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Short Peptide-Derived Bifunctional Brønsted Base Catalysts in Asymmetric Michael Reactions

DOCTORAL THESIS

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Summary

Peptide catalysis has proven to be an effective tool for the synthesis of enantiomerically enriched compounds with synthetic applications or that are precursors of molecules with biological and pharmacological interest. Their ability to interact through H-bonds with the substrates and form complex H-bond networks is extremely helpful for reaction stereocontrol. Likewise, asymmetric Brønsted base (BB) catalysis is also a well stablished activation protocol for a great variety of transformations, and especially interesting and effective are bifunctional BB catalysts bearing H-bond donors, which can activate the nucleophile and the electrophile at the same time. In this context, and in spite of the big progress in the realm of asymmetric catalysis, there are still many new and challenging reactions that have not been resolved and/or require improvement. So, the main goal of this Thesis has been to design and synthesize a new family of catalysts that combine a short peptide, a typical privileged H-bond donating scaffold used in organocatalysis (squaramide/ ureidoaminal) and a BB (Figure A), and to investigate them in some challenging transformations involving the generation of quaternary carbon stereocenters.

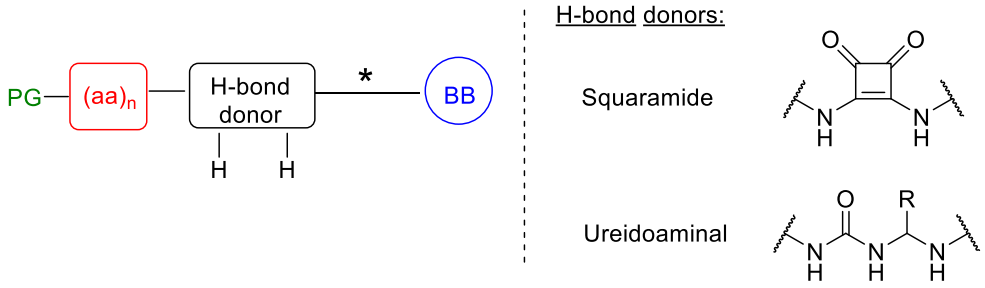


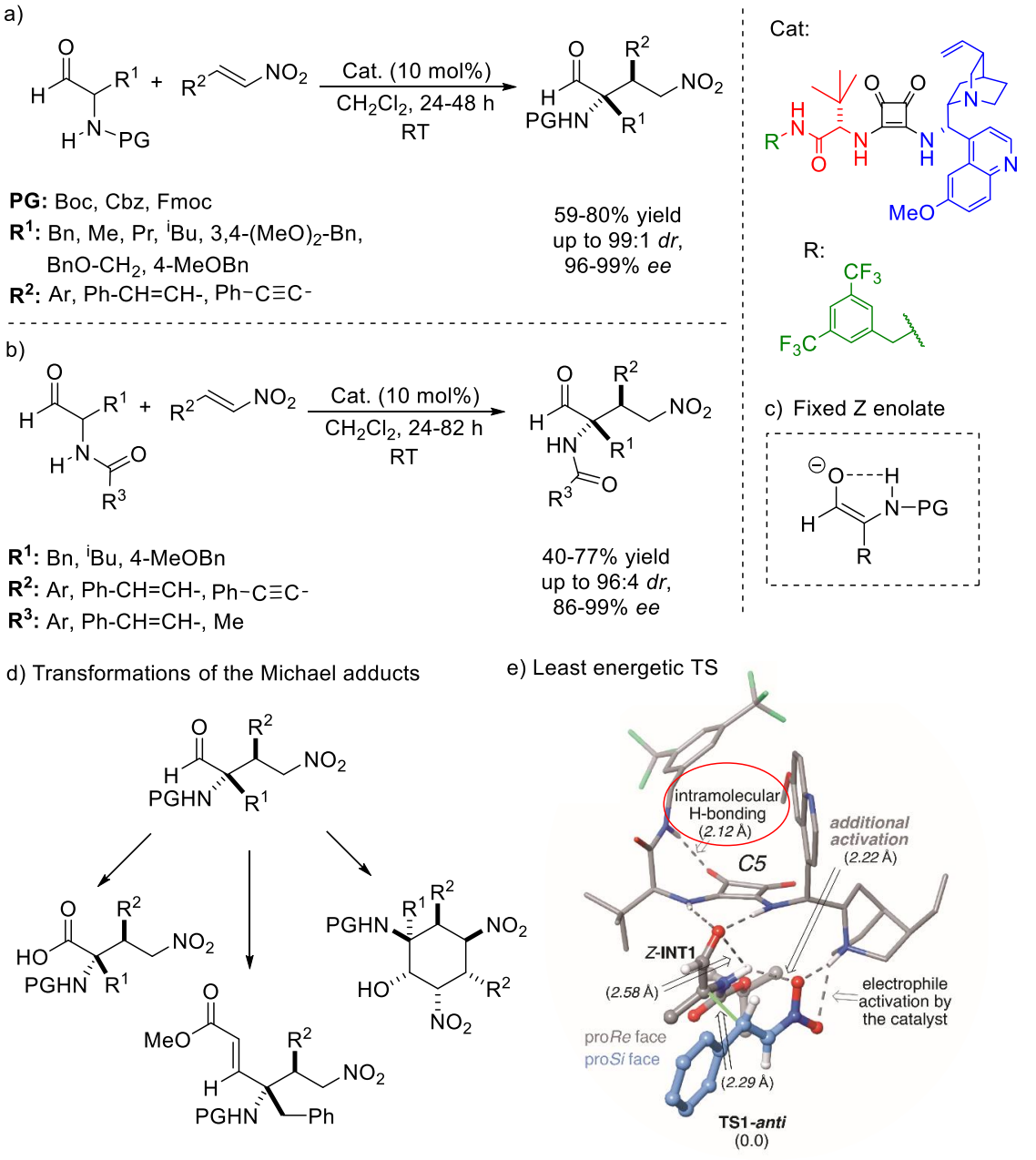
Figure A. Structure of new amino acid containing BB catalysts. aa: amino acid. PG: protecting group.

Aldehydes ($pk_a \approx 17$, in DMSO) are substrates in the limit of what a tertiary amine ($pk_a = 11\text{-}21$, in DMSO) could deprotonate, but at the beginning of this Thesis, aldehydes had not been investigated as pronucleophiles in BB catalysed asymmetric reactions. The main employed strategy to activate aldehydes has been the use of primary and secondary aminocatalysts that promote the reactions via enamine activation. However, the aminocatalysed α-functionalization of α-branched aldehydes still presents some problems in terms of reactivity and/or stereoselectivity due to steric hindrance. In Chapter 2 of this Thesis, we present the results of the investigation on the Michael addition of α-branched aldehydes to nitroolefins promoted by the new short peptide-derived BB catalysts depicted in Figure A. As pronucleophiles, α-branched α-amino and α-aryl acetaldehydes have been employed.

First, the results related to the investigation of the functionalization of α-amino aldehydes are presented, which leads to quaternary α-amino aldehydes in excellent yields and stereoselectivities (Scheme A). Until date, α-amino aldehydes had been

mainly used as electrophiles, being their role as pronucleophiles scarcely explored in catalytic transformations. Existing examples involve reactions promoted by aminocatalysts and are limited to either α-methyl aldehydes or very active electrophiles.

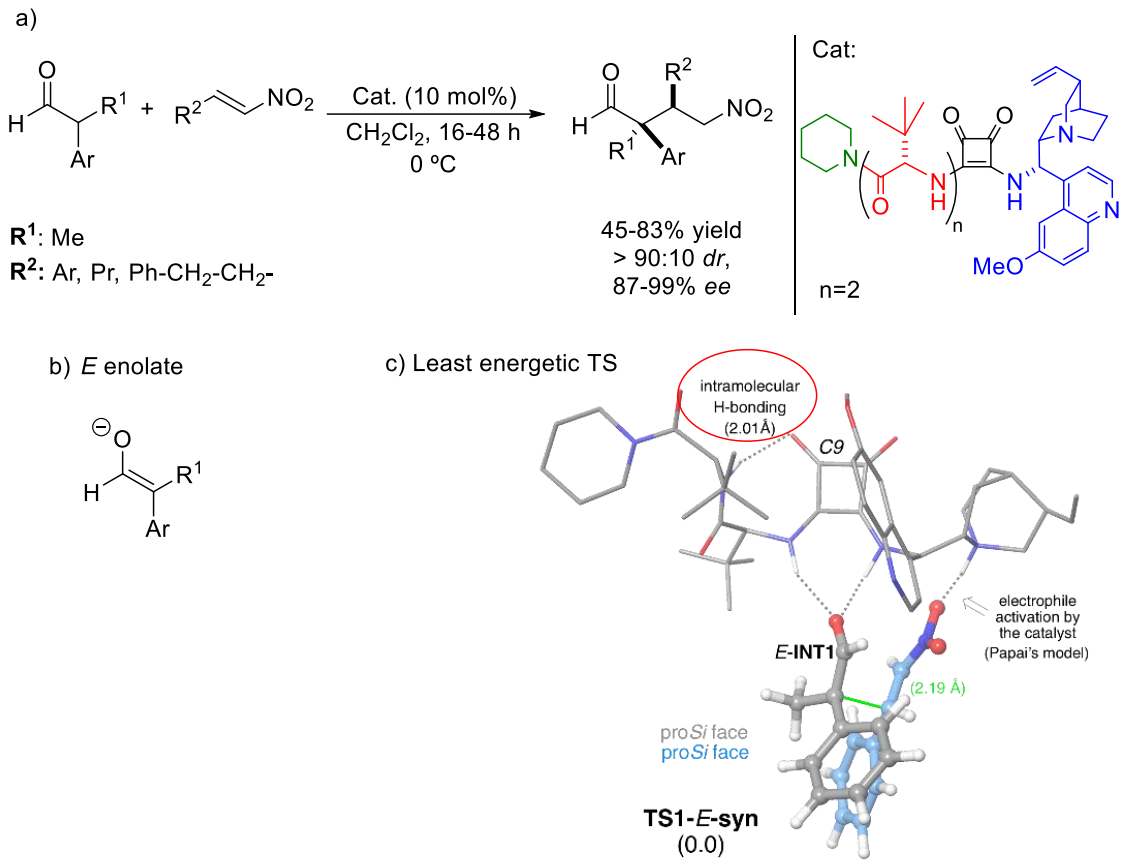
The Michael addition to nitroolefins of α-branched α-amino aldehydes with different *N*-protecting groups has been investigated (Scheme A). The most efficient catalyst for this reaction resulted that containing a squaramide as H-bond donating scaffold and a (*L*)-*tert*-Leucine unit that has been found to be key for stereocontrol.



Scheme A. a) Asymmetric Michael addition of N-Boc, N-Cbz and N-Fmoc protected α-branched α-amino aldehydes to nitroolefins. b) Asymmetric Michael addition of N-acyl α-amino aldehydes to nitroolefins. c) Fixed Z-enolate. d) Transformations of the Michael adducts. e) Least energetic transition state (TS).

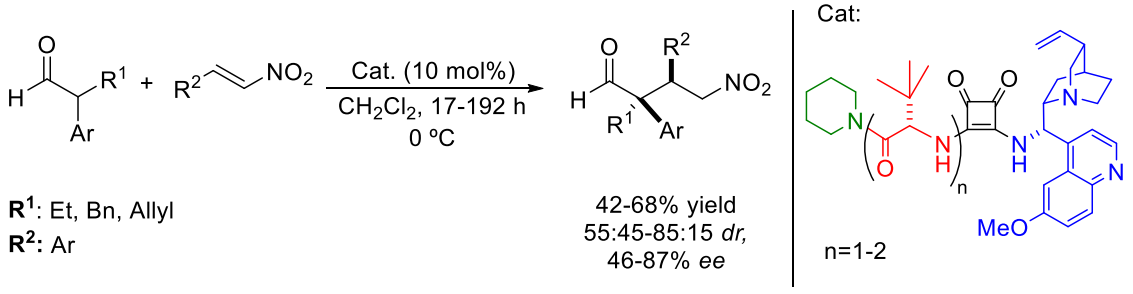
The reaction with *N*-Boc, *N*-Cbz and *N*-Fmoc protected α-amino aldehydes led to the Michael adducts in excellent stereoselectivity and very good yields (Scheme Aa). Aldehydes bearing aromatic and aliphatic *N*-acyl groups at C_α are also well tolerated, providing the final adducts, in general, with good yields and stereoselectivity (Scheme Ab). In the above reactions, nitrostyrenes with different substitution patterns, as well as nitroolefins with alkenyl and alkynyl substituents could be used as electrophiles. This protocol is especially useful since the final quaternary α-amino aldehydes are very interesting building blocks that have been transformed into tetrasubstituted α-amino acids, highly functionalized allyl amines and fully substituted cyclohexylamines, this latter through a one pot Michael-Michael-Henry tandem reaction (Scheme Ad). The role played by intramolekular H-bonds appears to be crucial in achieving the high reactivity and selectivity observed. On the one hand, the N-H···O=C interaction on the substrate α-amino aldehyde may increase the α-C acidity facilitating enolization, while the same interaction would favor formation of the *Z*- over the *E*- enolate (Scheme Ac). On the other hand, DFT calculations identified a preferred TS wherein the intramolecular N-H···O=C on the catalyst increases its H-bond donating ability, and positions the ^{t}Leu unit strategically for face selectivity (Scheme Ae).

Interestingly, α-branched aldehydes lacking the intramolecular H-bond may also participate in this Michael addition to nitroolefins by using a slightly modified peptide-derived squaramide-containing BB. Thus, the conjugate addition of α-methyl α-aryl acetaldehydes to nitroolefins triggered by the catalyst depicted in Scheme Ba provides the Michael adducts in excellent stereoselectivity in all cases, even for β-aliphatic nitroalkenes. In this case, the most efficient catalyst bears one or two units of (*L*)-*tert*-Leucine, followed by a terminal piperidine, being the reaction faster in the presence of the dimeric catalyst. DFT calculations predict that the reaction proceeds through the *E*-enolate (Scheme Bb), leading to the formation of the *syn*-adducts, instead of the *anti*-adducts obtained in the addition of the α-amino aldehydes. Once again, DFT calculations reveal the presence of an intramolecular interaction between the carbonyl group of the squaramide and the NH of the amino acid in the catalyst. Accordingly, the *tert*-butyl group is positioned in such a wat that one of the enolate faces is shielded (Scheme Bc).



Scheme B. a) Asymmetric Michal addition of α-methyl α-aryl acetaldehydes to nitroolefins. b) E-enolate. c) Least energetic transition state (TS).

The addition of α-branched α-aryl acetaldehydes with larger substituents at the alpha position can also be performed, although in general longer reaction times are needed and stereoselectivity varies from one R^1 to other (Scheme C). Thus, although this BB catalyst based strategy may be extended to other α,α-disubstituted aryl acetaldehydes, better conditions are still needed to improve both reaction time and stereocontrol.

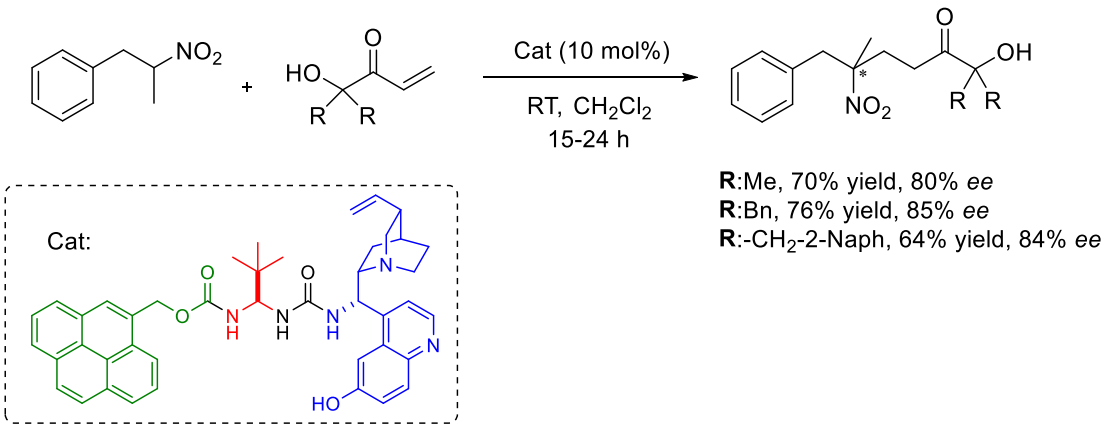


Scheme C. Exploration of α-branched α-aryl acetaldehydes with substituents other than methyl.

On the other hand, α-stereogenic nitroalkanes are interesting building blocks, since the nitro group can be transformed into a great variety of other functional groups, particularly amines, opening synthetic routes towards biorelevant molecules. In this context, the C_α-H functionalization of nitroalkanes is a straightforward option to access

compounds with increasing complexity. However, the α-functionalization of non-activated α-branched prostereogenic nitroalkanes remains essentially unexplored, probably due to the low reactivity and/or the difficulty in controlling the stereochemistry. In Chapter 3 of this Thesis, we address this challenge by employing α-hydroxy enones as electrophiles, a relatively highly reactive synthetic equivalents of enals, enones and acrylates, due to the presence of additional coordination points for interacting with the catalyst. This feature is especially interesting when using peptide-derived catalysts that have the ability to form multiple H-bonds with the substrates to limit the degree of freedom of the transition states (TSs).

In this investigation, different catalysts bearing one, two and three amino acid units have been tested in the conjugate addition of (2-nitropropyl)benzene to three α-hydroxy enones, the (*L*)-*tert*-Leucine-derived ureidopeptide like catalyst resulting the most efficient for this reaction (Scheme D). The two-point coordination ability of these templates through H-bonding in combination with the use of peptide-derived catalysts capable of forming multiple H-bonds were crucial for the formation of α-tertiary nitroalkanes in good yields and enantioselectivities among the best to date. The nature of the two geminal R substituents on the α-hydroxy enone has an impact on the reaction enantioselectivity, which increased from 80% (R=Me) to 84% (R= -CH_2-2-Naph) and 85% (R=Bn). Noteworthy, the reaction of the same nitroalkane with methyl acrylate only provides 45% conversion after 24 h, instead of the total conversion reached with α-hydroxy enones, corroborating the efficiency of these templates. It should be noted that under the present conditions no reaction was observed at all when sterically more hindered (2-nitrobutyl)benzene was employed as substrate regardless the Michael acceptor used.



R:Me, 70% yield, 80% *ee*
R:Bn, 76% yield, 85% *ee*
R:-CH_2-2-Naph, 64% yield, 84% *ee*

Scheme D. Asymmetric Michal addition of non-activated α-branched nitroalkanes to α-hydroxy enones.

Abbreviations and Acronyms

Standard abbreviations and acronyms have been used as recommended in "Guidelines for authors" (*J. Org. Chem.,* January **2015**). Additionally, the following abbreviations and acronyms have been employed:

*	Chiral
aa	Amino acid
AIB	2-Aminoisobutyric acid
Alk	Alkyl (group)
Asp	Asparagine
B	Base
BB	Brønsted base
Conv.	Conversion
$(DHQ)_2PHAL$	Hydroquinine 1,4-phtalazinediyl diether
$(DHQ)_2Pyr$	Hydroquinine 2,5-diphenyl-4,6-pyridineyl ether
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DMP	Dess-Martin periodinane
E	Electrophile
ee	Enantiomeric excess
EDCI	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide
EPC	Enantiomerically pure compounds
eq	Equivalent
EWG	Electron-withdrawing group

GABA	γ-aminoisubutyric acid analogues
Glu	Glutamine
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
His	Histidine
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenztriazole
Im	Imidazole
Leu	Leucine
LG	Leaving group
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MVK	Methyl vinyl ketone
Naph	Naphthyl
n.d.	Not determined
NMM	4-Methylmorpholine
n.o.	Not observed
o.n.	Overnight
PG	Protecting group
Phth	Phthalimide
PNBA	*p*-Nitrobenzoic Acid
Pro	Proline
Rac	Racemic
Ref.	Reference

TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	tert-Butyldiphenylsilyl
TEA	Triethylamine
TES	Triethyl silyl
Trp	Tryptophan
Val	Valine

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CHAPTER 1

INTRODUCTION

1. Introduction

The synthesis of enantiomerically pure compounds (EPC)[1] has become a field of increasing interests, especially since the realization that the two enantiomers of a chiral compound can show different biological properties. In the last years, several applications have been found for enantiomerically pure chiral compounds, not only in pharmacology and medicinal chemistry,[2] but also in the synthesis of pesticides,[3] cosmetics[4] and even in the design of new materials.[5] Different strategies have been developed for the preparation of these EPCs, among which asymmetric catalysis,[6] that consists on inducing chirality to an achiral compound by using a chiral catalyst, has proven to be a very useful and attractive technique. In this case, a substoichiometric amount of an enantiomerically pure compound can suffice to produce large amounts of mainly a single enantiomer of a chiral product.

In the field of asymmetric catalysis, organocatalysis[7] has growth significantly in the last two decades. In this strategy, chiral organic molecules are used as catalysts to promote reactions in a stereoselective way. Different classifications for organocatalysts have been proposed. One of the most widespread is the classification depending on the interaction between the substrate and the catalyst, which can be either covalent or non-covalent.[8] One representative example of covalent interaction is aminocatalysis,[9] in which

[1] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis)* in *Modern Synthetic Methods*, Salle and Sauerländer, **1980**.

[2] a) Guo-Qiang, L.; Qi-Dong, Y.; Jie-Fei, C. *Chiral Drugs: Chemistry and Biological Action*; Wiley, **2011**; b) McConathy, J.; Owens, M. J. *Prim. Care Companion J. Clin. Psychiatry* **2003**, *5* (2), 70–73; c) Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discov. Today* **2004**, *9* (3), 105–110.

[3] More than 30% of the registered pesticides in 2018 were chiral, but only 7% were commercialized as a pure enantiomer or stereo enriched mixture: de Albuquerque, N. C. P.; Carrão, D. B.; Habenschus, M. D.; de Oliveira, A. R. M. *J. Pharm. Biomed. Anal.* **2018**, *147*, 89–109.

[4] a) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron Asymmetry* **2003**, *14* (1), 1–42; b) Leffingwell, J. C.; Leffingwell, D. *Spec. Chem. Mag.* **2011**, *31*, 30–33.

[5] a) Hodgkinson, I.; Hong Wu, Q. *Adv. Mater.* **2001**, *13*, 889–897; b) Mallia, V. A.; Tamaoki, N. *Chem. Soc. Rev.* **2004**, *33* (2), 76–84.

[6] For general references on asymmetric catalysis, see: a) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*; Wiley, **2006**; b) Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101* (15), 5348–5355.

[7] a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley, **2005**; b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Enantioselective Organocatalysis*; Drug Discov Today, **2007**; c) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions*: *A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; Royal Society of Chemistry, **2010**; d) Dalko, P. I. *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Wiley, **2013**.

[8] This classification was outlined by Langenbeck in 1949: a) Langenbeck, W. *Die organischen Ktalysatoren und ihre Bziehungen zu den Fermenten (Organic Catalysts and Their Relations with Enzymes)*, 2nd., Springer, Berlin **1949**. For a more recent classification, see: b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43* (39), 5138–5175. For an alternative classification based on the acid/base reactivity of organocatalysts, see: c) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719–724.

[9] For pioneering works, see: a) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122* (10), 2395–2396; b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122* (17), 4243–4244; For

a primary or secondary amine condensates through the formation of a covalent bond with a carbonyl group of an aldehyde or ketone to form an enamine or iminium ion intermediate as a reactive species. The significance of this field has just been recognized by the Nobel Prize in Chemistry this year (2021), which has been awarded to Benjamin List and David MacMillan (Figure 1).[10] Almost contemporarily, works by Hayashi[11] and Jørgensen[12] disclosed diarylprolinol ethers, which have considerably facilitated the development of this new research field.[13] On the other hand, examples of organocatalysts working through non-covalent interactions are catalysts based on H-bonding[14] and Brønsted base[15] activation.

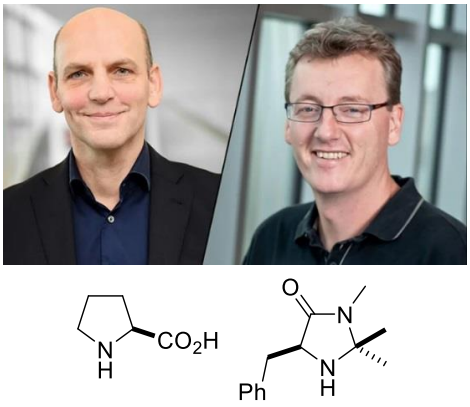


Figure 1. Benjamin List (left) and David W.C. MacMillan (right), Nobel Prize in Chemistry laureates in 2021. Below the pictures, the organocatalyst developed by each researcher.[9a,b]

some reviews on aminocatalysis, see: c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107* (12), 5471–5569; d) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51* (39), 9748–9770; e) Albrecht, L.; Jiang, H.; Jorgensen, K. A. *Chem. Eur. J.* **2014**, *20* (2), 358–368; f) Lv, J.; Zhang, Q.; Cai, M.; Han, Y.; Luo, S. *Chem. Asian J.* **2018**, *13* (7), 740–753.

[10] https://www.nobelprize.org/prizes/chemistry/2021/press-release/

[11] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44* (27), 4212–4215.

[12] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44* (5), 794–797.

[13] For reviews, see: a) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45* (47), 7876–7880; b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3* (6), 922–948; c) Jiang, H.; Albrecht, Ł.; Dickmeiss, G.; Jensen, K. L.; Jørgensen, K. A. TMS-Prolinol Catalyst in Organocatalysis. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: Dalko, P. I.); John Wiley & Sons, Ltd, **2013**, 1, 33–50; d) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54* (47), 13860–13874.

[14] For general reviews on the use of H-bonding in catalysis and their combination with other activating functionalities, see: a) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59* (3), 216–223; b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45* (10), 1520–1543; For selected examples on the use of H-bond catalysis as the only activation mode, see: c) Matador, E.; de Gracia Retamosa, M.; Monge, D.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J. M. *Chem. Eur. J.* **2018**, *24* (26), 6854–6860; d) Ray Choudhury, A.; Mukherjee, S. *Chem. Sci.* **2016**, *7* (12), 6940–6945; e) Zhang, H.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136* (47), 16485–16488.

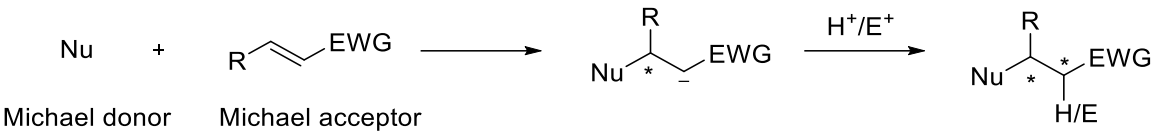
[15] For general reviews on Brønsted Base catalysis, which also include their use in combination with other activating functionalities, see: a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103* (8), 2985–3012; b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38* (2), 632–653; c) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 201–232; d) Yamashita, Y.; Kobayashi, S. *Synlett* **2021**, *32* (1), 14–22.

Another good source of the initial chirality needed for organocatalysis has been provided by peptides, which are available in nature as single stereoisomers. Peptides, by definition, are short chains of amino acids, which are connected to each other in a sequence through peptide bonds.[16] There does not seem to be an extended consensus about the maximum amount of residues of a peptide can have and when it starts to be considered a protein, but they typically contain up to 100 amino acid units, although peptides with more than 50-60 amino acids are sometimes considered "mini-proteins".[17] These amino acid chains tend to fold in space creating secondary structures, such as α-helix and β-shifts, which are stabilized by hydrogen-bonding.

In nature, enzymes promote a great variety of transformations with extraordinary stereoselectivity and substrate specificity. This is even more surprising considering they are composed by the finite number of existing natural amino acids, just like peptides. This amazing enzymatic selectivity is probably due to the 3D structure they adopt, but not only that. Some amino acid residues are strategically arrayed in space to interact with certain functional groups during the catalytic process.[18] Since, as mentioned above, peptides are also formed by amino acids, they could be considered as lower molecular weight mimics of enzymes, and subsequently, able to catalyze reactions with similar selectivity. Indeed, in the last couple of decades, many researchers have proved this theory true.[19] In fact, until today, different examples of stereoselective reactions catalysed by peptides have been reported in the literature, which include oxidations, reductions, group transfer reactions such as phosphorylations, sulfonylations and acylations, and C-C bond forming reactions among others.[18,19]

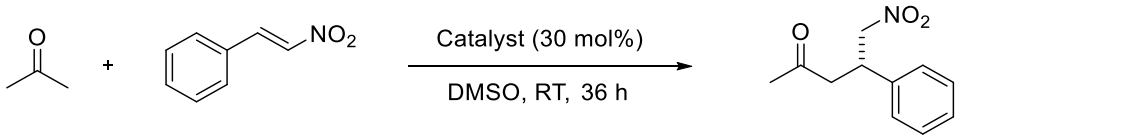
Regarding C-C bond forming reactions, the Michael or conjugate addition reaction7[c,20] is one of the most versatile and powerful transformations. It consists of a 1,4-addition of a nucleophile or Michael donor to an α,β-unsaturated compound named Michael acceptor. The formed anion intermediate can either be protonated or react with a second electrophile in a tandem reaction (Scheme 1). One or more stereocenters can be formed during this reaction, whose configuration could be controlled using a chiral catalyst, like a peptide.

[16] Peptide | Scitable by Nature Education https://www.nature.com/scitable/definition/peptide-317/ (accessed May 11, 2021).
[17] Hamley, I. W. *Introduction to Peptide Science*; Wiley, **2020**.
[18] Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107* (12), 5759–5812.
[19] For some reviews on this subject, see: a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; b) Wennemers, H. *Chem. Commun.* **2011**, *47* (44), 12036–12041; c) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. *Chem. Rev.* **2020**, *120* (20), 11479–11615.
[20] For the first described Michael reaction, see: Michael, A. *J. für Prakt. Chemie* **1887**, *35* (1), 349–356.



Scheme 1. General scheme for the Michael reaction.

Indeed, several examples of Michael additions catalysed by synthetic peptides in which a C-C bond is formed can be found in the literature. In most cases, the use of peptides instead of simple Proline provides better results in terms of yields and stereoselectivity and allows the use of lower catalyst loadings. The first of these peptide catalysed Michael reactions was described by Martin and List in 2003 and consisted of the addition of acetone to *trans-β*-nitrostyrene (Scheme 2).[21] They tested different dipeptides in the reaction and the best result was obtained with H-Pro-Val-OH, which afforded the product in a moderate *ee* (31%), but higher that simple Proline (7% *ee*). Following this work, peptide-catalysed Michael additions of different ketones, aldehydes, indoles and nitroalkanes have also been reported as outlined below.



Cat: H-Pro-OH: 97% yield, 7% *ee*
Cat: H-Pro-Val-OH: 65% yield, 31% *ee*

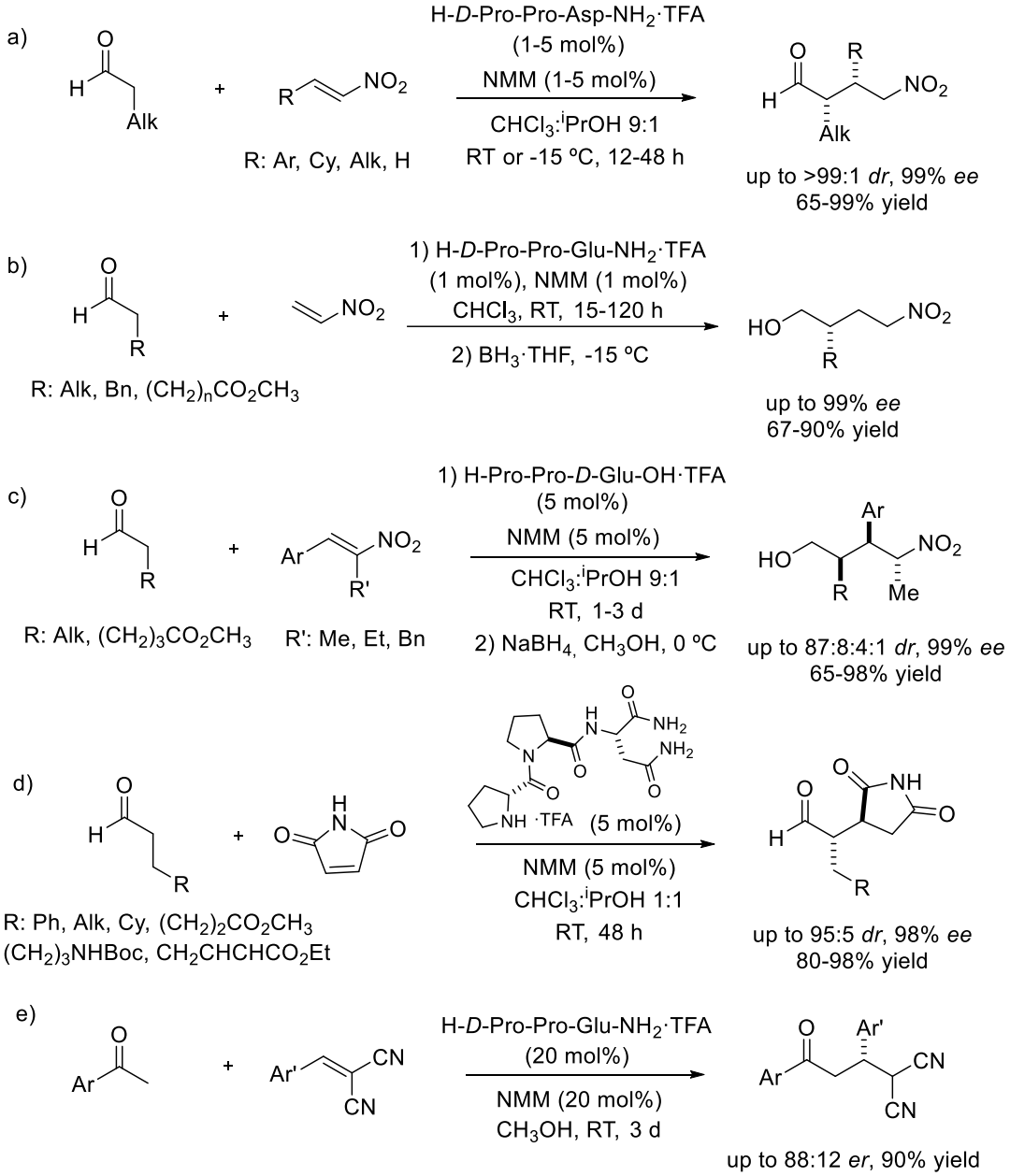
Scheme 2. First peptide catalysed Michael addition. ***List, 2003***.[21]

In 2006, Córdova's group expanded the scope of the previous Michael reaction to the addition of different cyclic ketones to nitrostyrenes.[22] They used Alanine-containing dipeptides that bear a primary amine instead of a secondary amine and managed to obtain selectivity of up to >36:1 *dr* and 98% *ee*. They also tested the reaction with 1-hydroxypropan-2-one and isobutyraldehyde as pronucleophiles but lower *ee* values were observed (29% and 58% respectively).

However, a few years later, Wennemers' group did an extensive work on the conjugate addition of linear aldehydes to nitroolefins reporting great selectivity values in the presence of Proline-containing tripeptides. They described the addition of aldehydes to *β*-substituted nitroolefins (Scheme 3a),[23] nitroethylene (Scheme 3b)[24] and α,β-disubstituted nitroolefins (Scheme 3c)[25] as electrophiles and in all cases the final adducts were obtained with up to excellent diastereoselectivities and almost as single enantiomers. They were able to promote the reaction with catalyst loadings as low as 1-

[21] Martin, H. J.; List, B. *Synlett* **2003**, *12*, 1901–1902.
[22] Xu, Y.; Zou, W.; Sundén, H.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348* (4–5), 418–424.
[23] Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, *47* (10), 1871–1874.
[24] Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611.
[25] Duschmalé, J.; Wennemers, H. *Chem. Eur. J.* **2012**, *18* (4), 1111–1120.

5 mol%, while for Proline catalysis usually 30 mol% of catalyst is needed.[26] In the two latter cases reduction of the final adducts was necessary to avoid racemization and/or epimerization during column chromatography purification.

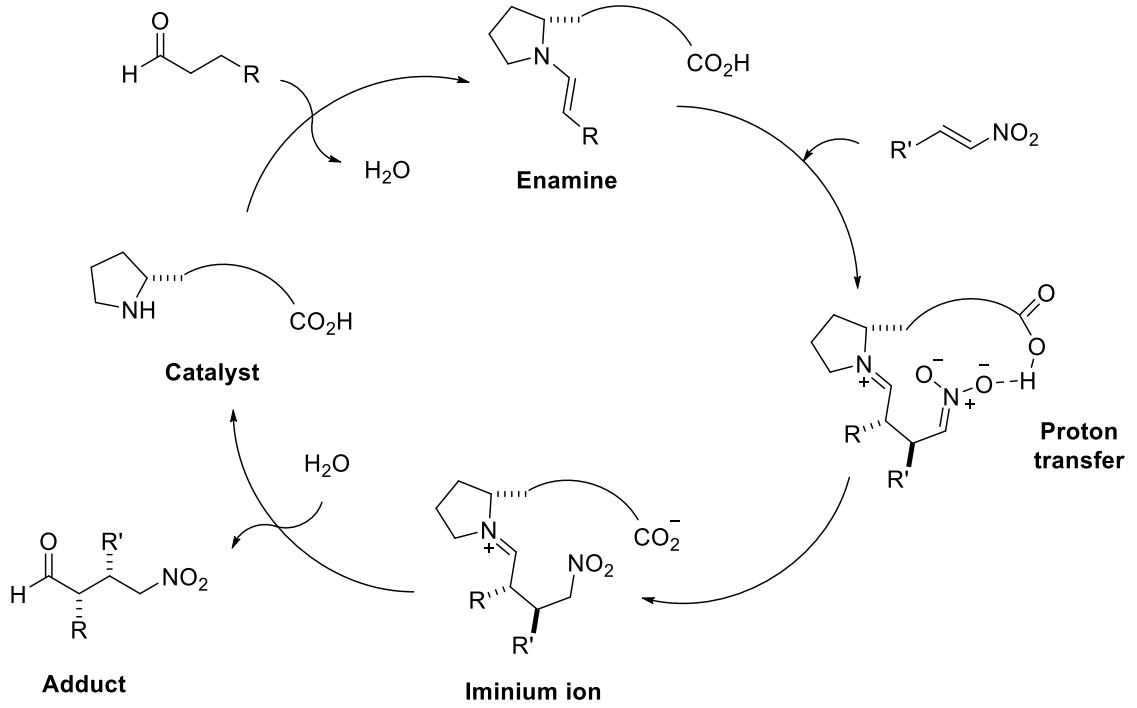


Scheme 3. Tripeptide-catalysed Michael addition of linear aldehydes to a) ß-substituted nitroolefins,[23] b) nitroethylene,[24] c) α,ß-disubstituted nitroolefins,[25] d) maleimide.[32] e) Michael addition of acetophenones to dicyanoolefins. [33] ***Wennemers, 2008-2017.***

The reactions were catalysed by tripeptides containing an *N*-terminal Proline residue for aminocatalysis, and either an Asparagine (Asp) or a Glutamine (Glu) as C-terminal unit, both bearing a carboxylic acid group on the side chain for proton transfer. The group, in collaboration with Pfaltz, confirmed that the reaction occurs via enamine

[26] Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7* (6), 1101–1103.

activation and not through an enol mechanism[27] and the proposed catalytic cycle (Scheme 4) is similar to that for Proline described by List and Houk, [28] in which the reaction proceeds through enamine activation by the terminal NH_2 group, while the free carboxylic acid offers a coordination point and assists on the proton transfer.



Scheme 4. Catalytic cycle via enamine proposed for the Michael addition of aldehydes to nitroolefins employing Proline-containing tripeptides. ***Wennemers and Pfaltz, 2013****.*[27]

Wennemers' group's work entailed a huge advance in the field of aminocatalysis in terms of catalyst loadings, which were significantly higher, typically 10-20 mol%, until that date for this type of reactions[29] and they demonstrated that reactions could efficiently proceed with loadings as low as 1 mol%. They also extended the protocol to reactions promoted by the catalyst immobilized on solid support[30] and in flow reaction setups with comparable stereoselectivity results.[31]

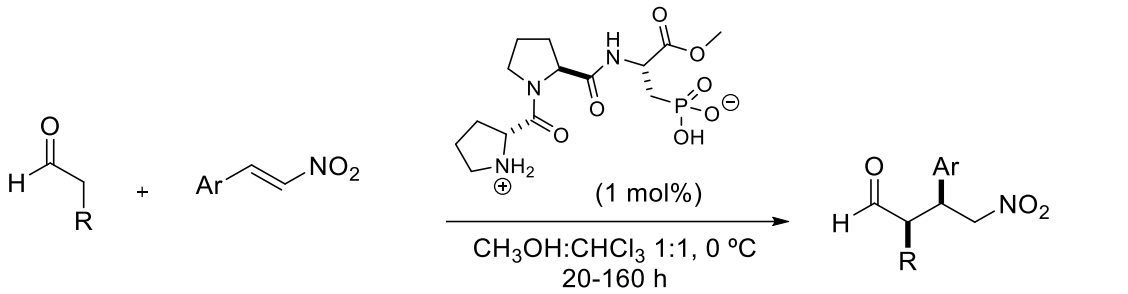
Wennemers also described the Michael addition of aldehydes to maleimide (Scheme 3d)[32] promoted by a similar catalyst, but in this case, it was more efficient in terms of reactivity to have both carboxylic acids on Aspartate as primary amides. It has

[27] Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, *52* (48), 12619–12623.
[28] a) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101* (16), 5839–5842; b) Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43* (43), 5766–5768.
[29] For some selected examples, see: a) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3* (23), 3737–3740; b) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44* (9), 1369–1371; c) Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2006**, *45* (36), 5984–5987.
[30] Arakawa, Y.; Wiesner, M.; Wennemers, H. *Adv. Synth. Catal.* **2011**, *353* (8), 1201–1206.
[31] Arakawa, Y.; Wennemers, H. *ChemSusChem* **2013**, *6* (2), 242–245.
[32] Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8571–8574.

been proposed that this is probably because H-bonding, rather than protonation, is critical for accelerating the bond formation process.

Likewise, they studied the addition of different acetophenones to dicyanoolefins catalysed by H-*D*-Pro-Pro-Glu-NH_2·TFA, the same tripeptide used for the addition to nitroethylene (Scheme 3e),[33] but higher catalyst loadings were needed in this case to reach acceptable stereoselectivity (up to 88:12 *er*).

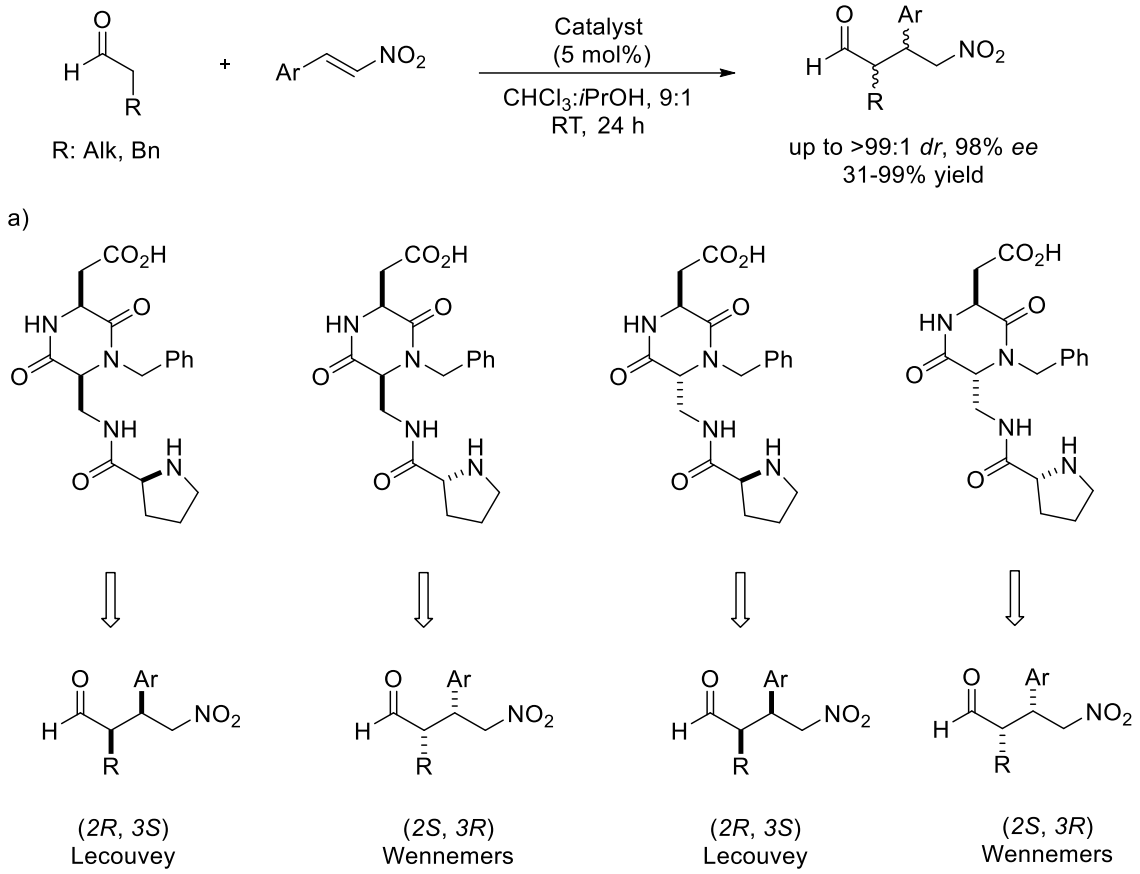
The formation of the opposite enantiomer for the same reaction reported by Wennemers in Scheme 3a was published by Lecouvey's group, by simply changing in the catalyst the carboxylic acid on the Aspartate residue for a phosphoric acid (Scheme 5).[34] They proposed that this divergence in the stereoselectivity could be due to the "difference between carboxylic acid and phosphoric acid in terms of spatial geometry and activation mode".



Scheme 5. Michael addition of aldehydes to nitrostyrenes catalysed by a phosphoric acid (PA) containing tripeptide. ***Lecouvey, 2016****.*[34]

For the same Michael addition, Piarulli and Gennari[35] were able to obtain both enantiomers of the adduct reported by Wennemers and Lecouvey, in excellent stereocelectivity results, with the same Proline-bearing diketopiperazine-derived catalyst, by simply changing the configuration of the stereocenters present in the catalyst (Scheme 6a). The configuration of the Proline residue seems to determine the stereochemistry of the obtained adduct, while the modification of the absolute configuration of the piperazine, from *S,S*- to *R,R*- did not influence the stereochemical outcome of the reaction. On the basis of the proposed transition state for the formation of the adduct (*2R, 3S*)-adduct, (Scheme 6b) the catalyst would promote the reaction via enamine, as it usually happens with Proline residues, and the free carboxylic acid attached to the piperazine would coordinate to the nitrostyrene assisting the *Si*-face approach.

[33] Schnitzer, T.; Wennemers, H. *Synlett* **2017**, *28* (11), 1282–1286.
[34] Cortes-Clerget, M.; Gager, O.; Monteil, M.; Pirat, J. L.; Migianu-Griffoni, E.; Deschamp, J.; Lecouvey, M. *Adv. Synth. Catal.* **2016**, *358* (1), 34–40.
[35] Durini, M.; Sahr, F. A.; Kuhn, M.; Civera, M.; Gennari, C.; Piarulli, U. *Eur. J. Org. Chem.* **2011**, *28*, 5599–5607.

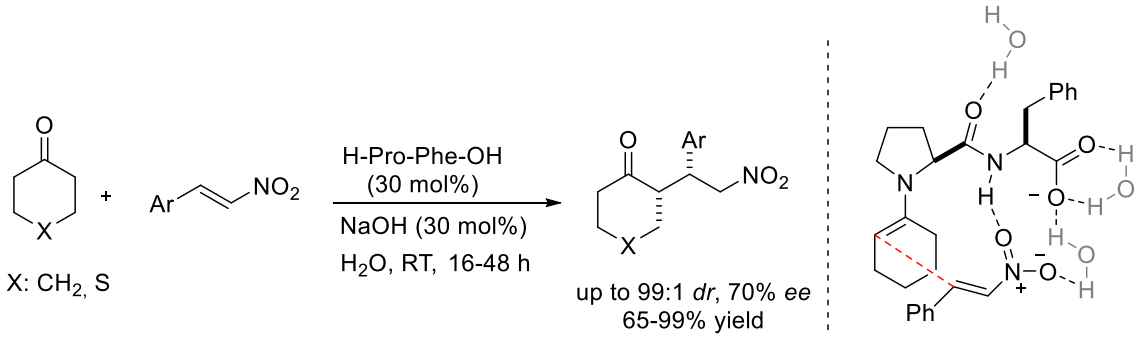


Scheme 6. Diketopiperazine catalysed Michael addition. a) Tested catalysts with variations of the configuration of each stereocenter and the obtained adduct in each case. b) Proposed transition state for the formation of the (*2R,3S*)*-adduct.* ***Piarulli and Gennari, 2011****.*[35]

Peptide-catalysed Michael additions of ketones have also been reported, although in these cases, significantly higher catalyst loadings are needed. The first example of this was reported by Tsogoeva in 2009 on the use of dipeptides like H-Pro-Phe-OH as promoters of the addition of cyclic ketones to nitrostyrenes in aqueous media (Scheme 7).[36] NaOH was used in catalytic amount to deprotonate the carboxylic acid of the dipeptide and make it soluble in water. According to the proposed transition state

[36] Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2009**, *7*, 4279–4284.

(Scheme 7), the dipeptide would condensate with the cyclic ketone to form an enamine while the NH on the Phenylalanine residue would coordinate to the nitro group. Some water molecules could also take part in the transition state creating a complex H-bond network. Final adducts were obtained in up to 99:1 *dr* and 70% *ee*. After that, in 2017, Wennemers reported the Michael addition of acetophenones to dicyanoolefins previously explained (Scheme 3e).



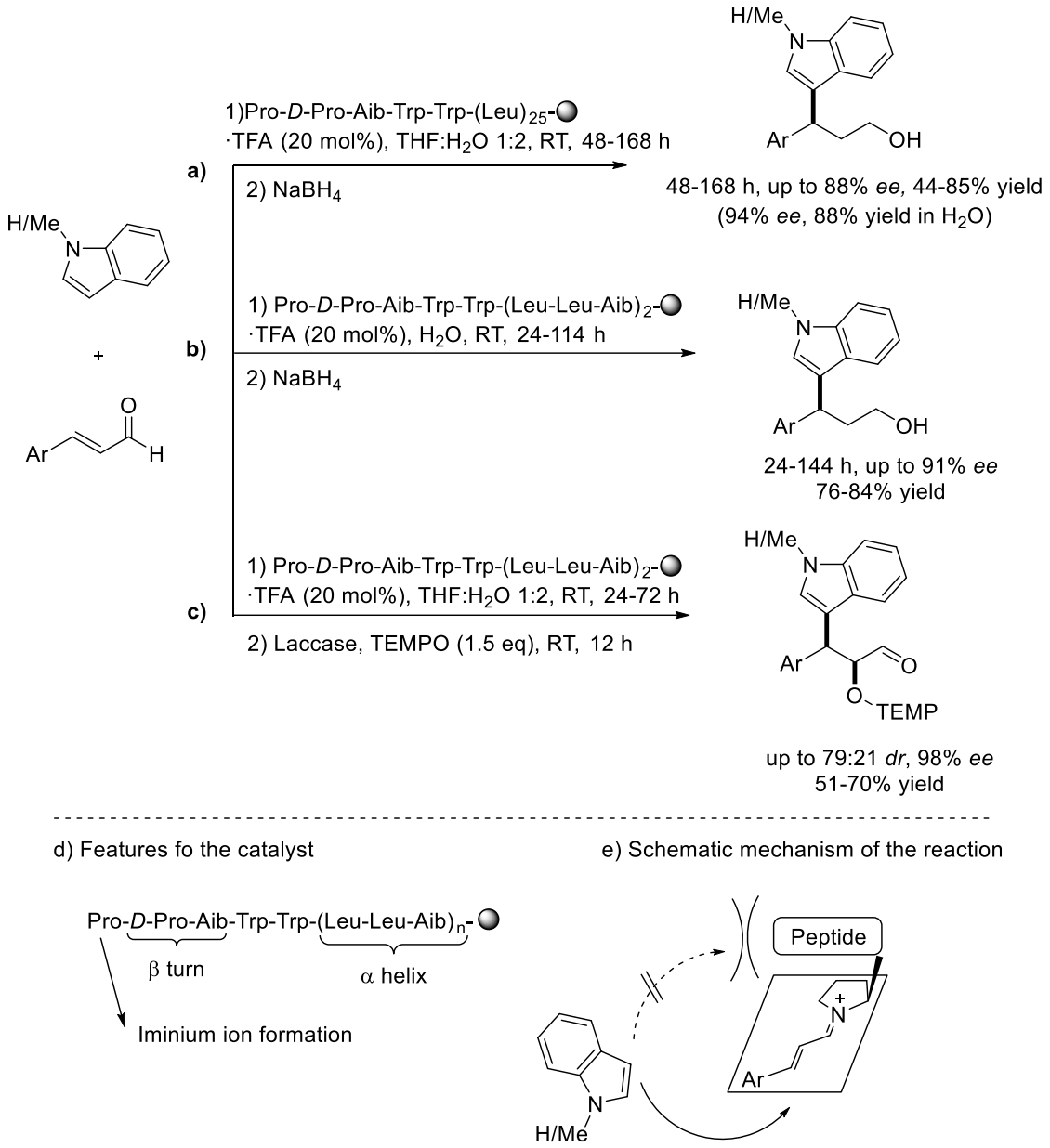
Scheme 7. Aqueous Michael addition with cyclic ketones catalysed by dipeptides. ***Tsogoeva, 2009****.*[36]

The conjugate addition of Michael donors other than aldehydes and ketones, such as indoles and nitroalkanes have also been investigated in peptide catalysis. The employed acceptors involve enals and enones, and these reactions proceed via iminium activation in the cases where the reaction is promoted by a Proline-derived peptide. Once again, in general high catalyst loadings are required, typically 20 mol% of the peptide catalyst and even so, the results are not good enough.

Kudo's group has extensively studied peptide catalysed Michael additions occurring via iminium ion activation. They first studied the Friedel-Crafts alkylation of indoles with enals (Scheme 8a)[37] employing solid-supported Proline-containing oligopeptides with a hydrophobic tether formed by Leucine units, in a mixture of THF/H_2O and the corresponding adducts were isolated as alcohols in up to 88% *ee* after *in situ* reduction with $NaBH_4$. However, they found out that in the absence of THF, enantioselectivity increased to 94% *ee*. By employing a catalyst with a shorter chain formed by Leucine and AIB, and in aqueous media, they were able to shorten the reaction times and the adducts were also obtained in up to 91% *ee* (Scheme 8b).[38,39] A one-pot alkylation oxidation sequence was also performed thanks to the compatibility of the catalyst with water, using laccase enzyme as oxidizer, and adducts were obtained in up to excellent *ee* values, albeit in moderate diastereomeric ratios (Scheme 8c).[40] As mentioned before, these catalysts operate through iminium ion activation of the electrophilic enal.

[37] Akagawa, K.; Yamashita, T.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2009**, *50* (40), 5602–5604.
[38] Akagawa, K.; Suzuki, R.; Kudo, K. *Adv. Synth. Catal.* **2012**, *354* (7), 1280–1286.
[39] For the addition of boronic acids to γ-hydroxy enals catalysed by a Proline containing resin-supported peptide, see: Akagawa, K.; Sugiyama, M.; Kudo, K. *Org. Biomol. Chem.* **2012**, *10* (25), 4839–4843.
[40] Akagawa, K.; Umezawa, R.; Kudo, K. *Beilstein J. Org. Chem.* **2012**, *8* (1), 1333–1337.

The terminal Proline forms the iminium ion while the rest of the peptide chain folds into a β-turn and an α-helix (Scheme 8d). These secondary structures hinder the approach of the nucleophile through one of the faces, favoring facial selectivity (Scheme 8e).[37]

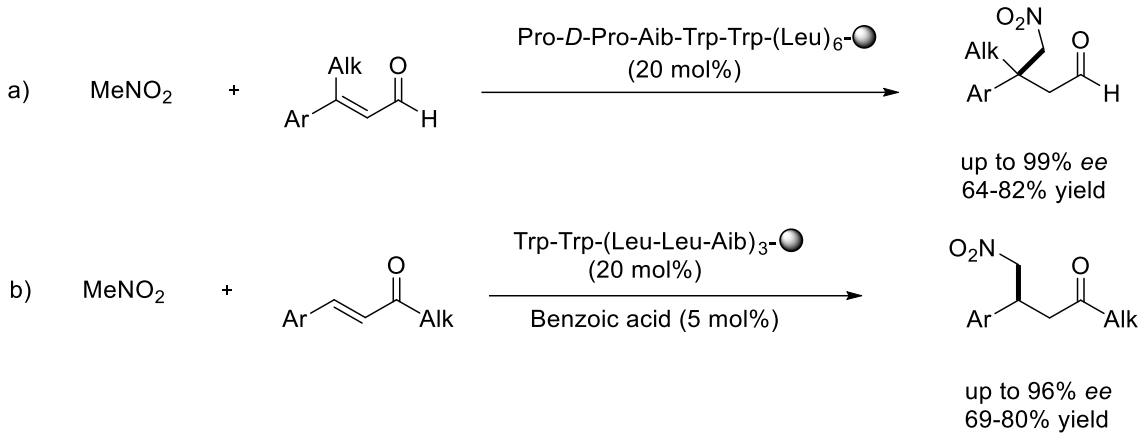


Scheme 8. Friedel-Crafts alkylation of indoles. ***Kudo, 2012.*** [37,38,40]

The addition of nitromethane to α,β-unsaturated aldehydes and ketones with Proline containing solid supported oligopeptides was also studied by Kudo's group (Scheme 9). For the addition to enals (Scheme 9a),[41] the employed catalyst was similar to the one reported for the alkylation of indoles (Scheme 8a), but with a six Leucine-residue tether. However, for the addition to enones (Scheme 9b),[42] a Tryptophan-terminal

[41] Akagawa, K.; Kudo, K. *Angew. Chem. Int. Ed.* **2012**, *51* (51), 12786–12789.
[42] Akagawa, K.; Suzuki, R.; Kudo, K. *Asian J. Org. Chem.* **2014**, *3* (4), 514–522.

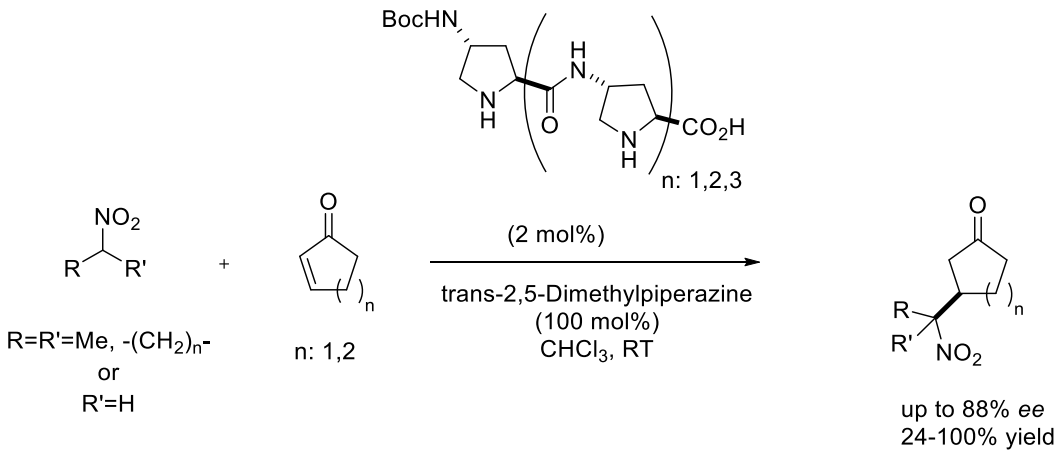
catalyst was used, which has a primary amine instead. In both cases, the reaction is supposed to occur through iminium ion activation promoted by the free amino group on the terminal amino acid and the adducts are obtained in great stereoselectivity.



Scheme 9. Addition of nitromethane to α,β-unsaturated carboxylic compounds. ***Kudo, 2012-2014****.*[41,42]

In the explained examples reported by Kudo, considerably high catalyst loadings were needed (20 mol%). In this context, Tsogoeva's group developed the Michael addition of more complex nitroalkanes to cyclic enones, but in this case, with only 2 mol% of the peptidic catalyst (Scheme 10). The reactions were promoted by dual activation, employing *trans*-2,5-dimethylpiperazine and Proline-based Boc-protected di-,[43] tri-[44] and tetrapeptides[43] that catalysed the reaction via iminium ion activation and the corresponding adducts were obtained in up to 88% *ee* (Scheme 10).[45] The *trans*-2,5-dimethylpiperazine additive seems to be essential for improving the stereocontrol. In all cases, the pronucleophilic nitroalkanes were either linear, or symmetrically disubstituted, which involved the formation of a single stereocenter.

[43] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron Asymmetry* **2006**, *17* (6), 989–992.
[44] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, *19*, 4014–4019.
[45] For a paper in which the same group uses the first Proline-free peptide in combination with a chiral diamine to catalyze the same reaction with 2-propane, see: Tsogoeva, S. B.; Jagtap, S. B. *Synlett* **2004**, *14*, 2624–2626.



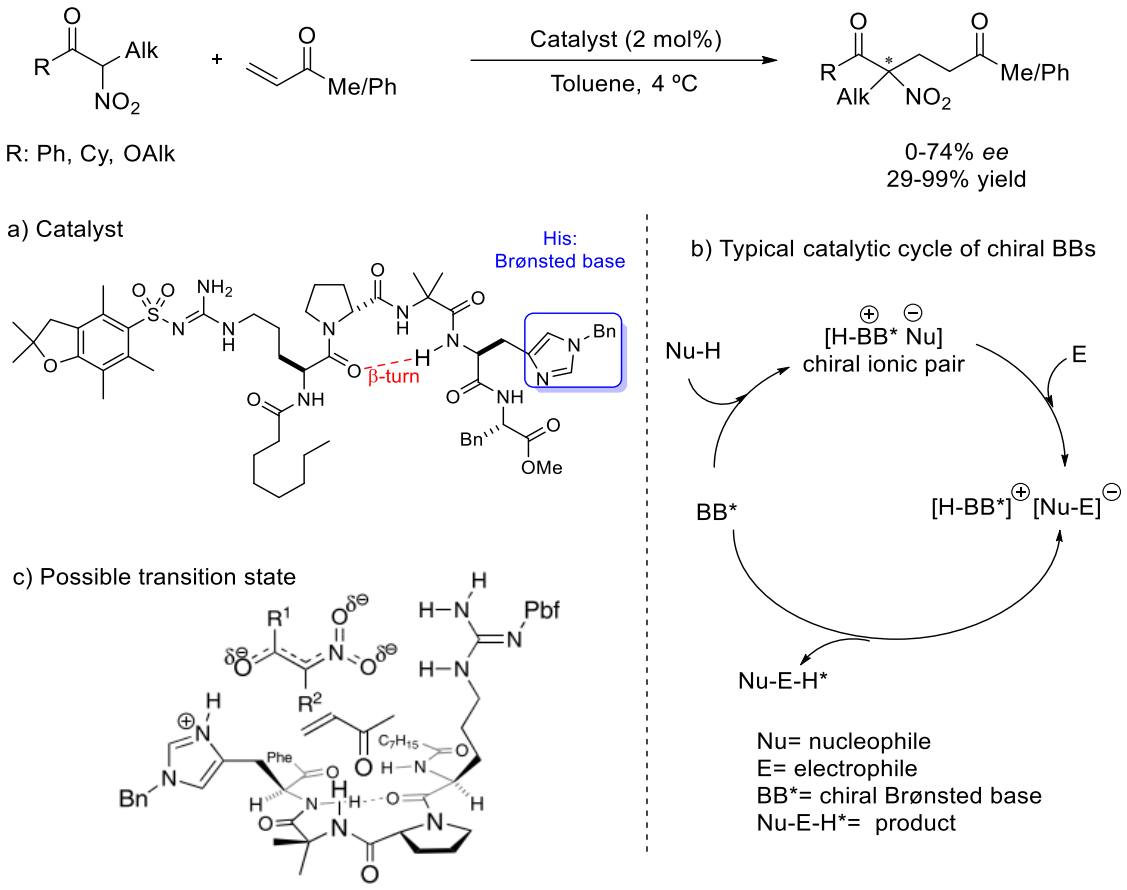
Scheme 10. Michael addition of nitroalkanes to cyclic enones catalysed by Boc-protected Proline-based di-, tri- and tetrapeptides. ***Tsogoeva, 2004-2006.***[43,44]

In all the previous examples, the peptide catalysts promote the reactions through either enamine or iminium ion activation. This has been the general operating way of these catalysts,[46] wherein in most of the cases additional interactions through H-bonding have been proposed. Other possibility for the activation of substrates in a Michael addition would be by peptides working through Brønsted base (BB) catalysis. Taking advantage of the basic nature of the side chain in some natural amino acids like Histidine, these units could be incorporated in the peptidic chain to play the role of Brønsted bases in the reaction. One of the main advantages of this BB activation strategy would be the possibility to broaden the donor and acceptor ranges tolerated by the C-C bond forming reactions, since BB catalysis is not limited to ketone and aldehydes as substrates, as it happens with aminocatalysis.

The first example of a peptide containing a natural amino acid behaving as a BB in a Michael reaction was developed by Miller and Linton (Scheme 11). In this development, the basic *N*-benzyl Histidine-containing peptide (Scheme 11a), catalysed the asymmetric conjugate addition of α-nitroketones to enones to produce the adducts with good yields and enantioselectivities ranging from 0 to 74%.[47] Authors claim that "the *N*-terminal octanoyl chain was introduced to increase solubility of the catalyst in organic solvents."

[46] For an specific case in which the peptide promotes the reaction through nucleophilic catalysis, see: Akagawa, K.; Sakai, N.; Kudo, K. *Angew. Chem. Int. Ed.* **2015**, *54* (6), 1822–1826.

[47] Linton, B. R.; Reutershan, M. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J. *Tetrahedron Lett.* **2007**, *48* (11), 1993–1997.



Scheme 11. Conjugate addition of α-nitroketones to enones catalysed by a BB containing peptide. a) Employed peptidic catalyst. b) Typical catalytic cycle of chiral BBs. C) Proposed transition state for the reaction. ***Linton and Miller, 2007***.[47]

In this reaction, the imidazole on Histidine behaves as a BB and therefore, follows the typical catalytic cycle for BB catalysis shown in Scheme 11b. In a first instance, this imidazole (BB in the scheme) deprotonates the pronucleophile to form an ionic pair, that then, reacts with the electrophile to create the new bond. Finally, the protonated base transfers the proton to the anionic intermediate liberating the product and the catalyst, which can re-enter the catalytic cycle. Since in this case the catalyst is chiral, a chiral ionic pair is formed which, assisted by the chiral peptide chain, leads to the synthesis of one enantiomer in higher proportion. The authors propose that the contribution of this chiral peptide to the stereoselectivity of the reaction could be attributed to the formation of a β-turn between the carbonyl on the Proline residue and the NH on the Histidine (transition state shown in Scheme 11c). This intramolecular H-bond would fold the catalyst creating a chiral cavity that would accommodate the substrates, thus facilitating the interaction in a specific manner.

Besides the basic imidazole present on Histidine, different nitrogen-based basic functionalities have been employed by organic chemists in the preparation of chiral BB catalysts, like guanidines, amidines and tertiary amines. This comprises nowadays a

significant research field known as BB catalysis. Among all the previously mentioned basic functionalities, tertiary amines are the weakest ones, but the most used in this type of catalysis, probably because due to their relatively low basicity, substrate specificity is easier to achieve, avoiding secondary reactions.

The previous examples show that one of the main features of peptides as catalysts is their ability to form H-bonds with the substrates. Organic chemists have mimicked this concept and have incorporated different moieties in synthetic catalysts that behave as H-bond donors. Catalysts that combine these moieties with Brønsted bases have been employed to successfully promote a wide variety of stereoselective transformations and constitute the field of asymmetric bifunctional BB catalysis.[48] Bifunctionality in BB catalysis is especially useful because, in the ionic pair formed in the catalytic cycle, (Scheme 11b) the interaction between the protonated catalyst and the substrates has a non-covalent nature, which makes it monodirectional and not very rigid. This allows a high degree of freedom for the transition state, thus complicating reaction stereocontrol. The incorporation of a H-bond donating moiety provides additional linking points for both substrates involved in the reaction, helping, on the one hand, to bring them closer favoring the reaction, and on the other hand, limiting the degree of freedom of the reactive complex to selectively form one stereoisomer among the others.

In the last decades, different H-bond donating scaffolds have been incorporated in bifunctional BB organocatalysts. These include thioureas, ureas, squaramides and ureidoaminals (Figure 2a).[49] Takemoto described the first bifunctional thiourea catalyst in 2003 (Figure 2a, 1),[50] and later Connon reported a urea (Figure 2a, 2)[51] and Rawal a squaramide (Figure 2a, 3),[52] both with a cinchona alkaloid as BB. Finally, in 2013, our group introduced the first bifunctional ureidopeptide-like BB catalyst (Figure 2a, 4).[53]

[48] The concept of bifunctional catalysis was originally applied in metal catalysis and soon extended to the field of organocatalysis For reviews on metal-ligand bifunctional catalysis, see: a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4* (3), 393–406; b) Ramasamy, B.; Ghosh, P. *Eur. J. Inorg. Chem.* **2016**, *2016* (10), 1448–1465.

[49] For general reviews on (thio)urea-BBs, see: a) Connon, S. J. *Chem. Commun.* **2008**, *22*, 2499–2510; b) Fang, X.; Wang, C. J. *Chem. Commun.* **2015**, *51* (7), 1185–1197; c) Visco, M. D.; Attard, J.; Guan, Y.; Mattson, A. E. *Tetrahedron Lett.* **2017**, *58* (27), 2623–2628; d) Yokoya, M.; Kimura, S.; Yamanaka, M. *Chem. Eur. J.* **2021**, *27* (18), 5601–5614; f) Maria, A.; Phillips, F.; Prechtl, M. H. G.; Pombeiro, A. J. L. *Catal.* **2021**, *11* (5), 569; For general reviews on squaramide-BBs, see: g) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17* (25), 6890–6899; h) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281; i) Zhao, B. L.; Li, J. H.; Du, D. M. *Chem. Rec.* **2017**, *17* (10), 994–1018; j) Marchetti, L. A.; Kumawat, L. K.; Mao, N.; Stephens, J. C.; Elmes, R. B. P. *Chem* **2019**, *5* (6), 1398–1485: k) Ref. 49f. For a review on *N,N*-diacylaminals, see: l) López, R.; Palomo, C. *Chem. Eur. J.* **2021**, *27* (1), 20–29.

[50] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125* (42), 12672–12673.

[51] McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44* (39), 6367–6370.

[52] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130* (44), 14416–14417.

[53] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52* (45), 11846–11851.

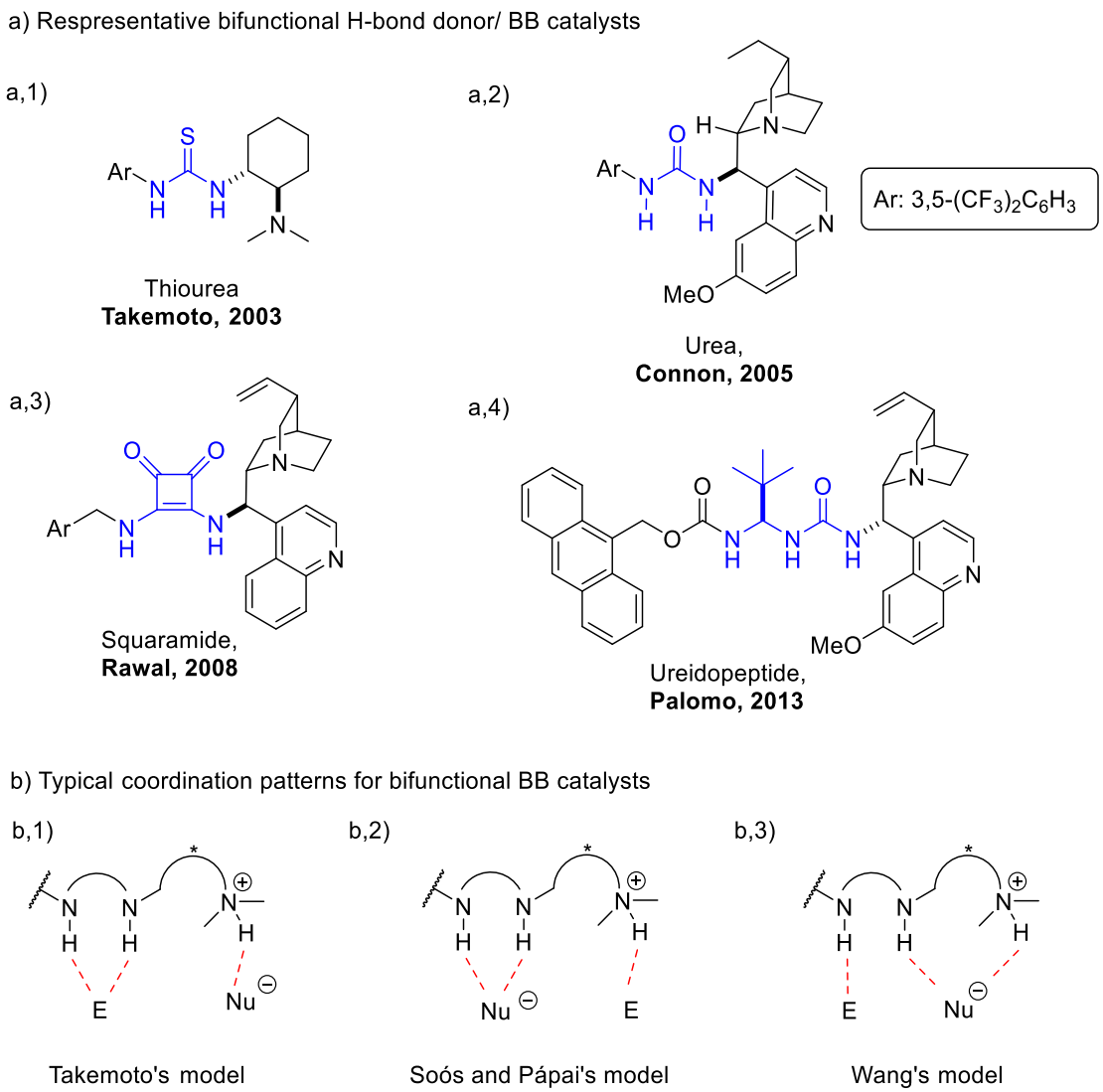


Figure 2. a) Representative bifunctional H-bond donor/ BB catalysts; in blue: H-bond donating moiety; b) Typical coordination patterns for bifunctional organocatalysts with reaction substrates.

The operating way of all these catalysts is similar. The tertiary amine deprotonates the pronucleophile providing a protonated nitrogen that becomes an additional H-bond donor. Therefore, as the catalyst exhibits some H-bond donors, they can coordinate to both substrates in more than one way during the transition state (Figure 2b). Three different coordination patterns have been proposed in this context. In Takemoto's model (Figure 2b, 1),[54] the electrophile is proposed to coordinate to the H-bond donor moiety and the anionic nucleophile interacts with the protonated tertiary amine. However, in Pápai's model (Figure 2b, 2),[55] the nucleophile coordinates to the bidentate donor and, the electrophile forms the H-bond with the protonated amine. Finally, in Wang's model (Figure 2b, 3),[56] the nucleophile is stabilized through coordination with the protonated

[54] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127* (1), 119–125.
[55] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128* (40), 13151–13160.
[56] Zhu, J. L.; Zhang, Y.; Liu, C.; Zheng, A. M.; Wang, W. *J. Org. Chem.* **2012**, *77* (21), 9813–9825.

amine and one of the H-bond donating N-Hs, and the other N-H coordinates to the electrophile. Although the former model is usually invoked, it is not always easy to predict which of these H-bonding patterns would operate in a given reaction, and each combination of substrates/catalyst often requires mechanistic studies.

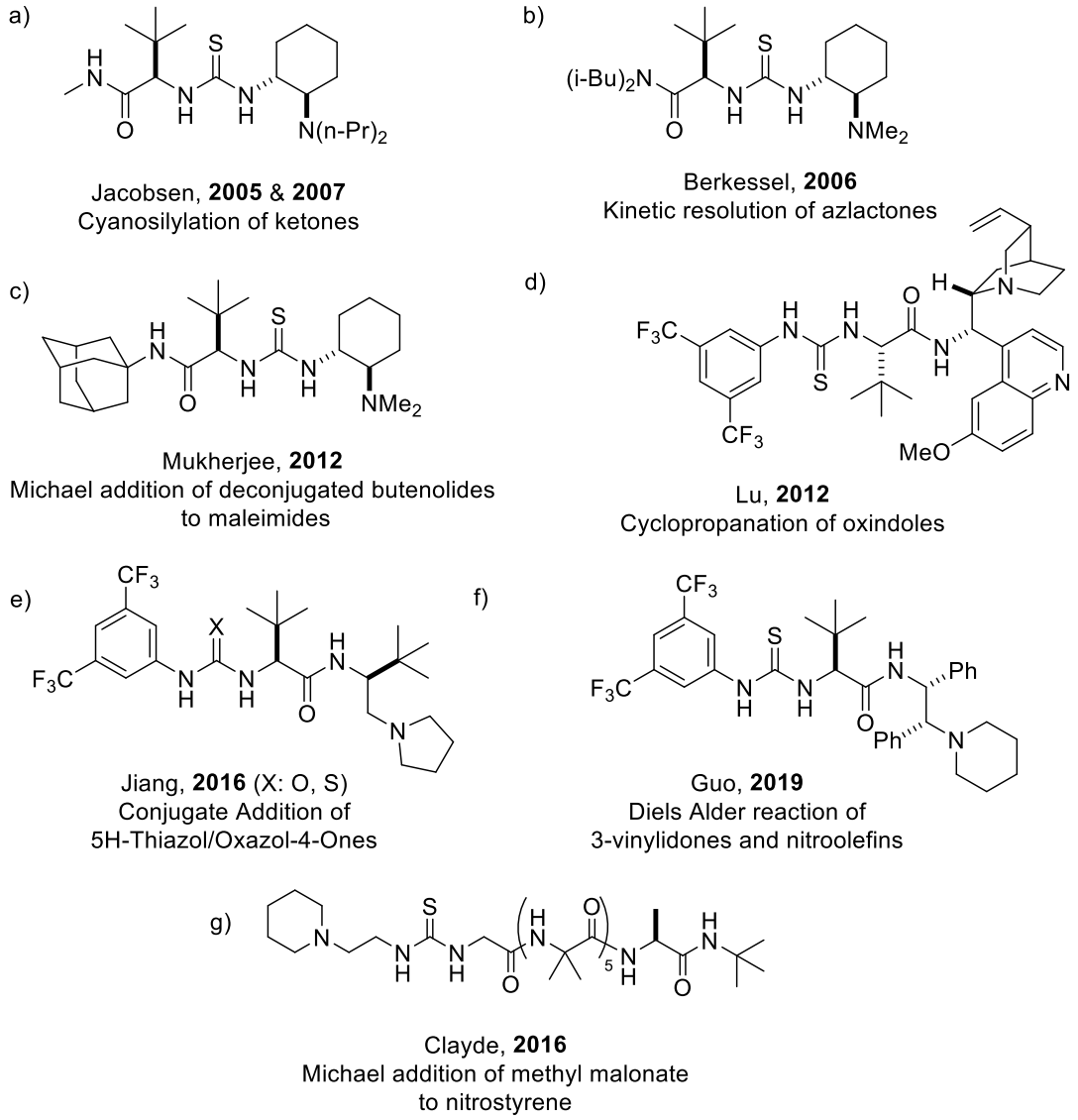


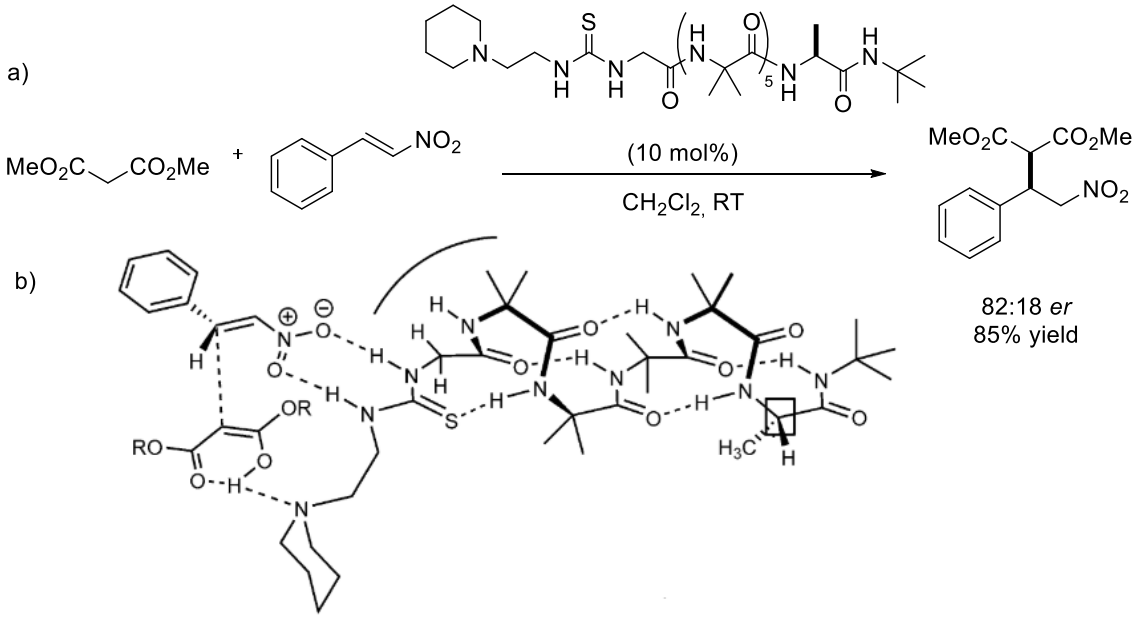
Figure 3. Described catalysts combining typical (thio)urea BB moieties and amino acids.[59]

In 2005, Jacobsen's group, after thoroughly studying amino acid containing ureas and thioureas as H-bond donating catalysts,[57] described the first of this type of amino acid containing catalysts that bear a Brønsted base (Figure 3a),[58] which was employed for the

[57] For some selected examples of the use of catalysts containing an amino acid and a urea or thiourea, see: a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed* **2000**, *39* (7) 1279–1281; b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124* (44), 12964–12965; c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; d) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133* (42), 16802–16805; e)Ref 14c-e.

[58] a) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127* (25), 8964–8965; b) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129* (51), 15872–15883.

cyanosilylation of ketones. Following this work, some additional examples of amino acid and H-bond donor containing Brønsted base catalysts have been published (Figure 3b-g).[59] In general, in the explored reactions, a significant improvement was observed in terms of stereoselectivity when an amino acid unit was present in the catalyst's structure, in comparison with similar catalysts lacking this moiety.



Scheme 12. a) Michael addition of methyl malonate to nitrostyrene catalysed by a base containing peptidic thiourea. b) Proposed transition state for the reaction. ***Clayden, 2016.***[60]

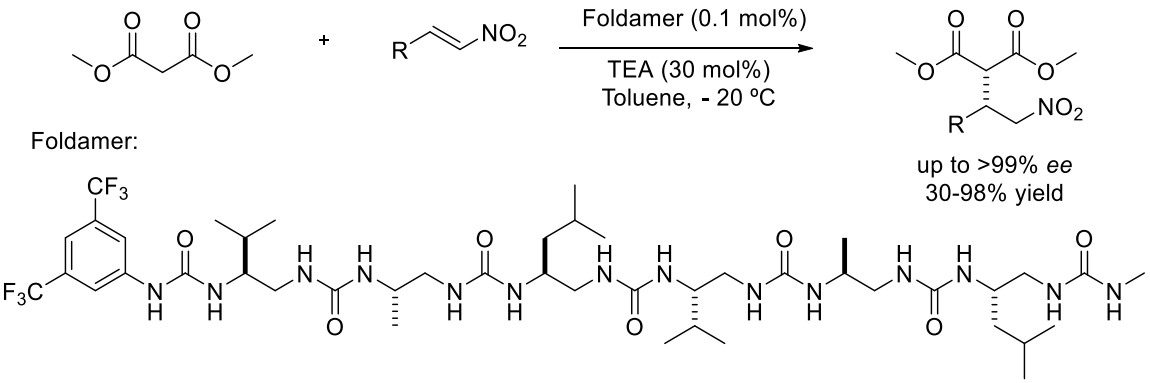
Clayden's group also described an interesting example of bifunctional BB catalysis in which the promoter bears a peptidic chain (Figure 3g, Scheme 12). In this case, the catalyst contains a single chiral amino acid unit, an Alanine, followed by an AIB chain, attached to a thiourea and a tertiary amine. Even though the chirality source is considerably far from the catalytic site, these catalysts were able to induce stereocontrol in the reaction due to the folded structure of the peptide. They demonstrated that the Michael addition of methyl malonate to nitrostyrene afforded the adducts in 82:18 *er* and 85% yield.

Another interesting approach for the use of peptide catalysts in BB activation is the synergic strategy in which a peptide or derivative and an achiral base are used as separate entities. A representative example of this type of catalysis, that has been scarcely explored, was described by our group and Guichard's group, in which the use of oligourea

[59] a) Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J. M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4* (23), 4319–4330; b) Manna, M. S.; Mukherjee, S. *Chem. Eur. J.* **2012**, *18* (48), 15277–15282; c) Dou, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18* (27), 8315–8319; d) Zhu, B.; Qiu, S.; Li, J.; Coote, M. L.; Lee, R.; Jiang, Z. *Chem. Sci.* **2016**, *7* (9), 6060–6067; e) Li, J.; Qiu, S.; Ye, X.; Zhu, B.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2016**, *81* (23), 11916–11923.

[60] LeBailly, B. A. F.; Byrne, L.; Clayden, J. *Angew. Chem. Int. Ed.* **2016**, *55* (6), 2132–2136.

foldamers in combination with TEA for the addition of malonates to nitroalkanes, provides the adducts in great selectivity by means of only 0.1 mol% of peptidic catalyst (Scheme 13).[61] This dual catalysis, among other advantages, facilitates the tuning of the catalyst and the base employed. Nevertheless, entropically speaking, having both functionalities in the same entity could also be favorable.



Scheme 13. Synergic catalysis with TEA and foldamers for the Michael addition of malonate to nitroolefins. ***Palomo and Guichard, 2017****.* [61]

To sum up, considering the privileged catalyst structures depicted in Figure 2a, some examples of urea and thiourea bifunctional Brønsted base catalysts that incorporate an amino acid or short peptide-derivative have been developed (see Figure 3). However, the combination of a short peptide-derivative with a squaramide or ureidoaminal unit and a BB in the same molecular entity had not been investigated at the beginning of this project. Accordingly, the aim of this Thesis has been the design and synthesis of a new family of bifunctional catalysts consisting of a BB (in purple), a squaramide or ureidoaminal unit (in blue) and a H-bond donating short peptide-derivative (in red) (Figure 4).[62]

Figure 4. Design of new catalyst families

As explained before, the incorporation of a peptide chain into the typical bifunctional BB structures could provide different benefits to the catalyst. On the one hand, a chain of amino acids with H-bond donating and accepting ability could form a

[61] 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* (36), 12524–12532.

[62] A few examples using this new family of squaric acid derived catalysts have been reported parallel to the development of this Thesis: a) Farid, U.; Aiello, M. L.; Connon, S. J. *Chem. Eur. J.* **2019**, *25* (43), 10074–10079; b) Majee, D.; Jakkampudi, S.; Arman, H. D.; Zhao, J. C. G. *Org. Lett.* **2019**, *21* (22), 9166–9170; c) Ray, B.; Mukherjee, S. *Tetrahedron* **2019**, *75* (24), 3292–3298; d) Zhang, N.; He, T.; Liu, Y.; Li, S.; Tan, Y.; Peng, L.; Li, D.; Shan, C.; Yan, H. *Org. Chem. Front.* **2019**, *6*, 451.

complex network of cooperative interactions with the substrates, favoring stereoselectivity and increasing the number of substrates that could be activated by the catalyst. Furthermore, the peptide chain could fold and create some steric hindrance that could also help stereoselectivity. Finally, since peptides are usually pretty polar, incorporating them into the catalyst could even allow to perform reactions in not so typical solvents like water.

In the last years, asymmetric catalysis has evolved significantly and gained importance as a versatile technique. However, there are some limitations that this strategy has not been able to address until today, such as substrate selectivity, the requirement of relatively high catalyst loadings, the catalysis of new reactions that have not been described yet and the reactivity and stereoselectivity problems that some known transformations still present. Among these, reactions involving the formation of quaternary stereocenters are especially interesting since they could provide more complex products, but they are still an uphill in many cases due to additional challenges they present like lower reactivity and stereocontrol problems due to steric hindrance.[63]

At the same time, as mentioned before, tertiary amines are relatively weak bases, having pk_a values between 11 and 21,[64] and therefore, the scope of substrates that they can activate is narrow. They usually require pronucleophiles with pk_a values no higher than 16-20 (Figure 5)[65,66] and therefore, their use has been mainly limited to 1,3-dicarbonyl compounds. Remarkably, aldehydes are just in the limit of this range. However, no examples of aldehydes as pronucleophiles in reactions catalysed by a bifunctional BB were found in the literature at the beginning of this Thesis.[67] This might be, on the one hand, due to the inherent high reactivity of the *ipso*-carbon of the aldehydes, which makes it a very good electrophile and subsequently susceptible to self-additions and other side reactions, together with the usual stereocontrol and activation challenges that the reaction of aldehydes with electrophiles may show.

[63] For information about the formation of tetrasubstituted stereocenters, see: a) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley, **2006**; b) Liu, Y.; Han, S. J.; Liu, W. B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48* (3), 740–751; For organocatalytic formation of tetrasubstituted stereocenters, see: c) Bella, M.; Gasperi, T. *Synthesis* **2009**, *2009* (10), 1583–1614.

[64] a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2010**, *16* (2), 450–455; b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14* (7), 1724–1727; c) Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16* (6), 1786–1789; d) Ho, J.; Zwicker, V. E.; Yuen, K. K. Y.; Jolliffe, K. A. *J. Org. Chem.* **2017**, *82* (19), 10732–10736.

[65] a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2008**, *47* (24), 4588–4591; b) Guang, J.; Rout, S.; Bihani, M.; Larson, A. J.; Arman, H. D.; Zhao, J. C. G. *Org. Lett.* **2016**, *18* (11), 2648–2651.

[66] Bordwell pKa Table: https://organicchemistrydata.org/hansreich/resources/pka/ (accessed May 25, 2021)

[67] Parallel to this Thesis, a rather specific example was reported of the addition of α-chloroaldehydes to β-alkylidene α-keto amides, in which the driving force of the process appears to be the cyclization of the final adduct: Li, Q. Z.; Liu, Y.; Leng, H. J.; Li, J. L. *Synlett* **2018**, *29* (20), 2601–2607.

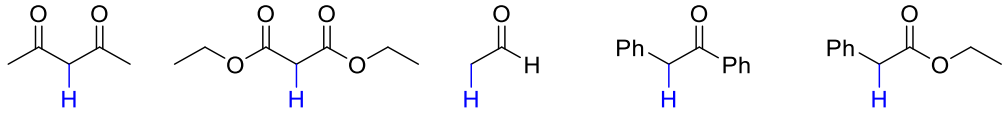


Figure 5. pK_a values of the α-carbon of different carbonyl pronucleophiles.[65,66]

Aminocatalysis has been able to provide solutions to the above problem and many approaches have been described to successfully synthesize a broad range of α-functionalized linear aldehydes. However, α-functionalization of α-branched aldehydes with this strategy has shown more problematic due to steric hindrance, and with few exceptions, existing examples lead to the formation of adducts in poor *ee* and/or *dr.* Considering this, the question of whether Brønsted base (BB) catalysis can work as a complementary alternative for the stereoselective α-functionalization of branched aldehydes is still open (see Chapter 2).

Additionally, simple linear nitroalkanes are quiet acidic substrates that can also be susceptible to soft enolization by relatively weak Brønsted bases and many examples of their reaction by BB activation have been described.[68] However, the addition of α-branched nitroalkanes has shown more problematic. In fact, several examples of efficient asymmetric activation of α-substituted nitroalkanes bearing an electron-withdrawing group (EWG) like a ketone, an ester or a halogen at the alpha position can be found in the literature, promoted by metal catalysts,[69,70] aminocatalysts[71] or bifunctional Brønsted bases.[72,73] In these cases, the presence of the EWG facilitates the reaction. Nevertheless, examples of non-activated α-substituted nitroalkanes are limited to symmetrically disubstituted pronucleophiles such as 2-nitropropane or carbocyclic nitroalkanes, during whose reaction no stereocenter is formed adjacent to the nitro group (Scheme 14a). The described Michael additions with these nitroalkanes are mainly focused on the use of enones as electrophiles and efficient results have been reported for both, linear and cyclic

[68] For some reviews, see: a) Dong, L.; Chen, F.-E. *RSC Adv.* **2020**, *10*, 2313–2326; b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971.

[69] For the addition to vinylidenebiphosphonates, see: Kato, Y.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Synlett* **2009**, *2009* (10), 1635–1638.

[70] For examples of the addition to acrylaldehyde and enones, see: Otani, T.; Sugawara, A.; Tamai, Y. *Tetrahedron Lett.* **2014**, *55* (35), 4923–4926.

[71] For two examples of the addition to cinnamaldehyde, see: Zhang, J.; Hu, Z.; Dong, L.; Xuan, Y.; Lou, C.-L.; Yan, M. *Tetrahedron Asymmetry* **2009**, *20* (3), 355–361.

[72] For additions to enones, see: a) Ref. 45 b) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4* (2), 173–176; c) Bera, K.; Satam, N. S.; Namboothiri, I. N. N. *J. Org. Chem.* **2016**, *81* (13), 5670–5680.

[73] For additions to nitroolefins, see: a) Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beilstein J. Org. Chem.* **2015**, *11* (1), 2577–2583; b) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356* (17), 3627–3648; c) Jörres, M.; Schiffers, I.; Atodiresei, I.; Bolm, C. *Org. Lett.* **2012**, *14* (17), 4518–4521; d) Kwiatkowski, J.; Lu, Y. *Chem. Commun.* **2014**, *50* (66), 9313–9316.

enones by aminocatalysis.[74,75] There is also a single example for the addition to cinnamaldehyde[76] and, as far as we know, the Michael reaction with α,β-unsaturated esters has not been investigated.

The lack of literature for the use of non-activated unsymmetrically substituted nitroalkanes as pronucleophiles (Scheme 14b) can probably be due to the difficulties in reactivity and stereocontrol that the formation of a quaternary stereocenters arrays.[63] A possible solution for these issues could be the use of highly reactive electrophiles such as α-hydroxy enones (Scheme 14c), which have been demonstrated to be efficient Michael acceptors by our research group in metal and metal-free catalysed reactions.[77]

The α-hydroxy enone moiety was first employed by our group in the chiral auxiliary strategy and showed to be very efficient in diastereoselective Diels-Alder additions,[78] 1,3-dipolar cycloadditions[79] and Michael additions.[80] This idea was then extended to enantioselective reactions, in the field of catalysis. The efficient use of α-hydroxy enones was later reported in metal catalysed cycloadditions[81,79] as well as Michael additions.[80a,82,83,84,85] A few years later, our group published the first example of the use of α-hydroxy enones as Michael acceptors in organocatalytic transformations.[86] Indeed, the addition of various challenging pronucleophiles like oxindoles, cyanoacetates,

[74] a) Ref. 43; b) Ref. 44; c) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4* (10), 2039–2049; d) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8* (21), 4787–4790; e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2* (19), 2975–2978; f) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53* (32), 11223–11236.

[75] a) Zhou, Y.; Liu, Q.; Gong, Y. *Org. Biomol. Chem.* **2012**, *10* (37), 7618–7627; b) Guo, X. T.; Shen, J.; Sha, F.; Wu, X. Y. *Synth.* **2015**, *47* (14), 2063–2072; c) Ref 74c.

[76] Gotoh, H.; Okamura, D.; Lshikawa, H.; Hayashl, Y. *Org. Lett.* **2007**, *9* (25), 5307–5309.

[77] a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41* (11), 4150–4164; b) Palomo, C.; Oiarbide, M.; García, J. M. *Encycl. Reagents Org. Synth.* **2019**, 1–7.

[78] a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124* (35), 10288–10289; b) Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J. *J. Org. Chem.* **2010**, *75* (5), 1458–1473.

[79] Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed.* **2005**, *44* (38), 6187–6190.

[80] a) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10* (13), 2637–2640; b) García, J. M.; Maestro, M. A.; Oiarbide, M.; Odriozola, J. M.; Razkin, J.; Palomo, C. *Org. Lett.* **2009**, *11* (17), 3826–3829.

[81] For Diels-Alder cycloadditions, see: Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125* (46), 13942–13943.

[82] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126* (30), 9188–9189.

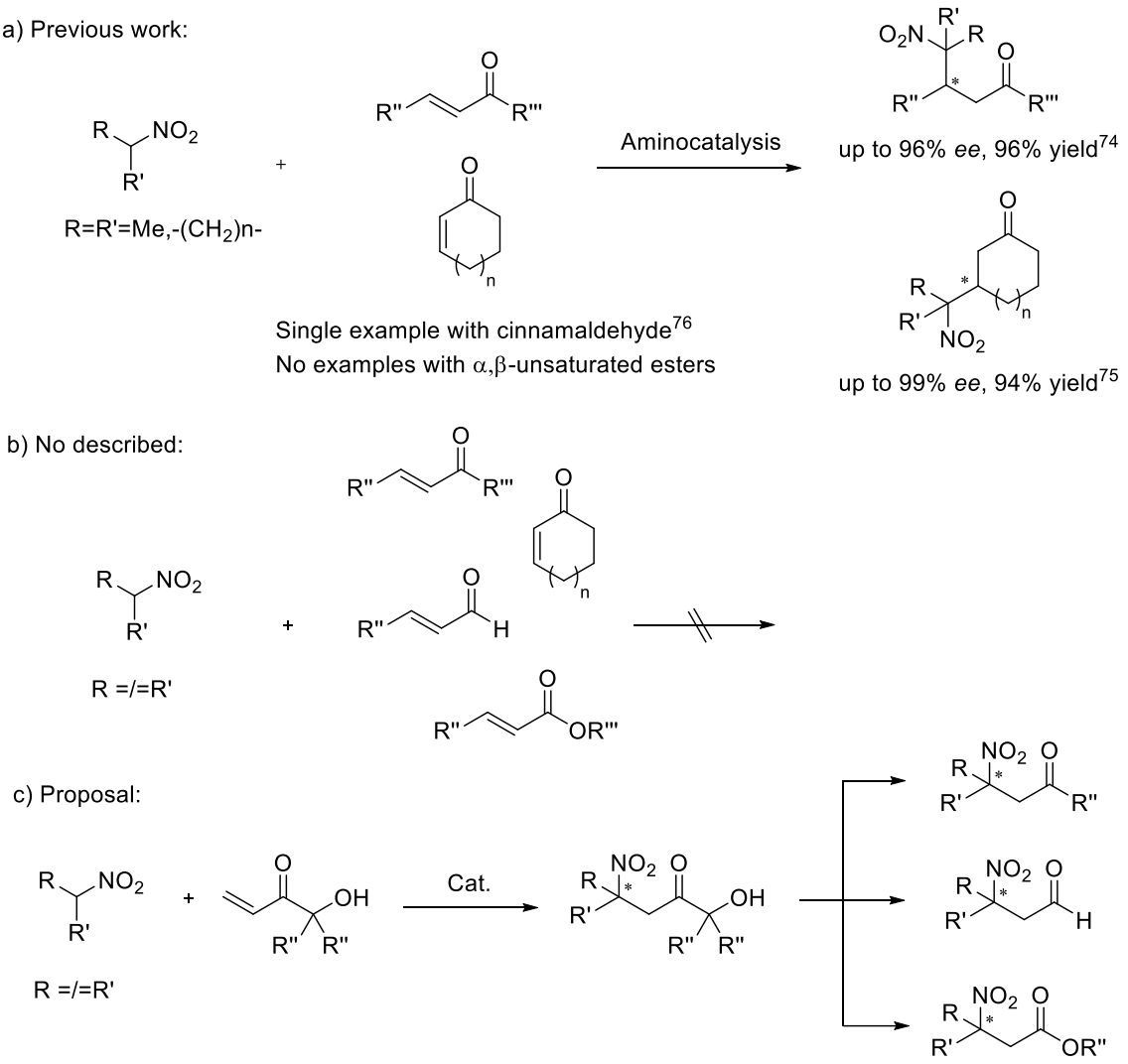
[83] For 1,3-dipolar cycloadditions, see: Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127* (12), 4154–4155.

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

[85] García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14* (29), 8768–8771.

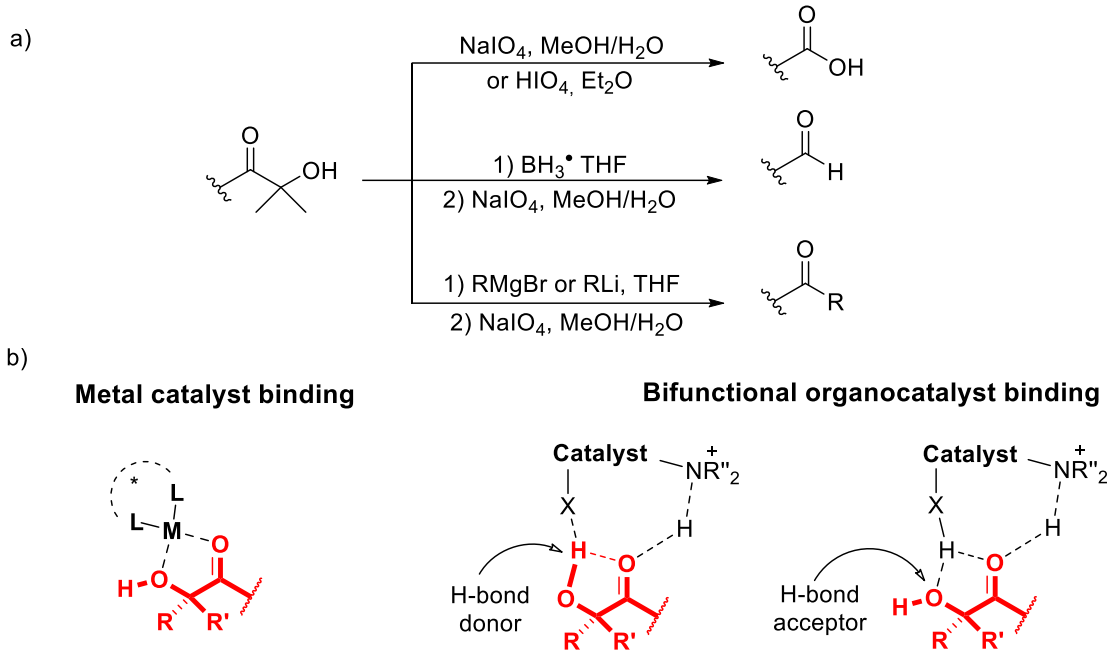
[86] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136* (51), 17869–17881.

oxazolones, thiazolones and azlactones to α-hydroxy enones was efficiently carried out in the presence of Brønsted base organocatalysts with very high levels of stereoselectivity.



Scheme 14. a) Described Michael additions of non-activated symmetrically substituted nitroalkanes to carbonylic electrophiles. b) Non investigated unsymmetrically substituted nitroalkanes in the conjugate addition to carbonylic electrophiles. c) Use α-hydroxy enones as an alternative.

The use of α-hydroxy enones as Michael acceptors is remarkably interesting because the α-hydroxy keto unit can be transformed in the final reaction adducts in carboxylic acid, aldehyde and ketone functionalities under the conditions shown in Scheme 15a , thus making the α-hydroxy enones efficient synthetic equivalents of enals, enones and α,β-unsaturated esters. Moreover, the α-hydroxy ketone moiety presents the advantage of having two different coordination points that are optimal for coordination with metal and/or H-bond donating catalysts (Scheme 15, b).



Scheme 15. a) Possible transformations of the α-hydroxy ketone moiety into carboxylic acid, aldehyde and ketone. b) Coordination patterns with metal and organocatalysts.

1.1. Objectives

In view of the previous precedents, the main goal of this Thesis has been the design and synthesis of the amino acid containing BB catalysts with a squaramide or ureidoaminal H-bond donor unit shown in Figure 6 and their screening in the reactions described below.

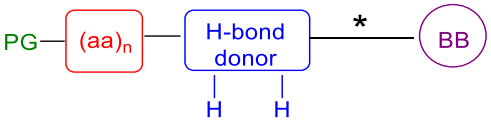


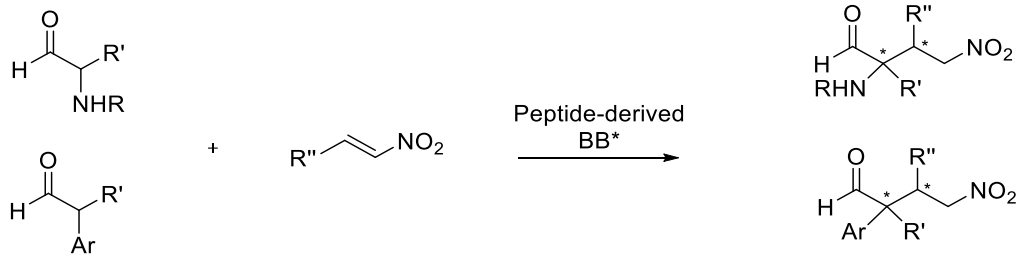
Figure 6. Schematic structure of new amino acid containing BB catalysts. aa: amino acid. PG: protecting group. H-Bond donor: squaramide/ureidoaminal.

Taking into account that, at the beginning of this project, the use of aldehydes as pronucleophiles in BB catalysis was an unexplored field, the α-functionalization of aldehydes was selected for testing the new catalysts depicted in Figure 6. In this context, the first goal of this Thesis has been to study the Michael addition of aldehydes to nitroolefins promoted by peptide derived bifunctional BB catalysts (Scheme 16).

As pronucleophiles, α-branched aldehydes with substituents of different nature at the α-position, such as α-amino aldehydes and α-aryl acetaldehydes were selected, since their reactions involve the formation of a quaternary stereocenter. As explained before, aldehydes have never been used as pronucleophiles in BB catalysis and the examples of α-functionalization of α-substituted aldehydes promoted by aminocatalysis, with few exceptions, presented some limitation in terms of stereoselectivity. Furthermore, in the

case of α-amino aldehydes, studies have mainly focused on their use as electrophiles and their α-functionalization promoted by aminocatalysis could arise regioselectivity issues because two nucleophilic carbons are present in the enamine intermediate.

In a first instance, nitroolefins were selected as acceptors[87] for preliminary investigations, because it was considered that the coordinating capability of this group together with the presence of the peptide counterpart in the catalyst would enhance reactivity towards the electrophile, thus avoiding autocondensation and other side reactions of the aldehyde. In addition, the resulting γ-nitroaldehydes are precursors of γ-aminoisubutyric acid analogues (GABAs), which present pharmacological activity[88] and the NO_2 group can be easily transformed into different functional groups. The results corresponding to this objective are explained in Chapter 2.



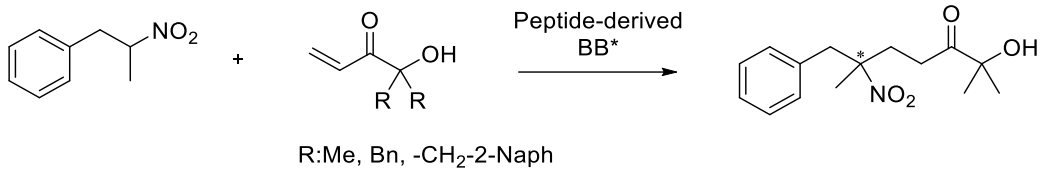
Scheme 16. Proposed Michael reaction between α-substituted aldehydes and nitroolefins promoted by a peptide-derived bifunctional BB catalyst.

Furthermore, this new peptide-derived bifunctional BB catalysts in Figure 6 could also be useful to promote other challenging reactions such as Michael additions of unsymmetrically α-substituted nitroalkanes. As previously mentioned, the use of non-activated α-branched nitroalkanes as pronucleophiles in which a stereocenter is formed at this alpha position remains unexplored. To face the problem of the low reactivity of these non-activated nitroalkanes, α-hydroxy enones were selected as the Michael acceptors due to their reactivity as noted above.

Therefore, the second objective of this Thesis has been to study the Michael addition of unsymmetrical α-substituted nitroalkanes lacking an additional activating group at the alpha position to α-hydroxy enones promoted by peptide derived BB catalysts. The results corresponding to this objective are explained in Chapter 3.

[87] For general reviews on nitroalkenes as Michael acceptors, see: a) Somanathan, R.; Chavez, D.; Antonio Servin, F.; Alfonso Romero, J.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya de Parrodi, C.; Gonzalez, J. *Curr. Org. Chem.* **2012**, *16* (20), 2440–2461; b) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gómez, C.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Molecules* **2017**, *22* (6), 895; For a theoretical evaluation of the Michael aceptor ability of nitroalkenes, see: c) Rai, V.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2006**, *20*, 4693–4703.

[88] a) Ballini, R. *Stud. Nat. Prod. Chem.* **1997**, *19*, 117–184; b) Gajcy, K.; Lochynski, S.; Librowski, T. *Curr. Med. Chem.* **2010**, *17* (22), 2338–2347; c) Andresen, H.; Aydin, B. E.; Mueller, A.; Iwersen-Bergmann, S. *Drug Test. Anal.* **2011**, *3* (9), 560–568; d) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini Rev. Med. Chem.* **2012**, *12* (7), 671–700.



Scheme 17. Proposed Michael addition of α-substituted nitroalkanes to α-hydroxy enones promoted by a peptide-derived bifunctional BB catalyst.

While the ketol moiety in the reaction adducts may be converted into aldehyde, ketone and carboxylic acid groups, an additional asset is the presence of a nitro group, which confers more versatility as it can be easily transformed into different functional groups, such as carbonyl through Nef reaction[89] or using Cr (II) salts,[90] carboxylic acid through Mioskowski reaction,[91] and primary amine[92] or hydroxylamine[93] by reduction. Conversion to nitrile oxides[94] and nucleophilic displacement of the nitro group in the adduct[95] is also possible.

[89] a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280* (2–3), 263–291; b) Pinnick, H. W. *The Nef Reaction. In Organic Reactions*; Wiley, **1990**; 655–792; c) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357* (11), 2371–2402.
[90] Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26* (32), 3777–3778.
[91] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62* (2), 234–235.
[92] a) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29* (45), 5733–5734; b) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130* (17), 5608–5609; c) Goksu, H.; Sert, H.; Kilbas, B.; Sen, F. *Curr. Org. Chem.* **2017**, *21* (9), 794–820.
[93] Feuer, H.; Bartlett, R. S.; Vincent, B. F.; Anderson, R. S. *J. Org. Chem.* **1965**, *30* (9), 2880–2882.
[94] Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82* (20), 5339–5342.
[95] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, *6*, 423–434.

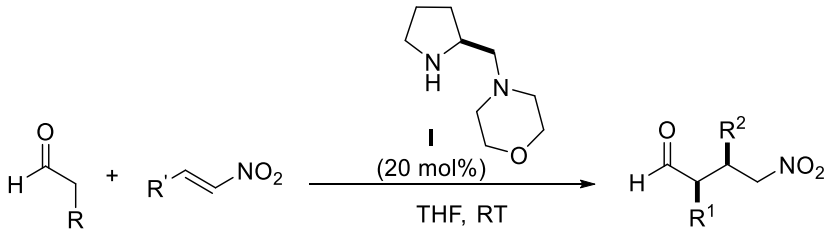
CHAPTER 2

MICHAEL ADDITION OF α-BRANCHED ALDEHYDES TO NITROOLEFINS

2. Michael addition of α-branched aldehydes to nitroolefins

2.1. Introduction

Highly substituted aldehydes are very useful building blocks for the synthesis of more complex compounds. In this context, protocols for the efficient functionalization of aldehydes are of high interest. However, the enantioselective α-functionalization of aldehydes is a challenging reaction, due to the inherent high reactivity of the *ipso*-carbon in that oxidation state, which could lead to side reactions like self-addition, Cannizzaro or Tishchenko disproportionations. These problems added to the usual stereocontrol and activation difficulties that the reaction of aldehydes with different electrophiles present make α-functionalization of aldehydes a challenging transformation. Even when employing chiral auxiliaries,[96] these problems are still not well resolved. In this context, aminocatalysis has proven to be a powerful tool in the enantioselective α-functionalization of linear aldehydes and, at present, efficient protocols for introducing different functionalities at the α-position in a stereoselective and efficient way are available.[97] Among the developed reactions, several examples of asymmetric Michael additions catalysed by primary and secondary amines can be found in the literature. The first enantioselective example was described by Barbas III and involved the use of the pyrrolidine derived catalyst **I** to promote the conjugate addition to nitrostyrenes, and the adducts were produced in excellent yields, great diastereoselectivities and up to 78% *ee* (Scheme 18).[29a]



Scheme 18. First catalytic asymmetric Michael addition of aldehydes to nitroolefins. ***Barbas III, 2001.***[29a]

Our group also developed a protocol for the asymmetric Michael addition of linear aldehydes to nitroolefins in which excellent stereoselectivity was achieved by employing a hydroxyproline-derived catalyst.[29c] Remarkably, the amount of aldehyde needed in the procedure described by Barbas (10 eq.) could be significantly reduced, to only 1.2 equivalents, in this new protocol. As mentioned in the introduction, peptide catalysed

[96] For a review, see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58* (12), 2253–2329.

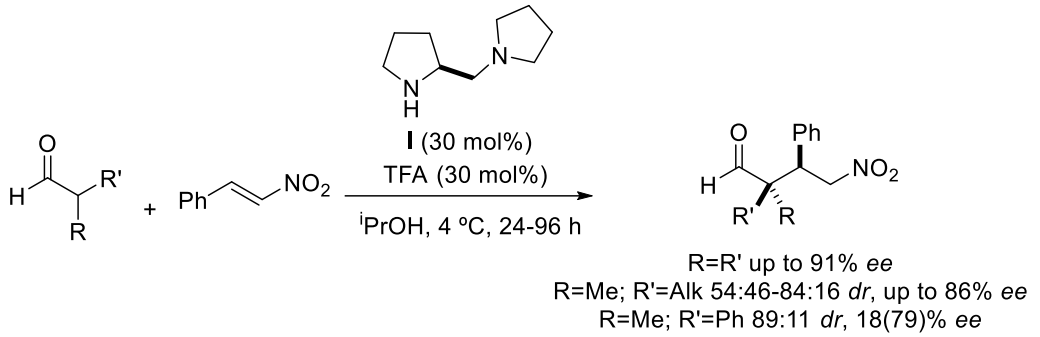
[97] For reviews, see: a) Ref. 87b b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38* (8), 2178–2189.

conjugate additions of linear aldehydes to nitroolefins that proceed through enamine catalysis have also been described by Wennemers,[23,24,25,32] Lecouvey[34] and Piarulli.[35] However, the activation of α-branched aldehydes via enamine catalysis appears to be more challenging. Condensation of the amine catalyst with the aldehydes is usually more complicated due to steric hindrance around the carbonyl group,[98] which could lead to *E/Z* enamine mixtures that might affect stereoselectivity. Moreover, the formed α-substituted enamines are less reactive[99] and because of the absence of the alpha hydrogen, some intermediates that inhibit the catalytic cycle could be irreversibly formed. These complications could explain why most of the described examples of α-functionalization of α-branched aldehydes are centered on the use of achiral substrates like isobutyraldehyde or cyclic aldehydes,[100] in which the *E/Z* enamine mixture issue is not present. In these cases, only one stereocenter is formed and the scope is significantly limited.

To date, the stereoselective functionalization of α-branched aldehydes with two different substituents has been less studied, but there are a few examples in the literature catalysed by primary and secondary amines.[101] The electrophiles employed in efficient examples of Michael additions include enones,[102] vinyl sulfones,[103,104] *N*-aryl maleimides,[105] β-nitro acrylates[106] and nitroolefins. Remarkably, most of the described cases are limited to α-methyl α-aryl aldehydes as pronucleophiles, and examples with substituents larger than methyl or α,α-dialkyl aldehydes are less efficient in terms of stereoselectivity. In particular, the addition reaction of aldehydes to nitroolefins is especially interesting since it provides an expedient route to γ-nitro aldehydes with

[98] Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14* (2), 536–539.
[99] Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9* (10), 2209–2218.
[100] For selected recent examples, see: a) Tuchman-Shukron, L.; Miller, S. J.; Portnoy, M. *Chem. Eur. J.* **2012**, *18* (8), 2290–2296; b) Simone, N. A. De; Meninno, S.; Talotta, C.; Gaeta, C.; Neri, P.; Lattanzi, A. *J. Org. Chem.* **2018**, *83* (17), 10318–10325; c) Martínez-Guillén, J. R.; Flores-Ferrándiz, J.; Gómez, C.; Gómez-Bengoa, E.; Chinchilla, R. *Molecules* **2018**, *23* (1), 141; d) Gorde, A. B.; Ramapanicker, R. *Eur. J. Org. Chem.* **2019**, *29*, 4745–4751
[101] Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70* (15), 2491–2513.
[102] a) Lnokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12* (7), 1616–1619; b) Yoshida, M.; Ukigai, H.; Shibatomi, K.; Hara, S. *Tetrahedron Lett.* **2015**, *56* (25), 3890–3893.
[103] For a protocol with a single example of the addition of 2-phenylpropanal, see: Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132* (48), 17074–17076.
[104] a) Rodrigo, E.; Morales, S.; Duce, S.; Ruano, J. L. G.; Cid, M. B. *Chem. Commun.* **2011**, *47* (40), 11267–11269; b) Miura, T.; Yuasa, H.; Murahashi, M.; Ina, M.; Nakashima, K.; Tada, N.; Itoh, A. *Synlett* **2012**, *23* (16), 2385–2388; c) Kanada, Y.; Yuasa, H.; Nakashima, K.; Murahashi, M.; Tada, N.; Itoh, A.; Koseki, Y.; Miura, T. *Tetrahedron Lett.* **2013**, *54* (36), 4896–4899; d) Nakashima, K.; Murahashi, M.; Yuasa, H.; Ina, M.; Norihiro, T.; Itoh, A.; Hirashima, S. I.; Koseki, Y.; Miura, T. *Molecules* **2013**, *18* (12), 14529–14542; e) Kawada, M.; Tsuyusaki, R.; Nakashima, K.; Akutsu, H.; Hirashima, S. ichi; Matsumoto, T.; Yanai, H.; Miura, T. *Chem. Asian J.* **2021**, *16* (16), 2272–2275.
[105] For a protocol with only two examples of unsymmetrical α-branched aldehydes, see: a) Kokotos, C. G. *Org. Lett.* **2013**, *15* (10), 2406–2409; For a more general protocol, see: b) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J.* **2012**, *18* (13), 4088–4098.
[106] For a protocol with a single efficient example, see: Yoshida, M.; Masaki, E.; Ikehara, H.; Hara, S. *Org. Biomol. Chem.* **2012**, *10* (27), 5289–5297.

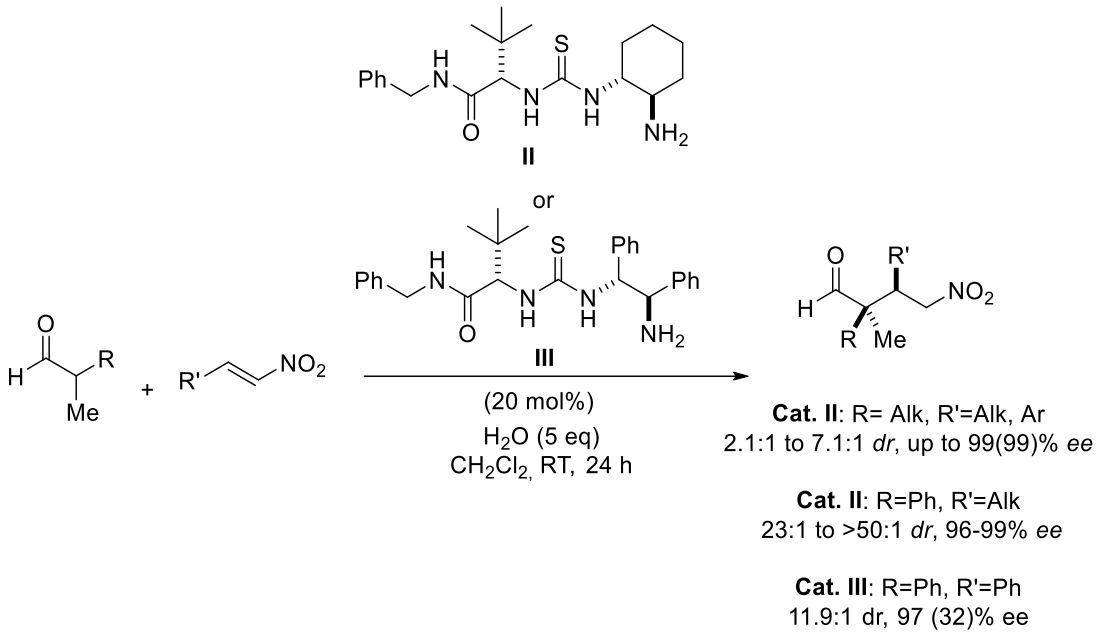
quaternary stereocenters.[107] In this context, the first addition of α-branched aldehydes to nitrostyrene was developed by Barbas III in 2004 (Scheme 19)[108] and the pyrrolidine-based catalyst **I** similar to the one used for linear aldehydes in 2001[29a] was used to promote the reaction. In this case, the adducts were obtained in moderate stereoselectivity for both α-aryl and α-alkyl aldehydes.



Scheme 19. First aminocatalysed addition of α-branched aldehydes to nitrostyrene. ***Barbas, 2004.***[108]

After Barbas's work, additional studies for the stereoselective Michael addition of unsymmetrically substituted α-branched aldehydes to nitroolefins have been described, but with few exceptions,[109,110] the existing protocols provide the adducts in low *ee* and/or *dr.*[111] The most efficient and general procedure for this reaction was described by Jacobsen in 2006. He used a bifunctional thiourea-derived primary amine as catalyst (**II**) to promote the transformation and the corresponding adducts were synthesized in excellent enantioselectivity in all the cases but variable diastereomeric ratios (Scheme 20).[110] For the addition of α,α-dialkyl aldehydes *dr* values ranging from 68:32 to >99:1 were obtained, which could be due to the presence of *E/Z* enamine mixtures in the alkyl aldehydes. Regarding α-aryl aldehydes, their addition to aliphatic nitroolefins was highly efficient in terms of enantio- and diastereoselectivity, but the reaction with nitrostyrenes required some modifications in the catalyst (Catalyst **III** in Scheme 20) to reach excellent results.

[107] D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601.
[108] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6* (15), 2527–2530.
[109] Szcześniak, P.; Staszewska-Krajewska, O.; Furman, B.; Młynarski, J. *ChemistrySelect* **2017**, *2* (9), 2670–2676.
[110] Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45* (38), 6366–6370.
[111] a) Ref. 110; b) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9* (4), 599–602; c) Ting, Y. F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem. Eur. J.* **2010**, *16* (23), 7030–7038; d) Chen, J. R.; Zou, Y. Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W. J. *Tetrahedron* **2010**, *66* (29), 5367–5372; e) Yoshida, M.; Sato, A.; Hara, S. *Org. Biomol. Chem.* **2010**, *8* (13), 3031–3036; f) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9* (1), 52–56; g) Porta, R.; Benaglia, M.; Coccia, F.; Cozzi, F.; Puglisi, A. *Adv. Synth. Catal.* **2015**, *357* (2–3), 377–383; h) Ref. 109.



Scheme 20. Michael addition of unsymmetrically substituted α-branched aldehydes to nitroolefins catalysed by a bifunctional thiourea-derived primary amine. ***Jacobsen, 2006.***[110]

Michael additions of α-branched α-hetero aldehydes like α-chloro and α-alkoxy aldehydes have been scarcely investigated and only few examples can be found in the literature and essentially all of them[67] proceed through enamine activation. Among α-branched α-heteroaldehydes, α-amino aldehydes are especially interesting since they are considered exceptionally valuable building blocks and they have applications in medicinal chemistry and pharmaceutical industry.[112] In fact, aldehydes can be transformed into a wide variety of functional groups, opening synthetic routes to highly substituted chiral amines.[113] Therefore, the preparation of enantiomerically pure quaternary α-amino aldehydes could be particularly useful.

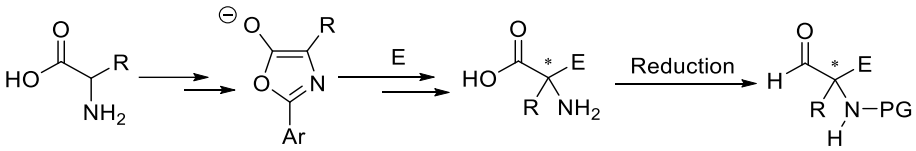
Although recent advances have been made with protocols consisting of the asymmetric hydrogenation of α-formyl enamides, which leads to tertiary α-amino aldehydes with very good enantioselectivities,[114] processes for the stereoselective synthesis of quaternary α-amino aldehydes have been little explored. The most employed synthetic routes nowadays consist of the stereoselective synthesis of quaternary α-amino acids or derivatives, followed by their selective reduction to prepare the desired quaternary α-amino aldehydes (Scheme 21). One of the reasons for this situation is the great number of protocols for the stereoselective synthesis of α-amino acid derivatives

[112] a) Hili, R.; Baktharaman, S.; Yudin, A. K. *Eur. J. Org. Chem.* **2008**, *31*, 5201–5213; b) Gryko, D.; Chałko, J.; Jurczak, J. *Chirality* **2003**, *15* (6), 514–541; c) Bergmeier, S. C. *Tetrahedron* **2000**, *56* (17), 2561–2576; d) Reetz, M. T. *Chem. Rev.* **1999**, *99* (5), 1121–1162; e) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164.

[113] Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, Germany, **2010**.

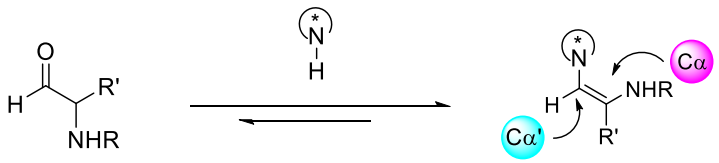
[114] Zhang, J.; Jia, J.; Zeng, X.; Wang, Y.; Zhang, Z.; Gridnev, I. D.; Zhang, W. *Angew. Chem. Int. Ed.* **2019**, *58* (33), 11505–11512.

that have been reported in the last years by using cyclic scaffold like azlactones[115] (depicted in Scheme 21) or chelated metal enolate systems.[116] This approach is especially useful for the control of the enolate configuration, which is key for an efficient stereocontrol and not so easy to achieve when using α-amino aldehydes as pronucleophiles. This could explain why the direct catalytic asymmetric synthesis of quaternary α-amino aldehydes, other than the α-amination of α-substituted aldehydes, has been very poorly investigated and there are no examples proceeding via enolate intermediates.



Scheme 21. Most employed method currently for the preparation of quaternary α-amino aldehydes by selective reduction of α-amino acid derivatives.

On the other hand, the existing protocols for the α-functionalization of α-amino aldehydes proceeding via enamine activation are very limited. One reason that can account for this fact is that once the aminocatalyst is condensed with the starting aldehyde, the nucleophile presents two enamines which could create a regioselectivity issue, that would be more prominent, with big substituents at the alpha position, since the attack of the α-carbon would be more congested (Scheme 22).



Scheme 22. Formation of two possible enamines in reactions of α-amino aldehydes via enamine.

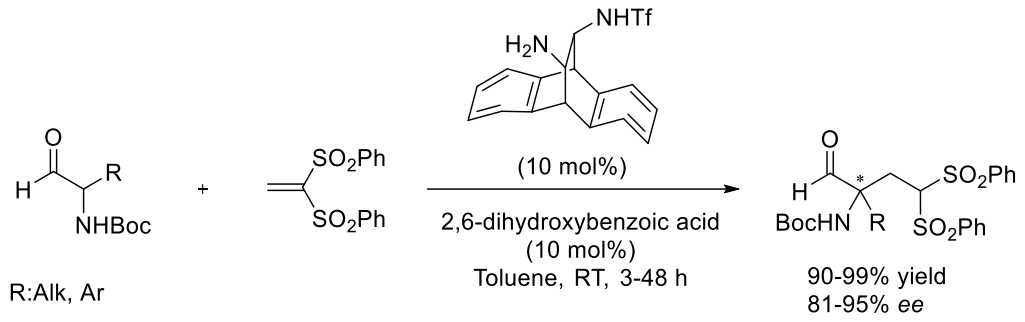
Only three efficient protocols have been reported in the literature for the preparation of quaternary α-amino aldehydes through the α-functionalization via enamine activation.[117] In a pioneer work by Maruoka in 2010 (Scheme 23),[103] they used a dihydroanthracene-derived primary amine to promote the Michael addition of

[115] For reviews, see: a) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19* (24), 2755–2762; b) Alba, A. N. R.; Rios, R. *Chem. Asian J.* **2011**, *6* (3), 720–734; c) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. *Chem. Eur. J.* **2016**, *22* (30), 10294–10318.

[116] a) Yamashita, Y.; Kobayashi, S. *Chem. Eur. J.* **2013**, *19* (29), 9420–9427; b) Wang, Y.; Song, X.; Wang, J.; Moriwaki, H.; Soloshonok, V. A.; Liu, H. *Amin. Acids* **2017**, *49* (9), 1487–1520; c) O'Donnell, M. J. *Tetrahedron* **2019**, *75* (27), 3667–3696.

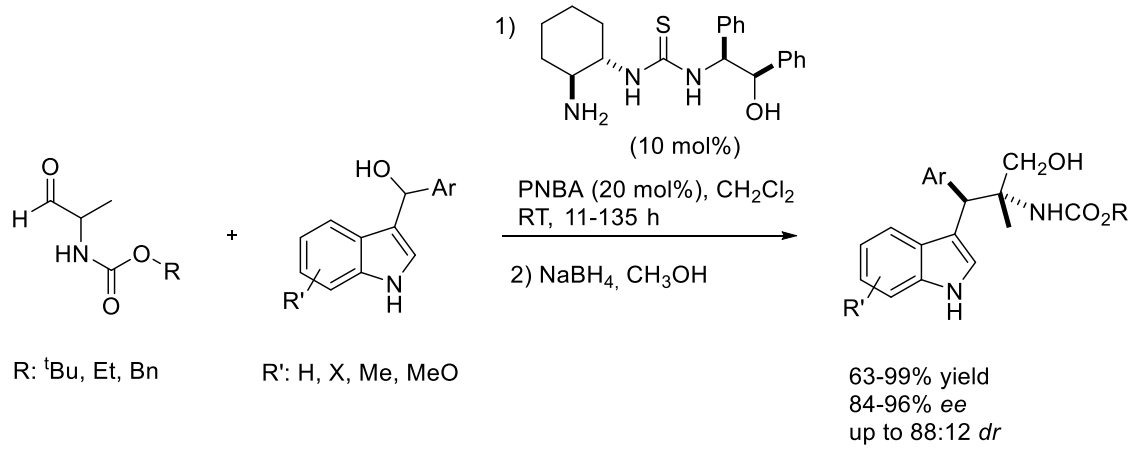
[117] Few papers have also reported a single example using α-amino aldehydes as pronucleophiles: a) Quintard, A.; Alexakis, A. *Chem. Commun.* **2010**, *46* (23), 4085–4087; b) Reference 106c; c) Reference 106d; d) Lang, S. B.; Locascio, T. M.; Tunge, J. A. *Org. Lett.* **2014**, *16* (16), 4308–4311; e) Song, L.; Gong, L.; Meggers, E. *Chem. Commun.* **2016**, *52* (49), 7699–7702.

substituted α-amino aldehydes with very good enantioselectivity results, but, it was limited to highly electrophilic vinyl sulfones.



Scheme 23. Michael addition of substituted α-amino aldehydes to vinyl sulfones. ***Maruoka, 2010.***[103]

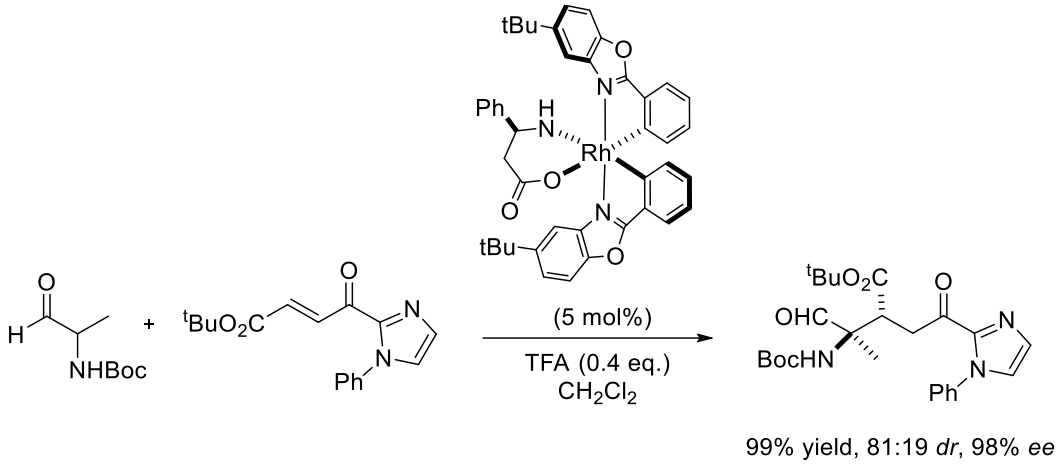
The other effective protocol reported by Guo and coworkers in 2014 was limited to α-methyl substituted α-amino aldehydes, as it happened to the Michael addition of α,α-disubstituted aldehydes to nitroolefins.[118] They studied the addition of α-amino aldehydes to 3‑indolylmethanols promoted by a thiourea-containing primary amine and obtained the adducts in excellent enantioselectivity and up to very good diastereomeric ratios (Scheme 24).



Scheme 24. Conjugate addition of α-amino aldehydes to 3‑indolylmethanols. ***Guo, 2014.***[118]

Worth of mentioning is the promising protocol developed by Meggers in which they use a transition metal in combination with the aminocatalyst for promoting the reaction with α,β-unsaturated 2-acyl imidazoles (Scheme 25).[117e] However, as it happened for Guo's development (Scheme 24), the only reported example bore a small substituent like methyl at the alpha position, probably due to the previously commented otherwise present regioselectivity issue (Scheme 22).

[118] Guo, Z. L.; Xue, J. H.; Fu, L. N.; Zhang, S. E.; Guo, Q. X. *Org. Lett.* **2014**, *16* (24), 6472–6475.

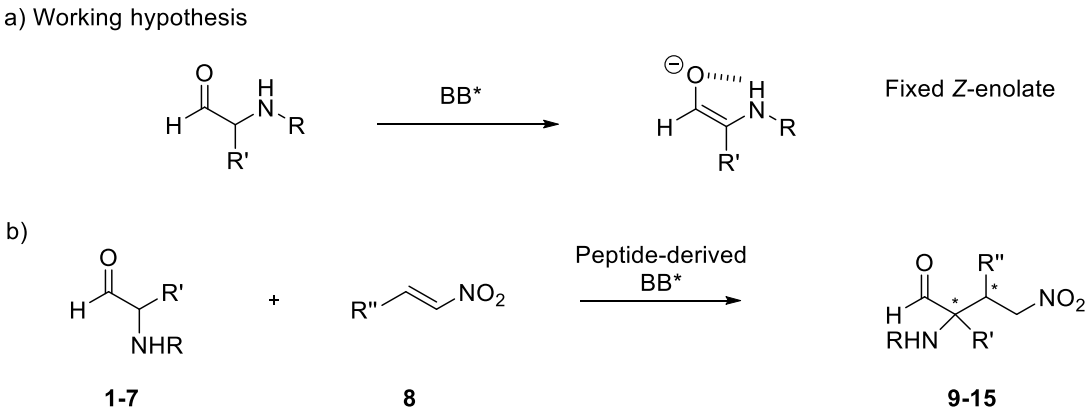


Scheme 25. Michael addition of an α-amino aldehyde to an α,β-unsaturated 2-acyl imidazole promoted by transition metal/enamine activation. ***Meggers, 2016.***[117e]

In this context, since the stereoselective aminocatalysed α-functionalization of α-amino aldehydes still presented some unsolved challenges, we wondered if the BB strategy could work as a complementary alternative for this reaction.

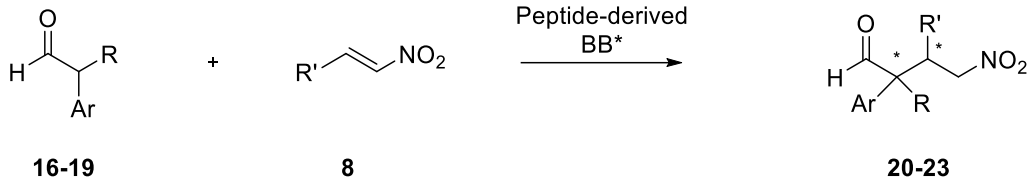
2.2. Objectives

Considering the limitations still present in the formation of quaternary stereocenters through the α-functionalization of α-amino aldehydes via enamine, we considered that bifunctional Brønsted base catalysts like the peptide derived BB catalysts explained in the introduction of this Thesis (Figure 6) could provide a solution. Additionally, we hypothesized that α-amino aldehydes could form an intramolecular H-bond between the NH group and the carbonyl, which, in principle, could fix the *Z*-enolate (Scheme 26a), assisting stereocontrol, while simultaneously increasing the acidity of the Cα-carbon facilitating its deprotonation. As a model reaction for preliminary studies, the Michael addition to nitroolefins was selected (Scheme 26b), whose adducts are of synthetic interest.[87]



Scheme 26. a) Hypothesized intramolecular interaction of the formed enolate. b) Michael addition of α-amino aldehydes to nitroolefins selected as the model reaction for preliminary studies.

Furthermore, we thought about expanding this chemistry to different α-branched aldehydes lacking this intramolecular H-bond. For this purpose, α-aryl acetaldehydes were selected as pronucleophiles for preliminary studies (Scheme 27), since they have not been explored as pronucleophiles in reactions promoted by BB catalysis either.



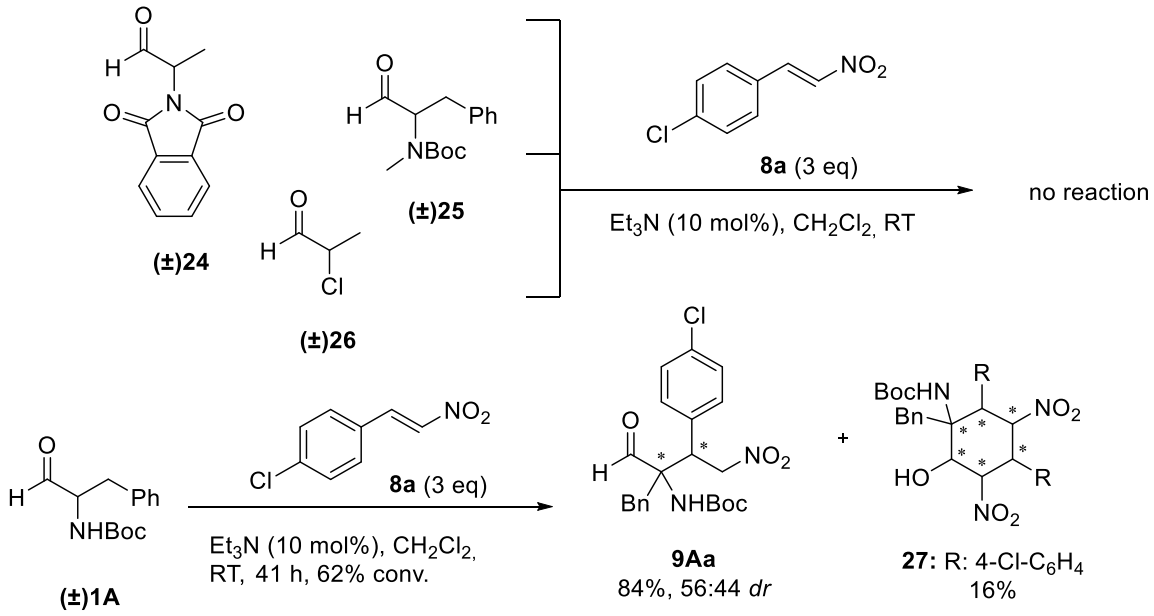
Scheme 27. Michael addition of α-branched α-aryl acetaldehydes to nitroolefins.

2.3. Results and discussion

2.3.1. Michael additions of α-amino aldehydes[119]

2.3.1.1. Preliminary experimental observations

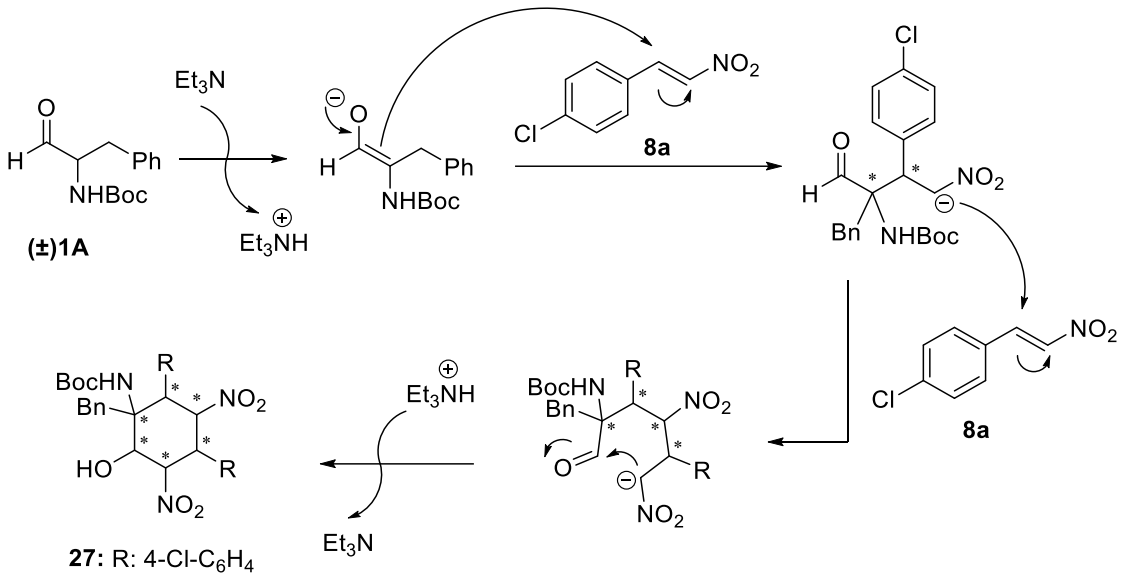
In a first instance, we began our study by exploring the reactivity of four representative α- substituted amino aldehydes like (±)-*N*-phthaloyl alaninal **24**,[120] (±)-*N*-methyl-*N*-Boc phenylalaninal **25**, 2-chloropropanal **26** and (±)-*N*-Boc phenylalaninal **1A** in their reaction with *p*-chloro nitrostyrene **8a** (3 eq.) and in the presence of Et_3N in CH_2Cl_2 at room temperature (Scheme 28). The results revealed that the only aldehyde that presented some reactivity was (±)-*N*-Boc phenylalaninal **1A,** which led after 41 h at room temperature to the expected adduct **9Aa** in 56:44 *dr* together with 16% of the cyclic product **27**. This product would come from a tandem Michael-Michael-Henry reaction, in which first, the deprotonated aldehyde would react with one molecule of nitroolefin, then the formed anionic intermediate would undergo the second Michael addition to another molecule of nitroolefin, and finally the six-member ring would form through a Henry reaction, as depicted in Scheme 29.



Scheme 28. Preliminary explorations with achiral Brønsted bases.

[119] García-Urricelqui, A.; de Cózar, A.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2021**, *27* (7), 2483–2492.

[120] Phthalimide was selected as protecting group because most of the described examples of aminocatalysed non substituted aldehydes as pronucleophiles use (±)-N-phthaloyl glicinal, see: a) Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6* (20), 3541–3544; b) Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. F. *Tetrahedron Lett.* **2007**, *48* (4), 693–696; c) Urushima, T.; Yasui, Y.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12* (13), 2966–2969; d) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2015**, *54* (48), 14363–14367.

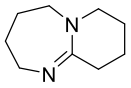
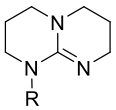
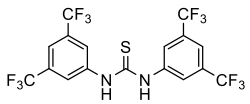
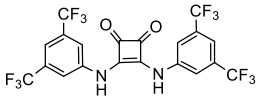


*Scheme 29. Proposed mechanism for the formation of cyclic compound **27**.*

Remarkably, the reaction with 2-chloropropanal **26** did not occur in the presence of a BB (Scheme 28), in spite of an existing precedent of a BB catalysed Michael addition of α-chloro aldehydes (see reference 67). This would confirm the hypothesis that the driving force for the described reaction was the cyclization of the final adduct.

Once established that (±)-*N*-Boc phenylalaninal **1A** was the only reactive aldehyde under the above conditions, the next step was the investigation of other BBs of variable basic strength (Table 1). Lower conversion was obtained when using DIPEA as catalyst (Table 1, entry 2) and stronger bases like DBU, TBD and MTBD led to nitrostyrene polymerization (Table 1, entries 3 and 4). When combining Et_3N with thiourea and squaramide H-bond donors, reaction conversion was increased, and specially, avoiding the formation of the cyclic byproduct **27a** (Table 1, entries 5 and 6). Noteworthy, no reaction was observed again for the addition of (±)-*N*-phthaloyl alaninal **24** and (±)-*N*-methyl-*N*-Boc phenylalaninal **25** in the presence of H-bond donors, which supports the idea that the NH group is necessary for the reaction to occur under soft enolization conditions.

*Table 1. Achiral BB screening for the addition of (±)-*N*-Boc phenylalaninal **1A** to* p*-chloro nitrostyrene **8a**.[a]*

Entry	Cat.	Base (mol%)	T(ºC)	t(h)	Conv. (%)[b]	9Aa (*dr*)[c]	27a
1	Et_3N	20	RT	17	31	>95 (58:42)	<5
				41	62	84 (56:44)	16
2	$^{i}Pr_2EtN$	20	RT	41	21	>99 (44:56)	<5
3	 (DBU)	10	0	1.5	<5[d]	0	0
4	 R:Me, MTBD	10	RT	20	<5[d]	0	0
	R:H, TBD		0	22	<5[d]	0	0
5	Et_3N / 	20	RT	15	48	>99 (51:49)	<5
6	Et_3N / 	20	RT	15	69	>95 (45:55)	<5

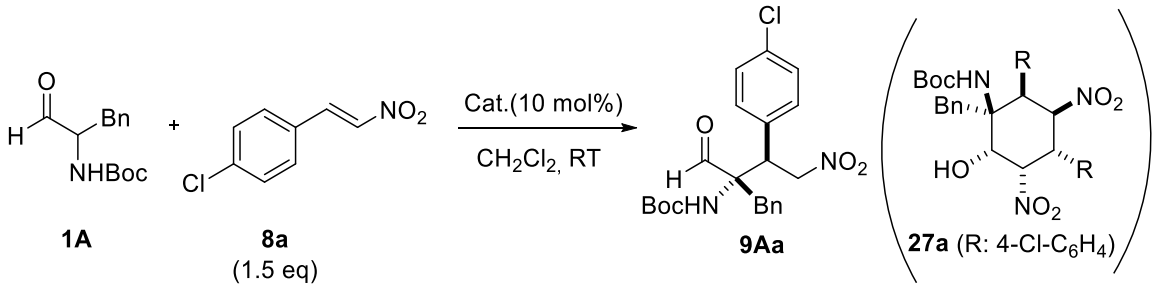
[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde 3:1). [b] Conversion determined by the disappearance of the starting aldehyde. [c] Determined by ^{1}H-NMR analysis. [d] Nitrostyrene polymerized.

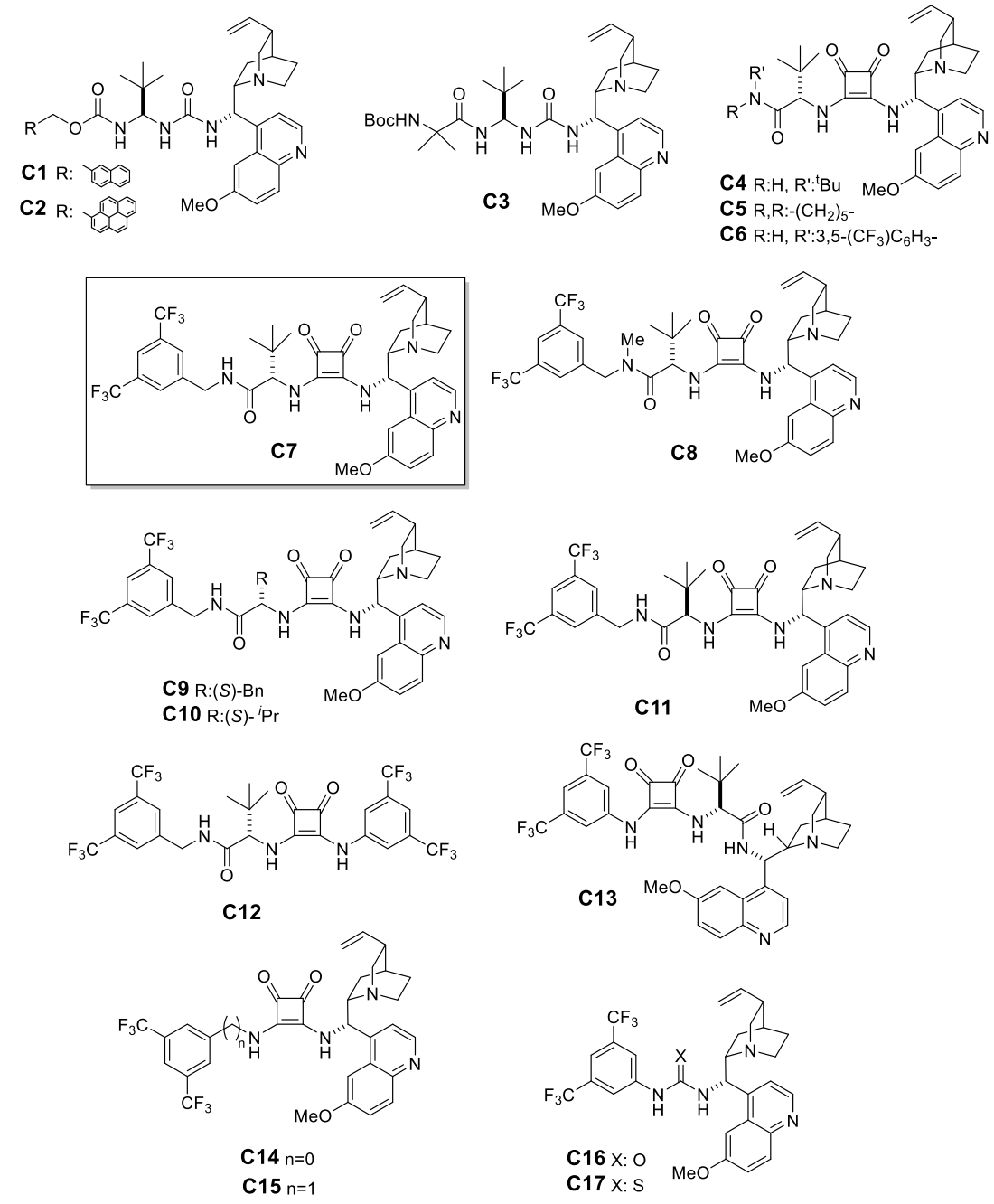
2.3.1.2. Catalyst screening and reaction optimization

After observing the results in Table 1, the next goal was to investigate if a chiral catalyst containing a BB and a H-bond donating moiety in its structure could promote the reaction between α-amino aldehydes and nitroolefins in a stereoselective way. The catalyst screening was performed for the reaction between (±)-*N*-Boc phenylalaninal **1A** and of *p*-chloro nitrostyrene **8a** (Scheme 30, Table 2). Reactions were carried out at RT with an aldehyde/nitroolefin 1:1.5 ratio and in the presence of 10 mol% of the catalyst.

First, ureidopeptide-like catalysts **C1**, **C2** and **C3**, previously designed by our research group,[53] were tested in the reaction (Table 2, entries 1-3) and a mixture of the expected Michael adduct **9Aa** and cyclic product **27a** in variable ratios (2-61%) was detected. However, in each case **9Aa** was obtained in poor diastereoselectivity and negligible enantioselectivity. Therefore, the replacement of the urea moiety by a squaramide unit that has more acidic H-bond donors[121] was considered for stereocontrol improvement. With this idea, *tert*-Leucine derived catalysts **C4**-**C7**, with different terminal amines, were synthesized and screened in the same reaction. All of the catalysts provided the *anti* adduct as the major product, according to Masamune's nomenclature,[122] in significantly better diastereomeric ratio than previously tested ureidopeptide-like catalysts and in excellent enantiomeric excess (Table 2, entries 4-7). Remarkably, a significant decrease on the detected cyclic product was observed. The best results in terms of stereoselectivity were obtained with **C6** and **C7**, but considering that the reaction in the presence of the latter required a shorter reaction time, benzylic terminal amine was selected as the most suitable. Experiments with catalyst **C8**, similar to **C7**, but with methylated terminal amine, provided adduct **9Aa** in worse diastereomeric ratio revealing the significance of the NH group of the terminal amine for stereocontrol (Table 2, entry 8). Further experiments with (*L*)-Phenylalanine and (*L*)-Valine catalysts **C9** and **C10** revealed that both were as effective as catalyst **C7** derived from (*L*)-*tert*-Leucine in terms of diastereoselectivity, but slightly worse regarding enantioselectivity. Moreover, the (*L)*-isomer seems to be the matched combination in this case, since catalyst **C11** coming from (*D*)-*tert*-Leucine provided lower stereoselectivity results (Table 2, entry 11).

[121] Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16*, 1786–1789.
[122] Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982***, 104*, 5521– 5523.





*Scheme 30. Catalysts tested in the Michael addition of N-Boc phenylalaninal **1A** to p-chloro nitrostyrene **8a**.*

*Table 2. Catalyst screening for the Michael addition of N-Boc phenylalaninal **1A** to p-chloro nitrostyrene **8a**.[a]*

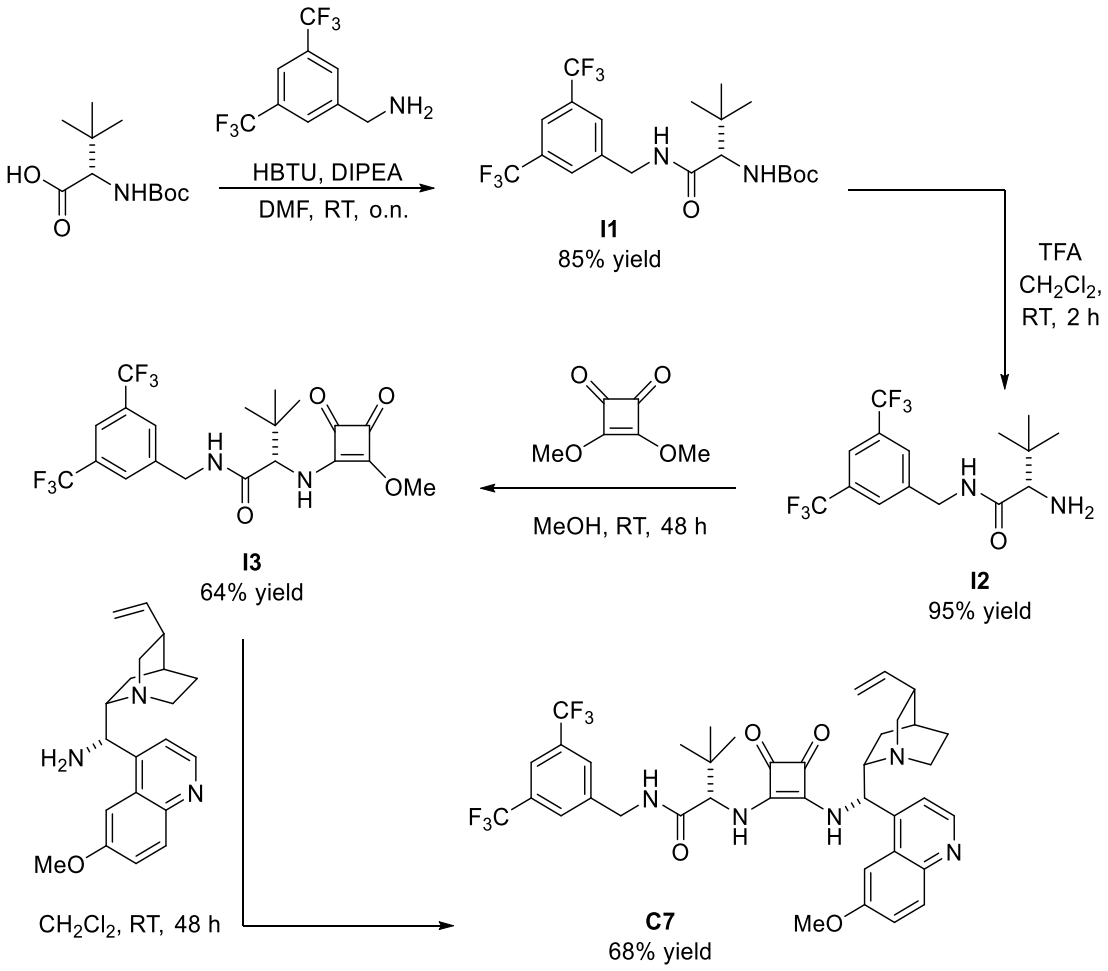
Entry	Cat.	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee*[e]
1	**C1**	RT	63	88 (61)	nd	39:61	nd
2	**C2**	RT	39	29 (2)	nd	64:36	nd
3	**C3**	RT	39	71(40)	31	50:50	37
4	**C4**	RT	66	>99(17)	81	83:17	89
5	**C5**	RT	91	>99(5)	70	89:11	84
6	**C6**	RT	45	>99(8)	77	89:11	98
7	**C7**	RT	24	96(9)	91	90:10	98
8	**C8**	RT	23	97(2)	81	85:15	97
9	**C9**	RT	15	90(3)	70	82:18	91
10	**C10**	RT	24	88(12)	69	86:14	94
11	**C11**	RT	15	98(5)	72	86:14	90
12	**C12**	RT	15	0 [f]	0	--	--
13	**C13**[g]	RT	120	58(no)	33	70:30	25
14	**C14**[g]	RT	21	92(28)	55	68:32	81
15	**C15**	RT	16	68(no)	64	66:34	73
16	**C16**	RT	20	79(no)	62	48:52	nd
17	**C17**	RT	18	44(no)	nd	73:27	nd

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of product **27a** coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC. nd: not determined. no: not observed. [f] In the presence of Et_3N (10 mol%) after 3 h 26% conversion and 57:43 dr were observed. In the presence of *i*Pr_2EtN (10 mol%) after 1 h 23% conversion and 52:48 dr were detected. [g] 20 mol% catalyst was used.

As expected, catalyst **C12** lacking a Brønsted base did not promote the reaction and even in the presence of Et_3N as external base conversion and diastereoselectivity were negligible (Table 2, entry 12). Not only the presence of the base is mandatory for the reaction to work efficiently, its position is also important, as 20 mol% of catalyst **C13**, that bears the base next to the amino acid unit instead of the squaramide provided adduct **9Aa** in lower *dr* and very poor enantiomeric excess (Table 2, entry 13). Typical standard squaramide, urea and thiourea catalysts **C14-C17** afforded lower stereoselectivity and

reactivity for the same reaction as well (Table 2, entries 14-17). Hence, catalyst **C7** was selected as the most efficient for the study of the reaction scope.

Catalyst **C7** could be easily prepared following the synthetic pathway depicted in Scheme 31. First *N*-Boc-(*L*)-*tert*-Leucine was coupled with the corresponding benzylic amine in the presence of HBTU and DIPEA leading to the formation of **I1** in 85% yield. After *N*-Boc-deprotection with TFA, the free amine **I2** was reacted with dimethyl squarate in MeOH to afford **I3** in 64% yield. Final coupling of **I3** with aminoquinine led to catalyst **C7** in 68% yield.

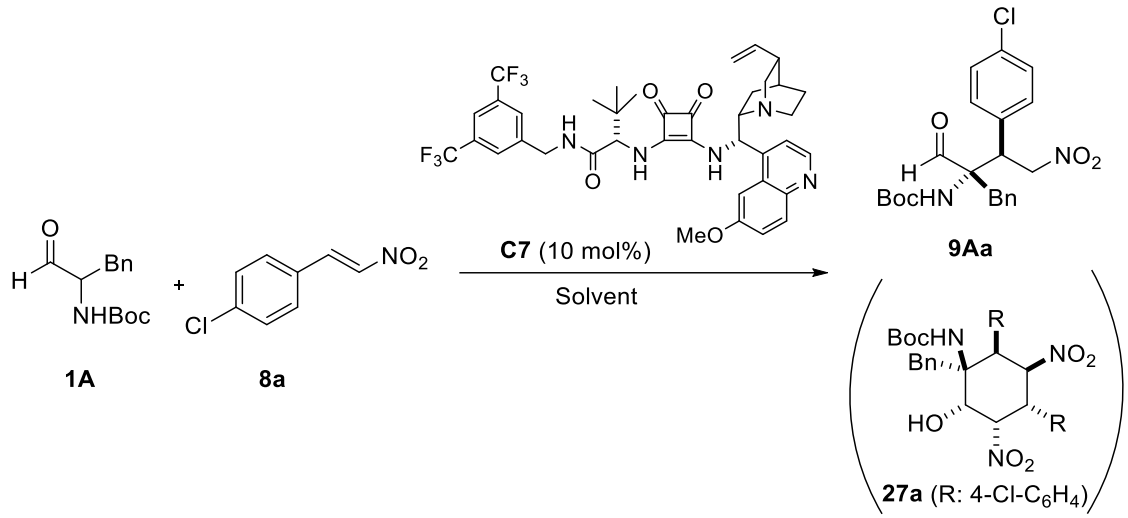


*Scheme 31. Synthesis of **C7**, the catalyst selected for the study of the reaction scope.*

Additional experiments in different solvents showed that the model reaction is as stereoselective in acetonitrile and 1,2-dichloroethane (1,2-DCE) as it is in dichloromethane (Table 3, entries 2, 3 and 6). However, while 1,2-DCE and CH_2Cl_2, that are of similar polarity, promoted reaction completion in only 24 h, the reaction in acetonitrile, that is significantly more polar, required longer reaction times to finish. THF slowed down the reaction too, although maintaining the stereoselectivity values (Table 3, entry 4). The reaction in toluene, which was the least polar solvent tested, was not as effective, since higher proportions of the cyclic side product were detected and slightly

lower stereoselectivity values were reached (Table 3, entry 1). Finally, the reaction in chloroform provided the reaction adduct in lower *dr* and was slower than in CH_2Cl_2 (Table 3, entry 5). When lowering the temperature to 0 ºC diastereoselectivity and reactivity decreased and more cyclic product was found in the reaction mixture (Table 3, entry 7).

*Table 3. Solvent screening for the addition of N-Boc phenylalaninal **1A** to p-chloro nitrostyrene **8a**.* [a]



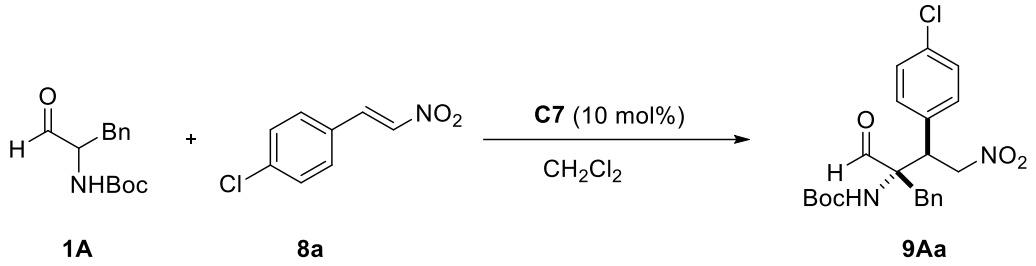
Entry	Solvent	Polarity index[123]	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee*[e]
1	**Toluene**	2.4	RT	40	92(16)	77	87:13	93
2	**CH_2Cl_2**	3.1	RT	24	96(9)	91	90:10	98
3	**1,2-DCE**	3.5	RT	24	95(12)	92	90:10	98
4	**THF**	4.0	RT	17	56(no)	31	89:11	98
5	**$CHCl_3$**	4.1	RT	40	89(12)	nd	83:17	nd
6	**CH_3CN**	5.8	RT	39	94(2)	81	90:10	98
7	**CH_2Cl_2**	3.1	0	114	99(22)	67	83:17	96

a 0.2 mmol scale in 0.6 mL of solvent (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of product **27a** coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC. nd: not determined. no: not observed.

All the previous reactions were carried out with racemic (±)-*N*-Boc phenylalaninal. An additional experiment with (*S*)-*N*-Boc phenylalaninal **1A** under the same reaction conditions provided the final adduct in similar reaction times and with comparable stereocontrol than racemic **1A** (Table 4). In consequence, racemic and enantiopure pronucleophiles were used for the scope of the reaction indistinctly.

[123] Snyder, L. R. *J. Chromatogr. Sci.* **1978**, *16* (6), 223–234.

Table 4. (±)-N-*Boc phenylalaninal vs (*S)-N-*Boc phenylalaninal as nucleophile.* [a]



1A **8a** **9Aa**

Entry	Nucleophile	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee*[e]
1	**(*S*)-1A**	RT	24	96(9)	91	90:10	98
2	***Rac*-1A**	RT	29	95(8)	61	90:10	97

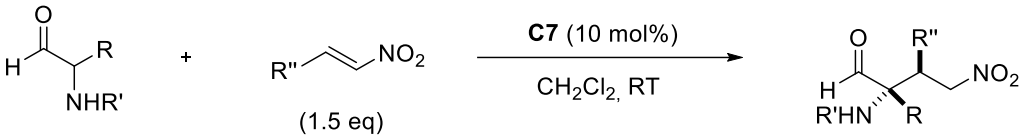
[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of the product coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

2.3.1.3. Reaction scope

We next investigated the scope of the reaction in the presence of catalyst **C7** under the optimized conditions (Scheme 32). The Michael addition tolerates nitrostyrenes with different substitution patterns bearing both electron-withdrawing and electron-donating groups providing excellent stereoselectivity results independently of their ortho, meta or para position (Table 5, adducts **9Ba**-**11Af**). Even in the case of **11Af** and **11Cf**, where an ortho-substituted nitrostyrene was employed, the reaction worked well but the catalyst loading had to be increased to 20 mol%. Nitroolefins containing alkenyl and alkynyl substituents also provided the final adducts in comparable stereoselectivity values (Table 5, adducts **11Ag** and **13Ai**). On the contrary, nitroalkane **8h** bearing a cyclohexyl group was unreactive under the presence of catalyst **C7** and the Michael donor.

Aldehydes *N*-protected with typical amino acid protecting groups as Boc, Fmoc and Cbz participated in the reaction reaching equally satisfactory stereoselectivity values for the *anti*-adducts. In some cases, the use of Fmoc as the protecting group, made the reaction go faster than when using their counterparts Boc or Cbz, like for adducts **9Ba** vs **9Ca** and **14Ab** vs **14Cb**.

Pronucleophiles derived from different amino acids could be employed in the reaction maintaining the levels of stereoselectivity even with some longer and branched carbon chains at the alpha position (Table 5, adducts **11** and **12**) as well as substituents in the α-benzylic ring of the aldehyde (adducts **13** and **15**). Amino aldehydes derived from α-amino acids with functionalized chains like Serine can also be employed (Table 5, adducts **14Ab** and **14Cb**). However, a limitation of this reaction seems to be the use of aldehydes with very bulky side chains like *N*-protected *tert*-leucinal and valinal, which were essentially unreactive under the optimized reaction conditions independently of the aldehyde *N*-protecting group (Boc, Cbz).



1 R:Bn
2 R:Me
3 R:Pr
4 R:^{i}Bu
5 R:3,4-$(MeO)_2C_6H_3CH_2$-
6 R:$BnOCH_2$-
7 R:4-$MeOC_6H_4CH_2$-

8a R": *p*-Cl-C_6H_4-
8b R": C_6H_5-
8c R": *p*-Me-C_6H_4-
8d R": *m*-MeO-C_6H_4-
8e R": *p*-Br-C_6H_4-
8f R": *o,p*-Me_2-C_6H_3-
8g R": Ph-CH=CH-
8h R": Cy
8i R": Ph−C≡C−

9 R:Bn
10 R:Me
11 R:Pr
12 R:^{i}Bu
13 R:3,4-$(MeO)_2C_6H_3CH_2$-
14 R:$BnOCH_2$-
15 R:4-$MeOC_6H_4CH_2$-

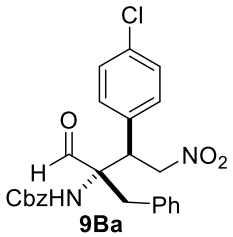
A R':Boc; **B** R':Cbz; **C** R':Fmoc

*Scheme 32. Scope of the Michael addition of α-amino aldehydes **1-7** to nitroolefins **8** catalysed by **C7.***

In general, the Michael additions were performed on a 0.2 mmol scale, but the reaction could be scaled up to 1 mmol without any loss in the stereoselectivity neither reactivity (see Experimental Section).

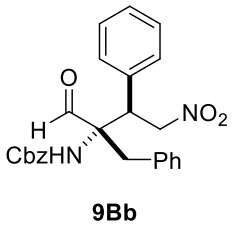
The configuration of adduct **9Bc** was determined by X-ray analysis (Figure 7)[119] and for the rest of the adducts it was assumed to be the same on the basis of a uniform reaction mechanism.

*Table 5. Scope of the Michael addition of α-amino aldehydes **1-7** to nitroolefins **8** catalysed by **C7**.*[a]



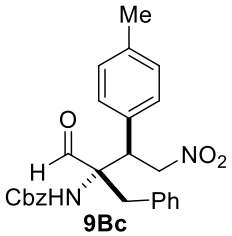
9Ba

39 h, 61% yield,
92:8 *dr*, 99% *ee*



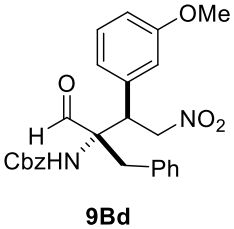
9Bb

39 h, 65% yield,
92:8 *dr*, 99% *ee*



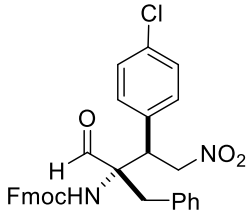
9Bc

24 h, 68% yield,
92:8 *dr*, 96% *ee*



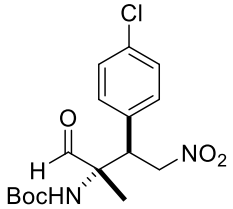
9Bd

24 h, 59% yield,[b]
91:9 *dr*, 97% *ee*



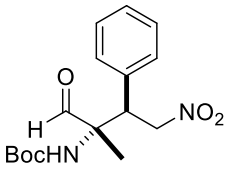
9Ca

23 h, 77% yield,[c]
96:4 *dr*, 99% *ee*



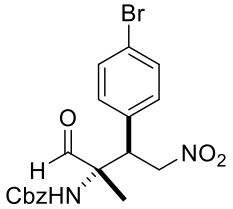
10Aa

87 h, 59% yield,[b]
90:10 *dr*, 97% *ee*



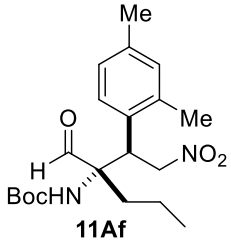
10Ab

63 h, 74% yield,
81:19 *dr*, 96% *ee*



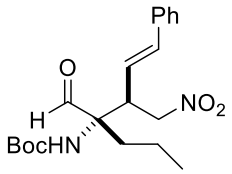
10Be

15 h, 65% yield,
86:14 *dr*, 97% *ee*



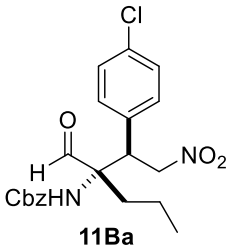
11Af

72 h, 80% yield,[d]
91:9 *dr*, 98% *ee*



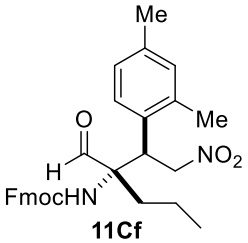
11Ag

44 h, 67% yield,[c]
88:12 *dr*, 97% *ee*



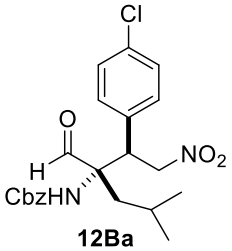
11Ba

55 h, 65% yield,
96:4 *dr*, 98% *ee*



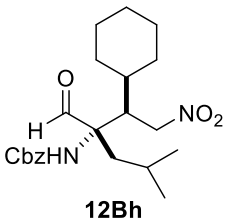
11Cf

72 h, 80% yield,[d]
91:9 *dr*, 99% *ee*



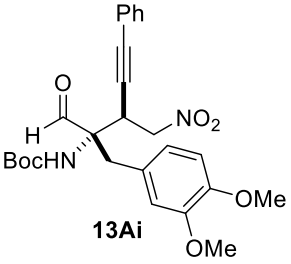
12Ba

39 h, 61% yield,
95:5 *dr*, 97% *ee*



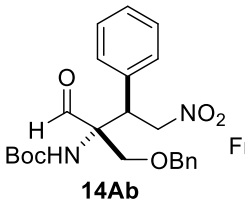
12Bh

39 h, n.r.



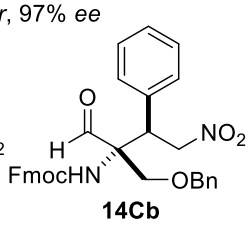
13Ai

87 h, 53% yield,
95:5 *dr*, 97% *ee*



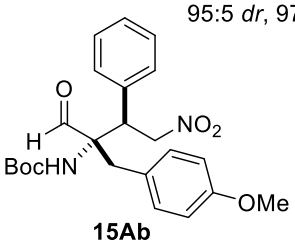
14Ab

88 h, 56% yield,
89:11 *dr*, 97% *ee*



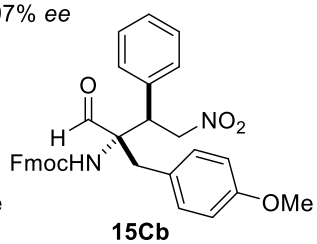
14Cb

15 h, 72% yield,
99:1 *dr*, 99% *ee*



15Ab

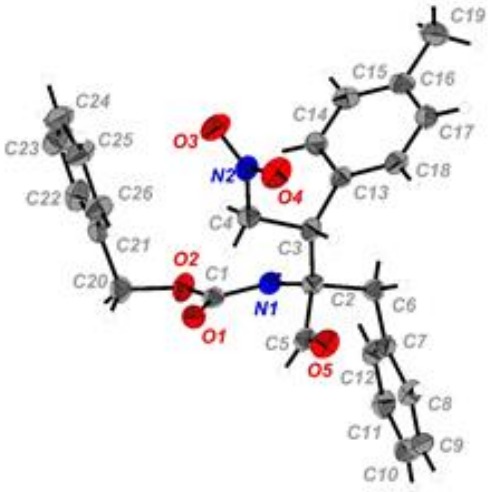
24 h, 80% yield,
88:12 *dr*, 97% *ee*

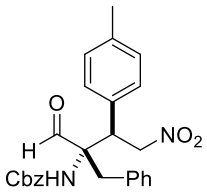


15Cb

24 h, 78% yield,
95:5 *dr*, >99% *ee*

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major isomer. Diastereomeric ratio determined by ^1H NMR (300 MHz) analysis on the crude product. Enantiomeric excess determined by chiral HPLC. [b] Less than 5% of the product coming from the tandem Michael-Michael-Henry reaction. [c] Yield for the isolated two isomers. [d] Reaction performed using 20 mol% of catalyst.



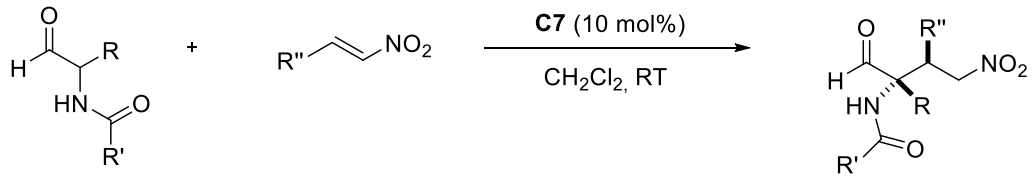


9Bc

*Figure 7. ORTEP diagram of adduct **9Bc.***

Besides carbamates, α-amino aldehydes bearing N-acyl groups also provide the corresponding Michael adduct after reacting with nitroolefins in the presence of **C7** (Scheme 33). Amino aldehydes with different aliphatic and aromatic N-acyl groups were tested and, in general, adducts were obtained in very good to excellent diastereoselectivities and essentially as a single enantiomer (Scheme *33. Scope of the* Michael addition of α-amino aldehydes 1, 4 and 7 to nitroolefins **8** catalysed by **C7.**

Table 6). However, an exception was amino aldehyde **1D** containing a pyridine ring, which afforded **9Db** in lower *dr* although with an acceptable *ee* for the major isomer.



1 R:Bn
2 R:Me
3 R:Pr
4 R:^{i}Bu
5 R:3,4-$(MeO)_2C_6H_3CH_2$-
6 R:$BnOCH_2$-
7 R:4-$MeOC_6H_4CH_2$-

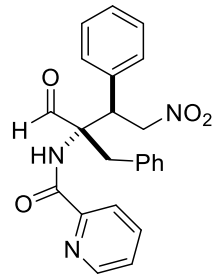
8a R": *p*-Cl-C_6H_4-
8b R": C_6H_5-
8c R": *p*-Me-C_6H_4-
8d R": *m*-MeO-C_6H_4-
8j R": 2-Naph-

9 R:Bn
10 R:Me
11 R:Pr
12 R:^{i}Bu
13 R:3,4-$(MeO)_2C_6H_3CH_2$-
14 R:$BnOCH_2$-
15 R:4-$MeOC_6H_4CH_2$-

D R':2-pyridyl; **E** R':Ph; **F** R':2-MeC_6H_4; **G** R':4-BrC_6H_4; **H** R':PhCH=CH-; **I** R':CH_3

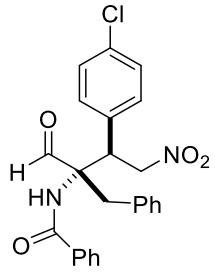
*Scheme 33. Scope of the Michael addition of α-amino aldehydes **1, 4** and **7** to nitroolefins **8** catalysed by **C7.***

*Table 6. Scope of the Michael addition of α-amino aldehydes **1**, **4** and **7** to nitroolefins **8** catalysed by **C7**.* [a]



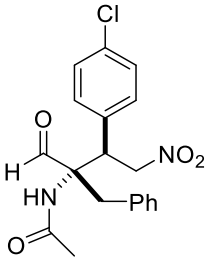
9Db

63 h, 40% yield,[b]
68:32 *dr*, 86% *ee*



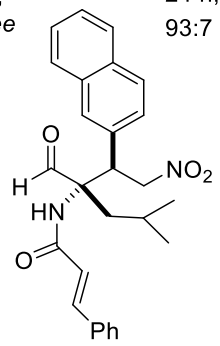
9Ea

24 h, 71% yield,[b,c]
93:7 *dr*, >99% *ee*



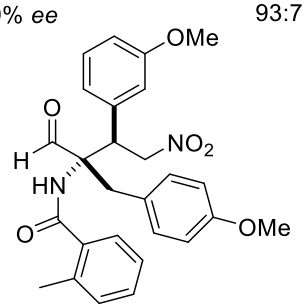
9Ia

40 h, 43% yield,
93:7 *dr*, >99% *ee*



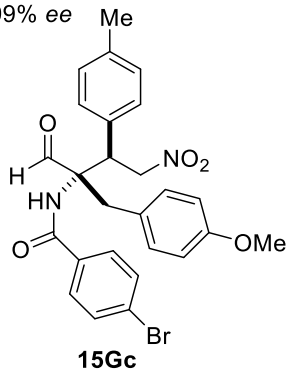
12Hk

64 h, 45% yield,
96:4 *dr*, >99% *ee*



15Fd

48 h, 77% yield,
85:15 *dr*, 99% *ee*



15Gc

82 h, 64% yield,
93:7 *dr*, 99% *ee*

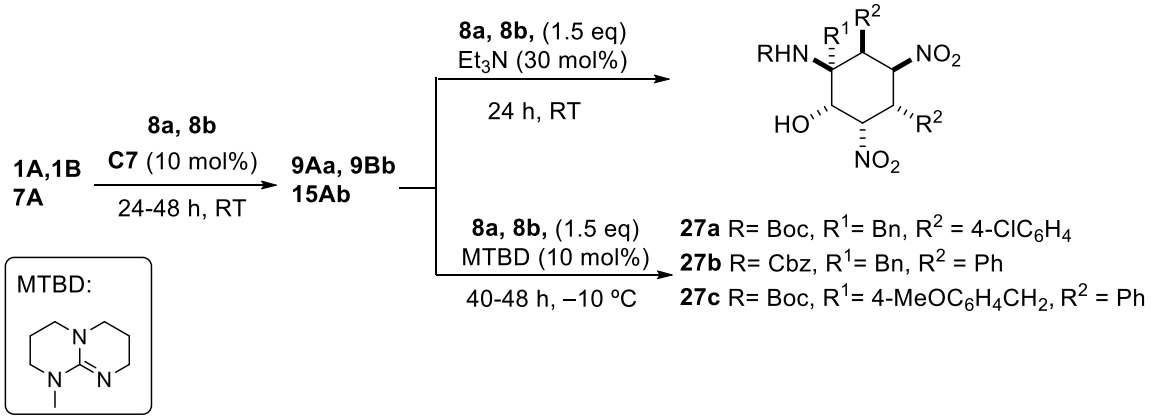
[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major isomer. Diastereomeric ratio determined by ^1H NMR (300 MHz) analysis on the crude product. Enantiomeric excess determined by chiral HPLC. [b] Yield for the isolated two isomers. [c] Less than 5% of the product coming from the tandem Michael-Michael-Henry reaction.

2.3.1.4. Adduct elaboration

In general, in all the previous reactions, 1.5 equivalents of the corresponding nitroolefins were employed. However, we found out that, by increasing the amount of the nitroolefin to 3 equivalents and adding an external base, the intermediate adducts may be converted, as noted in the preliminary experimental observations, into otherwise difficult to synthesize fully substituted cyclohexylamines bearing a tetrasubstituted stereogenic C_α-carbon (Table 7). These cycles that come from a Michael-Michael-Henry tandem reaction could be prepared in one pot. First, the previously optimized procedure for the preparation of the Michael adducts **9Aa**, **9Bb** and **15Ab** was followed and, once reaction completion was achieved, another 1.5 equivalents of nitroolefin and Et_3N (30 mol%) were added. The tandem reaction led to the formation of the cyclic compounds **27a**-**c**. As shown in Table 7, variations on the aromatic ring of the nitroolefin, as well as the protecting group and the side chain of the aldehyde were tolerated for this transformation with comparable reactivity and diastereoselectivity values. When using TEA as the external base for the cyclization step and performing the reaction at 0 ºC, the

cyclohexanes were obtained in an almost equimolar mixture of diastereomers for the carbon bearing the hydroxy group (Table 7, entry 1). Reaction conditions for the formation of the cycle were optimized by changing the base to MTBD and decreasing the temperature to -10 ºC and, even though longer reaction times were needed, diastereomeric ratio was significantly increased (Table 7, entry 2). The configuration of each stereogenic center was determined by NOESY experiments based on the previously known configuration of the two stereocenters formed during the first Michael addition (see Experimental Section).

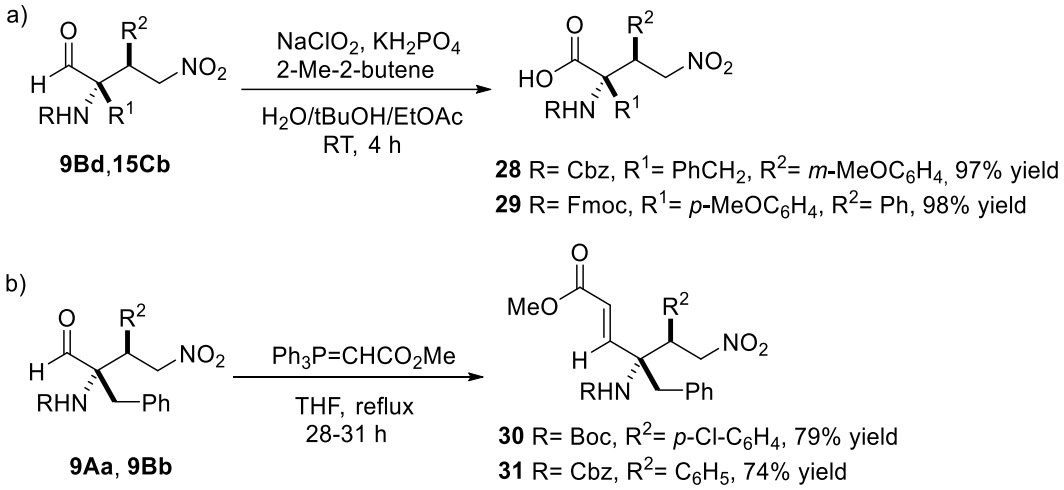
*Table 7. One pot synthesis of fully substituted cyclohexylamines **27**.[a]*



Entry	Base	Adduct	R	R^1	R^2	Yield (%)[b]	*dr*[c]
1	**Et_3N**	**27a**	Boc	Bn	4-ClC_6H_4	67	56:44
		27b	Cbz	Bn	Ph	74	68:32
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	80	65:35
2	**MTBD**	**27a**	Boc	Bn	4-ClC_6H_4	81	85:15
		27b	Cbz	Bn	Ph	83	80:20
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	82	88:12

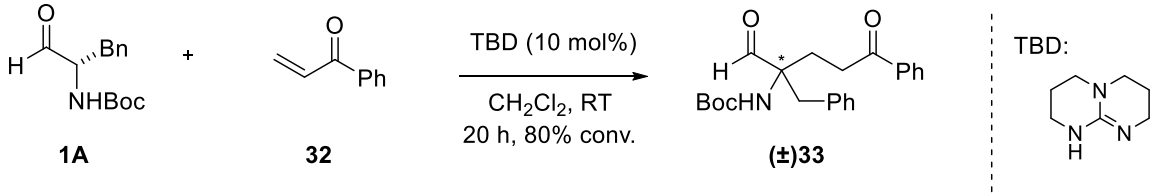
[a] Reactions conducted on a 0.5 mmol scale in 1.5 mL of CH_2Cl_2 (mol ratio for the first step: nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Sum of the yields of the separately isolated two isomers. [c] Diastereomeric ratio determined by ^1H NMR (300 MHz) analysis on the crude product.

The prepared Michael adducts could also be transformed in excellent yields into tetrasubstituted α-amino acids by their exposure to oxidative conditions, as depicted in Scheme 34 for representative examples **9Bd** and **15Cb** which provided α-amino acids **28** and **29** (Scheme 34, a). A Wittig reaction on the carbonyl of the aldehyde could also be performed to access highly functionalized allyl amines **30** and **31** with two, quaternary and tertiary, contiguous stereocenters in good yields (Scheme 34, b).



*Scheme 34. a) Oxidation of adduct to synthesize tetrasubstituted α-amino acids **28** and **29**. b) Wittig reaction to prepare highly functionalized allyl amines **30** and **31**.*

The tolerance of α-amino aldehydes to bases stronger than tertiary amines (see Table 1) makes them useful for reaction with less reactive electrophiles. As an example, the Michael addition of α-amino aldehyde **1A** to phenyl vinyl ketone **32** carried out in the presence of TBD as the catalyst afforded an 80% yield of the racemic mixture of the adduct **(±)33** after 20 h at RT (Scheme 35).



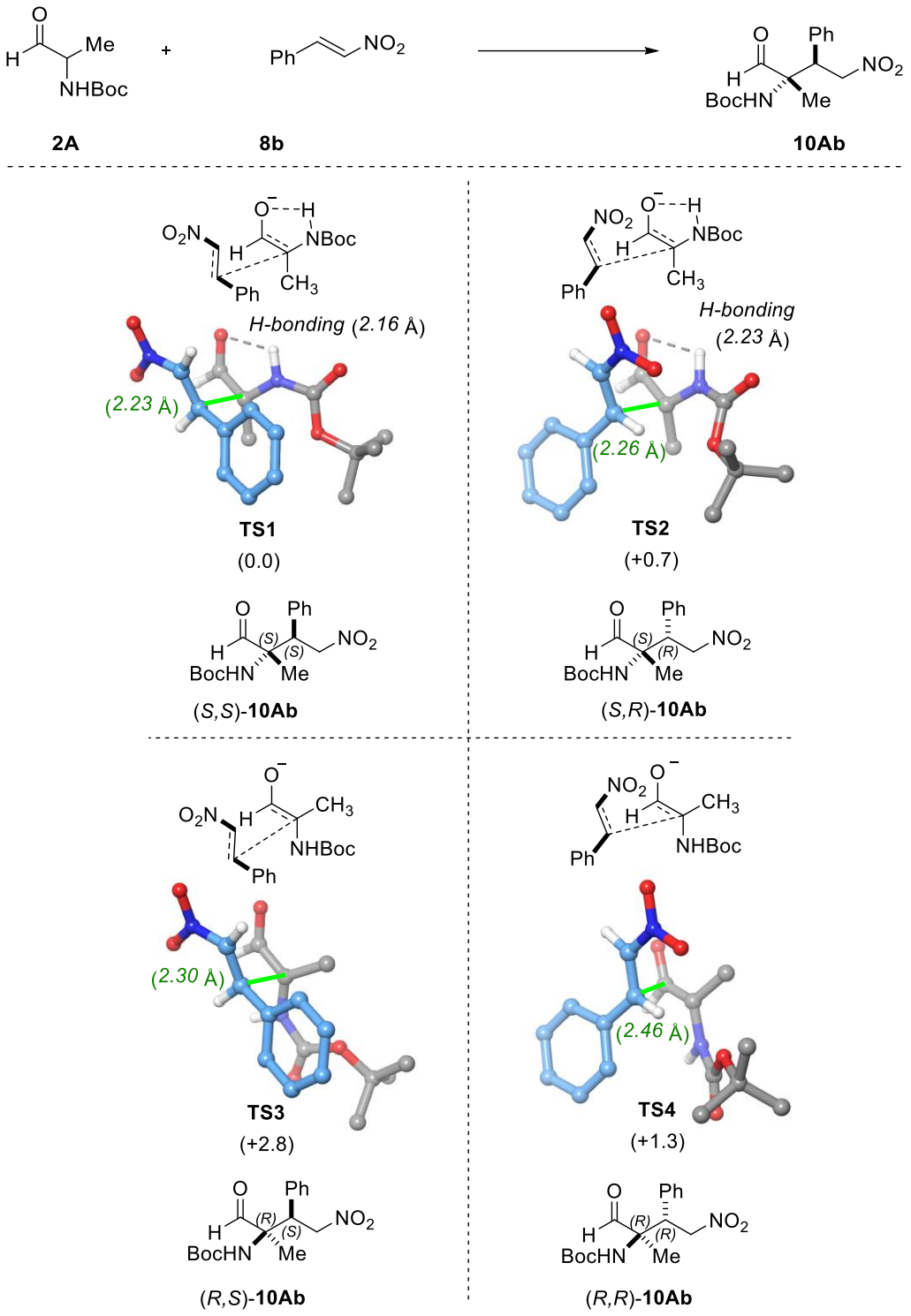
*Scheme 35. Michael addition of α-amino aldehyde **1A** to phenyl vinyl ketone **32**.*

2.3.1.5. Theoretical proofs and mechanistic observations

With the aim of better understanding the mechanism of the reaction, some computational studies within the DFT[124] framework were carried out in collaboration with our colleague Dr. Abel de Cózar. First, the C-C bond formation step for the model reaction between **2A** and **8b** was studied in the absence of catalyst (Scheme 36). The two possible enolate configurations were considered (*E*-enolate and *Z*-enolate). The results show the presence of the intramolecular H-bonding interaction hypothesized at the beginning of this study in transition states **TS1** and **TS2** coming from the *Z*-enolate (leading to adducts *S,S*-**10Ab** and *S,R*-**10Ab** subsequently), which renders them energetically favored over **TS3** and **TS4** coming from the aldehyde *E*-enolate (leading to adducts *R,S*-**10Ab** and *R,R*-**10Ab**). Among the two transition states that present the *Z* enolate, **TS1** wherein the *Z*-enolate approaches the prochiral *Si* face of the nitroolefin is 0.7 kcal mol^{-1} less energetic than **TS2**

[124] Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford: New York, **1989**.

wherein the *Z*-enolate approaches the *Re* face of the nitrolkane. This is translated into a theoretical *dr* of 76:24 in the absence of catalyst, which is in agreement with the observed *dr* for the racemic reaction of **2A** with **8b** in the presence of an achiral catalyst, leading to a 74:26 diastereomeric ratio.



*Scheme 36. Computed possible transition states for the non-catalysed reaction of N-Boc-alaninal **2A** and nitrostyrene **8b**. Relative Gibbs free energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). Below each TS, the adduct that would be obtained in that case.*

Then, to get a more insightful view of the reaction mechanism, calculations for the same reaction in the presence of catalyst **C7** were performed. The first question was to elucidate which was the preferred H-bonding pattern between the catalyst and the substrates in the reactive complex corresponding to the C-C bond forming step. As explained in the introduction, for reactions promoted by a bifunctional BB catalyst like **C7** three different coordination patterns between the catalyst and the substrates have been proposed (Figure 8). The catalyst could interact with the substrates following Takemoto's model (Model A),[50,54] Pápai's model (Model B)[55] or Wang's model (Model C).[56]

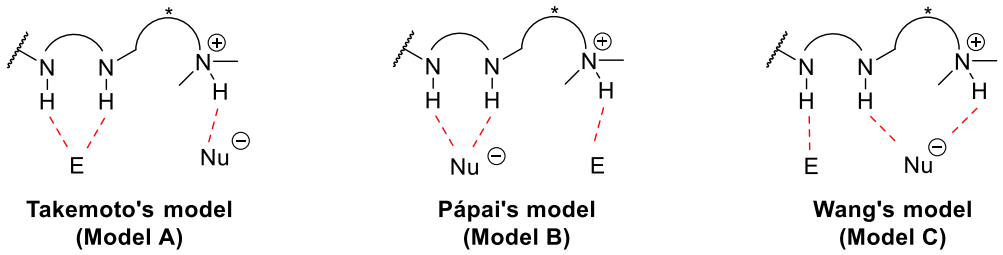


Figure 8. Three possible substrate-catalyst coordination patterns proposed for bifunctional BB activation mode.

Remarkably, all attempts to obtain reactive complexes following model C lead to their analogous model A in only few optimization steps. Therefore, model C was discarded for this reaction. Furthermore, calculations found that the least energetic reactive complexes following coordination models A and B were energetically very similar, so Curtin-Hammet kinetics were assumed for the study, in which the product ratio is considered dependent on the free Gibbs activation energy difference of the corresponding transition states.

Regarding the calculated transition states, the structures and relative Gibbs energies of the least energetic one for the reaction of **2A** and **8b** in the presence of **C7** are shown in Figure 9, as well as the adduct that would be obtained coming from each TS. In general, TS following Takemoto's coordination model (model A) were energetically less favored, so only TS for the model B following Pápai's model were considered (Figure 9). It is noteworthy to mention the intramolecular H-bond between the NH of the terminal amine and one of the carbonyls of the squaramide moiety present in catalyst **C7**, which was also observed in preliminary calculations of the catalyst **C7** alone. This intramolecular interaction that was present in all the calculated models, with negligible variations in the distance, increases the H-bond donating ability of the squaramide moiety and fixes the conformation that the catalyst adopts, where the position of the *tert*-Leucine seems crucial for face selectivity. An additional experimental proof of the significance of this H-bond is the fact that commercial squaramides **C14** and **C15** lacking this intramolecular interaction provided the final adduct **9Aa** in significantly lower stereoselectivity.

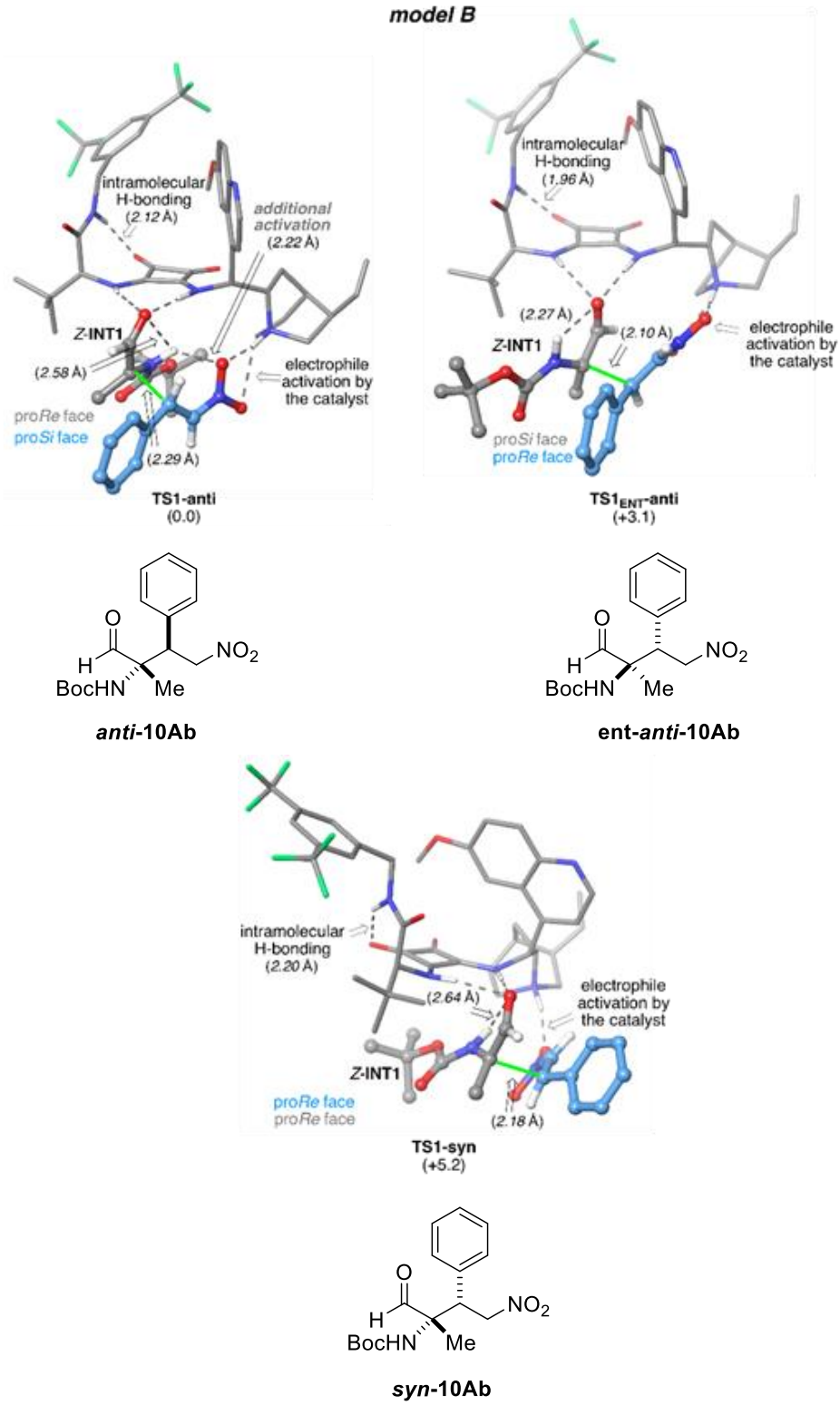


*Figure 9. Main geometrical features and relative Gibbs free energies of least energetic transition structures associated with the reaction of **2A** and **8b** catalysed by **C7** according to Pápai's (model B) model. Some hydrogen atoms are omitted for clarity. Energy values kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in blue and grey respectively. Below each TS, the adduct that would be obtained in that case.*

In all transition structures (Figure 9) a pseudo-eclipsed conformation between the new C–C bond was found, a structural feature that may justify the lack of reactivity of pronucleophilic aldehydes with sterically hindered side chains like *tert*-leucinal and valinal that was observed experimentally.

As observed for the non-catalysed reaction, the least energetic **TS1** for the addition in the presence of **C7** involves the participation of the *Z*-enolate, which is fixed by the intramolecular H-bond in the aldehyde. The big difference in the relative Gibbs free energies (over 3 kcal mol^{-1}) between **TS1-anti,** leading to the obtained ***anti*-10Ab** adduct, and **TS1-syn**, which leads to the formation of the syn diastereomer, is in accordance with the experimentally observed high diastereoselectivity towards the *anti*-adduct. Regarding the enantioselectivity of the *anti*-adduct that the experimental reaction provided, the excellent results were corroborated by the 5.2 kcal mol^{-1} difference in ΔG of **TS1-anti** and **TS_{ENT}-anti,** being the first one the least energetic. Among the three TSs depicted in Figure 9, **TS1-anti** was found to be the least energetic, probably due to an additional stabilizing H-bond between the NH on the amino aldehyde and one of the oxygens on the nitrostyrene that is only present in this TS. The obtained computational results are in agreement with the configuration of the adducts confirmed by X-ray analysis (Figure 7).

2.3.2. Michael additions of α-branched aryl acetaldehydes[125]

Inspired by the good results obtained with α-amino aldehydes, the extension of the study to other α-branched aldehydes was considered. We wondered if the reaction with aldehydes lacking the intramolecular interaction could be promoted by the same family of catalysts, and in that case, which would be the operating enolate geometry (Figure 10). So, in a first instance, α-aryl acetaldehydes were selected for preliminary studies.

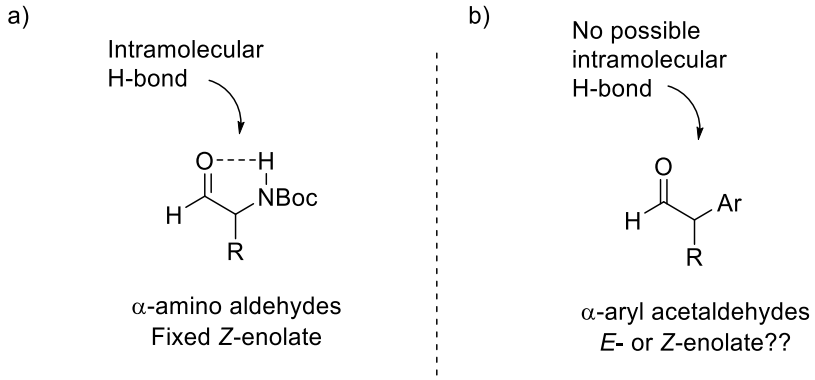
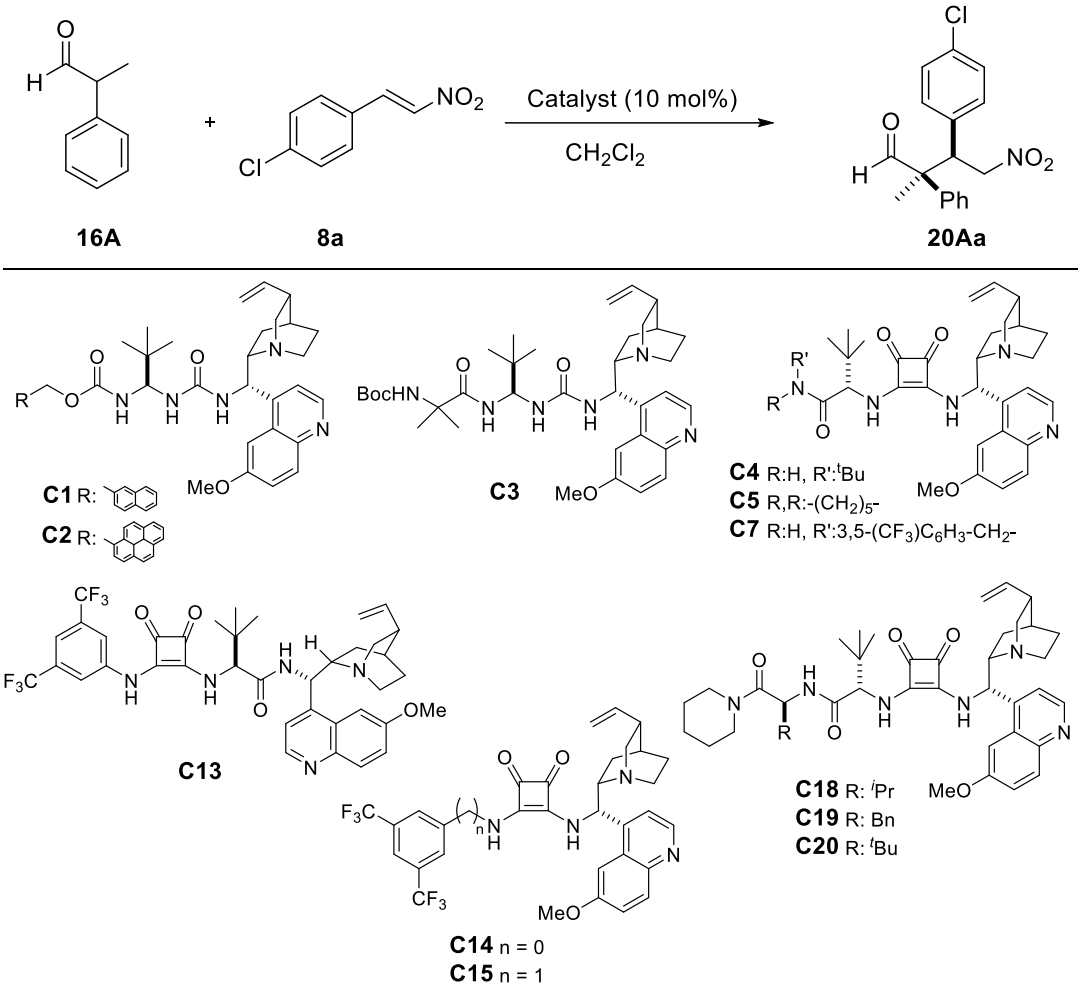


Figure 10. a) α-Amino aldehydes explored in the previous Michael addition. b) Proposed aldehydes to investigate the extension of the scope

[125] García-Urricelqui, A.; de Cózar, A.; Campano, T. E.; Mielgo, A.; Palomo, C. *Eur. J. Org. Chem.* **2021**, *25*, 3604–3612.

2.3.2.1. Preliminary experimental observations and catalyst screening

With that idea, initial studies were carried out with (±)-phenyl propionaldehyde **16A** as pronucleophile and the previously selected nitrostyrene **8a** as the electrophile (Scheme 37). First, ureidopeptide-like catalysts **C1**, **C2** and **C3** tested for the addition of α-amino aldehydes were also tried for this reaction and, in this case, the *syn* adduct was obtained in good diastereomeric ratios but very poor *ee* values (Table 8, entries 1-3). The reactions were carried out at RT with an aldehyde/nitroolefin 1:3 ratio and in the presence of 10 mol% of the catalyst. Remarkably, no cyclic product coming from a Michael-Michael-Henry tandem reaction, nor homoaldol products were observed.



*Scheme 37. Catalysts tested in the addition of (±)-2-phenyl propionaldehyde **16A** to nitrostyrene **8a**.*

Then, peptidic squaramide **C7** that had provided the best results for the α-amino aldehydes, as well as **C4** and **C5** with variations on the terminal amine, were tested in the reaction (Table 8, entries 4-6). Among them, piperidine containing **C5** gave the best results in terms of stereoselectivity, with 90:10 *dr* and 94% *ee*. At this point, with the idea of optimizing the obtained diastereomeric ratio, the incorporation of a second amino acid into the catalyst structure was considered to lengthen its peptidic chain and catalysts **C18**,

C19 and **C20**, bearing a Valine, Phenylalanine and *tert*-Leucine unit respectively were prepared. Whereas catalyst **C18** provided the final product in lower stereoselectivity than **C5**, **C19** produced **20Aa** in similar diastereo- and enantioselectivity results and with **C20,** the product was afforded in better *dr* but slightly lower *ee* values (Table 8, entries 7-9). By lowering the temperature to 0 ºC, results with **C20** improved to 95:5 *dr* and 94% *ee* (Table 8, entry 10). Reaction with **C13** demonstrated the relevance of the position of each scaffold in these catalysts, since in its presence the enantioselectivity dropped to 74% *ee* (Table 8, entry 11). Commercially available simpler squaramides **C14** and **C15** did not provide good enough diastereoselectivity either (Table 8, entries 12-13).

*Table 8. Catalyst screening for the addition of (±)-2-phenyl propionaldehyde **16A** to nitrostyrene **8a**.[a]*

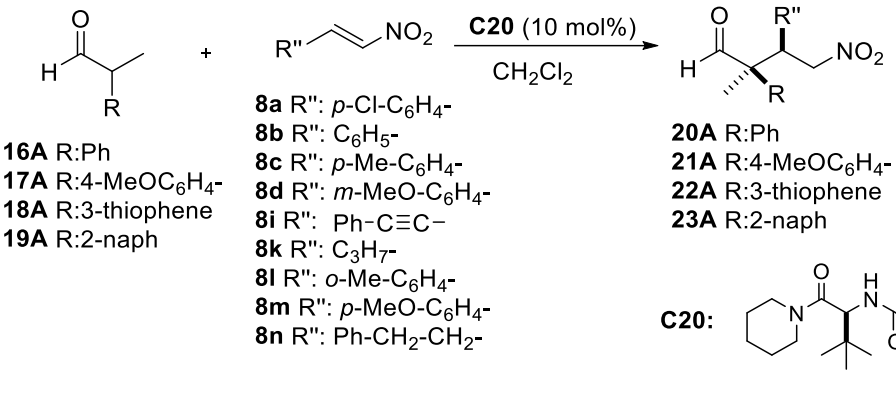
Entry	Cat.	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee*[e]
1	**C1**	RT	29	92	69	83:17	47
2	**C2**	RT	13	74	68	85:15	-2
3	**C3**	RT	72	88	90	81:19	24
4	**C4**	RT	35	98	85	88:12	89
5	**C5**	RT	30	98	89	90:10	94
6	**C7**	RT	72	>99	91	86:14	84
7	**C18**	RT	15	>99	87	86:14	85
8	**C19**	RT	20	>99	92	88:12	93
9	**C20**	RT	10	98	82	91:9	88
10		0	15	85	84	95:5	94
11	**C13**	RT	15	88	78	92:8	74
12	**C14**	RT	23	93	74	84:16	96
13	**C15**	RT	40	98	71	86:14	96

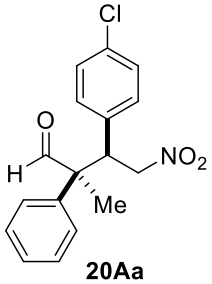
[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). [b] Determined by the disappearance of the starting aldehyde. [c] Yield of the isolated two diastereoisomers. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

2.3.2.2. Reaction scope

Once **C20** was selected as the best catalyst, different nucleophiles and electrophiles were tested to explore the scope of the reaction. First, the addition of (±)-phenyl propionaldehyde **16A** to different nitroolefins was studied to afford adducts **20Aa-20Am** (Table 9). The results show that the reaction tolerates nitrostyrenes with substituents in *para* (**8a**, **8c**, **8m**), *meta* (**8d**) and *ortho* (**8l**), as well as the more recalcitrant

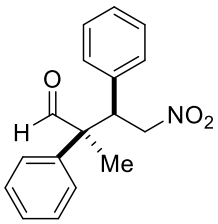
*Table 9. Scope for the Michael addition of α-methyl (hetero)aryl acetaldehydes **16A**-**19A** to nitroolefins **8** catalysed by **C20**.* [a]





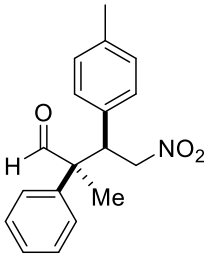
20Aa

15 h, 85% conv.,
84% yield,
95:5 *dr*, 94% *ee*



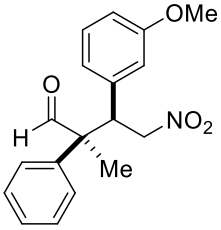
20Ab

27 h, 96% conv.,
83% yield,
94:6 *dr*, 96% *ee*



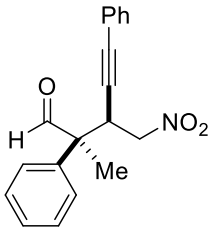
20Ac

23 h, > 99% conv.,
83% yield,
97:3 *dr*, 99% *ee*



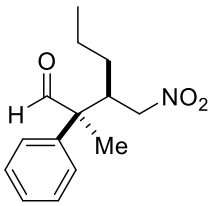
20Ad

23 h, > 99% conv.,
49% yield,
94:6 *dr*, 92% *ee*



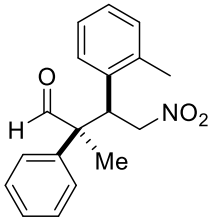
20Ai

22 h, 96% conv.,
72% yield,
90:10 *dr*, 96% *ee*



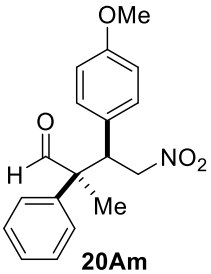
20Ak

69 h, 78% conv.,
57% yield,
96:4 *dr*, 99% *ee*[b]



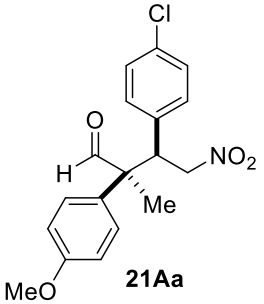
20Al

23 h, 92% conv.,
83% yield,
95:5 *dr*, 94% *ee*



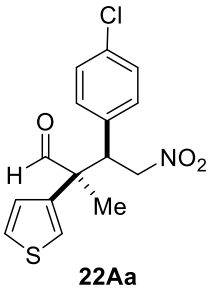
20Am

23 h, 95% conv.,
92% yield,
96:4 *dr*, 87% *ee*



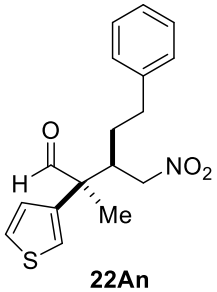
21Aa

47 h, 89% conv.,[c]
74% yield,
93:7 *dr*, 93% *ee*



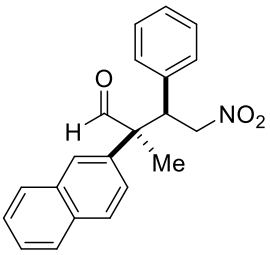
22Aa

16 h, >99% conv.,
80% yield,
91:9 *dr*, 94% *ee*



22An

16 h, 97% conv.,
45% yield,
90:10 *dr*, 97% *ee*



23Ab

16 h, >99% conv.,
71% yield,
98:2 *dr*, 91% *ee*

[a] Reactions conducted at 0 ºC on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major diastereoisomer. Diastereomeric ratio determined by 1H NMR (300 MHz) analysis on the crude product. Enantioselectivity determined by chiral HPLC. [b] Reaction carried out at rt. [c] Yield of the isolated two isomers.

aliphatic nitroolefins (**8k**, **8i**), providing the adducts with excellent stereoselectivity. Reaction scope can also be extended to different α-methyl aryl and heteroaryl acetaldehydes that gave adducts **21Aa**, **22Aa**, **22An** and **23Ab** in equally good enantioselectivity and diastereomeric ratios.

The relative and absolute configuration of adduct **20Ac** was determined by X-ray analysis (Figure 11)[125] and that of the rest of the adducts was assumed on the basis of a uniform reaction mechanism.

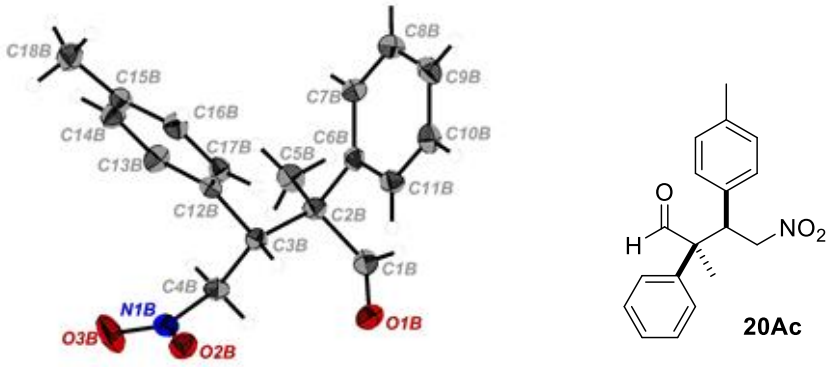


*Figure 11. ORTEP diagram of adduct **20Ac.***

In general, the dipeptide derived catalyst **C20**, which bears several H-bond donors[126] was superior to catalysts with a single amino acid in their structure, like **C5**, not only regarding stereocontrol, but also in terms of reaction conversion. In this context, some kinetic experiments were carried out for the reaction between (±)-phenyl propionaldehyde **16A** and *p*-chloro nitrostyrene **8a** in the presence of **C5** and **C20** (Figure 12). Indeed, data in Figure 12 confirm that the reaction progresses relatively faster when using dipeptide derived **C20**.

This above difference in reactivity was also detected when performing the reaction with α-ethyl and α-benzyl aldehydes **16B** and **16D** catalysed by **C5** or **C20** (Table 10). In the presence of dipeptide derived catalyst **C20** adduct **20Bb** was produced in 56% conversion after 67 h at 0 ºC, while it took 112 h to obtain the same conversion in the presence of **C5**. Similarly, adduct **20Dc** was formed in 85% conversion after 142 h in the presence of **C20**, but reaction proceeded more slowly with catalyst **C5**.

[126] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; b) Fanga, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

t (min)	Conversion (%)	
	C20	**C5**
0	10	9
15	24	-
30	38	23
45	48	-
60	55	33
75	62	-
90	66	43
105	70	-
120	74	50
150	79	56
180	84	62
240	88	71
300	92	78
420	95	88
600	98	93

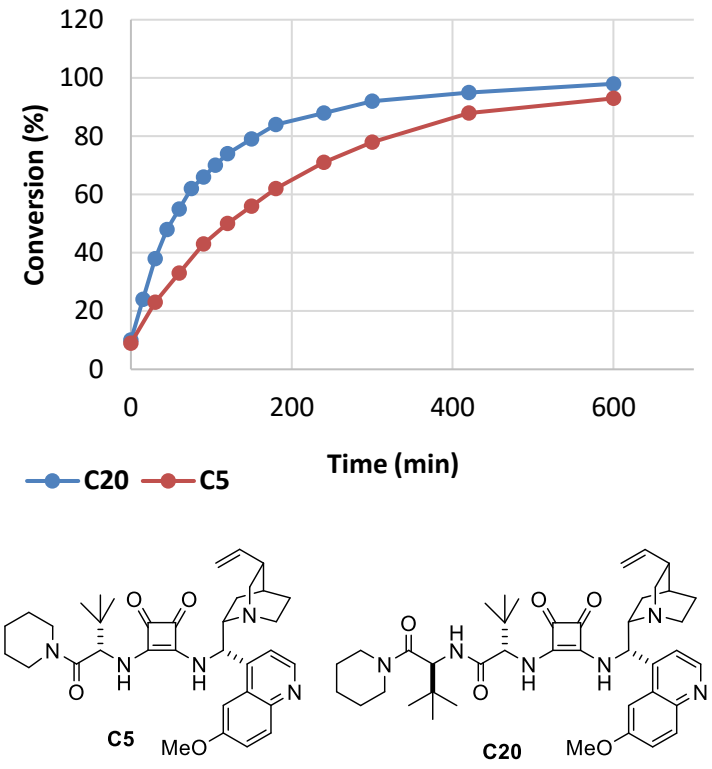
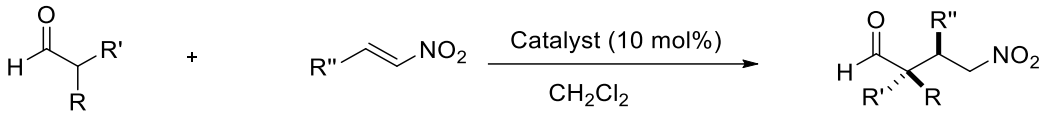


*Figure 12. Kinetic study for the evolution of the reaction between (±)-phenyl propionaldehyde **16A** and p-chloro nitrostyrene **8a** in the presence of **C5** and **C20.***

On the other hand, even though the reaction works with aldehydes with chains different than methyl at the alpha position, stereocontrol was more challenging and in general, a decrease in both reactivity and stereoselectivity was observed (Table 10). Adducts **20Bb** and **20Cc** with ethyl and allyl side chains were obtained with quite good diastereo- and enantioselectivity. However, adduct **20Dc** coming from the reaction of α-benzyl acetaldehyde **16D** with nitroolefin **8c** was afforded as almost an equimolar mixture of diastereomers and with moderate *ee* value. The reaction could also be performed with α-ethyl-3-thiophenyl acetaldehyde **18B** and the reaction proceeded faster than with its α-aryl acetaldehyde counterpart, but moderate stereoselectivity was achieved. Finally, the Michael addition of the more acidic aldehyde **19C** afforded the corresponding adduct **23Ca** with quite good *dr* but relatively low enantioselectivity. Hence, while this BB activation strategy may be extended to different α-branched aryl acetaldehydes,[127] a deeper optimization of reaction conditions might be needed to improve the stereocontrol and shorten the reaction times.

[127] An additional experiment involving the reaction of diphenylacetaldehyde with nitrostyrene at 0 ºC in the presence of **C20** revealed the formation of the corresponding adduct in 76% conversion after 68 h, but in racemic form. Using squaramide **C15** the product was formed in 30% *ee*. For more details, see the Experimental Section.

*Table 10. Scope for the Michael addition of α-branched (hetero)aryl acetaldehydes **16**-**19** to nitroolefins **8** catalysed by **C20/C5**.* [a]

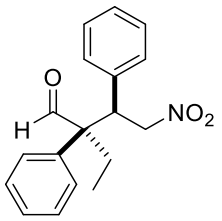


16 R:Ph
17 R:4-MeOC$_6$H$_4$-
18 R:3-thiophene
19 R:2-naph

8a R'': *p*-Cl-C$_6$H$_4$-
8b R'': C$_6$H$_5$-
8c R'': *p*-Me-C$_6$H$_4$-

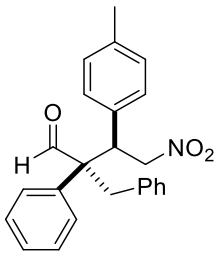
20 R:Ph
21 R:4-MeOC$_6$H$_4$-
22 R:3-thiophene
23 R:2-naph

A R': Me; **B** R': Et; **C** R': Allyl; **D** R': Bn



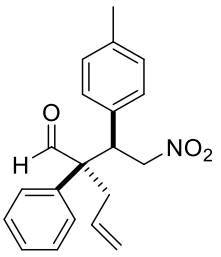
20Bb

C20: 67 h, 56% conv.,
160 h, 84% conv., 61% yield
83:17 *dr*, 78% *ee*
C5: 112 h, 56% conv., 45% yield
84:16 *dr*, 87% *ee*



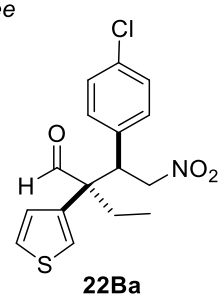
20Dc

C20: 142 h, 85% conv.,45% yield
57:43 *dr*, 40% *ee*
C5: 192 h, 79% conv., 59% yield
60:40 *dr*, 56% *ee*



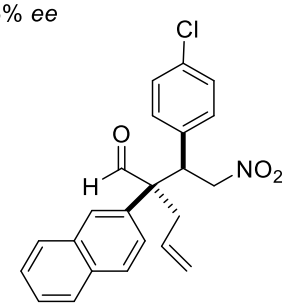
20Cc

C20: 64 h, 72% conv., 66% yield
85:15 *dr*, 77% *ee*



22Ba

C20:17 h, 47% conv., 42% yield
55:45 *dr*, 69% *ee*



23Ca

C20: 64 h, 90% conv., 68% yield
85:15 *dr*, 46% *ee*

[a] Reactions conducted at 0 ºC on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated both diastereoisomers after flash column chromatography. Diastereomeric ratio determined by ^{1}H NMR (300 MHz) analysis on the crude product. Enantioselectivity determined by chiral HPLC.

Interestingly, while preparing the racemic adducts for HPLC analysis, it was detected that the reaction of aldehyde **16A** with nitroolefin **8c** in the presence of Et_3N (30 mol%) at RT for 16 h provided adduct **rac-20Ab** in 71:29 *dr* (90:10 *dr* with catalyst **C20**). Similarly, the achiral catalyst **C31** promoted the reaction between **18A** and **8n** to afford the racemic adduct **22An** in 76:24 *dr* (90:10 *dr* with catalyst **C20**). Considering these data, a combination of both, the catalyst and the substrate, appears to be in control of the observed *syn* selectivity of the final adducts. Furthermore, to ensure that no resolution of the starting racemic aldehyde was occurring via enantioselective protonation, the starting racemic aldehyde **17A** was stirred in CH_2Cl_2 at 0 ºC for 16 h in the presence of catalyst **C20**

and after the usual work up treatment the aldehyde was recovered in complete racemic form.

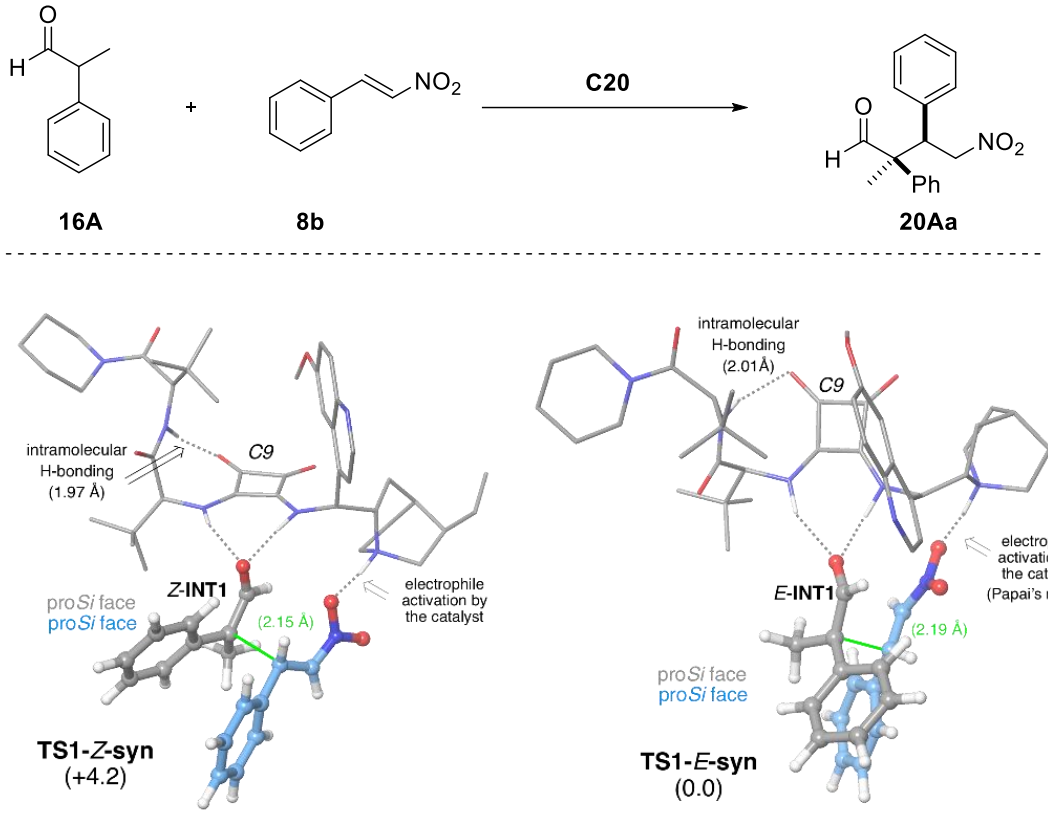
As an added asset, we were able to scale up the reaction between (±)-phenyl propionaldehyde **16A** and nitrostyrene **8b** to a 4 mmol scale and synthesized adduct **20Ab** in 82% yield and with 96:4 *dr* and 95% *ee* for the major *syn* isomer. Catalyst **C20** was recovered from this experiment in 87% yield.

2.3.2.3. Theoretical probes and mechanistic observations

In order to better understand this catalytic Michael reaction from a mechanistic point of view, some DFT calculations were performed by Dr. Abel de Cózar. The addition of (±)-phenyl propionaldehyde **16A** to nitrostyrene **8b** was selected for this task. Models A (Takemoto), B (Pápai) and C (Wang) in Figure 8 were studied and, as for the addition of α-amino aldehydes, all attempts to find transition states following Wang's model led to Takemoto's proposal and were discarded. Curtin-Hammett kinetics were also assumed for this case, where the product ratio is considered dependent on the free Gibbs energy difference of the transition states.

The calculations showed that the lowest in energy transition state (TS1) follows Pápai's activation model in which the protonated tertiary amine coordinates with the nitro group in the electrophile and the carbonyl in the aldehyde forms two H-bonds with the squaramide moiety. Regarding the configuration of the enolate, **TS1-*E*-syn** is 4.2 kcal/mol lower in energy than the *Z* counterpart (Scheme 38) probably due to steric repulsion between the oxygen and the phenyl group in the aldehyde.

As it was observed for catalyst **C7** for the reaction with α-amino aldehydes, catalyst **C20** also forms an intramolecular hydrogen bond between the carbonyl group of the squaramide and one of the NH of the amino acid. This interaction fixes the catalytic system forcing transition states like **TS1$_{ENT}$-*E*-syn** and **TS1-*E*-anti** (Figure 13) to a less optimal catalyst-substrate interaction. This is why, **TS1-*E*-syn** (Scheme 38) is the energetically most favored transition state leading to the formation of adduct *syn*-**20Ab** with a theoretically predicted enantioselectivity of 99% *ee* and >99:1 diastereomeric ratio, which is in good agreement with the experimental data.



