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

DOCTORAL THESIS

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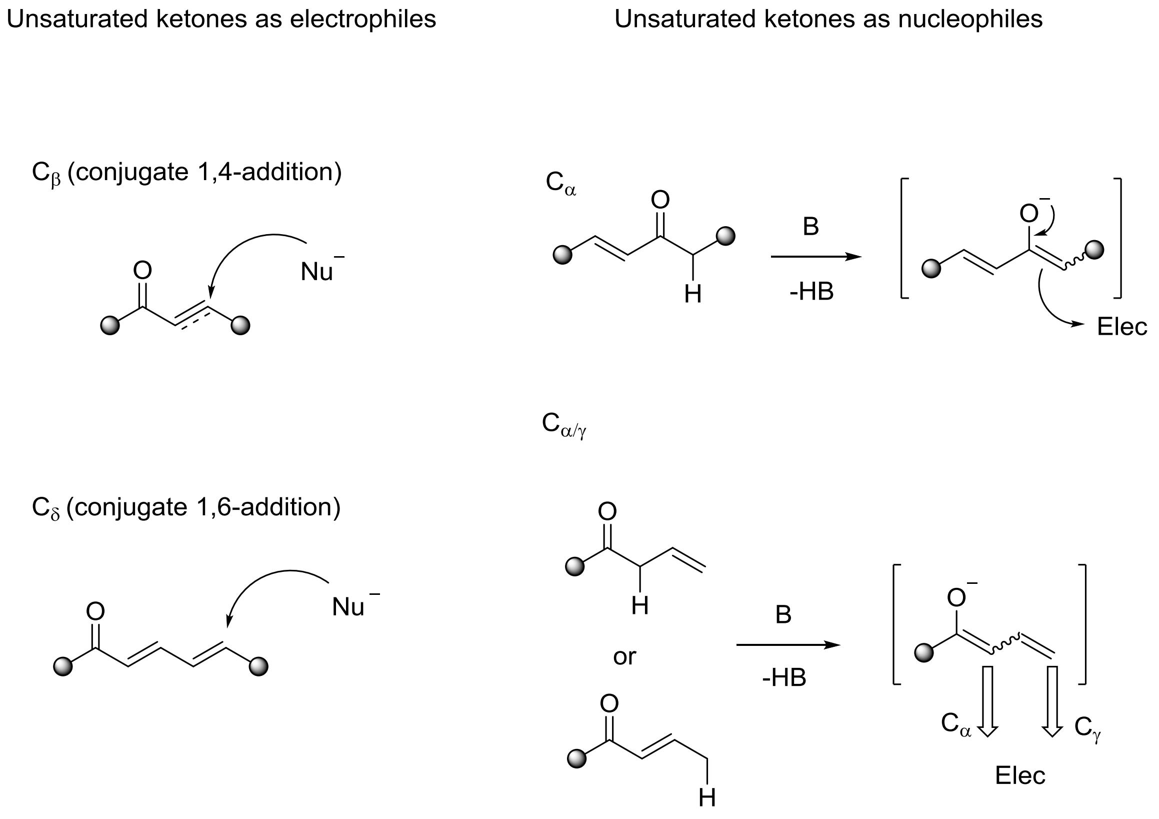
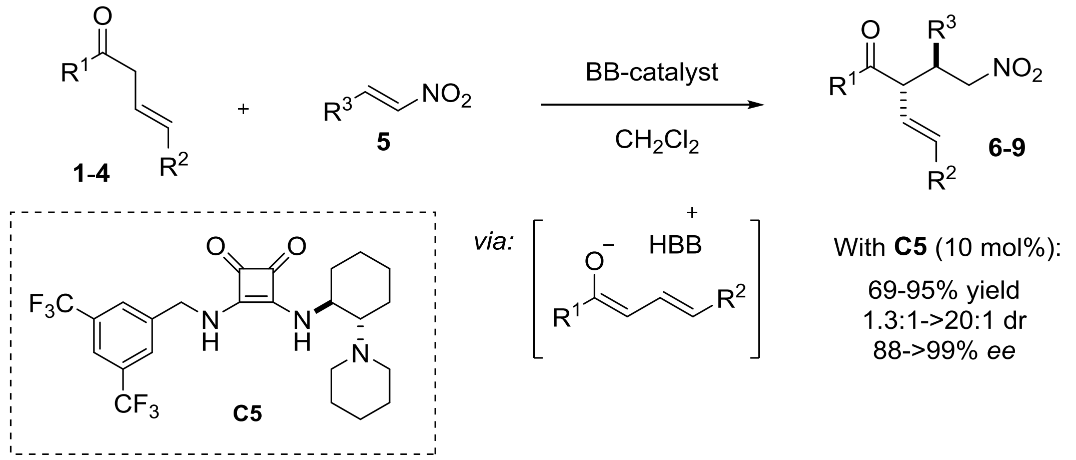
Summary

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.


Unsaturated ketones as electrophiles
Unsaturated ketones as nucleophiles
Cβ (conjugate 1,4-addition)
O
Nu⁻
Cα
O
H
B
-HB
O⁻
Elec
Cα/γ
Cδ (conjugate 1,6-addition)
O
Nu⁻
O
H
or
O
H
B
-HB
O⁻
Cα
Cγ
Elec

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

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.

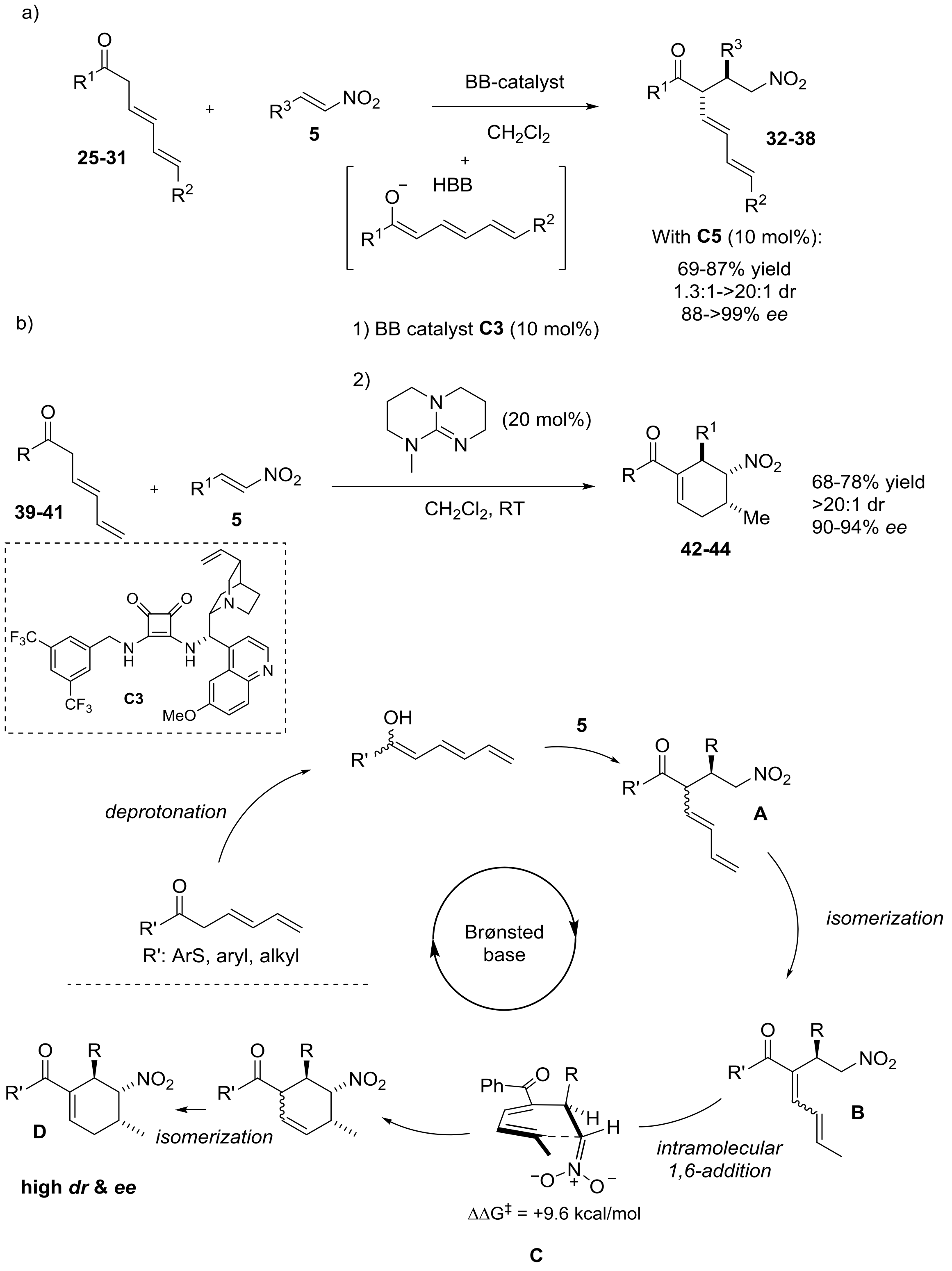


With **C5** (10 mol%):
69-95% yield
1.3:1->20:1 dr
88->99% *ee*

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

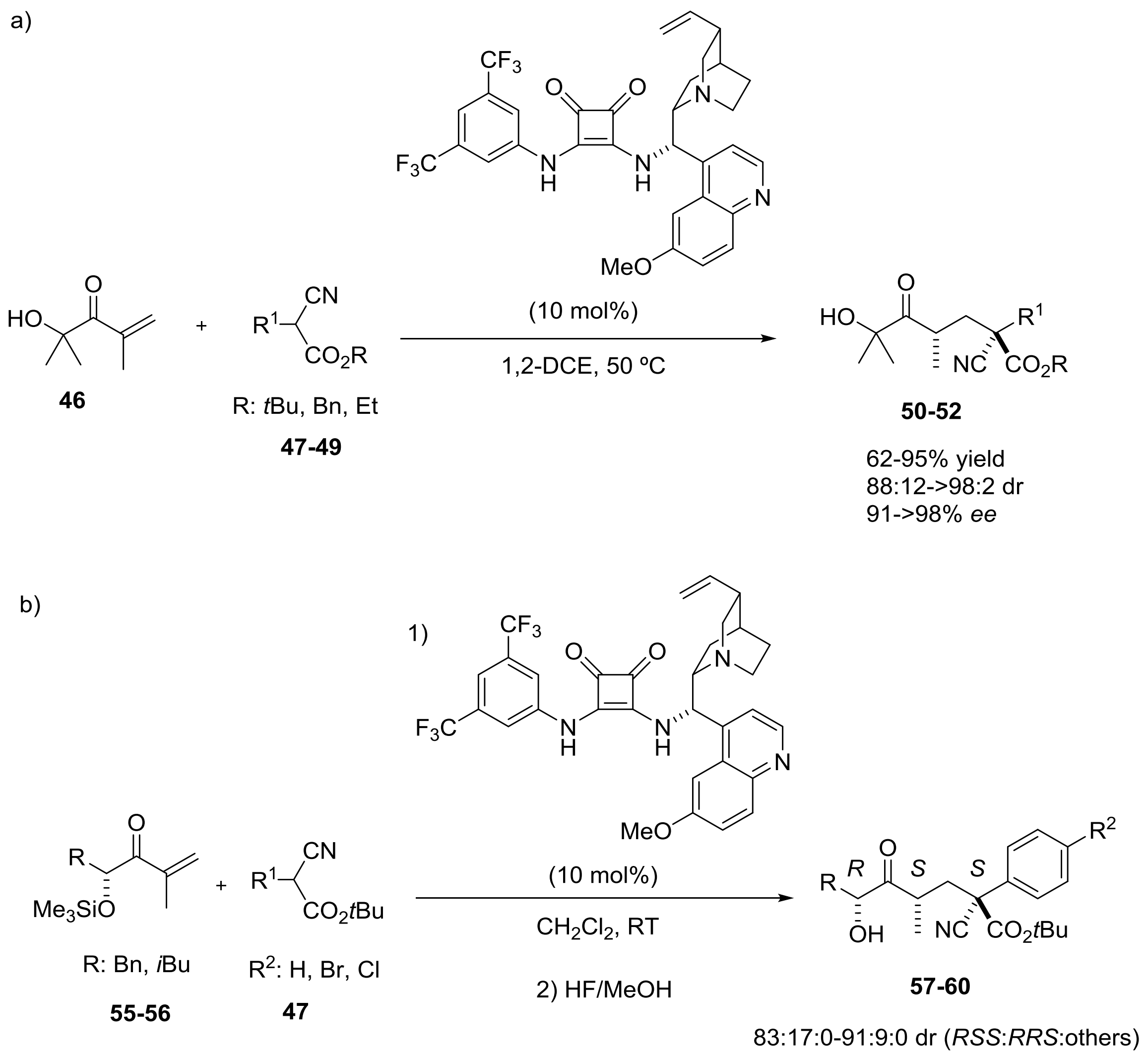
Under similar catalytic conditions, the transiently generated trienolates from doubly unsaturated ketones **25**-**31** reacted with nitroolefins **5** affording, again, the α-adducts **32**-**38** exclusively (Scheme Ca). This reactivity pattern is divergent from the reported [4+2] cycloaddition pathways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


a)
25-31
5
BB-catalyst
CH2Cl2
HBB
32-38
With C5 (10 mol%):
69-87% yield
1.3:1->20:1 dr
88->99% ee
b)
1) BB catalyst C3 (10 mol%)
2)
(20 mol%)
CH2Cl2, RT
39-41
5
42-44
68-78% yield
>20:1 dr
90-94% ee
C3
5
A
deprotonation
isomerization
Brønsted base
R': ArS, aryl, alkyl
B
intramolecular 1,6-addition
ΔΔG‡ = +9.6 kcal/mol
C
isomerization
D
high dr & ee

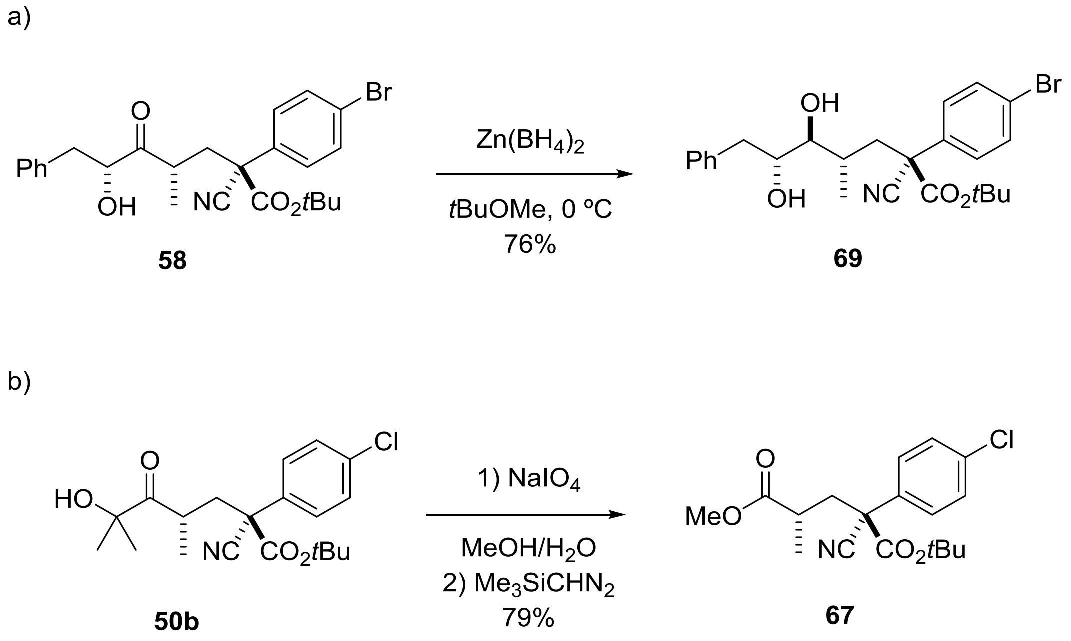
Scheme C. a) Trienolate mediated α-functionalization of dienones. b) Implementation of a one-pot diastereo- and enantioselective synthesis of cyclohexenes.

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).


a)
CF3
O
O
N
F3C
N H
N H
N
MeO
HO
O
+
CN
R1
CO2R
(10 mol%)
1,2-DCE, 50 ºC
HO
O
R1
NC
CO2R
46
R: tBu, Bn, Et
47-49
50-52
62-95% yield
88:12->98:2 dr
91->98% ee
b)
1)
CF3
O
O
N
F3C
N H
N H
N
MeO
R
O
Me3SiO
+
CN
R1
CO2tBu
(10 mol%)
CH2Cl2, RT
2) HF/MeOH
R
R
O
S
S
R2
OH
NC
CO2tBu
R: Bn, iBu
55-56
R2: H, Br, Cl
47
57-60
83:17:0-91:9:0 dr (RSS:RRS:others)

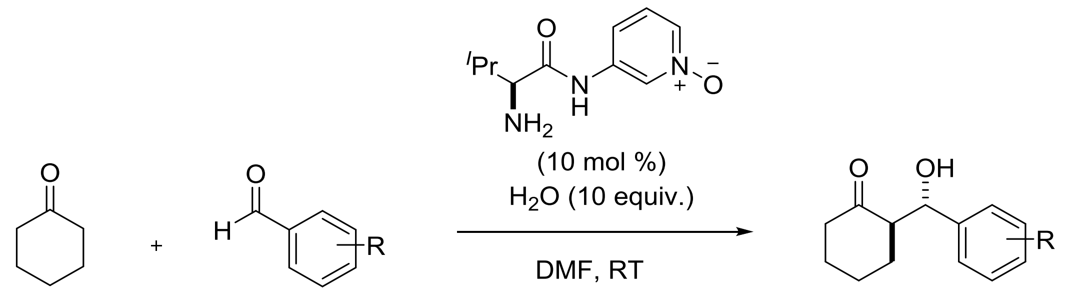
Scheme D. Tandem Michael/α-protonation reaction using α-methyl α´-oxy enones as Michael acceptors.

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).


a)
Ph
O
OH
NC
CO_2tBu
Br
58
$Zn(BH_4)_2$
tBuOMe, 0 °C
76%
OH
Ph
OH
NC
CO_2tBu
Br
69
b)
HO
O
NC
CO_2tBu
Cl
50b
1) $NaIO_4$
$MeOH/H_2O$
2) Me_3SiCHN_2
79%
O
MeO
NC
CO_2tBu
Cl
67

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.


ⁱPr
NH₂
O
N
H
N
+
O
−
(10 mol %)
H₂O (10 equiv.)
DMF, RT
O
H
R
+
O
OH
R

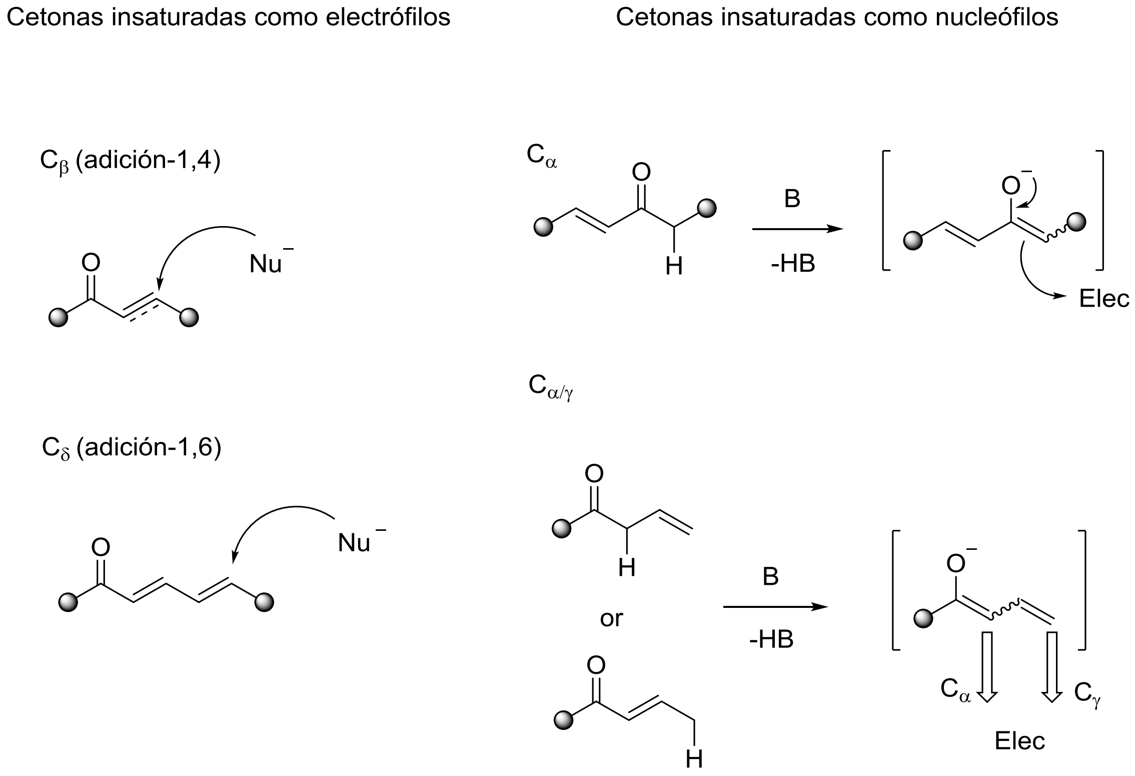
67

66-92% yield
60:40->99:1 dr
62.94% *ee*

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

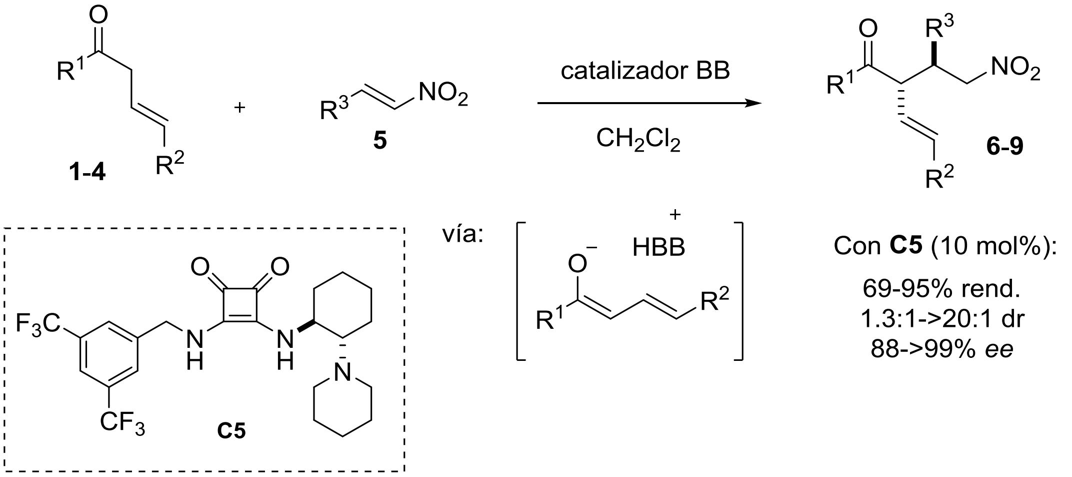
Resumen

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.

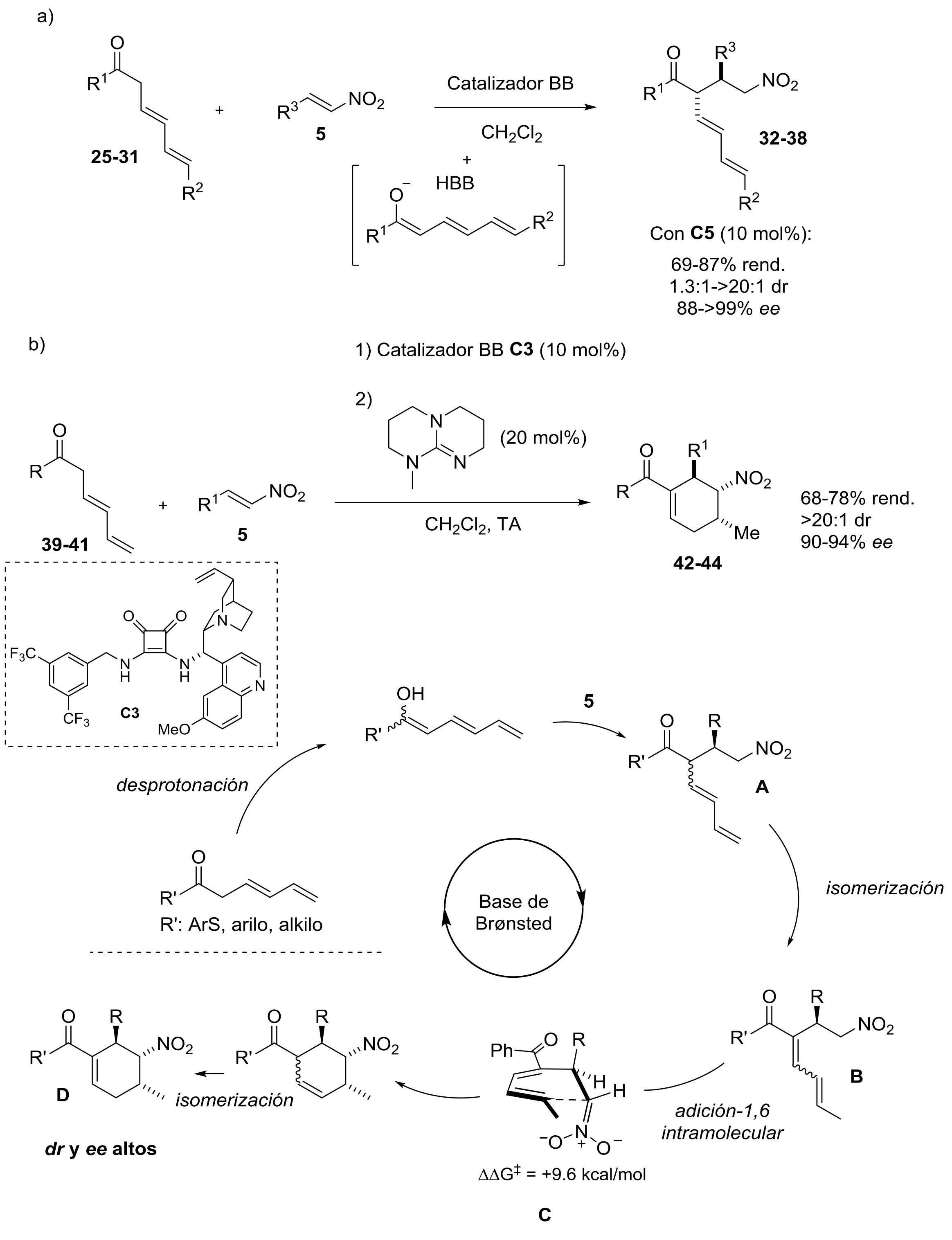
En la primera parte de esta Tesis, se muestra cómo los catalizadores bifuncionales de tipo amina terciaria/escuaramida pueden promover la adición de cetonas β,γ-insaturadas **1**-**4** a nitroolefinas **5** vía los correspondientes dienolatos, un proceso que transcurre no solo con muy buen enantio- y 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.

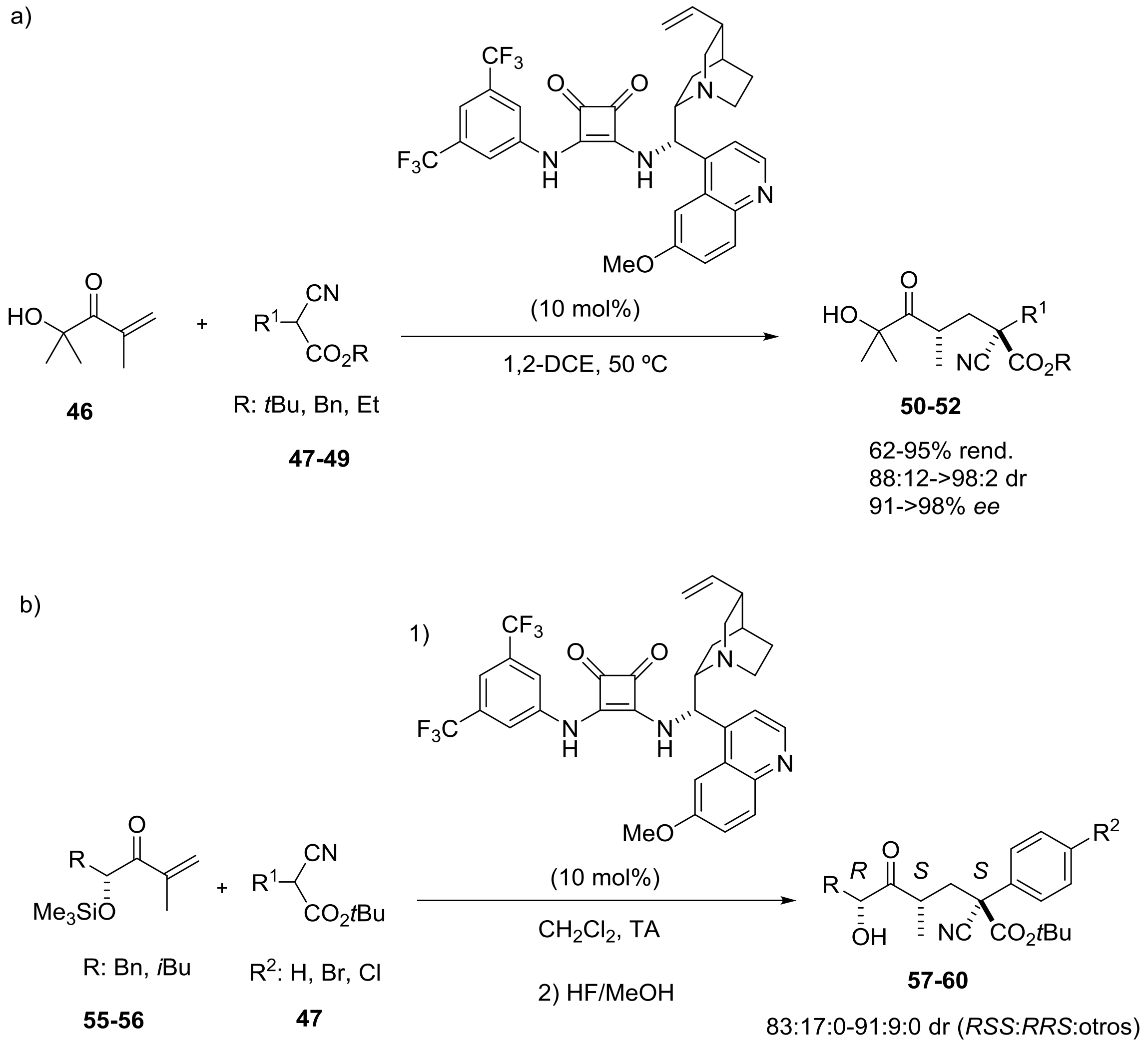
Bajo unas condiciones catalíticas similares, los trienolatos generados transitoriamente a partir de las cetonas doblemente insaturadas **25**-**31** reaccionan con nitroolefinas **5** dando lugar a los α-aductos **32**-**38** exclusivamente (Esquema Ca). Nuevamente, la regioselectividad observada difiere 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).


a)
25-31
5
Catalizador BB
CH2Cl2
+
HBB
32-38
Con C5 (10 mol%):
69-87% rend.
1.3:1->20:1 dr
88->99% ee
b)
1) Catalizador BB C3 (10 mol%)
2)
(20 mol%)
CH2Cl2, TA
39-41
5
42-44
68-78% rend.
>20:1 dr
90-94% ee
C3
desprotonación
R': ArS, arilo, alkilo
5
A
isomerización
Base de Brønsted
B
adición-1,6 intramolecular
ΔΔG‡ = +9.6 kcal/mol
C
isomerización
D
dr y ee altos

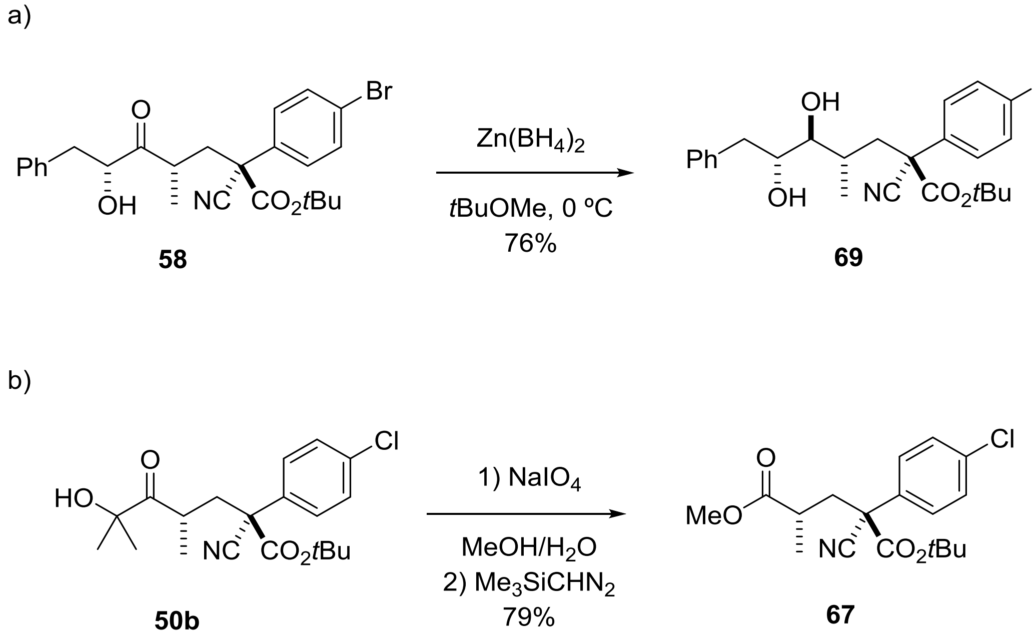
Esquema C. a) α-Funcionalización de dienonas vía trienolatos. b) Síntesis de ciclohexenos mediante un proceso one-pot entre cetonas β, γ, δ, ε-insaturadas y nitroolefinas.

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).


a)
CF3
O
O
F3C
N
H
N
H
N
N
MeO
HO
O
+
CN
R1
CO2R
(10 mol%)
1,2-DCE, 50 °C
HO
O
R1
NC
CO2R
46
R: tBu, Bn, Et
47-49
50-52
62-95% rend.
88:12->98:2 dr
91->98% ee
b)
1)
CF3
O
O
F3C
N
H
N
H
N
N
MeO
R
O
Me3SiO
+
CN
R1
CO2tBu
(10 mol%)
CH2Cl2, TA
2) HF/MeOH
R
R
O
S
S
R2
OH
NC
CO2tBu
R: Bn, iBu
R2: H, Br, Cl
55-56
47
57-60
83:17:0-91:9:0 dr (RSS:RRS:otros)

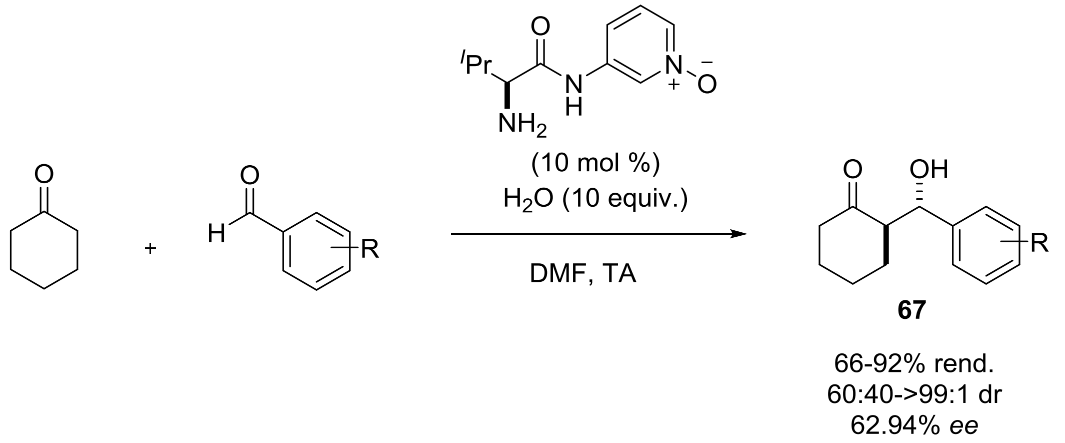
Esquema D. Proceso tándem de reacción de Michael/α-protonación utilizando α-metil α´-oxi enonas como equivalentes sintéticos del metacrilato como aceptores de Michael.

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).


a)
Zn(BH4)2
tBuOMe, 0 ºC
76%
58
69
b)
1) NaIO4
MeOH/H2O
2) Me3SiCHN2
79%
50b
67

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).


(10 mol %)
H2O (10 equiv.)
DMF, TA
67
66-92% rend.
60:40->99:1 dr
62.94% *ee*

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

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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.

---

[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.

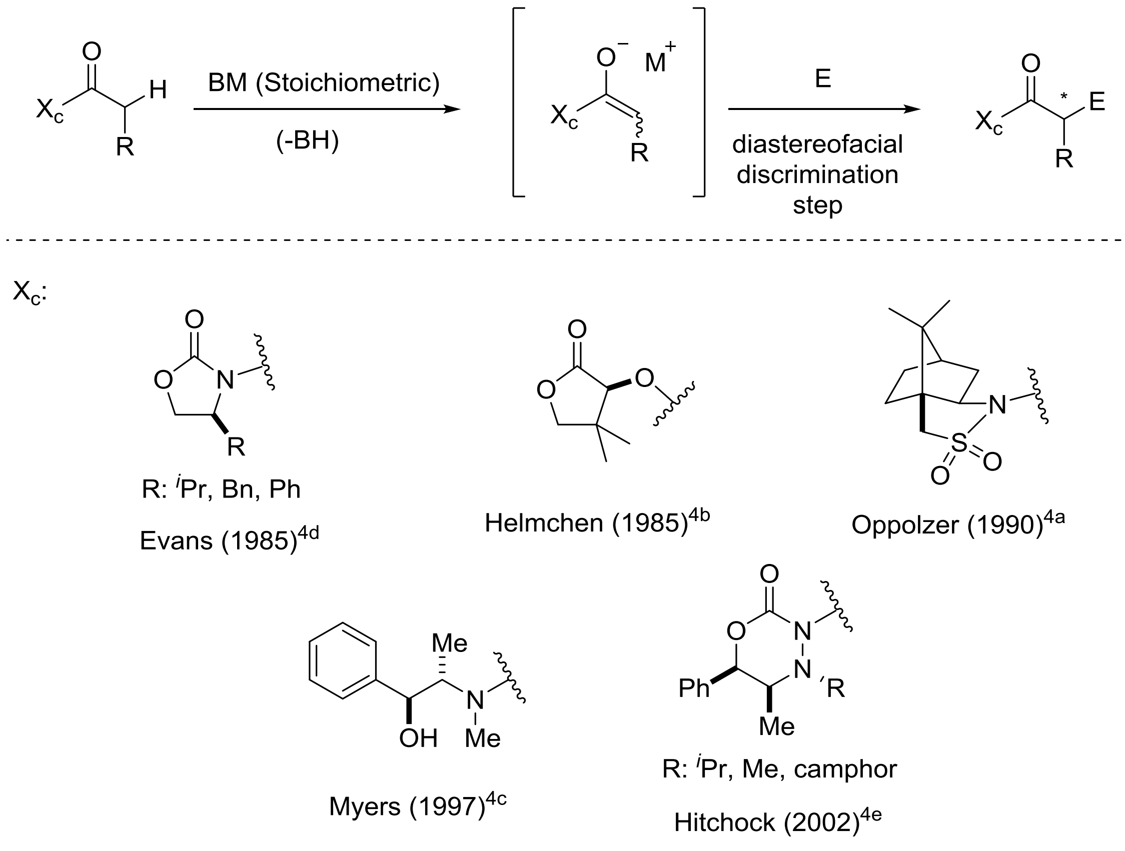
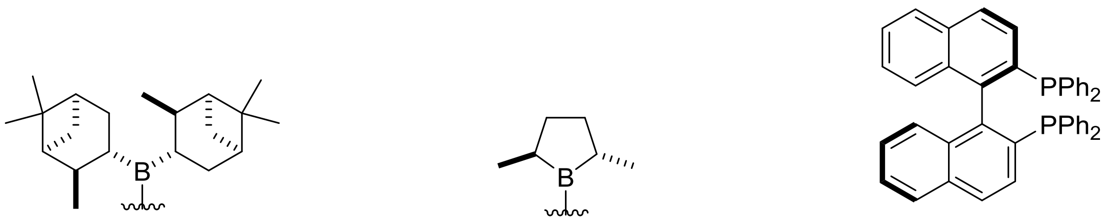

O
Xc
H
R
BM (Stoichiometric)
(-BH)
O⁻ M⁺
Xc
R
E
diastereofacial
discrimination
step
O
Xc
*
E
R
Xc:
O
O
N
R
R: iPr, Bn, Ph
Evans (1985)4d
O
O
O
Helmchen (1985)4b
N
S
O
O
Oppolzer (1990)4a
Me
N
OH
Me
Myers (1997)4c
O
O
N
N
Ph
R
Me
R: iPr, Me, camphor
Hitchock (2002)4e

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.

---

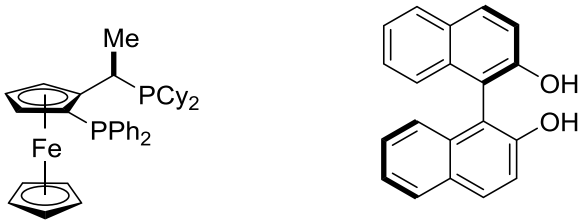
[5] Representative examples: a) Paterson, I.; Lister, M. S.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4748–4790. b) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281. c) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; 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.



Paterson (1986)[5a]
Boron enolates
(Aldol reaction)

Masamune (1986)[5b]
Boron enolates
(Aldol reaction)

Noyori (1980)[5c]
Ru, Rh and Pd enolates
(Mukaiyama aldol reaction)



Togni (1994)[5d]
(Aldol reaction)

Noyori (1979)[5e]
Early transition metals
(Aldol and Michael reactions)

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.

---

[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.

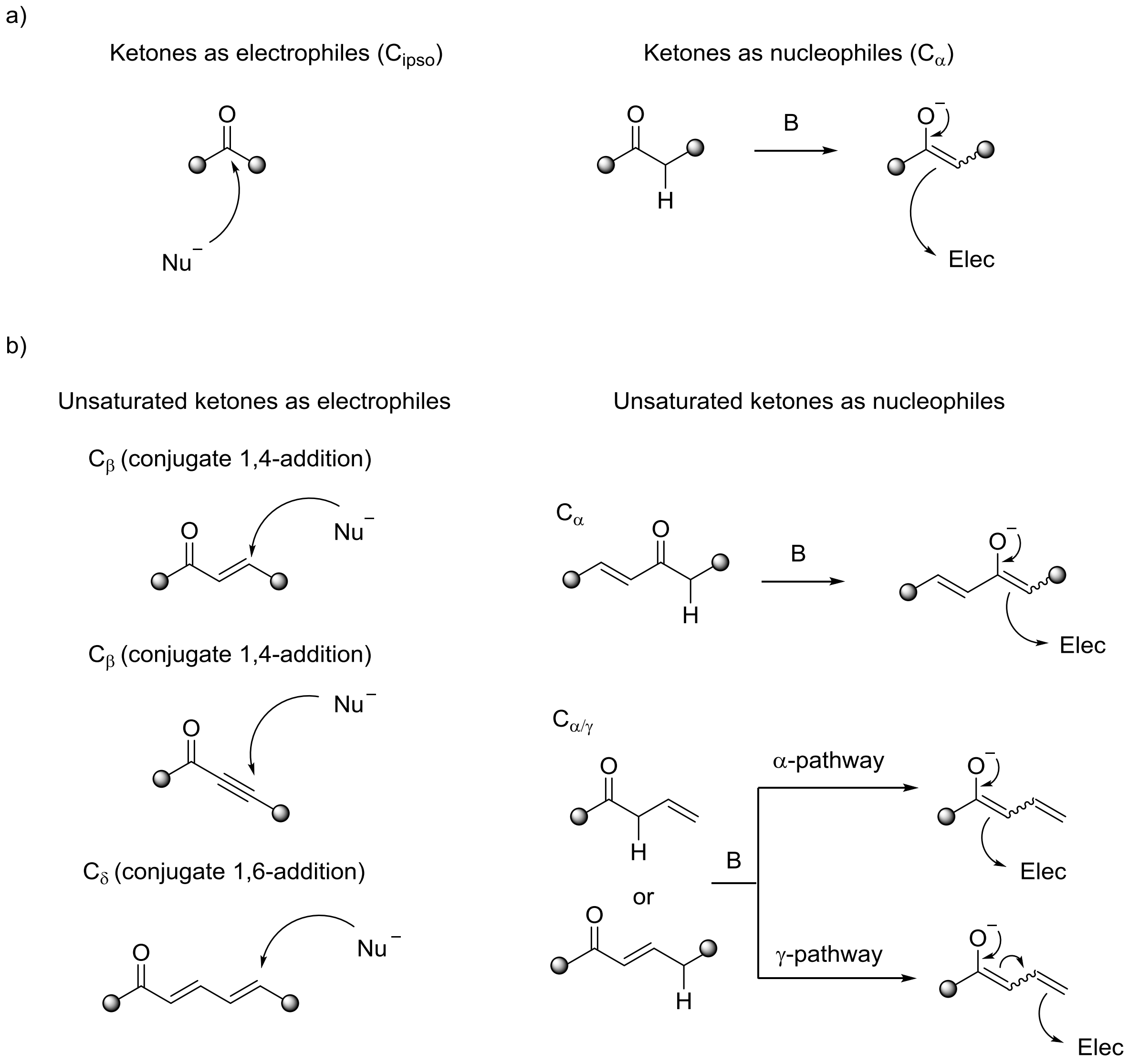

a)
Ketones as electrophiles (C$_{ipso}$)
Ketones as nucleophiles (C$_{\alpha}$)
O
Nu$^-$
B
H
O$^-$
Elec
b)
Unsaturated ketones as electrophiles
Unsaturated ketones as nucleophiles
C$_{\beta}$ (conjugate 1,4-addition)
C$_{\beta}$ (conjugate 1,4-addition)
C$_{\delta}$ (conjugate 1,6-addition)
C$_{\alpha}$
C$_{\alpha/\gamma}$
or
α-pathway
γ-pathway

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).

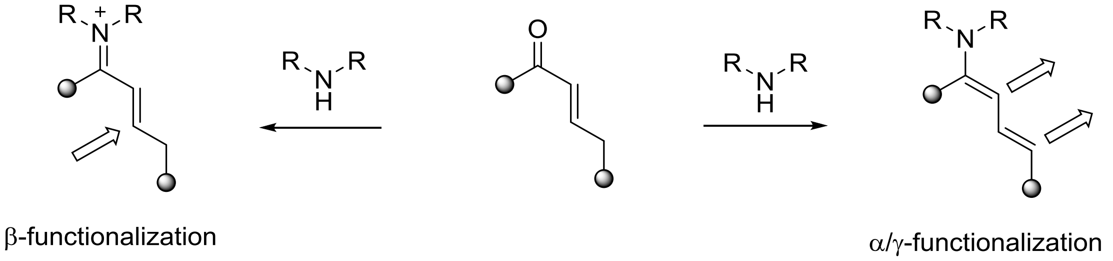


Figure 4. Activation of unsaturated ketones via enamine and iminium ion.

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.

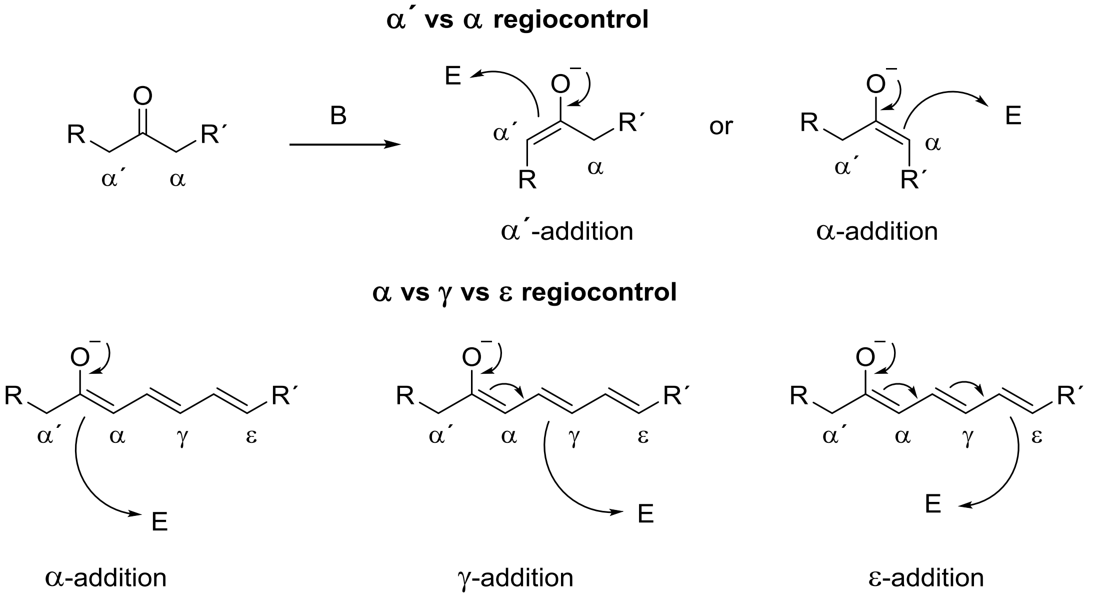

α´ vs α regiocontrol
O
R
R´
α´
α
B
E
O
α´
R´
R
α
or
O
R
E
α
α´
R´
α´-addition
α-addition
α vs γ vs ε regiocontrol
O
R
R´
α´
α
γ
ε
E
α-addition
O
R
R´
α´
α
γ
ε
E
γ-addition
O
R
R´
α´
α
γ
ε
E
ε-addition

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).

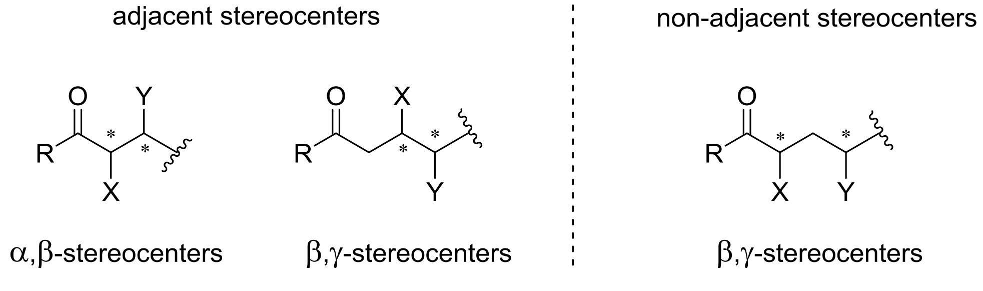

adjacent stereocenters
non-adjacent stereocenters
O
Y
R
*
*
X
O
X
R
*
*
Y
O
R
*
*
X
Y
α,β-stereocenters
β,γ-stereocenters
β,γ-stereocenters

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

---

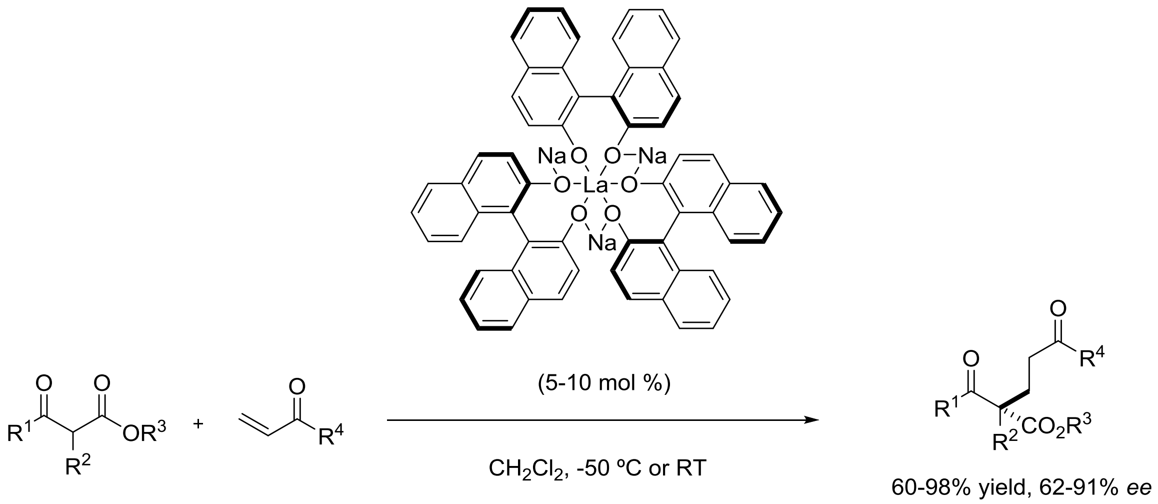
[8] a) *Enzyme Biocatalysis: Principles and Applications*, Ed. Illanes, A. **2008**, Springer, New York. b) Bommarius, A. S.; Riebel, B. R. *Biocatalysis: Fundamentals and Applications*, **2007**, Wiley-VCH. c) Pollard, D.J.; Woodley, J. M. *Trends Biotechnol.* **2007**, *25*, 66−73.

[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**.

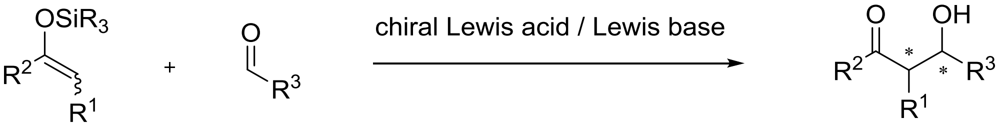
[11] For the concept of bifunctional metal complexes, see: a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393−406. b) Shibasaki, M.; Kanai, M.; Matsunaga, S. *Acc. Chem. Res.* **2009**, *42*, 1117−1127. c) Ito, J.; Nishimaya, H. *Bifunctional Molecular Catalysis. Topics in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

[12] Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561−5564.



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]



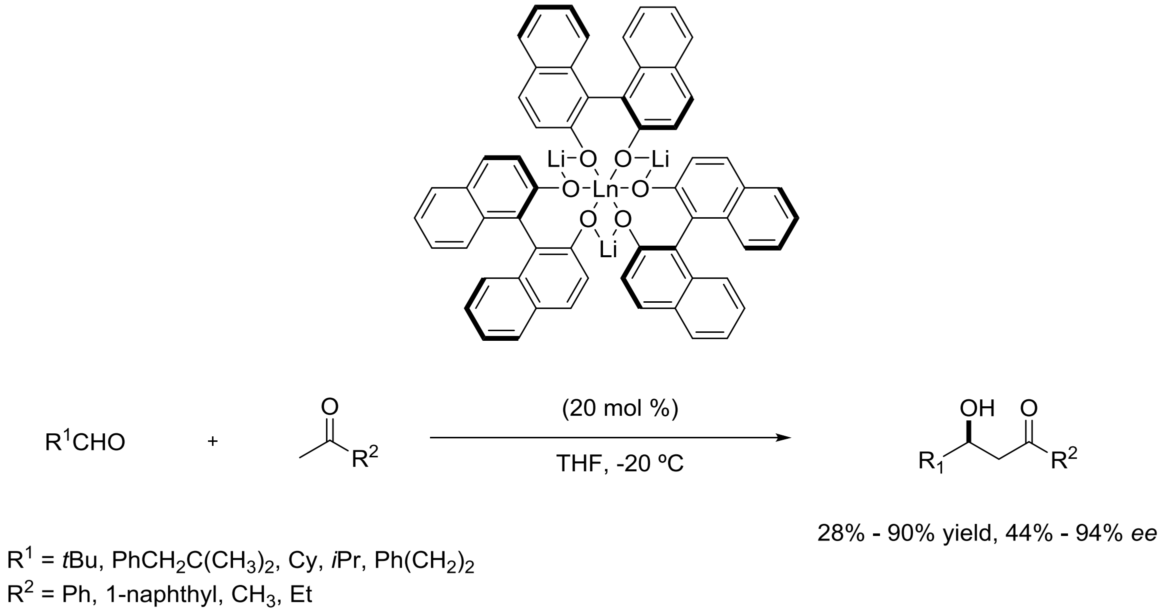
Scheme 2. General scheme of the Mukaiyama aldol reaction.

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

---

[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.


Li–O
O–Li
O–Ln–O
O
O
Li
(20 mol %)
THF, -20 ºC
R^1CHO
+
O
R^2
OH
O
R_1
R^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

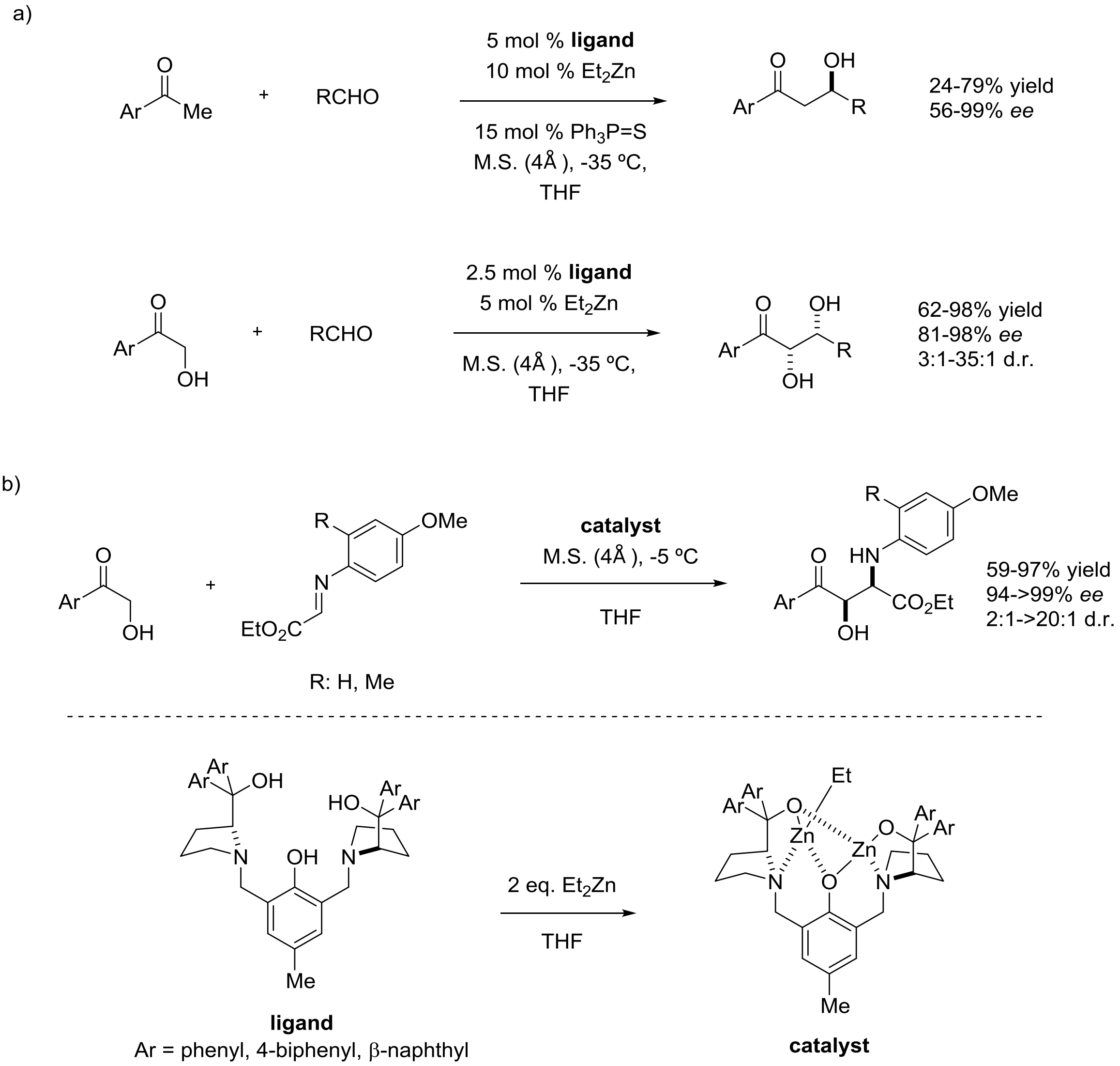
Scheme 3. First direct catalytic asymmetric aldol reaction performed by laboratory-designed catalyst.

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.


a)
Ar
Me
O
RCHO
5 mol % ligand
10 mol % Et2Zn
15 mol % Ph3P=S
M.S. (4Å), -35 ºC,
THF
OH
R
24-79% yield
56-99% ee
2.5 mol % ligand
5 mol % Et2Zn
M.S. (4Å), -35 ºC,
THF
62-98% yield
81-98% ee
3:1-35:1 d.r.
b)
R
OMe
N
EtO2C
R: H, Me
catalyst
M.S. (4Å), -5 ºC
THF
HN
CO2Et
59-97% yield
94->99% ee
2:1->20:1 d.r.
2 eq. Et2Zn
THF
Zn
Et
ligand
Ar = phenyl, 4-biphenyl, β-naphthyl
catalyst

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

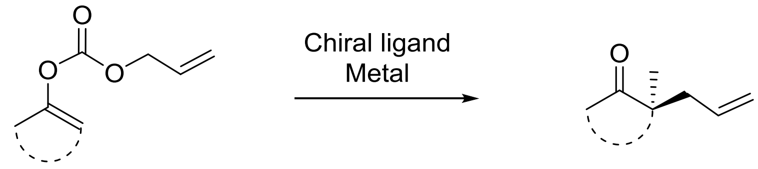
These pioneering examples paved the way for the study of the functionalization of enolizable carbonyl donors based on bifunctional metallic asymmetric catalysis.[17] However, the majority of these direct procedures are still limited to carbonyl compounds bearing an electron withdrawing group at the α-position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

---

[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.

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.

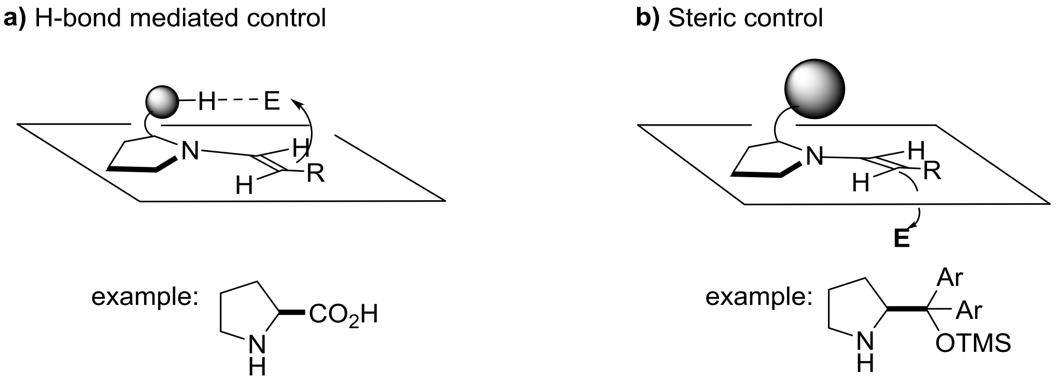


Figure 7. Two different mechanisms for enamine face-discrimination.

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]

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[25] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621.

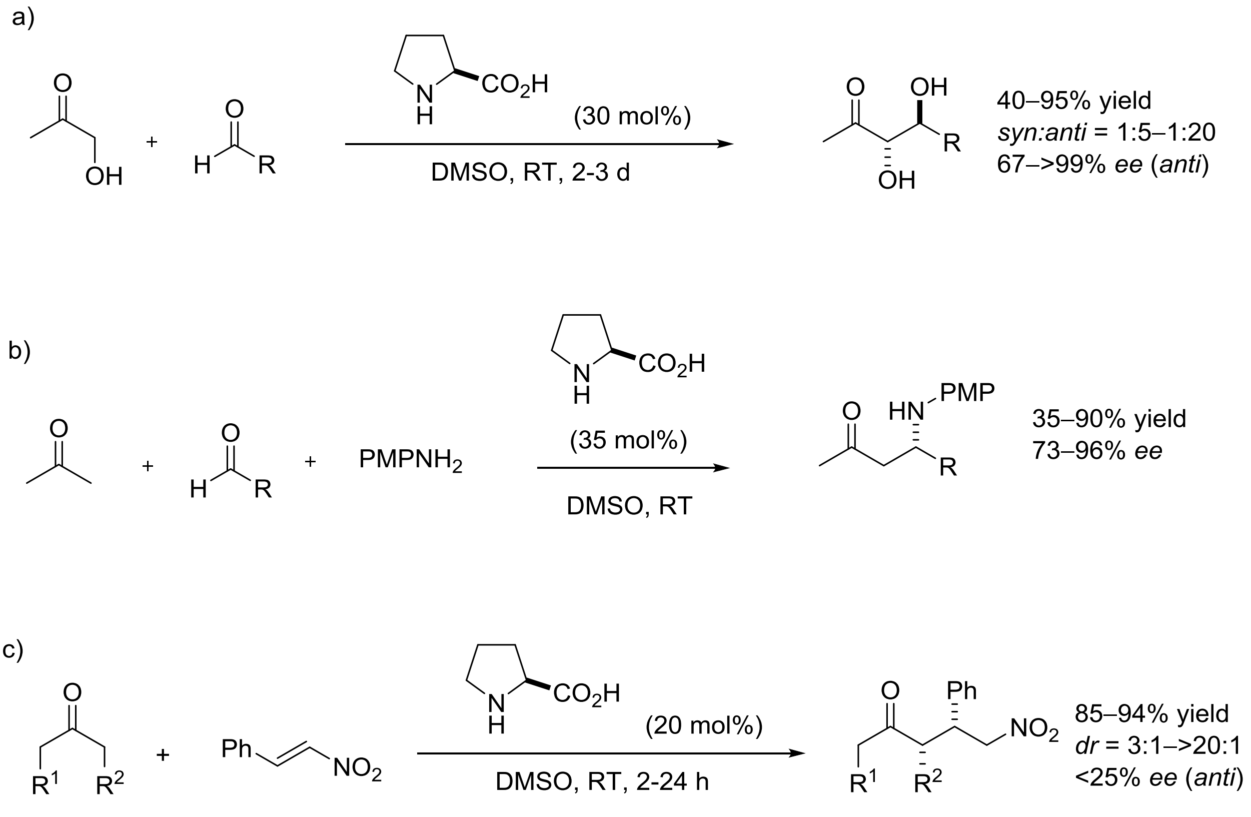
[26] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

[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.


a)
O
OH
+
O
H
R
N
H
CO2H
(30 mol%)
DMSO, RT, 2-3 d
O
OH
R
OH
40–95% yield
syn:anti = 1:5–1:20
67–>99% ee (anti)
b)
O
+
O
H
R
+
PMPNH2
N
H
CO2H
(35 mol%)
DMSO, RT
O
HN
PMP
R
35–90% yield
73–96% ee
c)
O
R1
R2
+
Ph
NO2
N
H
CO2H
(20 mol%)
DMSO, RT, 2-24 h
O
Ph
NO2
R1
R2
85–94% yield
dr = 3:1–>20:1
<25% ee (anti)

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.

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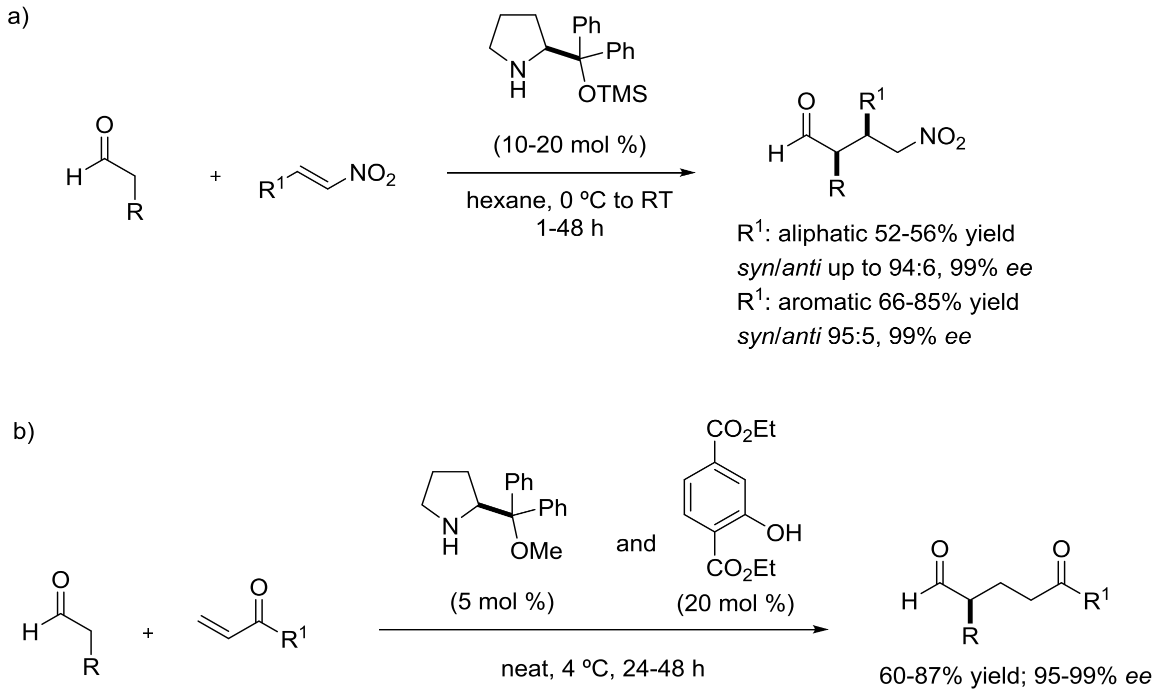
[31] Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208−11209.

[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.


a)
Ph
Ph
N
H
OTMS
O
H
R
+
R1
NO2
(10-20 mol %)
hexane, 0 °C to RT
1-48 h
O
R1
H
NO2
R
R1: aliphatic 52-56% yield
syn/anti up to 94:6, 99% ee
R1: aromatic 66-85% yield
syn/anti 95:5, 99% ee
b)
CO2Et
Ph
Ph
N
H
OMe
and
OH
CO2Et
O
H
R
+
O
R1
(5 mol %)
(20 mol %)
neat, 4 °C, 24-48 h
O
O
H
R1
R
60-87% yield; 95-99% ee

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

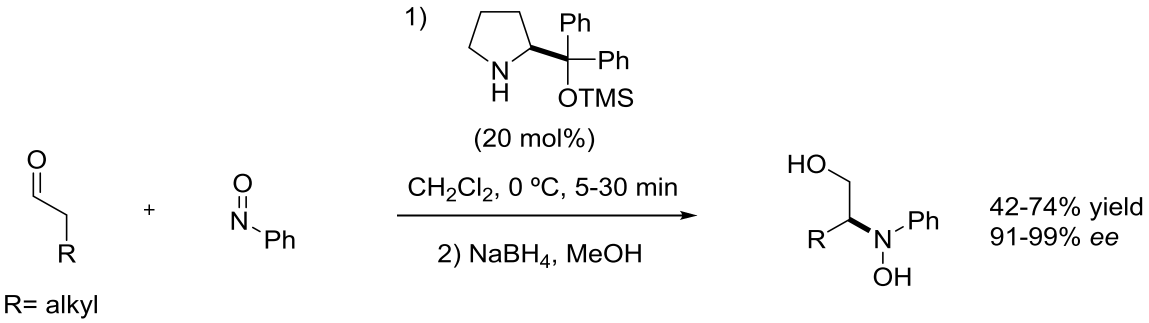
In 2007, our group demonstrated that simple diarylprolinol silyl ethers could promote the direct and regioselective oxyamination reaction of aldehydes with nitrosobenzene to afford the oxyaminated compounds in good yields and with excellent regio- and enantioselectivities (Scheme 8).[35]

---

[33] Hayashi, Y.; Gotoh, H.; Hayasi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

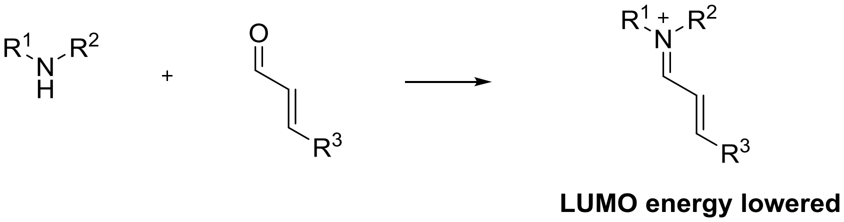
[34] Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253–4256.

[35] Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054–8056.


1)
Ph
Ph
N
H
OTMS
(20 mol%)
CH2Cl2, 0 °C, 5-30 min
2) NaBH4, MeOH
O
R
R= alkyl
+
O
N
Ph
HO
R
N
Ph
OH
42-74% yield
91-99% ee

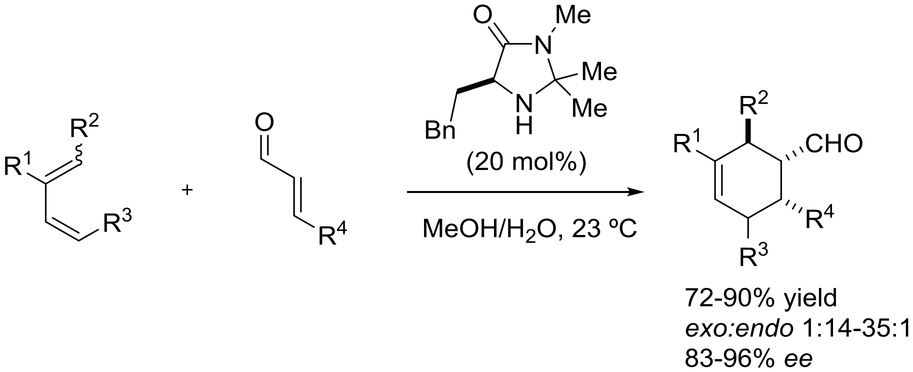
Scheme 8. Oxyamination reaction of aldehydes catalysed by α,α-diphenylprolinol trimethylsilyl ether.

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).


R1
N
R2
H
+
O
R3
R1 + R2
N
R3
LUMO energy lowered

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]

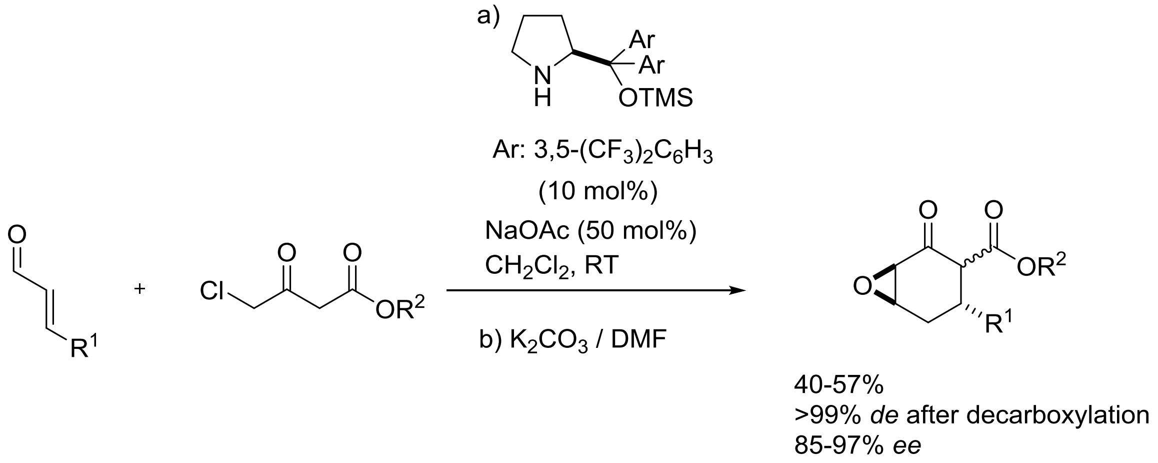

O
Me
N
Me
N
Me
Bn
H
(20 mol%)
MeOH/H2O, 23 °C
R2
R1
R3
+
O
R4
R2
R1
CHO
R4
R3
72-90% yield
exo:endo 1:14-35:1
83-96% ee

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

---

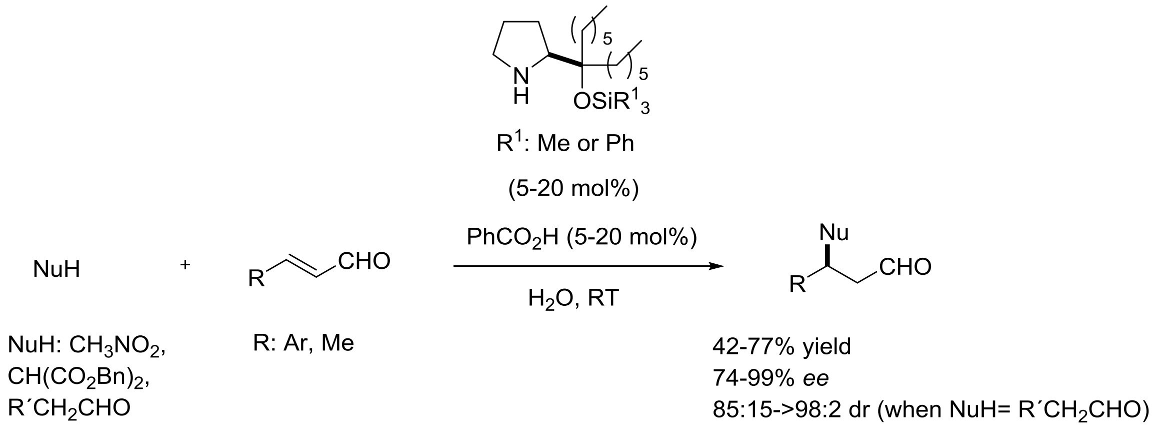
[36] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

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).


a)
Ar
Ar
N
H
OTMS
Ar: 3,5-(CF3)2C6H3
(10 mol%)
NaOAc (50 mol%)
CH2Cl2, RT
b) K2CO3 / DMF
O
R1
+
Cl
O
O
OR2
O
O
O
OR2
R1
40-57%
>99% de after decarboxylation
85-97% ee

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.


N
H
5
5
OSiR1 3
R1: Me or Ph
(5-20 mol%)
PhCO2H (5-20 mol%)
H2O, RT
NuH
+
R
CHO
NuH: CH3NO2,
CH(CO2Bn)2,
R´CH2CHO
R: Ar, Me
Nu
R
CHO
42-77% yield
74-99% ee
85:15->98:2 dr (when NuH= R´CH2CHO)

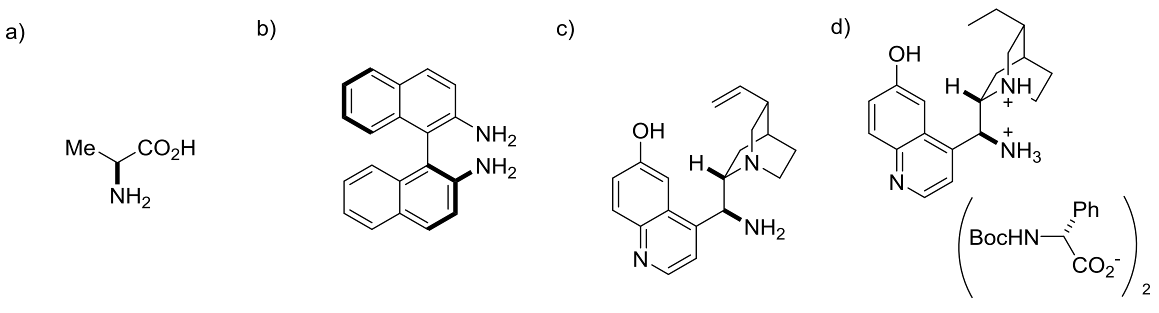
Scheme 12. Michael additions of carbon-centered nucleophiles with enals via water-compatible iminium activation.

---

[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).



Cordoba, 2005 **Ishihara, 2006** **Chen, 2007** **Melchiorre, 2007**

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.

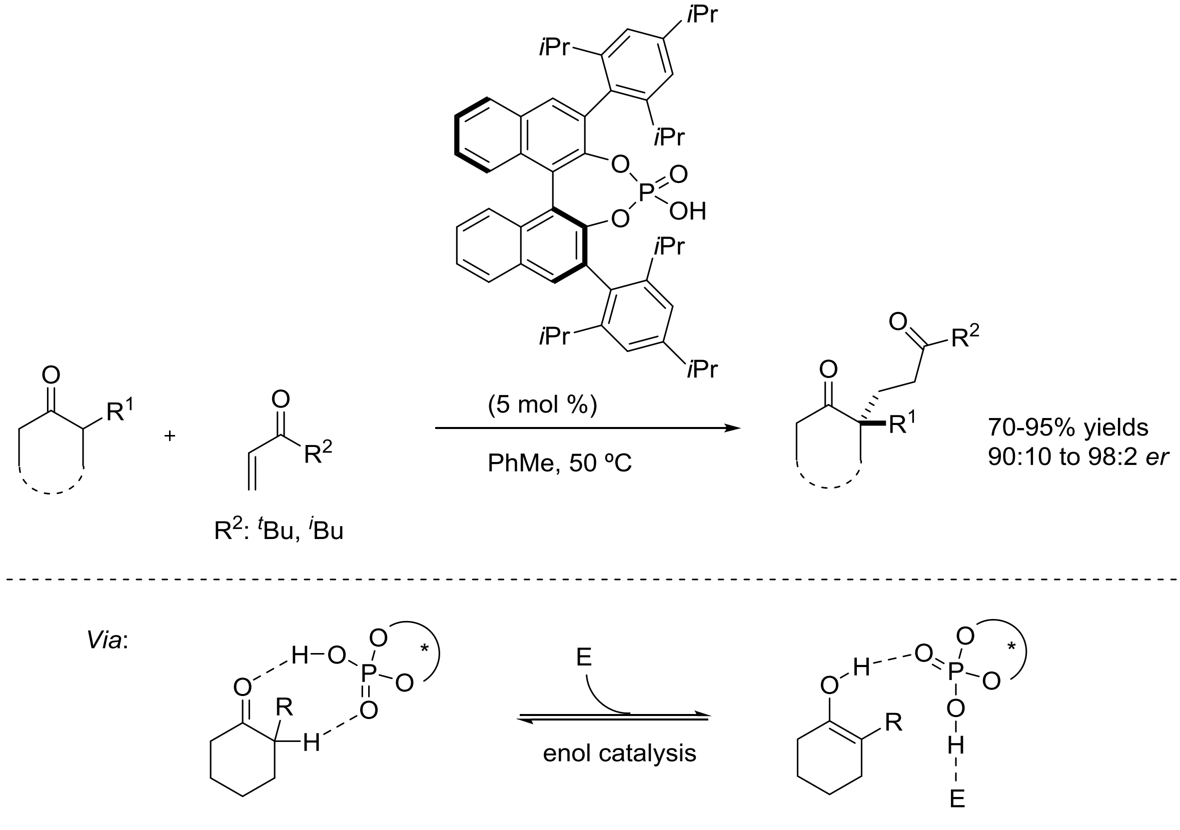
1.3.2.2. *Non-covalent catalysis*

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.



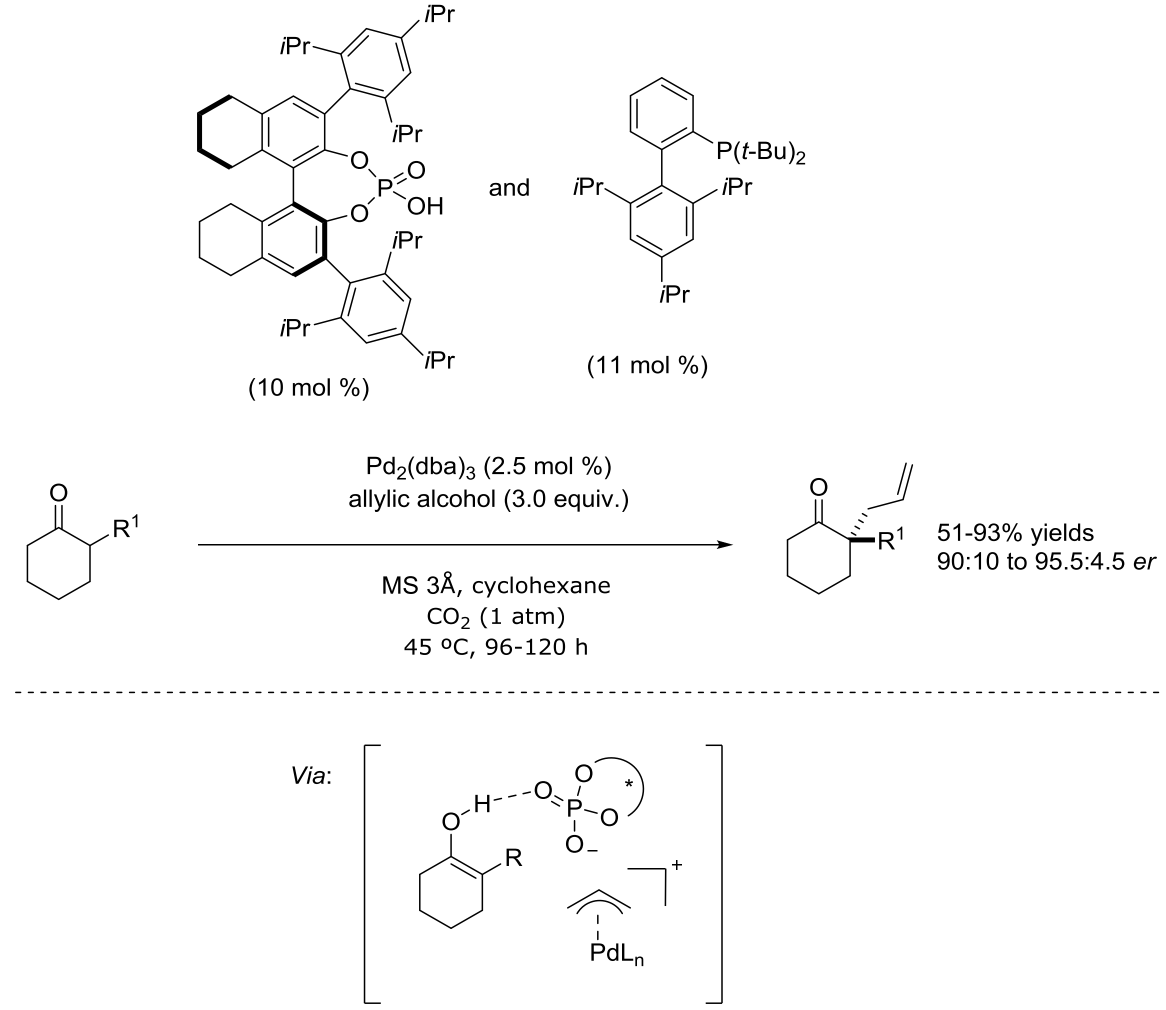
Scheme 13. Phosphoric acid catalysed addition of α-branched ketones to enones.

---

[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.


iPr
iPr
iPr
O
P
O
OH
O
iPr
iPr
iPr
(10 mol %)
and
P(t-Bu)2
iPr
iPr
iPr
(11 mol %)
O
R1
Pd2(dba)3 (2.5 mol %)
allylic alcohol (3.0 equiv.)
MS 3Å, cyclohexane
CO2 (1 atm)
45 °C, 96-120 h
O
R1
51-93% yields
90:10 to 95.5:4.5 er
Via:
O
H
O
P
O
O
O−
*
R
+
PdLn

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 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]

---

[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.

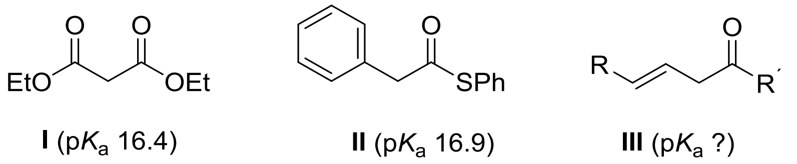


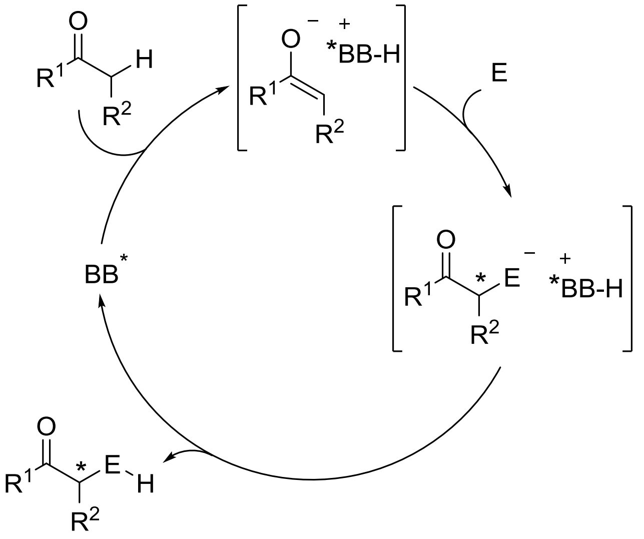
Figure 9. pK_a values of the α-protons of some pronucleophiles on DMSO.

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).

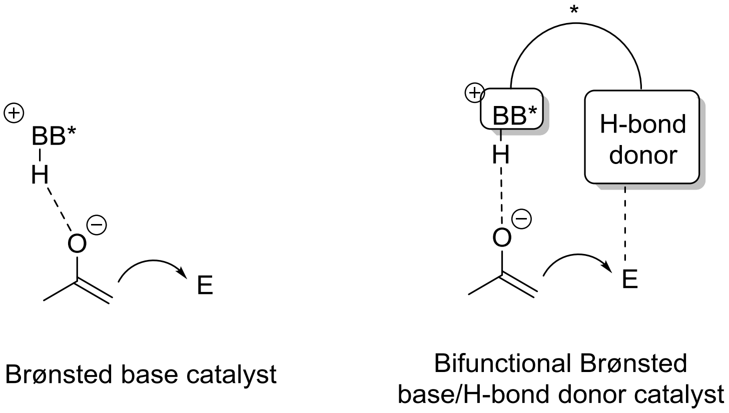


Figure 10. Transition states of Brønsted base catalysts vs. bifunctional Brønsted base/H-bond donor catalysts.

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).

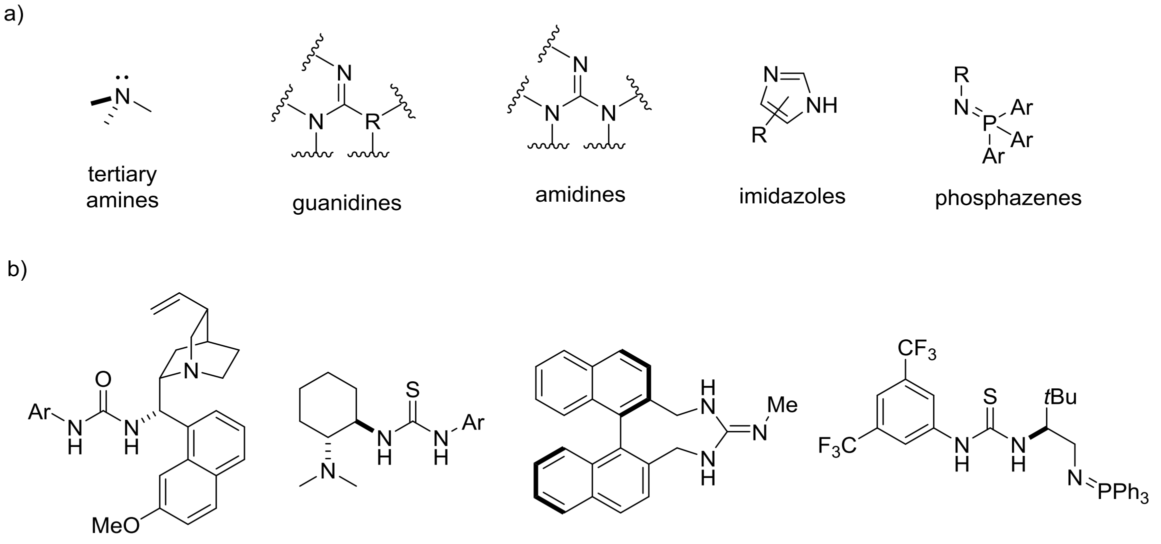


Figure 11. a) Basic moieties in chiral Brønsted base catalysts. b) Some representative chiral Brønsted base catalysts.

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 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.

---

[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.

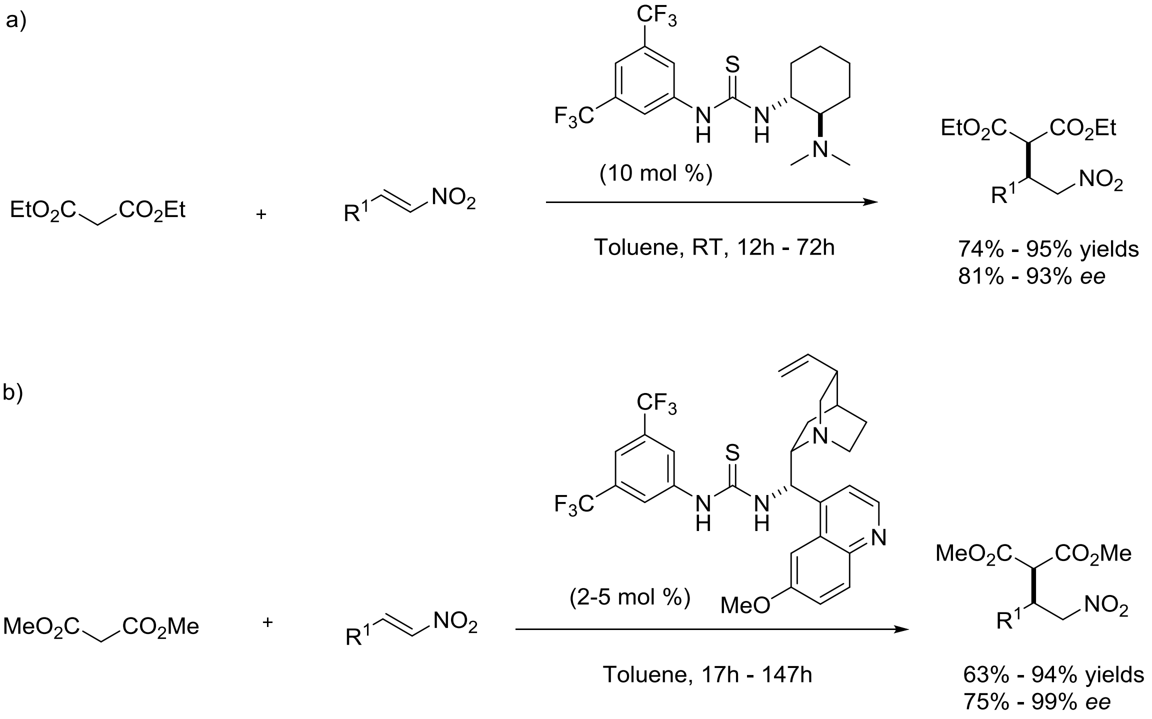
[47] For general reviews on cinchona alkaloids in asymmetric organocatalysis, see: a) Marcelli, T; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496−7504. b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229−1279. c) Yeobah, E. M. O.; Yeobah, S. O.; Singh, G. S. *Tetrahedron* **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.



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 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]

---

[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.

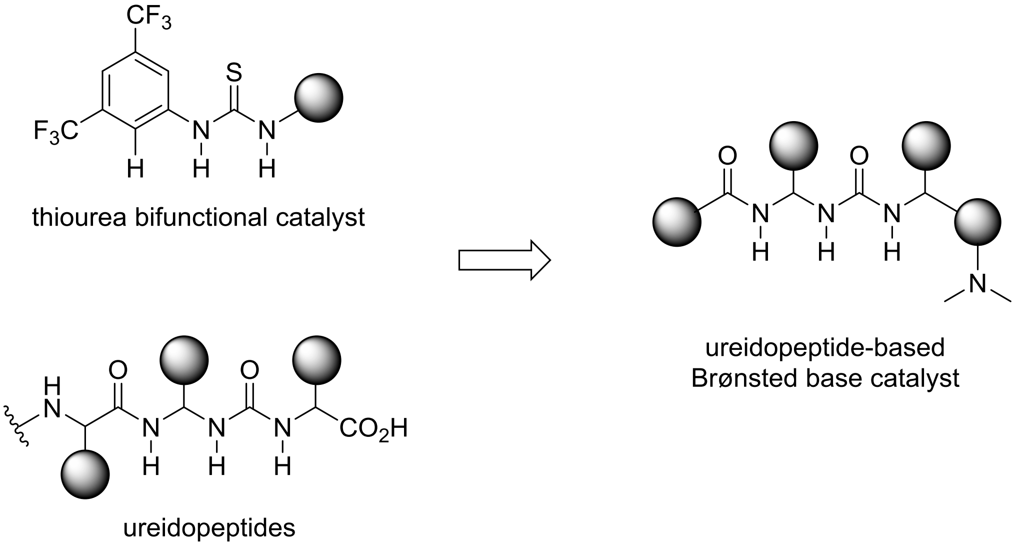


Figure 12. Desing of ureidopeptide-based Brønsted base catalysts.

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

---

[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.

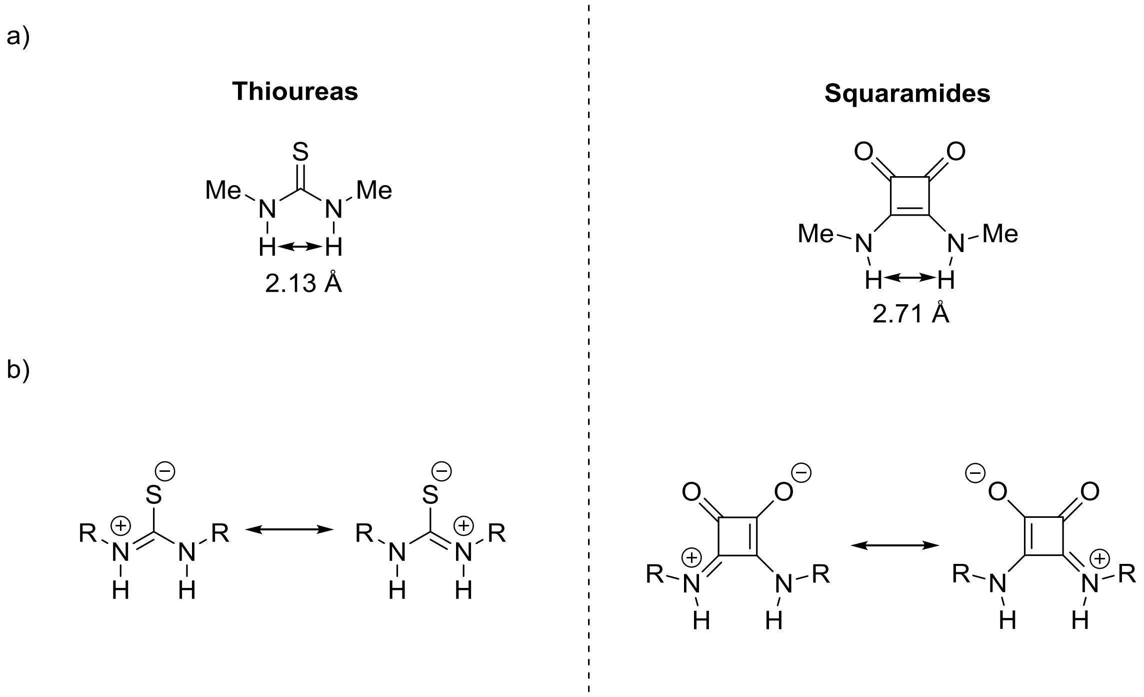
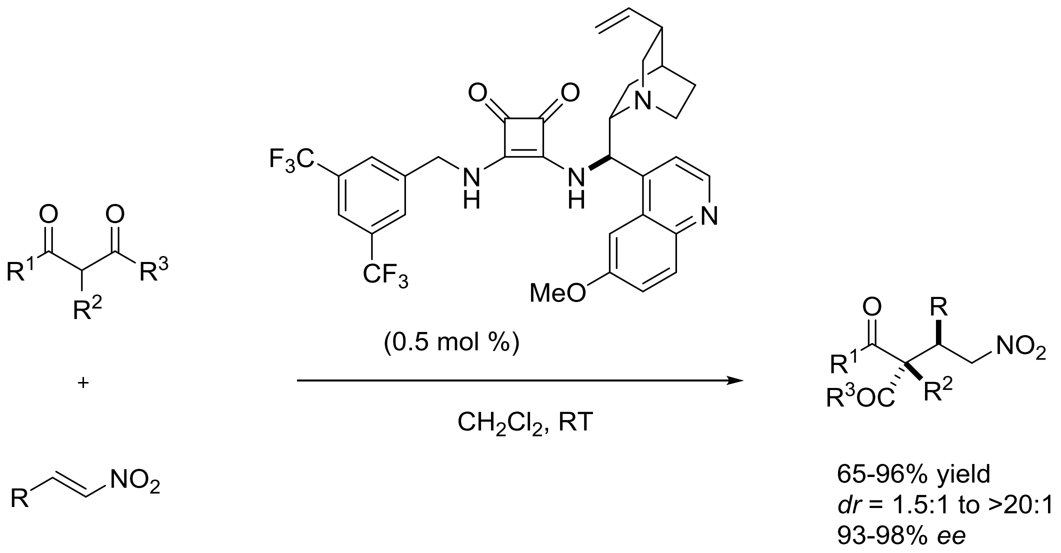


Figure 13. N−H group distance and lone pair delocalization in thioureas and squaramides.

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.

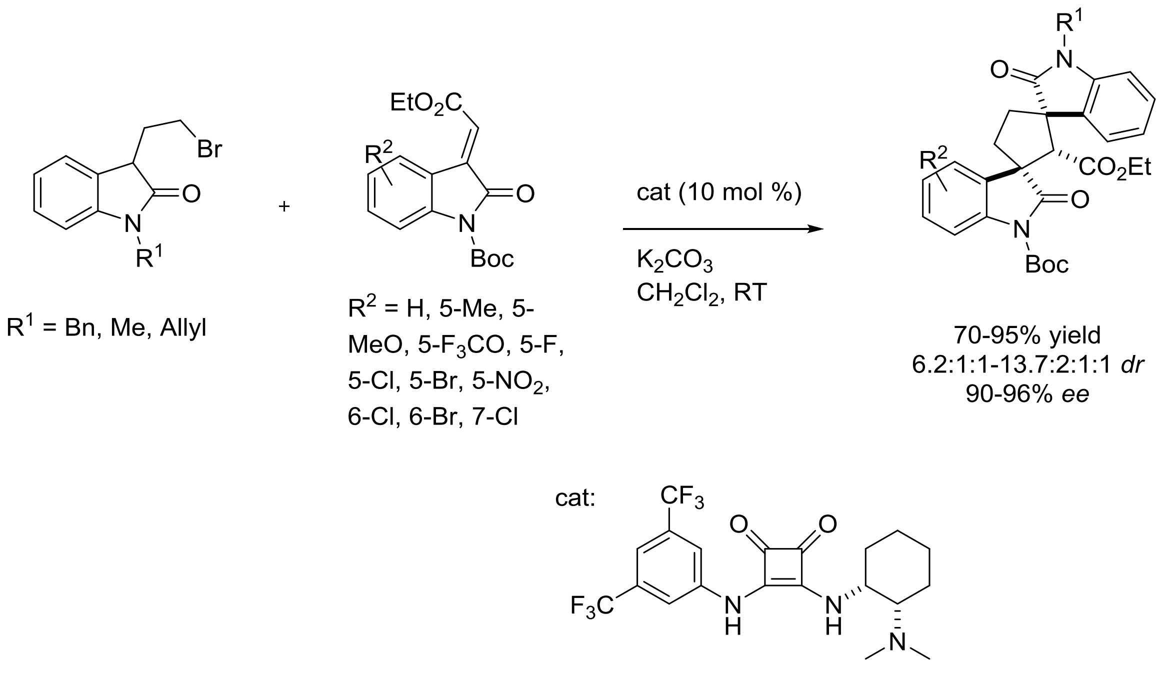
After Rawal´s pioneering work, many new squaramide catalysts were employed in different reactions.[61] These catalysts demonstrated to be efficient in many domino and tandem processes[62] where more complex molecules can be synthesized. Example of this is the Michael addition/alkylation sequence of 3-substituted 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.


Br
N
R1
O
+
EtO2C
R2
N
Boc
O
cat (10 mol %)
K2CO3
CH2Cl2, RT
R1
O
N
R2
CO2Et
O
N
Boc
R1 = Bn, Me, Allyl
R2 = H, 5-Me, 5-MeO, 5-F3CO, 5-F, 5-Cl, 5-Br, 5-NO2, 6-Cl, 6-Br, 7-Cl
70-95% yield
6.2:1:1-13.7:2:1:1 dr
90-96% ee
cat:
CF3
F3C
O
O
N
H
N
H
N

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.

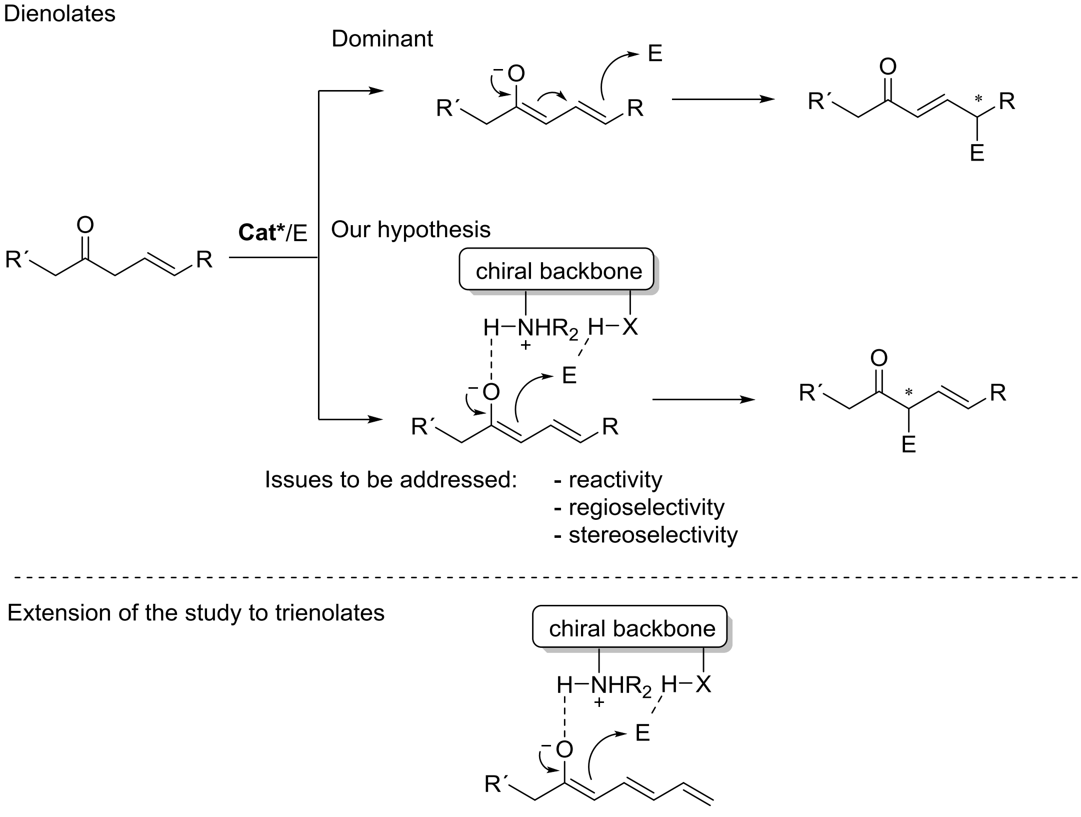
---

[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.

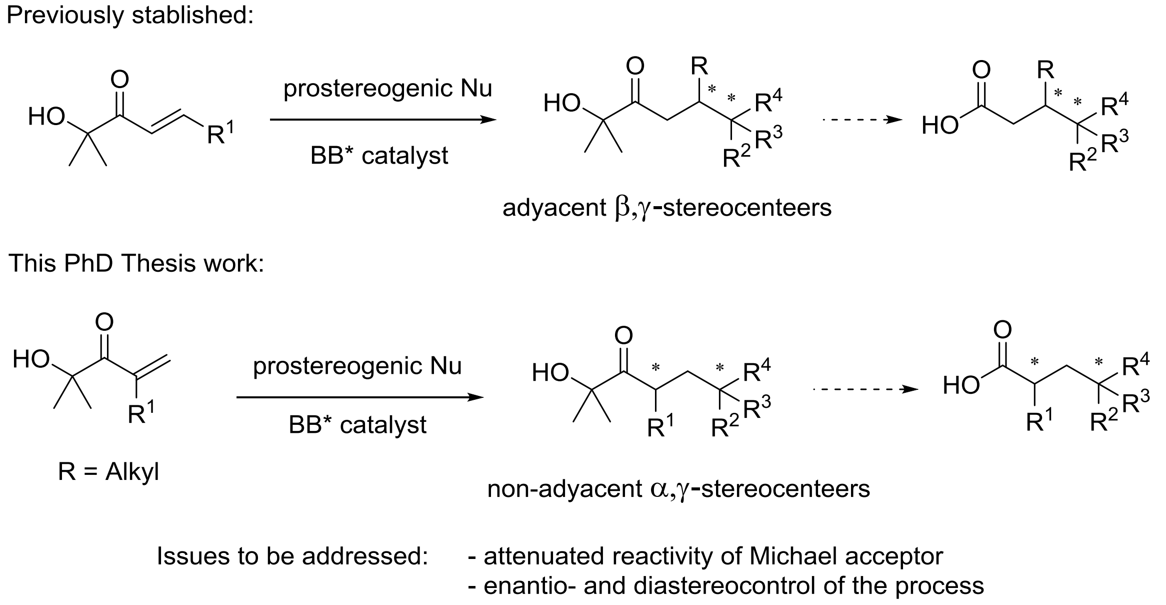
While di- and trienamine mediated catalysis is well studied in the recent years, the chemistry of transiently generated di- and trienolates remains poorly explored. The majority of catalytic reactions involving dienamines proceed through the γ-carbon atom of the unsaturated carbonyl substrate, and the 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.


Dienolates
Dominant
Cat*/E
Our hypothesis
chiral backbone
H−NHR2 H−X
E
R´
R
O
Issues to be addressed:
- reactivity
- regioselectivity
- stereoselectivity
Extension of the study to trienolates

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).

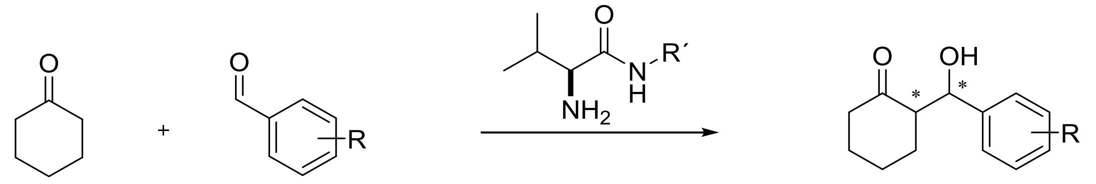

Previously stablished:
HO
O
R1
prostereogenic Nu
BB* catalyst
HO
O
R
*
*
R4
R3
R2
HO
O
R
*
*
R4
R3
R2
adyacent β,γ-stereocenteers
This PhD Thesis work:
HO
O
R1
R = Alkyl
prostereogenic Nu
BB* catalyst
HO
O
*
*
R4
R1
R2
R3
HO
O
*
*
R4
R1
R2
R3
non-adyacent α,γ-stereocenteers
Issues to be addressed:
- attenuated reactivity of Michael acceptor
- enantio- and diastereocontrol of the process

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

---

[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.



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

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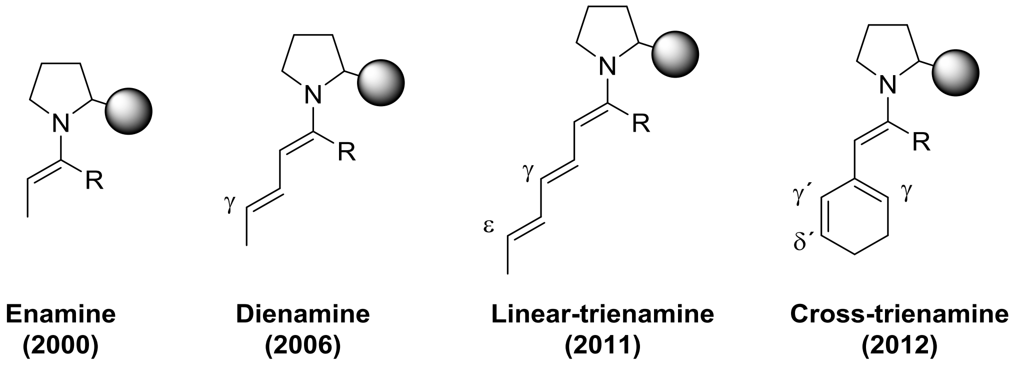
2. Controlling the α/γ/ε-Reactivity of Transiently Generated Di- and Trienolates in Organocatalytic Enantioselective Michael Reactions

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.



