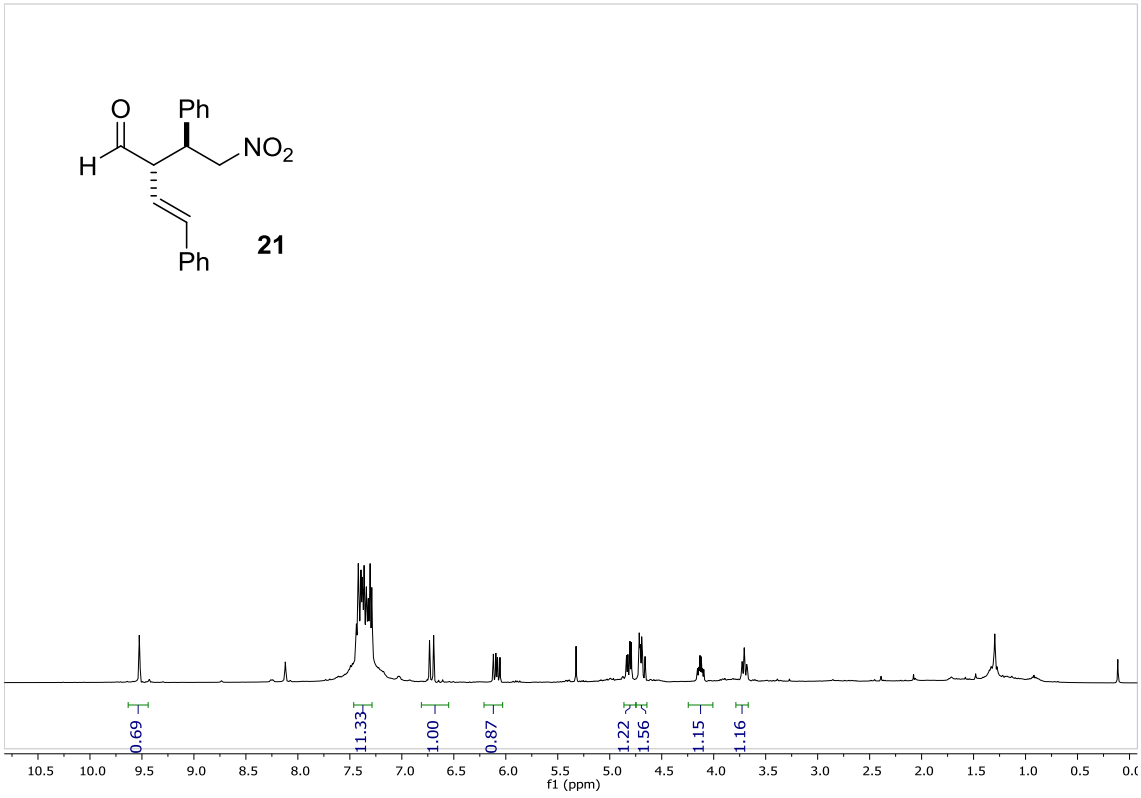
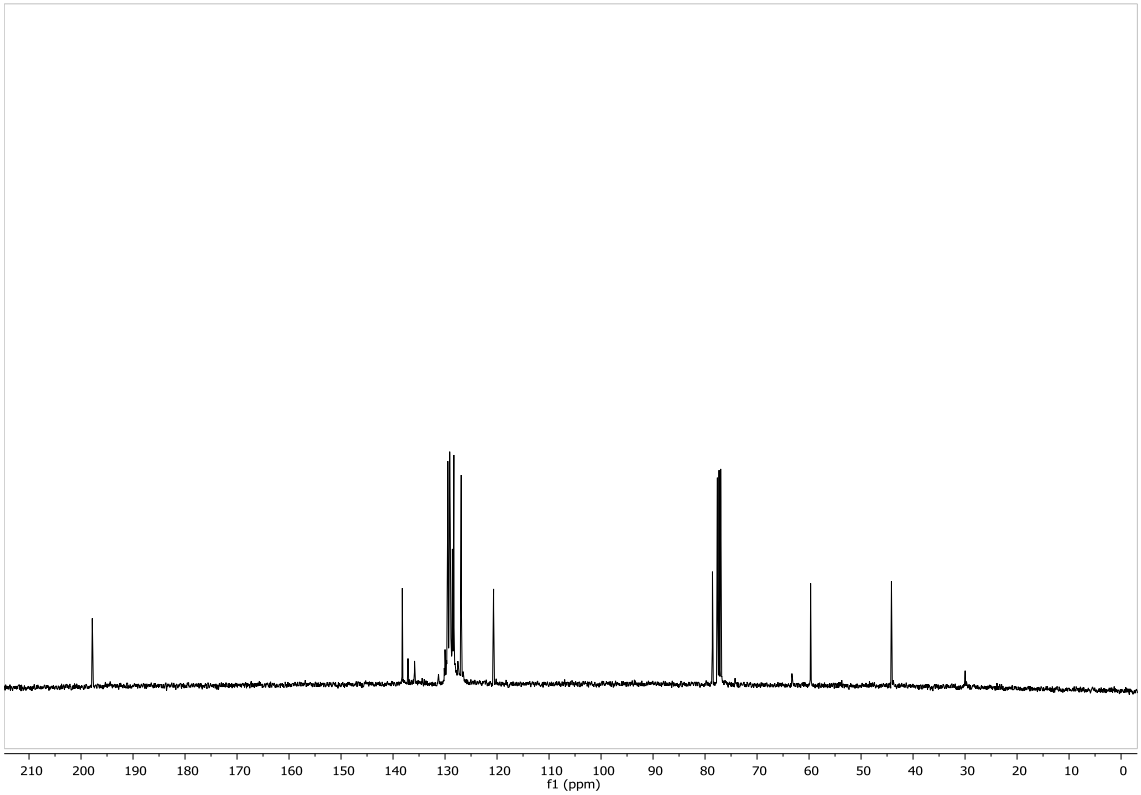
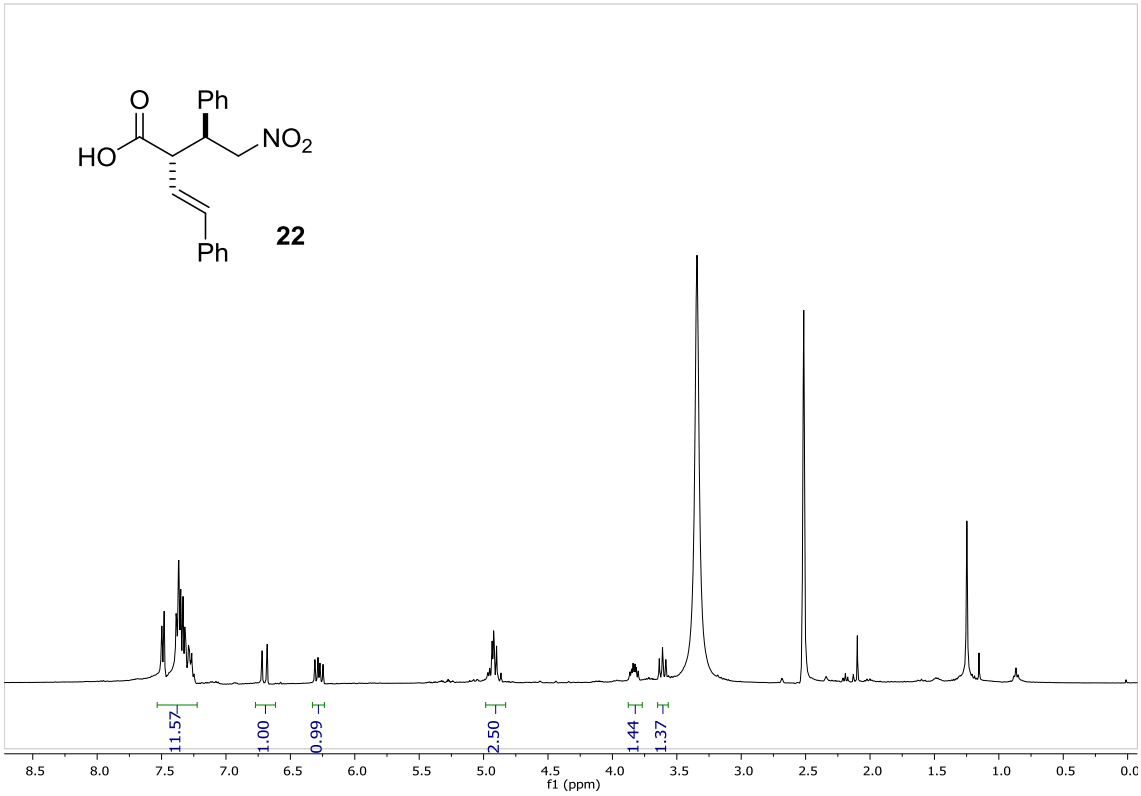
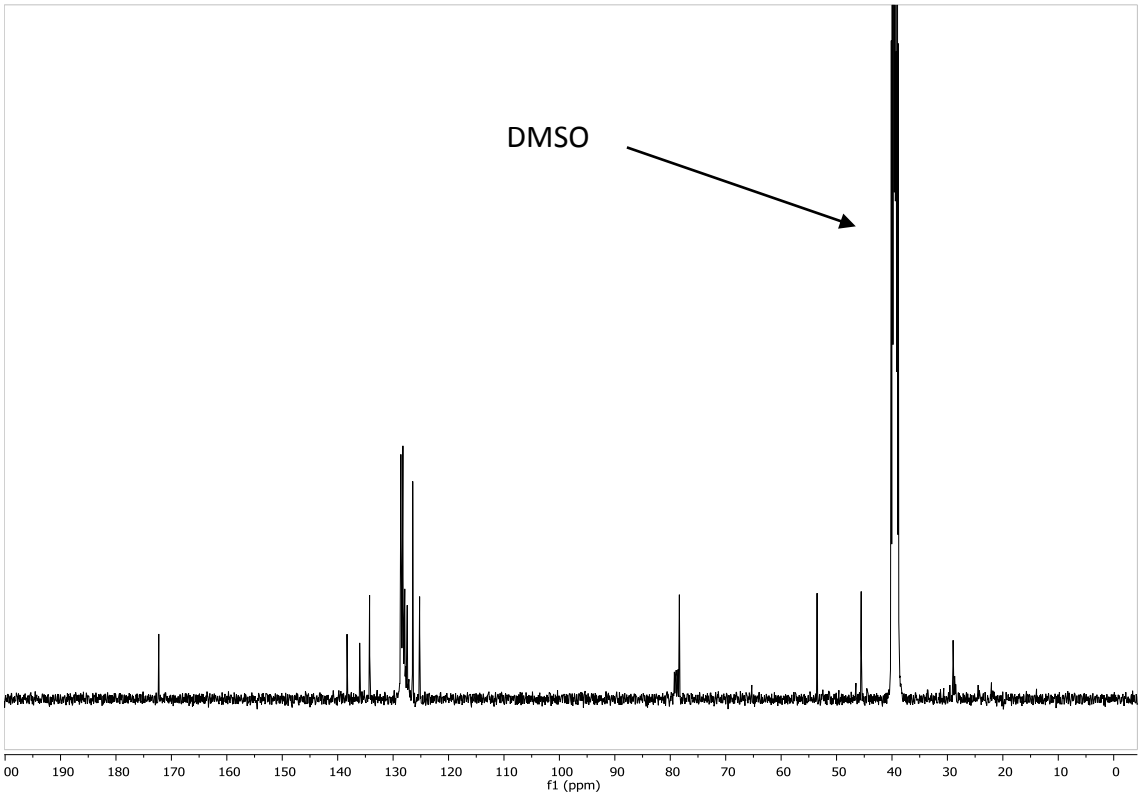
6.69
1.50
1.19
6.76
f1 (ppm)

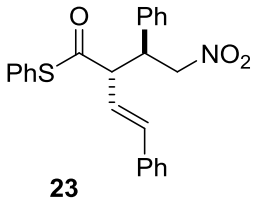

f1 (ppm)


O
Ph
H
NO2
Ph
21
0.69
11.33
1.00
0.87
1.22
1.56
1.15
1.16
f1 (ppm)

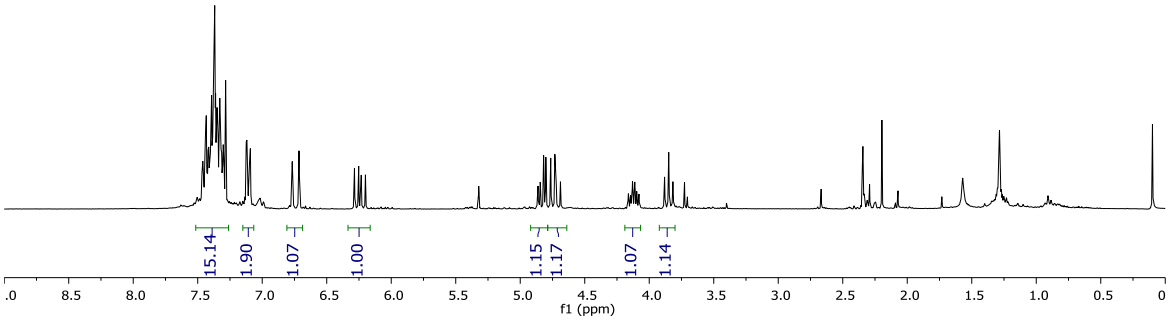

f1 (ppm)

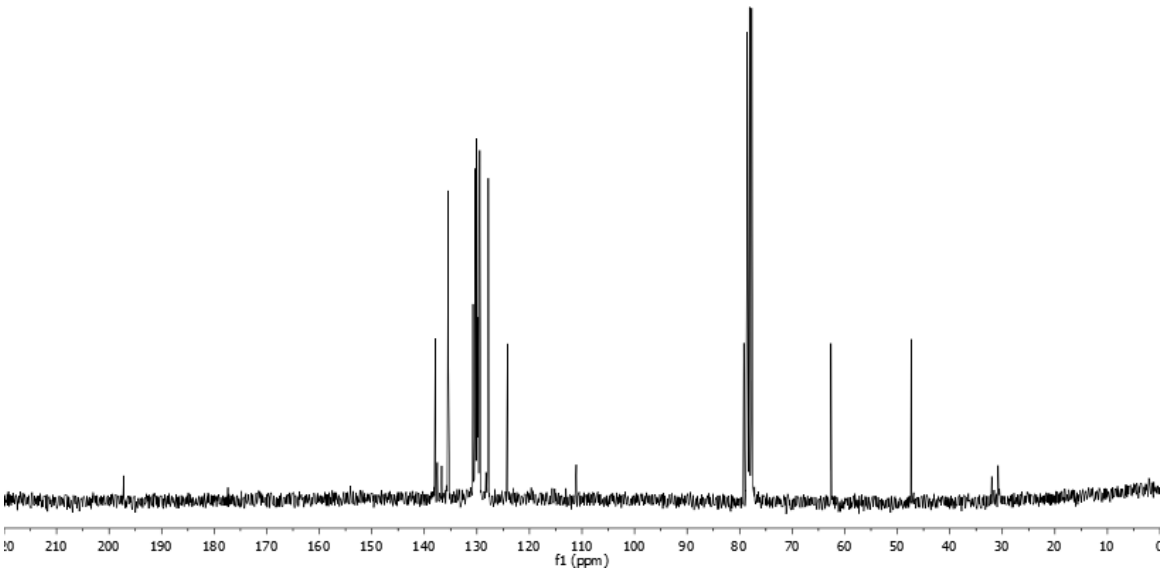

O
Ph
HO
NO2
Ph
22
11.57
1.00
0.99
2.50
1.44
1.37
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

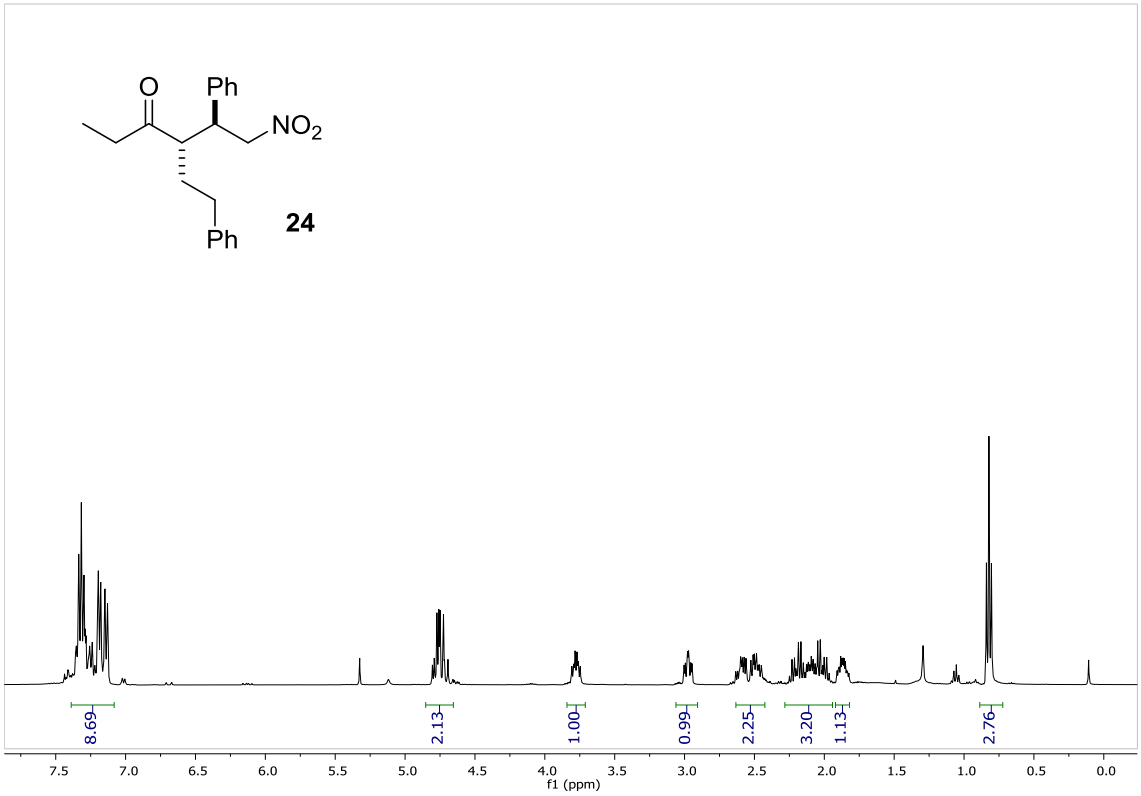

DMSO
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

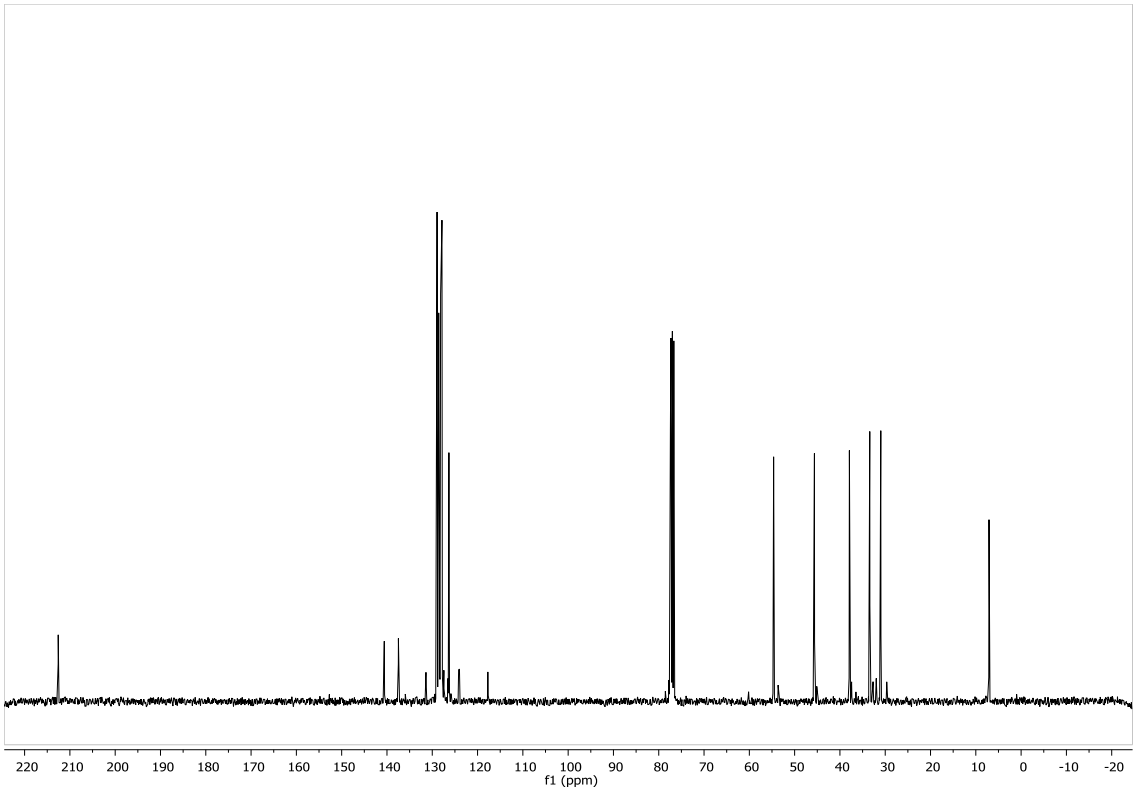


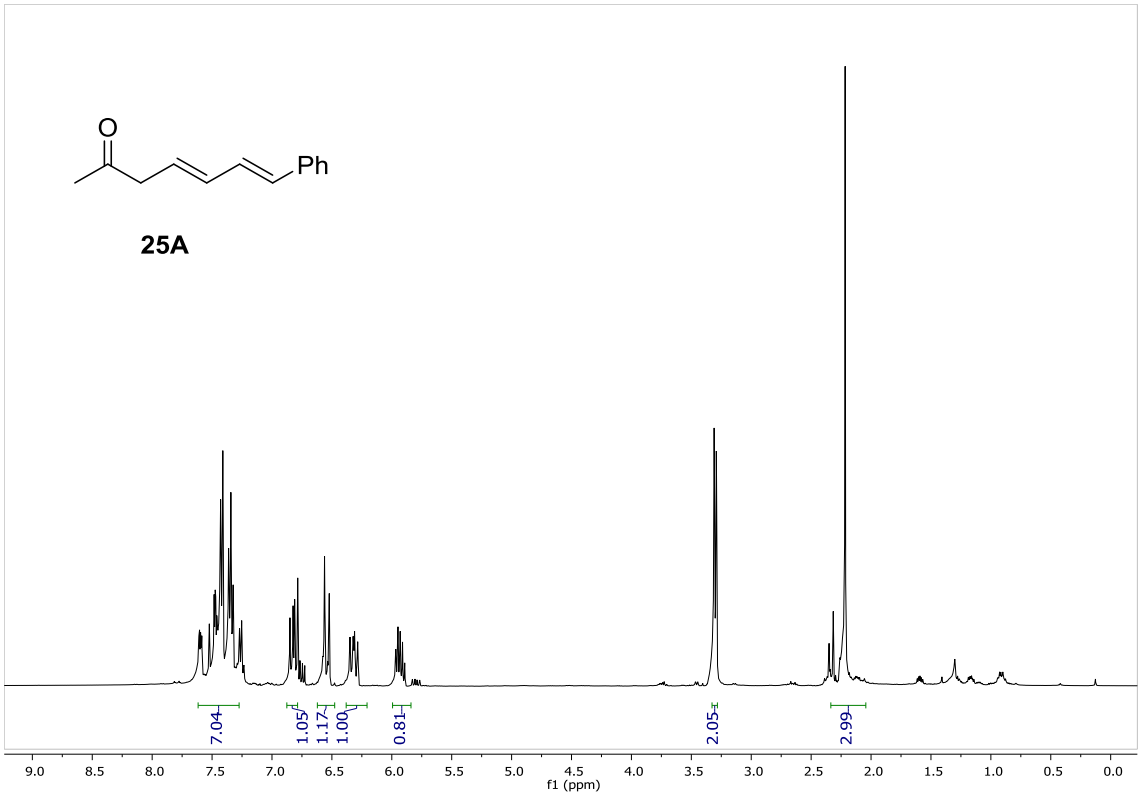
23

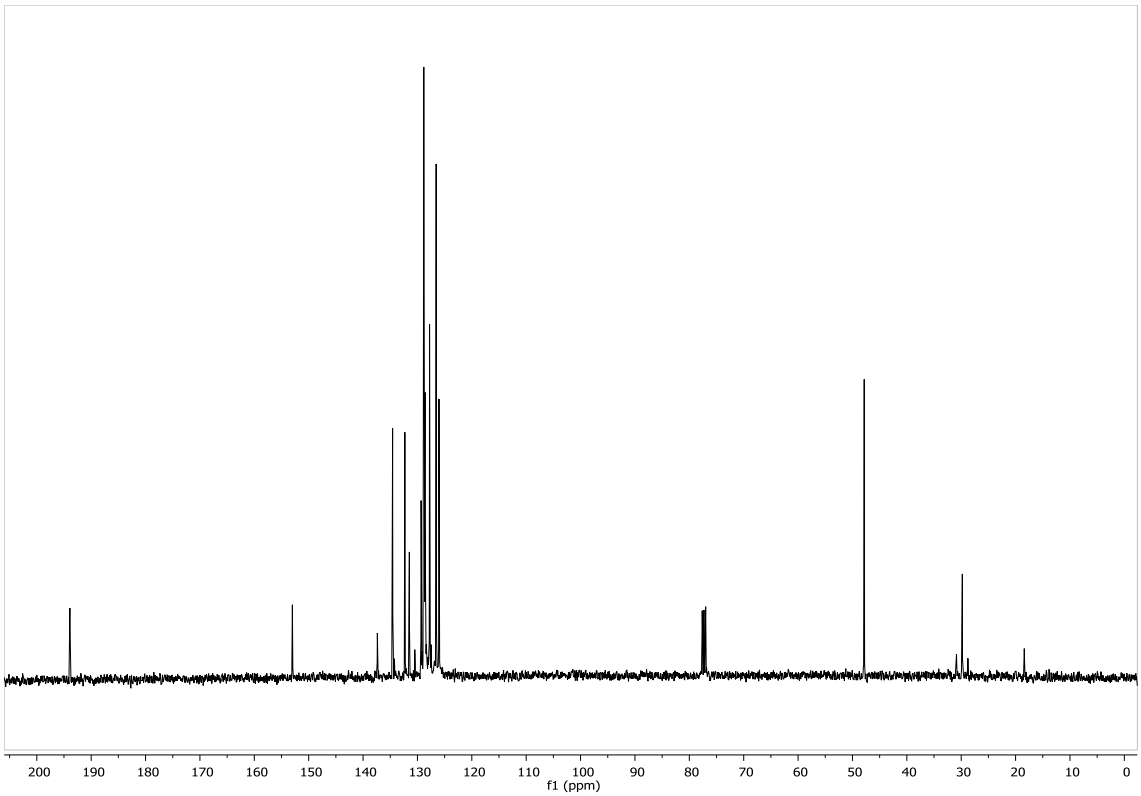


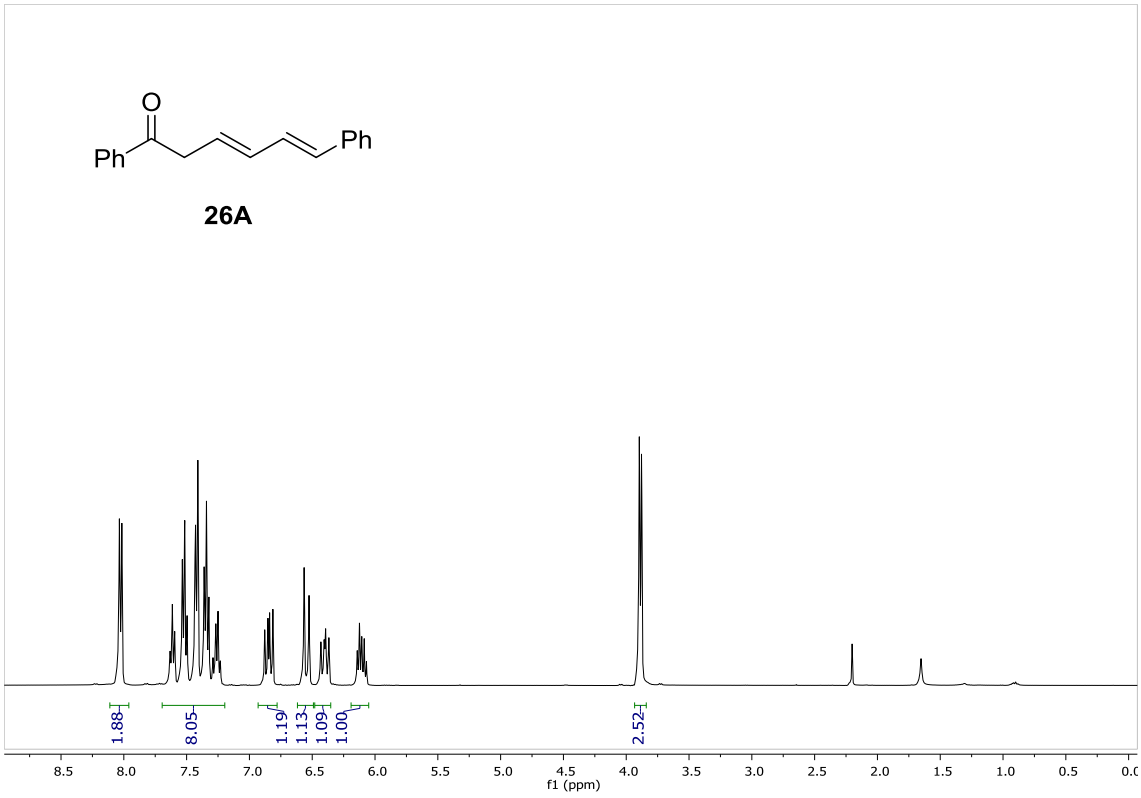


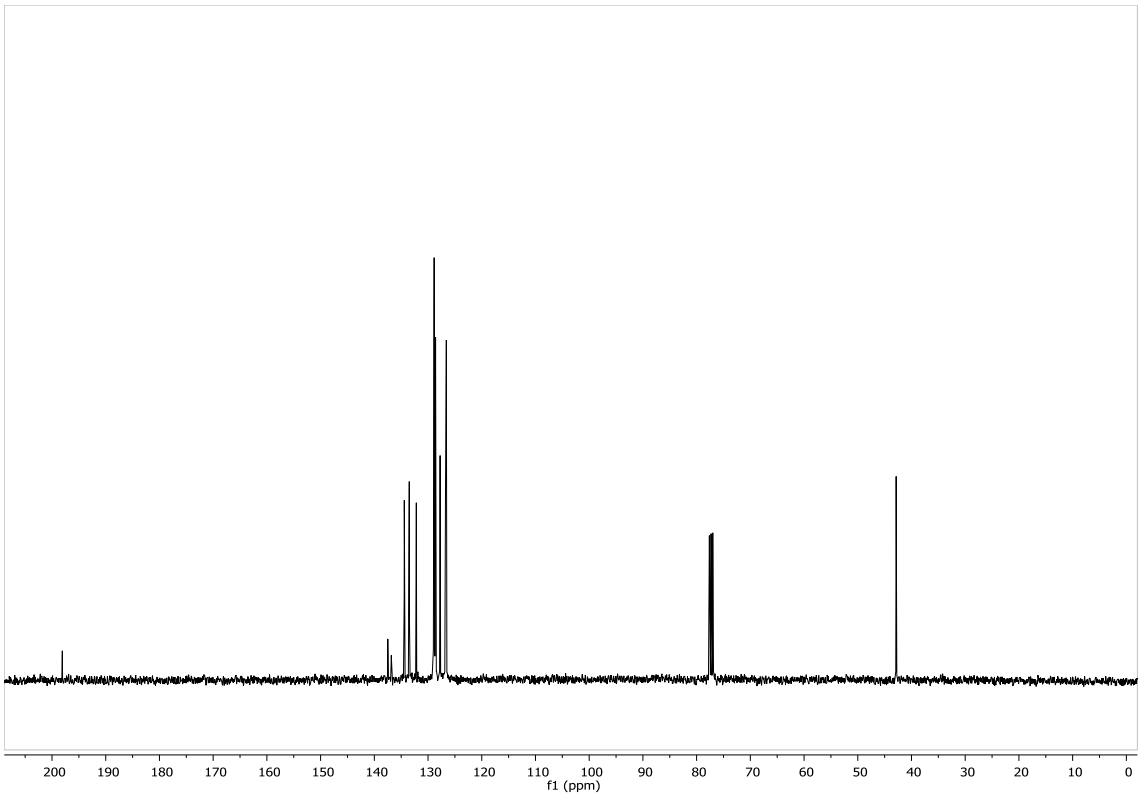

O
Ph
NO2
Ph
24
8.69
2.13
1.00
0.99
2.25
3.20
1.13
2.76
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

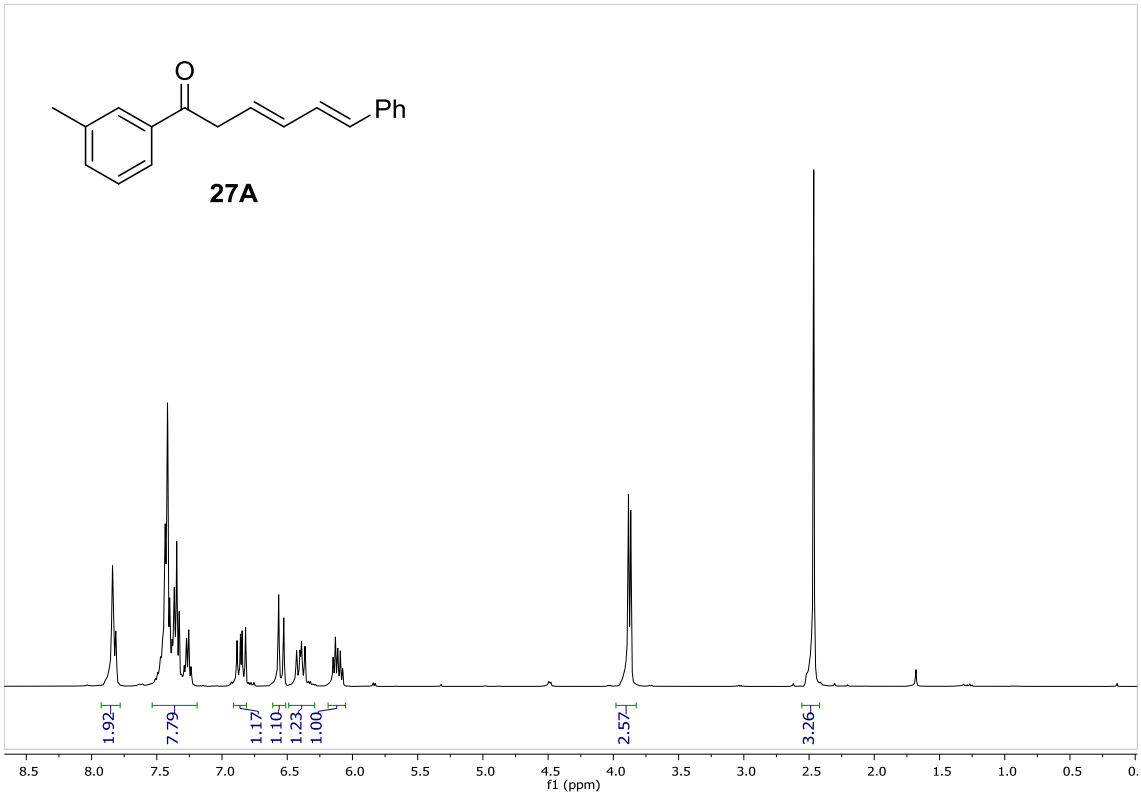

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

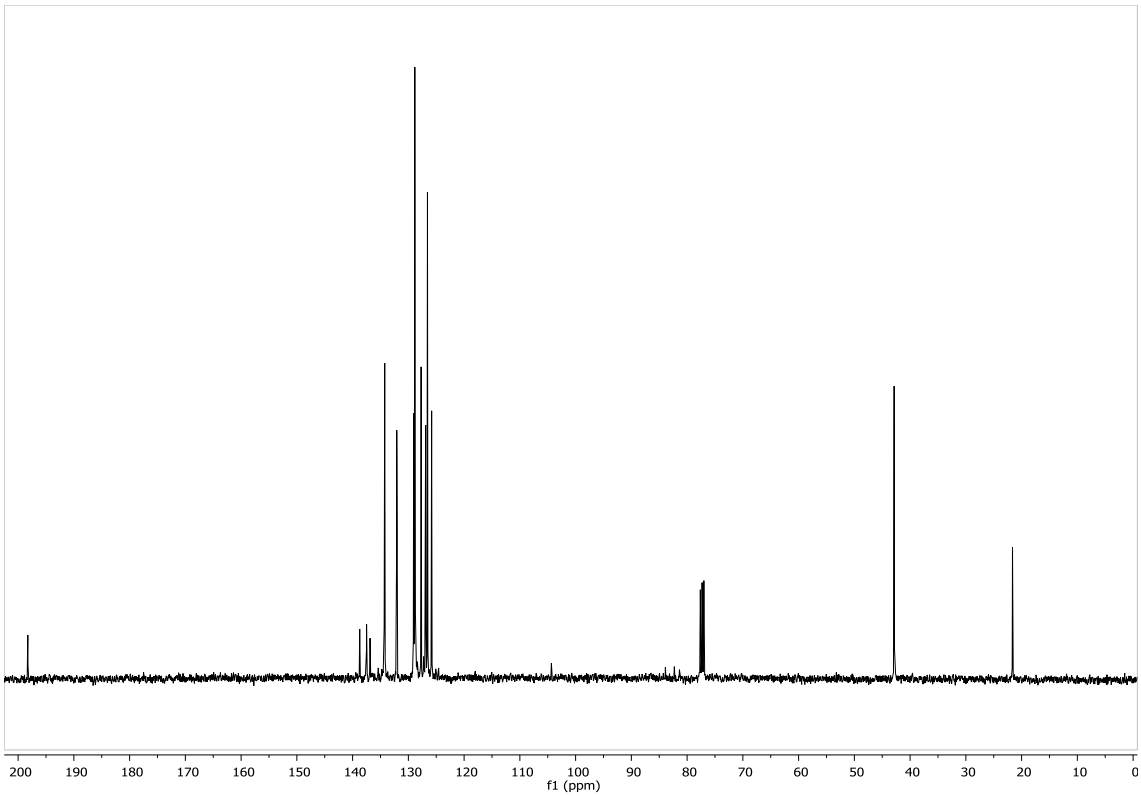

O
Ph
25A
7.04
1.05
1.17
1.00
0.81
2.05
2.99
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

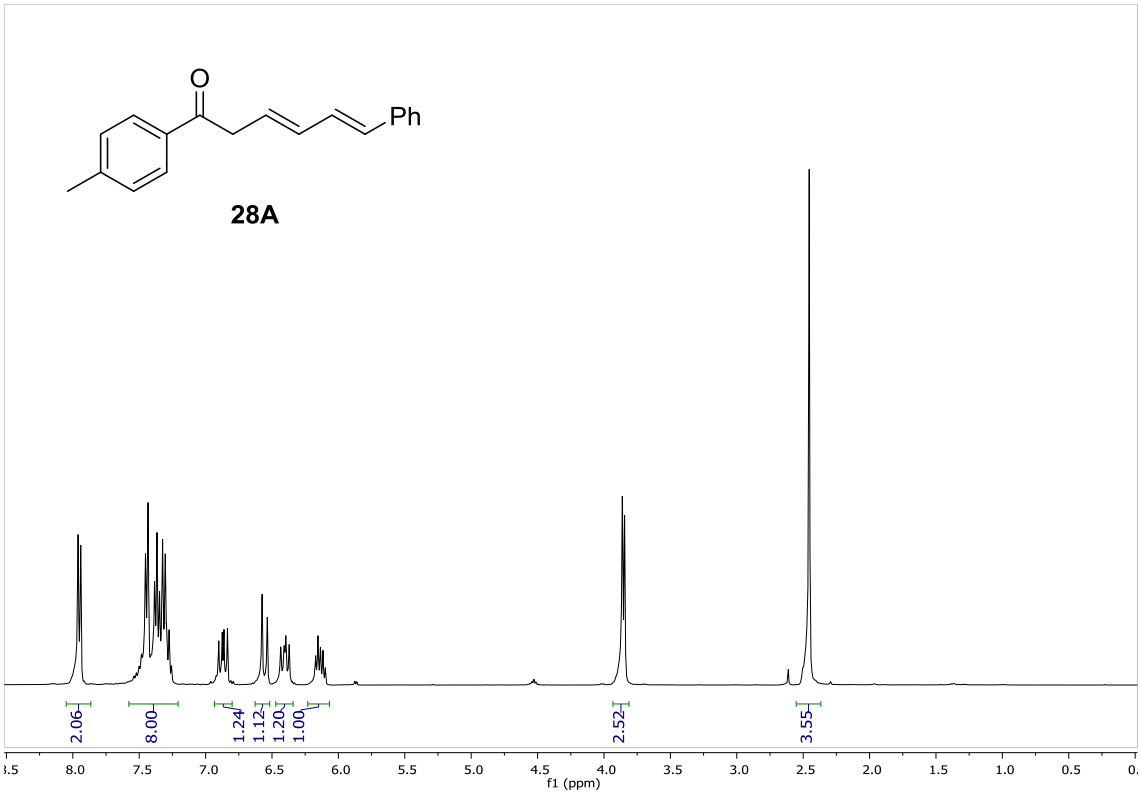

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

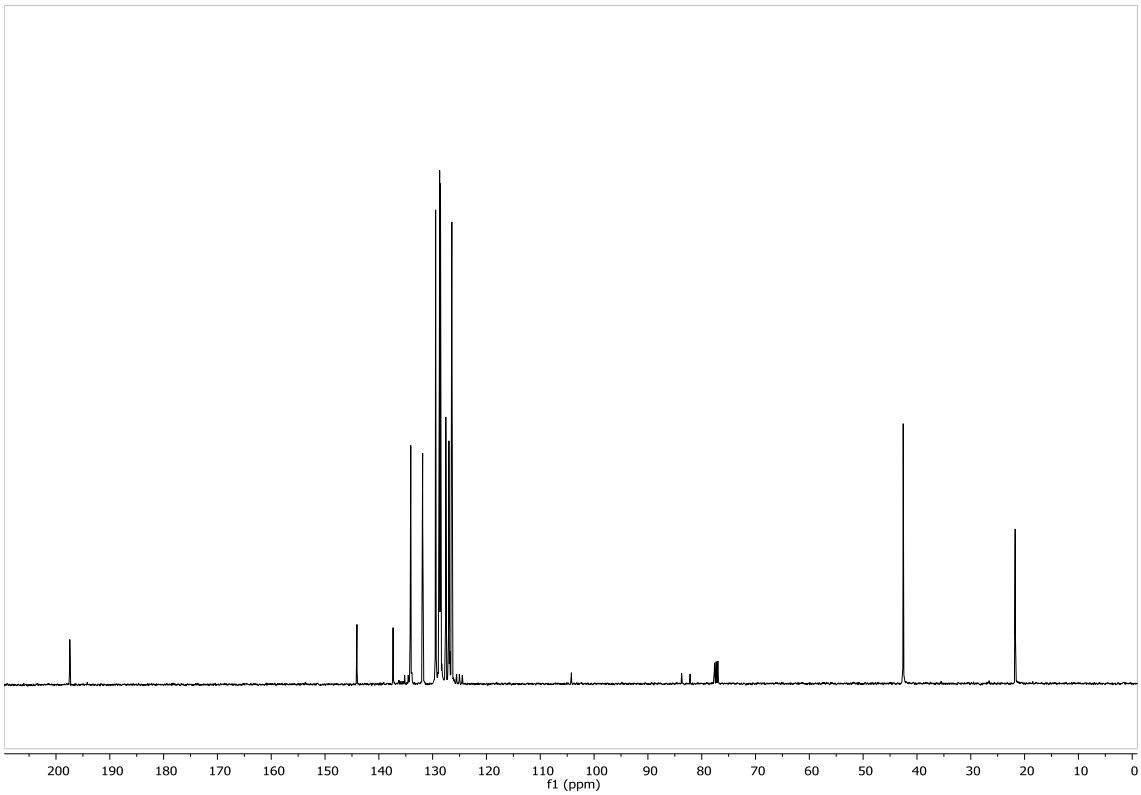

O
Ph
Ph
26A
1.88
8.05
1.19
1.13
1.09
1.00
2.52
f1 (ppm)

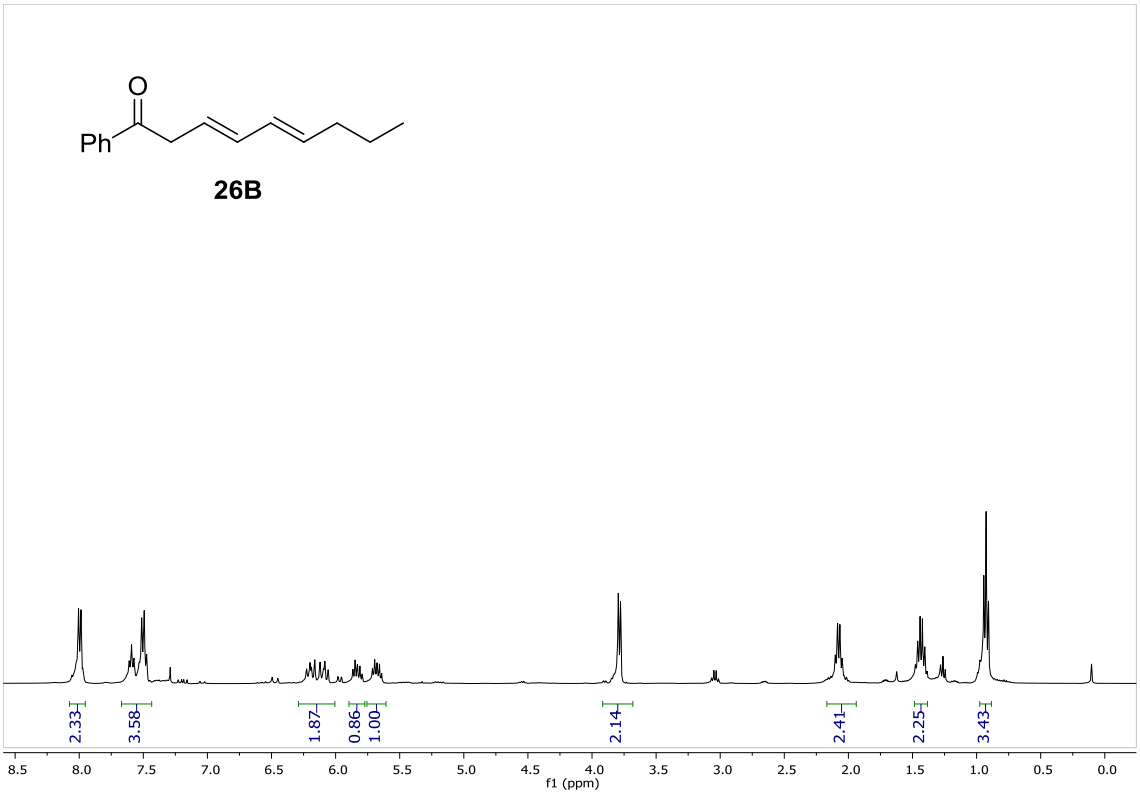

f1 (ppm)

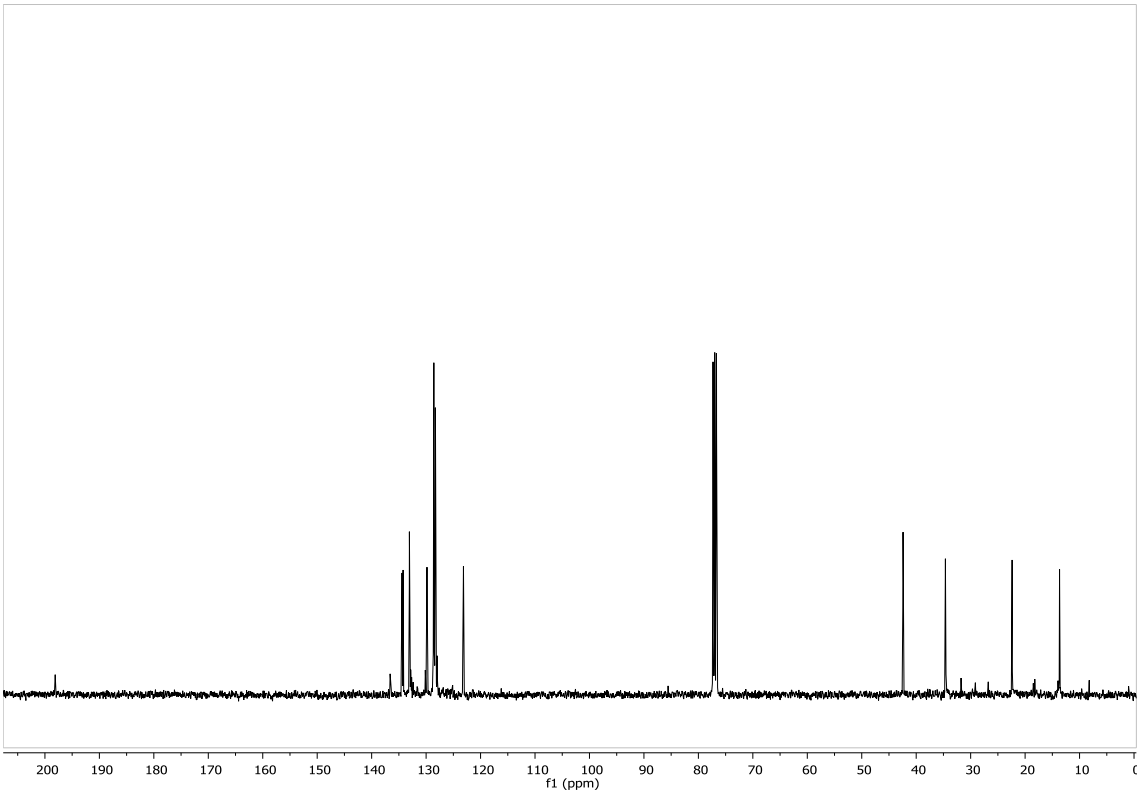

O
Ph
27A
1.92
7.79
1.17
1.10
1.23
1.00
2.57
3.26
f1 (ppm)

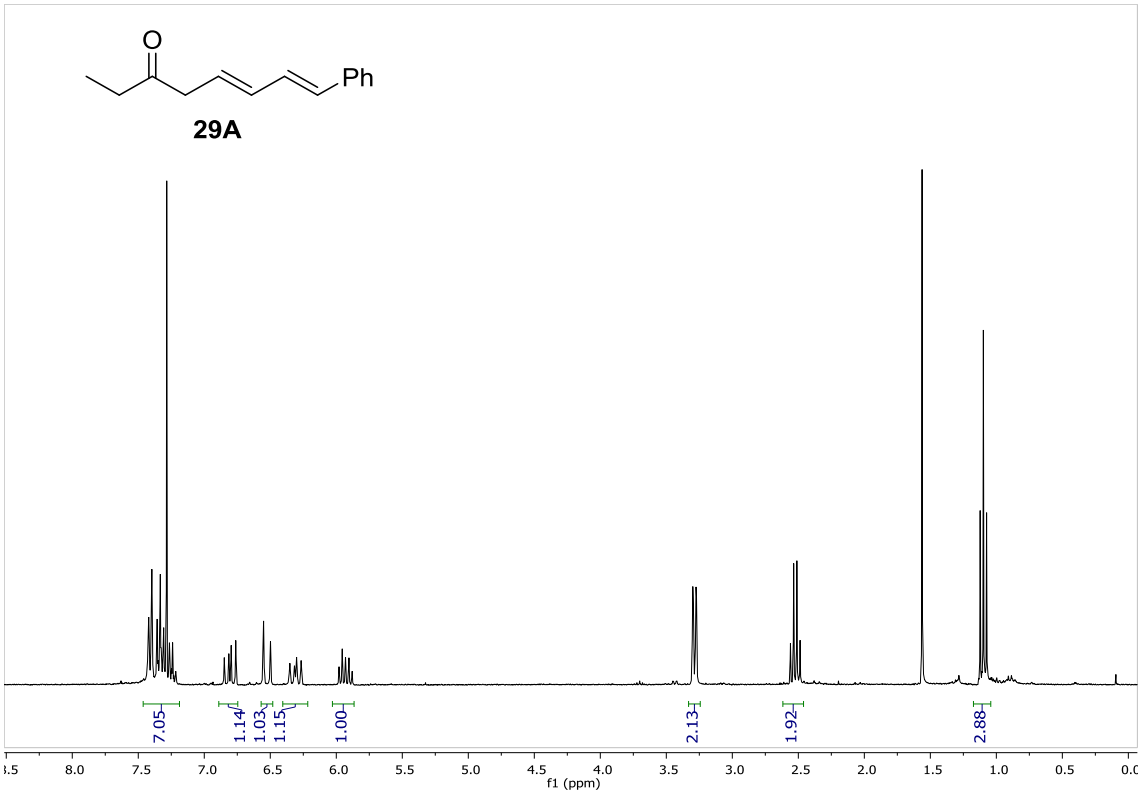

f1 (ppm)

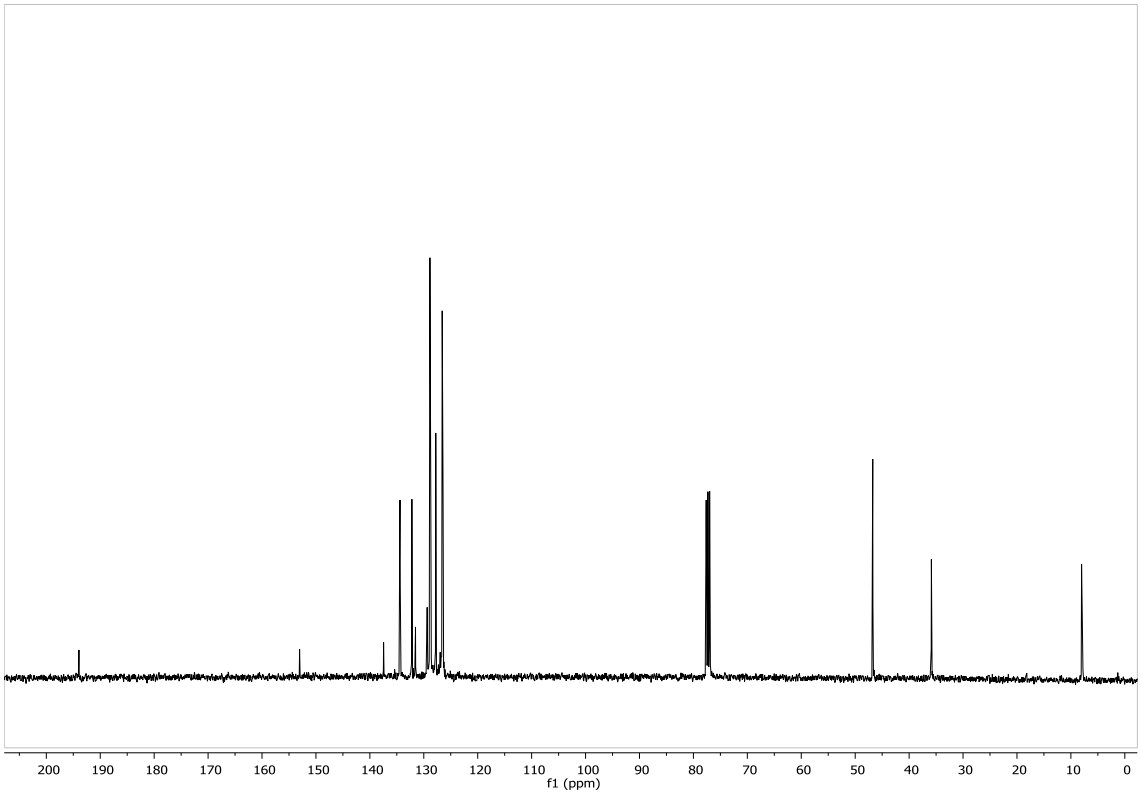

O
Ph
28A
2.06
8.00
1.24
1.12
1.20
1.00
2.52
3.55
f1 (ppm)

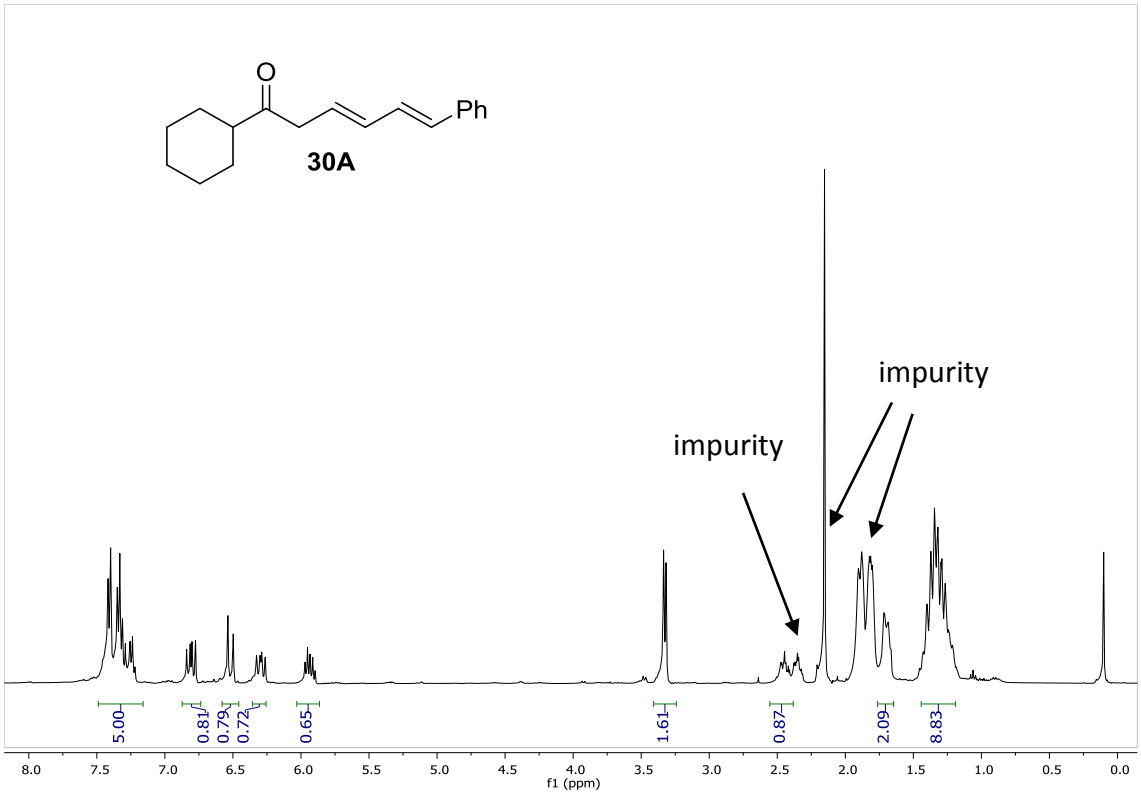

f1 (ppm)

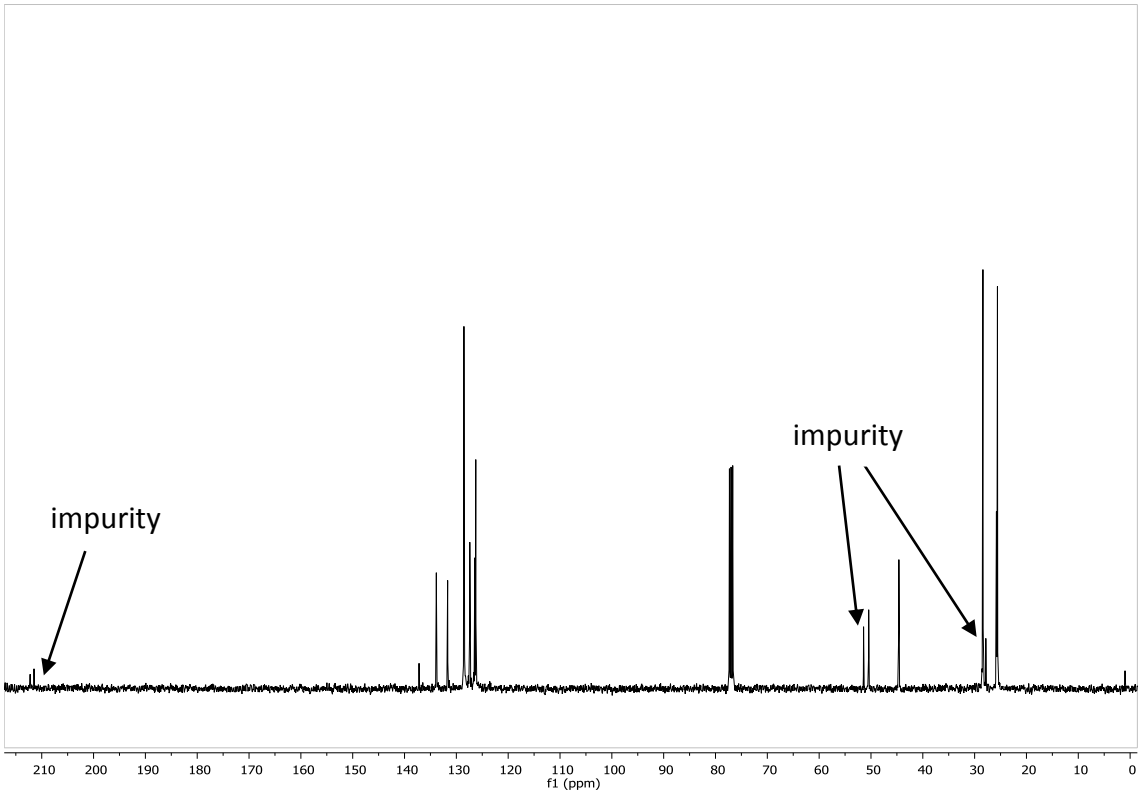

O
Ph
26B
2.33
3.58
1.87
0.86
1.00
2.14
2.41
2.25
3.43
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

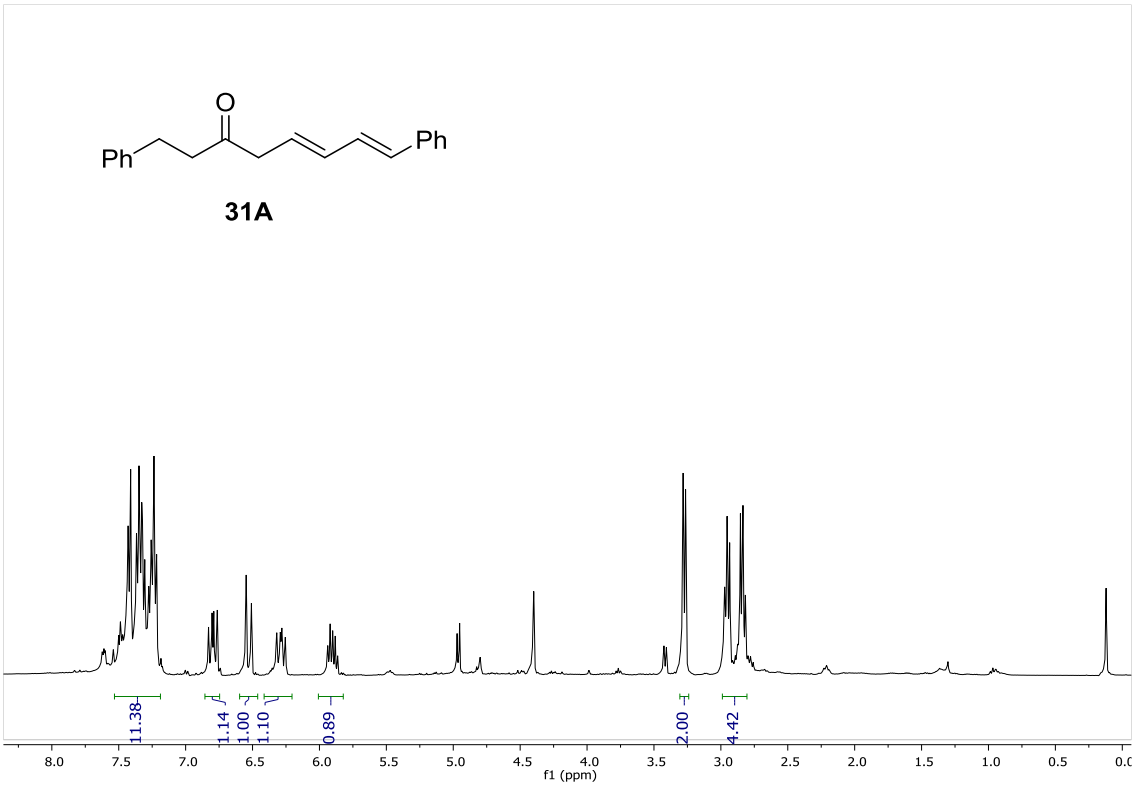

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

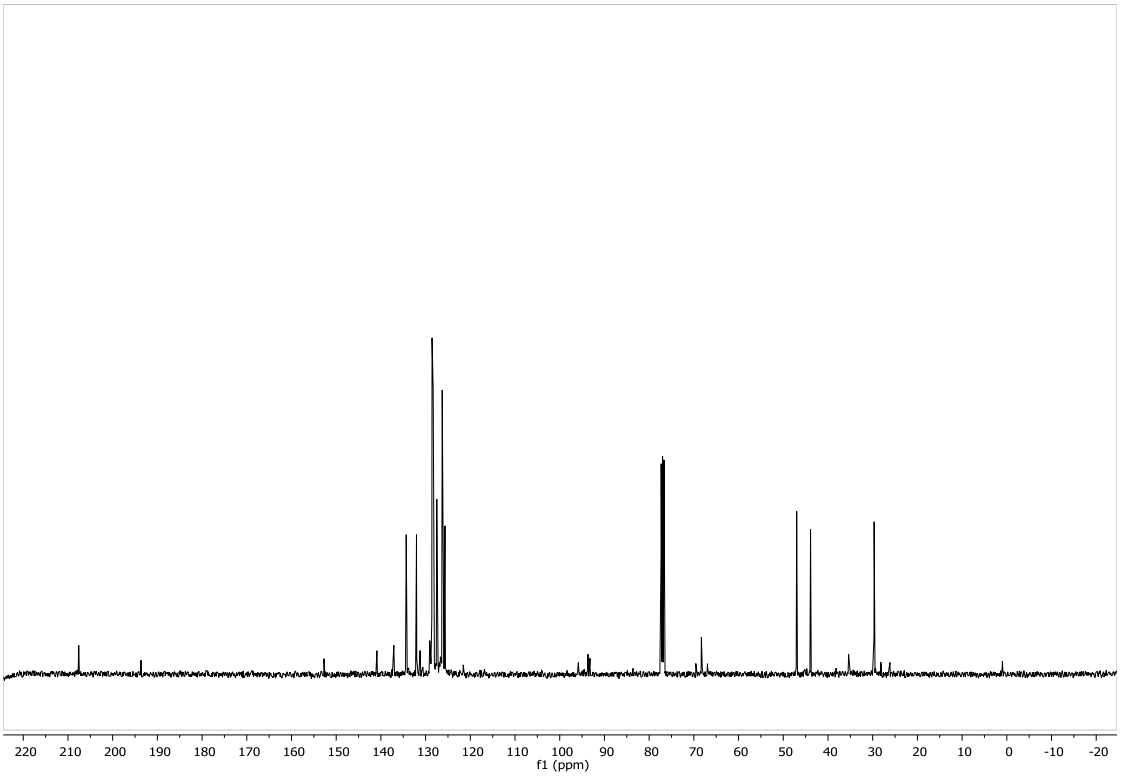

O
Ph
29A
7.05
1.14
1.03
1.15
1.00
2.13
1.92
2.88
f1 (ppm)

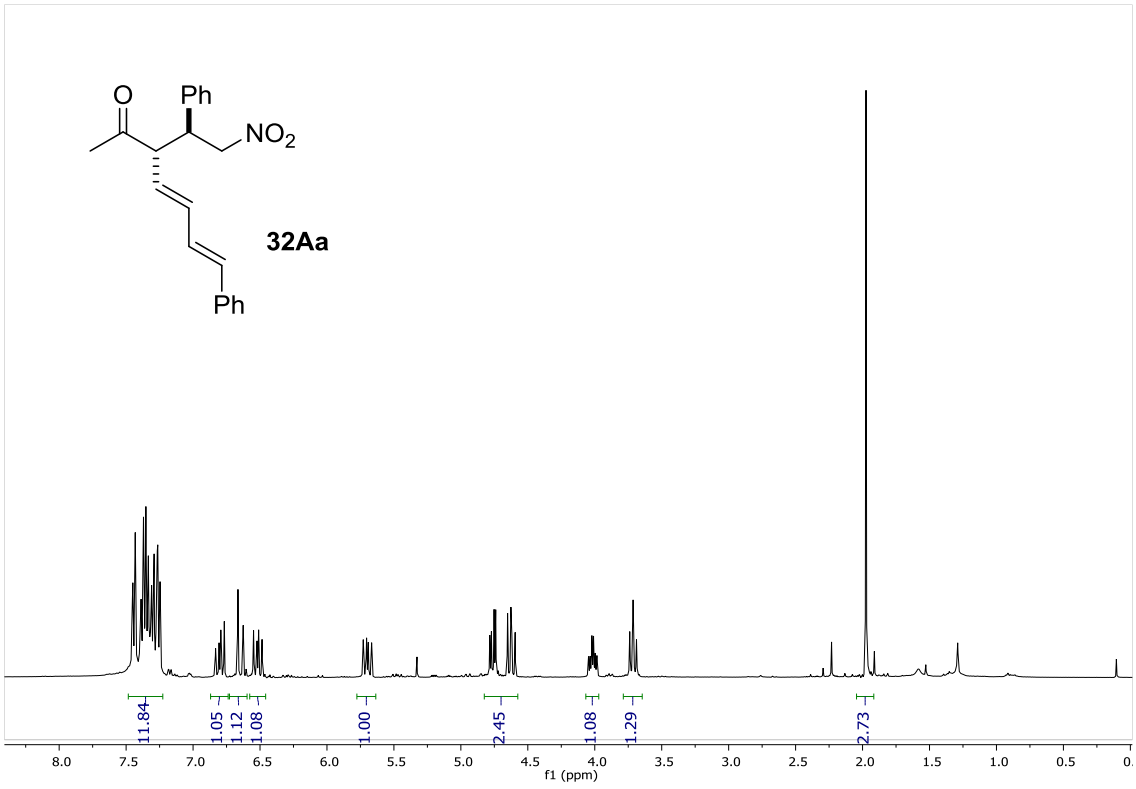

f1 (ppm)

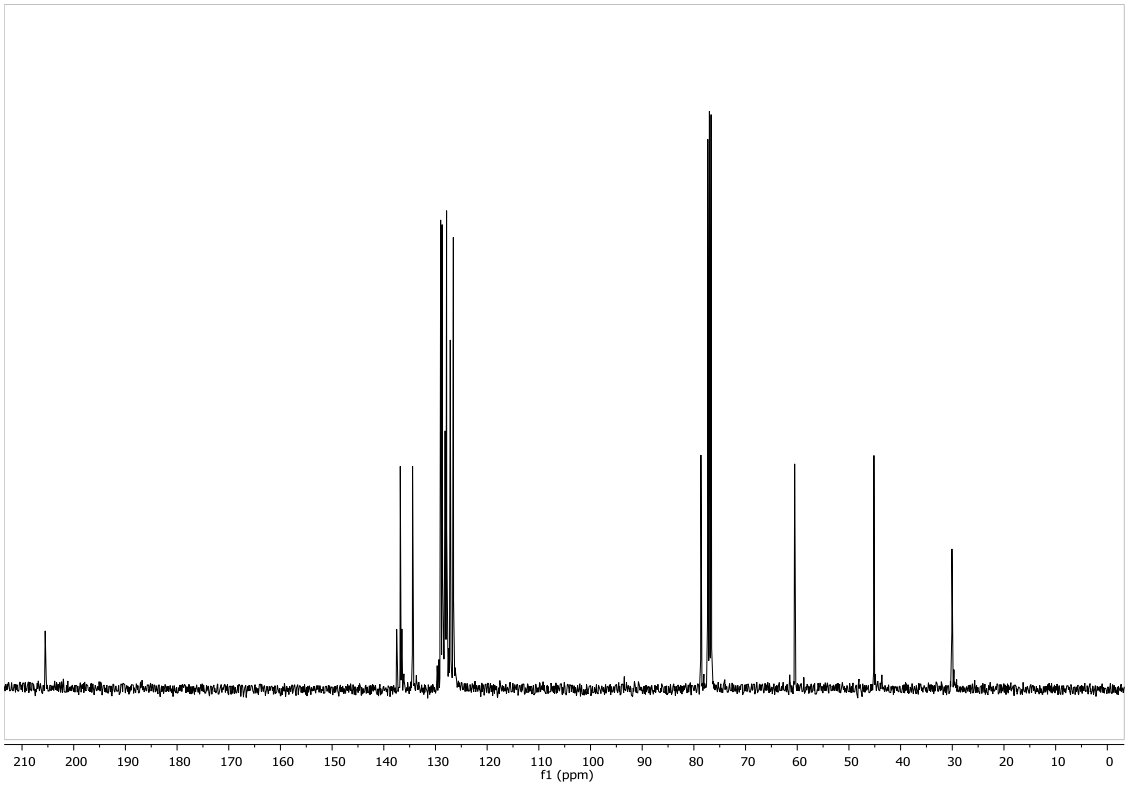

O
Ph
30A
impurity
impurity
5.00
0.81
0.79
0.72
0.65
1.61
0.87
2.09
8.83
f1 (ppm)

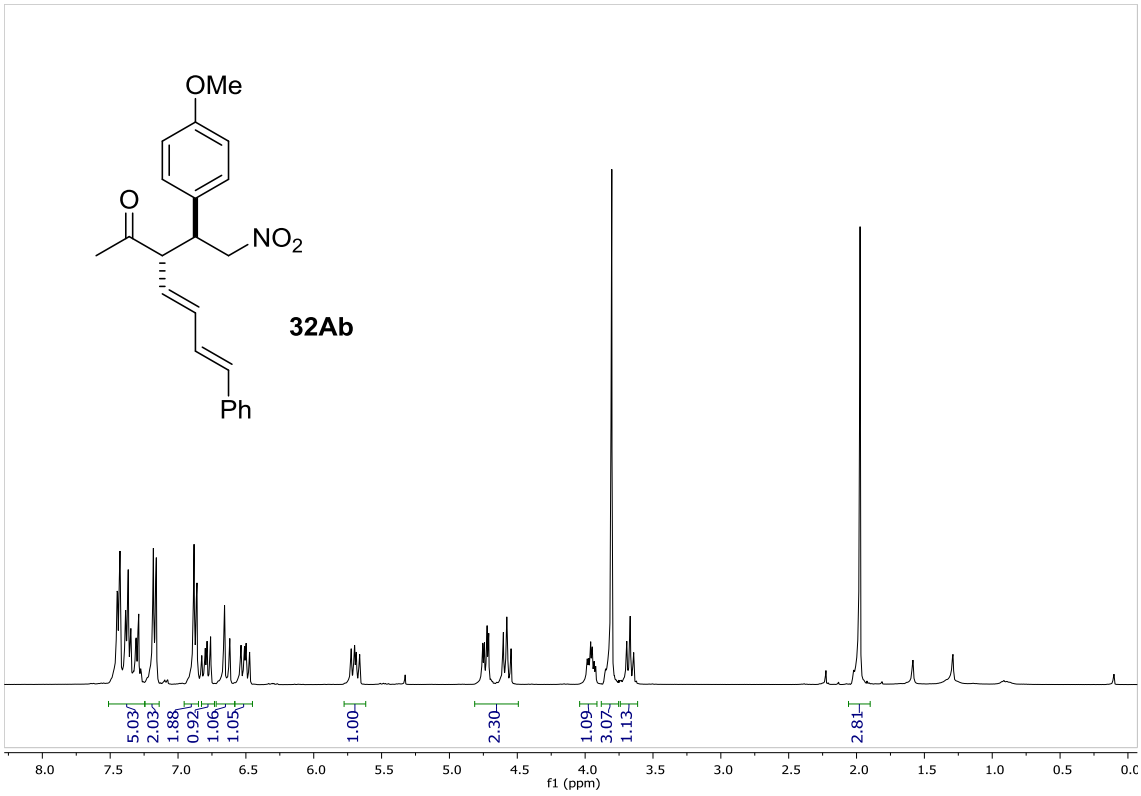

impurity
impurity
f1 (ppm)

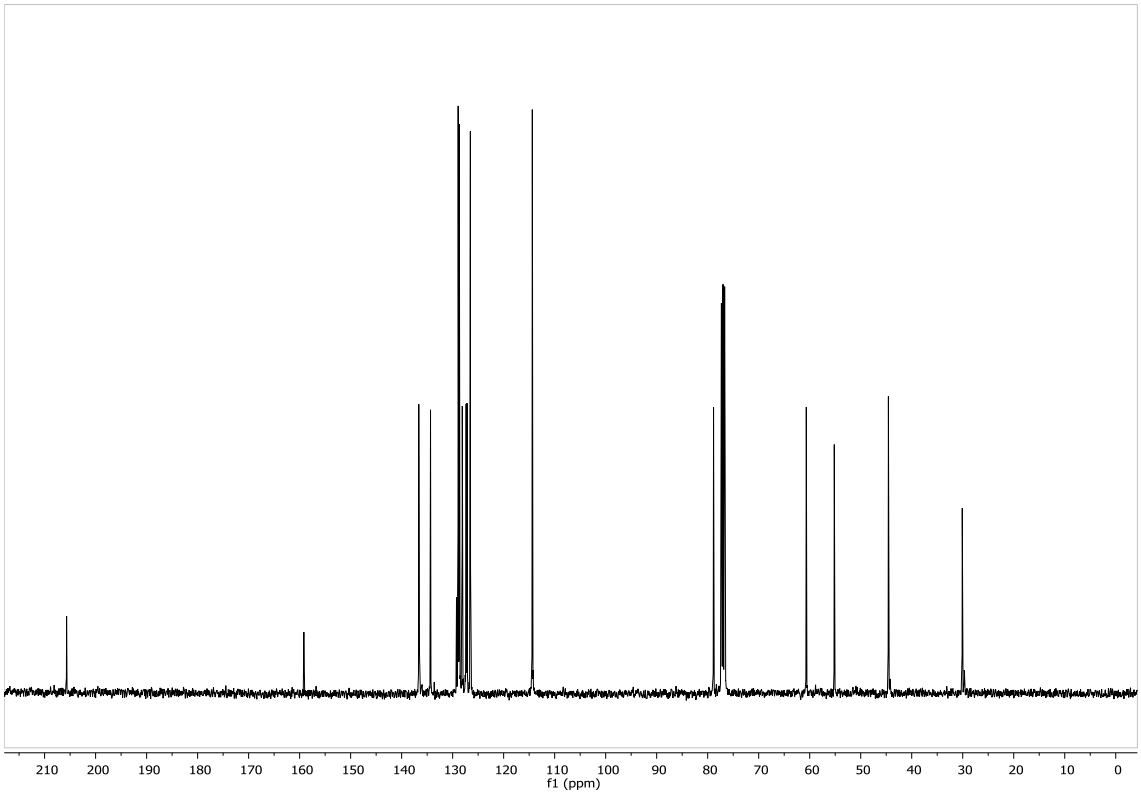

O
Ph
Ph
31A
11.38
1.14
1.00
1.10
0.89
2.00
4.42
f1 (ppm)

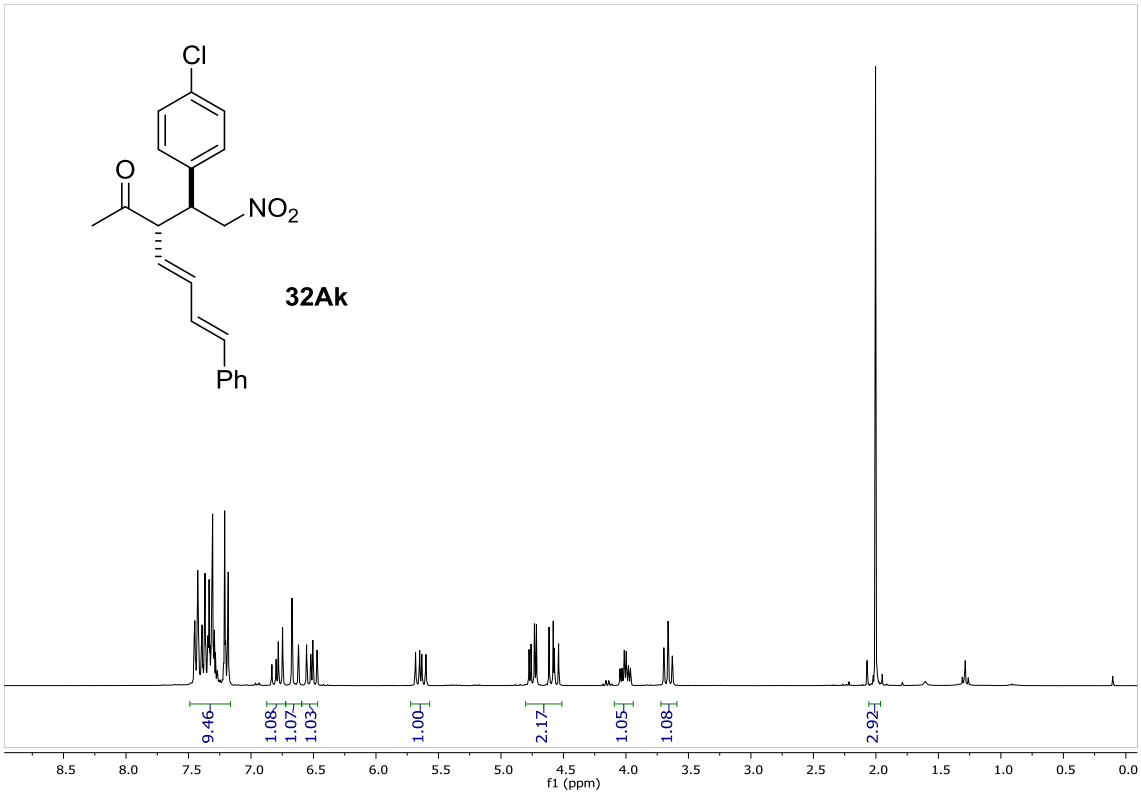

f1 (ppm)