*Scheme 38. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **16A** and **8b** catalysed by **C20** that lead to the formation of **20Ab** considering E– and Z–enolates. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.*

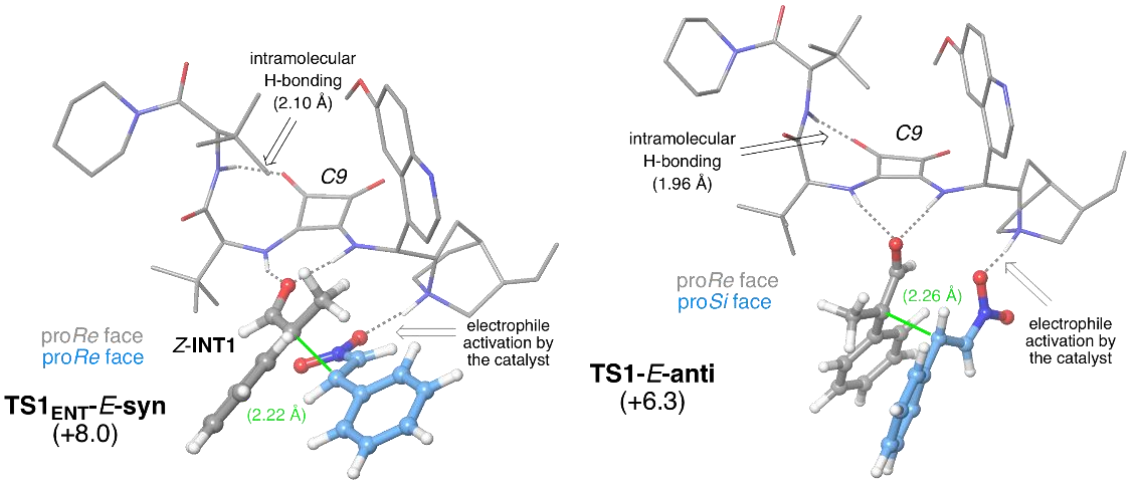
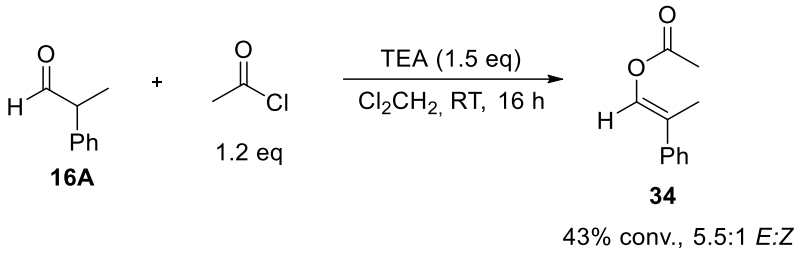


*Figure 13. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **16A** and **8b** catalysed by **C20** that lead to the formation of **20Ab**. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.*

Experiments aiming the isolation of the most stable enolate were in concordance with the results obtained with the DFT calculations, since treatment of (±)-phenyl propionaldehyde **16A** with TEA (1.5 eq) and acetyl chloride (1.2 eq) let to the formation of **34** in an *E/Z* mixture in 5.5:1 proportion (Scheme 39).



*Scheme 39. Formation of the E/Z enol acetates **34** from (±)-2-phenylpropanal **16A** in the presence of triethylamine (TEA) and acetyl chloride.*

To sum up, Michael addition of both α-amino and α-aryl aldehydes to nitroolefins has been efficiently promoted by Brønsted base catalysis for the first time, employing amino acid containing squaramide catalysts that form an intramolecular H-bond as shown by the DFT calculations. The use of α-amino aldehydes led to *anti* adducts while *syn* adducts could be prepared when using α-aryl α-methyl acetaldehydes, with excellent enantio- and diastereoselectivity in both cases.

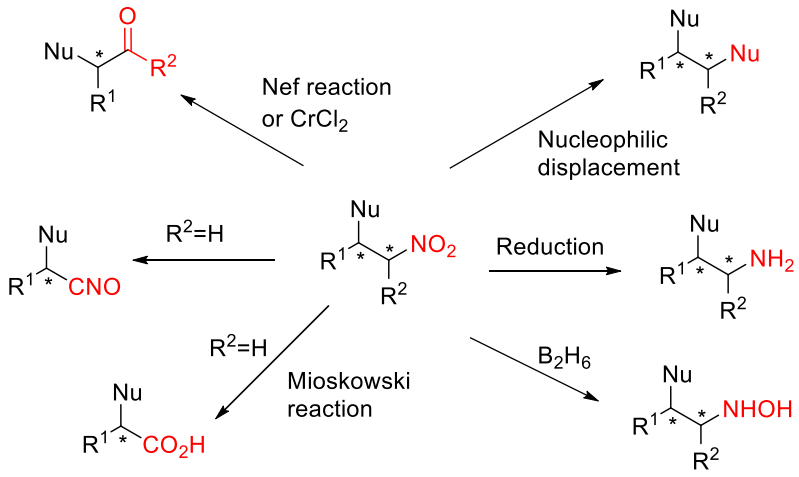
CHAPTER 3

MICHAEL ADDITION OF α-SUBSTITUTED NITROALKANES TO α- HYDROXY ENONES

3. Michael addition of α-substituted nitroalkanes to α-hydroxy enones

3.1. Introduction

Nitroalkanes are valuable building blocks in the synthesis of organic compounds, mainly because, as mentioned in the introduction of this Thesis, the nitro functionality is a very versatile functional group. Once the target reaction is performed, the remaining nitro group can be transformed into different functionalized groups to give access to many derivatives, such as carbonyl compounds,[89,90,91] primary amines,[92] hydroxylamines,[93] and nitrile oxides (Scheme 40).[94] Nucleophilic displacement of the nitro function[95] is also possible, which really broadens the scope of the products that can be prepared from nitro containing compounds.



Scheme 40. Possible transformations on the nitro group.

Regarding the reactivity of nitroalkanes, the presence of the nitro group at the alpha position decreases significantly the electron density of the α-H. In Figure 14, the pK_a values of the α carbon of some different nitroalkanes are shown. In general, although nitroalkanes can be considered susceptible to be deprotonated by weak BB catalysts (see the introduction), in the cases in which the only electron withdrawing group (EWG) at the alpha position is the NO_2 group (nitromethane, nitroethane and the substituted nitroalkanes in Figure 14b), they are in the limit of what a tertiary amine is able to deprotonate ($pK_a \approx 17$). As expected, the presence of additional groups like carbonyls or aromatic rings at the alpha carbon decreases the pK_a value significantly, potentially facilitating deprotonation under soft enolization conditions.

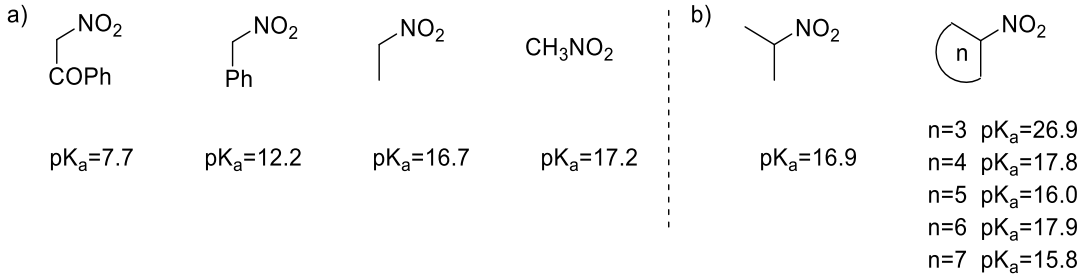


Figure 14. pK_a values of the α-carbon of different nitroalkanes (DMSO): a) non-substituted; b) α-substituted.[66]

Considering the above mentioned reasons, nitroalkanes could be good candidates as pronucleophiles for asymmetric BB catalysis. In this context, the use of α-substituted nitroalkanes would lead to the generation of a quaternary stereocenter, which is an additional challenge,[63] with the possibility of accessing highly functionalized enantioenriched nitroalkanes.

Literature precedents on the use of α-substituted nitroalkanes as pronucleophiles in asymmetric synthesis show that the majority of the examples involve the use of symmetrically substituted α-branched nitroalkanes, that is carrying two identical substituents, like 2-nitropropane and cyclic nitroalkanes (Figure 14b),[128,129] in which cases no stereocenter is formed at the α-carbon of the nitro group.

In relation to substituted nitroalkanes with two different groups at the alpha position, as far as we know, described examples are practically limited to activated nitroalkanes that bear an EWG, either a carbonyl or a halogen, at the α-carbon.[130] This is probably because, as depicted in Figure 14, the α-EWG lowers significantly the pk_a of the pronucleophile, facilitating its deprotonation under soft enolization conditions. Activation using both metal catalysts and organocatalysts has been investigated for these reactions, as it is described below. Noteworthy, many of the cases use bifunctional BB organocatalysts as promoters.

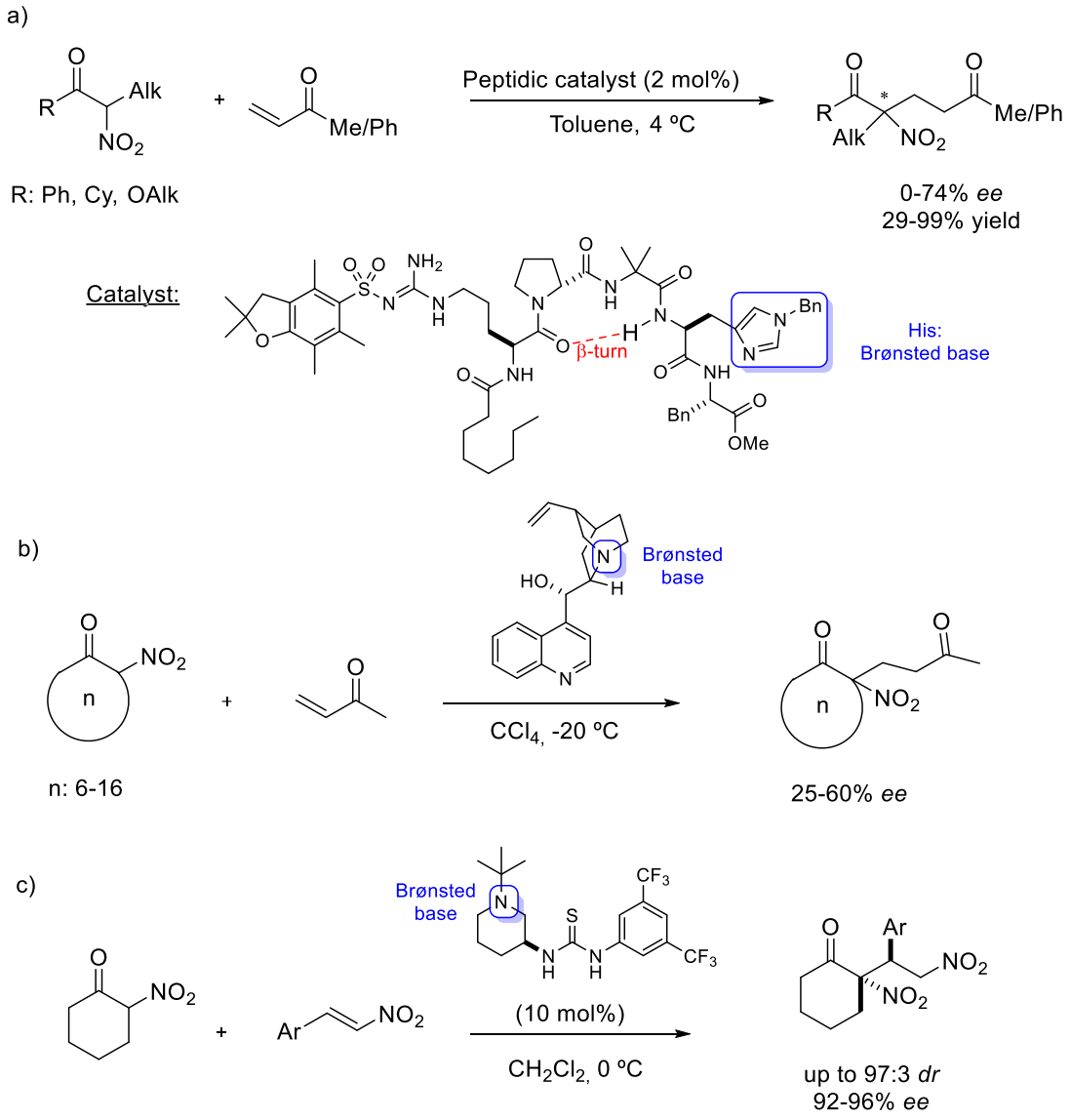
One of the few examples on the use of α-branched nitroalkanes with electron withdrawing groups at the alpha carbon in catalytic asymmetric reactions has been mentioned in the introduction of this Thesis, wherein a peptide catalyst was used to promote the reaction (Scheme 41a).[47] This example described by Miller in 2007 involves

[128] For a review, see: Ref. 107.

[129] For some examples of Henry reaction, see: a) Cruz-Acosta, F.; De Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2013**, *19* (49), 16550–16554; b) Das, A.; Kureshy, R. I.; Prathap, K. J.; Choudhary, M. K.; Rao, G. V. S.; Khan, N. U. H.; Abdi, S. H. R.; Bajaj, H. C. *Appl. Catal. A Gen.* **2013**, *459*, 97–105; c) Cai, Z.; Lan, T.; Ma, P.; Zhang, J.; Yang, Q.; He, W. *Tetrahedron* **2019**, *75* (34), 130469; For some examples of Michael addition, see: d) Yang, Y. Q.; Chen, X. K.; Xiao, H.; Liu, W.; Zhao, G. *Chem. Commun.* **2010**, *46* (23), 4130–4132; e) Ref 75a; f) Ref. 75b.

[130] For two examples of the use of α-substituted nitroalkanes with alkyl substituents as nucleophiles in racemic reactions, see: Dey, C.; Lindstedt, E.; Olofsson, B. *Org. Lett.* **2015**, *17*, 4554–4557,Chang, C.-Y.; Wu, Y.-K. *J. Org. Chem.* **2018**, *83* (11), 6217–6224.

the conjugate addition of α-keto nitroalkanes to enones and the corresponding adducts are obtained in up to 74% *ee* values. The promoter is a Histidine-containing peptide, in which that amino acid unit behaves as a BB while the rest of the peptidic chain provides a complex network of H-bond donors, able to coordinate with the substrates.



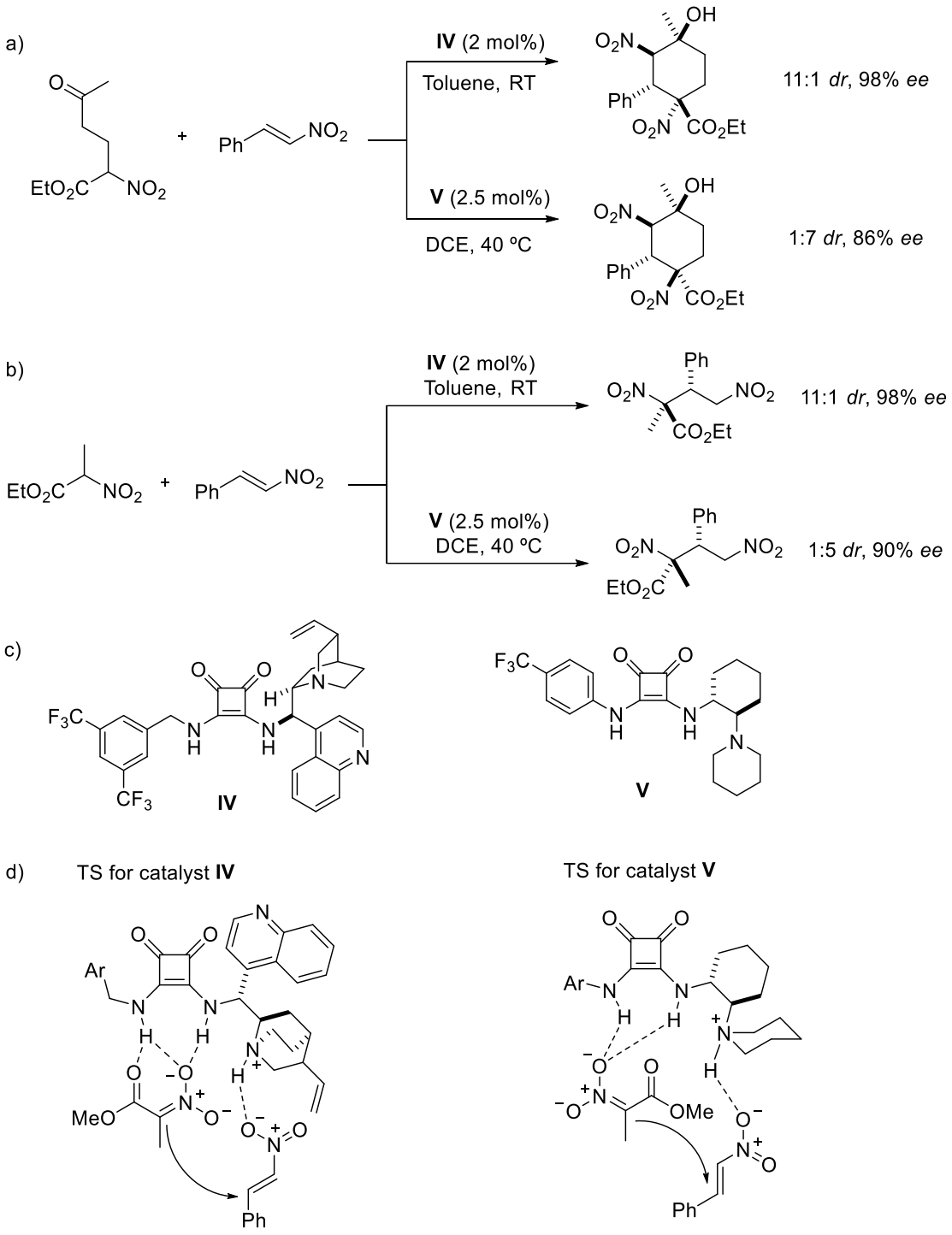
*Scheme 41. Michael addition of α-nitroalkanones to a) enones (**Miller, 2007**)[47] b) methyl vinyl ketone (**Hesse and Stanchev, 1993**)[131] and c) nitrostyrenes (**Bolm, 2012**)[73c] promoted by bifunctional BB catalysts.*

Before Miller, Hesse and Stanchev had also described the Michael addition of α-keto nitroalkanes to methyl vinyl ketone.[131] In this case, unlike Miller, they used cyclic pronucleophiles, as depicted in Scheme 41b. The reaction promoted by cinchonine provided enantiomeric excesses between 25% and 60%, depending on the ring size. Although the authors did not comment on the mechanism of the reaction, cinchonine-promoted reactions usually proceed through BB catalysis, while the free OH of the catalyst

[131] Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4* (2), 173–176.

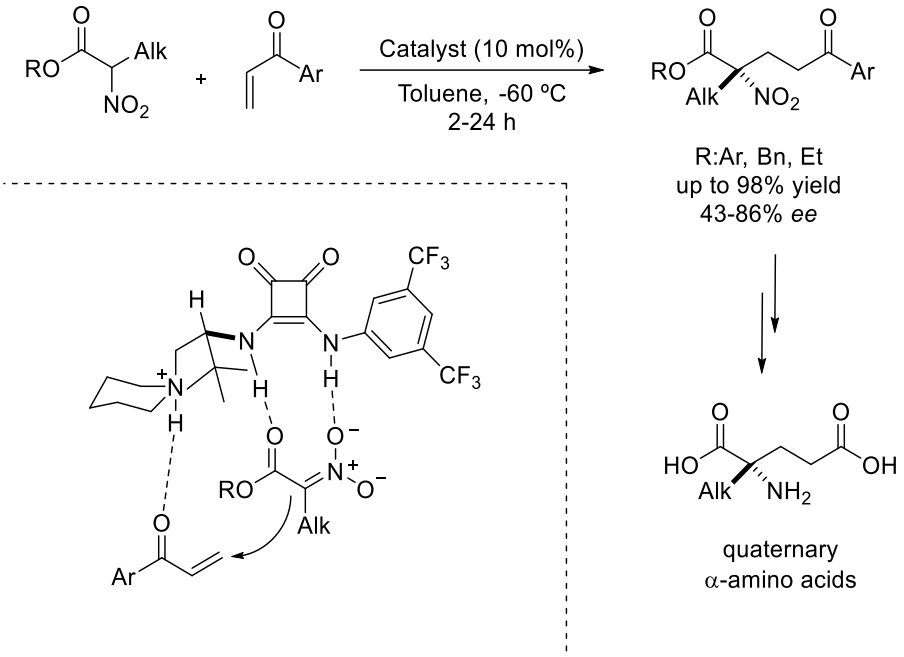
could also activate the substrates through H-bonding. Bolm and coworkers also studied α-nitrocyclohexanone and explored its addition to nitrostyrenes (Scheme 41c).[73c] They used a thiourea-derived bifunctional BB catalyst to promote the reaction, which resulted in excellent stereoselectivity. Although no mechanism for the reaction was proposed, the *N*-^{t}Bu-piperazine could play the role of the base, while the H-bond donating thiourea could activate the substrates by coordinating with them and decreasing the degree of freedom of the transition state (TS).

Besides α-keto nitroalkanes, different nitroalkanes bearing an α-carbonyl group have also been used in asymmetric catalysis, like α-nitro esters. Carrillo and Vicario's group studied in 2014 the Michael addition of these activated nitroalkanes to both nitroolefins and enones.[73a-b] For the addition to nitroolefins, pronucleophiles were designed bearing a carbonyl group at the delta position so that a tandem Michael-Henry reaction could take place, to provide fully substituted cyclohexanes (Scheme 42a). Curiously, by making small changes on the employed squaramide-derived bifunctional BB, one or another diastereomer of this ciclohexanes could selectively be prepared. The same diastereodivergent effect was observed when studying a single Michael addition of ethyl 2-nitropropionate to nitrostyrene (Scheme 42b). This stereodivergency appears to come from the way the nitroester coordinates with each catalyst (Scheme 42d). In both cases, this nitroester coordinates with the squaramide while the electrophile forms an H-bond with the cationic tertiary amine. However, for the reaction with catalyst **IV,** the pronucleophile interacts with the promoter through two different points and the nitro group lays next to the electrophile, while in the reaction with catalyst **V**, the pronucleophile appears to be linked by a single coordination point and approaching the electrophile through the other face.



Scheme 42. a) Diastereodivergent Michael-Michael-Henry tandem reaction of 2-nitro-5-oxohexanoate; b) Diastereodivergent Michael reaction of 2-nitropropionate. c) Employed catalysts. d) Calculated least energetic TS for the reaction promoted with each catalyst. ***Carrillo and Vicario, 2014-2015.***[73a-b]

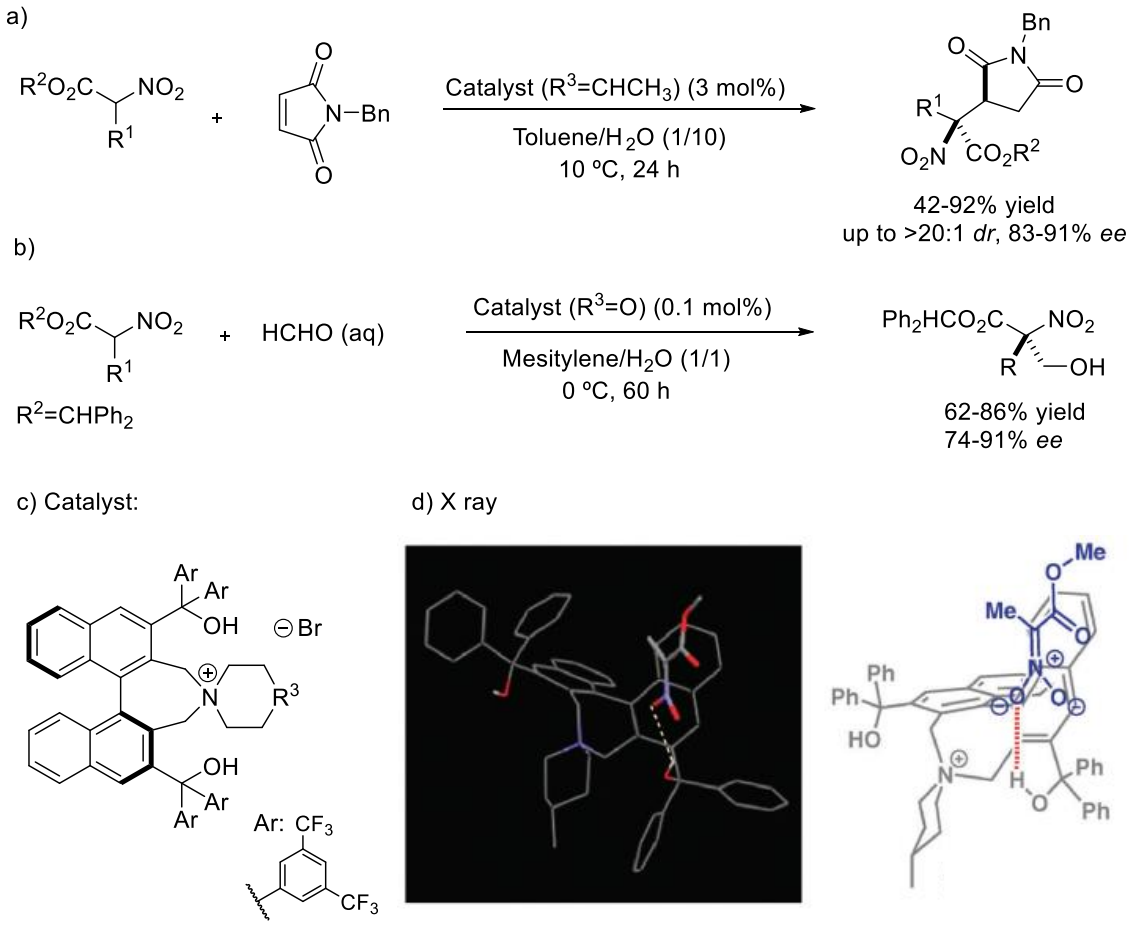
In 2016, Namboothiri's group studied the Michael addition of α-nitroesters to enones catalysed by a similar squaramide type BB obtaining the adducts with a bit lower enantioselectivity, which they then converted into quaternary α-amino acids (Scheme 43).[72c] The proposed coordination pattern for the reaction was similar to the one reported by Carrillo and Vicario for catalyst **IV** (Scheme 42c).



Scheme 43. Michael addition of α-nitroesters to enones, which after some transformations, leads to the preparation of quaternary α-amino acids. ***Namboothiri, 2016.***[72c]

α-Branched nitroesters have also been investigated in Michael additions under phase transfer catalysis conditions. Maruoka's group reported the reaction of α-nitroesters promoted by a bifunctional chiral phase transfer catalysts (Scheme 44c). First, they described the conjugate addition of these pronucleophiles to maleimides and the adducts were obtained in excellent diastereoselectivity and very good enantioselectivity (Scheme 44a).[132] They also studied the addition to aqueous formaldehyde achieving very good enantioselectivity results (Scheme 44b).[133] The reactions worked better in a neutral aqueous environment than in basic media, since retro-aldol reaction that is difficult to suppress under basic conditions was avoided. Furthermore, this lack of base represents an added asset in terms of atom economy since usually stoichiometric amounts of a base additive are required for this type of PTC reactions. The cationic catalyst employed for this reaction bears two free OH groups which appear to coordinate with the nucleophilic nitronate stabilizing it, as observed in the X-ray structure in Scheme 44d.

[132] Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47* (38), 10557–10559.
[133] Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem.* **2012**, *10* (30), 5753–5755.

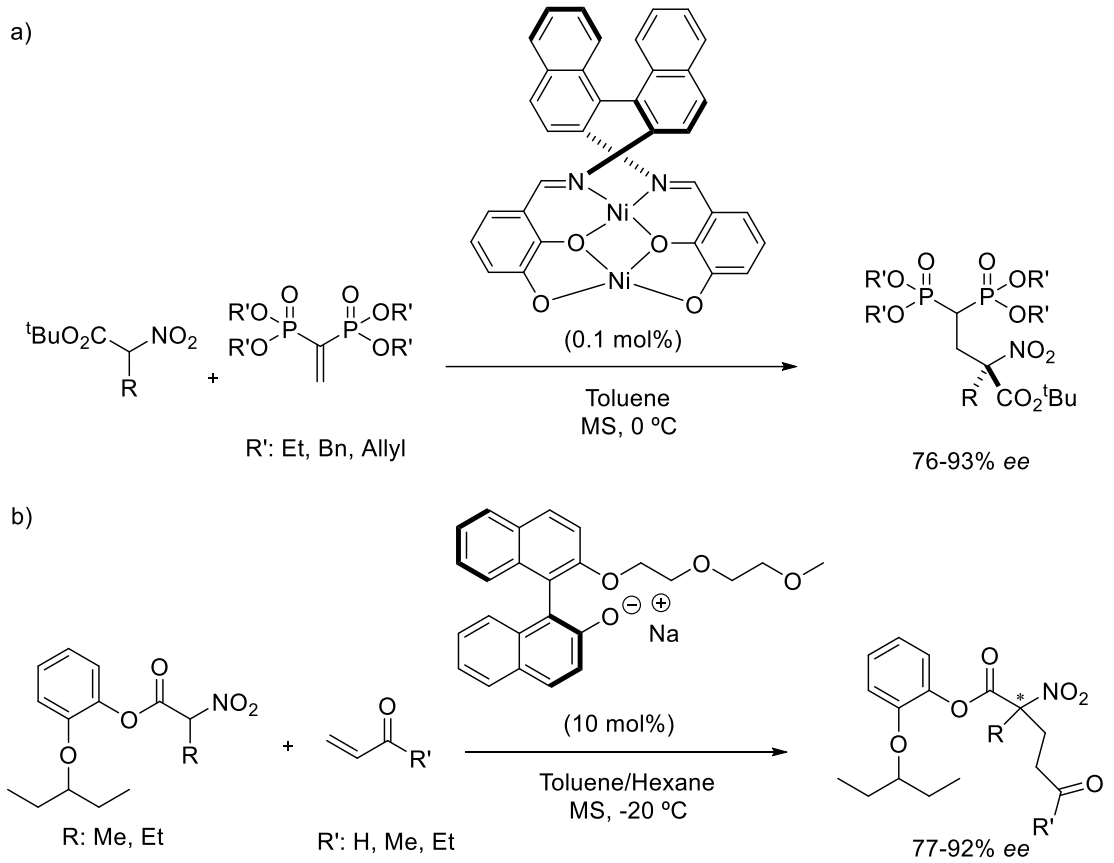


Scheme 44. Bifunctional PTC for a) diastereo- and enantioselective conjugate addition of α-nitroesters to maleimides and b) enantioselective aldol reaction of α-nitroesters. c) Employed catalyst. d) X-ray structure of the catalyst with the nucleophile. ***Maruoka, 2012.***[132,133]

In addition to the mentioned organocatalysed reactions of activated nitroalkanes bearing a carbonyl group at the alpha carbon, some few examples of Michael reactions of α-nitro esters promoted by metal catalysis have also been described. The conjugate addition of these pronucleophiles to vinylidenebiphosphonates, as well as to enones and enals, has been studied (Scheme 45).[134] For the addition to those bisphosphonates, Matsunaga and Shibasaki employed a Schiff base-nickel complex as catalyst that provided the final adducts with good to excellent enantioselectivity (Scheme 45, a).[69] The authors propose that this bimetallic species operates through a Lewis acid/Brønsted base cooperative mechanism, in which one of the Ni-aryloxy moieties would function as a BB, deprotonating the nitroester, while the other metal center could behave as a Lewis acid, coordinating with the electrophile. Tamai's group used a sodium catalyst instead, which also behaved as a base, promoting the reaction between aromatic α-nitro esters and some

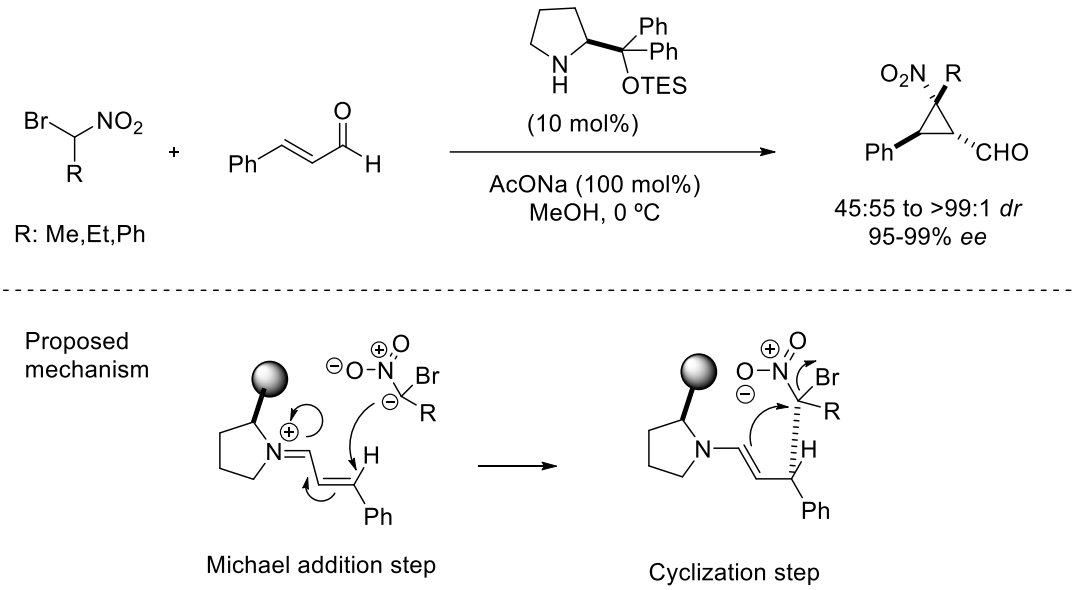
[134]For an asymmetric allylation of nitroalkanes bearing a *tert*-butyl ester catalysed by a palladium complex, see: Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *Nat. Chem.* **2012**, *4* (6), 473–477.

α,β-unsaturated ketones and aldehydes with comparable enantioselectivity results (Scheme 45, b).[70]



*Scheme 45. Metal catalysed Michael additions of α-nitroesters to a) vinylidenebisphosphonates (**Shibasaki, 2009**)[69] and b) enones and enals (**Tamai, 2014**).[70]*

Besides carbonyl groups, halogens have also been used to activate nitroalkanes by incorporating them at the alpha position of the pronucleophile. As far as we know, there are two asymmetric examples in which α-halonitroalkanes are used as pronucleophiles, one of them bearing a bromine, and the other with a fluorine atom. Yan and coworkers described the enantioselective Michael addition of 1-bromonitroalkanes to cinnamaldehyde in 2009 (Scheme 46).[71] The reaction catalysed by a Proline-derivative proceeds through a Michael addition followed by a cyclization, to afford nitrocyclopropanes with excellent enantioselectivity and variable diastereoselectivity. The proposed mechanism proceeds through the formation of an iminium ion between the secondary amine of the catalyst and the cinnamaldehyde. After the pronucleophile gets deprotonated, probably by the NaOAc additive, the bulky side chain of the Proline derivative directs its approach to the electrophile by the less shielded face (the *si* face). The subsequent intramolecular alkylation leads to the cyclic final product.



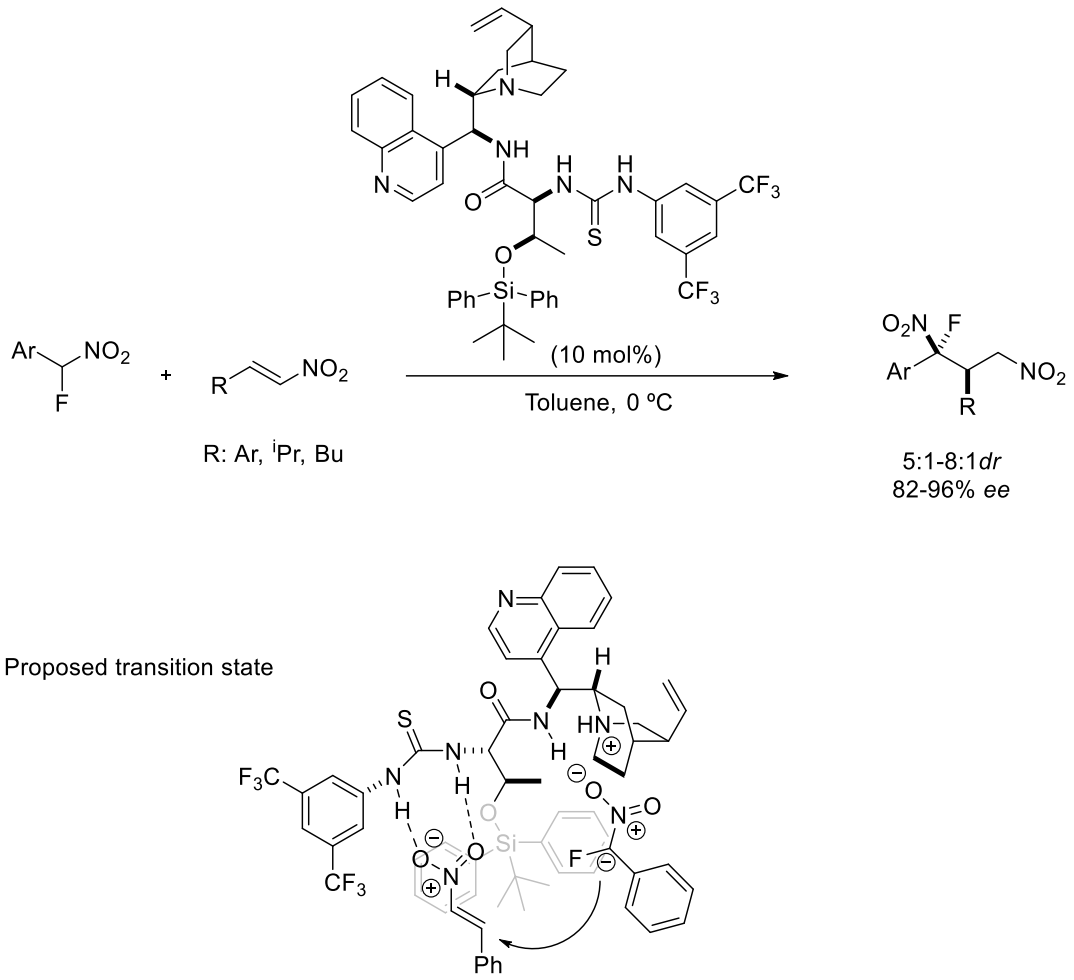
Scheme 46. Michael addition and cyclization of 1-bromonitroalkanes catalysed by a Proline-derivative. ***Yan, 2009****.*[71]

Lu and Kwiatkowski also described an asymmetric Michael addition of α-halonitroalkanes, in this case bearing a fluorine and an aromatic ring at the alpha position, and they employed a bifunctional BB catalyst containing a thiourea moiety instead of an aminocatalyst.[73d] The conjugate addition to different nitroolefins provided adducts in good *dr* and very good enantioselectivity, even with aliphatic nitroalkanes. Their proposed mechanism suggests that the base deprotonates the pronucleophile, which then interacts with the cationic tertiary amine, and the thiourea H-bond donor coordinates with the nitroolefin. The approach occurs selectively through one face since the other one is blocked by the bulky *tert*-butyldiphenylsilyl moiety of the catalyst (Scheme 47).

Although several examples of activated α-substituted nitroalkanes as pronucleophiles have been described, the use of unsymmetrically substituted α-branched nitroalkanes lacking an EWG at the alpha position is essentially unexplored in the realm of asymmetric synthesis.[135][136] Given these precedents, our research group, in collaboration with Prof. J. M. Garcia's group at the Public University of Navarra (UPNA) initiated a joint project to study α-substituted nitroalkanes lacking an EWG at the alpha carbon as pronucleophiles in conjugate additions.

[135] For a paper with only three examples of the Michael addition of 2-nitro-1-propanol derivatives to enones, in which the obtained highest *ee* is 63%, see: a) Ref. 74f; For a paper with a single example of Pd-Catalysed allylic alkylation of 2-benzyl nitroethane, in which they obtained excellent enantioselectivy, but a 1.1:1 *dr* mixture, see: b) Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63* (20), 4250–4257.

[136]For an example on the preparation of tertiary non-activated nitroalkanes by a Pd-catalysed decarboxylative allylic alkylation, see: Trost, B. M.; Schultz, J. E.; Bai, Y. *Angew. Chem. Int. Ed.* **2019**, *58* (34), 11820–11825.



Scheme 47. Stereoselective Michael addition of α-fluoronitroalkanes to nitroolefins catalysed by a bifunctional Brønsted base. ***Kwiatkowski, 2014.***[73d]

On this basis, for the study of the Michael addition of the α-alkyl nitroalkanes proposed in this project, α-hydroxy enones were selected as electrophiles, since it has been shown that they are efficient synthetic equivalents of acrylates, as well as enals and enones, as explained in the introduction of this Thesis (Scheme 15a, Introduction). Furthermore, they can form an intramolecular H-bond between the carbonyl group and the OH that would increase their reactivity as electrophiles.

The α-hydroxy ketone moiety was first employed by our group as template for the chiral auxiliary strategy. A camphor-derived α-oxy ketone, with both free and silylated hydroxy group was designed (Figure 15, a), which provided high levels of stereocontrol in

aldol reactions,[137] Mannich reactions,[138] α-alkylation reactions,[139] conjugate additions to nitroalkanes[140] and Darzens reactions.[141] Camphor-derived α-hydroxy enones were also synthesized (Figure 15, b), which showed to be very efficient in diastereoselective Diels-Alder additions,[78] 1,3-dipolar cycloadditions[79] and Michael additions.[80] In all the cases, the chiral auxiliary could be recovered at the end of the reaction by a ketol cleavage that afforded, depending upon the reaction conditions, the corresponding carboxylic acid, aldehyde or ketone (see Scheme 15a in the introduction), so that the chirality source could be recovered and reused.

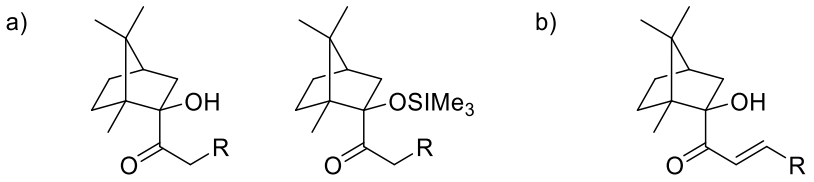


Figure 15. Camphor-derived chiral auxiliaries. ***Palomo****.*

This idea was then extended to enantioselective reactions, in the field of catalysis. α-Hydroxy enones were used in metal catalysed cycloadditions like Diels-Alder[81] and 1,3-dipolar cycloadditions,[79] as well as Michael acceptors in the conjugate additions of nucleophiles like carbamantes,[82] pyrroles/indoles,[83] nitroalkanes,[84] β-ketoesters[80a] and dialkyl zinc compounds,[85] as depicted in Scheme 48, and in all the cases excellent enantioselectivity results were achieved. Even more, α-hydroxy enones showed much better reactivity for reactions like the alkylation with dialkyl zinc derivatives, since only 20% conversion was reached with enals and essentially no reactivity was detected with α,β-unsaturated esters under the same reaction conditions. A main advantage of this new electrophile in comparison with its synthetically equivalent counterparts (enals, enones and α,β-unsaturated esters) is the ability to form a 1,4-bidentated coordination pattern with the catalyst which could limit the degree of freedom of the transition state (Scheme 48).[83]

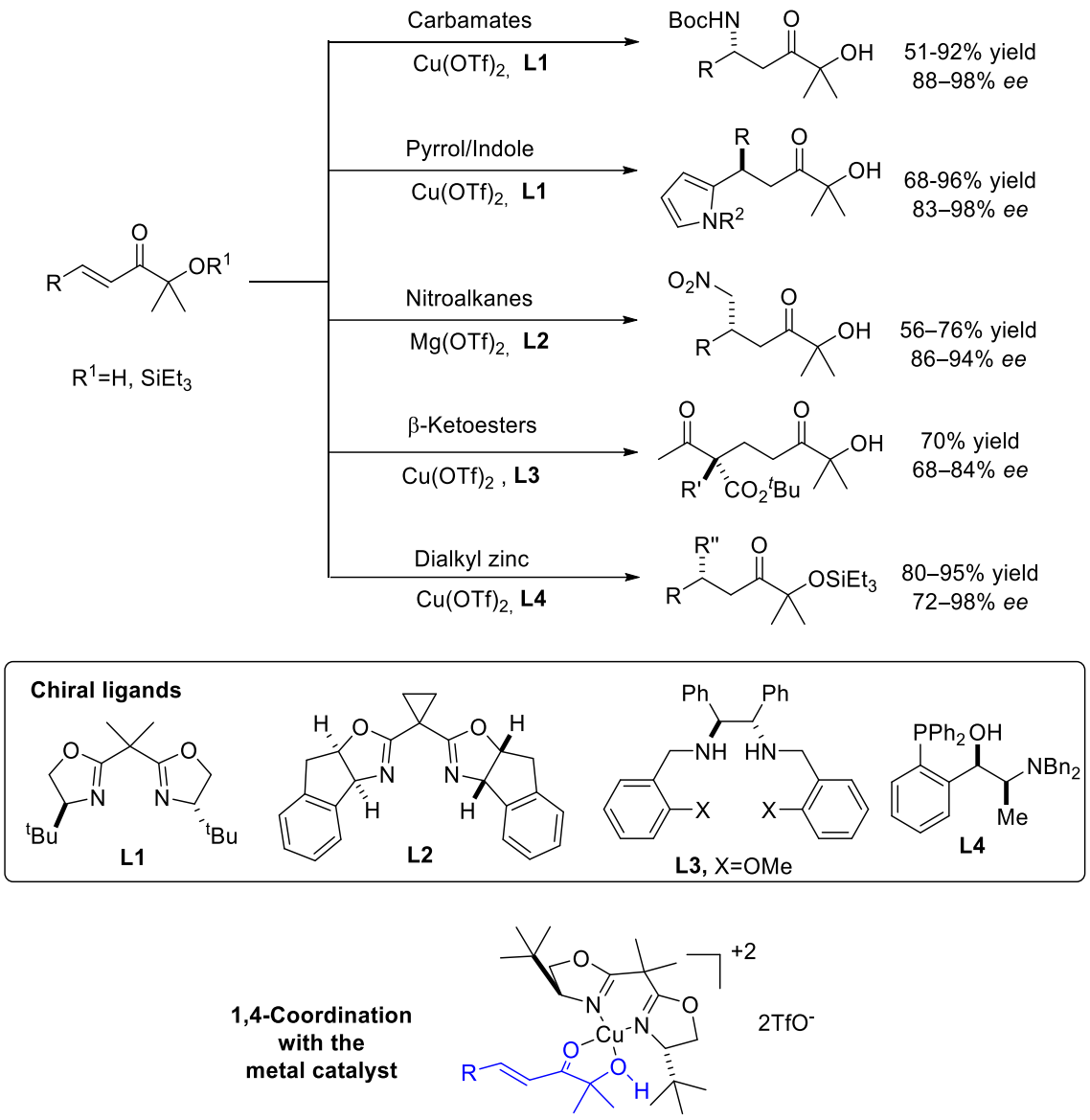
[137] a) Palomo, C.; Gonzalez, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem. Int. Ed* **1998**, *37* (1), 180–182; b) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64* (22), 8193–8200; c) Palomo, C.; Oiarbide, M.; Gómez-Bengoa, E.; Mielgo, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Bañuelos, P.; Linden, A. *ARKIVOC* **2005**, *6*, 377–392.

[138] a) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed* **2000**, *39* (6), 1063–1065; b) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124* (29), 8637–8643.

[139] Palomo, C.; Oiarbide, M.; Mielgo, A.; González, A.; García, J. M.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett.* **2001**, *3* (21), 3249–3252.

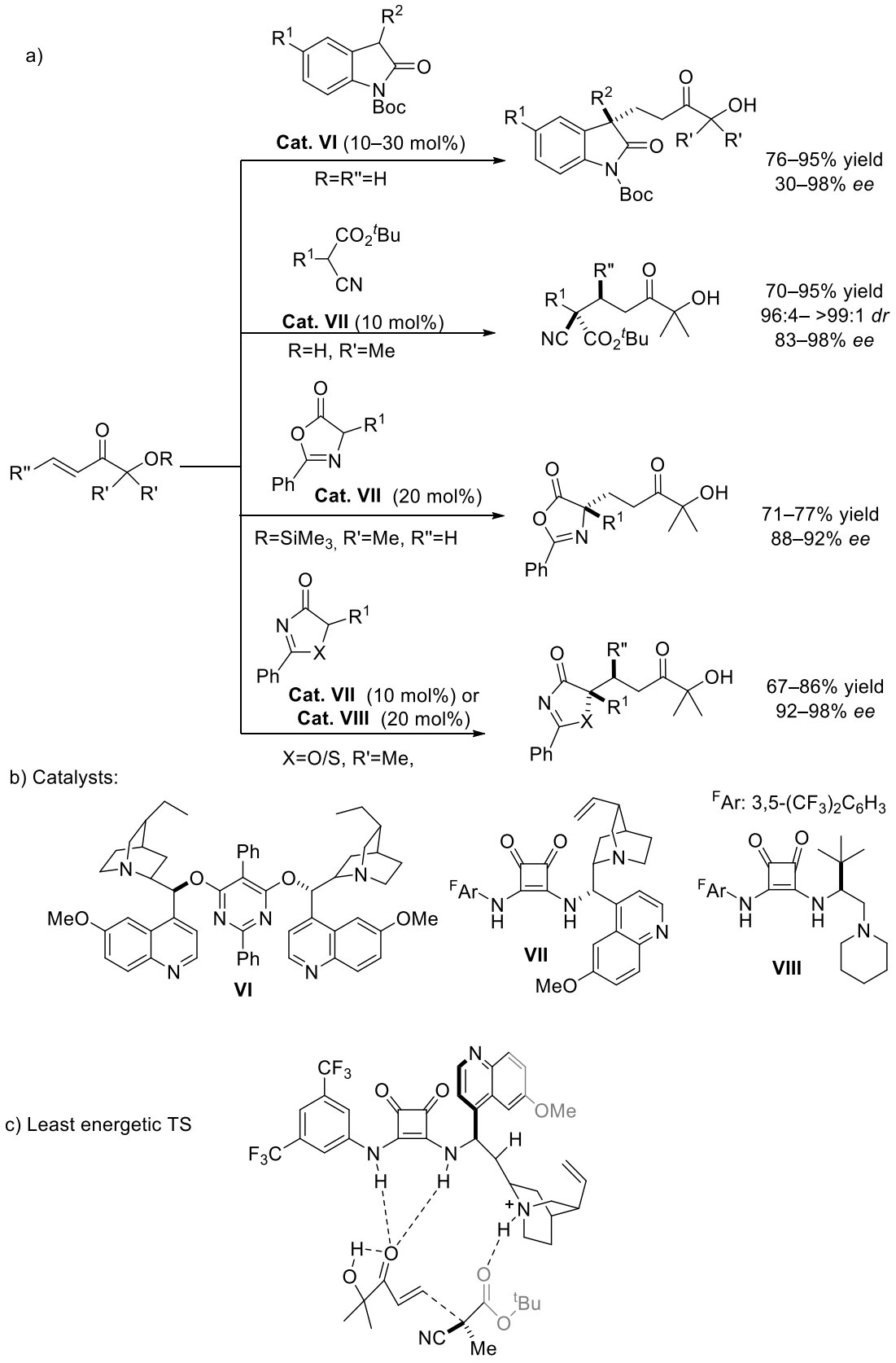
[140] Palomo, C.; Aizpurua, J. M.; Oiarbide, M.; García, J. M.; González, A.; Odriozola, I.; Linden, A. *Tetrahedron Lett.* **2001**, *42* (29), 4829–4831.

[141] Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. *J. Org. Chem.* **2000**, *65* (26), 9007–9012.



Scheme 48. Metal catalysed Michael additions to α-hydroxy enones. ***Palomo, 2004-2008.*** [80a,82,83,84]

A few years later, our research group also demonstrated the efficiency of α-hydroxy enones as Michael acceptors in organocatalytic transformations (Scheme 49a).[86] Indeed, the addition of various challenging pronucleophiles like oxindoles, cyanoacetates, oxazolones, thiazolones and azlactones to α-hydroxy enones was efficiently carried out in the presence of Brønsted base organocatalysts. Remarkably, quaternary stereocenters were created with excellent reactivity and stereocontrol in each case. Computational studies revealed that the bidentate coordination of α-hydroxy enones is not only beneficial for metal catalysed reactions, but also for organocatalysed transformations. Indeed, DFT studies for the conjugate addition of α-substituted cyanoacetates to α-hydroxy enones revealed that the Michael acceptor coordinates with the bifunctional catalysts while forming an intramolecular H-bond between the OH and the carbonyl, which should be the putative cause of the observed electrophile's high reactivity (Scheme 49c). In the meantime, the base on the catalyst deprotonates the nucleophile, while the

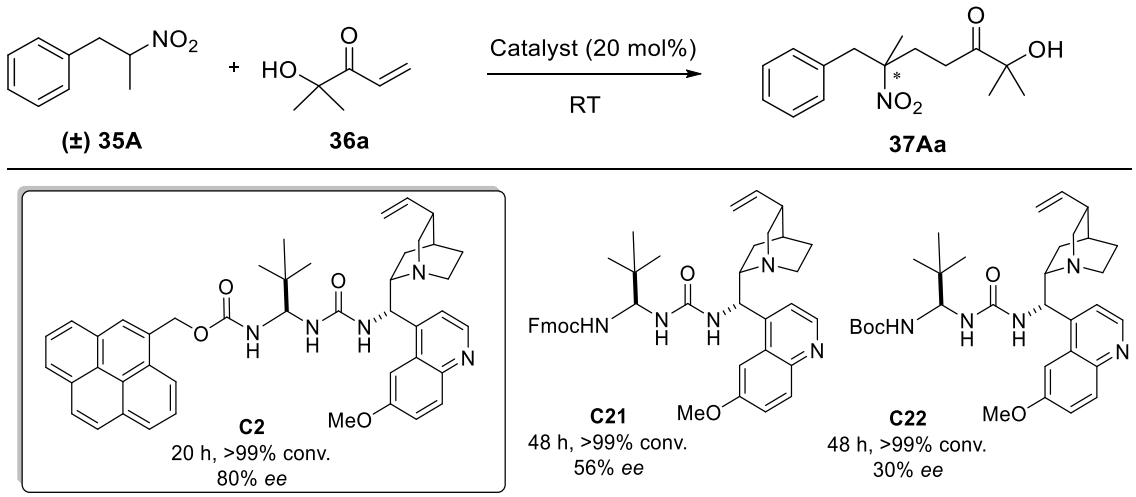


Scheme 49. a) Organocatalytic Michael additions to α-hydroxy enones. b) Employed catalysts. c) Least energetic TS for the conjugate addition of α-cyanoacetates. ***Palomo, 2014.***[86]

resultant ammonium ion coordinates with the ester carbonyl, bringing both substrates, nucleophile and electrophile, close.

Our collaborator Prof. Garcia and his group started the project by testing some bifunctional BB catalysts of different nature in the Michael addition of (2-nitropropyl)benzene (±)**35A** to α-hydroxy enone **36a** (Table 11). First, alkaloid derived cinchonine, quinidine, $(DHQ)_2PYR$ and $(DHQ)_2PHAL$ were evaluated and the reaction took place with total conversion in the presence of all of them, but very poor enantioselectivity was afforded in all cases. So then, some ureidopeptide-like BBs developed in our research group[53,142] were tested in the reaction, such as catalyst **C2** bearing a pyrene-derived carbamate, Fmoc-protected **C21** and Boc-protected **C22**. The best results in terms of both reactivity and stereoselectivity were provided by **C2**, which led to reaction completion after only 20 h and the formation of the final adduct in 80% *ee* (Table 11).

*Table 11. Summarized catalyst screening for the Michael addition of (2-nitropropyl)benzene **35A** to α-hydroxy enone **36a**. J. M. García (UPNA).* [a]



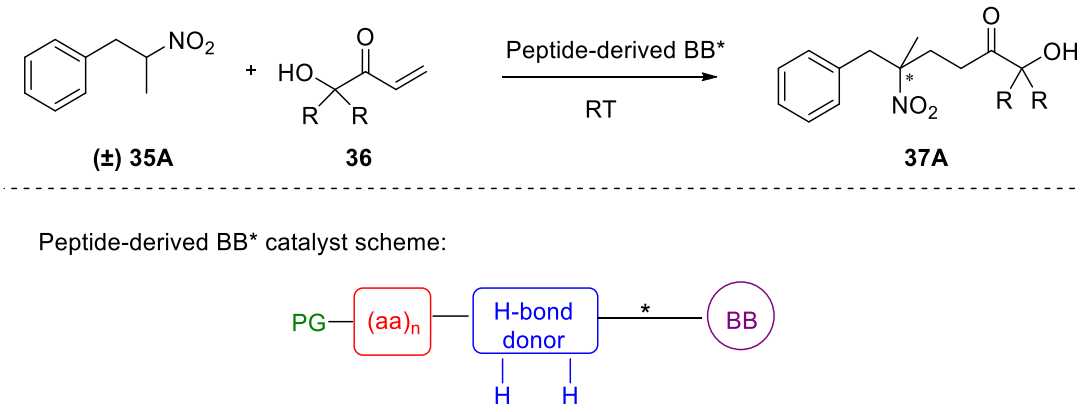
[a] Reactions carried out at RT on a 0.1 mmol scale 0.3 mL of $CHCl_3$ (mol ratio nitroalkane/ hydroxyenone/catalyst 5:1:0.2) Conversion determined by the disappearance of the starting α-hydroxy enone. Enantiomeric excess determined by chiral HPLC.

[142] Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20* (21), 6526–6531.

3.2. Objectives

As noted above, Prof. Garcia's group at the UPNA provided insight into the Michael addition of α-branched nitroalkanes promoted by bifunctional BB organocatalysts using α-hydroxy enones as electrophilic partners, but still a stereoselective improvement is required for reaction efficiency.

Literature precedents had revealed that peptides, on the one hand, and H-donor containing bifunctional BBs, on the other hand, were able to promote the reaction of nitroalkanes bearing an EWG at the alpha position. We wondered whether the combination of both, an α-amino acid or peptide and a BB, in the same molecule (Scheme 50) would provide a catalyst capable of promoting the addition of less reactive α-branched nitroalkanes to α-hydroxy enones.



*Scheme 50. Proposed Michael addition of α-substituted nitroalkane **(±)35A** to α-hydroxy enones **36**.*

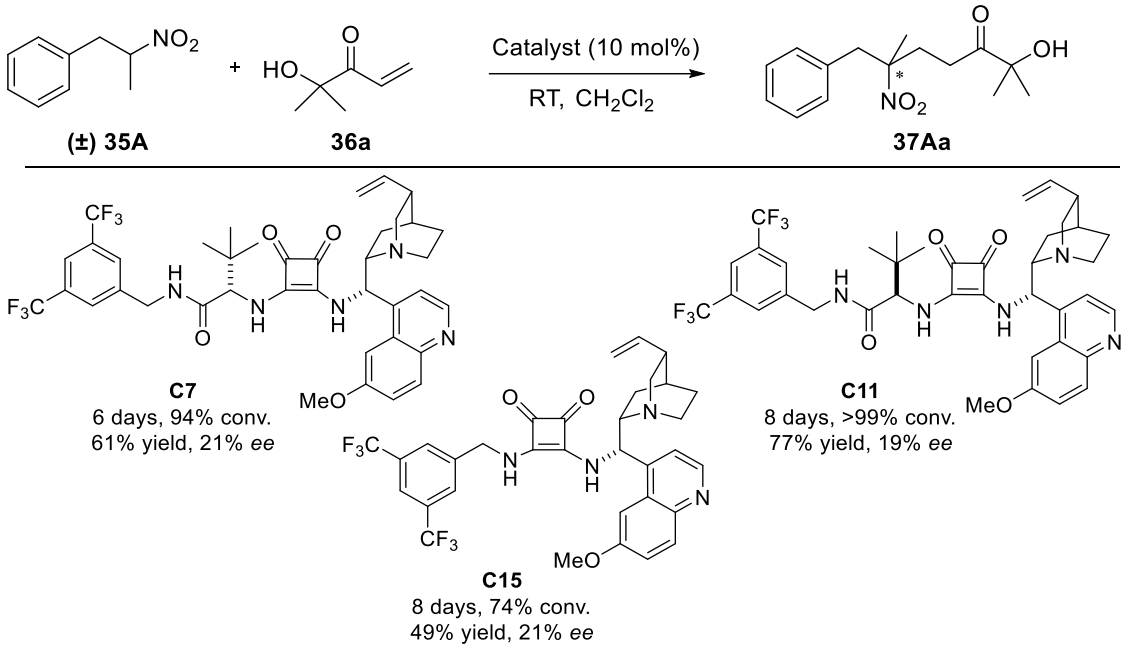
3.3. Results and discussion

3.3.1. 4-Hydroxy-4-methylpent-1-en-3-one: Catalyst screening

With the above idea in mind, catalysts that involves the combination of a peptidic chain with the typical bifunctional BB structures like squaramides and ureidoaminals were considered to explore the Michael addition of α-substituted nitroalkane (±)**35A** to α-hydroxy enones **36**, in a 5:1 nitroalkane/α-hydroxy enone ratio (Table 12).

First, squaramide-derived Brønsted bases were tested in the reaction, since no catalyst of this nature had been checked before and they had provided the best results for the conjugate addition of α-branched aldehydes to nitroolefins presented in Chapter 1. The reaction was first run in the presence of Rawal's squaramide **C15** and 8 days of reaction time were needed to reach 74% conversion. In terms of stereoselectivity, only 21% *ee* was obtained (Table 12). The catalyst that had afforded the best results for the addition of α-amino aldehydes (**C7**) and its diastereomer **C11** were also tested in the reaction, but once again very long reaction times were necessary for reaching high conversion levels (Table 12). Furthermore, the obtained enantioselectivity values were considerably low as well, in comparison with the best result until date (**C2,** 80% *ee*, Table 11), and there was no significant difference among the two diastereomeric catalysts.

*Table 12. Screening of squaramide-derived catalysts for the Michael addition of nitroalkane (±)**35A** to α-hydroxy enone **36a**.[a]*

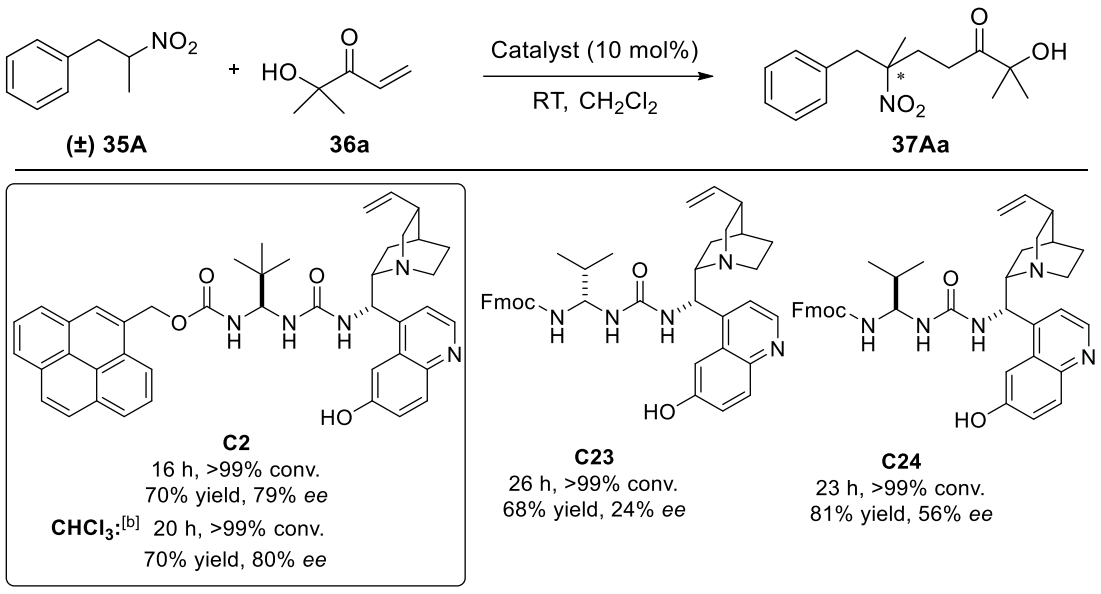


[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane/ α-hydroxy enone/catalyst 5:1:0.1) Conversion determined by the disappearance of the starting α-hydroxy enone. Enantiomeric excess determined by chiral HPLC.

Considering that squaramide-derived catalysts did not seem the most appropriate for this reaction, investigations were continued with ureidopeptide-like catalysts. The first step was to run the reaction with the catalyst that had provided the best enantioselectivity result until date (**C2**) but in CH_2Cl_2 instead of $CHCl_3$, but there was essentially no change in either selectivity or reactivity (Table 13), so the screening was performed in CH_2Cl_2 for convenience.

Since, as far as we knew, it had not been checked if the stereocenters present on **C2** were the matched combination for this particular reaction, catalysts **C23** and **C24**, which come from the opposite enantiomer of Valine, were synthesized to see which one provided better results (Table 13). Fmoc was selected as protecting group and Valine as the starting amino acid for reagent availability reasons. In the presence of catalyst **C24** higher enantioselectivity was reached (56% *ee vs* 24% *ee* for **C23**), and therefore catalysts coming from (*L*)-amino acids were established as the matched combination. These results were in agreement with the relatively high enantioselectivity values obtained with catalyst **C2** that also comes from an (*L*)-amino acid.

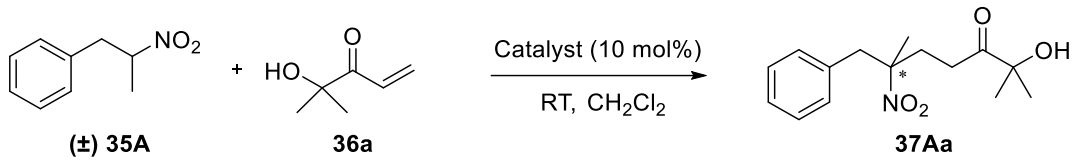
*Table 13. Catalyst screening for the Michael addition of nitroalkane (±)**35A** to α-hydroxy enone **36a** for finding the matched combination.[a]*

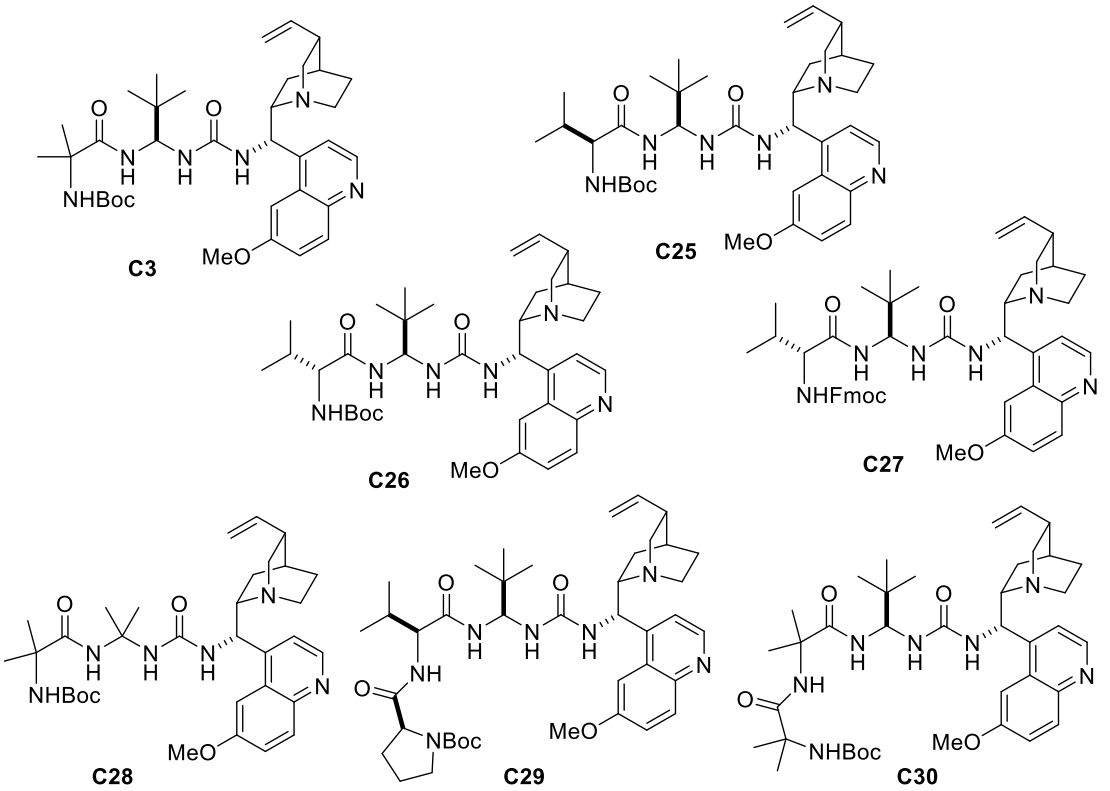


[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane/ α-hydroxy enone/catalyst 5:1:0.1) Conversion determined by the disappearance of the starting α-hydroxy enone. Enantiomeric excess determined by chiral HPLC. [b] Data obtained by Prof. Garcia's group with 20 mol% of catalyst.

Following with the main idea of this Thesis, which consists of incorporating in the structure of organocatalysts a peptidic chain that could form additional H-bonds, another amino acid unit was added to the ureidopeptide-like catalyst structure. Thus, catalysts **C25**, **C26** and **C3** were prepared, which maintain **C2**'s main structure but incorporate a Boc-protected (*L*)-Valine, (*D*)-Valine and AIB respectively. Between the diastereomeric catalysts **C25** and **C26**, the latter seems to be the matched combination for this reaction

*Table 14. Peptidic-catalyst screening for the addition of nitroalkane (±)**35A** to α-hydroxy enone **36a**.*[a]





Entry	Cat.	t (h)	Conv. (%)[b]	Yield (%)	*ee* (%)[c]
1	**C3**	16	>99	59	33
2	**C25**	42	>99	80	30
3	**C26**	22	>99	76	45
4	**C27**	25	>99	56	32
5	**C28**	22	>99	62	0
6	**C29**	20	>99	73	26
7	**C30**	26	>99	89	13

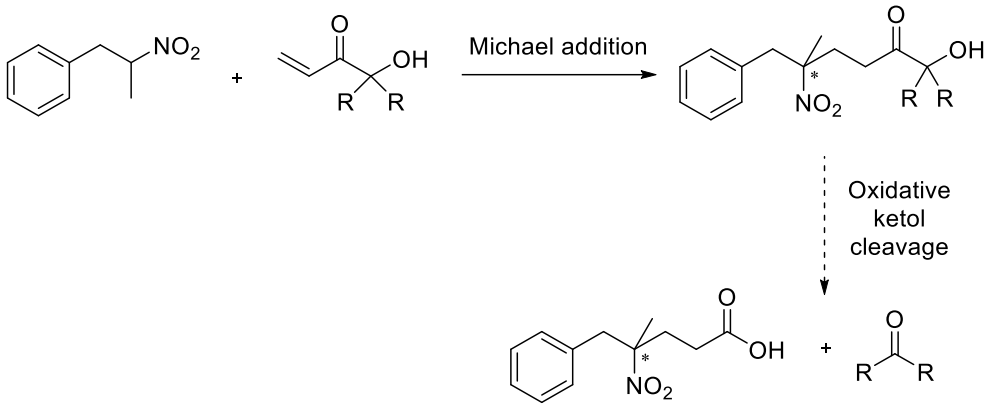
[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane/ α-hydroxy enone/catalyst 5:1:0.1) [b] Determined by the disappearance of the starting α-hydroxy enone. [c] Determined by chiral HPLC.

since the adduct was obtained in slightly higher *ee* (Table 14, entries 2 and 3). Results with catalyst **C3** lacking the additional stereogenic center were also lower that with **C26** (Table 14, entry 1), which could imply that chirality in the newly incorporated amino acid structure could be beneficial. Furthermore, although still significantly lower than the obtained best result (with **C2,** 80% *ee*), **C26** provided a little better enantioselectivity (45% *ee,* Table 14, entry 3) than **C22**, the corresponding Boc-protected catalyst with a single amino acid tested by Prof. Garcia's group (30% *ee,* Table 11). This suggested that, in this case, catalysts with two amino acid units could be more efficient in terms of stereoselectivity. So, since the Fmoc-protected monomer catalyst **C21** had provided better results than the Boc-protected monomer catalyst **C22** (Table 11), **C27** the analogous of **C22**, but which bears Fmoc as protecting group was prepared. However, with **C27** the adduct was obtained in only 32% *ee* (Table 14, entry 4), compared to the 56% *ee* provided by the Fmoc-protected monomer **C21** (Table 11).

Finally, **C28** incorporating only AIB units was considered with the idea of exploring the benefits or not of chirality in all the amino acid units of the catalyst. In this context, **C28** afforded the reaction adduct in its complete racemic form, thus demonstrating that chirality at the peptidic chain is required for inducting stereoselectivity in this reaction (Table 14, entry 5). Lengthening the peptidic chain to three amino acid units did not improve the enantioselectivity, as we can see by comparing dipeptide **C25** and tripeptide **C29** (Table 14, entries 2 and 6), and dipeptide **C3** and tripeptide **C30** (Table 14, entries 1 and 7).

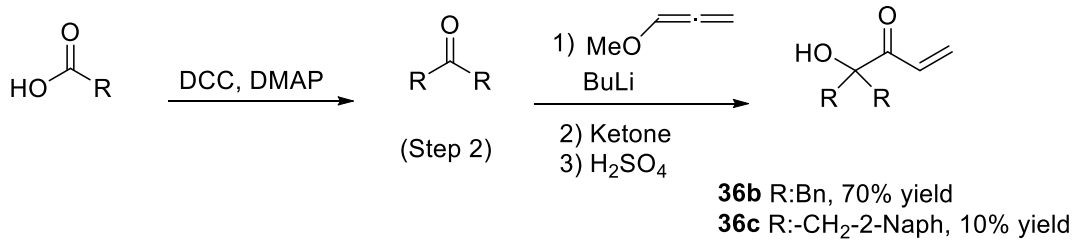
3.3.2. Related α-Hydroxy enone substrates and Michael acceptors

Despite all the efforts to improve the stereoselectivity of the reaction by modulating the catalyst, the best result was the 80% *ee* provided by **C2** (Table 11). At this point, and as another option, modifications in the structure of the electrophile were considered to see if higher *ee* values could be reached. Since α-hydroxy enones are masked equivalents of acrylates among others, the idea was to perform an oxidative cleavage after the asymmetric Michael addition, to access the corresponding carboxylic acid derivatives. Therefore, as depicted in Scheme 51, once the oxidative ketol cleavage is conducted, the R groups coming from the α-hydroxy enone are removed from the final molecule. Hence, this constitutes a very appropriate modulating point, since different substituents can be tested at this position without altering the ultimate final product of the reaction, and then recovering the ketone by-product formed, which can be reused.



Scheme 51. Possible oxidative ketol cleavage that can be performed after the Michael addition to obtain carboxylic acids and derivatives.

With this idea, α-hydroxy enones **36b** and **36c** bearing benzyl and 2-naphthylmethyl substituents at the alpha position were prepared following the synthetic route depicted in Scheme 52. First, the corresponding symmetric ketone was synthesized starting from the commercially available carboxylic acids,[86] followed by the reaction with 1-methoxypropa-1,2-diene to prepare the final electrophiles **36b** and **36c**.

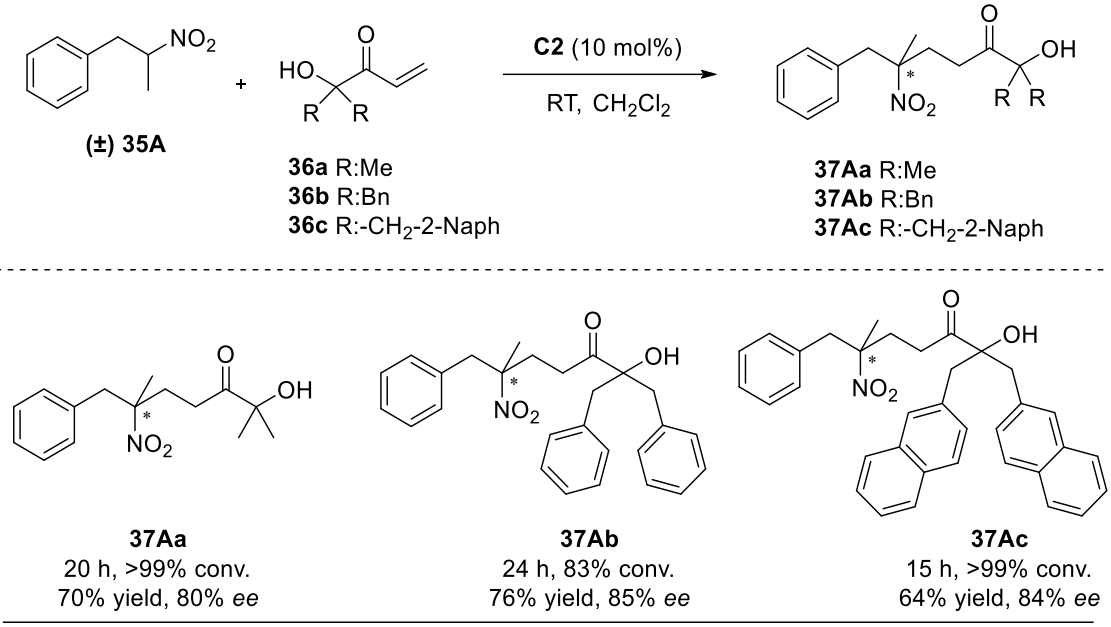


*Scheme 52. Synthetic route for the synthesis of α-hydroxy enones **36b** and **36c.***

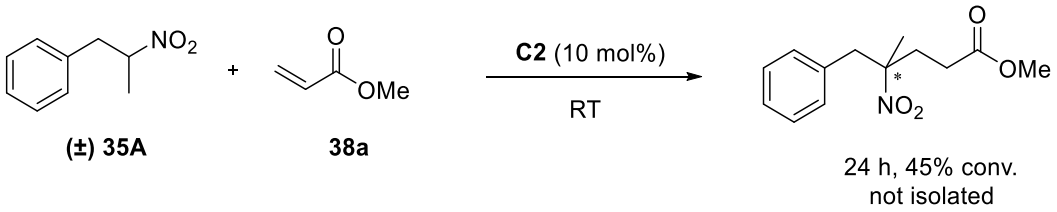
Once these new α-hydroxy enones were prepared, they were tested in the Michael addition of nitroalkane (±)**35A** promoted by catalyst **C2**. In both cases, enantioselectivity improved in comparison with the results obtained with α-hydroxy enone **36a**, reaching 85% *ee* for both the benzyl and naphthylmethyl bearing adducts **37Ab** and **37Ac** (Table 15). The configuration of adducts **37A** is yet to be determined.

On the other hand, worth of mention is the fact that the reaction with methyl acrylate **38a** under the optimized conditions was slower, as depicted in Scheme 53, as only 45% conversion was reached after 24 h at RT. This demonstrates that α-hydroxy enone is an effective synthetic equivalent of carboxylic acid derivatives.

*Table 15. Michael addition of nitroalkane (±)**35A** to different α-hydroxy enones promoted by catalyst **C2**.* [a]

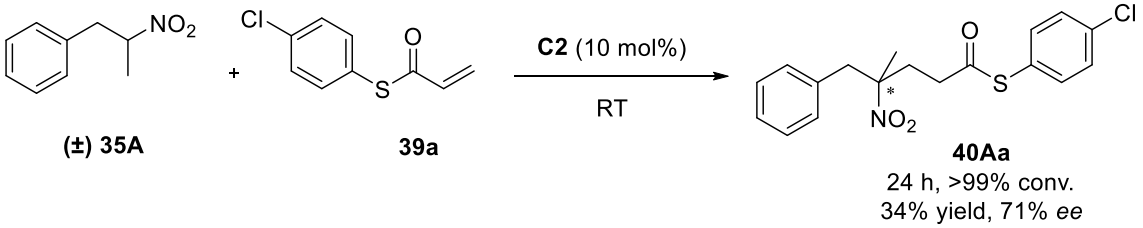


[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane/ α-hydroxy enone/catalyst 5:1:0.1) Conversion determined by the disappearance of the starting α-hydroxy enone. Enantiomeric excess determined by chiral HPLC.



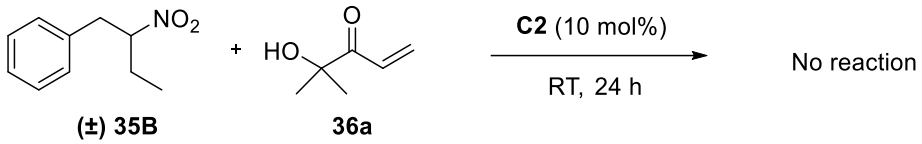
*Scheme 53. Michael addition of nitroalkane **35A** to methyl acrylate **38a** in the presence of catalyst **C2**.*

As expected, since thioacrylates are better electrophiles than their corresponding acrylate counterparts, the reaction with *p*-chloro phenyl thioacrylate **39a** worked more efficiently in terms of reactivity, although the obtained enantioselectivity was lower than with all the α-hydroxy enones tested (Scheme 54).



*Scheme 54. Michael addition of nitroalkane **35A** to p-chloro phenyl thioacrylate **39a.***

In order to explore the reaction scope with different nitroalkanes, (2-nitrobutyl)benzene **35B,** which bears a longer side chain at the alpha position, was tested in the reaction with α-hydroxy enone **36a** in the presence of **C2**, but no adduct was detected after 24 h at RT (Scheme 55).

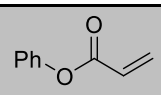
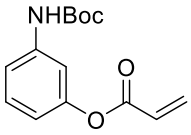
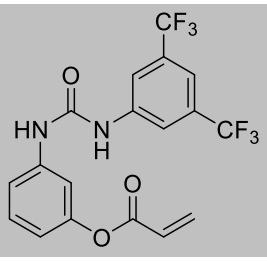
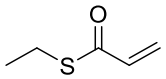
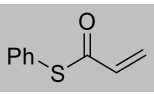
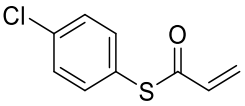
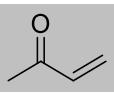
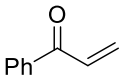


(±) 35B **36a**

*Scheme 55. Michael addition of (2-nitrobutyl)benzene **35B** to α-hydroxy enone **36a.***

Given that α-hydroxy enone **36a** was not able to react with the bulkier nitroalkane **35B**, several different electrophiles were tested in the reaction. To start with, some acrylates were prepared, like commonly known phenyl acrylate **38b.** But the reaction did not work with it either (Table 16, entry 1). So, some new potentially more active acrylates were considered.

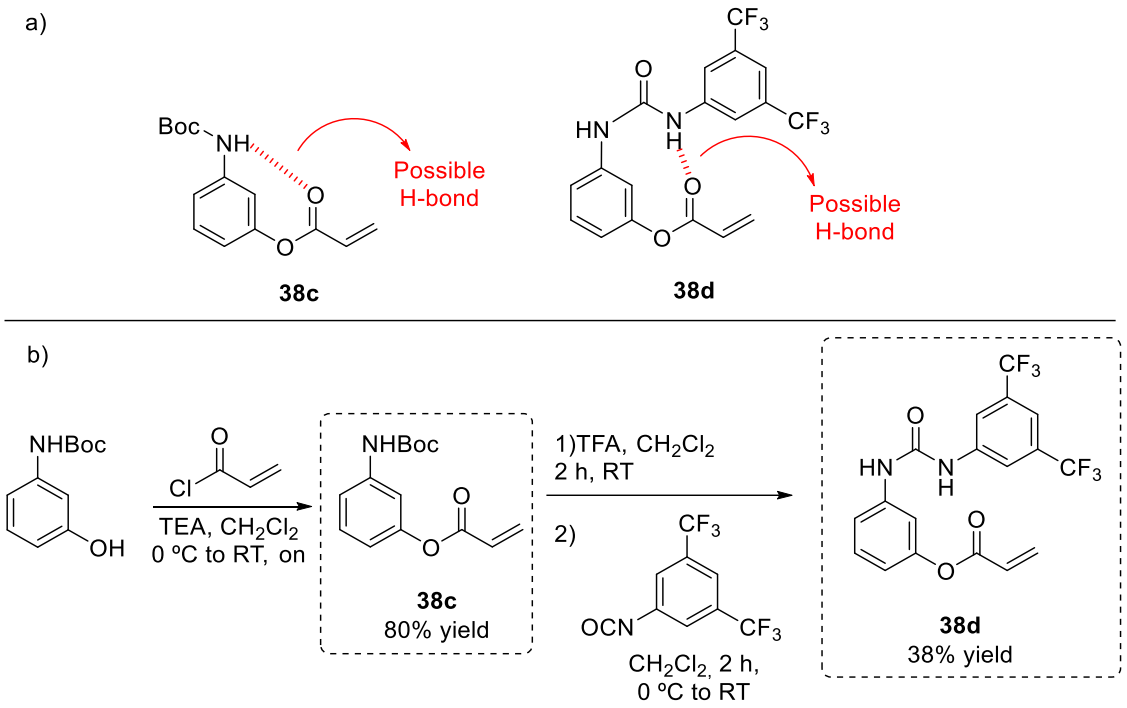
*Table 16. Michael addition of (2-nitrobutyl)benzene **35B** to different electrophiles in the presence of **C2**. [a]*

Entry	Electrophile		t (h)	Conv. (%)	Yield (%)	*ee* (%)
1	**38b**		24	No reaction	-	-
2	**38c**		23	No reaction	-	-
3	**38d**		24	No reaction	-	-
4	**39b**		24	No reaction	-	-
5	**39c**		48	No reaction		
6	**39a**		29	No reaction	-	-
7	**41a**		24	No reaction	-	-
8	**41b**		24	No reaction	-	-

[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane **35B**/ electrophile/catalyst 5:1:0.1). [b] Determined by the disappearance of the starting electrophile**.**

In a first instance, acrylates **38c** and **38d** were designed, which present a possible intramolecular hydrogen bond between the carbonyl and the amide NH that could increase the electrophilicity of the compound (Scheme 56a). These new electrophiles were prepared following the synthetic route depicted in Scheme 56b. However, under the previously optimized conditions, the reaction did not work with these electrophiles either

(Table 16, entries 2 and 3). At this point, it was considered to switch to thioacrylates, due to their higher electrophilicity, so thioacrylates **39b** and **39c**, described in the literature, as well as **39a**, previously employed with **35a**, were tested in the reaction, but none of them reacted with nitroalkane **35b** under the shown conditions (Table 16, entries 4-6). In the case of **39a**, some polymerization of the electrophile was detected in the reaction mixture.



*Scheme 56. a) Design of new acrylates **38c** and **38d** to use as electrophiles, b) Synthetic route to prepare **38c** and **38d**.*

Finally, typical enones **41a** and **41b** described in the literature were submitted to the reaction in the presence of catalyst **C2**. However, no adduct was detected after 24 h at room temperature for each case tested (Table 16, entries 7 and 8). In general, it seems like the Michael addition of **35b** and thereby related nitroalkanes might need a stronger base for deprotonation to react with a Michael acceptor.

CHAPTER 4

CONCLUSIONS

4. Conclusions

Two new subfamilies of short-peptide derived BB catalysts, one containing a squaramide unit and the other bearing a ureidoaminal functionality, have been developed, which demonstrated to perform exceedingly in promoting different challenging transformations.

On the one hand, α-branched aldehydes have been employed as pronucleophiles for the first time in BB catalysed reactions. The conjugate addition of both α-branched α-amino aldehydes and α-branched α-aryl acetaldehydes to nitroolefins has been efficiently performed using short-peptide derived squaramide containing BB catalysts. In the case of α-amino aldehydes, pronucleophiles with *N*-protecting groups, such as Boc, Cbz, Fmoc and *N*-acyl groups of different nature have been investigated. The addition of these aldehydes with different α-substituents (except for bulky groups like *tert*-butyl and *iso*-propyl) to nitrostyrenes bearing different substitution patterns at the aromatic ring, as well as nitroolefins containing alkenyl and alkynyl substituents provides the expected adducts in excellent yield and stereoselectivity. Furthermore, the obtained adducts could be transformed into tetrasubstituted α-amino acids and highly functionalized allyl amines by simple one-step transformations. Fully substituted cyclohexylamines bearing a tetrasubstituted stereocenter at the C_α have also been prepared one pot following a Michael-Michael-Henry tandem reaction, leading to only two of the 64 possible diastereoisomers and in a good ratio and very good yield.

In the case of α-branched aryl acetaldehydes, the addition reaction of α-methyl α-aryl pronucleophiles to both β-aromatic and β-aliphatic nitroolefins provided the corresponding adducts in high yields and excellent stereoselectivities using short peptide-derived squaramide-containing bifunctional BBs as catalysts. The reaction of such α-aryl aldehydes with substituents at different positions of the aromatic ring, as well as heteroaromatic rings and bigger aromatic systems also led to almost a single stereoisomer. For the addition of aryl acetaldehydes with alkyl substituents larger than methyl at the alpha position, the reaction required longer reaction times and proceeded in variable *dr* and *ee* values.

DFT calculations for the additions of α-branched aldehydes to nitroolefins have provided an insight into the mechanism of the reaction, underlining the significance of intramolecular H-bonds for reactivity and stereoselectivity, in both the α-amino aldehydes and the short peptide-derived catalysts that provided the best results.

On the other hand, the Michael addition of non-activated α-branched nitroalkanes to α-hydroxy enones has been efficiently promoted for the first time with short peptide-derived ureidopeptide-like BB catalysts bearing up to three amino acid units, although in terms of stereoselectivity, the best results were obtained with the catalyst containing a

single amino acid. The matched combination of the two chiral fragments of the catalyst was found to correspond to the catalysts prepared from quinidine and (*L*)-*tert*-Leucine. Furthermore, the chirality on the peptidic chain proved to be mandatory for inducing stereoselectivity.

Higher enantioselectivities were reached when performing the addition to α-hydroxy enones bearing substituents bigger than methyl at the alpha position, like benzyl and 2-naphthyl. Preliminary explorations using acrylate and thioacrylate esters as electrophiles showed that the above method could be extended to Michael acceptors other than α-hydroxy enones, although some changes might be needed in the catalyst and/or the reaction conditions. However, the conjugate addition to α-hydroxy enones is still more efficient in terms of both reactivity and stereoselectivity, confirming once again the utility of these electrophiles as efficient Michael acceptors.

CHAPTER 5

EXPERIMENTAL SECTION

5. Experimental section

5.1. Materials and general techniques

5.1.1. Reagents, solvents and products

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

Triethylamine, DIPA and DIPEA were purified by distillation. When anhydrous solvents were required, they were dried following established procedures.[143] Dichloromethane (Cl_2CH_2) was dried over CaH_2 and tetrahydrofuran was distilled over sodium/benzophenone. Analytical reagent grade MeOH and toluene were used without further drying. Analytical reagent grade DMF was dried over molecular sieves.

5.1.2. General experimental

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

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

Organic layers washed with aqueous phases were dried over $MgSO_4$ and filtered through cotton. Organic solvents were evaporated under reduced pressure using rotavapors Büchi R-100, 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.

5.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Biolock lamp VL-4LC, λ = 254 and 365 nm. In addition,

[143] Armanego, W. L. F.; Perrin, D. D., *Purification of Laboratory Chemicals,* 3rd Edition Butterworth-Heinemann, Oxford, **1988**.

TLC plates were stained with a dipping solution of potassium permanganate (1g) 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. In some particular cases non-acidic silica gel was used (specified in each case), which was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 h. After filtration, the residual water was evaporated in an oven at 80 ºC during 72 h.

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600-E (equipped with 2996 and 2998 photodiode array UV detector) employing Daicel Chiralpack columns (IF, IA, IB, IC, ID, OD-H).

5.1.4. Optical rotations

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

5.1.5. Melting points

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

5.1.6. NMR spectra

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26), $(CD_3)_2CO$ (δ = 2.05) and CD_3OD (δ = 3.31) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ (δ = 77.0), $(CD_3)_2CO$ (δ = 206.3) and CD_3OD (δ = 49.2) for ^{13}C NMR. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet, doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), doublet of quartets (dq), quartet of doublets (qd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplet of doublets (dtd), triplet of doublet of doublets (tdd), Coupling constants (*J*) are reported in Hertz (HZ). MestrReNova Mnova 11.0.4 program was used to process and edit the registered spectra.

5.1.7. Mass spectra

Mass 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).

5.1.8. Infrared spectra

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

5.1.9. X-ray diffraction analysis

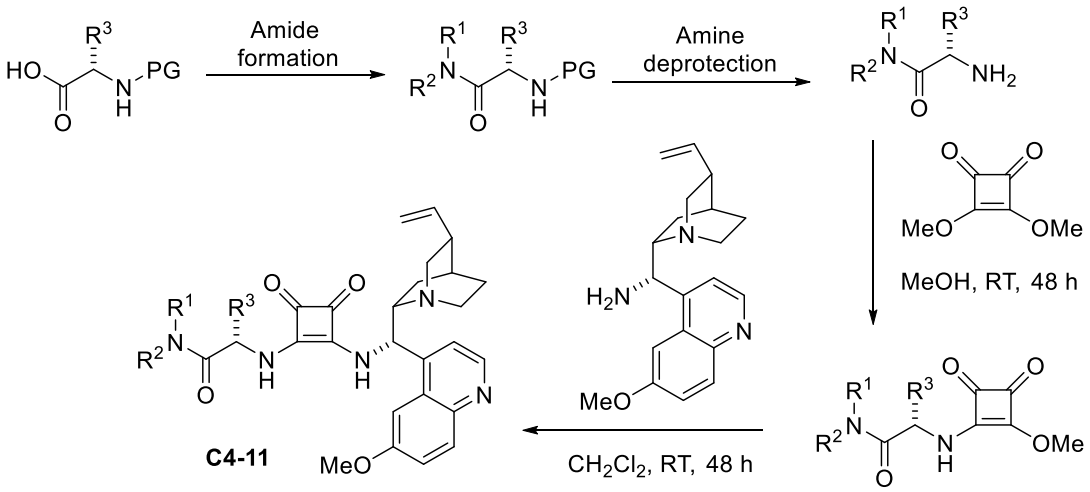
The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

5.2. Preparation of catalysts

Chiral catalysts **C1**,[53] **C14**,[144] **C15**,[52] **C16**,[51] and **C17**[145] and achiral catalyst **C31**[146] were prepared following the procedures described in the literature.

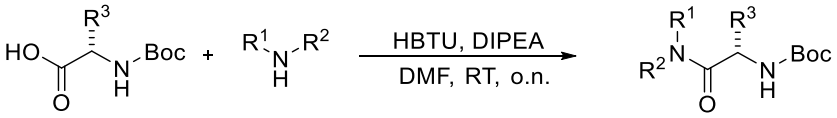
5.2.1. Synthesis of squaramidopeptides

*5.2.1.1. Catalysts **C4**-**C11***



Step 1: Amide formation

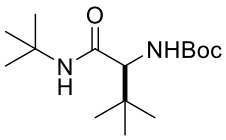
GENERAL PROCEDURE 1:[147]



To a stirred solution of the corresponding *N*-protected amino acid (1 eq) in dry DMF (2 mL/mmol) under inert atmosphere and at room temperature DIPEA (2 eq) and HBTU (1.5 eq) were added. After stirring for 1 h, the corresponding amine was added, and the mixture was allowed to react for 16 h. The reaction was quenched with HCl 1M (1.6 mL/mmol) and the mixture extracted with EtOAc (x3). The organic phases were collected and washed with HCl 1M (x3) and brine (x5), dried over $MgSO_4$ and evaporated under reduced pressure. When necessary, the obtained crude was purified by silica flash column chromatography on silica gel to give the desired compound.

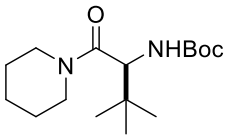
[144] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12* (23), 5450–5453.
[145] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7* (10), 1967–1969.
[146] Opalka, S. M.; Steinbacher,J. L.; Lambiris,B. A.; McQuade, D. T. *J. Org. Chem.* **2011**, *76*, 6503–6517.
[147] Synthesis procedure from: Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.*, **2010**, *16,* 13068–13071.

tert-Butyl (_S_)-(1-(_tert_-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



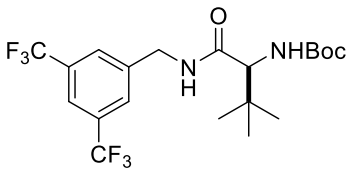
Prepared following the General Procedure 1 starting from Boc-(_L_)-_tert_-Leucine[148] (1.156 g, 5 mmol, 1 eq) and _tert_-butylamine (0.52 mL, 5 mmol, 1 eq). The crude was used in the next step without further purification. The product was obtained as a white solid (1.35 g, 4.7 mmol, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (br s, 1H), 3.65 (d, J = 9.4 Hz, 1H), 1.45 (s, 9H), 1.36 (s, 9H), 0.99 (s, 9H).

tert-Butyl (_S_)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate



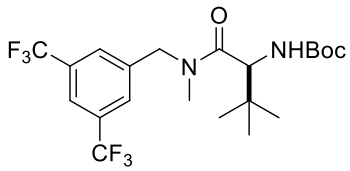
Prepared following the General Procedure 1 starting from Boc-(_L_)-_tert_-Leucine[148] (2.313 g, 10 mmol, 1 eq) and piperidine (1.09 mL, 11 mmol, 1.1 eq). The crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 90:10) to afford the product as a white solid (2.675 g, 9 mmol, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (d, J = 9.7 Hz, 1H), 4.54 (d, J = 9.7 Hz, 1H), 3.70-3.43 (m, 4H), 1.69-1.51 (m, 6H), 1.43 (s, 9H), 0.97 (s, 9H). All spectroscopic data were consistent with those previously reported.[147]

tert-Butyl (_S_)-(1-((3,5-bis(trifluoromethyl)benzyl)amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (I1)



Prepared following the General Procedure 1 starting from Boc-(_L_)-_tert_-Leucine[148] (1.979 g, 8.6 mmol, 1 eq) and 3,5-bis(trifluoromethyl)benzylamine (1.988 g, 8.6 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 80:20) to afford the product as a yellow foam (3.3485 g, 7.34 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.75 (s, 2H), 6.31 (t, 1H), 5.17 (d, J = 5.6 Hz, 1H), 4.57 (d, J = 6.1 Hz, 1H), 3.84 (d, J = 8.9 Hz, 2H), 1.42 (s, 9H), 1.02 (s, 9H). All spectroscopic data were consistent with those previously reported.[148]

tert-Butyl (_S_)-(1-((3,5-bis(trifluoromethyl)benzyl)(methyl)amino)-3,3-dimethyl-1-oxo butan-2-yl)carbamate



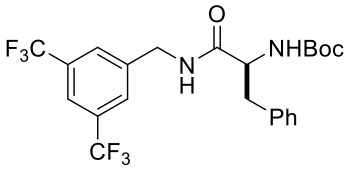
Prepared following the General Procedure 1 starting from Boc-(_L_)-_tert_-Leucine[148] (1.665 g, 7.2 mmol, 1.2 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-_N_-methylmethan amine[149] (1.539 g, 6 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (Hexane:EtOAc

[148] Manna, M. S.; Mukherjee, S. *Chem. Sci*. **2014**, *5*, 1627–1633.

[149] Synthesis procedure from: Arasappan, A. *Substituted pyridine and pyrimidine derivatives as antiviral agents and their preparation and use in treating viral infections PCT Int. Appl. WO 2011103441* **2011**.

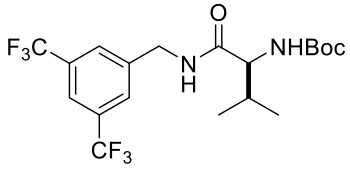
95:5) to afford the product as a yellow oil (2.360 g, 5 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 2H), 5.28 (d, J = 9.4 Hz, 1H), 4.78 (d, J = 15.1 Hz, 1H), 4.55 (d, J = 9.7 Hz, 1H), 3.14 (s, 3H), 1.43 (s, 1H), 1.01 (s, 9H).

tert-Butyl (_S_)-(1-((3,5-bis(trifluoromethyl)benzyl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate



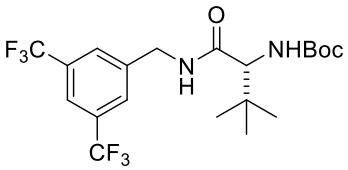
Prepared following the General Procedure 1 starting from commercially available Boc-(*L*)-Phenylalanine (1.592 g, 6 mmol, 1 eq) and 3,5-bis(trifluoromethyl) benzyl amine (1.459 g, 6 mmol, 1 eq). The crude product was used in the next step without further purification. White solid (2.943 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (s, 2H), 7.26 – 7.10 (m, 5H), 6.39 (t, J = 5.3 Hz, 1H), 5.00 (s, 1H), 4.46 (m, 2H), 4.40 – 4.29 (m, 1H), 3.08 (m, 2H), 1.39 (s, 9H).

tert-Butyl (_S_)-(1-((3,5-bis(trifluoromethyl)benzyl)amino)-3-methyl-1-oxobutan-2-yl) carbamate



Prepared following the General Procedure 2 starting from commercially available Boc-(*L*)-Valine (1.304 g, 6 mmol, 1 eq) and 3,5-bis(trifluoromethyl)benzylamine (1.459 g, 6 mmol, 1 eq). The crude product was used in the next step without further purification. White solid (2.534 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.73 (s, 2H), 6.98 (s, 1H), 5.08 (d, J = 8.7 Hz, 1H), 4.63 – 4.44 (m, 2H), 3.71 (m, 1H), 3.17 (m, 1H), 1.40 – 1.38 (m, 9H), 0.94 (dd, J = 11.7, 6.8 Hz, 6H).

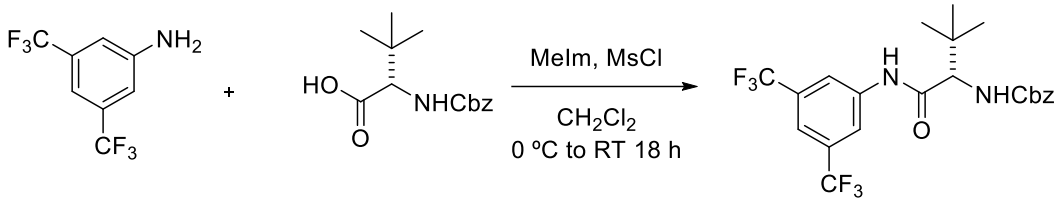
tert-butyl (_R_)-(1-((3,5-bis(trifluoromethyl)benzyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



Prepared following the General Procedure 1 starting from Boc-(*D*)-*tert*-Leucine[150] (1.062 g, 4.9 mmol, 1 eq) and 3,5-bis(trifluoromethyl)benzylamine (1.130 g, 4.9 mmol, 1 eq). The crude was used in the next step without further purification. Yellow oil (2.232 g, 4.89 mmol, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 3H), 6.80 (d, J = 63.3 Hz, 1H), 5.26 (s, 1H), 4.59 – 4.49 (m, 2H), 3.94 – 3.85 (m, 1H), 1.39 (d, J = 3.1 Hz, 9H), 1.00 (s, 9H).

[150] Prepared following the same procedure as for Boc-(*L*)-*tert*-Leucine (Ref. 148).

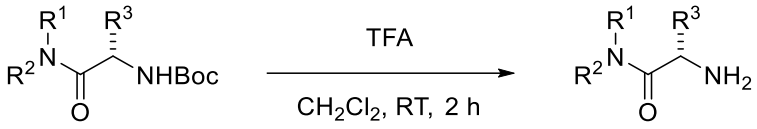
PROCEDURE 2:[151] **Benzyl (*S*)-(1-((3,5-bis(trifluoromethyl)phenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate**.



To a stirred solution of Cbz-(*L*)-*tert*-Leucine[148] (3.41 g, 12.9 mmol, 1 eq) in dry CH_2Cl_2 (43 mL, 3.3 mL/mmol) at 0 ºC, 1-methylimidazole (2.6 mL, 32.3 mmol, 2.5 eq) was added and the solution was stirred at the same temperature for 10 min. Then, the mixture was cooled to –5 ºC and methanesulfonyl chloride (1.5 mL, 19.4 mmol, 1.5 eq) was added and the resulting mixture was stirred for 20 min at the same temperature. Finally, 3,5-bis(trifluromethyl)aniline (2.2 mL, 14.2 mmol, 1.1 eq) was added and the mixture was allowed to reach RT and stirred for 16 h. The reaction was quenched with H_2O (25 mL) and EtOAc (25 mL) was added. The layers were separated and the organic layer was washed with brine (x3), dried over $MgSO_4$, filtered and the solvents were evaporated at reduced pressure. The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 90:10) to give the desired compound as a white foam (3.50 g, 7.25 mmol, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.92 (d, *J* = 1.1 Hz, 1H), 7.50 (s, 2H), 7.32 (s, 5H), 5.64 (d, *J* = 9.0 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 1.10 (s, 9H).

Step 2: Amine deprotection

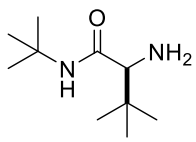
GENERAL PROCEDURE 1:[152]



To a stirred solution of the starting *N*-Boc compound (1 eq) in CH_2Cl_2 (1 mL/mmol) at 0 ºC TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach RT and then stirred for 2 h. Then, solvents were removed under reduced pressure and the remaining oil was redissolved in H_2O, cooled down to 0 ºC and basified with a sat. Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with $NaHCO_3$ sat. and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude product, which was used in the next step without further purification.

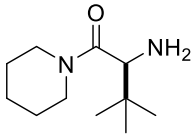
[151] Maoa, L.; Wanga, Z.; Lia, Y.; Hanb, X.; Zhou, W. *Synlett*, **2011**, *1*, 129–133.
[152] Adapted from: Müller, J.; Feifel, S. C.; Schmiederer, T.; Zocher, R.; Süssmuth, R. D. *ChemBioChem* **2009**, *10* (2), 323–328.

(*S*)-2-Amino-*N*-(*tert*-butyl)-3,3-dimethylbutanamide



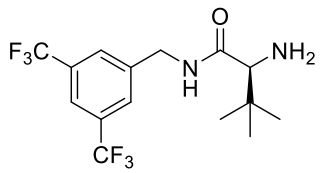
The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxo butan-2-yl)carbamate (1.35 g, 4.7 mmol, 1 eq). The desired product was obtained as a yellow oil (540.2 mg, 2.9 mmol, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67- 3.63 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H).

(*S*)-2-Amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one



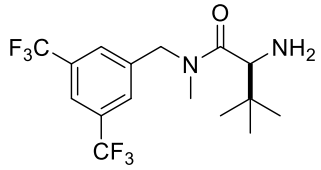
The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate (2.7464 g, 9.2 mmol, 1 eq). The desired product was obtained as a yellow oil (1.601 g, 8.1 mmol, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (m, 5H), 1.73 (d, J = 3.5 Hz, 2H), 1.59 (m, 6H), 0.97 (s, 9H). All spectroscopic data were consistent with those previously reported.[147]

(*S*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3,3-dimethylbutanamide (I2)



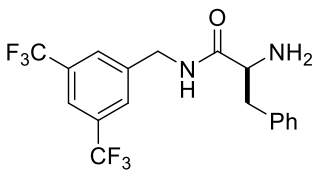
The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(1-((3,5-bis(trifluoro methyl) benzyl) amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (3.337 g, 7.3 mmol, 1 eq). The desired product was obtained as a white solid (2.468 g, 6.9 mmol, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (s, 2H), 7.56 (s, 1H), 4.56 (qd, J = 15.4, 6.7 Hz, 2H), 3.22 (s, 1H), 1.64 (s, 2H), 1.02 (s, 9H). All spectroscopic data were consistent with those previously reported.[148]

(*S*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*,3,3-trimethylbutanamide



The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(1-((3,5-bis(trifluoro methyl) benzyl) (methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (2.360 g, 5 mmol, 1 eq). The desired product was obtained as a yellow oil (1.759 g, 4.75 mmol, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.73 (s, 2H), 4.97 (d, J = 15.0 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 3.57 (s, 1H), 3.07 (s, 3H), 0.99 (s, 9H).

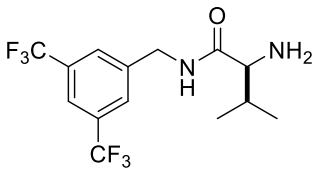
***(S)*-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3-phenylpropanamide**



The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(1-((3,5-bis(trifluoro methyl) benzyl) amino)-1-oxo-3-phenylpropan-2-yl) carbamate (2.943 g, 6 mmol, 1 eq). The desired product was obtained as a

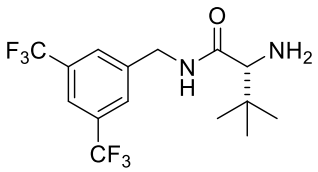
yellow solid (2.175 g, 5.6 mmol, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.78 (s, 1H), 7.70 (s, 2H), 7.35 – 7.15 (m, 5H), 4.54 (d, J = 6.1 Hz, 2H), 3.73 (s, 1H), 3.26 (dd, J = 13.6, 4.0 Hz, 1H), 2.87 – 2.80 (m, 1H), 1.92 – 1.53 (m, 2H).

(*S*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3-methylbutanamide



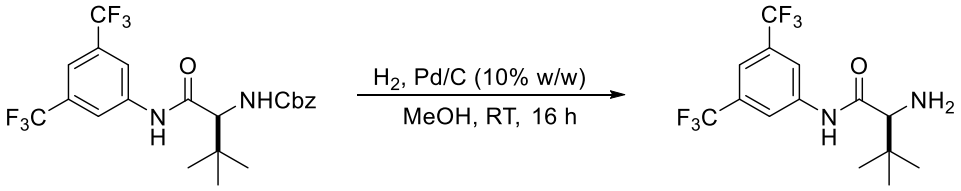
The title compound was prepared following the General Procedure 1 starting from *tert*-butyl (*S*)-(1-((3,5-bis(trifluoro methyl)benzyl) amino)-3-methyl-1-oxobutan-2-yl) carbamate (2.534 g, 6 mmol, 1 eq). The desired product was obtained as a yellow solid (1.890 g, 5.5 mmol, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.73 (d, J = 1.4 Hz, 2H), 4.57 (ddd, J = 15.5, 6.3 Hz, 2H), 3.36 (d, J = 3.7 Hz, 1H), 2.39 (m, 1H), 1.67 (s, 2H), 1.01 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H).

(*R*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3,3-dimethylbutanamide



The title compound was prepared following the General Procedure 1 starting from tert-butyl (R)-(1-((3,5-bis(trifluoro methyl)benzyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (2.232 g, 4.89 mmol, 1 eq). The desired product was obtained as a yellow oil (1.503 g, 4.22 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (s, 2H), 7.61 (s, 1H), 4.60 (dd, J = 15.5, 6.3 Hz, 1H), 4.51 (dd, J = 15.3, 6.1 Hz, 1H), 3.23 (s, 1H), 1.91 (s, 2H), 1.01 (s, 9H).

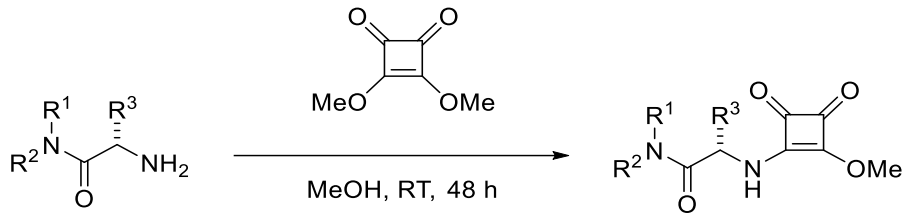
PROCEDURE 2: **(*S*)-2-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl butanamide**



To a stirred solution of benzyl (*S*)-(1-((3,5-bis(trifluoromethyl)phenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (5.44 g, 11.4 mmol, 1 eq) in MeOH (28 mL, 2.4 mL/mmol) and under Argon atmosphere, Pd on carbon (10%) (544 mg, 10% w/w) was added. The atmosphere was then changed from argon to hydrogen and the reaction mixture was stirred for 16 h at RT. After reaction completion, the mixture was filtered through zelite, washed with CH_2Cl_2 and the solvents were evaporated under reduced pressure. The title compound was obtained as a colorless gel (12.2 mmol, 6.16 g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.10 (s, 2H), 7.57 (s, 1H), 3.33 (s, 1H), 1.07 (s, 9H).

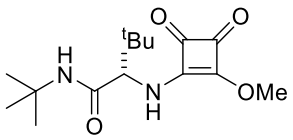
Step 3: Coupling of the first amine with the squarate

GENERAL PROCEDURE:[52]



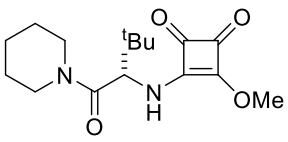
To a stirred solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (0.9 eq) in MeOH (2 mL/mmol) the corresponding amine (1 eq) was added. The reaction mixture was stirred at room temperature for 48 h and then filtered if a precipitate was formed. Otherwise, the solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography on silica gel.

(*S*)-*N*-(*tert*-Butyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide



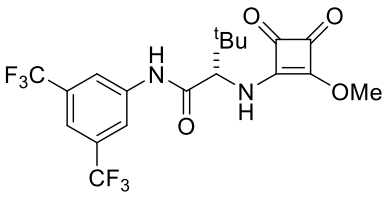
The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(*tert*-butyl)-3,3-dimethyl butanamide (540.2 mg, 2.9 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 80:20) to afford the product as a yellow oil (454 mg, 1.5 mmol, 59% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 3H), 4.31 (d, J = 9.6 Hz, 1H), 1.39 (s, 9H), 1.03 (s, 9H).

(*S*)-3-((3,3-Dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione



The title compound was prepared following the General Procedure starting from (*S*)-2-amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one (297 mg, 1.5 mmol, 1 eq). The product was isolated by filtration as a white solid (453 mg, 1.47 mmol, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 1H), 4.41 (s, 3H), 3.73-3.54 (m, 4H), 1.75-1.70 (m, 6H), 1.03 (s, 9H).

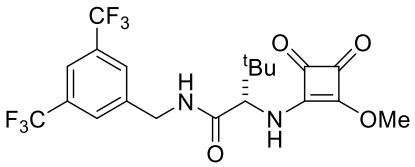
(*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide



The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)phenyl)-3,3-dimethylbutanamide (4.59 g, 13.4 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc

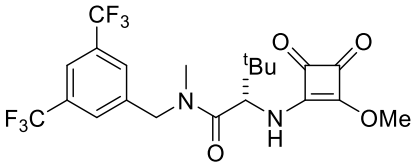
50:50) to afford the product as a yellow solid (3.37 g, 7.45 mmol, 56% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 9.65 (d, *J* = 11.2 Hz, 1H), 8.26 (s, 2H), 7.63 (s, 1H), 6.33 (s, 1H), 5.01 (d, *J* = 9.1 Hz, 1H), 4.45 (s, 3H), 1.14 (s, 9H).

(*S*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (I3)



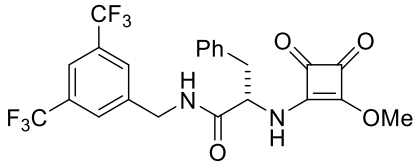
The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)benzyl)-3,3-dimethylbutanamide (1.610 g, 4.52 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 80:20) to afford the product as a white foam (1.357 g, 2.91 mmol, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.77 (s, 1H), 6.26 (d, J = 30.2 Hz, 1H), 4.82 – 4.60 (m, 2H), 4.52 (d, J = 5.9 Hz, 1H), 4.40 (s, 3H), 1.57 (s, 1H), 1.02 (s, 9H).

(*S*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*,3,3-trimethylbutanamide



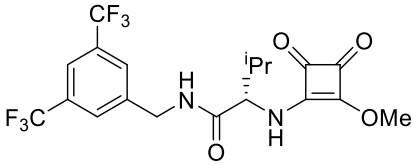
The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)benzyl)-N,3,3-trimethyl butanamide (1.759 g, 4.75 mmol, 1 eq). The product was isolated by filtration as a white solid (1.604 g, 3.34 mmol, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.72 (s, 2H), 6.13 (d, J = 9.9 Hz, 1H), 5. (d, J = 10.1 Hz, 1H), 5.17-5.06 (m, 1H), 5.01 (d, J = 14.9 Hz, 1H), 4.40 (s, 3H), 3.14 (s, 3H), 1.03 (s, 9H).

(*S*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-phenylpropanamide



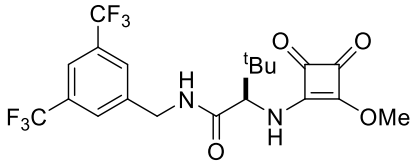
The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)benzyl)-3-phenylpropanamide (2.175 g, 5.57 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to afford the product as a white foam (2.074 g, 4.15 mmol, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (s, 2H), 7.24 – 7.07 (m, 5H), 7.03 (d, J = 5.4 Hz, 1H), 4.98 (s, 1H), 4.49 (m, 1H), 4.44 (m, 2H), 4.32 (s, 3H), 3.13 (d, J = 7.4 Hz, 2H).

(*S*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamide



The title compound was prepared following the General Procedure starting from (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)benzyl)-3-methylbutanamide (1.890 g, 5.5 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to afford the product as a white foam (2.118 g, 4.68 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 3H), 7.60 (d, J = 6.4 Hz, 1H), 6.20 (d, J = 9.4 Hz, 1H), 4.64 (dd, J = 15.1, 6.2 Hz, 2H), 4.55 (s, 1H), 4.38 (s, 3H), 2.11 (d, J = 14.3 Hz, 1H), 0.98 (dd, J = 6.8, 2.4 Hz, 6H).

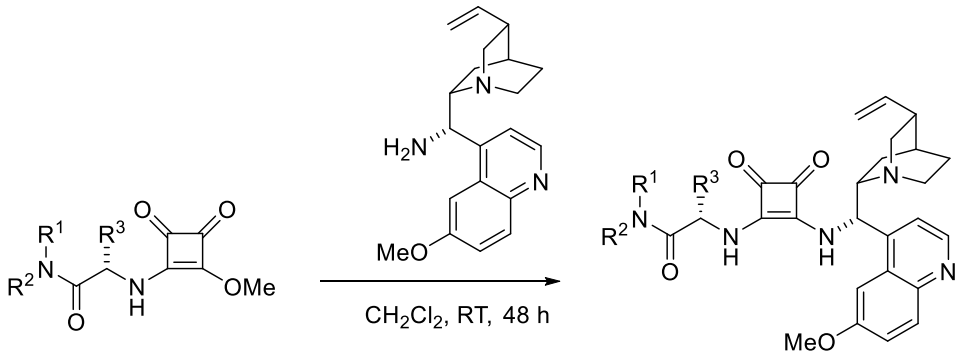
(*R*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide



The title compound was prepared following the General Procedure starting from (*R*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3,3-dimethylbutanamide (1.503 g, 4.22 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 70:30) to afford the product as a white foam (1.048 g, 2.25 mmol, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.74 (m, 3H), 7.59 (s, 1H), 6.17 (d, J = 9.8 Hz, 1H), 4.65 (s, 1H), 4.52 (dd, J = 15.1, 14.4, 6.0 Hz, 2H), 4.40 (s, 3H), 1.03 (s, 9H).

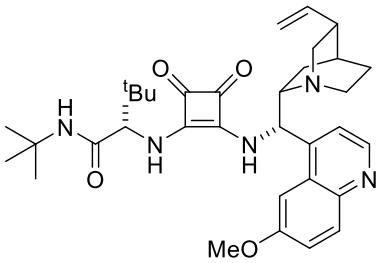
Step 4: Coupling of 9-amino-(9-deoxy) epiquinine with the monosubstituted squarate

GENERAL PROCEDURE:[52]



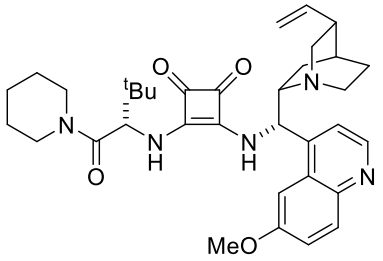
To a stirred solution of the previously prepared monosubstituted squarate (1 eq) in CH_2Cl_2 (5 mL/mmol) 9-amino-(9-deoxy) epiquinine[164] (1 eq) and TEA (1 eq) were added. The reaction mixture was stirred at room temperature for 48 h. Then, the solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography on silica gel.

Catalyst C4



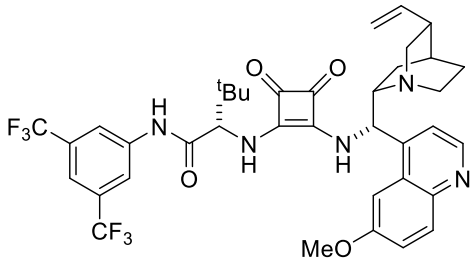
The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(*tert*-butyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl) amino)-3,3-dimethyl butanamide (454 mg, 1.5 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give a yellow solid (485 mg, 0.82 mmol, 55% yield). m.p.: 150-152 ºC. $[\alpha]_D^{24}$ = –78.12 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.72 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 4.5 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.33 (s, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 5.98 (dd, *J* = 17.2, 9.4 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.40 (s, 1H), 4.03 (s, 3H), 3.75-3.44 (m, 2H), 3.25 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.88-2.64 (m, 2H), 2.40-2.26 (m, 1H), 1.68-1.49 (m, 5H), 1.24 (s, 9H), 0.99 (s, 9H), 0.83-0.66 (m, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 184.8, 183.7, 170.5, 168.9, 160.0, 149.2, 146.5, 145.4, 143.8, 133.3, 129.5, 123.5, 121.0, 115.2, 103.1, 65.7, 61.3, 57.7, 57.1, 52.5, 42.0, 41.6, 36.6, 29.5, 29.4, 29.2, 28.0. UPLC-DAD-QTOF: $C_{34}H_{46}N_5O_4$ $[M+H]^+$ calcd.: 588.3550, found: 588.3548.

Catalyst C5



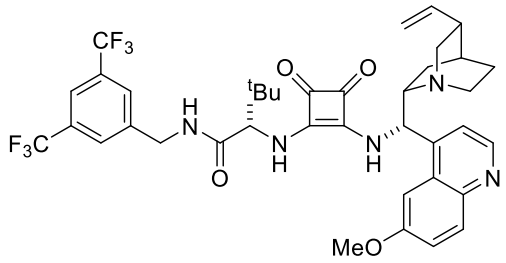
The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-3-((3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl) amino)-4-methoxycyclobut-3-ene-1,2-dione (419 mg, 1.36 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (98:2 CH_2Cl_2:MeOH) to give a yellow solid (530 mg, 0.88 mmol, 65% yield). Decomp. Tª: 157–159 °C. $[\alpha]_D^{24}$ = –87.72° (c=0.41, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.70 (d, *J* = 4.5 Hz, 1H), 7.98 (s, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.77 (br s, 1H), 7.58 (d, *J* = 4.6 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.24 (br s, 1H), 5.95 (ddd, *J* = 17.7, 10.2, 7.9 Hz, 1H), 5.39-5.24 (m, 1H), 5.04 (dt, *J* = 17.1, 1.5 Hz, 1H), 4.96 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.03 (s, 3H), 3.54 (m, 5H), 3.40-3.22 (m, 2H), 2.87-2.77 (m, 1H), 2.73 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.35 (t, *J* = 10.4 Hz, 1H), 1.81-1.25 (m, 11H), 0.94 (s, 9H), 0.84-0.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 182.6, 169.7, 168.4, 167.1, 159.6, 148.4, 145.5, 145.0, 141.8, 132.6, 128.2, 123.6, 120.0, 115.4, 101.0, 61.7, 58.9, 56.7, 56.5, 53.9, 48.5, 43.7, 41.5, 40.0, 36.4, 28.3, 28.1, 26.8, 26.5, 26.2, 24.9. UPLC-DAD-QTOF: $C_{35}H_{46}N_5O_4$ $[M+H]^+$ calcd.: 600.3550, found: 600.3545.

Catalyst C6



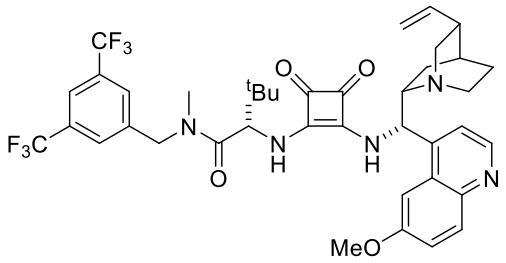
The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (678.5 mg, 1.5 mmol, 1 equiv). The crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to give a yellow solid (252.9 mg, 0.34 mmol, 23%). m.p.: 166-169 ºC. $[\alpha]_D^{24}$ = –17.1 (c=1.00, DMSO). ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (d, J = 3.9 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.97 (s, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.37 (d, J = 11.0 Hz, 1H), 6.09 (ddd, J = 17.6, 10.3, 7.7 Hz, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 4.67 (s, 1H), 4.33 (s, 1H), 3.94 (s, 3H), 3.67 (t, J = 7.9 Hz, 1H), 3.10 – 2.94 (m, 1H), 2.90 – 2.76 (m, 1H), 2.56 – 2.38 (m, 1H), 1.82 – 1.61 (m, 5H), 0.95 (s, 9H), 0.84 – 0.65 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 183.4, 183.0, 172.9, 172.2, 169.6, 167.9, 160.6, 148.5, 145.5, 145.3, 142.5, 140.9, 133.3 (q, J = 33.4 Hz), 132.0, 129.6, 124.3 (q, J = 272.0 Hz), 123.5, 120.5, 120.0, 118.0, 115.4, 103.2, 65.5, 63.6, 60.3, 56.8, 41.6, 40.7, 35.7, 34.8, 29.0, 28.3, 27.6, 26.7. UPLC-DAD-QTOF: $C_{38}H_{40}N_5O_4F_6$ $[M+H]^+$ calcd.: 744.2984, found: 744.2979.

Catalyst C7



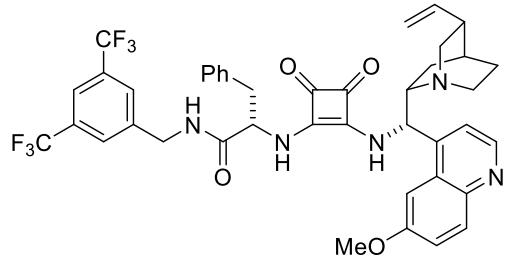
The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(3,5-bis(trifluoro methyl)benzyl)-2-((2-methoxy-3,4-dioxocyclo but-1-en-1-yl)amino)-3,3-dimethyl butanamide (1.398 g, 3 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give a yellow solid (1.545 g, 2.04 mmol, 68% yield). m.p.: 180-184 ºC. $[\alpha]_D^{24}$ = –104.3 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.65 (d, J = 4.2 Hz, 1H), 8.01 – 7.87 (m, 4H), 7.84 (s, 1H), 7.58 (d, J = 4.4 Hz, 1H), 7.39 (dd, J = 9.2, 2.6 Hz, 1H), 6.30 – 6.15 (m, 1H), 6.02 – 5.85 (m, 1H), 5.02 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.3 Hz, 1H), 4.78 – 4.57 (m, 2H), 4.38 (d, J = 15.3 Hz, 1H), 3.98 (s, 3H), 3.69 – 3.38 (m, 2H), 3.31 – 3.11 (m, 1H), 2.87 – 2.55 (m, 2H), 2.31 (s, 1H), 1.70 – 1.45 (m, 5H), 0.96 (s, 9H), 0.86 – 0.69 (m, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 184.0, 183.5, 171.2, 168.6, 167.9, 159.5, 148.6, 146.0, 144.9, 143.6, 143.2, 132.7, 132.0 (q, J = 33.1 Hz), 129.4, 128.9, 124.5 (q, J = 272.1 Hz), 123.0, 121.7, 120.4, 114.6, 102.5, 65.0, 60.7, 57.1, 56.4, 54.9, 42.8, 41.5, 41.0, 36.1, 29.0, 28.7, 27.3, 26.6. UPLC-DAD-QTOF: $C_{39}H_{42}N_5O_4F_6$ $[M+H]^+$ calcd.: 758.3141, found: 758.3138.

Catalyst C8



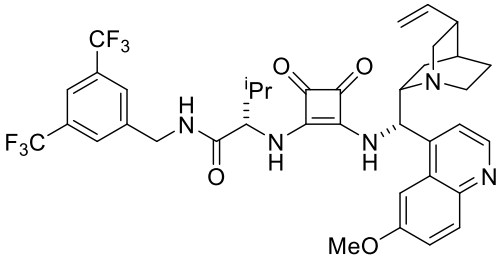
The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(3,5-bis (trifluoromethyl)benzyl)-2-((2-methoxy-3,4-di oxocyclobut-1-en-1-yl)amino)-*N*,3,3-trimethyl butanamide (891.7 mg, 1.86 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 97:3) to give a yellow solid (1.169 g, 1.52 mmol, 82% yield). m.p.: 153-157 ºC. $[\alpha]_D^{24}$ = –133.4 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.66 (d, J = 4.1 Hz, 1H), 8.02 – 7.93 (m, 2H), 7.92 – 7.75 (m, 3H), 7.55 (d, J = 4.5 Hz, 1H), 7.38 (dd, 1H), 6.24 (s, 1H), 5.88 (ddd, J = 17.6, 9.0 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.99 (d, J = 5.0 Hz, 1H), 4.98 – 4.90 (m, 1H), 4.87 (s, 1H), 4.39 (d, J = 15.1 Hz, 1H), 4.00 (s, 3H), 3.58 – 3.43 (m, 2H), 3.33 – 3.17 (m, 3H), 3.14 (s, 3H), 2.82 – 2.65 (m, 2H), 2.28 (s, 1H), 1.58 (s, 4H), 0.95 (s, 9H), 0.76 (s, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 184.0, 183.3, 172.1, 168.1, 168.0, 148.2, 144.8, 142.7, 141.9, 141.2, 132.4, 131.9 (q, J = 33.1 Hz), 129.3, 128.7, 128.6, 124.1 (qd, J = 272.6 Hz), 122.9, 121.7, 120.0, 114.4, 102.2, 59.2, 59.1, 56.7, 56.2, 50.9, 41.2, 40.5, 36.7, 36.6, 34.0, 28.6, 28.3, 26.9, 26.1. UPLC-DAD-QTOF: $C_{40}H_{44}N_5O_4F_6$ $[M+H]^+$ calcd.: 772.3297, found: 772.3306.

Catalyst C9



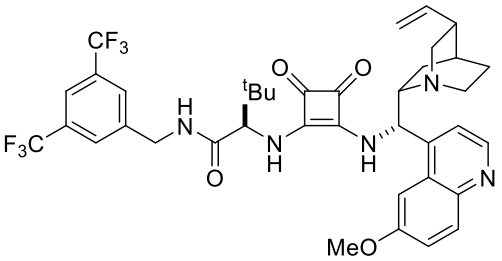
The title product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(3,5-bis(trifluoro methyl)benzyl)-2-((2-methoxy-3,4-dioxocyclo but-1-en-1-yl)amino)-3-phenylpropanamide (750.6 mg, 1.5 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give a yellow solid (946.1 mg, 1.19 mmol, 80% yield). m.p.: 158-162 ºC. $[\alpha]_D^{24}$ = –140.9º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.49 (dd, J = 9.2, 2.5 Hz, 1H), 7.17 (s, 5H), 6.23 (d, J = 11.0 Hz, 1H), 5.98 (ddd, J = 17.6, 10.3, 7.5 Hz, 1H), 5.17 – 5.01 (m, 2H), 4.93 (s, 1H), 4.40 (m, 2H), 4.01 (s, 3H), 3.56 (d, J = 8.6 Hz, 2H), 3.13 (m,2H), 2.93 – 2.72 (m, 2H), 2.46 (m, 1H), 1.69 (m, 5H), 0.79 – 0.66 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 183.9, 183.5, 172.6, 168.7, 168.3, 160.4, 148.2, 145.6, 145.3, 142.7, 142.3, δ 132.6 (q, J = 33.2 Hz), 137.1, 131.6, 130.3, 129.4, 129.2, 127.9, 124.6 (q, J = 272.0 Hz), 124.3, 121.9, 120.3, 115.3, 102.2, 60.8, 59.7, 56.9, 56.7, 54.5, 43.2, 41.7, 41.4, 40.5, 28.8, 28.2, 27.2. UPLC-DAD-QTOF: $C_{42}H_{40}N_5O_4F_6$ $[M+H]^+$ calcd.: 792.2984, found: 792.2999.

Catalyst C10



The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-(3,5-bis (trifluoromethyl)benzyl)-2-((2-methoxy-3,4-di oxocyclobut-1-en-1-yl)amino)-3-methylbutan amide (678.5 mg, 1.5 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give a white solid (719.5 mg, 0.97 mmol, 64% yield). m.p.: 170-173 ºC. $[\alpha]_D^{24}$ = –175.3 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.63 (d, J = 4.4 Hz, 1H), 8.05 – 7.94 (m, 2H), 7.84 (s, 2H), 7.82 (s, 1H), 7.64 (d, J = 4.6 Hz, 1H), 7.41 (dd, J = 9.2, 2.6 Hz, 1H), 6.28 (d, J = 8.7 Hz, 1H), 6.05 – 5.87 (m, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.95 (d, J = 10.3 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.38 (d, J = 15.6 Hz, 1H), 4.00 (s, 3H), 3.79 – 3.61 (m, 1H), 3.59 – 3.43 (m, 1H), 3.25 (dd, J = 13.4, 10.2 Hz, 1H), 2.83 (d, J = 13.5 Hz, 1H), 2.77 – 2.64 (m, 1H), 2.33 (s, 1H), 1.71 – 1.48 (m, 5H), 0.92 (d, J = 6.1 Hz, 6H), 0.83 – 0.71 (m, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 183.8, 183.5, 172.1, 168.7, 167.8, 159.4, 148.6, 146.0, 144.9, 143.4, 143.1, 132.7, 132.0 (q, J = 33.1 Hz), 129.0, 124.3 (q, J = 272.2 Hz), 123.0, 121.7, 121.6, 121.6, 120.4, 114.7, 111.0, 102.5, 62.8, 60.5, 56.9, 56.4, 42.7, 41.5, 40.9, 33.5, 29.0, 28.6, 27.2, 19.2, 18.1. UPLC-DAD-QTOF: $C_{38}H_{40}N_5O_4F_6$ $[M+H]^+$ calcd.: 744.2984, found: 744.3000.

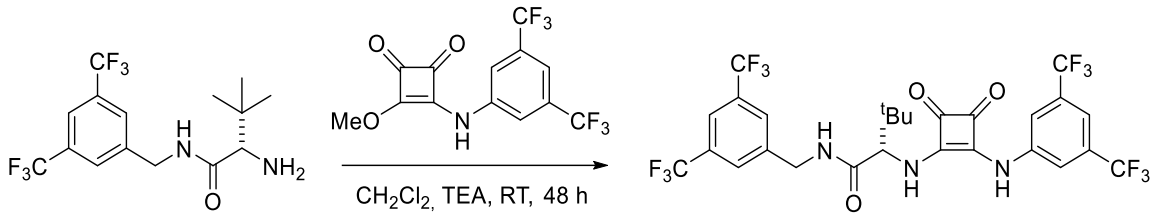
Catalyst C11



The desired product was obtained following the General Procedure starting from the previously prepared (*R*)-*N*-(3,5-bis(trifluoro methyl)benzyl)-2-((2-methoxy-3,4-dioxocyclo but-1-en-1-yl)amino)-3,3-dimethylbutanamide (466.4 mg, 1 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 95:5) to give a white solid (581.5 mg, 0.77 mmol, 77% yield). m.p.: 169-172 ºC. $[\alpha]_D^{24}$ = –100.5 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.72 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.2 Hz, 3H), 7.90 (s, 1H), 7.67 (d, J = 4.5 Hz, 1H), 7.40 (dd, J = 9.2, 2.6 Hz, 1H), 6.28 (s, 1H), 5.92 (ddd, J = 17.6, 10.2, 7.9 Hz, 1H), 4.98 (dd, J = 22.1, 13.8 Hz, 2H), 4.82 – 4.67 (m, 2H), 4.54 (d, J = 15.4 Hz, 1H), 3.98 (s, 3H), 3.73 – 3.56 (m, 1H), 3.55 – 3.39 (m, 1H), 3.30 – 3.13 (m, 1H), 2.86 – 2.60 (m, 2H), 2.32 (s, 1H), 1.71 – 1.46 (m, 5H), 0.91 (s, 9H), 0.86 – 0.74 (m, 1H).^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 183.6, 183.2, 171.2, 168.2, 167.6, 159.3, 148.4, 145.8, 144.6, 143.4, 142.8, 132.5, 131.9 (d, J = 33.5 Hz), 129.3, 128.8, 124.3 (q, J = 272.0 Hz), 122.9, 121.6, 120.4, 114.6, 102.4, 65.0, 60.4, 56.7, 56.2, 42.8, 41.3, 40.6, 36.0, 28.7, 28.3, 26.9, 26.4. UPLC-DAD-QTOF: $C_{39}H_{42}N_5O_4F_6$ $[M+H]^+$ calcd.: 758.3141, found: 758.3144.

*5.2.1.2. Catalysts **C12***

PROCEDURE:[153]

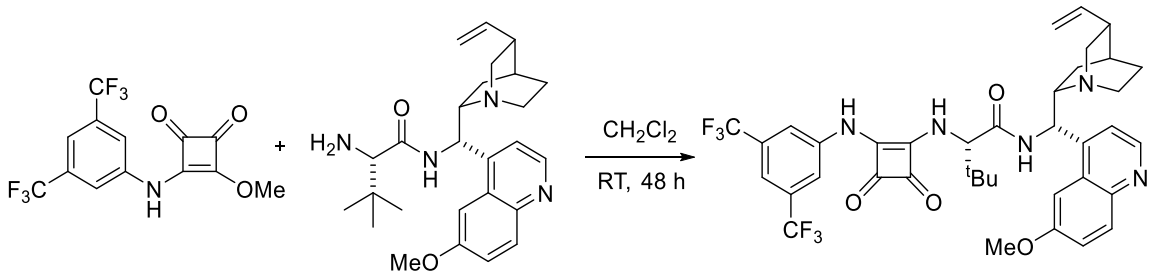


To a stirred solution of the previously prepared (*S*)-2-amino-*N*-(3,5-bis (trifluoromethyl)benzyl)-3,3-dimethylbutanamide[154] (844.5 mg, 2.37 mmol, 1 eq) in CH_2Cl_2 (20 mL) squaramide derived 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxy cyclobut-3-ene-1,2-dione[155] (803.4 mg, 2.37 mmol, 1 eq) and TEA (0.66 mL, 4.74 mmol, 2 eq) were added and the mixture was stirred at room temperature for 48 h. The reaction was quenched with NaOH 2M (20 mL) and the resulting mixture was stirred at room temperature for 4h and then, diluted with CH_2Cl_2 (32 mL) and H_2O (32 mL). The organic layer was separated, washed with brine (2 x 40 mL), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (Toluene:EtOAc 80:20) to afford the desired product as a yellow solid (997.3 mg, 1.5 mmol, 64% yield). m.p.: 144-149 ºC. $[\alpha]_D^{24}$ = 66.3º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.86 (s, 1H), 7.97 (s, 2H), 7.65 (s, 1H), 7.62 (s, 2H), 7.58 (s, 1H), 5.03 (d, J = 9.5 Hz, 1H), 4.43 (dd, J = 13.8, 11.2 Hz, 2H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 185.0, 171.3, 168.0, 164.7, 140.3, 139.3, 133.2 (q, J = 33.9 Hz), 132.1 (q, J = 33.4 Hz), 127.5, 123.1 (q, J = 276.3 Hz), 123.0 (q, J = 272.8 Hz), 121.6, 119.7, 117.8, 65.6, 42.6, 35.8, 26.3. UPLC-DAD-QTOF: $C_{27}H_{22}F_{12}N_3O_3$ $[M+H]^+$ calcd.: 664.1470, found: 664.1473.

[153] Adapted from: He, H. X.; Du, D. M. *European J. Org. Chem.* **2014**, *2014* (28), 6190–6199
[154] Preparation on page 119.
[155] Synthesis procedure from: see reference 144.

*5.2.1.3. Catalyst **C13***

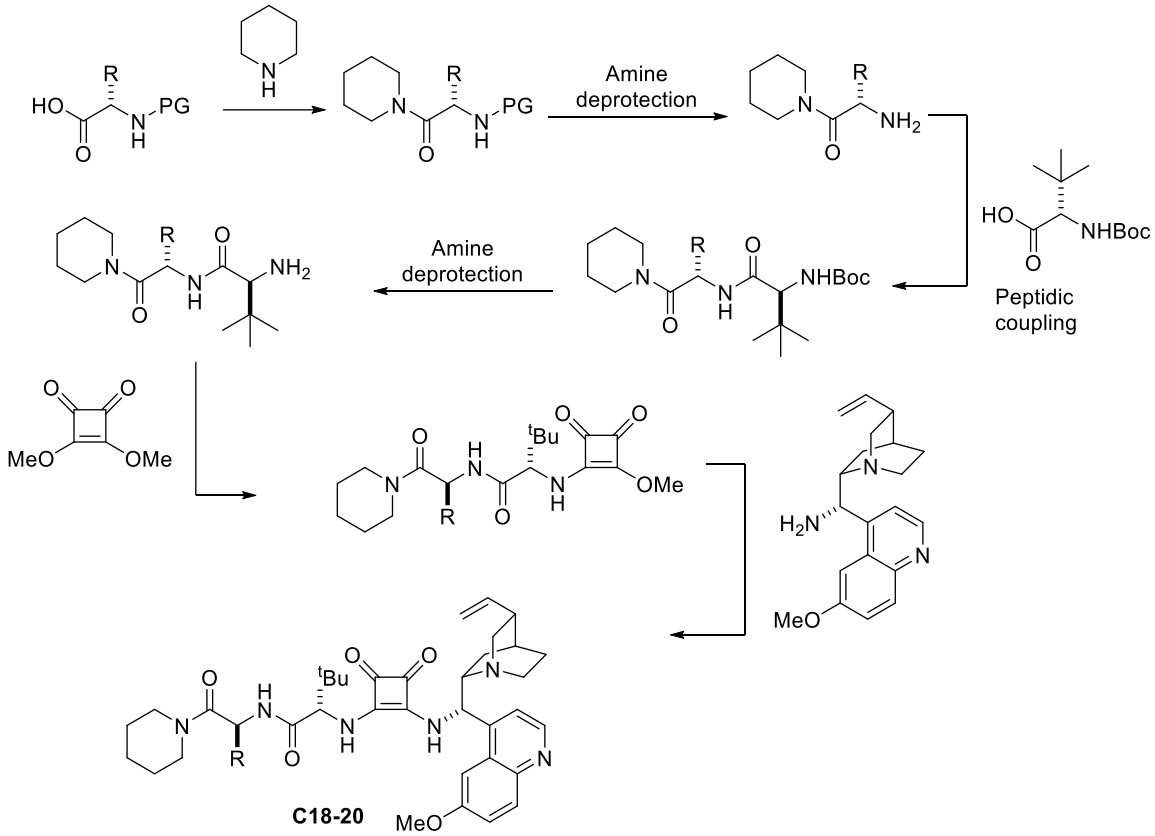
PROCEDURE:[52]



To a stirred solution of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxy cyclobut-3-ene-1,2-dione[155] (274.7 mg, 0.81 mmol, 1 eq) in CH_2Cl_2 (5 mL/mmol) (*S*)-2-amino-*N*-((S)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-3,3-dimethylbutanamide[156] (352.9 mg, 0.81 mmol, 1 eq) was added. The reaction mixture was stirred at room temperature for 48 h. Then, the solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to afford the desired product as a white solid (245.2 mg, 0.33 mmol, 41% yield). m.p.: 198-202 ºC. $[\alpha]_D^{24}$ = – 126.3º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 – 8.36 (m, 1H), 8.06 (s, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.76 – 7.60 (m, 2H), 7.59-7.46 (m, 1H), 7.46-7.32 (m, 2H), 7.22 (d, J = 7.3 Hz, 1H), 5.92 – 5.63 (m, 1H), 5.58 – 5.36 (m, 1H), 5.04 – 4.87 (m, 2H), 4.85 – 4.68 (m, 1H), 3.82 (s, 3H), 3.40 – 3.02 (m, 3H), 2.90 – 2.57 (m, 2H), 2.38 – 2.19 (m, 1H), 1.73 – 1.50 (m, 3H), 1.50 – 1.35 (m, 1H), 1.02 (s, 9H), 0.92 – 0.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 181.7, 169.8, 169.0, 163.2, 158.0, 147.7, 144.0, 141.2, 140.0, δ 132.7 (q, J = 33.5 Hz), 131.3, 128.4, 124.8, 121.2, 120.9, 119.4, 118.5, 116.4, 114.9, 102.5, 65.5, 60.2, 55.8, 55.6, 50.4, 41.2, 39.7, 35.6, 27.9, 27.5, 26.2, 25.9. UPLC-DAD-QTOF: $C_{38}H_{40}N_5O_4F_6$ $[M+H]^+$ calcd.: 744.2984, found: 744.2989.

[156] Synthesis procedure from: Dou, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18*, 8315–8319.

*5.2.1.4. Catalysts **C18-C20***



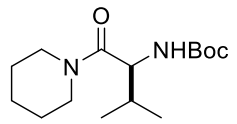
Step 1: Amide formation

GENERAL PROCEDURE: [157]

To a stirred solution of the corresponding *N*-protected amino acid (1 eq) in dry DMF (2 mL/mmol) under inert atmosphere and at room temperature DIPEA (2 eq) and HBTU (1.5 eq) were added. After stirring for 1 h, the corresponding amine was added, and the mixture was allowed to react for 16 h. The reaction was quenched with HCl 1M (1.6 mL/mmol) and the mixture extracted with EtOAc (x3). The organic phases were collected and washed with HCl 1M (x3) and brine (x5), dried over $MgSO_4$ and evaporated under reduced pressure. When necessary, the obtained crude was purified by silica flash column chromatography on silica gel to give the desired compound.

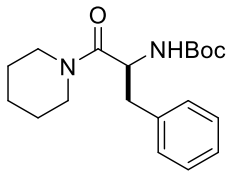
[157] Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16* (44), 13068–13071.

tert-Butyl (_S_)-(3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate



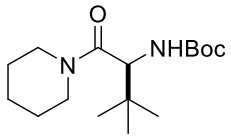
Prepared following the General Procedure starting from commercially available Boc-(*L*)-Valine (4.345 g, 20 mmol, 1 eq) and piperidine (2.17 mL, 22 mmol, 1.1 eq). The crude was purified by flash column chromatography on silica gel (80:20 Hexane:EtOAc) to afford the product as a yellow oil (5.629 g, 19.78 mmol, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J = 9.2 Hz, 1H), 4.48 (dd, J = 9.1, 5.3 Hz, 1H), 3.67 – 3.51 (m, 2H), 3.50-3.39 (m, 2H), 2.00 – 1.82 (m, 1H), 1.71 – 1.47 (m, 6H), 1.43 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). All spectroscopic data were consistent with those previously reported.[158]

tert-Butyl (_S_)-(1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)carbamate



Prepared following the General Procedure starting from commercially available Boc-(*L*)-Phenylalanine (2.653 g, 10 mmol, 1 eq) and piperidine (1.09 mL, 11 mmol, 1.1 eq). The crude was purified by flash column chromatography on silica gel (80:20 Hexane:EtOAc) to afford the product as a white solid (2.647 g, 7.9 mmol, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 3H), 7.22 – 7.15 (m, 2H), 5.44 (d, J = 8.4 Hz, 1H), 4.85 (q, J = 7.2 Hz, 1H), 3.48 (t, J = 4.9 Hz, 2H), 3.30 – 3.17 (m, 1H), 3.07 – 2.99 (m, 1H), 2.95 (d, J = 7.1 Hz, 2H), 1.56 – 1.44 (m, 4H), 1.41 (s, 9H), 1.41 – 1.34 (m, 2H).

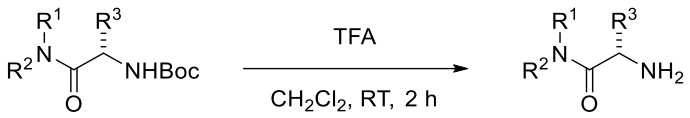
tert-Butyl (_S_)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate



The preparation of this compound is described on page 113.

Step 2: Amine deprotection

GENERAL PROCEDURE:[152]

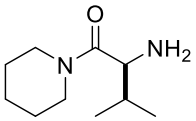


To a stirred solution of the starting *N*-Boc compound (1 eq) in CH_2Cl_2 (1 mL/mmol) at 0 ºC TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach RT and then stirred for 2 h. Then, solvents were removed under reduced pressure and the remaining oil was redissolved in H_2O, cooled down to 0 ºC and basified with a sat. Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with $NaHCO_3$ sat. and dried over $MgSO_4$. The solvents were removed under

[158] Richmond, M. L.; Seto, C. T. *J. Org. Chem.*, **2003**, *68*, 7505–7508.

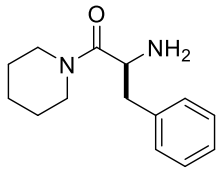
reduced pressure to afford the crude product, which was used in the next step without further purification.

(*S*)-2-Amino-3-methyl-1-(piperidin-1-yl)butan-1-one



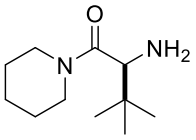
The title compound was prepared following the General Procedure starting from *tert*-butyl (*S*)-(3-methyl-1-oxo-1-(piperidin-1-yl) butan-2-yl)carbamate (2.844 g, 10 mmol, 1 eq). The desired product was obtained as a yellow oil (1.307 g, 7.1 mmol, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 – 3.54 (m, 2H), 3.53 (d, J = 4.9 Hz, 1H), 3.46 – 3.35 (m, 2H), 1.90 – 1.74 (m, 2H), 1.71 – 1.61 (m, 1H), 1.56 (m, 4H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H).

(*S*)-2-Amino-3-phenyl-1-(piperidin-1-yl)propan-1-one



The title compound was prepared following the General Procedure starting from *tert*-butyl (*S*)-(1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)carbamate (2.646 g, 7.9 mmol, 1 eq). The desired product was obtained as a yellow oil (1.459 g, 6.28 mmol, 80% yield). 1H NMR (400 MHz, Chloroform-d) δ 7.96 – 7.88 (m, 2H), 7.28 (q, J = 6.5, 5.7 Hz, 3H), 7.21 – 7.15 (m, 2H), 4.74 (s, 1H), 3.42 (d, J = 5.4 Hz, 2H), 3.30 – 3.07 (m, 3H), 2.84 (d, J = 11.8 Hz, 1H), 1.46 (d, J = 5.0 Hz, 3H), 1.43 – 1.33 (m, 2H), 0.91 (s, 1H). All spectroscopic data were consistent with those previously reported.[159]

(*S*)-2-Amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one



The preparation of this compound is described on page 116.

Step 3: Peptidic coupling

GENERAL PROCEDURE:[160]

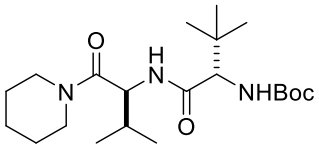
To a stirred solution of the corresponding free (1 eq) amine in DMF (1.4 mL/mmol) DIPEA (6 eq) and Boc-(*L*)-*tert*-Leucine[148] were added and the mixture was stirred for 10 min at RT. HATU (1.1 eq) was then added and the mixture was stirred at the same temperature for 16 h. The reaction was quenched with a 1:1 mixture of H_2O:EtOAc and

[159] Wu, G.; Liu, Y.; Rouh, H.; Ma, L.; Tang, Y.; Zhang, S.; Zhou, P.; Wang, J. Y.; Jin, S.; Unruh, D.; Surowiec, K.; Ma, Y.; Li, G. *Chem. Eur. J.* **2021**, *27* (30), 8013–8020.

[160] McAlpine S. R. *Combinatorial library of cyclic peptides as antibacterial agents,* U.S. Pat. Appl. Publ., 20040110228, 10 Jun, **2004.**

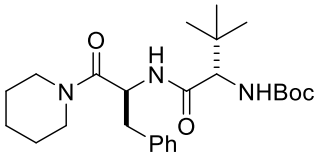
extracted with EtOAc (x2). The organic layers were combined, washed with brine (x3) and dried over $MgSO_4$. The crude was purified by flash column chromatography on silica gel.

tert-Butyl ((_S_)-3,3-dimethyl-1-(((_S_)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-1-oxobutan-2-yl)carbamate



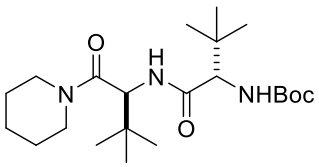
Prepared following the General Procedure starting (*S*)-2-amino-3-methyl-1-(piperidin-1-yl)butan-1-one (921.4 mg, 5 mmol, 1 eq) and Boc-(*L*)-*tert*-Leucine[148] (1.388 g, 6 mmol, 1.2 eq). The crude was purified by flash column chromatography on silica gel (80:20 Hexane:EtOAc) to afford the product as a white solid (1.846 g, 4.64 mmol, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 9.3 Hz, 1H), 4.82 (dd, J = 5.5, 4.5 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.52 (dt, J = 17.6, 5.6 Hz, 4H), 2.02 – 1.87 (m, 1H), 1.71 – 1.50 (m, 6H), 1.43 (s, 9H), 0.98 (s, 9H), 0.91 (dd, J = 20.6, 6.8 Hz, 6H).

tert-Butyl ((_S_)-3,3-dimethyl-1-oxo-1-(((_S_)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)amino)butan-2-yl)carbamate



Prepared following the General Procedure starting (*S*)-2-amino-3-phenyl-1-(piperidin-1-yl)propan-1-one (1.459g, 6.28 mmol, 1 eq) and Boc-(*L*)-*tert*-Leucine[148] (1.743 g, 7.54 mmol, 1.2 eq). The crude was purified by flash column chromatography on silica gel (80:20 Hexane:EtOAc) to afford the product as a white solid (2.351 g, 5.28 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.11 (m, 5H), 6.59 (d, J = 8.0 Hz, 1H), 5.25 – 5.06 (m, 2H), 3.84 (d, J = 9.3 Hz, 1H), 3.54 – 3.43 (m, 2H), 3.29 – 3.18 (m, 1H), 3.00 (dt, J = 13.3, 6.5 Hz, 3H), 1.45 (s, 14H), 0.95 (s, 9H).

tert-Butyl ((_S_)-1-(((_S_)-3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

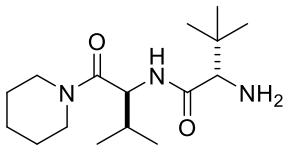


Prepared following the General Procedure starting (*S*)-2-amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one (1.601 g, 8.07 mmol, 1 eq) and Boc-(*L*)-*tert*-Leucine[148] (2.240 g, 9.68 mmol, 1.2 eq). The crude was purified by flash column chromatography on silica gel (80:20 Hexane:EtOAc) to afford the product as a white solid (3.026 g, 7.35 mmol, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 9.0 Hz, 1H), 5.18 (d, J = 8.7 Hz, 1H), 4.89 (d, J = 9.2 Hz, 1H), 3.83 (d, J = 9.1 Hz, 2H), 3.68 (s, 1H), 3.37 (d, J = 29.9 Hz, 2H), 1.72-1.49 (m, 6H), 1.43 (s, 9H), 0.97 (s, 9H), 0.97 (s, 9H).

Step 4: Amine deprotection

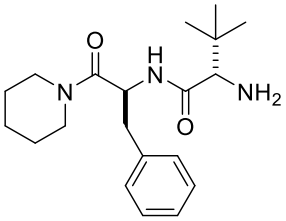
The General Procedure on page 128 was followed.

(*S*)-2-Amino-3,3-dimethyl-*N*-((*S*)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)butan amide



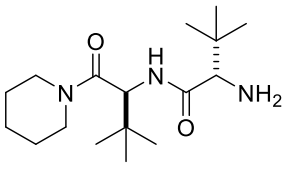
The title compound was prepared following the General Procedure starting from *tert*-butyl ((*S*)-3,3-dimethyl-1-(((*S*)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-1-oxobutan-2-yl) carbamate (1.846 g, 4.64 mmol, 1 eq). The desired product was obtained as a yellow oil (1.132 g, 3.8 mmol, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 9.3 Hz, 1H), 4.82 (dd, J = 5.5, 4.5 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.52 (dt, J = 17.6, 5.6 Hz, 4H), 2.02 – 1.87 (m, 1H), 1.71 – 1.50 (m, 6H), 1.43 (s, 9H), 0.98 (s, 9H), 0.91 (dd, J = 20.6, 6.8 Hz, 6H).

(*S*)-2-Amino-3,3-dimethyl-N-((S)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)butan amide



The title compound was prepared following the General Procedure starting from *tert*-Butyl ((*S*)-3,3-dimethyl-1-oxo-1-(((*S*)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)amino)butan-2-yl) carbamate (2.351 g, 5.28 mmol, 1 eq). The desired product was obtained as a yellow oil (1.554 g, 4.5 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 1H), 7.31 – 7.17 (m, 5H), 5.21 (td, J = 8.2, 6.6 Hz, 1H), 3.47 (t, J = 5.1 Hz, 2H), 3.27 (ddd, J = 13.3, 7.6, 3.2 Hz, 1H), 3.10 – 3.03 (m, 2H), 2.98 (t, J = 6.9 Hz, 2H), 1.58 (s, 2H), 1.52 – 1.33 (m, 6H), 0.93 (s, 9H).

(*S*)-2-Amino-*N*-((*S*)-3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)-3,3-dimethyl butanamide

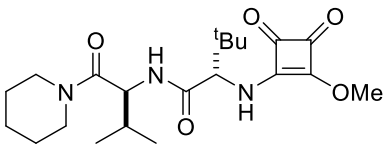


The title compound was prepared following the General Procedure starting from *tert*-butyl ((*S*)-1-(((*S*)-3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (3.026 g, 7.35 mmol, 1 eq). The desired product was obtained as a white solid (1.671 g, 5.37 mmol, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 9.1 Hz, 1H), 4.91 (d, J = 9.6 Hz, 1H), 3.69 (ddt, J = 14.2, 9.3, 5.0 Hz, 2H), 3.47 (ddt, J = 32.2, 11.8, 5.9 Hz, 2H), 3.11 (s, 1H), 1.63 (dq, J = 8.1, 4.8, 3.7 Hz, 4H), 1.53 (d, J = 9.0 Hz, 6H), 1.01 (s, 9H), 1.00 (s, 9H).

Step 5: Coupling of the first amine with the squarate[52]

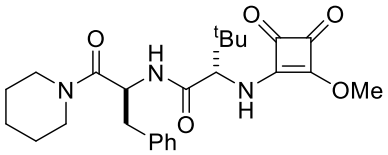
The General Procedure on page 118 was followed.

(*S*)-2-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl-*N*-((*S*)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)butanamide



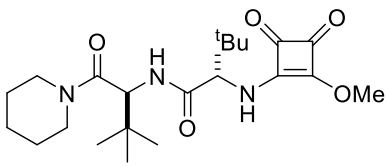
The title compound was prepared following the General Procedure starting from (*S*)-2-amino-3,3-dimethyl-*N*-((*S*)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)butanamide (780.1 mg, 2.62 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 30:70) to afford the product as a white foam (855.8 mg, 2.1 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, J = 8.0 Hz, 1H), 4.40 (s, 3H), 3.78 – 3.54 (m, 4H), 3.53 – 3.39 (m, 1H), 2.14 – 1.98 (m, 1H), 1.75 – 1.60 (m, 4H), 1.58 – 1.47 (m, 2H), 1.02 (s, 9H), 0.99 – 0.87 (m, 6H).

(*S*)-2-((2-Methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl-*N*-((*S*)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)butanamide



The title compound was prepared following the General Procedure starting from (*S*)-2-amino-3,3-dimethyl-*N*-((S)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)butan amide (2.3512 g, 5.28 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 30:70) to afford the product as a white foam (855.8 mg, 2.1 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 6.9 Hz, 3H), 7.15 – 7.06 (m, 2H), 6.70 – 6.60 (m, 1H), 5.14 (td, J = 7.7, 6.1 Hz, 1H), 4.40 (s, 3H), 3.53 (d, J = 3.9 Hz, 2H), 3.37 – 3.24 (m, 1H), 3.19 – 2.96 (m, 2H), 2.96 – 2.84 (m, 1H), 1.46 (dd, J = 15.6, 10.1 Hz, 6H), 0.97 (s, 9H).

(*S*)-*N*-((*S*)-3,3-Dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)-2-((2-methoxy-3,4-dioxo cyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide

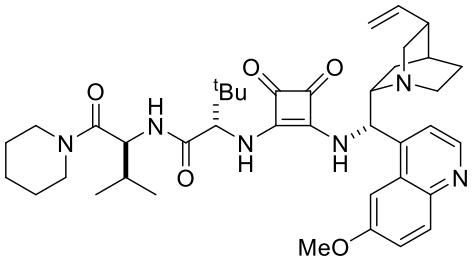


The title compound was prepared following the General Procedure starting from ((*S*)-2-amino-*N*-((*S*)-3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)-3,3-dimethylbutanamide (1.671 g, 5.37 mmol, 1 eq). The obtained crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to afford the product as a white foam (1.585 g, 3.76 mmol, 70% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 5.01 (s, 1H), 4.46 (s, 3H), 3.96 – 3.85 (m, 2H), 3.56 (dd, J = 12.9, 9.1 Hz, 1H), 3.30 (d, J = 9.5 Hz, 1H), 1.86 – 1.59 (m, 6H), 1.07 (d, J = 7.3 Hz, 18H).

Step 6: Coupling of 9-amino-(9-deoxy) epiquinine with the monosubstituted squarate

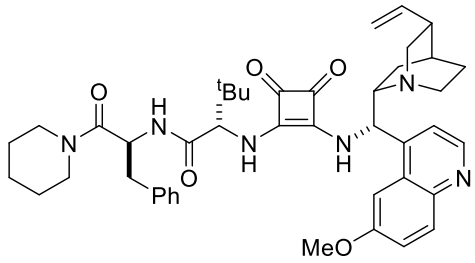
The General Procedure on page 120 was followed.

Catalyst C18



The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-2-((2-methoxy-3,4-dioxo cyclobut-1-en-1-yl)amino)-3,3-dimethyl-*N*-((*S*)-3-methyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)butan amide (855.8 mg, 2.1 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 95:5) to give a white solid (689.8 mg, 0.99 mmol, 47% yield). m.p.: 195-199 ºC. $[\alpha]_D^{24}$ = –96.60 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 4.4 Hz, 1H), 8.06 (d, J = 9.3 Hz, 1H), 7.61 (s, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.42 (dd, J = 9.2, 2.6 Hz, 1H), 6.44 (d, J = 11.3 Hz, 1H), 5.78 – 5.59 (m, 1H), 5.05 – 4.89 (m, 2H), 4.71 (dd, J = 8.5, 5.8 Hz, 1H), 4.43 (d, J = 9.9 Hz, 1H), 3.98 (s, 3H), 3.47 (d, J = 15.0 Hz, 4H), 3.28 (dd, J = 14.0, 10.2 Hz, 1H), 2.88 – 2.67 (m, 2H), 2.38 – 2.26 (m, 1H), 2.00 – 1.88 (m, 1H), 1.77 – 1.44 (m, 12H), 1.13 – 0.96 (m, 2H), 0.81 (dd, J = 20.9, 5.2 Hz, 6H), 0.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 182.8, 170.0, 169.5, 167.3, 159.0, 147.6, 144.9, 143.9, 141.2, 131.9, 127.9, 122.8, 119.2, 115.1, 101.2, 77.4, 65.0, 60.2, 56.2, 55.6, 53.5, 47.2, 46.9, 43.2, 40.8, 39.4, 35.1, 31.0, 27.7, 26.6, 26.4, 25.8, 24.6, 19.4, 17.2. UPLC-DAD-QTOF: $C_{40}H_{55}N_6O_5$ $[M+H]^+$ calcd.: 699.4234, found: 699.4235.

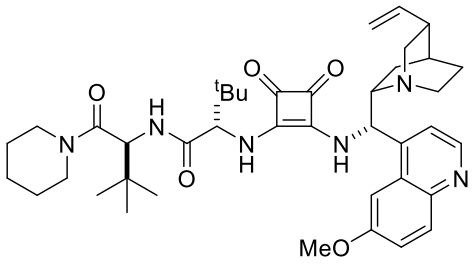
Catalyst C19



The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-2-((2-methoxy-3,4-dioxo cyclobut-1-en-1-yl)amino)-3,3-dimethyl-*N*-((*S*)-1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)butan amide (1.2847 g, 2.82 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give a white solid (869 mg, 1.16 mmol, 58% yield). m.p.: 198-205 ºC. $[\alpha]_D^{24}$ = –73.55 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, J = 3.5 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.72 (s, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 9.2, 2.5 Hz, 1H), 7.05 (s, 5H), 5.80-5.63 (m, 1H), 5.13-5.00 (m, 2H), 4.95 (d, J = 9.3 Hz, 1H), 4.42 (d, J = 8.1 Hz, 1H), 4.01 (s, 3H), 3.57-3.09 (m, 6H), 2.97-2.69 (m, 4H), 2.33 (s, 3H), 1.77 – 1.59 (m, 3H), 1.56 – 1.31 (m, 6H), 1.15 (dd, J = 12.7, 5.2 Hz, 1H), 0.59 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 169.2, 169.0, 147.8, 145.0, 144.4, 141.6, 136.1, 132.0, 129.5, 129.0, 128.3, 127.9, 126.8, 123.2, 122.9, 119.4, 114.7, 101.0, 65.9, 64.8, 56.1, 53.6, 50.0, 46.6, 43.3,

40.9, 39.7, 39.3, 35.0, 28.0, 27.7, 26.1, 25.6, 24.4. UPLC-DAD-QTOF: $C_{44}H_{55}N_6O_5$ $[M+H]^+$ calcd.: 747.4234, found: 747.4223.

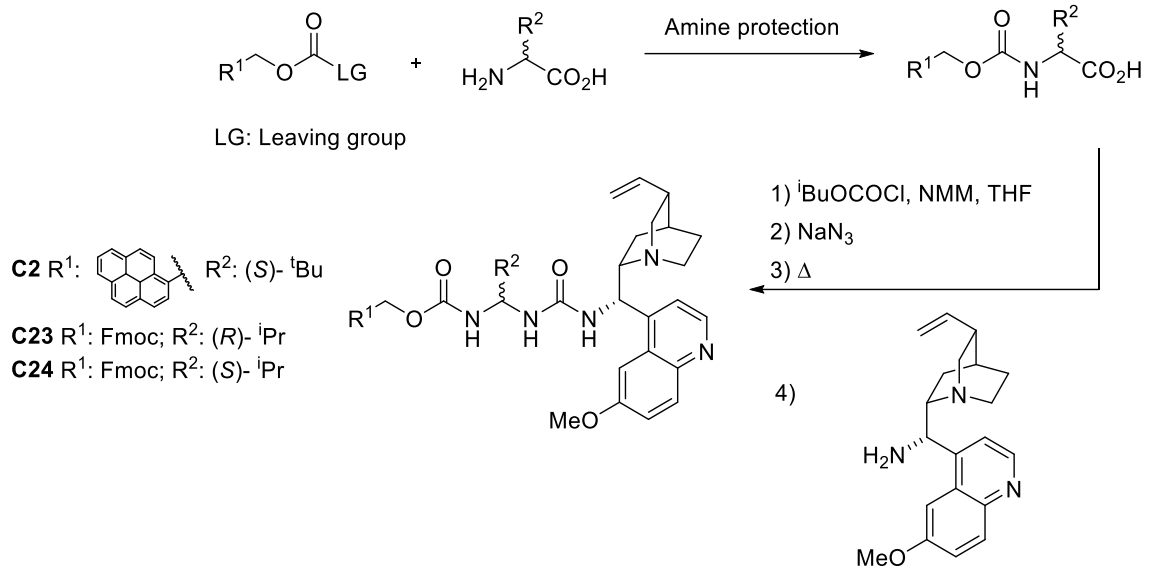
Catalyst C20



The desired product was obtained following the General Procedure starting from the previously prepared (*S*)-*N*-((*S*)-3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl butanamide (306.3 mg, 0.723 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 97:3) to give a white solid (262.9 mg, 0.37 mmol, 51% yield). m.p.: 188-195 ºC. $[\alpha]_D^{24}$ = –51.31 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.60 (s, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.45 – 7.38 (m, 1H), 6.33 (d, J = 7.3 Hz, 1H), 5.80 – 5.55 (m, 1H), 5.03 – 4.89 (m, 2H), 4.77 (d, J = 9.0 Hz, 1H), 4.41 (d, J = 9.6 Hz, 1H), 3.98 (s, 3H), 3.85 – 3.73 (m, 1H), 3.73 – 3.58 (m, 1H), 3.44 – 3.14 (m, 4H), 2.89 – 2.65 (m, 2H), 2.33 (s, 1H), 1.90 – 1.56 (m, 8H), 1.56 – 1.31 (m, 5H), 1.06 – 0.96 (m, 1H), 0.91 (s, 9H), 0.87 – 0.78 (m, 2H), 0.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) 184.0, 183.4, 170.4, 169.5, 168.0, 167.8, 159.5, 148.3, 145.6, 144.5, 141.6, 132.7, 128.3, 123.4, 119.9, 115.6, 101.6, 65.4, 61.4, 56.7, 56.3, 54.9, 53.8, 48.4, 43.8, 41.4, 39.9, 35.8, 35.6, 30.3, 28.2, 27.2, 26.7, 26.3, 25.1. UPLC-DAD-QTOF: $C_{41}H_{57}N_6O_5$ $[M+H]^+$ calcd.: 713.4390, found: 713.4390.

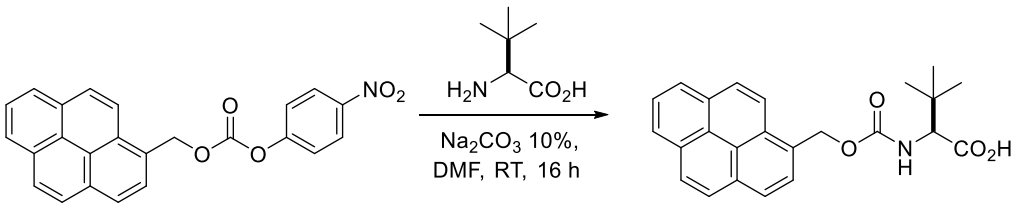
5.2.2. Synthesis of ureidopeptide-like catalysts

*5.2.2.1. Single amino acid derived catalysts **C2, C23** and **C24***



Step 1: Amine protection

PROCEDURE 1:[161] **(*S*)-3,3-Dimethyl-2-(((pyren-1-ylmethoxy)carbonyl)amino)butanoic acid**

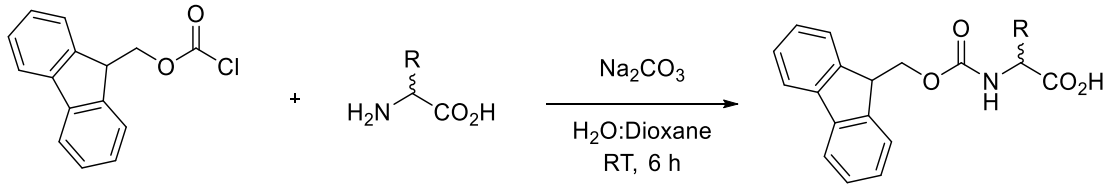


To a stirred solution of (*L*)-*tert*-Leucine (655 mg, 5 mmol, 1 eq) in Na_2CO_3 10% aqueous solution (13 mL, 2.6 mL/mmol) and DMF (5 mL, 1 mL/mmol) at 0 ºC a solution of 4-nitrophenyl (pyren-1-ylmethyl) carbonate[162] (1.9869 g, 5 mmol, 1 eq) in DMF (15 mL, 3 mL/mmol) was added dropwise and the mixture was stirred for 1 h at 0 ºC. The reaction mixture was then allowed to reach room temperature and stirred for 16 h. After quenching with H_2O (50 mL), the aqueous phase was washed with Et_2O (3 x 25 mL). Then, it was cooled to 0 ºC, acidified with HCl 3M and extracted with EtOAc (3 x 25 mL). The organic layers were washed with brine (5 x 25 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (Hexanes:EtOAc 50:50) to give the desired compound as a

[161] Adapted from: Lan, P.; Porco, J. A.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5* (5), 660–669.
[162] Synthesis procedure from: Okada, S.; Yamashita, S.; Furuta, T.; Iwamura, M. *Photochemistv and Photobiology* **1995**, *6,* 431–434.

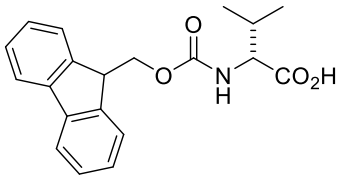
brown solid (835.3 mg, 2.14 mmol, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 7.93 (m, 9H), 5.95 – 5.76 (m, 2H), 5.33 (d, J = 9.5 Hz, 1H), 4.27 (d, J = 9.4 Hz, 1H), 1.02 (s, 9H).

GENERAL PROCEDURE 2:



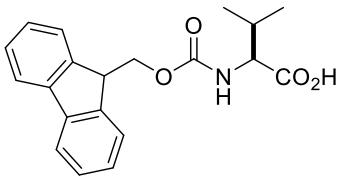
To a mixture of the free amino acid (1 eq) in H_2O (1.5 mL/mmol) and dioxane (1.5 mL/mmol) Na_2CO_3 (3 eq) was added dropwise at 0 ºC and the mixture was stirred at this temperature for 10 min. Then, (9*H*-fluoren-9-yl)methyl chloroformate was added, and the resulting mixture was stirred at RT for 6 h, then poured over H_2O (10 mL/mmol) and washed with Et_2O (x2). The aqueous layer was cooled to 0 ºC, acidified with HCl 3M and extracted with EtOAc (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude was used in the next step without further purification.

(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*D*-valine[142]



The title compound was prepared from *D*-Valine (234.3 mg, 2 mmol, 1 eq) following the General Procedure 2. White solid, 628.9 mg, 1.85 mmol, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.36 (dt, J = 26.2, 7.4 Hz, 4H), 5.24 (d, J = 9.0 Hz, 1H), 4.43 (d, J = 7.0 Hz, 2H), 4.36 (dd, J = 8.9, 4.8 Hz, 1H), 4.24 (t, J = 6.9 Hz, 1H), 2.25 (dd, J = 12.1, 6.5 Hz, 1H), 0.99 (m, 6H). All spectroscopic data were consistent with those previously described.

(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*L*-valine[163]

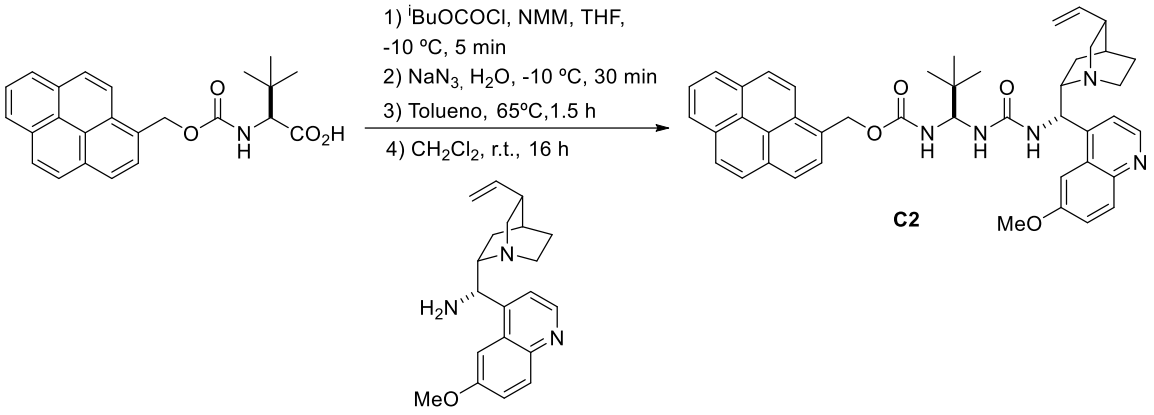


The title compound was prepared from *L*-Valine (234.3 mg, 2 mmol, 1 eq) following the General Procedure 2. White solid, 628.9 mg, 1.85 mmol, 90% yield. All spectroscopic data were consistent with those previously described. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.36 (dt, J = 26.2, 7.4 Hz, 4H), 5.24 (d, J = 9.0 Hz, 1H), 4.43 (d, J = 7.0 Hz, 2H), 4.36 (dd, J = 8.9, 4.8 Hz, 1H), 4.24 (t, J = 6.9 Hz, 1H), 2.25 (dd, J = 12.1, 6.5 Hz, 1H), 0.99 (m, 6H).

[163] Akaji, K.; Teruya, K.; Aimoto, S. *J. Org. Chem.* **2003**, *68* (12), 4755–4763.

Step 2: Curtius rearrangement

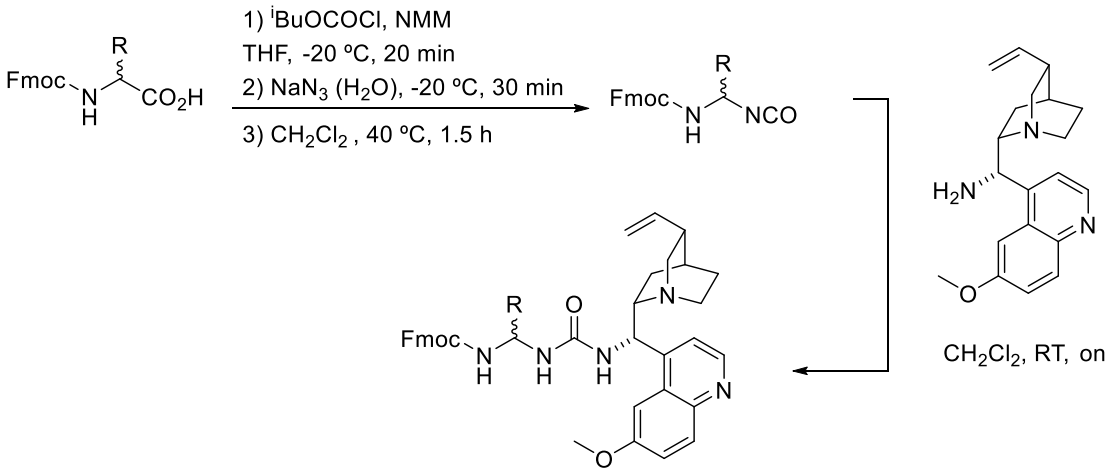
PROCEDURE 1: **Catalyst C2**



To a stirred solution of the previously prepared *N*-protected (*L*)-*tert*-Leucine (835.3 mg, 2.14 mmol, 1 eq) in dry THF (8.55 mL, 4 mL/mmol) at –10 ºC isobutyl chloroformate (0.3 mL, 2.14 mmol, 1 eq) and *N*-methylmorpholine (0.25 mL, 2.14 mmol, 1 eq) were added and the resulting suspension was stirred for 5 min at the same temperature. Then, a previously prepared solution of NaN_3 (214.4 mg, 3.22 mmol, 1.5 eq) in H_2O (2 mL) was added and the mixture was stirred for 30 min at –10 ºC. THF was then evaporated under reduced pressure and the resulting residue redissolved in CH_2Cl_2 (5mL/mmol). The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved in toluene (10.7 mL, 5mL/mmol) and stirred at 65 ºC until the disappearance of the azide band in the IR spectrum (±2140 cm^{-1}). After reaction completion the mixture was cooled to RT, 9-amino-(9-deoxy) epiquinine[164] (605.3 mg, 1.72 mmol, 0.9 eq) was added and the mixture was stirred at RT overnight. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on silica gel (98:2 CH_2Cl_2:MeOH as eluent) to afford the final product as a white solid (653.2 g, 0.92 mmol, 43% yield). m.p.: 160-162 ºC. $[\alpha]_D^{25}$ = 294.4 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 8.52 (d, J = 4.9 Hz, 1H), 8.31 – 7.92 (m, 9H), 7.74 (s, 1H), 7.36 (dd, J = 9.2, 2.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 6.39 (s, 1H), 5.79 (s, 3H), 5.16 – 4.91 (m, 4H), 4.78 (s, 2H), 3.96 (s, 3H), 3.39 (s, 1H), 3.30 – 3.08 (m, 3H), 2.81 (s, 1H), 2.62 (s, 2H), 2.26 (s, 2H), 1.69 – 1.21 (m, 7H), 0.89 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) 158.7, 158.4, 157.0, 148.0, 145.3, 132.2, 131.7, 131.2, 130.1, 129.0, 128.7, 128.4, 127.9, 126.7, 126.1, 126.01, 125.3, 125.2, 125.1, 123.9, 122.5, 119.4, 119.2, 115.8, 115.6, 102.7, 77.9, 67.48, 65.6, 60.5, 56.4, 55.9, 41.4, 36.0, 30.3, 30.2, 27.5, 27.5, 26.1. UPLC-DAD-QTOF: $C_{43}H_{45}N_5O_4$ $[M-H]^+$ calcd.: 710.3707, found: 710.3706.

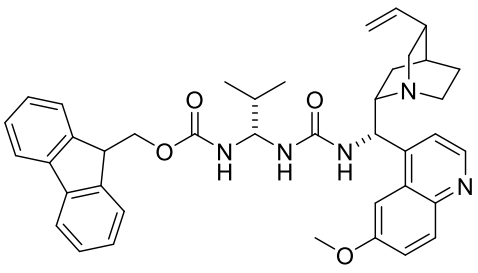
[164] Synthesis procedure from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality* **2003**, *15*, 127–134.

GENERAL PROCEDURE 2:[53] **Catalysts C23 and C24**



To a stirred solution of the *N*-protected amino acid in dry THF at -20 ºC isobutyl chloroformate (1 eq) and *N*-methylmorpholine (1 eq) were added and the resulting suspension was stirred for 20 min at the same temperature. Then, a previously prepared solution of NaN_3 (1.5 eq) in H_2O (0.7 mL/mmol) was added *in situ* and the mixture was stirred for 30 min at -20 ºC. The mixture was allowed to reach RT, the organic layer was separated, concentrated under reduced pressure and the resulting residue redissolved in CH_2Cl_2 (5mL/mmol). The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved again in dry CH_2Cl_2 (3mL/mmol) and stirred at 40 ºC until the disappearance of the azide band in the IR spectrum (±2140 cm^{-1}). After reaction completion the mixture was cooled to RT, 9-amino-(9-deoxy) epiquinine (0.8 eq) was added and the mixture was stirred at RT overnight. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on non-acidic silica gel.

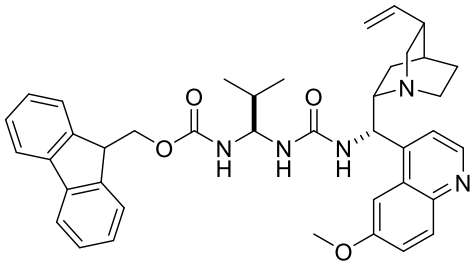
Catalyst C23



The title compound was prepared from (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*D*-valine (628.9 mg, 1.85 mmol, 1 eq) following the General Procedure 2. White solid, 462.4 mg, 0.7 mmol, 47% yield. m.p.: 79-84 ºC. $[\alpha]_D^{25}$ = -25.6 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.77 (dd, J = 7.5, 2.6 Hz, 2H), 7.67 (s, 1H), 7.56 (t, J = 7.0 Hz, 2H), 7.48 – 7.28 (m, 6H), 6.24 (s, 1H), 5.77 – 5.59 (m, 1H), 5.42 (s, 1H), 5.17 (m, 1H), 5.02 – 4.83 (m, 2H), 4.43 (t, J = 40.6 Hz, 3H), 4.19 (m, 1H), 3.95 (s, 3H), 3.08 (m, 3H), 2.66 (m, 2H), 2.37 – 2.11 (m, 2H), 1.69 – 1.47 (m, 6H), 1.46 – 1.29 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.5, 147.7, 144.8, 144.1, 141.5, 141.4, 131.7, 128.0, 127.3, 125.4, 125.3, 122.1, 120.2, 114.9, 102.4, 72.4, 71.4, 67.0,

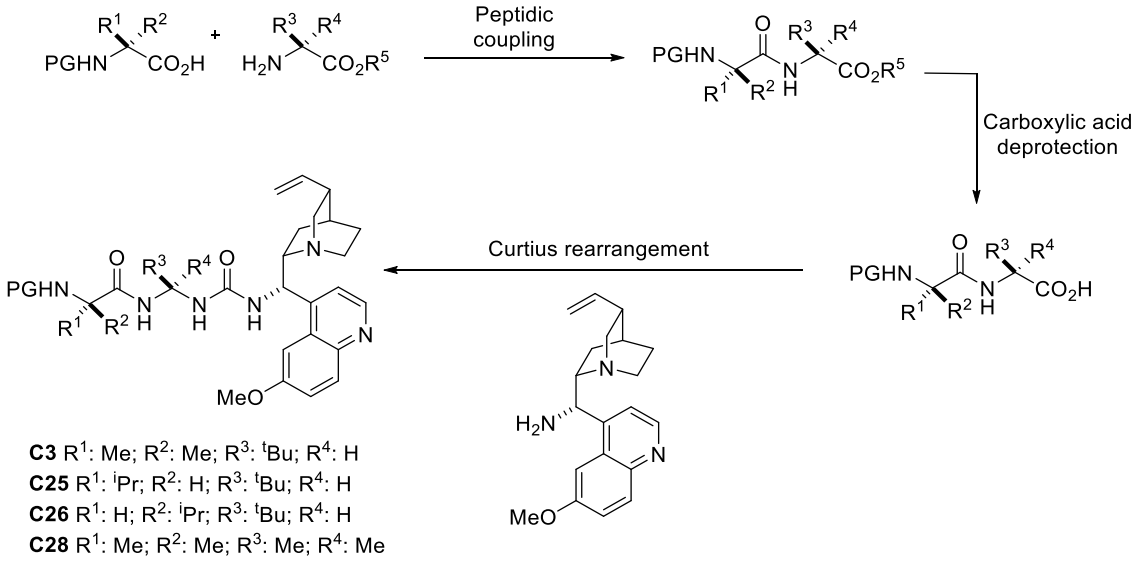
65.3, 61.7, 60.7, 55.9, 47.4, 41.1, 39.6, 32.5, 31.9, 27.9, 27.6, 26.5, 19.0, 18.8. UPLC-DAD-QTOF: $C_{40}H_{46}N_5O$ $[M+H]^+$ calcd.: 660.3550, found: 660.3553.

Catalyst C24



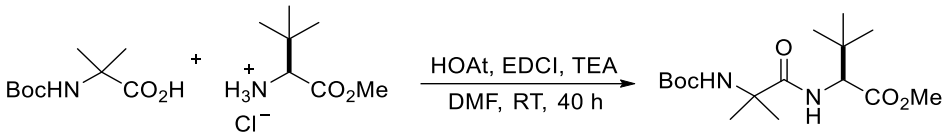
The title compound was prepared from (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-valine (678.8 mg, 2 mmol, 1 eq) following the General Procedure 2. White solid, 501.6 mg, 0.76 mmol, 48% yield. m.p.: 92-95 ºC. $[\alpha]_D^{25}$ = 85.4 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.77 (dd, J = 7.5, 2.6 Hz, 2H), 7.67 (s, 1H), 7.56 (t, J = 7.0 Hz, 2H), 7.48 – 7.28 (m, 6H), 6.24 (s, 1H), 5.77 – 5.59 (m, 1H), 5.42 (s, 1H), 5.17 (m, 1H), 5.02 – 4.83 (m, 2H), 4.43 (t, J = 40.6 Hz, 3H), 4.19 (m, 1H), 3.95 (s, 3H), 3.08 (m, 3H), 2.66 (m, 2H), 2.37 – 2.11 (m, 2H), 1.69 – 1.47 (m, 6H), 1.46 – 1.29 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.5, 147.7, 144.9, 144.1, 141.5, 141.4, 131.7, 128.0, 127.3, 125.4, 125.4, 122.1, 120.2, 114.9, 102.4, 72.4, 71.4, 67.0, 65.3, 61.7, 60.7, 55.9, 47.4, 41.1, 39.6, 32.5, 32.0, 27.9, 27.6, 26.5, 19.0, 18.8. UPLC-DAD-QTOF: $C_{40}H_{46}N_5O_4$ $[M+H]^+$ calcd.: 660.3550, found: 660.3553.

*5.2.2.2. Dipeptide derived catalysts **C3, C25, C26** and **C28***



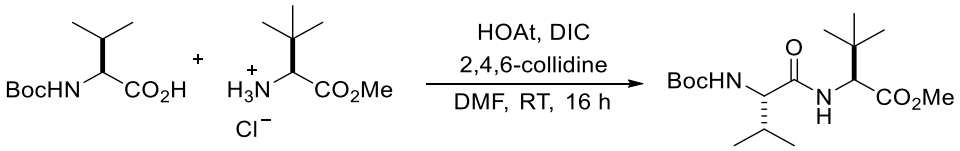
Step 1: Peptidic coupling

PROCEDURE 1:[165] **Methyl (*S*)-2-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanamido) -3,3-dimethylbutanoate**



Boc-AIB[166] (2.032 g, 10 mmol, 1 eq), (*L*)-^{t}Leu-OMe[167] (1.815 g, 10 mmol, 1 eq), EDCI (2.876 g, 15 mmol, 1.5 eq) and HOAt (1.565 g, 11.5 mmol, 1.15 eq) were dissolved in DMF (20 mL) and the mixture was stirred at RT for 20 min. Then, TEA (1.2 eq) was added dropwise and the resulting yellow suspension was stirred at RT for 16 h. The reaction was quenched by the addition of HCl 1M (30 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (5 x 30 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to afford the product as a white solid (1.831 g, 5.54 mmol, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H), 4.87 (s, 1H), 4.40 (d, J = 9.2 Hz, 1H), 3.70 (s, 3H), 1.52 (s, 3H), 1.45 (m, 12H), 0.98 (s, 9H).

PROCEDURE 2: **Methyl (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoate**



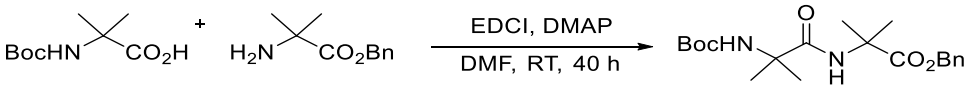
To a solution of commercially available Boc-*L*-Val (1.183 g, 5.45 mmol, 1 eq) and (*L)*-^{t}Leu-OMe chlorohydrate[167] (1.089 g, 6 mmol, 1.1 eq) in DMF (16 mL) HOAt (858 mg, 6.3 mmol, 1.15 eq) was added. The resulting mixture was stirred under N_2 at RT for 20 min and then cooled down to 0 ºC. DIC (1.27 mL, 8.18 mmol, 1.5 eq) and 2,4,6-collidine (0.8 mL, 6 mmol, 1.1 eq) were added and the solution was stirred at RT for 16 h. The reaction mixture was diluted with EtOAc and the organic phase washed with 1N HCl, saturated $NaHCO_3$ and brine (x5) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude was purified by silica column flash chromatography (Hexane: EtOAc 80:20). White solid, 1.376 g, 4 mmol, 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, J = 8.7 Hz, 1H), 5.05 (d, J = 8.6 Hz, 1H), 4.42 (d, J = 9.3 Hz, 1H), 3.87 (dd, J = 8.6, 6.7 Hz, 1H), 3.70 (s, 3H), 2.11 (m, 1H), 1.42 (s, 9H), 1.06 – 0.83 (m, 15H).

[165] Adapted from: Babine, Robert Edwards, et al. *PTC Int. Appl.* 2002018369, **2002**.
[166] Synthesis procedure from: Rodrigues, L. M.; Fonseca, J. I.; Maia, H. L. S. *Tetrahedron* **2004**, *60*, 8929.
[167] Synthesis procedure from: Anantharaj, S.; Jayakannan, M. *Biomacromolecules* **2012**, *13*, 2446–2455.

PROCEDURE 3: **Benzyl (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoate**

To a solution of Boc-(*D*)-Val[168] (391.1 mg, 1.8 mmol, 1 eq) and (*L*)-^{t}Leu-OBn (438 mg, 1.98 mmol, 1.1 eq) in DMF (5.4 mL) HOAt (318.5 mg, 2.34 mmol, 1.3 eq) was added. The resulting mixture was stirred under N_2 at RT for 20 min and then cooled down to 0 ºC. DIC (0.42 mL, 2.7 mmol, 1.5 eq) was added and the solution was stirred at RT for 16 h. The reaction mixture was diluted with EtOAc and the organic phase washed with 1N HCl (x3), saturated $NaHCO_3$ (x3) and brine (x5) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude was purified by silica column flash chromatography (Hexane: EtOAc 90:10). White solid, 721 mg, 1.71 mmol, 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 3H), 5.15 (d, *J* = 8.5 Hz, 1H), 4.95 (s, 1H), 4.49 (d, *J* = 9.4 Hz, 1H), 3.98 (s, 1H), 2.37 – 2.13 (m, 1H), 1.45 (s, 9H), 1.04 – 0.91 (m, 12H), 0.88 (d, *J* = 6.9 Hz, 4H).

PROCEDURE 4: **Benzyl 2-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanamido)-2-methylpropanoate**

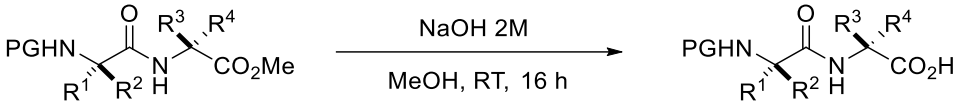


Boc-AIB[166] (3.642 g, 18 mmol, 1 eq), AIB-OBn[169] (3.479 g, 18 mmol, 1 eq), EDCI (5.176 g, 27 mmol, 1.5 eq) and DMAP (2.418 g, 19.8 mmol, 1.1 eq) were dissolved in DMF (40 mL) and the mixture was stirred at RT for 40 h. The reaction was quenched by the addition of HCl 1M (50 mL) and the mixture was extracted with EtOAc (x3). The organic layers were combined, washed with brine (x10) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was used in the next step without further purification. White solid (4.399 g, 11.6 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 1.42 (s, 12 H), 1.55 (s, 9 H), 4.97 (s, 1 H), 5.15 (s, 2 H), 7.33 (m, 5 H). All spectroscopic data were consistent with those previously reported.[170]

[168] Synthesis procedure from: Yu, S.; Pan, X.; Ma, D. *Chem. Eur. J.* **2006**, *12* (25), 6572–6584.
[169] Synthesis procedure from: Bender, D. M.; Peterson, J. A.; McCarthy, J. R.; Gunaydin, H.; Takano, Y.; Houk, K. N. *Org. Lett.* **2008**, *10* (3), 509–511.
[170] Aizpurua, J. M.; Palomo, C.; Loinaz, I. *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P. ., Horvath, I. T., Eds.; Wiley Blackwell, **2004**, 459–461.

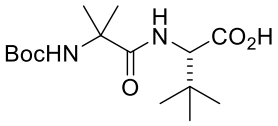
Step 2: Carboxylic acid deprotection

GENERAL PROCEDURE 1:[171]



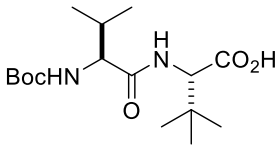
To a stirred suspension of the corresponding methyl ester protected dipeptide (1 eq) in MeOH (5 mL/mmol), NaOH 2M (3.2 eq) was added and the resulting suspension was stirred at RT overnight. Then, MeOH was evaporated under reduced pressure and the mixture was cooled down to 0 ºC, acidified with HCl 3M to pH=2 and extracted with EtOAc (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was used in the next step without further purification.

(*S*)-2-(2-((*tert*-Butoxycarbonyl)amino)-2-methylpropanamido)-3,3-dimethylbutanoic acid



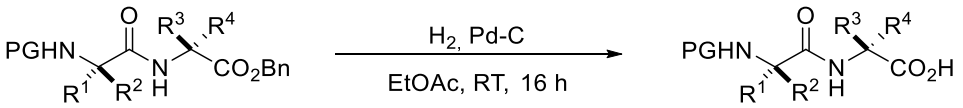
The title compound was prepared from methyl (*S*)-2-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanamido)-3,3-dimethylbutanoate (1.652 g, 5 mmol, 1 eq) following the General Procedure 1. Yellow oil, 1.609 g, 5 mmol, quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.39 (d, J = 8.8 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.44 (s, 9H), 1.04 (s, 9H).

(*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoic acid



The title compound was prepared from methyl (*S*)-2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoate (601.8 mg, 1.8 mmol, 1 eq) following the General Procedure 1. White foam, 595 mg, 1.8 mmol, quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 4.33 (m, 1H), 3.93 (d, J = 7.4 Hz, 1H), 2.05 (m, 1H), 1.47 (s, 9H), 1.05 (s, 9H), 0.97 (dd, J = 6.5, 4.0 Hz, 6H).

GENERAL PROCEDURE 2:[172]

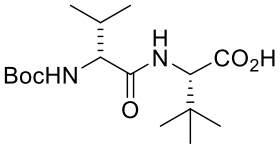


[171] Adapted from: Hata, R.; Nonaka H.; Takakusagi, Y.; Ichikawa, K.; Sando, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 1765–1768.

[172] Adapted from : Kaplan, J. M.; Shang, J.; Gobbo, P.; Antonello, S.; Armelao, L.; Chatare, V.; Ratner, D. M.; Andrade, R. B.; Maran, F. *Langmuir* **2013**, *29* (26), 8187–8192.

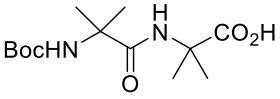
To a stirred solution of the corresponding benzyl ester protected dipeptide (1 eq) in EtOAc (5 mL/mmol) under inert atmosphere, Pd-C (10% w/w) was added. The atmosphere was changed to H_2 and the resulting suspension was stirred at RT overnight. Then, the resulting suspension was filtered through Celite and the solvents were evaporated under reduced pressure. The crude was used in the next step without further purification.

(*S*)-2-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoic acid



The title compound was prepared from benzyl (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoate (1.367 g, 3.25 mmol, 1 eq) following the General Procedure 2. White foam, 1.047 g, 3.16 mmol, 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.35 (s, 1H), 4.54 – 4.38 (m, 2H), 2.10 (s, 1H), 1.43 (s, 9H), 1.06 – 0.78 (m, 15H).

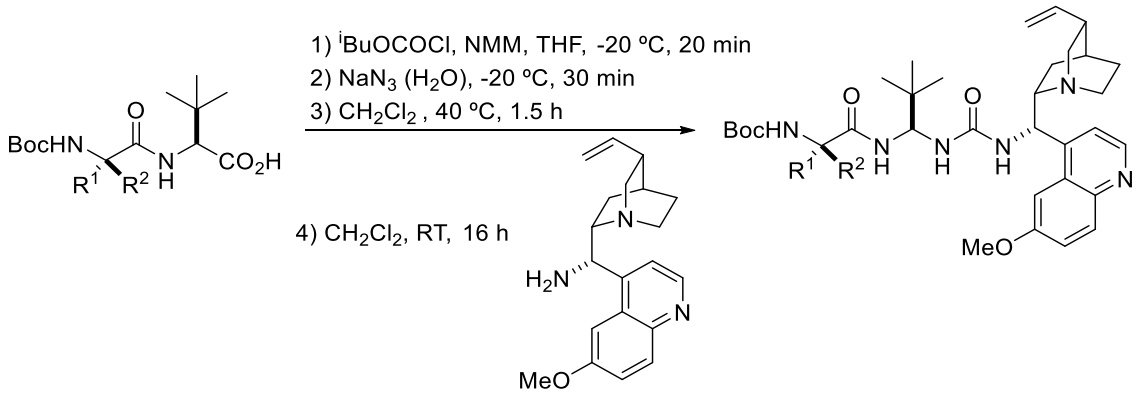
2-(2-((*tert*-Butoxycarbonyl)amino)-2-methylpropanamido)-2-methylpropanoic acid



The title compound was prepared from benzyl 2-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanamido)-2-methylpropanoate (1.892 g, 5 mmol, 1 eq) following the General Procedure 2. White foam, 1.247 g, 4.3 mmol, 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 4.94 (s, 1H), 1.56 (s, 6H), 1.48 (s, 6H), 1.45 (s, 9H).

Step 3: Curtius rearrangement

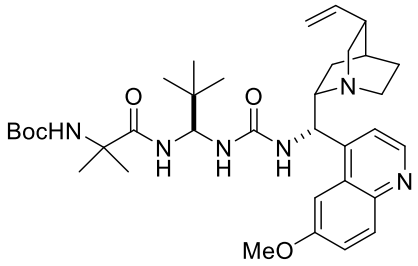
GENERAL PROCEDURE 1:



To a stirred solution of the corresponding Boc protected dipeptide (1 eq) in dry THF under inert atmosphere and at -20 ºC isobutyl chloroformate (1 eq) and *N*-methylmorpholine (1 eq) were added and the resulting suspension was stirred for 20 min at the same temperature. Then, a previously prepared solution of NaN_3 (1.5 eq) in H_2O (0.7 mL/mmol) was added and the mixture was stirred for 30 min at -20 ºC. The organic

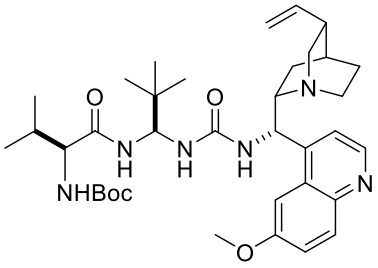
layer was separated, concentrated under reduced pressure and the resulting residue redissolved in CH_2Cl_2 (5mL/mmol). The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved again in dry CH_2Cl_2 (3mL/mmol) and stirred at 40 ºC until the disappearance of the azide band in the IR spectrum (±2140 cm^{-1}). After reaction completion the mixture was cooled to RT, 9-amino-(9-deoxy) epiquinine[164] (0.8 eq) was added and the mixture was stirred at RT overnight. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on non-acidic silica gel.

Catalyst C3



The desired product was obtained following the General Procedure 1 starting from the previously prepared (S)-2-(2-((tert-butoxycarbonyl)amino)-2-methylpropanamido)-3,3-dimethylbutanoic acid (632.6 mg, 2 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give the product as a white solid (412.3 mg, 0.65 mmol, 32% yield). m.p.: 131-134 ºC. $[\alpha]_D^{25}$ = –15.7 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 4.6 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 6.4, 3.4 Hz, 2H), 7.21 (s, 1H), 6.52 (s, 1H), 5.76 (ddd, J = 17.4, 10.3, 7.3 Hz, 1H), 5.48 (s, 1H), 5.26 (s, 1H), 5.12 (m, 1H), 4.97 (dd, J = 13.7, 7.2 Hz, 3H), 3.92 (s, 3H), 3.44 – 3.13 (m, 6H), 2.85 – 2.59 (m, 2H), 2.27 (s, 1H), 1.55 (m, 4H), 1.33 (d, J = 4.4 Hz, 12H), 1.05 (s, 3H), 0.80 (d, J = 21.9 Hz, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 158.6, 158.1, 155.5, 148.0, 146.2, 145.2, 142.0, 132.0, 129.3, 122.5, 119.8, 115.1, 102.8, 80.9, 65.0, 60.2, 57.4, 56.4, 41.6, 39.9, 35.9, 28.8, 28.3, 28.1, 27.3, 26.2, 26.0, 25.5. UPLC-DAD-QTOF: $C_{35}H_{53}N_6O_5$ $[M-H]^+$ calcd.: 637.4077, found: 637.4097.

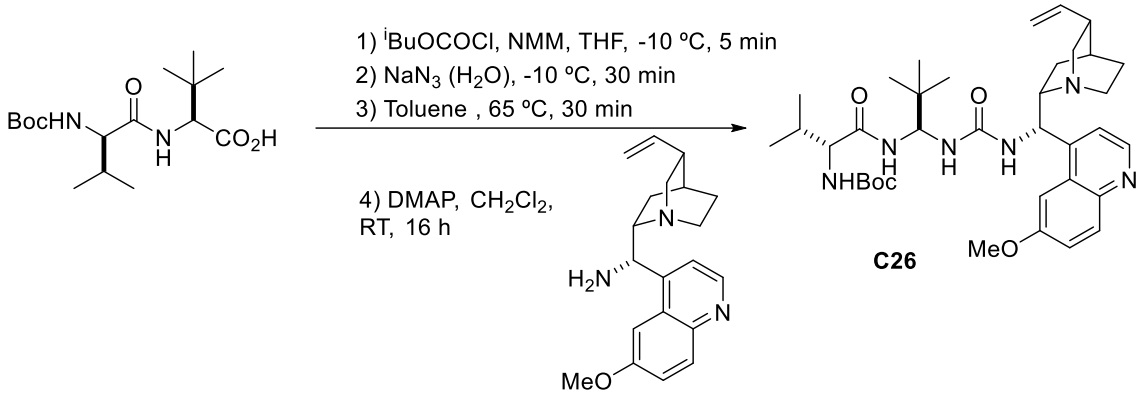
Catalyst C25



The desired product was obtained following the General Procedure 1 starting from the previously prepared (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoic acid (660.4 mg, 2 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give the product as a white solid (763.8 mg, 1.17 mmol, 66% yield). m.p.: 142-145 ºC. $[\alpha]_D^{25}$ = –177.5 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (d, J = 4.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 2.6 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.45 (dd, J = 9.2, 2.6 Hz, 1H), 5.93 (ddd, J = 17.5, 10.3, 7.5 Hz, 1H), 5.62 (d, J = 10.5 Hz, 1H), 5.10 (t, J = 14.2 Hz, 2H), 4.02 (s, 3H), 3.79 (d, J = 7.8 Hz, 1H), 3.57 (s, 2H), 3.44 (dd, J = 13.4, 10.3 Hz, 1H), 2.96 (dd, J = 14.3, 4.7 Hz, 2H), 2.51 (d, J = 4.4 Hz, 1H), 2.09 – 1.90 (m, 1H),

1.87 – 1.57 (m, 4H), 1.45 (s, 9H), 0.98 – 0.83 (m, 15H). ^{13}C NMR (75 MHz, CD_3OD) δ 174.0, 159.9, 159.1, 148.2, 145.2, 141.7, 131.3, 130.0, 123.7, 120.7, 115.6, 103.3, 80.4, 64.9, 61.9, 61.0, 56.6, 56.4, 54.8, 42.4, 40.2, 36.5, 31.5, 28.7, 27.7, 27.0, 25.8, 20.0, 18.7. UPLC-DAD-QTOF: $C_{41}H_{62}N_7O_6$ $[M+H]^+$ calcd.: 651.4234, found: 651.4234.

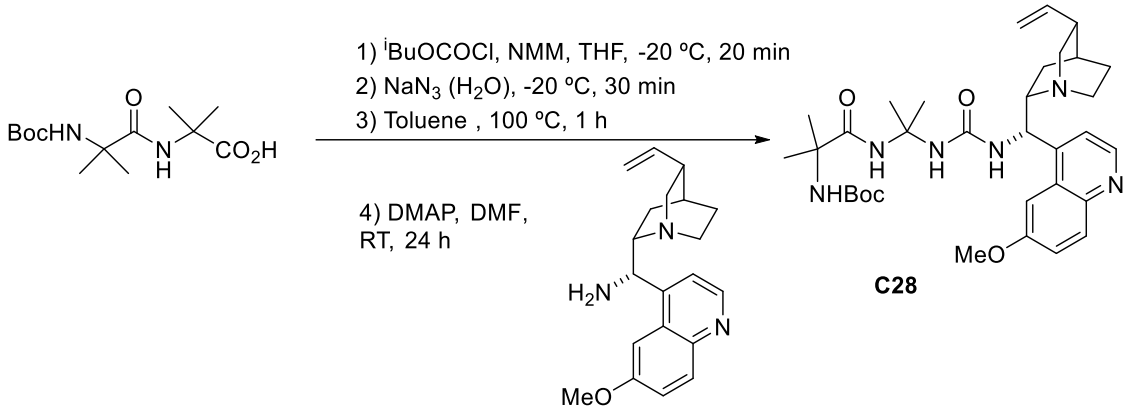
PROCEDURE 2: **Catalyst C26**



To a stirred solution of (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutan amido)-3,3-dimethylbutanoic acid (1.047 g, 3.16 mmol, 1 eq) in dry THF (12.6 mL) under inert atmosphere and at -10 ºC isobutyl chloroformate (0.45 mL, 3.6 mmol, 1 eq) and *N*-methylmorpholine (0.45 mL, 3.16 mmol, 1 eq) were added and the resulting suspension was stirred for 5 min at the same temperature. Then, a previously prepared solution of NaN_3 (316 mg, 4.74 mmol, 1.5 eq) in H_2O (3 mL) was added and the mixture was stirred for 30 min at -10 ºC. The organic layer was separated, concentrated under reduced pressure and the resulting residue redissolved in CH_2Cl_2.The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved toluene (15.8 mL) and stirred at 65 ºC until the disappearance of the azide band in the IR spectrum (±2140 cm-1). After reaction completion (30 min) the mixture was cooled to RT and toluene was evaporated under reduced pressure. The resulting mixture was redissolved in CH_2Cl_2 (16.2 mL) and 9-amino-(9-deoxy) epiquinine[164] (0.9 eq) was added. The reaction mixture was cooled down to 0 ºC, DMAP (30 mol%) was added and the mixture was stirred at RT overnight. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 98:2) to give the product as a white solid (1.296 g, 1.99 mmol, 63% yield). m.p.: 139-142 ºC. $[\alpha]_D^{25}$= –18.83 (c=1.00, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 4.6 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.77 (s, 1H), 7.36 (dd, J = 9.2, 2.6 Hz, 1H), 7.31 (d, J = 4.4 Hz, 1H), 6.57 (s, 1H), 5.79 (ddd, J = 17.5, 10.3, 7.3 Hz, 1H), 5.45 (s, 1H), 5.19 (t, J = 9.2 Hz, 1H), 5.05 (d, J = 14.7 Hz, 2H), 4.94 (s, 1H), 3.97 (s, 3H), 3.94 – 3.82 (m, 1H), 3.45 – 3.20 (m, 2H), 2.98 – 2.66 (m, 2H), 2.48 – 2.32 (m, 1H), 2.11 – 1.99 (m, 1H), 1.76 – 1.49 (m, 4H), 1.39 (s, 9H), 1.29 – 1.21 (m, 1H), 0.95 – 0.83 (m, 12H), 0.80 (s, 1H), 0.75 – 0.59 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.70, 157.76, 157.56, 155.68, 147.45, 145.41, 144.36, 140.41, 131.20, 128.33, 121.53, 118.93, 114.85, 101.99, 79.15, 64.25, 60.18, 59.07, 55.50, 53.37, 40.89, 38.78, 34.98,

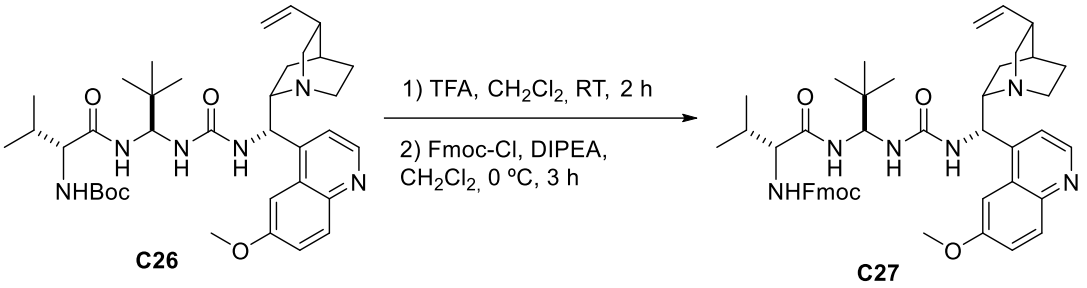
31.54, 29.46, 28.19, 27.29, 27.16, 25.73, 25.20, 19.27, 17.01. UPLC-DAD-QTOF: $C_{36}H_{54}N_6O_5$ $[M+H]^+$ calcd.: 651.4232, found: 651.4234.

PROCEDURE 3: **Catalyst C28**



To a stirred solution of 2-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanamido)-2-methylpropanoic acid (288 mg, 1 mmol, 1 eq) in dry THF (4 mL) under inert atmosphere and at -20 ºC isobutyl chloroformate (0.13 mL, 1 mmol, 1 eq) and *N*-methylmorpholine (0.11 mL, 1 mmol, 1 eq) were added and the resulting suspension was stirred for 20 min at the same temperature. Then, a previously prepared solution of NaN_3 (98 mg, 1.5 mmol, 1.5 eq) in H_2O (1 mL) was added and the mixture was stirred for 30 min at -20 ºC. The organic layer was separated, concentrated under reduced pressure and the resulting residue redissolved in CH_2Cl_2.The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved toluene (5 mL) and stirred at 100 ºC until the disappearance of the azide band in the IR spectrum (±2140 cm-1). After reaction completion (1 h) the mixture was cooled to RT and toluene was evaporated under reduced pressure. The resulting mixture was redissolved in DMF (5 mL) and 9-amino-(9-deoxy) epiquinine[164] (323 mg, 1 mmol, 1 eq) was added. The reaction mixture was cooled down to 0 ºC, DMAP (25 mg, 0.2 mmol, 20 mol%) was added and the mixture was stirred at RT for 24 h. The solvent was evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on non-acidic silica gel (Hexanes:EtOAc 1:1) to give the product as a white solid (275.2 mg, 0.452 mmol, 45% yield). m.p.: 100-103 ºC. $[\alpha]_D^{24}$= –8.25 (c=0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 4.6 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.36 (d, J = 4.6 Hz, 1H), 7.32 (dd, J = 9.2, 2.7 Hz, 1H), 5.79 – 5.61 (m, 1H), 5.43 (s, 1H), 5.09 (s, 1H), 4.98 – 4.85 (m, 2H), 3.95 (s, 3H), 3.24 – 3.02 (m, 3H), 2.72 – 2.56 (m, 3H), 2.30 – 2.15 (m, 1H), 1.65 – 1.49 (m, 3H), 1.44 (s, 3H), 1.41 (s, 9H), 1.38 (s, 6H), 1.34 (s, 3H), 0.96 – 0.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.3, 157.8, 155.0, 147.5, 146.2, 144.6, 141.6, 131.5, 128.8, 121.8, 119.2, 114.4, 101.8, 80.5, 71.8, 71.1, 61.8, 57.0, 56.7, 56.1, 55.7, 41.0, 39.7, 28.3, 28.0, 27.6, 26.1, 25.7, 25.3, 25.0. UPLC-DAD-QTOF: $C_{33}H_{49}N_6O_5$ $[M+H]^+$ calcd.: 609.7751, found: 609.7920.

*5.2.2.3. Dipeptide derived catalyst **C27***



Step 1: Amine deprotection[152]

To a stirred solution of the starting *N*-Boc compound (150 mg, 0.23 mmol, 1 eq) in CH_2Cl_2 (0.23 mL, 1 mL/mmol) at 0 ºC TFA (0.46 mL, 2 mL/mmol) was added dropwise. The mixture was allowed to reach RT and then stirred for 2 h. Then, solvents were removed under reduced pressure and the remaining oil was redissolved in H_2O, cooled down to 0 ºC and basified with a sat. Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with $NaHCO_3$ sat. and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude product as a yellow oil (117 mg, 0.21 mmol, 91% yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (t, J = 4.5 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 2.7 Hz, 1H), 7.40 – 7.19 (m, 2H), 7.04 – 6.90 (m, 1H), 5.69 (ddd, J = 17.5, 10.2, 7.3 Hz, 1H), 5.46 (s, 1H), 5.11 (t, J = 9.0 Hz, 1H), 5.02 – 4.89 (m, 2H), 3.88 (s, 3H), 3.36 (s, 2H), 3.20 (dd, J = 13.8, 10.1 Hz, 1H), 3.09 (d, J = 4.2 Hz, 1H), 2.91 – 2.59 (m, 4H), 2.34 – 2.21 (m, 1H), 1.65 – 1.39 (m, 4H), 0.89 – 0.69 (m, 16H), 0.46 (s, 2H).

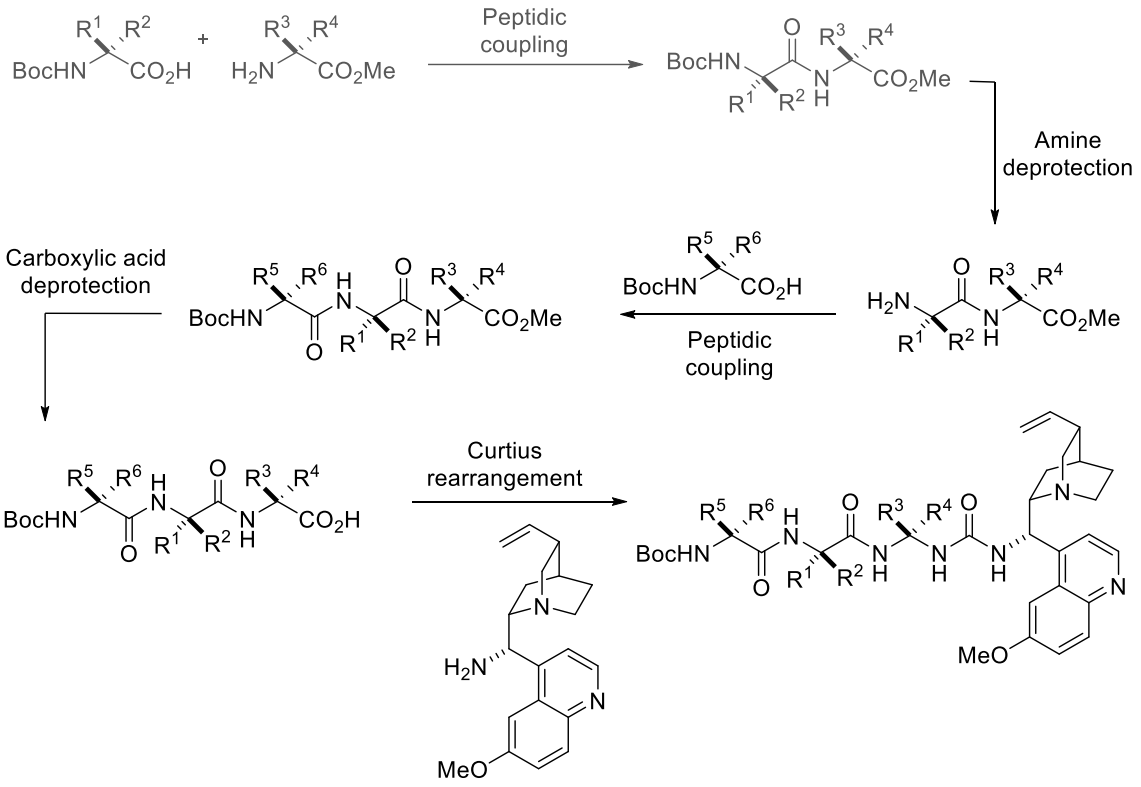
Step 2: Amine protection forming an Fmoc carbamate[173]

To a stirred solution of the free amine (117 mg, 0.21 mmol, 1 eq) in CH_2Cl_2 (1.8 mL, 8.4 mL/mmol), DIPEA (0.08 mL, 0.46 mmol, 2.2 eq) was added and the mixture was cooled down to 0 ºC. A solution of Fmoc-Cl (64.5 mg, 0.25 mmol, 1.2 eq) in CH_2Cl_2 (0.48mL, 2.3 mL/mmol) was added then and the resulting mixture was stirred at the same temperature for 3 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (0.85 mL) and the organic phase was separated, washed with $NaHCO_3$ sat (x3) and brine and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude was purified by flash column chromatography on non-acidic silica gel (CH_2Cl_2:MeOH 99:1) to give the product as a white solid (92.8 mg, 0.12 mmol, 58% yield). m.p.: 103-107 ºC. $[\alpha]_D^{24}$= –7.74 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 4.3 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.77 – 7.68 (m, 3H), 7.54 (t, J = 7.0 Hz, 2H), 7.43 – 7.21 (m, 6H), 6.86 (s, 1H), 6.54 (s, 1H), 5.72 (ddd, J = 17.4, 10.1, 7.5 Hz, 1H), 5.63 – 5.53 (m, 1H), 5.43 – 5.32 (m, 1H), 5.21 (t, J = 8.6 Hz, 1H), 5.06 – 4.88 (m, 2H), 4.40 (t, J = 8.8 Hz, 1H), 4.27 – 4.13 (m, 2H), 4.06 – 3.99

[173] Granger, B. A.; Brown, D. G. *Bioorg. Med. Chem. Lett.* **2016**, *26* (21), 5304–5307.

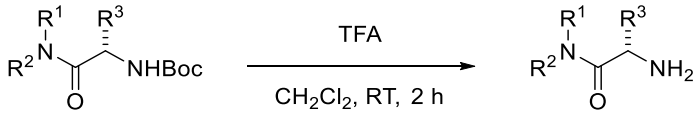
(m, 1H), 3.90 (s, 3H), 3.29 – 3.15 (m, 2H), 2.85 – 2.62 (m, 2H), 2.34 – 2.22 (m, 1H), 2.04 – 1.92 (m, 1H), 1.67 – 1.60 (m, 1H), 1.58 – 1.38 (m, 3H), 1.30 – 1.23 (m, 3H), 0.90 – 0.81 (m, 6H), 0.77 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 158.0, 157.6, 156.6, 147.7, 144.9, 144.0, 143.8, 141.4, 141.1, 131.7, 128.6, 127.9, 127.2, 125.2, 121.8, 120.1, 120.1, 114.9, 102.3, 77.4, 67.2, 64.7, 60.5, 60.2, 55.8, 47.3, 41.1, 39.3, 35.3, 31.4, 29.8, 27.5, 26.2, 25.5, 19.4, 17.5. UPLC-DAD-QTOF: $C_{46}H_{57}N_6O_5$ $[M+H]^+$ calcd.: 773.4390, found: 773.4412.

*5.2.2.4. Tripeptide derived catalysts **C29** and **C30***



Step 1: Amine deprotection

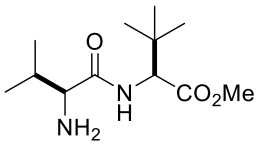
GENERAL PROCEDURE:[152]



To a stirred solution of the starting *N*-Boc compound (1 eq) in CH_2Cl_2 (1 mL/mmol) at 0 ºC TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach RT and then stirred for 2 h. Then, solvents were removed under reduced pressure and the remaining oil was redissolved in H_2O, cooled down to 0 ºC and basified with a sat. Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with $NaHCO_3$ sat. and dried over $MgSO_4$. The solvents were removed under

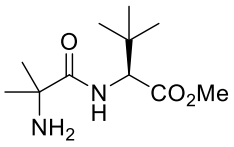
reduced pressure to afford the crude product, which was used in the next step without further purification.

Methyl (*S*)-2-((*S*)-2-amino-3-methylbutanamido)-3,3-dimethylbutanoate



The title product was prepared starting from previously prepared methyl (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3,3-dimethylbutanoate (688.5 mg, 2 mmol, 1 eq) following the General Procedure. Yellow oil, 437.5 mg, 1.9 mmol, 95% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.4 Hz, 1H), 4.41 (d, *J* = 9.5 Hz, 1H), 3.64 (s, 3H), 2.39 – 2.25 (m, 1H), 0.99 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 6H). All spectroscopic data were consistent with those previously reported. [174]

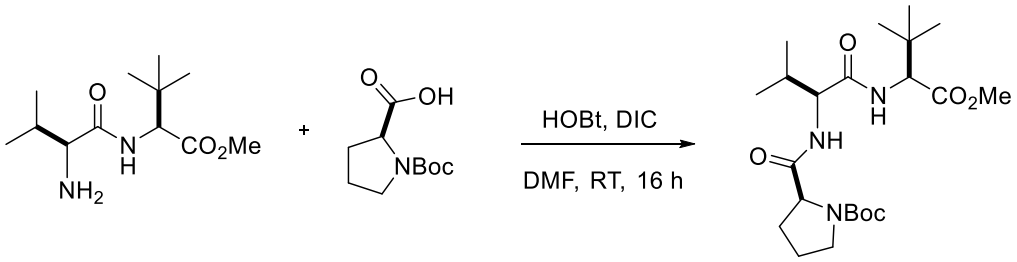
Methyl (*S*)-2-(2-amino-2-methylpropanamido)-3,3-dimethylbutanoate



The title product was prepared starting from previously prepared methyl (*S*)-2-(2-((*tert*-butoxycarbonyl)amino)-2-methyl propanamido)-3,3-dimethylbutanoate (1.953 g,5.9 mmol, 1 eq) following the General Procedure. Yellow oil, 1.2995 g, 5.6 mmol, 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 4.35 (d, J = 9.6 Hz, 1H), 3.71 (s, 3H), 1.64 (s, 2H), 1.37 (s, 6H), 0.98 (s, 9H).

Step 2: Peptidic coupling

PROCEDURE 1:[175] ***tert*-Butyl (*S*)-2-(((*S*)-1-(((*S*)-1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate**

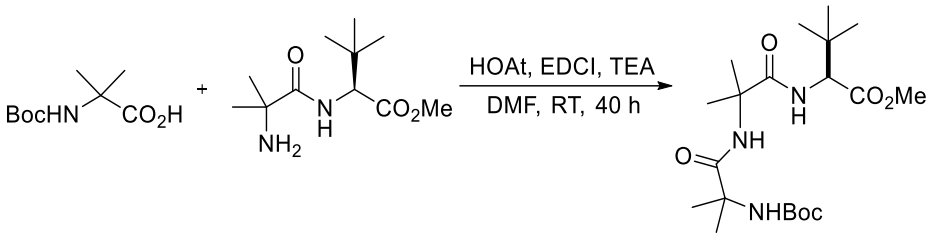


To a solution of methyl (*S*)-2-((*S*)-2-amino-3-methylbutanamido)-3,3-dimethyl butanoate (1.046 g, 1.9 mmol, 1 eq) in DMF (6 mL) *N*-Boc proline 25 (450 mg, 2.09 mmol, 1.1 eq) and HOBt (0.3 g, 2.5 mmol, 1.28 eq) were added and the mixture was stirred for 20 min at RT. The reaction mixture was then cooled down to 0 ºC and DIC (0.4 mL, 2.66 mmol, 1.4 eq) was added. The resulting mixture was stirred at RT for 16 h and then diluted with EtOAc and washed with H_2O (3x5 mL), brine (5x5 mL) and $NaHCO_3$ (3x5 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was evaporated under

[174] Victor, F.; Lamar, J.; Snyder, N.; Yip, Y.; Guo, D.; Yumibe, N.; Johnson, R. B.; Wang, Q. M.; Glass, J. I.; Chen, S.; *Bioorg. Med. Chem, Lett.* **2004,** *14*, 257-261.
[175] Revelou, P.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2012**, *68* (42), 8732–8738.

reduced pressure and the crude was purified by silica column flash chromatography (CH_2Cl_2: MeOH 85:15). The desired product was obtained as a white solid, 750.7 mg, 1.7 mmol, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 5.30 (s, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 4.22 (m, 2H), 3.81 (m, 1H), 3.71 (s, 3H), 2.57 – 2.47 (m, 1H), 2.29 (m, 4H), 1.55 (s, 9H), 1.46 (s, 6H), 0.97 (s, 9H).

PROCEDURE 2: **Methyl (*S*)-12-(*tert*-butyl)-2,2,6,6,9,9-hexamethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatri decan-13-oate**



Boc-AIB[176] (1.138 g, 5.6 mmol, 1 eq), AIB-(*L*)-^{t}Leu-OMe[177] (1.299 g, 5.6 mmol, 1 eq), EDCI (1.610 g, 8.4 mmol, 1.5 eq) and HOAt (876.4 g, 6.44 mmol, 1.15 eq) were dissolved in DMF (11 mL) and the mixture was stirred at RT for 20 min. Then, TEA (0.92 mL, 6.72 mmol, 1.2 eq) was added dropwise and the resulting yellow suspension was stirred at RT for 16 h. The reaction was quenched by the addition of HCl 1M (15 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (5 x 15 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography on silica gel (Hexane:EtOAc 50:50) to afford the product as a white solid (1.7736 g, 4.3 mmol, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 1H), 6.76 (s, 1H), 4.83 (s, 1H), 4.42 (d, J = 8.9 Hz, 1H), 3.69 (s, 3H), 1.55 (s, 3H), 1.47 (m, 18H), 1.01 (s, 9H).

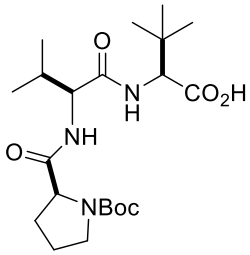
[176] Synthesis procedure from: Rodrigues, L. M.; Fonseca, J. I.; Maia, H. L. S. *Tetrahedron* **2004**, *60*, 8929.
[177] Synthesis procedure from: Anantharaj, S.; Jayakannan, M. *Biomacromolecules* **2012**, *13*, 2446–2455.

Step 3: Carboxylic acid deprotection

GENERAL PROCEDURE:[171]

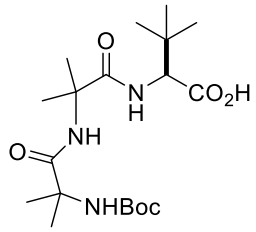
The General Procedure on page 142 was followed.

(*S*)-2-((*S*)-2-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-3-methylbutanamido)-3,3-dimethylbutanoic acid



The title compound was prepared from *tert*-Butyl (*S*)-2-(((*S*)-1-(((*S*)-1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (750.7 mg, 1.7 mmol, 1 eq) following the General Procedure. White solid, 513 mg, 1.2 mmol, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.30 (s, 1H), 4.45 (d, J = 9.1 Hz, 1H), 4.31 (m, 2H), 3.82 – 3.68 (m, 1H), 2.21 (m, 1H), 1.89 (m, 4H), 1.44 (s, 9H), 1.01 (s, 9H), 0.90 (m, 6H).

(*S*)-12-(*tert*-Butyl)-2,2,6,6,9,9-hexamethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid

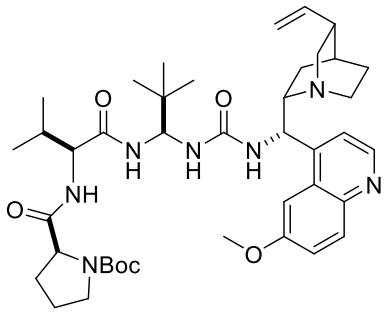


The title compound was prepared from methyl (*S*)-12-(*tert*-butyl)-2,2,6,6,9,9-hexamethyl-4,7,10-trioxo-3-oxa-5,8,11-triaza tridecan-13-oate following the General Procedure. White solid, 1.7263 g, 4.3 mmol, quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 6.73 (s, 2H), 4.94 (s, 2H), 4.32 (d, J = 8.0 Hz, 2H), 1.50 (d, J = 2.8 Hz, 14H), 1.48 – 1.42 (m, 36H), 1.10 (s, 21H).