Enamine (2000) **Dienamine (2006)** **Linear-trienamine (2011)** **Cross-trienamine (2012)**

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]

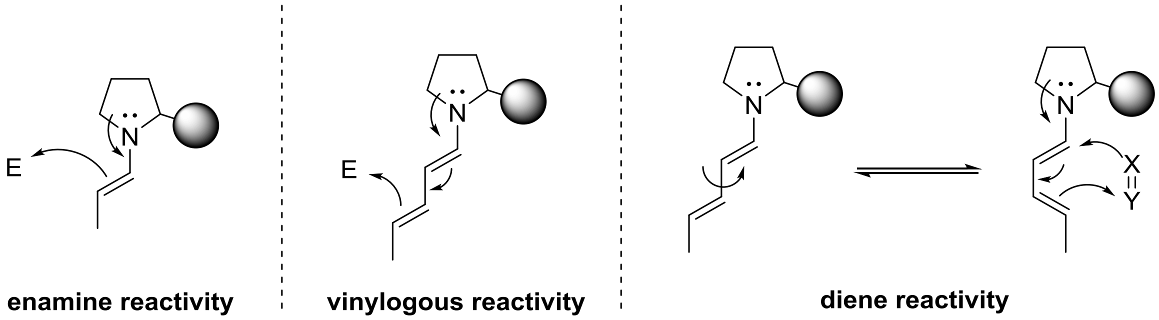


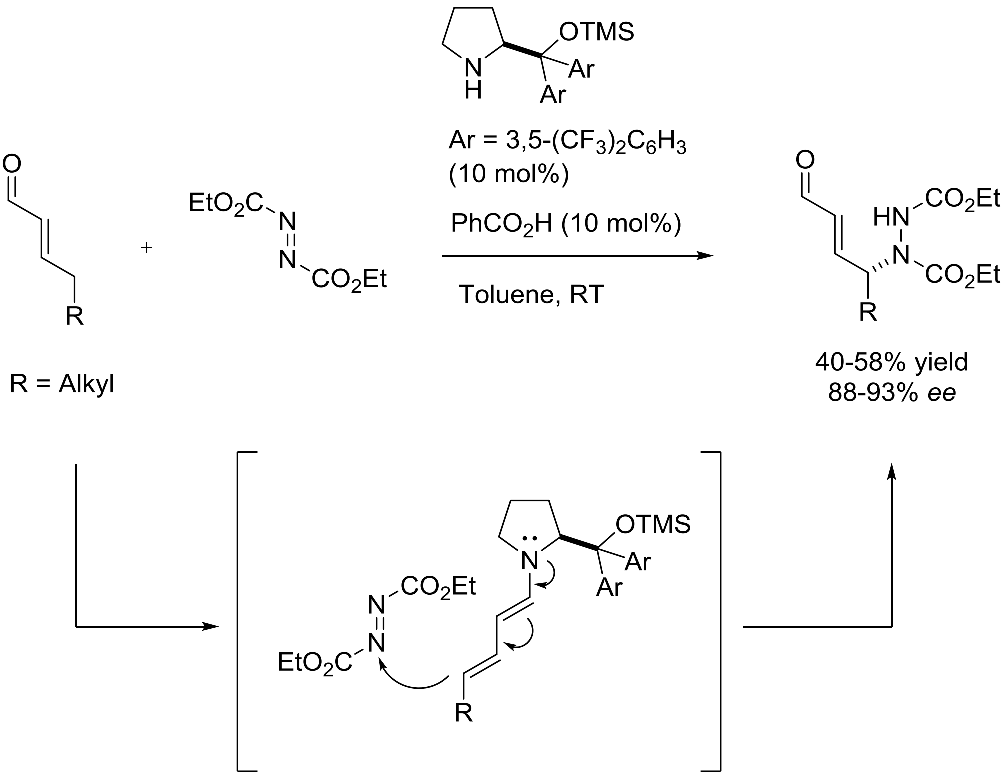
Figure 15. Reactivity modes of dienamines.

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.



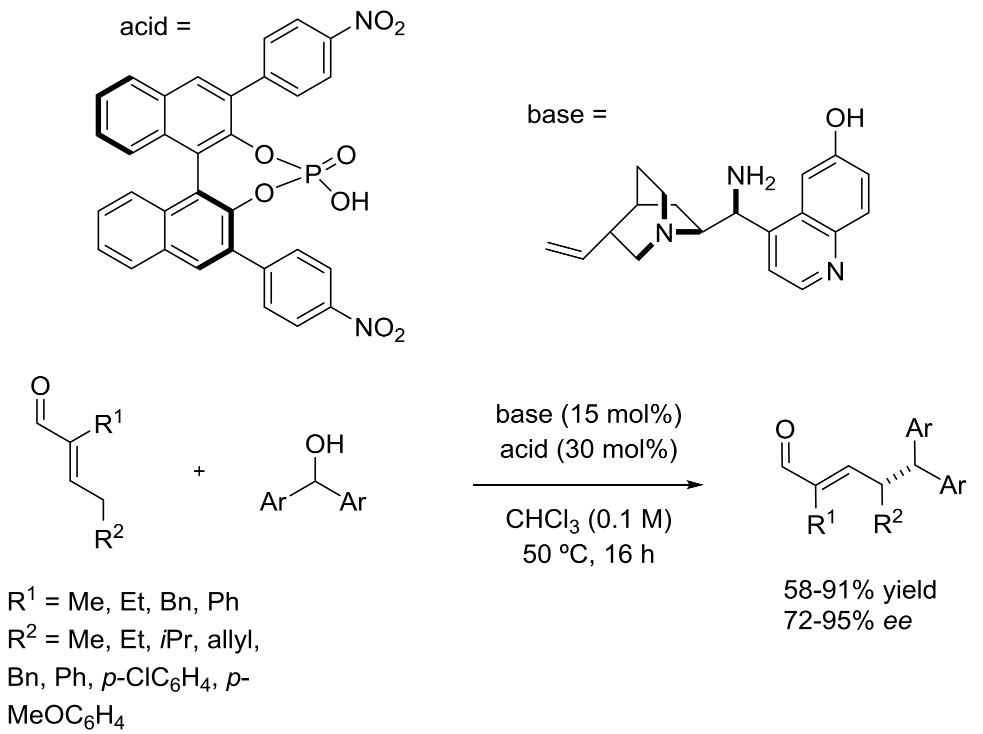
OTMS
N
H
Ar
Ar
Ar = 3,5-(CF3)2C6H3
(10 mol%)
PhCO2H (10 mol%)
Toluene, RT
O
R
R = Alkyl
+
EtO2C
N
N
CO2Et
HN
CO2Et
40-58% yield
88-93% ee

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.

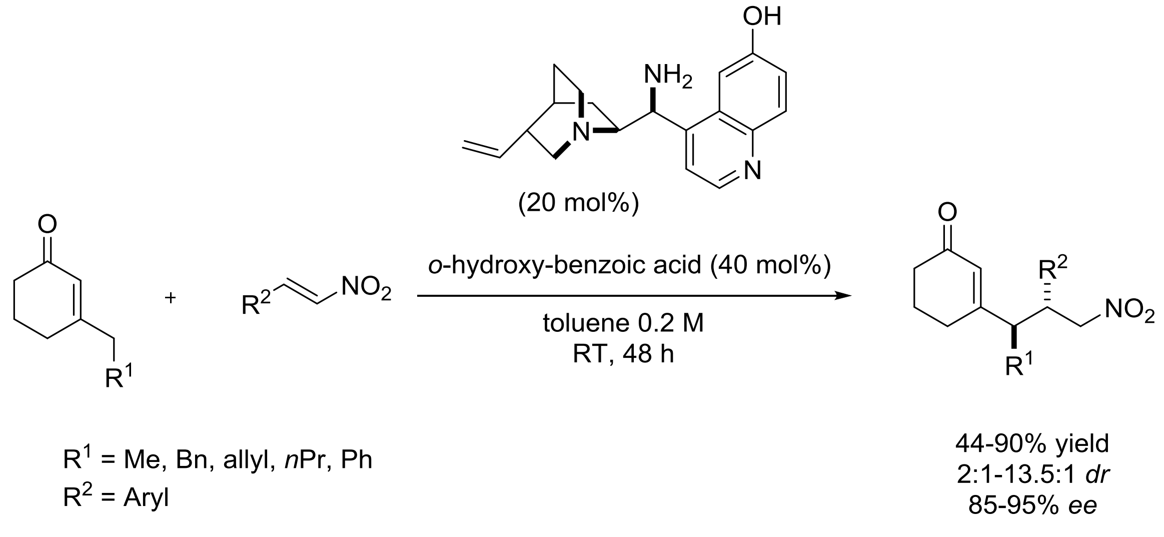

acid =
NO2
O
P
O
OH
NO2
base =
OH
NH2
N
N
O
R1
R2
+
OH
Ar
Ar
base (15 mol%)
acid (30 mol%)
CHCl3 (0.1 M)
50 °C, 16 h
O
Ar
Ar
R1
R2

R^1 = Me, Et, Bn, Ph
R^2 = Me, Et, *i*Pr, allyl, Bn, Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$

58-91% yield
72-95% *ee*

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.


OH
NH2
N
N
(20 mol%)
O
R1
+
R2
NO2
o-hydroxy-benzoic acid (40 mol%)
toluene 0.2 M
RT, 48 h
O
R2
NO2
R1

R^1 = Me, Bn, allyl, *n*Pr, Ph
R^2 = Aryl

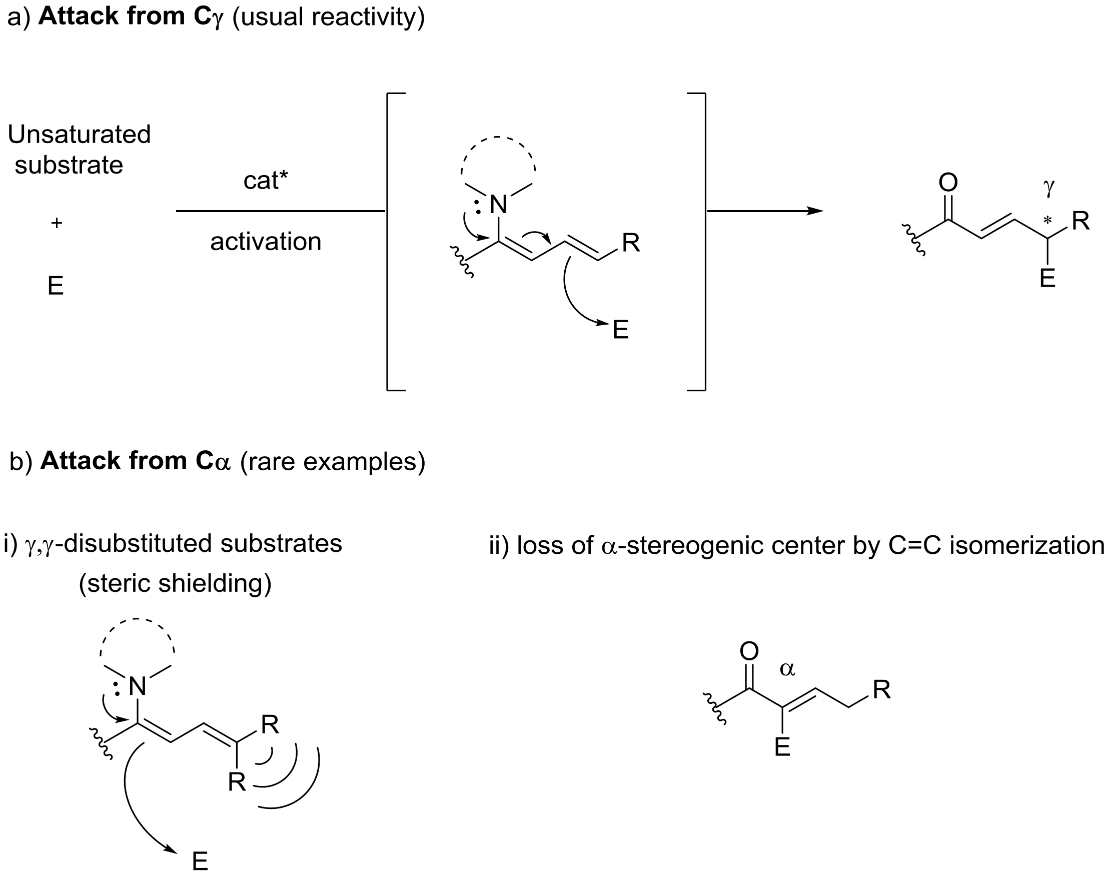
44-90% yield
2:1-13.5:1 *dr*
85-95% *ee*

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).


a) **Attack from Cγ** (usual reactivity)

b) **Attack from Cα** (rare examples)

i) γ,γ-disubstituted substrates (steric shielding)

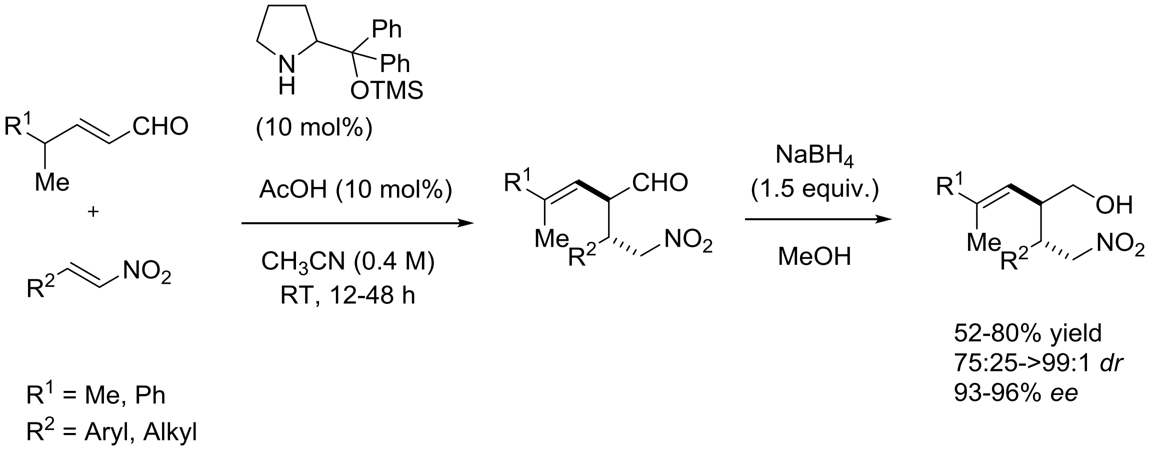
ii) loss of α-stereogenic center by C=C isomerization

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

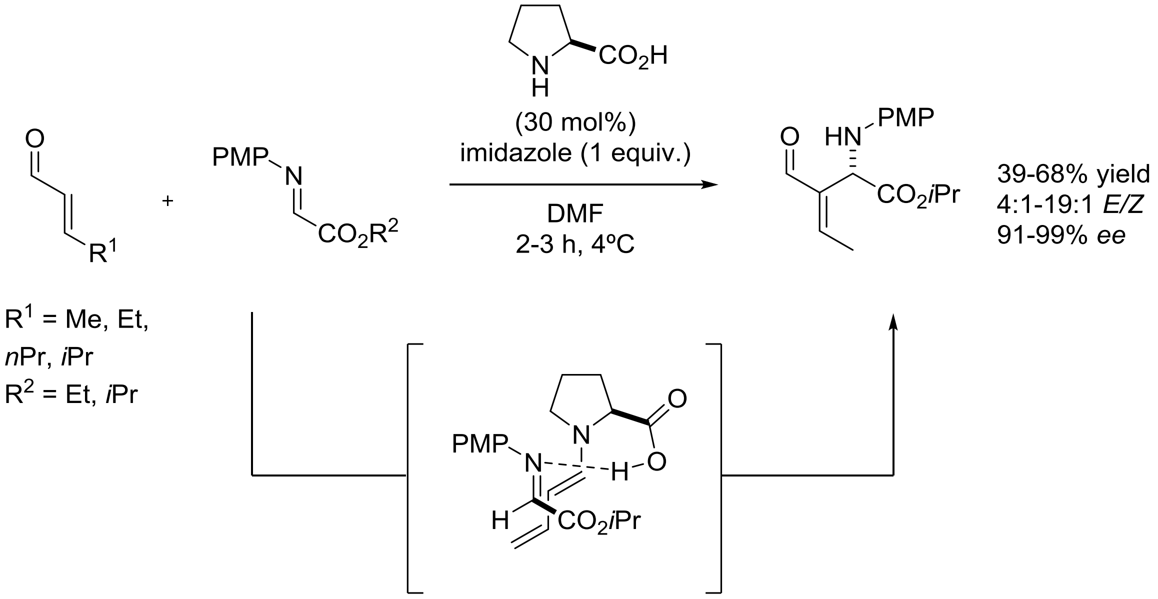
---

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


Ph
Ph
N
H
OTMS
(10 mol%)
AcOH (10 mol%)
CH3CN (0.4 M)
RT, 12-48 h
R1
CHO
Me
+
R2
NO2
NaBH4
(1.5 equiv.)
MeOH
OH
52-80% yield
75:25->99:1 dr
93-96% ee
R1 = Me, Ph
R2 = Aryl, Alkyl

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.


N
H
CO2H
(30 mol%)
imidazole (1 equiv.)
DMF
2-3 h, 4°C
O
R1
+
PMP
N
CO2R2
O
HN
PMP
CO2iPr
39-68% yield
4:1-19:1 E/Z
91-99% ee
R1 = Me, Et,
nPr, iPr
R2 = Et, iPr
PMP
N
H
O
O
H
CO2iPr

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

---

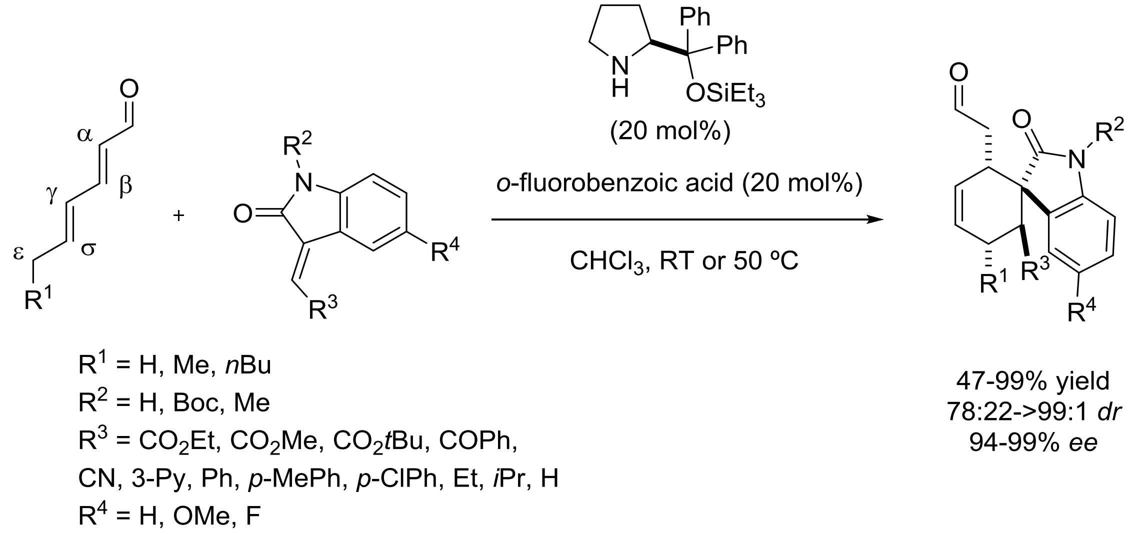
[73] Utsumi, N.; Zhang, H.; Tanaka, F. Barbas III, C. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1878–1880.

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).



R^1 = H, Me, *n*Bu
R^2 = H, Boc, Me
R^3 = CO_2Et, CO_2Me, CO_2tBu, COPh, CN, 3-Py, Ph, *p*-MePh, *p*-ClPh, Et, *i*Pr, H
R^4 = H, OMe, F

47-99% yield
78:22->99:1 *dr*
94-99% *ee*

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

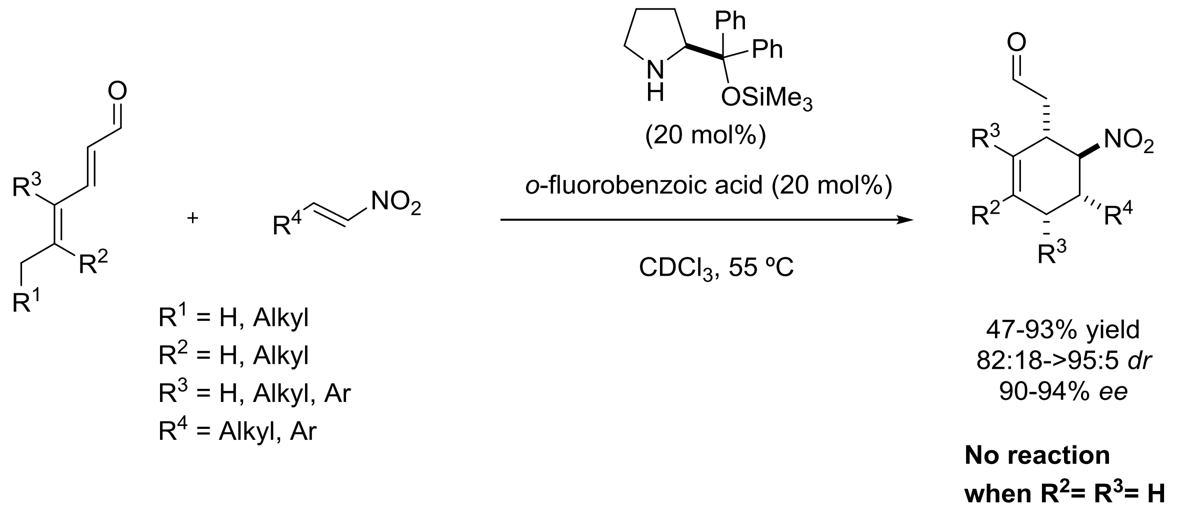
Soon after, Chen and co-workers further extended the scope of trienamine catalysis for asymmetric Diels-Alder reactions with nitroalkenes as dienophiles for the first time.[76] Interestingly, the introduction of electron-donating alkyl substituents at C4 and C5 positions of the 2,4-dienals was found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

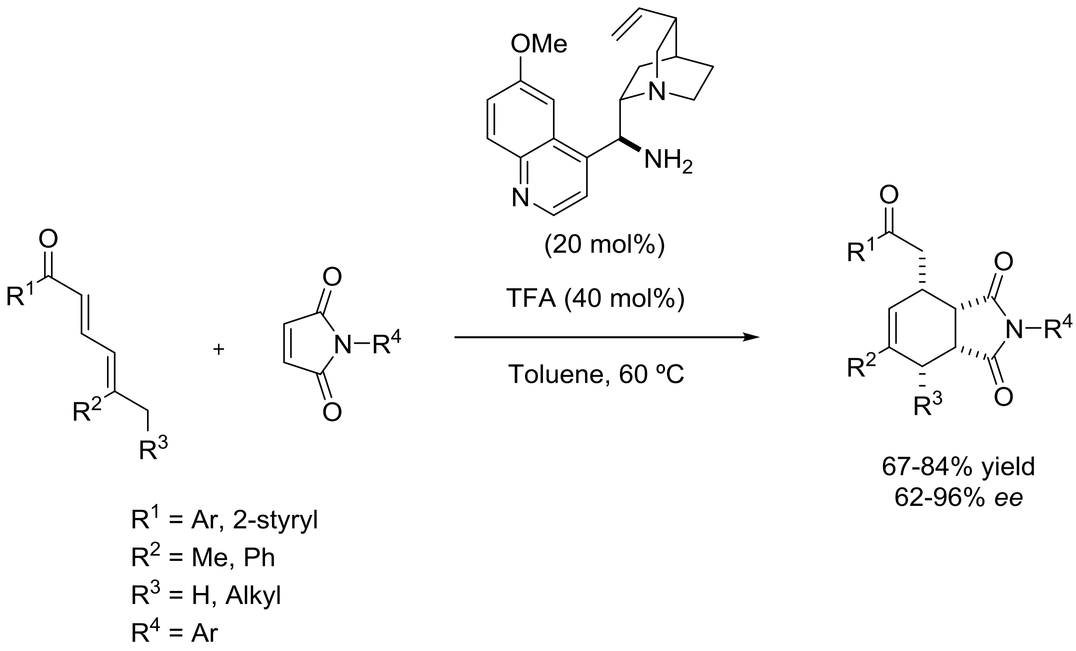

(20 mol%)
o-fluorobenzoic acid (20 mol%)
CDCl3, 55 ºC
R1 = H, Alkyl
R2 = H, Alkyl
R3 = H, Alkyl, Ar
R4 = Alkyl, Ar
47-93% yield
82:18->95:5 dr
90-94% ee
No reaction
when R2= R3= H

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.


OMe
NH2
N
(20 mol%)
TFA (40 mol%)
Toluene, 60 ºC
O
R1
R2
R3
+
N–R4
67-84% yield
62-96% ee
R1 = Ar, 2-styryl
R2 = Me, Ph
R3 = H, Alkyl
R4 = Ar

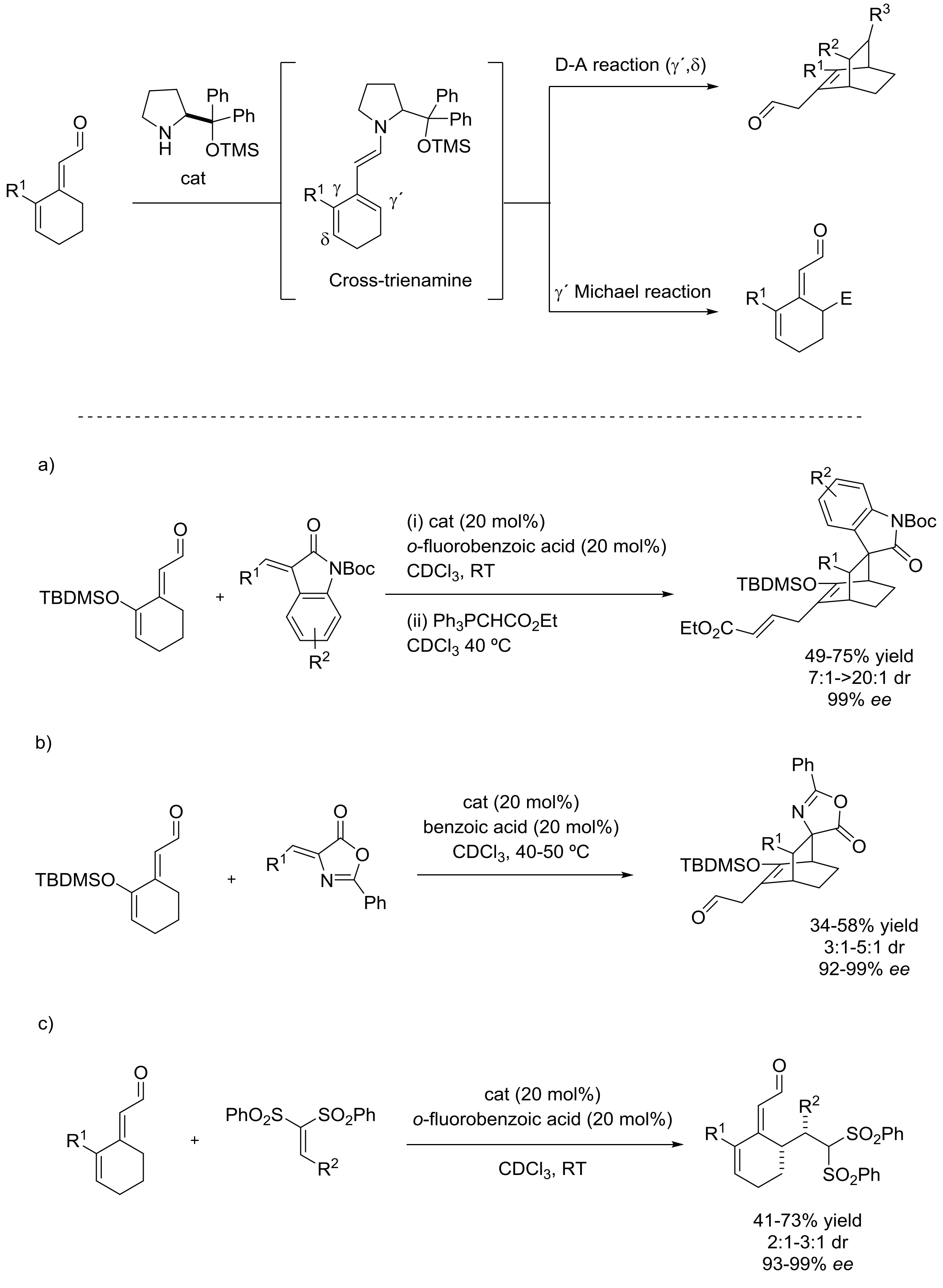
Scheme 30. Diels–Alder cycloaddition of δ,δ-disubstituted 2,4-dienones via trienamine catalysis.

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.


cat
D-A reaction (γ´,δ)
γ´ Michael reaction
Cross-trienamine
a)
(i) cat (20 mol%)
o-fluorobenzoic acid (20 mol%)
CDCl3, RT
(ii) Ph3PCHCO2Et
CDCl3 40 ºC
49-75% yield
7:1->20:1 dr
99% ee
b)
cat (20 mol%)
benzoic acid (20 mol%)
CDCl3, 40-50 ºC
34-58% yield
3:1-5:1 dr
92-99% ee
c)
cat (20 mol%)
o-fluorobenzoic acid (20 mol%)
CDCl3, RT
41-73% yield
2:1-3:1 dr
93-99% ee

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

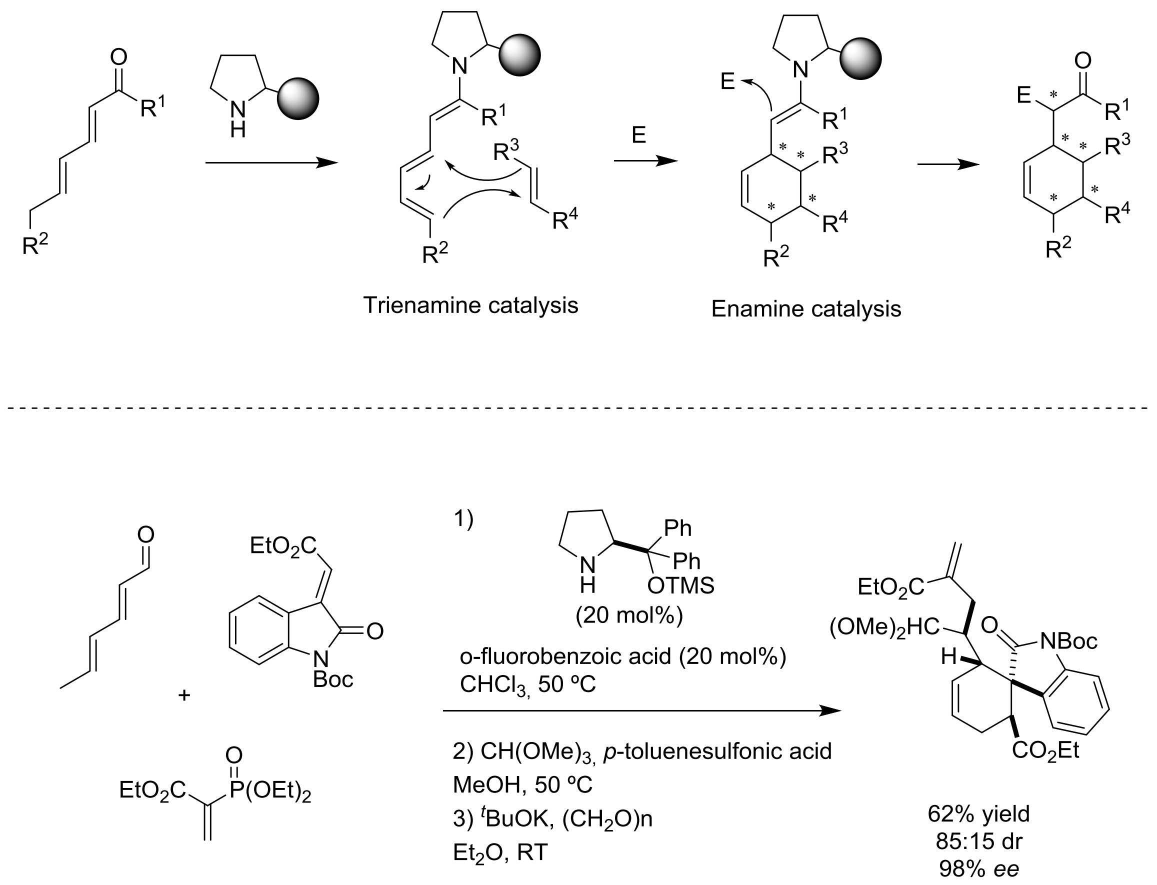
Although generally the concept of trienamine catalysis has been applied in the context of the Diels−Alder reaction, cross-conjugated trienamines may also react through Michael type addition selectively at the γ´-position. Thus, reaction of cyclic 2,4-dienals with vinyl bis-sulfones proceed through the 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.


O
R1
N
H
R2
N
R1
R3
R4
R2
Trienamine catalysis
E
E
N
R1
R3
R4
R2
Enamine catalysis
E
O
R1
R3
R4
R2
O
EtO2C
N
Boc
O
+
O
EtO2C
P(OEt)2
1)
N
H
Ph
Ph
OTMS
(20 mol%)
o-fluorobenzoic acid (20 mol%)
CHCl3, 50 ºC
2) CH(OMe)3, p-toluenesulfonic acid
MeOH, 50 ºC
3) tBuOK, (CH2O)n
Et2O, RT
EtO2C
(OMe)2HC
H
O
NBoc
CO2Et
62% yield
85:15 dr
98% ee

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.

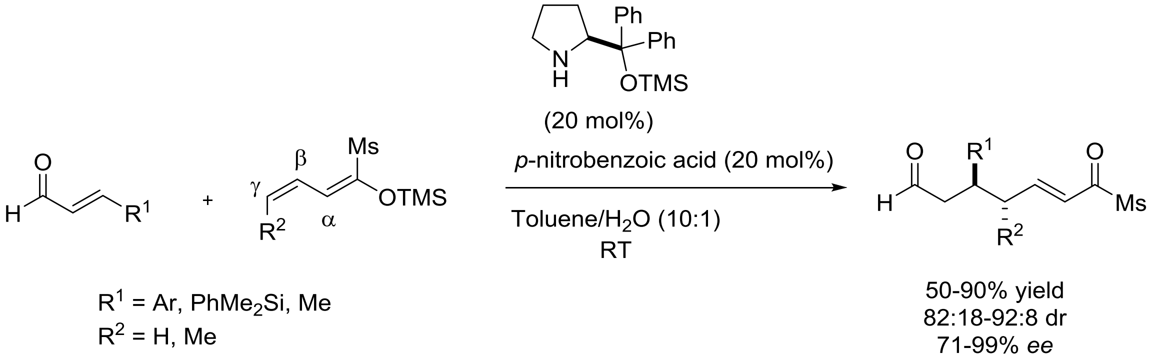
2.1.2.1. *Dienolate mediated catalysis*

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.

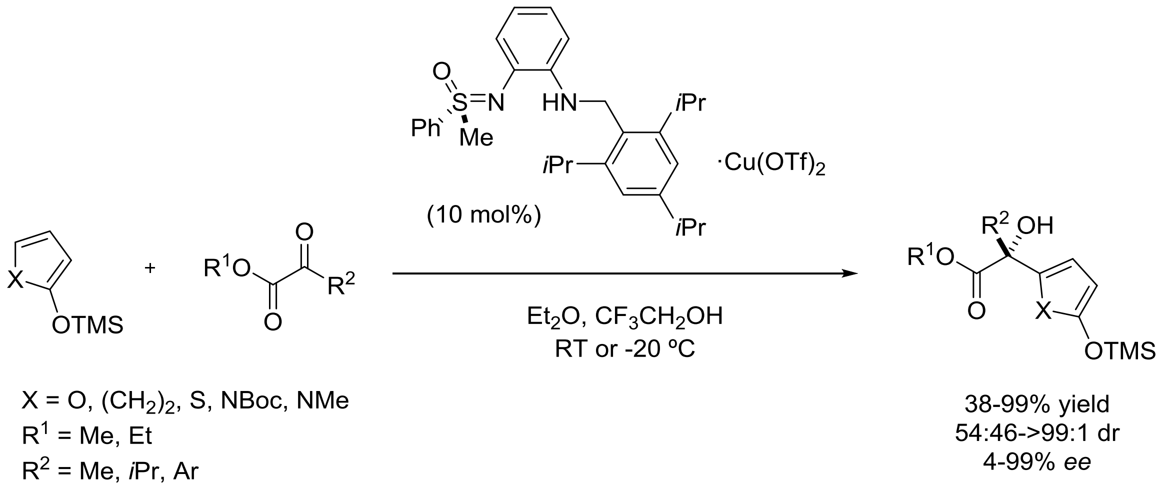
Bolm and co-workers developed a vinylogous Mukaiyama aldol reaction between heterocyclic dienoxy silanes and α-keto esters catalysed by an amino sulfoximine copper complex. The γ-selective reaction leads to adducts bearing a quaternary stereogenic center (Scheme 34).[82]

---

[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.

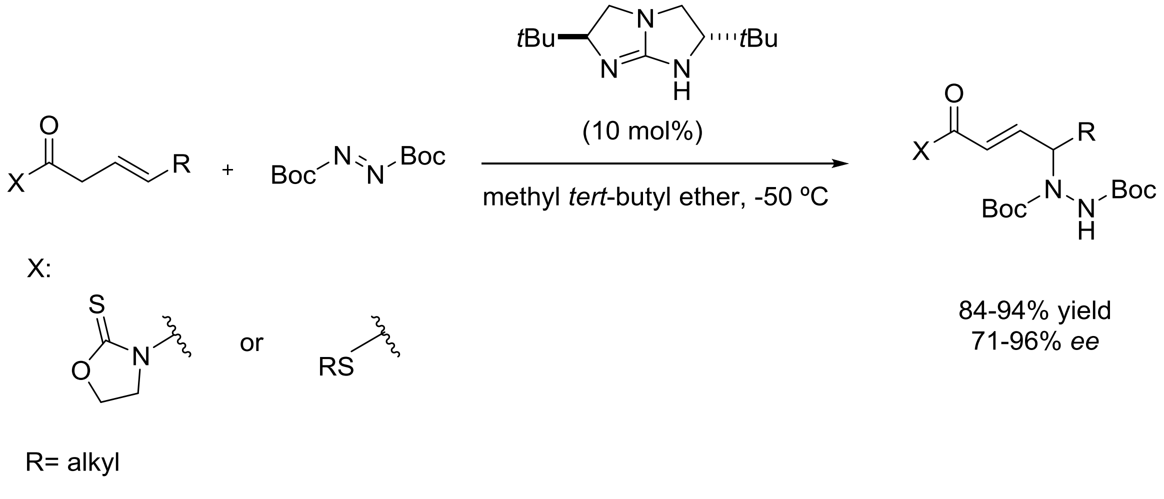
[81] Gupta, V.; Sudhir, A. V.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 12609−12612.

[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.


(10 mol%)
·Cu(OTf)2
Et2O, CF3CH2OH
RT or -20 ºC
X = O, (CH2)2, S, NBoc, NMe
R1 = Me, Et
R2 = Me, iPr, Ar
38-99% yield
54:46->99:1 dr
4-99% ee

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]


(10 mol%)
methyl tert-butyl ether, -50 ºC
X:
or
R= alkyl
84-94% yield
71-96% ee

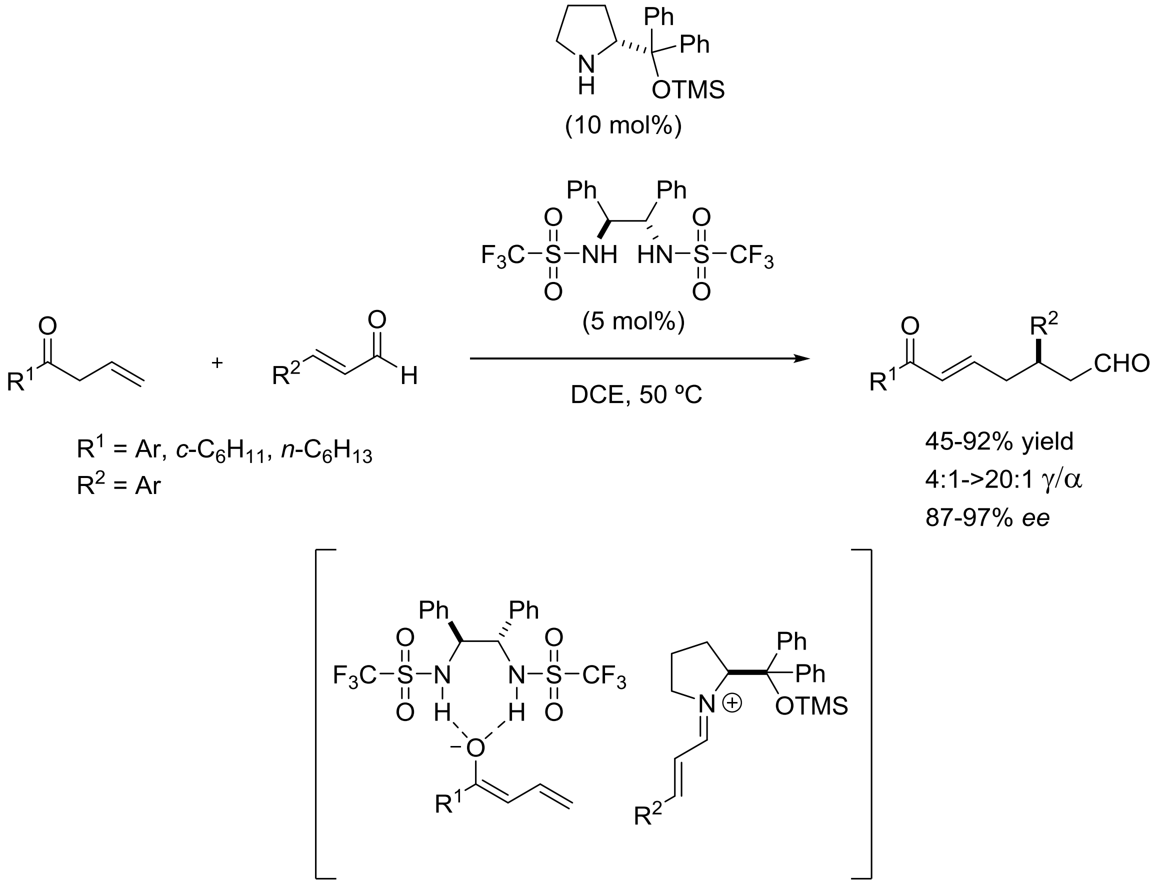
Scheme 35. γ-Selective asymmetric functionalization of β,γ-unsaturated thioesters and activated amides.

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

---

[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.

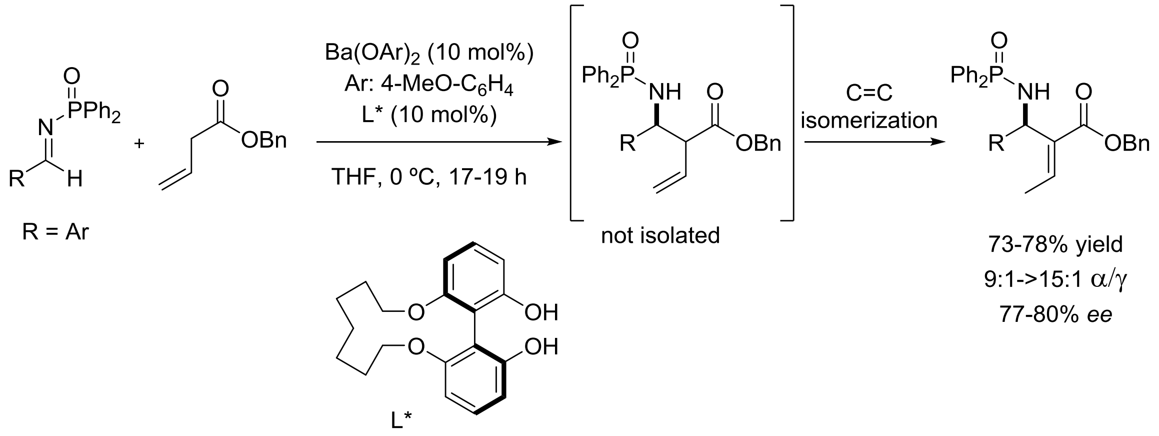

Ph
Ph
N
H
OTMS
(10 mol%)
Ph
Ph
O
O
F3C-S-NH
HN-S-CF3
O
O
(5 mol%)
DCE, 50 ºC
O
R1
+
R2
O
H
R1 = Ar, c-C6H11, n-C6H13
R2 = Ar
O
R1
R2
CHO
45-92% yield
4:1->20:1 γ/α
87-97% ee
F3C-S-N
N-S-CF3
H
H
-O
R1
N⊕
OTMS
R2

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).

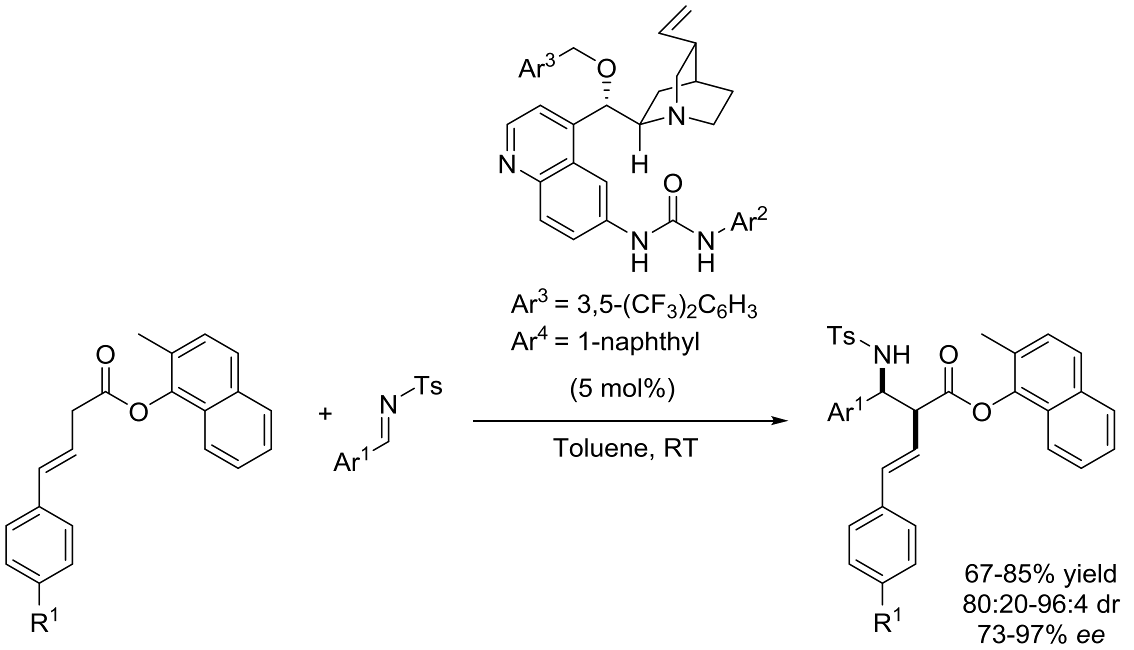
---

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


Ba(OAr)2 (10 mol%)
Ar: 4-MeO-C6H4
L* (10 mol%)
THF, 0 ºC, 17-19 h
R = Ar
not isolated
C=C isomerization
73-78% yield
9:1->15:1 α/γ
77-80% ee
L*

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]

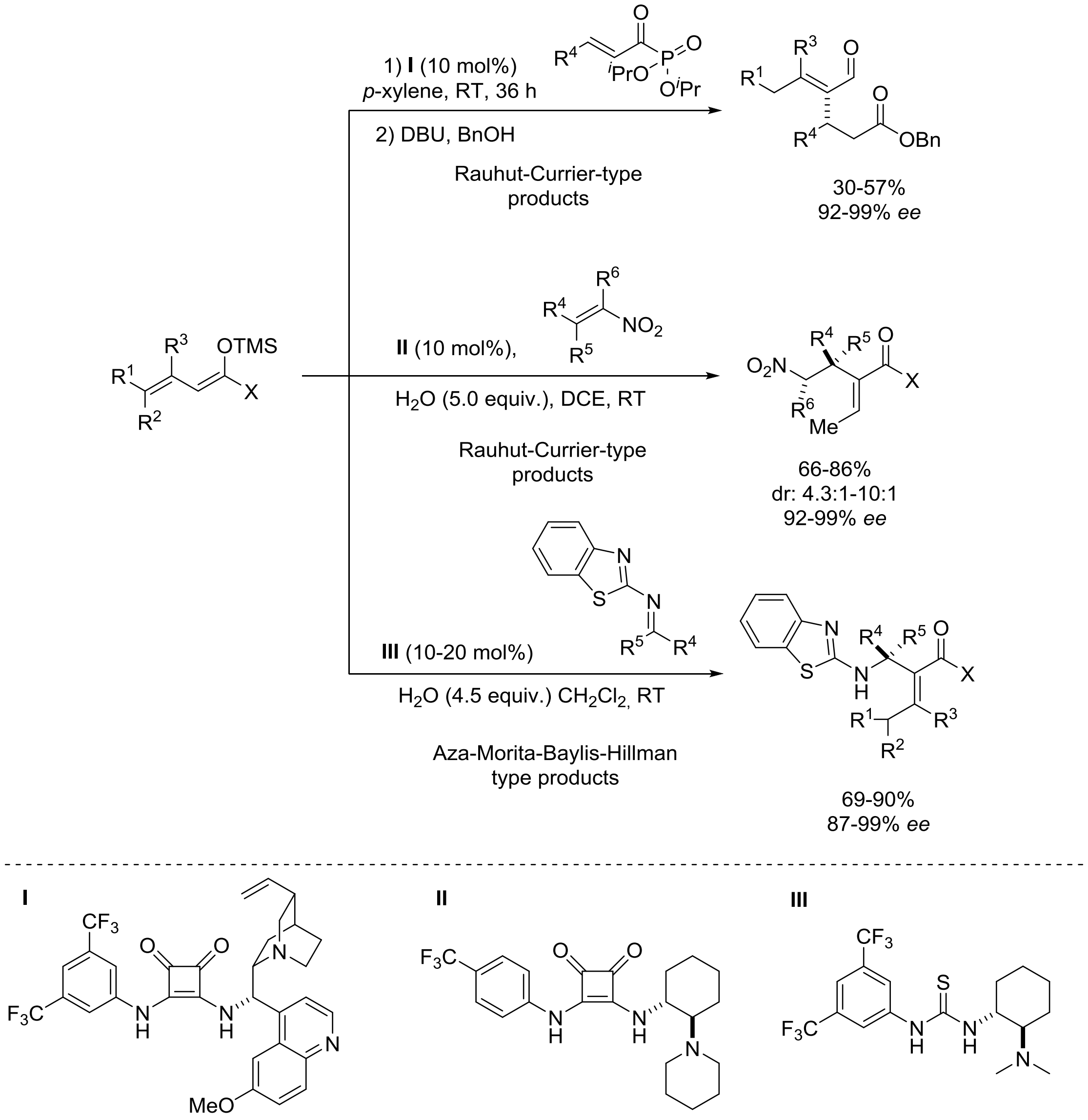

Ar3 = 3,5-(CF3)2C6H3
Ar4 = 1-naphthyl
(5 mol%)
Toluene, RT
67-85% yield
80:20-96:4 dr
73-97% ee

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]

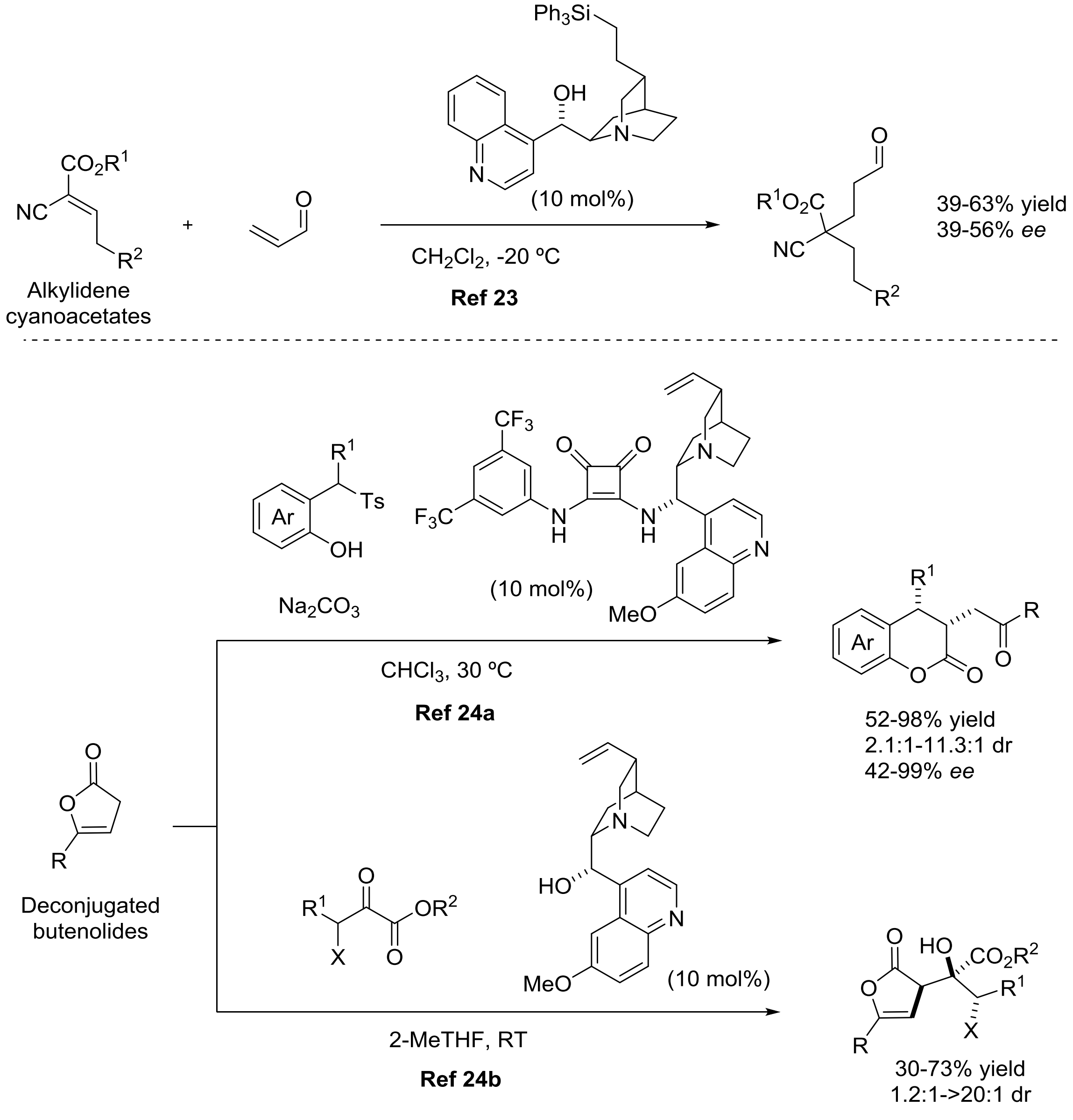

1) I (10 mol%)
p-xylene, RT, 36 h
2) DBU, BnOH
Rauhut-Currier-type products
30-57%
92-99% ee
II (10 mol%),
H2O (5.0 equiv.), DCE, RT
Rauhut-Currier-type products
66-86%
dr: 4.3:1-10:1
92-99% ee
III (10-20 mol%)
H2O (4.5 equiv.) CH2Cl2, RT
Aza-Morita-Baylis-Hillman type products
69-90%
87-99% ee
OTMS
X
OBn
I
II
III

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]


Ph3Si
OH
N
(10 mol%)
CO2R1
NC
R2
Alkylidene cyanoacetates
+
O
CH2Cl2, -20 °C
Ref 23
R1O2C
NC
R2
39-63% yield
39-56% ee
CF3
R1
Ts
Ar
OH
F3C
N H
N H
O
O
N
MeO
Na2CO3
(10 mol%)
CHCl3, 30 °C
Ref 24a
R1
Ar
O
O
R
O
52-98% yield
2.1:1-11.3:1 dr
42-99% ee
O
R
Deconjugated butenolides
R1
O
OR2
X
O
HO
N
MeO
(10 mol%)
2-MeTHF, RT
Ref 24b
HO
CO2R2
R1
X
R
30-73% yield
1.2:1->20:1 dr

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

---

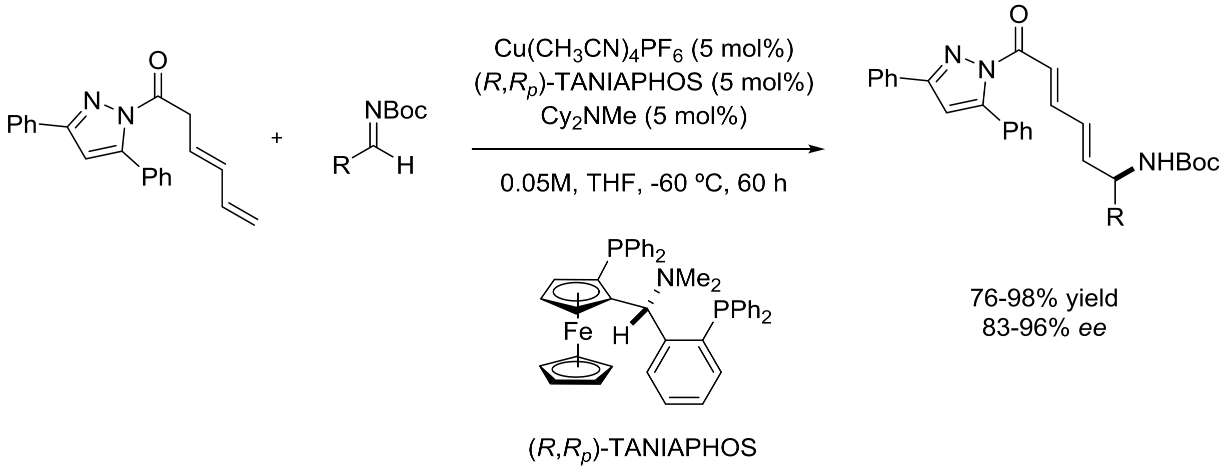
[88] Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407–5410.

[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]


Ph
N
N
O
Ph
+
NBoc
R
H
Cu(CH3CN)4PF6 (5 mol%)
(R,Rp)-TANIAPHOS (5 mol%)
Cy2NMe (5 mol%)
0.05M, THF, -60 °C, 60 h
NHBoc
R
PPh2
NMe2
PPh2
Fe
H
(R,Rp)-TANIAPHOS
76-98% yield
83-96% ee

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

---

[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.

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).

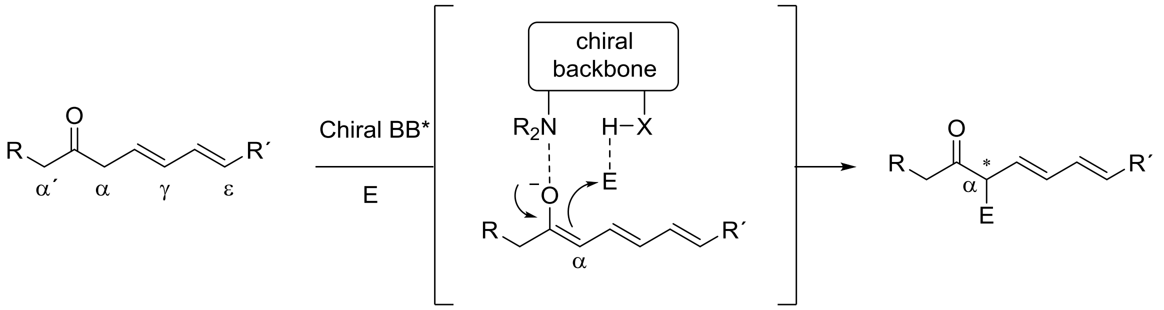


Figure 16. Working hypothesis.

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 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.

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

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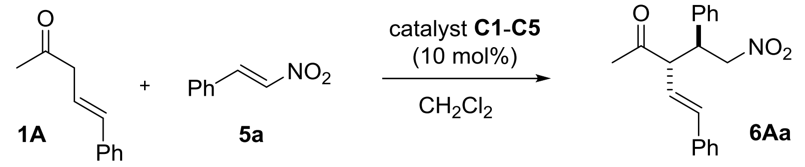
[93] a) McCooey, S. H.; Connon, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367−6370. b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. c) Vakulya, B.; Varga, S; Csampai, A.; Sojs, T. *Org. Lett.* **2005**, *7*, 1967−1969. d) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding,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

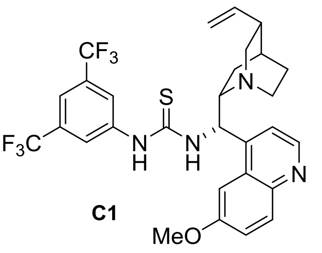
[94] a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. b) Zhu, Y.; Malerich, J. P.; Rawal, V. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 153−156.

[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.

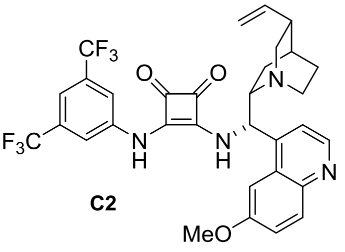
Table 1. Catalyst screening for the reaction of **1A** with **5a** to give **6Aa**.[a]





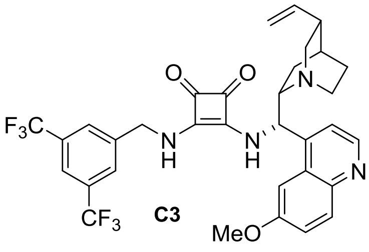
C1

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*



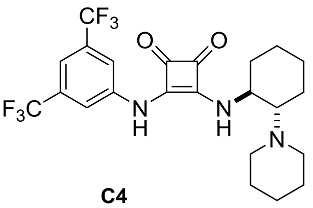
C2

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



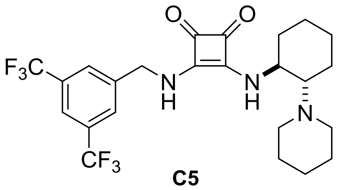
C3

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



C4

16 h, 0 ºC, 1.2:1; 97% *ee*



C5

20 h, 0 ºC, 6.4:1; 96% *ee*

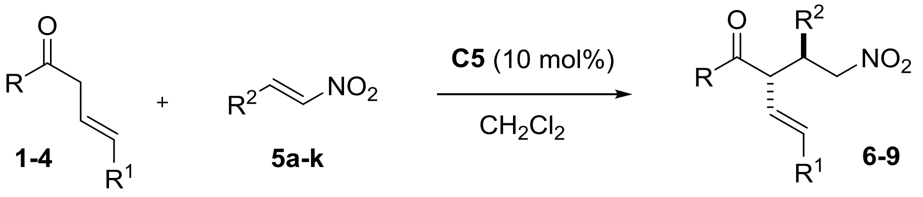
[a]Reactions carried out on 0.2 mmol scale, with **1A** (1.5 equiv.), **5a** (1 equiv.) and catalyst (10 mol%) in CH_2Cl_2. Diastereomeric ratio and *ee* values determined by HPLC analysis of crude material on a chiral stationary phase. *ee* values correspond to the major diastereomers.

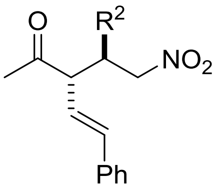
Once the reaction conditions had been optimized for the model reaction, various β,γ-unsaturated ketones and nitroolefins were examined. The reaction tolerates both aliphatic and aromatic β,γ-unsaturated ketones (**1**-**4**) and nitroolefins with either electron-rich, electron-neutral, or electron-poor 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 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.

---

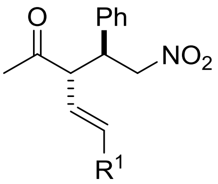
[97] Separation of diastereomers, while not systematic, was posible by column chromatography in some instances. See the experimental section for details.

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

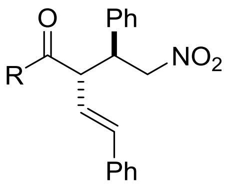




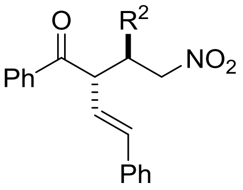
6Aa	R^2: Ph	80%, dr 6.4 : 1, 96% *ee* (>99%)
6Ab	R^2: 4-$MeOC_6H_4$	95%, dr 5.2 : 1, 98% *ee* (98%)
6Ac	R^2: 4-MeC_6H_4	90%, dr 5.7 : 1, 97% *ee* (95%)
6Ad	R^2: 3-MeC_6H_4	72%, dr 7.3 : 1, 96% *ee* (>99%)
6Ae	R^2: 2-ClC_6H_4	72%, dr 6.7 : 1, 90% *ee* (60%)
6Ah	R^2: $CH_3(CH_2)_4$	30% conv after 24h
6Ai	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).

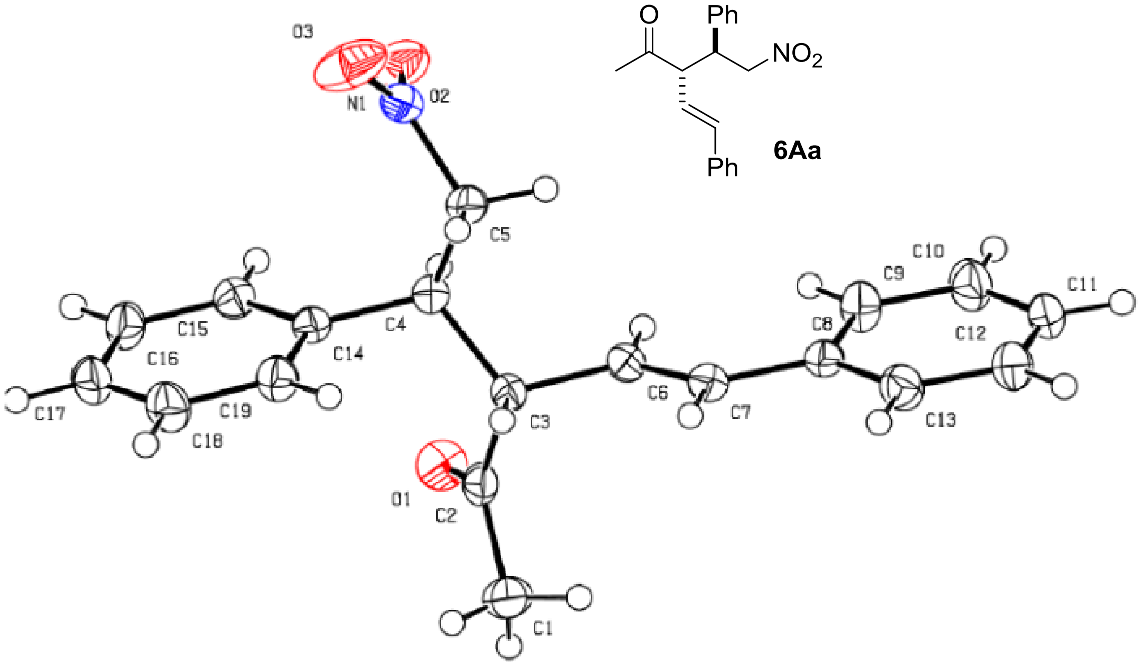


Figure 17. ORTEP diagram of compound **6Aa**.

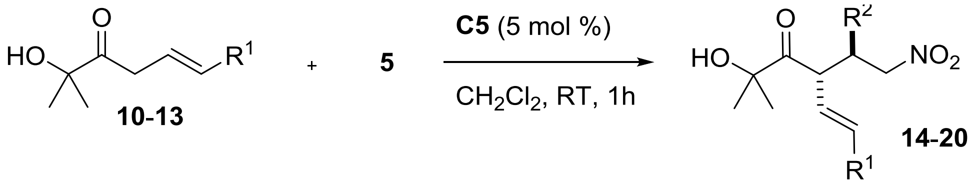
At this stage we decided to extend this method to β´,γ´-unsaturated α-hydroxy ketones **10**-**13**. α-Hydroxy ketones can be smoothly transformed into carboxylic acids through oxidative cleavage, and our group has developed a number of metal- and organocatalysed methodologies based on the use of α-hydroxy 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.

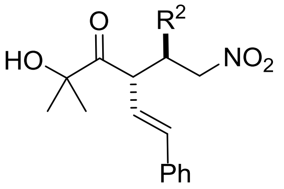
Gratifyingly, reactions of the unsaturated ketols **10**-**13** with nitroolefins **5** in the presence of **C5** led to the corresponding α-addition adducts **14**-**20** in high yield, essentially full diastereoselectivity, and enantioselectivities that were typically greater than 95% (Table 3). The 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).

---

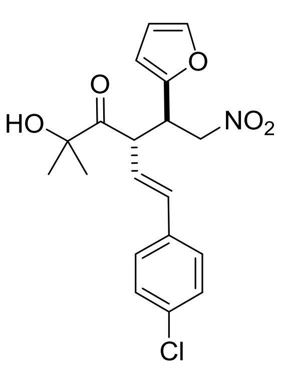
[98] a) For a review on α´-hydroxy ketones as templates, see: Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150–4164. b) Badiola, B.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *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*.

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

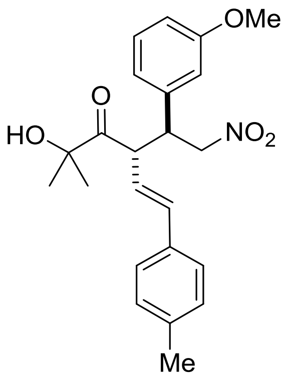




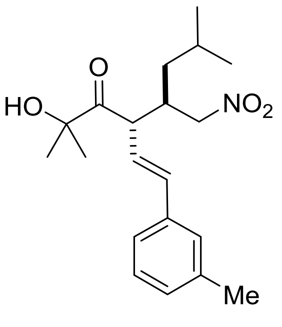
14 R_2: Ph 85%, dr >20:1, 97% *ee*
15 R_2: 4-MeC_6H_4 79%, dr >20:1, 96% *ee*
16 R_2: 4-ClC_6H_4 82%, dr >20:1, 95% *ee*
17 R_2: 4-$MeOC_6H_4$ 75%, dr >20:1, 94% *ee*



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



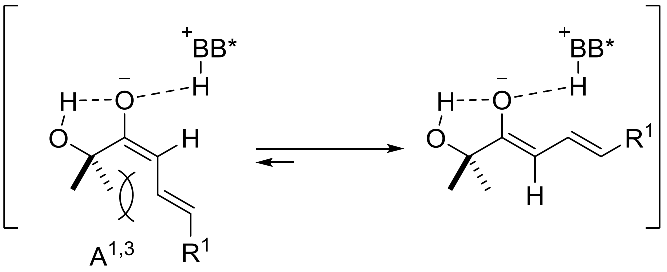
19 75%, dr >20:1, 90% *ee*



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

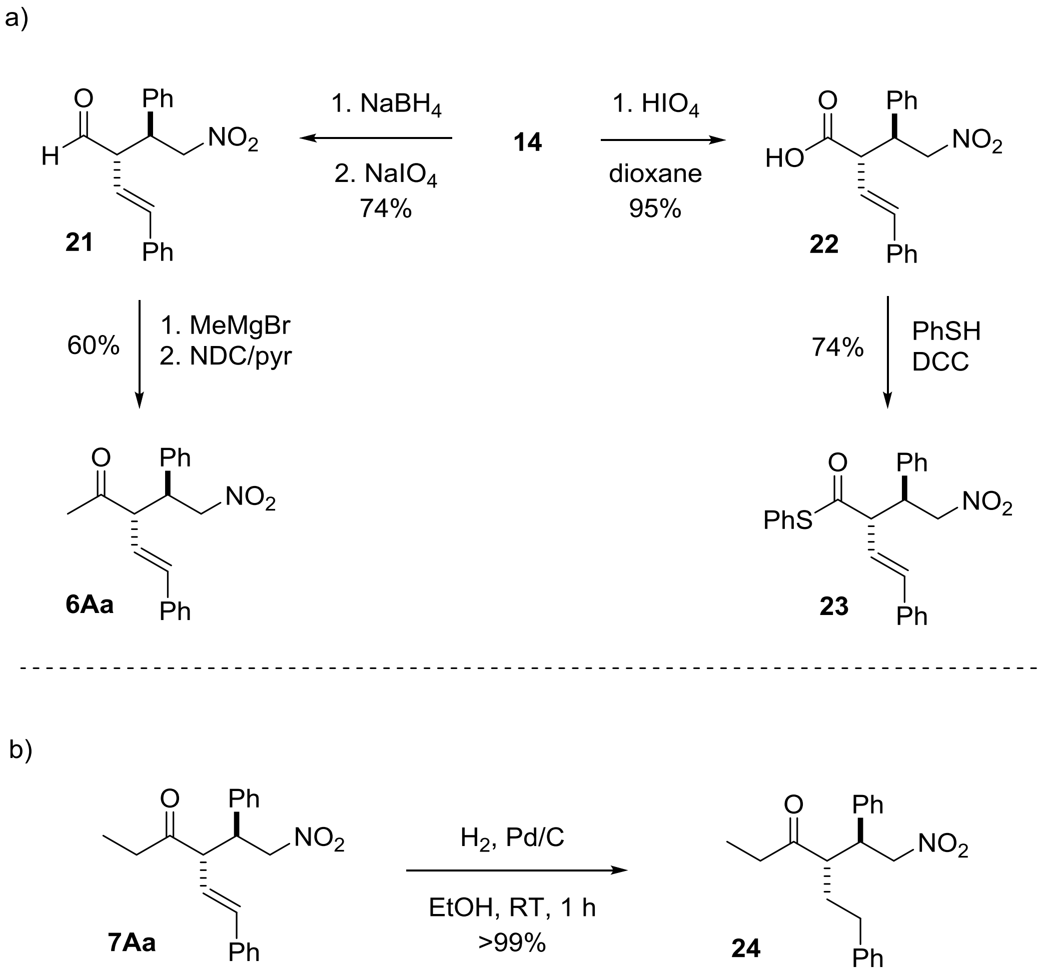
---

[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 ^{1}H 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).


a)
21
1. NaBH$_4$
2. NaIO$_4$
74%
14
1. HIO$_4$
dioxane
95%
22
60%
1. MeMgBr
2. NDC/pyr
6Aa
74%
PhSH
DCC
23
b)
7Aa
H$_2$, Pd/C
EtOH, RT, 1 h
>99%
24

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.

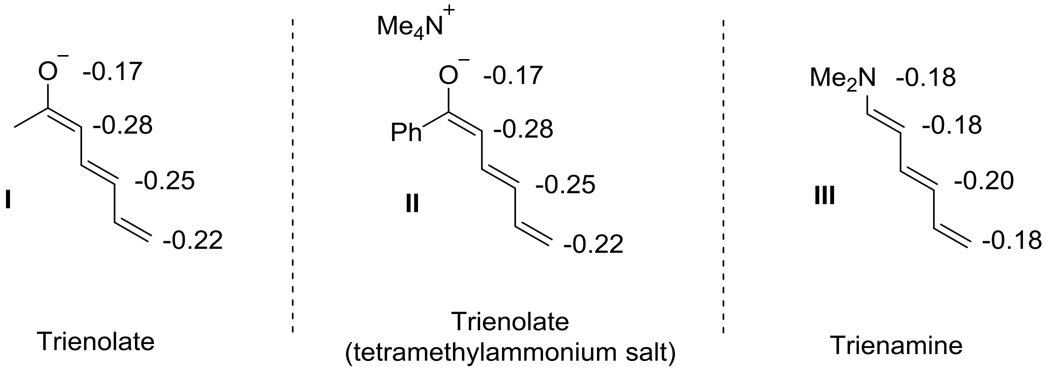


Figure 18. Fukui indices of relevant atoms in selected trienolate and trienamine systems.

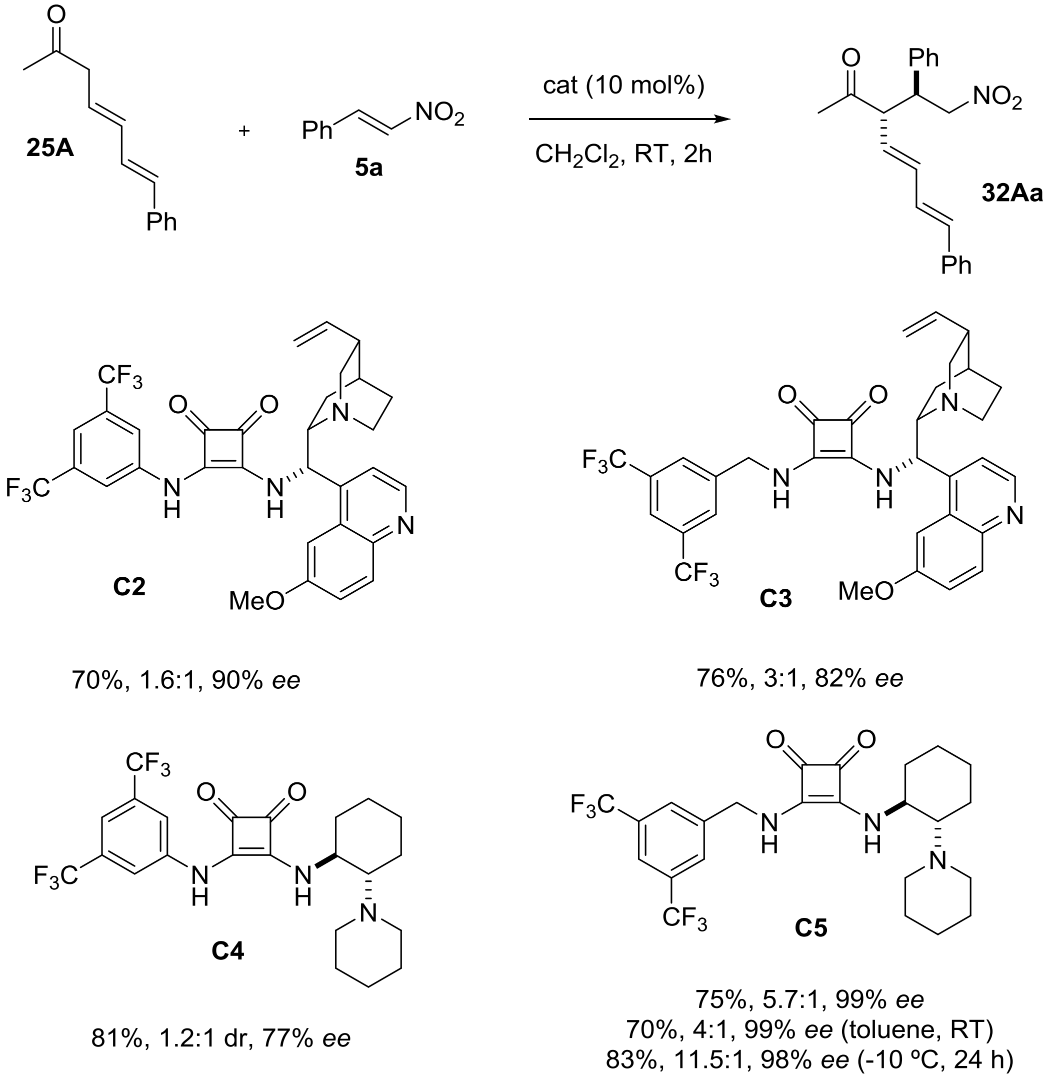
We commenced the experimental study by evaluating several available bifunctional Brønsted base catalysts for the reaction between doubly unsaturated methyl ketone **25A** and nitrostyrene **5a**. Concordant with the above prediction, product **32Aa** arising from attack through Cα of the ketone was obtained 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 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**.

---

[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.

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



70%, 1.6:1, 90% *ee*

76%, 3:1, 82% *ee*

81%, 1.2:1 dr, 77% *ee*

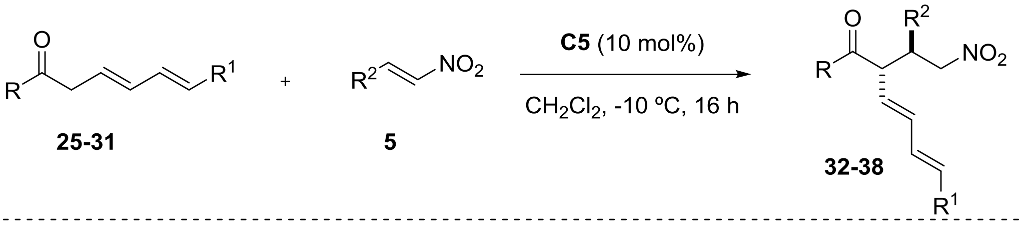
75%, 5.7:1, 99% *ee*
70%, 4:1, 99% *ee* (toluene, RT)
83%, 11.5:1, 98% *ee* (-10 °C, 24 h)

---

[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.

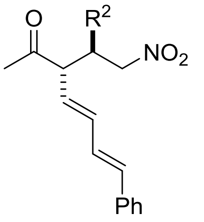
With **C5** selected as the best catalyst for the model reaction, a series of enolizable dienones were tested for the above reaction with nitroalkenes. As shown in Table 5, various nitroalkenes with electron rich (**5b** and **5d**) and poor β-aryl (**5k**) substituents reacted equally well with dienone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



O
R
R1
+
R2
NO2
C5 (10 mol%)
CH2Cl2, -10 ºC, 16 h
O
R2
R
NO2
R1

25-31 **5** **32-38**



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*

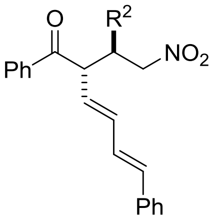
32Ak R^2: 4-ClC_6H_4 76%, 13.3:1 dr, > 99% *ee*

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*

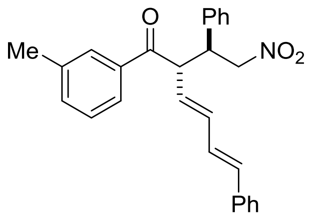


O
R2
Ph
NO2
Ph

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

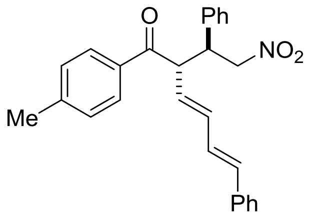
33Ab R^2: 4-$MeOC_6H_4$ 75%, 10.1:1 dr, 92% *ee*[b]

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



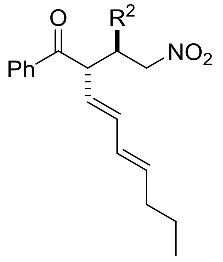
O
Ph
Me
NO2
Ph

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



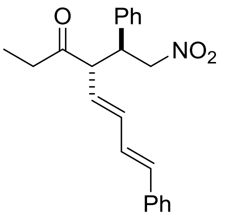
O
Ph
NO2
Me
Ph

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

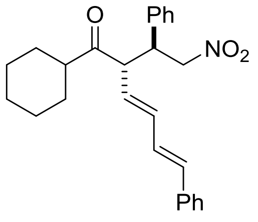


33Bb R^2: 4-$MeOC_6H_4$
82%, 15.7:1 dr, 96% *ee*

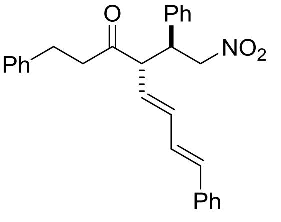
33Bd R^2: 3-MeC_6H_4
75%, 7.3:1 dr, 88% *ee*



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



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



O
Ph
Ph
NO2
Ph

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).

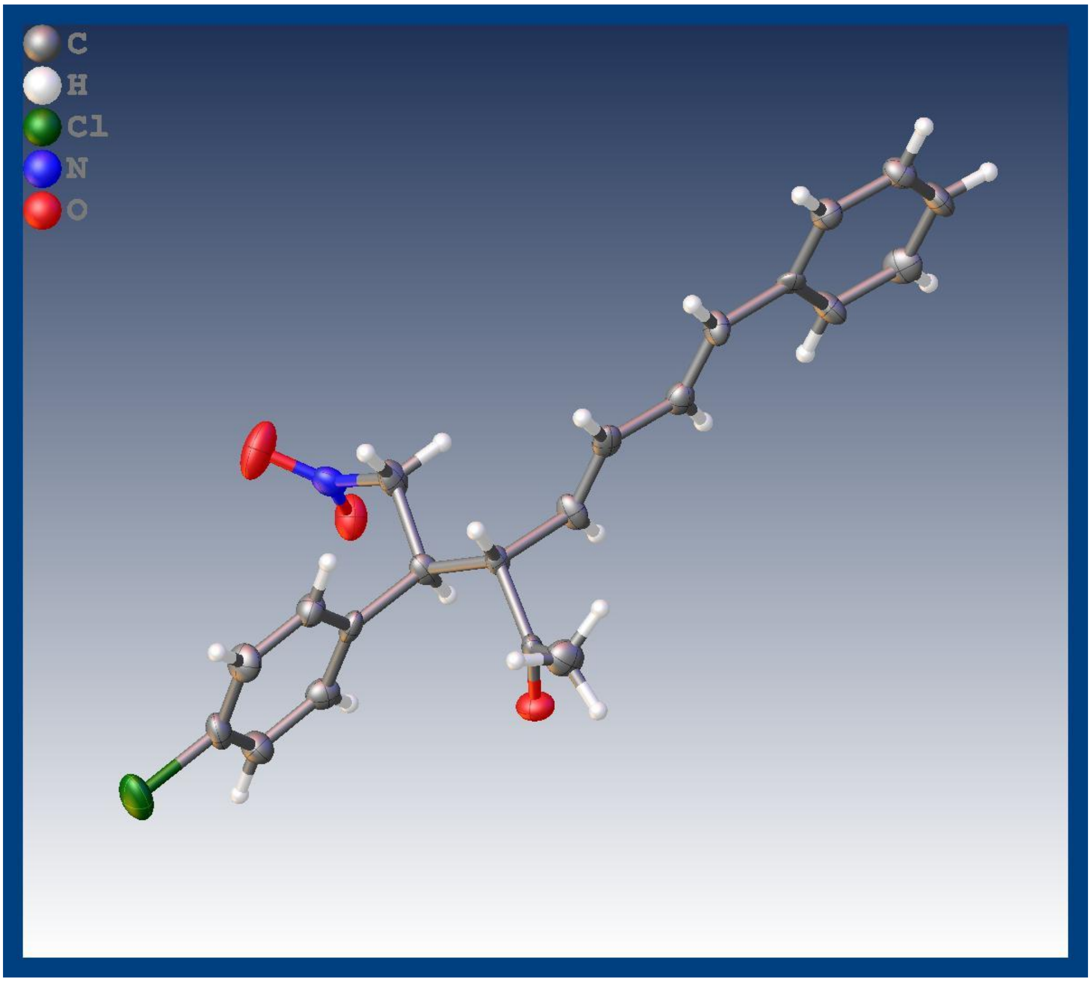


Figure 19. X-Ray image for compound **32Ak**.

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).

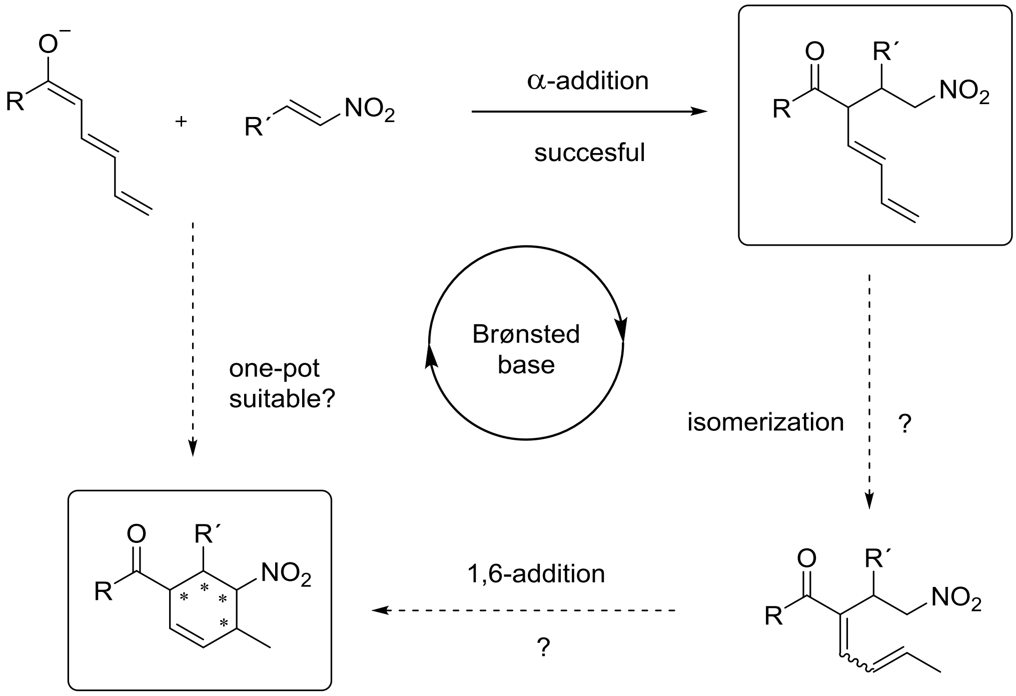
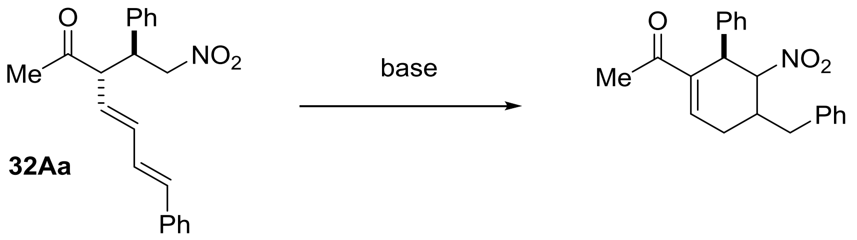
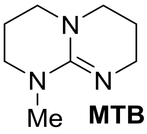
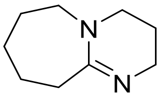

α-addition
succesful
Brønsted
base
one-pot
suitable?
isomerization
?
1,6-addition
?

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.

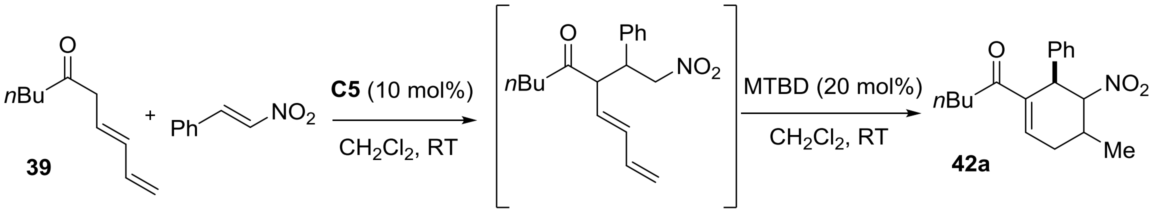
Table 6. Attempted base-promoted carbocyclization of adducts **32Aa** and **39**.



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.

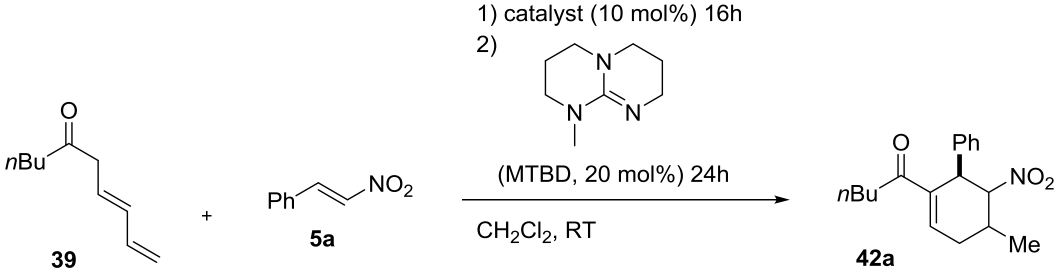
A different behaviour was found when dienone **39** was used. After α-functionalization using bifunctional Brønsted base/H-bond donor catalyst **C5**, isomerization of the adduct could be promoted by guanidine MTBD (20 mol%) to obtain cyclohexene **42a** (Scheme 44).

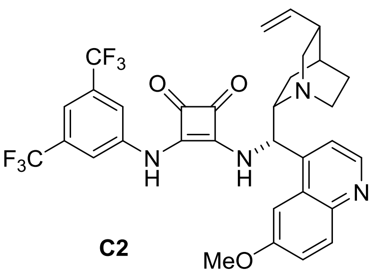


Scheme 44. Synthesis of cyclohexene **42a** via α-functionalization and posterior cyclization starting from dienone **39**.

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**.

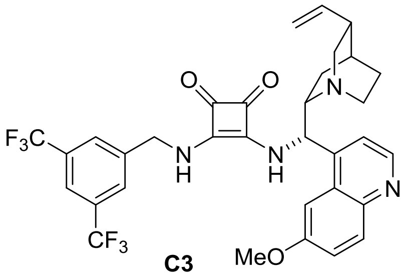
Table 7. Catalyst screening for the addition of **39** to **5a** leading to **42a**.[a]


1) catalyst (10 mol%) 16h
2)
(MTBD, 20 mol%) 24h
CH2Cl2, RT
nBu
O
Ph
NO2
Me
+
39
5a
42a


CF3
F3C
N
H
O
N
MeO

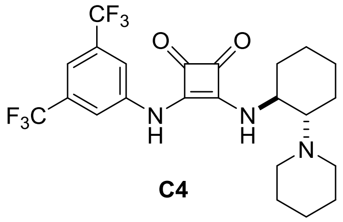
C2

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


F3C
CF3
N
H
O
N
MeO

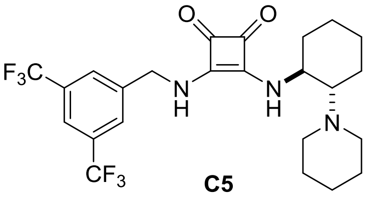
C3

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


CF3
F3C
N
H
O
N

C4

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


F3C
CF3
N
H
O
N

C5

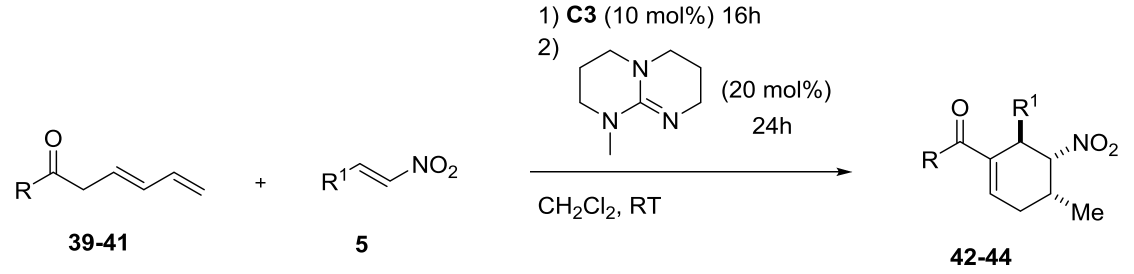
75%, >20:1 dr, 90% *ee*

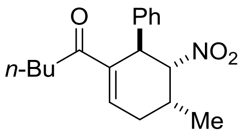
---

[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.

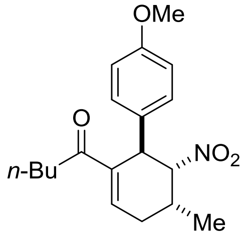
Next, we investigated the behaviour of ketones **39**-**41** under the above optimized conditions. As shown in Table 8, the reaction of unsaturated ketone **39**-**41** with nitrostyrenes **5** in the presence of 10 mol% catalyst **C3** was stirred for 16h to afford the α-substituted adducts, which were 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]

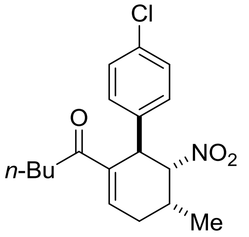




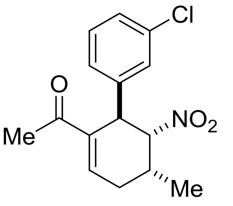
42a 71%, >20:1 dr, 93% *ee*



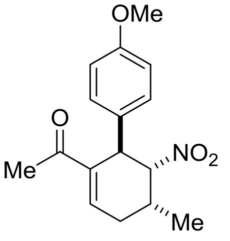
42b 77%, >20:1 dr, 90% *ee*



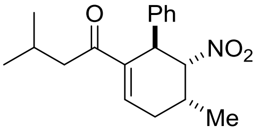
42k 75%, >20:1 dr, 94% *ee*



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



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



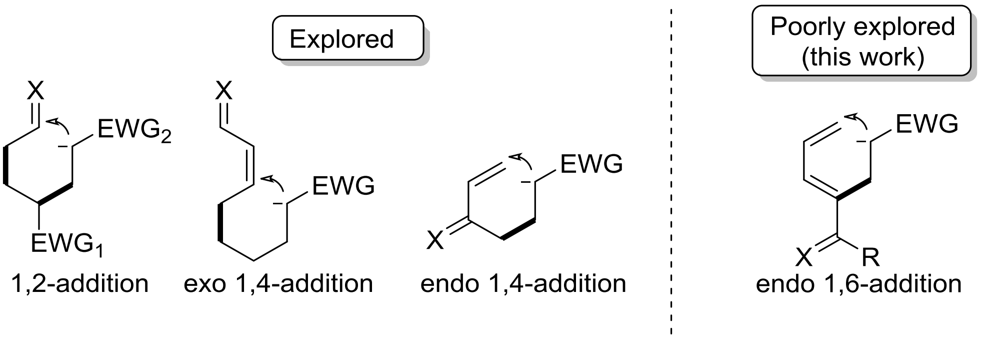
44a 68%, >20:1 dr, 92% *ee*

[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] 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]

---

[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.;



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

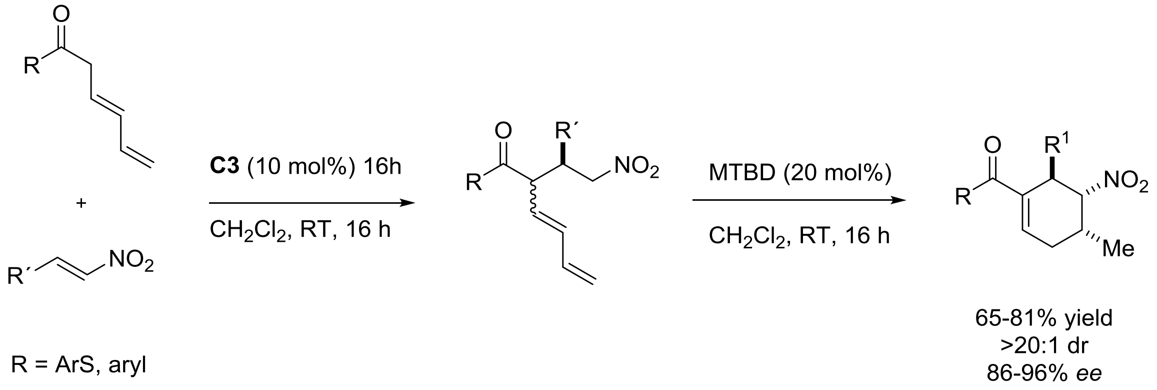
The suitability of this Brønsted base-catalysed one-pot access to cyclohexene systems *via* in-situ generated trienolates demonstrated to be not limited to doubly unsaturated alkyl ketones **39**-**41**, but also applicable to other unsaturated carbonyl compounds. In this regard, parallel experiments 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.

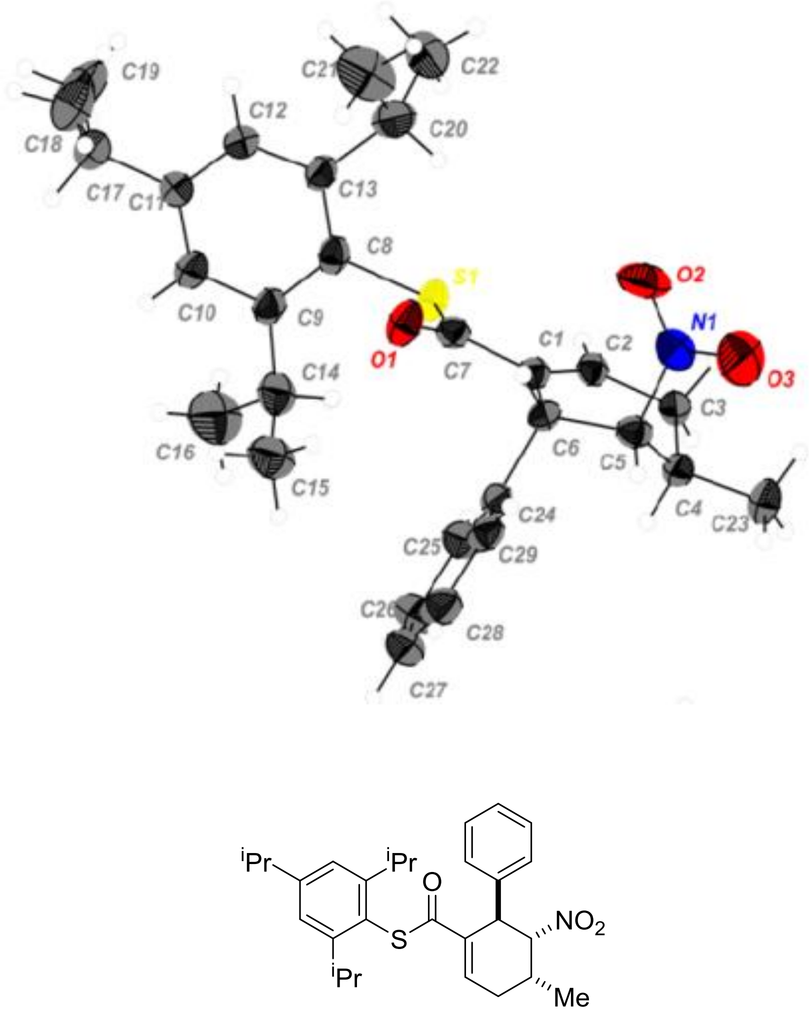
[102] Reviews on conjugate 1,6-additions: (General) a) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109–3128. b) Csáky, A. G.; Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080–4102. (Organocatalytic) c) Biju, A. T. *ChemCatChem* **2011**, *3*, 1847–1849.

[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.


O
R
+
R´
NO$_2$
R = ArS, aryl
C3 (10 mol%) 16h
CH$_2$Cl$_2$, RT, 16 h
O
R´
R
NO$_2$
MTBD (20 mol%)
CH$_2$Cl$_2$, RT, 16 h
O
R^1
R
NO$_2$
Me
65-81% yield
>20:1 dr
86-96% *ee*

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

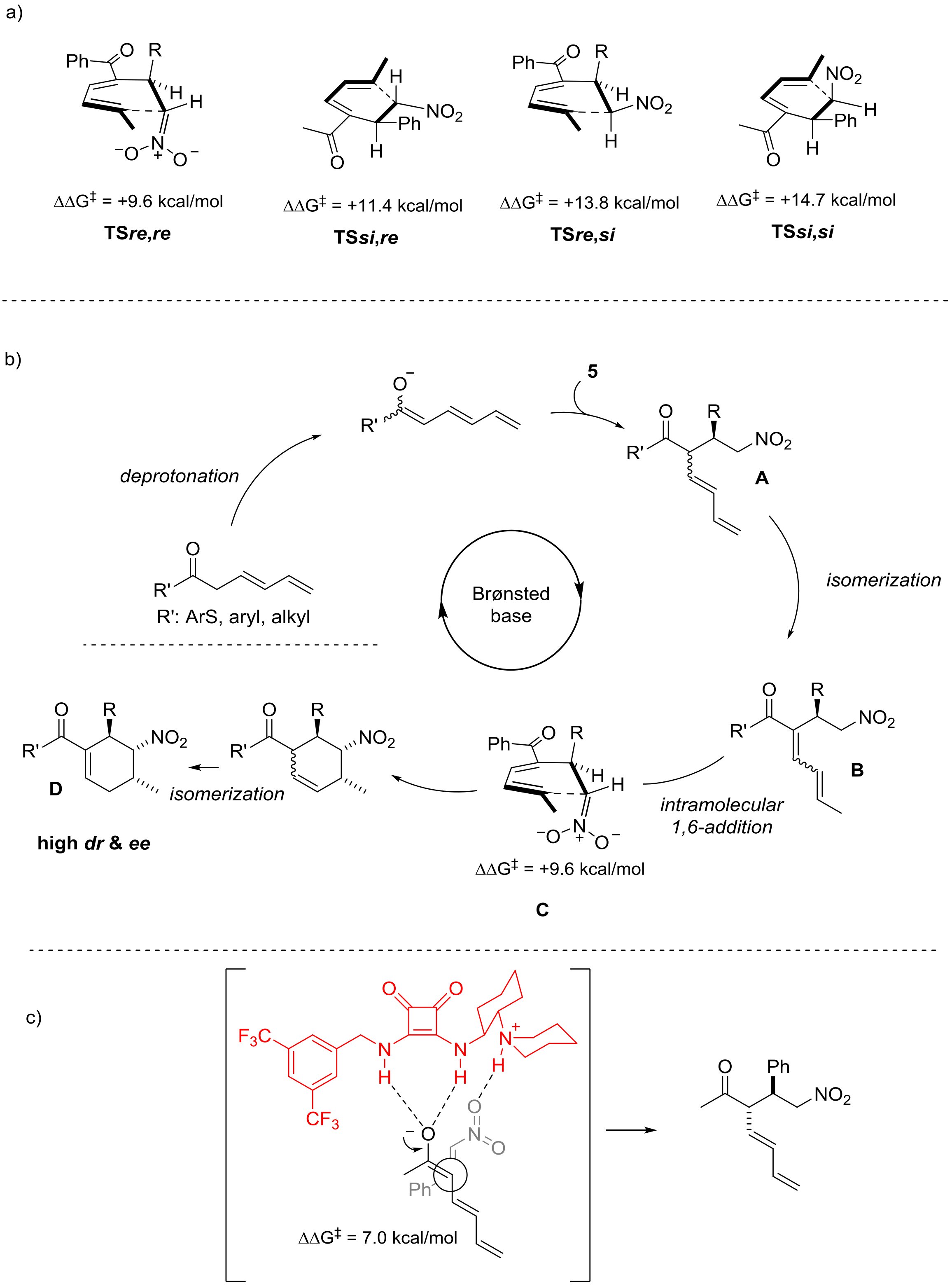

C19
C21
C22
C12
C20
C18
C17
C11
C13
C8
S1
O2
C10
C9
N1
O1
C1
C2
O3
C7
C14
C3
C16
C6
C5
C15
C4
C24
C23
C25
C29
C26
C28
C27
^{i}Pr
^{i}Pr
O
NO$_2$
S
^{i}Pr
Me

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.


a)
ΔΔG‡ = +9.6 kcal/mol
TSre,re
ΔΔG‡ = +11.4 kcal/mol
TSsi,re
ΔΔG‡ = +13.8 kcal/mol
TSre,si
ΔΔG‡ = +14.7 kcal/mol
TSsi,si
b)
5
A
deprotonation
isomerization
Brønsted base
R': ArS, aryl, alkyl
B
intramolecular 1,6-addition
ΔΔG‡ = +9.6 kcal/mol
C
isomerization
D
high dr & ee
c)
ΔΔG‡ = 7.0 kcal/mol

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 85

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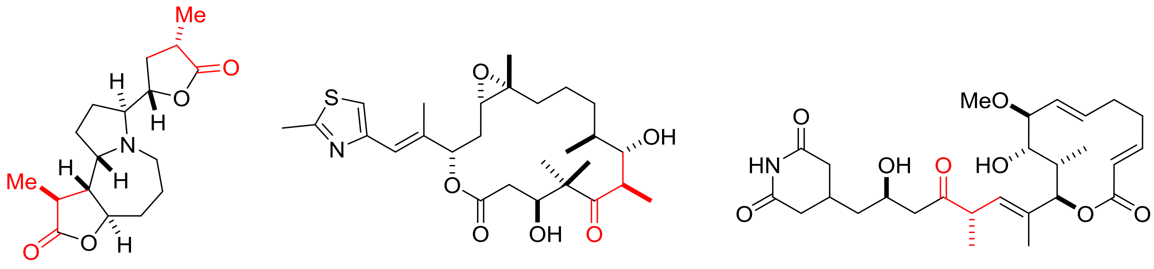
3. α-Substituted α´-Oxyenones as Methacrylate Equivalents in Organocatalytic Asymmetric Michael Reactions

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)

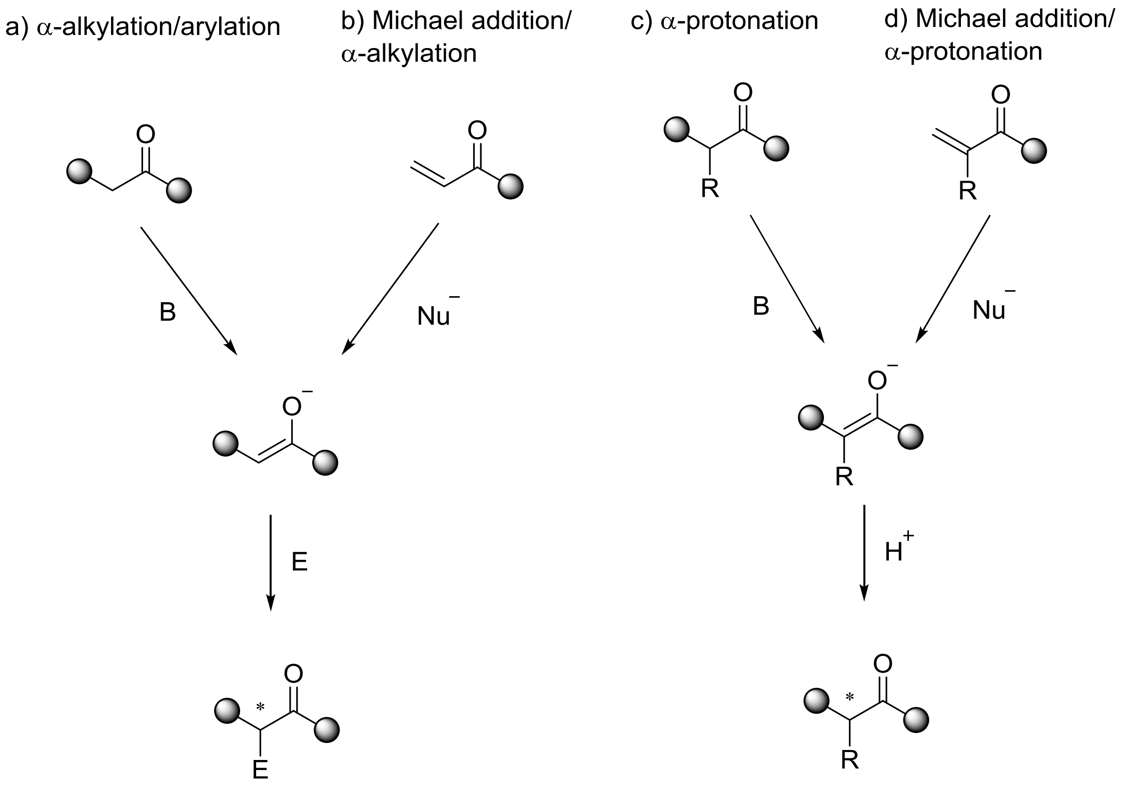
Lactimidomycin
(antifungal, antiviral, anticancer)

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).

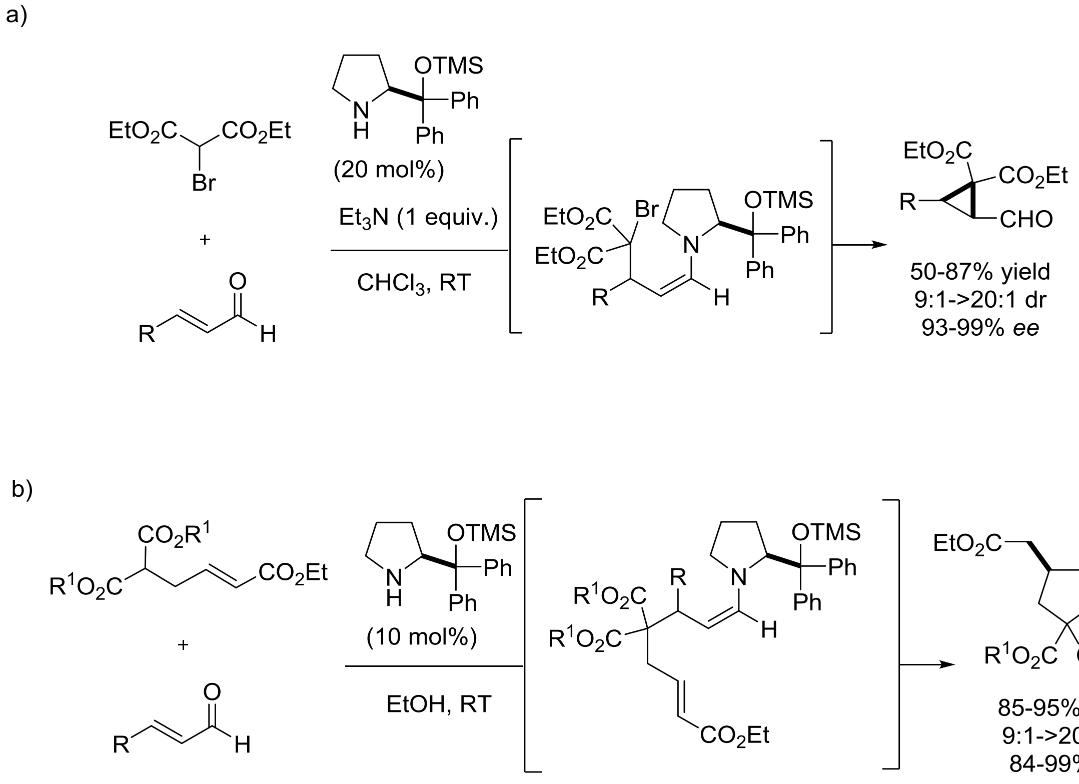

a) α-alkylation/arylation
b) Michael addition/ α-alkylation
c) α-protonation
d) Michael addition/ α-protonation
O
R
B
Nu⁻
E
H⁺
*

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 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]

---

[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.


a)
EtO2C CO2Et
Br
+
O
R H
OTMS
N
H
Ph
Ph
(20 mol%)
Et3N (1 equiv.)
CHCl3, RT
EtO2C Br
EtO2C
R
N
OTMS
Ph
Ph
H
EtO2C
R
CO2Et
CHO
50-87% yield
9:1->20:1 dr
93-99% ee
b)
CO2R1
R1O2C
CO2Et
+
O
R H
OTMS
N
H
Ph
Ph
(10 mol%)
EtOH, RT
R1O2C
R1O2C
R
N
OTMS
Ph
Ph
H
CO2Et
EtO2C
CHO
R
R1O2C CO2R1
85-95% yield
9:1->20:1 dr
84-99% ee

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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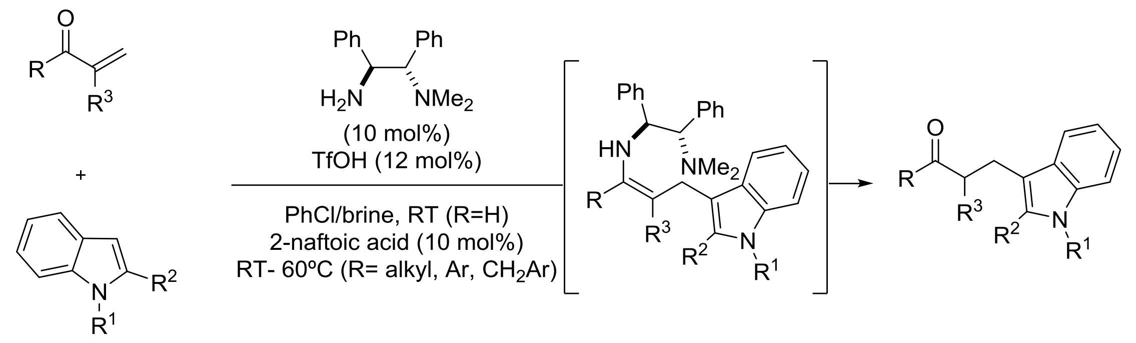
[106] Rios, R.; Sundén, H.; Vesely, J.; Zhao, G. L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Cat.* **2007**, *349*, 1028–1032. For a pioneering work of tandem Michael addition/α-alkylation processes, see: Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479.