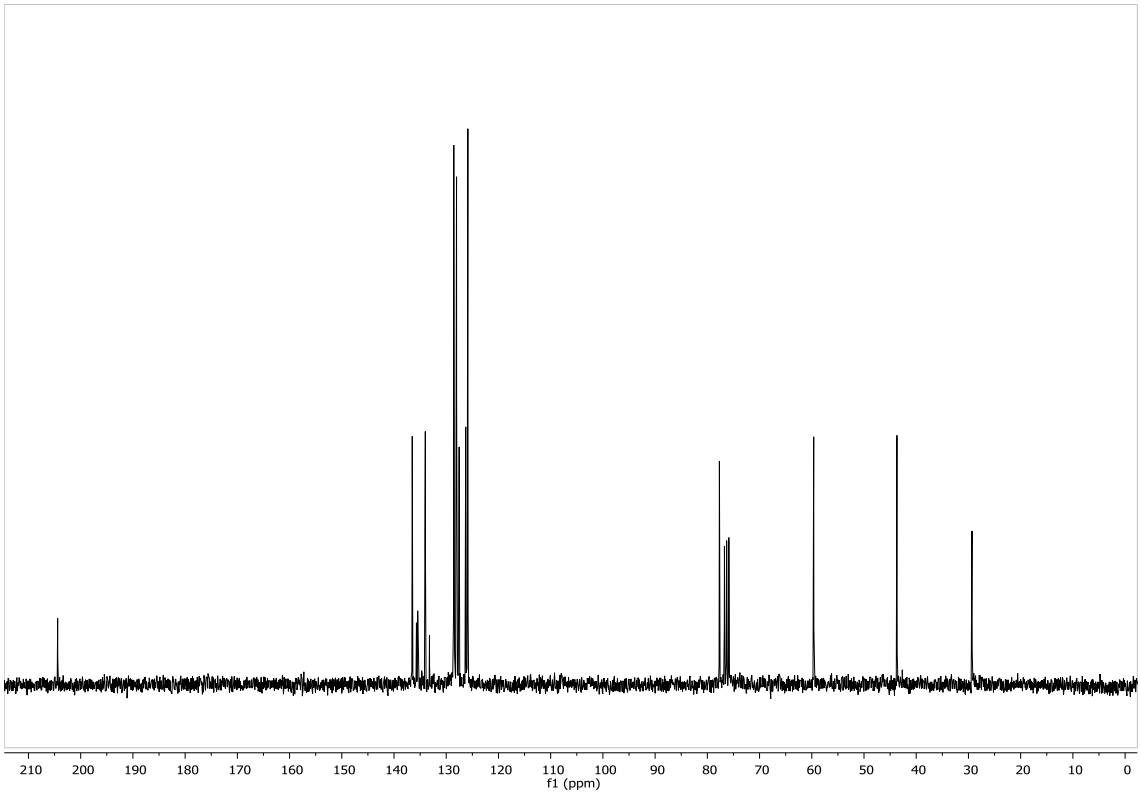

O
Ph
NO2
32Aa
Ph
11.84
1.05
1.12
1.08
1.00
2.45
1.08
1.29
2.73
f1 (ppm)

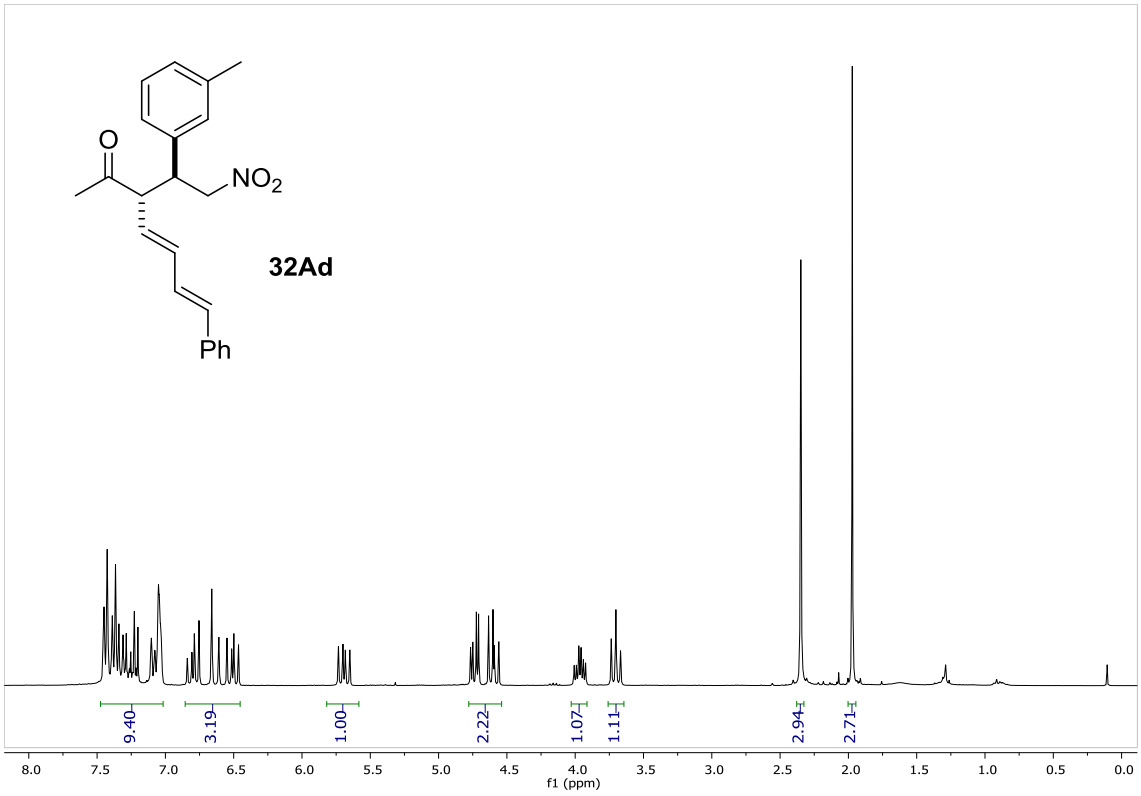

f1 (ppm)

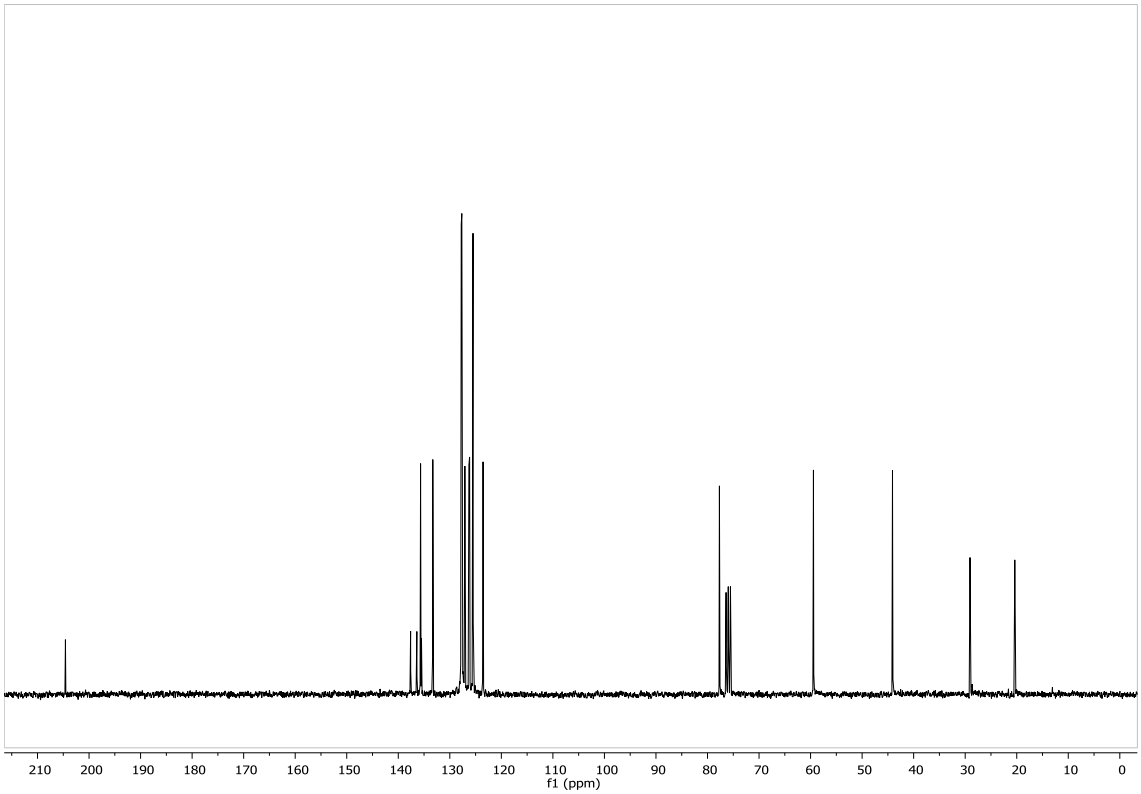

OMe
O
NO2
32Ab
Ph
5.03
2.03
1.88
0.92
1.06
1.05
1.00
2.30
1.09
3.07
1.13
2.81
f1 (ppm)

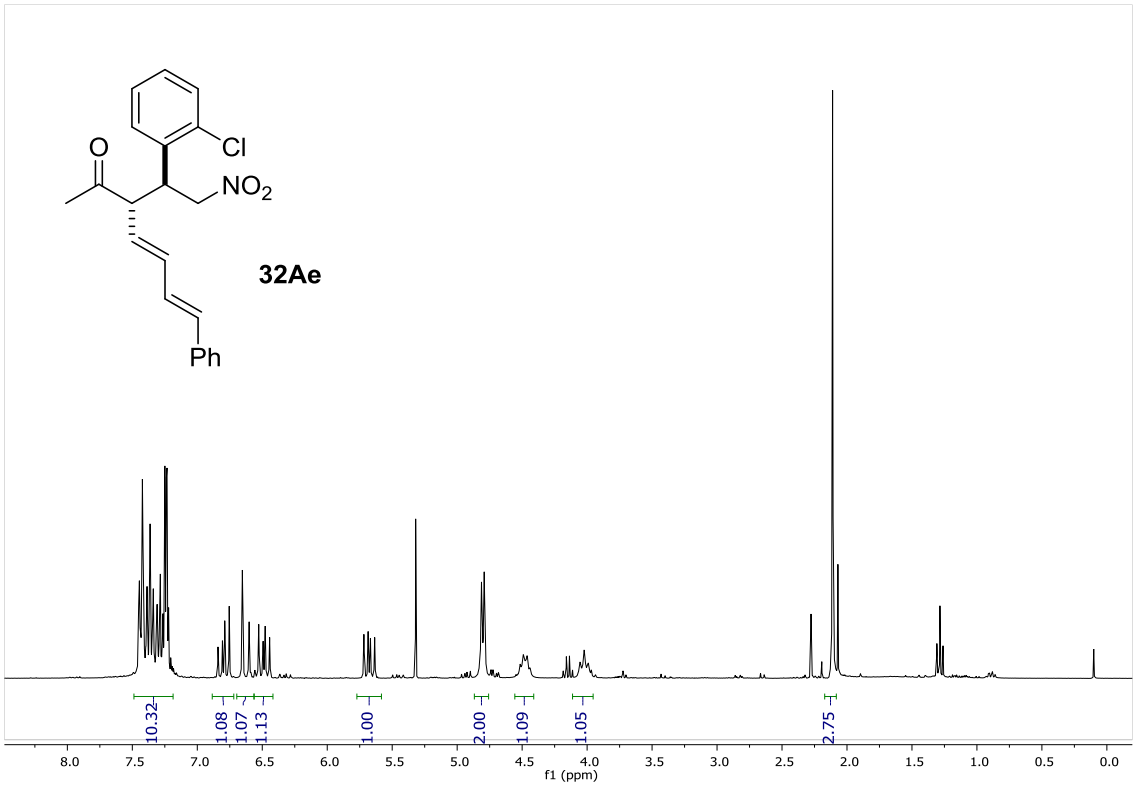

f1 (ppm)

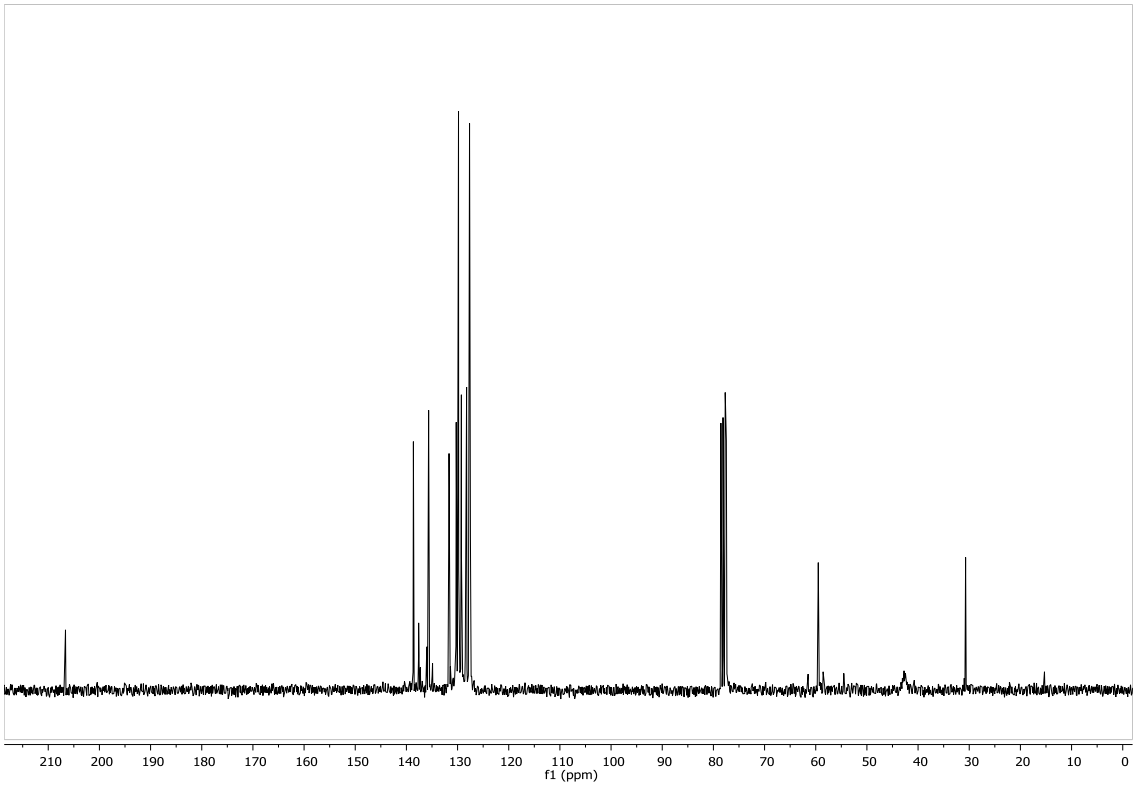

Cl
O
NO2
Ph
32Ak
9.46
1.08
1.07
1.03
1.00
2.17
1.05
1.08
2.92
f1 (ppm)

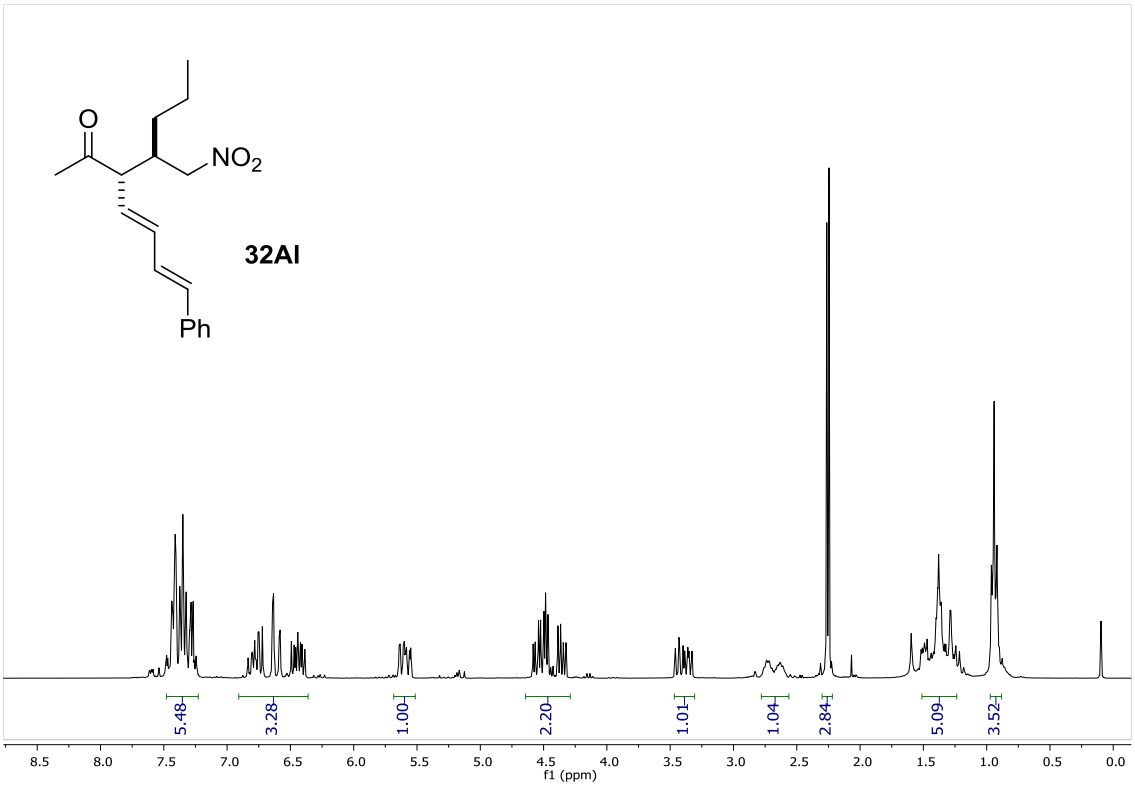

f1 (ppm)

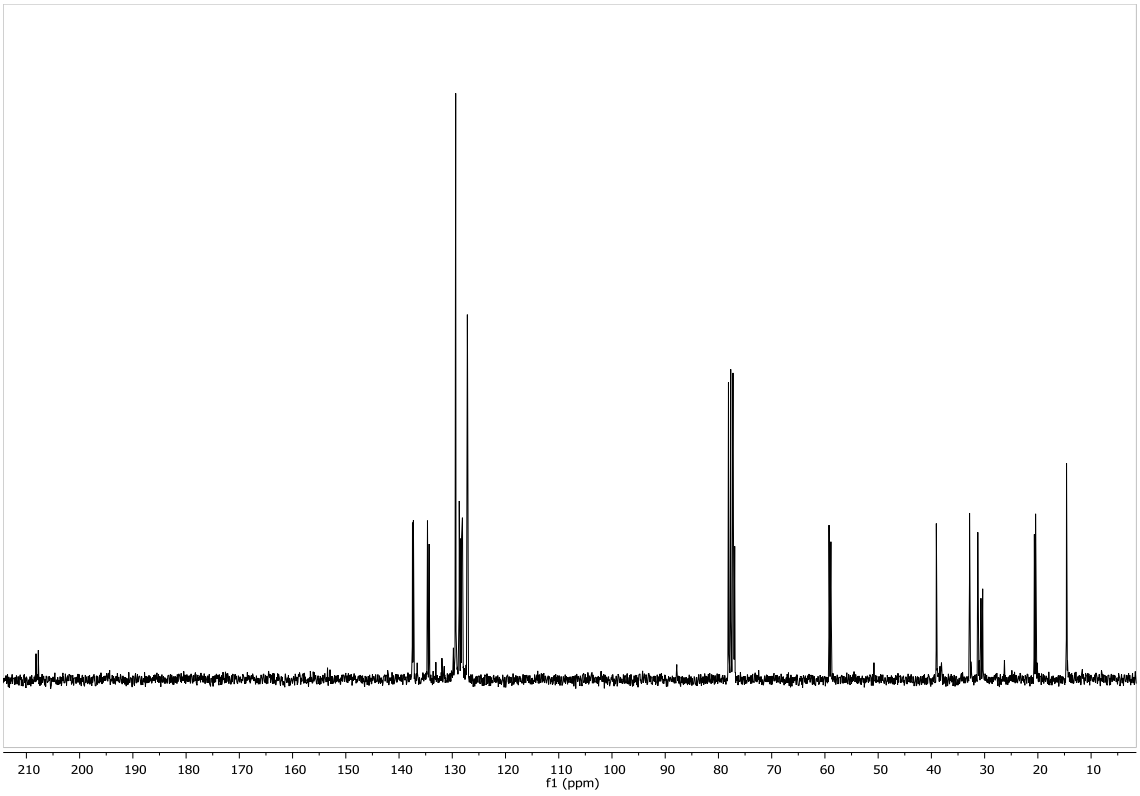

O
NO2
Ph
32Ad
9.40
3.19
1.00
2.22
1.07
1.11
2.94
2.71
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

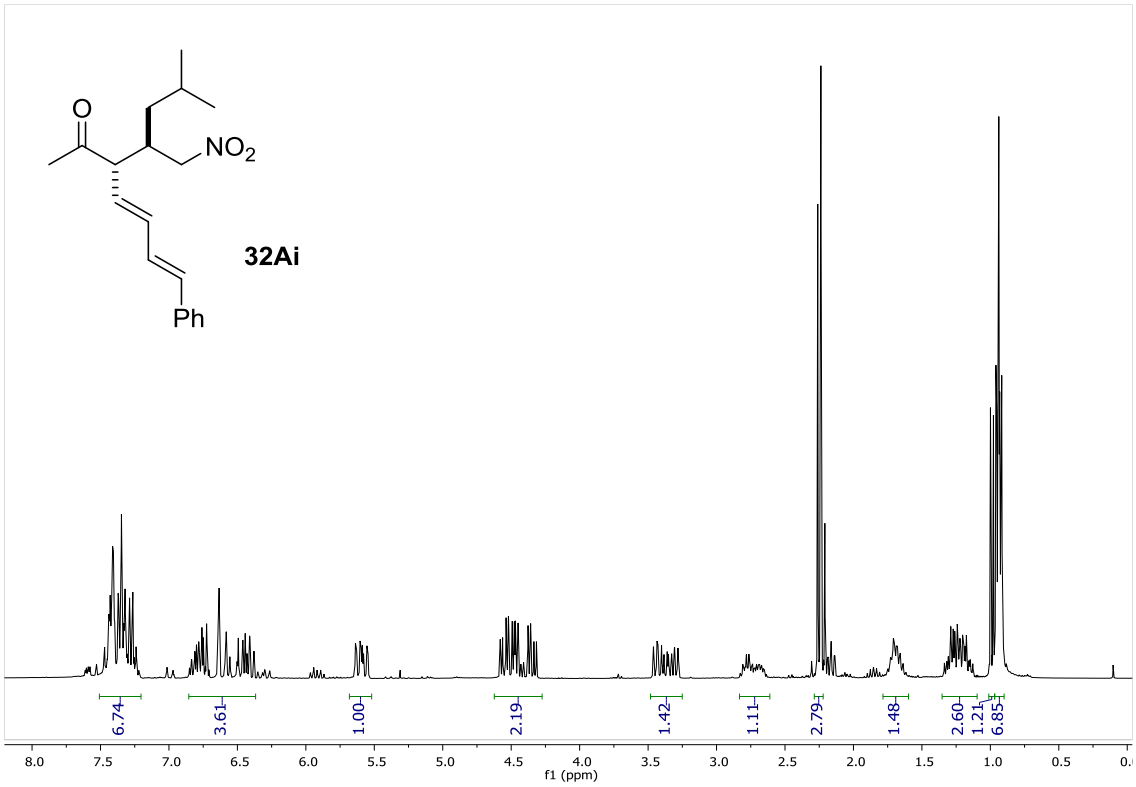

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

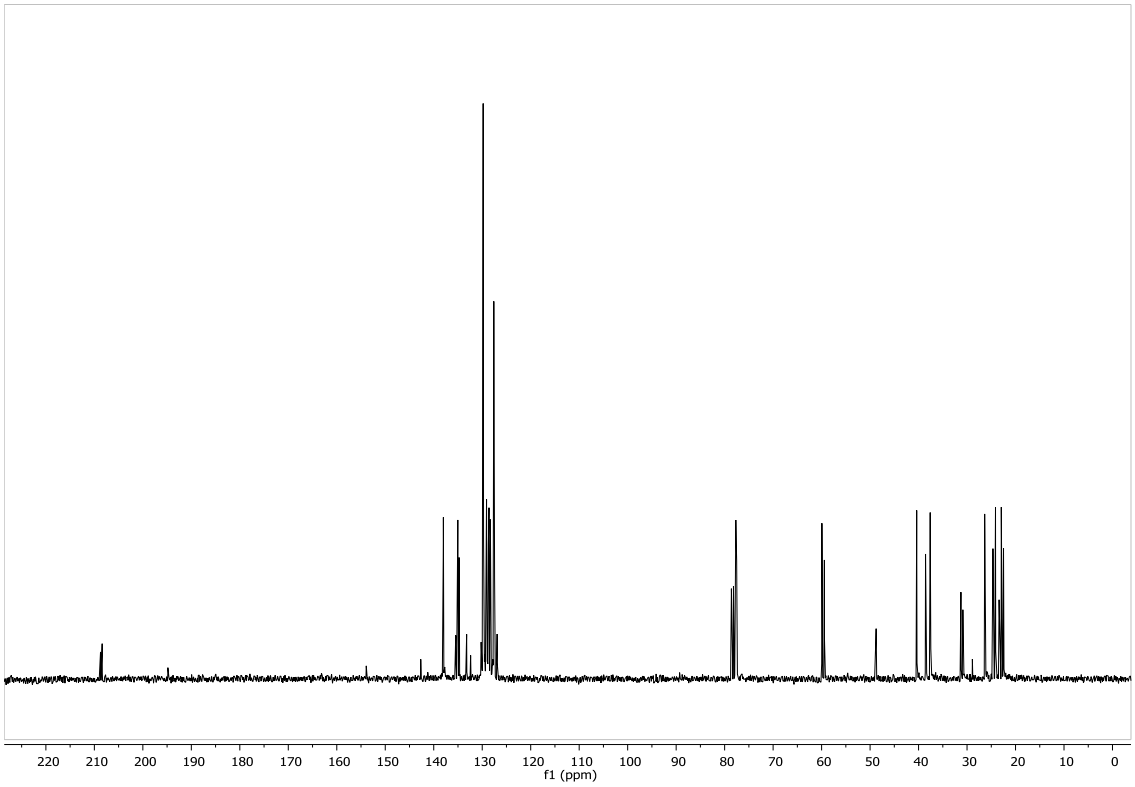

O
Cl
NO2
Ph
32Ae
10.32
1.08
1.07
1.13
1.00
2.00
1.09
1.05
2.75
f1 (ppm)

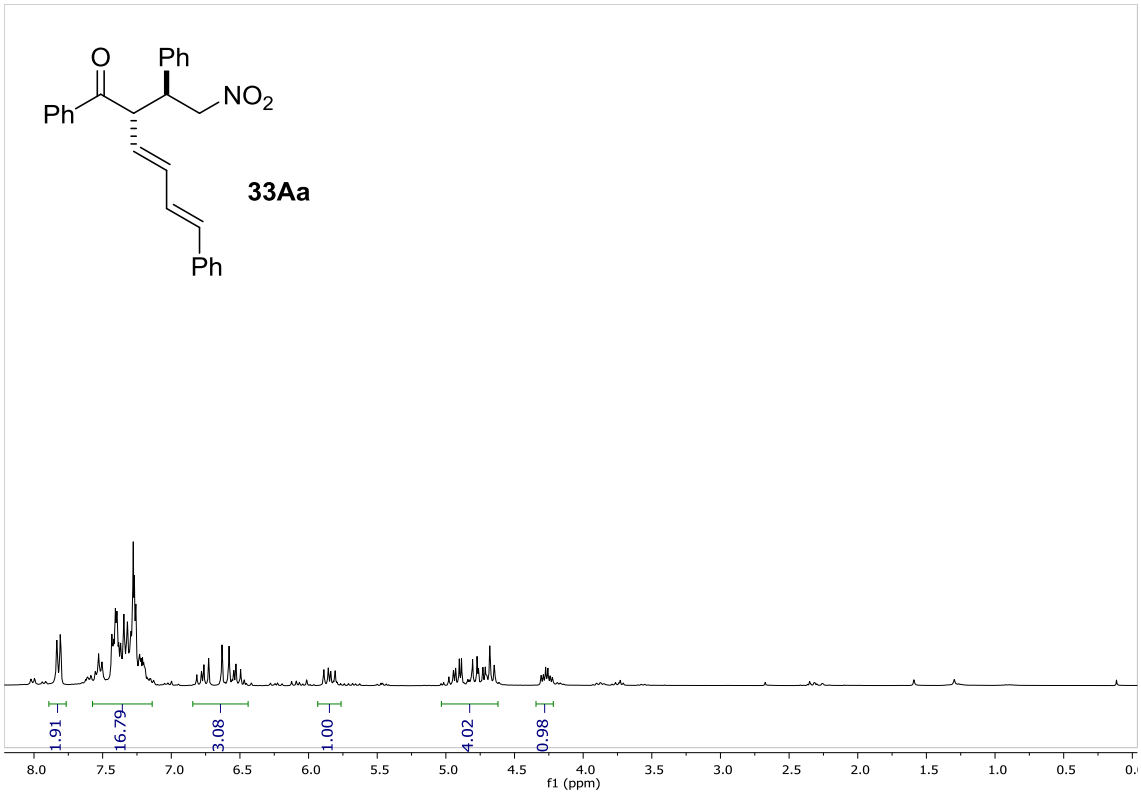

f1 (ppm)

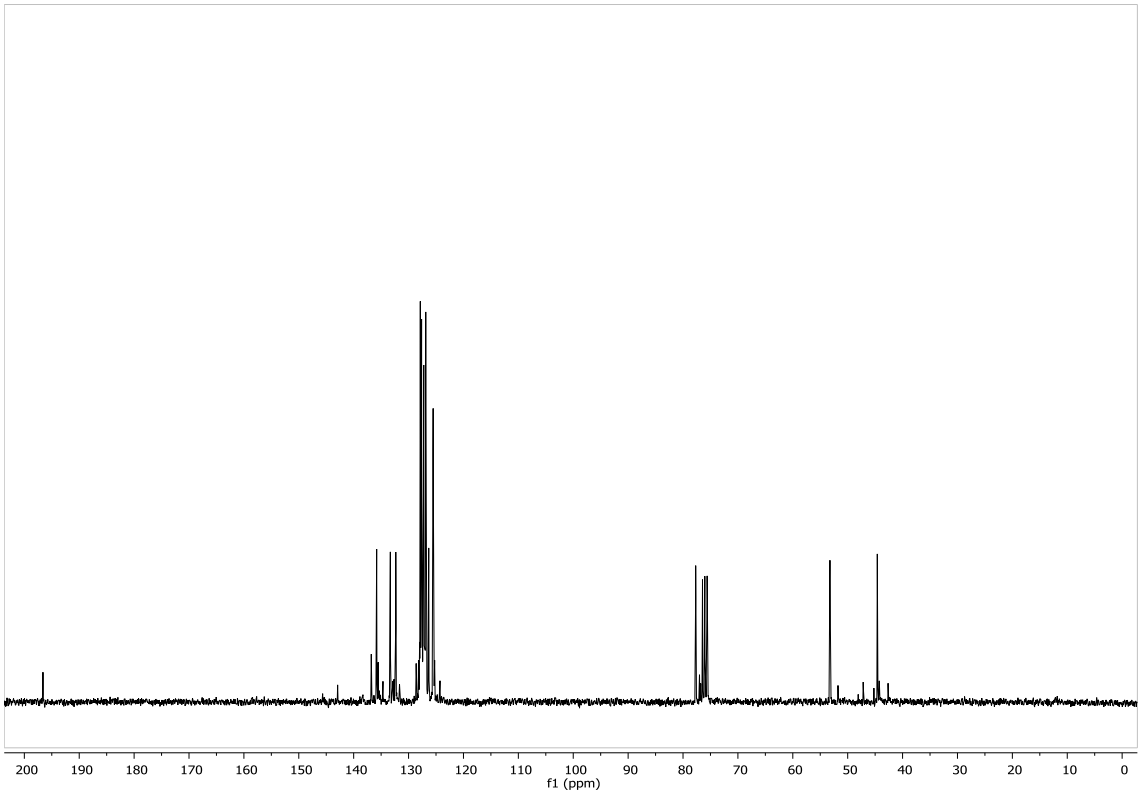

O
NO2
32AI
Ph
5.48
3.28
1.00
2.20
1.01
1.04
2.84
5.09
3.52
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

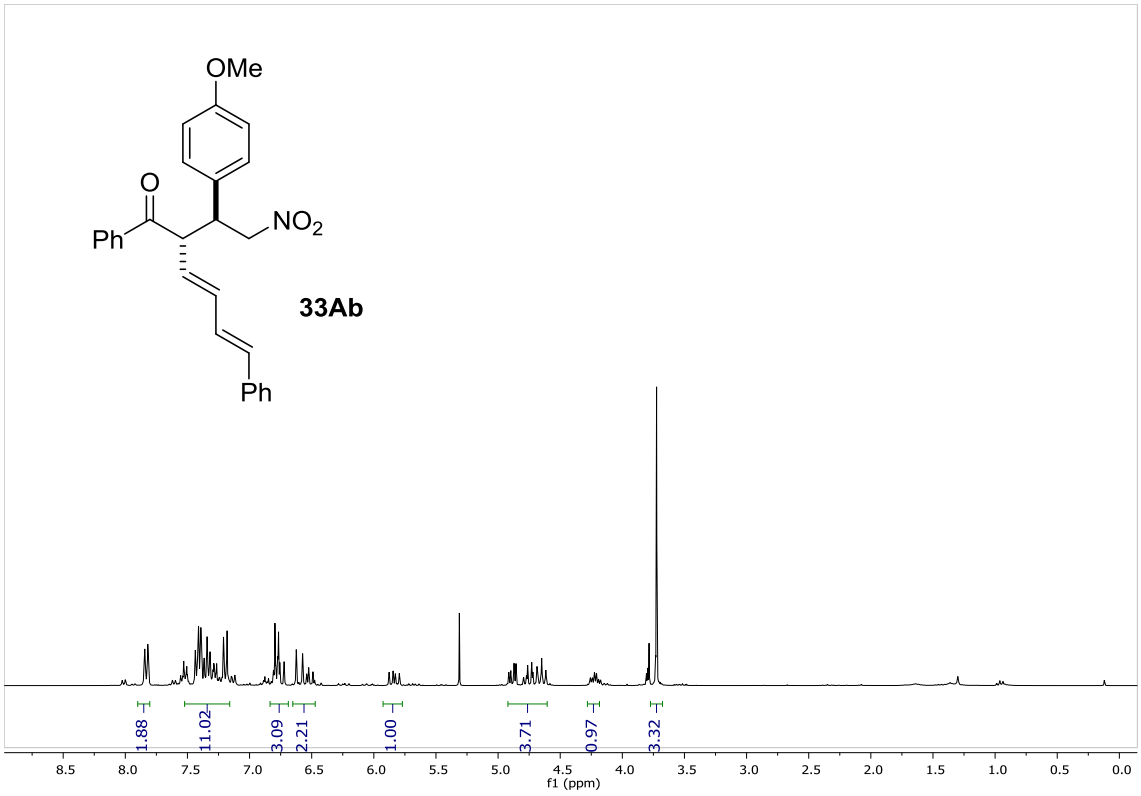

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

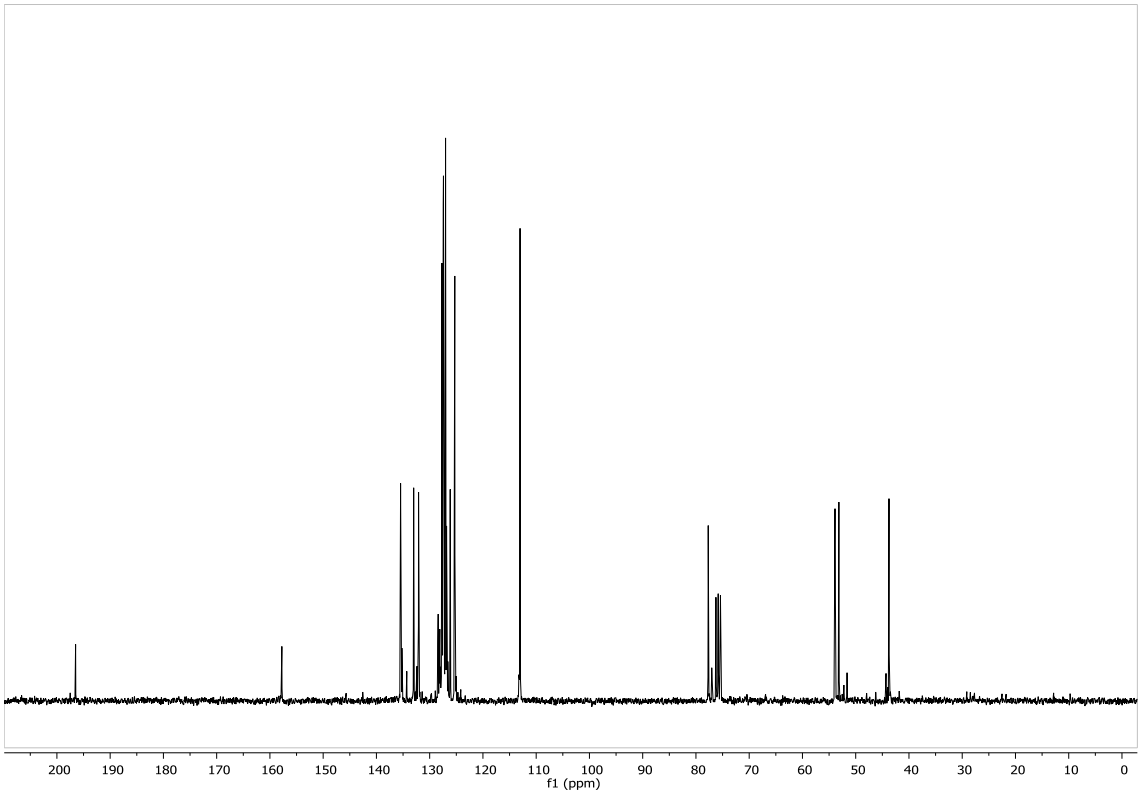

O
NO2
32Ai
Ph
6.74
3.61
1.00
2.19
1.42
1.11
2.79
1.48
2.60
1.21
6.85
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

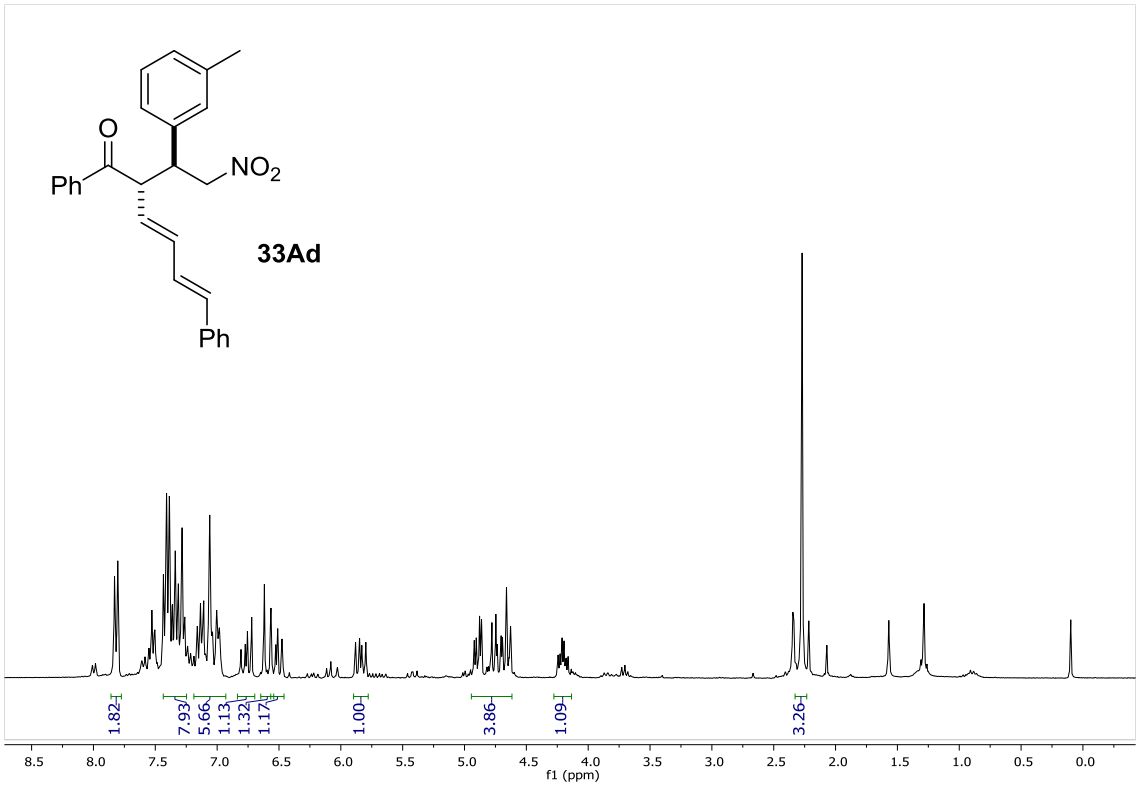

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

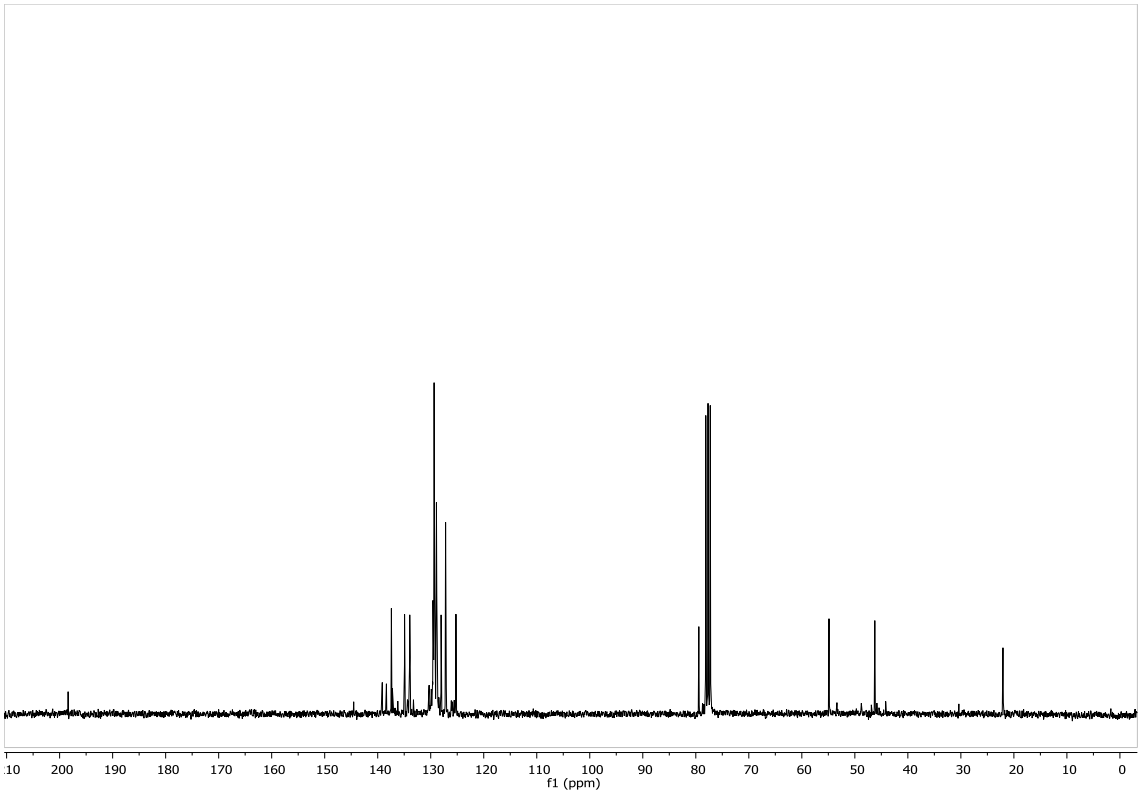

O
Ph
Ph
NO2
33Aa
Ph
1.91
16.79
3.08
1.00
4.02
0.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

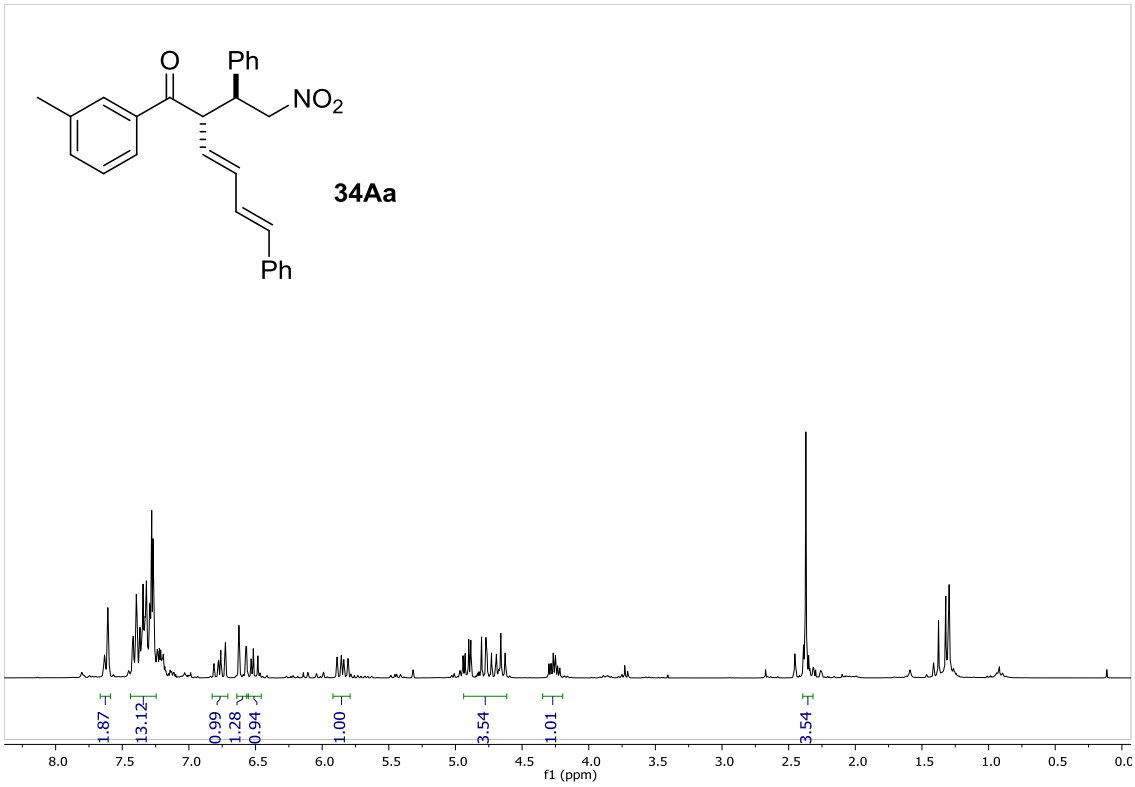

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

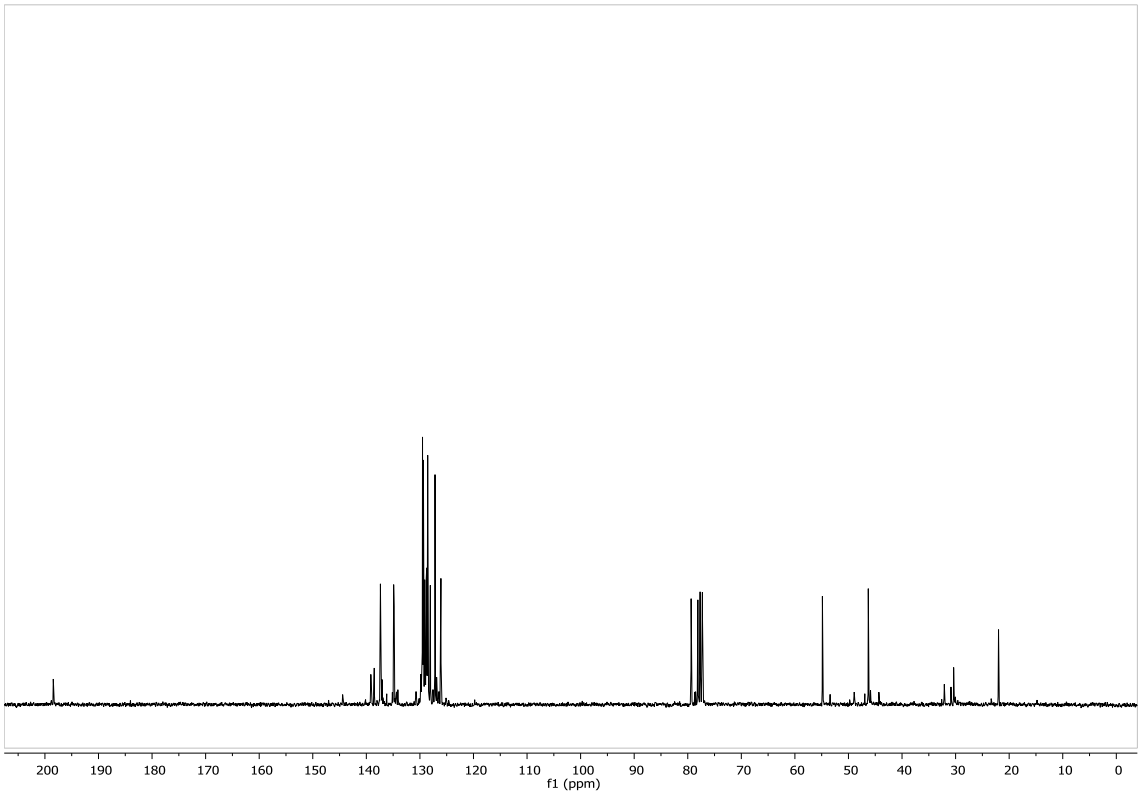

OMe
O
Ph
NO2
33Ab
Ph
1.88
11.02
3.09
2.21
1.00
3.71
0.97
3.32
f1 (ppm)

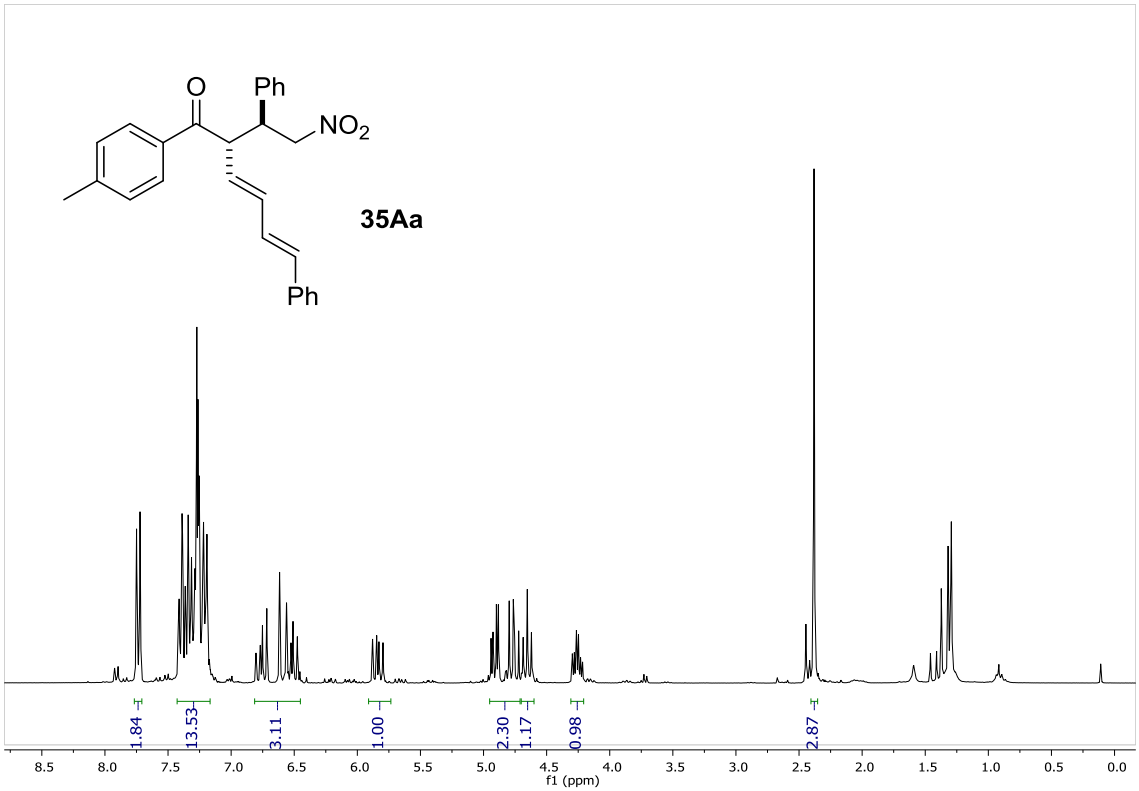

f1 (ppm)

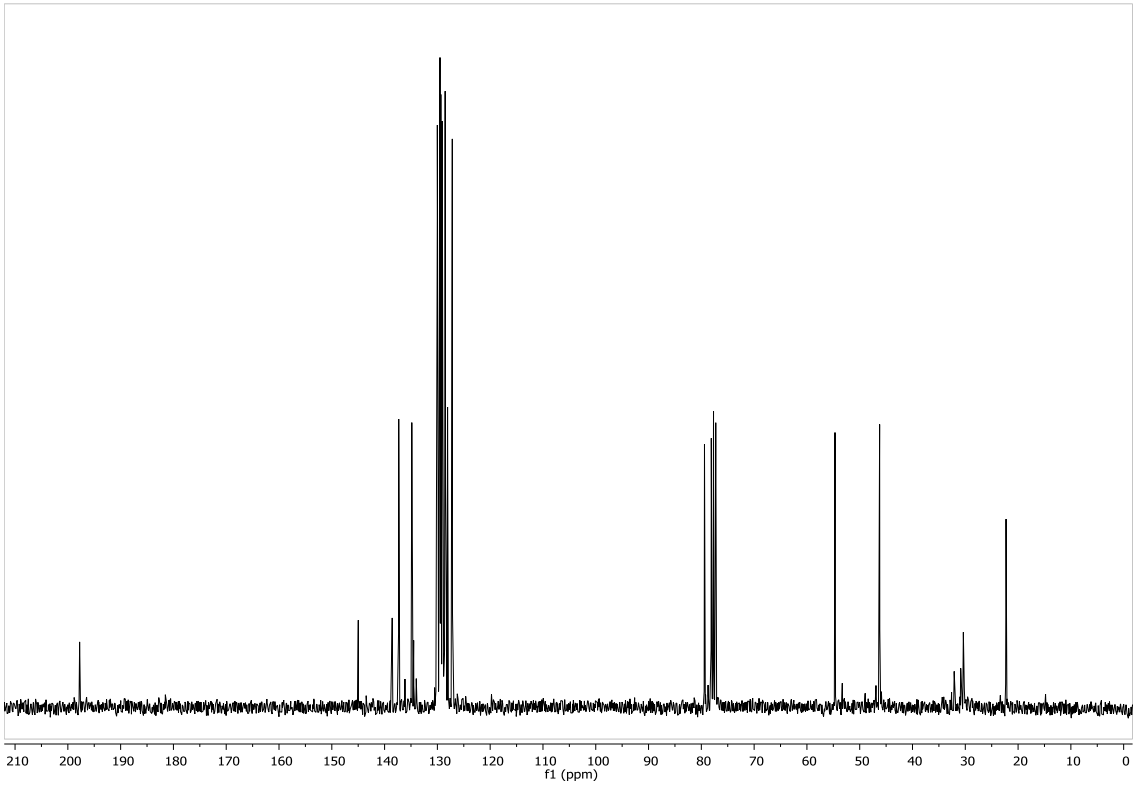

O
Ph
NO2
33Ad
Ph
1.82
7.93
5.66
1.13
1.32
1.17
1.00
3.86
1.09
3.26
f1 (ppm)

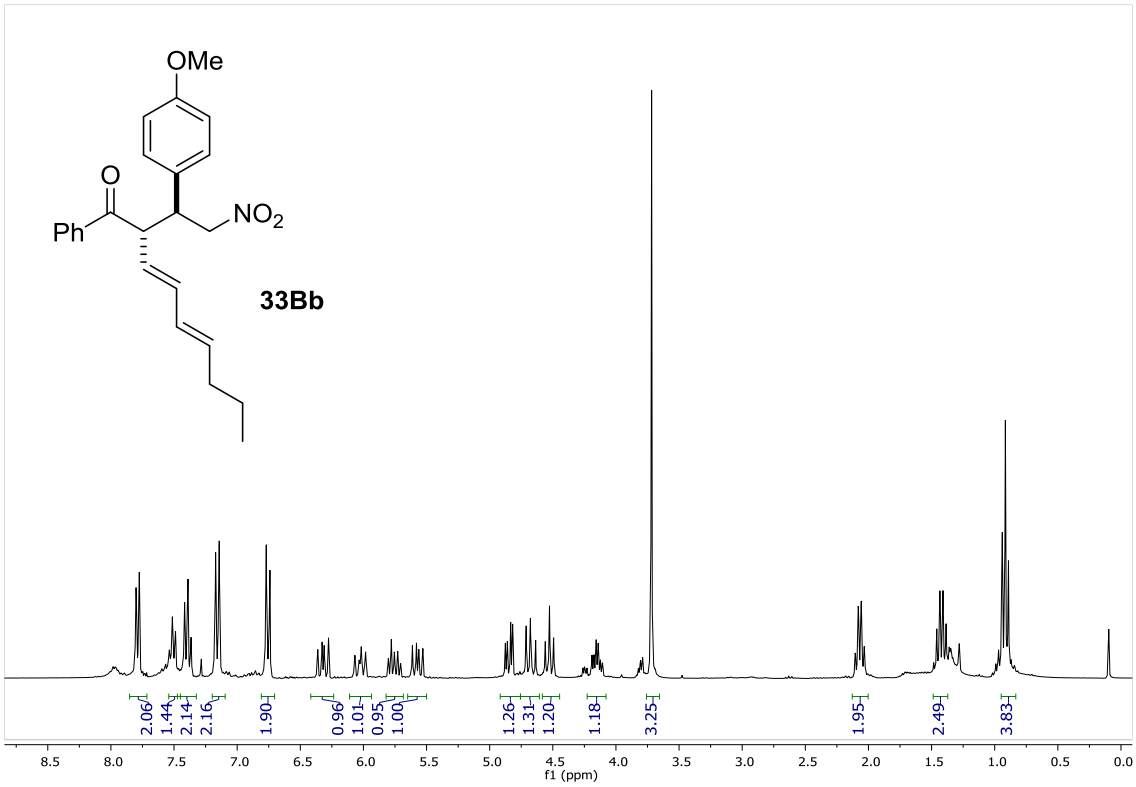

f1 (ppm)

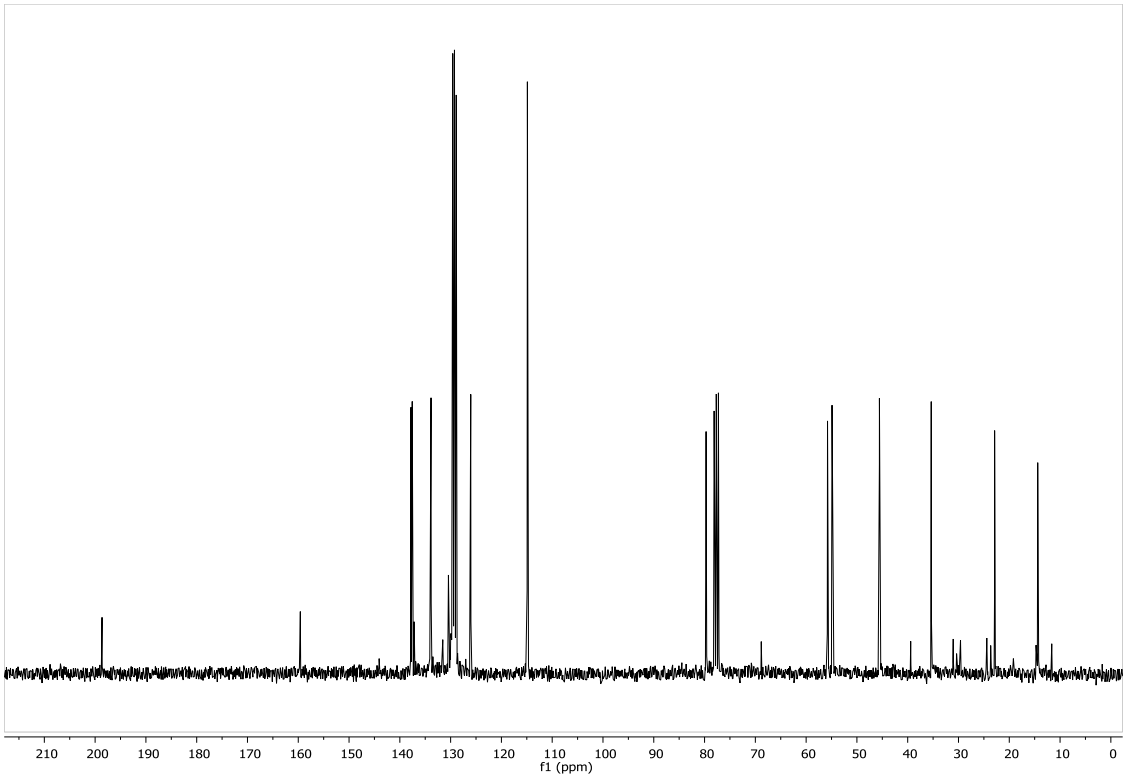

O
Ph
NO2
34Aa
Ph
1.87
13.12
0.99
1.28
0.94
1.00
3.54
1.01
3.54
f1 (ppm)

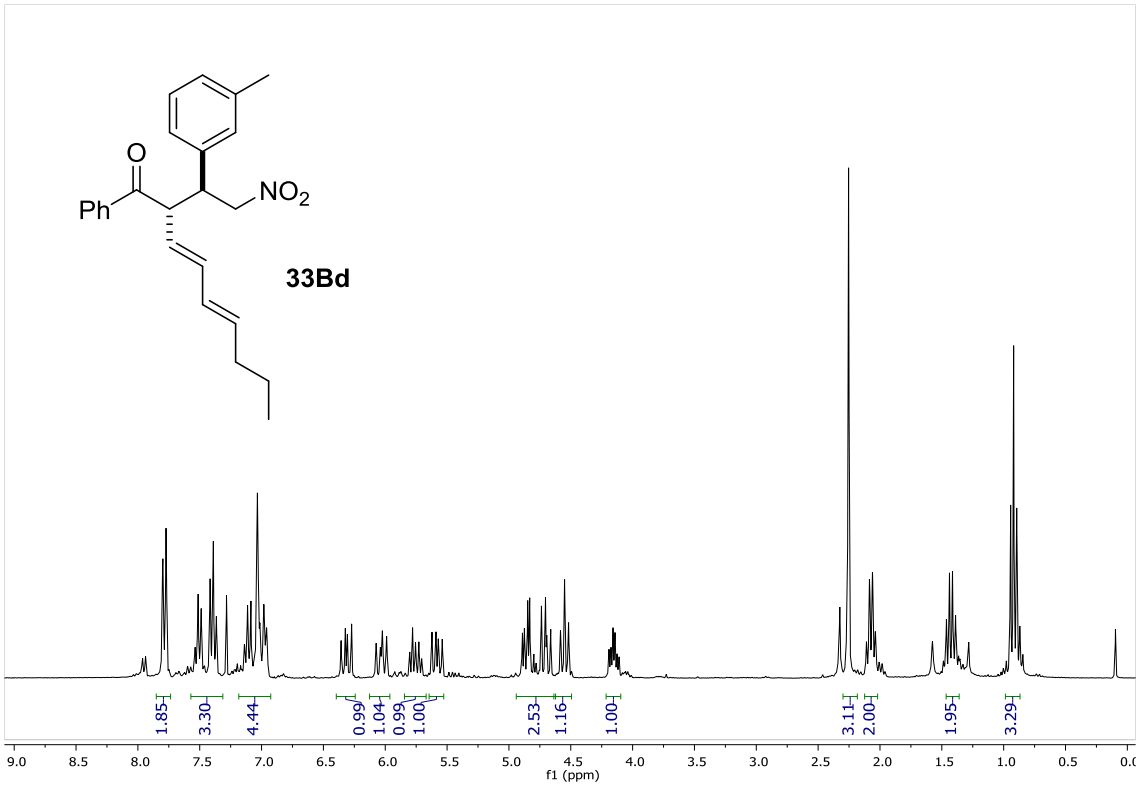

f1 (ppm)

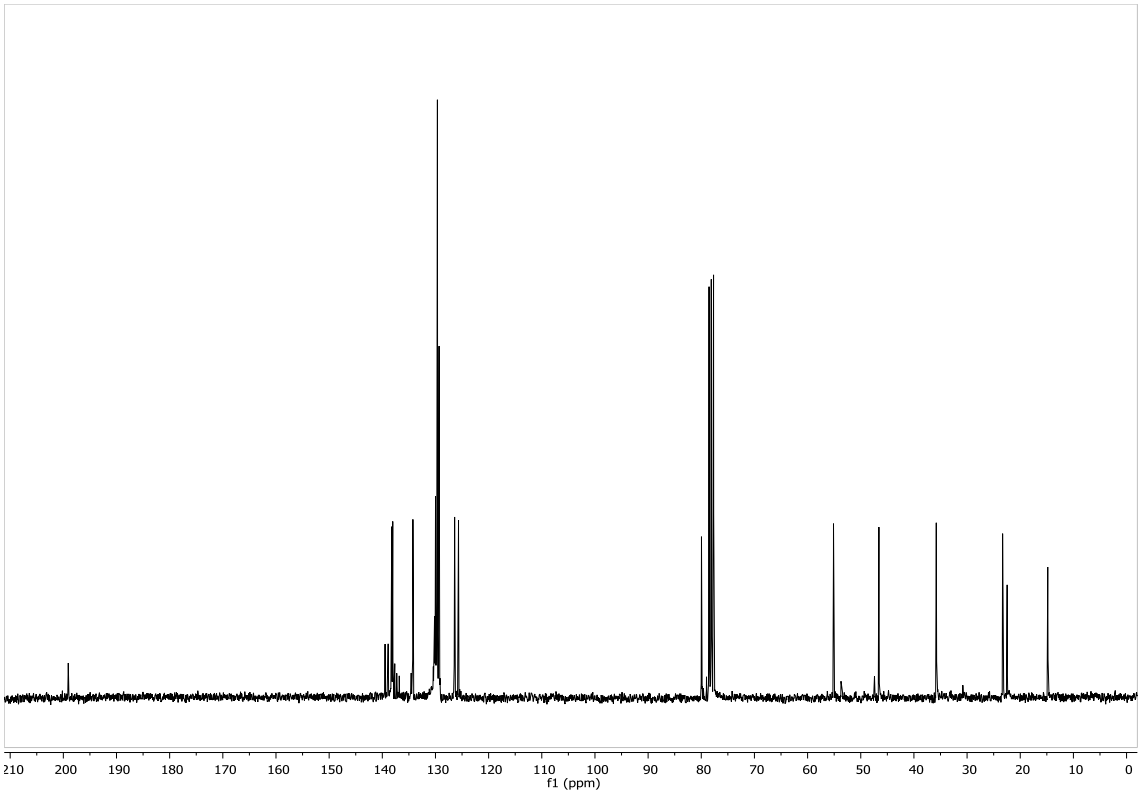

O
Ph
NO2
35Aa
Ph
1.84
13.53
3.11
1.00
2.30
1.17
0.98
2.87
f1 (ppm)

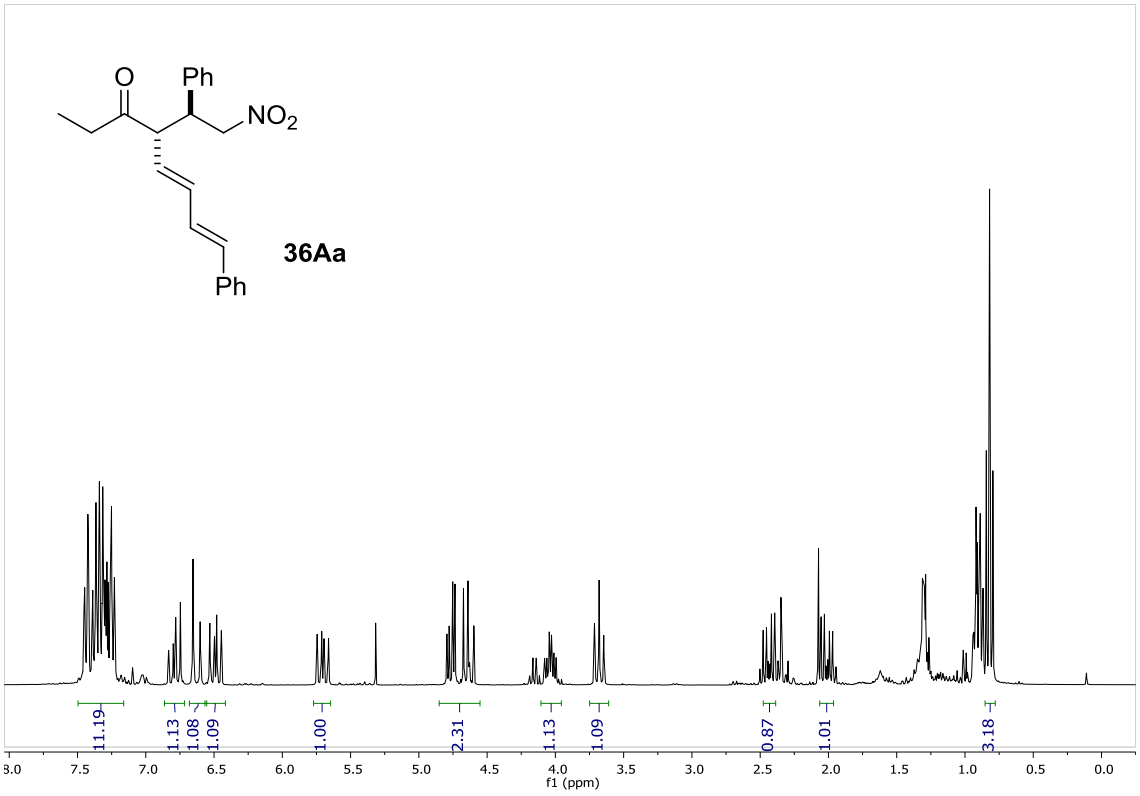

f1 (ppm)

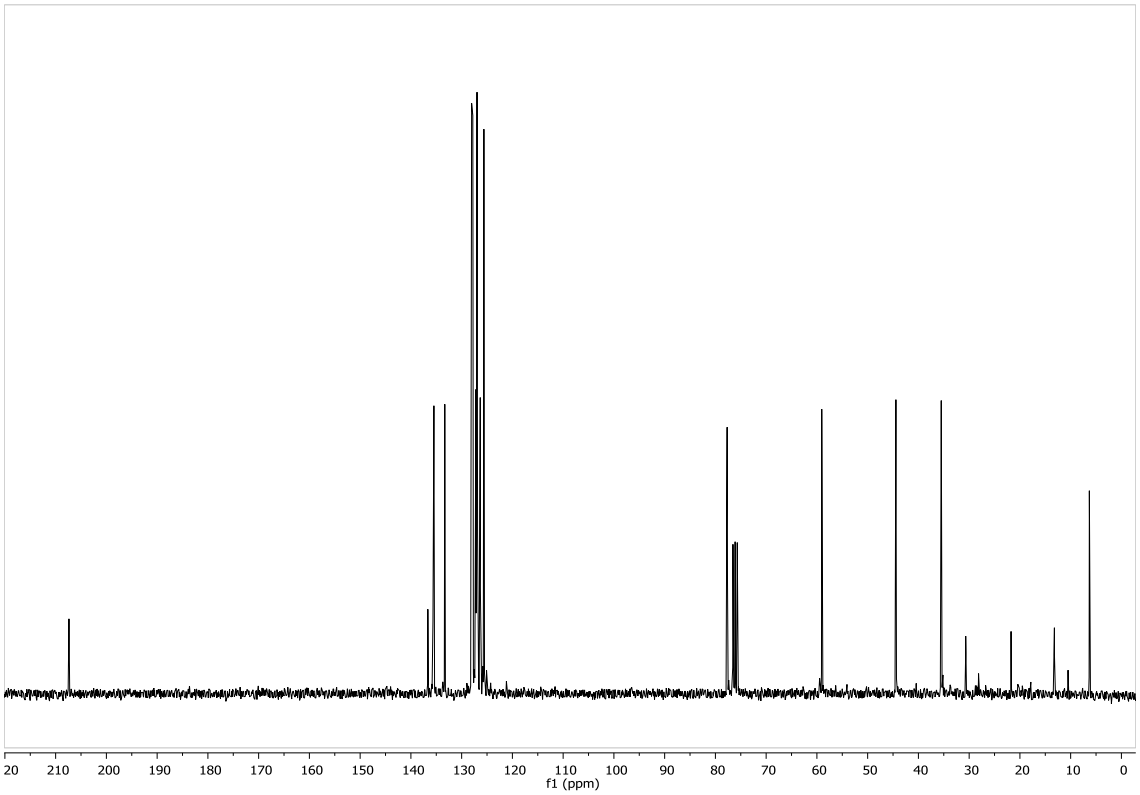

OMe
O
Ph
NO2
33Bb
2.06
1.44
2.14
2.16
1.90
0.96
1.01
0.95
1.00
1.26
1.31
1.20
1.18
3.25
1.95
2.49
3.83
f1 (ppm)

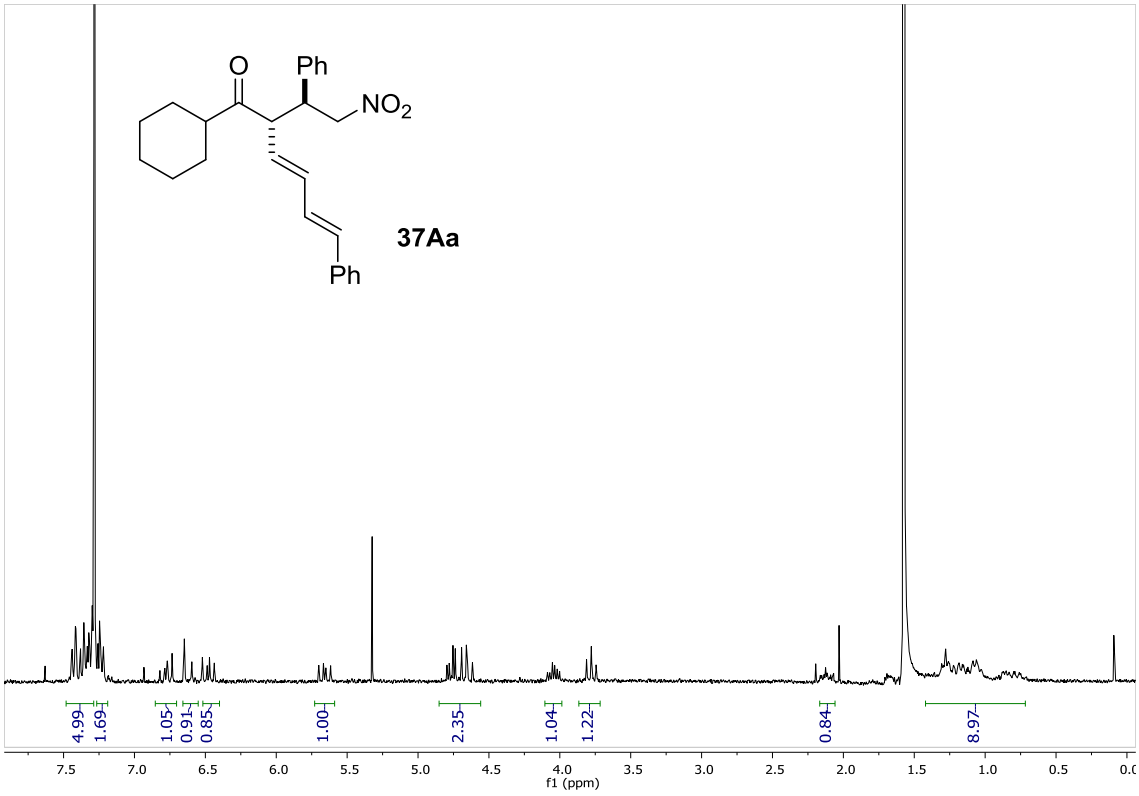

f1 (ppm)

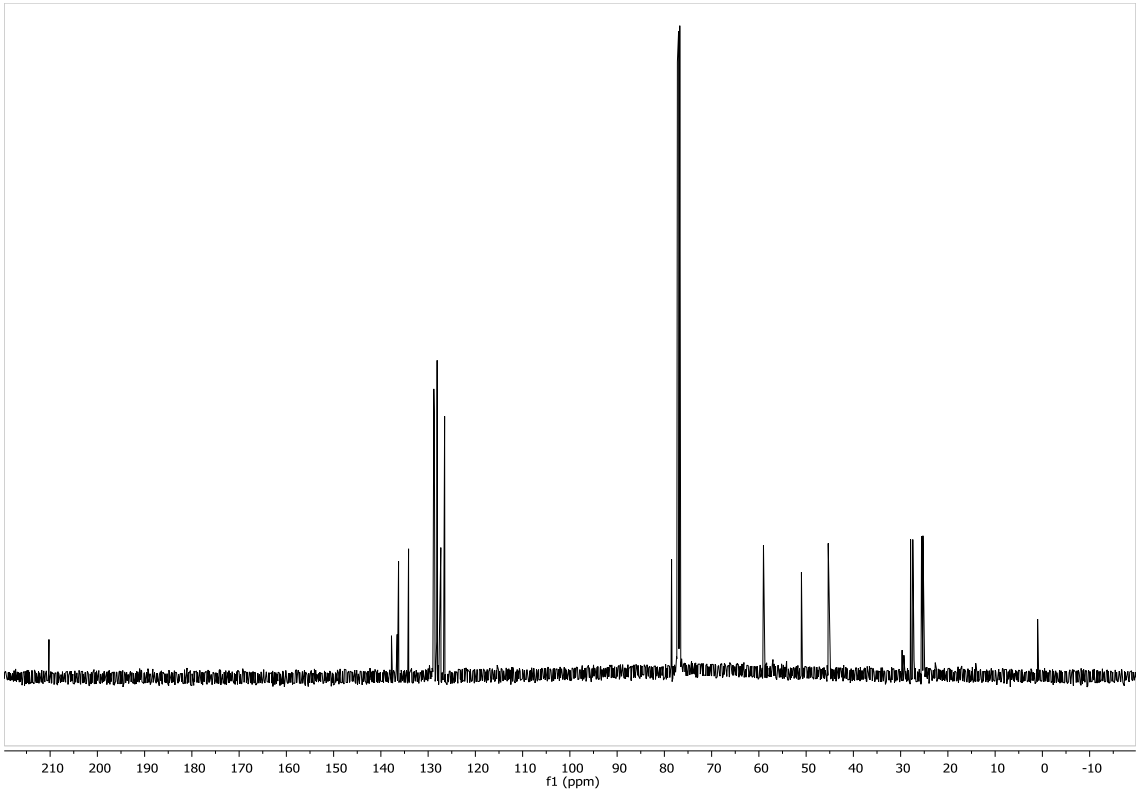

O
Ph
NO2
33Bd
1.85
3.30
4.44
0.99
1.04
0.99
1.00
2.53
1.16
1.00
3.11
2.00
1.95
3.29
f1 (ppm)

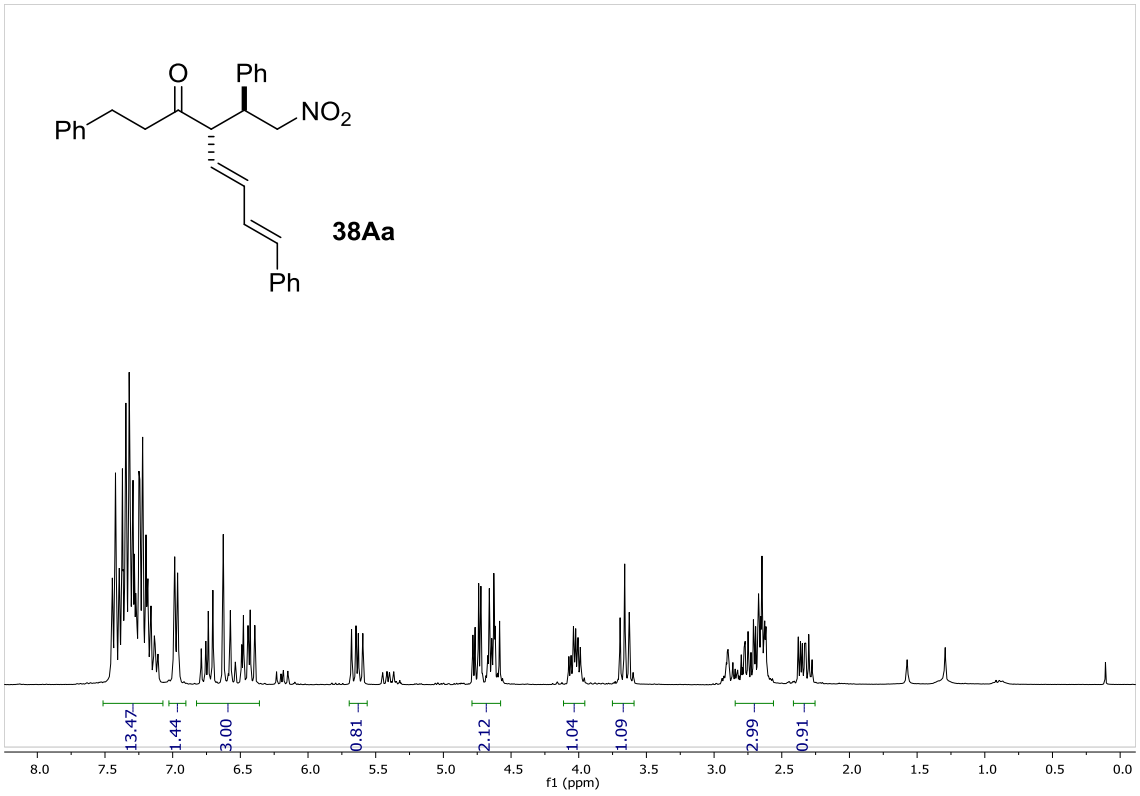

f1 (ppm)