Step 4: Curtius rearrangement

The General Procedure 1 reported on page 143 was followed.

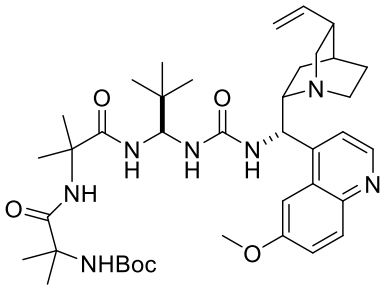
Catalyst C29



The desired product was obtained following the General Procedure 1 starting from the previously prepared (*S*)-2-((*S*)-2-((*S*)-1-(*tert*-butoxycarbonyl) pyrrolidine-2-carboxamido)-3-methylbutanamido)-3,3-dimethylbutanoic acid (427.5 mg, 1 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH 95:5) to give the product as a white solid (299 mg, 0.4 mmol, 40% yield). m.p.: 130-133 ºC. $[\alpha]_D^{25}$ = –181.3 (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.77 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 31.4 Hz, 1H), 6.51 (d, *J* = 45.8 Hz, 1H), 5.77 (dt, *J* = 17.4, 9.0 Hz, 1H), 5.29 (s, 1H), 5.16 (d, *J* = 17.8 Hz, 1H), 5.03 – 4.88 (m, 2H), 4.34 – 4.19 (m, 1H), 4.14 – 4.00 (m, 1H), 3.96 (s, 3H), 3.38 (s, 2H), 3.22

(d, *J* = 10.0 Hz, 3H), 2.73 (dt, *J* = 13.2, 8.2 Hz, 2H), 2.33 – 2.19 (m, 5H), 1.86 (s, 3H), 1.60 (d, *J* = 20.8 Hz, 5H), 1.44 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 1H), 0.87 (s, 9H), 0.77 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.7, 158.0, 157.6, 146.9, 144.2, 140.4, 136.4, 131.0, 128.4, 127.6, 121.9, 118.4, 117.1, 100.9, 80.0, 64.9, 59.8, 59.1, 55.4, 53.2, 46.8, 41.8, 36.3, 33.7, 28.5, 27.9, 27.7, 27.6, 26.3, 24.9, 24.7, 23.9, 23.8, 18.9, 16.9. UPLC-DAD-QTOF: $C_{41}H_{62}N_7O_6$ $[M+H]^+$ calcd.: 748.4762, found: 748.4772.

Catalyst C30



The desired product was obtained following the General Procedure 1 starting from the previously prepared (*S*)-12-(*tert*-Butyl)-2,2,6,6,9,9-hexamethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid (803 mg, 2 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel (Hexanes:EtOAc 50:50) to give the product as a white solid (157.2 mg, 0.22 mmol, 11% yield). m.p.: 112-116 ºC. $[\alpha]_D^{25}$ = –7.5 (c=0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 4.6 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.42 – 7.29 (m, 2H), 6.28 (d, J = 16.1 Hz, 2H), 5.81 (ddd, J = 17.4, 10.3, 7.4 Hz, 1H), 5.47 (s, 1H), 5.20 (t, J = 9.1 Hz, 1H), 4.99 (dd, J = 13.7, 9.3 Hz, 2H), 4.81 (d, J = 13.9 Hz, 2H), 3.97 (s, 3H), 3.25 (dd, J = 13.7, 10.1 Hz, 3H), 2.95 – 2.61 (m, 2H), 2.28 (d, J = 12.9 Hz, 3H), 1.60 (d, J = 24.7 Hz, 4H), 1.38 (dt, J = 15.2, 6.2 Hz, 21H), 0.95 (s, 10H). 13C NMR (75 MHz, $CDCl_3$) δ 175.2, 173.7, 158.5, 158.1, 148.2, 146.6, 145.4, 142.5, 132.0, 129.5, 122.4, 120.0, 115.0, 103.0, 81.8, 65.4, 60.6, 57.8, 57.6, 56.8, 56.4, 41.5, 40.4, 36.0, 28.8, 28.7, 28.3, 27.5, 27.0, 26.8, 26.1, 25.1. UPLC-DAD-QTOF: $C_{39}H_{60}N_7O_6$ $[M+H]^+$ calcd.: 722.4605, found: 722.4601.

5.3. Experimental section for Chapter 2

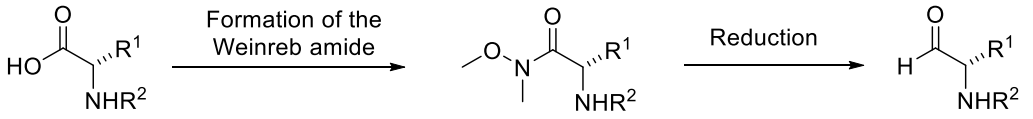
5.3.1. Synthesis of starting materials

Starting pronucleophiles **24**,[178] **25**,[179] **26**[180] employed in the preliminary studies were prepared following the procedures described in the literature.

*5.3.1.1. Synthesis of nitroalkenes **8a-8n***

Nitroalkenes **8b-d**, **8e** and **8m** were obtained from commercial sources and **8a**,[181] **8j**,[181] **8g**,[182] **8h**,[184] **8i**,[182] **8j**,[183] **8k**,[184] **8l**[184] and **8n**[185] were prepared following the procedures described in the literature.

*5.3.1.2. Synthesis of Carbamate protected α-amino aldehydes **1-7***



1 R^1: Bn, **2** R^1: Me, **3** R^1: Pr, **4** R^1: ^{i}Bu,
5 R^1: 3,4-$(MeO)_2$-Bn, **6** R^1: BnO-CH_2,
7 R^1: 4-MeOBn

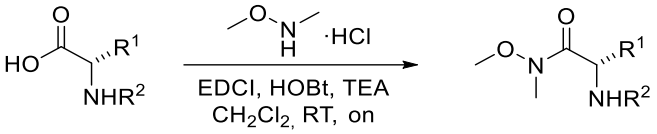
A R^2:Boc, **B** R^2:Cbz, **C** R^2:Fmoc

In general, the synthesis was carried out starting from enantiomerically pure (*L*) amino acids, but the racemic ones can also be used for the asymmetric Michael additions without any loss in reactivity or stereoselectivity.

[178] Trifonova, A.; Andersson, P. G. *Tetrahedron: Asymmetry* **2004**, *15*, 445–452.
[179] Moas-Héloire, V.; Renault, N.; Batalha, V.; Rincon Arias, A.; Marchivie, M.; Yous, S.; Deguine, N.; Buée, L.; Chavatte, P.; Blum, D.; Lopes, L.; Melnyk, P.; Agouridas, L. *Eur. J. Med. Chem.* **2015**, *106*, 15–25.
[180] Halland, N.;Braunton, A.; Bachmann, A.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 15, 4790–4791.
[181] Changzhu, X.; Jianguo, D.; Lichao, M.; Guomei, L.; Minli, T. *Tetrahedron* **2013**, *69,* 4749–4757.
[182] Tissot, M.; Alexakis, A. *Chem. Eur. J.*, **2013**, *19*, 11352 – 11363.
[183] Jakubea, P.; Cockfield, C. M.; Hynes, P. S.; Cleator, E.; Dixon, D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 1147–1155.
[184] Trost, M. B.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438–2439.
[185] Martin J. L.; Lear, J.; Kawamoto, Y.;Umemiya, S.; Wong,A. R.; Kwon,E.; Sato,I.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 12986 –12990.

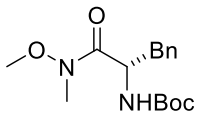
Step 1: Formation of the Weinreb amide

GENERAL PROCEDURE:[186]



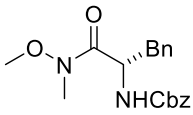
To a stirred solution of the corresponding *N*-protected amino acid (1 eq) in dry CH_2Cl_2 (10mL/mmol) EDCI (1.2 eq) and HOBt (1.1 eq) were added and the mixture was stirred for 10 min at RT. *N*,*O*-Dimethylhydroxylamine hydrochloride (1.2 eq) and dry TEA (2.4 eq) were then added and the reaction mixture was stirred at the same temperature overnight. Then, the mixture was diluted with EtOAc and washed with HCl 0.1M (x3), Na_2CO_3 10% (x2) and brine (x2). The organic layer was collected, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was obtained pure enough and was employed in the next step without further purification.

tert-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from commercially available Boc-(*L*)-Phenylalanine (2.653 g, 10 mmol, 1 eq). Colorless oil (3.083 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 5H), 5.15 (d, J = 9.0 Hz, 1H), 5.01 – 4.86 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 3.05 (dd, J = 13.6, 6.1 Hz, 1H), 2.88 (dd, J = 13.5, 5.7 Hz, 1H), 1.38 (d, J = 3.1 Hz, 9H). All spectroscopic data were consistent with those previously reported.[187]

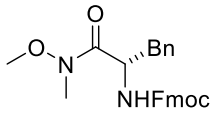
Benzyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from commercially available Cbz-(*L*)-Phenylalanine (2.395 g, 8 mmol, 1 eq). White solid (2.066 g, 6 mmol, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 7.28 – 7.22 (m, 3H), 7.18 – 7.11 (m, 2H), 5.45 (d, J = 8.9 Hz, 1H), 5.08 (dd, J = 12.1, 8.1 Hz, 2H), 5.04 – 4.96 (m, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 3.08 (dd, J = 13.7, 6.1 Hz, 1H), 2.91 (dd, J = 13.6, 7.2 Hz, 1H). All spectroscopic data were consistent with those previously reported.[188]

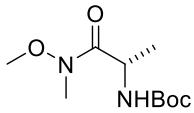
[186] Adapted from: Debaene, F.; Da Silva, J. A.; Pianowski, Z.; Duran, F. J. *Tetrahedron* **2007**, *63*, 6577–6586.
[187] Nguyen, T.; Coover, R. A.; Verghese, J.; Moran, R. G.; Ellis, K. C. *ACS Med. Chem. Lett.* **2014**, *5*, 462–467.
[188] Kappel, J. C.; Barany, G. *J. Peptide Sci.* **2005**, *11*, 525–535.

(9*H*-Fluoren-9-yl)methyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate



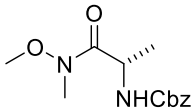
The title compound was prepared following the General Procedure starting from commercially available Fmoc-(*L*)-Phenylalanine (1.937 g, 5 mmol, 1 eq). White foam (1.932 g, 4.49 mmol, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, J = 7.6, 2H), 7.56 (t, J = 6.9 Hz, 2H), 7.46 – 7.35 (m, 2H), 7.34 – 7.22 (m, 5H), 7.21 – 7.12 (m, 2H), 5.49 (d, J = 9.0 Hz, 1H), 5.03 (d, J = 7.9 Hz, 1H), 4.37 (dd, J = 10.4, 7.3 Hz, 1H), 4.27 (d, J = 8.1 Hz, 1H), 4.18 (t, J = 7.1 Hz, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 3.10 (dd, J = 13.7, 6.1 Hz, 1H), 2.95 (dd, J = 13.6, 7.2 Hz, 1H). All spectroscopic data were consistent with those previously reported.[189]

***tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate**



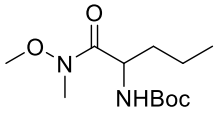
The title compound was prepared following the General Procedure starting from commercially available Boc-(*L*)-Alanine (1.135 g, 6 mmol, 1 eq). White solid (1.140 g, 4.9 mmol, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (d, J = 7.2 Hz, 1H), 4.74 – 4.61 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.44 (s, 9H), 1.31 (d, J = 6.9 Hz, 3H). All spectroscopic data were consistent with those previously reported.[190]

Benzyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from commercially available Cbz-(*L*)-Alanine (2.232 g, 10 mmol, 1 eq). White solid (2.323 g, 8.72 mmol, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (d, J = 8.3 Hz, 1H), 5.10 (dd, J = 17.8, 12.4 Hz, 2H), 4.82 – 4.67 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.35 (d, J = 6.9 Hz, 5H). All spectroscopic data were consistent with those previously reported.[188]

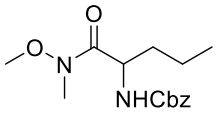
tert-butyl (1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from Boc-(±)-Norvaline[191] (1.411 g, 6.5 mmol, 1 eq). White solid (1.418 g, 5.45 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (d, J = 8.6 Hz, 1H), 4.66 (d, J = 10.3 Hz, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.78 – 1.60 (m, 2H), 1.54 (dd, J = 8.8, 4.7 Hz, 2H), 1.43 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H). All spectroscopic data were consistent with those previously reported.[192]

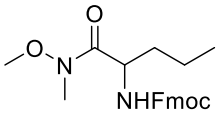
[189] Lawton, G. R.; Apella, D. H. *J. Am. Chem. Soc.* **2004**, *126*, 12762–12763.
[190] Ivkovic, J.; Lembacher-Faduma, C.; Breinbauer, R. *Org. Biomol. Chem.* **2015**, *13*, 10456–10460.
[191] Synthesis procedure from: Yadav, V. N.; Comotti, A.; Sozzani, P.; Bracco, S.; Bonge-Hansen, T.; Hennum, M.; Görbitz, C. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 15684–15688.
[192] Johansson, A.; Poliakov, A.; Åkerblom, E.; Wiklund, K.; Lindeberg, G.; Winiwarter, S.; Danielson, U. H.; Samuelsson, B.; Hallberg, A. *Bioor. Med. Chem.* **2003**, *11*, 2551–2568.

Benzyl (1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamate



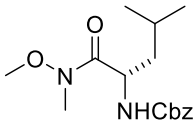
The title compound was prepared following the General Procedure starting from Cbz-(±)-Norvaline[193] (938.1 mg, 3.73 mmol, 1 eq). Yellow oil (547.2 mg, 1.87 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.41 (d, J = 9.2 Hz, 1H), 5.09 (dd, J = 12.6, 6.5 Hz, 1H), 4.75 (m, 1H), 3.78 (s, 3H), 3.21 (s, 3H), 1.78 – 1.62 (m, 1H),), 1.61 – 1.47 (m, 1H), 1.46 – 1.32 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). All spectroscopic data were consistent with those previously reported.[194]

(9*H*-Fluoren-9-yl)methyl (1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from Fmoc-(±)-Norvaline[195] (2.2226 g, 6.5 mmol, 1 eq). Yellow oil (2.0267 g, 5.30 mmol, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 5.9 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 7.4 Hz, 2H), 5.46 (d, J = 9.2 Hz, 1H), 4.84 – 4.69 (m, 1H), 4.45 – 4.31 (m, 2H), 4.23 (t, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.21 (s, 3H), 1.82 – 1.70 (m, 1H), 1.68 – 1.58 (m, 1H), 1.41 – 1.30 (m, 3H), 0.97 – 0.81 (m, 3H). All spectroscopic data were consistent with those previously reported.[196]

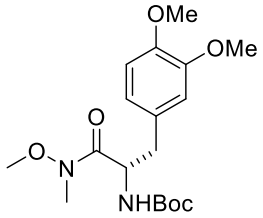
Benzyl (*S*)-(1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from commercially available Cbz-(*L*)-Leucine (2.122 g, 8 mmol, 1 eq). Colorless oil (2.076 g, 6.73 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.32 (d, J = 9.4 Hz, 1H), 5.15 – 5.03 (m, 2H), 4.79 (q, J = 8.0 Hz, 1H), 3.79 (s, 3H), 3.20 (s, 3H), 1.72 (dp, J = 13.2, 6.6 Hz, 1H), 1.47 (dd, J = 7.8, 6.1 Hz, 2H), 0.97 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H). All spectroscopic data were consistent with those previously reported.[197]

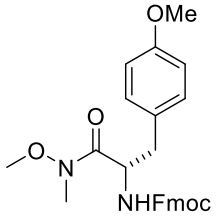
[193] Synthesis procedure from: Fraser, B. H.; Mulder, R. J.; Perlmutter, P. *Tetrahedron* **2006**, *62*, 2857–2867.
[194] Oka, T.; Yasusa, T.; Ando, T.; Watanabe, M.; Yoneda, F.; Ishida, T.; Knoll, J. *Bioorg. Med. Chem*. **2001**, *9*, 1213–1219.
[195] Synthesis procedure from: Chen, L.; Sun, W.; Li, J.; Liu, Z.; Ma, Z.; Zhang, W.; Du, L.; Xu, W.; Fanga, H.; Li, M. *Org. Biomol. Chem*. **2013**, *11*, 378–382.
[196] Iera, J. A.; Jenkins, L. M. M.; Kajiyama, H.; Kopp, J. B.; Appella, D. H. *Bioorg. Med. Chem. Lett.* **2010**, *20,* 6500–6503.
[197] Mallik, S. K.; Li, D. Y.; Cui, M.; Song, H.; Park, H.; Kim, H. S. *Arch. Pharm. Res.* **2012**, *35*, 469–479.

tert-Butyl (_S_)-(3-(3,4-dimethoxyphenyl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl) carbamate



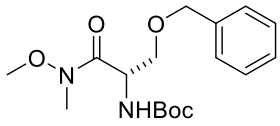
The title compound was prepared following the General Procedure starting from Boc-3,4-dimethoxy-(*L*)-Phenylalanine[198] (2.252 g, 10 mmol, 1 eq). Orange foam (3.2094 g, 8.7mmol, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.69 (s, 2H), 5.16 (d, J = 9.0 Hz, 1H), 5.01 – 4.84 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.16 (s, 3H), 2.99 (dd, J = 13.7, 6.5 Hz, 1H), 2.85 (dd, J = 13.3, 6.5 Hz, 1H), 1.40 (s, 9H).

(_9H_-Fluoren-9-yl)methyl (_S_)-(1-(methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxo propan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from Fmoc-(*L*)-Tyrosine[199] (2.252 g, 10 mmol, 1 eq). Orange foam (3.2094 g, 8.7 mmol, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 6.8 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (d, J = 7.4 Hz, 2H), 7.14 – 7.01 (m, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.45 (d, J = 9.6 Hz, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.37 (dd, J = 9.8, 7.3 Hz, 1H), 4.32 – 4.24 (m, 1H), 4.19 (t, J = 6.8 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.19 (s, 3H), 3.04 (dd, J = 14.3, 6.5 Hz, 1H), 2.89 (dd, J = 12.6, 6.5 Hz, 1H).

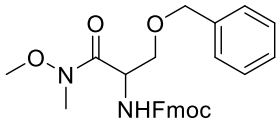
tert-Butyl (_S_)-(3-(benzyloxy)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate



The title compound was prepared following the General Procedure starting from commercially available Boc-*O*-Bn-(*L*)-Serine (1.476 g, 5 mmol, 1 eq). Brown oil (993 mg, 2.96 mmol, 59% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 5.42 (d, J = 8.2 Hz, 1H), 4.88 (dt, J = 8.1, 4.1 Hz, 1H), 4.53 (dd, J = 12.2 Hz, 2H), 3.71 (s, 3H), 3.67 (dd, J = 3.5 Hz, 2H), 3.21 (s, 3H), 1.43 (s, 9H). All spectroscopic data were consistent with those previously reported.[200]

[198] Synthesis procedure from: Sohora, M.; Vazdar, M.; Sovic, I.; Mlinaric-Majerski, K.; Basaric, N. *J. Org. Chem.* **2018**, *83*, 14905−14922.
[199] Synthesis procedure from: Sohora, M.; Vazdar, M.; Sovic, I.; Mlinaric-Majerski, K.; Basaric, N. *J. Org. Chem.* **2018**, *83*, 14905−14922.
[200] Dragulescu-Andrasi, A.; Rapireddy, S.; Frezza, Brian M.; Gayathri, C.; Gil, R. R.; Ly, D. H. *J. Am. Chem. Soc.* **2006**, *128*, 10258−10267.

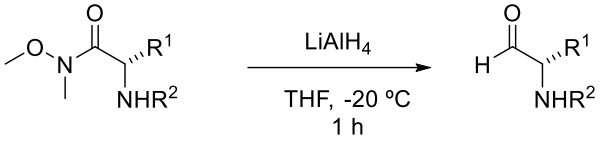
(9*H*-Fluoren-9-yl)methyl (3-(benzyloxy)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl) carbamate



The title compound was prepared following the General Procedure starting from Fmoc-*O*-Bn-(±)-Serine[201] (2.922 g, 7 mmol, 1 eq). Yellow oil (2.8716 g, 6.23 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.60 (q, J = 6.3 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.36 – 7.27 (m, 7H), 5.75 (d, J = 8.8 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.56 (q, J = 12.2 Hz, 2H), 4.36 (d, J = 7.8 Hz, 2H), 4.23 (t, J = 7.1 Hz, 1H), 3.78 – 3.67 (m, 5H), 3.23 (s, 3H).

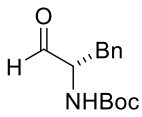
Step 2: Reduction

GENERAL PROCEDURE:[186]



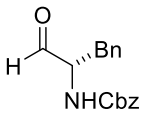
To a solution of the corresponding amide (1 eq) in dry THF (10 mL/mmol) under Argon and at -20 ºC $LiAlH_4$ (1.2 mmol/mmol) was added portionwise and H_2 formation was observed. The reaction mixture was stirred at the same temperature for 1 hour and then, the reaction was quenched with EtOAc and HCl 0.1M and allowed to warm up to RT. When total destruction of the lithium salts was observed (aprox. 1 h), the mixture was extracted with EtOAc (x3), the organic layers were washed with HCl 0.1M (x3), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica flash column chromatography on silica gel when needed.

***tert*-Butyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (1A)**



The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (2.323 g, 7.55 mmol, 1 eq). White solid (1.128 g, 4.53 mmol, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.35 – 7.27 (m, 2H), 7.17 (dd, J = 6.5, 1.6 Hz, 1H), 5.09 – 4.97 (m, 1H), 4.49 – 4.36 (m, 1H), 3.12 (d, J = 6.5 Hz, 2H), 1.44 (s, 9H). All spectroscopic data were consistent with those previously reported.[202]

Benzyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (1B)

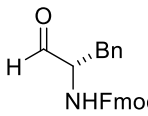


The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (2.065 g, 6 mmol, 1 eq). White solid (1.045 g, 3.69 mmol, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65

[201] Synthesis procedure from: Marchiori, F.; Borin, G.; Calderan, A.; Chessa, G. *Int. J. Peptide Protein Res.* **1987**, *30*, 822–831.
[202] Johnson, E. P.; Hubieki, M. P.; Combs, A. P.; Teleha, C. A. *Synthesis* **2011,** *24*, 4023–4026.

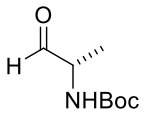
(s, 1H), 7.44 – 7.27 (m, 8H), 7.17 – 7.08 (m, 2H), 5.27 (d, *J* = 5.5 Hz, 1H), 5.12 (s, 3H), 4.52 (q, *J* = 6.6 Hz, 1H), 3.15 (d, *J* = 6.6 Hz, 2H). All spectroscopic data were consistent with those previously reported.[190]

(9*H*-Fluoren-9-yl)methyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (1C)



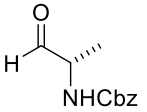
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (1.932 g, 4.5 mmol, 1 eq). White solid (1.087 g, 2.93 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.61 – 7.52 (m, 2H), 7.46 – 7.37 (m, 2H), 7.35 – 7.27 (m, 5H), 7.13 (d, J = 7.0 Hz, 2H), 5.29 (d, J = 3.6 Hz, 1H), 4.56 – 4.35 (m, 3H), 4.22 (t, J = 6.8 Hz, 1H), 3.16 (d, J = 6.5 Hz, 2H). All spectroscopic data were consistent with those previously reported.[203]

***tert*-Butyl (*S*)-(1-oxopropan-2-yl)carbamate (2A)**



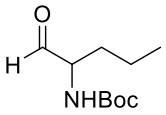
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (1.140 g, 4.9 mmol, 1 eq). White solid (808 mg, 4.66 mmol, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 5.07 (s, 1H), 4.36 – 4.15 (m, 1H), 1.45 (s, 9H), 1.34 (d, *J* = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[190]

Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (2B)



The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (1.332 g, 5 mmol, 1 eq). Colorless oil (573.4 mg, 2.77 mmol, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.36 (m, 5H), 5.37 (m, 1H), 5.13 (m, 2H), 4.32 (m, 1H), 1.38 (d, *J* = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[203]

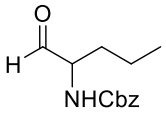
***tert*-Butyl (1-oxopentan-2-yl)carbamate (3A)**



The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (1.419 g, 5.45 mmol, 1 eq). Colorless oil (526.5 mg, 2.62 mmol, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.36 (m, 5H), 5.37 (m, 1H), 5.13 (m, 2H), 4.32 (m, 1H), 1.38 (d, *J* = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[194]

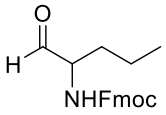
[203] Wang, G.; Mahesh, U.; Chen, G. Y. J.; Yao, S. Q. *Org. Lett.* **2003**, *5*, 737–740.

Benzyl (1-oxopentan-2-yl)carbamate (3B)



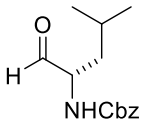
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (547.2 mg, 1.87 mmol, 1 eq). Yellow oil (227.2 mg, 0.97 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.42 – 7.29 (m, 5H), 5.12 (s, 2H), 4.33 (q, *J* = 7.0 Hz, 1H), 1.89 (m, 1H), 1.68 – 1.50 (m, 1H), 1.40 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). All spectroscopic data were consistent with those previously reported.[194]

(9H-fluoren-9-yl)methyl (1-oxopentan-2-yl)carbamate (3C)



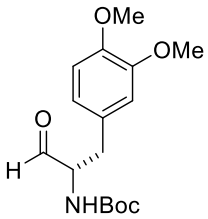
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (2.0267 g, 5.3 mmol, 1 eq). White solid (853.7 mg, 2.64 mmol, 50%). 1H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (td, J = 7.4, 1.2 Hz, 2H), 5.31 – 5.26 (m, 1H), 4.44 (d, J = 6.9 Hz, 2H), 4.32 (q, J = 6.8 Hz, 1H), 4.23 (t, J = 6.8 Hz, 1H), 2.02 – 1.85 (m, 1H), 1.72 – 1.57 (m, 1H), 1.39 – 1.31 (m, 2H), 0.98 – 0.81 (m, 3H). All spectroscopic data were consistent with those previously reported.[197]

Benzyl (*S*)-(4-methyl-1-oxopentan-2-yl)carbamate (4B)



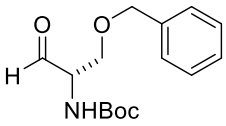
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (2.067 g, 6.73 mmol, 1 eq). Colorless oil (889.1 mg, 3.6 mmol, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.44 – 7.28 (m, 5H), 5.23 – 5.14 (m, 1H), 5.13 (s, 2H), 4.39 – 4.26 (m, 1H), 1.84 – 1.63 (m, 2H), 1.48 – 1.34 (m, 1H), 0.97 (t, J = 6.1 Hz, 6H). All spectroscopic data were consistent with those previously reported. [203]

***tert*-Butyl (*S*)-(1-(3,4-dimethoxyphenyl)-3-oxopropan-2-yl)carbamate (5A)**



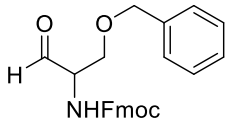
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (3.209 g, 8.71 mmol, 1 eq). Colorless oil (1.588 g, 5.13 mmol, 59% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.71 – 6.64 (m, 2H), 5.07 (d, J = 5.5 Hz, 1H), 4.37 (d, J = 6.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.03 (d, J = 6.5 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 155.5, 149.1, 148.2, 128.2, 121.5, 112.5, 111.5, 80.2, 60.9, 56.0, 55.9, 35.1, 28.4. UPLC-DAD-QTOF: $C_{17}H_{27}NO_6Na$ $[M+Na]^+$ calcd.: 364.1736, found: 364.1727.

tert-Butyl (_S_)-(1-(benzyloxy)-3-oxopropan-2-yl)carbamate (6A)



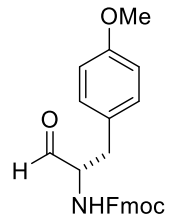
The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (993 mg, 2.96 mmol, 1 eq). Yellow oil (535.5 mg, 1.92 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.39 – 7.26 (m, 5H), 5.41 (d, J = 7.1 Hz, 1H), 4.51 (d, J = 3.0 Hz, 2H), 4.36 – 4.27 (m, 1H), 3.99 (dd, J = 9.7, 3.5 Hz, 1H), 3.71 (dd, J = 9.6, 4.2 Hz, 1H), 1.46 (s, 9H). All spectroscopic data were consistent with those previously reported.[204]

(9*H*-Fluoren-9-yl)methyl (1-(benzyloxy)-3-oxopropan-2-yl)carbamate (6C)



The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (2.8716 g, 6.23 mmol, 1 eq). Colorless oil (1.212 g, 3.02 mmol, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.38 – 7.23 (m, 7H), 5.69 (d, J = 6.9 Hz, 1H), 4.59 – 4.47 (m, 2H), 4.46 – 4.32 (m, 3H), 4.24 (t, J = 6.9 Hz, 1H), 4.04 (dd, J = 9.7, 2.9 Hz, 1H), 3.75 (dd, J = 9.6, 3.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 156.3, 143.8, 141.5, 137.3, 128.7, 128.2, 127.9, 127.2, 125.2, 120.2, 73.7, 67.7, 67.4, 60.6, 47.3. UPLC-DAD-QTOF: $C_{26}H_{27}NO_5Na$ $[M+Na]^+$ calcd.: 456.1787, found: 456.1785.

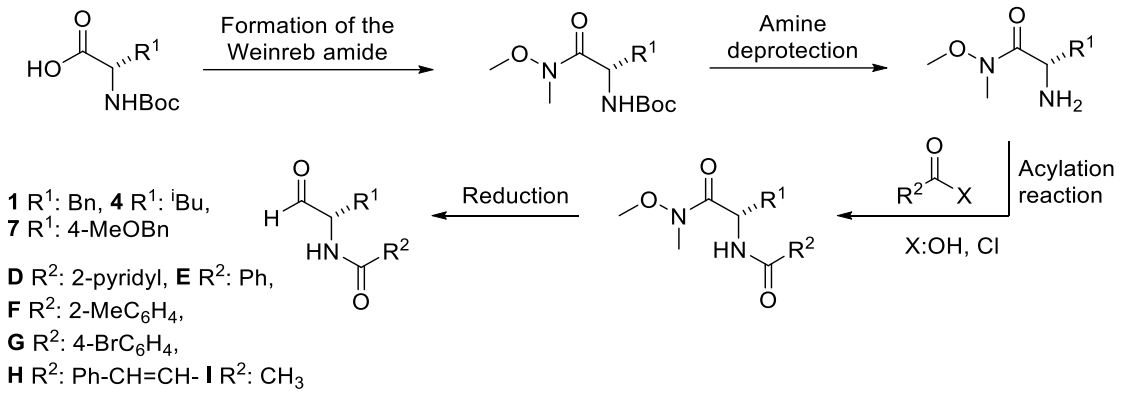
(9*H*-Fluoren-9-yl)methyl (*S*)-(1-(4-methoxyphenyl)-3-oxopropan-2-yl)carbamate (7C)



The title compound was prepared following the General Procedure starting from the corresponding Weinreb amide (1.772 g, 3.85 mmol, 1 eq). White solid (990.3 mg, 2.47 mmol, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.58 (dd, J = 7.1, 3.7 Hz, 2H), 7.42 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 5.39 (d, J = 5.9 Hz, 1H), 4.53 – 4.35 (m, 3H), 4.22 (t, J = 6.8 Hz, 1H), 3.77 (s, 3H), 3.10 (d, J = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 158.8, 155.9, 143.8, 141.4, 130.4, 127.8, 127.2, 125.1, 120.1, 114.3, 67.0, 61.3, 55.3, 47.3, 34.5. UPLC-DAD-QTOF: $C_{25}H_{24}NO_4$ $[M+H]^+$ calcd.: 402.1705, found: 402.1704.

[204] Xu, G. G.; Etzkorn, F. A.; *Org. Lett.* **2010**, *12*, 696–699.

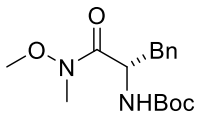
*5.3.1.3. Synthesis of N-Acyl α-amino aldehydes **1, 4** and **7***



Step 1: Formation of the Weinreb amide

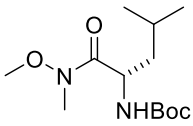
The General Procedure on page 154 was followed.

***tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate**



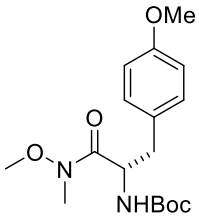
The synthesis of this compound is described on page 154.

***tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate**



The title compound was prepared following the General Procedure starting from Boc-(*L*)-Leucine[149] (2.313 g, 10 mmol, 1 eq). Yellow oil (2.478 g, 9.03 mmol, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, J = 9.7 Hz, 1H), 4.72 (br s, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 1.79 – 1.57 (m, 2H), 1.53-1.48 (m, 1H), 1.44 (d, J = 2.4 Hz, 9H), 0.95 (dd, J = 10.8, 6.6 Hz, 6H). All spectroscopic data were consistent with those previously reported.[205]

***tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl) carbamate**



The title compound was prepared following the General Procedure starting from Boc-(*L*)-Tyr(Me)-OH[206] (5.907 g, 20 mmol, 1 eq). Yellow oil (6.373 g, 18.8 mmol, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 – 7.04 (m, 2H), 6.85 – 6.77 (m, 2H), 5.14 (d, J = 7.6 Hz, 1H), 4.90 (m, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.16 (s, 2H), 2.99 (dd, J = 13.7, 6.1 Hz, 1H),

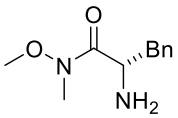
[205] Ko, E.; Burgess, K. *Org. Lett.* **2011**, *13*, 980–983.
[206] Synthesis procedure from: Alfei, S.; Castellaro, S. *Macromol. Res.* **2017**, *25*, 1172–1186.

2.88 – 2.77 (m, 1H), 1.39 (s, 9H). All spectroscopic data were consistent with those previously reported.[207]

Step 2: Amine deprotection

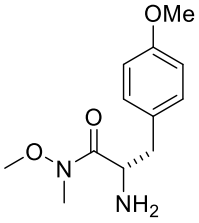
The General Procedure on page 148 was followed.

(*S*)-2-Amino-*N*-methoxy-*N*-methyl-3-phenylpropanamide



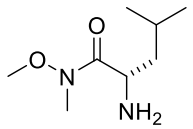
The title compound was prepared following the General Procedure starting from the previously prepared corresponding Weinreb amide (2.899 g, 9.4 mmol, 1 eq). The desired product was obtained as a yellow oil (1.8575 g, 8.9 mmol, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 5H), 4.07 – 3.97 (m, 1H), 3.62 (s, 3H), 3.20 (s, 3H), 3.07 (dd, J = 13.3, 5.5 Hz, 1H), 2.72 (dd, J = 13.3, 8.1 Hz, 1H), 1.62 (s, 2H).

(*S*)-2-Amino-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropanamide



The title compound was prepared following the General Procedure starting from the previously prepared corresponding Weinreb amide (3.133 g, 9.26 mmol, 1 eq). The reaction mixture was not treated due to its high solubility in water. The solvent was removed under reduced pressure and quantitative yield was assumed. The resulting crude was used in the next step as the trifluoroacetate salt.

(*S*)-2-Amino-*N*-methoxy-*N*,4-dimethylpentanamide

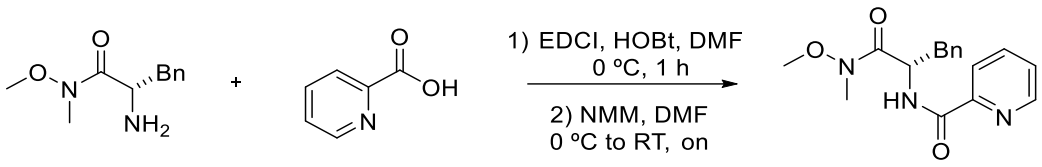


The title compound was prepared following the General Procedure starting from the previously prepared corresponding Weinreb amide (1.154 g, 4.2 mmol, 1 eq). The reaction mixture was not treated due to its high solubility in water. The solvent was removed under reduced pressure and quantitative yield was assumed. The resulting crude was used in the next step as the trifluoroacetate salt.

[207] Velmourougane, G.; Harbut, M. B.; Dalal, S.; McGowan, S.; Oellig, C. A.; Meinhardt, N.; Whisstock, J. C.; Klemba, M.; Greenbaum, D. C. *J. Med. Chem.* **2011**, *54*, 1655–1666.

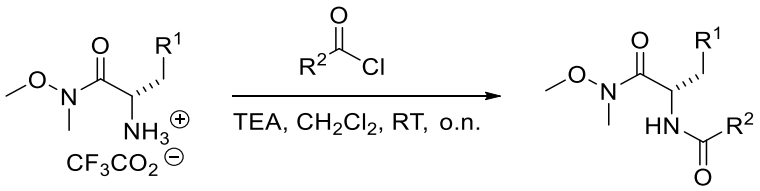
Step 3: Acylation reaction

PROCEDURE 1:[186] **(*S*)-*N*-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl) picolinamide**



To a stirred solution of picolinic acid (353.12 mg, 2.87 mmol, 1.1 eq) in dry DMF (7.5 mL, 2.9 mL/mmol) at 0 ºC EDCI (600.8 mg, 3.13 mmol, 1.2 eq) and HOBt (422.9 mg, 3.13 mmol, 1.1 eq) were added and the mixture was stirred at the same temperature for 1 h. A solution of (*S*)-2-amino-*N*-methoxy-*N*-methyl-3-phenylpropanamide (544.1 mg, 2.61 mmol, 1 eq) and NMM (1.12 mL) in dry DMF (3.8 mL, 1.5 mL/mmol) was added at 0 ºC and the reaction mixture was allowed to warm up to RT while stirring overnight. The obtained mixture was then poured over a flask with ice/citric acid 5% (75 mL) and then extracted with EtOAc (x3). The organic layer was washed with brine (x3) and $NaHCO_3$ sat. (x2), dried over $MgSO_4$ and evaporated under reduced pressure. Finally, the crude product was purified by flash column chromatography on silica gel (Hexanes:EtOAc 60:40) to afford the product as a colorless oil (436.8 mg, 1.39 mmol, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 9.3 Hz, 1H), 8.56 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.11 (dt, J = 7.8, 1.1 Hz, 1H), 7.81 (td, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.31-7.18 (m, 5H), 5.47 (q, J = 7.6 Hz, 1H), 3.67 (s, 3H), 3.28 – 3.13 (m, 4H), 3.08 (dd, J = 13.5, 7.2 Hz, 1H).

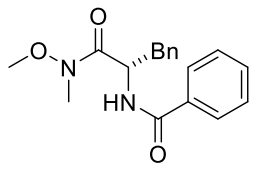
GENERAL PROCEDURE 2:[208]



To a stirred solution of the corresponding free amine or amine salt (1 eq) in CH_2Cl_2 (5 mL/mmol) at 0 ºC TEA (5 eq) was added dropwise. After checking that the pH was basic, the corresponding acid chloride (1.5 eq) was added, and the mixture was stirred at room temperature overnight. Then, the reaction mixture was washed with NH_4Cl (x3) and brine (x2), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

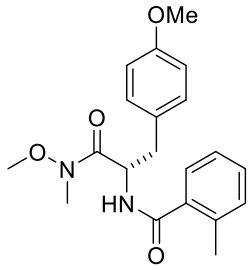
[208] Morwick, T.; Hrapchak, M.; DeTuri, M.; Campbell S. *Org. Lett.* **2002**, *4*, 2665–2668.

(*S*)-*N*-(1-(Methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide



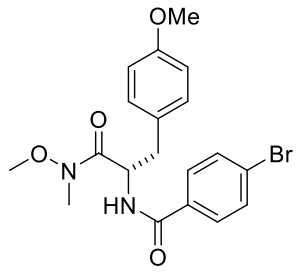
The title compound was prepared following General Procedure 2 starting from (*S*)-2-amino-*N*-methoxy-*N*-methyl-3-phenylpropanamide (408.3 mg, 1.95 mmol, 1 eq) and benzoyl chloride (0.27 mL, 2.34 mmol, 1.2 eq). The crude product was purified by flash column chromatography on silica gel using 70:30 Hexane:EtOAc as eluent to afford the product as a colorless oil (397.1 mg, 1.27 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.52 – 7.36 (m, 3H), 7.32 – 7.21 (m, 3H), 7.21 – 7.15 (m, 2H), 6.82 (d, J = 8.3 Hz, 1H), 5.52 – 5.39 (m, 1H), 3.74 (s, 3H), 3.27 – 3.22 (m, 1H), 3.21 (s, 3H), 3.10 (dd, J = 13.6, 6.4 Hz, 1H). All spectroscopic data were consistent with those previously reported.[209]

(*S*)-*N*-(1-(Methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)-2-methylben zamide



The title compound was prepared following General Procedure 2 starting from (*S*)-2-amino-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methyl propanemide trifluoroacetate salt (8.8 mmol, 1 eq) and 2-methylbenzoyl chloride[210] (13.2 mmol, 1.5 eq). The crude product was purified by flash column chromatography on silica gel using 50:50 Hexane:EtOAc as eluent to afford the product as a yellow foam (1.987 g, 5.57 mmol, 63% yield of two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.40 (d, J = 7.3 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H), 3.78 (s, 6H), 3.22 (s, 3H), 3.18 (dd, J = 13.4, 8.1 Hz, 1H), 2.97 (dd, J = 13.9, 7.1 Hz, 1H), 2.35 (s, 3H).

(*S*)-4-Bromo-*N*-(1-(methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl) benzamide

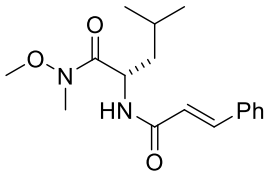


The title compound was prepared following General Procedure 2 starting from (*S*)-2-amino-*N*-methoxy-3-(4-methoxy phenyl)-*N*-methylpropanamide trifluoroactetate salt (9.26 mmol, 1 eq) and 4-bromobenzoyl chloride (3.048 g, 13.89 mmol, 1.5 eq). The crude product was purified by flash column chromatography on silica gel using 70:30 Hexane:EtOAc as eluent to afford the product as a yellow foam (2.533 g, 6.01 mmol, 65% yield of two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 1.6 Hz, 2H), 7.95 (s,

[209] Studer, A.; Seebach, D. *Liebigs Ann. Chem.* **1995**, 217–222.
[210] Synthesis procedure from: Bisht, R.; Hoque, E.; Chattopadhyay, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 15762–15766.

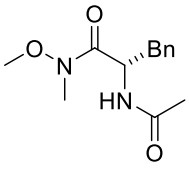
1H), 7.44 (s, 1H), 5.29 (td, J = 9.2, 4.1 Hz, 1H), 3.89 (s, 3H), 3.26 (s, 3H), 1.70 (dtt, J = 23.2, 13.7, 4.1 Hz, 3H), 1.00 (dd, J = 14.1, 6.4 Hz, 6H).

(*S*)-2-Cinnamamido-*N*-methoxy-*N*,4-dimethylpentanamide



The title compound was prepared following General Procedure 2 starting from (*S*)-2-amino-*N*-methoxy-*N*,4-dimethyl pentanamide trifluoroacetate salt (4.2 mmol, 1 eq) and cinnamoyl chloride (1.0496 g, 6.3 mmol, 1.5 eq). The crude product was purified by flash column chromatography on silica gel using 70:30 Hexane:EtOAc as eluent to afford the product as a colorless foam (883.9 mg, 2.9 mmol, 69% yield of two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 15.6 Hz, 1H), 7.58 – 7.44 (m, 2H), 7.44 – 7.33 (m, 3H), 6.46 (d, J = 15.6 Hz, 1H), 6.33 (d, J = 9.1 Hz, 1H), 5.34 – 5.18 (m, 1H), 3.87 (s, 3H), 3.25 (s, 3H), 1.82 – 1.67 (m, 1H), 1.62 – 1.55 (m, 2H), 1.03 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H).

(*S*)-2-Acetamido-*N*-methoxy-*N*-methyl-3-phenylpropanamide

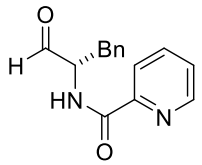


The title compound was prepared following General Procedure 2 starting from (*S*)-2-amino-*N*-methoxy-*N*-methyl-3-phenylpropanamide (416.5 mg, 2 mmol, 1 eq) and acetyl chloride (0.29 mL, 4 mmol, 2 eq). The crude product was purified by flash column chromatography on silica gel using EtOAc as the eluent to afford the product as a yellow oil (367.5 mg, 1.47 mmol, 73% yield of two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 3H), 7.18 – 7.09 (m, 2H), 6.15 (d, J = 8.1 Hz, 1H), 5.33 – 5.18 (m, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 3.09 (dd, J = 13.7, 6.3 Hz, 1H), 2.95 (dd, J = 13.6, 6.6 Hz, 1H), 1.96 (s, 3H).

Step 4: Reduction

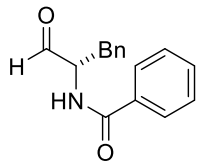
The General Procedure on page 158 was followed

(*S*)-*N*-(1-oxo-3-phenylpropan-2-yl)picolinamide (1D)



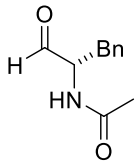
The title compound was prepared from (*S*)-*N*-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)picolinamide (436.8 mg, 1.39 mmol, 1 eq) following the General Procedure. The product was obtained as an orange foam (235.8 mg, 0.93 mmol, 67% yield) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.60 – 8.50 (m, 1H), 8.17 (dt, J = 7.8, 1.2 Hz, 1H), 7.85 (td, J = 7.7, 1.8 Hz, 1H), 7.44 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.34 – 7.18 (m, 5H), 4.89 (q, J = 6.9 Hz, 1H), 3.27 (d, J = 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 164.7, 149.2, 148.5, 137.5, 136.0, 129.4, 129.0, 127.2, 126.6, 122.4, 59.9, 35.5. UPLC-DAD-QTOF: $C_{15}H_{15}N_2O_2$ $[M+H]^+$ calcd.: 255.1134, found: 255.1138.

(*S*)-*N*-(1-Oxo-3-phenylpropan-2-yl)benzamide (1E)



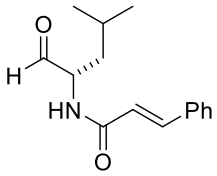
The title compound was prepared from (*S*)-*N*-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (154 mg, 0.5 mmol, 1 eq) following the General Procedure. The product was obtained as a white solid (99.4 mg, 0.48 mmol, 96% yield) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.76 – 7.71 (m, 2H), 7.54 – 7.40 (m, 3H), 7.36 – 7.27 (m, 3H), 7.23 – 7.17 (m, 2H), 6.66 (d, J = 4.9 Hz, 1H), 4.98 – 4.91 (m, 1H), 3.41 – 3.23 (m, 2H). All spectroscopic data were consistent with those previously reported.[211]

(*S*)-*N*-(1-Oxo-3-phenylpropan-2-yl)acetamide (1I)



The title compound was prepared from (*S*)-2-acetamido-*N*-methoxy-*N*-methyl-3-phenylpropanamide (367.5 mg, 1.47 mmol, 1 eq) following the General Procedure. The product was obtained as a yellow foam (191.3 mg, 1 mmol, 68% yield) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 1.0 Hz, 1H), 7.35 – 7.20 (m, 5H), 6.08 (s, 1H), 4.76 – 4.66 (m, 1H), 3.15 (dd, J = 6.4, 2.8 Hz, 2H), 1.99 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 135.7, 129.4, 128.9, 127.3, 59.9, 35.2, 23.1. UPLC-DAD-QTOF: $C_{11}H_{14}NO_2$ $[M+H]^+$ calcd.: 192.1025, found: 192.1023.

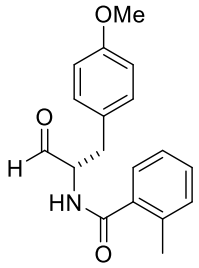
(*S*)-*N*-(4-Methyl-1-oxopentan-2-yl)cinnamamide (4H)



The title compound was prepared from (*S*)-2-cinnamamido-*N*-methoxy-*N*,4-dimethylpentanamide (883.9 mg, 2.9 mmol, 1 eq) following the General Procedure. The crude was purified by flash column chromatography on silica gel using 80:20 Hexane:EtOAc as eluent to afford the product as a yellow oil (449.4 g, 1.8 mmol, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.61 (d, J = 15.7 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.32-7.21 (m, 3H), 6.90 (d, J = 7.0 Hz, 1H), 6.56 (dd, J = 15.7, 1.7 Hz, 1H), 4.76 – 4.49 (m, 1H), 1.83 – 1.64 (m, 2H), 1.53 – 1.44 (m, 1H), 0.92 (dd, J = 6.1, 4.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 166.5, 141.9, 134.6, 129.9, 128.8, 127.9, 120.0, 57.6, 37.8, 24.83, 23.1, 21.9. UPLC-DAD-QTOF: $C_{15}H_{20}NO_2$ $[M+H]^+$ calcd.: 246.1494, found: 246.1493.

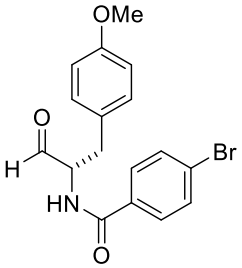
[211] Pan, H.; Xie, Y.; Liua, M.; Shi, Y. *RSC Adv.* **2014**, *4*, 2389–2392.

(*S*)-*N*-(1-(4-Methoxyphenyl)-3-oxopropan-2-yl)-2-methylbenzamide (7F)



The title compound was prepared from (*S*)-*N*-(1-(methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)-2-methylbenzamide (1.243 g, 3 mmol, 1 eq) following the General Procedure. The crude was purified by flash column chromatography on silica gel using 70:30 Hexane:EtOAc as eluent to afford the product as a colorless oil (1.365 g, 4.59 mmol, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.30 (d, J = 7.2 Hz, 2H), 7.24 – 7.16 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.29 (d, J = 5.6 Hz, 1H), 4.91 (q, J = 6.6 Hz, 1H), 3.78 (s, 3H), 3.24 (d, J = 6.7 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 170.0, 159.0, 136.6, 135.4, 131.3, 130.5, 130.4, 127.4, 127.0, 125.9, 114.4, 60.3, 55.4, 34.4, 20.0. UPLC-DAD-QTOF: $C_{18}H_{20}NO_3$ $[M+H]^+$ calcd.: 298.1443, found: 298.1445.

(*S*)-4-Bromo-*N*-(1-(4-methoxyphenyl)-3-oxopropan-2-yl)benzamide (7G)

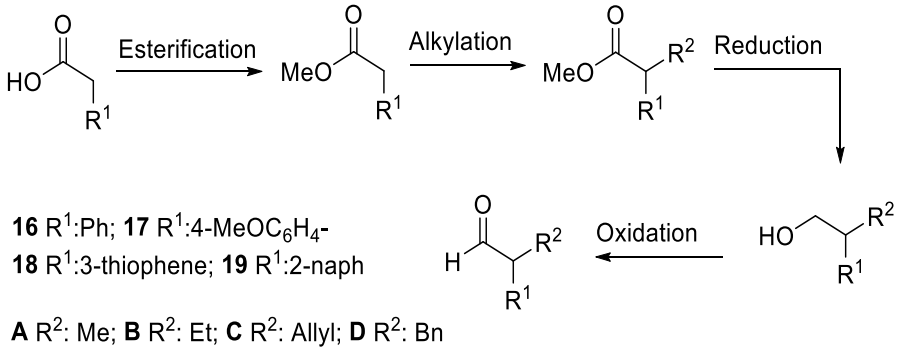


The title compound was prepared from (*S*)-4-bromo-*N*-(1-(methoxy (methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl) benzamide (2.533 g, 6.01 mmol, 1 eq) following the General Procedure. The product was obtained as a white solid (2.0374 g, 5.62 mmol, 94% yield) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.67 – 7.48 (m, 4H), 7.08 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 5.9 Hz, 1H), 4.90 (q, J = 6.3 Hz, 1H), 3.78 (s, 3H), 3.30 (dd, J = 14.2, 5.5 Hz, 1H), 3.21 (dd, J = 14.2, 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 166.4, 159.0, 132.6, 132.1, 130.5, 128.8, 127.2, 126.9, 114.4, 60.4, 55.4, 34.4. UPLC-DAD-QTOF: $C_{17}H_{17}NO_3Br$ $[M+H]^+$ calcd.: 362.0392, found: 362.0388.

*5.3.1.4. Synthesis of α-aryl acetaldehydes **16-19***

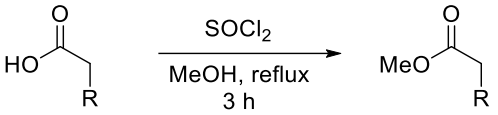
(±)-2-Propionaldehyde (**16A**) was commercially available and was distilled before used and saved under nitrogen at -30 ºC.

PROCEDURE A: *Synthesis of **16C, 17A, 18A, 18B, 19A** and **19C***



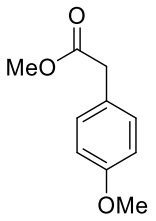
Step 1: Esterification

GENERAL PROCEDURE:[212]



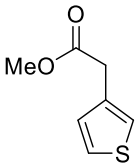
To a stirred solution of the starting carboxylic acid (1 eq) in MeOH (2 mL/mmol) at 0 ºC $SOCl_2$ (2 eq) was added dropwise and the mixture was stirred at reflux for 3 h in a flask equipped with a $CaCl_2$-filled drying tube (reaction followed by TLC). After reaction completion the solvent was evaporated, the residue was redissolved in DCM and washed with $NaHCO_3$ (x3), H_2O (x3) and brine (x3). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the desired product, which was used in the next step without further purification.

(±) Methyl 2-(4-methoxyphenyl)acetate



The title compound was prepared following the General Procedure starting from 4-methoxyphenylacetic acid (2.492 g, 15 mmol) and obtained as a yellow oil (2.108 g, 11.7 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.57 (s, 2H). All spectroscopic data were consistent with those previously reported.[213]

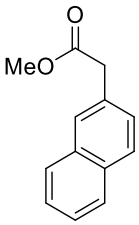
(±) Methyl 2-(thiophen-3-yl)acetate



The title compound was prepared following the General Procedure starting from 3-thiopheneacetic acid (1.421 g, 10 mmol) and obtained as a yellow oil (1.416 g, 9.07 mmol, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, J = 4.9, 3.0 Hz, 1H), 7.15 (dd, J = 2.5, 1.7 Hz, 1H), 7.04 (dd, J = 4.9, 1.3 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 2H). All spectroscopic data were consistent with those previously reported.[214]

[212] Xie, J.; Yang, F.; Zhang, M.; Lam, C.; Qiao, Y.; Xiao, J.; Zhang, D.; Ge, Y.; Fu, L.; Xie, D. *Bioorg. Med. Chem. Lett.* **2017**, *27* (2), 131–134.
[213] Revelant, G.; Dunand, S.; Hesse, S.; Kirsch, G. *Synthesis* **2011**, *2011* (18), 2935–2940.
[214] Baek, M. G.; Stevens, R. C.; Charych, D. H. *Bioconjug. Chem.* **2000**, *11* (6), 777–788.

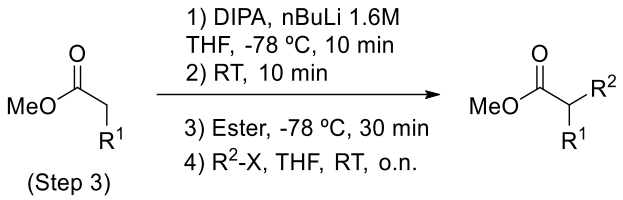
(±) Methyl 2-(naphthalen-2-yl)acetate



The title compound was prepared following the General Procedure starting from 2-naphthylacetic acid (1.862 g, 10 mmol) and obtained as a white solid (1.745 g, 8.71 mmol, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 3H), 7.76 – 7.72 (m, 1H), 7.52 – 7.39 (m, 3H), 3.81 (s, 2H), 3.72 (s, 3H). All spectroscopic data were consistent with those previously reported.[215]

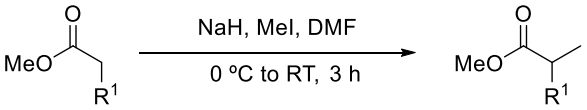
Step 2: Alkylation

GENERAL PROCEDURE 1:[216]



To a stirred solution of DIPA (1 eq) in THF (3 mL/mmol) under inert atmosphere and at -78 ºC n-BuLi (1.6M, 1 eq) was added dropwise and the mixture was stirred at the same temperature for 10 min. The reaction mixture was then stirred at RT for another 10 min and cooled down to -78 ºC again. A solution of the corresponding ester (1 eq) in THF (0.3 mL/mmol) was then added dropwise and the resulting mixture was stirred for 30 min at the same temperature. Finally, the corresponding alkyl halide was added and the solution was allowed to reach RT and stirred overnight. The reaction was quenched with NH_4Cl and extracted with EtOAc (x3). The organic layers were combined and washed with brine (x3) and dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified when needed by flash column chromatography on silica gel.

GENERAL PROCEDURE 2:[217]

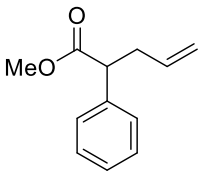


To a stirred suspension of NaH (60% in mineral oil, 0.95 eq) in dry DMF (3 mL/mmol) under inert atmosphere and at 0 ºC the corresponding ester (1 eq) was added dropwise. The mixture was stirred at 0 ºC for 5 min and then MeI (1 eq) was added dropwise at the same temperature. The reaction mixture was allowed to reach room temperature while stirring and the reaction was followed by TLC (80:20 Hexane:EtOAc)

[215] Terao, Y.; Miyamoto, K.; Ohta, H. *Chem. Commun.* **2006**, No. 34, 3600–3602.
[216] Adapted from: Morofuji, T.; Shimizu, A.; Yoshida, J. I. *J. Am. Chem. Soc.* **2013**, *135* (13), 5000–5003.
[217] Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139* (3), 1029–1032.

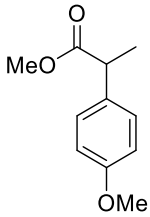
until reaction completion. The reaction was then quenched with NH_4Cl and extracted with Et_2O (x2). The organic layers were combined, washed with H_2O (x2) and brine (x5) and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude, which was purified when needed.

(±) Methyl 2-phenylpent-4-enoate



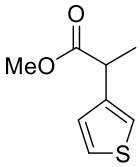
The title compound was prepared following the General Procedure 1 starting from commercially available methyl 2-phenylacetate (1.127 g, 8 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a colorless oil (1.210 g, 6.36 mmol, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.73 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.13 – 4.95 (m, 2H), 3.72 – 3.59 (m, 4H), 2.90 – 2.77 (m, 1H), 2.58 – 2.45 (m, 1H). All spectroscopic data were consistent with those previously reported.[220]

(±) Methyl 2-(4-methoxyphenyl)propanoate



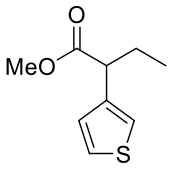
The title compound was prepared following the General Procedure 2 starting from methyl 2-(4-methoxyphenyl)acetate (571.2 mg, 3.17 mmol, 1 eq). The product was obtained as an orange oil (548.8 mg, 2.83 mmol, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 6.90 – 6.82 (m, 2H), 3.79 (d, J = 1.1 Hz, 3H), 3.70 – 3.68 (m, 1H), 3.65 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) Methyl 2-(thiophen-3-yl)propanoate



The title compound was prepared following the General Procedure 1 starting from methyl 2-(thiophen-3-yl)acetate (1.181 g, 7.56 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a yellow oil (1.006 g, 5.91 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 1H), 7.14 – 7.11 (m, 1H), 7.06 (dd, J = 5.0, 1.3 Hz, 1H), 3.85 (q, J = 7.2 Hz, 1H), 3.68 (s, 3H), 1.51 (d, J = 7.2 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

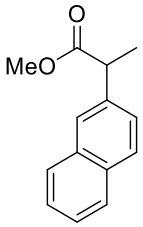
(±) Methyl 2-(thiophen-3-yl)butanoate



The title compound was prepared following the General Procedure 1 starting from methyl 2-(thiophen-3-yl)acetate (2.535 g, 16.2 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:Et_2O) to afford the title product as a colorless oil (1.821 g, 9.88 mmol, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.27 (dd, J = 4.9, 2.9 Hz, 1H), 7.13 (dd, J = 3.5, 1.3 Hz, 1H), 7.05 (dd, J = 5.0, 1.2 Hz, 1H), 3.68 (s, 3H), 3.61 (t, J =

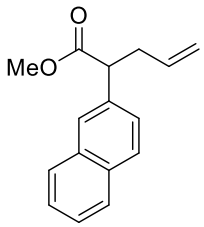
7.6 Hz, 1H), 2.13 – 1.98 (m, 1H), 1.89 – 1.74 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[218]

(±) Methyl 2-(naphthalen-2-yl)propanoate



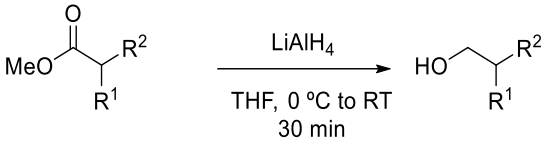
The title compound was prepared following the General Procedure 1 starting from methyl 2-(naphthalen-2-yl)acetate (1.001 g, 5 mmol, 1 eq). The crude product was obtained as colorless oil (1.053 g, 4.92 mmol, 98% yield) and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 3H), 7.74 (br s, 1H), 7.51 – 7.41 (m, 3H), 3.90 (q, J = 7.1 Hz, 1H), 3.67 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H). All spectroscopic data were consistent with those previously reported.[219]

(±) Methyl 2-(naphthalen-2-yl)pent-4-enoate



The title compound was prepared following the General Procedure 1 starting from methyl 2-(naphthalen-2-yl)acetate (703.9 mg, 3.52 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a colorless oil (660.4 mg, 2.75 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 3H), 7.75 (d, J = 1.8 Hz, 1H), 7.50 – 7.41 (m, 3H), 5.75 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H), 5.15 – 4.99 (m, 2H), 3.86 – 3.78 (m, 1H), 3.67 (s, 3H), 2.99 – 2.85 (m, 1H), 2.69 – 2.57 (m, 1H). All spectroscopic data were consistent with those previously reported.[220]

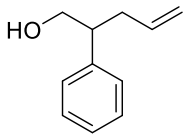
Step 3: Reduction[217]



To a suspension of $LiAlH_4$ (2 mmol/mmol) in dry THF (2.5 mL/mmol) under Argon and at 0 ºC a solution of the corresponding ester (1 eq) in dry THF (0.8 mL/mmol) was added dropwise and H_2 formation was observed. The reaction mixture was allowed to reach room temperature and stirred for 30 min (reaction completion followed by TLC). Then, the reaction was quenched with $Na_2SO_4 \cdot 10\ H_2O$ and the mixture was stirred at room temperature until full destruction of $LiAlH_4$. The suspension was finally filtered under Celite and washed with CH_2Cl_2. The solvents were removed under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel when needed.

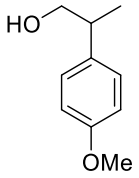
[218] Press, J.; Mcnally, J. *J. Heterocyclic Chem.* **1988**, *25*, 1571–1581.
[219] Ijima, Y.; Matoishi, K.; Terao, Y.; Doi, N.; Yanagawa, H.; Ohta, H. *Chem. Commun.* **2005**, 877–879.
[220] Yip, S. Y. Y.; Aïssa, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6870 –6873.

(±) 2-Phenylpent-4-en-1-ol



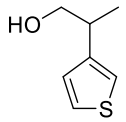
The title compound was prepared following the General Procedure starting from methyl 2-phenylpent-4-enoate (1.210 g, 6.36 mmol) and obtained as a colorless oil (878.2 mg, 5.41 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 2H), 7.32 – 7.20 (m, 3H), 5.75 (dddd, J = 16.8, 10.1, 7.5, 6.5 Hz, 1H), 5.12 – 4.94 (m, 2H), 3.90 – 3.71 (m, 2H), 3.00 – 2.84 (m, 1H), 2.61 – 2.35 (m, 2H). All spectroscopic data were consistent with those previously reported.[222]

(±) 2-(4-Methoxyphenyl)propan-1-ol



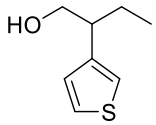
The title compound was prepared following the General Procedure starting from methyl 2-(4-methoxyphenyl)propanoate (548.8 mg, 2.83 mmol) and obtained as a yellow oil (417.2 mg, 2.51 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.71 – 3.62 (m, 1H), 2.96 – 2.85 (m, 2H), 1.25 (d, J = 7.0 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) 2-(Thiophen-3-yl)propan-1-ol



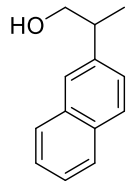
The title compound was prepared following the General Procedure starting from methyl 2-(thiophen-3-yl)propanoate (657.1 mg, 3.86 mmol) and obtained as a white foam (406 mg, 2.82 mmol, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 4.9, 3.0 Hz, 1H), 7.07 – 7.04 (m, 1H), 7.02 (dd, J = 5.0, 1.3 Hz, 1H), 3.69 (m, 1H), 3.56 (m, 1H), 3.08 (m, 1H), 1.29 (d, J = 7.0 Hz, 3H).

(±) 2-(Thiophen-3-yl)butan-1-ol



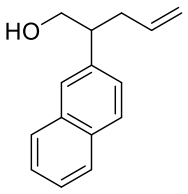
The title compound was prepared following the General Procedure starting from methyl 2-(thiophen-3-yl)butanoate (754.9 mg, 4.1 mmol) and obtained as a yellow oil (480.2 mg, 3.07 mmol, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 5.0, 3.0 Hz, 1H), 7.05 (dd, J = 3.2, 1.1 Hz, 1H), 6.98 (dd, J = 5.0, 1.3 Hz, 1H), 3.81 – 3.63 (m, 2H), 2.90 – 2.79 (m, 1H), 1.74 (ddd, J = 13.2, 7.4, 5.8 Hz, 1H), 1.65 – 1.56 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H).

(±) 2-(Naphthalen-2-yl)propan-1-ol



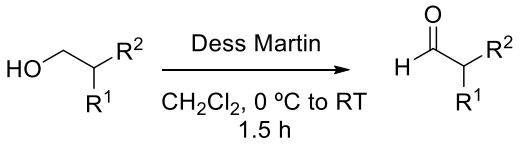
The title compound was prepared following the General Procedure starting from methyl 2-(naphthalen-2-yl)propanoate (1.053 g, 4.92 mmol)). The crude product was purified by flash column chromatography on silica gel (90:10 Hexane:EtOAc) to afford the title product as a white solid (584.9 mg, 3.14 mmol, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 3H), 7.71 – 7.66 (m, 1H), 7.50 – 7.42 (m, 2H), 7.39 (dd, J = 8.5, 1.8 Hz, 1H), 3.81 (dd, J = 7.0, 5.8 Hz, 2H), 3.21 – 3.07 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) 2-(Naphthalen-2-yl)pent-4-en-1-ol



The title compound was prepared following the General Procedure starting from methyl 2-(naphthalen-2-yl)pent-4-enoate (660.4 mg, 2.75 mmol) and obtained as a colorless oil (437.1 mg, 2.06 mmol, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 3H), 7.68 (d, J = 1.8 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.37 (dd, J = 8.5, 1.8 Hz, 1H), 5.86 – 5.66 (m, 1H), 5.14 – 4.90 (m, 2H), 3.96 – 3.81 (m, 2H), 3.16 – 2.99 (m, 1H), 2.64 – 2.44 (m, 2H). All spectroscopic data were consistent with those previously reported.[221]

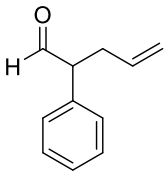
Step 4: Dess Martin oxidation[217]



To a stirred solution of the corresponding alcohol (1 eq) in CH_2Cl_2 (2.5 mL/mmol) at 0 ºC and under inert atmosphere DMP (1.1 eq) was added in one portion. The reaction mixture was allowed to warm up to room temperature and stirred until reaction completion (followed by TLC). Then, the reaction was quenched with $Na_2S_2O_3$ sat. and $NaHCO_3$ sat. The mixture was extracted with CH_2Cl_2 (x3) and the organic layers were collected, washed with H_2O (x2) and brine (x3), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude was purified by flash column chromatography on silica gel.

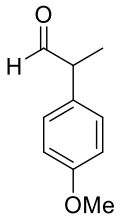
[221] Hartung, J.; Kneuer, R.; Laug, S.; Schmidt, P.; Špehar, K.; Svoboda, I.; Fuess, H. *Eur. J. Org. Chem*. **2003**, 4033–4052.

(±) 2-Phenylpent-4-enal (16C)



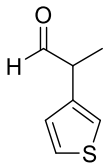
The title compound was prepared following the General Procedure starting from 2-phenylpent-4-en-1-ol (878.2 mg, 5.41 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (95:5 Hexane:EtOAc) to afford the title product as a colorless oil (618.2 mg, 3.85 mmol, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, J = 1.7 Hz, 1H), 7.43 – 7.27 (m, 3H), 7.23 – 7.16 (m, 2H), 5.72 (ddt, J = 17.1, 10.1, 6.9 Hz, 1H), 5.11 – 4.96 (m, 2H), 3.62 (ddd, J = 8.2, 7.0, 1.7 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.50 (s, 1H). All spectroscopic data were consistent with those previously reported.[222]

(±) 2-(4-Methoxyphenyl)propanal (17A)



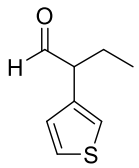
The title compound was prepared following the General Procedure starting from 2-(4-methoxyphenyl)propan-1-ol (417.2 mg, 2.51 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a colorless oil (267.1 mg, 1.63 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 1.5 Hz, 1H), 7.13 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.59 (qd, J = 7.0, 1.5 Hz, 1H), 1.42 (d, J = 7.1 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) 2-(Thiophen-3-yl)propanal (18A)



The title compound was prepared following the General Procedure starting from 2-(thiophen-3-yl)propan-1-ol (406 mg, 2.86 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a yellow oil (397.1 mg, 1.27 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 9.65 (d, J = 1.8 Hz, 1H), 7.36 (dd, J = 5.0, 2.9 Hz, 1H), 7.12 (ddd, J = 2.9, 1.3, 0.7 Hz, 1H), 6.99 (dd, J = 4.9, 1.3 Hz, 1H), 3.75 (qd, J = 7.1, 1.7 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) 2-(Thiophen-3-yl)butanal (18B)

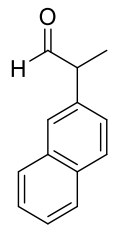


The title compound was prepared following the General Procedure starting from 2-(thiophen-3-yl)butan-1-ol (240.7 mg, 1.54 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a yellow oil (111.8 mg, 0.72 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 4.9, 3.0 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.96 (dd, J = 5.0, 1.2 Hz, 1H), 3.55 (td, J = 7.4,

[222] Farid, U.; Aiello, M. L.; Connon, S. J. *Chem. Eur. J.* **2019**, *25*, 10074–10079.

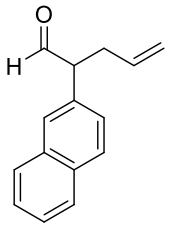
2.4 Hz, 1H), 2.09 (dq, J = 14.2, 7.3 Hz, 1H), 1.79 (dq, J = 14.9, 7.5 Hz, 1H), 0.93 (t, J = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[223]

(±) 2-(Naphthalen-2-yl)propanal (19A)



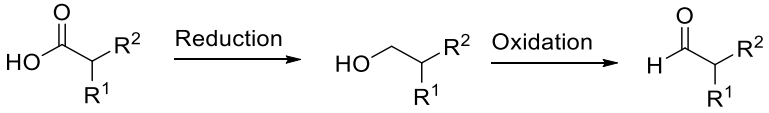
The title compound was prepared following the General Procedure starting from 2-(naphthalen-2-yl)propan-1-ol (584.9 mg, 3.14 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a white solid (448.5 mg, 2.43 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, J = 1.4 Hz, 1H), 7.89 – 7.79 (m, 3H), 7.68 (d, J = 1.8 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.32 (dd, J = 8.5, 1.8 Hz, 1H), 3.81 (qd, J = 7.1, 1.2 Hz, 1H), 1.54 (d, J = 7.0 Hz, 3H). All spectroscopic data were consistent with those previously reported.[217]

(±) 2-(Naphthalen-2-yl)pent-4-enal (19C)



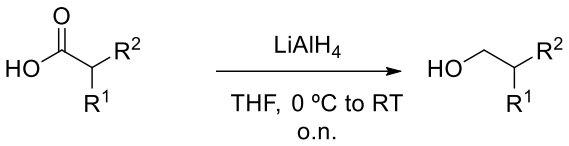
The title compound was prepared following the General Procedure starting from 2-(naphthalen-2-yl)pent-4-en-1-ol (437.1 mg, 2.06 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a colorless oil (338.8 mg, 1.61 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, J = 1.6 Hz, 1H), 7.92 – 7.76 (m, 3H), 7.70 (d, J = 1.8 Hz, 1H), 7.60 – 7.45 (m, 3H), 7.41 – 7.28 (m, 1H), 5.78 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.15 – 4.97 (m, 2H), 3.81 (ddd, J = 8.3, 6.8, 1.7 Hz, 1H), 3.05 – 2.91 (m, 1H), 2.73 – 2.55 (m, 1H). All spectroscopic data were consistent with those previously reported.[224]

PROCEDURE B: *Synthesis of **16B** and **16D***



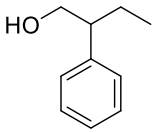
[223] Tamaru, Y.; Yamada, Y.; Yoshida, Z-I. *Tetrahedron*, **1979**, *35*, 329–340.
[224] Zhang, M.; Hu, Y.; Zhang, S. *Chem. Eur. J.* **2009**, *15*, 10732–10735.

Step 1: Reduction[225]



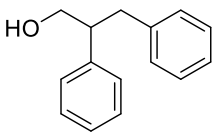
To a suspension of $LiAlH_4$ (0.975 mmol/mmol) in dry THF (0.4 mL/mmol) under Argon and at 0 ºC a solution of the corresponding ester (1 eq) in dry THF (1.45 mL/mmol) was added dropwise and H_2 formation was observed. The reaction mixture allowed to reach room temperature and stirred overnight. Then, the reaction was quenched with $Na_2SO_4 \cdot 10\ H_2O$ and stirred at room temperature until full destruction of $LiAlH_4$. The suspension was finally filtered under Celite and washed with CH_2Cl_2. The solvents were removed under reduced pressure to afford the product.

(±) 2-Phenylbutan-1-ol



The title compound was prepared following the General Procedure starting from 2-phenylbutanoic acid (1.642 g, 10 mmol) and obtained as a colorless oil (1.469 g, 9.78 mmol, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 7.27 – 7.16 (m, 3H), 3.85 – 3.65 (m, 2H), 2.69 (ddt, J = 9.2, 7.8, 5.7 Hz, 1H), 1.83 – 1.65 (m, 1H), 1.65 – 1.48 (m, 1H), 1.35 – 1.22 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[226]

(±) 2,3-Diphenylpropan-1-ol



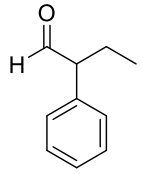
The title compound was prepared following the General Procedure starting from 2,3-diphenylpropionic acid (1.358 g, 6 mmol) and obtained as a colorless oil (1.261 g, 5.94 mmol, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 6.99 (m, 10H), 3.80 (d, J = 6.1 Hz, 2H), 3.09 (dd, J = 12.6, 5.8 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.91 (dd, J = 13.0, 7.2 Hz, 1H). All spectroscopic data were consistent with those previously reported.[227]

[225] Stratakis, M.; Kalaitzakis, D.; Stavroulakis, D.; Kosmas, G.; Tsangarakis C. *Org. Lett.* **2003**, *5*, 3471–3474.
[226] Lee, Y.; Park, J.; Cho, S. H. *Angew. Chem. Int. Ed.* **2018**, *57*, 12930–12934.
[227] Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2011**, *133*, 4260–4263.

Step 2: Dess Martin oxidation

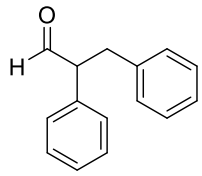
The General Procedure on page 174 was followed.

(±) 2-Phenylbutanal (16B)



The title compound was prepared following the General Procedure starting from 2-phenylbutan-1-ol (1.469 g, 9.78 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (98:2 Hexane:EtOAc) to afford the title product as a colorless oil (1.121 g, 7.56 mmol, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, J = 2.1 Hz, 1H), 7.43 – 7.27 (m, 3H), 7.23 – 7.15 (m, 2H), 3.41 (ddd, J = 8.4, 6.6, 2.1 Hz, 1H), 2.21 – 1.99 (m, 1H), 1.86 – 1.68 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[228]

(±) 2,3-Diphenylpropanal (16D)

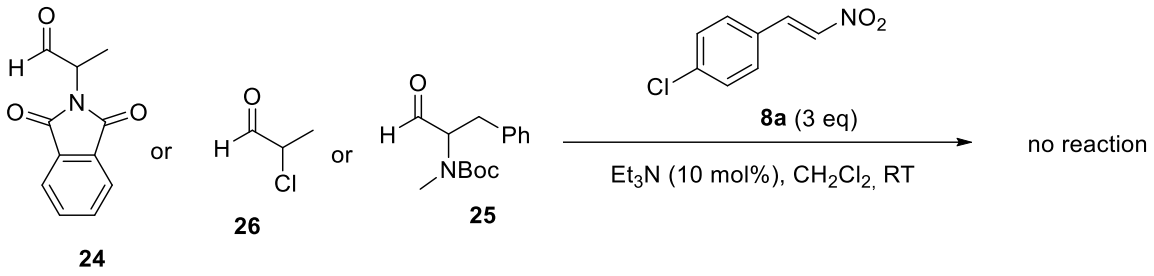


The title compound was prepared following the General Procedure starting from 2,3-diphenylpropan-1-ol (1.261 g, 5.94 mmol, 1 eq). The crude product was purified by flash column chromatography on silica gel (95:5 Hexane:EtOAc) to afford the title product as a white solid (526.6 mg, 2.50 mmol, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, J = 1.5 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.24 – 7.09 (m, 5H), 7.09 – 7.01 (m, 2H), 3.84 (ddd, J = 8.1, 6.7, 1.5 Hz, 1H), 3.48 (dd, J = 14.0, 6.8 Hz, 1H), 2.98 (dd, J = 14.0, 7.9 Hz, 1H). All spectroscopic data were consistent with those previously reported.[229]

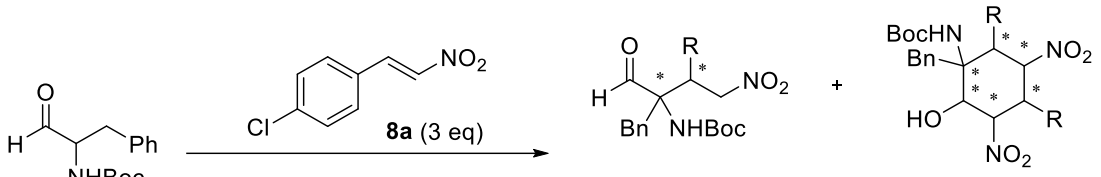
[228] Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, *20*, 3281–3291.
[229] Sato, S.; Takeda, N.; Miyoshi, T.; Ueda, M.; Miyata, O. *Eur. J. Org. Chem.* **2015**, 3899–3904.

5.3.2. Catalytic conjugate addition of α-amino aldehydes to nitroolefins

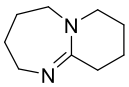
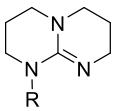
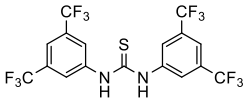
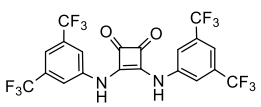
5.3.2.1. Preliminary explorations with achiral bases



24 **26** **25**

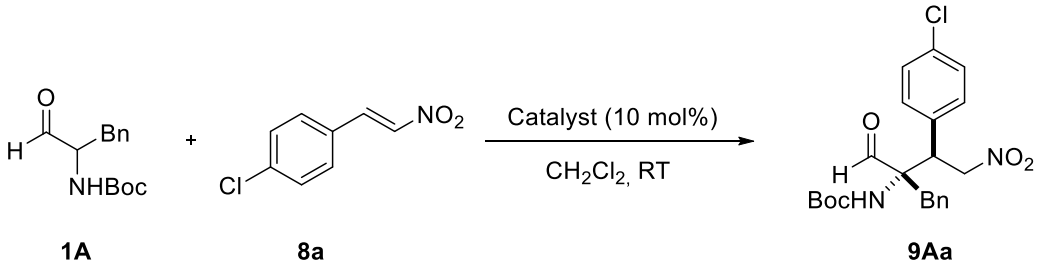


1A

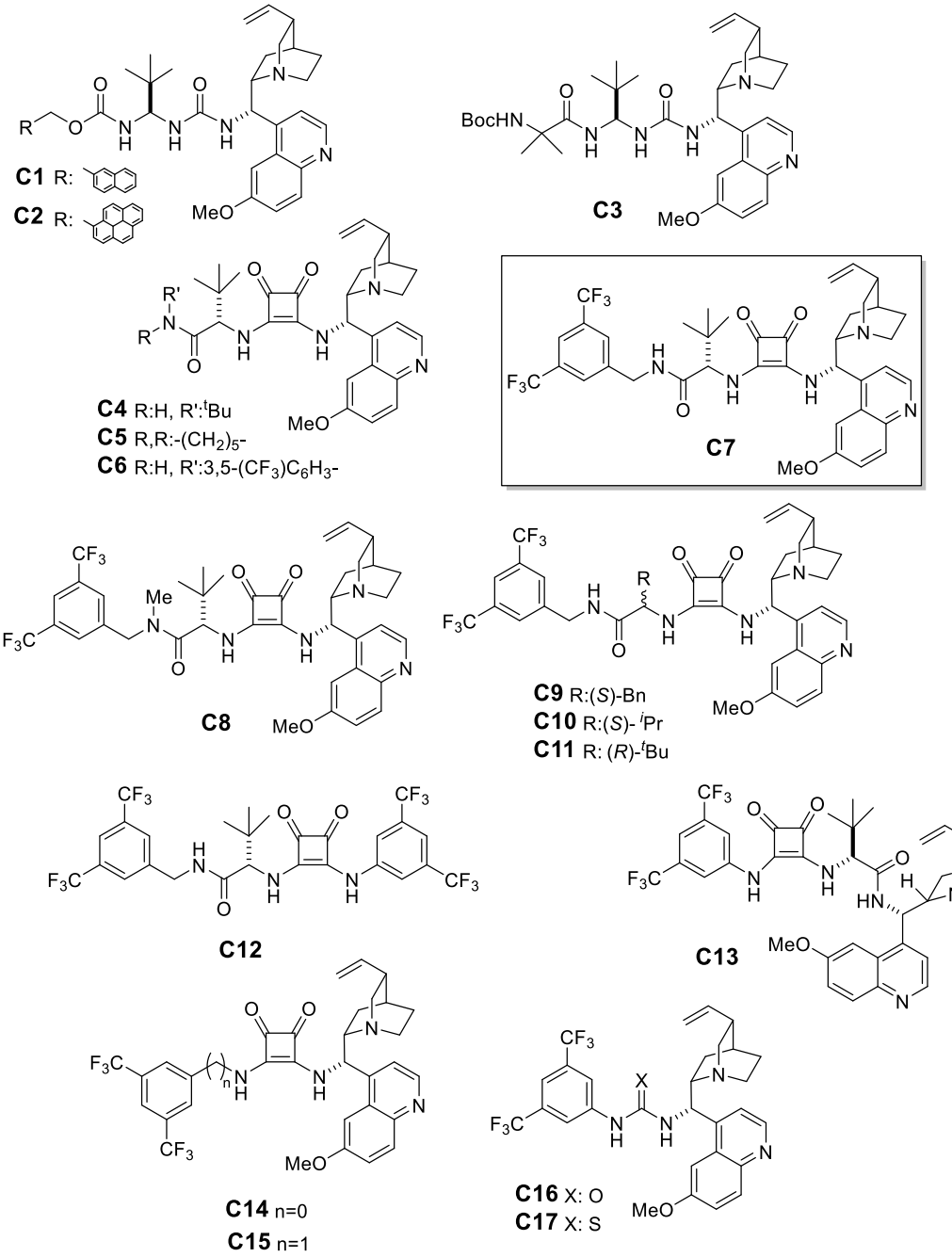
Entry	Cat.	Base (mol%)	T (ºC)	T(h)	Conv. (%)[b]	9Aa (dr)[c]	27a
1	Et_3N	20	RT	17	31	>95 (58:42)	<5
				41	62	84 (56:44)	16
2	$^{i}Pr_2EtN$	20	RT	41	21	>99 (44:56)	<5
3	 (DBU)	10	0	1.5	<5[d]	0	0
4	 R:Me, MTBD	10	RT	20	<5[d]	0	0
	R:H, TBD		0	22	<5[d]	0	0
5	Et_3N / 	20	RT	15	48	>99 (51:49)	<5
6	Et_3N / 	20	RT	15	69	>95 (45:55)	<5

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde 3:1). [b] Conversion determined by the disappearance of the starting aldehyde. [c] Determined by ^{1}H-NMR analysis. [d] Nitrostyrene polymerized.

*5.3.2.2. Catalyst screening for the model reaction between **1A** and **8a***



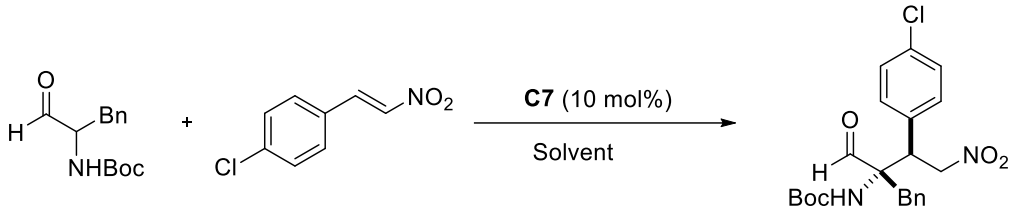
1A **8a** **9Aa**



Entry	Cat.	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	dr[d]	*ee*[e]
1	**C1**	RT	63	88 (61)	nd	39:61	nd
2	**C2**	RT	39	29 (2)	nd	64:36	nd
3	**C3**	RT	39	71(40)	31	50:50	37
4	**C4**	RT	66	>99(17)	81	83:17	89
5	**C5**	RT	91	>99(5)	70	89:11	84
6	**C6**	RT	45	>99(8)	77	89:11	98
7	**C7**	RT	24	96(9)	91	90:10	98
8	**C8**	RT	23	97(2)	81	85:15	97
9	**C9**	RT	15	90(3)	70	82:18	91
10	**C10**	RT	24	88(12)	69	86:14	94
11	**C11**	RT	15	98(5)	72	86:14	90
12	**C12**	RT	15	0 [f]	0	--	--
13	**C13**[g]	RT	120	58(no)	33	70:30	25
14	**C14**[g]	RT	21	92(28)	55	68:32	81
15	**C15**	RT	16	68(no)	64	66:34	73
16	**C16**	RT	20	79(no)	62	48:52	nd
17	**C17**	RT	18	44(no)	nd	73:27	nd

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of product **27a** coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC. nd: not determined. no: not observed. [f] In the presence of Et_3N (10 mol%) after 3 h 26% conversion and 57:43 dr were observed. In the presence of *i*Pr_2EtN (10 mol%) after 1 h 23% conversion and 52:48 dr were detected. [g] 20 mol% catalyst was used.

*5.3.2.3. Solvent screening for the reaction between **1A** and **8a** with **C5***

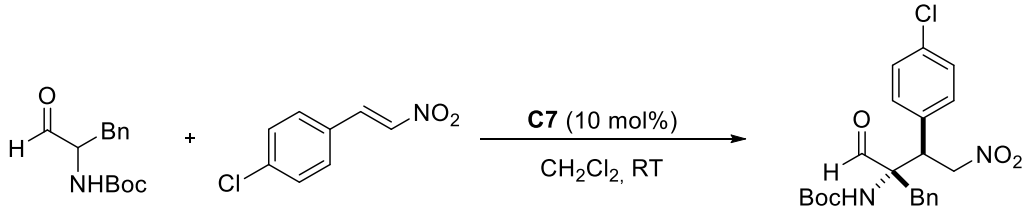


1A **8a** **9Aa**

Entry	Solvent	Polarity index[123]	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*ee*[e]
1	**Toluene**	2.4	RT	40	92(16)	77	87:13	93
2	**CH_2Cl_2**	3.1	RT	24	96(9)	91	90:10	98
3	**1,2-DCE**	3.5	RT	24	95(12)	92	90:10	98
4	**THF**	4.0	RT	17	56(no)	31	89:11	98
5	**$CHCl_3$**	4.1	RT	40	89(12)	nd	83:17	nd
6	**CH_3CN**	5.8	RT	39	94(2)	81	90:10	98
7	**CH_2Cl_2**	3.1	0ªC	114	99(22)	67	83:17	96

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of product **27a** coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC. nd: not determined. no: not observed.

*5.3.2.4. (±)-*N*-Boc phenylalaninal **(±)-1A** vs (S)-*N*-Boc phenylalaninal **(S)-1A** as pronucleophile*

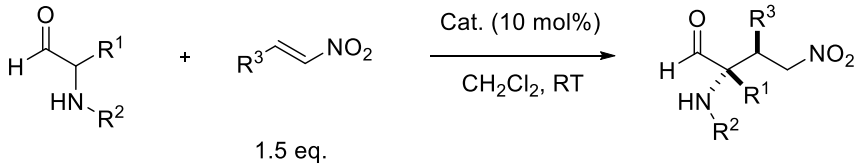


1A **8a** **9Aa**

Entry	Nucleophile	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	dr[d]	*ee*[e]
1	**(*S*)-1A**	RT	24	96(9)	91	90:10	98
2	***Rac*-1A**	RT	29	95(8)	61	90:10	97

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 1.5:1:0.1). [b] Determined by the disappearance of the starting aldehyde. In brackets, the percentage of the product coming from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization is indicated. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

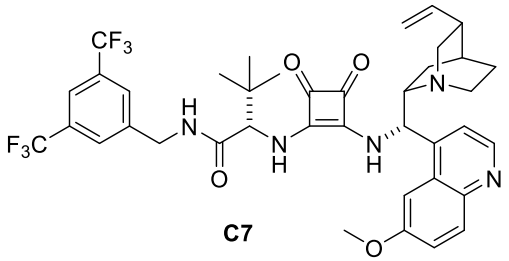
5.3.2.5. Reaction scope



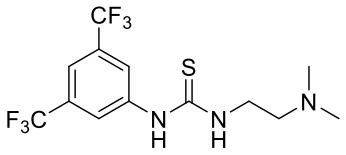
9 R^1: Bn, **10** R^1: Me, **11** R^1: Pr, **12** R^1: ^{i}Bu,
13 R^1: 3,4-$(MeO)_2$-Bn, **14** R^1: BnO-CH_2,
15 R^1: 4-MeOBn

A R^2: Boc, **B** R^2: Cbz, **C** R^2: Fmoc,
D R^2: 2-pyridyl-CO-, **E** R^2: Ph-CO-,
F R^2: 2-MeC_6H_4-CO-, **G** R^2: 4-BrC_6H_4-CO-,
H R^2: Ph-CH=CH-CO-, **I** R^2: CH_3-CO-

a R^3: *p*-Cl-C_6H_4-, **b** R^3: C_6H_5-, **c** R^3: *p*-Me-C_6H_4-,
d R^3: *m*-MeO-C_6H_4, **e** R^3: *p*-Br-C_6H_4-,
f R^3: *o,p*-$Me_2C_6H_3$-, **g** R^3: Ph-CH=CH-,
h R^3: Cy, **i** R^3:Ph−C≡C-



C7



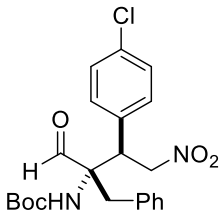
C31

GENERAL PROCEDURE:

The corresponding amino aldehyde (0.2 mmol, 1 eq), the nitroolefin (0.3 mmol, 1.5 eq) and catalyst **C7** (15.16 mg, 0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting solution was stirred at room temperature for the indicated time. The reaction completion was followed by ^{1}H NMR and, after the indicated time, the mixture was directly submitted to flash column chromatography on silica gel. Reaction conversions and diastereomeric ratios were determined by ^{1}H NMR analysis. Enantiomeric ratios were determined by chiral HPLC.

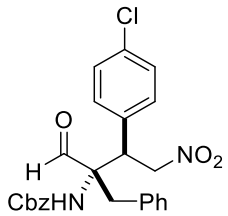
The corresponding racemic reactions were run following the above procedure using achiral catalyst **C31** (30 mol%).

tert-Butyl ((2*S*,3*S*)-2-benzyl-3-(4-chlorophenyl)-4-nitro-1-oxobutan-2-yl)carbamate (9Aa)



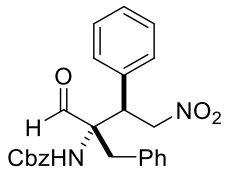
Prepared following the General Procedure starting from α-amino aldehyde **1A**, nitroolefin **8a** and catalyst **C7** to afford a 90:10 mixture of diastereomers. The major diastereomer was isolated as a white foam (78.79 mg, 0.182 mmol, 91% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=0.5 mL/min). Retention times: 46.1 min (major) and 54.0 min (minor) $[\alpha]_D^{24}$ = –41.46º (c=1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.38 – 7.27 (m, 5H), 7.18 (d, J = 8.4 Hz, 2H), 7.05 – 6.98 (m, 2H), 5.03 (dd, J = 13.3, 3.3 Hz, 1H), 4.87 (s, 1H), 4.76 (t, J = 12.6 Hz, 1H), 4.34 – 4.27 (m, 1H), 2.99 (d, J = 14.0 Hz, 1H), 2.75 (d, J = 14.1 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 130.9, 130.3, 129.4, 129.0, 128.0, 76.9, 48.9, 42.2, 28.4. UPLC-DAD-QTOF: $C_{22}H_{25}ClN_2O_5Na$ $[M+Na]^+$ calcd.: 455.1350, found: 455.1347.

Benzyl ((2*S*,3*S*)-2-benzyl-3-(4-chlorophenyl)-4-nitro-1-oxobutan-2-yl)carbamate (9Ba)



Prepared following the General Procedure starting from α-amino aldehyde **1B,** nitroolefin **8a** and catalyst **C7** to afford a 92:8 mixture of diastereomers. The major diastereomer was isolated as a white foam (56.96 mg, 0.122 mmol, 61% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min). Retention times: 63.0 min (minor) and 96.2 min (major) $[\alpha]_D^{25}$ = –65.75º (c=0.50, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.46 – 7.31 (m, 5H), 7.30 – 7.26 (m, 2H), 7.25 (d, J = 1.6 Hz, 2H), 7.15 – 7.04 (m, 3H), 6.96 (m, 2H), 5.20 – 4.96 (m, 4H), 4.72 (t, J = 12.6 Hz, 1H), 4.31 (dd, J = 11.8, 3.5 Hz, 1H), 3.02 (d, J = 14.1 Hz, 1H), 2.76 (d, J = 14.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 155.8, 135.6, 134.8, 132.9, 132.5, 130.8, 130.2, 129.4, 129.0, 128.91, 128.6, 128.0, 110.1, 76.6, 68.0, 65.7, 48.9, 42.2. UPLC-DAD-QTOF: $C_{25}H_{24}ClN_2O_5$ $[M+H]^+$ calcd.: 467.1374, found: 467.1381.

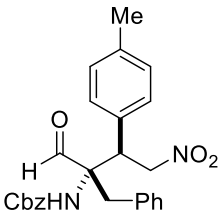
Benzyl ((2*S*,3*S*)-2-benzyl-4-nitro-1-oxo-3-phenylbutan-2-yl)carbamate (9Bb)



Prepared following the General Procedure starting from α-amino aldehyde **1B,** nitroolefin **8b** and catalyst **C7** to afford a 92:8 mixture of diastereomers. The major diastereomer was isolated as a white foam (56.22 mg, 0.13 mmol, 65% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 90:10,

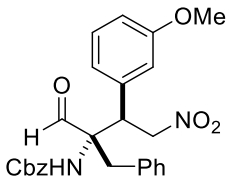
flow rate= 1 mL/min Retention times: 24.0 min (minor) and 31.9 min (major). $[\alpha]_D^{24}$ = –43.92º (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.46 – 7.28 (m, 7H), 7.25 (dd, J = 5.0, 1.8 Hz, 4H), 7.19 – 7.11 (m, 2H), 6.96 (dd, J = 6.4, 3.1 Hz, 2H), 5.20 – 4.97 (m, 4H), 4.76 (t, J = 12.6 Hz, 1H), 4.29 (dd, J = 11.8, 3.6 Hz, 1H), 3.06 (d, J = 14.2 Hz, 1H), 2.77 (d, J = 14.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 155.9, 135.7, 134.3, 132.8, 130.3, 129.4, 129.1, 128.9, 128.8, 128.8, 128.8, 128.5, 127.9, 76.7, 67.8, 65.8, 49.4, 41.9. UPLC-DAD-QTOF: $C_{25}H_{25}N_2O_5$ $[M+H]^+$ calcd.: 433.1763, found: 433.1766.

Benzyl ((2*S*,3*S*)-2-benzyl-4-nitro-1-oxo-3-(*p*-tolyl)butan-2-yl)carbamate (9Bc)



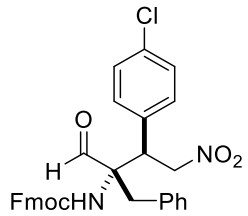
Prepared following the General Procedure starting from α-amino aldehyde **1B**, nitroolefin **8c** and catalyst **C7** to afford a 92:8 mixture of diastereomers. The major diastereomer was isolated as a white solid (60.72 mg, 0.136 mmol, 68% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 90/10, flow rate= 1 mL/min). Retention times: 25.4 min (minor) and 35.0 min (major). m.p.: 144-146 ºC. $[\alpha]_D^{24}$ = –46.95º (c=1.00, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.39 (td, J = 7.2, 2.1 Hz, 4H), 7.24 (dd, J = 5.0, 1.8 Hz, 4H), 7.12 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 6.96 (dd, J = 6.4, 3.1 Hz, 2H), 5.18 – 4.94 (m, 4H), 4.73 (t, J = 12.5 Hz, 1H), 4.21 (dd, J = 12.0, 3.6 Hz, 1H), 3.06 (d, J = 14.2 Hz, 1H), 2.79 (d, J = 14.2 Hz, 1H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 155.9, 138.6, 135.8, 132.9, 131.0, 130.3, 129.9, 129.3, 128.9, 128.8, 128.8, 128.5, 127.8, 76.8, 67.8, 65.8, 49.0, 41.7, 21.2. UPLC-DAD-QTOF: $C_{26}H_{27}N_2O_5$ $[M+H]^+$ calcd.: 447.1920, found: 447.1917.

Benzyl ((2*S*,3*S*)-2-benzyl-3-(3-methoxyphenyl)-4-nitro-1-oxobutan-2-yl)carbamate (9Bd)



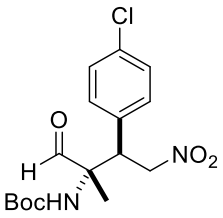
Prepared following the General Procedure starting from α-amino aldehyde **1B**, nitroolefin **8d** and catalyst **C7** to afford a 91:9 mixture of diastereomers. The major diastereomer was isolated as a white foam (54.6 mg, 0.118 mmol, 59% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min). Retention times: 14.0 min (minor) and 18.5 min (major). $[\alpha]_D^{24}$ = –33.81º (c=1.00, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.45 – 7.31 (m, 5H), 7.26 – 7.20 (m, 4H), 6.96 (dd, J = 6.4, 3.1 Hz, 2H), 6.88 – 6.81 (m, 1H), 6.76 – 6.67 (m, 2H), 5.20 – 4.93 (m, 4H), 4.77 – 4.64 (m, 1H), 4.23 (dd, J = 11.8, 3.5 Hz, 1H), 3.75 (s, 3H), 3.06 (d, J = 14.2 Hz, 1H), 2.77 (d, J = 14.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 159.9, 155.9, 135.8, 132.81, 130.3, 130.2, 128.9, 128.8, 128.5, 127.8, 121.6, 115.7, 113.7, 76.7, 67.8, 65.7, 55.3, 49.3, 42.0. UPLC-DAD-QTOF: $C_{26}H_{27}N_2O_6$ $[M+H]^+$ calcd.: 463.1869, found: 463.1862.

(9*H*-Fluoren-9-yl)methyl ((2*S*,3*S*)-2-benzyl-3-(4-chlorophenyl)-4-nitro-1-oxobutan-2-yl) carbamate (9Ca)



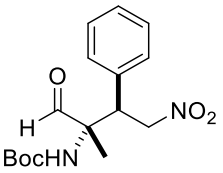
Prepared following the General Procedure starting from α-amino aldehyde **1C**, nitroolefin **8a** and catalyst **C7** to afford a 96:4 mixture of diastereomers. The title compound (dr 96:4) was isolated as a white foam (85.0 mg, 0.153 mmol, 77% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times for the major diastereomer: 39.1 min (minor) and 49.3 min (major) and for minor diastereomer: 42.2 min (major) and 46.1 min (minor). $[\alpha]_D^{24}$ = –16.82º (c=1.00, 99% *ee*, 96:4 dr, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.83 (dd, J = 7.3, 2.8 Hz, 2H), 7.54 (t, J = 7.9 Hz, 2H), 7.49 – 7.39 (m, 2H), 7.39 – 7.30 (m, 2H), 7.26 – 7.19 (m, 5H), 6.90 (dd, J = 6.4, 2.8 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.96 (dd, J = 11.1, 4.9 Hz, 1H), 4.83 (dd, J = 13.5, 3.2 Hz, 1H), 4.75 (s, 1H), 4.52 (dd, J = 11.1, 4.7 Hz, 1H), 4.40 – 4.28 (m, 1H), 4.18 (t, J = 4.6 Hz, 2H), 2.85 (d, J = 14.1 Hz, 1H), 2.40 (d, J = 14.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 155.8, 143.5, 143.0, 141.7, 134.7, 132.9, 132.16, 130.9, 130.2, 129.3, 128.97, 128.39, 128.08, 128.00, 127.58, 127.30, 125.01, 124.68, 120.25, 120.15, 76.33, 65.82, 64.8, 48.9, 47.8, 43.4. UPLC-DAD-QTOF: $C_{32}H_{28}ClN_2O_5$ $[M+H]^+$ calcd.: 555.1687, found: 555.1688.

***tert*-Butyl ((2*S*,3*S*)-3-(4-chlorophenyl)-2-methyl-4-nitro-1-oxobutan-2-yl)carbamate (10Aa)**



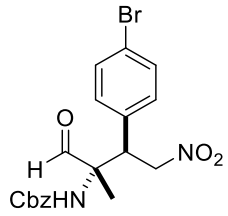
Prepared following the General Procedure starting from α-amino aldehyde **2A,** nitroolefin **8a** and catalyst **C7** to afford a 90:10 mixture of diastereomers. The major diastereomer was isolated as a white foam (41.8 mg, 0.117 mmol, 59% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate= 0.5 mL/min). Retention times: 43.0 min (minor) and 54.5 min (major). $[\alpha]_D^{25}$ = –74.29º (c=0.25, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.05 – 8.00 (m, 1H), 7.46 – 7.42 (m, 1H), 7.36 – 7.32 (m, 2H), 7.20 – 7.16 (m, 2H), 5.04 (dd, J = 13.4, 3.6 Hz, 1H), 4.63 (dd, J = 13.4, 12.1 Hz, 1H), 4.13 (dd, J = 12.0, 3.6 Hz, 1H), 1.50 (s, 9H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 133.4, 131.7, 130.7, 129.3, 129.0, 110.1, 76.6, 62.6, 48.4, 29.9, 28.4, 22.5. UPLC-DAD-QTOF: $C_{16}H_{21}ClN_2O_5Na$ $[M+Na]^+$ calcd.: 379.1037, found: 379.1041.

tert-Butyl ((2*S*,3*S*)-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl)carbamate (10Ab)



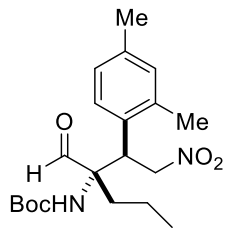
Prepared following the General Procedure starting from α-amino aldehyde **2A,** nitroolefin **8b** and catalyst **C7** to afford an 81:19 mixture of diastereomers. The major diastereomer was isolated as a white foam (47.7 mg, 0.148 mmol, 74% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times: 17.6 min (minor) and 20.4 min (major). $[\alpha]_D^{25}$ = 6.20º (c=1.00, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.39 – 7.29 (m, 3H), 7.25 – 7.19 (m, 2H), 5.04 (dd, J = 13.3, 3.7 Hz, 1H), 4.74 (s, 1H), 4.68 (dd, J = 13.3, 12.1 Hz, 1H), 4.12 (dd, J = 12.0, 3.7 Hz, 1H), 1.50 (s, 9H), 0.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 155.3, 134.8, 129.3, 129.0, 128.5, 81.8, 76.8, 62.7, 49.0, 28.4, 22.5. UPLC-DAD-QTOF: $C_{16}H_{23}N_2O_5Na$ $[M+Na]^+$ calcd.: 345.1426, found: 345.1438.

Benzyl ((2*S*,3*S*)-3-(4-bromophenyl)-2-methyl-4-nitro-1-oxobutan-2-yl)carbamate (10Be)



Prepared following the General Procedure starting from α-amino aldehyde **2B,** nitroolefin **8e** and catalyst **C7** to afford an 86:14 mixture of diastereomers. The major diastereomer was isolated as a white foam (56.15 mg, 0.129 mmol, 65% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min) after silica column flash chromatography (Hexane:EtOAc 90:10). Retention times: 17.9 min (minor) and 23.4 min (major). $[\alpha]_D^{24}$ = –58.03º (c=0.50, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.52 – 7.28 (m, 7H), 7.03 (d, J = 8.4 Hz, 2H), 5.16 (s, 2H), 4.97 (br s, 1H), 4.66 – 4.53 (m, 1H), 4.11 (dd, J = 12.0, 3.5 Hz, 1H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 155.9, 135.5, 133.6, 132.2, 130.9, 129.0, 128.9, 128.7, 122.8, 76.2, 68.2, 62.9, 48.4, 22.4. UPLC-DAD-QTOF: $C_{19}H_{20}BrN_2O_5$ $[M+H]^+$ calcd.: 435.0556, found: 435.0541.

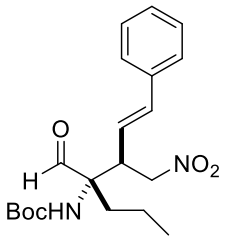
tert-Butyl ((2*S*,3*S*)-2-(2,4-dimethylphenyl)-3-formyl-1-nitrohexan-3-yl)carbamate (11Af)



Prepared following the General Procedure starting from α-amino aldehyde **3A** and nitroolefin **8f**, but using 20 mol% of catalyst **C7**, to afford a 91:9 mixture of diastereomers. The major diastereomer was isolated as a white foam (60.55 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 99:1, flow rate= 1 mL/min). Retention times: 12.5 min (minor) and 15.0 min (major). $[\alpha]_D^{25}$ = –23.12º (c=1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 5.7 Hz, 1H), 4.96 (d, J = 13.2 Hz, 2H), 4.71 – 4.59 (m, 1H), 4.52 (dd, J = 11.8, 3.4 Hz,

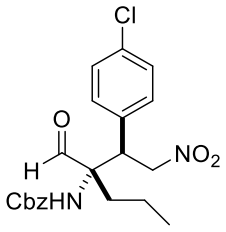
1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.50 (s, 9H), 1.44 – 1.20 (m, 4H), 0.79 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 155.6, 138.3, 137.7, 132.3, 130.41, 127.2, 126.9, 81.4, 77.8, 66.2, 43.1, 37.9, 28.4, 21.1, 20.1, 16.5, 14.5. UPLC-DAD-QTOF: $C_{20}H_{30}N_2O_5Na$ $[M+Na]^+$ calcd.: 401.2052, found: 401.2052.

tert-Butyl ((3*S*,4*S*,*E*)-4-formyl-3-(nitromethyl)-1-phenylhept-1-en-4-yl)carbamate (11Ag)



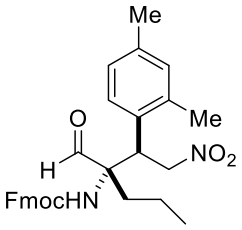
Prepared following the General Procedure starting from α-amino aldehyde **3A**, nitroolefin **8g** and catalyst **C7** to afford an 88:12 mixture of diastereomers. The title compound (dr 88:12) was isolated as a yellow foam (50.44 mg, 0.134 mmol, 67% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess for the major diastereomer was found to be 97% and was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min). Retention times: 17.3 min (minor) and 23.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.38 – 7.24 (m, 5H), 6.54 (d, J = 15.8 Hz, 1H), 6.06 (dd, J = 15.7, 10.0 Hz, 1H), 5.09 – 4.99 (m, 1H), 4.76 (dd, J = 12.3, 3.5 Hz, 1H), 4.31 (dd, J = 12.3, 11.2 Hz, 1H), 3.66 (td, J = 10.6, 3.5 Hz, 1H), 1.86 – 1.70 (m, 1H), 1.67 – 1.54 (m, 1H), 1.46 (s, 9H), 1.33 – 1.21 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 155.2, 136.6, 136.1, 128.7, 128.4, 126.8, 122.1, 81.4, 77.2, 65.5, 46.4, 36.6, 28.3, 16.1, 14.2. UPLC-DAD-QTOF: $C_{20}H_{28}N_2O_5Na$ $[M+Na]^+$ calcd.: 399.1896, found: 399.1892.

Benzyl ((2*S*,3*S*)-2-(4-chlorophenyl)-3-formyl-1-nitrohexan-3-yl)carbamate (11Ba)



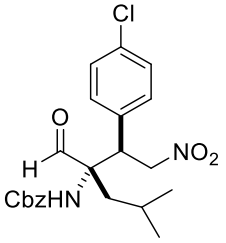
Prepared following the General Procedure starting from α-amino aldehyde **3B**, nitroolefin **8a** and catalyst **C7** to afford a 96:4 mixture of diastereomers. The major diastereomer was isolated as a white foam (54.8 mg, 0.13 mmol, 65% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak ID Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times: 24.0 min (minor) and 33.4 min (major). $[\alpha]_D^{24}$ = –39.30º (c=1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.48 – 7.32 (m, 5H), 7.29 – 7.22 (m, 2H), 7.10 – 7.03 (m, 2H), 5.16 (s, 2H), 5.06 (s, 1H), 4.96 (dd, J = 13.4, 3.5 Hz, 1H), 4.61 (t, J = 12.7 Hz, 1H), 4.20 (dd, J = 12.0, 3.5 Hz, 1H), 1.53 – 1.33 (m, 2H), 1.33 – 1.17 (m, 2H), 0.79 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 155.8, 135.6, 134.5, 133.1, 130.5, 130.2, 129.2, 128.9, 128.6, 76.8, 68.0, 65.9, 47.2, 37.6, 16.3, 14.1. UPLC-DAD-QTOF: $C_{21}H_{24}ClN_2O_5$ $[M+H]^+$ calcd.: 419.1374, found: 419.1368.

(9*H*-Fluoren-9-yl)methyl ((2*S*,3*S*)-2-(2,4-dimethylphenyl)-3-formyl-1-nitrohexan-3-yl) carbamate (11Cf)



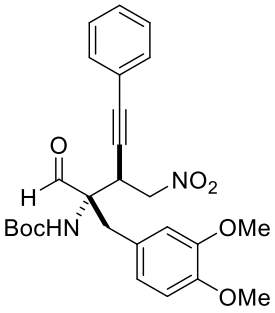
Prepared following the General Procedure starting from α-amino aldehyde **3C** and nitroolefin **8f**, but using 20 mol% of catalyst **C7**, to afford a 91:9 mixture of diastereomers. The major diastereomer was isolated as a white foam (80.0 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times: 33.5 min (minor) and 39.1 min (major). $[\alpha]_D^{24}$ = 1.00º (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.63 (dd, J = 9.9, 7.1 Hz, 2H), 7.50 – 7.34 (m, 4H), 6.93 (s, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.51 (d, J = 7.9 Hz, 1H), 4.97 (dd, J = 11.0, 4.9 Hz, 1H), 4.83 – 4.75 (m, 2H), 4.61 (dd, J = 11.0, 4.6 Hz, 1H), 4.47 – 4.38 (m, 1H), 4.23 (t, J = 4.9 Hz, 1H), 2.27 (d, J = 5.0 Hz, 6H), 1.16 – 1.03 (m, 4H), 0.78 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 155.9, 143.7, 143.2, 138.3, 132.2, 128.34, 128.05, 127.59, 127.24, 126.84, 124.90, 124.75, 120.22, 66.17, 65.90, 47.92, 42.99, 35.78, 24.92, 23.16, 21.10, 20.10, 13.82. UPLC-DAD-QTOF: $C_{30}H_{33}N_2O_5$ $[M+Na]^+$ calcd.: 501.2345, found: 501.2371.

Benzyl ((2*S*,3*S*)-2-(4-chlorophenyl)-3-formyl-5-methyl-1-nitrohexan-3-yl)carbamate (12Ba)



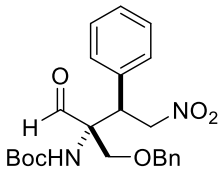
Prepared following the General Procedure starting from α-amino aldehyde **4B**, nitroolefin **8a** and catalyst **C7** to afford a 95:5 mixture of diastereomers. The major diastereomer was isolated as a white foam (53.1 mg, 0.123 mmol, 61% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times: 16.0 min (minor) and 18.8 min (major). $[\alpha]_D^{24}$ = –27.67º (c=1.00, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.48 – 7.34 (m, 5H), 7.26 – 7.20 (m, 2H), 7.01 (d, J = 8.5 Hz, 2H), 5.15 (d, J = 2.9 Hz, 2H), 4.96 (dd, J = 13.3, 3.7 Hz, 1H), 4.66 (t, J = 12.6 Hz, 1H), 4.27 (dd, J = 12.0, 3.6 Hz, 1H), 1.73 (dt, J = 12.8, 6.4 Hz, 1H), 1.61 (dd, J = 14.3, 6.1 Hz, 1H), 1.49 (dd, J = 14.3, 6.2 Hz, 1H), 0.88 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 155.6, 135.7, 134.5, 133.1, 130.6, 130.3, 129.1, 128.9, 128.6, 76.5, 67.8, 66.4, 48.9, 44.9, 24.4, 24.1, 23.6. UPLC-DAD-QTOF: $C_{22}H_{26}ClN_2O_5$ $[M+H]^+$ calcd.: 433.1530, found: 433.1532.

tert-Butyl ((2*S*,3*S*)-2-(3,4-dimethoxybenzyl)-3-(nitromethyl)-1-oxo-5-phenylpent-4-yn-2-yl) carbamate (13Ai)



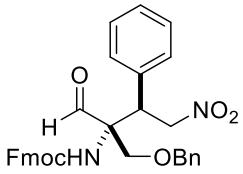
Prepared following the General Procedure starting from α-amino aldehyde **5A,** nitroolefin **8i** and catalyst **C7** to afford a 95:5 mixture of diastereomers. The major diastereomer was isolated as an orange foam (51.15 mg, 0.106 mmol, 53% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min). Retention times: 23.5 min (minor) and 36.0 min (major). $[\alpha]_D^{24}$ = 26.23º (c=0.50, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.50 – 7.29 (m, 8H), 5.16 (s, 1H), 4.84 (d, J = 13.9 Hz, 1H), 4.37 (d, J = 12.1 Hz, 1H), 4.05 (dd, J = 11.1, 3.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.19 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 155.3, 149.1, 148.9, 132.0, 129.1, 128.6, 124.7, 123.0, 122.0, 113.6, 111.4, 83.8, 82.0, 76.4, 65.6, 56.1, 56.0, 40.9, 37.2, 28.3. UPLC-DAD-QTOF: $C_{26}H_{30}N_2O_7Na$ $[M+Na]^+$ calcd.: 505.1951, found: 505.1957.

tert-Butyl ((2*R*,3*S*)-1-(benzyloxy)-2-formyl-4-nitro-3-phenylbutan-2-yl)carbamate (14Ab)



Prepared following the General Procedure starting from α-amino aldehyde **6A**, nitroolefin **8b** and catalyst **C7** to afford an 89:11 mixture of diastereomers. The major diastereomer was isolated as a white foam (48.01 mg, 0.112 mmol, 56% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak ID Hexane:^{i}PrOH 98:2, flow rate= 0.5 mL/min). Retention times: 50.8 min (minor) and 63.8 min (major). $[\alpha]_D^{24}$ = –12.03º (c=1.00, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.38 – 7.27 (m, 6H), 7.20 (ddd, J = 6.8, 4.6, 2.6 Hz, 4H), 5.07 – 4.92 (m, 2H), 4.75 (dd, J = 13.3, 11.8 Hz, 1H), 4.42 – 4.30 (m, 3H), 3.27 (q, J = 9.6 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 134.5, 129.3, 129.0, 128.7, 128.5, 128.4, 128.0, 76.8, 73.8, 46.0, 29.8, 28.3.). UPLC-DAD-QTOF: $C_{23}H_{28}N_2O_6Na$ $[M+Na]^+$ calcd.: 451.1845, found: 451.1849. UPLC-DAD-QTOF: $C_{23}H_{29}N_2O_6$ $[M+H]^+$ calcd.: 429.1981, found: 429.1963.

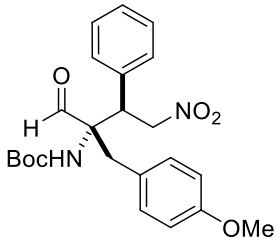
(9*H*-Fluoren-9-yl)methyl ((2*R*,3*S*)-1-(benzyloxy)-2-formyl-4-nitro-3-phenylbutan-2-yl) carbamate (14Cb)



Prepared following the General Procedure starting from α-amino aldehyde **6C**, nitroolefin **8b** and catalyst **C7** to afford essentially a single diastereomer (99:1). The major diastereomer was isolated as a white foam (79.2 mg, 0.144 mmol, 72% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10).

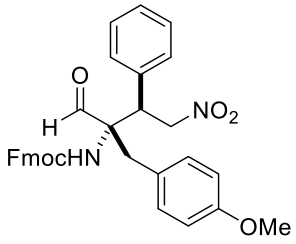
The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min). Retention times: 33.0 min (minor) and 36.7 min (major). $[\alpha]_D^{23}$ = 22.3 (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.83 (dd, J = 7.2, 3.7 Hz, 2H), 7.62 (dd, J = 13.8, 7.1 Hz, 2H), 7.48 – 7.35 (m, 4H), 7.35 – 7.27 (m, 3H), 7.22 (q, J = 7.9, 6.6 Hz, 3H), 7.17 – 7.09 (m, 2H), 6.87 (d, J = 7.5 Hz, 2H), 4.98 (dd, J = 11.0, 5.1 Hz, 1H), 4.92 – 4.78 (m, 2H), 4.54 (dd, J = 10.9, 4.5 Hz, 1H), 4.42 (t, J = 12.6 Hz, 1H), 4.32 – 4.17 (m, 4H), 3.19 – 3.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 155.9, 143.7, 143.1, 141.7, 136.5, 134.1, 129.2, 128.8, 128.65, 128.4, 128.3, 128.0, 127.9, 127.5, 127.3, 125.0, 124.6, 120.2, 120.1, 76.1, 73.6, 70.6, 66.0, 65.4, 47.8, 45.7. UPLC-DAD-QTOF: $C_{33}H_{31}N_2O_6$ $[M+H]^+$ calcd.: 551.2182, found: 551.2181.

tert-Butyl ((2*S*,3*S*)-2-formyl-1-(4-methoxyphenyl)-4-nitro-3-phenylbutan-2-yl) carbamate (15Ab)



Prepared following the General Procedure starting from α-amino aldehyde **7A**, nitroolefin **8b** and catalyst **C7** to afford an 88:12 mixture of diastereomers. The major diastereomer was isolated as a white foam (68.56 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min). Retention times: 19.8 min (major) and 24.7 min (minor). $[\alpha]_D^{23}$ = 20.3 (c=1.00, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.39 – 7.29 (m, 3H), 7.25 – 7.19 (m, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.04 (dd, J = 13.2, 3.7 Hz, 1H), 4.87 (s, 1H), 4.77 (dd, J = 13.2, 11.9 Hz, 1H), 4.26 (dd, J = 11.8, 3.3 Hz, 1H), 3.78 (s, 3H), 2.96 (d, J = 14.3 Hz, 1H), 2.69 (d, J = 14.3 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 159.4, 155.6, 134.9, 131.6, 129.8, 129.4, 129.3, 128.9, 125.03, 114.4, 81.7, 65.7, 55.6, 49.6, 41.5, 28.6. UPLC-DAD-QTOF: $C_{23}H_{29}N_2O_6$ $[M+H]^+$ calcd.: 429.1981, found: 429.2001.

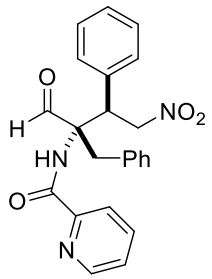
(9*H*-Fluoren-9-yl)methyl ((2*S*,3*S*)-2-formyl-1-(4-methoxyphenyl)-4-nitro-3-phenylbutan-2-yl)carbamate (15Cb)



Prepared following the General Procedure starting from α-amino aldehyde **7C**, nitroolefin **8b** and catalyst **C7** to afford a 95:5 mixture of diastereomers. The major diastereomer was isolated as a white foam (85.9 mg, 0.156 mmol, 78% yield) after silica column flash chromatography (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min). Retention times: 21.3 min (major) and 26.4 min (minor). $[\alpha]_D^{22}$ = 13.9 (c=1.00, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.83 (dd, J = 7.3, 3.9 Hz, 2H), 7.55 (t, J = 7.1 Hz, 2H), 7.48 – 7.39 (m, 2H), 7.37 (q, J = 7.6 Hz, 2H), 7.29 (d, J = 6.5 Hz, 3H), 6.94 (d, J = 7.7 Hz, 2H), 6.83 (d, J = 8.7

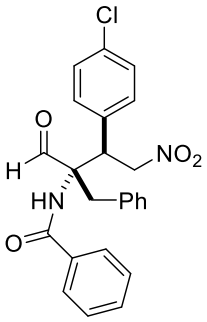
Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 4.95 – 4.79 (m, 3H), 4.57 – 4.38 (m, 2H), 4.20 (d, J = 4.2 Hz, 1H), 4.18-4.13 (m, 1H), 3.76 (s, 3H), 2.86 (d, J = 14.3 Hz, 1H), 2.42 (d, J = 14.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 159.2, 155.8, 134.4, 131.3, 129.6, 129.0, 128.5, 128.3, 128.0, 127.5, 127.2, 125.0, 124.8, 124.2, 120.1, 114.2, 76.5, 65.1, 55.3, 49.3, 47.7, 42.3. UPLC-DAD-QTOF: $C_{33}H_{31}N_2O_6$ $[M+H]^+$ calcd.: 551.2182, found: 551.2194.

***N*-((2S,3S)-2-benzyl-4-nitro-1-oxo-3-phenylbutan-2-yl)picolinamide (9Db)**



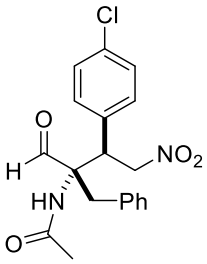
Prepared following the General Procedure starting from α-amino aldehyde **1D**, nitroolefin **8b** and catalyst **C7** to afford a 68:32 mixture of diastereomers. The title compound was isolated as a 67:33 diastereomer mixture and as a white foam (32.68 mg, 0.081 mmol, 40% yield) after flash column chromatography on silica gel (Hexane:EtOAc 80:20). The enantiomeric excess for the major diastereomer was found to be 86% and was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min). Retention times for the major diastereomer: 51.7 min (major) and 56.5 min (minor); and for the minor diastereomer: 27.9 min (major) and 34.6 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H, minor diastereomer), 8.68 – 8.62 (m, 1H, mayor diastereomer), 8.59 (s, 1H, major diastereomer), 8.52 (dd, J = 3.9, 1.6 Hz, 1H, minor diastereomer), 8.27 – 8.19 (m, 1H, minor diastereomer), 8.19 – 8.09 (m, 1H, mayor diastereomer), 7.97 – 7.84 (m, 2H, both diastereomers), 7.60 – 7.49 (m, 1H, mayor diastereomer), 7.49 – 7.43 (m, 1H, minor diastereomer), 7.40 – 7.27 (m, 10H, both diastereomers), 7.23 (d, J = 2.4 Hz, 3H, both diastereomers), 7.09 (td, J = 6.8, 2.0 Hz, 4H, both diastereomers), 6.94 (dd, J = 6.3, 3.0 Hz, 1H, mayor diastereomer), 5.13 (ddd, J = 13.1, 5.7, 3.8 Hz, 2H, both diastereomers), 5.03 – 4.89 (m, 1H, minor diastereomer), 4.83 (dd, J = 11.3, 3.9 Hz, 1H, minor diastereomer), 4.80 – 4.67 (m, 1H, major diastereomer), 4.43 (dd, J = 12.0, 3.5 Hz, 1H, major diastereomer), 4.08 (d, J = 14.0 Hz, 1H, minor diastereomer), 3.25 (d, J = 14.0 Hz, 1H, minor diastereomer), 3.02 (d, J = 14.2 Hz, 1H, major diastereomer), 2.74 (d, J = 14.1 Hz, 1H, mayor diastereomer). ^{13}C NMR (75 MHz, $CDCl_3$) both diastereomers, δ 200.5, 198.6, 165.0, 164.8, 148.8, 148.6, 148.5, 148.3, 137.9, 137.6, 134.6, 134.2, 134.0, 132.7, 130.5, 130.0, 129.9, 129.7, 129.4, 129.3, 129.2, 129.0, 128.8, 128.7, 128.7, 127.8, 127.5, 127.3, 127.3, 126.9, 122.72, 122.2, 77.30, 76.5, 64.9, 49.8, 49.1, 43.9, 37.2, 29.8. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_4$ $[M+H]^+$ calcd.: 404.1610, found: 404.1610.

_N_-((2_S_,3_S_)-2-benzyl-3-(4-chlorophenyl)-4-nitro-1-oxobutan-2-yl)benzamide (9Ea)



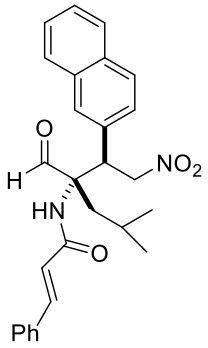
Prepared following the General Procedure starting from α-amino aldehyde **1E**, nitroolefin **8a** and catalyst **C7** to afford a 93:7 mixture of diastereomers. The title compound was isolated as a 91:9 diastereomer mixture and as a white foam (62.04 mg, 0.142 mmol, 71% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess for the major diastereomer was found to be >99% and was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min). Retention times: 41.1 min (minor) and 52.8 min (major). $[\alpha]_D^{24}$ = –41.53º (c=1.00, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.64 – 7.52 (m, 3H), 7.46 (t, J = 7.5 Hz, 2H), 7.37 – 7.23 (m, 5H), 7.18 (d, J = 8.4 Hz, 2H), 7.02 (dd, J = 6.9, 2.5 Hz, 2H), 6.35 (s, 1H), 5.17 (dd, J = 13.4, 3.7 Hz, 1H), 4.82 (t, J = 12.7 Hz, 1H), 4.48 (dd, J = 12.0, 3.6 Hz, 1H), 3.17 (d, J = 14.1 Hz, 1H), 2.94 (d, J = 14.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 167.8, 134.9, 133.2, 132.9, 132.7, 130.9, 130.5, 130.2, 129.4, 129.2, 129.2, 128.2, 127.0, 76.9, 65.4, 49.0, 42.4. UPLC-DAD-QTOF: $C_{24}H_{22}ClN_2O_4$ $[M+H]^+$ calcd.: 437.1268, found: 437.1264.

_N_-((2_S_,3_S_)-2-Benzyl-3-(4-chlorophenyl)-4-nitro-1-oxobutan-2-yl)acetamide (9Ia)



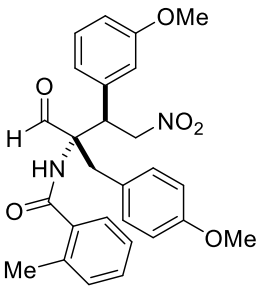
Prepared following the General Procedure starting from α-amino aldehyde **1I**, nitroolefin **8a** and catalyst **C7** to afford a 93:7 mixture of diastereomers. The major diastereomer was isolated as a white foam (32.23 mg, 0.086 mmol, 43% yield) after flash column chromatography on silica gel (Hexane:EtOAc 80:20). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min). Retention times: 12.6 min (major) and 19.0 min (minor). m.p.: 193-196 ºC. $[\alpha]_D^{24}$ = –36.71º (c=1.00, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.16 (d, J = 8.5 Hz, 2H), 7.00 – 6.95 (m, 2H), 5.69 (s, 1H), 5.06 (dd, J = 13.4, 3.8 Hz, 1H), 4.74 (dd, J = 13.4, 12.0 Hz, 1H), 4.37 (dd, J = 11.9, 3.8 Hz, 1H), 3.03 (d, J = 14.1 Hz, 1H), 2.80 (d, J = 14.1 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 170.9, 134.9, 133.1, 132.6, 130.8, 130.1, 129.4, 129.1, 128.1, 76.7, 65.5, 48.7, 42.0, 23.1. UPLC-DAD-QTOF: $C_{19}H_{20}ClN_2O_4$ $[M+H]^+$ calcd.: 375.1112, found: 375.1118.

_N_-((2_S_,3_S_)-3-Formyl-5-methyl-2-(naphthalen-2-yl)-1-nitrohexan-3-yl)cinnamamide (12Hj)



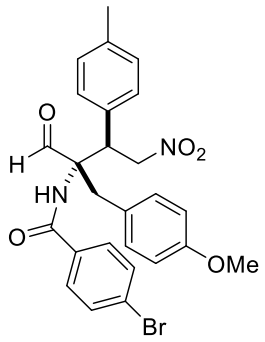
Prepared following the General Procedure starting from α-amino aldehyde **4H**, nitroolefin **8j** and catalyst **C7** to afford a 96:4 mixture of diastereomers. The major diastereomer was isolated as a white foam (40.0 mg, 0.09 mmol, 45% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min Retention times: 23.1 min (minor) and 39.7 min (major). $[\alpha]_D^{25}$ = –64.48º (c=0.50, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.86 – 7.70 (m, 4H), 7.65 (s, 1H), 7.60 – 7.47 (m, 4H), 7.45 – 7.37 (m, 3H), 7.31 (dd, J = 8.5, 1.6 Hz, 1H), 6.47 (d, J = 15.6 Hz, 1H), 5.83 (s, 1H), 5.19 (dd, J = 13.3, 3.7 Hz, 1H), 4.91 (t, J = 12.7 Hz, 1H), 4.56 (dd, J = 11.9, 3.6 Hz, 1H), 1.91-1.77 (m, 1H), 1.69 – 1.60 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 166.2, 144.1, 134.2, 133.2, 133.2, 132.1, 130.7, 129.2, 129.0, 128.8, 128.3, 128.1, 127.8, 126.8, 126.8, 118.4, 76.98, 66.6, 49.6, 45.3, 24.6, 24.3, 23.7. UPLC-DAD-QTOF: $C_{27}H_{29}N_2O_4$ $[M+H]^+$ calcd.: 445.2127, found: 445.2121.

_N_-((2_S_,3_S_,_E_)-2-Formyl-1-(4-methoxyphenyl)-3-(nitromethyl)-5-phenylpent-4-en-2-yl)-2-methylbenzamide (15Fd)



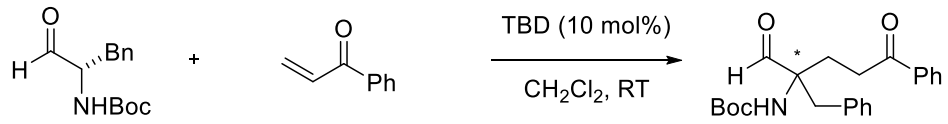
Prepared following the General Procedure starting from α-amino aldehyde **7F**, nitroolefin **8d** and catalyst **C7** to afford an 85:15 mixture of diastereomers. The major diastereomer was isolated as a white foam (73.4 mg, 0.154 mmol, 77% yield) after flash column chromatography on silica gel (Hexane:EtOAc 80:20). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 70:30, flow rate= 1 mL/min). Retention times: 17.6 min (minor) and 28.3 min (mayor). $[\alpha]_D^{25}$ = –7.10º (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30 – 7.15 (m, 3H), 7.09 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 6.89 – 6.74 (m, 5H), 6.13 (s, 1H), 5.19 (dd, J = 13.3, 3.6 Hz, 1H), 4.89 (t, J = 12.6 Hz, 1H), 4.41 (dd, J = 11.8, 3.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.19 (d, J = 14.4 Hz, 1H), 2.97 (d, J = 14.4 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 170.3, 160.0, 159.3, 136.9, 136.1, 134.1, 131.7, 131.4, 131.0, 130.3, 126.8, 126.1, 124.9, 121.5, 115.9, 114.3, 113.7, 77.1, 66.0, 55.4, 55.3, 49.3, 40.9, 20.0. UPLC-DAD-QTOF: $C_{27}H_{29}N_2O_6$ $[M+H]^+$ calcd.: 477.2026, found: 477.2024.

4-Bromo-*N*-((2*S*,3*S*,*E*)-2-formyl-1-(4-methoxyphenyl)-3-(nitromethyl)-5-phenylpent-4-en-2-yl)benzamide (15Gf)



Prepared following the General Procedure starting from α-amino aldehyde **7G**, nitroolefin **8f** and catalyst **C7** to afford a 93:7 mixture of diastereomers. The major diastereomer was isolated as a white foam (67.3 mg, 0.128 mmol, 64% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min). Retention times: 25.5 min (minor) and 31.4 min (major). $[\alpha]_D^{25}$ = –78.84º (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.28 (s, 1H), 5.14 (dd, J = 13.2, 3.8 Hz, 1H), 4.84 (d, J = 13.1 Hz, 1H), 4.37 (dd, J = 11.9, 3.7 Hz, 1H), 3.75 (s, 3H), 3.20 (d, J = 14.4 Hz, 1H), 3.02 (d, J = 14.4 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 166.8, 159.3, 138.8, 132.4, 131.8, 131.3, 131.2, 130.0, 129.2, 128.6, 127.5, 124.9, 114.4, 76.8, 66.1, 55.4, 48.9, 40.4, 21.2. UPLC-DAD-QTOF: $C_{26}H_{26}BrN_2O_5$ $[M+H]^+$ calcd.: 525.1025, found: 525.1030.

5.3.2.6. Preliminary experiments with phenyl vinyl ketone as electrophile



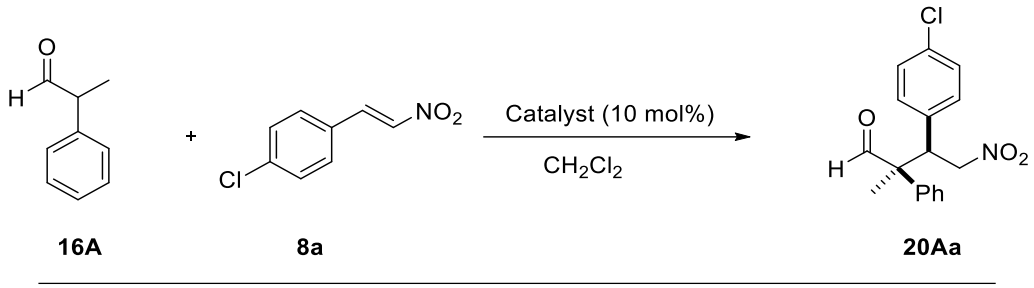
1A **32** **33**

Amino aldehyde **1A** (49.9 mg, 0.2 mmol, 1 eq), phenyl vinyl ketone **32**[230] (79.24 mg, 0.6 mmol, 3 eq) and TBD (2.8 μL, 0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting mixture was stirred at room temperature for 20 h. The reaction was followed by ^{1}H NMR and the reaction mixture was directly submitted to flash column chromatography on silica gel (Hexane:EtOAc 95:5). The product was obtained as a colorless oil (60.63 mg, 0.159 mmol, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.92 (dd, J = 8.3, 1.2 Hz, 2H), 7.60 – 7.50 (m, 1H), 7.48 – 7.40 (m, 2H), 7.25 (td, J = 5.4, 3.5 Hz, 3H), 7.07 (dd, J = 7.5, 1.7 Hz, 2H), 5.23 (s, 1H), 3.48 (d, J = 14.0 Hz, 1H), 3.20 (d, J = 14.0 Hz, 1H), 3.05 (ddd, J = 17.3, 8.1, 5.7 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.66 (dt, J = 13.9, 6.6 Hz, 1H), 2.32 (dt, J = 14.3, 7.5 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 154.7, 136.6, 135.3, 133.4, 130.2, 128.8, 128.5, 128.2, 127.2, 80.0, 66.4, 39.4, 32.8, 28.5, 27.7. UPLC-DAD-QTOF: $C_{23}H_{28}NO_4$ [M+H]+ calcd.: 381.1940, found: 381.1936.

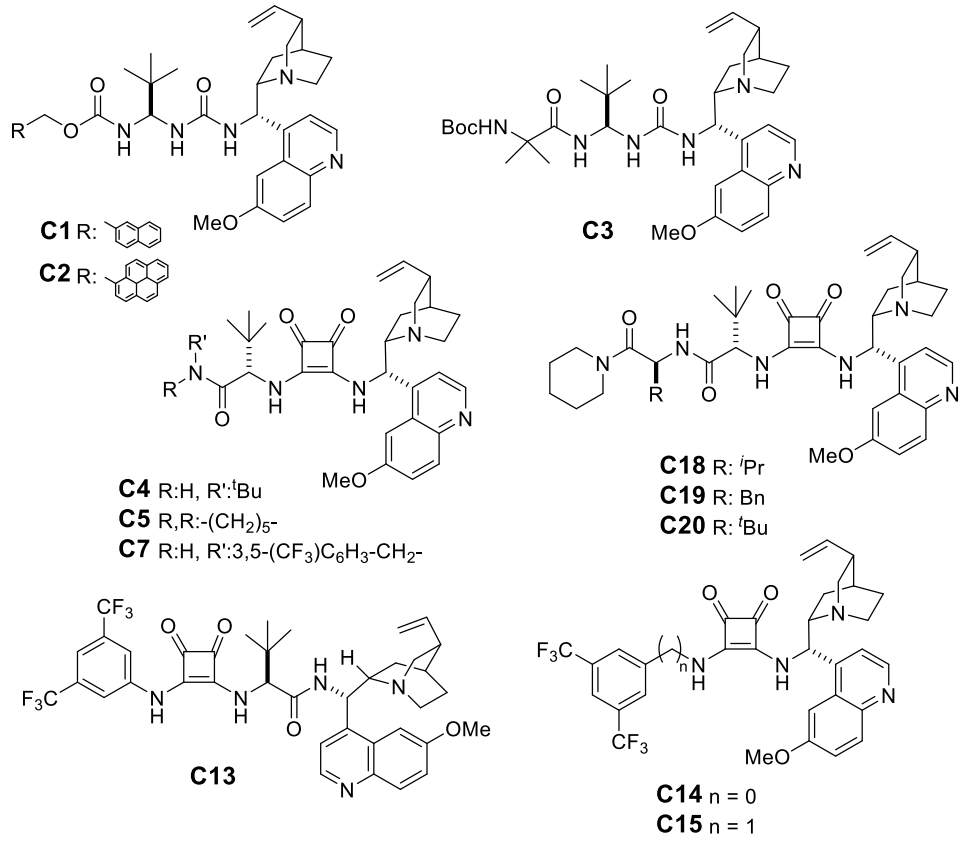
[230] Synthesis procedure from: Dimirjian, C. A.; Reis, M. C.; Balmond, E. I.; Turman, N. C.; Rodriguez, E. P.; Di Maso, M. J.; Fettinger, J. C.; Tantillo, D. J.; Shaw, J. T. *Org. Lett.* **2019**, *21*, 18, 7209–7212.

5.3.3. Catalytic conjugate addition of α-aryl acetaldehydes

*5.3.3.1. Catalyst screening for the model reaction between **16A** and **8a***



16A **8a** **20Aa**

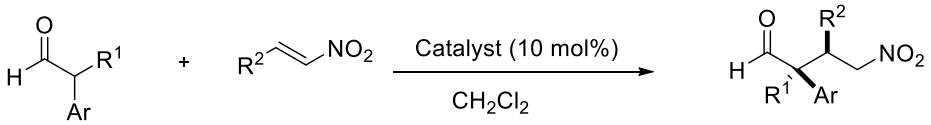


C1 R:
C2 R:
C3
C4 R:H, R':^{t}Bu
C5 R,R:-$(CH_2)_5$-
C7 R:H, R':3,5-$(CF_3)C_6H_3$-CH_2-
C18 R: ^{i}Pr
C19 R: Bn
C20 R: ^{t}Bu
C13
C14 n = 0
C15 n = 1

Entry	Cat.	T(ºC)	t(h)	Conv. (%)[b]	Yield (%)[c]	dr[d]	*ee*[e]
1	**C1**	RT	29	92	69	83:17	47
2	**C2**	RT	13	74	68	85:15	-2
3	**C3**	RT	72	88	90	81:19	24
4	**C4**	RT	35	98	85	88:12	89
5	**C5**	RT	30	98	89	90:10	94
7	**C7**	RT	72	>99	91	86:14	84
8	**C18**	RT	15	>99	87	86:14	85
9	**C19**	RT	20	>99	92	88:12	93
10	**C20**	RT	10	98	82	91:9	88
		0	15	85	84	95:5	94
13	**C13**	RT	15	88	78	92:8	74
14	**C14**	RT	23	93	74	84:16	96
15	**C15**	RT	40	98	71	86:14	96

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). [b] Determined by the disappearance of the starting aldehyde. [c] Yield of the isolated two diastereoisomers. [d] Determined by 1H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

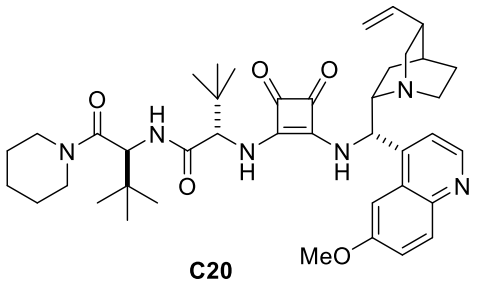
5.3.3.2. Reaction scope



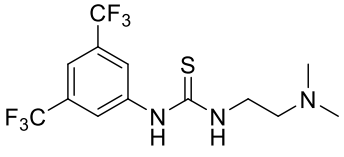
20 Ar: Ph, **21** Ar: 4-MeOC_6H_4-
22 Ar: 3-thiophene, **23** Ar :2-naph

A R^1: Me; **B** R^1: Et; **C** R^1: Allyl; **D** R^1: Bn

a R^2: *p*-Cl-C_6H_4-, **b** R^2: C_6H_5-,
c R^2: *p*-Me-C_6H_4-, **d** R^2: *m*-MeO-C_6H_4,
i R^2: Ph−C≡C-, **k** R^2: Pr, **l** R^2: *o*-Me-C_6H_4-,
m R^2: *p*-MeO-C_6H_4-, **n** R^2: Ph-CH_2-CH_2-



C20



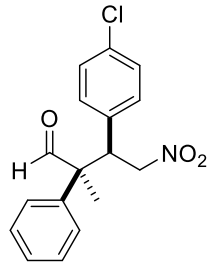
C31

GENERAL PROCEDURE:

The corresponding aldehyde (0.2 mmol, 1 eq), the nitroolefin (0.6 mmol, 3 eq) and catalyst **C20** (or **C5**) (0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting solution was stirred at 0 ºC for the indicated time. Reaction completion was followed by ^1H NMR and after the indicated time the mixture was directly submitted to flash column chromatography on silica gel. Reaction conversions and diastereomeric ratios were determined by ^1H NMR. Enantiomeric ratios were determined by chiral HPLC.

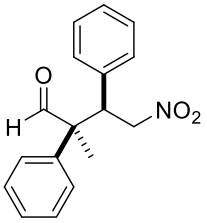
The corresponding racemic reactions were ran following the above procedure but using achiral catalyst **C31** (30 mol%).

(*2S*,*3R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-phenylbutanal (20Aa)



Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8a** and catalyst **C20** to afford a 95:5 diastereomer mixture. The product was isolated as a colorless oil in a 88:12 diastereomeric ratio (53.9 mg, 0.169 mmol, 84% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 21.6 min (minor) and 23.1 min (major). $[\alpha]_D^{20}$ = 105.26º (c=1.00, 88:12 dr, 94% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.49 – 7.11 (m, 5H), 7.07 (dd, *J* = 7.7, 2.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.05 – 4.83 (m, 2H), 4.21 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 138.6, 135.7, 132.3, 130.9, 130.1, 130.0, 129.0, 78.0, 58.2, 50.7, 18.1. UPLC-DAD-QTOF: $C_{17}H_{16}ClNO_3Na$ $[M+Na]^+$ calcd.: 340.0716, found: 340.0731.

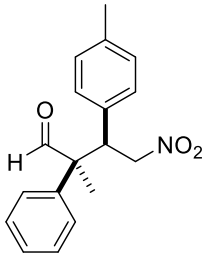
(*2S*,*3R*)-2-Methyl-4-nitro-2,3-diphenylbutanal (20Ab)



Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8b** and catalyst **C20** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a colorless oil (46.8 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 21.8 min (minor) and 39.2 min (major). $[\alpha]_D^{23}$ = 113.99º (c=1.00, 96% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.40 – 7.26 (m, 4H), 7.21 – 6.92 (m, 6H), 5.17 – 4.81 (m, 2H), 4.22 (dd, *J* = 11.5, 3.8 Hz, 1H), 1.55 (s, 3H). All the spectroscopic data were consistent with those previously reported.[231]

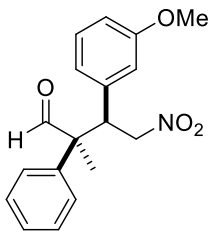
[231] Felluga, F.; Nitti, P.; Pitacco, G; Valentin, E. *J. Chem. Soc. Perkin Trans. 1,* **1992**, 2331–2335.

(*2S*,*3R*)-2-Methyl-4-nitro-2-phenyl-3-(p-tolyl)butanal (20Ac)



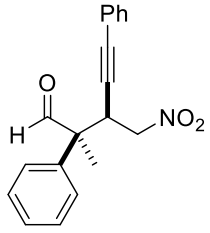
Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8c** and catalyst **C20** to afford a 97:3 diastereomer mixture. The product was isolated as a colorless solid in a 91:9 diastereomeric ratio (49.2 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate=1 mL/min). Retention times: 12.5 min (minor) and 18.1 min (major). $[\alpha]_D^{23}$ = 89.77º (c=1.00, 91:9 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.42 – 7.24 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15 – 4.75 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 138.7, 133.5, 130.9, 130.5, 130.4, 130.3, 129.4, 128.7, 77.7, 58.0, 50.8, 22.3, 18.4. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1266.

(*2S*,*3R*)-3-(3-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (20Ad)



Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8d** and catalyst **C20** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a white foam (30.9 mg, 0.099 mmol, 49% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate=1 mL/min). Retention times: 18.8 min (minor) and 25.9 min (major). $[\alpha]_D^{23}$ = 83.10º (c=1.00, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.38 – 7.21 (m, 3H), 7.15 – 7.00 (m, 3H), 6.68 (dd, J = 8.3, 2.5 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.45 – 6.32 (m, 1H), 5.00 (dd, J = 13.2, 11.4 Hz, 1H), 4.84 (dd, J = 13.2, 3.9 Hz, 1H), 4.17 (dd, J = 11.4, 3.8 Hz, 1H), 3.61 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 159.3, 137.4, 137.0, 129.2, 129.1, 128.2, 127.5, 121.4, 115.4, 113.4, 76.2, 75.2, 56.7, 55.2, 49.7, 16.8. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1209.

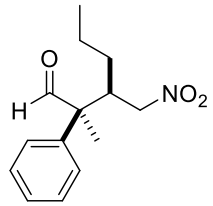
(2*S*,3*R*)-2-Methyl-3-(nitromethyl)-2,5-diphenylpent-4-ynal (20Ai)



Prepared following the General Procedure, starting from aldehyde **16A**, nitroolefin **8i** and catalyst **C20** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (44.1 mg, 0.143 mmol, 72% yield) after flash column chromatography on silica gel (Hexane:EtOAc 98:2). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 24.7 min (minor) and 39.1 min (major). $[\alpha]_D^{23}$ = 74.32º (c=0.50, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.49 – 7.37 (m, 3H), 7.37 – 7.31 (m, 2H), 7.30 – 7.19 (m, 5H), 4.65 – 4.51 (m, 2H), 4.19 (dd,

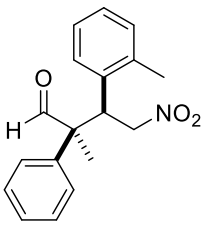
J = 9.6, 4.9 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 136.8, 131.8, 129.4, 128.7, 128.6, 128.3, 127.5, 122.3, 86.4, 84.5, 76.4, 55.8, 38.2, 17.0. UPLC-DAD-QTOF: $C_{19}H_{17}NO_3Na$ $[M+Na]^+$ calcd.: 330.1106, found: 330.1098.

(*2S*,*3R*)-2-Methyl-3-(nitromethyl)-2-phenylhexanal (20Ak)



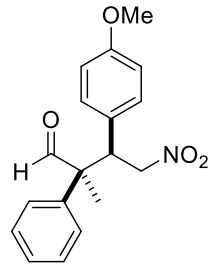
Prepared following the General Procedure, but at room temperature, starting from aldehyde **16A**, nitroolefin **8k** and catalyst **C20** to afford a 96:4 diastereomer mixture. The product was isolated as a yellow oil (28.4 mg, 0.114 mmol, 57% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 13.7 min (minor) and 18.3 min (major). $[\alpha]_D^{20}$ = 30.45º (c=1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.46 – 7.39 (m, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.29 (m, 1H), 7.29 – 7.27 (m, 1H), 4.48 (dd, J = 13.4, 4.3 Hz, 1H), 4.28 (dd, J = 13.4, 7.3 Hz, 1H), 3.14 (ddt, J = 8.6, 4.3, 2.7 Hz, 1H), 1.48 (s, 3H), 1.28 – 0.99 (m, 4H), 0.74 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 137.7, 129.3, 128.2, 127.5, 77.8, 57.0, 41.8, 31.8, 21.0, 15.3, 14.1. UPLC-DAD-QTOF: $C_{14}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 272.1263, found: 272.1263.

(*2S*,*3R*)-2-Methyl-4-nitro-2-phenyl-3-(o-tolyl)butanal (20Al)



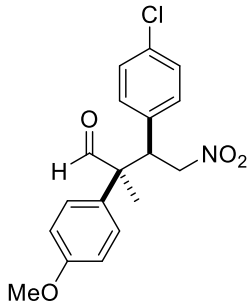
Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8l** and catalyst **C20** to afford a 95:5 diastereomer mixture. The product was isolated as a colorless oil (49.3 mg, 0.166 mmol, 83% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 17.3 min (major) and 19.3 min (minor). $[\alpha]_D^{23}$ = 88.18º (c=1.00, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.31 (dt, J = 6.5, 3.8 Hz, 4H), 7.22 – 7.14 (m, 1H), 7.12 (dd, J = 7.4, 1.4 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 5.05 (dd, J = 13.1, 11.5 Hz, 1H), 4.89 (dd, J = 13.2, 3.7 Hz, 1H), 4.59 (dd, J = 11.4, 3.7 Hz, 1H), 2.07 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 138.4, 137.9, 134.6, 131.0, 129.0, 128.2, 127.6, 127.3, 127.2, 126.1, 77.2, 56.9, 43.7, 19.8, 17.7. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1256.

(*2S*,*3R*)-3-(4-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (20Am)



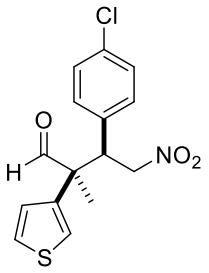
Prepared following the General Procedure starting from aldehyde **16A**, nitroolefin **8m** and catalyst **C20** to afford a 96:4 diastereomer mixture. The product was isolated as a yellow oil in a 92:8 diastereomeric ratio (57.5 mg, 0.184 mmol, 92% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 25.7 min (minor) and 47.9 min (major). $[\alpha]_D^{23}$ = 95.45º (c=1.00, 92:8 dr, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37 – 7.29 (m, 3H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.07-4.78 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 160.2, 138.7, 131.6, 130.3, 129.7, 129.3, 128.6, 127.3, 114.9, 77.7, 58.0, 56.4, 50.3, 18.2. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1213.

(*2S*,*3R*)-3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-methyl-4-nitrobutanal (21Aa)



Prepared following the General Procedure starting from aldehyde **17A**, nitroolefin **8a** and catalyst **C20** to afford a 93:7 diastereomer mixture. The final product was isolated as a colorless oil in a 93:7 diastereomeric ratio (51.5 mg, 0.148 mmol, 74% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 33.4 min (minor) and 37.3 min (major). $[\alpha]_D^{21}$ = 104.35º (c=1.00, 93:7 dr, 93% *ee*, 93:7 dr, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.15 – 7.07 (m, 2H), 6.98 – 6.90 (m, 2H), 6.89 – 6.77 (m, 4H), 4.94 (dd, J = 13.1, 11.2 Hz, 1H), 4.85 (dd, J = 13.1, 4.3 Hz, 1H), 4.16 (dd, J = 11.2, 4.3 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 159.5, 134.2, 133.7, 131.1, 130.7, 129.5, 128.7, 128.5, 128.3, 76.1, 56.0, 55.4, 49.0, 16.4. UPLC-DAD-QTOF: $C_{18}H_{18}ClNO_4Na$ $[M+Na]^+$ calcd.: 370.0822, found: 370.0822.

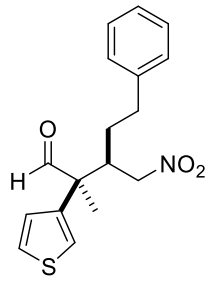
(2*S*,3*R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-(thiophen-3-yl)butanal (22Aa)



Prepared following the General Procedure starting from aldehyde **18A**, nitroolefin **8a** and catalyst **C20** to afford a 91:9 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (51.9 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=0.5 mL/min). Retention times: 82.6 min (minor) and 98.1 min (major). $[\alpha]_D^{24}$ = 128.59º (c=1.00, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz,

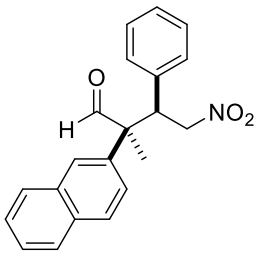
$CDCl_3$) δ 9.54 (s, 1H), 7.37 (dd, J = 5.1, 3.0 Hz, 1H), 7.20 – 7.13 (m, 2H), 6.94 – 6.84 (m, 4H), 4.95 (dd, J = 13.2, 11.5 Hz, 1H), 4.78 (dd, J = 13.2, 4.0 Hz, 1H), 4.16 (dd, J = 11.4, 3.9 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 138.3, 134.0, 134.0, 130.5, 128.7, 127.5, 126.1, 123.4, 76.1, 54.7, 49.0, 17.8. UPLC-DAD-QTOF: $C_{15}H_{14}NO_3SClNa$ $[M+Na]^+$ calcd.: 346.0281, found: 346.0282.

(2*S*,3*R*)-2-Methyl-3-(nitromethyl)-5-phenyl-2-(thiophen-3-yl)pentanal (22An)



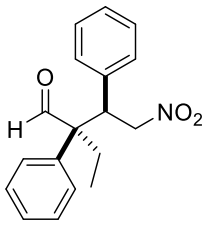
Prepared following the General Procedure starting from aldehyde **18A**, nitroolefin **8n** and catalyst **C20** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (28.9 mg, 0.091 mmol, 45% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 24.9 min (major) and 26.8 min (minor). $[\alpha]_D^{21}$ = 21.39º (c=1.00, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.38 (dd, J = 5.1, 2.9 Hz, 1H), 7.25 – 7.14 (m, 3H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.02 – 6.95 (m, 2H), 6.92 (dd, J = 5.1, 1.4 Hz, 1H), 4.50 (dd, J = 13.2, 4.6 Hz, 1H), 4.34 (dd, J = 13.2, 7.2 Hz, 1H), 3.17 – 3.05 (m, 1H), 2.59 (ddd, J = 16.7, 8.4, 3.4 Hz, 1H), 2.33 (ddd, J = 13.6, 9.7, 7.2 Hz, 1H), 1.73-1.55 (m, 2H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 140.8, 138.8, 128.6, 128.5, 127.4, 126.4, 126.2, 123.4, 77.5, 55.4, 41.2, 34.3, 31.8, 15.7. UPLC-DAD-QTOF: $C_{17}H_{19}NO_3SNa$ $[M+Na]^+$ calcd.: 340.0983, found: 340.0982.

(2*S*,3*R*)-2-Methyl-2-(naphthalen-2-yl)-4-nitro-3-phenylbutanal (23Ab)



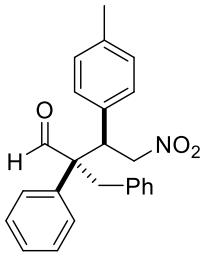
Prepared following the General Procedure starting from aldehyde **19A**, nitroolefin **8b** and catalyst **C20** to afford a 98:2 diastereomer mixture. The product was isolated as a white foam (47.3 mg, 0.142 mmol, 71% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 19.1 min (major) and 21.7 min (minor). $[\alpha]_D^{21}$ = 175.05º (c=1.00, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.88 – 7.72 (m, 3H), 7.54 – 7.44 (m, 3H), 7.23 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 5.1, 2.0 Hz, 3H), 6.99 (dd, J = 5.2, 1.6 Hz, 2H), 5.10 (dd, J = 13.1, 11.5 Hz, 1H), 4.87 (dd, J = 13.1, 3.8 Hz, 1H), 4.31 (dd, J = 11.5, 3.8 Hz, 1H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 135.5, 134.8, 133.2, 132.7, 129.5, 129.2, 128.4, 128.2, 127.9, 127.7, 127.0, 126.9, 126.8, 124.4, 76.5, 57.0, 49.9, 17.5. UPLC-DAD-QTOF: $C_{21}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 356.1263, found: 356.1259.

(2*S*,3*R*)-2-Ethyl-4-nitro-2,3-diphenylbutanal (20Bb)



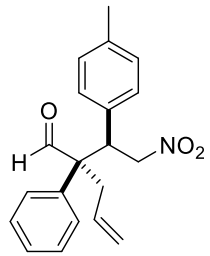
Prepared following the General Procedure starting from aldehyde **16B**, nitroolefin **8b** and catalyst **C20** to afford an 83:17 diastereomer mixture. The product was isolated as a white oil in an 82:18 diastereomeric ratio (36.3 mg, 0.122 mmol, 61% yield) after flash column chromatography on silica gel (Hexane:EtOAc 98:2). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 12.5 min (major) and 15.9 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.47 – 7.36 (m, 3H), 7.29 – 7.21 (m, 3H), 7.18 – 7.11 (m, 2H), 7.11 – 7.02 (m, 2H), 4.98 (dd, J = 13.2, 11.7 Hz, 1H), 4.68 (dd, J = 13.3, 3.4 Hz, 1H), 4.16 (dd, J = 11.7, 3.4 Hz, 1H), 1.96 (dq, J = 14.4, 7.1 Hz, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 137.0, 135.4, 129.8, 129.3, 128.6, 128.2, 128.1, 128.0, 77.1, 51.0, 27.8, 9.0. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1255.

(2S,3R)-2-Benzyl-4-nitro-2-phenyl-3-(p-tolyl)butanal (20Dc)



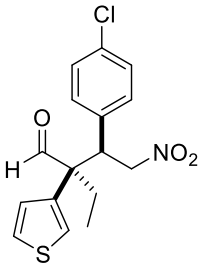
Prepared following the General Procedure starting from aldehyde **16D**, nitroolefin **8c** and catalyst **C20** to afford a 57:43 diastereomer mixture. The product was isolated as a white solid in a 63:37 diastereomeric ratio (33.6mg, 0.09 mmol, 45% yield) after flash column chromatography on silica gel (Hexane:EtOAc 98:2). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times for the major diastereomer: 34.3 min (minor) and 60.5 min (major) and for minor diastereomer: 15.1 min (minor) and 16.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H, minor diastereomer), 9.69 (s, 1H, mayor diastereomer), 7.47 – 7.40 (m, 3H, mayor diastereomer), 7.36 (d, J = 7.2 Hz, 3H, minor diastereomer), 7.18 – 7.11 (m, 7H, both diastereomers), 7.11 – 6.99 (m, 9H, both diastereomers), 6.97 (dd, J = 6.5, 3.1 Hz, 2H, both diastereomers), 6.77 (d, J = 8.1 Hz, 2H, mayor diastereomer), 6.64 (dd, J = 8.0, 1.5 Hz, 2H), 4.91 (dd, J = 13.2, 11.8 Hz, 1H, minor diastereomer), 4.79 (dd, J = 12.0, 3.3 Hz, 1H, mayor diastereomer), 4.68 (dd, J = 13.2, 3.2 Hz, 1H, minor diastereomer), 4.38 – 4.27 (m, 2H, both diastereomers), 4.22 (dd, J = 11.9 Hz, 1H, mayor diastereomer), 3.30 – 3.18 (m, 2H, minor diastereomer), 3.19 – 3.07 (m, 2H, mayor diastereomer), 2.34 (s, 3H, minor diastereomer), 2.31 (s, 3H, mayor diastereomer). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 204.3, 138.3, 138.1, 137.5, 135.6, 134.6, 134.6, 132.0, 131.5, 130.5, 130.5, 130.3, 129.9, 129.6, 129.5, 129.3, 129.2, 129.0, 128.8, 128.7, 128.5, 128.2, 128.1, 127.2, 126.9, 77.4, 77.3, 60.6, 59.6, 51.1, 47.3, 42.2, 41.7, 21.2. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 396.1576, found: 396.1573.

(*S*)-2-((*R*)-2-Nitro-1-(p-tolyl)ethyl)-2-phenylpent-4-enal (20Cc)



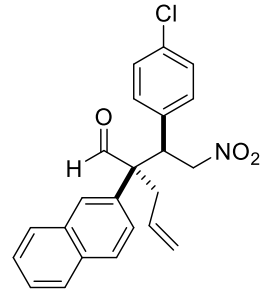
Prepared following the General Procedure starting from aldehyde **16C**, nitroolefin **8c** and catalyst **C20** to afford an 85:15 diastereomer mixture. The product was isolated as a colorless oil in a 79:21 diastereomeric ratio (42.7 mg, 0.132 mmol, 66% yield) after flash column chromatography on silica gel (Hexane:EtOAc 99:1). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 10.7 min (minor) and 12.2 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.46 – 7.31 (m, 3H), 7.15 (dd, J = 6.8, 1.6 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 5.58 – 5.37 (m, 1H), 5.10 – 4.96 (m, 3H), 4.69 (dd, J = 13.2, 3.4 Hz, 1H), 4.11 (dd, J = 11.7, 3.3 Hz, 1H), 2.77 (ddt, J = 14.7, 5.9, 1.4 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 138.2, 132.4, 130.1, 129.9, 129.5, 129.2, 129.2, 128.4, 128.0, 120.2, 77.8, 59.5, 50.9, 39.2, 21.4. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 346.1419, found: 346.1411.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-ethyl-4-nitro-2-(thiophen-3-yl)butanal (22Ba)



Prepared following the General Procedure starting from aldehyde **18B**, nitroolefin **8a** and catalyst **C20** to afford a 55:45 diastereomer mixture. The product was isolated as a yellow oil in a 62:38 diastereomeric ratio (28.4 mg, 0.084 mmol, 42% yield) after flash column chromatography on silica gel (Hexane:EtOAc 98:2). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times for the major diastereomer: 12.4 min (major) and 13.4 min (minor) and for minor diastereomer: 21.5 min (major) and 31.1 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.44 (dd, J = 5.1, 2.9 Hz, 1H), 7.27 – 7.18 (m, 2H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.01 – 6.90 (m, 3H), 4.86 (dd, J = 13.3, 11.6 Hz, 1H), 4.65 (dd, J = 13.3, 3.7 Hz, 1H), 4.07 (dd, J = 11.6, 3.7 Hz, 1H), 1.95 (qd, J = 7.4, 1.1 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 131.0, 130.9, 128.8, 128.6, 127.3, 126.3, 123.9, 77.0, 57.9, 50.4, 28.2, 9.1. UPLC-DAD-QTOF: $C_{17}H_{20}NO_4S$ $[M+ CH_3OH-Cl]^+$ calcd.: 334.1113, found: 334.1113.

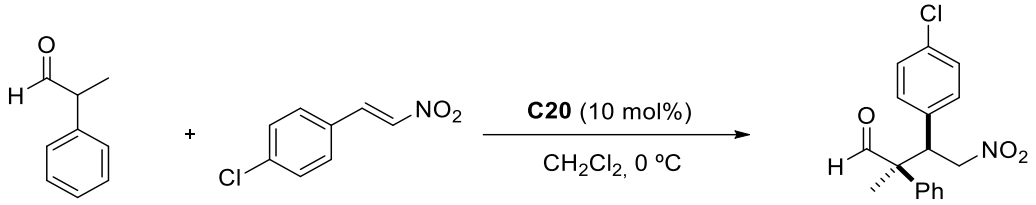
(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-(naphthalen-2-yl)pent-4-enal (23Ca)



Prepared following the General Procedure starting from aldehyde **19C**, nitroolefin **8a** and catalyst **C20** to afford an 85:15 diastereomer mixture. The product was isolated as a white foam in a 80:20 diastereomeric ratio (53.6 mg, 0.136 mmol, 68% yield) after flash column chromatography on silica gel (Hexane:EtOAc 98:2). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 98:2, flow rate=1 mL/min).

Retention times: 17.5 min (minor) and 29.5 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.88 – 7.77 (m, 2H), 7.60 – 7.52 (m, 1H), 7.51 – 7.45 (m, 1H), 7.31 – 7.13 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 5.61 – 5.43 (m, 1H), 5.16 – 5.01 (m, 3H), 4.70 (dd, J = 13.4, 3.3 Hz, 1H), 4.21 (dd, J = 11.7, 3.2 Hz, 1H), 2.92 (dd, J = 14.8, 5.5 Hz, 1H), 2.65 (dd, J = 14.7, 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 134.3, 134.0, 133.8, 133.2, 132.8, 131.8, 131.3, 129.6, 128.8, 128.3, 127.8, 127.6, 127.2, 127.1, 124.4, 120.5, 76.7, 59.3, 50.4, 38.7. UPLC-DAD-QTOF: $C_{23}H_{20}ClNO_3Na$ $[M+Na]^+$ calcd.: 416.1029, found: 416.1033.

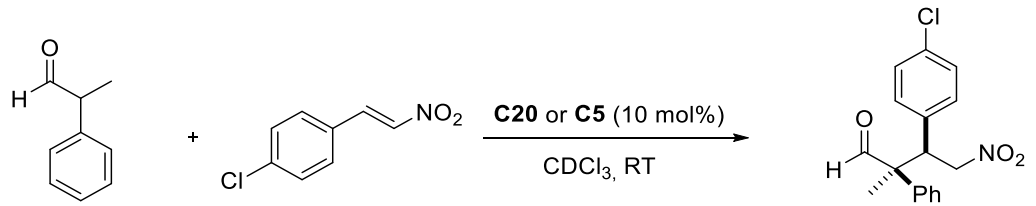
*5.3.3.3. Scale synthesis of **20Aa***



16A **8a** **20Aa**

Aldehyde (±)**16A** (0.536 mL, 4 mmol, 1 eq), nitroolefin **8a** (1.789 g, 12 mmol, 3 eq) and catalyst **C20** (285 mg, 0.4 mmol, 10 mol%) were dissolved in CH_2Cl_2 (12 mL) and the resulting solution was stirred at 0 ºC for 16 h (94% conversion, 94:6 dr). The mixture was directly submitted to flash column chromatography on silica gel (Hexane:EtOAc 95:5). The final product was obtained in 82% yield. Catalyst was recovered from the column in 87% yield. Reaction conversions and diastereomeric ratios were determined by ^{1}H NMR. Enantiomeric excess (95 % *ee*) was determined by chiral HPLC.

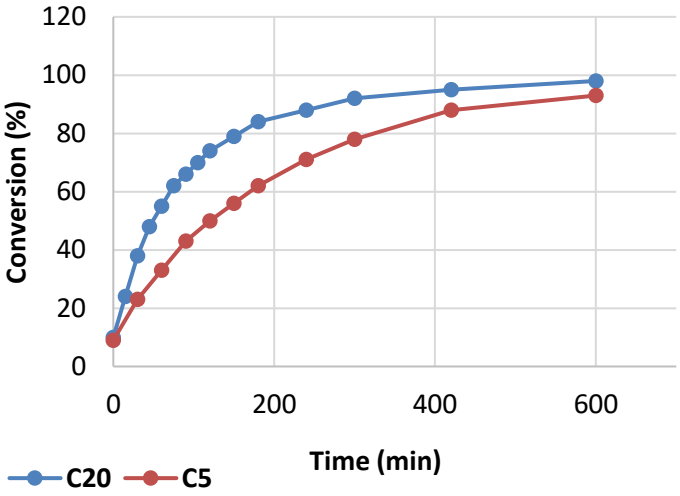
*5.3.3.4. Kinetic study for the reaction between **16A** and **8a** with **C20/C5***



16A **8a** **20Aa**

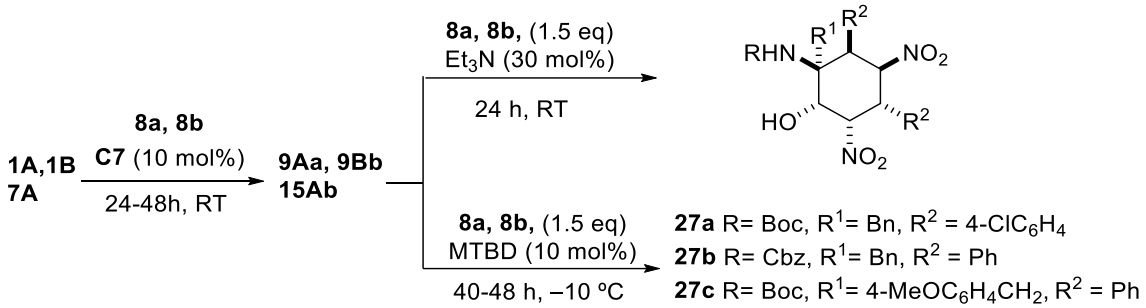
Aldehyde (±)**16A** (26.78 µL, 0.2 mmol, 1 eq), nitroolefin **8a** (110.15 mg, 0.6 mmol, 3 eq) and the corresponding catalyst (0.02 mmol, 10 mol%) were dissolved in $CDCl_3$ (0.6 mL) and the resulting mixture was transferred to an NMR tube and allowed to react at room temperature for the indicated time. The reaction conversion was followed by ^{1}H NMR.

t (min)	Conversion (%)	
	C20	C5
0	10	9
15	24	-
30	38	23
45	48	-
60	55	33
75	62	-
90	66	43
105	70	-
120	74	50
150	79	56
180	84	62
240	88	71
300	92	78
420	95	88
600	98	93



5.3.4. Chemical elaboration of the adducts

*5.3.4.1. Preparation of the cyclized products **27a-c***



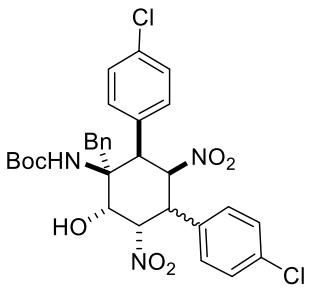
Entry	Base	Adduct	R	R^1	R^2	Yield (%)[c]	dr[d]
1	**Et_3N**	**27a**	Boc	Bn	4-ClC_6H_4	67	56:44
		27b	Cbz	Bn	Ph	74	68:32
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	80	65:35
2	**MTBD**	**27a**	Boc	Bn	4-ClC_6H_4	81	85:15
		27b	Cbz	Bn	Ph	83	80:20
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	82	88:12

[a] Reactions conducted on a 0.5 mmol scale in 1.5 mL of CH_2Cl_2 (mol ratio for the first step: nitroolefin/aldehyde/catalyst 1.5:1:0.1). Sum of the yields of the separately isolated two isomers. Diastereomeric ratio determined by ^{1}H NMR (300 MHz) analysis on the crude product.

GENERAL PROCEDURE:

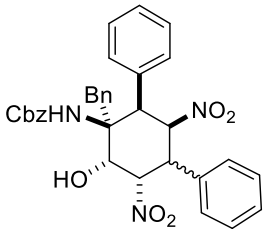
The corresponding amino aldehyde **1A** or **1B** or **7A** (0.5 mmol, 1 eq), the nitroolefin **8a** or **8b** (0.75 mmol, 1.5 eq) and catalyst **C7** (0.05 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting solution was stirred at room temperature. The reaction was followed by ^{1}H NMR and after reaction completion (determined by the disappearance of the starting aldehyde). Mixture was cooled down to –10 ºC and 10 mol% of MTBD and the corresponding nitroolefin (1.5 eq) were added. The reaction mixture was stirred for 16 h and more nitroolefin (1.5 eq) was added. The reaction mixture was then stirred for another 24 h. The mixture was directly submitted to flash column chromatography on silica gel. Reaction conversions and diastereomeric ratios were determined by ^{1}H NMR analysis.

tert-Butyl ((1*S*,2*S*,3*S*,4*R*,5*S*)-1-benzyl-2,4-bis(4-chlorophenyl)-6-hydroxy-3,5-dinitro cyclohexyl)carbamate (27a)



The title compound was prepared following the General Procedure and starting from amino aldehyde **1A**, nitroolefin **8a** and catalyst **C7**. The crude was obtained as an 85:15 diastereomer mixture and was directly submitted to flash column chromatography on silica gel (Hexane: EtOAc 80:20). Overall yield: 81%. The major diastereomer was isolated as a yellow foam in 71% yield (218.9 mg, 0.375 mmol). Data for the major diastereomer: $[\alpha]_D^{25}$ = –36.55º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, J = 7.4 Hz, 4H), 7.33 (s, 5H), 7.32 – 7.27 (m, 3H), 7.24 (s, 1H), 5.32 (dd, J = 13.3, 7.0 Hz, 1H), 5.27 (dd, J = 12.3, 3.1 Hz, 1H), 4.76 (s, 1H), 4.70 – 4.55 (m, 2H), 4.33 (d, J = 7.0 Hz, 1H), 3.95 (d, J = 13.6 Hz, 1H), 3.22 (d, J = 14.2 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 135.0, 134.9, 134.6, 133.2, 131.0, 130.6, 130.3, 129.8, 129.6, 129.1, 128.7, 128.0, 88.1, 87.8, 80.6, 70.2, 60.4, 52.6, 40.0, 39.4, 28.3. UPLC-DAD-QTOF: $C_{30}H_{31}Cl_2N_3O_7Na$ $[M+Na]^+$ calcd.: 638.1437, found: 638.1433. The minor diastereomer was isolated as a white foam in 10% yield (30.83 mg, 0.05 mmol). Data for the minor diastereomer: $[\alpha]_D^{25}$ = –17.85º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 4H), 7.20 – 7.06 (m, 7H), 7.03 (dd, J = 7.7, 1.8 Hz, 2H), 6.24 (dd, J = 12.8, 1.6 Hz, 1H), 5.58 (s, 1H), 5.50 – 5.41 (m, 1H), 5.09 (t, J = 5.7 Hz, 1H), 4.47 (dd, J = 12.8, 5.8 Hz, 1H), 3.91 (d, J = 5.6 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 3.05 (d, J = 3.6 Hz, 1H), 2.73 (d, J = 13.7 Hz, 1H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 135.2, 135.1, 132.2, 131.7, 130.6, 129.8, 129.7, 129.1, 129.0, 128.4, 127.0, 94.3, 83.8, 69.7, 61.7, 46.9, 43.31, 41.2, 29.9, 28.6. UPLC-DAD-QTOF: $C_{30}H_{31}Cl_2N_3O_7Na$ $[M+Na]^+$ calcd.: 638.1437, found: 638.1439.

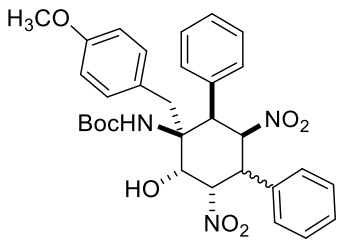
Benzyl ((1*S*,3*S*,4*R*,5*S*,6*S*)-1-benzyl-2-hydroxy-3,5-dinitro-4,6-diphenylcyclohexyl)carba mate (27b)



The title compound was prepared following the General Procedure and starting from amino aldehyde **1B**, nitroolefin **8b** and catalyst **C7**. The crude was obtained as an 80:20 diastereomer mixture and was directly submitted to flash column chromatography on silica gel (Hexane: EtOAc 90:10). Overall yield: 83%. The major diastereomer was isolated as a white foam in 71% yield (206.5 mg, 0.355 mmol). Data for the major diastereomer: $[\alpha]_D^{25}$ = –11.82º (c=0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 3H), 7.38 – 7.24 (m, 13H), 7.20 (dt, J = 6.8, 2.8 Hz, 4H), 5.40 (dd, J = 12.7, 7.0 Hz, 1H), 5.30 (dd, J = 12.3, 3.2 Hz, 1H), 5.01 (d, J = 12.2 Hz, 1H), 4.90 – 4.85 (m, 2H), 4.85 – 4.81 (m, 1H), 4.73 (t, J = 12.6 Hz, 1H), 4.21 (d, J = 7.0 Hz, 1H), 3.68 (d, J = 14.3 Hz, 1H), 3.44 (d, J = 14.2 Hz, 1H), 3.30 – 3.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 134.9, 134.4, 131.9, 131.2, 130.6, 129.9, 129.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 127.9, 127.6, 110.1, 88.4, 87.9, 70.5, 67.0, 60.8, 52.2, 39.8,

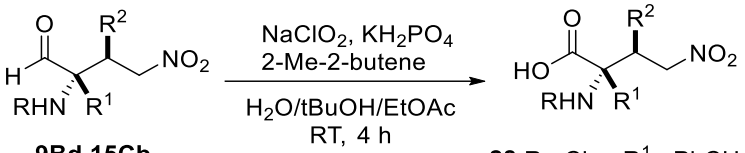
39.6. UPLC-DAD-QTOF: $C_{31}H_{35}N_3O_8Na$ $[M+Na]^+$ calcd.: 604.2054, found: 604.2057. The minor diastereomer was isolated as a white foam in 12% yield (34.90 mg, 0.06 mmol). Data for the minor diastereomer: : $[\alpha]_D^{26}$ = –29.04º (c=1.00, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 4H), 7.36-7.31 (m, 3H), 7.28 (s, 3H), 7.27 – 7.22 (m, 3H), 7.19 (dd, J = 6.5, 2.7 Hz, 2H), 7.14 (d, J = 7.0 Hz, 1H), 7.10 – 6.97 (m, 4H), 6.36 (d, J = 12.8 Hz, 3H), 5.75 (s, 1H), 5.53 (s, 1H), 5.25 – 5.13 (m, 2H), 5.05 (d, J = 12.2 Hz, 1H), 4.51 (dd, J = 12.8, 5.7 Hz, 1H), 3.95 (d, J = 5.5 Hz, 1H), 3.35 (d, J = 13.7 Hz, 1H), 2.63 (d, J = 13.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 136.5, 135.0, 133.5, 133.1, 130.6, 129.8, 129.6, 129.4, 129.1, 129.0, 128.8, 128.6, 128.4, 127.8, 127.2, 110.1, 94.3, 83.9, 69.2, 67.1, 61.83, 47.6, 43.8, 41.9. UPLC-DAD-QTOF: $C_{31}H_{35}N_3O_8Na$ $[M+Na]^+$ calcd.: 604.2054, found: 604.2053.

tert-Butyl ((1*S*,3*S*,4*R*,5*S*,6*S*)-2-hydroxy-1-(4-methoxybenzyl)-3,5-dinitro-4,6-diphenyl cyclohexyl)carbamate (27c)



The title compound was prepared following the General Procedure and starting from amino aldehyde **7A**, nitroolefin **8b** and catalyst **C7**. The crude was obtained as an 88:12 diastereomer mixture and was directly submitted to flash column chromatography on silica gel (Hexane:EtOAc 90:10). Overall yield: 82%. The major diastereomer was isolated as a white foam in 75% yield (216.54 mg, 0.375 mmol). Data for the major diastereomer: $[\alpha]_D^{26}$ = –29.03º (c=0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 12H), 6.94 (d, J = 8.7 Hz, 2H), 5.39 (dd, J = 12.7, 7.0 Hz, 1H), 5.31 (dd, J = 12.4, 3.1 Hz, 2H), 4.78 – 4.69 (m, 3H), 4.27 (d, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.80 – 3.74 (m, 1H), 3.29 (d, J = 14.4 Hz, 1H), 3.22 (d, J = 4.5 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 154.7, 135.0, 132.5, 131.6, 131.6, 129.2, 128.9, 128.8, 128.5, 128.5, 126.7, 114.4, 88.5, 88.1, 80.4, 70.4, 60.7, 55.4, 52.6, 39.9, 38.9, 28.3. UPLC-DAD-QTOF: $C_{31}H_{35}N_3O_8Na$ $[M+Na]^+$ calcd.: 600.2316, found: 600.2312. The minor diastereomer was isolated as a white foam in 7% yield (20.22 mg, 0.035 mmol). Data for the minor diastereomer: $[\alpha]_D^{26}$ = –24.12º (c=0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 10H), 7.01 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 6.36 (dd, J = 12.8, 1.6 Hz, 1H), 5.63 (s, 1H), 5.55 – 5.49 (m, 1H), 5.19 (t, J = 5.7 Hz, 1H), 4.52 (dd, J = 12.8, 5.7 Hz, 1H), 3.95 (d, J = 5.6 Hz, 1H), 3.76 (s, 3H), 3.30 (d, J = 13.9 Hz, 1H), 2.95 (d, J = 3.4 Hz, 1H), 2.70 (d, J = 13.9 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 154.3, 133.9, 133.3, 131.5, 129.6, 129.4, 128.9, 128.9, 127.7, 127.3, 113.9, 94.5, 84.0, 69.4, 61.6, 55.3, 47.6, 42.8, 41.9, 29.8, 28.6. UPLC-DAD-QTOF: $C_{31}H_{35}N_3O_8Na$ $[M+Na]^+$ calcd.: 600.2316, found: 600.2319.

5.3.4.2. Oxidation of the reaction adducts[232]



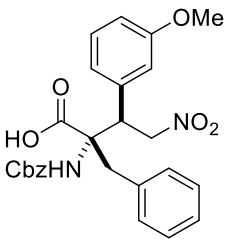
9Bd,**15Cb**

28 R= Cbz, R^1= $PhCH_2$, R^2= *m*-$MeOC_6H_4$, 97% yield
29 R= Fmoc, R^1= *p*-$MeOC_6H_4$, R^2= Ph, 98% yield

GENERAL PROCEDURE:

To a stirred solution of the corresponding adduct (0.1 mmol, 1 eq) in 1.12 mL of a solvent mixture of H_2O/^{t}BuOH/EtOAc (1.5:2:1) 2-methyl-2-butene was added and the resulting mixture was stirred for 5 min. at room temperature. KH_2PO_4 (40.84 mg, 0.3 mmol, 3 eq) and $NaClO_2$ (80%, 32.64 mg, 0.2 mmol, 2 eq) were then added and the reaction mixture was stirred for 4 h at the same temperature. After reaction completion followed by ^{1}H NMR, 1.5 mL of HCl 3M were added and the aqueous phase was extracted with EtOAc (x3). The organic phases were combined and dried over $MgSO_4$. The solvents were evaporated under reduced pressure to provide the corresponding amino acid derivatives.

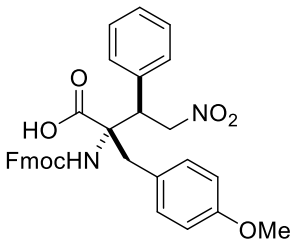
(2*S*,3*S*)-2-Benzyl-2-(((benzyloxy)carbonyl)amino)-3-(3-methoxyphenyl)-4-nitrobutanoic acid (28)



The title compound was prepared following the General procedure starting from adduct **9Bd** (46.4 mg, 0.1 mmol, 1 eq). The product was obtained as a white foam (44.1 mg, 0.092 mmol, 97% yield). $[\alpha]_D^{24}$ = –7.09º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.44-7.32 (m, 5H), 7.21-7.10 (m, 3H), 7.03 (d, J = 7.0 Hz, 2H), 6.83 – 6.76 (m, 1H), 6.71 (d, J = 7.8 Hz, 2H), 5.42 (s, 1H), 5.24 – 5.07 (m, 4H), 4.91 (dd, J = 10.6, 4.4 Hz, 1H), 3.86 (d, J = 13.1 Hz, 1H), 3.68 (s, 3H), 3.29 (d, J = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 159.8, 154.8, 137.1, 136.4, 134.8, 130.8, 130.0, 129.9, 129.6, 128.8, 128.7, 128.6, 127.6, 120.8, 114.9, 113.8, 77.3, 67.3, 67.0, 55.3, 47.6, 39.2. UPLC-DAD-QTOF: $C_{26}H_{26}N_2O_7Na$ $[M+Na]^+$ calcd.: 501.1638, found: 501.1641.

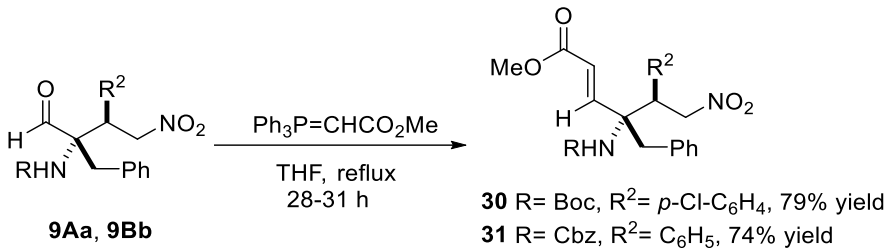
[232] Adapted from: Rajeswari, T.; Tanaka, F.; Barbas III, C. F. *Org. Lett.* **2004**, *6*, 3541–3544.

(*2S*,3*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-(4-methoxybenzyl)-4-nitro-3-phenylbutanoic acid (29)



The title compound was prepared following the General procedure starting from adduct **15Cb** (55.03 mg, 0.1 mmol, 1 eq). The product was obtained as a white foam (54.7 mg, 0.0965 mmol, 98% yield). $[\alpha]_D^{24}$ = –6.71º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.40 (d, J = 7.4 Hz, 2H), 7.33 – 7.18 (m, 5H), 7.14 (d, J = 6.9 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.5 Hz, 1H), 5.40 (s, 1H), 5.22 – 5.13 (m, 2H), 4.94 – 4.82 (m, 1H), 4.56 – 4.39 (m, 2H), 4.23 (t, J = 6.7 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.70 (s, 3H), 3.25 (d, J = 13.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 159.0, 154.7, 143.7, 141.4, 135.4, 130.8, 129.0, 128.6, 128.5, 127.93, 127.2, 126.5, 125.3, 125.2, 120.1, 114.2, 77.2, 67.17, 67.0, 55.3, 47.7, 47.3, 38.6. UPLC-DAD-QTOF: $C_{33}H_{31}N_2O_7$ $[M+H]^+$ calcd.: 567.2131, found: 567.2129.

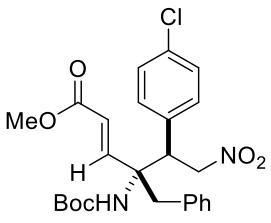
5.3.4.3. Wittig reaction



GENERAL PROCEDURE:

To a stirred solution of methyl (triphenylphosphoranylidene)acetate (3 eq) in dry THF (16 mL/mmol) at 0 ºC the corresponding adduct (1 eq) was added and the solution was stirred at reflux until reaction completion (followed by the disappearance of the aldehyde by ^{1}H NMR). The solvent was then removed under reduced pressure and the mixture was purified by flash column chromatography on silica gel.

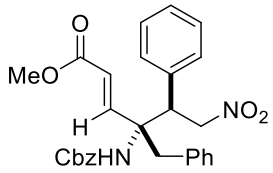
Methyl (4*R*,5*S*,*E*)-4-benzyl-4-((tert-butoxycarbonyl)amino)-5-(4-chlorophenyl)-6-nitro hex-2-enoate (30)



The title compound was prepared following the General Procedure starting from methyl (triphenylphosphoranylidene) acetate (250.76 mg, 0.75 mmol, 3 eq) and adduct **9Aa** (108.23 mg, 0.25 mmol, 1 eq). Reaction completion was found after 28 h. The crude was purified by flash column chromatography on silica gel using 90:10 Hexane:EtOAc as the eluent system to afford the product as a white foam (96 mg, 0.196 mmol, 79% yield). $[\alpha]_D^{21}$ = 1.49º (c=1.00, CH_2Cl_2).

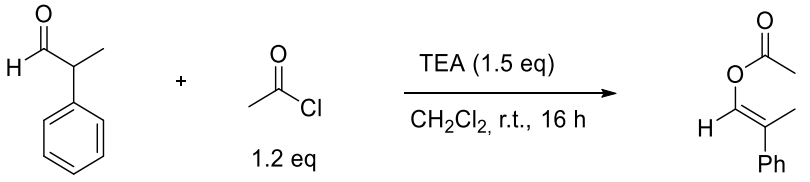
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 7.20 – 7.14 (m, 2H), 7.02 (dd, J = 6.6, 2.9 Hz, 2H), 6.95 (d, J = 16.0 Hz, 1H), 5.51 (d, J = 16.0 Hz, 1H), 5.03 – 4.91 (m, 2H), 4.50 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.69 (d, J = 12.6 Hz, 1H), 3.24 (d, J = 13.2 Hz, 1H), 3.01 (d, J = 13.4 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 154.5, 147.0, 134.5, 134.2, 133.9, 130.9, 130.7, 129.0, 128.5, 127.6, 122.4, 80.5, 77.4, 61.6, 52.1, 50.4, 42.8, 28.4. UPLC-DAD-QTOF: $C_{25}H_{29}N_2O_6ClNa$ $[M+Na]^+$ calcd.: 511.1612, found: 511.1609.

Methyl (4*R*,5*S*,*E*)-4-benzyl-4-(((benzyloxy)carbonyl)amino)-6-nitro-5-phenylhex-2-enoate (31)



The title compound was prepared following the General Procedure starting from methyl (triphenylphosphoranylidene) acetate (857.58 mg, 2.56 mmol, 3 eq) and adduct **9Bd** (370.0 mg, 0.85 mmol, 1 eq). Reaction completion was found after 31 h. The crude was purified by flash column chromatography on silica gel using 80:20 Hexane:EtOAc as the eluent system to afford the product as a white foam (308.1 mg, 0.63 mmol, 74% yield). $[\alpha]_D^{24}$ = –8.72º (c=1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.32 – 7.25 (m, 4H), 7.25 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 7.01 – 6.95 (m, 2H), 5.65 (d, J = 16.1 Hz, 1H), 5.08 (d, J = 8.0 Hz, 2H), 5.01 – 4.93 (m, 2H), 4.69 (s, 1H), 4.39 – 4.29 (m, 1H), 3.76 (s, 3H), 3.10 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 154.8, 147.5, 136.1, 134.7, 134.0, 130.6, 129.6, 129.4, 128.8, 128.6, 128.6, 128.5, 128.5, 127.5, 122.0, 77.4, 67.0, 61.4, 52.0, 50.9, 42.8. UPLC-DAD-QTOF: $C_{28}H_{29}N_2O_6$ $[M+H]^+$ calcd.: 489.2026, found: 489.2026.

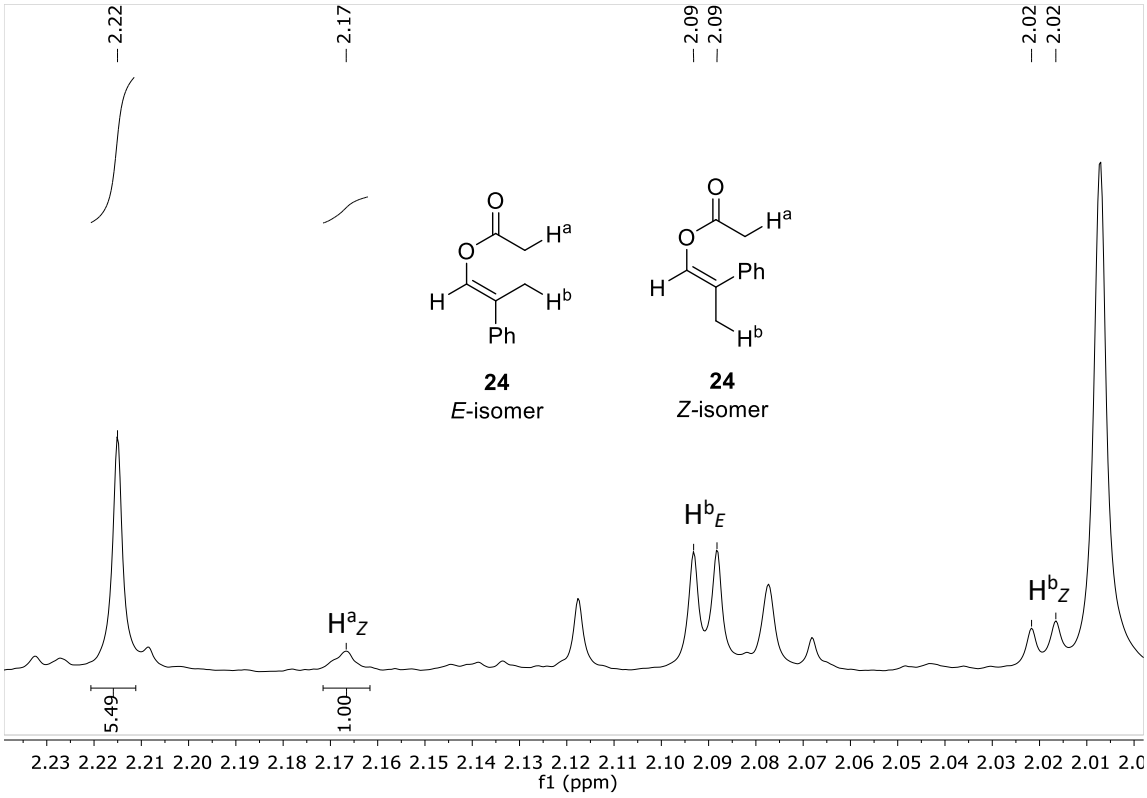
5.3.5. Enol acetate (34) formation



(±) 16A **34**
43% conv., 5.5:1 *E*:*Z*

Aldehyde (±)**16A** (134 µL, 1 mmol, 1 eq) was dissolved in DCM (2 mL) at 0 ºC and first, TEA (208 µL, 1.5 mmol, 1.5 eq) and then, acetyl chloride (85.3 µL, 1.2 mmol, 1.2 eq) were added dropwise. The resulting mixture was stirred at room temperature for 16 h to afford the enol acetate **24** in 43% conversion and 5.5:1 ratio for the *E*:*Z* isomers. Both *E* and *Z* isomers were identified by ^{1}H NMR as they were described in the literature.[233]

[233] For the *E* isomer: Liu, C.; Yuan, J.; Zhang, J.; Wang, Z.; Zhang, Z.; Zhang, W. *Org. Lett.* **2018**, *20*, 108–111; Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc*. **2008**, *130*, 2424–2425. For both isomers: Sharley, J. S.; Collado Pérez, A. M.; Espinos Ferri, E.; Fernandez Miranda, A.; Baxendale, I. R. *Tetrahedron* **2016**, *72*, 2947-2954.



5.3.6. Theoretical calculations

5.3.6.1. Conjugate addition of α-amino aldehydes to nitroolefins

5.3.6.1.1. Reactive Complexes Analysis

In order to have a complete overview of the reaction mechanism, we decided to perform an initial analysis of the possible reaction complexes considering different H–bond patterns between the catalyst and the reagents. For that we considered the main models collected in Figure 4 of the main manuscript that corresponds to Takemoto's [model A] Papai's [model B] and Wang's [model C] approaches. In addition, due to the chemical structure of **C7**, two possible internal H–bonding interactions in the catalyst (namely, Ar–moiety and Chinchone–moiety) were considered in each model.

Our results show that all the reactive complexes presenting Ar–moiety internal H–bonding interactions in the catalyst following either model A or model B H–bond patterns are energetically accessible; that is, it is not possible to assess which pattern is the preferred one. Remarkably, all our attempts to obtain reactive complexes following model C led to their model A analogous in only few optimization steps.

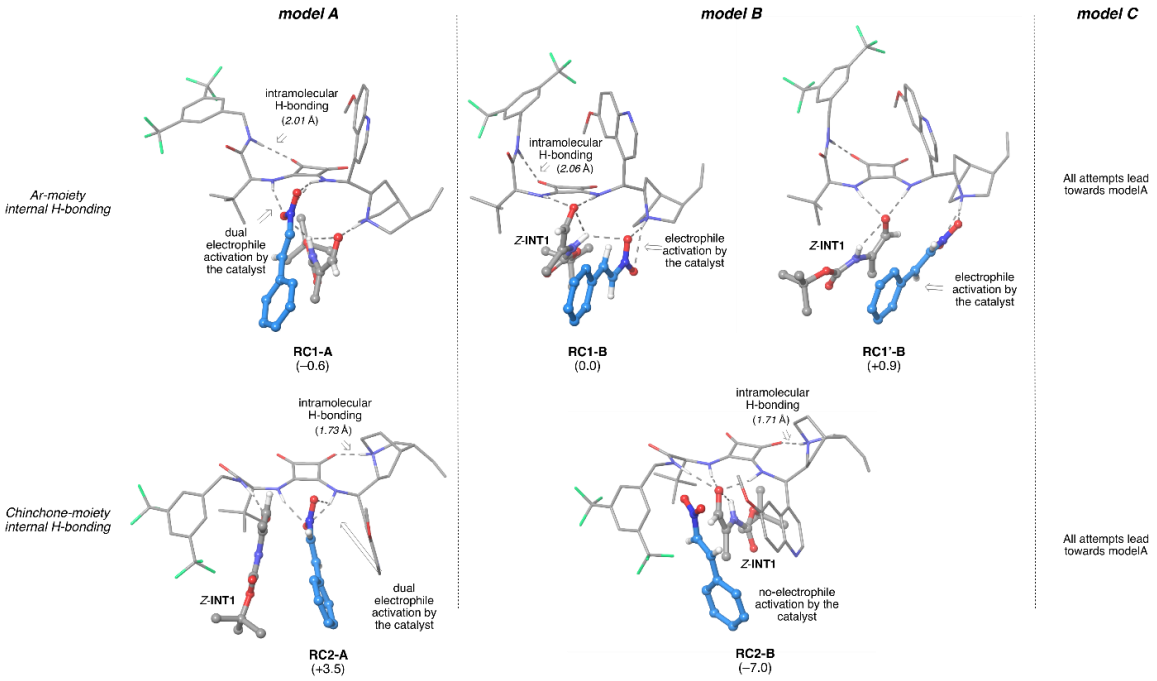


*Figure 16. Main geometrical features and relative Gibbs free energies of least energetic reactive complexes associated with the reaction of **1A** and **8b** catalysed by **C7** according to Takemoto's and Pápai's model. Some hydrogen atoms are omitted for clarity. Energy values kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K).*

It is worth to mention that complexes presenting Chinchone–moiety internal H–bonding interactions in the catalyst lead to energetically unfavorable compounds (**RC2-A**) or unreactive species (**RC2-B**). In this latter compound, the enolate shows three H–bonding interactions with the catalyst, avoiding any catalyst–electrophile interaction. Within this pattern, the reaction cannot occur since the electrophile is not activated, and both prochiral faces of *Z*-**INT1** are blocked.

As a consequence, in the following study, species following model C H–bond pattern or with Chinchone–moiety internal H–bonding interaction in the catalyst were discarded.

5.3.6.1.2. Exploration of different Transition Structures considering feasible substrate–catalyst combinations

In Figure 17 are collected the main geometrical features and relative Gibbs free energies of the least energetic transition structures corresponding to the **C7** catalysed reaction of **1A** and **8b**.

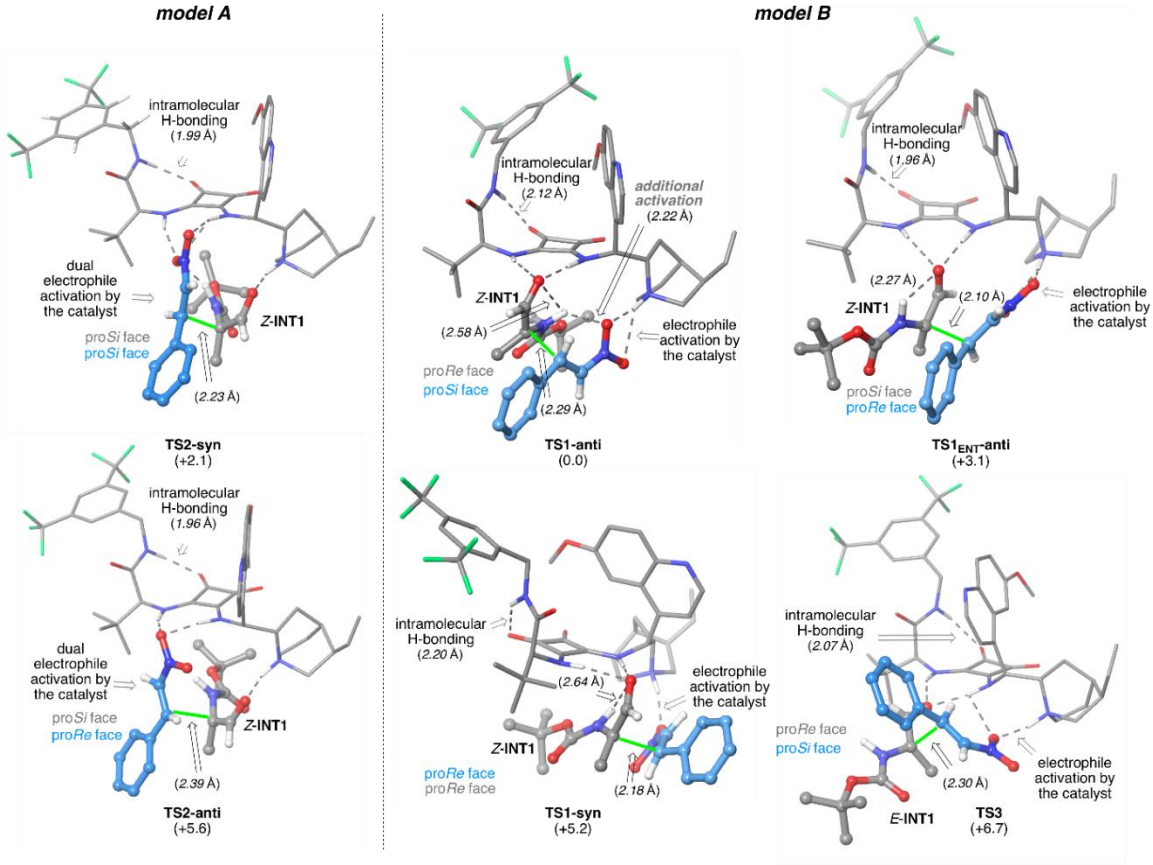


*Figure 17. Main geometrical features and relative Gibbs free energies of least energetic transition structures associated with the reaction of **1A** and **8b** catalysed by **C7** according to Takemoto's and Pápai's model. Some hydrogen atoms are omitted for clarity. Energy values kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in blue and grey respectively.*

Our calculations show that transition structures following Papai's hypothesis (model B) are the most favored ones, despite both model A and model B **RC** being energetically accessible. We interpret it as consequence of the higher energy required to distort the geometry of the electrophile from the reactive complex geometry towards the transition structure due to the presence of two **C7**–**8b** H–bonding interactions in **TS2-syn/anti**. In fact, placing the electrophile close to the squaramide core drastically reduces its degrees of freedom. (Note that with one H–bonding interaction, the electrophile can rotate freely, but with two H–interactions that rotation is not possible). That effect is particularly relevant when using a 1,4–acceptor electrophile, where the electrophile reactive carbon atom lies far away from the catalyst, and therefore, far away from the enolate coordinated to the catalyst 'arm'. This same effect was observed in the case of **TS1$_{ENT}$-anti**, where the enolate reactive carbon also lies far away from the catalyst, and therefore from the electrophile.

Additionally, we computed **TS3** in which the enolate present an *E* conformation. As expected, reaction involving *E*-enolates are energetically inaccessible.

5.3.6.1.3. Computational methods

All the computational studies were carried out by means of Gaussian 16[234] suite of programs. The calculations were performed within the Density Functional Theory[124] (DFT) framework using the B3LYP[235] functional in combination with 6-31G(d) or 6-311+G(d,p) basis sets. Dispersion corrections are included by means of Grimme's D3 model.[236] Solvent effects were estimated using the polarizable continuum model[237] (PCM) within the self-consistent reaction field (SCRF) approach.[238] All SCRF-PCM calculations were performed using CH_2Cl_2 (ε =8.93) as model solvent. Thermal corrections were computed at the same level of theory as the optimization and were not scaled. All stationary points were characterized by harmonic analysis. Reactants and products have positive definite Hessian matrices. Transition structures show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the studied reaction coordinate. Activation and reaction (Gibbs) energies were calculated at the corresponding temperature considering species directly connected to the computed transition structures in order to compute solvated standard conditions.

[234]Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J.; Gaussian, Inc., Wallingford CT, **2016**.

[235] Becke, A. D. *J. Chem. Phys,* **1993**, *98*, 5648–5650.

[236] Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. J. *Chem. Phys.* **2010**, *132*, 154104.

[237] Stevens, W. J.; Basch, H.; Krauss, M. *J. Chem. Phys.* **1984**, *81*, 6026–6034.

[238] Glendening, E. D.; Streitwieser, A. *J. Chem. Phys.* **1994**, *100*, 2900–2904.

5.3.6.1.4. Energies, thermal corrections and cartesian coordinates of all computed stationary points

Table 17. Total electronic energies[a] (E, in a.u.), zero-point correction of the energy[b] (ZPCE), thermal corrections to Gibbs free energies[b] (TCGFE, in a.u.), and number of imaginary frequencies[c] (NIMAG) of all stationary points discussed in the main text.

Structure	E	Z	TC	NIMAG
TS1	-	0.	0.3	1 (–
TS2	-	0.	0.3	1 (–
TS3	-	0.	0.3	1 (–
TS4	-	0.	0.3	1 (–
RC1-A	-	1.	1.0	0
RC1-B	-	1.	1.0	0
RC1'-B	-	1.	1.0	0
RC2-A	-	1.	1.0	0
RC2-B	-	1.	1.0	0
TS1-anti	-	1.	1.0	1(–
TS1-syn	-	1.	1.0	1 (–
$TS1_{ENT}$-anti	-	1.	1.0	1 (–
TS2-syn	-	1.	1.0	1 (–
TS2-anti	-	1.	1.0	1 (–
TS3	-	1.	1.0	1 (–

[a]Computed at B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level. [b]Computed at 298.15 K at B3LYP-D3(PCM)/6-31G(d) level. [c]If NIMAG=1, the imaginary frequency ν (in parentheses) is given in cm^{-1}.

5.3.6.2. Conjugate addition of α-aryl acetaldehydes

5.3.6.2.1. Computational methods

All the computational studies were carried out by means of Gaussian 16[234] suite of programs. The calculations were performed within the Density Functional Theory[124] (DFT) framework using the B3LYP[235] functional in combination with 6-31G(d) or 6-311+G(d,p) basis sets. Dispersion corrections are included by means of Grimme's D3 model.[236] Solvent effects were estimated using the polarizable continuum model[237] (PCM) within the self-consistent reaction field (SCRF) approach[238] by means of single point energy calculation of gas phase optimized structures. All SCRF-PCM calculations were performed using CH_2Cl_2 (ε =8.93) as model solvent. Thermal corrections were computed at the same level of theory as the optimization and were not scaled. All stationary points were characterized by harmonic analysis. Reactants and products have positive definite Hessian matrices. Transition structures show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the studied reaction coordinate. Activation and reaction (Gibbs) energies were calculated at the corresponding temperature considering species directly connected to the computed transition structures.

*Table 18. Total electronic energies[a] (E, in a.u.), zero point correction of the energy[b] (ZPCE), thermal corrections to Gibbs free energies[b] (TCGFE, in a.u.), and number of imaginary frequencies[c] (NIMAG) of stationary points associated with the reaction of **16A** and **8b** catalysed by **C20** discussed in the main text.*

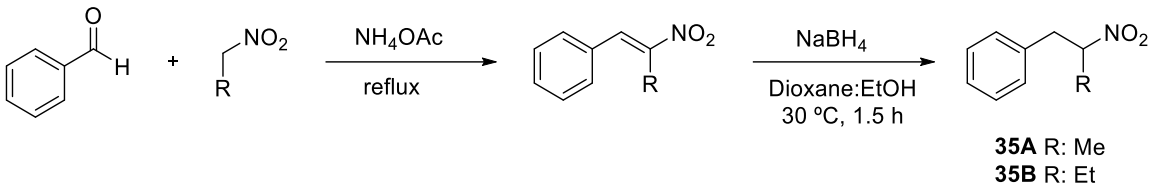
Structure	E	ZPCE	TC	NIMAG
RC-*E*	-	1.249	1.1	0
RC-*Z*	-	1.249	1.1	0
RC$_{TAKEMOTO}$-*E*	-	1.248	1.1	0
RC$_{TAKEMOTO}$-*Z*	-	1.247	1.1	0
TS1-*E*-syn	-	1.249	1.1	1 (-
TS1$_{ENT}$-*E*-syn	-	1.248	1.1	1 (-
TS1-*E*-anti	-	1.249	1.1	1 (-
TS1$_{ENT}$-*E*-anti	-	1.249	1.1	1 (-
TS1-*Z*-syn	-	1.249	1.1	1 (-
TS1$_{ENT}$-*Z*-syn	-	1.249	1.1	1 (-
TS1-*Z*-anti	-	1.249	1.1	1 (-
TS1$_{ENT}$-*Z*-anti	-	1.248	1.1	1 (-
TS1$_{TAKEMOTO}$-	-	1.249	1.1	1 (-
TS1$_{TAKEMOTO}$-	-	1.250	1.1	1 (-
PROD- *E*	-	1.250	1.1	0

[a]Computed at B3LYP-D3(PCM)/6-311+G(d,p) level. [b]Computed at 298.15 K at B3LYP-D3/6-31G(d). [c]If NIMAG=1, the imaginary frequency ν in parentheses is given in cm^{-1}.

5.4. Experimental section for Chapter 3

5.4.1. Synthesis of starting materials

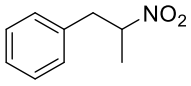
*5.4.1.1. Synthesis of nitroalkanes **35A** and **35B***



GENERAL PROCEDURE:[239]

To a stirred mixture of benzaldehyde (1 eq) and the corresponding nitroalkane ammonium acetate (1 eq) was added and the reaction mixture was refluxed until reaction completion. The nitroalkane excess was then evaporated and the resulting mixture was redissolved in EtOAc, washed with H_2O (x2) and brine (x3) and dried over $MgSO_4$. Solvents were removed under reduced pressure to afford the crude nitroalkene, which was then dissolved in dioxane (0.75 mL/mmol) and slowly added (during 45 min) to a mixture of $NaBH_4$ (2.16 eq) in EtOH/dioxane (1 mL/mmol, 1:3 proportion) at 30 ºC. The reaction mixture was stirred at 30 ºC for another 45 minutes and then quenched with an ice/ water mixture (2 mL/mmol) followed by acetic acid 50% (0.5 mL/mmol). After the gas evolution stopped, the aqueous phase was extracted with CH_2Cl_2 (x3). The organic layers were combined, washed with H_2O (x3) and brine, and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by flash column chromatography on silica gel.

(2-Nitropropyl)benzene (35A)

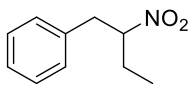


The title compound was prepared following the General Procedure starting from commercially available benzaldehyde (2.03 g, 20 mmol, 1 eq) and nitroethane (60 mL, 3 mL/mmol). Reaction completion for the first step was found after 2 h. The crude was purified by flash column chromatography on silica gel using 98:2 Hexane:EtOAc as the eluent system to afford the product as a yellow oil (1.6521 g, 10 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.39 – 7.19 (m, 4H), 4.88 – 4.76 (m, 1H), 3.41 – 3.34 (dd, J = 14.0, 7.4 Hz, 1H), 3.09 – 3.01 (dd, J = 14.0, 6.9 Hz, 1H), 1.60 – 1.58 (d, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 135.4,

[239] For the Henry reaction, see: a) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W.; Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52* (15), 4235–4238. For the reduction, see: b) Ref 240.

128.8, 128.6, 127.2, 84.3, 41.0, 18.6. All spectroscopic data were consistent with those previously reported.[240]

(2-Nitrobutyl)benzene (35B)



The title compound was prepared following the General Procedure starting from commercially available benzaldehyde (1.02 mL, 10 mmol, 1 eq) and nitropropane (20 mL, 2 mL/mmol). Reaction completion for the first step was found after 2 days. The crude was purified by flash column chromatography on silica gel using 95:5 Hexane:EtOAc as the eluent system to afford the product as a yellow liquid (1.683 g, 9.39 mmol, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 3H), 7.19 – 7.12 (m, 2H), 4.70 – 4.56 (m, 1H), 3.27 (dd, J = 14.1, 8.5 Hz, 1H), 3.03 (dd, J = 14.2, 5.9 Hz, 1H), 2.09 – 1.94 (m, 1H), 1.91 – 1.76 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H). All spectroscopic data were consistent with those previously reported.[241]

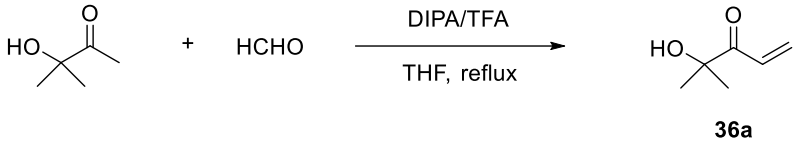
5.4.1.2. Synthesis of electrophiles

Enones **41a** was commercially available and enone **41b** was prepared following the procedures described in the literature.[242]

5.4.1.2.1. Synthesis of α-hydroxy enones

α-Hydroxy enone **36b** was prepared following the procedure described in the literature.[86]

4-Hydroxy-4-methylpent-1-en-3-one (36a)[86]



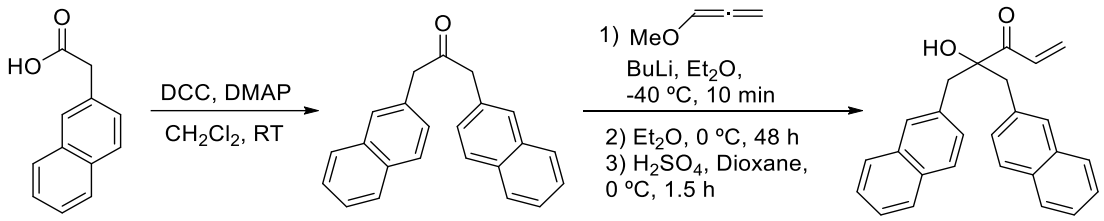
36a

3-Hydroxy-3-methyl-2-butanone (2.65 mL, 25 mmol, 1 eq) and paraformaldehyde (1.5 g, 50 mmol, 2 eq) were added to a previously prepared solution of DIPA (7 mL, 50 mmol, 2 eq) and TFA (4.8 mL, 62.5 mmol, 2.5 eq) in dry THF (125 mL). The mixture was stirred at reflux and more paraformadehyde (1.5 g 50 mmol, 2 eq) was added portionwise during 6 h (every 2 h aprox.). Then, the mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with HCl 1N (2 x 37.5 mL), NaOH 1M (2 x 37.5 mL) and brine (2 x 37.5 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by flash column

[240] Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C. *Synth.* **1985**, *1985* (9), 886–887.
[241] Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012**, *134* (24), 9942–9945.
[242] Del Pozo, S.; Vera, S.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2017**, *139* (43), 15308–15311

chromatography on silica gel using Et_2O as eluent. The product was obtained as a colorless liquid in quantitative yield. 1H-NMR (300 MHz, CDCl3), δ (ppm) = 6.83 – 6.74 (dd, J = 17.0, 10.3 Hz, 1H), 6.60 – 6.54 (dd, J = 17.0, 1.9 Hz, 1H), 5.90 – 5.86 (dd, J = 10.3, 1.9 Hz, 1H), 1.43 (s, 6H). 13C-NMR (75 MHz, CDCl3), δ (ppm) = 202.44, 130.76, 128.95, 75.27, 25.48. All spectroscopic data were consistent with those previously reported.[86]

4-Hydroxy-5-(naphthalen-2-yl)-4-(naphthalen-2-ylmethyl)pent-1-en-3-one (36c)



36c

Step 1:[243]

To a stirred solution of DCC (3.11 g, 15.09 mmol, 1.006 eq) and DMAP (0.46 g, 3.77 mmol, 25 mol%) in CH_2Cl_2 (35 mL) at room temperature and under inert atmosphere a previously prepared solution of 2-(naphthalen-2-yl)acetic acid (2.793 g, 15 mmol, 1 eq) in CH_2Cl_2 (23 mL) was added dropwise and the solution, which turned orange, was stirred at the same temperature overnight. The resulting mixture was filtered, the solvents were removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (Hexanes:EtOAc 90:10). The product was obtained as a yellow oil (3.026 g, 9.75 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 6H), 7.64 – 7.59 (m, 2H), 7.52 – 7.42 (m, 4H), 7.29 (d, J = 1.8 Hz, 2H), 3.92 (s, 4H). All spectroscopic data were consistent with those previously reported.[244]

Step 2: [86]

To a stirred solution of the previously prepared 1-methoxypropa-1,2-diene (0.15 mL, 1.8 mmol, 0.8 eq) in dry Et_2O (3.6 mL) under N_2 atmosphere and at -40 ºC n-BuLi (2.5M, 0.8 mL, 2 mmol, 1 eq) was added dropwise. The mixture was stirred for 10 min at the same temperature and then a suspension of the previously prepared 1,3-di(naphthalen-2-yl)propan-2-one (620 mg, 2 mmol, 1 eq) in dry Et_2O (4 mL) was added slowly for 5 min. Finally, the mixture was warmed up to 0 ºC, stirred for 48 h and the reaction was slowly quenched with H_2O (5 mL) and allowed to reach RT. The mixture was extracted with EtOAc (x3) and the organic layers were combined and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the intermediate as a brown oil. This intermediate was dissolved in dioxane (5 mL) and added to a 5% solution of H_2SO_4

[243] Adapted from: Sauriat-Dorizon, H.; Maris, T.; Wuest, J. D.; Enright, G. D. *J. Org. Chem.* **2003**, *68* (2), 240–246.
[244] Harrington, L. E.; Britten, J. F.; Nikitin, K.; McGlinchey, M. J. *ChemPlusChem* **2017**, *82* (3), 433–441.

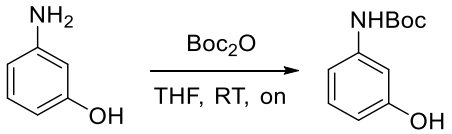
(4.3 mL) at 0 ºC. The mixture was stirred at the same temperature overnight and then warmed up to RT, saturated with NaCl and extracted with Et_2O (x5). The organic layers were combined, washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel (Hexanes:EtOAc 95:5). The product was obtained as a yellow solid (78.7 g, 0.2 mmol, 10% yield). m.p.: 115-118 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.68 (m, 8H), 7.49 (tdd, J = 5.2, 3.5, 1.6 Hz, 4H), 7.41 (dd, J = 8.4, 1.8 Hz, 2H), 7.06 (dd, J = 17.0, 10.4 Hz, 1H), 6.40 (dd, J = 17.0, 1.7 Hz, 1H), 5.85 (dd, J = 10.4, 1.7 Hz, 1H), 3.43 (d, J = 13.9 Hz, 2H), 3.33 (d, J = 13.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 133.3, 133.0, 132.6, 131.0, 130.0, 129.1, 128.7, 127.8, 127.7, 127.7, 126.0, 125.7, 82.0, 44.6. UPLC-DAD-QTOF: $C_{26}H_{22}O_2Na$ $[M+Na]^+$ calcd.: 389.1518, found: 389.1514.

5.4.1.2.2. Synthesis of acrylate esters

Methyl acrylate **38a** was commercially available.

Step 1: Amine protection with Boc

PROCEDURE:[245] ***tert*-butyl (3-hydroxyphenyl)carbamate**

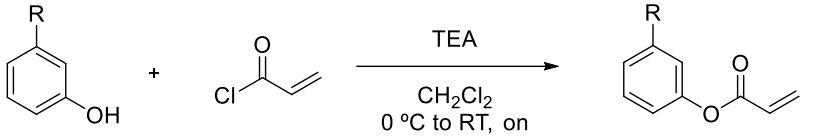


To a stirred solution of 3-aminophenol (545.6 mg, 5 mmol, 1 eq) in THF (2.5 mL) at room temperature Boc_2O (1.091 g, 5.1 mmol, 1.02 eq) was added. The reaction mixture was stirred at the same temperature overnight and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (Hexanes:EtOAc 98:2). The product was obtained as a colorless oil in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 2H), 6.74 (ddd, J = 8.1, 2.0, 0.8 Hz, 1H), 6.52 (ddd, J = 8.1, 2.5, 0.8 Hz, 1H), 6.48 (s, 1H), 1.51 (s, 9H).

[245] Adapted from: Tayama, E.; Toma, Y. *Tetrahedron* **2015**, *71* (4), 554–559.

Step 2: Coupling with acryloyl chloride.

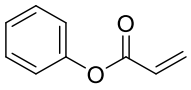
GENERAL PROCEDURE:[246]



38b R: H
38c R: NHBoc

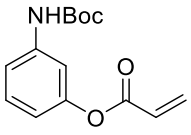
To a stirred solution of the corresponding alcohol (1 eq) in dry CH_2Cl_2 (3.5 mL/mmol) TEA (1.5 eq) was added and the mixture was cooled down to 0 ºC. Then, acryloyl chloride (1.2 eq) was added dropwise and the solution turned to yellow. The reaction mixture was allowed to reach room temperature and stirred overnight. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel.

Phenyl acrylate (38b)



The title compound was prepared following the General Procedure starting from commercially available phenol (376.4 mg, 4 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel using 95:5 Hexane:EtOAc as the eluent system to afford the product as a yellow liquid (486.6 g, 3.3 mmol, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.32 – 7.21 (m, 1H), 7.19 – 7.13 (m, 2H), 6.64 (dd, J = 17.3, 1.4 Hz, 1H), 6.36 (dd, J = 17.3, 10.4 Hz, 1H), 6.04 (dd, J = 10.4, 1.4 Hz, 1H).. All spectroscopic data were consistent with those previously reported.[246]

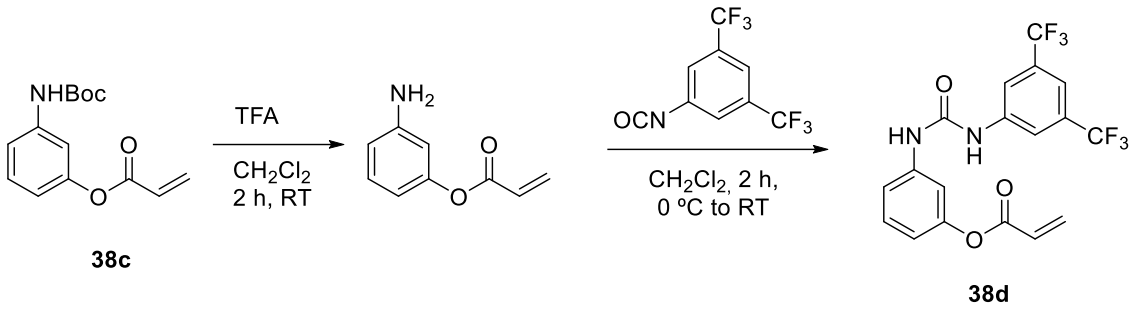
3-((*tert*-Butoxycarbonyl)amino)phenyl acrylate (38c)



The title compound was prepared following the General Procedure starting from previously prepared *tert*-butyl (3-hydroxyphenyl)carbamate (1.046, 5 mmol, 1 eq). The crude was purified by flash column chromatography on silica gel using 90:10 Hexane:EtOAc as the eluent system to afford the product as a white solid (1.047 g, 3.98 mmol, 80% yield). m.p.: 73-76 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.31 – 7.20 (m, 1H), 7.11 – 7.01 (m, 1H), 6.80 (dtd, J = 8.1, 1.5, 0.8 Hz, 1H), 6.65 (d, J = 8.9 Hz, 1H), 6.58 (dd, J = 17.3, 0.8 Hz, 1H), 6.29 (dd, J = 17.3, 10.4 Hz, 1H), 5.99 (dd, J = 10.4, 0.7 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 152.6, 151.2, 139.7, 132.7, 129.6, 128.0, 116.0, 115.8, 111.9, 80.8, 28.4. UPLC-DAD-QTOF: $C_{14}H_{17}NO_4Na$ $[M+Na]^+$ calcd.: 286.1055, found: 286.1062.

[246] Xiao, Q.; He, Q.; Li, J.; Wang, J. *Org. Lett.* **2015**, *17* (24), 6090–6093.

3-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)phenyl acrylate (38d)



38c **38d**

Step 1: Amine deprotection[152]

To a solution of 3-((*tert*-butoxycarbonyl)amino)phenyl acrylate (38c) (263.3 mg, 1 mmol, 1 eq) in CH_2Cl_2 (1 mL) at 0 ºC TFA (2 mL) was added dropwise. The mixture was allowed to reach RT and then stirred for 2 h. Then, solvents were removed under reduced pressure and the remaining oil was redissolved in H_2O, cooled down to 0 ºC and basified with a sat. Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with $NaHCO_3$ sat. and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude product as an orange oil (188.8 mg, 1 mmol, quantitative yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J = 8.0 Hz, 1H), 6.62 – 6.44 (m, 3H), 6.30 (dd, J = 17.3, 10.4 Hz, 1H), 5.99 (dd, J = 10.4, 1.4 Hz, 1H), 3.48 (s, 2H).

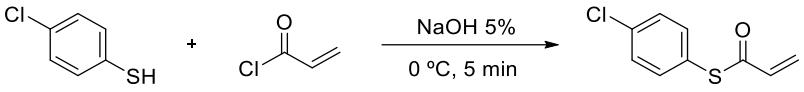
Step 2: Coupling with the isocyanate

To a stirred solution of the previously prepared 3-aminophenyl acrylate (163.2 mg, 1 mmol, 1 eq) in dry CH_2Cl_2 (1 mL), under inert atmosphere and at 0 ºC 1-isocyanato-3,5-bis(trifluoromethyl)benzene (0.17 mL, 1 mmol, 1 eq) was added dropwise and the reaction mixture was stirred at room temperature. Reaction was followed by IR spectroscopy by disappearance of the isocyanate band (2267 cm^{-1}). Then, after 3 h the solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (Hexanes:EtOAc 80:20). The product was obtained as a white solid (160.3 mg, 0.38 mmol, 38% yield). m.p.: 136-138 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.53 – 7.37 (m, 3H), 7.15 (t, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.78 – 6.65 (m, 3H), 6.40 (dd, J = 17.2, 10.4 Hz, 1H), 6.18 (dd, J = 10.4, 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.0, 150.8, 140.2, 139.5, 134.7, 132.3 (q, J = 33.3 Hz), 130.1, 127.4, 123.3 (q, J = 274.5 Hz), 118.6, 118.5, 118.1, 116.4, 116.2, 113.6, 110.1. UPLC-DAD-QTOF: $C_{18}H_{13}N_2O_2F_6$ $[M+H]^+$ calcd.: 419.0830, found: 419.0830.

5.4.1.2.3. Synthesis of thioacrylate esters

Thioacrylate esters **39b** and **39c** were prepared following the procedures described in the literature.[247]

_S_-(4-chlorophenyl) prop-2-enethioate (39a)[248]

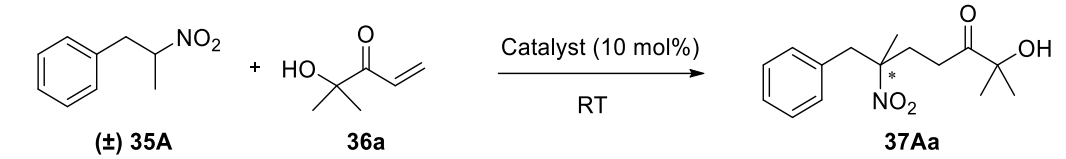


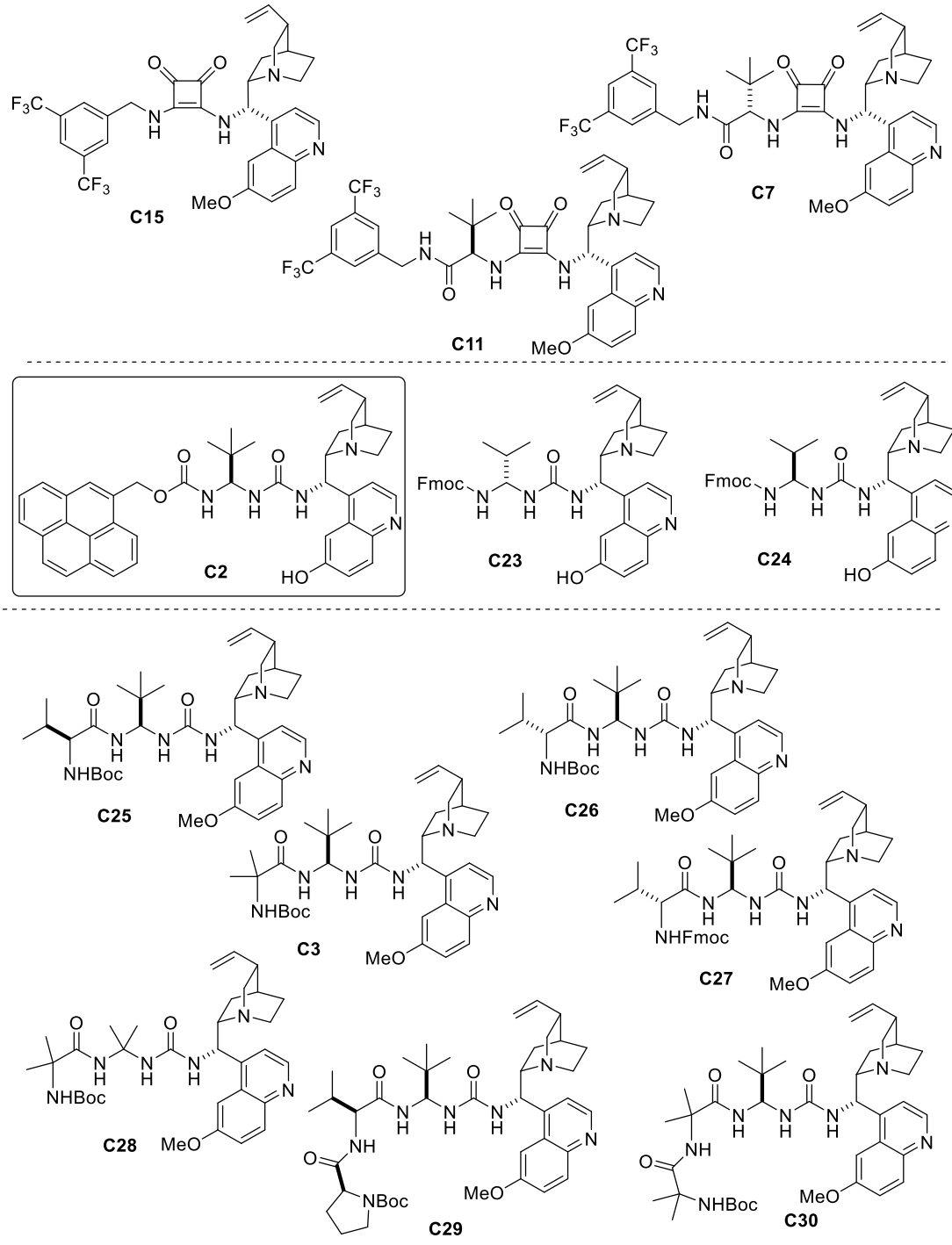
To a stirred suspension of 4-chlorobenzenethiol (0.51 mL, 5 mmol, 1 eq) in NaOH 5% in H_2O (8 mL/mmol) at 0 ºC acryloyl chloride (1.22 mL, 50 mmol, 10 eq) was added and the mixture was stirred at 0 ºC for 5 min and quickly extracted with CH_2Cl_2 (30 mL x2). The organic layers were combined, washed with $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (Hexanes:EtOAc 70:30). The product was obtained as a colorless oil (56.9 mg, 0.35 mmol, 4% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 4H), 6.55 – 6.35 (m, 2H), 5.83 (dd, J = 8.4, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.04, 136.08, 135.93, 134.33, 129.62, 127.98, 125.75. UPLC-DAD-QTOF: $C_9H_7ClOSNa$ $[M+Na]^+$ calcd.: 220.9804, found: 220.9802.