[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, ${}^iC_4H_9$, nC_7H_{15}, Ar, CH_2Ar

72-95% yield
84-91% *ee*

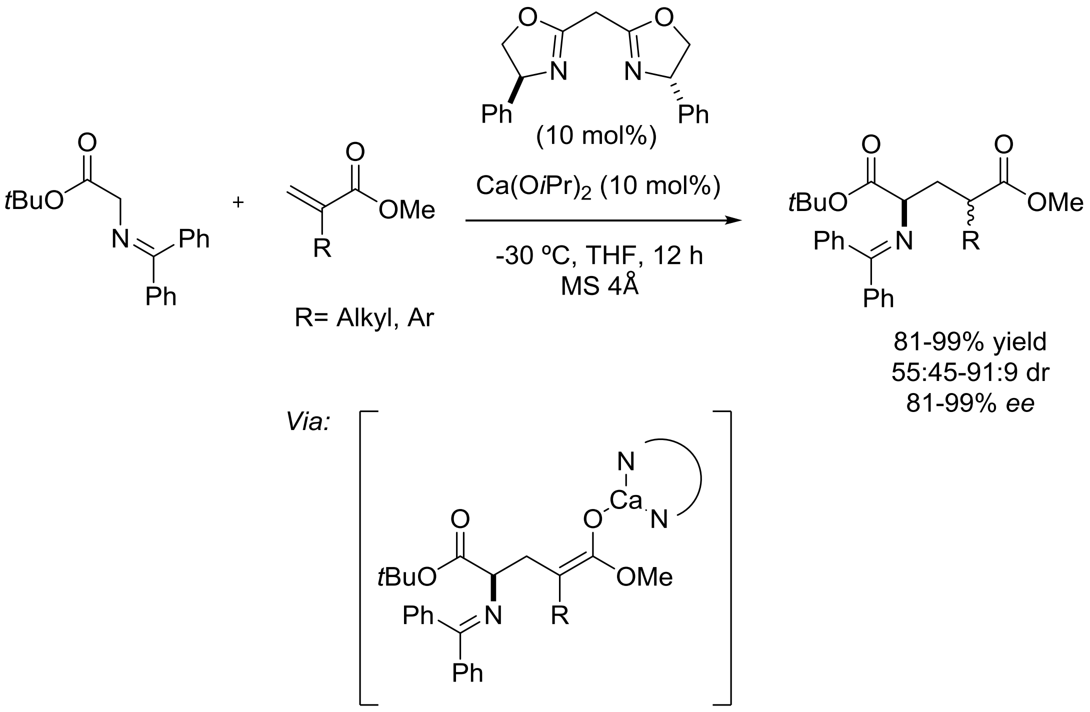
Scheme 50. Organocatalytic Michael addition/α-protonation reaction between α-substituted indoles and α-substituted acroleines.

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

---

[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.



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

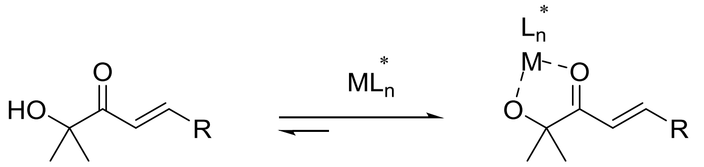
3.1.2. α´-Hydroxy enones as Michael acceptor templates

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 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.

---

[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.*



(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.

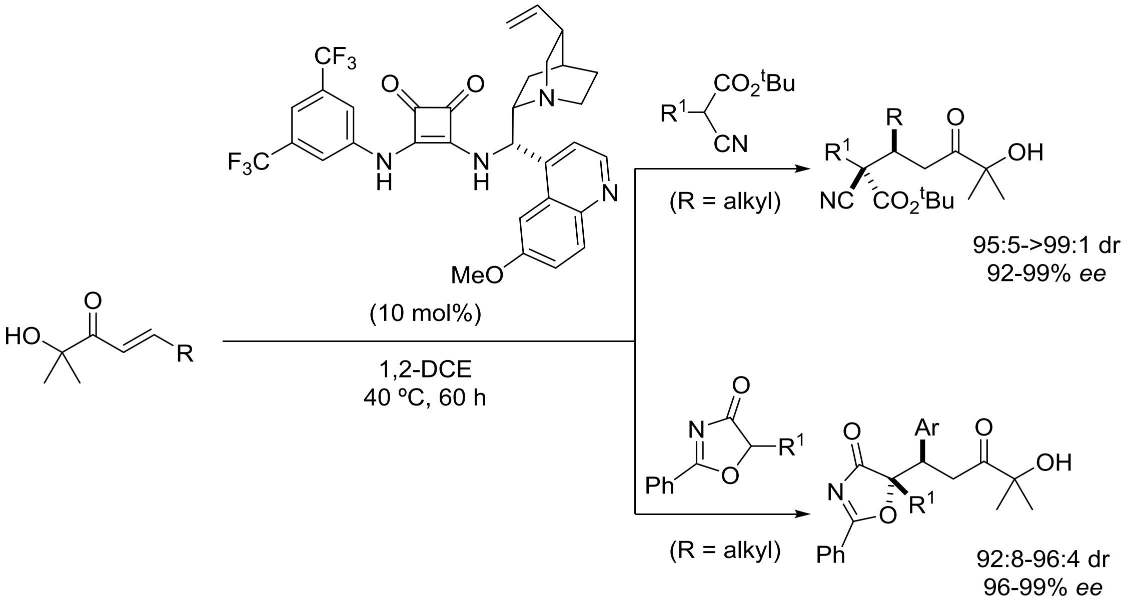
[120] García, J. M.; Gónzalez, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768–8771.

[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).

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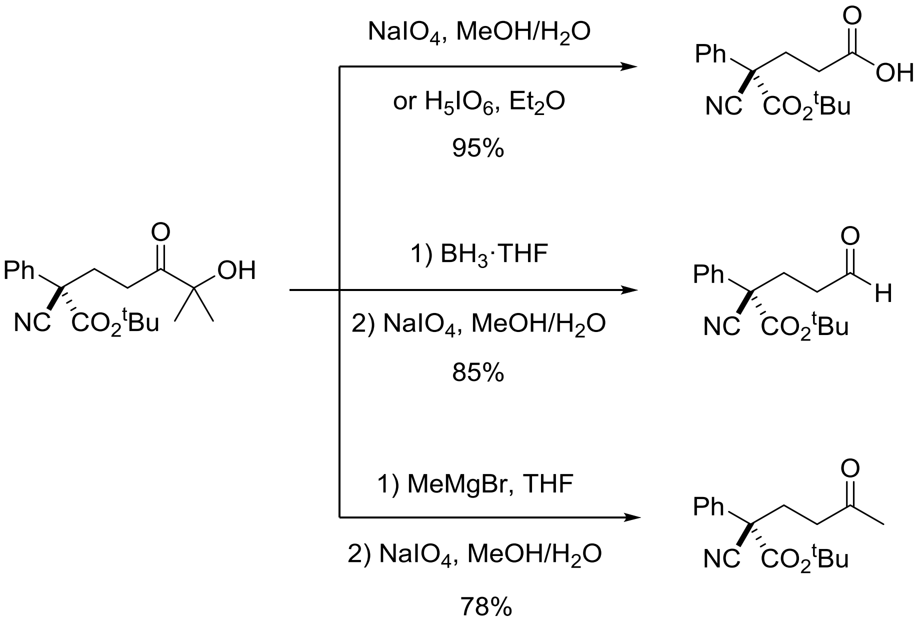
[123] Lee, S.; Lim, C. J.; Kim,S.; Subramaniam, R.; Zimmerman, J.; Sibi, M. P. *Org. Lett.* **2006**, *8*, 4311–4313.

[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.



NaIO4, MeOH/H2O
or H5IO6, Et2O
95%
1) BH3·THF
2) NaIO4, MeOH/H2O
85%
1) MeMgBr, THF
2) NaIO4, MeOH/H2O
78%
Ph
NC
CO2tBu
OH
O
H

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

---

[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.

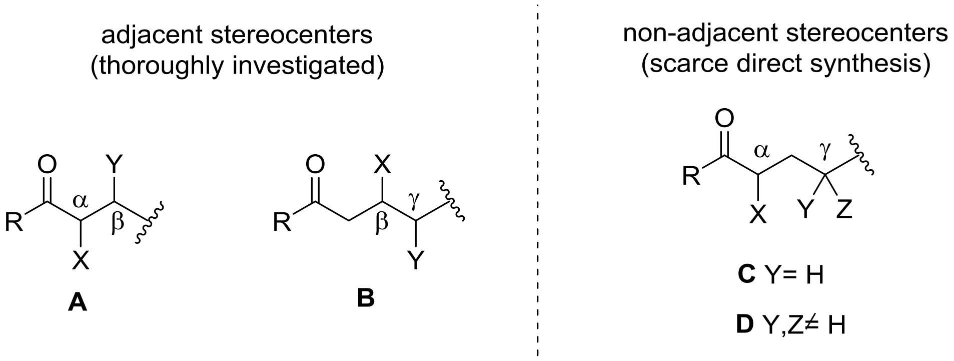

adjacent stereocenters
(thoroughly investigated)
non-adjacent stereocenters
(scarce direct synthesis)
O
Y
R
α
β
X
A
O
X
R
β
γ
Y
B
O
R
α
γ
X
Y
Z
C Y= H
D Y,Z≠ H

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).

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[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.

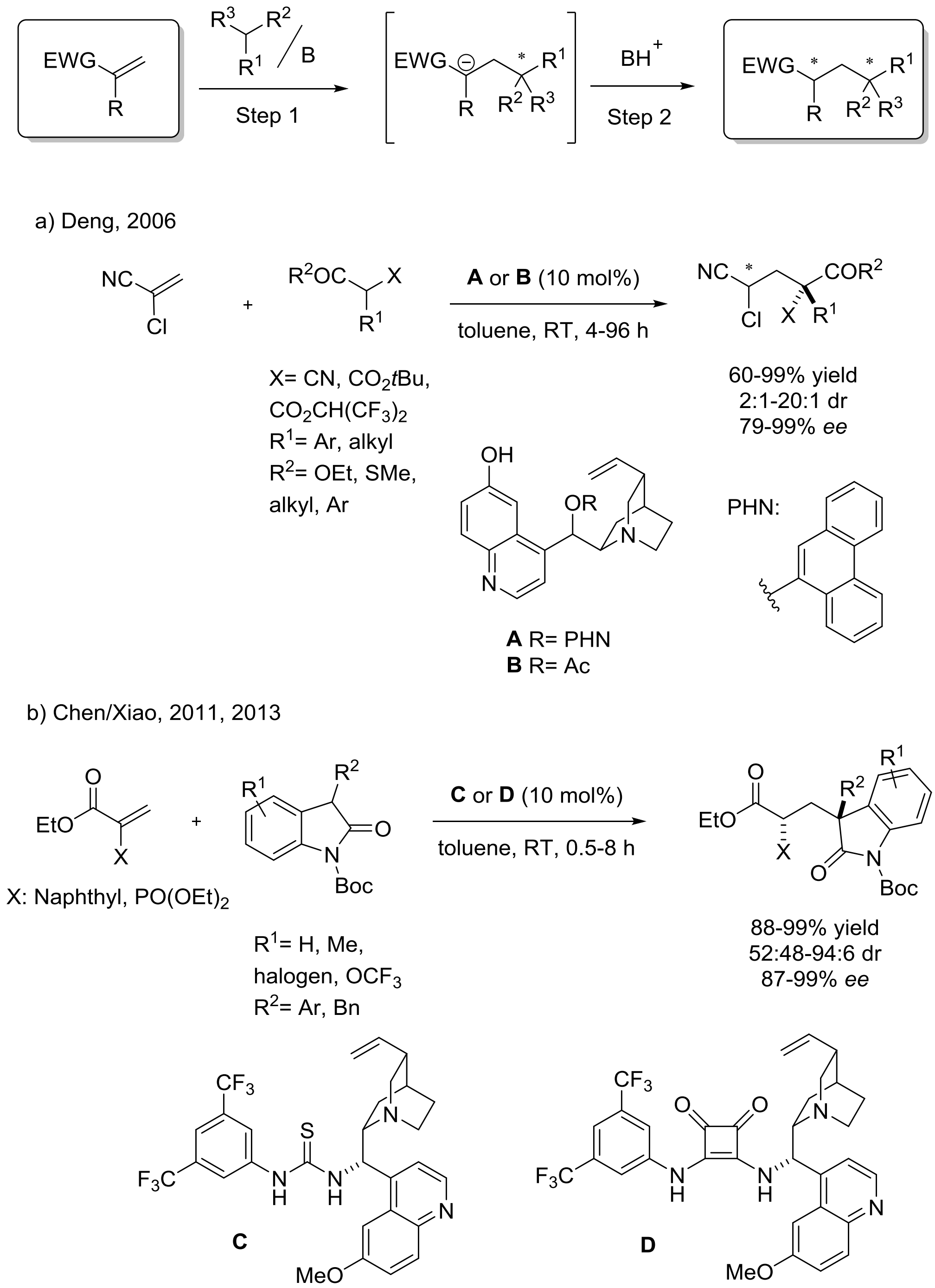
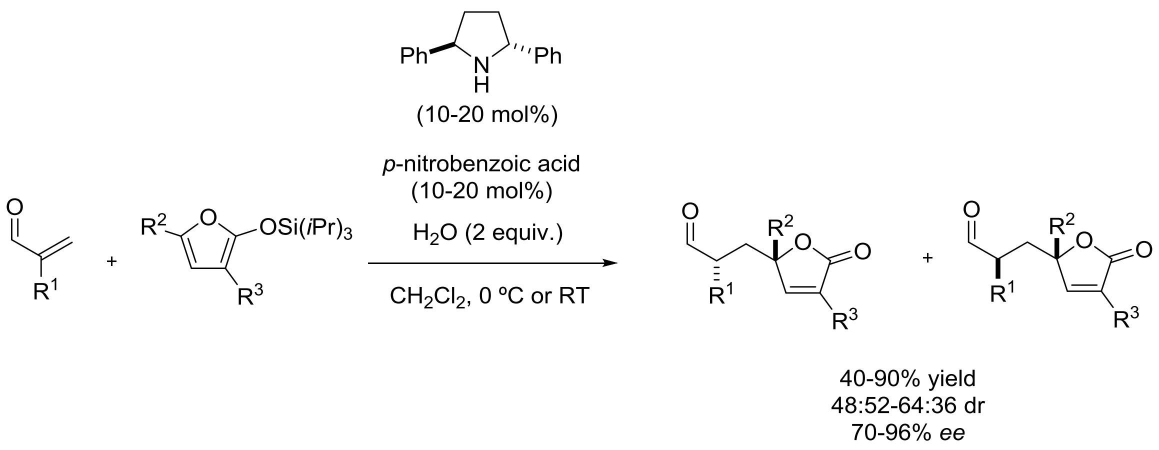

EWG
R
R3 R2 R1 / B
Step 1
EWG * R1
R R2 R3
BH+
Step 2
EWG * * R1
R R2 R3
a) Deng, 2006
NC
Cl
+
R2OC X
R1
A or B (10 mol%)
toluene, RT, 4-96 h
NC * COR2
Cl X R1
X= CN, CO2tBu, CO2CH(CF3)2
R1= Ar, alkyl
R2= OEt, SMe, alkyl, Ar
60-99% yield
2:1-20:1 dr
79-99% ee
OH
OR
N
N
PHN:
A R= PHN
B R= Ac
b) Chen/Xiao, 2011, 2013
O
EtO
X
X: Naphthyl, PO(OEt)2
+
R1
R2
O
N
Boc
R1= H, Me, halogen, OCF3
R2= Ar, Bn
C or D (10 mol%)
toluene, RT, 0.5-8 h
O
EtO
X
R2
R1
O
N
Boc
88-99% yield
52:48-94:6 dr
87-99% ee
CF3
F3C
S
N H
N H
N
N
MeO
C
CF3
F3C
O O
N H
N H
N
N
MeO
D

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

---

[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.

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.

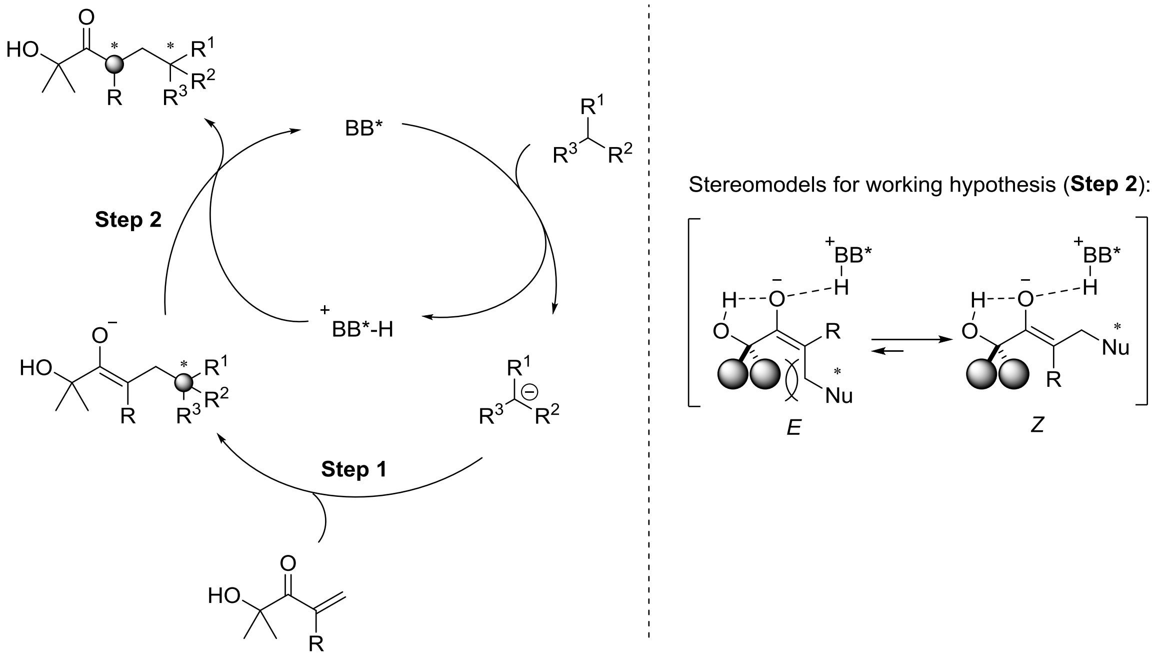
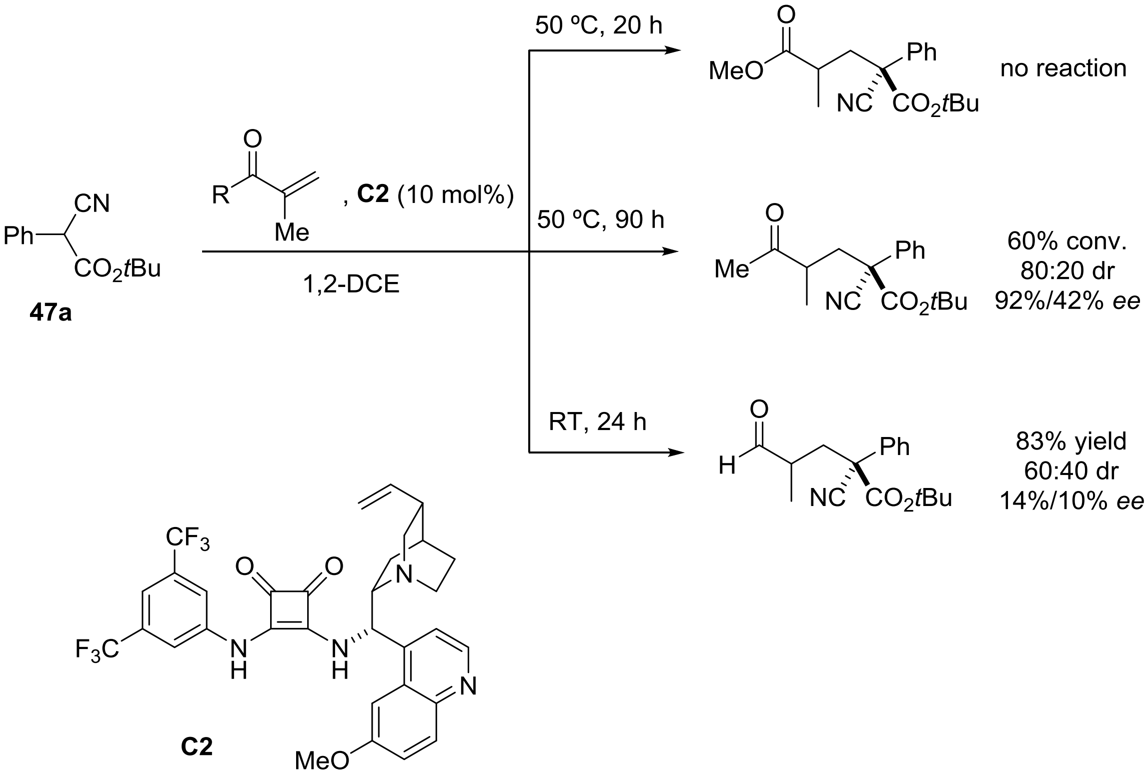


Figure 25. Construction of nonadjacent tertiary/quaternary stereocenters and working hypothesis for designed methacrylate equivalent.

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]


CN
Ph
CO2tBu
47a
R
O
Me
, C2 (10 mol%)
1,2-DCE
50 °C, 20 h
MeO
Ph
NC
CO2tBu
no reaction
50 °C, 90 h
Me
60% conv.
80:20 dr
92%/42% ee
RT, 24 h
H
83% yield
60:40 dr
14%/10% ee
CF3
F3C
N
H
C2
MeO

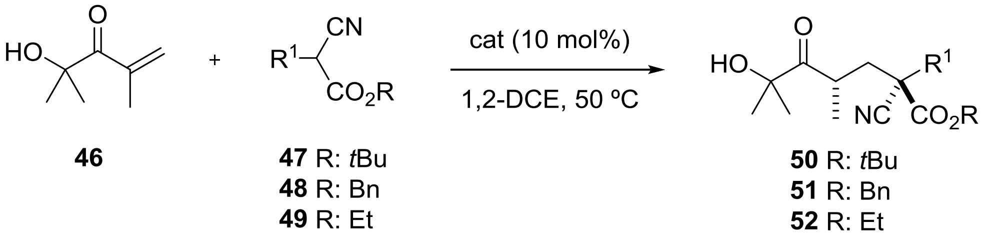
Scheme 55. Difficulties in the addition of α-cyanoester **47a** to α-methyl α,β-unsaturated ester, ketone or aldehyde under best reaction conditions.

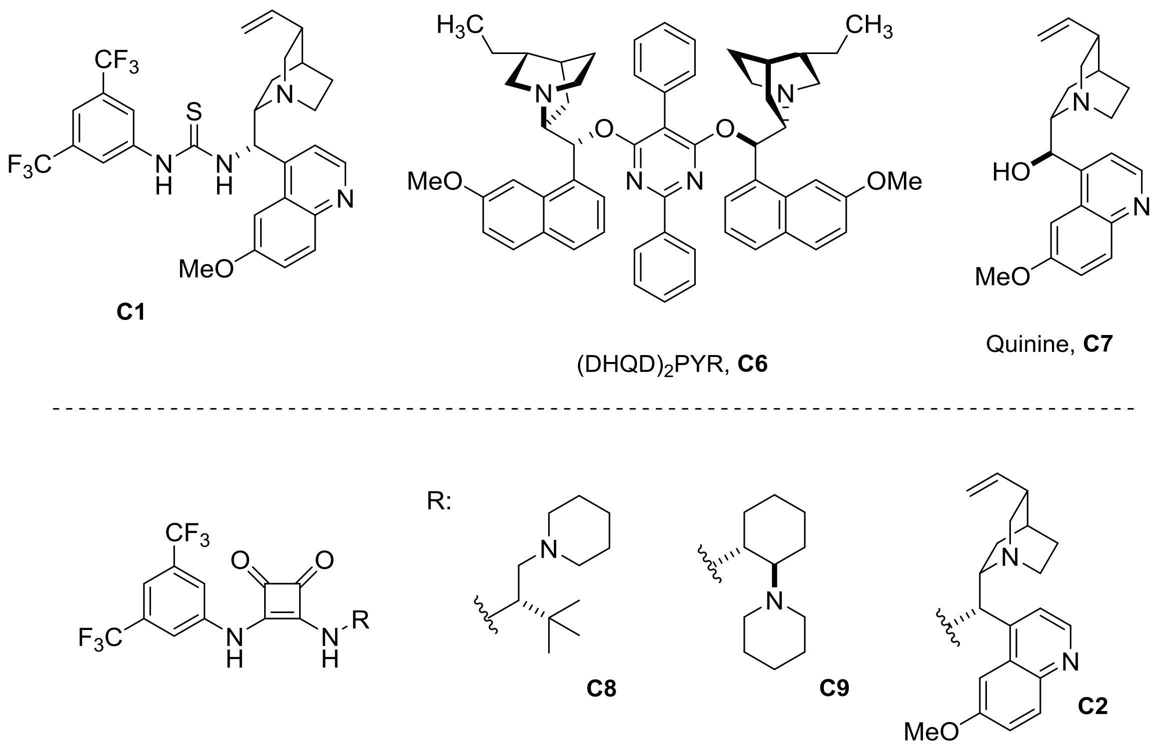
Next, the suitability of Brønsted base catalysts to trigger these Michael reactions was reassessed, but using α-alkyl α′-hydroxy enones as the Michael acceptor, with the hope to overcome the two main challenges in these reactions: a) the attenuated reactivity of α-alkyl-substituted enones as Michael 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]


cat (10 mol%)
1,2-DCE, 50 °C
46
47 R: tBu
48 R: Bn
49 R: Et
50 R: tBu
51 R: Bn
52 R: Et


C1
(DHQD)2PYR, C6
Quinine, C7
R:
C8
C9
C2

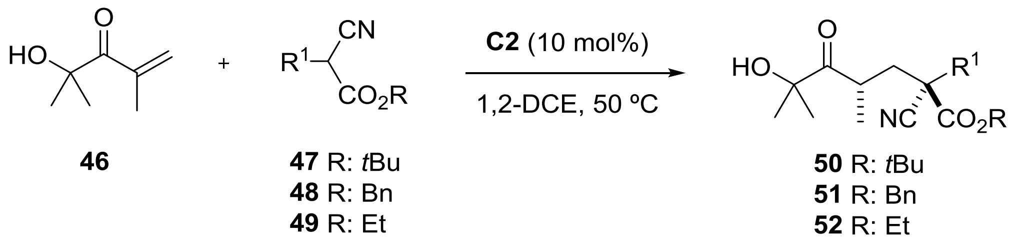
Catalyst	t (h)	Conv (%)	Yield (%)[b]	dr	*ee* (%)[c]
C1	72	70	46	80:20	68
C2[d]	96	n.d.	40	>99:1	99
C2	24	100	81	>99:1	98
C6	72	100	72	70:30	30
C7	72	65	49	75:25	16
C8	72	23	n.d.[e]	n.d.	n.d.
C9	40	100	75	75:25	−12

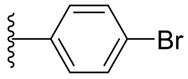
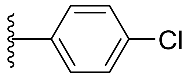
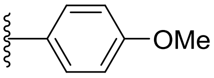
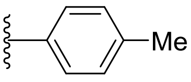
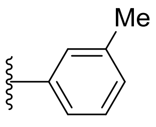
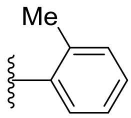
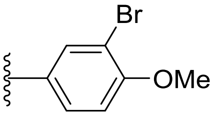
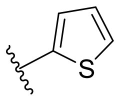
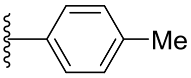
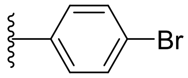
[a] Reactions conducted on a 0.2 mmol scale in 1,2-DCE (0.4 mL) at 50 °C, using 1.5 equiv. of **47a** and 10 mol% catalyst. [b] Yields of isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at room temperature. [e] n.d.: not determined.

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**.


HO
O
+
CN
R1
CO2R
C2 (10 mol%)
1,2-DCE, 50 °C
HO
O
R1
NC
CO2R
46
47 R: tBu
48 R: Bn
49 R: Et
50 R: tBu
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.

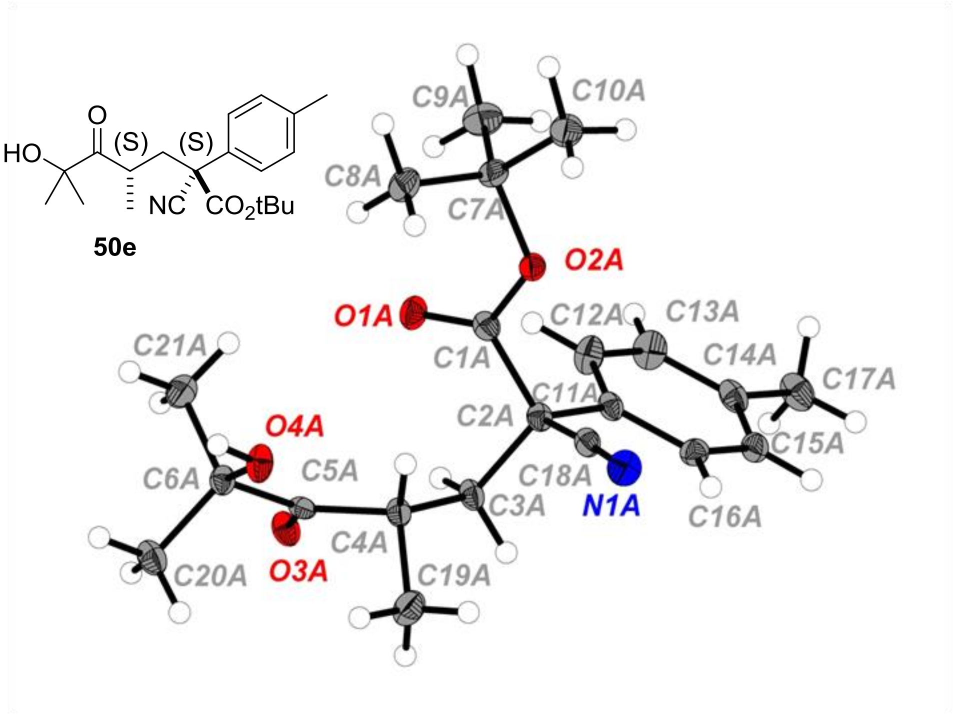


Figure 26. ORTEP diagram of compound **50e**.

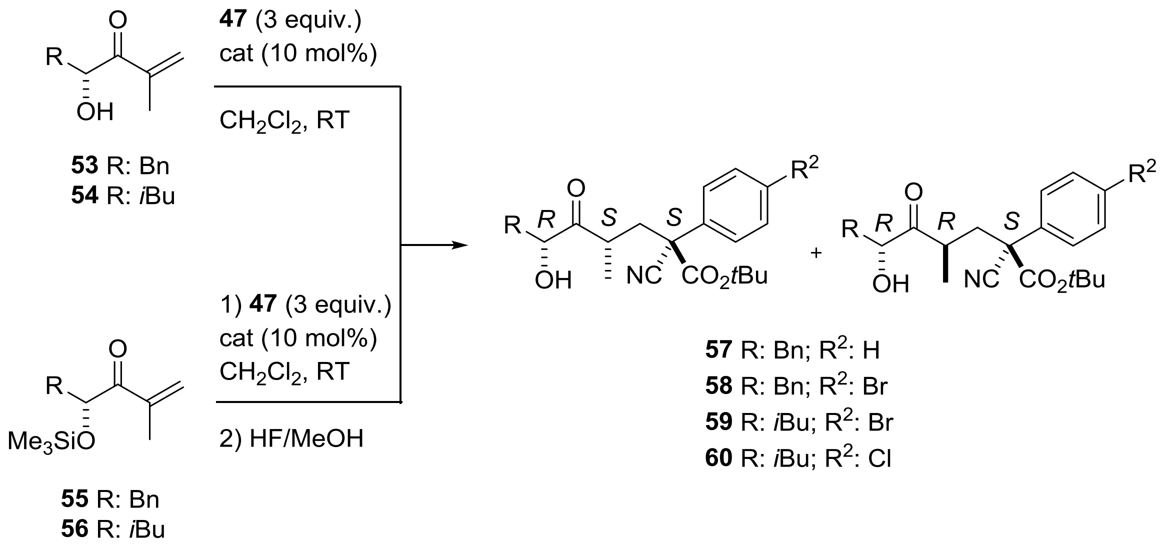
3.2.5. Double asymmetric induction

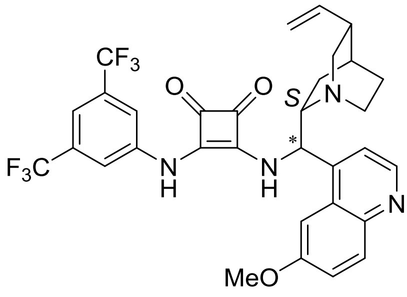
Double asymmetric induction refers to reactions in which a new stereocenter is generated under the influence of two or more chiral units. In our context, the addition reaction of α-cyanoacetates to *chiral* α´-oxy α-substituted enones catalysed by chiral Brønsted bases would be interesting as adducts 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.

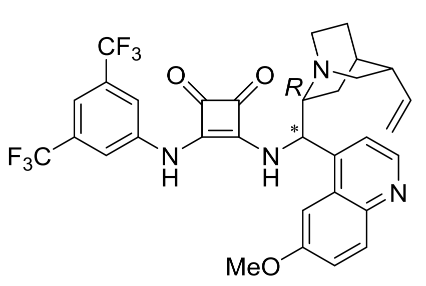
As the results in Table 11 show, the stereochemical outcome of the reactions varies notably depending on the catalyst used. The investigation was started with Et_3N as the only base (entries 1 and 8) and using the α´-hydroxy enones **53** (entry 1) and **55** (entry 8) as the only asymmetric promoters.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


47 (3 equiv.)
cat (10 mol%)
CH2Cl2, RT
53 R: Bn
54 R: iBu
1) 47 (3 equiv.)
cat (10 mol%)
CH2Cl2, RT
2) HF/MeOH
55 R: Bn
56 R: iBu
57 R: Bn; R2: H
58 R: Bn; R2: Br
59 R: iBu; R2: Br
60 R: iBu; R2: Cl



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

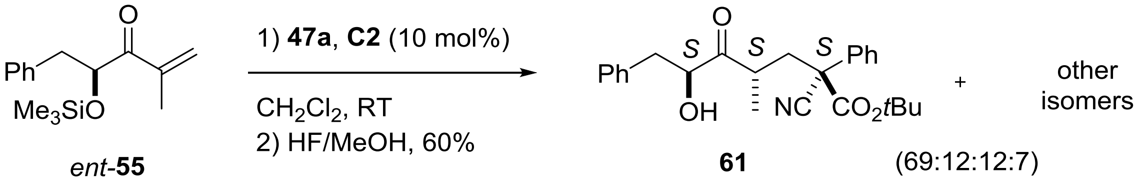


(*R*,*S**) **C11**
(*R*,*R**) **C12**

Entry	R	enone	cyanoester	catalyst	t (h)	product	Yield (%)	*RSS*:*RRS*:others
1	**Bn**	**53**	**47a**	Et₃N	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**	Et₃N	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.

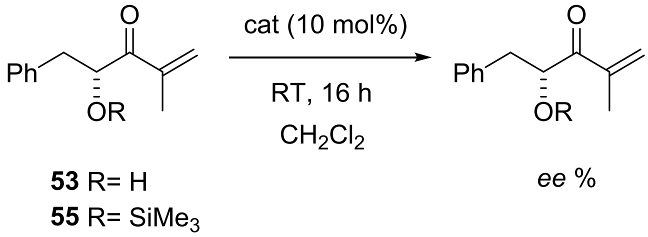
At this point it remained unclear whether the above substrate/catalyst combinations correspond to a matched stereochemical relationship. To answer that question, the reaction between **47a** and the (*S*)-configured ent-**55** was carried out in the presence of catalyst **C2**. As the data in Scheme 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.

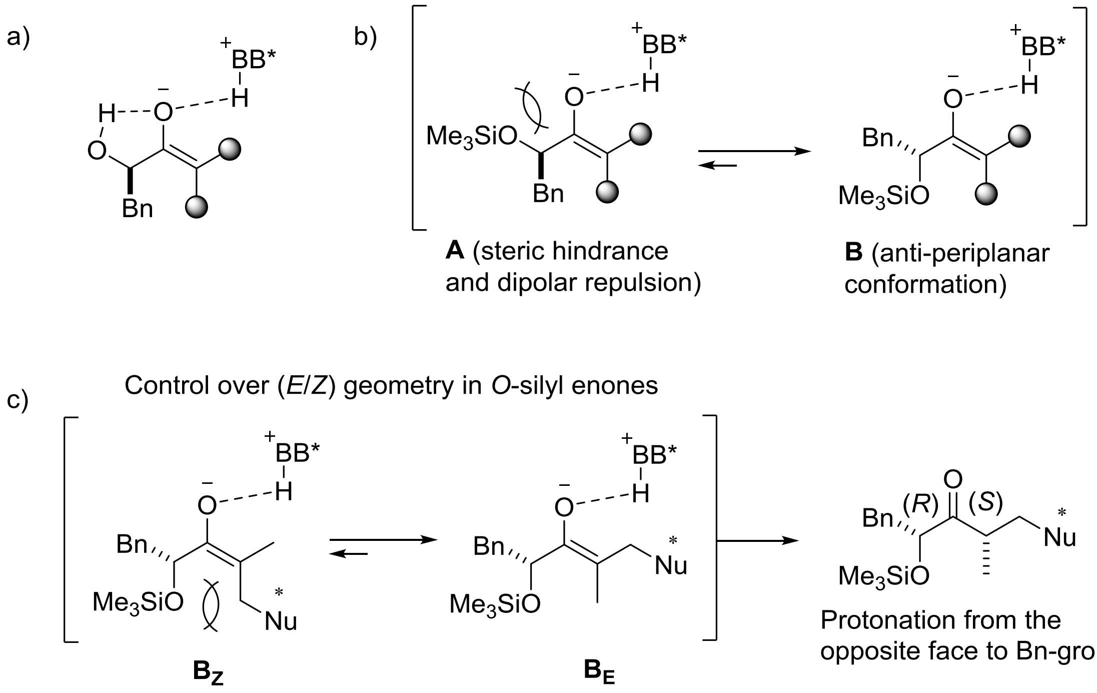
Table 12. Configurational stability of chiral enones **53** and **55** in the presence of different bases (10 mol%).[a]



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

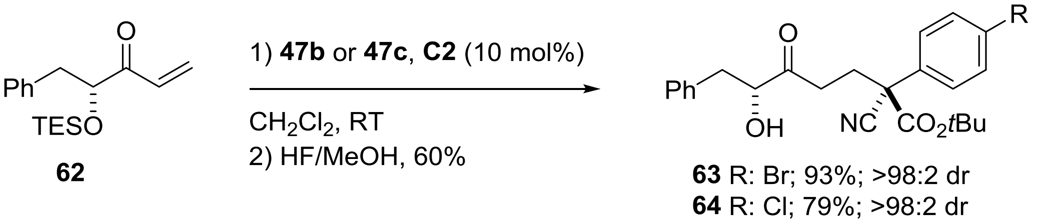
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.2 mL). [b] Determined by GC analysis. [c] *ee* measured by GC after 72 h.

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**.


a)
b)
A (steric hindrance and dipolar repulsion)
B (anti-periplanar conformation)
c)
Control over (E/Z) geometry in O-silyl enones
Bz
BE
Protonation from the opposite face to Bn-group

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.


62
1) 47b or 47c, C2 (10 mol%)
CH2Cl2, RT
2) HF/MeOH, 60%
63 R: Br; 93%; >98:2 dr
64 R: Cl; 79%; >98:2 dr

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.

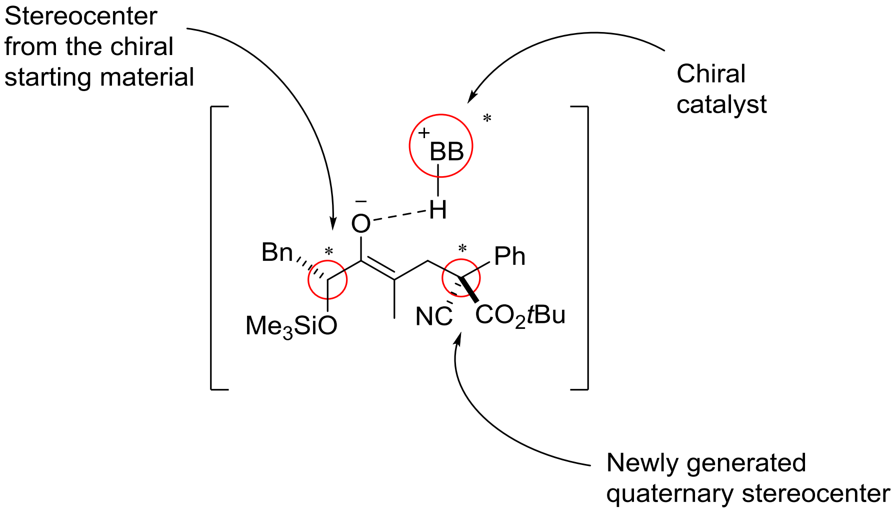


Figure 27. Transition state bearing three chiral inducers.

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**.

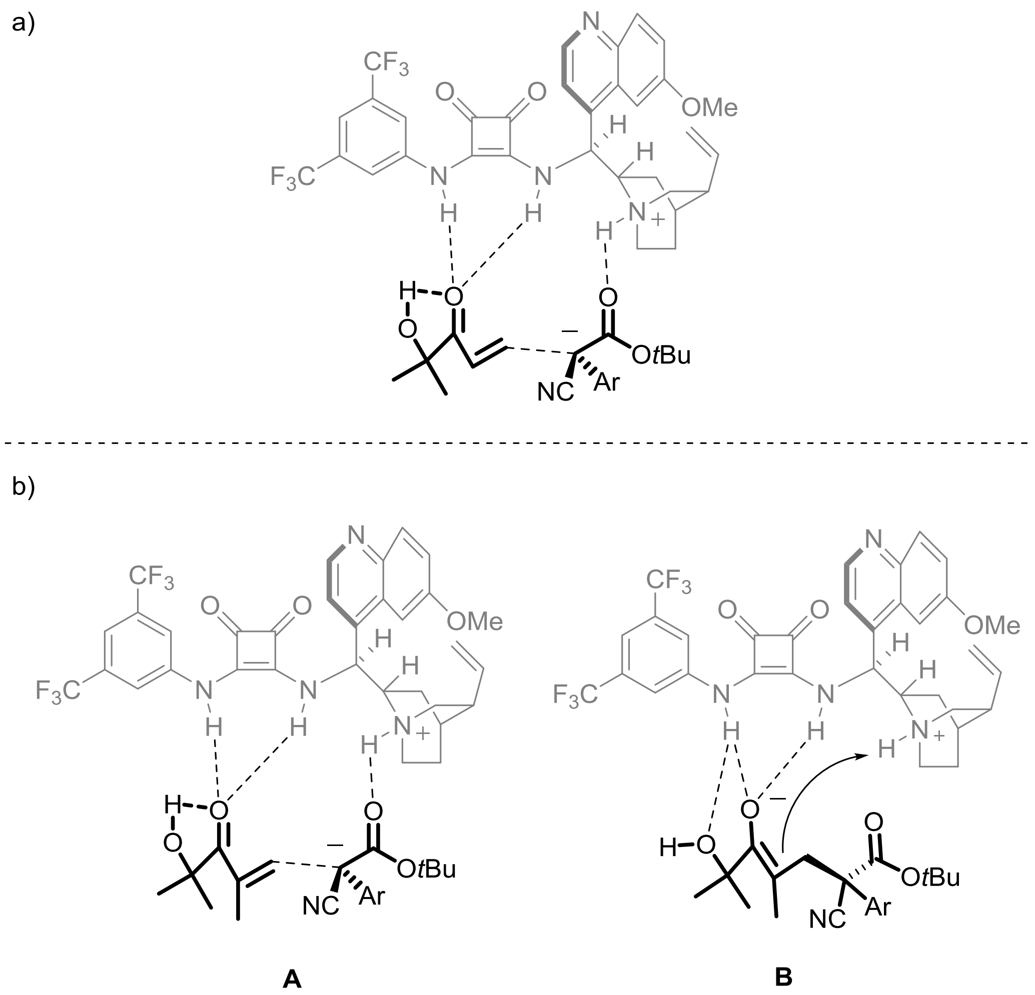
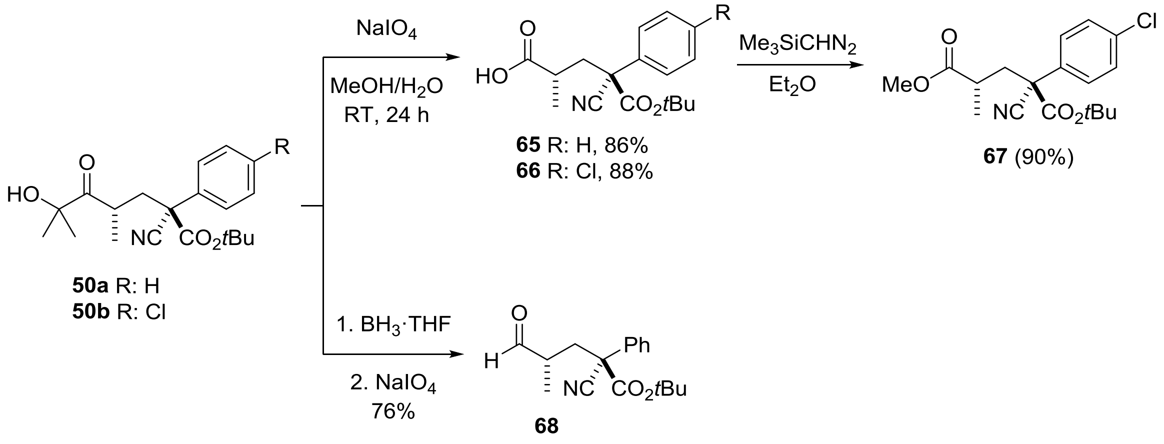


Figure 28. a) Transition State for the addition of α-cyanoacetates to α-unsubstituted α´-hydroxy enones. b) Proposed approaching models for the addition and protonation steps, respectively.

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.

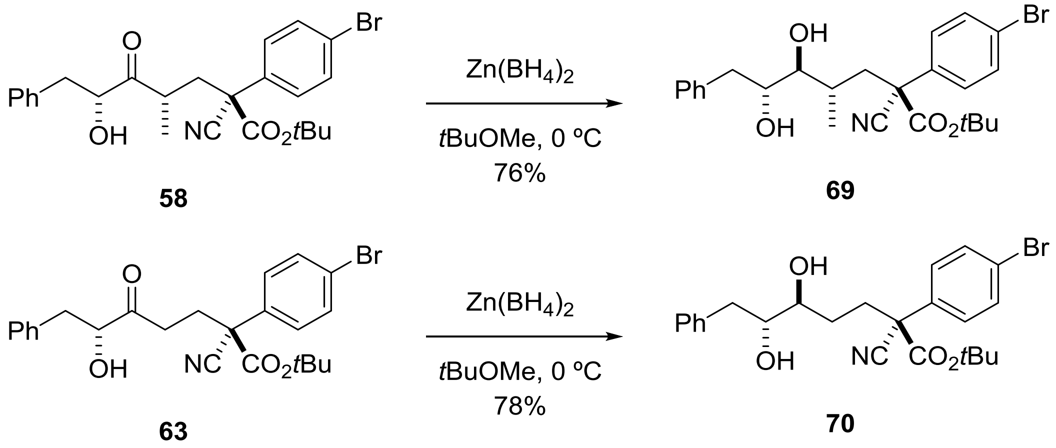
3.2.7. Elaboration of the adducts

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.


NaIO4
MeOH/H2O
RT, 24 h
Me3SiCHN2
Et2O
1. BH3·THF
2. NaIO4
76%
50a R: H
50b R: Cl
65 R: H, 86%
66 R: Cl, 88%
67 (90%)
68

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]


Zn(BH4)2
tBuOMe, 0 °C
76%
Zn(BH4)2
tBuOMe, 0 °C
78%
58
69
63
70

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

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[131] Experiments performed by Dr. Badiola.

[132] Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653–2656.

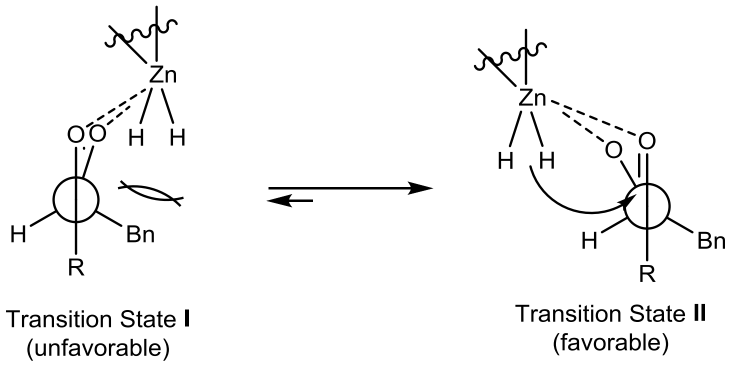
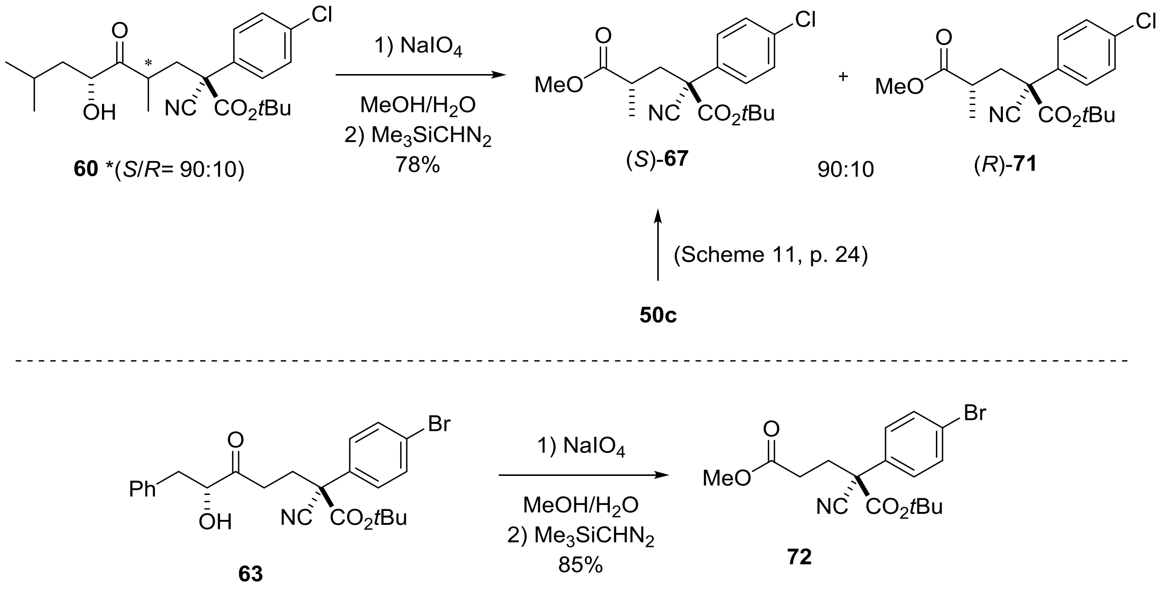

Zn
O
O
H
H
H
Bn
R
Transition State **I**
(unfavorable)
Zn
H
H
O
O
H
Bn
R
Transition State **II**
(favorable)

Figure 29. Transition state for the Zn(BH4)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**.


O
OH
NC
CO2*t*Bu
Cl
*
60 *(*S*/*R*= 90:10)
1) NaIO4
MeOH/H2O
2) Me3SiCHN2
78%
MeO
O
NC
CO2*t*Bu
Cl
(*S*)-**67**
+
90:10
MeO
O
NC
CO2*t*Bu
Cl
(*R*)-**71**
(Scheme 11, p. 24)
50c
Ph
O
OH
NC
CO2*t*Bu
Br
63
1) NaIO4
MeOH/H2O
2) Me3SiCHN2
85%
MeO
O
NC
CO2*t*Bu
Br
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.

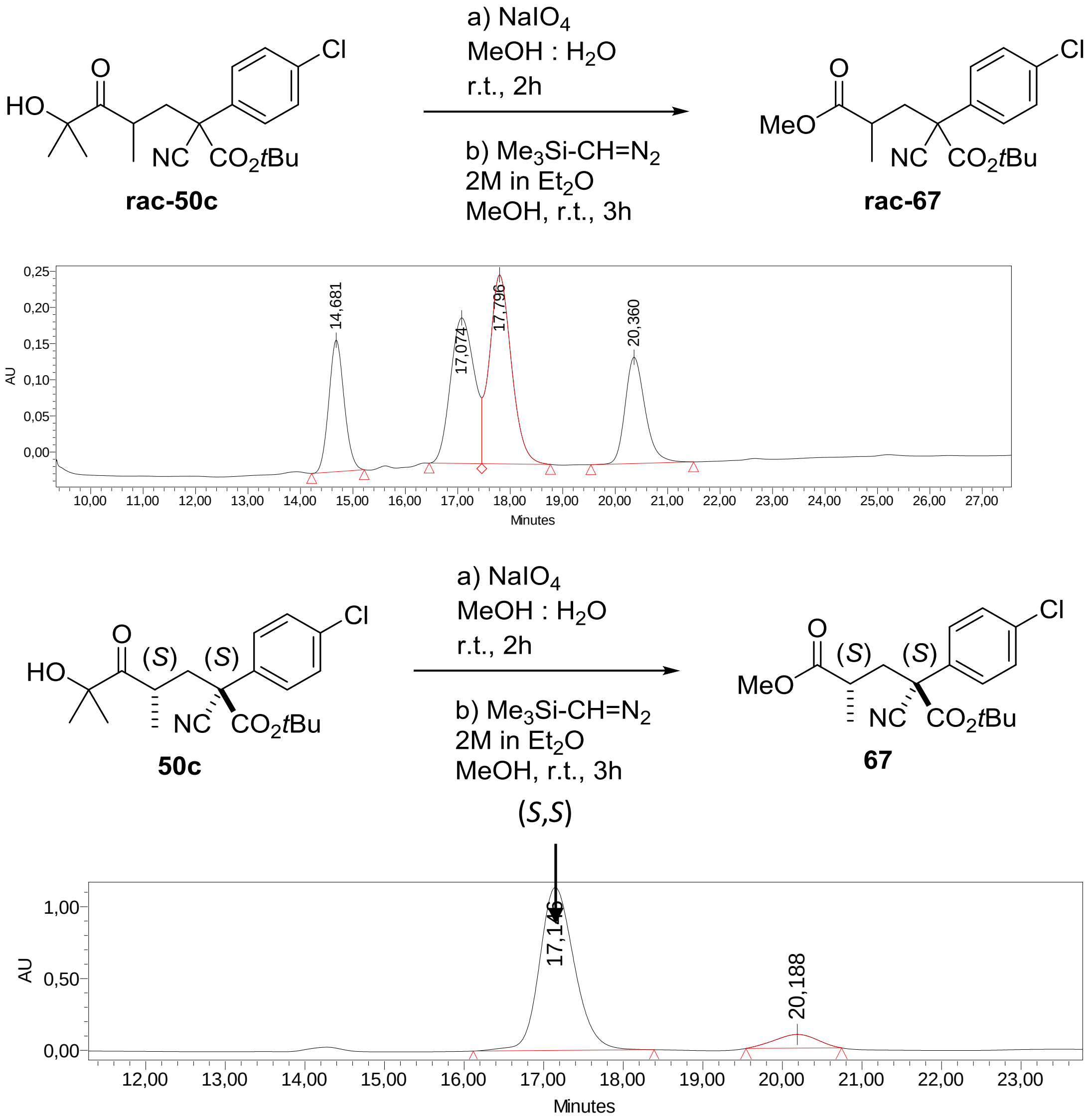


Figure 30. HPLC chromatogram of compound **67**.

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).

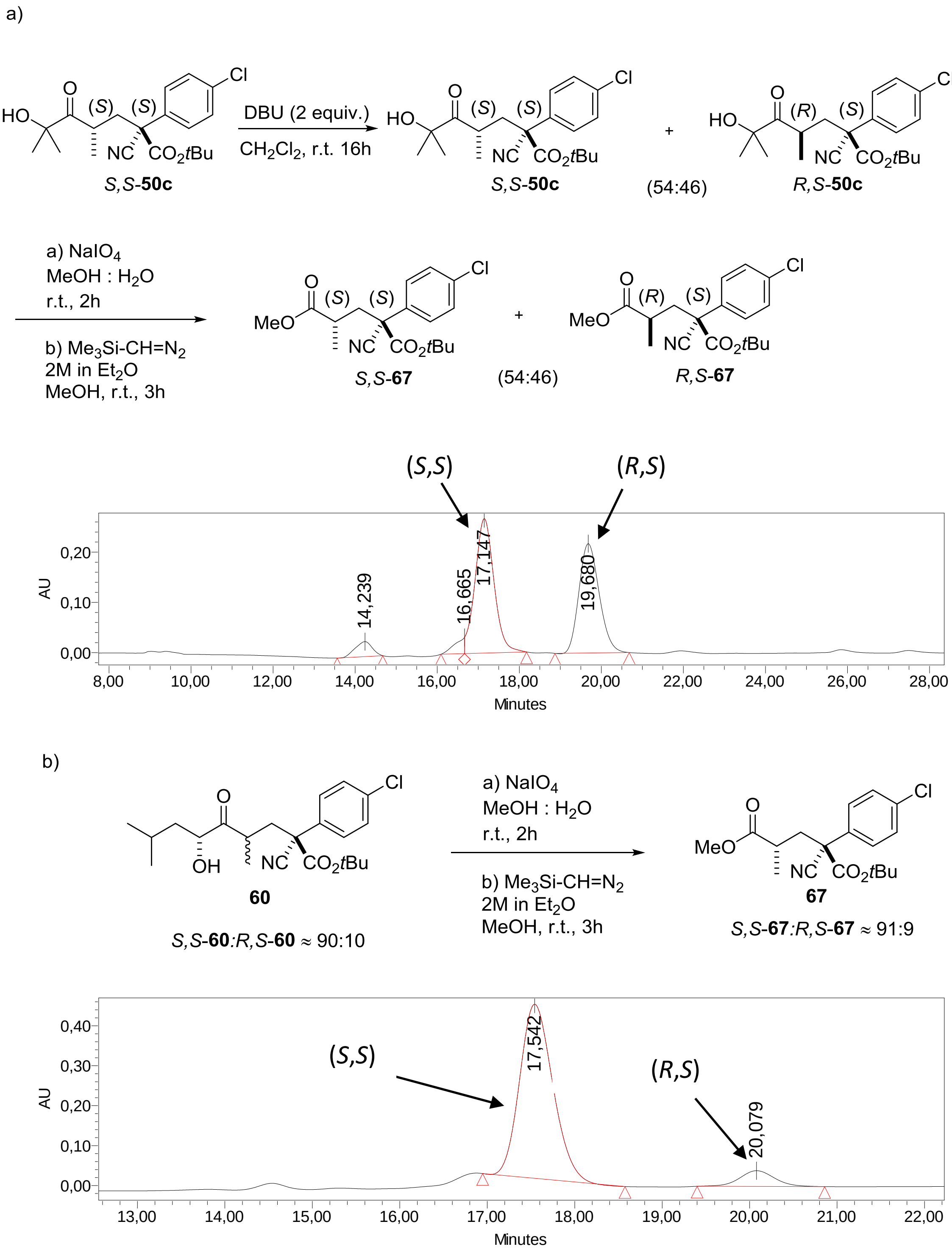

a)
HO
O
(S)
(S)
Cl
NC
CO2tBu
S,S-50c
DBU (2 equiv.)
CH2Cl2, r.t. 16h
S,S-50c
+
(54:46)
(R)
R,S-50c
a) NaIO4
MeOH : H2O
r.t., 2h
b) Me3Si-CH=N2
2M in Et2O
MeOH, r.t., 3h
MeO
S,S-67
(54:46)
R,S-67
(S,S)
(R,S)
14,239
16,665
17,147
19,680
AU
0,00
0,10
0,20
8,00
10,00
12,00
14,00
16,00
18,00
20,00
22,00
24,00
26,00
28,00
Minutes
b)
OH
60
S,S-60:R,S-60 ≈ 90:10
67
S,S-67:R,S-67 ≈ 91:9
(S,S)
(R,S)
17,542
20,079
0,00
0,10
0,20
0,30
0,40
13,00
14,00
15,00
16,00
17,00
18,00
19,00
20,00
21,00
22,00
Minutes

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.

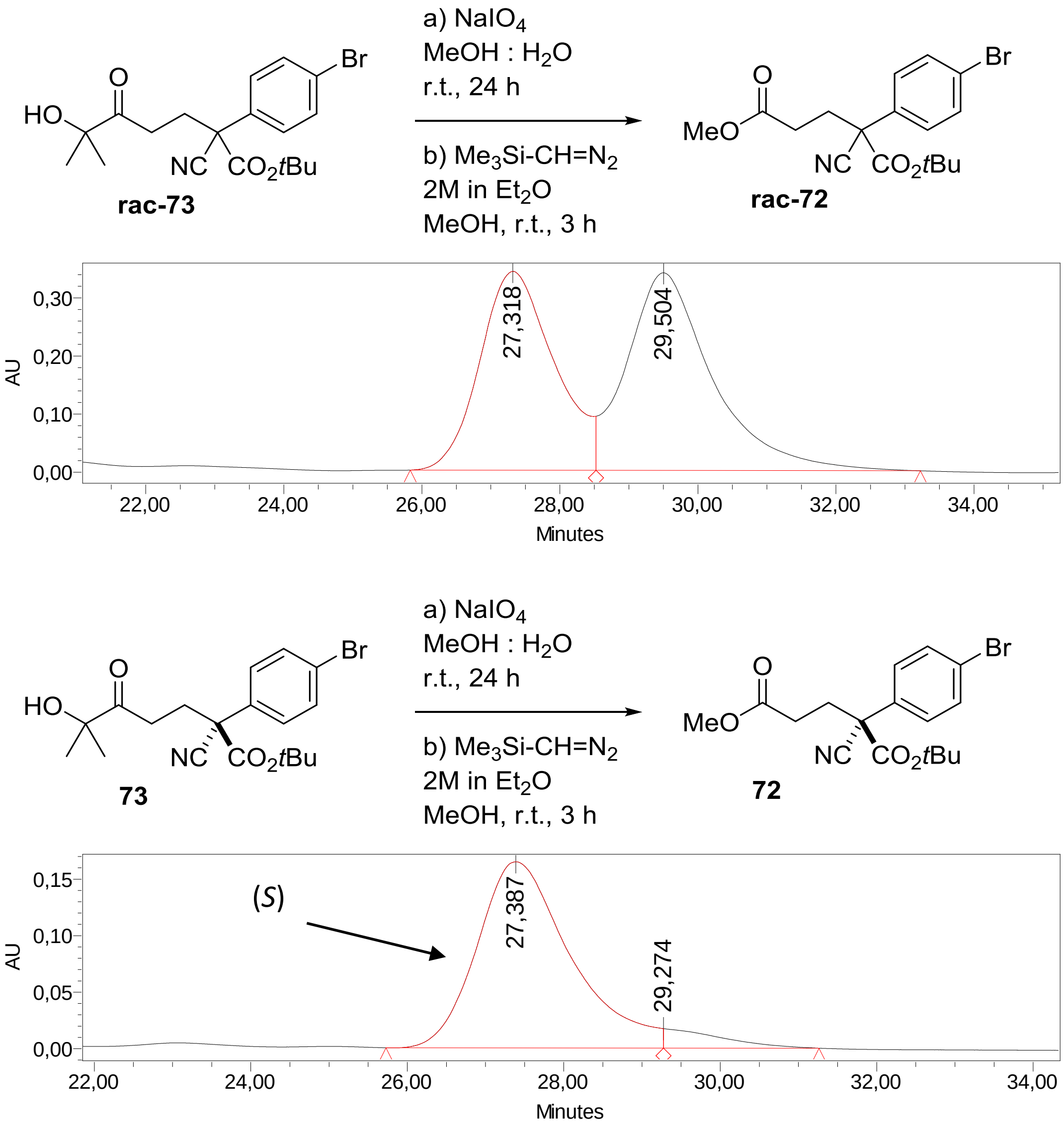


Figure 32. HPLC chromatogram of compound **72**.

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

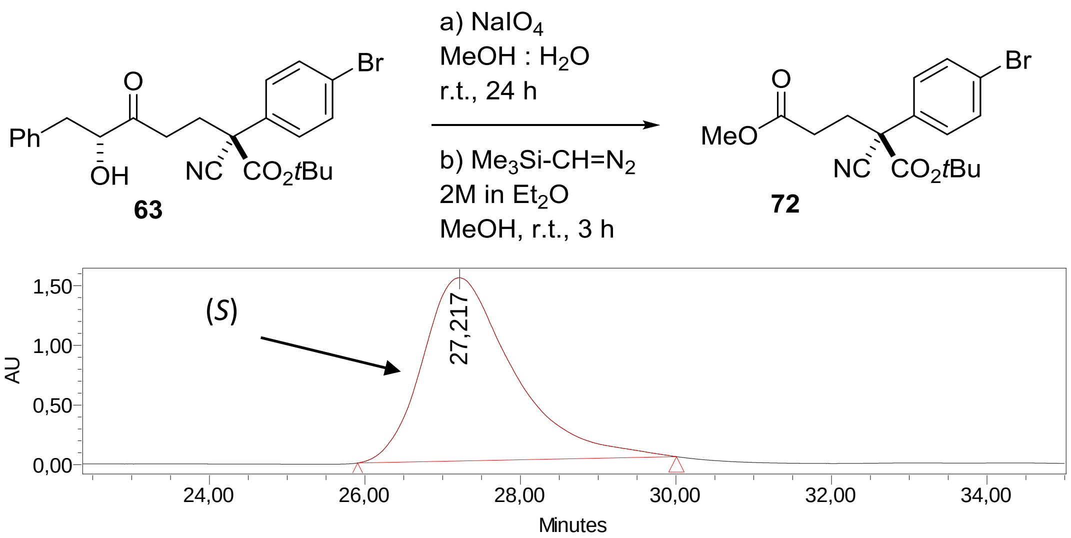

Ph
OH
O
NC
CO2tBu
Br
63
a) NaIO4
MeOH : H2O
r.t., 24 h
b) Me3Si-CH=N2
2M in Et2O
MeOH, r.t., 3 h
MeO
O
NC
CO2tBu
Br
72
(S)
27,217
AU
1,50
1,00
0,50
0,00
24,00
26,00
28,00
30,00
32,00
34,00
Minutes

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 121

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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-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.

---

[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.

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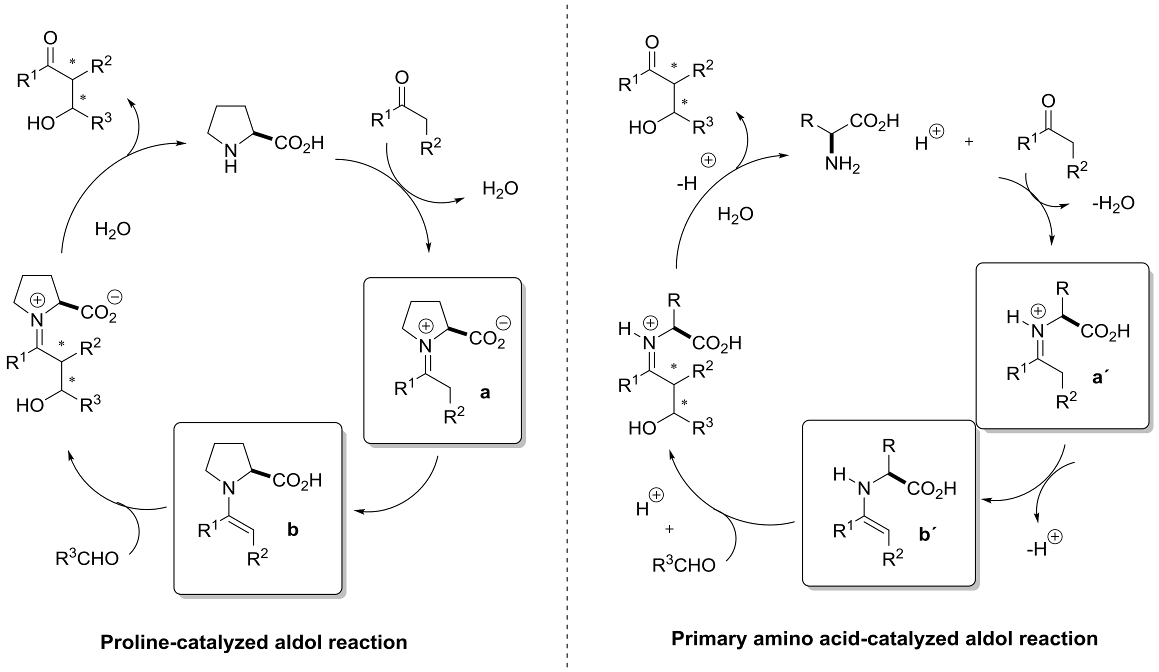
[135] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

[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.

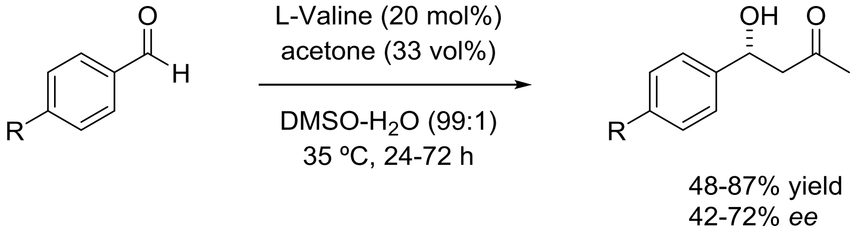
[139] Tanaka, F.; Thayumanavan, R.; Mase, N; Barbas III, C. F. *Tetrahedron Lett.* **2004**, *45*, 325−328.


Proline-catalyzed aldol reaction
Primary amino acid-catalyzed aldol reaction
a
b
a´
b´
H2O
-H2O
R3CHO

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

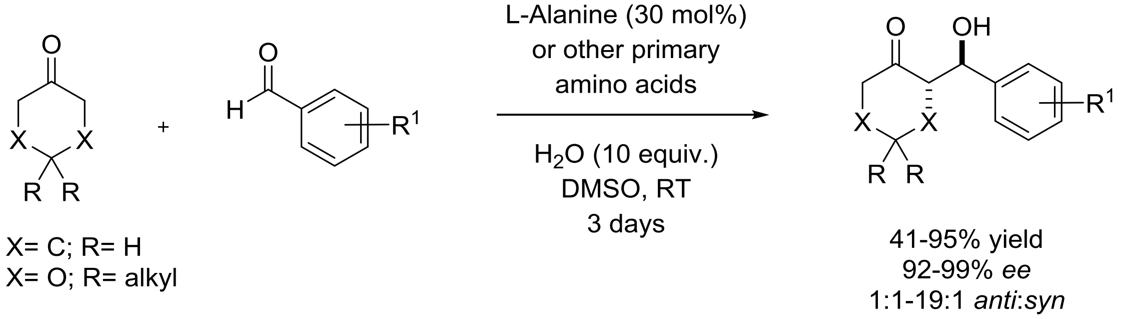
4.1.3. Intermolecular aldol reactions catalysed by primary amino acids and their derivatives

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.


L-Valine (20 mol%)
acetone (33 vol%)
DMSO-H2O (99:1)
35 ºC, 24-72 h
48-87% yield
42-72% ee

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.

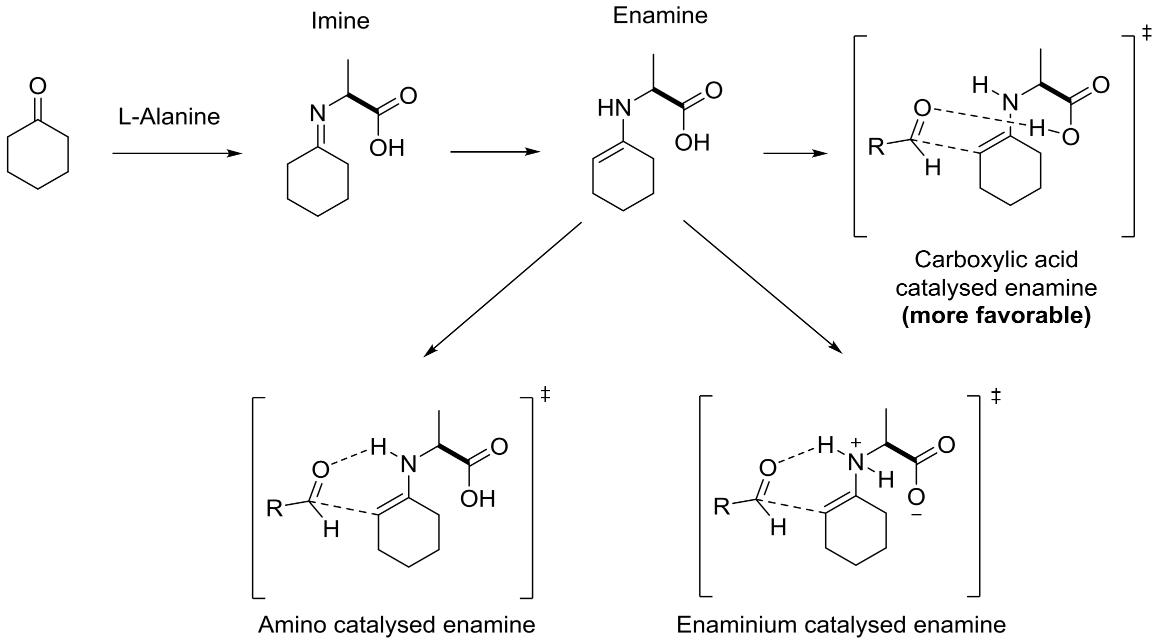


Scheme 64. Intermolecular aldol reaction catalysed by a number of primary amino acids.

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.

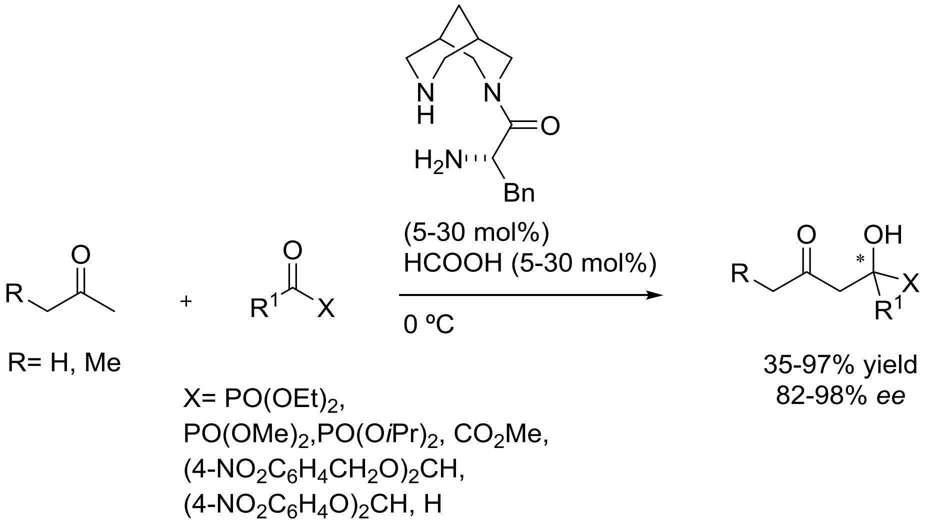

Imine
Enamine
L-Alanine
Carboxylic acid catalysed enamine
(more favorable)
Amino catalysed enamine
Enaminium catalysed enamine

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.

---

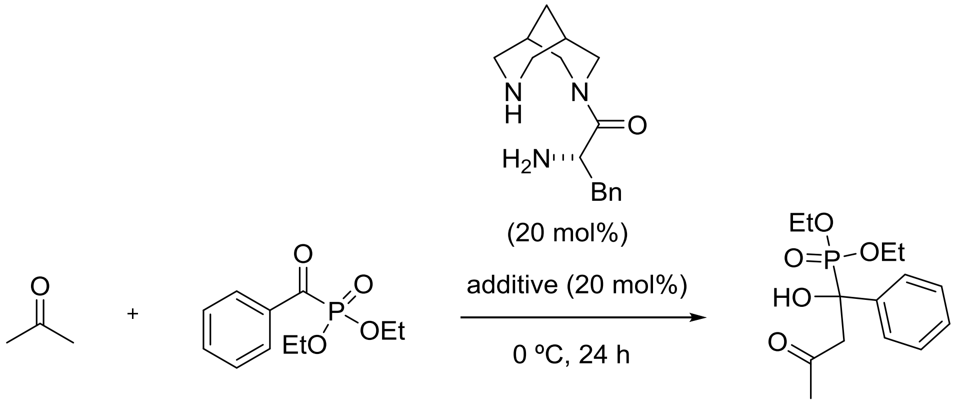
[141] Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654–5655.


N
H
N
O
H_2N
Bn
(5-30 mol%)
HCOOH (5-30 mol%)
0 ºC
R
O
R= H, Me
+
O
R^1
X
X= $PO(OEt)_2$, $PO(OMe)_2$,$PO(OiPr)_2$, CO_2Me, $(4\text{-}NO_2C_6H_4CH_2O)_2CH$, $(4\text{-}NO_2C_6H_4O)_2CH$, H
O
OH
*
X
R^1
35-97% yield
82-98% ee

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.


N
H
N
O
H_2N
Bn
(20 mol%)
additive (20 mol%)
0 ºC, 24 h
O
+
O
P
O
EtO
OEt
EtO
O=P-OEt
HO
O

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.

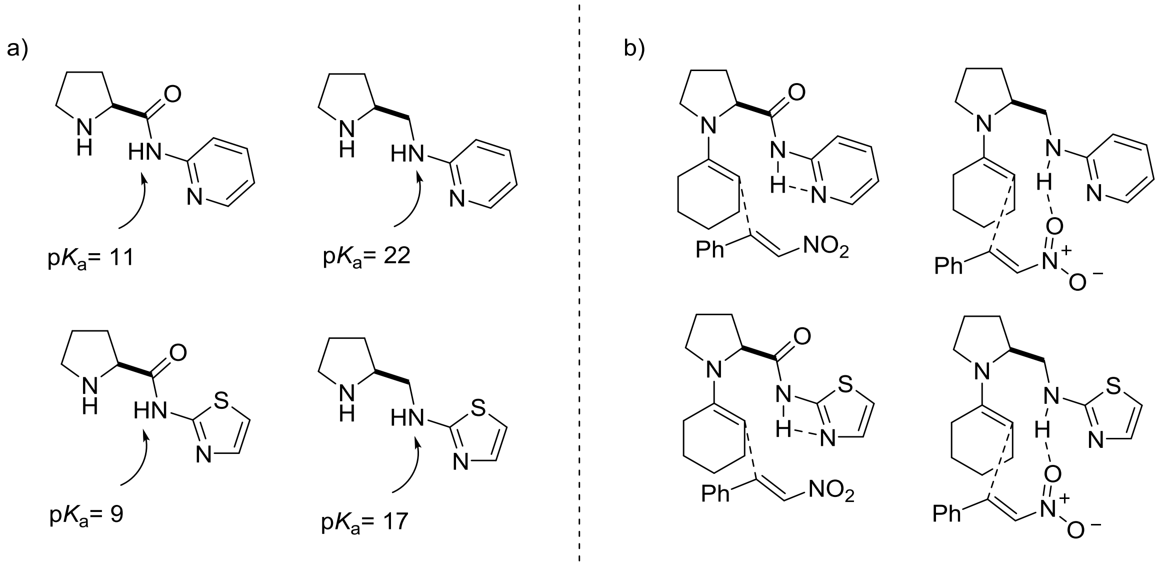
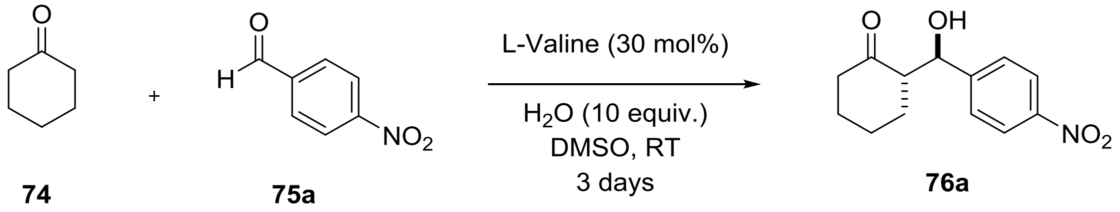


Figure 34. p*K*a values and transition states for designed amino acid derived catalyst.

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.



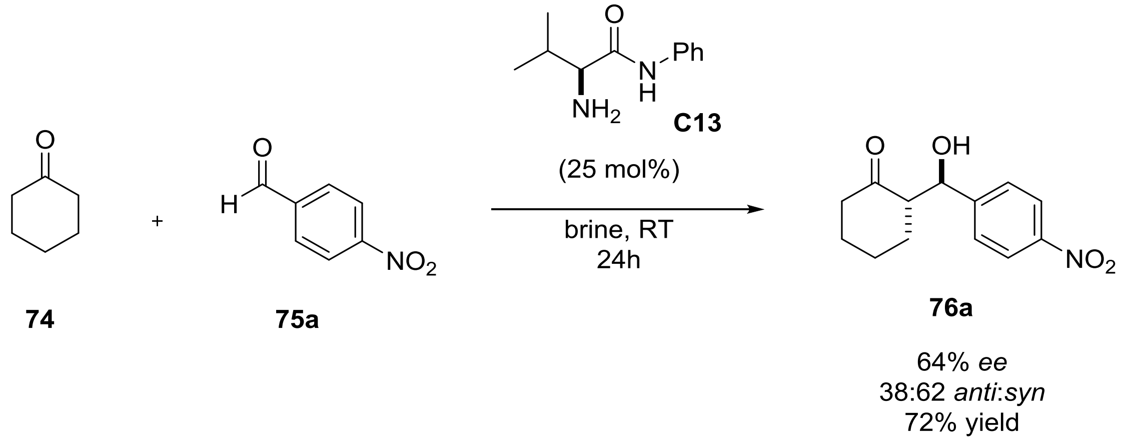
74 **75a** **76a**

>99% *ee*
37:1 *anti*:*syn*
98% yield

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.



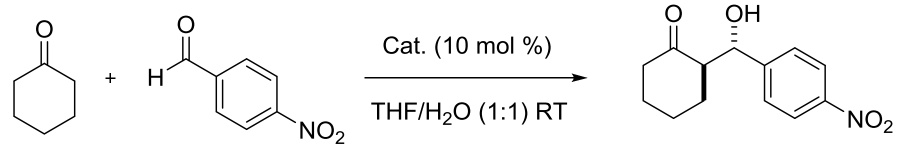
Scheme 68. *N*-phenyl-L-valinamide (**C13**) promoted asymmetric aldol reaction between cyclohexanone **74** and aldehyde **75a**.

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.

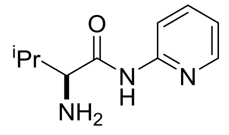
---

[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]

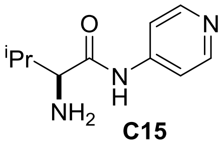


74 **75a** **76a**



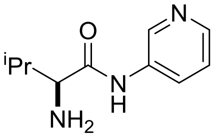
C14

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



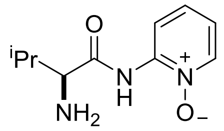
C15

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



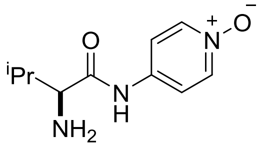
C16

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



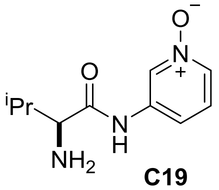
C17

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



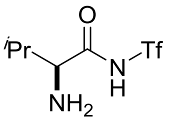
C18

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*



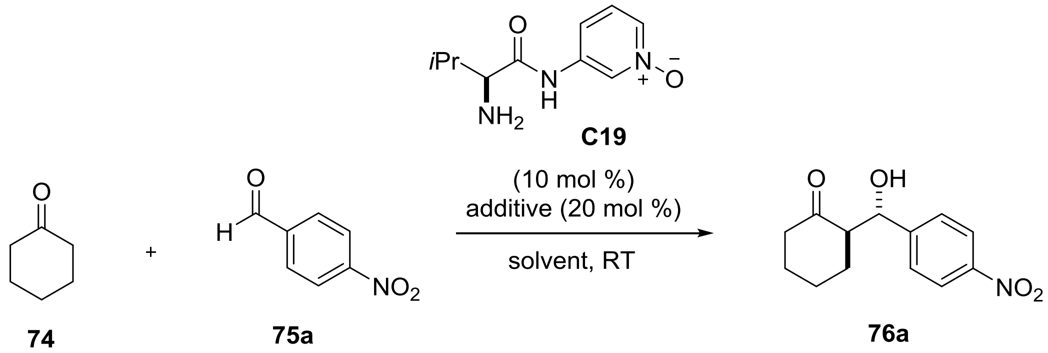
C20

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]

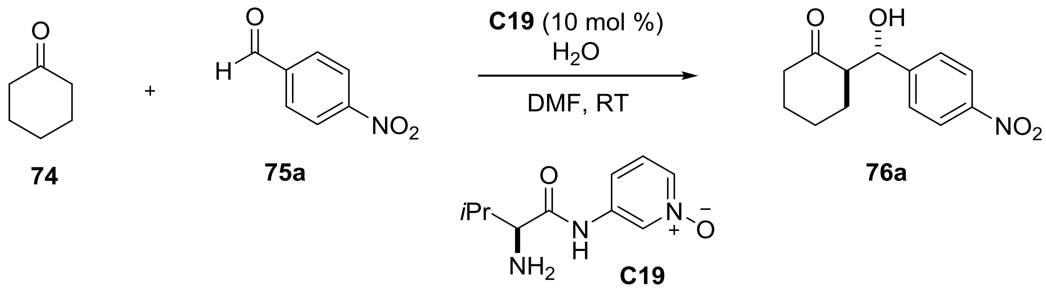


entry	solvent	additive	time	conv. (*anti*/*syn*)	*ee* (*anti*)
1	THF/H_2O	--	5 days	100% (85/15)	90%
2	DMF/H_2O	--	5 days	100% (86/14)	91%
3	MeCN/H_2O	--	6 days	90% (82/18)	43%
4	EtOH/H_2O	--	5 days	100% (85/15)	89%
5	Sat. NaCl	--	6 days	31% (84/16)	n.d.
6	neat	--	6 days	24% (74/26)	n.d.
7	DMF/H_2O	$PhCO_2H$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



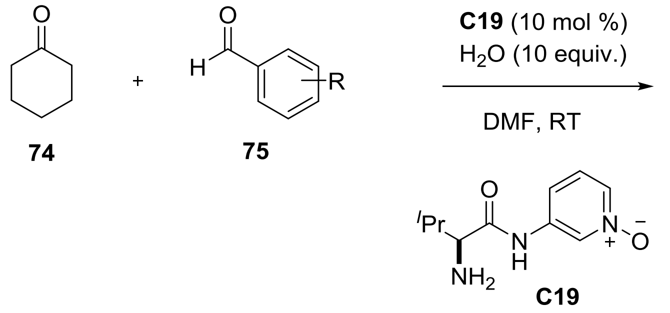
entry	solvent	additive	time	conv. (*anti*/*syn*)	*ee* (*anti*)
1	DMF	--	24h	13% (n.d.)	n.d.
2	DMF	H_2O (5 equiv.)	72h	58% (89/11)	88%
3	DMF	H_2O (10 equiv.)	72h	95% (91/9)	94%
4	DMF	H_2O (30 equiv.)	72h	76% (93/7)	88%
5	DMF	H_2O (50 equiv.)	72h	60% (90/10)	85%
6	DMF/H_2O (1:1)	--	72h	62% (86/14)	91%

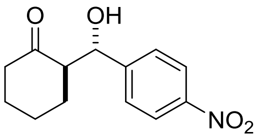
[a] Reactions carried out on 0.1 mmol scale, with **74** (30 equiv.), catalyst (10 mol%) and water in 0.3 mL of DMF. Diastereomeric ratios and *ee* values determined by HPLC analysis on a chiral stationary phase. Conversion determined by ^{1}H NMR analysis.

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**.

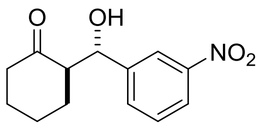
Table 17. Scope of the reaction between **74** and **75** catalysed by **C19**.[a]





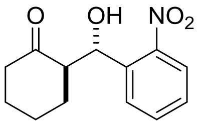
76a

72 h; 86%
dr 91:9; 94% *ee*



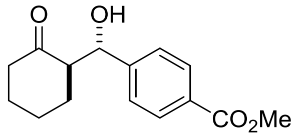
76b

7 days; 80%
dr 86:14; 90% *ee*



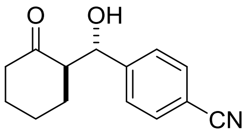
76c

7 days; 66%
dr 95:5; 89% *ee*



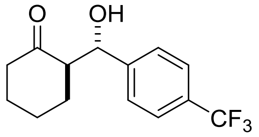
76d

7 days; 67%
dr 66:34; 90% *ee*



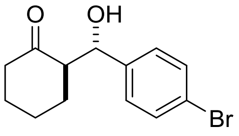
76e

88h; 76%
dr 60:40; 62% ee



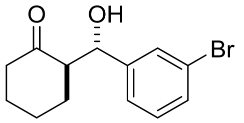
76f

88h; 86%
dr 71:29; 86% ee



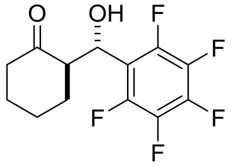
76g

5 days; 73%
dr 86:14; 91% ee



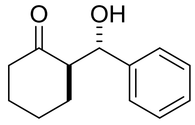
76h

88h; 80%
dr 78:22; 91% *ee*



76i

64h; 92 %
dr >99:1; 80% *ee*



76j

64h; 15% conv.
dr n.d.; ee n.d.

[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

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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.

$(DHQD)_2$PYR (**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]

---

[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} $deg \cdot cm^2 \cdot g^{-1}$; 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

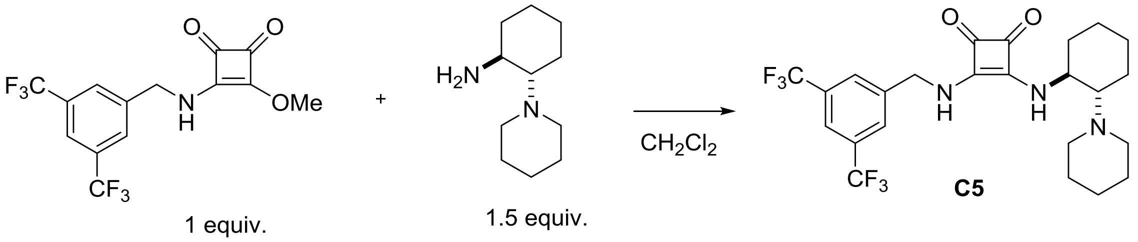
Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on either a Waters 600 (equipped with Photodiode Array Detector Waters 2996) or Shimadzu 20A instrument. The used columns were Chiralpack AS-H, AD-H, AY-H, IA, IB and IC; and flow/solvent conditions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

---

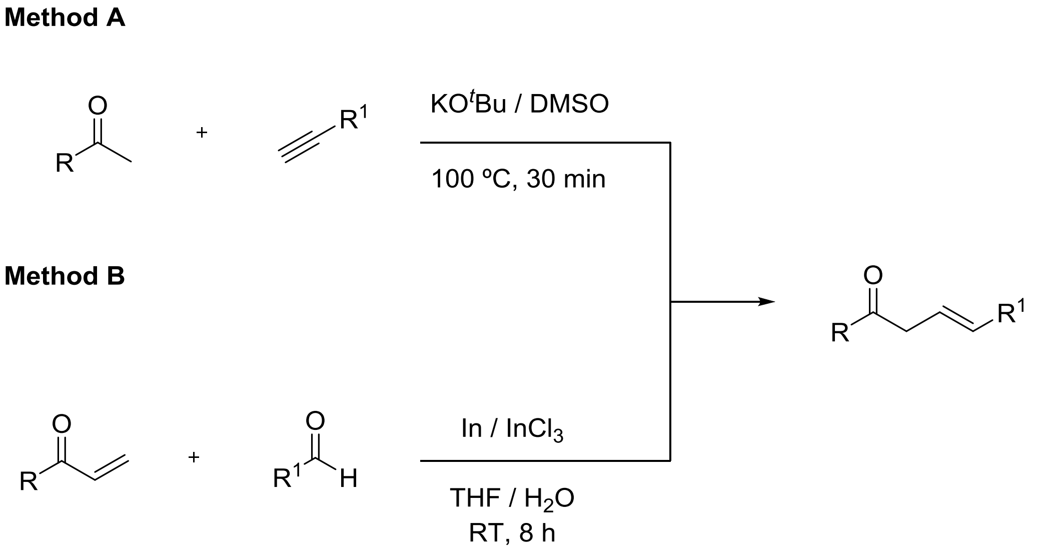
[153] **Ent-C5**: a) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028–2031. b) Baran, R.; Veverková, E.; Skvorcová, A.; Sebesta, R. *Org. Biomol. Chem.* **2013**, *11*, 7705–7711.

[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

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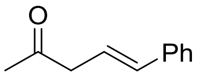
[156] B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem.* **2012**, 77, 6880–6886.

[157] S. Kang, T. S. Jang, G. Keum, S. B. Kang, S. Y. Han, Y. Kim, *Org. Lett.* **2000**, 2, 3615–3617.

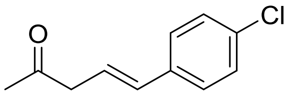
(15 mmol, 3 equiv.) in a mixture of THF and H_2O (1 : 1, 30 mL) was stirred at room temperature for 8 h. After the addition of 1 M HCl (15 mL), the reaction mixture was stirred for 30 min and extracted with ethyl acetate (50 mL × 4). The combined organic phases were washed with brine (100 mL) and dried 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)



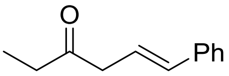
Prepared according to Method B starting from methyl vinyl ketone and benzaldehyde. The title compound was isolated as a colourless oil. Yield: 561 mg (70%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.20 (m, 5H), 6.52 (dt, *J* = 15.8, 1.3 Hz, 1H), 6.35 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.38 (dd, *J* = 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)



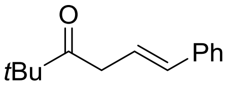
Prepared according to Method B starting from methyl vinyl ketone and 4-chlorobenzaldehyde. The title compound was isolated as a colourless oil. Yield: 730 mg (75%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 4H), 6.46 (dt, *J* = 15.9, 1.2 Hz, 1H), 6.33 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.38 (d, *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)



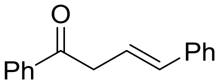
Prepared according to Method B starting from ethyl vinyl ketone and benzaldehyde. The title compound was isolated as a colourless oil. Yield: 793 mg (92%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.23 (m, 5H), 6.57 – 6.44 (m, 1H), 6.36 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.33 (d, *J* = 6.9 Hz, 2H), 2.53 (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)



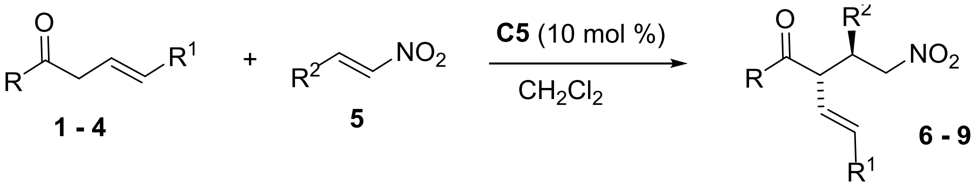
Prepared according to Method A starting from 3,3-dimethyl-2-butanone and phenylacetylene. The title compound was isolated as a brown oil. Yield: 860 mg (85%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.21 (m, 5H), 6.50 (d, *J* = 16.2 Hz, 1H), 6.46 – 6.35 (m, 1H), 3.48 (d, *J* = 6.1 Hz, 2H), 1.24 (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)



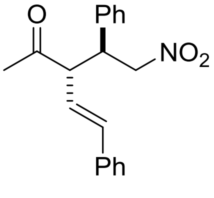
Prepared according to Method A starting from acetophenone and phenylacetylene. The title compound was isolated as a white solid. Yield: 889 mg (80 %). m. p.: 86 – 88 °C. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.13 – 8.02 (m, 2H), 7.69 – 7.21 (m, 8H), 6.61 (d, *J* = 16.1 Hz, 1H), 6.58 – 6.47 (m, 1H), 3.96 (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)

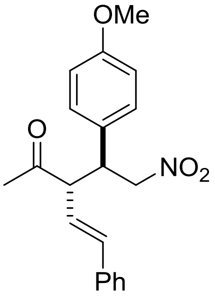


Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 51 mg (83%). m. p.: 131 – 133 °C. $[\alpha]_D^{25}$ = −47.6° (c=0.5, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-*d*) 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.

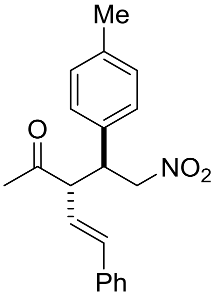
(*S*,*E*)-3-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ab)



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.

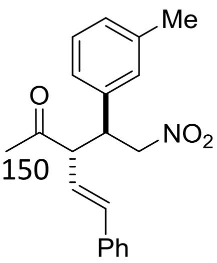
(*S*,*E*)-3-((*S*)-2-Nitro-1-(p-tolyl)ethyl)-5-phenylpent-4-en-2-one (6Ac)



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.

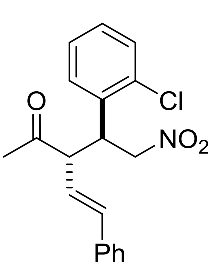
(*S*,*E*)-3-((*S*)-1-(3-Methoxyphenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ad)



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.

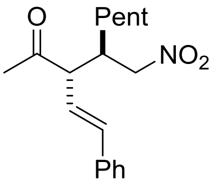
(*S*,*E*)-3-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-5-phenylpent-4-en-2-one (6Ae)



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.

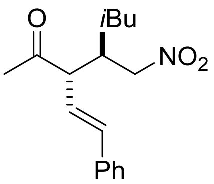
The enantiomeric and diastereomeric purity were determined on crude material before column chromatography by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 95/5, flow rate= 1 mL/min.

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



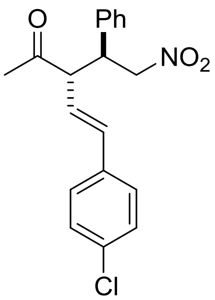
Prepared according to the general procedure starting from allyl ketone **1A** and nitroalkene **5h**. 30 % conversion was obtained after 24 h. The resulting mixture was not separated nor further analyzed.

(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.

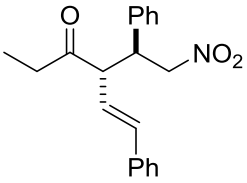
(*S*,*E*)-5-(4-Chlorophenyl)-3-((*S*)-2-nitro-1-phenylethyl)pent-4-en-2-one (6Ba)



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). ^1H 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.

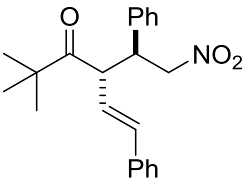
(*S*,*E*)-4-((*S*)-2-Nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (7Aa)



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). ^1H 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.

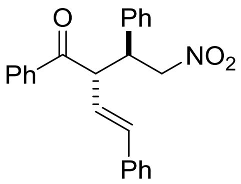
(*S*,*E*)-2,2-Dimethyl-4-((*S*)-2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (8Aa)



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). ^1H 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.

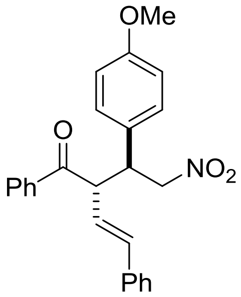
(*S*,*E*)-2-((*S*)-2-Nitro-1-phenylethyl)-1,4-diphenylbut-3-en-1-one (9Aa)



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). ^1H 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.

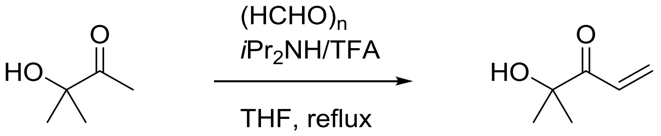
(*S*,*E*)-2-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,4-diphenylbut-3-en-1-one (9Ab)



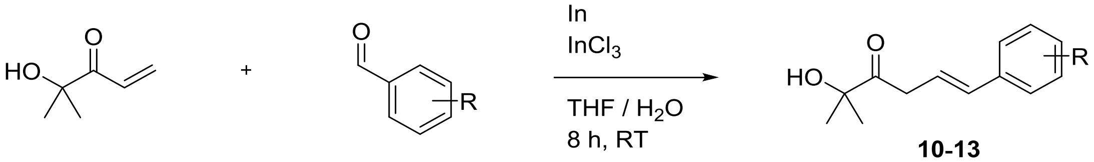
Prepared according to the general procedure starting from allyl ketone **4A** and nitroalkene **5a**. The title compound was isolated as a mixture of diastereomers (dr 8.1:1) as a colourless oil. Yield: 63 mg (78%). ^1H NMR major isomer (300 MHz, Chloroform-*d*) δ 7.95 – 7.76 (m, 2H), 7.63 – 7.09 (m, 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%.



10-13

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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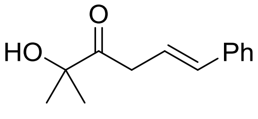
[158] a) Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun*. **2010**, *46*, 1715-1717. b) For an alternative method see: E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881.

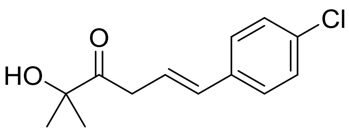
[159] Adapted from: S. Kang, T. S. Jang, G. Keum, S. B. Kang, S. Y. Han, Y. Kim, *Org. Lett.* **2000**, 2, 3615–3617.

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



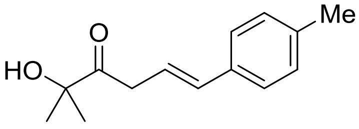
Prepared according to the general procedure starting from benzaldehyde. The title compound was isolated as a colourless oil. Yield: 129 mg (63%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.24 (m, 5H), 6.63 – 6.45 (m, 1H), 6.37 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.55 (dd, *J* = 6.7, 1.3 Hz, 2H), 1.47 (s, 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)



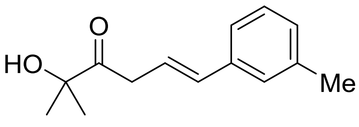
Prepared according to the general procedure starting from 4-chlorobenzaldehyde. The title compound was isolated as a yellow oil. Yield: 162 mg (68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.07 (m, 4H), 6.44 (dt, *J* = 15.9, 1.3 Hz, 1H), 6.34 (s, 1H), 3.52 (dd, *J* = 6.7, 1.3 Hz, 2H), 1.44 (s, 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)



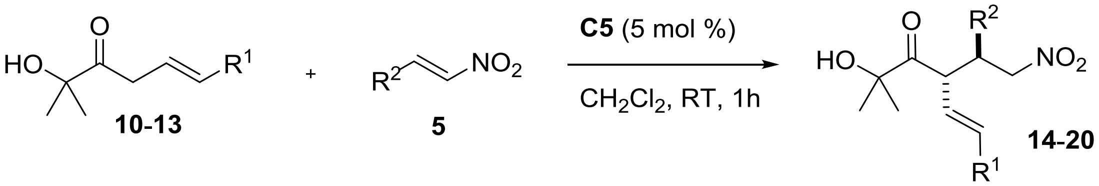
Prepared according to the general procedure starting from 4-methylbenzaldehyde. The title compound was isolated as a yellow oil. Yield: 157 mg (72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.33 (s, 1H), 3.53 (dd, *J* = 6.8, 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)



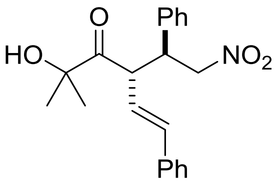
Prepared according to the general procedure starting from 3-methylbenzaldehyde. The title compound was isolated as a yellow oil. Yield: 157 mg (72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.15 (m, 4H), 6.58 – 6.44 (m, 1H), 6.37 (s, 1H), 3.53 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.38 (s, 3H), 1.46 (s, 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).

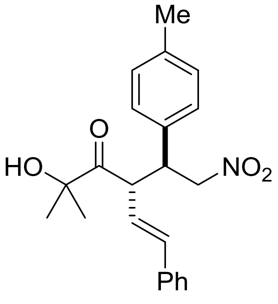
(*S*,*E*)-2-Hydroxy-2-methyl-4-((*S*)-2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (14)



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). ^1H 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.

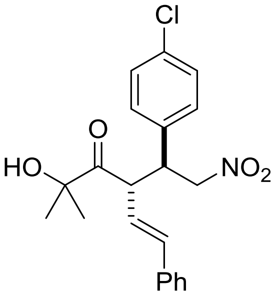
(*S*,*E*)-2-Hydroxy-2-methyl-4-((*S*)-2-nitro-1-(p-tolyl)ethyl)-6-phenylhex-5-en-3-one (15)



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). ^1H 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.

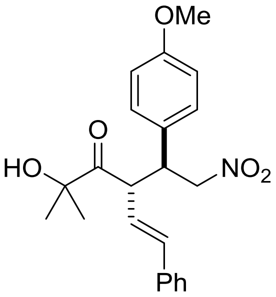
(*S*,*E*)-4-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (16)



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). ^1H 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.

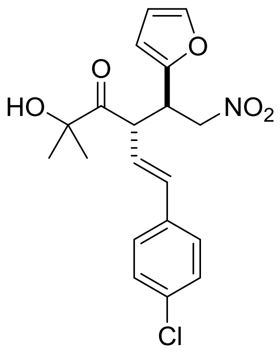
(*S*,*E*)-2-Hydroxy-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-methyl-6-phenylhex-5-en-3-one (17)



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). ^1H 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.

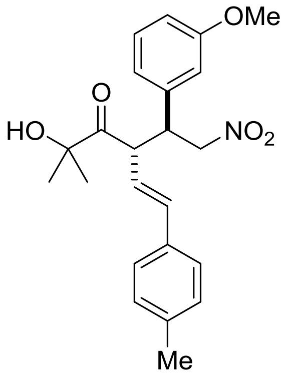
(*S*,*E*)-6-(4-Chlorophenyl)-4-((*R*)-1-(furan-2-yl)-2-nitroethyl)-2-hydroxy-2-methylhex-5-en-3-one (18)



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). ^1H 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.

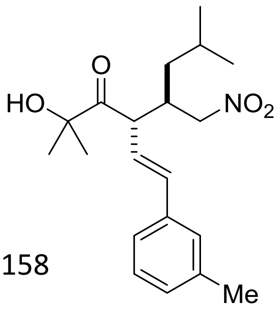
(*S*,*E*)-2-Hydroxy-4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-2-methyl-6-(p-tolyl)hex-5-en-3-one (19)



Prepared according to the general procedure starting from allylic ketol **12** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 60 mg (75%). $[\alpha]_D^{25}$ = −128.9° (c= 0.1, 90% *ee*, CH_2Cl_2). ^1H 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)



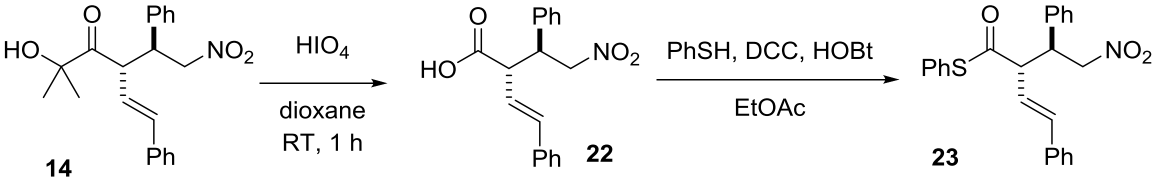
Prepared according to the general procedure starting from allylic ketol 1**3** and nitroalkene **5i** and running the reaction for 16 h. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 57 mg (82%). $[\alpha]_D^{25}$ = −162.9° (c= 1, 98% *ee*,

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.

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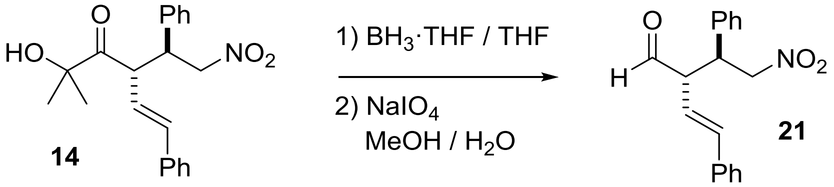
[160] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881.

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.

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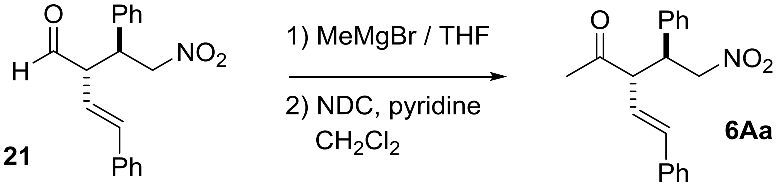
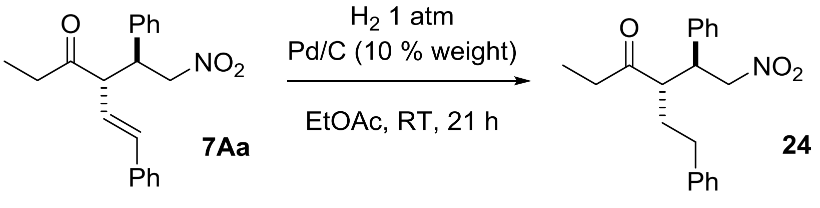
[161] Zhang, S. J.; Hu, W. X. *Synth. Commun.* **2010**, *40*, 3093–3100.

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**.

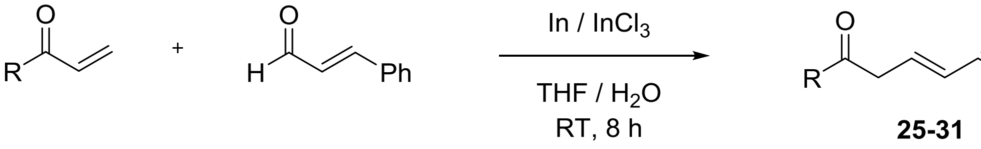
6.2.6.4. *Hydrogenation of 7Aa to obtain adduct 24*



(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

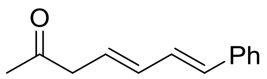
Hz, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.6, 140.6, 137.5, 131.4, 128.9, 128.6, 128.2, 128.2, 126.3, 77.4, 54.6, 45.6, 37.9, 33.4, 31.0, 7.1. UPLC-DAD-QTOF: $C_{20}H_{23}NO_3$ $[M+H]^+$ calcd.: 326,1756, found: 326,1750.