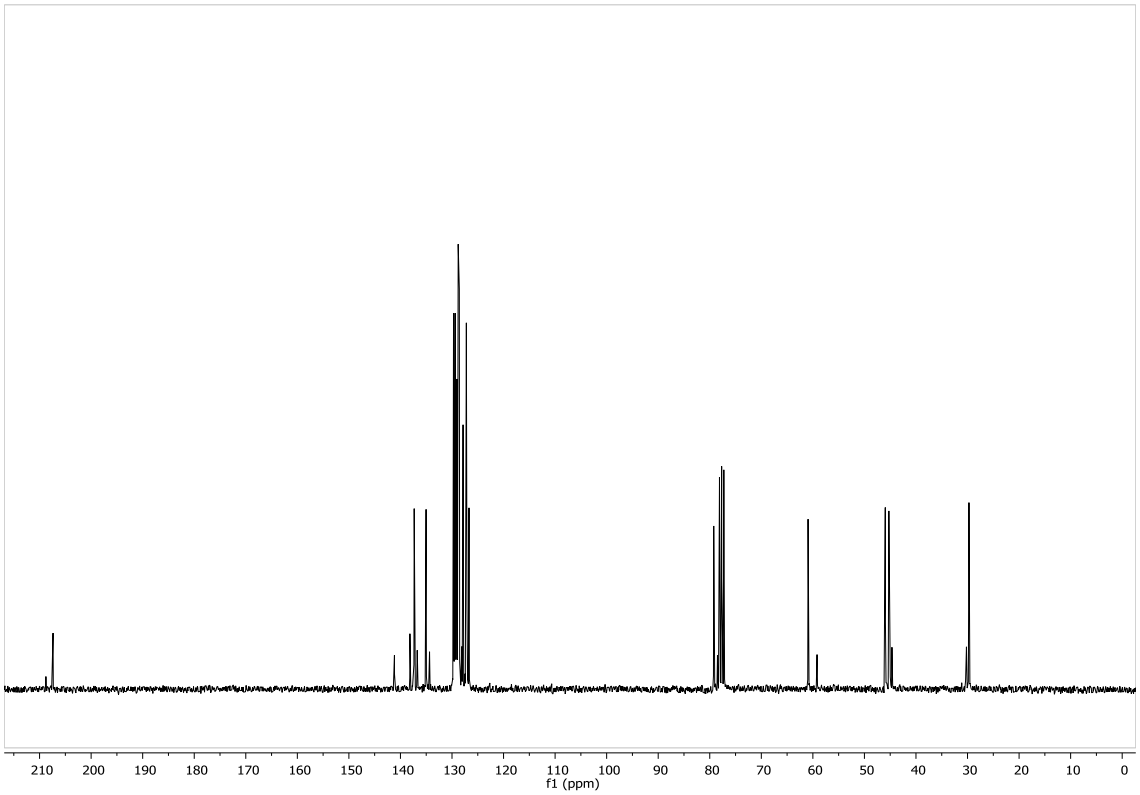

O
Ph
NO2
Ph
36Aa
11.19
1.13
1.08
1.09
1.00
2.31
1.13
1.09
0.87
1.01
3.18
f1 (ppm)

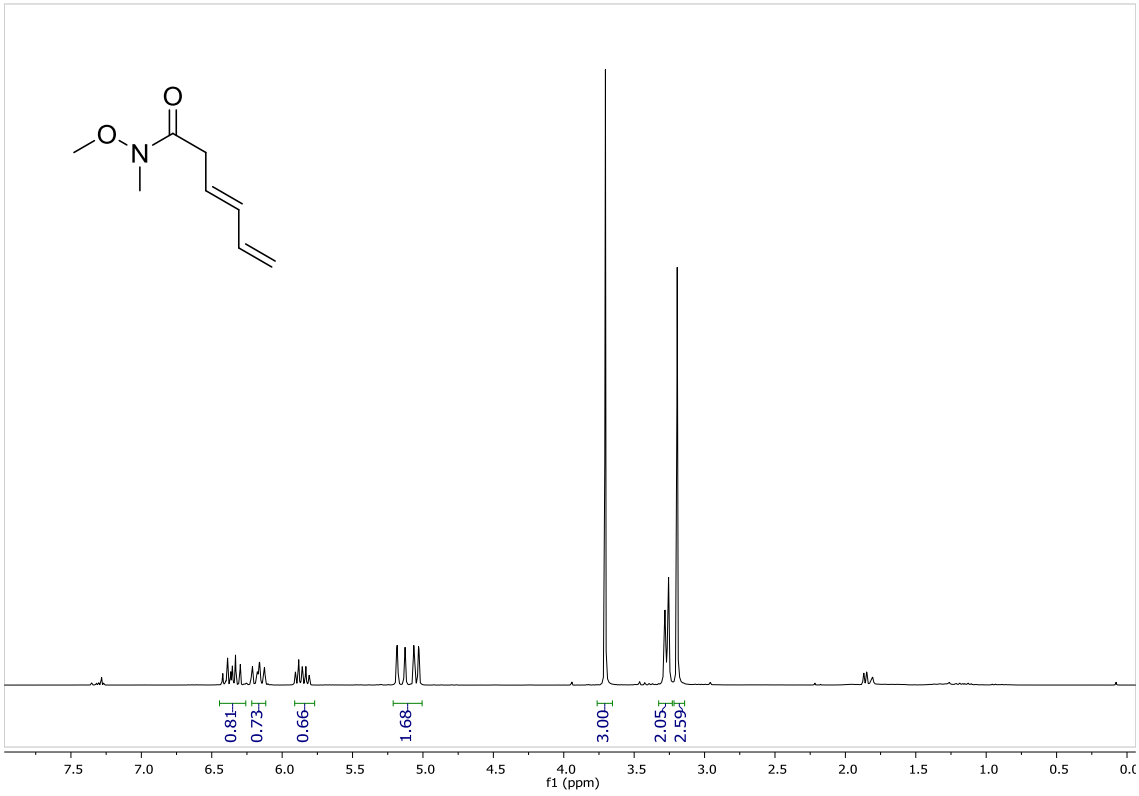

f1 (ppm)

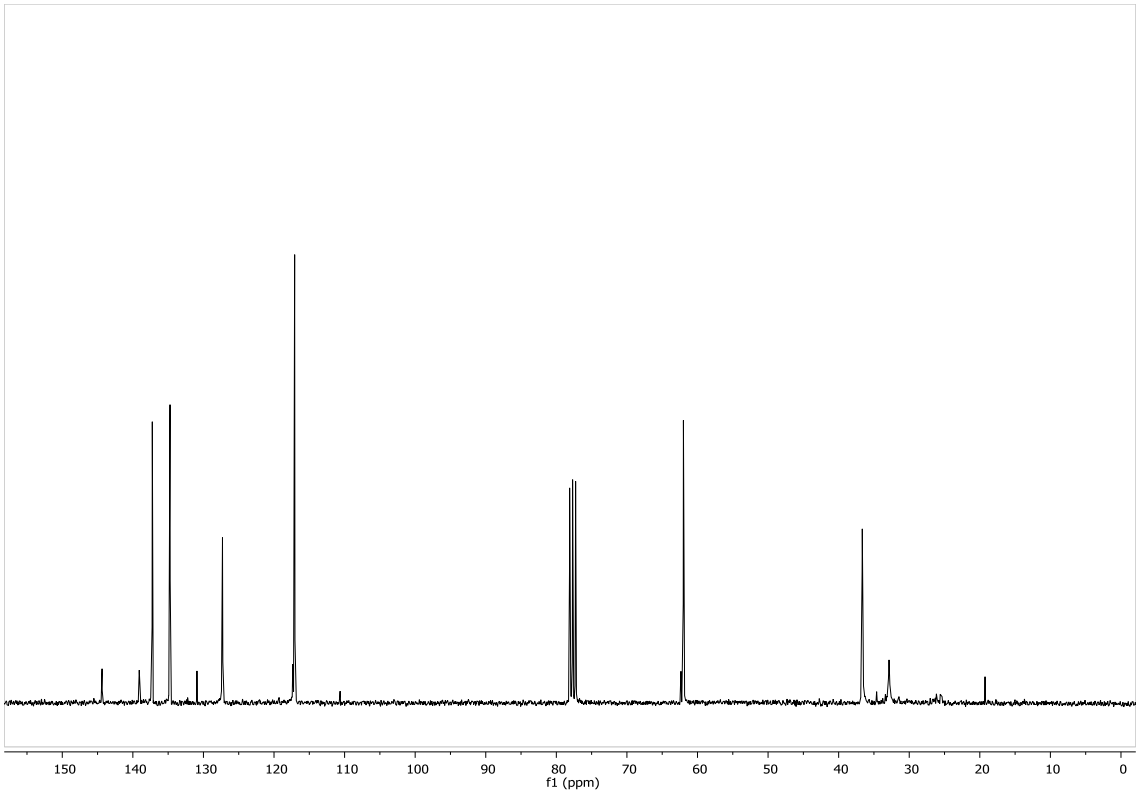

O
Ph
NO2
37Aa
Ph
4.99
1.69
1.05
0.91
0.85
1.00
2.35
1.04
1.22
0.84
8.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

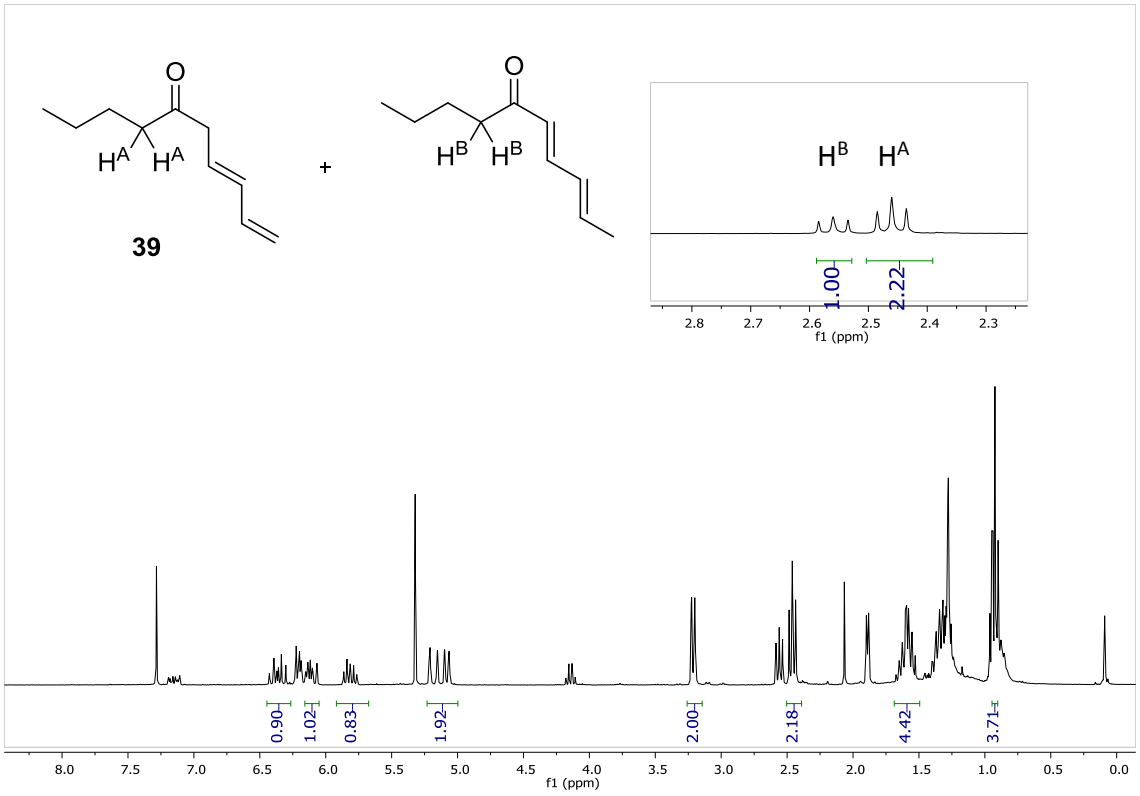

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

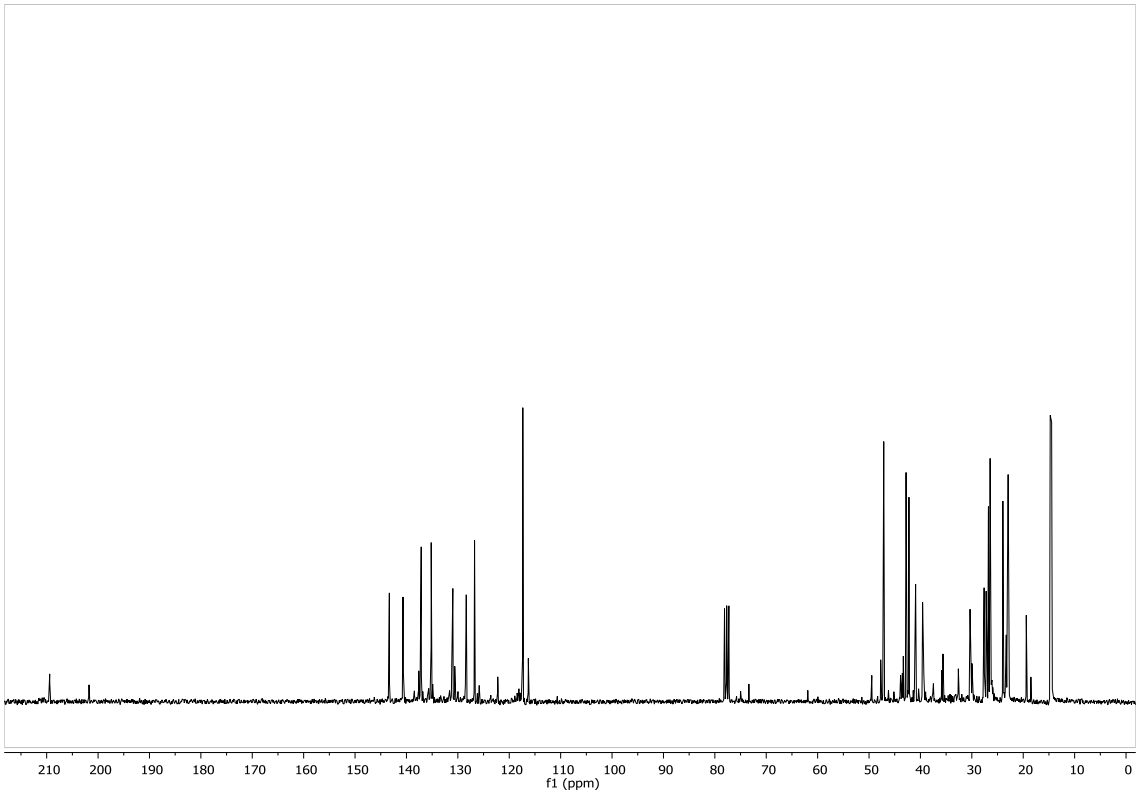

O
Ph
Ph
NO2
38Aa
Ph
13.47
1.44
3.00
0.81
2.12
1.04
1.09
2.99
0.91
f1 (ppm)

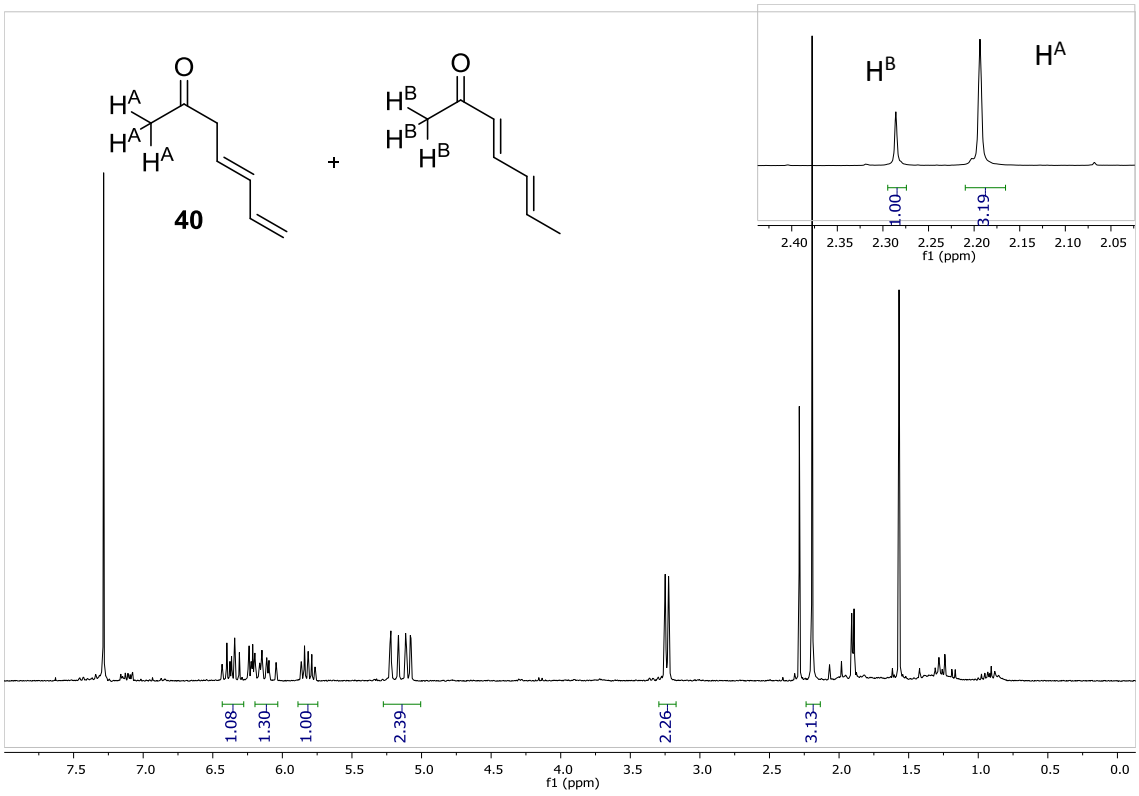

f1 (ppm)

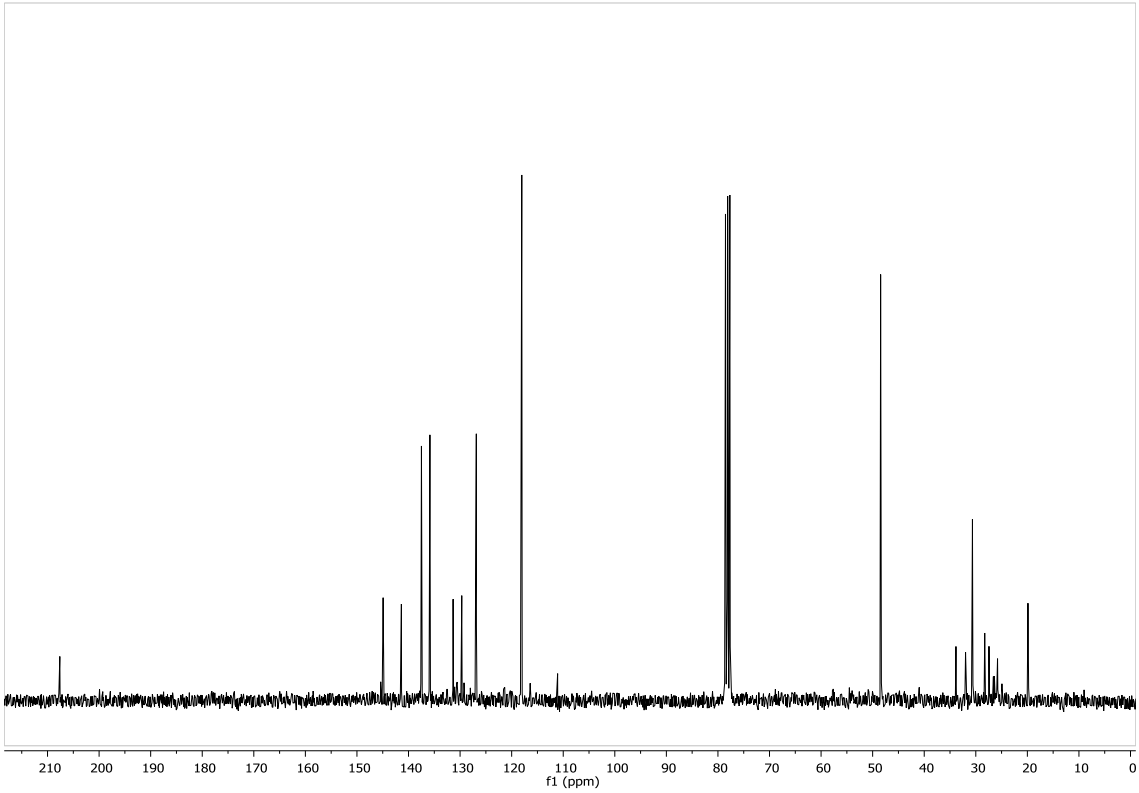

O
O
N
0.81
0.73
0.66
1.68
3.00
2.05
2.59
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

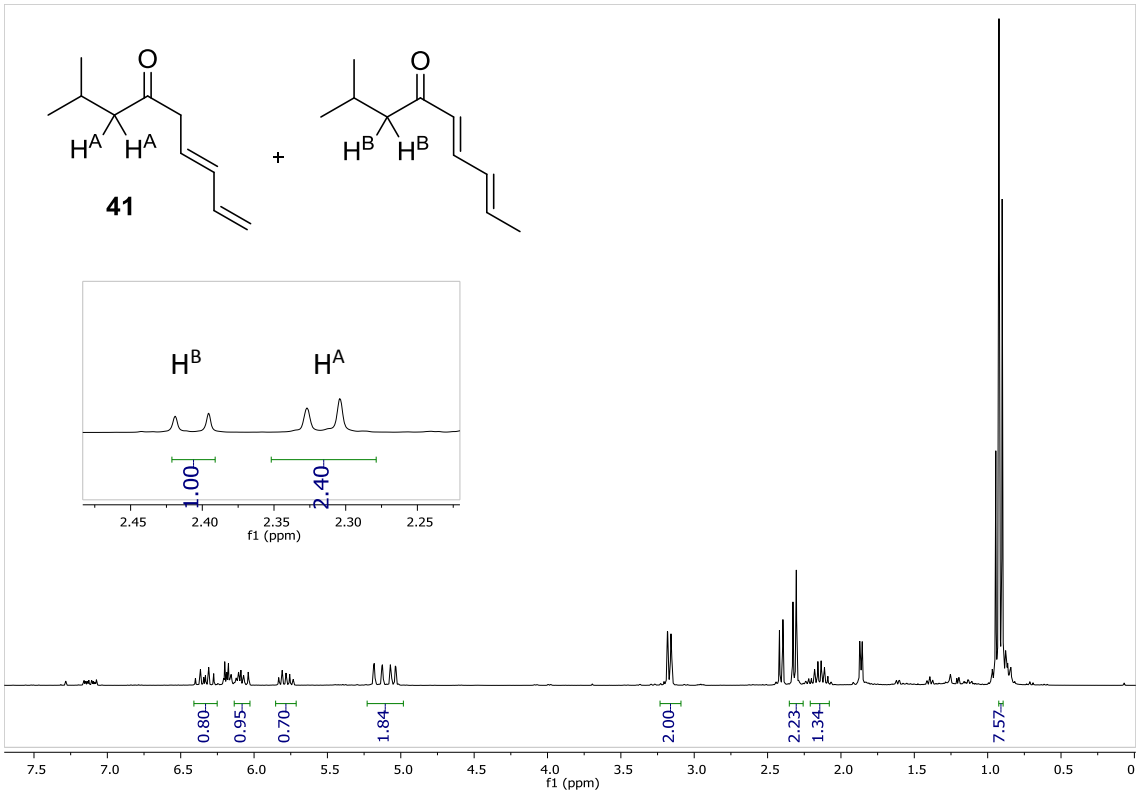

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

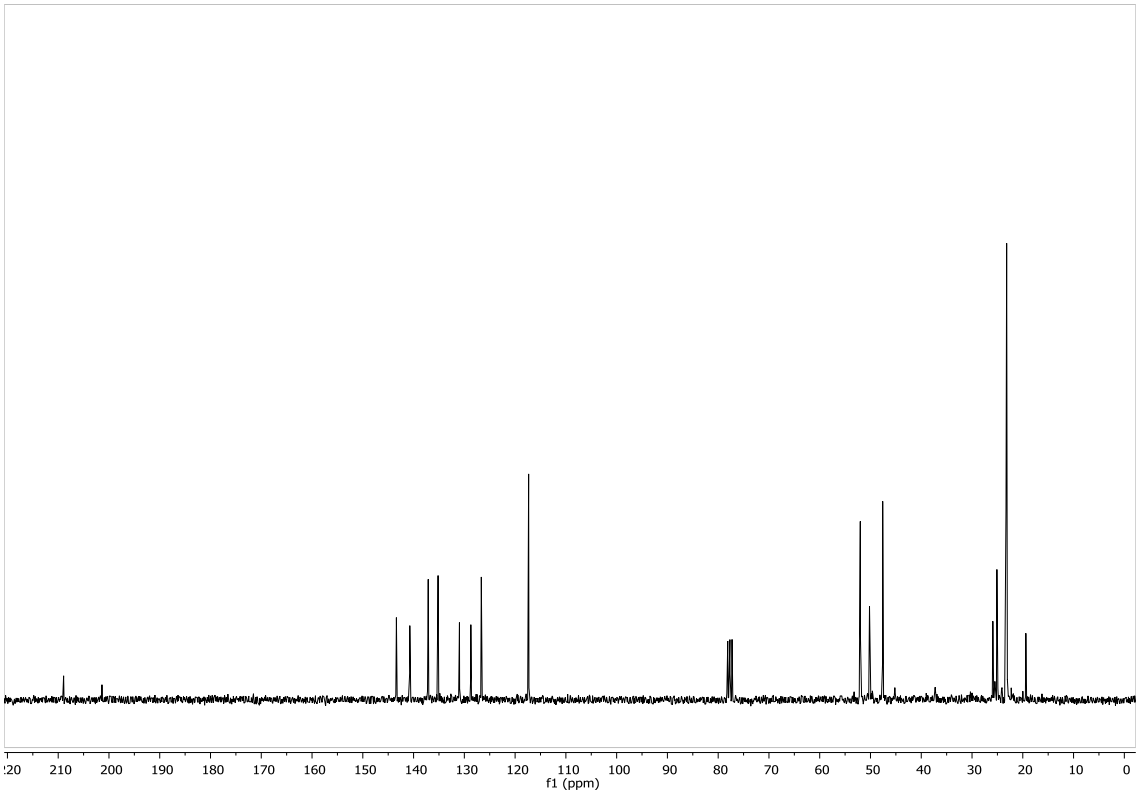

O
H^A H^A
39
+
O
H^B H^B
H^B H^A
1.00
2.22
2.8 2.7 2.6 2.5 2.4 2.3
f1 (ppm)
0.90
1.02
0.83
1.92
2.00
2.18
4.42
3.71
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

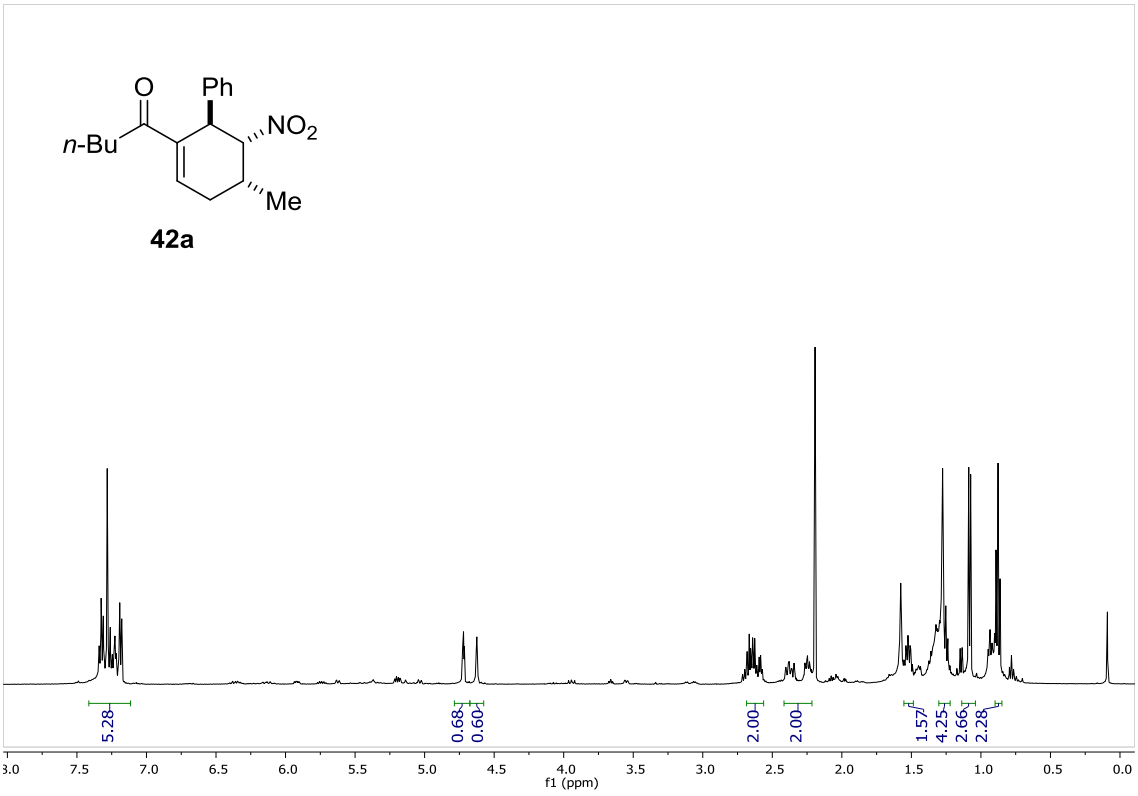

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

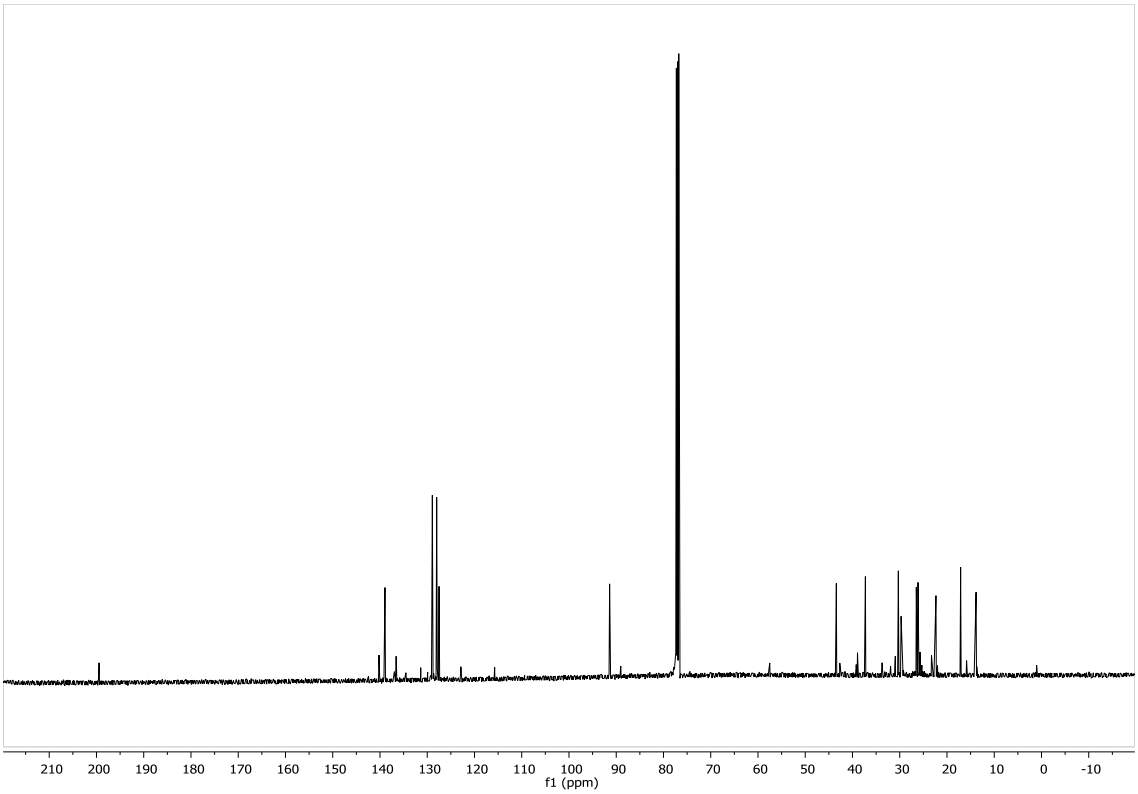

H^A
H^A
H^A
O
40
+
H^B
H^B
H^B
O
H^B
H^A
1.00
3.19
2.40 2.35 2.30 2.25 2.20 2.15 2.10 2.05
f1 (ppm)
1.08
1.30
1.00
2.39
2.26
3.13
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

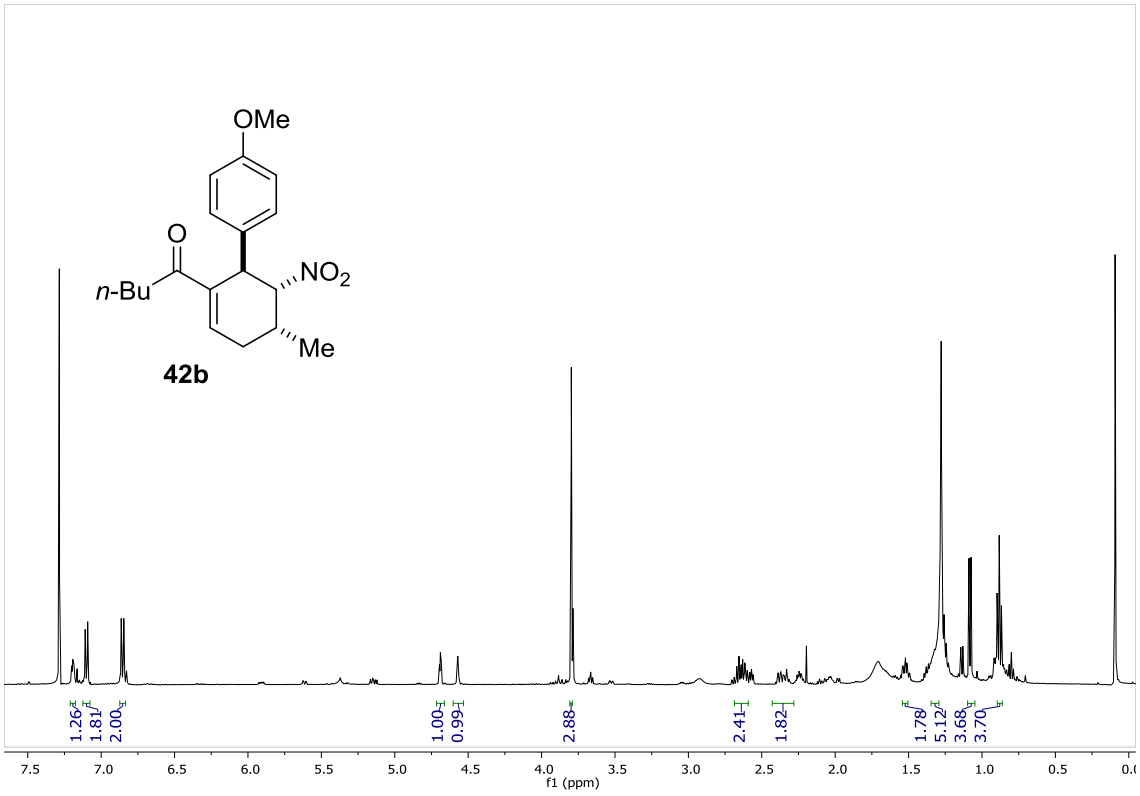

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

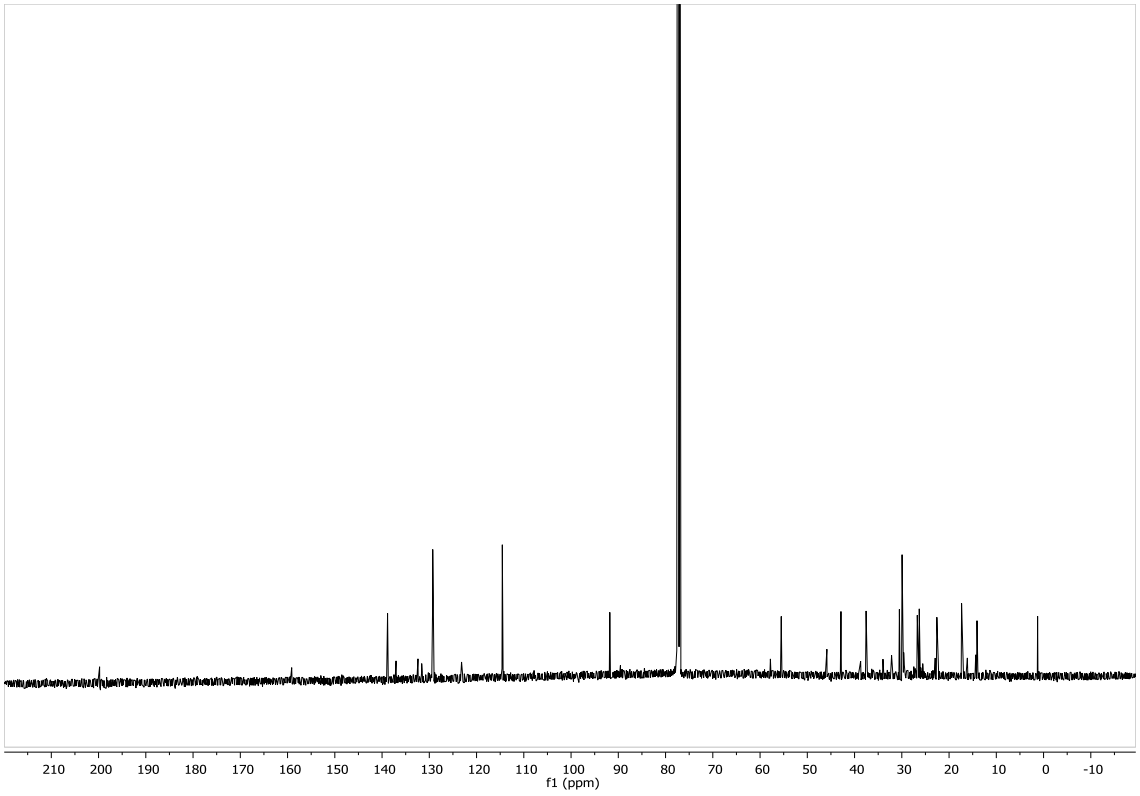

O
HA HA
41
+
O
HB HB
HB
HA
1.00
2.40
2.45 2.40 2.35 2.30 2.25
f1 (ppm)
0.80
0.95
0.70
1.84
2.00
2.23
1.34
7.57
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

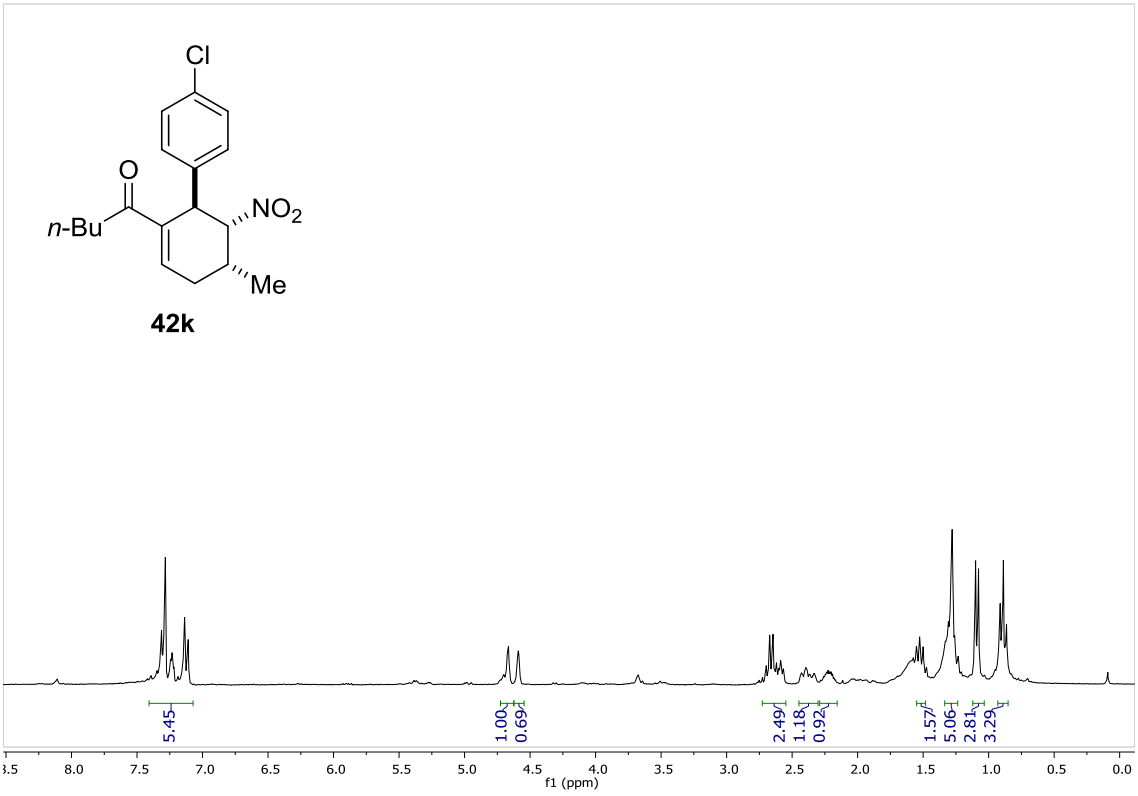

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

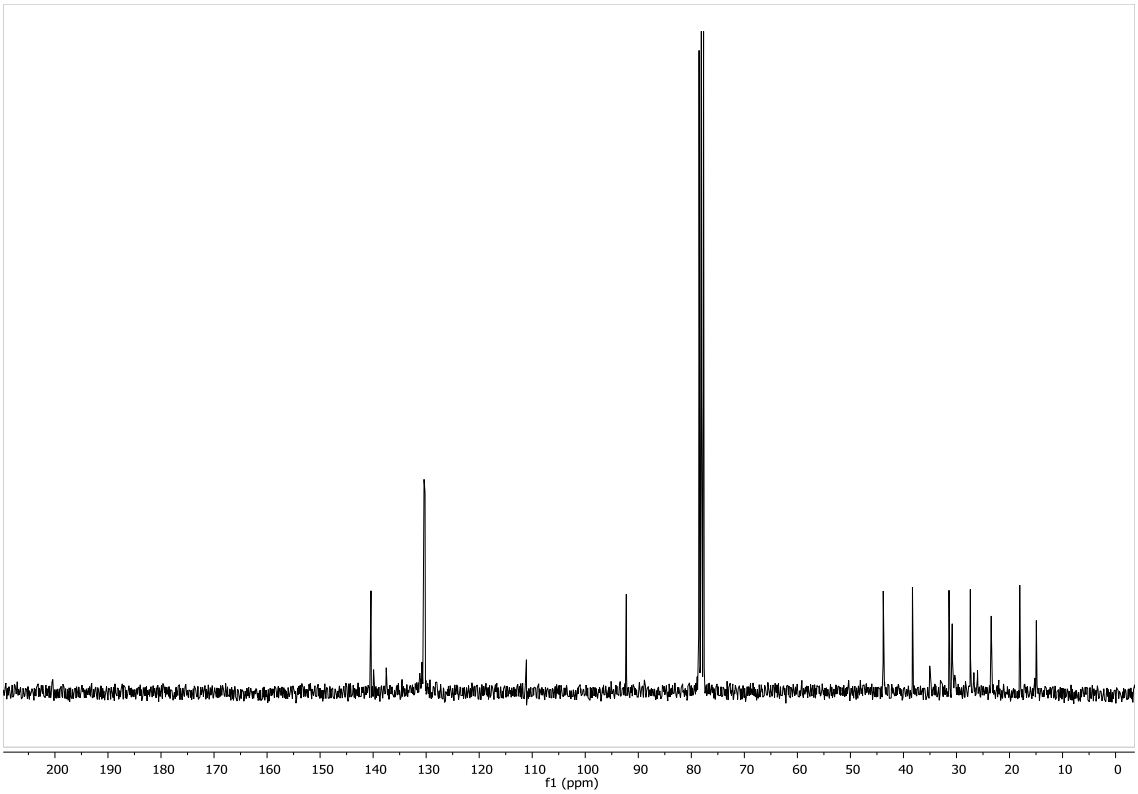

O
Ph
n-Bu
NO2
Me
42a
5.28
0.68
0.60
2.00
2.00
1.57
4.25
2.66
2.28
f1 (ppm)

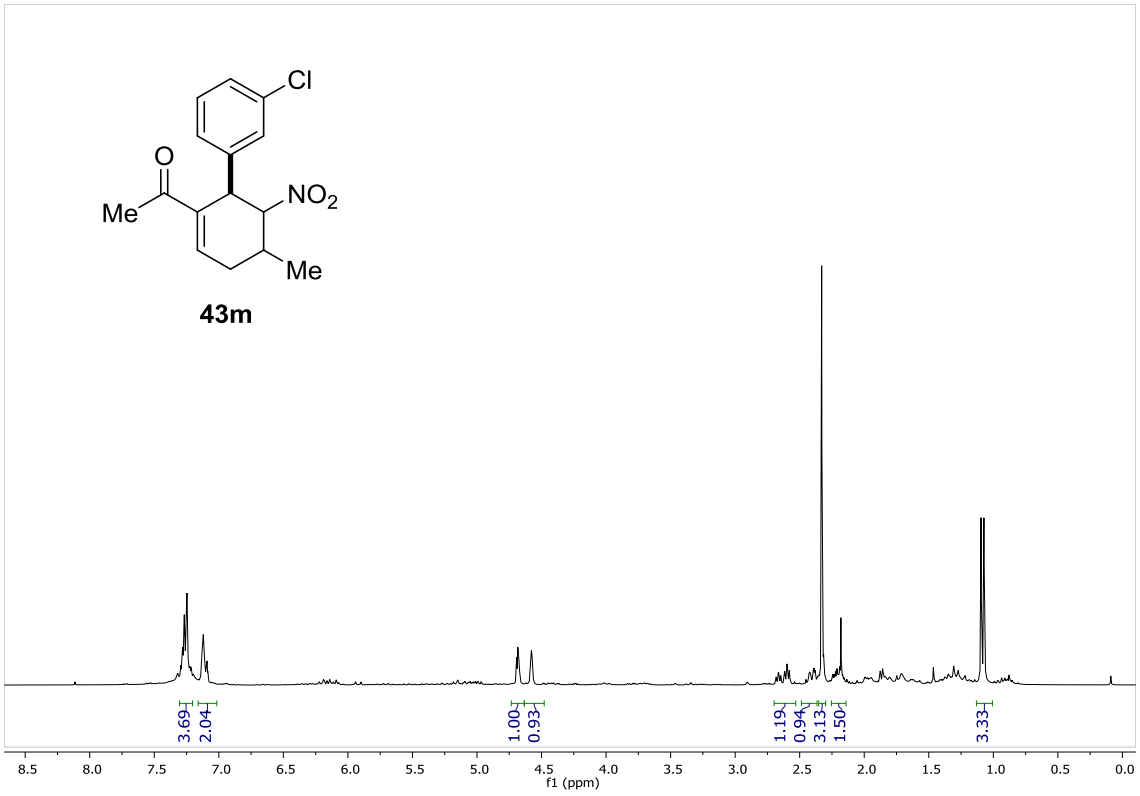

f1 (ppm)

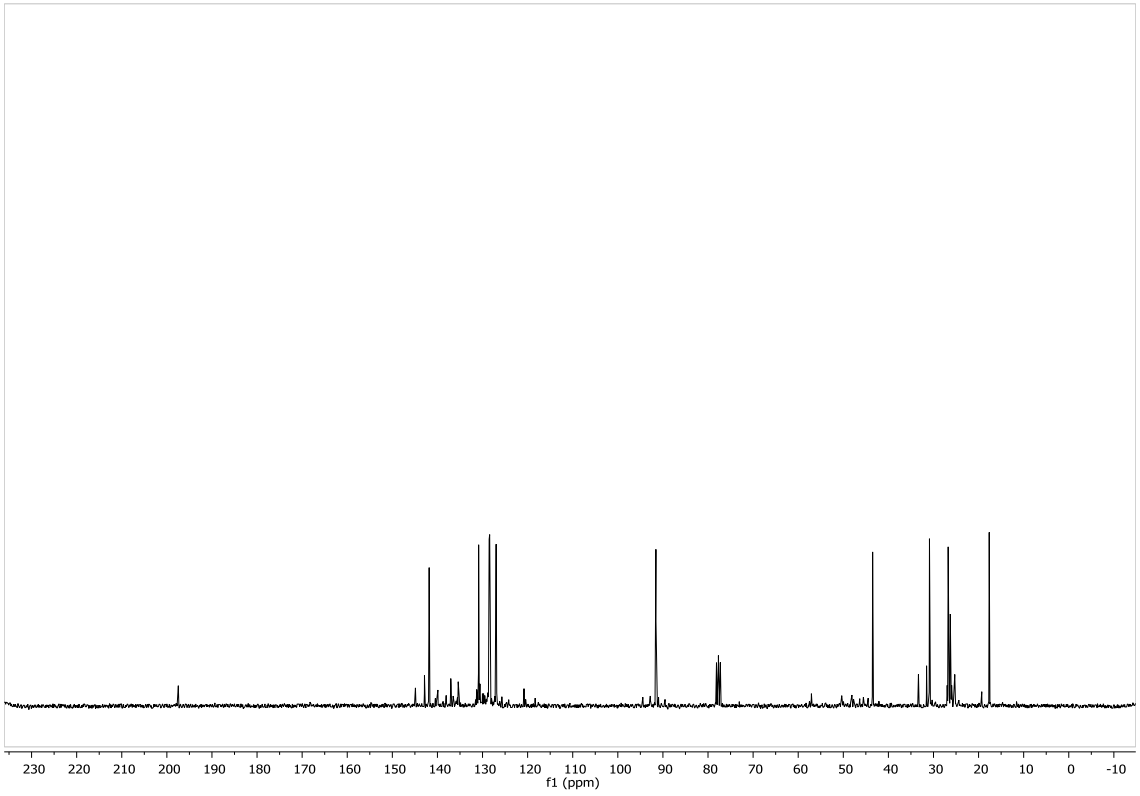

OMe
O
n-Bu
NO2
Me
42b
1.26
1.81
2.00
1.00
0.99
2.88
2.41
1.82
1.78
5.12
3.68
3.70
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

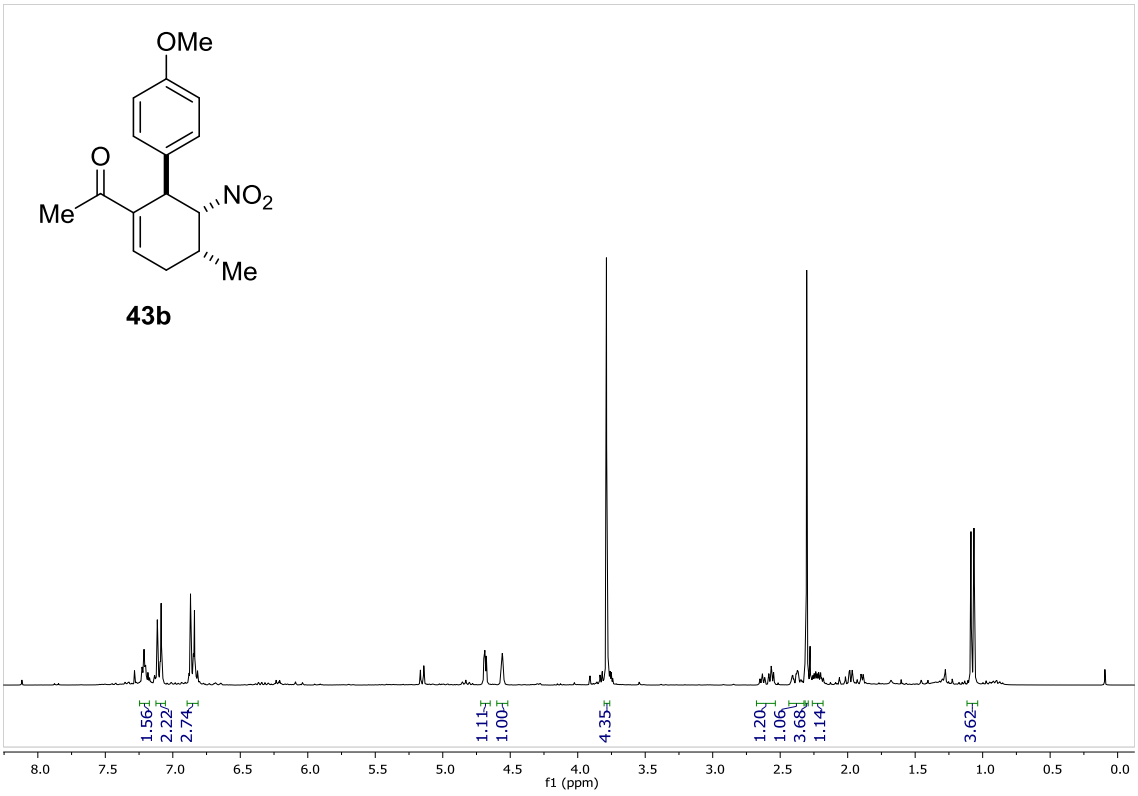

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

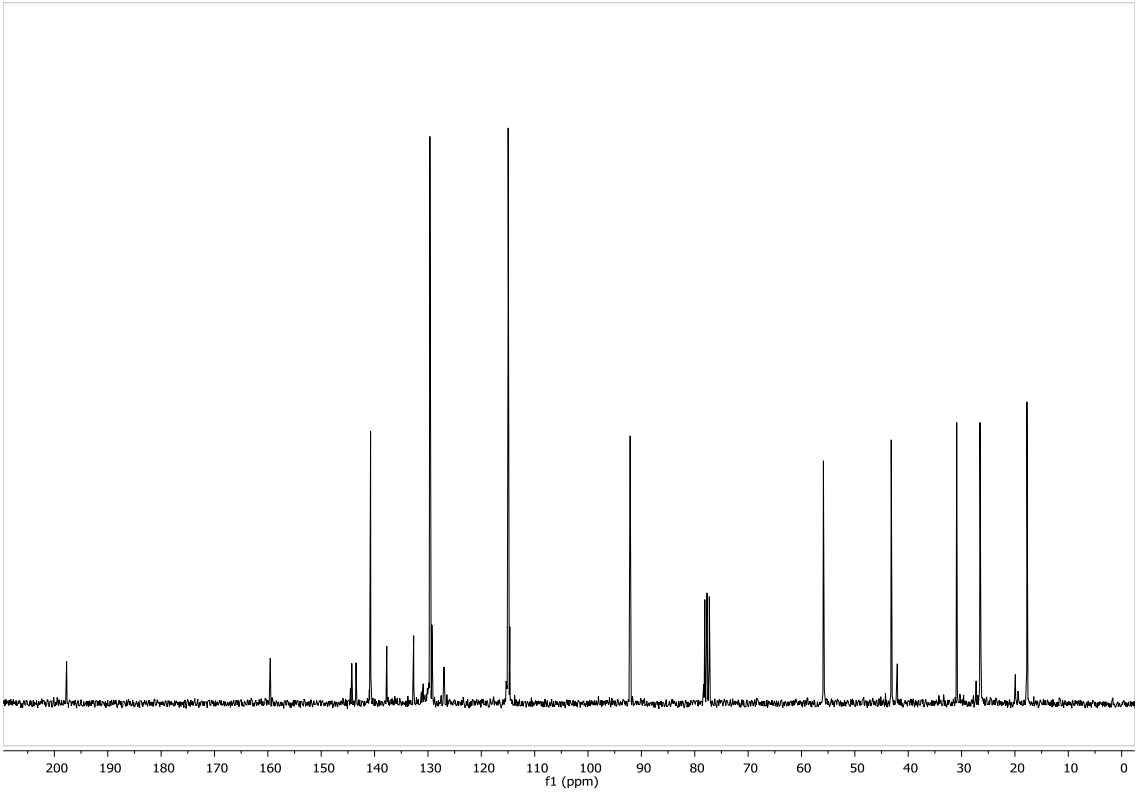

Cl
O
n-Bu
NO2
Me
42k
5.45
1.00
0.69
2.49
1.18
0.92
1.57
5.06
2.81
3.29
f1 (ppm)

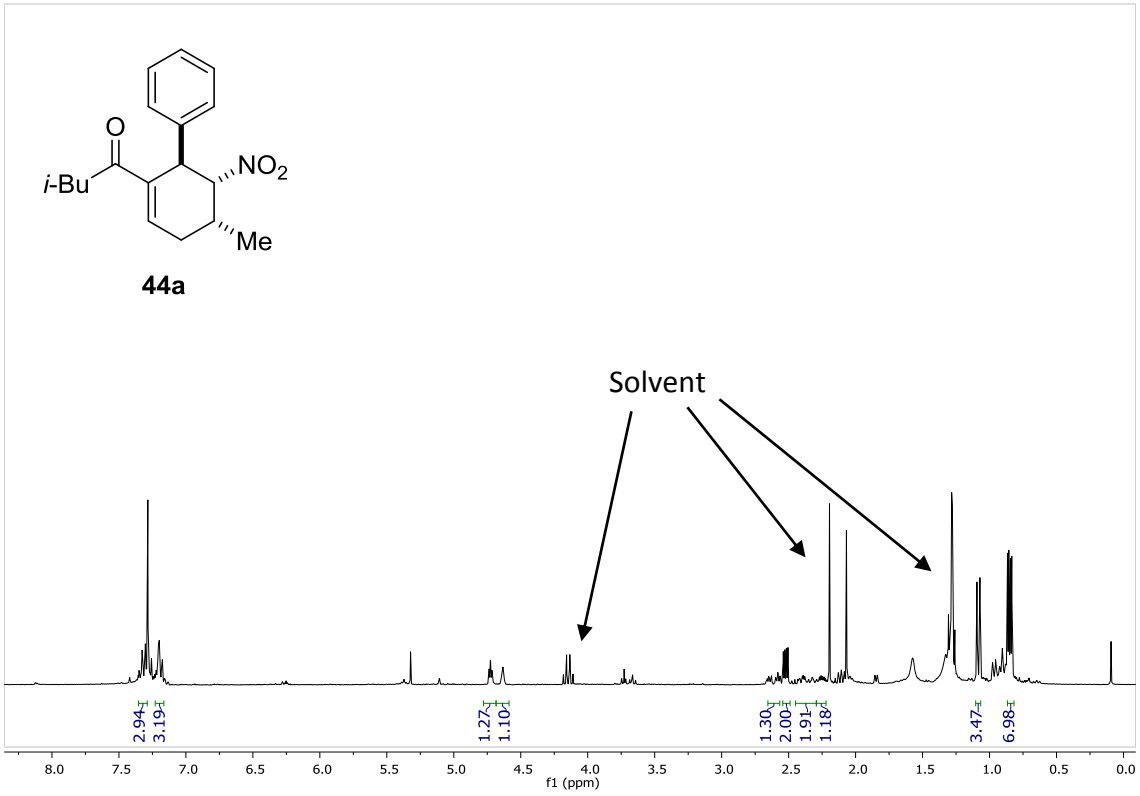

f1 (ppm)

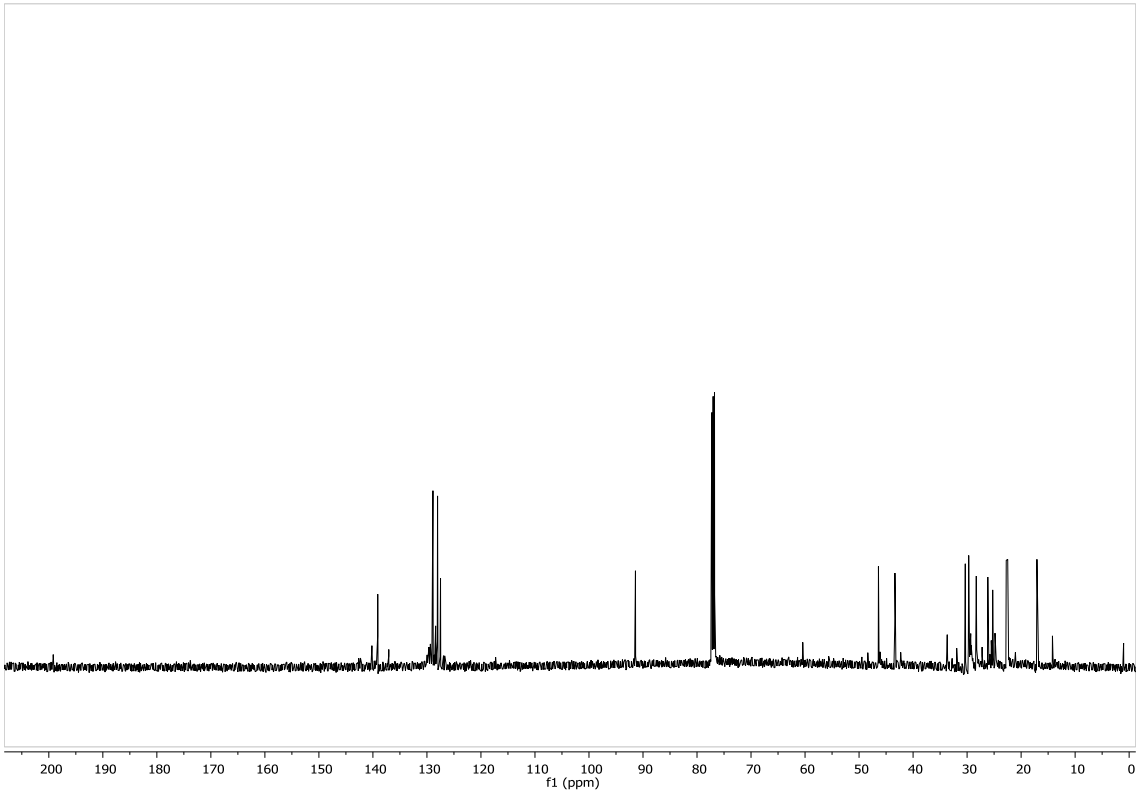

Cl
O
Me
NO2
Me
43m
3.69
2.04
1.00
0.93
1.19
0.94
3.13
1.50
3.33
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

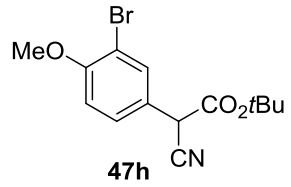

OMe
O
Me
NO2
Me
43b
1.56
2.22
2.74
1.11
1.00
4.35
1.20
1.06
3.68
1.14
3.62
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

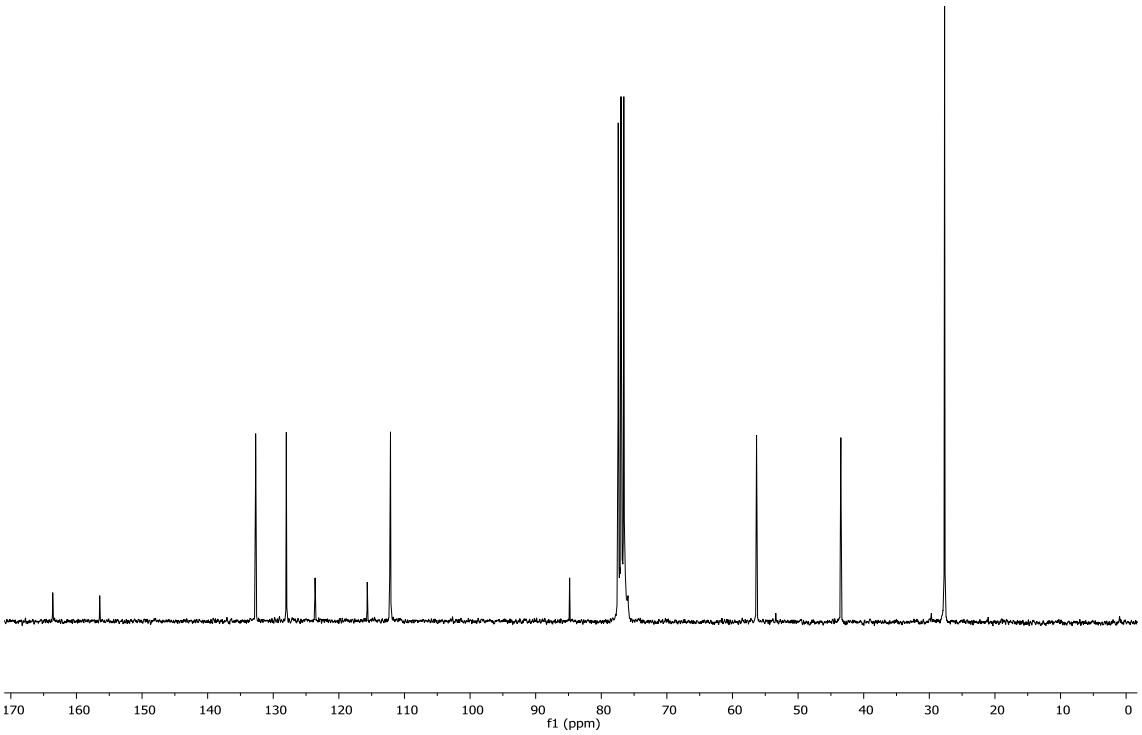

O
i-Bu
NO2
Me
44a
Solvent
2.94
3.19
1.27
1.10
1.30
2.00
1.91
1.18
3.47
6.98
f1 (ppm)

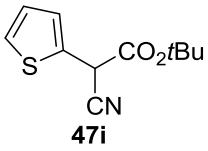

f1 (ppm)

6.5.2. NMR spectra of Chapter 3



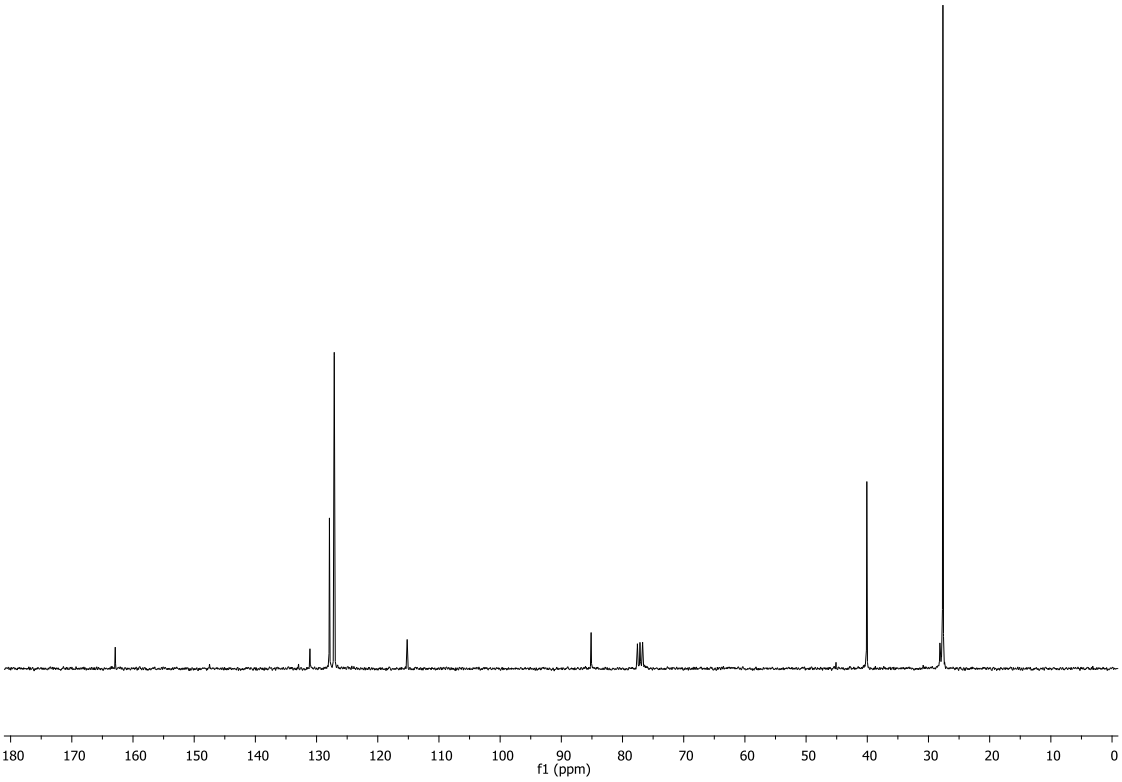
47h

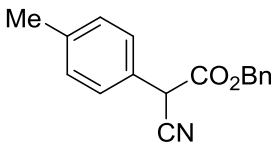



S
CO2tBu
CN

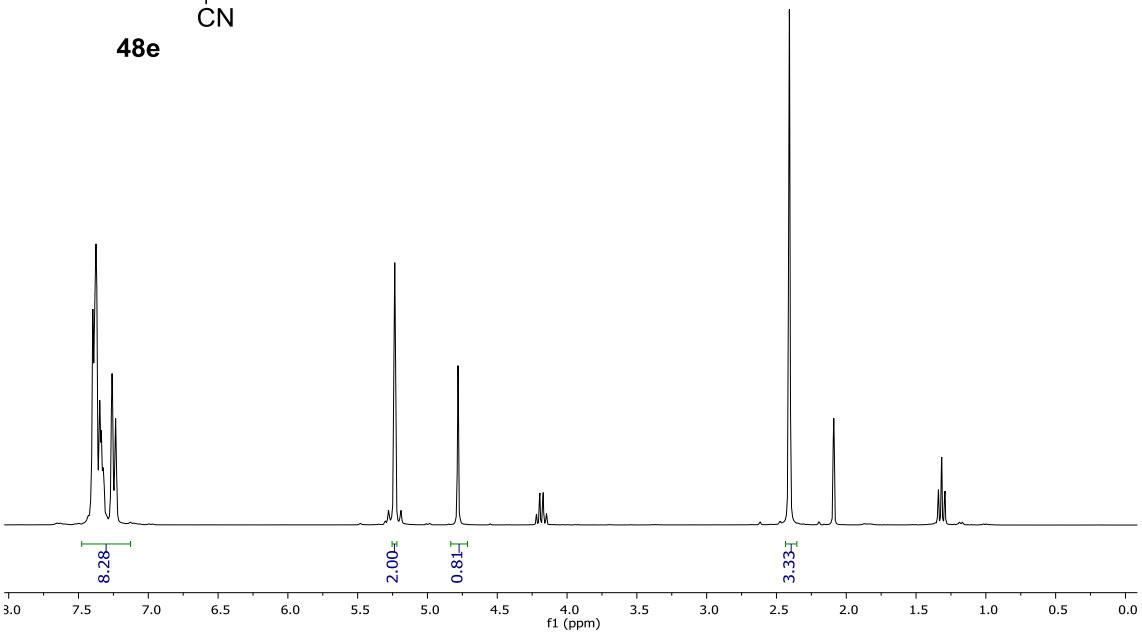
47i

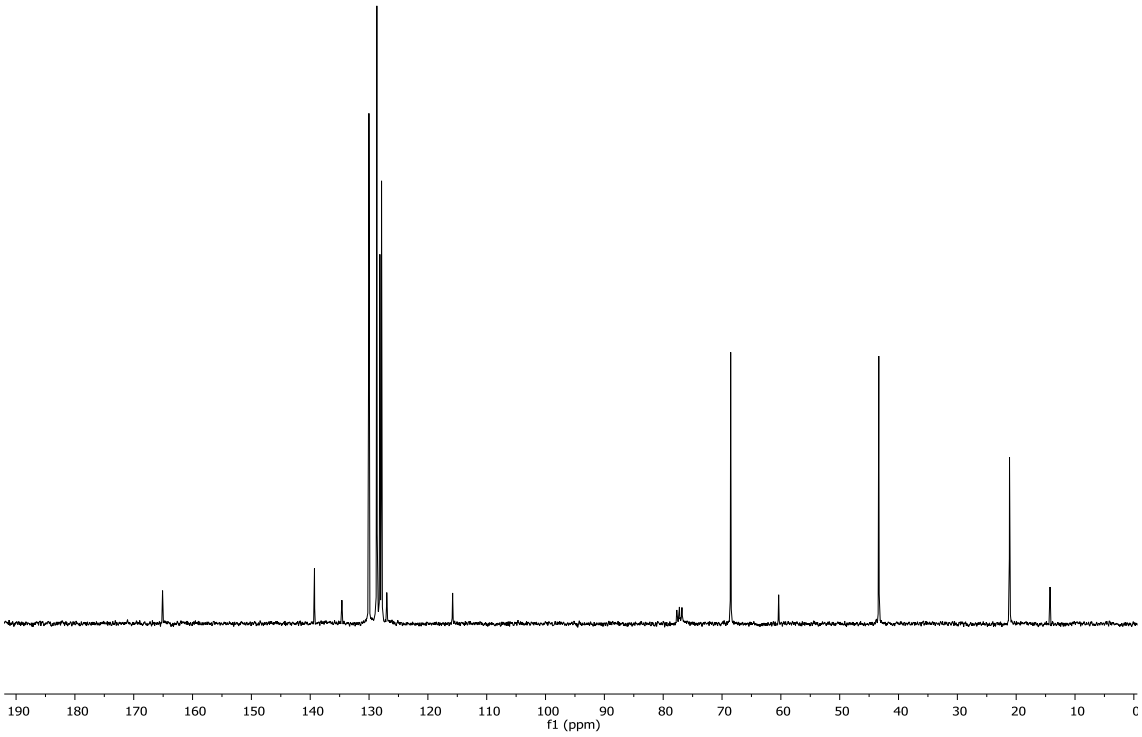
3.74
1.02
12.17
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

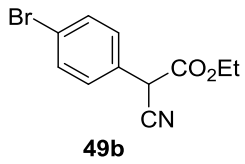

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



48e

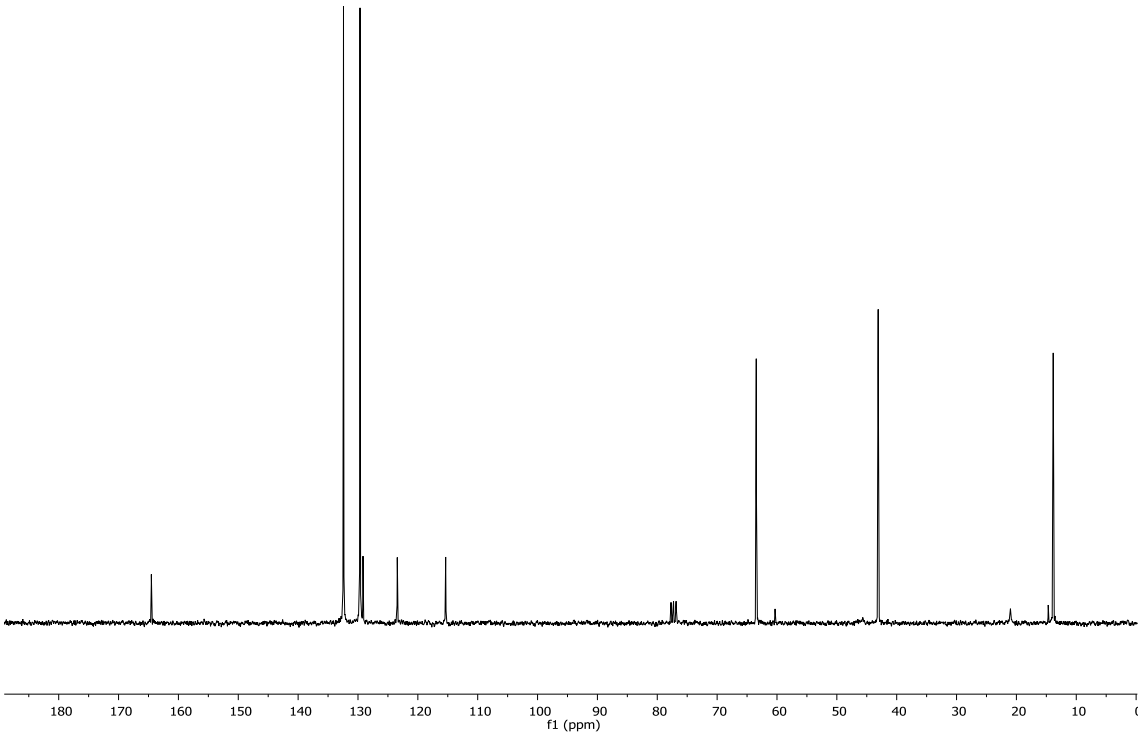


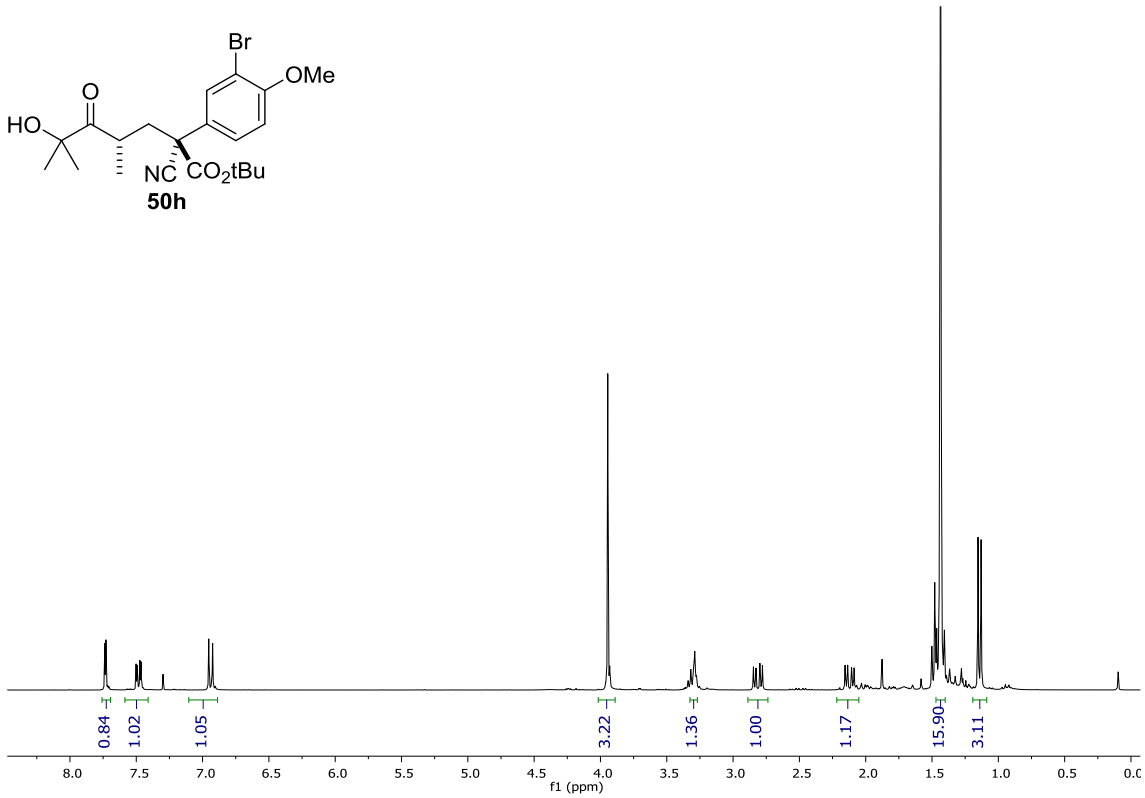


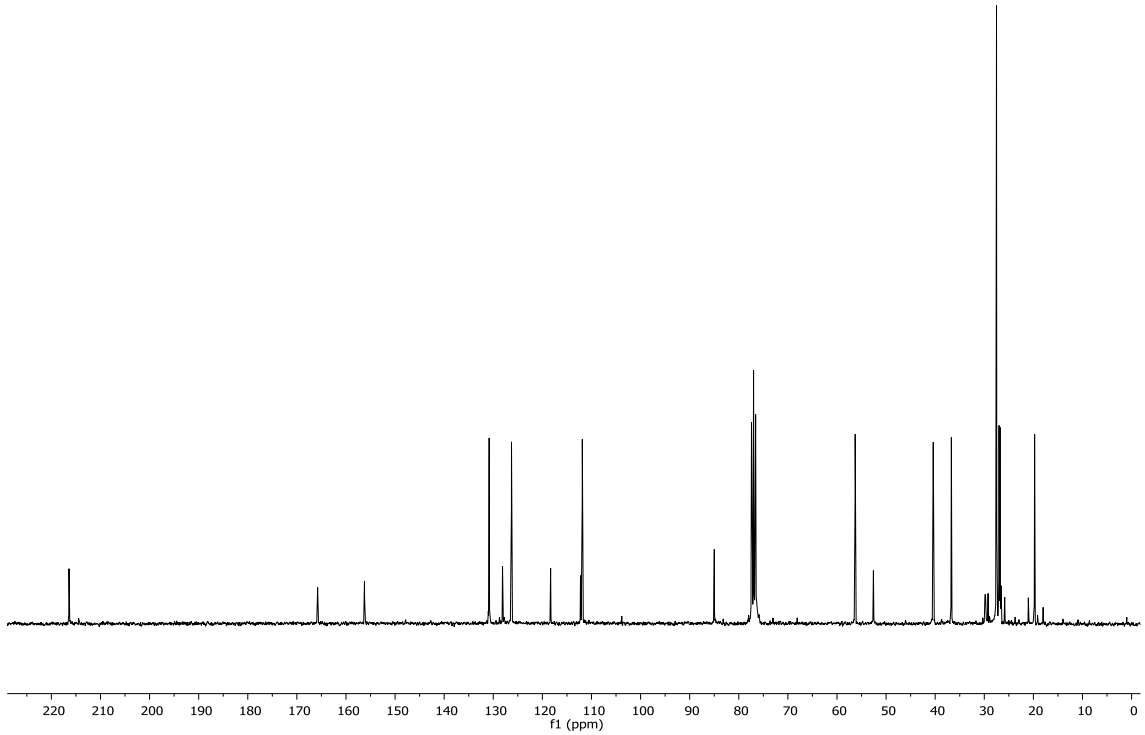

Br
CO2Et
CN

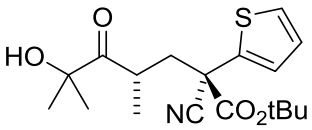
49b

3.93
0.85
2.00
3.26
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

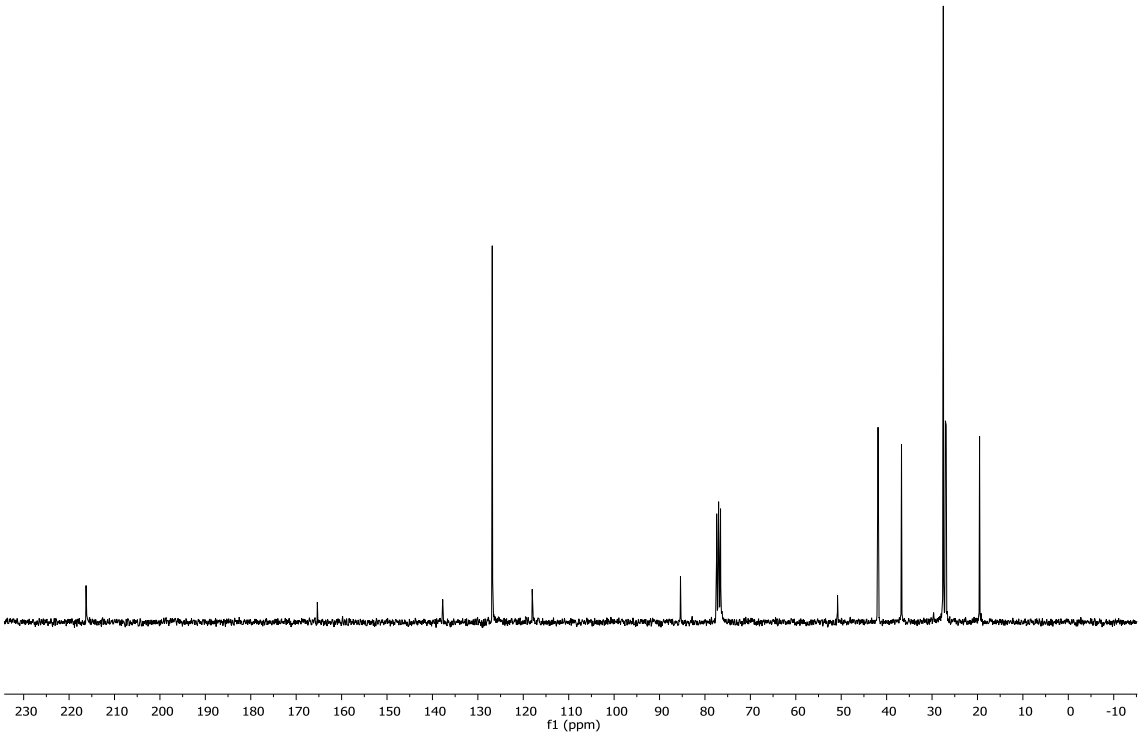

Br
OMe
O
HO
NC
CO2tBu
50h
0.84
1.02
1.05
3.22
1.36
1.00
1.17
15.90
3.11
f1 (ppm)