[247] Zhou, G.; Yost, J. M.; Sauer, S. J.; Coltart, D. M. *Org. Lett.* **2007**, *9* (22), 4663–4665.
[248] Wei, M.-X.; Wang, C.-T.; Du, J.-Y.; Qu, H.; Yin, P.-R.; Bao, X.; Ma, X.-Y.; Zhao, X.-H.; Zhang, G.-B.; Fan, C.-A. *Chem. Asian J.* **2013**, *8* (9), 1966–1971.

5.4.2. Catalytic conjugate addition of α-substituted nitroalkanes to α-hydroxy enones and (thio)acrylate esters

*5.4.2.1. Catalyst screening for the model reaction between **35A** and **36a***

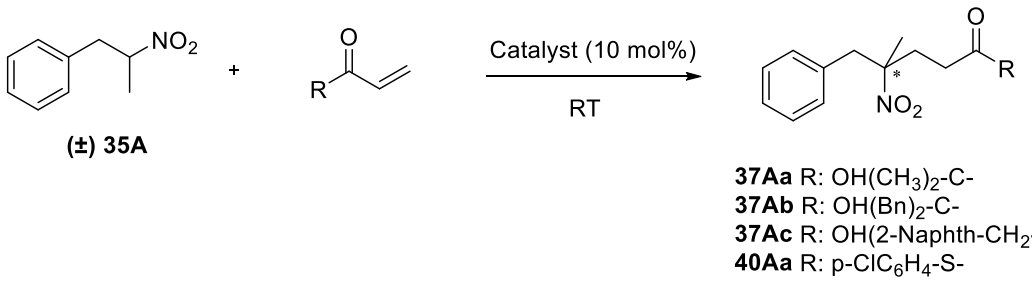




Entry	Cat.	Solvent	t(h)	Conv. (%)[b]	Yield (%)	*ee*[c]
1	**C15**	CH_2Cl_2	8 days	74	49	21
2	**C7**	CH_2Cl_2	6 days	94	61	21
3	**C11**	CH_2Cl_2	8 days	>99	77	19
4	**C2**	CH_2Cl_2	16	>99	70	79
5[d]		$CHCl_3$	20	>99	-	80
6	**C23**	CH_2Cl_2	26	>99	68	24
7	**C24**	CH_2Cl_2	23	>99	81	56
8	**C25**	CH_2Cl_2	42	>99	80	30
9	**C26**	CH_2Cl_2	22	>99	76	45
10	**C3**	CH_2Cl_2	16	>99	59	33
11	**C27**	CH_2Cl_2	25	>99	56	32
12	**C28**	CH_2Cl_2	22	>99	62	0
13	**C29**	CH_2Cl_2	20	>99	73	26
14	**C30**	CH_2Cl_2	26	>99	89	13

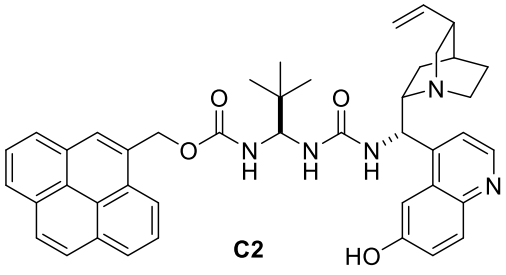
[a] Reactions carried out at RT on a 0.2 mmol scale 0.2 mL of solvent (mol ratio nitroalkane/ hydroxy enone/catalyst 5:1:0.1) [b] Determined by the disappearance of the starting α-hydroxy enone. [c] Determined by chiral HPLC. [d] Data obtained by Prof. Garcia's group with 20 mol% of catalyst.

*5.4.2.2. Reaction scope of the conjugate addition of (±)**35A** to different α-hydroxy enones and (thio)acrylate esters*



(±) 35A

37Aa R: $OH(CH_3)_2$-C-
37Ab R: $OH(Bn)_2$-C-
37Ac R: $OH(2\text{-Naphth-}CH_2\text{-})_2$-C-
40Aa R: p-ClC_6H_4-S-



C2

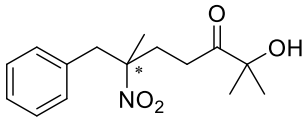
GENERAL PROCEDURE:

To a stirred solution of the corresponding α-hydroxy enone or thioacrylate (0.2 mmol, 1 eq) and nitroalkane **35A** (169.1 mg, 1 mmol, 5 eq) in CH_2Cl_2 (0.2 mL) catalyst **C2** (13.2 mg, 0.02 mmol, 10%) was added and the mixture was stirred at room temperature.

The reaction was followed by TLC (80:20 Hexane: EtOAc). After reaction completion (15-24 h), the mixture was concentrated under reduced pressure and purified by silica column flash chromatography. Reaction conversions were determined by ^{1}H NMR. Enantiomeric ratios were determined by chiral HPLC.

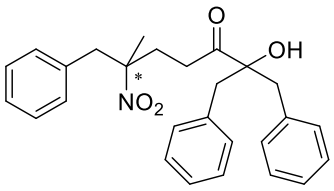
The racemic reactions were run following the above procedure, using TEA (30 mol%) as catalyst.

2-Hydroxy-2,6-dimethyl-6-nitro-7-phenylheptan-3-one (37Aa)



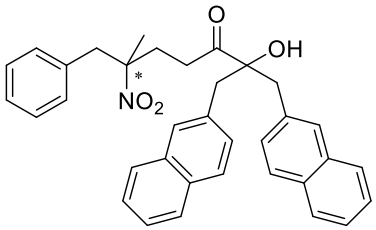
Prepared following the General Procedure starting from nitroalkane **35A** and α-hydroxy enone **36a.** The product was isolated as a white solid (39.1 mg, 0.14 mmol, 70% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 98:2, flow rate=1 mL/min). Retention times: 44.7 min (major) and 49.4 min (minor). m.p.: 79-84 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35 – 7.32 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.15 – 7.11 (dd, *J* = 7.1, 2.4 Hz, 2H), 3.44 – 3.39 (m, 1H), 3.15 – 3.10 (d, *J* = 13.9 Hz, 1H), 2.61 – 2.59 (m, 2H), 2.21 – 2.08 (m, 2H), 1.52 (s, 3H), 1.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 213.1, 134.6, 130.5, 129.0, 128.1, 91.5, 46.9, 33.4, 30.7, 27.0, 21.8. UPLC-DAD-QTOF: $C_{15}H_{21}NO_4Na$ $[M+Na]^+$ calcd.: 302.1368, found: 302.1366.

2-Benzyl-2-hydroxy-6-methyl-6-nitro-1,7-diphenylheptan-3-one (37Ab)



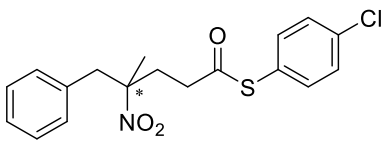
Prepared following General Procedure starting from nitroalkane **35A** and α-hydroxy enone **36b.** The product was isolated as a white solid (69 mg, 0.15 mmol, 76% yield) after flash column chromatography on silica gel (Hexane:EtOAc 90:10). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 95:5, flow rate=1 mL/min). Retention times: 15.7 min (major) and 19.4 min (minor). m.p.: 131-133 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 13H), 7.06 – 6.96 (m, 2H), 3.25 (d, J = 13.9 Hz, 1H), 3.17 (dd, J = 13.7, 7.3 Hz, 2H), 3.04 – 2.94 (m, 2H), 2.91 (d, J = 13.9 Hz, 1H), 2.27 – 2.18 (m, 2H), 2.19 – 2.05 (m, 1H), 1.83 – 1.68 (m, 1H), 1.59 (s, 1H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 135.4, 135.4, 134.4, 130.2, 130.2, 128.7, 128.7, 128.6, 127.7, 127.4, 127.3, 91.0, 83.1, 46.2, 45.4, 45.1, 33.8, 32.6, 21.3. UPLC-DAD-QTOF: $C_{27}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 454.1994, found: 454.1996.

2-Hydroxy-6-methyl-1-(naphthalen-2-yl)-2-(naphthalen-2-ylmethyl)-6-nitro-7-phenylheptan-3-one (37Ac)



Prepared following the General Procedure starting from nitroalkane **35A** and α-hydroxy enone **36c**. The product was isolated as a yellow solid (67.6 mg, 0.128 mmol, 64% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 90:10, flow rate=1 mL/min). Retention times: 21.1 min (major) and 35.0 min (minor). m.p.: 142-144 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.69 (m, 6H), 7.64 (d, J = 4.9 Hz, 2H), 7.49 – 7.39 (m, 4H), 7.36 – 7.27 (m, 2H), 7.23 – 7.13 (m, 3H), 6.89 (dd, J = 7.6, 1.8 Hz, 2H), 3.35 (dd, J = 13.7, 5.2 Hz, 2H), 3.25 – 3.03 (m, 4H), 2.76 (d, J = 13.9 Hz, 1H), 2.43 – 2.20 (m, 2H), 2.06 (ddd, J = 15.6, 10.3, 5.5 Hz, 1H), 1.67 (ddd, J = 15.0, 10.6, 4.9 Hz, 1H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 135.4, 135.4, 134.4, 130.2, 130.2, 128.7, 128.7, 128.6, 127.7, 127.4, 127.3, 91.0, 83.1, 46.2, 45.4, 45.1, 33.8, 32.6, 21.3. UPLC-DAD-QTOF: $C_{35}H_{33}NO_4Na$ $[M+Na]^+$ calcd.: 554.2307, found: 554.2305.

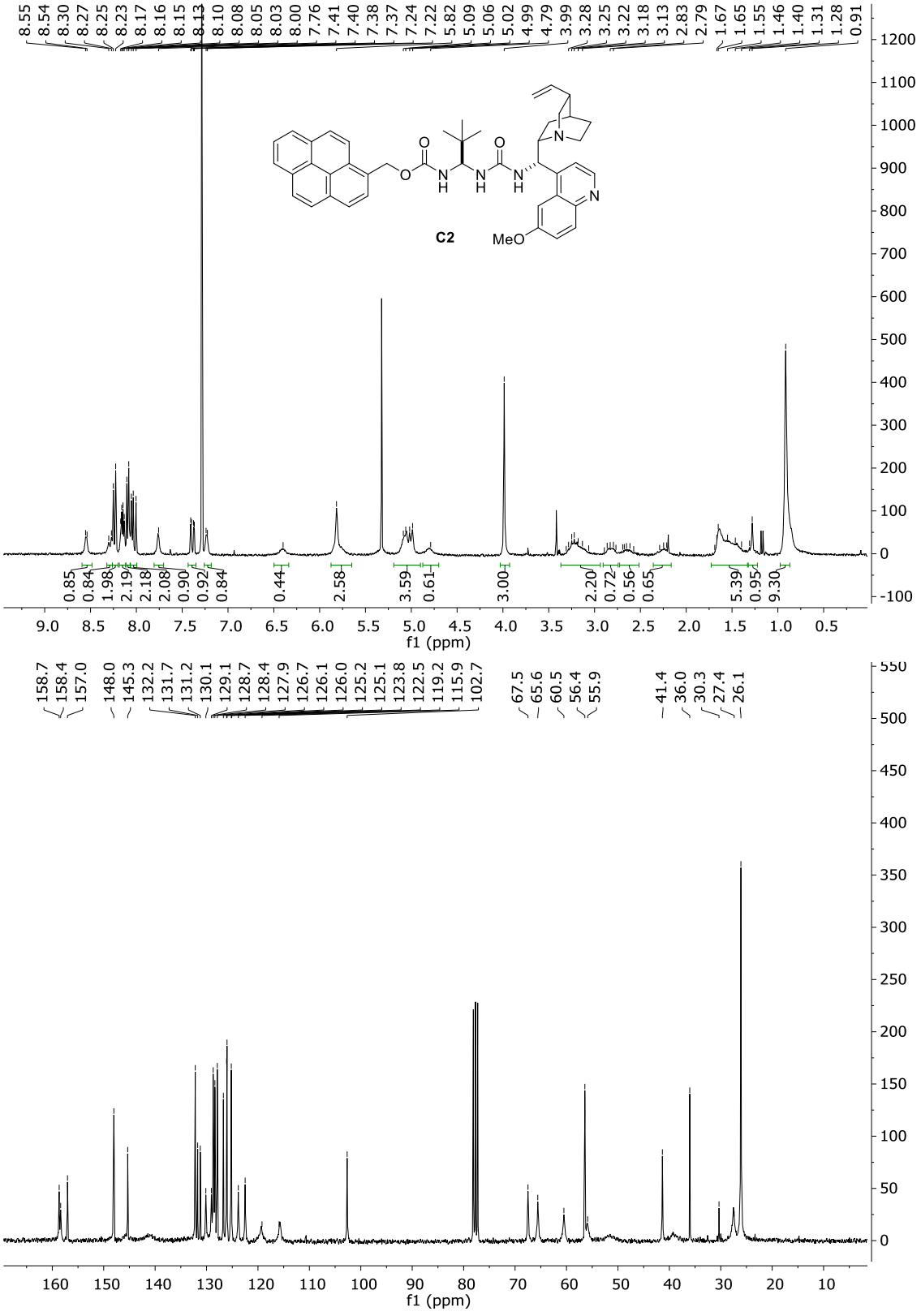
***S*-(4-Chlorophenyl) 4-methyl-4-nitro-5-phenylpentanethioate (40Aa)**

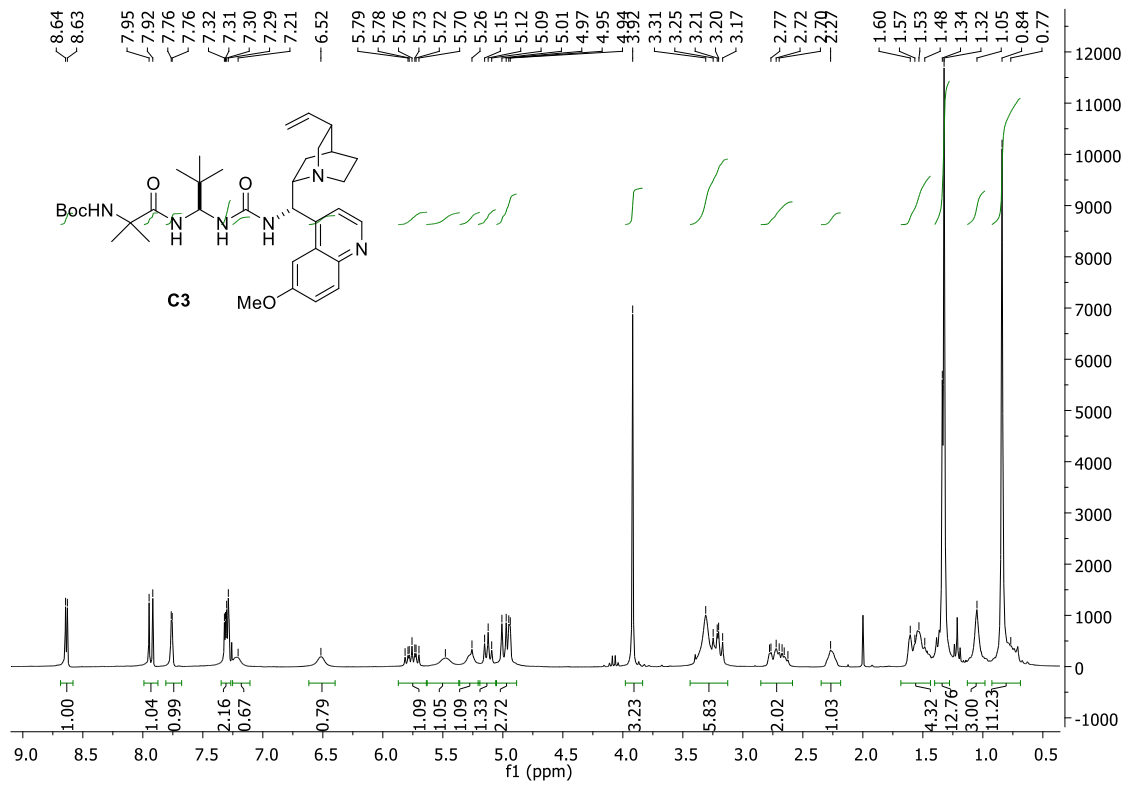


Prepared following the General Procedure starting from nitroalkane **35A** and thioacrylate **39a**. The product was isolated as a white foam (32.0 mg, 0.088 mmol, 44% yield) after flash column chromatography on silica gel (Hexane:EtOAc 95:5).The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 99:1, flow rate=1 mL/min). Retention times: 24.6 min (minor) and 27.1 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.35 – 7.25 (m, 5H), 7.12 – 7.05 (m, 2H), 3.34 (d, J = 13.9 Hz, 1H), 3.09 (d, J = 13.9 Hz, 1H), 2.76 – 2.66 (m, 2H), 2.54 (ddd, J = 15.4, 9.9, 5.6 Hz, 1H), 2.18 (ddd, J = 14.6, 9.4, 6.4 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 136.2, 135.8, 134.1, 130.2, 129.7, 128.8, 127.9, 125.7, 91.0, 46.4, 38.4, 34.1, 21.6.

5.5. Representative NMR spectra

5.5.1. NMR spectra of catalysts

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1.34
1.32
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0.77
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C3
MeO
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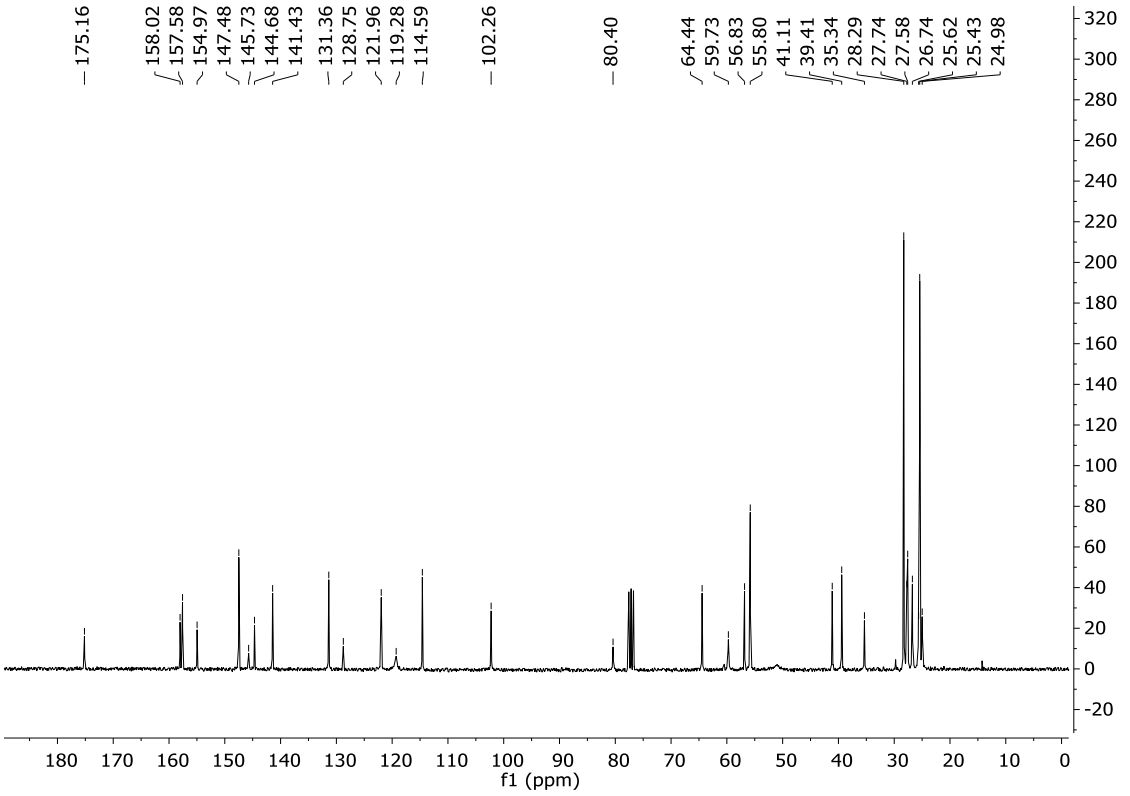
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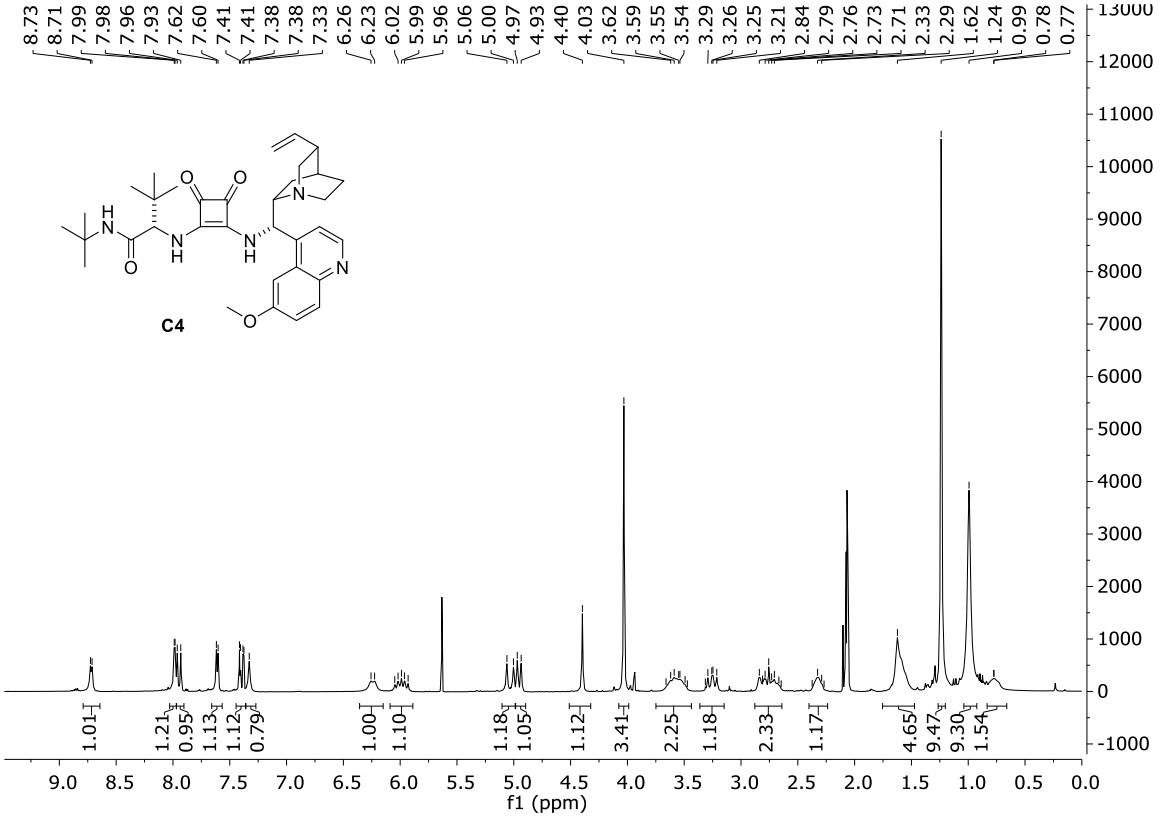
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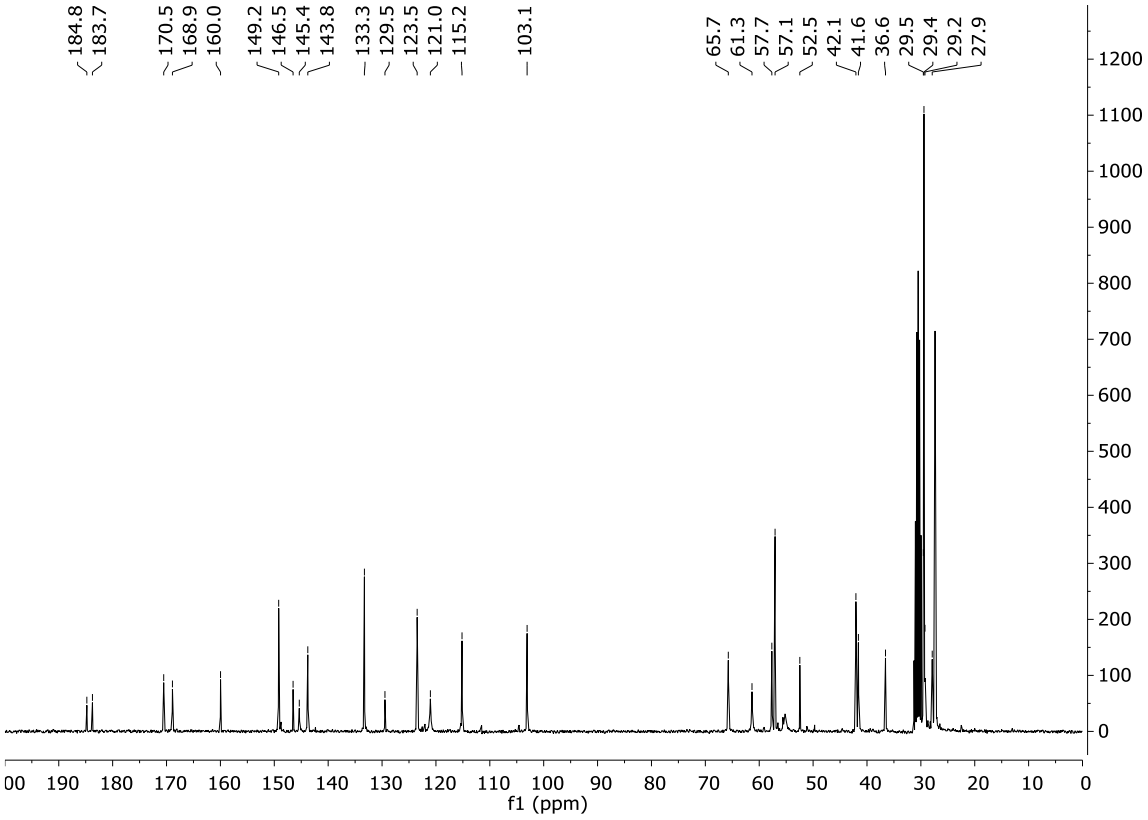
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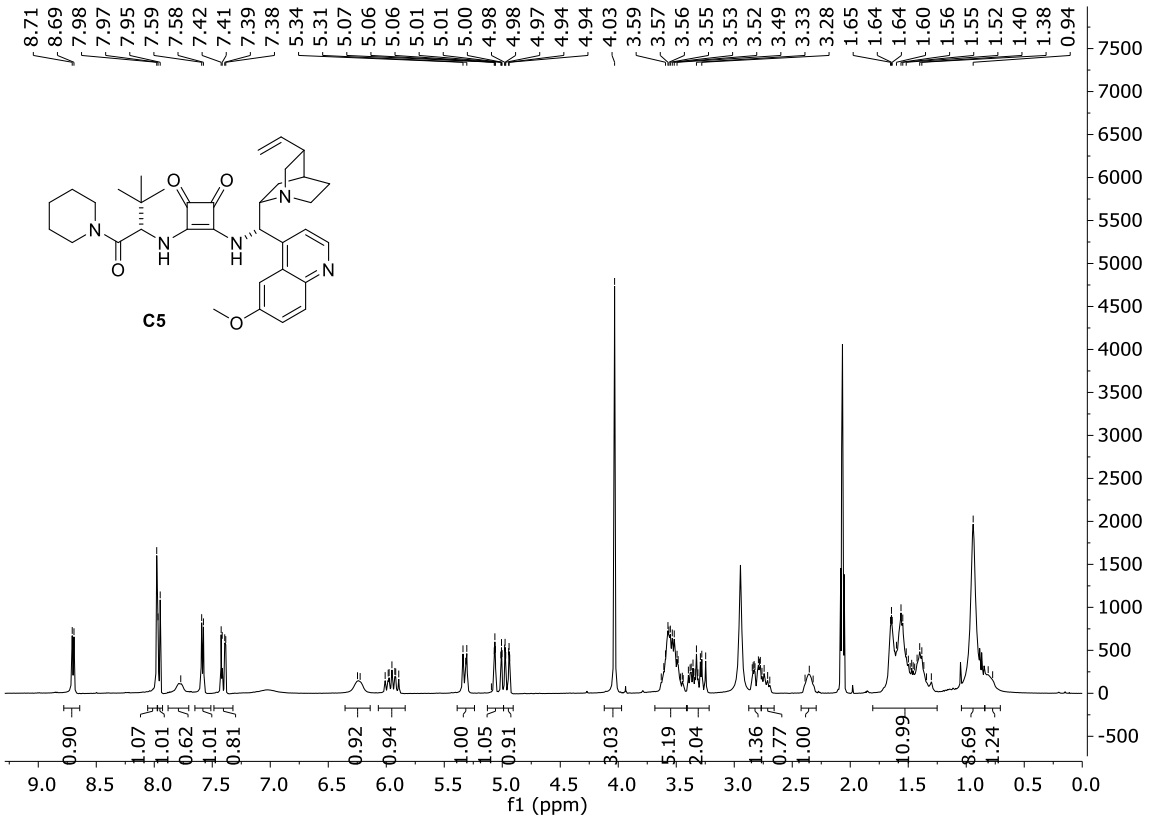
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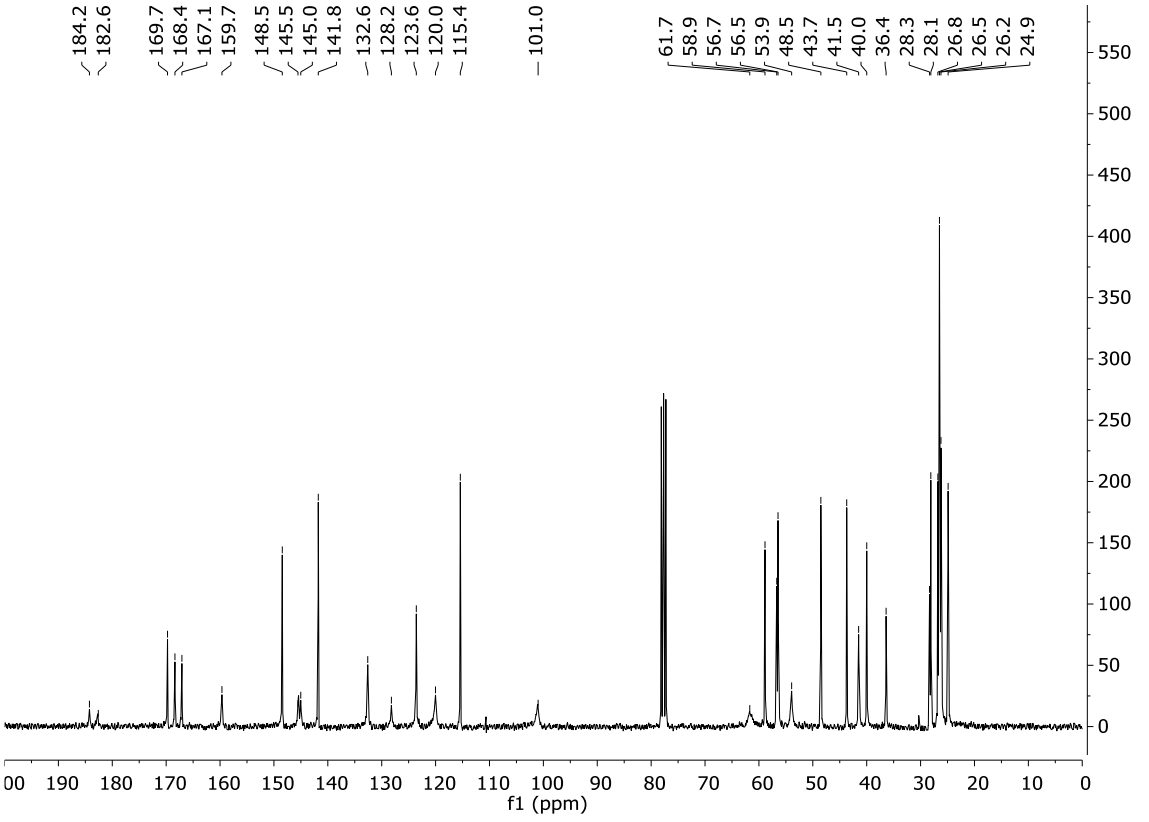
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123.6
120.0
115.4
101.0
61.7
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56.7
56.5
53.9
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24.9
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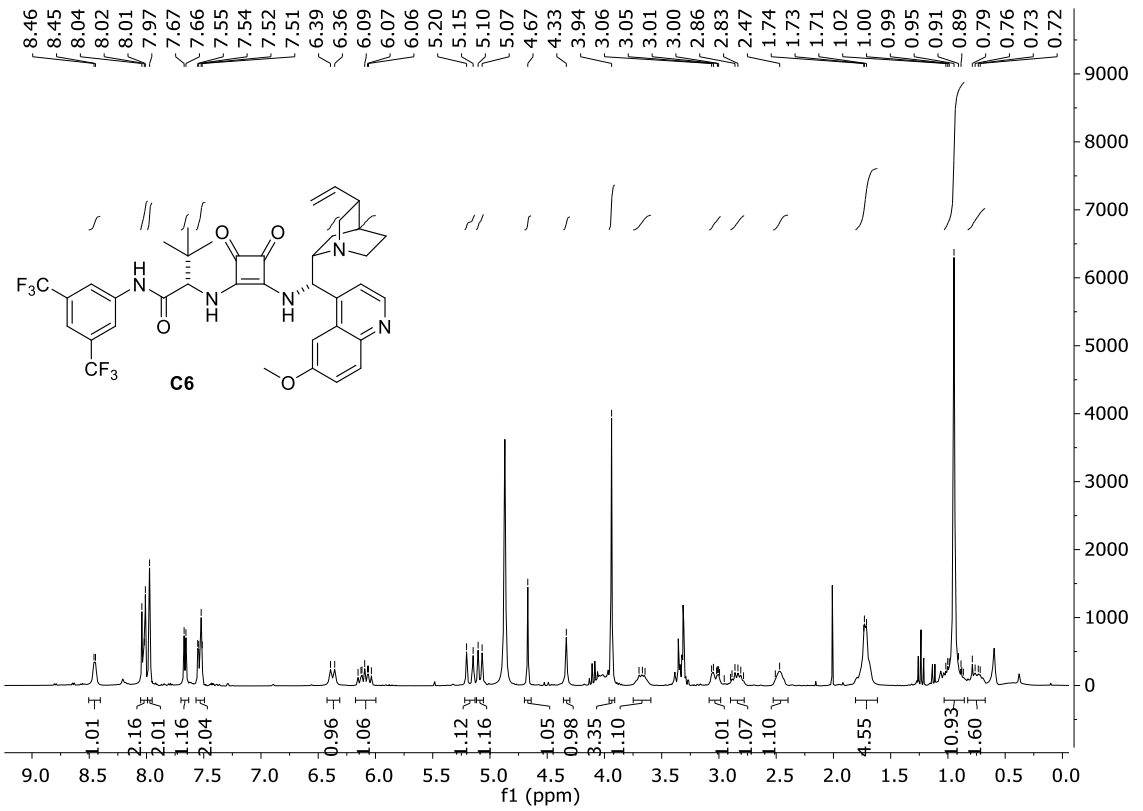
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6.06
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C6
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2.04
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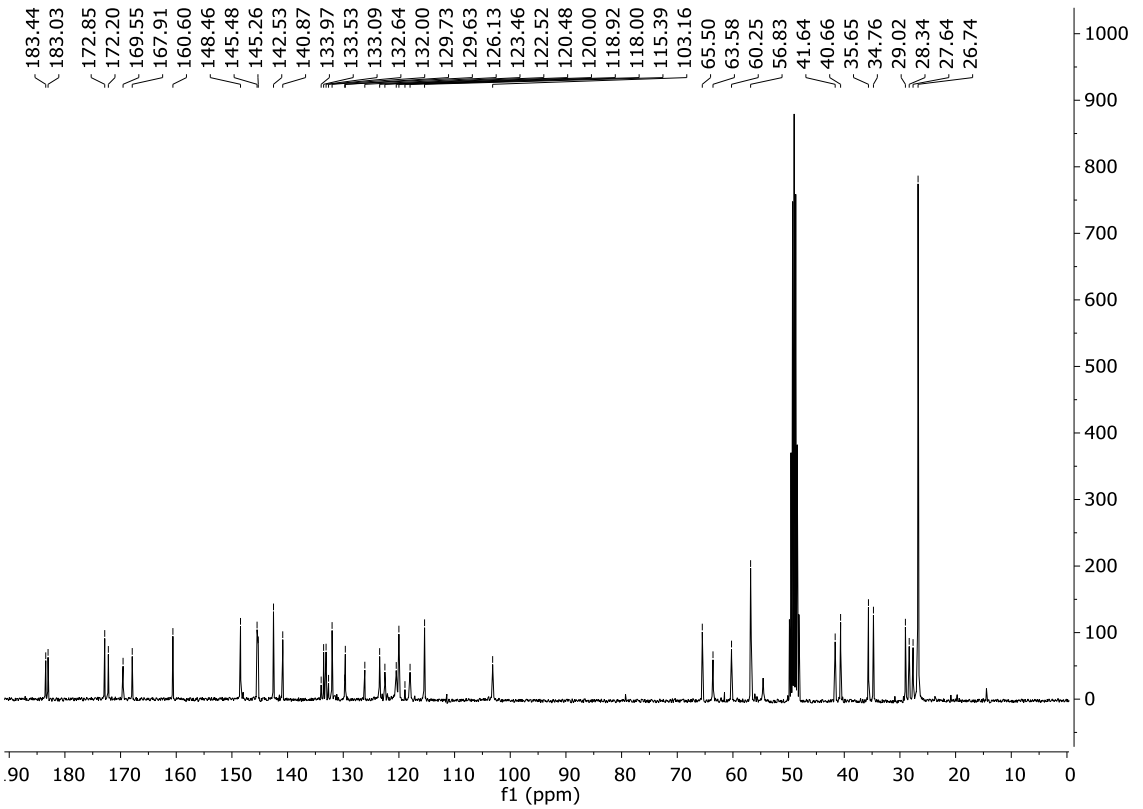
f1 (ppm)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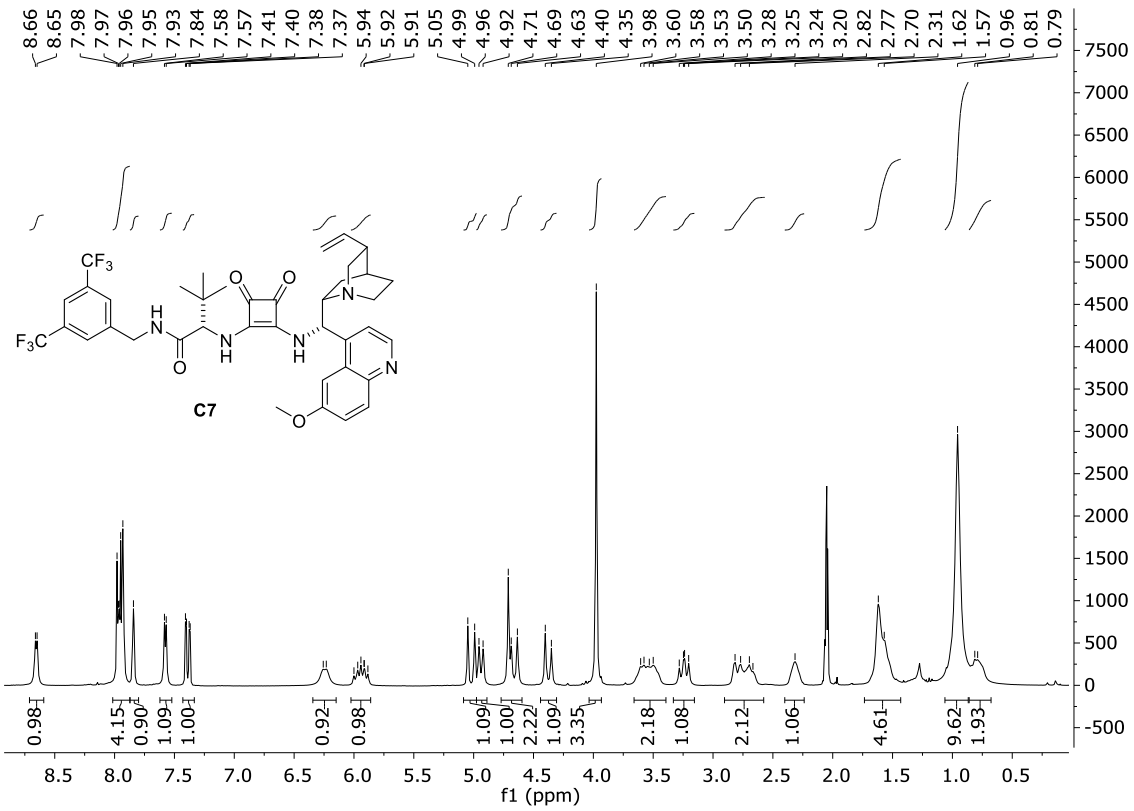
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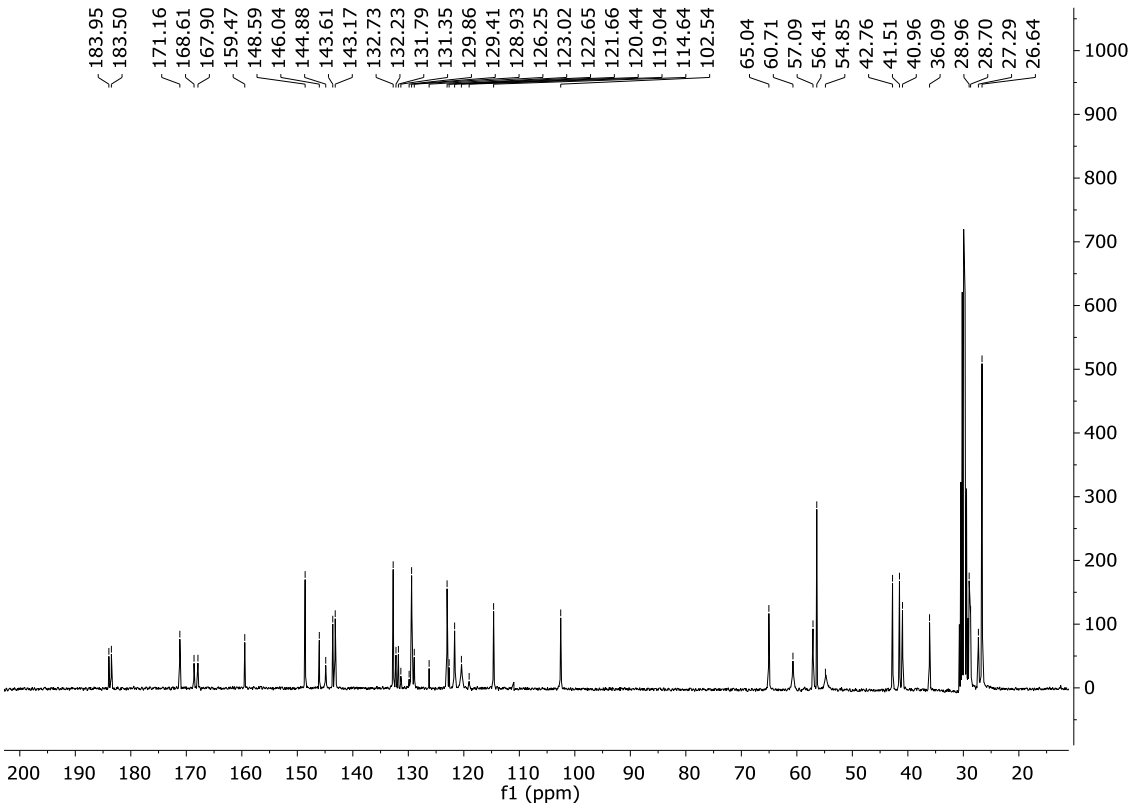
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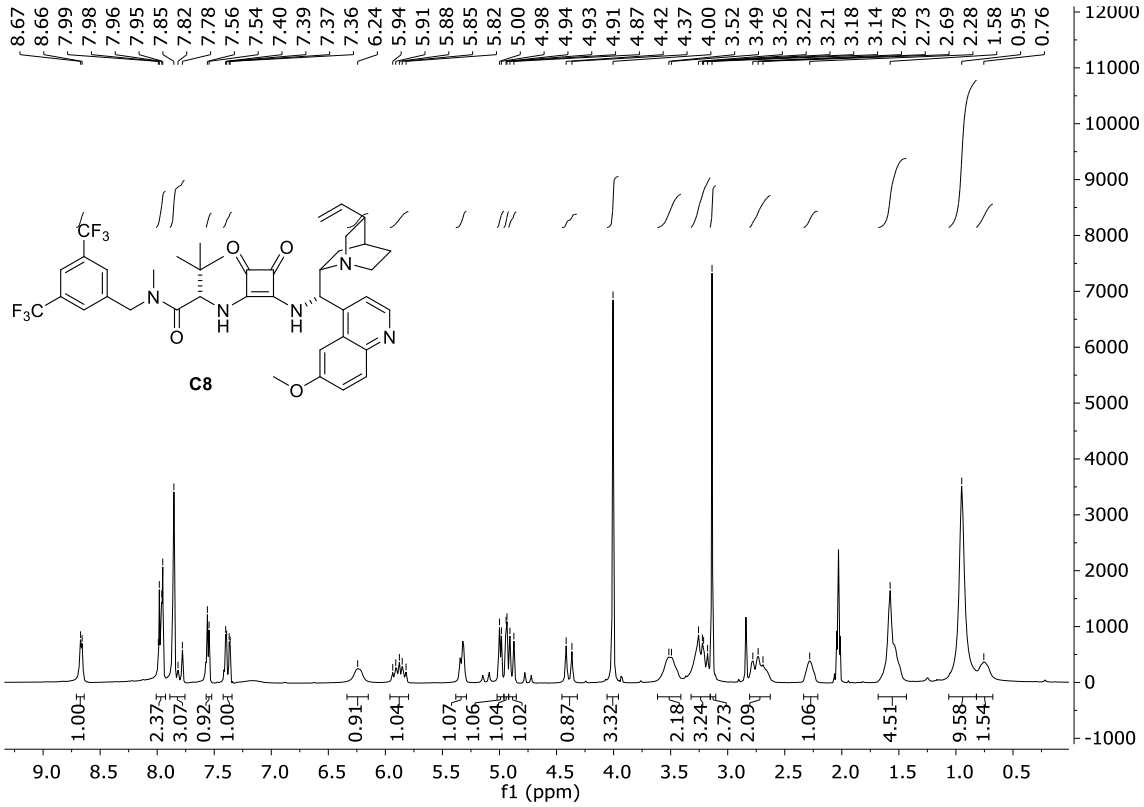
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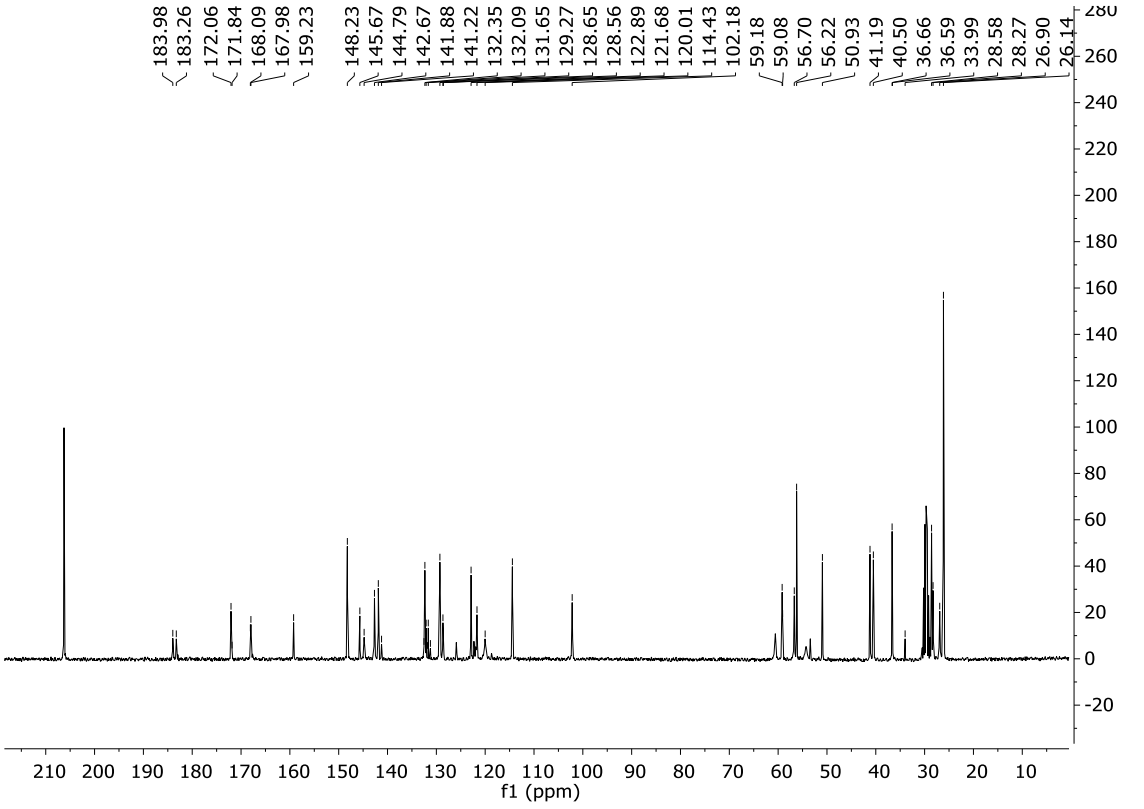
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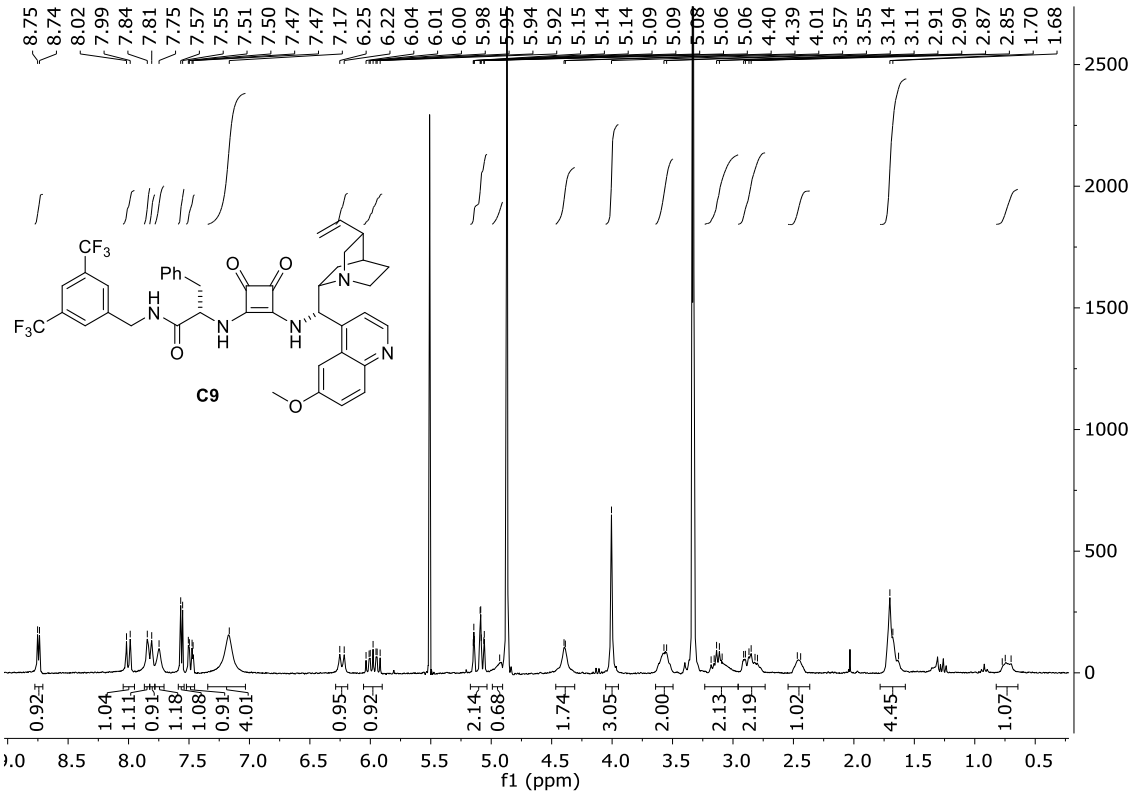
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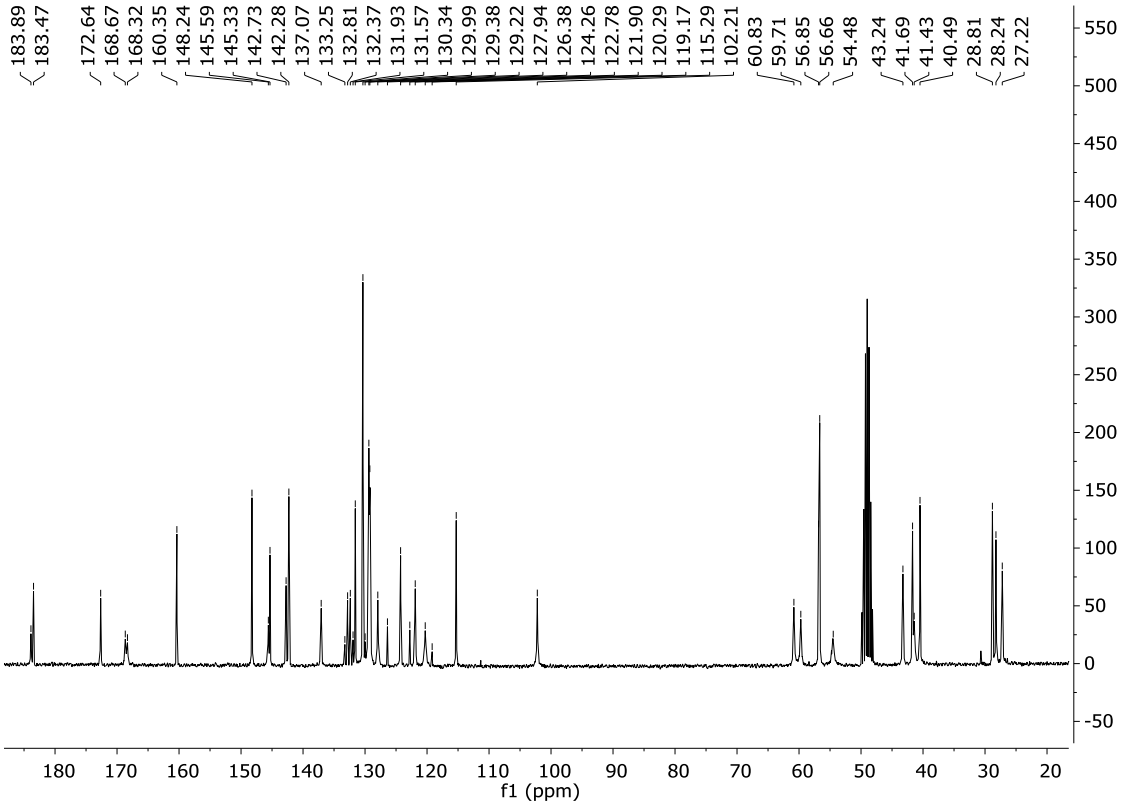
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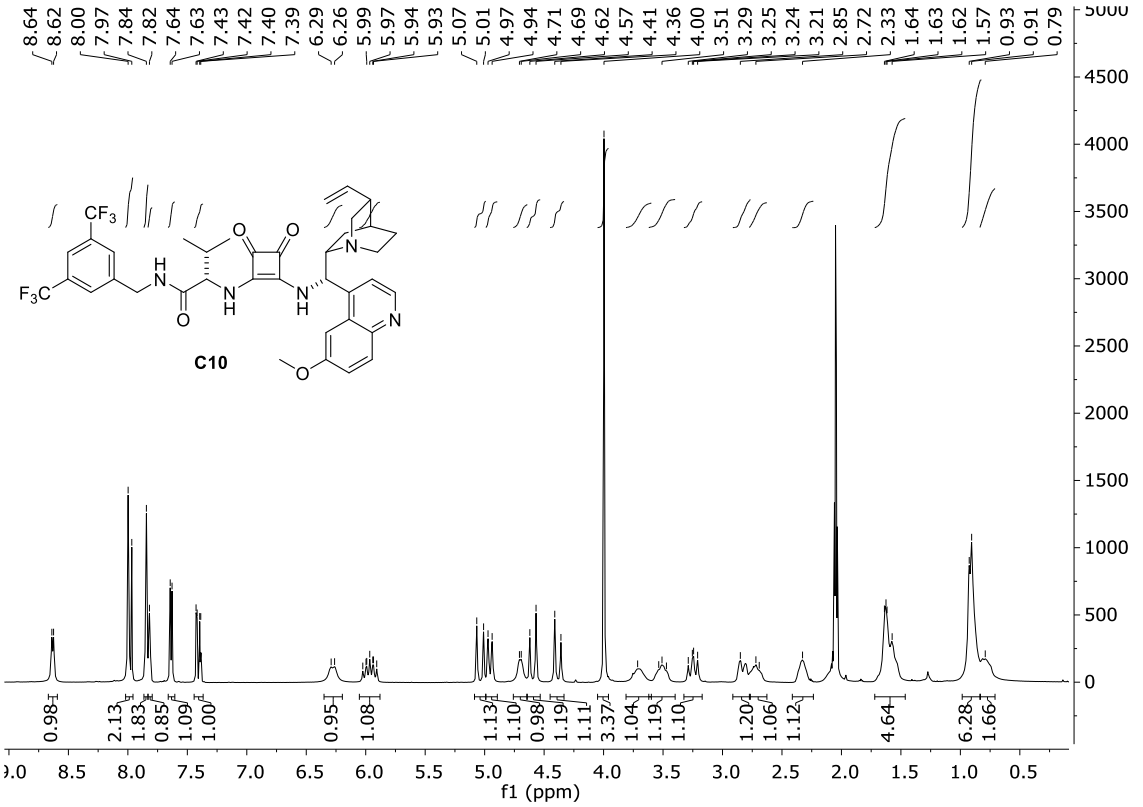
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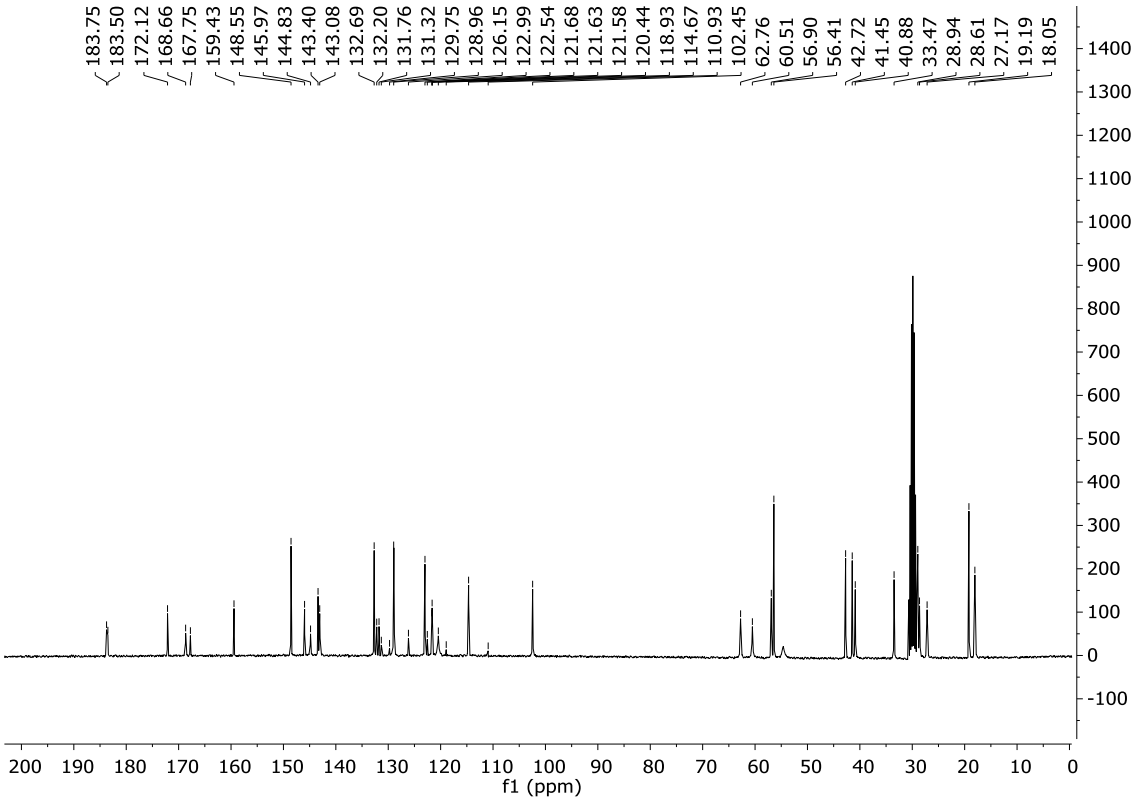
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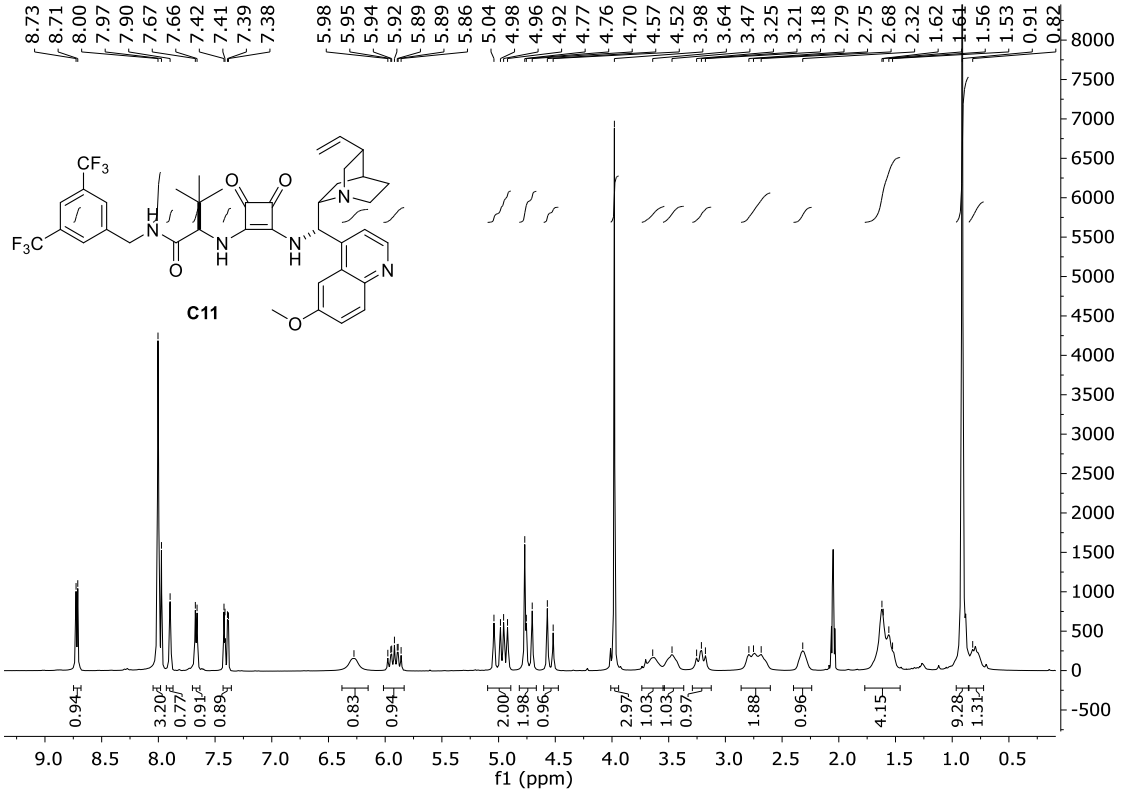
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3.47
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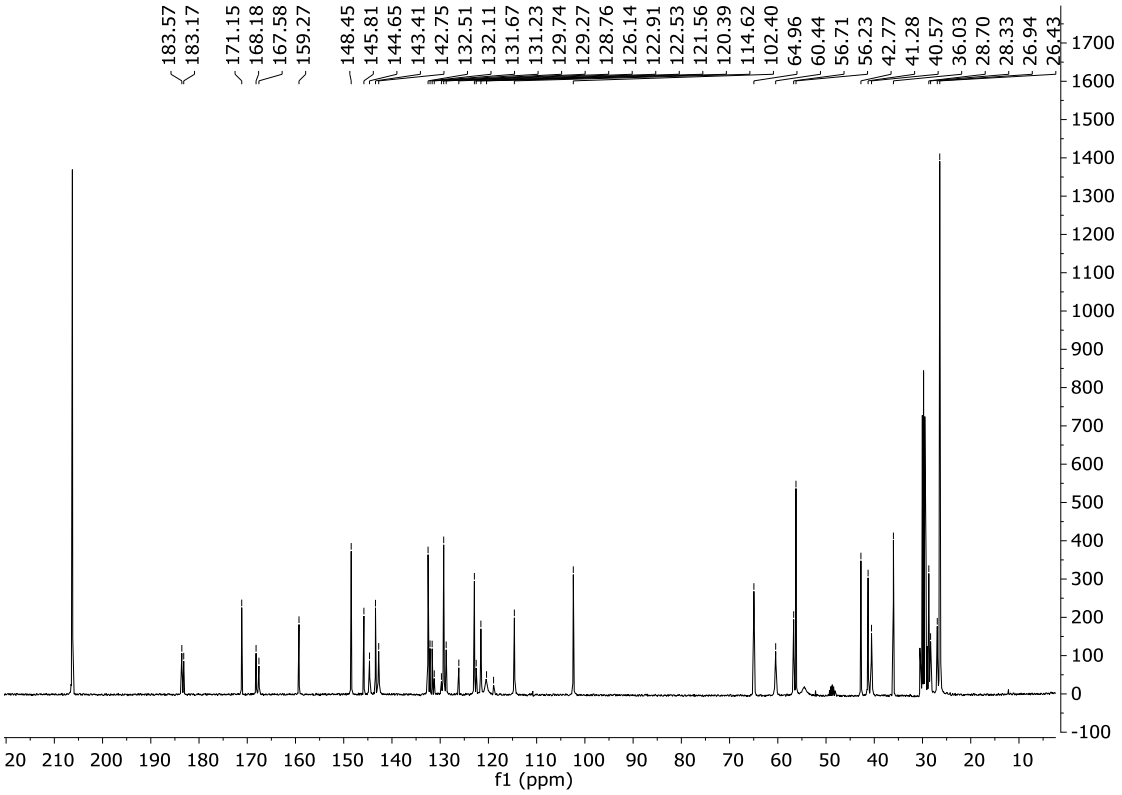
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142.75
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131.23
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129.27
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126.14
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122.53
121.56
120.39
114.62
102.40
64.96
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28.33
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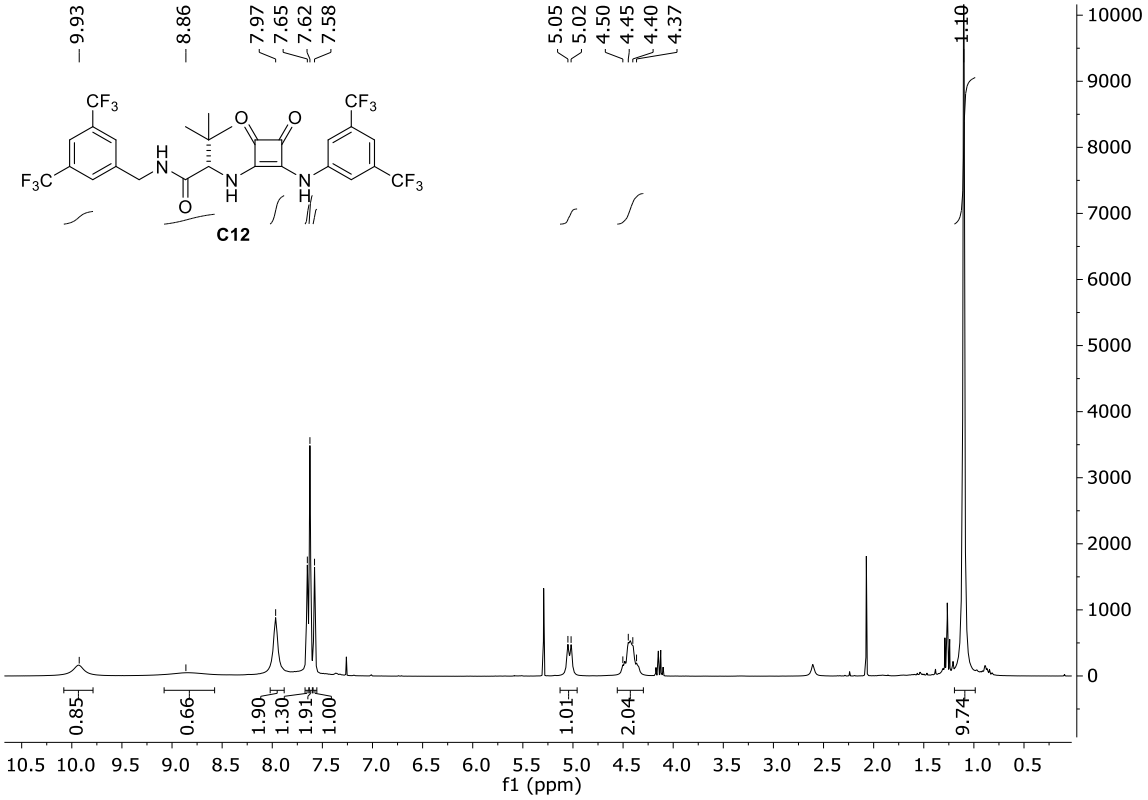
26.43
f1 (ppm)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F3C
CF3
CF3
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O
O
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N
N
H
N
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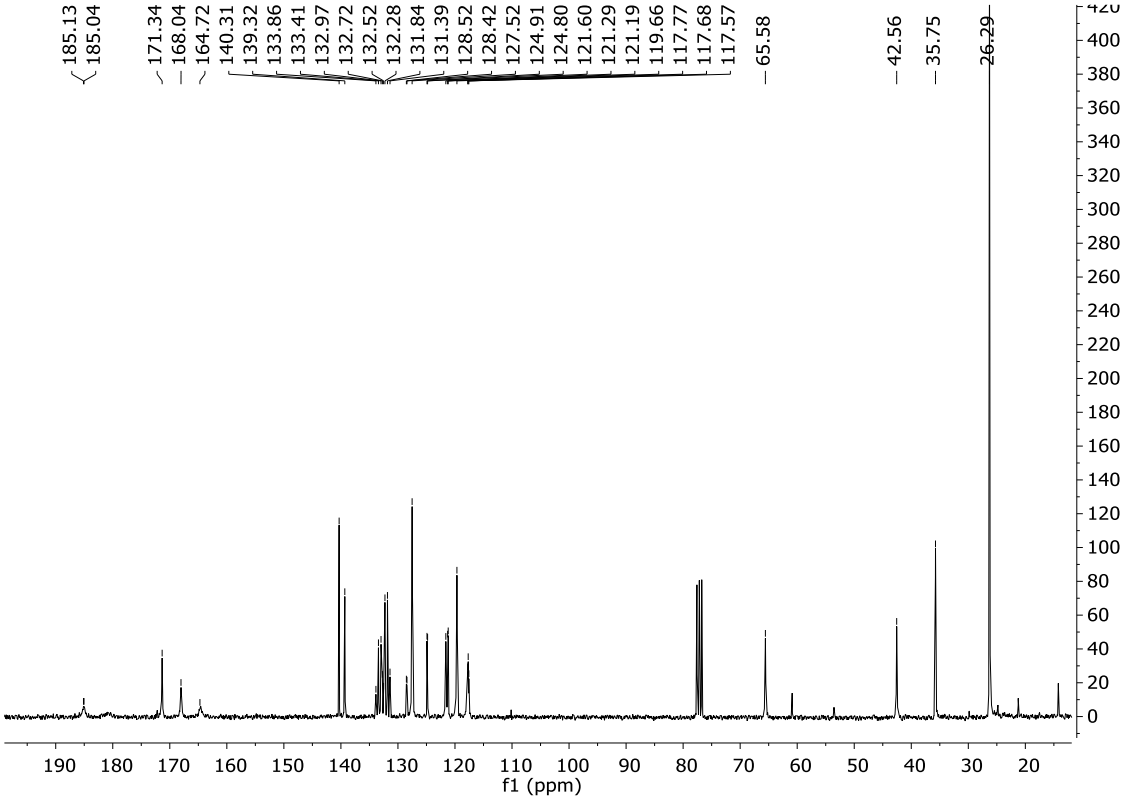
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131.39
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127.52
124.91
124.80
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117.68
117.57
65.58
42.56
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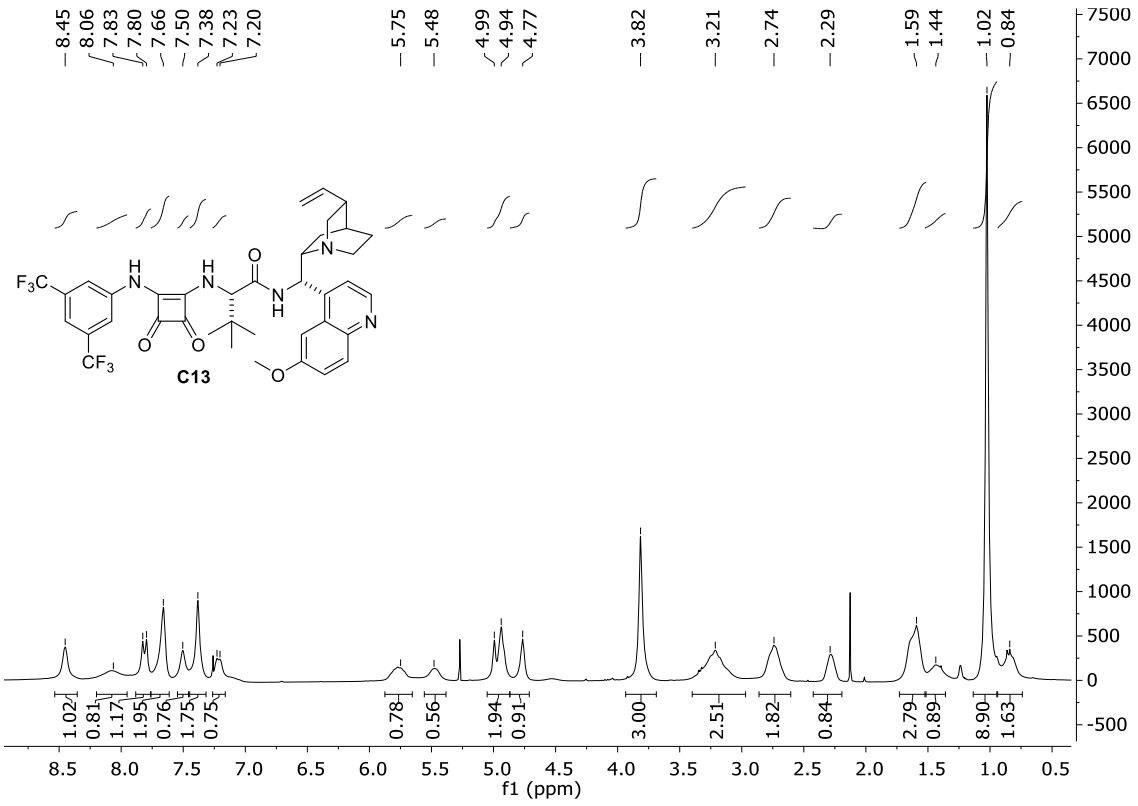
26.29
f1 (ppm)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4.94
4.77
3.82
3.21
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2.29
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1.02
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1.95
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1.75
0.75
0.78
0.56
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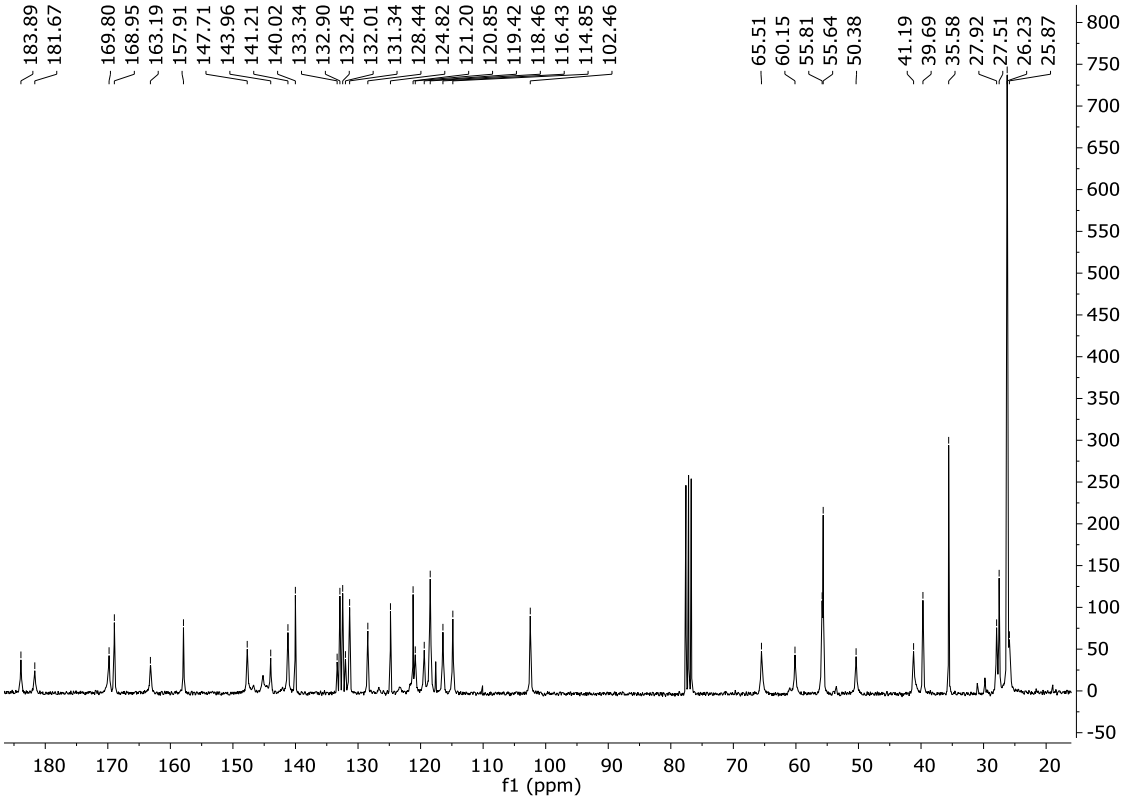
0.84
2.79
0.89
8.90
1.63
f1 (ppm)

C13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132.45
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116.43
114.85
102.46
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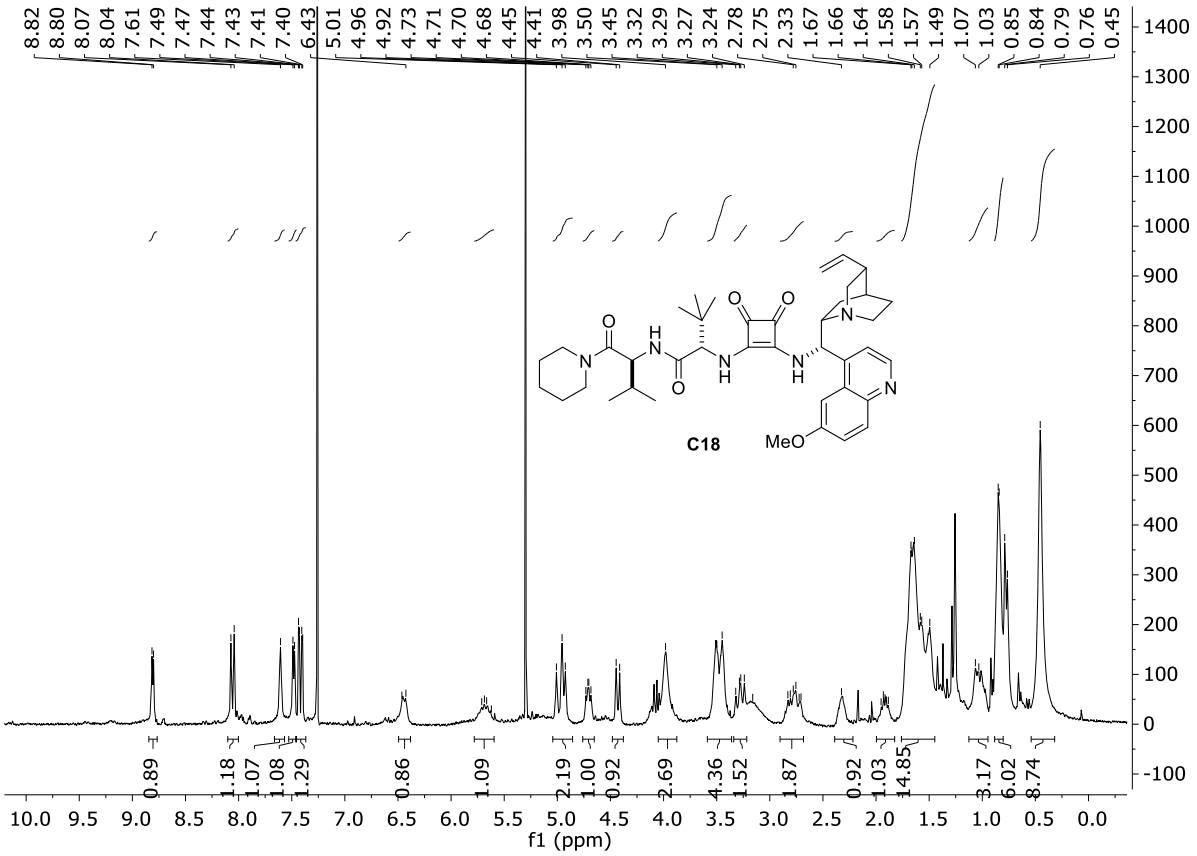
25.87
f1 (ppm)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4.96
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4.71
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3.24
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1.07
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1.09
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6.02
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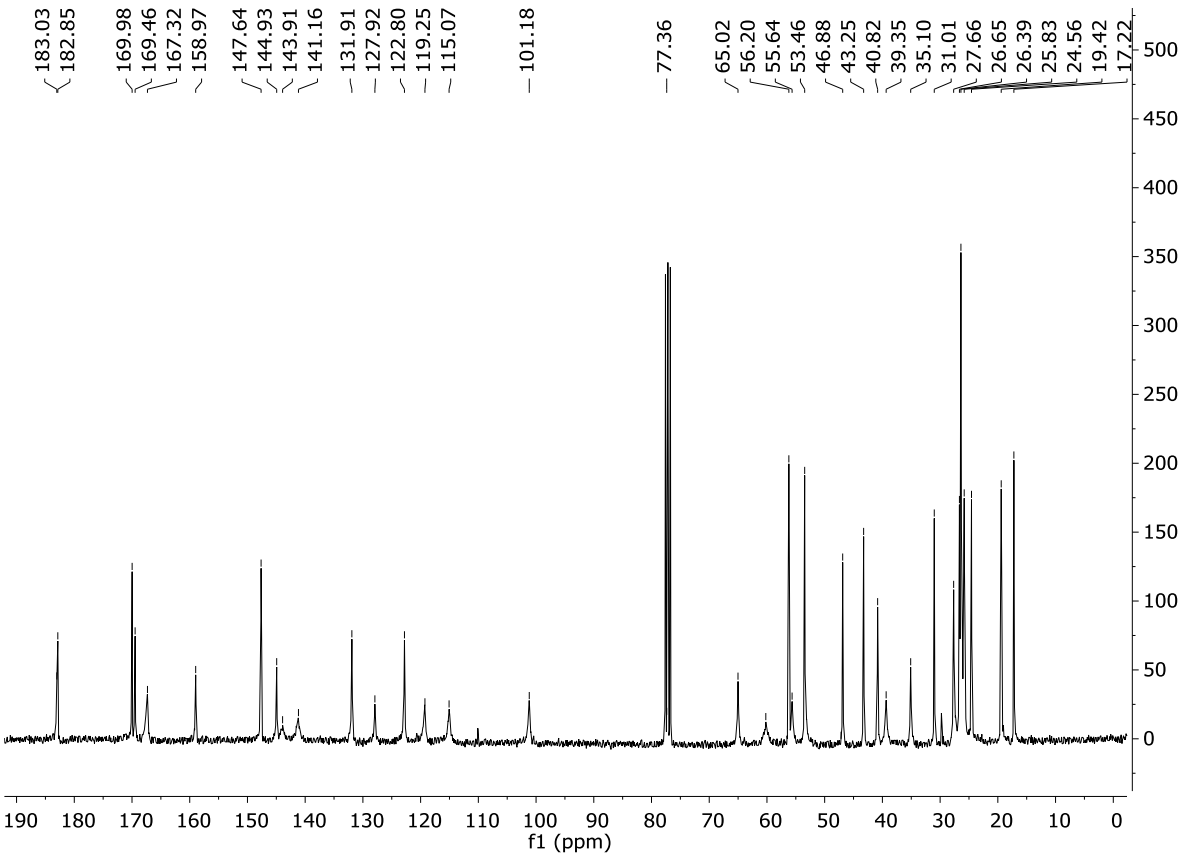
C18
MeO
f1 (ppm)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53.46
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43.25
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25.83
24.56
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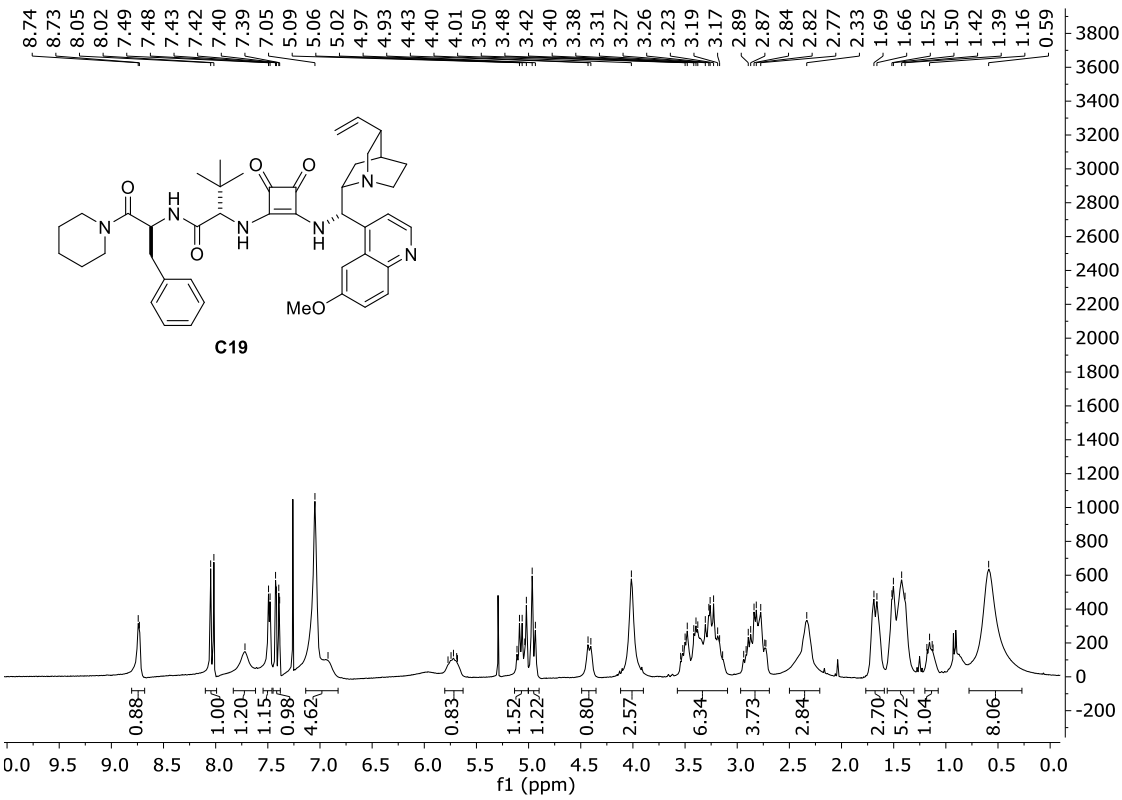
17.22
f1 (ppm)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5.02
4.97
4.93
4.43
4.40
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3.42
3.40
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3.31
3.27
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3.17
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2.84
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MeO
C19
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2.70
5.72
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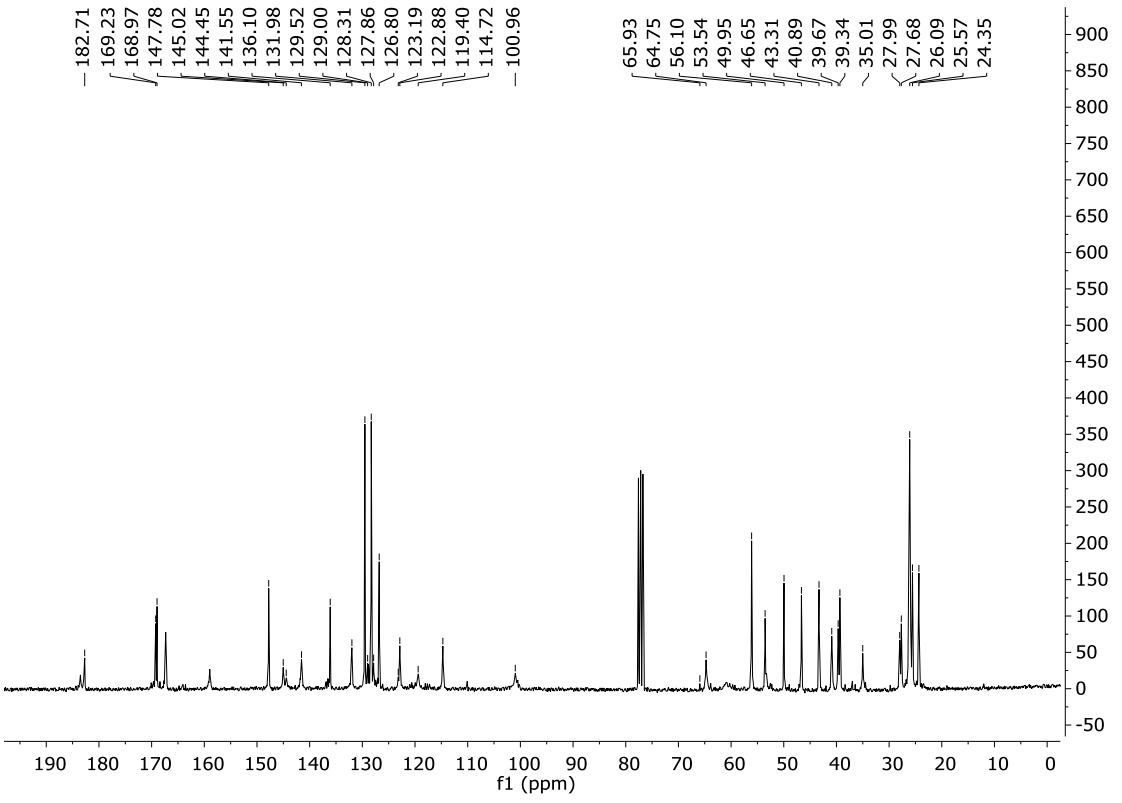
8.06
f1 (ppm)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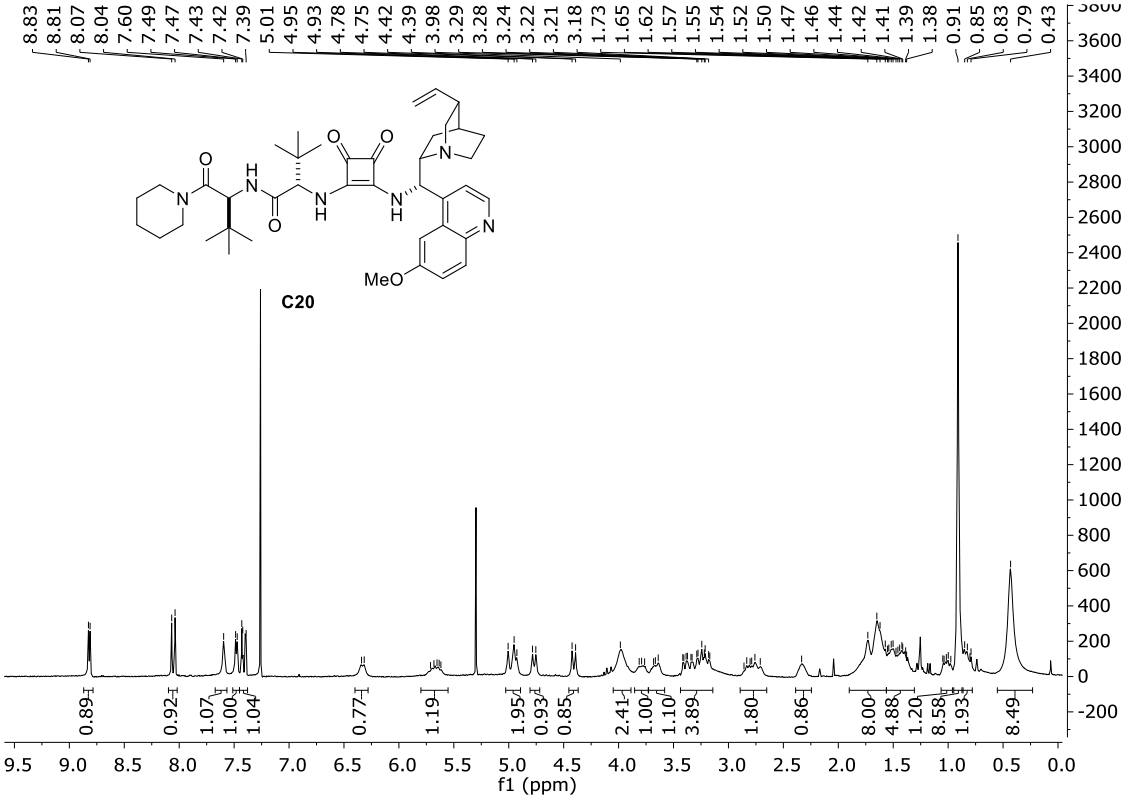
24.35
f1 (ppm)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C20
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8.49
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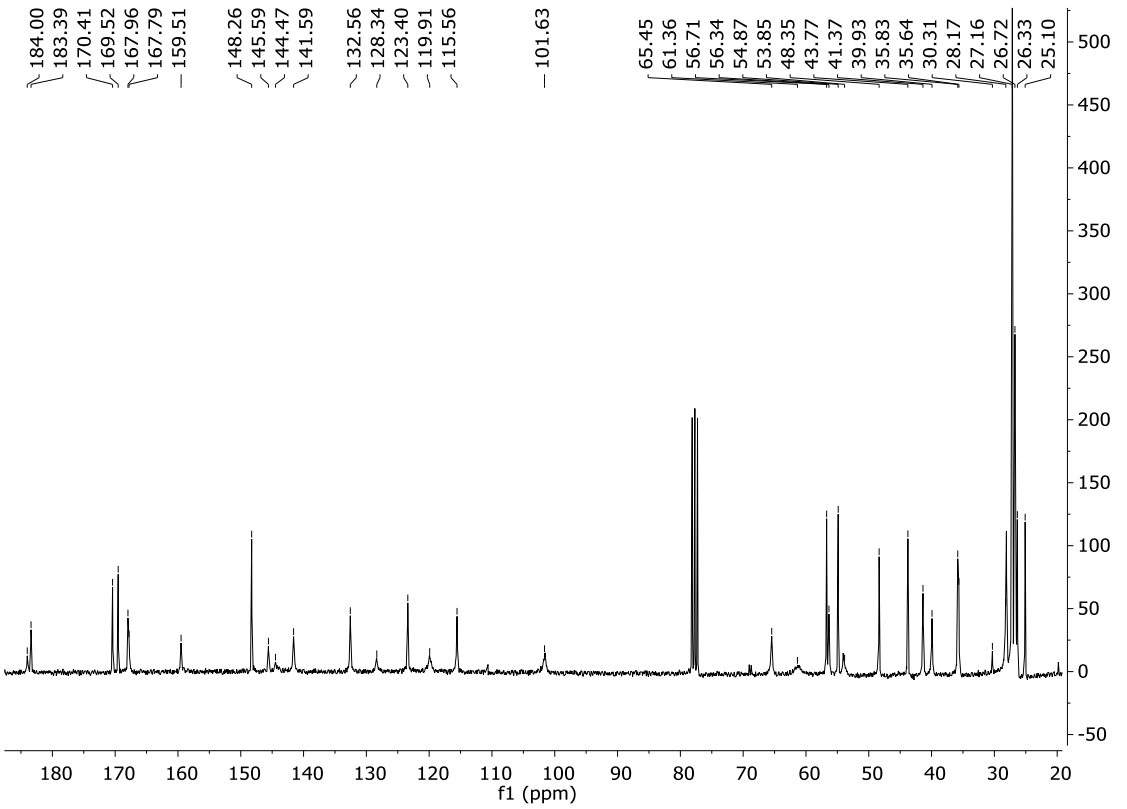
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56.34
54.87
53.85
48.35
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41.37
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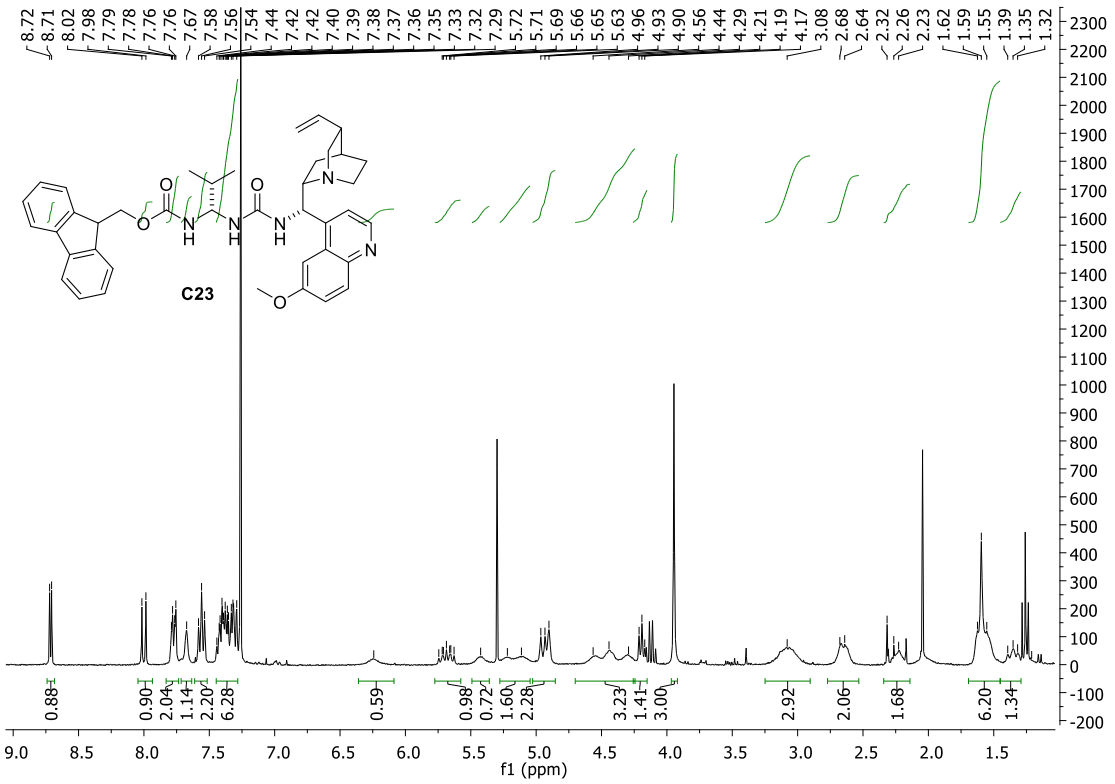
35.83
35.64
30.31
28.17
27.16
26.72
26.33
25.10
f1 (ppm)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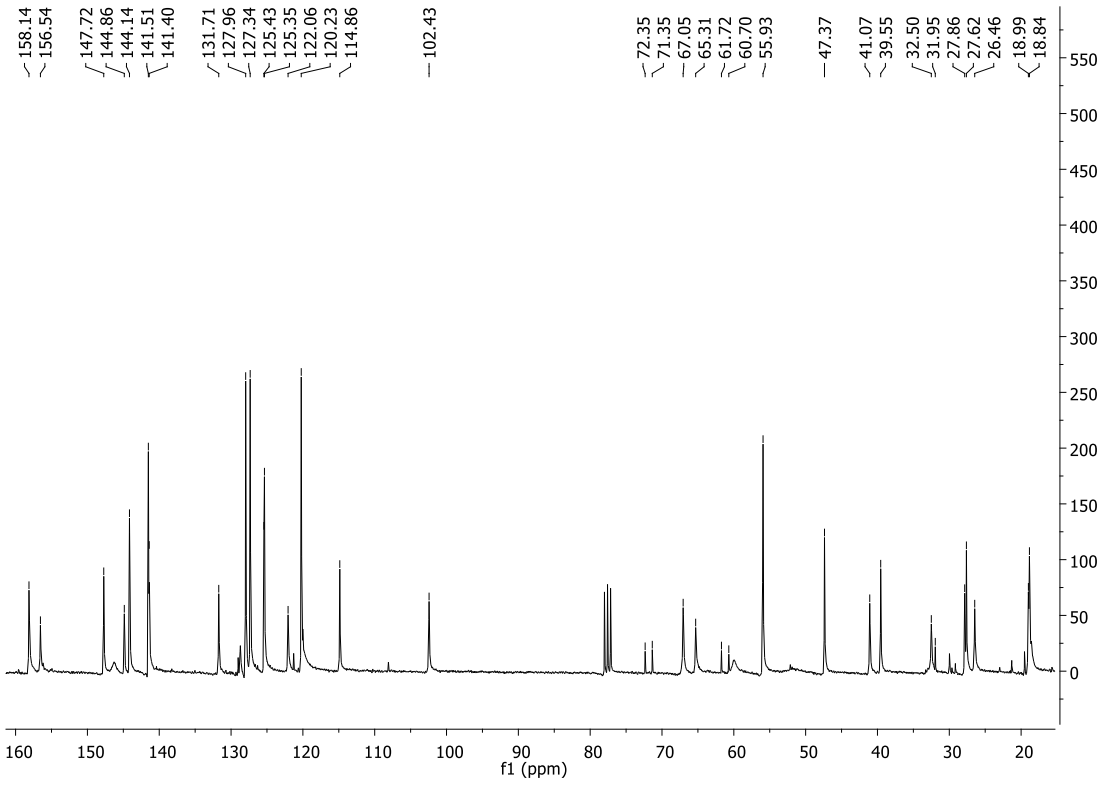
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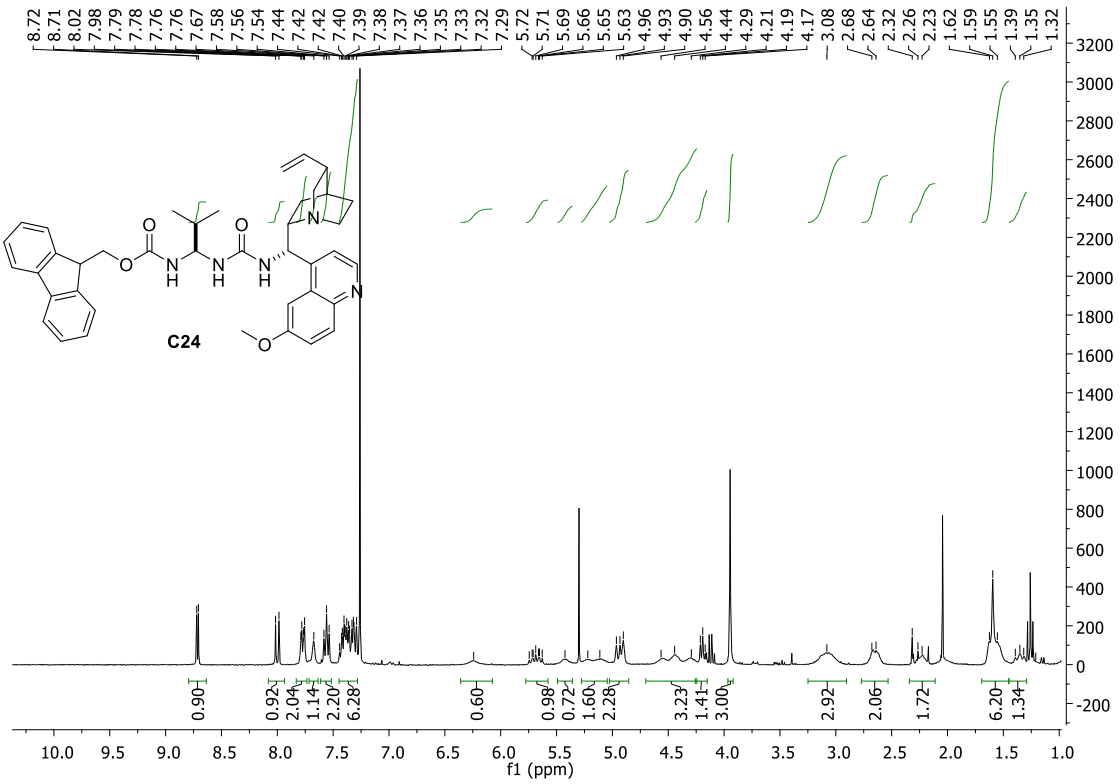
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7.39
7.38
7.37
7.36
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7.33
7.32
7.29
5.72
5.71
5.69
5.66
5.65
5.63
4.96
4.93
4.90
4.56
4.44
4.29
4.21
4.19
4.17
3.08
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2.26
2.23
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1.55
1.39
1.35
1.32
C24
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2.04
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2.20
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0.60
0.98
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3.00
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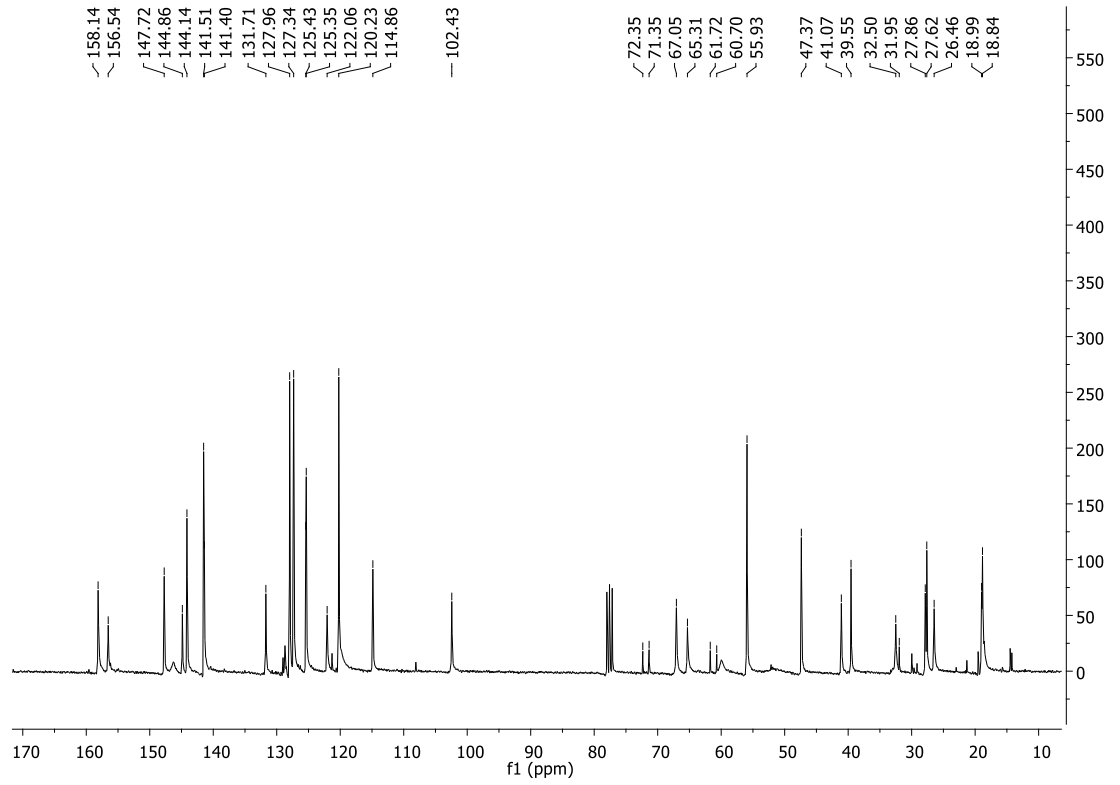
2.06
1.72
6.20
1.34
f1 (ppm)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120.23
114.86
102.43
72.35
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61.72
60.70
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27.62
26.46
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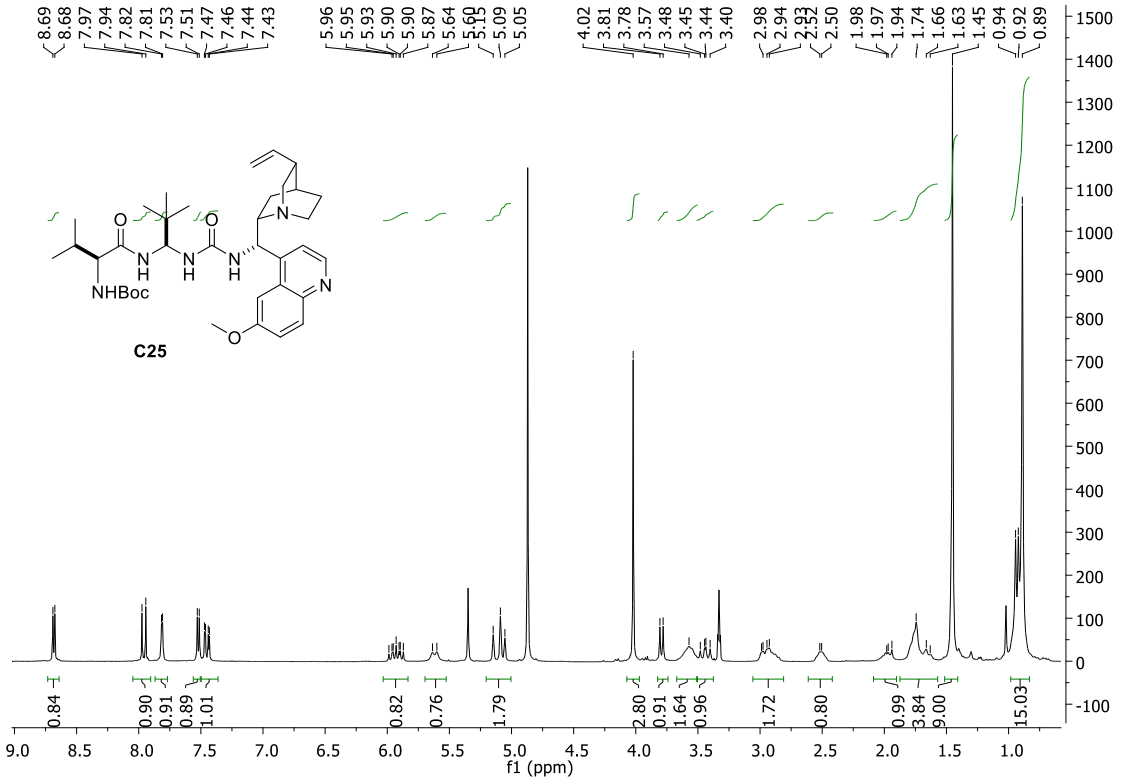
18.84
f1 (ppm)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7.43
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5.95
5.93
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5.90
5.87
5.64
5.60
5.15
5.09
5.05
4.02
3.81
3.78
3.57
3.48
3.45
3.44
3.40
2.98
2.94
2.52
2.50
1.98
1.97
1.94
1.74
1.66
1.63
1.45
0.94
0.92
0.89
NHBoc
C25
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0.91
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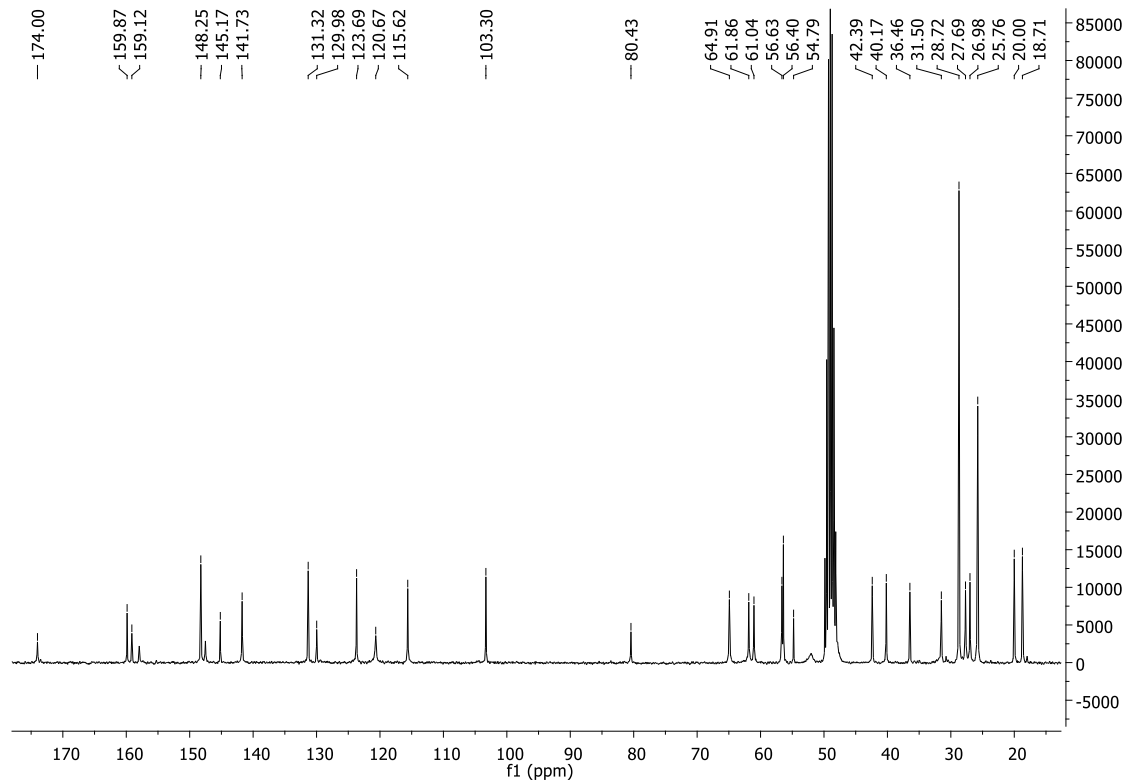
15.03
f1 (ppm)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18.71
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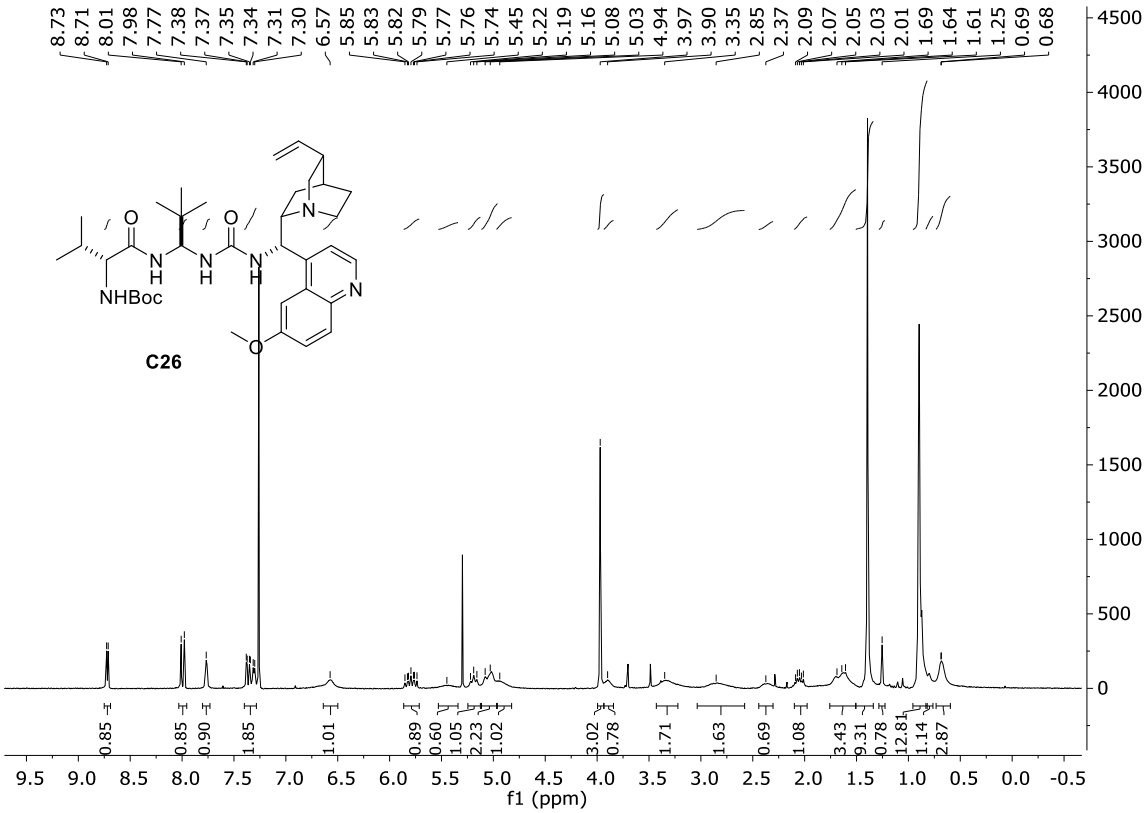
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2.09
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1.64
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NHBoc
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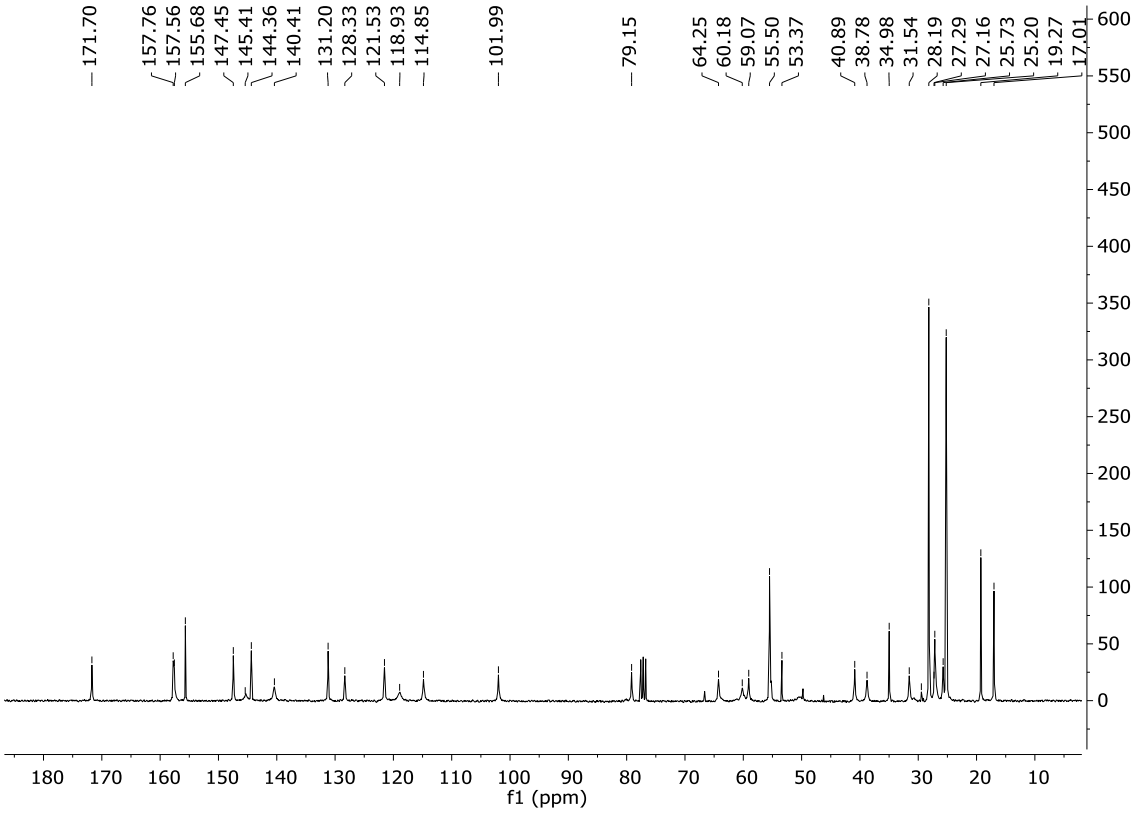
2.87
f1 (ppm)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53.37
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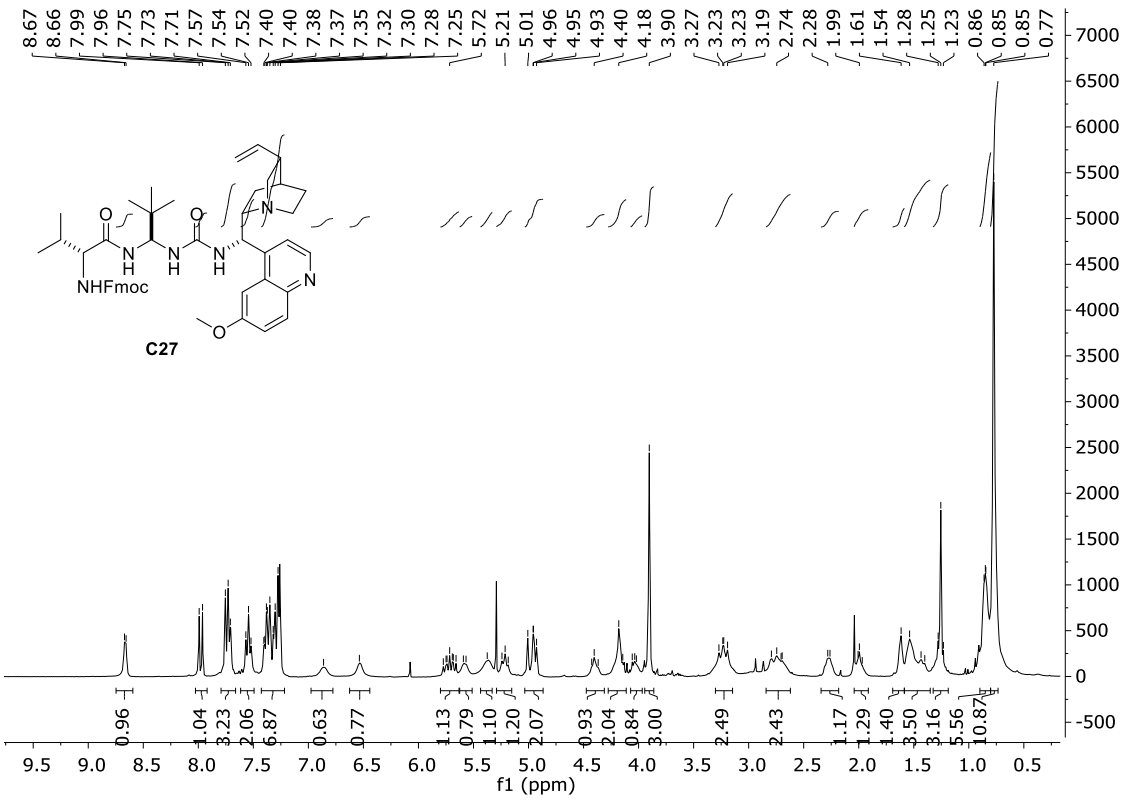
25.20
19.27
17.01
f1 (ppm)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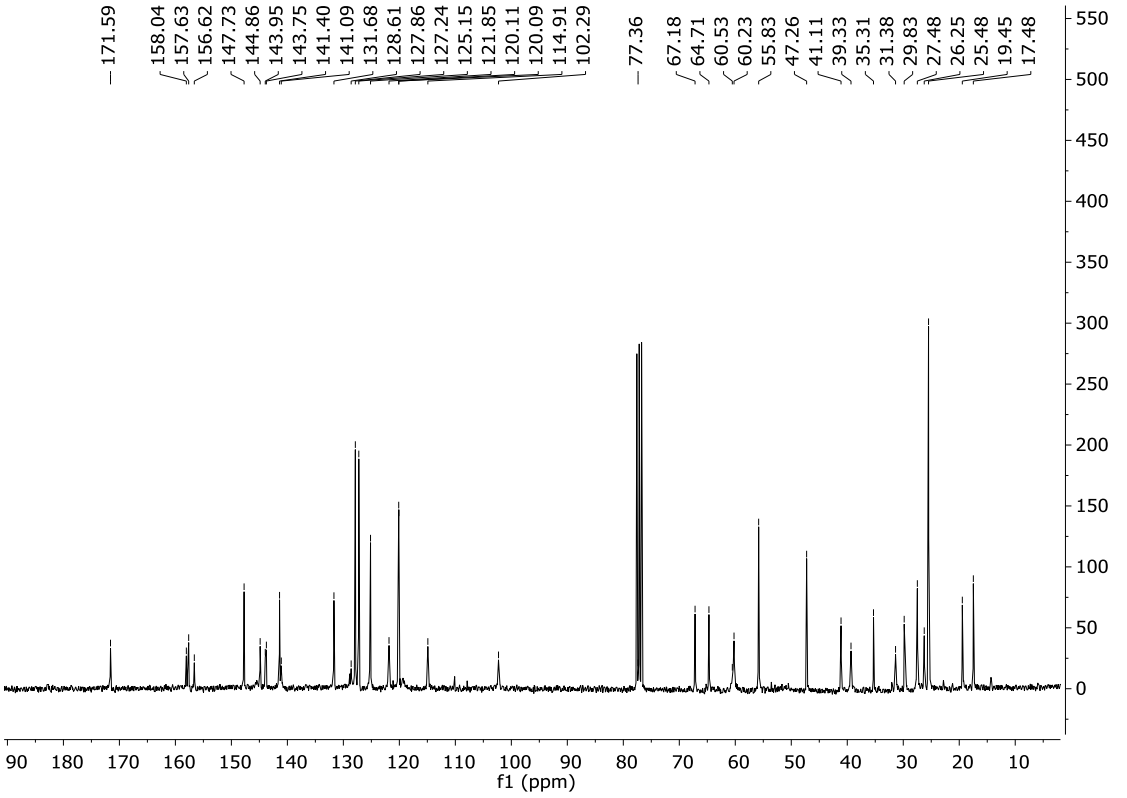
NHFmoc
C27
0.96 1.04 3.23 2.06 6.87 0.63 0.77 1.13 0.79 1.10 1.20 2.07 0.93 2.04 0.84 3.00 2.49 2.43 1.17 1.29 1.40 3.50 3.16 5.56 10.87
f1 (ppm)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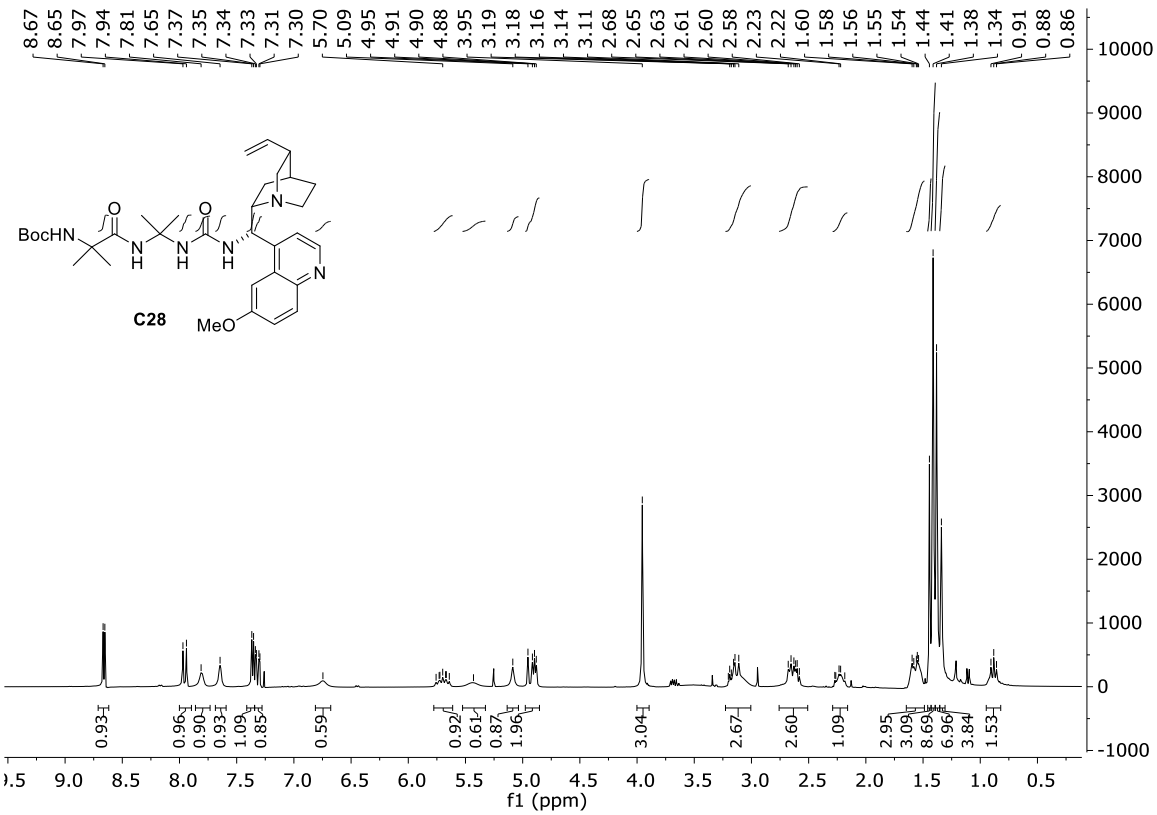
f1 (ppm)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BocHN
O
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H
O
N
H
N
H
N
MeO
C28
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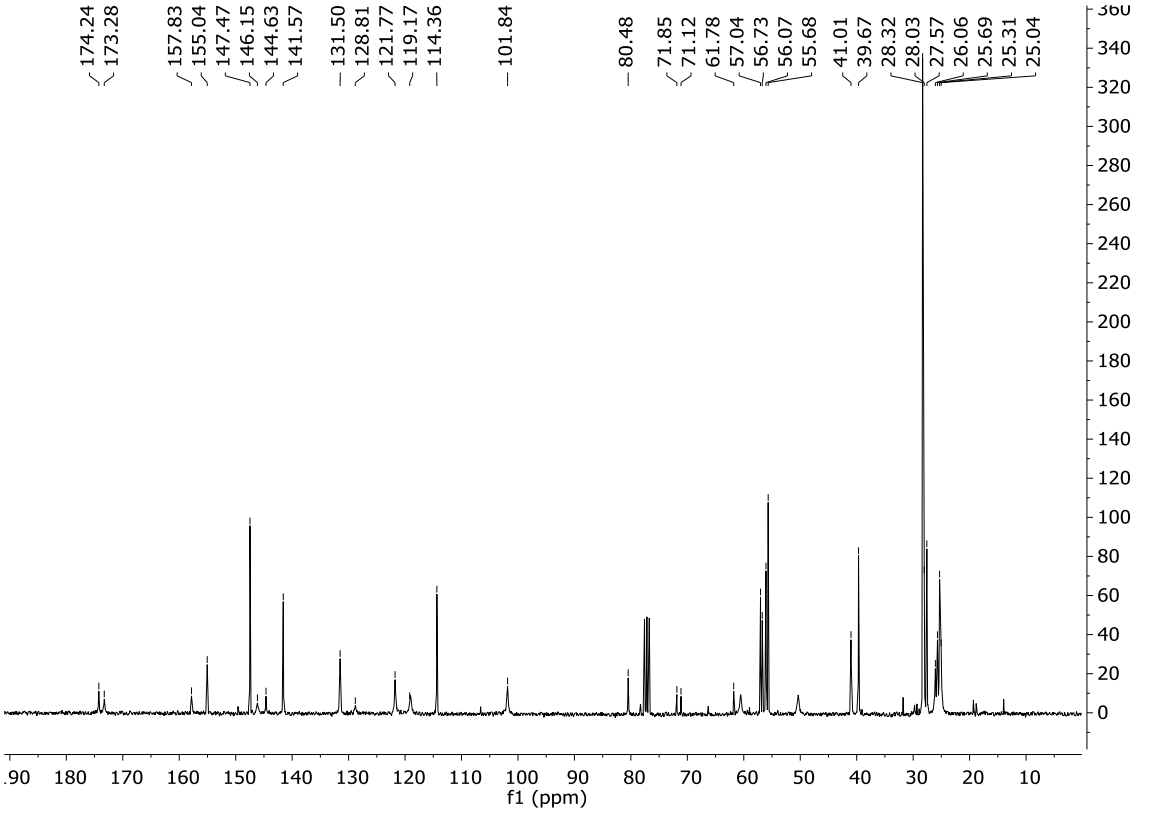
f1 (ppm)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101.84
80.48
71.85
71.12
61.78
57.04
56.73
56.07
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28.03
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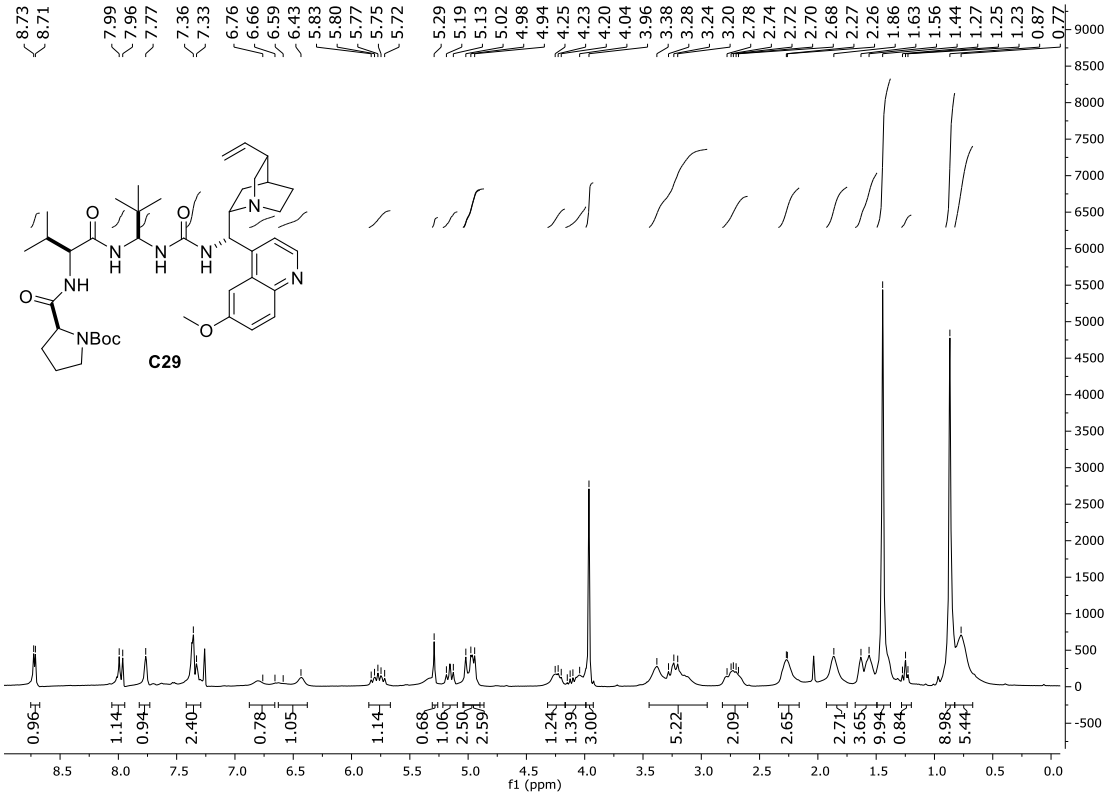
25.31
25.04
f1 (ppm)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5.80
5.77
5.75
5.72
5.29
5.19
5.13
5.02
4.98
4.94
4.25
4.23
4.20
4.04
3.96
3.38
3.28
3.24
3.20
2.78
2.74
2.72
2.70
2.68
2.27
2.26
1.86
1.63
1.56
1.44
1.27
1.25
1.23
0.87
0.77
NBoc
C29
0.96
1.14
0.94
2.40
0.78
1.05
1.14
0.68
1.06
2.50
2.59
1.24
1.39
3.00
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2.09
2.65
2.71
3.65
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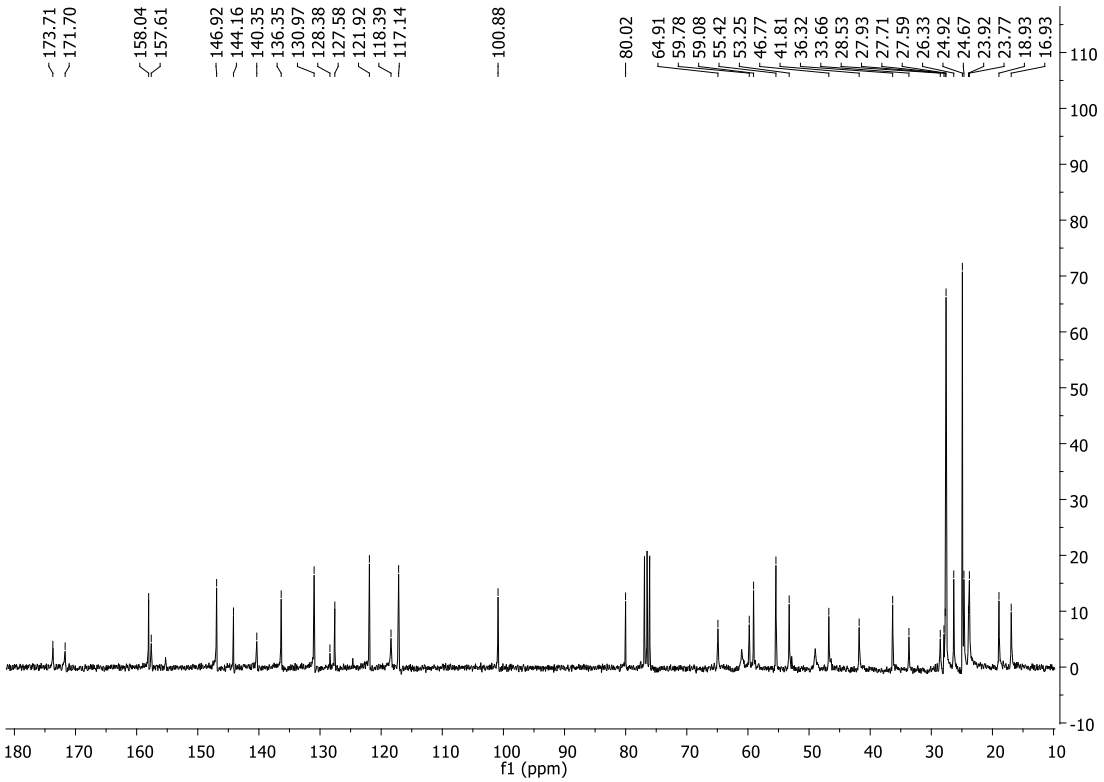
f1 (ppm)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136.35
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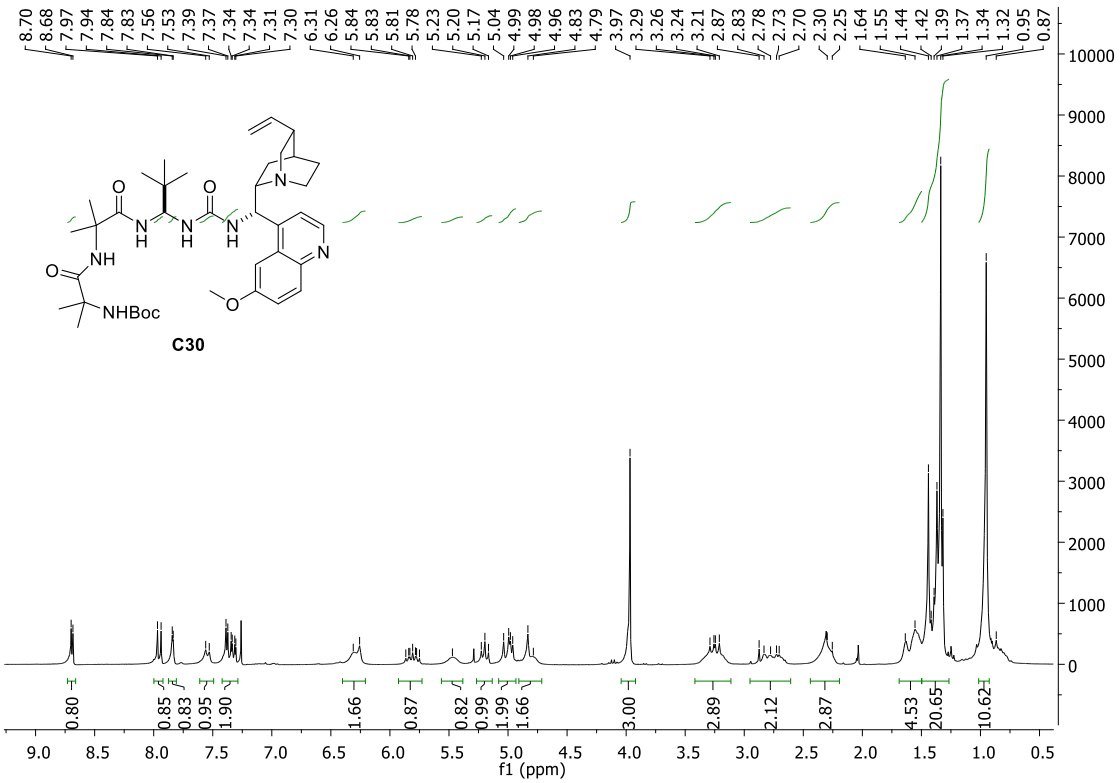
127.58
121.92
118.39
117.14
100.88
80.02
64.91
59.78
59.08
55.42
53.25
46.77
41.81
36.32
33.66
28.53
27.93
27.71
27.59
26.33
24.92
24.67
23.92
23.77
18.93
16.93
f1 (ppm)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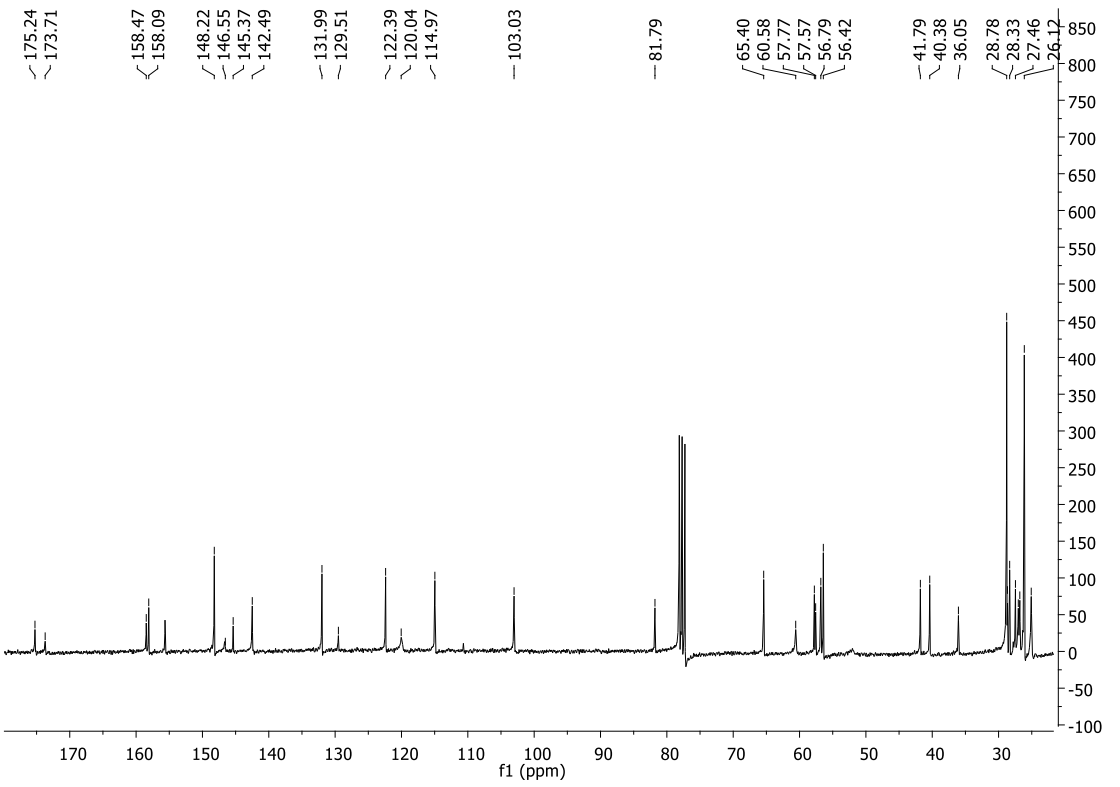
7.31
7.30
6.31
6.26
5.84
5.83
5.81
5.78
5.23
5.20
5.17
5.04
4.99
4.98
4.96
4.83
4.79
3.97
3.29
3.26
3.24
3.21
2.87
2.83
2.78
2.73
2.70
2.30
2.25
1.64
1.55
1.44
1.42
1.39
1.37
1.34
1.32
0.95
0.87
NH
NHBoc
C30
0.80
0.85
0.83
0.95
1.90
1.66
0.87
0.82
0.99
1.99
1.66
3.00
2.89
2.12
2.87
4.53
20.65
10.62
f1 (ppm)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114.97
103.03
81.79
65.40
60.58
57.77
57.57
56.79
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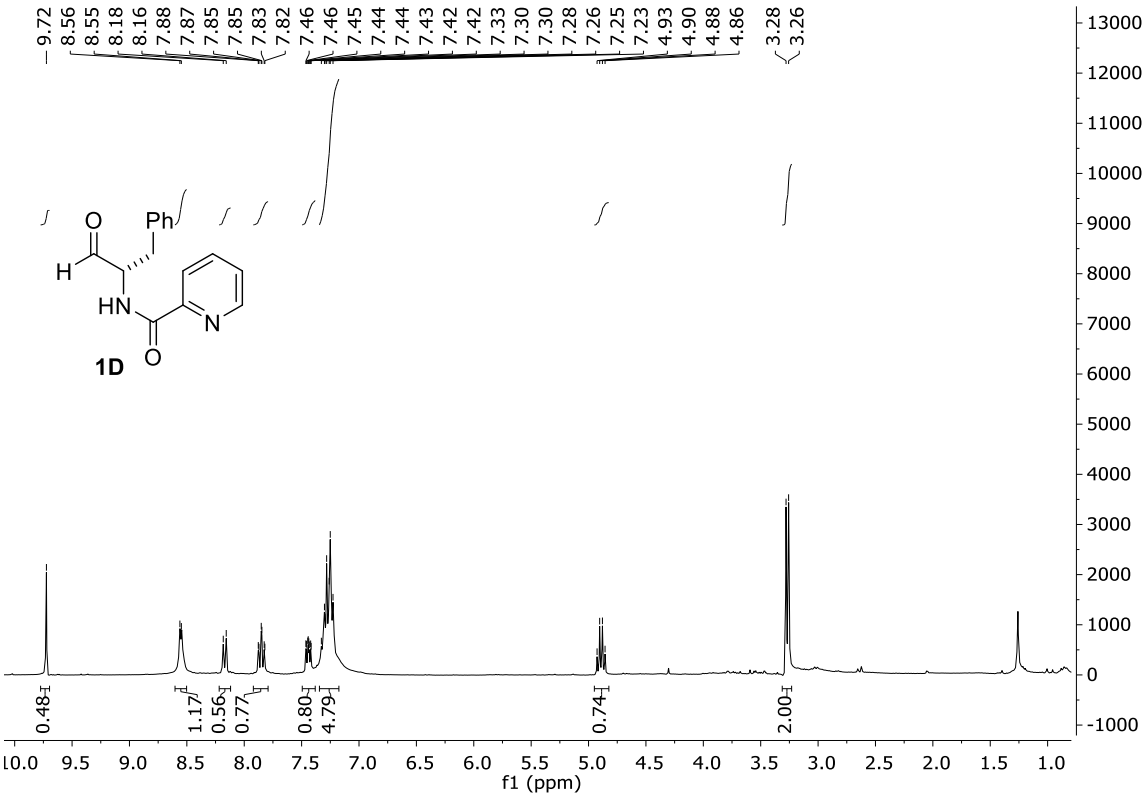
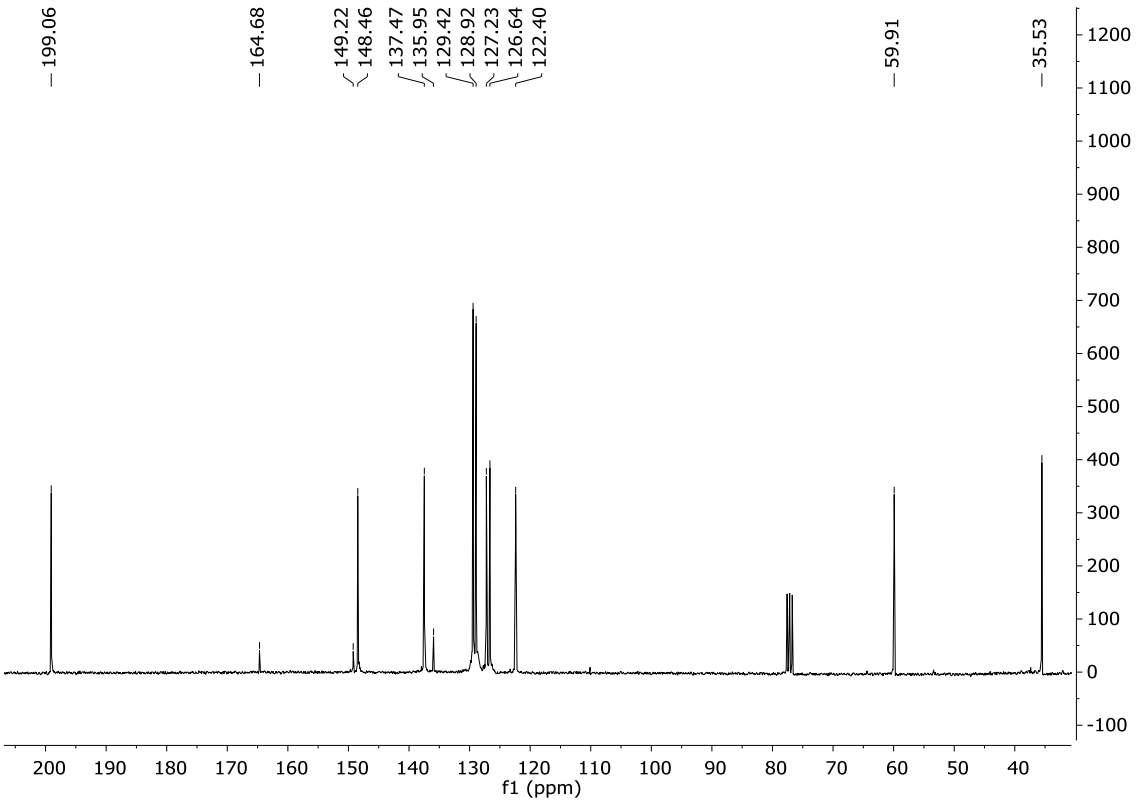
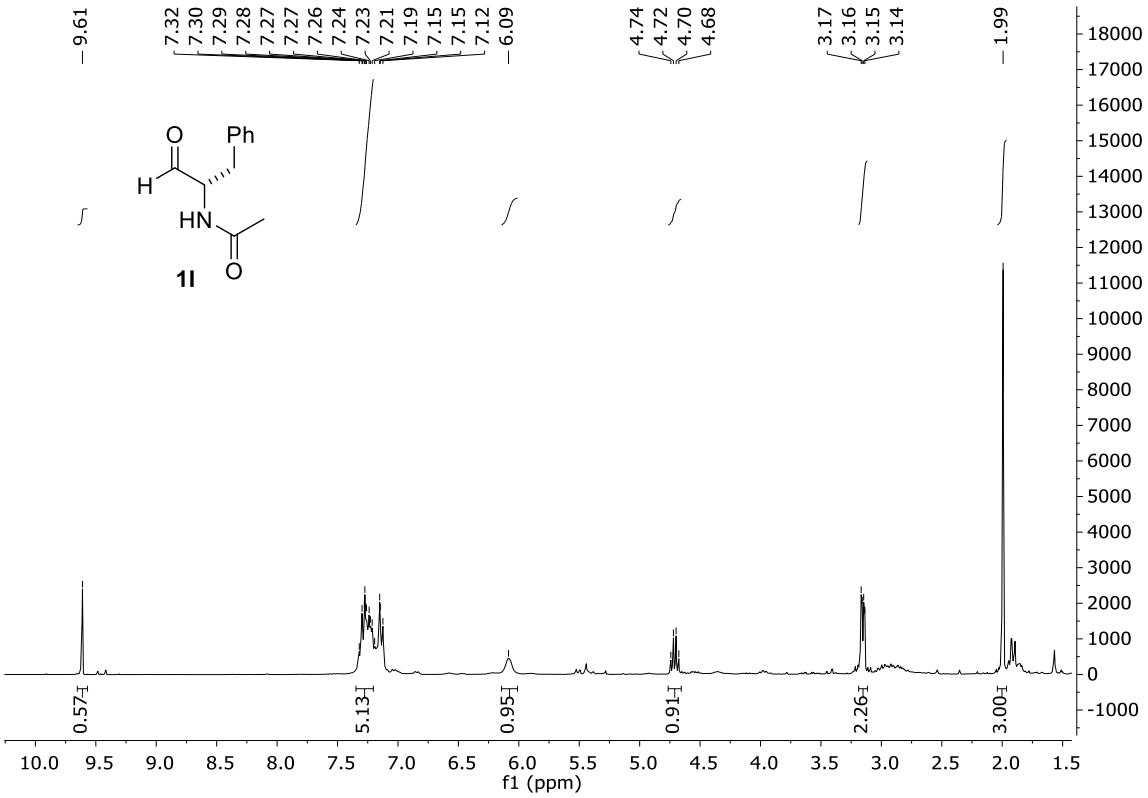
36.05
28.78
28.33
27.46
26.12
f1 (ppm)

5.5.2. NMR spectra of Chapter 2



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7.23
7.21
7.19
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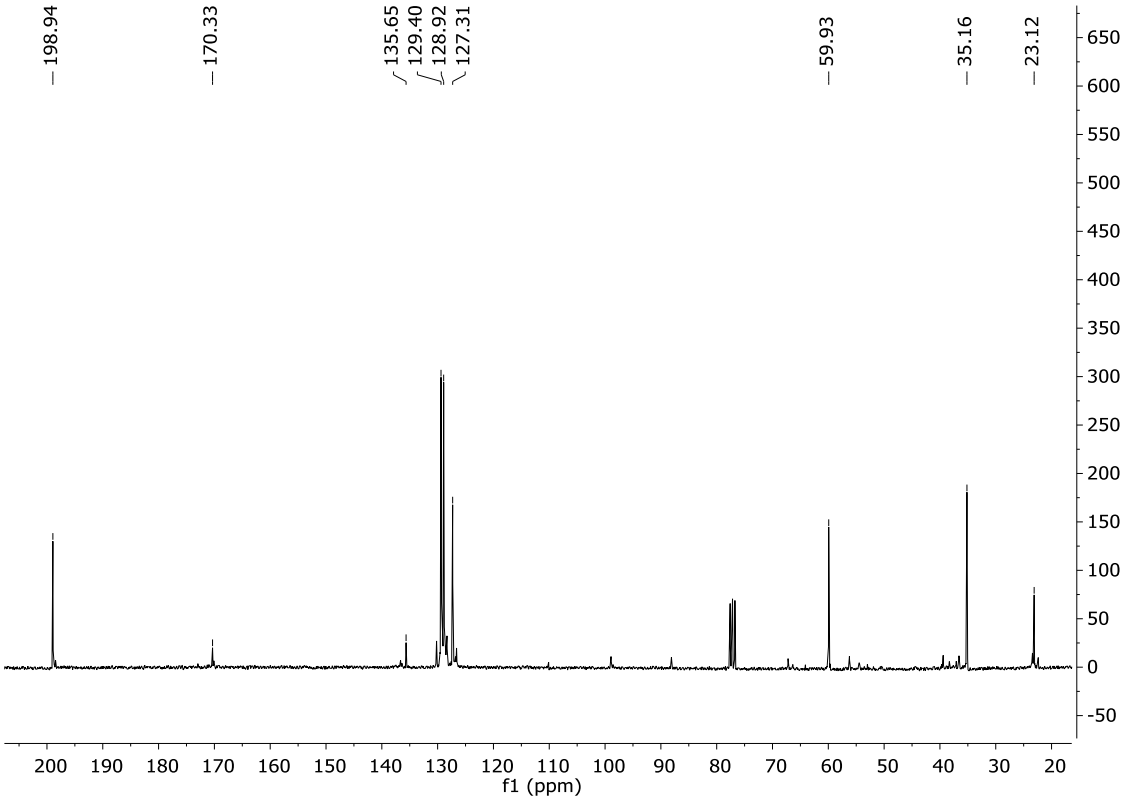
7.15
7.12
6.09
4.74
4.72
4.70
4.68
3.17
3.16
3.15
3.14
1.99
O
Ph
H
HN
O
1l
0.57
5.13
0.95
0.91
2.26
3.00
f1 (ppm)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127.31
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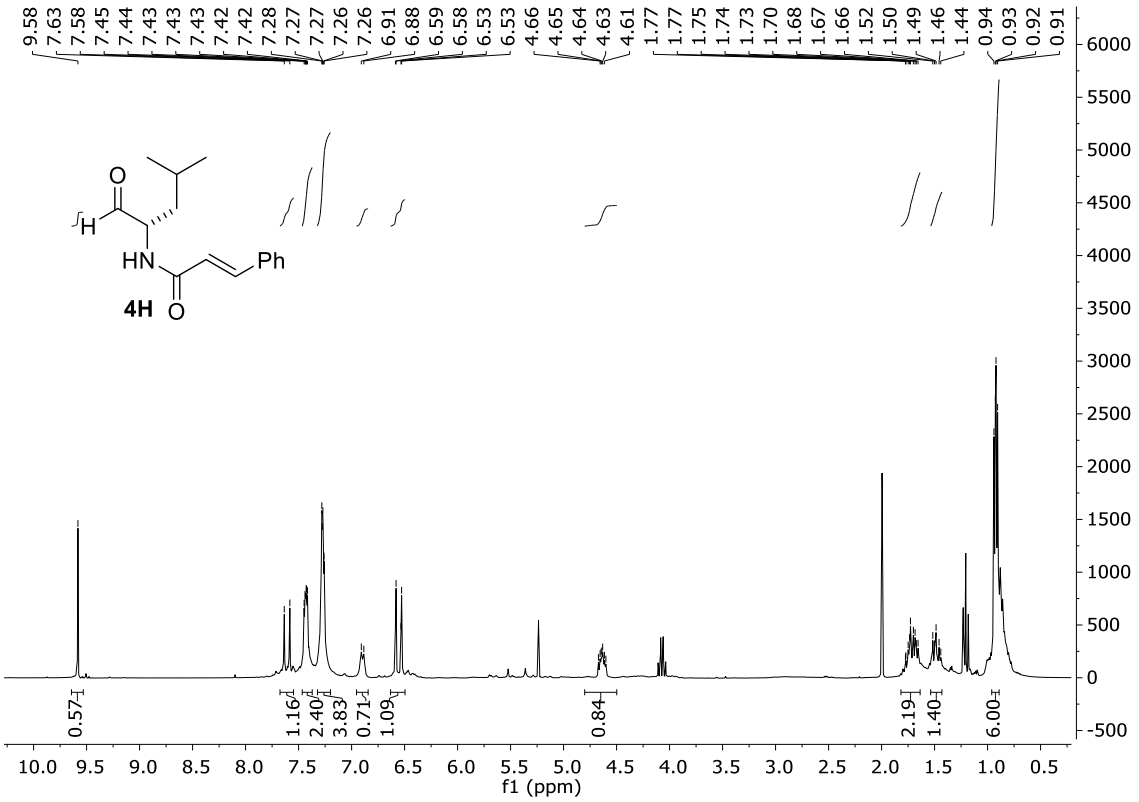
23.12
f1 (ppm)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7.63
7.58
7.45
7.44
7.43
7.43
7.43
7.42
7.42
7.28
7.27
7.27
7.26
7.26
6.91
6.88
6.59
6.58
6.53
6.53
4.66
4.65
4.64
4.63
4.61
1.77
1.77
1.75
1.74
1.73
1.70
1.68
1.67
1.66
1.52
1.50
1.49
1.46
1.44
0.94
0.93
0.92
0.91
O
H
HN
Ph
O
4H
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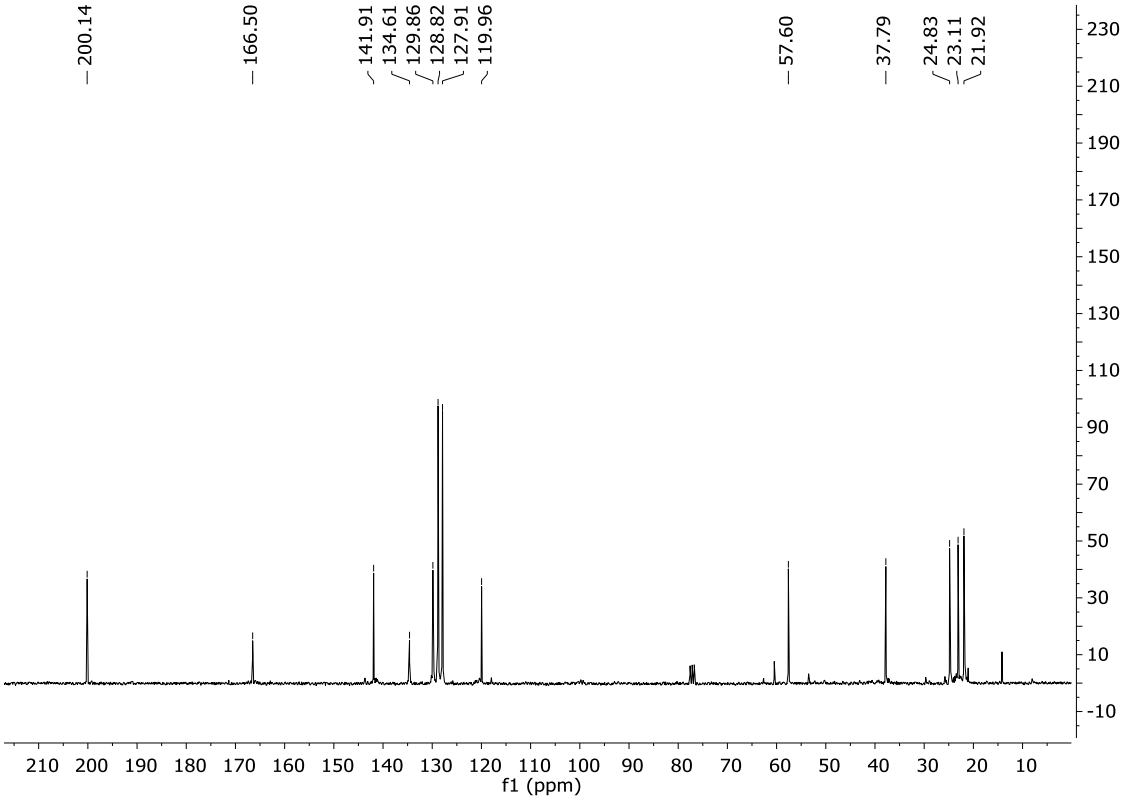
2.40
3.83
0.71
1.09
0.84
2.19
1.40
6.00
f1 (ppm)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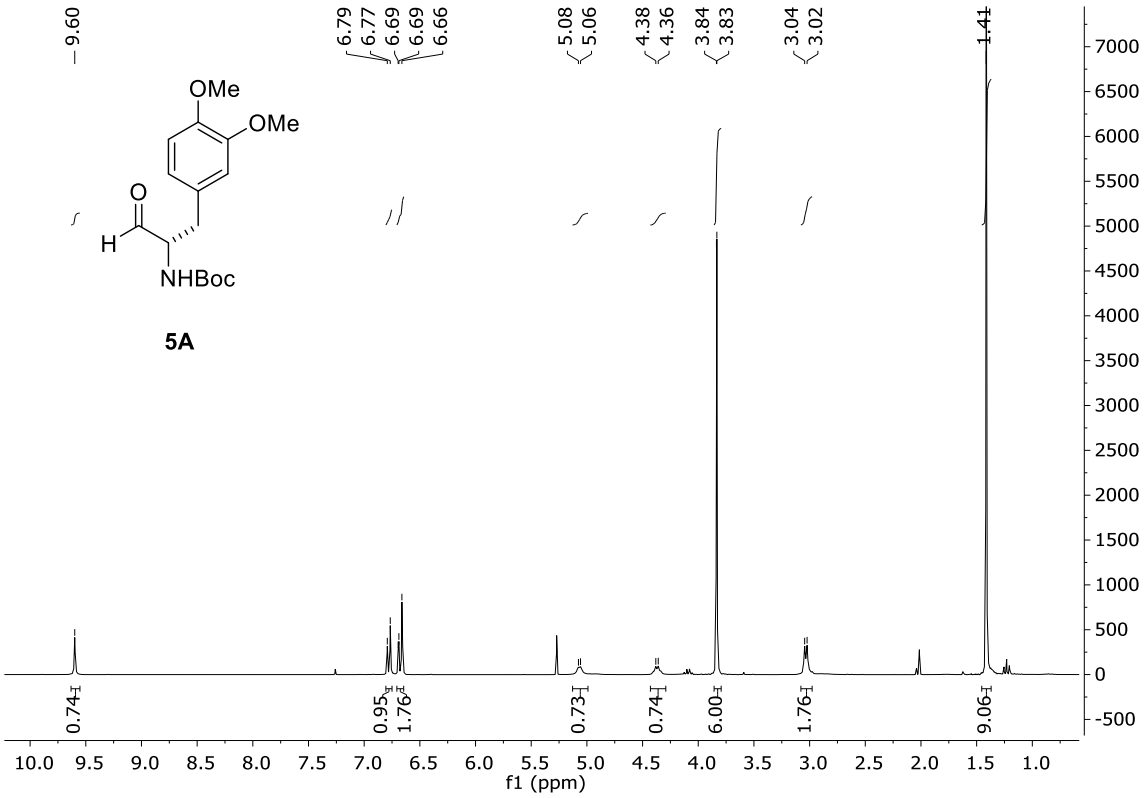
128.82
127.91
119.96
57.60
37.79
24.83
23.11
21.92
f1 (ppm)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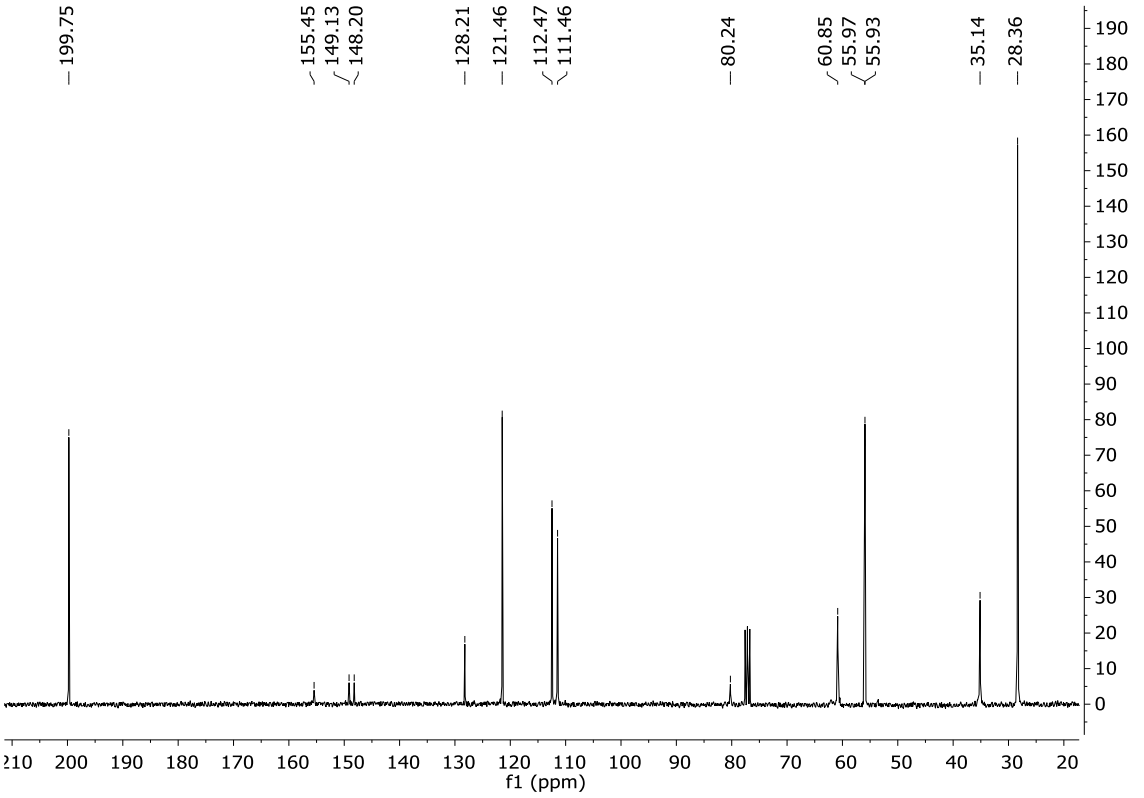
6.79
6.77
6.69
6.69
6.66
5.08
5.06
4.38
4.36
3.84
3.83
3.04
3.02
1.41
OMe
OMe
O
H
NHBoc
5A
0.74
0.95
1.76
0.73
0.74
6.00
1.76
9.06
f1 (ppm)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55.97
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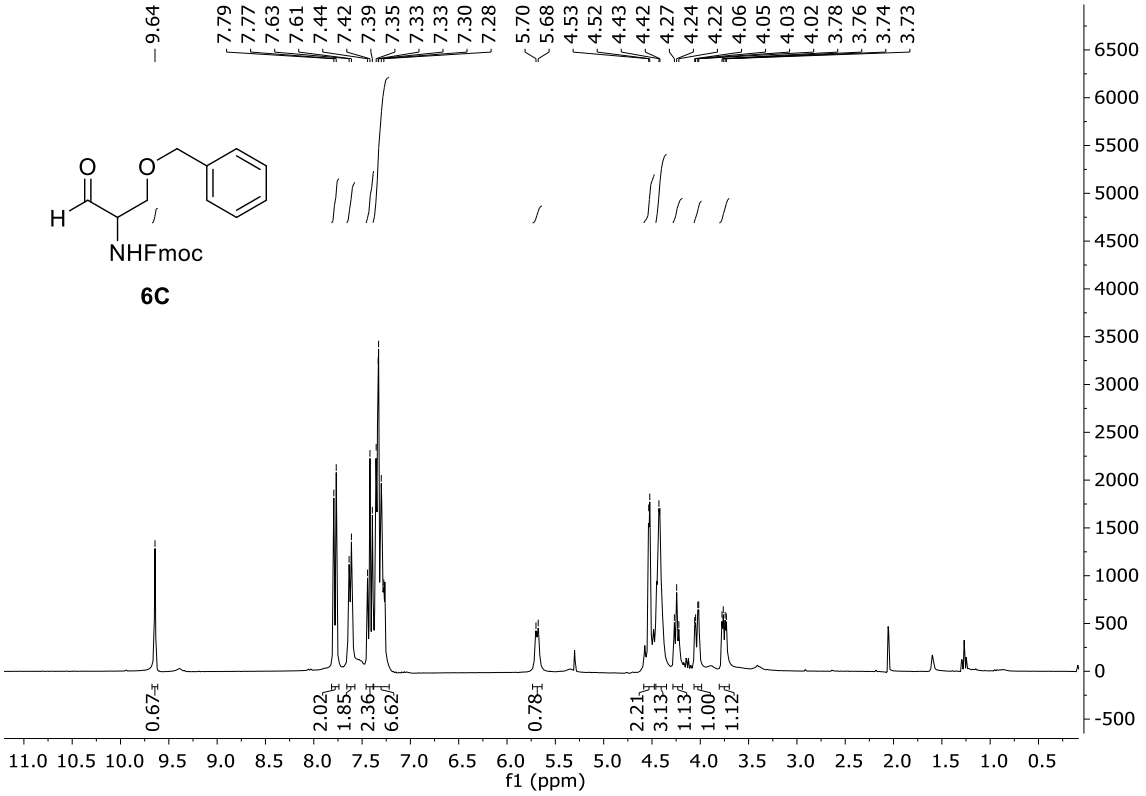
28.36
f1 (ppm)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7.33
7.30
7.28
5.70
5.68
4.53
4.52
4.43
4.42
4.27
4.24
4.22
4.06
4.05
4.03
4.02
3.78
3.76
3.74
3.73
O
O
H
NHFmoc
6C
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1.13
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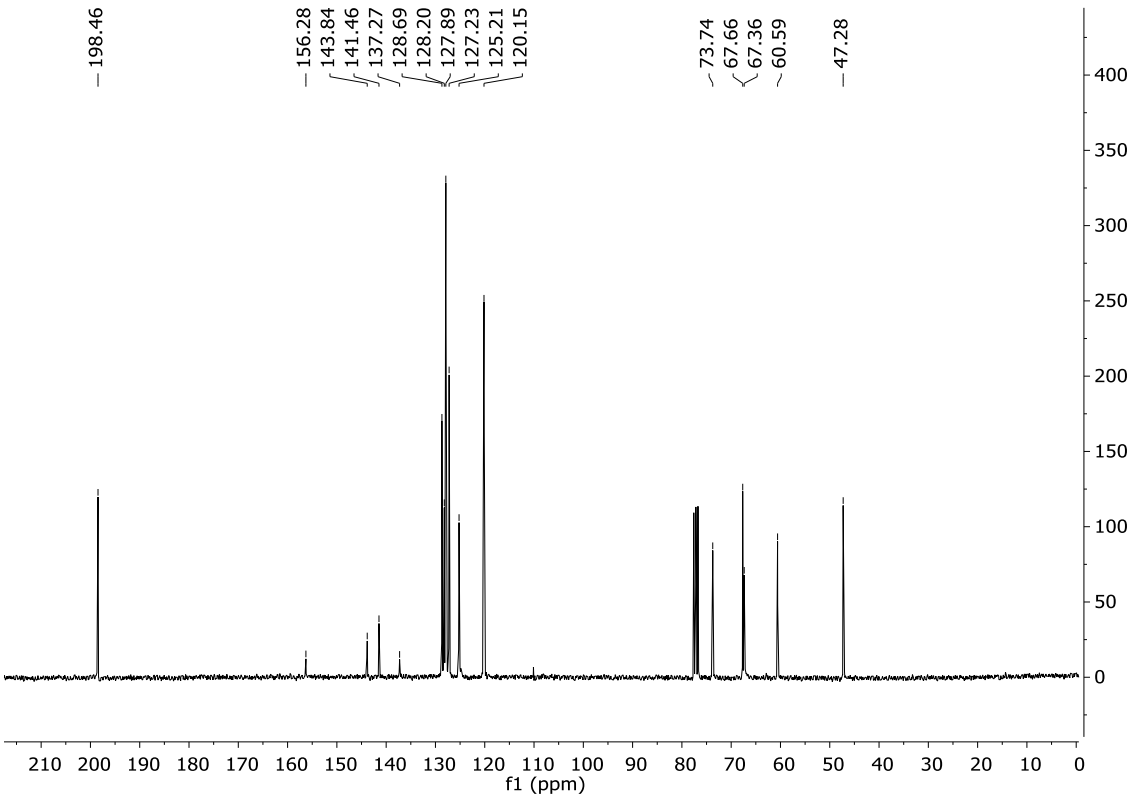
1.12
f1 (ppm)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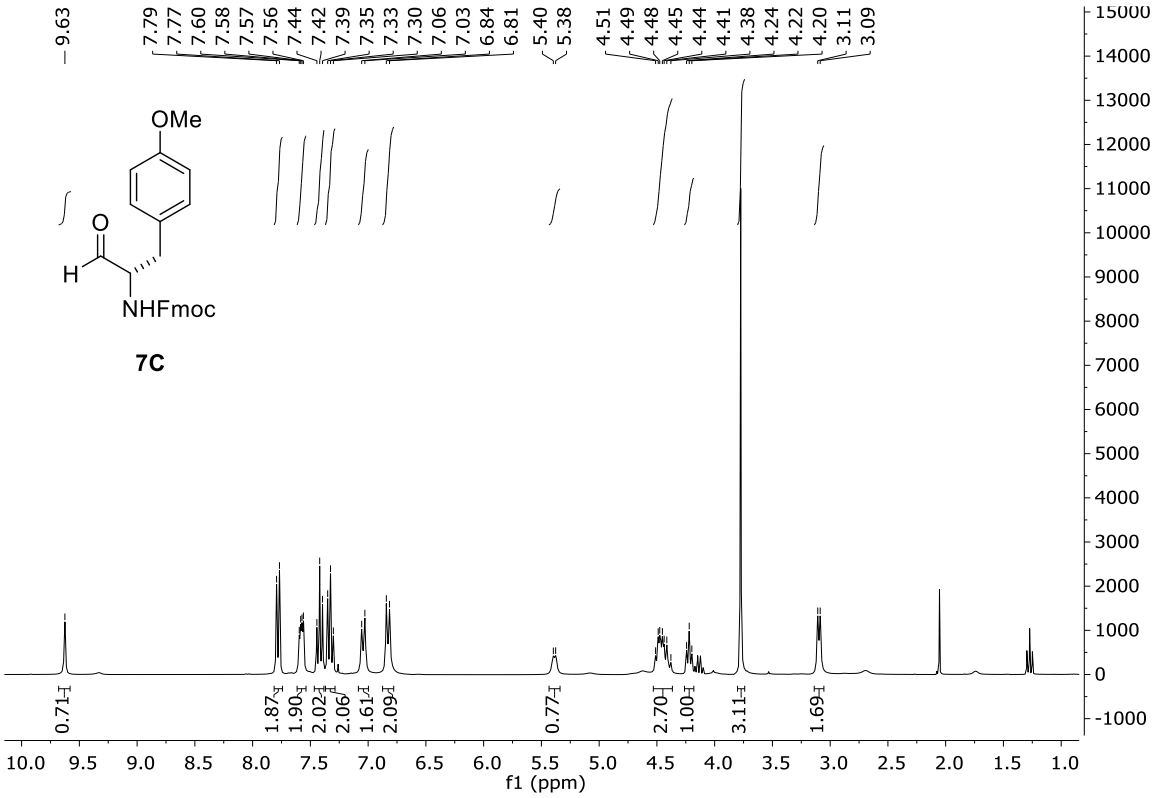
127.23
125.21
120.15
73.74
67.66
67.36
60.59
47.28
f1 (ppm)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7.42
7.39
7.35
7.33
7.30
7.06
7.03
6.84
6.81
5.40
5.38
4.51
4.49
4.48
4.45
4.44
4.41
4.38
4.24
4.22
4.20
3.11
3.09
OMe
O
H
NHFmoc
7C
0.71
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1.90
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2.06
1.61
2.09
0.77
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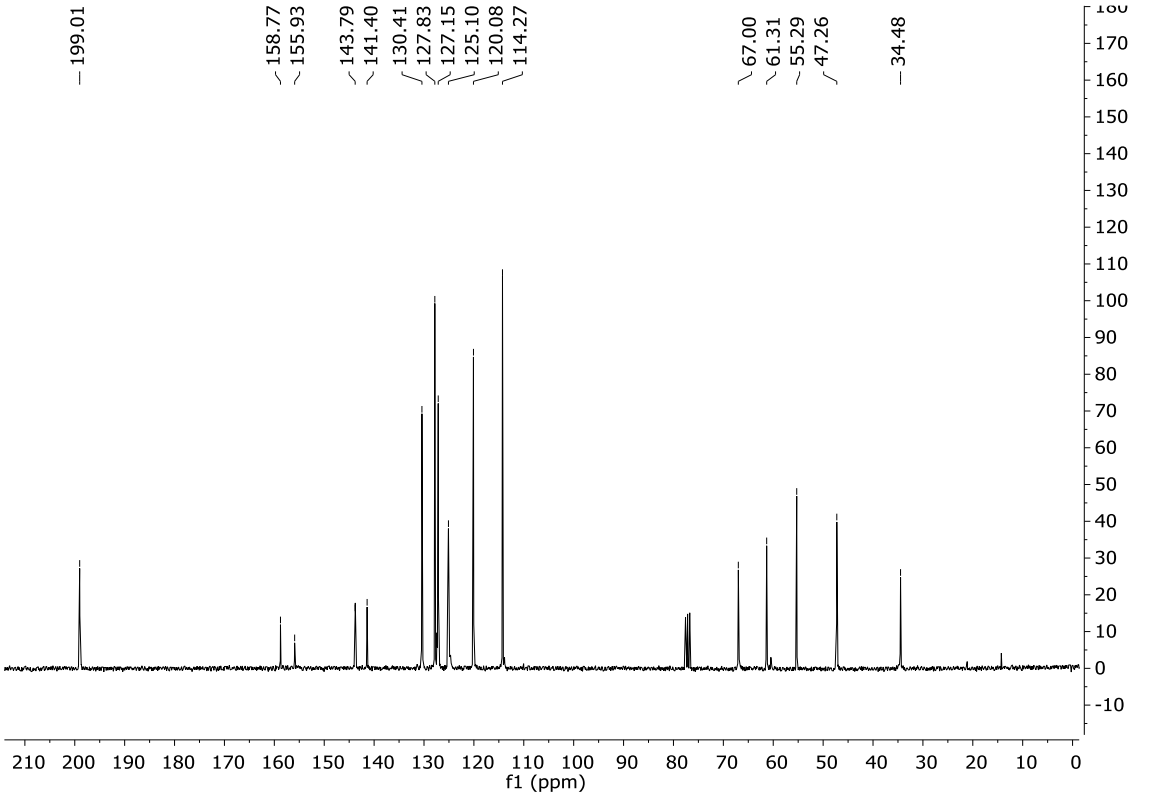
1.00
3.11
1.69
f1 (ppm)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127.15
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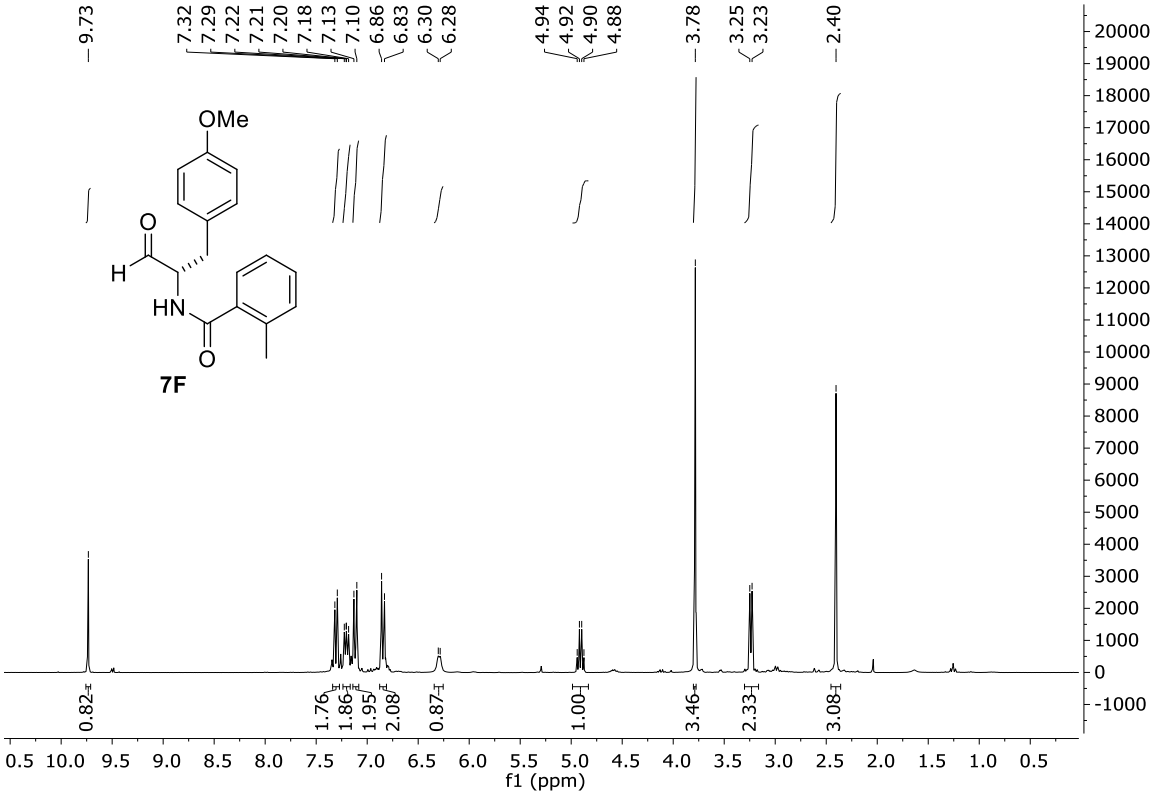
114.27
67.00
61.31
55.29
47.26
34.48
f1 (ppm)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7.18
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7.10
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6.83
6.30
6.28
4.94
4.92
4.90
4.88
3.78
3.25
3.23
2.40
OMe
O
H
HN
O
7F
0.82
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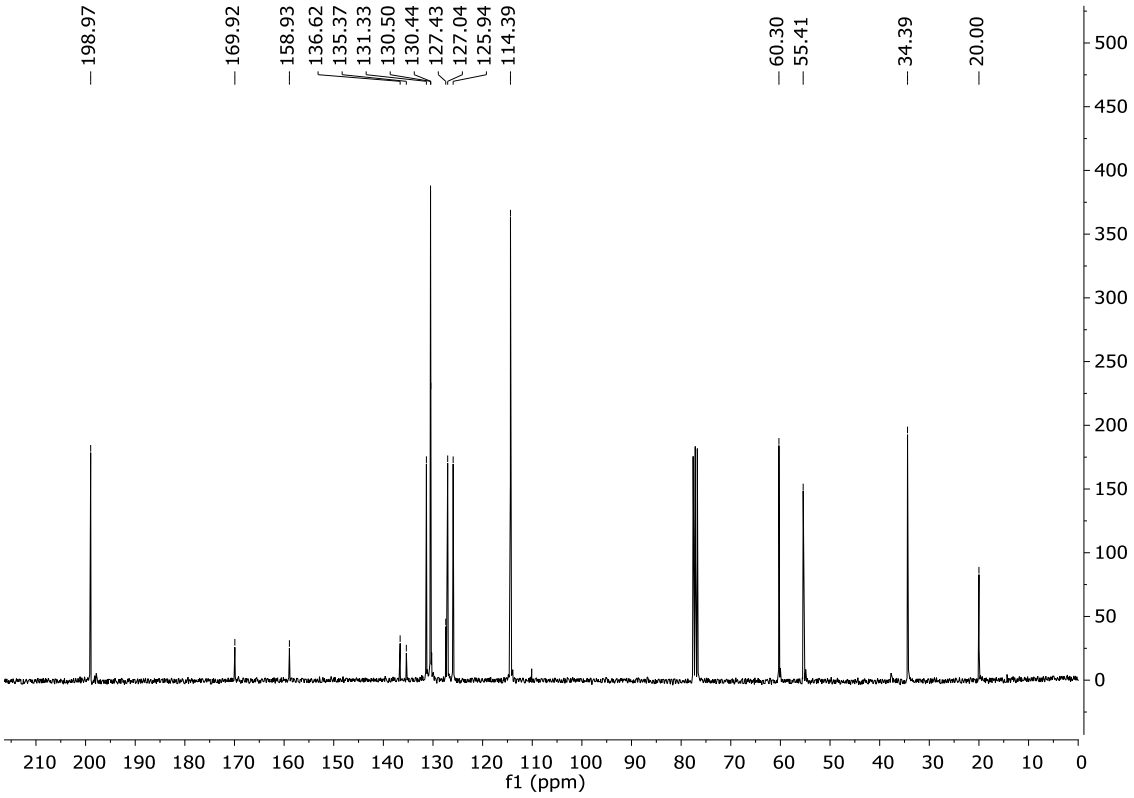
1.86
1.95
2.08
0.87
1.00
3.46
2.33
3.08
f1 (ppm)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125.94
114.39
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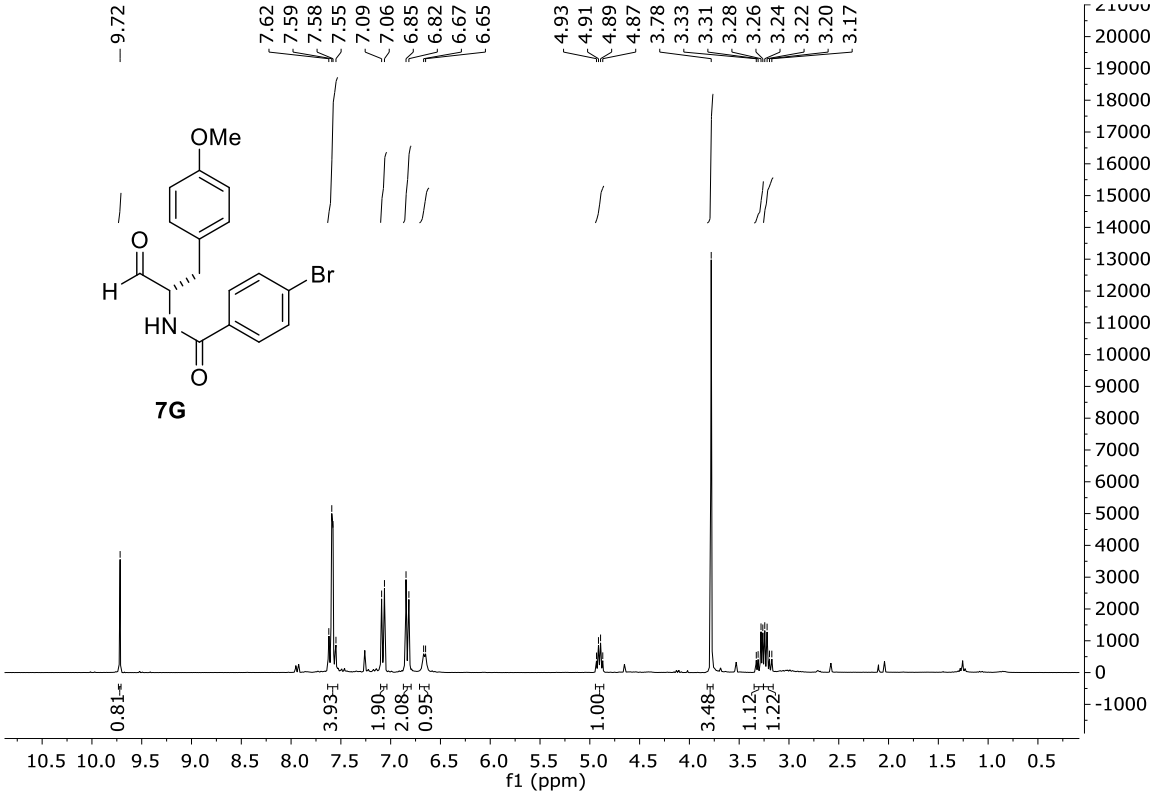
55.41
34.39
20.00
f1 (ppm)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6.82
6.67
6.65
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4.89
4.87
3.78
3.33
3.31
3.28
3.26
3.24
3.22
3.20
3.17
OMe
O
H
HN
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Br
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3.48
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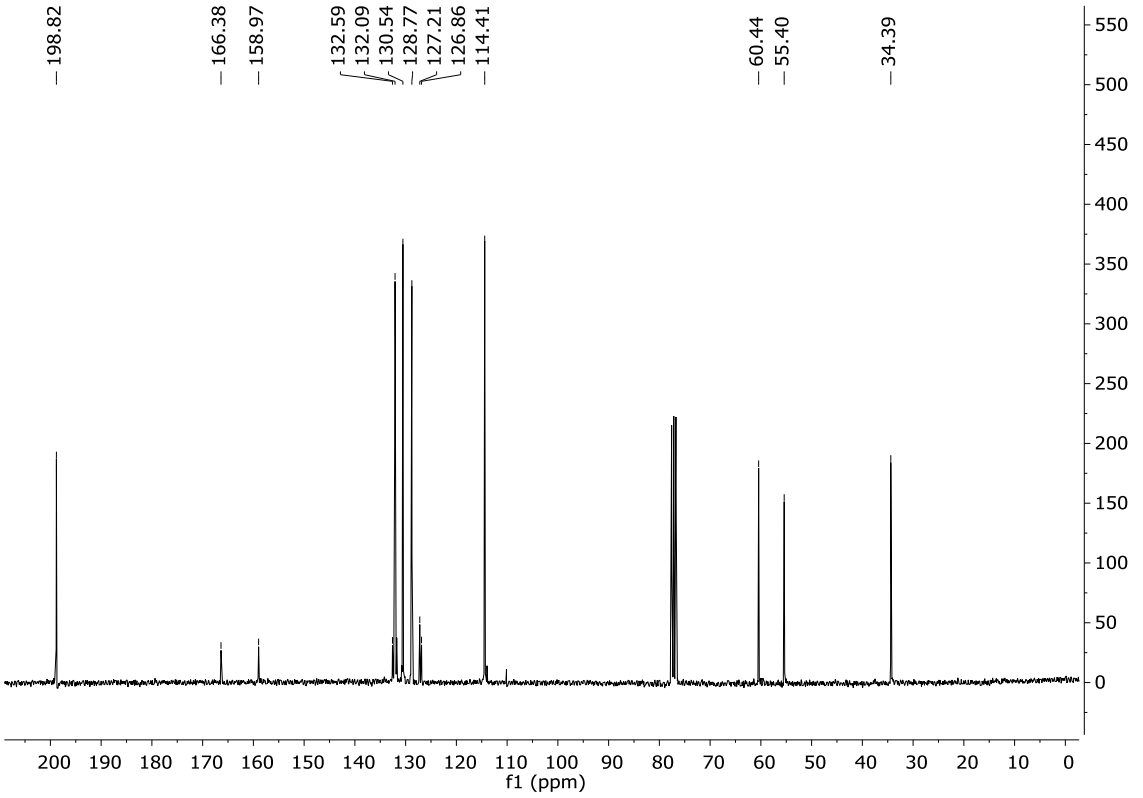
1.22
f1 (ppm)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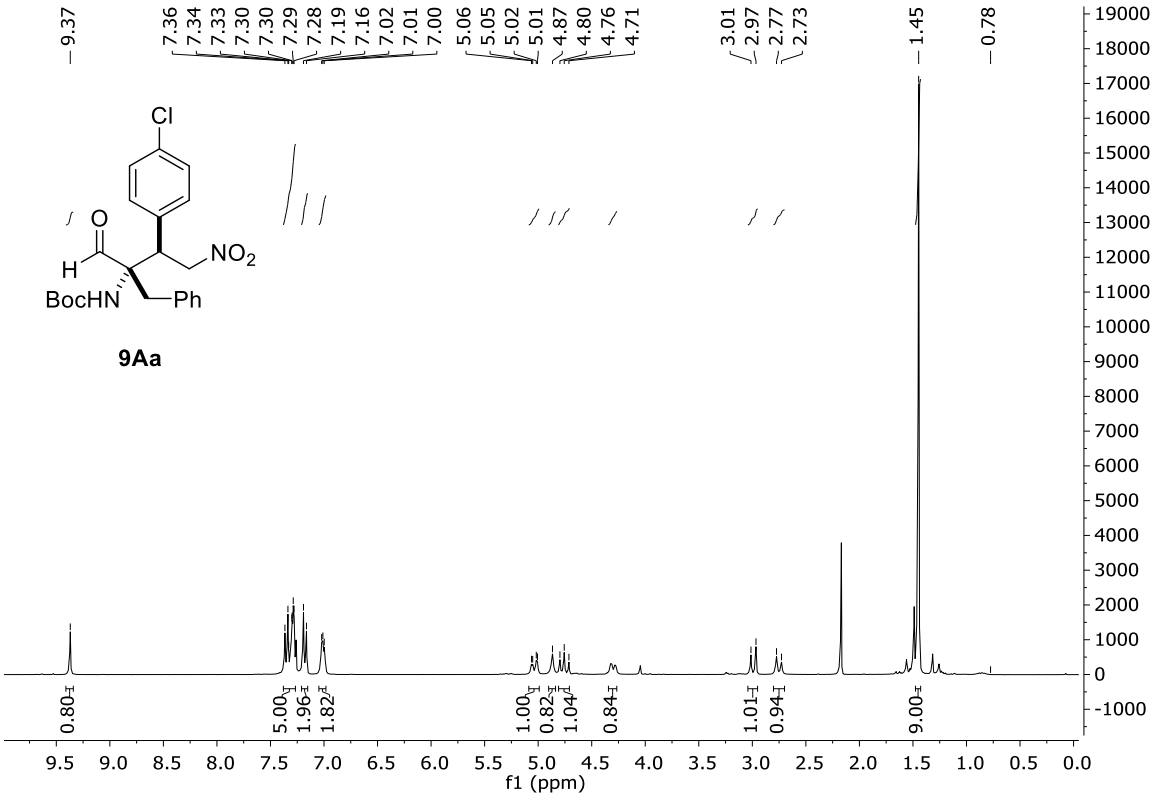
126.86
114.41
60.44
55.40
34.39
f1 (ppm)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7.28
7.19
7.16
7.02
7.01
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5.06
5.05
5.02
5.01
4.87
4.80
4.76
4.71
3.01
2.97
2.77
2.73
1.45
0.78
Cl
O
H
BocHN
NO2
Ph
9Aa
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1.82
1.00
0.82
1.04
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1.01
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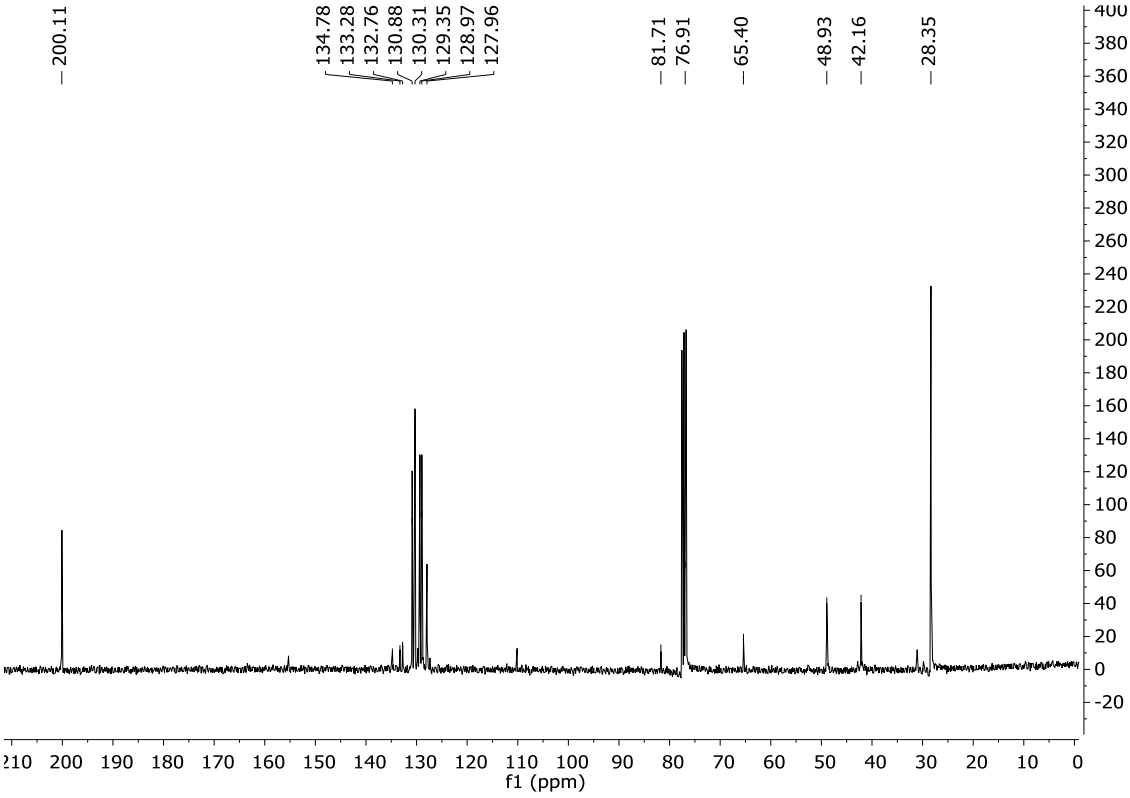
9.00
f1 (ppm)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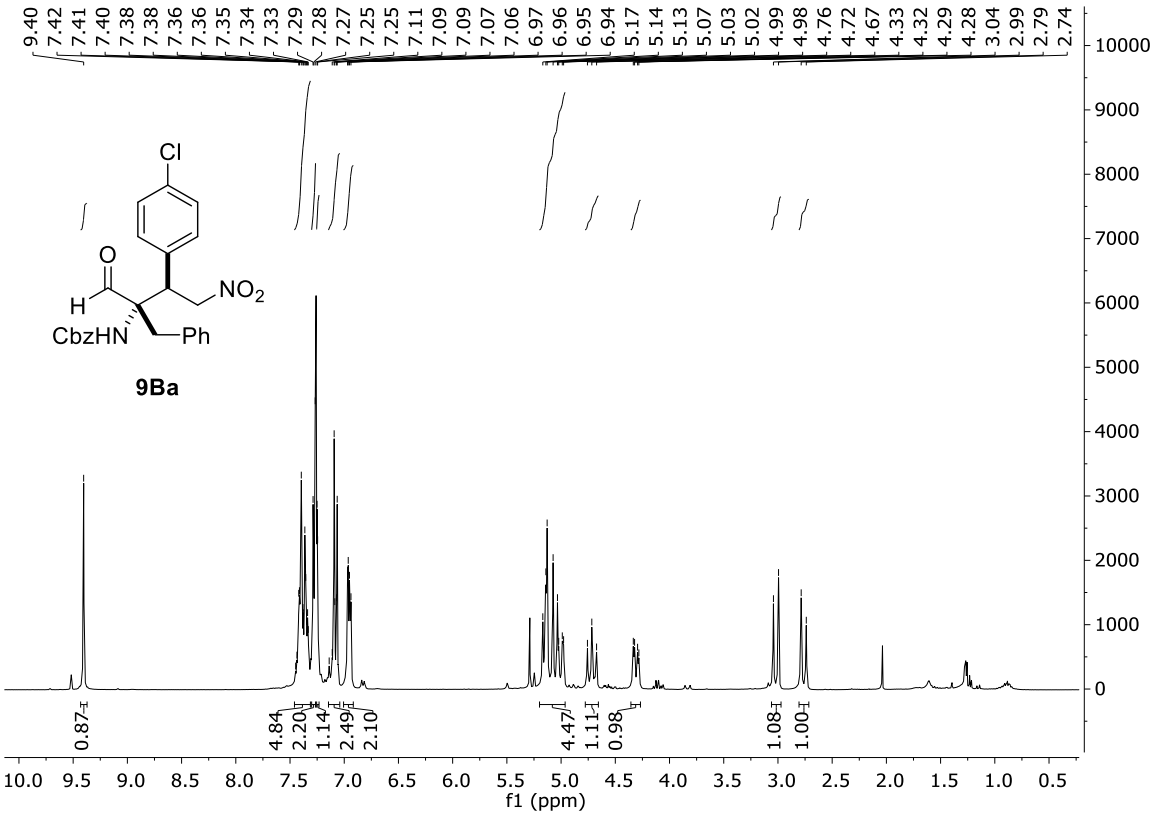
48.93
42.16
28.35
f1 (ppm)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Cl
O
H
CbzHN
NO2
Ph
9Ba
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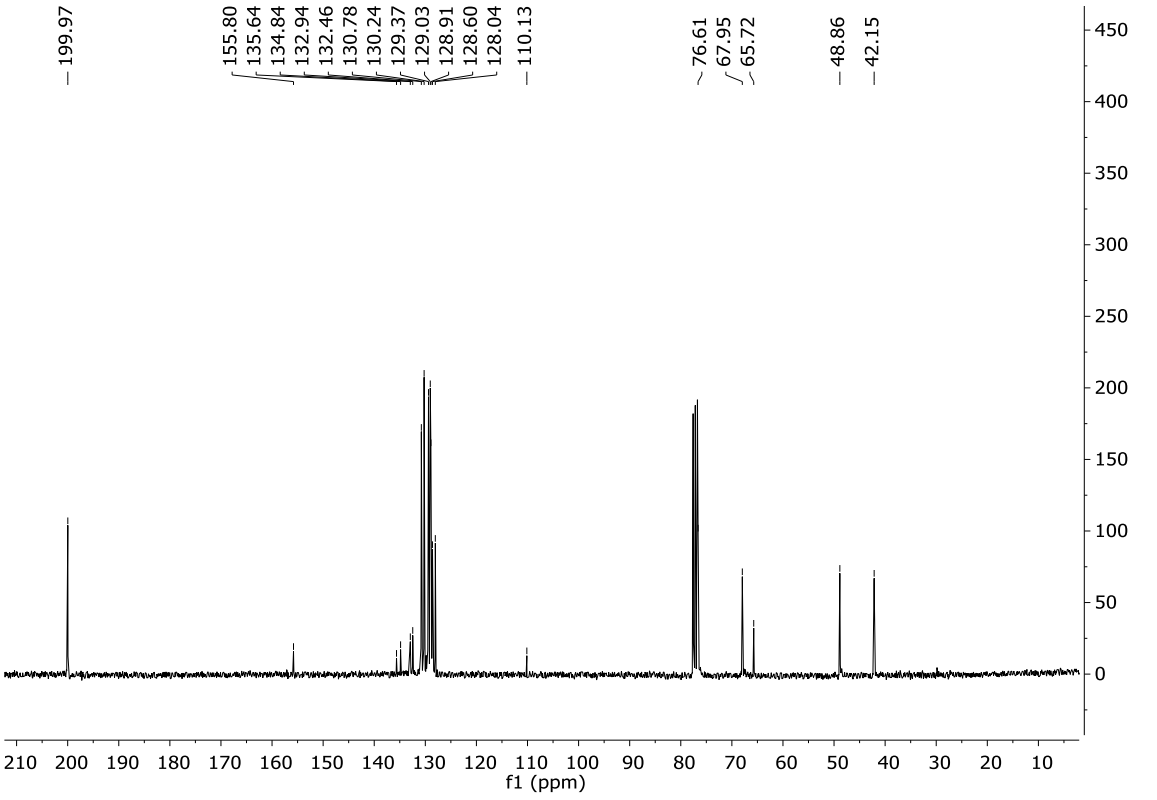
f1 (ppm)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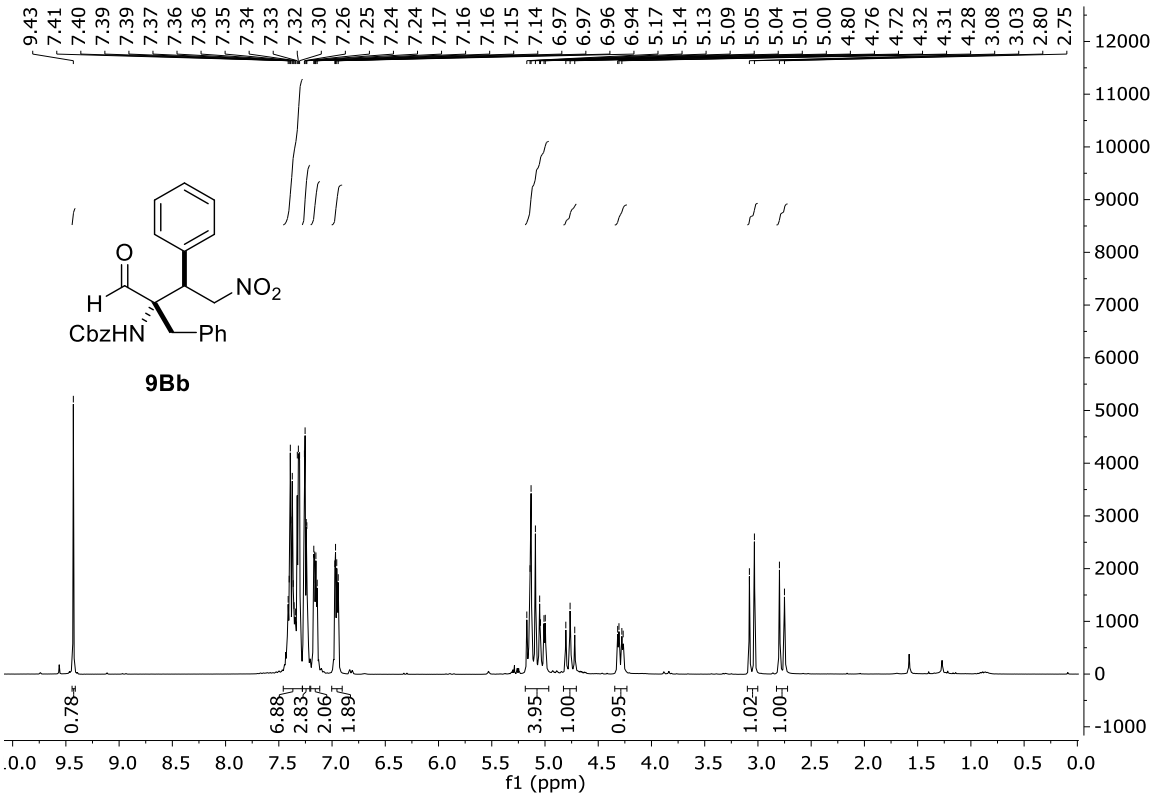
110.13
76.61 67.95 65.72
48.86
42.15
f1 (ppm)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7.24
7.17
7.16
7.16
7.15
7.14
6.97
6.97
6.96
6.94
5.17
5.14
5.13
5.09
5.05
5.04
5.01
5.00
4.80
4.76
4.72
4.32
4.31
4.28
3.08
3.03
2.80
2.75
O
H
CbzHN
NO2
Ph
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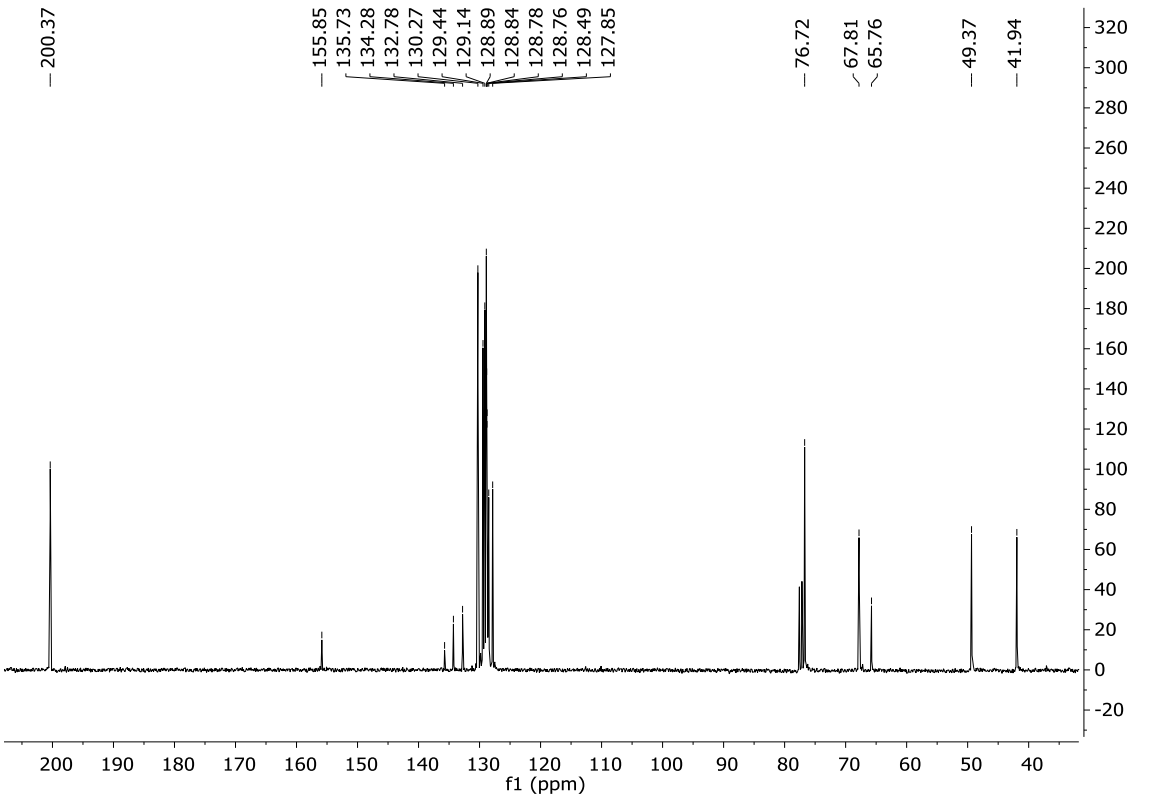
3.95
1.00
0.95
1.02
1.00
f1 (ppm)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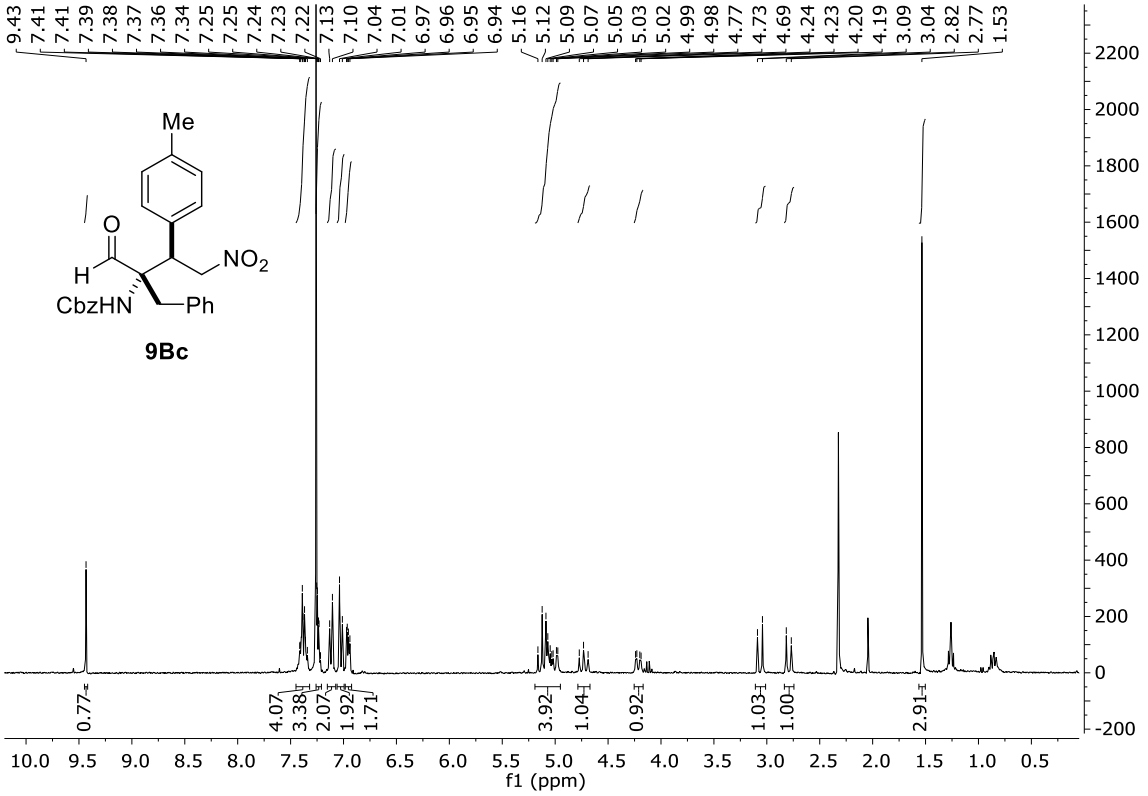
127.85
76.72
67.81
65.76
49.37
41.94
f1 (ppm)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5.16 5.12 5.09 5.07 5.05 5.03 5.02 4.99 4.98 4.77 4.73 4.69 4.24 4.23 4.20 4.19 3.09 3.04 2.82 2.77 1.53
Me
O
H
CbzHN
NO2
Ph
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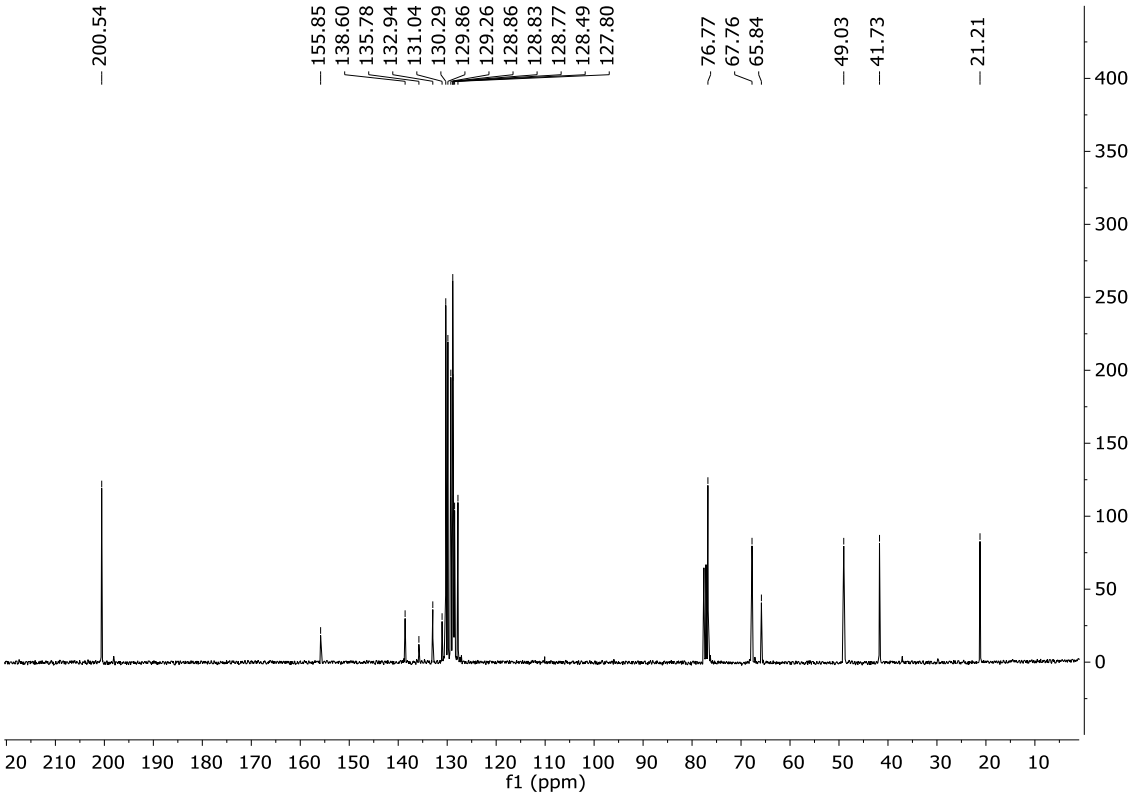
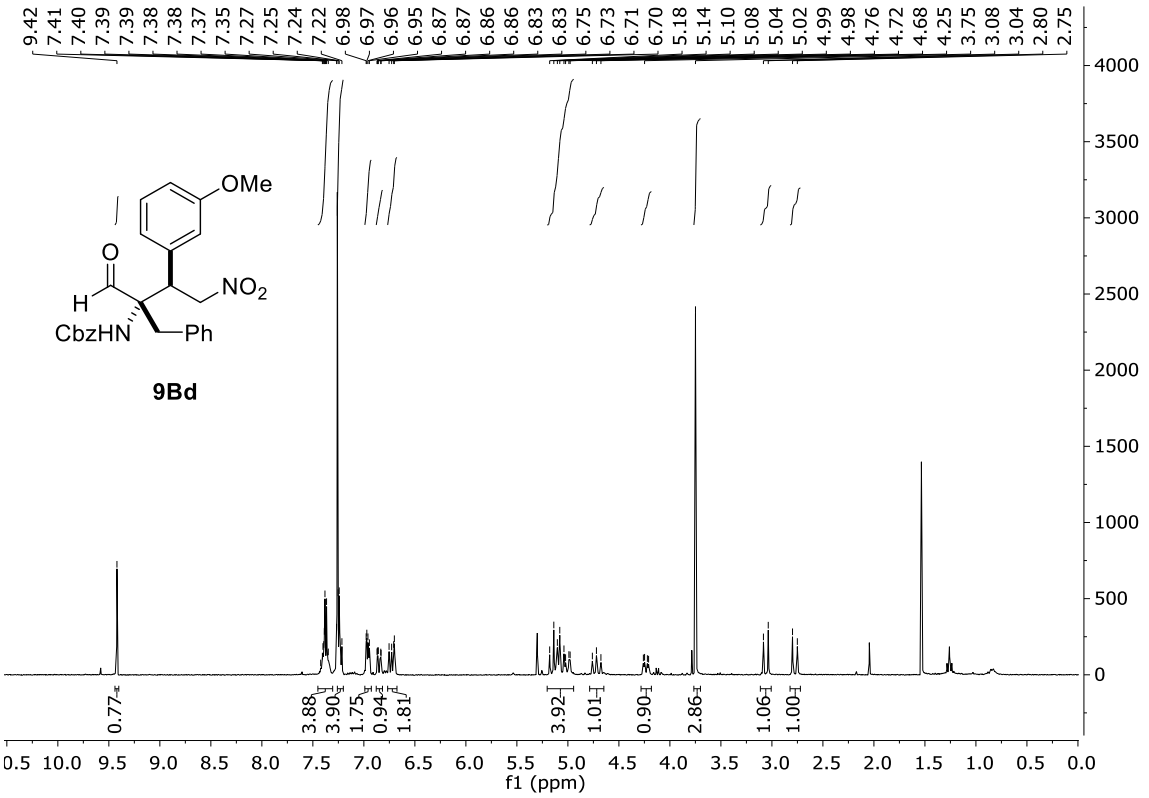
f1 (ppm)


200.54
155.85 138.60 135.78 132.94 131.04 130.29 129.86 129.26 128.86 128.83 128.77 128.49 127.80
76.77 67.76 65.84
49.03 41.73
21.21
f1 (ppm)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OMe
O
H
CbzHN
NO2
Ph
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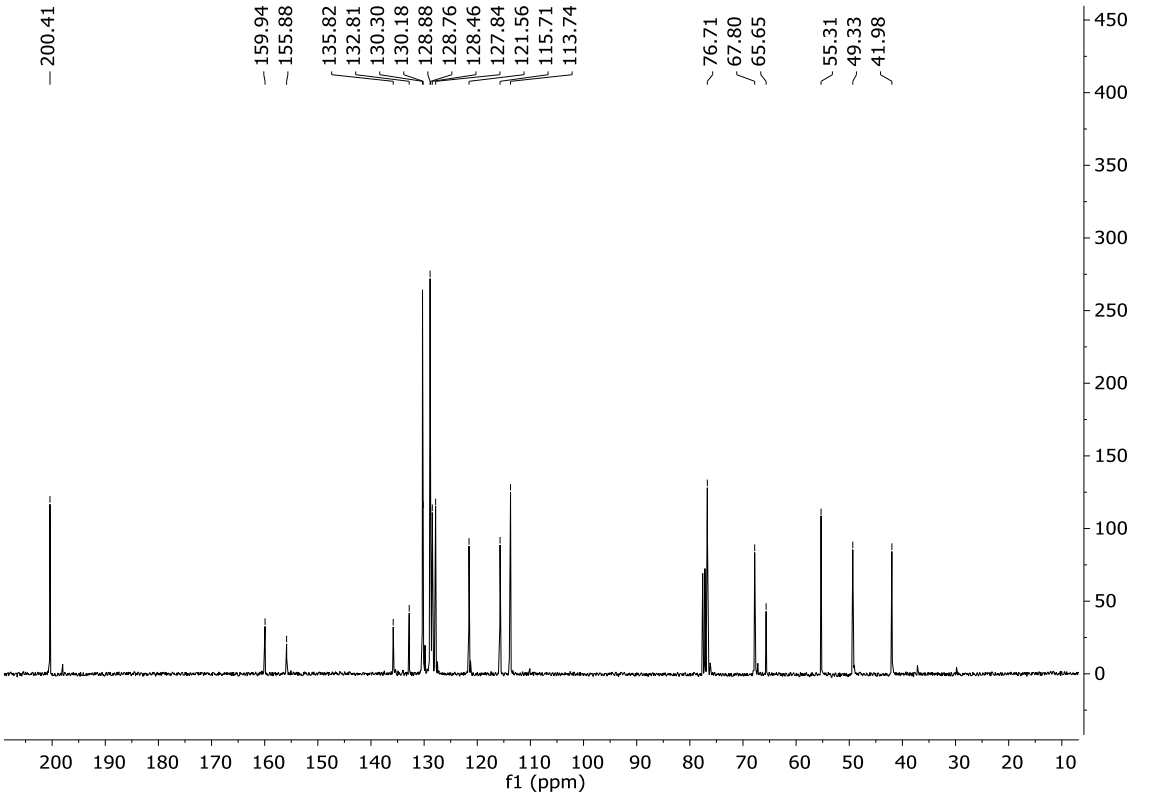
f1 (ppm)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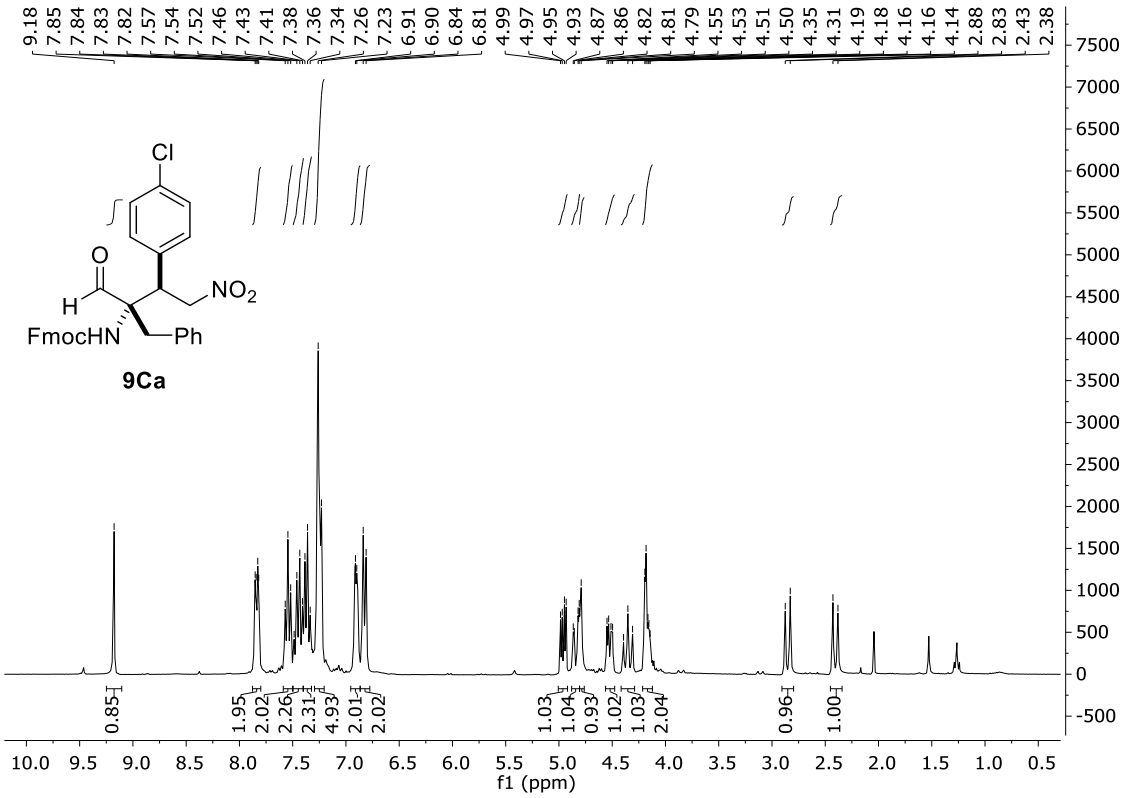
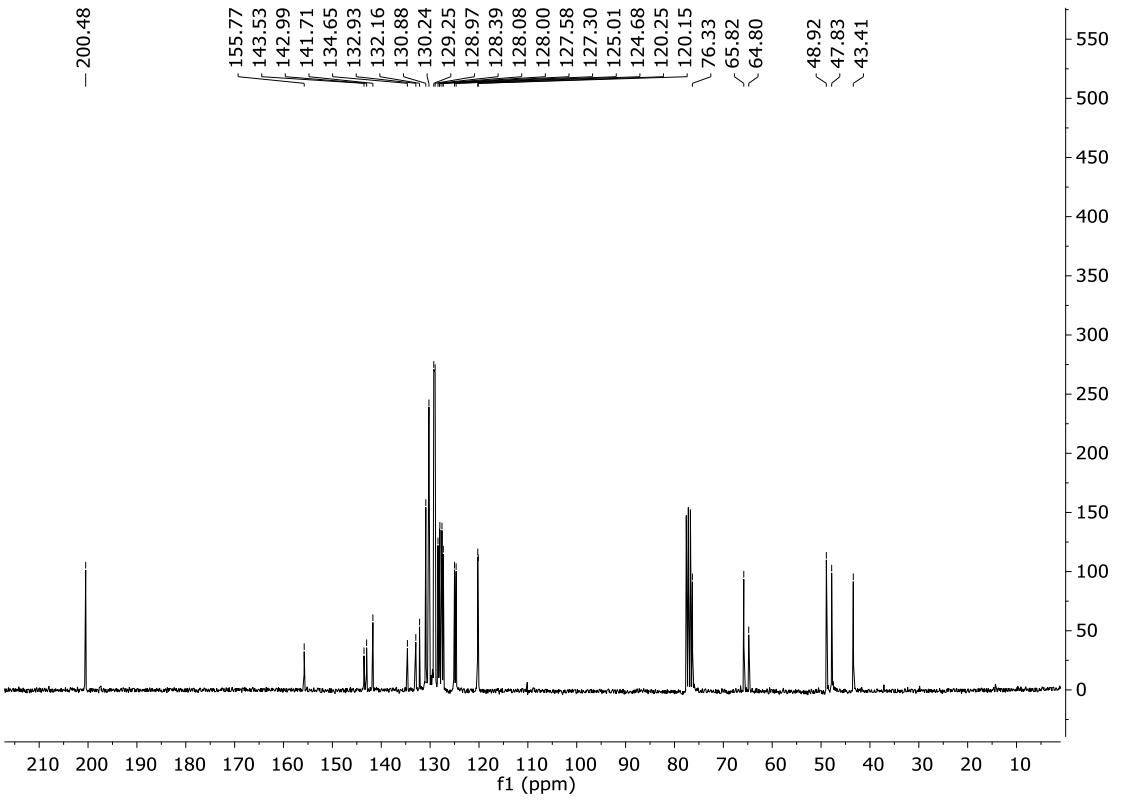
159.94 155.88 135.82 132.81 130.30 130.18 128.88 128.76 128.46 127.84 121.56 115.71 113.74
76.71 67.80 65.65
55.31 49.33 41.98
f1 (ppm)