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



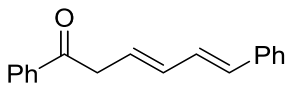
Procedure adapted from ref 157. A mixture of trans-cinnamaldehyde (5.0 mmol, 1 equiv.), In powder (1.15 g, 10 mmol, 2 equiv.), $InCl_3$ (553 mg, 2.5 mmol, 0.5 equiv.) and the corresponding vinyl ketone (15 mmol, 3 equiv.) in a mixture of THF and H_2O (1 : 1, 30 mL) was stirred at room temperature for 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)



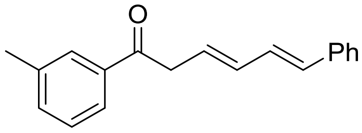
Prepared according to the general procedure starting from methyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a yellow oil. Yield: 605 mg (65%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.65 – 7.20 (m, 5H), 6.82 (dd, J = 15.6, 10.3 Hz, 1H), 6.55 (dd, J = 15.7, 5.5 Hz, 1H), 6.41 – 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)



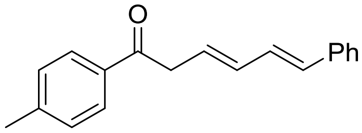
Prepared according to the general procedure starting from phenyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a yellow oil. Yield: 720 mg (58%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 – 7.94 (m, 2H), 7.69 – 7.17 (m, 8H), 6.85 (dd, J = 15.6, 10.3 Hz, 1H), 6.55 (d, J = 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)



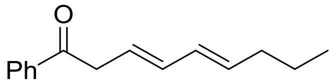
Prepared according to the general procedure starting from 1-(*m*-tolyl)prop-2-en-1-one and *trans*-cinnamaldehyde. The title compound was isolated as a white solid. Yield: 787 mg (60%). m. p.: 89 – 91 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 – 7.75 (m, 2H), 7.54 – 7.10 (m, 8H), 6.85 (dd, J = 15.7, 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)



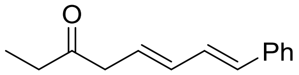
Prepared according to the general procedure starting from 1-(*p*-tolyl)prop-2-en-1-one and *trans*-cinnamaldehyde. The title compound was isolated as a white solid. Yield: 892 mg (68%). m. p.: 86 – 88 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, J = 7.9 Hz, 2H), 7.56 – 7.22 (m, 8H), 6.97 – 6.75 (m, 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.

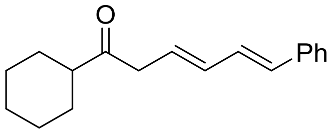
(5*E*,7*E*)-8-Phenylocta-5,7-dien-3-one (28)



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,

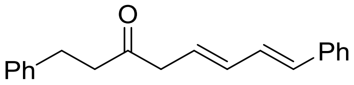
Chloroform-d) δ 7.66 – 7.22 (m, 5H), 6.88 – 6.76 (m, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.32 (dd, J = 15.3, 10.3 Hz, 1H), 5.94 (dt, J = 14.9, 7.3 Hz, 1H), 3.29 (d, J = 7.3 Hz, 2H), 2.53 (q, J = 7.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 194.0, 137.4, 134.4, 132.2, 128.9, 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)



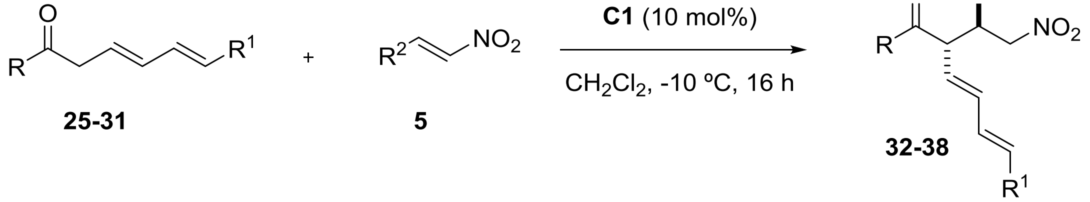
Prepared according to the general procedure starting from cyclohexyl vinyl ketone and *trans*-cinnamaldehyde. The title compound was isolated as a mixture of compound **6A** and an unidentified byproduct in a 1 : 1 ratio. Yield of the mixture: 1.02 g (80%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 – 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)

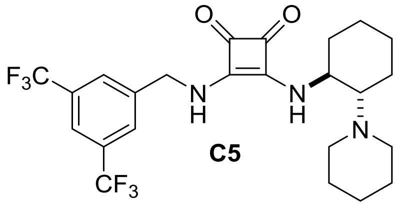


Prepared according to the general procedure starting from 5-phenylpent-1-en-3-one and *trans*-cinnamaldehyde. The title compound was isolated as a colourless oil. Yield: 954 mg (69%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.50 – 7.18 (m, 10H), 6.80 (dd, J = 15.7, 10.5 Hz, 1H), 6.53 (d, J = 15.6 Hz, 1H), 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



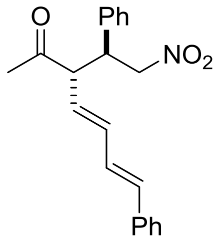
25-31 **5** **32-38**



C5

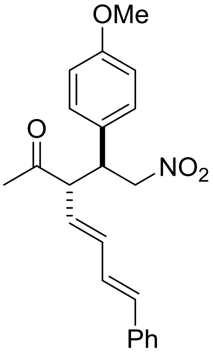
General procedure: To a mixture of the corresponding allyl ketone (0.3 mmol, 1.5 equiv.) and nitroalkene (0.2 mmol, 1 equiv.) in dichloromethane (0.4 mL), the catalyst (0.02 mmol, 10 mol%) was added at −10 °C unless otherwise stated. The resulting mixture was stirred at −10 °C unless otherwise stated 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). ^1H 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.

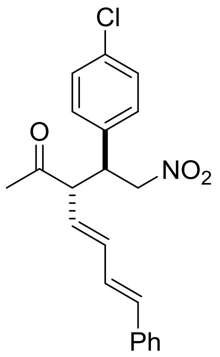
(*S*,4*E*,6*E*)-3-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-7-phenylhepta-4,6-dien-2-one (32Ab)



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). ^1H 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 –

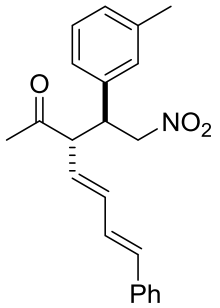
4.52 (m, 2H), 3.96 (dtd, J = 10.1, 5.6, 4.7, 1.9 Hz, 1H), 3.81 (d, J = 2.1 Hz, 3H), 3.67 (td, J = 10.2, 2.1 Hz, 1H), 1.98 (d, J = 2.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 205.7, 159.2, 136.6, 134.3, 129.2, 128.9, 128.7, 128.1, 127.4, 127.2, 126.5, 114.4, 78.8, 60.7, 55.2, 44.6, 30.1. UPLC-DAD-QTOF: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



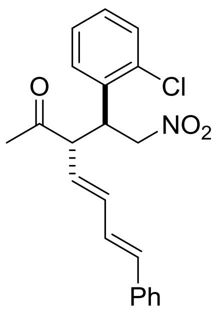
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5k**. The title compound was isolated as a single diastereomer as a white solid. Yield: 56 mg (76%). m. p.: 137 – 139 °C. $[\alpha]_D^{25}$ = −107° (c= 1, >99% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, Chloroform-d) 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). ^1H 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.

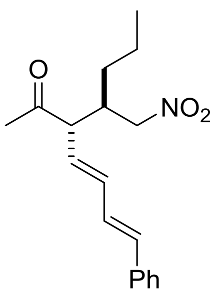
(*S*,4*E*,6*E*)-3-((*S*)-1-(2-Chlorophenyl)-2-nitroethyl)-7-phenylhepta-4,6-dien-2-one (32Ae)



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). ^1H 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

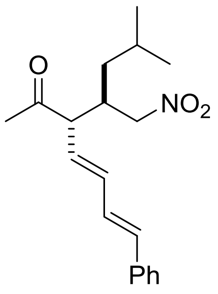
206.6, 138.6, 137.6, 135.7, 131.7, 130.3, 129.8, 129.3, 128.4, 128.2, 127.7, 127.5, 77.5, 59.5, 30.7. UPLC-DAD-QTOF: $C_{21}H_{21}ClNO_3$ $[M+H]^+$ calcd.: 370.1210, found: 370.1210.

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



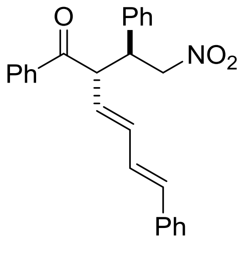
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5l**. The title compound was isolated as a mixture of diastereomers (dr 57 : 43) as a colourless oil. Yield: 50 mg (83%). ^{1}H NMR major diastereomer (300 MHz, Chloroform-d) δ 7.35 (s, 5H), 6.75 (ddd, J = 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)



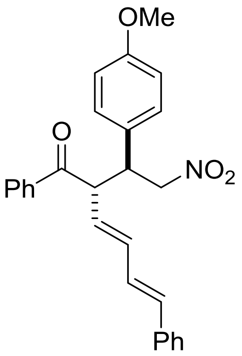
Prepared according to the general procedure starting from allyl ketone **25A** and nitroalkene **5i**. The title compound was isolated as a mixture of diastereomers (dr 59 : 41) as a colourless oil. Yield: 45 mg (72%). ^{1}H NMR major diastereomer (300 MHz, Chloroform-d) δ 7.52 – 7.18 (m, 5H), 6.88 – 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)



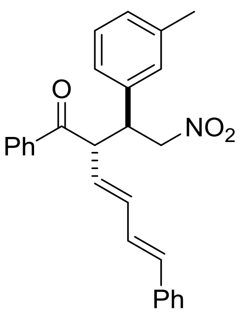
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 64 mg (80%). m. p.: 144 – 146 °C. $[\alpha]_D^{25} = -86.1°$ (c= 0.5, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) 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)



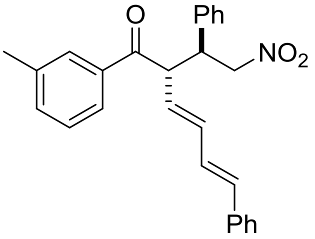
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a white solid. Yield: 64 mg (75%). m. p.: 133 – 135 °C. [α]$_D^{25}$ = −13.4° (c= 0.2, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) 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)



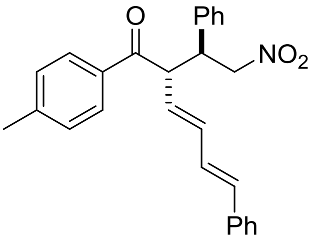
Prepared according to the general procedure starting from allyl ketone **26A** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a white solid. Yield: 57 mg (69%). m. p.: 130 – 132 °C. [α]$_D^{25}$ = −28.0° (c= 1, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) 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)



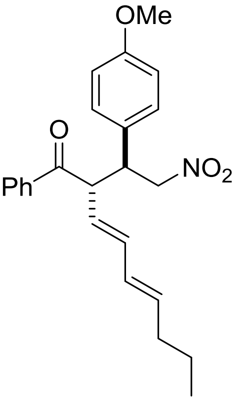
Prepared according to the general procedure starting from allyl ketone **27A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 62 mg (76%). m. p.: 145 – 147 °C. [α]$_D^{25}$ = −125.6° (c= 1, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) 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)



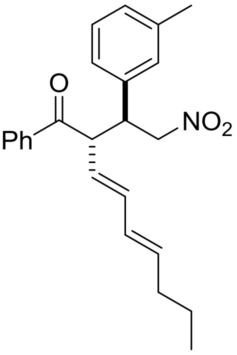
Prepared according to the general procedure starting from allyl ketone **28A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 71 mg (87%). m. p.: 133 – 135 °C. $[\alpha]_D^{25}$ = −38.0° (c= 0.4, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) 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)



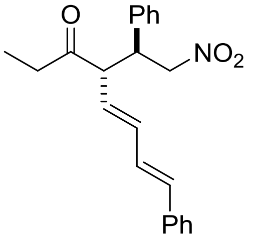
Prepared according to the general procedure starting from allyl ketone **26B** and nitroalkene **5b**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 64 mg (82%). $[\alpha]_D^{25}$ = −139.9° (c= 1.2, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.88 – 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)



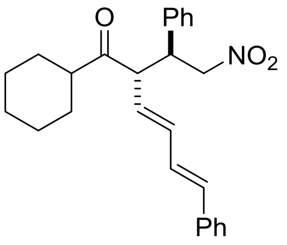
Prepared according to the general procedure starting from allyl ketone **26B** and nitroalkene **5d**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 57 mg (75%). $[\alpha]_D^{25}$ = −43.5° (c= 0.4, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.78 (dt, 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)



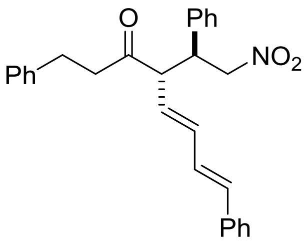
Prepared according to the general procedure starting from allyl ketone **29A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a white solid. Yield: 60 mg (85%). m. p.: 113 – 115 °C. $[\alpha]_D^{25}$ = −92.8° (c= 1.5, >99% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, Chloroform-*d*) 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)



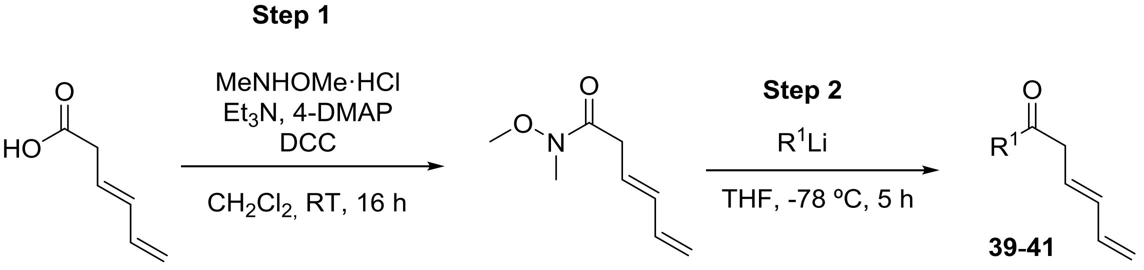
Prepared according to the general procedure starting from allyl ketone **30A** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a colourless oil. Yield: 68 mg (85%). $[\alpha]_D^{25}$ = −60.3° (c= 1, 94% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.20 (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 %). ^1H 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)

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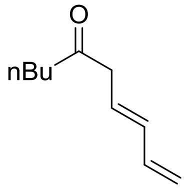
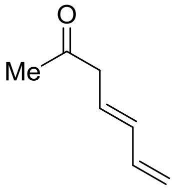
[162] Adapted from: A. Dermenci, R.E. Whittaker, G. Dong, *Org.Lett.* **2013**, *15*, 2242-2245.



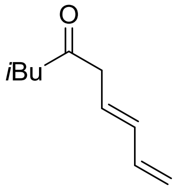
Prepared according to the general procedure for aliphatic ketones starting from *n*-buthyllithium. The title compound was isolated as a yellow oil as a mixture of isomers (desired product / isomerized product: 70/30). Yield: 182 mg (60%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.36 (dt, *J* = 16.9, 10.2 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.

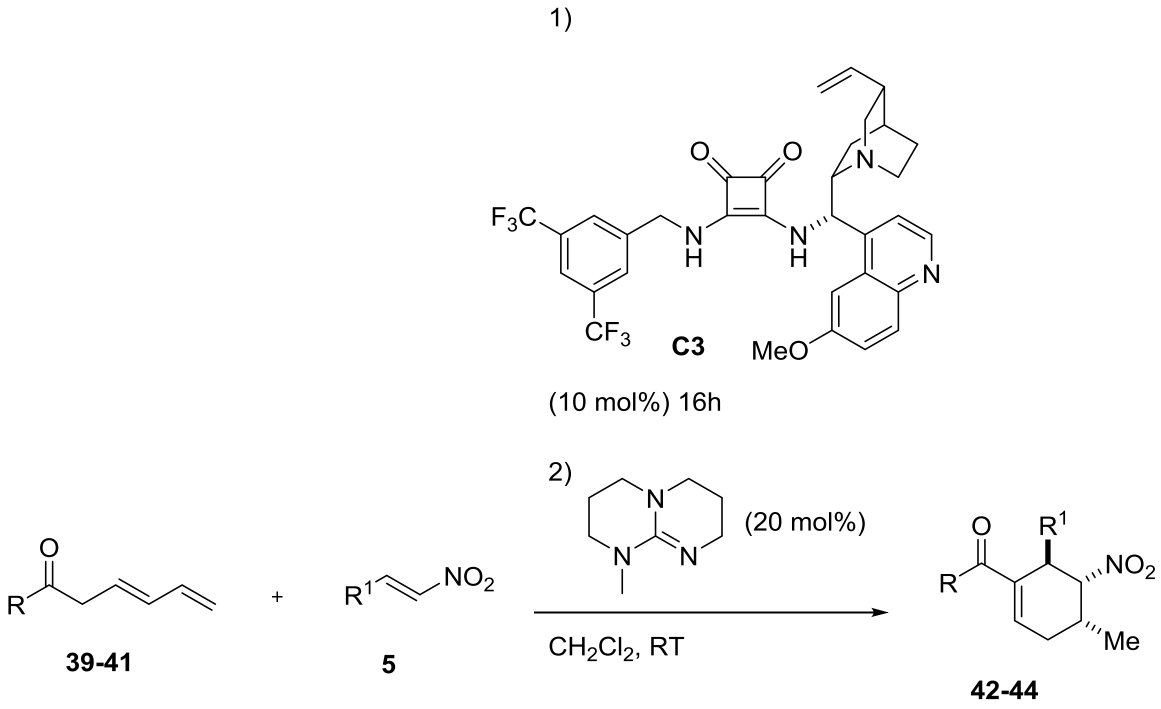
(*E*)-2-Methylnona-6,8-dien-4-one (41)



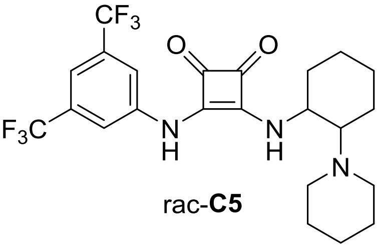
Prepared according to the general procedure for aliphatic ketones starting from isobuthyllithium. The title compound was isolated as a yellow oil as a mixture of isomers (desired product / isomerized product: 67/33). Yield: 100 mg (33%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.42 – 6.26 (m, 1H), 6.15 – 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.

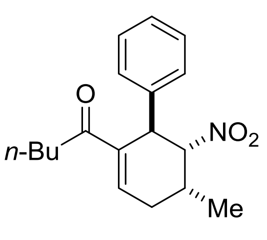

1)
F$_3$C
CF$_3$
C3
MeO
N
H
(10 mol%) 16h
2)
(20 mol%)
CH$_2$Cl$_2$, RT
R
R^1
NO$_2$
Me
39-41
5
42-44

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



rac-**C5**

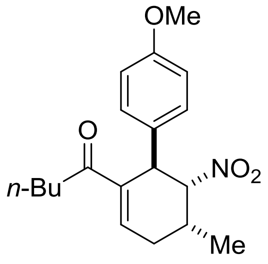
1-((1*R*,5*R*,6*R*)-5-Methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42a)



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$_2$Cl$_2$). ^{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).

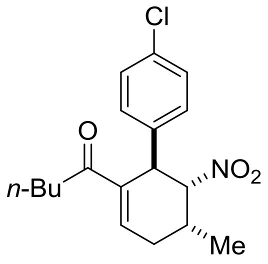
1-((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42b)



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). ^1H 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).

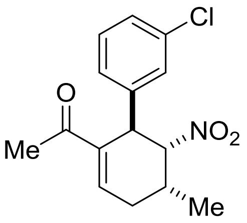
1-((1*R*,5*R*,6*R*)-4'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pentan-1-one (42k)



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). ^1H 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).

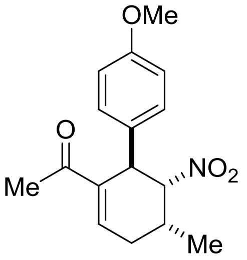
1-((1*R*,5*R*,6*R*)-3'-Chloro-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (43m)



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). ^1H 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).

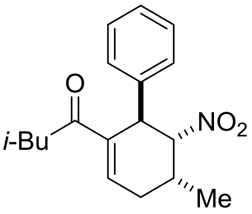
1-((1*R*,5*R*,6*R*)-4'-Methoxy-5-methyl-6-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (43b)



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). ^1H 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)

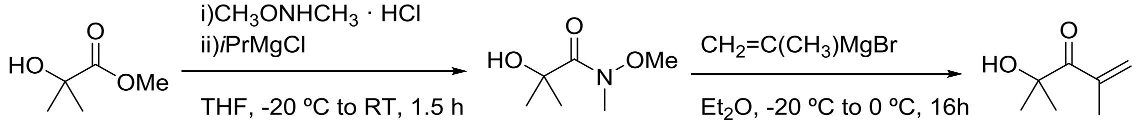


Prepared according to the general procedure starting from allyl ketone **41** and nitroalkene **5a**. The title compound was isolated as a single diastereomer as a yellow oil. Yield: 41 mg (68%). $[\alpha]_D^{25}$ = −17.8° (*c*= 0.5, 94% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, Chloroform-d) δ 7.36 – 7.29 (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



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%). ^1H 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

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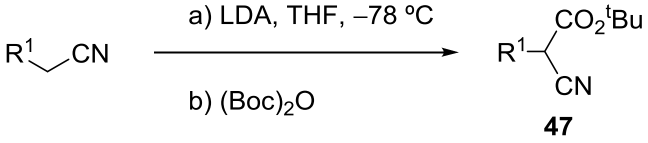
[163] F. Miege, B. M. Trost, *J. Am. Chem. Soc.,* **2014**, 136, 3016-3019.

(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]

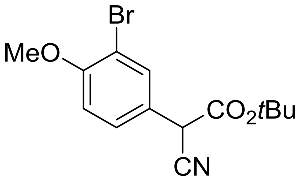
6.3.2. Preparation of α-cyanoesters 47-49

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



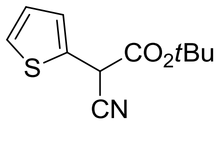
A solution of starting alkyl nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) previously cooled to −78 °C. The reaction mixture was allowed to stir at –78 °C for 45 min, and then at room temperature for an additional 45 min. The reaction mixture 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,

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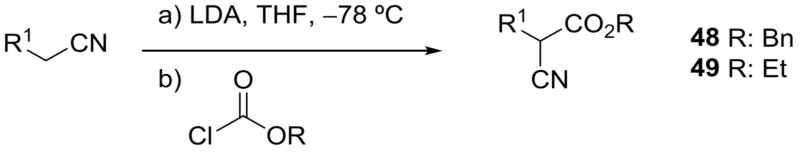
[164] A. Basheer, M. Mishima, I. Marek, *Org. Lett.*, **2011**, 13, 4076-4079.
[165] B. M. Trost, J. R. Miller, C. M. Hoffman Jr., *J. Am. Chem. Soc.* **2011**, *133*, 8165–8167.

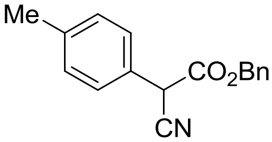
131.1, 127.9, 127.1, 115.2, 85.1, 40.1, 27.6. UPLC-DAD-QTOF: $C_{11}H_{14}NO_2S$ $[M]^+$ calcd.: 224.0746, found: 224.0745.

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



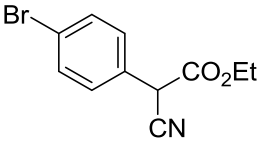
A solution of the corresponding nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to –78 °C. The reaction mixture was allowed to stir at –78 °C for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture 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)



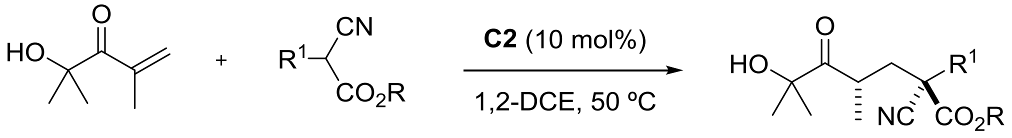
Yield: 886 mg (67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 9H), 5.23 (s, 2H), 4.78 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 139.3, 134.6, 130.0, 128.7, 128.2, 127.9, 127.0, 115.8, 68.5, 43.4, 21.1. UPLC-DAD-QTOF: $C_{17}H_{15}NO_2Na$ $[M+Na]^+$ calcd.: 288.1000, found: 288.1000.

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



Yield: 1.24 g (92 %). ^1H 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

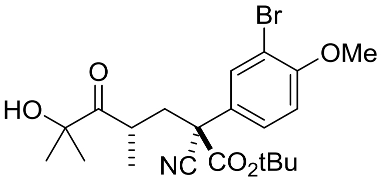


46 **47** R: *t*Bu **48** R: Bn **49** R: Et **50** R: *t*Bu **51** R: Bn **52** R: Et

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).

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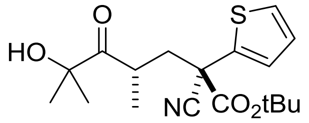
[166] E. Badiola, Doctoral Thesis, α'-Oxy Enones and Pyrrolidin-2,3-diones as Efficient New Templates in Asymmetric Organocatalytic Michael Reactions, EHU/UPV, 2016.

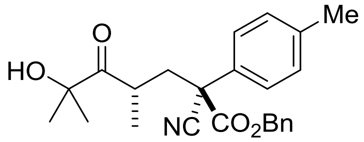
(2*S*,4*S*)-*tert*-Butyl 2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(thiophen-2-yl)heptanoate (50i)



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).

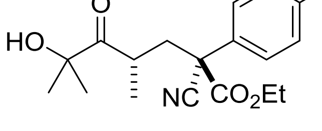
Benzyl (2S,4S)-2-cyano-6-hydroxy-4,6-dimethyl-5-oxo-2-(p-tolyl)heptanoate (51e)



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)



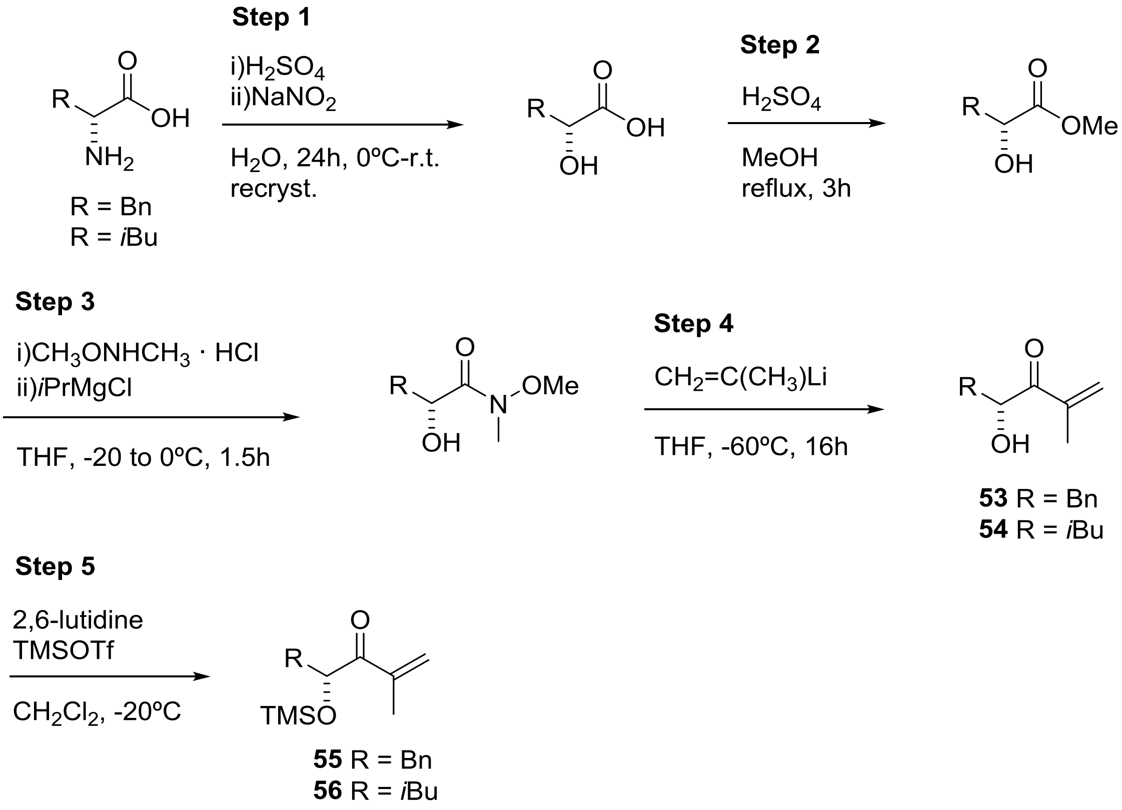
Prepared according to the general procedure starting from cyanoacetate **49b** (80 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 70 mg (88%). $[\alpha]_D^{25}$ = +12.5 (c=1, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.39 (m, 4H), 4.39 – 4.15 (m, 2H), 3.35 (qd, *J* = 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.

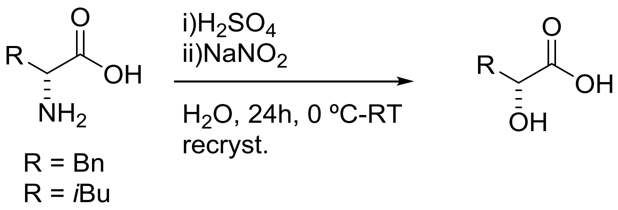
6.3.4. Preparation of chiral α′-oxyenones 53-56


Step 1
i)H2SO4
ii)NaNO2
H2O, 24h, 0ºC-r.t.
recryst.
R = Bn
R = iBu
Step 2
H2SO4
MeOH
reflux, 3h
Step 3
i)CH3ONHCH3 · HCl
ii)iPrMgCl
THF, -20 to 0ºC, 1.5h
Step 4
CH2=C(CH3)Li
THF, -60ºC, 16h
Step 5
2,6-lutidine
TMSOTf
CH2Cl2, -20ºC

53 R = Bn
54 R = *i*Bu

55 R = Bn
56 R = *i*Bu

Step 1: Preparation of (*R*)-2-hydroxy acids:[167]

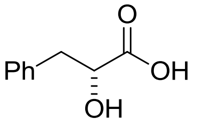

i)H2SO4
ii)NaNO2
H2O, 24h, 0 ºC-RT
recryst.
R = Bn
R = iBu

---

[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.

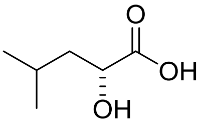
To a suspension of the corresponding amino acid (50 mmol) in water (27.5 mL), an aqueous solution of sulfuric acid (2N, 27.5 mL) was added dropwise at 0 °C. At the same temperature, an aqueous solution of sodium nitrite (2N, 27.5 mL) was also added dropwise. The reaction mixture was stirred at 0 °C for 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



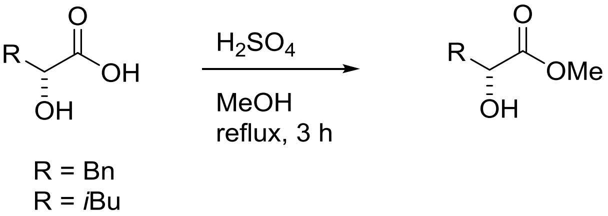
Prepared according to the general procedure starting from D-phenylalanine (50 mmol, 8.26 g). Product obtained as white crystals after recrystallization. Yield: 4.15 g (50%). ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[167]

(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

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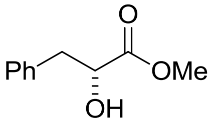
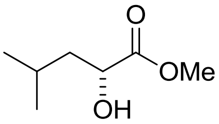
[168] M. Poterala; J. Plenkiewicz *Tetrahedron*, **2011**, 22, 294-299.



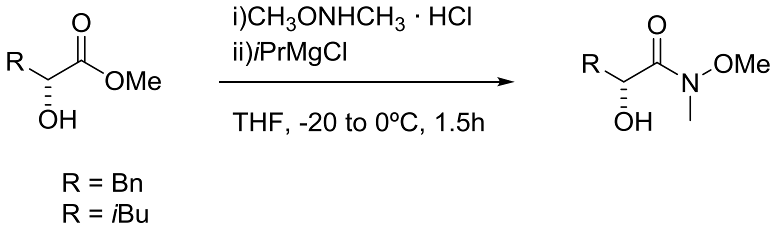
Product obtained as yellow oil. Yield: 7.28 g (100%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[168]

(*R*)-Methyl 2-hydroxy-4-methylpentanoate



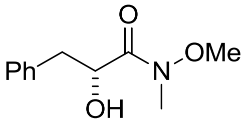
Product obtained as colorless oil. Yield: 4.97 g (85%). ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature. [168]

Step 3: Preparation of (*R*)-2-hydroxy-N-methoxy-N-methylamides:[169]



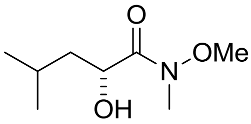
To a solution of the corresponding hydroxy ester (10 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (15 mmol, 1.5 equiv.) in THF (35 mL), a 2M solution of ^{i}PrMgCl in THF (40 mmol, 4 equiv.) was added at −20°C. The reaction mixture was stirred for 1.5 h at 0°C. The reaction was then quenched 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,

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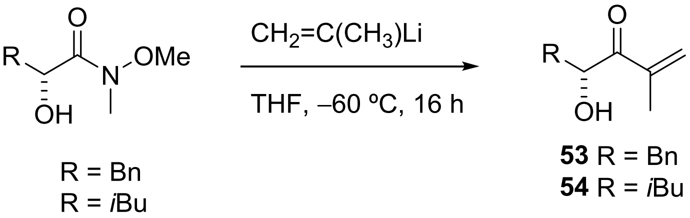
[169] Procedure adapted from: Miege, F.; Trost, B. M. *J. Am. Chem. Soc.,* **2014**, 136, 3016-3019.
[170] M. R. Aronoff, N. A. Bourjaily, K. A. Miller, *Tetrahedron*, **2010**, 51, 6375-6377.

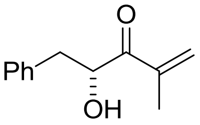
6.7 Hz, 1H), 1.52 – 1.42 (m, 2H), 0.98 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 67.3, 61.2, 44.0, 24.6, 23.6, 21.3. UPLC-DAD-QTOF: $C_8H_{17}NO_3$ $[M]^+$ calcd.: 176.1287, found: 176.1289.

Step 4: Preparation of hydroxyenones 53 and 54:



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).

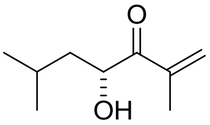
(*R*)-4-Hydroxy-2-methyl-5-phenylpent-1-en-3-one (53)



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).

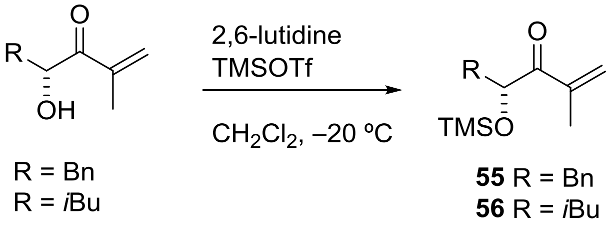
(*R*)-4-Hydroxy-2,6-dimethylhept-1-en-3-one (54)



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.

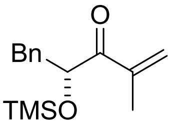
The enantiomeric purity was determined by GC analysis (Chiral column HYDRODEX β-6TBDM. Temperature gradient: 100ºC for 1 min., 10ºC/min. until minute 11, 200ºC until minute 22).

Step 5: Preparation of silyloxyenones 55 and 56:



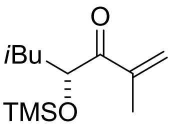
To a solution of the corresponding hydroxyenone (2 mmol) in CH_2Cl_2 (20 mL) cooled to −20°C, were added successively 2,6-lutidine (0.55 mL, 4.8 mmol, 2.4 equiv.) and TMSOTf (0.72 mL, 4 mmol, 2 equiv.). The mixture was stirred at −20 °C for 3 h and then EtOAc (40 mL) was added. The organic phase was 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)



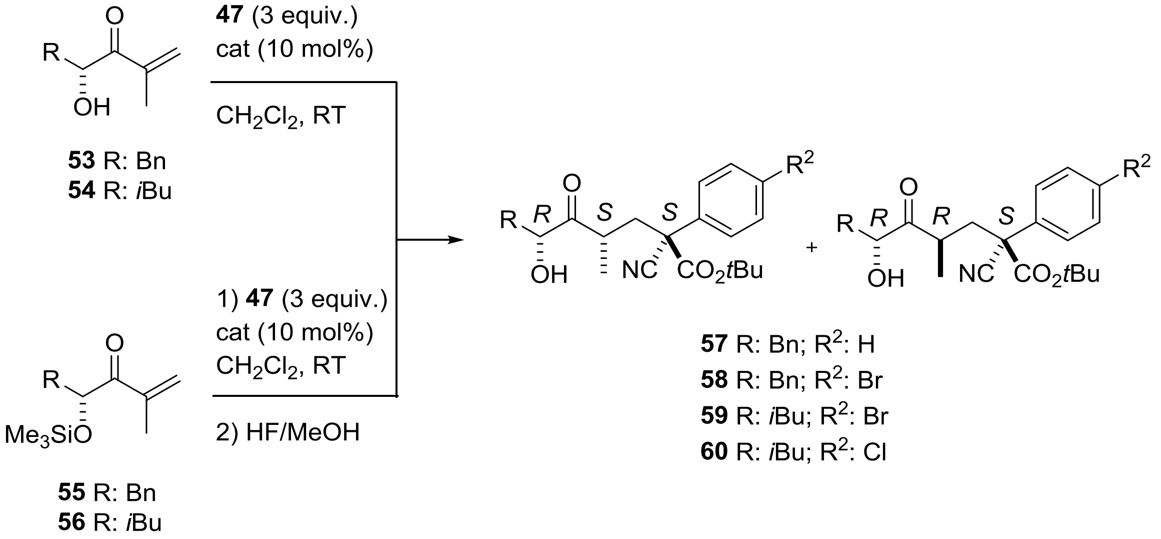
Product obtained as a yellow oil. Yield: 399 mg (72%). $[\alpha]_D^{23}$= -1.7 (c=0.8, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 5H), 6.14 (s, 1H), 5.87 (dd, *J* = 1.4, 0.8 Hz, 1H), 4.84 (dd, *J* = 9.0, 4.0 Hz, 1H), 2.96 (ddd, *J* = 22.5, 13.5, 6.5 Hz, 2H), 1.93 (dd, *J* = 1.3, 0.9 Hz, 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). ^1H 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

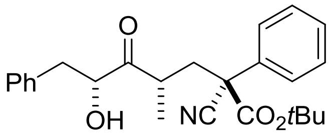

47 (3 equiv.)
cat (10 mol%)
CH2Cl2, RT
53 R: Bn
54 R: iBu
1) 47 (3 equiv.)
cat (10 mol%)
CH2Cl2, RT
2) HF/MeOH
55 R: Bn
56 R: iBu
57 R: Bn; R2: H
58 R: Bn; R2: Br
59 R: iBu; R2: Br
60 R: iBu; R2: Cl
R
OH
Me3SiO
R2
NC
CO2tBu
R S S
R R S
+

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)

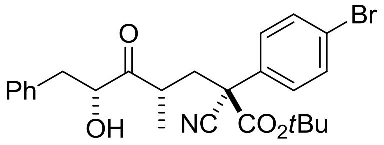

Ph
O
OH
NC
CO2tBu

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.

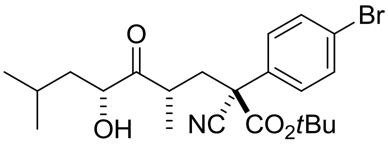
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4-methyl-5-oxo-7-phenylheptanoate (58)



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.

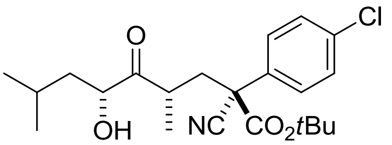
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (59)



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.

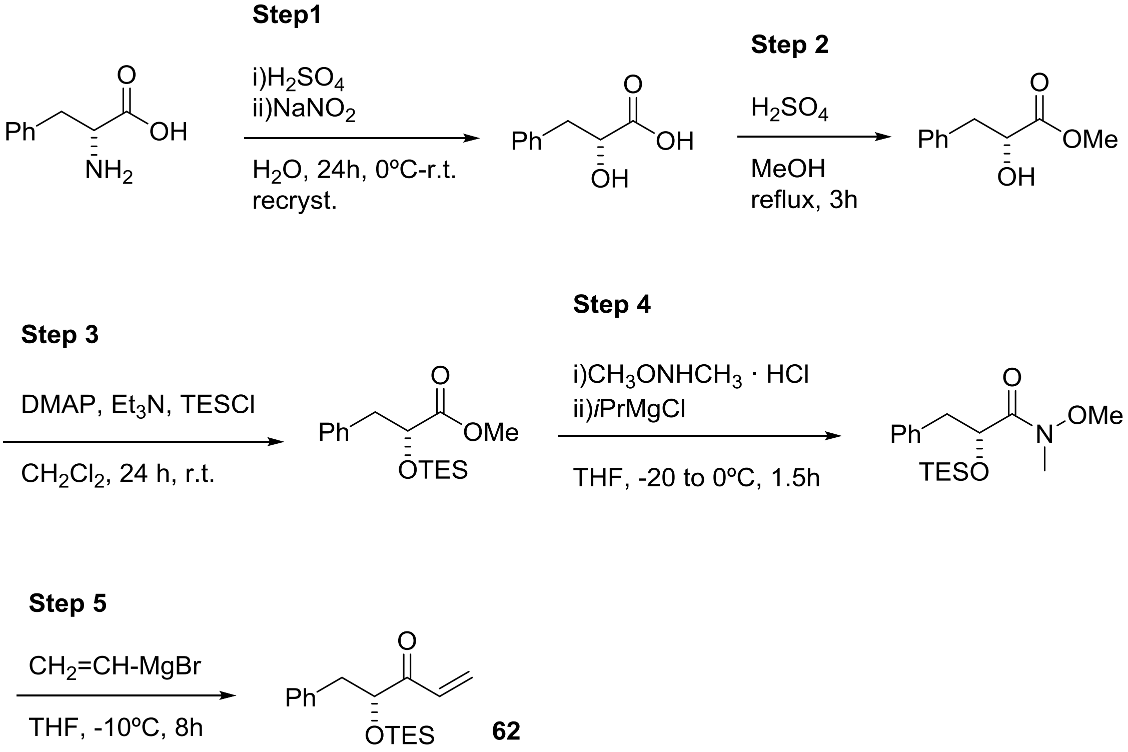
(2*S*,4*S*,6*R*)-*tert*-Butyl 2-(4-chlorophenyl)-2-cyano-6-hydroxy-4,8-dimethyl-5-oxononanoate (60)


O
Cl
OH
NC
CO_2tBu

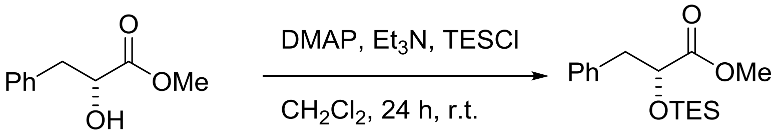
Prepared according to the general procedure starting from hydroxyenone **56** and cyanoacetate **47c**, and using catalyst **C2**. The title compound was isolated as an oil. Yield: 65 mg (80%). $[\alpha]_D^{23}$ = -0.8 (c=0.7, dr: 90:10:0:0, CH_2Cl_2). ^1H NMR major diastereomer (300 MHz, $CDCl_3$) δ 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 ^1H NMR analysis.

6.3.6. Preparation of chiral α´-silyloxyenone 62

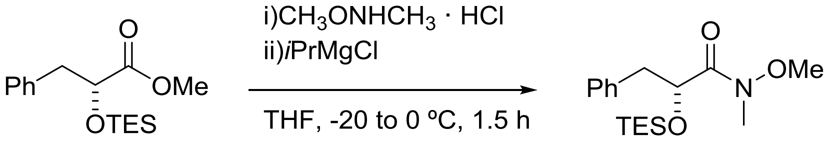

Step1
i)H_2SO_4
ii)$NaNO_2$
H_2O, 24h, 0ºC-r.t.
recryst.
Ph
O
OH
NH_2
Step 2
H_2SO_4
MeOH
reflux, 3h
OMe
Step 3
DMAP, Et_3N, TESCl
CH_2Cl_2, 24 h, r.t.
OTES
Step 4
i)$CH_3ONHCH_3 \cdot HCl$
ii)*i*PrMgCl
THF, -20 to 0ºC, 1.5h
N
TESO
Step 5
$CH_2=CH\text{-}MgBr$
THF, -10ºC, 8h
62

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). ^1H 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 ^iPrMgCl 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). ^1H 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

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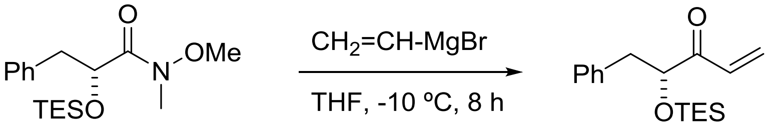
[171] Procedure adapted from: J. M. García, A. Gozalez, B. G. Kardak, J. M. Odriozola, M. Oiarbide, J. Razkin, C. Palomo, *Chem. Eur. J.*, **2008**, *14*, 8768–8771.

[172] Procedure adapted from: F. Miege, B. M. Trost, *J. Am. Chem. Soc.,* **2014**, *136*, 3016–3019.

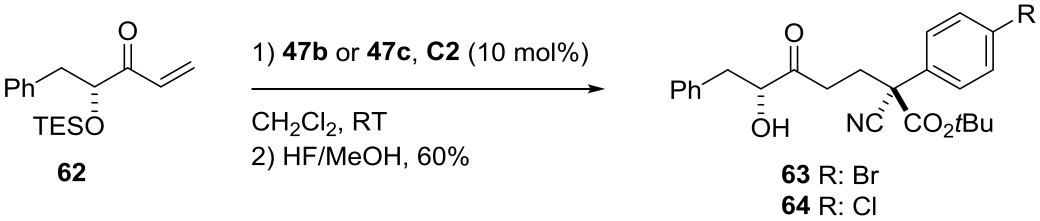
(t, *J* = 7.8 Hz, 9H), 0.60 – 0.42 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.6, 137.7, 129.6, 128.1, 126.4, 70.8, 61.0, 41.2, 32.4, 6.4, 4.4. UPLC-DAD-QTOF: $C_{17}H_{30}NO_3Si$ [M+H]$^+$ cald.: 324.1995, found: 324.1999.

Step 5. Preparation of (*R*)-5-phenyl-4-((triethylsilyl)oxy)pent-1-en-3-one (62)



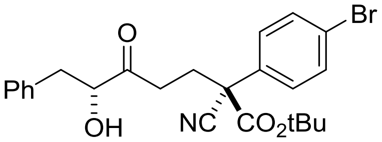
To a solution of the silyloxy amide (458 mg, 1.4 mmol) in dry THF (4 mL), a 0.7 M solution of vinylmagnesium bromide in THF was added at 0 °C. The reaction mixture was stirred for 24 h at 0 °C. The reaction was then quenched with an aqueous saturated solution of NH$_4$Cl (10 mL) and extracted with CH$_2$Cl$_2$ (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$_2$Cl$_2$). ^{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



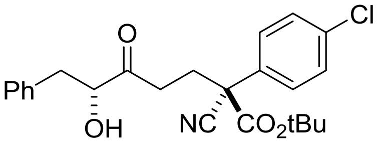
General Procedure: To a solution of the corresponding *tert*-butyl cyanoacetate **47** (0.6 mmol) and α′-silyloxy enone **62** (0.2 mmol, 1 equiv.) in CH$_2$Cl$_2$ (0.4 mL), **C2** (0.02 mmol) was added and the resulting mixture was stirred at 20 °C until consumption of the α′-oxy enone (monitored by ^{1}H-NMR). The reaction mixture was quenched with HCl 1N (5 mL) and the solution was extracted with CH$_2$Cl$_2$ (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). ^1H 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.

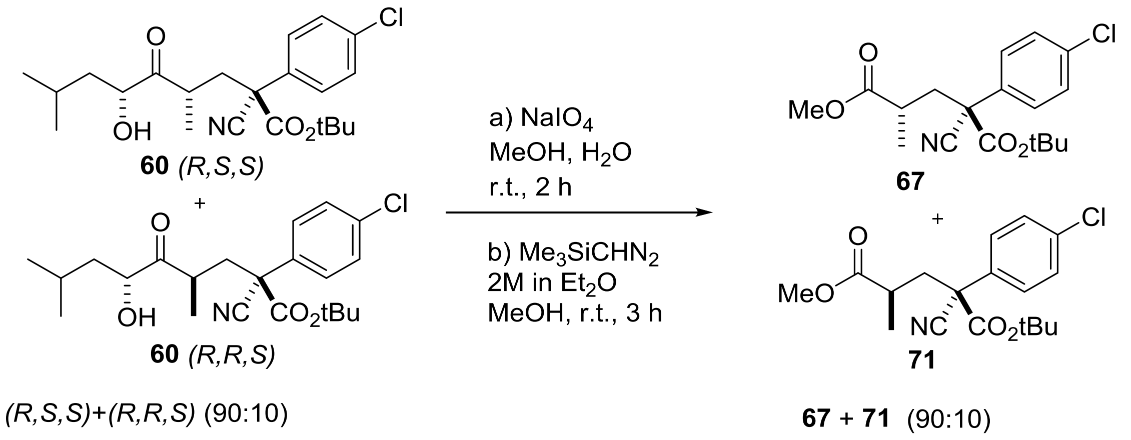
***tert*-Butyl (2S,6R)-2-(4-chlorophenyl)-2-cyano-6-hydroxy-5-oxo-7-phenylheptanoate (64)**



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). ^1H 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.

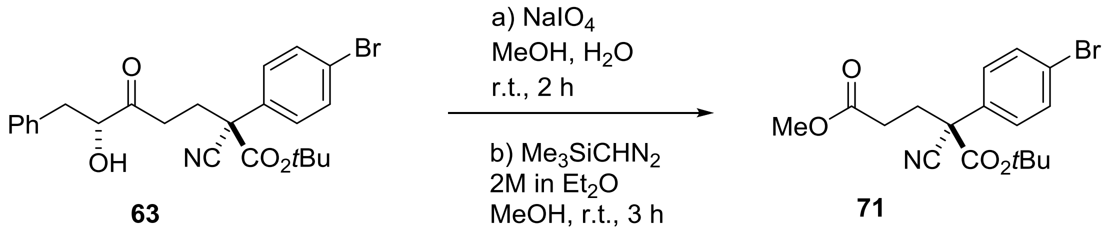
6.3.8. Chemical elaboration of adducts

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

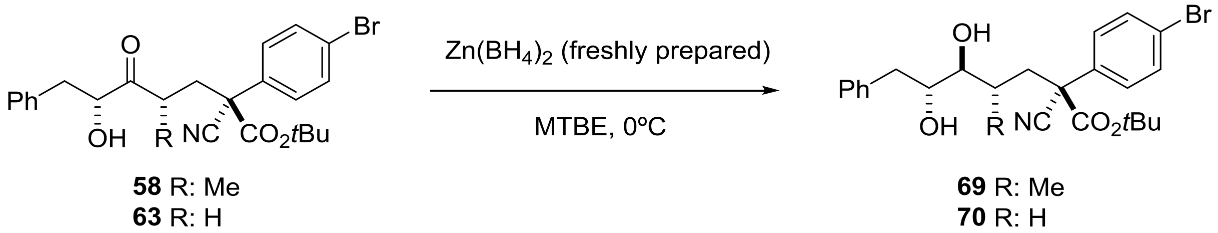
Procedure adapted from 160. A suspension of $NaIO_4$ (171 mg, 0.79 mmol) in water (0.38 mL) was added to a solution of adduct **60** (90:10 mixture of diastereomers, 65 mg, 0.16 mmol) in methanol (0.79 mL). The mixture was stirred at room temperature until the starting material dissapeared (monitored 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*

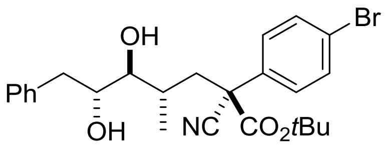


Preparation of zinc borohydride

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.

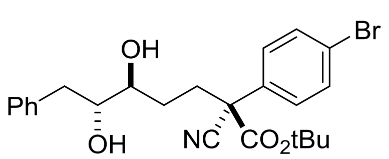
General procedure for the reduction of 69 and 70: To a solution the corresponding α´-hydroxy ketones (0.6 mmol, 290 mg) in dry MTBE (2 mL) a solution of zinc borohydride in MTBE was added at 0 °C (25 mL) and the mixture was stirred at 0 °C for 10-15 minutes. The reaction mixture was quenched with water 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.

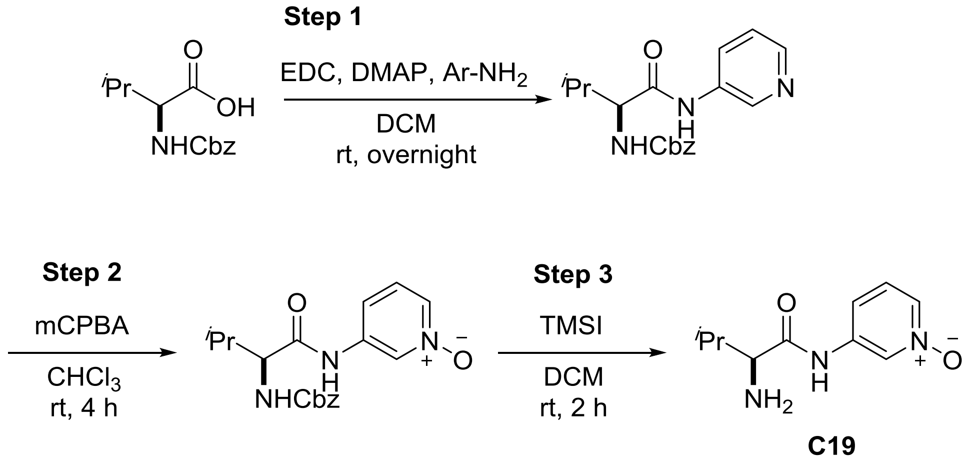
tert-Butyl (2S,5S,6R)-2-(4-bromophenyl)-2-cyano-5,6-dihydroxy-7-phenylheptanoate 70



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



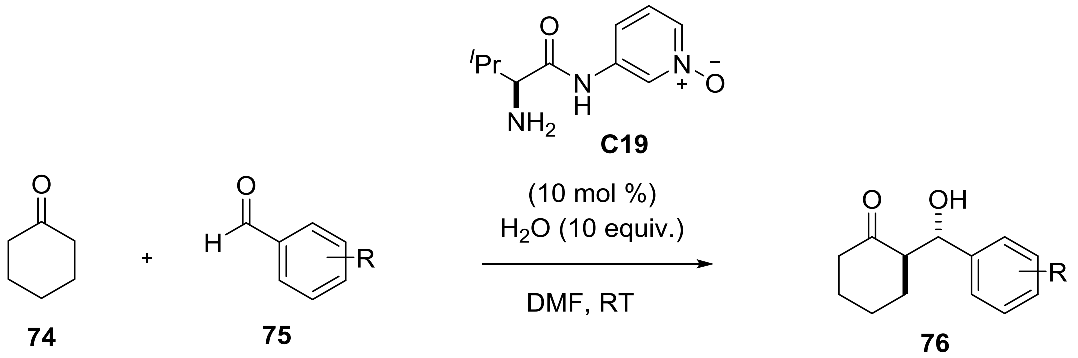
Step 1. To a stirring solution of N-Benzyloxycarbonyl-L-valine (2.51 g, 10.0 mmol, 1.0 equiv.) and 3-aminopyridina (1.41 g, 15 mmol, 1.5 equiv.) in CH_2Cl_2 (30.0 mL) at room temperature EDC (2.87, 15.0 mmol, 1.5 equiv.) and 4-DMAP (1.83 g, 15.0 mmol, 15.0 equiv.) were added. The reaction was allowed 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). ^1H NMR (495 MHz, Methanol-*d*$_4$) δ 9.03 (t, *J* = 1.9 Hz,

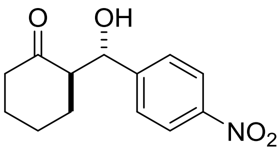
1H), 8.16 – 8.01 (m, 1H), 7.74 – 7.63 (m, 1H), 7.47 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.30 – 3.17 (m, 1H), 2.04 (pd, *J* = 6.9, 5.4 Hz, 1H), 0.97 (dd, *J* = 33.3, 6.9 Hz, 6H). ^{13}C NMR (125 MHz, Methanol-*d*$_4$) δ 174.8, 138.6, 134.0, 130.9, 126.4, 120.1, 60.9, 32.2, 18.5. UPLC-DAD-QTOF: $C_{10}H_{16}N_3O_2$ [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)

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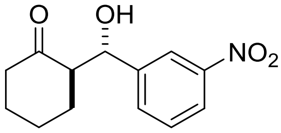
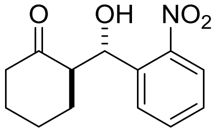
[173] a) Gryko, D.; Lipínski, R. *Eur. J. Org. Chem.* **2006**, 3864–3876. b) Suri, J. T.; Ramachary, D. B.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 1383–1385.



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.

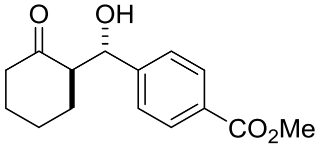
(*R*)-2-((*S*)-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (76c)



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.

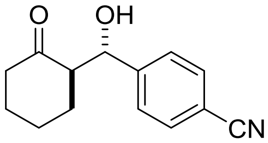
Methyl 4-((*S*)-hydroxy((*R*)-2-oxocyclohexyl)methyl)benzoate (76d)



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.

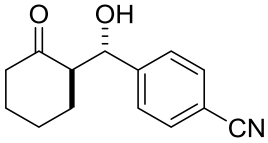
4-((*S*)-Hydroxy((*R*)-2-oxocyclohexyl)methyl)benzonitrile (76e)



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.

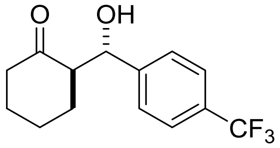
4-((*S*)-Hydroxy((*R*)-2-oxocyclohexyl)methyl)benzonitrile (76e)



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.

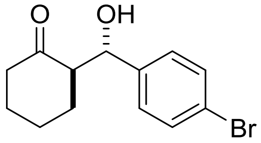
(*R*)-2-((*S*)-Hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (76f)



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.

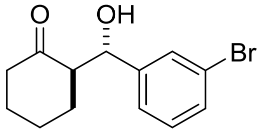
(*R*)-2-((*S*)-(4-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (76g)



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.

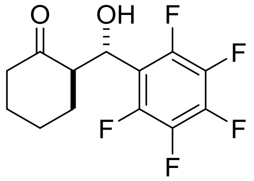
(*R*)-2-((*S*)-(3-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (76h)



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)

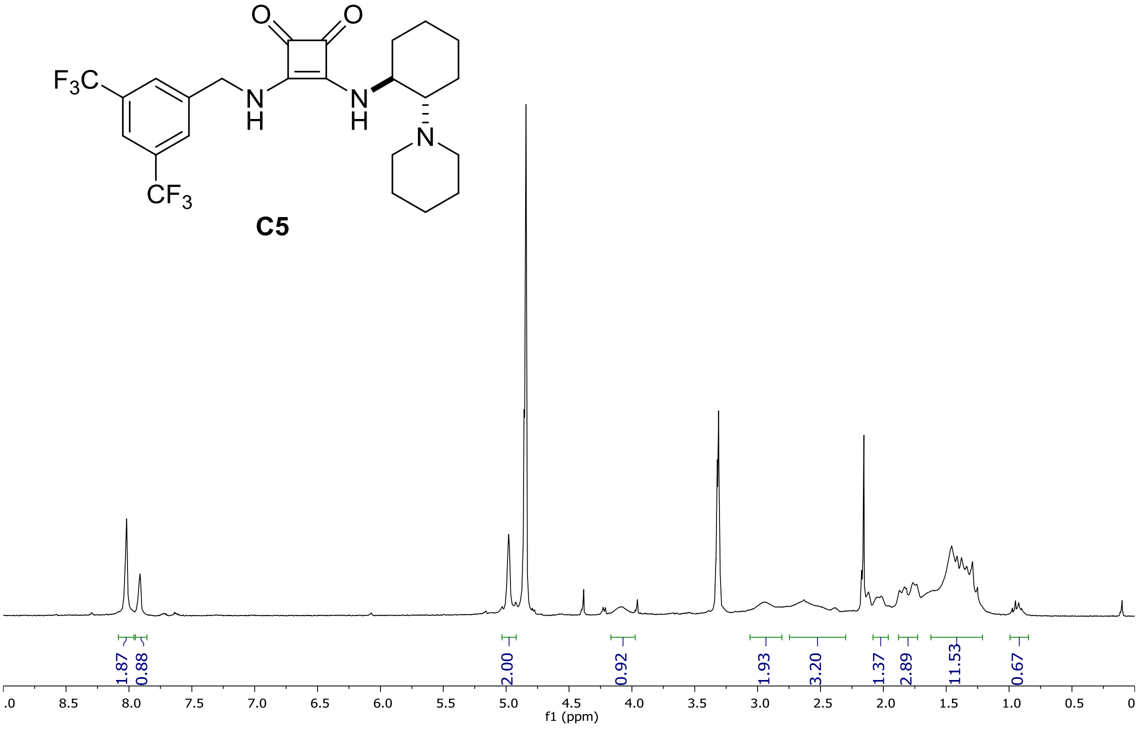


Prepared following the general procedure starting from cyclohexanone **74** and 2,3,4,5,6-pentafluorobenzaldehyde **75i**. Yield: 92% (55 mg).

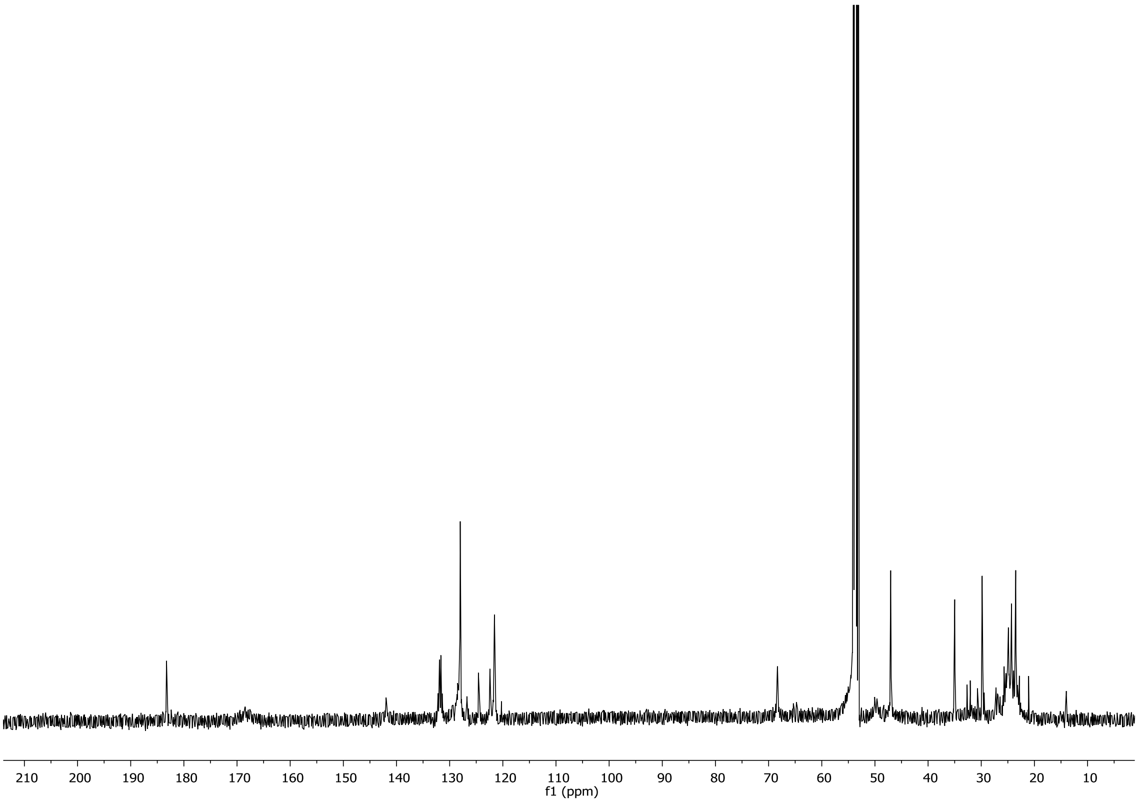
The enantiomeric and diastereomeric purity was determined by HPLC analysis (Daicel Chiralpack AD-H hexane/isopropanol 10/1, flow rate= 0.5 mL/min.

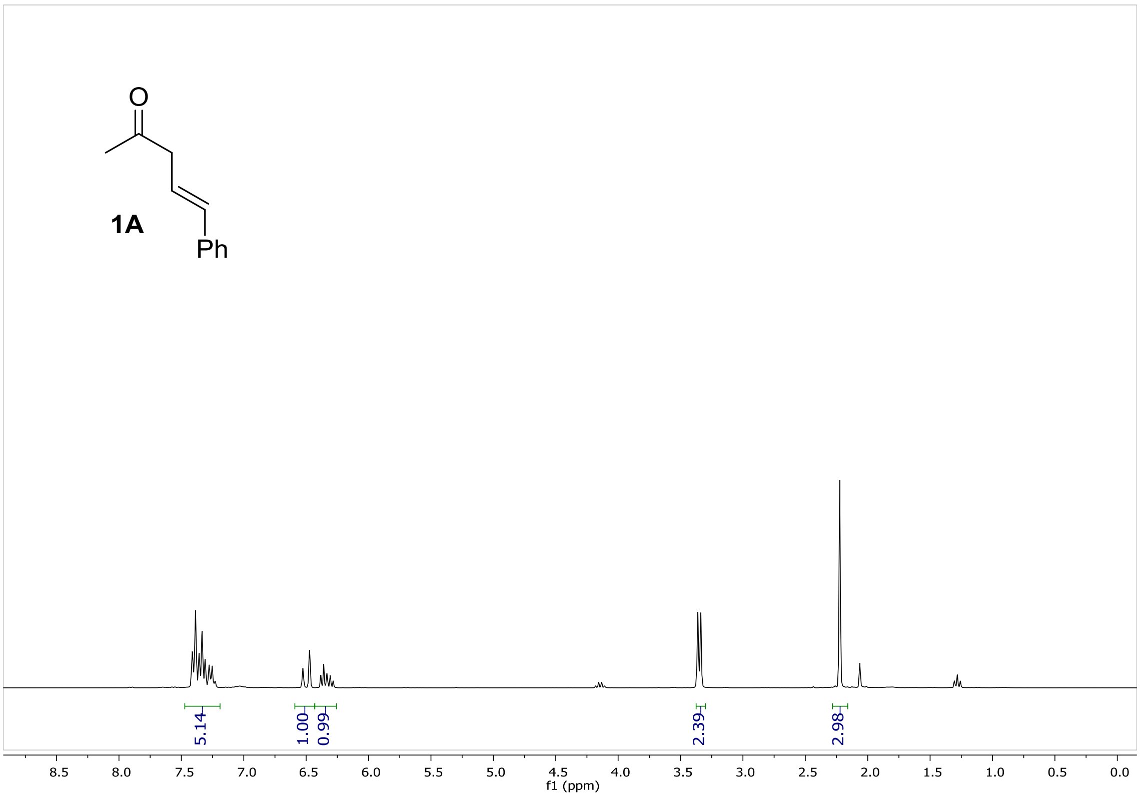
6.5. NMR spectra

6.5.1. NMR spectra of Chapter 2



C5

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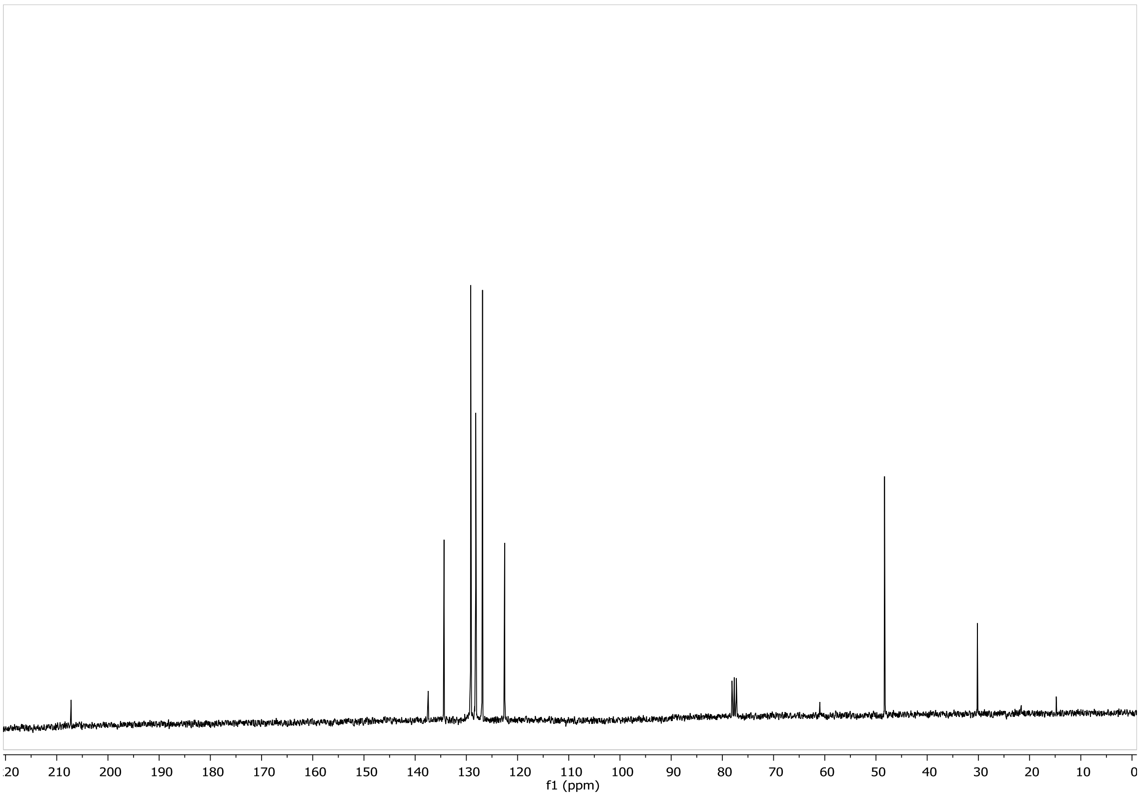
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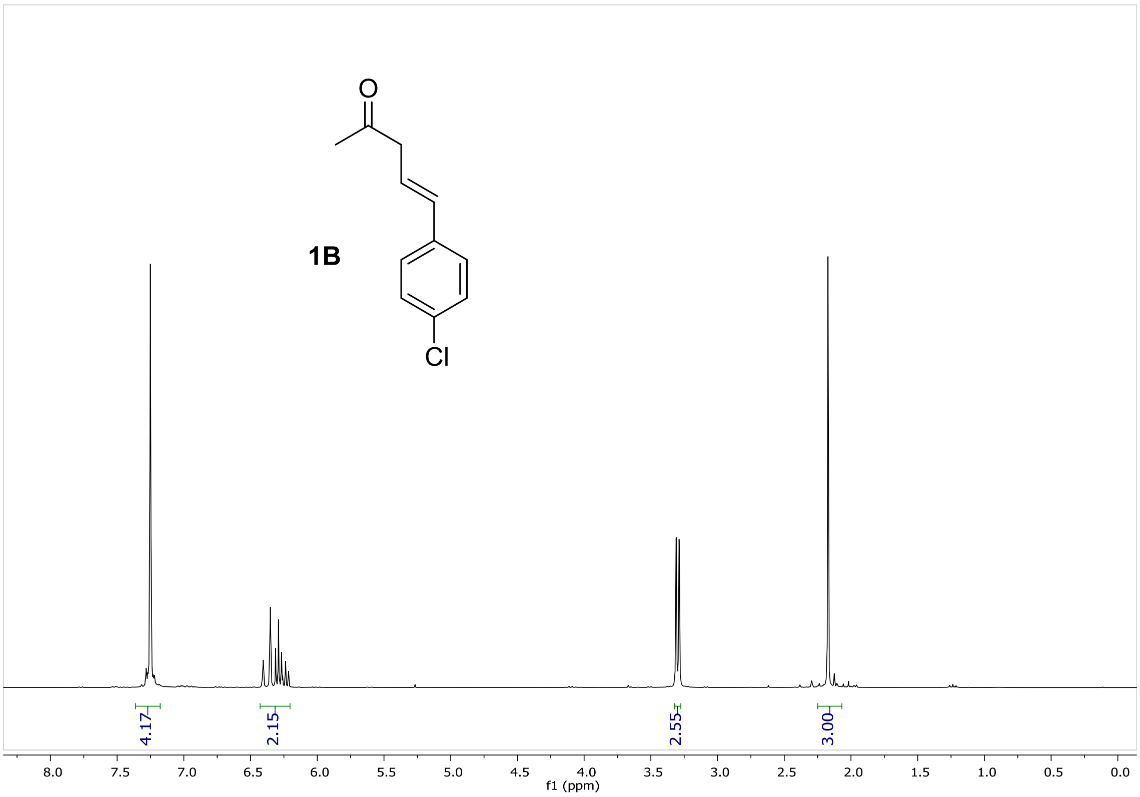
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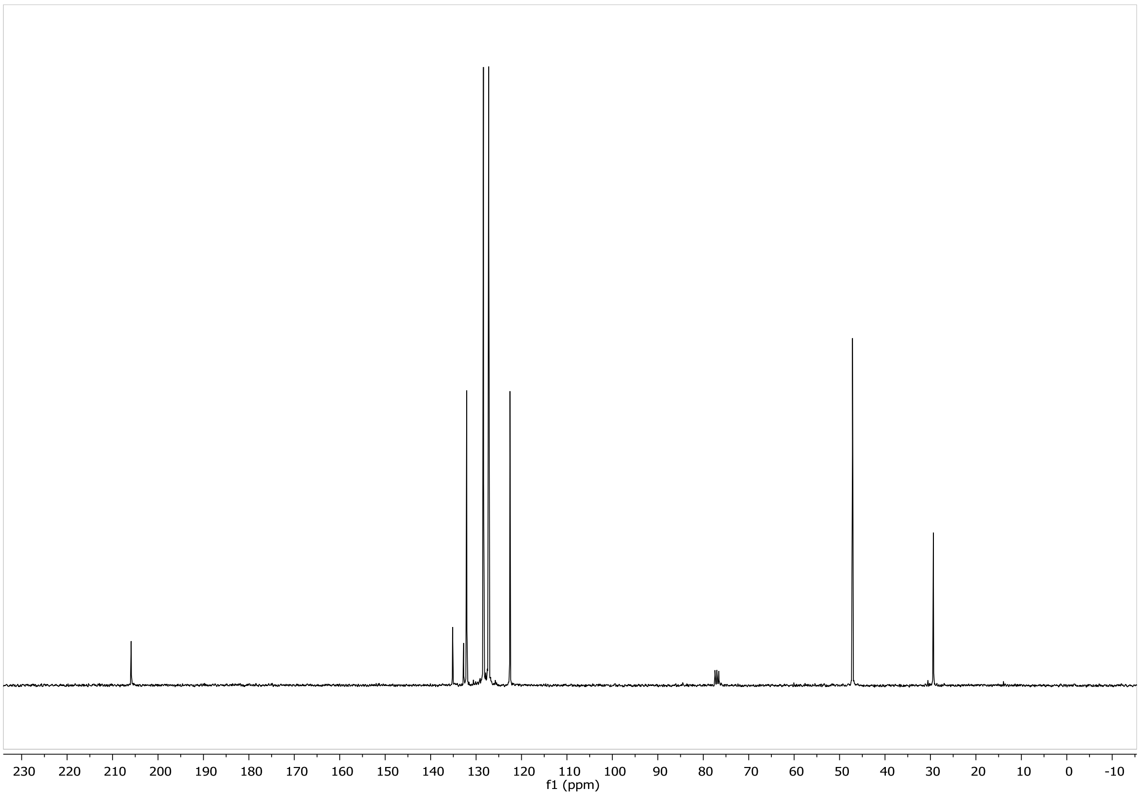
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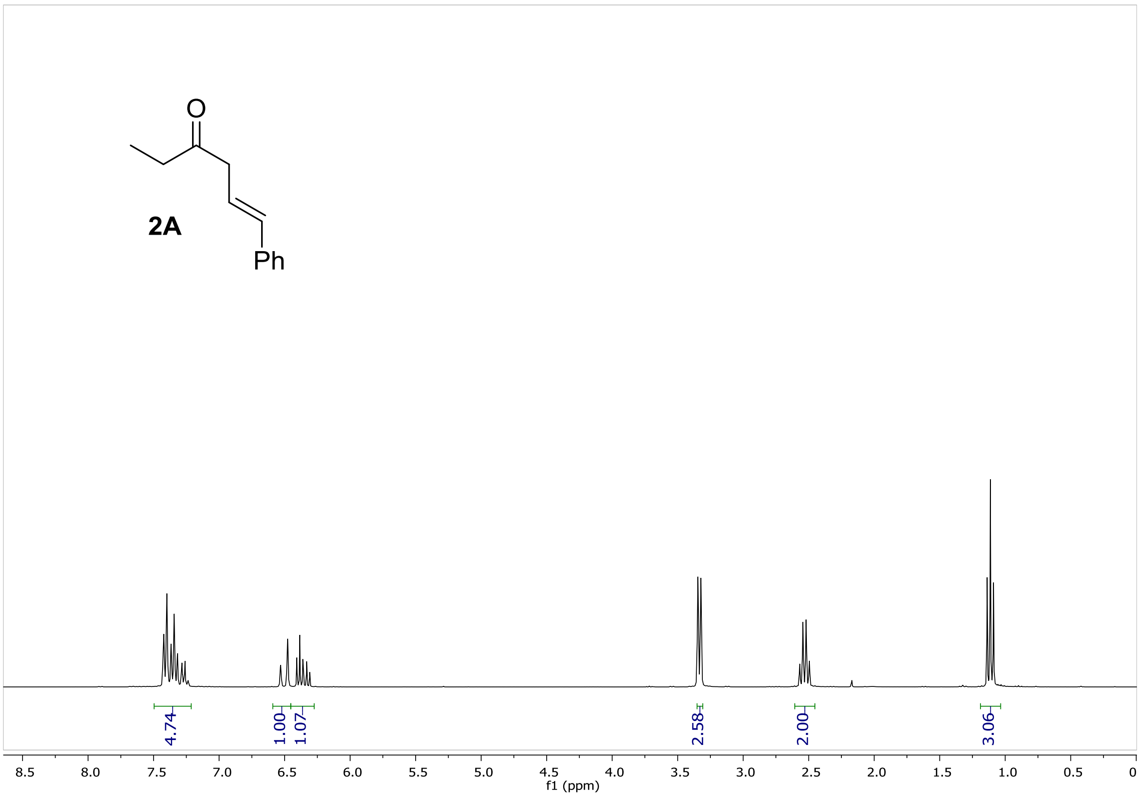
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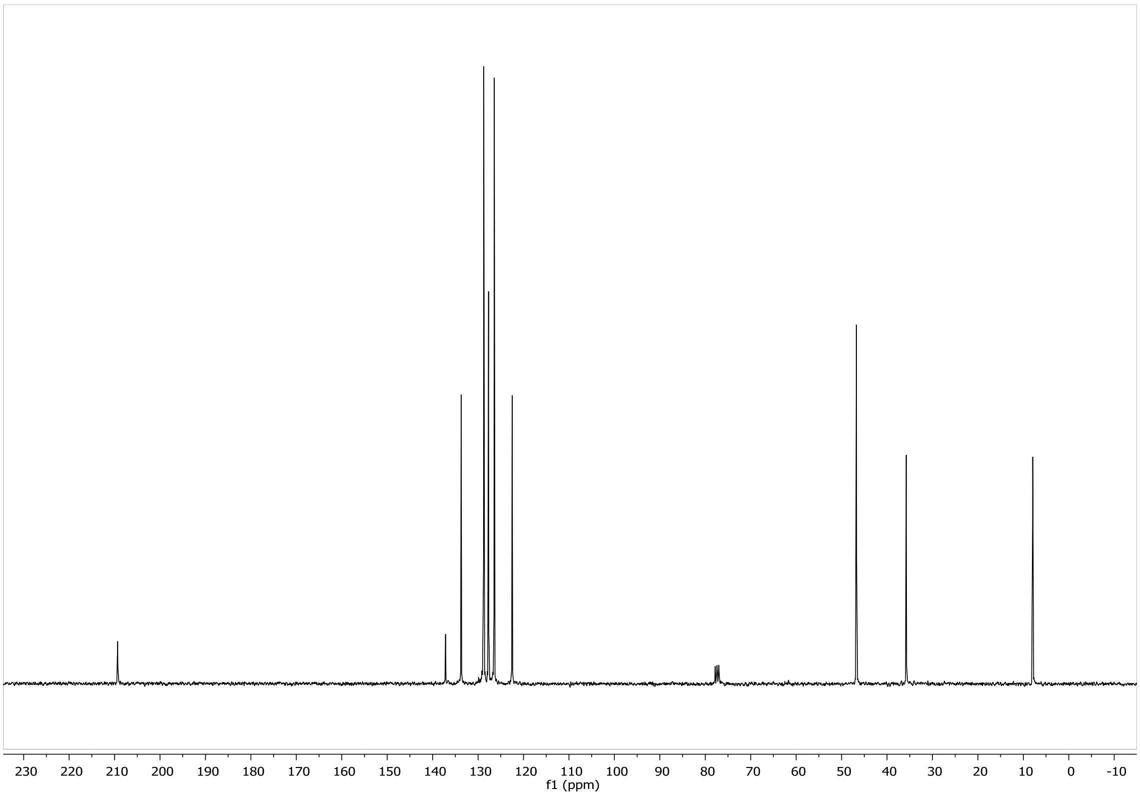
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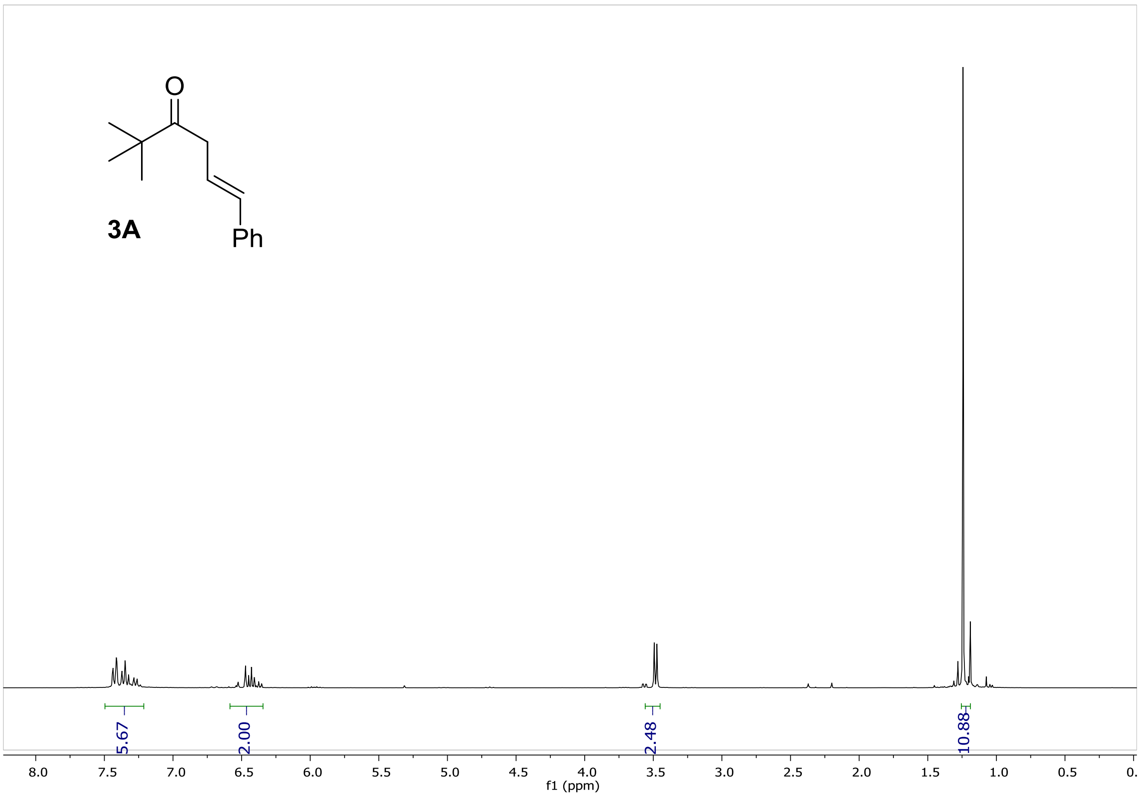
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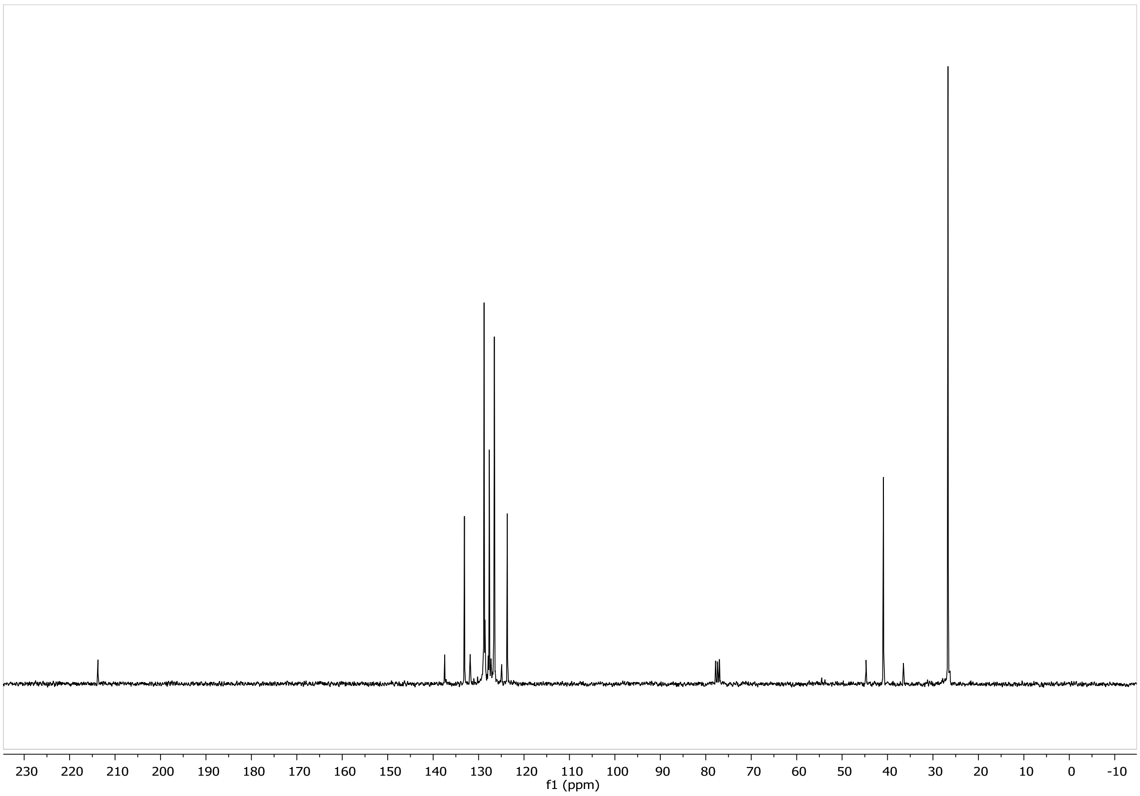
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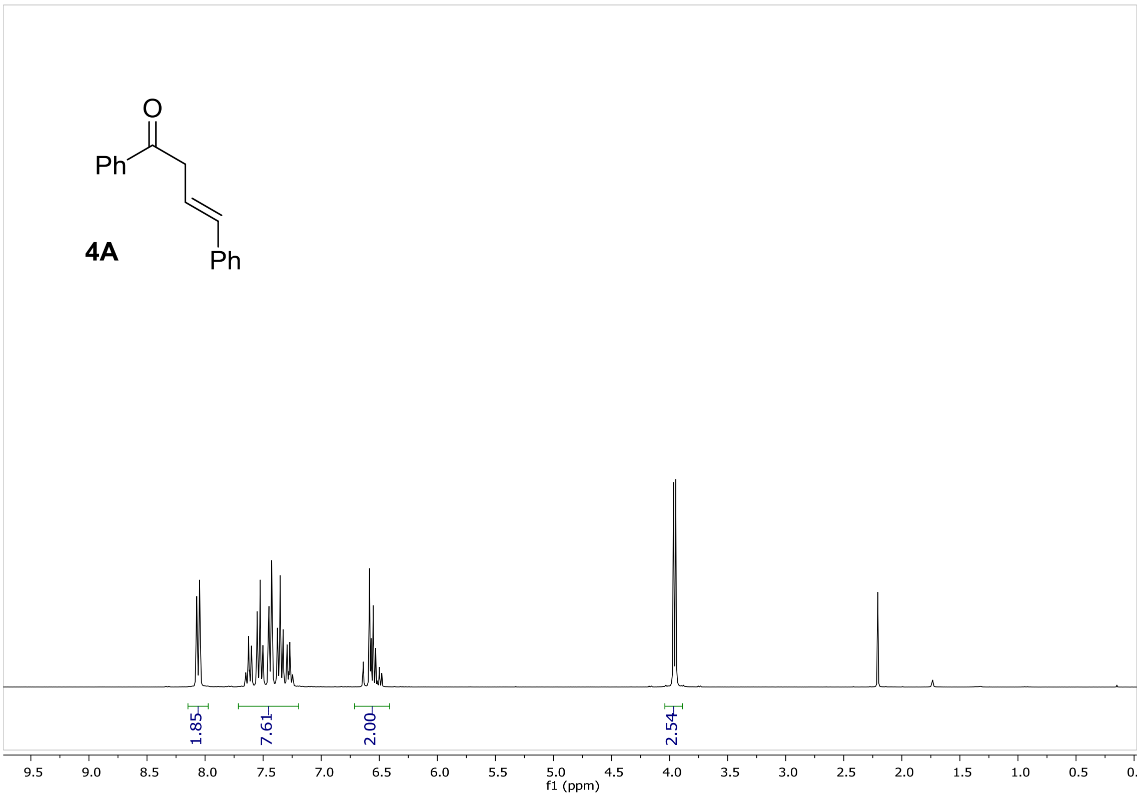
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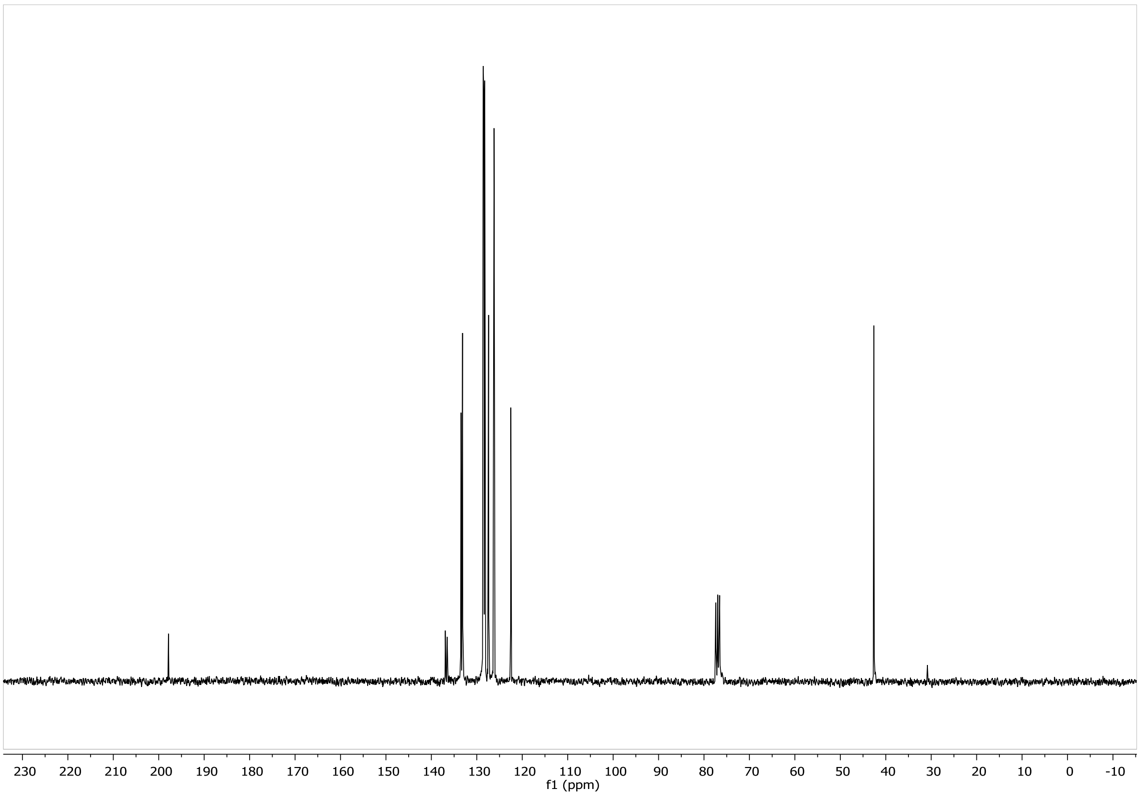
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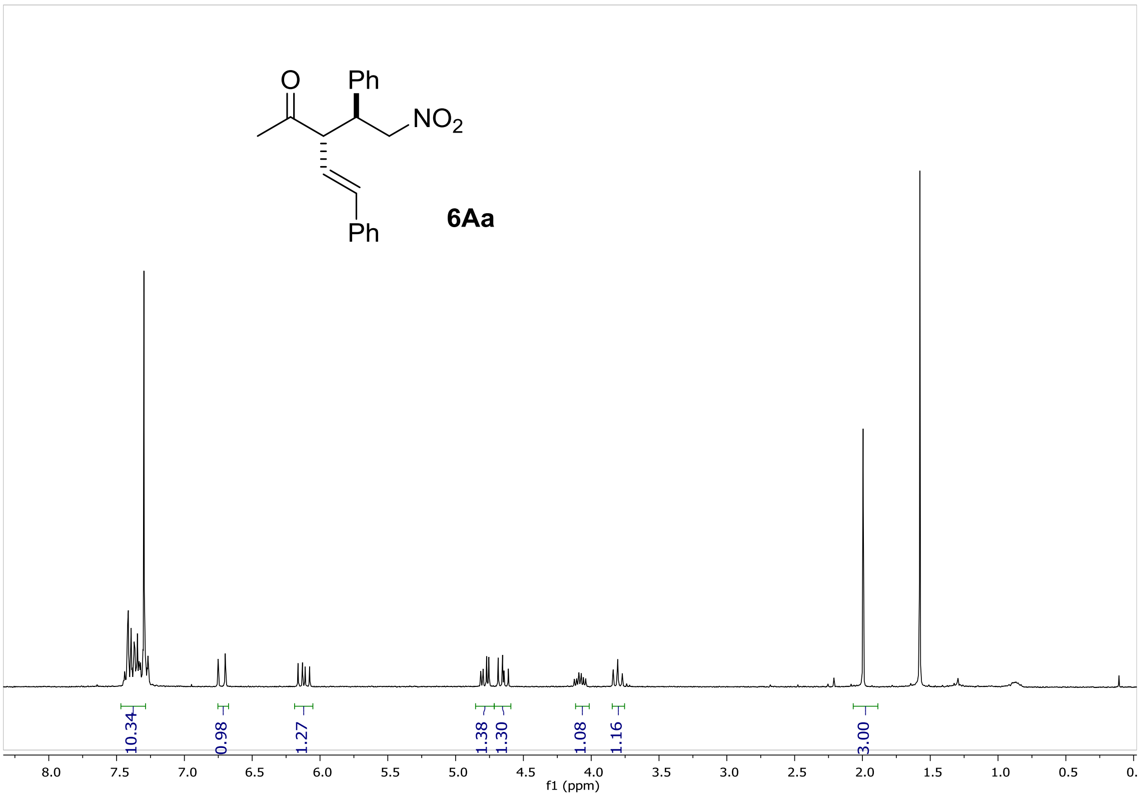

6Aa

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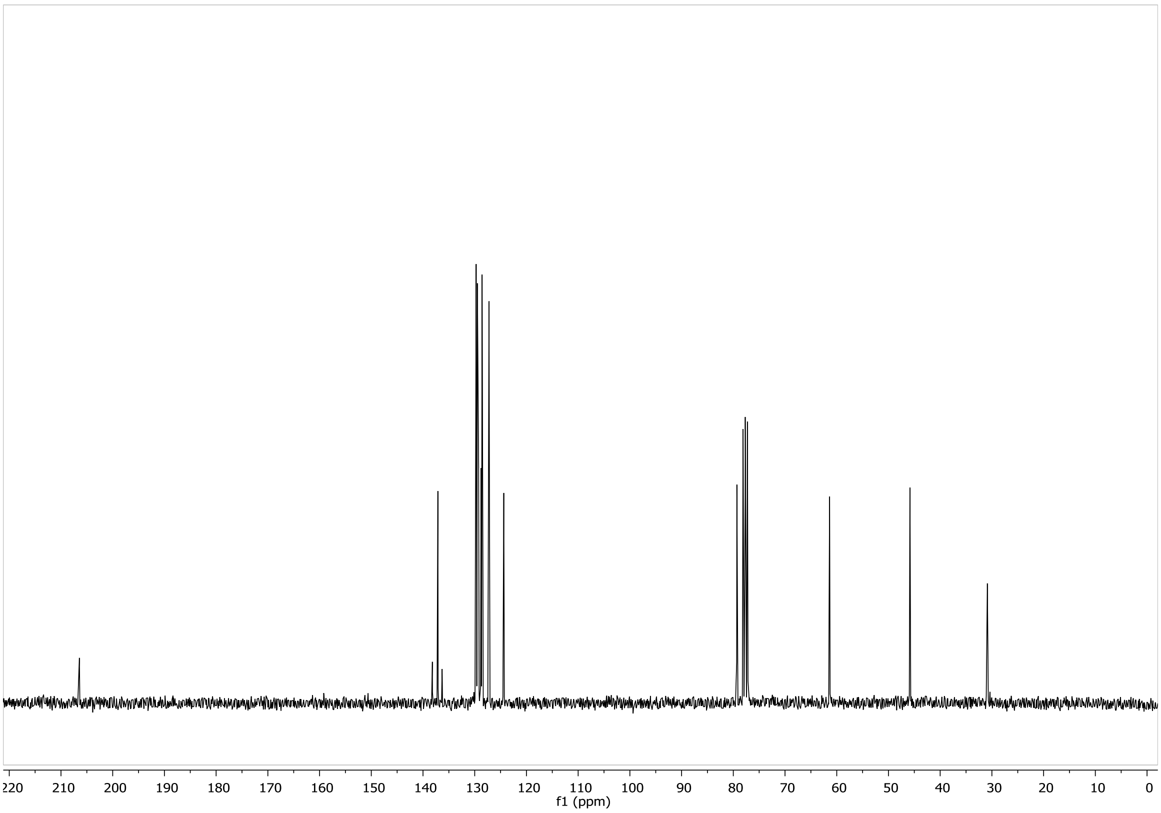

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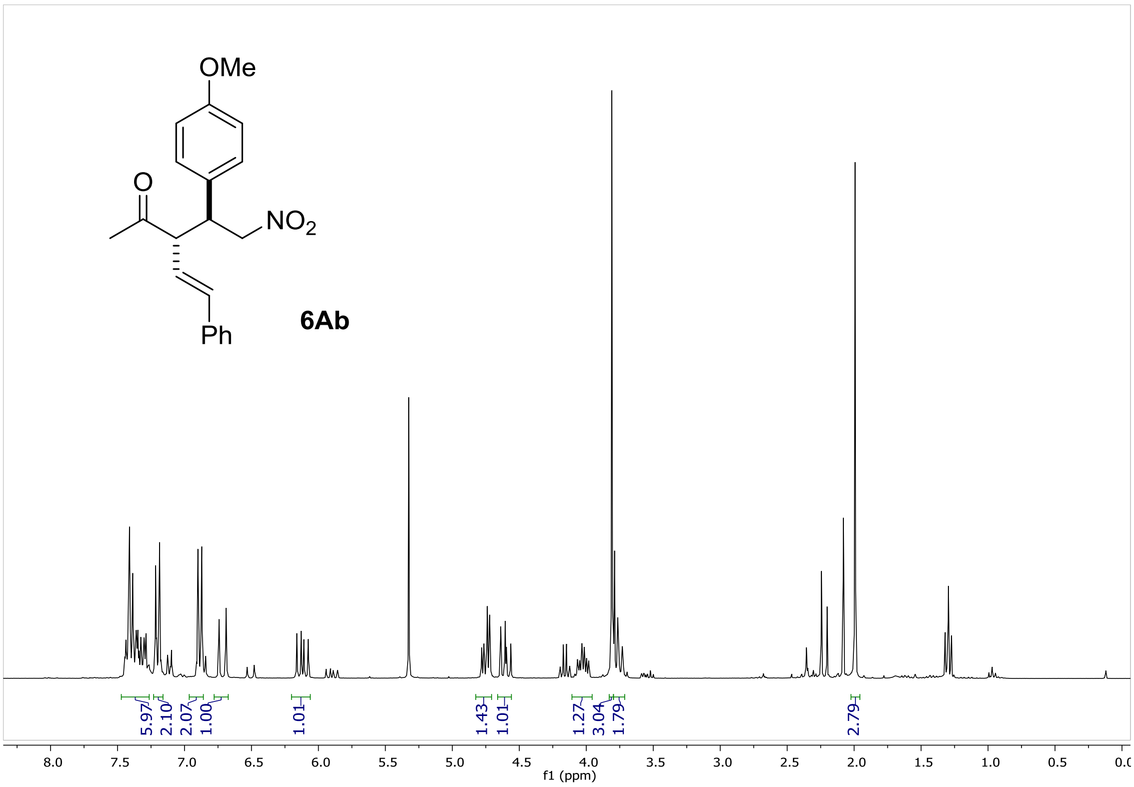
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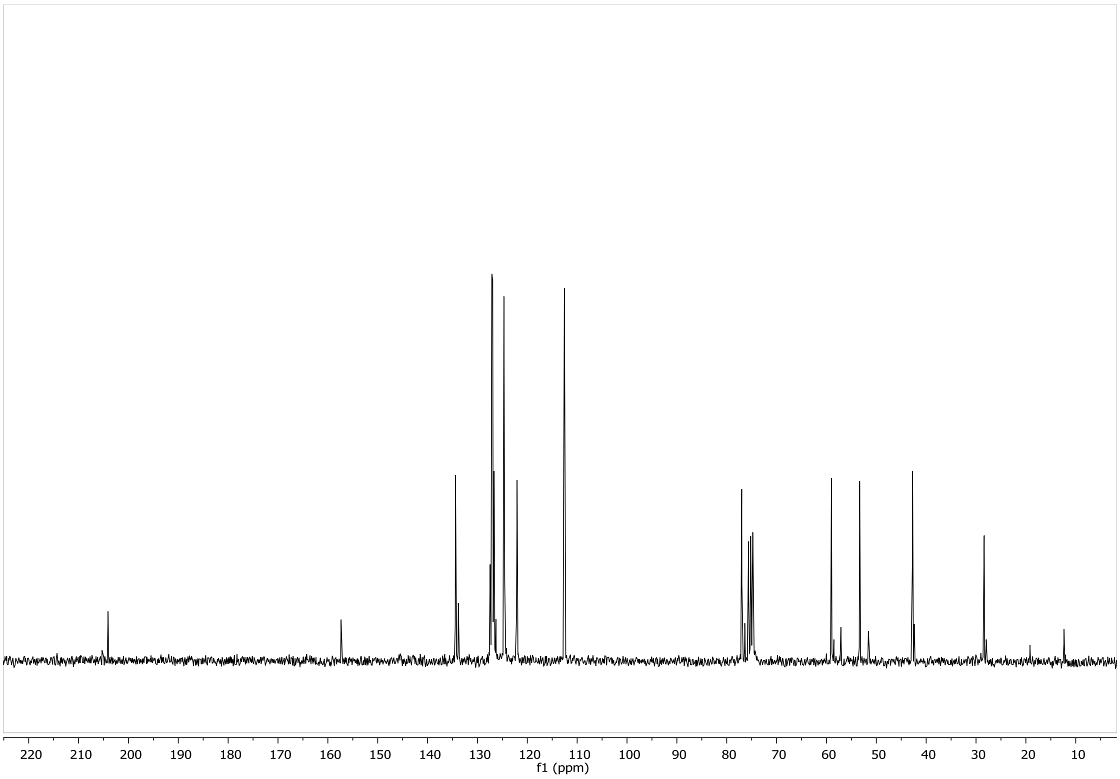
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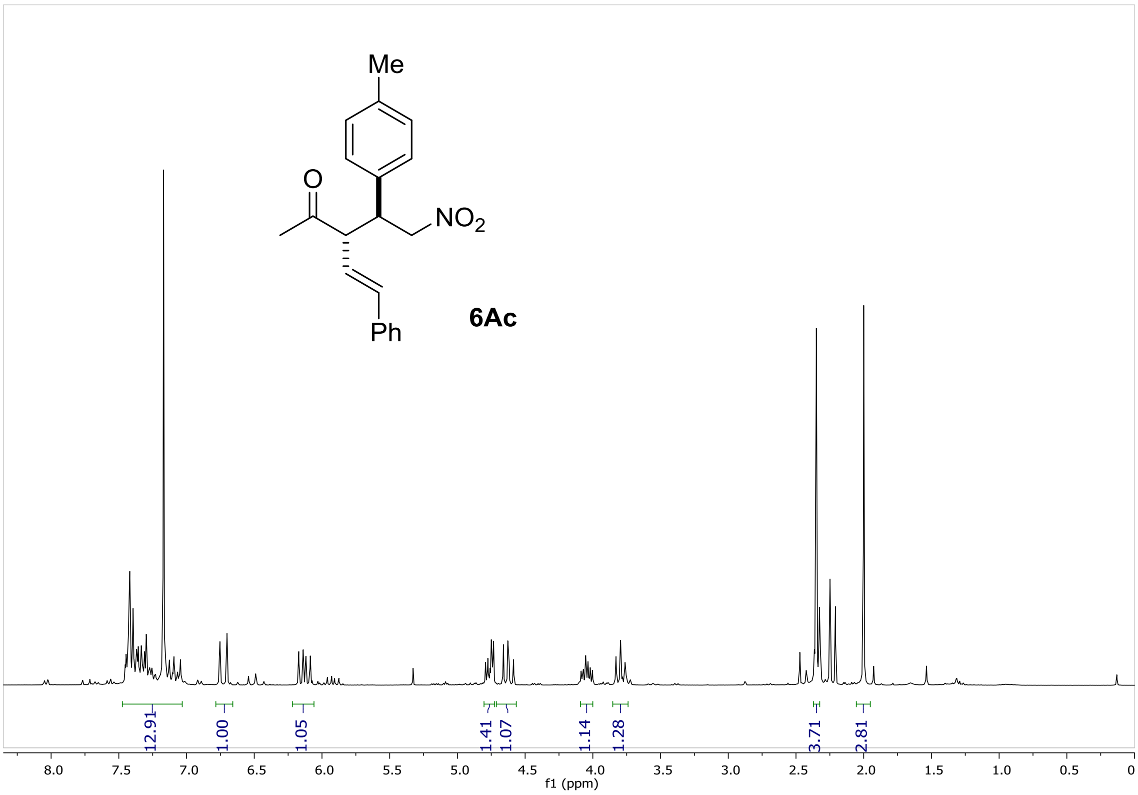
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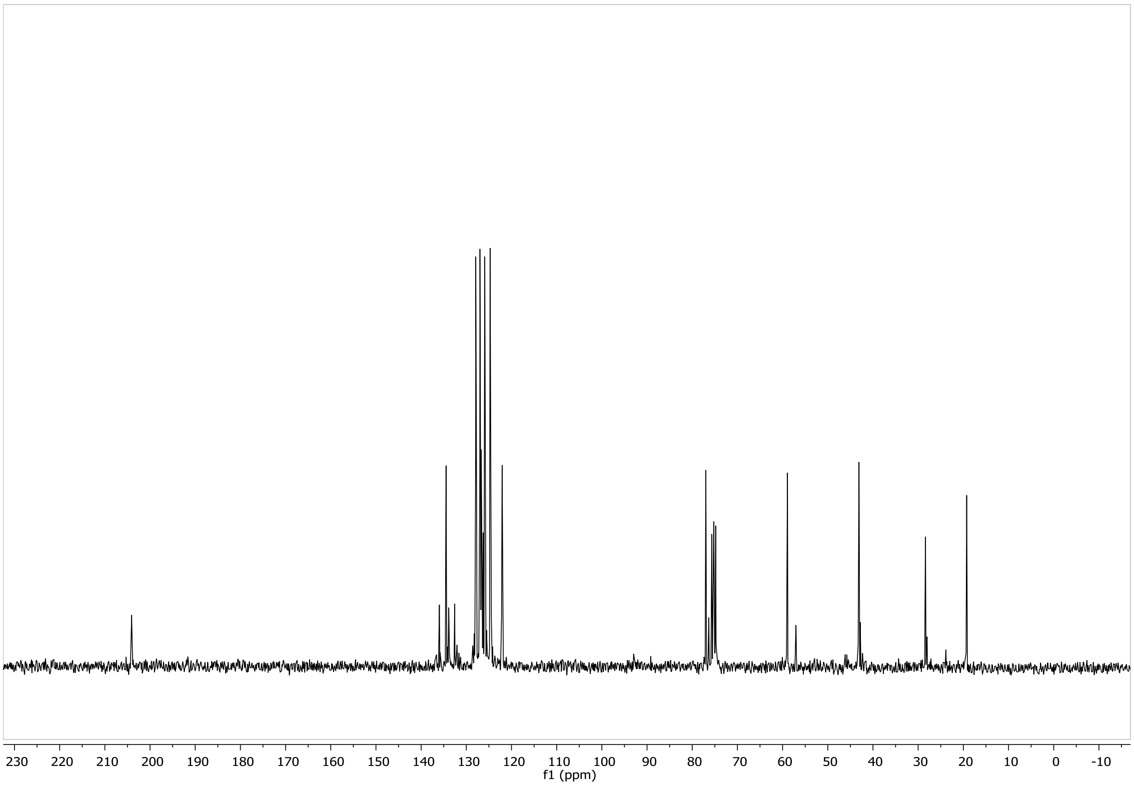
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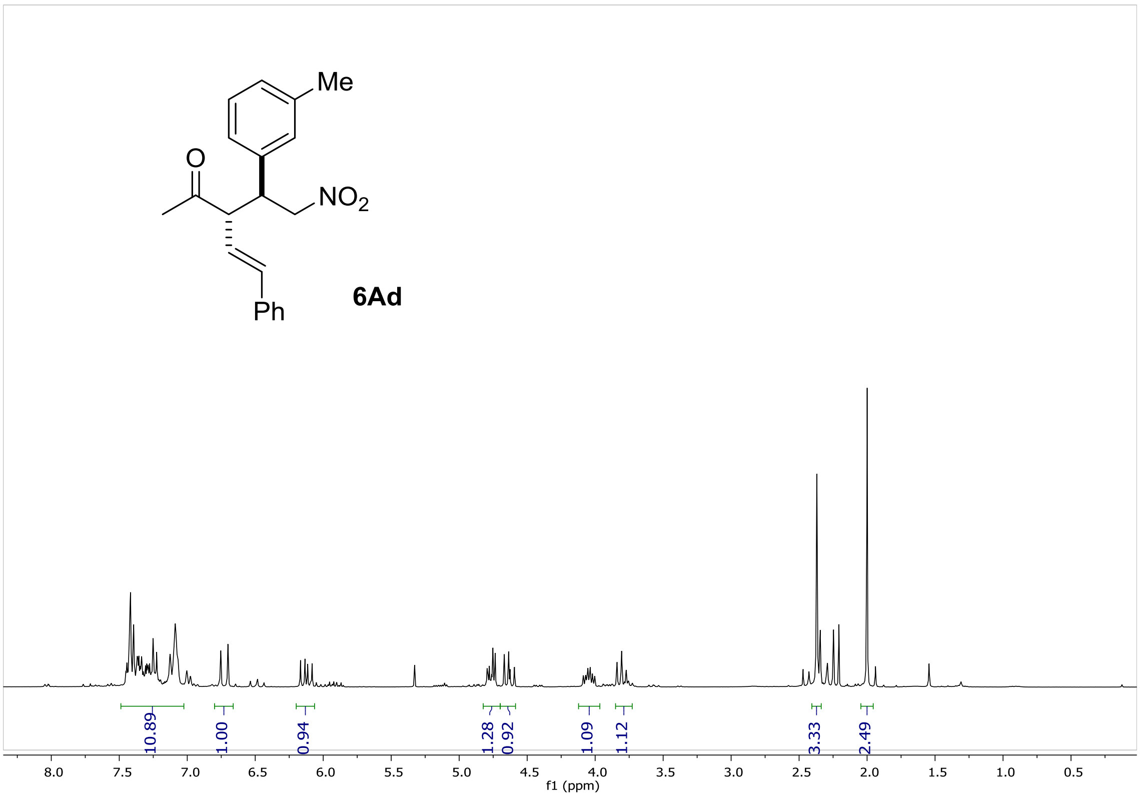
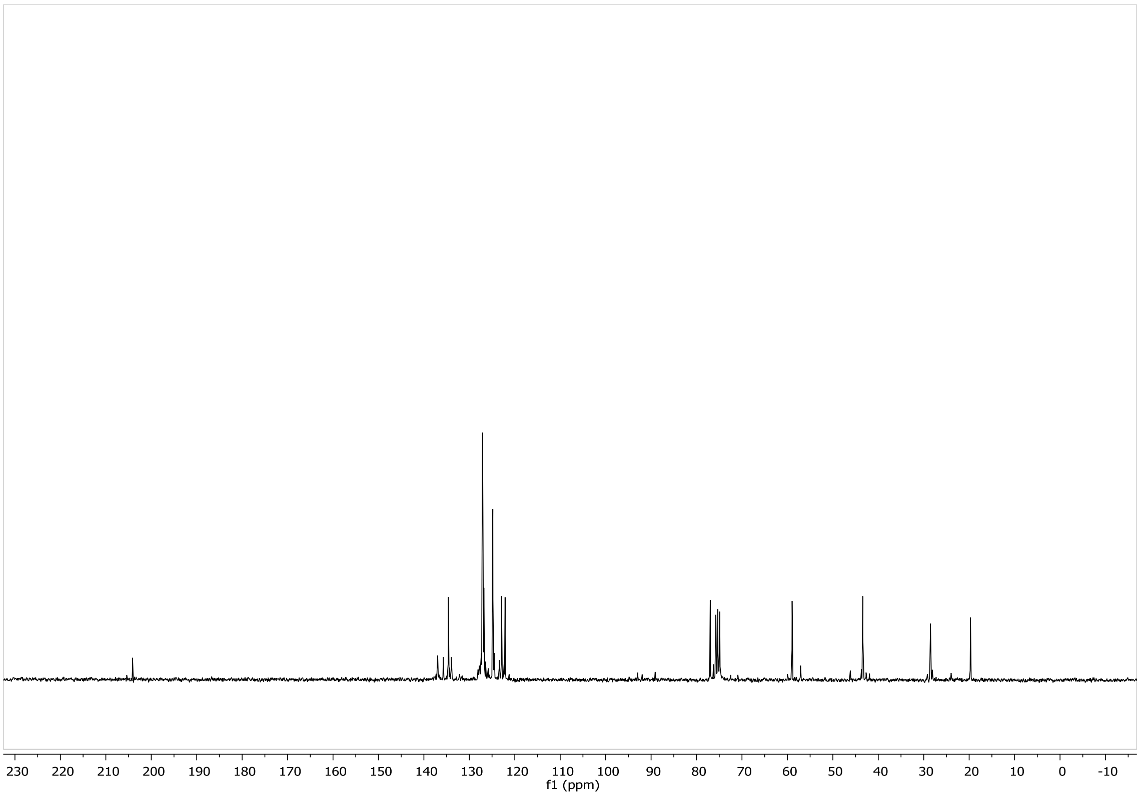
f1 (ppm)