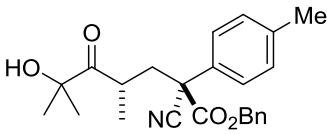

f1 (ppm)


O
S
HO
NC
CO2tBu

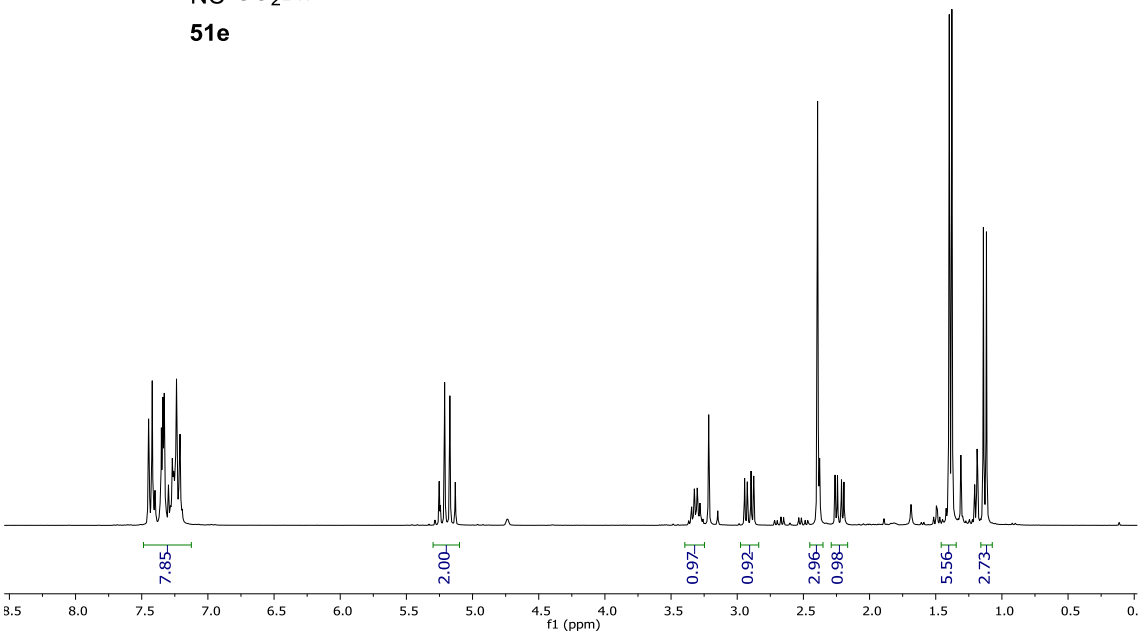
50i

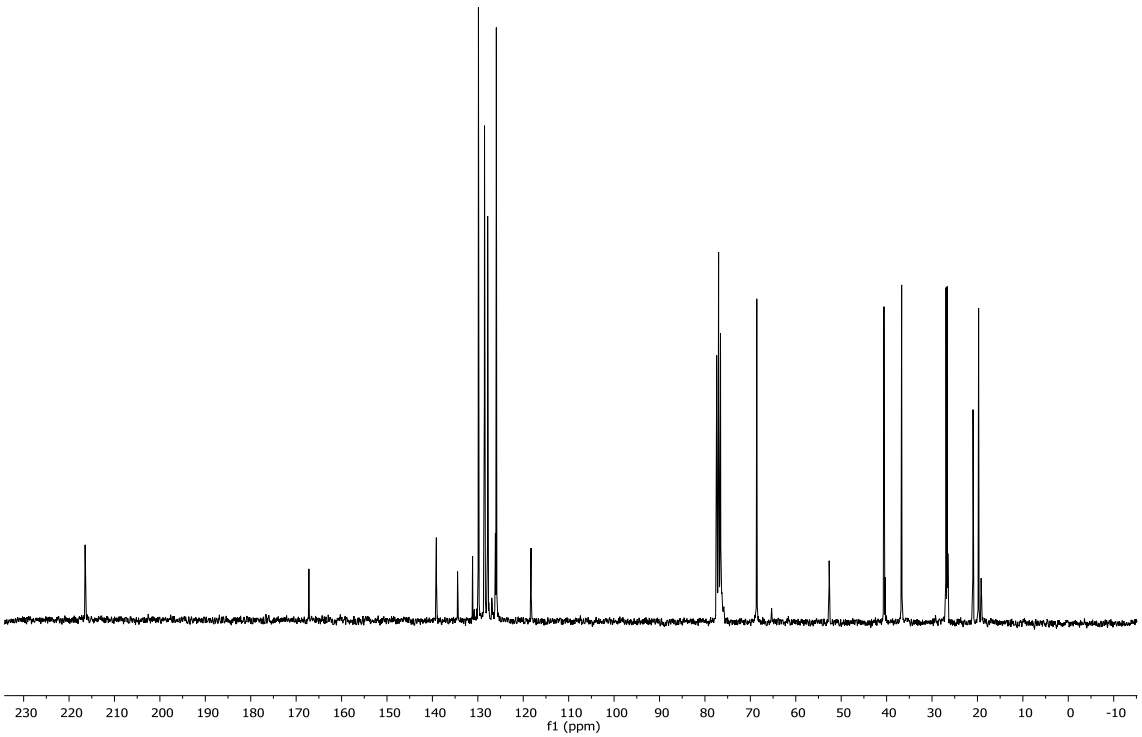
2.47
0.97
1.00
1.03
8.93
6.28
2.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

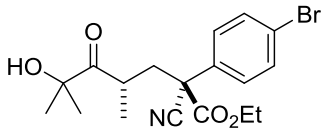

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



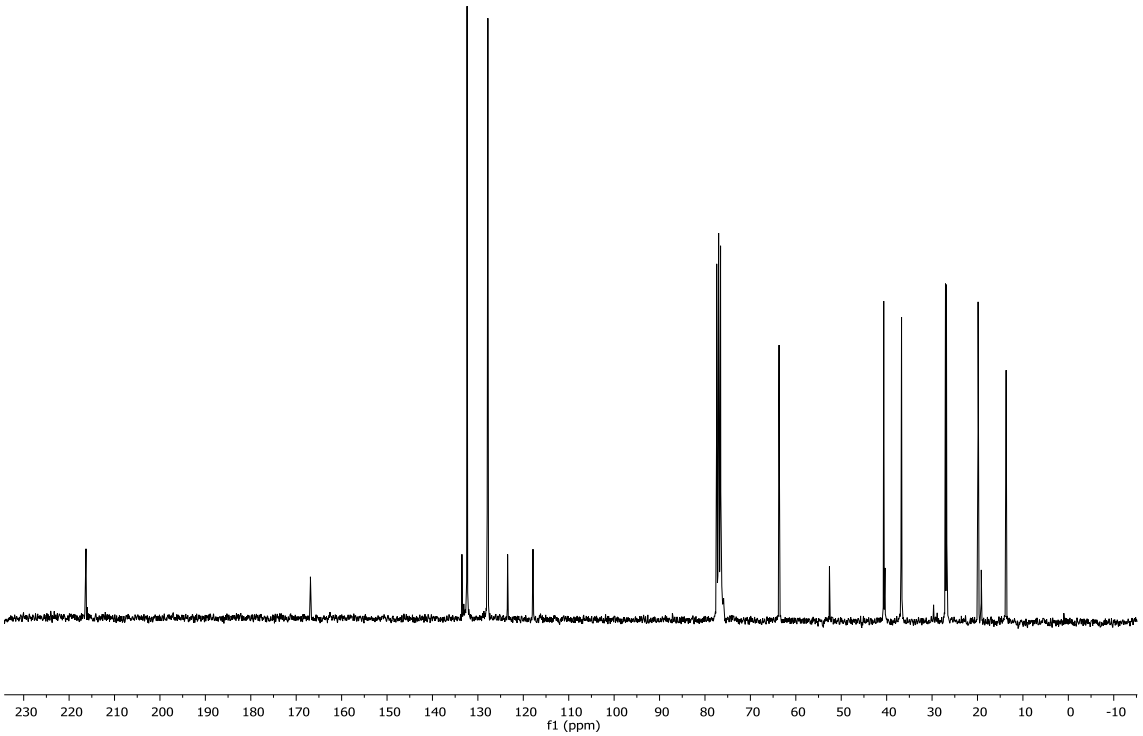
51e

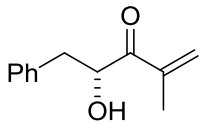




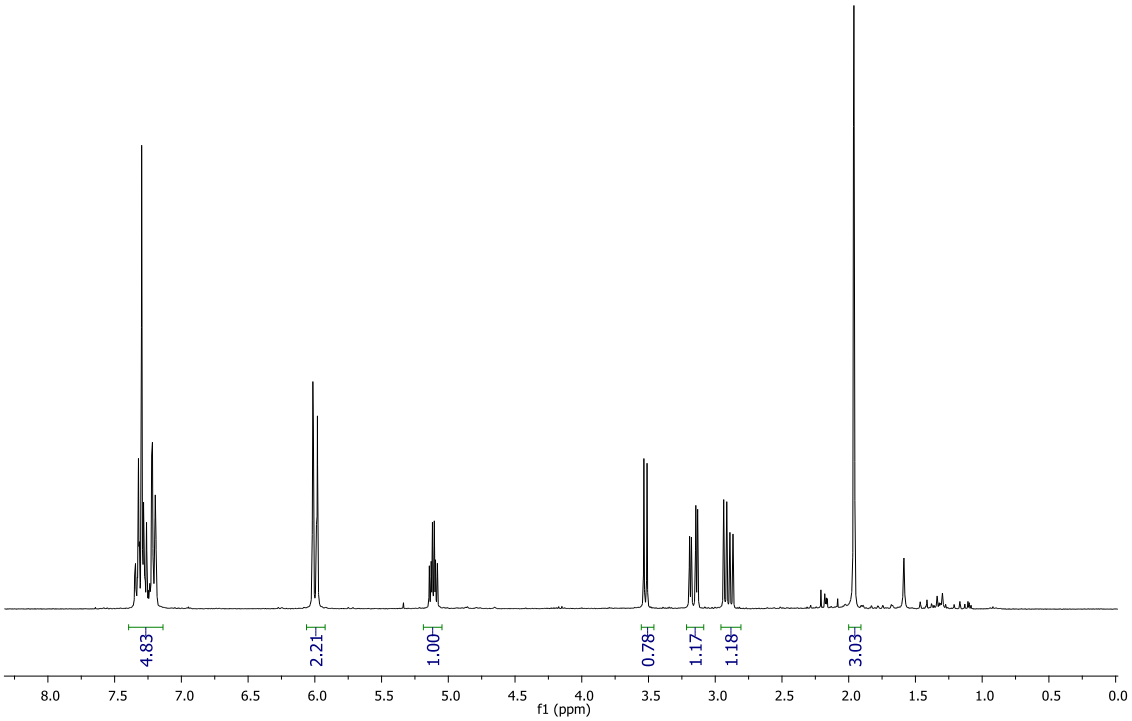


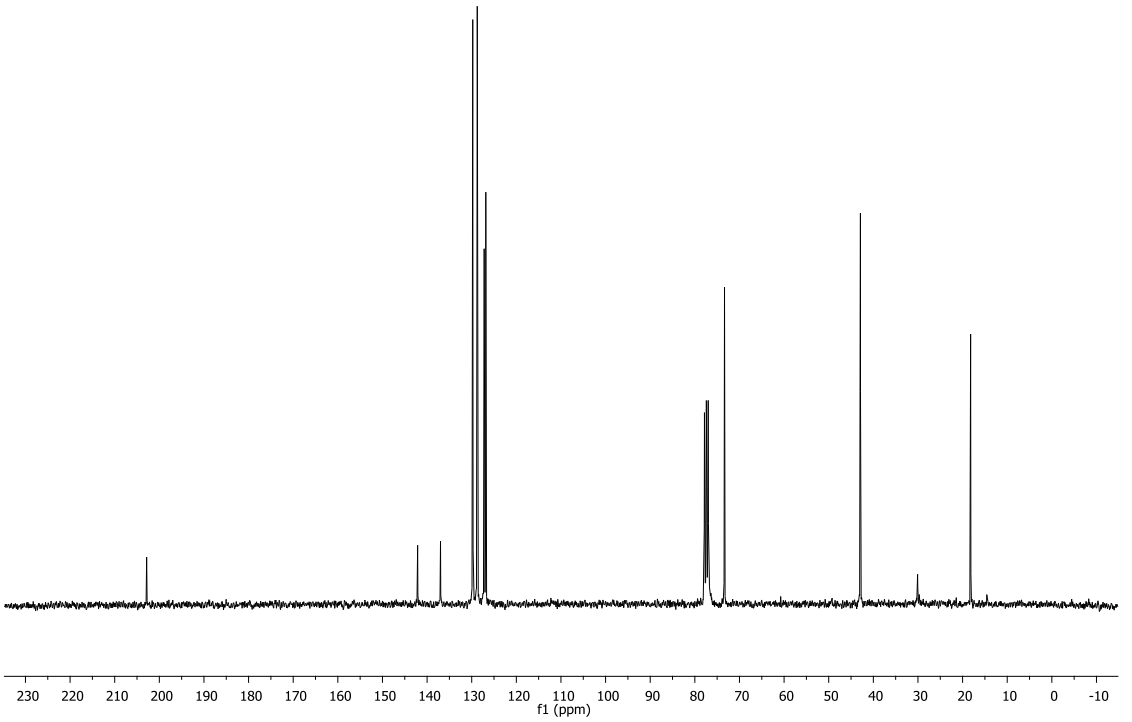
52b

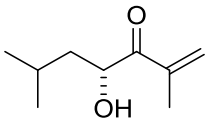



O
Ph
OH

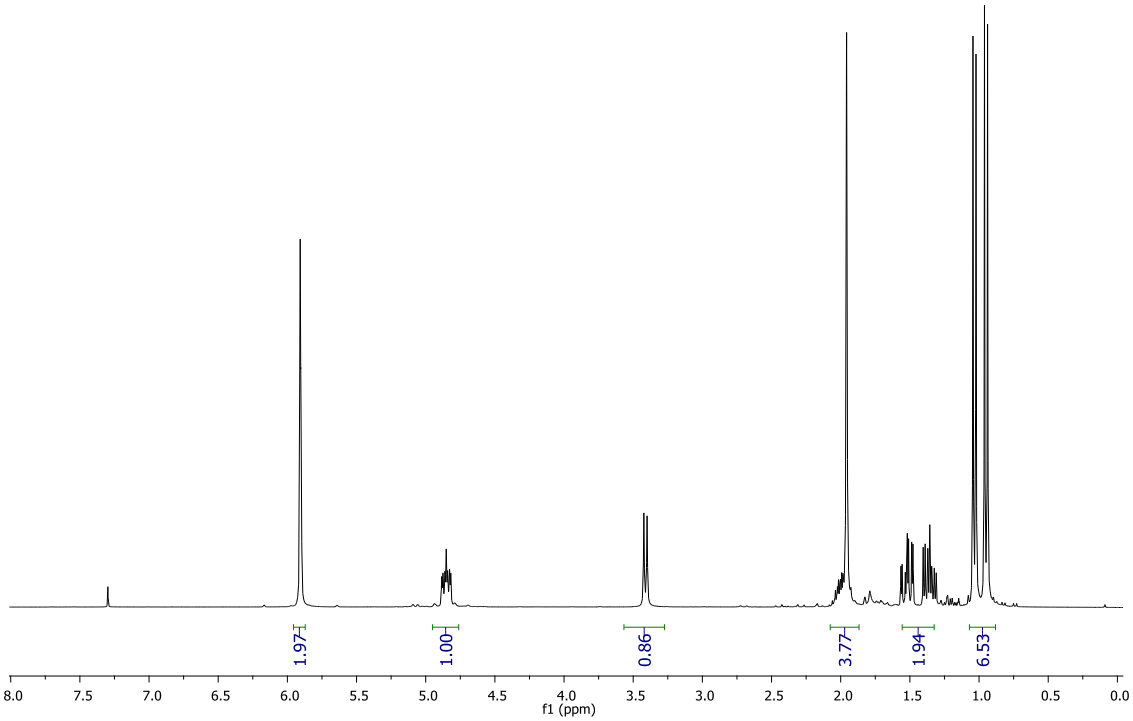
53

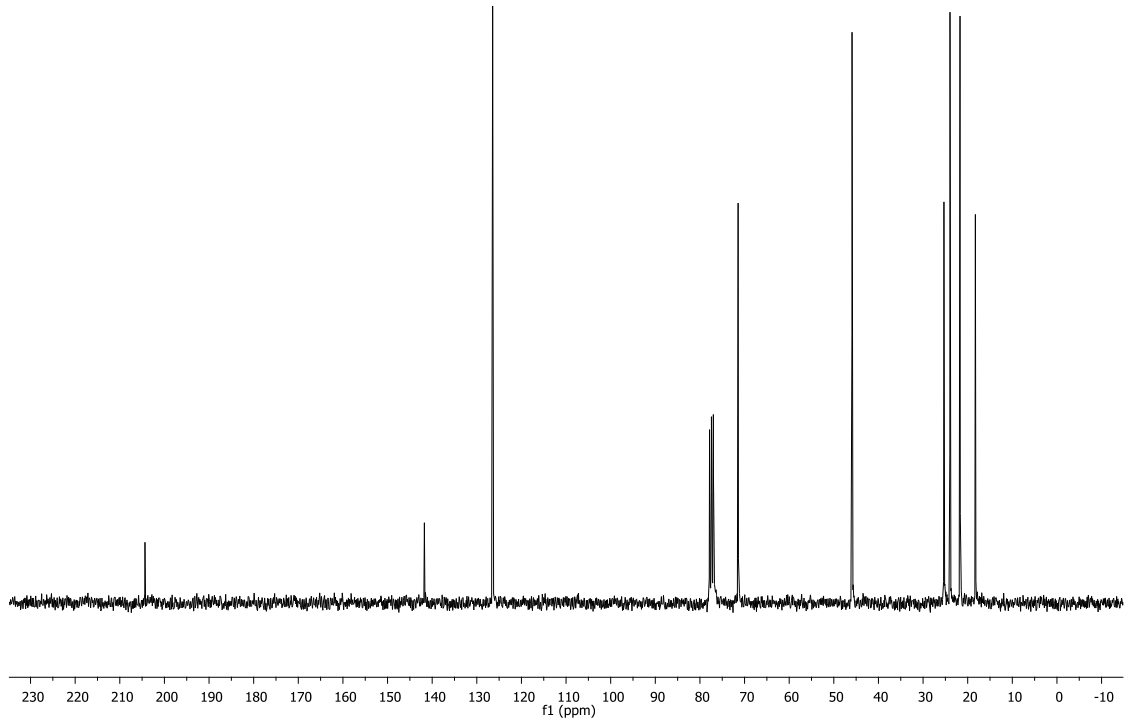

4.83
2.21
1.00
0.78
1.17
1.18
3.03
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

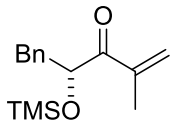

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OH

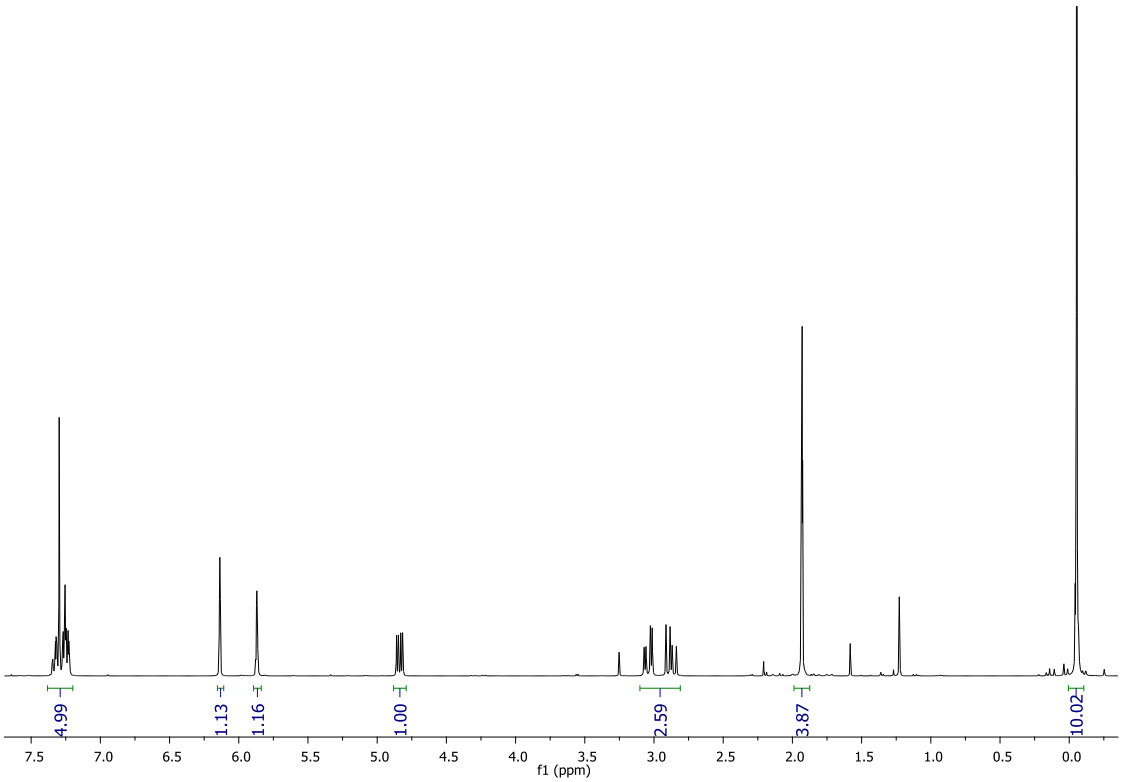
54

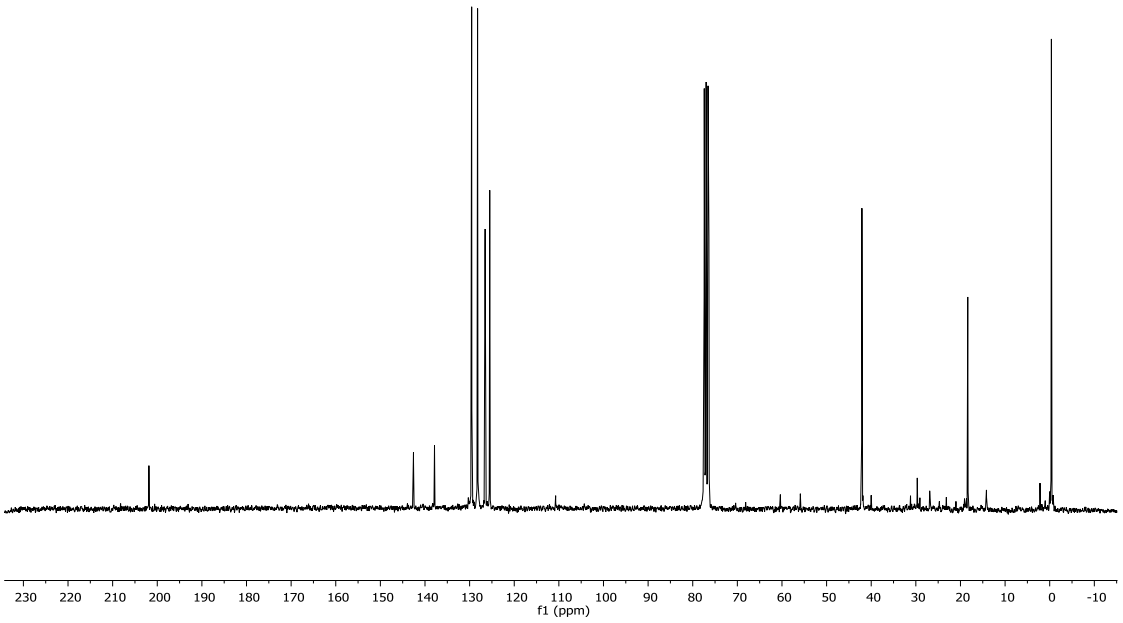

1.97
1.00
0.86
3.77
1.94
6.53
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

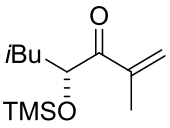

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Bn
TMSO

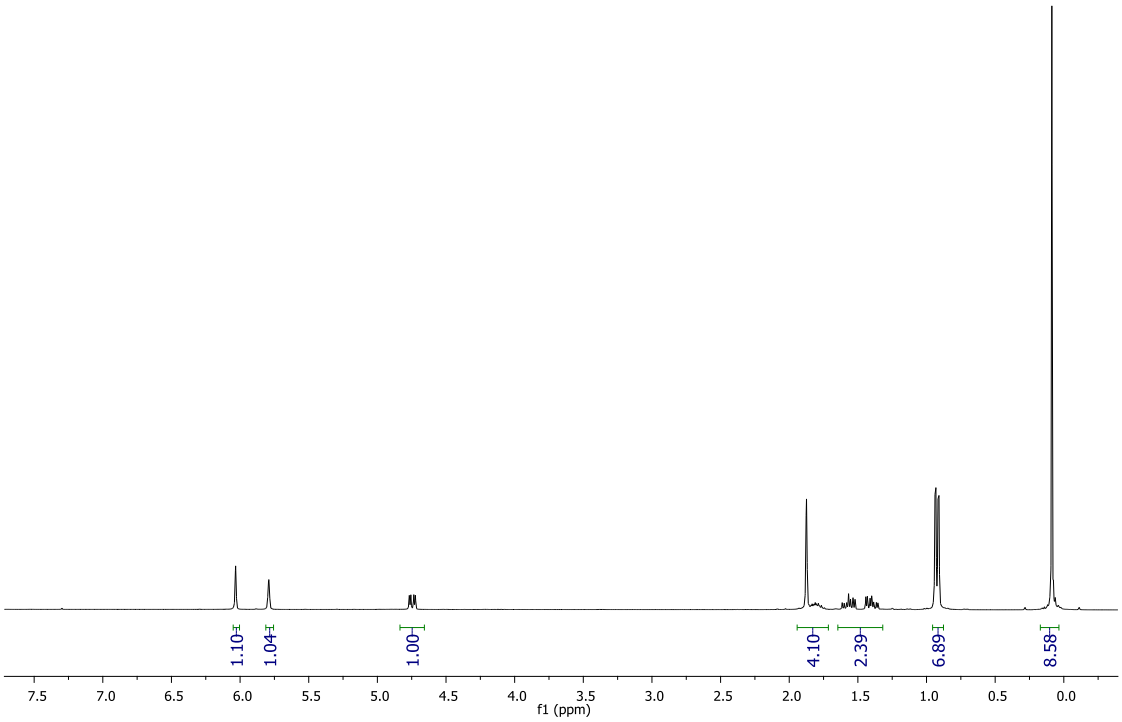
55

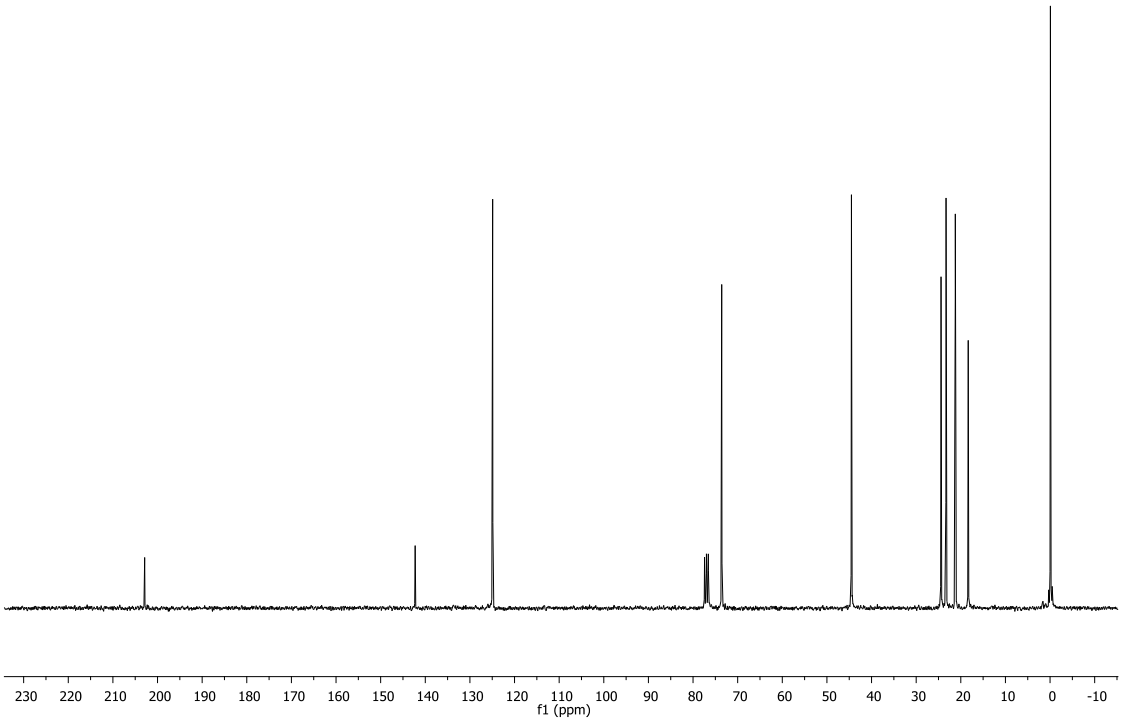

4.99
1.13
1.16
1.00
2.59
3.87
10.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
iBu
TMSO

56


1.10
1.04
1.00
4.10
2.39
6.89
8.58
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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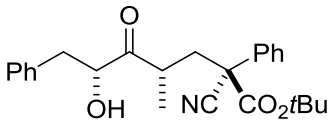
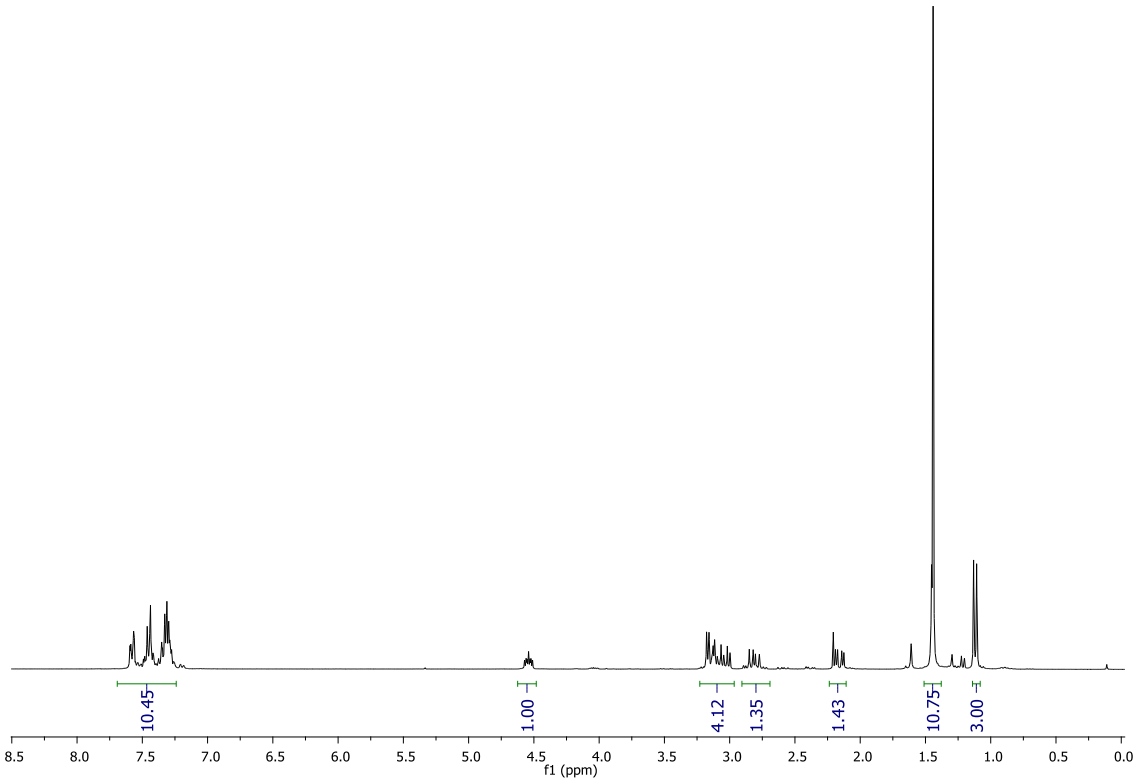
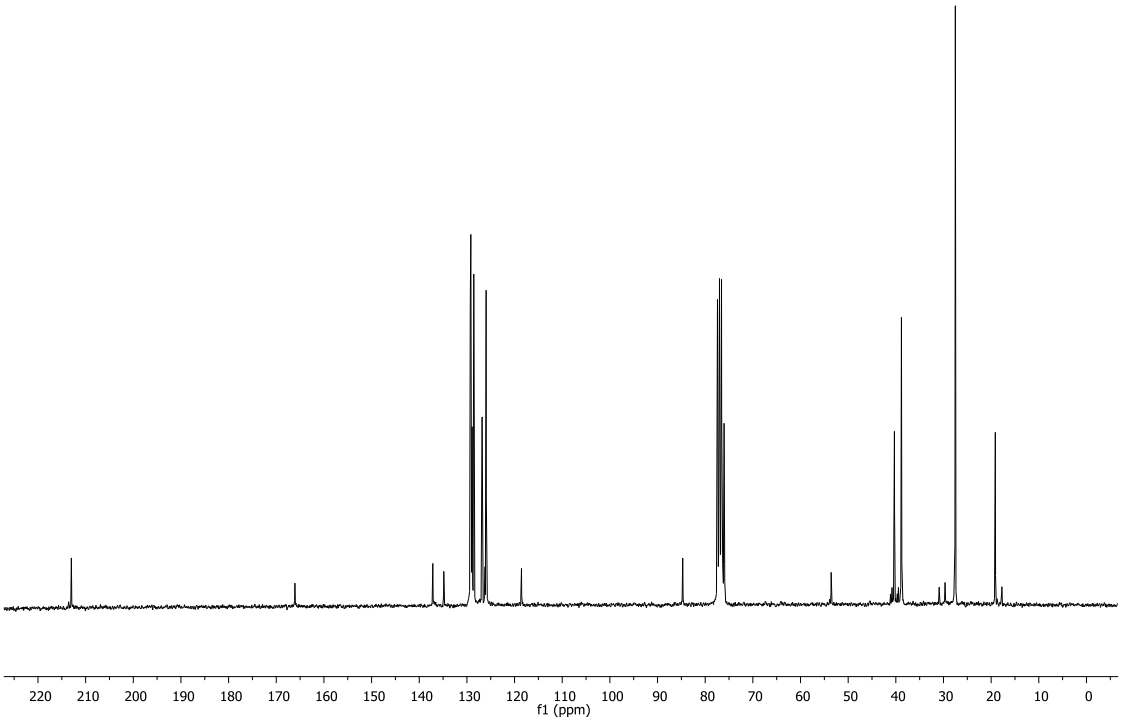
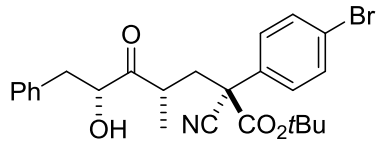
f1 (ppm)


O
Ph
Ph
OH
NC
CO2tBu

57

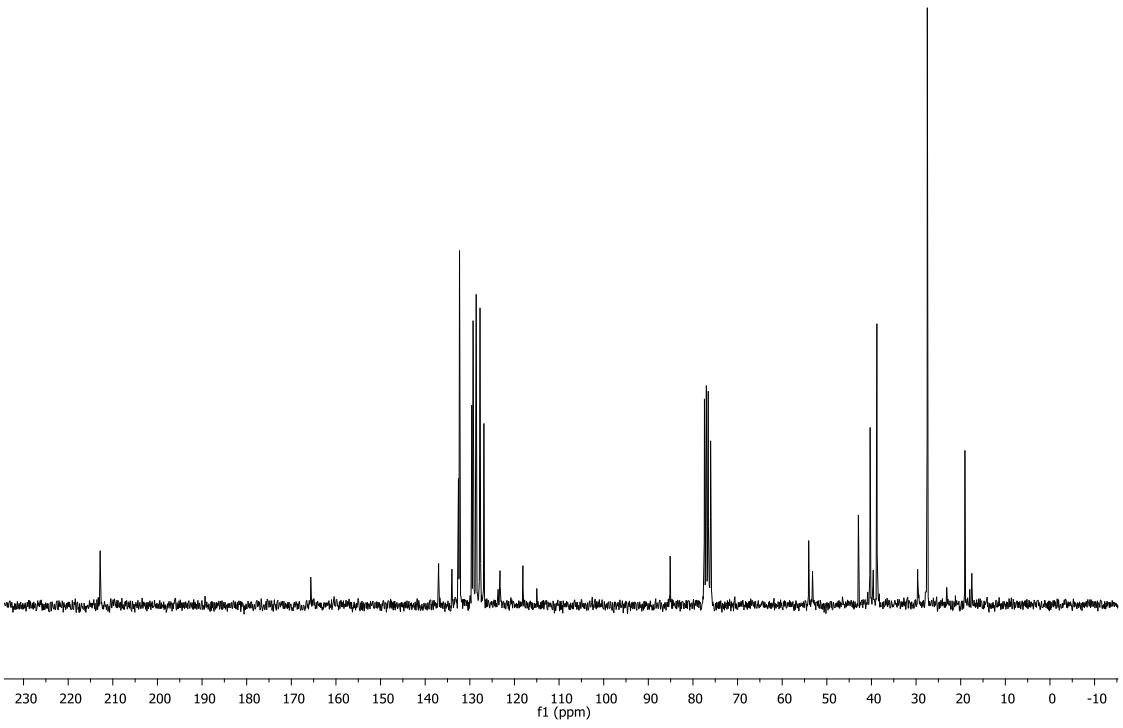

10.45
1.00
4.12
1.35
1.43
10.75
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
O
Ph
OH
NC
CO2tBu

58

12.86
1.00
4.34
1.17
1.18
11.05
3.20
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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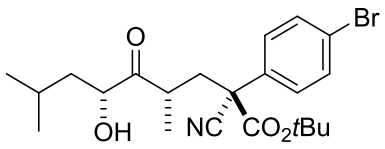
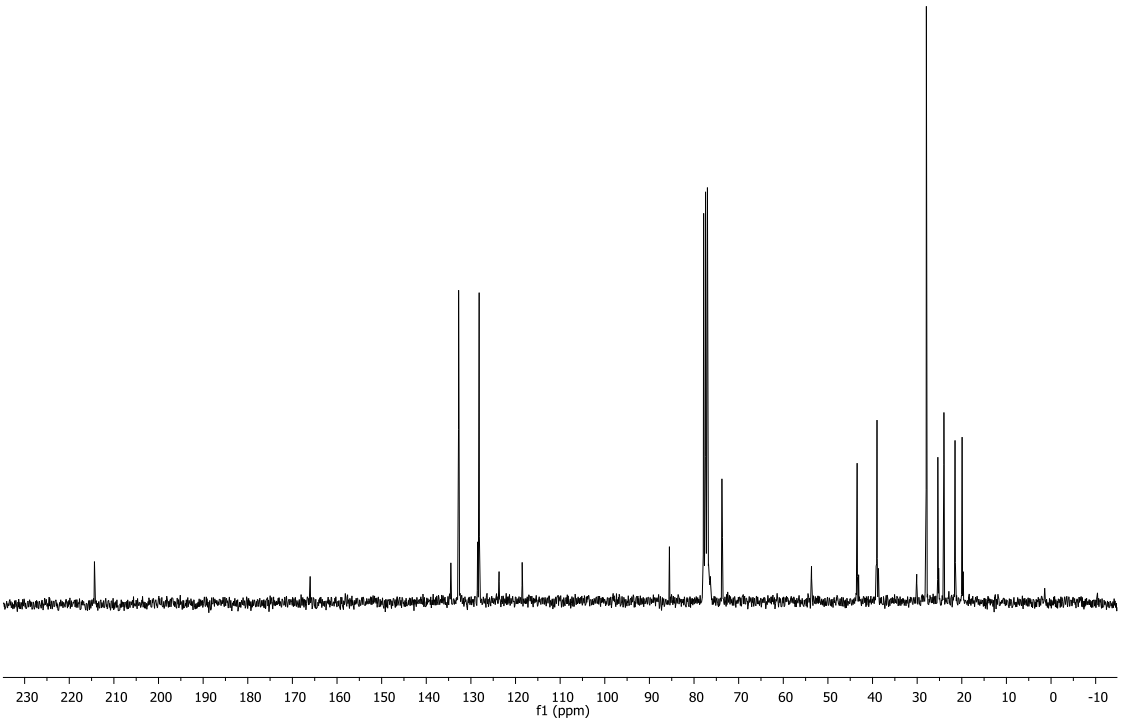
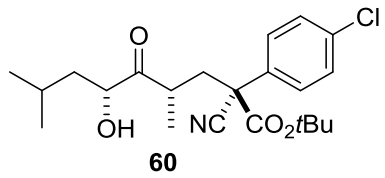
f1 (ppm)


Br
O
OH
NC
CO2tBu

59

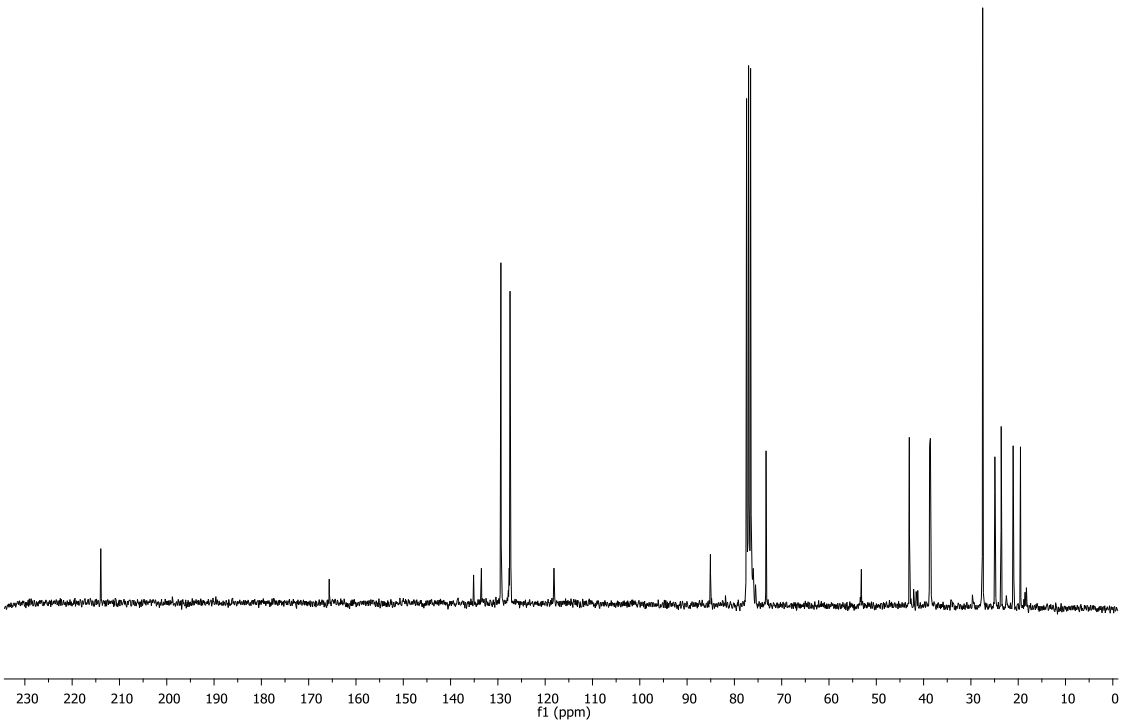
3.96
1.00
0.74
2.25
2.20
9.64
2.94
2.95
6.46
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

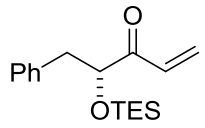

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
Cl
OH
NC
CO2tBu

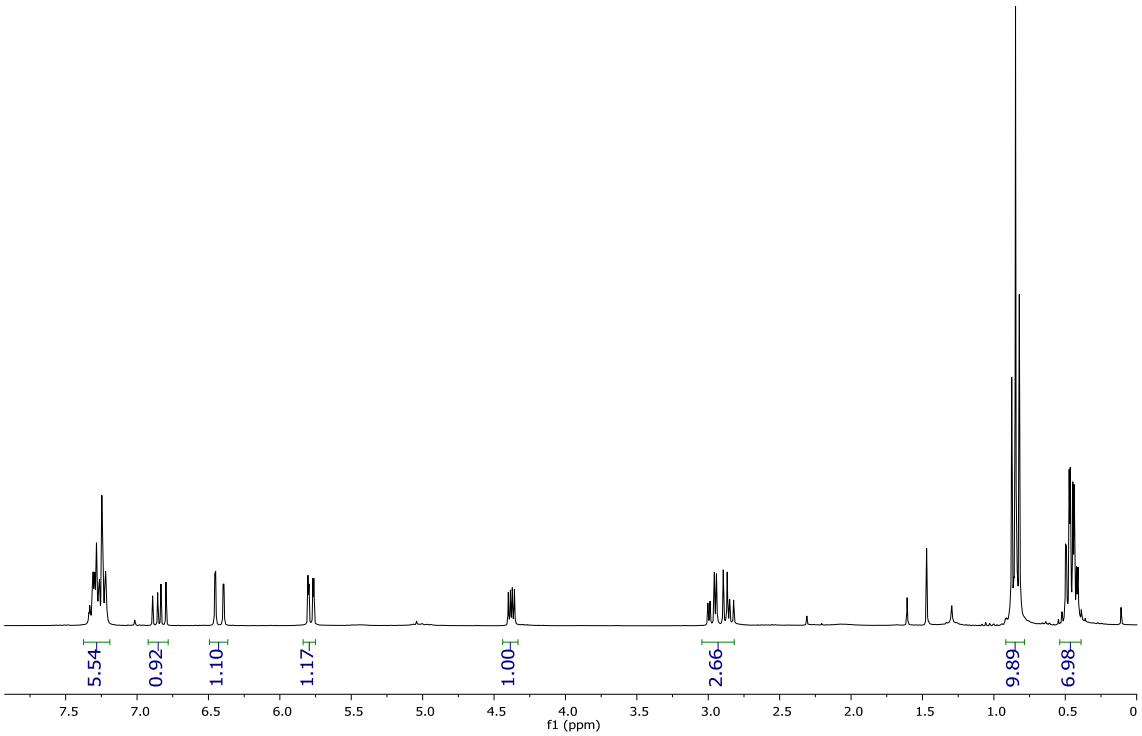
60

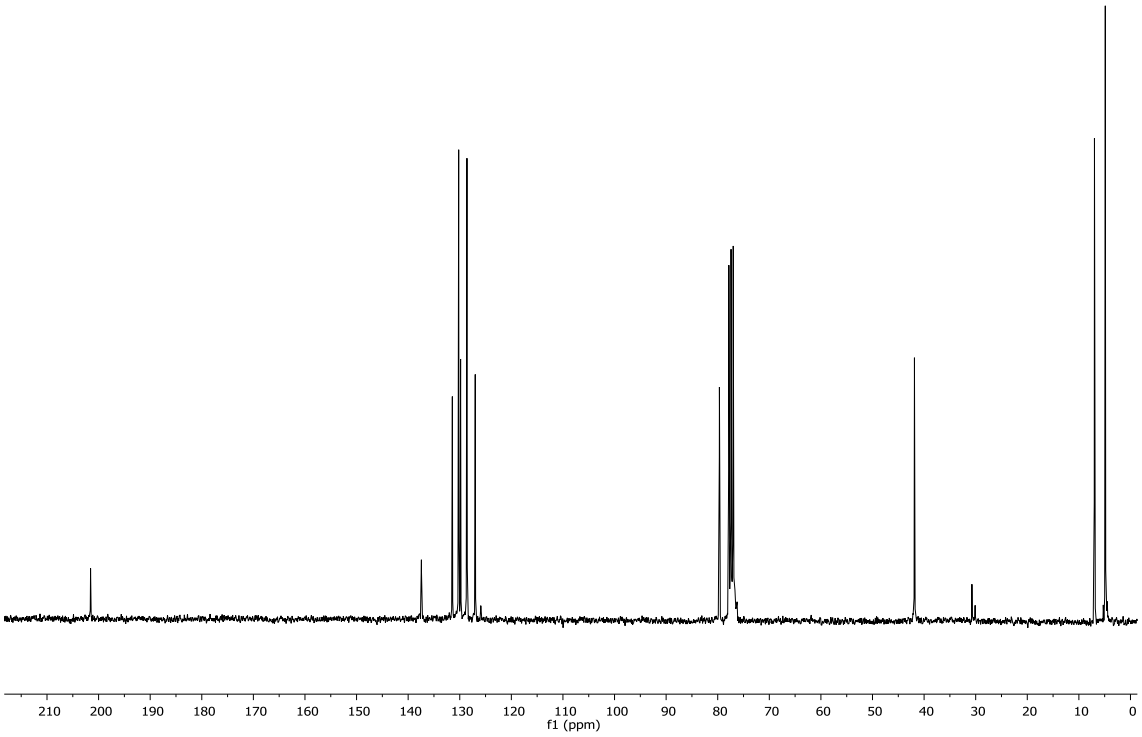
4.42
1.00
0.75
1.03
1.28
2.41
14.05
3.10
6.55
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

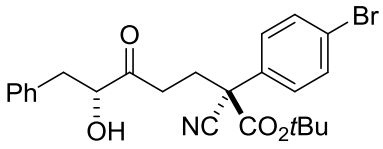

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
Ph
OTES

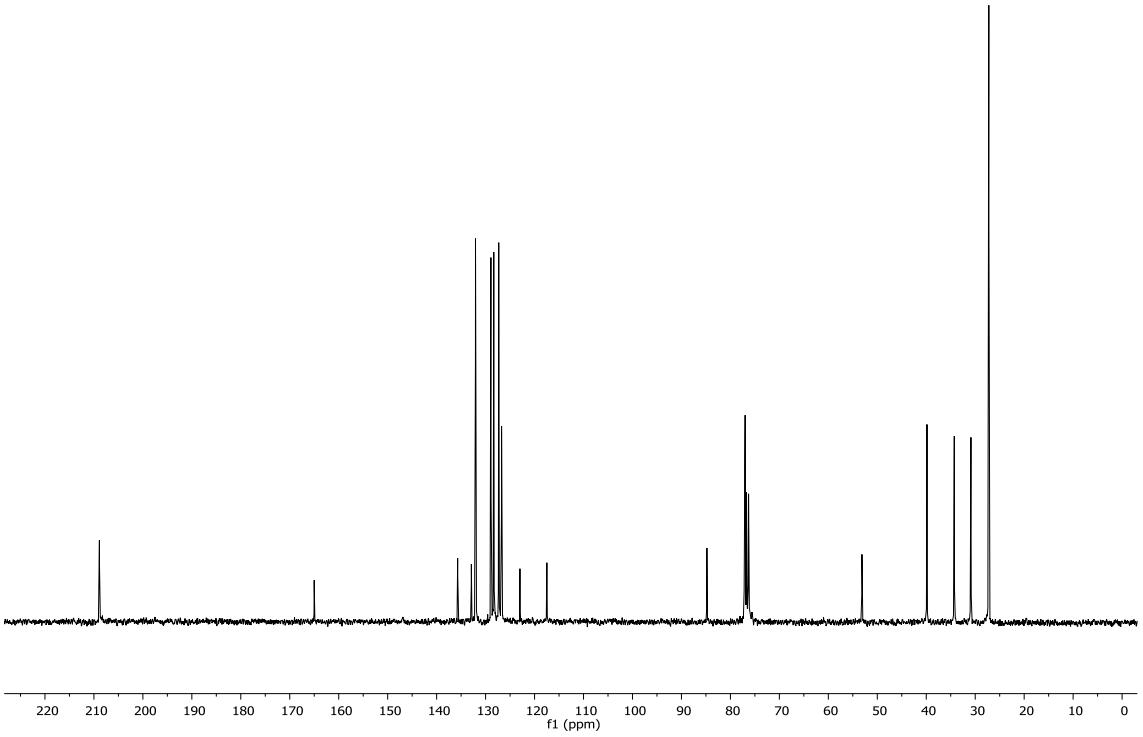
62

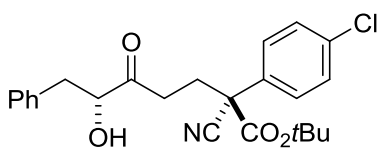

5.54
0.92
1.10
1.17
1.00
2.66
9.89
6.98
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

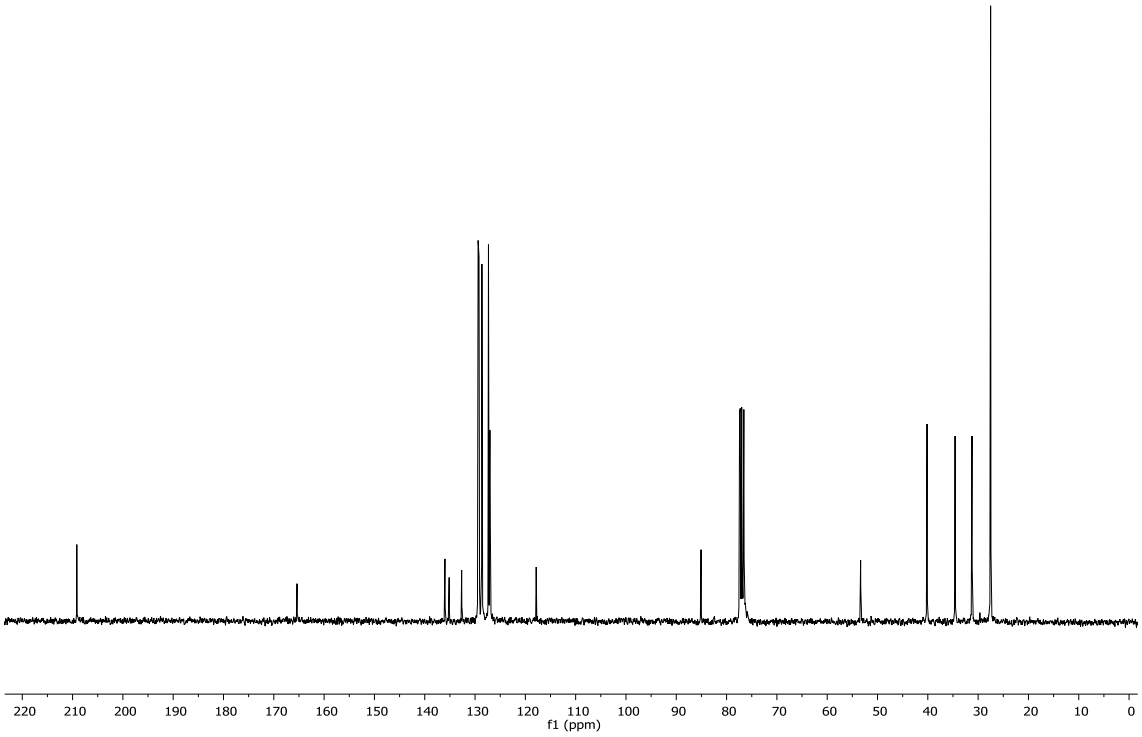


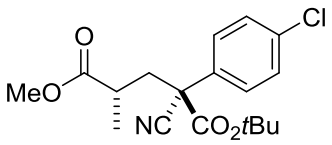
63





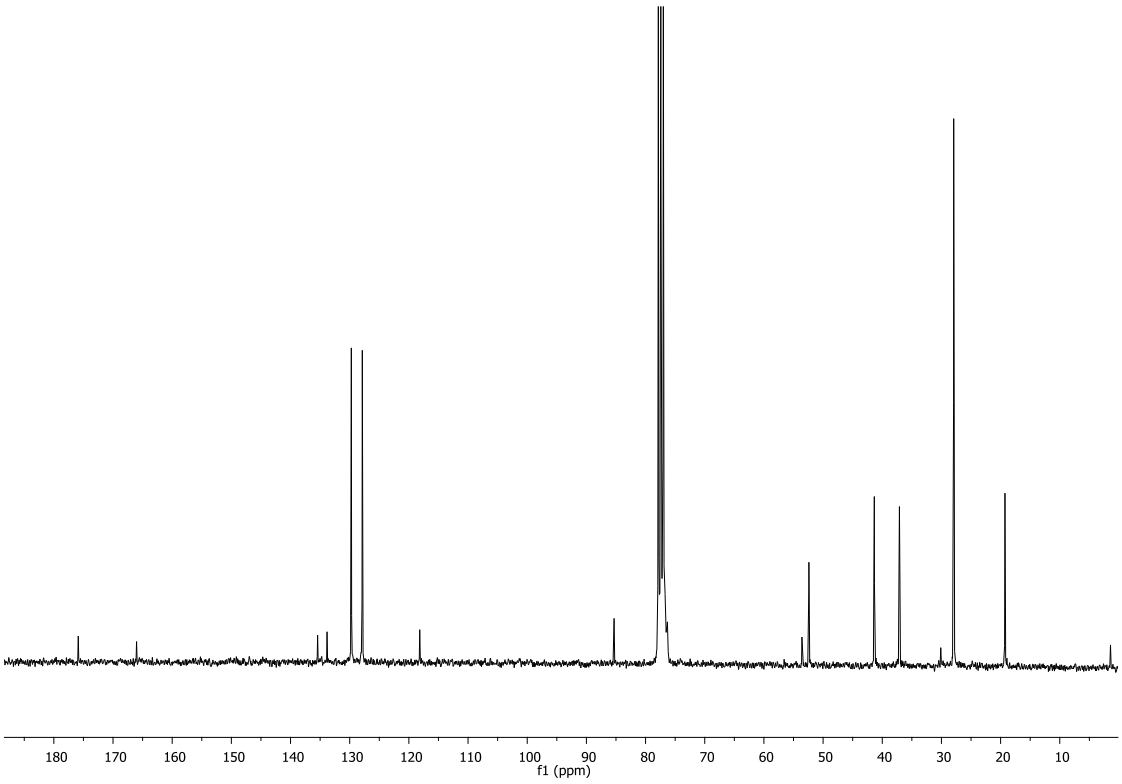
64

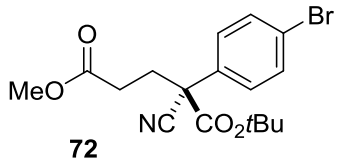



O
MeO
NC
CO2tBu
Cl

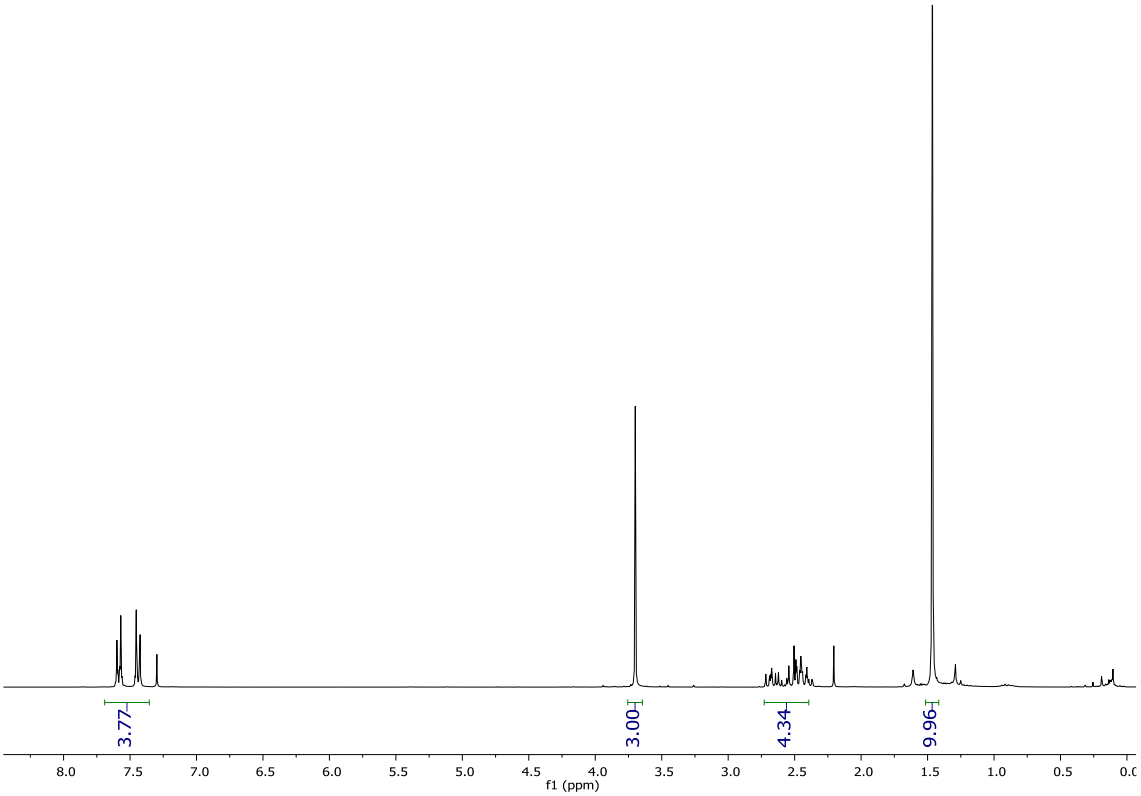
67

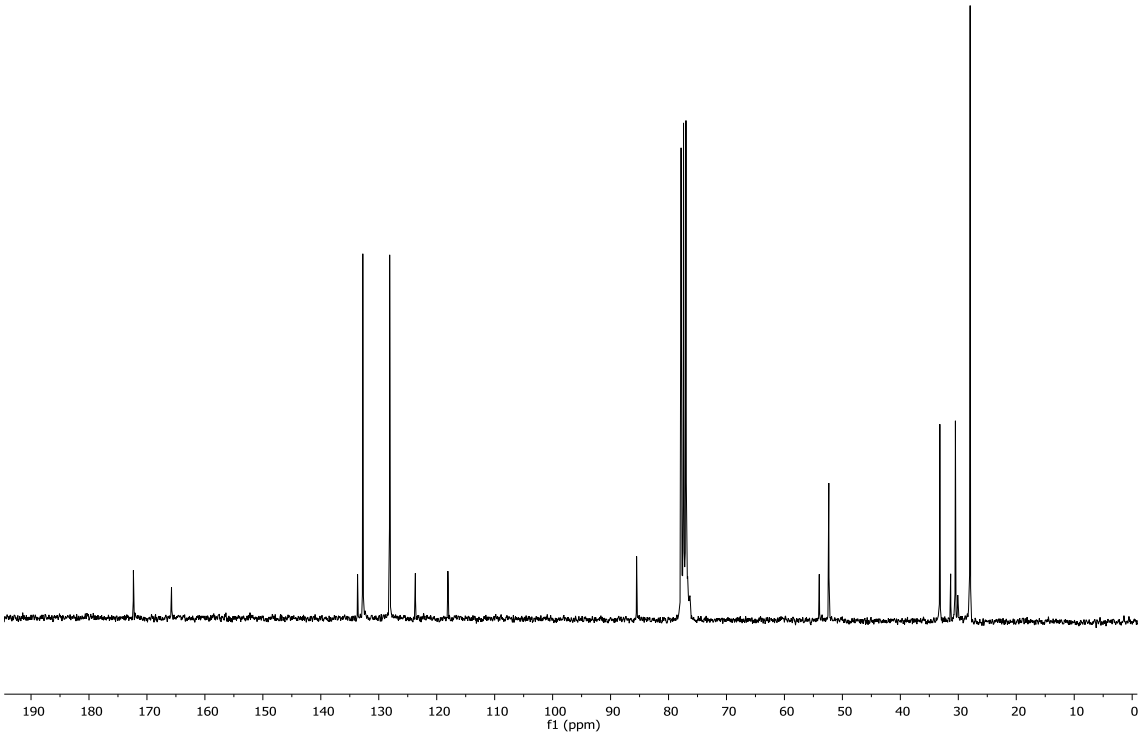
3.54
2.78
1.16
1.00
1.17
9.08
3.15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

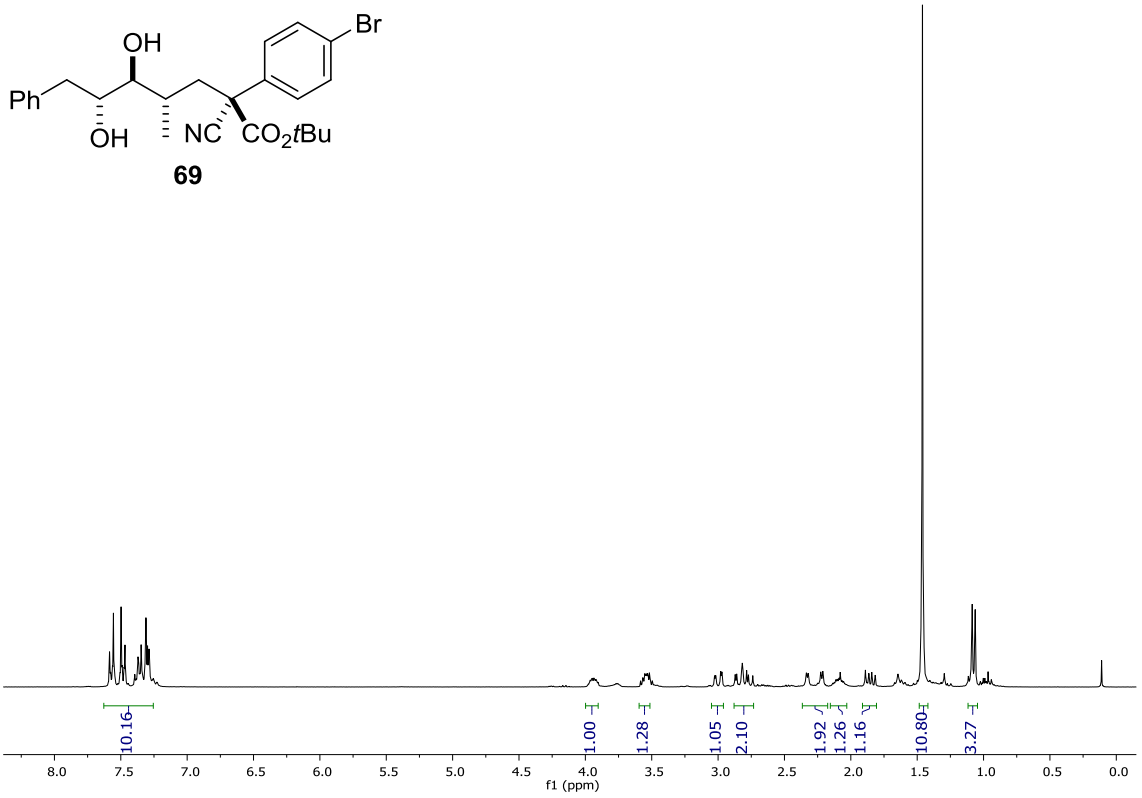

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)



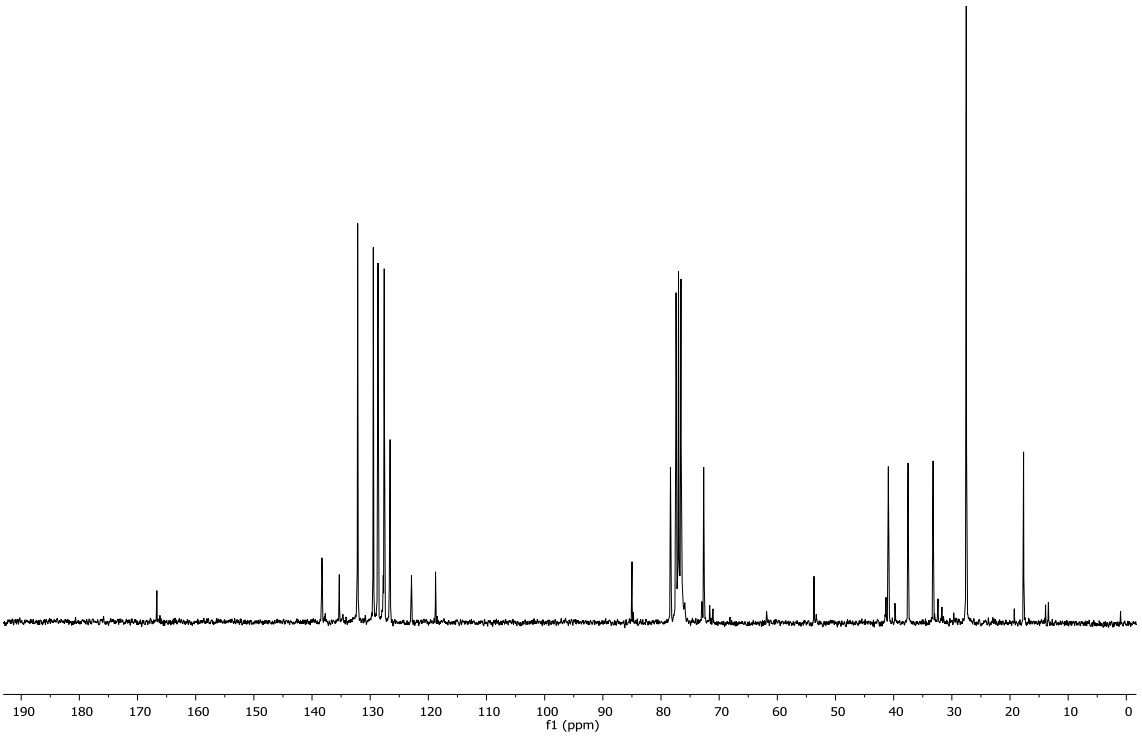
72

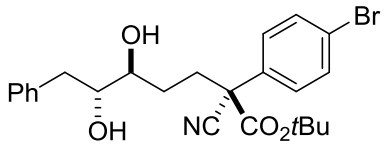




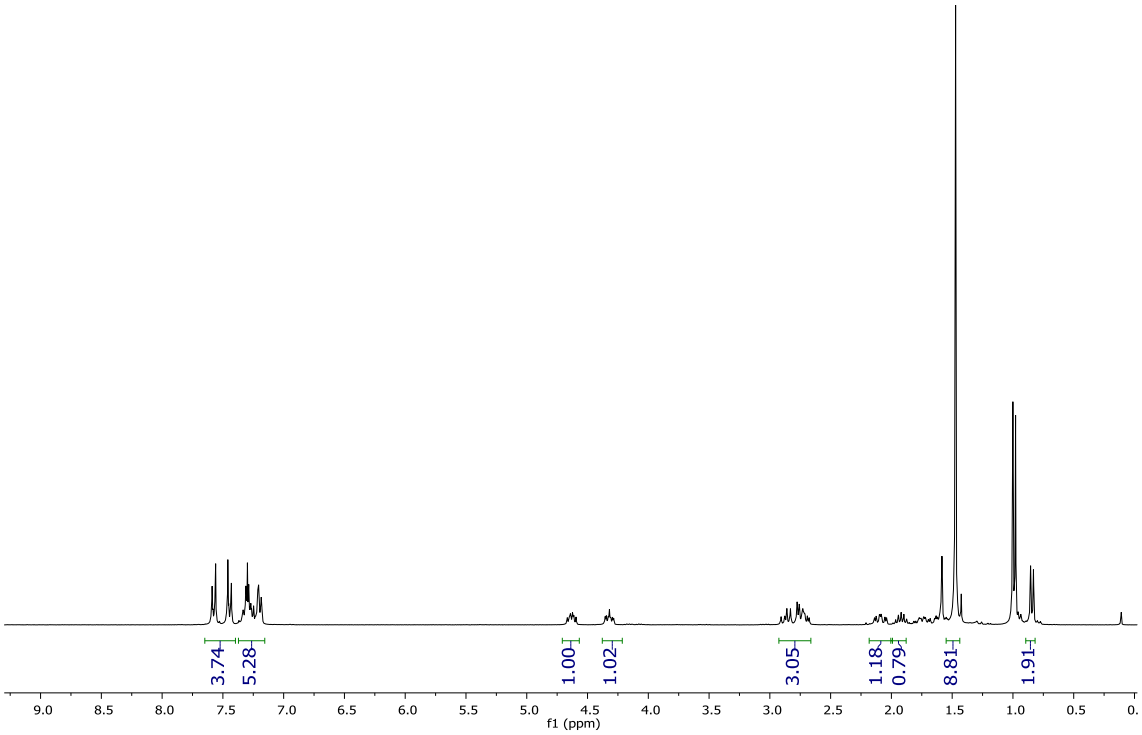

OH
Ph
OH
NC
CO2tBu
Br
10.16
1.00
1.28
1.05
2.10
1.92
1.26
1.16
10.80
3.27
f1 (ppm)

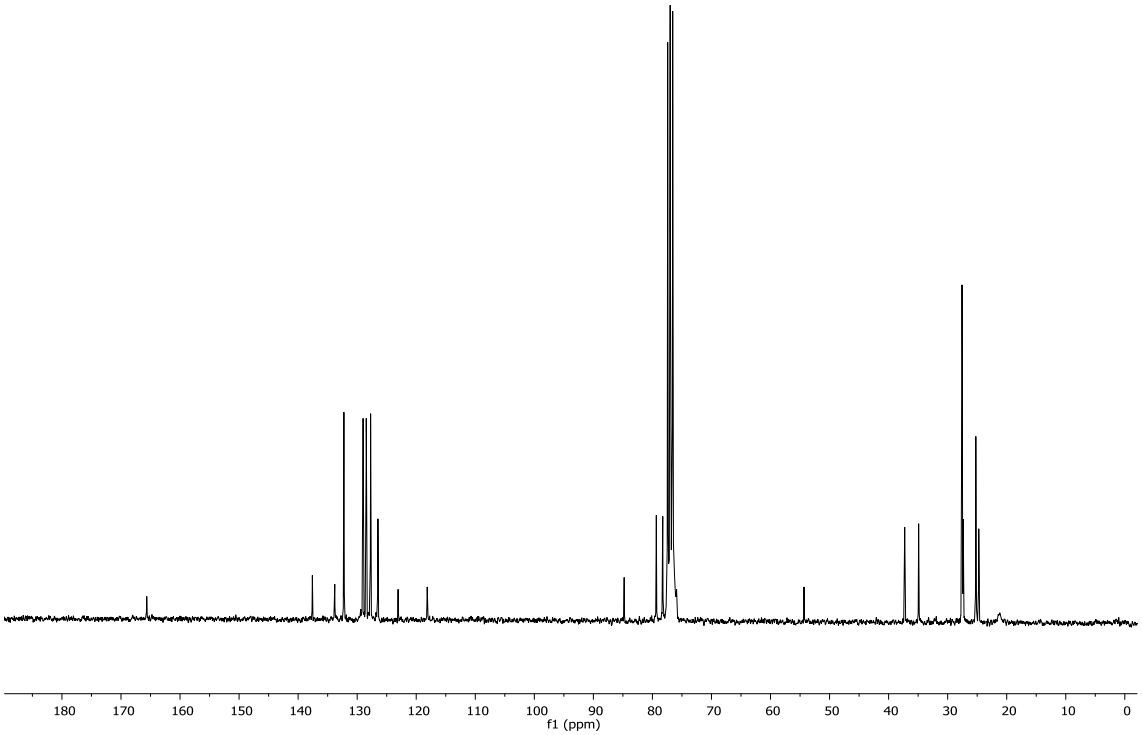
69


f1 (ppm)

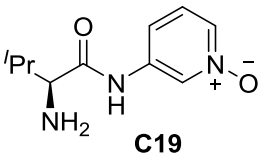

OH
Br
Ph
OH
NC
CO2tBu

70

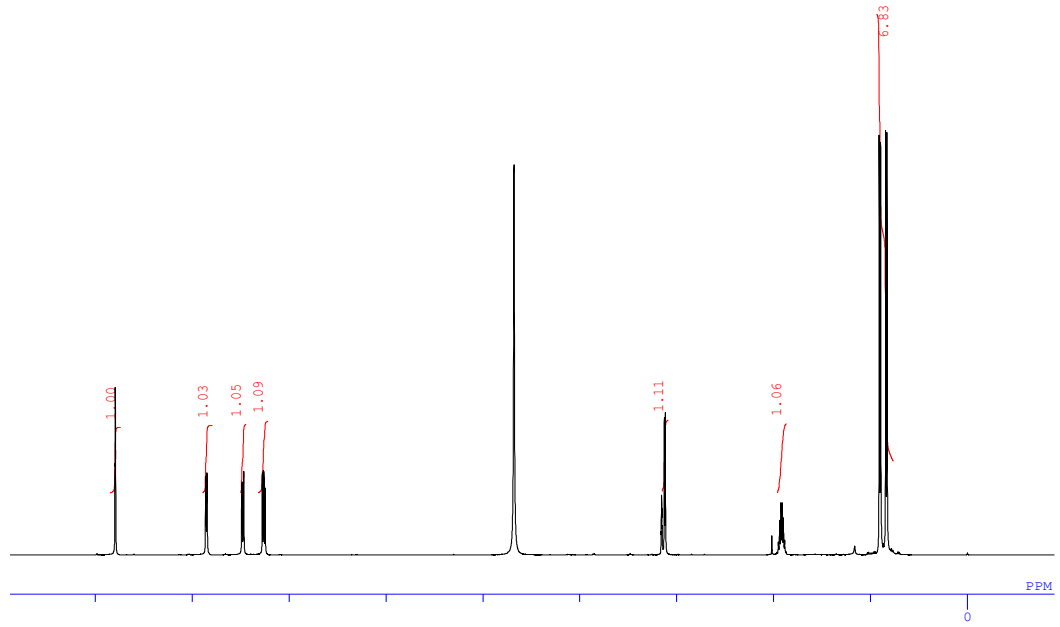

3.74
5.28
1.00
1.02
3.05
1.18
0.79
8.81
1.91
f1 (ppm)

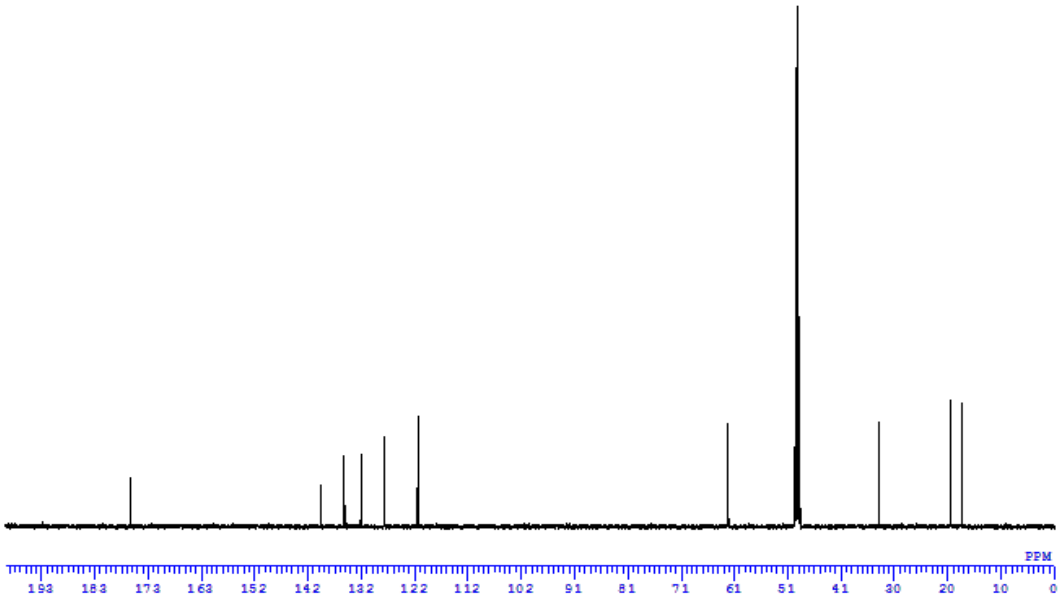

f1 (ppm)

6.5.3. NMR spectra of Chapter 4



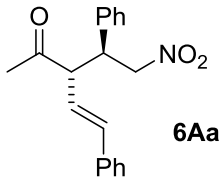
C19





6.6. Determination of diastereomeric ratios and enantiomeric excesses

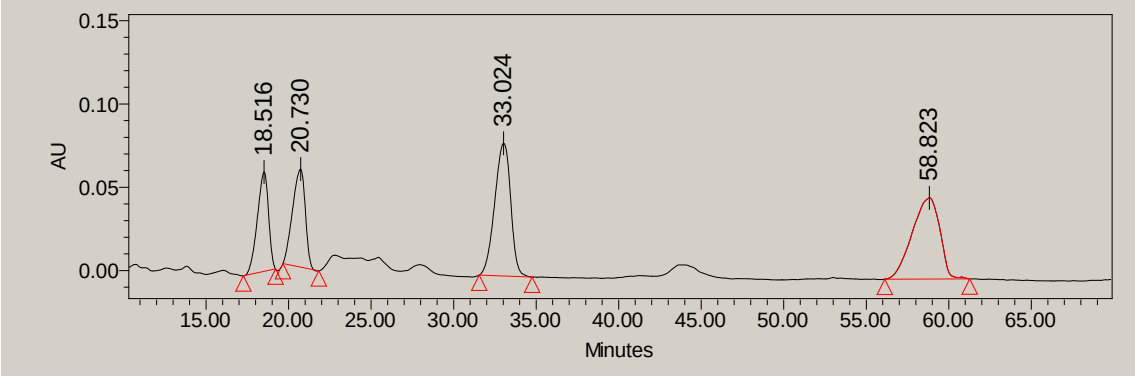
6.6.1. HPLC chromatograms of Chapter 2



6Aa

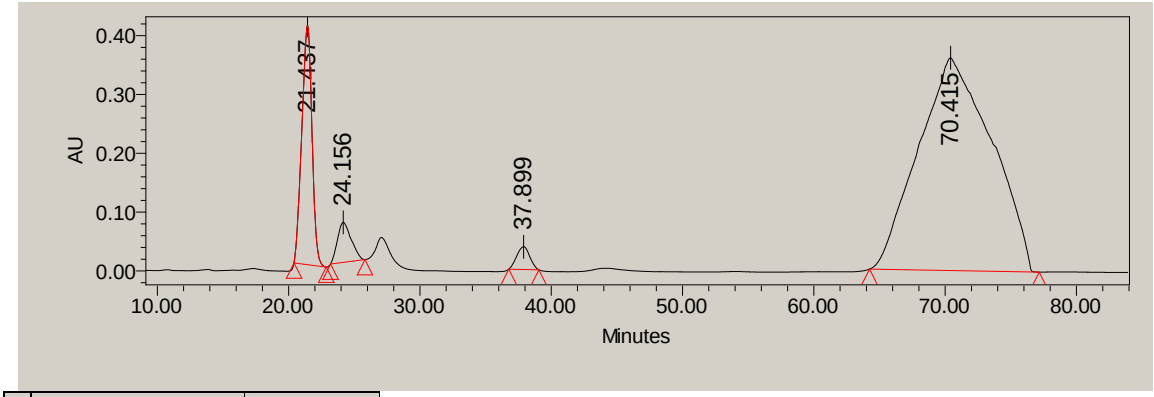
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**6Aa**