9.18 7.85 7.84 7.83 7.82 7.57 7.54 7.52 7.46 7.43 7.41 7.38 7.36 7.34 7.26 7.23 6.91 6.90 6.84 6.81
4.99 4.97 4.95 4.93 4.87 4.86 4.82 4.81 4.79 4.55 4.53 4.51 4.50 4.35 4.31 4.19 4.18 4.16 4.16 4.14 2.88 2.83 2.43 2.38
Cl
O
H
FmocHN
NO2
Ph
9Ca
0.85 1.95 2.02 2.26 2.31 4.93 2.01 2.02 1.03 1.04 0.93 1.02 1.03 2.04 0.96 1.00
f1 (ppm)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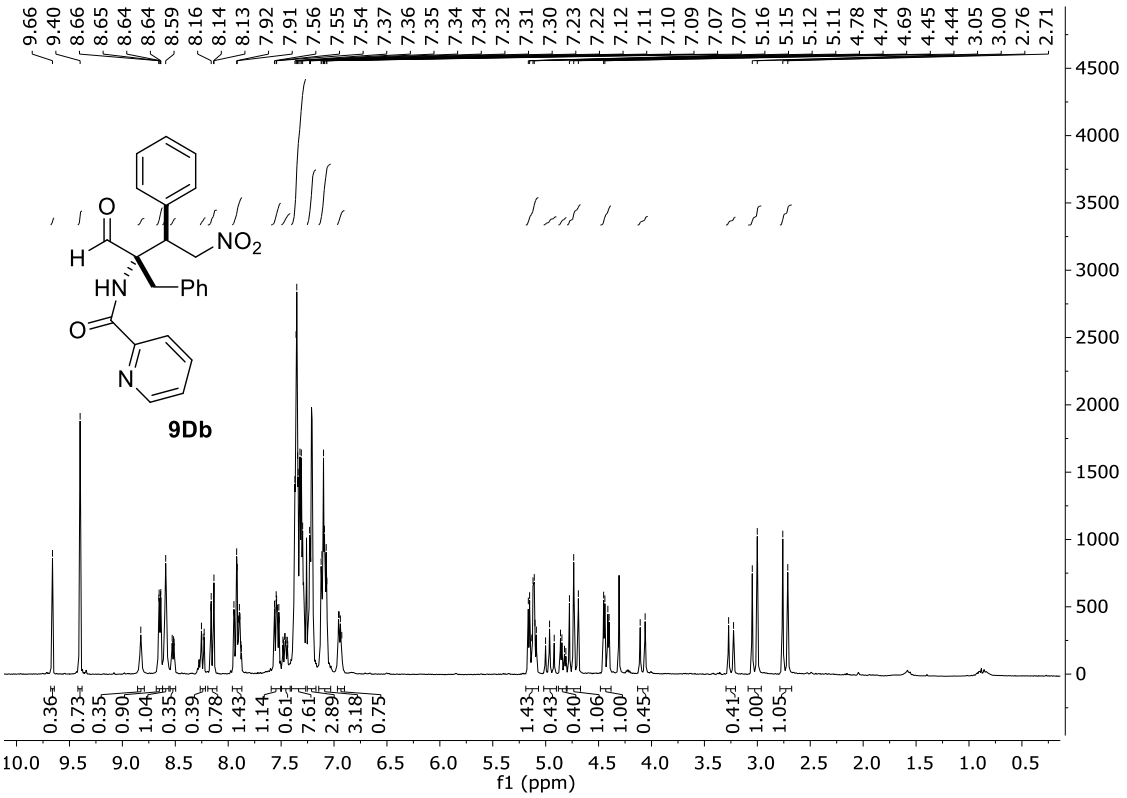
155.77 143.53 142.99 141.71 134.65 132.93 132.16 130.88 130.24 129.25 128.97 128.39 128.08 128.00 127.58 127.30 125.01 124.68 120.25 120.15 76.33 65.82 64.80 48.92 47.83 43.41
f1 (ppm)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8.13
7.92
7.91
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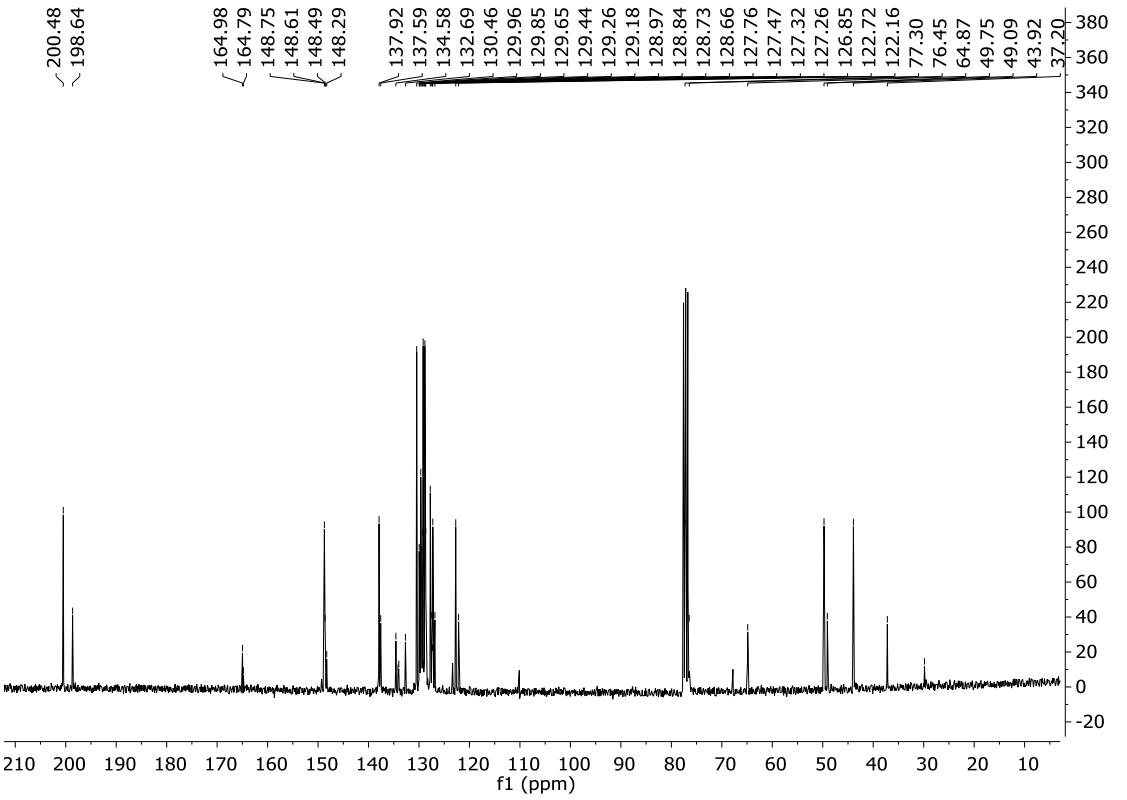
7.55
7.54
7.37
7.36
7.35
7.34
7.34
7.32
7.31
7.30
7.23
7.22
7.12
7.11
7.10
7.09
7.07
7.07
5.16
5.15
5.12
5.11
4.78
4.74
4.69
4.45
4.44
3.05
3.00
2.76
2.71
O
H
HN
O
N
NO2
Ph
9Db
0.36
0.73
0.35
0.90
1.04
0.35
0.39
0.78
1.43
1.14
0.61
7.61
2.89
3.18
0.75
1.43
0.43
0.40
1.06
1.00
0.45
0.41
1.00
1.05
f1 (ppm)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164.79
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148.49
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137.59
134.58
132.69
130.46
129.96
129.85
129.65
129.44
129.26
129.18
128.97
128.84
128.73
128.66
127.76
127.47
127.32
127.26
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122.16
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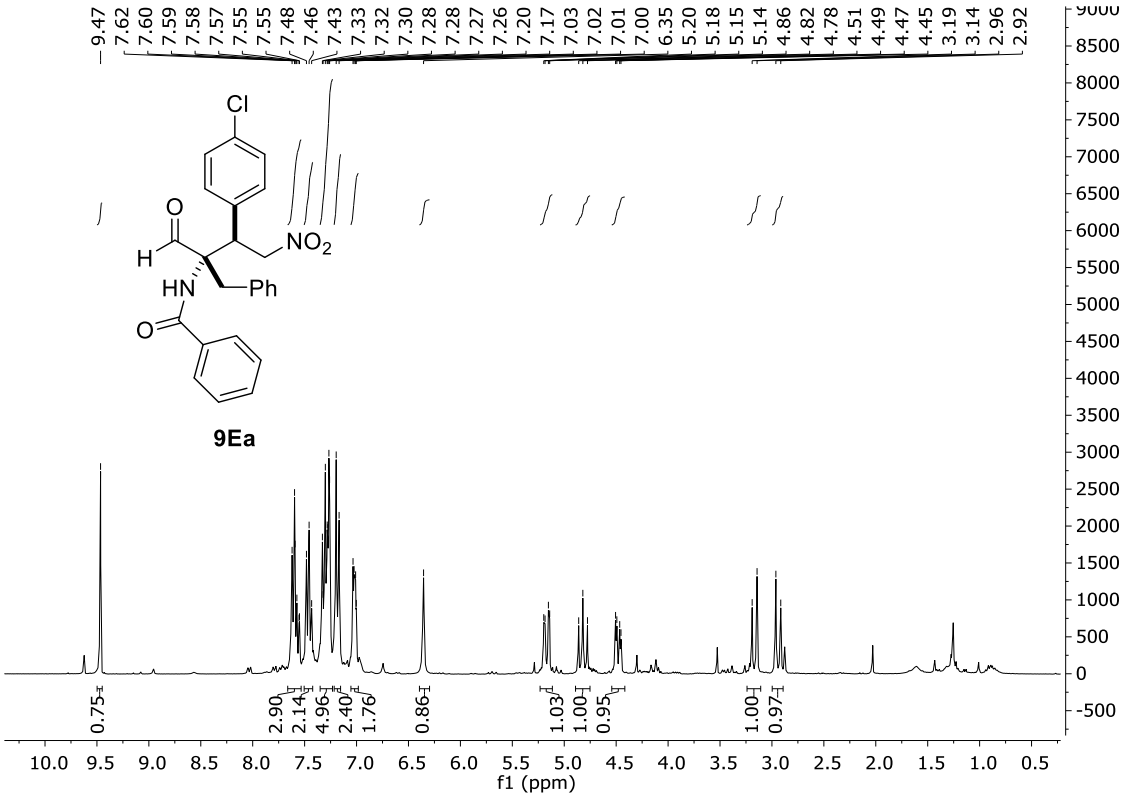
76.45
64.87
49.75
49.09
43.92
37.20
f1 (ppm)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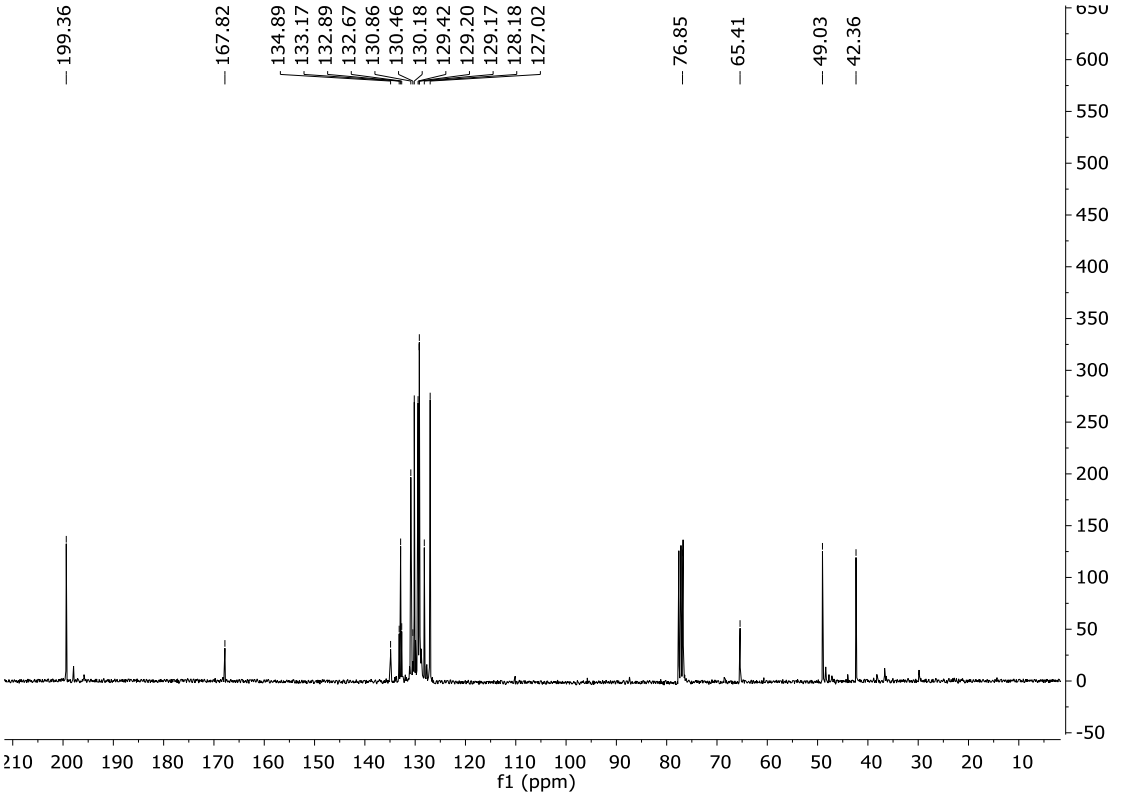
7.57
7.55
7.55
7.48
7.46
7.43
7.33
7.32
7.30
7.28
7.28
7.27
7.26
7.20
7.17
7.03
7.02
7.01
7.00
6.35
5.20
5.18
5.15
5.14
4.86
4.82
4.78
4.51
4.49
4.47
4.45
3.19
3.14
2.96
2.92
Cl
O
H
HN
O
NO2
Ph
9Ea
0.75
2.90
2.14
4.96
2.40
1.76
0.86
1.03
1.00
0.95
1.00
0.97
f1 (ppm)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167.82
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133.17
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132.67
130.86
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130.18
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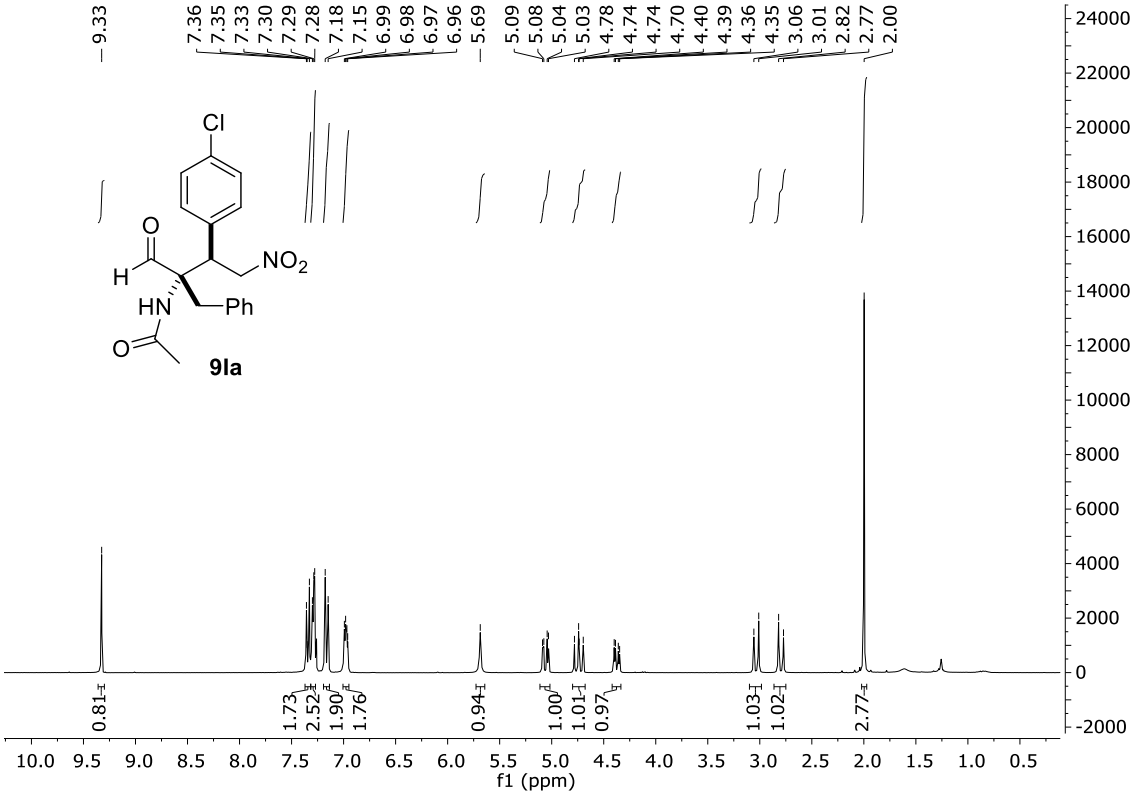
129.20
129.17
128.18
127.02
76.85
65.41
49.03
42.36
f1 (ppm)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7.36
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7.28
7.18
7.15
6.99
6.98
6.97
6.96
5.69
5.09
5.08
5.04
5.03
4.78
4.74
4.74
4.70
4.40
4.39
4.36
4.35
3.06
3.01
2.82
2.77
2.00
Cl
O
H
HN
O
NO2
Ph
9Ia
0.81
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2.52
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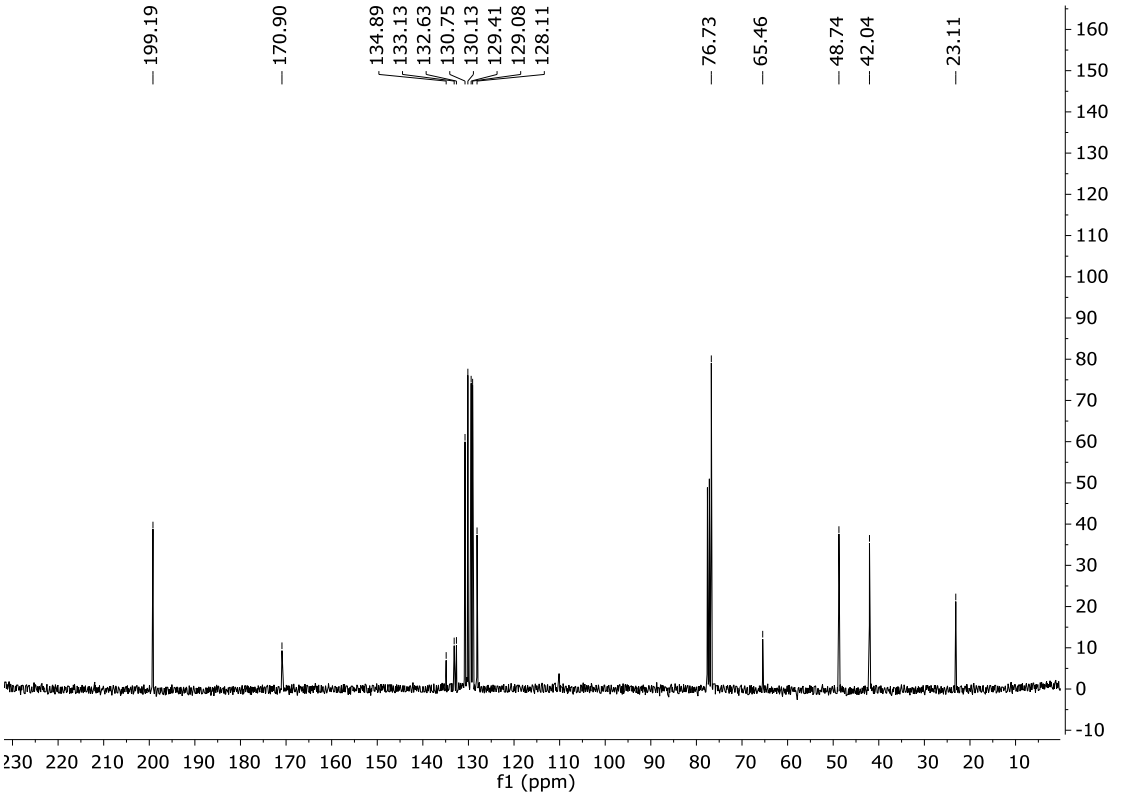
1.76
0.94
1.00
1.01
0.97
1.03
1.02
2.77
f1 (ppm)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170.90
134.89
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129.41
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128.11
76.73
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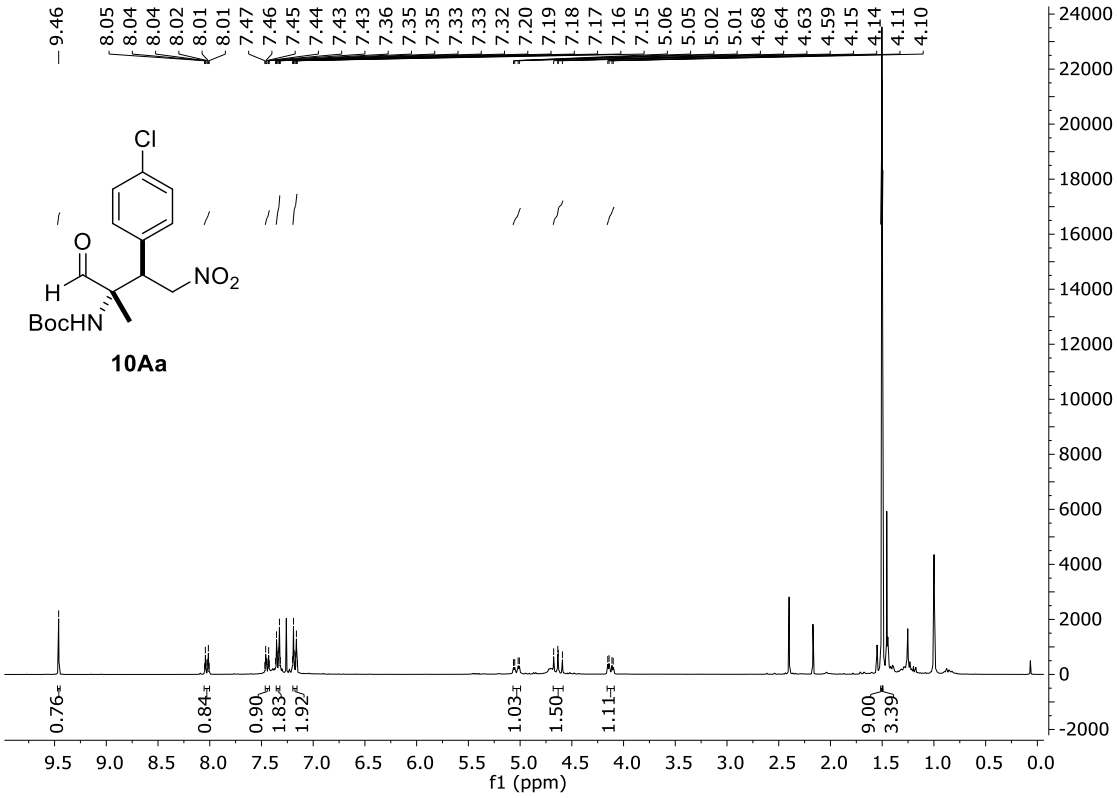
48.74
42.04
23.11
f1 (ppm)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8.04
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7.47
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7.44
7.43
7.43
7.36
7.35
7.35
7.33
7.33
7.32
7.20
7.19
7.18
7.17
7.16
7.15
5.06
5.05
5.02
5.01
4.68
4.64
4.63
4.59
4.15
4.14
4.11
4.10
Cl
O
H
NO2
BocHN
10Aa
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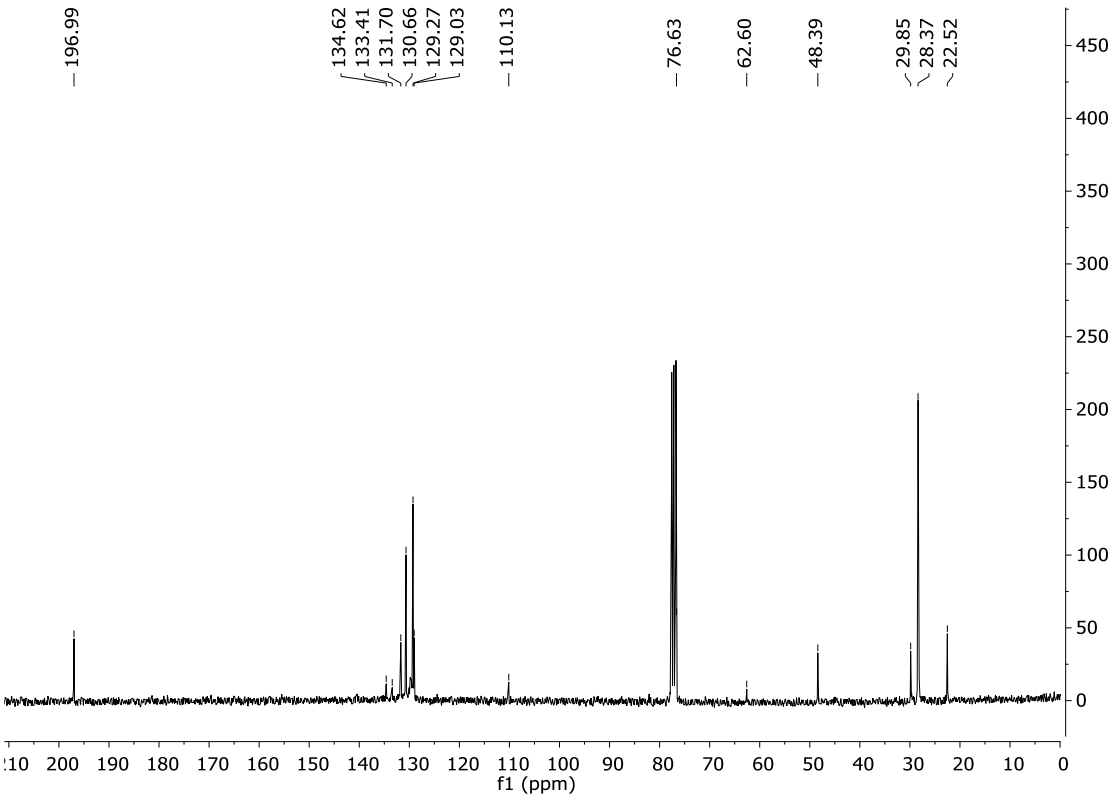
0.90
1.83
1.92
1.03
1.50
1.11
9.00
3.39
f1 (ppm)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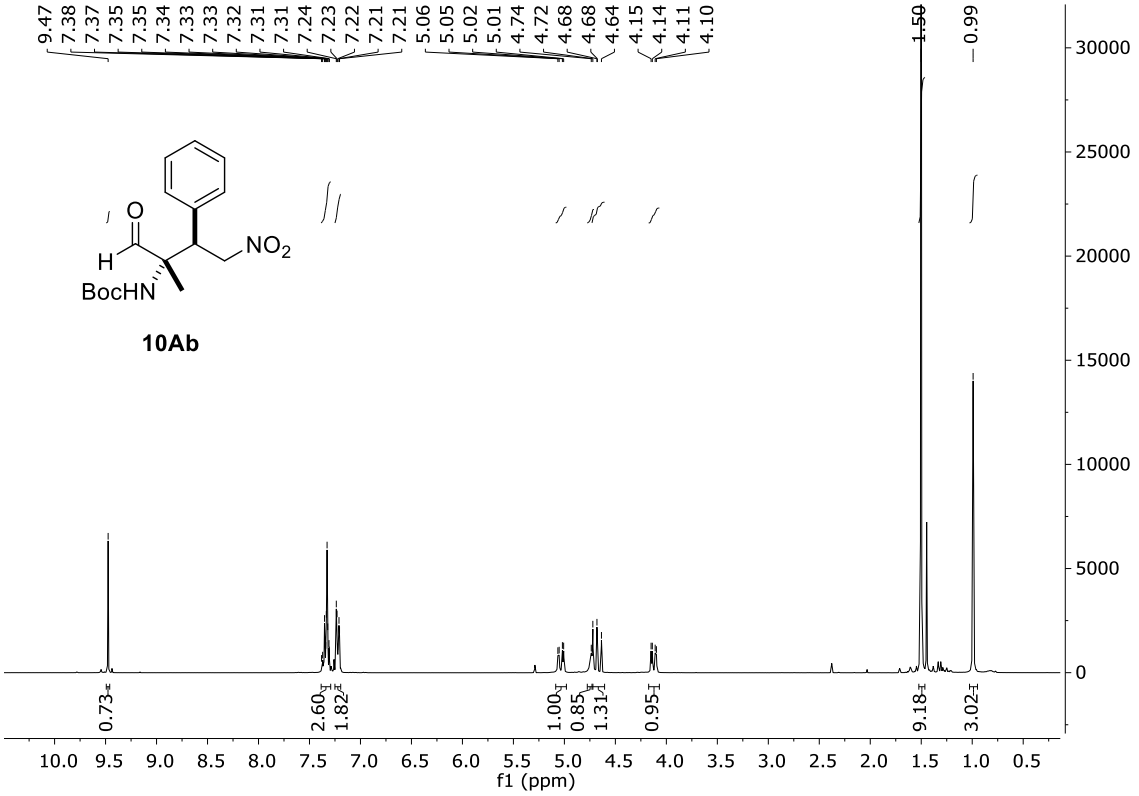
110.13
76.63
62.60
48.39
29.85
28.37
22.52
f1 (ppm)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7.22
7.21
7.21
5.06
5.05
5.02
5.01
4.74
4.72
4.68
4.68
4.64
4.15
4.14
4.11
4.10
1.50
0.99
O
H
BocHN
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1.00
0.85
1.31
0.95
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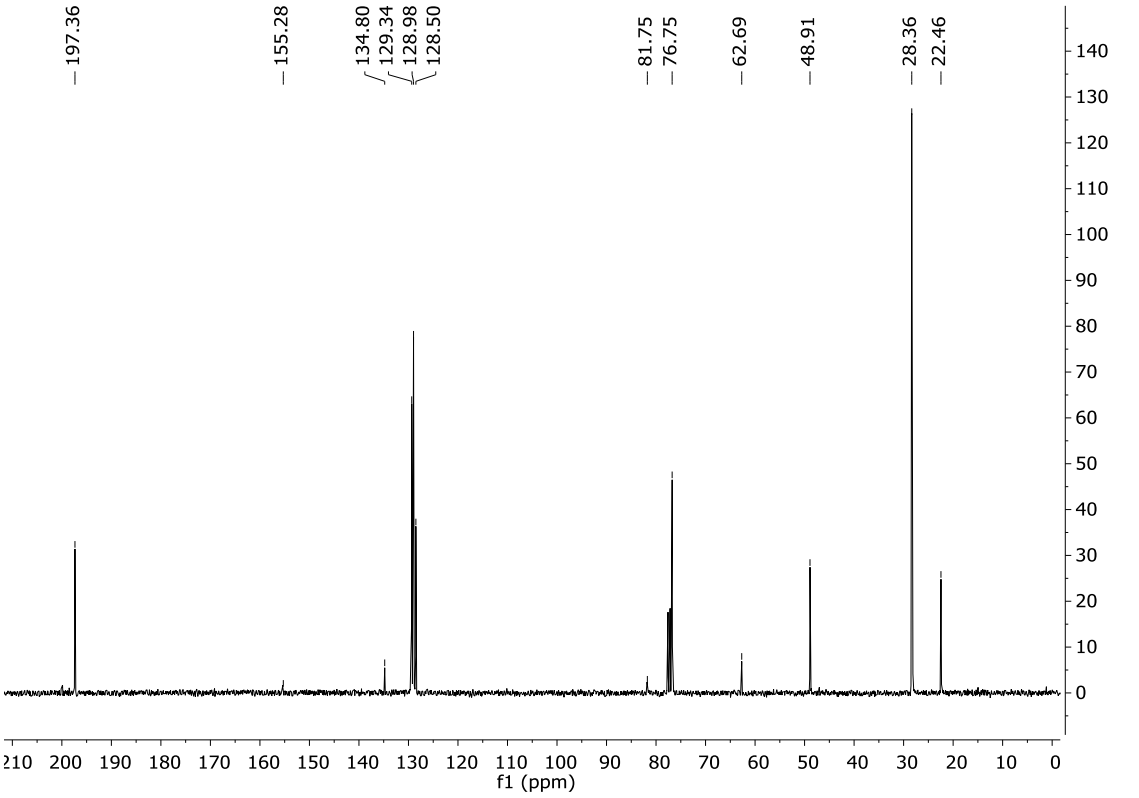
3.02
f1 (ppm)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62.69
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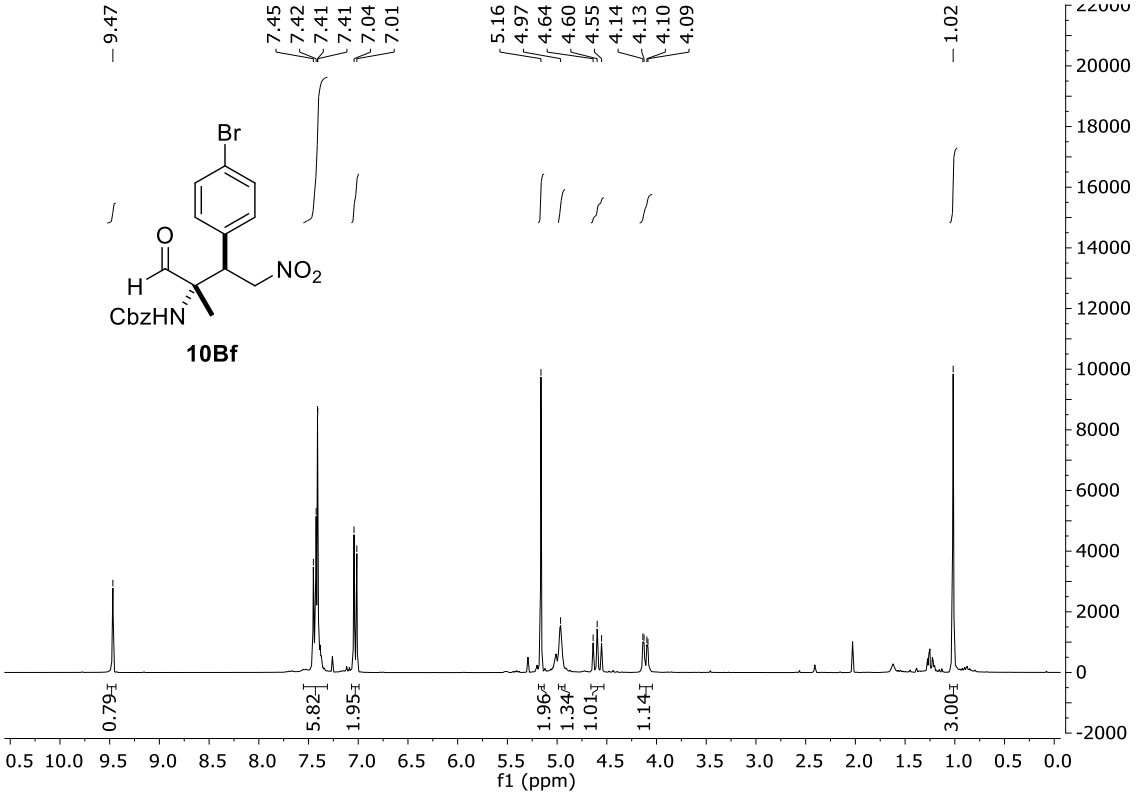
28.36
22.46
f1 (ppm)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4.60
4.55
4.14
4.13
4.10
4.09
1.02
Br
O
H
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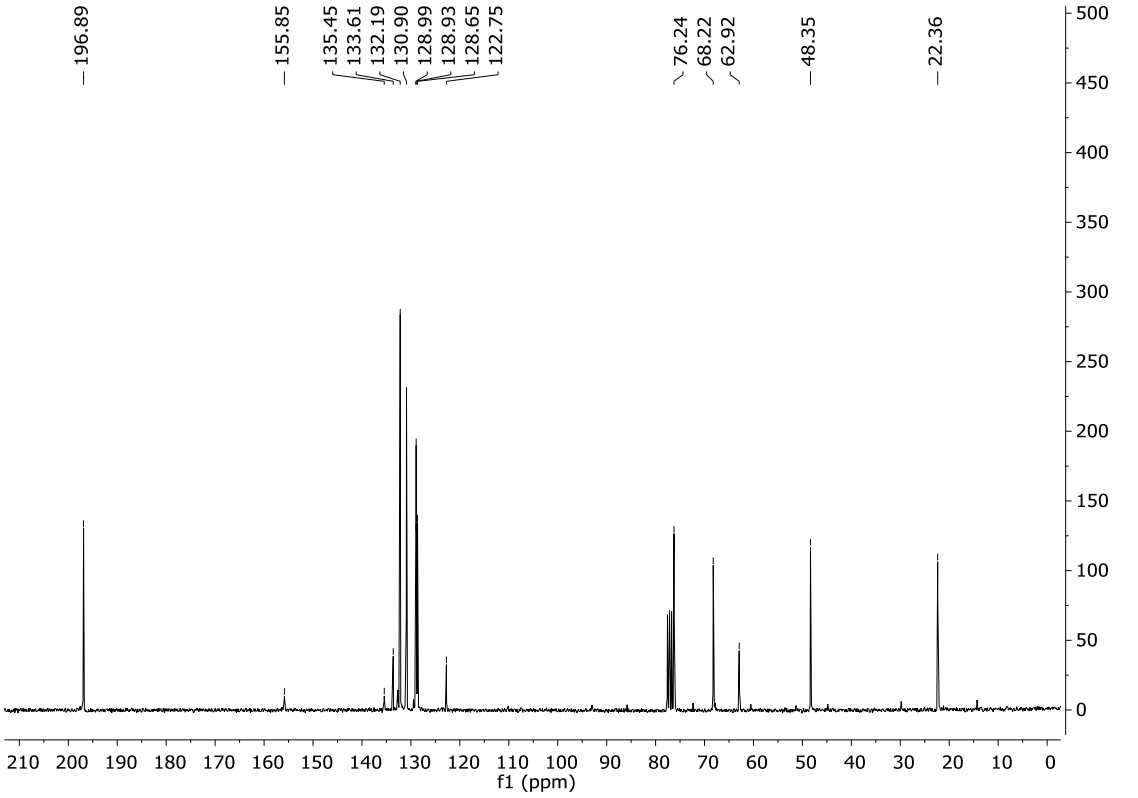
1.96
1.34
1.01
1.14
3.00
f1 (ppm)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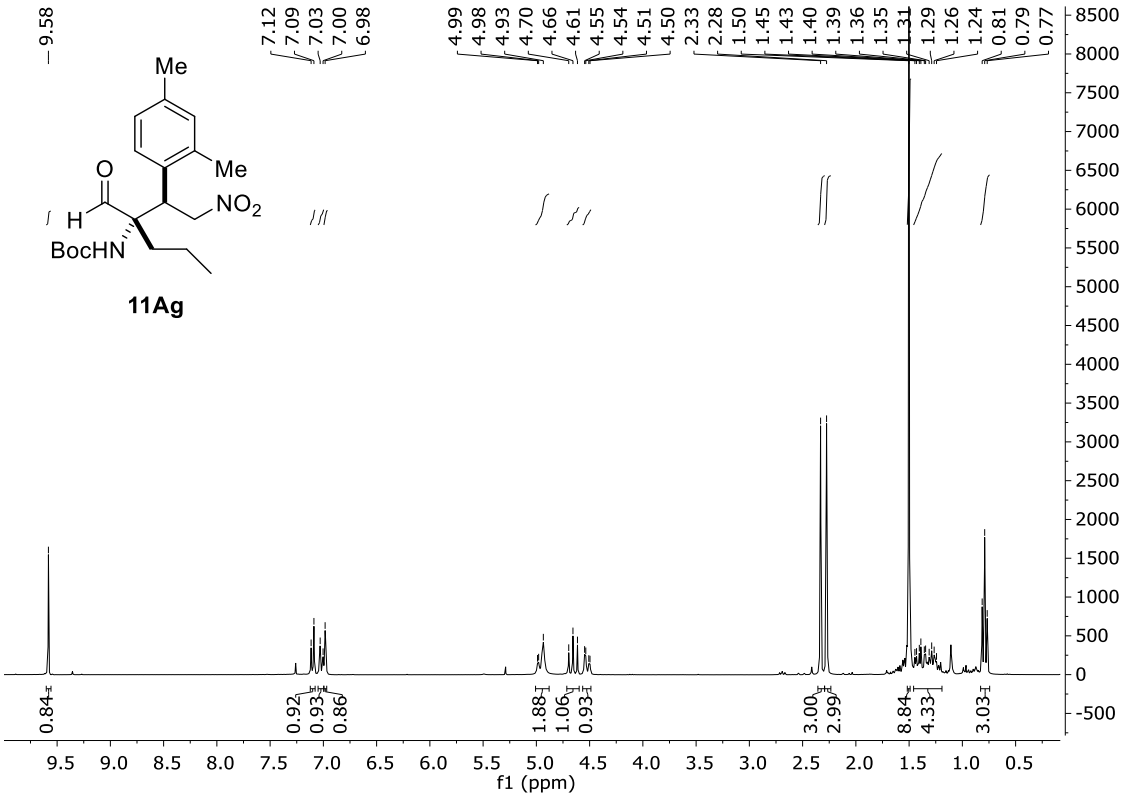
68.22
62.92
48.35
22.36
f1 (ppm)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4.55
4.54
4.51
4.50
2.33
2.28
1.50
1.45
1.43
1.40
1.39
1.36
1.35
1.31
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1.26
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Me
Me
O
H
NO2
BocHN
11Ag
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3.00
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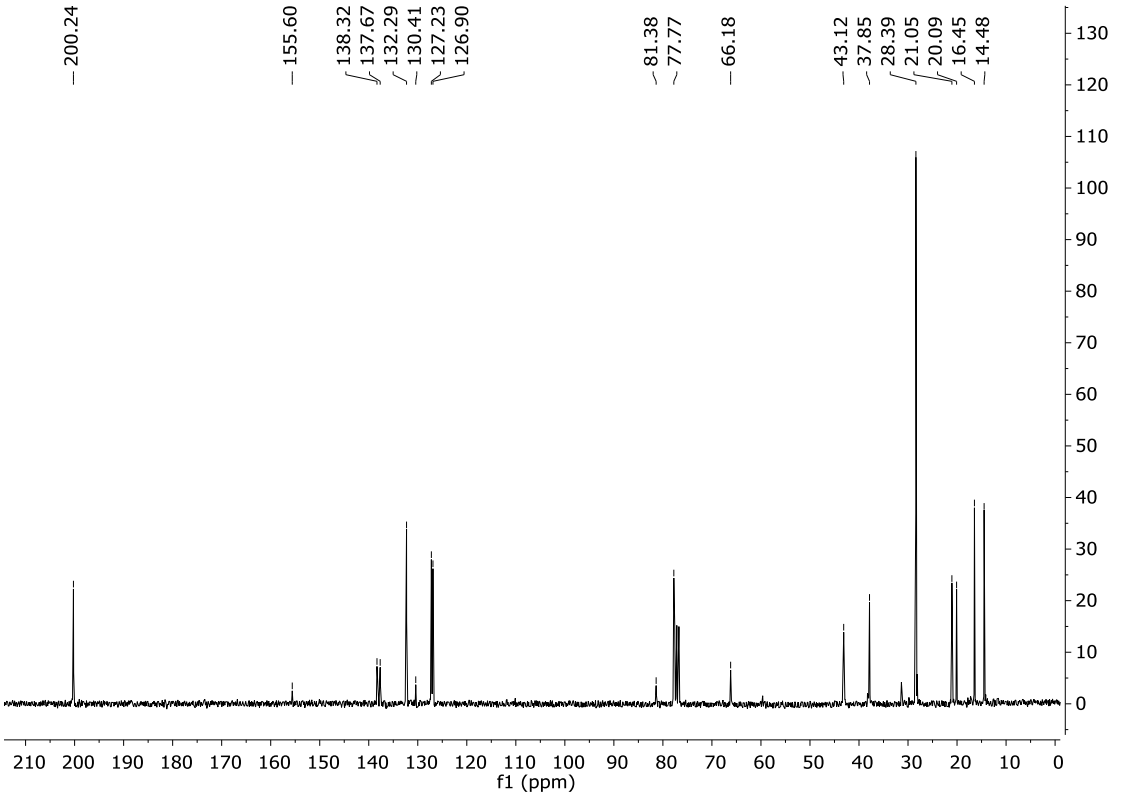
3.03
f1 (ppm)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130.41
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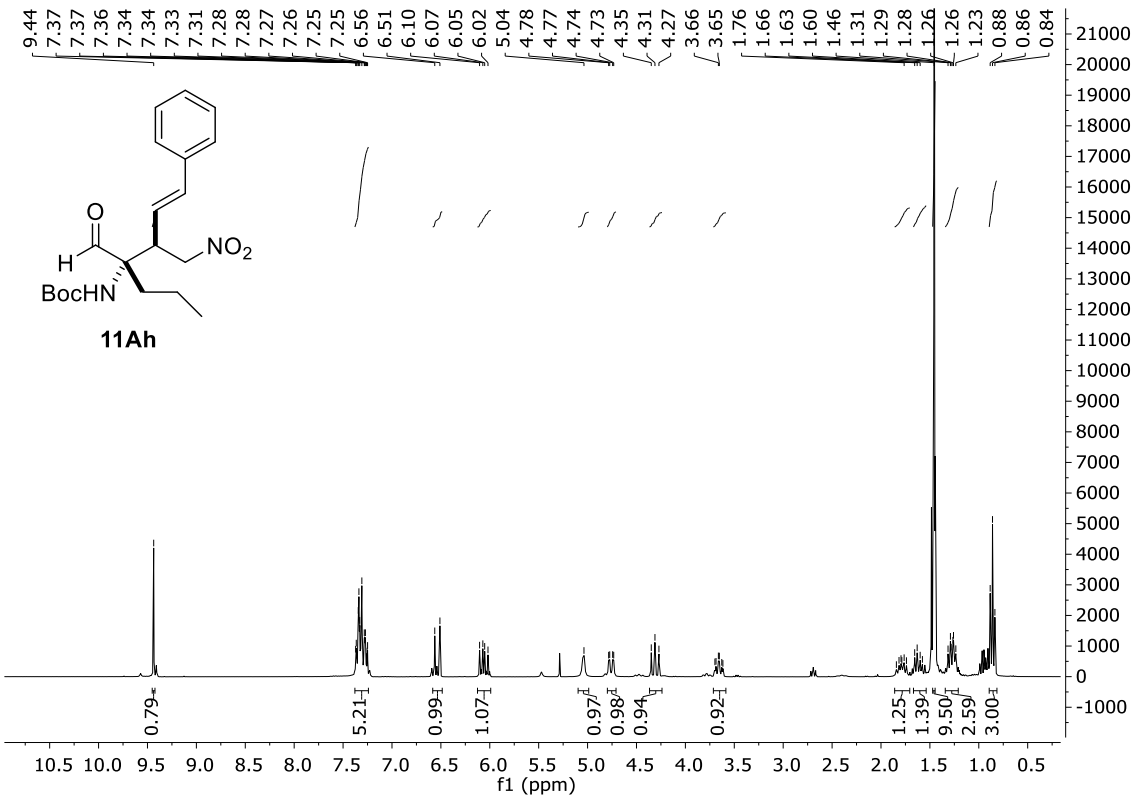
20.09
16.45
14.48
f1 (ppm)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6.56
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1.63
1.60
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1.31
1.29
1.28
1.26
1.26
1.23
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O
H
BocHN
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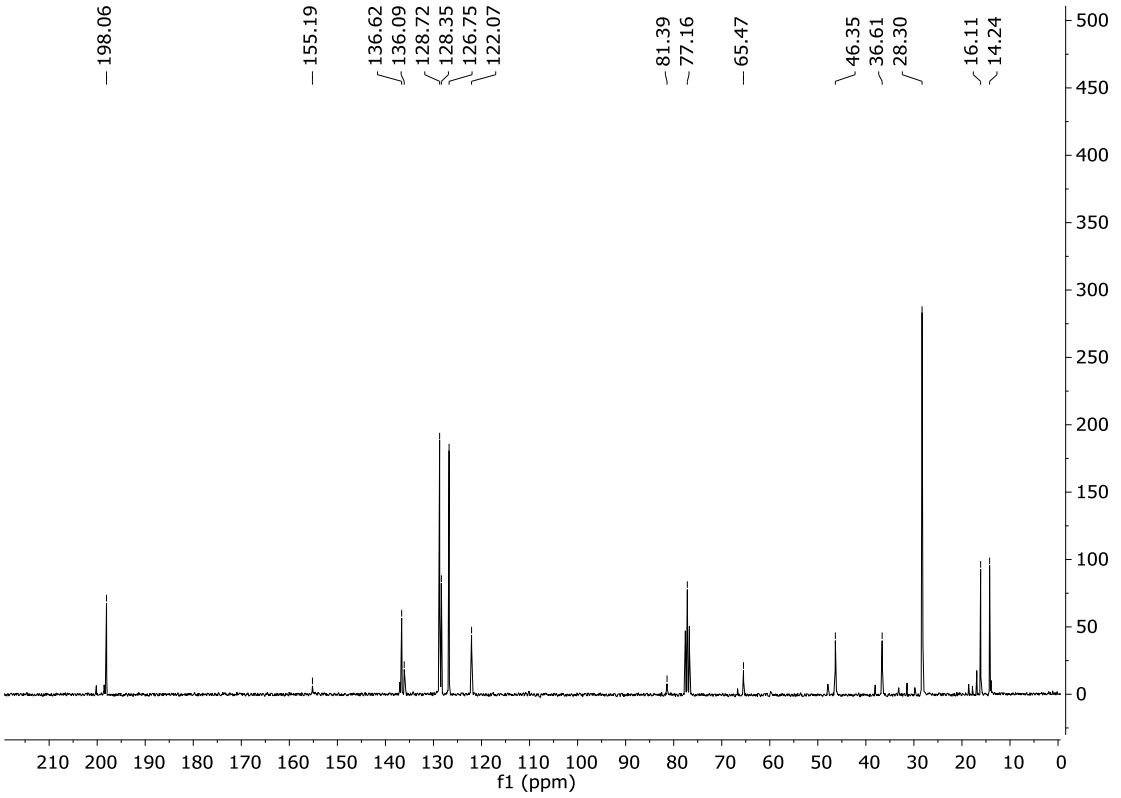
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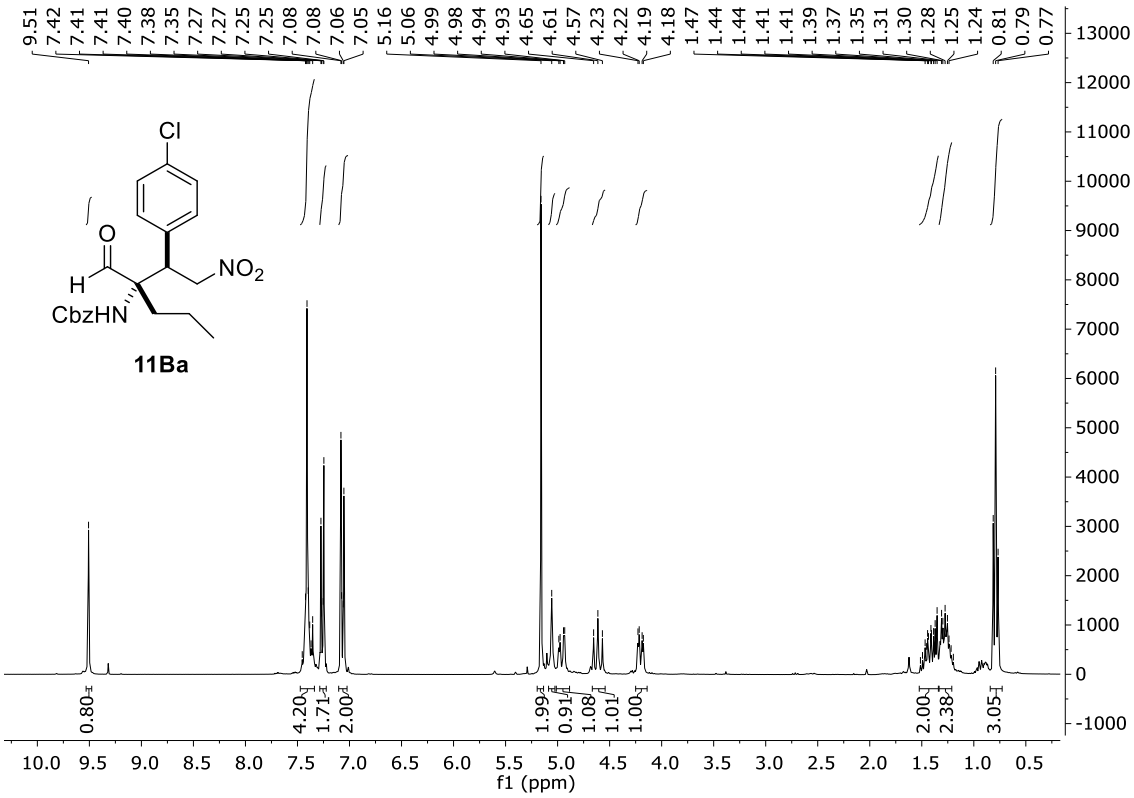
46.35
36.61
28.30
16.11
14.24
f1 (ppm)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Cl
O
H
CbzHN
NO2
11Ba
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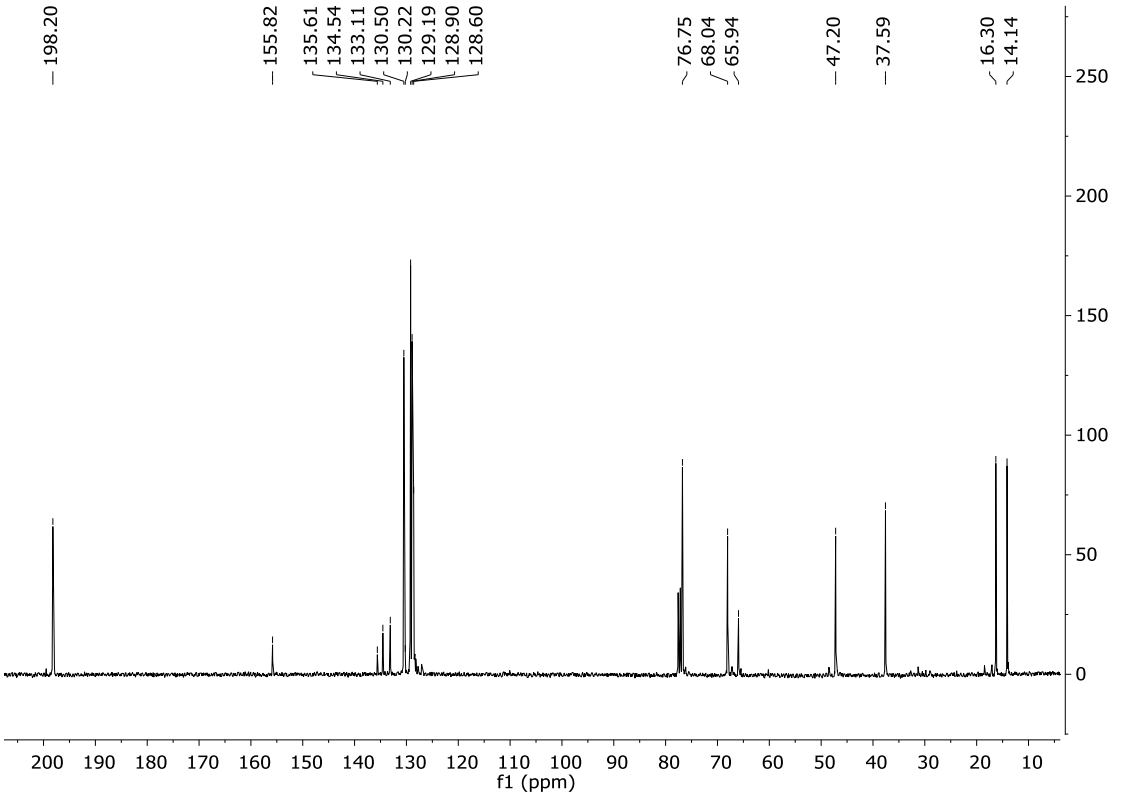
f1 (ppm)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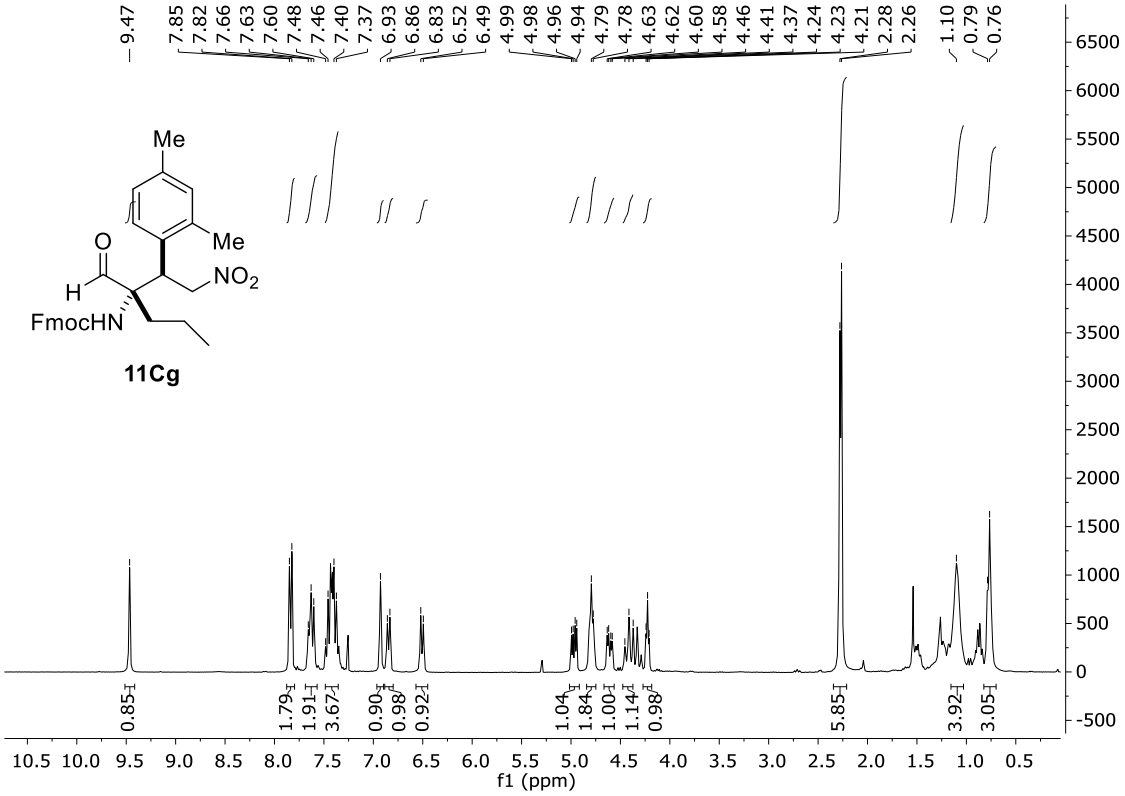
f1 (ppm)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4.46
4.41
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4.24
4.23
4.21
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2.26
1.10
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0.76
Me
Me
O
H
NO2
FmocHN
11Cg
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1.79
1.91
3.67
0.90
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1.84
1.00
1.14
0.98
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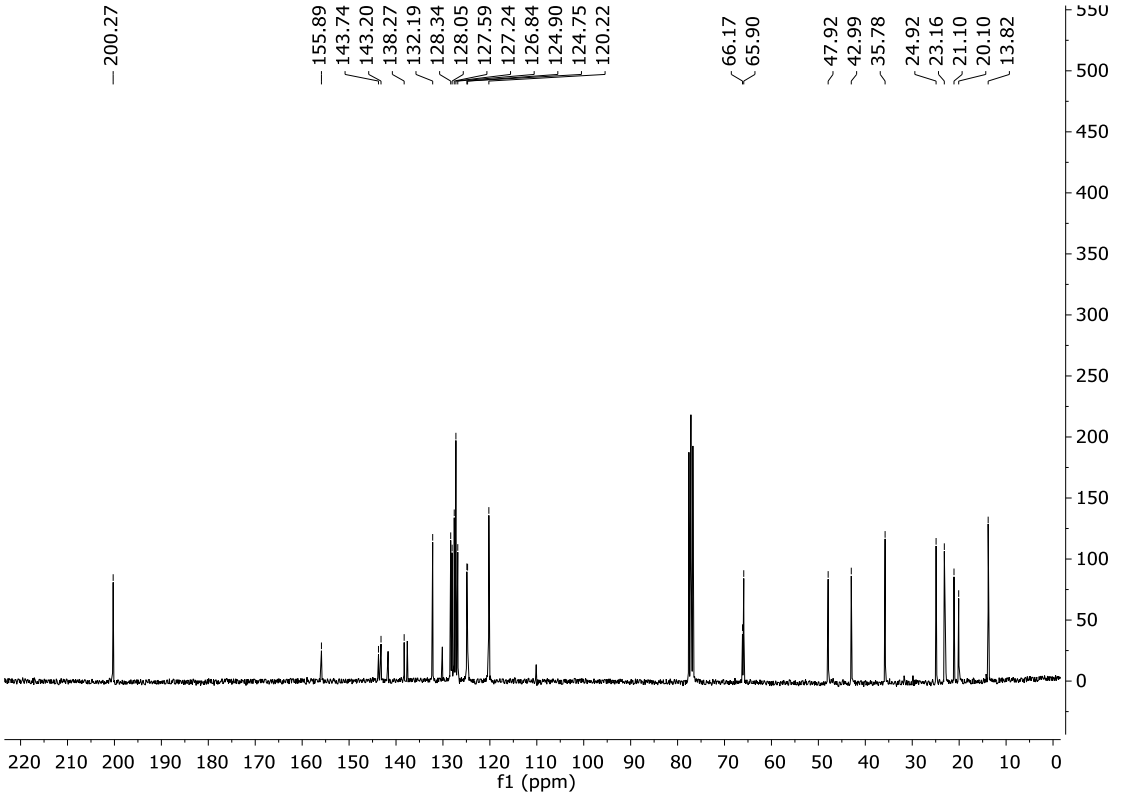
3.05
f1 (ppm)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124.75
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21.10
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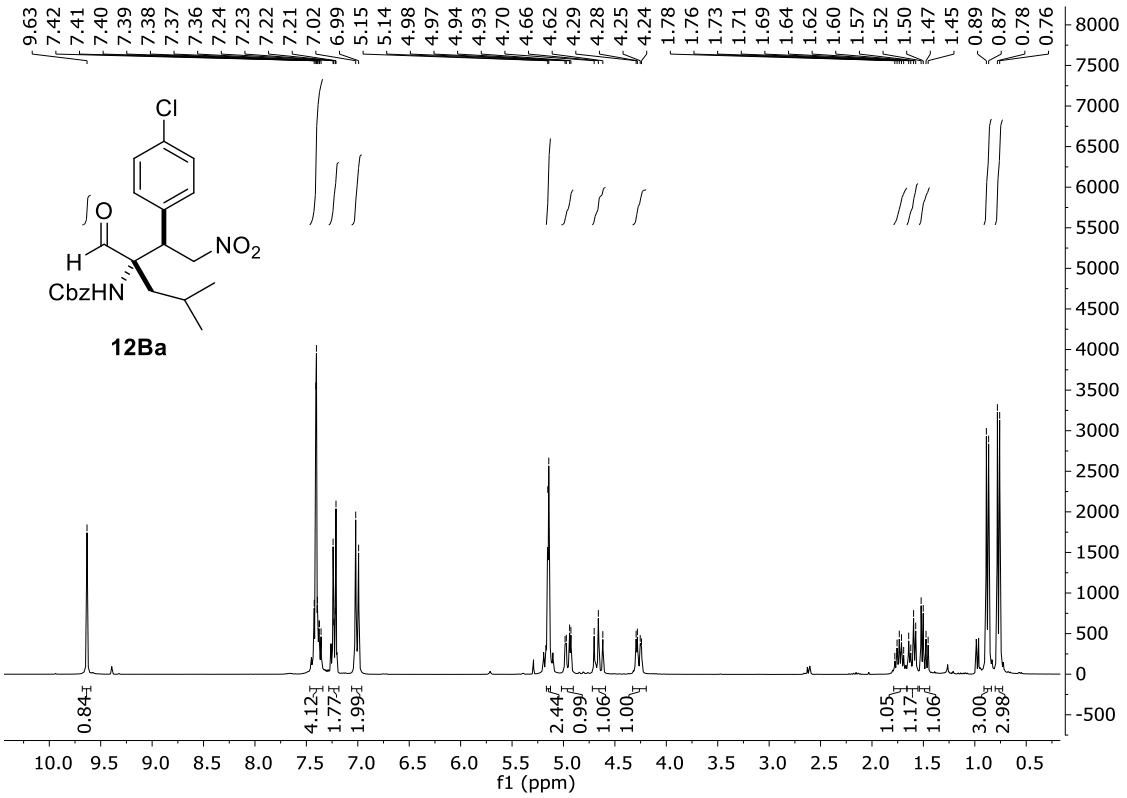
13.82
f1 (ppm)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5.15
5.14
4.98
4.97
4.94
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4.28
4.25
4.24
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1.76
1.73
1.71
1.69
1.64
1.62
1.60
1.57
1.52
1.50
1.47
1.45
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0.87
0.78
0.76
Cl
O
H
NO2
CbzHN
12Ba
0.84
4.12
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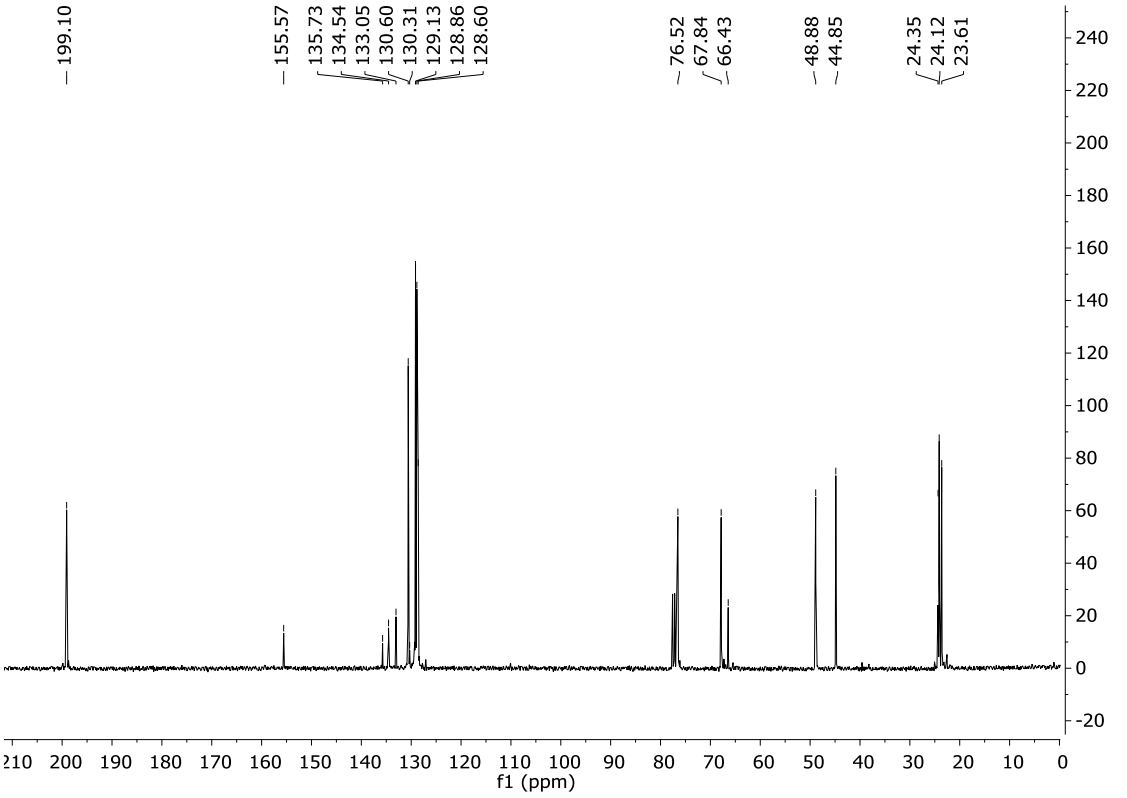
1.00
1.05
1.17
1.06
3.00
2.98
f1 (ppm)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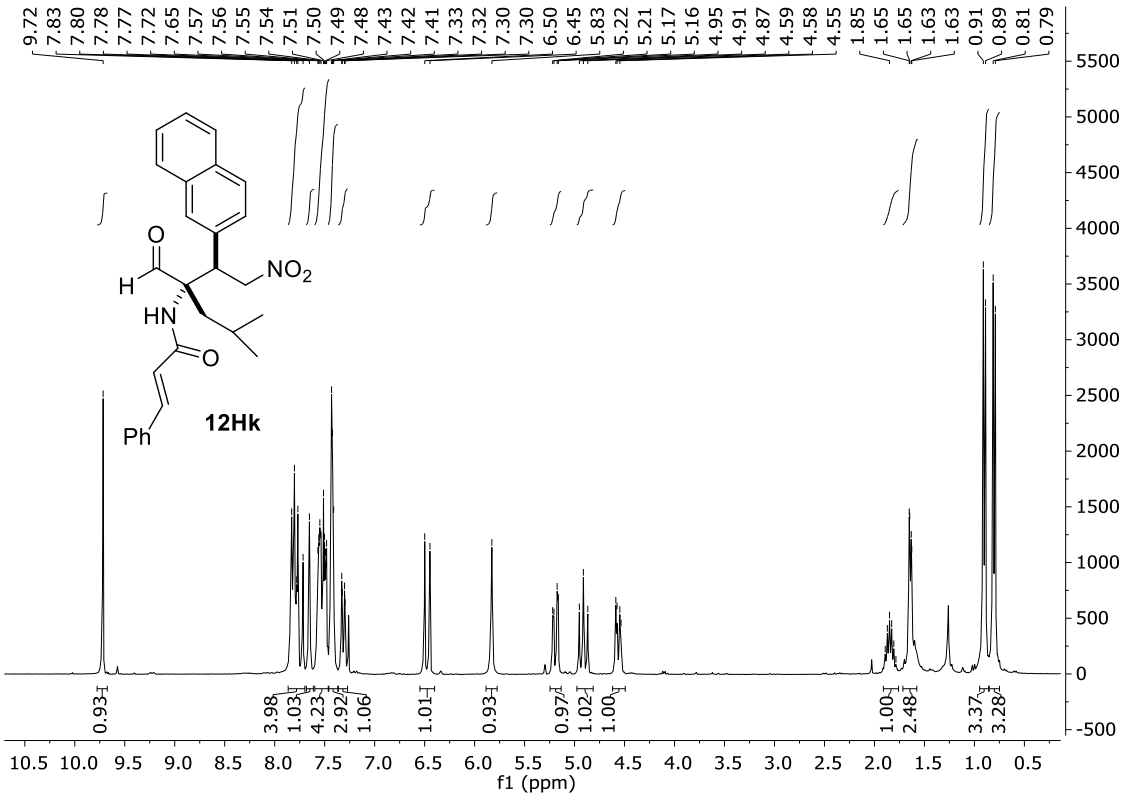
44.85
24.35
24.12
23.61
f1 (ppm)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O
H
HN
O
NO2
Ph
12Hk
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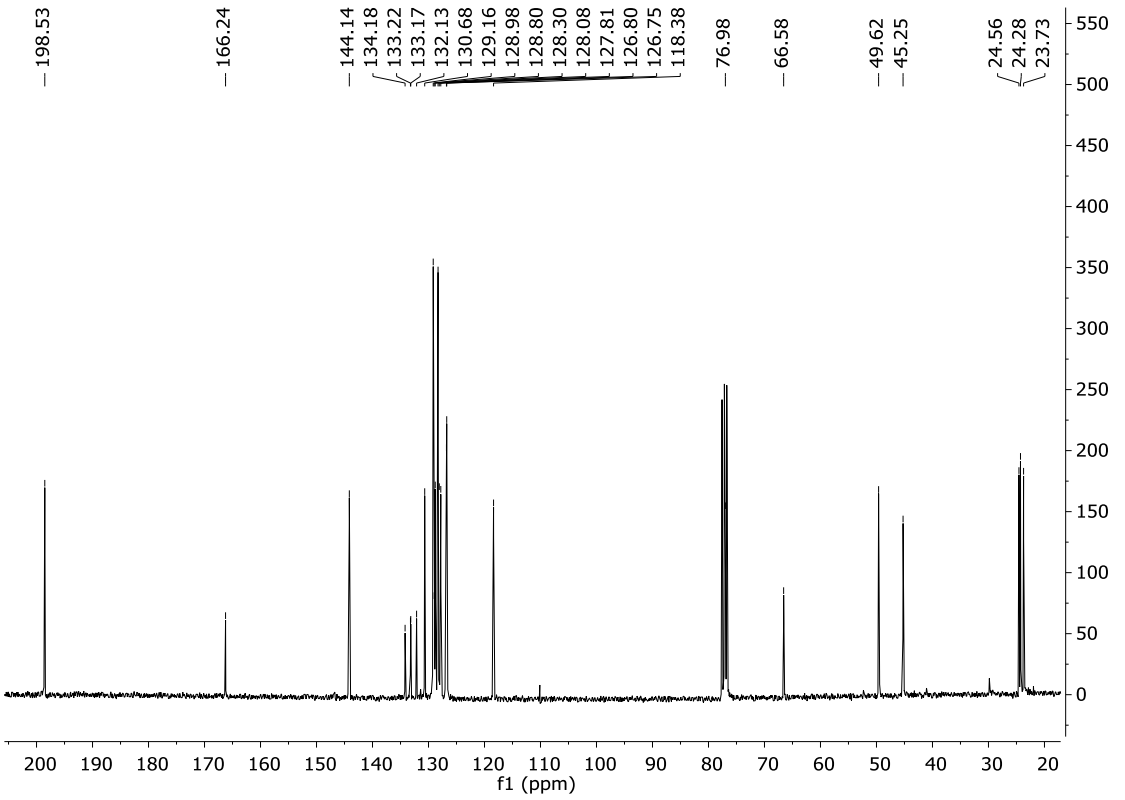
f1 (ppm)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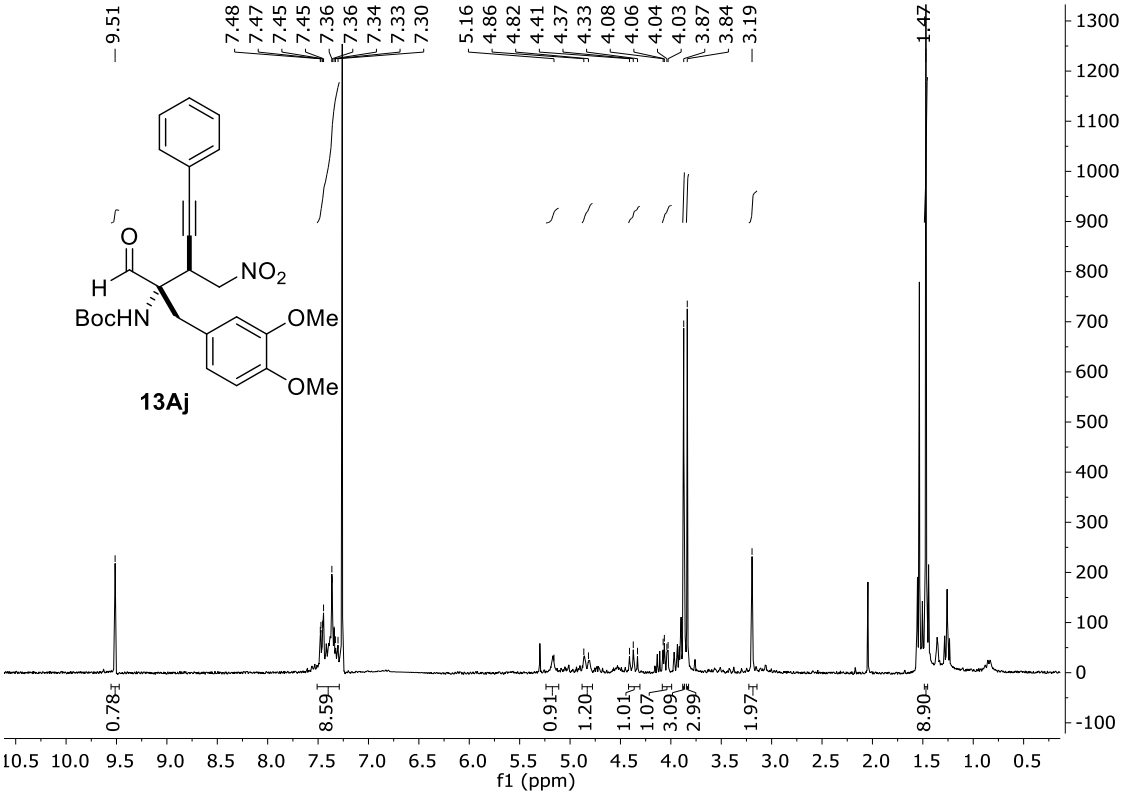
f1 (ppm)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7.33
7.30
5.16
4.86
4.82
4.41
4.37
4.33
4.08
4.06
4.04
4.03
3.87
3.84
3.19
1.47
O
H
BocHN
NO2
OMe
OMe
13Aj
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1.01
1.07
3.09
2.99
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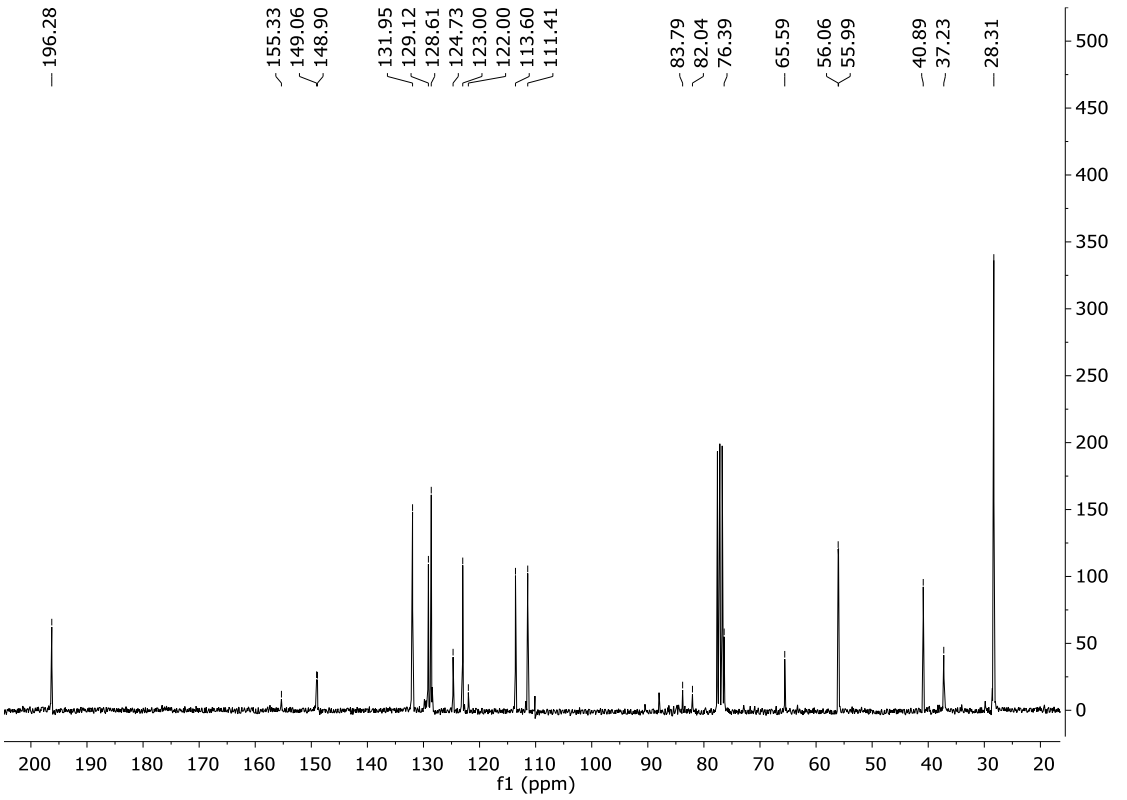
8.90
f1 (ppm)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124.73
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122.00
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76.39
65.59
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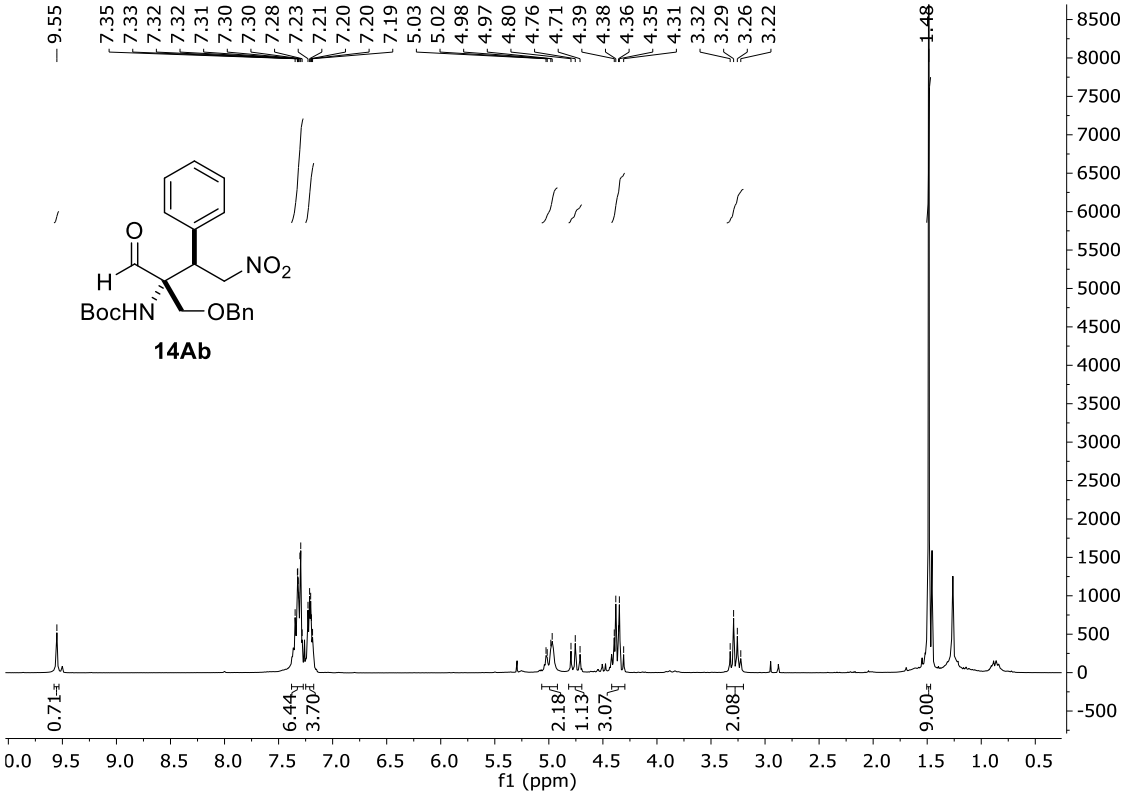
40.89
37.23
28.31
f1 (ppm)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7.30
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7.23
7.21
7.20
7.20
7.19
5.03
5.02
4.98
4.97
4.80
4.76
4.71
4.39
4.38
4.36
4.35
4.31
3.32
3.29
3.26
3.22
1.48
O
H
NO2
BocHN
OBn
14Ab
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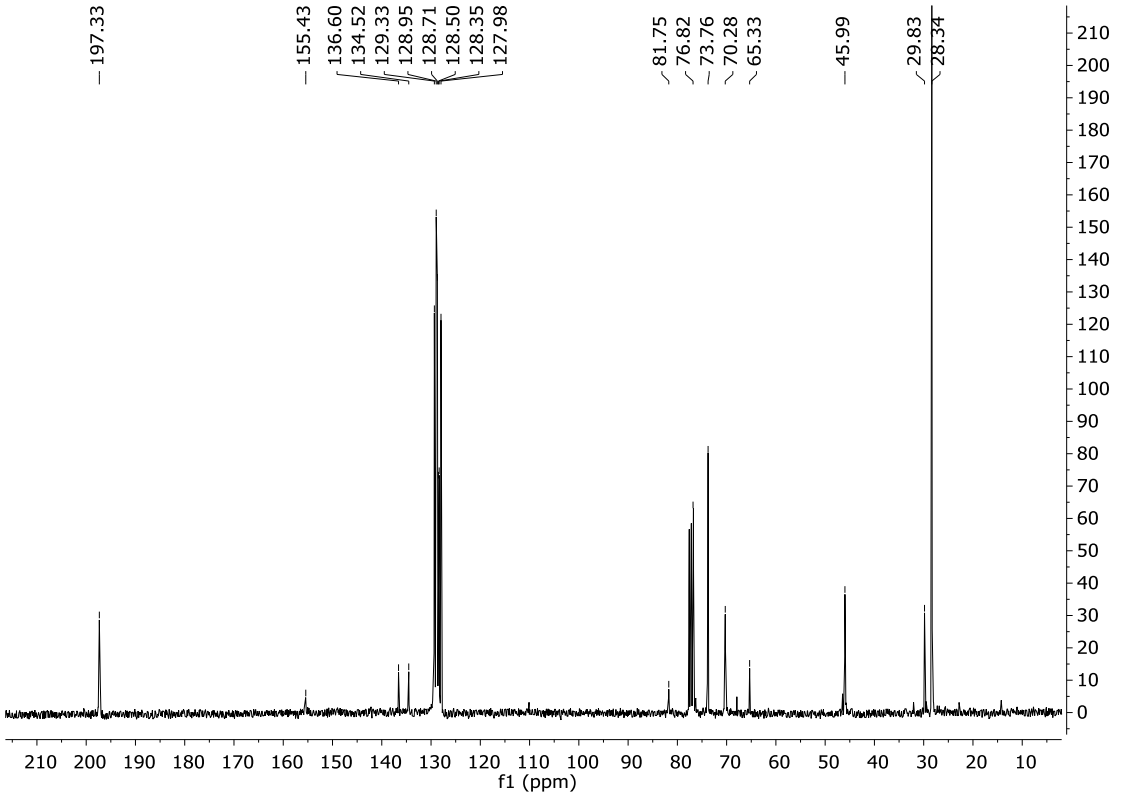
6.44
3.70
2.18
1.13
3.07
2.08
9.00
f1 (ppm)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129.33
128.95
128.71
128.50
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127.98
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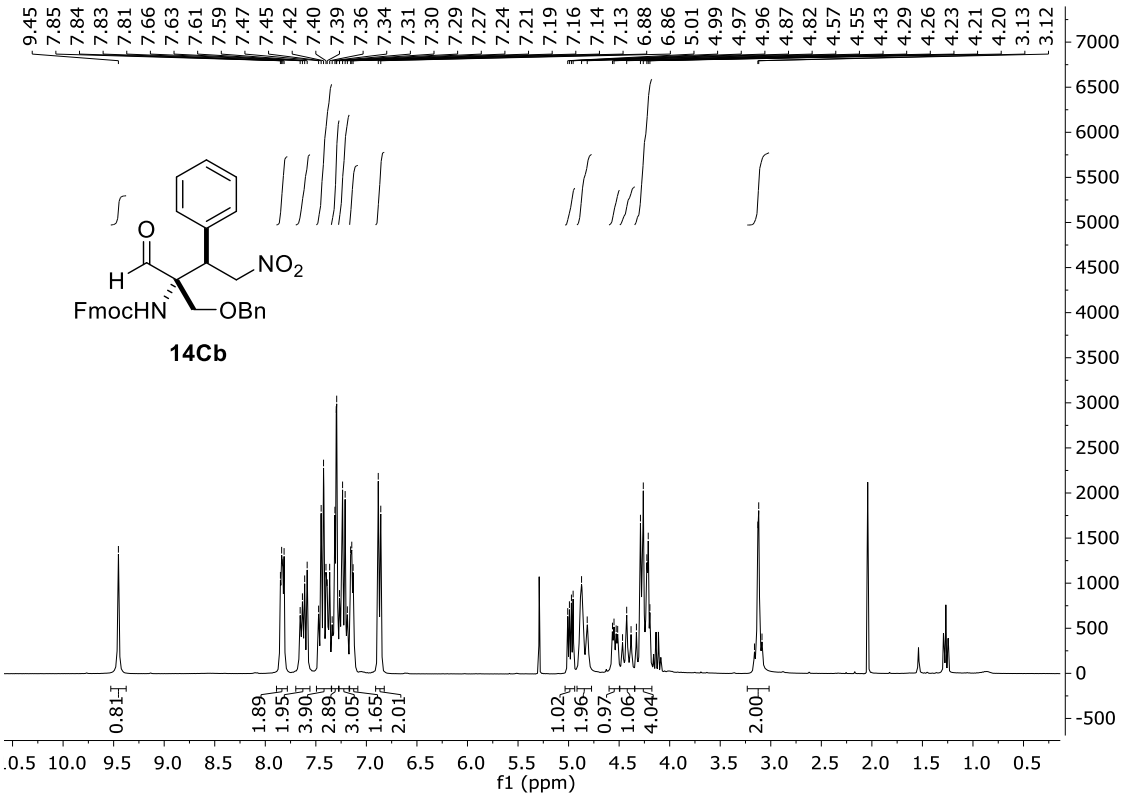
76.82
73.76
70.28
65.33
45.99
29.83
28.34
f1 (ppm)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7.47
7.45
7.42
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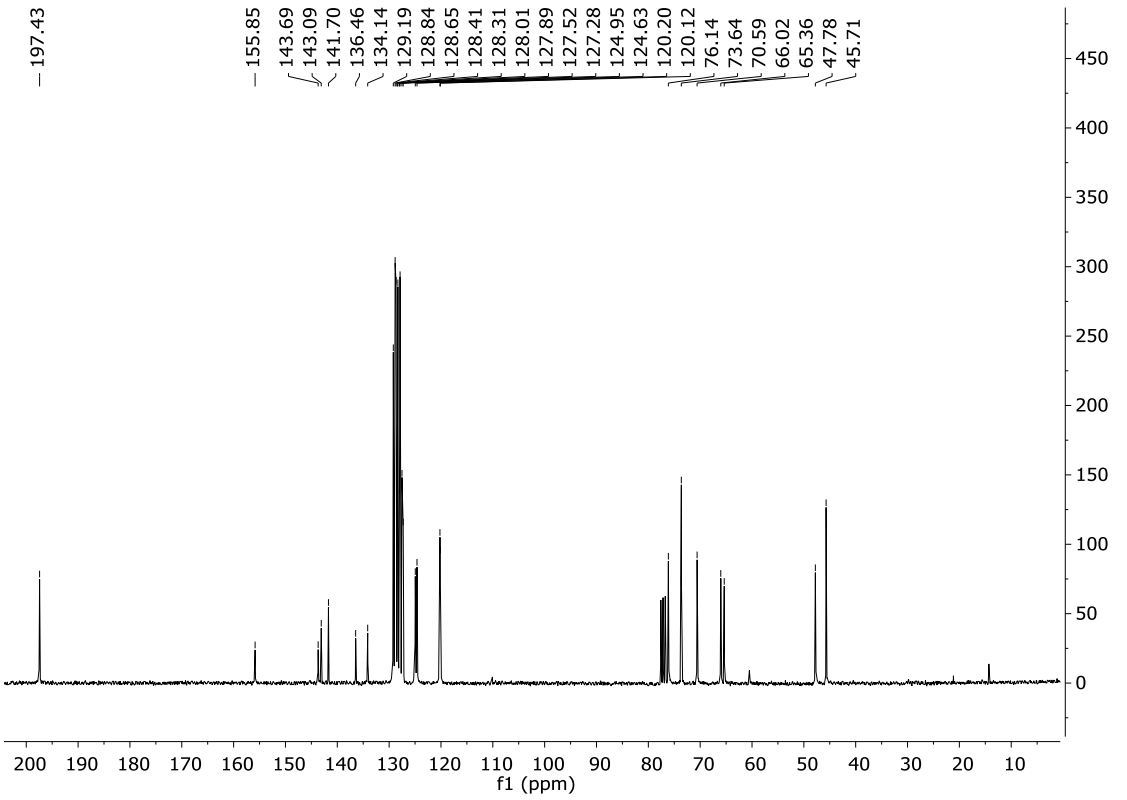
7.36
7.34
7.31
7.30
7.29
7.27
7.24
7.21
7.19
7.16
7.14
7.13
6.88
6.86
5.01
4.99
4.97
4.96
4.87
4.82
4.57
4.55
4.43
4.29
4.26
4.23
4.21
4.20
3.13
3.12
O
H
NO2
FmocHN
OBn
14Cb
0.81
1.89
1.95
3.90
2.89
3.05
1.65
2.01
1.02
1.96
0.97
1.06
4.04
2.00
f1 (ppm)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128.01
127.89
127.52
127.28
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120.12
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73.64
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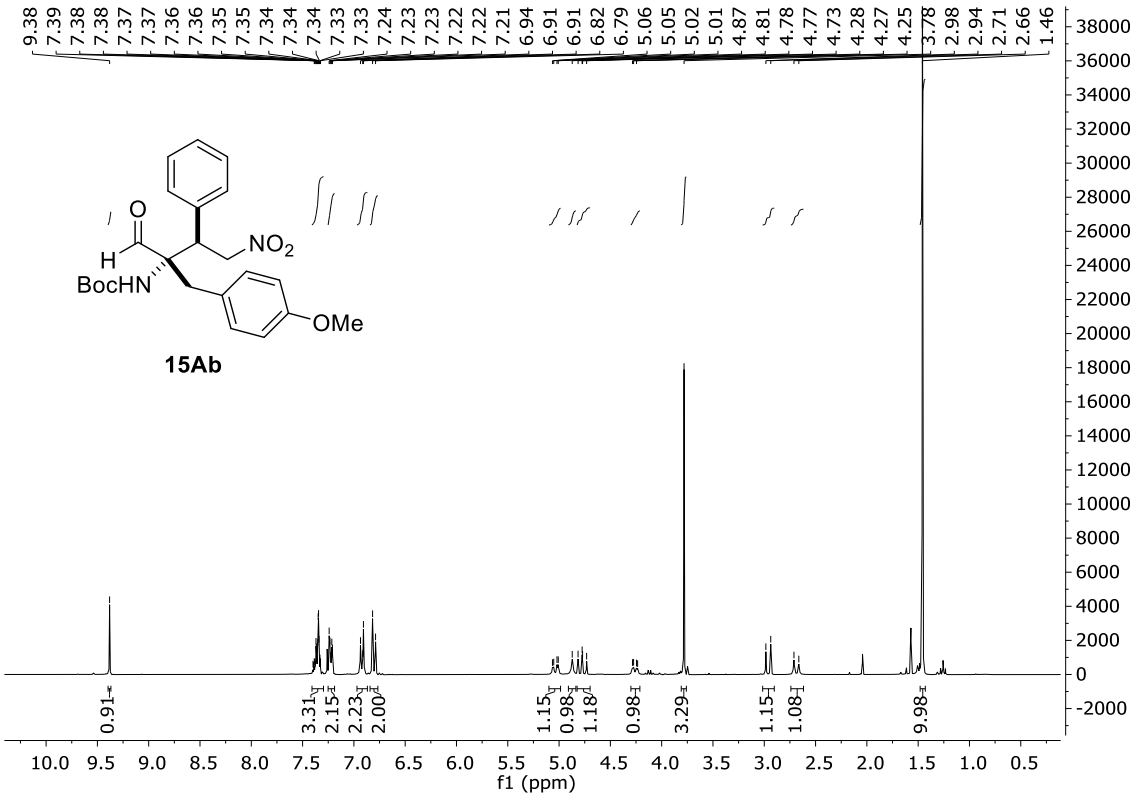
65.36
47.78
45.71
f1 (ppm)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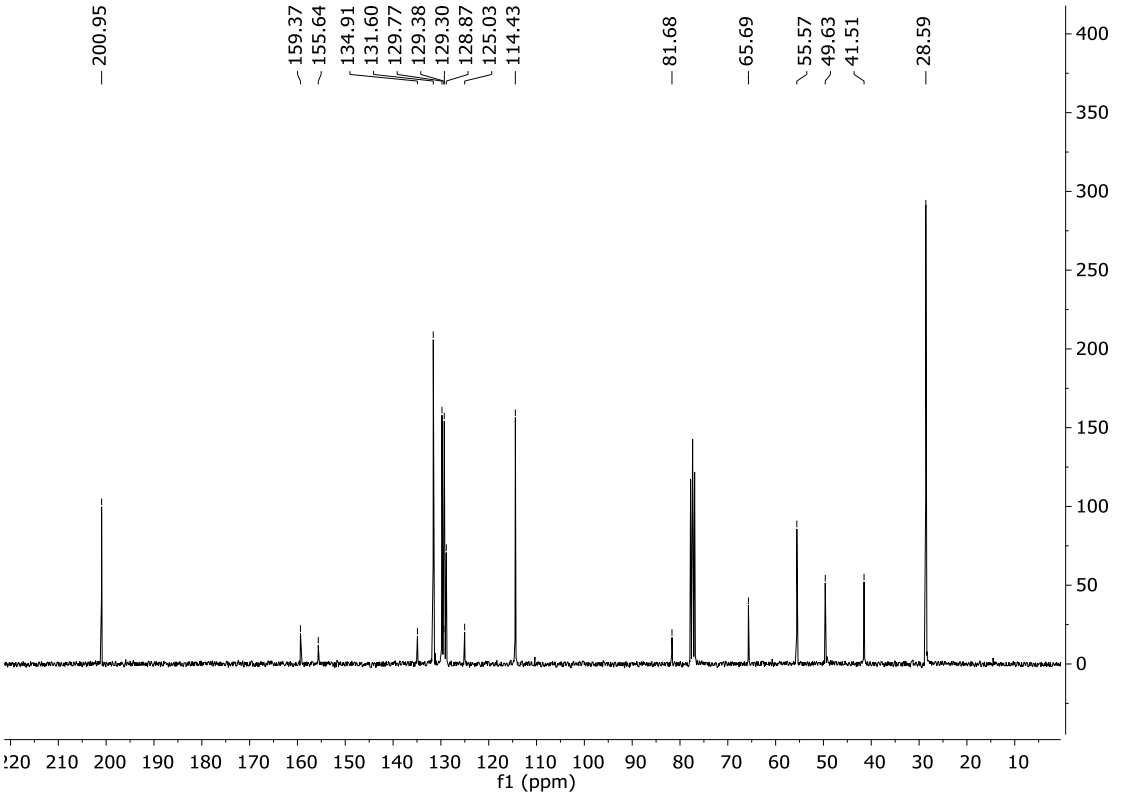
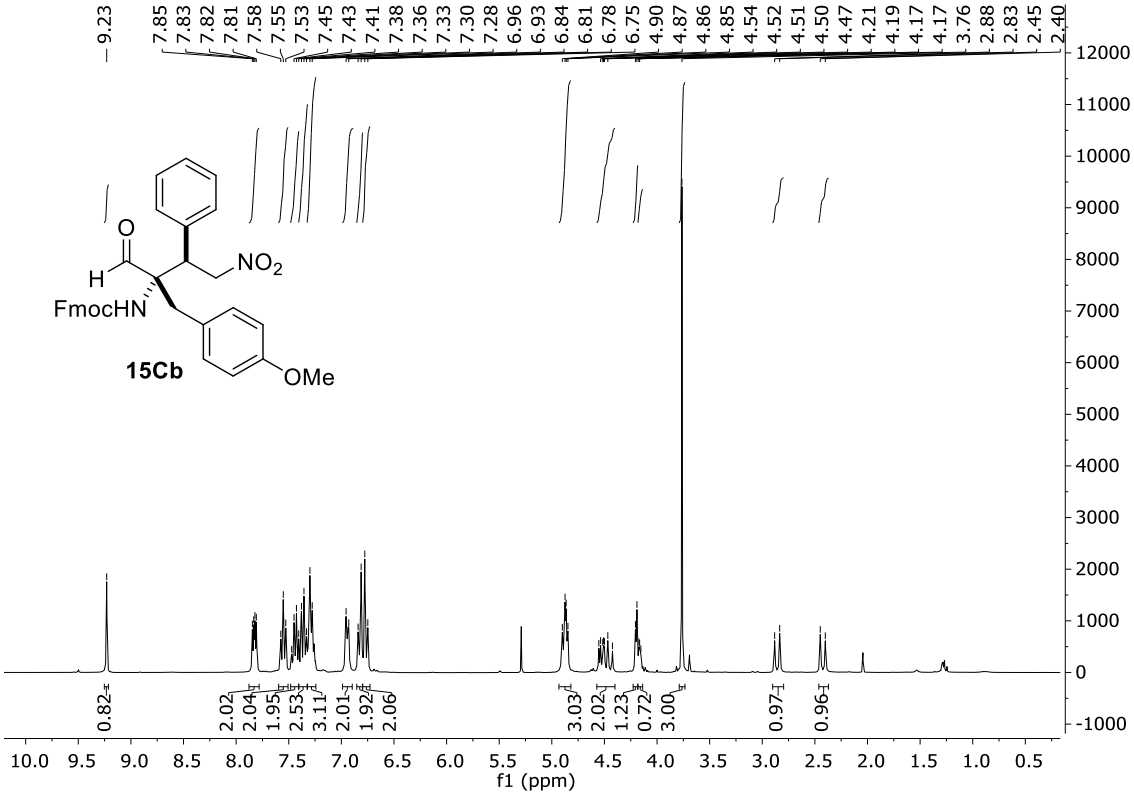
O
H
BocHN
NO2
OMe
15Ab
0.91 3.31 2.15 2.23 2.00 1.15 0.98 1.18 0.98 3.29 1.15 1.08 9.98
f1 (ppm)


200.95
159.37 155.64 134.91 131.60 129.77 129.38 129.30 128.87 125.03 114.43
81.68 65.69 55.57 49.63 41.51 28.59
f1 (ppm)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7.82
7.81
7.58
7.55
7.53
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7.43
7.41
7.38
7.36
7.33
7.30
7.28
6.96
6.93
6.84
6.81
6.78
6.75
4.90
4.87
4.86
4.85
4.54
4.52
4.51
4.50
4.47
4.21
4.19
4.17
4.17
3.76
2.88
2.83
2.45
2.40
O
H
FmocHN
NO2
OMe
15Cb
0.82
2.02
2.04
1.95
2.53
3.11
2.01
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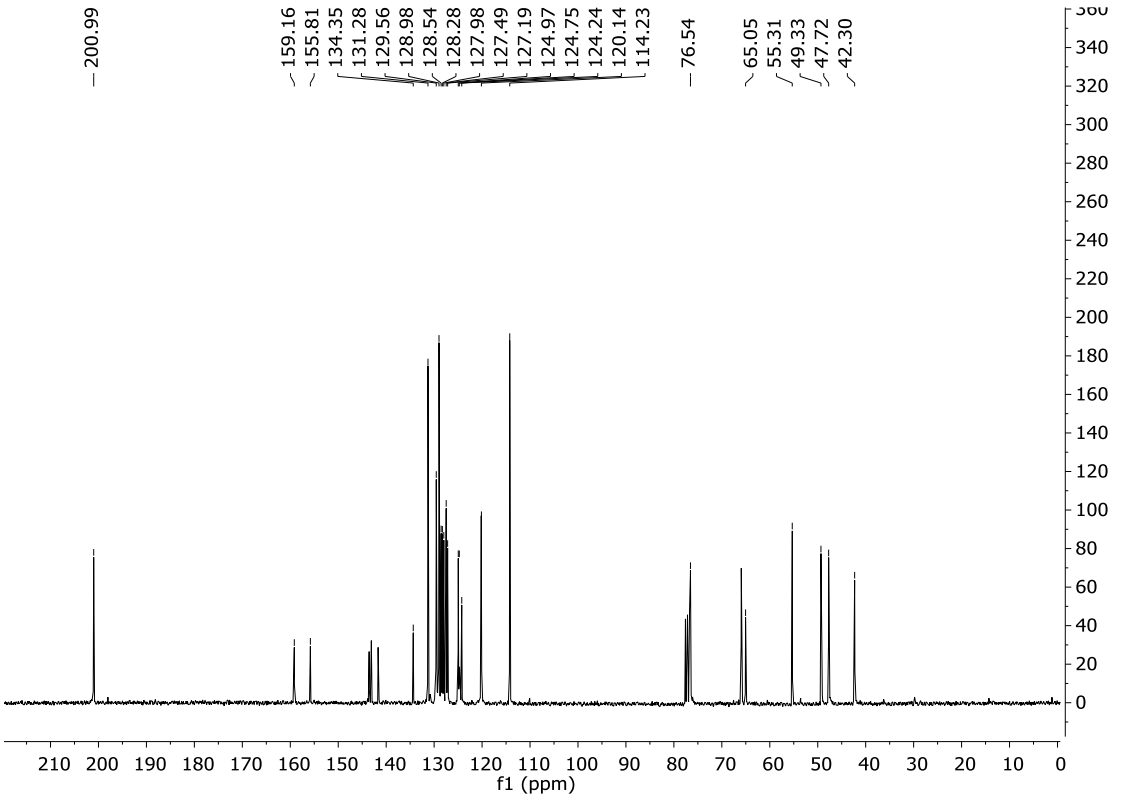
2.06
3.03
2.02
1.23
0.72
3.00
0.97
0.96
f1 (ppm)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127.19
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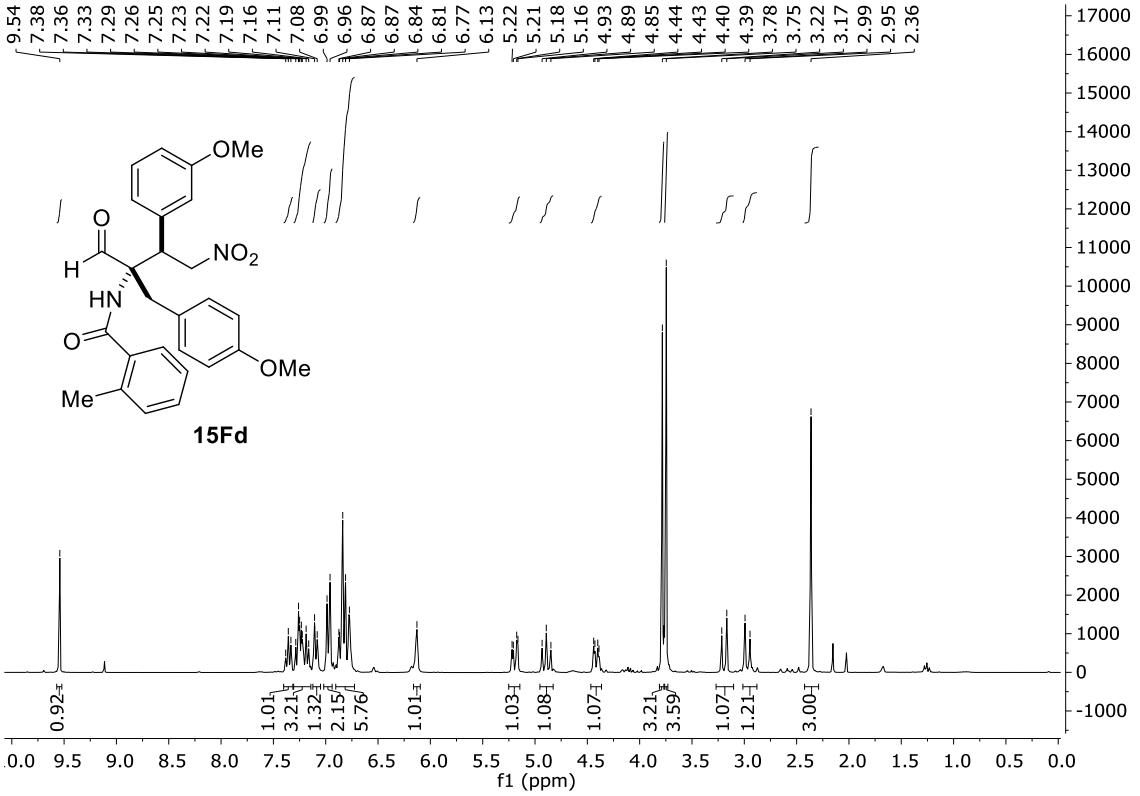
120.14
114.23
76.54
65.05
55.31
49.33
47.72
42.30
f1 (ppm)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OMe
O
H
NO2
HN
O
OMe
Me
15Fd
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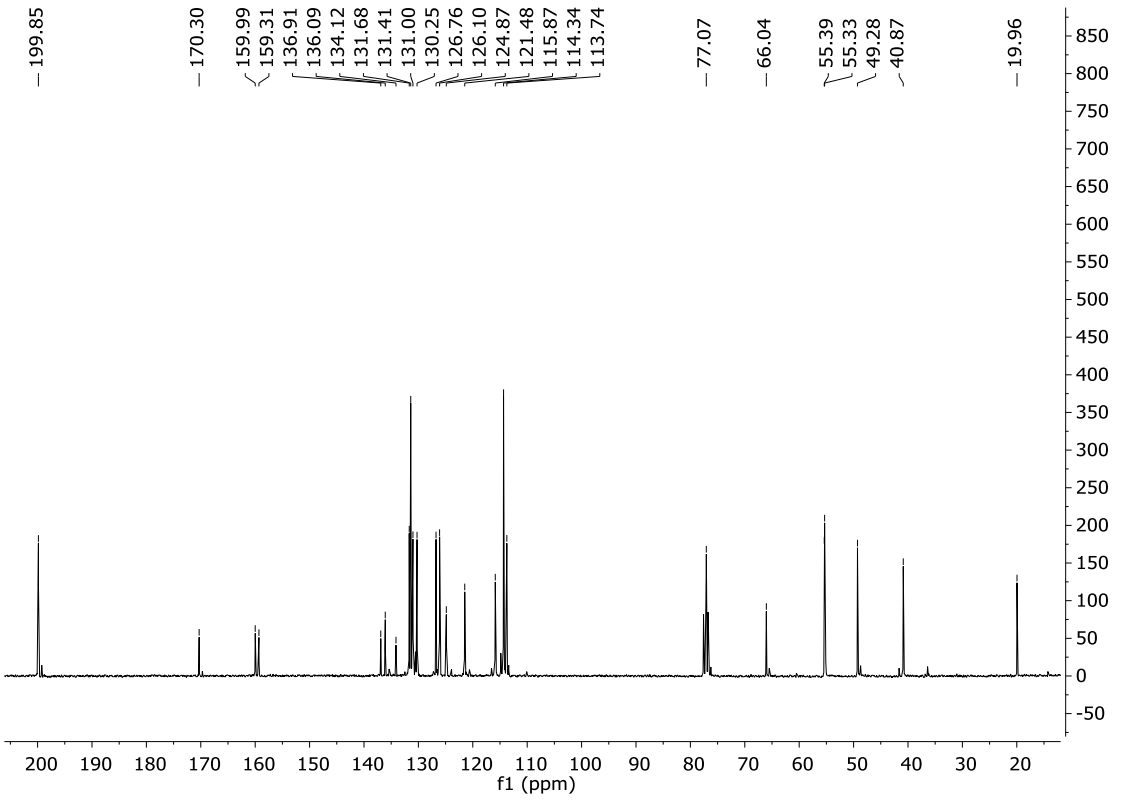
f1 (ppm)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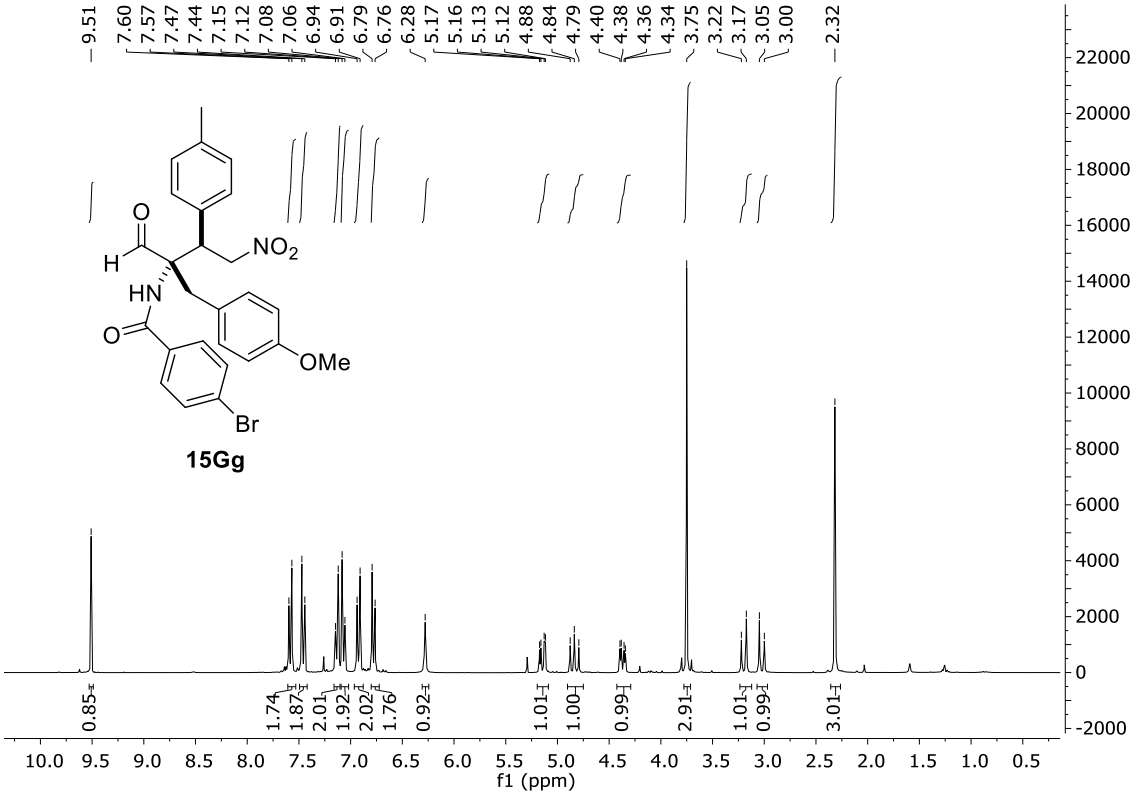
f1 (ppm)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6.94
6.91
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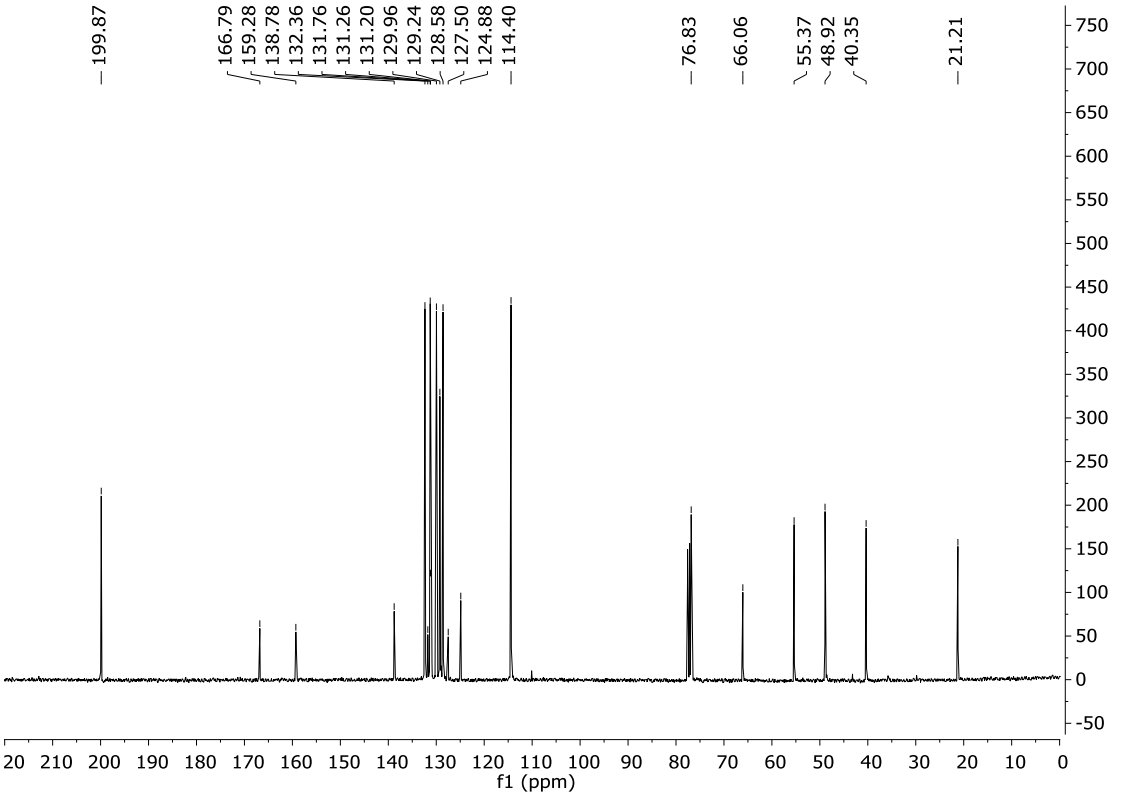
6.76
6.28
5.17
5.16
5.13
5.12
4.88
4.84
4.79
4.40
4.38
4.36
4.34
3.75
3.22
3.17
3.05
3.00
2.32
O
H
HN
O
NO2
OMe
Br
15Gg
0.85
1.74
1.87
2.01
1.92
2.02
1.76
0.92
1.01
1.00
0.99
2.91
1.01
0.99
3.01
f1 (ppm)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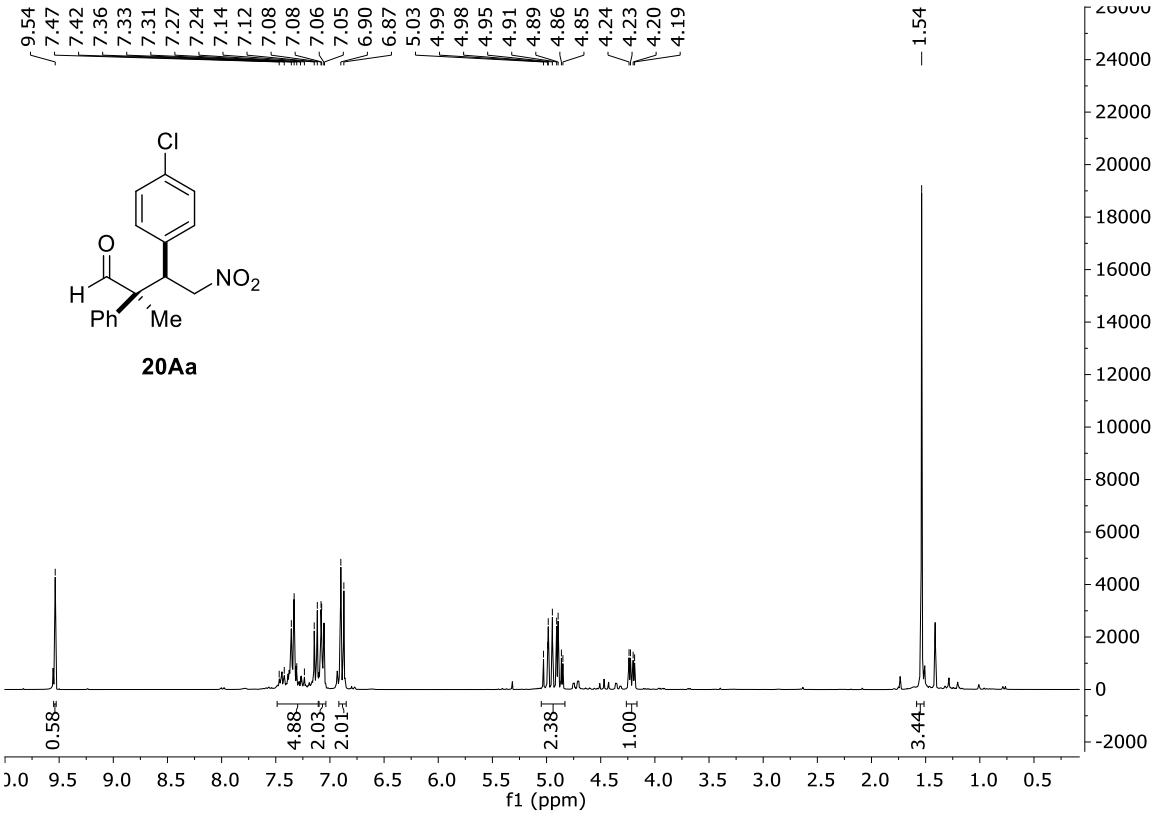
55.37
48.92
40.35
21.21
f1 (ppm)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7.14
7.12
7.08
7.08
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7.05
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4.95
4.91
4.89
4.86
4.85
4.24
4.23
4.20
4.19
1.54
Cl
O
H
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Ph
Me
20Aa
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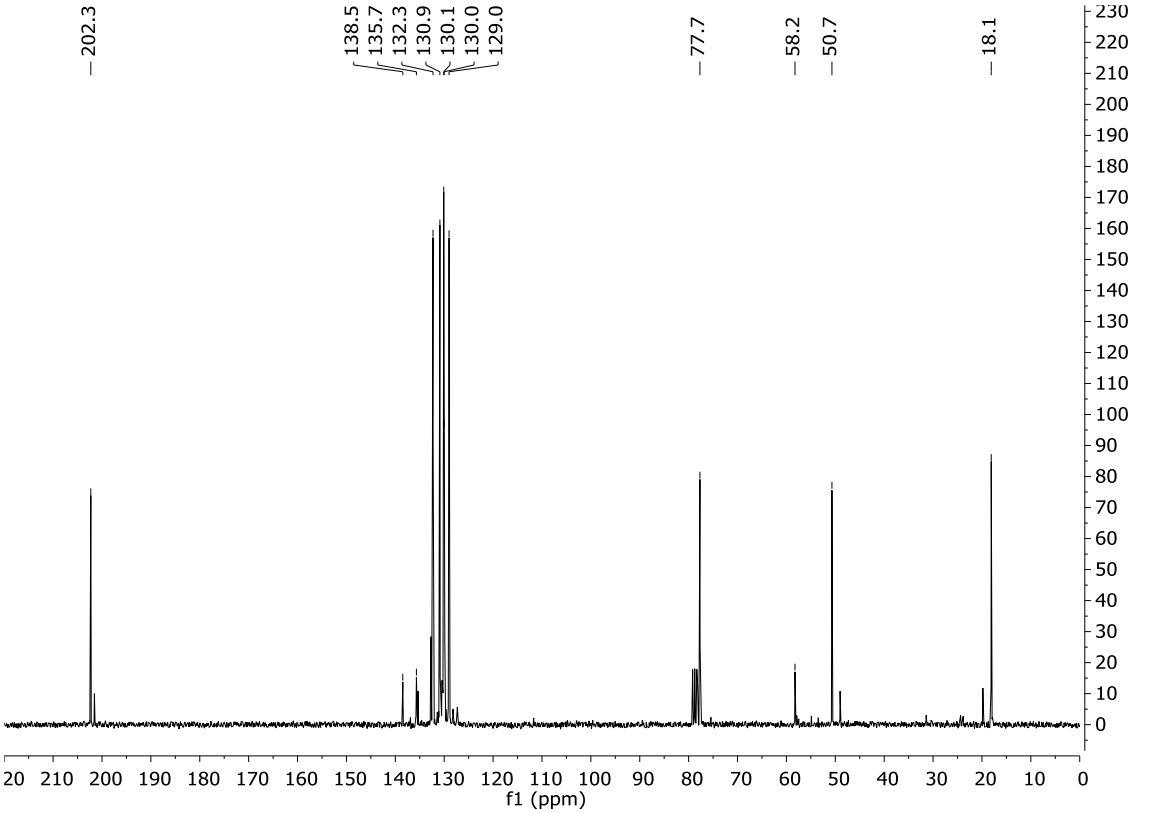
4.88
2.03
2.01
2.38
1.00
3.44
f1 (ppm)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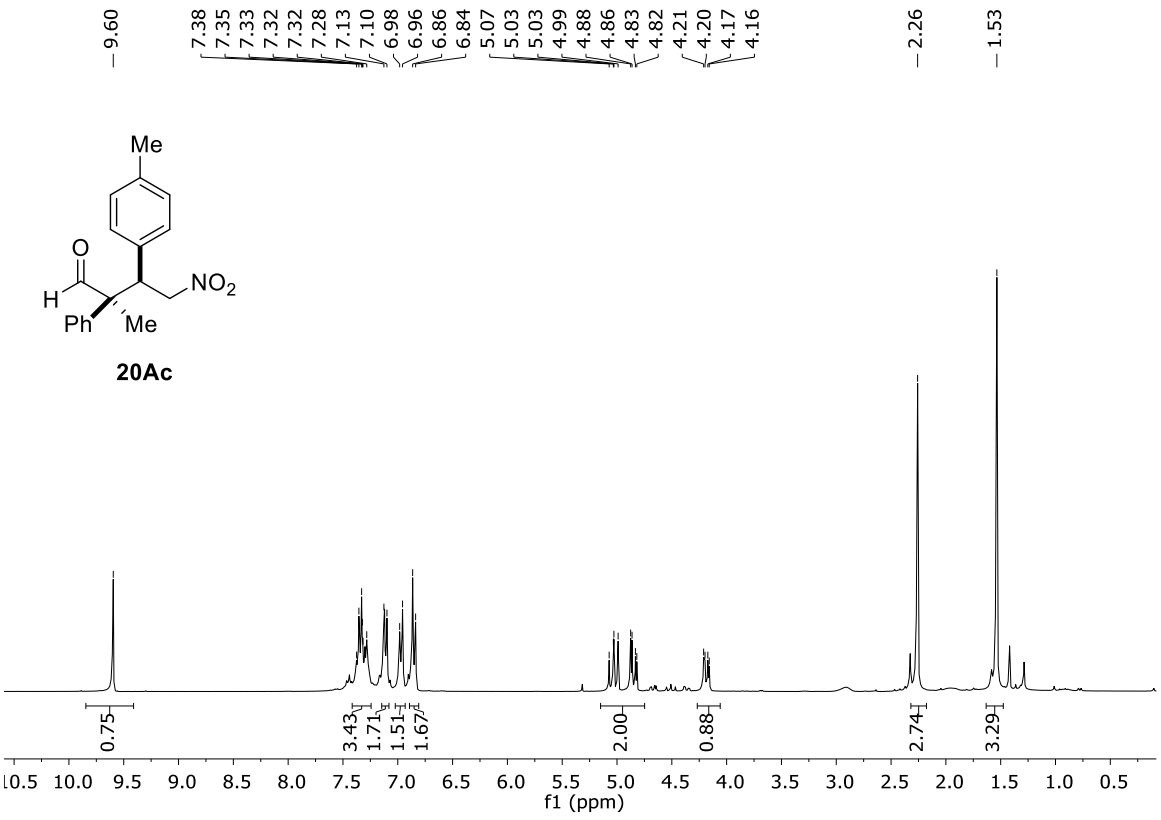
129.0
77.7
58.2
50.7
18.1
f1 (ppm)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7.35
7.33
7.32
7.32
7.28
7.13
7.10
6.98
6.96
6.86
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5.07
5.03
5.03
4.99
4.88
4.86
4.83
4.82
4.21
4.20
4.17
4.16
2.26
1.53
Me
O
H
NO2
Ph
Me
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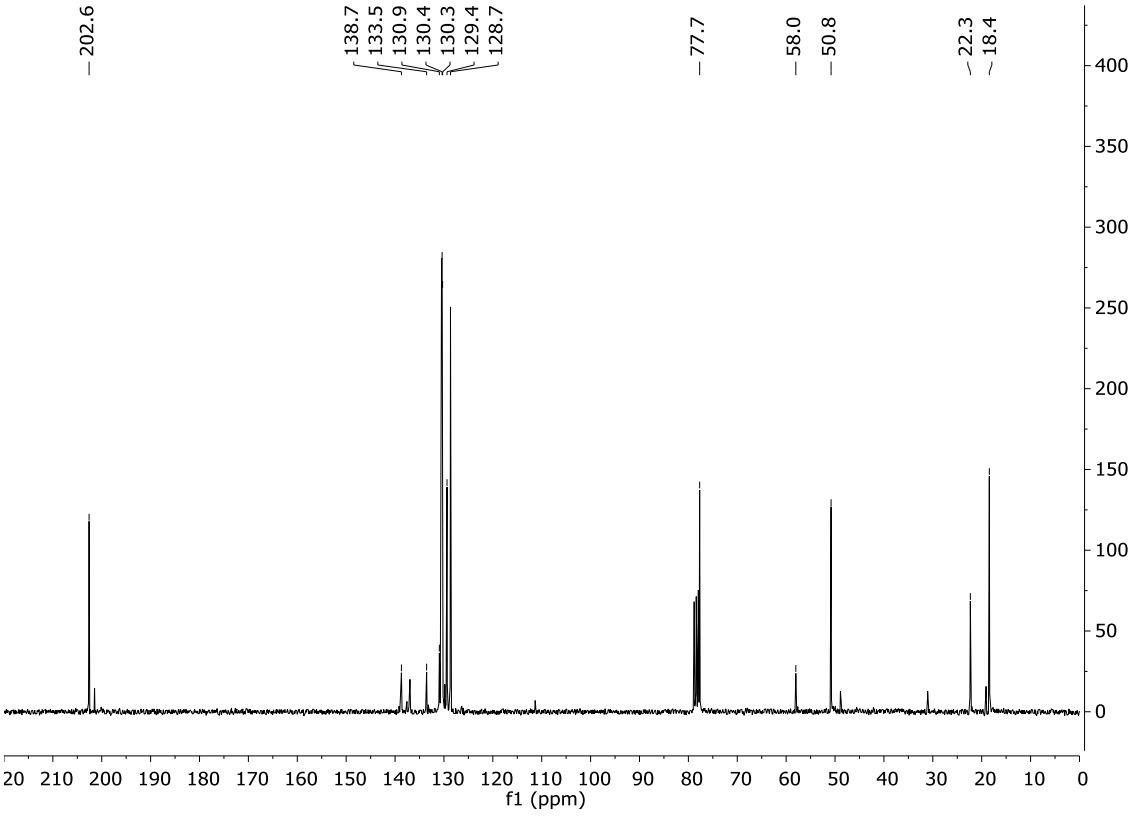
1.71
1.51
1.67
2.00
0.88
2.74
3.29
f1 (ppm)

20Ac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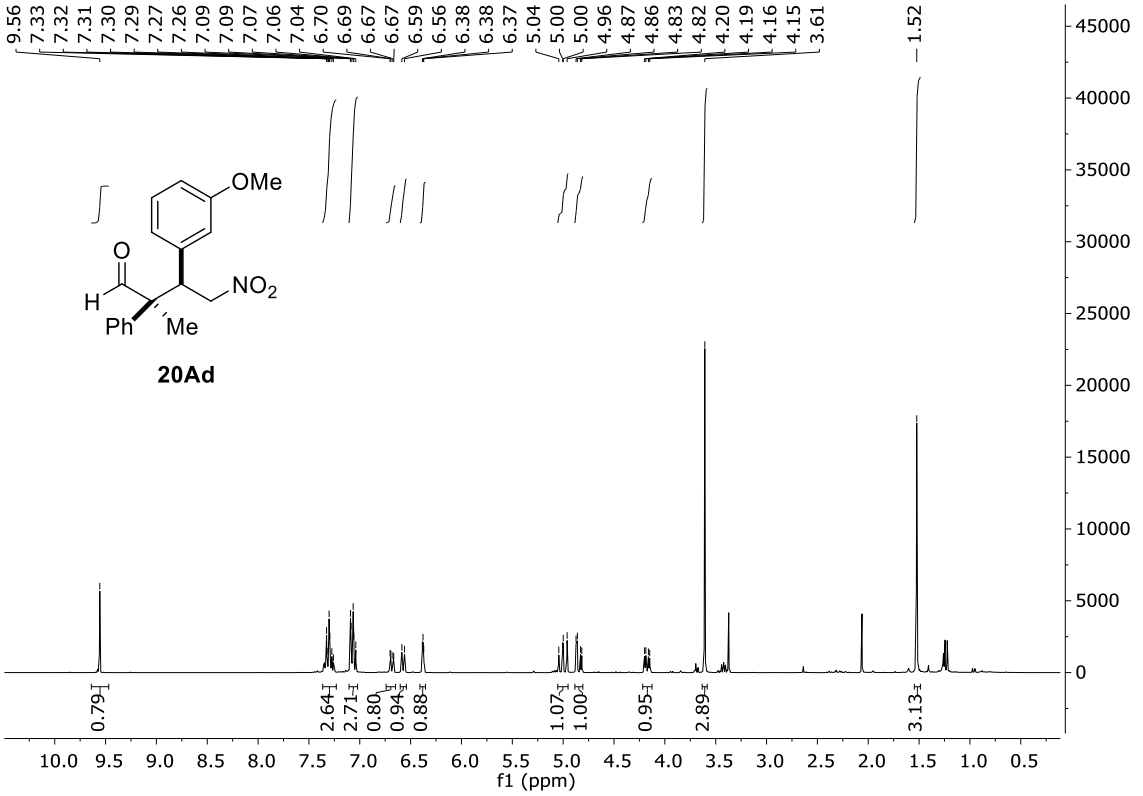
129.4
128.7
77.7
58.0
50.8
22.3
18.4
f1 (ppm)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7.09
7.07
7.06
7.04
6.70
6.69
6.67
6.67
6.59
6.56
6.38
6.37
5.04
5.00
5.00
4.96
4.87
4.86
4.83
4.82
4.20
4.19
4.16
4.15
3.61
1.52
OMe
O
H
NO2
Ph
Me
20Ad
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0.94
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1.07
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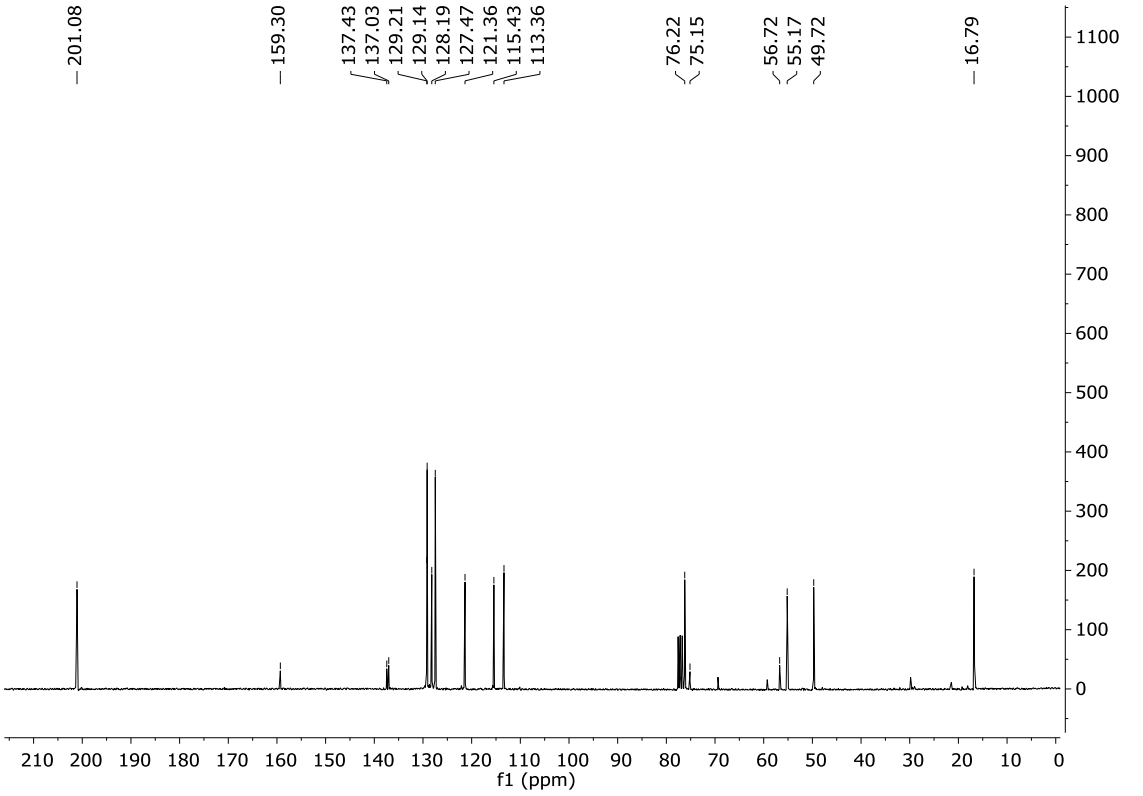
3.13
f1 (ppm)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127.47
121.36
115.43
113.36
76.22
75.15
56.72
55.17
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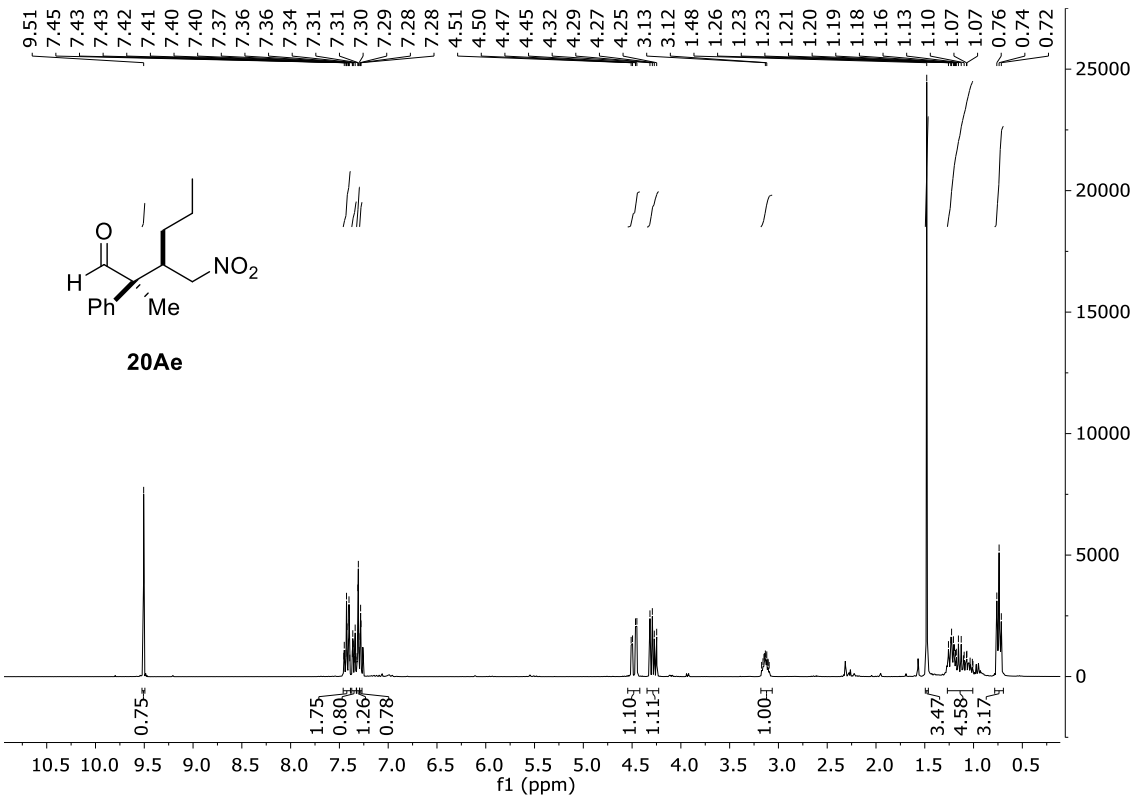
16.79
f1 (ppm)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4.51 4.50 4.47 4.45 4.32 4.29 4.27 4.25 3.13 3.12 1.48 1.26 1.23 1.23 1.21 1.20 1.19 1.18 1.16 1.13 1.10 1.07 1.07 0.76 0.74 0.72
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H
Ph
Me
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20Ae
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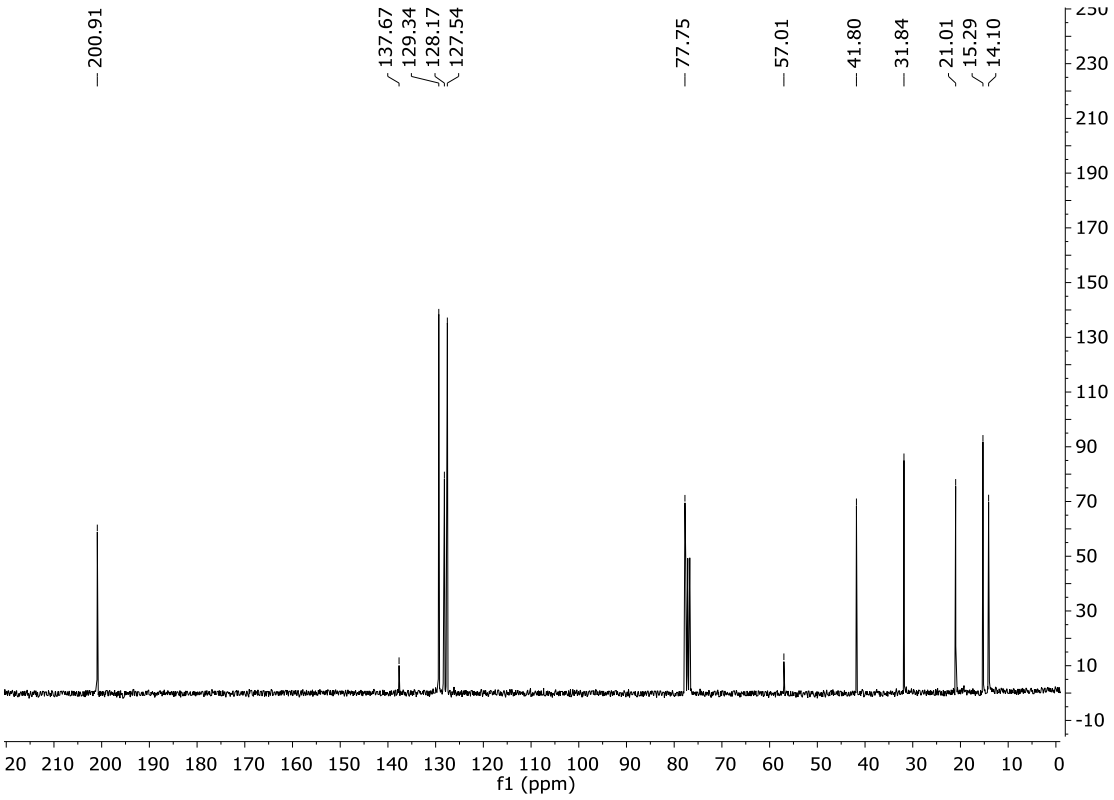
f1 (ppm)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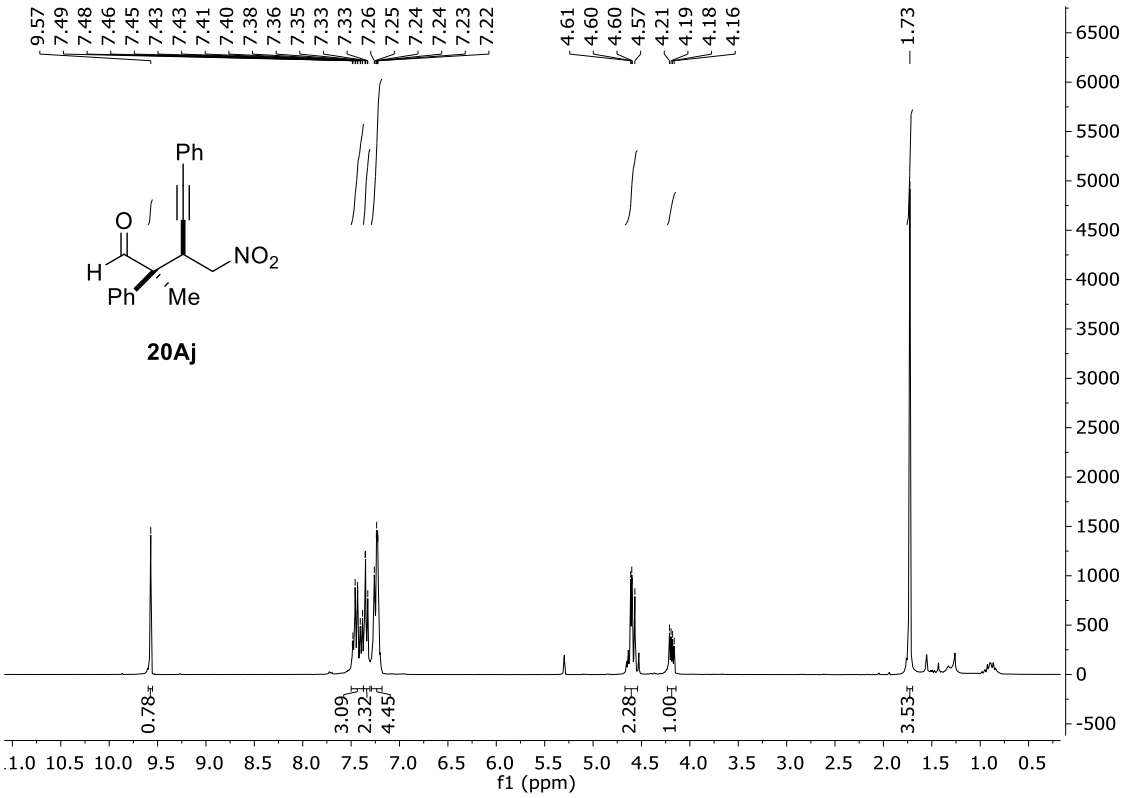
41.80
31.84
21.01 15.29 14.10
f1 (ppm)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7.33
7.33
7.26
7.25
7.24
7.24
7.23
7.22
4.61
4.60
4.60
4.57
4.21
4.19
4.18
4.16
1.73
Ph
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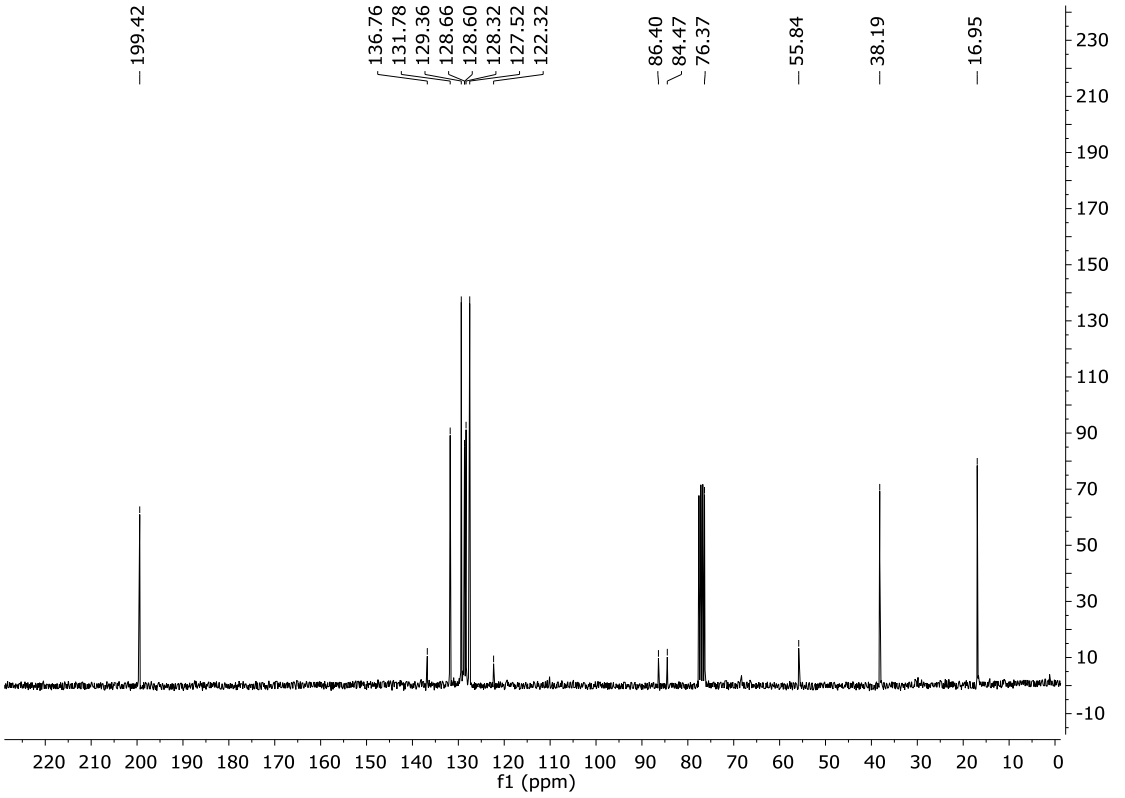
f1 (ppm)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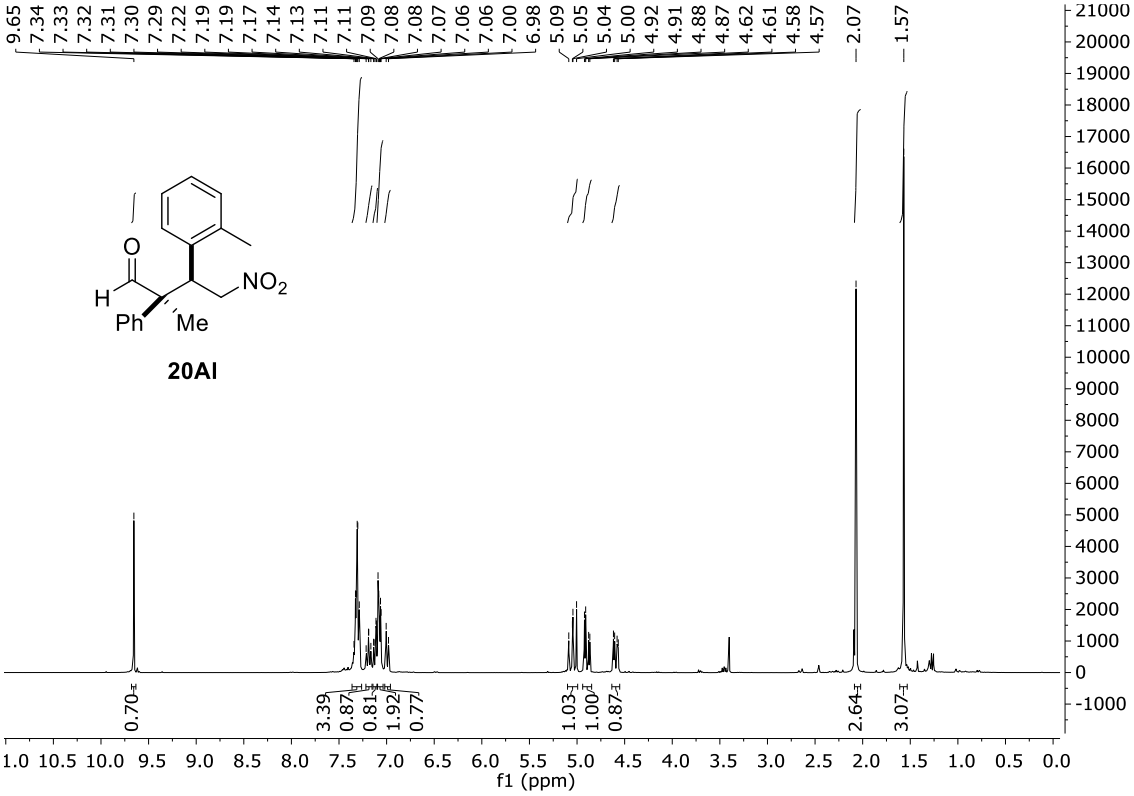
84.47
76.37
55.84
38.19
16.95
f1 (ppm)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7.11
7.11
7.09
7.08
7.08
7.07
7.06
7.06
7.00
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5.05
5.04
5.00
4.92
4.91
4.88
4.87
4.62
4.61
4.58
4.57
2.07
1.57
O
H
NO2
Ph
Me
20AI
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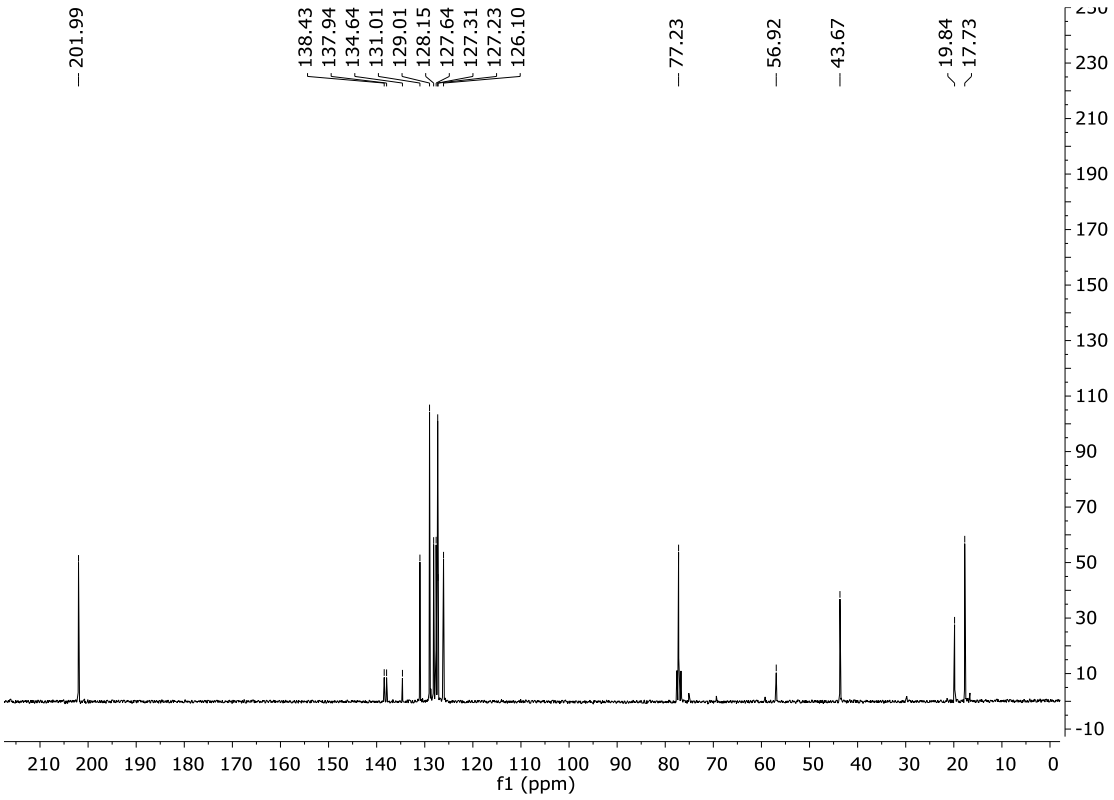
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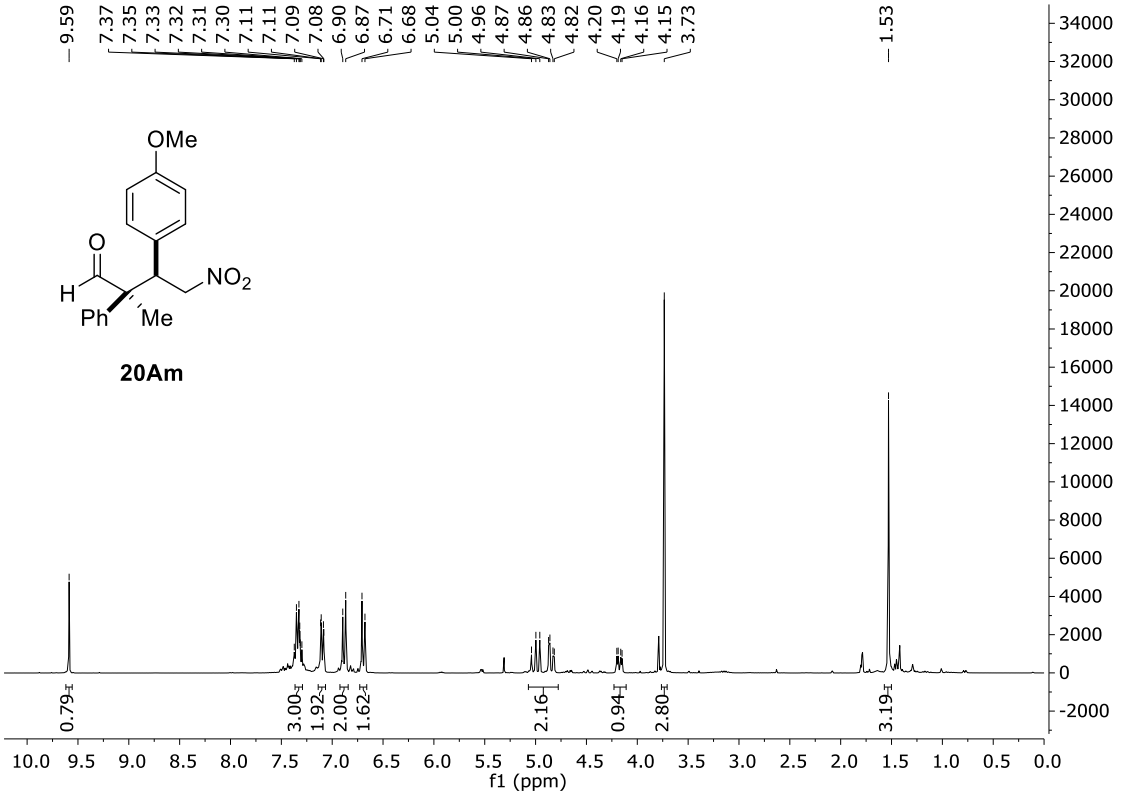
43.67
19.84
17.73
f1 (ppm)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7.08
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5.04
5.00
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4.86
4.83
4.82
4.20
4.19
4.16
4.15
3.73
1.53
OMe
O
H
NO2
Ph
Me
20Am
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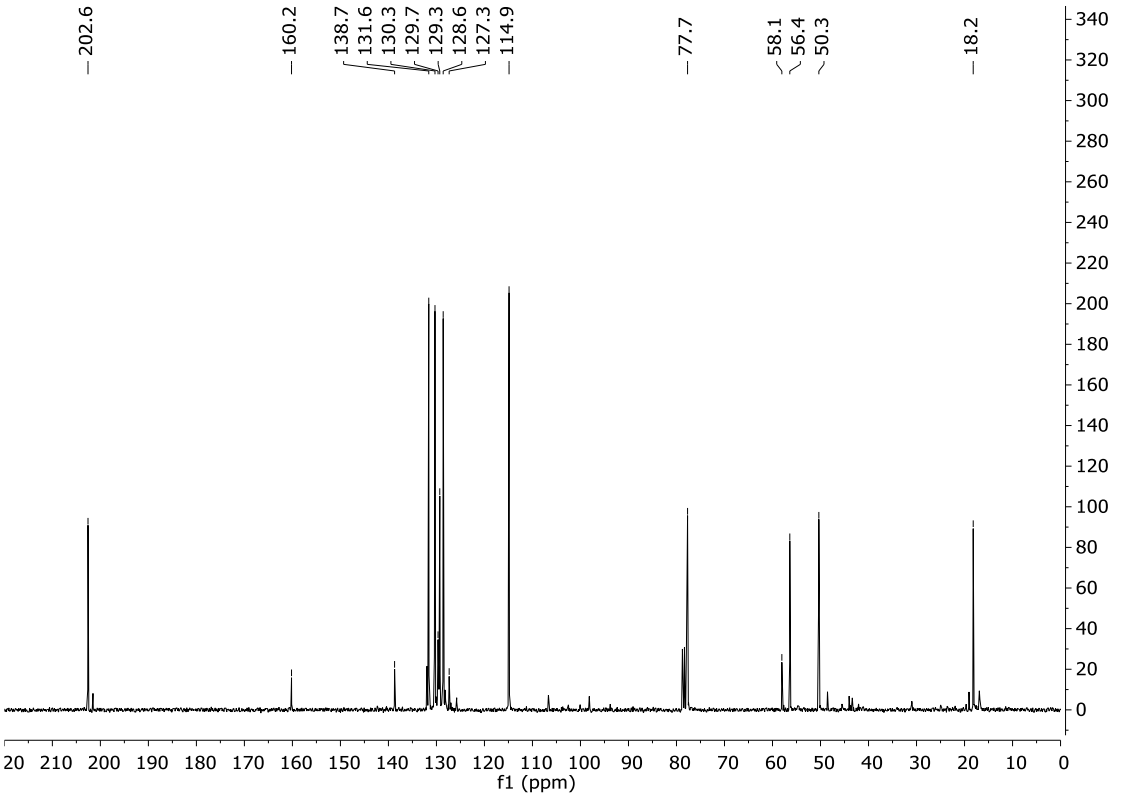
2.00
1.62
2.16
0.94
2.80
3.19
f1 (ppm)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129.7
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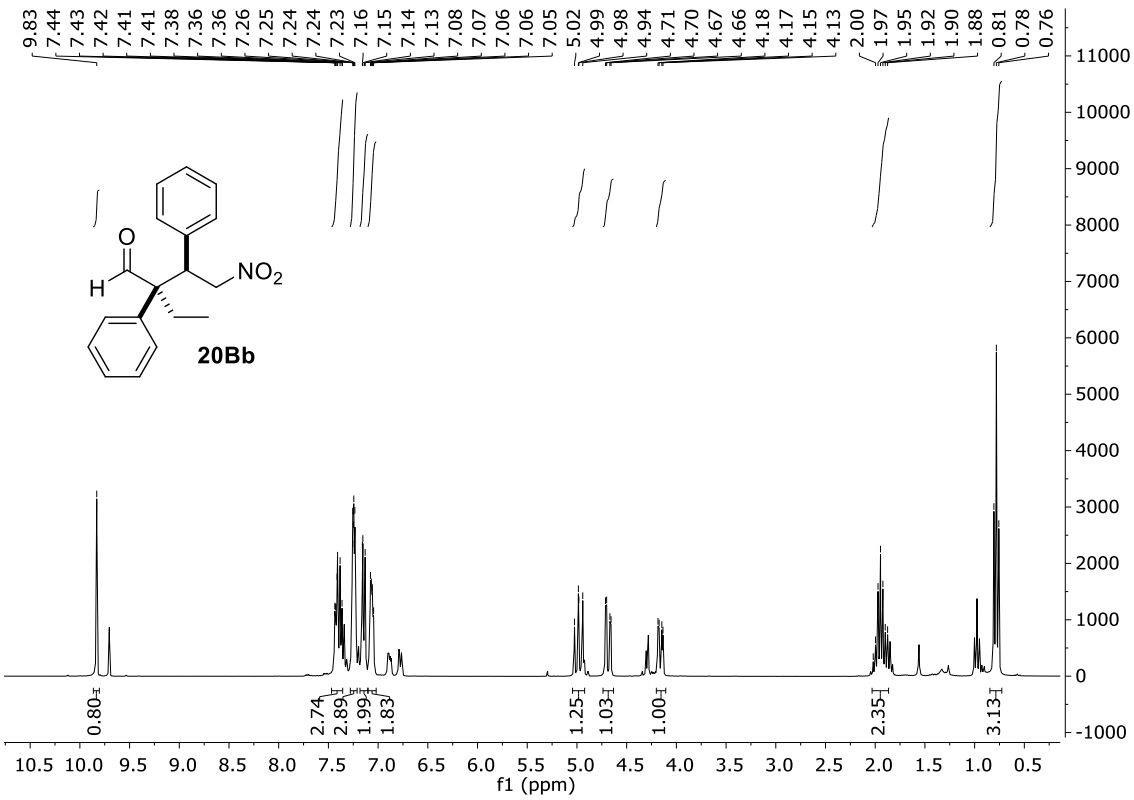
127.3
114.9
77.7
58.1
56.4
50.3
18.2
f1 (ppm)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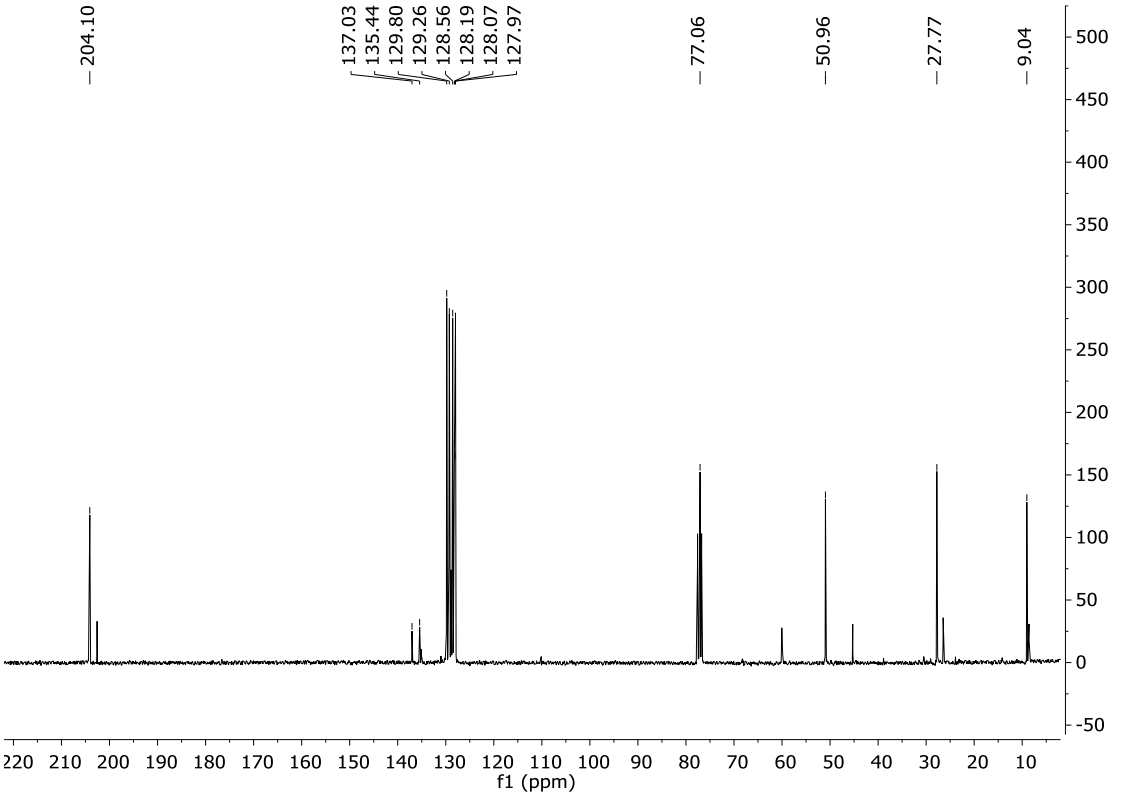
O
H
NO2
20Bb
0.80 2.74 2.89 1.99 1.83 1.25 1.03 1.00 2.35 3.13
f1 (ppm)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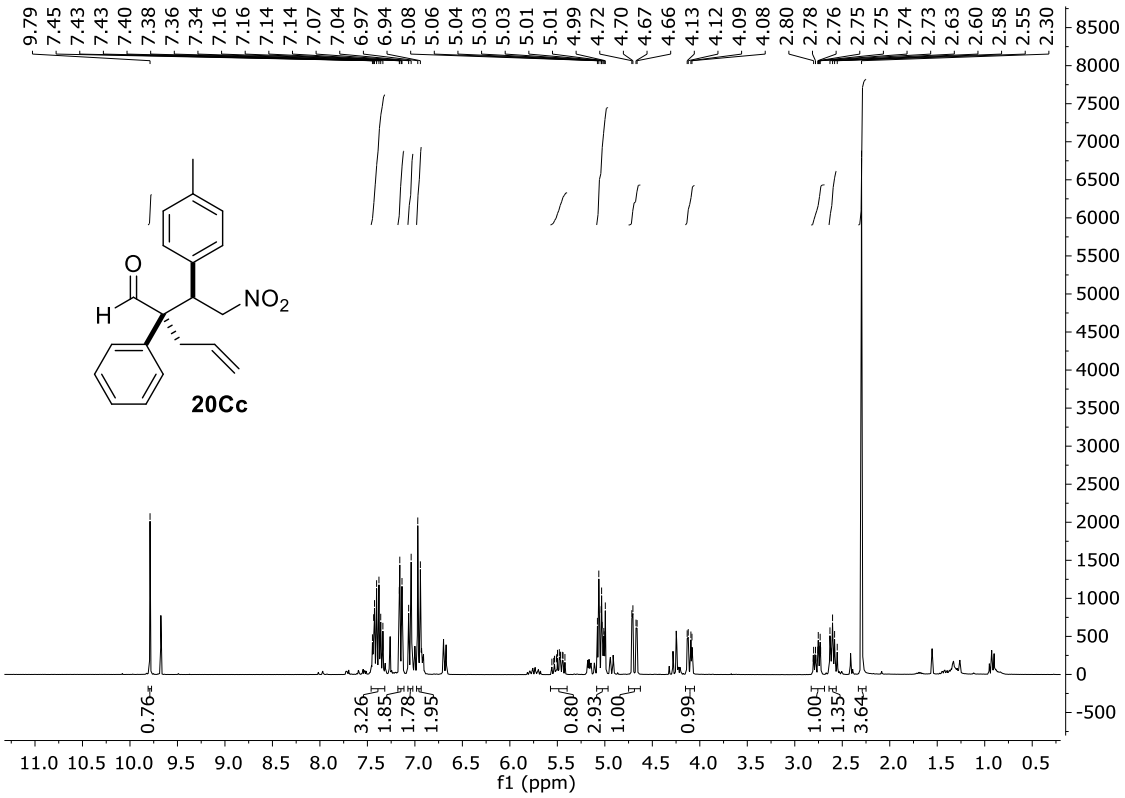
77.06
50.96
27.77
9.04
f1 (ppm)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7.38
7.36
7.34
7.16
7.16
7.14
7.14
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5.08
5.06
5.04
5.03
5.03
5.01
5.01
4.99
4.72
4.70
4.67
4.66
4.13
4.12
4.09
4.08
2.80
2.78
2.76
2.75
2.75
2.74
2.73
2.63
2.60
2.58
2.55
2.30
O
H
NO2
20Cc
0.76
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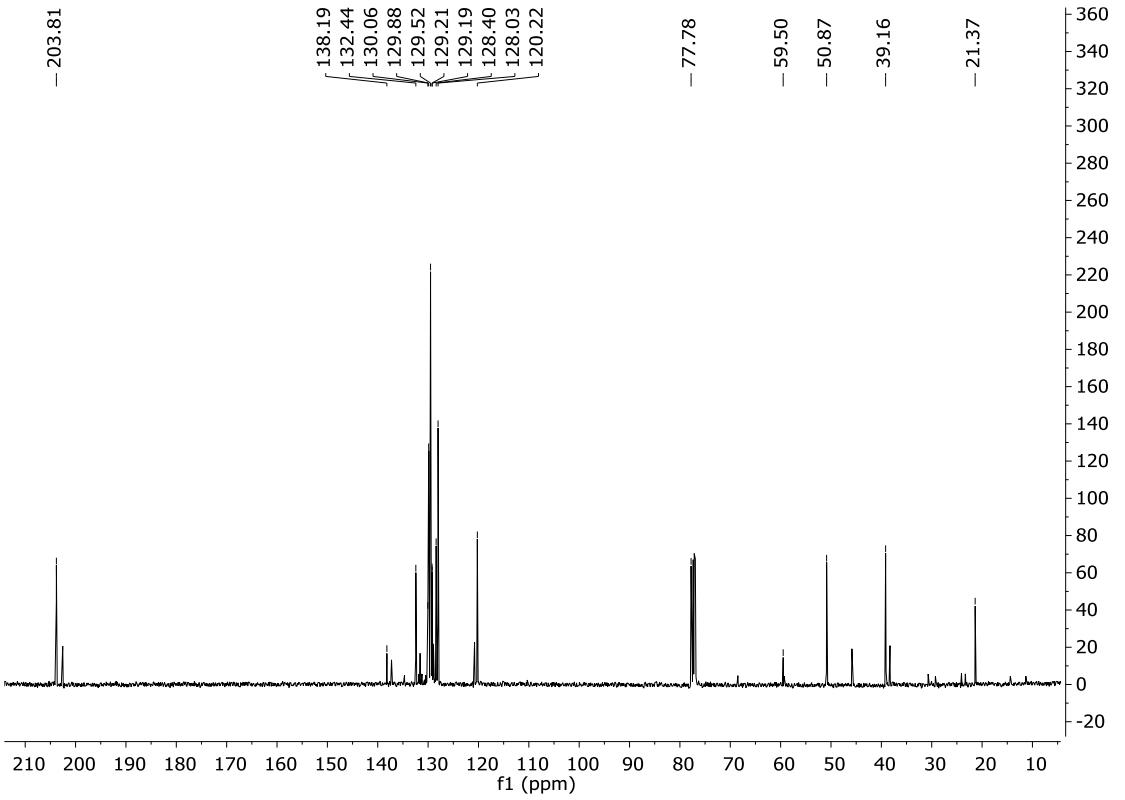
2.93
1.00
0.99
1.00
1.35
3.64
f1 (ppm)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128.03
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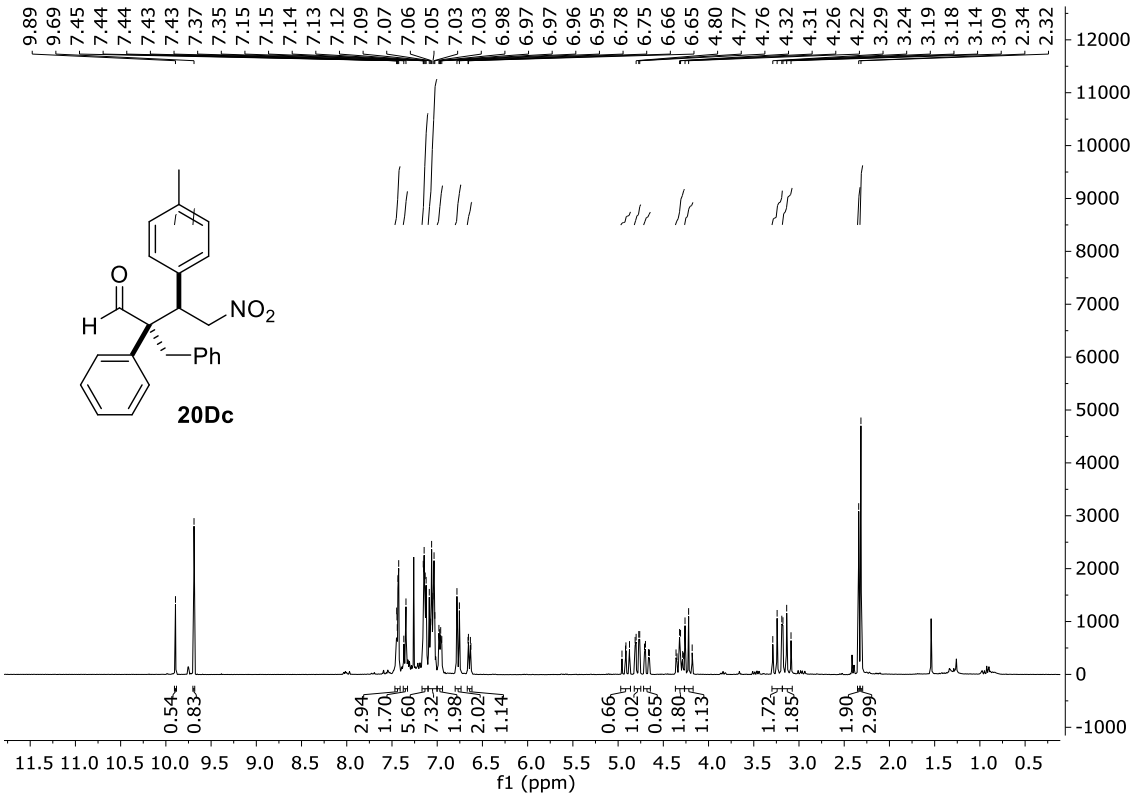
50.87
39.16
21.37
f1 (ppm)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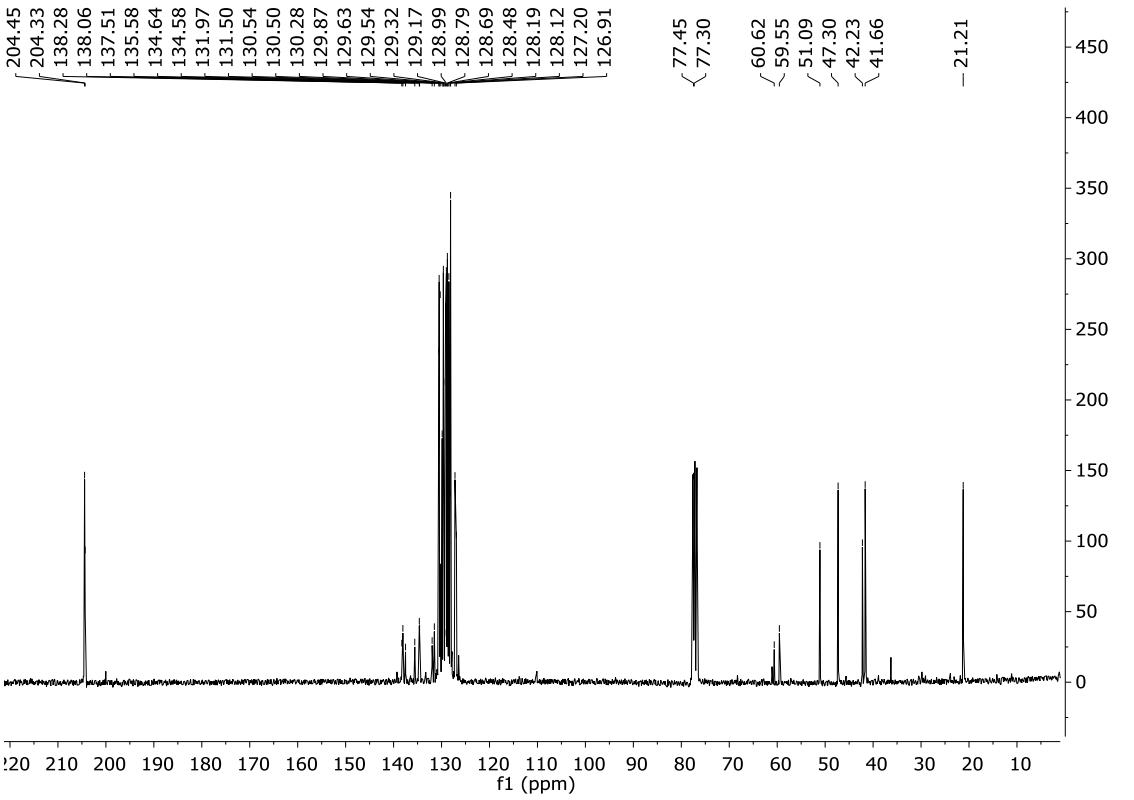
O
H
NO2
Ph
20Dc
0.54 0.83 2.94 1.70 5.60 7.32 1.98 2.02 1.14 0.66 1.02 0.65 1.80 1.13 1.72 1.85 1.90 2.99
f1 (ppm)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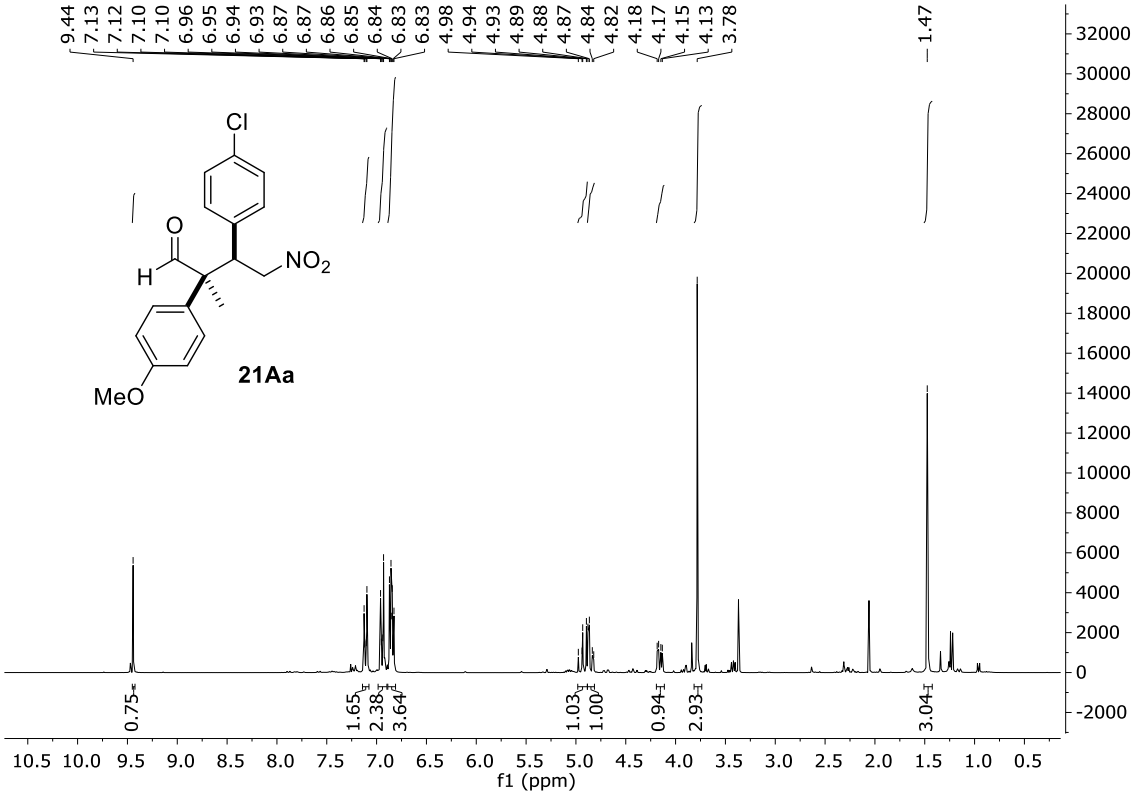
60.62 59.55 51.09 47.30 42.23 41.66
21.21
f1 (ppm)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6.93
6.87
6.87
6.86
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6.83
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4.94
4.93
4.89
4.88
4.87
4.84
4.82
4.18
4.17
4.15
4.13
3.78
1.47
Cl
O
H
NO2
MeO
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0.94
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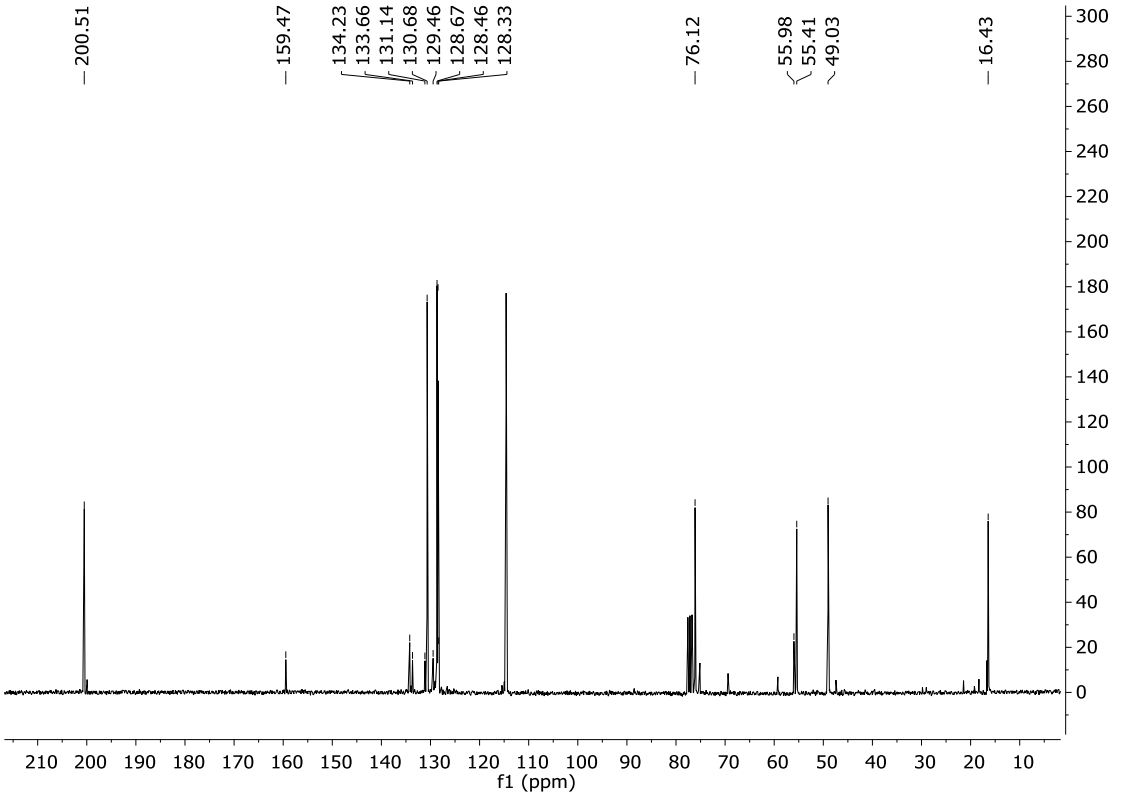
3.04
f1 (ppm)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16.43
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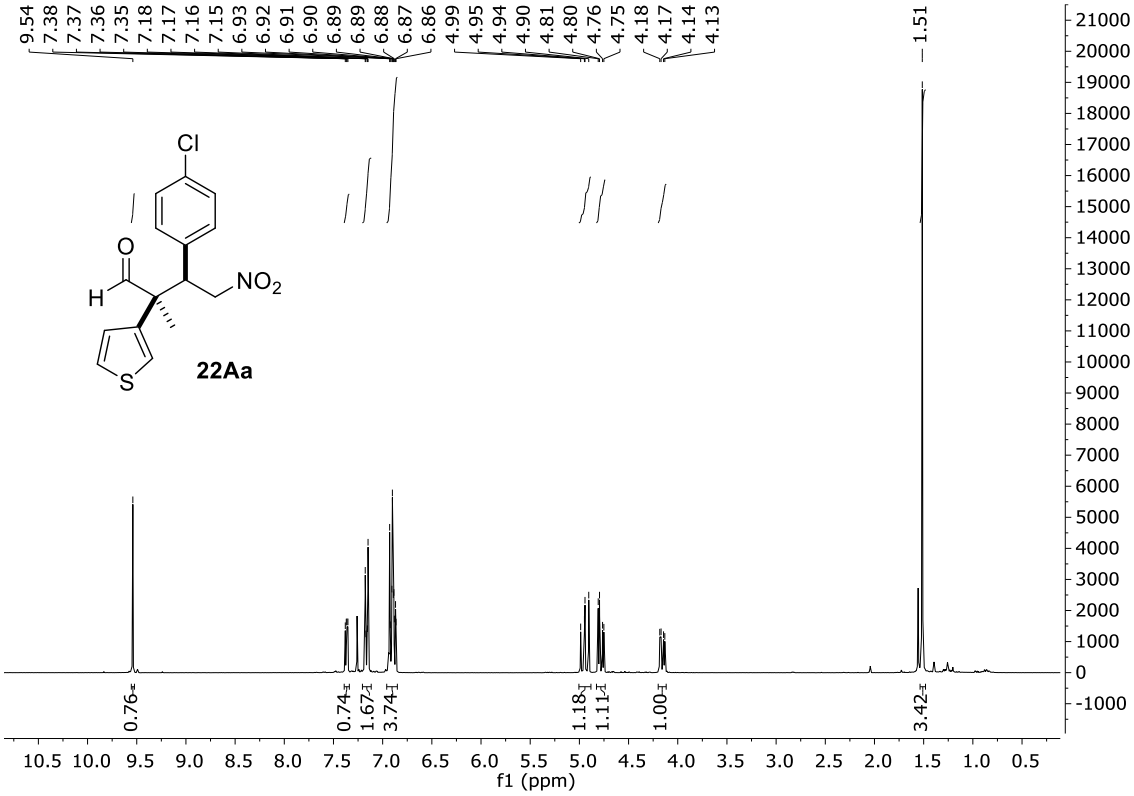
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4.76
4.75
4.18
4.17
4.14
4.13
1.51
Cl
O
H
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3.74
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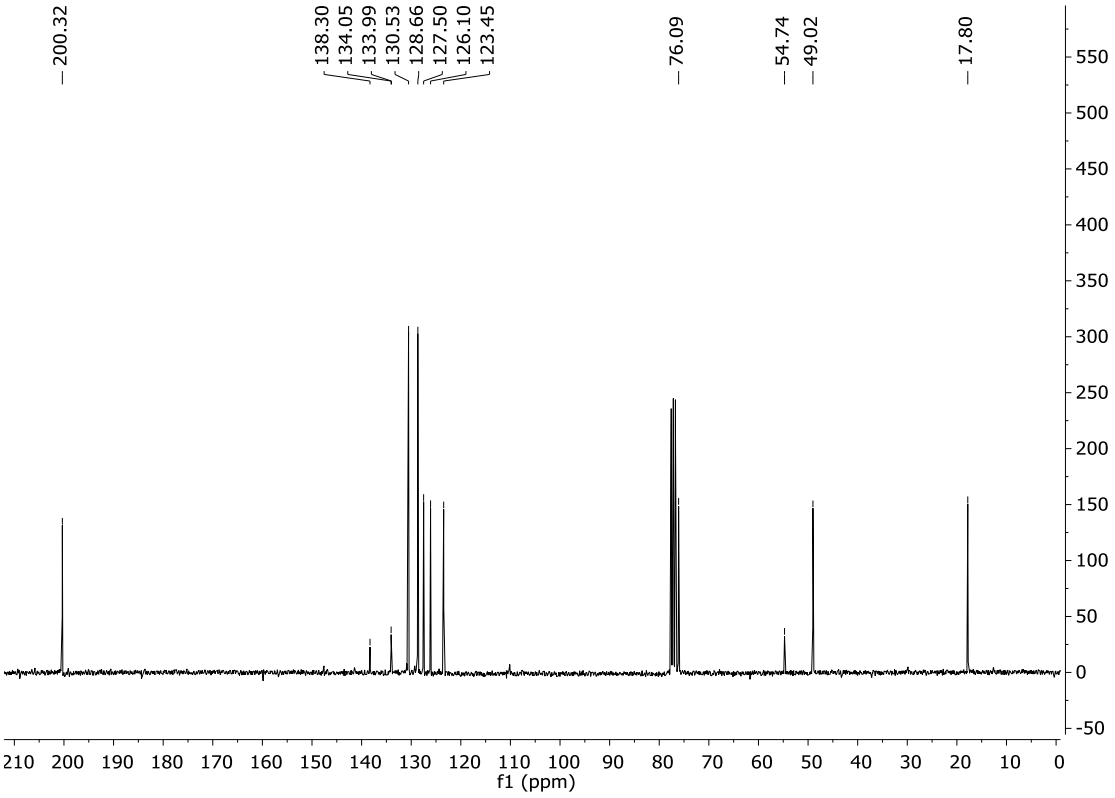
1.11
1.00
3.42
f1 (ppm)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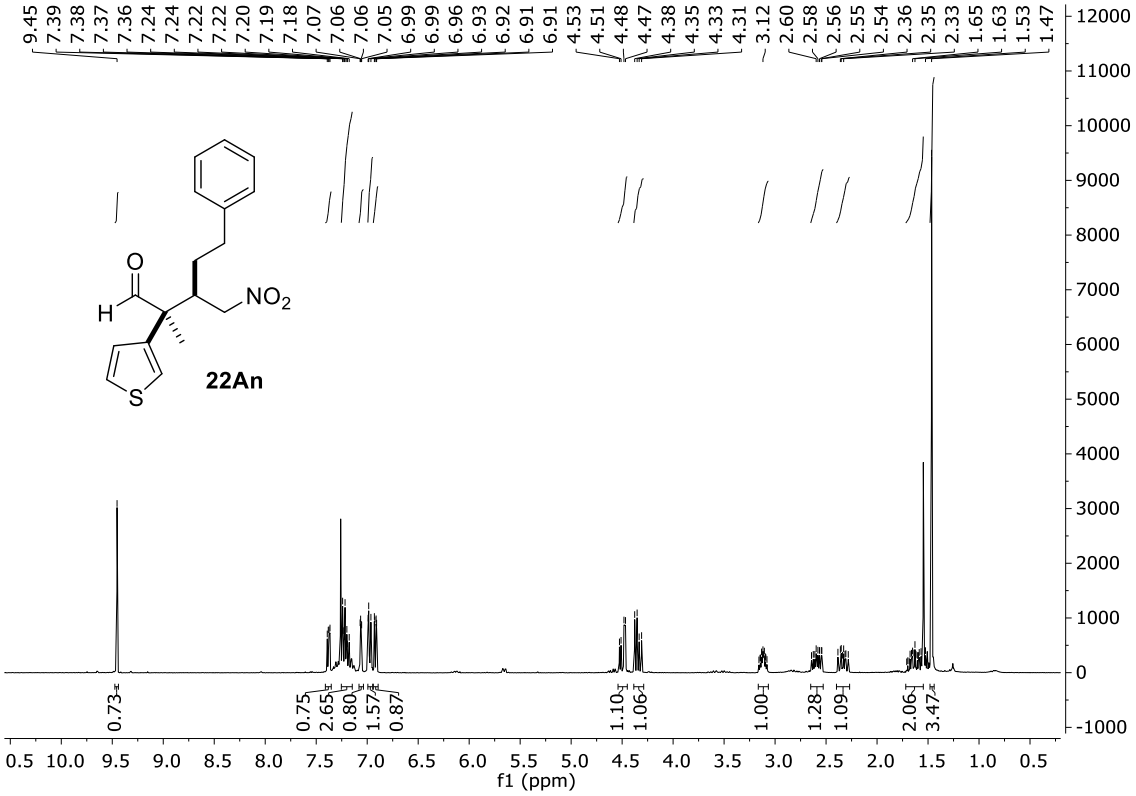
49.02
17.80
f1 (ppm)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7.24
7.22
7.22
7.20
7.19
7.18
7.07
7.06
7.06
7.05
6.99
6.99
6.96
6.93
6.92
6.91
6.91
4.53
4.51
4.48
4.47
4.38
4.35
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4.31
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2.58
2.56
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2.54
2.36
2.35
2.33
1.65
1.63
1.53
1.47
O
H
NO2
S
22An
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1.00
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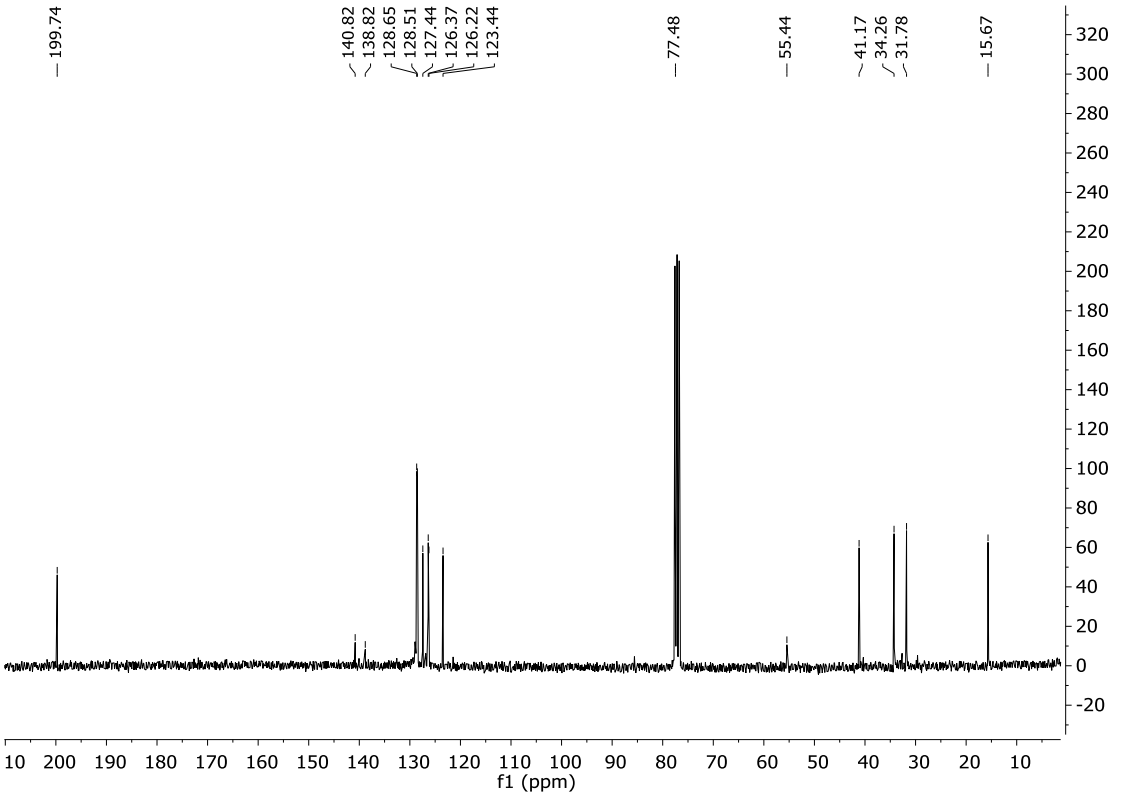
1.09
2.06
3.47
f1 (ppm)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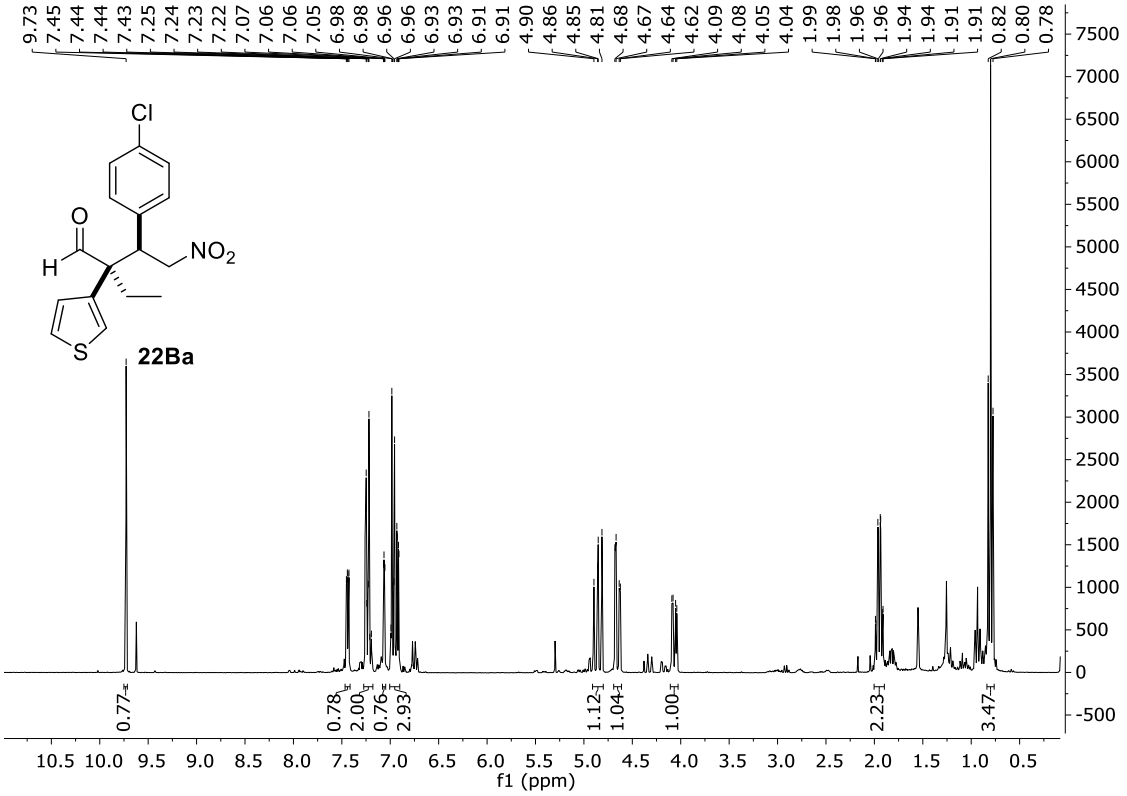
41.17
34.26
31.78
15.67
f1 (ppm)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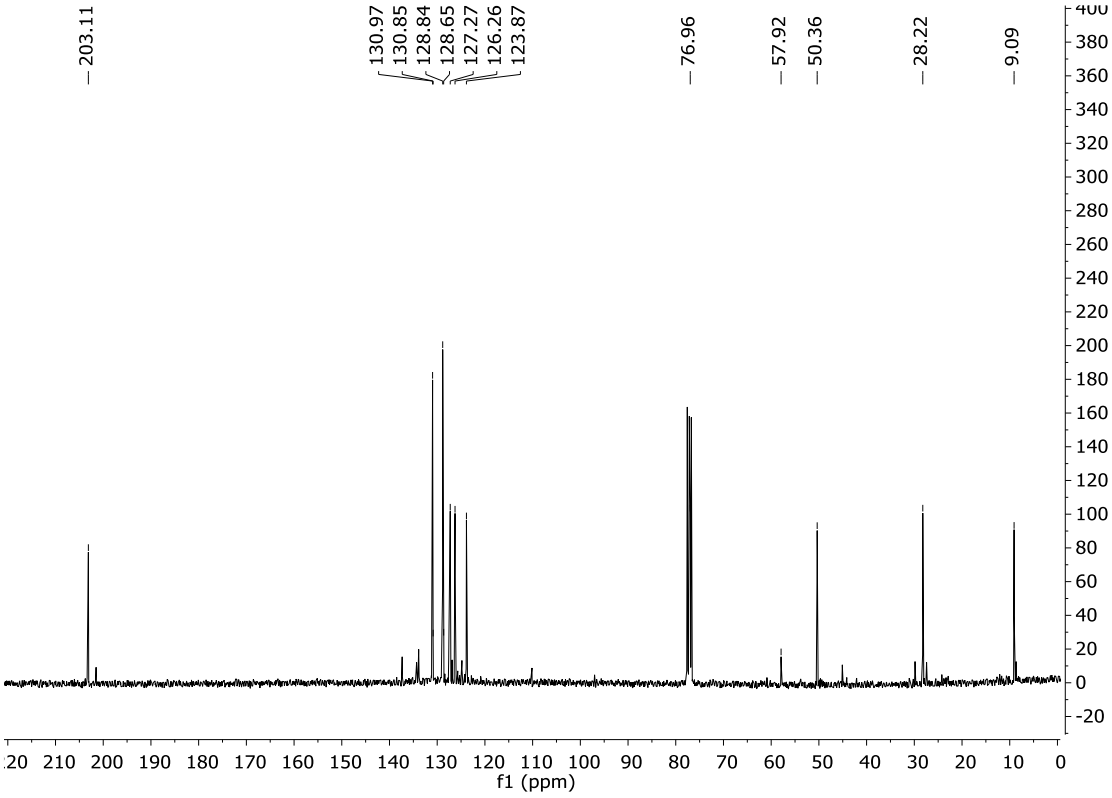
Cl
O
H
NO2
S
22Ba
0.77 0.78 2.00 0.76 2.93 1.12 1.04 1.00 2.23 3.47
f1 (ppm)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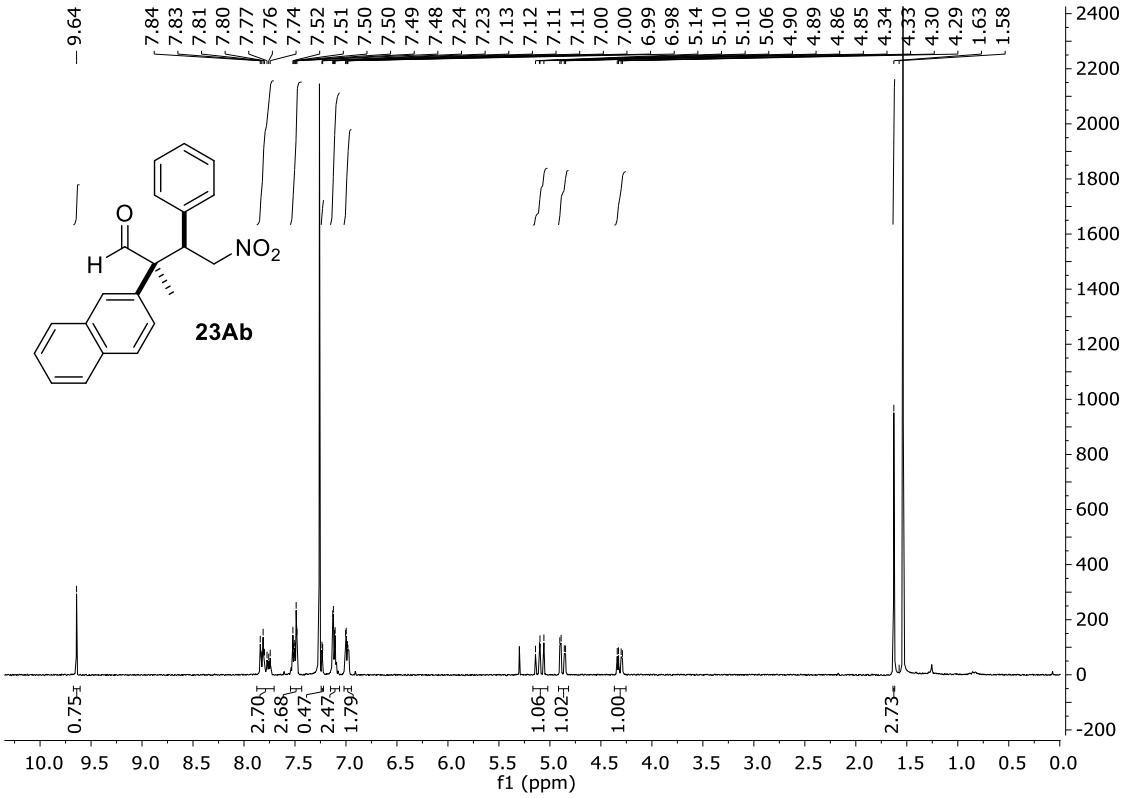
f1 (ppm)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7.50
7.49
7.48
7.24
7.23
7.13
7.12
7.11
7.11
7.00
7.00
6.99
6.98
5.14
5.10
5.10
5.06
4.90
4.89
4.86
4.85
4.34
4.33
4.30
4.29
1.63
1.58
O
H
NO2
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1.79
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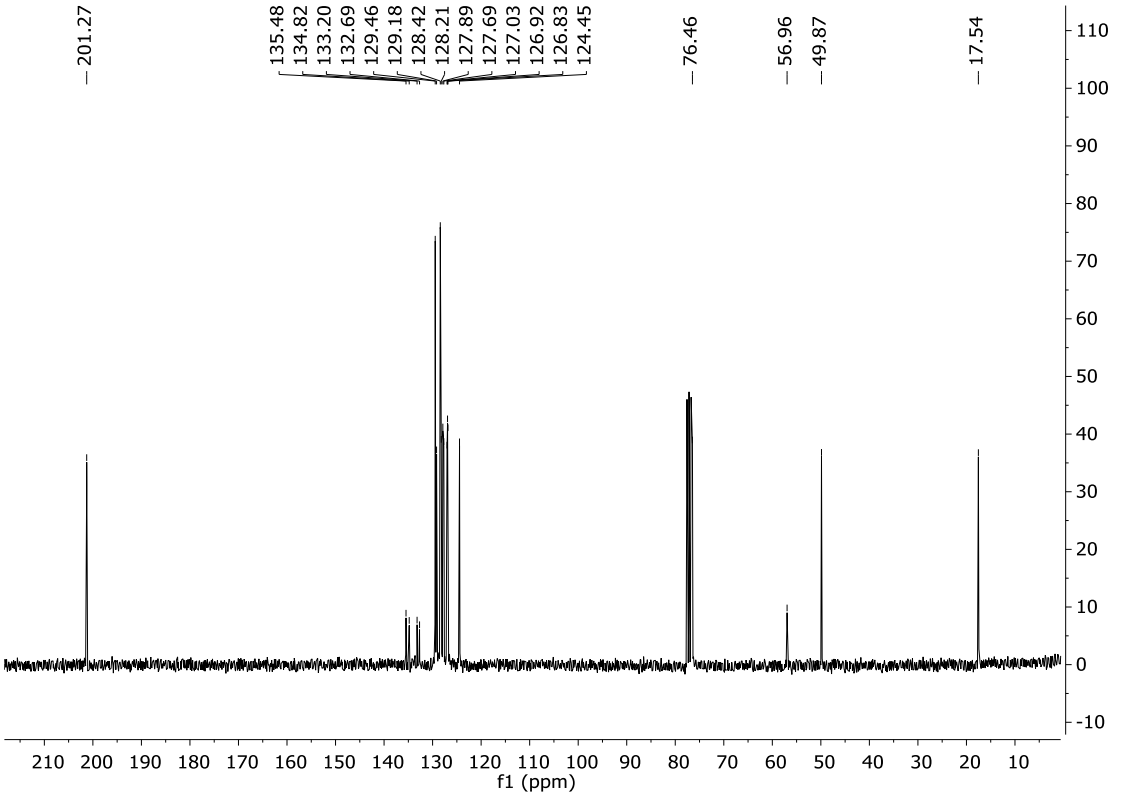
1.02
1.00
2.73
f1 (ppm)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127.03
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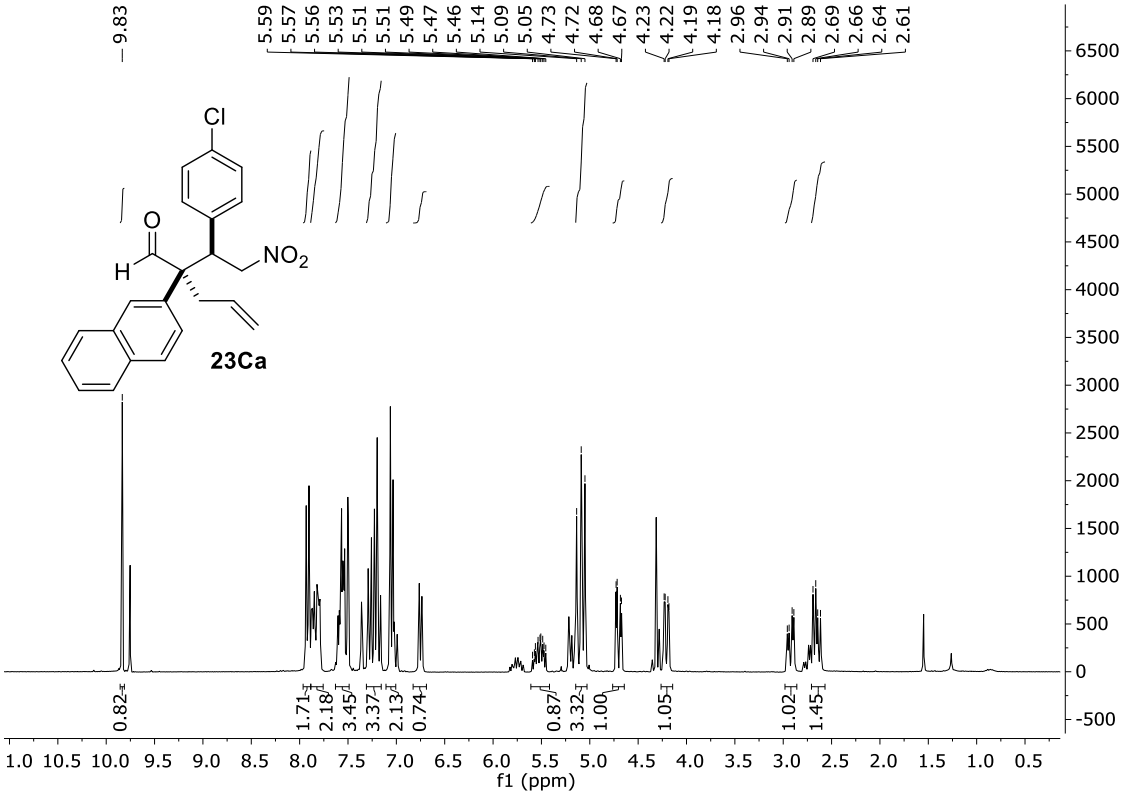
76.46
56.96
49.87
17.54
f1 (ppm)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5.46
5.14
5.09
5.05
4.73
4.72
4.68
4.67
4.23
4.22
4.19
4.18
2.96
2.94
2.91
2.89
2.69
2.66
2.64
2.61
Cl
O
H
NO2
23Ca
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1.71
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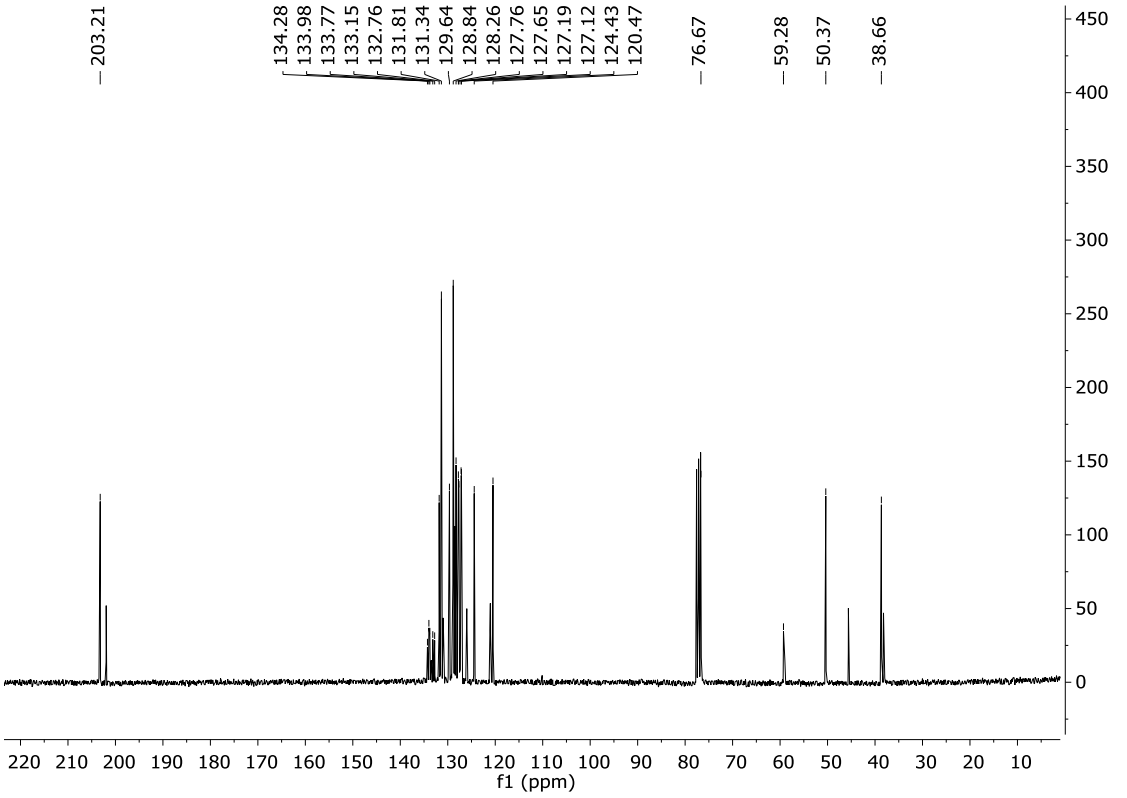
2.13
0.74
0.87
3.32
1.00
1.05
1.02
1.45
f1 (ppm)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127.76
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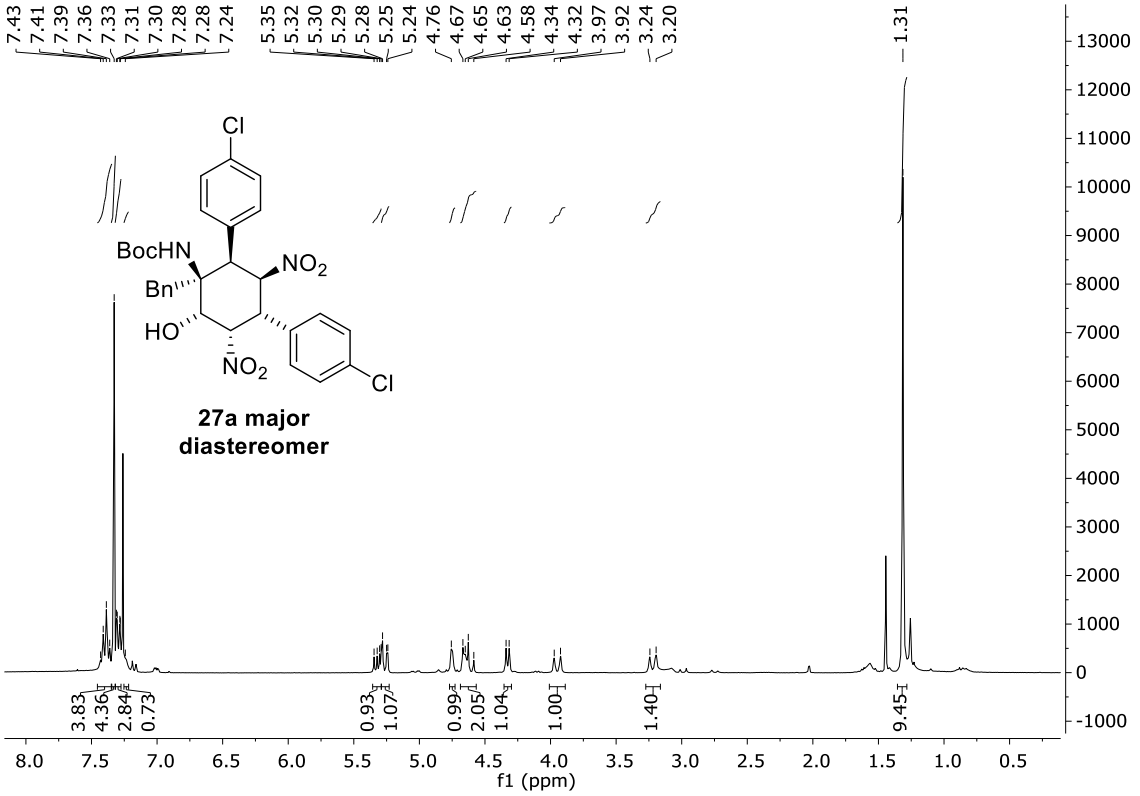
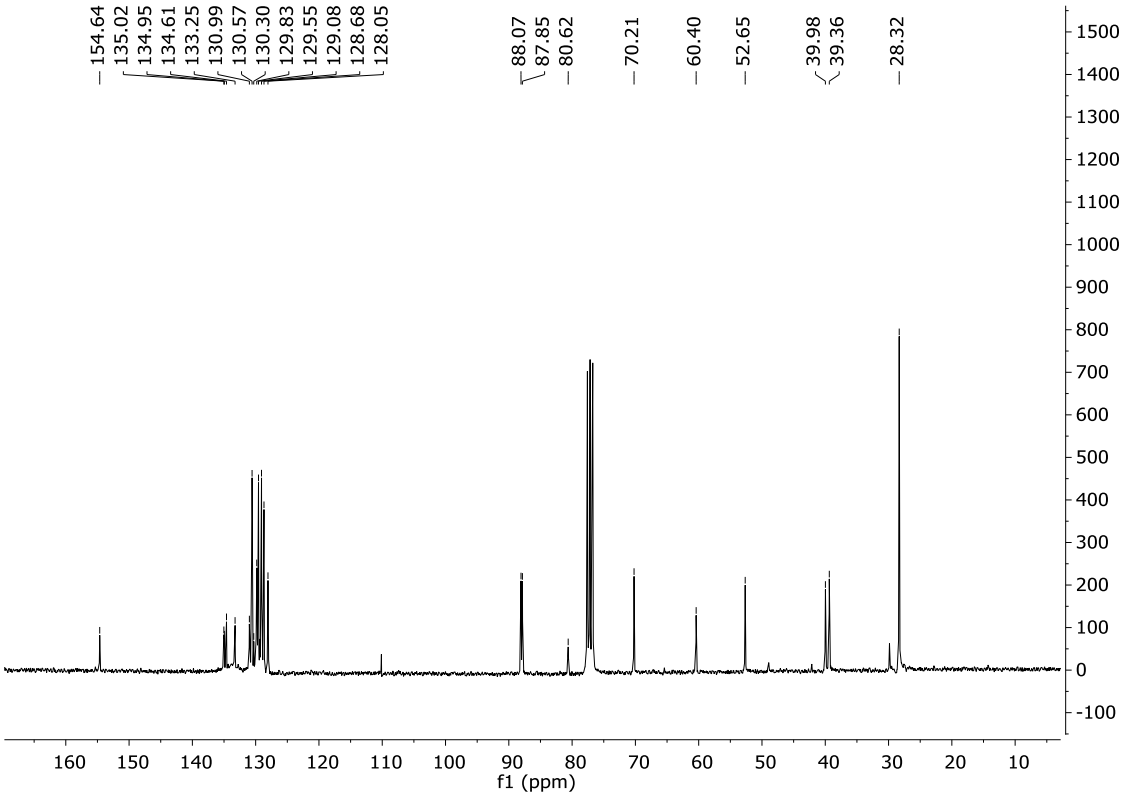
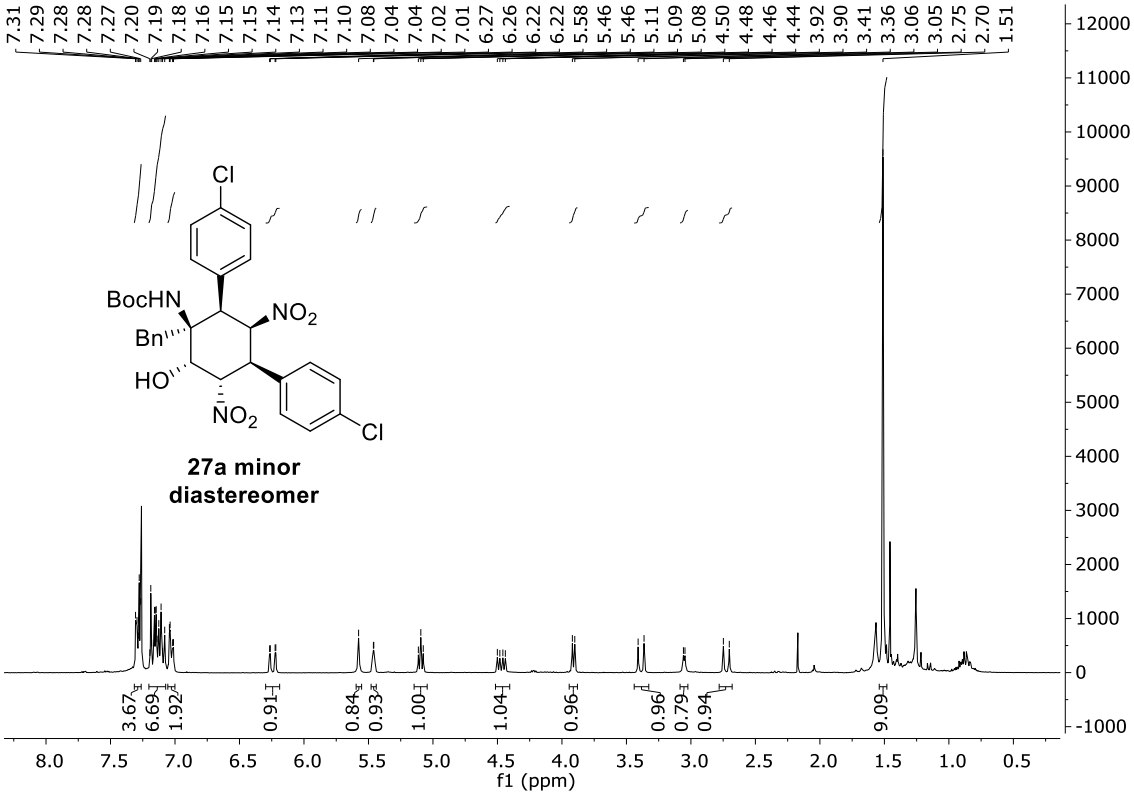
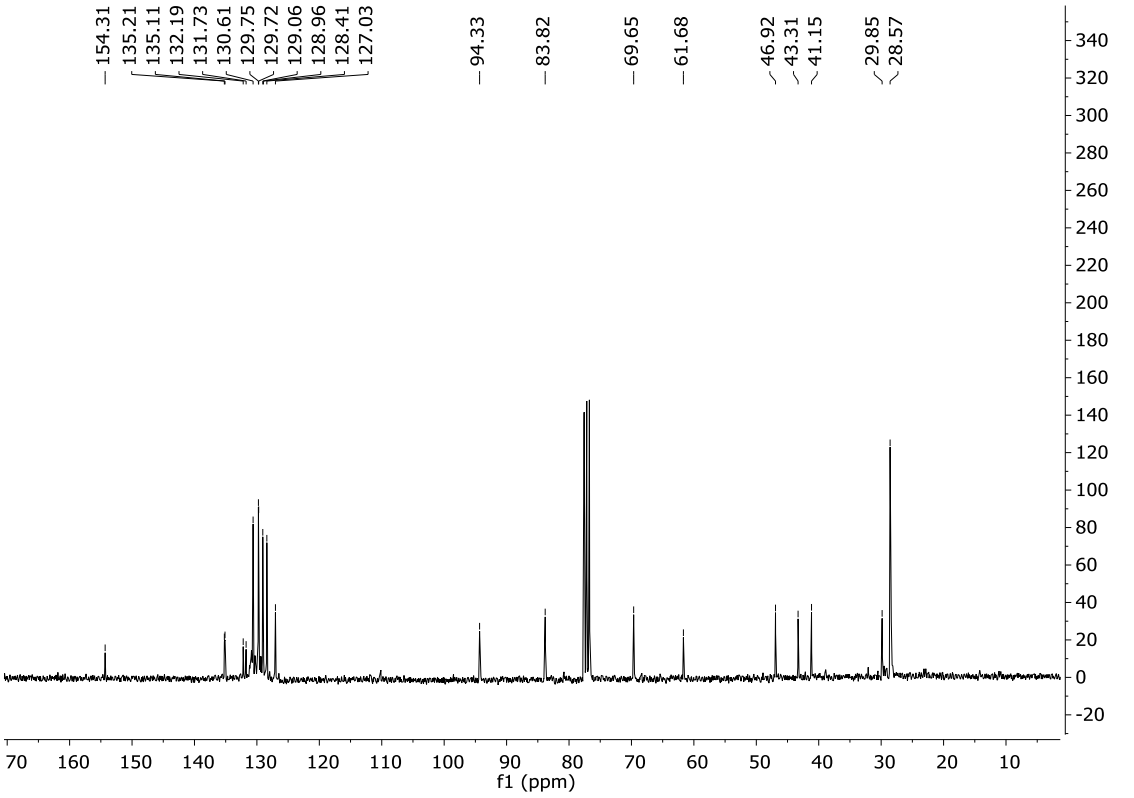
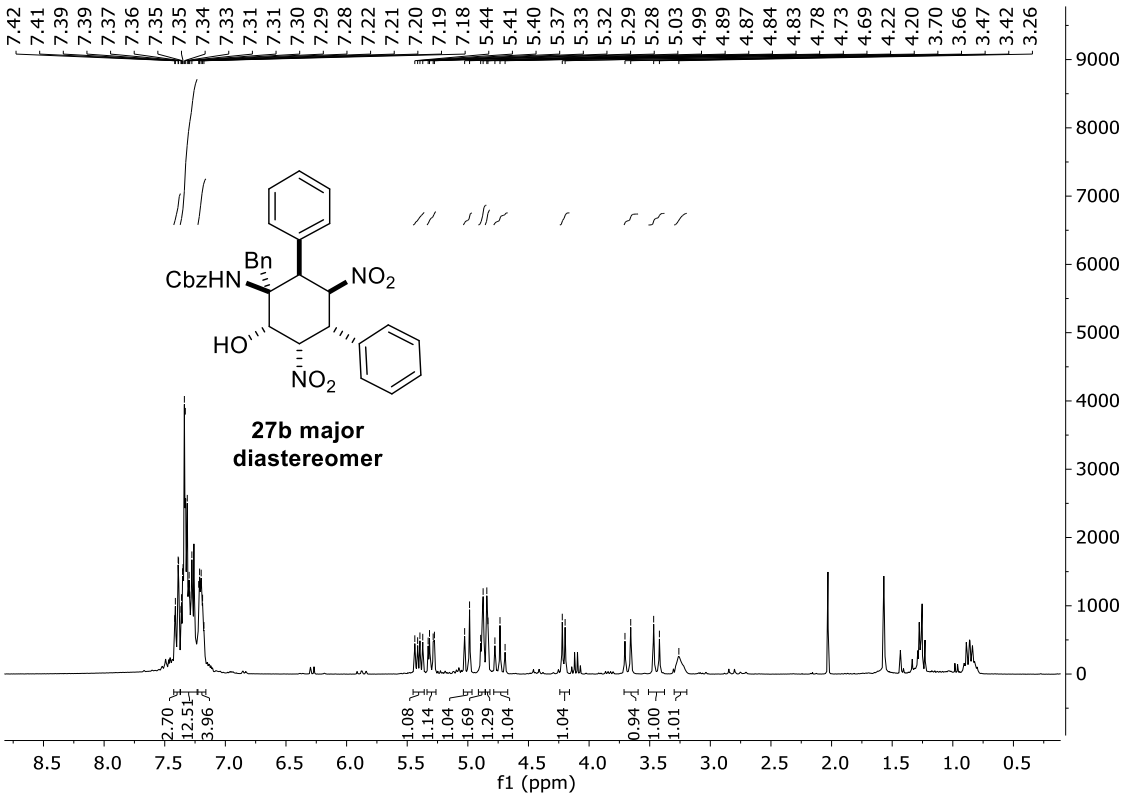
127.12
124.43
120.47
76.67
59.28
50.37
38.66
f1 (ppm)