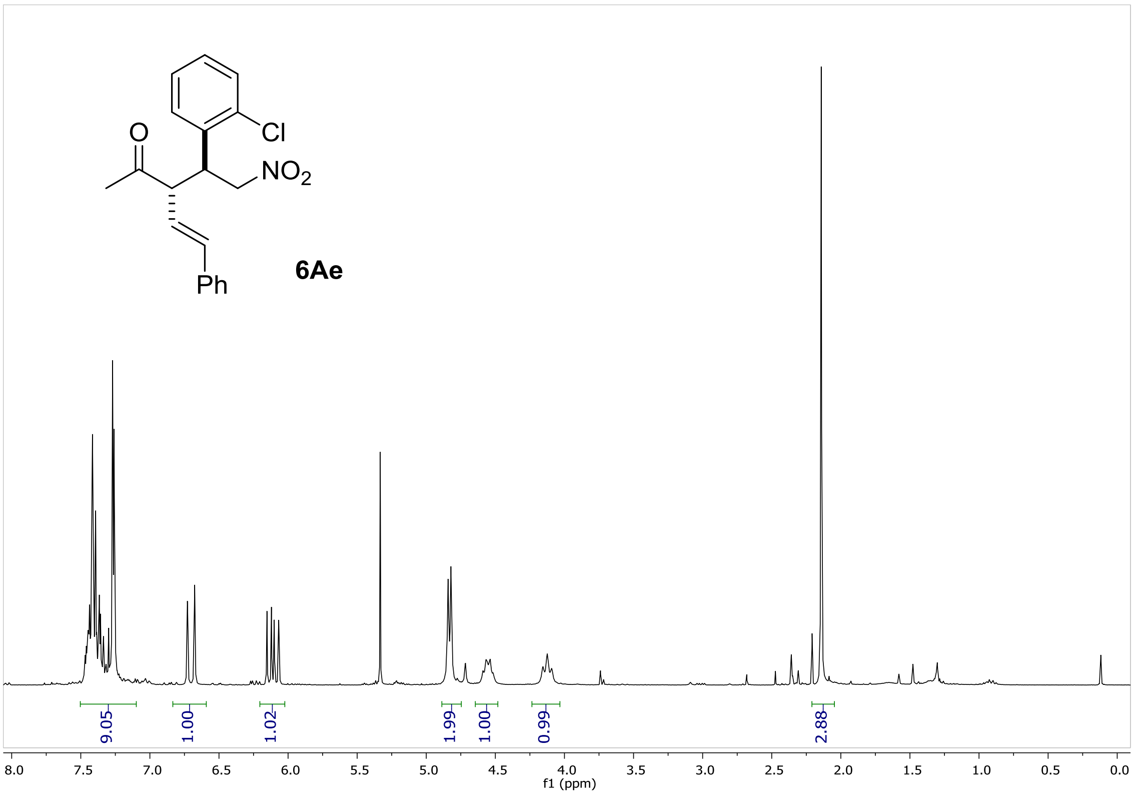


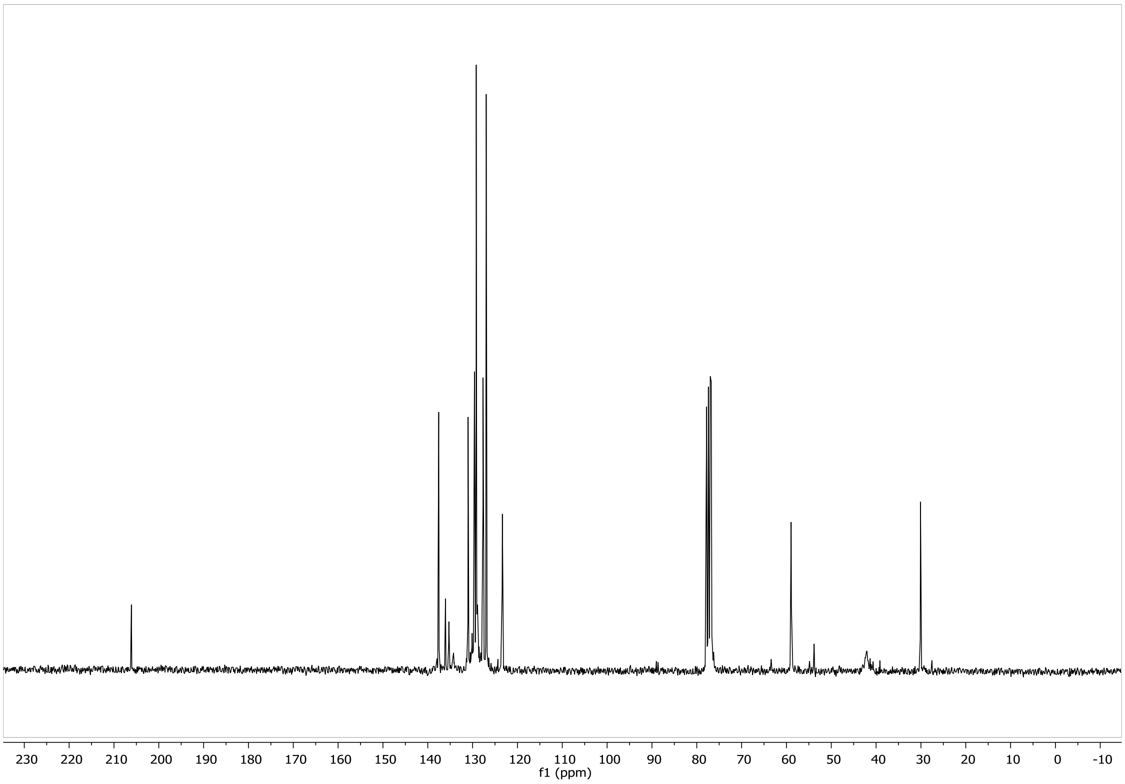
6Ad

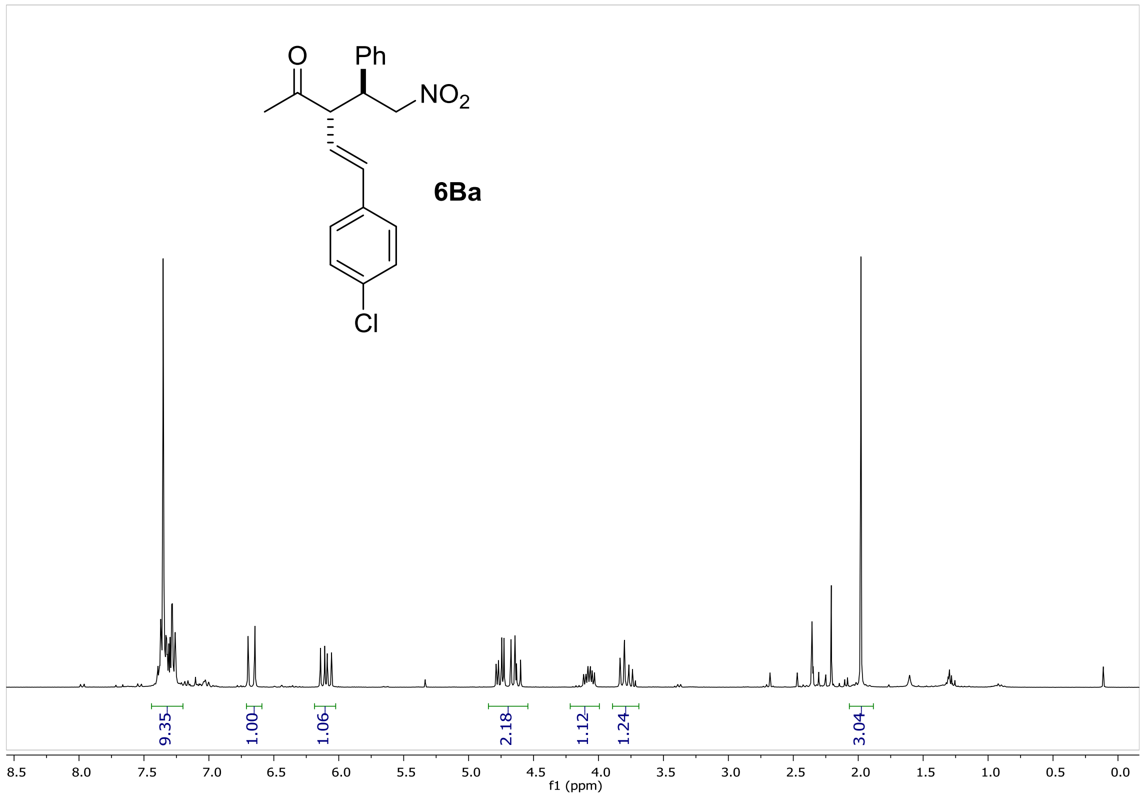
Me
O
NO2
Ph
10.89
1.00
0.94
1.28
0.92
1.09
1.12
3.33
2.49
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

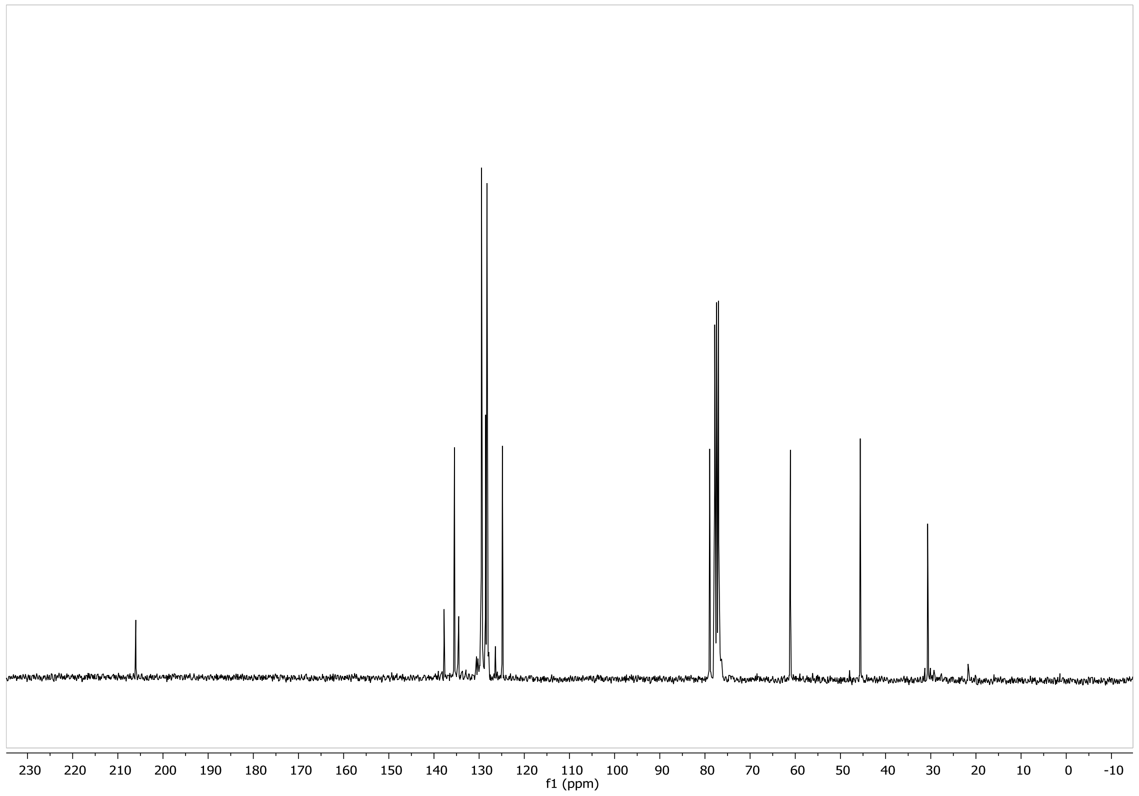


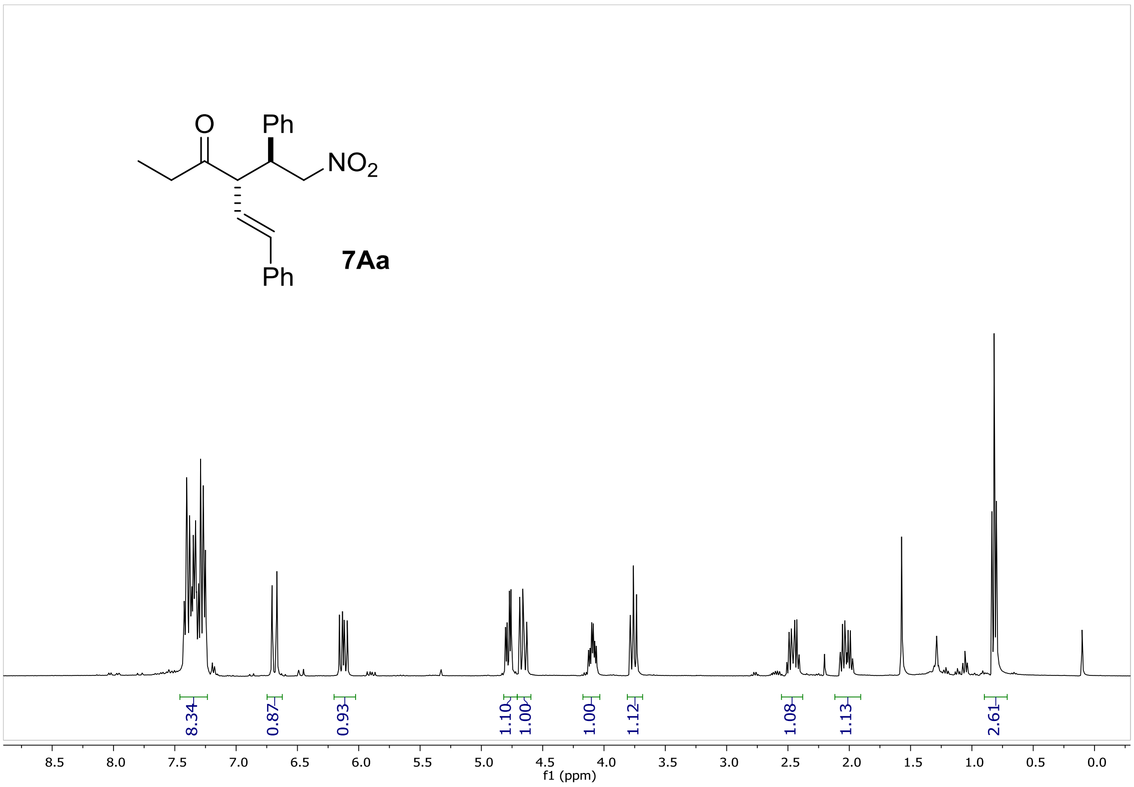
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

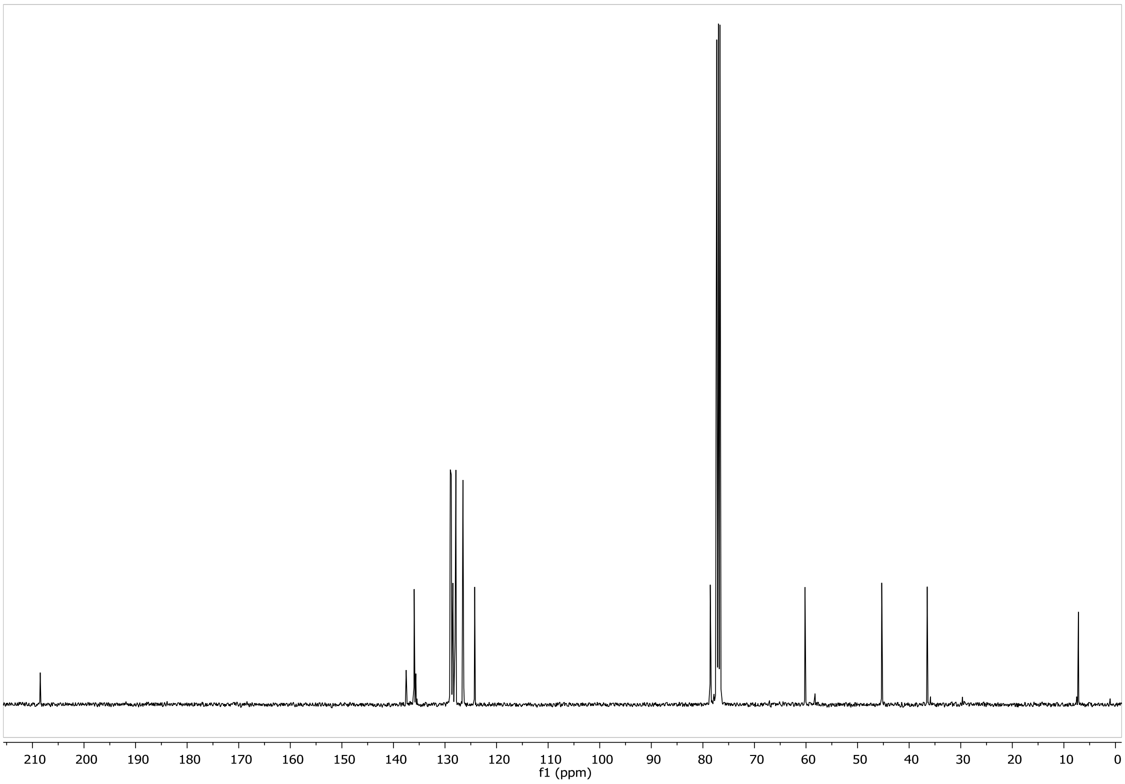

O
Cl
NO2
Ph
6Ae
9.05
1.00
1.02
1.99
1.00
0.99
2.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

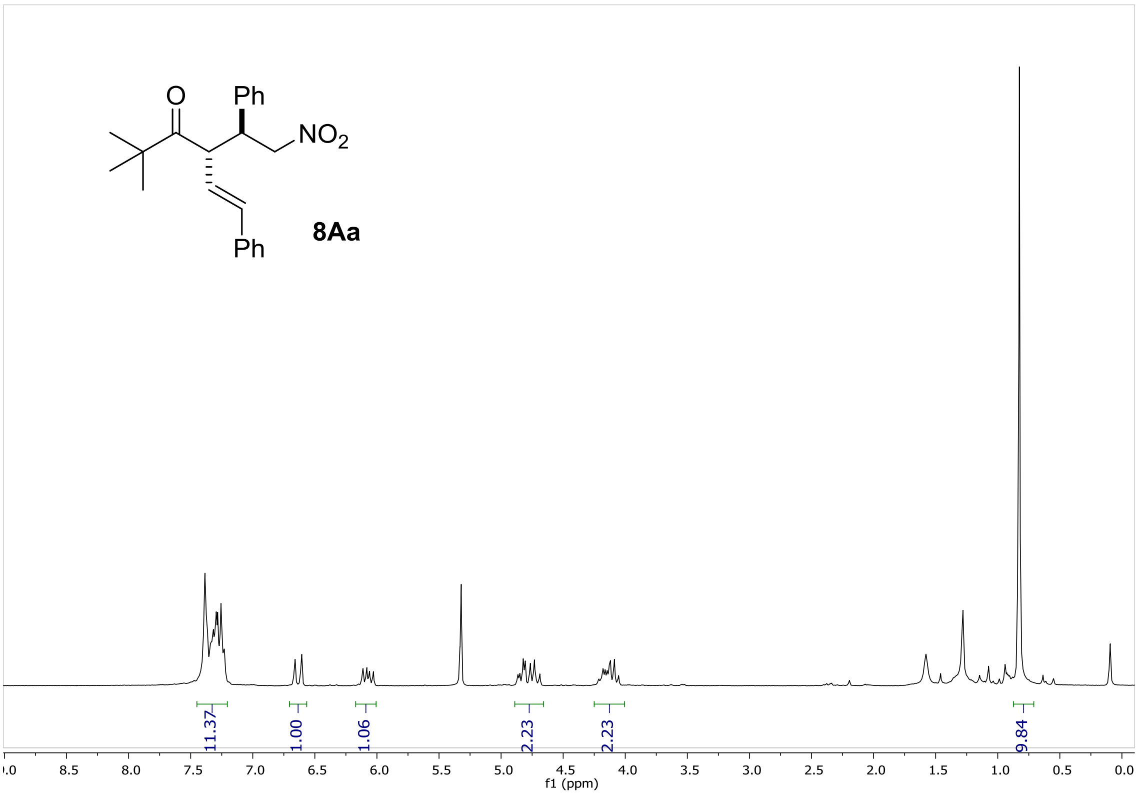

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

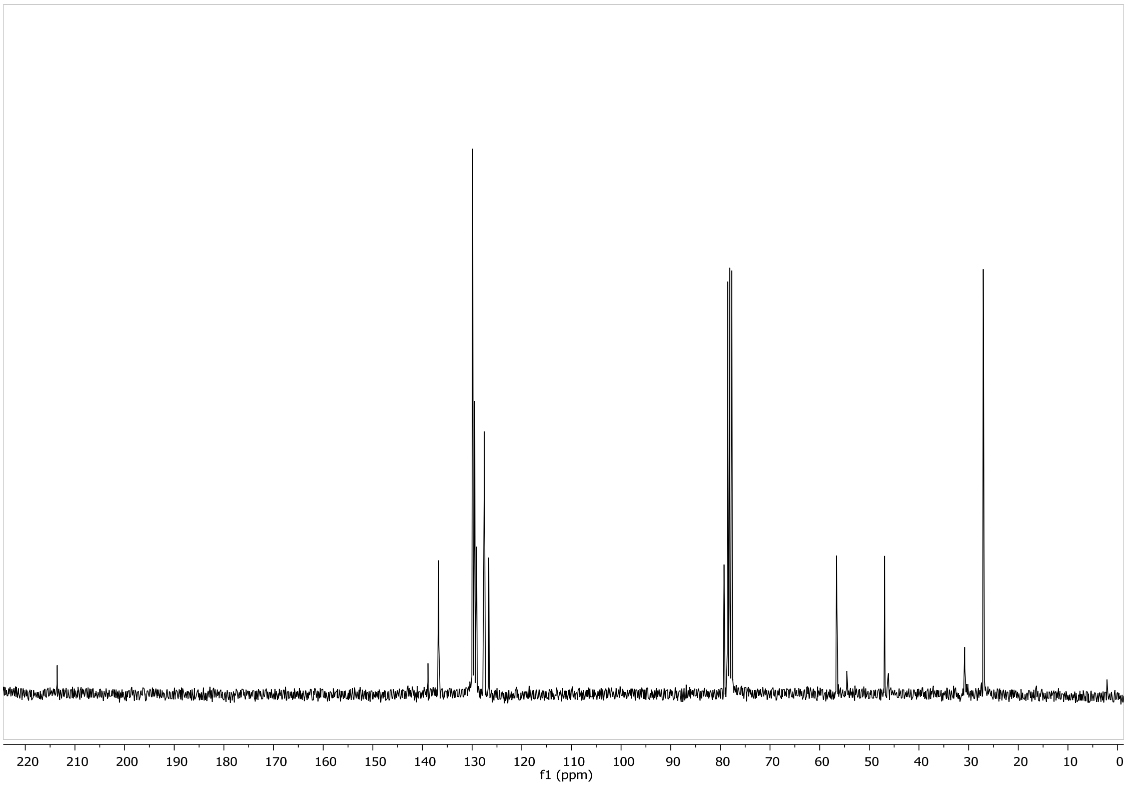

O
Ph
NO2
6Ba
Cl
9.35
1.00
1.06
2.18
1.12
1.24
3.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

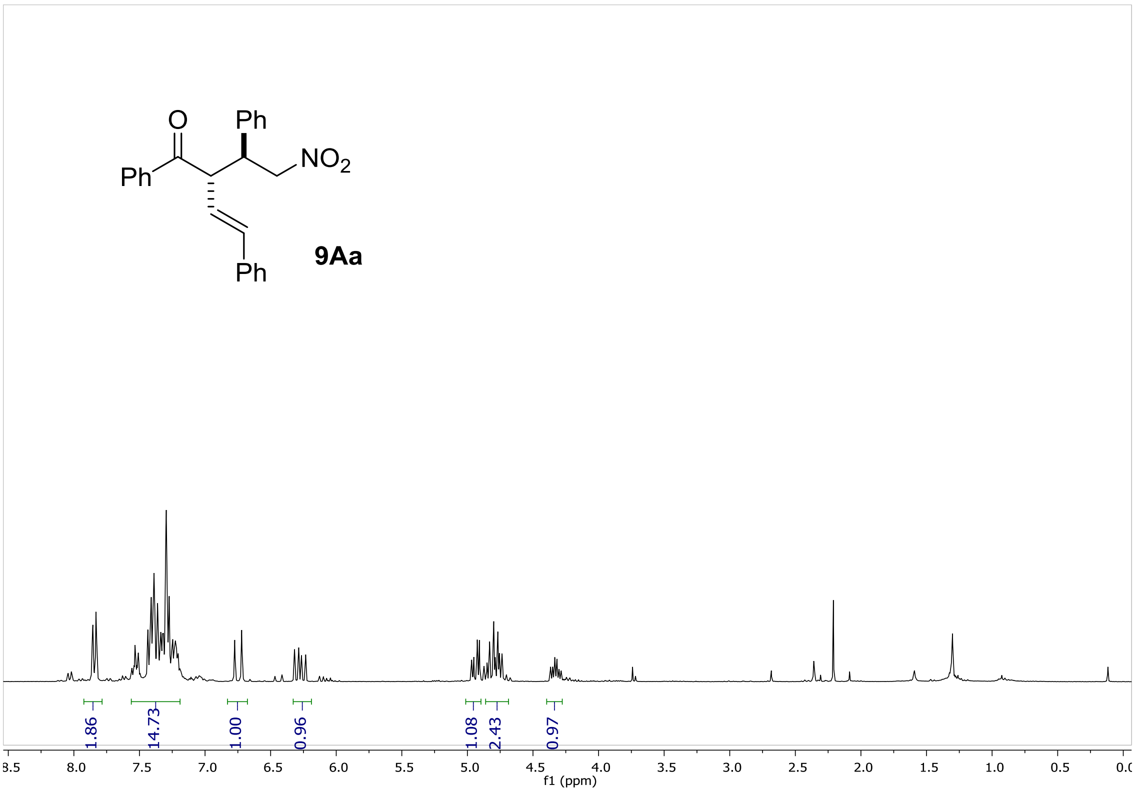

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

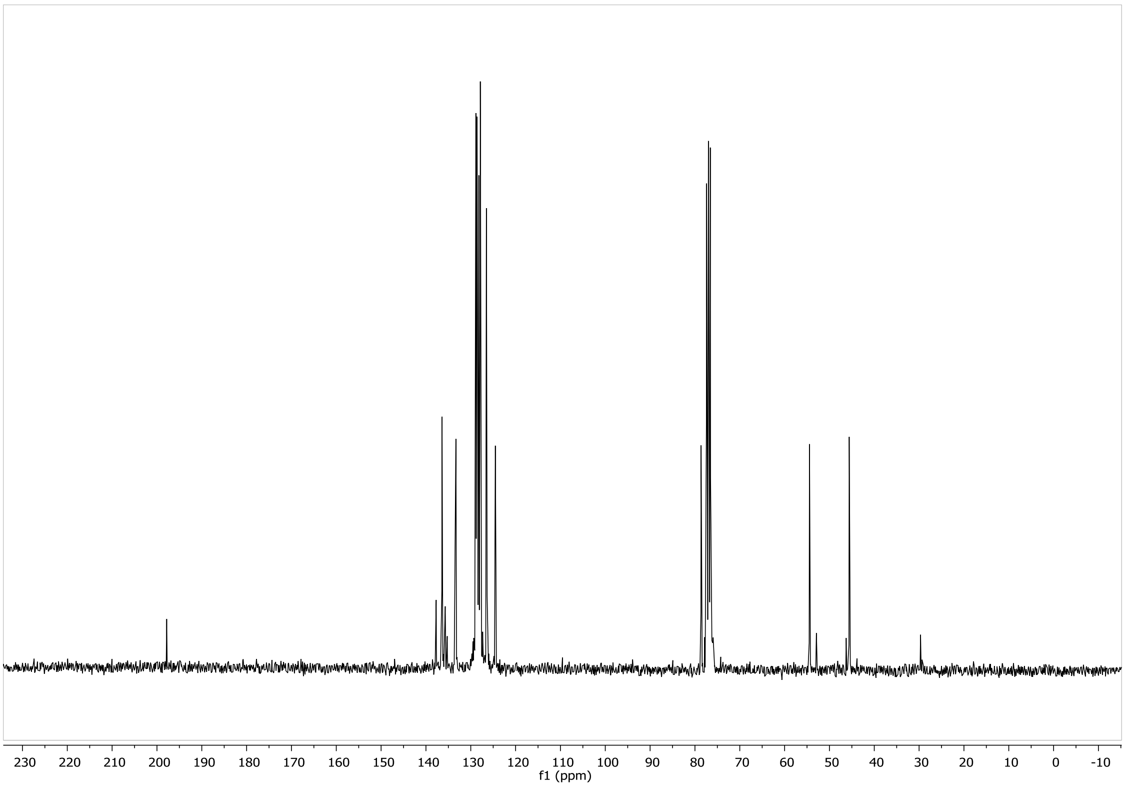

O
Ph
NO2
Ph
7Aa
8.34
0.87
0.93
1.10
1.00
1.00
1.12
1.08
1.13
2.61
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

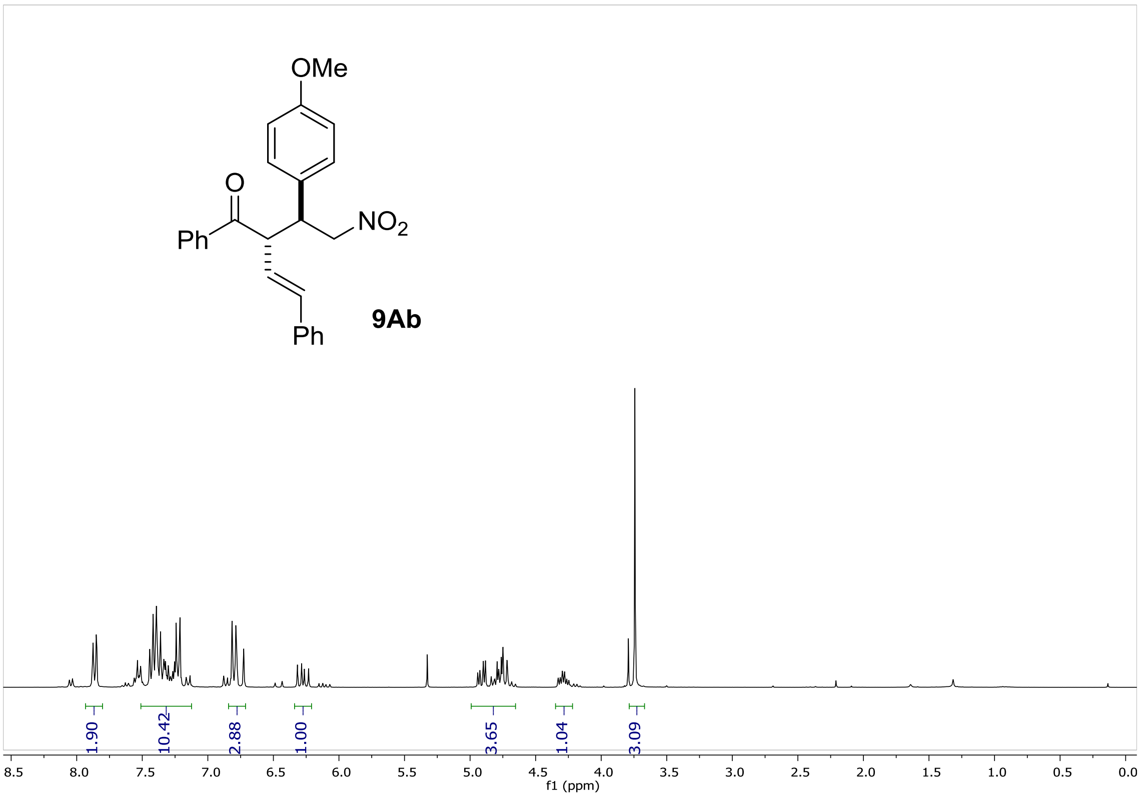

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8Aa
Ph
NO2
O
Ph
11.37
1.00
1.06
2.23
2.23
9.84
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)

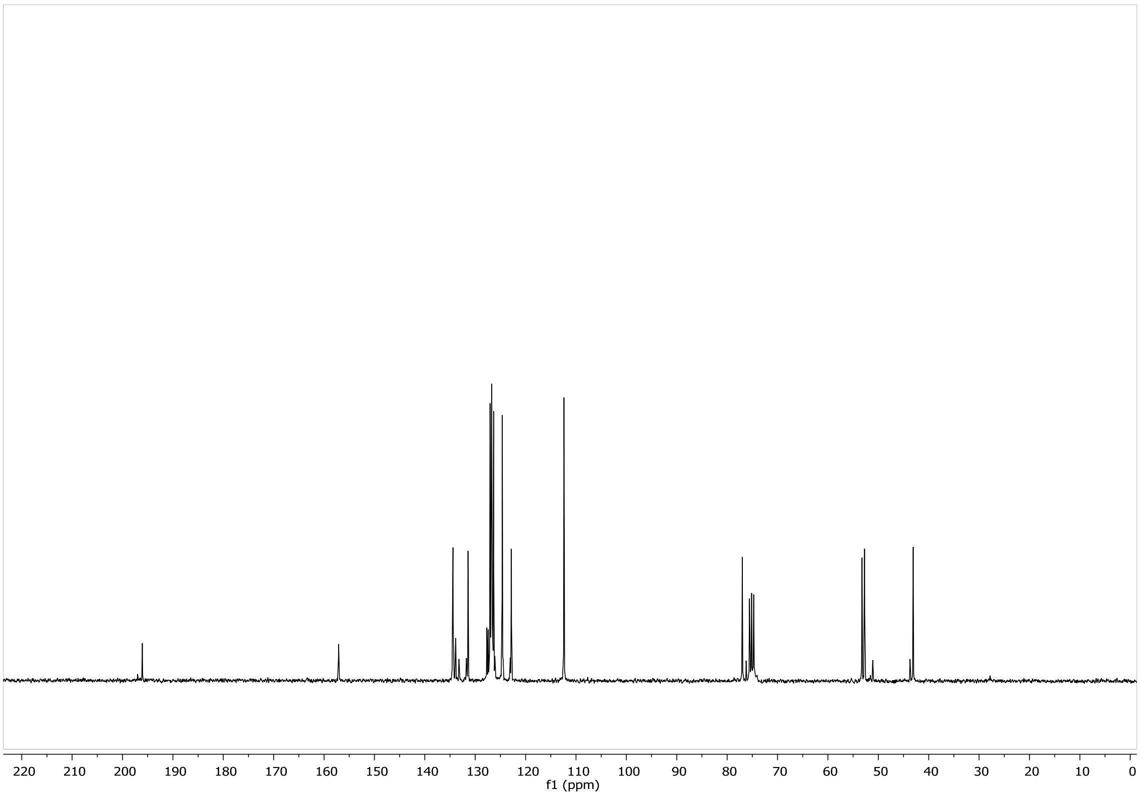

O
Ph
Ph
NO2
Ph
9Aa
1.86
14.73
1.00
0.96
1.08
2.43
0.97
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


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)

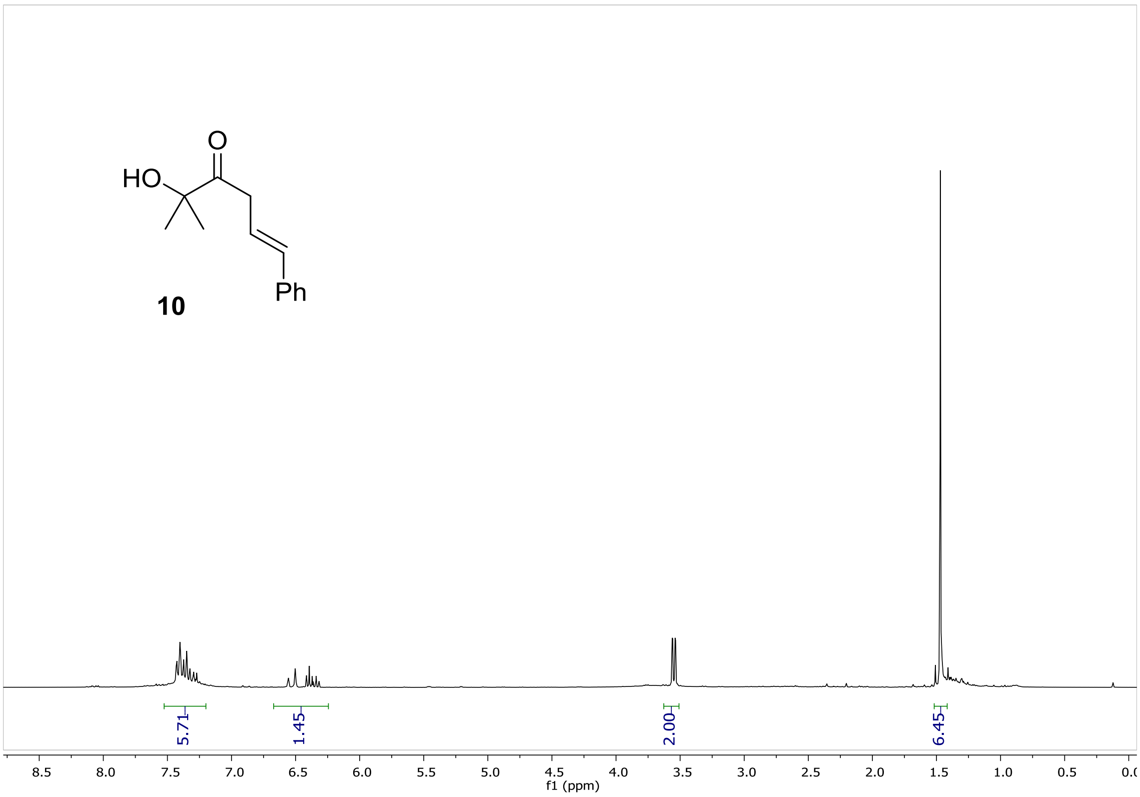


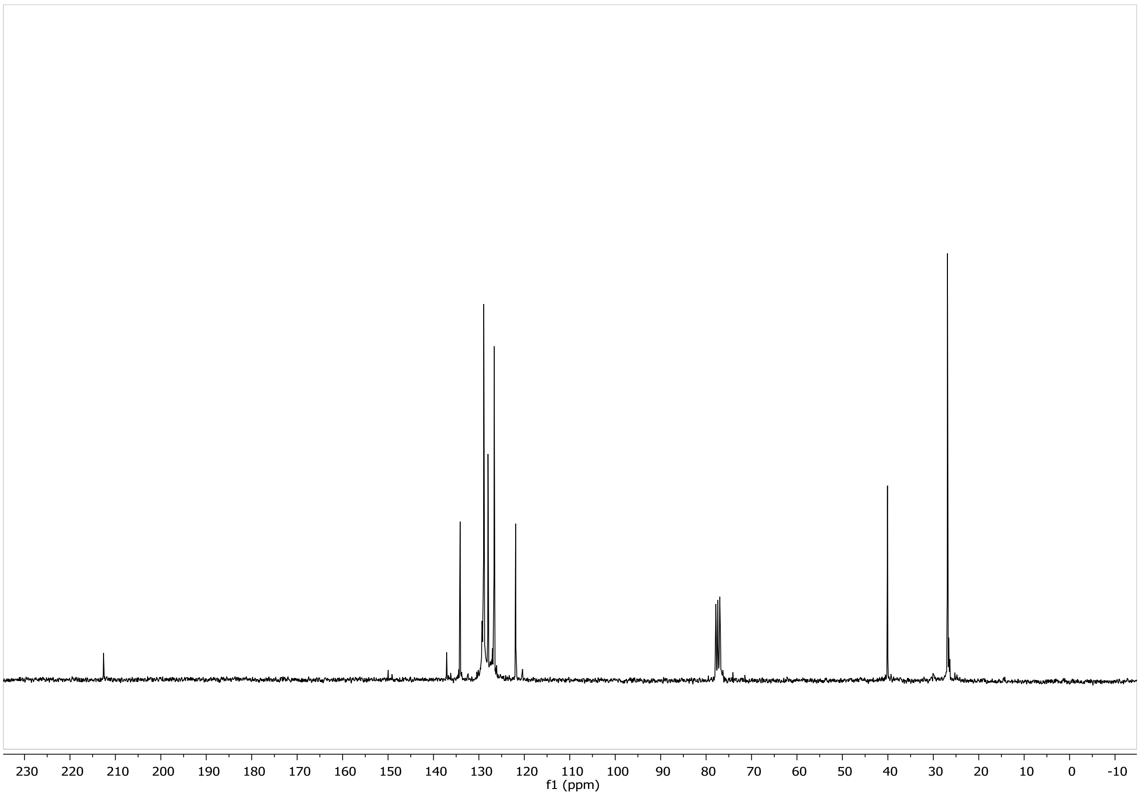
9Ab

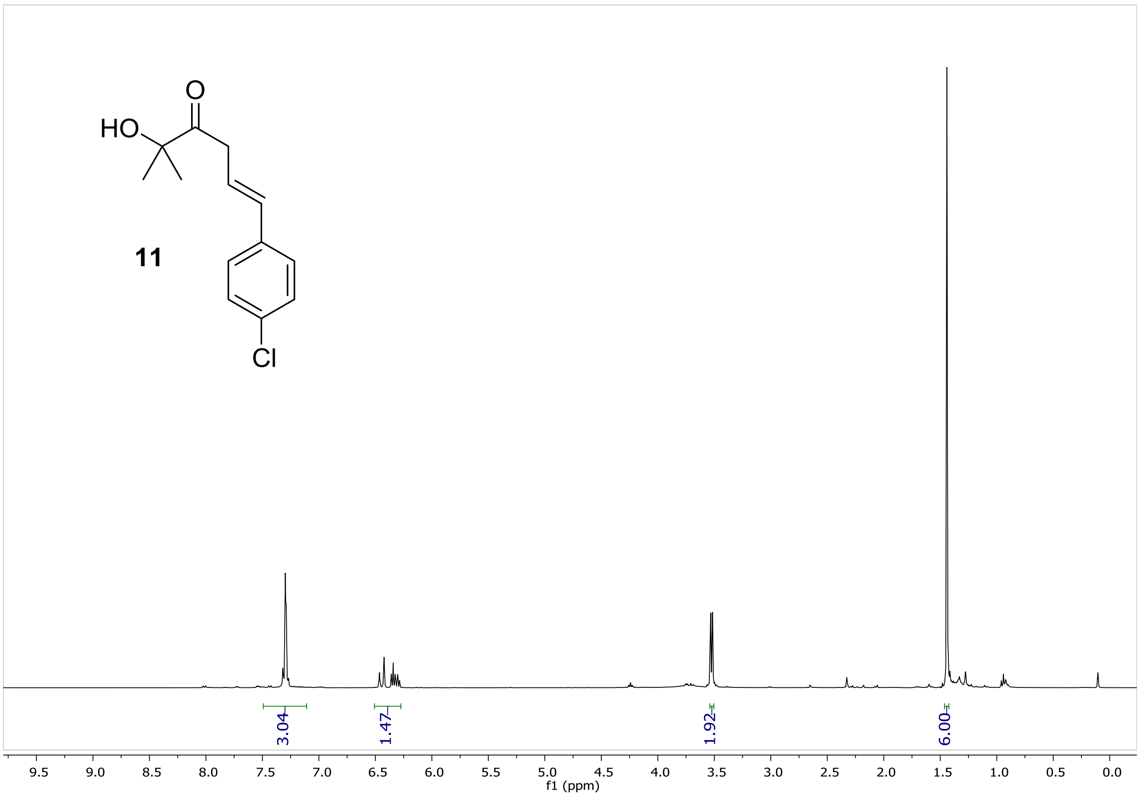
OMe
O
Ph
NO2
Ph
1.90
10.42
2.88
1.00
3.65
1.04
3.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



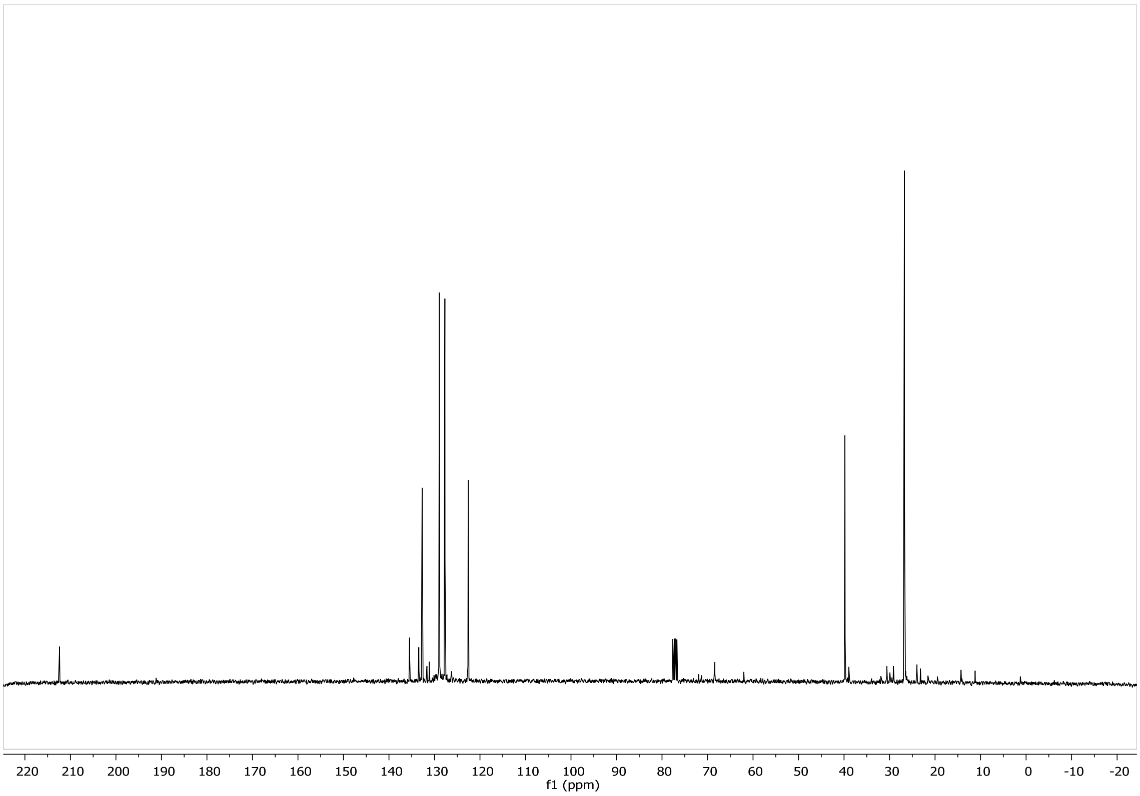
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

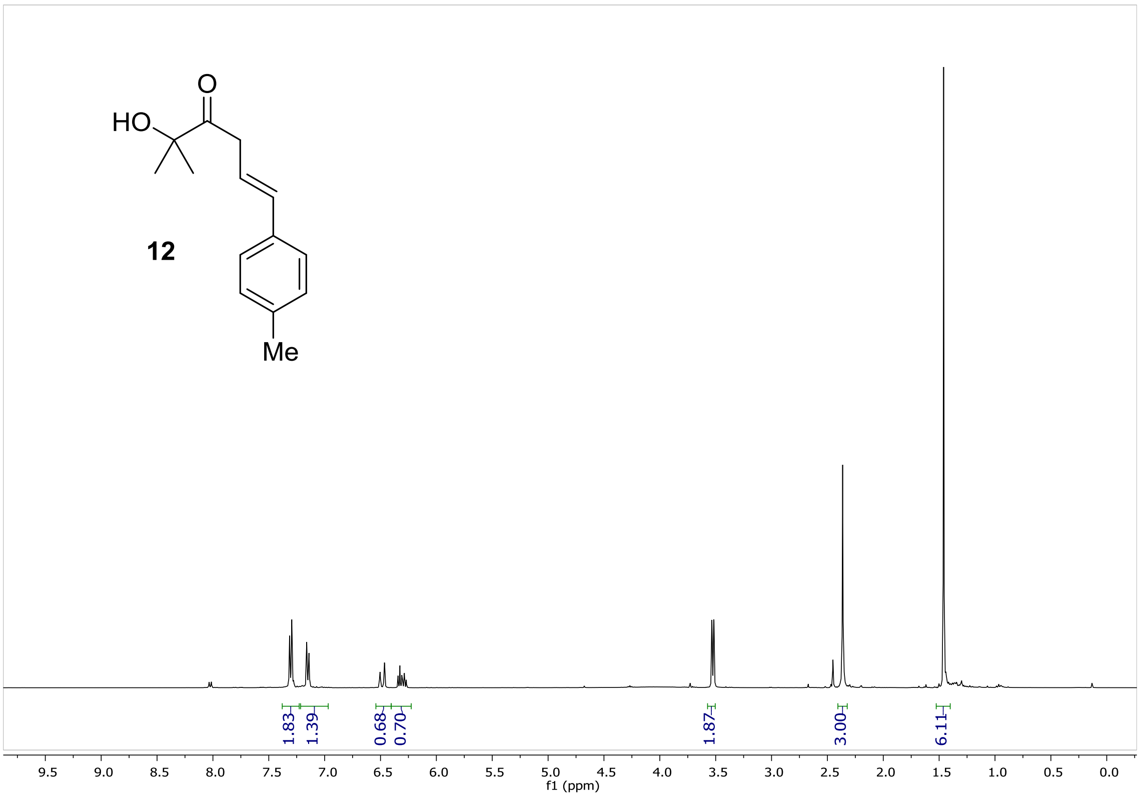

O
HO
Ph
10
5.71
1.45
2.00
6.45
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

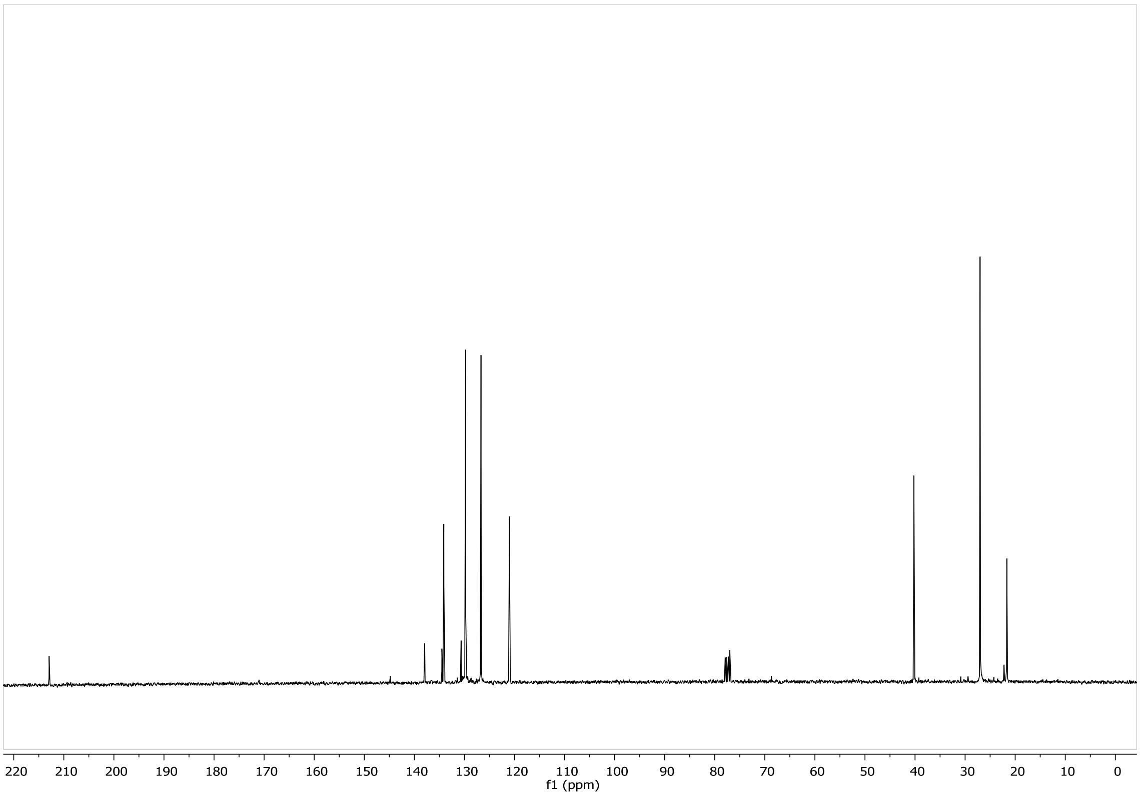

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

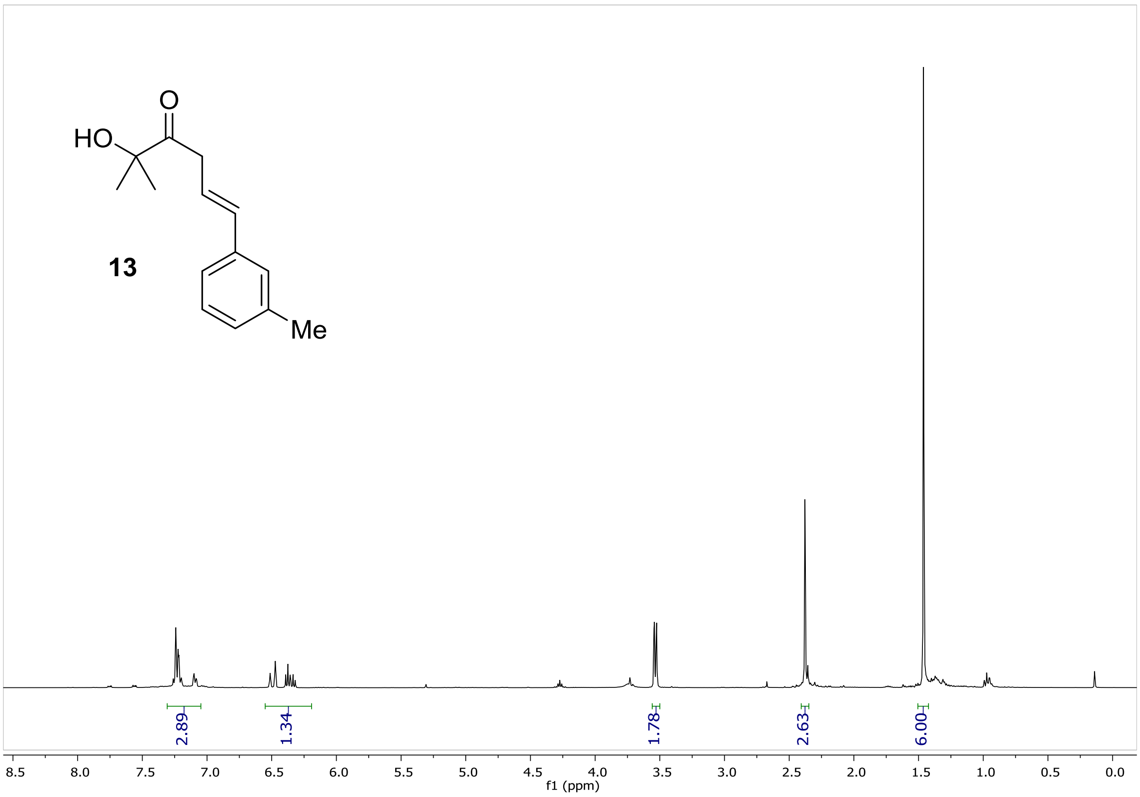

HO
O
Cl
3.04
1.47
1.92
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

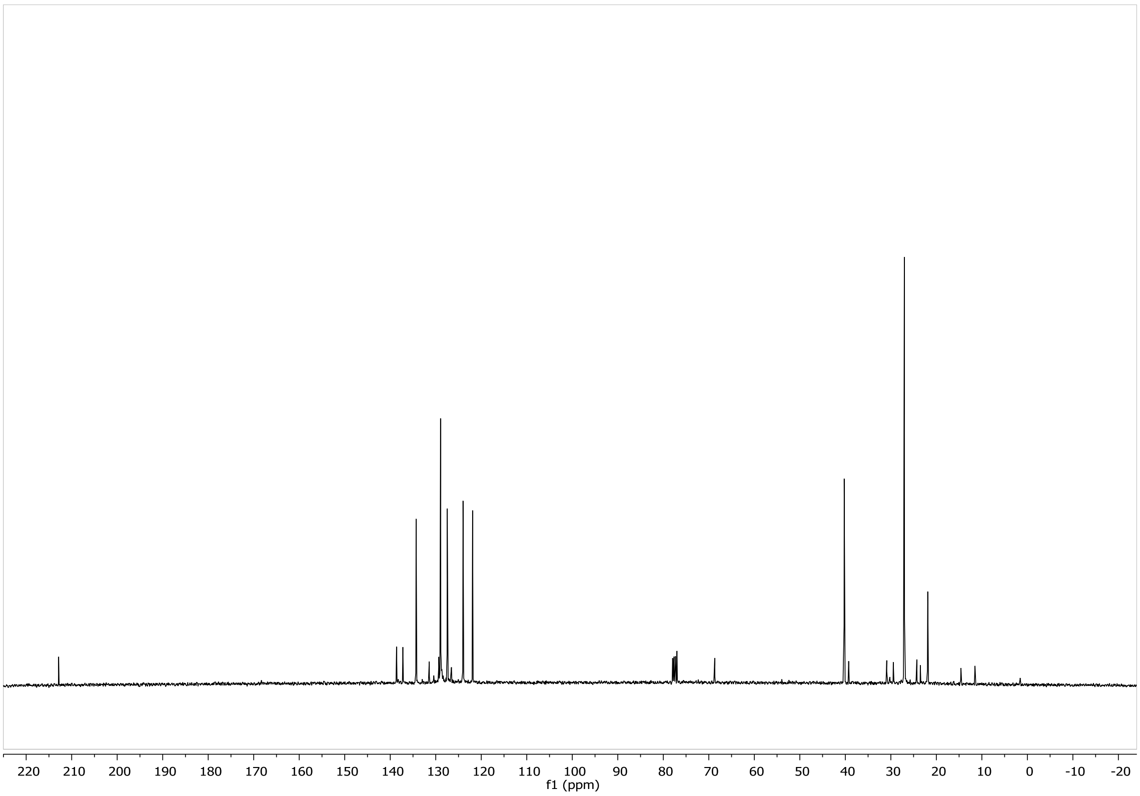
11

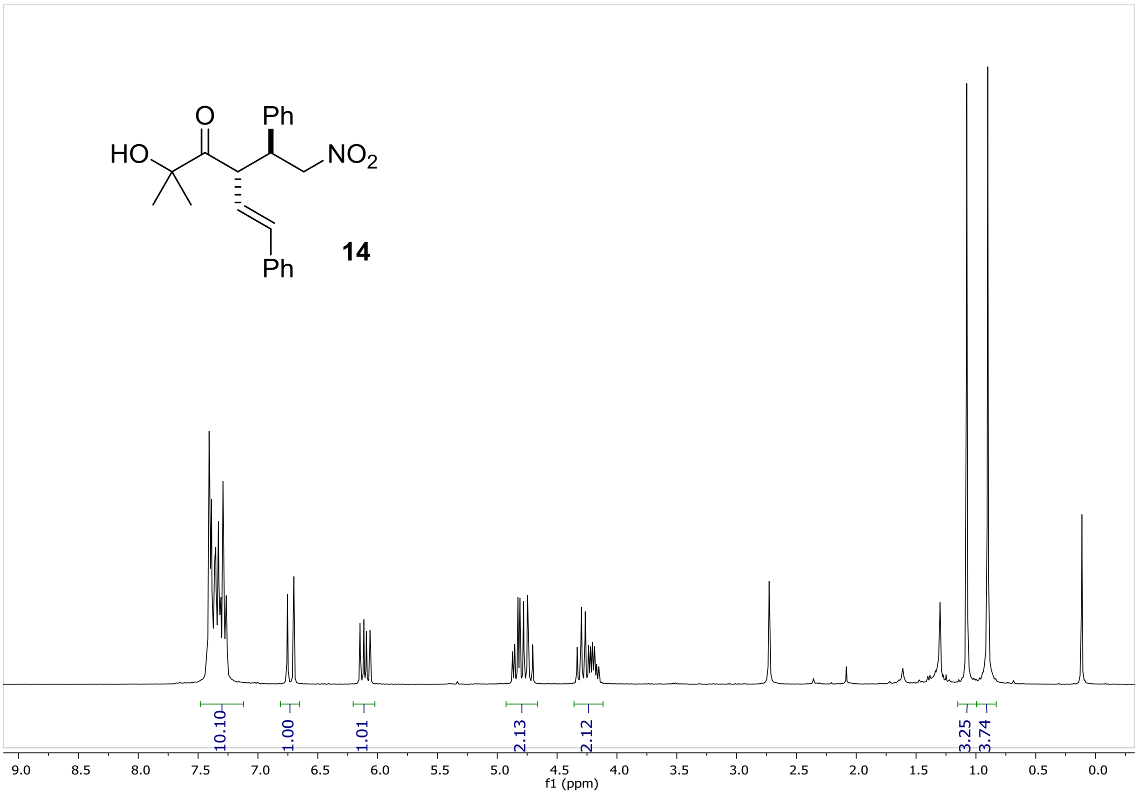

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

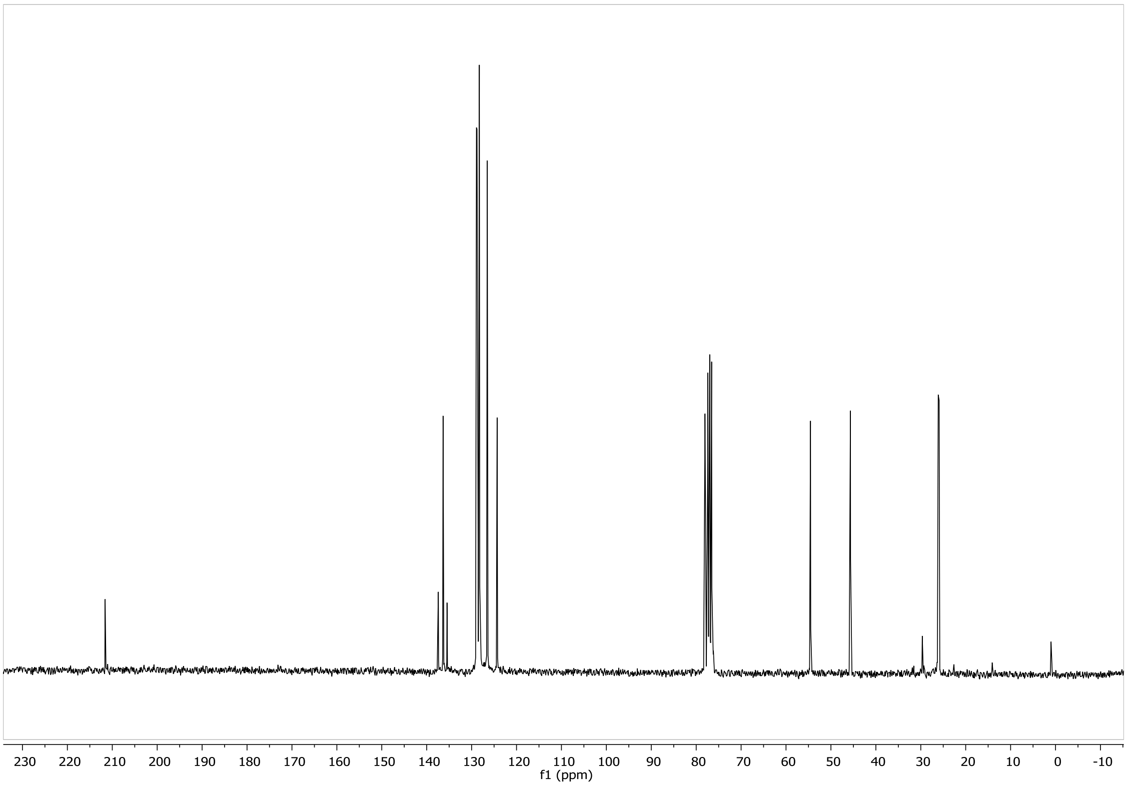

O
HO
12
Me
1.83
1.39
0.68
0.70
1.87
3.00
6.11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

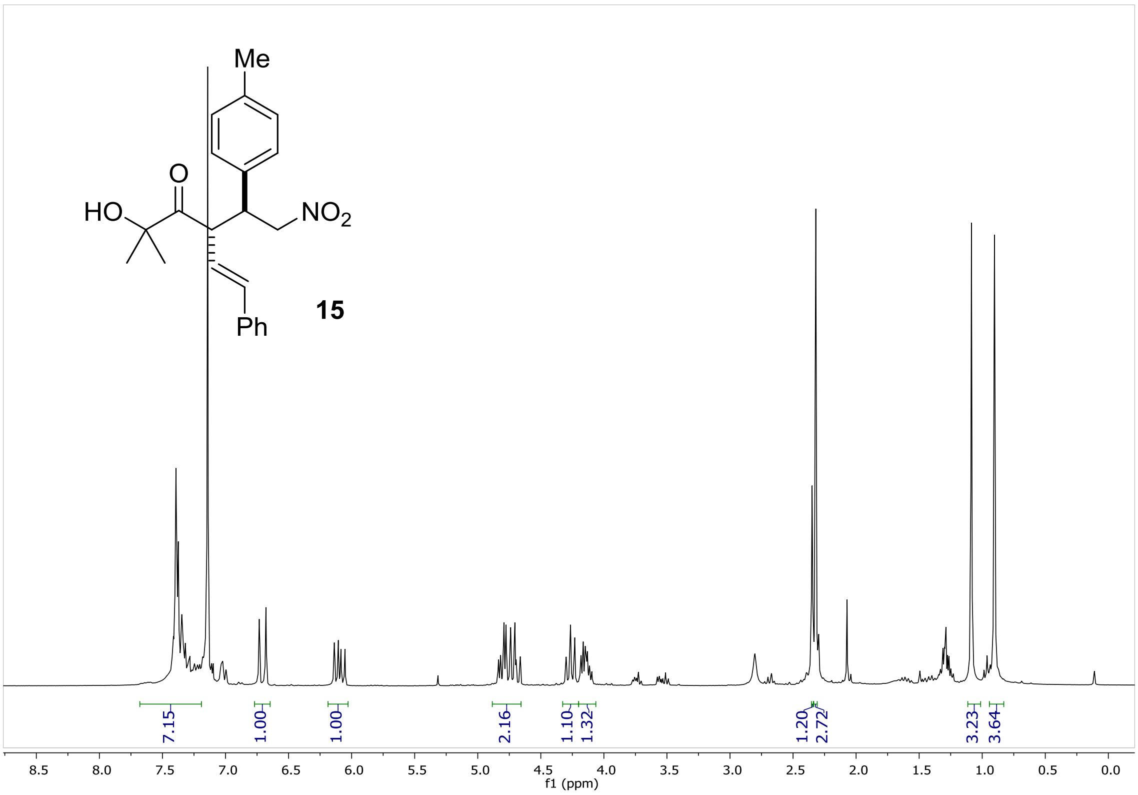

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

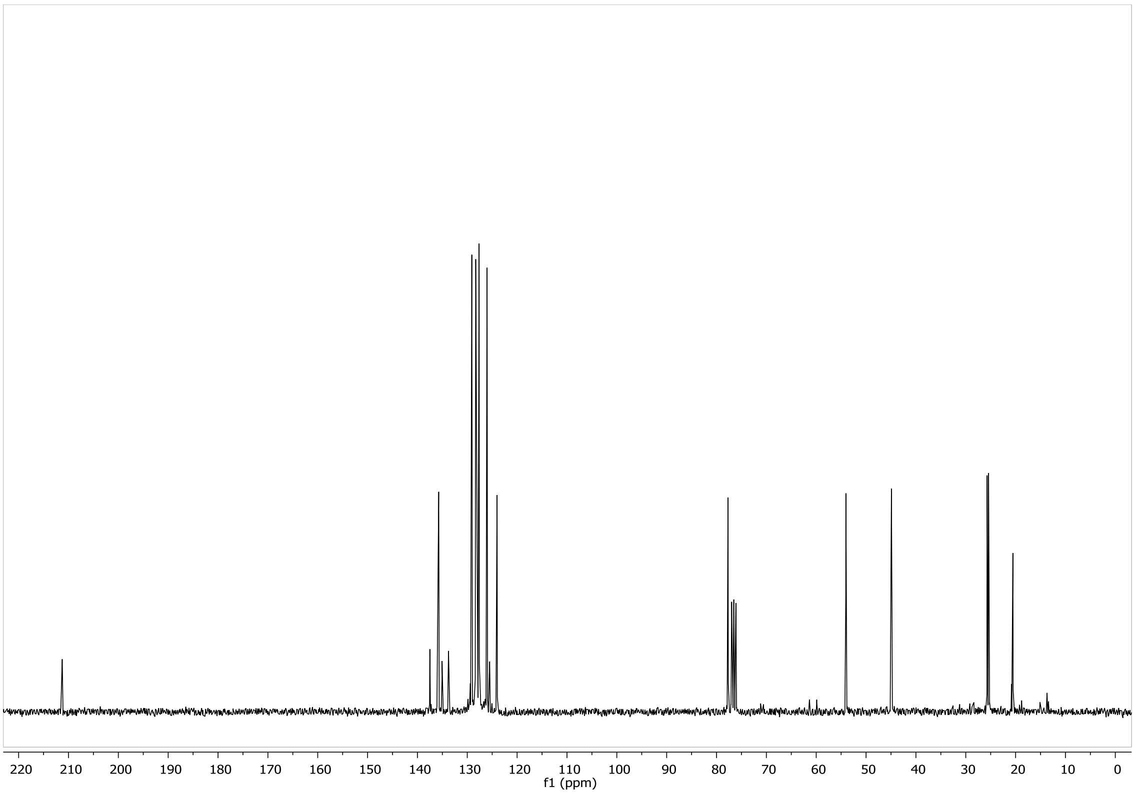

HO
O
Me
13
2.89
1.34
1.78
2.63
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

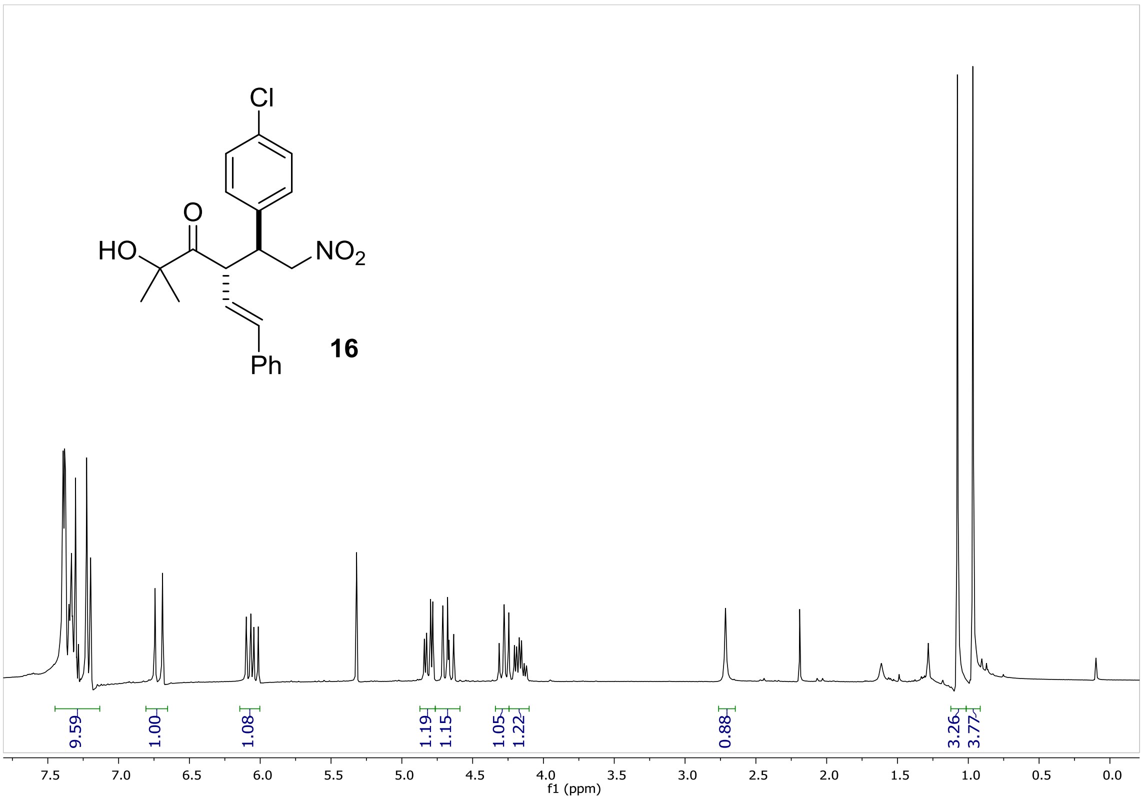

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

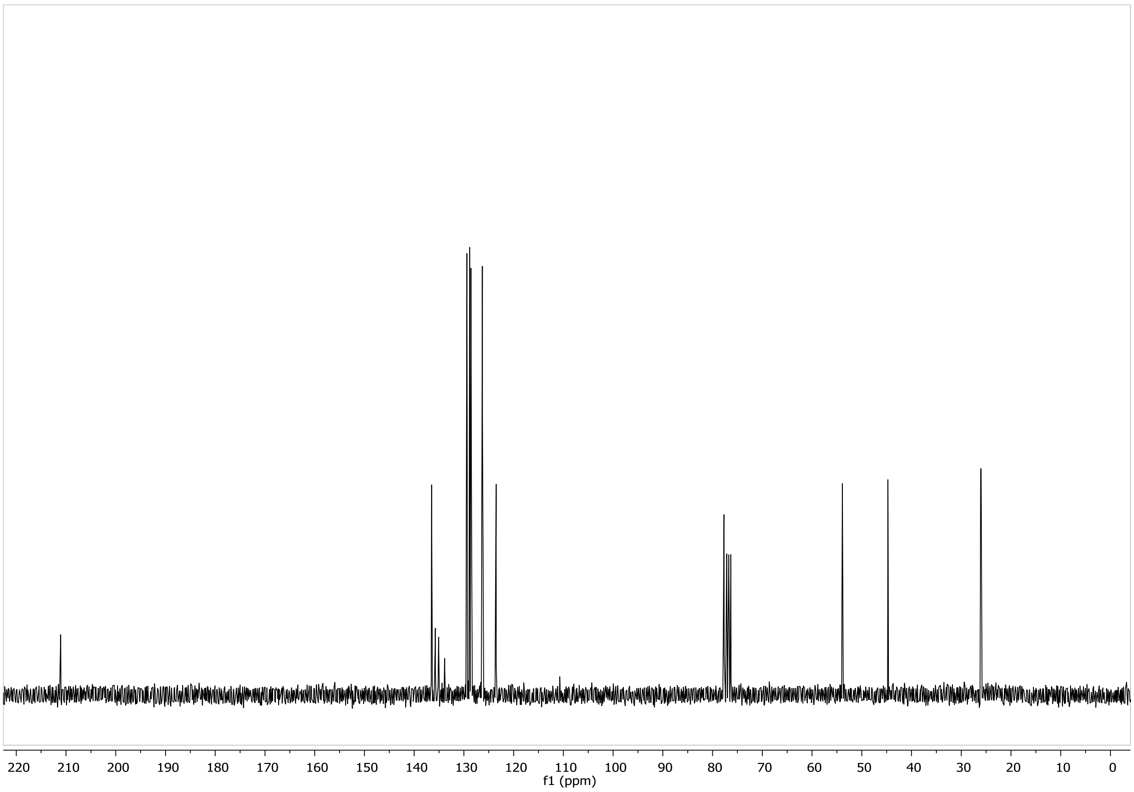

O
Ph
HO
NO2
Ph
14
10.10
1.00
1.01
2.13
2.12
3.25
3.74
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

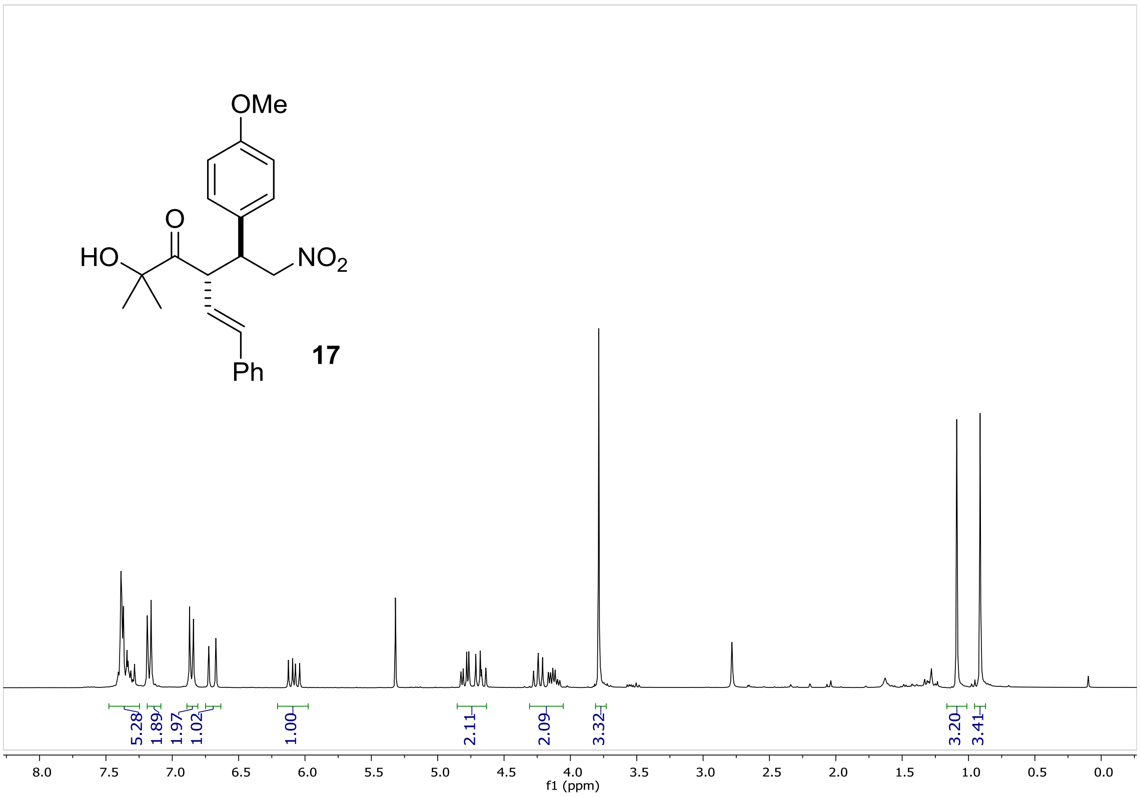

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

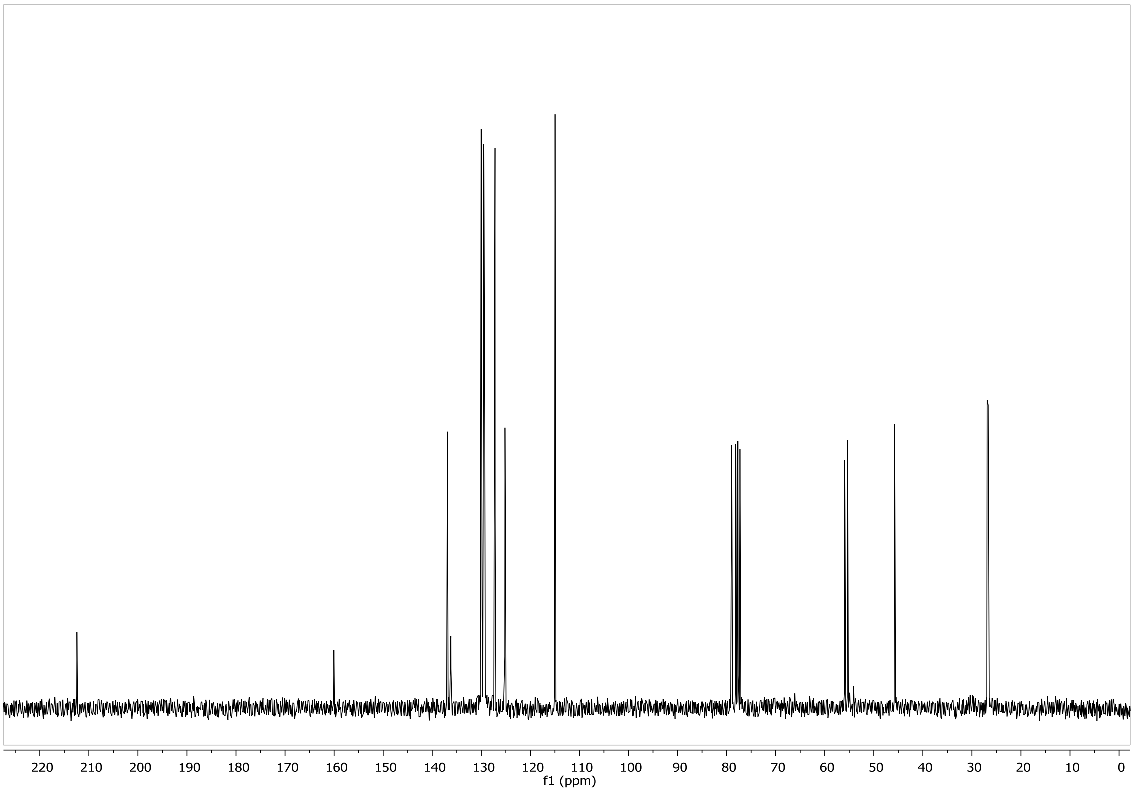

Me
O
HO
NO2
Ph
15
7.15
1.00
1.00
2.16
1.10
1.32
1.20
2.72
3.23
3.64
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

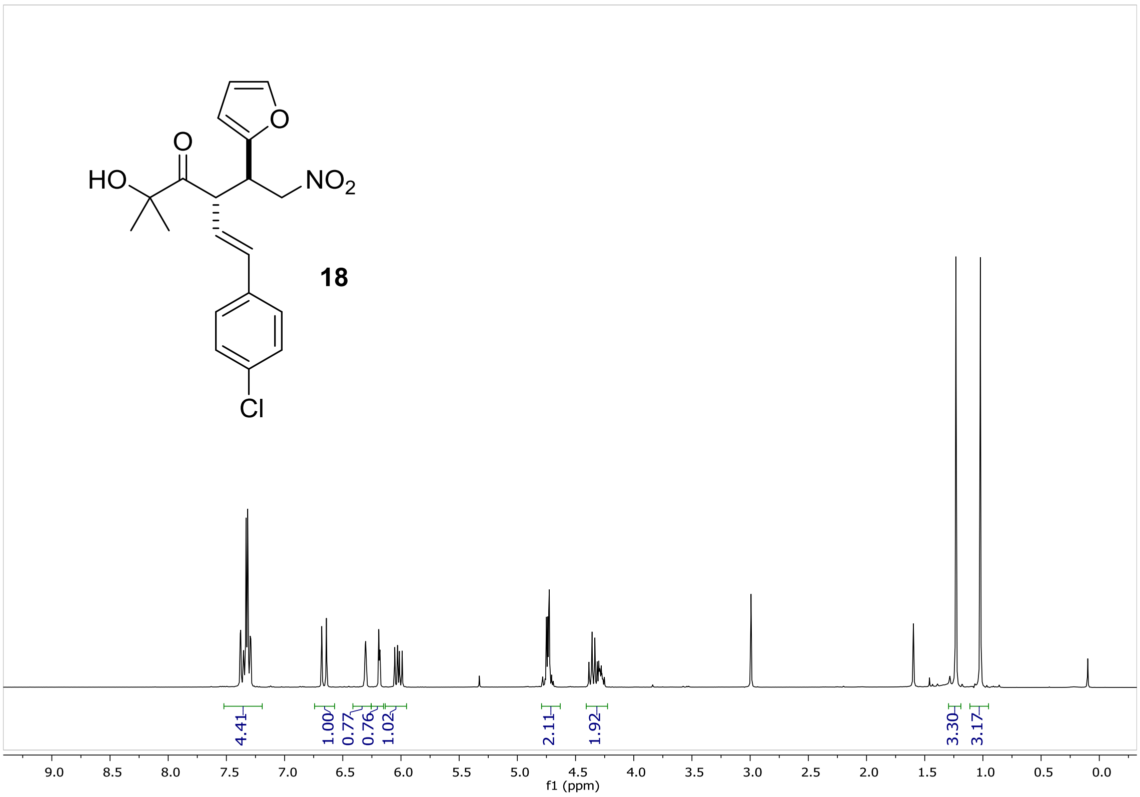

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

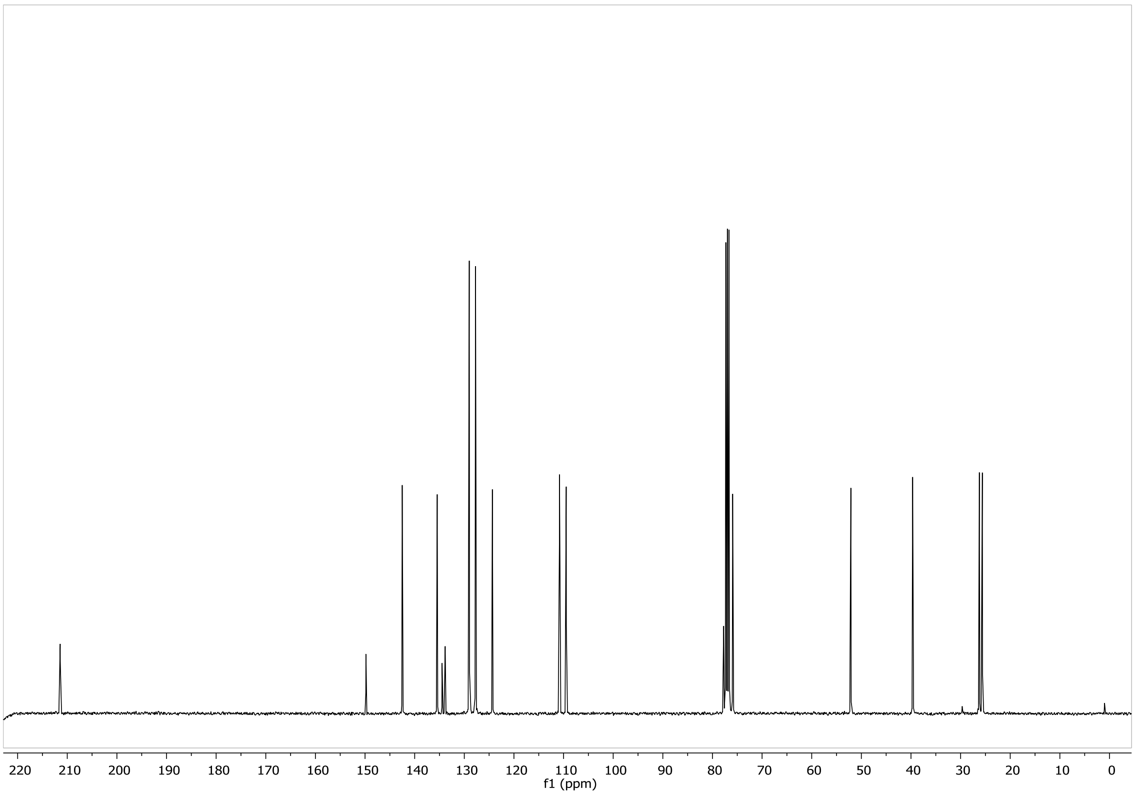

Cl
O
HO
NO2
Ph
16
9.59
1.00
1.08
1.19
1.15
1.05
1.22
0.88
3.26
3.77
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

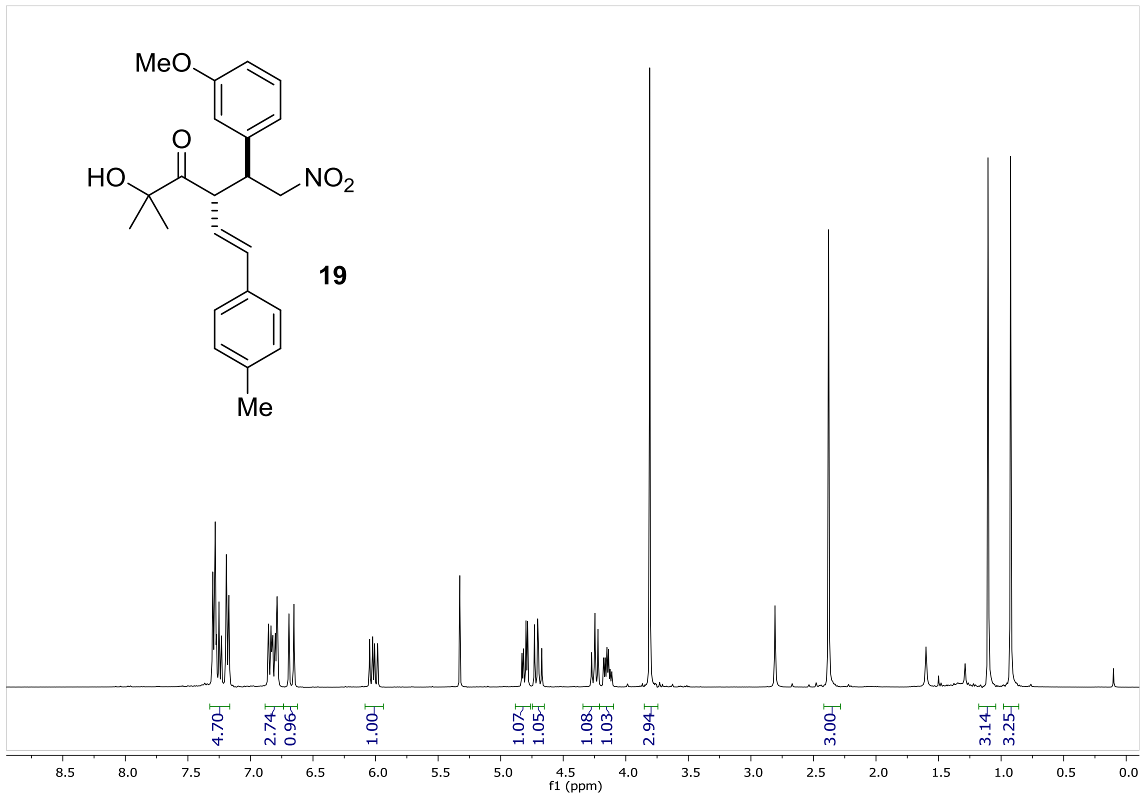

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

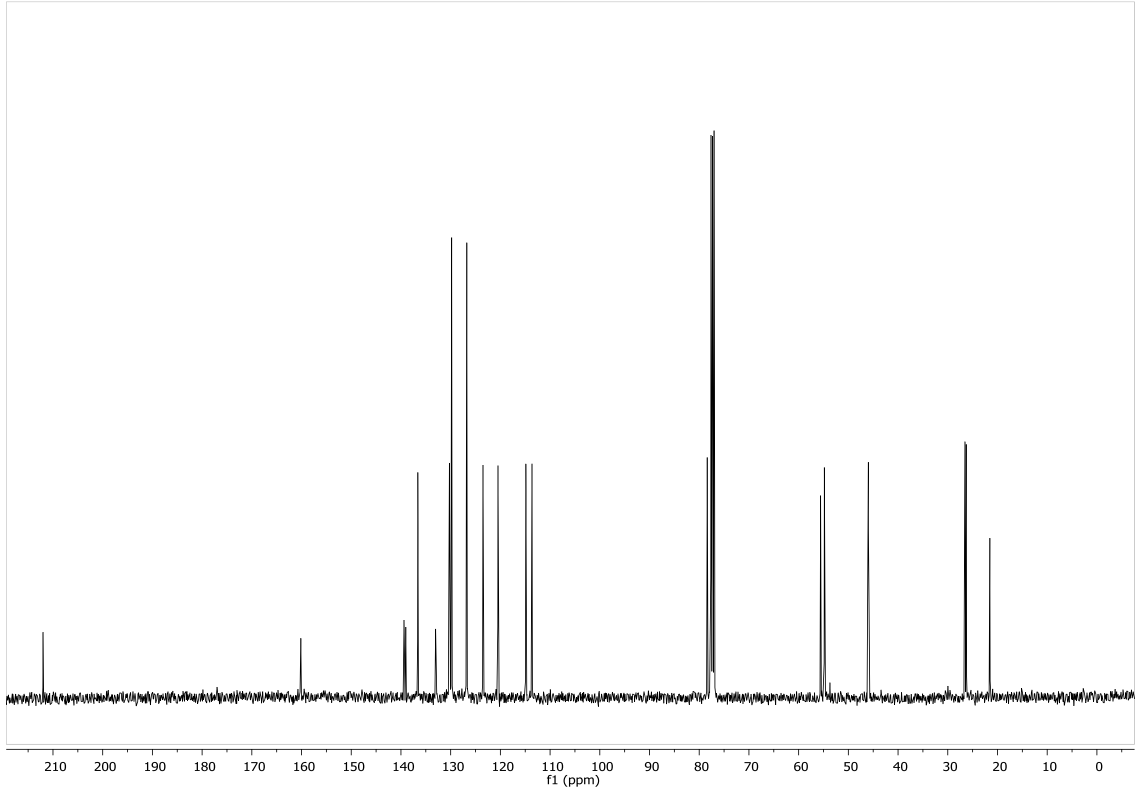

OMe
O
HO
NO2
Ph
17
5.28
1.89
1.97
1.02
1.00
2.11
2.09
3.32
3.20
3.41
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

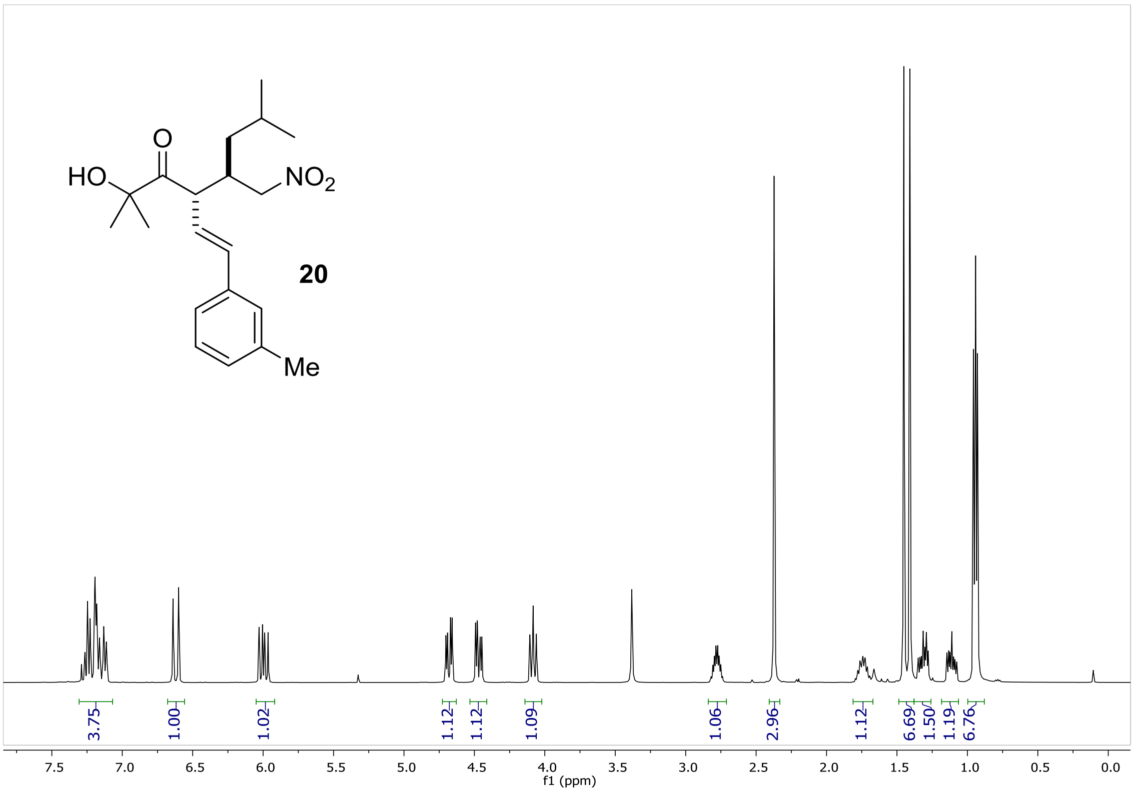

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

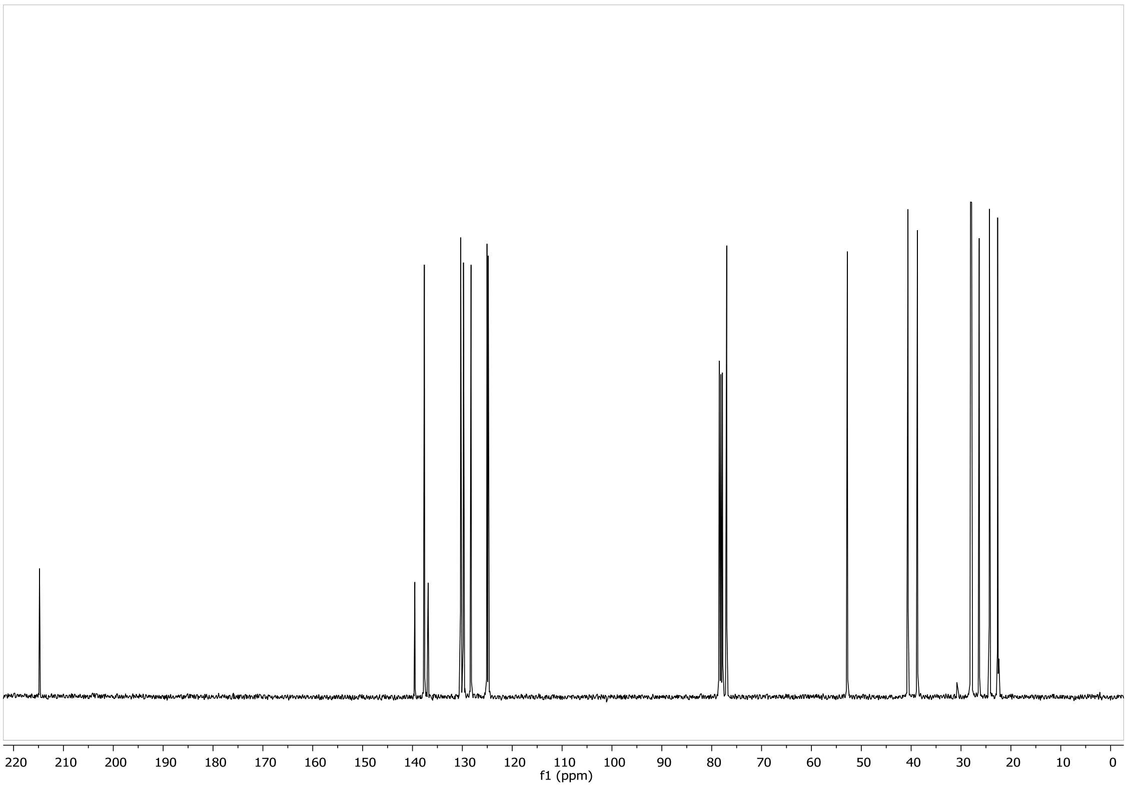

O
O
HO
NO$_2$
18
Cl
4.41
1.00
0.77
0.76
1.02
2.11
1.92
3.30
3.17
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

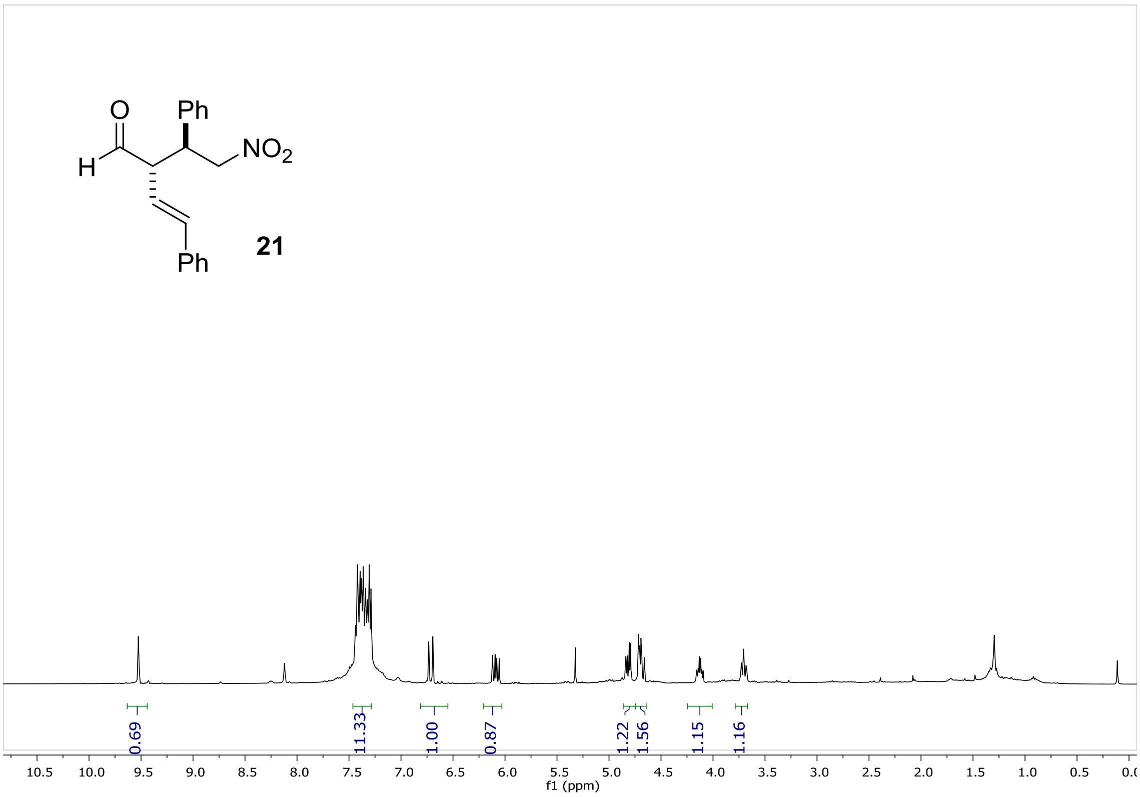

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

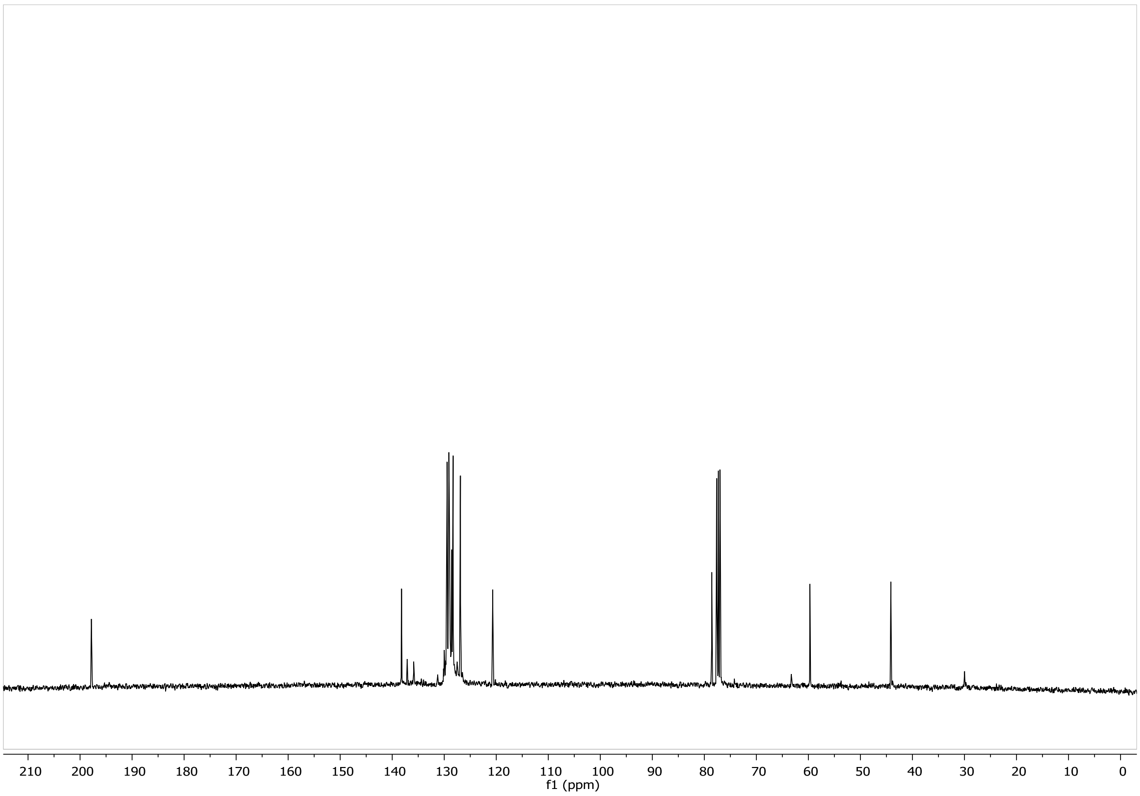

MeO
O
HO
NO2
19
Me
4.70
2.74
0.96
1.00
1.07
1.05
1.08
1.03
2.94
3.00
3.14
3.25
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

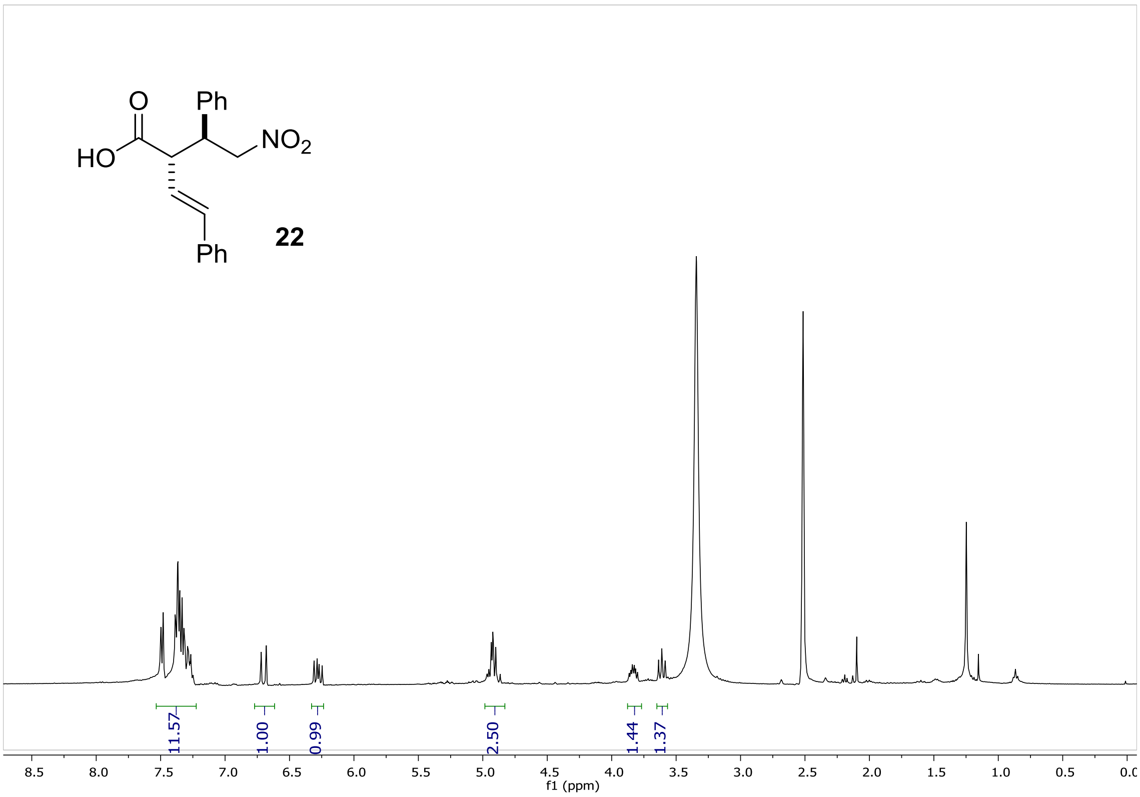

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

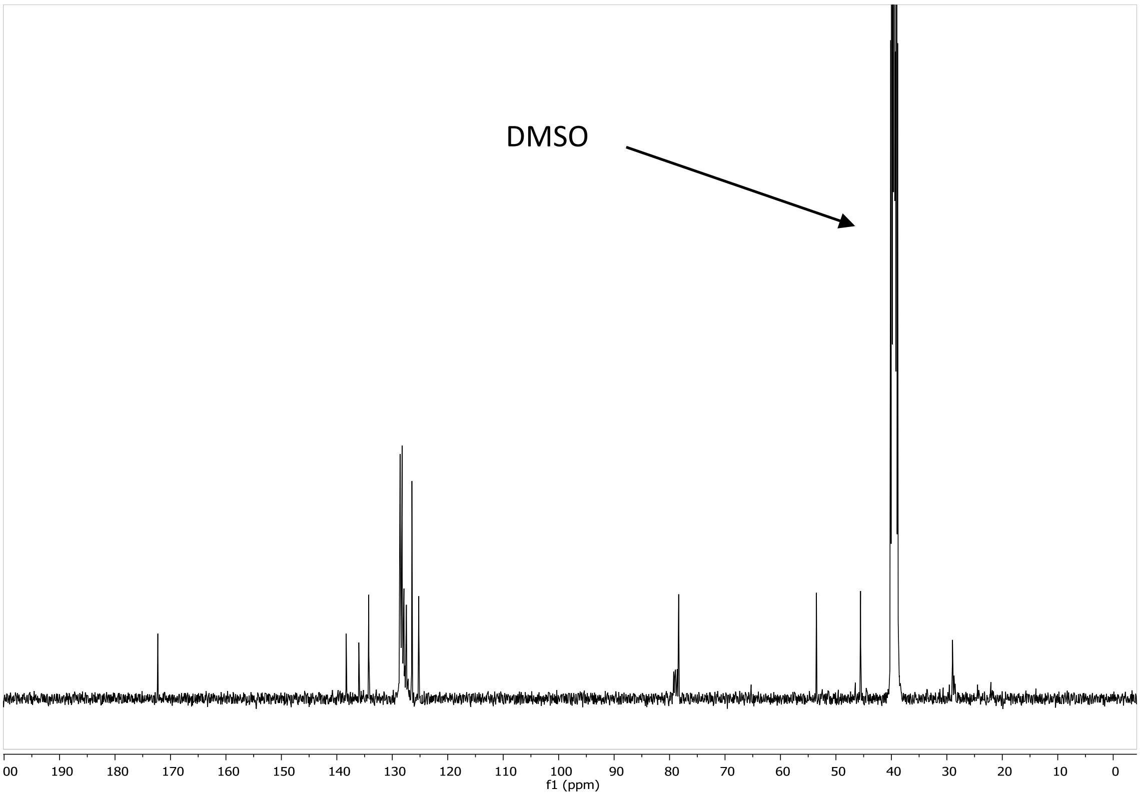

HO
O
NO2
Me
20
3.75
1.00
1.02
1.12
1.12
1.09
1.06
2.96
1.12
6.69
1.50
1.19
6.76
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