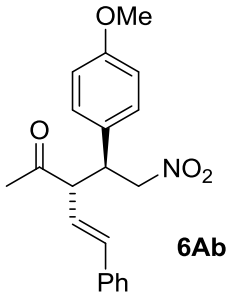
	Retention Time	% Area
1	18.516	16.52
2	20.730	18.48
3	33.024	31.61
4	58.823	33.40

Scalemic **6Aa**



	Retention Time	% Area
1	21.437	12.89
4	70.415	82.62
3	37.899	1.57
2	24.156	2.92

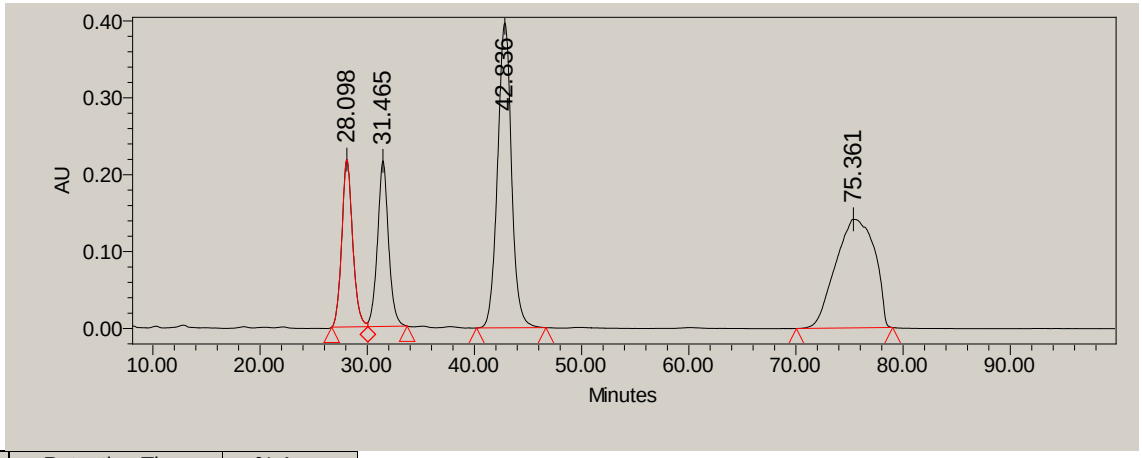
dr 5.2:1 *ee* 96 %



6Ab

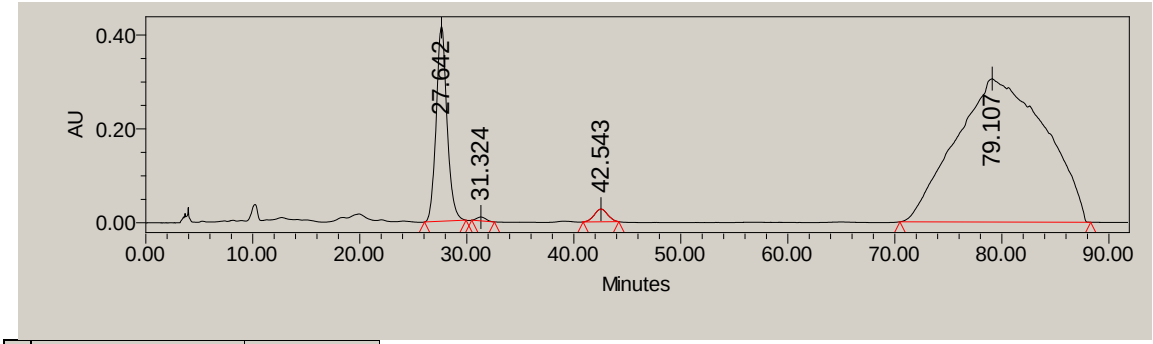
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

Rac-**6Ab**



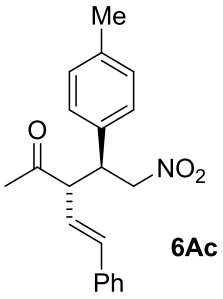
	Retention Time	% Area
1	28.098	15.00
2	31.465	15.03
3	42.836	35.00
4	75.361	34.97

Scalemic **6Ab**



	Retention Time	% Area
4	79.107	84.75
3	42.543	1.12
2	31.324	0.23
1	27.642	13.90

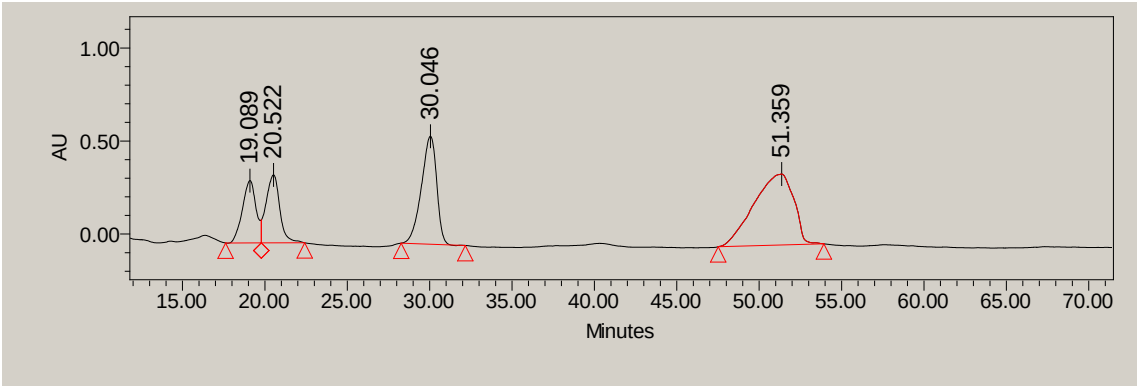
dr 5.2:1 *ee* 98 %



6Ac

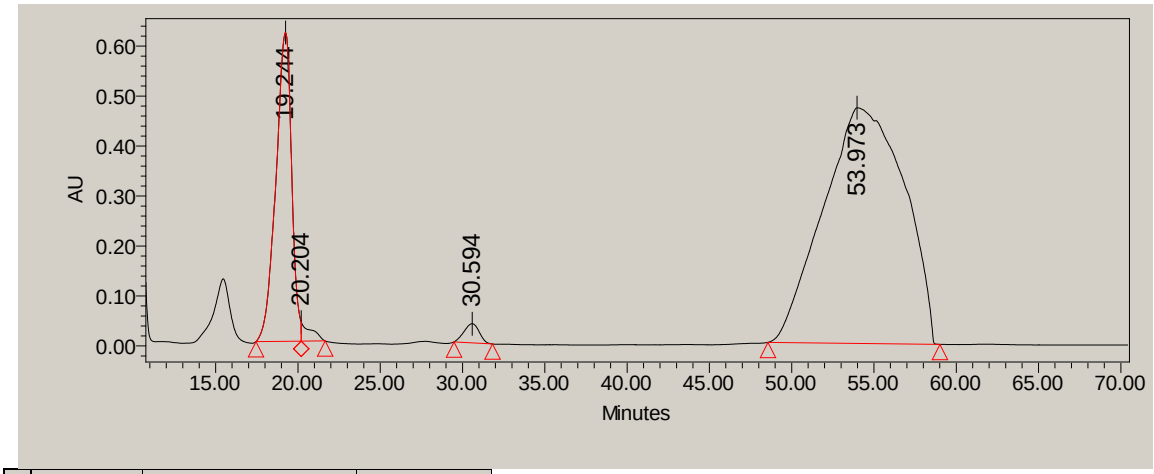
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**6Ac**



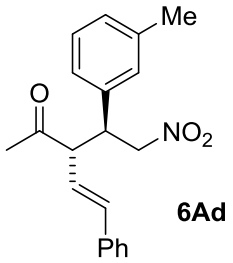
	Retention Time	% Area
1	19.091	13.41
2	20.531	14.07
3	30.046	32.81
4	51.401	39.71

scalemic-**6Ac**



	Name	Retention Time	% Area
1		19.244	14.91
2		20.204	0.76
4		53.973	83.14
3		30.594	1.19

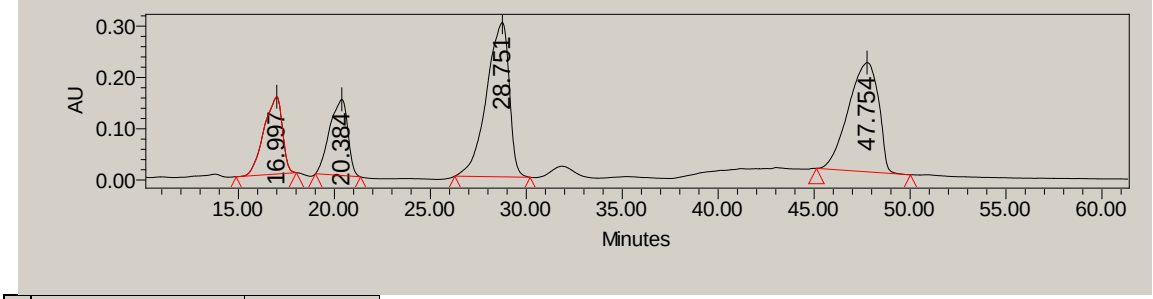
dr 5.7:1 *ee* 97 %



6Ad

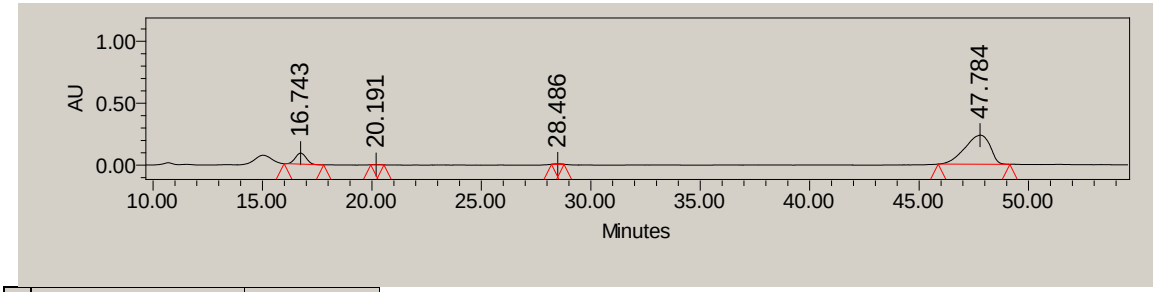
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**6Ad**



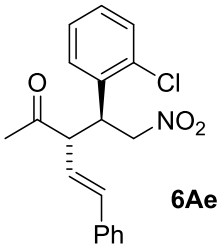
	Retention Time	% Area
1	16.997	14.80
2	20.384	14.37
3	28.751	36.53
4	47.754	34.30

scalemic-**6Ad**



	Retention Time	% Area
1	16.743	14.85
2	20.191	0.17
3	28.486	1.93
4	47.808	83.04

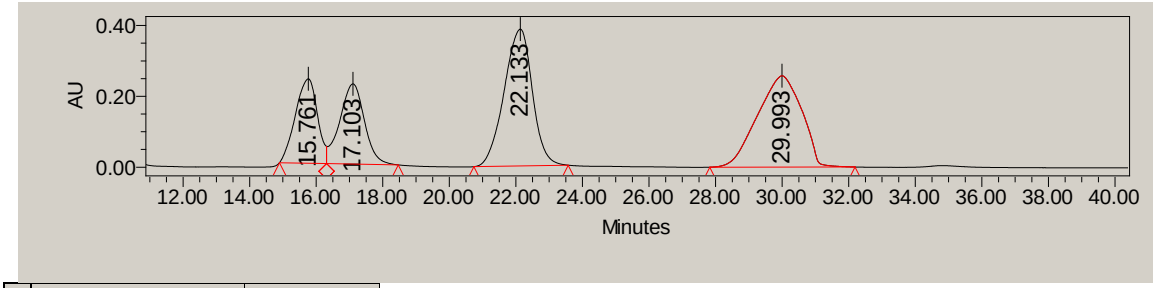
dr 7.3:1 *ee* 96 %



6Ae

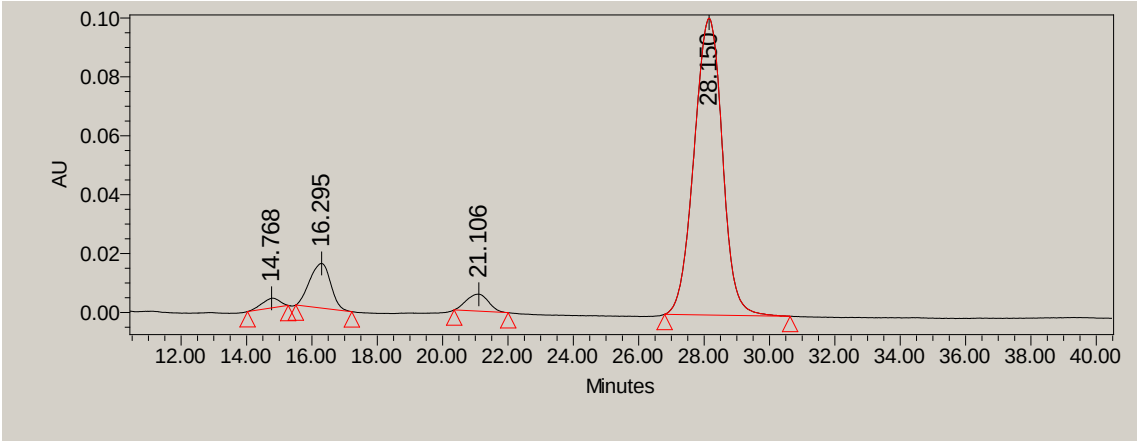
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**6Ae**



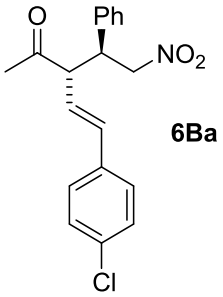
	Retention Time	% Area
4	29.993	34.34
3	22.133	32.92
2	17.103	16.94
1	15.761	15.80

scalemic-**6Ae**



	Retention Time	% Area
4	28.150	85.06
3	21.106	3.78
2	16.295	9.44
1	14.768	1.72

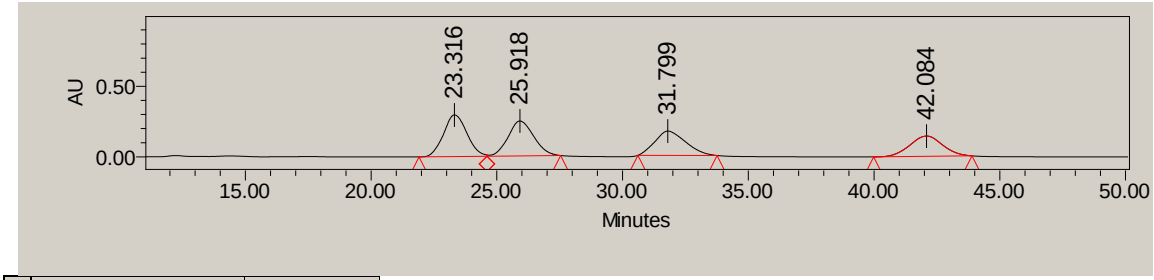
dr 6.7:1 *ee* 90 %



6Ba

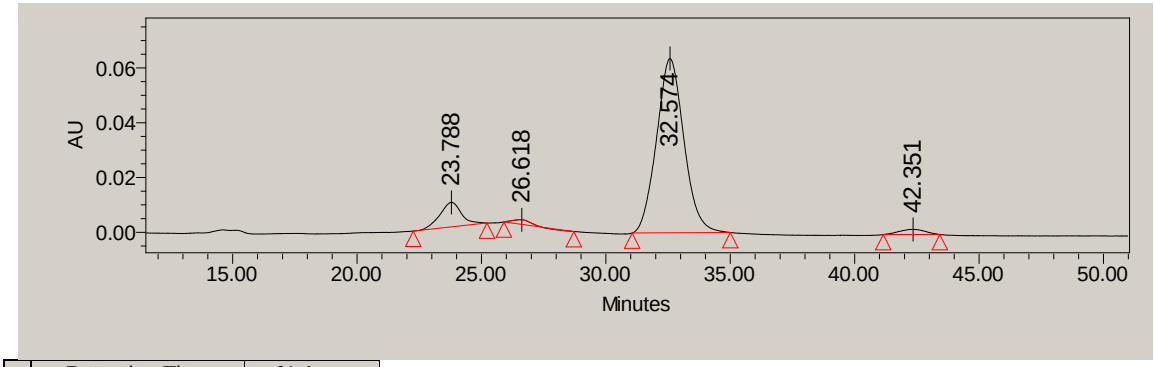
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 98/2, flow rate= 1 mL/min.

rac-**6Ba**



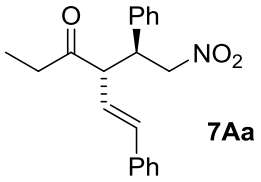
	Retention Time	% Area
4	42.084	20.25
3	31.799	22.77
2	25.918	27.33
1	23.316	29.65

scalemic-**6Ba**



	Retention Time	% Area
1	23.760	8.62
2	26.692	2.29
3	32.570	86.29
4	42.265	2.79

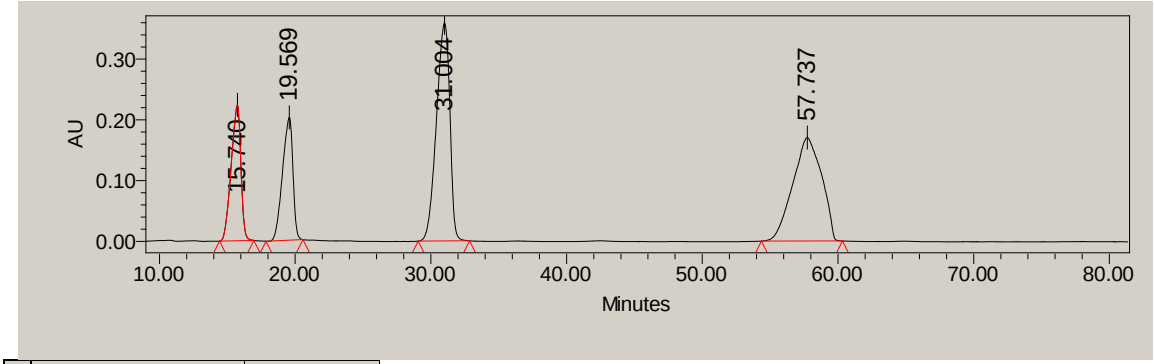
dr 9.0:1 *ee* 92 %



7Aa

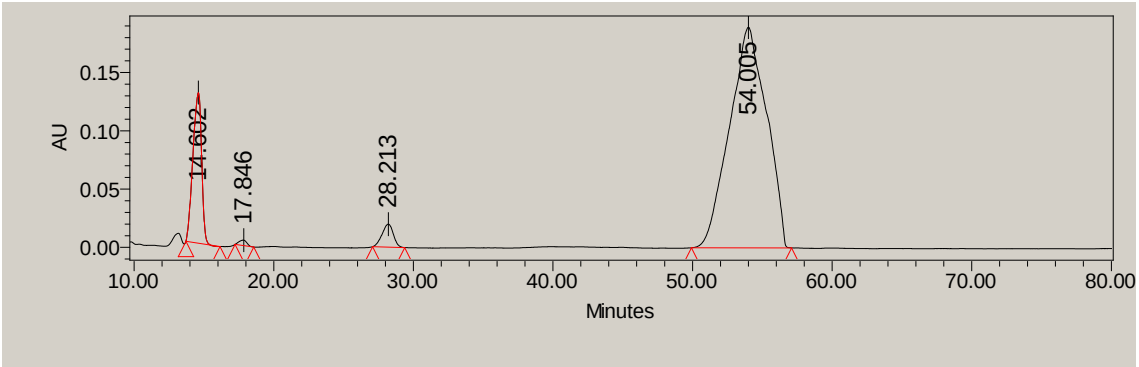
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**7Aa**



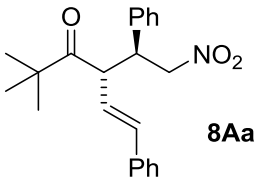
	Retention Time	% Area
1	15.740	15.45
2	19.569	14.98
3	31.004	34.39
4	57.737	35.18

scalemic-7Aa



	Retention Time	% Area
1	14.604	10.96
2	17.836	0.53
3	28.182	2.70
4	54.022	85.81

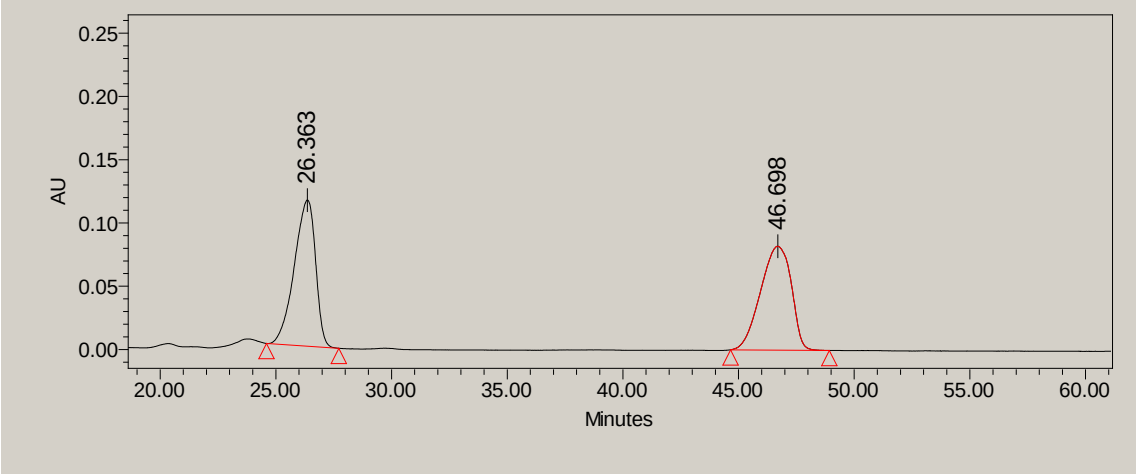
dr 7.3:1 *ee* 95 %



8Aa

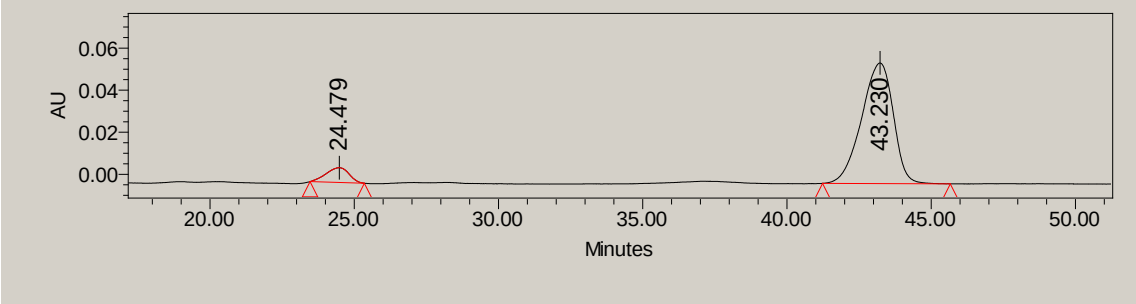
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**8Aa**



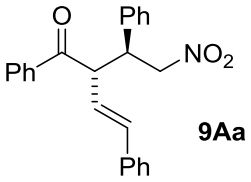
	Retention Time	% Area
2	46.698	50.61
1	26.363	49.39

scalemic-**8Aa**



	Retention Time	% Area
1	24.479	8.11
2	43.230	91.89

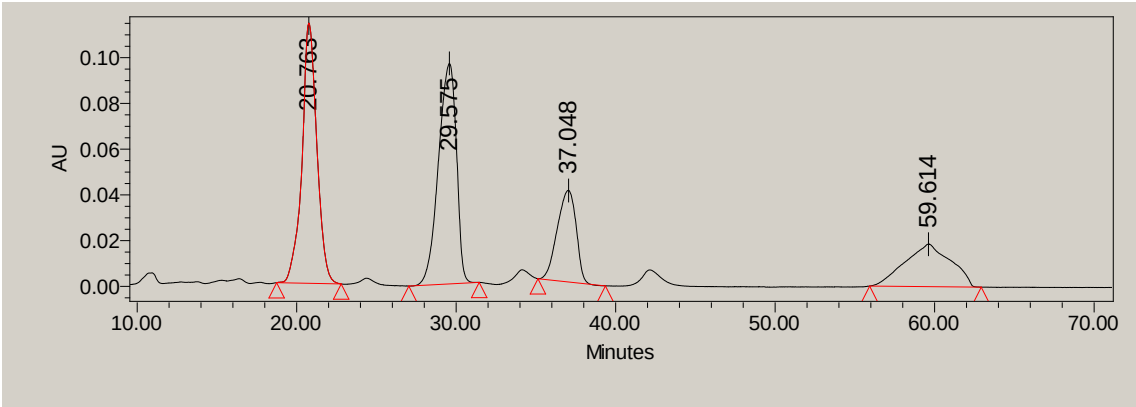
dr >20:1 *ee* 84 %



9Aa

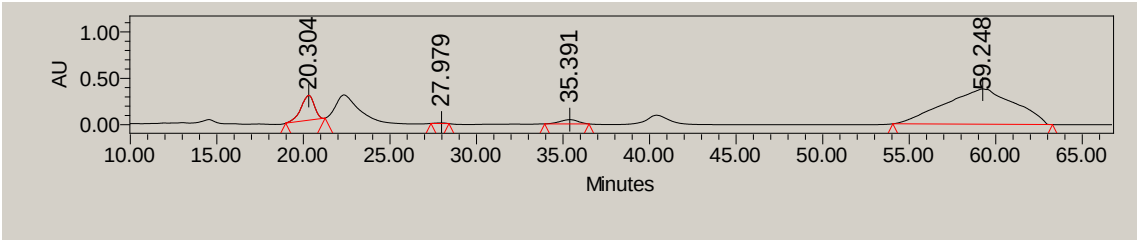
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**9Aa**



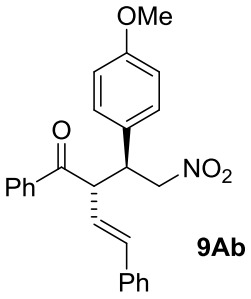
	Retention Time	% Area
1	20.763	33.68
2	29.575	34.37
3	37.048	14.99
4	59.614	16.95

scalemic-**9Aa**



	Retention Time	% Area
1	20.304	11.43
2	27.979	0.20
3	35.391	2.63
4	59.248	85.74

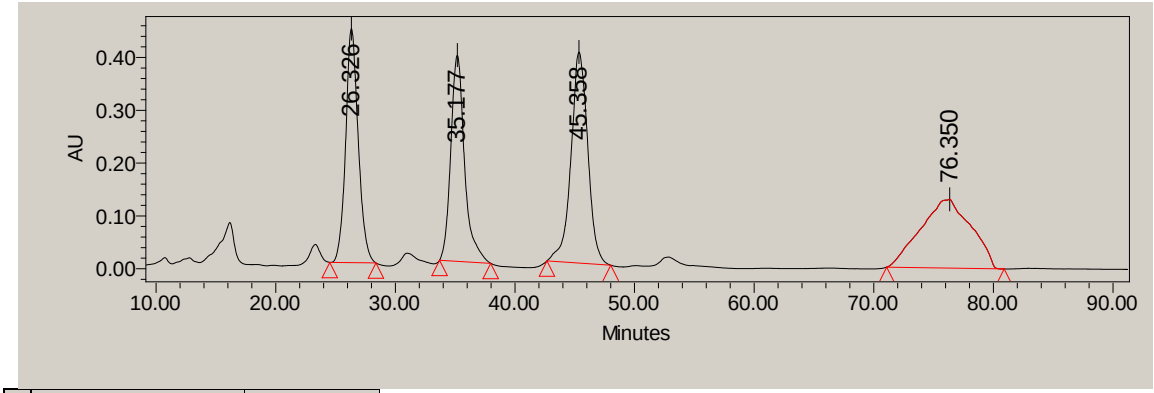
dr 6.7:1 *ee* 95 %



9Ab

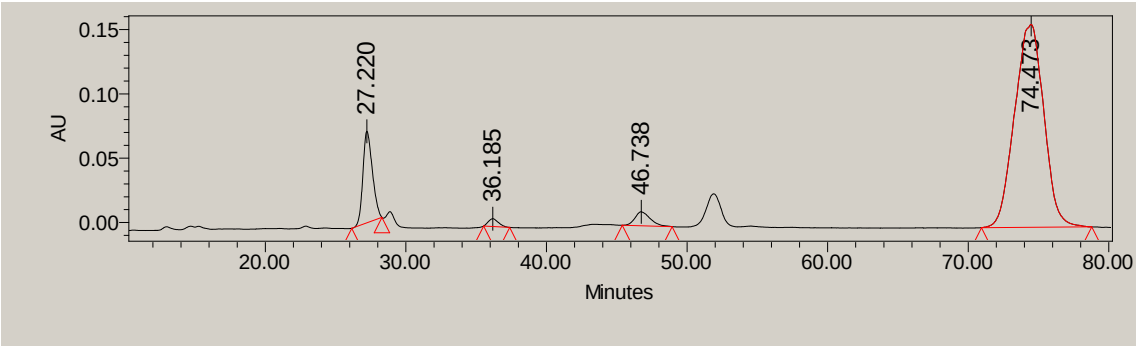
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

rac-**9Ab**



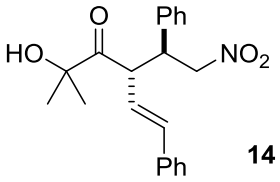
	Retention Time	% Area
4	76.350	27.15
3	45.358	27.68
2	35.177	22.20
1	26.326	22.97

scalemic-**9Ab**



	Retention Time	% Area
4	74.473	83.68
3	46.738	3.01
2	36.185	1.12
1	27.220	12.19

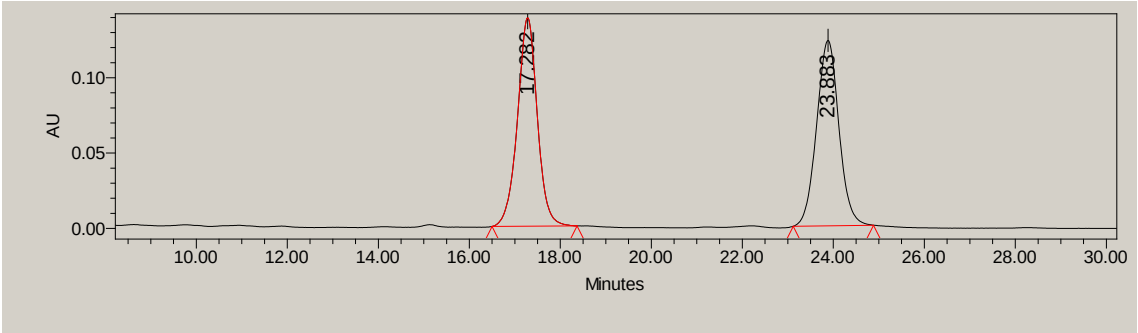
dr 8.1:1 *ee* 97 %



14

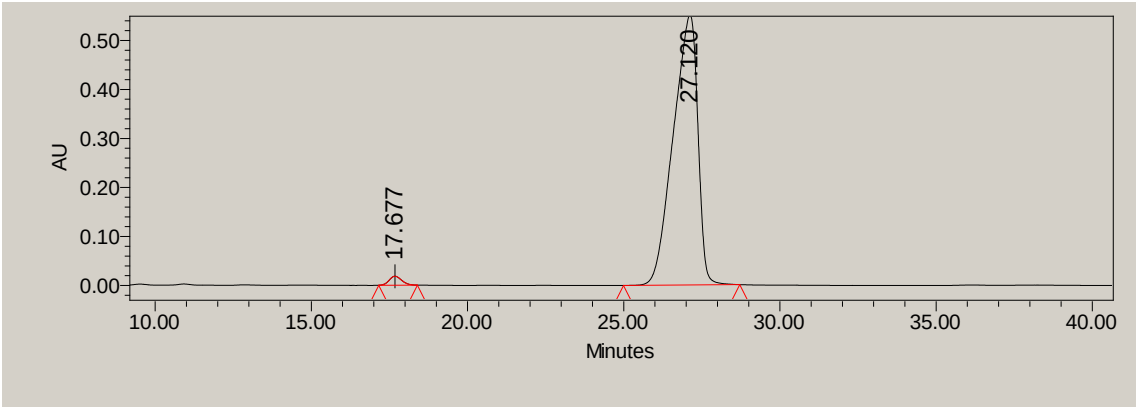
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 90/10, flow rate= 1.0 mL/min.

rac-**14**



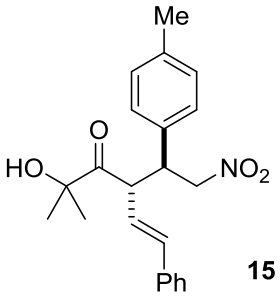
	Retention Time	% Area
1	17.282	50.01
2	23.883	49.99

scalemic-**14**



	Retention Time	% Area
1	17.677	1.67
2	27.120	98.33

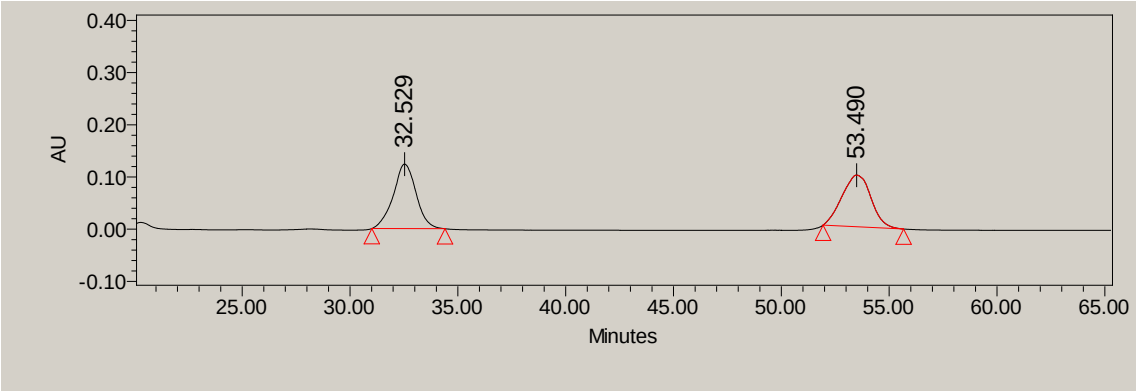
dr >20:1 *ee* 97 %



15

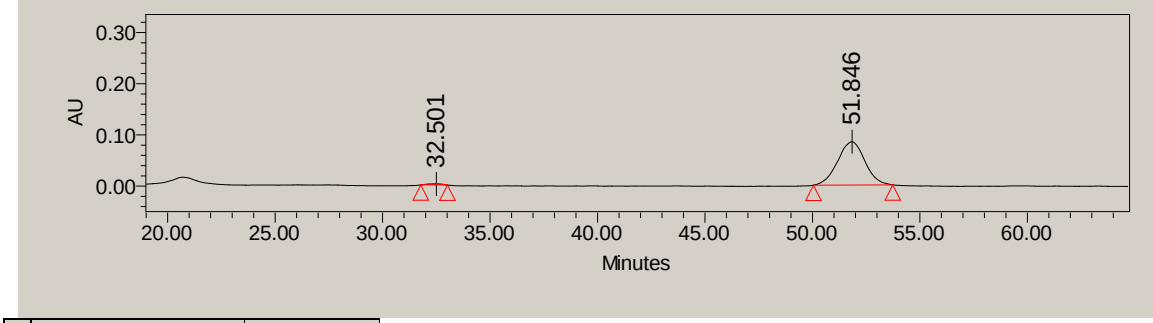
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

rac-**15**



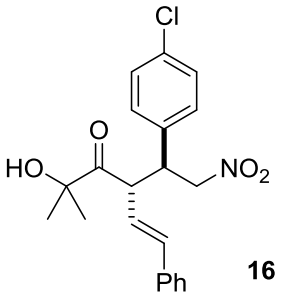
	Retention Time	% Area
2	53.490	50.36
1	32.529	49.64

scalemic-**15**



	Retention Time	% Area
1	32.501	2.40
2	51.848	97.60

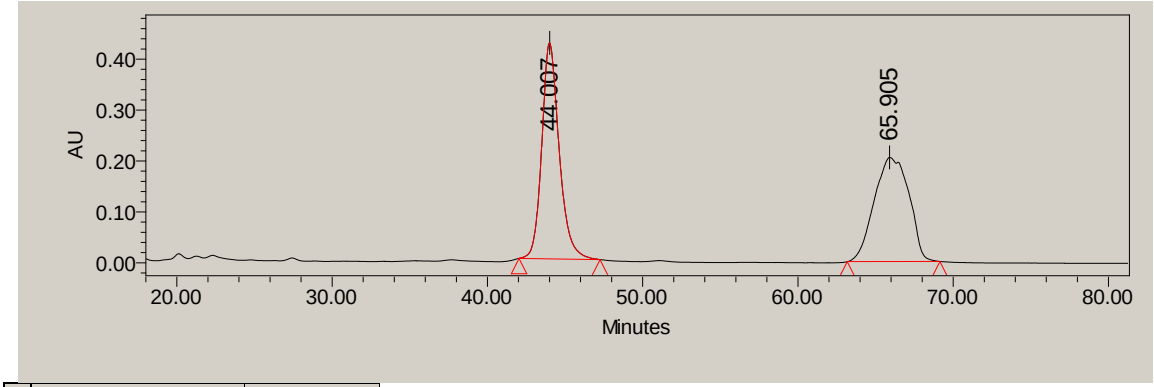
dr >20:1 *ee* 97 %



16

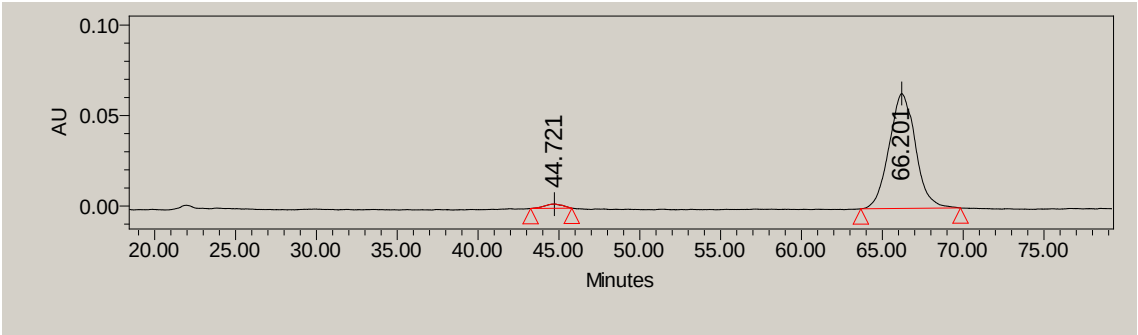
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

rac-**16**



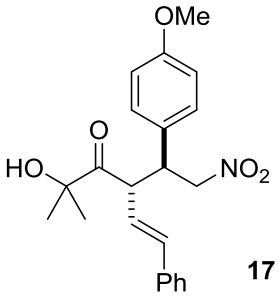
	Retention Time	% Area
1	44.007	50.81
2	65.905	49.19

scalemic-**16**



	Retention Time	% Area
1	44.721	2.47
2	66.201	97.53

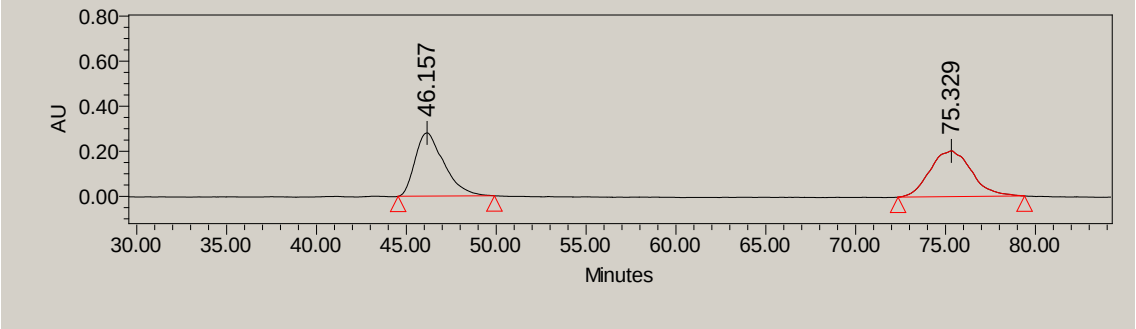
dr >20:1 *ee* 95 %



17

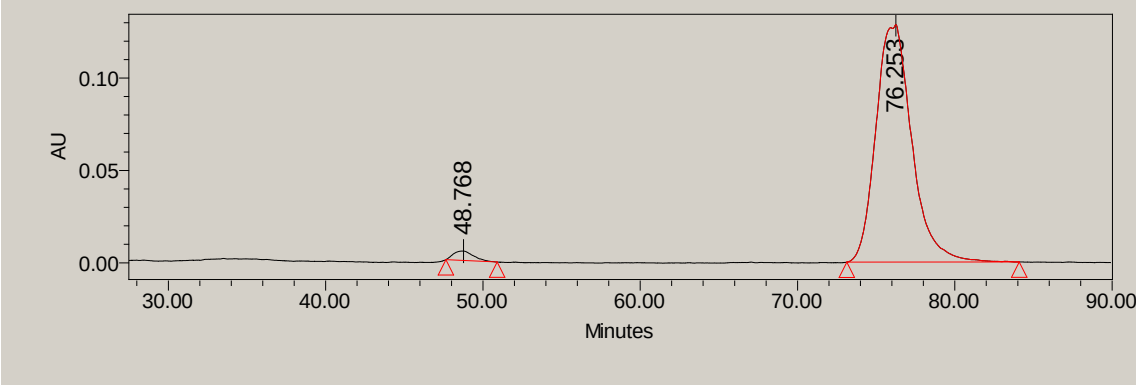
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

rac-**17**



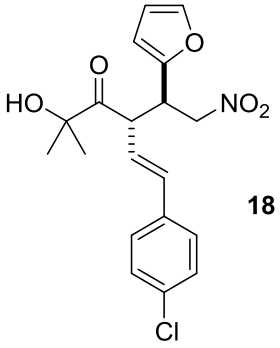
	Retention Time	% Area
2	75.329	51.11
1	46.157	48.89

scalemic-**17**



	Retention Time	% Area
2	76.253	97.85
1	48.768	2.15

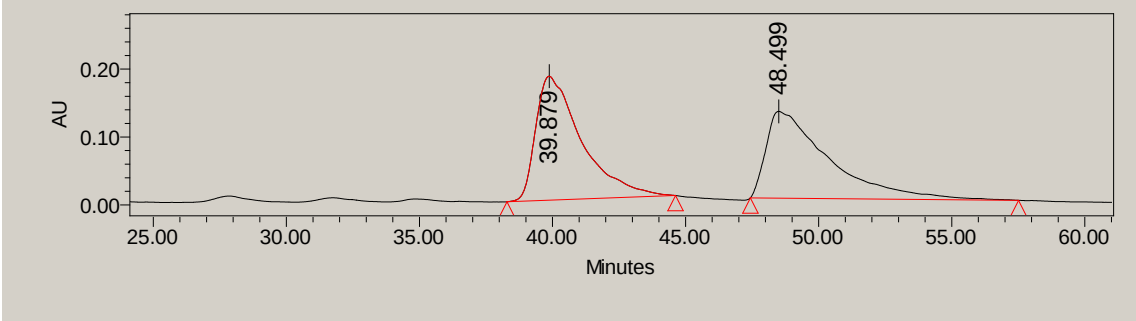
dr >20:1 *ee* 94 %



18

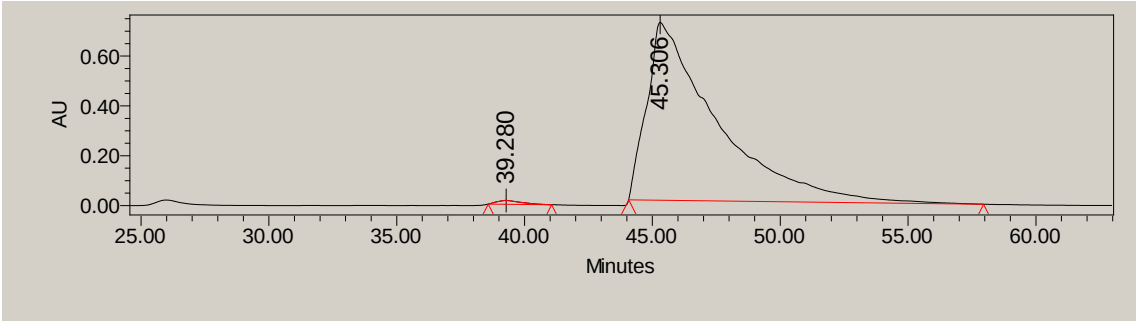
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

rac-**18**



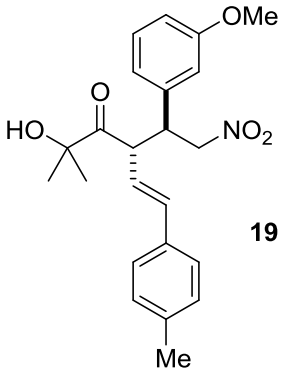
	Retention Time	% Area
1	39.879	51.01
2	48.499	48.99

scalemic-**18**



	Retention Time	% Area
1	39.280	0.75
2	45.306	99.25

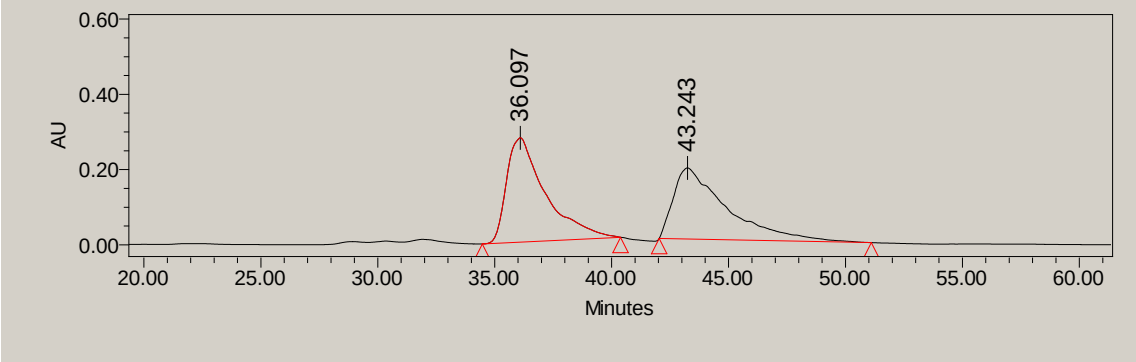
dr >20:1 ***ee*** **98 %**



19

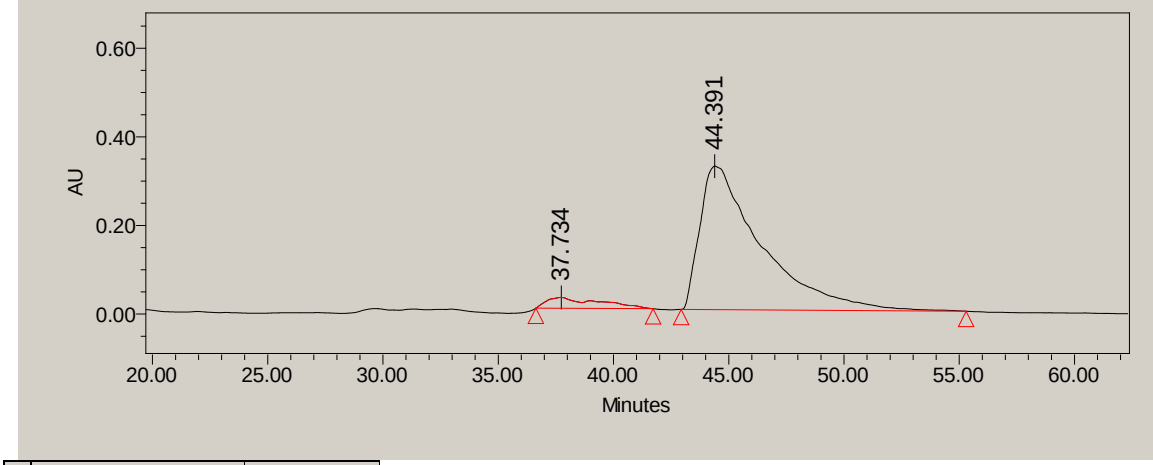
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 95/5, flow rate= 1.0 mL/min.

rac-**19**



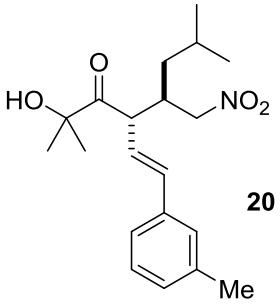
	Retention Time	% Area
1	36.097	51.73
2	43.243	48.27

scalemic-**19**



	Retention Time	% Area
1	37.734	4.79
2	44.391	95.21

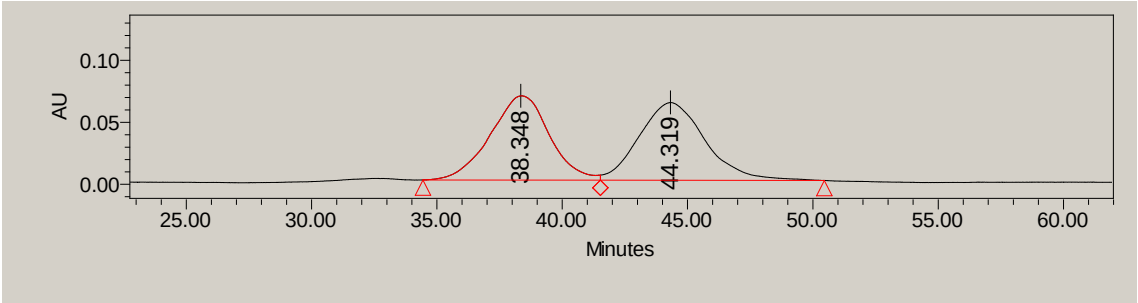
dr >20:1 *ee* 90 %



20

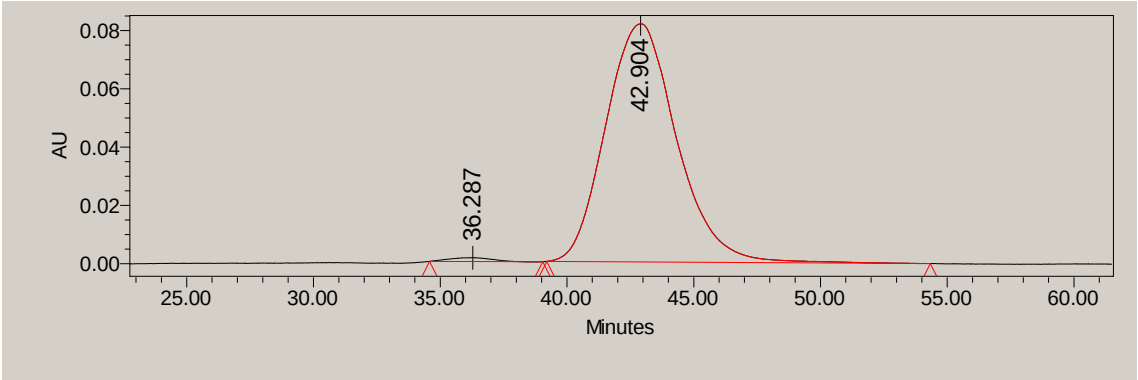
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 99/1, flow rate= 1.0 mL/min.

rac-**20**



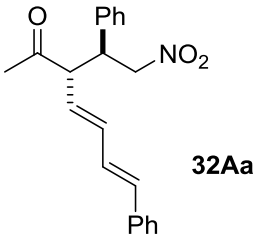
	Retention Time	% Area
1	38.348	49.32
2	44.319	50.68

scalemic-**20**



	Retention Time	% Area
2	42.904	99.02
1	36.287	0.98

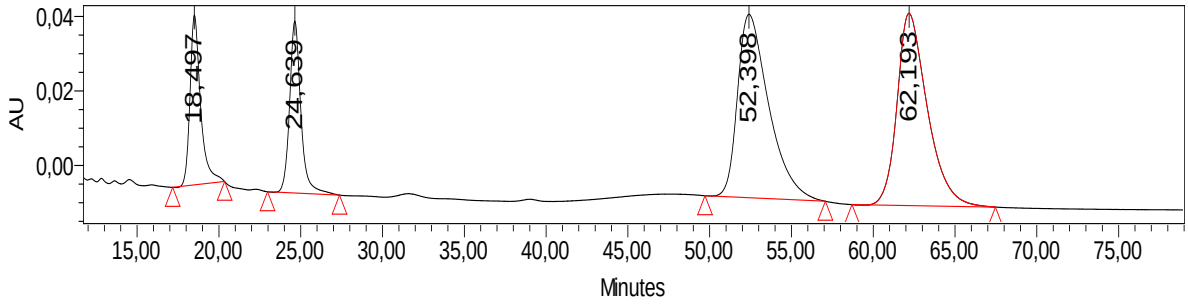
dr >20:1 *ee* 98 %



32Aa

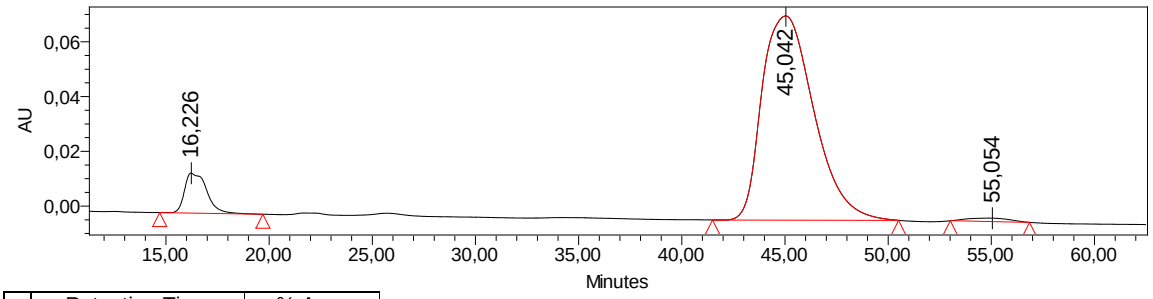
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**32Aa**



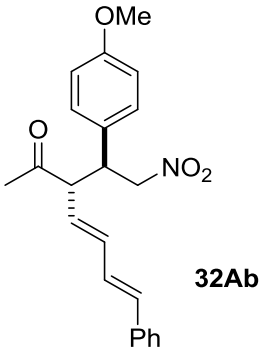
	Retention Time	% Area
1	18,497	11,81
2	24,639	12,66
3	52,398	37,47
4	62,193	38,06

Scalemic-**32Aa**



	Retention Time	% Area
1	16,226	7,59
2	45,042	91,18
3	55,054	1,23

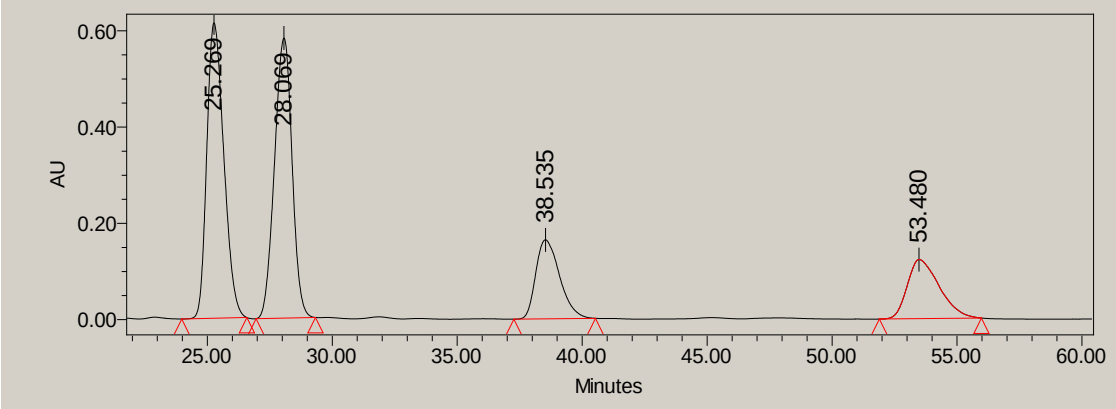
dr 11.5 : 1 *ee* 98 %



32Ab

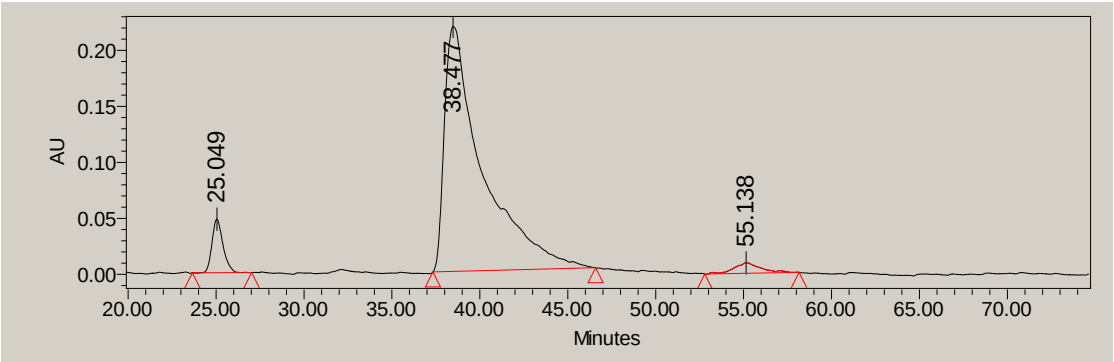
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 98/2, flow rate = 1 mL/min).

Rac-**32Ab**



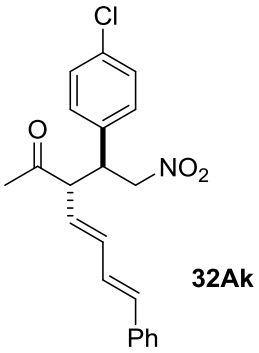
	Retention Time	% Area
1	25.269	36.60
2	28.069	35.89
3	38.535	13.75
4	53.480	13.75

Scalemic-**32Ab**



	Retention Time	% Area
1	25.049	5.95
2	38.477	91.94
3	55.138	2.11

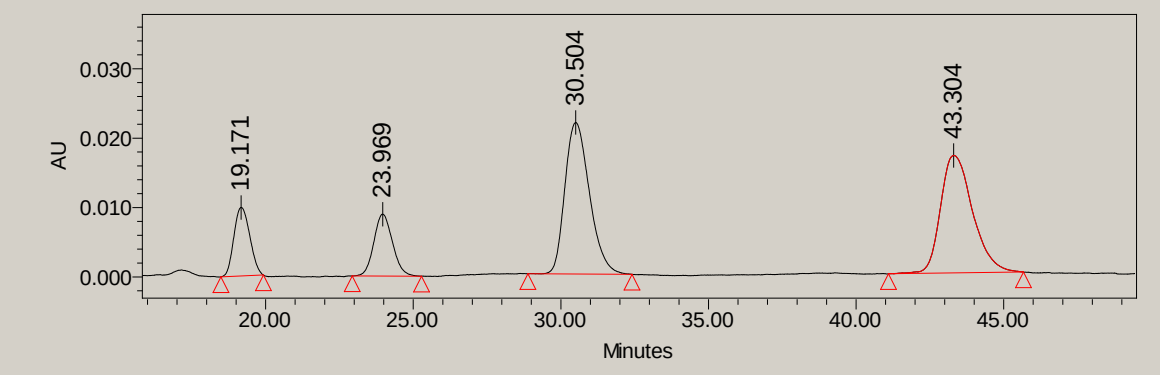
dr 15.7 : 1 *ee* 96 %



32Ak

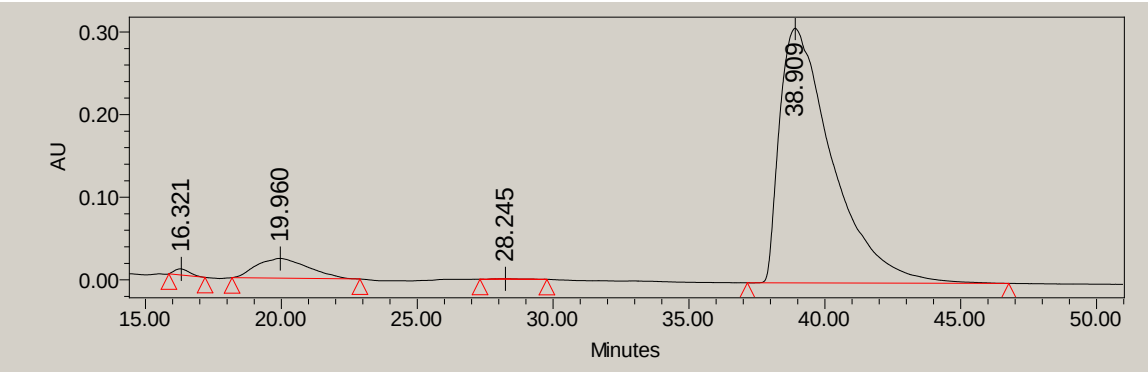
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 95/5, flow rate = 1 mL/min).

Rac-**32Ak**



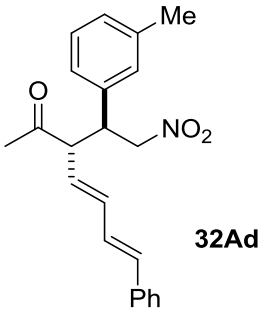
	Retention Time	% Area
1	19.171	11.20
2	23.969	11.86
3	30.504	38.24
4	43.304	38.70

Scalemic-**32Ak**



	Retention Time	% Area
1	16.321	0.50
2	19.960	6.81
3	28.245	0.10
4	38.909	92.58

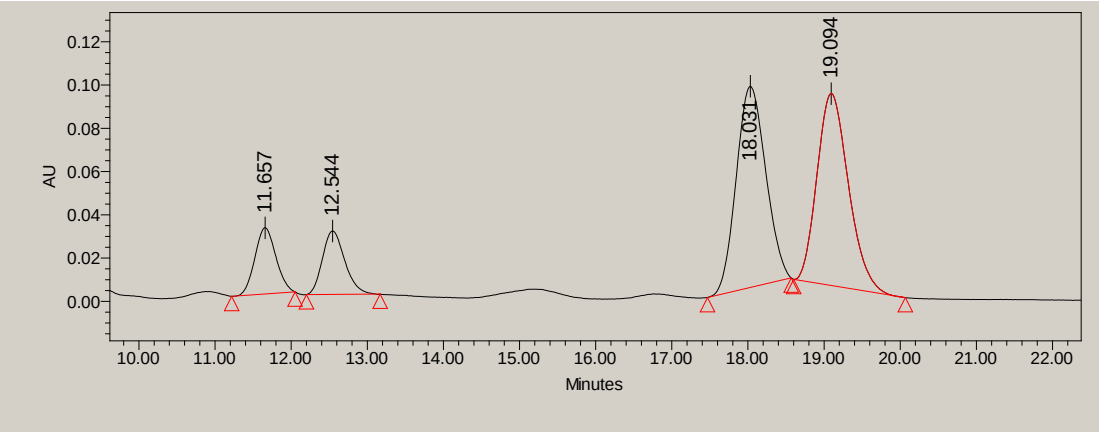
dr 13.3 : 1 *ee* >99 %



32Ad

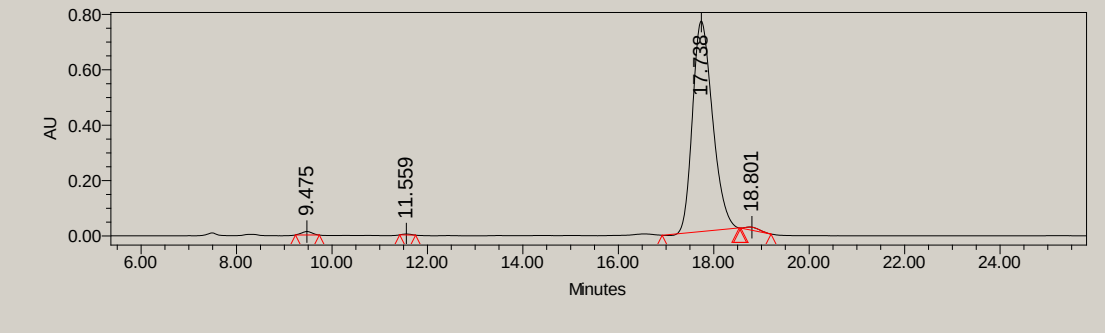
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 90/10, flow rate = 0.75 mL/min).

Rac-**32Ad**



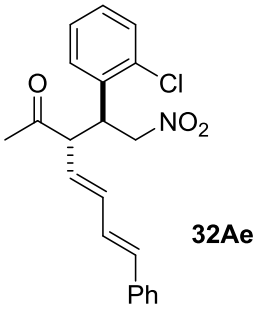
	Retention Time	% Area
1	11.657	9.43
2	12.544	9.61
3	18.031	40.09
4	19.094	40.87

Scalemic-**32Ad**



	Retention Time	% Area
1	9.475	0.83
2	11.559	0.17
3	17.738	98.05
4	18.801	0.95

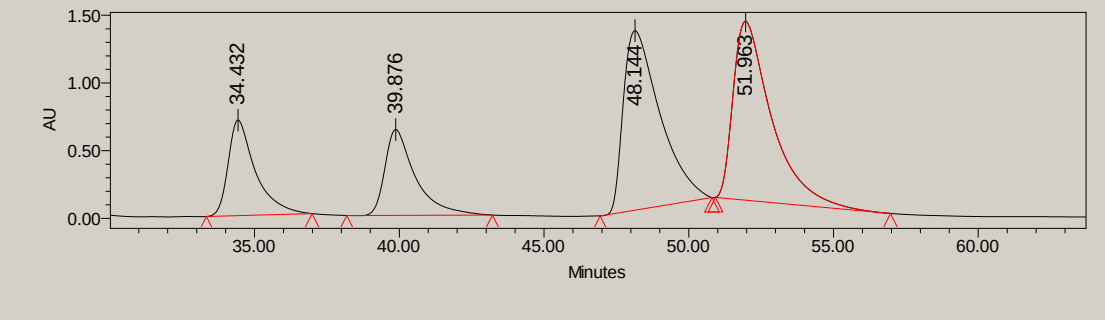
dr >20 : 1 *ee* 98 %



32Ae

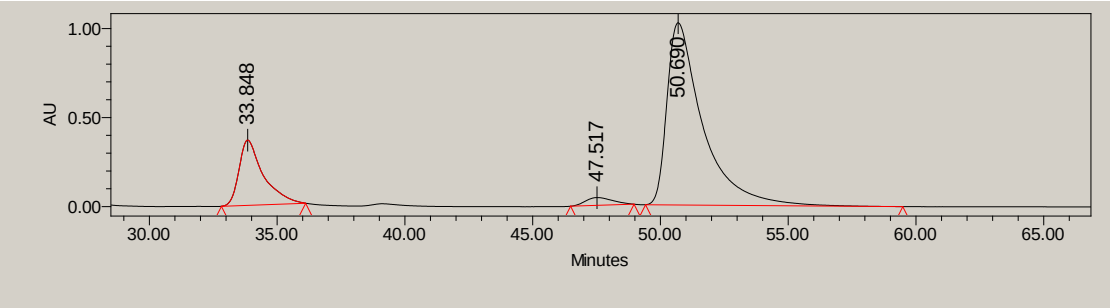
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA+IA hexane/ispropanol 90/10, flow rate = 0.5 mL/min).

Rac-**32Ae**



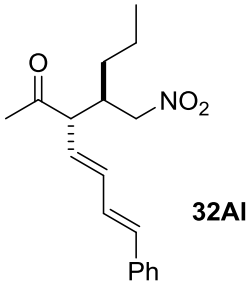
	Retention Time	% Area
1	34.432	13.91
2	39.876	13.96
3	48.144	35.26
4	51.963	36.86

Scalemic-**32Ae**



	Retention Time	% Area
1	33.848	19.00
2	47.517	2.54
3	50.690	78.47

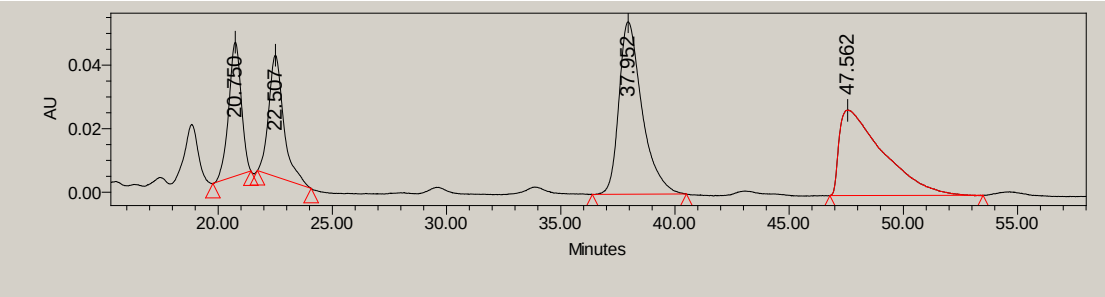
dr 4.3 : 1 *ee* 94 %



32Al

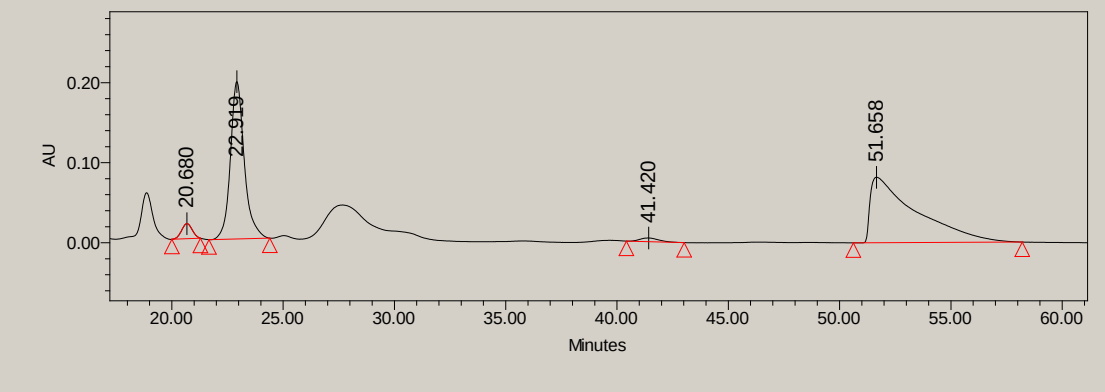
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 99/1, flow rate = 0.5 mL/min).

Rac-**32Al**



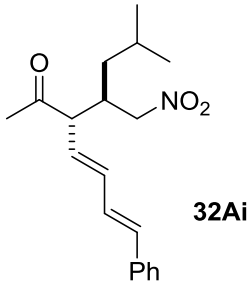
	Retention Time	% Area
1	20.750	14.93
2	22.507	16.21
3	37.952	35.48
4	47.562	33.38

Scalemic-**32Al**



	Retention Time	% Area
1	20.680	2.96
2	22.919	40.34
3	41.420	1.28
4	51.658	55.42

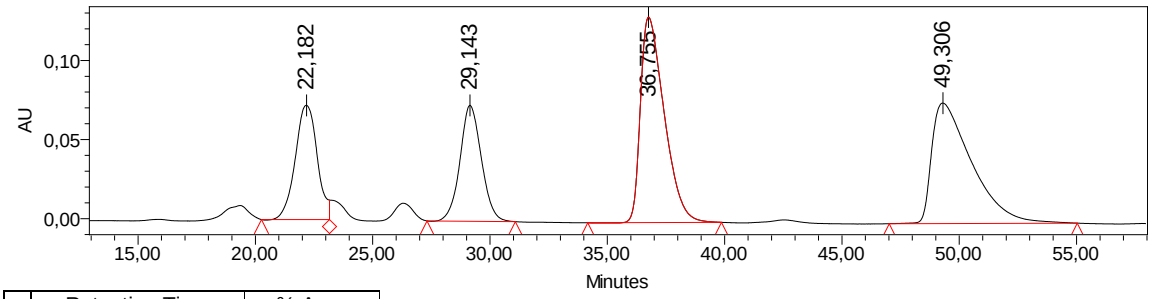
dr 1.3 : 1 *ee* 95 %



32Ai

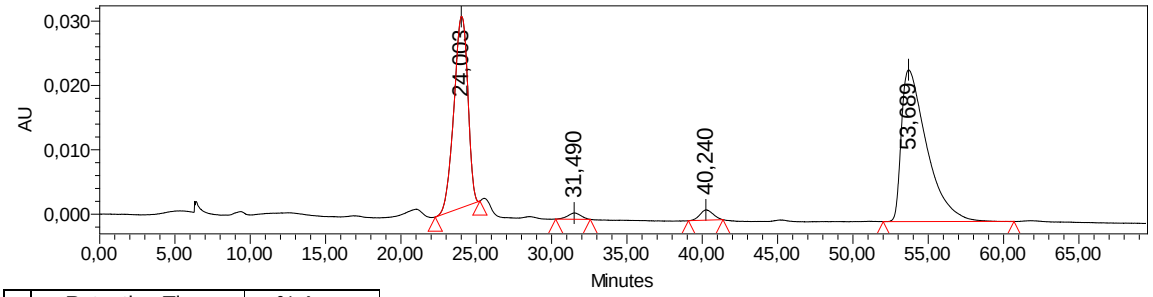
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 99/1, flow rate = 0.5 mL/min).

Rac-**32Ai**



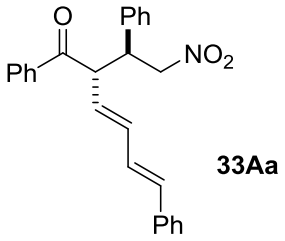
	Retention Time	% Area
1	22,182	17,10
2	29,143	16,92
3	36,755	33,22
4	49,306	32,76

Scalemic-**32Ai**



	Retention Time	% Area
1	24,003	39,63
2	31,490	1,21
3	40,240	2,01
4	53,689	57,15

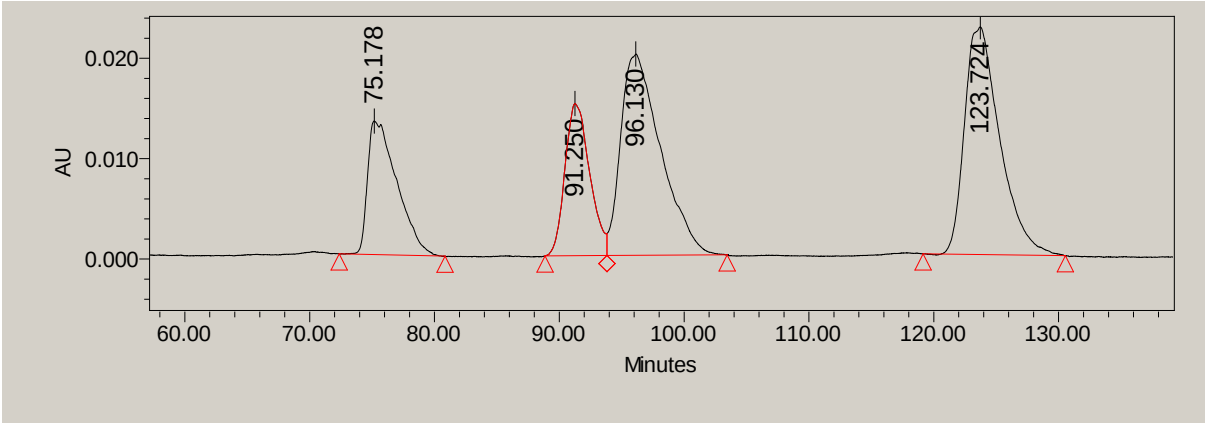
dr 1.4 : 1 *ee* 94 %



33Aa

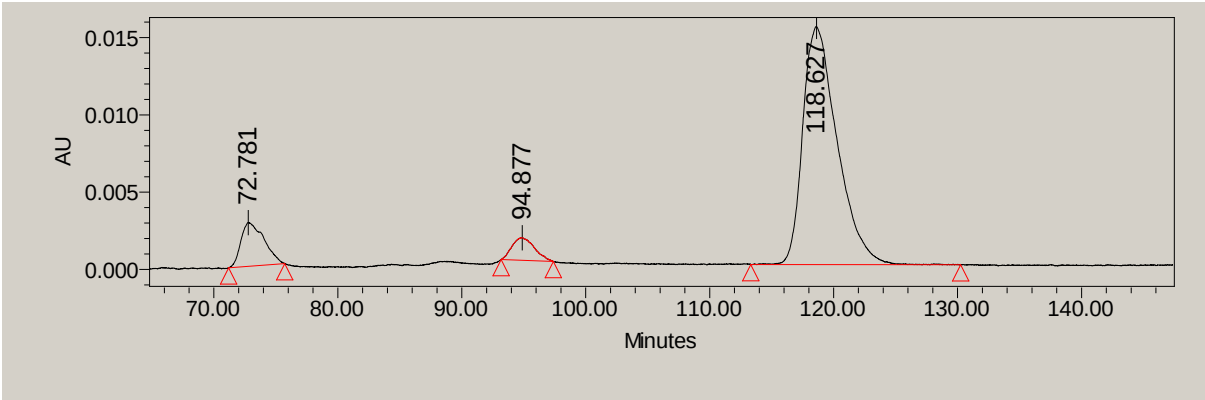
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ispropanol 98/2, flow rate = 1 mL/min).

Rac-**33Aa**



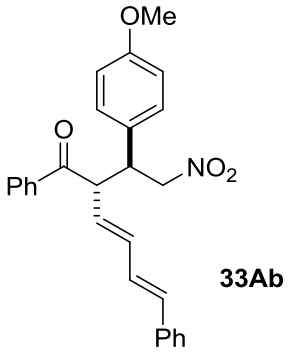
	Retention Time	% Area
1	75.178	16.49
2	91.250	15.82
3	96.130	33.83
4	123.724	33.86

Scalemic-**33Aa**



	Retention Time	% Area
1	72.781	10.40
2	94.877	5.22
3	118.627	84.39

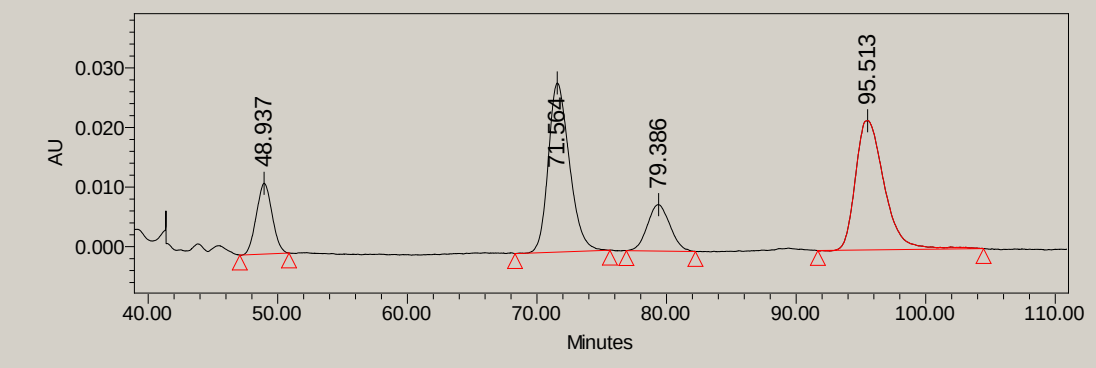
dr 9 : 1 *ee* 90%



33Ab

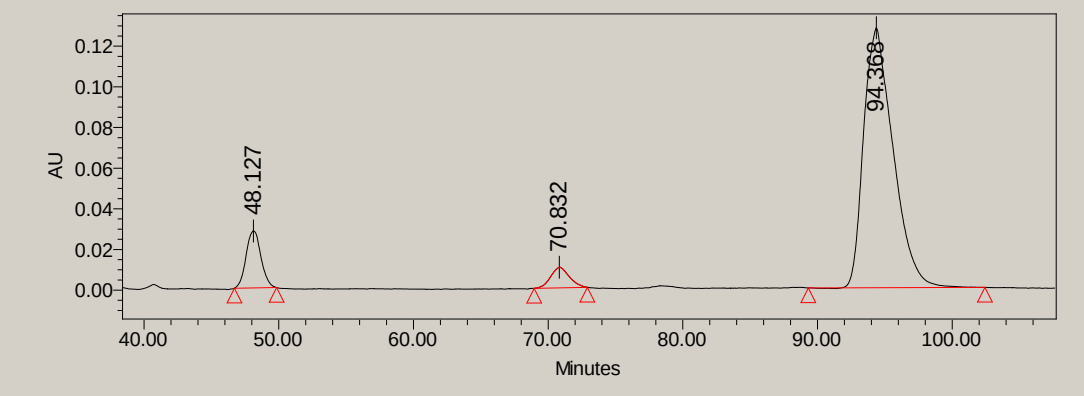
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IC+IA hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**33Ab**



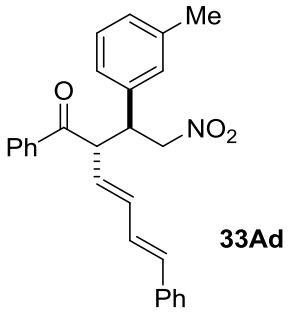
	Retention Time	% Area
1	48.937	11.79
2	71.564	37.72
3	79.386	11.09
4	95.513	39.40

Scalemic-**33Ab**



	Retention Time	% Area
1	48.127	9.47
2	70.832	4.27
3	94.368	86.25

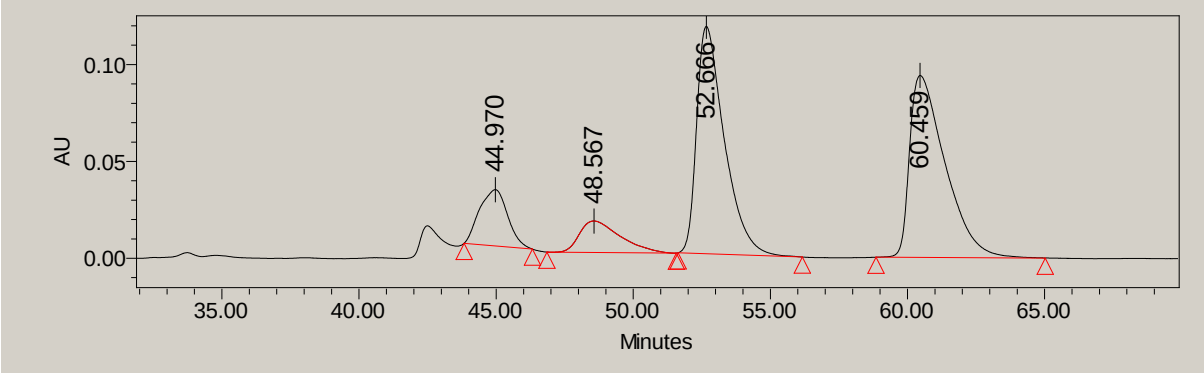
dr 10.1 : 1 *ee* 92 %



33Ad

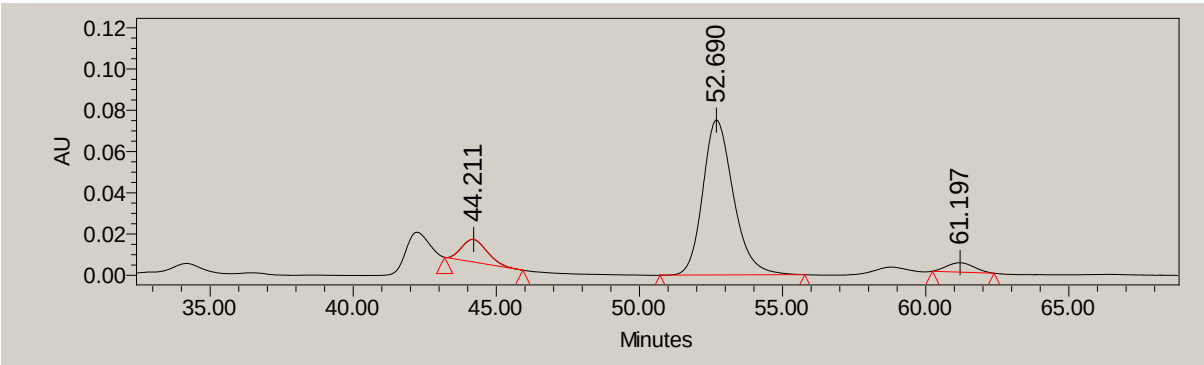
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IB+IB hexane/ethanol 98/2, flow rate = 1 mL/min).