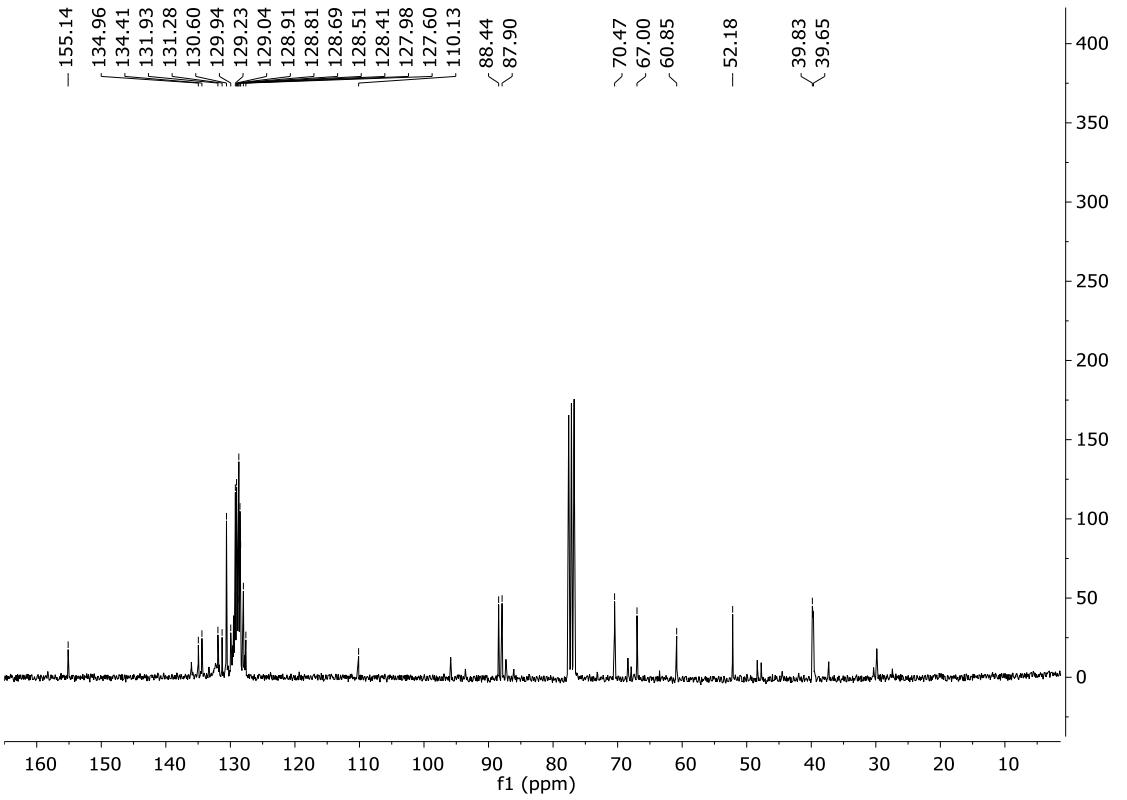

7.43
7.41
7.39
7.36
7.33
7.31
7.30
7.28
7.28
7.24
5.35
5.32
5.30
5.29
5.28
5.25
5.24
4.76
4.67
4.65
4.63
4.58
4.34
4.32
3.97
3.92
3.24
3.20
1.31
Cl
BocHN
NO2
Bn
HO
NO2
Cl
27a major
diastereomer
3.83
4.36
2.84
0.73
0.93
1.07
0.99
2.05
1.04
1.00
1.40
9.45
f1 (ppm)

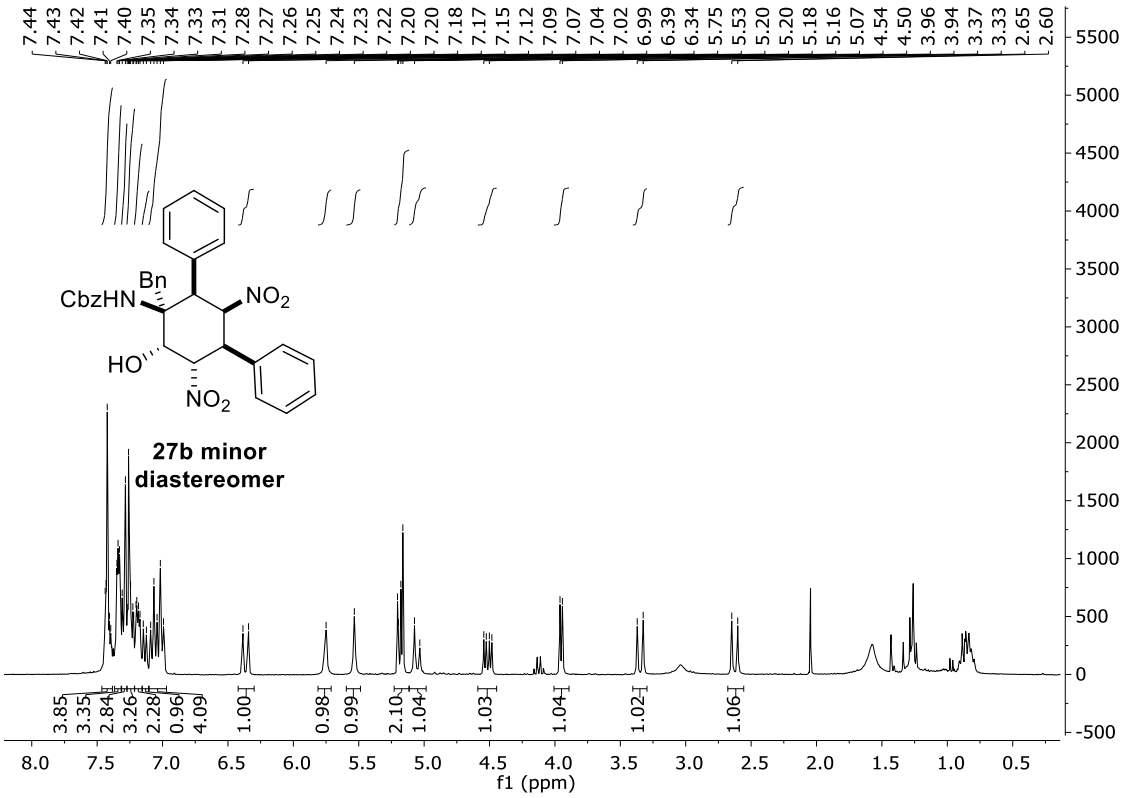

154.64
135.02
134.95
134.61
133.25
130.99
130.57
130.30
129.83
129.55
129.08
128.68
128.05
88.07
87.85
80.62
70.21
60.40
52.65
39.98
39.36
28.32
f1 (ppm)

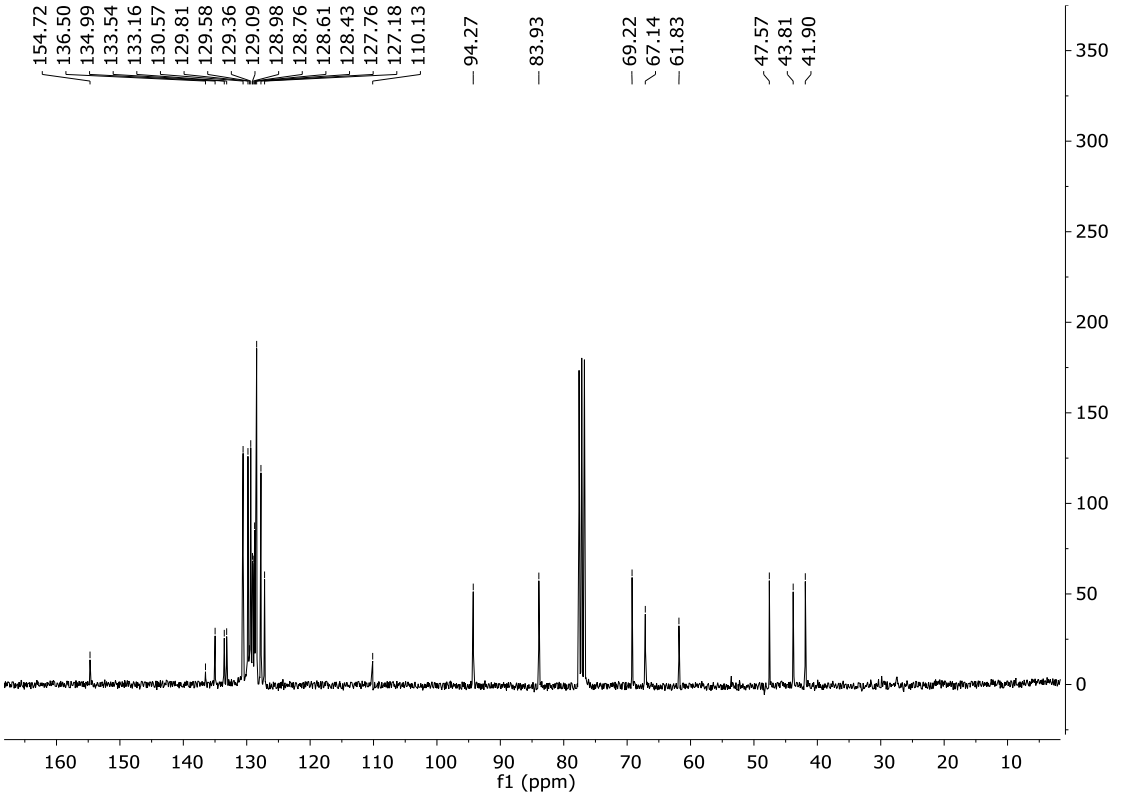

7.31 7.29 7.28 7.28 7.27 7.20 7.19 7.18 7.16 7.15 7.15 7.14 7.13 7.11 7.10 7.08 7.04 7.04 7.02 7.01 6.27 6.26 6.22 6.22 5.58 5.46 5.46 5.11 5.09 5.08 4.50 4.48 4.46 4.44 3.92 3.90 3.41 3.36 3.06 3.05 2.75 2.70 1.51
Cl
BocHN
Bn
HO
NO2
NO2
Cl
27a minor diastereomer
3.67 6.69 1.92 0.91 0.84 0.93 1.00 1.04 0.96 0.96 0.79 0.94 9.09
f1 (ppm)

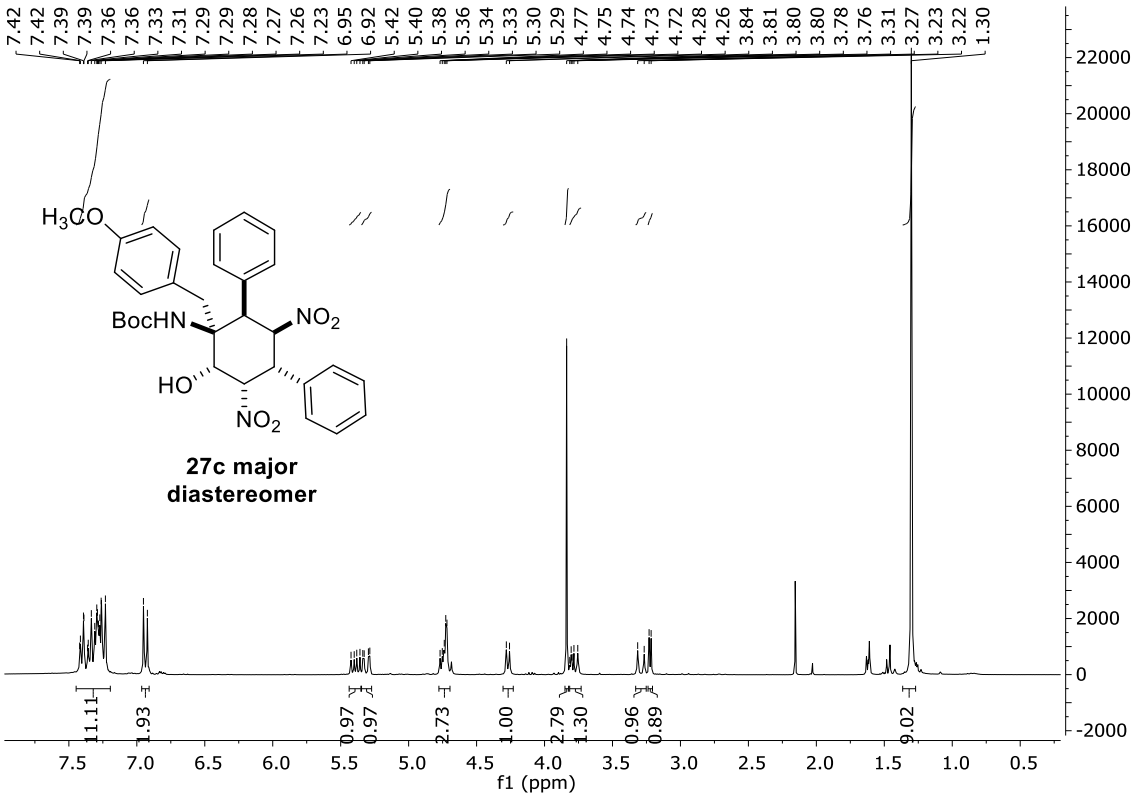

154.31 135.21 135.11 132.19 131.73 130.61 129.75 129.72 129.06 128.96 128.41 127.03 94.33 83.82 69.65 61.68 46.92 43.31 41.15 29.85 28.57
f1 (ppm)

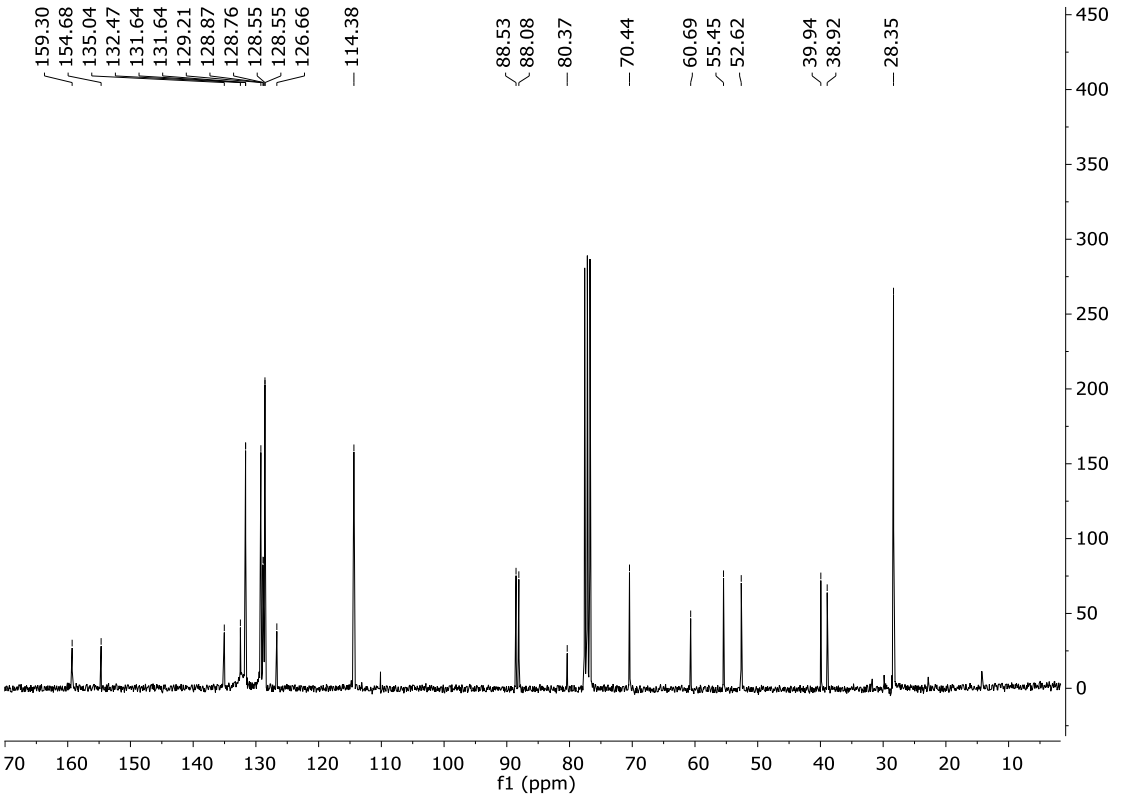

7.42 7.41 7.39 7.39 7.37 7.36 7.35 7.35 7.34 7.33 7.31 7.31 7.30 7.29 7.28 7.22 7.21 7.20 7.19 7.18 5.44 5.41 5.40 5.37 5.33 5.32 5.29 5.28 5.03 4.99 4.89 4.87 4.84 4.83 4.78 4.73 4.69 4.22 4.20 3.70 3.66 3.47 3.42 3.26
Bn
CbzHN
NO2
HO
NO2
27b major diastereomer
2.70 12.51 3.96 1.08 1.14 1.04 1.69 1.29 1.04 1.04 0.94 1.00 1.01
f1 (ppm)

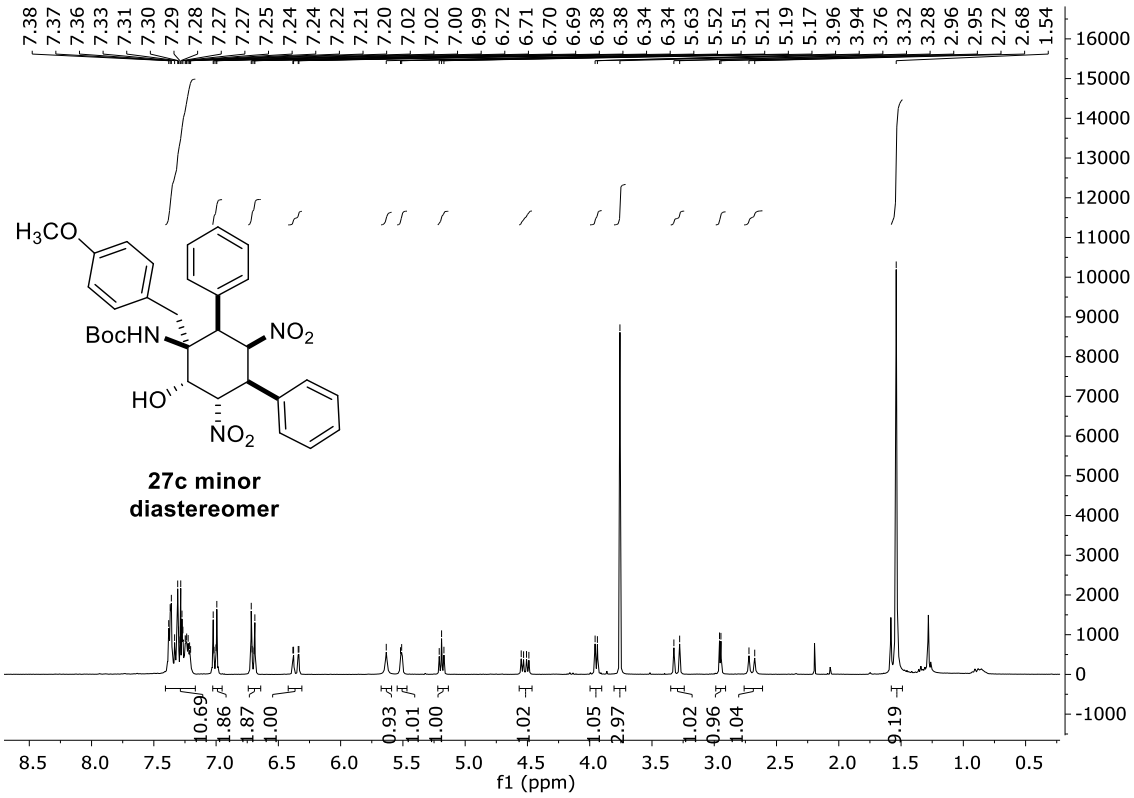

155.14 134.96 134.41 131.93 131.28 130.60 129.94 129.23 129.04 128.91 128.81 128.69 128.51 128.41 127.98 127.60 110.13 88.44 87.90 70.47 67.00 60.85 52.18 39.83 39.65
f1 (ppm)

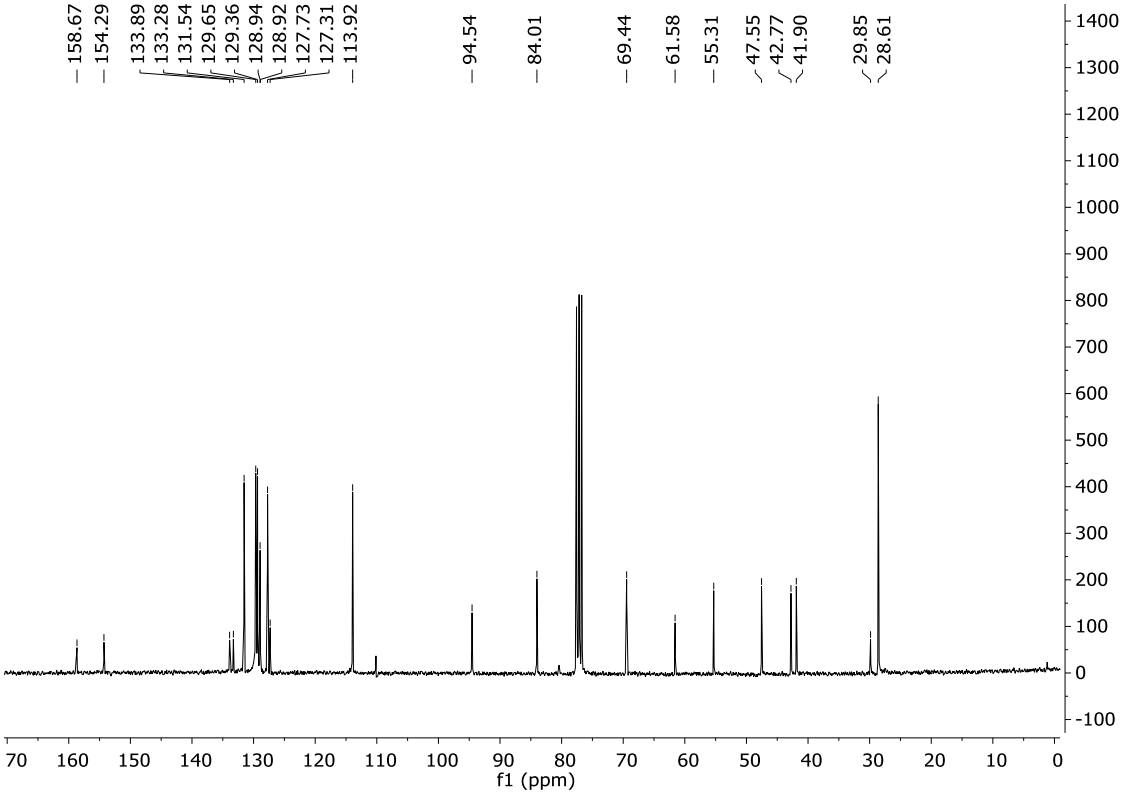

7.44 7.43 7.42 7.41 7.40 7.35 7.34 7.33 7.31 7.28 7.27 7.26 7.25 7.24 7.23 7.22 7.20 7.20 7.18 7.17 7.15 7.12 7.09 7.07 7.04 7.02 6.99 6.39 6.34 5.75 5.53 5.20 5.20 5.18 5.16 5.07 4.54 4.50 3.96 3.94 3.37 3.33 2.65 2.60
Bn
CbzHN
NO2
HO
NO2
27b minor diastereomer
3.85 3.35 2.84 3.26 2.28 0.96 4.09 1.00 0.98 0.99 2.10 1.04 1.03 1.04 1.02 1.06
f1 (ppm)

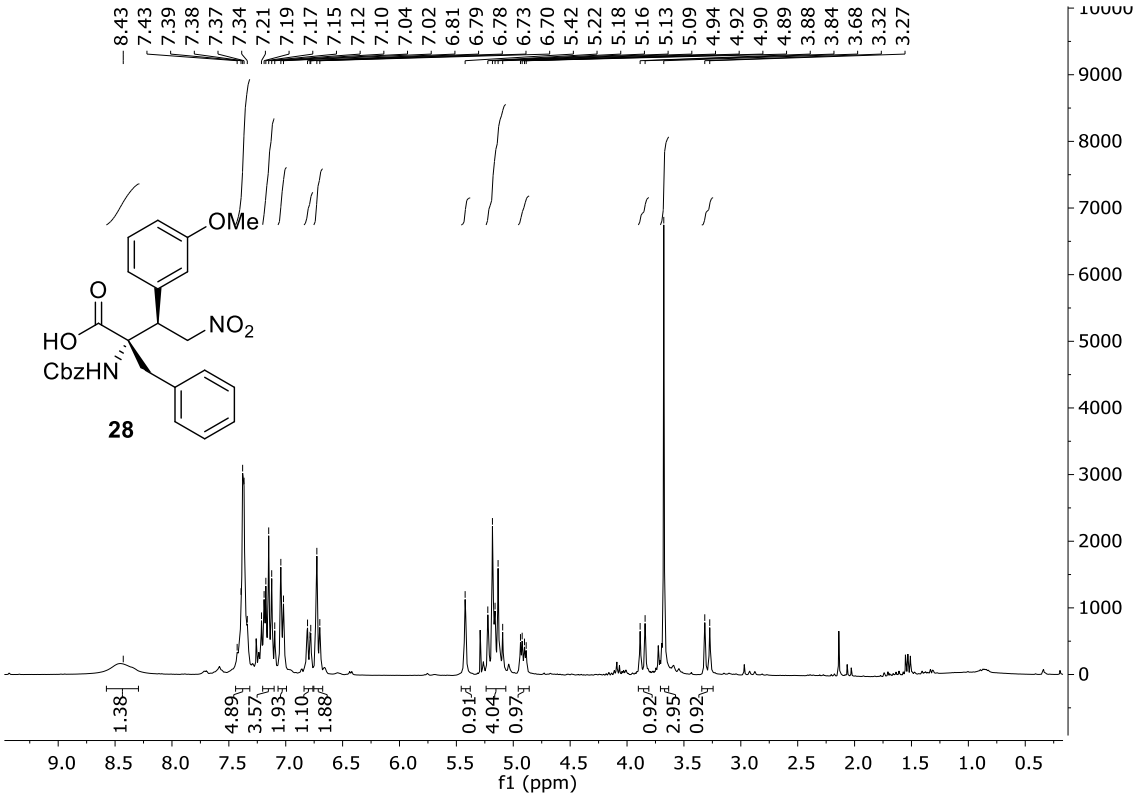

154.72 136.50 134.99 133.54 133.16 130.57 129.81 129.58 129.36 129.09 128.98 128.76 128.61 128.43 127.76 127.18 110.13
94.27
83.93
69.22 67.14 61.83
47.57 43.81 41.90
f1 (ppm)


7.42 7.42 7.39 7.39 7.36 7.36 7.33 7.31 7.29 7.29 7.28 7.27 7.26 7.23 6.95 6.92 5.42 5.40 5.38 5.36 5.34 5.33 5.30 5.29 4.77 4.75 4.74 4.73 4.72 4.28 4.26 3.84 3.81 3.80 3.80 3.78 3.76 3.31 3.27 3.23 3.22 1.30
H3CO
BocHN
NO2
HO
NO2
27c major diastereomer
11.11 1.93 0.97 0.97 2.73 1.00 2.79 1.30 0.96 0.89 9.02
f1 (ppm)


159.30 154.68 135.04 132.47 131.64 131.64 129.21 128.87 128.76 128.55 128.55 126.66 114.38 88.53 88.08 80.37 70.44 60.69 55.45 52.62 39.94 38.92 28.35
f1 (ppm)


7.38 7.37 7.36 7.33 7.31 7.30 7.29 7.28 7.27 7.27 7.25 7.24 7.24 7.22 7.21 7.20 7.02 7.02 7.00 6.99 6.72 6.71 6.70 6.69 6.38 6.38 6.34 6.34 5.63 5.52 5.51 5.21 5.19 5.17 3.96 3.94 3.76 3.32 3.28 2.96 2.95 2.72 2.68 1.54
H3CO
BocHN
NO2
HO
NO2
27c minor diastereomer
10.69 1.86 1.87 1.00 0.93 1.01 1.00 1.02 1.05 2.97 1.02 0.96 1.04 9.19
f1 (ppm)


158.67 154.29 133.89 133.28 131.54 129.65 129.36 128.94 128.92 127.73 127.31 113.92 94.54 84.01 69.44 61.58 55.31 47.55 42.77 41.90 29.85 28.61
f1 (ppm)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7.43
7.39
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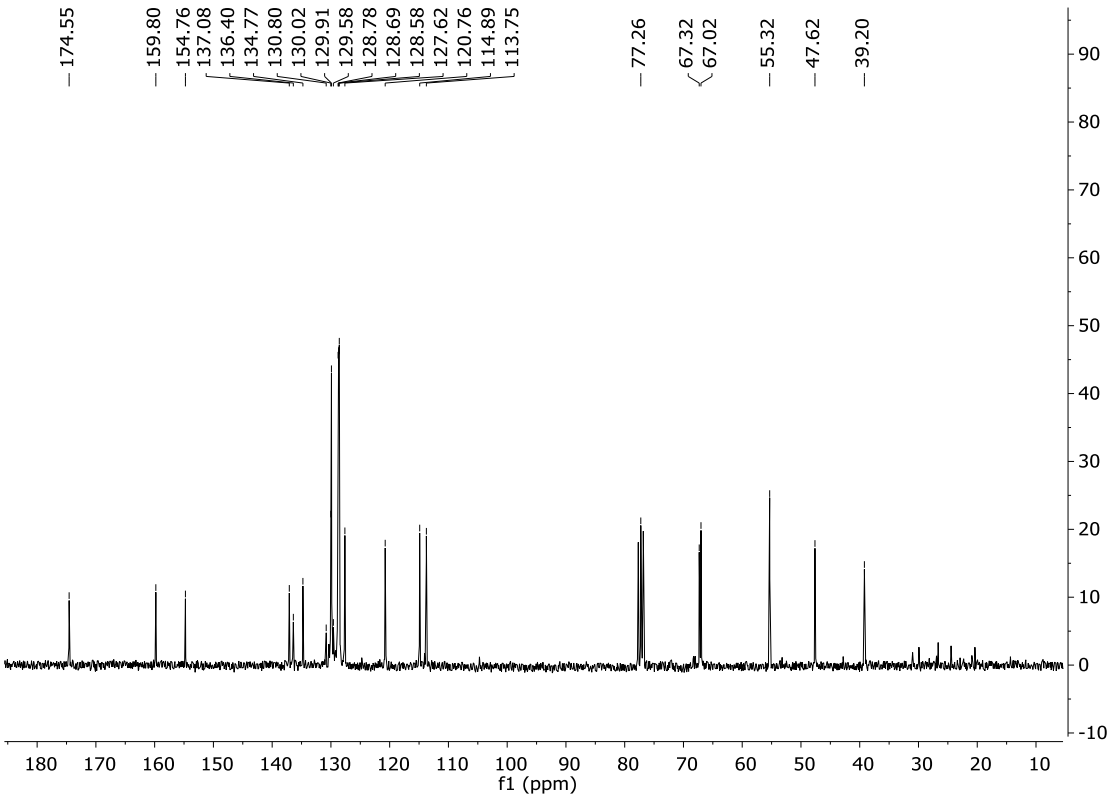
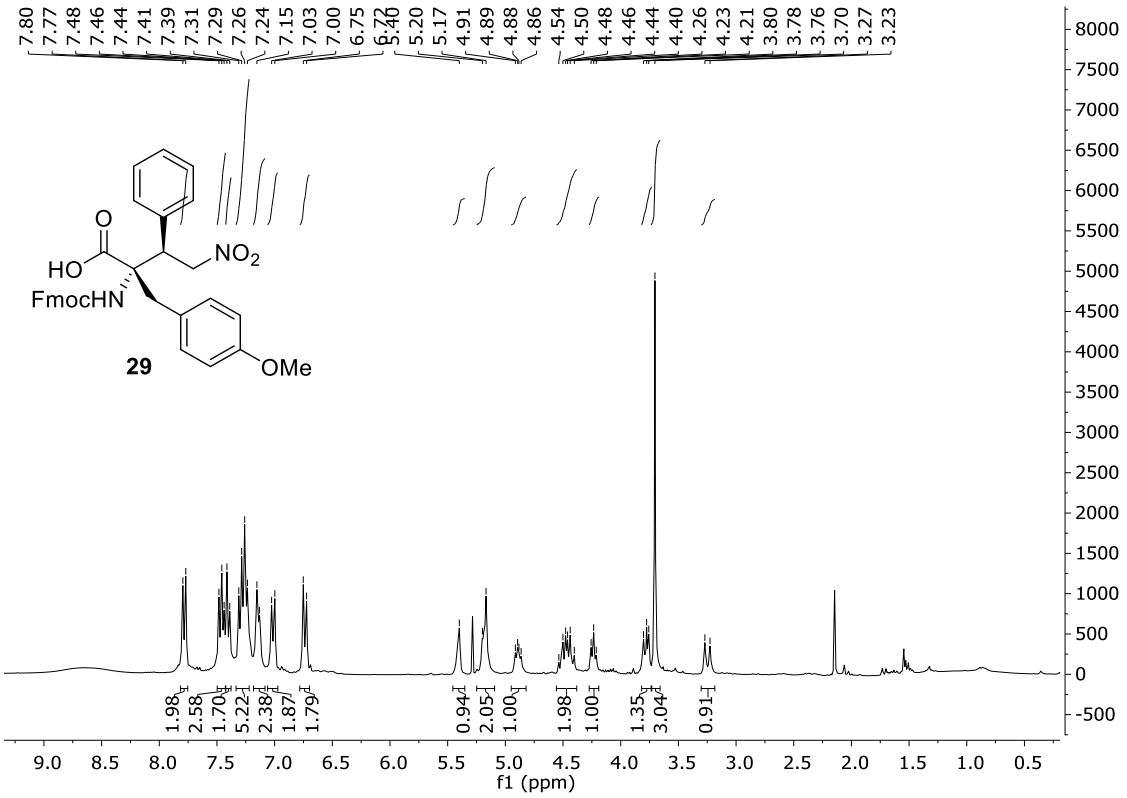
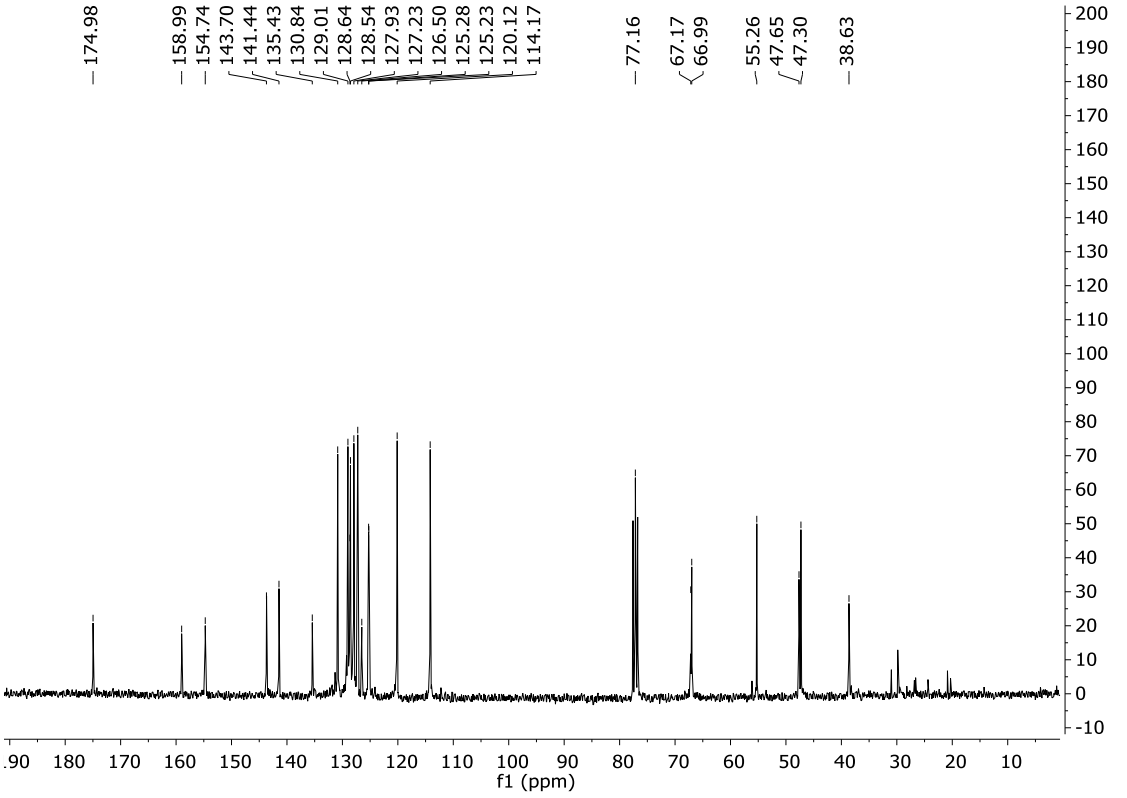
7.37
7.34
7.21
7.19
7.17
7.15
7.12
7.10
7.04
7.02
6.81
6.79
6.78
6.73
6.70
5.42
5.22
5.18
5.16
5.13
5.09
4.94
4.92
4.90
4.89
3.88
3.84
3.68
3.32
3.27
OMe
O
HO
CbzHN
NO2
28
1.38
4.89
3.57
1.93
1.10
1.88
0.91
4.04
0.97
0.92
2.95
0.92
f1 (ppm)


174.55
159.80
154.76
137.08
136.40
134.77
130.80
130.02
129.91
129.58
128.78
128.69
128.58
127.62
120.76
114.89
113.75
77.26
67.32
67.02
55.32
47.62
39.20
f1 (ppm)


7.80
7.77
7.48
7.46
7.44
7.41
7.39
7.31
7.29
7.26
7.24
7.15
7.03
7.00
6.75
5.20
5.17
4.91
4.89
4.88
4.86
4.54
4.50
4.48
4.46
4.44
4.40
4.26
4.23
4.21
3.80
3.78
3.76
3.70
3.27
3.23
O
HO
FmocHN
NO2
OMe
29
1.98
2.58
1.70
5.22
2.38
1.87
1.79
0.94
2.05
1.00
1.98
1.00
1.35
3.04
0.91
f1 (ppm)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154.74
143.70
141.44
135.43
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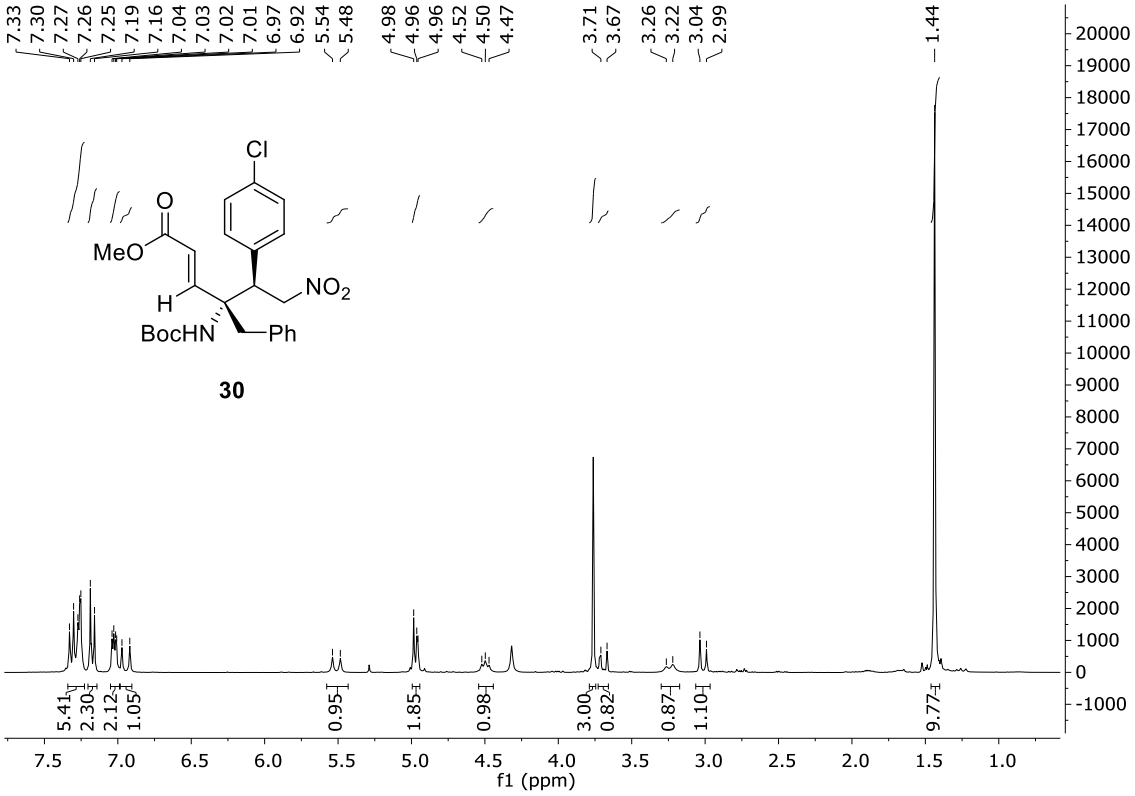
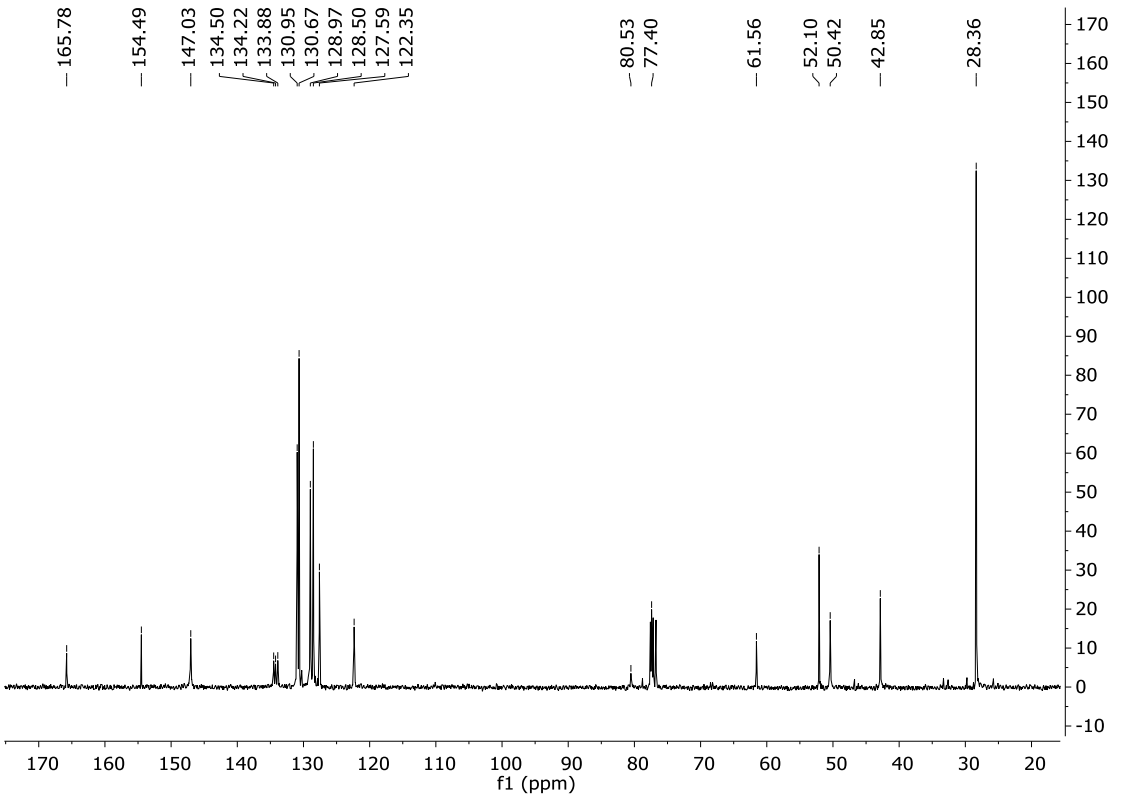
129.01
128.64
128.54
127.93
127.23
126.50
125.28
125.23
120.12
114.17
77.16
67.17
66.99
55.26
47.65
47.30
38.63
f1 (ppm)


7.33
7.30
7.27
7.26
7.25
7.19
7.16
7.04
7.03
7.02
7.01
6.97
6.92
5.54
5.48
4.98
4.96
4.96
4.52
4.50
4.47
3.71
3.67
3.26
3.22
3.04
2.99
1.44
Cl
O
MeO
H
BocHN
NO2
Ph
30
5.41
2.30
2.12
1.05
0.95
1.85
0.98
3.00
0.82
0.87
1.10
9.77
f1 (ppm)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154.49
147.03
134.50
134.22
133.88
130.95
130.67
128.97
128.50
127.59
122.35
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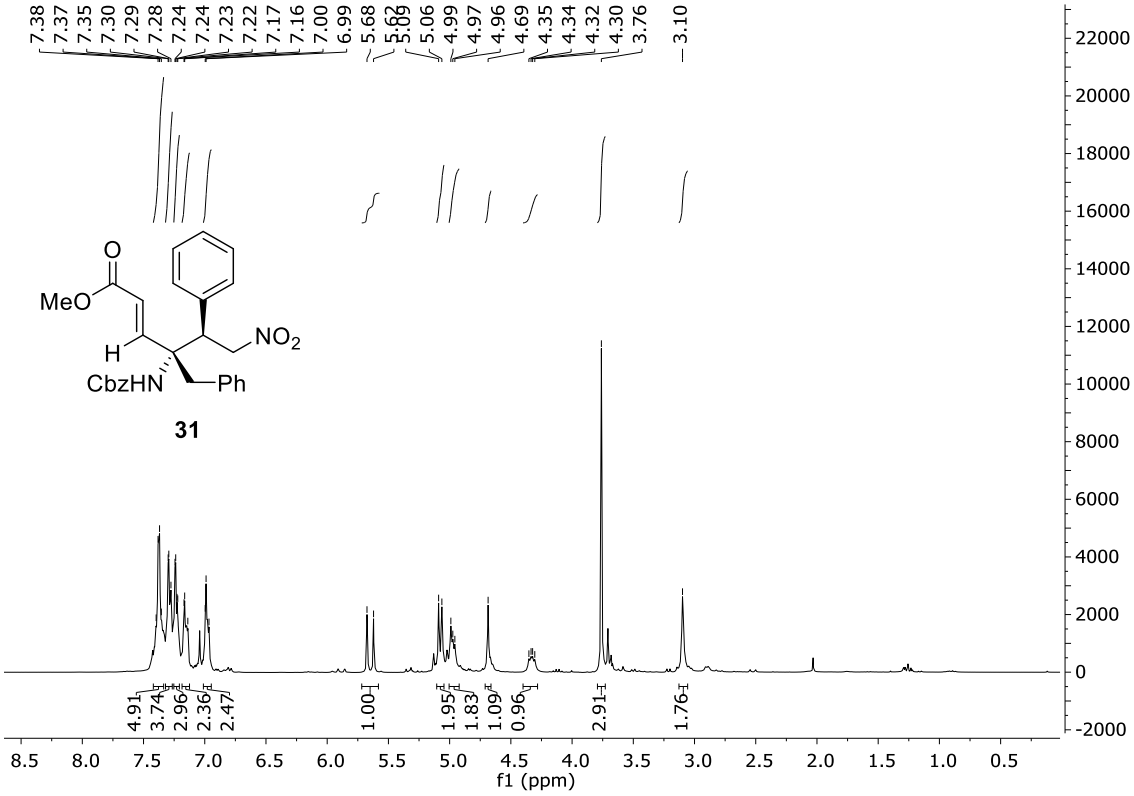
52.10
50.42
42.85
28.36
f1 (ppm)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7.29
7.28
7.24
7.24
7.23
7.22
7.17
7.16
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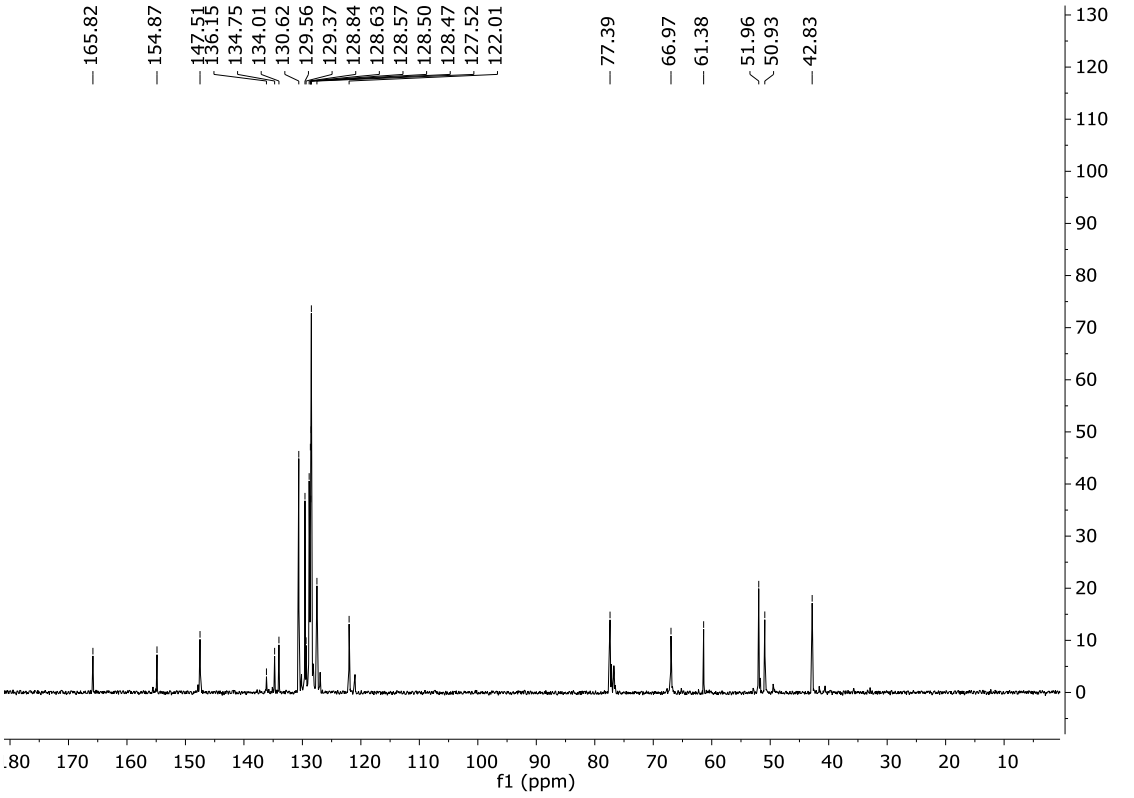
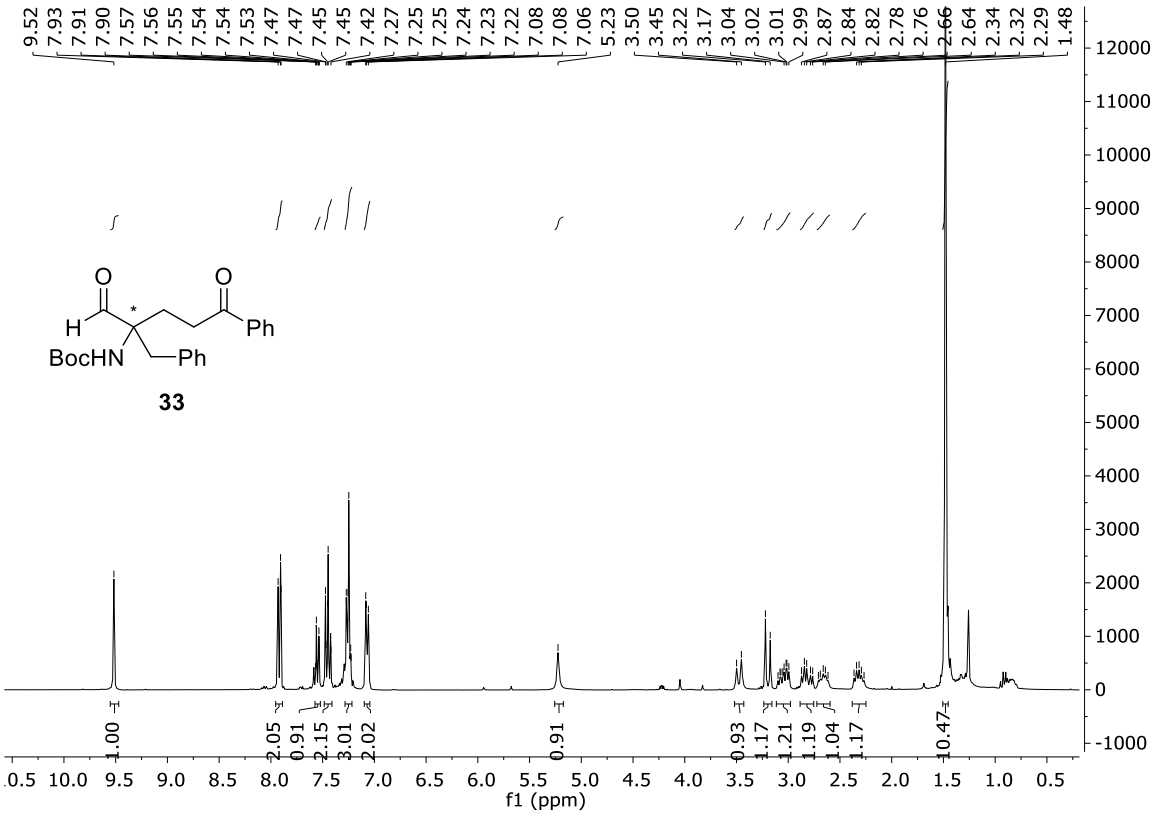
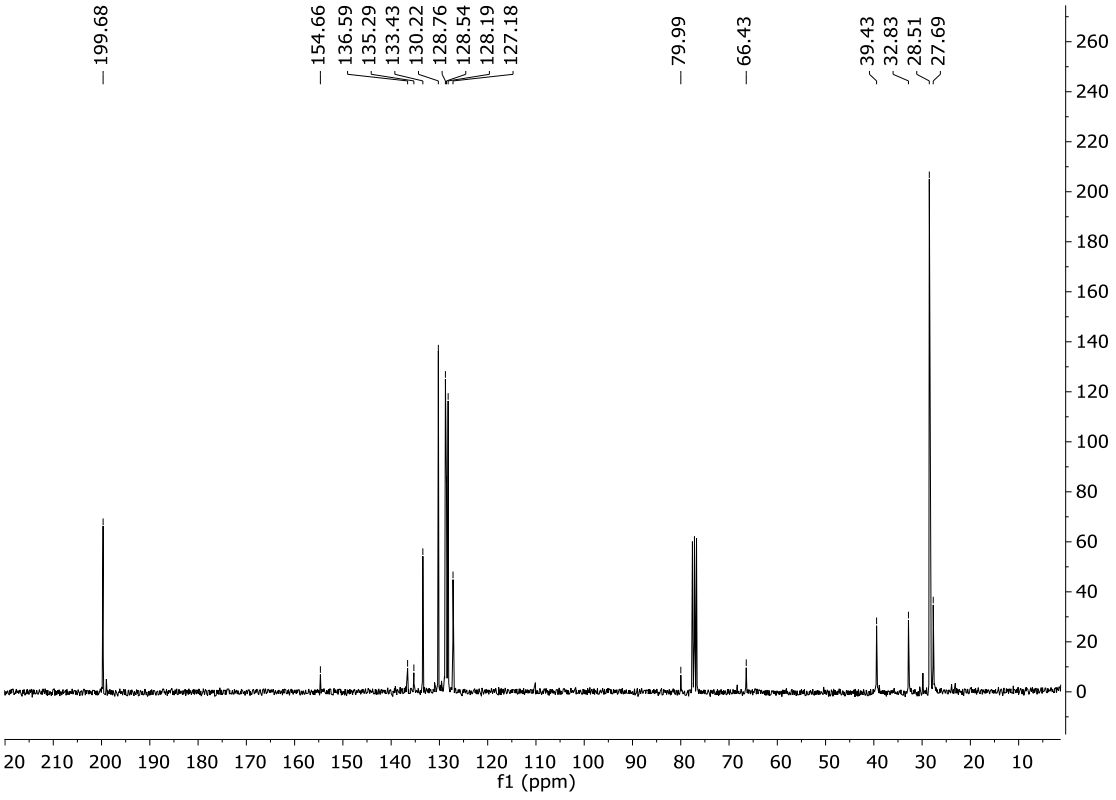
6.99
5.68
5.62
5.09
5.06
4.99
4.97
4.96
4.69
4.35
4.34
4.32
4.30
3.76
3.10
MeO
O
H
CbzHN
NO2
Ph
31
4.91
3.74
2.96
2.36
2.47
1.00
1.95
1.83
1.09
0.96
2.91
1.76
f1 (ppm)


165.82
154.87
147.51
136.15
134.75
134.01
130.62
129.56
129.37
128.84
128.63
128.57
128.50
128.47
127.52
122.01
77.39
66.97
61.38
51.96
50.93
42.83
f1 (ppm)

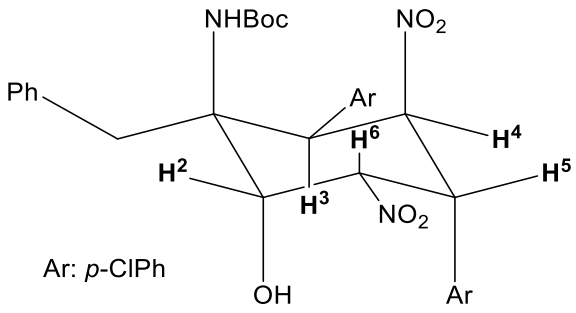

9.52 7.93 7.91 7.90 7.57 7.56 7.55 7.54 7.54 7.53 7.47 7.47 7.45 7.45 7.42 7.27 7.25 7.25 7.24 7.23 7.22 7.08 7.08 7.06 5.23 3.50 3.45 3.22 3.17 3.04 3.02 3.01 2.99 2.87 2.84 2.82 2.78 2.76 2.66 2.64 2.34 2.32 2.29 1.48
1.00 2.05 0.91 2.15 3.01 2.02 0.91 0.93 1.17 1.21 1.19 1.04 1.17 10.47
f1 (ppm)

O
O
H
*
Ph
BocHN
Ph

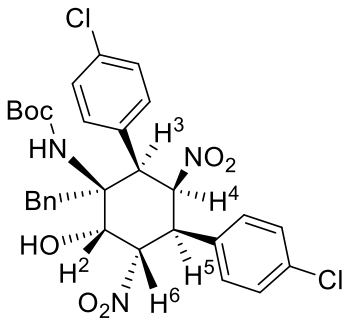
33


199.68 154.66 136.59 135.29 133.43 130.22 128.76 128.54 128.19 127.18 79.99 66.43 39.43 32.83 28.51 27.69
f1 (ppm)

*5.5.2.1. COSY, HSQC, HMBC and NOE experiments for compound **27***

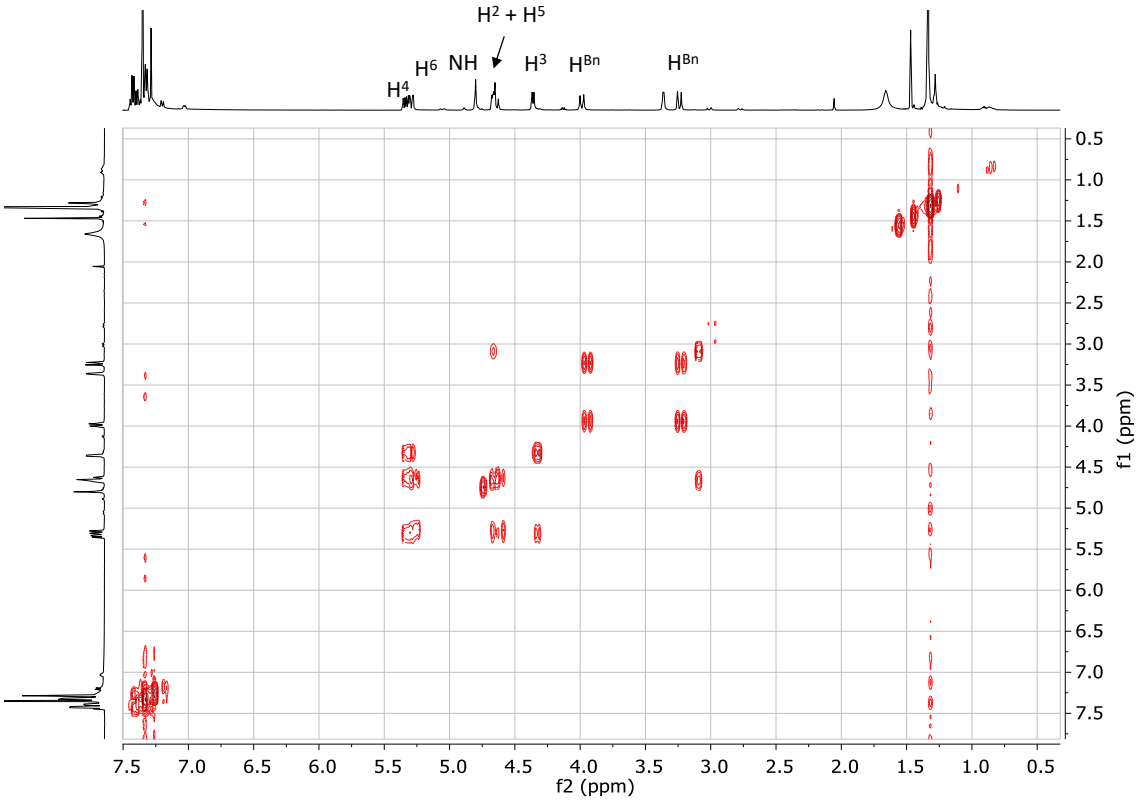


16a major

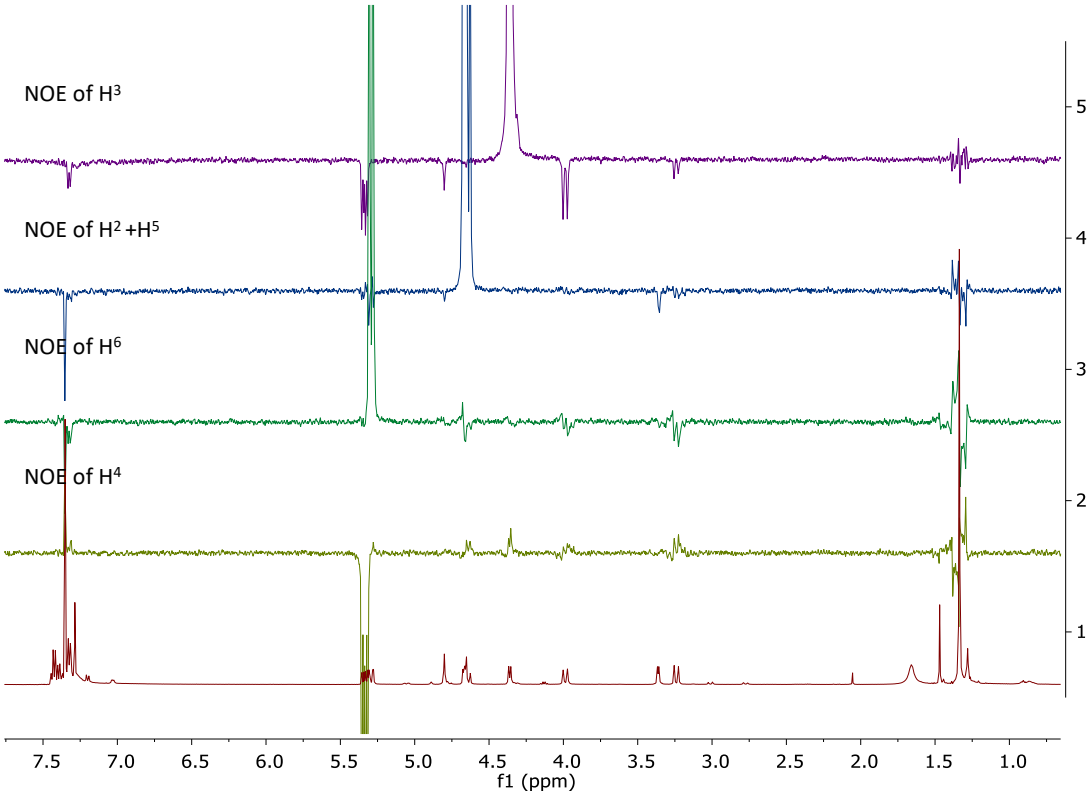


16a major

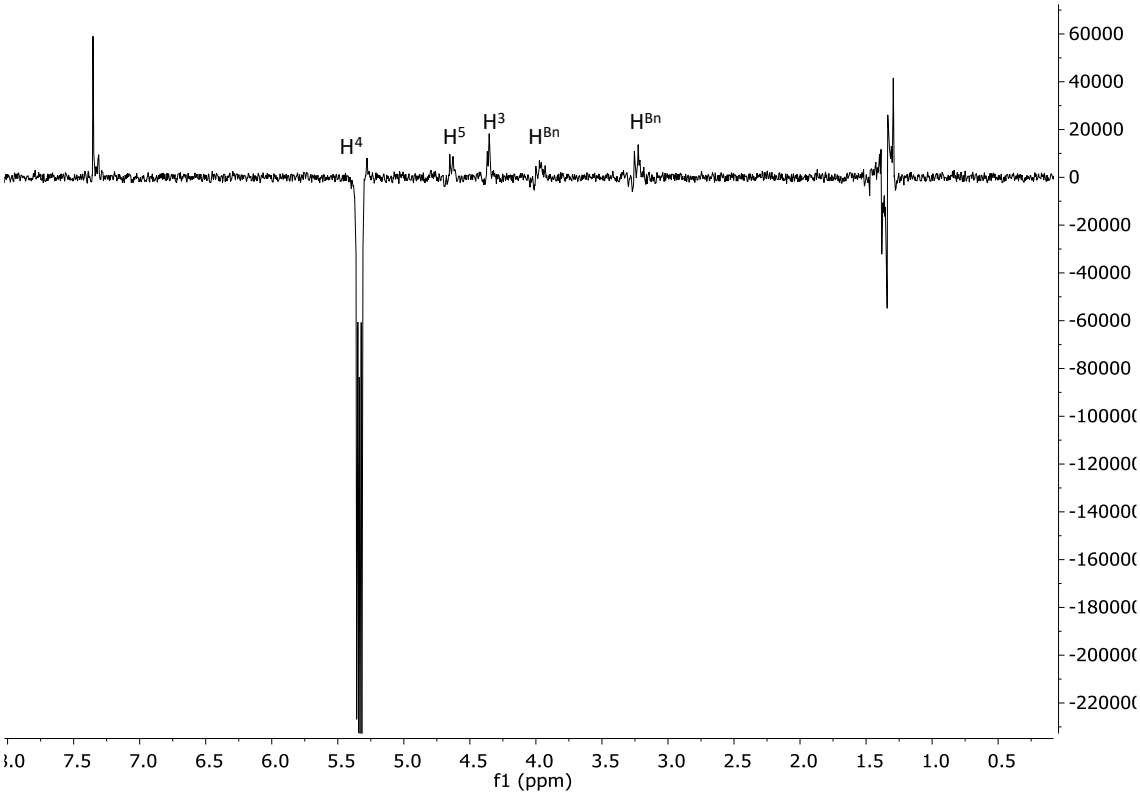
COSY of 16a major



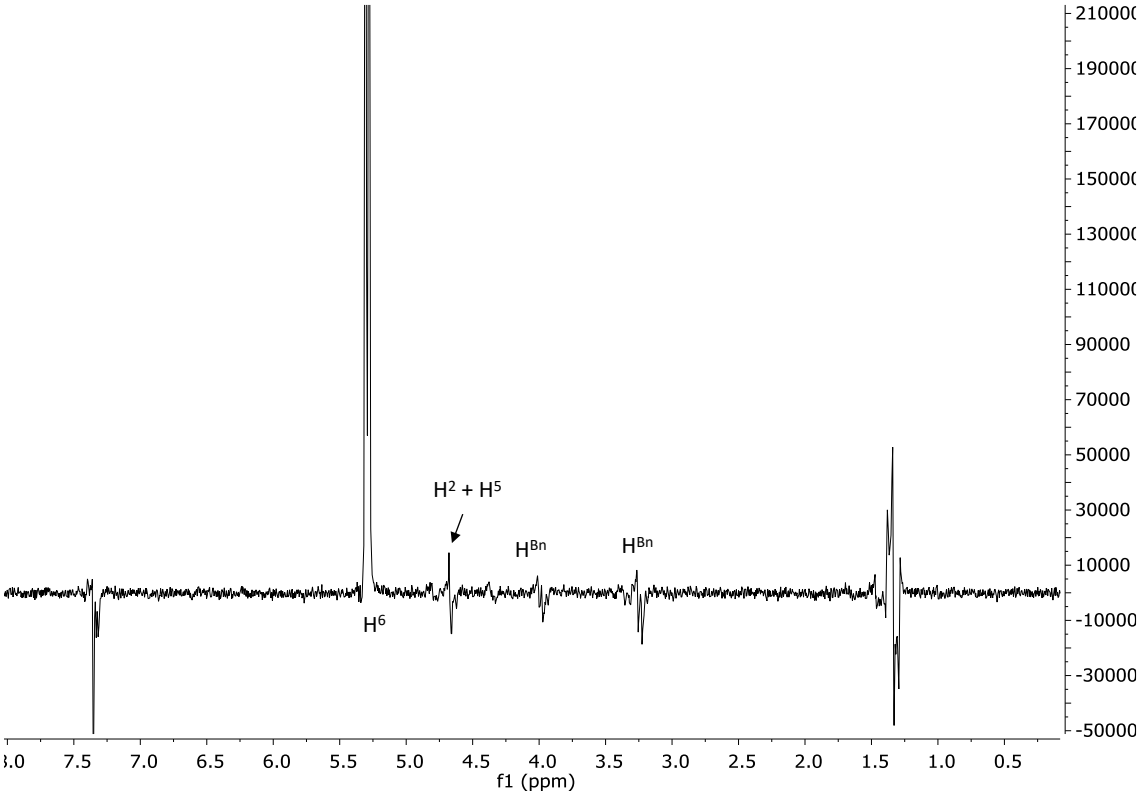
NOE of 16a major



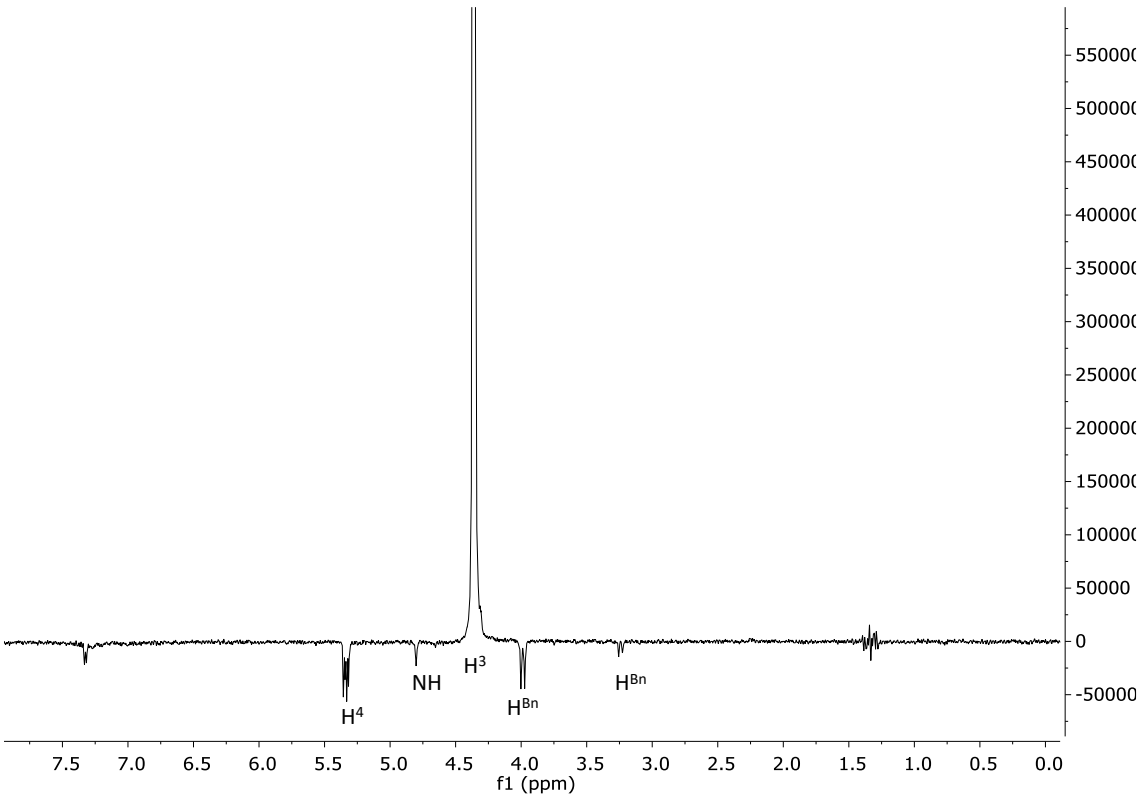
NOE of H^4: H^5, H^3 and H^{Bn} can be seen.

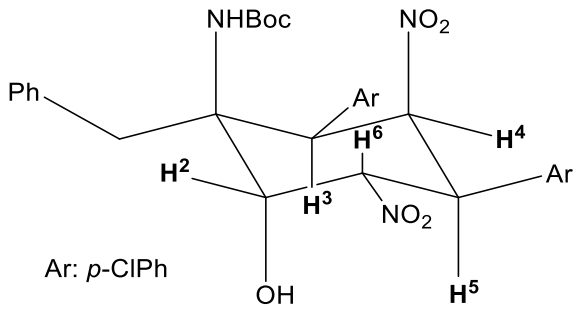


NOE of H^6: H^2, H^5 and H^{Bn} can be seen.

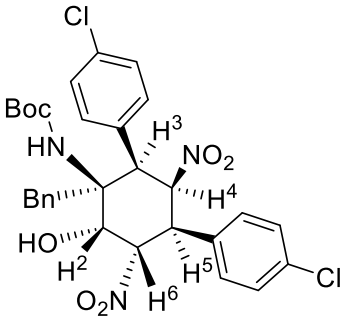


NOE of H^3: H^4, NH and H^{Bn} can be seen.



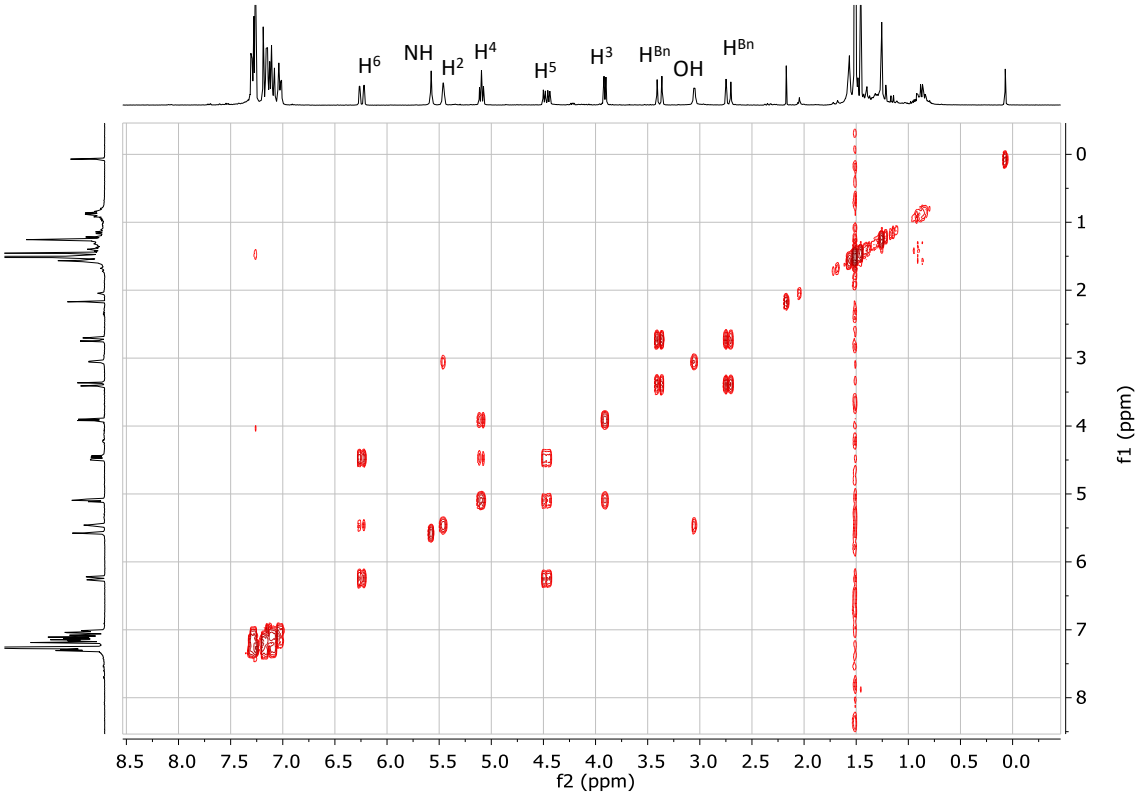


16a minor

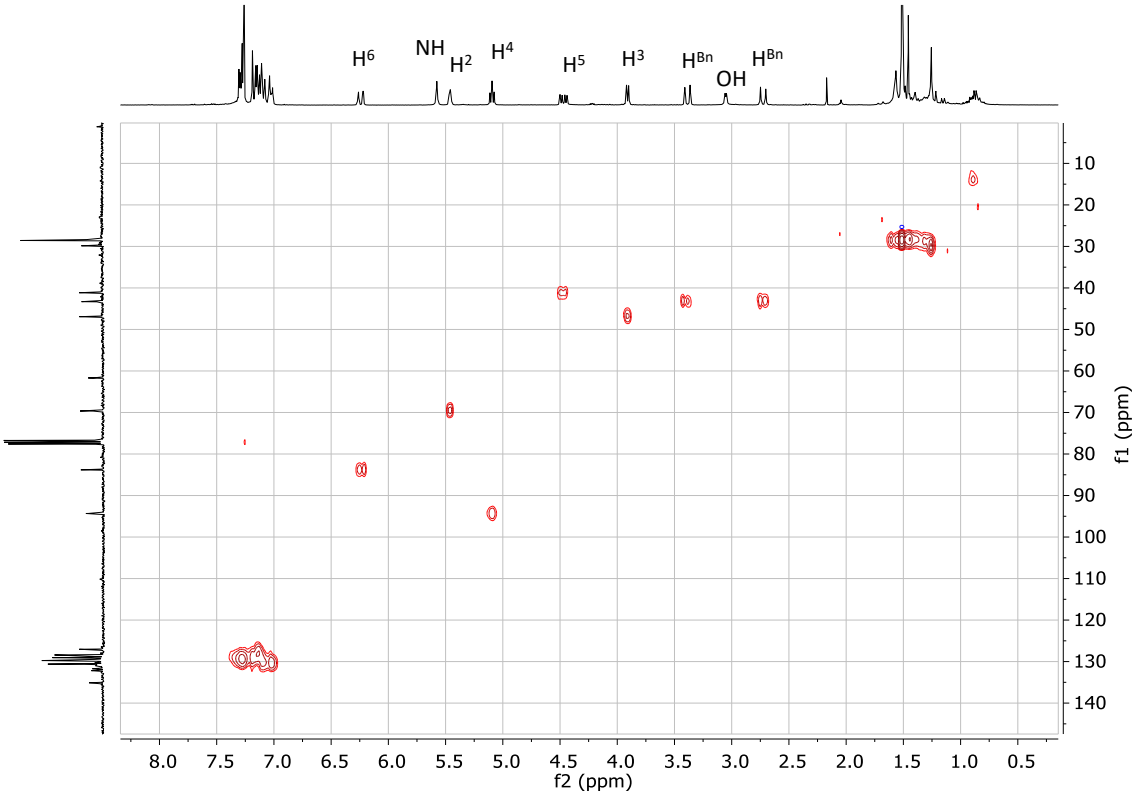


16a minor

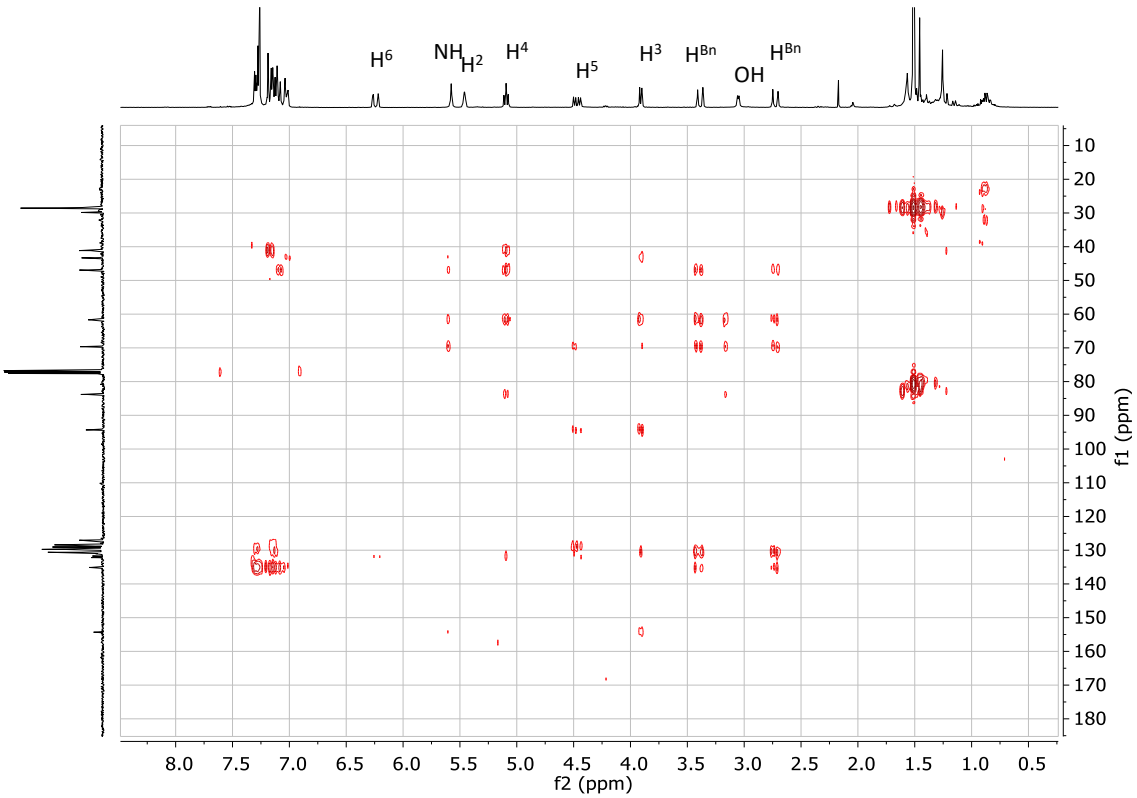
COSY of 16a minor



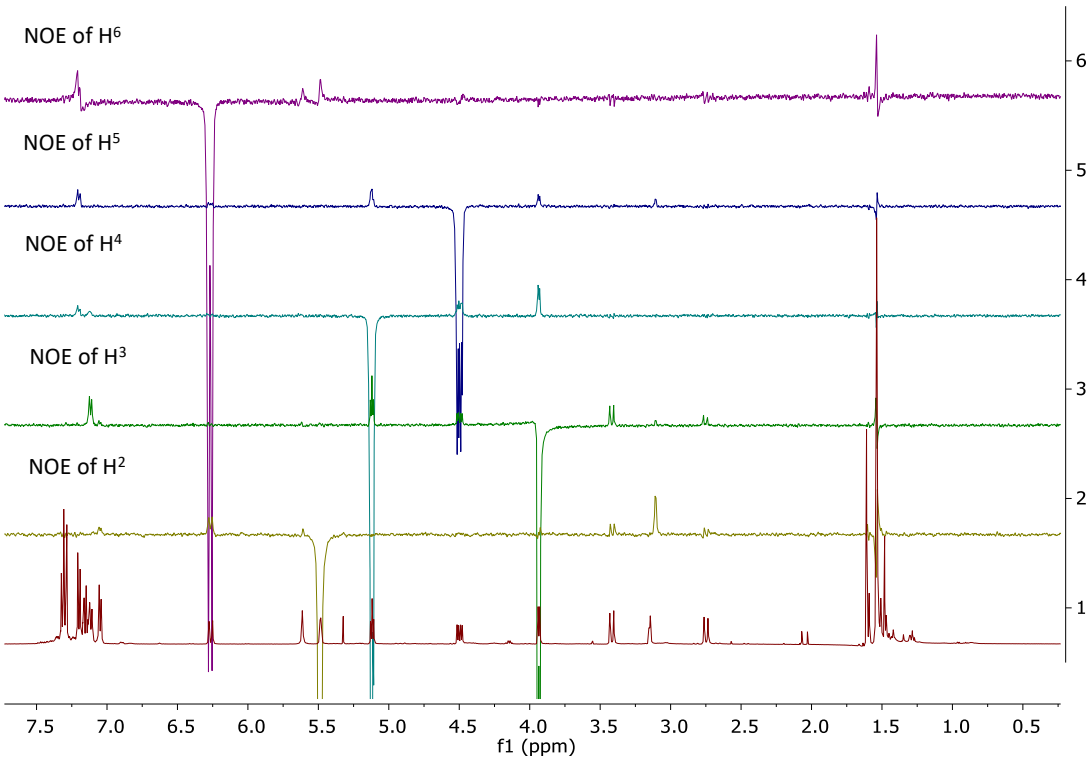
HSQC of 16a minor



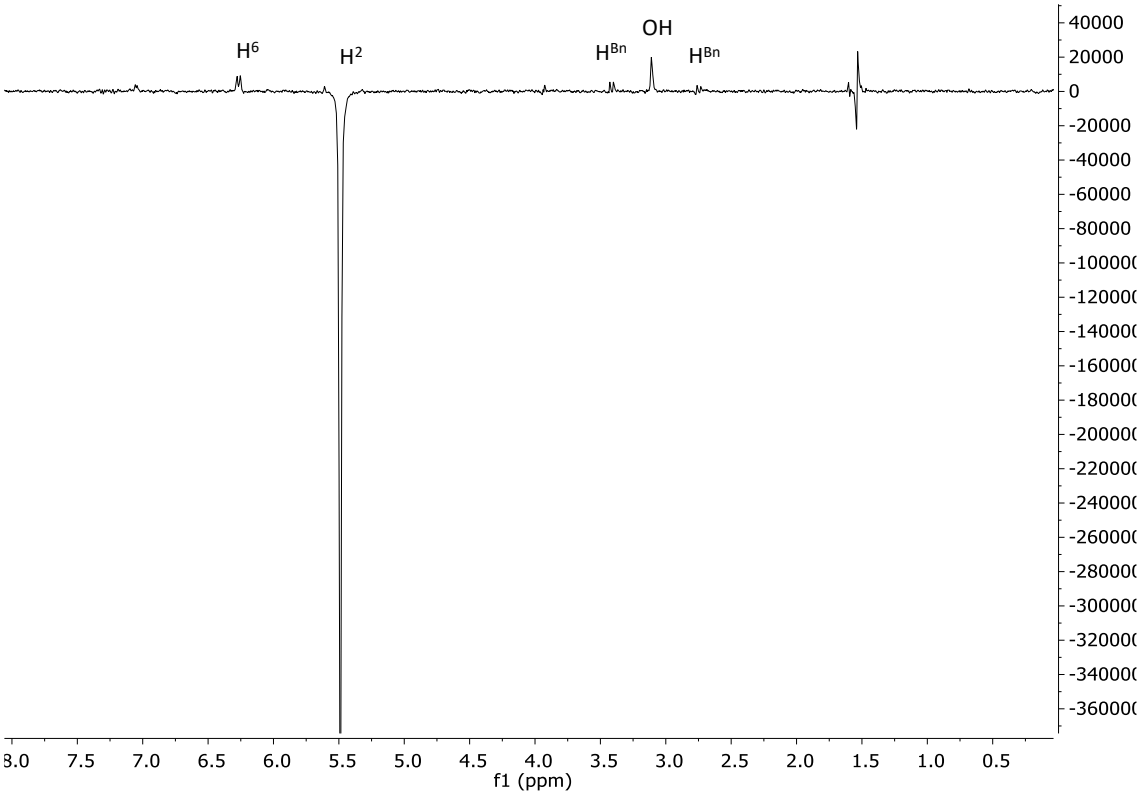
HMBC of 16a minor



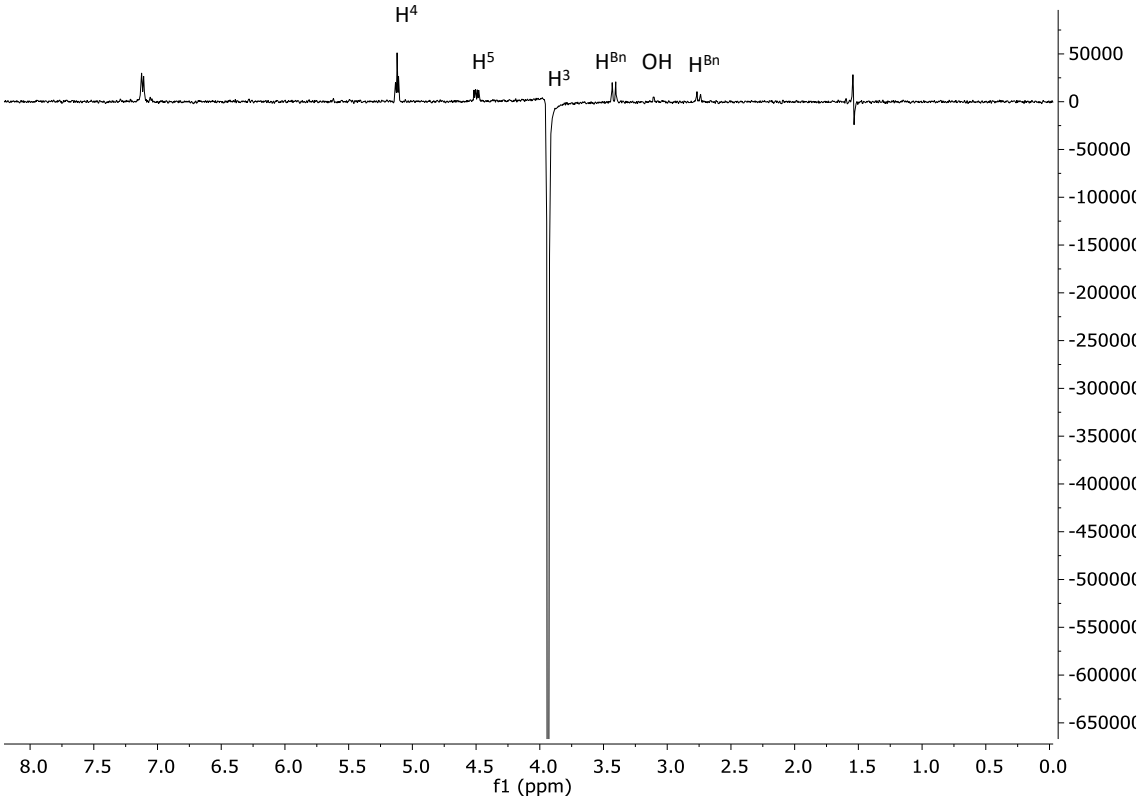
NOE of 16a minor



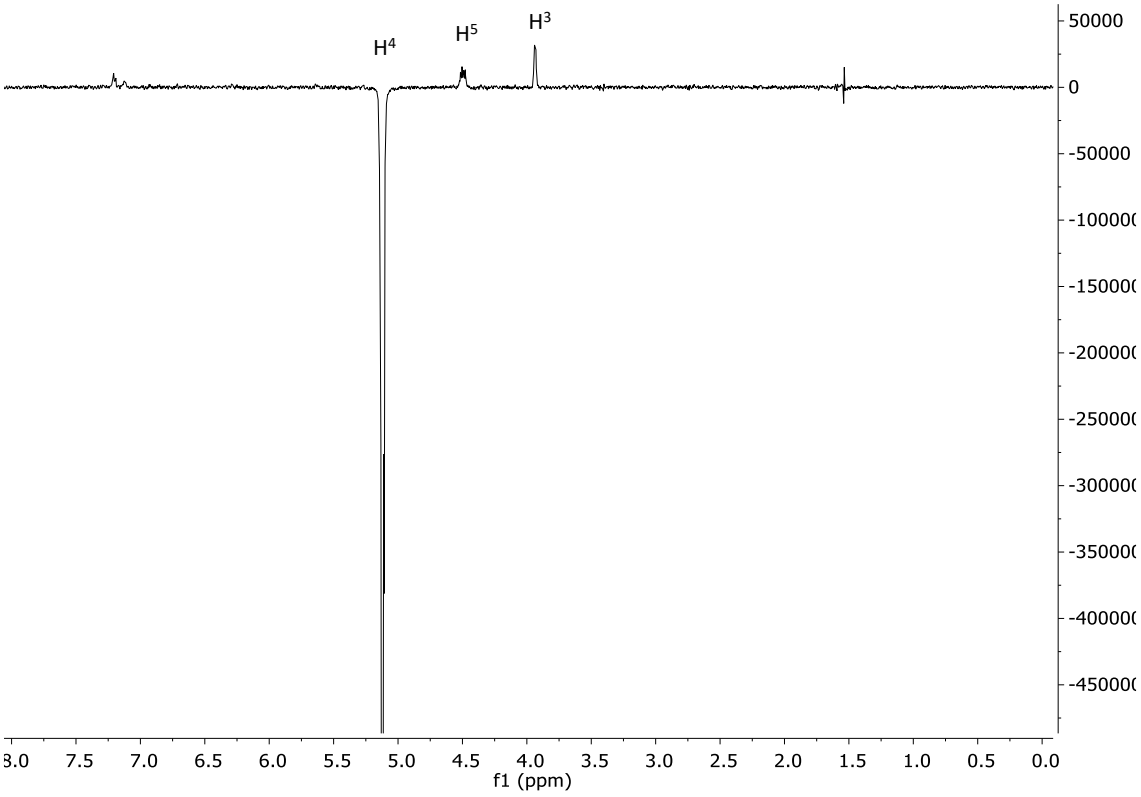
NOE of H^2: H^6, H^{Bn} and OH can be seen.



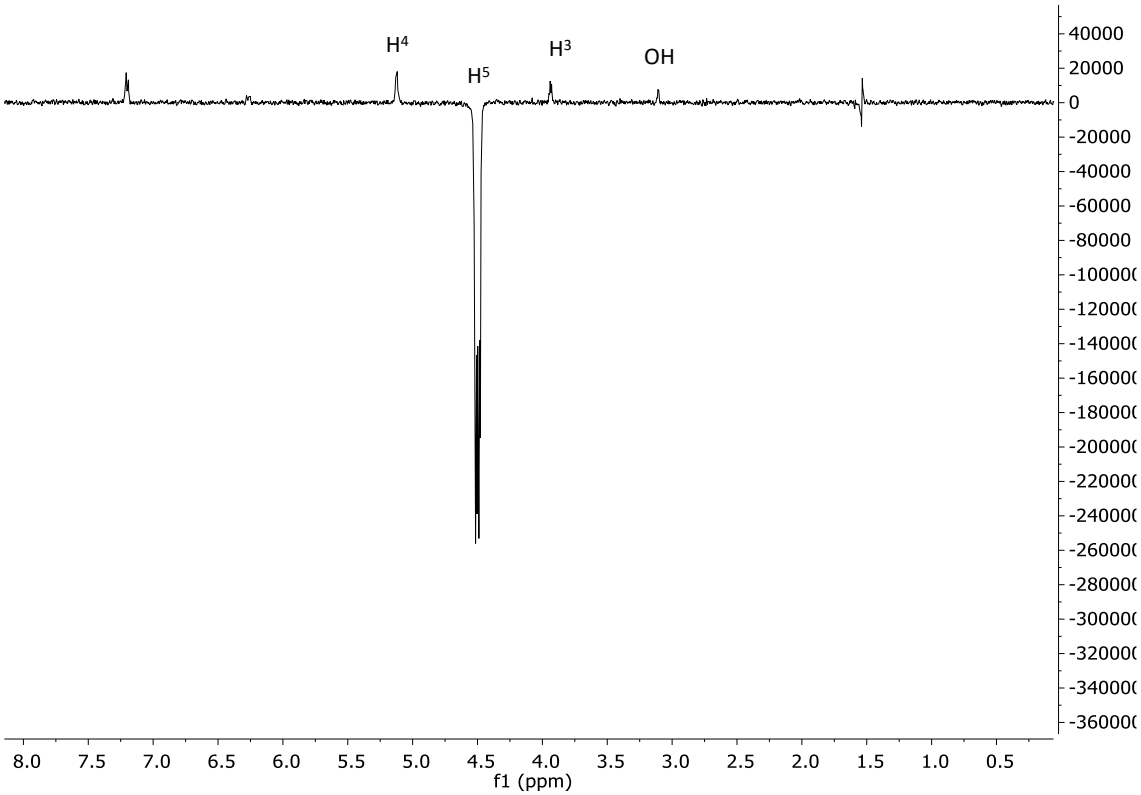
NOE of H^3: H^4, H^5, H^{Bn} and OH can be seen.



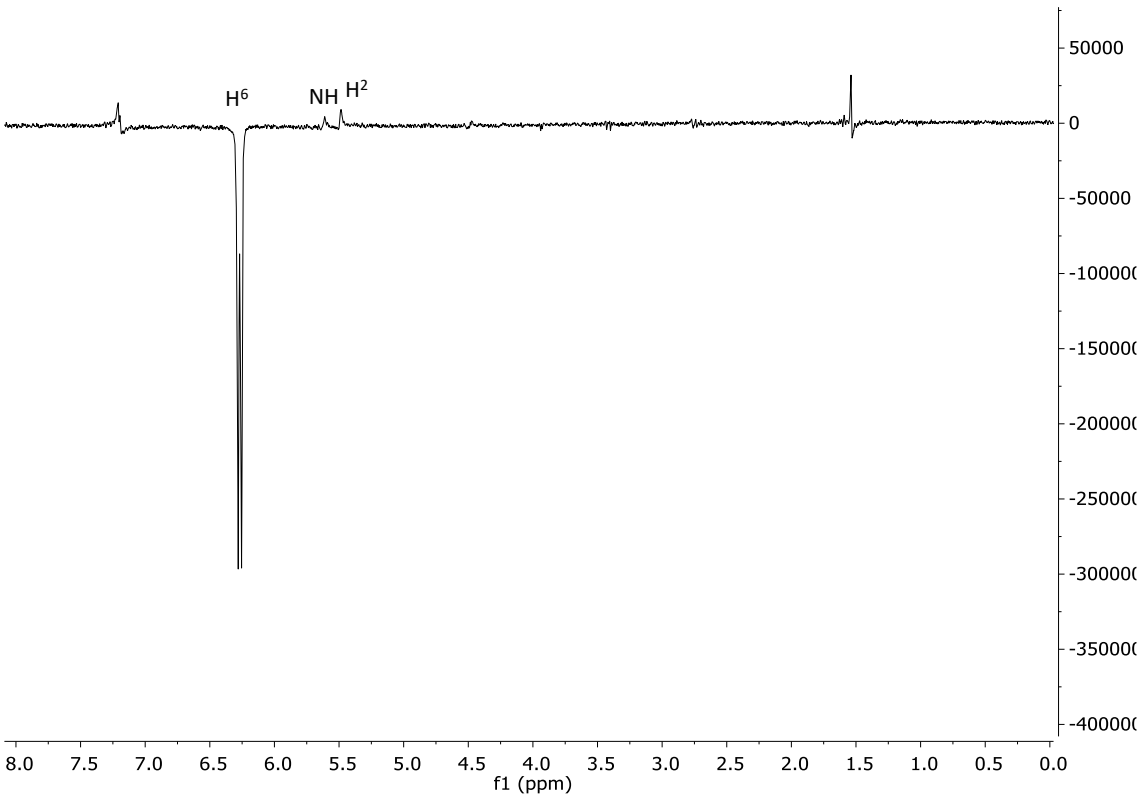
NOE of H^4: H^5 and H^3 can be seen.

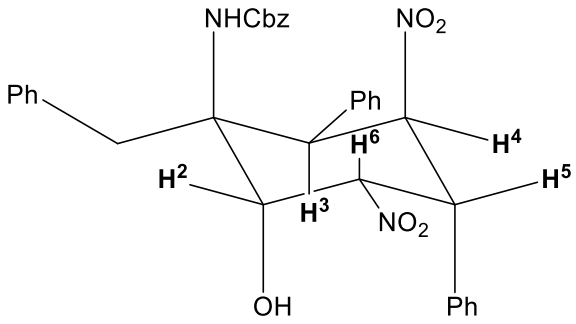


NOE of H^5: H^4, H^3 and OH can be seen.

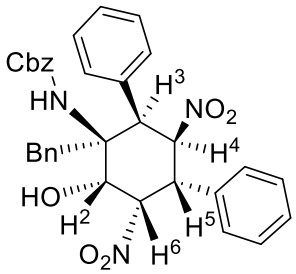


NOE of H^6: H^2 and NH can be seen.



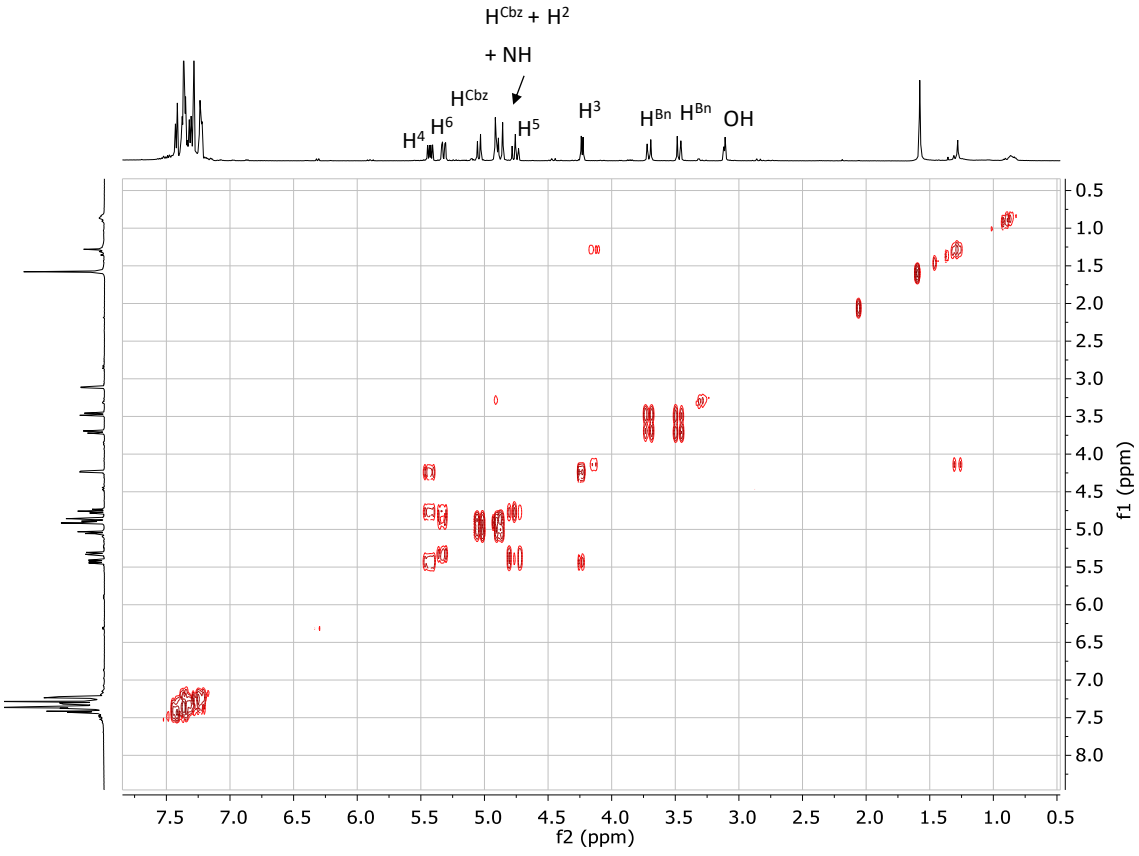


16b major

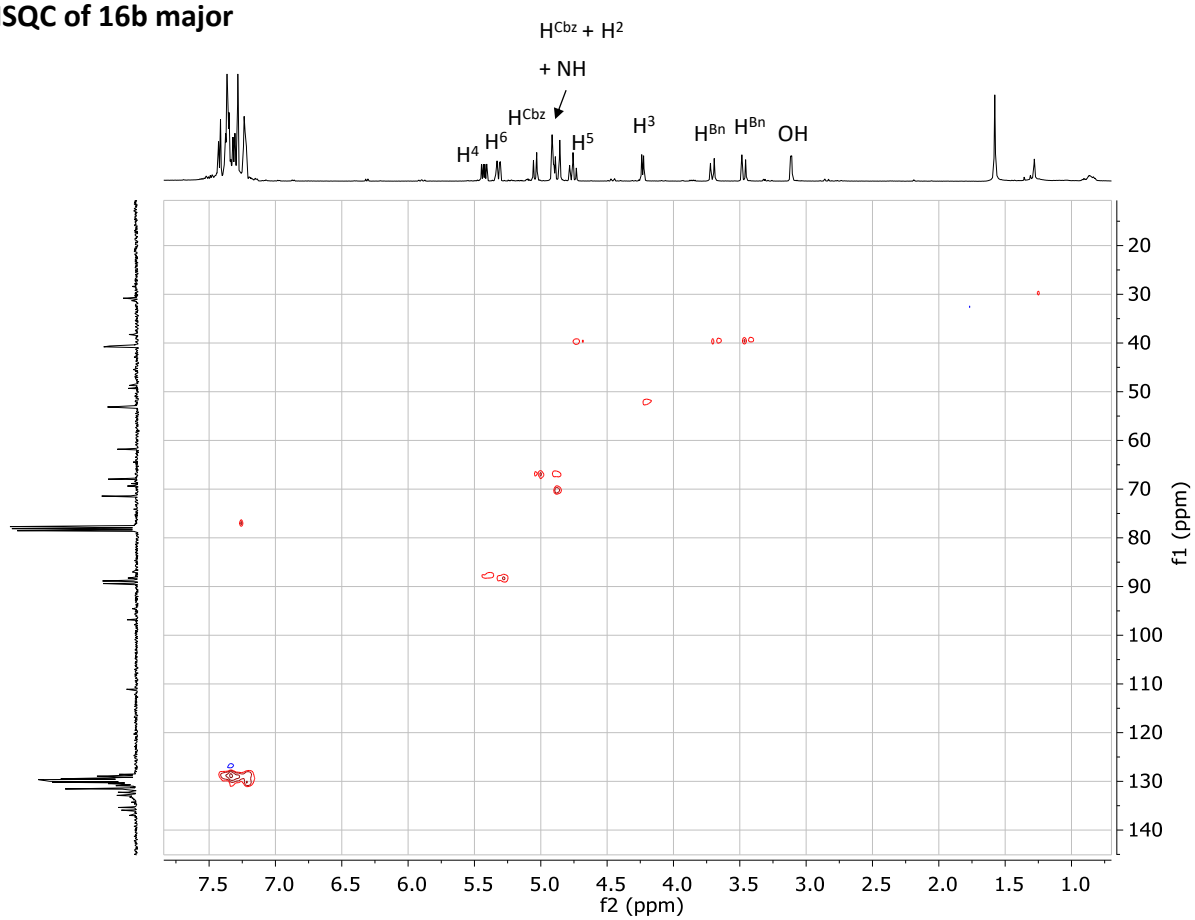


16b major

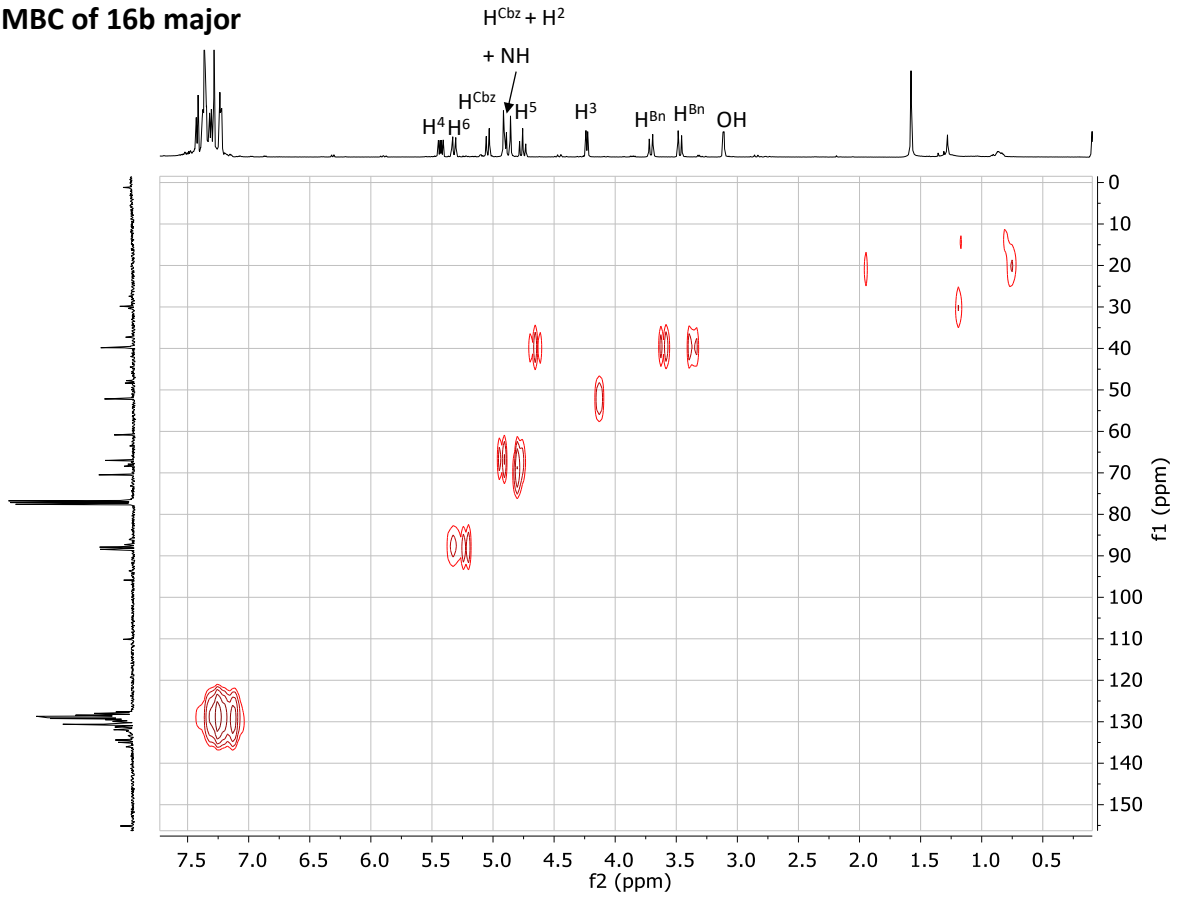
COSY of 16b major



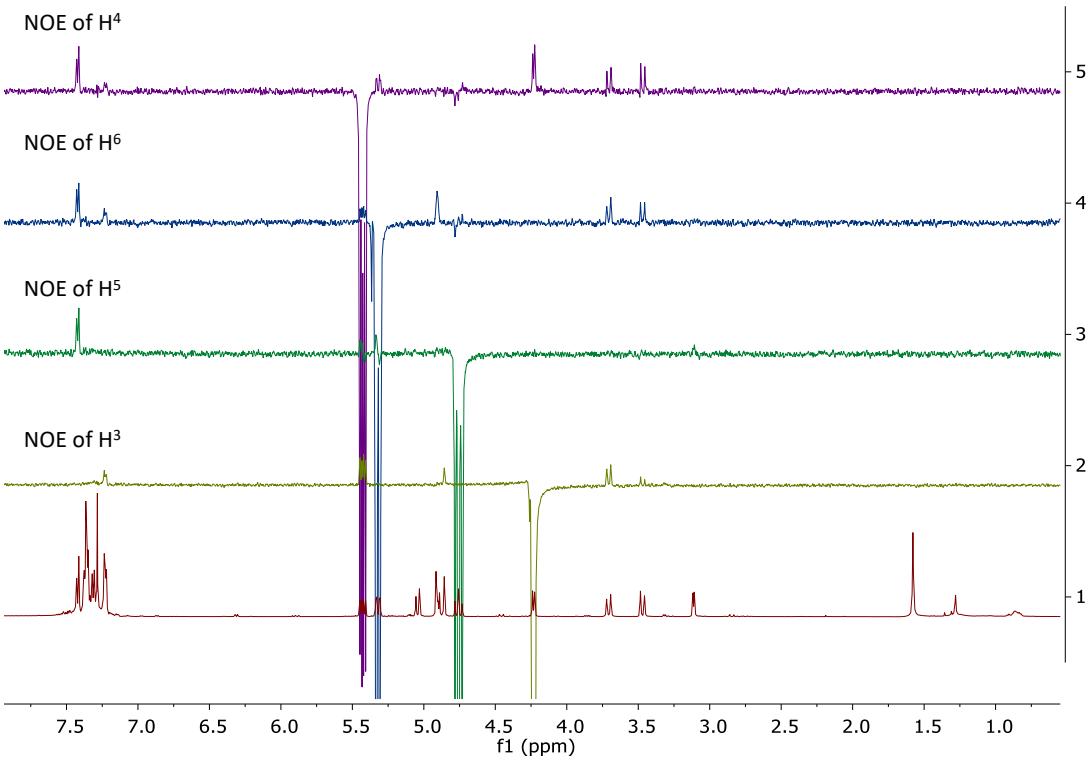
HSQC of 16b major



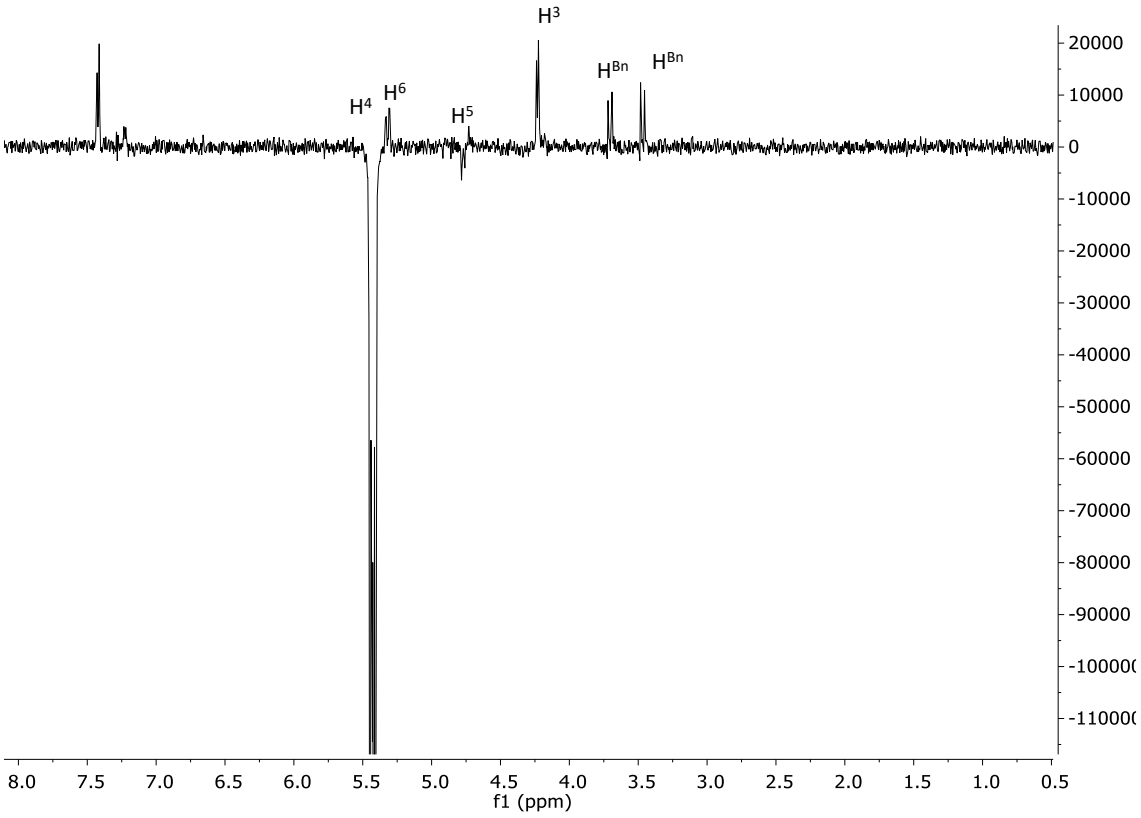
HMBC of 16b major



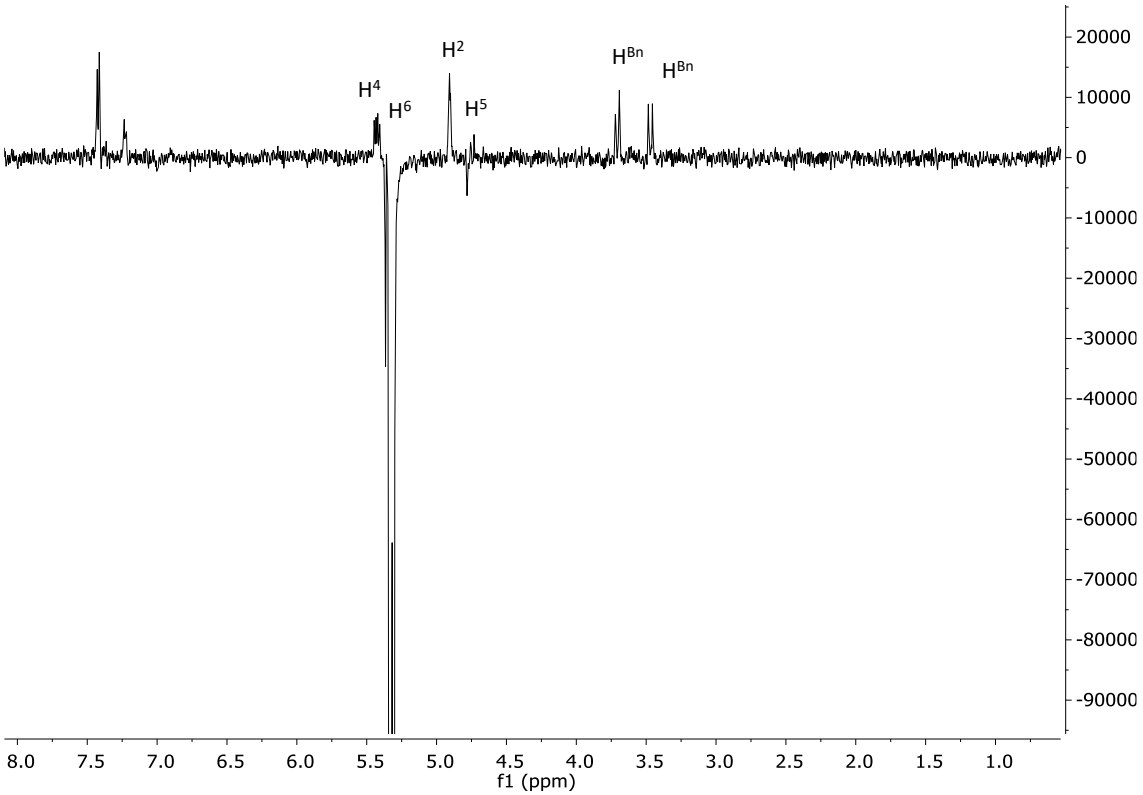
NOE of 16b major



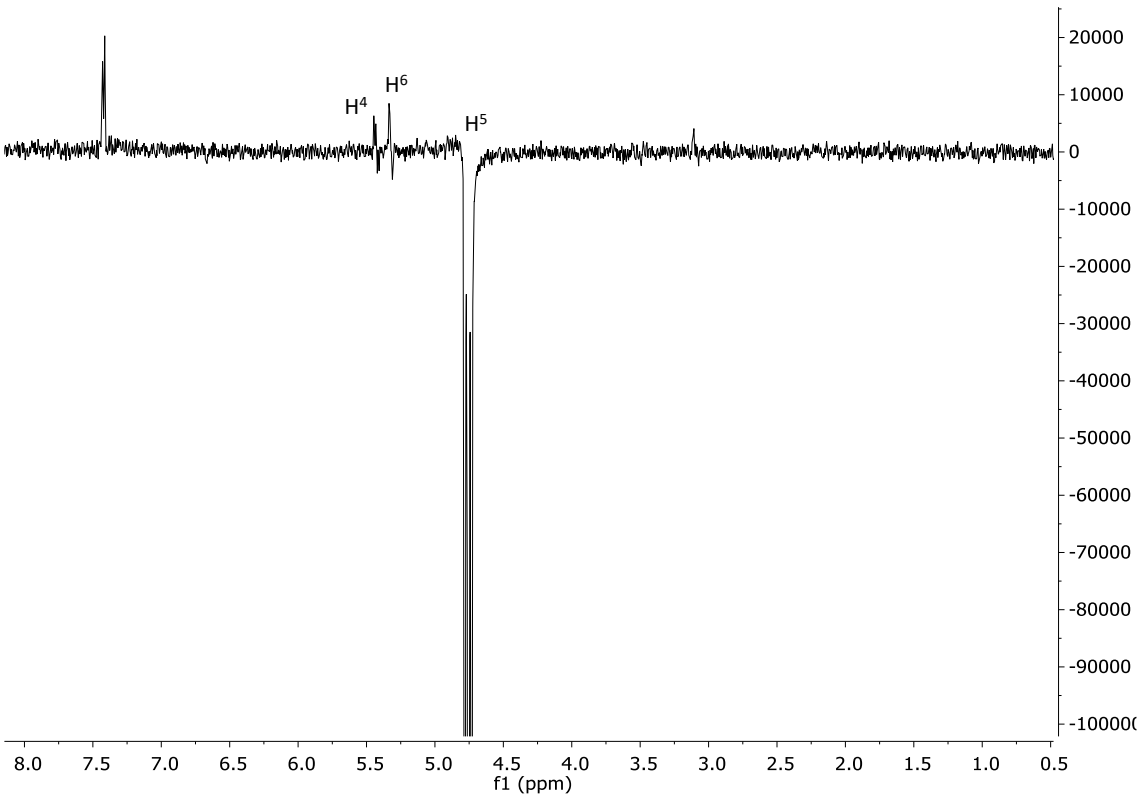
NOE of H^4: H^6, H^5, H^3 and H^{Bn} can be seen.



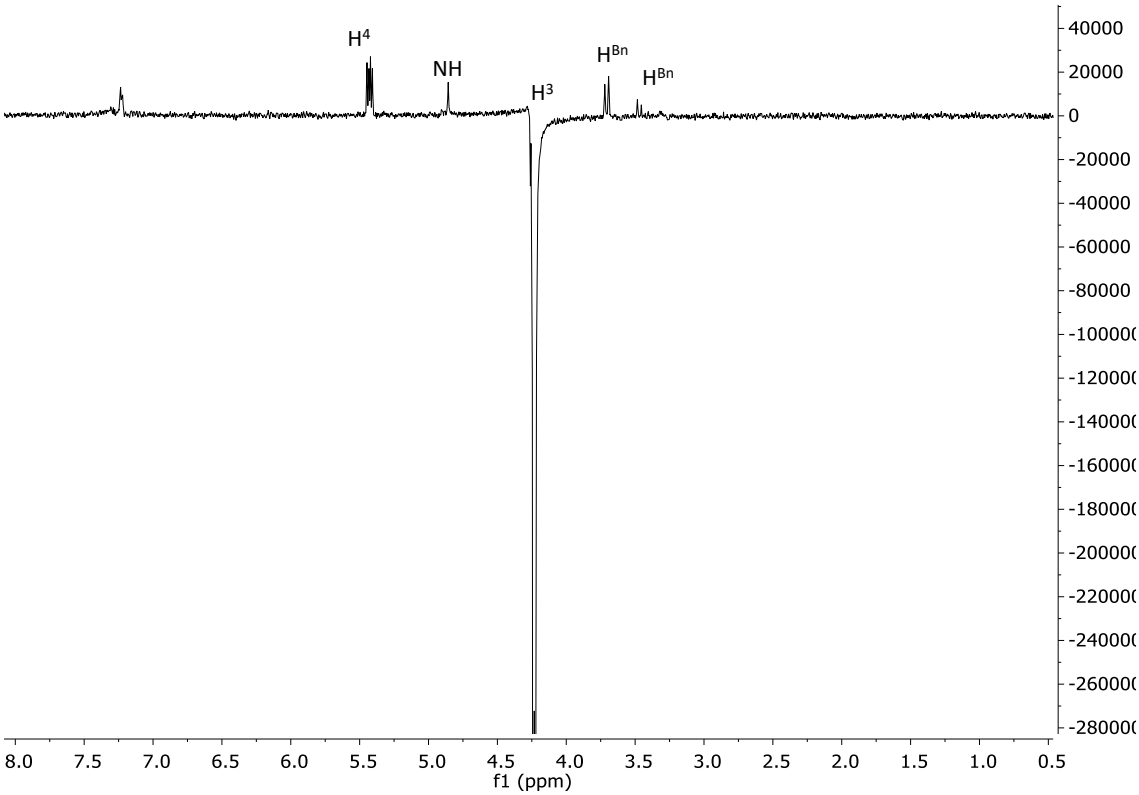
NOE of H^6: H^4, H^2, H^5 and H^{Bn} can be seen.

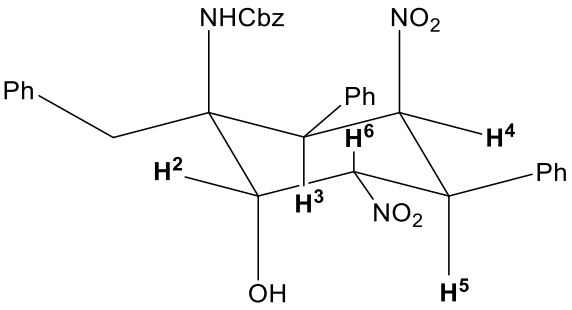


NOE of H^5: H^4 and H^6 can be seen.

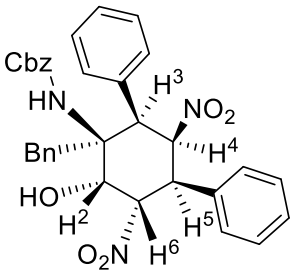


NOE of H^3: H^4, NH and H^{Bn} can be seen.



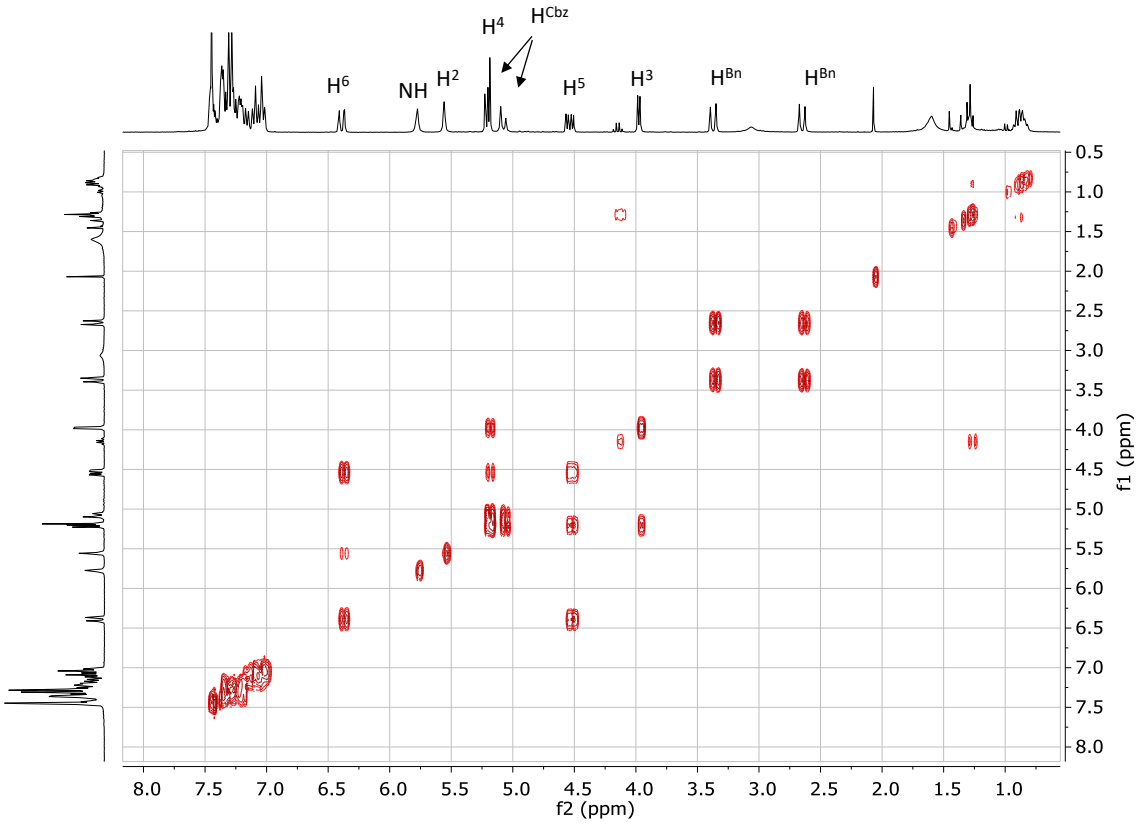


16b minor

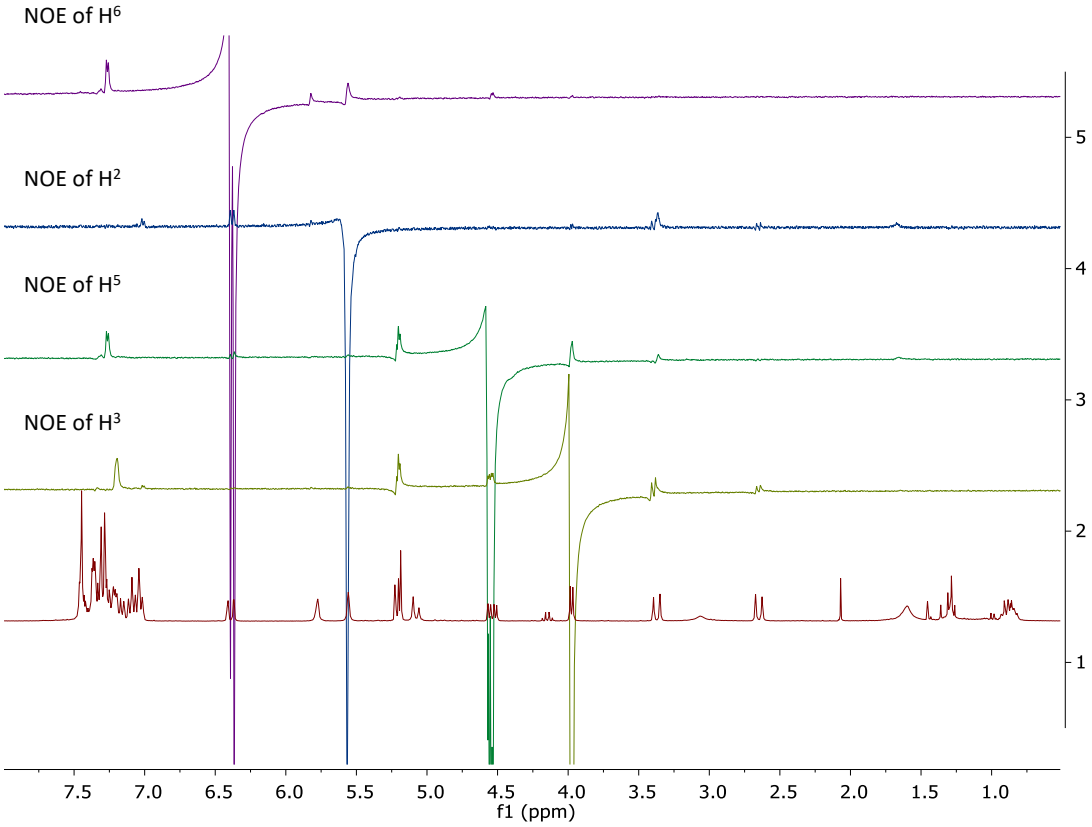


16b minor

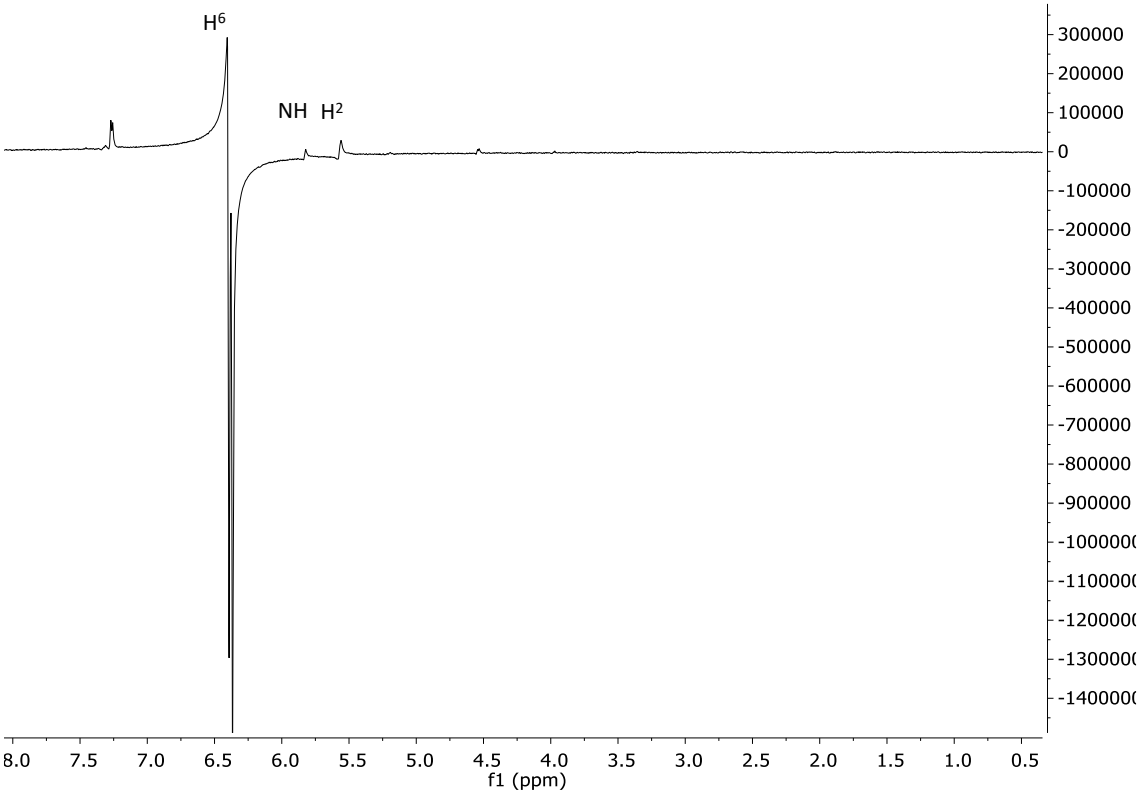
COSY of 16b minor



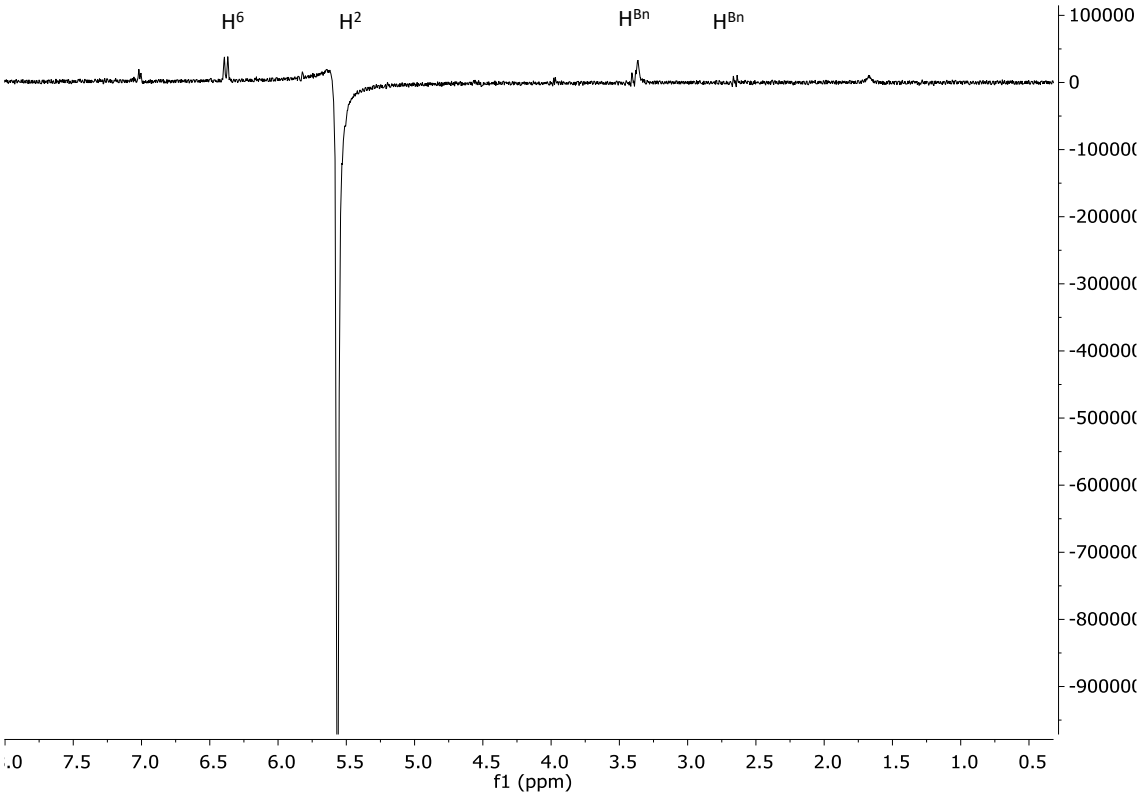
NOE of 16b minor



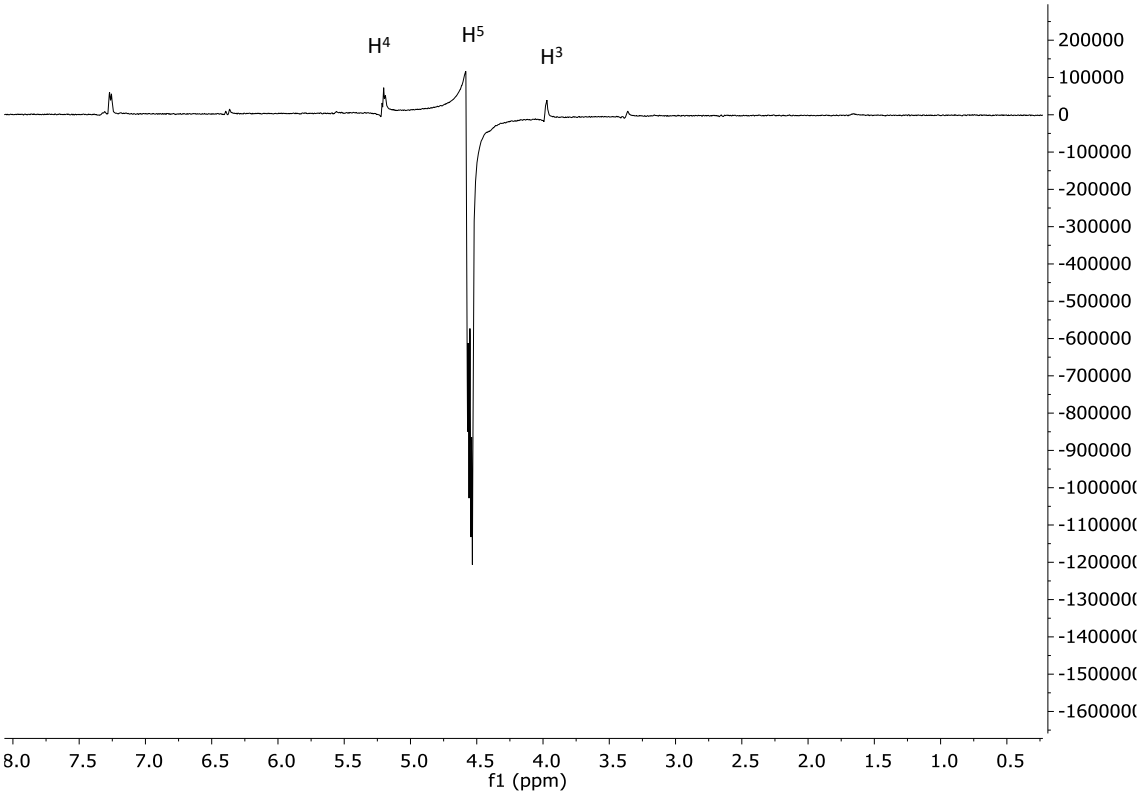
NOE of H^6: H^2 and NH can be seen.



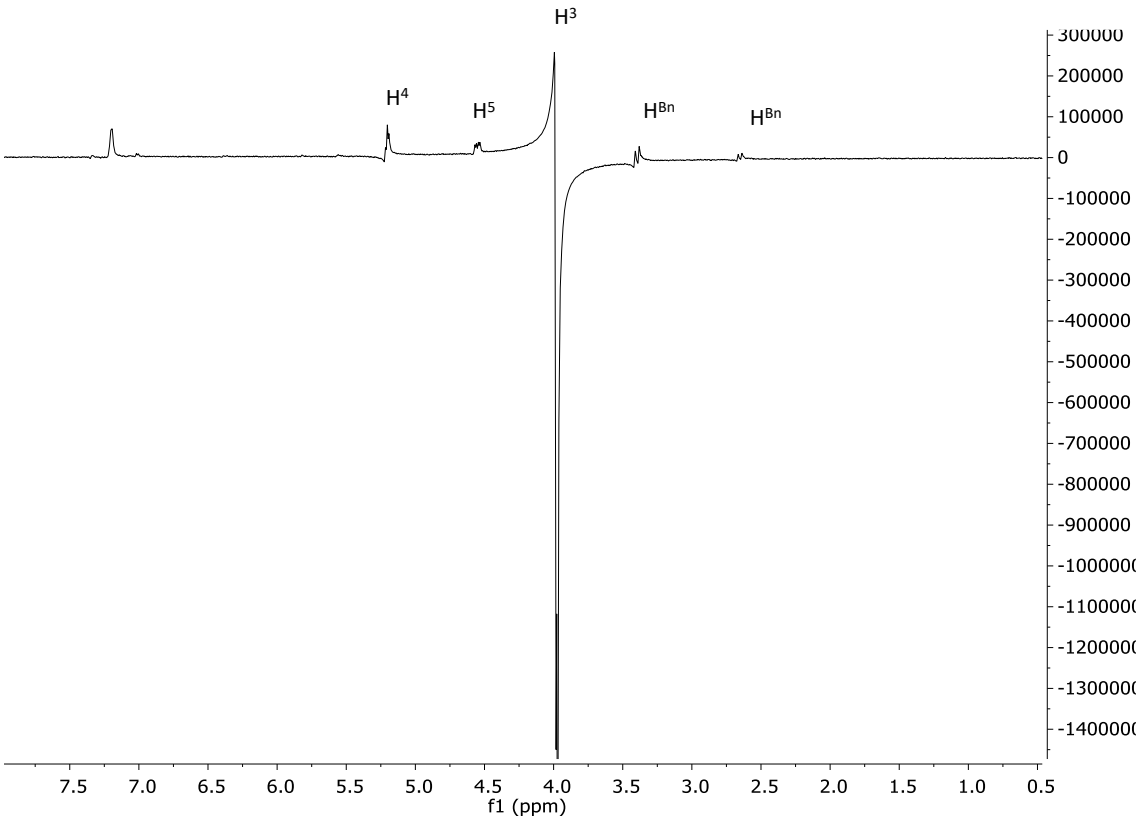
NOE of H^2: H^6 and H^{Bn} can be seen.



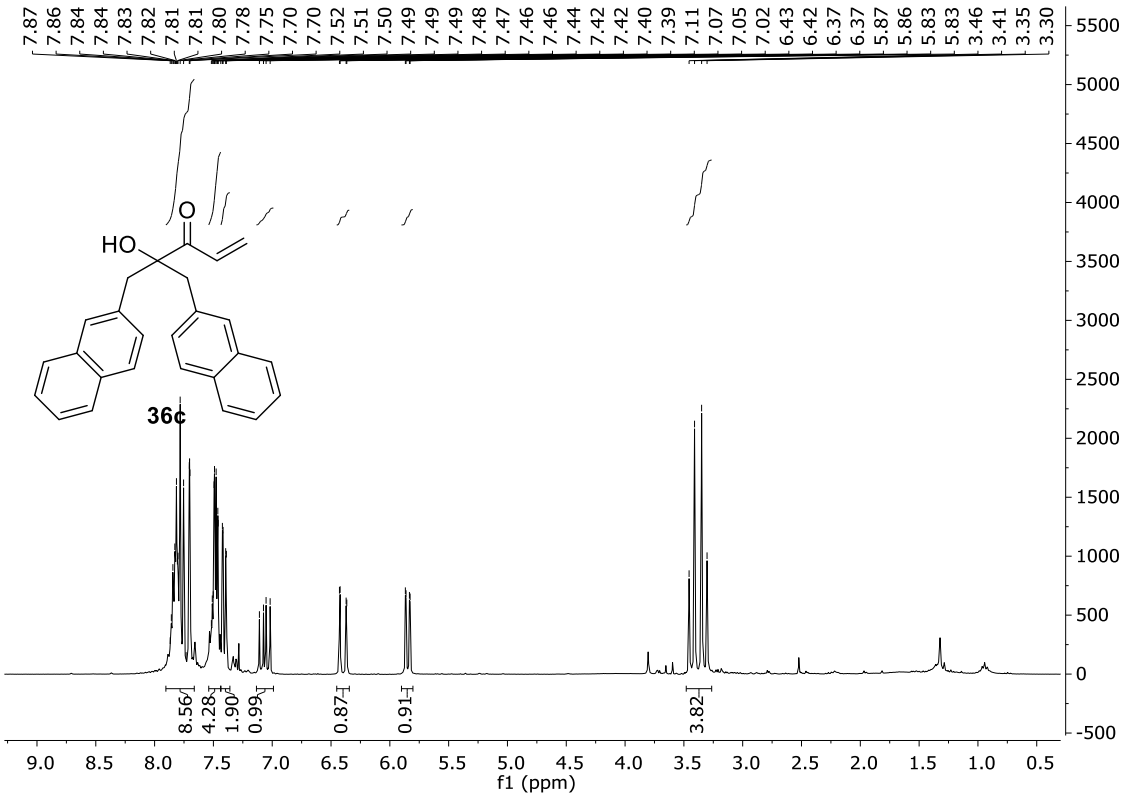
NOE of H^5: H^4 and H^3 can be seen

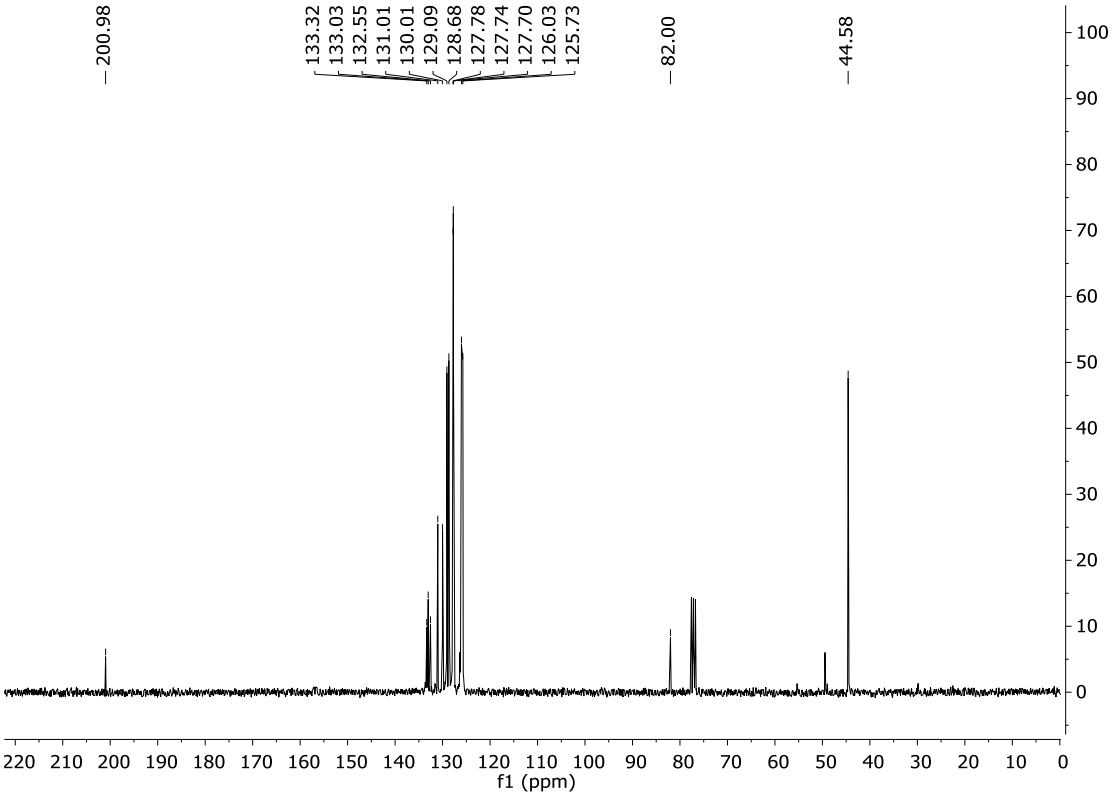


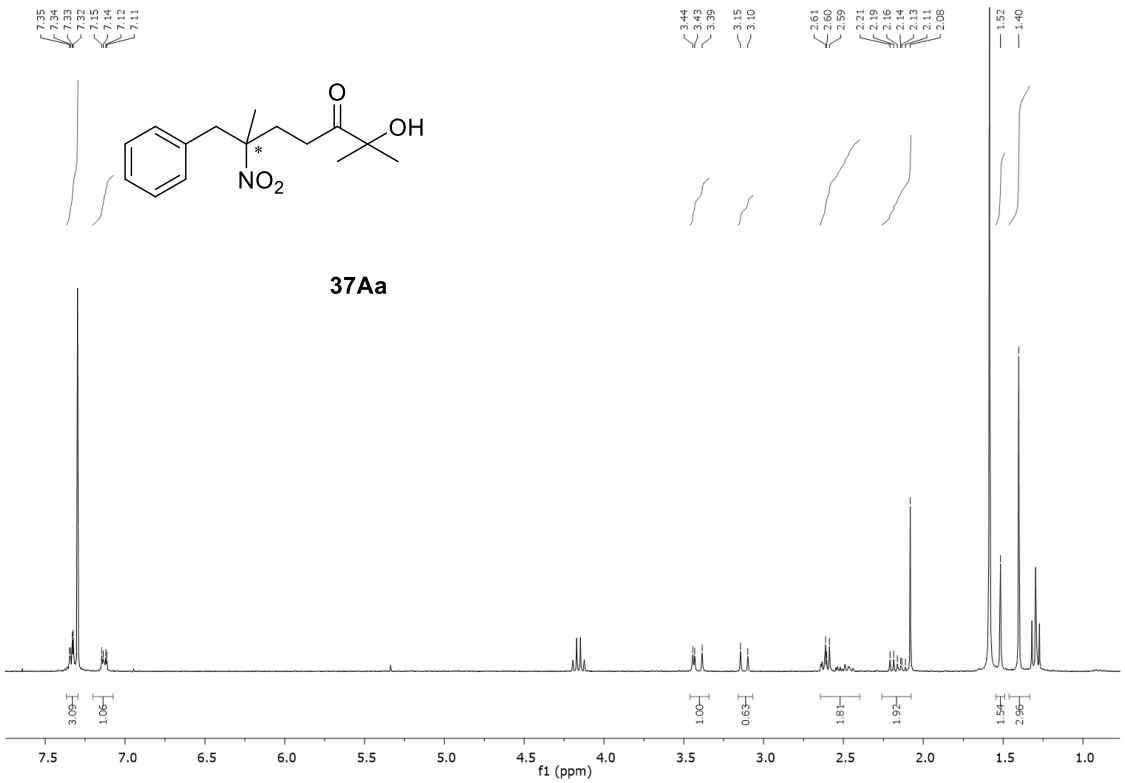
NOE of H^3: H^4, H^5 and H^{Bn} can be seen.



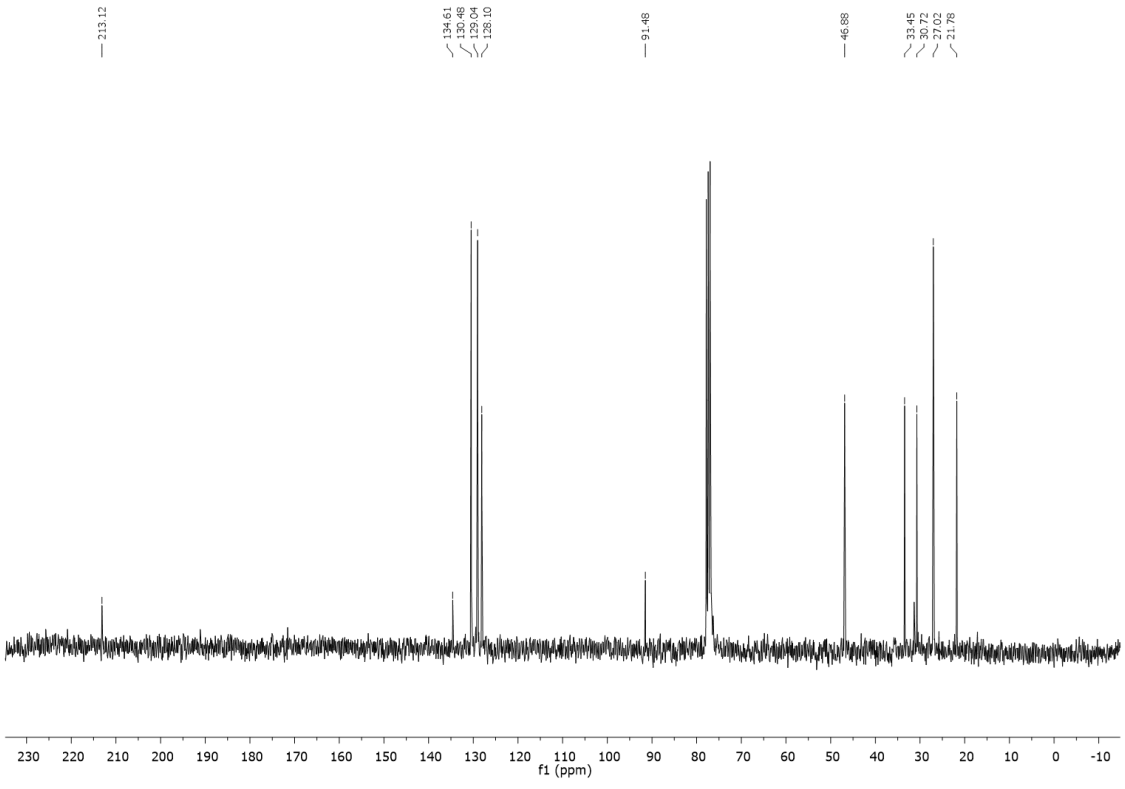
5.5.3. NMR spectra of Chapter 3

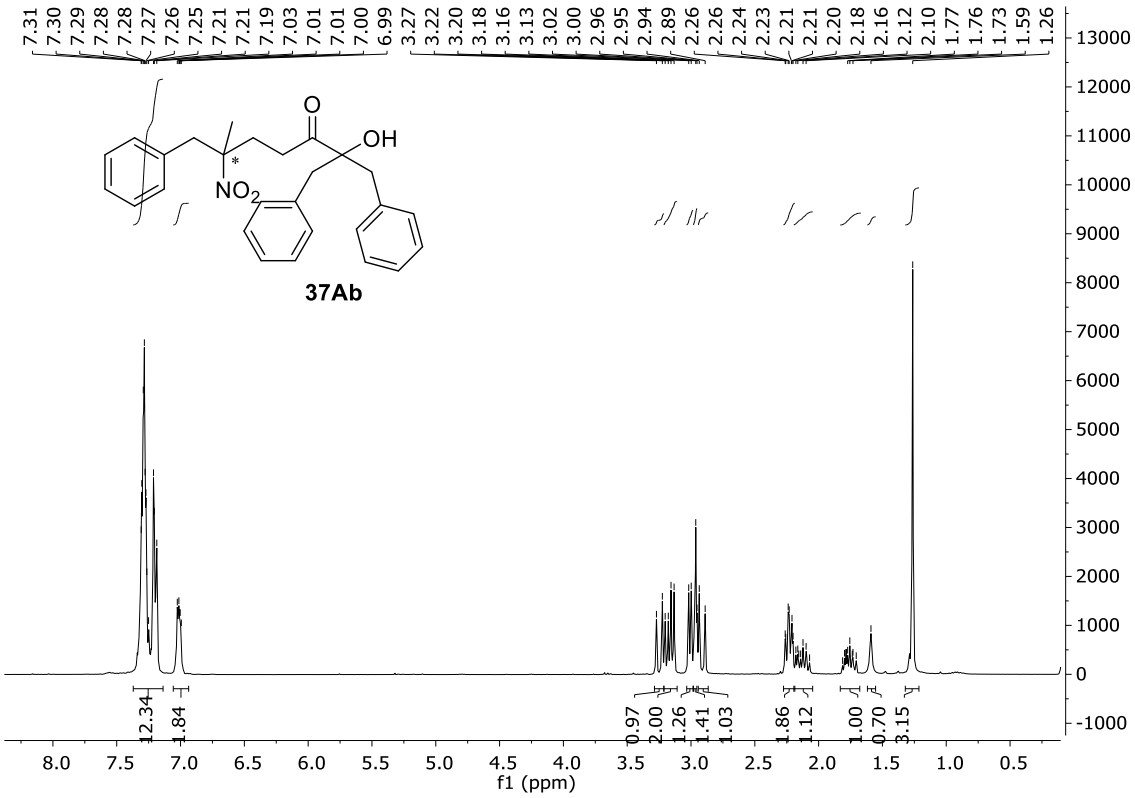


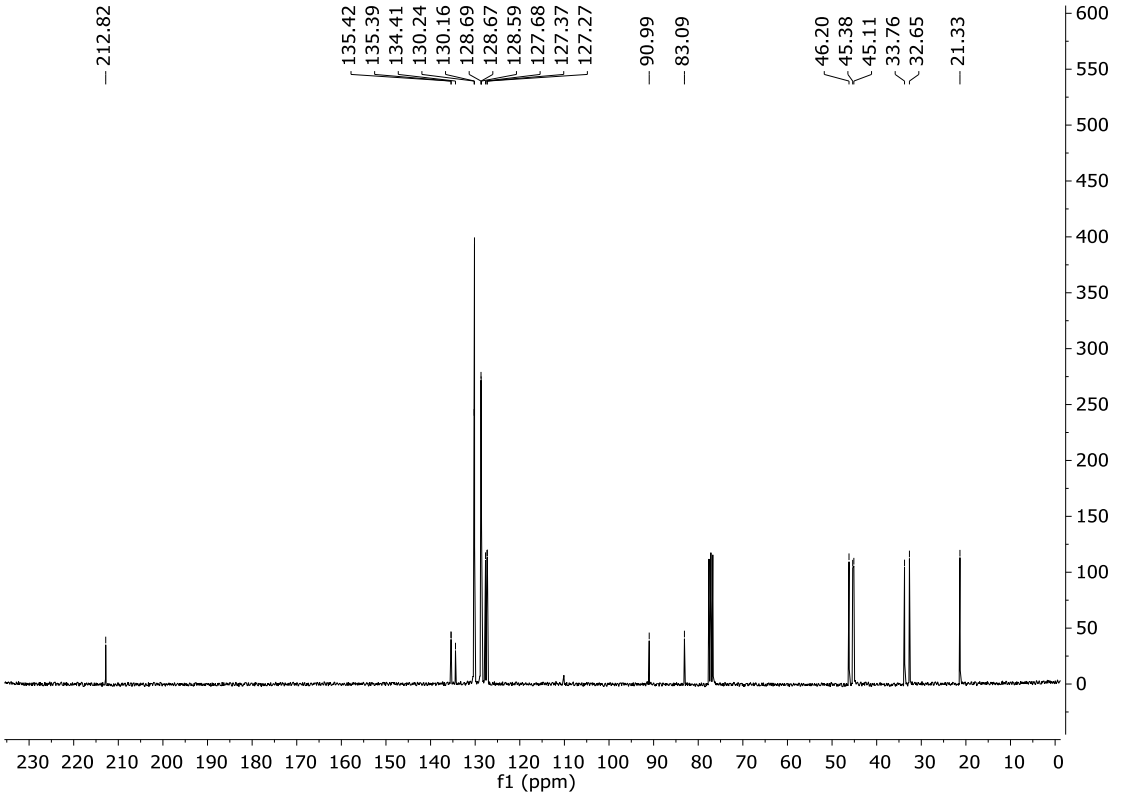


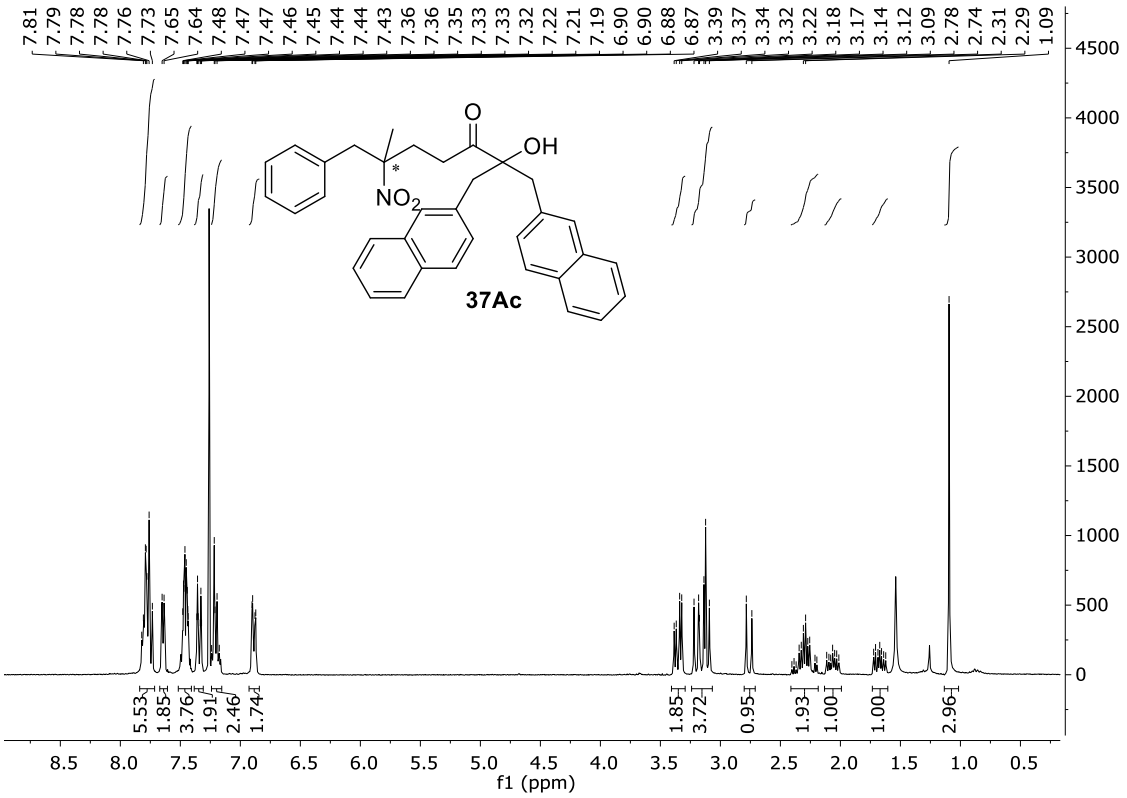

7.35
7.34
7.33
7.32
7.15
7.14
7.12
7.11
3.44
3.43
3.39
3.15
3.10
2.61
2.60
2.59
2.21
2.19
2.16
2.14
2.13
2.11
2.08
1.52
1.40
O
OH
*
NO2
3.09
1.06
1.00
0.63
1.81
1.92
1.54
2.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

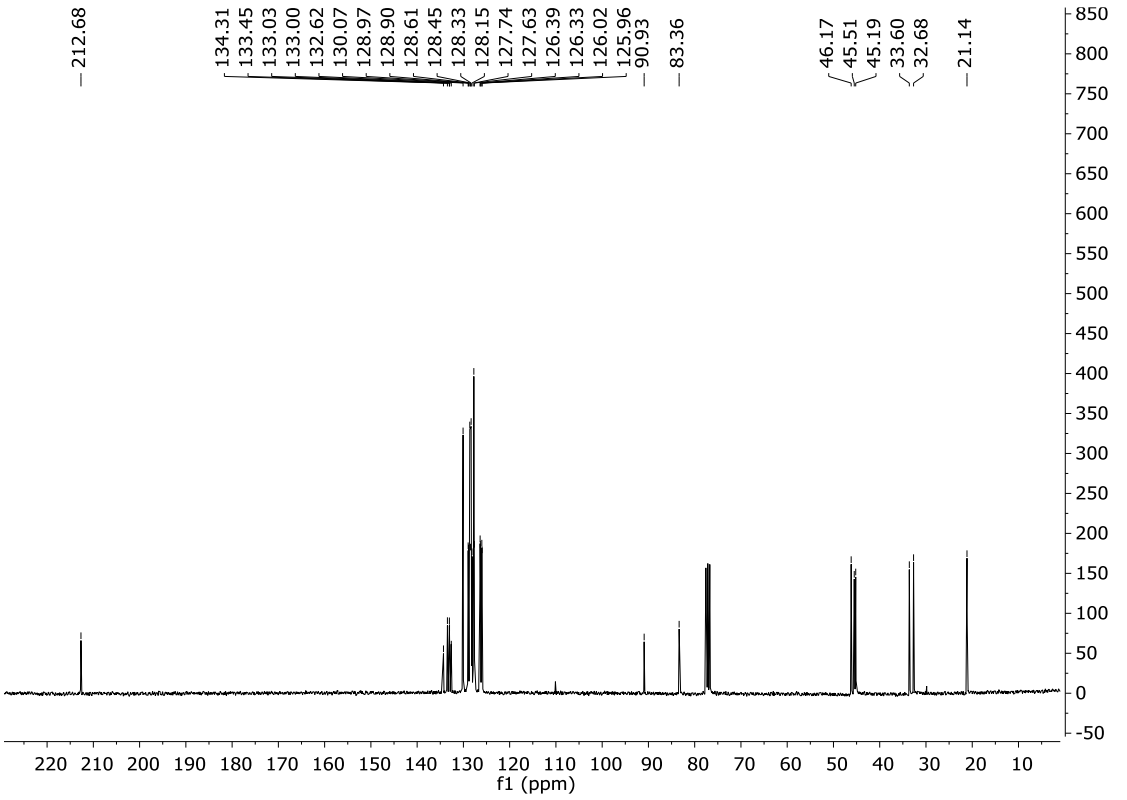
37Aa

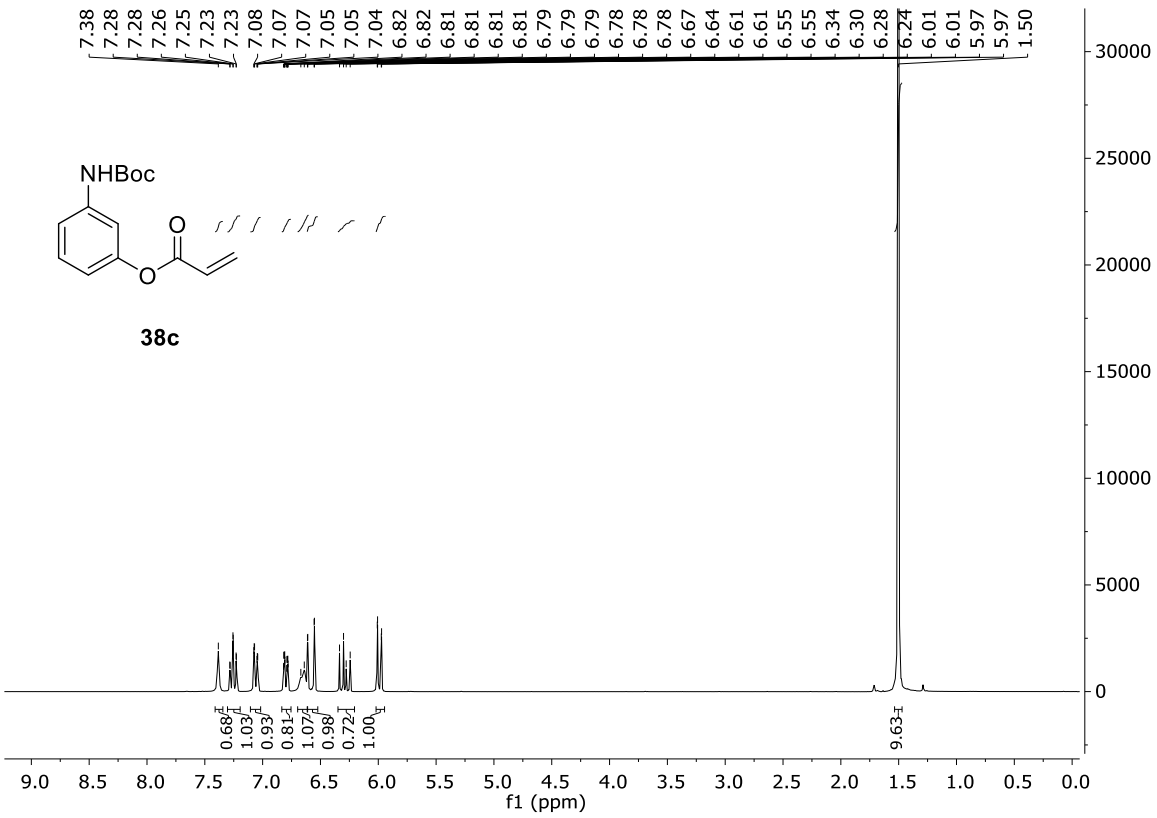

213.12
134.61
130.48
129.04
128.10
91.48
46.88
33.45
30.72
27.02
21.78
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

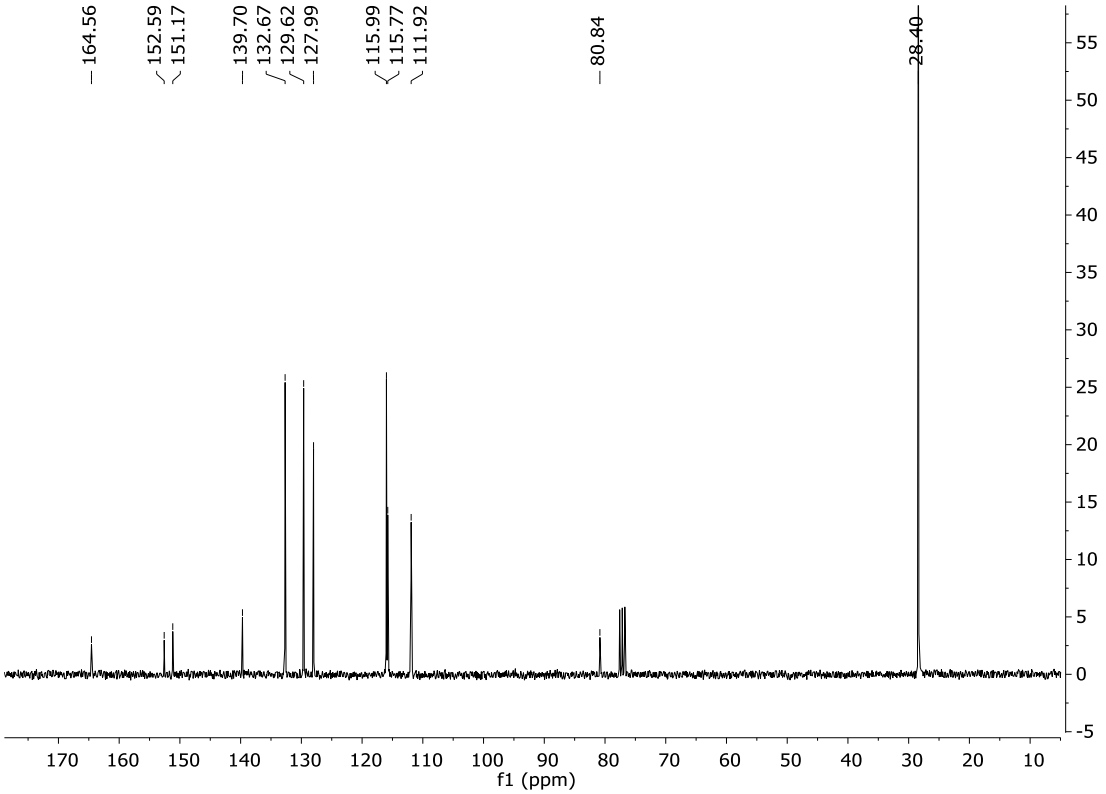

7.31 7.30 7.29 7.28 7.27 7.26 7.25 7.21 7.21 7.19 7.03 7.01 7.01 7.00 6.99
3.27 3.22 3.20 3.18 3.16 3.13 3.02 3.00 2.96 2.95 2.94 2.89 2.26 2.26 2.24 2.23 2.21 2.21 2.20 2.18 2.16 2.12 2.10 1.77 1.76 1.73 1.59 1.26
O
OH
NO2
*
37Ab
12.34
1.84
0.97
2.00
1.26
1.41
1.03
1.86
1.12
1.00
0.70
3.15
f1 (ppm)

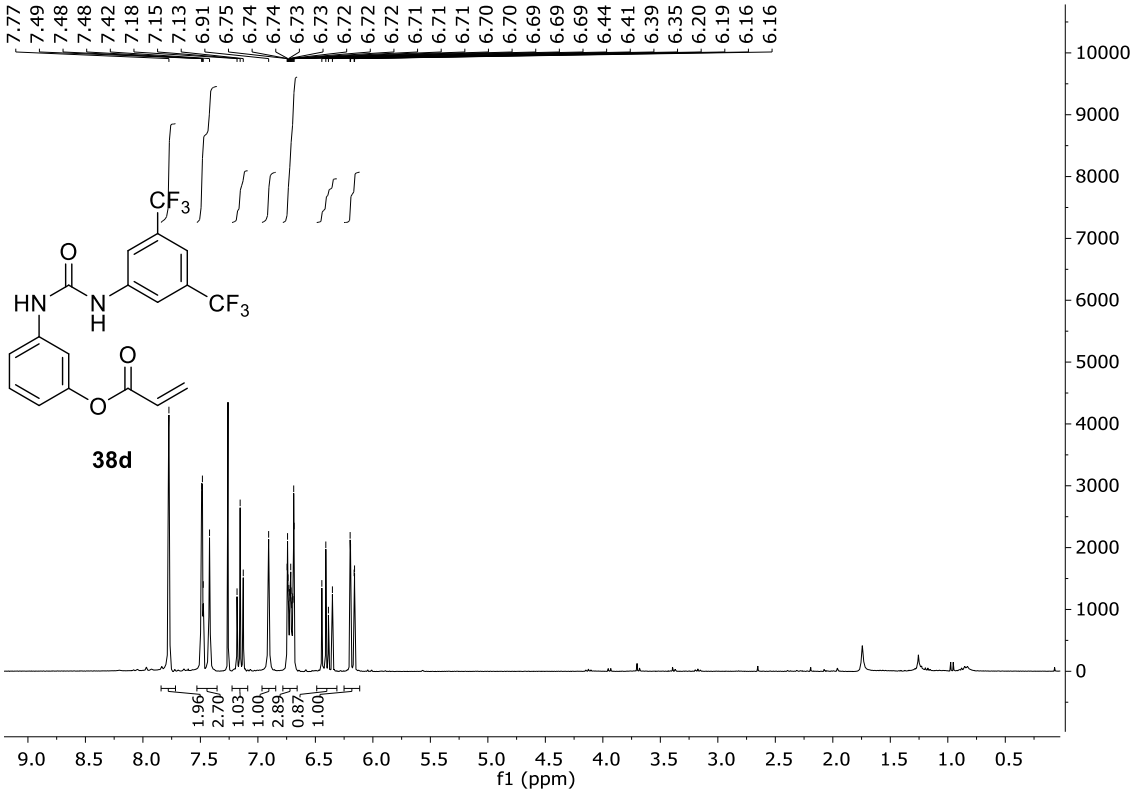

212.82
135.42 135.39 134.41 130.24 130.16 128.69 128.67 128.59 127.68 127.37 127.27
90.99
83.09
46.20 45.38 45.11
33.76
32.65
21.33
f1 (ppm)

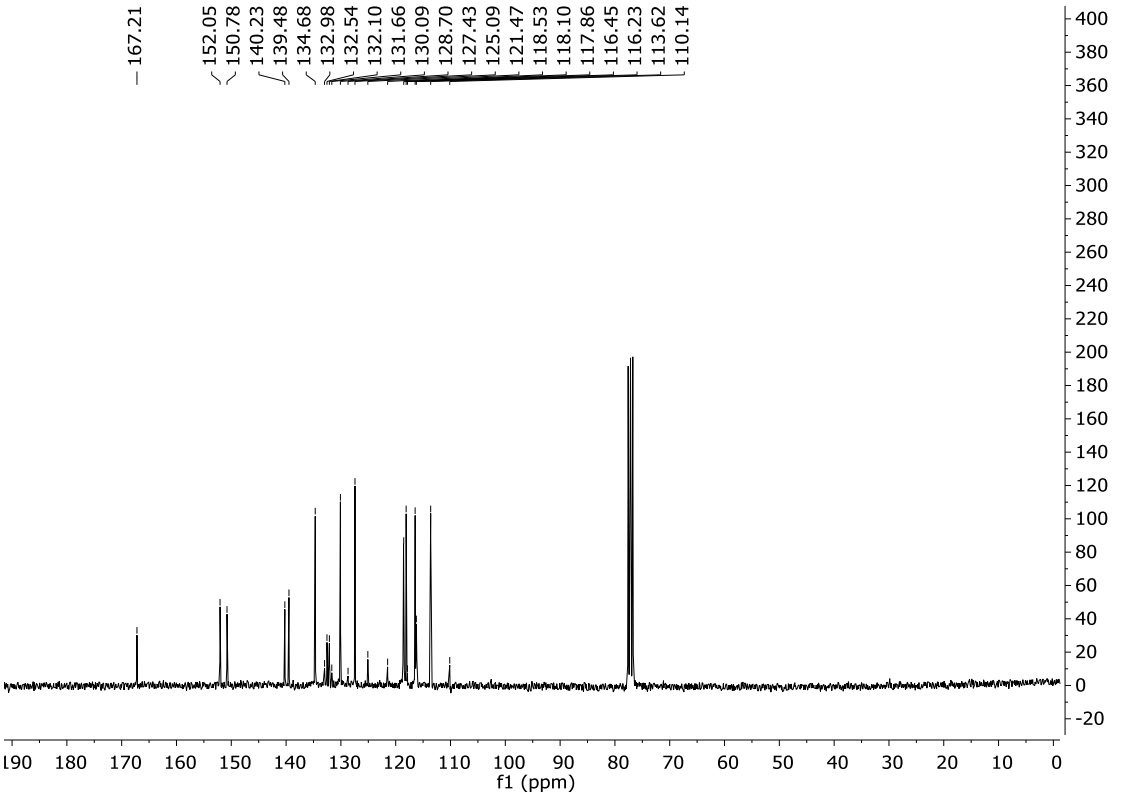

7.81 7.79 7.78 7.78 7.76 7.73 7.65 7.64 7.48 7.47 7.47 7.46 7.45 7.44 7.44 7.43 7.36 7.36 7.35 7.33 7.33 7.32 7.22 7.21 7.19 6.90 6.90 6.88 6.87 3.39 3.37 3.34 3.32 3.22 3.18 3.17 3.14 3.12 3.09 2.78 2.74 2.31 2.29 1.09
O
OH
NO2
*
37Ac
5.53 1.85 3.76 1.91 2.46 1.74 1.85 3.72 0.95 1.93 1.00 1.00 2.96
f1 (ppm)

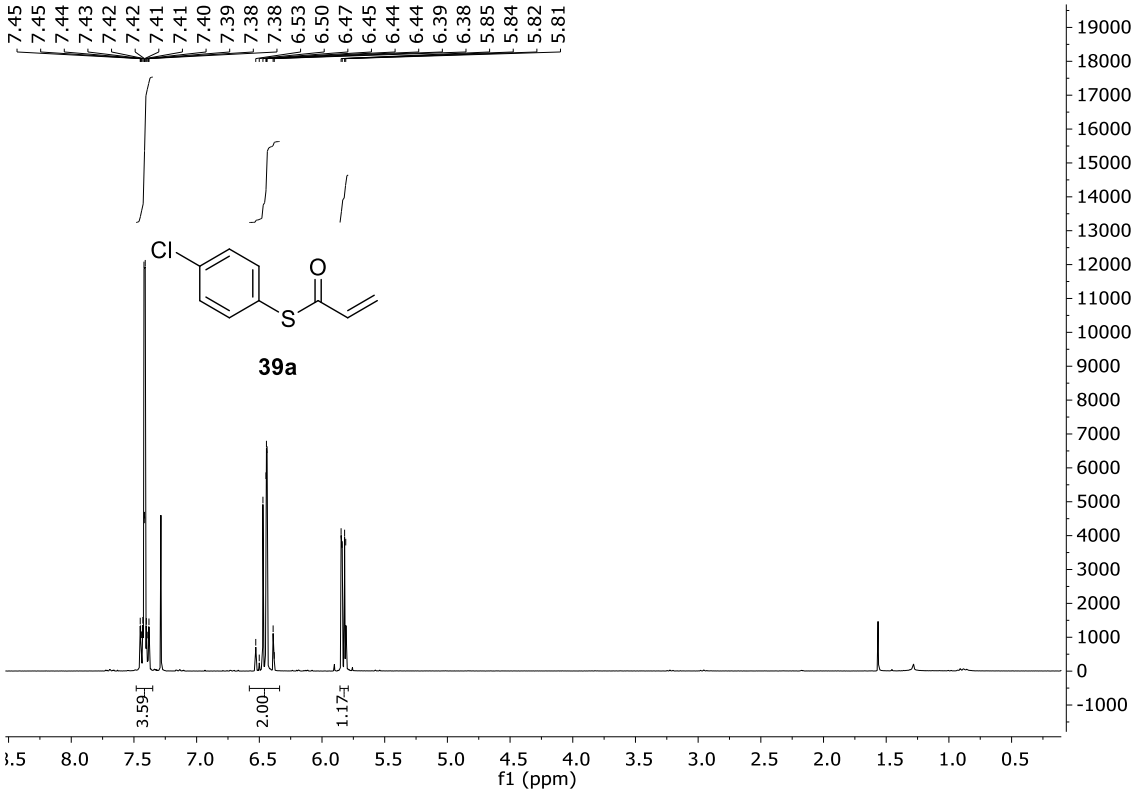

212.68
134.31 133.45 133.03 133.00 132.62 130.07 128.97 128.90 128.61 128.45 128.33 128.15 127.74 127.63 126.39 126.33 126.02 125.96
90.93
83.36
46.17 45.51 45.19 33.60 32.68
21.14
f1 (ppm)

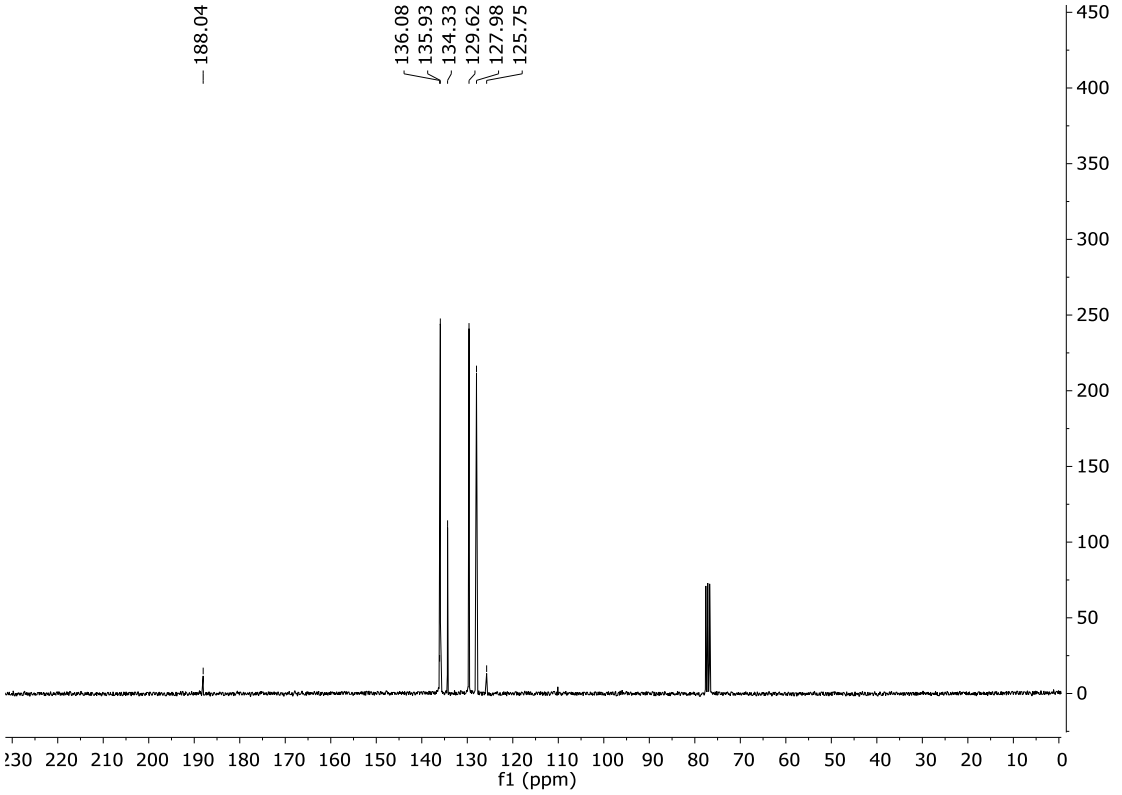

7.38
7.28
7.28
7.26
7.25
7.23
7.23
7.08
7.07
7.07
7.05
7.05
7.04
6.82
6.82
6.81
6.81
6.81
6.81
6.79
6.79
6.79
6.78
6.78
6.78
6.67
6.64
6.61
6.61
6.55
6.55
6.34
6.30
6.28
6.24
6.01
6.01
5.97
5.97
1.50
NHBoc
O
O
38c
0.68
1.03
0.93
0.81
1.07
0.98
0.72
1.00
9.63
f1 (ppm)

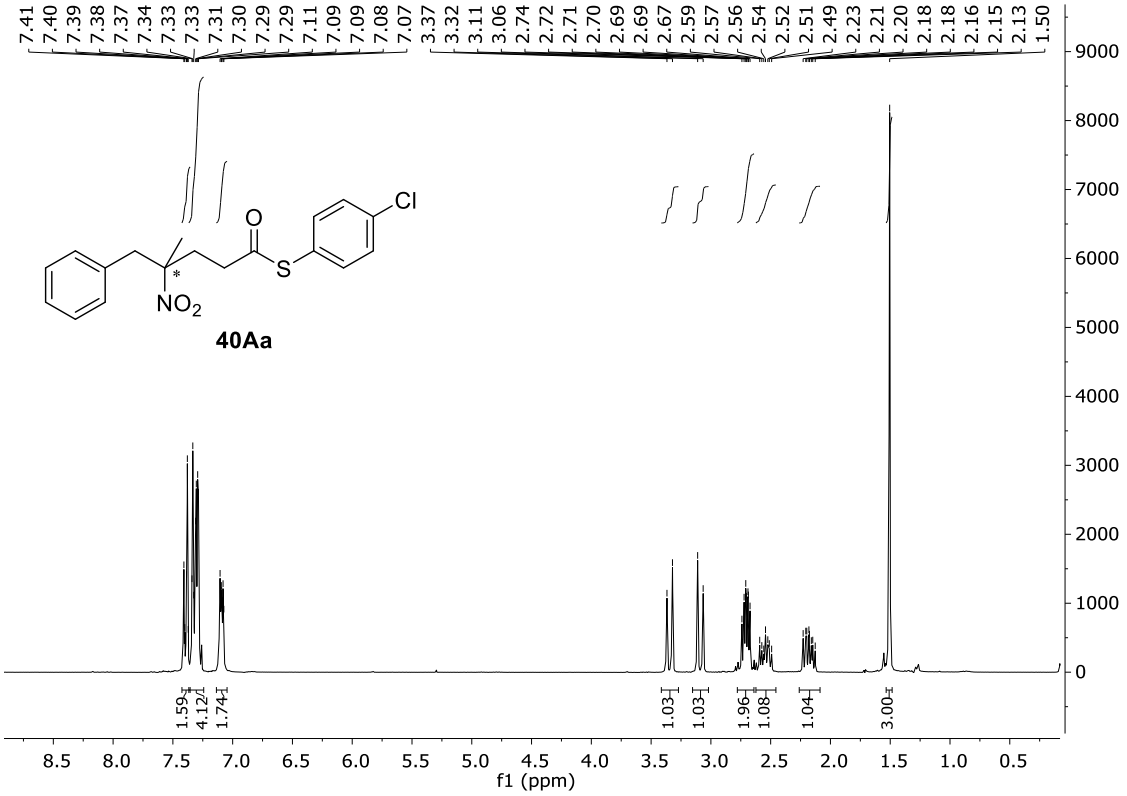

164.56
152.59
151.17
139.70
132.67
129.62
127.99
115.99
115.77
111.92
80.84
28.40
f1 (ppm)

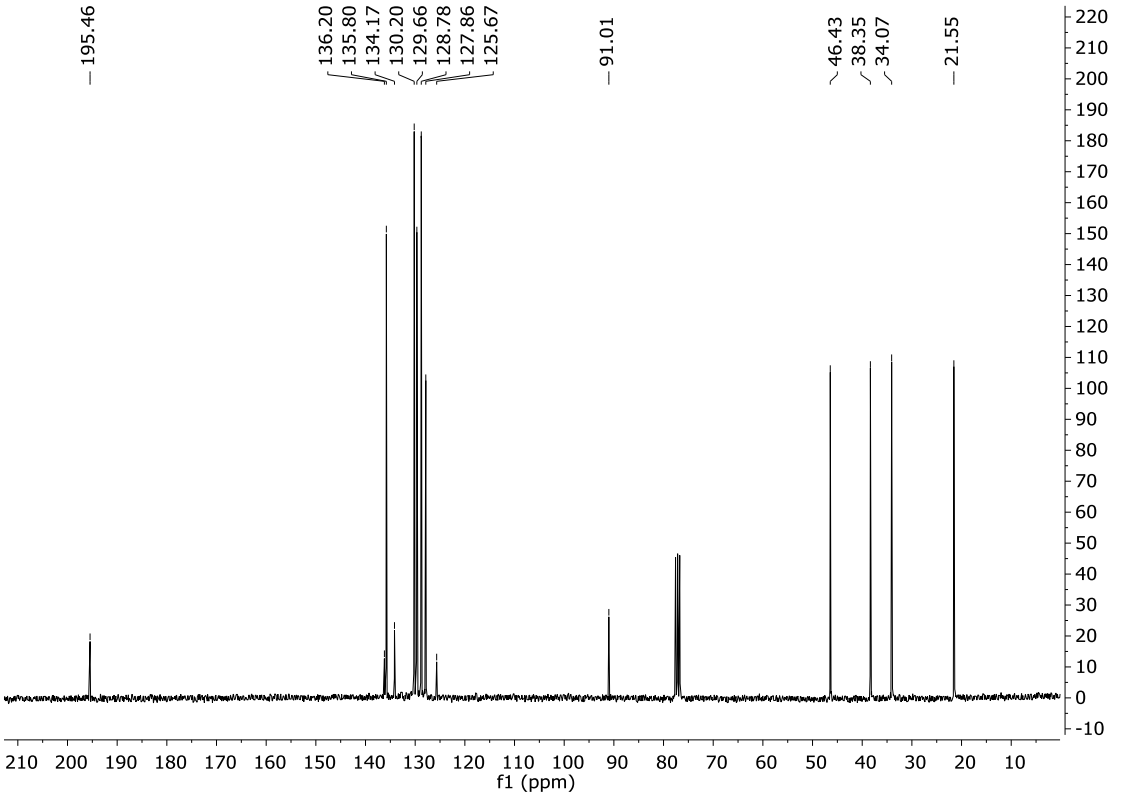

7.77
7.49
7.48
7.48
7.42
7.18
7.15
7.13
6.91
6.75
6.74
6.74
6.73
6.73
6.72
6.72
6.72
6.71
6.71
6.71
6.70
6.70
6.69
6.69
6.69
6.44
6.41
6.39
6.35
6.20
6.19
6.16
6.16
CF3
O
HN
N
H
CF3
O
O
38d
1.96
2.70
1.03
1.00
2.89
0.87
1.00
f1 (ppm)


167.21
152.05
150.78
140.23
139.48
134.68
132.98
132.54
132.10
131.66
130.09
128.70
127.43
125.09
121.47
118.53
118.10
117.86
116.45
116.23
113.62
110.14
f1 (ppm)

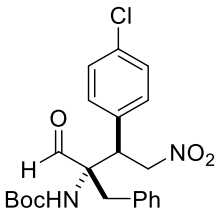

7.45
7.45
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.38
7.38
6.53
6.50
6.47
6.45
6.44
6.44
6.39
6.38
5.85
5.84
5.82
5.81
Cl
O
S
39a
3.59
2.00
1.17
f1 (ppm)


188.04
136.08
135.93
134.33
129.62
127.98
125.75
f1 (ppm)


7.41 7.40 7.39 7.38 7.37 7.34 7.33 7.33 7.31 7.30 7.29 7.29 7.11 7.09 7.09 7.08 7.07
3.37 3.32 3.11 3.06 2.74 2.72 2.71 2.70 2.69 2.69 2.67 2.59 2.57 2.56 2.54 2.52 2.51 2.49 2.23 2.21 2.20 2.18 2.18 2.16 2.15 2.13 1.50
Cl
O
S
NO2
*
40Aa
1.59 4.12 1.74 1.03 1.03 1.96 1.08 1.04 3.00
f1 (ppm)


195.46
136.20 135.80 134.17 130.20 129.66 128.78 127.86 125.67
91.01
46.43 38.35 34.07
21.55
f1 (ppm)

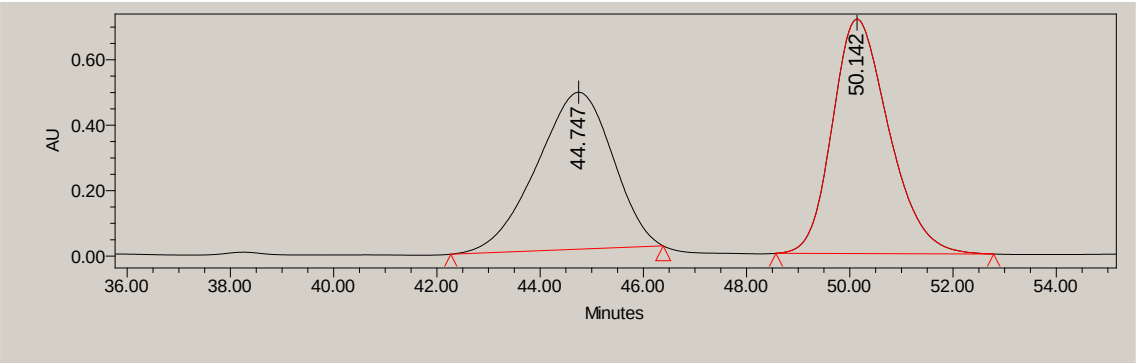
5.6. HPLC chromatograms



9Aa

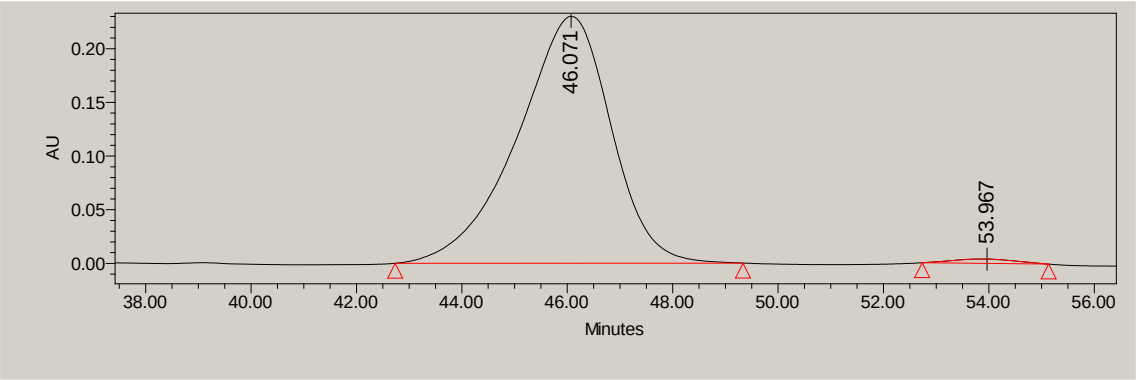
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 9Aa



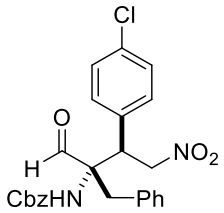
	Retention Time	% Area
1	44.747	48.72
2	50.142	51.28

9Aa



	Retention Time	% Area
1	46.071	98.83
2	53.967	1.17

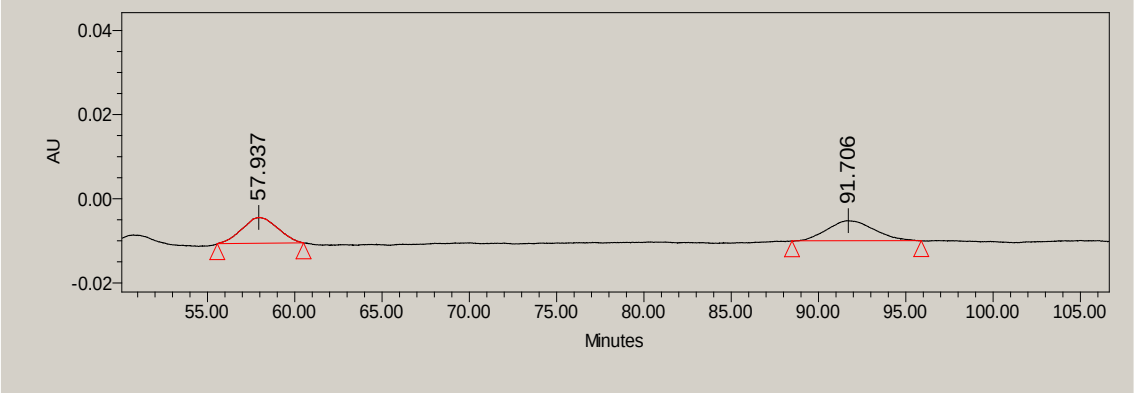
98% ee



9Ba

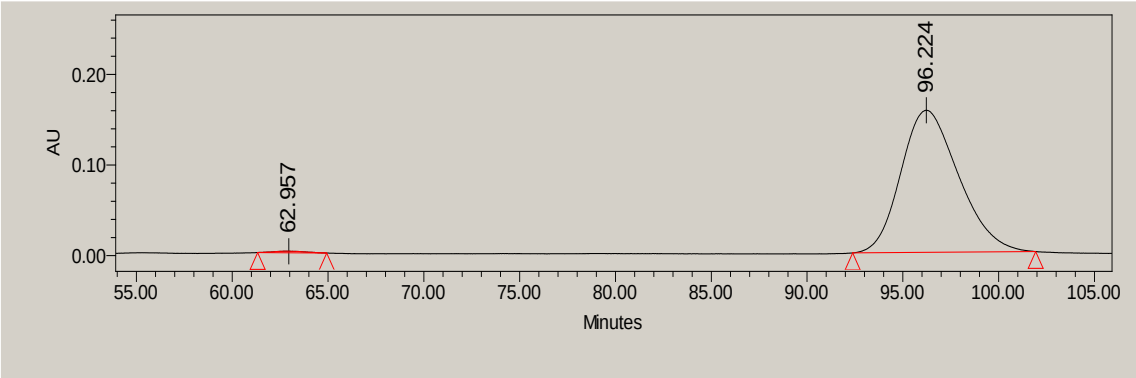
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±)9Ba



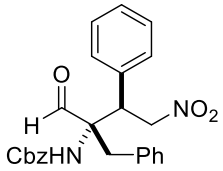
	Retention Time	% Area
1	57.937	49.38
2	91.706	50.62

9Ba



	Retention Time	% Area
1	62.957	0.59
2	96.224	99.41

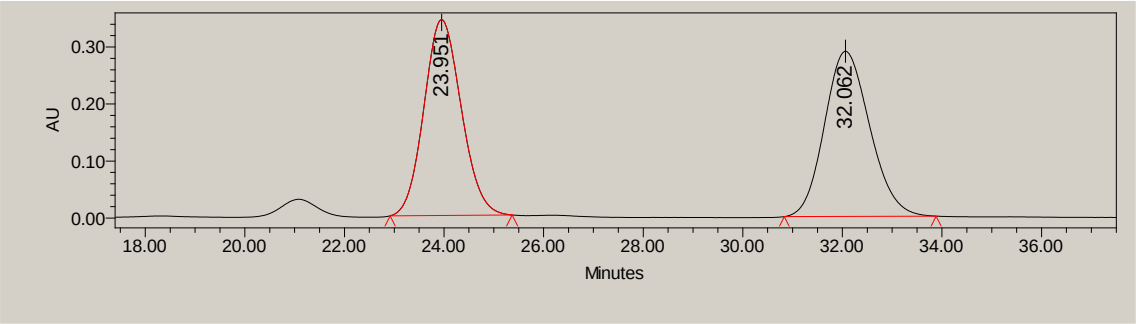
99% ee



9Bb

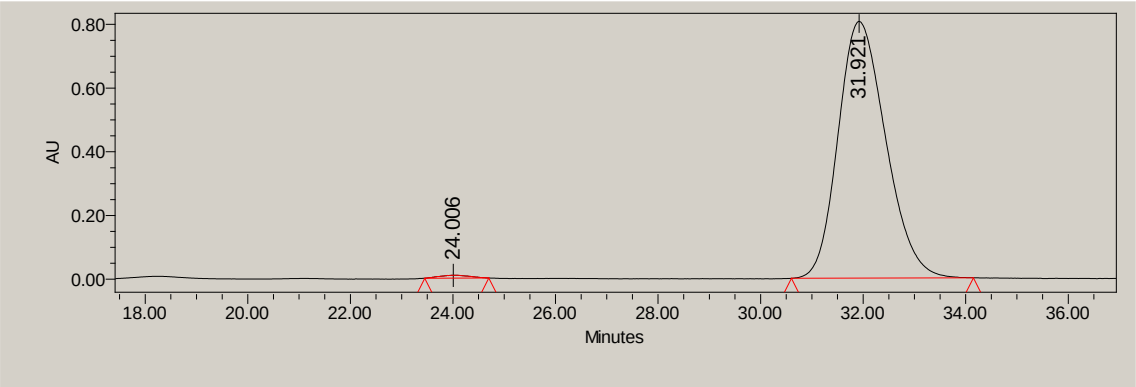
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 9Bb



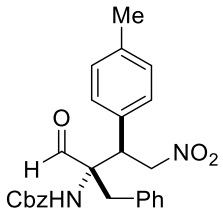
	Retention Time	% Area
1	23.951	49.45
2	32.062	50.55

9Bb



	Retention Time	% Area
1	24.006	0.70
2	31.921	99.30

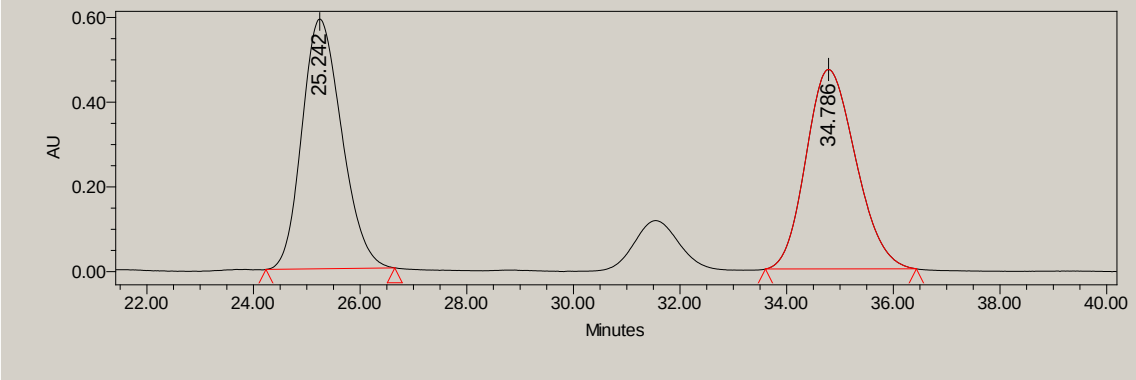
99% ee



9Bc

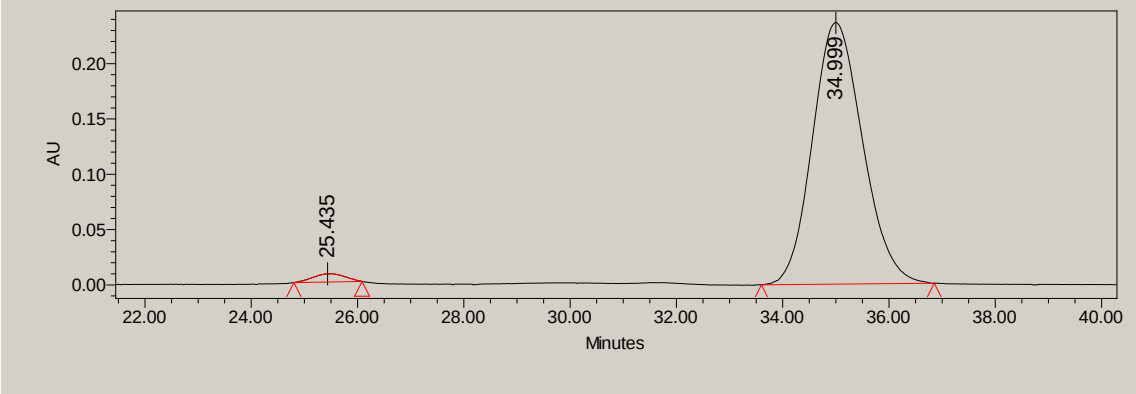
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 9Bc



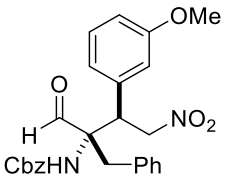
	Retention Time	% Area
1	25.242	50.01
2	34.786	49.99

9Bc



	Retention Time	% Area
1	25.435	1.98
2	34.999	98.02

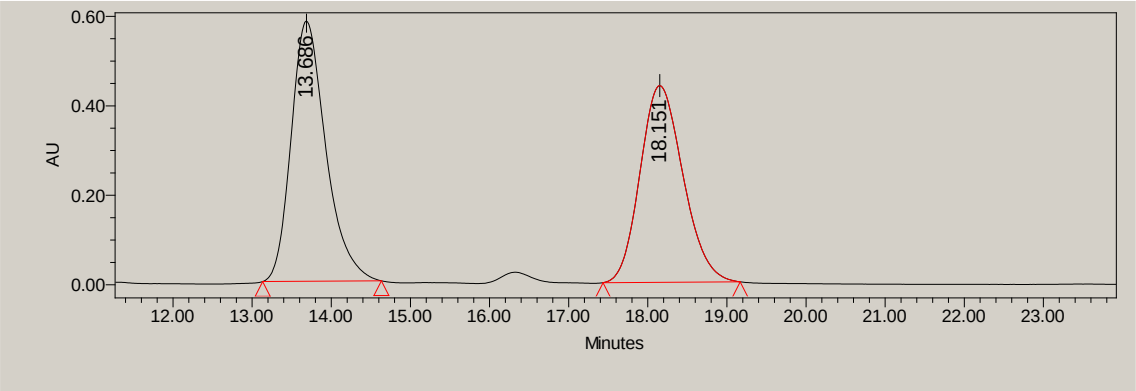
96% ee



9Bd

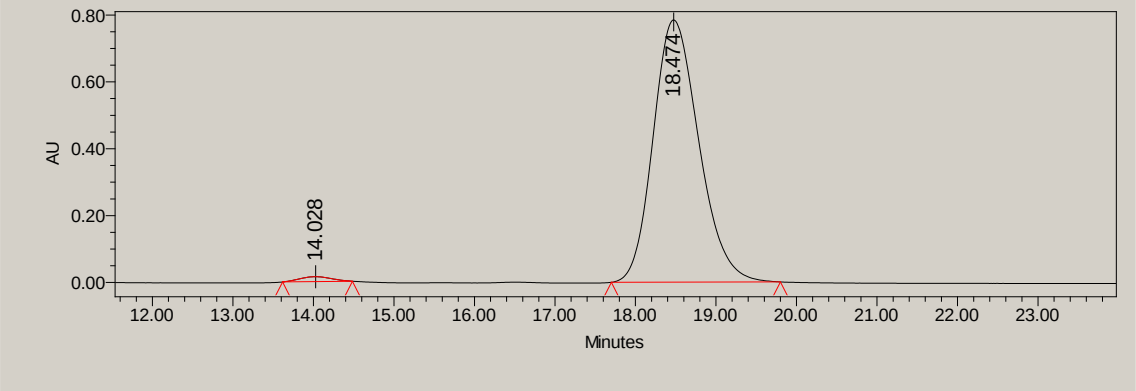
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min).

(±) 9Bd



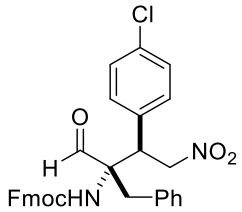
	Retention Time	% Area
1	13.686	51.67
2	18.151	48.33

9Bd



	Retention Time	% Area
1	14.028	1.27
2	18.474	98.73

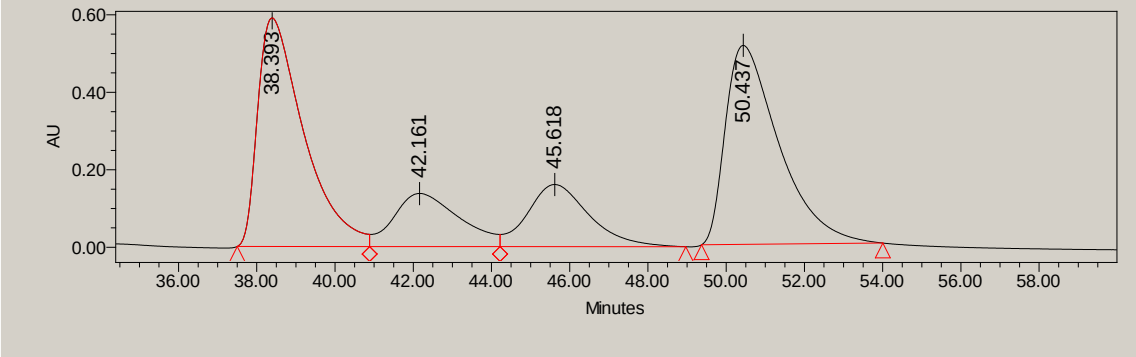
97% ee



9Ca

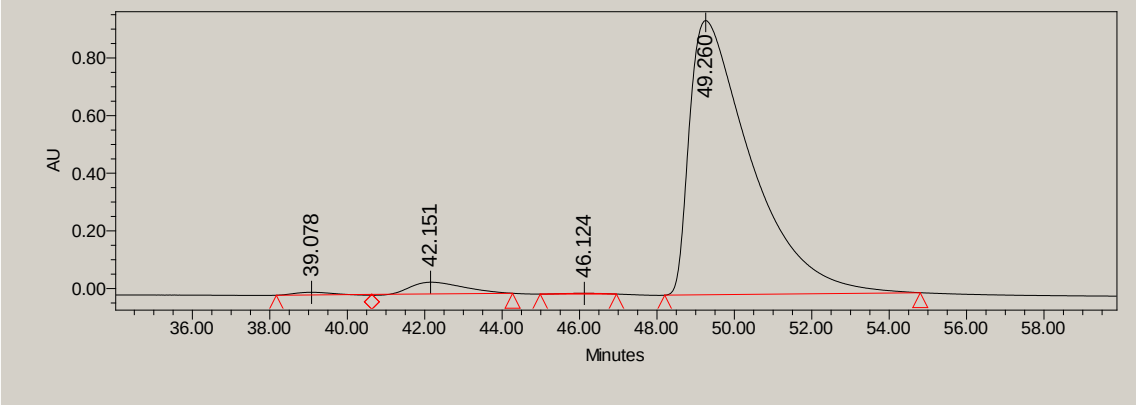
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IF Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 9Ca



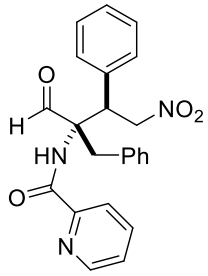
	Retention Time	% Area
1	38.393	36.96
2	42.161	12.22
3	45.618	13.42
4	50.437	37.40

9Ca



	Retention Time	% Area
1	39.078	0.57
2	42.151	3.72
3	46.124	0.09
4	49.260	95.62

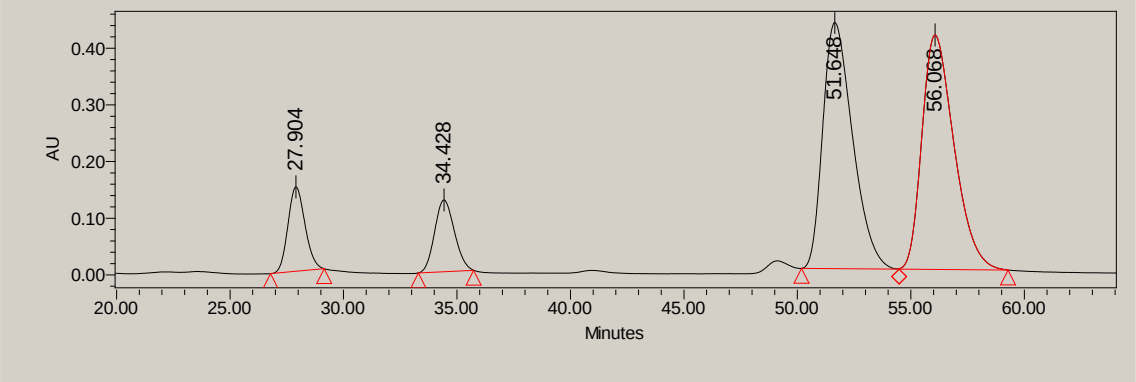
99(95)% ee



9Db

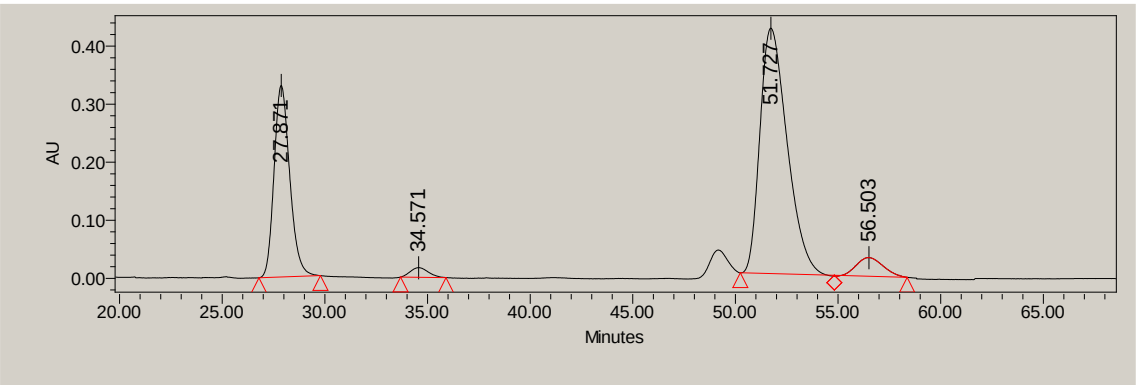
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 9Db



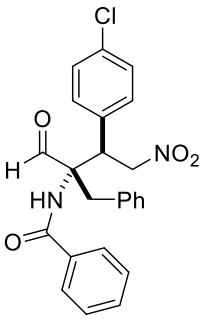
	Retention Time	% Area
1	27.904	8.12
2	34.428	8.00
3	51.648	41.42
4	56.068	42.46

9Db



	Retention Time	% Area
1	27.871	28.99
2	34.571	1.67
3	51.727	64.49
4	56.503	4.84

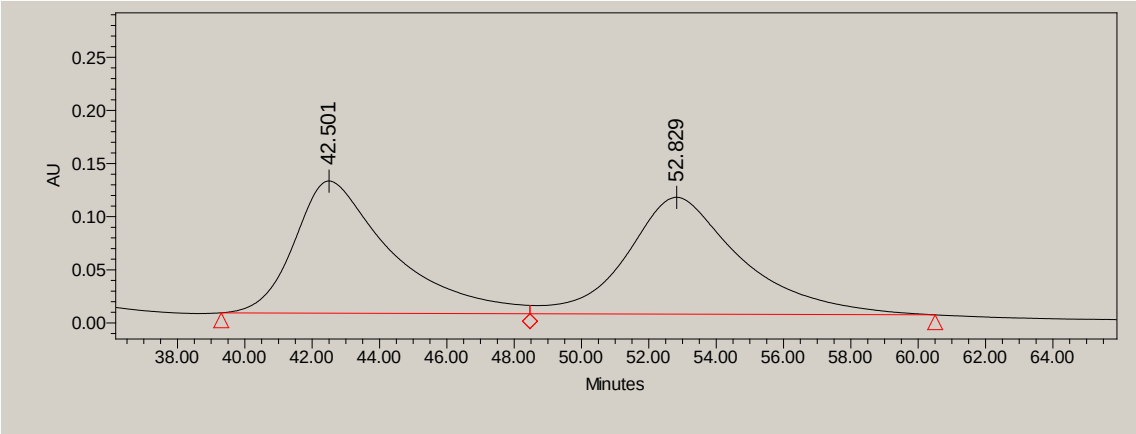
86(89)%ee



9Ea

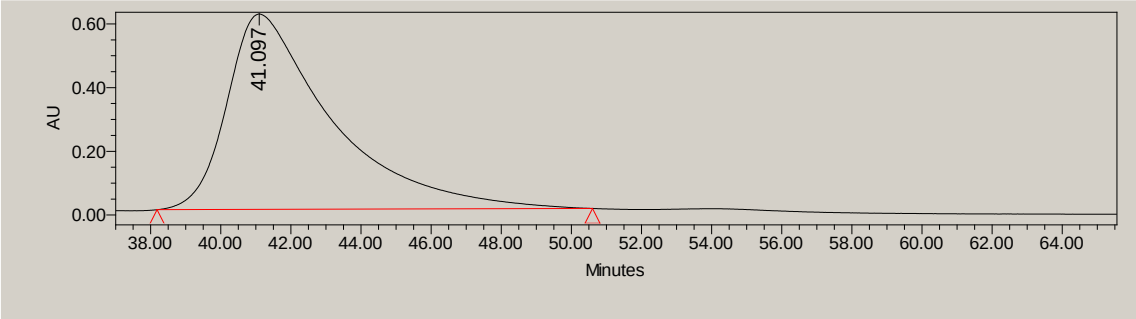
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IB Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 9Ea



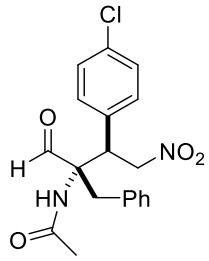
	Retention Time	% Area
1	42.501	48.84
2	52.829	51.16

9Ea



	Retention Time	% Area
1	41.097	100.00

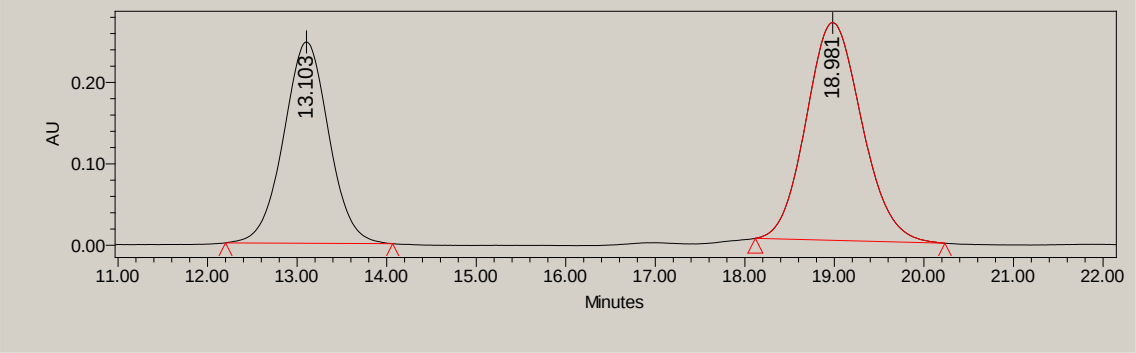
>99% ee



9Ia

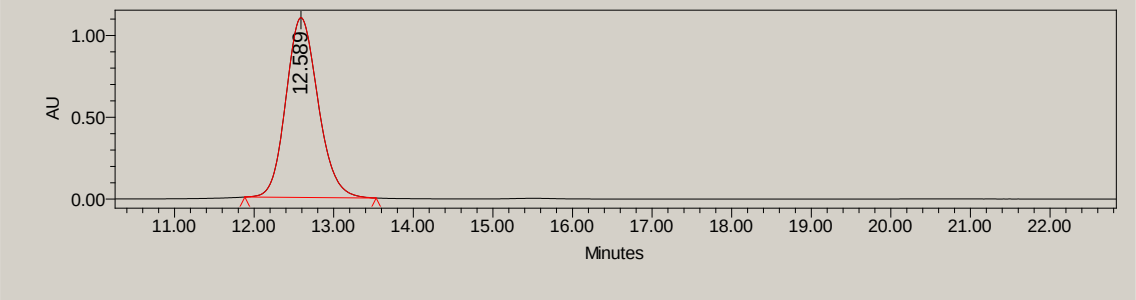
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min).

(±) 9Ia



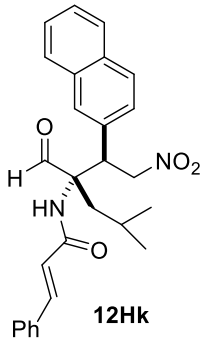
	Retention Time	% Area
1	13.103	42.80
2	18.981	57.20

9Ia



	Retention Time	% Area
1	12.589	100.00

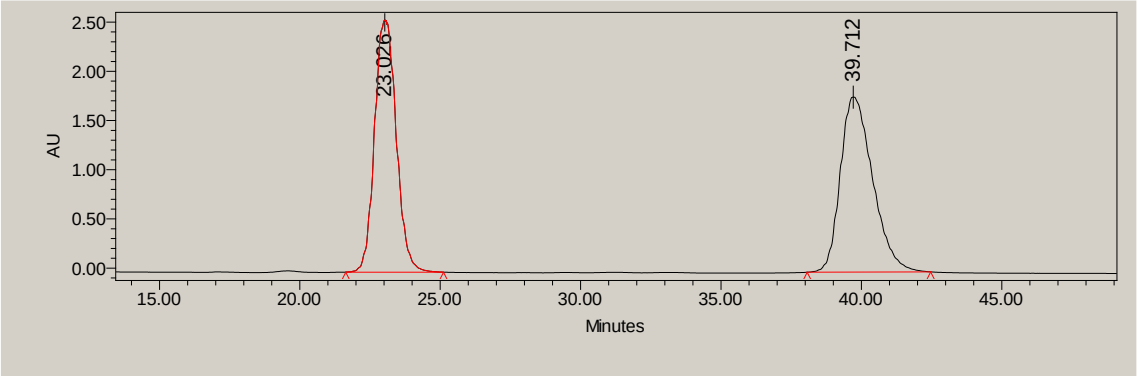
>99% ee



12Hk

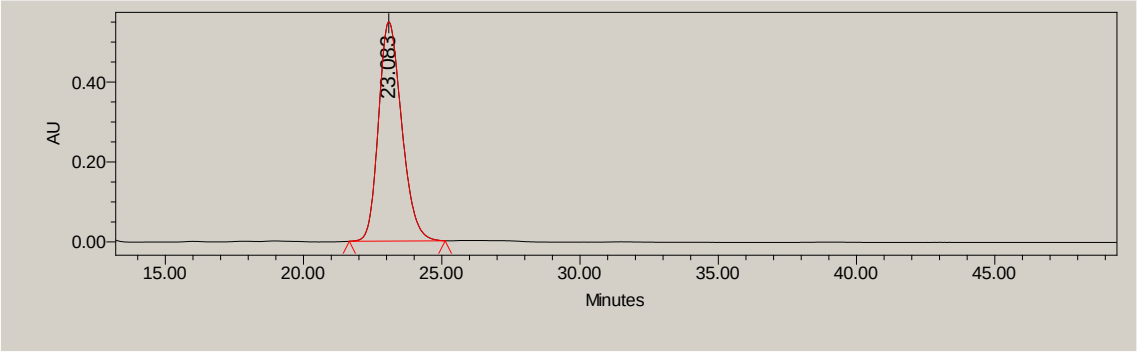
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min).

(±) 12Hk



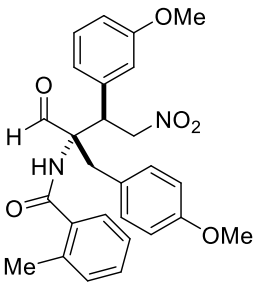
	Retention Time	% Area
1	23.026	49.08
2	39.712	50.92

12Hk



	Retention Time	% Area
1	23.063	100.00

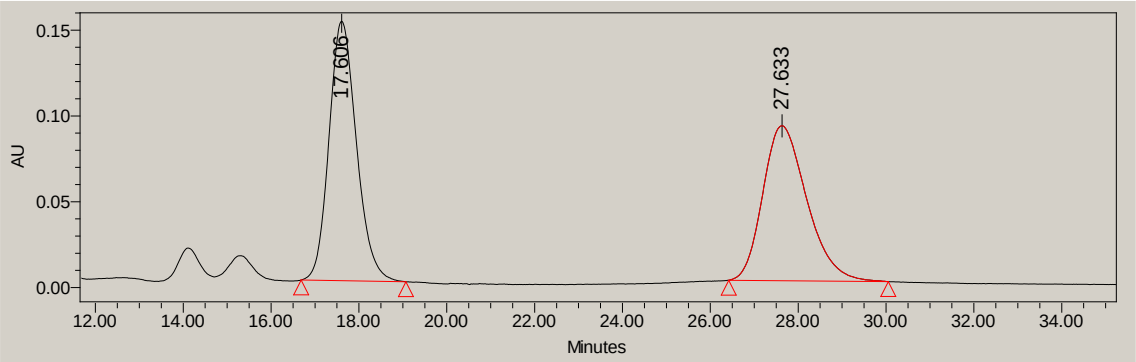
>99%ee



15Fd

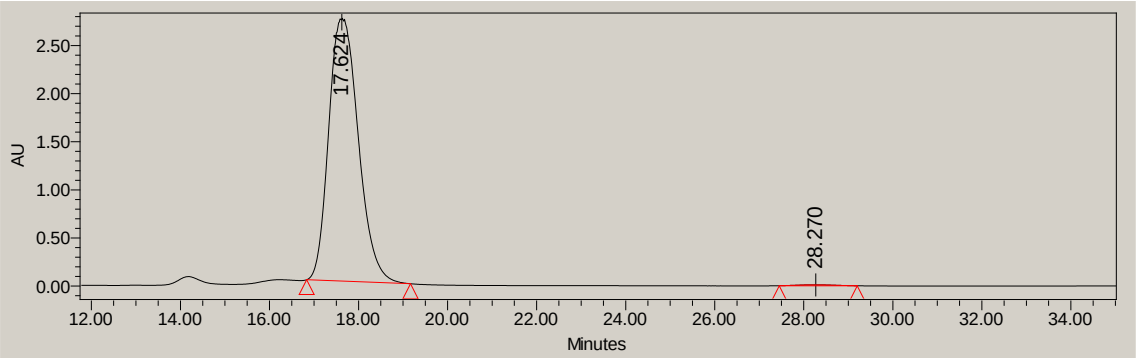
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 70:30, flow rate= 1 mL/min).

(±) 15Fd



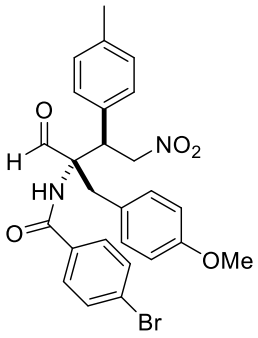
	Retention Time	% Area
1	17.606	51.09
2	27.633	48.91

15Fd



	Retention Time	% Area
1	17.624	99.57
2	28.270	0.43

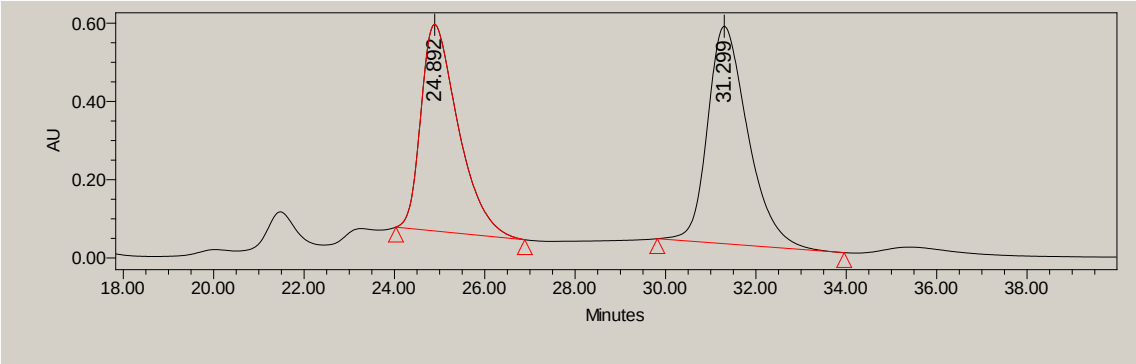
99% ee



15Gg

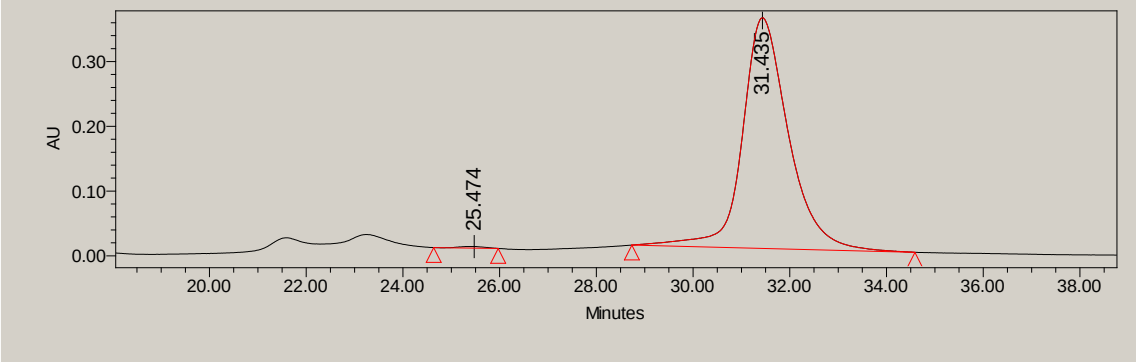
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IF Hexane:^{i}PrOH 80:20, flow rate= 1 mL/min).