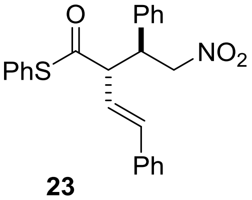

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


21
O
Ph
H
NO2
Ph
0.69
11.33
1.00
0.87
1.22
1.56
1.15
1.16
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

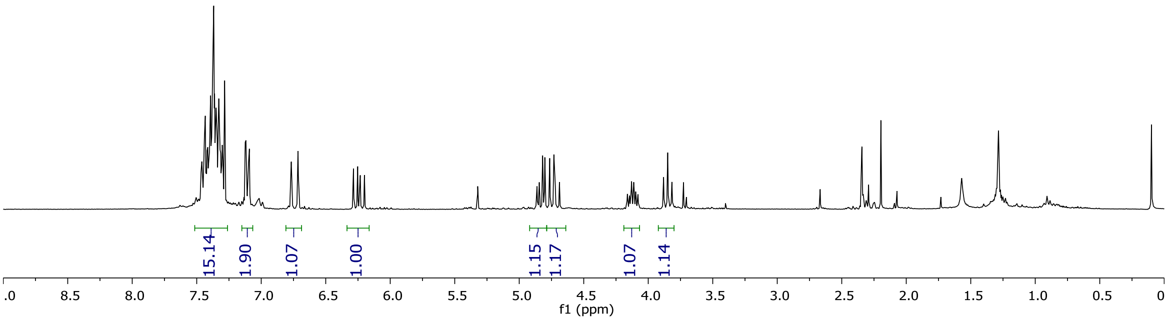

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

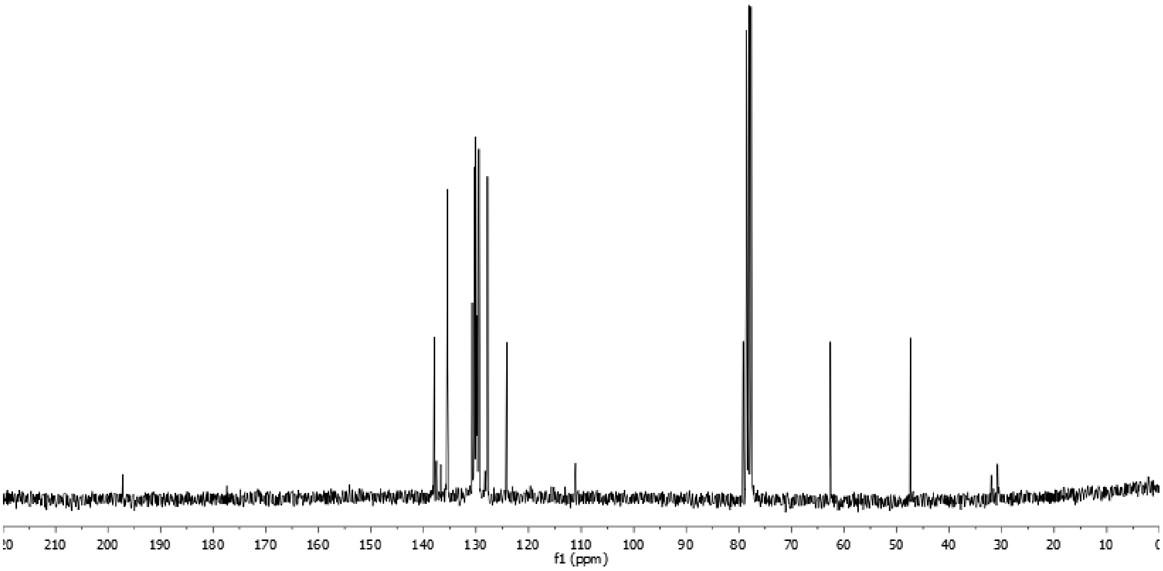

O
Ph
HO
NO2
Ph
22
11.57
1.00
0.99
2.50
1.44
1.37
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

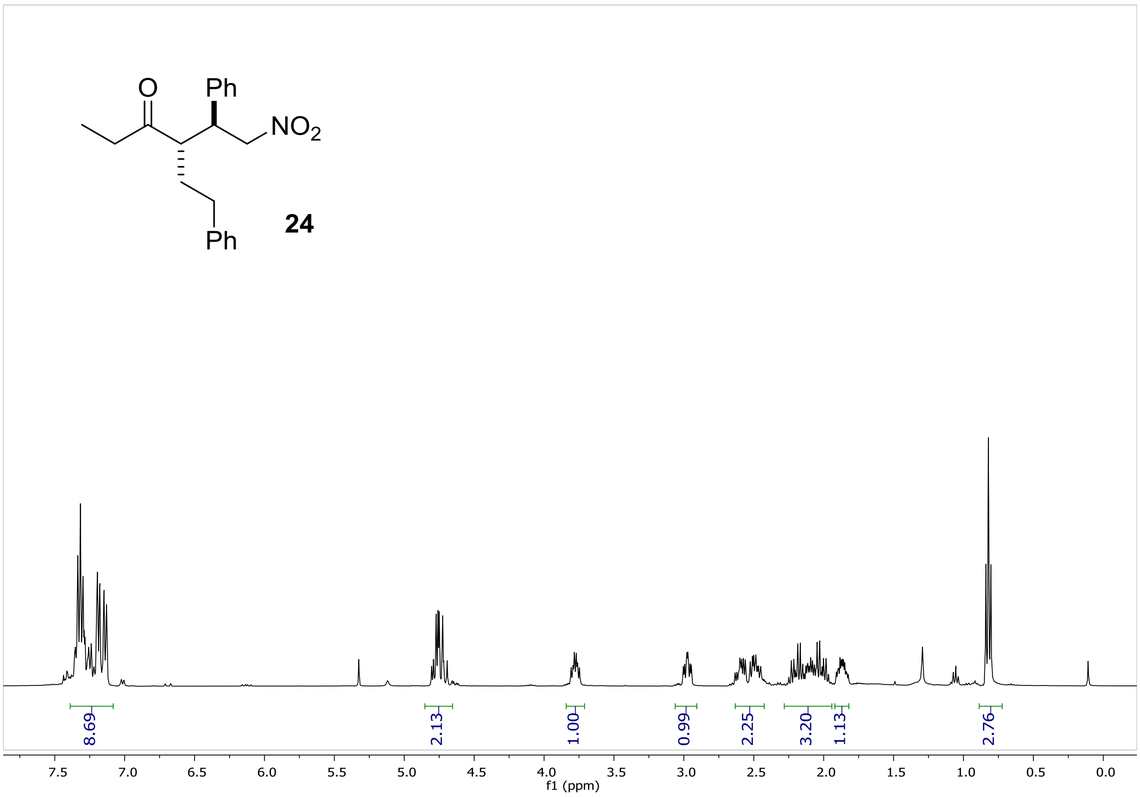

DMSO
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

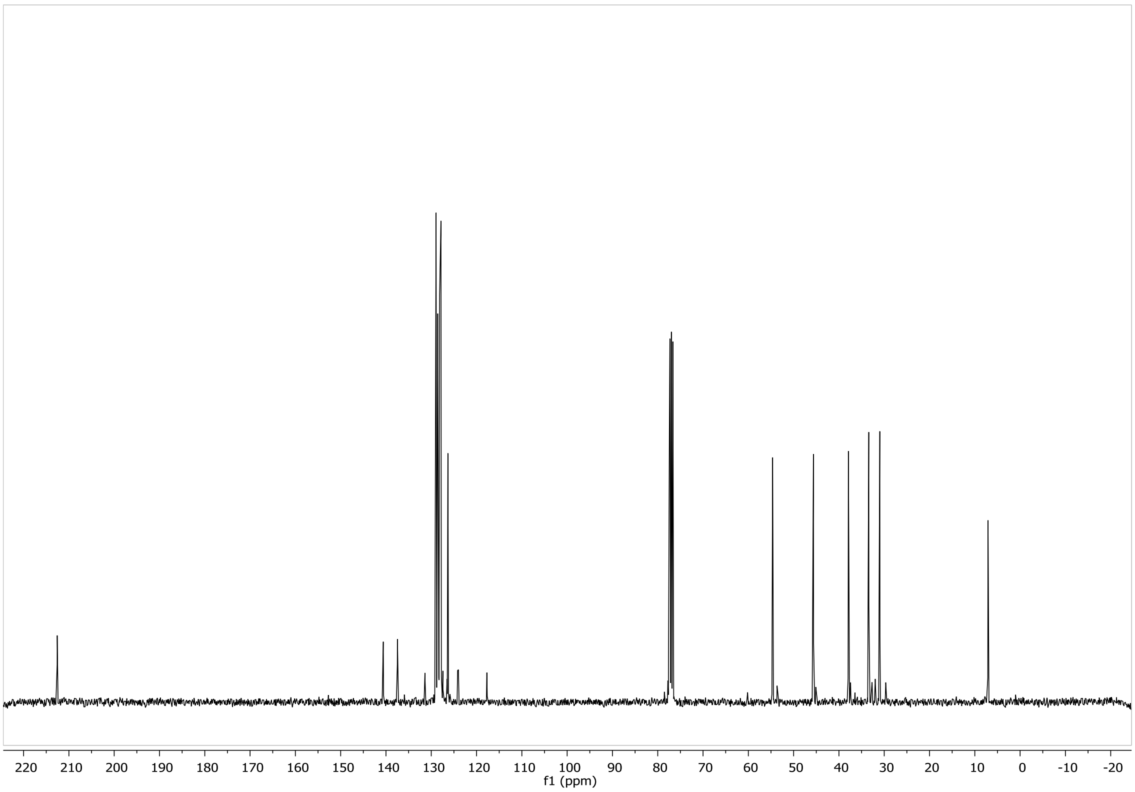

O
Ph
NO$_2$
PhS
Ph

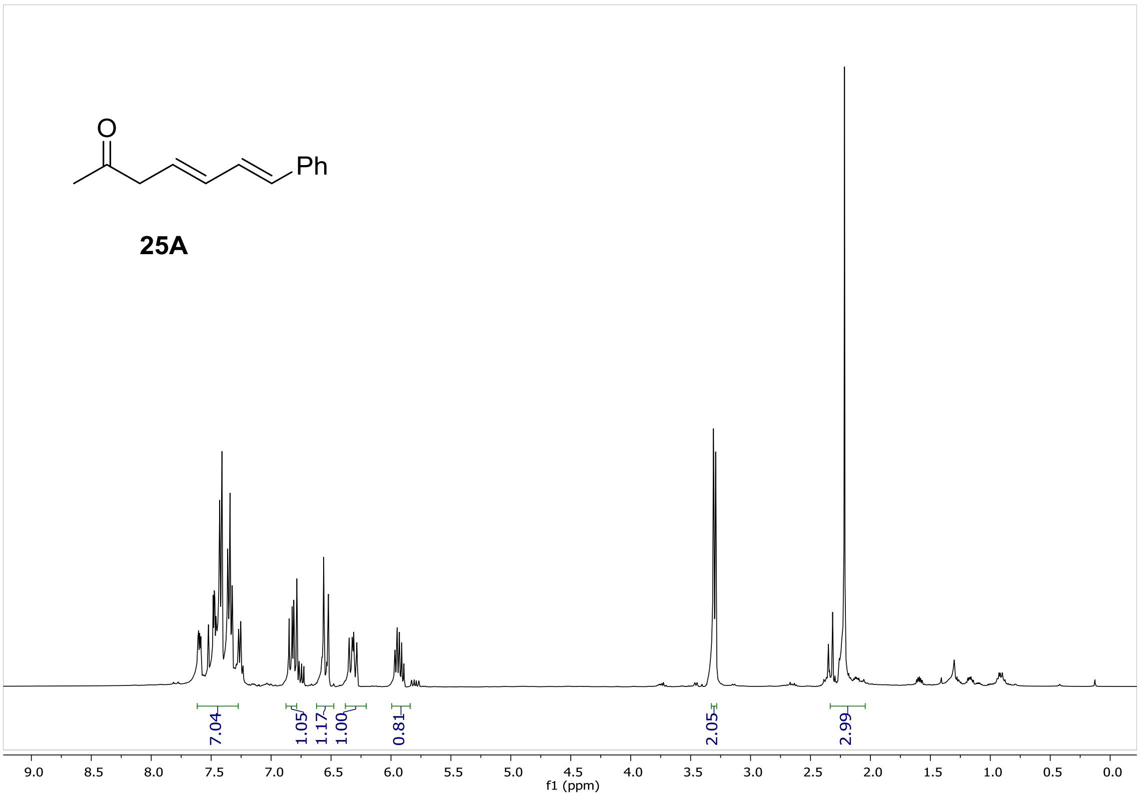
23

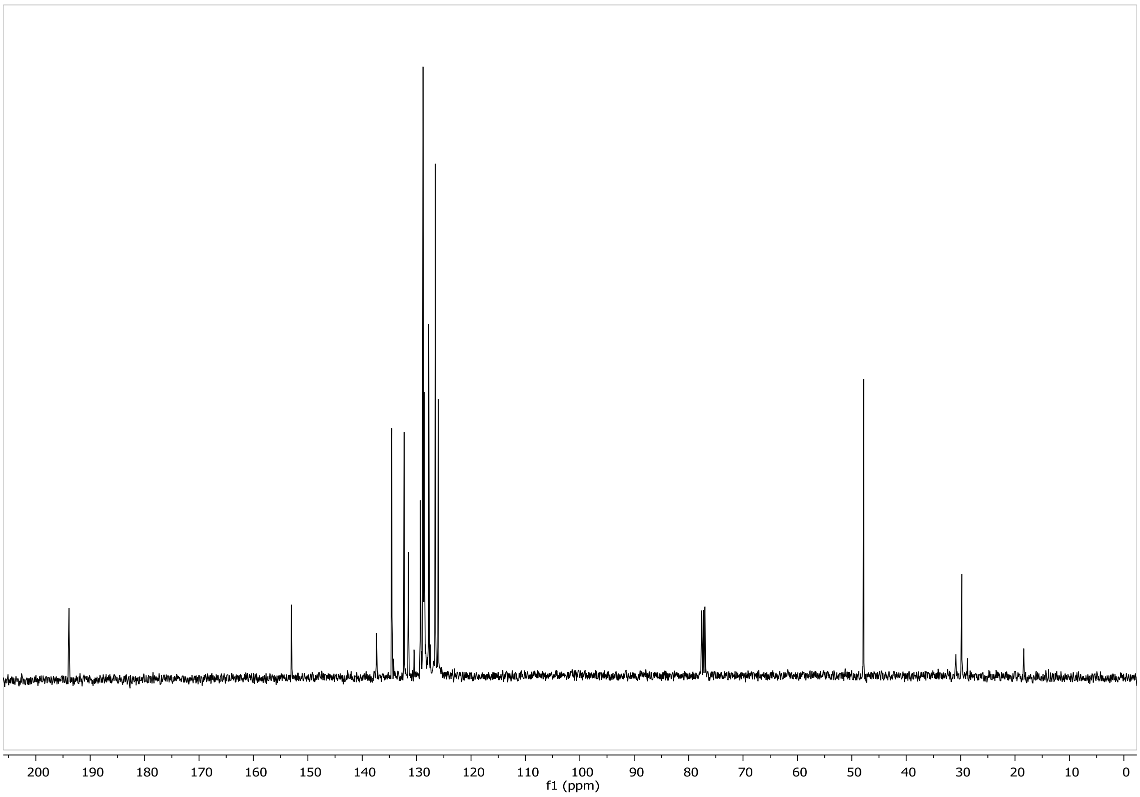

15.14
1.90
1.07
1.00
1.15
1.17
1.07
1.14
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

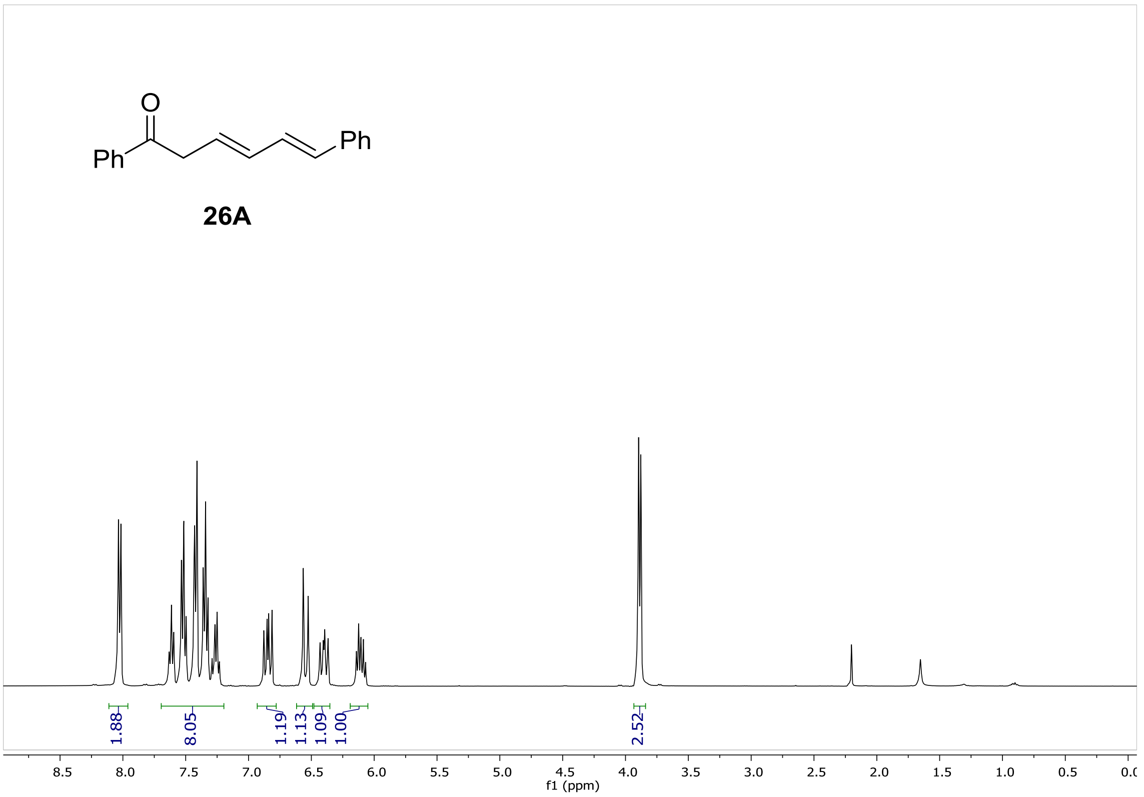

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Ph
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)

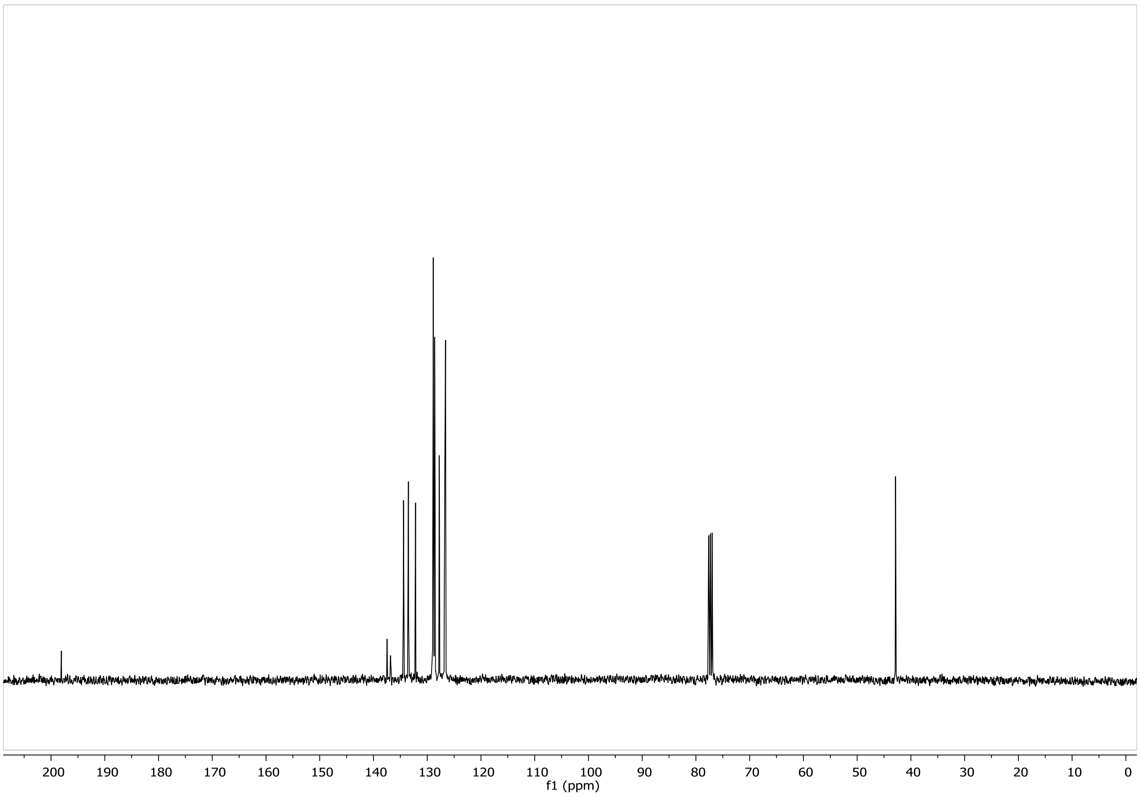

O
Ph
25A
7.04
1.05
1.17
1.00
0.81
2.05
2.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

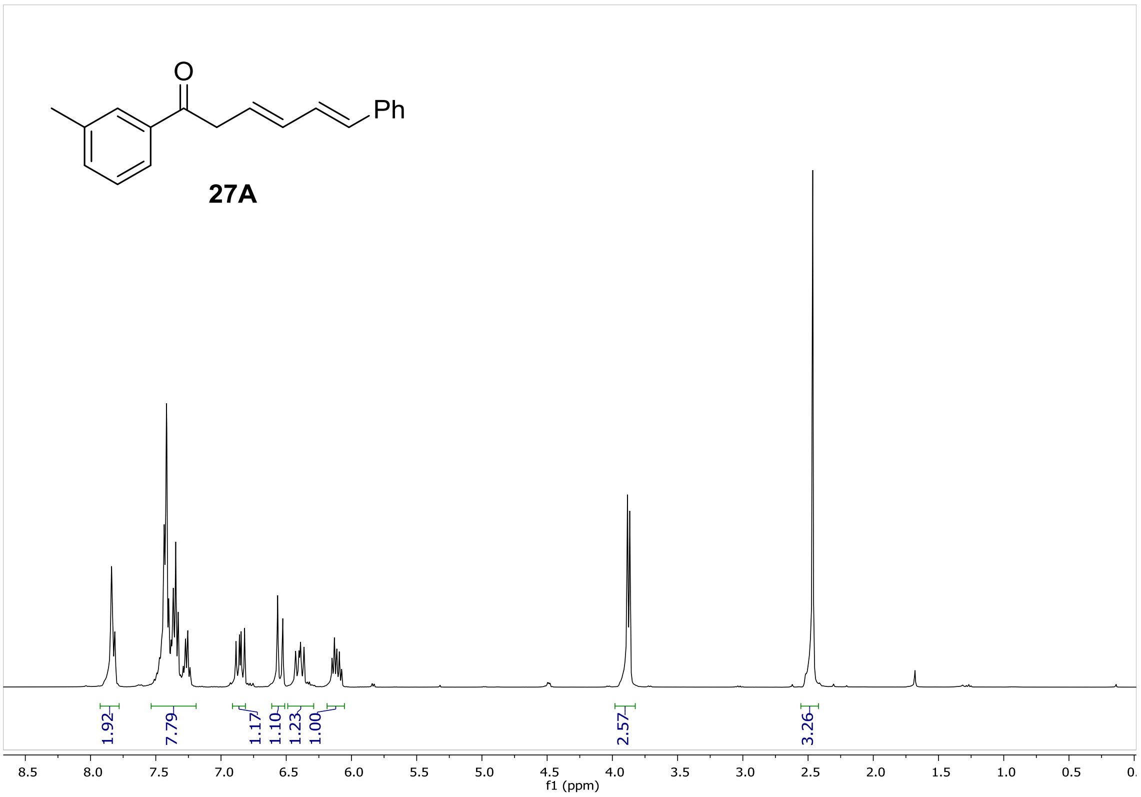


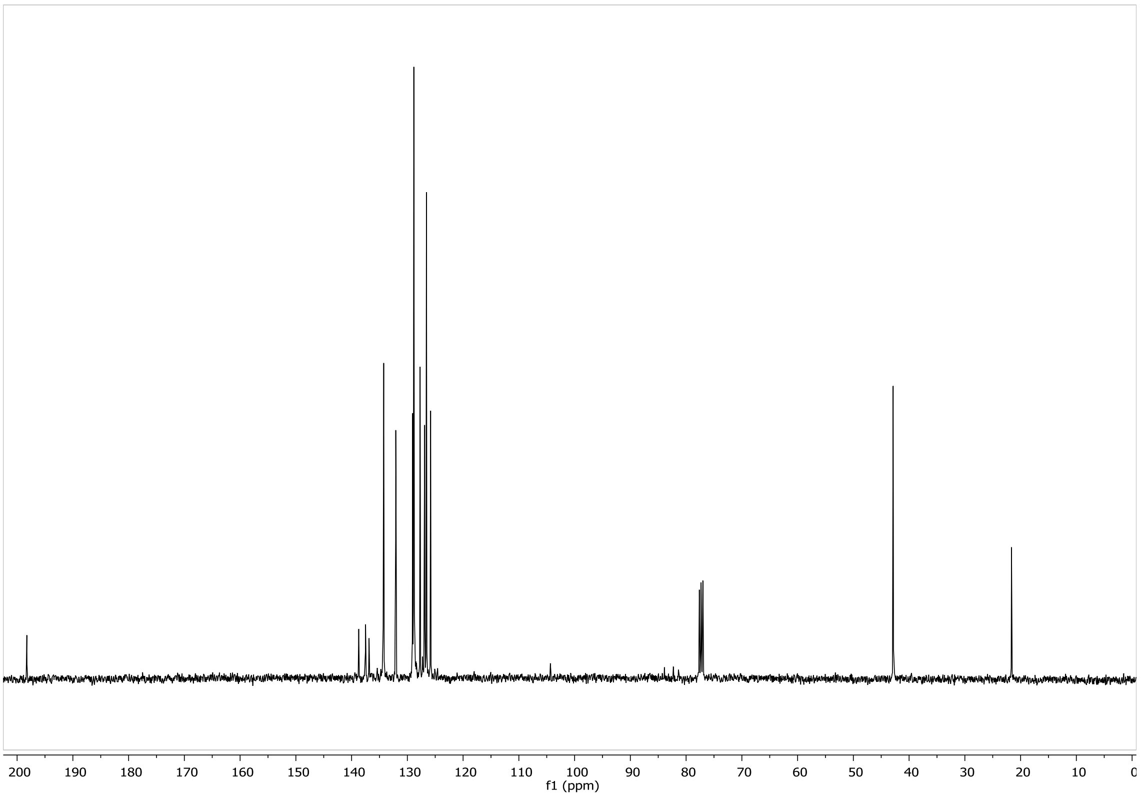
26A

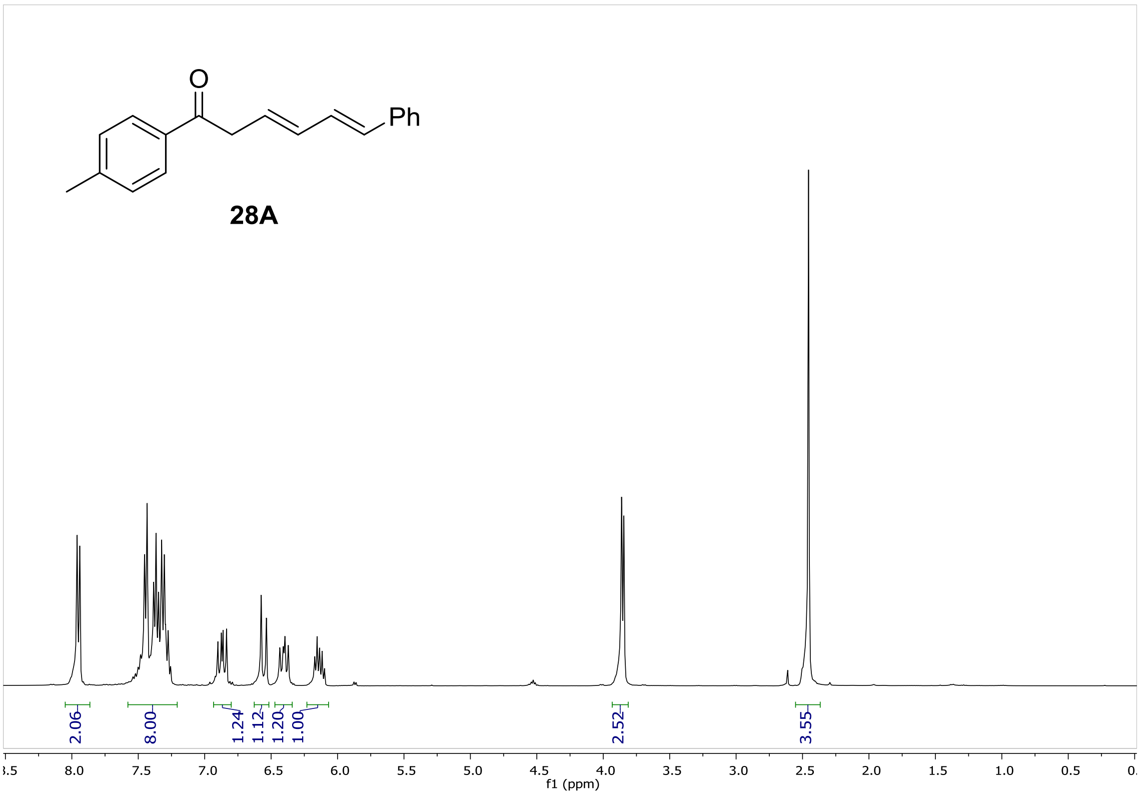
O
Ph
Ph
1.88
8.05
1.19
1.13
1.09
1.00
2.52
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

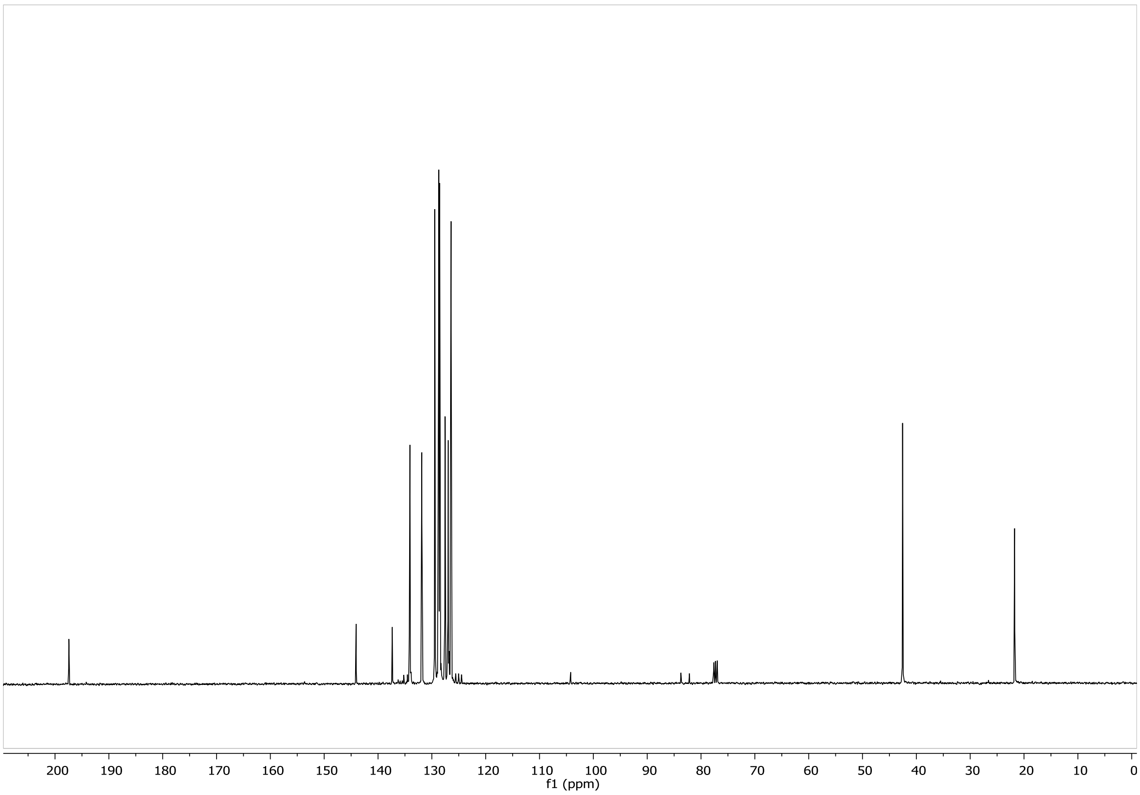


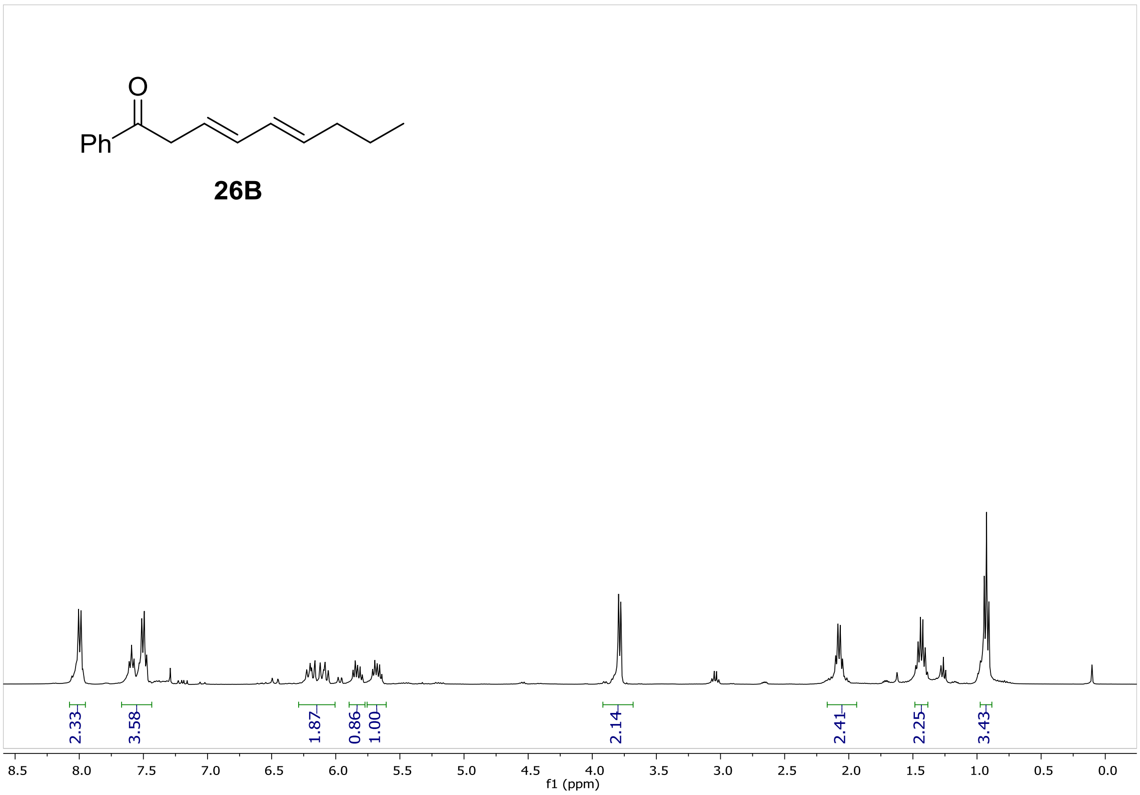
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Ph
27A
1.92
7.79
1.17
1.10
1.23
1.00
2.57
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.
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)

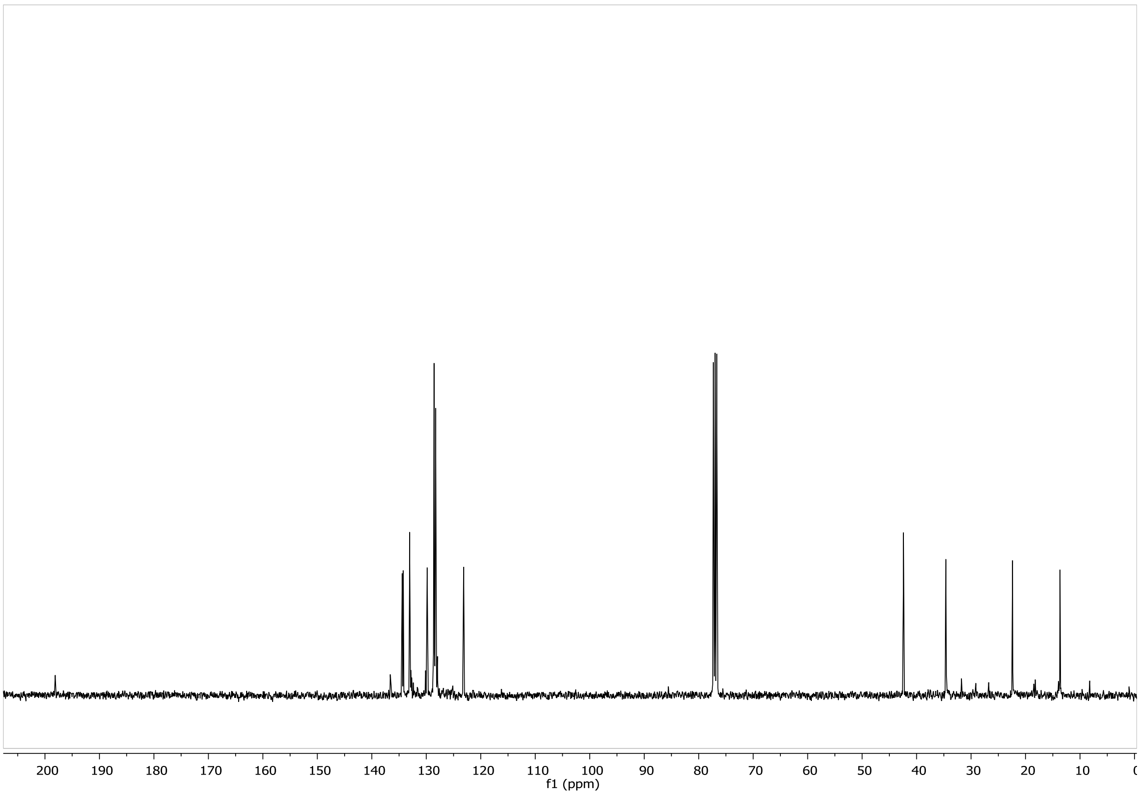

O
Ph
28A
2.06
8.00
1.24
1.12
1.20
1.00
2.52
3.55
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

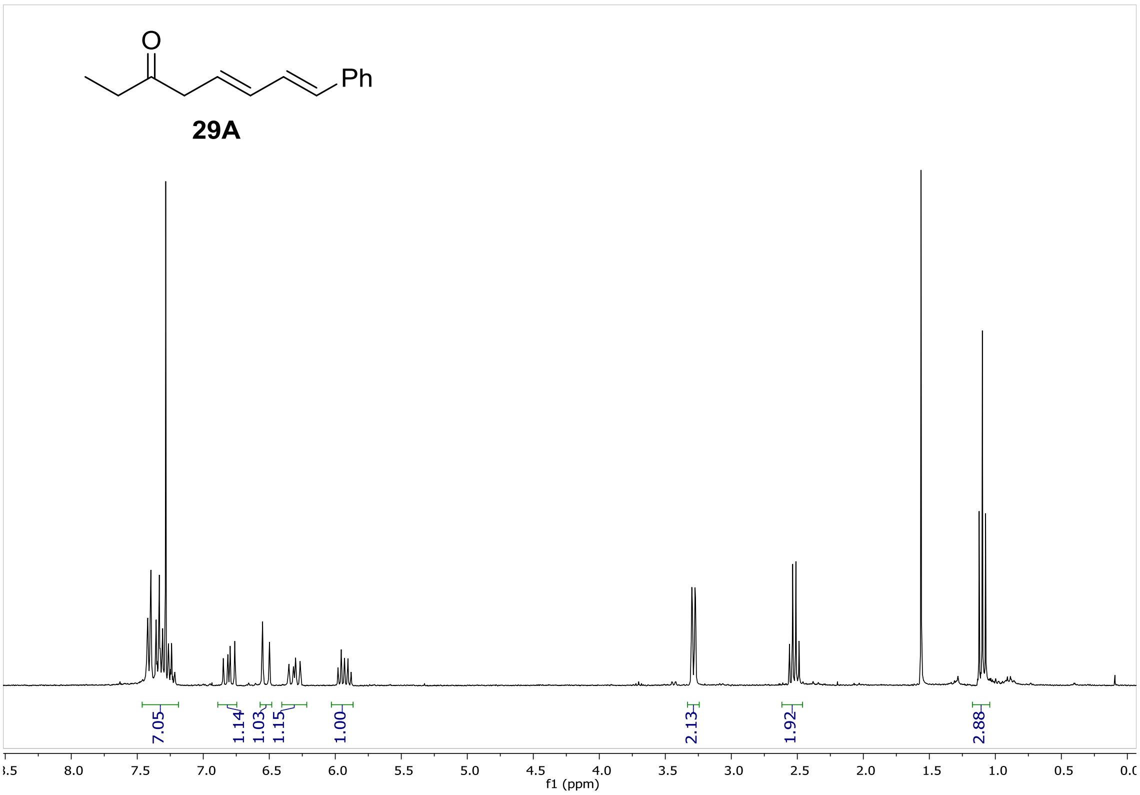


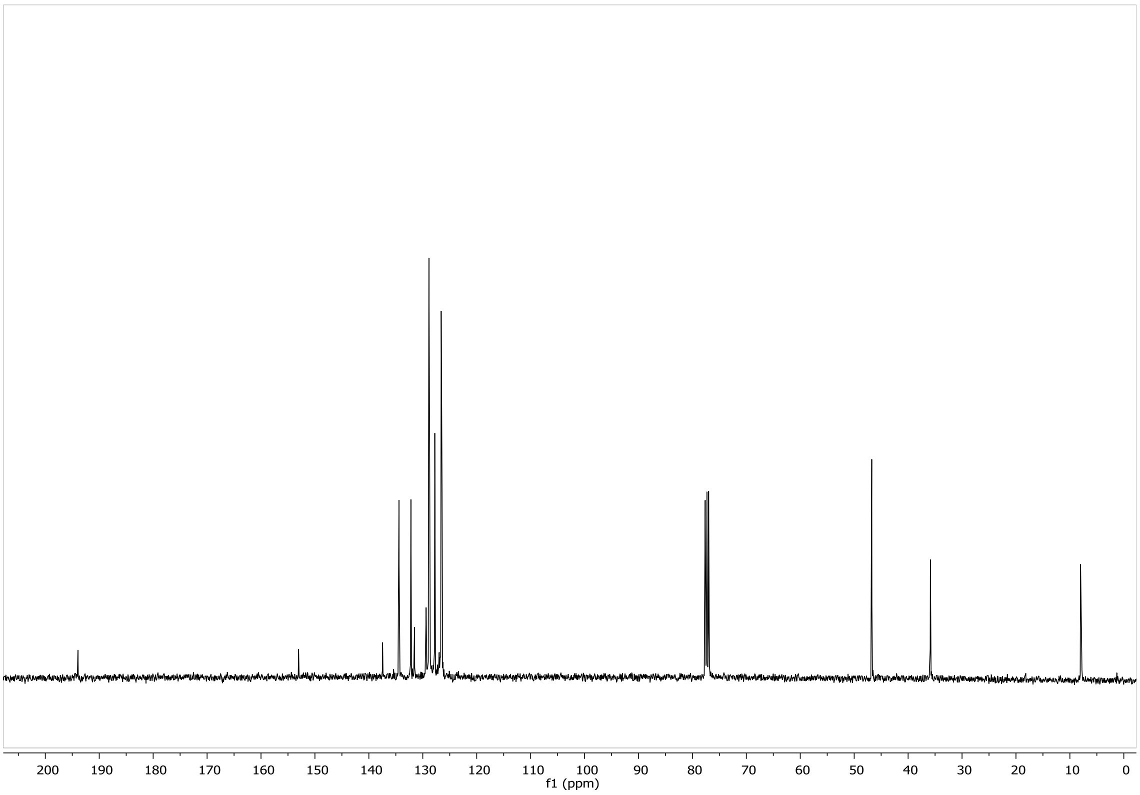
26B

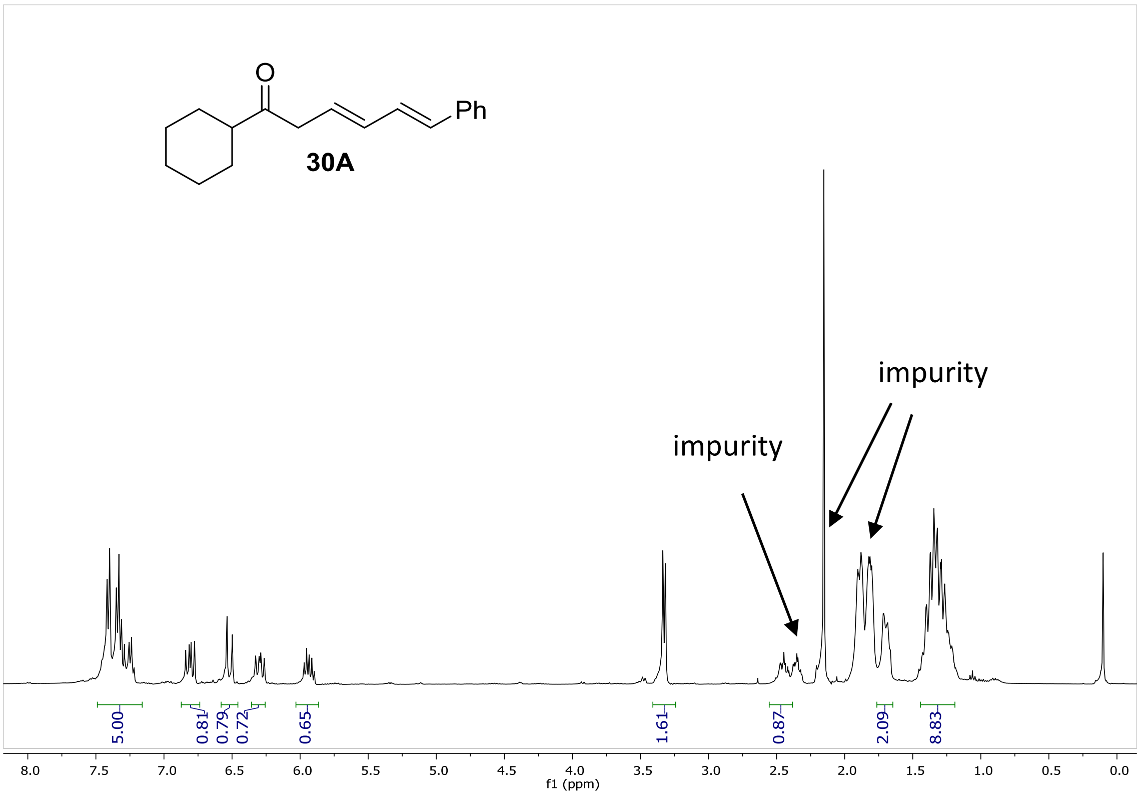
O
Ph
2.33
3.58
1.87
0.86
1.00
2.14
2.41
2.25
3.43
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

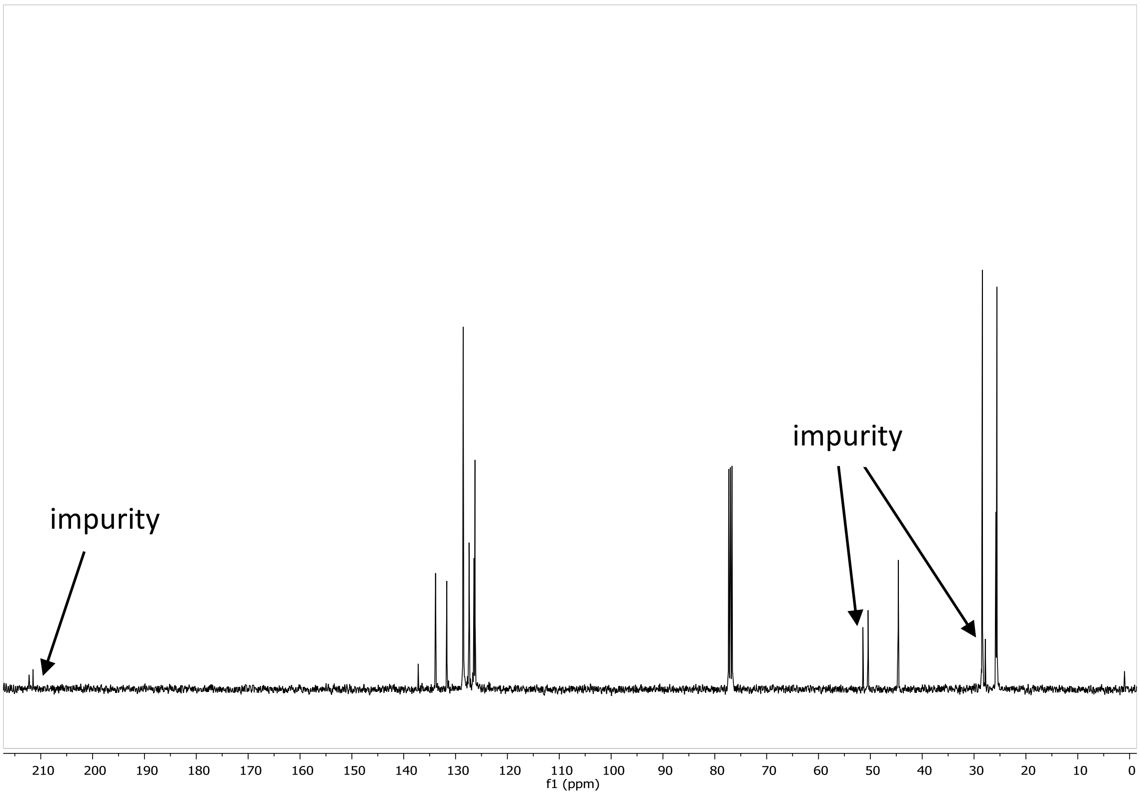


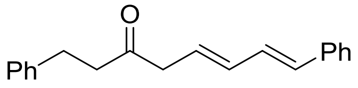
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
Ph
29A
7.05
1.14
1.03
1.15
1.00
2.13
1.92
2.88
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)

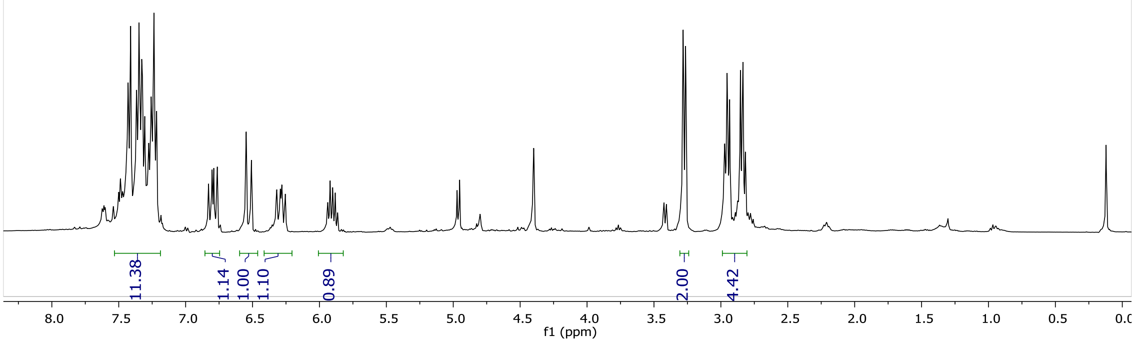

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

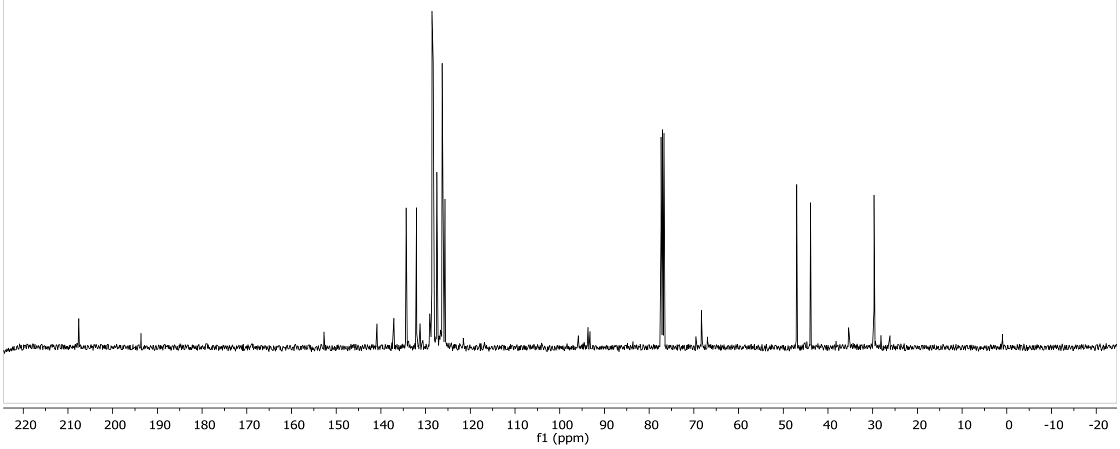

O
Ph
30A
impurity
impurity
5.00
0.81
0.79
0.72
0.65
1.61
0.87
2.09
8.83
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

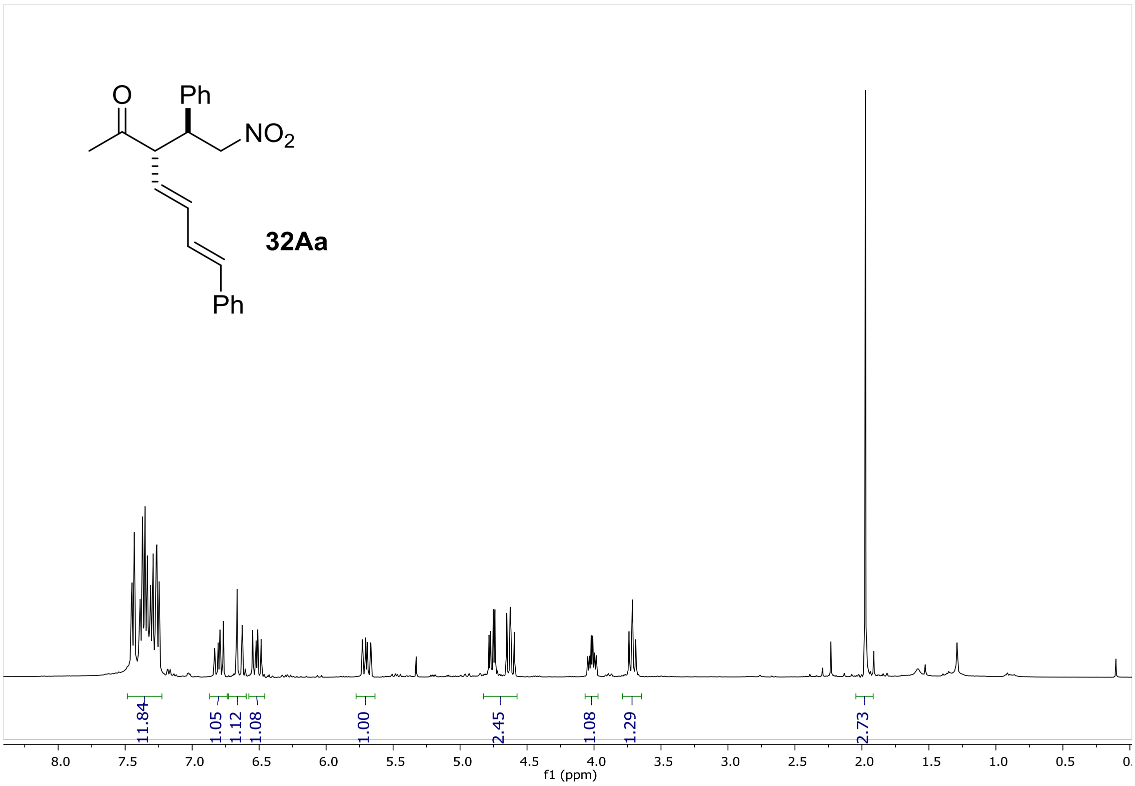

impurity
impurity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

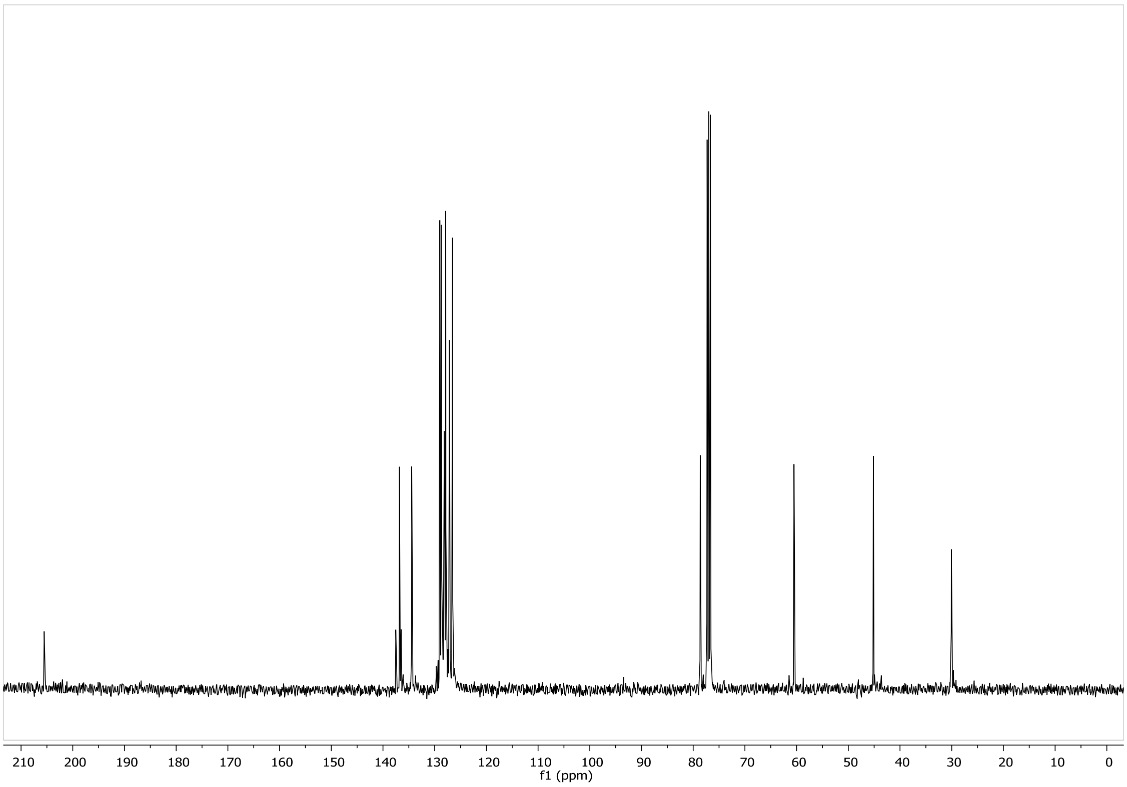

O
Ph
Ph

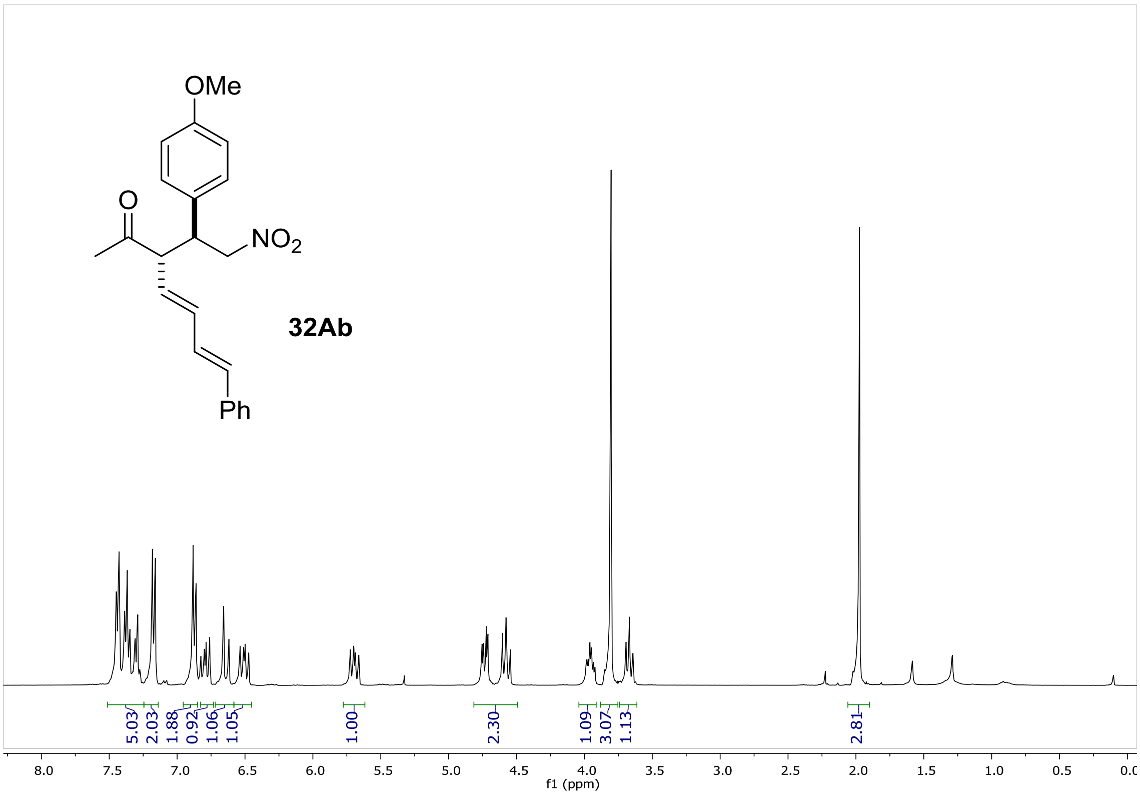
31A

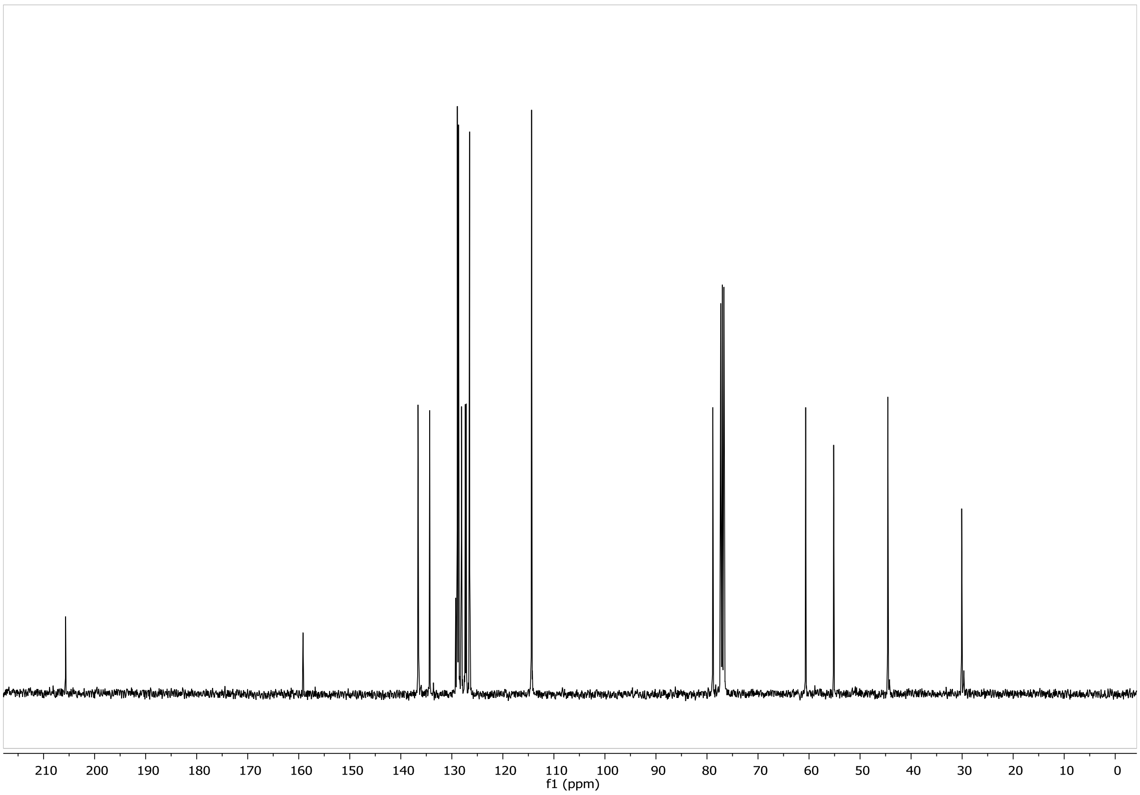

11.38
1.14
1.00
1.10
0.89
2.00
4.42
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

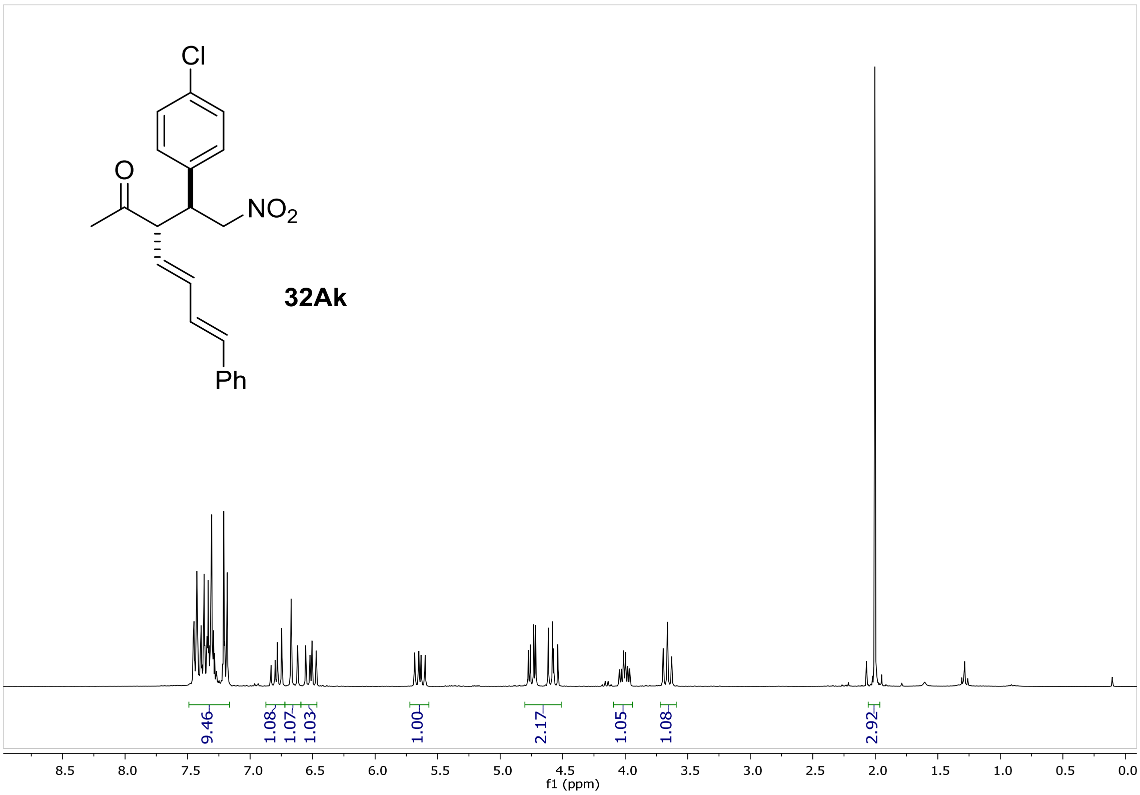

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


O
Ph
NO2
32Aa
Ph
11.84
1.05
1.12
1.08
1.00
2.45
1.08
1.29
2.73
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)


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

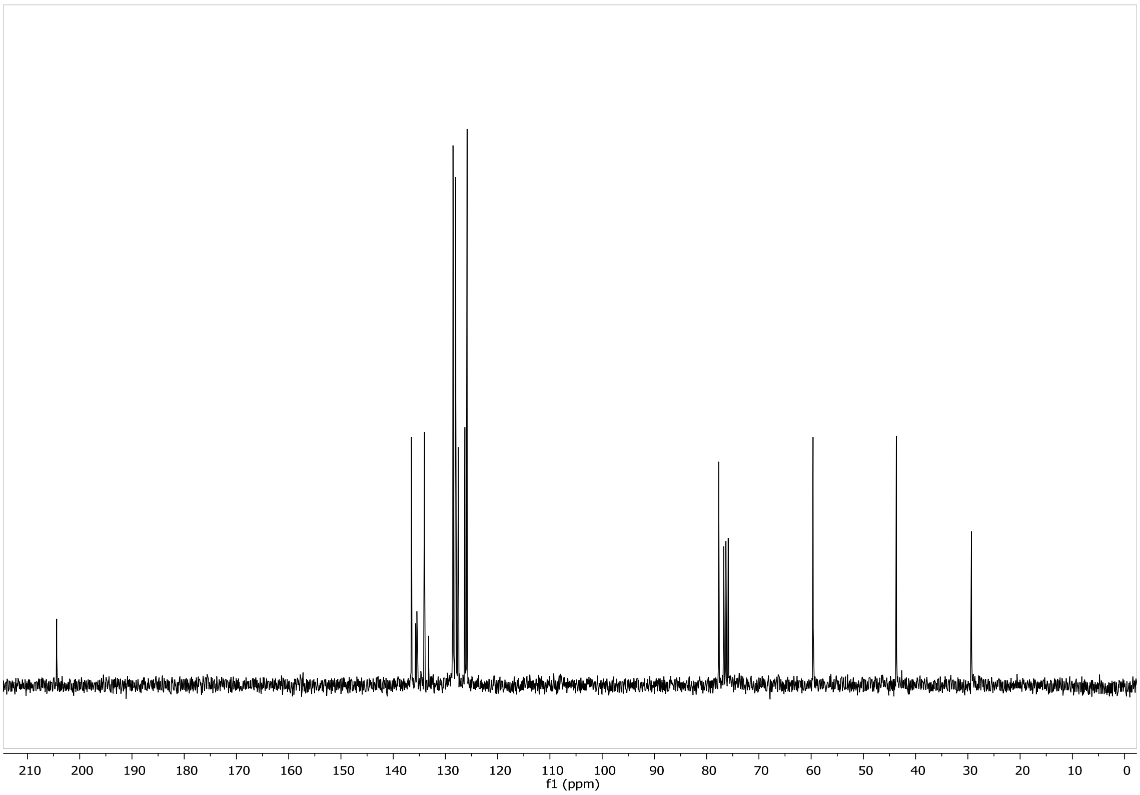

OMe
O
NO2
Ph
32Ab
5.03
2.03
1.88
0.92
1.06
1.05
1.00
2.30
1.09
3.07
1.13
2.81
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

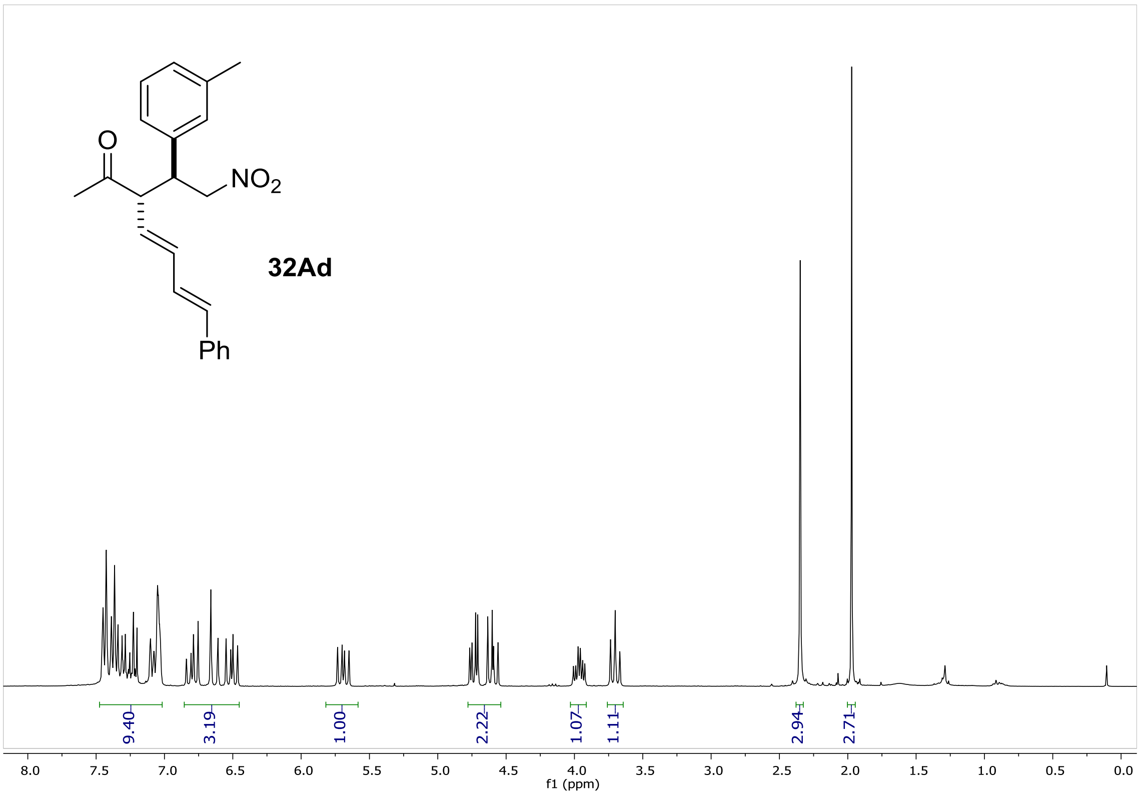


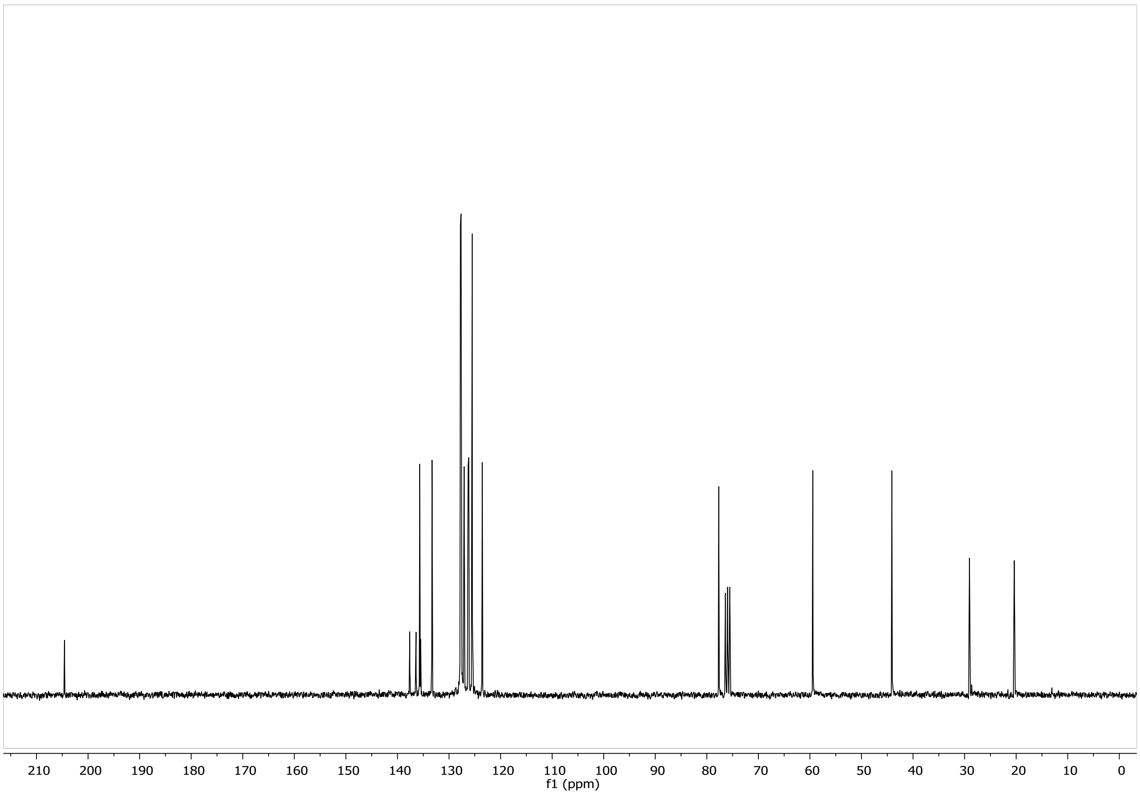
32Ak

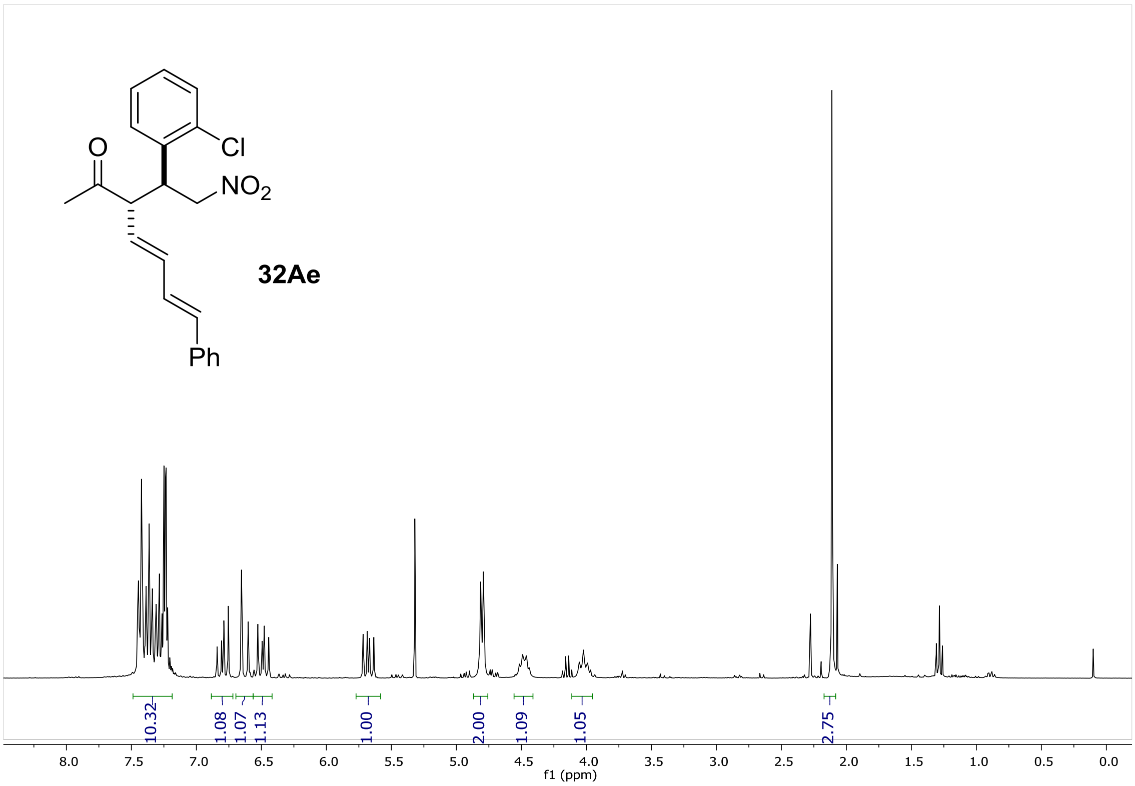
Cl
O
NO2
Ph
9.46
1.08
1.07
1.03
1.00
2.17
1.05
1.08
2.92
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

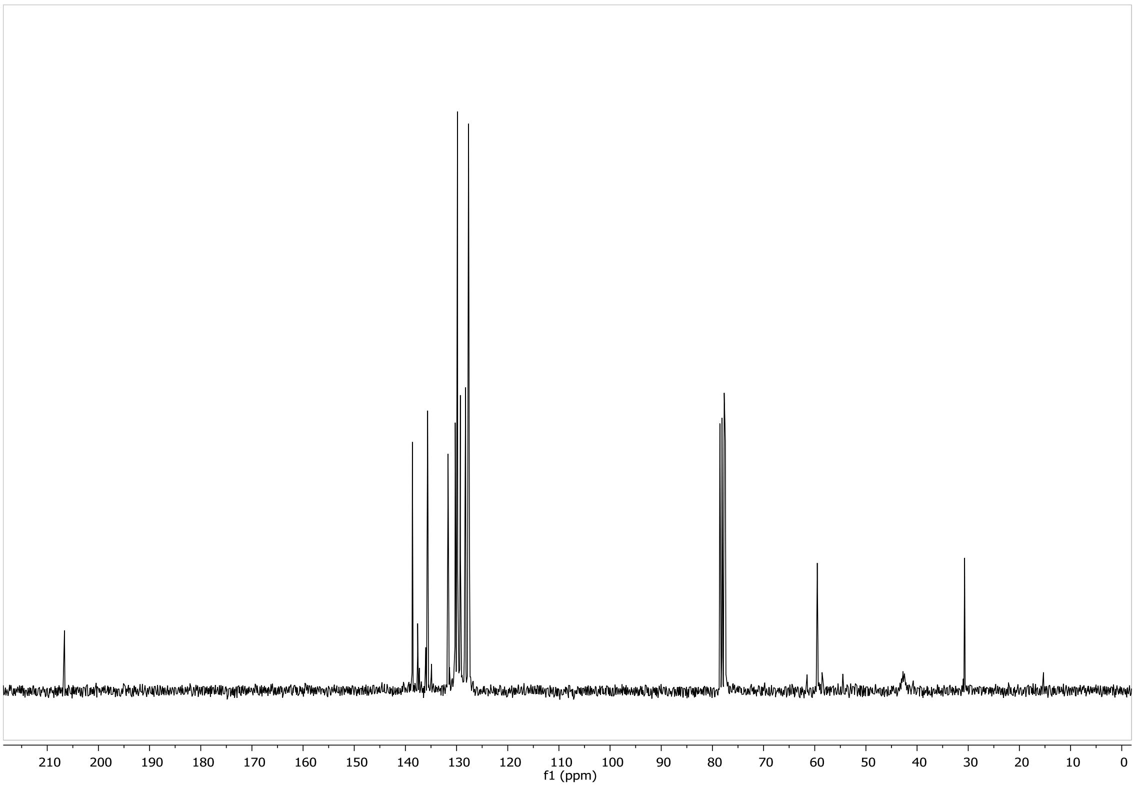


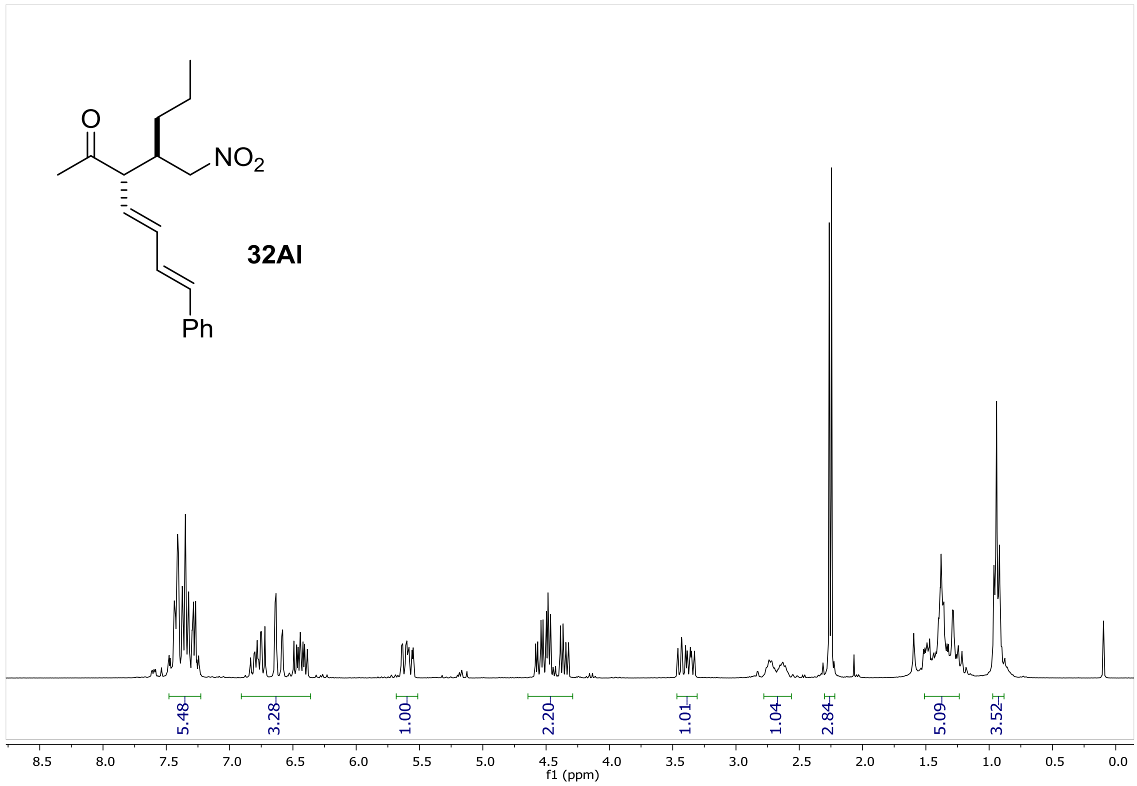
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

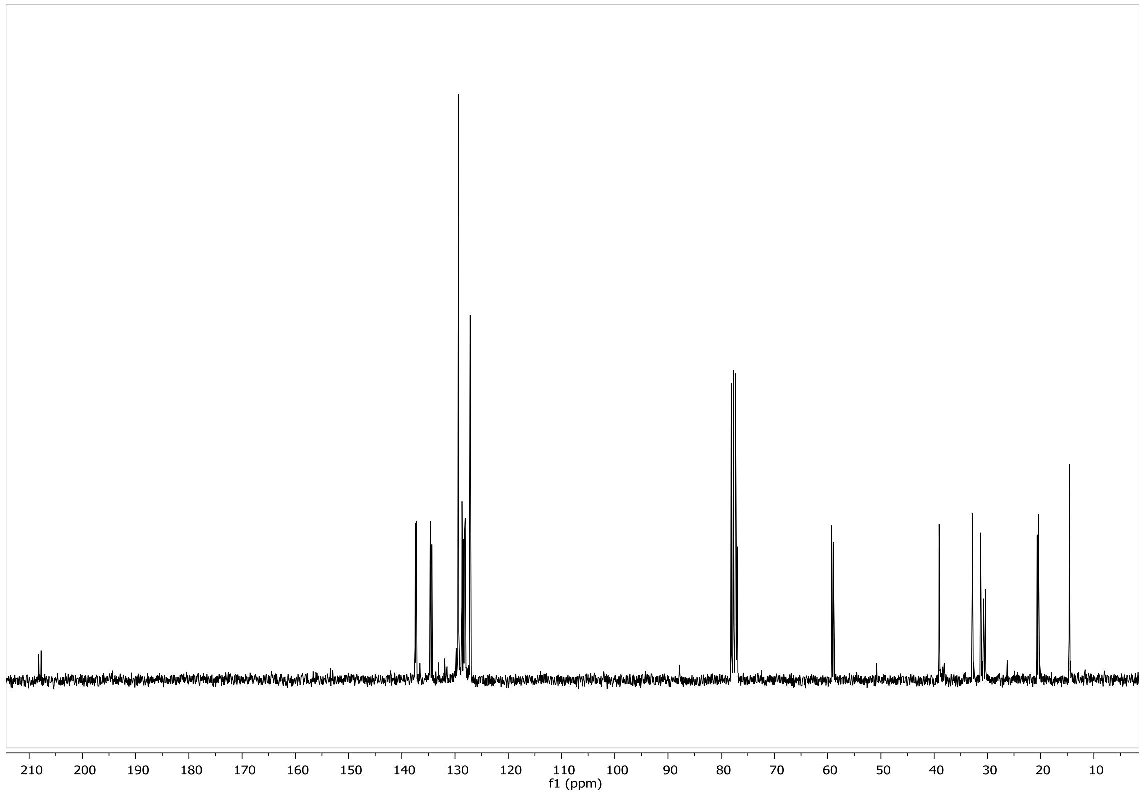

O
NO2
32Ad
Ph
9.40
3.19
1.00
2.22
1.07
1.11
2.94
2.71
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

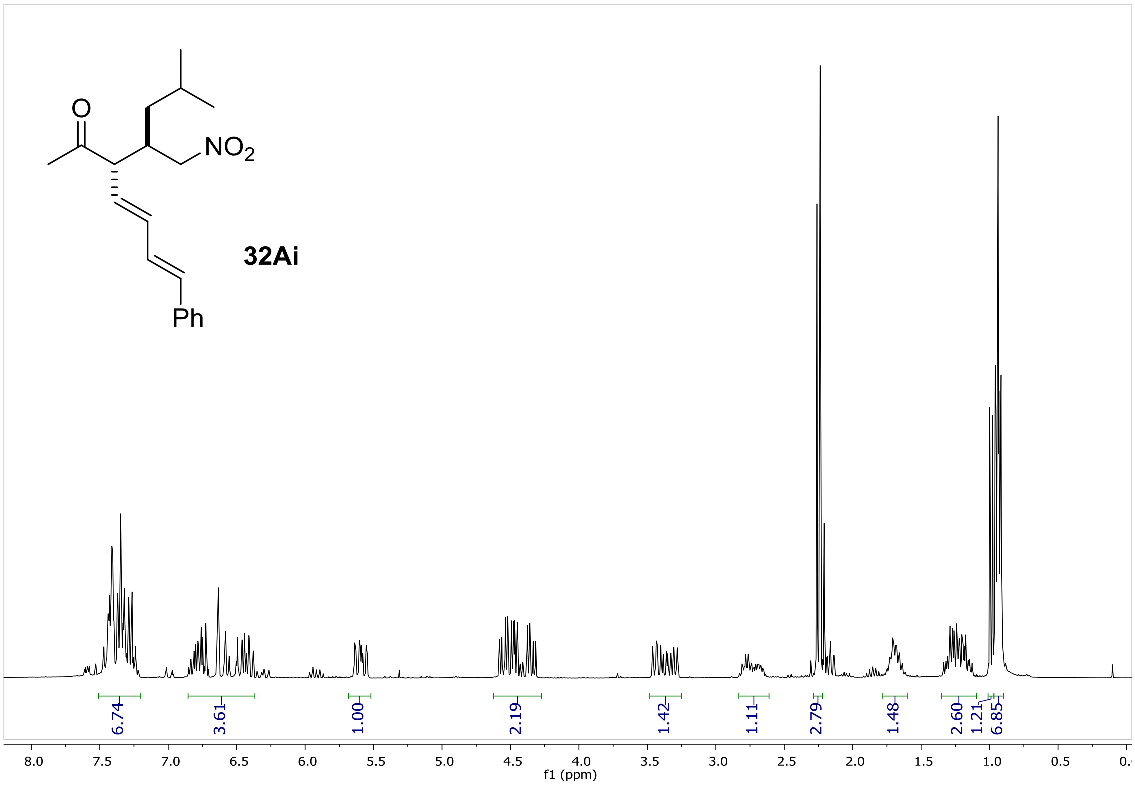

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

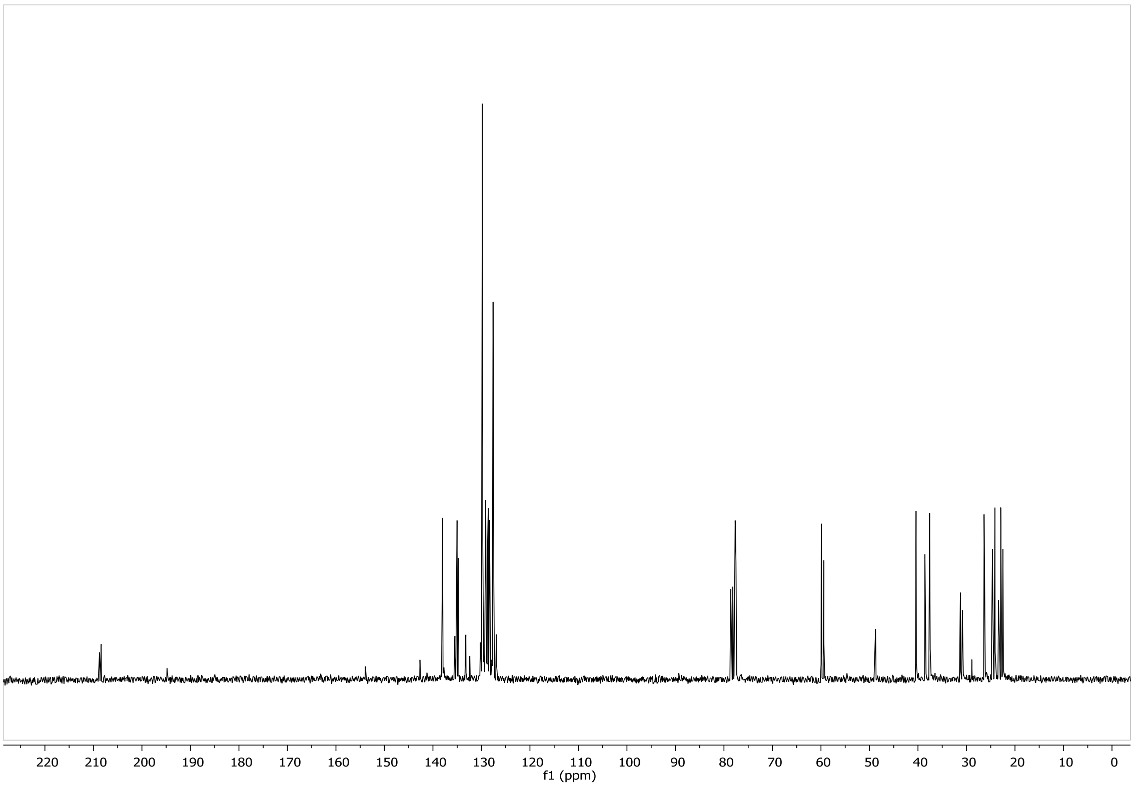

O
Cl
NO2
32Ae
Ph
10.32
1.08
1.07
1.13
1.00
2.00
1.09
1.05
2.75
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

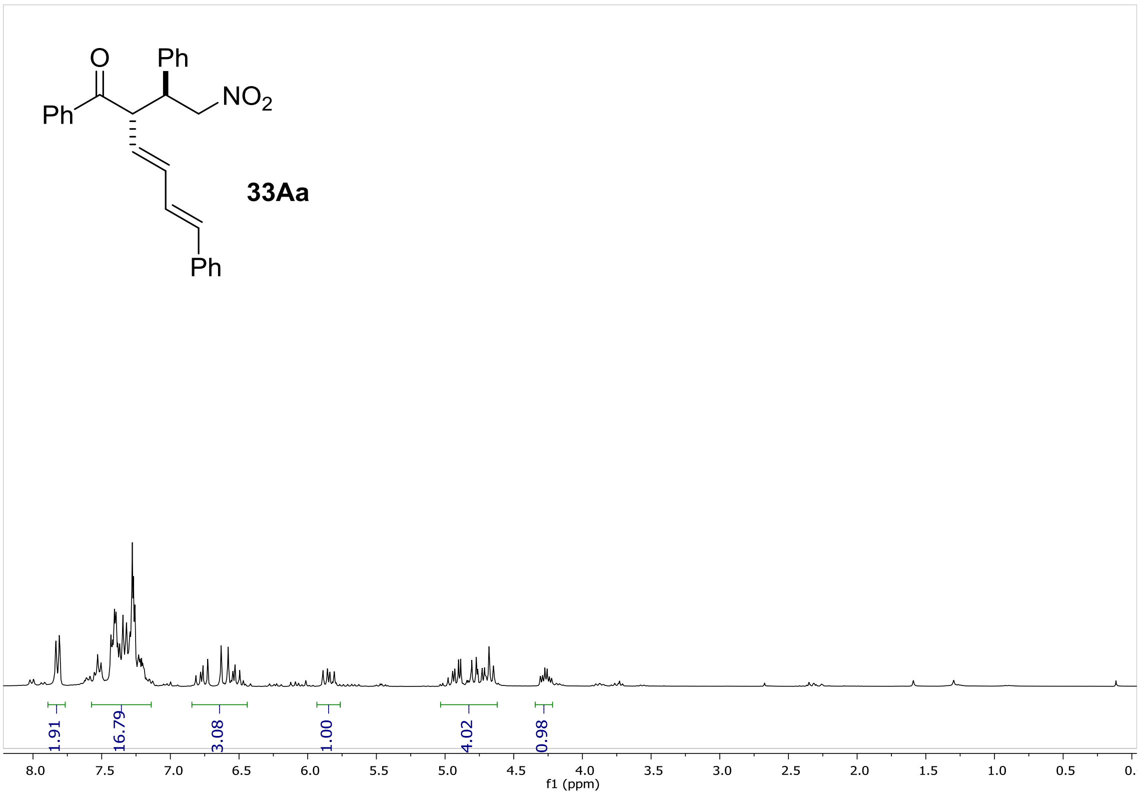

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

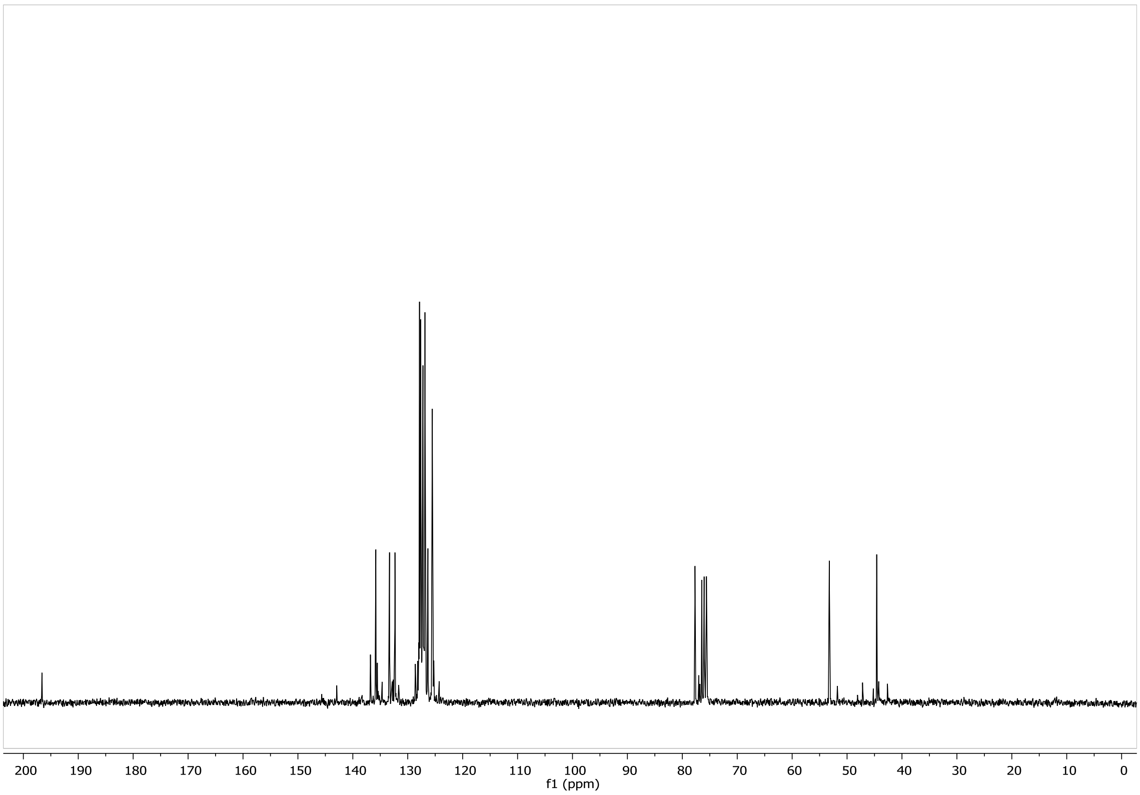

O
NO2
32Al
Ph
5.48
3.28
1.00
2.20
1.01
1.04
2.84
5.09
3.52
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

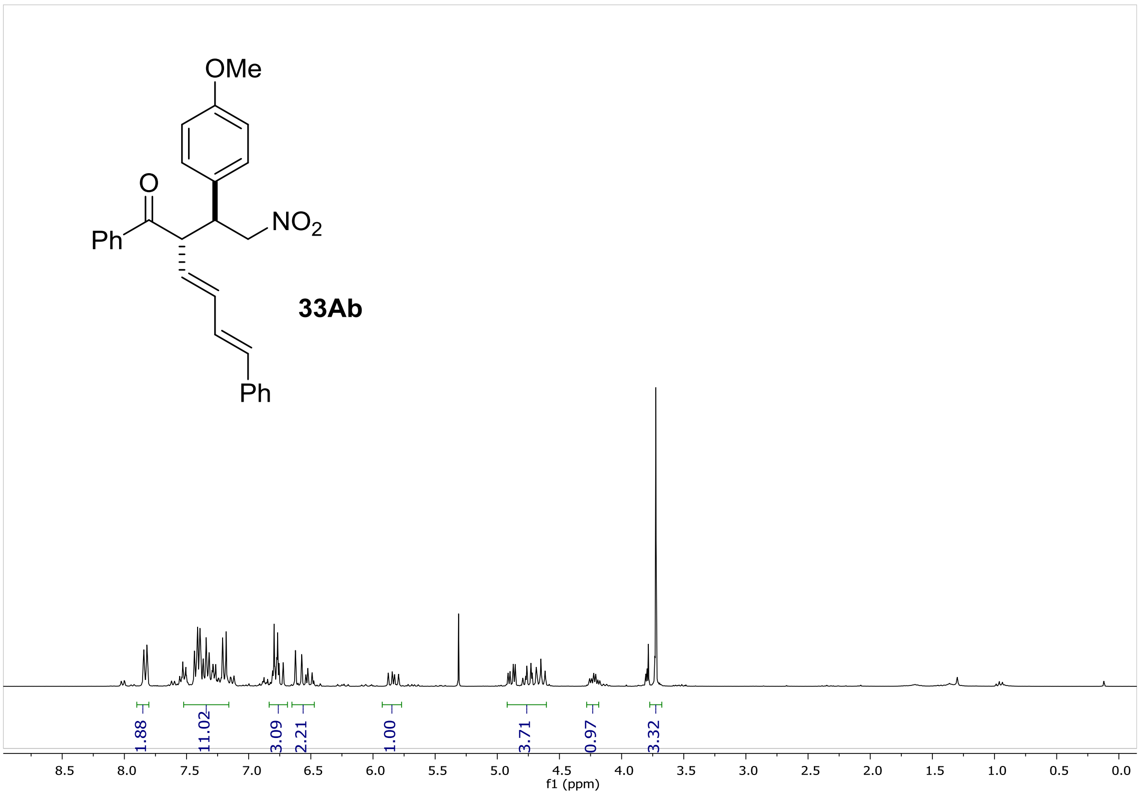

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

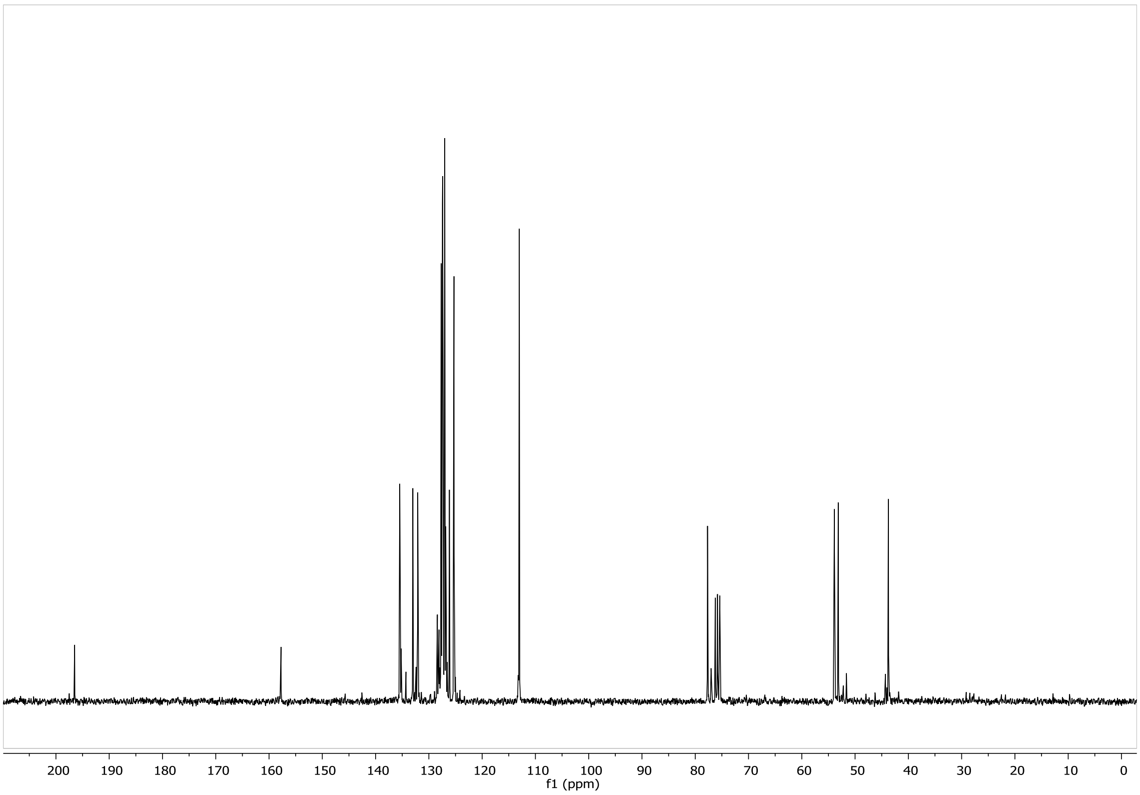

O
NO2
32Ai
Ph
6.74
3.61
1.00
2.19
1.42
1.11
2.79
1.48
2.60
1.21
6.85
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

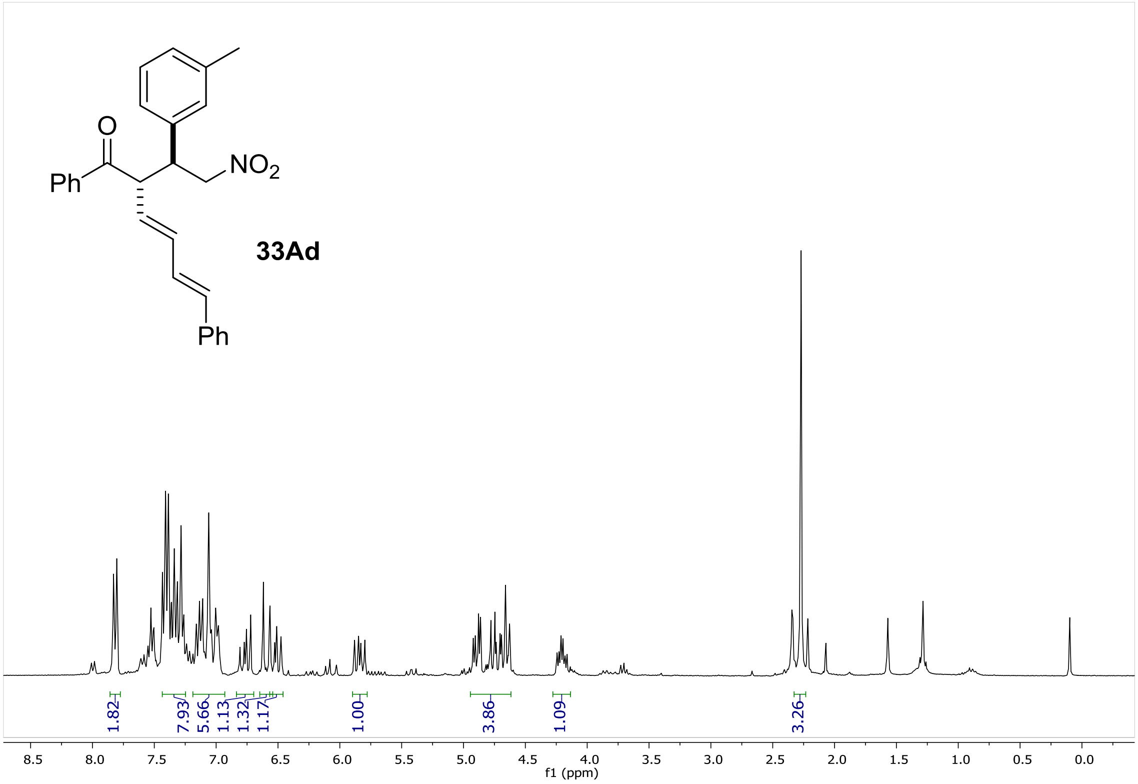

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Ph
Ph
NO2
Ph
33Aa
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
0.
f1 (ppm)

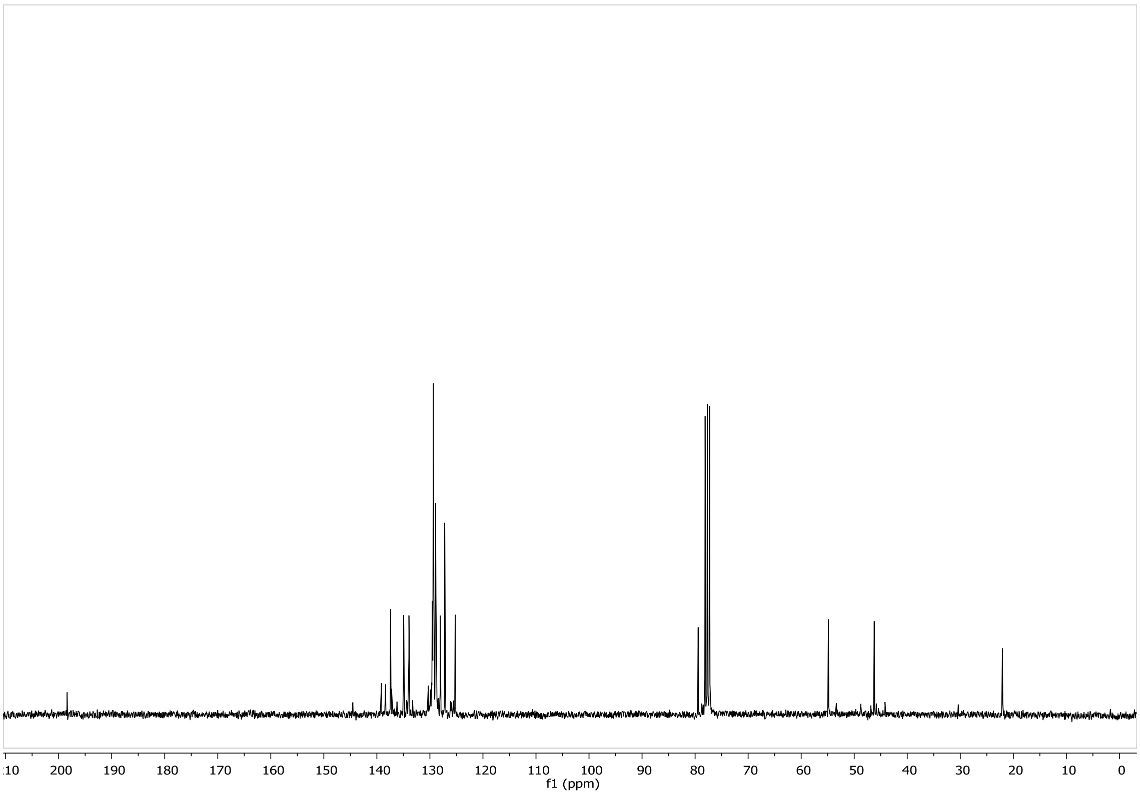

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

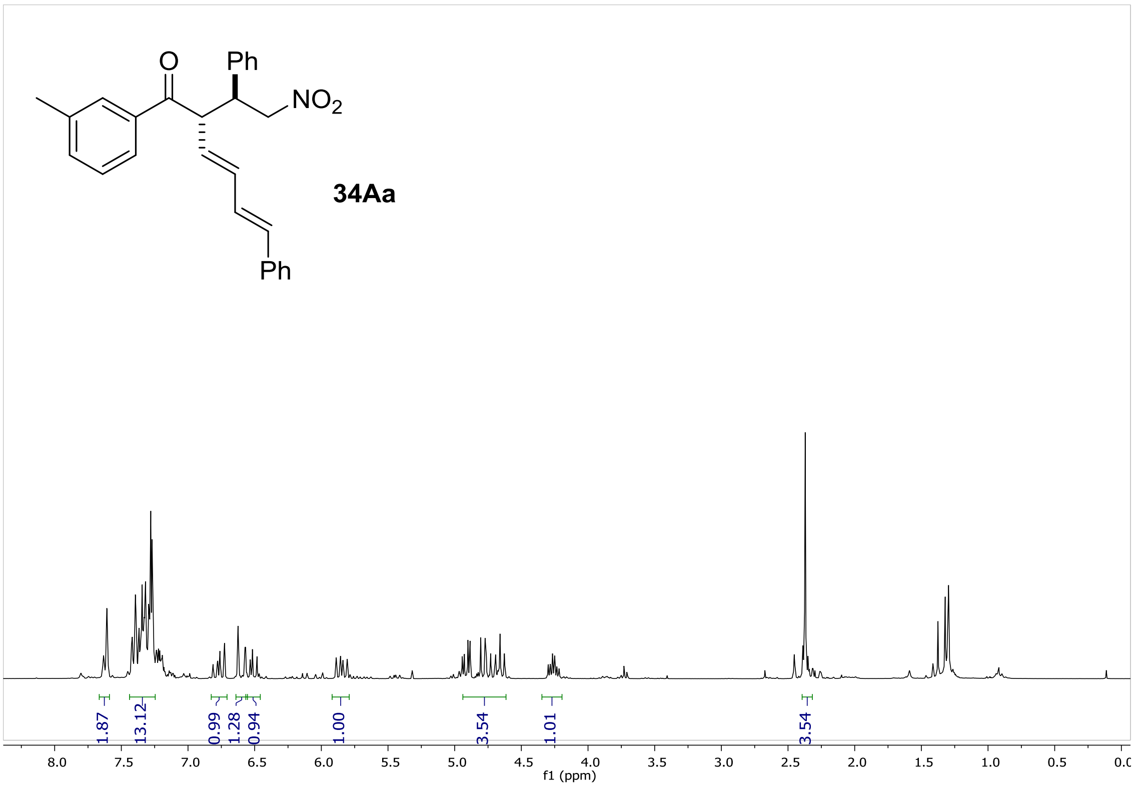

OMe
O
Ph
NO2
Ph
33Ab
1.88
11.02
3.09
2.21
1.00
3.71
0.97
3.32
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