Rac-**33Ad**



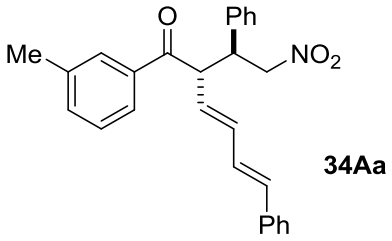
	Retention Time	% Area
1	44.970	10.11
2	48.567	8.19
3	52.666	40.35
4	60.459	41.36

Scalemic-**33Ad**



	Retention Time	% Area
1	44.211	10.31
2	52.690	85.14
3	61.197	4.56

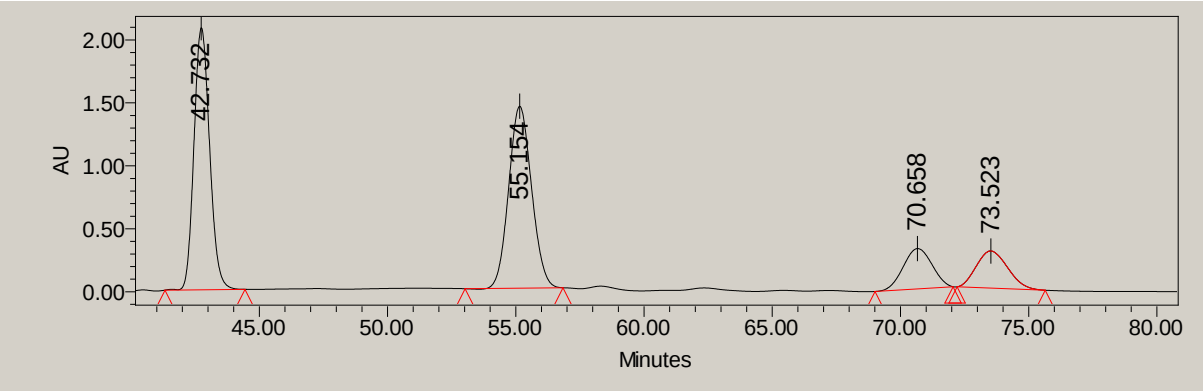
dr 9 : 1 *ee* 90 %



34Aa

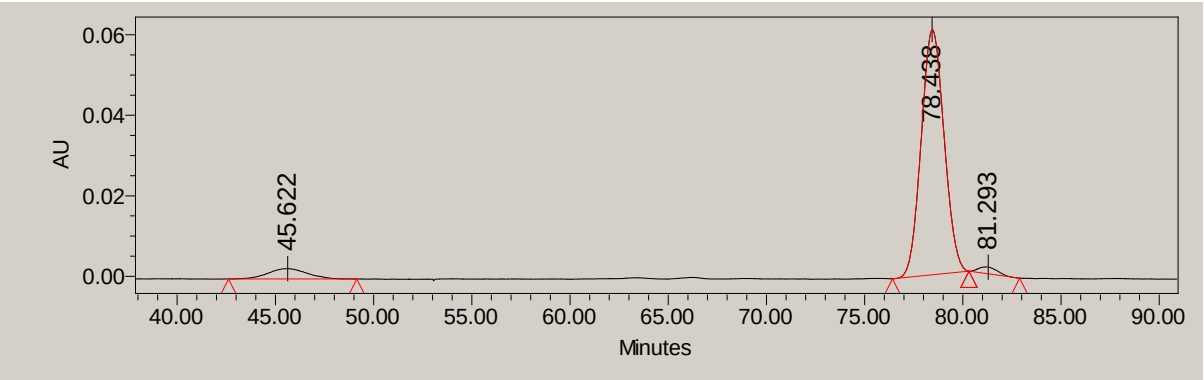
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IC hexane/ethanol 98/2, flow rate = 0.5 mL/min).

Rac-**34Aa**



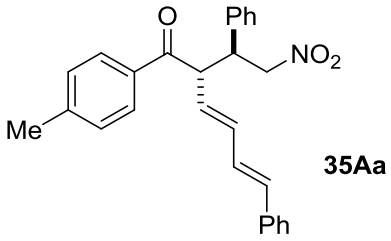
	Retention Time	% Area
1	42.732	38.66
2	55.154	39.38
3	70.658	10.98
4	73.523	10.98

Scalemic-**34Aa**



	Retention Time	% Area
1	45.622	6.62
2	78.438	91.36
3	81.293	2.03

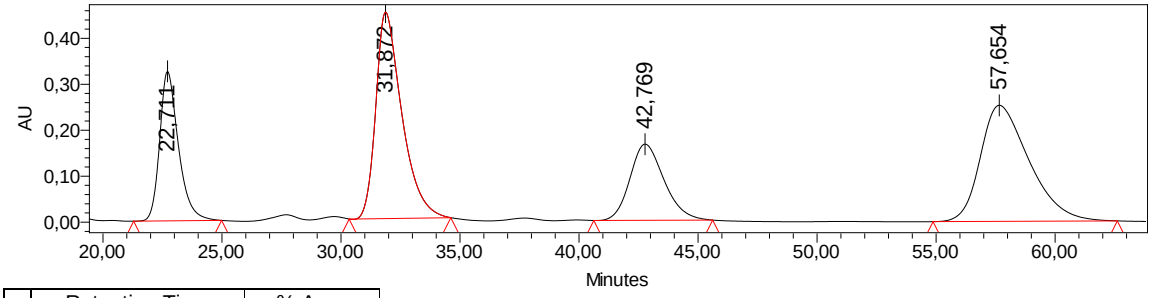
dr 13.3 : 1 *ee* 96 %



35Aa

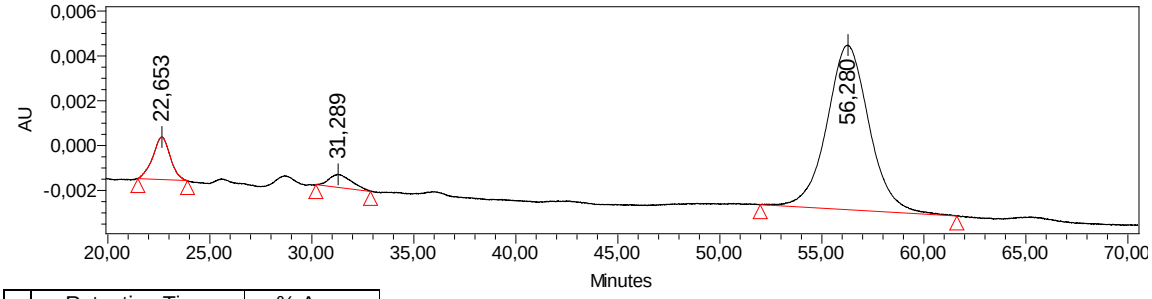
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**35Aa**



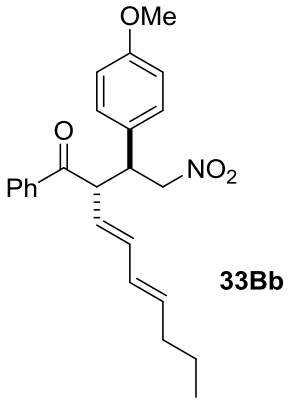
	Retention Time	% Area
1	22,711	17,06
2	31,872	32,75
3	42,769	15,81
4	57,654	34,38

Scalemic-**35Aa**



	Retention Time	% Area
1	22,653	9,25
2	31,289	3,68
3	56,280	87,07

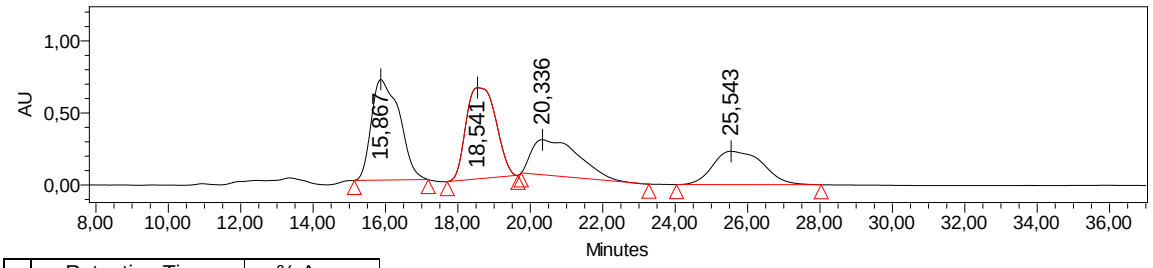
dr 10.1 : 1 *ee* 92 %



33Bb

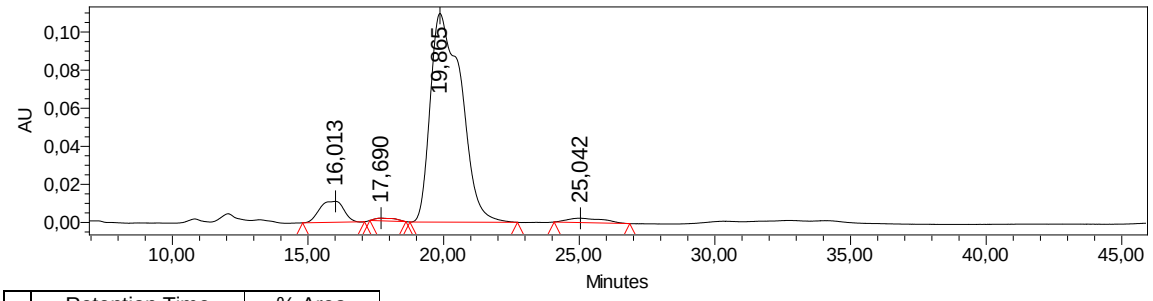
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/isopropanol 95/5, flow rate = 1 mL/min).

Rac-**33Bb**



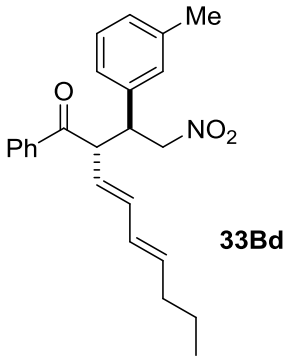
	Retention Time	% Area
1	15,867	31,77
2	18,541	30,44
3	20,336	19,13
4	25,543	18,66

Scalemic-**33Bb**



	Retention Time	% Area
1	16,013	7,12
2	17,690	0,80
3	19,865	89,82
4	25,042	2,26

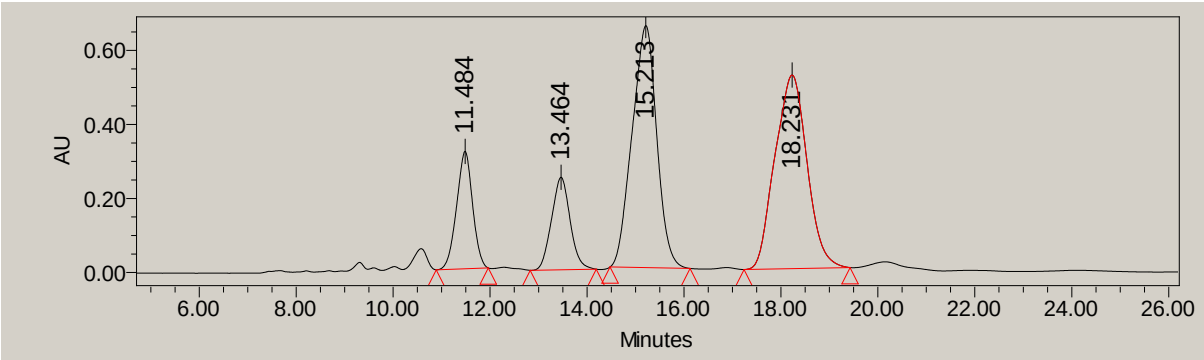
dr 15.7 : 1 *ee* 96 %



33Bd

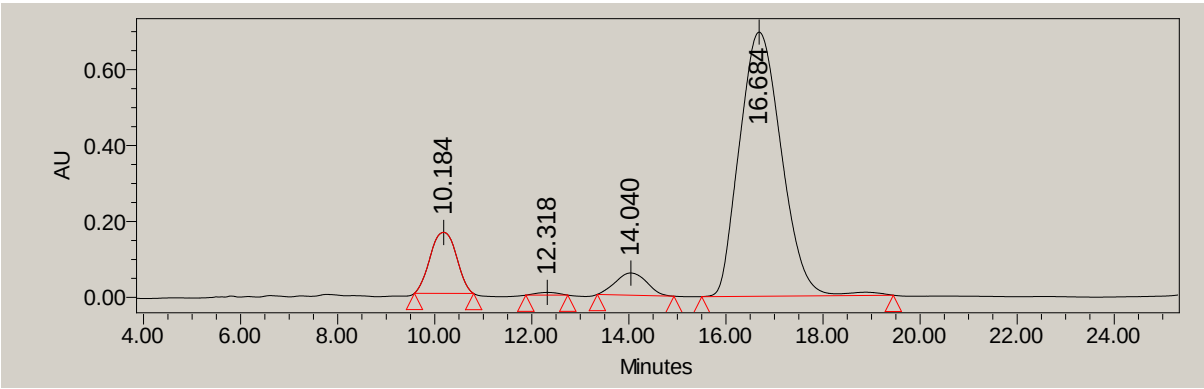
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/isopropanol 98/2, flow rate = 1 mL/min).

Rac-**33Bd**



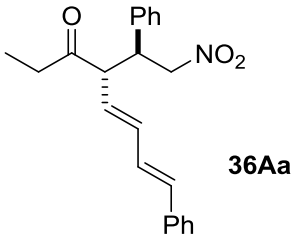
	Retention Time	% Area
1	11.484	11.90
2	13.464	10.92
3	15.213	37.80
4	18.231	39.39

Scalemic-**33Bd**



	Retention Time	% Area
1	10.184	11.96
2	12.318	0.45
3	14.040	5.16
4	16.684	82.44

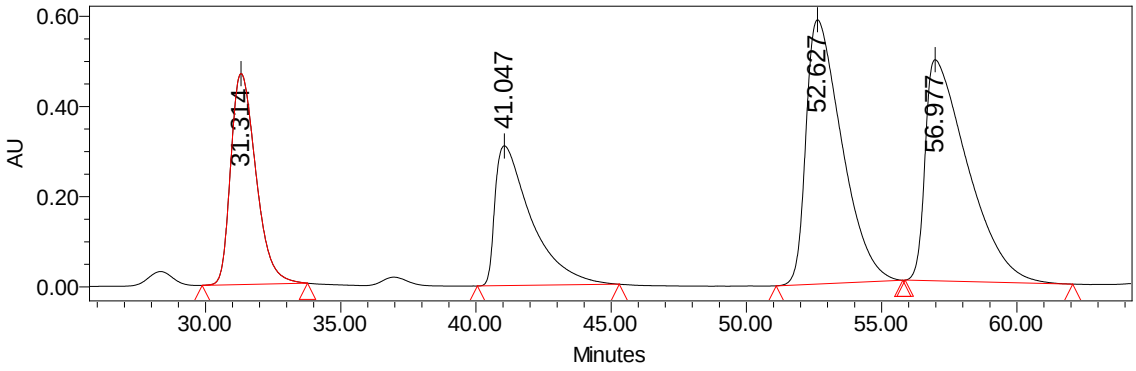
dr 7.3 : 1 *ee* 88%



36Aa

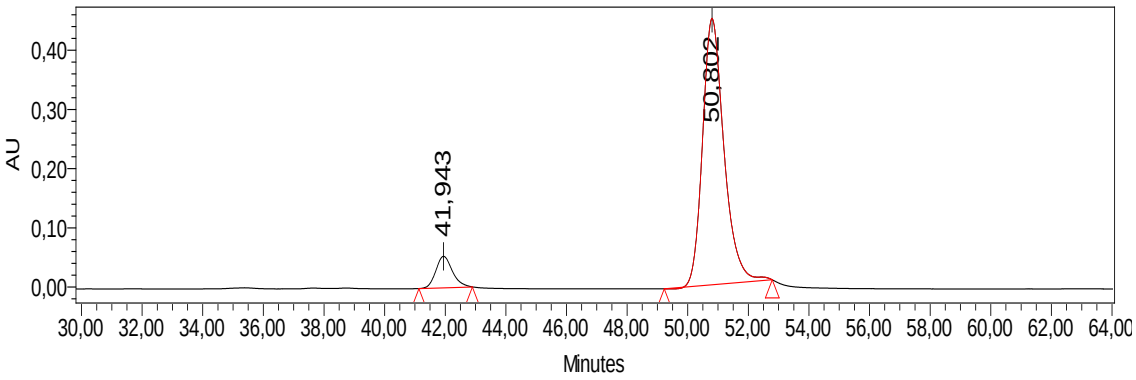
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/ethanol 97/3, flow rate = 0.6 mL/min).

Rac-**36Aa**



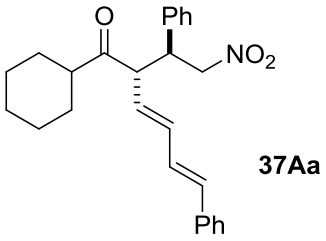
	Retention Time	% Area
1	31.314	18.16
2	41.047	17.34
3	52.627	32.34
4	56.977	32.16

Scalemic-**36Aa**



	Retention Time	% Area
1	41.943	8.37
2	50.802	91.63

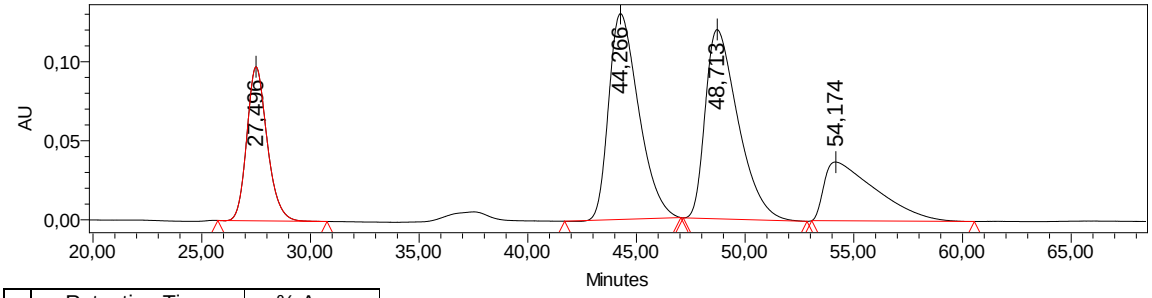
dr 11.5 : 1 *ee* >99 %



37Aa

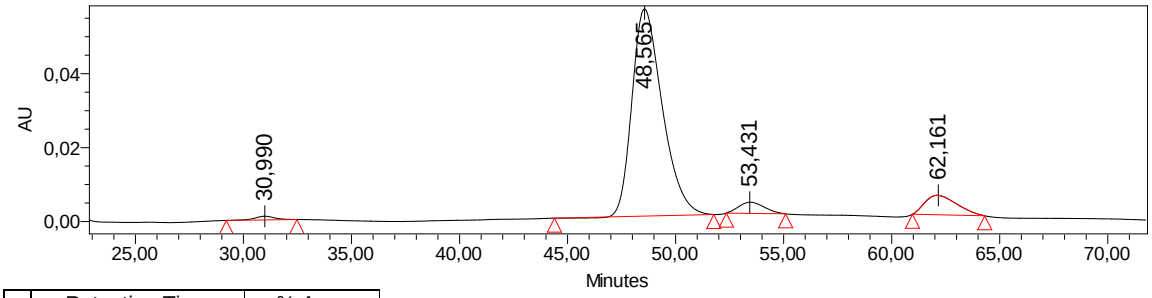
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/isopropanol 99/1, flow rate = 1 mL/min).

Rac-**37Aa**



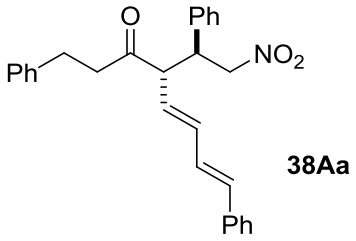
	Retention Time	% Area
1	27,496	16,87
2	44,266	33,33
3	48,713	33,46
4	54,174	16,35

Scalemic-**37Aa**



	Retention Time	% Area
1	30,990	1,03
2	48,565	86,50
3	53,431	3,94
4	62,161	8,53

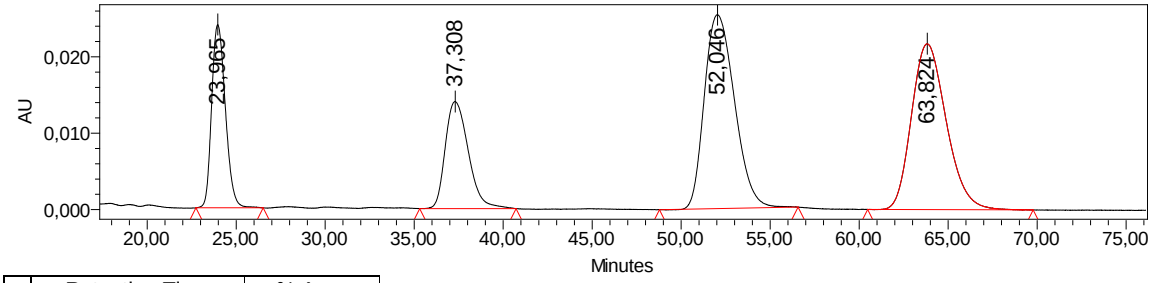
dr 9 : 1 *ee* 94 %



38Aa

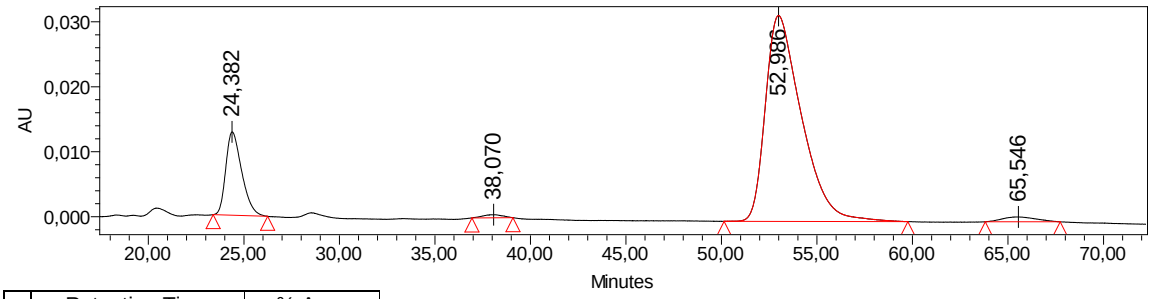
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ADH hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**38Aa**



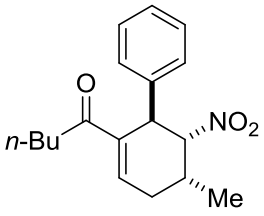
	Retention Time	% Area
1	23,965	15,13
2	37,308	14,88
3	52,046	35,28
4	63,824	34,71

Scalemic-**38Aa**



	Retention Time	% Area
1	24,382	14,78
2	38,070	0,70
3	52,986	82,70
4	65,546	1,82

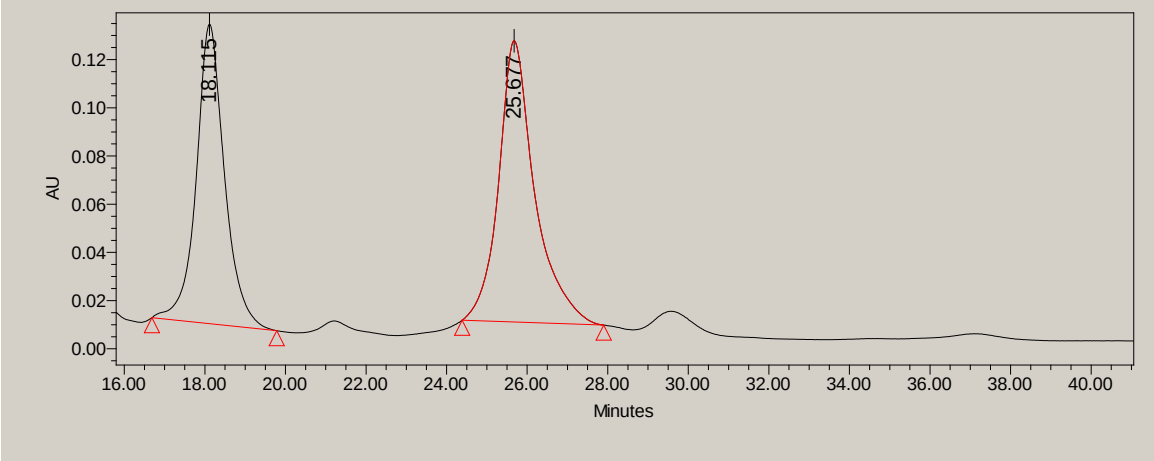
dr 5.7 : 1 *ee* 96 %



42a

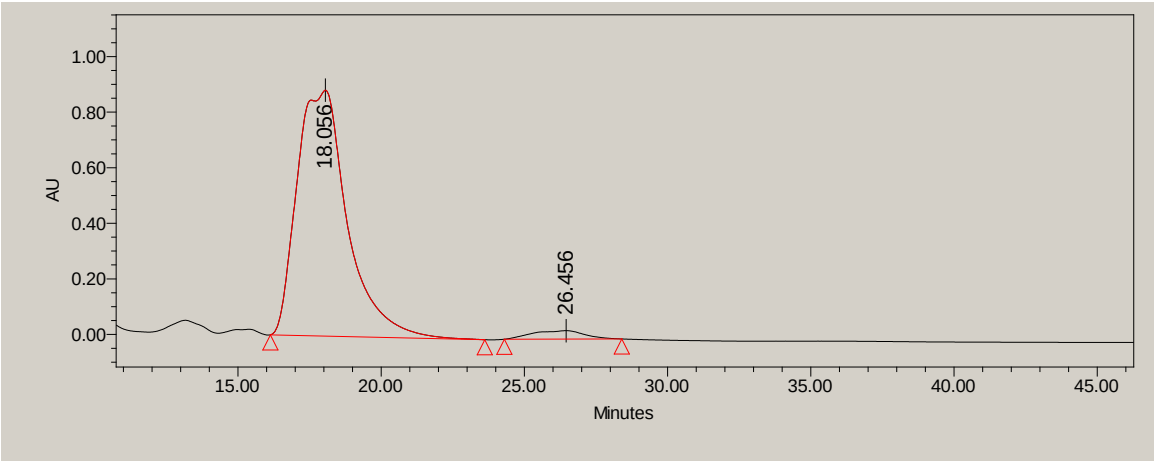
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/ethanol 98/2, flow rate = 0.5 mL/min).

Rac-**42a**



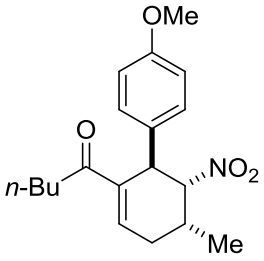
	Retention Time	% Area
1	18.115	48.42
2	25.677	51.58

Scalemic-**42a**



	Retention Time	% Area
1	18.056	96.56
2	26.456	3.44

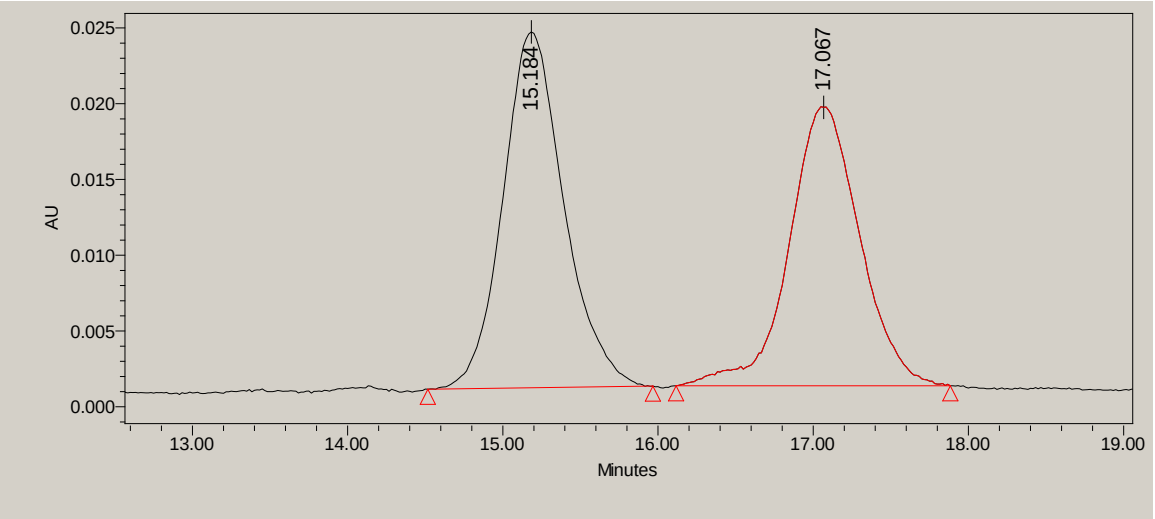
dr >20:1, 93% *ee*



42b

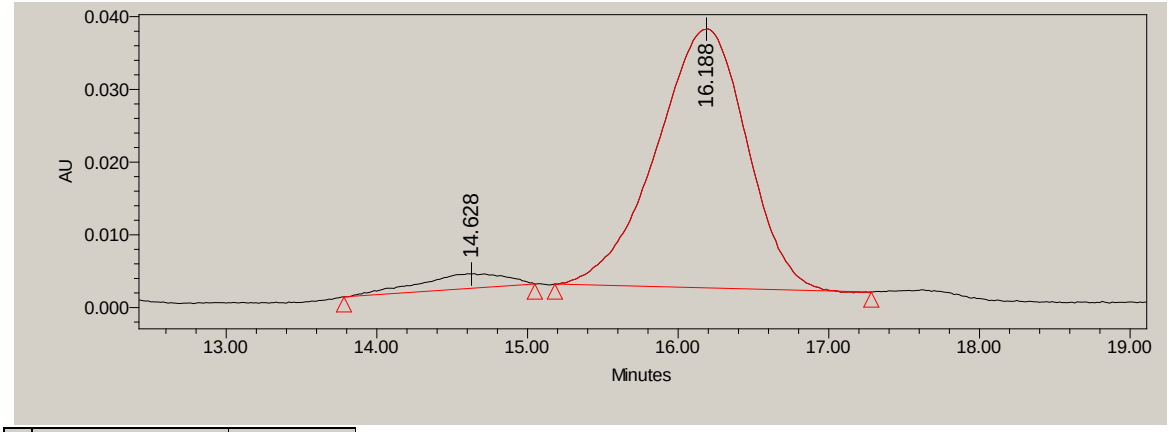
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack ID hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**42b**



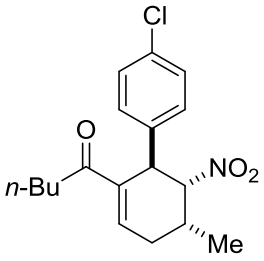
	Retention Time	% Area
1	15.184	52.39
2	17.067	47.61

Scalemic-**42b**



	Retention Time	% Area
1	14.628	5.28
2	16.188	94.72

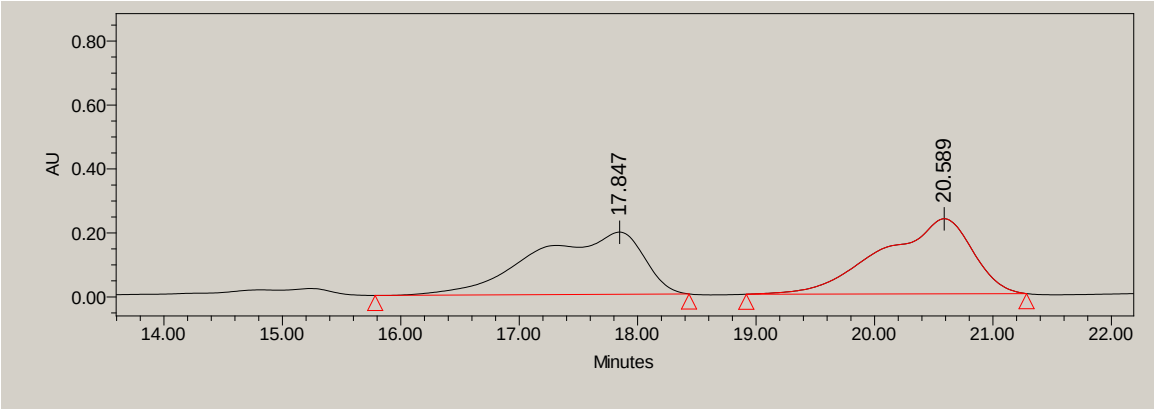
dr >20:1, 90% *ee*



42k

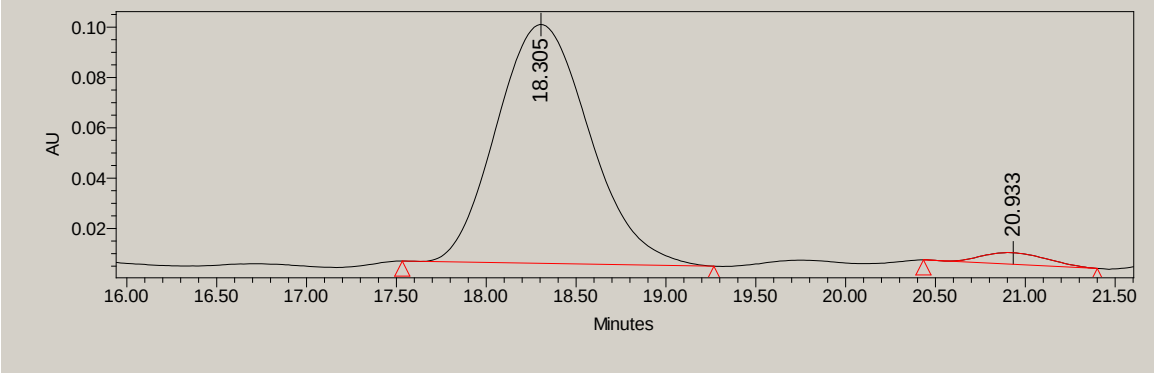
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IC hexane/ethanol 95/5, flow rate = 0.75 mL/min).

Rac-**42k**



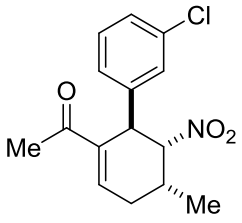
	Retention Time	% Area
1	17.847	48.36
2	20.589	51.64

Scalemic-**42k**



	Retention Time	% Area
1	18.305	96.74
2	20.933	3.26

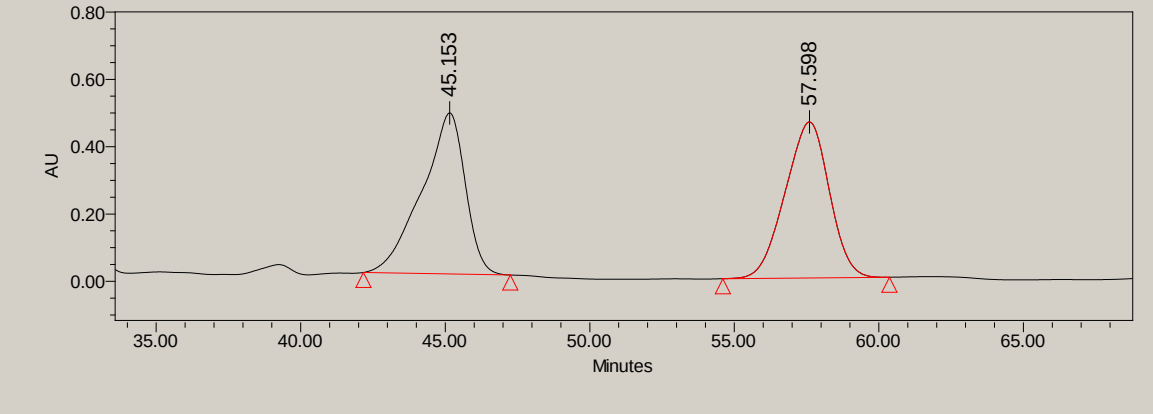
dr >20:1, 94% *ee*



43m

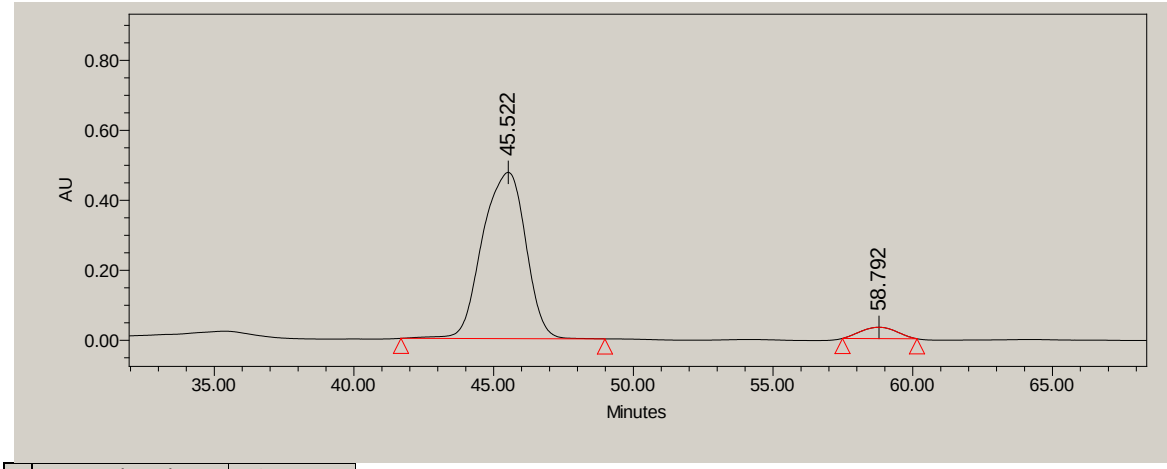
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IC hexane/ethanol 95/5, flow rate = 0.5 mL/min).

Rac-**43m**



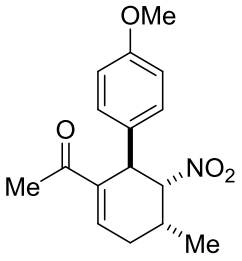
	Retention Time	% Area
1	45.153	50.40
2	57.598	49.60

Scalemic-**43m**



	Retention Time	% Area
1	45.522	94.63
2	58.792	5.37

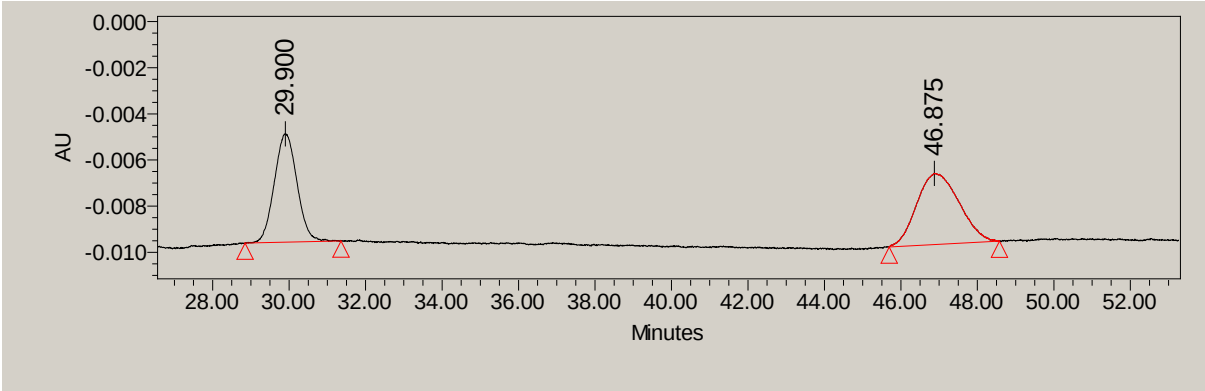
dr >20:1, 90 % *ee*



43b

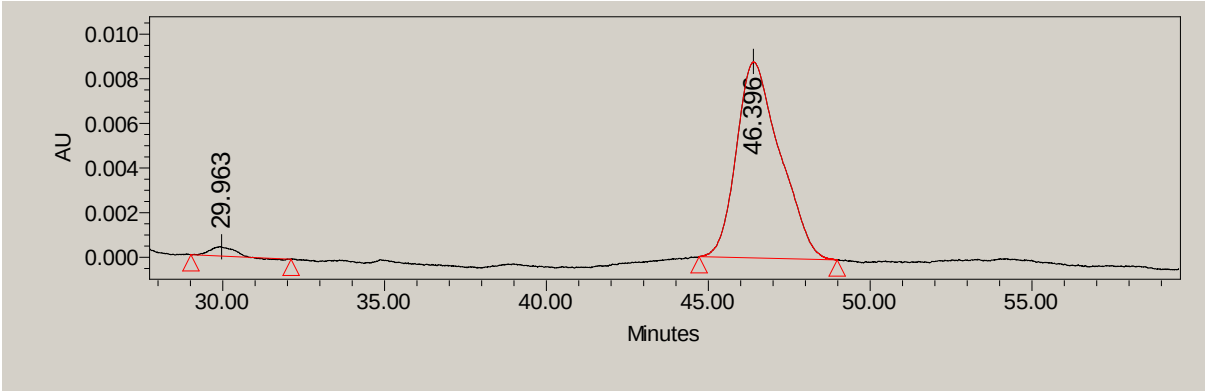
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IC hexane/ethanol 95/5, flow rate = 0.5 mL/min).

Rac-**43b**



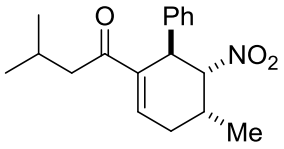
	Retention Time	% Area
1	29.900	48.20
2	46.875	51.80

Scalemic-**43b**



	Retention Time	% Area
1	29.963	3.42
2	46.396	96.58

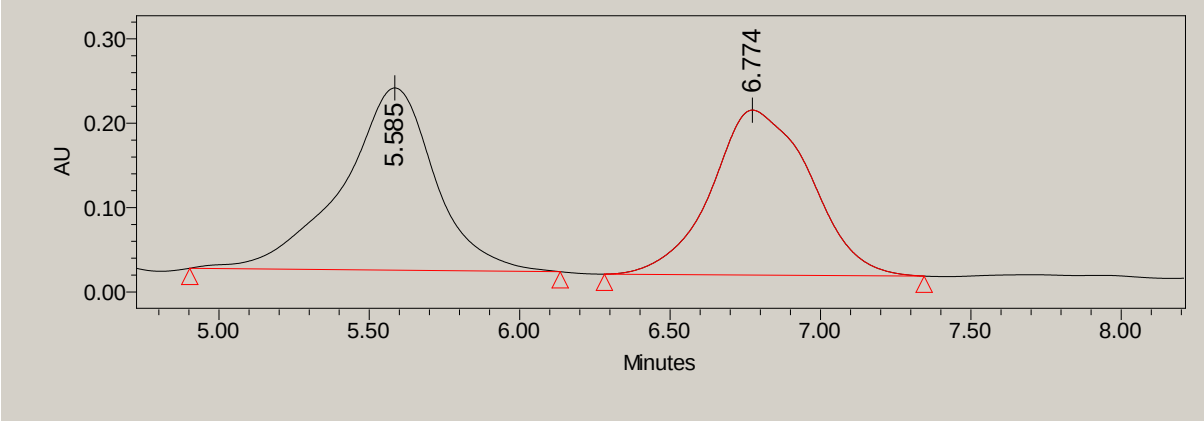
dr >20:1, 93% *ee*



44a

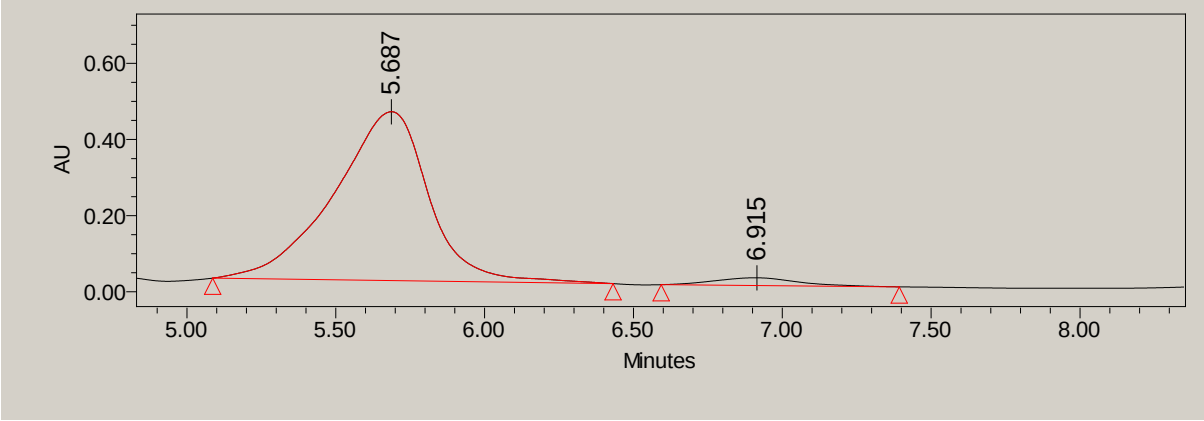
The enantiomeric purity were determined on crude material before column chromatography by HPLC analysis (Daciel Chiralpack IA hexane/ethanol 95/5, flow rate = 1 mL/min).

Rac-**44a**



	Retention Time	% Area
1	5.585	50.80
2	6.774	49.20

Scalemic-**44a**

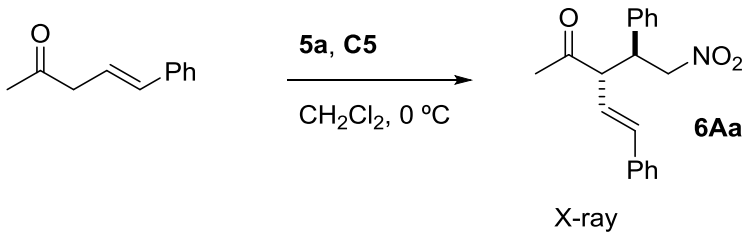


	Retention Time	% Area
1	5.687	96.12
2	6.915	3.88

dr >20:1, 92% *ee*

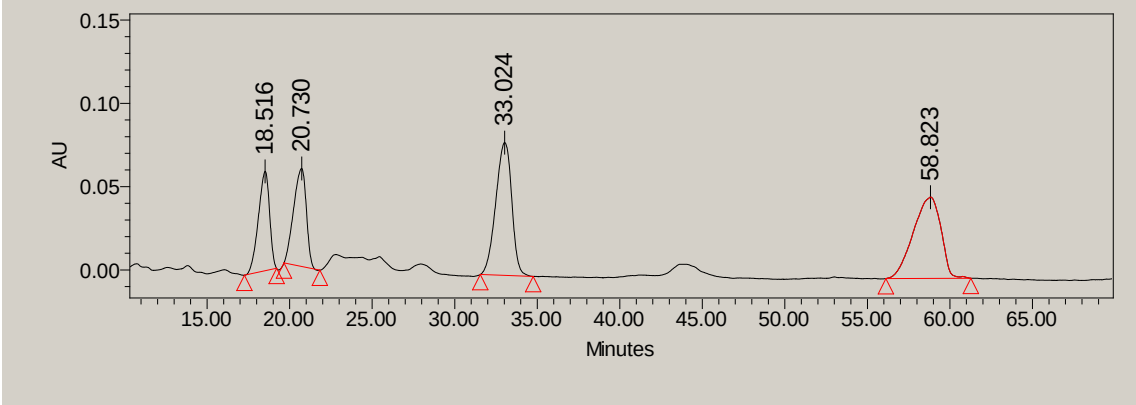
6.6.1.1. *Assignment of configuration to adduct 14*

Configurational identity of adduct **14** was established by correlation of HPLC chromatogram of the corresponding methyl ketone derivative **6Aa**, as follow:



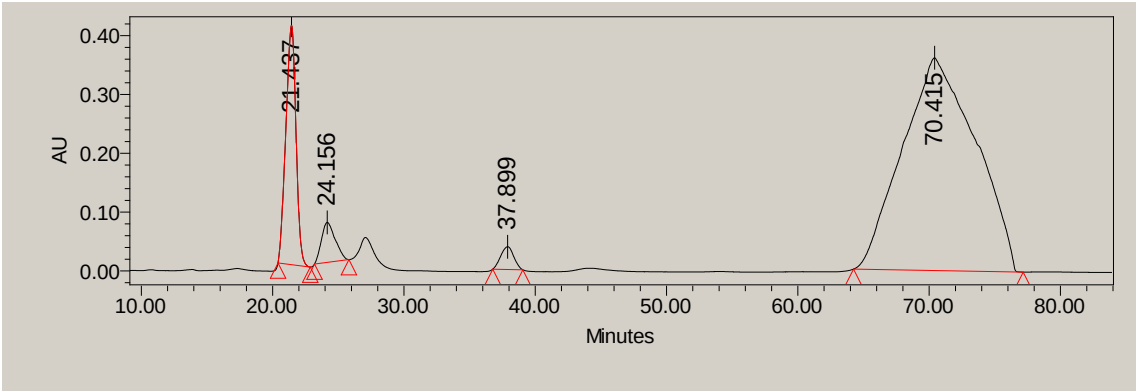
X-ray

rac-**6Aa**

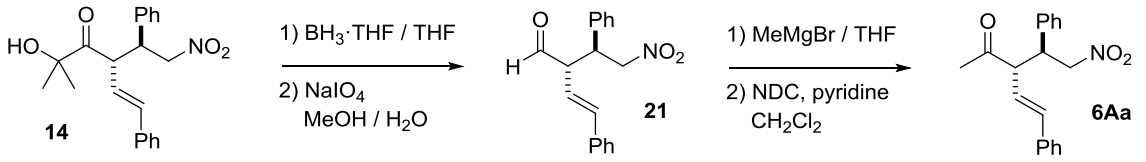


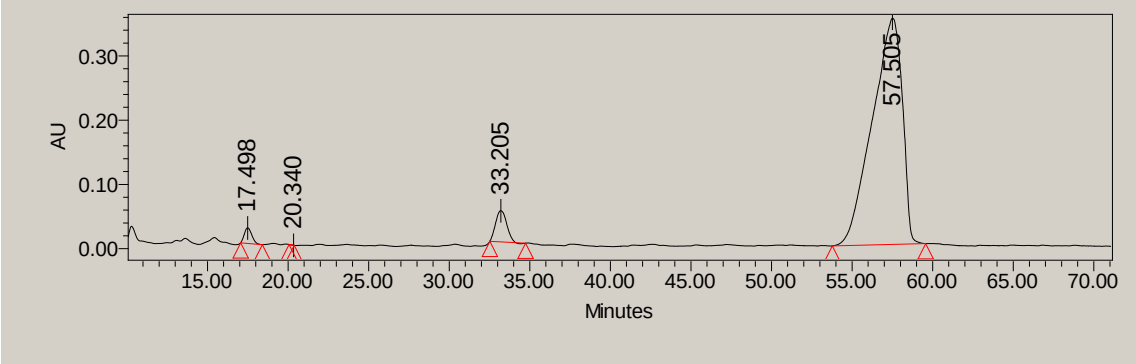
	Retention Time	% Area
1	18.516	16.52
2	20.730	18.48
3	33.024	31.61
4	58.823	33.40

scalemic **6Aa**



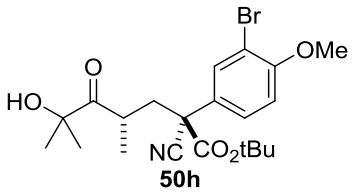
	Retention Time	% Area
1	21.437	12.89
4	70.415	82.62
3	37.899	1.57
2	24.156	2.92





	Name	Retention Time	% Area
1		17.498	1.59
2		20.340	0.00
3		33.205	4.85
4		57.505	93.56

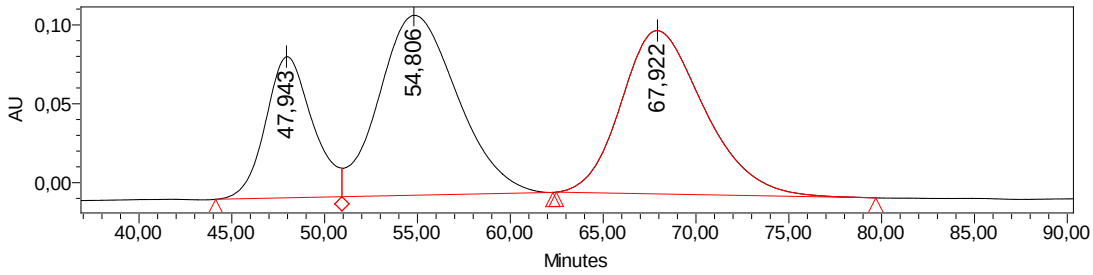
6.6.2. HPLC/GC chromatograms of Chapter 3



50h

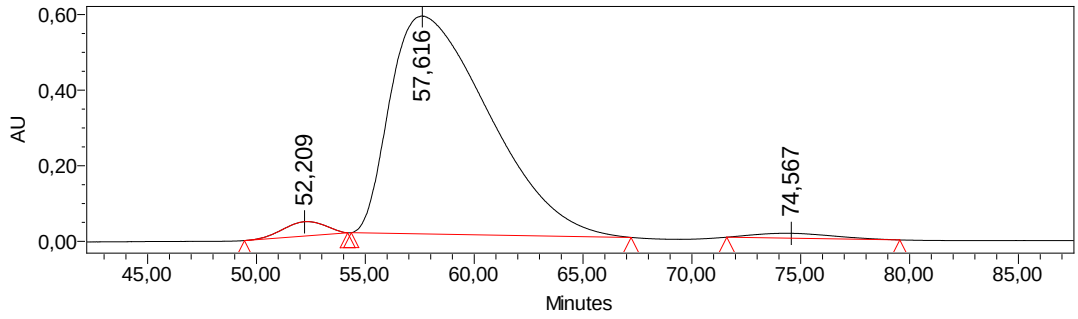
Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 54.8 min (major.) and 67.9 min (minor.). Processed Channel Descr.: PDA 245.0 nm.

Rac-**50h**



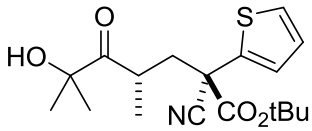
	Retention Time	% Area
1	47,943	19,36
2	54,806	41,05
3	67,922	39,60

Scalemic **50h**



	Retention Time	% Area
1	52,209	2,69
2	57,616	95,62
3	74,567	1,69

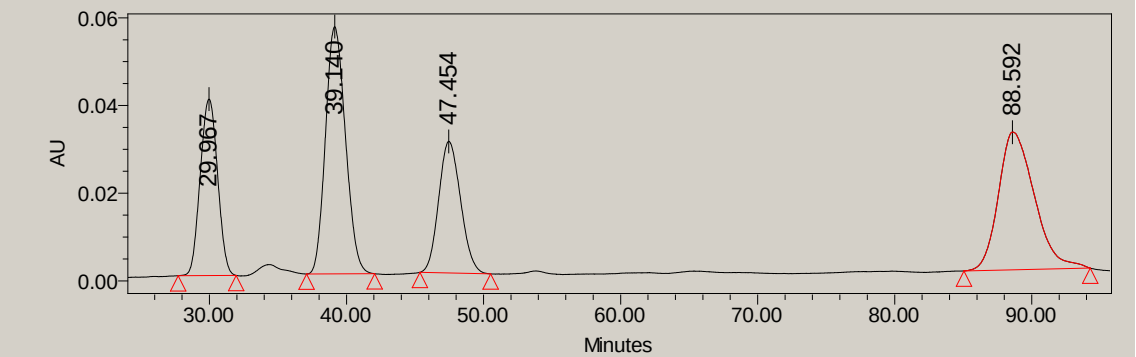
dr 97:3, 96% *ee*



50i

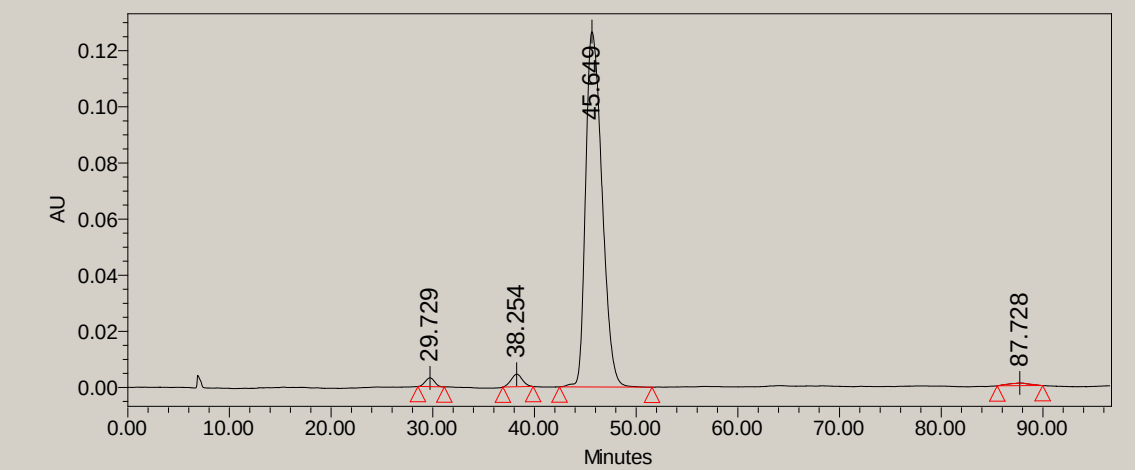
Daicel Chiralpak AY-H hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 29.9 min (minor.) and 47.4 min (major.). Processed Channel Descr.: PDA 245.0 nm.

Rac-**50i**



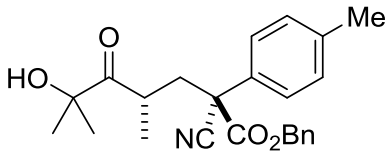
	Retention Time	% Area
1	29.967	19.33
2	39.140	31.20
3	47.454	18.19
4	88.592	31.28

Scalemic **50i**



	Retention Time	% Area
1	29.729	1.35
2	38.254	2.34
3	45.649	95.37
4	87.728	0.94

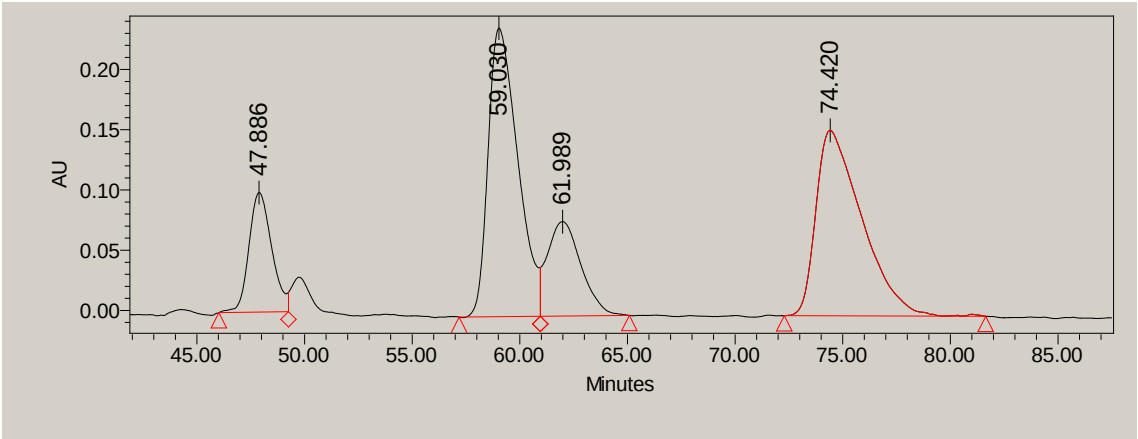
dr 96:4, 97% *ee*



51e

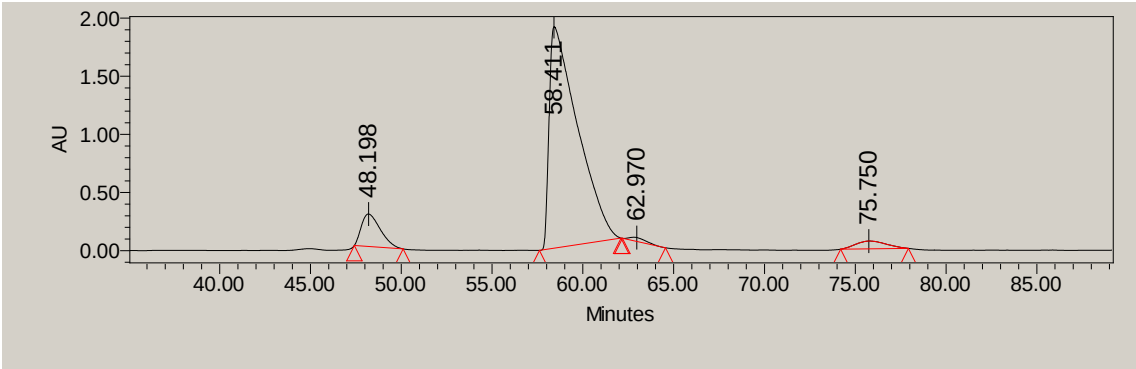
Daicel Chiralpak IC+AY-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 74.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm.

Rac-**6e**



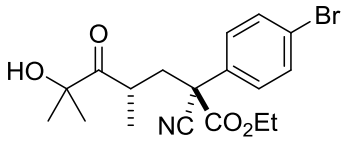
	Retention Time	% Area
1	47.886	11.89
2	59.030	37.23
3	61.989	13.86
4	74.420	37.01

Scalemic **6e**



	Retention Time	% Area
1	48.198	8.57
2	58.411	87.19
3	62.970	0.90
4	75.750	3.34

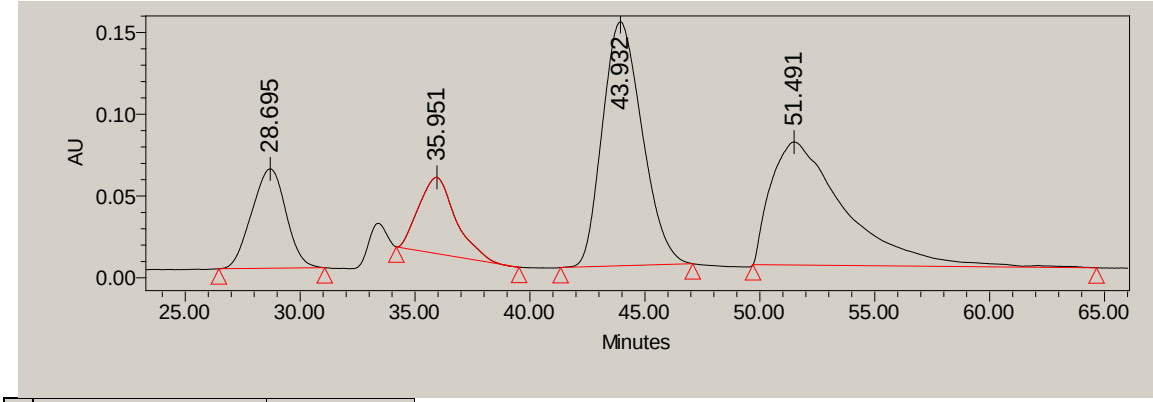
dr 90:10, 92% *ee*



52b

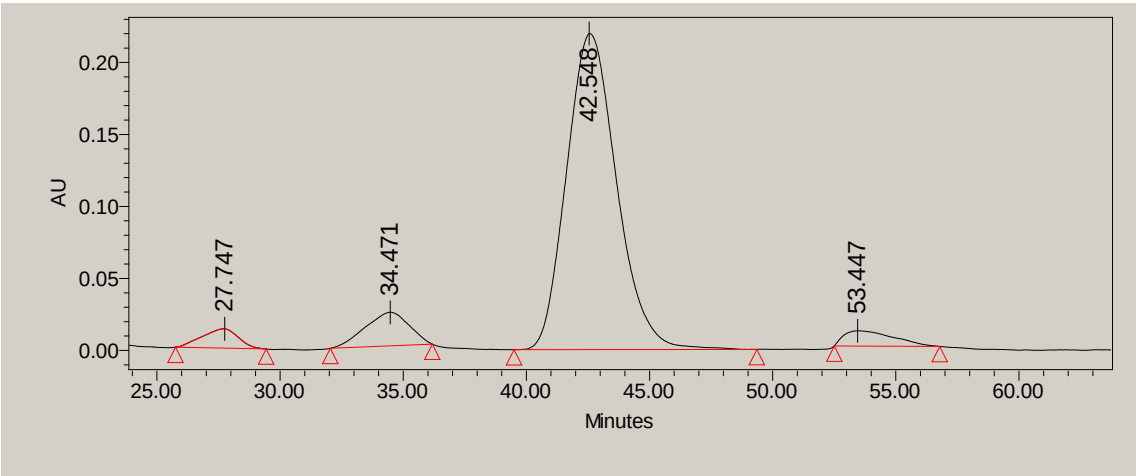
Daicel Chiralpak IC hexane/isopropanol 97/3, flow rate= 0.6 mL/min, retention times: 43.9 min (major.) and 51.4 min (minor.). Processed Channel Descr.: PDA 235.0 nm.

Rac-**7b**



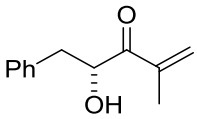
	Retention Time	% Area
1	28.695	13.57
2	35.951	11.20
3	43.932	38.67
4	51.491	36.56

Scalemic **7b**



	Retention Time	% Area
1	27.747	3.72
2	34.471	7.84
3	42.548	84.42
4	53.447	4.02

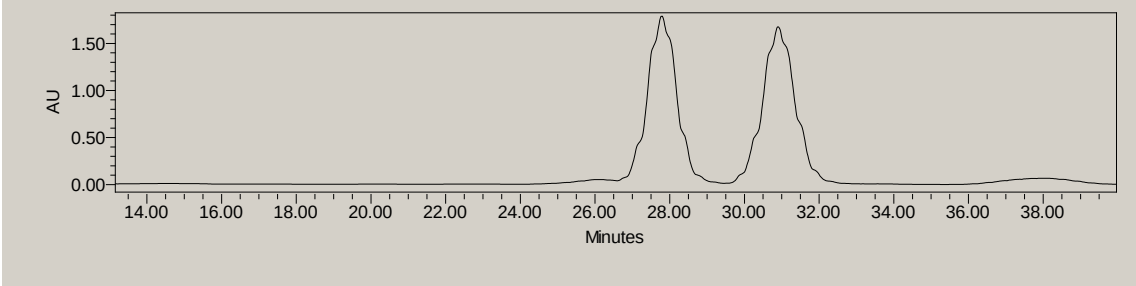
dr 88:12, 91% *ee*



53

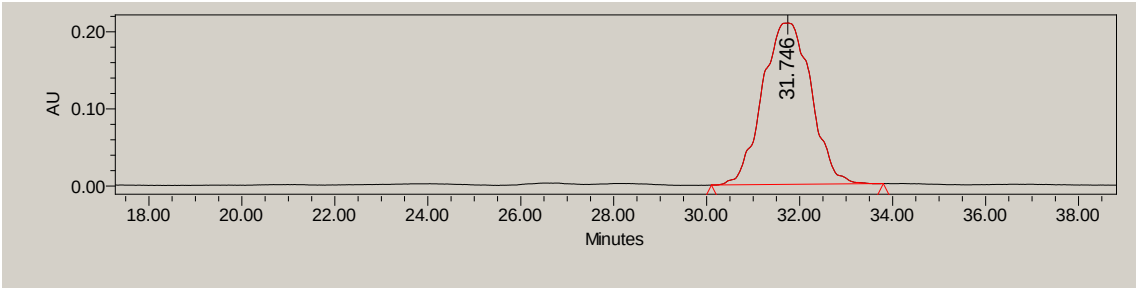
Chiralpak column AS-H, 95:5 Hexane:i-PrOH, 0.5 mL/min, λ=210 nm.

Rac-**53**



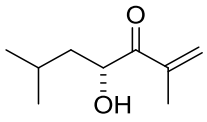
	Retention Time	% Area	Height
1	27.784	48.62	1756589
2	30.901	51.38	1657162

Scalemic-**53**



	Retention Time	% Area	Height
1	31.746	100.00	209263

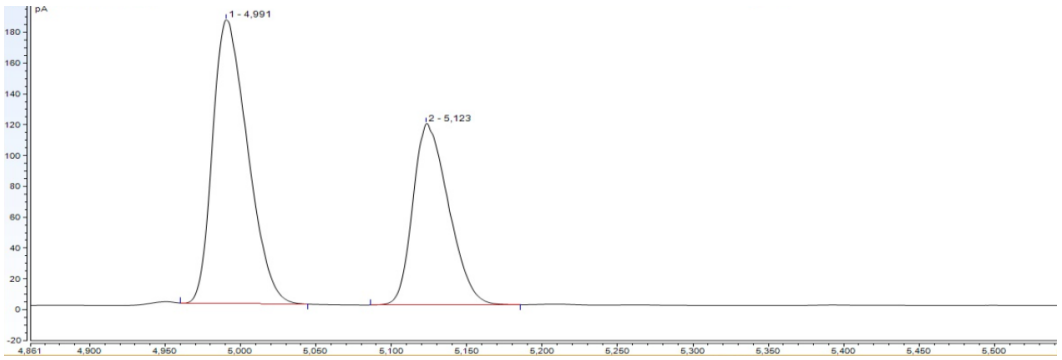
>99% *ee*



54

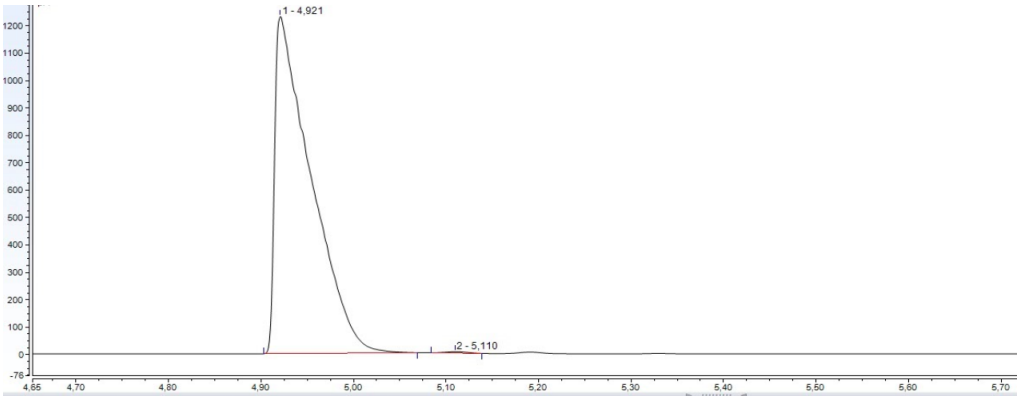
Gas Chromatography: Performed using a Thermo Scientific Trace 1300 equipment with a FID. Chiral column HYDRODEX β-6TBDM, 25 m, 0.25 mm ID. Temperature gradient: 1) 100 °C for 1 min; 2) from 100 °C to 200 °C at a heating rate of 10ºC/min (11 min); 3) 200 °C for an additional 11 min.

Rac-**54**



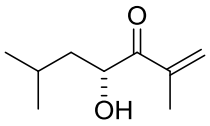
RT	Area (%)
4.99	60.5
5.12	39.5

Scalemic-**54**



RT	Area (%)
4.92	99.7
5.11	0.3

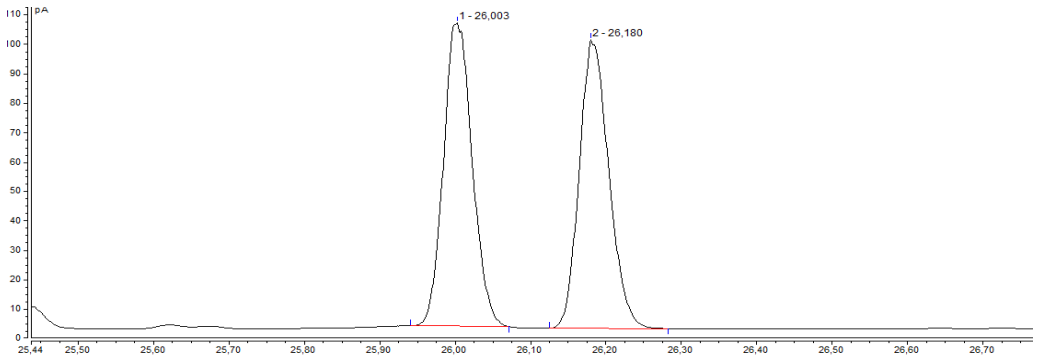
99% *ee*



62

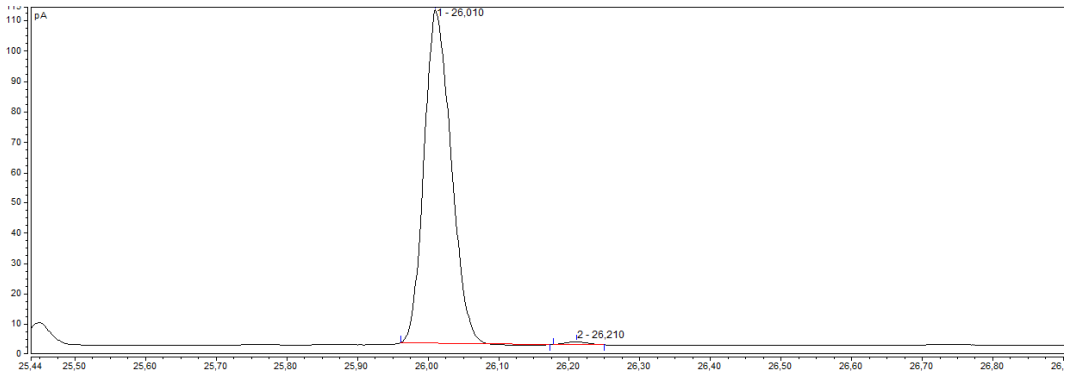
Gas Chromatography: Performed using a Thermo Scientific Trace 1300 equipment with a FID. Chiral column HYDRODEX β-6TBDM, 25 m, 0.25 mm ID. Temperature gradient: 1) 100 ºC for 1 min; 2) from 100 ºC to 200 ºC at a heating rate of 10ºC/min (11 min); 3) 200 ºC for an additional 11 min.