(±) 15Gg



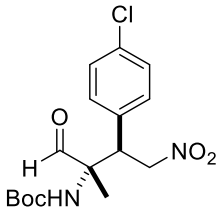
	Retention Time	% Area
1	24.891	49.19
2	31.299	50.81

15Gg



	Retention Time	% Area
1	25.474	0.39
2	31.435	99.61

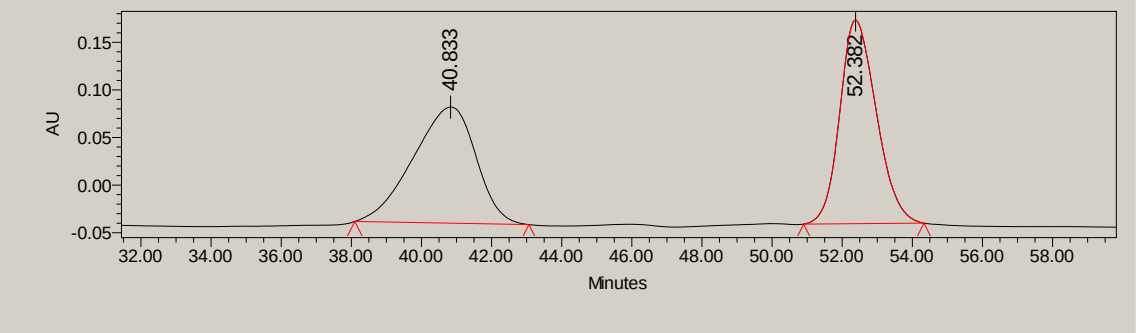
99% ee



10Aa

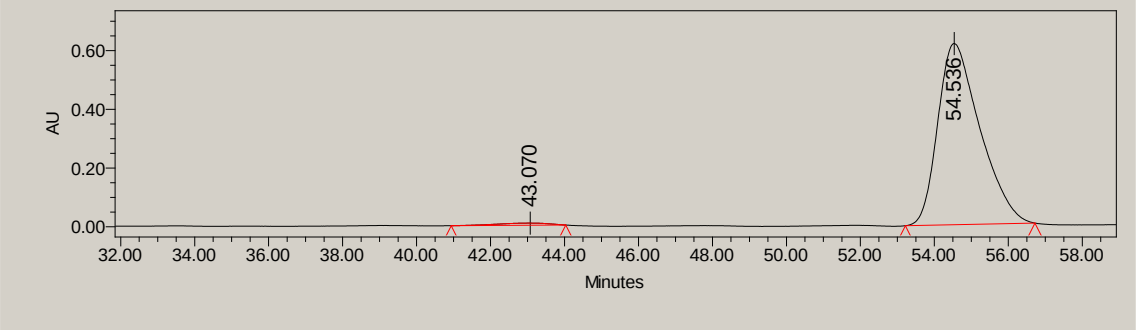
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IF Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 10Aa



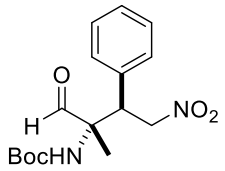
	Retention Time	% Area
1	40.833	49.52
2	52.382	50.48

10Aa



	Retention Time	% Area
1	43.070	1.47
2	54.536	98.53

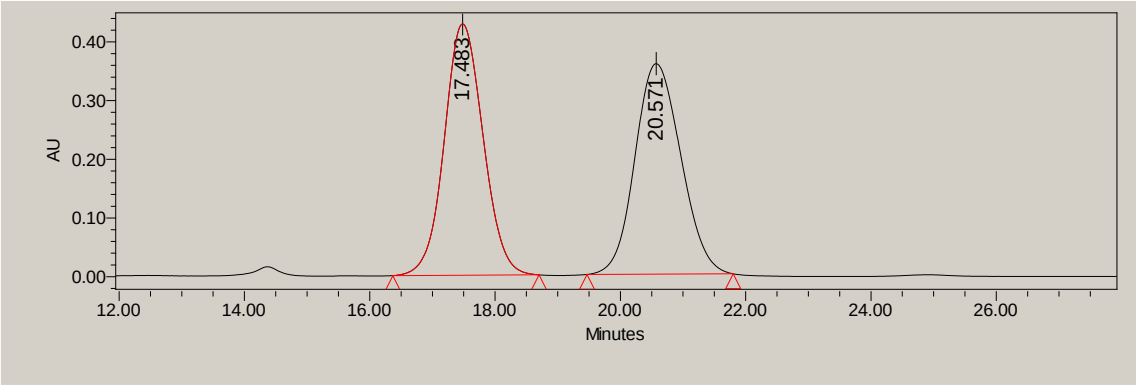
97% ee



10Ab

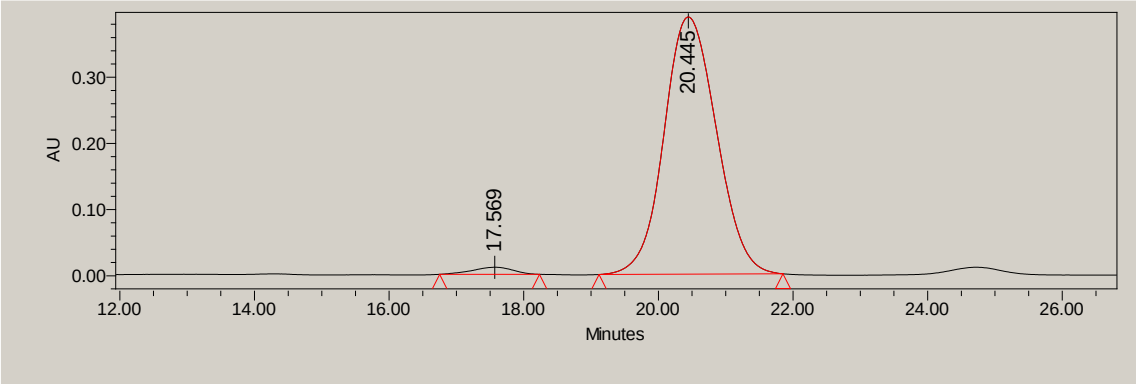
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 10Ab



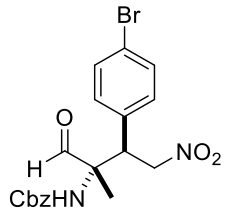
	Retention Time	% Area
1	17.483	50.30
2	20.571	49.70

10Ab



	Retention Time	% Area
1	17.569	2.08
2	20.445	97.92

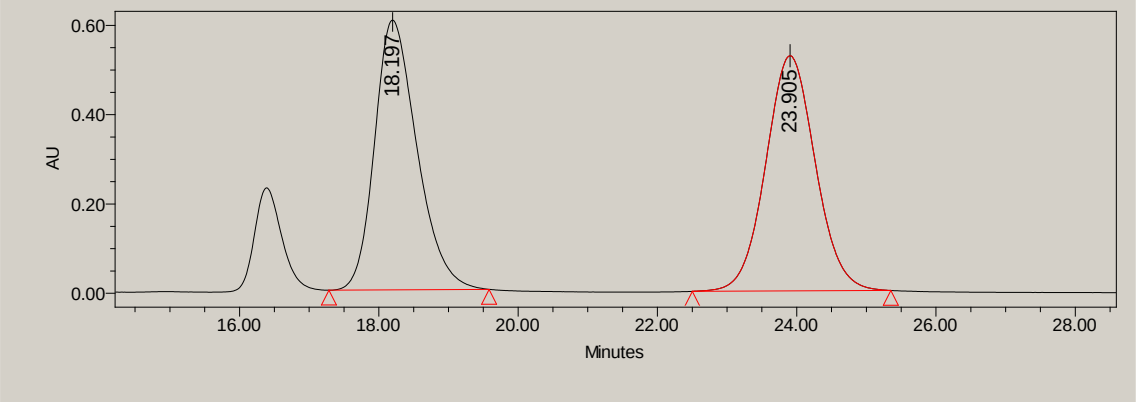
96% ee



10Bf

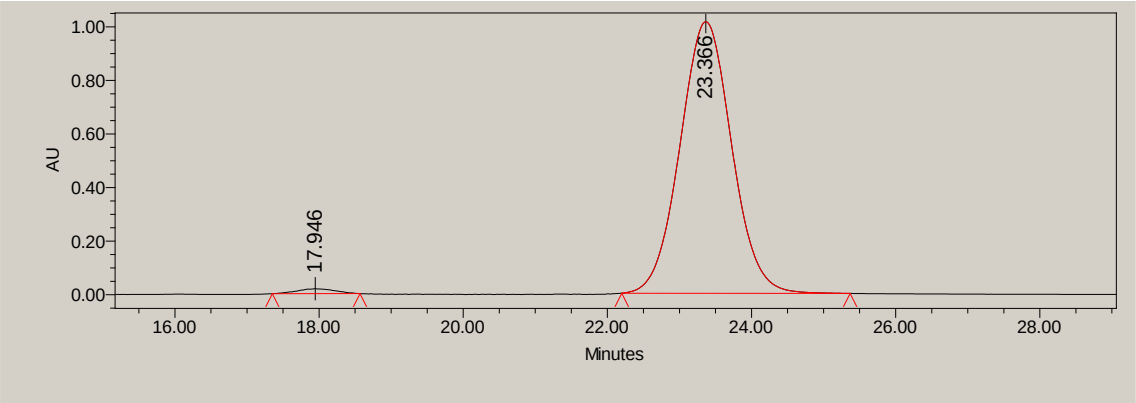
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 10Bf



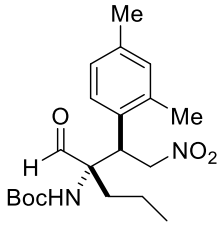
	Retention Time	% Area
1	18.197	49.45
2	23.905	50.55

10Bf



	Retention Time	% Area
1	17.946	1.30
2	23.366	98.70

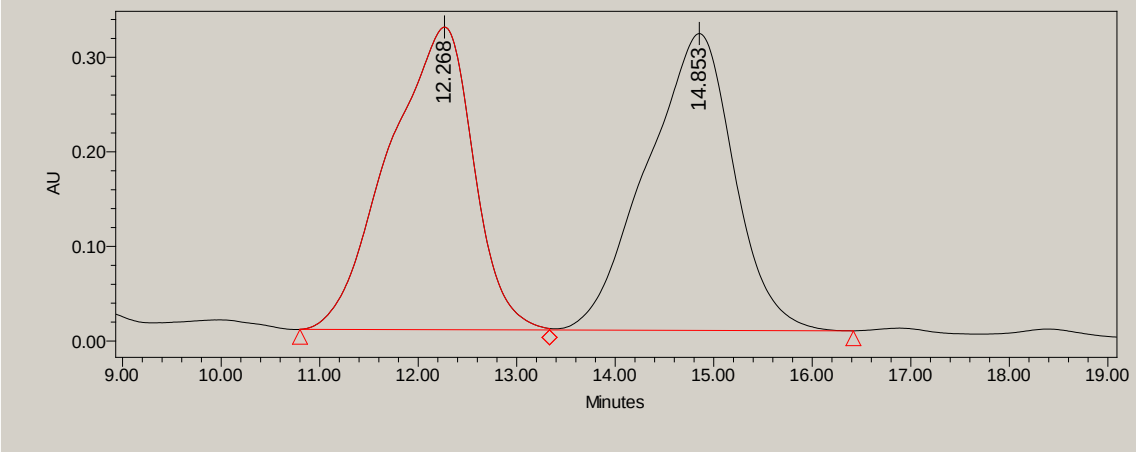
97% ee



11Ag

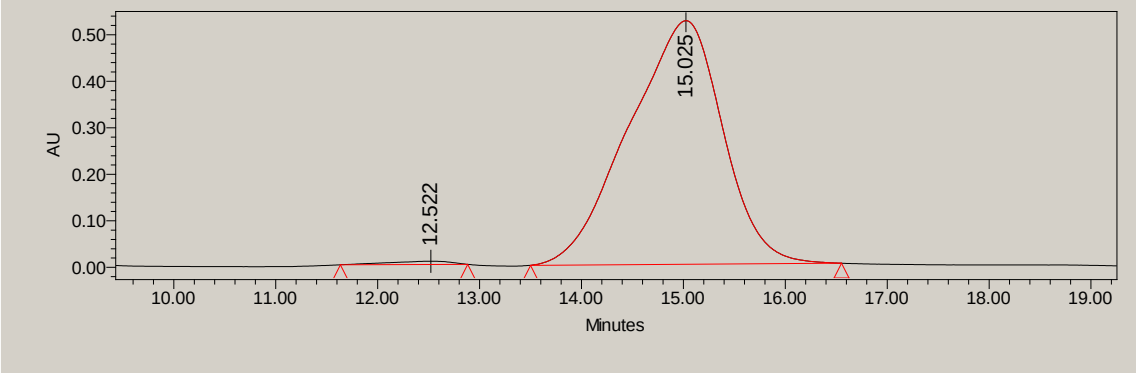
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IF Hexane:^{i}PrOH 99:1, flow rate= 1 mL/min).

(±) 11Ag



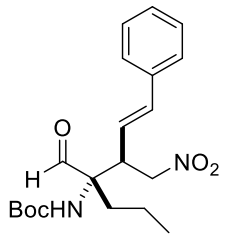
	Retention Time	% Area
1	12.268	49.80
2	14.853	50.20

11Ag



	Retention Time	% Area
1	12.522	1.07
2	15.025	98.93

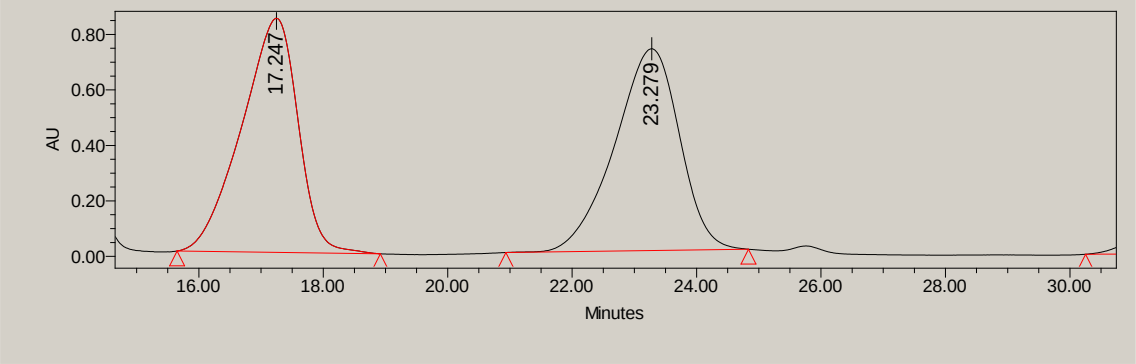
98% ee



11Ah

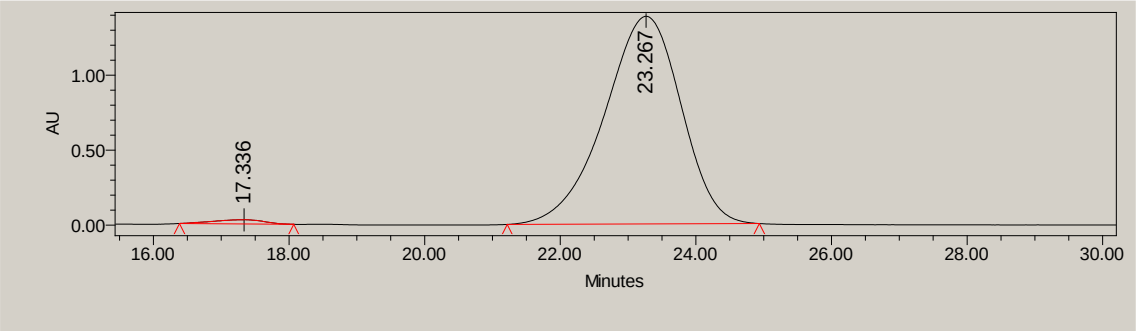
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 11Ah



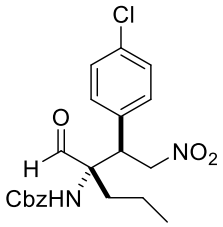
	Retention Time	% Area
1	17.247	50.29
2	23.279	49.71

11Ah



	Retention Time	% Area
1	17.336	1.30
2	23.267	98.70

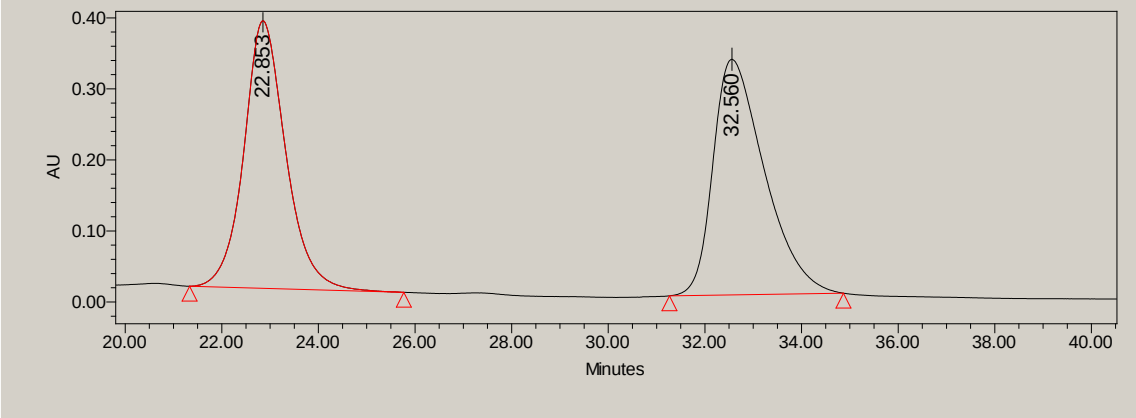
97% ee



11Ba

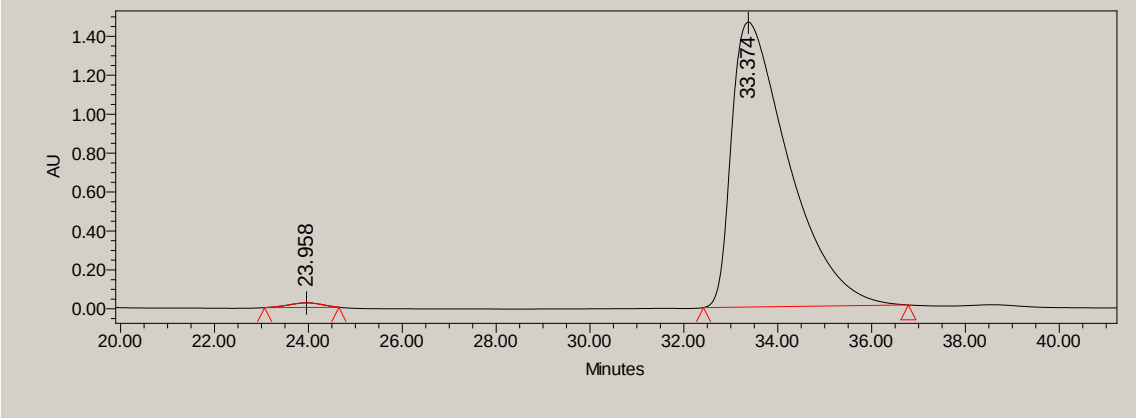
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak ID Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 11Ba



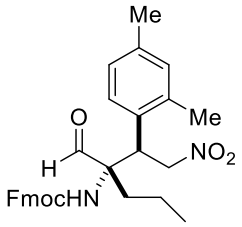
	Retention Time	% Area
1	22.853	48.09
2	32.560	51.91

11Ba



	Retention Time	% Area
1	23.958	0.93
2	33.374	99.07

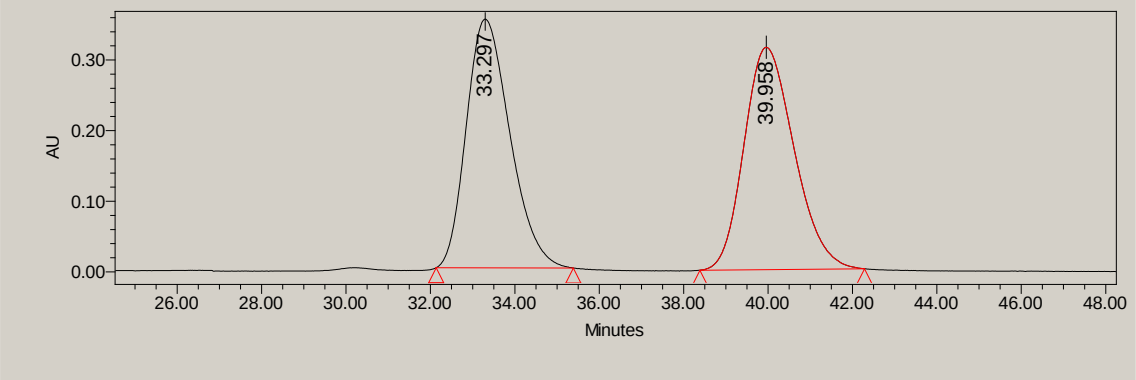
98% ee



11Cg

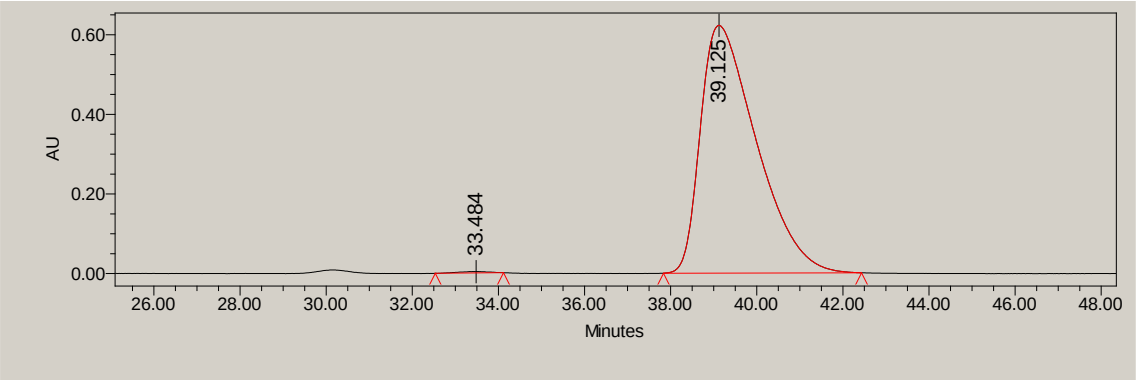
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 11Cg



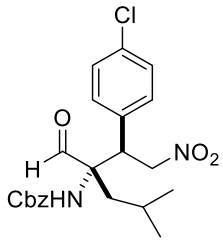
	Retention Time	% Area
1	33.297	49.36
2	39.958	50.64

11Cg



	Retention Time	% Area
1	33.484	0.31
2	39.125	99.69

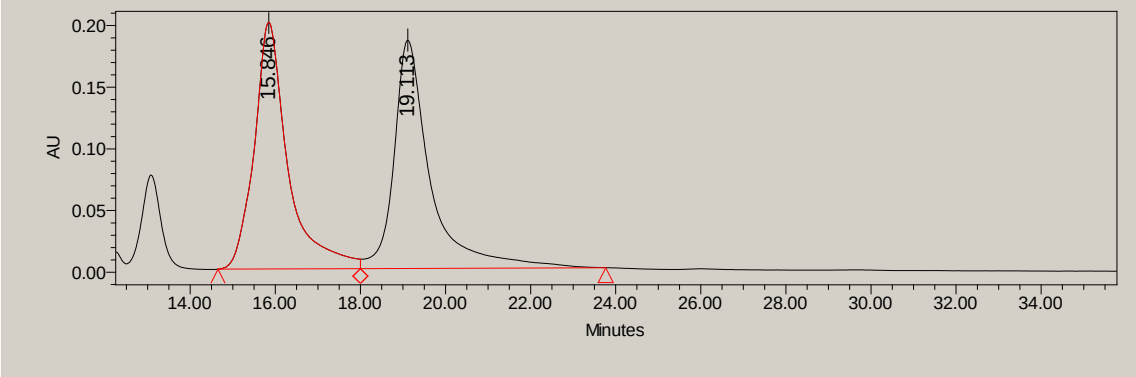
99% ee



12Ba

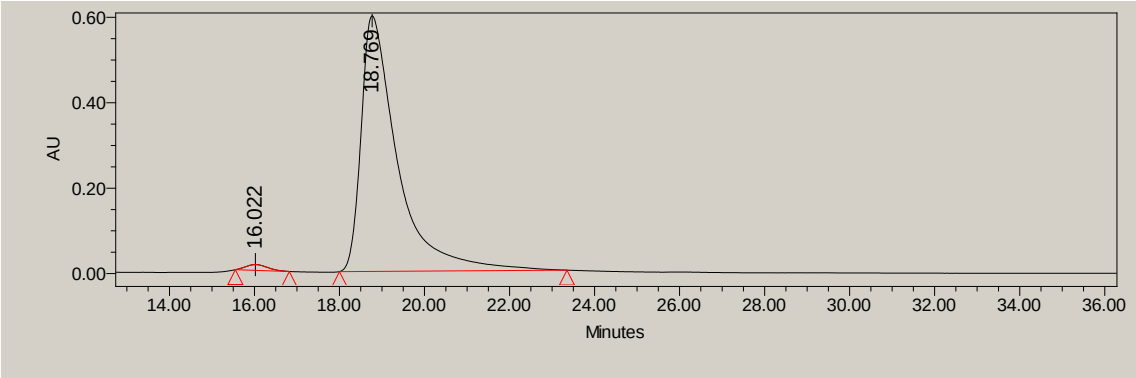
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IB Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 12Ba



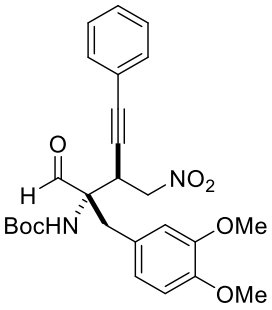
	Retention Time	% Area
1	15.846	49.99
2	19.113	50.01

12Ba



	Retention Time	% Area
1	16.022	1.33
2	18.769	98.67

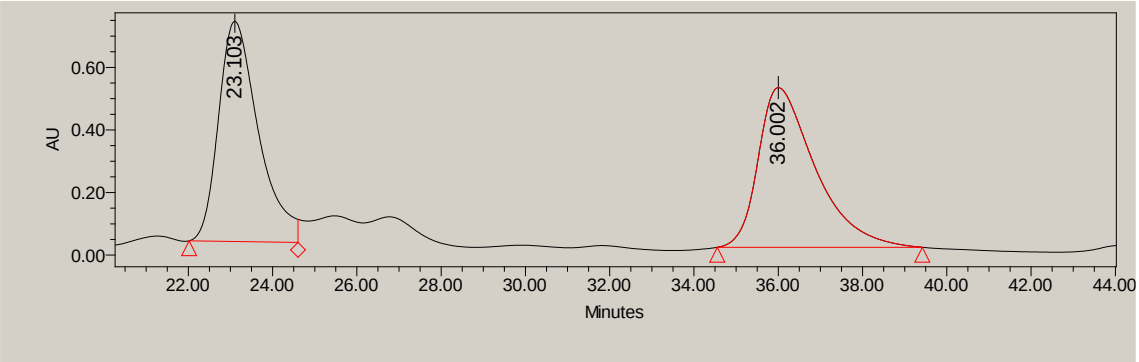
97% ee



13Ai

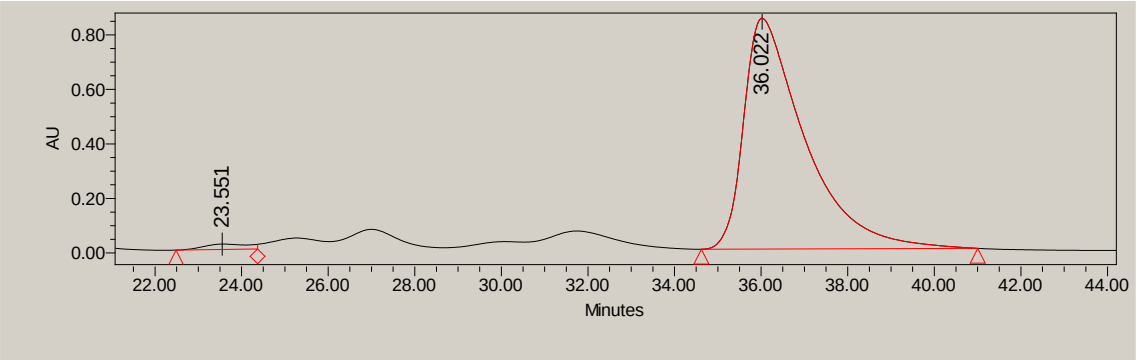
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 13Ai



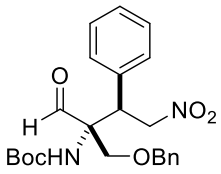
	Retention Time	% Area
1	23.103	49.09
2	36.002	50.91

13Ai



	Retention Time	% Area
1	23.551	1.69
2	36.022	98.31

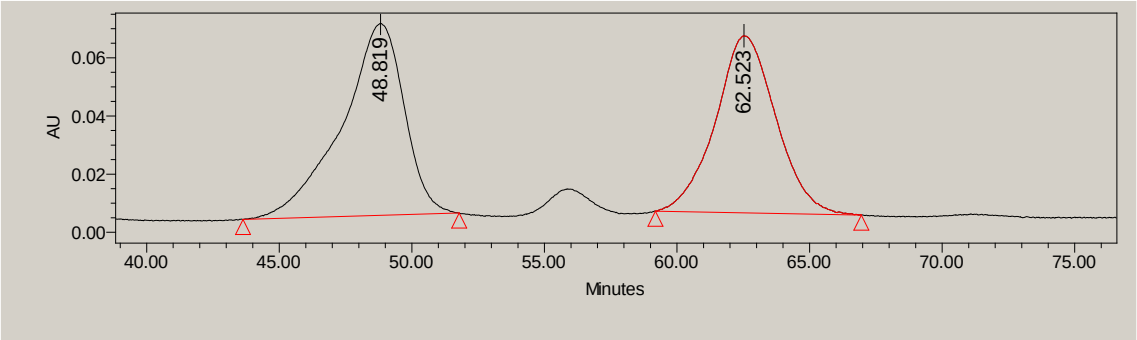
97% ee



14Ab

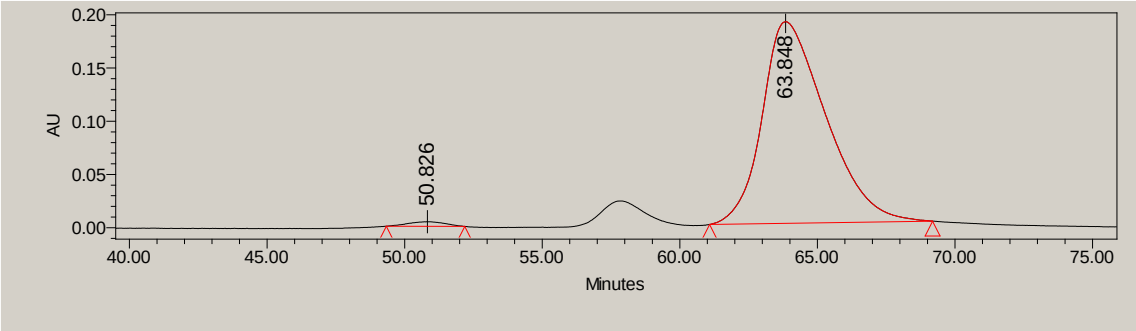
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak ID Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 14Ab



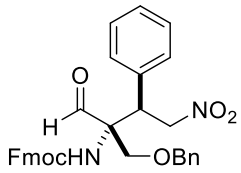
	Retention Time	% Area
1	48.819	52.72
2	62.523	47.28

14Ab



	Retention Time	% Area
1	50.826	1.29
2	63.848	98.71

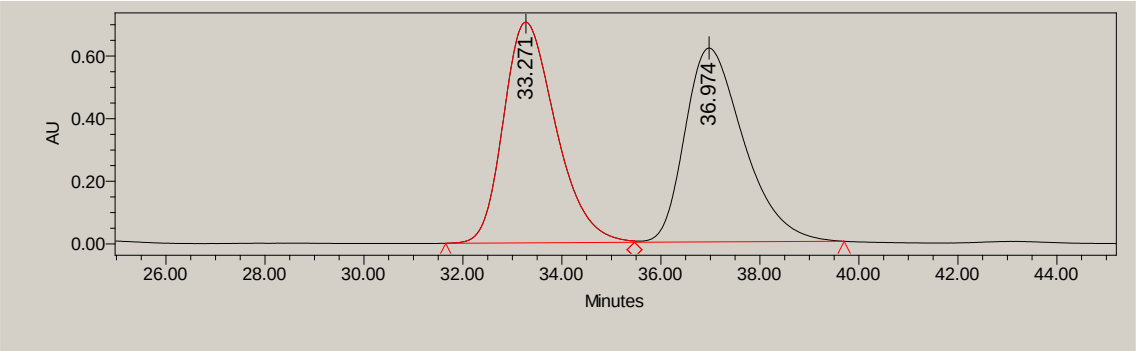
97% ee



14Cb

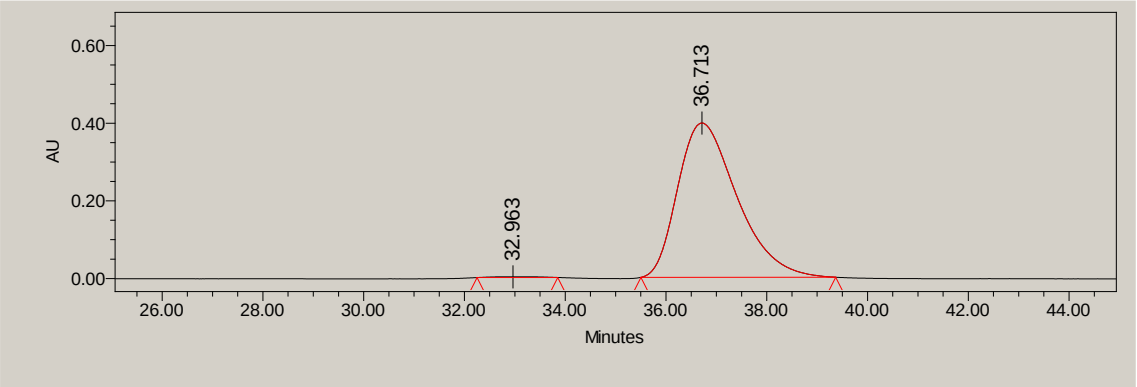
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 14Cb



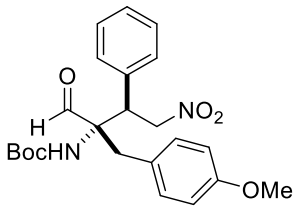
	Retention Time	% Area
1	33.271	50.34
2	36.974	49.66

14Cb



	Retention Time	% Area
1	32.963	0.42
2	36.713	99.58

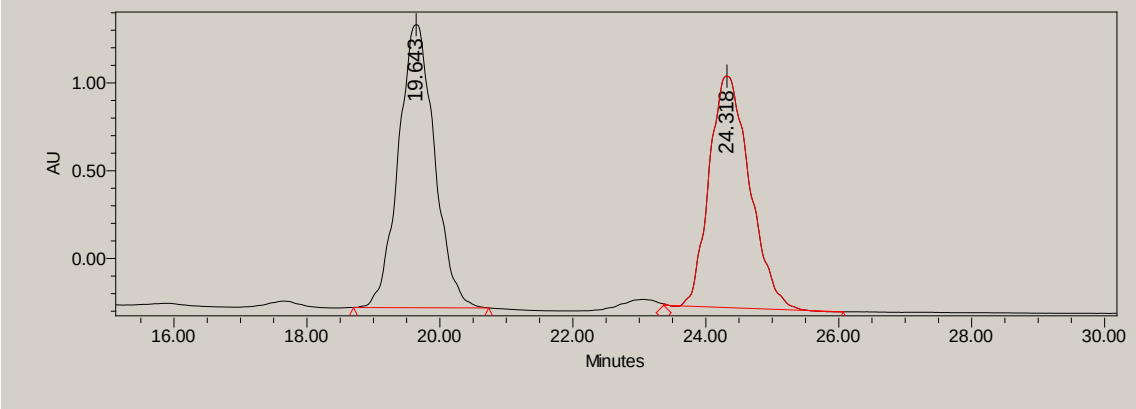
99% ee



15Ab

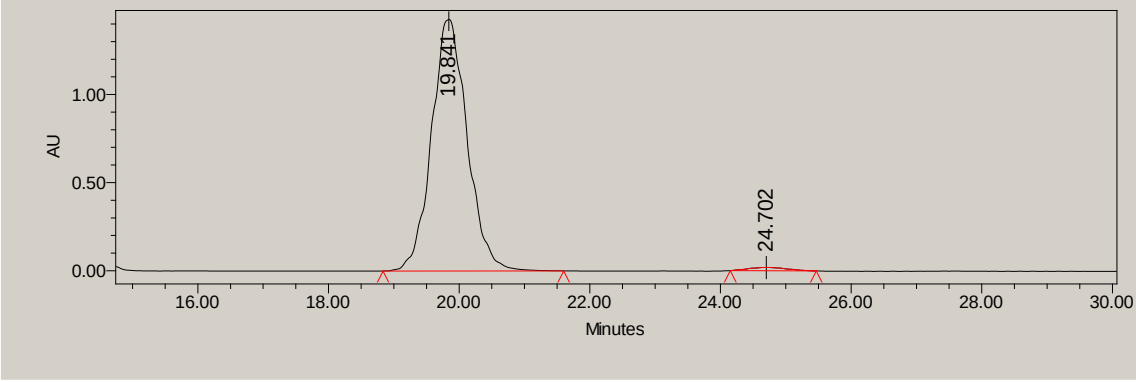
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH80:20, flow rate= 1 mL/min).

(±) 15Ab



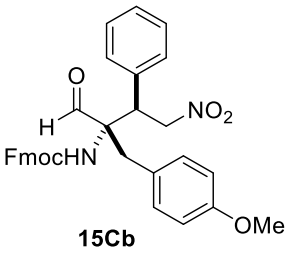
	Retention Time	% Area
1	19.643	52.13
2	24.318	47.87

15Ab



Retention Time	% Area
19.841	98.60
24.702	1.40

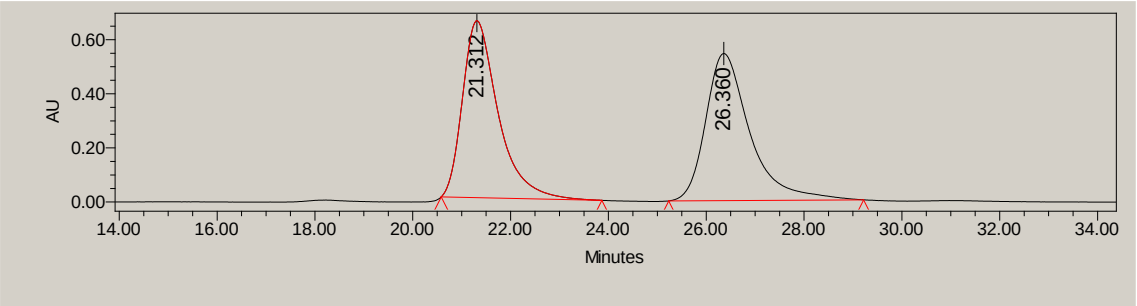
97% ee



15Cb

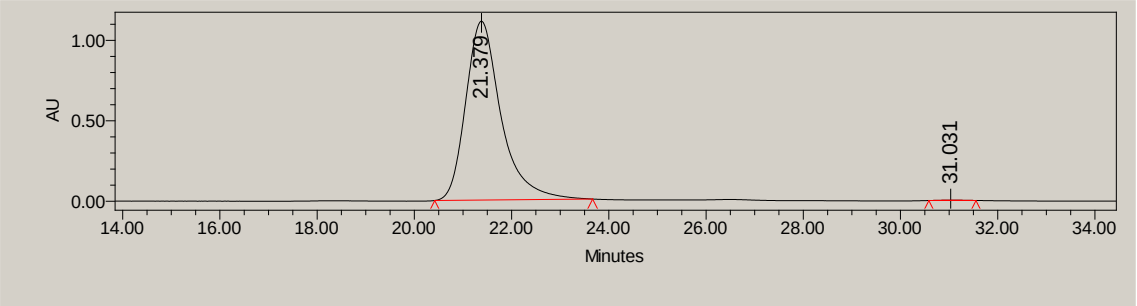
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 15Cb



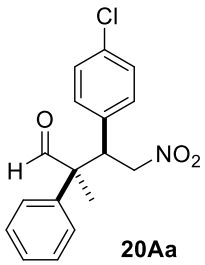
	Retention Time	% Area
1	21.312	49.31
2	26.360	50.69

15Cb



	Retention Time	% Area
1	21.379	100

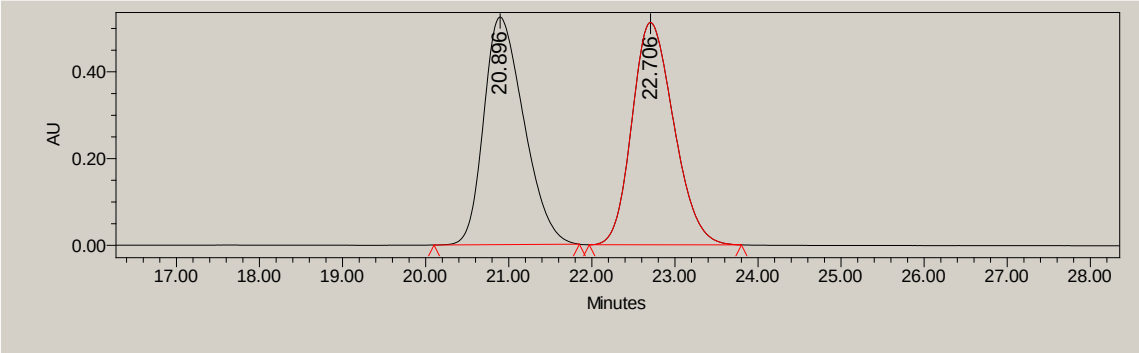
>99% ee



20Aa

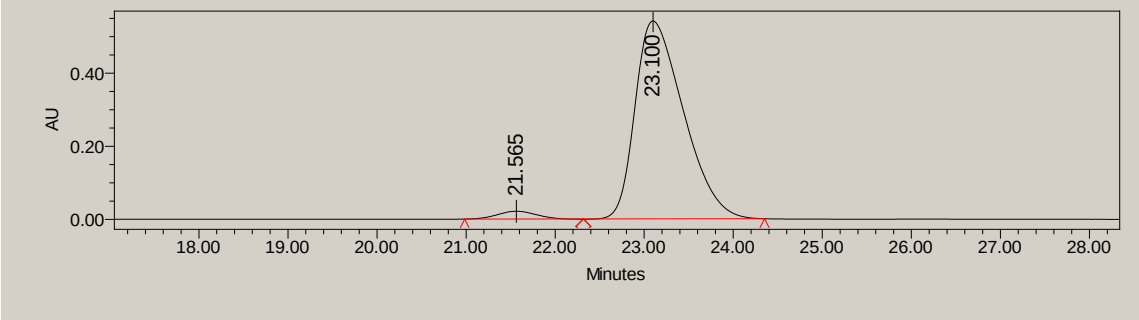
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 20Aa



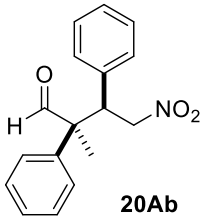
	Retention Time	% Area
1	20.896	49.54
2	22.706	50.46

20Aa



	Retention Time	% Area
1	21.565	3.07
2	23.100	96.93

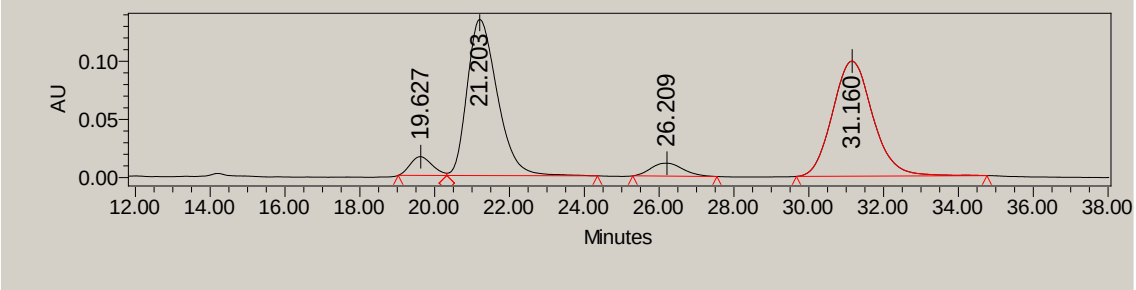
94% ee



20Ab

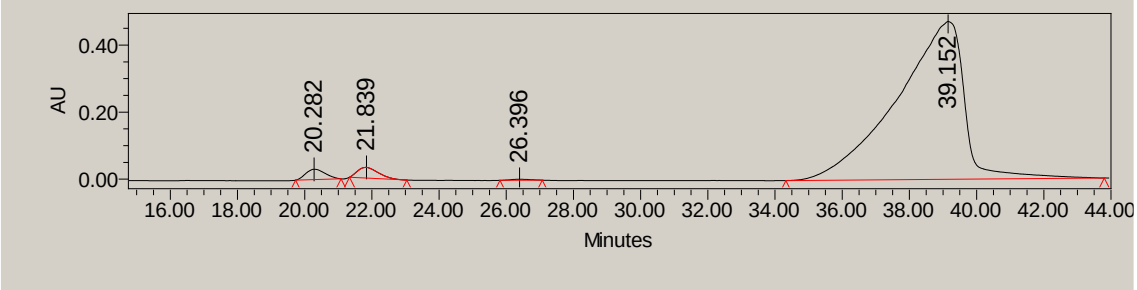
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 20Ab



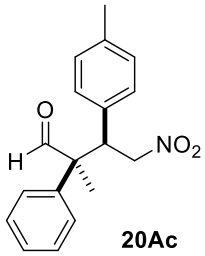
	Retention Time	% Area
1	19.627	4.05
2	21.203	46.23
3	26.209	4.10
4	31.160	45.62

20Ab



	Retention Time	% Area
1	20.282	1.81
2	21.839	2.01
3	26.396	0.18
4	39.152	96.00

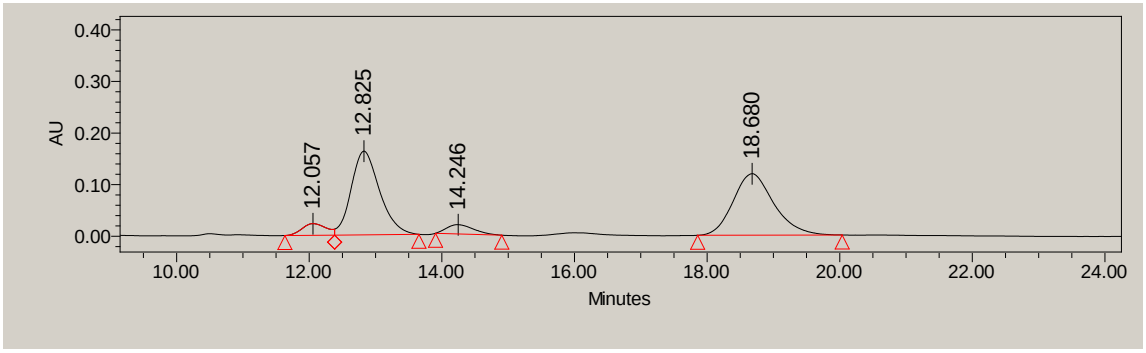
96% ee



20Ac

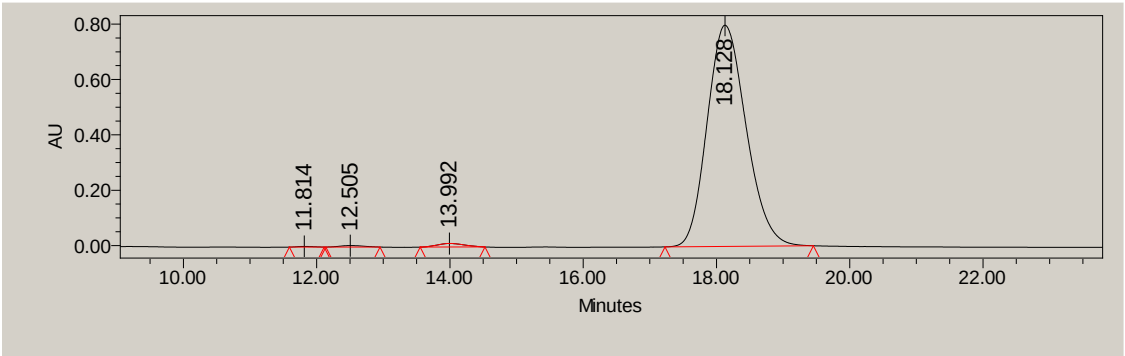
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 20Ac



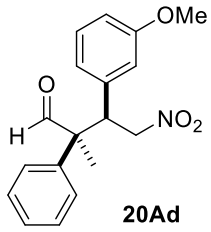
	Retention Time	% Area
1	12.057	5.27
2	12.825	43.96
3	14.246	4.63
4	18.680	46.14

20Ac



	Retention Time	% Area
1	11.814	0.11
2	12.505	0.38
3	13.992	1.11
4	18.128	98.40

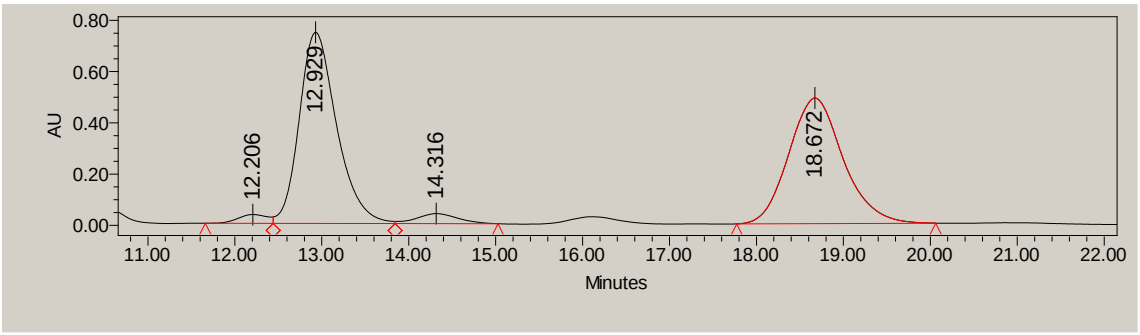
99% ee



20Ad

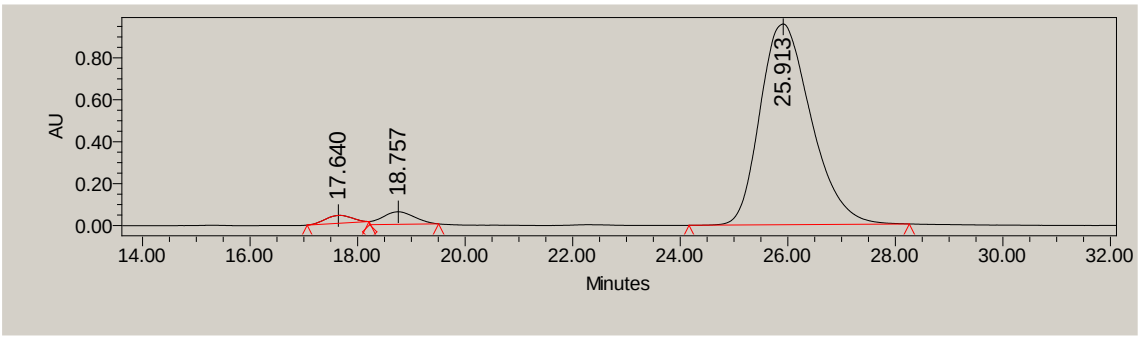
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H Hexane:^{i}PrOH 90:10, flow rate= 1 mL/min).

(±) 20Ad



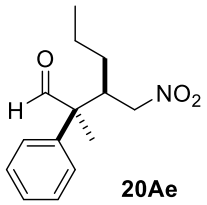
	Retention Time	% Area
1	12.207	1.80
2	12.929	48.53
3	14.324	2.22
4	18.672	47.46

20Ad



	Retention Time	% Area
1	17.640	1.90
2	18.757	3.71
3	25.913	94.39

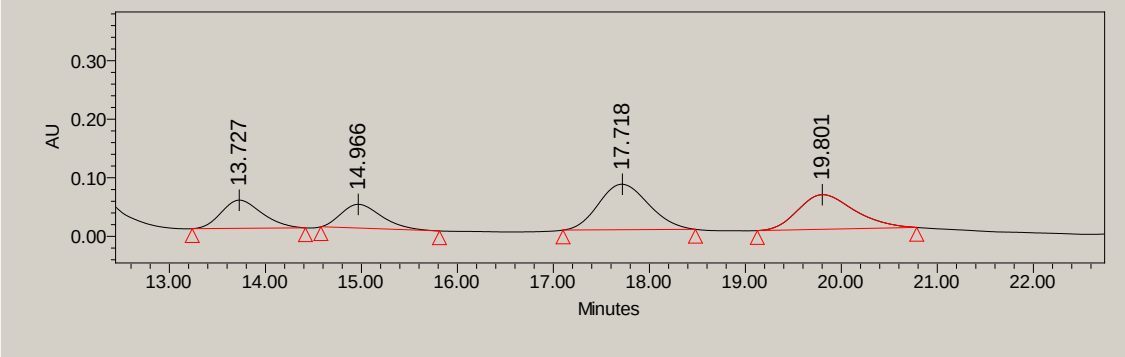
92% ee



20Ae

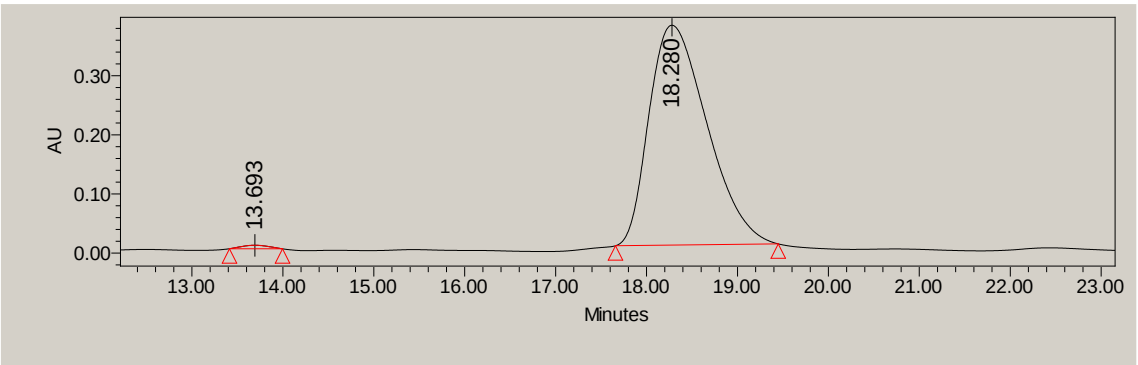
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 20Ae



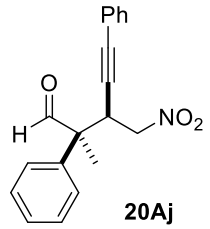
	Retention Time	% Area
1	13.727	18.02
2	14.966	15.17
3	17.718	35.96
4	19.801	30.85

20Ae



	Retention Time	% Area
1	13.693	0.74
2	18.280	99.26

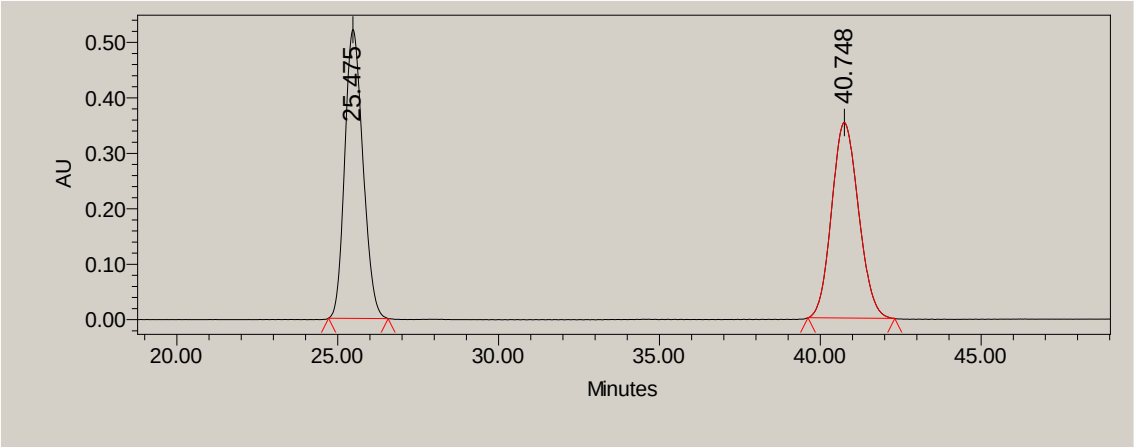
99% ee



20Aj

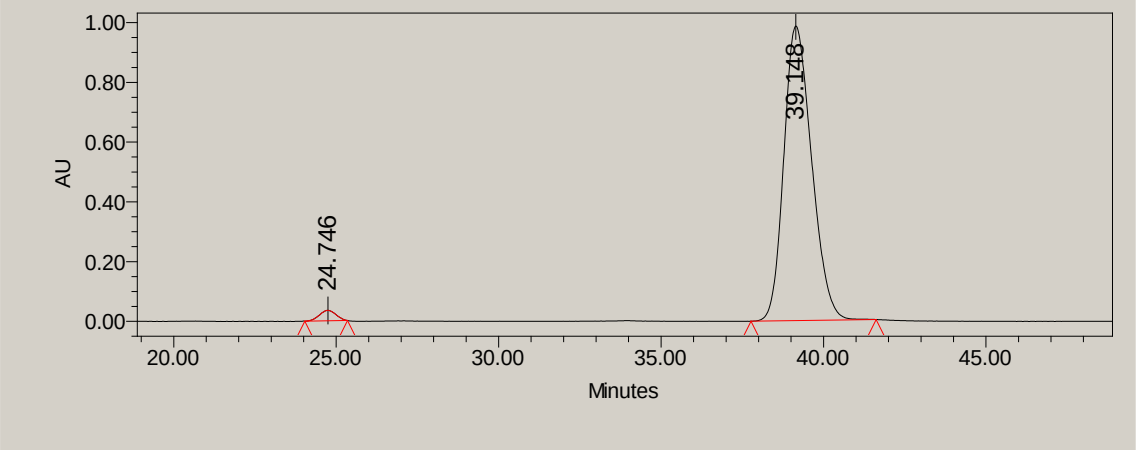
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 20Aj



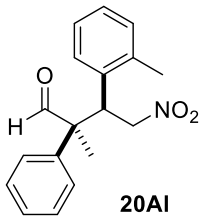
	Retention Time	% Area
1	25.475	49.97
2	40.748	50.03

20Aj



	Retention Time	% Area
1	24.746	2.07
2	39.148	97.93

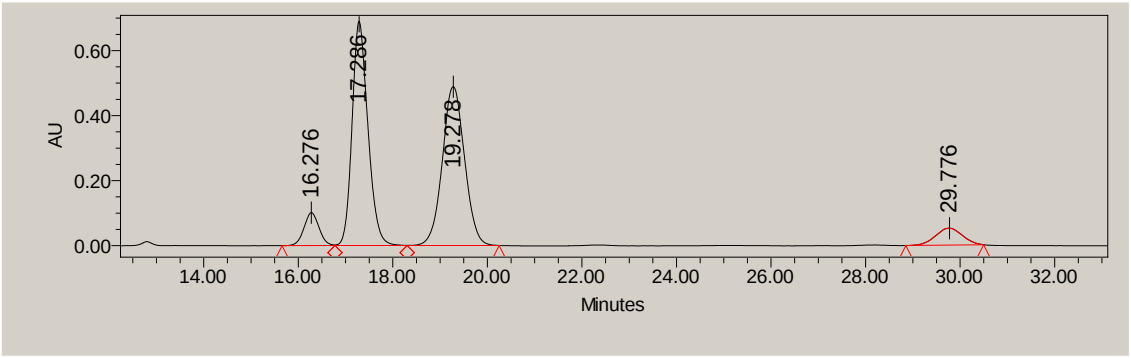
96% ee



20Al

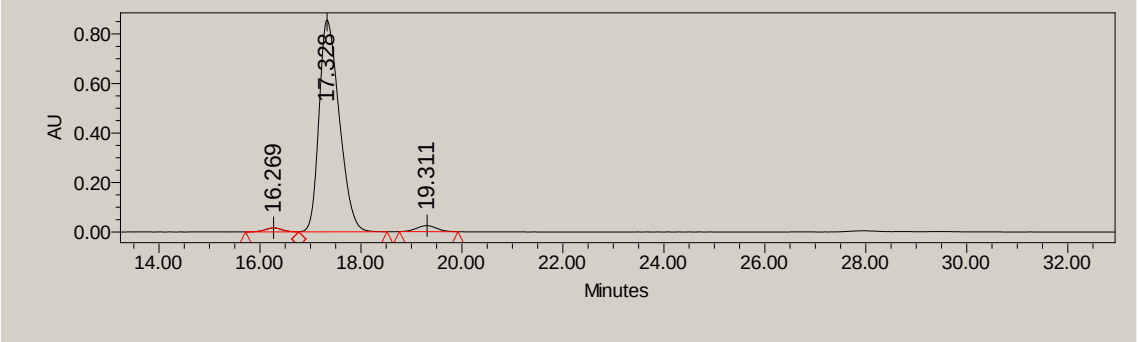
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 20Al



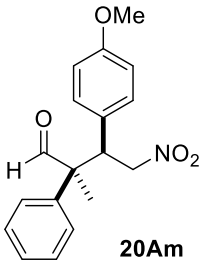
	Retention Time	% Area
1	16.276	6.15
2	17.286	44.21
3	19.278	44.00
4	29.776	5.64

20Al



	Retention Time	% Area
1	16.269	1.52
2	17.328	95.76
3	19.311	2.73

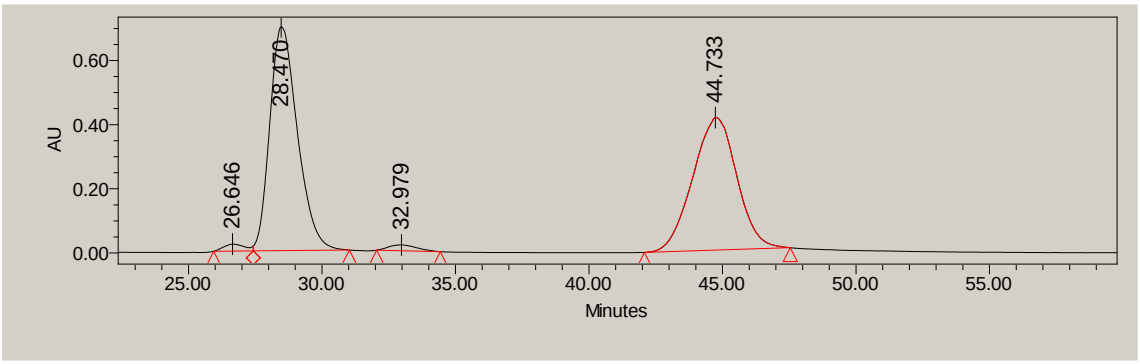
94% ee



20Am

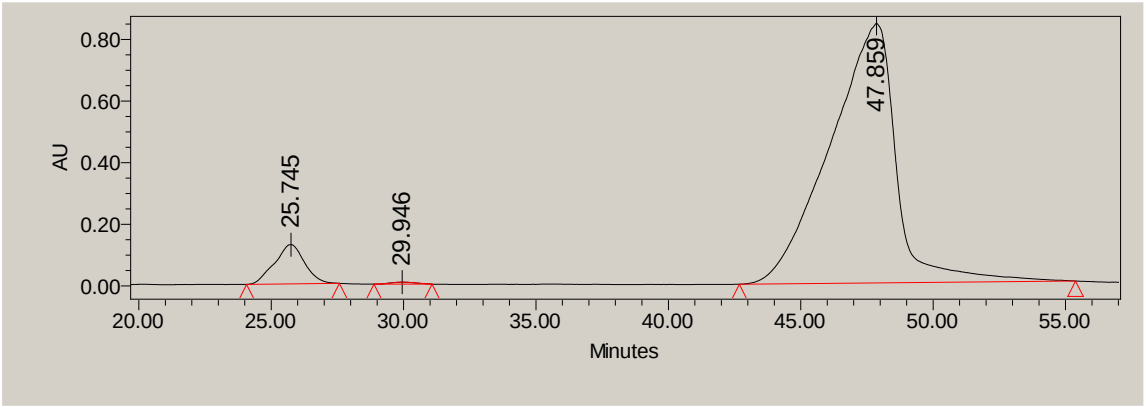
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 20Am



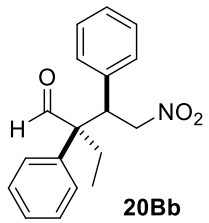
	Retention Time	% Area
1	26.646	1.21
2	28.470	50.15
3	32.979	1.33
4	44.733	47.31

20Am



	Retention Time	% Area
1	25.745	6.39
2	29.946	0.27
3	47.859	93.34

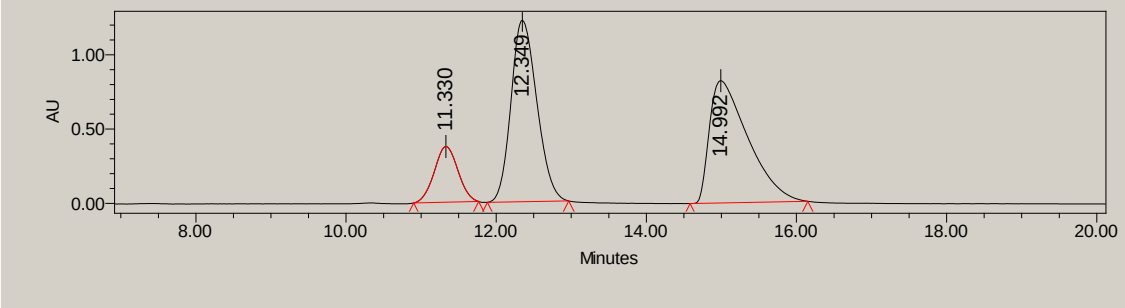
87% ee



20Bb

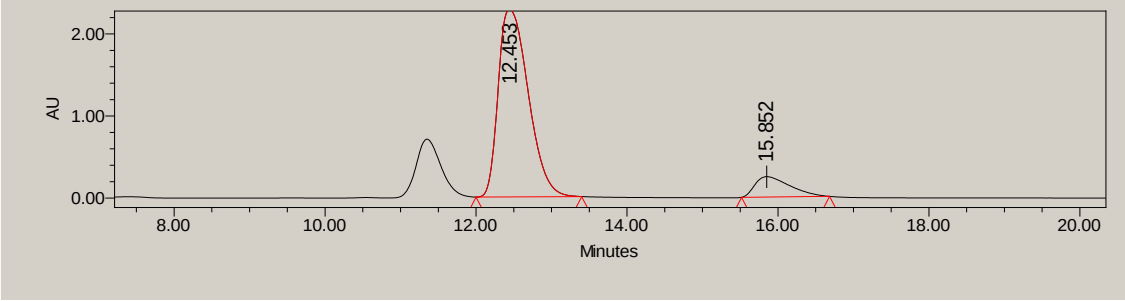
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IF Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 20Bb



	Retention Time	% Area
1	11.330	12.33
2	12.349	43.76
3	14.992	43.91

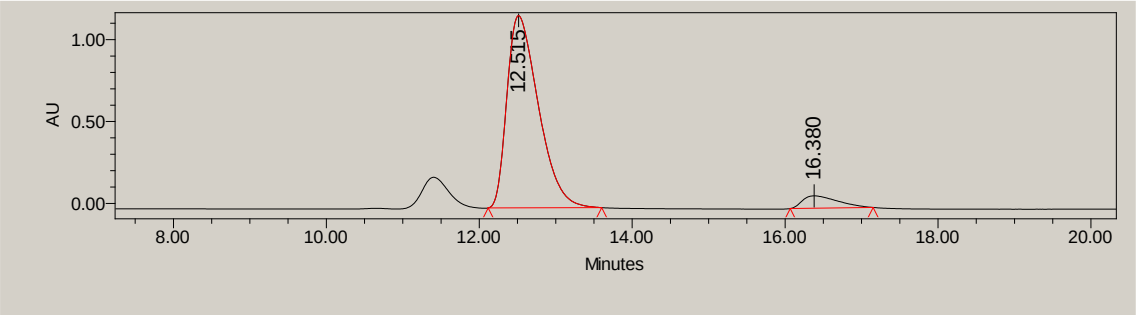
20Bb with catalyst **C20**



	Retention Time	% Area
1	12.453	88.81
2	15.852	11.19

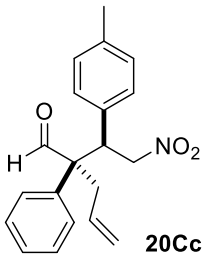
78% ee

20Bb with catalyst **C5**



	Retention Time	% Area
1	12.515	93.29
2	16.380	6.71

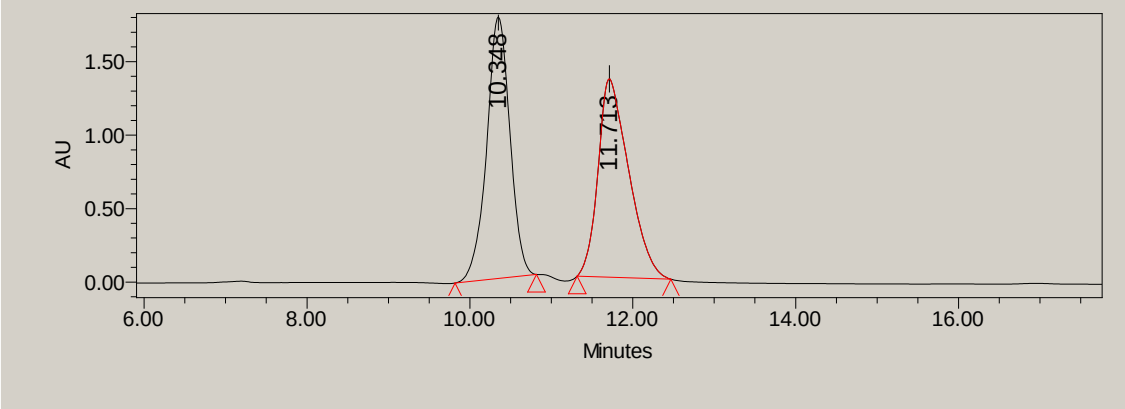
87% ee



20Cc

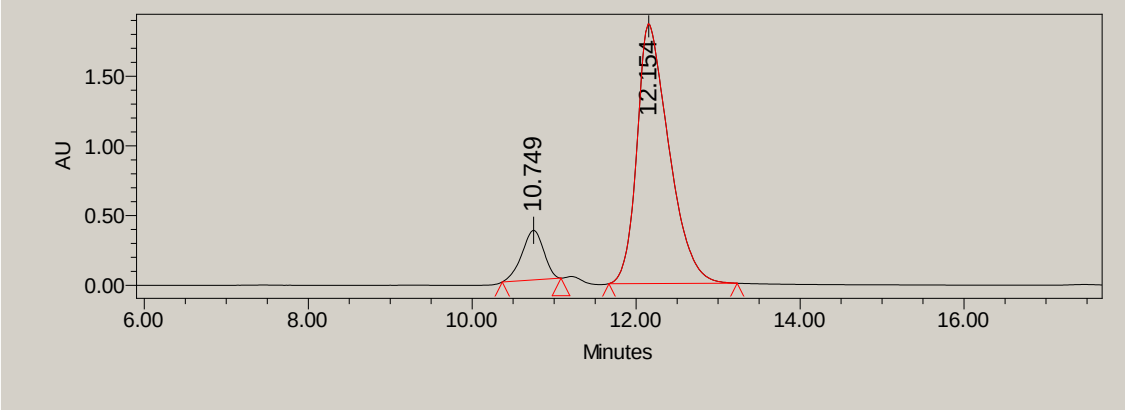
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IB Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 20Cc



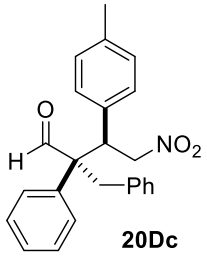
	Retention Time	% Area
1	10.348	50.03
2	11.713	49.97

20Cc



	Retention Time	% Area
1	10.749	11.52
2	12.154	88.48

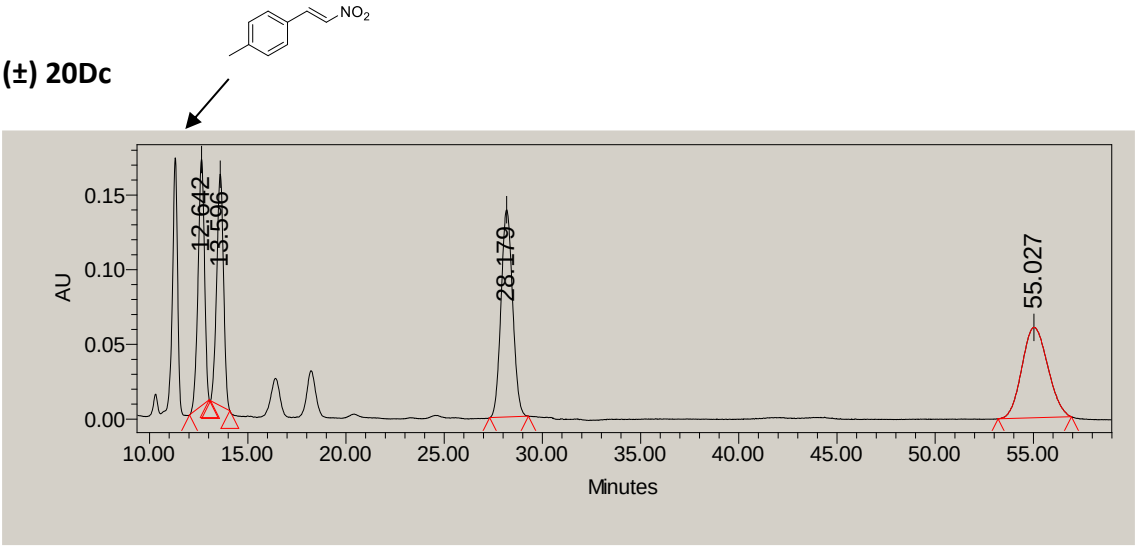
77% ee



20Dc

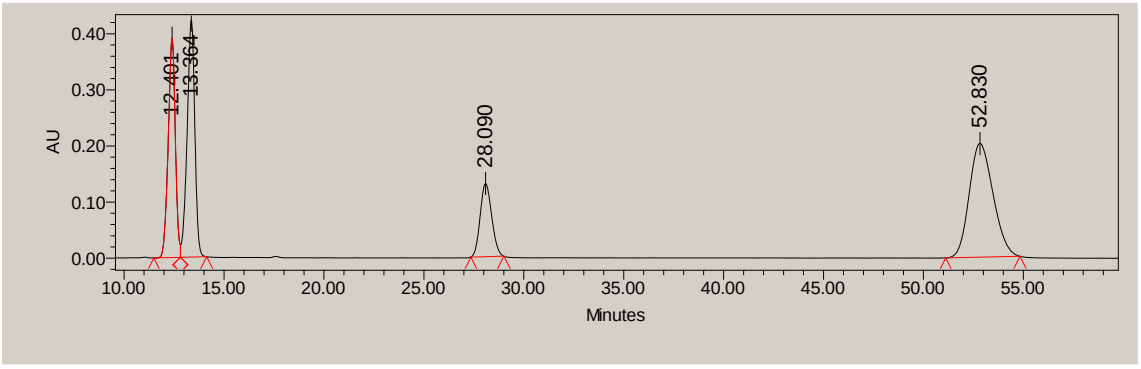
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 20Dc



	Retention Time	% Area
1	12.642	19.99
2	13.596	19.96
3	28.179	30.45
4	55.027	29.60

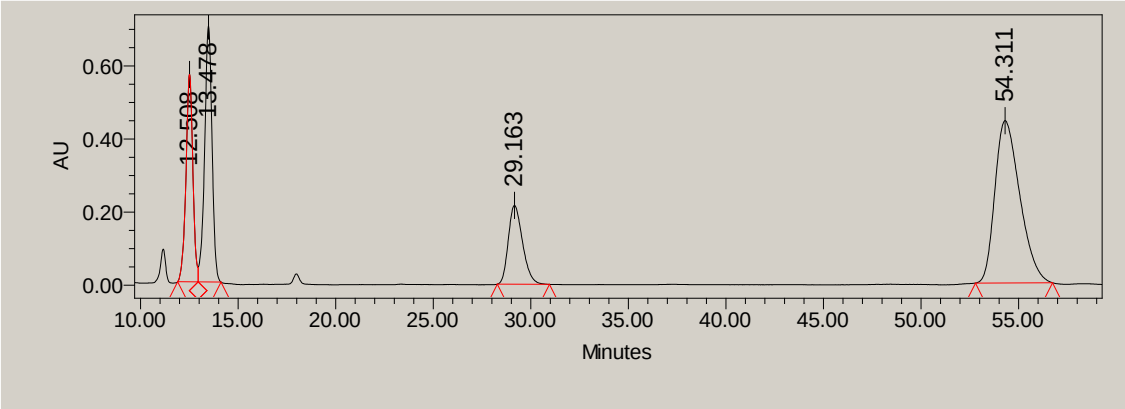
20Dc with catalyst **C20**



	Retention Time	% Area
1	12.401	22.49
2	13.364	26.20
3	28.090	12.16
4	52.830	39.15

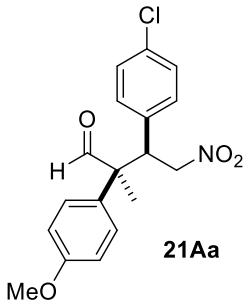
53(8)% ee

20Dc with catalyst **C5**



	Retention Time	% Area
1	12.508	16.88
2	13.478	22.25
3	29.163	13.23
4	54.311	47.64

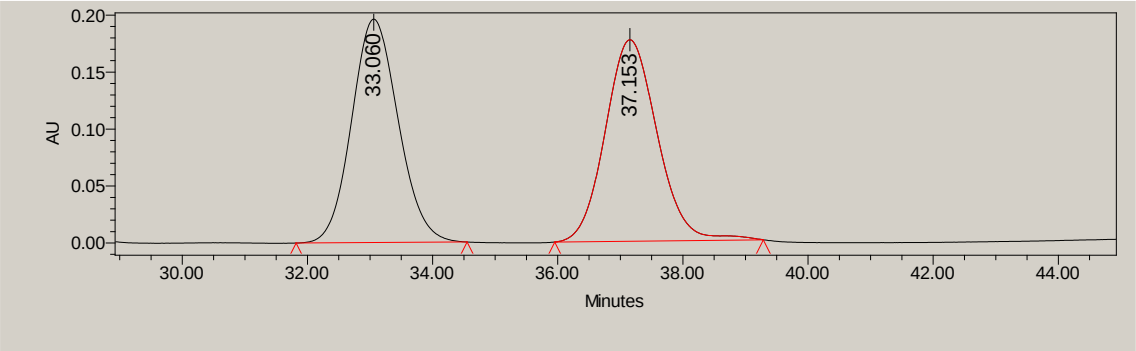
56(14)% ee



21Aa

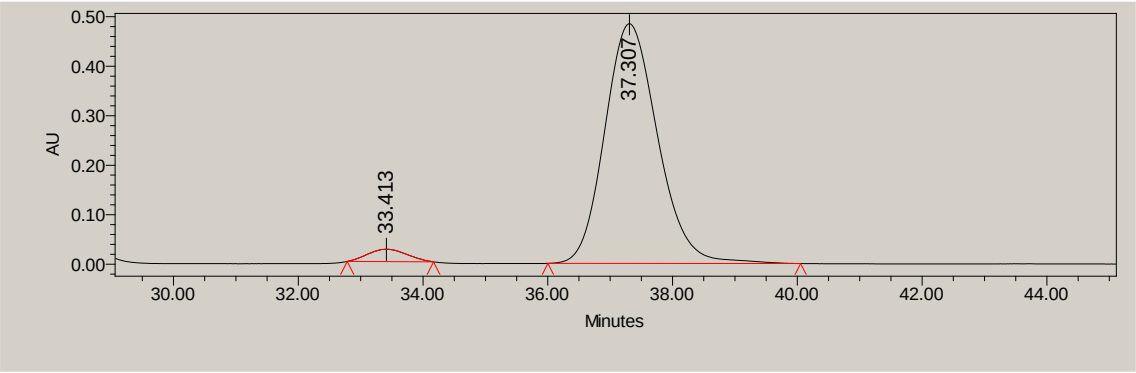
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 21Aa



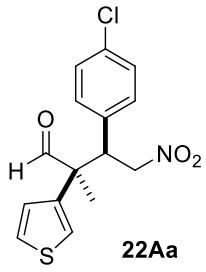
	Retention Time	% Area
1	33.060	49.85
2	37.153	50.15

21Aa



	Retention Time	% Area
1	33.413	3.68
2	37.307	96.32

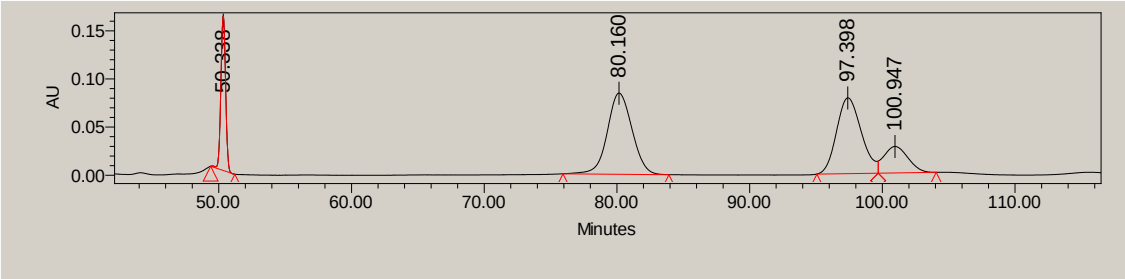
93% ee



22Aa

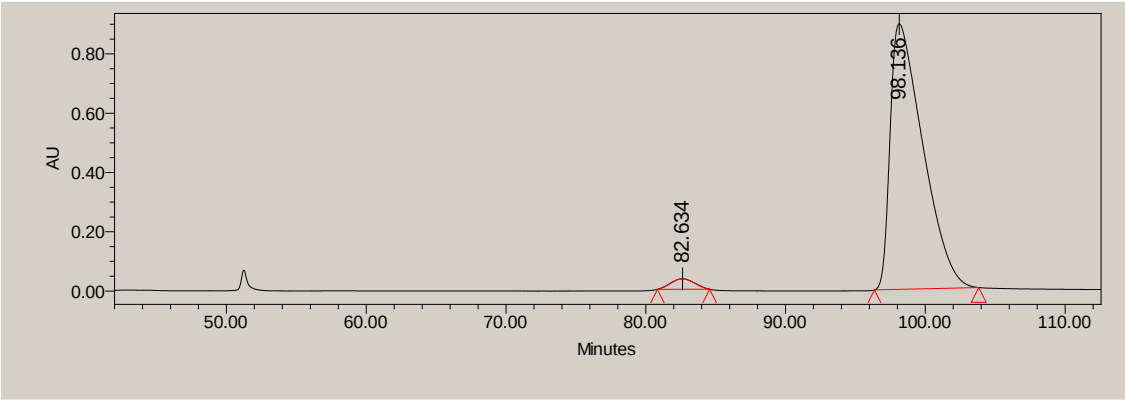
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 98:2, flow rate= 0.5 mL/min).

(±) 22Aa



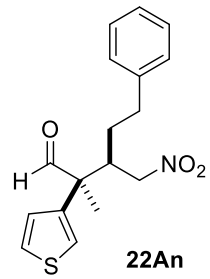
	Retention Time	% Area
1	50.338	13.95
2	80.160	38.20
3	97.398	35.72
4	100.947	12.14

22Aa



	Retention Time	% Area
1	82.634	2.78
2	98.136	97.22

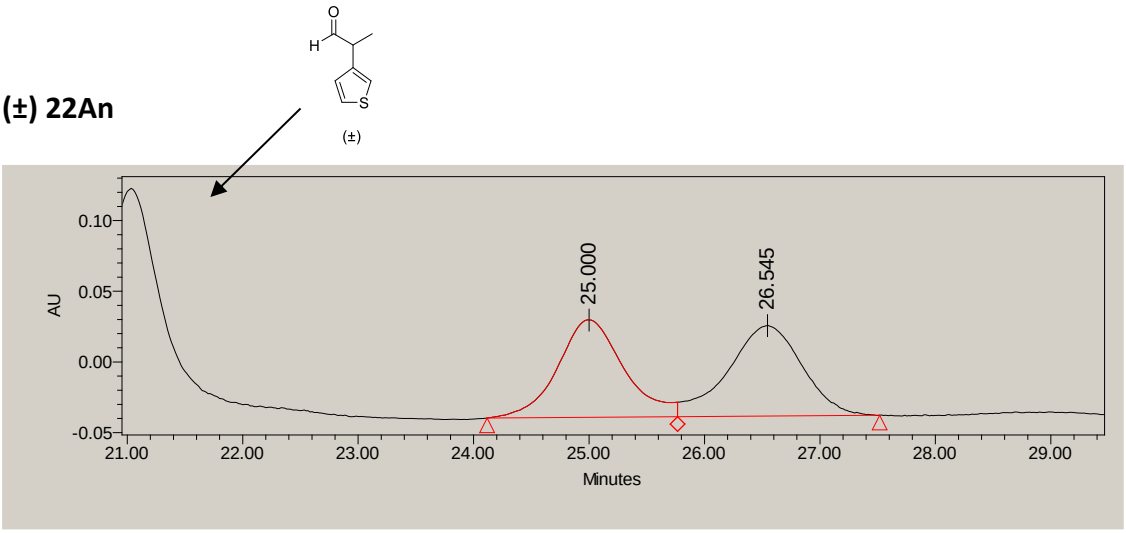
94% ee



22An

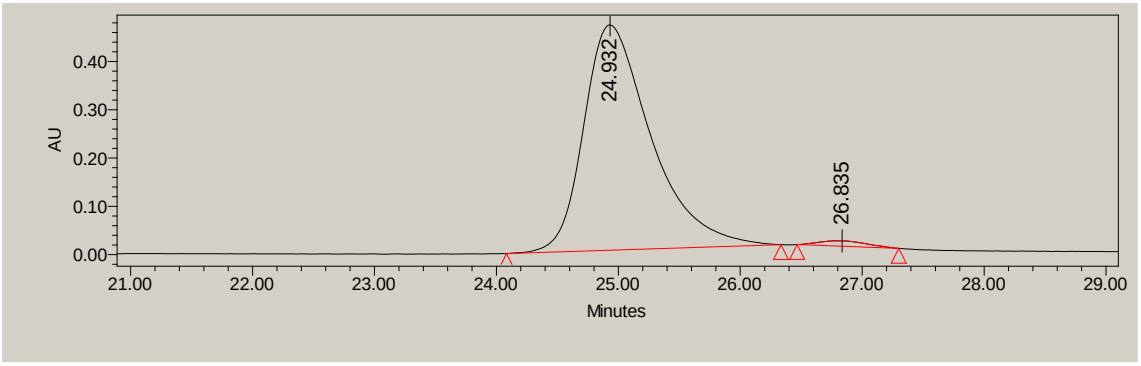
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IB Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 22An



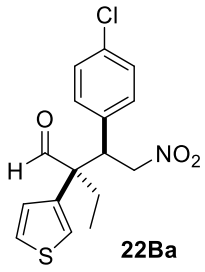
	Retention Time	% Area
1	25.000	49.07
2	26.545	50.93

22An



	Retention Time	% Area
1	24.932	98.34
2	26.835	1.66

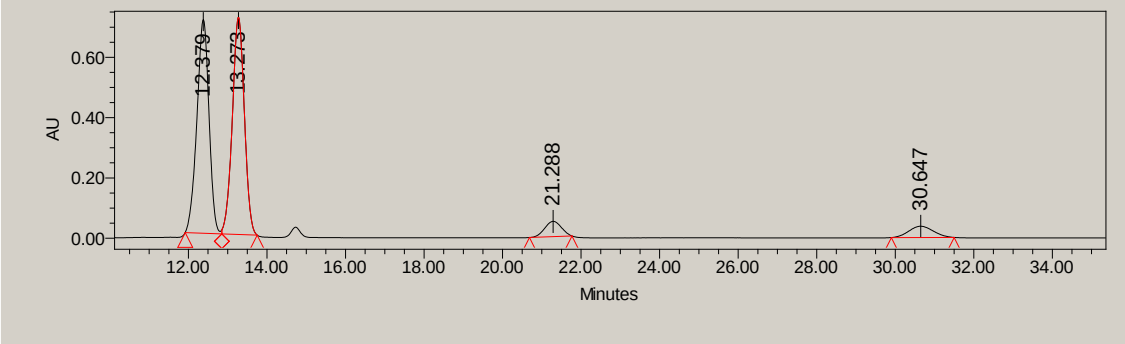
97% ee



22Ba

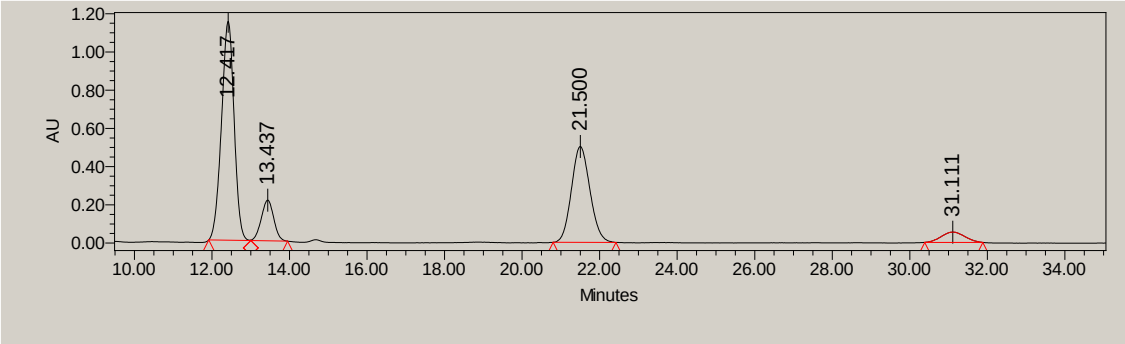
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IC Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 22Ba



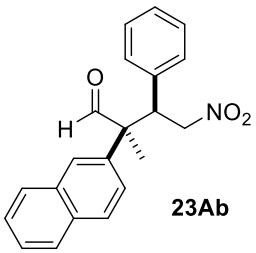
	Retention Time	% Area
1	12.379	45.04
2	13.273	45.72
3	21.288	4.44
4	30.647	4.80

22Ba



	Retention Time	% Area
1	12.417	52.18
2	13.437	9.57
3	21.500	33.66
4	31.111	4.58

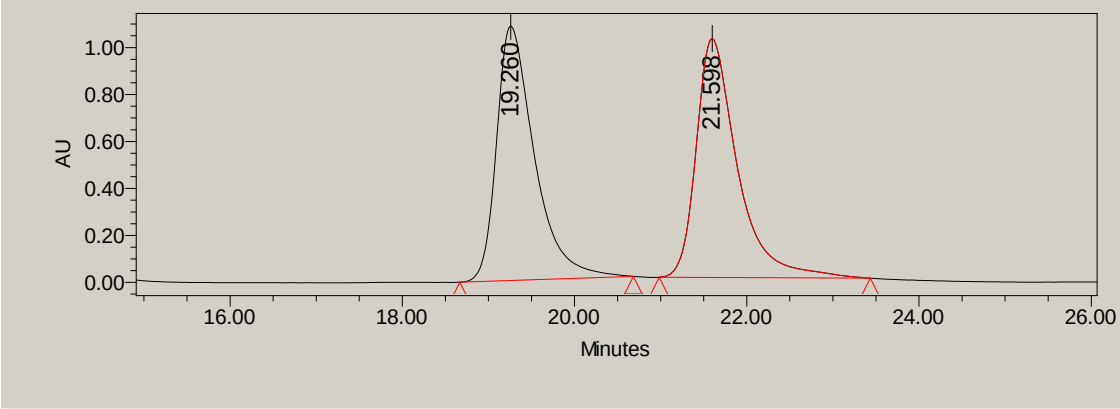
69(76)% ee



23Ab

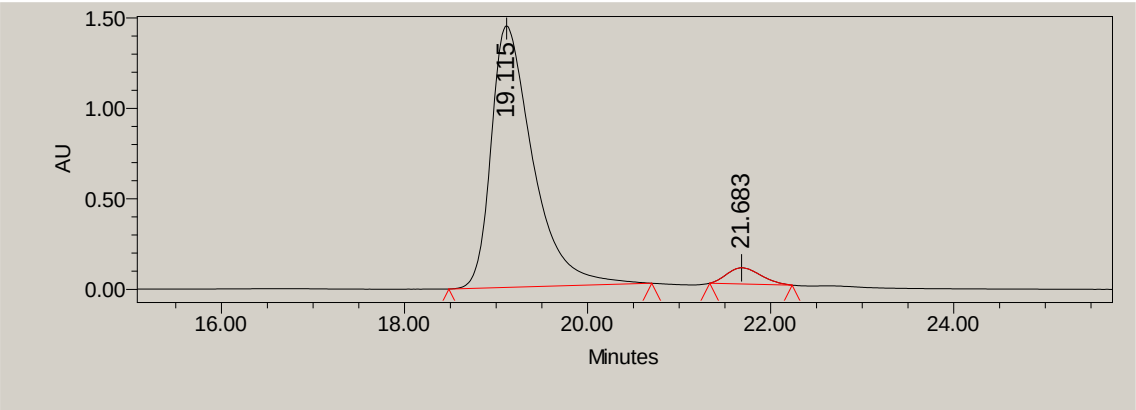
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IB Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 23Ab



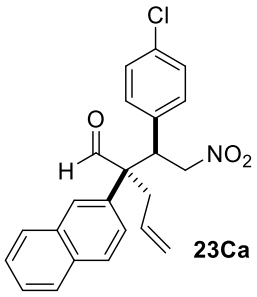
	Retention Time	% Area
1	19.260	49.44
2	21.598	50.56

23Ab



	Retention Time	% Area
1	19.115	95.56
2	21.683	4.44

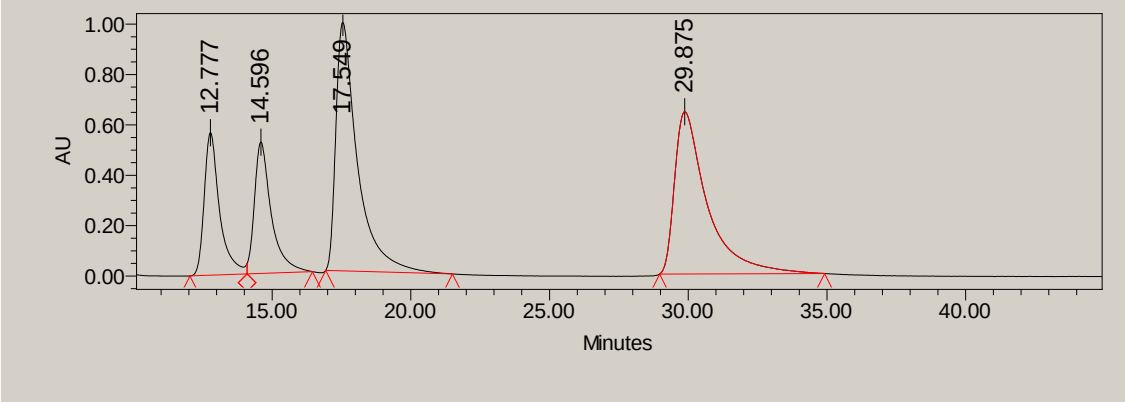
91% ee



23Ca

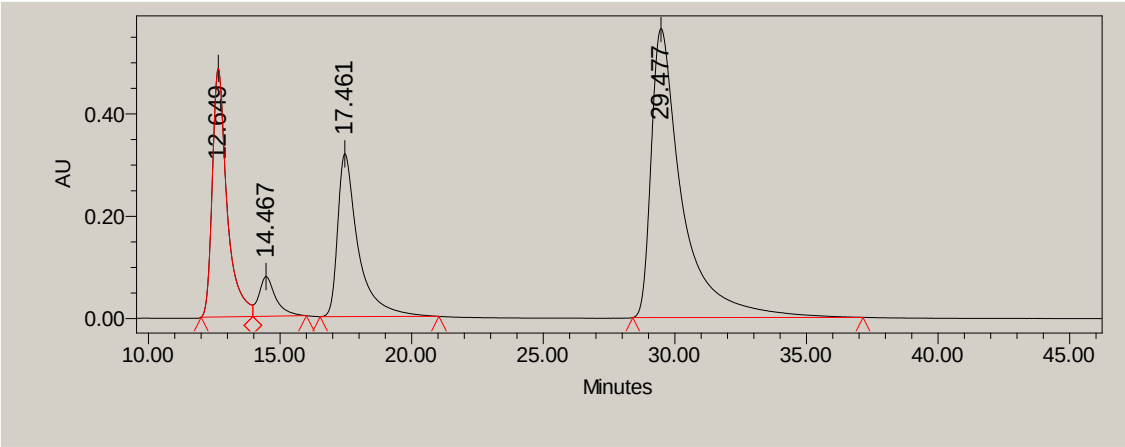
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 23Ca



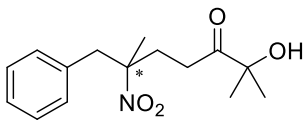
	Retention Time	% Area
1	12.777	14.62
2	14.596	14.64
3	17.549	35.60
4	29.875	35.14

23Ca



	Retention Time	% Area
1	12.649	21.96
2	14.467	4.02
3	17.461	20.09
4	29.477	53.92

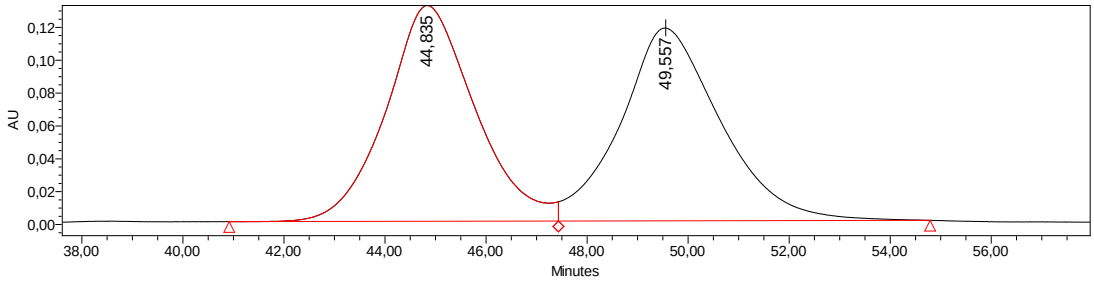
46(69)% ee



37Aa

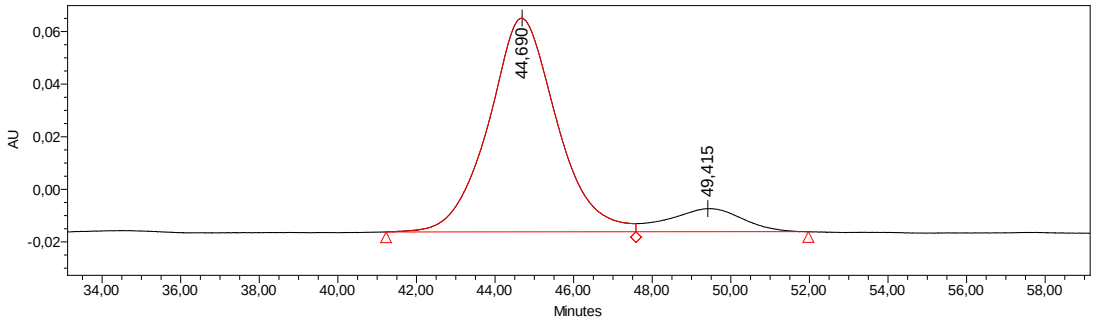
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 98:2, flow rate= 1 mL/min).

(±) 37Aa



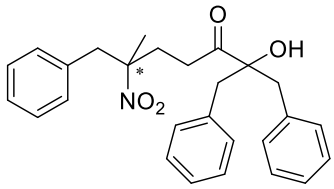
	Retention Time	% Area
1	44,835	49,94
2	49,557	50,06

37Aa



	Retention Time	% Area
1	44,690	89,55
2	49,415	10,45

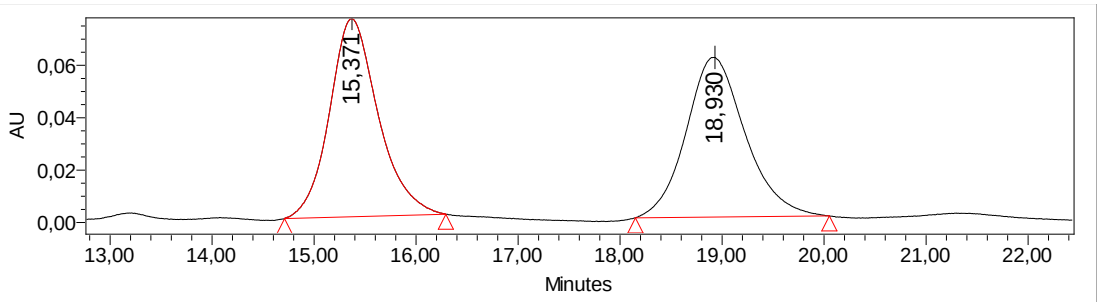
80% ee



37Ab

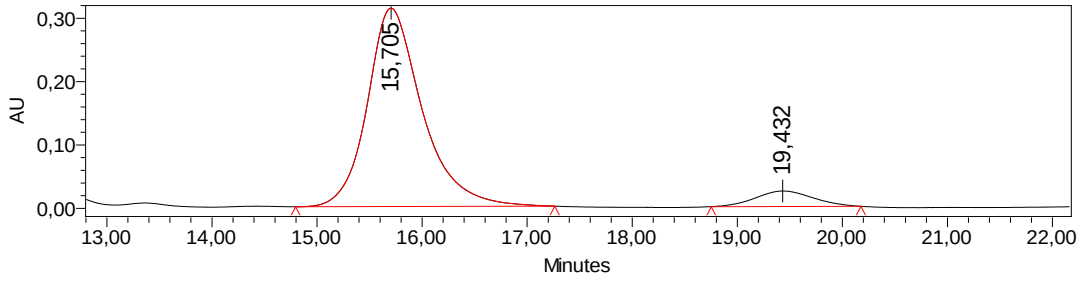
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 37Ab



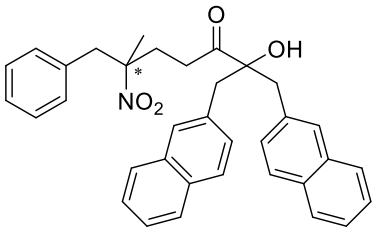
	Retention Time	% Area
1	15,371	50,53
2	18,930	49,47

37Ab



	Retention Time	% Area
1	15,705	92,41
2	19,432	7,59

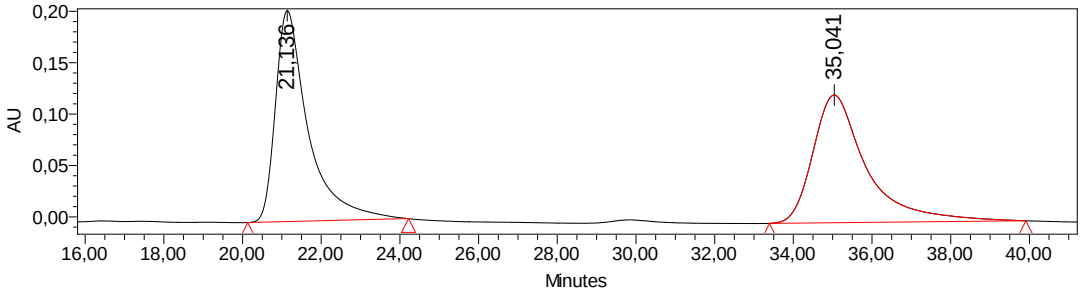
85% ee



37Ac

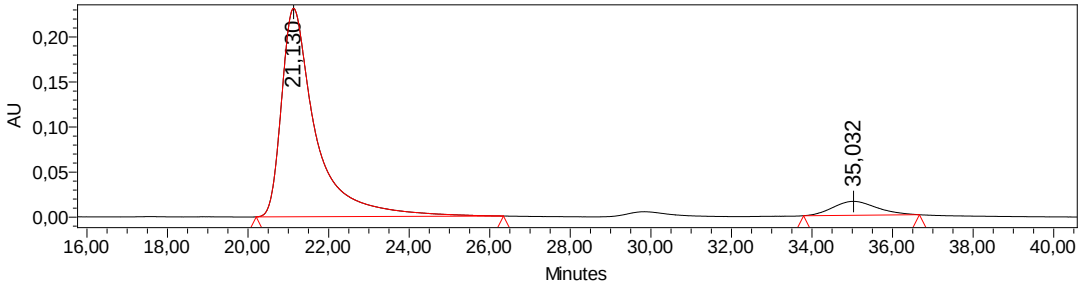
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 95:5, flow rate= 1 mL/min).

(±) 37Ac



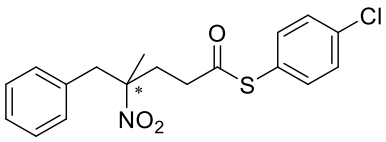
	Retention Time	% Area
1	21,136	50,32
2	35,041	49,68

37Ac



	Retention Time	% Area
1	21,130	92,08
2	35,032	7,92

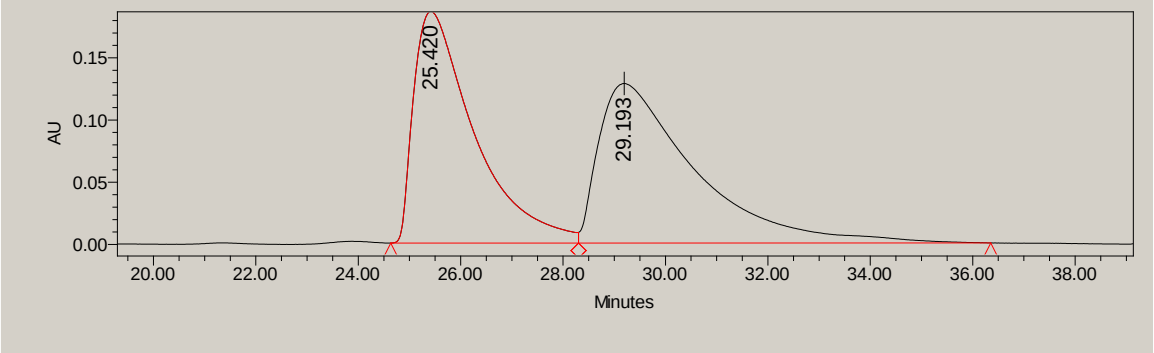
84% ee



40Aa

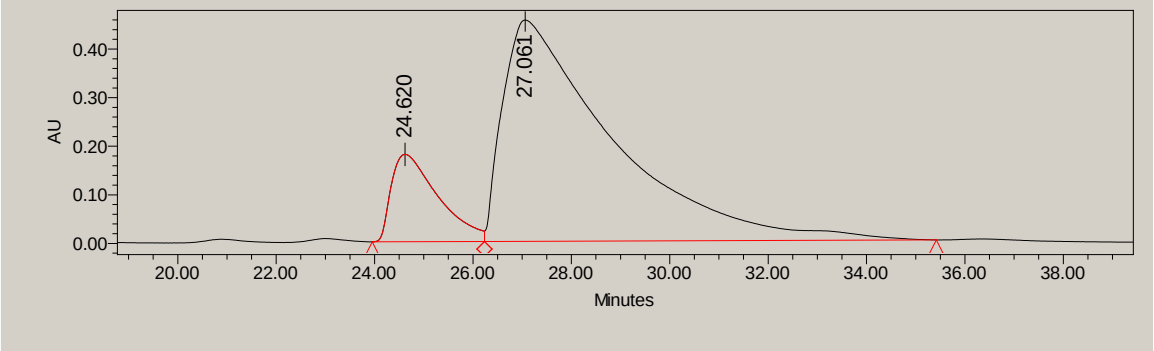
The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA Hexane:^{i}PrOH 99:1, flow rate= 1 mL/min).

(±) 40Aa



	Retention Time	% Area
1	25.420	48.58
2	29.197	51.42

40Aa

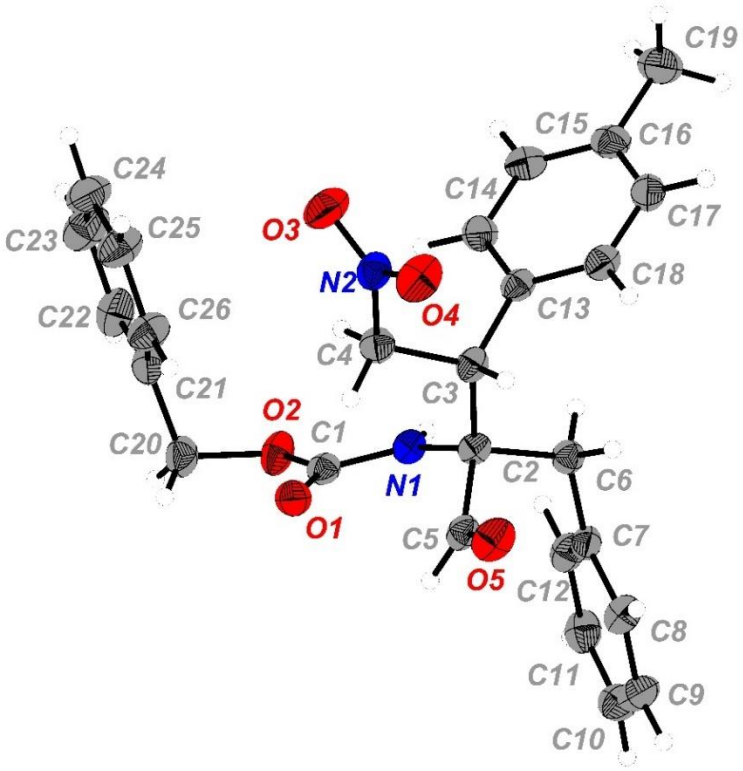


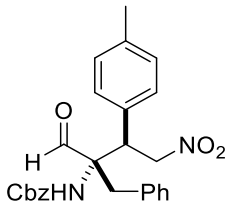
	Retention Time	% Area
1	24.620	14.28
2	27.061	85.72

71% ee

5.7. X-Ray analysis

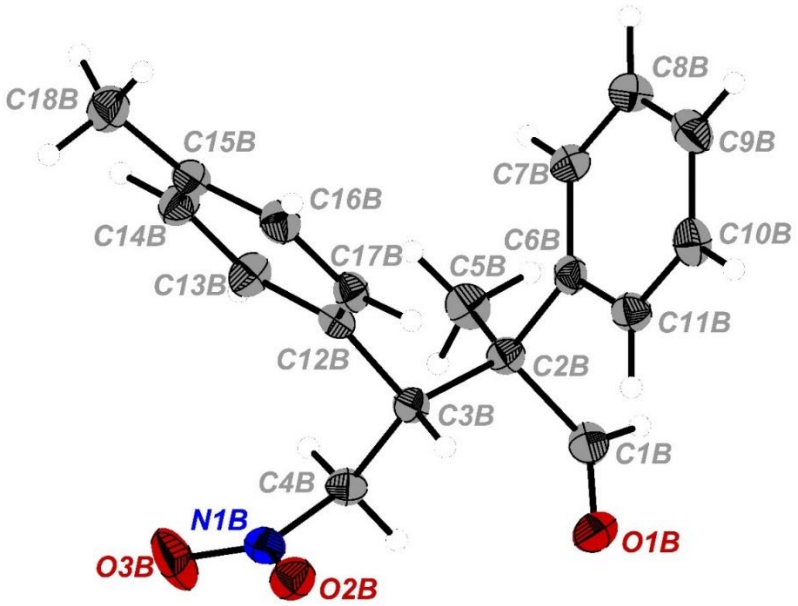
5.7.1. ORTEP diagram of compound 9Bc

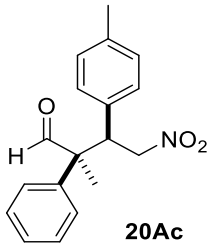




9Bc

5.7.2. ORTEP diagram of compound 20Ac





20Ac

CHAPTER 6

PUBLICATIONS

Asymmetric Catalysis

Probing α-Amino Aldehydes as Weakly Acidic Pronucleophiles: Direct Access to Quaternary α-Amino Aldehydes by an Enantioselective Michael Addition Catalyzed by Brønsted Bases

Ane García-Urricelqui,[a] Abel de Cózar,[a, b] Antonia Mielgo,*[a] and Claudio Palomo*[a]

Abstract: The high tendency of α-amino aldehydes to undergo 1,2-additions and their relatively low stability under basic conditions have largely prevented their use as pronucleophiles in the realm of asymmetric catalysis, particularly for the production of quaternary α-amino aldehydes. Herein, it is demonstrated that the chemistry of α-amino aldehydes may be expanded beyond these limits by documenting the first direct α-alkylation of α-branched α-amino aldehydes with nitroolefins. The reaction produces densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity. DFT modeling leads to the proposal that intramolecular hydrogen bonding between the NH group and the carbonyl oxygen atom in the starting α-amino aldehyde is key for reaction stereocontrol.

Introduction

Chiral α-amino aldehydes are exceptionally valuable building blocks in chemical synthesis and have applications in medicinal chemistry and the pharmaceutical industry.[1] The aldehyde function can be transformed into a wide variety of other functional groups, leading to a diversity of substituted chiral amines, which are also of significance in the fields of natural products and bioactive substances.[2] Despite this interest, little progress has been made in the development of methods for the stereoselective synthesis of α-amino aldehydes. Although recent advances have been made through the asymmetric hydrogenation of α-formyl enamides, which leads to tertiary α-amino aldehydes with very good enantioselectivities,[3] direct catalytic asymmetric synthesis of quaternary α-amino aldehydes,[4] other than the α-amination of α-substituted aldehydes, specifically α-substituted aryl acetaldehydes, have been very poorly investigated.[5] In general, α-functionalization of α-amino aldehydes is subjected to side reactions, such as self-additions and Cannizzaro or Tishchenko disproportionations, particularly under basic conditions,[6] a problem that may be attributed to the sum of the attenuated reactivity of the tertiary carbon nucleophile, plus the high reactivity of the aldehyde function against 1,2-additions. In addition to these challenges, stereochemical control elements for an effective catalytic direct α-amino aldehyde enolate alkylation are still unknown. Even in the realm of chiral-auxiliary-based asymmetric methodologies, these problems are not well resolved.[7] Unsurprisingly, whereas there are a large number of studies realized in connection with the use of α-amino aldehydes as electrophiles,[1] in which useful levels of *anti*-Felkin–Anh selectivity (Figure 1 a) have generally been observed,[8] their chemistry as nucleophiles (Figure 1 b) remains essentially undeveloped.

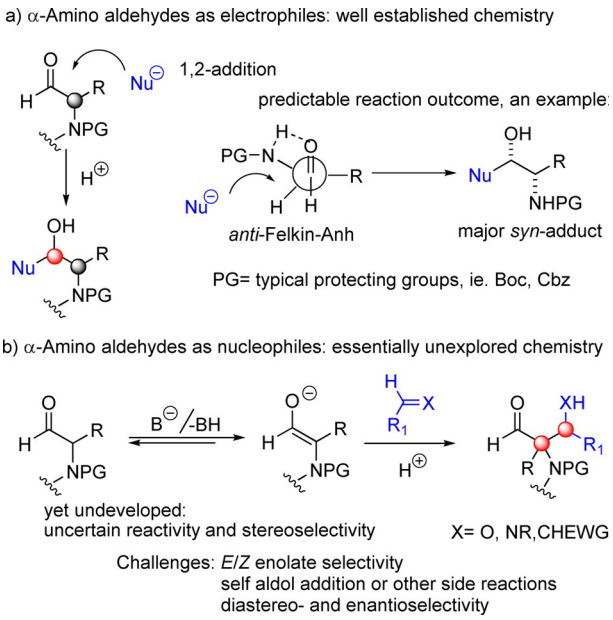


Figure 1. Chemistry of α-amino aldehydes. Nu = nucleophile, Boc = *tert*-butoxycarbonyl, Cbz = carboxybenzyl, EWG = electron-withdrawing group.

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Herein, we report the first Brønsted base (BB) catalysis strategy towards solving the problem of asymmetric catalytic enolate α-alkylation of α-amino aldehydes by documenting their reaction with nitroolefins, leading to densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity. An internal hydrogen bond is postulated as a key preorganizational element.

Results and Discussion

Background and working hypothesis

Currently, the most employed method for the production of quaternary α-amino aldehydes is selective reduction of the corresponding quaternary α-amino acid and/or derivative.[1] This situation is due, at least in part, to the great number of existing methods for the stereoselective synthesis of the latter,[9] wherein control of the enolate configuration, a critical issue for stereoselectivity,[10] is easily achieved through the use of cyclic scaffolds, such as azlactones[11] (Figure 2a) or chelated metal enolate systems,[9,12] whereas for α-amino aldehydes this type of approach to generate configurationally defined enolates is not easy to accomplish. Pioneering studies from the laboratory of Maruoka,[13a] have revealed enamine catalysis[14] (Figure 2b), to afford a solution to this problem, but the use of highly reactive β-unsubstituted Michael acceptors seems to be necessary. One inherent drawback associated with enamines of N-protected α-aminoacetaldehyde[15] is that both Cα and Cα′ positions of the double bond may be effective sites for the reaction.[15a–c] Apparently, this scenario becomes more complicated if enamines of α-substituted α-amino aldehydes are involved, in which the Cα site is sterically congested, and thus, reaction at this position with bulky acceptors is difficult. As a matter of fact, Guo and co-workers have shown that, using 3-indolylarylmethanols as electrophiles, the reaction of α-amino aldehydes through the enamine pathway is essentially limited to *N*-ethoxycarbonyl alaninal and is essentially inefficient with α-amino aldehydes with longer chain lengths (Et, *n*Pr, and benzyl (Bn)).[16] The combined use of transition-metal/enamine catalysis, as introduced by Meggers et al.[17] for the Michael reaction of N-Boc-alaninal with α,β-unsaturated 2-acylimidazoles, seems to be quite promising. However, no examples involving longer chain α-amino aldehydes are reported with this dual-catalyst system. Although these pioneering works set the basis for further studies to address the problem of α-amino aldehyde α-alkylation through the enamine pathway in a much broader sense, as an alternative to this activation strategy, BB catalysis relies on the deprotonation of a C–H pronucleophile as a primary activation element and, in theory, presents no apparent inherent limitation.[18] However, in addition to the problems associated with the α-functionalization of aldehydes noted above, there is a rather specific example that documents the reaction of α-chloroaldehydes with β-alkylidene α-keto amides, wherein the final cyclization of the resultant addition adduct appears to be the driving force of the process.[19] Therefore the utility of this type of catalysis for aldehyde activation is still an open question. Inspired by the well-known tendency of α-amino aldehydes to undergo racemization, as well by the fact that this tendency increases if a weak base is present,[1,20] we reasoned that, upon exposure to a weak chiral BB, N-protected α-amino aldehydes could easily generate a transient enolate ion pair (Figure 2c), which should be more reactive than that of the corresponding enamine, and thus, eventually drive the catalytic addition process forward. We presumed that, in a similar way to how hydrogen bonding plays an important role in the reactions of N-alkoxycarbonyl α-amino aldehydes acting as electrophiles (see above), it could also participate in the present approach by stabilizing the corresponding (*Z*)-enolate, thereby enabling effective substrate/catalyst preorganization and transition-state stabilization. If this were the case, a practical new platform for direct catalytic α-functionalization of α-amino aldehydes could be made feasible, in which β-substituted Michael acceptors might be well tolerated, leading to products with quaternary and tertiary vicinal stereocenters in a single synthetic operation. To prove this hypothesis, we elected to use nitroolefins[21] as the electrophilic reaction partners because the resulting γ-nitroaldehyde adducts could be transformed into other products of increased complexity.[22]

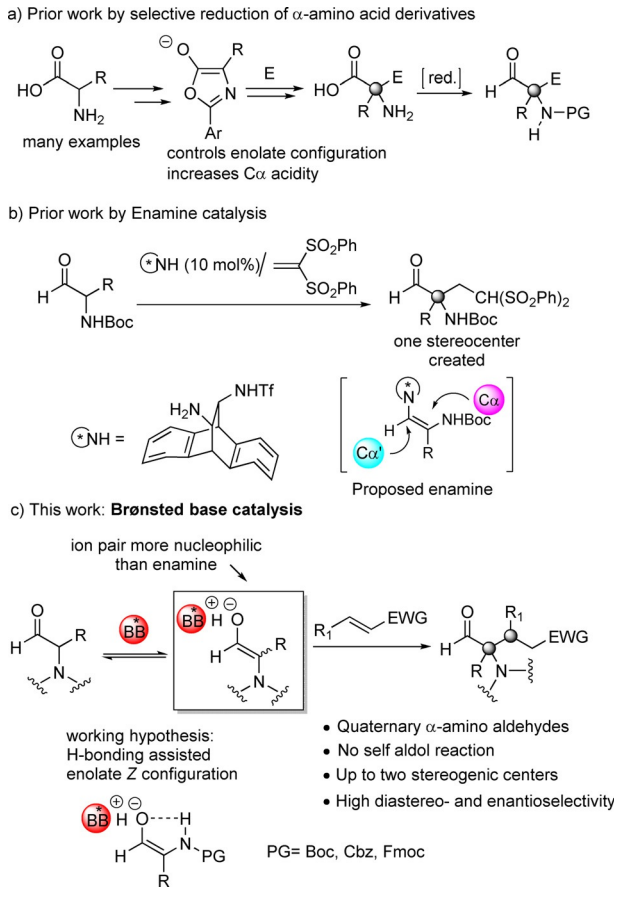

Figure 2. Previous work on direct catalytic asymmetric synthesis of quaternary α-amino aldehydes and the new proposed method. Fmoc = fluorenylmethoxycarbonyl, BB* = chiral Brønsted base.

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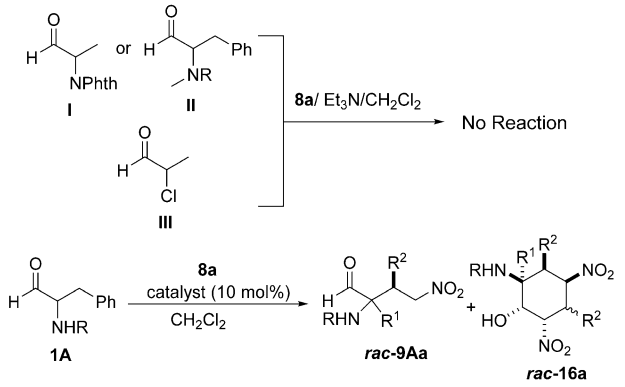
Preliminary experimental observations

Given the problems associated with enolizable aldehydes, apart from the fact that α-functionalization of α-amino aldehydes assisted by BB catalysts remains unassessed, we began our study by examining the reactivity of three representative enolizable α-amino aldehydes, (+/−)-*N*-phthaloyl alaninal **I**, (+/−)-*N*-methyl-*N*-Boc phenylalaninal **II**, and (+)-*N*-Boc phenylalaninal **1 A**, against nitroolefin **8 a** (Scheme 1), using several BBs of variable basic strength. We found that, although no reaction takes place starting from **I** or **II** in the presence of Et_3N, the reaction of **1 A** with **8 a** led, after 48 h at room temperature, to product **9 Aa** as an almost equimolar mixture of diastereomers (Table 1, entry 1). The reaction proceeded with modest conversion and was accompanied by a small amount of cyclized product **16 a**, which resulted from three consecutive Michael–Michael–Henry reactions.[23] Hünig's base (Table 1, entry 2) was less effective than that of Et_3N and stronger bases, such as the amidine base DBU and guanidines such as MTBD and TBD (Table 1, entries 3 and 4), led to polymerization of the nitroolefin to a great extent,[24] and no adducts derived from **1 A** were observed. The conversion into **9 Aa** could be increased (Table 1, entries 5 and 6) in the presence of either thiourea or squaramide hydrogen-bond donors, but no increase in diastereoselectivity nor in the production of cyclized product **16 a** was observed. Again, no reaction took place starting from **I** or **II** with combinations of Et_3N/thiourea or Et_3N/squaramide. These results revealed that 1) under these smooth basic reaction conditions, nitroolefin polymerization may be avoided; 2) the product distribution from the reaction of these α-amino aldehydes with these acceptors could be perfectly controlled by simply using a BB/hydrogen-bonding bifunctional catalyst to afford only the corresponding addition product; and, most remarkably, 3) the free N–H bond in the starting aldehyde seems to be necessary for transient α-amino aldehyde enolate generation by means of weak BBs. Presumably, an intramolecular hydrogen-bonding interaction between the NH group and the carbonyl oxygen atom increases the Cα acidity of the α-amino aldehyde, albeit no enolate *E*/*Z* selectivity is produced. As suggested previously, α-chloro aldehyde **III** (Scheme 1) did not react either with nitrostyrene under similar reaction conditions.

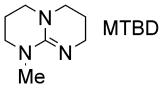
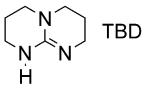
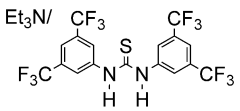
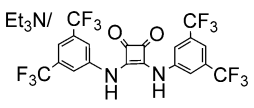


Scheme 1. Preliminary experiments on the reaction of representative α-aminoaldehydes **I** (Phth = phthaloyl), **II**, and **1 A** (R = Boc), and α-chloro aldehyde **III**, with nitrostyrene **8 a** (R^2 = 4-ClC_6H_4).

Catalyst screening and reaction optimization

In view of the observations noted above, the next question we addressed was to establish which BB/hydrogen-bonding bi-

Table 1. Base screening for the reaction of **1 A** with nitroolefin **8 a**.[a]

Entry	Catalyst	Base [mol%]	*T* [°C]	*t* [h]	Conversion[b] [%]	**9 Aa** [%] (d.r.)[c]	**16 a** [%]
1	Et_3N	20	RT	17	31	>95 (58:42)	<5
				41	62	84 (56:44)	16
2	*i*Pr_2EtN	20	RT	41	21	>99 (44:56)	<5
3	DBU	10	0	1.5	<5[d]	0	0
4	 MTBD	10	RT	20	<5[d]	0	0
5	 TBD	10	0	22	<5[d]	0	0
6		20	RT	15	48	>99 (51:49)	<5
7		20	RT	15	69	>95 (45:55)	<5

[a] Reactions were conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; mol ratio nitroolefin/aldehyde = 3:1). DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, MTBD = 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [b] Conversion determined by disappearance of the starting aldehyde by ^{1}H-NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy analysis. [d] Nitrostyrene polymerized.

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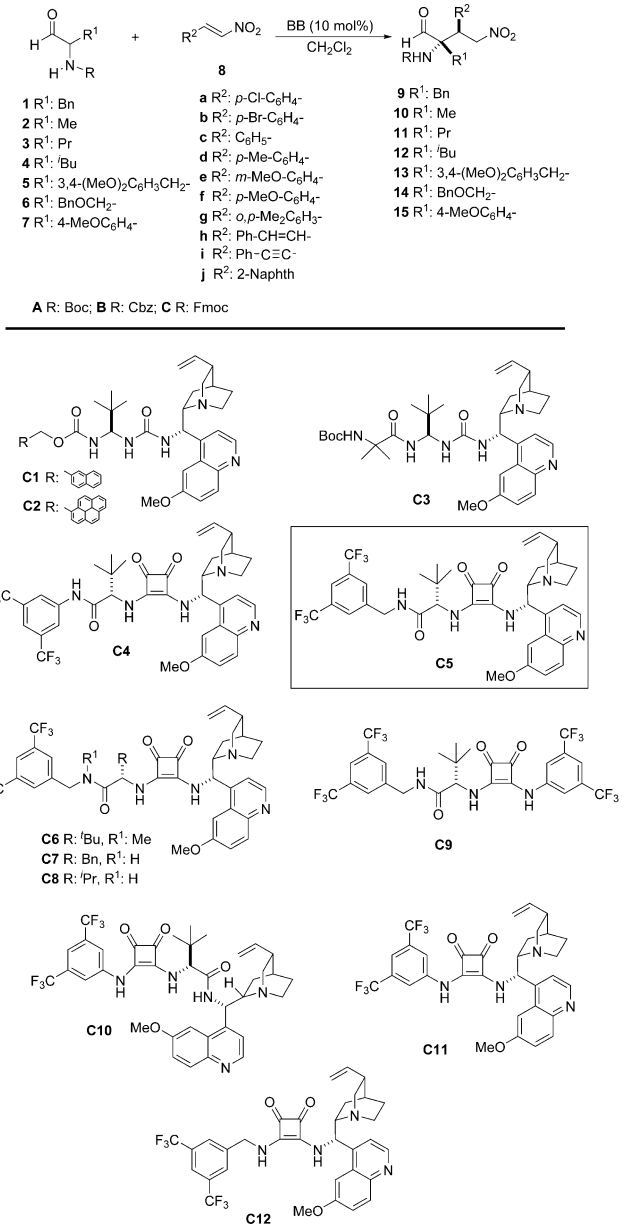
functional catalyst could control both diastereo- and enantioselectivity of the reaction. The study was initiated by examining the reaction of **1 A** with **8 a** by using ureidopeptide-derived BBs **C1**, **C2**, and **C3** (Scheme 2), previously reported by us, which proved to be effective in conjugate additions to nitroolefins.[25] However, in each case, product **9 Aa** was produced with very poor diastereoselectivity and negligible enantioselectivity (Table 2, entries 1–3). With the aim of improving stereocontrol, we modified the catalyst by replacing the urea unit by a squaric acid moiety to increase the hydrogen-bonding capability.[26,27] L-*tert*-Leucine-derived catalysts **C4**, **C5**, and **C6** were prepared[28] and, to our delight, not only better diastereoselectivities, but also enantioselectivities were provided from these bifunctional BBs (Table 2, entries 4–6). The best result was attained with catalyst **C5**, which afforded product **9 Aa** in a diastereomeric ratio of 90:10 and in 98% *ee* for the major isomer.[29] Although similar results were achieved with catalyst **C4**, a longer reaction time was required for completion (Table 2, entry 4).



Scheme 2. Direct asymmetric Michael additions of α-amino aldehydes to nitroolefins promoted by BB catalysts **C1**–**C12**.

Further experiments with L-phenylalanine and L-valine derivatives **C7** and **C8** revealed that both were equally as effective as that of *tert*-leucine-derived catalyst **C5**, in terms of diastereoselectivity, but slightly worse regarding enantioselectivity. Catalyst **C9**, lacking the BB,[28] was completely unfruitful in promoting the reaction, even when an external base was employed as a cocatalyst (Table 2, entry 9). Importantly, not only is the cinchona base needed for reaction effectivity, but also its position in the catalyst seems to be critical for efficient enantiocontrol, as illustrated by the result obtained with known catalyst **C10**[30] (Table 2, entry 10). Therefore, this catalyst conception, in which the squaramide moiety is between the α-amino acid residue and the BB, seems to be quite promising. In support of this assumption is the fact that, during the preparation of this manuscript, two independent contributions concerning this subclass of squaramide catalysts have been reported.[31] Further proof of the robustness of this subclass of catalysts was provided by the reaction of **1 A** with **8 a** with commercially available standard squaramides **C11** and **C12**, which led to **9 Aa** in lower levels of diastereo- and enantioselectivity (Table 2, entries 11 and 12).[32] On the other hand, although these reactions were performed in dichloromethane, 1,2-dichloroethane and acetonitrile may also be employed as solvents with equal effectiveness, but toluene and tetrahydrofuran were inefficient in terms of either reaction conversion or side-product formation.[28]

Reaction scope: Variation of aldehyde and nitroolefin

As highlighted by the results in Table 3, the reaction promoted by catalyst **C5** was equally efficient for nitroolefins (**8 b**–**h**) carrying both electron-withdrawing and -donating substitution patterns on the aromatic ring, independently of their *o*, *m*, or *p* positions.

In general, the reactions were performed on a 0.2 mmol scale, but increasing the scale up to 1 mmol the same results were observed without loss of stereochemical information. α-Amino aldehydes with typical N-protecting groups, that is, N-Boc, N-Cbz, and N-Fmoc, participate in such a reaction to give adducts **9**–**15** in very good *anti*-diastereoselectivity and excellent enantioselectivity for the major isomer. As a general trend, reactions with N-Fmoc-protected α-amino aldehydes proceeded somewhat faster, typically within 20–24 h, than those of related N-Boc- and N-Cbz-protected aldehydes. An initially limited applicability of this catalyst system was observed. α-Amino aldehydes with bulky side chains, such as N-protected *tert*-leucinal and valinal, were quite unreactive under the above reaction conditions, independently of the protective group. The relative and absolute configuration of compound **9 Bd** was established by means of X-ray single-crystal structural analysis and that of the remaining adducts was assumed on the basis of a uniform reaction mechanism.[33]

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Table 2. Catalyst screening for the 1,4-addition of **1A** to **8a** to afford **9Aa**.[a]

Entry	Catalyst	*t* [h]	*T* [°C]	Conversion[b] [%]	Yield [%][c]	d.r.[d]	*ee*[e] [%]
1	**C1**	63	RT	88 (61)	n.d.	39:61	n.d.
2	**C2**	39	RT	29 (2)	n.d.	64:36	n.d.
3	**C3**	39	RT	71 (40)	31	50:50	37
4	**C4**	45	RT	>99 (8)	77	89:11	98
5	**C5**	24	RT	96 (9)	91	90:10	98
6	**C6**	23	RT	97 (2)	81	85:15	97
7	**C7**	15	RT	90 (3)	70	82:18	91
8	**C8**	24	RT	88 (12)	69	86:14	94
9	**C9**	15	RT	0[f]	0	–	–
10	**C10**[g]	120	RT	58 (n.o.)	33	70:30	25
11	**C11**	21	RT	92 (28)	55	68:32	81
12	**C12**	16	RT	68 (n.o.)	64	66:34	73

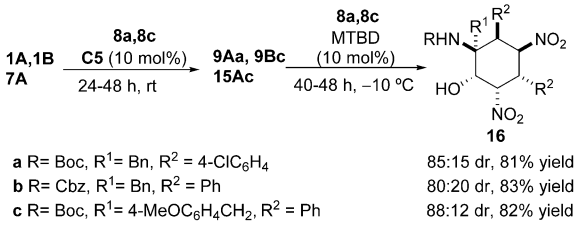
[a] Reactions were conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; mol ratio nitroolefin/aldehyde/catalyst = 1.5:1:0.1). [b] Determined by disappearance of the starting aldehyde by ^{1}H-NMR spectroscopy. The percentage of product obtained from the tandem reaction of the Michael adduct with a second molecule of **8a** followed by cyclization is indicated in parentheses. n.d. = not determined; n.o. = not observed. [c] Yield of the isolated major isomer. [d] Determined by ^{1}H NMR (300 MHz) spectroscopic analysis of the crude product. [e] Enantiomeric excess (*ee*) determined by chiral HPLC. [f] In the presence of Et_3N (10 mol%) after 39 h, 26% conversion and 57:43 d.r. were observed. In the presence of iPr_2EtN (10 mol%) after 15 h, 23% conversion and 52:48 d.r. were observed. [g] 20 mol% catalyst was used.

The approach may also be extended to α-amino aldehydes bearing aromatic and aliphatic N-acyl groups (Table 4), to yield the corresponding products with very good diastereo- and enantioselectivity as well. An exception was α-aminoaldehyde **17** bearing the pyridine ring, which afforded product **23** with lower d.r., albeit with an acceptable *ee* for the major isomer.

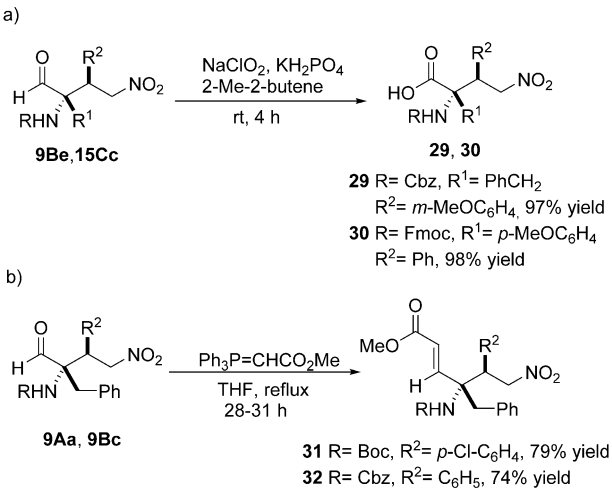
Adduct elaboration: Fully Cα-substituted amines

In general, in these reactions we employed 1.5 equivalents of the corresponding nitroolefin, but with the use of 3 equivalents in combination with an amine base, the intermediate adducts may be converted, as noted at the onset of this work, into otherwise difficult to synthesize fully substituted cyclohexylamines bearing a tetrasubstituted stereogenic Cα-carbon. For example, as shown in Scheme 3, compound **16a** was prepared, in nonracemic form, through the reaction of α-amino aldehyde **1A** with nitroolefin **8a** by using catalyst **C5** followed by triethylamine (TEA; 30 mol%), for the last two Michael–Henry reaction steps. The product was obtained in a single-pot operation as an almost equimolar mixture of diastereomers that were epimeric at Cγ. The ratio of diastereomers could be increased to 85:15 by using MTBD (10 mol%) as a base and carrying out the reaction at −10° C.[34] Cyclohexylamines **16b** and **16c** were also produced with similar results in a one-pot operation from **1B** and **7A** and nitroolefin **8c**. Under these conditions, polymerization of the corresponding nitroolefin also occurred, although to a small extent. In each case, the configuration of the isolated adducts was established by means of NOE experiments.[28]

On the other hand, simple exposure of adducts **9Be** and **15Cc** to standard oxidative conditions provided N-acyl quaternary α-amino acids **29** and **30** with two adjacent, quaternary and tertiary, stereocenters in essentially quantitative yield (Scheme 4a). In addition to these transformations, the Wittig reaction provides N-protected allyl amines that are fully substituted at Cα and ready for subsequent functional-group elaborations (Scheme 4b).[35]



Scheme 3. One-pot procedure for the preparation of fully substituted cyclohexylamines tetrasubstituted at C_1.



Scheme 4. Access to a) quaternary α-amino acids and b) fully α-substituted allylamines.

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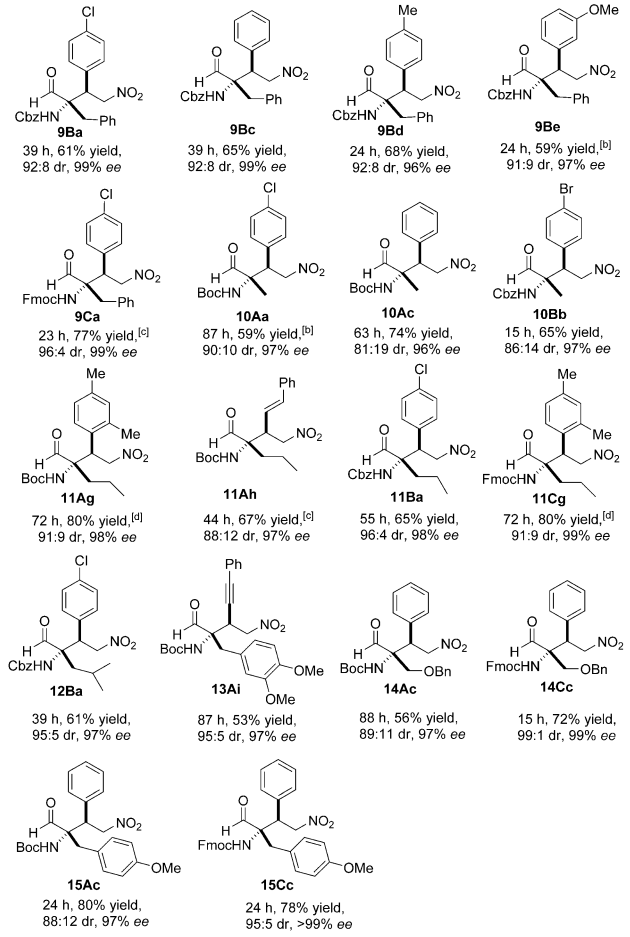
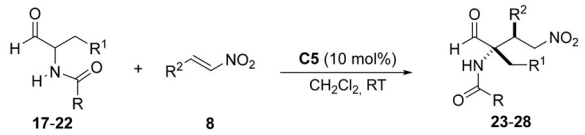
Table 3. Scope of the Michael reaction of α-amino aldehydes **1–7** with nitroolefins **8** assisted by **C5**.[a]



[a] Reactions were conducted at RT on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; mol ratio nitroolefin/aldehyde/catalyst = 1.5:1:0.1). Yield of the isolated major isomer. Diastereomeric ratio determined by ^{1}H NMR (300 MHz) spectroscopic analysis of the crude product. Enantiomeric excess determined by chiral HPLC. [b] Less than 5% of the product resulted from the tandem reaction of the Michael adduct with a second molecule of nitroalkene followed by cyclization. [c] Yield of the two isolated isomers. [d] Reaction was performed with 20 mol% of catalyst.

Table 4. Reaction of α-amino aldehydes **17–22** with nitroolefins **8**.[a]



Compound	R	R^1	R^2	*t* [h]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
23	2-pyridyl	Ph	Ph	63	40[f]	68:32	86
24	Ph	Ph	4-ClC_6H_4	24	71[f]	93:7	>99[e]
25	2-MeC_6H_4	4-MeOC_6H_4	3MeOC_6H_4	48	77	85:15	99
26	4-BrC_6H_4	4-MeOC_6H_4	4-MeC_6H_4	82	64	93:7	99
27	PhCH_2=CH_2	$(Me)_2$CH	2-naphthyl	64	45	96:4	>99
28	CH_3	Ph	4-ClC_6H_4	40	43	93:7	>99

[a] Reactions were conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; mol ratio nitroolefin/aldehyde/catalyst = 1.5:1:0.1). [b] Yield of the isolated major *anti* isomer. [c] Determined by ^{1}H NMR (300 MHz) spectroscopic analysis of the crude product. [d] Enantiomeric excess determined by chiral HPLC. [e] 5% of the cyclized product resulted from a tandem Michael–Michael–Henry reaction. [f] Yield of the two isolated isomers.

Theoretical proofs and mechanistic observations

A rationale for the above experimental observations is provided within the DFT framework[36] through energies calculated for the transition state for the carbon–carbon bond-forming step in its four possible combinations (Figure 3). In the first instance, we examined the noncatalyzed reaction between **1A** and **8c**, and the calculations showed the existence of an intramolecular hydrogen-bonding interaction in transition states **TS1** and **TS2** resulting from the aldehyde (*Z*)-enolate, which rendered them energetically favored over **TS3** and **TS4** ((*E*)-enolates). In addition, the energy barrier for the approach of the (*Z*)-enolate to the prochiral *Si* face of **8c** (**TS1**) was found to be the less energetic one, although the energetic difference with **TS2** (reaction with the *Re* prochiral face of **8c**) is only

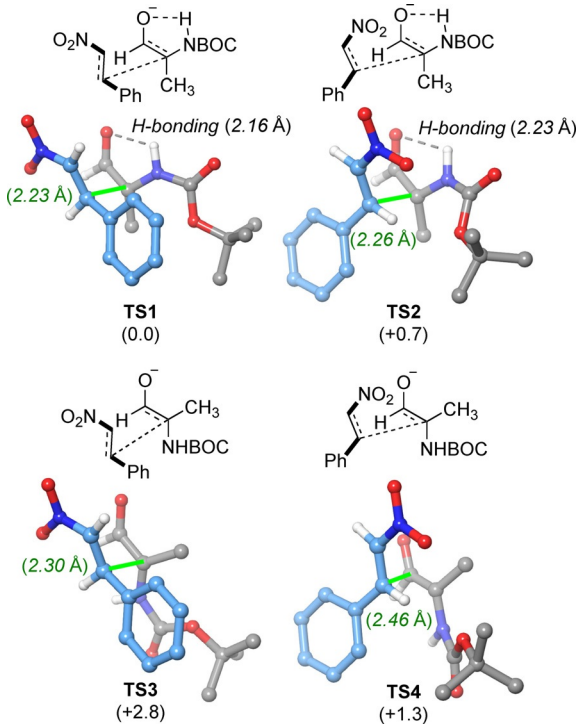


Figure 3. Computed possible transition states for the noncatalyzed reaction of **1A** and **8c**. Relative Gibbs free energy values in kcal mol^{-1} were computed at the B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K).

0.7 kcal mol^{-1} and will be associated with a lower theoretical d.r. (d.r.$_{theor}$ ≈ 76:24). To gain further insight into the behavior of the catalyst, we next studied the transition states for the same reaction in the presence of catalyst **C5**. The first question to elucidate was the preferred hydrogen-bonding pattern formed

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between the catalyst and both substrates in the transition state corresponding to the C–C bond-forming step. In this respect, up to (at least) three different ternary complexes (A,[37] B,[38] and C;[39] Figure 4) have been proposed for reactions involving noncovalent cooperative activation of the intervening nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)–tertiary amine catalyst. In most cases, moreover, different activation modes have been invoked for reactions involving similar nucleophile and/or electrophile partners.[40]

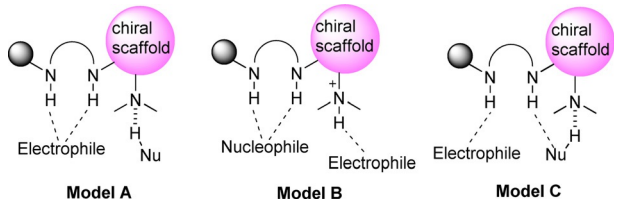

Figure 4. Three alternative substrate–catalyst combinations proposed for bifunctional BB activation mode.

Therefore the question of whether or not a unified H-bonding network (A, B, C, other) could be applied to different reactions within this category catalysis seems remain unexplored and more data are desirable. For the study, we assumed Curtin–Hammett kinetics, in which the product ratio should depend on the free Gibbs activation energy difference of the corresponding transition structures. Interestingly, with catalyst **C5**, a strong hydrogen-bonding interaction between the NH from the *tert*-leucine residue and the carbonyl of the squaramide (1.9–2.1 Å) was observed with negligible variations in the distance in each model.

A direct consequence of this intramolecular binding is that, although it increases the hydrogen-bonding capability,[41] the catalyst adopts a fix conformation, wherein the position of the *tert*-butyl group seems to be important for facial selectivity. In fact, commercially available standard squaramides **C12** and **C13** (Table 1, entries 12–13), lacking this intramolecular hydrogen-bonding interaction, provided adduct **9Aa** in lower levels of diastereo- and enantioselectivity. The study shows that, in the least energetic transition structures (Figure 5), the catalyst–reagent coordination patterns follows the Papai's model B (**TS1**), in which the nucleophile (enolate (*Z*)-**INT1**) interacts with the squaramide core of **C5**, and the electrophile (**8c**) is activated by a hydrogen-bonding interaction with the cinchona moiety of **C5**. As previously observed for the noncatalyzed reaction, here again the transition states involving the (*Z*)-enolate are less energetic than those involving the (*E*)-enolate and in all of them the intramolecular aldehyde hydrogen-bonding interaction between the carbonyl oxygen atom and NH is maintained. In addition, considerable energetic discrimination over the possible approach over the pro-*Si* and pro-*Re* faces of **8c** was obtained as a consequence of an additional hydrogen-bonding interaction between the NH group of (*Z*)-**INT1** and the nitro group of **8c** found in **TS1**-*anti* (2.22 Å) that is not present in **TS1**-*syn*, thus favoring the formation of *anti*-Michael

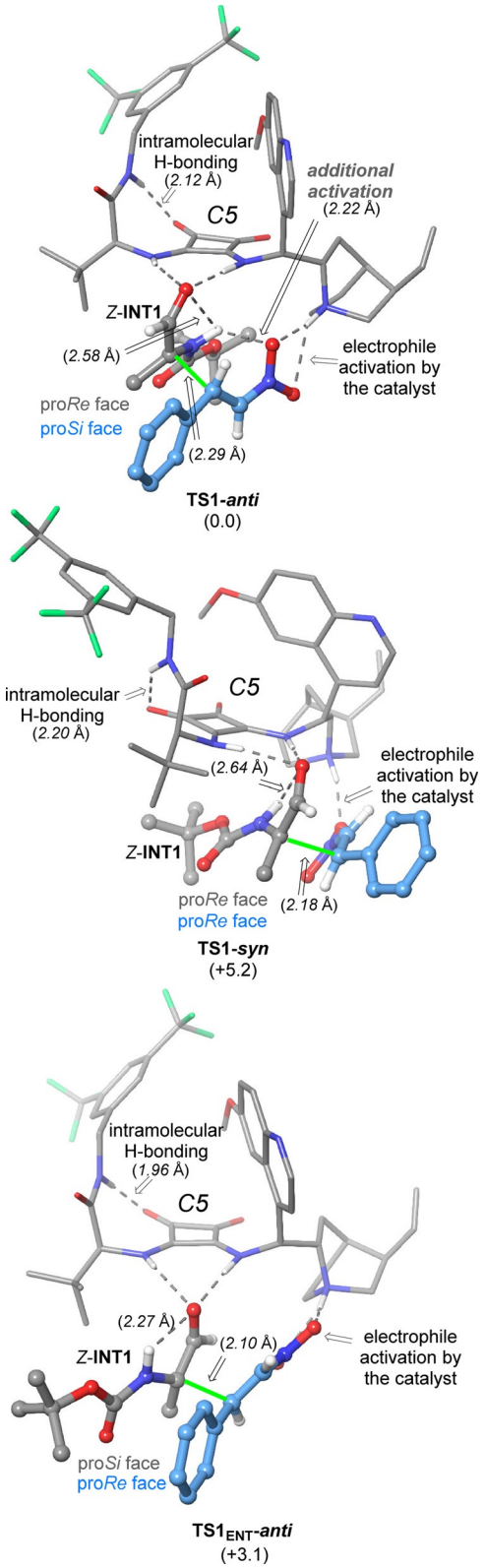

Figure 5. Main geometrical features and relative Gibbs free energies of least energetic transition structures **TS1** and **TS2** associated with the reaction of **1A** and **8c** catalyzed by **C5** according to the Papai's model. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311 + G(d,p)//B3LYP-D3(PCM)/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in blue and grey, respectively.

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adducts. This result clearly supports putative α-amino aldehyde intramolecular hydrogen bonding as a key preorganizational element. In addition, in all transition structures, a pseudo-eclipsed conformation between the new C–C bond was found; this is a structural feature that may justify the absence of reaction of sterically hindered aldehydes (see above). Finally, in **TS1ENT**-*anti*, the least energetic transition state leading to the 2*R*,3*R* *anti*-Michael adduct, the strong intramolecular hydrogen-bonding interaction that fixes **INT1** in a *Z* conformation places the N–H bond of (*Z*)-**INT1** far away from the squaramide core and, more importantly, from the electrophile. In this conformation, the long distance between that N–H bond and the nitro group of **8c** avoids any interaction between them. As a consequence, **TS1ENT**-*anti* is 3.1 kcal mol^{-1} less stable than **TS1**-*anti*, which provides the experimentally observed 2*S*,3*S* *anti*-Michael adduct.

Conclusion

We have demonstrated that asymmetric α-functionalization of α-branched N-acyl amino aldehydes may be accomplished by using BB noncovalent catalysis. The method is operationally very simple and employs a readily available bifunctional BB catalyst to enable the direct generation of a transient aldehyde enolate ion pair, which reacts with nitroolefins in high diastereo- and enantioselectivity. Therefore, this realization complements the covalent enamine activation approach and represents a practical direct entry to the stereoselective construction of α-amino aldehydes and derivatives therefrom featuring two vicinal quaternary and tertiary carbon stereocenters. The present work underscores, for the first time, from both theoretical and experimental standpoints, the role of an internal hydrogen bond as a key preorganizational element during aldehyde enolate alkylation, as well as a basis for expanding the chemistry of α-amino aldehydes beyond the limits of their general and quite exclusive use as electrophiles.[42]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · Brønsted bases · hydrogen bonds · Michael addition · quaternary stereocenters

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[34] Experiments carried out with cycloadduct **16a** as a 73:27 mixture of diastereomers in the presence of 10 mol % MTBD at −10 °C for 1.5 h revealed the absence of epimerization as the adduct was recovered in 71:29 d.r. However, after allowing the mixture to reach room temperature and further stirring for 1 h, adduct **16a** was recovered in 62:38 d.r., together with 19% of the adduct resulting from the first Michael addition. It is worth mentioning that adducts in Table 3 obtained from the first Michael addition are stable after stirring in CH_2Cl_2 in the presence of 10 mol% **C5** at RT for 116 h.

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syn-Selective Michael Reaction of α-Branched Aryl Acetaldehydes with Nitroolefins Promoted by Squaric Amino Acid Derived Bifunctional Brønsted Bases

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Here we describe a direct access to 2,2,3-trisubstituted *syn* γ-nitroaldehydes by addition of α-branched aryl acetaldehydes to nitroolefins promoted by a cinchona based squaric acid-derived amino acid peptide. Different α-methyl arylacetaldehydes react with β-aromatic and β-alkyl nitroolefins to afford the Michael adducts in high enantioselectivity and *syn*-selectivity. NMR experiments and DFT calculations predict the reaction to occur through the intermediacy of *E*-enolate. The interaction between the substrates and the catalyst follows Pápai's model, wherein an intramolecular H-bond interaction in the catalyst between the NH group of one of the *tert*-leucines and the squaramide oxygen seems to be key for discrimination of the corresponding reaction transition states.

Introduction

Organocatalysis has experienced a significant growth over the last years and today a broad range of efficient asymmetric transformations for different substrates is available.[1] In this context an extensive number of chiral bifunctional Brønsted base (BB) mediated reactions has been reported, most of them triggered by bifunctional tertiary amines.[2] Despite this progress, the use of these tertiary amine catalysts has been mainly limited to relatively acidic substrates ($pKa < 17$)[3] and their application with aldehydes as pronucleophiles has been hardly investigated.[4] The inherent high reactivity of the carbon atom in that oxidation state which hamper effective control of side reactions,[5] may account for this lack of studies, a complication that has to be added to the usual problems associated with aldehyde activation and reaction enantiocontrol. Aminocatalysis[6] has shown to be an excellent option to solve these problems and, at present, a broad range of efficient reactions to access α-functionalized aldehydes in high stereoselectivity is available. In particular, the addition reaction of aldehydes to nitroolefins provides an expedient route to γ-nitro aldehydes, important intermediates in synthesis.[7] However, the application of this reaction to α-branched aldehydes has shown problematic, mainly because of the difficulty for the condensation of the amine catalyst with the α-branched aldehyde due to steric hindrance, the relatively lower reactivity of the resulting α,α-disubstituted enamine and the difficulty in controlling the E/Z enamine selectivity.[8] The first use of α-branched aldehydes for this reaction was reported by Barbas III in 2004.[9] Following this work, several amine catalysts have also been investigated[10] and, albeit with few exceptions,[10a,e] most provide the adducts in modest selectivity (poor *dr* and/or poor *ee*). In this context, the question of whether BB catalysis can work as a complementary alternative for the stereoselective α-functionalization of aldehydes is still open.

Recently we reported the first use of α-substituted α-amino aldehydes as pronucleohiles in a BB catalyzed Michael addition to nitroolefins[11–13] (Scheme 1a). The reaction is promoted by the *tert*-leucine derived catalysts of type **I** and produces densely functionalized products bearing up to two, quaternary and tertiary, vicinal stereocenters with high diastereo- and enantioselectivity.[11] Notably, no side reactions nor homoaldol products are observed under these conditions and an intramolecular H-bonding between the NH group and the carbonyl oxygen atom in the starting α-amino aldehyde appears to be key for both reactivity and stereocontrol. We wondered whether this BB activation strategy might be extended to α-branched aldehydes lacking the above noted intramolecular H-bonding, such as α-branched aryl acetaldehydes (Scheme 1b), particularly α-methyl aryl acetaldehydes, which might produce compounds of biological interest having quaternary carbon stereocenters.[14] In this instance, we expected that the BB catalyst might control both enolate configuration and face discrimination during reaction, thus enhancing the utility of the approach.

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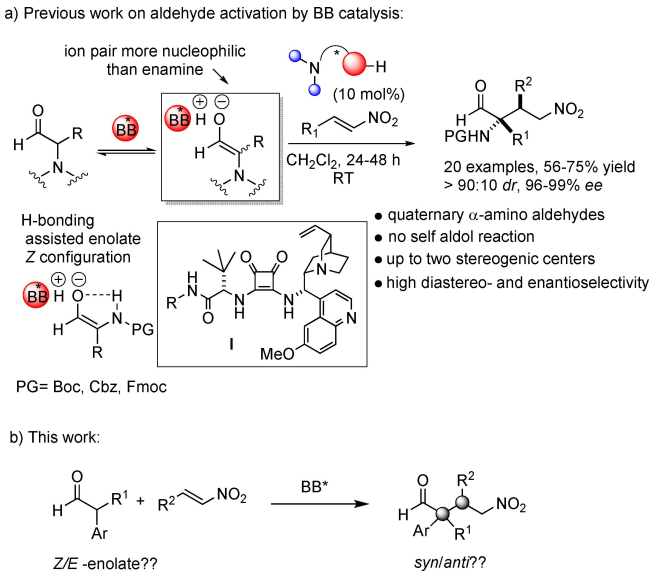
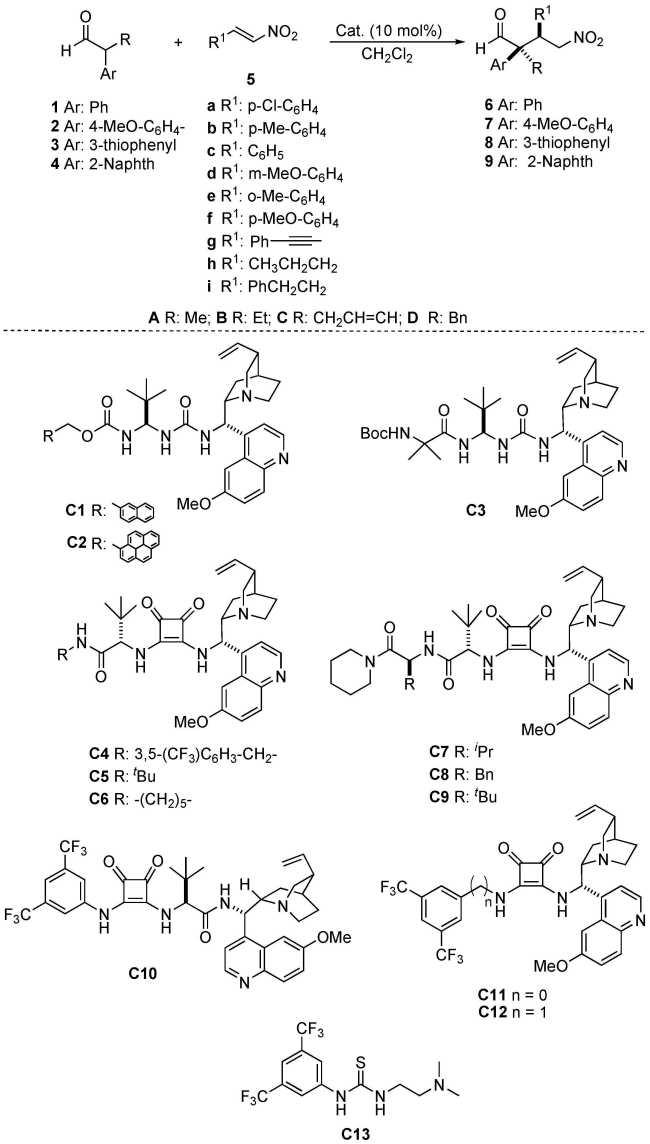


Scheme 1. Activation of α-branched aldehydes by BB catalysis. a) Previous work on α-branched α-amino aldehydes. b) This work by using α-branched aryl acetaldehydes.

Results and discussion

Preliminary experimental observations and catalyst screening

Our initial studies were carried out on the reaction between rac-2-phenylpropionaldehyde **1A** and nitroolefin **5a** (Scheme 2). First attempts using ureidopeptide derived bifunctional Brønsted bases previously developed by us[15] (**C1**, **C2** and **C3**) showed that the reaction indeed proceeded to afford γ-nitroaldehyde **6Aa** with moderate *syn* diastereoselectivity,[16] but the enantioselectivity was essentially negligible (Table 1, entries 1–3). The reaction catalyzed by the *tert*-leucine derived squaric acid **C4**, which provided the best results for α-branched α-amino aldehydes,[11] afforded the Michael adduct in better enantioselectivity and quite good *syn* selectivity (84% *ee*, 86:14 *dr*, entry 4), but improvement was still needed. Variations at the amide terminus in catalyst **C4** led to **C5** and **C6** and the reaction in the presence of these catalysts (entries 5 and 6) showed significant stereoselectivity improvement. Whilst the *tert*-butylamine derived catalyst **C5** provided **6Aa** in better enantio- and diastereoselectivity, catalyst **C6** led to excellent enantioselectivity and quite good diastereoselectivity. At this point and, with the aim to further improve reaction diastereoselectivity, we considered the incorporation of a second amino acid unit in catalyst **C6**. Accordingly, catalysts **C7**, **C8** and **C9**,[17,18] were synthesized and tested. Whereas **C7** provided adduct **6Aa** in lower diastereo- and enantioselectivity than **C6**, catalyst **C8** produced **6Aa** in similar diastereo- and enantioselectivity. In the presence of **C9**, which incorporates two *tert*-leucine units, product **6Aa** was obtained in higher *syn* selectivity, although slightly lower enantioselectivity. Lowering the temperature to 0 °C, the reaction using this catalyst led to product **6Aa** with better diastereo- and enantioselectivity in reasonable time



Scheme 2. Catalyst screened in the Michael addition of (±)**1A** to **5a**.

(entry 10). The position of the amino acid unit in these catalysts seems also to be significant as the reaction in the presence of **C10**, which incorporates the *tert*-leucine unit at other position, provided adduct **6Aa** in lower enantioselectivity.[19] Further proof of the robustness of this subclass of catalysts was provided from the reaction of **1A** with **5a** using the commercially available standard squaramides **C11** and **C12** which led to **6Aa** in good enantioselectivity but in both cases with lower levels of diastereoselectivity.[20] Therefore, the scope of the reaction was studied with the dipeptide derived catalyst **C9**.

Reaction scope

As the results in Table 2 show, the above conditions were equally efficient for the Michael addition of rac-2-phenyl-

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Table 1. Catalyst screening for the 1,4-addition of (±)-2-propionaldehyde **1A** to nitroolefin **5a** to afford **6Aa**.[a]

Entry	Cat	t [h]	T [°C]	Conv. [%][b]	Yield [%][c]	dr[d]	ee[e]
1	**C1**	29	rt	92	69	83:17	47
2	**C2**	13	rt	74	68	85:15	−2
3	**C3**	72	rt	88	90	81:19	24
4	**C4**	72	rt	>99	91	86:14	84
5	**C5**	35	rt	98	85	88:12	89
6	**C6**	30	rt	98	89	90:10	94
7	**C7**	15	rt	>99	87	86:14	85
8	**C8**	20	rt	>99	92	88:12	93
9	**C9**	10	rt	98	82	91:9	88
10		15	0	85	84	95:5	94
11	**C10**	15	rt	88	78	92:8	74
12	**C11**	23	rt	93	74	84:16	96
13	**C12**	40	0	98	71	86:14	96

[a] Reactions conducted on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). [b] Determined by the disappearance of the starting aldehyde. [c] Yield of the isolated two isomers. [d] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [e] Determined by chiral HPLC.

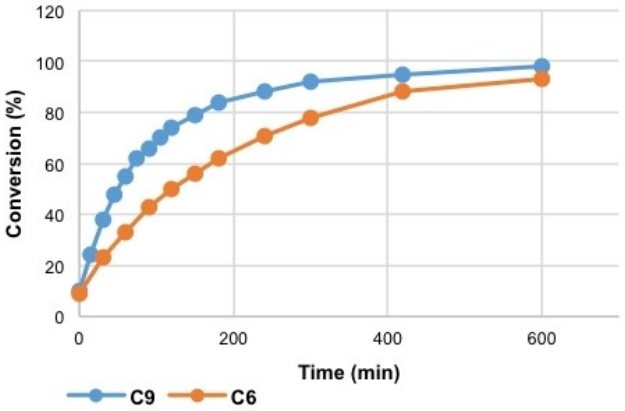
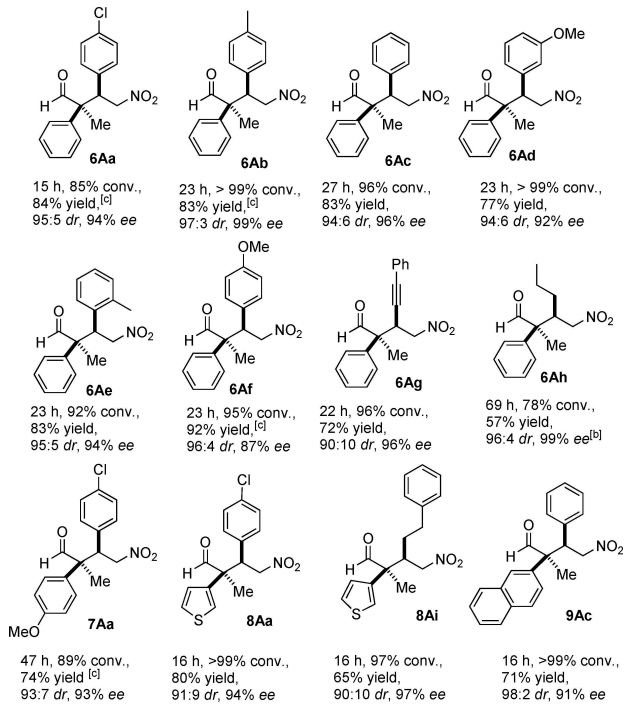


Figure 1. Conversion evolution of the reaction between **rac-1A** and nitroolefin **5a** in the presence of **C6** and **C9** catalysts at RT.

Table 2. Scope of the Michael reaction of α-methyl aryl/heteroaryl acetaldehydes **1**–**4** with nitroolefins **5a**–**i** assisted by **C9**.[a]



[a] Reactions conducted at 0 °C on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the isolated major diastereoisomer. Diastereomeric ratio determined by ^{1}H NMR (300 MHz) analysis on the crude product. Enantioselectivity determined by chiral HPLC. [b] Reaction carried out at RT. [c] Yield of the isolated two isomers.

propionaldehyde **1A** to different nitroolefins (**5b**–**h**). The reaction tolerates well nitrostyrenes carrying both electron-withdrawing and electron-donating substituents at the aromatic ring of the nitroolefin independently of the substituent position. In every case the corresponding adducts **6Aa**–**6Ah** were obtained in excellent enantioselectivity and very good *syn*-diastereoselectivity. Significantly, the most recalcitrant β-aliphatic nitroolefins such as **5g** and **5h** also react under these conditions to provide the Michael adducts **6Ag** and **6Ah** with excellent enantio- and *syn*-diastereocontrol. Similarly, the reaction may be extended to other aryl and heteroaryl α-methyl acetaldehydes leading to Michael adducts such as **7Aa**, **8Aa**, **8Ai** and **9Ac** with excellent diastereo- and enantioselectivity. In general, the dipeptide derived catalyst **C9**, which bears several H-bond donors,[21] is somewhat better than **C4**–**C6** catalysts not only regarding reaction stereoselectivity,[22] but also with respect to the reaction conversion. For instance, the reaction between **1A** and **5a** at RT in the presence of **C6** and **C9**, Figure 1, shows that with the former catalyst the reaction progresses relatively slower than with the dipeptide derived catalyst **C9**.

The above difference between both catalysts was also observed in the reaction of the ethyl and benzyl derivatives **1B** and **1D** with nitroolefins **5c** and **5b** respectively (Table 3). In the presence of **C9**, the Michael adduct **6Bc** was produced after 67 h at 0 °C in 56% conversion, while catalyst **C6** necessitates 112 h to reach the same conversion. Likewise, adduct **6Db** was formed in 85% conversion after 142 h of reaction when **C9** was used, but in the presence of **C6** the reaction progresses more slowly.

On the other hand, as shown in Table 3, under the usual conditions and in the presence of catalyst **C9** a decrease in both reactivity and stereoselectivity was observed when changing from α-methyl aryl acetaldehydes to other α-substituted derivatives. With α-ethyl and α-allyl phenyl acetaldehydes **1B** and **1C** adducts **6Bc** and **6Cb** were obtained in quite good diastereo- and enantioselectivity (83:17 *dr* and 78% *ee* for **6Bc** and 85:15 *dr* and 77% *ee* for **6Cb**). However, in the case of the α-benzyl acetaldehyde **1D** poor diastereomeric ratio and enantiomeric excess were measured in the synthesis of **6Db** (57:43 *dr* and 40% *ee*). The α-ethyl 3-thiophenyl acetaldehyde **3B** also reacted with *p*-chloro nitrostyrene **5a**, although the Michael adduct **8Ba** was produced in moderate stereoselectivity. Finally, the more acidic α-allyl 2-naphthylace-

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taldehyde **4C** proved to be more active as 90% conversion was detected after 64 h reaction and adduct **9Ca** was obtained in quite good diastereoselectivity, (85:15 *dr*) albeit in relatively poor enantiomeric excess (46% *ee*). Accordingly, while this BB approach may be extended to other α,α-disubstituted aryl acetaldehydes,[23] better conditions are still needed to improve both reaction time and stereocontrol. In this respect, during the preparation of racemic adducts we observed that reaction of **1A** with nitroolefin **5c** carried out in the presence of triethylamine (30 mol%) at RT for 16 h led to ***rac*-6Ac** in 71:29 *dr*, (90:10 *dr* with **C9**). Similarly, reaction of **3A** with **5i** promoted by catalyst **C13** (10 mol%) at RT provided after 16 h ***rac*-8Ai** in 76:24 *dr* while using the chiral catalyst **C9** the adduct was formed in 90:10 *dr*. Thus, a combination of both, substrate and catalyst control may be operating for the observed *syn* selectivity. A single crystal X-ray analysis of **6Ab** (Figure 2)[24] confirmed both its relative and absolute configuration and that of the remaining adducts was assumed on the basis of a uniform reaction mechanism.

Other interesting point of this protocol is that these transformations can be scaled up without loss of yield nor stereoselectivity as shown by the reaction of rac-2-phenyl-propionaldehyde **1A** with nitroolefin **5c** on a 4 mmol scale, which provided adduct **6Ac** in 82% yield and with 94:6 *dr* and 95% *ee* for the major *syn*-isomer. Notably, the catalyst was recovered after flash column chromatography in 87% yield.[25]

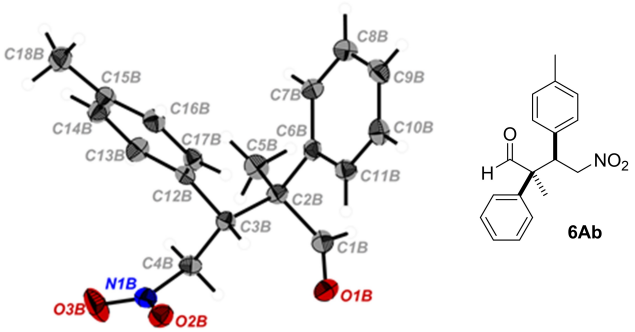


Figure 2. ORTEP diagram of compound **6Ab**. View of the molecular structure of **6Ab** with 50% probability displacement ellipsoids.

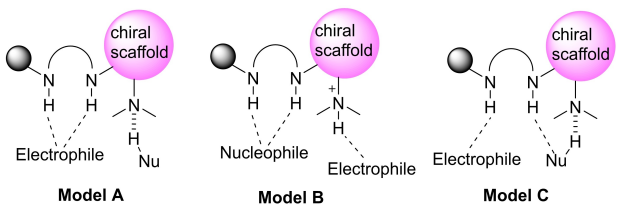
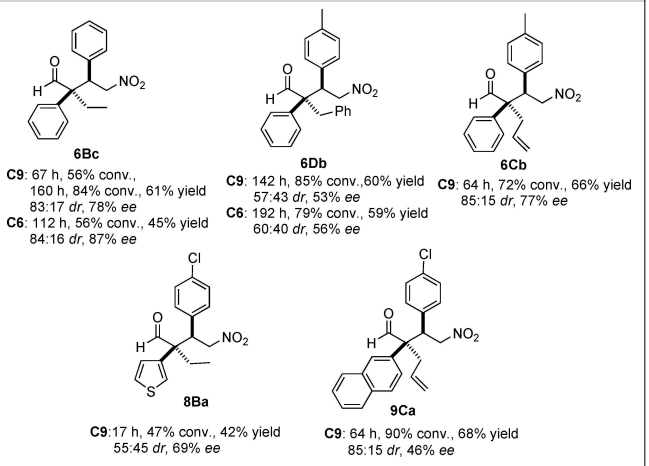


Figure 3. Three alternative substrate-catalyst combinations proposed for bifunctional Brønsted base activation mode.

Table 3. Scope of the Michael reaction of α-branched aryl/heteroaryl acetaldehydes **1**–**4** with nitroolefins **5a**–**c** assisted by **C9**/**C6**.[a]



[a] Reactions conducted at 0 °C on a 0.2 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/aldehyde/catalyst 3:1:0.1). Conversion determined by the disappearance of the starting aldehyde. Yield of the two diastereoisomers. Diastereomeric ratio determined by ^1H NMR (300 MHz) analysis on the crude product. Enantioselectivity determined by chiral HPLC.

Theoretical probes and mechanistic observations

In order to get insights into the mechanism of the reaction and the origin of the *syn*-selectivity in these transformations, we next performed some DFT calculations[26] on the reaction of rac-2-phenylpropionaldehyde **1A** with nitrostyrene **5c** promoted by **C9**.

Up to (at least) three different non covalent coordination patterns (model A or Takemoto's proposal, model B or Pápai's proposal and model C or Wang's proposal, Figure 3) have been documented for reactions promoted by bifunctional thiourea (or squaramide)-tertiary amine catalysts.[27] In our reaction we identified two of the previous H-bonding net activation modes, Takemoto's proposal (electrophile dual-activation by the squaramide core, model A) and Pápai's proposal (nucleophile dual-activation by the squaramide core, model B). All attempts to find transition structures following Wang's model (squaramide-activation of both reagents) evolved to Takemoto's model and therefore were discarded. For this study, we considered that the system behaves under Curtin–Hammett kinetic scenario, where the product ratio depends on the free Gibbs activation energy difference of the corresponding transition structure, and both *E*- and *Z*-enolate configurations were evaluated.

Our calculations show that the less energetic transition structures,[25] correspond to a Pápai's activation mode wherein the enolate interacts with the squaramide core of the catalyst and the nitroolefin is activated through H-bonding interaction with the cinchona moiety of **C9**, as previously described for the Michael addition of α-amino aldehydes to β-nitro styrenes catalyzed by analogous BB catalysts.[11] Remarkably, transition structures involving *E*-enolates are more stabilized than analogues from *Z*-enolates, as shown by the energy difference of +4.2 kcal mol^{-1} between **TS1-*E*-syn** and **TS1-*Z*-syn** (Figure 4),

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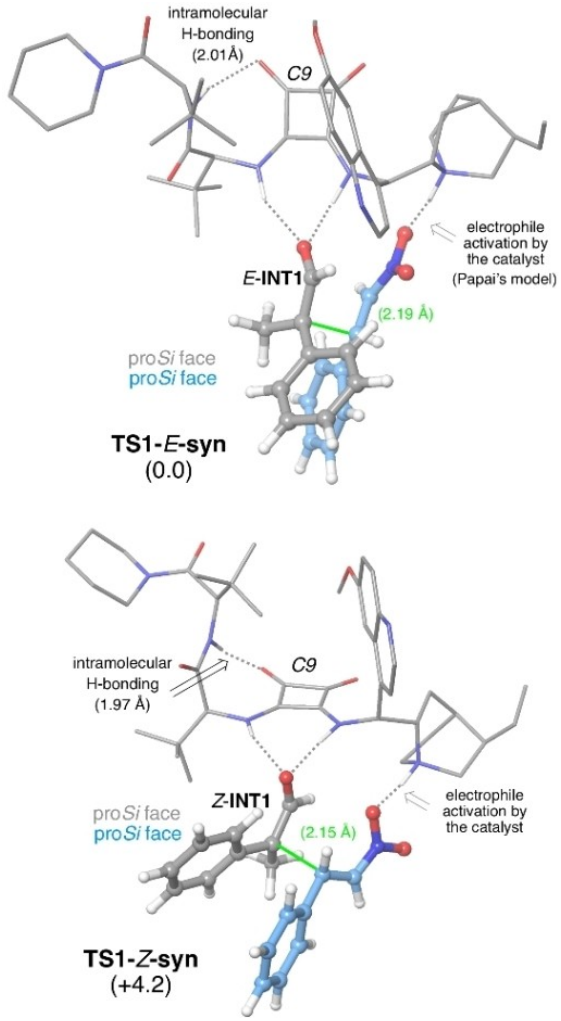


Figure 4. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **1A** and **5c** catalyzed by **C9** that lead to the formation of *syn-S,R*-**6Ac** considering *E*- and *Z*-enolates. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311 + G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.

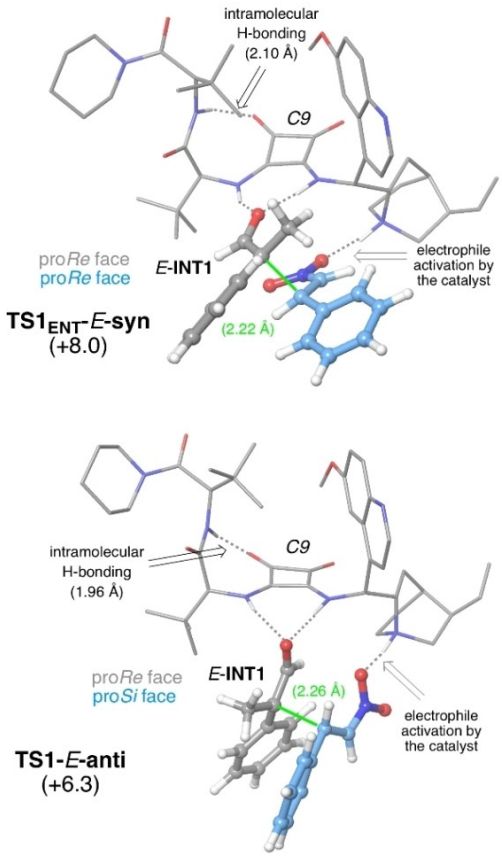
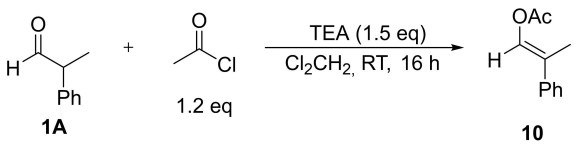


Figure 5. Main geometrical features and relative Gibbs free energies of least energetic transition structures TS1 associated with the reaction of **1A** and **5c** catalyzed by **C9** that lead to the formation of *syn-S,R*-**6Ac** considering *E*- and *Z*-enolates. Some hydrogen atoms are omitted for clarity. Energy values in kcal mol^{-1} computed at B3LYP-D3(PCM)/6-311 + G(d,p)//B3LYP-D3/6-31G(d) level (298 K). The reactive prochiral faces of the aldehyde and nitroalkene are given in grey and blue respectively.

despite reactive complexes involving *Z*-enolates being close in energy to their *E*- counterparts. This is a consequence of the higher deformation required to adopt the geometry of the transition structure in *Z*-enolates, where oxygen–phenyl repulsion during the C–C bond formation leads to an additional torsion in the phenyl group.

Noteworthy, the observed facial selection is consequence of the existence of an intramolecular H-bonding interaction between the NH of one of the *tert*-leucines and the carbonyl of squaramide moiety that fix the catalyst conformation independently of the activation mode considered. Within this conformational restricted catalytic system, **TS1**-*E*-**syn** was found to be the least energetic transition structure due to a lower steric hindrance between the *t*-butyl group of *tert*-leucine and the phenyl group of the enolate, thus yielding compound *syn-S,R*-**6Ac**. Note that in **TS1$_{ENT}$**-*E*-**syn** and **TS1**-*E*-**anti** (Figure 5) the enolate has to rotate due to steric hindrance, leading to less optimal catalyst-substrate H-bonding interactions. These calculations predict a theoretical *ee* of 99% and *dr* > 99:1, in good agreement with the experimental results.

Concordant with the above DFT observations, treatment of rac-2-phenylpropionaldehyde **1A** with triethylamine (TEA) (1.5 equiv.) and acetyl chloride (1.2 equiv.) in Cl_2CH_2 at RT for 16 h provided a 5.5:1 (85:15) mixture of the corresponding **10** *E* and Z enol acetates[28,29] (Scheme 3).



Scheme 3. Formation of the *E*/*Z* enol acetates from rac-2-phenylpropionaldehyde **1A** in the presence of triethylamine (TEA) and acetyl chloride.

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Conclusion

In summary, we have demonstrated that the α-functionalization of α-methyl aryl acetaldehydes may be accomplished by Brønsted base activation catalysis, thus providing a complementary alternative platform to the known enamine strategy. The protocol seems to work through the formation of the corresponding *E* ammonium enolate by the action of a cinchona based squaric acid-derived amino acid peptide. Further reaction of the transient ammonium enolate with different nitroolefins provides 2,2,3-trisubstituted *syn* γ-nitroaldehydes in high enantio- and diastereoselectivity and in the absence of homoaldol reaction.

Experimental Section

Catalytic conjugate additions of α-branched aryl/heteroaryl acetaldehydes to nitroolefins.

General Procedure: The corresponding aldehyde (0.2 mmol, 1 equiv), nitroolefin (0.6 mmol, 3 equiv) and catalyst **C6** or **C9** (0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (0.6 mL) and the resulting mixture was stirred at 0 °C. Reaction completion was followed by ^{1}H NMR and after the indicated time the mixture was directly submitted to flash column chromatography on silica gel. Reaction conversions and diastereomeric ratios were determined by ^{1}H NMR. Enantiomeric ratios were determined by chiral HPLC.

The corresponding racemic reactions were run following the above procedure but using achiral catalyst **C13** (30 mol%).

(*2S,3R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-phenylbutanal (6Aa). Prepared according to the General Procedure starting from aldehyde **1 A**, nitroolefin **5 a** and catalyst **C9** to afford a 95:5 diastereomer mixture. The major diastereoisomer was isolated as a colorless oil in an 88:12 diastereomeric ratio (53.9 mg, 0.169 mmol, 84% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 21.6 min (minor) and 23.1 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.49–7.11 (m, 5H), 7.07 (dd, *J* = 7.7, 2.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.05–4.83 (m, 2H), 4.21 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 138.6, 135.7, 132.3, 130.9, 130.1, 130.0, 129.0, 78.0, 58.2, 50.7, 18.1. UPLC-DAD-QTOF: $C_{17}H_{16}ClNO_3Na$ $[M+Na]^+$ calcd.: 340.0716, found: 340.0731.

(*2S,3R*)-2-Methyl-4-nitro-2-phenyl-3-(p-tolyl)butanal (6Ab). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5 b** and catalyst **C9** to afford a 97:3 diastereomer mixture. The product was isolated as a colorless solid in a 91:9 diastereomeric ratio (49.2 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate = 1 mL/min). Retention times: 12.5 min (minor) and 18.1 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.42–7.24 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15–4.75 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 138.7, 133.5, 130.9, 130.5, 130.4, 130.3, 129.4, 128.7, 77.7, 58.0, 50.8, 22.3, 18.4. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1266.

(*2S,3R*)-2-Methyl-4-nitro-2,3-diphenylbutanal (6Ac). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5 c** and catalyst **C9** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a colorless oil (46.8 mg, 0.165 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 21.8 min (minor) and 39.2 min (major). $[\alpha]_D^{23} = 113.99°$ (c = 1, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.40–7.26 (m, 4H), 7.21–6.92 (m, 6H), 5.17–4.81 (m, 2H), 4.22 (dd, *J* = 11.5, 3.8 Hz, 1H), 1.55 (s, 3H). All the spectroscopic data were consistent with those previously reported.[30]

(*2S,3R*)-3-(3-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (6Ad). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5 d** and catalyst **C9** to afford a 94:6 diastereomer mixture. The major diastereoisomer was isolated as a white foam (48.3 mg, 0.154 mmol, 77% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 90:10, flow rate = 1 mL/min). Retention times: 18.8 min (minor) and 25.9 min (major). $[\alpha]_D^{23} = 83.10°$ (c = 1, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.38–7.21 (m, 3H), 7.15–7.00 (m, 3H), 6.68 (dd, J = 8.3, 2.5 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.45–6.32 (m, 1H), 5.00 (dd, J = 13.2, 11.4 Hz, 1H), 4.84 (dd, J = 13.2, 3.9 Hz, 1H), 4.17 (dd, J = 11.4, 3.8 Hz, 1H), 3.61 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.08, 159.30, 137.43, 137.03, 129.21, 129.14, 128.19, 127.47, 121.36, 115.43, 113.36, 76.22, 75.15, 56.72, 55.17, 49.72, 16.79. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1209.

(*2S,3R*)-2-Methyl-4-nitro-2-phenyl-3-(o-tolyl)butanal (6Ae). Prepared according to the General Procedure starting from aldehyde **1 A**, nitroolefin **5 e** and catalyst **C9** to afford a 95:5 diastereomer mixture. The major diastereoisomer was isolated as a colorless oil (49.3 mg, 0.166 mmol, 83% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 17.3 min (major) and 19.3 min (minor). $[\alpha]_D^{23} = 88.18°$ (c = 1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.31 (dt, J = 6.5, 3.8 Hz, 4H), 7.22-7.14 (m, 1H), 7.12 (dd, J = 7.4, 1.4 Hz, 1H), 7.10–7.04 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 5.05 (dd, J = 13.1, 11.5 Hz, 1H), 4.89 (dd, J = 13.2, 3.7 Hz, 1H), 4.59 (dd, J = 11.4, 3.7 Hz, 1H), 2.07 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.99, 138.43, 137.94, 134.64, 131.01, 129.01, 128.15, 127.64, 127.31, 127.23, 126.10, 77.23, 56.92, 43.67, 19.84, 17.73. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1256.

(*2S,3R*)-3-(4-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (6Af). Prepared according to the General Procedure starting from aldehyde **1A**, nitroolefin **5 f** and catalyst **C9** to afford a 96:4 diastereomer mixture. The product was isolated as a yellow oil in a 92:8 diastereomeric ratio (57.5 mg, 0.184 mmol, 92% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 25.7 min (minor) and 47.9 min (major). $[\alpha]_D^{23} = 95.45°$ (c = 1, 92:8 dr, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37–7.29 (m, 3H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.07–4.78 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 160.2, 138.7, 131.6, 130.3, 129.7, 129.3, 128.6, 127.3, 114.9, 77.7, 58.0, 56.4, 50.3, 18.2. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1213.

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(2*S*,3*R*)-2-Methyl-3-(nitromethyl)-2,5-diphenylpent-4-ynal (6Ag). Prepared according to the General Procedure, starting from aldehyde **1A**, nitroolefin **5g** and catalyst **C9** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (44.1 mg, 0.143 mmol, 72% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 24.7 min (minor) and 39.1 min (major). $[\alpha]_D^{23} = 74.32°$ (c = 0.5, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.49–7.37 (m, 3H), 7.37–7.31 (m, 2H), 7.30–7.19 (m, 5H), 4.654.51 (m, 2H), 4.19 (dd, J = 9.6, 4.9 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.42, 136.76, 131.78, 129.36, 128.66, 128.60, 128.32, 127.52, 122.32, 86.40, 84.47, 76.37, 55.84, 38.19, 16.95. UPLC-DAD-QTOF: $C_{19}H_{17}NO_3Na$ $[M+Na]^+$ calcd.: 330.1106, found: 330.1098.

(2*S*,3*R*)-2-Methyl-3-(nitromethyl)-2-phenylhexanal (6Ah). Prepared according to the General Procedure, but at room temperature, starting from aldehyde **1A**, nitroolefin **5h** and catalyst **C9** to afford a 96:4 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (28.4 mg, 0.114 mmol, 57% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak OD-H Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 13.7 min (minor) and 18.3 min (major). $[\alpha]_D^{20} = 30.45°$ (c = 1, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.46–7.39 (m, 2H), 7.38–7.32 (m, 1H), 7.32–7.29 (m, 1H), 7.29–7.27 (m, 1H), 4.48 (dd, J = 13.4, 4.3 Hz, 1H), 4.28 (dd, J = 13.4, 7.3 Hz, 1H), 3.14 (ddt, J = 8.6, 4.3, 2.7 Hz, 1H), 1.48 (s, 3H), 1.28–0.99 (m, 4H), 0.74 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.91, 137.67, 129.34, 128.17, 127.54, 77.75, 57.01, 41.80, 31.84, 21.01, 15.29, 14.10. UPLC-DAD-QTOF: $C_{14}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 272.1263, found: 272.1263.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-methyl-4-nitrobutanal (7Aa). Prepared according to the General Procedure starting from aldehyde **2A**, nitroolefin **5a** and catalyst **C9** to afford a 93:7 diastereomer mixture. The final product was isolated as a colorless oil in a 93:7 diastereomeric ratio (51.5 mg, 0.148 mmol, 74% yield) after flash column chromatography on silica gel (90:10 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 33.4 min (minor) and 37.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.15–7.07 (m, 2H), 6.98–6.90 (m, 2H), 6.89–6.77 (m, 4H), 4.94 (dd, J = 13.1, 11.2 Hz, 1H), 4.85 (dd, J = 13.1, 4.3 Hz, 1H), 4.16 (dd, J = 11.2, 4.3 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.51, 159.47, 134.23, 133.66, 131.14, 130.68, 129.46, 128.67, 128.46, 128.33, 76.12, 55.98, 55.41, 49.03, 16.43. UPLC-DAD-QTOF: $C_{18}H_{18}ClNO_4Na$ $[M+Na]^+$ calcd.: 370.0822, found: 370.0822.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-methyl-4-nitro-2-(thiophen-3-yl)butanal (8Aa). Prepared according to the General Procedure starting from aldehyde **3A**, nitroolefin **5a** and catalyst **C9** to afford a 91:9 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (51.9 mg, 0.16 mmol, 80% yield) after flash column chromatography on silica gel (90:10 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate = 0.5 mL/min). Retention times: 82.6 min (minor) and 98.1 min (major). $[\alpha]_D^{24} = 128.59°$ (c = 1, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.37 (dd, J = 5.1, 3.0 Hz, 1H), 7.20-7.13 (m, 2H), 6.94–6.84 (m, 4H), 4.95 (dd, J = 13.2, 11.5 Hz, 1H), 4.78 (dd, J = 13.2, 4.0 Hz, 1H), 4.16 (dd, J = 11.4, 3.9 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.32, 138.30, 134.05, 133.99, 130.53, 128.66, 127.50, 126.10, 123.45, 76.09, 54.74, 49.02, 17.80. UPLC-DAD-QTOF: $C_{15}H_{14}NO_3SClNa$ $[M+Na]^+$ calcd.: 346.0281, found: 346.0282.

(2*S*,3*R*)-2-Methyl-3-(nitromethyl)-5-phenyl-2-(thiophen-3-yl)pentanal (8Ai). Prepared according to the General Procedure starting from aldehyde **3A**, nitroolefin **5i** and catalyst **C9** to afford a 90:10 diastereomer mixture. The major diastereoisomer was isolated as a yellow oil (41.3 mg, 0.13 mmol, 65% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane : ^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 24.9 min (major) and 26.8 min (minor). $[\alpha]_D^{21} = 21.39°$ (c = 1, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.38 (dd, J = 5.1, 2.9 Hz, 1H), 7.25–7.14 (m, 3H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.02–6.95 (m, 2H), 6.92 (dd, J = 5.1, 1.4 Hz, 1H), 4.50 (dd, J = 13.2, 4.6 Hz, 1H), 4.34 (dd, J = 13.2, 7.2 Hz, 1H), 3.17–3.05 (m, 1H), 2.59 (ddd, J = 16.7, 8.4, 3.4 Hz, 1H), 2.33 (ddd, J = 13.6, 9.7, 7.2 Hz, 1H), 1.73–1.55 (m, 2H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.74, 140.82, 138.82, 128.65, 128.51, 127.44, 126.37, 126.22, 123.44, 77.48, 55.44, 41.17, 34.26, 31.78, 15.67. UPLC-DAD-QTOF: $C_{17}H_{19}NO_3SNa$ $[M+Na]^+$ calcd.: 340.0983, found: 340.0982.

(2*S*,3*R*)-2-Methyl-2-(naphthalen-2-yl)-4-nitro-3-phenylbutanal (9Ac). Prepared according to the General Procedure starting from aldehyde **4A**, nitroolefin **5c** and catalyst **C9** to afford a 98:2 diastereomer mixture. The major diastereoisomer was isolated as a white foam (47.3 mg, 0.142 mmol, 71% yield) after flash column chromatography on silica gel (95:5 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times: 19.1 min (major) and 21.7 min (minor). $[\alpha]_D^{21} = 175.05°$ (c = 1, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.88–7.72 (m, 3H), 7.54–7.44 (m, 3H), 7.23 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 5.1, 2.0 Hz, 3H), 6.99 (dd, J = 5.2, 1.6 Hz, 2H), 5.10 (dd, J = 13.1, 11.5 Hz, 1H), 4.87 (dd, J = 13.1, 3.8 Hz, 1H), 4.31 (dd, J = 11.5, 3.8 Hz, 1H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.27, 135.48, 134.82, 133.20, 132.69, 129.46, 129.18, 128.42, 128.21, 127.89, 127.69, 127.03, 126.92, 126.83, 124.45, 76.46, 56.96, 49.87, 17.54. UPLC-DAD-QTOF: $C_{21}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 356.1263, found: 356.1259.

(2*S*,3*R*)-2-Ethyl-4-nitro-2,3-diphenylbutanal (6Bc). Prepared according to the General Procedure starting from aldehyde **1B**, nitroolefin **5c** and catalyst **C9** to afford an 83:17 diastereomer mixture. The product was isolated as a white oil in an 82:18 diastereomeric ratio (36.3 mg, 0.122 mmol, 61% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IF Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 12.5 min (major) and 15.9 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.47–7.36 (m, 3H), 7.29–7.21 (m, 3H), 7.18–7.11 (m, 2H), 7.11–7.02 (m, 2H), 4.98 (dd, J = 13.2, 11.7 Hz, 1H), 4.68 (dd, J = 13.3, 3.4 Hz, 1H), 4.16 (dd, J = 11.7, 3.4 Hz, 1H), 1.96 (dq, J = 14.4, 7.1 Hz, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.10, 137.03, 135.44, 129.80, 129.26, 128.56, 128.19, 128.07, 127.97, 77.06, 50.96, 27.77, 9.04. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.125.

(*S*)-2-((*R*)-2-Nitro-1-(p–tolyl)ethyl)-2-phenylpent-4-enal (6Cb). Prepared according to the General Procedure starting from aldehyde **1C**, nitroolefin **5b** and catalyst **C9** to afford an 85:15 diastereomer mixture. The product was isolated as a colorless oil in a 79:21 diastereomeric ratio (42.7 mg, 0.132 mmol, 66% yield) after flash column chromatography on silica gel (99:1 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IB Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 10.7 min (minor) and 12.2 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.46–7.31 (m, 3H), 7.15 (dd, J = 6.8, 1.6 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 5.58–5.37 (m, 1H), 5.10–4.96 (m, 3H), 4.69 (dd, J = 13.2, 3.4 Hz, 1H), 4.11 (dd, J = 11.7, 3.3 Hz, 1H), 2.77 (ddt, J = 14.7, 5.9, 1.4 Hz, 1H), 2.67-2.55 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.81, 138.19, 132.44,

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130.06, 129.88, 129.52, 129.21, 129.19, 128.40, 128.03, 120.22, 77.78, 59.50, 50.87, 39.16, 21.37. UPLC-DAD-QTOF: $C_{20}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 346.1419, found: 346.1411.

(2*S*,3*R*)-2-Benzyl-4-nitro-2-phenyl-3-(p–tolyl)butanal (6Db). Prepared according to the General Procedure starting from aldehyde **1D**, nitroolefin **5 b** and catalyst **C9** to afford a 57:43 diastereomer mixture. The product was isolated as a white solid in a 63:37 diastereomeric ratio (44.8 mg, 0.12 mmol, 60% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times for the major diastereomer: 34.3 min (minor) and 60.5 min (major) and for minor diastereomer: 15.1 min (minor) and 16.3 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H, minor diastereomer), 9.69 (s, 1H, mayor diastereomer), 7.47–7.40 (m, 3H, mayor diastereomer), 7.36 (d, J = 7.2 Hz, 3H, minor diastereomer), 7.18–7.11 (m, 7H, both diastereomers), 7.11–6.99 (m, 9H, both diastereomers), 6.97 (dd, J = 6.5, 3.1 Hz, 2H, both diastereomers), 6.77 (d, J = 8.1 Hz, 2H, mayor diastereomer), 6.64 (dd, J = 8.0, 1.5 Hz, 2H), 4.91 (dd, J = 13.2, 11.8 Hz, 1H, minor diastereomer), 4.79 (dd, J = 12.0, 3.3 Hz, 1H, mayor diastereomer), 4.68 (dd, J = 13.2, 3.2 Hz, 1H, minor diastereomer), 4.38–4.27 (m, 2H, both diastereomers), 4.22 (dd, J = 11.9 Hz, 1H, mayor diastereomer), 3.30–3.18 (m, 2H, minor diastereomer), 3.19–3.07 (m, 2H, mayor diastereomer), 2.34 (s, 3H, minor diastereomer), 2.31 (s, 3H, mayor diastereomer). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.45, 204.33, 138.28, 138.06, 137.51, 135.58, 134.64, 134.58, 131.97, 131.50, 130.54, 130.50, 130.28, 129.87, 129.63, 129.54, 129.32, 129.17, 128.99, 128.79, 128.69, 128.48, 128.19, 128.12, 127.20, 126.91, 77.45, 77.30, 60.62, 59.55, 51.09, 47.30, 42.23, 41.66, 21.21. UPLC-DAD-QTOF: $C_{24}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 396.1576, found: 396.1573.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-ethyl-4-nitro-2-(thiophen-3-yl) butanal (8Ba). Prepared according to the General Procedure starting from aldehyde **3B**, nitroolefin **5 a** and catalyst **C9** to afford a 55:45 diastereomer mixture. The product was isolated as a yellow oil in a 62:38 diastereomeric ratio (28.4 mg, 0.084 mmol, 42% yield) after flash column chromatography on silica gel (98:2 Hexane: EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IC Hexane:^{i}PrOH 95:5, flow rate = 1 mL/min). Retention times for the major diastereomer: 12.4 min (major) and 13.4 min (minor) and for minor diastereomer: 21.5 min (major) and 31.1 min (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.44 (dd, J = 5.1, 2.9 Hz, 1H), 7.27–7.18 (m, 2H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H), 7.01–6.90 (m, 3H), 4.86 (dd, J = 13.3, 11.6 Hz, 1H), 4.65 (dd, J = 13.3, 3.7 Hz, 1H), 4.07 (dd, J = 11.6, 3.7 Hz, 1H), 1.95 (qd, J = 7.4, 1.1 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.11, 130.97, 130.85, 128.84, 128.65, 127.27, 126.26, 123.87, 76.96, 57.92, 50.36, 28.22, 9.09. UPLC-DAD-QTOF: $C_{17}H_{20}NO_4S$ $[M+CH_3OH–Cl]^+$ calcd.: 334.1113, found: 334.1113.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-2-(naphthalen-2-yl) pent-4-enal (9Ca). Prepared according to the General Procedure starting from aldehyde **4C**, nitroolefin **5 a** and catalyst **C9** to afford an 85:15 diastereomer mixture. The product was isolated as a white foam in an 80:20 diastereomeric ratio (53.6 mg, 0.136 mmol, 68% yield) after flash column chromatography on silica gel (98:2 Hexane:EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chirapak IA Hexane:^{i}PrOH 98:2, flow rate = 1 mL/min). Retention times: 17.5 min (minor) and 29.5 min (major). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.88–7.77 (m, 2H), 7.60–7.52 (m, 1H), 7.51–7.45 (m, 1H), 7.31–7.13 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 5.61–5.43 (m, 1H), 5.16–5.01 (m, 3H), 4.70 (dd, J = 13.4, 3.3 Hz, 1H), 4.21 (dd, J = 11.7, 3.2 Hz, 1H), 2.92 (dd, J = 14.8, 5.5 Hz, 1H), 2.65 (dd, J = 14.7, 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.21, 134.28, 133.98, 133.77, 133.15, 132.76, 131.81, 131.34, 129.64, 128.84, 128.26, 127.76, 127.65, 127.19, 127.12, 124.43, 120.47, 76.67, 59.28, 50.37, 38.66. UPLC-DAD-QTOF: $C_{23}H_{20}ClNO_3Na$ $[M+Na]^+$ calcd.: 416.1029, found: 416.1033.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: α-branched arylacetaldehydes · Brønsted bases · Michael reaction · nitroolefins · organocatalysis

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[23] An additional experiment involving the reaction of diphenylacetaldehyde with nitrostyrene at 0°C in the presence of **C9** revealed the formation of the corresponding adduct in 76% conversion after 68 h, but in racemic form. Using squaramide **C12** the product was formed in 30% *ee*.
[24] Deposition Number 2070327 (for **6Ab**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
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Peptido Laburretatik Eratorritako Brønsted Baseak Katalizatzaile Bifuntzional Moduan Michael Erreakzio Asimetrikoetan

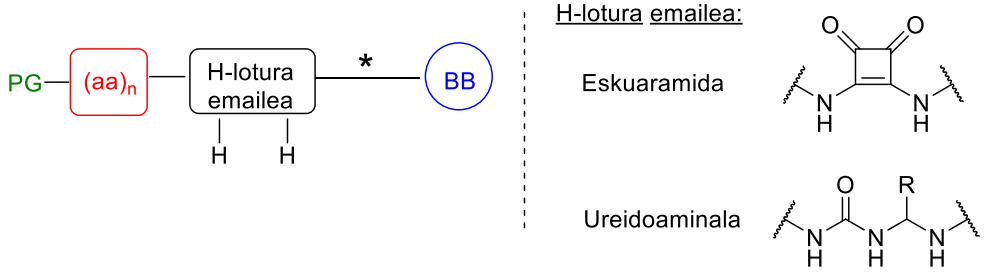
TESI DOCTORALA

ANE GARCIA URRICELQUI

Donostia, 2022

Laburpena

Peptido bidezko katalisia enantiomerikoki aberastutako konposatuen sintesirako tresna erabilgarri bat izan daitekeela frogatua gelditu da azken urteetan. Konposatu hauek hainbat aplikazio sintetiko izan ditzakete eta aktibitate biologiko edo interes farmakologikoa duten molekula konplexuagoak prestatzeko erabil daitezke. Peptidoek substratuekin H-loturen bidez elkar eragiteko eta H-lotura sare konplexuak osatzeko duten gaitasuna bereziki erabilgarria da erreakzioen estereokontrolerako. Bestalde, Brønsted base (BB) bidezko katalisi asimetrikoa ere nabarmenki hedatu da azken urteetan. Bereziki aipagarriak dira BBz eta H-lotura emailez osatutako katalizatzaile bifuntzionalak, zeinak gai diren erreakzio batean parte hartzen duten susbstratuak (nukleozalea eta elektroizalea) batera aktibatzeko. Esparru honetan aurrerapen handiak egin badira ere, ikertu gabe dauden edo erronka bat suposatzen duten erreakzio asko daude oraindik, ikerkuntza eta hobekuntzak behar dituztenak. Testuinguru honetan, Tesi honen helburu nagusia organokatalizatzaile familia berri bat diseinatu eta sintetizatzea izan da, ezaugarri hauek dituena: (1) aminoazido edo peptido labur batetik eratorria izatea, (2) ohiko H-lotura emaile egitura bat izatea (espreski eskuaramida edo ureidoaminala); eta (3) BB unitate bat izatea (A Irudia); eta ondoren, berauen eraginkortasuna neurtzea estereozentro kuaternarioak sortzen diren hainbat erreakzio zailetan.

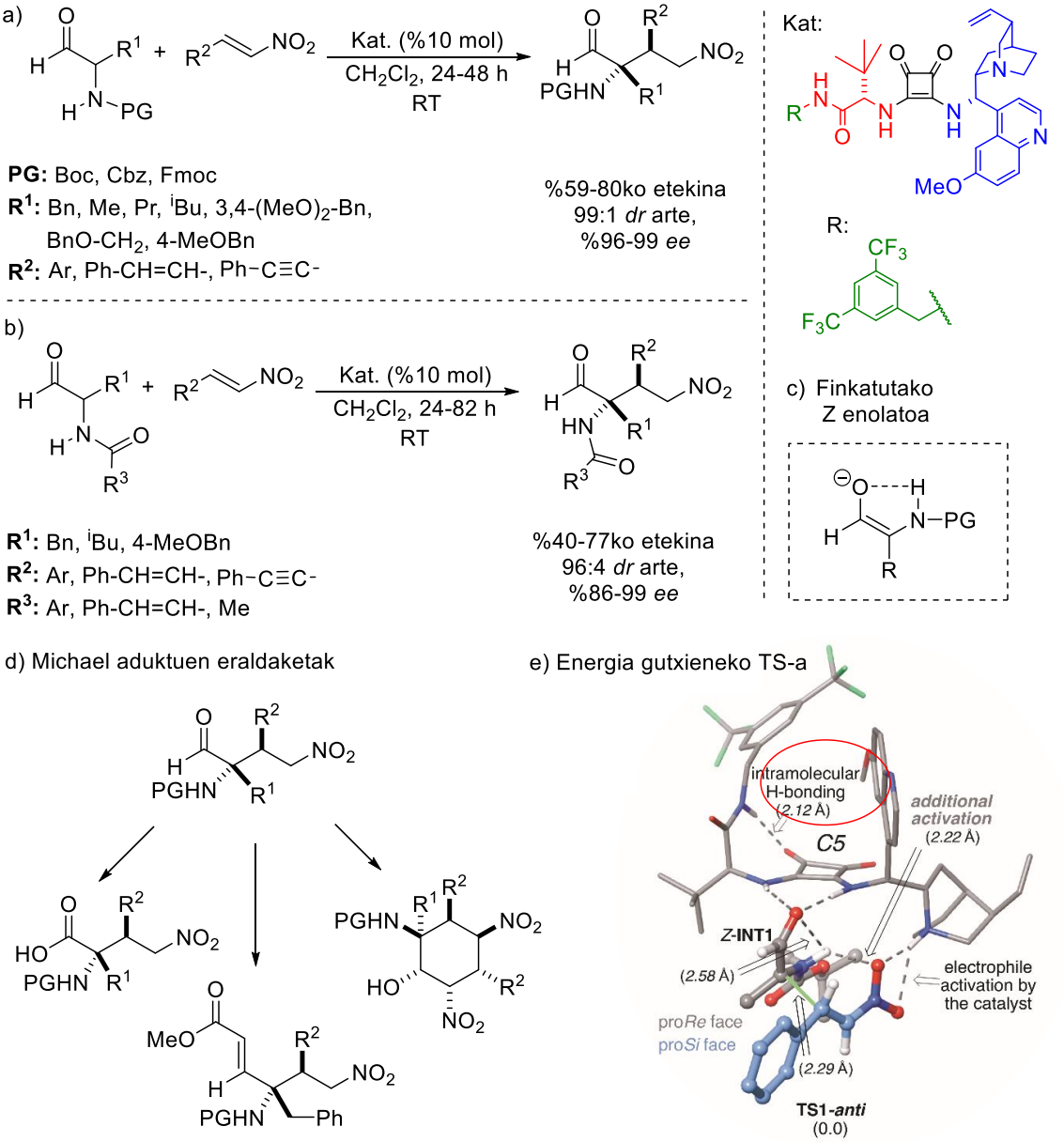


A Irudia. Aminoazidoak daramatzaten BB katalizatzaile berrien egituraren eskema. aa: aminoazidoa. PG: talde babeslea (protecting group).

Aldehidoak ($pk_a \approx 17$, DMSO-tan) amina tertziario batek ($pk_a = 11\text{-}21$, DMSO-tan) desprotonatu ditzakeen konposatuen multzoan sar ditzakegu. Hala ere, Tesi honen hasieran, aldehidoak nukleozale moduan dituzten eta BB bidezko katalisian oinarritzen diren erreakzio asimetrikoak ikertu gabe zeuden. Aldiz, aldehidoen enamina bidezko aktibazioa ongi ezaguna zen, baina aktibazio honetan oinarritzen den katalisiak hainbat arazo ditu α-ordezkatutako aldehidoen α-funtzionalizazioa burutu nahi denenen, bai erreaktibotasunaren aldetik eta bai erreakzioaren estereoselektibotasunari dagokionez. Tesi honen 2. Kapituluan, α-ordezkatutako aldehidoen eta nitroolefinen arteko Michael erreakzioari dagokion ikerketaren emaitzak aurkezten dira, non peptido laburretatik eratorritako BB katalizatzaile bifuntzional familia berri bat erabiltzen den erreakzioa

bultzatzeko. Azterketa honetan, α-ordezkatutako α-amino aldehidoak eta α-aril azetaldehidoak erabili dira pronukleozale moduan.

Hasteko, α-amino aldehidoen α-funtzionalizazioari dagozkion emaitzak aurkezten dira, non amaierako α-amino aldehido kuaternarioak etekin eta estereoselektibitate bikainekin lortzen diren (A eskema). Orain arte, α-amino aldehidoak elektroizale bezala erabiliak izan dira gehien bat, eta ez dira ia ikertu pronukleozale moduan erreakzio katalitikoetan. Aldehidoak nukleozale bezala erabiliz bibliografian aurki daitezkeen adibideetan aminokatalizatzaileak erabili dira erreakzioak sustatzeko eta α-metil ordezkatutako aldehidoetara edo oso elektroizale aktiboetara mugatutako eraldaketak dira.

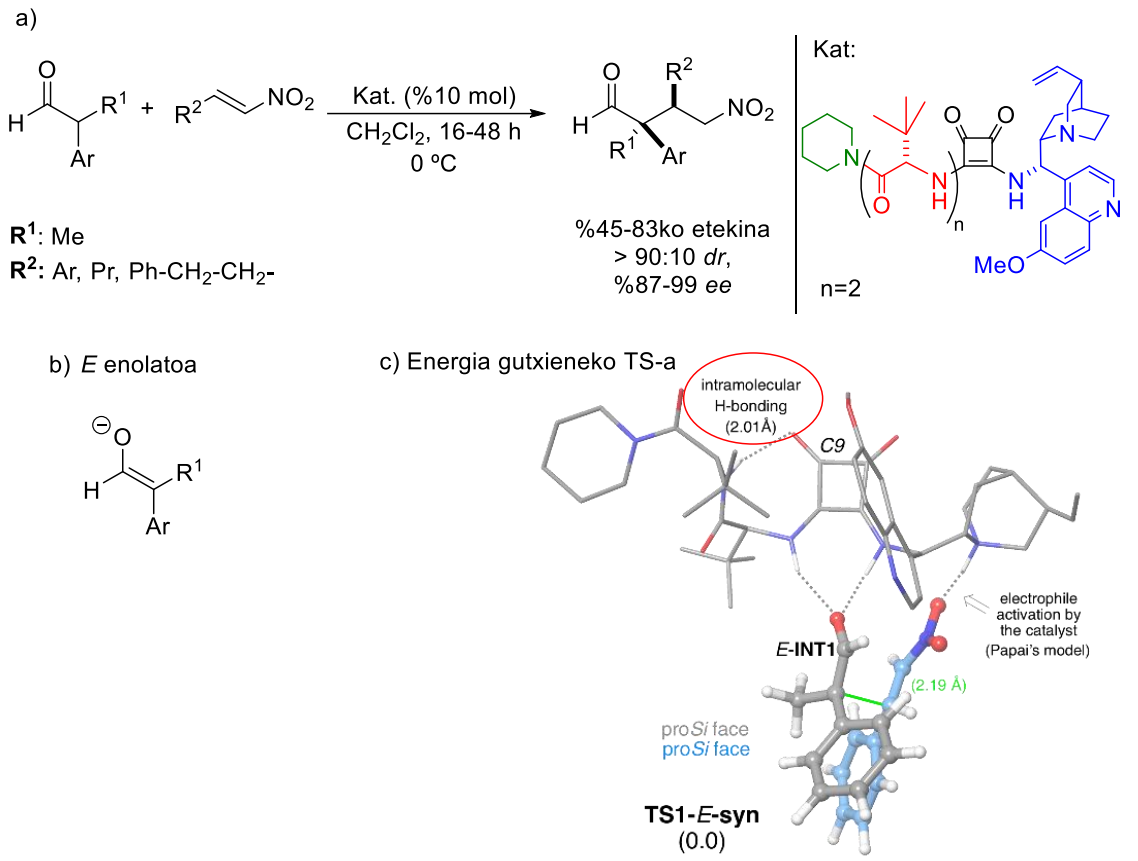


A Eskema. a) N-Boc, N-Cbz eta N-Fmoc babestutako α-ordezkatutako α-amino aldehidoen eta nitroolefinen arteko Michael erreakzio asimetrikoa. b) N-azil α-ordezkatutako α-amino aldehidoen eta nitroolefinen arteko Michael erreakzio asimetrikoa. c) Finkatutako Z enolatoa. d) Michael aduktuen eraldaketak. e) Energia gutxieneko trantsizio egoera (TS, transition state).

Nitroolefinetarako Michael adizioa *N*-posizioan funtzio talde desberdinak dituzten α-amino aldehidoekin ikertua izan da (A Eskema). Erreakzio honetarako katalizatzaile eraginkorrenak eskuaramida H-lotura emaile bat darama eta a (*L*)-*tert*-Leuzina unitate bat, funtsezkoa dena estereokontrolerako.

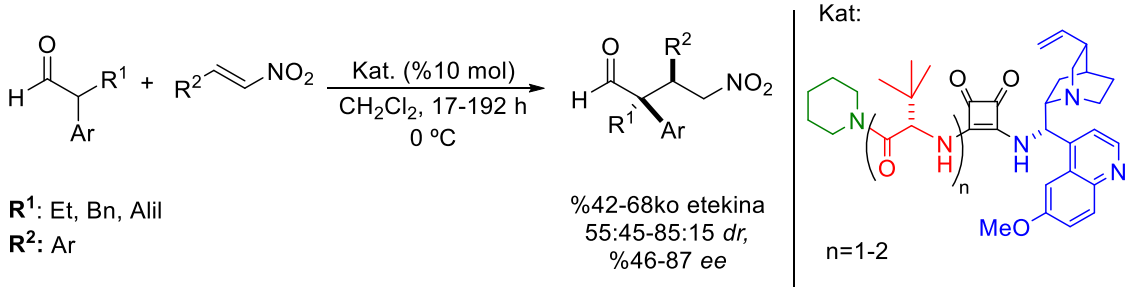
Substratuari dagokionez, *N*-posizioan Boc, Cbz eta Fmoc ohiko taldeak daramatzaten α-amino aldehidoekin Michael erreakzioak estereoselektibitate bikainekin eta oso etekin onetan burutu dira (Aa Eskema). Horiez gain, *N*-azil talde aromatiko eta alifatikoak ere onartzen ditu erreakzioak, orokorrean etekin eta estereoselektibitate onak lortuz (Ab Eskema). Elektroizale bezala, ordezkapen patroi desberdinak dituzten nitroestirenoak, eta alkenil eta alkinil ordezkatzaileak dituzten nitroolefinak erabil daitezke. Protokolo honen erabilgarritasuna azaltzeko asmoz, lortutako α-amino aldehido kuaternarioak interes handiko molekula konplexuagoetan eraldatu ahal izan dira, esaterako, tetraordezkatutako α-aminoazidoak, funtzionalizazio maila handiko alilaminak eta guztiz ordezkatutako ziklohexilaminak (Ad Eskema). Lortutako estereoselektibitate eta erreaktibotasun bikainak α-amino aldehidoek molekulabarneko H-loturak osatzeko duten gaitasunari lotu dakioke. Alde batetik, α-amino aldehidoan osatzen den N-H···O=C elkarrekintzak α-karbonoaren azidotasuna handituz enolizazioa errazteaz gain, nagusiki *Z*-enolatoa sortzea hobetsi dezake (Ac Eskema). Bestalde, DFT kalkuluek konfirmatu dute energetikoki egonkorragoa den trantsizio egoeran katalizatzailea N-H···O=C motako lotura bat osatzeko gai dela, zeinak ^{t}Leu unitatea estrategikoki kokatzen duen aurpegietako bat blokeatuz eta beraz, selektibitate ona justifikatuz (Ae Eskema).

Azpimarratzekoa da α-ordezkatutako aldehido arruntek, eta beraz, molekulabarneko H-loturak osatzeko gai ez direnek ere antzeko Michael adizioetan parte har dezaketela frogatu dela, erabilitako katalizatzailean aldaketa txiki batzuk eginez. Hala, α-metil α-aril azetaldehido desberdinen nitroolefinetarako adizio konjokatua estereoselektibitate bikainarekin gauzatu daiteke, nitroalkeno β-alifatikoak ere erabiliz. Erreakzio honetan, α-amino aldehidoen kasuan ez bezala (*anti*-aduktuak), *sin* konfiguraziodun aduktuak osatzen dira (Ba Eskema). Emaitza estereokimiko honekin bat datoz DFT kalkuluak, non ikusi den *E*-enolatoaren bidez gertatzen den erreakzioa (Bb Eskema). Erreakzio hauetarako katalizatzaile eraginkorrenek *N*-muturrean piperidina daramate eta (*L*)-*tert*-Leuzina unitate bat ala bi dituzte, dipeptidoaren presentzian erreakzioa azkarragoa izanik. α-Amino aldehidoen erreakzioarekin gertatzen den bezala, DFT kalkuluek katalizatzaileak eskuaramidaren karbonilo baten eta aminoazidoaren NH-aren arteko molekulabarneko elkarrekintza bat osatzen duela erakutsi dute. H-lotura honek aurpegi selektibitatean laguntzen du, aminoazidoaren *tert*-butil taldearen posizioak kontrako aldeko hurbilketa estaltzen baitu (Bc Eskema).



B Eskema. a) α-Metil α-aril azetaldehidoen eta nitroolefinen arteko Michael erreakzio asimetrikoa. b) E-enolatoa. c) Energia gutxieneko trantsizio egoera (TS).

Alfa posizioan metiloa baino ordezkatzaile handiagoak dituzten α-aril azetaldehidoen adizio konjokatua ere burutu daiteke protokolo berdinarekin, baina orokorrean erreakzio denbora luzeagoak behar dira eta estereoselektibitatea aldakorragoa da R^1 ordezkatzailearen arabera (C Eskema). Hortaz, BB estrategia hau beste α,α-diordezkatutako aril azetaldehidoetara zabal badaiteke ere, baldintza egokiagoak bilatzea beharrezkoa da erreakzio-denborak eta estereokontrola hobetzeko.

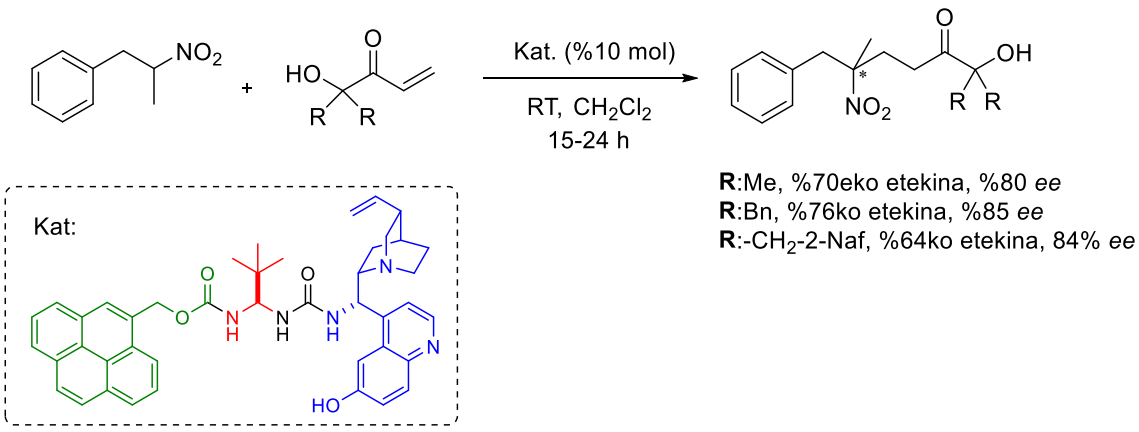


C. Eskema. Metil ez diren beste taldeekin α- ordezkatutako α-aril azetaldehidoen ikerketa.

Bestalde, nitroalkano α-estereogenikoen sorrera ere interesgarria da nitro taldea funtzio talde ugaritan bihur daitekeelako, bereziki aminetan, interes biologikoko molekulentzako ibilbide sintetiko berriak irekiz. Horretarako biderik zuzenetarikoa nitroalkano proestereogenikoen α-funtzionalizazioa burutzea litzateke, dagokion

elektroizale batekin erreakzionaraziz. Gaur gaurkoz, ordea, aktibatu gabeko α-ordezkatutako nitroalkanoetatik abiatuz prozesu hori modu katalitikoan eta asimetrikoan egitea ahalbidetzen duten metodorik ez dira apenas ezagutzen, seguruenik erreaktibotasun baxuarengatik edota estereokimika kontrolatzeko arazoengatik. Tesi honen 3. Kapituluan, erronka hau ikertu da, elektroizale giltzarri moduan α-hidroxi enonak erabiliz, zeinak erreaktibotasun erlatiboki handia izateaz gain, enalen, enonen eta akrilato sistemen baliokide sintetikotzat har daitezkeen. Elektroizale hauek elkar eragiteko bi koordinazio puntu dituzte eta ezaugarri honek bereziki aproposak bilakatzen ditu peptidoetatik eratorritako katalizatzaileekin batera erabiltzeko, azken hauek substratuekin hainbat H-lotura sortzeko gaitasuna baitute, trantsizio egoeren (TS, transition state) askatasun maila mugatuz.

Ikerketa honetan, bat, bi eta hiru aminoazido unitatez osatutako hainbat katalizatzaile probatu dira (2-nitropropil)benzenoaren eta α-hidroxi enona desberdinen arteko erreakzioa bideratzeko, eraginkorrena D Eskeman irudikatutako (*L*)-*tert*-Leuzinatik eratorritako ureidopeptido motako katalizatzailea suertatu delarik. Hidroxi enonaren alfa posizioko ordezkatzaileak aldatuz, aduktuak metil hidroxi enonarekin lortutako etekin berdinarekin eta %85 arteko *ee* balioarekin lortu dira. Nabarmentzekoa da Michael erreakzio katalitiko honetan hidroxi enonek erakutsitako erabateko konbertsioa kontutan harturik, pareko erreakzioan metil akrilatoek %45eko konbertsioa ematen dutela 24 h-ren buruan, α-hidroxi enonen erabilgarritasuna azpimarratuz. Azkenik, ikusi da eragozpen esteriko handiagoa duen (2-nitrobutil)benzeno pronukleozaleak erreakzio kondizio berdinetan ez duela α-hidroxi enonarekin ezta beste antzeko Michael hartzaileekin ere erreakzionatzen.



D Eskema. Aktibatu gabeko α-ordezkatutako nitroalkanoen eta α-hidroxi enonen arteko Michael erreakzio asimetrikoa.

Laburdura eta akronimoak

"Guidelines for authors" liburuxkan (*J. Org. Chem.,* **2015eko** Urtarrila) gomendatzen diren laburdura eta akronimoak erabili dira. Horretaz gain, jarraian agertzen diren laburdura eta akronimoak ere erabili izan dira.

*	Kiral
aa	Aminoazido
AIB	Azido 2-aminoisobutirikoa
Alk	Alkil
Asp	Asparagina
B	Base
BB	Brønsted base
DIPEA	Diisopropiletilamina
E	Elektroizale
ee	Enantiomero soberakina
EPC	Konposatu enantiopuruak
eq	Baliokide
Erref.	Erreferentzia
EWG	Talde elektro-erakarlea
GABA	Azido γ-aminoisubutirikoak
Glu	Glutamina
HBTU	*N,N,N',N'*-Tetrametil-*O*-(1*H*-benzotriazol-1-il)uronio hexafluorofosfatoa
His	Histidina
Im	Imidazola
Konb.	Konbertsio
Leu	Leuzina

MTBD	7-Metil-1,5,7-triazabiziklo[4.4.0]dek-5-enoa
Naf	Naftil
nd	Ez zehaztua
NMM	4-Metilmorfolina
no	Ez behatua
n.r.	Erreakziorik ez
o.n.	Gau osoa
PG	Talde babeslea
PNBA	Azido *p*-nitrobenzoikoa
Pro	Prolina
Rac	Errazemiko
TBD	1,5,7-triazabiziklo[4.4.0]dek-5-enoa
TEA	Trietilamina
Trp	Triptofanoa
Val	Balina

Aurkibidea

1. KAPITULUA

SARRERA

1. Sarrera

Konposatu kiral baten bi enantiomeroek ezaugarri biologiko desberdinak izan ditzaketela aurkitu zenetik, konposatu enantiopuruen (EPC, Enantiomerically Pure Compounds)[1] sintesiaren inguruko interesa nabarmenki handitu da. Azken urteetan, konposatu enantiopuru hauen erabilera desberdinak jorratu dira, ez bakarrik farmakologia eta kimika medikoa[2] bezalako esparruetan, baizik eta pestiziden[3] eta kosmetikoen[4] sintesian, eta material berrien diseinuan ere.[5] Honen ondorioz, EPC hauen sintesirako estrategia desberdinak garatu dira, eta hauen artean katalisi asimetrikoa[6] oso teknika erabilgarri eta erakargarria dela frogatu da. Katalisi asimetrikoa konposatu akiral batean kiralitatea sortzean datza, enantiopurua den konposatu baten kantitate subestekiometrikoak erabiliz, eta teknika honekin amaierako produktuaren enantiomero bakarraren kantitate handiak lor daitezke katalizatzailearen kantitate gutxirekin.

Katalisi asimetrikoaren alorrean, organokatalisiak[7] garrantzi handia bereganatu du azken bi hamarkadetan. Estrategia hau molekula organiko kiral txikiak katalizatzaile moduan erabiltzean datza erreakzio estereoselektiboak sustatzeko. Organokatalisi motak sailkatzeko irizpide desberdinak proposatu dira, eta onartuena substratuaren eta katalizatzailearen arteko elkarreragina hartzen du aintzat, zeina kobalentea ala ez-kobalentea izan daitekeen.[8] Elkarrekintza kobalentean oinarritzen den organokatalisi

[1] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis)* in *Modern Synthetic Methods*, Salle and Sauerländer, **1980**.

[2] a) Guo-Qiang, L.; Qi-Dong, Y.; Jie-Fei, C. *Chiral Drugs: Chemistry and Biological Action*; Wiley, **2011**; b) McConathy, J.; Owens, M. J. *Prim. Care Companion J. Clin. Psychiatry* **2003**, *5* (2), 70–73; c) Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discov. Today* **2004**, *9* (3), 105–110.

[3] 2018an erregistratutako pestiziden %30 baino gehiago kiralak ziren, baina %7 bakarrik merkaturatu zen enantiomero puru edo nahasketa estereoaberastu gisa: de Albuquerque, N. C. P.; Carrão, D. B.; Habenschus, M. D.; de Oliveira, A. R. M. *J. Pharm. Biomed. Anal.* **2018**, *147*, 89–109.

[4] a) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron Asymmetry* **2003**, *14* (1), 1–42; b) Leffingwell, J. C.; Leffingwell, D. *Spec. Chem. Mag.* **2011**, *31*, 30–33.

[5] a) Hodgkinson, I.; Hong Wu, Q. *Adv. Mater.* **2001**, *13*, 889–897; b) Mallia, V. A.; Tamaoki, N. *Chem. Soc. Rev.* **2004**, *33* (2), 76–84.

[6] Katalisi asimetrikoaren inguruko erreferentzia orokorretarako, ikus: a) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*; Wiley, **2006**; b) Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101* (15), 5348–5355.

[7] a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley, **2005**; b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Enantioselective Organocatalysis*; Drug Discov Today, **2007**; c) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions*: *A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; Royal Society of Chemistry, **2010**; d) Dalko, P. I. *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Wiley, **2013**.

[8] Sailkapen hau Langenbeck-ek argitaratu zuen 1949an: a) Langenbeck, W. *Die organischen Ktalysatoren und ihre Bziehungen zu den Fermenten (Organic Catalysts and Their Relations with Enzymes)*, 2nd., Springer, Berlin **1949**. Sailkapen berriago baterako, ikus: b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43* (39), 5138–5175. Organokatalizatzialearen azido/base erreaktibotasunean oinarritutako sailkapen baterako, ikus: c) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719–724.

adibide bat aminokatalisia[9] da, zeinetan katalizatzailearen amina primario edo sekundario bat aldehido edo zetona baten karboniloarekin kondentsatzen den. Kasu hauetan sortzen diren bitartekari edo espezie erreaktiboak enamina edo iminio ioia dira. Esparru honen garrantzia Kimikako Nobel Sariaren bidez aintzatetsi da aurten (2021), Benjamin List eta David MacMillan ikerlariei aitortua (1 Irudia).[10] Ia aldi berean, Hayashi[11] eta Jørgensenek[12] haiek diseinatutako diarilprolinol katalizatzaileak argitaratu zituzten, zeinek nabarmenki erraztu duten ikerketa esparru honen garapena.[13] Bestalde, elkarrekintza ez-kobalentearen adibide dira H-lotura[14] edo Brønsted base[15] bidezko katalisia, besteak beste.