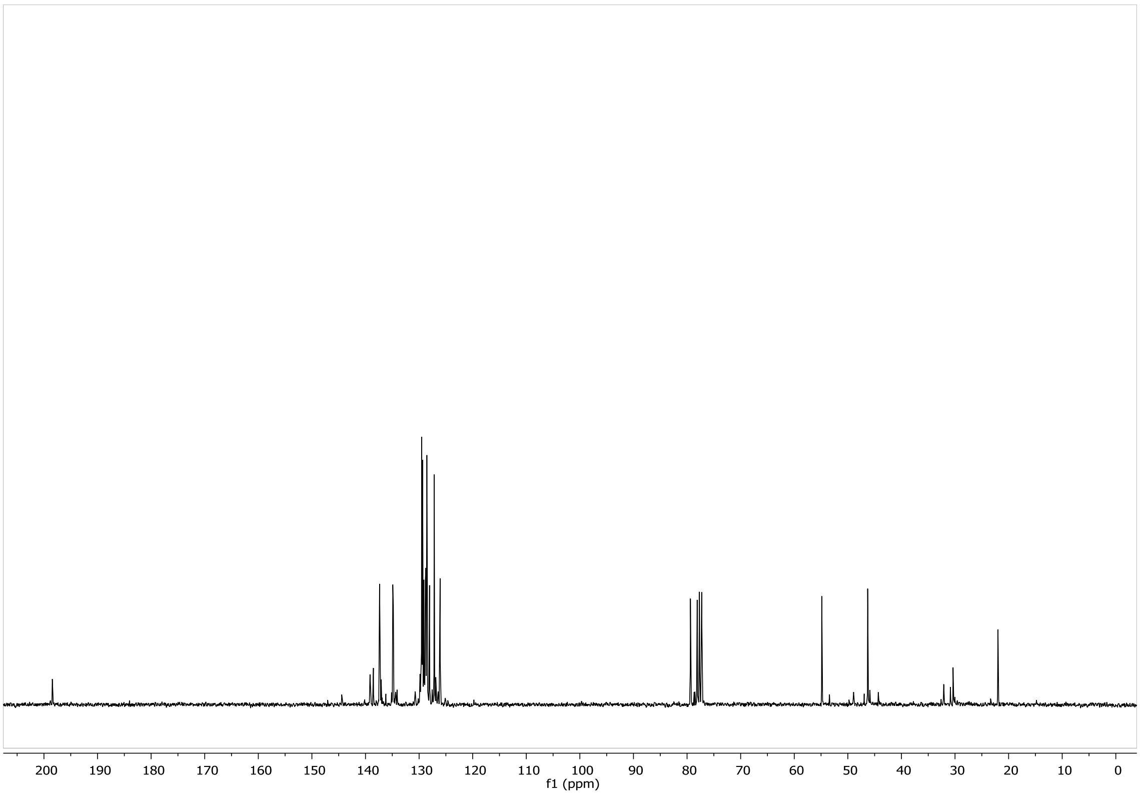

O
Ph
NO2
Ph
1.82
7.93
5.66
1.13
1.32
1.17
1.00
3.86
1.09
3.26
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

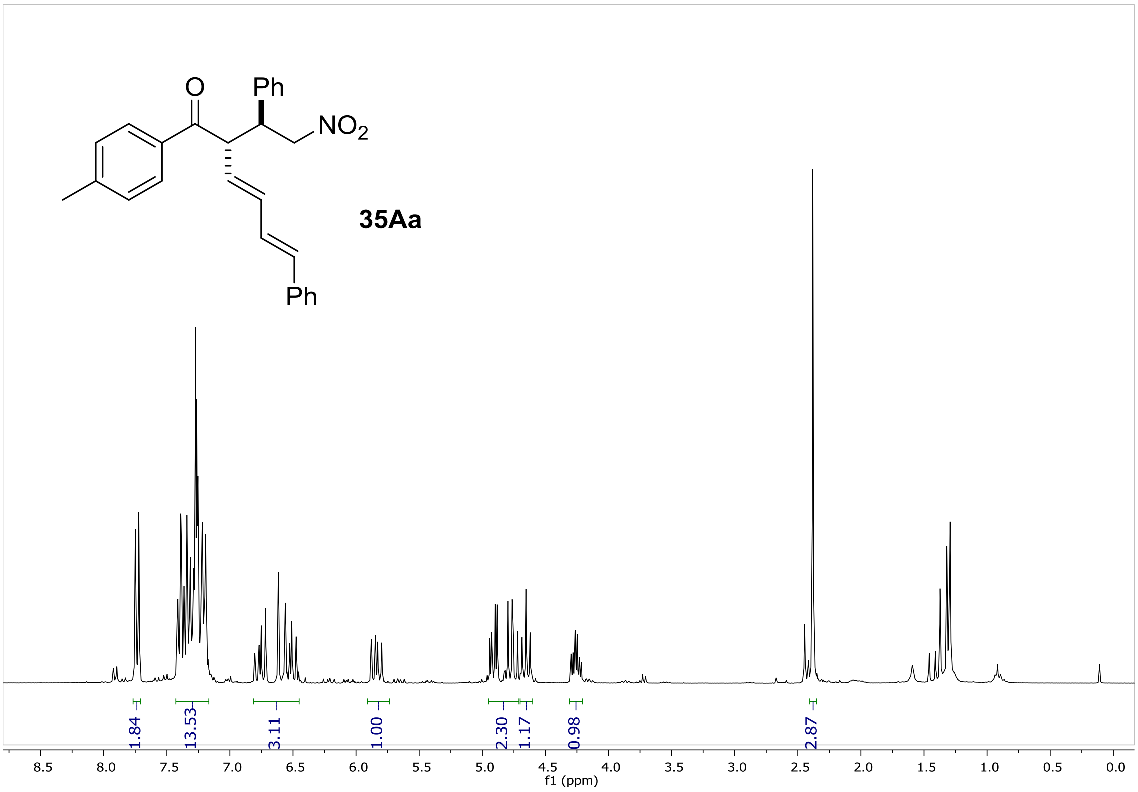
33Ad

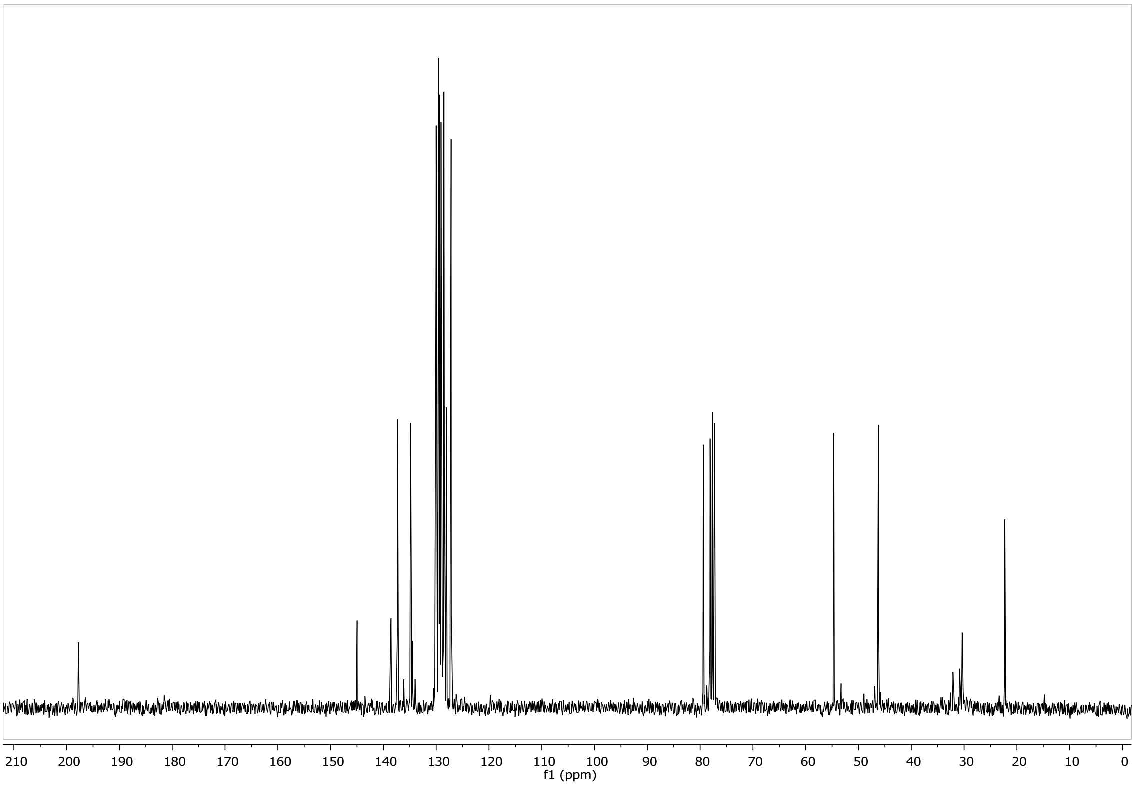

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

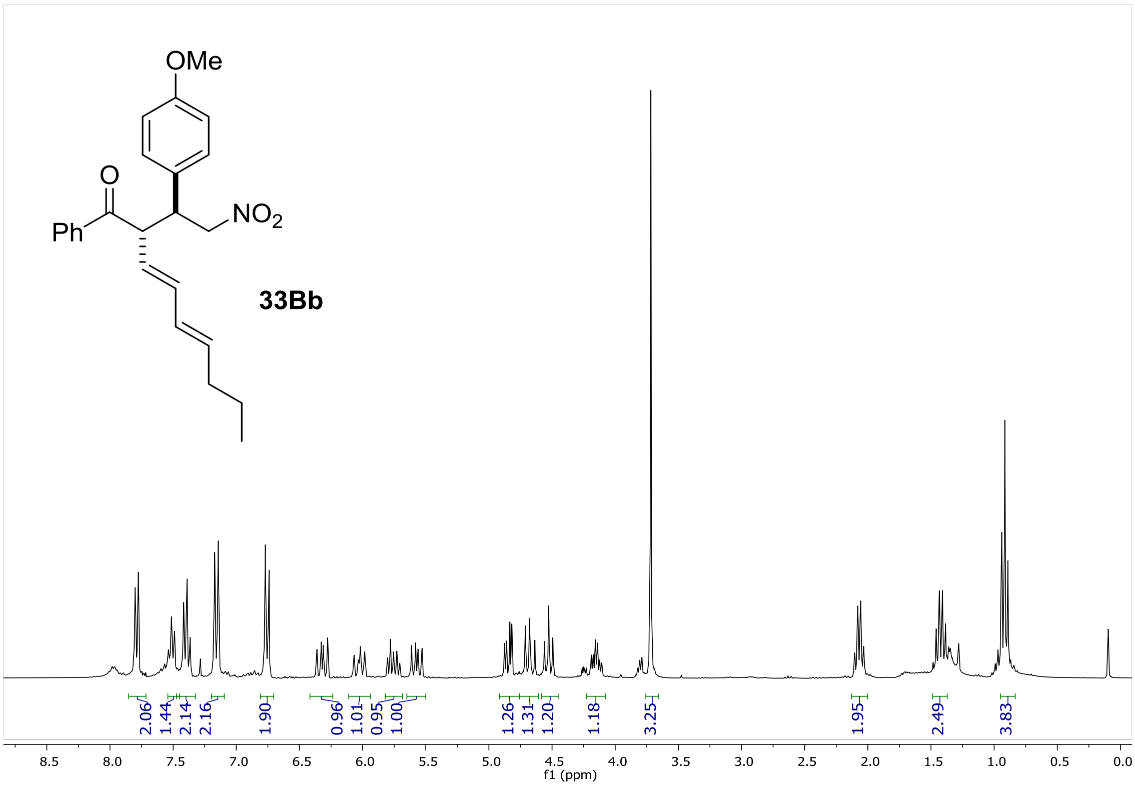

O
Ph
NO2
Ph
1.87
13.12
0.99
1.28
0.94
1.00
3.54
1.01
3.54
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

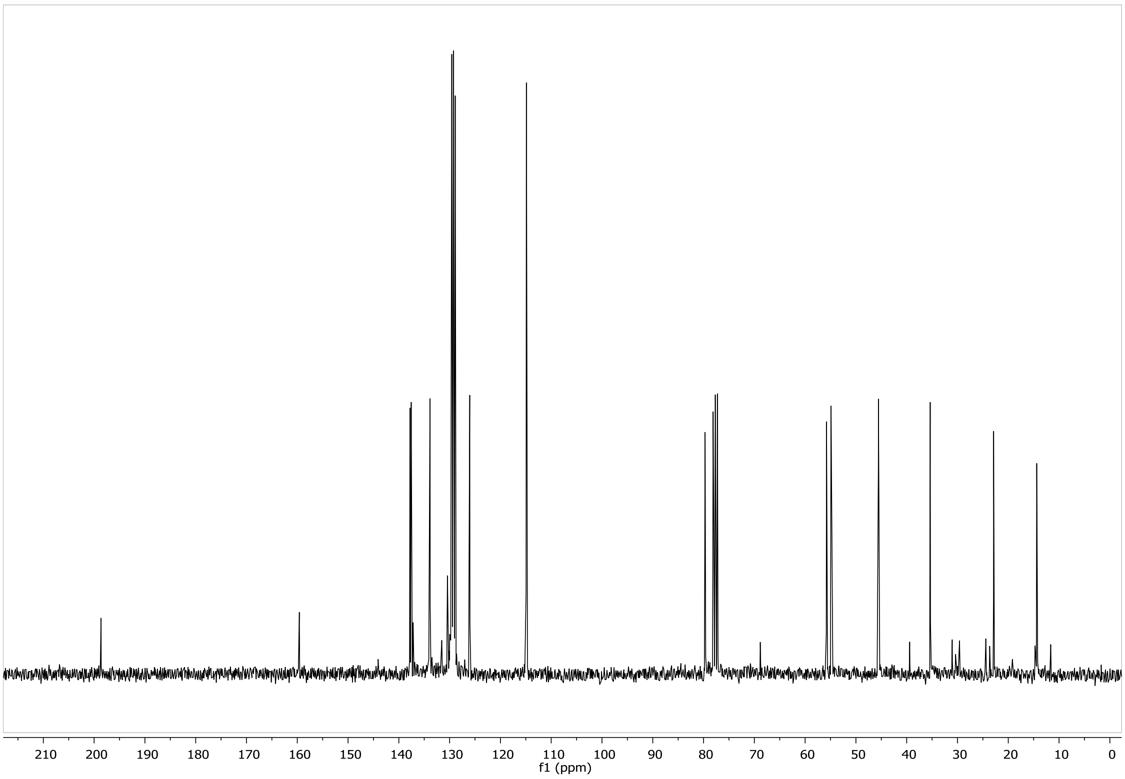
34Aa

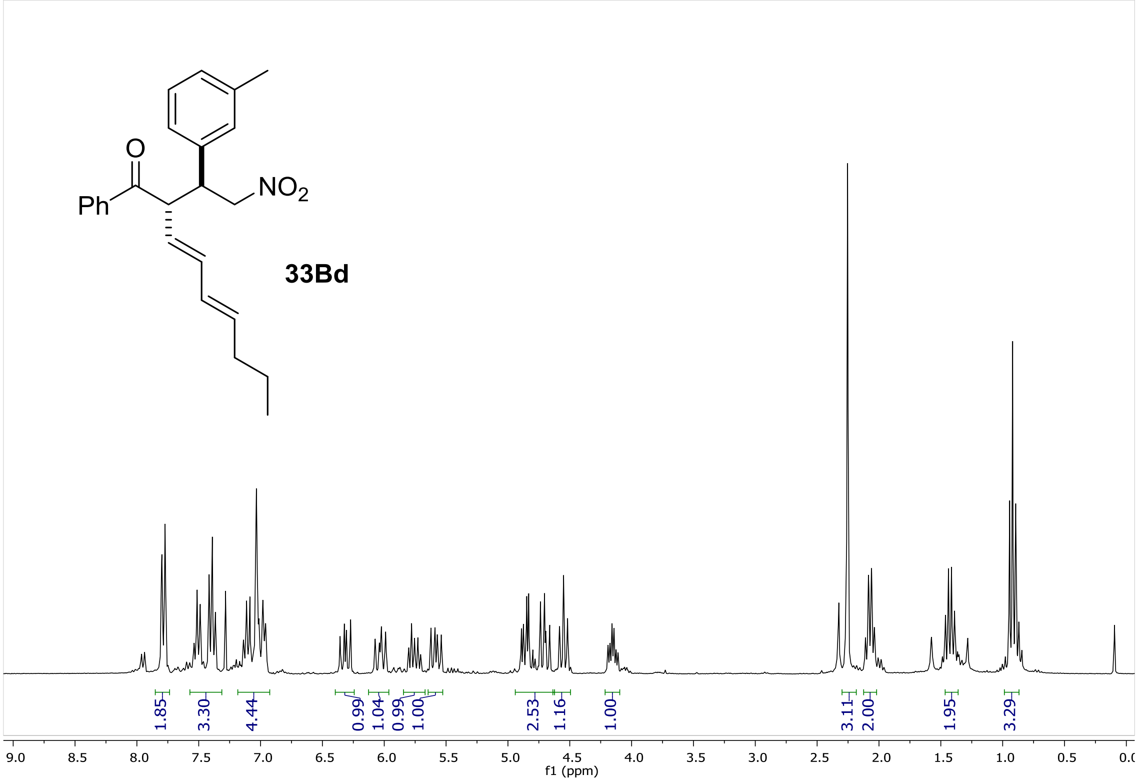

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

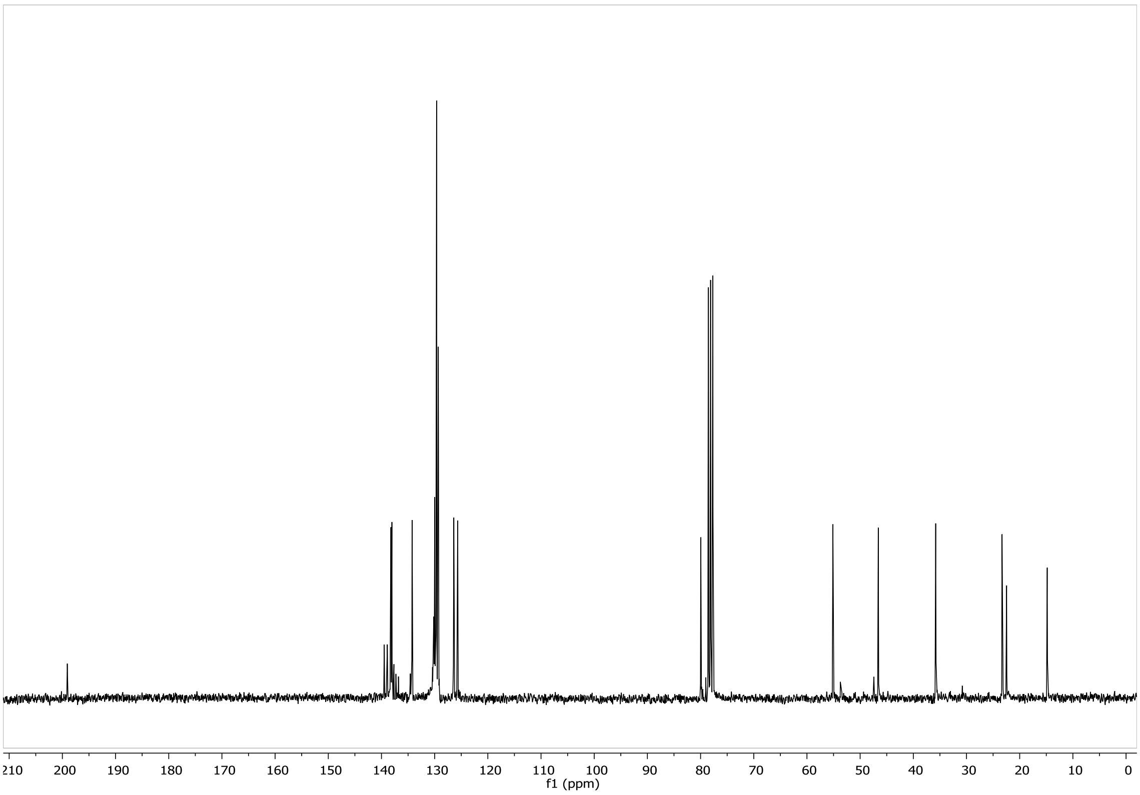

O
Ph
NO2
Ph
35Aa
1.84
13.53
3.11
1.00
2.30
1.17
0.98
2.87
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

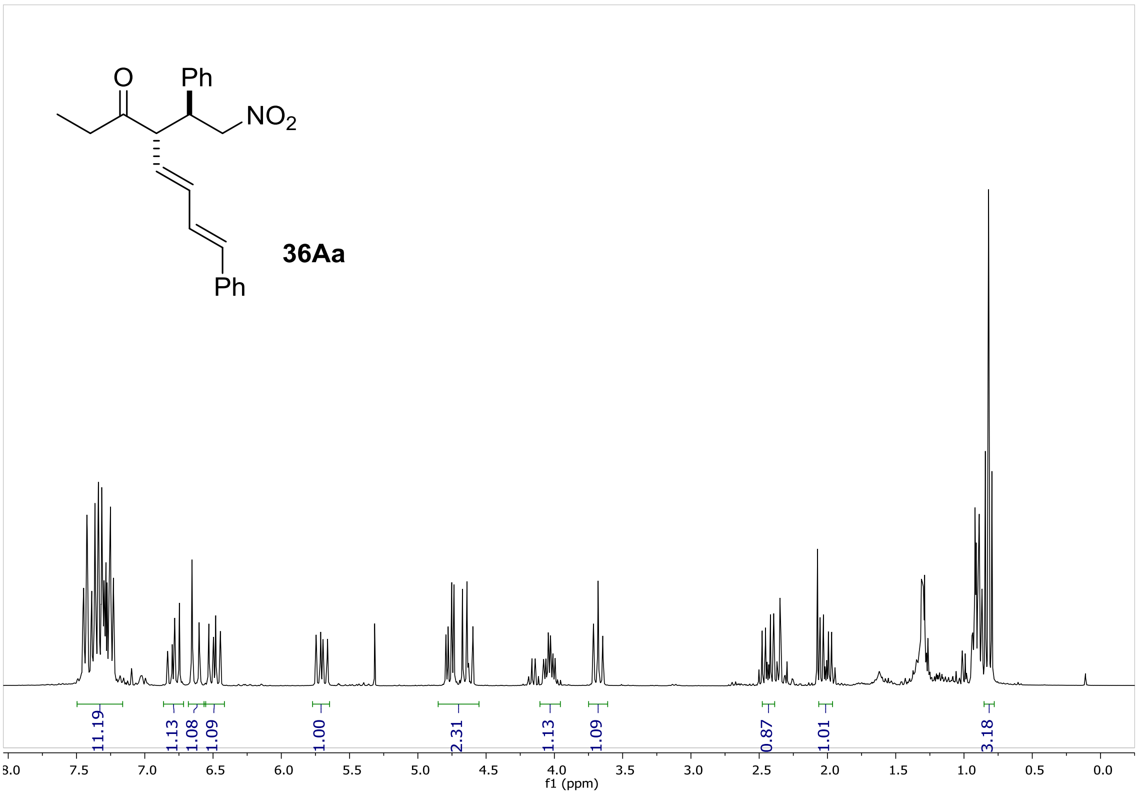

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
O
Ph
NO_2
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
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)

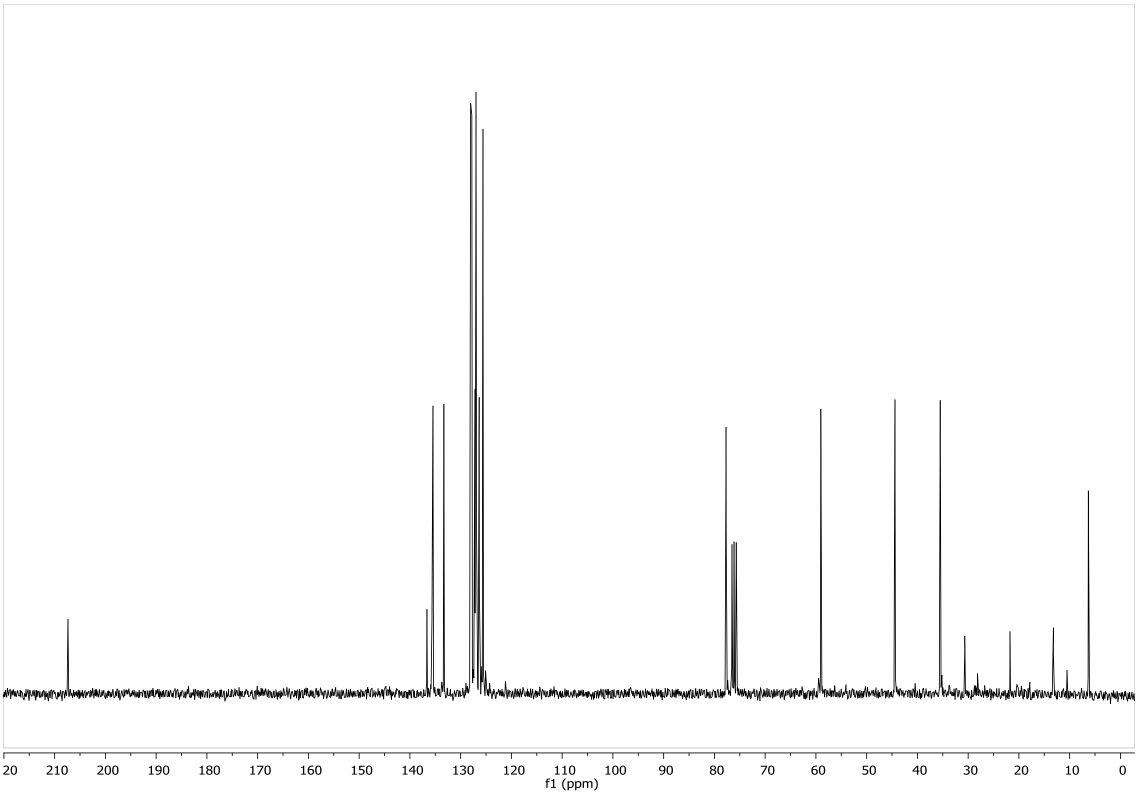

O
Ph
NO2
33Bd
1.85
3.30
4.44
0.99
1.04
0.99
1.00
2.53
1.16
1.00
3.11
2.00
1.95
3.29
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

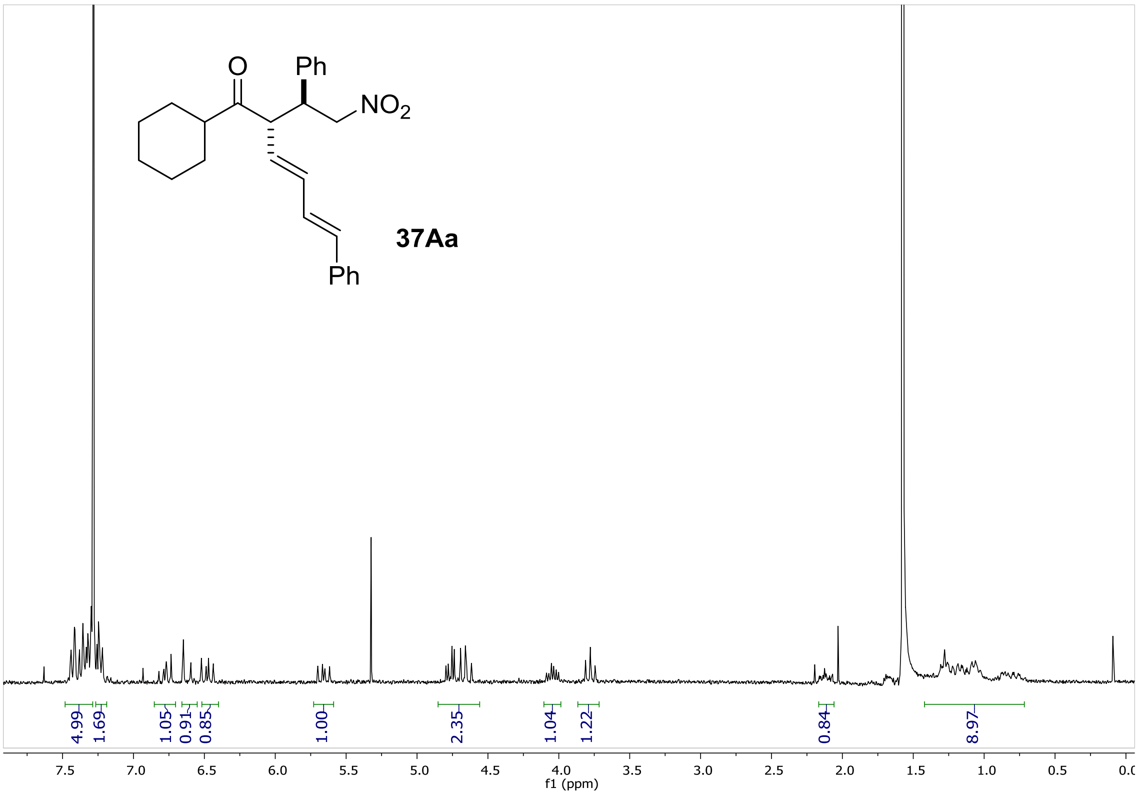


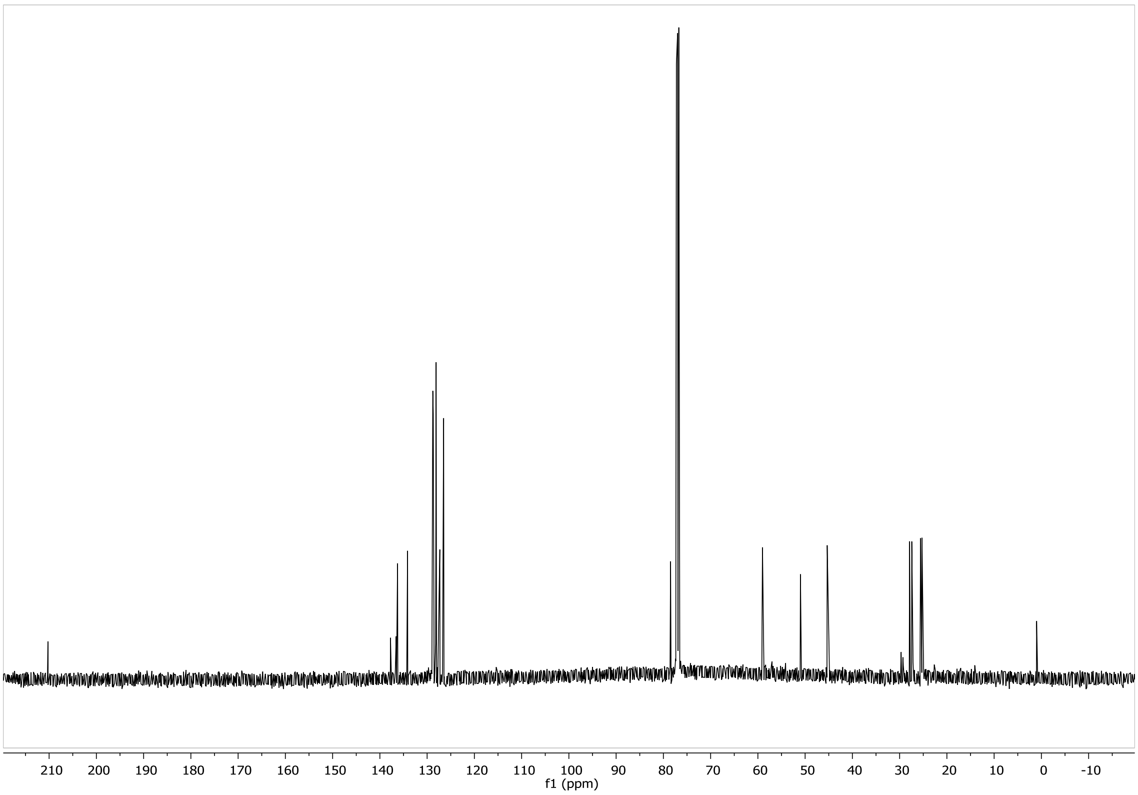
36Aa

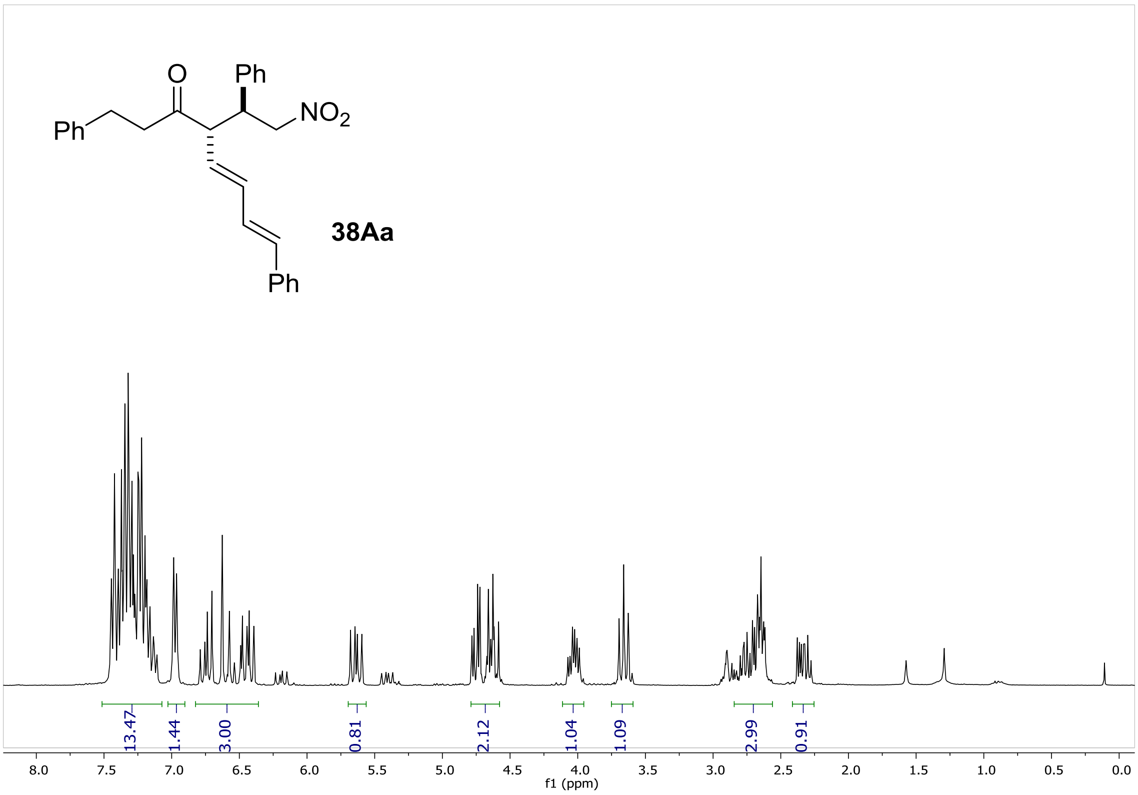
O
Ph
NO2
Ph
11.19
1.13
1.08
1.09
1.00
2.31
1.13
1.09
0.87
1.01
3.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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)

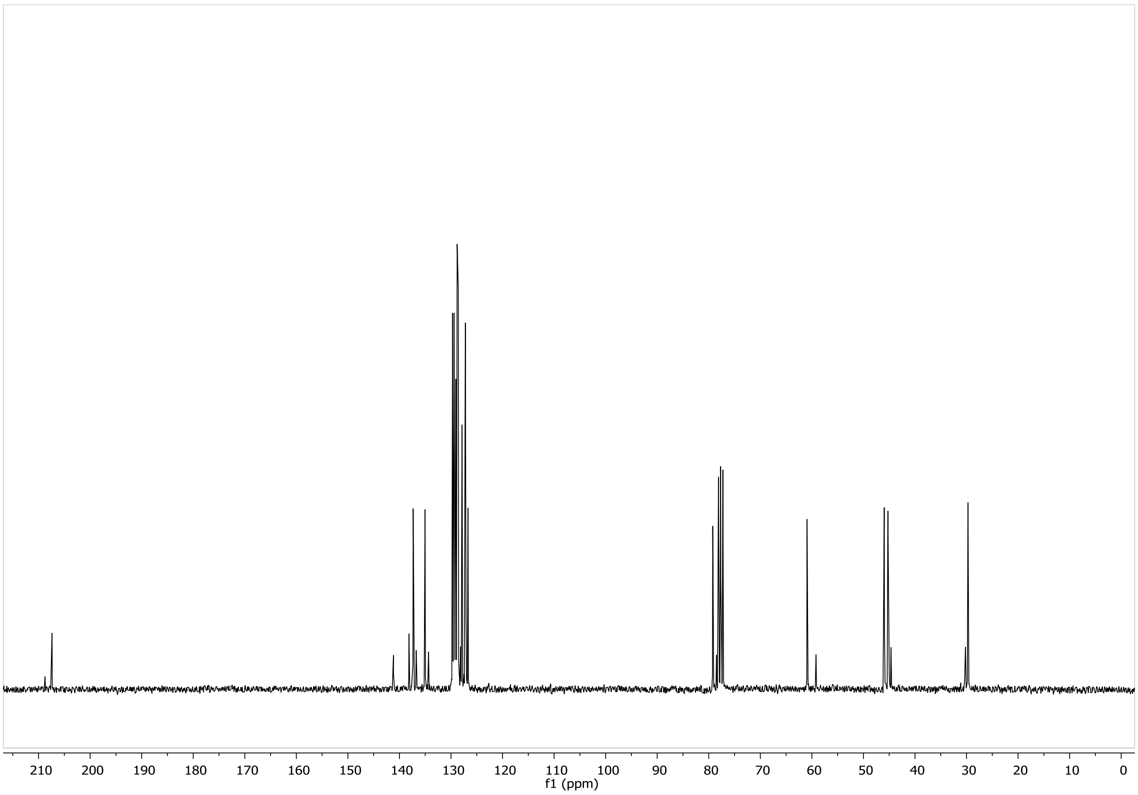

O
Ph
NO_2
Ph
37Aa
4.99
1.69
1.05
0.91
0.85
1.00
2.35
1.04
1.22
0.84
8.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


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)

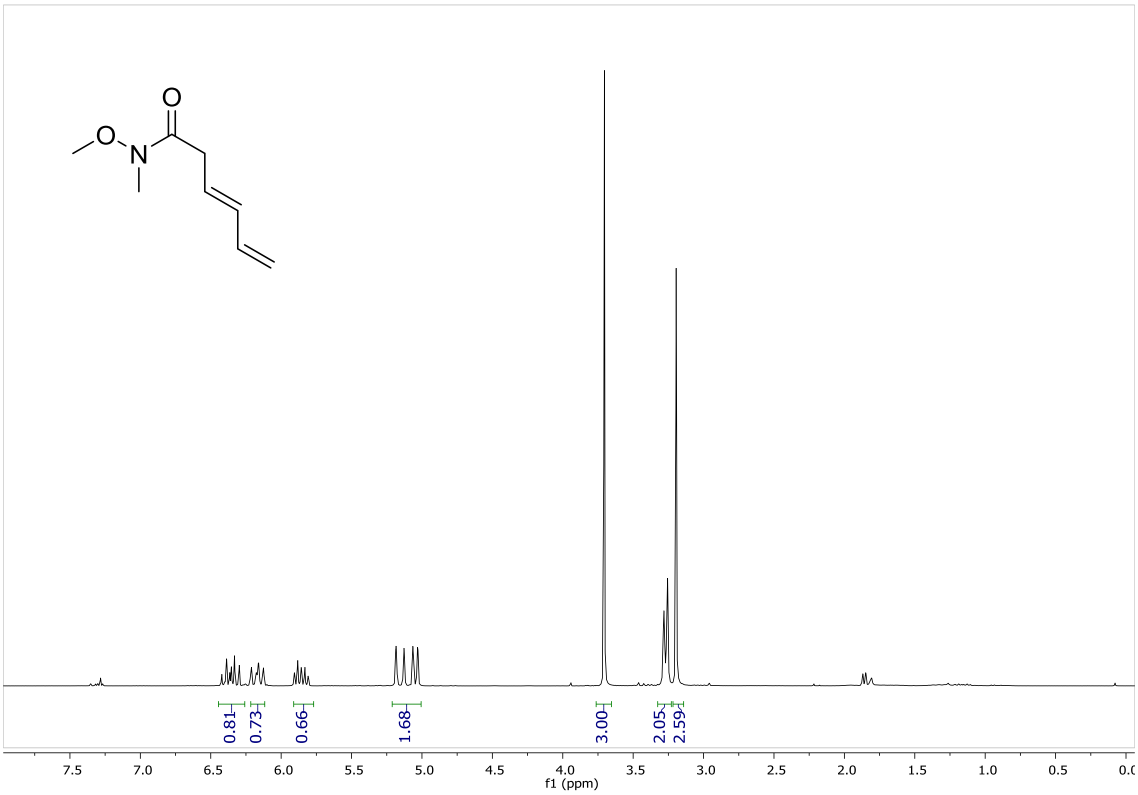


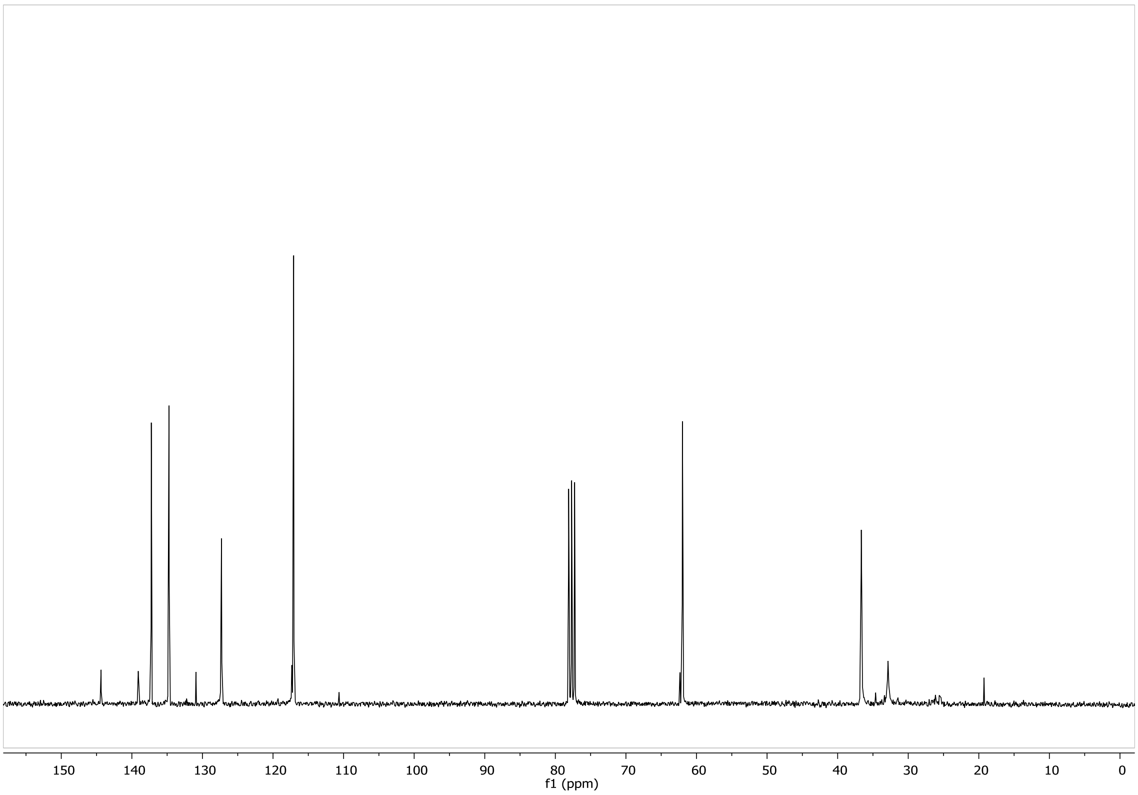
38Aa

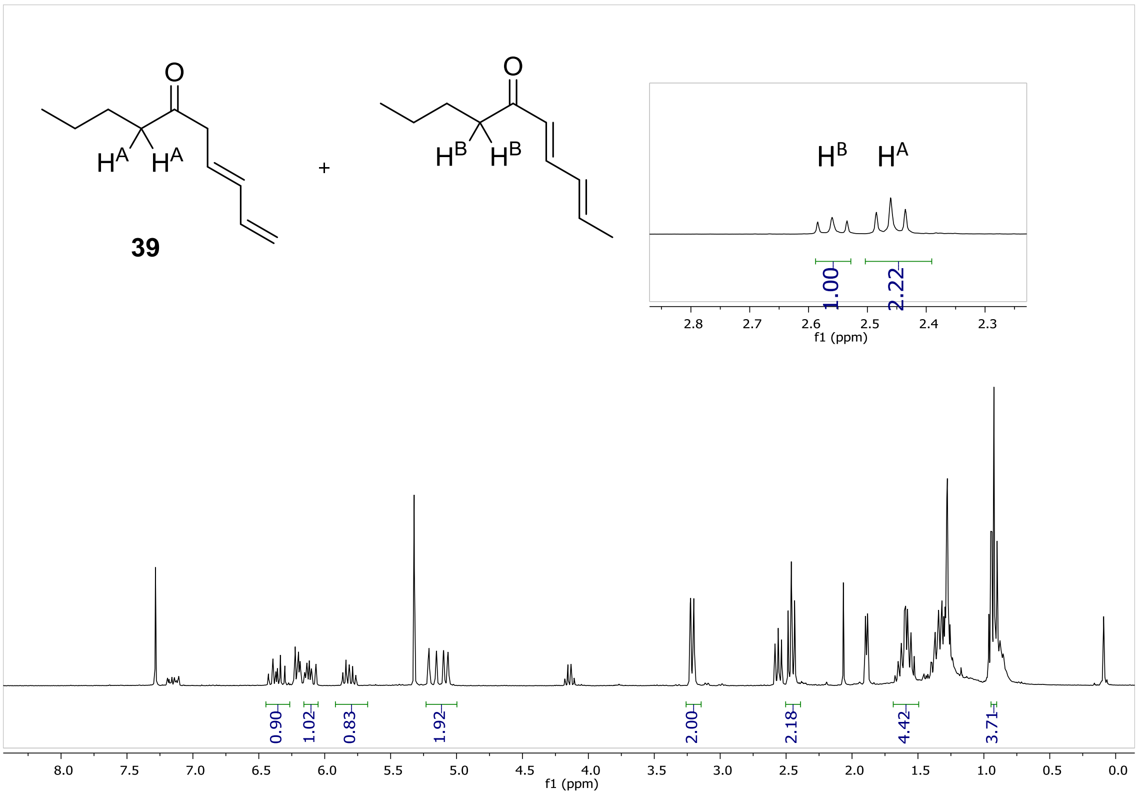
O
Ph
NO2
Ph
Ph
13.47
1.44
3.00
0.81
2.12
1.04
1.09
2.99
0.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

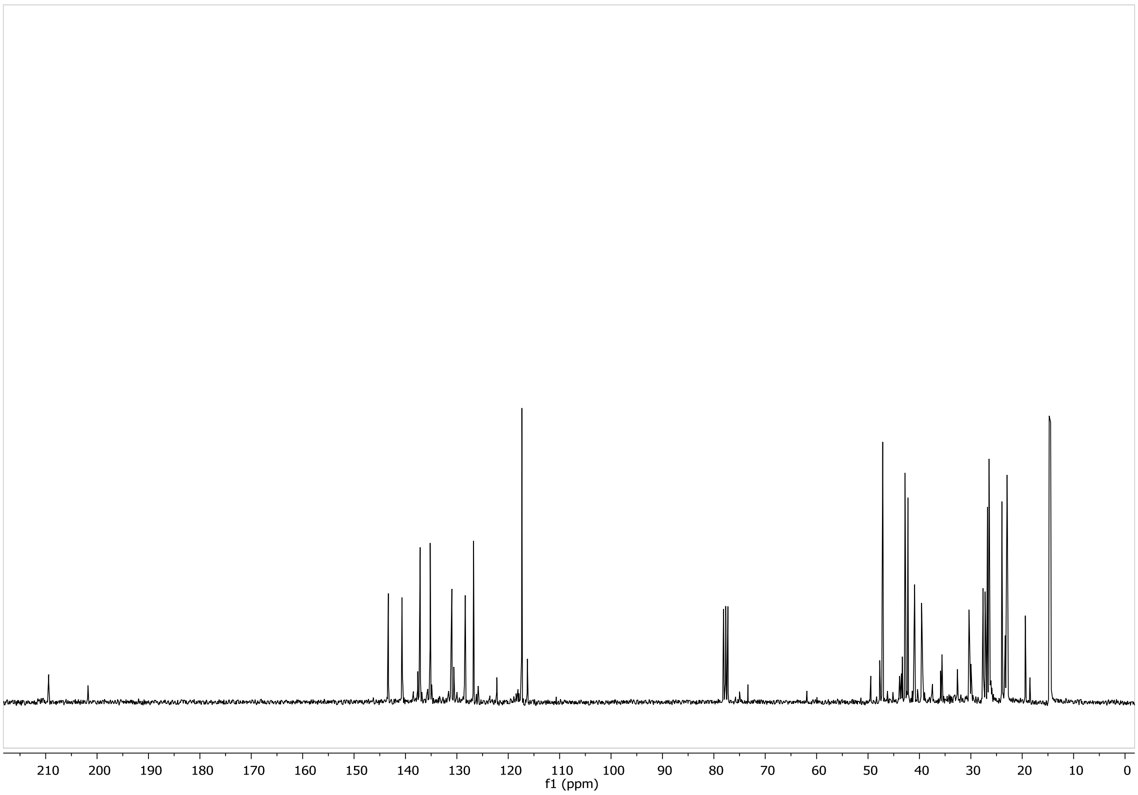


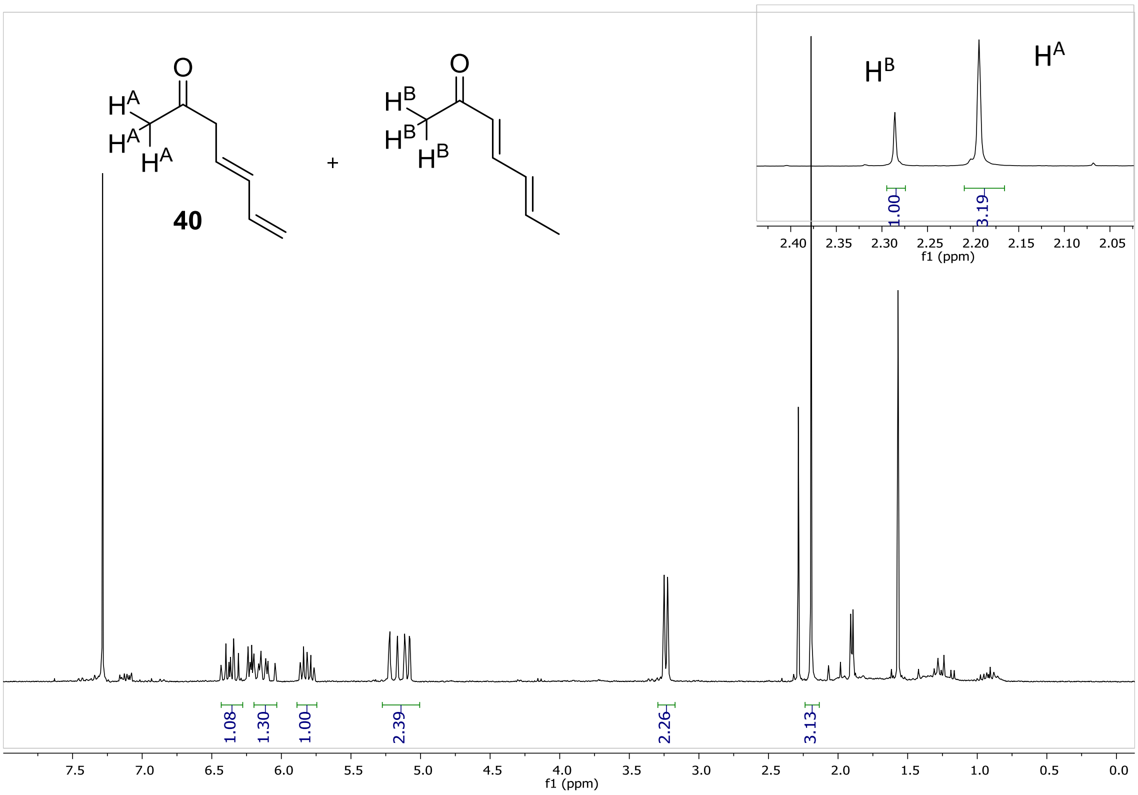
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

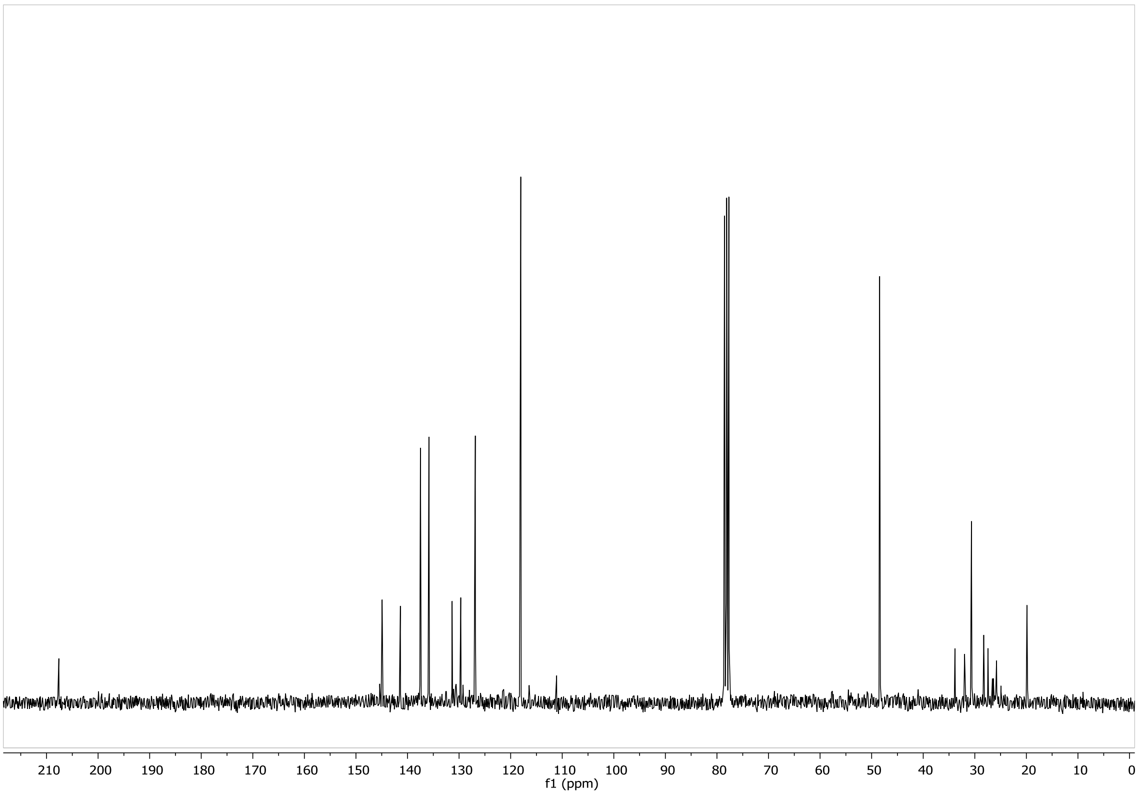

O
O
N
0.81
0.73
0.66
1.68
3.00
2.05
2.59
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

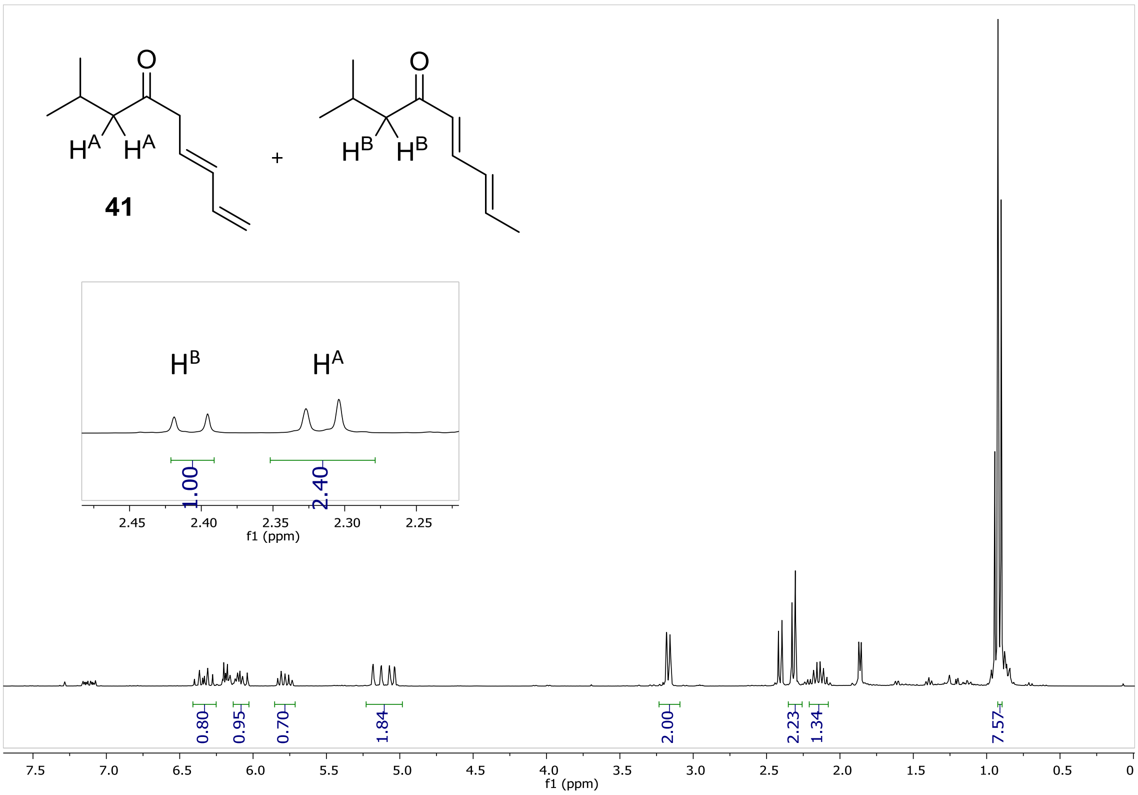

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

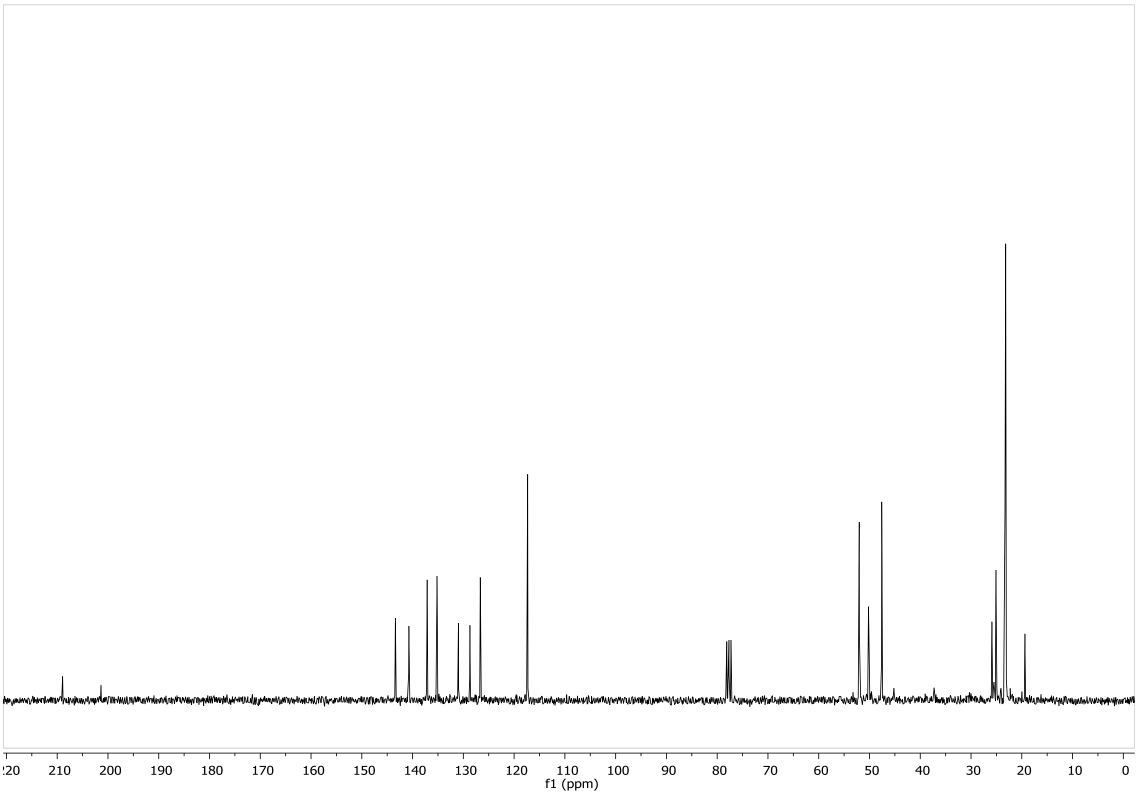

O
H^A H^A
39
+
O
H^B H^B
H^B H^A
1.00
2.22
2.8 2.7 2.6 2.5 2.4 2.3
f1 (ppm)
0.90
1.02
0.83
1.92
2.00
2.18
4.42
3.71
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

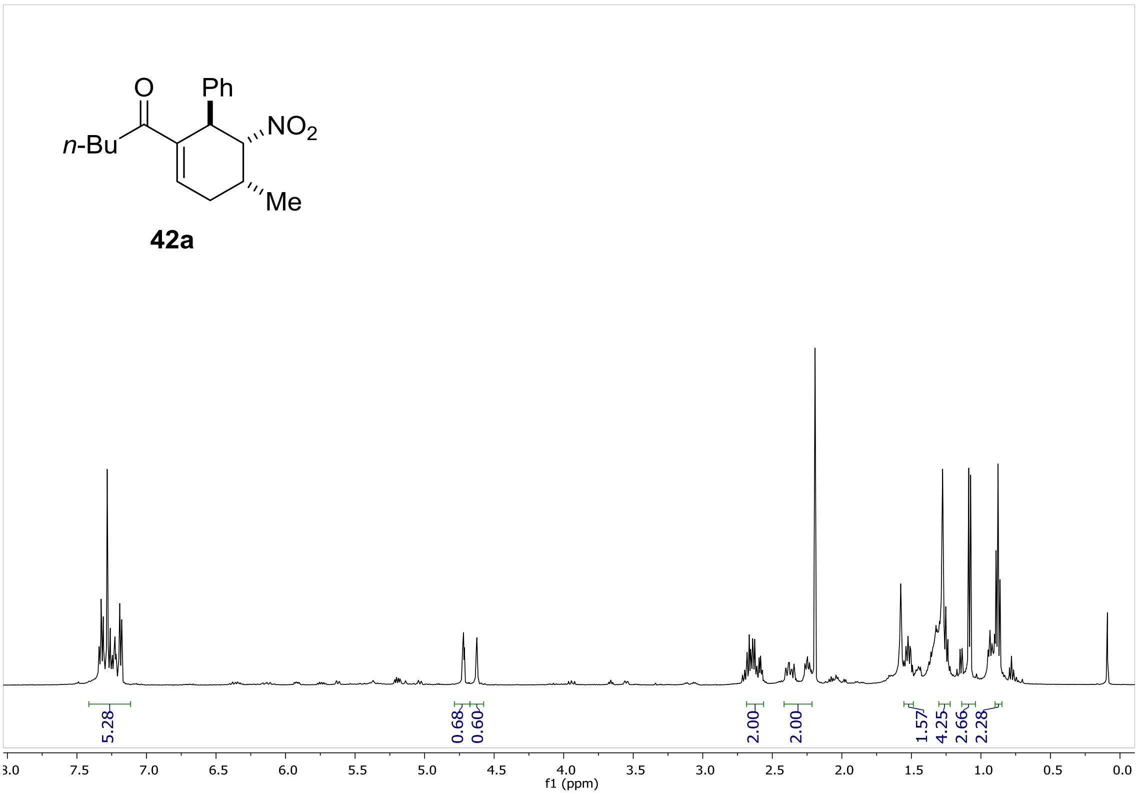

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

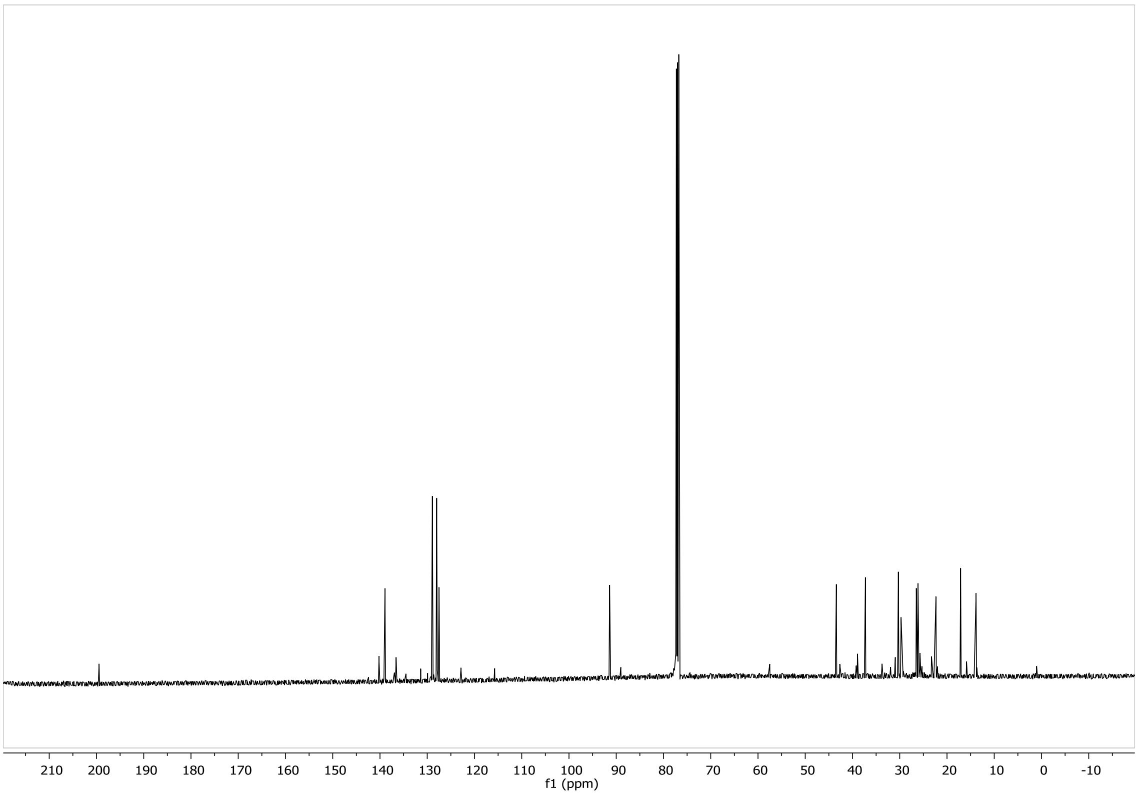

O
H^A
H^A
H^A
40
+
O
H^B
H^B
H^B
H^B
H^A
1.00
3.19
2.40 2.35 2.30 2.25 2.20 2.15 2.10 2.05
f1 (ppm)
1.08
1.30
1.00
2.39
2.26
3.13
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

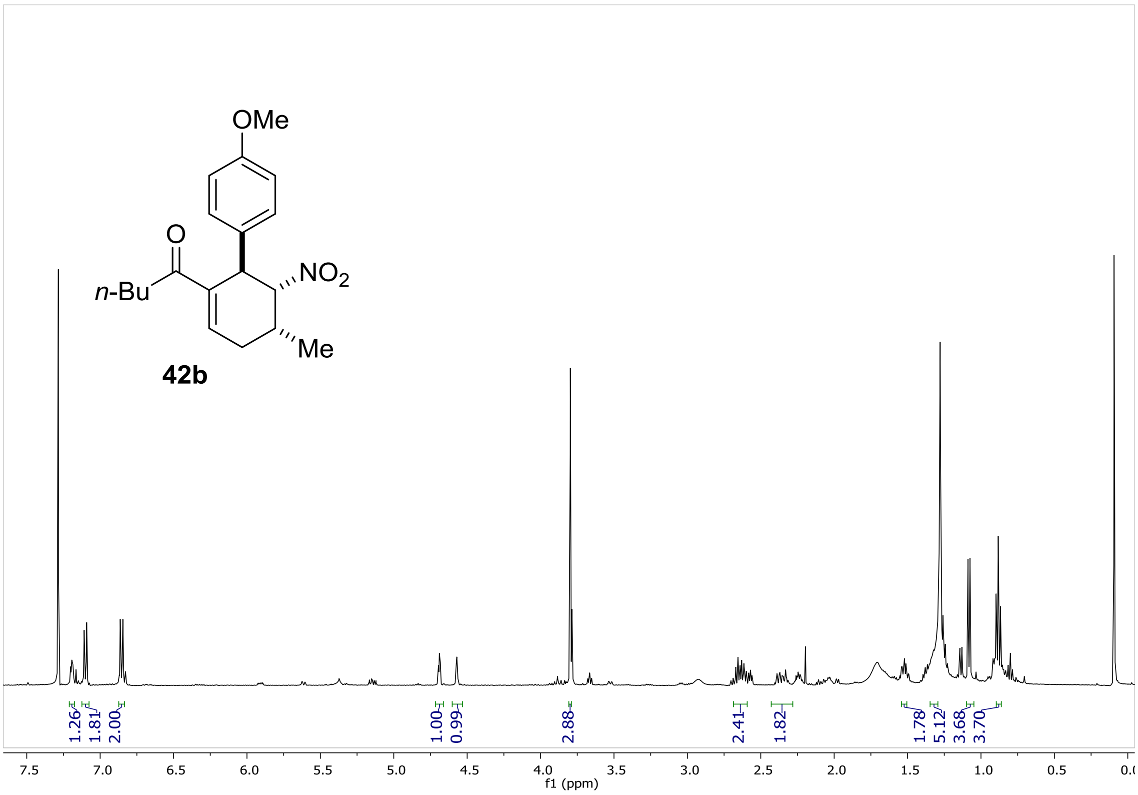

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
H^A H^A
41
+
O
H^B H^B
H^B
H^A
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)

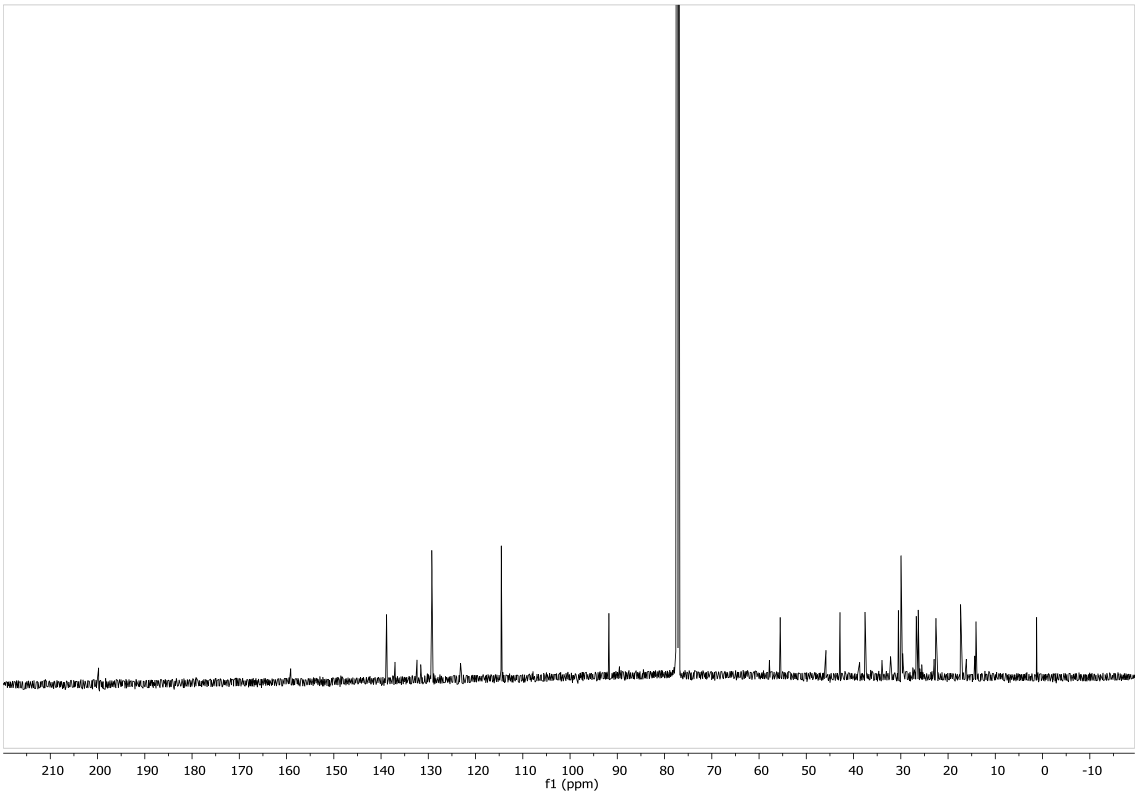

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

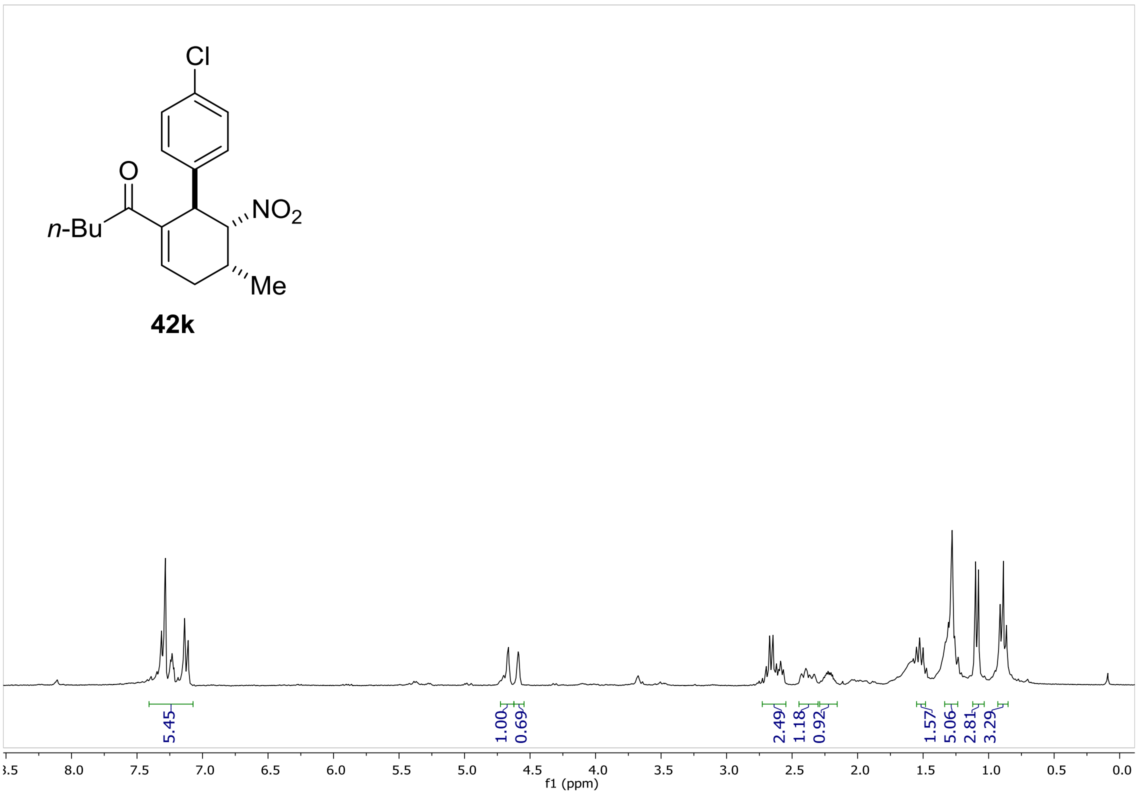

O
Ph
n-Bu
NO$_2$
Me
42a
5.28
0.68
0.60
2.00
2.00
1.57
4.25
2.66
2.28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

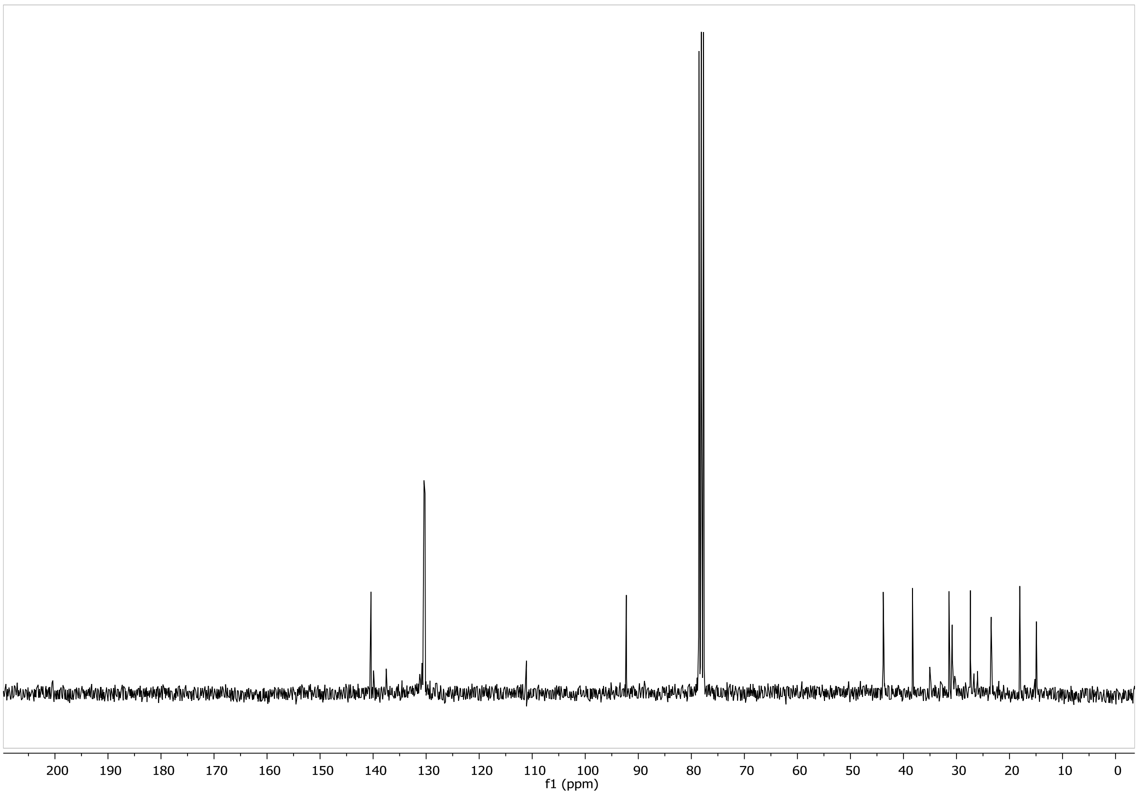

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

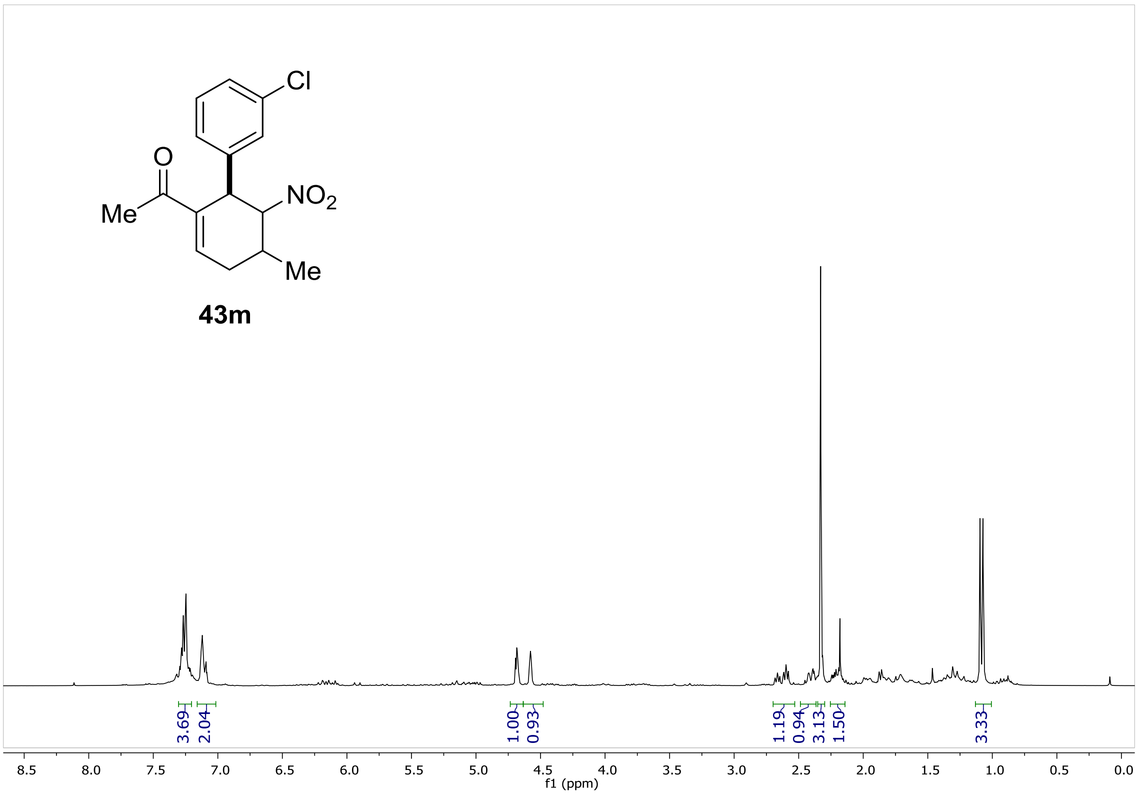

42b

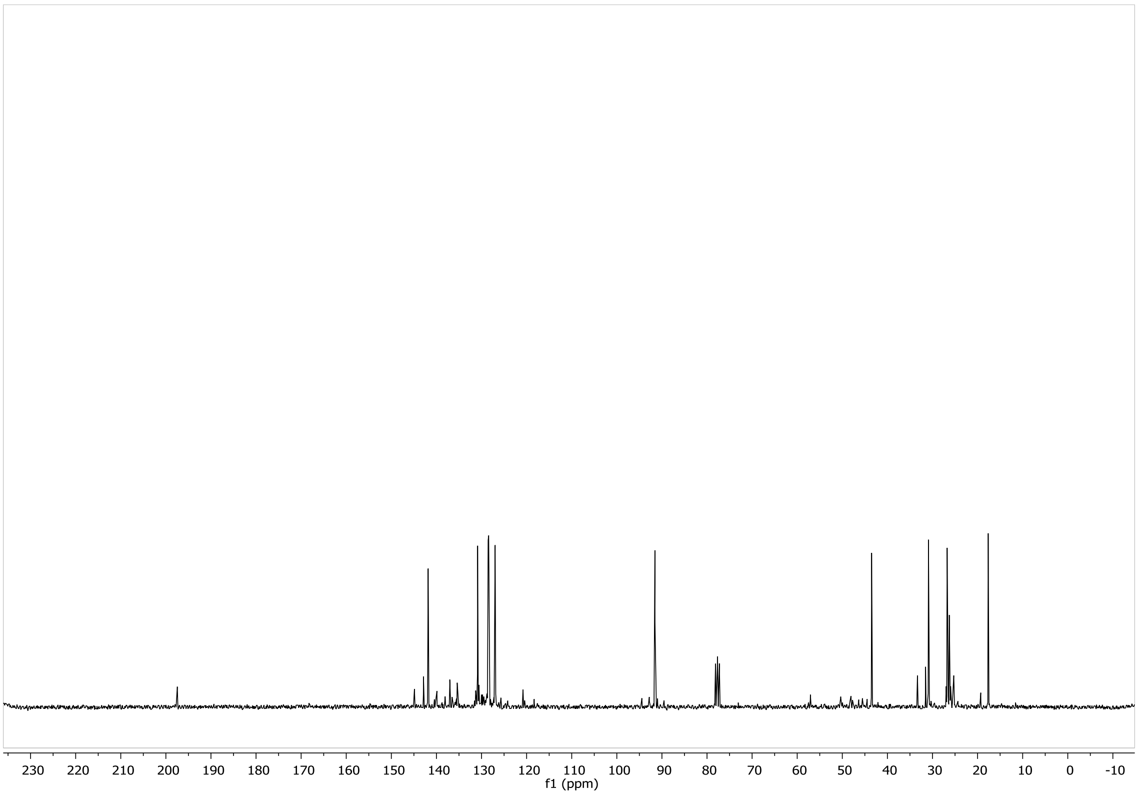
OMe
O
n-Bu
NO2
Me
1.26
1.81
2.00
1.00
0.99
2.88
2.41
1.82
1.78
5.12
3.68
3.70
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

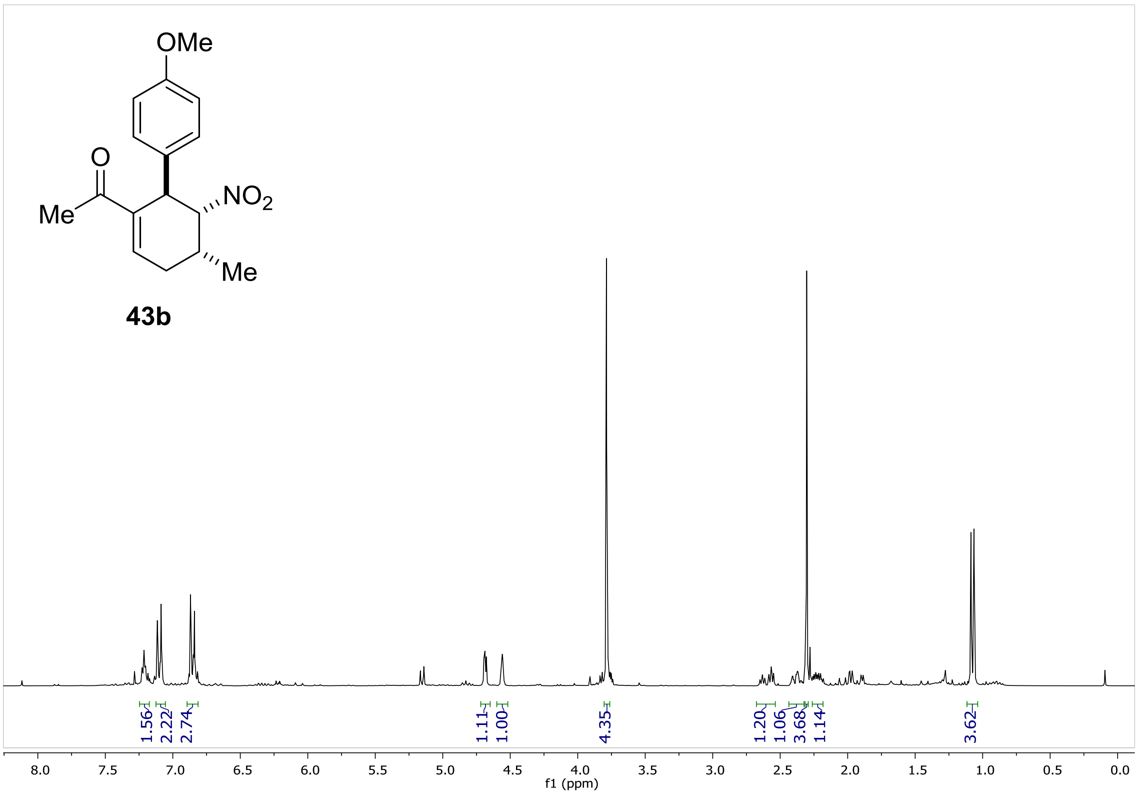

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Cl
O
NO2
n-Bu
Me
42k
5.45
1.00
0.69
2.49
1.18
0.92
1.57
5.06
2.81
3.29
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)

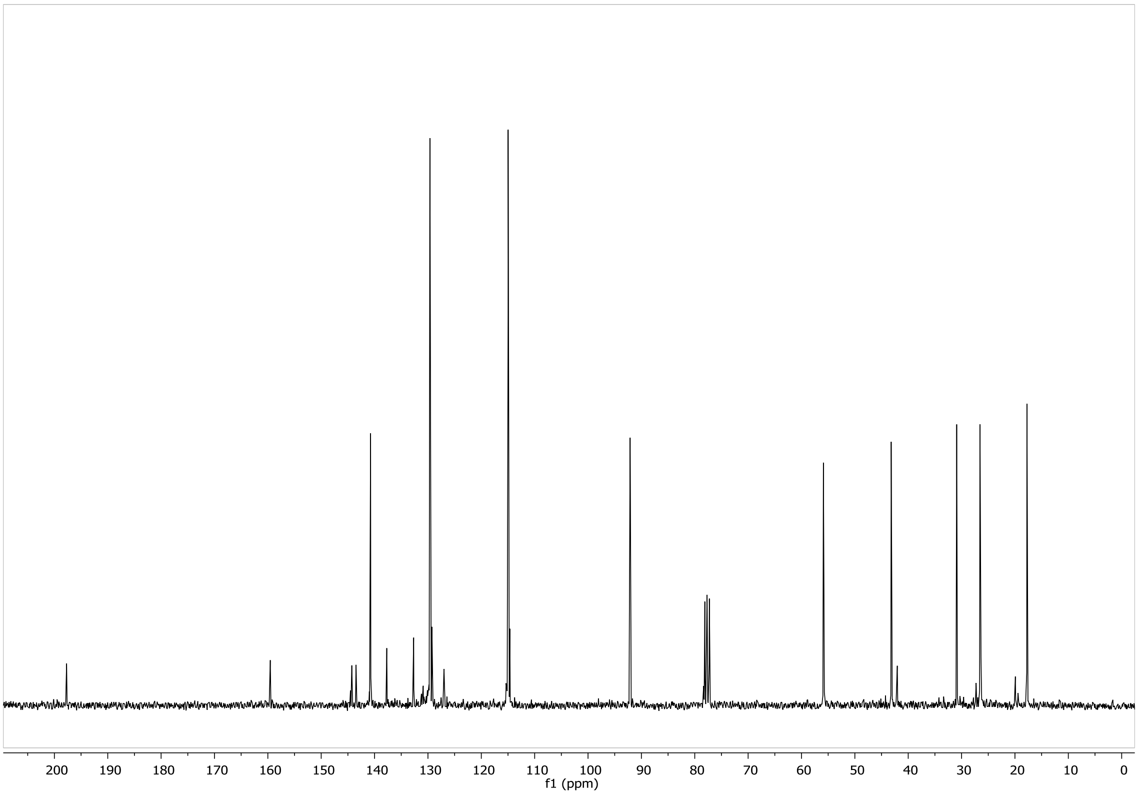

43m
Cl
O
NO2
Me
Me
3.69
2.04
1.00
0.93
1.19
0.94
3.13
1.50
3.33
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


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)

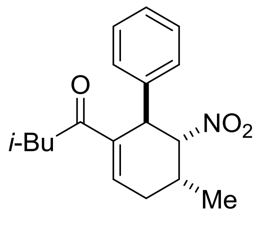


43b

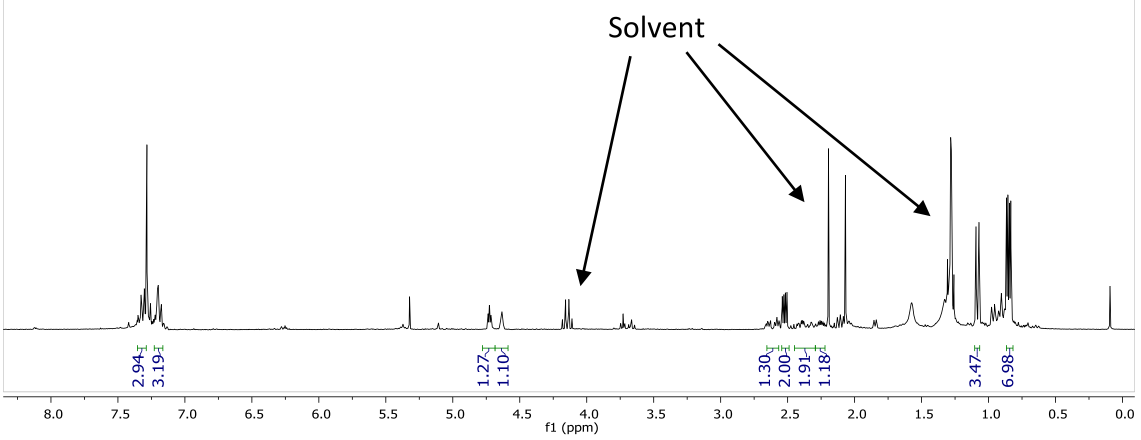
OMe
O
Me
NO2
Me
1.56
2.22
2.74
1.11
1.00
4.35
1.20
1.06
3.68
1.14
3.62
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

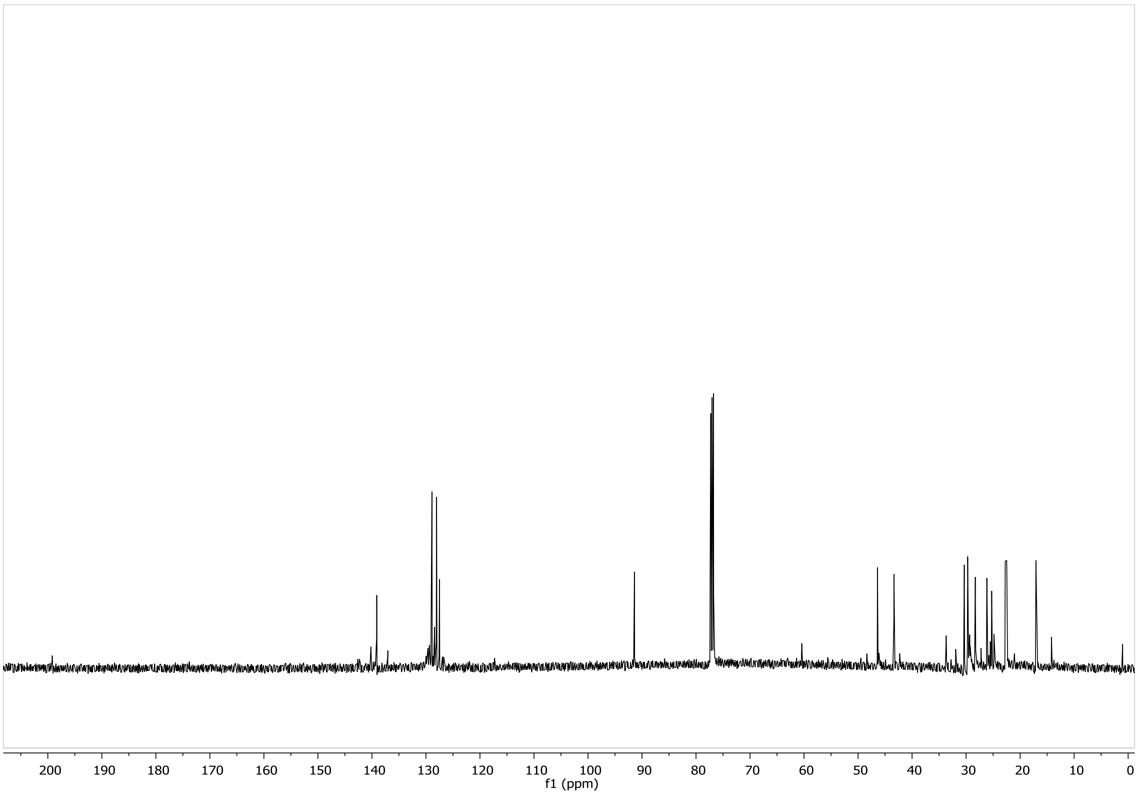


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

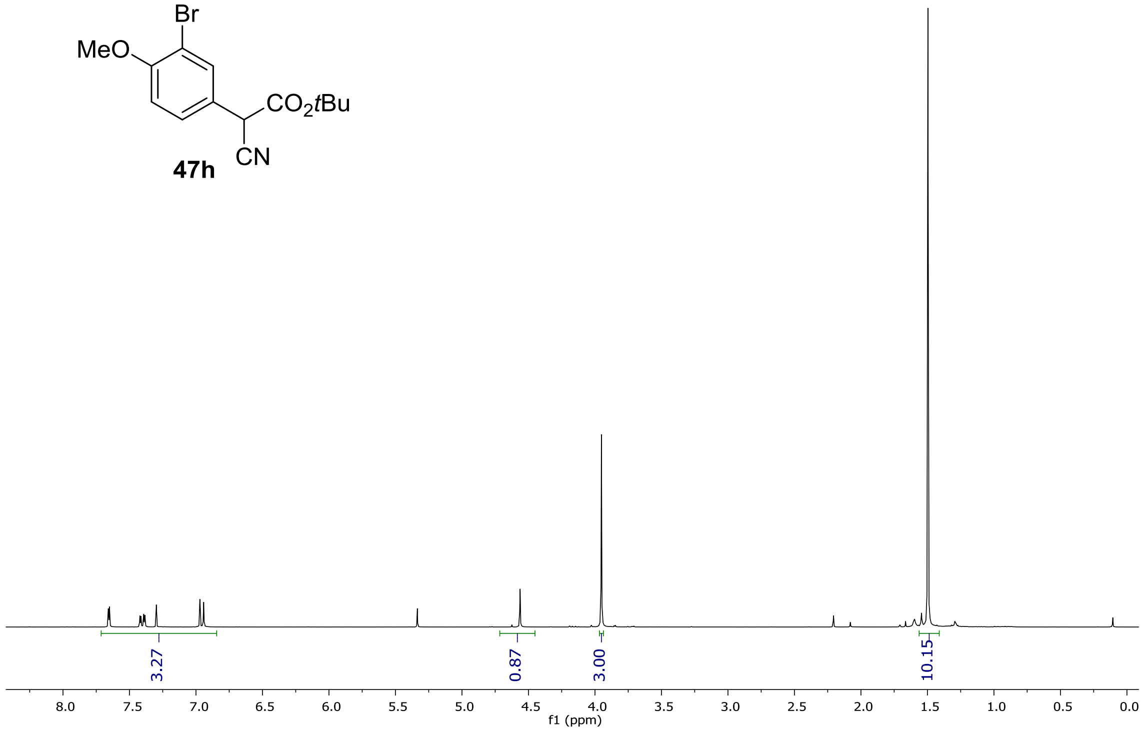

O
i-Bu
NO2
Me

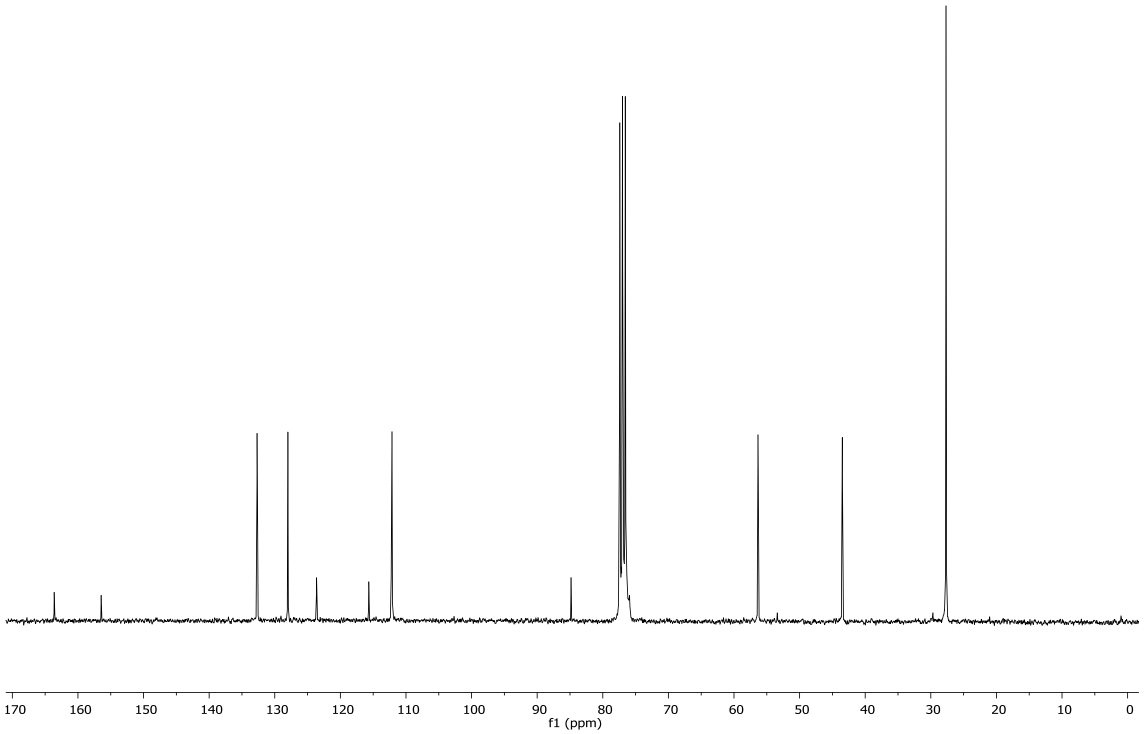
44a

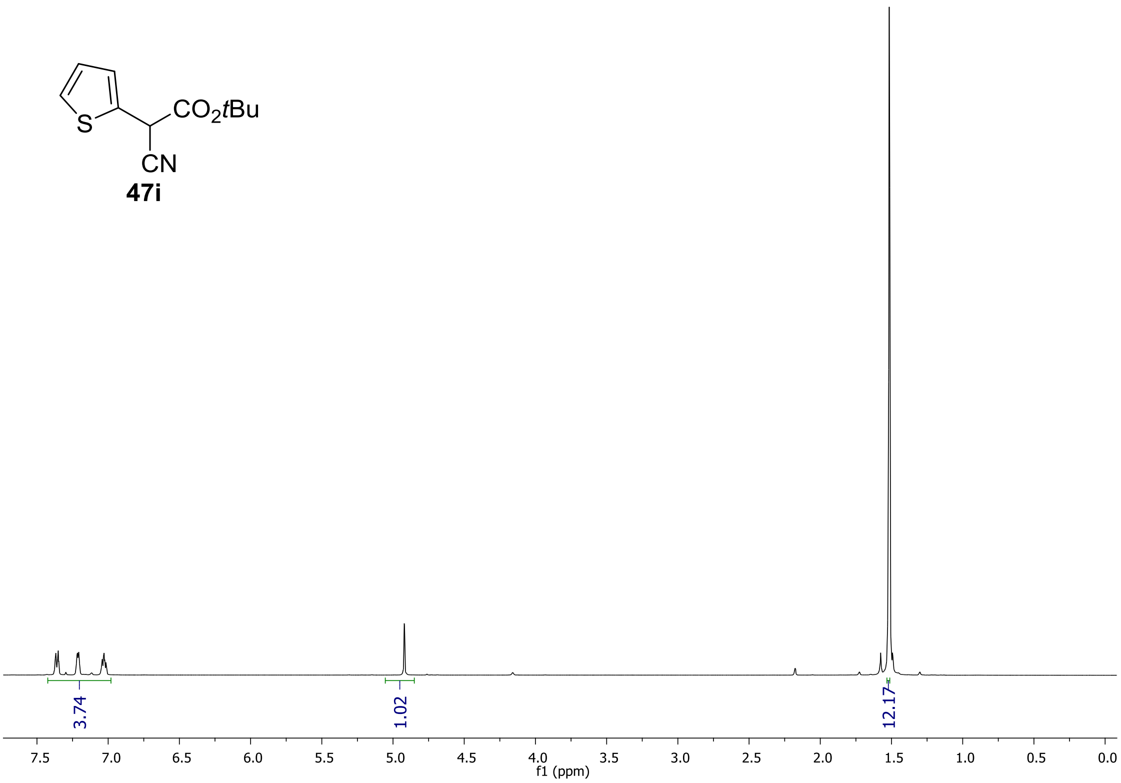

Solvent
2.94
3.19
1.27
1.10
1.30
2.00
1.91
1.18
3.47
6.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