Rac-**62**



RT	Area (%)
26.00	49.22
26.18	50.78

Scalemic-**62**



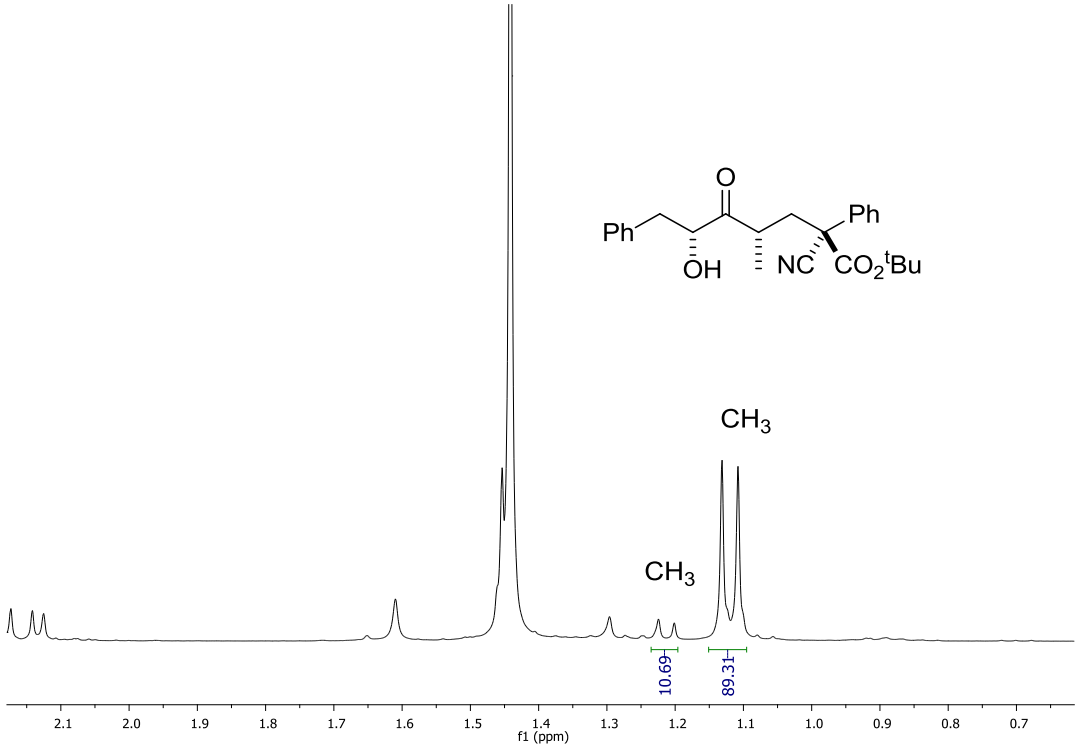
RT	Area (%)
26.01	99.53
26.21	0.47

99% *ee*

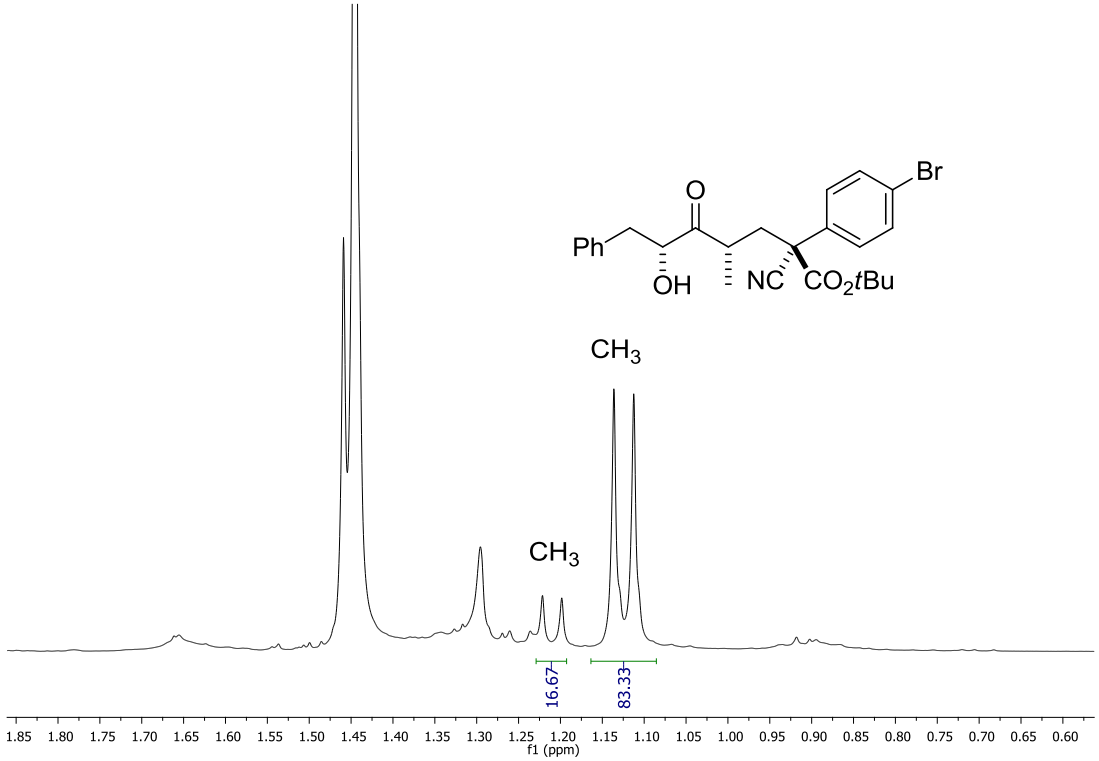
6.6.3. Determination of diastereomeric ratios of adducts 57-60 by ^{1}H-NMR analysis

(1H NMR insets corresponding to reaction crudes)

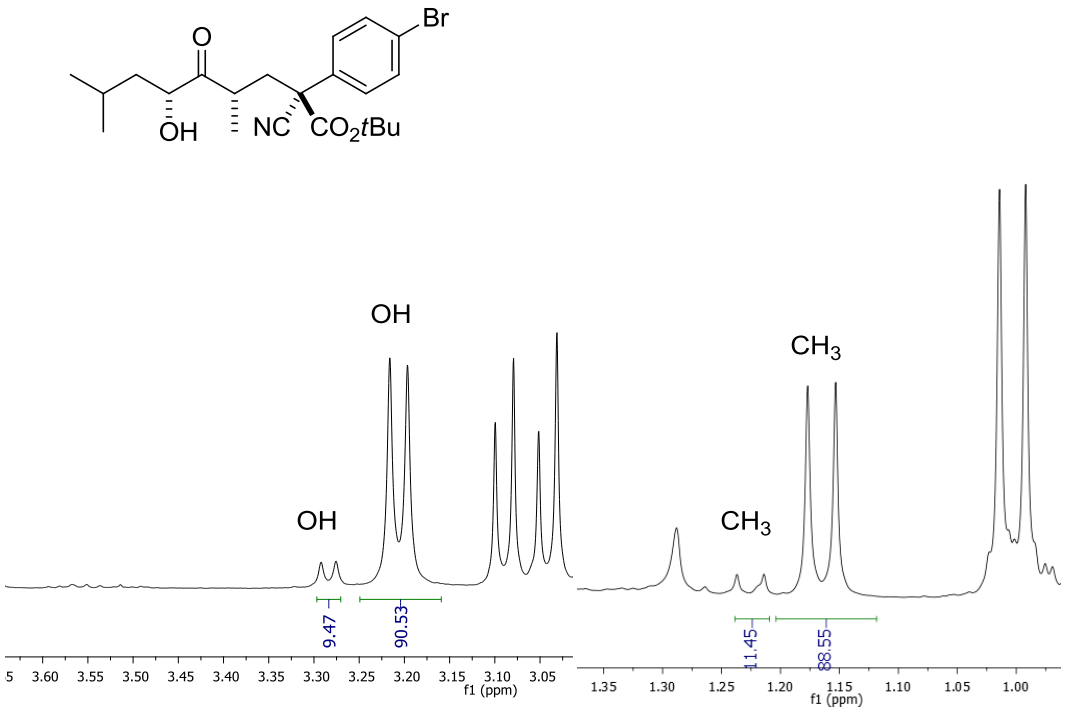
Adduct **57**:



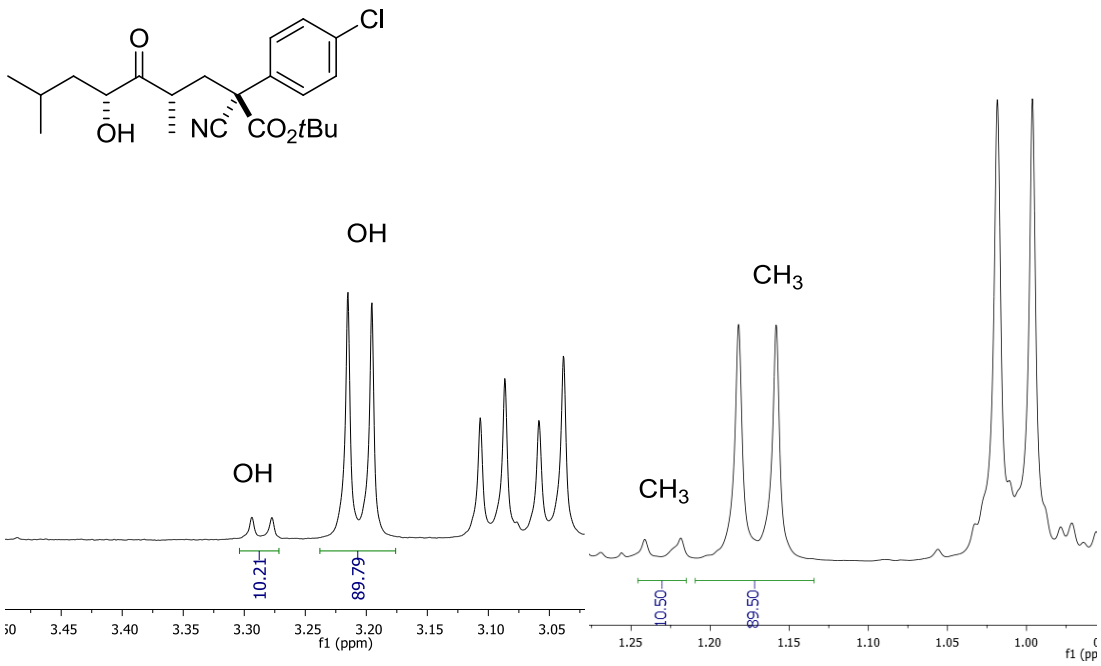
Adduct **58**:



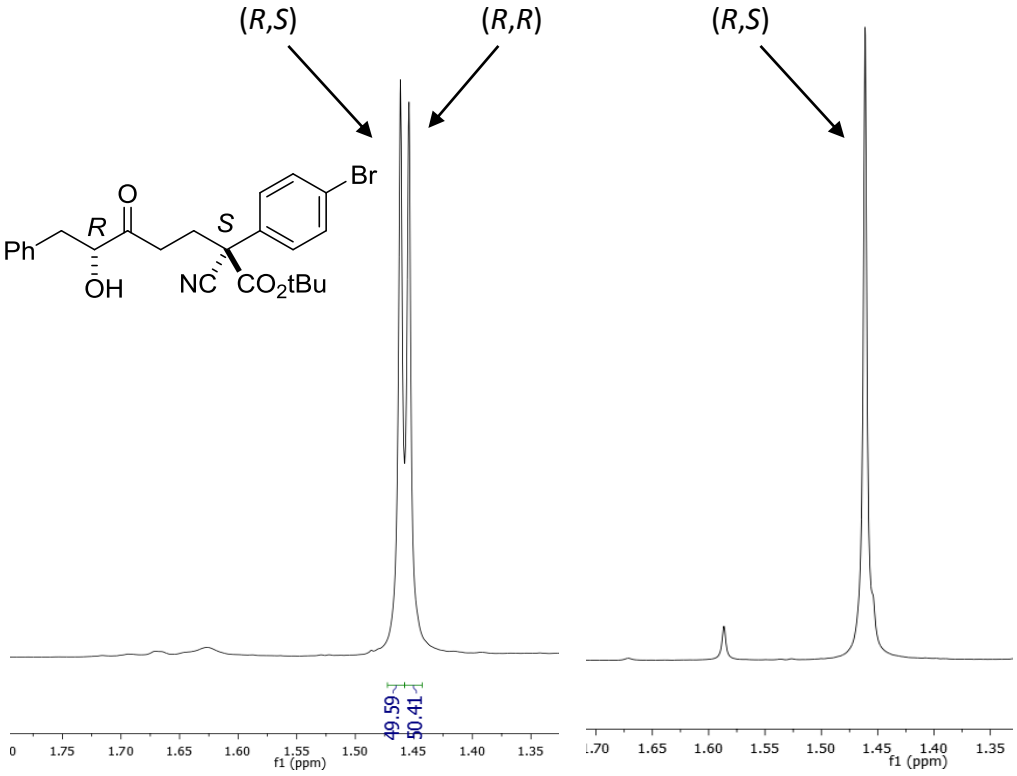
Adduct **59**:



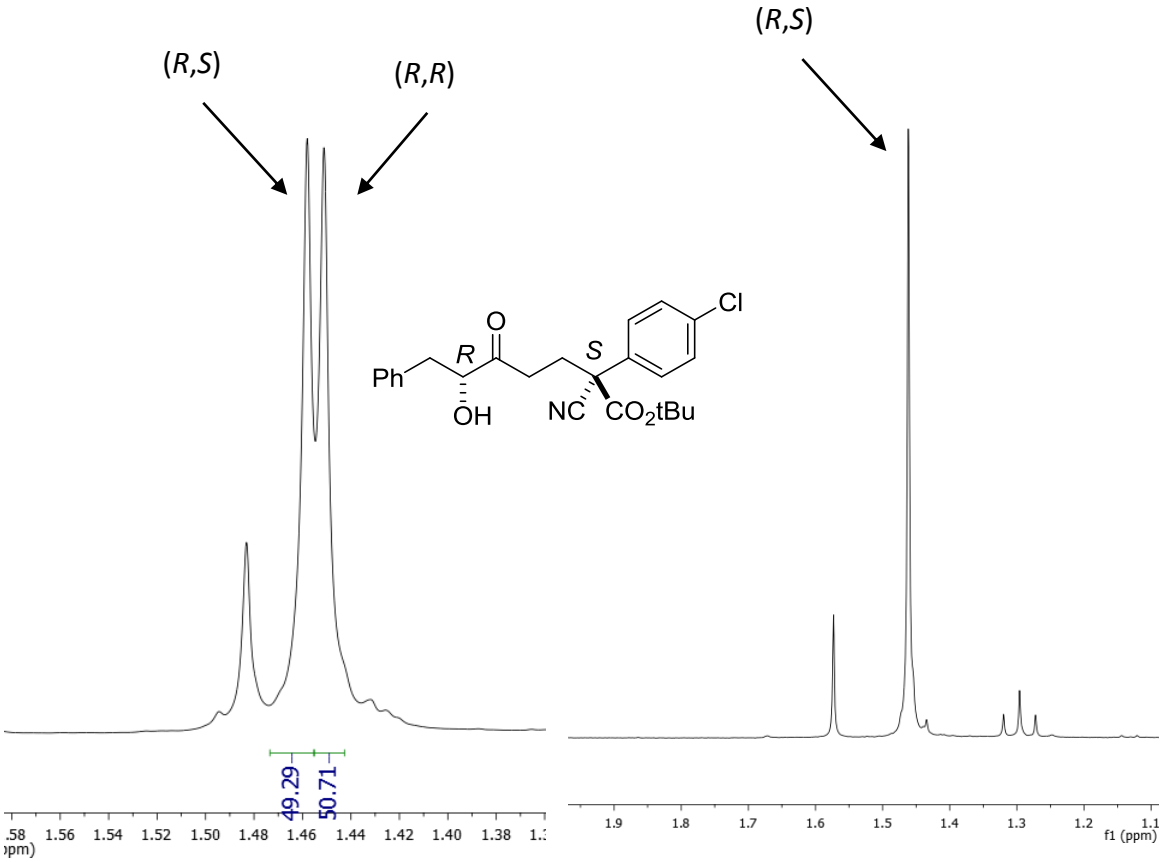
Adduct **60**:



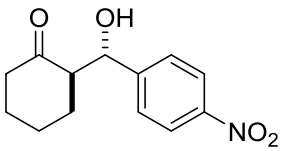
Adduct **63**:



Adduct **64**:



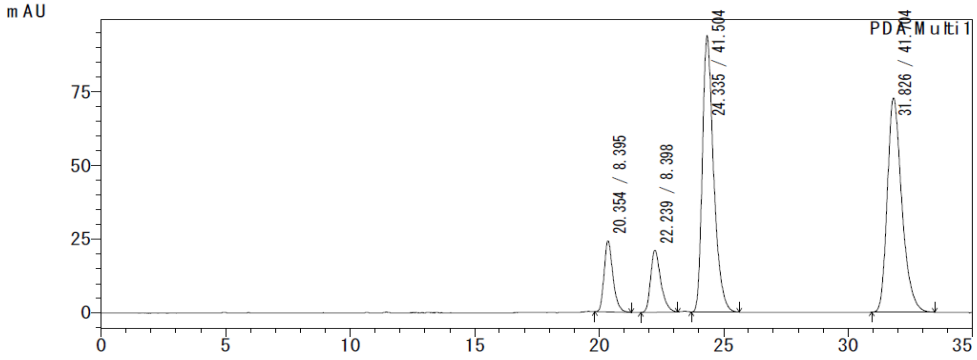
6.7. HPLC chromatograms of Chapter 4



76a

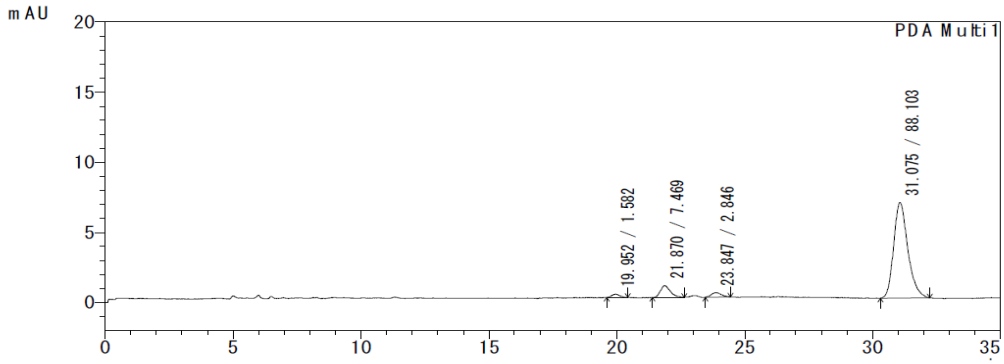
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 5/1, flow rate= 0.6 mL/min.

Rac-**76a**



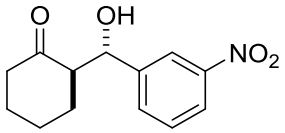
	Retention Time	% Area
1	20.354	8.39
2	22.239	8.39
3	24.335	41.50
4	31.826	41.70

Scalemic-**76a**



	Retention Time	% Area
1	19.95	1.58
2	21.87	7.47
3	23.85	2.85
4	31.08	88.10

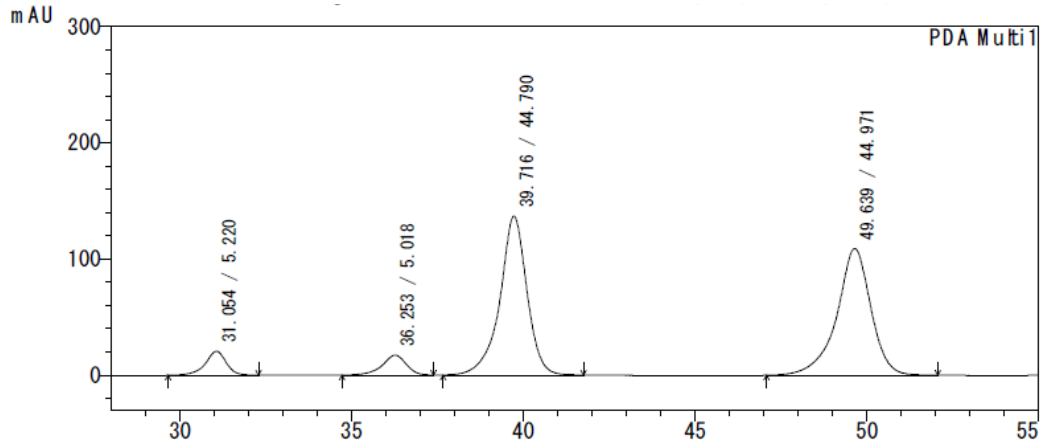
dr 91:9, 94% *ee*



76b

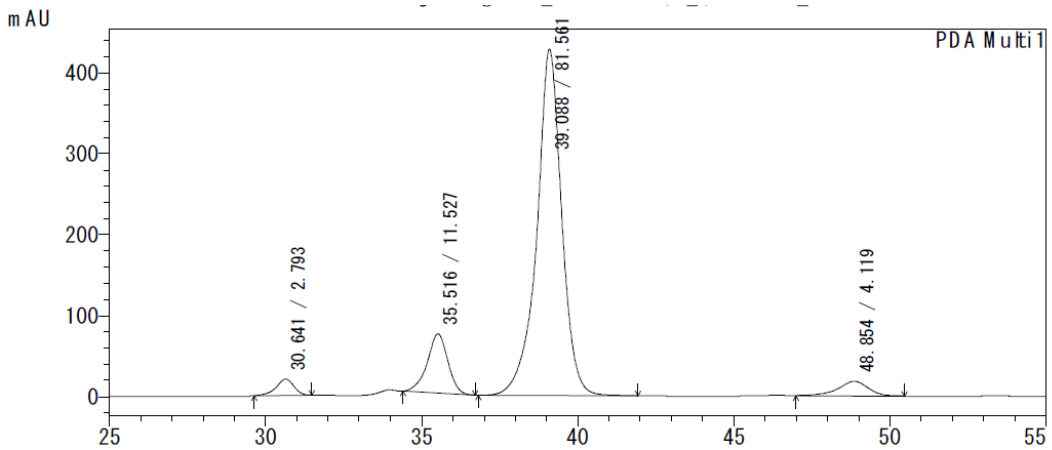
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

Rac-**76b**



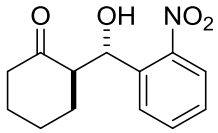
	Retention Time	% Area
1	31.05	5.22
2	36.25	5.02
3	39.72	44.79
4	49.64	44.97

Scalemic-**76b**



	Retention Time	% Area
1	30.64	2.79
2	35.52	11.53
3	39.09	81.56
4	48.85	4.12

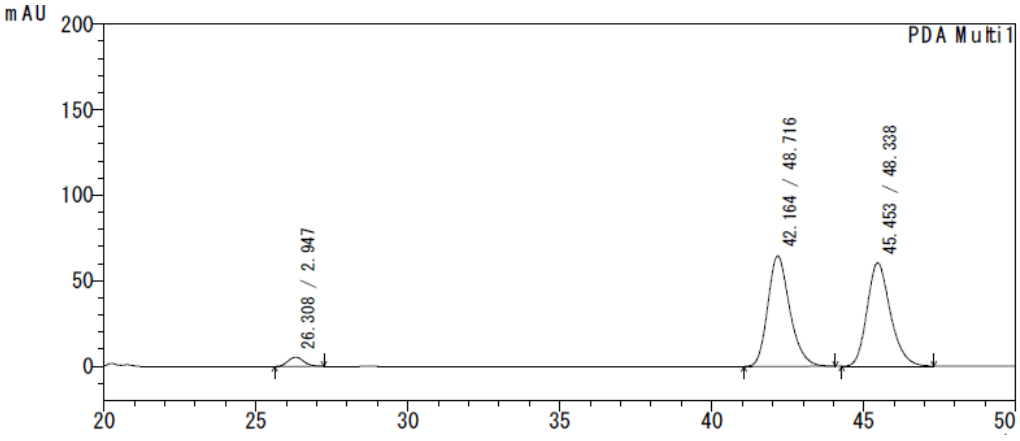
dr 86:14, 90% *ee*



76c

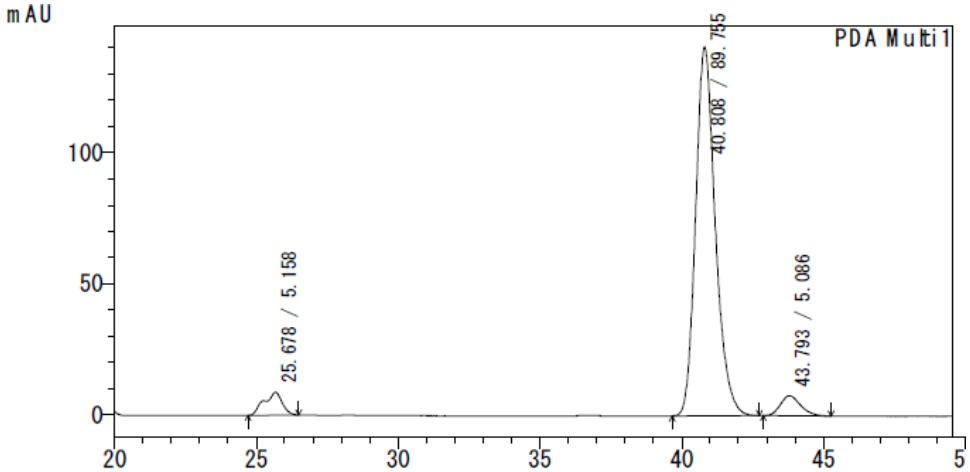
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

Rac-**76c**



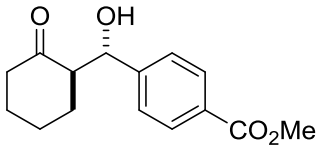
	Retention Time	% Area
1	26.31	2.95
2	42.16	48.72
3	45.45	48.34

Scalemic-**76c**



	Retention Time	% Area
1	25.68	5.16
2	40.80	89.76
3	43.79	5.09

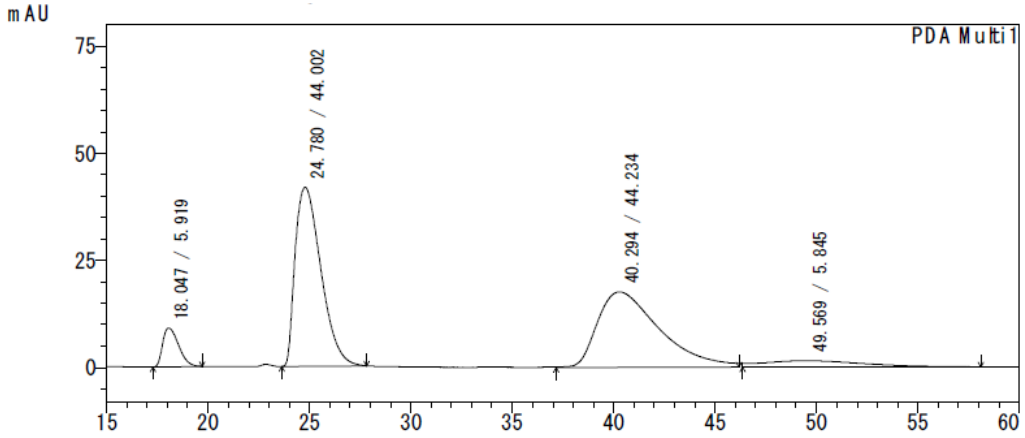
dr 95:5, 89% *ee*



76d

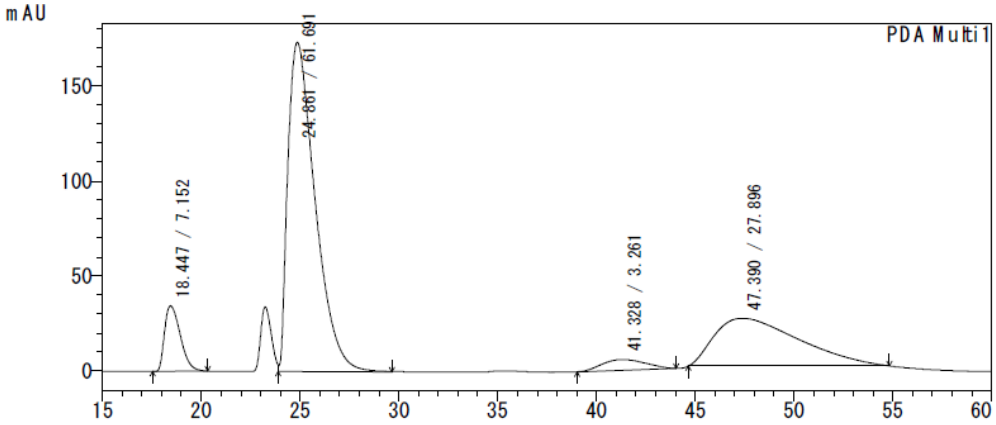
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AS-H hexane/isopropanol 4/1, flow rate= 0.5 mL/min.

Rac-**76d**



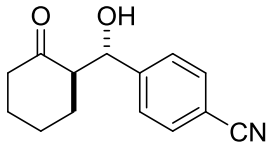
	Retention Time	% Area
1	18.05	5.92
2	24.78	44.00
3	40.29	44.23
4	49.57	5.84

Scalemic-**76d**



	Retention Time	% Area
1	18.45	7.15
2	24.86	61.69
3	41.33	3.26
4	47.39	27.89

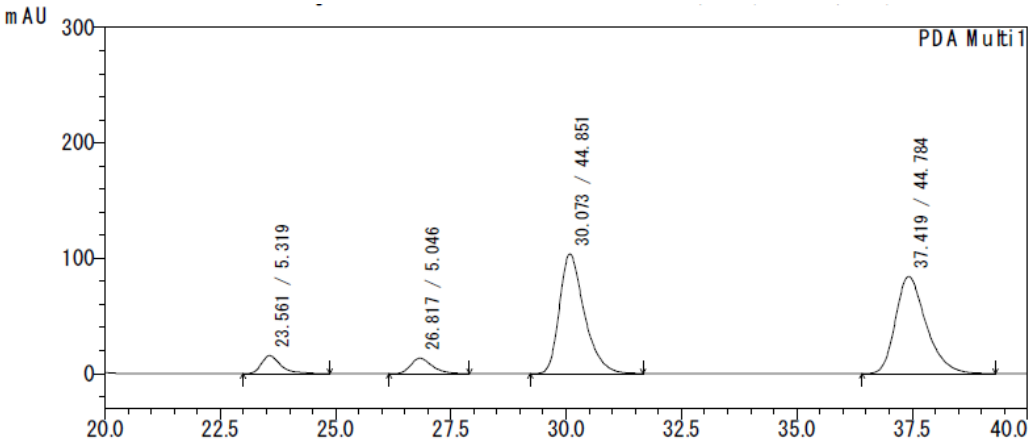
dr 66:34, 90% *ee*



76e

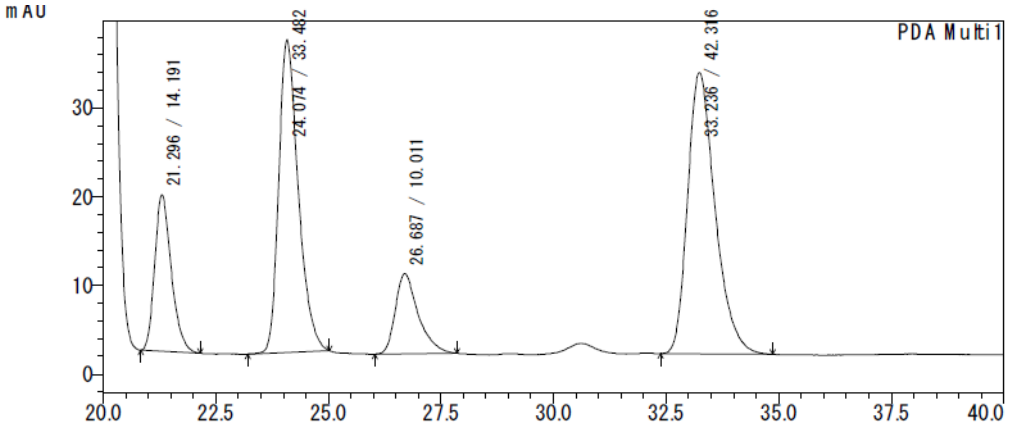
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 85/15, flow rate= 0.5 mL/min.

Rac-**76e**



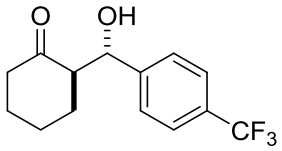
	Retention Time	% Area
1	23.56	5.32
2	26.82	5.05
3	30.07	44.85
4	37.42	44.78

Scalemic-**76e**



	Retention Time	% Area
1	21.30	14.19
2	24.07	33.48
3	26.69	10.01
4	33.23	42.32

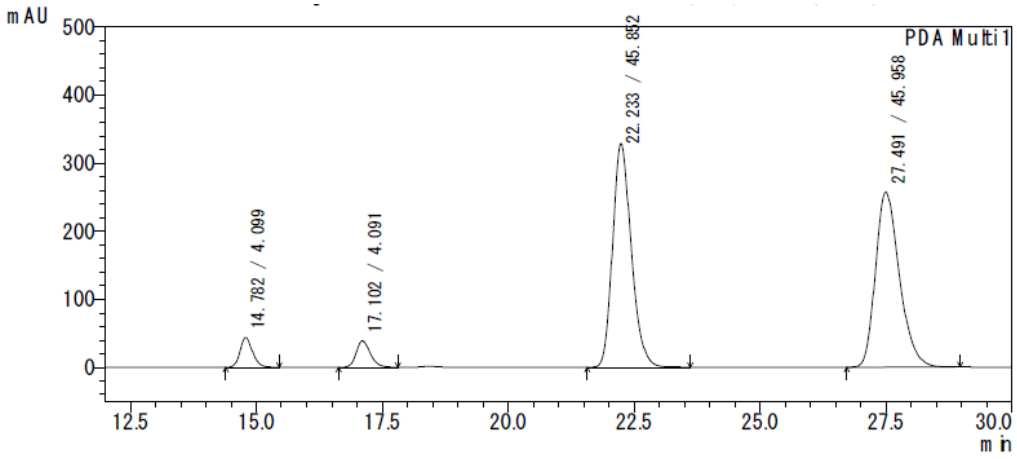
dr 60:40, 62% *ee*



76f

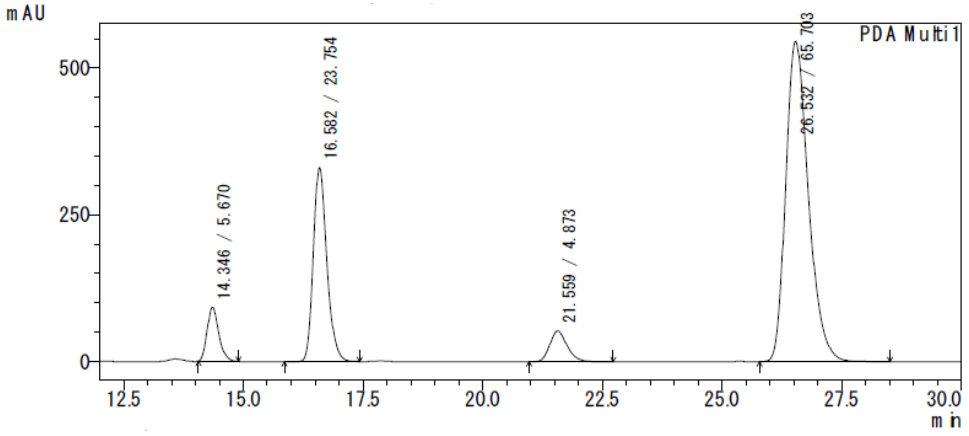
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

Rac-**76f**



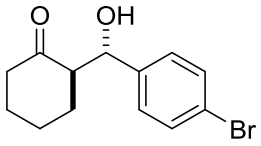
	Retention Time	% Area
1	14.78	4.10
2	17.10	4.09
3	22.23	45.85
4	27.49	45.96

Scalemic-**76f**



	Retention Time	% Area
1	14.34	5.67
2	16.58	23.75
3	21.56	4.87
4	26.53	65.70

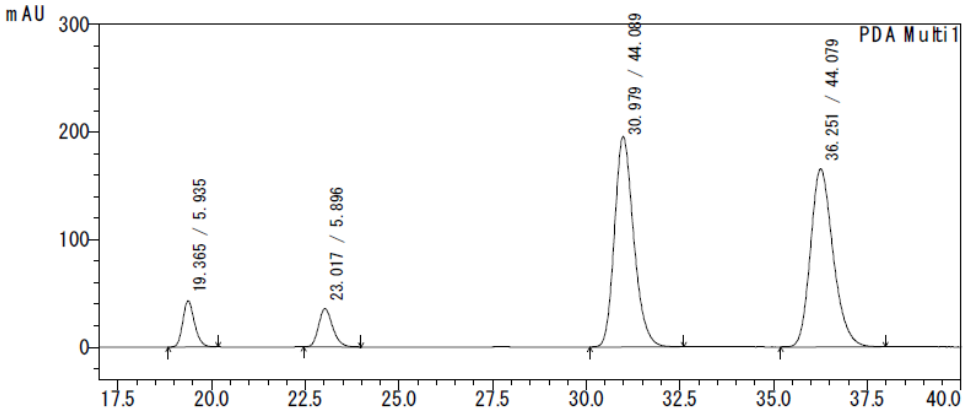
dr 71:29, 86% *ee*



76g

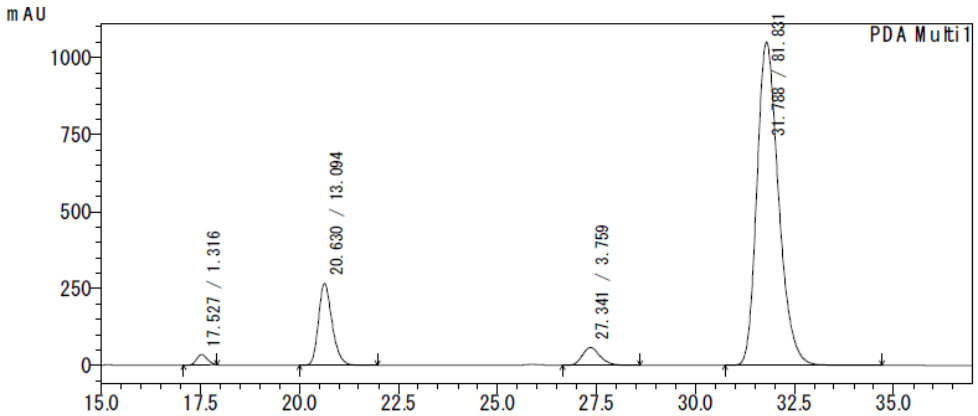
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min.

Rac-**76g**



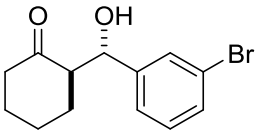
	Retention Time	% Area
1	19.36	5.93
2	23.02	5.90
3	30.98	44.09
4	36.25	44.08

Scalemic-**76g**



	Retention Time	% Area
1	17.53	1.32
2	20.63	13.09
3	27.34	3.76
4	31.79	81.83

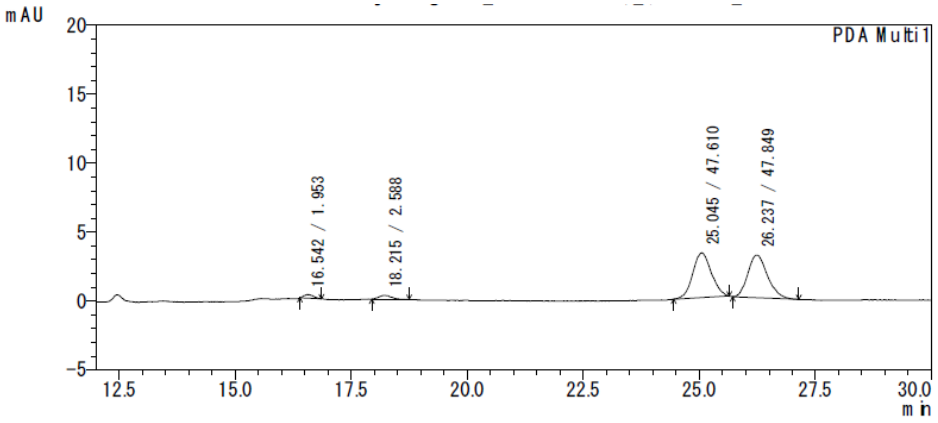
dr 86:14, 91% *ee*



76h

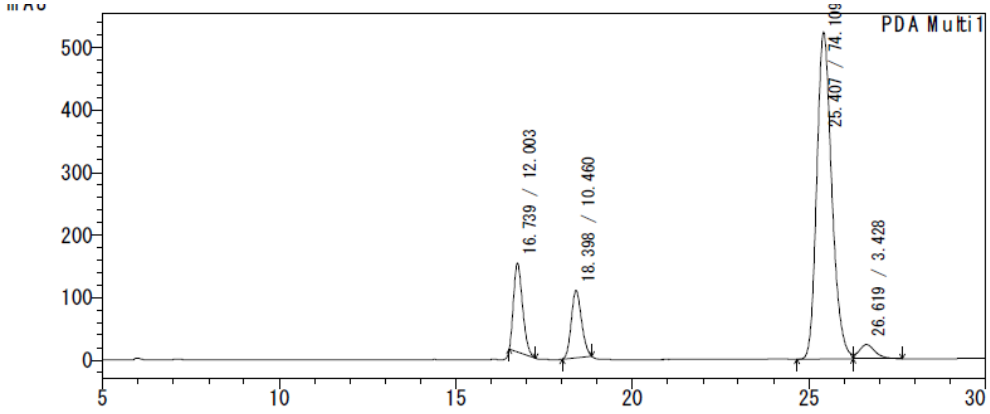
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 90/10, flow rate= 0.5 mL/min.

Rac-**76h**



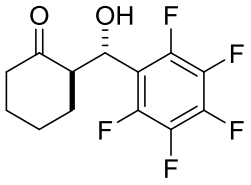
	Retention Time	% Area
1	16.54	1.95
2	18.21	2.59
3	25.04	47.61
4	26.24	47.85

Scalemic-**76h**



	Retention Time	% Area
1	16.74	12.00
2	18.40	10.46
3	25.41	74.11
4	26.62	3.43

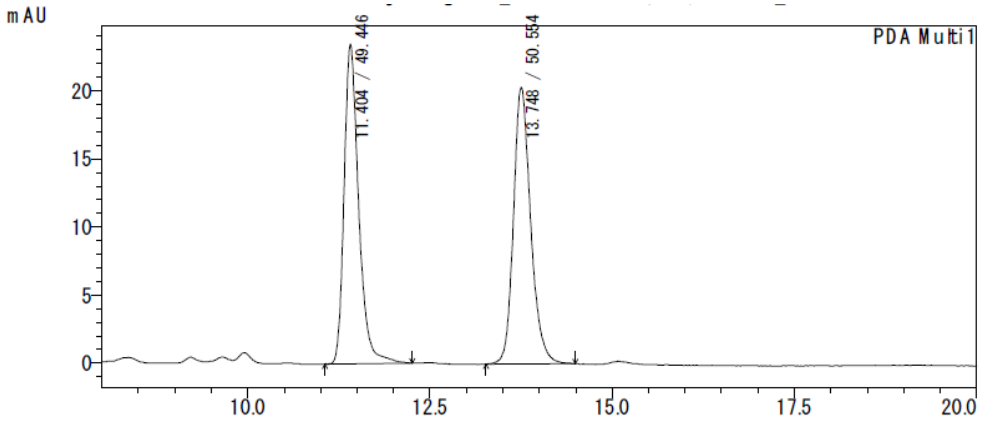
dr 78:22, 91% *ee*



76i

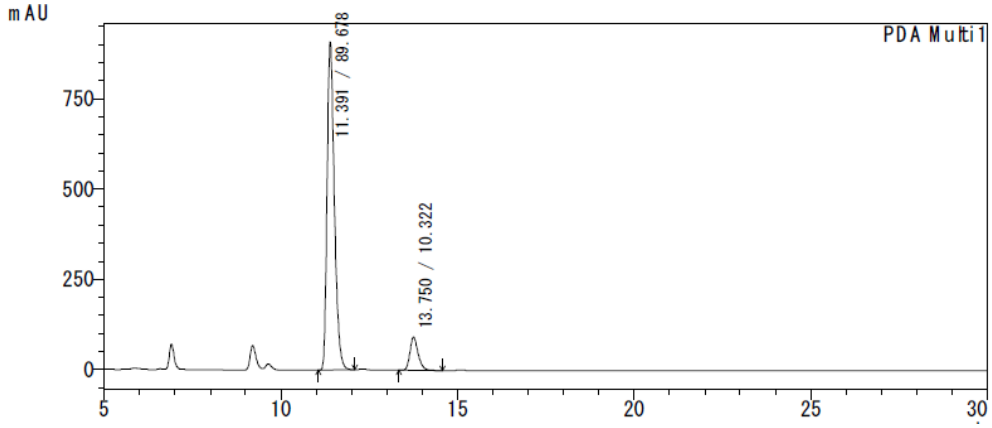
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

Rac-**76i**



	Retention Time	% Area
1	11.40	49.45
2	13.74	50.55

Scalemic-**76i**

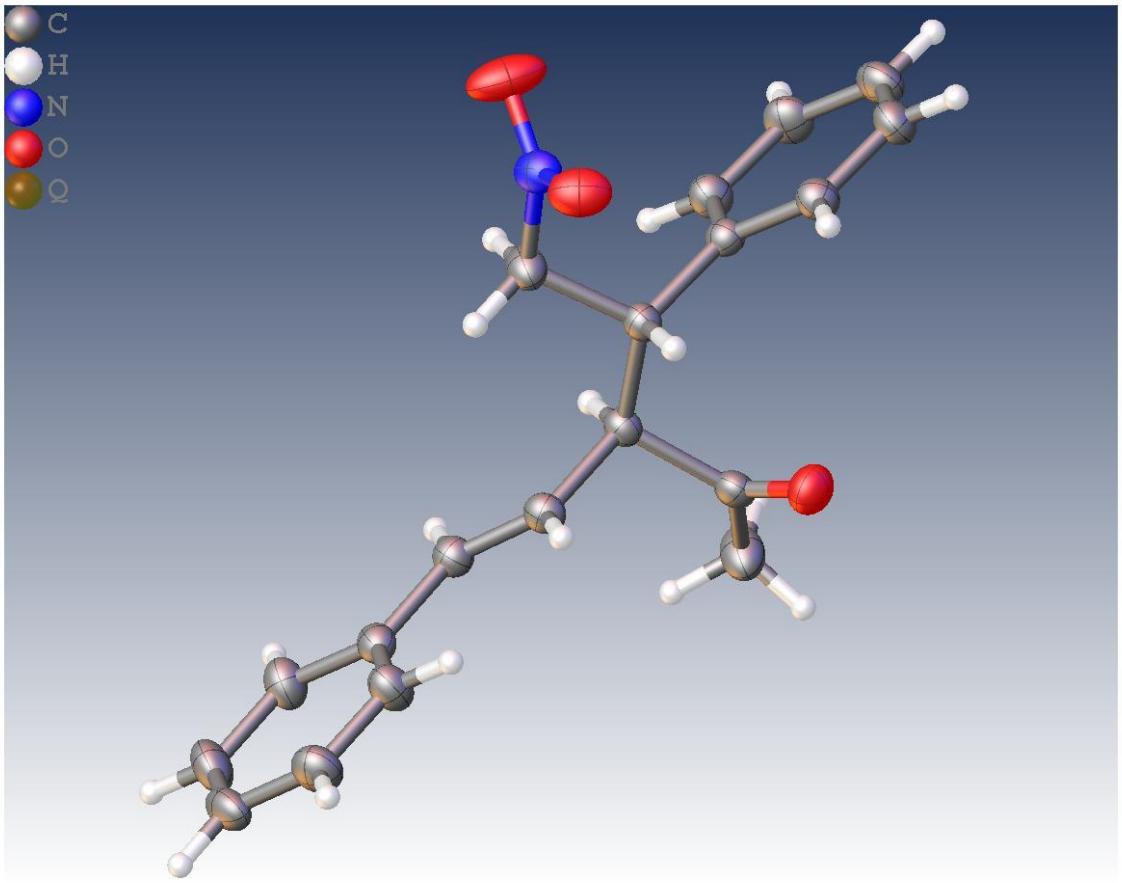


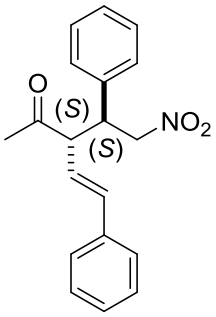
	Retention Time	% Area
1	11.39	89.68
2	13.75	10.32

dr >99:1, 80% *ee*

6.8. X-Ray analysis

6.8.1. ORTEP diagram of compound 6Aa





6Aa

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Asymmetric Organocatalysis

Asymmetric Assembly of All-Carbon Tertiary/Quaternary Nonadjacent Stereocenters through Organocatalytic Conjugate Addition of α-Cyanoacetates to a Methacrylate Equivalent

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Abstract: An efficient, highly diastereo- and enantioselective assembly of acyclic carbonyl fragments possessing nonadjacent all-carbon tertiary/quaternary stereoarrays is reported based on a Brønsted base catalyzed Michael addition/α-protonation sequence involving α-cyanoacetates and 2,4-dimethyl-4-hydroxypenten-3-one as novel methacrylate equivalent.

Introduction

Acyclic carbonyl compounds possessing multiple stereocenters are important building blocks for the construction of complex natural products and bioactive molecules. Huge advances have been made in the stereoselective synthesis of these stereoarrays, particularly carbonyl compounds with contiguous stereocenters at α,β- or β,γ-positions (**A** and **B**, Figure 1). In contrast, direct asymmetric entries to the α,γ-branched analogues **C**, bearing two nonadjacent stereocenters, are less common,[1] and rarely involve construction of a quaternary stereocenter as in **D**.[2,3] Among the few precedents, Deng reported a Brønsted base catalyzed Michael/α-protonation reaction cascade, which implies α-chloroacrylonitrile as the Michael acceptor,[4] and later on the group of Chen and Xiao described[5] a similar tandem reaction involving ethyl 2-phthalimidoacrylate or ethyl α-phosphonoacrylates as the doubly activated Michael acceptor (Figure 2). However, the extension of this methodology to inherently less reactive α-alkyl-substituted Michael acceptors, that is, methacrylates, remains challenging, despite the fact that the resulting α-alkyl- and more specifically α-methylcarbonyl units are present in a number of natural products and bioactive targets. In that respect, Kobayashi has reported[6] a $Ca(BOX)_2$-catalyzed (BOX = bis(oxazolidine)) conjugate addition of glycine Schiff bases to α-substituted acrylate derivatives, albeit no example involving generation of a quaternary center was gathered. More recently Pihko has described[7] enantioselective Mukaiyama–Michael addition reactions of methacrolein through iminium activation; however, this reaction led to an approximately 1:1 mixture of the two possible diastereomers. To the best of our knowledge, highly enantiose-

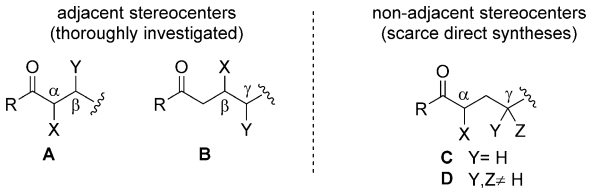

Figure 1. Acyclic carbonyl compounds with different stereoarrays.

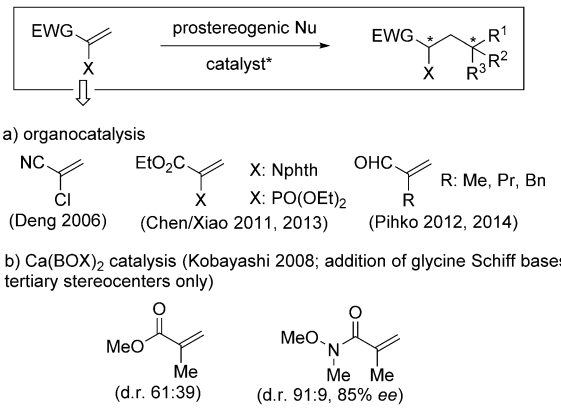

Figure 2. Advances in tandem addition/protonation approaches for the asymmetric assembly of α,γ-nonadjacent stereocenters.

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lective Michael reactions with methacrylates or equivalents to provide carbonyl compounds with all-carbon tertiary/quaternary nonadjacent stereocenters have not been realized yet. Here we present an effective asymmetric direct entry to such stereoarrays that is founded upon the development of a newly designed methacrylate equivalent in combination with Brønsted base catalysis.

Results and Discussion

Hypothesis and working plan

The challenge posed by α-alkyl-substituted Michael acceptors is not only associated to their attenuated reactivity against neutral C-pronucleophiles, but also concerns stereocontrol during the key C–C bond formation (step 1, Figure 3a) and the subsequent α-protonation (step 2).[8]

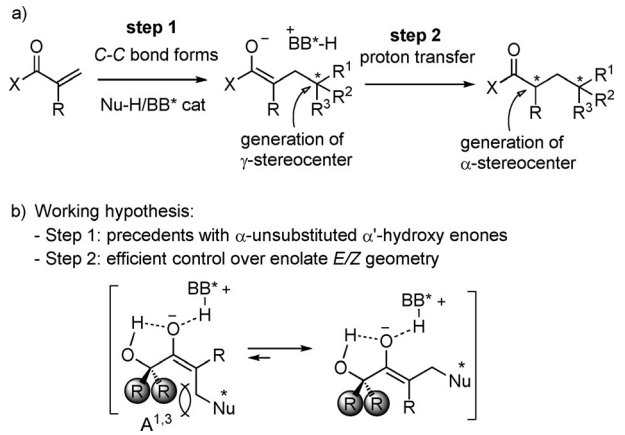
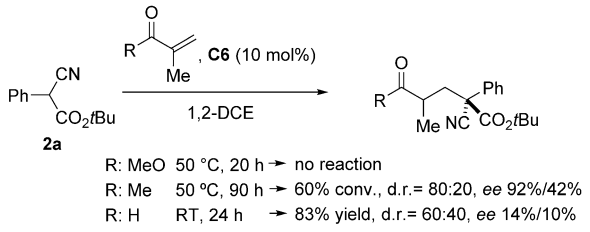


Figure 3. Construction of nonadjacent tertiary/quaternary stereocenters and working hypothesis for designed methacrylate equivalent.

Preliminary studies involving the reaction of 2-phenyl α-cyanoacetate **2a**[9] and some elementary α-substituted Michael acceptors revealed these difficulties. For instance attempts to react **2a** with methyl methacrylate in the presence of several mono- and bifunctional Brønsted base catalysts all led to recovery of unreacted material (Scheme 1). Under similar conditions, 3-methylbutenone resulted essentially unreactive at ambient temperature; 60% conversion was hardly achieved only after 90 h at 50 °C. Finally, methacrolein was more reactive, but led to unselective reaction.[7]



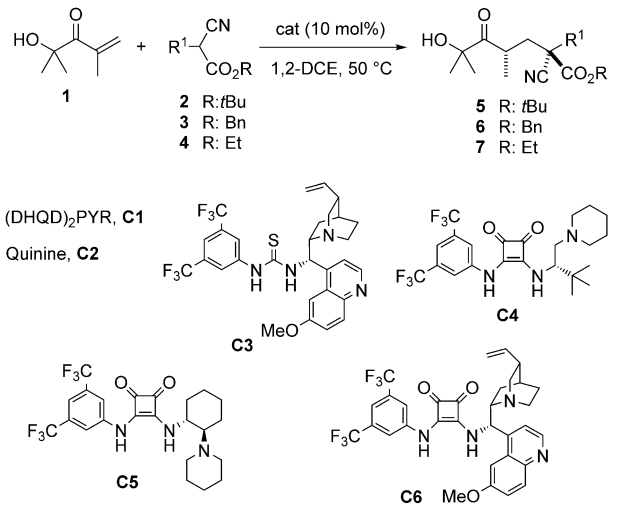
Scheme 1. Difficulties in the addition of α-cyanoester **2a** to α-methyl α,β-unsaturated ester, ketone or aldehyde under best reaction conditions.

Recently we have introduced α-unsubstituted α′-hydroxy enones as efficient acrylate equivalents in Brønsted base catalyzed enantioselective conjugate additions.[10] Both the remarkable reaction acceleration and the high level of asymmetric induction observed in these reactions were rationalized by assuming hydrogen-bond-mediated effective substrate–catalyst complexation, with the ketol moiety of substrate forming tight 1,4-proton chelates. Now we hypothesize that by using the parent α-substituted α′-hydroxy enones, the unique capacity of these type of bidentate substrates[11] to act as both hydrogen-bond donor and acceptor, in cooperation with a proper Brønsted base catalyst, may also be translated to the α-stereocenter-determining step 2. If so, a shortcut to the challenging construction of acyclic carbonyl adducts with nonadjacent stereocenters would be provided. Specifically, it is predicted that the evolved enolate from step 1 would preferentially adopt a *Z* configuration because of unfavorable $A^{1,3}$ strain in the chelated *E* form (Figure 3b), thus overcoming the problem of ill-defined enolate geometry in asymmetric α-protonations.[12,13] Eventually, the prevalence of such dynamic hydrogen-bond networks may also help during proton transfer (shuttle). To achieve high overall selectivity, however, both chiral units, namely the catalyst and the newly generated stereocenter at γ, have to work in concert in step 2, an inherent difficult of the process that at the outset remained unclear. In this respect, as far as we know, α-substituted α′-hydroxy enones have never been employed in catalytic asymmetric conjugate additions.[14]

Catalysts screening and reaction optimization

The investigation was started by studying the reaction of the newly prepared α′-hydroxy enone **1**[15] with α-substituted cyanoacetate **2a** in the presence of several bifunctional Brønsted bases (Scheme 2).[16] Among the catalysts examined, that is, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2PYR$; **C1**), quinine (**C2**), the thiourea-aminoquinine **C3**[17] and the squaramides **C4**,[18] **C5**,[19] and **C6**,[20] the last proved to be superior as shown in Table 1. Using this catalyst, the reaction between 2-phenyl α-cyanoacetate **2a** and **1** at ambient temperature afforded adduct **5a** with essentially perfect enantio- and diastereocontrol (d.r. > 99:1, 99% *ee*; entry 6). This result indicates that not only the initial addition that renders the γ-stereocenter, but also the subsequent α-protonation, both proceeded with remarkable face selectivity. Interestingly, this almost perfect chirality transfer was reproduced (entry 7) when the reaction was run at 50 °C, which allowed attaining full reaction conversion at shorter time (24 h).

Under these conditions (10 mol% **C6** in 1,2-DCE at 50 °C) the reaction of **1** worked equally well with an array of 2-aryl α-cyanoacetates **2** to afford the corresponding adducts **5** as essentially single diastereomer in yields within the range from 62% to 95% and *ee* values greater than 95% in most cases. As Table 2 shows, these results seem to be independent upon the meta/para substitution pattern of the aromatic ring or their electron donating/withdrawing character. Entry 6 was an ex-



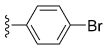
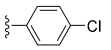
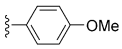
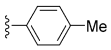
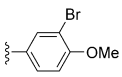
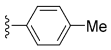
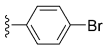
Scheme 2. Reaction of **1** with α-cyanoacetates catalyzed by chiral Brønsted bases.

Table 1. Catalyst screening for the reaction of **1** with **2a** (R^1 = Ph).[a]

	Catalyst	*t* [h]	Conv [%]	Yield [%][b]	d.r.	*ee* [%][c]
1	**C1**	72	100	72	70:30	30
2	**C2**	72	65	49	75:25	16
3	**C3**	72	70	46	80:20	68
4	**C4**	72	23	n.d.[e]	n.d.	n.d.
5	**C5**	40	100	75	75:25	−12
6[d]	**C6**	96	n.d.	40	>99:1	99
7	**C6**	24	100	81	>99:1	98

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C (molar ratio of **1**/**2a**/catalyst 1:1.5:0.1). [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at room temperature. [e] n.d.: not determined.

Table 2. Scope of the conjugate addition of α-cyanoacetates to **1**.[a]

	R^1	Product	*t* [h]	Yield [%][b]	d.r.	*ee* [%][c]
1		**5b**	24	69	98:2	98
2		**5c**	24	95	98:2	96
3		**5d**	40	70	>98:2	>98
4		**5e**	40	67	98:2	>98
5		**5f**	40	83	>98:2	97
6		**5g**	40	NR[d]	–	–
7		**5h**	16	62	97:3	96
8		**5i**	20	72	96:4	97
9		**6e**	24	76	90:10	92
10		**7b**	24	88	88:12	91

[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C (molar ratio of **1**/cyanoester/**C6** 1:1.5:0.1). [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] NR: no reaction.

ception probably because of steric constraints imposed by the *ortho* substituent. Using the less sterically demanding benzyl and ethyl cyano esters **3** and **4**, a slight loss of stereoselection was produced (entries 9 and 10), albeit it was still acceptable. The configuration of adduct **5e** was established by a single-crystal X-ray analysis[21] and that of the remaining adducts by assuming a uniform reaction mechanism.

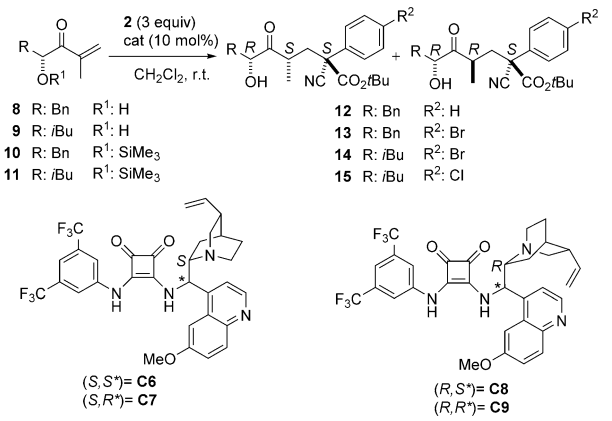
Double asymmetric induction

Given the paucity of methods for the construction of tertiary/quaternary nonadjacent stereocenters, this organocatalytic Michael/protonation cascade was next extended to chiral α′-oxy enones **8/9** and **10/11**,[22] a type of substrate that, as far as we know, have neither been previously investigated within the realm of organocatalysis.[23,24] As the results in Table 3 show, the stereochemical outcome of the reactions varies notably depending on the catalysts used. With Et_3N as the only promoter (entries 1 and 8), adducts **12** and **14** were produced with moderate diastereoselectivity (ratio of *RSS*/other isomers 60:40 and 71:29, respectively). Again, the best catalyst was **C6**, which afforded only two out of the four possible diastereomers in all the cases studied (entries 2, 3, 6, 9 and 10), with remarkable diastereoselectivity (*RSS*/*RRS*/others up to 91:9:0). Catalyst **C7** led to no reaction (entry 4), and **C8** and **C9** led to poor selectivity (entries 5 and 7). It is worth noting that in the above reactions *O*-silylated enones **10**/**11** behaved in a more superior fashion than hydroxy enones **8**/**9** as the results in entries 2/3 (d.r. of 67:32 and 89:11, respectively) and 8/9 (d.r. of 71:29 and 91:9, respectively) show.[25]

At this point it remained unclear whether the above substrate/catalyst combinations correspond to a matched stereochemical relationship. To answer that question, the reaction between **2a** and the (*S*)-configured ent-**10** was carried out in the presence of catalyst **C6**. As the data in Scheme 3 show, a 69:12:12:7 mixture of diastereomers was obtained, with (*S*,*S*,*S*)-**16** as the major product. By comparison with data in entry 3 of Table 3, it seems clear that the pair **10**/**C6**, with the configurations (*R*)-substrate/(*S*,*S*)-catalyst, corresponds to the matched combination. Experiments using bifunctional Brønsted base catalysts derived from other chiral 1,2-primary/tertiary diamines also revealed (*R*)-substrate/(*S*,*S*)-catalyst as the best combination to induce formation of adducts of *RSS* configuration.[26]

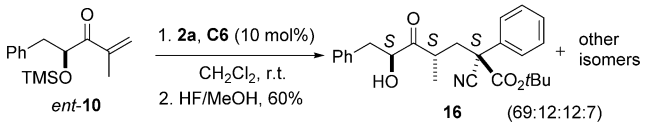
Given these observations and the absence of studies concerning double asymmetric induction in this field, we next examined briefly the reaction of chiral α′-hydroxy enones without substituents at Cα position. Under optimized conditions it was

Table 3. Michael addition/protonation cascade involving chiral enones (double asymmetric induction).[a]



	Enone	Cat	*t* [h]	Product	Yield [%]	*RSS*:*RRS*:others
1	**8**	Et_3N	24	**12**	75[b]	60:23:17:0
2	**8**	**C6**	24	**12**	70[b]	67:32:0:0
3	**10**	**C6**	60	**12**	73	89:11:0:0
4	**10**	**C7**	24	**12**	NR[e]	–
5	**10**	**C8**	64	**12**	70	49:41:10:0
6	**10**	**C6**	72	**13**	75[c]	83:17:0:0
7	**10**	**C9**	72	**13**	65[c,d]	22:21:57:0
8	**9**	Et_3N	24	**14**	83[b]	71:29:0:0
9	**11**	**C6**	72	**14**	90[c]	91:9:0:0
10	**11**	**C6**	72	**15**	80[c]	90:10:0:0

[a] Reactions conducted on a 0.2 mmol scale in 0.4 mL CH_2Cl_2 using 3 equiv α-cyanoester **2a–c**. [b] Yield of isolated product (mixture of isomers). [c] Yield of isolated product (mixture of isomers) after desilylation with HF/MeOH. [d] Configuration of major isomer unknown. [e] NR: no reaction.



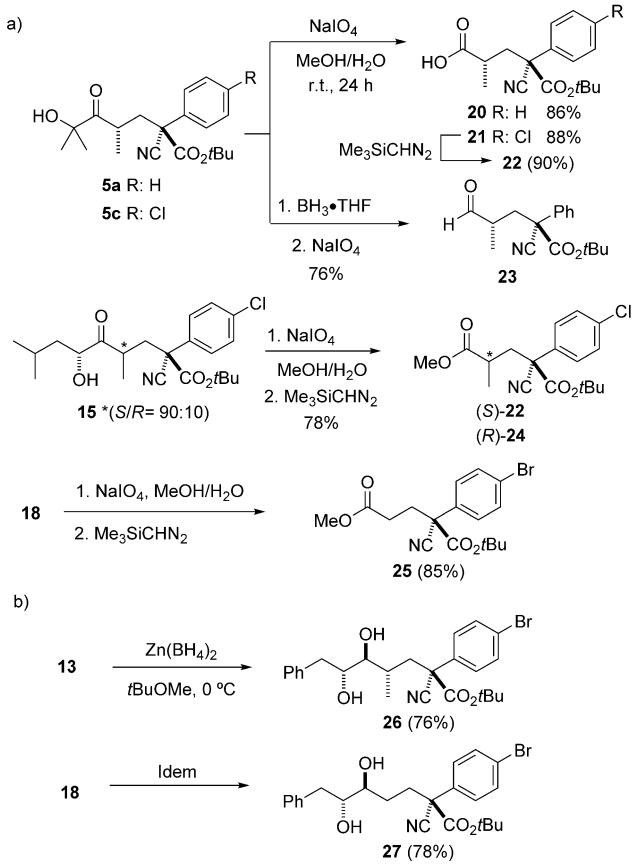
Scheme 3. Reaction involving substrate/catalyst mismatchaed combination. TMS: trimethylsilyl.

found that reaction of **17** with either **2b** or **2c** produced the corresponding adducts **18** and **19**, respectively, essentially as single diastereomers (Scheme 4). This result thus confirms that generation of the quaternary stereocenter proceeds with almost perfect asymmetric induction with catalyst **C6** for both α-substituted and unsubstituted enones.

Scheme 4. Generation of a quaternary γ-stereocenter in chiral α-unsubstituted α′-hydroxy ketones. TES: triethylsilyl.

Adduct elaboration and proposed reaction models

The results obtained are of special interest in that treatment of adducts **5a** and **5c** with $NaIO_4$ in $MeOH/H_2O$ provides the carboxylic acids **20** and **21** in 86% and 88% yield, respectively, along with acetone as the only organic side product formed (Scheme 5).



Scheme 5. Elaboration of adducts: a) conversion of ketol into carboxy and aldehyde functions; b) stereoselective 1,2-diol formation.

Acid **21** was transformed into its methyl ester **22** for comparative purposes, vide infra. Alternatively, reduction of the carbonyl group of **5a** followed by diol cleavage as above furnished the aldehyde **23** in 76% yield over the two steps. Thus, the lack of reactivity and selectivity associated with methacrylate esters and methacrolein (vide supra) may now be remediated with this new methacrylate equivalent. Finally, to confirm the stereochemical assignment of reactions involving double asymmetric induction (Table 3), adduct **15** (90:10 diastereomeric mixture) was subjected to the oxidative cleavage conditions to afford the same product **22** to that obtained from **5c**, along with the minor isomer **24**. Similarly, **18** upon oxidative cleavage of the ketol moiety as above and subsequent esterification of the resulting carboxylic acid provided the methyl

ester **25**. The absolute configuration of both **24** and **25** was established by chemical correlation.[26] In addition to the above transformations, stereoarrays bearing up to four stereogenic centers may also be produced from this approach. Thus, diols **26** and **27** were obtained as essentially single *anti*-diol isomer through reduction of the respective α′-hydroxy ketone **13** and **18** with $Zn(BH_4)_2$.[27]

The high fidelity with which chirality is transferred from the catalyst to the reaction products could be explained by the stereomodels depicted in Figure 4. By analogy to previously calculated TS geometries for the related conjugate addition of cyanoesters to α-unsubstituted enone analog to **1**,[10] ternary complex **A** would account for the conjugate addition step, which would proceed with the catalyst interacting with both reaction components through several hydrogen bonds. Once the addition adduct is formed, the local negative charge would no longer be located in the cyano esther moiety, but in the enolate site. This will weaken the hydrogen bond between the protonated quinuclidine and the cyano esther carbonyl. Finally, proton transfer, either directly from the protonated catalyst to the enolate or alternatively mediated by some proton–shuttle mechanism, would preferentially occur through the enolate *Re* face, as depicted in proposed model **B**.

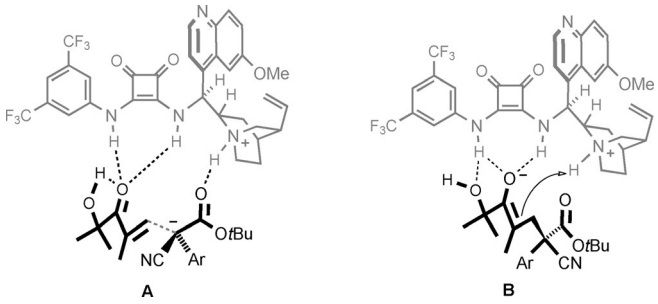


Figure 4. Proposed approaching models for the addition and protonation steps, respectively.

Conclusion

Direct approaches to the construction of acyclic carbonyl compounds with nonadjacent all carbon tertiary/quaternary stereocenters that proceed with high diastereo- and enantioselectivity are lacking. Here an effective solution to this longstanding problem is reported based on a bifunctional Brønsted base catalyzed Michael/α-protonation cascade that involves 2,4-dimethyl-4-hydroxypenten-3-one as design methacrylate equivalent. A key feature of this template is the ability to act as either hydrogen-bond donor or/and acceptor, a distinguishing feature among known bidentate enoate equivalents employed in organocatalysis.[11] Control experiments with other elementary Michael acceptors lacking such ambivalent character led to inferior reactivity and/or selectivity. This design element also demonstrated successful in Michael/protonation cascades involving chiral α′-oxyenones. In this latter case, double asymmetric induction occurs with substrate/catalyst matched combination providing adducts in up to >98:2 d.r. The obtained adducts are easily transformed into the corresponding acyclic carboxylic acids, aldehydes, and 1,2-diols with up to four configurationally-defined stereocenters. We believe this new family of enoate equivalents will rapidly find further applications in organocatalysis.

Experimental Section

Selected experimental procedures

All experimental details can be found in the Supporting Information. The material includes compound characterization, stereochemical determinations and copies of spectra of new compounds.

4-Hydroxy-2,4-dimethylpent-1-en-3-one (1): To a solution of commercial methyl 2-hydroxy-2-methylpropanoate (15 mmol, 1.77 g) and *N*,*O*-dimethylhydroxylamine hydrochloride (22.5 mmol, 2.14 g, 1.5 equiv) in THF (50 mL), a 2 M solution of *i*PrMgCl in THF (60 mmol, 4 equiv) was added at −20 °C. Once the reaction mixture was stirred for 1.5 h at room temperature, it was quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to obtain the desired Weinreb amide product. Yield: 1.99 g (90%), colorless oil. To a solution of this material (10 mmol, 1.85 g) in Et_2O (20 mL) at −20 °C, a solution of isopropenyl magnesium bromide (0.5 M in THF, 60 mL, 3 equiv) was added, and the resulting mixture was stirred at 0 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with Et_2O (2×50 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O 95:5) to obtain compound **1**. Yield: 833 mg (65%), colorless oil; ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[28]

Preparation of chiral α′-hydroxy enones 8/9: To a solution of methyl 2-hydroxy-3-phenylpropanoate or methyl 2-hydroxy-4-methylpentanoate (10 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv) in THF (35 mL), at −20 °C a 2 M solution of *i*PrMgCl in THF (40 mmol, 20 mL, 4 equiv) was added. The reaction mixture was stirred for 1.5 h at 0 °C. The reaction was then quenched with an aqueous saturated solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to obtain the corresponding Weinreb amide. To a solution of 2-bromopropene (9 mmol, 0.79 mL, 3 equiv) in Et_2O (5 mL) at −78 °C, a solution of *tert*-butyllithium (1.6 M in pentane, 6.75 mL, 3.6 equiv) was added, and the resulting mixture was stirred at the same temperature for 1 h. Subsequently, a solution of the corresponding Weinreb amide (3 mmol) in Et_2O (10 mL) was added and the reaction mixture was stirred at −60 °C for 16 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent hexane/ethyl acetate 95:5).

Preparation of chiral α′-silyloxy enones 10/11: To a solution of the corresponding α′-hydroxy enone **8/9** (2 mmol) in CH_2Cl_2 (20 mL) at −20 °C, were added successively 2,6-lutidine (0.55 mL,

4.8 mmol, 2.4 equiv) and TMSOTf (0.72 mL, 4 mmol, 2 equiv), and the mixture was stirred at the same temperature for 3 h. EtOAc (40 mL) was then added, and the organic phase was washed with saturated aqueous solutions of $NaHCO_3$ (40 mL), $CuSO_4$ (3×40 mL), $NaHCO_3$ (2×40 mL) and NaCl (40 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 99:1) to obtain pure compounds **10**/**11**.

General procedure for the catalytic conjugate addition of α-cyanoacetates to 1: To a solution of the corresponding α-cyanoacetate **2** (0.3 mmol, 1.5 equiv) and α′-hydroxy enone **1** (26 mg, 0.2 mmol) in 1,2-DCE (0.4 mL), catalyst **C6** (13 mg, 0.02 mmol) was added, and the resulting mixture was stirred at 50 °C until consumption of enone **1** (monitored by ^{1}H NMR spectroscopy). Then the reaction was quenched with HCl 1 N and the mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the corresponding addition/α-protonation adduct, which was purified by flash column chromatography (eluent hexane/ethyl acetate 95:5).

Catalytic conjugate addition of α-cyanoacetates 2 to chiral α′-oxy enones: To a solution of the corresponding *tert*-butyl cyanoacetate **2** (0.6 mmol) and the corresponding α′-oxy enone **8**–**11** (0.2 mmol, 1 equiv) in CH_2Cl_2 (0.4 mL), the catalyst (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α′-oxy enone (monitored by ^{1}H NMR spectroscopy; see Table 3 for reaction times). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure.

*Reactions from α′-hydroxy enone **8/9***: The residue was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95:5).

*Reactions from α′-silyloxy enone **10/11***: The residue was dissolved in MeOH (0.5 mL) and a solution of concentrated fluorhydric acid in MeOH (10 mmol, 0.2 mL) was added. The resulting mixture was stirred at 20 °C for 2 h. Then the solvent was evaporated and the resulting residue was basified to pH 7 with a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2×4 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The oily product was submitted to purification by flash column chromatography (eluent hexane/ethyl acetate 95:5.)

Conversion of adduct 5a into carboxylic acid 20: A suspension of sodium periodate $NaIO_4$ (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of α-hydroxy ketone **5a** (69 mg, 0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TCL, 24 h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated. The product was purified by flash column chromatography (hexanes/EtOAc 80:20) to afford carboxylic acid **20** (52 mg, 86% yield, colorless oil).

Conversion of adduct 5a into aldehyde 23: BH_3·THF (1 M, 0.4 mL, 0.4 mmol) was added to a solution of α-hydroxy ketone **5a** (69 mg, 0.2 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, as above. The crude material was purified by flash column chromatography on silica gel (eluting with hexanes/EtOAc 95:5) to give compound **23** (44 mg, 76% yield, oil).

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Keywords: asymmetric organocatalysis · Brønsted bases · Michael reactions · quaternary stereocenters · stereoselective protonation

[1] a) K. L. Kimmel, J. D. Weaver, M. Lee, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 9058–9061; b) B. Zheng, H. Wang, Y. Han, C. Liu, Y. Peng, *Chem. Commun.* **2013**, *49*, 4561–4563; c) N. V. G. Moorthy, R. Dyapa, S. V. Pansare, *Org. Lett.* **2015**, *17*, 5312–5315.

[2] For classic examples of multistep approaches to α,γ-substituted carbonyl patterns en route to erythromycins, see: a) E. J. Corey, P. B. Hopkins, S. K. Sung-eun, Y. Krishnan, P. Nambiar, J. R. Falck, *J. Am. Chem. Soc.* **1979**, *101*, 7131–7134; b) R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217; c) G. Stork, D. R. Rychnovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1565–1567; d) J. Mulzer, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1452–1454; *Angew. Chem.* **1991**, *103*, 1484–1486; e) R. Stürmer, K. Ritter, R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101–103; *Angew. Chem.* **1993**, *105*, 112–114.

[3] For a racemic synthesis of a α,γ-substituted carbonyl pattern with all-carbon quaternary/tertiary nonadjacent stereocenters, see: J.-H. Fan, W.-T. Wei, M.-B. Zhou, R.-J. Song, J.-H. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 6650–6654; *Angew. Chem.* **2014**, *126*, 6768–6772.

[4] a) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; b) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768–769; for an extension to 2-oxindoles as pronucleophiles, see: c) X. Li, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 14290–14294.

[5] a) S.-W. Duan, J. An, J. R. Chen, W. J. Xiao, *Org. Lett.* **2011**, *13*, 2290–2293; b) S.-W. Duan, Y.-Y. Liu, W. Ding, T.-R. Li, D.-Q. Shi, J. R. Chen, W. J. Xiao, *Synthesis* **2013**, 1647–1653.

[6] T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332.

[7] a) E. K. Kemppainen, G. Sahoo, A. Valkonen, P. M. Pihko, *Org. Lett.* **2012**, *14*, 1086–1089; b) E. K. Kemppainen, G. Sahoo, A. Piisola, A. Hamza, B. Kótai, I. Pápai, P. M. Pihko, *Chem. Eur. J.* **2014**, *20*, 5983–5993. Also, see: c) N. Fu, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2013**, *19*, 15669–15681.

[8] For a recent approach to overcome problems associated with the enantioselective conjugate addition to methacrylate esters, see: a) A. J. M. Farley, C. Sandford, D. J. Dixon, *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995. For recent reviews on conjugate addition/enantioselective protonation, see: b) S. Oudeyer, J.-F. Briére, V. Levacher, *Eur. J. Org. Chem.* **2014**, 6103–6119; c) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359–369; d) J. P. Phelan, J. A. Ellman, *Beilstein J. Org. Chem.* **2016**, *12*, 1203–1228.

[9] For the interest in α-functionalized 2-cyanoacetates, see: a) S. Jautza, R. Peters, *Synthesis* **2010**, 365–388; b) M. D. Díaz de Villegas, J. A. Gálvez, R. Badorrey, P. López Ram de Viv, *Adv. Synth. Catal.* **2014**, *356*, 3261–3288.

[10] 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.

[11] Recent review on unsaturated carboxylic acid equivalents in asymmetric organocatalysis: a) D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. Eur. J.* **2015**, *21*, 4494 – 4504; use of α,β-unsaturated amides and related systems in conjugate additions: b) K. M. Byrd, *Beilstein J. Org. Chem.* **2015**, *11*, 530 – 562; c) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2015**, *115*, 9922 – 9980.

[12] Unsaturated carbonyl compounds used as Michael acceptors in conjugate addition/enantioselective protonation usually are cyclic, because the cycle unequivocally determines the configuration of evolving enolate. Examples of acyclic acceptors leading to a single stereocenter are given. Iminium activation with enals: a) N. Fu, L. Zhang, J. Li, S. Luo, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2011**, *50*, 11451 – 11455; *Angew. Chem.* **2011**, *123*, 11653 – 11657; iminium activation with enones: b) ref. [7c]; c) L. Cui, L. Zhang, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2014**, 3540 – 3545; d) N. Fu, L. Zhang, S. Luo, *Org. Lett.* **2015**, *17*, 382 – 385; Zn^{II} or Ca^{II} catalysis with unsaturated imides: e) M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem. Int. Ed.* **2008**, *47*, 9913 – 9915; *Angew. Chem.* **2008**, *120*, 10061 – 10063; f) T. Poisson, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7890 – 7892; Rh catalysis with dehydro amino acids: g) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159 – 6169; acyclic acceptor leading to two contiguous stereocenters: h) M. P. Sibi, G. Petrovic, J. Zimmerman, *J. Am. Chem. Soc.* **2005**, *127*, 2390 – 2391; for further examples, see reference [8].

[13] During the preparation of this manuscript, an organocatalytic conjugate addition/protonation sequence leading to nonadjacent stereocenters was reported, although using a cyclic Michael acceptor (N-itaconimide): B. Zhu, R. Lee, J. Li, X. Ye, S.-N. Hong, S. Qiu, M. L. Coote, Z. Jiang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1299 – 1303; *Angew. Chem.* **2016**, *128*, 1321 – 1325.

[14] Use of α′-hydroxy enones in asymmetric transformations: C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2012**, *41*, 4150 – 4164.

[15] This enone could be prepared from commercial methyl 2-hydroxy-2-methylpropanoate and isopropenylmagnesium bromide in two steps (59% overall yield). See the Supporting Information for details.

[16] Reviews on Brønsted bases: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; b) *Science of Synthesis: Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, In *Asymmetric Organocatalysis, Vol. 291, Top. Curr. Chem.* (Ed.: B. List), Springer, New York, **2010**, pp. 145 – 200.

[17] 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. Soós, *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.

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

[19] a) J. P. Malerich, K. Hagihara, 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.

[20] 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.

[21] CCDC 1470018 (**5e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] These enones were easily prepared from the corresponding α-hydroxy acids. See the Supporting Information for details.

[23] *Science of Synthesis: Asymmetric Organocatalysis, Vols. 1 & 2* (Eds.: B. List, K. Maruoka), Thieme, Stuttgart, **2012**.

[24] Reactions with chiral α-unsubstituted α′-hydroxy enones leading to tertiary stereocenters. Conjugate additions: a) W.-Y. Zhang, D. J. Jakiela, A. Maul, C. Knors, J. W. Lauher, P. Helquist, D. Enders, *J. Am. Chem. Soc.* **1988**, *110*, 4652 – 4660; b) E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, *45*, 545 – 555; c) J. M. García, M. A. Maestro, M. Oiarbide, J. M. Odriozola, J. Razkin, C. Palomo, *Org. Lett.* **2009**, *11*, 3826 – 3829; d) L. C. Kopel, M. S. Ahmed, F. T. Halaweish, *Steroids* **2013**, *78*, 1119 – 1125; Diels – Alder reactions: e) W. Choy, L. A. Reed, III, S. Masamune, *J. Org. Chem.* **1983**, *48*, 1137 – 1139; f) S. Masamune, L. A. Reed, III, J. T. Davis, W. Choy, *J. Org. Chem.* **1983**, *48*, 4441 – 4444; g) B. Stammen, U. Berlage, R. Kinderman, M. Kaiser, B, Günther, W. S. Sheldrick, P. Welzel, W. R. Roth, *J. Org. Chem.* **1992**, *57*, 6566 – 6575; h) P. Bañuelos, J. M. García, E. Gómez-Bengoa, A. Herrero, J. M. Odriozola, M. Oiarbide, C. Palomo, J. Razkin, *J. Org. Chem.* **2010**, *75*, 1458 – 1473; Cycloaddition with nitrones: i) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González, A. Linden, *Angew. Chem. Int. Ed.* **2005**, *44*, 6187 – 6190; *Angew. Chem.* **2005**, *117*, 6343 – 6346.

[25] No racemization occurred when **8** and **10** were stirred in the presence of Et_3N, **C6** or DBU. Partial epimerization of product **13** appeared only upon prolonged exposure to DBU. See the Supporting Information for details.

[26] See the Supporting Information for details.

[27] T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, *24*, 2653 – 2656.

[28] A. Basheer, M. Mishima, I. Marek, *Org. Lett.* **2011**, *13*, 4076 – 4079.

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Controlling the α/γ-Reactivity of Vinylogous Ketone Enolates in Organocatalytic Enantioselective Michael Reactions

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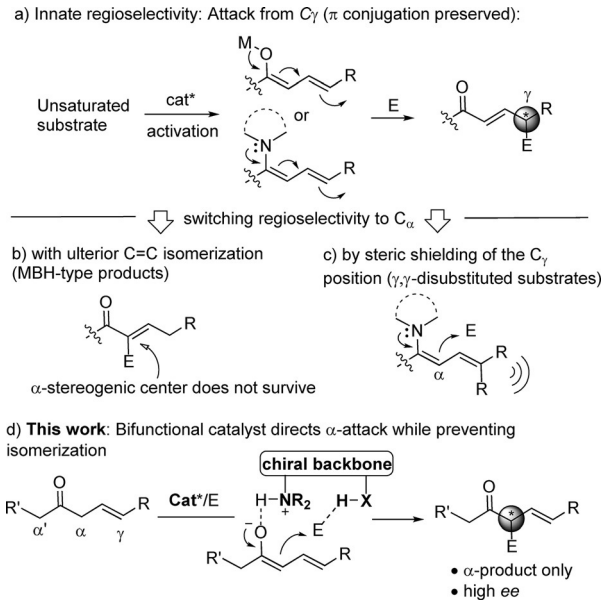
Abstract: *The first regio-, diastereo-, and enantioselective direct Michael reaction of β,γ-unsaturated ketones with nitroolefins is enabled by Brønsted base/hydrogen-bonding bifunctional catalysis. A squaramide-substituted tertiary amine catalyzes the reaction of a broad range of β,γ-unsaturated ketones 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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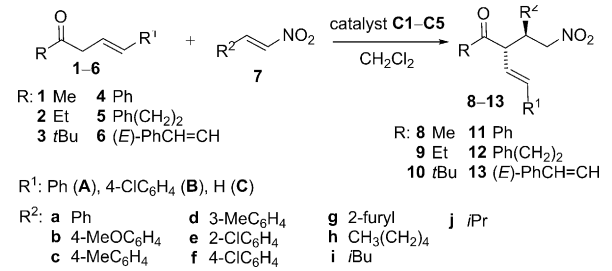
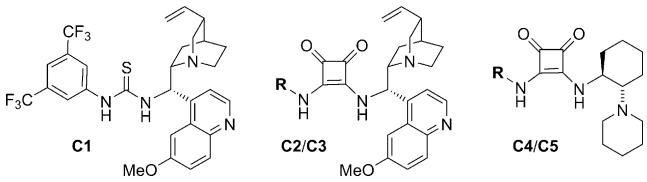


Scheme 2. Catalyst-controlled enantioselective direct reactions of β,γ-unsaturated ketones with nitroalkenes.

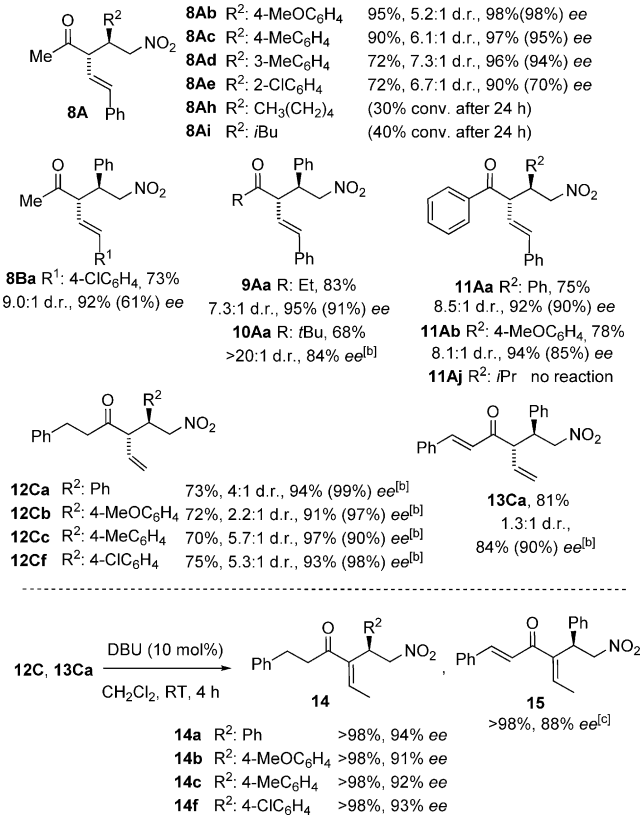
Table 1: Catalyst screening for the reaction of **1A** with **7a** to give **8Aa**.[a]



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]



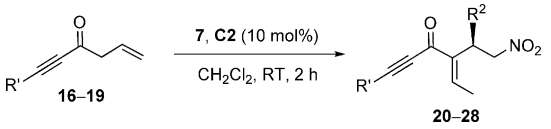
[a] Unless otherwise stated, all reactions were carried out on 0.2 mmol scale with 1.5 equiv of the ketone and 10 mol% **C5** at 0°C in CH_2Cl_2 (0.4 mL). Diastereomeric ratios determined by HPLC analysis. Yields of isolated products after column chromatography are given. The *ee* values were determined 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]

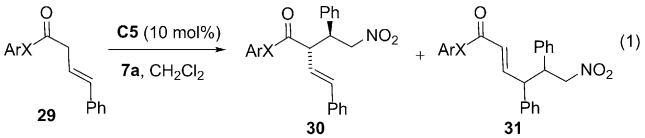
Table 3: Catalytic reactions with β′,γ′-unsaturated ynones **16–24**.[a]



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**.

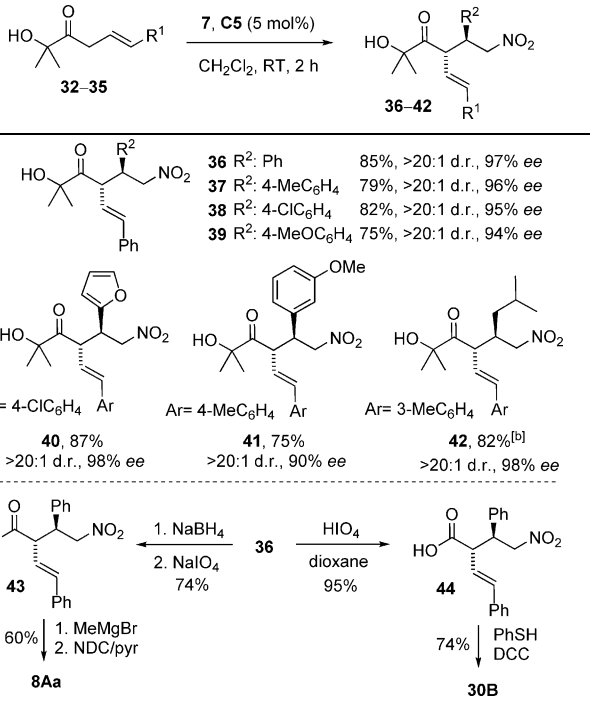
Attempts to translate the present conditions to simple β,γ-unsaturated esters and equivalents, a substrate category that, to the best of our knowledge, has never been employed in enantioselective direct conjugate additions,[26] revealed a divergent behavior. As illustrated in Equation (1), the **C5**-catalyzed 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]

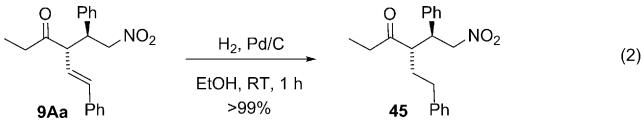


[a] Reactions carried out on 0.2 mmol scale, using 1.1 equiv of the nitroolefin and 5 mol% **C5** at room temperature, unless otherwise stated, in 0.4 mL CH_2Cl_2. Diastereomeric ratios determined by ^{1}H NMR analysis of crude samples. Yields of isolated products after chromatographic purification are 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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Organocatalysis

α-Hydroxy Ketones as Masked Ester Donors in Brønsted Base Catalyzed Conjugate Additions to Nitroalkenes

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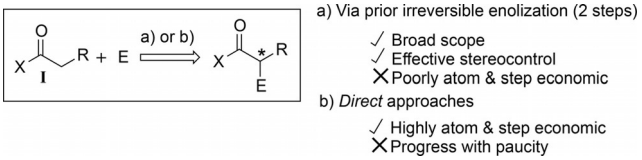
Abstract: The catalyst-controlled enantioselective direct addition reaction of enolizable esters and related carboxylic acid derivatives to π electrophiles remains a difficult synthetic transformation. In this study, the suitability of α-hydroxy ketones as ester equivalents capable of being activated by bifunctional Brønsted base catalysts in the context of conjugate addition reactions to nitroolefins is demonstrated. The scope of the reaction, which affords the corresponding Michael adducts with very high stereoselectivity (diastereomeric ratio (d.r.) ≥95:5, up to 99% enantiomeric excess (*ee*)), and its limitations are explored, as is the aftermath elaboration of adducts into densely functionalized enantioenriched products.

Introduction

The addition of an enolizable carbonyl compound to a π-electrophile represents a fundamental entry to new carbon–carbon bonds, resulting in synthetically useful α-modified carbonyl compounds. Stereoselective variants involving an enolizable substrate in the carboxylic acid oxidation state and using chiral stoichiometric reagents and auxiliaries have been well established, but commonly require a previous, irreversible enolization step (Scheme 1 a).[1] In contrast, direct protocols (that is, without a separate enolization process and consumption of stoichiometric base) involving enolizable esters, amides, or similar and a chiral catalyst are less developed (Scheme 1 b). Catalytic activation of esters and ester-like substrates is challenging owing to their diminished carbon acidity. Some progress in the area has been made involving enolizable thioamides/lactams,[2] amides,[3] nitriles,[4] imides,[5] and free carboxylic acids,[6] in which a chiral metallic catalyst in combination with sub-[2–4] or superstoichiometric[5,6] base is used. The covalent activation of carboxylic acids and esters by chiral N-heterocyclic carbene (NHC) and isothiourea catalysts has also been reported to afford mainly lactone- and lactam-type cyclic products.[7] In addition, few examples of Brønsted base catalyzed, noncovalent activation of reactive ester equivalents (acyl silanes and phosphonates, thioesters, pyrazoleamides, cyclic anhydrides) have been documented.[8,9] However, in many instances, control of the diastereo- and enantioselectivity of the reaction is still a challenge.



Scheme 1. State of the art of asymmetric α functionalization of carboxylic acid derivatives (E: electrophile; X: heteroatom).

Although all of these studies deal with enolizable substrates of type **I** (Scheme 1; acyl-heteroatom systems), a conceptually different, but in practice equivalent, strategy involves the use of α-hydroxy ketones as carboxylic acid surrogates. Early work by the groups of Heathcock[10] and Masamune,[11] independently, established a route to α-modified carboxylic acids upon an enolization/α′-functionalization/ketol scission sequence starting from chiral α-hydroxy ketones **II** (Scheme 2 a). More recently, the approach was further advanced, so that the chiral information source was no longer sacrificially destroyed during ketol oxidative scission.[12] Moreover, the scission step is easy to modify to access the corresponding ketone and aldehyde products as well. However, and despite its potential and practicality, to the best of our knowledge, no direct version of this approach, relying on a combination of an achiral α-hydroxy ketone and a suitable chiral catalyst, has been reported so far. Herein, we show that achiral α-hydroxy ketones **III** react smoothly with nitroalkenes in the presence of bifunctional Brønsted base catalysts to afford the corresponding Michael

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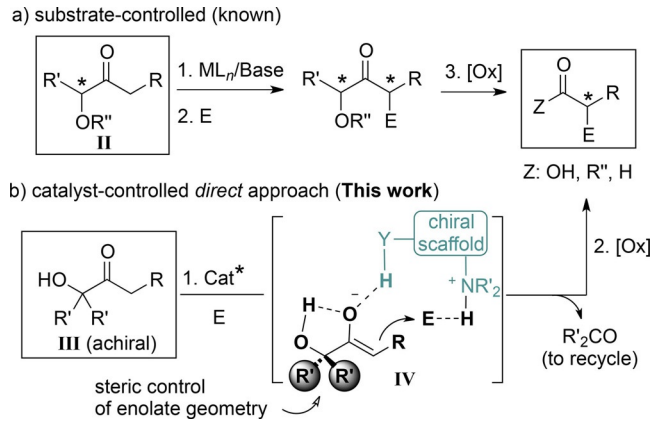


Scheme 2. α-Hydroxy ketones as donor carboxylic acid equivalents.

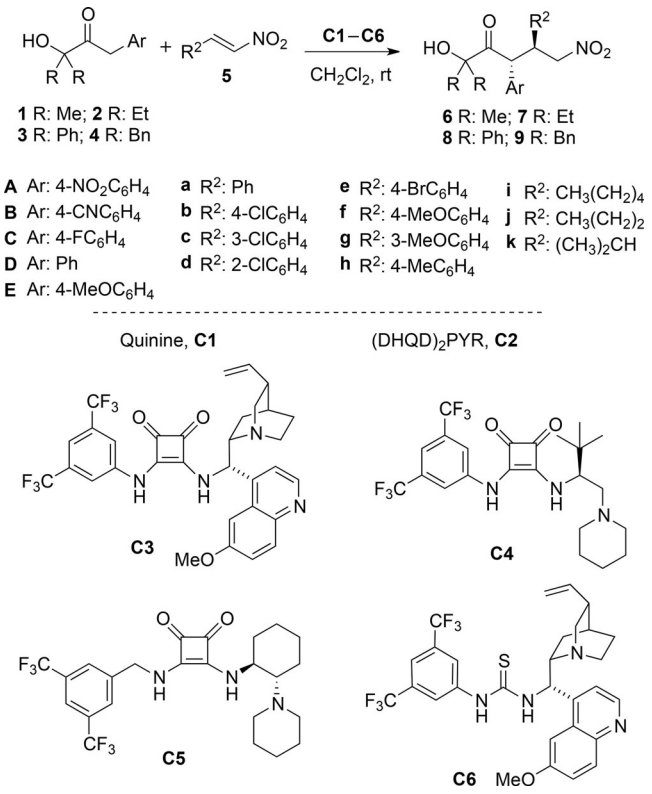
adducts in high stereoselectivity. This constitutes the first demonstration of achiral α-hydroxy ketones as ester and aldehyde donor equivalents in the context of asymmetric catalysis.[13]

Results and Discussion

The underlying idea is that substrate **III** may be activated by a bifunctional tertiary amine/hydrogen-bond-donor catalyst, as in model **IV**, to ultimately attack a suitable π-electrophilic reaction partner and lead, after final ketol scission, to enantioenriched α-branched carboxylic acids and derivatives. For initial validation of the idea, the reaction of **1A** with **5a** was selected and several Brønsted bases were screened (Scheme 3).

As shown by the results in Table 1, both **C1** and **C2** were able to promote the addition reaction; thus demonstrating the feasibility of α-hydroxy ketones for activation with mild bases, but led to suboptimal enantioselectivity (Table 1, entries 1 and 2). Among several bifunctional catalysts examined, squaramide **C3**[14] provided the addition adduct **6Aa** in nearly quantitative yield after 5 h at room temperature, but with as-yet unsatisfactory selectivity (Table 1, entry 3). Catalysts **C4**[15] and **C5** behaved similarly, both affording slightly better enantiocontrol (70 and 69% *ee*, respectively; Table 1, entries 4 and 5). Finally, thiourea catalyst **C6**[16] proved to be superior in this reaction to afford a product with 80% *ee* (Table 1, entry 6). Then, the influence of the two R groups at Cα of the ketol substrate, which can be readily prepared through the method reported by Qi et al. from the corresponding alkyne, CO_2, and simple ketones as starting materials,[17] was examined. Upon moving from **1A** (R = Me) to **2A** (R = Et) and **3A** (R = Ph), there is not much impact on the reaction selectivity (compare Table 1, entries 3–5 with 6–8 and 9). However, the reaction employing **4A** (R = Bn) led to an outstanding 99% *ee* with either catalyst **C3** or **C6** (Table 1, entries 10 and 12). Notably, in all of the above experiments, essentially a single diastereomer was observed by ^{1}H NMR spectroscopy (d.r. ≥ 95:5).

Based on the above results, ketone **4A** and catalyst **C6** were selected for exploring the scope of the reaction with regard to the nitroalkene component. As shown from the data in Table 2, several β-aryl-substituted nitroalkenes, including electron-poor (Table 2, entries 1–4) and -rich (Table 2, entries 5–7) systems, participate in the reaction with **4A** to afford the corresponding products **9A** in good yields and essentially perfect stereocontrol (d.r. ≥ 95:5, 99% *ee*) in all cases. Importantly, the



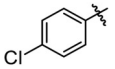
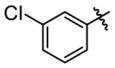
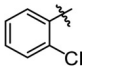
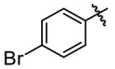
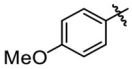
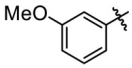
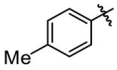
Scheme 3. Conjugate addition of α-hydroxy ketones to nitroalkenes catalyzed by Brønsted bases **C1**–**C6**. Bn = benzyl, (DHQD)$_2$PYR = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether.

Table 1. Screening of catalysts and ketol template for the reaction with **5a**.[a]

Entry	Reaction	Catalyst	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1		**C1**	72	97	10[d]
2		**C2**	72	86	−50[d]
3	**1A** + **5a** $\xrightarrow[\text{R: Me}]{\text{cat}}$ **6Aa**	**C3**	5	98	60
4		**C4**	72	97	70
5		**C5**	72	96	69
6		**C6**	72	98	80[d]
6		**C3**	24	97	76
7	**2A** + **5a** $\xrightarrow[\text{R: Et}]{\text{cat}}$ **7Aa**	**C4**	48	55[e]	72
8		**C6**	24	97	80
9	**3A** + **5a** $\xrightarrow[\text{R: Ph}]{\text{cat}}$ **8Aa**	**C6**	24	87	80
10		**C3**	24	75	99
11	**4A** + **5a** $\xrightarrow[\text{R: Bn}]{\text{cat}}$ **9Aa**	**C4**	72	70[e]	88
12		**C6**	24	99	99

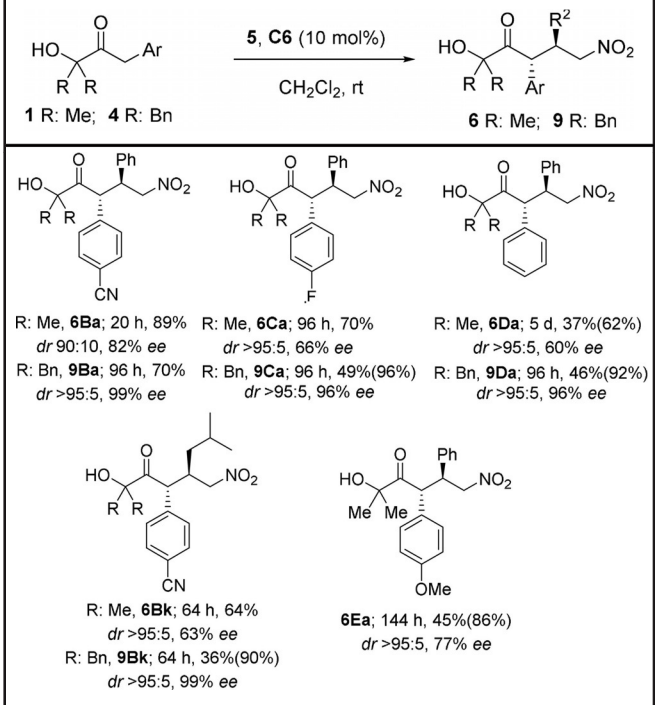
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:2:0.1 molar ratio of ketone/**5a**/catalyst); diastereomeric ratio (d.r.) > 95:5 in all entries was determined by ^{1}H NMR spectroscopy (300 MHz) analysis of the crude sample. [b] Yields of products isolated after chromatography. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [d] The reaction was performed at −20 °C. [e] Conversion; yield not determined.

Table 2. Scope of the reaction of **4A** with nitroalkenes **5** catalyzed by **C6**.[a]

Entry	Nitroalkene	R^2	Product	*t* [h]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**5b**		**9Ab**	16	86	>95:5	99
2	**5c**		**9Ac**	16	81	>95:5	99
3	**5d**		**9Ad**	16	77	>95:5	99
4	**5e**		**9Ae**	16	93	>95:5	99
5	**5f**		**9Af**	16	92	>95:5	99
6	**5g**		**9Ag**	16	80	>95:5	99
7	**5h**		**9Ah**	16	85	>95:5	99
8	**5i**	$CH_3(CH_2)_4$	**9Ai**	72	75	>95:5	96
9	**5j**	$CH_3(CH_2)_2$	**9Aj**	44	76	>95:5	99
10	**5k**	$(CH_3)_2CH$	**9Ak**	120	45 (75)[e]	90:10	97

[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; molar ratio of **4A**/**5**/catalyst, for R^2 = aromatic, 1:2:0.1; for R^2 = aliphatic, 1:3:0.2) at RT, unless otherwise stated. [b] Yields of products isolated after chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis by using a chiral stationary phase. [e] Yield in parenthesis based on recovered starting material.

Table 3. Scope of the reaction regarding the α-hydroxy ketone.[a]



[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:3:0.1 or 1:1.2:0.1 molar ratios of ketone/**5a**/catalyst). Yields in parentheses are based on recovered starting material.

more challenging alkyl-substituted nitroalkenes, such as **5i** and **5j**, were also competent reaction partners that afforded the corresponding adducts **9Ai** and **9Aj** in 75 and 76% yield, diastereomeric ratios of ≥95:5, and *ee* values of 96 and 99%, respectively. In these instances, longer times were required for useful conversion. With the more demanding isopropyl nitroalkene **5k**, reactivity was an issue, but selectivity remained still high (90:10 d.r., 97% *ee* for the major diastereomer).

Next the reaction scope with respect to the α′-aryl substituent of the α-hydroxy ketone was studied. As shown by the data in Table 3, the reaction tolerates electron-poor, neutral, or electron-rich aryl substituents. However, in the last case, the reaction proceeded very slowly. For instance, the reaction of **5a** and **4B**, with a *p*-cyanophenyl group at Cα′, proceeded to completion in about 96 h to afford adduct **9Ba** in good yield as essentially a single isomer. Reactions of the *p*-fluorophenyl and phenyl analogues **4C** and **4D**, respectively, were incomplete after 96 h (isolated in yields of 49 and 46%, respectively), although selectivity remained high in both cases (>95:5 d.r.; 96% *ee*). The reaction of **4E** was impractical; however, the *gem*-dimethyl analogue **1E** could react with **5a** to afford adduct **6Ea** as a single diastereomer in 45% yield (86% based on recovered starting material) and 77% *ee*. These experiments show again the influence of the ketol R group; sterically more demanding α,α-dibenzyl ketols **4** require longer reaction times than those of α,α-dimethyl congeners **1**, but lead to considerably better diastereo- (d.r. ≥95:5) and enantioselectivities (96–99% *ee*). Importantly, high selectivity was also attained in the reaction of **4B** with **5k** to afford adduct **9Bk** as a single diastereomer and 99% *ee*. The absolute configuration of adduct **9Ab** was established by single-crystal X-ray structure analysis,[18] and those of the remaining adducts by analogy and by assuming a uniform reaction mechanism.

Based on the most accepted transition-state models for conjugate addition reactions catalyzed by these types of (thio)urea bifunctional catalysts, in which protonated quinuclidine activates the electrophile,[19] stereomodel **V** may be invoked to account for the observed reaction outcome (Figure 1a). The active role played by the free hydroxy group of template **1A** is apparent if reaction conversions are compared with those obtained with derivative **1A′**. As shown by control experiments in Figure 1b, although the **C6**-catalyzed reaction of **5a** with **1A** to produce **6Aa** is essentially over after 10 h at room temperature, the reaction involving **1A′** progresses much more slowly, with around 50% conversion reached after 20 h. The same trend was observed for the reaction of the O-TMS derivative of **1B**.[20]

Additional control experiments with the related (thio)esters and aldehydes (Scheme 4) as the donor component further demonstrated the importance of the α-hydroxy ketone template in this development. For example, methyl *p*-nitrophenylacetate did not react at all with **5a** in dichloromethane in the presence of catalyst **C6** (10 mol%).[21] More reactive thioester **10** barely reacted under the same conditions to reach a maximum conversion of 55% after 96 h,[8c,d] which gives rise to

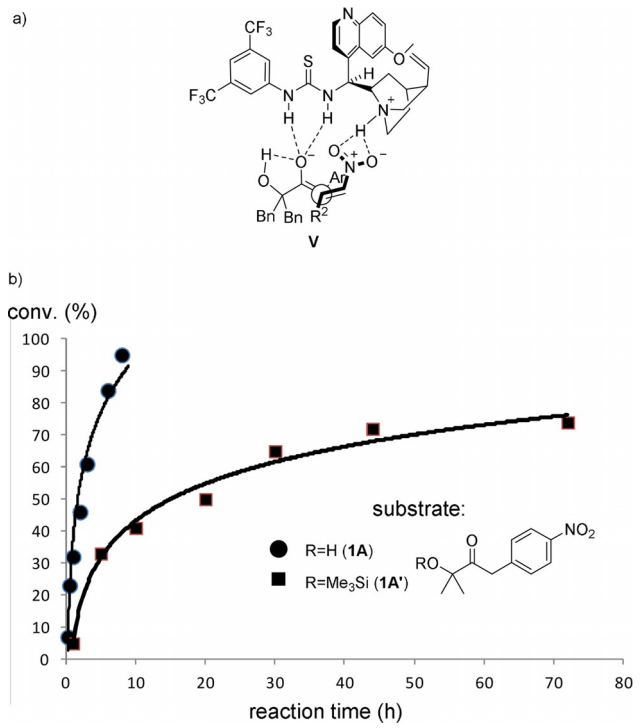
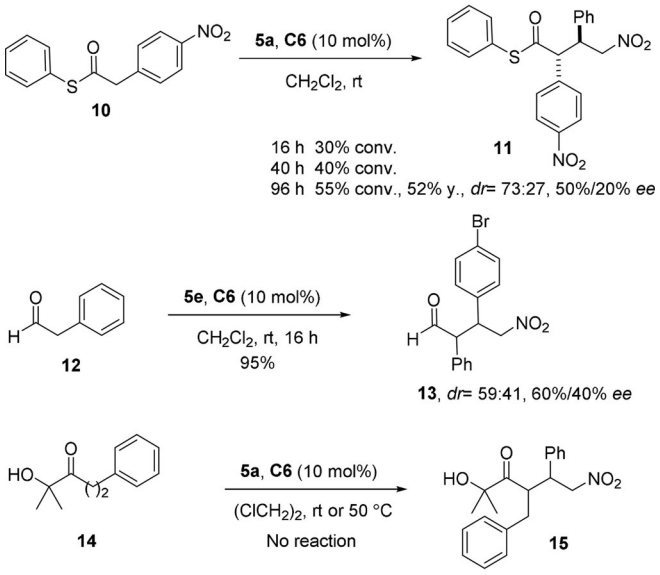


Figure 1. a) Structure of the proposed stereomodel. b) Progress of the **C6**-catalyzed reaction of **5a** with **1A** and trimethylsilyl (TMS) derivative **1A′**.



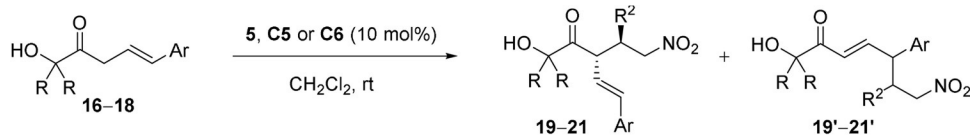
Scheme 4. Unsuitable ketone and thioester substrates.

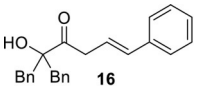
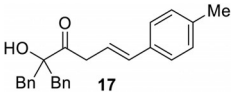
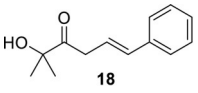
product **11** with poor selectivity. As expected, reactivity was not a problem with phenylacetaldehyde (**12**), but the resulting aldehyde **13** was configurationally unstable and an almost equimolar mixture of epimers was isolated. One limitation of the method is the unsuitability of α-hydroxy ketones with decreasing α′-carbon acidity, such as **14**, which remains intact after 24 h under the above catalytic conditions (or even at 50 °C). In this respect, we recently found that related β′,γ′-unsaturated ketols, which upon enolization would form a vinylogous enolate, were competent substrates for this reaction with nitroolefins.[22] Additionally, thus-generated vinylogous enolates proved to react with high regio- (α vs. γ) and stereoselectivity. At this stage, we set out to complement these previous studies with additional entries and establish which types of ketol substructures were optimum with respect to both reactivity and selectivity. As shown by the results in Table 4, the catalyzed reaction of ketones **16** and **17** with **5a** proceeded virtually to completion within a few hours at room temperature to afford the corresponding Michael adducts **19** and **20**, although accompanied by variable amounts of the corresponding γ-regioisomers **19′** and **20′** (Table 4, entries 1–4). For these reactions, catalyst **C5** was more active than **C6**, although both provided high levels of diastereo- and enantiocontrol (essentially a single stereoisomer was isolated). However, neither catalyst was able to control the α- versus γ-regioselectivity properly (product ratios from 41:59 to 74:26, at best). Experiments with the parent *gem*-dimethyl ketone **18** instead demonstrated once again that this regioselectivity issue could be properly addressed. With this ketol substrate, and catalyst **C6**, mixtures of the corresponding α- and γ-adducts **21**/**21′** were obtained again (Table 4, entries 6, 8, 10, and 12). However, with catalyst **C5**, the corresponding adduct **21** could be obtained exclusively. For instance, for the reaction of **18** with **5a**, product **21a** was isolated in 85% yield, as essentially a single diastereomer and with 97% *ee* (Table 4, entry 5). This pattern was reproduced with **5b**, **5c**, **5f**, and **5i**, giving rise to the corresponding adducts **21** as clean products, which were isolated in high yields, with essentially perfect diastereoselectivity and 94–98% *ee* (Table 4, entries 7, 9, 11, and 13).

Adducts obtained through the above catalytic reactions may serve as versatile platforms in synthesis. For instance, the oxidative cleavage of the ketol moiety in **9Aa** by treatment with H_5IO_6 afforded the arylacetic acid **22** in 89% yield (Scheme 5), along with dibenzyl ketone as the only organic side product, which could be recovered and reused.[23] Compound **22** was then transformed into **11** under standard conditions. Thus, the lack of reactivity and selectivity associated with simple arylacetic esters and thioesters may be circumvented by using α-hydroxy ketones as donor ester equivalents. Alternatively, the reduction of the ketol carbonyl in **9Aa** with borane and subsequent treatment with H_5IO_6, as above, gave aldehyde **24** in 67% yield over two steps. It should be noted that in no case was epimerization at the α-carbon observed; an important feature of the present approach, upon considering the high tendency of these compounds (i.e., arylacetic aldehydes, see above) towards base-promoted isomerization. On the other hand, the C–NO_2 group in **9Aa** could be oxidized under Mioskowski conditions,[24] without affecting the ketol moiety, to deliver carboxylic acid **23**. The first oxidation run was incomplete (36%), but, by applying further oxidation runs to the recovered unoxidized material, product **23** was isolated in a combined yield of 71%.

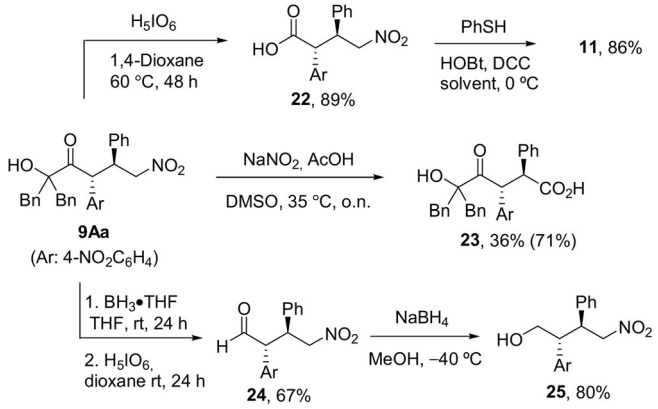
One particular advantage of the high regio- and stereoselectivity observed in the reactions with β′,γ′-unsaturated ketols is that a simple hydrogenation of the C=C bond in the resulting

Table 4. Alkenyl ketols **16–18** as ester donor equivalents.[a]

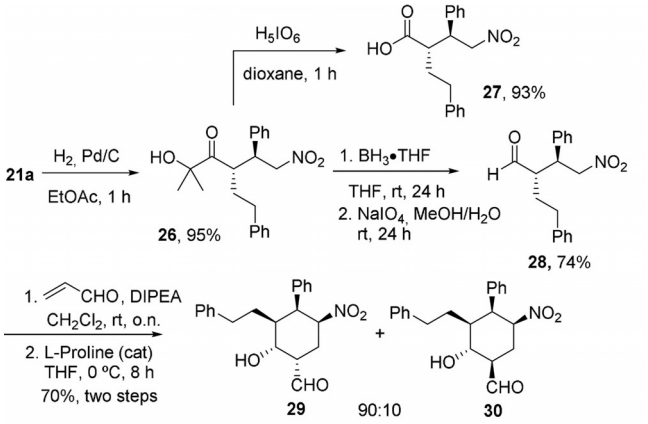


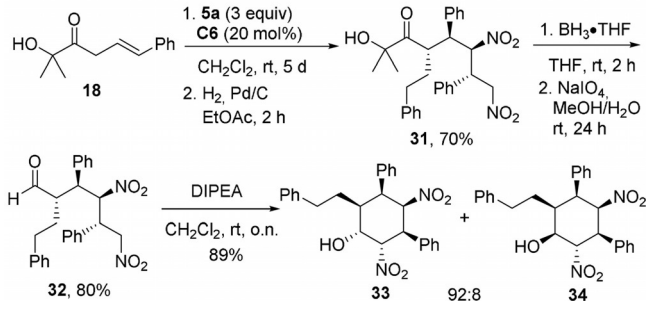
Entry[b]	Ketol substrate	Nitroalkene R^2	Product	Cat.	T [°C]	t [h]	Ratio α/γ	Yield [%][c]	d.r.[d]	*ee* [%][e]
1		**5a**, Ph	**19/19′**	**C5**	20	2	72:28	63	>95:5/>95:5	>98/84
2				**C6**	20	2	41:59	35	>95:5/>95:5	>98/94
3				**C5**	20	2	74:26	70	>95:5/>95:5	98/>98
4		**5a**, Ph	**20/20′**	**C6**	20	16	44:56	38	>95:5/>95:5	98/>98
5		**5a**, Ph	**21a/21′a**	**C5**	20	2.5	>98:2	85	>95:5/–	97/–
6				**C6**	−10	20	86:14	68	>95:5/>95:5	95/ND
7		**5b**, 4-ClC_6H_4	**21b/21′b**	**C5**	20	2.5	>98:2	82	>95:5/–	95/–
8				**C6**	−10	14	68:32	60	>95:5/>95:5	83/66
9		**5c**, 3-ClC_6H_4	**21c/21′c**	**C5**	20	3	>98:2	91	>95:5/–	96/–
10				**C6**	−20	16	61:39	57	>95:5/>95:5	81/71
11		**5f**, 4-$MeOC_6H_4$	**21f/21′f**	**C5**	20	2.5	>98:2	75	>95:5/–	94/–
12				**C6**	−20	16	96:4	77	>95:5/–	87/ND
13		**5i**, $CH_3(CH_2)_4$	**21i/21′i**	**C5**	20	14	>98:2	94	>95:5/–	98/–

[a] Reactions conducted on **16–18** (0.2 mmol) in CH_2Cl_2 (0.3 mL) at RT, unless otherwise stated. Molar ratios of **16–18**/**5**/catalyst: 1.5:1:0.1 (for **C6**) or 1:1.1:0.05 (for **C5**). [b] For entries 5, 7, and 11, see ref. [22]. [c] Yields of isomers **19–21** isolated after chromatography. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis by using a chiral stationary phase. ND: not determined.



Scheme 5. Scission of ketol and nitro moieties of the adducts. HOBt = 1-hydroxybenzotriazole, DCC = *N*,*N*′-dicyclohexylcarbodiimide.





Scheme 6. Further possibilities for the elaboration of adducts. DIPEA = *N*,*N*-diisopropylethylamine.

adducts (e.g., **21a**; Scheme 6) gives access to compounds such as **26**, which are otherwise difficult to obtain (formally derived from less acidic ketones, see above). Then, ketol scission, as above, would provide the corresponding acid **27** or aldehyde **28** in high yields. With aldehyde **28** in hand, a suitable Michael/aldol domino process,[25,26] involving acrolein as a reaction partner, allowed the fully enantiocontrolled construction of densely substituted cyclohexanecarbaldehydes **29** and **30** in 70% combined yield and a 90:10 ratio.[27] This ratio was temperature-dependent and, if the reaction mixture was warmed to room temperature and stirred for 2 h, the ratio of isomers **29** and **30** obtained was 65:35. This observation might suggest that the intramolecular aldol process becomes increasingly reversible at temperatures above 0 °C or, alternatively, proline is able to epimerize **29**, unless temperature is kept low. Similarly, hydrogenation of the adduct resulting from a **C6**-catalyzed

double Michael reaction of **18** gave rise to branched aliphatic ketone **31**, which was transformed into aldehyde **32** in 80% yield over two steps. Final treatment of **32** with DIPEA smoothly afforded the corresponding hexasubstituted cyclohexanes **33** and **34** in a ratio of 92:8 and combined yield of 89%.[26g] The configurations of cyclic products **29/30** and **33/34** were preliminary established through the correlation of the H–H coupling constants in their ^{1}H NMR spectra, and then confirmed by single-crystal X-ray analysis of **33**.[20]

A distinguishing feature of the two reaction sequences in Scheme 6 is that both aldehydes **28** and **32** have a relative α/β *anti* configuration. Accordingly, this approach complements previous syntheses of related cyclohexane systems based on enamine-mediated domino processes,[26g,27] which proceeded via the corresponding aldehydes with relative α/β *syn* configuration instead.

Conclusion

Enolizable α-hydroxy α,α-disubstituted ketones were introduced as efficient ester and aldehyde donor equivalents in asymmetric catalysis. The reactivity and stereoselectivity profile of these templates could be easily modulated by varying the size of the *gem*-R substituents at Cα; the α,α-dibenzyl-substituted congeners provided the best enantiocontrol with the selected reaction and catalysts. Specifically, the conjugate addition reaction to nitroalkenes, including challenging β-alkyl-substituted nitroalkenes, proceeded smoothly under bifunctional Brønsted base catalysis to afford adducts with very high diastereo- and enantioselectivity (d.r. ≥95:5, up to 99% *ee*). Elaboration of the resulting adducts through smooth oxidative ketol cleavage gave access to the corresponding enantioenriched α-branched carboxylic acid and aldehyde products, including aryl acetics,[28] and dibenzylacetone byproduct, which could be separated and recycled. Additional reaction sequences were also applicable to construct densely functionalized carbocycles with complementary relative configuration, compared with previous methods based on enamine catalysis. Extension of this catalytic methodology to other π electrophiles is currently under investigation.[29]

Experimental Section

Catalytic conjugate addition of α-hydroxy ketones to nitroalkenes

Method A: Benzylic ketols: Catalyst **C1**–**C6** (10 mol%) was added to a mixture of the corresponding benzylic ketol **1**–**4** (1 equiv, 0.1 mmol) and nitroalkene **5** (2.0 equiv, 0.2 mmol for aromatic nitroalkenes; 3.0 equiv, 0.3 mmol for aliphatic nitroalkenes), in dichloromethane (0.3 mL) at room temperature (or cooled to the corresponding temperature). The resulting suspension was stirred at the same temperature, until consumption of the α-hydroxy ketone, as monitored by ^{1}H NMR spectroscopy. The mixture was quenched with 2 M HCl (1 mL) and extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent hexane/AcOEt 95:5 to 90:10).

Method B: Allylic ketols: Catalyst **C5** (6 mg, 0.01 mol, 5 mol%) was added at room temperature or −20 °C to a solution of the corresponding allylic ketol **16**–**18** (0.2 mmol, 1 equiv) and nitroalkene **5** (0.22 mmol, 1.1 equiv) in dichloromethane (0.4 mL), and the resulting mixture was stirred at that temperature until completion of the reaction (2–20 h, as determined by TLC). Then the reaction mixture was submitted to flash column chromatography (eluent hexane/ethyl acetate 90:10). The same procedure was employed for the reactions involving catalyst **C6**, but with a molar ratio of ketone/**5**/catalyst of 1.5:1:0.1.

Representative examples

Compound 9Aa: Compound **9Aa** was prepared from **4A** (37.5 mg, 0.1 mmol) and **5a** (29.8 mg, 0.2 mmol), according to the general procedure, with catalyst **C6**. White solid; yield: 51.9 mg, 0.099 mmol, 99%; $[\alpha]_D^{25} = -97.0^\circ$ ($c = 0.54$, 99% *ee*, CH_2Cl_2); m.p. 187–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 8.7$ Hz, 2H), 7.42–7.24 (m, 8H), 7.16 (d, $J = 9.3$ Hz, 2H), 7.00–6.88 (m, 3H), 6.86–6.75 (m, 2H), 6.58 (d, $J = 7.1$ Hz, 2H), 5.00 (d, $J = 11.0$ Hz, 1H), 4.43 (dd, $J = 12.0$, 10.3 Hz, 1H), 4.28 (dd, $J = 11.0$, 4.0 Hz, 1H), 4.17 (dd, $J = 12.1$, 4.0 Hz, 1H), 3.01 (d, $J = 13.5$ Hz, 1H), 2.27 (dd, $J = 28.1$, 13.6 Hz, 2H), 1.95 (d, $J = 13.7$ Hz, 1H), 1.75 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.9$, 147.2, 139.9, 137.4, 134.6, 134.2, 130.8, 130.1, 129.8, 129.1, 128.8, 128.5, 128.5, 128.1, 127.3, 126.5, 124.0, 83.4, 78.1, 55.5, 46.2, 42.8, 42.4 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{31}H_{27}N_2O_6$ $[M-H]^-$: 523.1869; found: 523.1880; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL min^{-1}, retention times: 16.7 (major) and 22.7 min (minor)).

Compound 21a: Compound **21a** was prepared from **18** (40.8 mg, 0.2 mmol) and **5a** (32.8 mg, 0.22 mmol) with **C5**. White solid; yield: 60 mg, 85%; $[\alpha]_D^{25} = -60.3^\circ$ ($c = 1$, 97% *ee*, CH_2Cl_2); m.p. 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.24 (m, 10H), 6.73 (d, $J = 15.9$ Hz, 1H), 6.10 (dd, $J = 15.9$, 9.5 Hz, 1H), 4.95–4.69 (m, 2H), 4.37–4.11 (m, 2H), 1.08 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.6$, 128.9, 128.8, 128.6, 128.3, 126.5, 124.3, 78.0, 54.5, 45.7, 26.1, 25.9 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 354.1705; found: 354.1707; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90:10, flow rate = 1.0 mL min^{-1}, retention times: 17.6 (minor) and 27.1 min (major)).

Hydrogenation of 21a to obtain 26: Pd/C (10% w/w) was added (21 mg) to a solution of **21a** (206.6 mg, 0.58 mmol) in dry EtOAc (20 mL). Air was evacuated by applying vacuum and H_2 was introduced; this process was repeated two additional times. The reaction mixture was stirred under H_2 atmosphere at room temperature for 1 h. Then, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford **26** as a white solid (196 mg, 95%). $[\alpha]_D^{25} = +5.53^\circ$ ($c = 0.32$, 94% *ee*, CH_2Cl_2); m.p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.19 (m, 8H), 7.14–7.06 (m, 2H), 4.90–4.76 (m, 2H), 4.09–4.01 (m, 1H), 3.70–3.64 (m, 1H), 2.64–2.39 (m, 2H), 2.12–1.97 (m, 1H), 1.96–1.81 (m, 1H), 1.30 (s, 1H), 1.25 (s, 3H), 1.18 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 215.3$, 140.6, 138.0, 129.0, 128.6, 128.1, 128.0, 128.0, 126.3, 75.9, 48.7, 44.2, 33.2, 29.8, 26.6 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{25}NO_4Na$ $[M+Na]^+$: 378.1681; found: 378.1686.

Scission of 26 to give 28: BH_3·THF complex (1 M, 1.5 mL, 1.5 mmol) was added to a solution of **26** (178 mg, 0.5 mmol) in dry THF (1.5 mL) at 0 °C, and the resulting solution was stirred at room temperature for 24 h. Then MeOH (2.5 mL) was added and the re-

sulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue was submitted to oxidation as follows. A suspension of $NaIO_4$ (535 mg, 2.5 mmol) in water (1.25 mL) was added to a solution of the obtained diol (0.5 mmol) in methanol (2.5 mL). The mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3×6 mL) and CH_2Cl_2 (2×6 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1) to afford **28** as a colorless oil (110 mg, 74%). ^{1}H NMR (400 MHz, ($CDCl_3$): δ = 9.54 (d, J = 2.8 Hz, 1H), 7.36–7.14 (m, 10H), 4.80 (dd, J = 6.8, 13.2 Hz, 1H), 4.76 (dd, J = 8.4, 13.2 Hz, 1H), 3.85 (dt, J = 6.8, 8.4 Hz, 1H), 2.75–2.60 (m, 1H), 2.64–2.39 (m, 3H), 2.06 (m, 1H), 1.90 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 140.3, 136.0, 135.9, 129.2, 128.7, 128.3, 128.2, 126.5, 77.7, 52.7, 44.5, 33.2, 29.2 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{18}H_{19}NO_3Na$ $[M+Na]^+$: 320.1263; found: 320.1272.

Michael-aldol domino reaction involving 28 and acrolein to give cycloadducts 29 and 30: DIPEA (10.2 μL, 0.06 mmol) was added to a solution of **28** (59.4 mg, 0.2 mmol) and acrolein (26.6 μL, 0.4 mmol) in CH_2Cl_2 (0.8 mL), and the solution was stirred overnight at room temperature. CH_2Cl_2 (5 mL) was added and the mixture was washed with 1 M HCl (5 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent was evaporated to afford the corresponding dialdehyde. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 9.61 (d, J = 2.4 Hz, 1H), 7.40–7.13 (m, 10H), 5.28 (m, 1H), 3.52 (dd, J = 5.6, 10.4 Hz, 1H), 2.65 (m, 2H), 2.53 (m, 1H), 2.48 (t, J = 6.8 Hz, 2H), 1.94 (m, 1H), 1.90 (t, J = 6.8 Hz, 2H), 1.74 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 199.3, 140.5, 134.4, 129.3, 129.2, 128.6, 128.5, 128.4, 126.4, 88.8, 51.6, 51.0, 39.5, 33.3, 29.6, 24.4 ppm.

L-Proline (2.1 mg, 0.02 mmol) was added to a solution of the above-obtained dialdehyde in THF (0.4 mL) at 0 °C, and the mixture was stirred at the same temperature for 8 h. CH_2Cl_2 (5 mL) was added and the mixture was washed with water (2×5 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent was evaporated to afford a mixture of epimers **29** and **30** in a ratio of 90:10. Combined yield: 49.5 mg (70%, two steps). Each isomer was separated by quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 1:1) and stored at −30 °C. Major isomer (**29**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1H), 7.35–6.98 (m, 10H), 4.91 (dt, J = 6.0, 11.6 Hz, 1H), 4.50 (dd, J = 6.0, 10.8 Hz, 1H), 4.00 (t, J = 5.6 Hz, 1H), 3.36 (dt, J = 4.4, 5.6 Hz, 1H), 2.67 (m, 1H), 2.60 (m, 2H), 2.50 (m, 1H), 2.15–2.00 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.5, 141.4, 134.3, 130.4, 128.8, 128.6, 128.4, 128.2, 126.0, 82.8, 70.1, 50.2, 47.7, 44.2, 33.0, 30.5, 23.1 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$: 376.1525; found: 376.1527. Minor isomer (**30**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.92 (s, 1H), 7.36–7.00 (m, 10H), 4.83 (ddd, J = 4.4, 5.6, 12.0 Hz, 1H), 4.33 (t, J = 10.4 Hz, 1H), 4.06 (t, J = 5.6 Hz, 1H), 2.70–2.66 (m, 1H), 2.57–2.38 (m, 4H), 2.17 (m, 1H), 2.00 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 141.4, 133.6, 130.6, 128.9, 128.4, 128.3, 128.2, 126.0, 85.6, 68.8, 54.2, 47.9, 45.5, 32.8, 30.2, 23.0 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$: 376.1525; found: 376.1527.

Synthesis of 31 (sequential double Michael/reduction of 18): catalyst **C6** (23.8 mg, 0.04 mmol, 20 mol%) was added at room temperature to a solution of **18** (40.9 mg, 0.2 mmol, 1 equiv) and **5a** (89.5 mg, 0.6 mmol, 3 equiv) in dichloromethane (0.4 mL), and the resulting mixture was stirred until completion of the reaction (5 days). Then the reaction mixture was submitted to flash column chromatography (hexane/ethyl acetate 90:10). The residue was dissolved in dry EtOAc (40 mL) and 10% Pd/C was added (10.1 mg). Air was evacuated under vacuum and H_2 was introduced (this process was carried out three times). The reaction mixture was stirred under H_2 atmosphere at room temperature for 2 h. Then, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford **31** as an oil (70.6 mg, 70%). $[\alpha]_D^{24} = +13.9^\circ$ (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.05 (m, 15H), 5.49 (dd, J = 11.2, 3.6 Hz, 1H), 5.02 (dd, J = 14.0, 11.2 Hz, 1H), 4.88 (dd, J = 14.0, 3.6 Hz, 1H), 3.93 (dd, J = 11.2, 5.2 Hz, 1H), 3.84 (dt, J = 10.8, 3.4 Hz, 1H), 3.71–3.67 (m, 1H), 3.00 (br s, 1H), 2.56–2.42 (m, 2H), 2.23–2.12 (m, 1H), 1.87–1.75 (m, 1H), 1.22 (s, 3H), 1.21 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.8, 141.0, 136.3, 135.1, 129.5, 129.4, 128.9, 128.7, 128.5, 128.4, 127.2, 126.2, 93.0, 73.5, 48.9, 47.8, 43.9, 33.3, 30.4, 28.1, 27.1 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{29}H_{36}N_3O_6$ $[M+NH_4]^+$: 522.2604; found: 522.2611.

Sequential reduction/oxidative cleavage of 31 to give 32: BH_3·THF complex (1 M, 1.5 mL, 1.5 mmol) was added to a solution of **31** (252 mg, 0.5 mmol) in dry THF (1.5 mL) at 0 °C, and the resulting solution was stirred at room temperature for 24 h. Then MeOH (2.5 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the resulting diol product was subjected to oxidative scission by treatment with $NaIO_4$. A suspension of $NaIO_4$ (535 mg, 2.5 mmol) in water (1.25 mL) was added to a solution of the diol (0.5 mmol) in methanol (2.5 mL). The mixture was stirred overnight at room temperature. Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with Et_2O (3×6 mL) and CH_2Cl_2 (2×6 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1) to afford **32** as a colorless oil (179 mg, 80%). $[\alpha]_D^{23} = +16.4^\circ$ (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (dd, J = 2.0, 0.8 Hz, 1H), 7.49–6.98 (m, 15H), 5.62 (dd, J = 11.6, 3.6 Hz, 1H), 5.02 (dd, J = 14.0, 11.0 Hz, 1H), 4.83 (dd, J = 4.2 Hz, 1H), 2.74–2.60 (m, 2H), 2.47–2.42 (m, 1H), 2.01–1.92 (m, 1H), 1.75–1.66 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 140.2, 134.9, 133.3, 129.9, 129.5, 129.3, 129.2, 129.0, 128.7, 128.4, 127.1, 126.5, 92.9, 73.6, 51.2, 49.3, 43.5, 33.5, 29.7 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{26}H_{26}N_2NaO_5$ $[M+Na]^+$: 469.1739; found: 469.1730.

Conversion of 32 into 33 and 34 (intramolecular Henry reaction of 32): DIPEA (3.5 μL, 0.02 mmol) was added to a solution of **32** (44.6 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 20 h. CH_2Cl_2 (5 mL) was added and the mixture was washed with 1 M HCl (5 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent was evaporated to afford a mixture of epimeric **33** and **34** in a ratio of 92:8. Major isomer **33** was separated as a white solid by quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1). Yield: 37 mg (82%); m.p. 191–193 °C; $[\alpha]_D^{25} = -38.3^\circ$ (c = 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.05 (m, 15H), 6.17 (dd, J = 12.6, 2.2 Hz, 1H), 5.26 (t, J = 5.2 Hz, 1H), 4.74 (t, J = 2.4 Hz, 1H), 4.42 (dd, J = 12.4, 5.2 Hz, 1H), 4.03 (t, J = 5.2 Hz, 1H), 2.81–2.74 (m, 1H), 2.56–2.48 (m, 1H), 2.47–2.42 (m, 1H), 2.22–2.09 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 136.3, 133.8, 129.3, 129.0, 128.8, 128.5, 128.4, 128.3, 127.9, 127.2, 126.2, 91.6, 83.5, 71.1, 45.4, 42.4, 42.1, 35.4, 27.6 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{26}H_{30}N_3O_5$ $[M+NH_4]^+$: 464.2185; found: 464.2190.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: addition · asymmetric catalysis · esters · organocatalysis · synthesis design

[1] a) D. A. Evans, G. Helmchen, M. Rüping, "*Chiral Auxiliaries in Asymmetric Synthesis*" in *Asymmetric Synthesis – The Essentials* (Eds.: M. Christmann, S. Brase), Wiley-VCH, Weinheim, **2007**, pp. 3 – 9; b) J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109 – 9118; *Angew. Chem.* **2013**, *125*, 9280 – 9289.

[2] a) M. Iwata, R. Yazaki, Y. Suzuki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 18244 – 18245; b) Y. Suzuki, R. Yazaki, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 5026 – 5029; *Angew. Chem.* **2009**, *121*, 5126 – 5129; c) M. Iwata, R. Yazaki, M. Kumagai, M. Shibasaki, *Tetrahedron: Asymmetry* **2010**, *21*, 1688 – 1694; d) Y. Kawato, S. Chaudhary, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2013**, *19*, 3802 – 3806; e) D. Sureshkumar, Y. Kawato, M. Iwata, N. Kumagai, M. Shibasaki, *Org. Lett.* **2012**, *14*, 3108 – 3111; f) K. Alagiri, S. Lin, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 5301 – 5303; g) N. Majumdar, N. Saito, L. Yin, N. Kumagai, M. Shibasaki, *Org. Lett.* **2015**, *17*, 3362 – 3365.

[3] H. Suzuki, I. Sato, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2015**, *137*, 4336 – 4339.

[4] a) Y. Kawato, N. Kumagai, M. Shibasaki, *Chem. Commun.* **2013**, *49*, 11227 – 11229; b) T. Deng, W. Wang, C. Cai, *Eur. J. Org. Chem.* **2014**, 7259 – 7264.

[5] D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706 – 8707.

[6] Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 7075 – 7078.

[7] For selected examples, see: a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154 – 2157; b) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim, Y. R. Chi, *Org. Lett.* **2013**, *15*, 4956 – 4959; c) C. Simal, T. Lebl, A. M. Slawin, A. D. Smith, *Angew. Chem. Int. Ed.* **2012**, *51*, 3653 – 3657; *Angew. Chem.* **2012**, *124*, 3713 – 3717; d) L. C. Morrill, T. Lebl, A. M. Z. Slawin, A. D. Smith, *Chem. Sci.* **2012**, *3*, 2088 – 2093; e) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox, A. D. Smith, *Chem. Sci.* **2013**, *4*, 4146 – 4155; f) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714 – 2720; g) S. S. M. Spoehrle, T. H. West, J. E. Taylor, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 11895 – 11902; for selected reviews, see: h) L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214 – 6226; i) P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2014**, *53*, 1485 – 1487; *Angew. Chem.* **2014**, *126*, 1509 – 1511.

[8] For acyl silanes, see: a) L. Wu, G. Li, Q. Fu, L. Yu, Z. Tang, *Org. Biomol. Chem.* **2013**, *11*, 443 – 447; for thioesters, see: b) 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; c) M. C. Kohler, J. M. Yost, M. R. Garnsey, D. M. Coltart, *Org. Lett.* **2010**, *12*, 3376 – 3379; d) J. Guang, A. J. Larson, J. C. G. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 523 – 529; for pyrazoleamides, see: e) B. Tan, G. Hernández-Torres, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2012**, *51*, 5381 – 5385; *Angew. Chem.* **2012**, *124*, 5477 – 5481; f) T.-Z. Li, X.-B. Wang, F. Sha, X.-Y. Wu, *J. Org. Chem.* **2014**, *79*, 4332 – 4339; for acyl phosphonates, see: g) 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; h) 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; for cyclic anhydrides, see: i) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett.* **2012**, *14*, 1850 – 1853; for β,γ-unsaturated (thio)esters, see: j) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648 – 2651; k) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2012**, *51*, 2382 – 2386; *Angew. Chem.* **2012**, *124*, 2432 – 2436.

[9] In a biomimetic strategy, malonic acid half-thioesters can be used as acetate equivalents (decarboxylation-driven enolate formation); for pioneering studies on metal catalysis, see: a) S. Orlandi, M. Benaglia, F. Cozzi, *Tetrahedron Lett.* **2004**, *45*, 1747 – 1749; b) D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2005**, *127*, 7284 – 7285; for a review on organocatalytic enantioselective reactions based on this strategy, see: c) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394 – 405.

[10] a) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, J. E. Sohn, *J. Am. Chem. Soc.* **1979**, *101*, 7077 – 7079; b) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, S. D. Young, *J. Org. Chem.* **1981**, *46*, 2290 – 2300; c) N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 2499 – 2506.

[11] a) S. Masamune, Sk. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557 – 558; *Angew. Chem.* **1980**, *92*, 573 – 575; b) S. Masamune, W. Choy, F. A. J. Kerdesky, B. Imperiali, *J. Am. Chem. Soc.* **1981**, *103*, 1566 – 1568; c) S. Masamune, T. Kaiho, D. S. Garvey, *J. Am. Chem. Soc.* **1982**, *104*, 5521 – 5523.

[12] For the aldol reaction, see: a) C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez, A. Linden, *Angew. Chem. Int. Ed.* **1998**, *37*, 180 – 182; *Angew. Chem.* **1998**, *110*, 190 – 192; b) C. Palomo, M. Oiarbide, J. M. Aizpurua, A. González, J. M. García, C. Landa, I. Odriozola, A. Linden, *J. Org. Chem.* **1999**, *64*, 8193 – 8200; for the Mannich reaction, see: c) C. Palomo, M. Oiarbide, M. C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden, *Angew. Chem. Int. Ed.* **2000**, *39*, 1063 – 1066; *Angew. Chem.* **2000**, *112*, 1105 – 1107; d) C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martín-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637 – 8643.

[13] For an example of a *p*-anisyl ketone acting as an ester donor equivalent, see: Q. Guo, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 508 – 511.

[14] 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.

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

[16] 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. Soós, *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.

[17] H. He, C. Qi, X. Hu, Y. Guan, H. Jiang, *Green Chem.* **2014**, *16*, 3729 – 3733; also, see the Supporting Information.

[18] CCDC 514777 (**9 Ab**) and 1588229 (**33**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre. See the Supporting Information for details.

[19] a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631 – 5639; b) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 9041 – 9044.

[20] See the Supporting Information.

[21] The reaction between methyl *p*-nitrophenylacetate and **5 a** has been reported to proceed in polar solvents, such as DMSO and DMF, in the presence of several bifunctional Brønsted base catalysts, although adducts are obtained with poor diastereoselectivity and essentially no enantiocontrol: a) S.-G. Kim, *Lett. Org. Chem.* **2012**, *9*, 572 – 576; for related reactivity, see: b) J. Do, S.-G. Kim, *Tetrahedron Lett.* **2011**, *52*, 2353 – 2355.

[22] For the α- versus γ-regioselectivity control in catalytic Michael reactions of vinylogous ketone enolates, see: I. Iriarte, O. Olaizola, S. Vera, I. Gamboa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 8860 – 8864; *Angew. Chem.* **2017**, *129*, 8986 – 8990.

[23] This is in contrast with the sole example described in ref. [13], in which oxidative cleavage of the C–C bond led to the formation of *p*-methoxyphenol as non-reusable waste.

[24] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234 – 235.

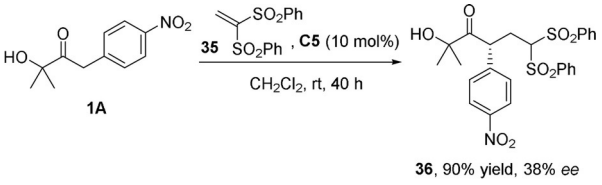
[25] For selected reviews on organocatalytic cascade or domino reactions, see: a) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832 – 1844; b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390 – 2431; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; d) H. Pellissier, *Asymmetric Domino Reactions*, RSC Publishing, Cambridge, **2013**.

[26] For nitroalkenes in the synthesis of carbocyclic compounds, see: a) A. Z. Halimehjani, I. N. N. Namboothiri, S. E. Hooshmanda, *RSC Adv.* **2014**, *4*, 31261 – 31299; for reviews on six-membered carbocycles, see: b) G. Koutoulogenis, N. Kaplaneris, C. G. Kokotos, *Beilstein J. Org. Chem.* **2016**, *12*, 462 – 495; c) X. Yang, J. Wang, P. Li, *Org. Biomol. Chem.* **2014**, *12*, 2499 – 2513; d) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909 – 1930; for examples of catalytic Michael – Michael – Henry reactions, see: e) S. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soos, *Org. Lett.* **2011**, *13*, 5416 – 5419; f) O. Baslé, W. Raimondi, M.-M. Sánchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246 – 5249; g) Z. Mao, Y. Jia, Z. Xu, R. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1401 – 1406.

[27] For pioneering work, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863; also, see: b) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu, D. J. Dixon, *Angew. Chem. Int. Ed.* **2009**, *48*, 9834 – 9838; *Angew. Chem.* **2009**, *121*, 10018 – 10022.

[28] For interest in aryl acetic acids, see: Y.-S. Feng, W. Wu, Z.-Q. Xu, Y. Li, M. Li, H.-J. Xu, *Tetrahedron* **2012**, *68*, 2113 – 2120, and references therein.

[29] In preliminary experiments (see scheme below), we observed that vinyl sulfones **35** were also suitable acceptor reagents for this reaction; thus opening up new opportunities from a synthetic point of view. However, to date, we have been unable to achieve useful levels of enantioselectivity with these acceptors.



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Asymmetric Catalysis

Enantioselective Addition of Alkynyl Ketones to Nitroolefins Assisted by Brønsted Base/H-Bonding Catalysis

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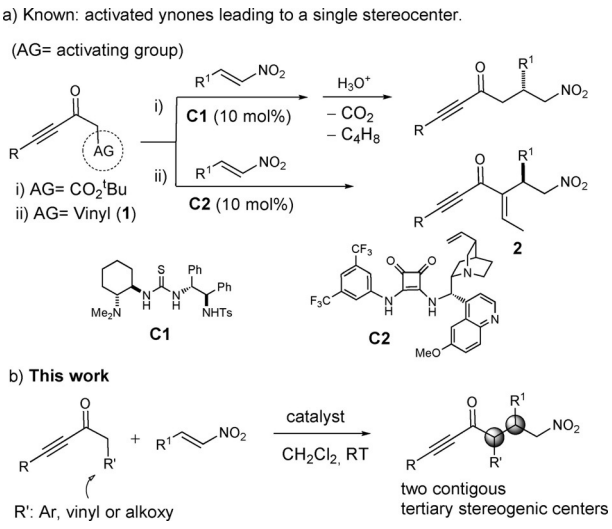
Abstract: Various sets of enolizable alkynyl ketones (including methyl ynones with α-aryl, α-alkenyl, and α-alkoxy groups) were able to react smoothly with nitroolefins with the assistance of bifunctional Brønsted base/H-bond catalysts to provide adducts with two consecutive tertiary stereocenters in 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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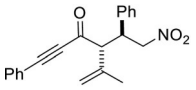
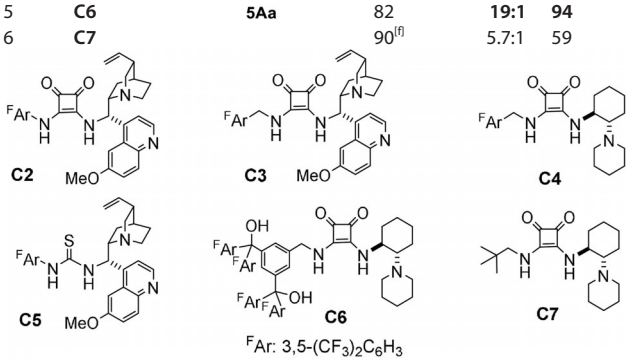
During recent studies on the catalyst-controlled reactivity of transiently generated vinylogous ketone enolates,[11] we have found that alkynyl allyl ketones are a suitable subset of allyl ketones for their reaction with nitroolefins in the presence of bifunctional Brønsted base/H-bond catalysts like **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

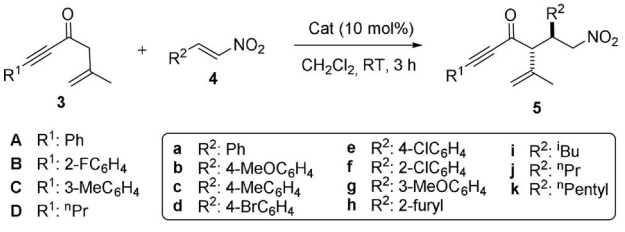


[a] Reactions performed on a 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3A**/**4a**/cat 2:1:0.1. [b] Combined yield of diastereomers after chromatography. [c] Determined by chiral HPLC after filtration through a short path of SiO_2. [d] *ee* of major diastereomer determined by chiral HPLC. [e] 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

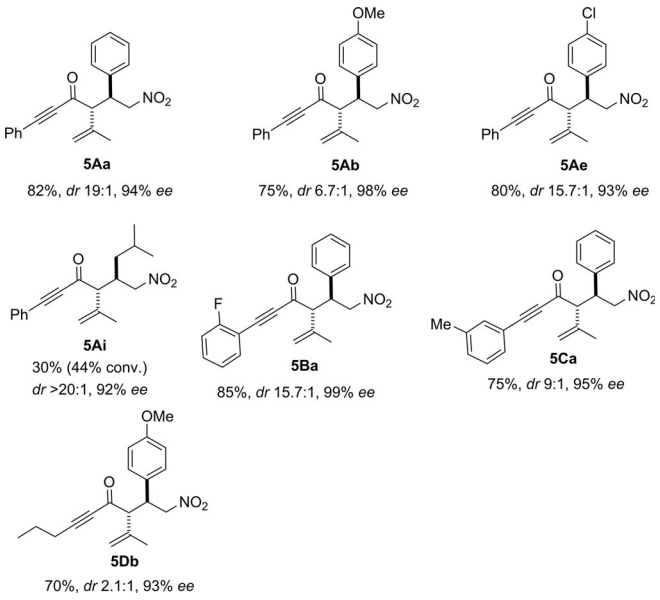
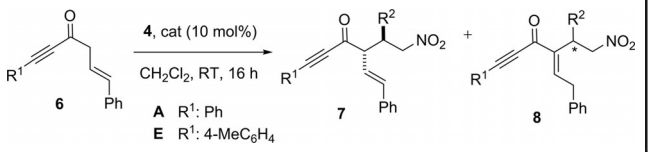


Figure 1. C6-catalyzed conjugate addition of alkenyl ynones **3** to nitroolefins **4**. Reactions performed on a 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3**/**4**/catalyst 2:1:0.1. Variable amounts of isomerized starting material were observed in most entries; yield of major diastereomer after 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]

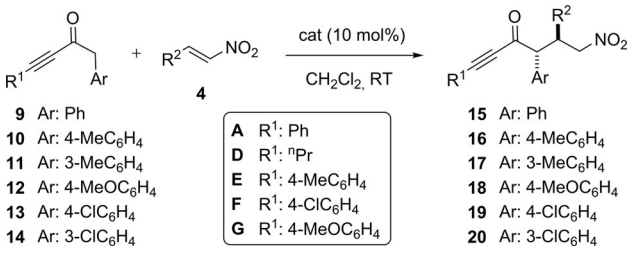


Entry	R^1	R^2	Catalyst	Ratio[b] **7**/**8**	Yield of **7** [%][c]	*dr*[b]	*ee* [%][d]
1	Ph	Ph	**C4**	66:34	38	1.3:1	88/90
2	Ph	Ph	**C6**	>95:5	56	1:1	94/>98
3	Ph	4-MeC_6H_4	**C4**	83:17	47	1.2:1	91/89
4	Ph	4-MeC_6H_4	**C6**	>95:5	62	1.4:1	95/85
5	Ph	2-ClC_6H_4	**C4**	81:19	46	1.2:1	96/93
6	Ph	2-ClC_6H_4	**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**

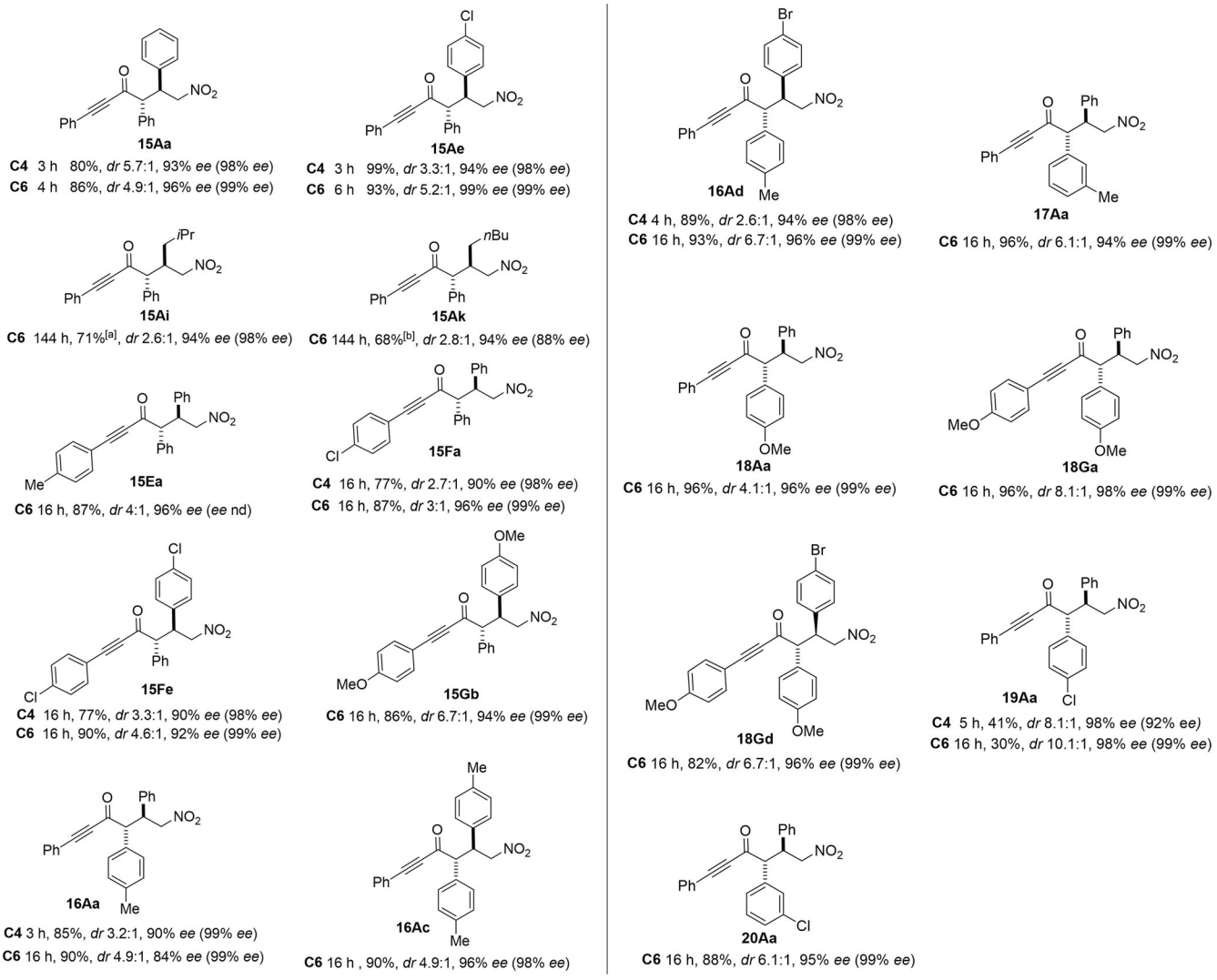


Figure 2. Scope of the catalytic, enantioselective addition of alkynyl ketones **9**–**14** to nitroolefins **4**. Reactions performed on a 0.1 mmol scale in 0.3 mL CH_2Cl_2; molar ratio of **9**–**14**/**4**/cat 1:1.2:0.1. Combined yield of diastereomers after chromatography; *dr* and *ee* determined 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.

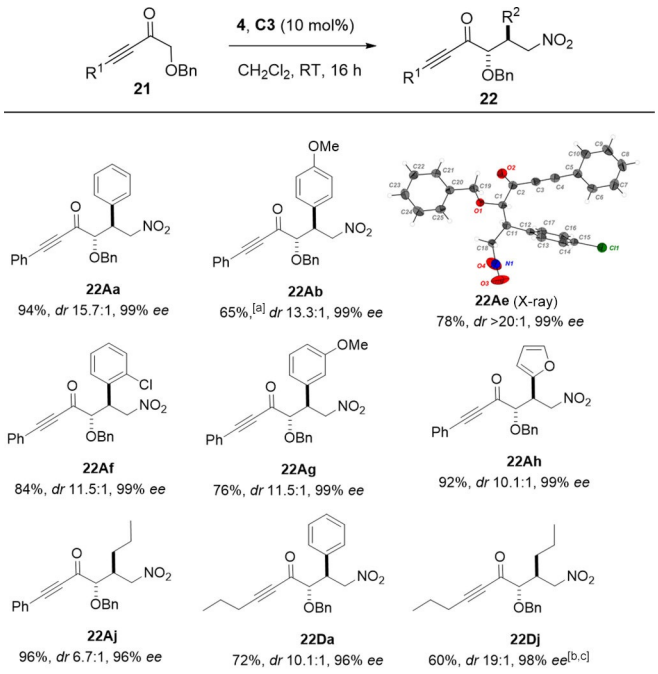
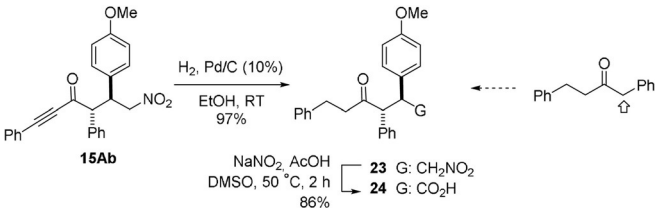


Figure 3. Catalytic, enantioselective reaction of benzyloxy ynones **21** with nitroolefins **4**. Reactions performed on 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **21**/**4**/catalyst 1:2:0.1. Yields of isolated product after chromatography; *ee* determined by chiral HPLC before chromatography. [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

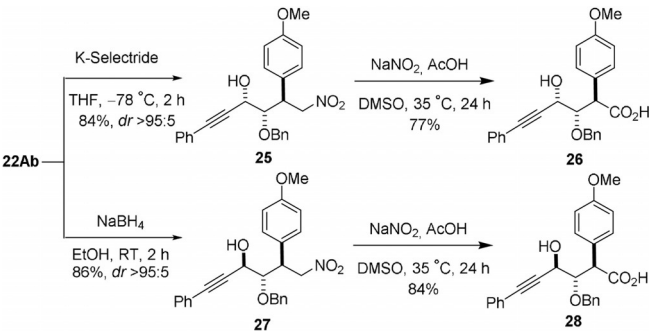
An interesting aspect of the above catalytic reactions is that adducts can be transformed into polyfunctionalized structures with two or more contiguous tertiary stereocenters by using simple chemical protocols. For instance, reduction of the alkynyl moiety in adducts provides dissymmetric alkyl alkyl 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.



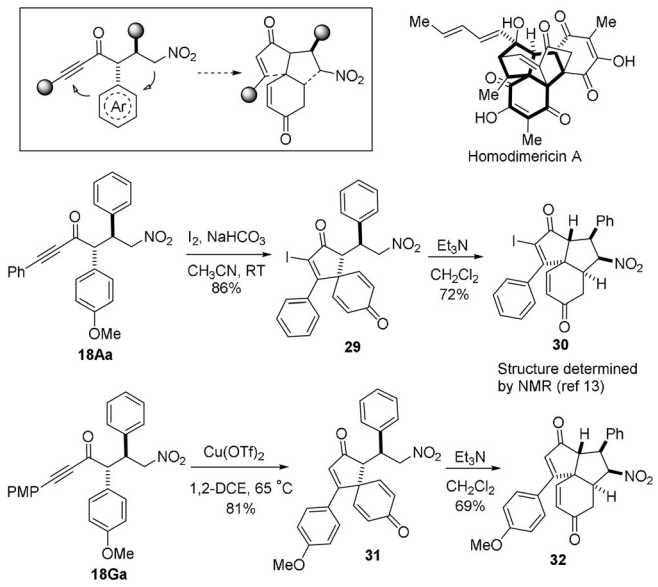
Scheme 4. Reduction of adducts to α-branched alkyl alkyl ketones.

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.

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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

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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).

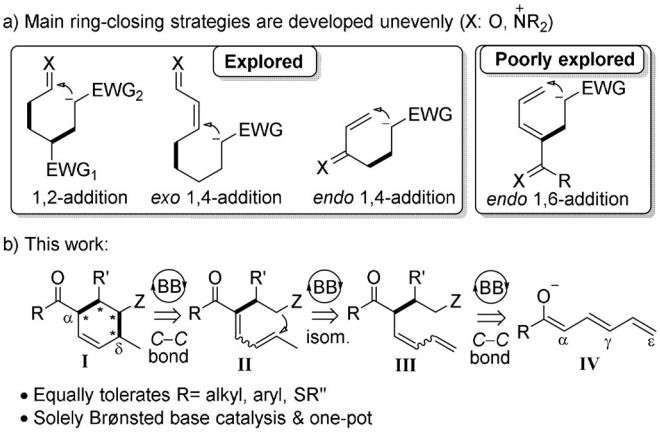

Figure 1. Catalytic one-pot construction of six-membered carbocycles.

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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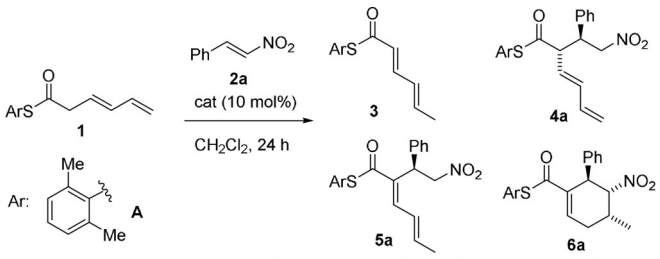
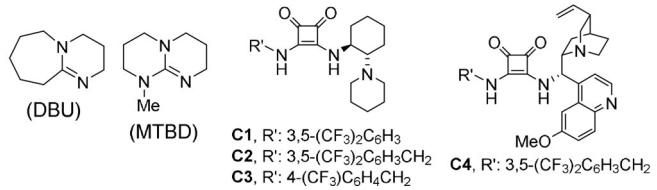
Table 1: Catalyst-dependent product distribution in the reaction of polyunsaturated thioester **1A** with nitrostyrene.[a]





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]

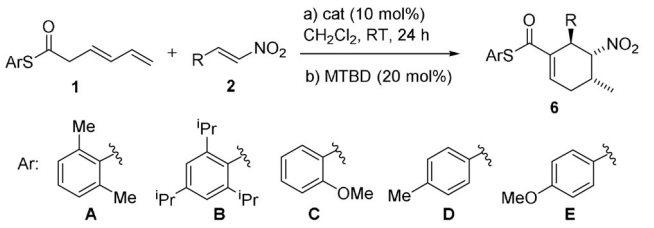
We presumed that this cycloadduct might be formed through cyclization of acyclic precursor **5Aa**, followed by double bond isomerization. To prove this assumption the same reaction was carried out at 0°C affording a mixture of **3A**, isomerized α-adduct **5Aa**, and **6Aa** (entry 5). When this mixture 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.

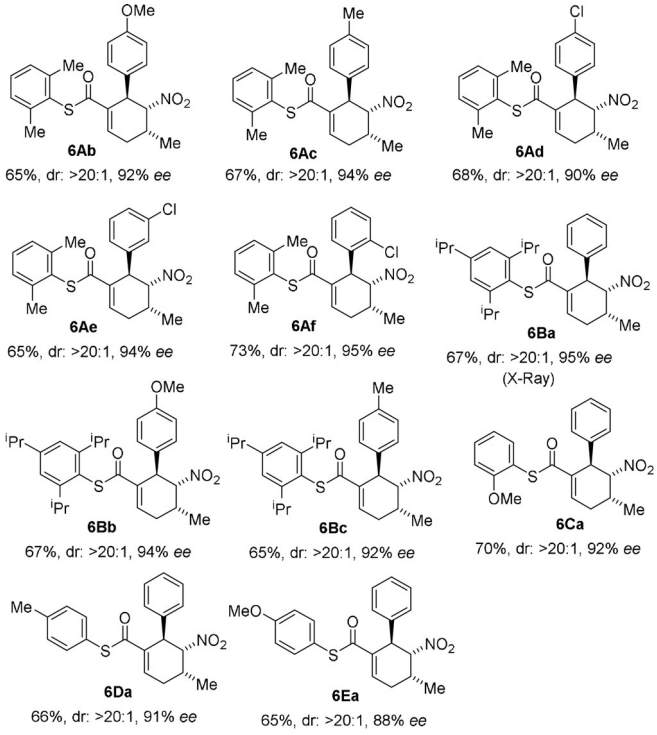
The validity of this new, one-pot, enantio- and diastereoselective carbocyclization approach was also tested with deconjugated dienones **7–12**. As shown in Table 3, the reaction of unsaturated ketone **7** with nitrostyrene **2a** in the presence of 10 mol% catalyst **C4** cleanly afforded α-addition 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]

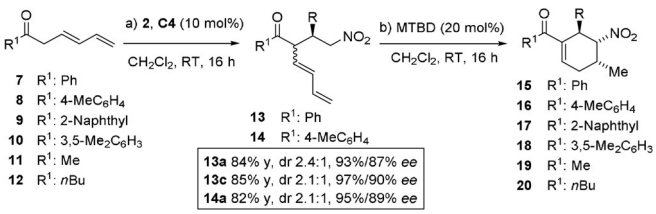


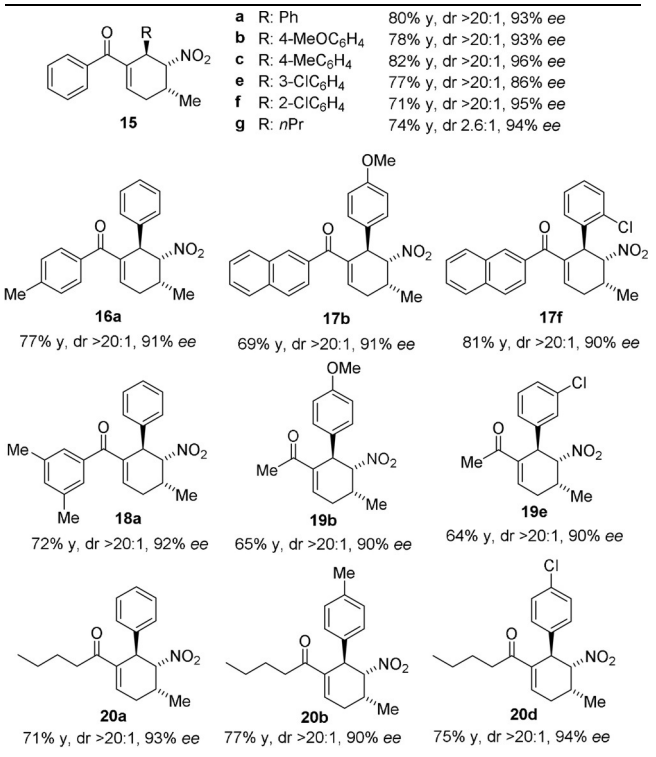
R= **a**: Ph; **b**: 4-$MeOC_6H_4$; **c**: 4-MeC_6H_4; **d**: 4-ClC_6H_4; **e**: 3-ClC_6H_4; **f**: 2-ClC_6H_4; **g**: *n*Pr



[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]

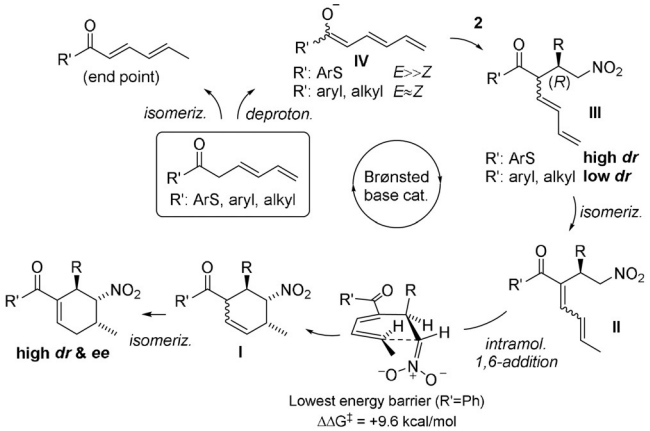




[a] Reactions carried out at 0.1 mmol scale, using 1.2 equiv of **7**–**12** and in 0.1 mL DCM at room temperature. Yield after chromatography. The dr values are determined by ^{1}H NMR (300 MHz). The *ee*s are determined by chiral HPLC.

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),

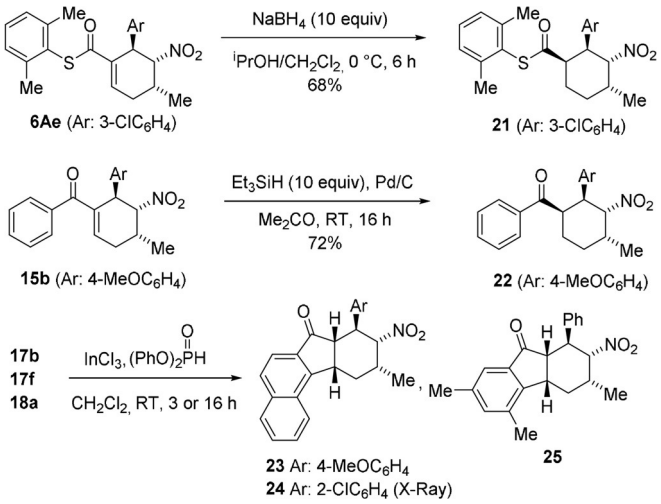


Scheme 1. Plausible course of the one-pot reactions sequence.

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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