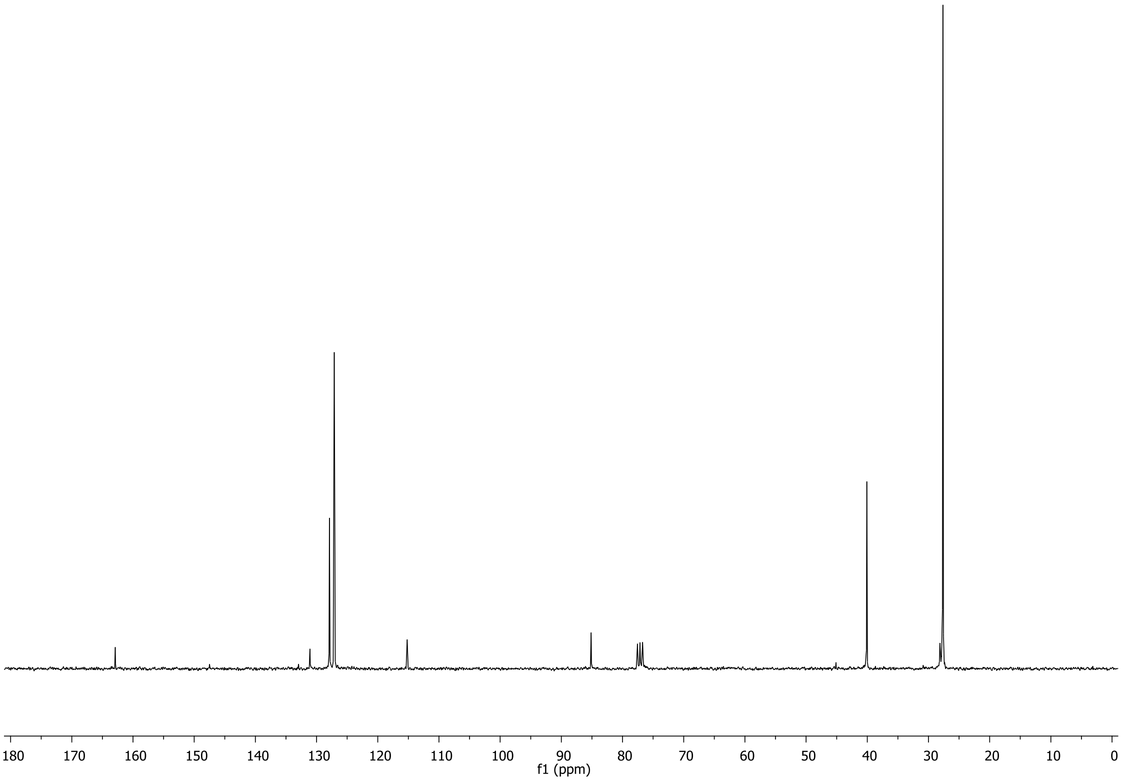
6.5.2. NMR spectra of Chapter 3

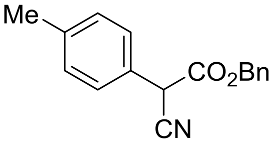




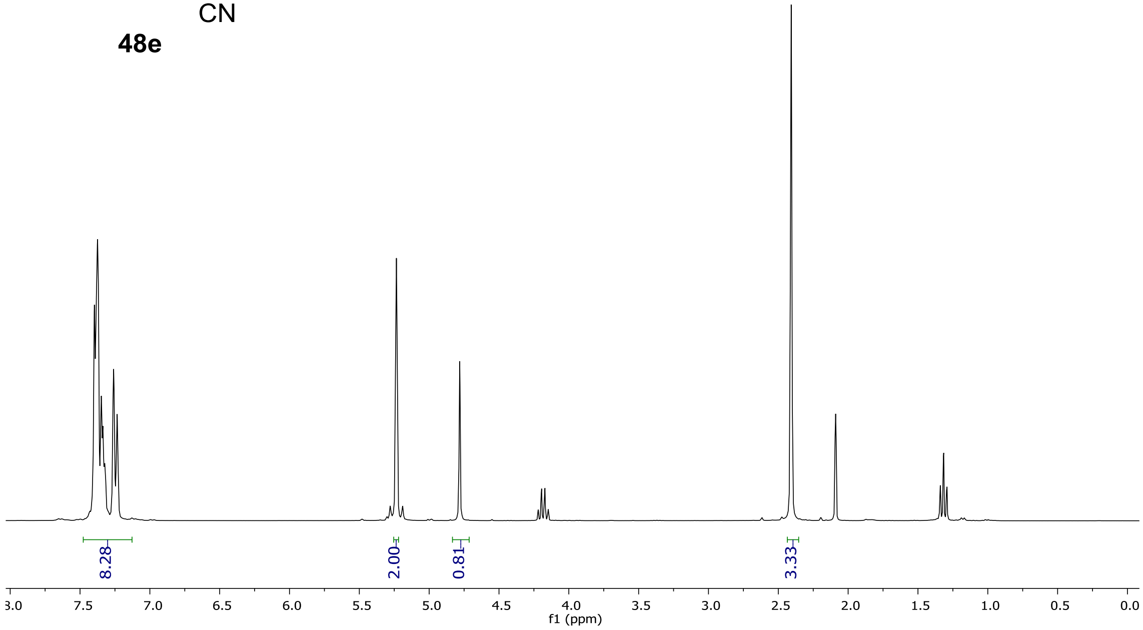

S
CO2tBu
CN
3.74
1.02
12.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

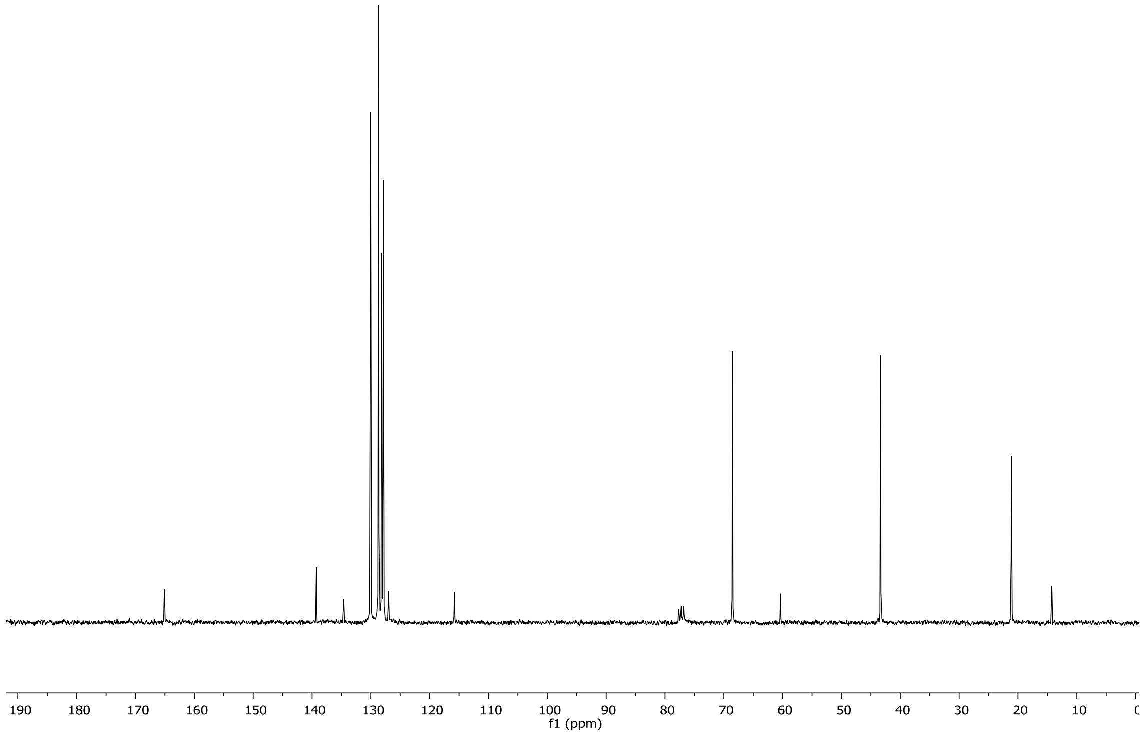
47i

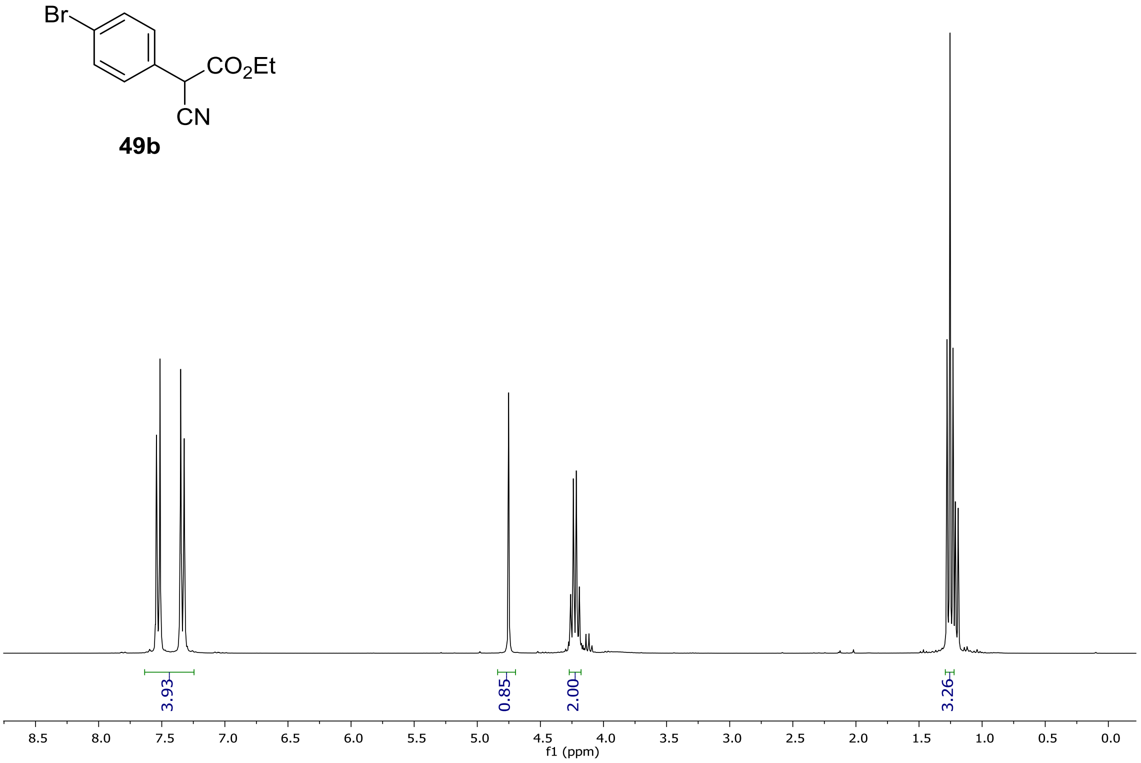

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

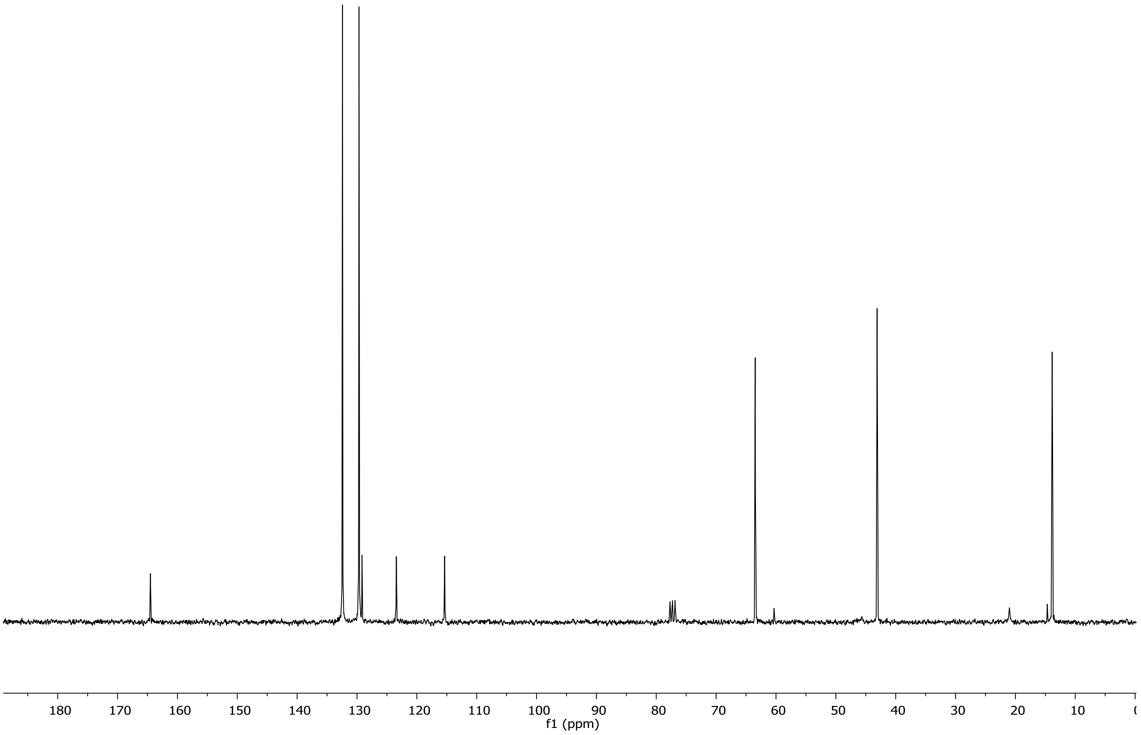

Me
CO2Bn
CN

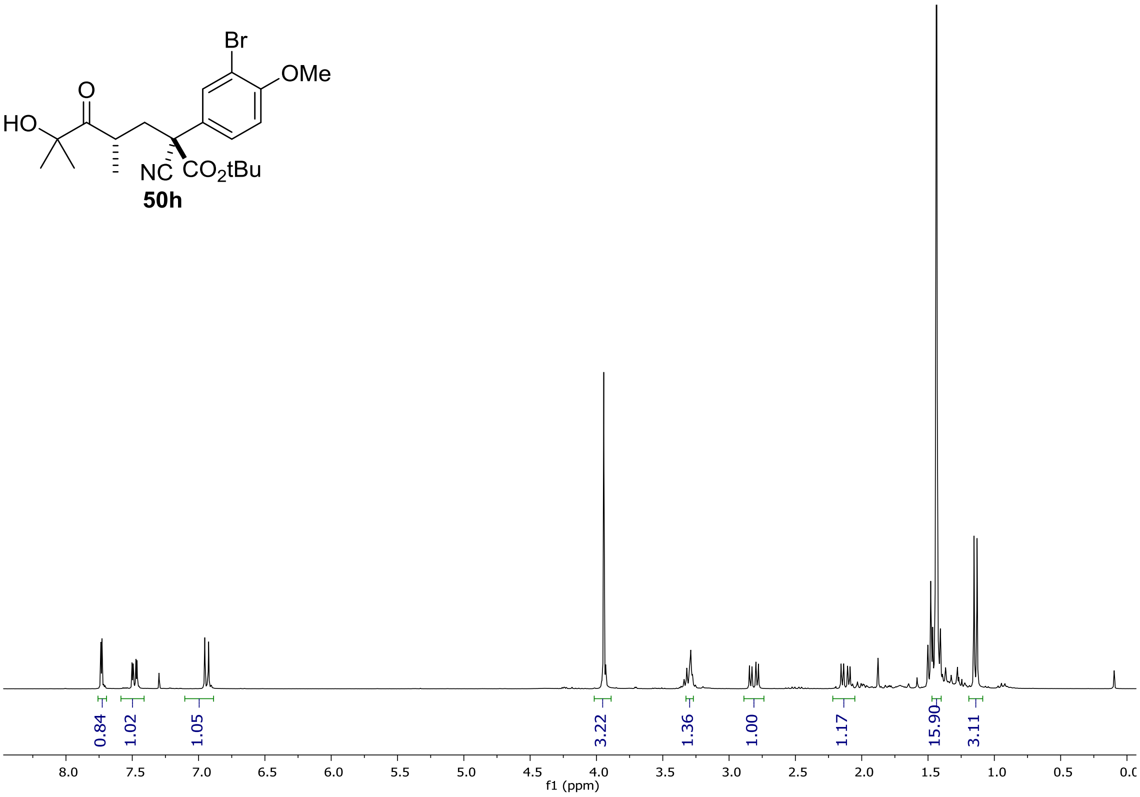
48e


8.28
2.00
0.81
3.33
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

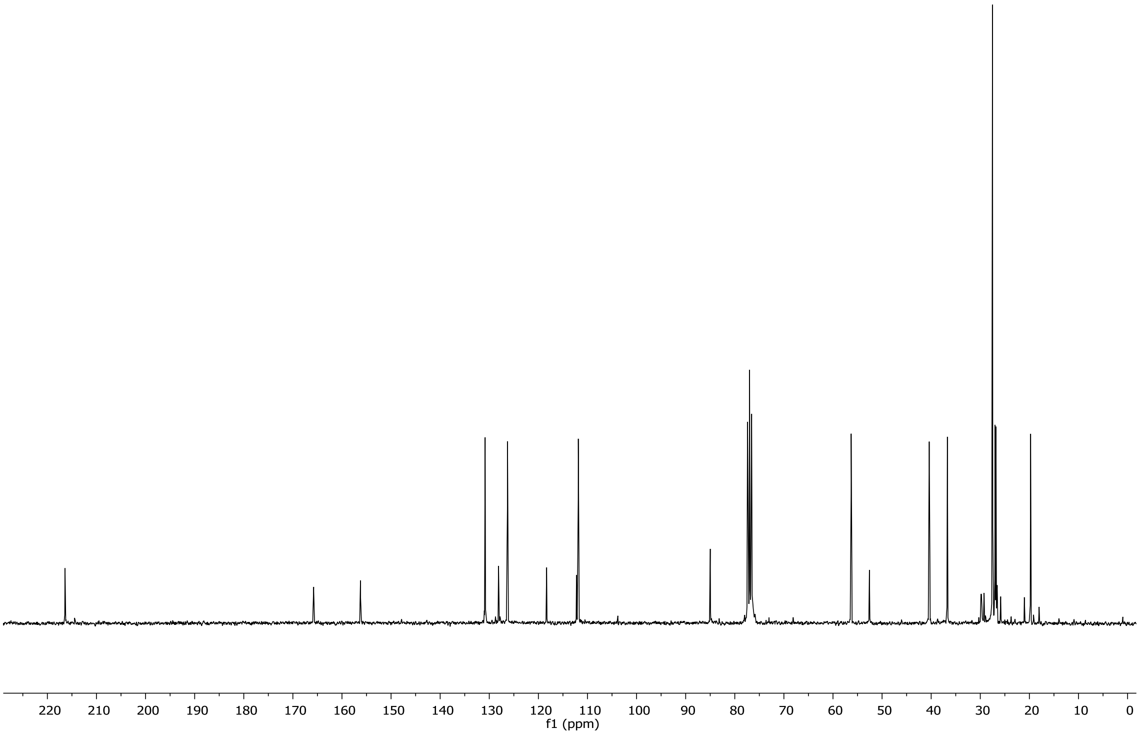

49b
Br
CO2Et
CN
3.93
0.85
2.00
3.26
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

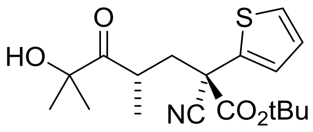

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Br
OMe
O
HO
NC
CO2tBu

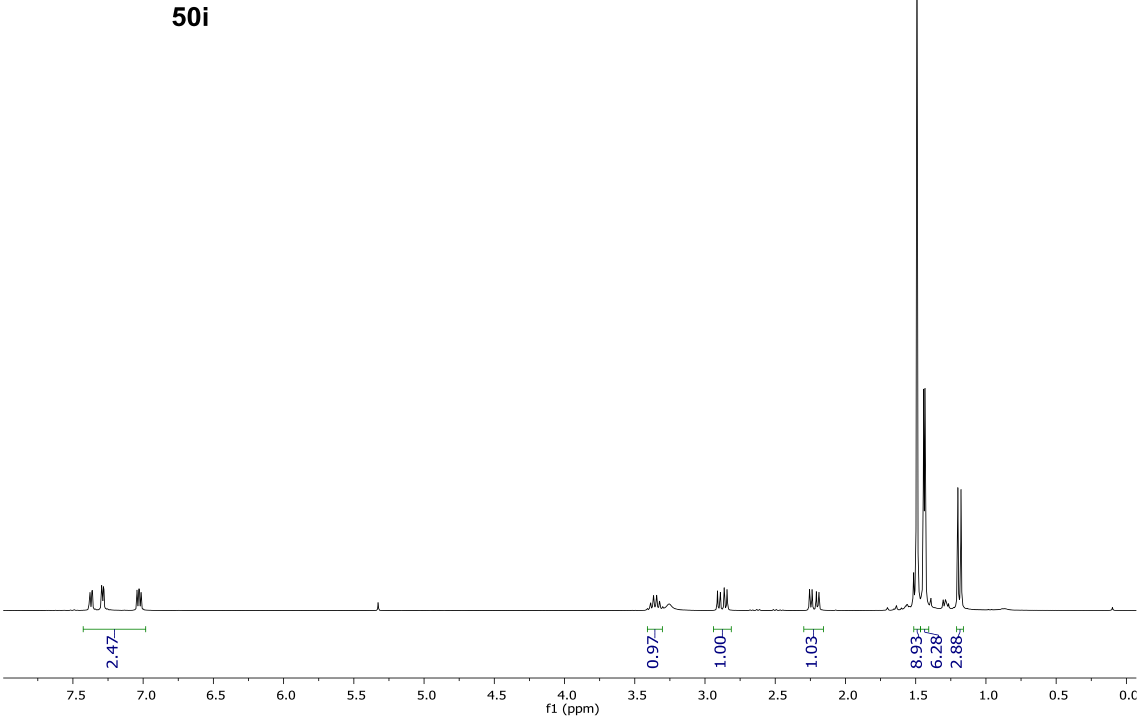
50h

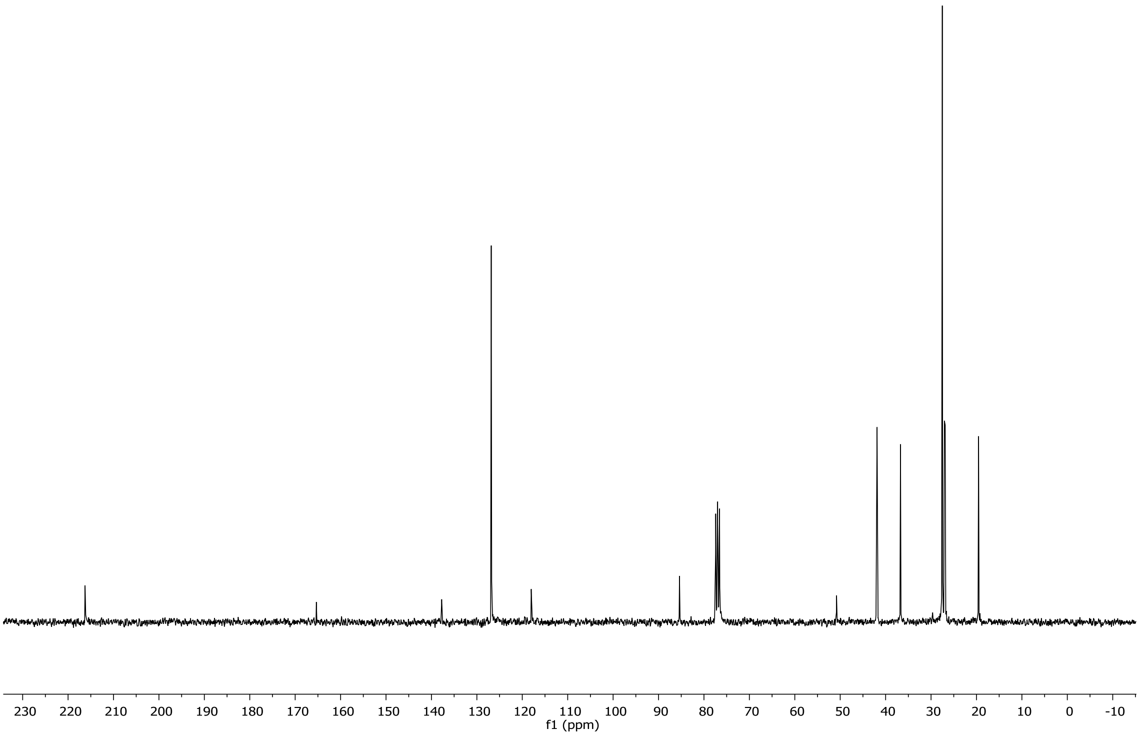
0.84
1.02
1.05
3.22
1.36
1.00
1.17
15.90
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

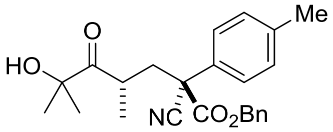

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
S
HO
NC
CO2tBu

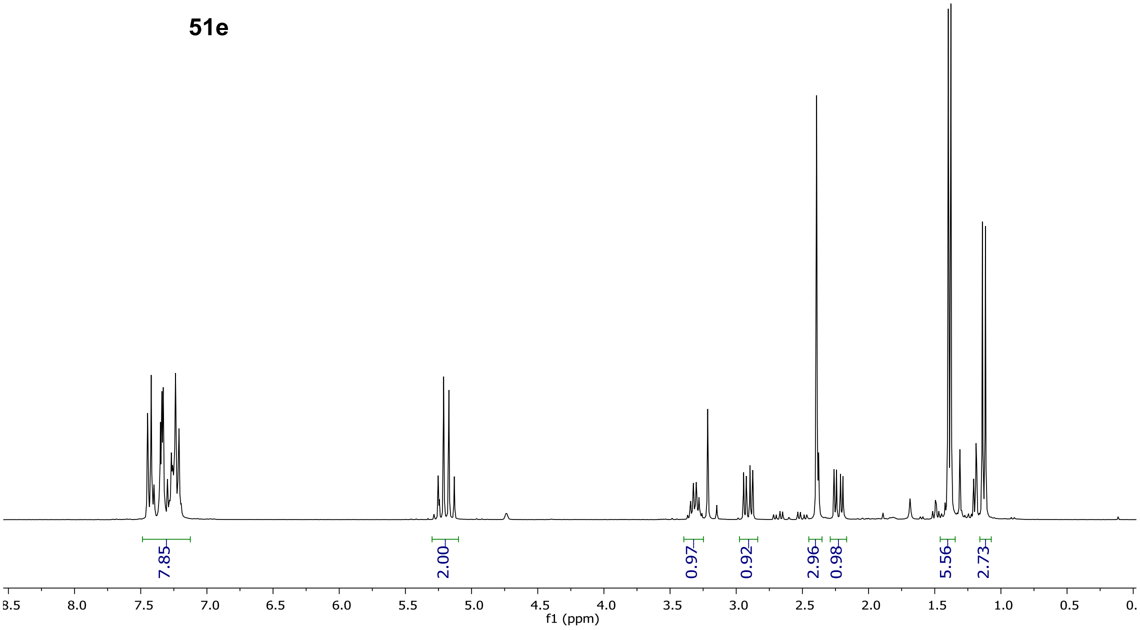
50i

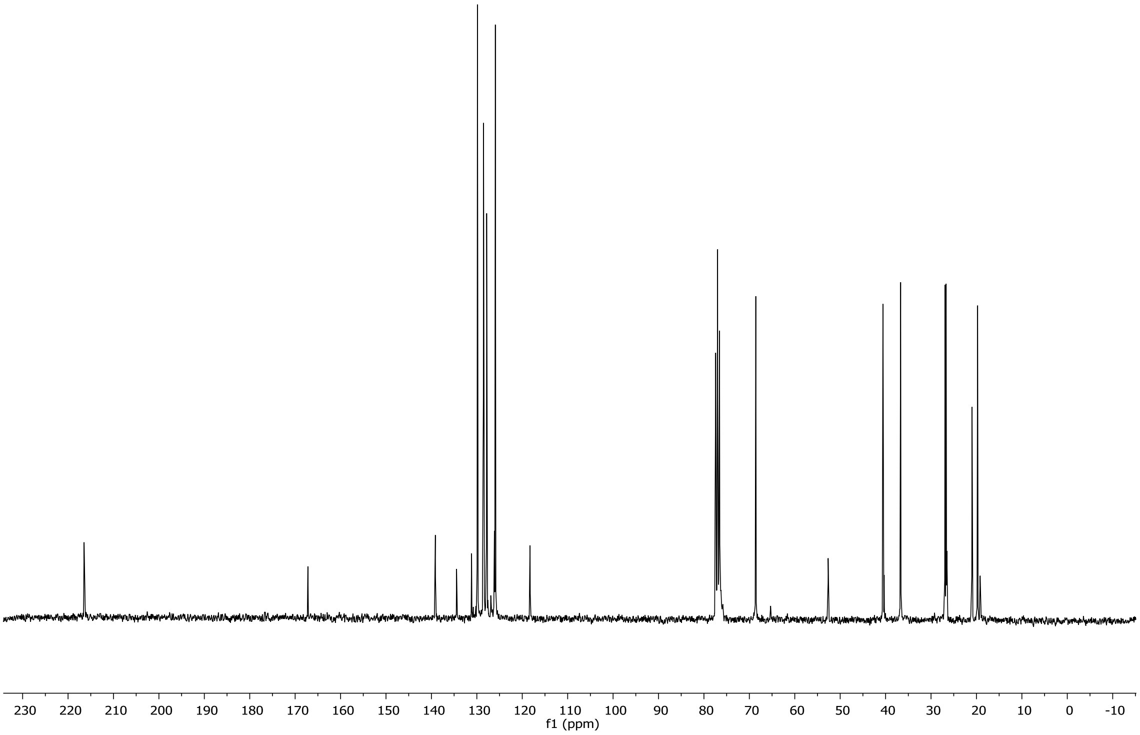

2.47
0.97
1.00
1.03
8.93
6.28
2.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

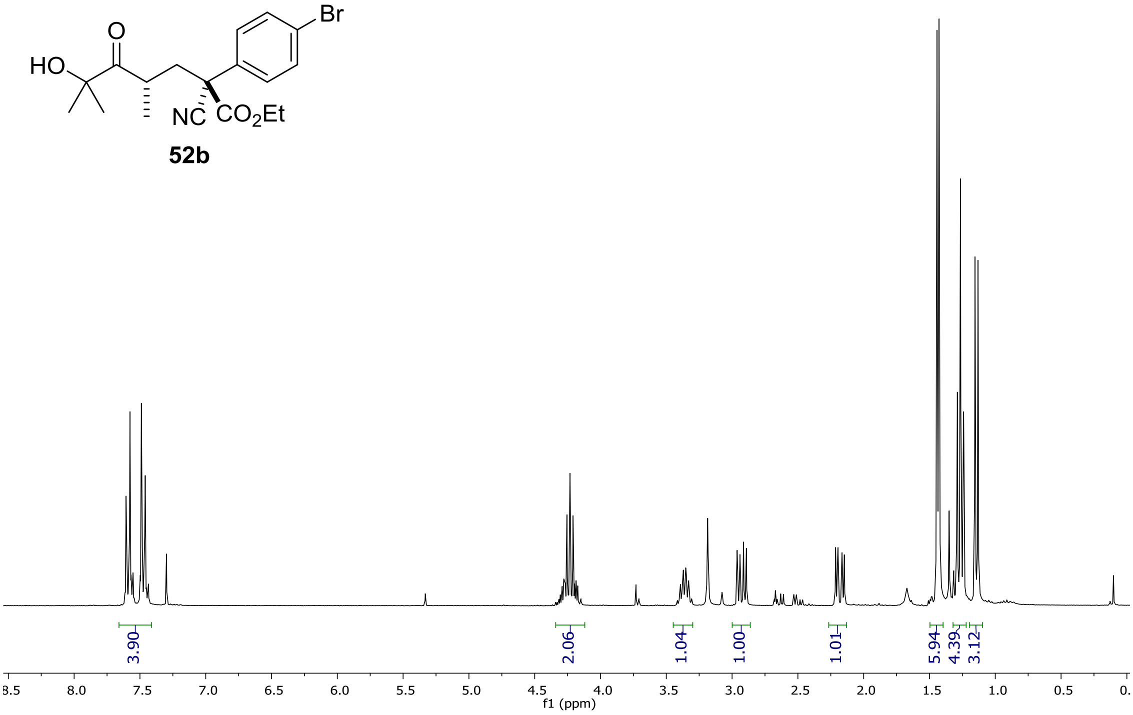

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

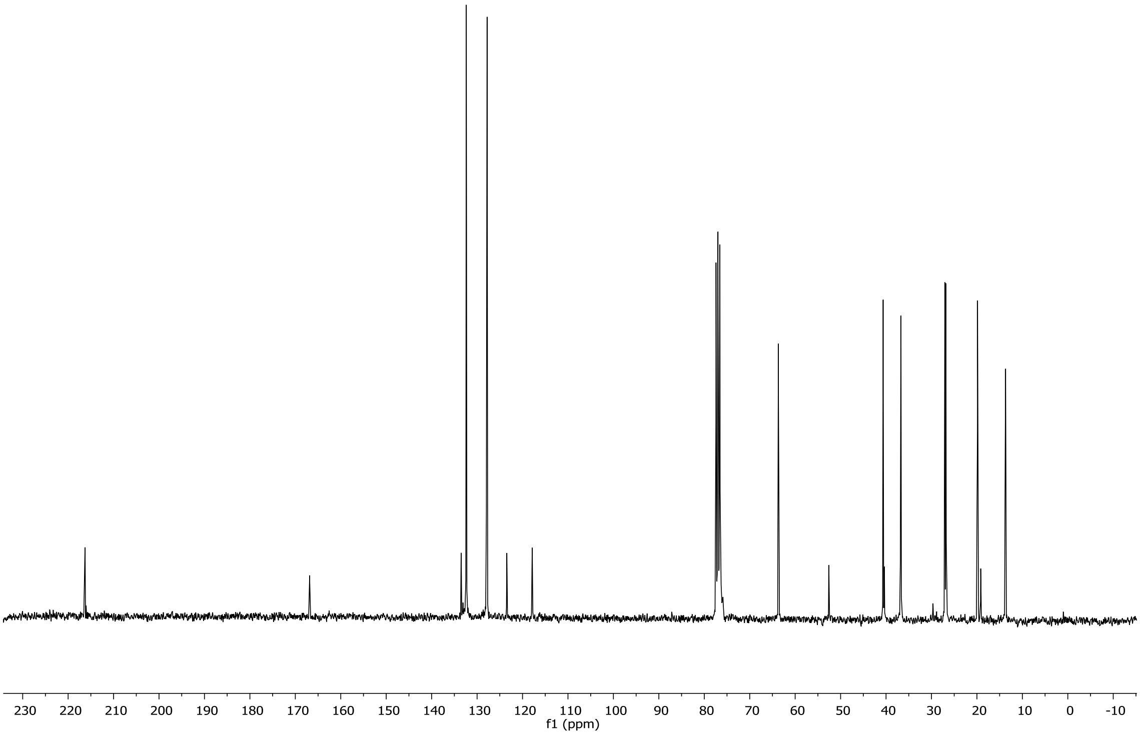

Me
O
HO
NC
CO2Bn

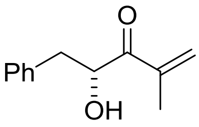
51e


7.85
2.00
0.97
0.92
2.96
0.98
5.56
2.73
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)

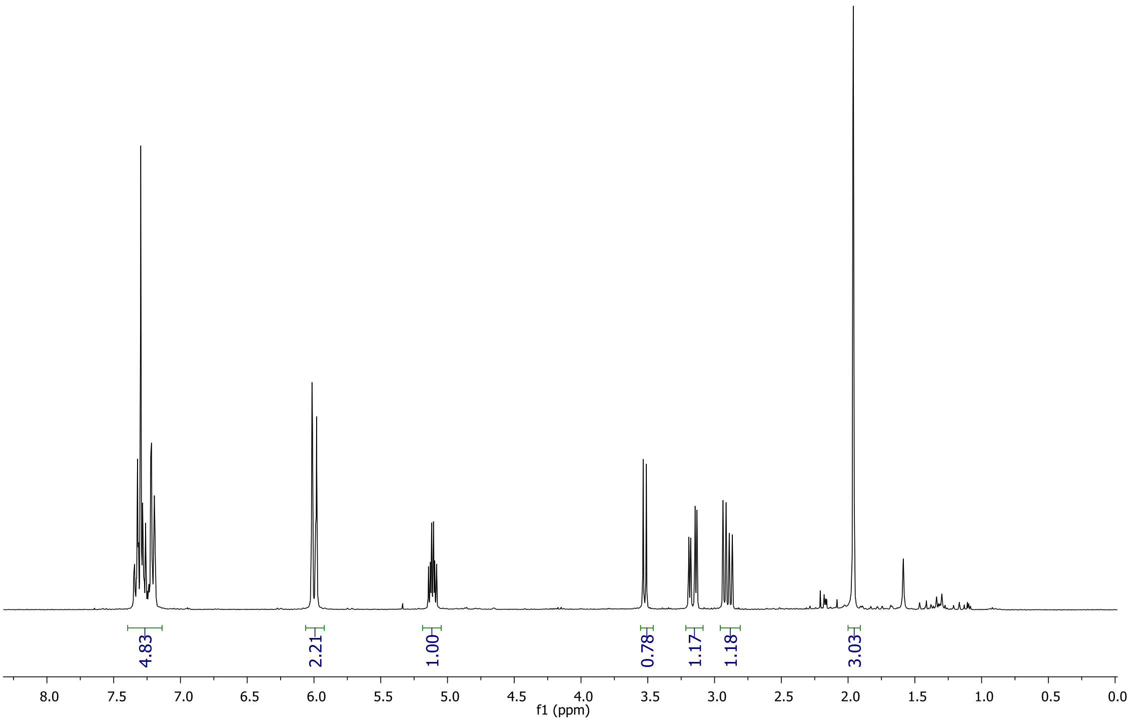

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

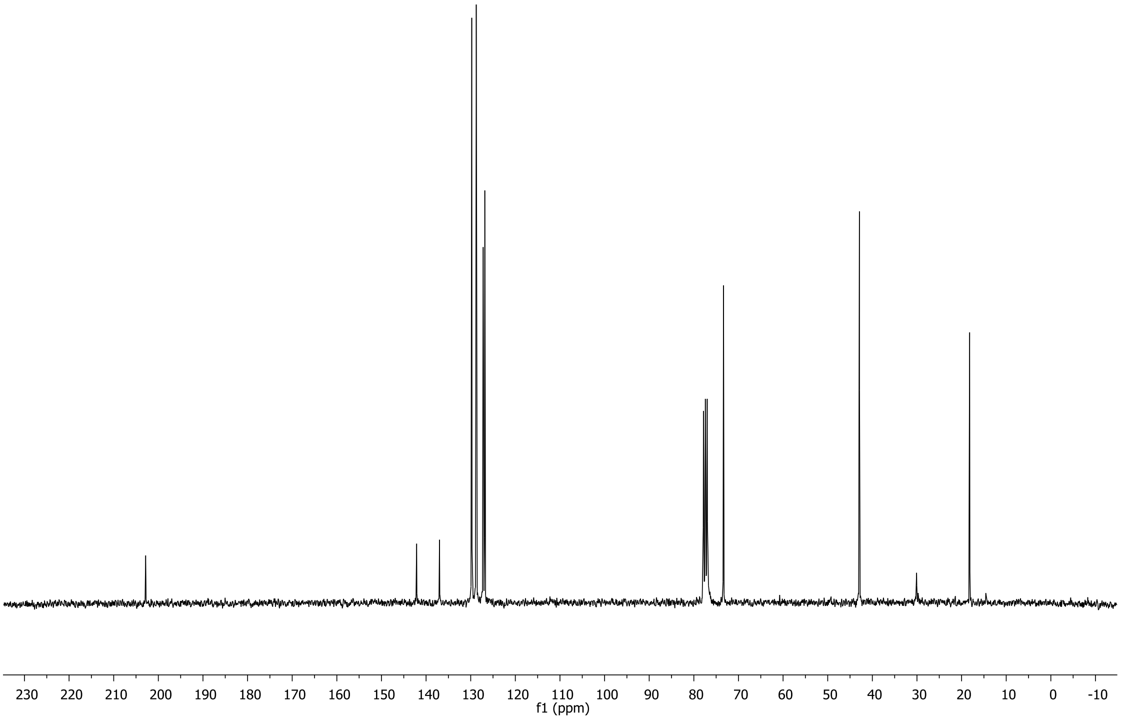

HO
O
Br
NC
CO2Et
52b
3.90
2.06
1.04
1.00
1.01
5.94
4.39
3.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

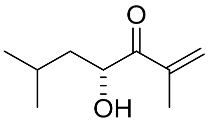

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



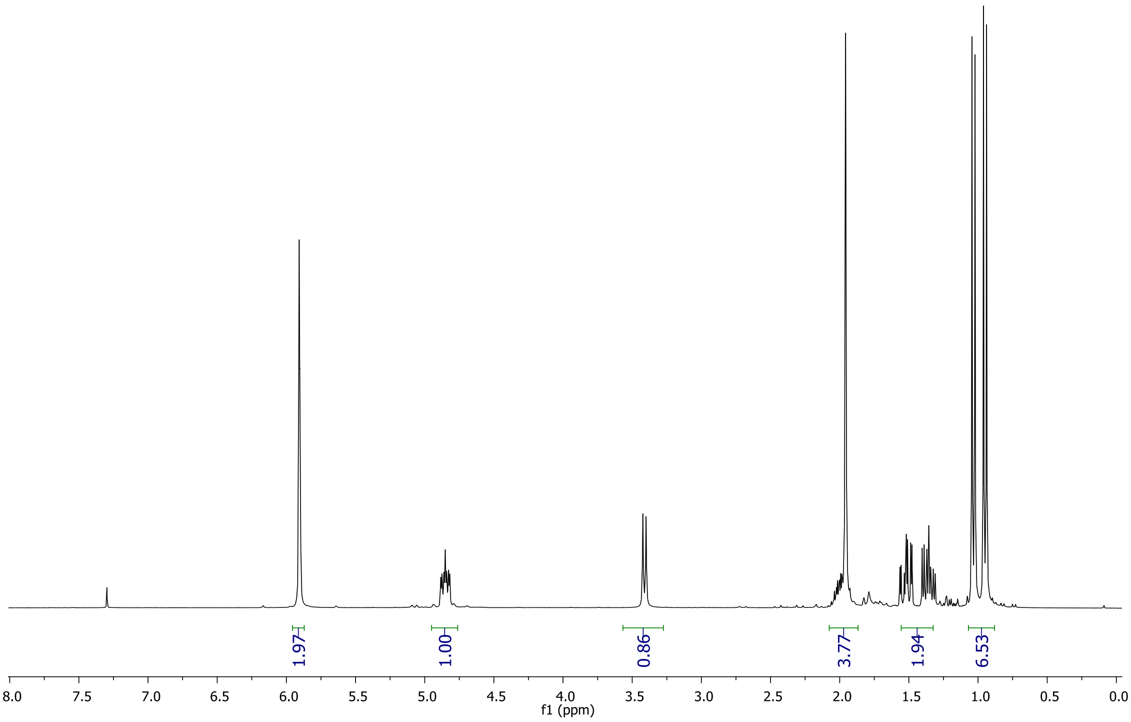
53

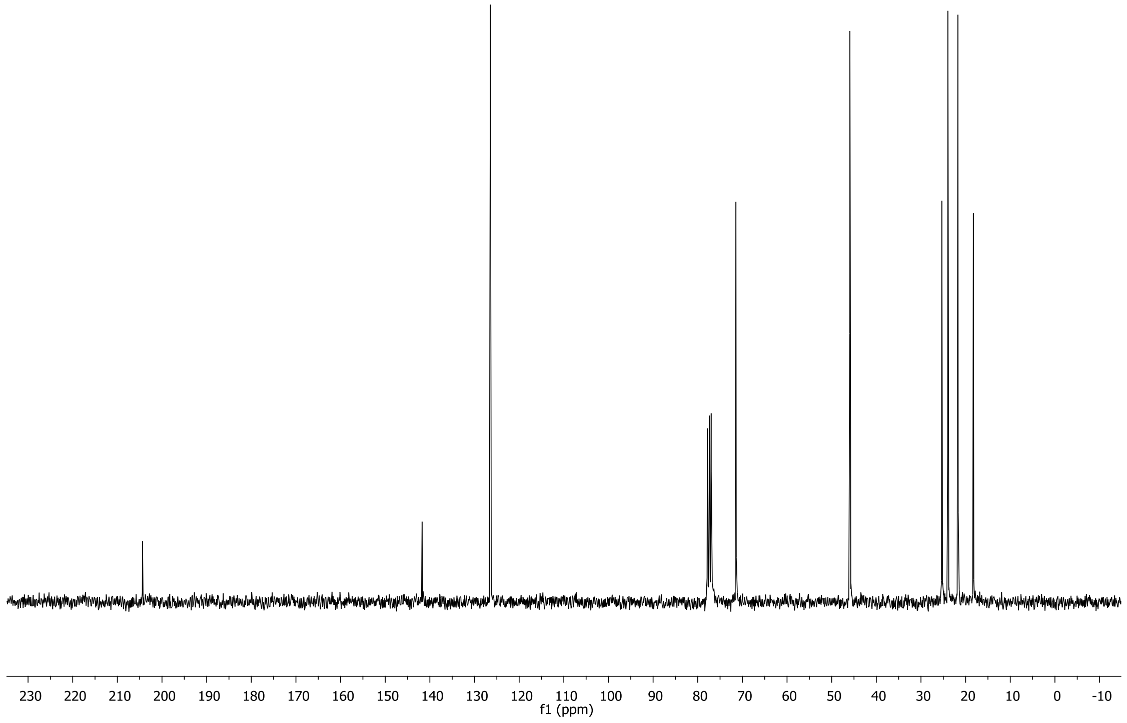

4.83
2.21
1.00
0.78
1.17
1.18
3.03
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

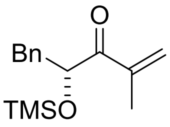

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OH

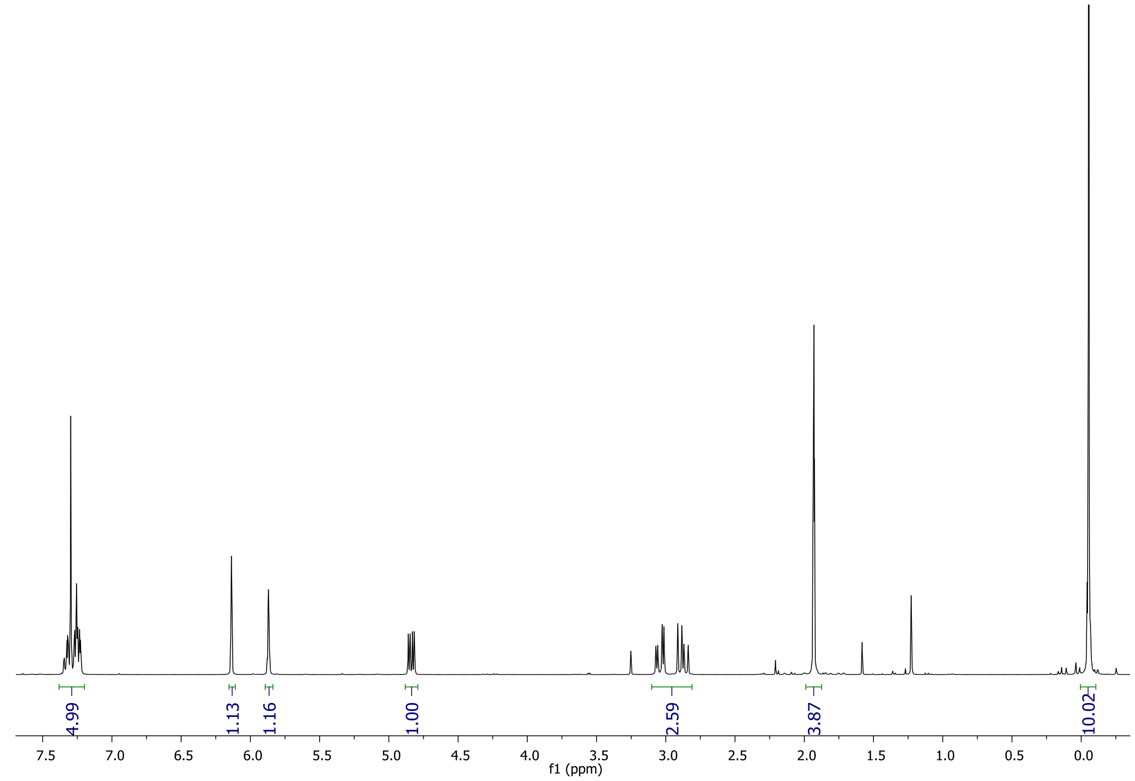
54

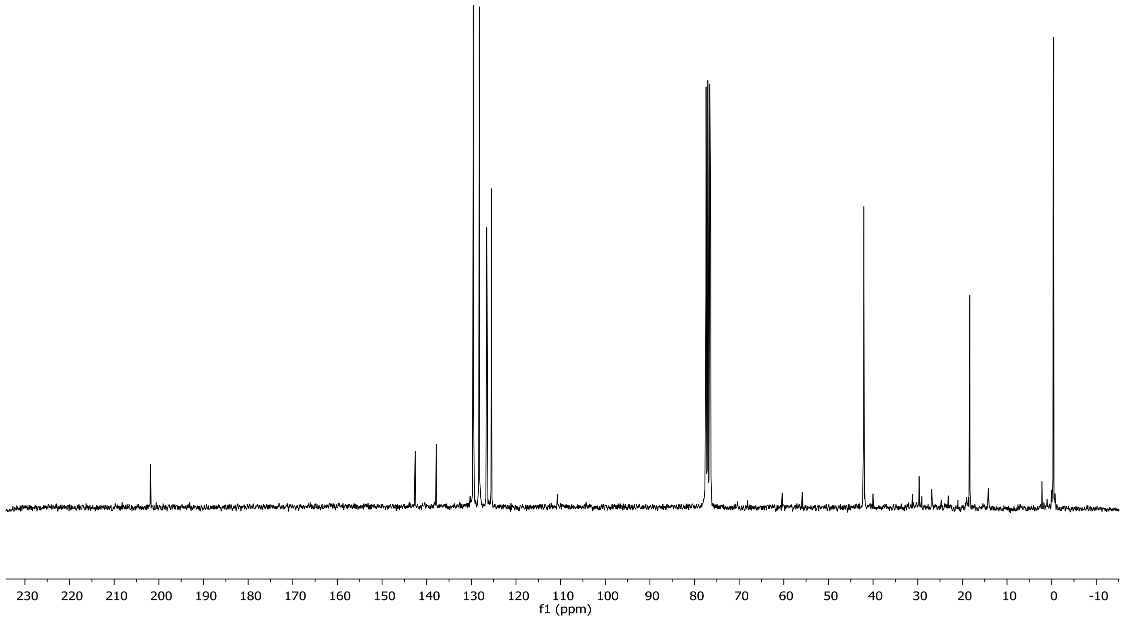

1.97
1.00
0.86
3.77
1.94
6.53
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

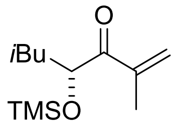

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
Bn
TMSO

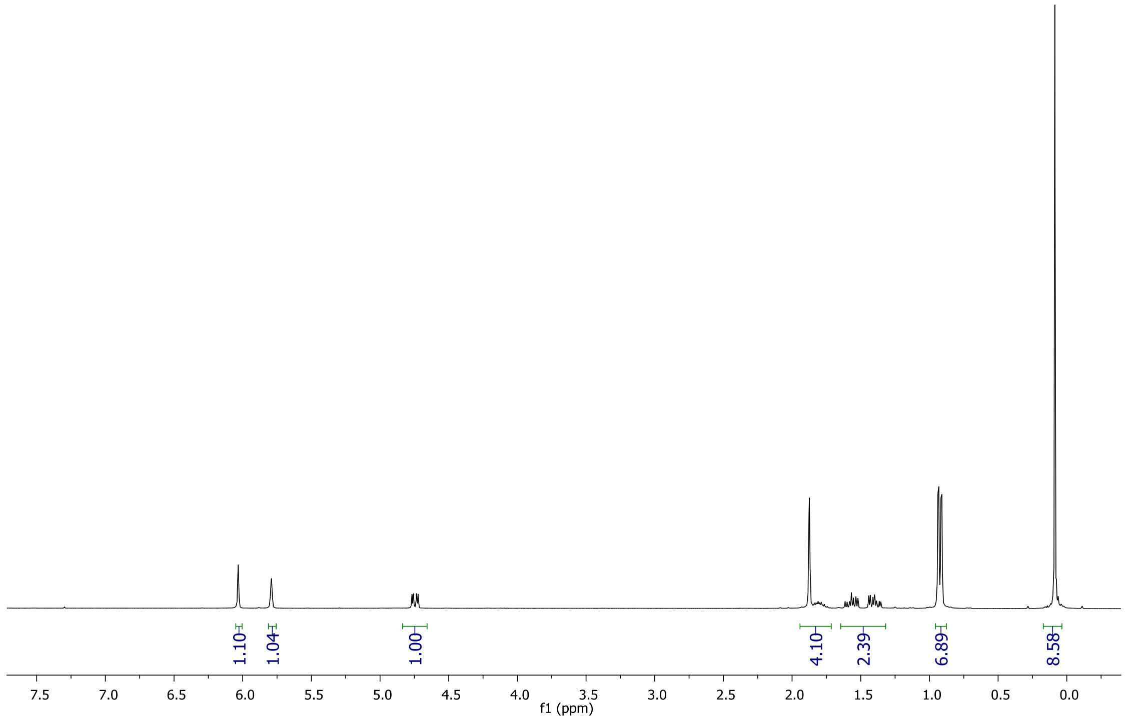
55

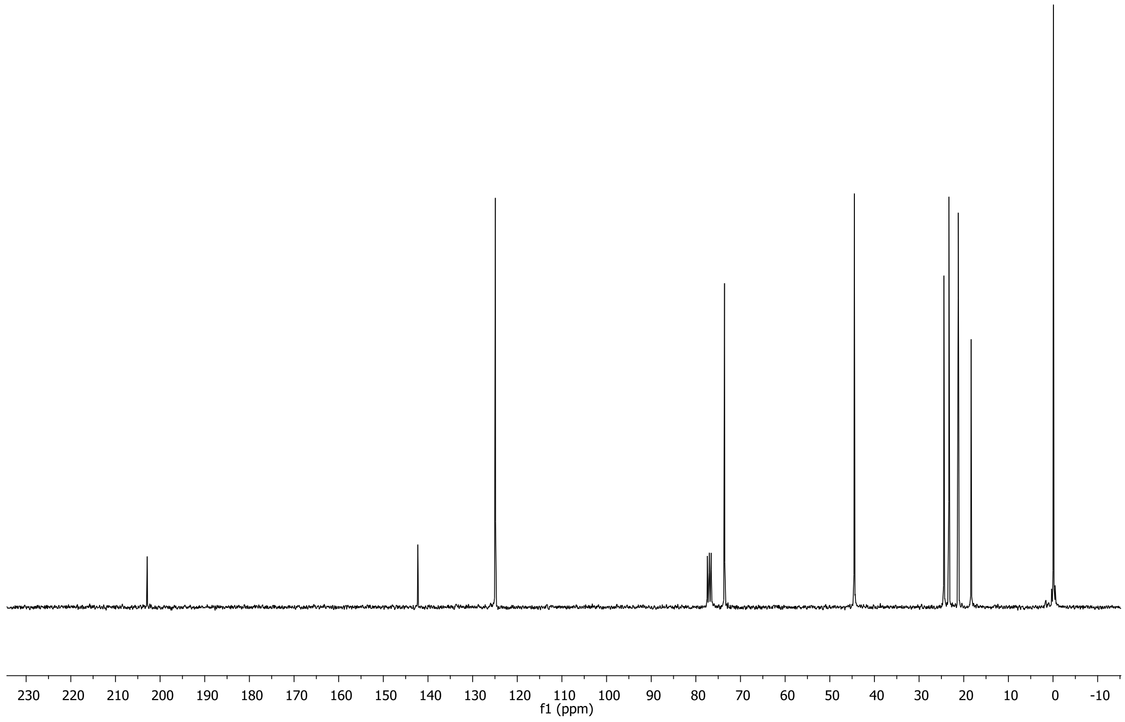

4.99
1.13
1.16
1.00
2.59
3.87
10.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

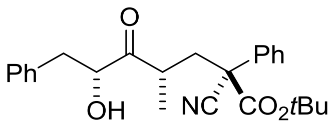

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
iBu
TMSO

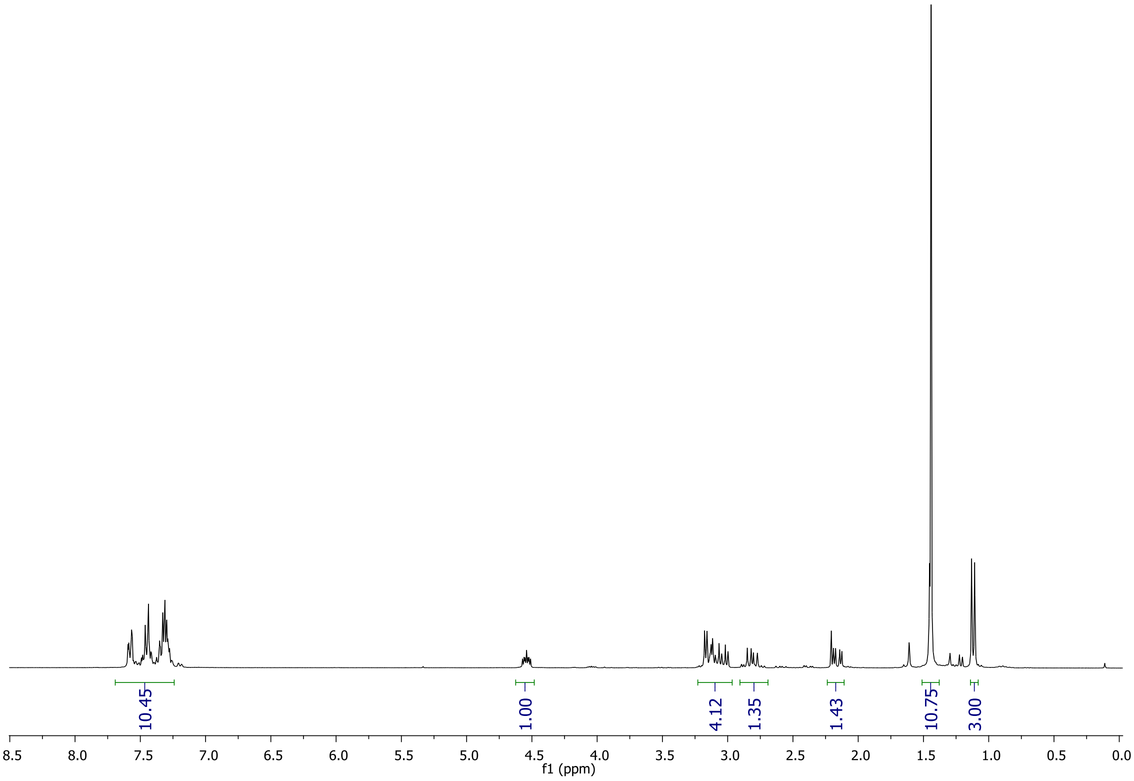
56

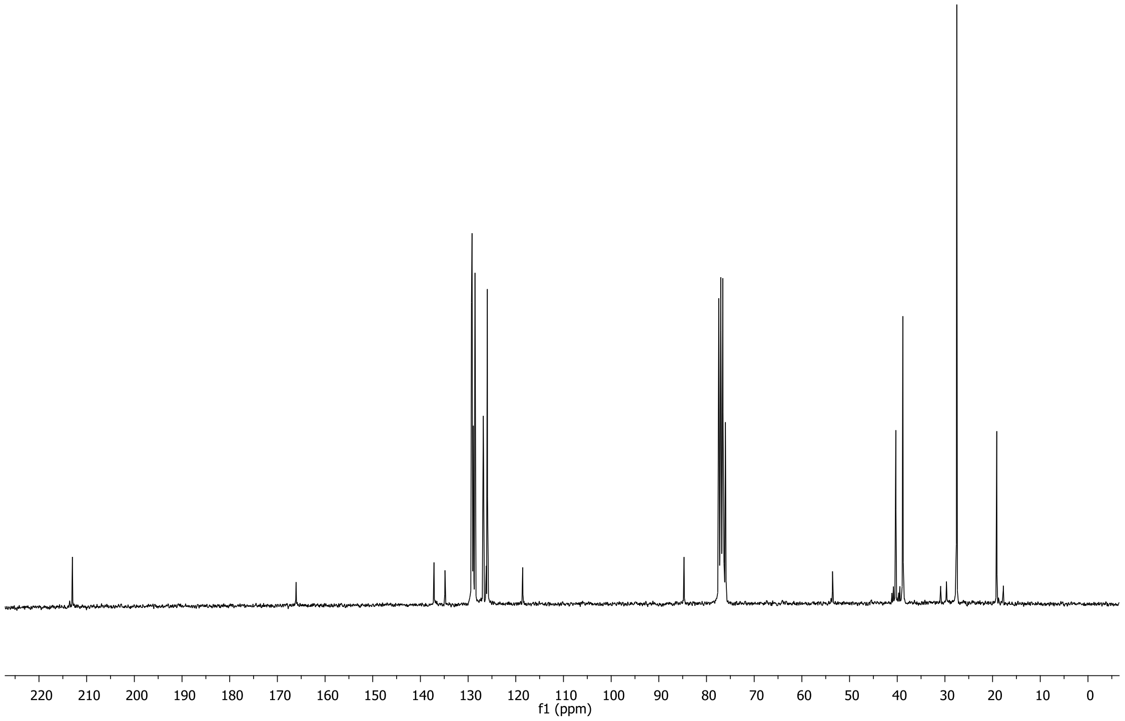

1.10
1.04
1.00
4.10
2.39
6.89
8.58
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

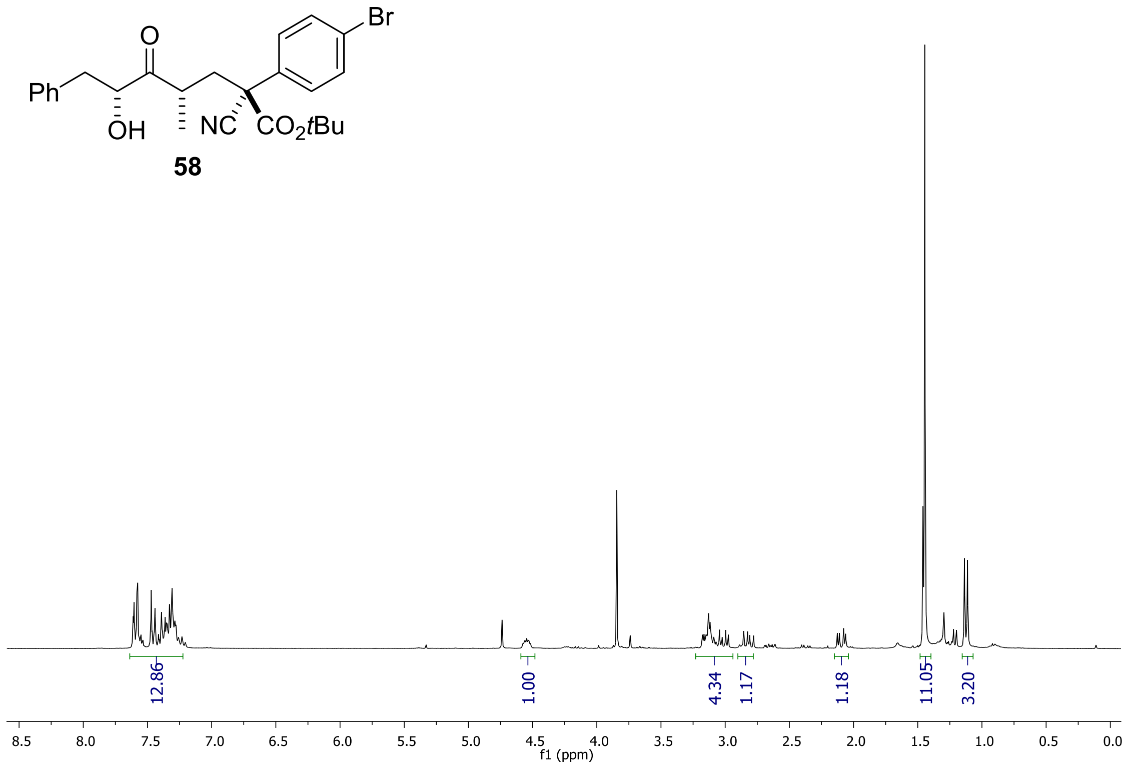

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

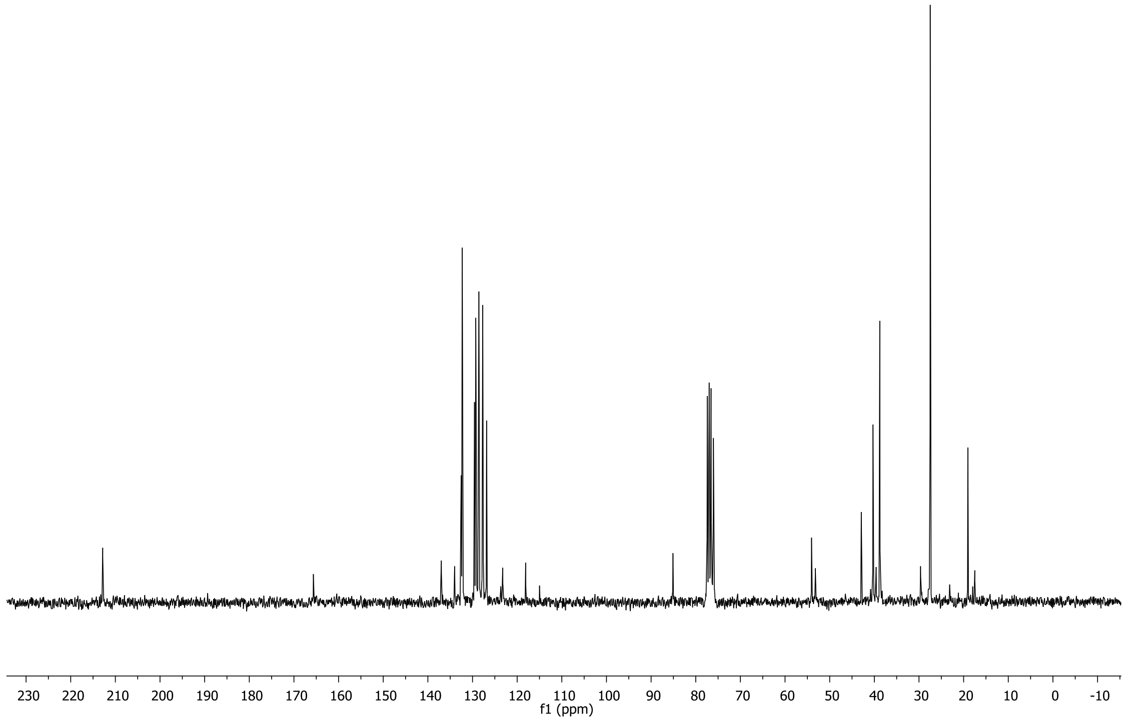

Ph
O
Ph
OH
NC
CO2tBu

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)

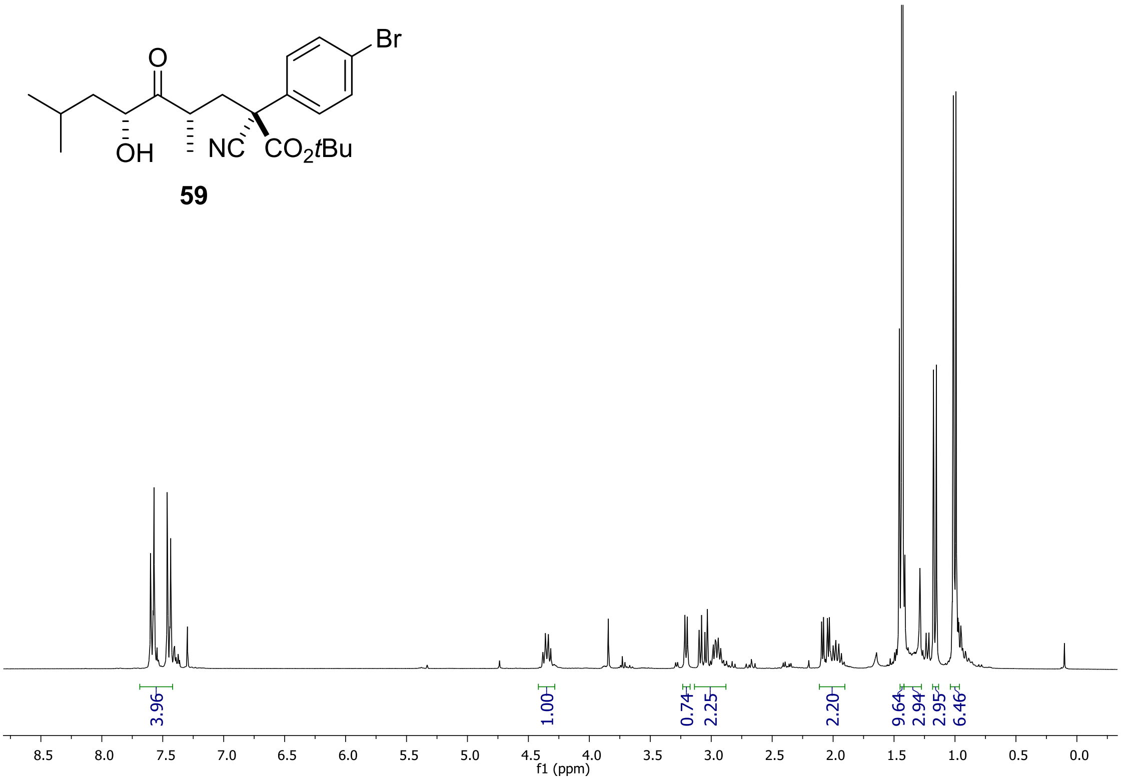

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

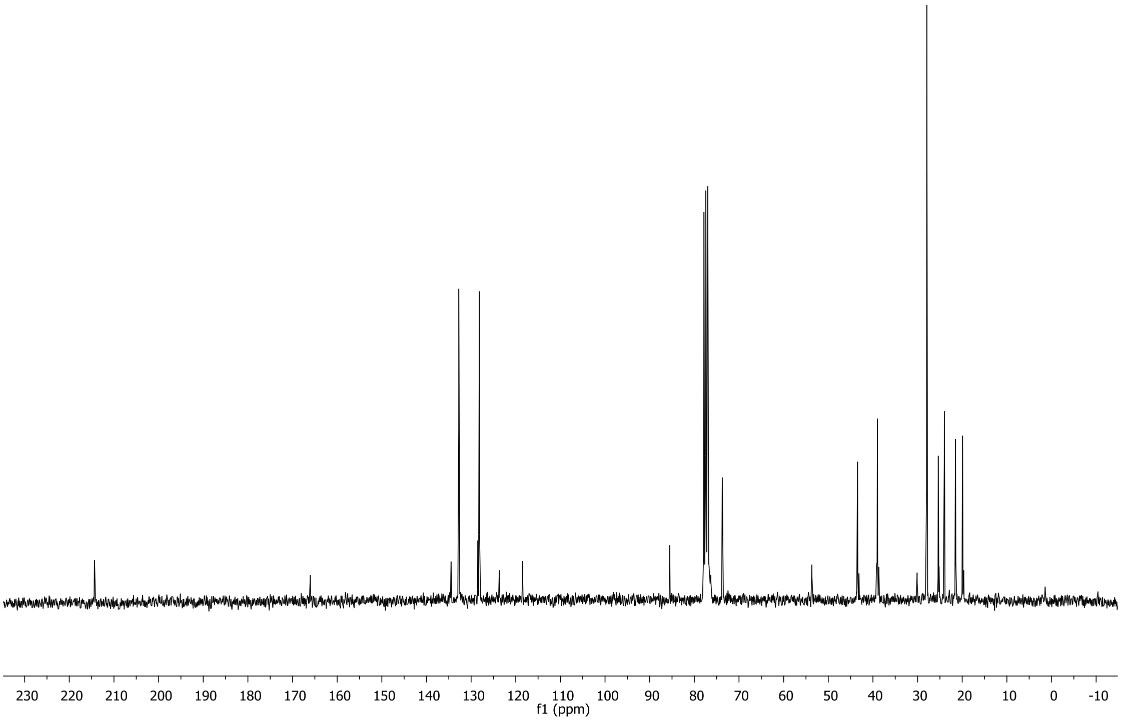

Br
O
Ph
OH
NC
CO2tBu
58
12.86
1.00
4.34
1.17
1.18
11.05
3.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


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)

Br
O
OH
NC
CO2tBu

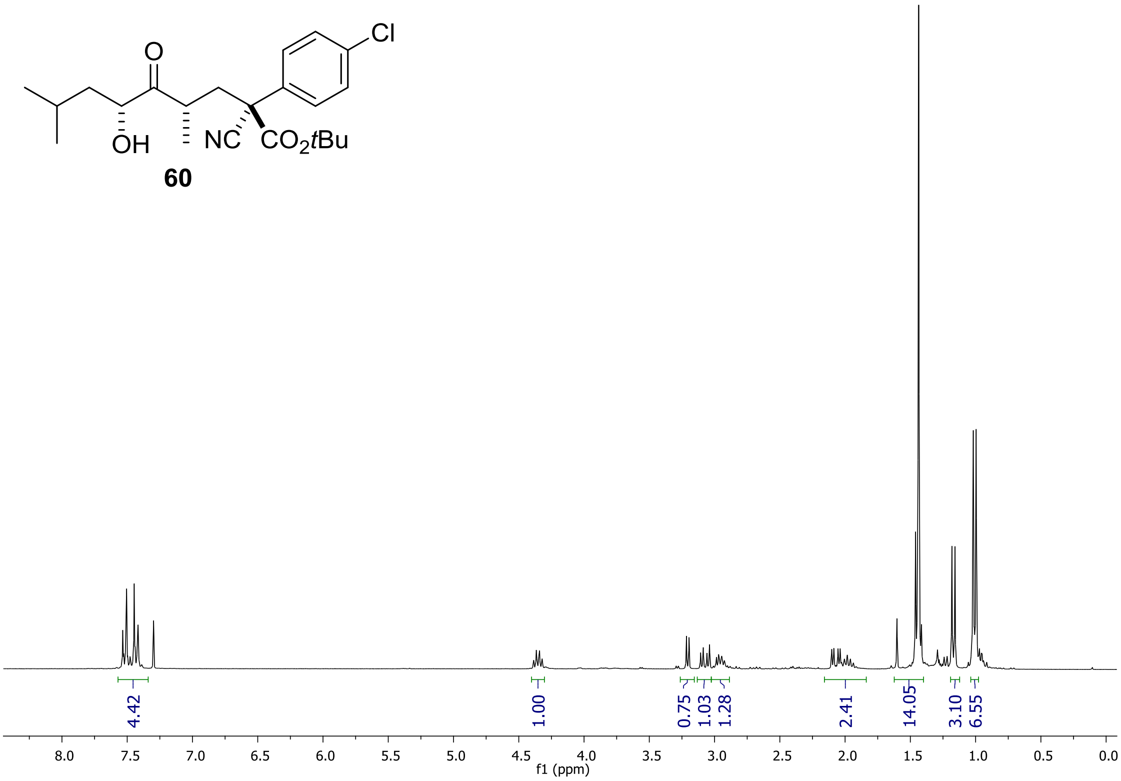
59

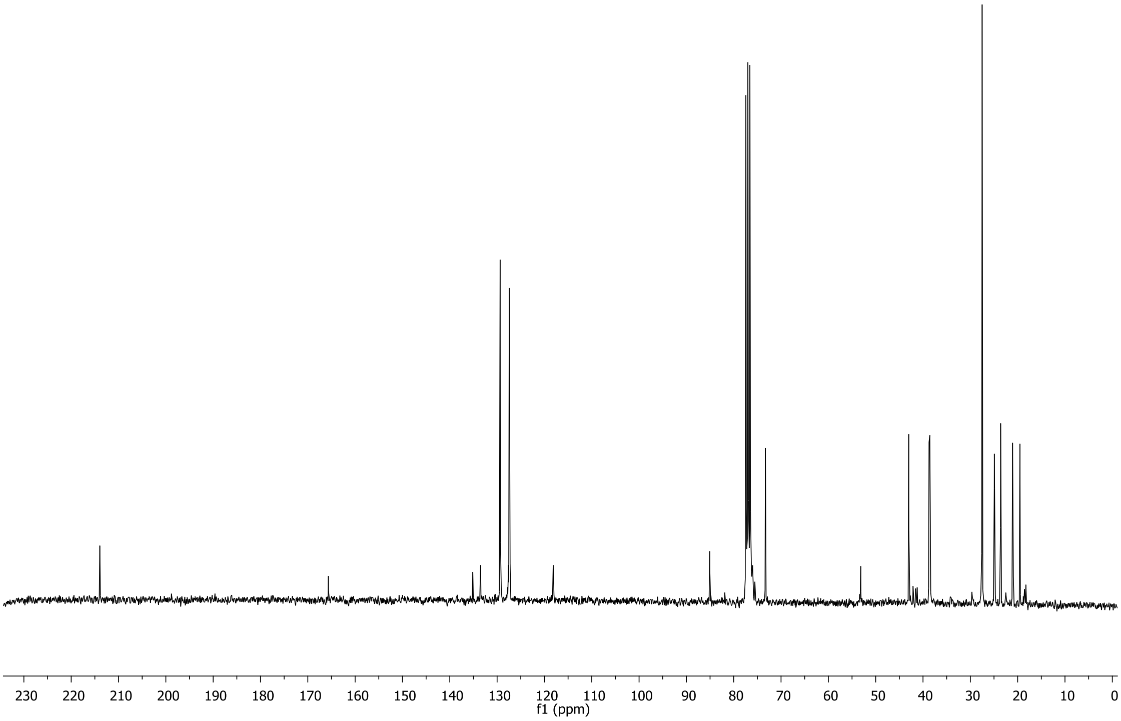

3.96
1.00
0.74
2.25
2.20
9.64
2.94
2.95
6.46
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

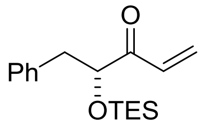

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Cl
O
OH
NC
CO2tBu

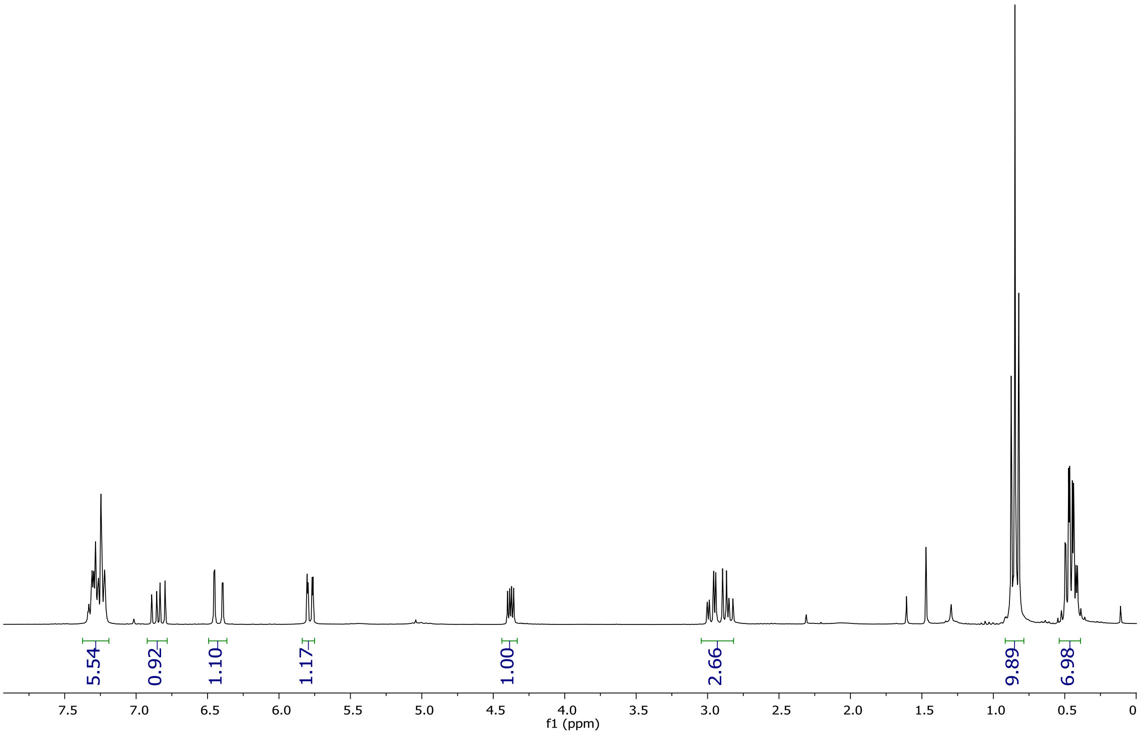
60

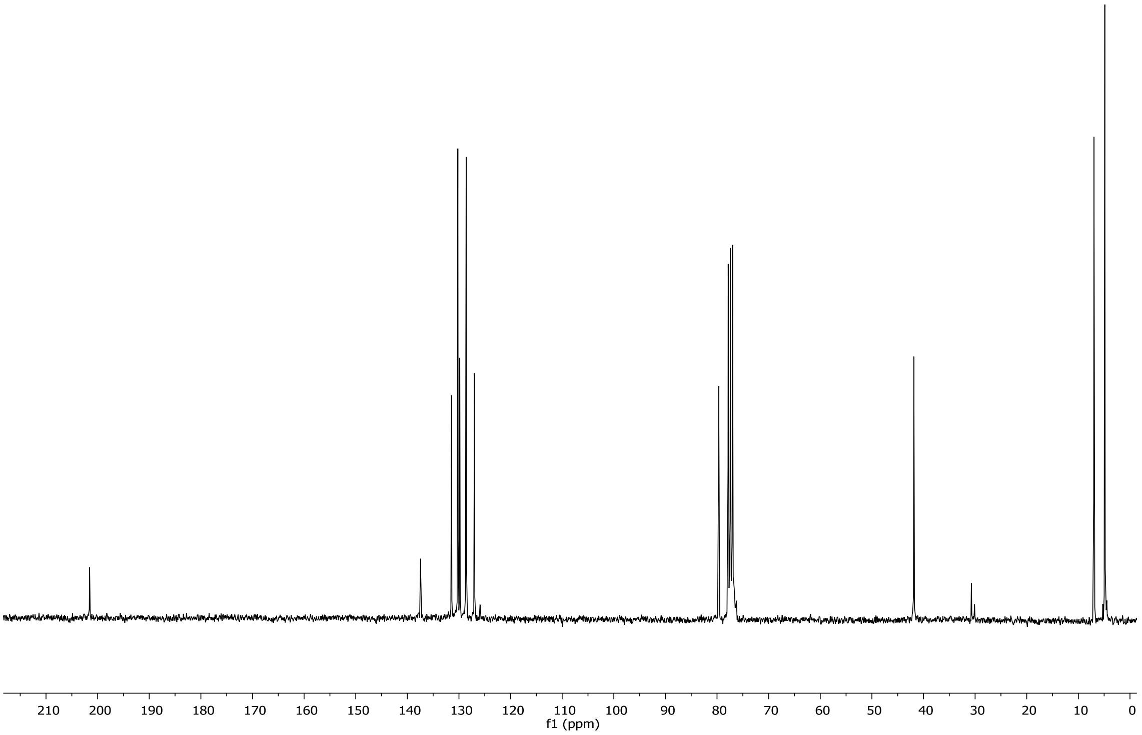

4.42
1.00
0.75
1.03
1.28
2.41
14.05
3.10
6.55
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

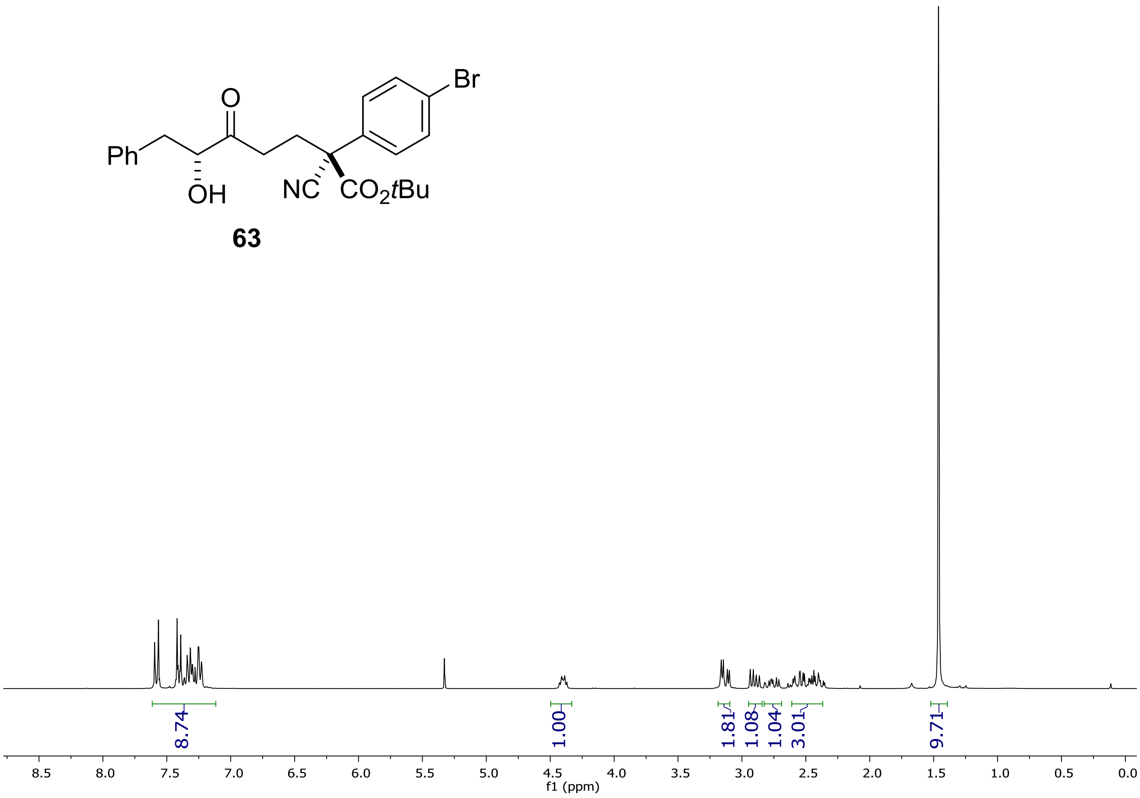

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

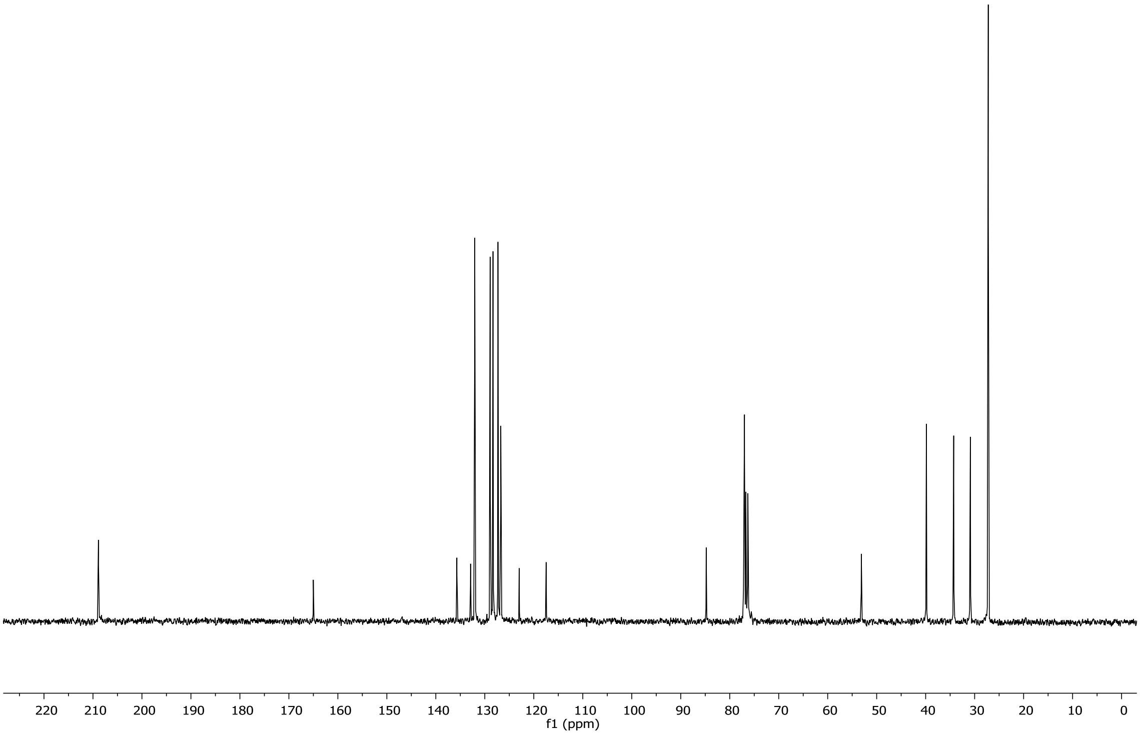

O
Ph
OTES

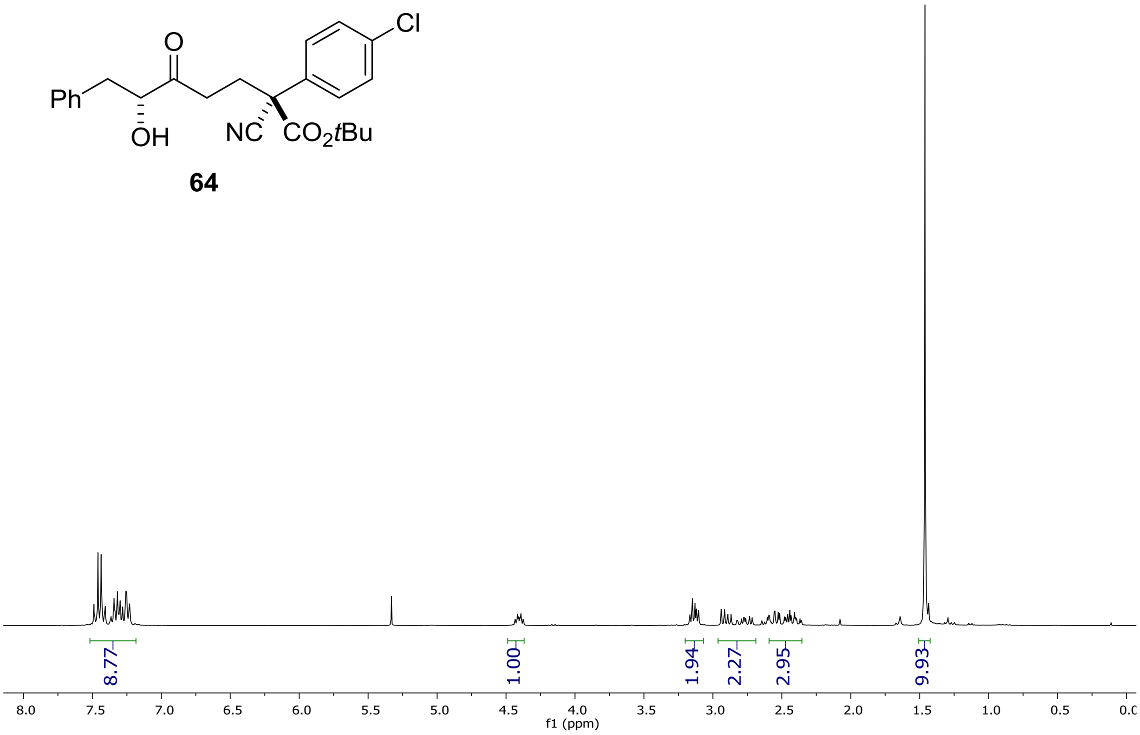
62

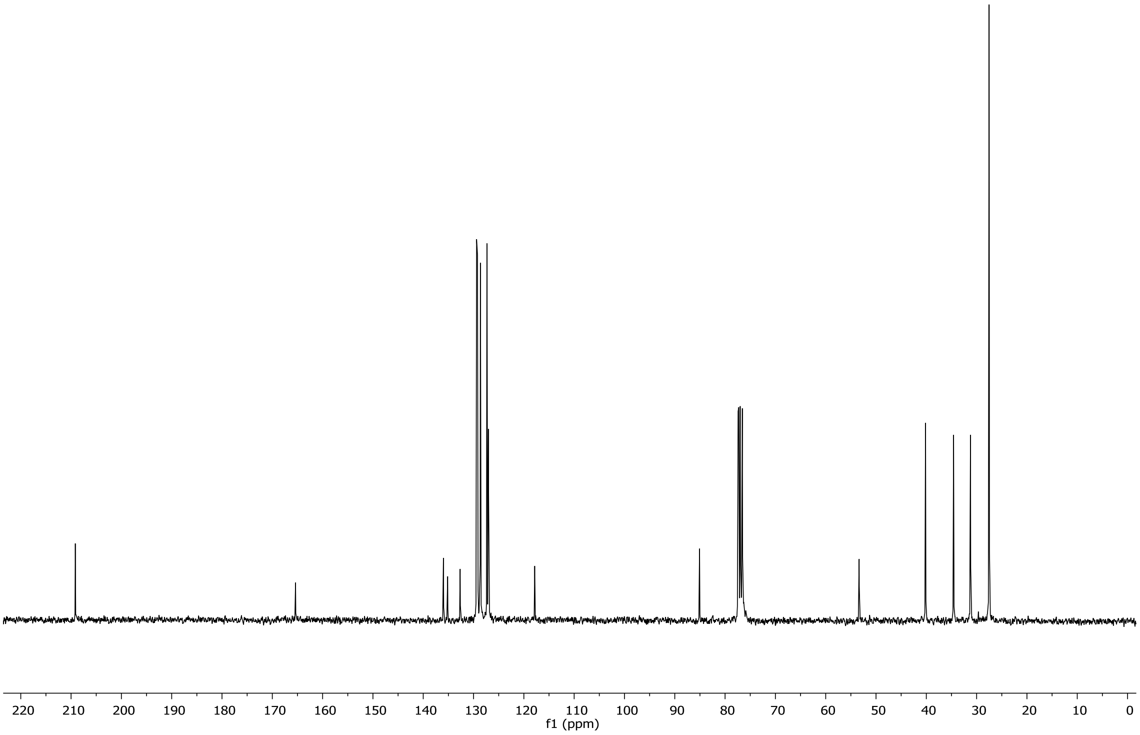

5.54
0.92
1.10
1.17
1.00
2.66
9.89
6.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

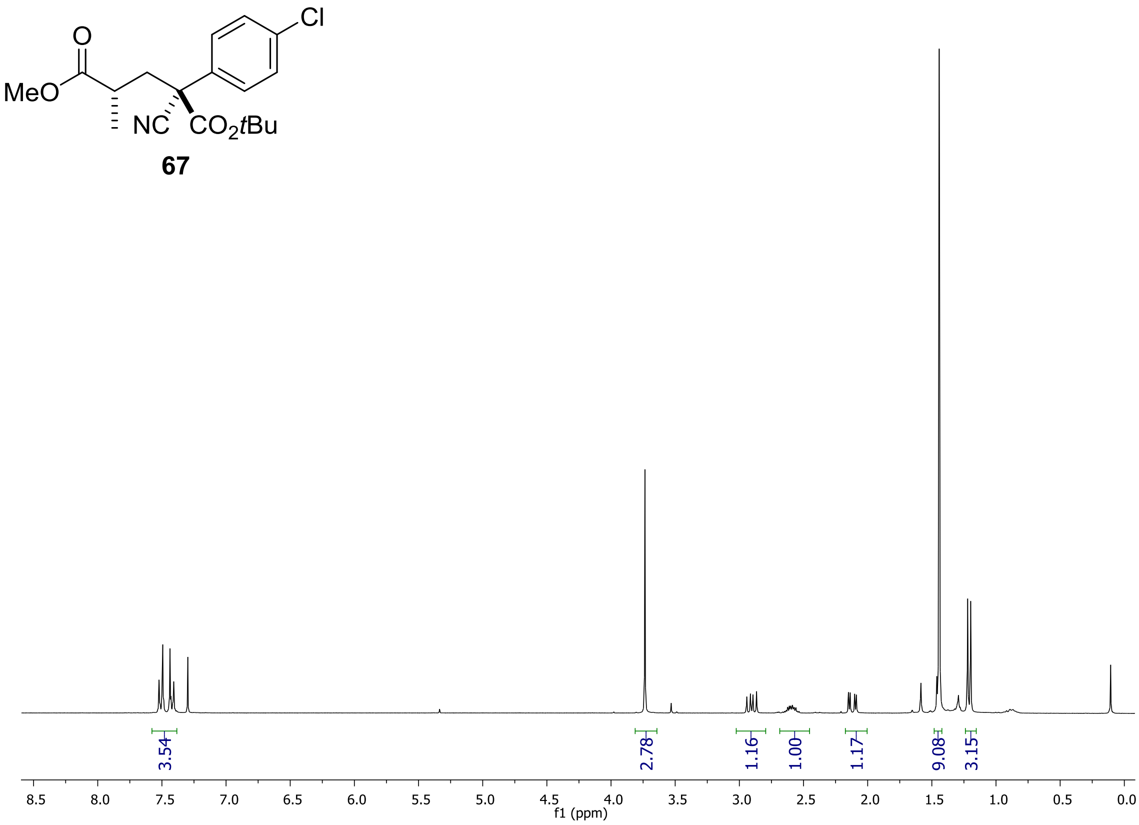

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
O
Ph
OH
NC
CO2tBu
63
8.74
1.00
1.81
1.08
1.04
3.01
9.71
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)

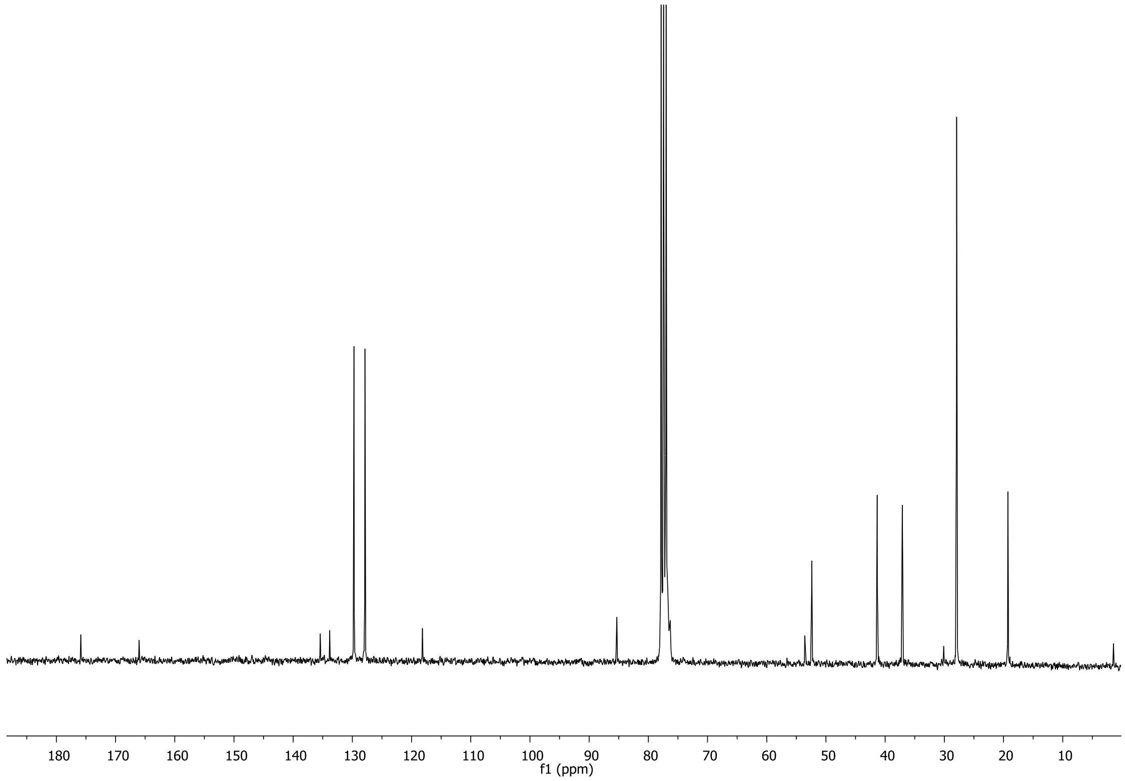

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

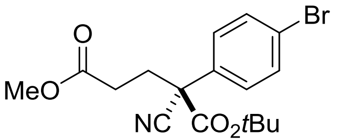

Ph
O
OH
NC
CO$_2$tBu
Cl
64
8.77
1.00
1.94
2.27
2.95
9.93
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


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)

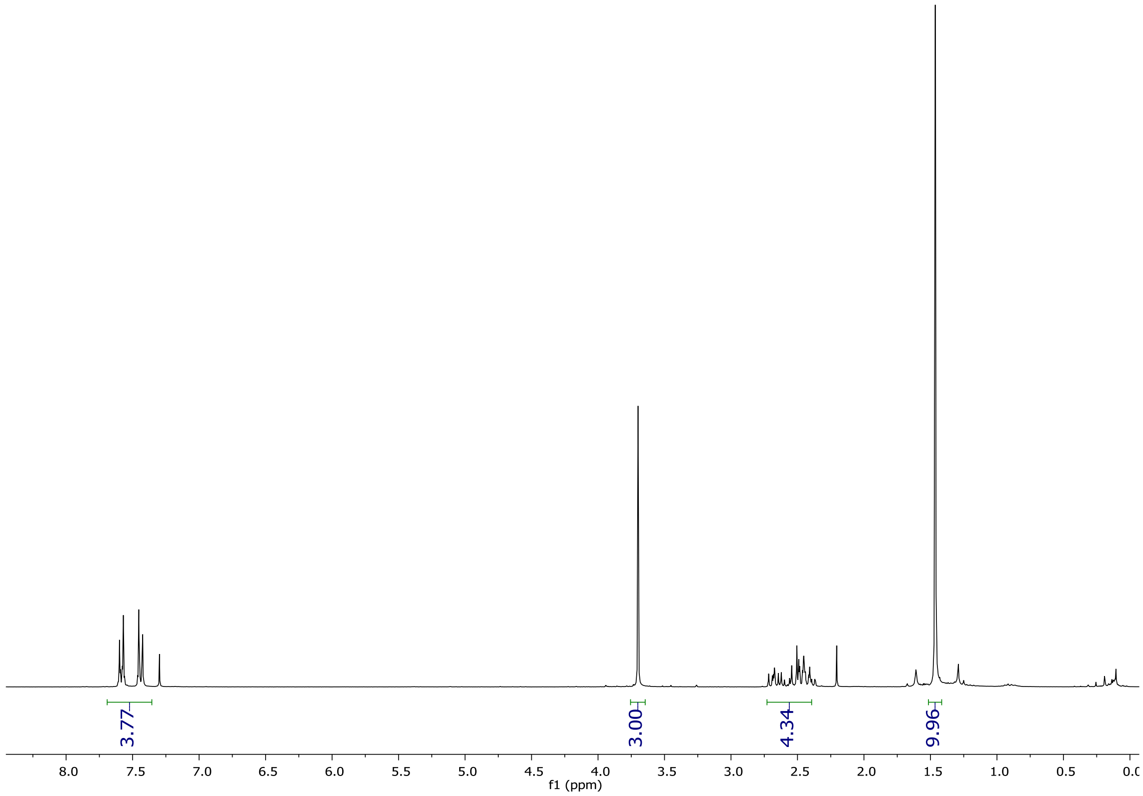

MeO
O
Cl
NC
CO2tBu
3.54
2.78
1.16
1.00
1.17
9.08
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

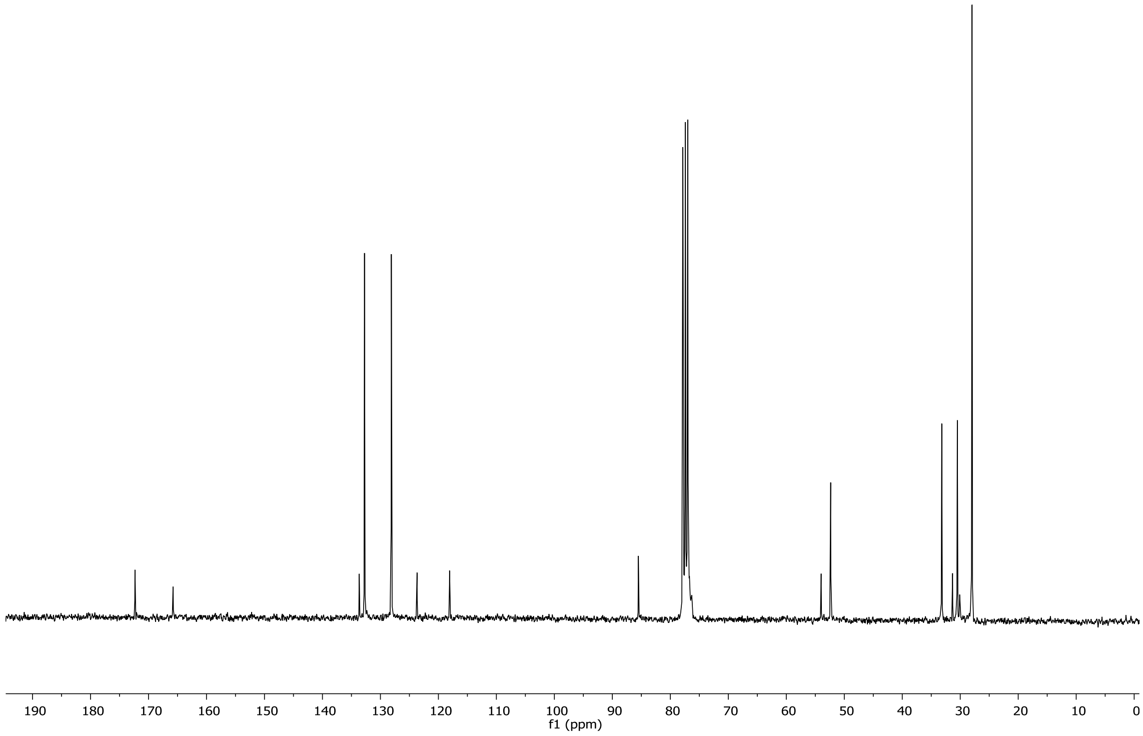
67

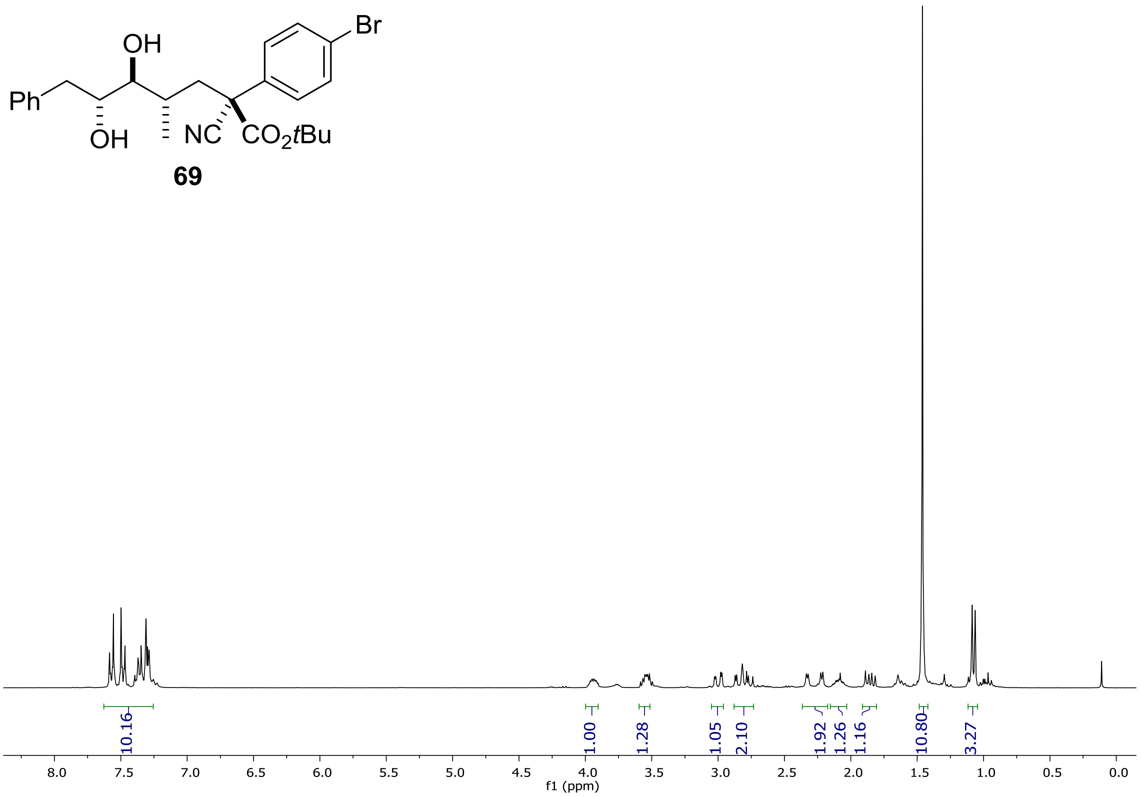

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

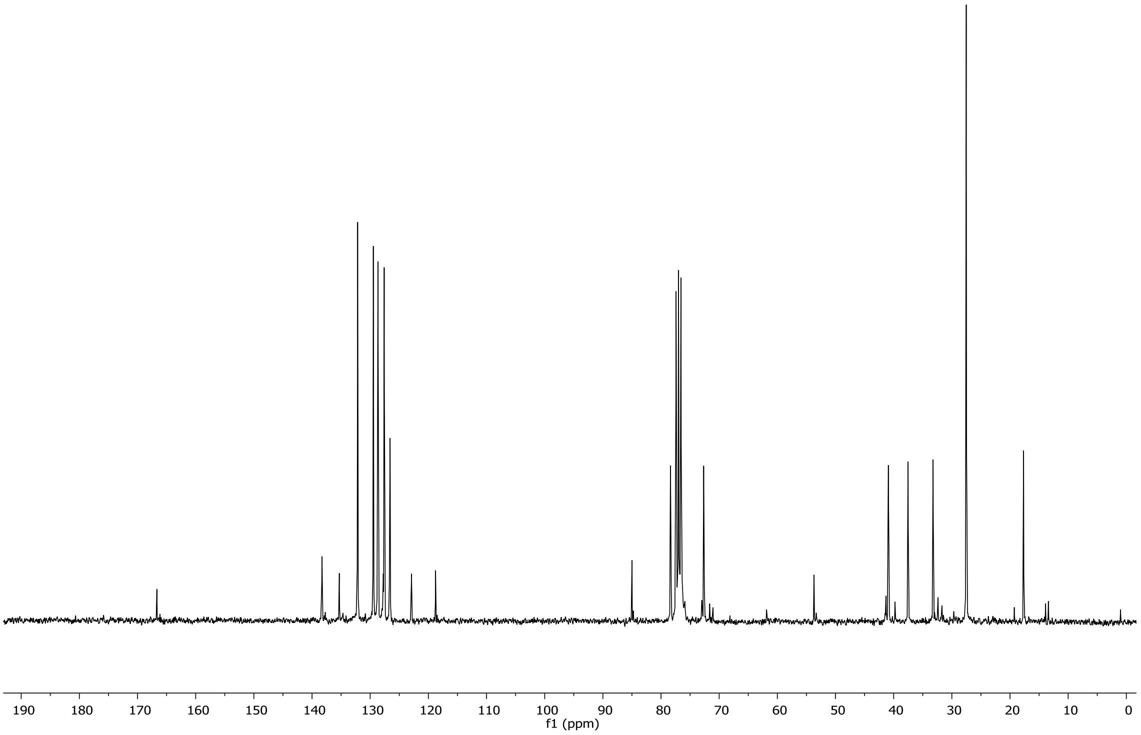

Br
O
MeO
NC
CO2tBu

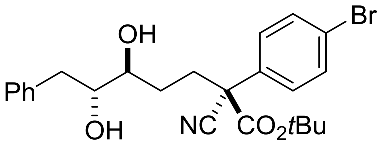
72


3.77
3.00
4.34
9.96
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)

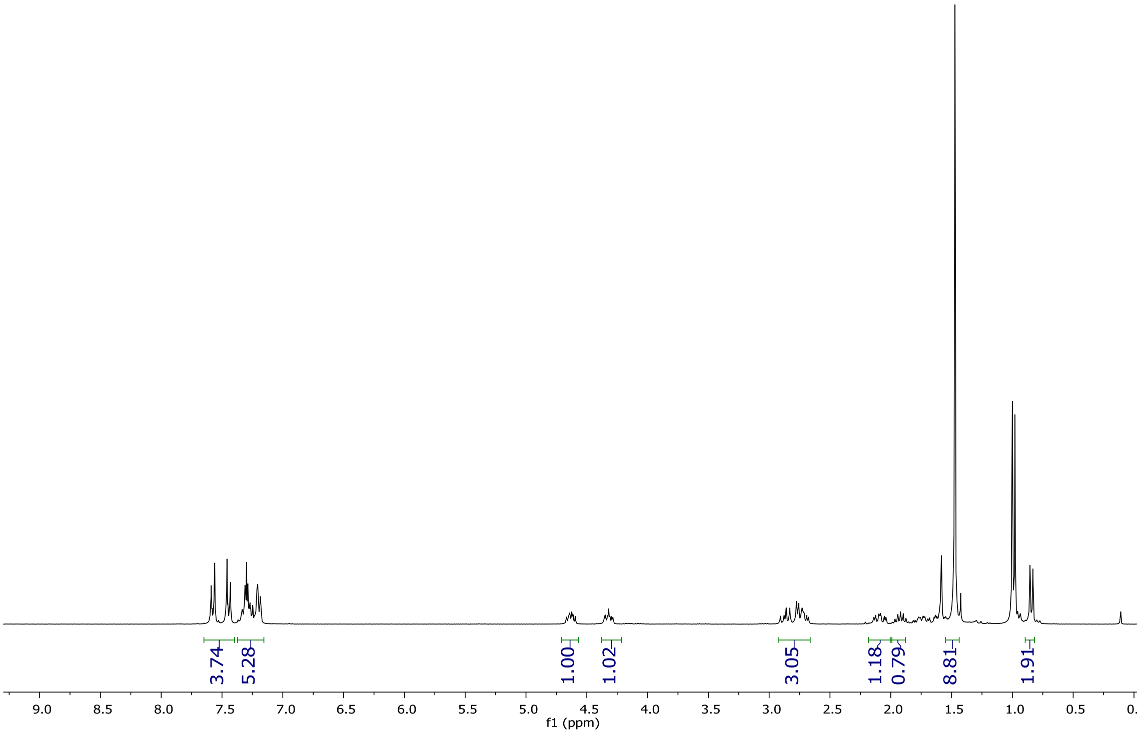

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

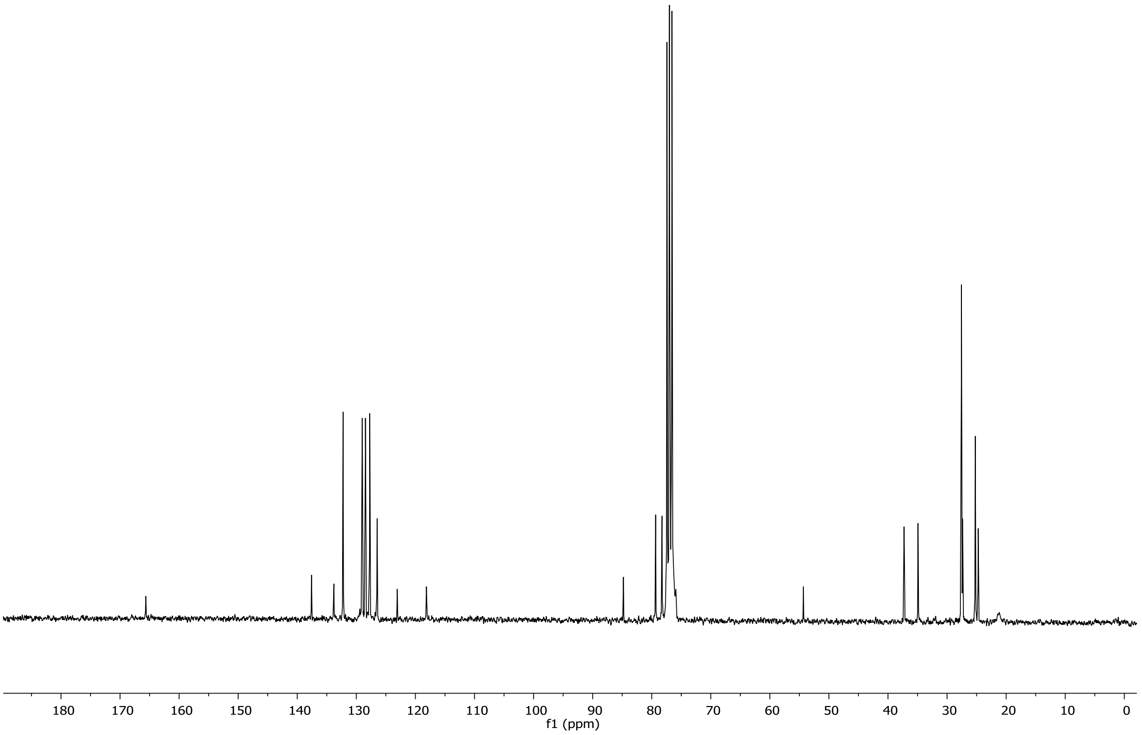

OH
Br
Ph
OH
NC
CO2tBu
69
10.16
1.00
1.28
1.05
2.10
1.92
1.26
1.16
10.80
3.27
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

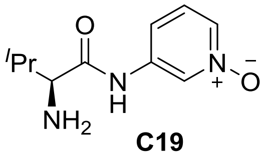

Br
OH
Ph
OH
NC
CO2tBu

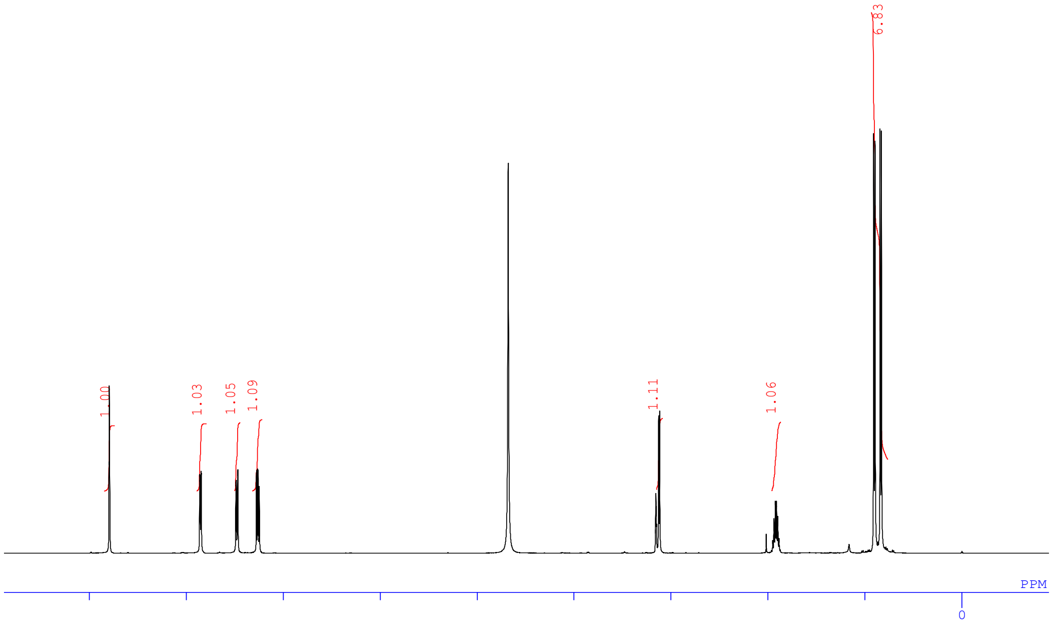
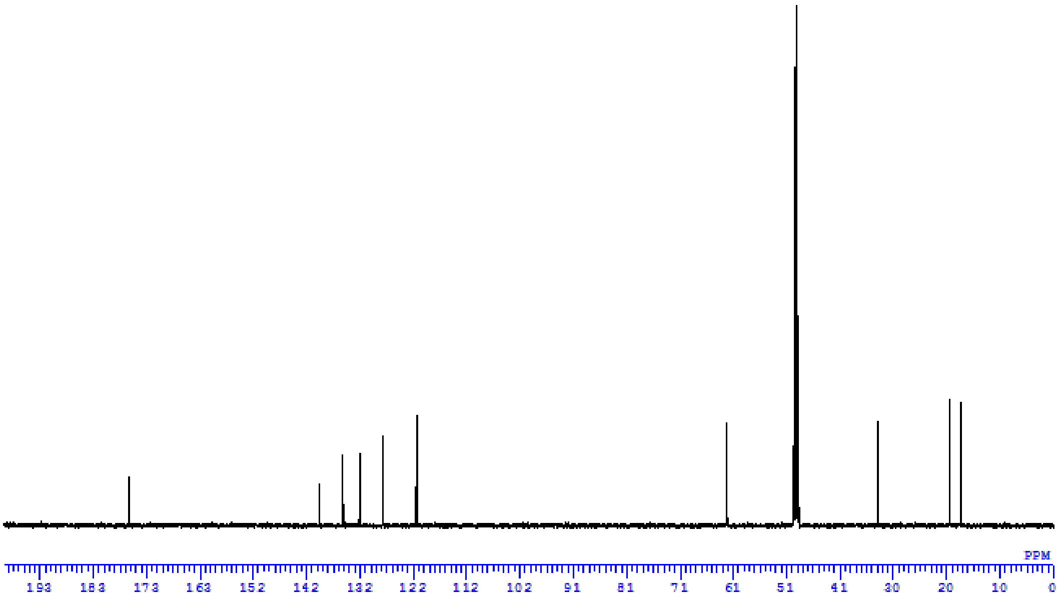
70


3.74
5.28
1.00
1.02
3.05
1.18
0.79
8.81
1.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

6.5.3. NMR spectra of Chapter 4



C19