List et al. MacMillan et al.

1 Irudia. Benjamin List (ezker) eta David W. C. MacMillan (eskuin), 2021eko Kimikako Nobel Sariaren irabazleak. Azpian, ikerlari bakoitzak garatu zuen organokatalizatzailea.[9a,b]

[9] Lehenengo lanetarako, ikus: a) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122* (10), 2395–2396; b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122* (17), 4243–4244; Aminokatalisiari buruzko berrikuspenetarako, ikus: c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107* (12), 5471–5569; d) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51* (39), 9748–9770; e) Albrecht, L.; Jiang, H.; Jorgensen, K. A. *Chem. Eur. J.* **2014**, *20* (2), 358–368; f) Lv, J.; Zhang, Q.; Cai, M.; Han, Y.; Luo, S. *Chem. Asian J.* **2018**, *13* (7), 740–753.

[10] https://www.nobelprize.org/prizes/chemistry/2021/press-release/

[11] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44* (27), 4212–4215.

[12] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44* (5), 794–797.

[13] Berrikuspenetarako, ikus: a) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45* (47), 7876–7880; b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3* (6), 922–948; c) Jiang, H.; Albrecht, Ł.; Dickmeiss, G.; Jensen, K. L.; Jørgensen, K. A. TMS-Prolinol Catalyst in Organocatalysis. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: Dalko, P. I.); John Wiley & Sons, Ltd, **2013**, 1, 33–50; d) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54* (47), 13860–13874.

[14] Gaiari buruzko berrikuspenetarako, ikus: a) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59* (3), 216–223; b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45* (10), 1520–1543; Aukeratutako adibide batzuetarako, ikus: c) Matador, E.; de Gracia Retamosa, M.; Monge, D.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J. M. *Chem. Eur. J.* **2018**, *24* (26), 6854–6860; d) Ray Choudhury, A.; Mukherjee, S. *Chem. Sci.* **2016**, *7* (12), 6940–6945; e) Zhang, H.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136* (47), 16485–16488.

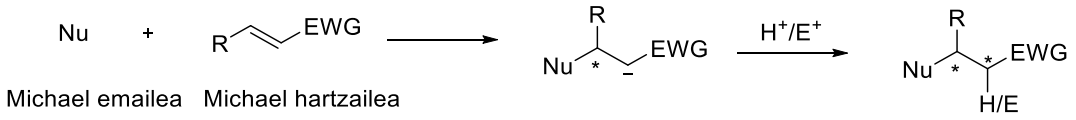
[15] Brønsted Base bidezko katalisiari buruzko berrikuspenetarako, ikus: a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103* (8), 2985–3012; b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38* (2), 632–653; c) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 201–232; d) Yamashita, Y.; Kobayashi, S. *Synlett* **2021**, *32* (1), 14–22.

Peptidoek organokatalisirako behar den hasierako kiralitate-iturri on bat eskaini izan dute, naturan estereoisomero bakar moduan eskuragarri baitaude. Peptidoak, definizioz, aminoazido kate laburrak dira, lotura peptidikoen bidez elkarren artean konektatzen direnak.[16] Ez dago adostasun handirik peptido batek izan ditzakeen aminoazido unitate maximoaren inguruan, eta noiz uzten dioten peptido izateari eta proteinatzat hartzen diren. Hala ere, normalean, peptidoek gehienez 100 aminoazido unitate arte izaten dituzte, nahiz eta 50-60 aminoazido baino gehiago dituzten peptidoak "mini-proteinatzat" hartzen diren batzuetan.[17] Aminoazido kate hauek espazioan tolesteko joera dute, bigarren mailako egiturak sortuz, hala nola, α-helizeak eta β-bira, zeinak hidrogeno-loturen bidez egonkortzen diren.

Naturan, entzimek eraldaketa ugari sustatzen dituzte, estereoselektibitate eta substratu hautakortasun apartarekin. Gaitasun hau are harrigarriagoa da, peptidoekin gertatzen zen bezala, entzimak aminoazido naturalen kopuru finitu batez osatuta daudela kontutan hartzen badugu. Entzimek duten hautakortasun gaitasun hori, dirudienez, sortzen duten egitura tridimentsionalari zor zaio, baina ez hori bakarrik. Izan ere, entzimen aminoazido batzuk espazioan estrategikoki kokatuta daude, prozesu katalitikoan substratuen funtzio talde jakin batzuekin elkarreragiteko.[18] Aurretik aipatu bezala, peptidoak ere aminoazidoz osatuta daudenez, entzimen pisu molekular txikiagoko baliokide bezala har daitezke, eta hortaz, erreakzio estereoselektiboak katalizatzeko gai dira ere, azken hamarkadetan ikertzaile askok frogatu dutenez.[19] Izan ere, peptidoek katalizatutako erreakzio estereoselektiboen hainbat adibide argitaratu dira, besteak beste, oxidazioak, erredukzioak, talde-transferentzia erreakzioak (fosforilazioak, sulfonilazioak eta azilazioak) eta C-C loturak sortzeko erreakzioak.[18,19]

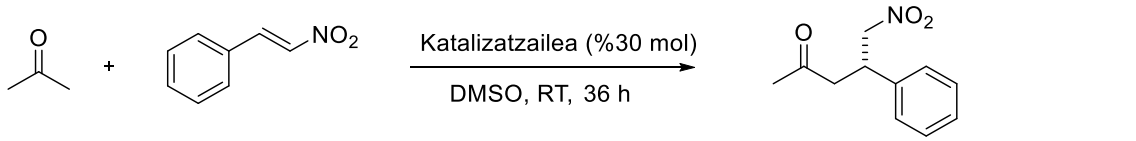
C-C loturak sortzeko erreakzioei dagokienez, Michael adizioa[7c,20] erabilgarri eta moldagarrienetarikoa da. Eraldaketa honetan, Michael emaile batek (nukleozalea) Michael hartzaile batekin (elektroizale α,β-asegabea) erreakzionatzen du 1,4-adizioa emanez. Ondoren, eratzen den bitartekari anionikoa protonatu egin daiteke edo tandem-erreakzio baten bidez bigarren elektroizale batekin erreakzionatu (1 Eskema). Prozesu honetan estereozentro bat edo gehiago sor daitezkeenez, horien konfigurazioa kontrolatzeko katalizatzaile kiralak erabil daitezke, besteak beste, lehendik aipatutako peptidoak.

[16] Peptide | Scitable by Nature Education https://www.nature.com/scitable/definition/peptide-317/ (accessed May 11, 2021).
[17] Hamley, I. W. *Introduction to Peptide Science*; Wiley, **2020**.
[18] Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107* (12), 5759–5812.
[19] Gaiari buruzko berrikuspen batzuetarako, ikus: a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; b) Wennemers, H. *Chem. Commun.* **2011**, *47* (44), 12036–12041; c) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. *Chem. Rev.* **2020**, *120* (20), 11479–11615.
[20] Deskribatu zen lehenengo Michael erreakziorako, ikus: Michael, A. *J. für Prakt. Chemie* **1887**, *35* (1), 349–356.



1 Eskema. Michael erreakzioaren eskema orokorra.

Hain zuzen, C-C lotura berri bat sortzen duten hainbat Michael adizio argitaratu dira, zeinetan peptido batek eragiten duen erreakzioa. Kasu gehienetan, peptidoekin katalizatutako erreakzioak eraginkorragoak dira, bai etekinari bai estereoselektibitateari dagokionez, prolina hutsa katalizatzaile moduan erabiltzen denean baino. Gainera, peptidoek karga katalitiko baxuagoen erabilera ahalbidetzen dute. Martin eta List-ek peptido batekin katalizatutako lehenengo Michael adizioa deskribatu zuten 2003an, azetonaren eta trans-β-nitroestirenoaren arteko erreakzioan datzana (2 Eskema).[21] Hainbat dipeptido probatu zituzten erreakzioa katalizatzeko, eta emaitzarik onena H-Pro-Val-OH-rekin lortu zuten. Dipeptido honekin lortutako enatioselektibitate oso ona izan ez bazen ere (%31 *ee*), prolina sinplearekin baino emaitza hobeak lortu ziren (%7 *ee*). Lan horren ondoren, peptidoek katalizatutako beste zetona, aldehido, indol eta nitroalkanoen Michael adizioak ere deskribatuak izan dira, jarraian azaltzen den bezala.



Kat: H-Pro-OH: %97ko etekina, %7 *ee*
Kat: H-Pro-Val-OH: %65eko etekina, %31 *ee*

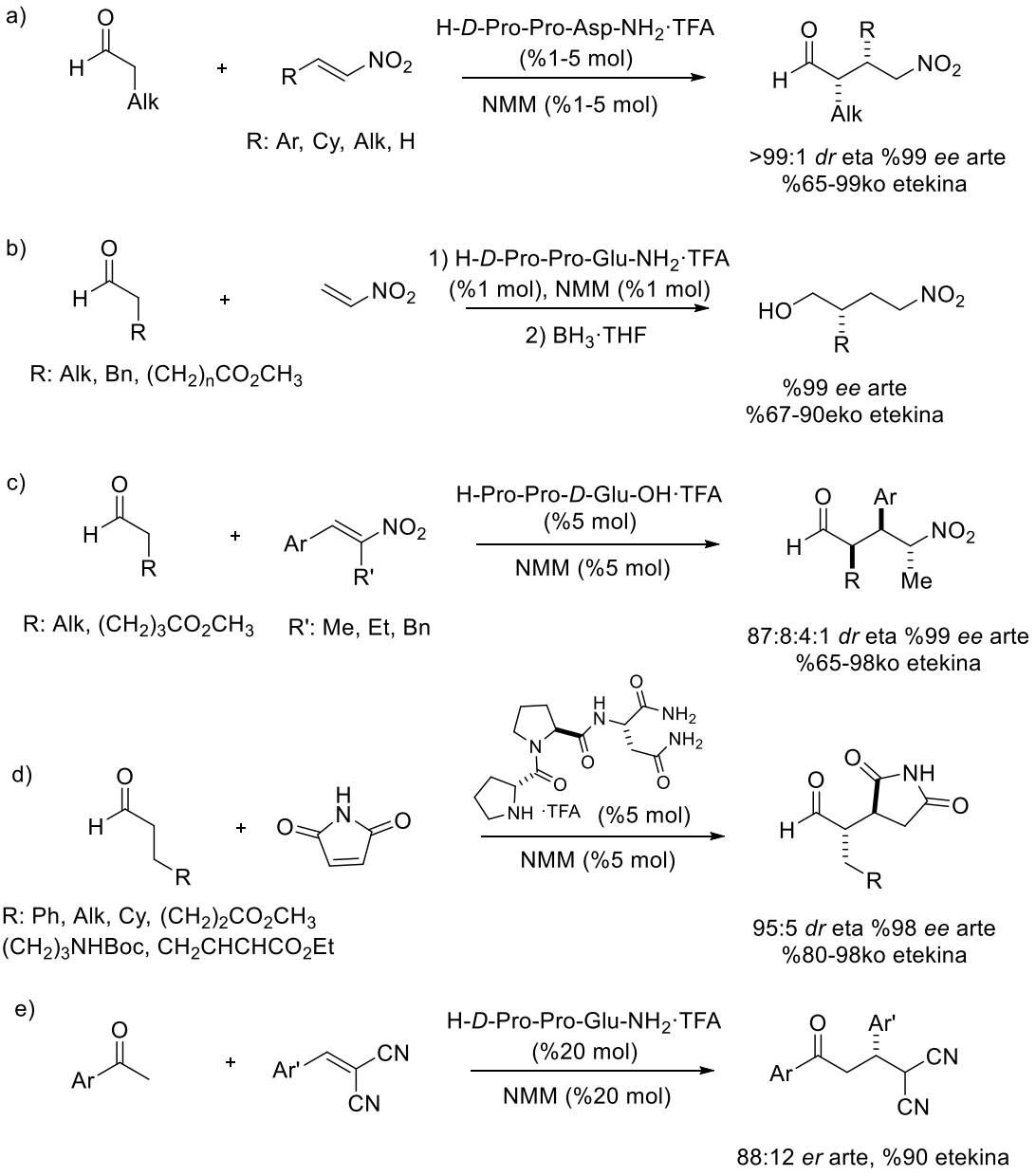
2 Eskema. Peptidoekin katalizatutako lehenengo Michael adizioa. ***List, 2003***.[21]

2006an, Córdovaren taldeak List-ek deskribatutako Michael adizioa beste nitroestireno eta zetona zikliko desberdinetara zabaldu zuen.[22] Alanina zuten dipeptidoak erabili zituzten katalizatzaile moduan, amina sekundario baten ordez amina primario bat zeramatenak, eta 36:1 *dr* eta %98 *ee* arteko estereoselektibatea izatea lortu zuten. Erreakzioa 1-hidroxipropan-2-ona eta isobutiraldehido pronukleozaleekin ere probatu zuten, baina enantioselektibatete balio txikiagoak hauteman ziren (%29 eta %58 *ee*, hurrenez hurren).

Hala ere, urte batzuk geroago, Wennemers-en taldeak lan handia egin zuen aldehido linealen nitroolefinetarako adizio konjokatuarekin. Estereoselektibitate balio bikainak lortu zituzten adizio konjokatu desberdinentzat prolina duten tripeptidoen presentzian: β-ordezkatutako nitroolefinetara (3a Eskema),[23] nitroetilenora (3b Eskema)[24]

[21] Martin, H. J.; List, B. *Synlett* **2003**, *12*, 1901–1902.
[22] Xu, Y.; Zou, W.; Sundén, H.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348* (4–5), 418–424.
[23] Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, *47* (10), 1871–1874.
[24] Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611.

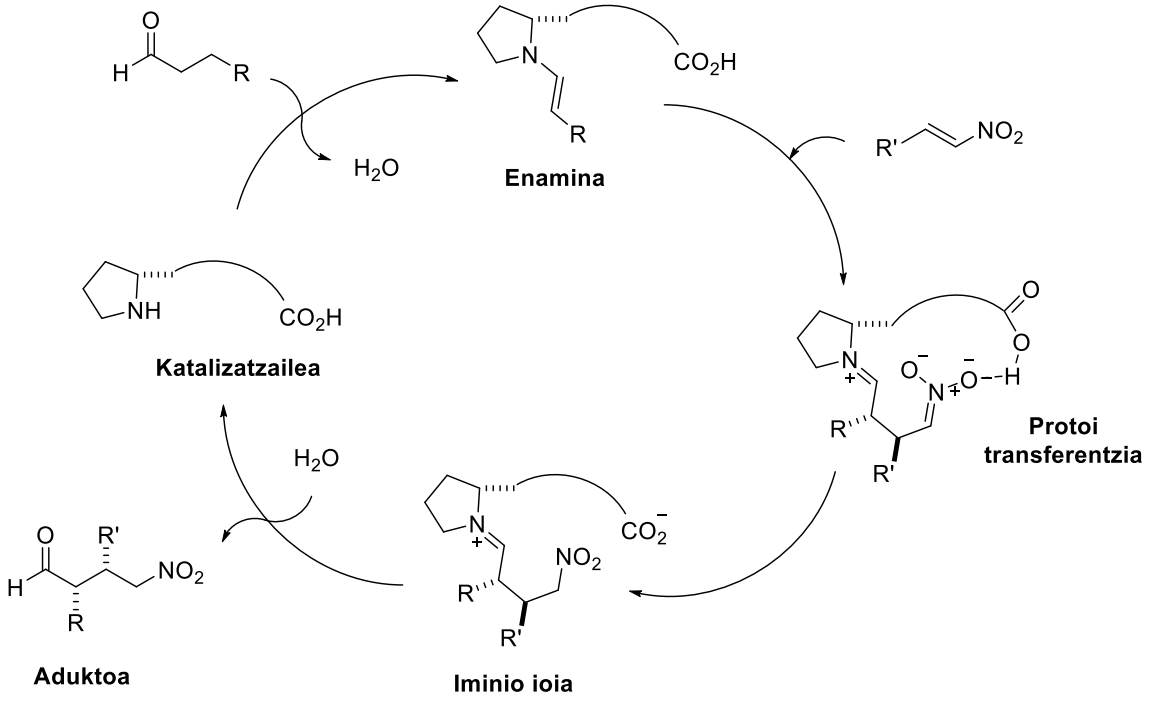
eta α,β- diordezkatutako nitroolefinetara (3c Eskema).[25] Azken bi kasuetan, amaierako aduktuak erreduzitzea beharrezkoa izan zen zutabe kromatografikoan errazemizazioa saihesteko. Gainera, katalizatzaile karga %1 eta %5 artera jaistea lortu zuten, normalean prolinaren %30 behar den erreakzioetarako.[26]



3 Eskema. Tripeptidoekin katalizatutako aldehido linealen Michael erreakzioa a) β-ordezkatutako nitroalkenoekin,[23] b) nitroetilenoarekin,[24] c) α,β-ordezkatutako nitroalkenoekin,[25] d) maleimidekin.[32] e) Azetofenonen Michael adizioa dizianoolefinetara.[33] ***Wennemers, 2008-2017.***

[25] Duschmalé, J.; Wennemers, H. *Chem. Eur. J.* **2012**, *18* (4), 1111–1120.
[26] Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7* (6), 1101–1103.

Erreakzioak katalizatzeko erabilitako tripeptidoek *N*-terminalean prolina bat damate aminokatalisirako, eta asparagina (Asp) edo glutamina (Glu) unitate bat *C*-terminalean, azido karboxiliko bat dutenak alboko katean, protoiak transferitzeko. Pfaltz-ekin lankidetzan, Wennemers-en taldeak erreakzioa enamina aktibazioaren bidez gertatzen zela baieztatu zuen, ez enol mekanismoaren bidez.[27] Erreakzioak eskeman adierazitako ziklo katalitikoa jarraitzen zuela proposatu zuten (4 Eskema), List eta Houk-ek prolinak katalizatutako erreakzioetarako deskribatu zutenaren antzekoa dena.[28] Ziklo katalitikoan, peptidoaren muturreko NH_2-ak pronukleozalea aktibatzen du enamina bidez, azido karboxilikoak protoi transferentzian laguntzen duen eta koordinazio puntu bat eskaintzen duen bitartean.



4 Eskema. Enamina bidezko ziklo katalitikoa, prolina daukan tripeptido batek eragindako aldehidoen eta nitroalkenoen arteko Michael erreakzioarentzat. ***Wennemers eta Pfaltz, 2013****.*[27]

Wennemers-en lanak aurrerapauso handia suposatu zuen karga katalitikoei dagokienez, aminokatalisiaren alorrean; izan ere, karga horiek askoz handiagoak ziren ordura arte erreakzio mota horietarako, %10-20 bitartekoak,[29] eta bere taldeak erreakzioak eraginkorrak izan zitezkeela frogatu zuen %1 mol bezain karga txikiekin. Halaber, euskarri solidotan ainguratutako katalizatzaile peptidikoak erabiltzeko prozedura

[27] Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, *52* (48), 12619–12623.

[28] a) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101* (16), 5839–5842; b) Clemente, F. R.; Houk, K. N. *Angew. Chemie - Int. Ed.* **2004**, *43* (43), 5766–5768.

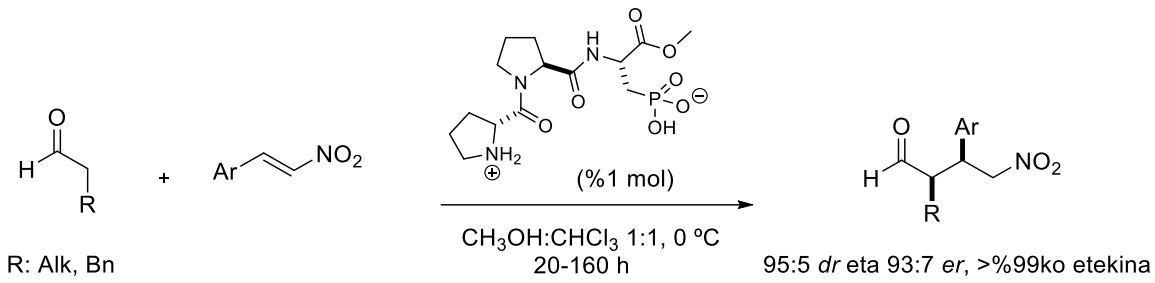
[29] Aukeratutako adibide batzuentzako, ikus: a) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3* (23), 3737–3740; b) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44* (9), 1369–1371; c) Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2006**, *45* (36), 5984–5987.

bat deskribatu zuen,[30] hala nola, erreakzioa fluxuan burutzeko protokolo bat,[31] bi kasuetan estereoselektibitate emaitzak mantenduz.

Wennemers eta bere lankideek aldehidoa eta maleimiden arteko Michael erreakzioa ere deskribatu zuten (3d Eskema),[32] antzeko katalizatzaile batek sustatuta. Baina kasu horretan, erreaktibotasunari dagokionez, eraginkorragoa izan zen peptidoaren aspartato unitateko bi azido karboxilikoak amida primario moduan izatea. Izan ere, erreakzio honetarako, talde funtzional horiek, protonazioa baino, H-lotura funtzioa betetzeak erreakzioa azkartzen duela proposatu zuten autoreek.

Era berean, talde berdinak dizianoolefinetarako azetofenonen adizio konjokatua aztertu zuten, H-D-Pro-Glu-NH_2·TFA, nitroetilenoari gehitzeko erabilitako tripeptido bera, katalizatzaile moduan erabiliz (3e Eskema).[33] Baina kasu honetan, katalizatzaile-karga handiagoa, %20 molekoa, behar izan zen estereoselektibitate onargarriak lortzeko (88:12 *er* arte).

Lecouvey-ren taldeak Wennemers-ek argitaratutako (3a Eskema) erreakziorako kontrako enantiomeroa prestatzea lortu zuen 2016an, Wennemers-en katalizatzailean aspartato unitatearen azido karboxilikoa azido fosforiko batengatik aldatuz (5 Eskema). Autoreen arabera, enantioespezifitate desberdintasun horren zergatia "azido karboxilikoaren eta azido fosforikoaren arteko diferentziak eragin lezake, geometria espazialari eta aktibazio moduari dagokienez". [34]

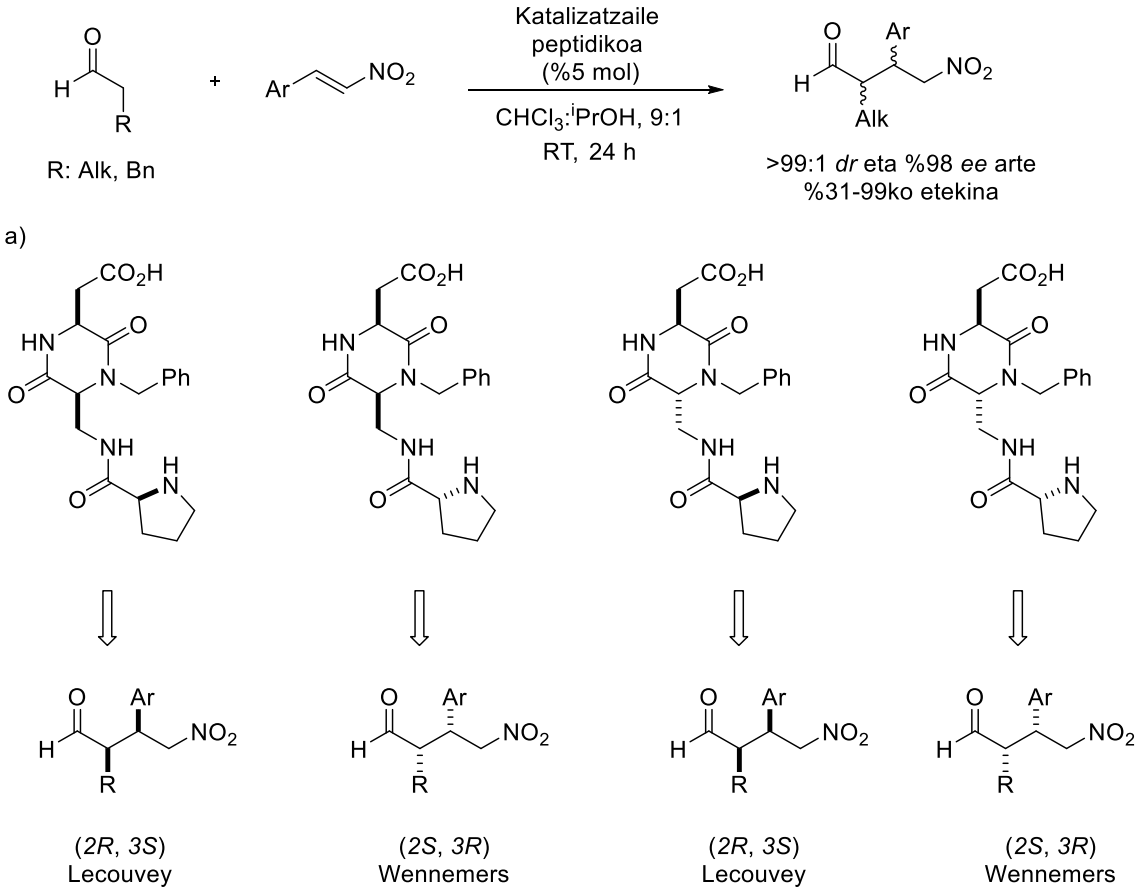


5 Eskema. Azido fosforiko bat daraman tripeptido batez eragindako aldehidoen eta nitroestirenoen arteko Michael erreazkioa. ***Lecouvey, 2016****.*[34]

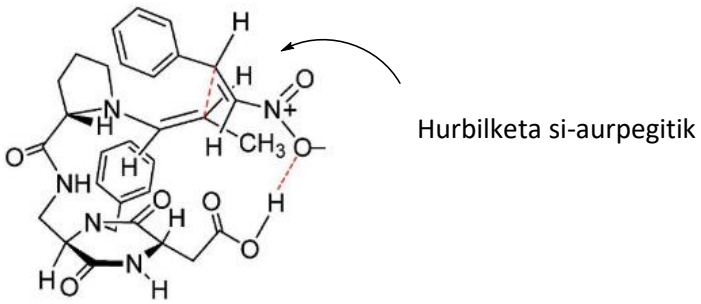
Piarulli-k eta Gennari-k[35] Wennemers eta Lecouvey-ek argitaratutako erreakzio berdineko aduktuaren bi enantiomeroak prestatzea lortu zuten estereoselektibitate bikainarekin, prolina daraman dizetopiperazinak katalizatzaile berdinarekin, kiralitate zentroen konfigurazioa aldatuz (6a Eskema). Dirudienez, katalizatzailearen prolinaren

[30] Arakawa, Y.; Wiesner, M.; Wennemers, H. *Adv. Synth. Catal.* **2011**, *353* (8), 1201–1206.
[31] Arakawa, Y.; Wennemers, H. *ChemSusChem* **2013**, *6* (2), 242–245.
[32] Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8571–8574.
[33] Schnitzer, T.; Wennemers, H. *Synlett* **2017**, *28* (11), 1282–1286.
[34] Cortes-Clerget, M.; Gager, O.; Monteil, M.; Pirat, J. L.; Migianu-Griffoni, E.; Deschamp, J.; Lecouvey, M. *Adv. Synth. Catal.* **2016**, *358* (1), 34–40.
[35] Durini, M.; Sahr, F. A.; Kuhn, M.; Civera, M.; Gennari, C.; Piarulli, U. *Eur. J. Org. Chem.* **2011**, *28*, 5599–5607.

konfigurazioak lortutako aduktuaren estereokimika zehazten du eta piperazinaren kiralitate zentroen konfigurazioaren aldaketek, berriz, ez dute eraginik estereoselektibitatean. Autoreek proposatutako trantsizio-egoeraren arabera (6b Eskema), katalizatzaileak enaminaren bidez sustatuko luke erreakzioa, prolina-unitateak dituzten katalizatzaileekin gertatu ohi den bezala, eta piperazinari lotutako azido karboxiliko librea nitroestirenoarekin koordinatuko litzateke, erreakzioa si-aurpegitik gerta dadin lagunduz.

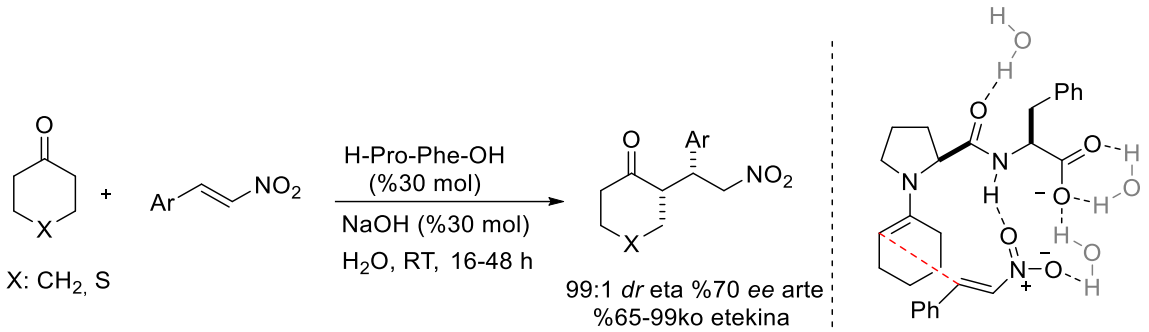


b) Proposatutako trantsizio egoera, (*2R,3S*)-aduktura daramana



6 Eskema. Dizetopiperazinak katalizatutako Michael adizioa. a) Erreakzioan probatutako katalizatzaileak kiralitate zentroetan egindako aldaketekin eta kasu bakoitzean lortutako aduktua. b) Proposatutako trantsizio-egoera (2R,3S)-aduktura daramana. ***Piarulli eta Gennari, 2011***.[35]

Peptidoek katalizatutako zetonen Michael adizioak ere ikertu dira, nahiz eta kasu hauetan karga katalitiko askoz handiagoak behar diren. Horren lehen adibidea Tsogoevak argitaratu zuen 2009an, zeinetan H-Pro-Phe-OH bezalako dipeptidoak erabiliz, zetona ziklikoen nitroestirenoetarako adizio konjokatua katalizatu zuen, ura disolbatzaile moduan erabiliz (7 Eskema).[36] NaOH kantitate katalitikoan erabili zen dipeptidoaren azido karboxilikoa desprotonatzeko eta uretan disolbatu ahal izateko. Autoreek proposatutako trantsizio egoeraren (TS, transition state) arabera (7 Eskema), dipeptidoaren amina primarioa zetonarekin kondentsatuko litzateke enamina sortzeko, fenilalaninaren NH-a elektroizalearen nitro taldearekin koordinatzen den bitartean. Ur molekula batzuek ere TS-an parte hartuko lukete H-lotura sare konplexu bat sortuz. Erreakzio aduktuak 99:1 *dr* eta %70 *ee* arteko estereoselektibitatearekin lortu ziren. Honen ondoren, 2017an, Wennemers-ek aurretik azaldutako azetofenonen eta dizianoolefinen arteko erreakzioa argitaratu zuen (3e Eskema).



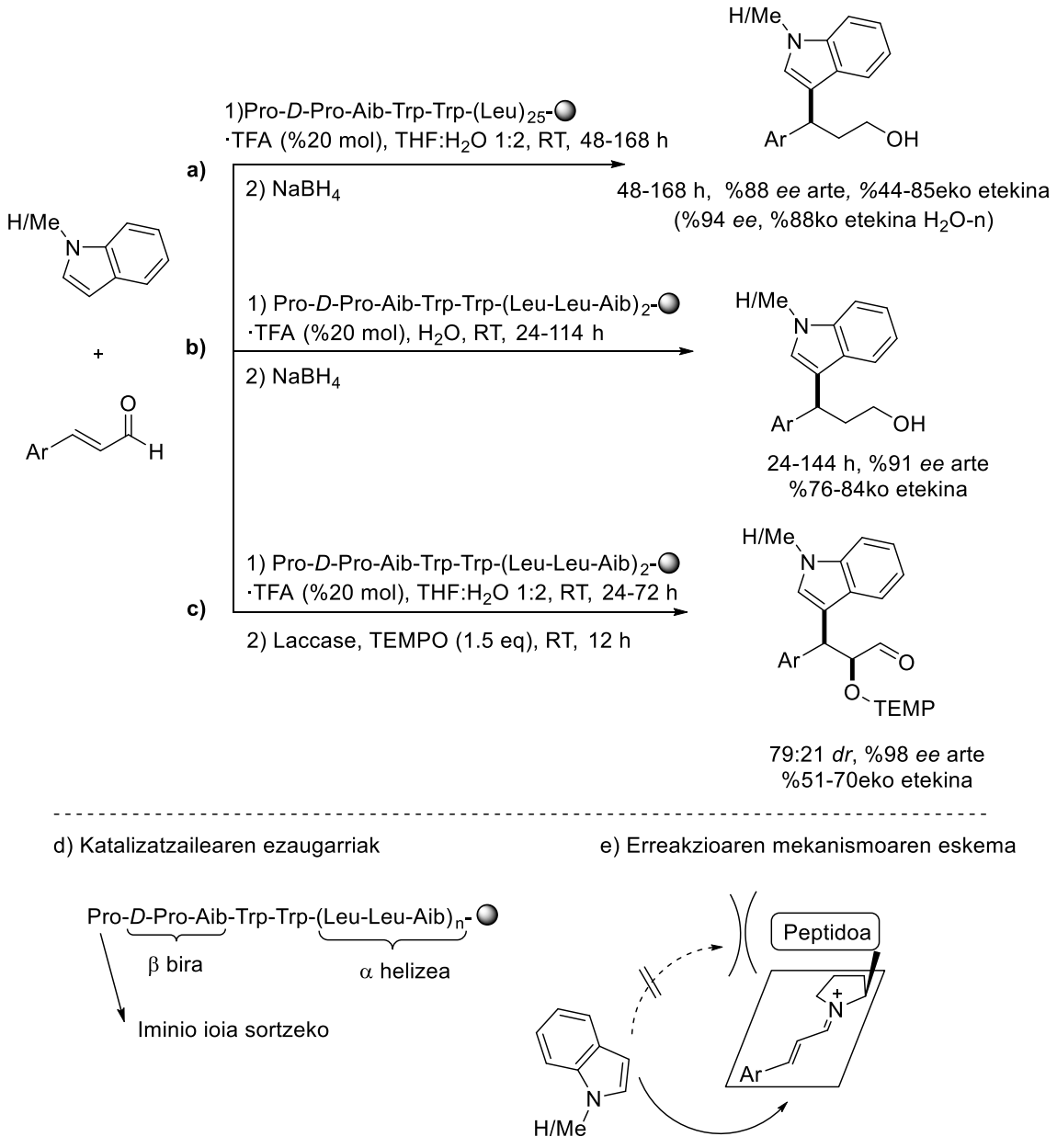
7 Eskema. Dipeptidoek katalizatutako zetona ziklikoen Michael adizioa ingurune akuosoetan. ***Tsogoeva, 2009****.*[36]

Aldehido eta zetonen adizio konjokatuetaz aparte, beste Michael emaile desberdinen adizioak ere ikertuak izan dira peptidoetatik eratorritako katalizatzaileek eragindakoak, hala nola, indol eta nitroalkanoenak. Nukleozale hauen enal eta enonetarako adizioak deskribatu dira zeinetan prolinatik eratorritako peptidoek iminio bidez aktibatzen dituzte substratoak. Kasu hauetan ere, peptido katalizatzailearen karga handiak behar dira, %20 mol normalean, eta hala ere emaitzak ez dira behar bezain onak.

Kudo-ren taldeak sakonki ikertu ditu iminio ioi aktibazio bidez ematen diren peptidoek katalizatutako Michael adizioak. Lehenik, indolen Friedel-Crafts alkilazioa aztertu zuten enalak erabiliz (8a Eskema)[37] THF/H_2O disolbatzaile nahaste batean eta solidotan ainguratutako prolina daramaten oligopeptidoak katalizatzaile moduan erabiliz. Leuzina unitatez osatutako kate hidrofobiko bat daramaten oligopeptido hauekin erreakzioa katalizatu eta gero aduktuak $NaBH_4$-rekin erreduzitu egin ziren, amaierako alkoholak %88 arteko *ee*-tan lortuz. Hala ere, erreakzioa THF-rik gabe jartzerakoan enantioselektibitatea %94 *ee*-ra arte igotzen zela aurkitu zuten. Gainera, ura disolbatzaile

[36] Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2009**, *7*, 4279–4284.
[37] Akagawa, K.; Yamashita, T.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2009**, *50* (40), 5602–5604.

bakartzat mantenduz eta leuzina eta Aib-z osatutako kate motzagoa zuen katalizatzaile bat erabiliz erreakzio-denborak murriztea lortu zen enantioselektibitate balioak mantenduz (8b Eskema).[38,39] Hortaz gain, talde berdinak alkilazio-oxidazio sekuentzia bat burutu zuen ontzi bakarrean, katalizatzaileak urarekiko duen tolerantziari esker, *laccase* entzima oxidatzaile moduan erabiliz. Aduktuak enantioselektibitate balio bikainekin lortu ziren, baina hala-holako diastereoselektibitatearekin (8c Eskema).[40]



8 Eskema. Indolen Friedel-Crafts alkilazioa. ***Kudo, 2012.*** [37,38,40]

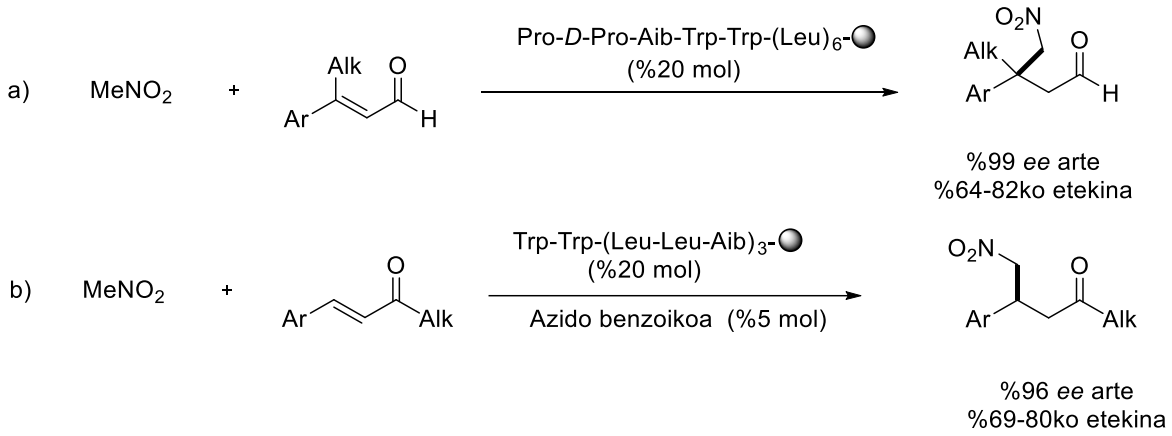
[38] Akagawa, K.; Suzuki, R.; Kudo, K. *Adv. Synth. Catal.* **2012**, *354* (7), 1280–1286.

[39] Prolina daramaten erretxina batean ainguratutako peptidoek katalizatutako azido boronikoen eta γ–hidroxi enalen arteko erreakziorako, ikus: Akagawa, K.; Sugiyama, M.; Kudo, K. *Org. Biomol. Chem.* **2012**, *10* (25), 4839–4843.

[40] Akagawa, K.; Umezawa, R.; Kudo, K. *Beilstein J. Org. Chem.* **2012**, *8* (1), 1333–1337.

Esan bezala, katalizatzaile oligopeptidiko hauek elektroizalea, kasu honetan enala iminio ioi bidez aktibatzen dute. Iminio hori sortzeko katalizatzaileak *N*-terminaleko prolina erabiltzen du, gainerako kate peptidikoa egitura sekundarioak sortuz tolesten den heinean (β-bira bat eta α-helize bat, 8d Eskema). Egitura sekundario hauek elektroizalearen aurpegi bat estaltzen dute, nukleozalea beste aurpegitik gerturatu dadin erraztuz (8e Eskema). [37]

Nitrometanoaren eta aldehido eta zetona α,β-asegabeen arteko erreakzioa ere ikertu zuen Kudoren taldeak solidotan ainguratutako katalizatzaile oligopeptidikoak erabiliz (9 Eskema). Enaletarako adizioari dagokionez (9a Eskema),[41] indolen alkilazioarentzako (8a Eskema) deskribatu zuten oligopeptidoaren oso antzeko bat erabili zuten, baina sei leuzina unitaterekin bakarrik. Bestalde, enonen adiziorako (9b Eskema),[42] muturreko aminoazido bezala triptofanoa duen katalizatzaile bat erabili zuten, zeinak amina sekundario baten ordez amina primario bat daukan. Bi kasuetan, erreakzioa imino ioi aktibazio bidez ematen da, oligopeptidoaren amina askeak katalizatuta, aduktuak estereoselektibitate bikainarekin lortuz.

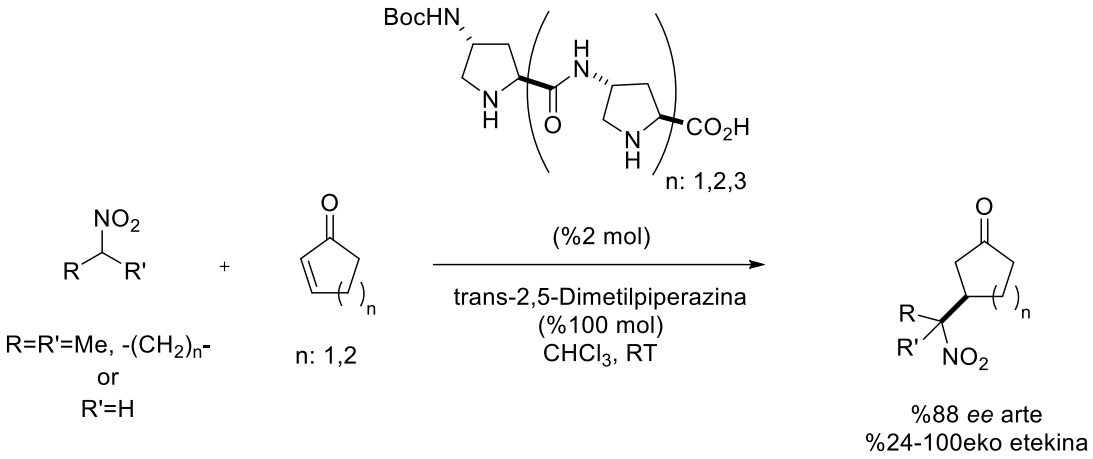


9 Eskema. Nitrometanoaren eta konposatu karboxiliko α,β-asegabeen arteko erreakzioa. ***Kudo, 2012-2014.***[41,42]

Aurretik azaldutako Kudok argitaratutako prozeduretan, karga katalitiko nabarmenki handiak erabili behar izan ziren (%20 mol). Testuinguru honetan, Tsogoevaren taldeak katalizatzaile peptidikoaren %2 molekin bakarrik eragindako nitroalkano eta enona ziklikoen arteko Michael erreakzioa deskribatu zuen (10 Eskema). Nitroalkano konplexuago hauen adizioa aktibazio bikoitzaren bidez katalizatu zen, alde batetik trans-2,5-dimetilpiperazina, eta bestetik Boc-ekin babestutako prolinan-oinarritutako di-,[43] tri-[44] eta tetrapeptidoak[43] erabiliz. Iminio ioi bidezko aktibazio honekin amaierako aduktuak

[41] Akagawa, K.; Kudo, K. *Angew. Chem. Int. Ed.* **2012**, *51* (51), 12786–12789.
[42] Akagawa, K.; Suzuki, R.; Kudo, K. *Asian J. Org. Chem.* **2014**, *3* (4), 514–522.
[43] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron Asymmetry* **2006**, *17* (6), 989–992.
[44] Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, *19*, 4014–4019.

%88 arteko enantiomero soberarekin prestatu ziren (10 Eskema).[45] Trans-3,5-dimetilpiperazinaren presentzia ezinbestekoa dirudi estereoselektibitatea hobetzeko. Aipatzekoa da kasu guztietan nukleozale bezala erabilitako nitroalkanoak linealak edo simetrikoki ordezkatuak zirela, beraz estereozentro bakarra sortzen zen erreakzioan.



10 Eskema. Boc-babestutako prolinan-oinarritutako di-, tri- eta tetrapeptidoek katalizatutako nitroalkanoen eta enona ziklikoen arteko Michael erreakzioa. ***Tsogoeva, 2004-2006.***[43,44]

Aurretik azaldutako kasu guztietan, katalizatzaile peptidikoek enamina edo iminio bidez aktibatzen zituzten erreakzio substratuak, eta hau izan da orokorrean katalizatzaile peptidikoek operatzeko izan duten modua.[46] Gainera, kasu gehienetan, H-lotura bidezko interakzioak ere proposatuak izan dira trantsizio egoeretan. Hala ere, Michael adizioak katalizatzeko beste aukera bat BB bidez operatzen duten katalizatzaile peptidikoak erabiltzea izan liteke. Aminoazido natural batzuek, albo katean dituzten talde funtzionalen ondorioz, berezko izaera basikoa dute (hala nola, histidina), eta aminoazido hauetatik eratorritako katalizatzaileak erabil litezke erreakzioak BB bidez eragiteko. Gainera, BB estrategia erabiltzearen abantaila nagusi bat nukleozale eta elektroizale mota gehiago erabili ahal izatea izango litzateke, BB katalisia ez baitago aldehido eta zetonetara mugatuta, aminokatalisian gertatzen den moduan.

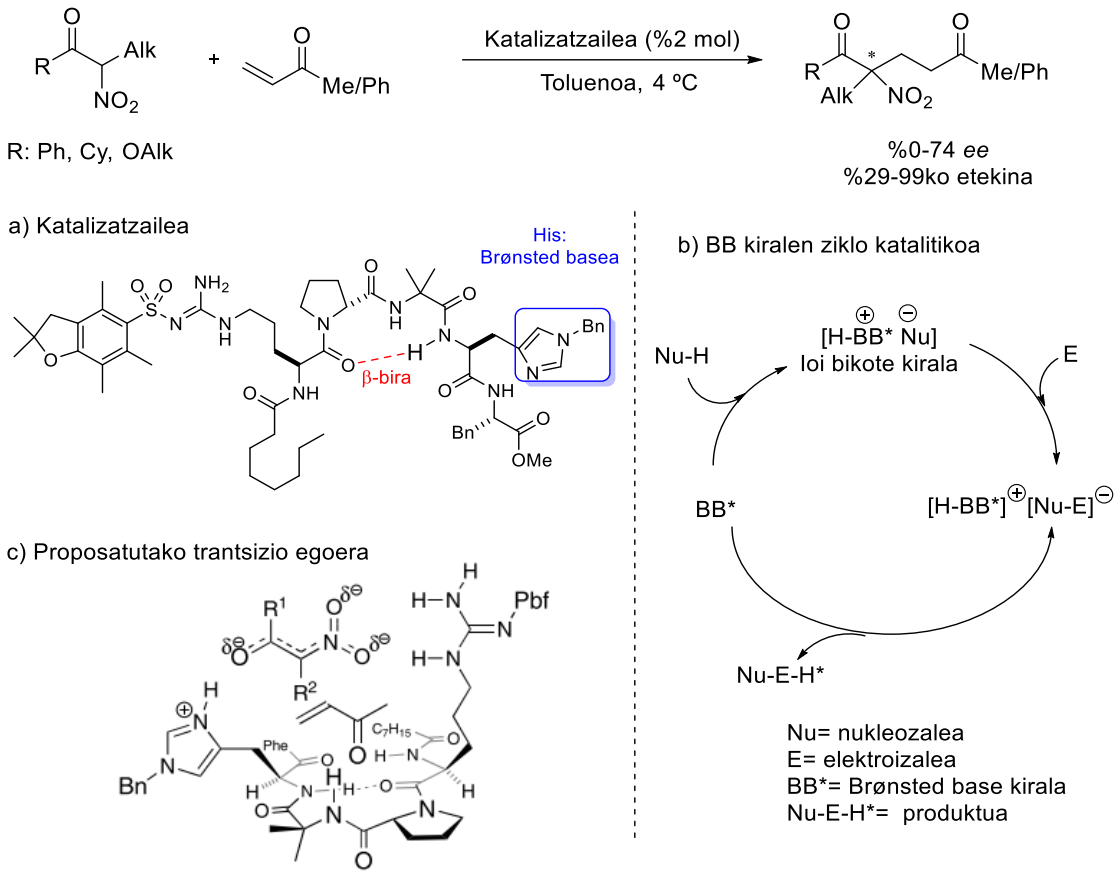
Miller eta Linton-ek BB bezala jokatzen zuen aminoazido bat zeraman katalizatzaile peptidiko bat erabili zuten lehenengo aldiz Michael erreakzio bat eragiteko (11 Eskema).[47] Artikulu horretan, α-nitrozetonen eta enonen arteko adizio konjokatu asimetrikoa ikertu zuten 11 Eskeman irudikatzen den *N*-benzil histidina basiko bat zeraman peptidoarekin, erreakzio aduktuak oso etekin onetan eta %0-74 tarteko enantioselektibitate soberarekin

[45] Artikulu batentzako non prolinarik ez duen peptido bat lehenengo aldiz erabiltzen den erreakzio bat katalizatzeko, ikus: Tsogoeva, S. B.; Jagtap, S. B. *Synlett* **2004**, *14*, 2624–2626.

[46] Kasu espezifiko batentzako, zeinetan peptidoak katalisi nukleofiliko bidez eragiten duen erreakzioa, ikus: Akagawa, K.; Sakai, N.; Kudo, K. *Angew. Chem. Int. Ed.* **2015**, *54* (6), 1822–1826.

[47] Linton, B. R.; Reutershan, M. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J. *Tetrahedron Lett.* **2007**, *48* (11), 1993–1997.

lortuz. Autoreek diotenez, oktanoil katea katalizatzailea disolbatzaile organikoetan errazago disolbatzeko gehitu zen.



11 Eskema. BB bat duen peptido batek katalizatutako α-nitrozetonen enonetarako adizio konjokatua. a) Erreakziorako erabilitako katalizatzailea. b) BB kiralen ziklo katalitikoa. C) Proposatutako trantsizio egoera. ***Linton eta Miller, 2007***.[47]

Erreakzio honetan katalizatzaileko histidinaren albo katean dagoen imidazolak BB moduan jokatzen duenez, erreakzio honek Brønsted baseen ohiko ziklo katalitikoa jarraitzen du (11b Eskema). Hasteko, imidazol honek (eskeman BB izendatua) pronukleozalea desprotonatzen du ioi bikotea osatuz, zeinak elektroizalearekin erreakzionatzen duen C-C lotura berria sortuz. Azkenik, protonatutako base katalitikoak protoia transferitu egiten dio bitartekari anionikoari alde batetik produktua sortuz, eta bestetik katalizatzailea berreskuratuz, zeinak ziklo katalitiko berri bat has dezakeen. Kasu honetan, katalizatzailea kirala denez, zikloan osatzen den ioi bikotea ere kirala izango da eta peptidoaren kate kiralaren laguntzarekin, enantiomero bat proportzio handiagoan sintetiza daiteke. Linton eta Miller-en adibidean, autoreen arabera, peptidoaren kate kiralak enantioselektibitatean lagundu egiten du β-bira bat sortzen duelako prolinaren karboniloaren eta histidinaren NH-aren artean. β-bira honek barrunbe kiral bat osatzen du non substratuak kokatzen diren eta haien arteko interakzioa modu jakin batean ematea errazten da (11c Eskema).

Histidinak daraman imidazolaz gain, nitrogenoan oinarritutako beste talde funtzional basiko batzuk ere erabiliak izan dira BB katalizatzaile kiralak prestatzeko, hala nola, guanidinak, amidinak eta amina tertziarioak. Hauek denek, guar egun, BB katalisia bezala ezagutzen den ikerkuntza alorra osatzen dute. Aipatutako talde funtzional basikoen artean, amina tertziarioak dira base ahulenak, baina katalisi asimetrikoan gehien erabiltzen direnak. Izan ere, haien basikotasun erlatiboki baxuari esker substratu espezifikotasuna lortzea eta albo erreakzioak ekiditea errazagoa da.

Aurreko adibidean ikusi den bezala, katalizatzaile peptidikoen ezaugarri nagusietako bat substratuekin H-loturak sortzeko gaitasuna da. Kimikari organikoek ezaugarri hau imitatu dute katalizatzaile sintetikoetan H-lotura emaile bezala jokatzen duten atalak gehituz. H-lotura emaile hauek eta BB-ak konbinatzen dituzten katalizatzaileak asko erabili dira modu eraginkor batean erreakzio estereoselektibo ugari eragiteko eta ikerketa alor honi BB katalisi asimetriko bifuntzionala deritzo.[48] BB katalisi bifuntzionala bereziki erabilgarria da BB-en ziklo katalitikoan (11b Eskema) sortzen den ioi bikotearen arteko interakzioa ez kobalentea delako, eta beraz, norabide bakarrekoa eta ez oso zurruna. Interakzioaren izaera honen ondorioz, konplexu erreaktiboek askatasun maila altua eduki dezakete erreakzioaren estereokontrola zailduz. Baina katalizatzaileak H-lotura emaile bat ala gehiago badaramatza bi substratuentzako koordinazio puntu gehiago daude eskuragarri, beraz, substratu hauek hurbiltzea errazagoa da erreakzioa eman dadin eta gainera, konplexu erreaktiboen askatasun maila murriztu egiten da estereoisomero posibleen artean baten sintesia bermatuz.

Azken hamarkadetan, H-lotura emaile moduan joka dezaketen talde funtzional desberdinak erantsi dira BB organokatalizatzaile bifuntzionalen egituretan, esaterako, tioureak, ureak, eskuaramidak eta ureidoaminalak (2a Irudia).[49] Takemoto-k lehenengo tiourea katalizatzaile bifuntzionala deskribatu zuen 2003an (2a Irudia, 1),[50] eta horren ondoren, Connon-ek eta Rawal-ek lehenengo urea[51] eta eskuaramidak[52] argitaratu zituzten hurrenez hurren (2a Irudia, 2 eta 3), bietan BB moduan kininatik eratorritako

[48] Bifuntzionalitatearen kontzeptua katalisi metalikoaren esparruan aplikatu zen lehenengoz eta jarraian organokatalisi alorrera zabaldu zen. Katalizatzaile metaliko bifuntzionalen berrikuspenentzako, ikus: a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4* (3), 393–406; b) Ramasamy, B.; Ghosh, P. *Eur. J. Inorg. Chem.* **2016**, *10*, 1448–1465.

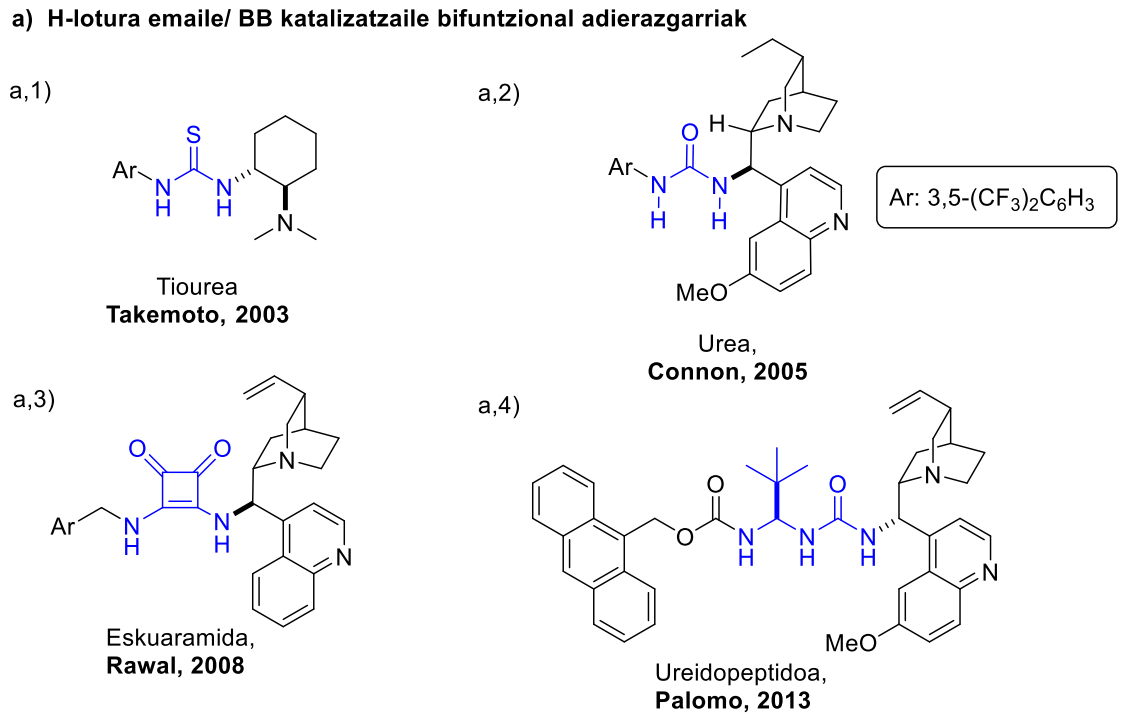
[49] (Tio)urea-BB berrikuspenetarako, ikus: a) Connon, S. J. *Chem. Commun.* **2008**, *22*, 2499–2510; b) Fang, X.; Wang, C. J. *Chem. Commun.* **2015**, *51* (7), 1185–1197; c) Visco, M. D.; Attard, J.; Guan, Y.; Mattson, A. E. *Tetrahedron Lett.* **2017**, *58* (27), 2623–2628; d) Yokoya, M.; Kimura, S.; Yamanaka, M. *Chem. Eur. J.* **2021**, *27* (18), 5601–5614; f) Maria, A.; Phillips, F.; Prechtl, M. H. G.; Pombeiro, A. J. L. *Catal.* **2021**, *11* (5), 569; Eskuaramida-BB berrikuspenetarako, ikus: g) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17* (25), 6890–6899; h) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281; i) Zhao, B. L.; Li, J. H.; Du, D. M. *Chem. Rec.* **2017**, *17* (10), 994–1018; j) Marchetti, L. A.; Kumawat, L. K.; Mao, N.; Stephens, J. C.; Elmes, R. B. P. *Chem* **2019**, *5* (6), 1398–1485: k) Erref. 49f. Ureidoaminal-BB berrikuspenerako, ikus: l) López, R.; Palomo, C. *Chem. Eur. J.* **2021**, *27* (1), 20–29.

[50] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125* (42), 12672–12673.

[51] McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44* (39), 6367–6370.

[52] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130* (44), 14416–14417.

alkaloide bat erabiliz. Azkenik, gure ikerketa taldeak lehenengo BB katalizatzaile ureidopeptidikoak diseinatu zituen 2013an (2a Irudia, 4).[53]

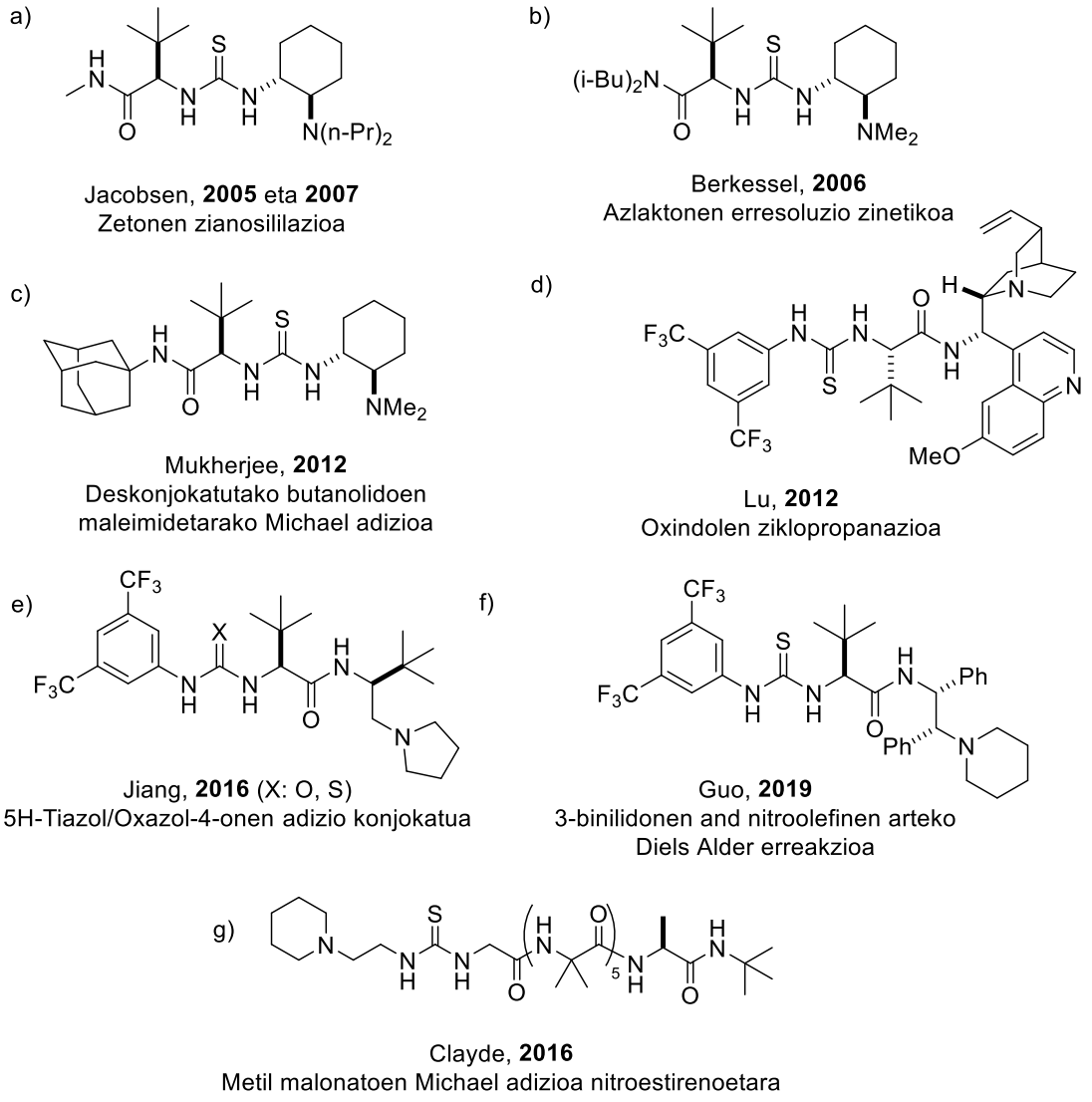


2 Irudia. a) H-lotura emaile/ BB katalizatzaile bifuntzional adierazgarriak. b) Ohiko koordinazio ereduak BB organokatalizatzaile bifuntzionalentzat.

Katalizatzaile hauen aritzeko modua antzekoa da: amina tertziarioak pronukleozalea desprotonatzen du, protonatutako nitrogeno bat sortuz, zeinak H-lotura emaile moduan joka dezakeen. Beraz, katalizatzaileek hainbat H-lotura emaile dituzte eskuragarri, trantsizio egoeran bi substratuak koordinatzeko aukera ugari eskainiz (2b Irudia). Testuinguru honetan, koordinatzeko hiru patroi desberdin proposatu dira. Takemoto-ren koordinazio ereduan (2b Irudia, 1),[54] elektroizalea H-lotura emailearekin koordinatuko litzateke, nukleozale anionikoa protonatutako amina tertziarioarekin elkarreragiten duen heinean. Bestalde, Pápai-k proposatutako modeloan (2b Irudia, 2),[55]

[53] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52* (45), 11846–11851.
[54] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127* (1), 119–125.
[55] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128* (40), 13151–13160.

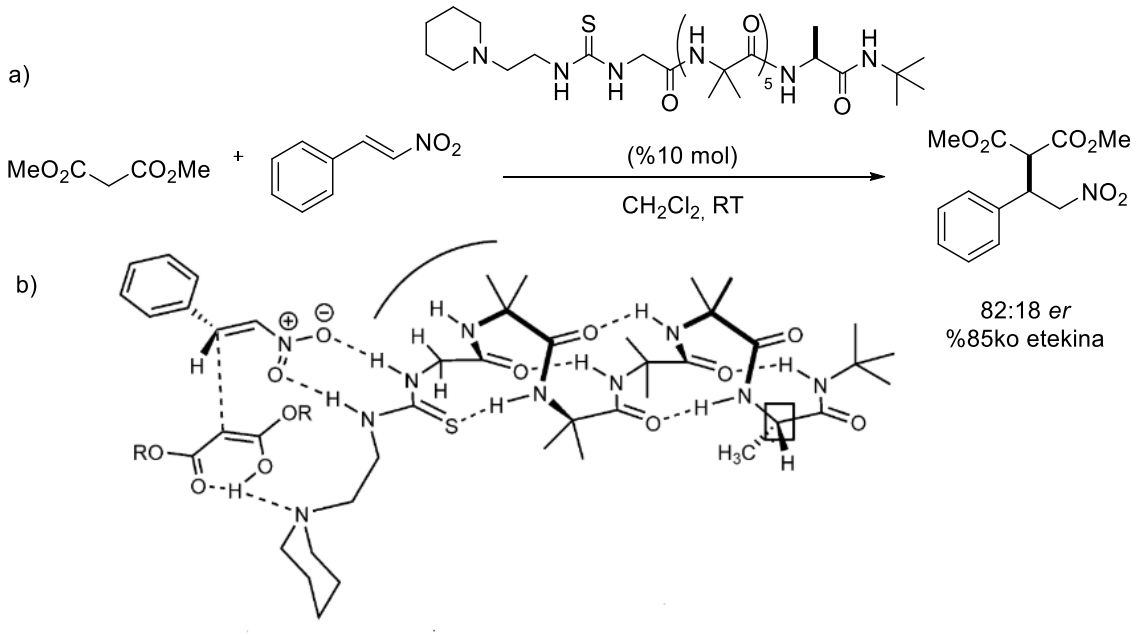
nukleozalea H-lotura emailearen bi NH-ekin koordinatuko litzateke eta elektroizaleak H-lotura bat sortuko luke base protonatuarekin. Azkenik, Wang-en ereduan (2b Irudia, 3),[56] nukleozalea bi interakzioren bidez egonkortuko litzateke, amina tertziario protonatuarekin eta H-lotura emailearen NH-etako batekin koordinatuz, elektroizalea libre gelditu den beste NH-arekin koordinatzen den bitartean. Kasu gehienetan, ez da erraza izaten erreakzio jakin batek jarraituko duen koordinazio patroia aurresatea eta substratu/katalizatzaile konbinaketa bakoitzerako mekanismoa ikertzea beharrezkoa izaten da.



3 Irudia. (Tio)urea-BB eta aminoazidoak konbinatzen dituzten deskribatutako katalizatzaileak.[59]

[56] Zhu, J. L.; Zhang, Y.; Liu, C.; Zheng, A. M.; Wang, W. *J. Org. Chem.* **2012**, *77* (21), 9813–9825.

2005ean, Jacobsen-en taldeak, aminoazidoak eta H-lotura emaile diren (tio)ureak dituzten katalizatzaileak sakonki ikertu ondoren,[57] BB bat zeraman mota honetako lehenengo katalizatzailea prestatu zuten (3a Irudia).[58] Katalizatzaile berri hau zetonen zianosililazio erreakzioa modu eraginkorrean eragiteko erabili zuten. Lan aintzindari honen ondoren, beste hainbat katalizatzaile argitaratu dira aminoazido, egituran H-lotura emaileak eta BB-ak daramatzatenak (3b-g Irudia).[59] Orokorrean, katalizatzaile hauek erabiliak izan diren erreakzioetan hobekuntza nagusia lortu da, antzeko egiturako baina aminoazido gabeko katalizatzaileekin alderatuta.



12 Eskema. a) Tiourea eta BB bat daraman katalizatzaile peptidiko batek eragindako metil malonatoen eta nitroestirenoen arteko erreakzioa. b) Erreakzioarentzat proposatutako trantsizio egoera. ***Clayden, 2016.***[60]

Clayden-en taldeak ere BB katalizatzaile bifuntzional interesgarri bat argitaratu zuen, kate peptidiko bat eta tiourea unitate bat daramana (3g Irudia, 12 Eskema). Katalizatzaile berri honek aminoazido kiral bakarra dauka, alanina bat, AIB unitateez osatutako kate akiral bati atxikituta, jarraian, tiourea-BB atal bat duena. Beraz, metil malonatoaren eta nitroestirenoaren arteko adizio konjokaturako, aduktua 82:18 *er* eta

[57] Aminoazido eta (tio)urea bat daramaten katalizatzaileen erabilerari buruz aukeratutako adibide batzuentzako, ikusi: a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed* **2000**, *39* (7) 1279–1281; b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124* (44), 12964–12965; c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; d) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133* (42), 16802–16805; e) Erref 14c-e.

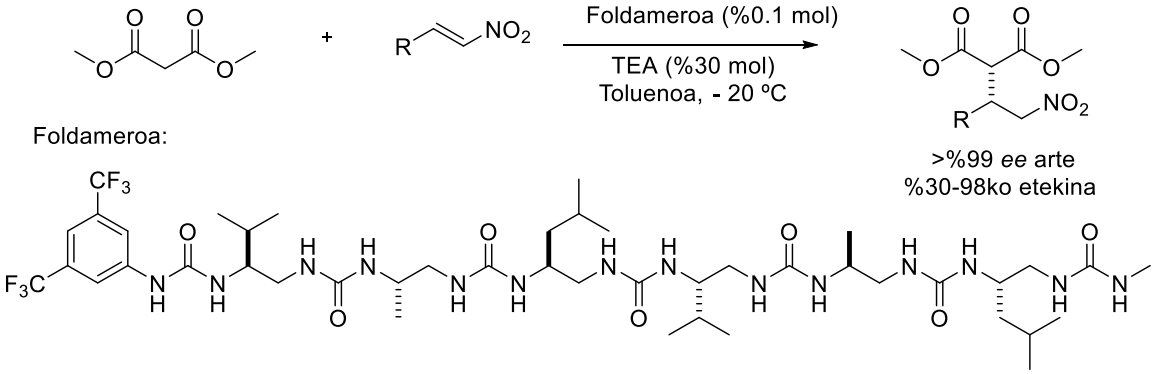
[58] a) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127* (25), 8964–8965; b) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129* (51), 15872–15883.

[59] a) Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J. M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4* (23), 4319–4330; b) Manna, M. S.; Mukherjee, S. *Chem. Eur. J.* **2012**, *18* (48), 15277–15282; c) Dou, X.; Lu, Y. *Chem. Eur. J.* **2012**, *18* (27), 8315–8319; d) Zhu, B.; Qiu, S.; Li, J.; Coote, M. L.; Lee, R.; Jiang, Z. *Chem. Sci.* **2016**, *7* (9), 6060–6067; e) Li, J.; Qiu, S.; Ye, X.; Zhu, B.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2016**, *81* (23), 11916–11923.

[60] LeBailly, B. A. F.; Byrne, L.; Clayden, J. *Angew. Chem. Int. Ed.* **2016**, *55* (6), 2132–2136.

%65eko etekinarekin lortu zen. Nahiz eta kiralitate iturri den alanina hori erreakzio katalitikoa ematen ari den lekutik nahiko urruti egon, peptidoa tolesturik dagoen egiturarengatik, estereoselektititatea induzitzea lortu zen.

BB eta peptidoen bidezko aktibazioaren konbinatzeko beste modu interesgarri bat estrategia sinergikoa izan daiteke, non peptido bat eta BB akiral bat bi molekula desberdinetan dauden. Estrategia honen adibide nabarmen bat gure taldeak eta Guichard-en taldeak elkarlanean argitaratutako oligourea foldameroen erabilera izan daiteke. Kasu honetan, peptidoetatik eratorritako molekula hauek TEA-rekin batera erabili ziren malonatoen eta nitroolefinen arteko erreakzio konjokatua katalizatzeko, eta % 0.1 mol peptido soilik erabiliz, estereoselektibitate bikaineko aduktuak prestatu ziren (13 Eskema).[61] Katalisi sinergiko honen abantaila nagusietako bat peptidoa eta erabiltzen den basea erraz molda daitezkeela da. Hala ere, ikuspuntu entropiko batetik, bi funtzio talde katalitikoak molekula berdinean izatea onuragarriagoa izan daiteke.



13 Eskema. Katalisi sinergikoa TEA eta foldameroekin malonato eta nitroolefinen arteko Michael erreakziorako. ***Palomo eta Guichard, 2017****.* [61]

Laburbilduz, 2 Irudian agertzen diren H-lotura emaileetaz baliatuz, aminoazido edo peptido laburrak atxikiturik daramatzaten hainbat tiourea/urea BB bifuntzional deskribatu dira katalizatzaile moduan erabiltzeko (3 Irudia). Hala ere, eskuaramida/ureidoaminalen eta BB-en konbinaketa peptidoekin ikertu gabeko esparrua zen Tesi honen hasieran.[62] Honen ondorioz, Tesi honen helburua katalizatzaile familia berri baten diseinu eta sintesia izan da, BB bat (morez), eskuaramida edo ureidoaminal unitate bat (urdinez) eta H-lotura emaile bezala jokatuko duen aminoazido edo peptido labur bat (gorriz) daukana (4 Irudia).

[61] 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* (36), 12524–12532.

[62] Tesi honen iragatean, adibide batzuk argitaratu dira, non eskuaramidatik eratorritako katalizatzaile peptidiko familia berri hau erabili duten: a) Farid, U.; Aiello, M. L.; Connon, S. J. *Chem. Eur. J.* **2019**, *25* (43), 10074–10079; b) Majee, D.; Jakkampudi, S.; Arman, H. D.; Zhao, J. C. G. *Org. Lett.* **2019**, *21* (22), 9166–9170; c) Ray, B.; Mukherjee, S. *Tetrahedron* **2019**, *75* (24), 3292–3298; d) Zhang, N.; He, T.; Liu, Y.; Li, S.; Tan, Y.; Peng, L.; Li, D.; Shan, C.; Yan, H. *Org. Chem. Front.* **2019**, *6*, 451.

4. Irudia. Katalizatzaile familia berrien diseinua.

Aurretik azaldu den moduan, BB bifuntzional tipikoen egituran kate peptidiko bat gehitzeak hainbat abantaila eskaini diezaioke katalizatzaileari. Alde batetik, kate peptidikoak H-loturak sortzeko duen gaitasunari esker, interakzio sare konplexu bat sor daiteke substratuekin, estereoselektibitatean lagun dezakeena. Gainera, hainbat interakzio-puntu eskuragarri egoteak koordinatzeko modu desberdinak eskaintzen dituenez, katalizatzaile berdinak aktiba dezakeen substratu kopurua handi daiteke. Bestalde, kate peptidikoa bere buruarekin H-loturak sortuz toles liteke eragozpen esterikoa sortuko lukeen egitura bat osatuz, zeina estereoselektibitatean lagungarri izan liteke ere. Azkenik, peptidoak orokorrean nahiko egitura polarrak direnez, erreakzioak normalean erabili ezin diren disolbatzaile ezberdinetan aurrera eramateko aukera eskain dezakete, esaterako, uretan.

Azken urteetan, katalisi asimetrikoak bilakaera nabarmena izan du eta garrantzia irabaziz joan da estrategia erabilgarri eta moldaerraza den heinean. Hala ere, badaude muga batzuk oraindik gainditu ez direnak, esaterako, substratuekiko selektibitatea, karga katalitiko altuen beharra, oraindik deskribatu gabe dauden erreakzioak eragiteko katalizatzaileen beharra eta ezagutzen diren erreakzio batzuetan erreaktibotasun eta estereoselektibitate arazoak. Hauen artean, zentro estereogeniko kuaternarioen sorrera dakarten erreakzioak bereziki interesgarriak dira produktu konplexuagoak sortzeko aukera eskaintzen baitute, baina kasu askotan, erronka bat dira oraindik, erreaktibotasun baxuagoa eta eragozpen esterikoak sortutako estereokontrol arazoen ondorioz.[63]

Era berean, aipatu den moduan, amina tertziarioak base erlatiboki ahulak dira, 11 eta 21 arteko pk_a dutenak,[64] beraz, nahiko mugatuta dago base hauek aktiba dezaketen substratua mota. Orokorrean, gehienez 16-20 balioko pk_a duten pronukleozaleak aktiba daitezke amina tertziarioak erabiliz (5 Irudia),[65,66] beraz, konposatu 1,3-dikarbonilikoen erreakzioak eragiteko erabili dira gehien bat. Nabarmentzekoa da aldehidoak pk_a tarte

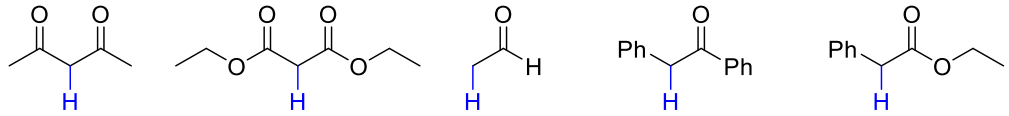
[63] Tetraordezkatutako estereozentroen sintesiari buruzko informaziorako, ikus: a) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley, **2006**; b) Liu, Y.; Han, S. J.; Liu, W. B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48* (3), 740–751; Organokatalizatzaileak erabiliz sortutako tetraordezkatutako estereozentroentzako, ikus: c) Bella, M.; Gasperi, T. *Synthesis* **2009**, *2009* (10), 1583–1614.

[64] a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2010**, *16* (2), 450–455; b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14* (7), 1724–1727; c) Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16* (6), 1786–1789; d) Ho, J.; Zwicker, V. E.; Yuen, K. K. Y.; Jolliffe, K. A. *J. Org. Chem.* **2017**, *82* (19), 10732–10736.

[65] a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2008**, *47* (24), 4588–4591; b) Guang, J.; Rout, S.; Bihani, M.; Larson, A. J.; Arman, H. D.; Zhao, J. C. G. *Org. Lett.* **2016**, *18* (11), 2648–2651.

[66] Bordwell-en pKa taula: https://organicchemistrydata.org/hansreich/resources/pka/ (atzipena 2021eko Maiatzaren 25a)

horren muga barruan daudela. Hala ere, Tesi honen hasieran ez zegoen argitaratutako BB bidez katalizatutako erreakziorik non aldehidoak pronukleozale bezala erabiltzen ziren.[67] Bibliografia falta honen arrazoietako bat ipso-karbonoak elektroizale bezala duen erreaktibotasun altua izan liteke, autokondentsazioa eta beste albo erreakzioak ematea erraz lezakeena, eta ohiko estereokontrol eta aldehidoen aktibazio arazoei batzen zaiona.



5 Irudia. Pronukleozale karbonilodun desberdinen α-karbonoen pK_a balioak.[65,66]

Aminokatalisia arazo hauei erantzun bat emateko gai izan da eta α-funtzionalizatutako aldehido lineal ugari modu eraginkor batean prestatu dira teknika honi esker. Hala ere, aminokatalizatutako α-ordezkatutako aldehidoen α-funtzionalizazioa korapilatsuagoa gertatu da eragozpen esterikoa dela medio, eta salbuespen gutxi kenduta, deskribatu diren adibideetan amaierako aduktuak enantioselektibitate eta/edo diastereoselektibitate baxuekin lortu dira. Hau kontutan harturik, galdetzekoa da Brønsted base bidezko katalisia estrategia osagarri moduan funtziona dezakeen α-ordezkatutako aldehidoen α-funtzionalizaziorako (Ikus 2. Kapitulua).

Horretaz gain, nitroalkano lineal sinpleak substratu nahiko azidoak dira eta erlatiboki ahulak diren Brønsted base baten bidez enoliza daitezke, beraz, BB-ekin katalizatutako nitroalkano hauen hainbat erreakzio deskribatu dira.[68] Hala ere, α-ordezkatutako nitroalkanoen adizioak arazo gehiago aurkeztu ditu. Alfa posizioan zetona, ester edo halogenoak bezalako talde elektroi-erakarle (EWG) bat daramaten nitroalkano α-ordezkatuen hainbat adizio deskribatu dira, katalisi metaliko,[69,70] aminokatalisi[71] edo BB

[67] Tesi honen iragatean, adibide oso espezifiko bat argitaratu zen α-kloroaldehido eta β-alkiliden α-zeto amiden arteko adizioa deskribatzen zuena, zeinetan dirudienez amaierako aduktuaren ziklazioari esker ematen den erreakzioa: Li, Q. Z.; Liu, Y.; Leng, H. J.; Li, J. L. *Synlett* **2018**, *29* (20), 2601–2607.

[68] Berrikuspen batzuentzako, ikus: a) Dong, L.; Chen, F.-E. *RSC Adv.* **2020**, *10*, 2313–2326; b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971.

[69] Binilidenbifosfonatoen adiziorako, ikus: Kato, Y.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Synlett* **2009**, *2009* (10), 1635–1638.

[70] Akrilaldehidoen eta enonen adizioen adibideetarako, ikus: Otani, T.; Sugawara, A.; Tamai, Y. *Tetrahedron Lett.* **2014**, *55* (35), 4923–4926.

[71] Zinamaldeidoaren adizioaren bi adibiderako, ikus: Zhang, J.; Hu, Z.; Dong, L.; Xuan, Y.; Lou, C.-L.; Yan, M. *Tetrahedron Asymmetry* **2009**, *20* (3), 355–361.

bidez eragindakoak,[72,73] kasu hauetan EWG horrek erreakzioa errazten baitu. Baina aktibatu gabeko α-ordezkatutako nitroalkanoen erabilera pronukleozale bezala simetrikoki ordezkatutakoetara mugatuta dago, esaterako 2-nitropropano eta nitroalkano ziklikoetara, non ez den zentro estereogenikorik sortzen nitro taldearen ondoko karbonoan (14a Eskema). Deskribatutako nitroalkano hauen Michael adizioetan enonak erabili dira elektroizale bezala nagusiki eta protokolo eraginkorrak argitaratu dira bai enona lineal bai ziklikoekin, aminokatalizatzaileak erabiliz.[74,75] Adibide bakar bat ere argitaratu da non zinamaldehidorako adizioa deskribatzen den,[76] baina ez da artikulurik topatu non ester α,β- asegabeen Michael erreakzioak ikertzen diren.

Ez-simetrikoki ordezkatutako nitroalkano ez aktibatuen bibliografia gabezia pronukleozale moduan (14b Eskema), esterozentro kuaternario baten sorrerak dakarren erreaktibotasun eta estereokontrol zailtasunen ondorio izan daiteke.[63] Arazo honen konponbide posible bat elektroizale oso erreaktiboen erabilera izan daiteke, hala nola, α-hidroxi enonak (14c Eskema). Gure ikerketa taldeak Michael hartzaile hauek oso eraginkorrak izan daitezkeela frogatu du metalek katalizatutako eta organokatalizatutako hainbat erreakzioetan.[77]

[72] Enonen adizioetarako, ikus: a) Erref. 45 b) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4* (2), 173–176; c) Bera, K.; Satam, N. S.; Namboothiri, I. N. N. *J. Org. Chem.* **2016**, *81* (13), 5670–5680.

[73] NItroolefinak elektroizale diren adizioetarako, ikus: a) Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beilstein J. Org. Chem.* **2015**, *11* (1), 2577–2583; b) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356* (17), 3627–3648; c) Jörres, M.; Schiffers, I.; Atodiresei, I.; Bolm, C. *Org. Lett.* **2012**, *14* (17), 4518–4521; d) Kwiatkowski, J.; Lu, Y. *Chem. Commun.* **2014**, *50* (66), 9313–9316.

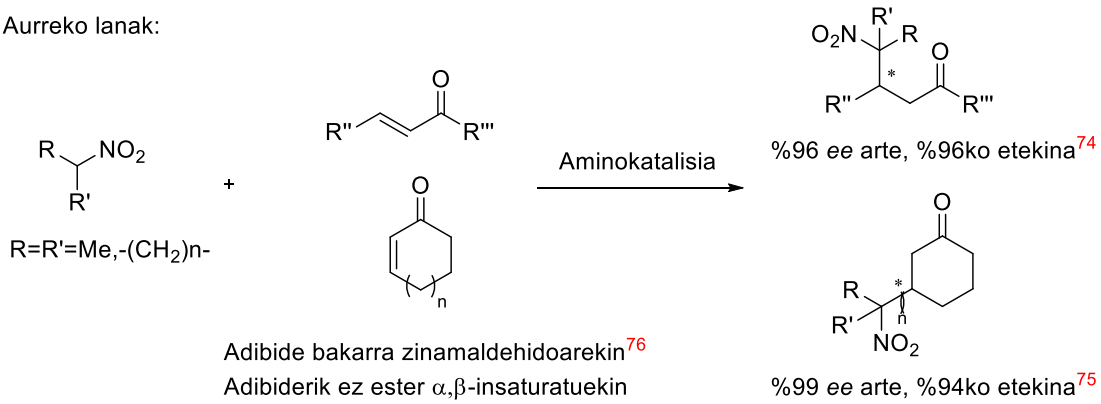
[74] a) Erref. 43; b) Erref. 44; c) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4* (10), 2039–2049; d) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8* (21), 4787–4790; e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2* (19), 2975–2978; f) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53* (32), 11223–11236.

[75] a) Zhou, Y.; Liu, Q.; Gong, Y. *Org. Biomol. Chem.* **2012**, *10* (37), 7618–7627; b) Guo, X. T.; Shen, J.; Sha, F.; Wu, X. Y. *Synth.* **2015**, *47* (14), 2063–2072; c) Erref 74c.

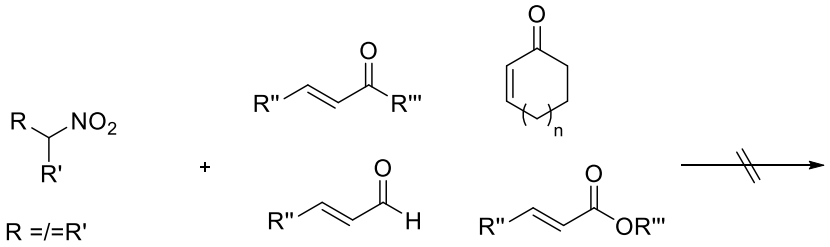
[76] Gotoh, H.; Okamura, D.; Lshikawa, H.; Hayashl, Y. *Org. Lett.* **2007**, *9* (25), 5307–5309.

[77] a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41* (11), 4150–4164; b) Palomo, C.; Oiarbide, M.; García, J. M. *Encycl. Reagents Org. Synth.* **2019**, 1–7.

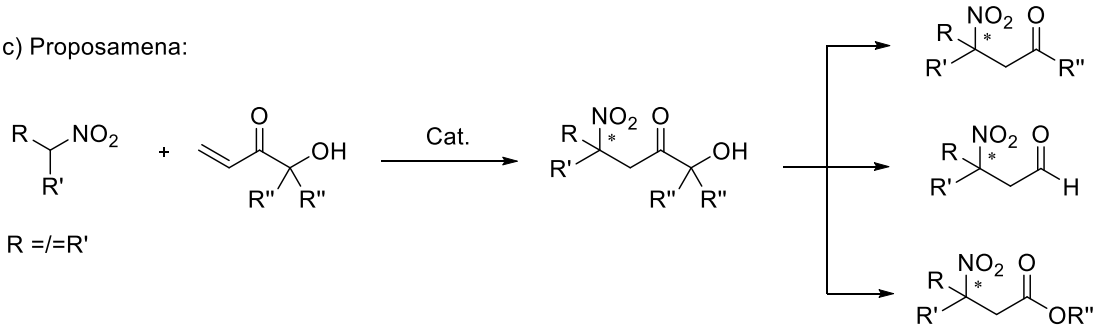
a) Aurreko lanak:



b) Deskribatu gabe:



c) Proposamena:



14 Eskema. a) Deskribatutako aktibatu-gabeko simetrikoki ordezkatutako nitroalkanoen karbonilodun elektroizaleetarako Michael adizioak. b) Ikertu gabeko ez-simetrikoki ordezkatutako nitroalkanoen karbonilodun elektroizaleetarako adizio konjokatuak. c) α-Hidroxi enonen erabileraren proposamena.

α-Hidroxi enona funtzio taldea gure taldeak erabili zuen lehenengo aldiz laguntzaile-kiral estrategian Diels-Alder zikloadizio,[78] zikloadizio 1,3-dipolar[79] eta Michael adizio[80] diastereoselektibo desberdinak aurrera eramateko. Ideia hau erreakzio enantioselektiboetara zabaldu zen gero, katalisiaren bidez, eta metalek katalizatutako

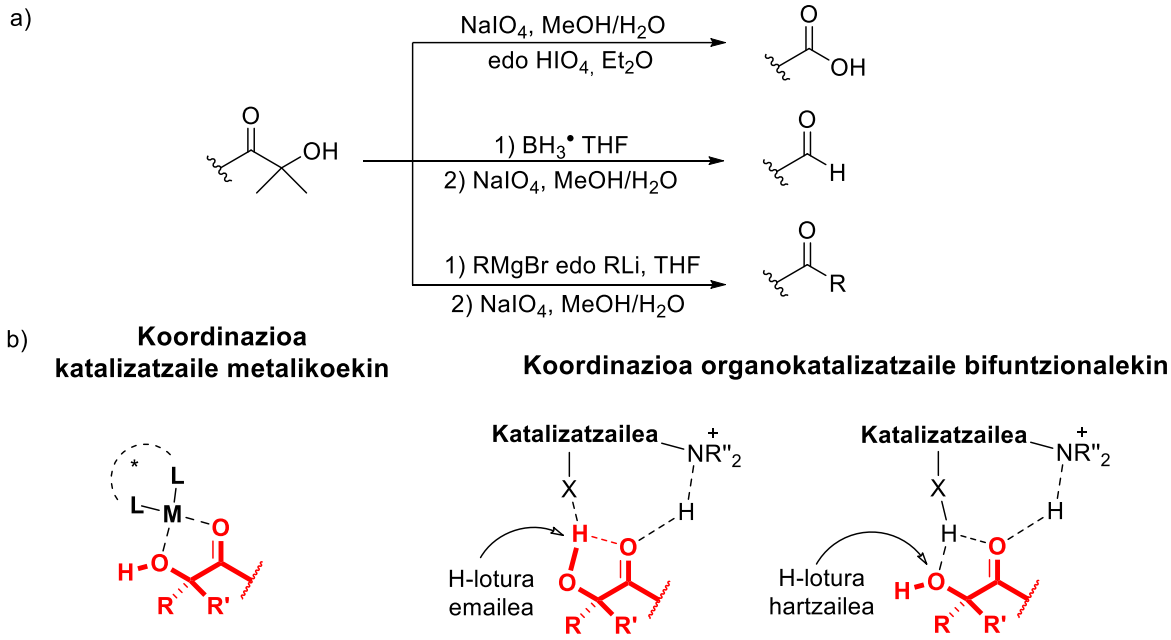
[78] a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124* (35), 10288–10289; b) Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J. *J. Org. Chem.* **2010**, *75* (5), 1458–1473.

[79] Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed.* **2005**, *44* (38), 6187–6190.

[80] a) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10* (13), 2637–2640; b) García, J. M.; Maestro, M. A.; Oiarbide, M.; Odriozola, J. M.; Razkin, J.; Palomo, C. *Org. Lett.* **2009**, *11* (17), 3826–3829.

hainbat zikloadizio[81,79] eta Michael erreakzio[80a,82,83,84,85] eraginkor deskribatu ziren. Urte batzuk geroago, gure taldean, α-hidroxi enonak Michael hartzaile bezala erabili ziren lehenengoz organokatalizatutako erreakzioetan.[86] Oxindolak, oxazolonak, tiazolonak, zianoazetatoak eta azlaktonak bezalako pronukleozaleak α-hidroxi enonetara gehitu ziren BB katalizatzaile bifuntzionalak erabiliz, primerako estereoselektibitatea lortuz.

α-Hidroxi enonen erabiliera Michael hartzaile moduan bereziki interesgarria da amaierako aduktuko α-hidroxi zetona taldea aldehido, zetona edo azido karboxiliko bihur daitekeelako eskeman adierazi diren erreakzio baldintzetan (15a Eskema). Hortaz, α-hidroxi enonak oso erabilgarriak izan daitezke enal, enona edo ester α,β-asegabeen baliokide sintetiko moduan. Gainera, abantaila nabarmen bat aurkezten dute bi puntu desberdin eskaintzen dituztelako katalizatzaileekin koordinatzeko edo H-loturak sortzeko. (15b Eskema).



15 Eskema. a) α-Hidroxi zetona atala azido karboxiliko, aldehido edo zetonatan bihurtzeko aukera. b) α-Hidroxi enona katalizatzaile metalikoekin eta organokatalizatzaileekin koordinatzeko moduak.

[81] Diels-Alder zikloadizioentzat, ikus: Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125* (46), 13942–13943.

[82] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126* (30), 9188–9189.

[83] Zikloadizio 1,3-dipolarrentzat, ikus: Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127* (12), 4154–4155.

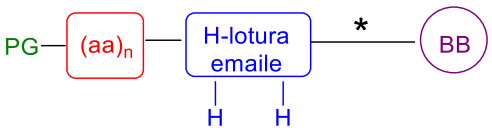
[84] Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161–1164.

[85] García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14* (29), 8768–8771.

[86] 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* (51), 17869–17881.

1.1. Helburuak

Aurretik azaldutako aurrekariak ikusita, Tesi honen helburu nagusia aminoazidoak eta H-lotura emaile diren eskuaramida/ureidoaminalak daramatzaten BB katalizatzaileen diseinua eta sintesia izan da (6 Irudia), hala nola, katalizatzaile berri hauen erabilera jarraian deskribatzen diren erreakzioetan.



6 Irudia. Aminoazido eta BB-ak daramatzan katalizatzaile berrien egitura eskematikoa. PG:talde babeslea. aa: aminoazido. H-lotura emailea: eskuaramida/ureidoaminala.

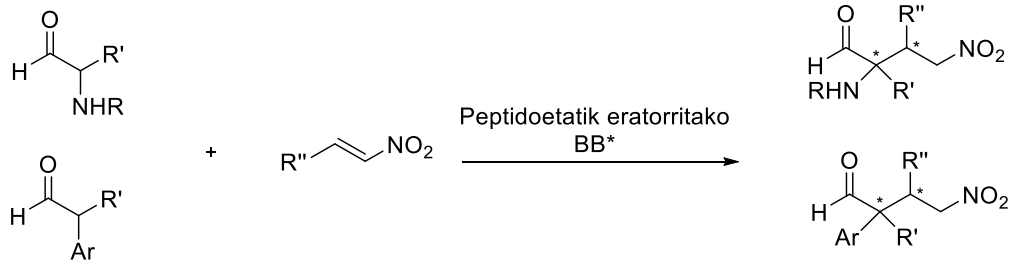
Kontuan hartuz proiektu hau hasi zenean aldehidoen erabilera pronukleozale moduan BB bidez katalizatutako erreakzioetan ikertu gabeko esparrua zela, aldehidoen α-funtzionalizazio erreakzioa aukeratu zen 6 Irudian azaltzen diren katalizatzaile berriak ikertzeko. Beraz, Tesi honen lehenengo helburu nagusia peptidoetatik eratorritako BB katalizatzaile bifuntzionalek eragindako aldehidoen eta nitroolefinen arteko Michael erreakzioa ikertzea izan da (16 Eskema).

Pronukleozale bezala α-ordezkatutako aldehidoak aukeratu ziren, izaera desberdinetako ordezkatzaileak zituztenak, esaterako, α-amino aldehidoak eta α-aril azetaldehidoak. Izan ere, substratu hauen α-funtzionalizazioan estereozetro kuaternarioak sortzen dira, erronka gehigarri bat dena. Sarreran azaldu den moduan, aldehidoak ez dira inoiz erabili pronukleozale gisa BB bidez katalizatutako erreakzioetan eta aminokatalisi bidez eragindako haien α-funtzionalizazioak, salbuespen gutxi batzuetan ez ezik, muga nabarmenak aurkezten ditu estereoselektibitatearen ikuspuntutik. Gainera, α-amino aldehidoak, nagusiki elektroizale moduan erabiliak izan dira orain arte, eta aminokatalisi bidez eragindako haien α-funtzionalizazioak arazoak aurkez litzake erregioselektibitatekin, erreakzio bitartekarian nukleozale diren bi enamina desberdin sortzen direlako.

Hasiera batean, ikerketaren hastapenetarako, nitroolefinak aukeratu ziren Michael hartzaile moduan,[87] nitro taldeak daukan koordinatzeko gaitasun handiarengatik. Izan ere, katalizatzailearen atal peptidikoarekin koordinatuz gero, elektroizalearen erreaktibotasuna hobetuko litzateke, aldehidoaren autokondentsazioa eta beste albo erreakzioak ekidituz. Horretaz gain, Michael erreakzioa honen γ-nitroaldehido aduktuak

[87] Nitroalkanoen Michael hartzaile erabileraren berrikuspenetarako, ikus: a) Somanathan, R.; Chavez, D.; Antonio Servin, F.; Alfonso Romero, J.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya de Parrodi, C.; Gonzalez, J. *Curr. Org. Chem.* **2012**, *16* (20), 2440–2461; b) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gómez, C.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Molecules* **2017**, *22* (6), 895; Nitroalkanoen Michael hartzaile izateko gaitasunaren ebaluaketa teoriko batentzako, ikus: c) Rai, V.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2006**, *20*, 4693–4703.

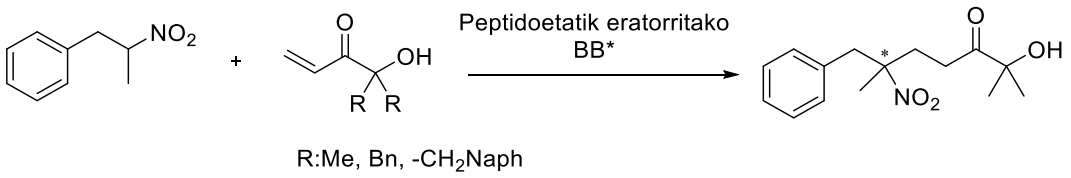
azido γ-aminoisubutirikoen (GABA)[88] aurrekariak dira, zeinak aktibitate farmakologikoa aurkezten duten. Bestalde, aduktuetako NO_2 taldea hainbat talde funtzional desberdinetan erraz bihur daiteke. Helburu honi dagozkion emaitzak 2. Kapituluan aurki daitezke.



16 Eskema. Proposatutako α-ordezkatutako aldehidoen eta nitroolefinen arteko Michael erreakzioa peptidoetatik eratorritako BB katalizatzaile bifuntzionalek eragindakoa.

Horretaz gain, 6 Irudian proposatutako katalizatzaile familia berri honen diseinua oraindik erronka bat diren beste erreakzio batzuk eragiteko ere erabilgarria izan daiteke, esaterako, ez-simetrikoki α-ordezkatutako nitroalkanoen Michael adizioa. Lehen aipatu bezala, aktibatu gabeko α-ordezkatutako nitroalkanoak ez dira inoiz ikertu pronukleozale moduan alfa posizioan estereozentro berriak sortzen dituzten erreakzioetan. Nitroalkano ez aktibatu hauen erreaktibotasun baxuaren arazoari aurre egiteko, α-hidroxi enonak aukeratu dira elektroizale bezala, aurretik azaldu den haien erreaktibotasun handiarengatik.

Beraz, Tesi honen bigarren helburua talde aktibatzailerik ez duten ez-simetrikoki ordezkatutako nitroalkanoen eta α-hidroxi enonen arteko Michael erreakzioa ikertzea izan da, 6 Irudiko peptidoetatik eratorritako BB bifuntzional berriak katalizatzaile moduan erabiliz (17 Eskema). Helburu honi dagozkion emaitzak 3. Kapituluan jaso dira.



17 Eskema. Proposatutako α-ordezkatutako nitroalkanoen eta α- hidroxi enonen arteko Michael erreakzioa peptidoetatik eratorritako BB katalizatzaile bifuntzionalekin eragindakoa.

α-Hidroxizetona taldea aldehido, zetona edo azido karboxiliko bihur daitekeen bezala, erreakzio hauetan lortutako aduktuetako nitro taldea ere talde funtzional desberdinetara eralda daiteke, lortutako aduktuei garrantzi gehigarri bat eskainiz. Izan

[88] a) Ballini, R. *Stud. Nat. Prod. Chem.* **1997**, *19*, 117–184; b) Gajcy, K.; Lochynski, S.; Librowski, T. *Curr. Med. Chem.* **2010**, *17* (22), 2338–2347; c) Andresen, H.; Aydin, B. E.; Mueller, A.; Iwersen-Bergmann, S. *Drug Test. Anal.* **2011**, *3* (9), 560–568; d) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini Rev. Med. Chem.* **2012**, *12* (7), 671–700.

ere, nitro oso talde moldaerraza da eta karbonilo bihur daiteke Nef erreakzioaren bidez[89] edo Cr(II) gatzekin,[90] azido karboxiliko Mioskowski erreakzioarekin,[91] eta amina primario[92] ala hidroxilamina[93] erredukzio bidez. Horretaz gain, nitro taldea nitrilo oxidotan ere bihur daiteke[94] edo erreakzio nukleozale baten bidez ordezka daiteke.[95]

[89] a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280* (2–3), 263–291; b) Pinnick, H. W. *The Nef Reaction. In Organic Reactions*; Wiley, **1990**; 655–792; c) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357* (11), 2371–2402.

[90] Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26* (32), 3777–3778.

[91] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62* (2), 234–235.

[92] a) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29* (45), 5733–5734; b) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130* (17), 5608–5609; c) Goksu, H.; Sert, H.; Kilbas, B.; Sen, F. *Curr. Org. Chem.* **2017**, *21* (9), 794–820.

[93] Feuer, H.; Bartlett, R. S.; Vincent, B. F.; Anderson, R. S. *J. Org. Chem.* **1965**, *30* (9), 2880–2882.

[94] Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82* (20), 5339–5342.

[95] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, *6*, 423–434.

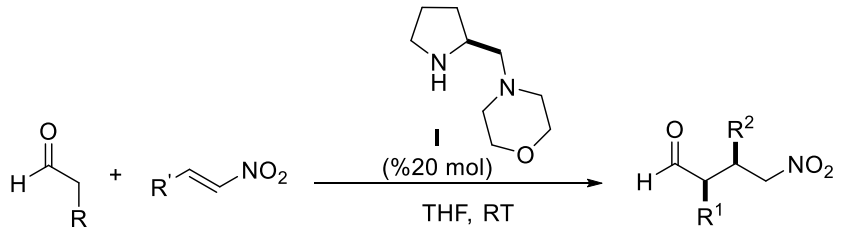
2. KAPITULUA

α-ORDEZKATUTAKO ALDEHIDOEN ETA NITROOLEFINEN ARTEKO MICHAEL ERREAKZIOA

2. α-Ordezkatutako aldehidoen eta nitroolefinen arteko Michael erreakzioa

2.1. Sarrera

Ordezkapen maila handiko aldehidoak oso konposatu erabilgarriak dira konplexutasun handiko konposatuen sintesirako. Hortaz, aldehidoen funtzionalizazio eraginkorra burutzeko protokoloak garatzea bereziki interesgarria da. Hala ere, aldehidoen α-funtzionalizazio enantioselektiboak erronka bat suposa dezake oraindik, *ipso*-karbonoak oxidazio egoera horretan duen erreaktibotasun altuak autokondentsazio, Cannizzaro eta Tishchenko albo erreakzioak ematea hobesten duelako. Arazo hauek aldehidoen eta elektroizale desberdinen arteko erreakzioaren ohiko estereokontrol eta aktibazio zailtasunei gehitzen zaizkienez, aldehidoen α-funtzionalizazioa erronka bat kontsidera daiteke. Laguntzaile kiralak erabiliz,[96] ez da lortu arazo hauek guztiz ebaztea. Testuinguru honetan, aminokatalisia aldehido linealen α-funtzionalizazio enantioselektiboetarako teknika erabilgarri bat izan daitekeela frogatu da, eta gaur egun, aldehidoen alfa posizioan estereoselektiboki funtzio talde desberdinak gehitzeko protokolo eraginkorrak eskuragarri daude.[97] Argitaratutako erreakzioen artean, amina primario eta sekundarioekin katalizatutako hainbat Michael adizio asimetriko aurki daitezke. Lehenengo adibide enantioselektiboa Barbas III-ak deskribatu zuen aldehido linealen. Bere taldeak pirrolidinatik eratorritako **I** katalizatzailea erabili zuen nitroestirenoetarako adizio konjokatua bultzatzeko. Aduktuak etekin eta diastereoselektibitate bikainarekin eta %78 arteko *ee*-rekin prestatu ziren (18 Eskema).[29a]



18 Eskema. Aldehidoen eta nitroolefinen arteko lehenengo Michael erreakzio aminokatalitiko asimetrikoa. ***Barbas III, 2001.***[29a]

[96] Berrikuspen baterako, ikus: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58* (12), 2253–2329.

[97] Berrikuspenetarako, ikus: a) Erref. 87b; b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38* (8), 2178–2189.

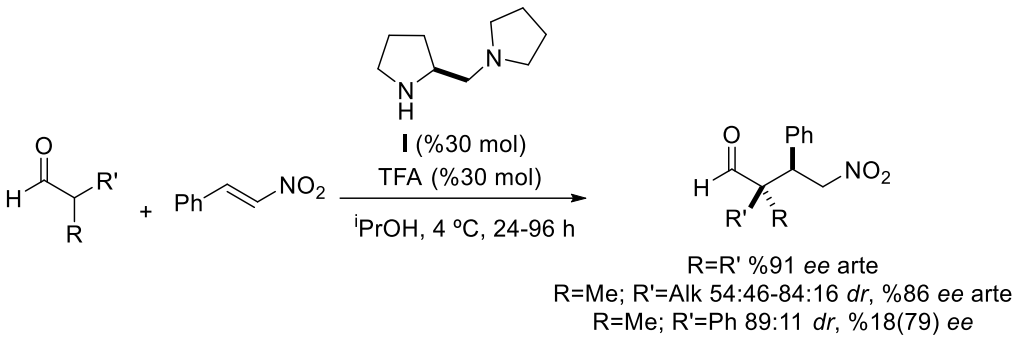
Gure ikerketa taldeak ere aldehido linealen eta nitroolefinen arteko Michael erreakzio asimetrikorako prozedura bat argitaratu zuen, non hidroxiprolinatik eratorritako katalizatzaile bat erabiliz, primerako estereoselektibitateak lortu ziren.[29c] Nabarmentzekoa da beharrezko aldehido kantitatea 1.2 baliokidera murriztea lortu zela protokolo berri honetan, Barbas III-ren prozedurarekin alderatuz (10 ek.). Sarreran aipatu bezala, peptidoetatik eratorritako katalizatzaileek eragindako ordezkatu gabeko aldehidoen eta nitroolefinen arteko erreakzioak ere deskribatuak izan dira. Wennemers,[23,24,25,32] Lecouvey[34] eta Piarulli-k[35] argitaratutako adizio konjokatu hauek enamina katalisi bidez dihardute. Baina enamina bidezko α-ordezkatutako aldehidoen aktibazioa erronka handiagoa izan daiteke. Izan ere, kasu hauetan, katalizatzailearen amina eta substratuaren aldehidoaren arteko kondentsazioa zailagoa da karboniloaren inguruan dagoen eragozpen esterikoa dela eta,[98] eta beraz, *E*- eta *Z*-enamina nahasteak aurki daitezke, estereoselektibitatean eragina izan dezaketenak. Hare gehiago, sortzen diren α-ordezkatutako enamina horiek ez dira enamina linealak bezain erreaktiboak,[99] α-H horren falta dela medio, eta ziklo katalitikoa inibi lezaketen bitartekari batzuk sor daitezke. Zailtasun guzti hauek azal lezakete deskribatutako α-ordezkatutako aldehidoen α-funtzionalizazioa nagusiki hasierako substratu akiraletan (isobutiraldehidoa edo aldehido ziklikoak) zentratua egotea.[100] Izan ere, kasu hauetan ez dago *E/Z* enamina nahasteak egoteko aukerarik. Hala ere, estereozentro bakarra sortzen da erreakzio hauetan eta haien erabilera substratu nabarmenki gutxiagoetara mugatua dago.

Gaur egun arte, bi ordezkatzaile desberdin dituzten α-ordezkatutako aldehidoen funtzionalizazio estereoselektiboa gutxiago ikertu izan da eta amina primario eta sekundarioekin katalizatutako adibide gutxi batzuk aurki daitezke bibliografian.[101] α-Ordezkatutako aldehido hauen Michael adizio eraginkorretan enonak,[102] binil

[98] Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14* (2), 536–539.
[99] Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9* (10), 2209–2218.
[100] Azken urteetan argitaratutako adibide batzuentzako, ikus: a) Tuchman-Shukron, L.; Miller, S. J.; Portnoy, M. *Chem. Eur. J.* **2012**, *18* (8), 2290–2296; b) Simone, N. A. De; Meninno, S.; Talotta, C.; Gaeta, C.; Neri, P.; Lattanzi, A. *J. Org. Chem.* **2018**, *83* (17), 10318–10325; c) Martínez-Guillén, J. R.; Flores-Ferrándiz, J.; Gómez, C.; Gómez-Bengoa, E.; Chinchilla, R. *Molecules* **2018**, *23* (1), 141; d) Gorde, A. B.; Ramapanicker, R. *Eur. J. Org. Chem.* **2019**, *29*, 4745–4751.
[101] Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70* (15), 2491–2513.
[102] a) Lnokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12* (7), 1616–1619; b) Yoshida, M.; Ukigai, H.; Shibatomi, K.; Hara, S. *Tetrahedron Lett.* **2015**, *56* (25), 3890–3893.

sulfonak,[103,104] *N*-aril maleimidak,[105] β-nitro akrilatoak[106] eta nitroolefinak erabili dira elektroizale moduan. Nabarmenki, argitaratutako prozedura gehienak pronukleozale moduan α-metil α-aril aldehidoen erabilerara mugatuak daude eta metilo baino ordezkatzaile handiagoko α,α-dialkil aldehidoekin deskribatutako adibideak ez dira estereoselektiboki hain eraginkorrak.

α-Ordezkatutako aldehidoen nitroolefinetarako adizio konjokatua bereziki interesgarria izan daiteke estereozentro kuaternario bat daramaten γ-nitroaldehidoak prestatzeko ibilbide sintetiko bat eskaintzen duelako.[107] Mota honetako lehenengo erreakzioa Barbas III-k garatu zuen 2004. urtean (19 Eskema)[108], 2001ean aldehido lineal adiziorako[29a] erabilitako pirrolidinatik eratorritako **I** katalizatzailearekin. α-Alkil eta α-aril aldehidoetatik eratorritako aduktuak neurrizko estereoselektibitatearekin prestatu ziren.



19 Eskema. α-Ordezkatutako aldehidoen eta nitroestirenoen arteko deskribatutako lehenengo adizioa. ***Barbas, 2004.***[108]

Barbas III-ren lana eta gero, beste ikerketa desberdinak argitaratu dira ez-simetrikoki α-ordezkatutako aldehidoen eta nitroolefinen arteko Michael erreakziorako,

[103] 2-Fenilpropanalaren adizioaren adibide bakarra duen protokolo batentzako, ikus: Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132* (48), 17074–17076.

[104] a) Rodrigo, E.; Morales, S.; Duce, S.; Ruano, J. L. G.; Cid, M. B. *Chem. Commun.* **2011**, *47* (40), 11267–11269; b) Miura, T.; Yuasa, H.; Murahashi, M.; Ina, M.; Nakashima, K.; Tada, N.; Itoh, A. *Synlett* **2012**, *23* (16), 2385–2388; c) Kanada, Y.; Yuasa, H.; Nakashima, K.; Murahashi, M.; Tada, N.; Itoh, A.; Koseki, Y.; Miura, T. *Tetrahedron Lett.* **2013**, *54* (36), 4896–4899; d) Nakashima, K.; Murahashi, M.; Yuasa, H.; Ina, M.; Norihiro, T.; Itoh, A.; Hirashima, S. I.; Koseki, Y.; Miura, T. *Molecules* **2013**, *18* (12), 14529–14542; e) Kawada, M.; Tsuyusaki, R.; Nakashima, K.; Akutsu, H.; Hirashima, S. ichi; Matsumoto, T.; Yanai, H.; Miura, T. *Chem. Asian J.* **2021**, *16* (16), 2272–2275.

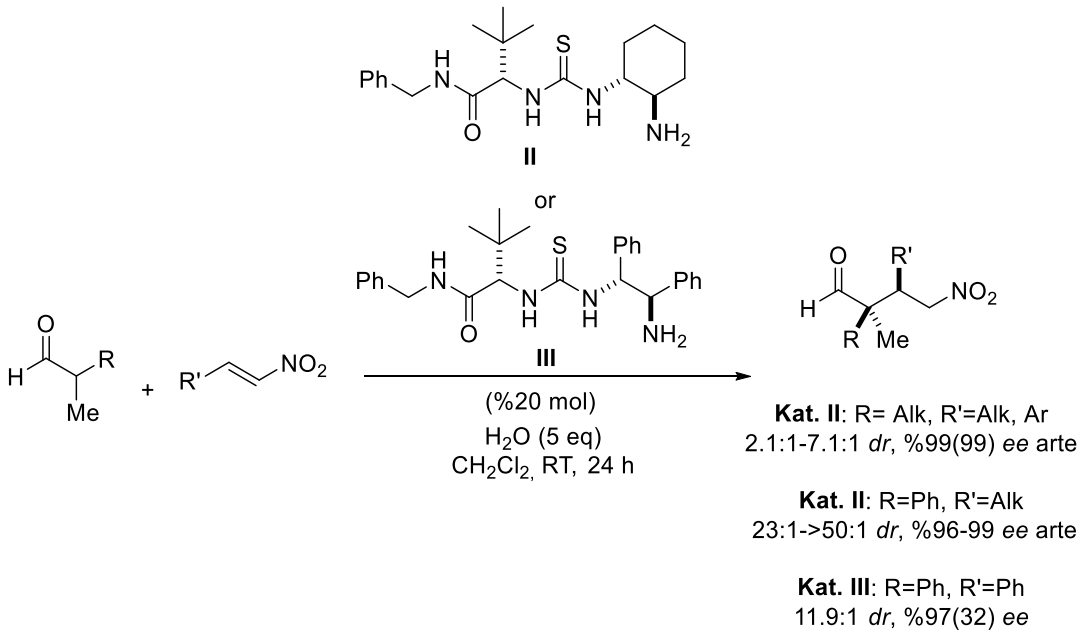
[105] Ez-simetrikoki α-ordezkatutako aldehidoak erabiliz deskribatutako bi adibide dituen protokolo baterako, ikus: a) Kokotos, C. G. *Org. Lett.* **2013**, *15* (10), 2406–2409; For a more general protocol, see: b) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J.* **2012**, *18* (13), 4088–4098.

[106] Adibide eraginkor bakarra duen artikulu batentzako, ikus: Yoshida, M.; Masaki, E.; Ikehara, H.; Hara, S. *Org. Biomol. Chem.* **2012**, *10* (27), 5289–5297.

[107] D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601.

[108] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6* (15), 2527–2530.

baina salbuespen gutxi batzuk izan ezik,[109,110] deskribatutako protokoloekin aduktuak *ee* edota *dr* baxuan lortzen dira.[111] Erreakzio honetarako prozedura orok eta eraginkorrena Jacobsenek argitaratu zuen 2006. urtean, non tioureatik eratorritako **II** amina primario bifuntzionala erabili zuen erreakzioa eragiteko, enantioselektibitate bikainak baina *dr* aldakorragoa lortuz (20 Eskema).[110] Alde batetik, α,α-dialkil ordezkatutako aldehidoen adiziorako 2.1:1 eta 7.1:1 arteko ratio diastereomerikoak lortu ziren, *E/Z*-enaminen nahaste baten presentziak eragin litzakeena. Bestalde, α-aril aldehidoen eta nitroolefina alifatikoen arteko erreakziorako estereoselektibitate bikainak hauteman ziren, baina α-aril aldehidoen nitroestirenoetarako adizio konjokatua sustatzeko moldaketa txiki batzuk egin behar izan ziren katalizatzailean, aduktuak estereoselektibitate bikainarekin prestatzeko (**III**, 20 Eskema).



20 Eskema. Tioureatik eratorritako amina primario bifuntzionalekin katalizatutako ez-simetrikoki α-ordezkatutako aldehidoen eta nitroolefinen arteko Michael erreakzioa. ***Jacobsen, 2006.***[110]

Bestalde, α-kloro eta α-alkoxi bezalako α-hetero ordezkatutako aldehidoen Michael adizioak ia ez dira ikertu, beraz, oso adibide gutxi aurkitu dira bibliografian eta ia guztiak[67] aminokatalizatzaileak erabiliz sustatu dira. α-Ordezkatutako α-heteroaldehidoen artean, α-amino aldehidoak bereziki interesgarriak dira molekula konplexuagoak prestatzeko aurrekari baliagarriak kontsideratzen baitira eta kimika

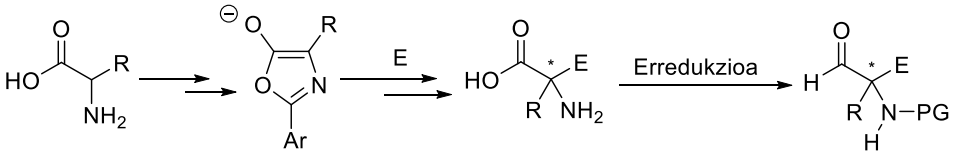
[109] Szcześniak, P.; Staszewska-Krajewska, O.; Furman, B.; Młynarski, J. *ChemistrySelect* **2017**, *2* (9), 2670–2676.

[110] Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45* (38), 6366–6370.

[111] a) Erref. 110; b) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9* (4), 599–602; c) Ting, Y. F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem. Eur. J.* **2010**, *16* (23), 7030–7038; d) Chen, J. R.; Zou, Y. Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W. J. *Tetrahedron* **2010**, *66* (29), 5367–5372; e) Yoshida, M.; Sato, A.; Hara, S. *Org. Biomol. Chem.* **2010**, *8* (13), 3031–3036; f) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9* (1), 52–56; g) Porta, R.; Benaglia, M.; Coccia, F.; Cozzi, F.; Puglisi, A. *Adv. Synth. Catal.* **2015**, *357* (2–3), 377–383; h) Erref. 109.

medikoan eta industria farmazeutikoan erabil daitezkeelako.[112] Izan ere, aldehidoa beste hainbat funtzio talde desberdinetan erraz eralda daiteke, oso ordezkatutako amina kiralen prestakuntzarako ibilbide sintetiko berriak irekiz.[113] Hortaz, α-amino aldehido kuaternario enantiomerikoki puruen prestakuntza nabarmenki erabilgarria izan daiteke.

Azken urteetan α-amino aldehido tertziarioak oso enantioselektibitate onekin prestatzeko aurrerapenak egin dira α-formil enamiden hidrogenazio asimetrikoa bezalako protokoloekin,[114] baina α-amino aldehido kuaternarioak estereoselektiboki prestatzeko prozedurak erlatiboki gutxi ikertu dira. Gaur egun gehien erabiltzen den ibilbide sintetikoa α-aminoazido edo deribatuen prestakuntzan datza, ondoren hauen erredukzio selektiboa burutzeko (21 Eskema). Honen arrazoi nagusietako bat azken urteetan α-aminoazido deribatuen sintesi estereoselektiborako deskribatu diren prozedura kantitate altua izan daiteke, esaterako, azlaktonak bezalako egitura ziklikoak erabiliz, [115] 21 Eskeman ikusten den bezala, edo sistema metaliko kelatuak erabiliz.[116] Metodo hau bereziki interesgarria da enolatoaren konfigurazio kontrolatzeko, eta beraz, estereoselektibitatearen ikuspuntutik erreakzioa eraginkorra izan dadin, izan ere, hau lortzea ez da hain erraza α-amino aldehidoak pronukleozale bezala erabiltzean. Azken honek azal lezake zergatik α-amino aldehido kuaternarioen sintesi katalitiko asimetrikoa ez den ia ikertu, α-ordezkatutako aldehidoen α-aminazioaz aparte, eta zergatik ez dagoen enolato bidezko deskribatutako adibiderik.



21 Eskema. Gaur egun α-amino aldehido kuaternarioak prestatzeko gehien erabiltzen den metodoa, non α-aminoazido edo deribatuak selektiboki erreduzitzen diren.

Bestalde, α-amino aldehidoen α-funtzionalizaziorako existitzen diren protokoloak enamina aktibazio bidez funtzionatzen dute eta oso gutxi dira. Honen arrazoi bat izan liteke aminokatalizatzailea hasierako aldehidoaren kondentsatzen denean sortzen den

[112] a) Hili, R.; Baktharaman, S.; Yudin, A. K. *Eur. J. Org. Chem.* **2008**, *31*, 5201–5213; b) Gryko, D.; Chałko, J.; Jurczak, J. *Chirality* **2003**, *15* (6), 514–541; c) Bergmeier, S. C. *Tetrahedron* **2000**, *56* (17), 2561–2576; d) Reetz, M. T. *Chem. Rev.* **1999**, *99* (5), 1121–1162; e) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164.

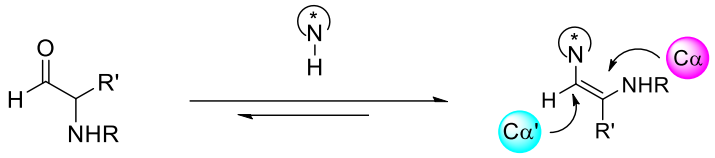
[113] Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, Germany, **2010**.

[114] Zhang, J.; Jia, J.; Zeng, X.; Wang, Y.; Zhang, Z.; Gridnev, I. D.; Zhang, W. *Angew. Chem. Int. Ed.* **2019**, *58* (33), 11505–11512.

[115] Berrikuspenetarako, ikus: a) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19* (24), 2755–2762; b) Alba, A. N. R.; Rios, R. *Chem. Asian J.* **2011**, *6* (3), 720–734; c) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. *Chem. Eur. J.* **2016**, *22* (30), 10294–10318.

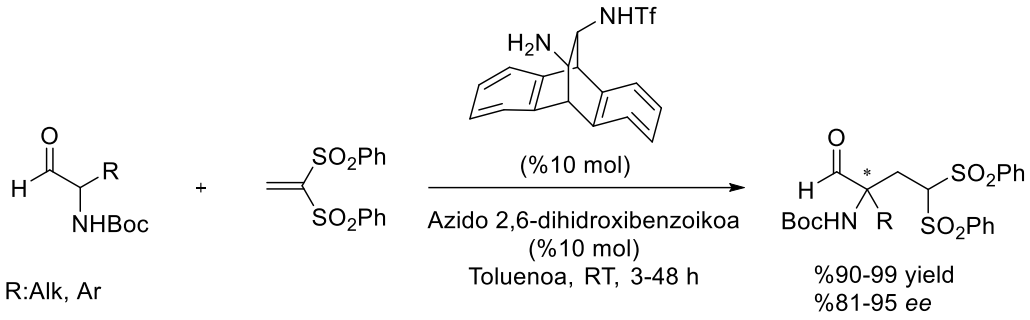
[116] a) Yamashita, Y.; Kobayashi, S. *Chem. Eur. J.* **2013**, *19* (29), 9420–9427; b) Wang, Y.; Song, X.; Wang, J.; Moriwaki, H.; Soloshonok, V. A.; Liu, H. *Amin. Acids* **2017**, *49* (9), 1487–1520; c) O'Donnell, M. J. *Tetrahedron* **2019**, *75* (27), 3667–3696.

bitartekarian bi enamina sor daitezkeelako, eta beraz erreakzioaren erregioselektibitatea kontrolatzea zailagoa izan daiteke, bereziki aldehidoak alfa posizioan eragozpen esteriko handiko ordezkatzaileak baditu, α-karbonoa esterikoki eragotziagoa dagoelako (22 Eskema).



22 Eskema. Bi enamina posible sortzen dira aminokatalizatutako α-amino aldehidoen erreakzioetan.

Prozedura eraginkorrak deskribatzen dituzten hiru artikulu besterik ez dira aurkitu literaturan aminokatalizatutako α-amino aldehidoen α-funtzionalizaziorako.[117] Lehenengoa Maruokak argitaratu zuen 2010. urtean (23 Eskema)[103] eta dihidroantrazenotik eratorritako amina primario bat erabiltzen da α-amino aldehidoen Michael adizioa katalizatzeko. Kasu honetan, aduktuak oso etekin eta enantioselektibitate altuekin lortzen dira, baina protokoloa bereziki erreaktiboak diren binil sulfonak bezala elektroizaleetara mugatuta dago.

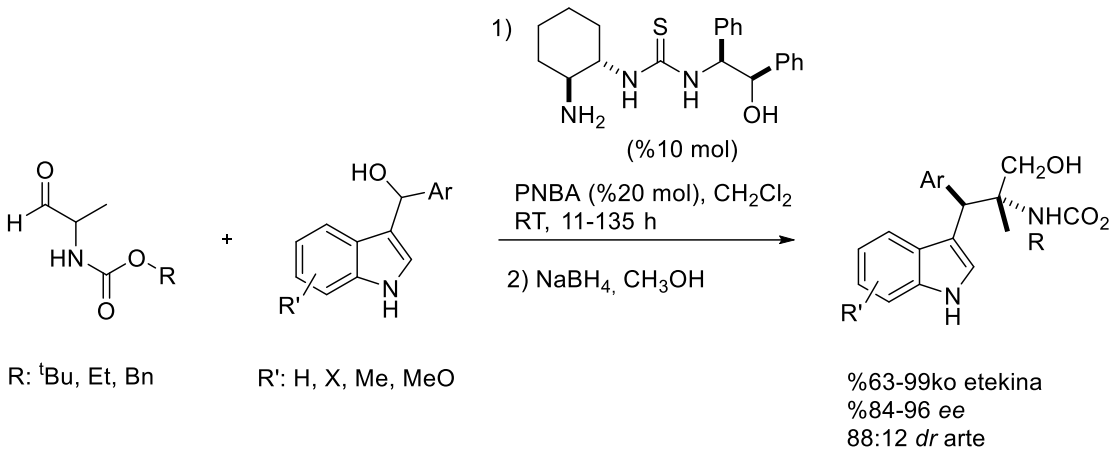


23 Eskema. α-Ordezkatutako α-amino aldehidoen eta binil sulfonen arteko Michael erreakzioa. ***Maruoka, 2010****.*[103]

Guo eta bere langileek ere beste prozedura eraginkor bat deskribatu zuten 2014ean α-amino aldehido ez linealen α-funtzionalizaziorako, baina α-metil ordezkatutako pronukleozaleetara mugatuta dago.[118] Tioureatik eratorritako amina primario batekin katalizatutako 3-indoilmetanoletarako adizio konjokatua ikertu zuten, enantioseletibitate bikain eta oso diastereoselektibitate onetara helduz (24 Eskema).

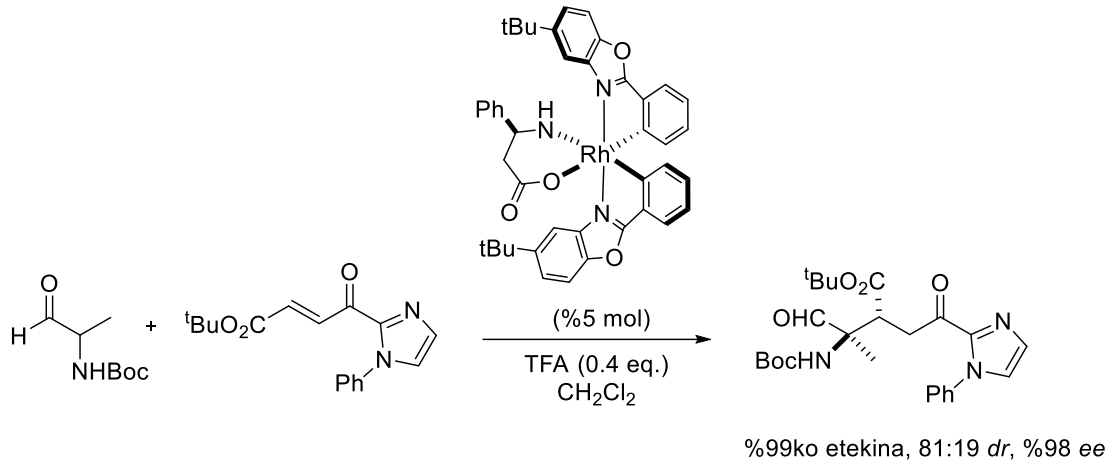
[117] Hainbat artikulu argitaratu dira non α-amino aldehidoak pronukleozale bezala erabiltzen diren adibide bakarra deskribatzen den: a) Quintard, A.; Alexakis, A. *Chem. Commun.* **2010**, *46* (23), 4085–4087; b) Erref. 106c; c) Erref. 106d; d) Lang, S. B.; Locascio, T. M.; Tunge, J. A. *Org. Lett.* **2014**, *16* (16), 4308–4311; e) Song, L.; Gong, L.; Meggers, E. *Chem. Commun.* **2016**, *52* (49), 7699–7702.

[118] Guo, Z. L.; Xue, J. H.; Fu, L. N.; Zhang, S. E.; Guo, Q. X. *Org. Lett.* **2014**, *16* (24), 6472–6475.



24 Eskema. α-Amino aldehidoen adizio konjokatua 3 -indoilmetanoletara. ***Guo, 2014.***[118]

Aipatzekoa da ere Meggers-ek deskribatutako protokoloa, non trantsizio metal bat aminokatalizatzaile batekin elkarlanean erabiltzen den 2-azil imidazol α,β-asegabeetarako adizioa eragiteko (25 Eskema).[117e] Hala ere, kasu honetan α-amino aldehidoen adizioaren adibide bakarra argitaratu zuten eta, Guo-ren artikuluan gertatzen zen bezala (24 Eskema), α-metil ordezkatutako pronuklozaleetara mugatua dagoela dirudi. Honen arrazoia izan liteke, aurrez aipatu den bezala, alfa posizioan metilo baino handiagoak diren ordezkatzaileak edukitzeak erregioselektibitate arazoak ekar litzakelako (22 Eskema).

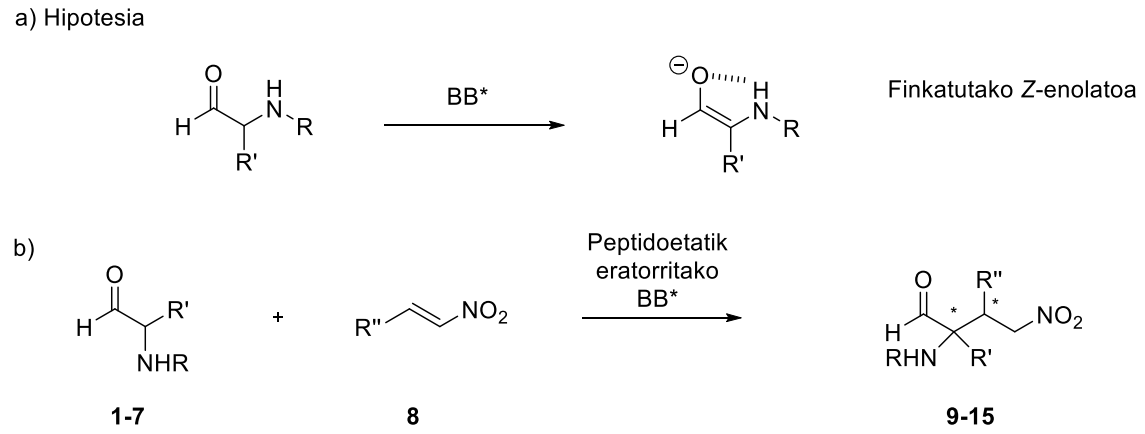


25 Eskema. Trantsizio metal/enamina bidezko N-Boc-glizinalaren eta 2-azil imidazol α,β-asegabe baten arteko Michael erreakzioa. ***Meggers, 2016.***[117e]

Beraz, aminokatalisi bidez eragindako α-amino aldehidoen α-funtzionalizazio estereoselektiboak oraindik ebatzi gabeko hainbat erronka aurkezten dituenez, BB estrategiak alternatiba osagarri moduan funtziona lezakela planteatu zen.

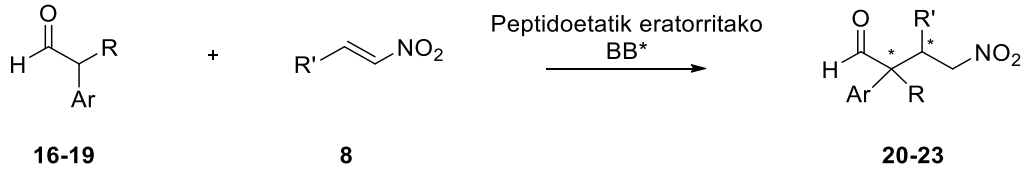
2.2. Helburuak

Kontutan hartuz enamina bidez eragindako α-amino aldehidoen α-funtzionalizazioan estereozentro kuaternarioen formakuntza erronka bat izaten jarraitzen duela, Tesi honen sarreran (6 Irudia) aurkeztutako peptidoetatik eratorritako BB katalizatzaile bifuntzionalek soluzio bat eskain zezaketela planteatu zen. Gainera, α-amino aldehido hauek NH-aren eta karboniloaren arteko molekulabarneko H-lotura bat sor zezaketela planteatu zen (26a Eskema). Elkarrekintzako honek, alde batetik, *Z*-enolatoa finkatuko luke, estereokontrola lagunduz, eta bestalde, α-karbonoaren azidotasuna handi lezake, aldehidoaren desprotonazioa erraztuz. Aurre ikerketetarako, α-amino aldehidoen nitroolefinetarako Michael adizioa aukeratu zen erreakzio-eredu moduan (26b Eskema), lortutako aduktuen interes sintetikoa dela medio.[87]



26 Eskema. a) Proposatutako molekulabarneko elkarrekintza, Z-enolatoa finkatuko lukeena. b) Aurre ikerketetarako aukeratutako α-amino aldehidoen eta nitroolefinen arteko Michael erreakzio eredua.

Gainera, ikerketa hau molekulabarneko H-lotura hori ez duten beste α-ordezkatutako aldehidoetara zabaltzea planteatu zen. Kasu honetan, α-aril azetaldehidoak aukeratu ziren hasierako ikerketetarako (27 Eskema), BB bidez katalizatutako erreakzio asimetrikoetan pronukleozale bezala ikertu ez baitira.



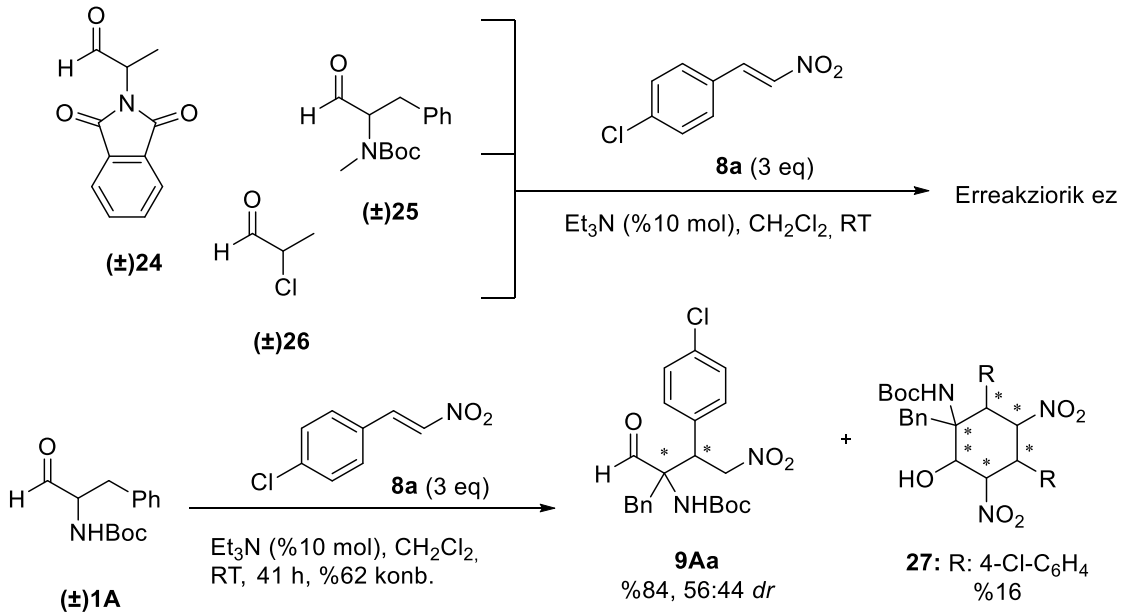
27 Eskema. α-Ordezkatutako α-aril azetaldehidoen Michael adizioa nitroolefinetara.

2.3. Emaitzak eta eztabaida

2.3.1. α-Amino aldehidoen Michael adizioak[119]

2.3.1.1. Hasierako behaketa esperimentalak

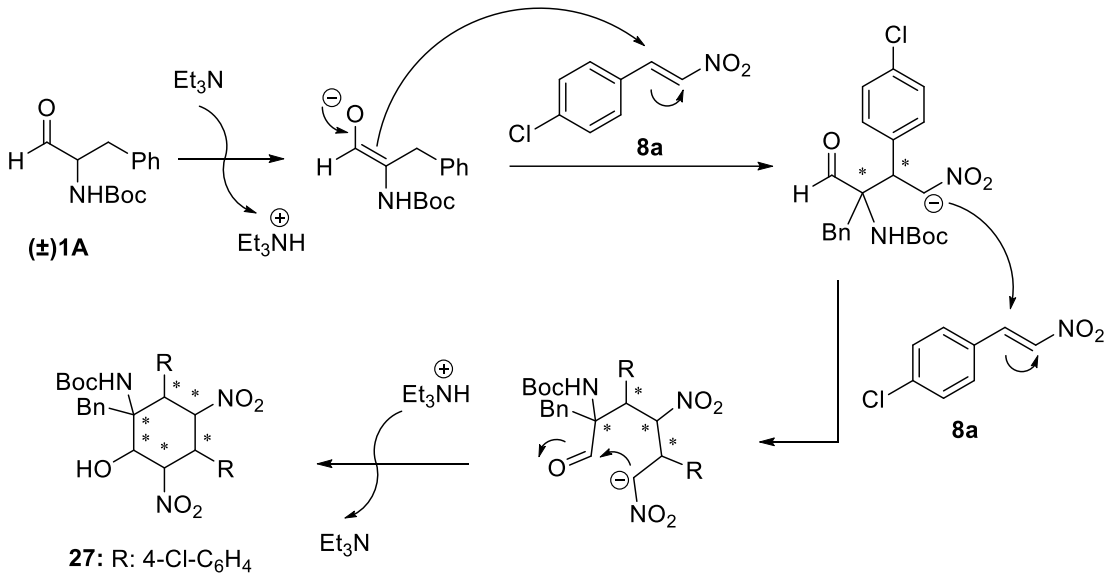
Hasiera batean, lau α-ordezkatutako amino aldehido adierazgarriren erreaktibotasuna esploratu zen, esaterako **24** (±)-*N*-ftaloil alaninal,[120] **25** (±)-*N*-metil-*N*-Boc fenilalaninal, **26** 2-kloropropanal eta **1A** (±)-*N*-Boc fenilalaninal aldehidoen eta **8a** *p*-kloro nitroestirenoaren arteko erreakzioa CH_2Cl_2-tan, giro tenperaturan eta Et_3N-ren presentzian (28 Eskema). Emaitzei begira, baldintza horietan **1A** (±)-*N*-Boc fenilalaninalak bakarrik erreakzionatzen duela ikus daiteke, 41 ordu ondoren aduktuaren %62ko konbertsioa lortuz, 56:44 *dr*-an, **27** produktu ziklikoaren %16-arekin batera. Azken produktu zikliko hau Michael-Michael-Henry tandem erreakzio batetik dator, non hasteko, desprotonatutako aldehidoak nitroolefina molekula bati gehitzen zaion, bitartekari anioniko bat osatuz, zeinak bigarren nitroolefina molekula batekin erreakzionatzen Michael adizio baten bidez, eta azkenik ziklohexiloa ixten da Henry erreakzio batekin (29 Eskema).



28 Eskema. Brønsted base akiralekin egindako aurre miaketak.

[119] García-Urricelqui, A.; de Cózar, A.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2021**, *27* (7), 2483–2492.

[120] Ftalimida aukeratu zen talde babesle moduan aminokatalizatutako aldehído lineak nukleozale moduan erabiltzen dituzten deskribatutako adibide gehienek (±)-*N*-ftaloil glicinal erabiltzen dutelako: a) Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6* (20), 3541–3544; b) Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. F. *Tetrahedron Lett.* **2007**, *48* (4), 693–696; c) Urushima, T.; Yasui, Y.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12* (13), 2966–2969; d) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2015**, *54* (48), 14363–14367.

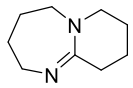
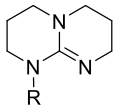
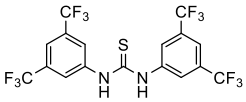
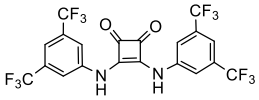


*29 Eskema. **27** Konposatu ziklikoaren sorrerarako proposatutako mekanismoa.*

Aipatzeko da **26**2-kloropropanalak ez zuela erreakzionatu BB-aren presentzian (28 Eskema), literaturan BB bidez katalizatutako α-kloro aldehidoen Michael adizio baten aurrekari bat existitzen bada ere (ikus 67. erreferentzia). Beraz, konfirma daiteke adibide horretan, erreakzioa bultzatzen duen indarra amaierako aduktuaren ziklazioa dela.

Behin adierazitako baldintzetan erreakzionatzen zuen aldehido bakarra **1A** (±)-*N*-Boc fenilalaninala zela ikusita, hurrengo urratsa basikotasun desberdineko BB-en presentzian erreakzioa ikertzea izan zen (1 Taula). Et_3N-ren presentzian baino konbertsio baxuagoa lortu zen DIPEA erabiltzerakoan (1 Taula, 2. sarrera), eta DBU, TBD eta MTBD bezalako base sendoagoekin nitroestirenoaren polimerizazioa besterik ez zen hauteman (1 Taula, 3. eta 4. sarrerak). Et_3N eta tiourea edo eskuaramida bezalako H-lotura emaileak konbinatzerakoan, lortutako konbertsioa handiagotu zen, eta bereziki, **27** produktu ziklikoaren sorrera ekidin zen (1 Taula, 5 eta 6 sarrerak). Aipatzekoa da, H-lotura emaileen presentzian ere ez zela ez **24** (±)-*N*-ftaloil alaninal eta ez **25** (±)-*N*-metil-*N*-Boc fenilalaninalaren erreakziorik detektatu, pronukleozaleak enolizazio baldintza ahuletan erreakzionatzeko NH askea izatea beharrezkoa dela frogatuz.

*1 Taula. BB akiralekin egindako ikerketak **1A** (±)-N-Boc fenilalaninal eta **8a** p-kloro nitroestirenoaren arteko erreakziorako. [a]*

Sarrera	Kat.	Basea (%mol)	T(ºC)	t(h)	Konb.[b] (%)	9Aa (*dr*)[c]	27a
1	Et_3N	20	RT	17	31	>95 (58:42)	<5
				41	62	84 (56:44)	16
2	$^{i}Pr_2EtN$	20	RT	41	21	>99 (44:56)	<5
3	 (DBU)	10	0	1.5	<5[d]	0	0
4	 R:Me, MTBD	10	RT	20	<5[d]	0	0
	R:H, TBD		0	22	<5[d]	0	0
5	Et_3N / 	20	RT	15	48	>99 (51:49)	<5
6	Et_3N / 	20	RT	15	69	>95 (45:55)	<5

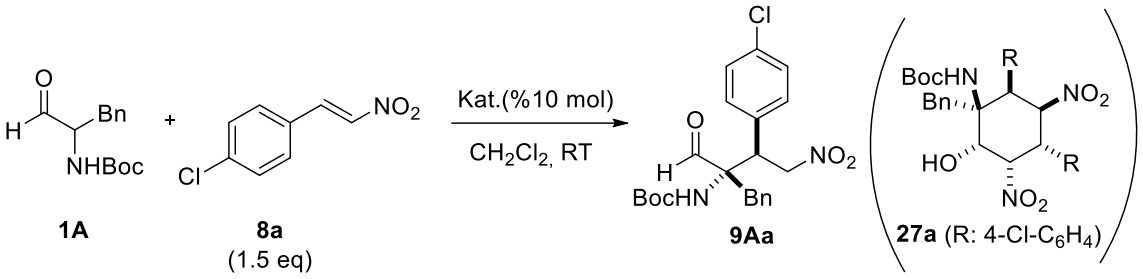
[a] Erreakzioak 0.1 mmol eskalan burutu ziren 0.3 mL CH_2Cl_2-tan (nitroolefina/aldehido mol ratioa 3:1). [b] Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. [c] ^{1}H-RMN analisiaren bidez zehaztua. [d] Polimerizatutako nitroestirenoa.

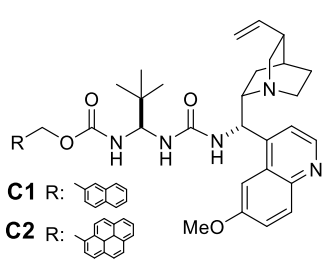
2.3.1.2. Katalizatzaileen azterketa eta erreakzio baldintzen optimizazioa

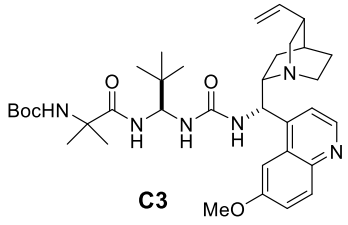
1 Taulako emaitzak aztertu eta gero, hurrengo helburua BB bat eta H-lotura emaile bat daramaten katalizatzaile kiralek α-amino aldehidoen eta nitroolefinen arteko erreakzio asimetrikoa eragin zezaketen ikertzea izan zen. Katalizatzaileen azterketarako **1A** (±)-*N*-Boc fenilalaninal eta **8a** *p*-kloro nitroestirenoaren arteko erreakzioa hartu zen eredutzat (30 Eskema, 2 Taula). Erreakzioak giro tenperaturan (RT) burutu ziren, 1:1.5 aldehido/nitroolefina proportzioan eta katalizatzaileen %10-en presentzian.

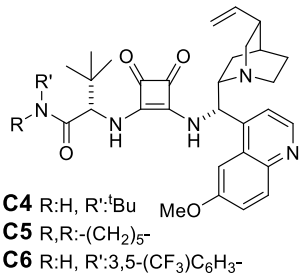
Hasteko, gure ikerketa taldeak aurretik diseintatutako[53] ureidopeptido motako **C1**, **C2** eta **C3** katalizatzaileak probatu ziren (2 Taula, 1-3 sarrerak) eta **9Aa** Michael aduktuaren eta **27a** produktu ziklikoaren arteko nahasteak hauteman ziren, proportzio aldakorretan (**27a**-ren %2-61), baina **9Aa** aduktua diastereoselektibitate baxuan eta ia enantioselektibitaterik gabe lortu zen kasu guztietan. Beraz, urea unitatea H-lotura emaile azidoagoak[121] dituen eskuaramida unitate batekin ordezkatzea erabaki zen, estereokontrola hobetzeko intentzioarekin. Horretarako, *tert*-Leuzina eta amina terminal desberdinak daramatzaten **C4**-**C7** katalizatzaileak sintetizatu eta erreakzioan probatu ziren. Katalizatzaile berri guztien presentzian *anti*-aduktua hauteman zen produktu nagusi bezala, Masamune-ren nomenklatura jarraituz.[122] Gainera, *dr* balioak ureidopeptido motako katalizatzaileen presentzian baino nabarmenki altuagoak izan ziren kasu guztietan eta **27a** albo produktuaren askoz proportzio baxuagoa hauteman zen (2 Taula, 4-7 sarrerak). Estereoselektibitatearen aldetik, **C6** eta **C7** katalizatzaileak izan ziren eraginkorrenak, baina kontutan hartuz bigarrenaren presentzian erreakzioa azkarrago bukatu zela, amina terminal hori kontsideratu zen aproposena. **C7**-ren antzekoa den baina amina terminala metilatua duen **C8**-rekin egindako esperimentuek NH taldea horrek estereokontrolerako duen garrantzia ezagutarazi zuten (2 Taula, 8. sarrera). Erreakzioa (*L*)-Fenilalanina eta (*L*)-Balina daramaten **C9** eta **C10** katalizatzaileen presentzian **C7**-rekin bezain diastereoselektiboa suertatu zen, baina lortutako enantiomero soberakinak ez ziren hain onak izan. Hare gehiago, erreakzio "matched" egoera (*L*)-*tert*-Leuzinaren eta kinidina deribatuaren konbinaketari dagokiola dirudi, (*D*)-*tert*-Leuzinatik eratorritako **C11** katalizatzaileak estereoselektibitate baxuagoa ematen baitu (2 Taula, 11. sarrera)

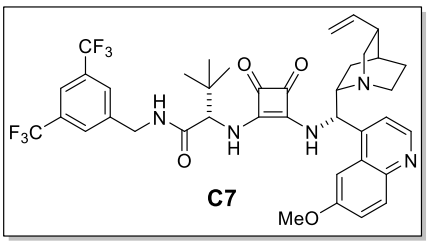
[121] Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16*, 1786–1789.
[122] Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521– 5523.

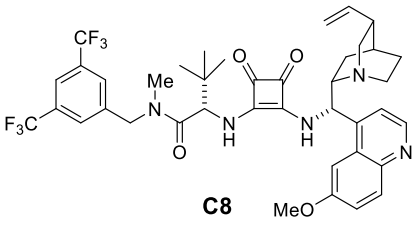


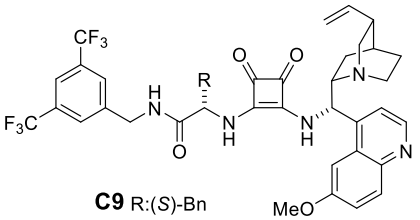


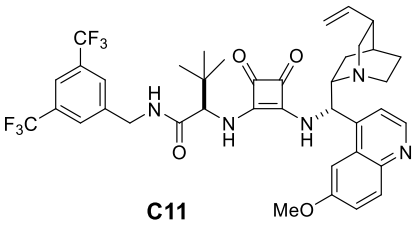


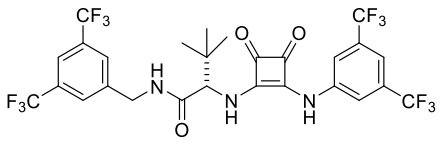


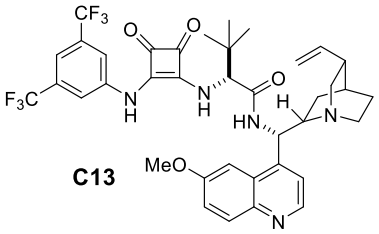


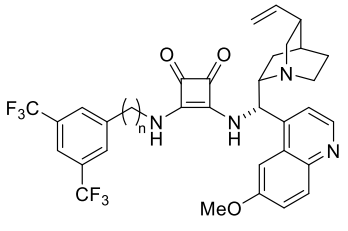


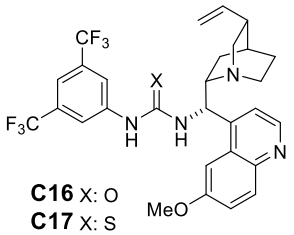












*30 Eskema. **1A** (±)-N-Boc fenilalaninal eta **8a** p-kloro nitroestirenoaren arteko erreakziorako aztertutako katalizatzaileak.*

*2 Taula. **1A** (±)-N-Boc fenilalaninal eta **8a** p-kloro nitroestirenoaren arteko erreakziorako katalizatzaileen azterketa.[a]*

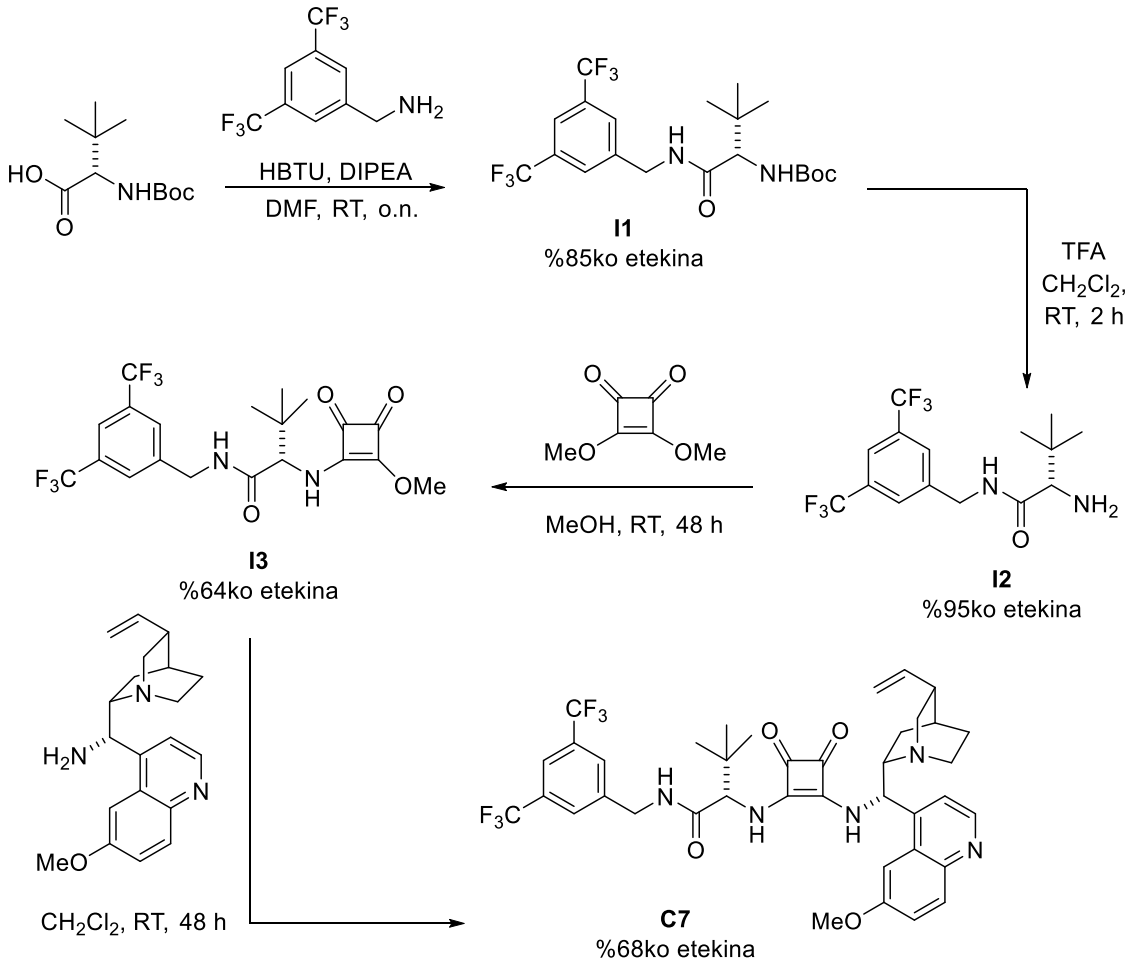
Sarrera	Kat.	T(ºC)	t(h)	Konb. (%)[b]	Etekina (%)[c]	*dr*[d]	*ee*[e]
1	**C1**	RT	63	88 (61)	nd	39:61	nd
2	**C2**	RT	39	29 (2)	nd	64:36	nd
3	**C3**	RT	39	71(40)	31	50:50	37
4	**C4**	RT	66	>99(17)	81	83:17	89
5	**C5**	RT	91	>99(5)	70	89:11	84
6	**C6**	RT	45	>99(8)	77	89:11	98
7	**C7**	RT	24	96(9)	91	90:10	98
8	**C8**	RT	23	97(2)	81	85:15	97
9	**C9**	RT	15	90(3)	70	82:18	91
10	**C10**	RT	24	88(12)	69	86:14	94
11	**C11**	RT	15	98(5)	72	86:14	90
12	**C12**	RT	15	0 [f]	0	--	--
13	**C13**[g]	RT	120	58(no)	33	70:30	25
14	**C14**[g]	RT	21	92(28)	55	68:32	81
15	**C15**	RT	16	68(no)	64	66:34	73
16	**C16**	RT	20	79(no)	62	48:52	nd
17	**C17**	RT	18	44(no)	nd	73:27	nd

[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). [b] Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Parentesi artean **27a** produktuaren ehunekoa, Michael aduktuaren eta bigarren nitroalkano molekula baten arteko Michael erreakzio gehi ziklazio batetik datorrena. [c] Isolatutako diastereoisomero nagusiaren etekina. [d] ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. [e] HPLC kiral bidez zehaztua. nd: ez zehaztua. no: ez behatua. [f] Et_3N %10 molen presentzian 3 h eta gero %26ko konbertsioa eta 57:43 *dr*. *i*Pr_2EtN %10 molen presentzian 1h eta gero %23ko konbertsioa eta 52:48 *dr.* [g] %20 mol katalizatzaile erabili zen.

Espero zen moduan, Brønsted base gabeko **C12** katalizatzaileak ez zuen erreakziorik sustatu, eta honen eta Et_3N-ren presentzian lortutako konbertsio eta diastereoselektibitatea ere baztergarriak izan ziren (2 Taula, 12. sarrera). Base baten presentzia ezinbestekoa izateaz gain, honek katalizatzailean duen posizioak ere garrantzia du erreakzioaren eraginkortasunerako, izan ere, basea eskuaramidaren ondoan ordez aminoazidoari lotuta daraman **C13** katalizatzailearen %20 molekin **9Aa** aduktua *dr* baxuagoan eta oso enantioselektibitate xumearekin lortu baitzen (2 Taula, 13. sarrera).

Ohiko eskuaramida, urea eta tiourea (**C14-C17**) desberdinen presentzian ere erreaktibotasun eta estereoselektibitate kaskarragoak hauteman ziren (2 Taula, 14-17 sarrerak). Ondorioz, **C7** aukeratu zen katalizatzaile egokiena bezala erreakzioaren beste substratuetarako hedapena ikertzeko.

C7 katalizatzaile berria erraz presta daiteke azpian irudikatutako prozedura sintetikoa jarraituz (31 Eskema). Hasteko, *N*-Boc-(*L*)-*tert*-Leuzina eta amina benzilikoa akoplatu egiten dira HBTU eta DIPEA-ren laguntzaz, **I1** bitartekaria %85-eko etekinarekin prestatuz. *N*-Boc taldea TFA-rekin desbabestu ondoren, **I2** amina askea dimetil eskuaratoarekin erreakzionarazten da MeOH-tan **I3** %64-ko etekinarekin lortuz. Azkenik, **I3**-ren eta kinidina deribatuaren arteko akoplamenduak **C7** katalizatzailea ematen du %68-ko etekinean.

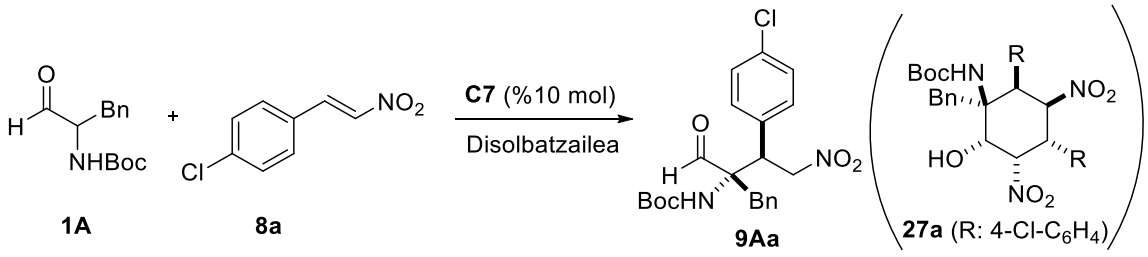


*31 Eskema. Beste substratuetarako erreakzioaren hedapena ikertzeko aukeratutako **C7** katalizatzailearen sintesia.*

Disolbatzaile desberdinetan egindako esperimentuek erakutsi zuten erreakzioaren estereoselektibitatea ia berdina dela diklorometano (3 Taula, 2. sarrera) ordez azetonitrilo edo 1,2-dikloroetano (1,2-DCE) erabiltzerakoan (3 Taula, 3 eta 6 sarrerak). Baina erreaktibotasunari dagokionez, antzeko polaritatea duten CH_2Cl_2 eta 1,2-DCE-tan

konbertsio ia totala 24 ordutan lortzen zen bitartean, polarragoa den azetonitrilotan erreakzio-denbora luzeagoak behar ziren. THF-tan ere erreakzioa mantsoagoa zen, antzeko estereoselektibitateak hauteman baziren ere (3 Taula, 4. sarrera). Toluenotan (erreakzioan probatutako disolbatzaile apolarrena) erreakzioa ez zen hain eraginkorra suertatu, **27** produktu ziklikoaren proportzio handiagoa lortzen zelako, eta estereoselektibitatea ere ez zen bikaina (3 Taula, 1. sarrera). Azkenik, erreakzioa kloroformotan burutzean ere *dr* balio baxuagoak lortu ziren eta erreakzioa mantsotu zen. Diklorotan, baina 0 ºC-tan, burututako erreakzioan produktu ziklikoaren proportzio gehiago hauteman zen ere (3 Taula, 7. sarrera).

*3 Taula. **1A** (±)-N-Boc fenilalaninal eta **8a** p-kloro nitroestirenoaren arteko Michael erreakziorako disolbatzaileen azterketa.[a]*



Sarrera	Disolbatzailea	Polaritate indizea[123]	T(ºC)	t(h)	Konb. (%)[b]	Etekina (%)[c]	*dr*[d]	*ee*[e]
1	**Toluenoa**	2.4	RT	40	92(16)	77	87:13	93
2	**CH_2Cl_2**	3.1	RT	24	96(9)	91	90:10	98
3	**1,2-DCE**	3.5	RT	24	95(12)	92	90:10	98
4	**THF**	4.0	RT	17	56(no)	31	89:11	98
5	**$CHCl_3$**	4.1	RT	40	89(12)	nd	83:17	nd
6	**CH_3CN**	5.8	RT	39	94(2)	81	90:10	98
7	**CH_2Cl_2**	3.1	0ªC	114	99(22)	67	83:17	96

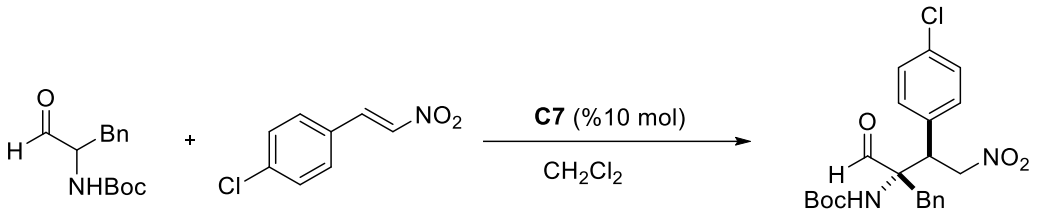
[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL disolbatzailetan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). [b] Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Parentesi artean **27a** produktuaren ehunekoa, Michael aduktuaren eta bigarren nitroalkano molekula baten arteko Michael adizio gehi ziklazio batetik datorrena .[c] Isolatutako diastereoisomero nagusiaren etekina. [d] ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. [e] HPLC kiral bidez zehaztua. nd: ez zehaztua. no: ez behatua.

Orain arte azaldutako esperimentu guztietan (±)-*N*-Boc fenilalaninal errazemikoa erabili zen. Erreakzio baldintza berdinetan **1A** (*S*)-*N*-Boc fenilalaninala erabiltzean, antzeko erreakzio-denbora behar izan zen **9Aa** aduktua estereoselektibitate berdinarekin

[123] Snyder, L. R. *J. Chromatogr. Sci.* **1978**, *16* (6), 223–234.

prestatzeko (4 Taula). Beraz, pronukleozale errazemiko ala enantiopuruak erabil daitezke erreakzioan eraginik izan gabe.

4 Taula. Nukleozale bezala (±)-N-Boc fenilalaninal vs (S)-N-Boc fenilalaninalen erabilera.[a]



1A **8a** **9Aa**

Sarrera	Nukleozalea	T(ºC)	t(h)	Konb. (%)[b]	Etekina (%)[c]	*dr*[d]	*ee*[e]
1	**(*S*)-1A**	RT	24	96(9)	91	90:10	98
2	***Rac*-1A**	RT	29	95(8)	61	90:10	97

[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). [b] Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Parentesi artean **27a** produktuaren ehunekoa, Michael aduktuaren eta bigarren nitroalkano molekula baten arteko Michael erreakzio gehi ziklazio batetik datorrena. [c] Isolatutako diastereoisomero nagusiaren etekina. [d] 1H-RMN analisiaren bidez erreakzio gordinean zehaztua. [e] HPLC kiral bidez zehaztua.

2.3.1.3. Erreakzioaren hedapena beste substratuetara

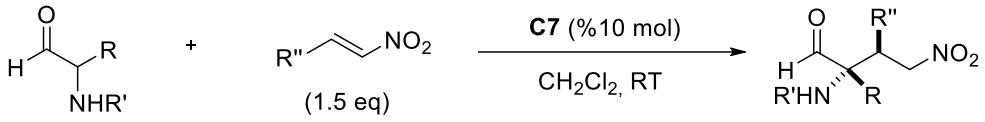
Ondoren, beste substratuetarako erreakzioaren hedapena ikertu zen, **C7** katalizatzailea erabilita eta optimizatutako baldintzetan (32 Eskema). Michael adizioak ordezkapen patroi desberdinak dituzten nitroestirenoak onartzen ditu, talde elektro-emaile nahiz elektroi-erakarleekin, ordezkatzaile hauek *orto*, *meta* ala *para* posizioak egonda ere estereoelektibitate balio bikainak lortuz (5 Taula, **9Ba**-**11Af** aduktuak). **11Af** eta **11Cf** aduktuen kasuan ere, non *orto*-ordekzatutako nitroestireno bat erabiltzen den, erreakzioak primeran funtzionatu zuen, katalizatzaile karga %20 molera igoz. Alkenil eta alkinil ordezkatzaileak dituzten nitrooefinak ere erabil daitezke, aduktuak antzeko estereoselektibitate balioetan eskuratuz (5 Taula, **11Ag** eta **13Ai** aduktuak). Hala ere, ziklohexil talde bat daraman **8h** nitroalkeno β-alifatikoarekin ez zen erreakziorik hauteman, **C7**-ren presentzian.

N-Boc, *N*-Fmoc eta *N*-Cbz bezala babestutako aldehidoak erabil daitezke *anti*-aduktuak estereoselektibitate bikainarekin lortuz kasu guztietan. Kasu batzuetan, *N*-Fmoc talde babeslea erabiltzeak erreakzioa azkartzea eragin zuen, *N*-Boc eta *N*-Cbz-rekin babestutako substratuekin konparatuz, esaterako, **9Ba** vs **9Ca** eta **14Ab** vs **14Cb** kasuetan.

Alfa posizioan erlatiboki handiak diren albo kateak (5 Taula, **11** eta **12** aduktuak) eta ordezkatutako eraztun aromatiko benzilikoak (**13** eta **15** aduktuak) dituzten α- amino aldehidoak erabil daitezke erreakziorako, estereoselektibitate balioak mantenduz. Funtzionalizatutako albo kateak dituzten aldehidoekin ere erreakzioak modu

eraginkorrean funtzionatzen du (5 Taula, **14Ab** eta **14Cb** aduktuak). Michael adizio honen muga bat alfa posizioan esterikoki oso eragotziak diren ordezkatzaileak dituzten aldehidoen erabilera dirudi, hala nola, *N*-babestutako *tert*-leucinal eta balinal pronukleozaleak, zeinek ez zuten erreaktibotasunik erakutsi optimizatutako erreakzio baldintzetan, erabilitako talde babeslea edozein dela ere.

Orokorrean, aldehidoen 0.2 mmol erabiliz burutu dira Michael adizioak, baina 1 mmoletara handi daiteke eskala, erreaktibotasun eta estereoselektibitate galerarik jasan gabe (Ikus Experimental Section).



1 R:Bn
2 R:Me
3 R:Pr
4 R:^{i}Bu
5 R:3,4-$(MeO)_2C_6H_3CH_2$-
6 R:$BnOCH_2$-
7 R:4-$MeOC_6H_4CH_2$-

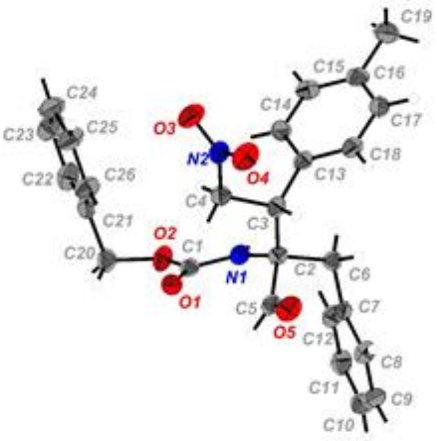
8a R": *p*-Cl-C_6H_4-
8b R": C_6H_5-
8c R": *p*-Me-C_6H_4-
8d R": *m*-MeO-C_6H_4-
8e R": *p*-Br-C_6H_4-
8f R": *o,p*-Me_2-C_6H_3-
8g R": Ph-CH=CH-
8h R": Cy
8i R": Ph−C≡C−

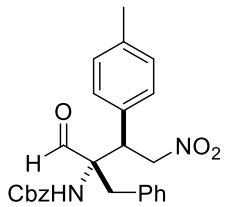
9 R:Bn
10 R:Me
11 R:Pr
12 R:^{i}Bu
13 R:3,4-$(MeO)_2C_6H_3CH_2$-
14 R:$BnOCH_2$-
15 R:4-$MeOC_6H_4CH_2$-

A R':Boc; **B** R':Cbz; **C** R':Fmoc

32 Eskema. ***C7****-rekin katalizatutako Michael adizioaren hedapena* ***1-7*** *α-amino aldehido eta* ***8*** *nitroolefinetara.*

9Bc aduktuaren konfigurazio erlatibo eta absolutua X-izpi analisi bidez zehaztu zen (7 Irudia)[119] eta gainerako aduktuentzako konfigurazio berdina onartu zen, erreakzio-mekanismo uniformean oinarrituz.

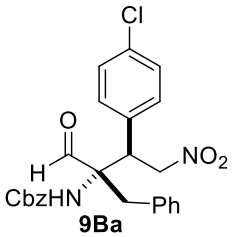
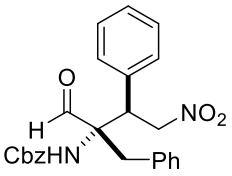
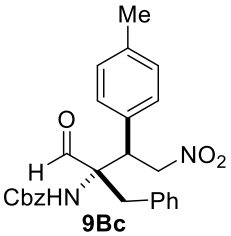
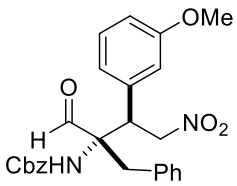
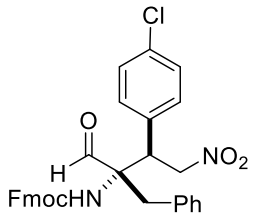
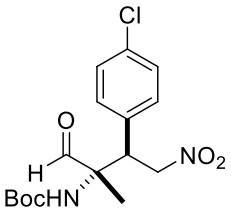
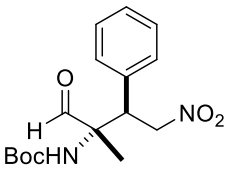
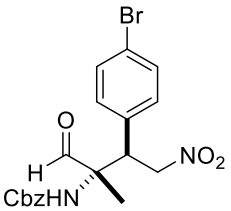
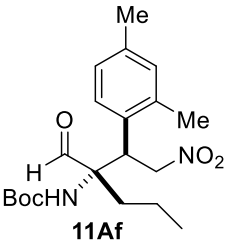
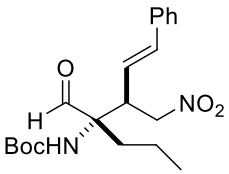
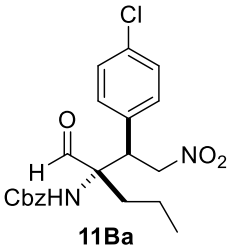
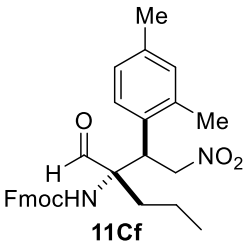
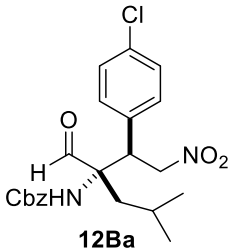
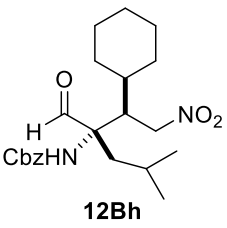
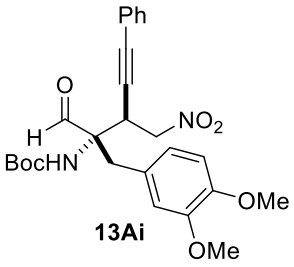
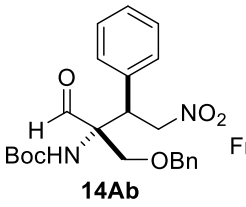
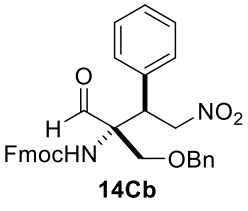
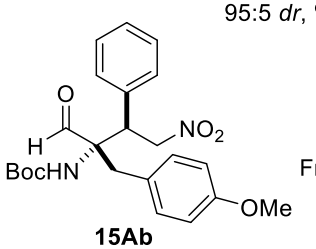
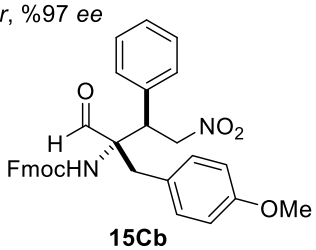




9Bc

7 Irudia. ***9Bc*** *aduktuaren ORTEP diagrama.*

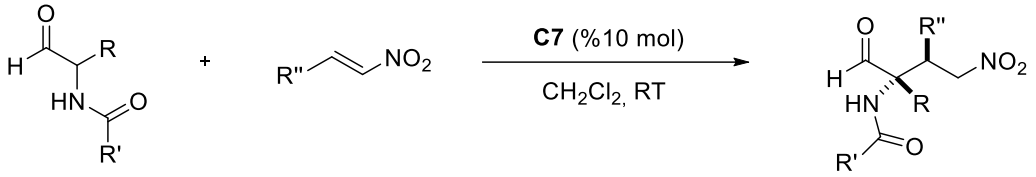
*5 Taula. **C7**-k katalizatutako Michael adizioaren hedapena **1-7** α-amino aldehido eta **8** nitroolefinetara.* [a]

 **9Ba**	 **9Bb**	 **9Bc**	 **9Bd**
39 h, %61eko etekina, 92:8 *dr*, %99 *ee*	39 h, %65eko etekina, 92:8 *dr*, %99 *ee*	24 h, %68ko etekina, 92:8 *dr*, %96 *ee*	24 h, %59ko etekina,[b] 91:9 *dr*, %97 *ee*
 **9Ca**	 **10Aa**	 **10Ab**	 **10Be**
23 h, %77ko etekina,[c] 96:4 *dr*, %99 *ee*	87 h, %59ko etekina,[b] 90:10 *dr*, %97 *ee*	63 h, %74ko etekina, 81:19 *dr*, %96 *ee*	15 h, %65eko etekina, 86:14 *dr*, %97 *ee*
 **11Af**	 **11Ag**	 **11Ba**	 **11Cf**
72 h, %80ko etekina,[d] 91:9 *dr*, %98 *ee*	44 h, %67ko etekina,[c] 88:12 *dr*, %97 *ee*	55 h, %65eko etekina, 96:4 *dr*, %98 *ee*	72 h, %80ko etekina,[d] 91:9 *dr*, %99 *ee*
 **12Ba**	 **12Bh**	 **13Ai**	
39 h, %61eko etekina, 95:5 *dr*, %97 *ee*	39 h, n.r.	87 h, %53ko etekina, 95:5 *dr*, %97 *ee*	
 **14Ab**	 **14Cb**	 **15Ab**	 **15Cb**
88 h, %56ko etekina, 89:11 *dr*, %97 *ee*	15 h, %72ko etekina, 99:1 *dr*, %99 *ee*	24 h, %80ko etekina, 88:12 *dr*, %97 *ee*	24 h, %78ko etekina, 95:5 *dr*, %>99 *ee*

[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Isolatutako diastereoisomero nagusiaren etekina ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. HPLC kiral bidez zehaztua. [b] Michael-Michael-Henry tandem erreakziotik datorren aduktuaren %5 baino gutxiago. [c] Isolatutako bi diastereoisomeroen etekina. [d] %20 mol katalizatzaile erabiliz burututako erreakzioa.

N-azil α-amino aldehidoak ere erabil daitezke nitroolefinetarako Michael adizioa burutzeko (6 Taula). *N*-azil talde aromatiko eta alifatiko desberdinak probatu dira, eta orokorrean, diastereoselektibitate oso on edo bikainak eta funtsean enantiomero bakarra lortuz. Salbuespen bakarra piridina eraztun bat duen **1D** amino aldehidoa suertatu zen, kasu horretan **9Dd** aduktua neurrizko *ee* baina *dr* baxuan lortu baitzen.

*6 Taula. **C7**-k katalizatutako Michael adizioaren hedapena N-azil ordezkatutako **1, 4** eta **7** α-amino aldehido eta **8** nitroolefinetara.* [a]

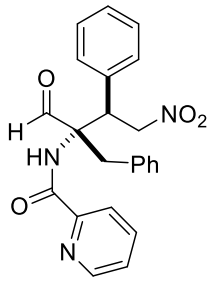


1 R:Bn
2 R:Me
3 R:Pr
4 R:^{i}Bu
5 R:3,4-$(MeO)_2C_6H_3CH_2$-
6 R:$BnOCH_2$-
7 R:4-$MeOC_6H_4CH_2$-

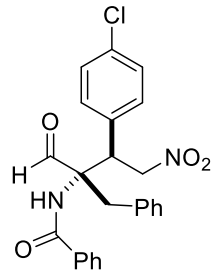
8a R'': *p*-Cl-C_6H_4-
8b R'': C_6H_5-
8c R'': *p*-Me-C_6H_4-
8d R'': *m*-MeO-C_6H_4-
8j R'': 2-Naf

9 R:Bn
10 R:Me
11 R:Pr
12 R:^{i}Bu
13 R:3,4-$(MeO)_2C_6H_3CH_2$-
14 R:$BnOCH_2$-
15 R:4-$MeOC_6H_4CH_2$-

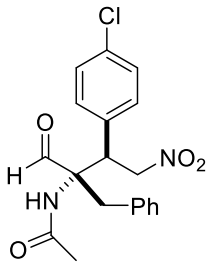
D R':2-piridil; **E** R':Ph; **F** R':2-MeC_6H_4; **G** R':4-BrC_6H_4; **H** R':PhCH=CH-; **I** R':CH_3



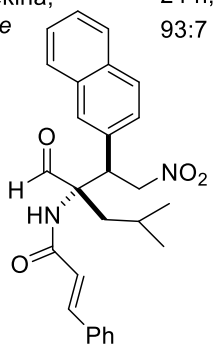
9Db
63 h, %40ko etekina,[b]
68:32 *dr*, %86 *ee*



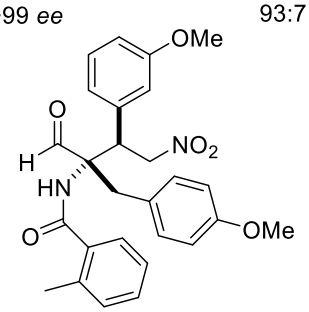
9Ea
24 h, %71eko etekina,[b,c]
93:7 *dr*, %>99 *ee*



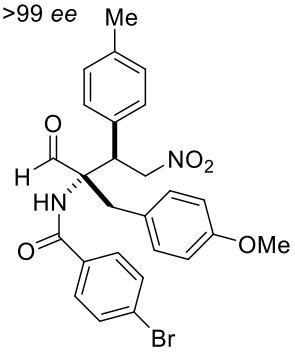
9Ia
40 h, %43ko etekina,
93:7 *dr*, %>99 *ee*



12Hk
64 h, %45eko etekina,
96:4 *dr*, >99% *ee*



15Fd
48 h, %77ko etekina,
85:15 *dr*, %99 *ee*



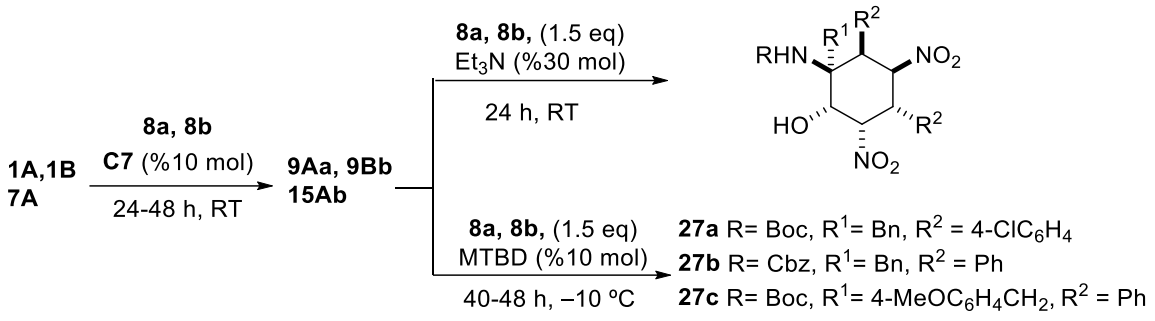
15Gc
82 h, %64ko etekina,
93:7 *dr*, %99 *ee*

[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Isolatutako diastereoisomero nagusiaren etekina ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. HPLC kiral bidez zehaztua. [b] Isolatutako bi diastereoisomeroen etekina. [c] Michael-Michael-Henry tandem erreakziotik datorren aduktuaren %5 baino gutxiago.

2.3.1.4. Aduktuen eraldaketak

Aurretik azaldutako erreakzioetan nitroolefinaren 1.5 baliokide erabili dira, baina, elektroizalearen baliokide kopurua 3-ra handituz eta kanpo base bat gehituz, aduktuak proiektuaren hasierako behaketetan hautemandako **27** ziklohexilaminetan bihur daitezkeela aurkitu zen (7 Taula). "One-pot" Michael-Michael-Henry tandem erreakzio batetik datozen eta estereozentro kuaternario bat duten guztiz ordezkatutako ziklohexilamina hauek bereziki interesgarriak dira, beste ibilbide sintetiko batetik prestatzea zaila izan daitekeelako. Hasteko, Michael aduktuak prestatzeko optimizatutako prozedura jarraitu zen, **9Aa**, **9Bb** eta **15Ab** aduktuak lortuz, eta konbertsio totala hauteman ondoren, nitroolefinaren 1.5 baliokide gehiago eta Et_3N (% 30 mol) gehitu ziren, **27a-c** produktu ziklikoak prestatzeko. Eraldaketa hau egiteko eraztun aromatiko desberdinetako nitroestirenoak erabil daitezke, hala nola, talde babeslean eta albo katea desberdineko aldehidoak, kasu guztietan antzeko *dr* eta etekinak lortuz (7 Taula).

*7 Taula. Guztiz ordezkatutako **27** ziklohexilaminen sintesia.* [a]



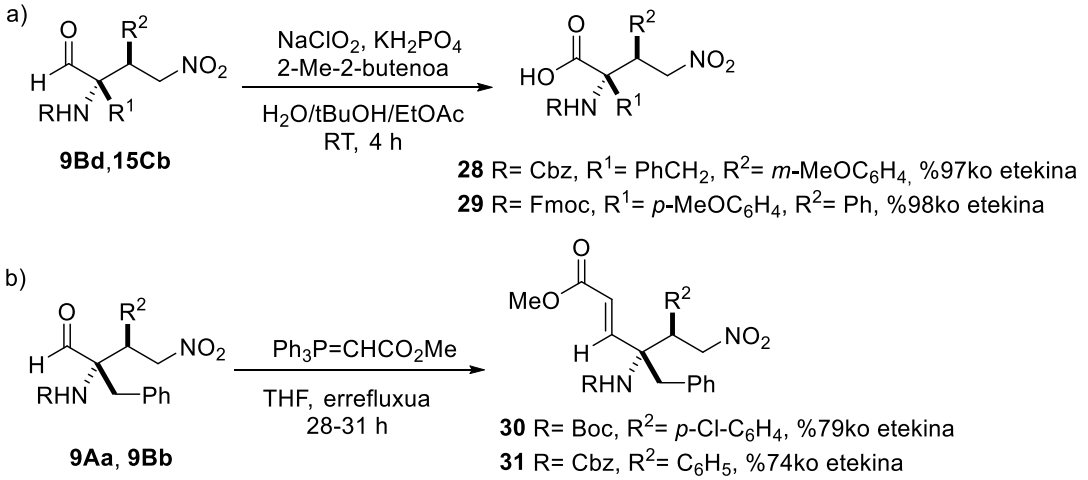
Sarrera	Basea	Aduktua	R	R^1	R^2	Etekina (%)[b]	*dr*[c]
1	**Et_3N**	**27a**	Boc	Bn	4-ClC_6H_4	67	56:44
		27b	Cbz	Bn	Ph	74	68:32
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	80	65:35
2	**MTBD**	**27a**	Boc	Bn	4-ClC_6H_4	81	85:15
		27b	Cbz	Bn	Ph	83	80:20
		27c	Boc	4-$MeOC_6H_4CH_2$	Ph	82	88:12

[a] Erreakzioak 0.5 mmol eskalan burutu ziren 1.5 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 1.5:1:0.1). [b] Bereizirik isolatutako bi isomeroen etekinen batura. [c] ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua.

Et_3N erabiltzean eta erreakzioa 0 ºC-tan burutzean, OH taldea daraman karbonoan epimero diren ziklohexilaminen bi diastereoisomeroak ia proportzio berdinean hauteman ziren (7 Taula, 1. sarrera), baina erreakzio baldintzak optimizatzea lortu zen base bezala MTBD erabiliz eta tenperatura -10 ºC-tara jaitsiz. Kasu honetan, nahiz eta denbora gehiago behar izan erreakzioa amaitzeko, *dr*-a nabarmenki hobetu zen (7 Taula, 2.

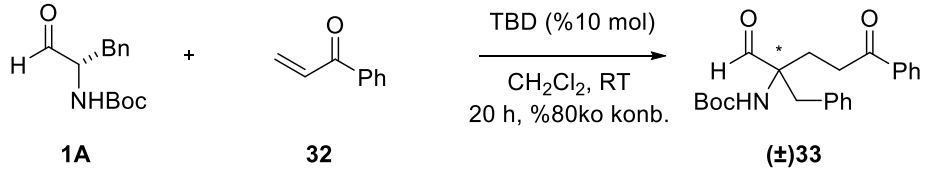
sarrera). **27** produktuen estereozentro bakoitzaren konfigurazioa NOESY esperimentuen bidez zehaztu zen, lehenengo Michael adiziotik datozen bi estereozentroak oinarritzat hartuz (Ikus Experimental Section).

Aurretik prestatutako Michael aduktuak tetraordezkatutako α-aminoazidoetan ere bihur daitezke, 33 Eskeman agertzen diren erreakzio kondizio oxidatzaileetan. Adibide bezala, **9Bd** eta **15Cb** aduktuetatik hasita **28** eta **29** aminoazidoak etekin bikainekin prestatu ziren (33a Eskema). Gainera, aldehidoaren karboniloan Wittig erreakzio bat burutu daiteke aldameneko bi estereozentro (tertziario eta kuaternario) dituzten funtzionalizazio maila handiko **30** eta **31** alilaminak etekin onetan lortuz (33b Eskema).



*33 Eskema. a) Tetraordezkatutako **28** eta **29** α-aminoazidoen sintesia aduktuak oxidatuz. b) Funtzionalizatutako **30** eta **31** alilaminen sintesia Wittig erreakzioaren bidez.*

α-Amino aldehidoek amina tertziarioak baino sendoagoak diren baseei dieten tolerantzia (Ikus 1 Taula) erabilgarria izan daiteke hain erreaktiboak ez diren elektroizaleekin erreakzionarazteko. Esaterako, **1A** α-amino aldehido eta **32** fenil binil zetonaren arteko erreakzioa burutu zen, katalizatzaile moduan TBD erabiliz, **(±)33** aduktu errazemikoaren %80ko konbertsioa lortuz, 20 h RT-n erreakzionatu ondoren (34 Eskema).

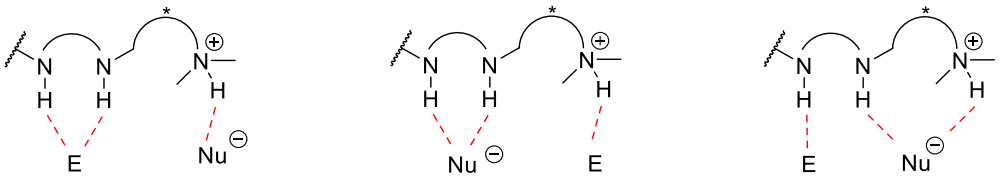


*34 Eskema. **1A** α-Amino aldehidoaren Michael adizioa **32** fenil binil zetonara.*

2.3.1.5. Mekanismoaren behaketak eta froga teorikoak

Erreakzioaren mekanismoa hobeto ulertzeko helburuarekin, DFT[124] kalkulu konputazionalak egin ziren, Dr. Abel de Cózar ikerlariarekin elkarlanean. Hasteko, **2A** eta **8b** substratuen arteko erreakzioa eredutzat hartuz, C-C loturaren sorrera urratsa ikertu zen, katalizatzailerik gabe (35 Eskema). Enolatoaren bi konfigurazio posible hartu ziren aintzat (*E*-enolatoa eta *Z*-enolatoa). Lortutako emaitzek proiektua hasi aurretik proposatutako pronukleozalearen molekulabarneko H-loturaren presentzia konfirmatu zuten, *Z*-enolatoa duten **TS1** eta **TS2**-an ikus daitekeena (*S,S*-**10Ab** eta *S,R*-**10Ab** aduktuetara daramatenak, hurrenez hurren). Bi trantsizio egoera hauek energetikoki hobetsita daude, *E*-enolatotik datozen eta molekulabarneko elkarrekintza hori ez duten **TS3** eta **TS4-**ekin alderatuz (*R,S*-**10Ab** eta *R,R*-**10Ab** aduktuetara daramatenak, hurrenez hurren). *Z*-enolatoa duten bi trantsizio egoeren artean, **TS1-**ek, non enolatoa nitroolefinaren *Si* aurpegitik hurbiltzen den, 0.7 kcal mol^{-1} gutxiago ditu **TS2**-k baino, zeinetan *Z*-enolatoa *Re* aurpegitik hurbiltzen den. Honek 76:24 *dr*-a aurresaten du katalizatzaile gabeko erreakziorako. Datu hau bat dator katalizatzaile akiral bat erabiliz burututako **2A** eta **8b**-ren arteko erreakziorako hautemandako 74:26 *dr*-arekin.

Erreakzio-mekanismoaren ikuspegi sakonago bat lortzeko, erreakzio berdinarentzako kalkuluak burutu ziren, baina **C7** katalizatzailearen presentzian. Ebatzi beharreko lehenengo zalantza C-C lotura sortzen den urratsean, konplexu erreaktiboan, katalizatzailearen eta substratuen arteko koordinazioak jarraitzen duen patroia da. Tesi honen sarreran azaldu bezala, **C7** bezalako BB katalizatzaile bifuntzionalekin eragindako erreakzioetarako hiru koordinazio patroi proposatuak izan dira (8 Irudia). Katalizatzailearen substratuen arteko elkarrekintzak Takemoto-ren eredua (A Eredua),[50,54] Pápai-ren eredua (B eredua)[55] ala Wang-en eredua (C eredua)[56] jarrai dezake.

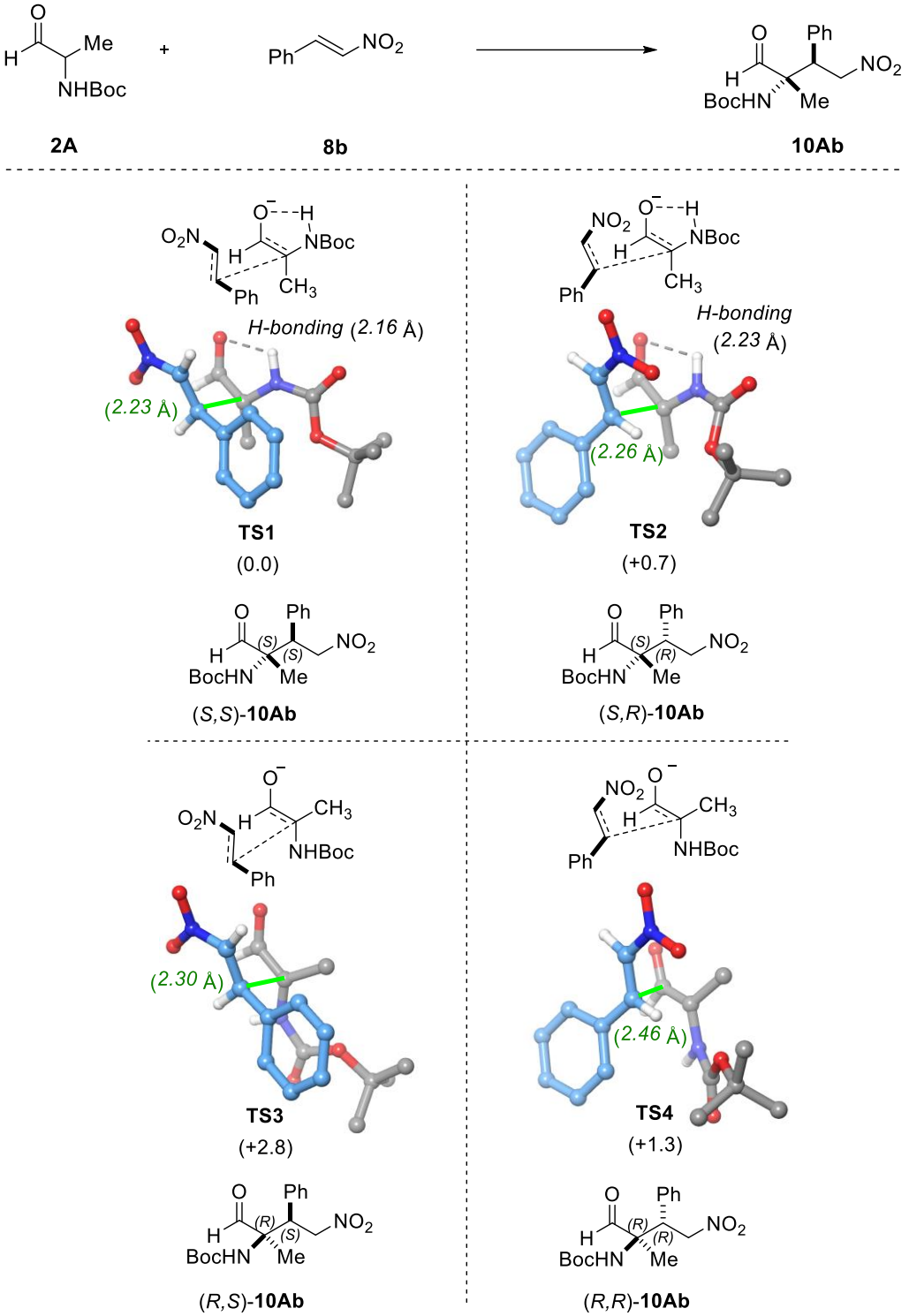


8 Irudia. BB bifuntzionalen bidezko aktibaziorako proposatutako hiru substratu-katalizatzaile koordinazio eredu posible.

Azpimarratzekoa da C eredua jarraitzen duten konplexu erreaktiboak kalkulatzeko saiakera guztiek A eredura zeramatela optimizazio urrats gutxi batzuen ondoren. Hortaz, erreakzio honetarako C eredua baztertu zen. Gainera, A eta B ereduak jarraitzen dituzten energia gutxieneko konplexu erreaktiboek energetikoki oso antzekoak direla aurkitu zen,

[124] Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford: New York, **1989**.

beraz, ikerketa honetarako Curtin-Hammett zinetika onartu zen, non produktuen proportzioa trantsizio egoera desberdinen arteko Gibbs-en aktibazio energia askeen arteko desberdintasunak markatzen duen.

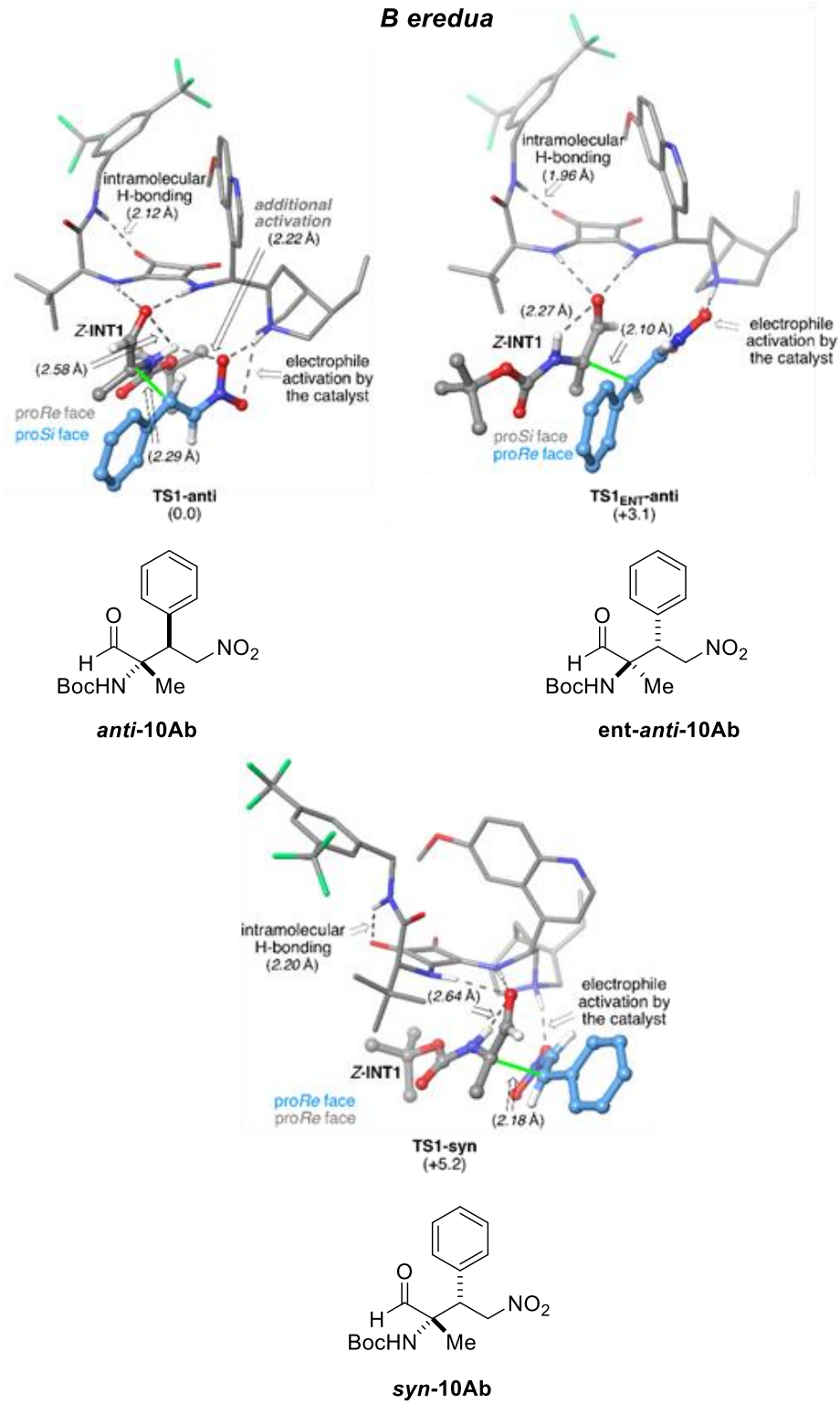


35 Eskema. ***2A*** *N-Boc-alaninal eta* ***8b*** *nitroestirenoaren arteko erreakzio ez-katalizatuarentzako konputazionalki kalkulatutako trantsizio egoera (TS) posibleak. B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K)-rekin kalkulatutako Gibbs-en energia aske erlatiboak, kcal mol^{-1}-etan. TS bakoitzaren azpian egoera horretan lortuko litzatekeen aduktua adierazten da.*

Trantsizio egoeretarako egindako kalkuluei dagokienez, **C7**-k katalizatutako **2A** eta **8b**-ren arteko erreakziorako energia gutxieneko TS egiturak eta haien Gibbs energia erlatiboak 9 Irudian agertzen dira, hala nola, TS bakoitzetik lortuko litzatekeen aduktua. Orokorrean, Takemotoren koordinazio eredua (A eredua) jarraitzen duten TS-ak enegetikoki gaitzetsiak daudenez, Pápai-ren eredua (B eredua) jarraitzen dutenak bakarrik kontsideratu ziren (9 Irudia). Nabarmentzekoa da **C7** katalizatzailearen amina terminalaren NH-aren eta eskuaramidaren karboniloetako baten arteko molekulabarneko H-lotura, katalizatzailearekin bakarrik egindako kalkuluetan ere hauteman zena. Kalkulatutako modelo guztietan, distantzien arteko ia aldaketarik gabe agertzen den elkarrekintza honek eskuaramida egituraren H-lotura emaile gaitasuna handitzen du eta katalizatzaileak hartzen duen konformazioa finkatzen du, *tert*-butil taldea aurpegi selektibitaterako estrategikoki kokatuz. H-lotura honen garrantziaren froga gehigarri bat da molekulabarneko elkarrekintza hau osatu ezin duten **C14** eta **C15** katalizatzaile komertzialekin **9Aa** aduktua estereoselektibitate baxuagoan lortzen dela.

Trantsizio egoera guztietan (9 Irudia) pseudo-eklipsatutako konformazio bat hauteman zen C-C lotura berria sortzeko orduan, esperimentalki ikusitako esterikoki eragotziagoak diren albo kateak dituzten aldehido pronukleozaleen erreaktibotasun falta azal dezakeena (*tert*-leucinal eta balinal).

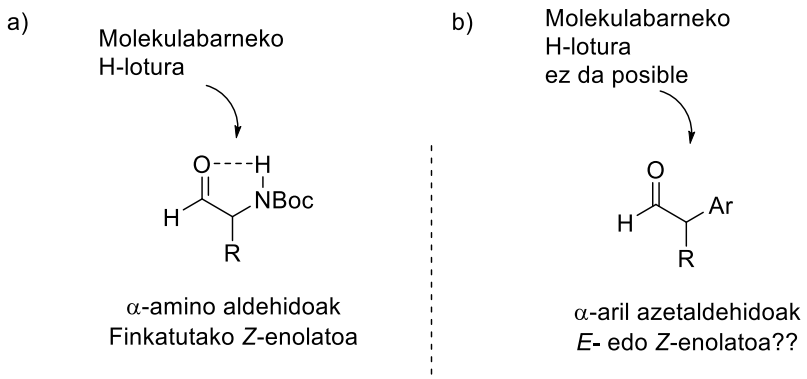
Katalizatzaile gabeko erreakzioarentzako egindako kalkuluetan ikusi zen bezala, **C7**-ren presentzian ere, energia gutxieneko **TS1**-ean, molekulabarneko H-lotura baten bidez finkatutako aldehidoaren *Z*-enolatoak hartzen du parte adizioan. ***anti*-10Ab** produktura daraman **TS1-anti**-ren eta *syn* diastereoisomerora daraman **TS1-syn**-en arteko Gibbs-en energia aske erlatiboen arteko desberdintasun nabaria (3 kcal mol^{-1} baino gehiago) esperimentalki lortutako diastereoselektibitate bikainekin bat dator. *Anti* aduktuaren enantioselektibitateari dagokionez, primerako emaitza esperimentalak **TS1-anti** eta **TS_{ENT}-anti** trantsizio egoeren arteko ΔG-en 5.2 kcal mol^{-1} desberdintasunarekin azal daitekeena, lehenengo trantsizio egoera izanik energetikoki hobetsia dagoena. 9 Irudiko hiru TS-en artean, energia gutxienekoa **TS1-anti** dela aurkitu zen, seguruenik TS honetan bakarrik osatzen den amino aldehidoaren NH taldearen eta nitroestirenoaren oxigenoetako baten arteko H-lotura gehigarriak egonkortzen duelako. Kalkulu konputazionalekin lortutako emaitzak bat datoz X-izpi analisiaren bidez zehaztutako *anti*-aduktuen konfigurazioarekin (7 Irudia).



9 Irudia. ***C7****-rekin katalizatutako* ***2A*** *nukleozalearen eta* ***8b*** *nitroestirenoaren arteko erreakziorako, Pápai-ren ereduaren (B eredua) arabera, energia gutxieneko trantsizio egoeren (TS) Gibbs-en energia aske erlatiboak eta ezaugarri geometriko nagusiak. Hidrogeno atomo batzuk ezkutatu dira irudia argiago ikusteko. Energia balioak (kcal mol^{-1}-etan) B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K)-rekin kalkulatu dira. TS bakoitzaren azpian egoera horretan lortuko litzatekeen aduktua adierazten da.*

2.3.2. α-Ordezkatutako aril azetaldehidoen Michael adizioak[125]

α-Amino aldehidoekin lortutako emaitza bikainak kontutan hartuta, ikerketa beste α-ordezkatutako aldehidoetara luzatzea kontsideratu zen. Amino aldehidoek osatzen duten molekulabarneko elkarrekintza hori ez duten aldehidoen adizioa familia berdineko katalizatzaileekin eragin zitekeen ikertu nahi izan zen, eta kasu horretan enolatoaren geometria zein izango litzatekeen aztertu (10 Irudia). Hortaz, hasiera batean, aurre ikerketentzako α-aril azetaldehidoak aukeratu ziren.



10 Irudia. a) Aurreko adizioetan ikertutako α-amino aldehidoak. b) Erreakzioaren hedapena ikertzeko proposatutako aldehidoak.

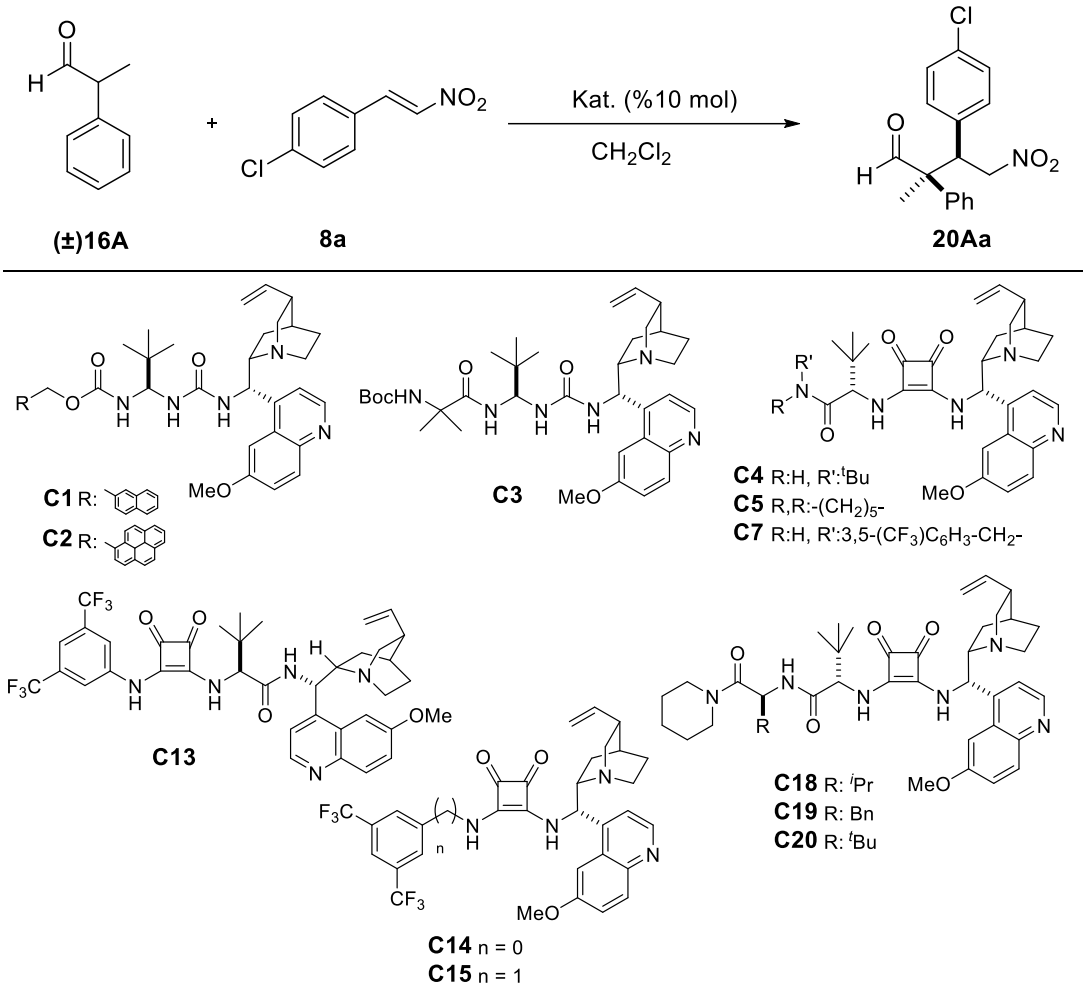
2.3.2.1. Hasierako behaketa esperimentalak eta katalizatzaileen azterketa

Azaldutako ideia horrekin, hasiera bateko ikerketak **16A** (±)-fenil propionaldehidoa nukleozale bezala eta **8a** nitroestirenoa elektroizale bezala erabiliz burutu ziren (36 Eskema). Hasteko, α-amino aldehidoen adiziorako ere probatutako ureidopeptido motako **C1**, **C2** eta **C3** katalizatzaileak erabili ziren erreakzioa sustatzeko, eta kasu hauetan, *syn* aduktua diastereoisomero proportzio onean baina *ee* balio xumeekin lortu zen (8 Taula, 1-3 sarrerak). Erreakzioak giro tenperaturan burutu ziren, 1:3 aldehido/nitroolefina proportzioan eta %10 mol katalizatzaile erabiliz. Nabarmentzekoa da ez zela ez Michael-Michael-Henry tandem erreakziotik eratorritako ziklorik ez homoaldolikaren produkturik hauteman adizio hauetan.

Jarraian, α-amino aldehidoentzako emaitzarik hoberenak eman zituen peptido laburretatik eratorritako **C7** eskuaramida probatu zen, hala nola, amina terminala aldatuz prestatutako **C4** eta **C5** katalizatzaileak (8 Taula, 4-6 sarrerak). Hauen artean, piperidina daraman **C5** katalizatzailearekin lortu ziren estereoselektibitate emaitza hoberenak, hau da, 90:10 *dr* eta %94 *ee.* Momentu horretan, diastereoselektibitatea optimizatzeko intentzioarekin, katalizatzaileen egituran bigarren aminoazido bat gehitzea erabaki zen, kate peptidikoa luzatuz. **C18**, **C19** eta **C20** prestatu ziren, Balina, Fenilalanina eta *tert*-

[125] García-Urricelqui, A.; de Cózar, A.; Campano, T. E.; Mielgo, A.; Palomo, C. *Eur. J. Org. Chem.* **2021**, *25*, 3604–3612.

Leuzina unitate berri bat daramatenak. **C18**-rekin amaierako produktua lortu zen, baina momentura arte eraginkorrena zen **C5**-ekin baino estereoselektibitate baxuagoan (8 Taula, 7. sarrera). Aldiz, **C19**-k **C5**-en antzeko diastereo- eta enantioselektibitatea sustatu zituen **20Aa** aduktuarentzat, eta azkenik, **C20**-ren presentzian *dr* balio hobea baina *ee* pixka bat baxuagoa lortu zen (8 Taula, 8-9 sarrerak). Tenperatura 0 ºC-tara jaitsiz, **C20**-k eskainitako emaitzak hobetu ziren, 95:5 *dr* eta %94 *ee* balioak eskuratuz (8 Taula, 10. sarrera). Basea eskuaramidaren ondoan ordez aminoazido unitateari atxikiturik duen **C13**-rekin burututako erreakzioak agerian utzi zuen katalizatzailearen atal bakoitzaren posizioaren garrantzia, enantioselektibitatea %74 arte jaitsi baitzen (8 Taula, 11. sarrera). Komertzialak diren **C14** eta **C15**-ren presentzian ere diastereoselektibitate emaitza eskasagoak lortu ziren (8 Taula, 12-13 sarrerak)



*36 Eskema. **16A** (±)-2-Fenil propionaldehidoaren eta **8a** p-kloro nitroestirenoaren arteko Michael erreakzioan aztertutako katalizatzaileak.*

8 Taula. ***16A*** *(±)-2-Fenil propionaldehidoaren eta* ***8a*** *p-kloro nitroestirenoaren arteko erreakziorako katalizatzaileen azterketa.*[a]

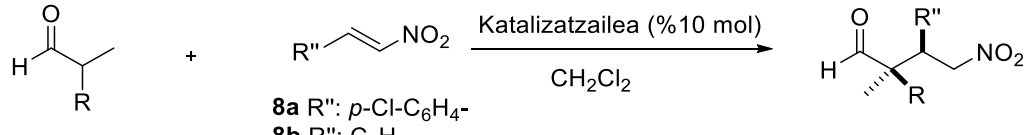
Sarrera	Kat.	T(ºC)	t(h)	Konb. (%)[b]	Etekina (%)[c]	*dr*[d]	*ee*[e]
1	**C1**	RT	29	92	69	83:17	47
2	**C2**	RT	13	74	68	85:15	-2
3	**C3**	RT	72	88	90	81:19	24
4	**C4**	RT	35	98	85	88:12	89
5	**C5**	RT	30	98	89	90:10	94
6	**C7**	RT	72	>99	91	86:14	84
7	**C18**	RT	15	>99	87	86:14	85
8	**C19**	RT	20	>99	92	88:12	93
9	**C20**	RT	10	98	82	91:9	88
10		0	15	85	84	95:5	94
11	**C13**	RT	15	88	78	92:8	74
12	**C14**	RT	23	93	74	84:16	96
13	**C15**	RT	40	98	71	86:14	96

[a] Erreakzioak 0.2 mmol eskalan burutu ziren 0.6 mL CH_2Cl_2-tan (nitroolefina/aldehido/katalizatzaile mol ratioa 3:1:0.1). [b] Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. [c] Isolatutako bi diastereoisomeroen etekina. [d] ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. [e] HPLC kiral bidez zehaztua.

2.3.2.2. Erreakzioaren hedapena beste substratuetara

Behin **C20** katalizatzaile eraginkorrena bezala aukeraturik, erreakzioan nukleozale eta elektroizale desberdinak probatu ziren, erreakzioren beste substratuetarako hedapena ikertzeko. Hasteko, **16A** (±)-fenil propionaldehidoaren Michael adizioak burutu ziren hainbat nitroolefinetara, **20Aa-20Am** aduktuak lortuz (9 Taula). Emaitzek erakusten dutenez, erreakzioak *para* (**8a**, **8c**, **8m**), *meta* (**8d**) eta *orto* (**8l**) ordezkatutako nitroestirenoak onartzen ditu, hala nola **8k** eta **8i** nitroalkeno alifatikoak, kasu guztienetan estereoselektibitate bikainak lortuz. Beste α-metil aril eta heteroaril azetaldehido desberdinak ere erabil daitezke, **21Aa**, **22Aa**, **22An** eta **23Ab** aduktuak primerako *dr* eta *ee* balioekin prestatuz.

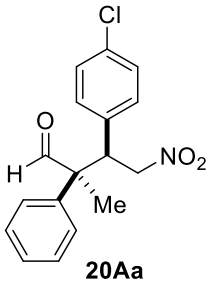
9 Taula. ***C20****-k katalizatutako erreakzioaren hedapena* ***16A-19A*** *α-metil (hetero)aril azetaldehidoetara.* [a]



16A R:Ph
17A R:4-MeOC$_6$H$_4$-
18A R:3-tiofeno
19A R:2-naftil

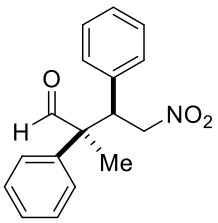
8a R": *p*-Cl-C$_6$H$_4$-
8b R": C$_6$H$_5$-
8c R": *p*-Me-C$_6$H$_4$-
8d R": *m*-MeO-C$_6$H$_4$-
8i R": Ph−C≡C−
8k R": C$_3$H$_7$-
8l R": *o*-Me-C$_6$H$_4$-
8m R": *p*-MeO-C$_6$H$_4$-
8n R": Ph-CH$_2$-CH$_2$-

20A R:Ph
21A R:4-MeOC$_6$H$_4$-
22A R:3-tiofeno
23A R:2-naftil



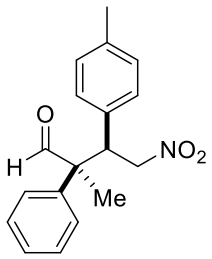
20Aa

15 h, %85eko konb., %84ko etekina, 95:5 *dr*, %94 *ee*



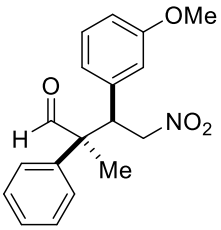
20Ab

27 h, %96ko konb., %83ko etekina, 94:6 *dr*, %96 *ee*



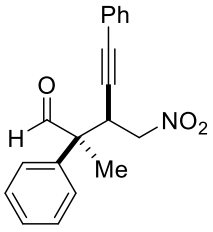
20Ac

23 h, %>99ko konb., %83ko etekina, 97:3 *dr*, %99 *ee*



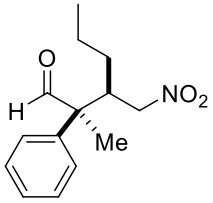
20Ad

23 h, %>99ko konb., %49ko etekina, 94:6 *dr*, %92 *ee*



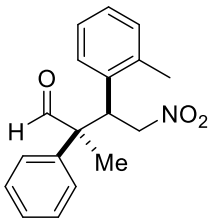
20Ai

22 h, %96ko konb., %72ko etekina, 90:10 *dr*, %96 *ee*



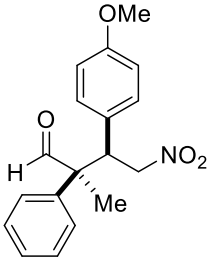
20Ak

69 h, %78ko konb., %57ko etekina, 96:4 *dr*, %99 *ee*[b]



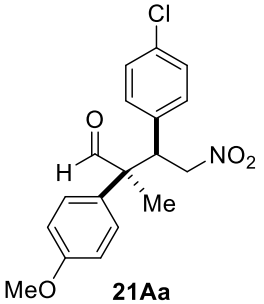
20Al

23 h, %92ko konb., %83ko etekina, 95:5 *dr*, %94 *ee*



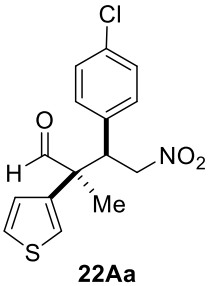
20Am

23 h, %95eko konb., %92ko etekina, 96:4 *dr*, %87 *ee*



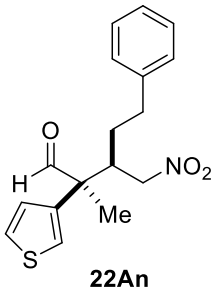
21Aa

47 h, %89ko konb., %74ko etekina,[c] 93:7 *dr*, %93 *ee*



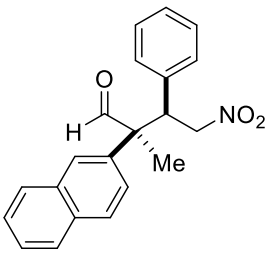
22Aa

16 h, %>99ko konb., %80ko etekina, 91:9 *dr*, %94 *ee*



22An

16 h, %97ko konb., %45eko etekina, 90:10 *dr*, %97 *ee*

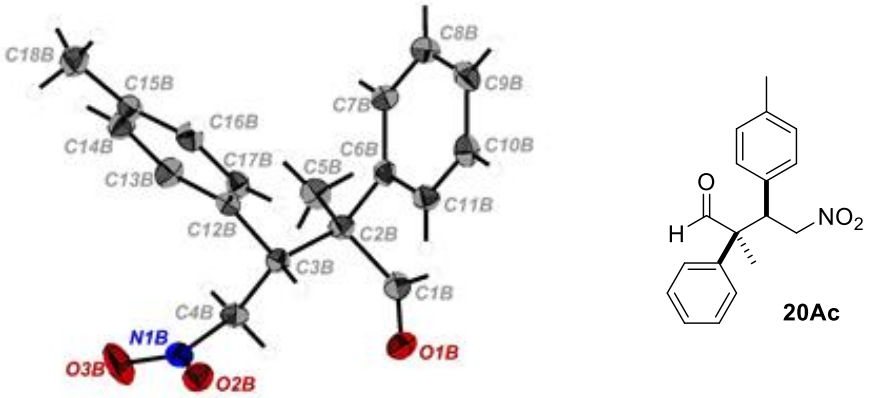


23Ab

16 h, %>99ko konb., %71eko etekina, 98:2 *dr*, %91 *ee*

[a] Erreakzioak 0 ºC-tan burutu ziren 0.2 mmol eskalan eta 0.6 mL CH_2Cl_2-tan (nitroolefina/ aldehido/katalizatzaile mol ratioa 3:1:0.1). Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Isolatutako diastereoisomero nagusiaren etekina. *dr*-a ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. Enantiomero soberakina HPLC kiral bidez zehaztua. [b] RT-n burututako erreakzioa. [c] Isolatutako bi diastereoisomeroen etekina.

20Ac aduktuaren konfigurazio erlatibo eta absolutua X-izpi analisi bidez zehaztu zen (11 Irudia)[125] eta gainerako aduktuentzako konfigurazio berdina onartu zen, erreakzio-mekanismo uniformean oinarrituz.



11 Irudia. ***20Ac*** *aduktuaren ORTEP diagrama.*

Orokorrean, hainbat H-lotura emaile[126] dituen dipeptidotik eratorritako **C20** katalizatzailea amino azido bakarra daraman **C5** baino eraginkorragoa suertatu zen, ez bakarrik esterokontrolari dagokionez, baina baita lortutako erreakzio konbertsioan ere. Hau kontutan hartuta, esperimentu zinetikoak burutu ziren **16A** (±)-fenil propionaldehidoaren eta **8a** nitroestirenoaren arteko erreakziorako, **C5** eta **C20**-ren presentzian (12 Irudia). Jasotako datuek **C20** katalizatzaile dipeptidikoarekin erreakzioa erlatiboki azkarrago funtzionatzen duela baieztatzen dute.

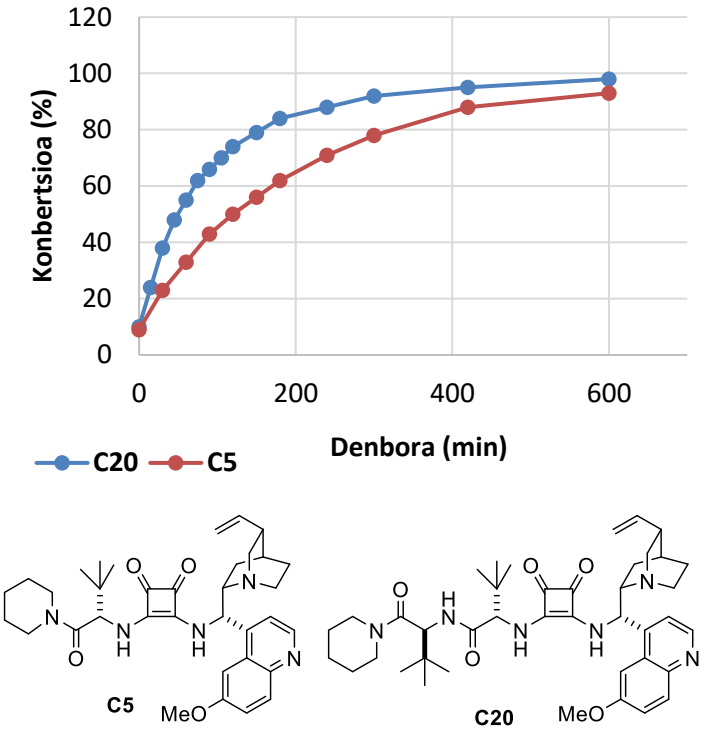
C20 eta **C5**-en artean hautemandako erreaktibotasun desberdintasun hau **16B** eta **16D** α-etil eta α-benzil azetaldehidoekin burututako erreakzioetan ere nabaria da (10 Taula). Dipeptidotik eratorritako katalizatzailearen presentzian **20Bb** aduktuaren %56-ko konbertsioa lortu zen 0 ºC-tan 67 orduz erreakzionatu eta gero. Aldiz, 112 ordu behar izan ziren **C5** erabiliz konbertsio berdina eskuratzeko. **20Dc** aduktuaren kasuan ere antzekoa gertatu zen, izan ere, **C20** erabiltzerakoan 142 h behar izan ziren %85-eko konbertsioa lortzeko, baina erreakzioa mantsoagoa izan zen **C5**-rekin.

Bestalde, erreakzioak alfa posizioan metilo ez diren beste albo kateak dituzten aldehidoekin ongi funtzionatzen duen arren, kasu hauetan estereokontrola erronka handiagoa da, eta orokorrean beherakada bat nabaritu zen erreaktibotasun eta estereoselektibitatean (10 Taula). Etilo eta alilo taldeak dituzten **20Bb** eta **20Cc** aduktuak diastereo- eta enantioselektibitate nahiko onekin lortu ziren, baina **16D** benzil azetaldehidoarekin eta **8c** nitroolefinarekin burututako erreakzioan **20Dc** aduktuaren diastereoisomeroen ia nahaste ekimolekularra eta enantiomero sobera apala hauteman ziren. Michael adizioa **18B** α-etil-3-tiofenil azetaldehidoarekin ere burutu daiteke eta α-

[126] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; b) Fanga, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

aril azetaldehido baliokidearekin baino azkarragoa da, baina neurrizko estereoselektibitatea eskuratu zen kasu honetan. Azkenik, azidoagoa den **19C** aldehidoa erabiliz **23Ca** aduktua nahiko *dr* onean baina enantioselektibitate baxuan eskuratu zen. Beraz, nahiz eta posible den BB katalizatzaileen bidezko aktibazio estrategia hau beste α-ordezkatutako aril azetaldehidoetara hedatu,[127] erreakzio balditzen optimizazioa beharrezkoa izango litzateke estereokontrola hobetzeko eta erreakzio-denborak murrizteko.

t (min)	Konbertsioa (%)	
	C20	C5
0	10	9
15	24	-
30	38	23
45	48	-
60	55	33
75	62	-
90	66	43
105	70	-
120	74	50
150	79	56
180	84	62
240	88	71
300	92	78
420	95	88
600	98	93



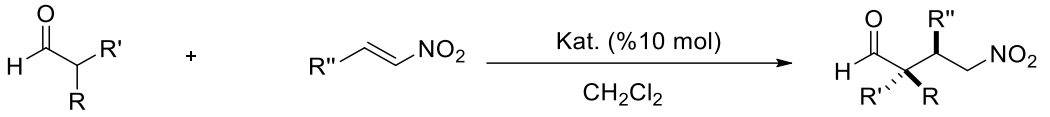
12 Irudia. ***C5*** *eta* ***C20*** *katalizatzaileen presentzian* ***16A*** *(±)-2-fenil propionaldehidoaren eta* ***8a*** *p-kloro nitroestirenoaren arteko erreakzioren eboluziorako burututako ikerketa zinetikoak.*

HPLC analisirako aduktu errazemikoak prestatzerakoan, Et_3N-rekin (%30 mol) katalizatutako **16A** aldehidoaren eta **8c** nitroolefinaren arteko erreakzioa RT-n burutzean, 16 ordu eta gero **rac-20Ab** aduktua 71:29 *dr*-an lortu zen (90:10 *dr* **C20** erabiliz). **C31** katalizatzaile kiralaren presentzian ere **22An** aduktua 76:24 *dr*-an eskuratu zen (90:10 *dr* **C20** erabiliz). Datu hauek kontutan harturik, erreakzio asimetrikoetan lortutako *syn* estereoselektibitatearen kontrola substratuaren eta katalizatzailearen eraginen konbinaketa bat dela pentsa daiteke. Hare gehiago, hasierako aldehido errazemikoen erresoluziorik ematen ez dela baieztatzeko, hasierako **17A** pronukleozalea 0 ºC-tan eta

[127] Difenilazetaldehido eta nitroestirenoaren arteko erreakzioa burutu zen 0 ºC-tan **C20** katalizatzailearen presentzian eta kasu honetan dagokion aduktua %76ko konbertsioan eskuratu zen 68 h ondoren, baina nahaste errazemikoan. **C15** eskuaramida erabiliz erreakzio berdinerako %30eko *ee* hauteman zen. Zehaztasun gehiagorako, ikus Experimental Section atala.

CH_2Cl_2-tan irabiatu zen 16 orduz **C20**-ren presentzian, eta ohiko tratamenduaren ondoren nahasketa errazemikoa berreskuratu zen.

*10 Taula. **C20**-k katalizatutako Michael erreakzioaren hedapena **16-19** α-ordezkatutako (hetero)aril azetaldehido eta **8** nitroestirenoetara.* [a]

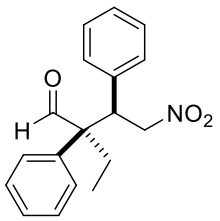


16 R:Ph
17 R:4-MeOC$_6$H$_4$-
18 R:3-tiofeno
19 R:2-naftil

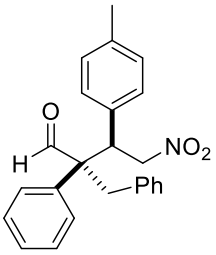
8a R'': *p*-Cl-C$_6$H$_4$-
8b R'': C$_6$H$_5$-
8c R'': *p*-Me-C$_6$H$_4$-

20 R:Ph
21 R:4-MeOC$_6$H$_4$-
22 R:3-tiofeno
23 R:2-naftil

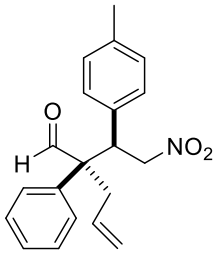
A R': Me; **B** R': Et; **C** R': Alilo; **D** R': Bn



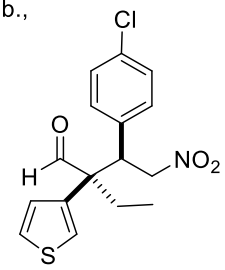
20Bb
C9: 67 h, %56ko konb., 160 h, %84ko konb., %61eko etekina, 83:17 *dr*, %78 *ee*
C6: 112 h, %56ko konb., %45eko etekina 84:16 *dr*, %87 *ee*



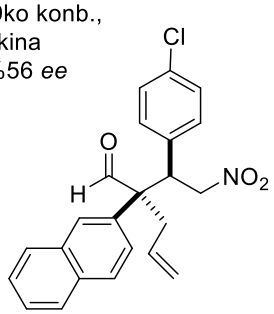
20Dc
C9: 142 h, %85eko konb., %45eko etekina 57:43 *dr*, %40 *ee*
C6: 192 h, %79ko konb., %59ko etekina 60:40 *dr*, %56 *ee*



20Cc
C9: 64 h, %72ko konb., %66ko etekina 85:15 *dr*, %77 *ee*



22Ba
C9:17 h, %47ko konb., %42ko etekina 55:45 *dr*, %69 *ee*



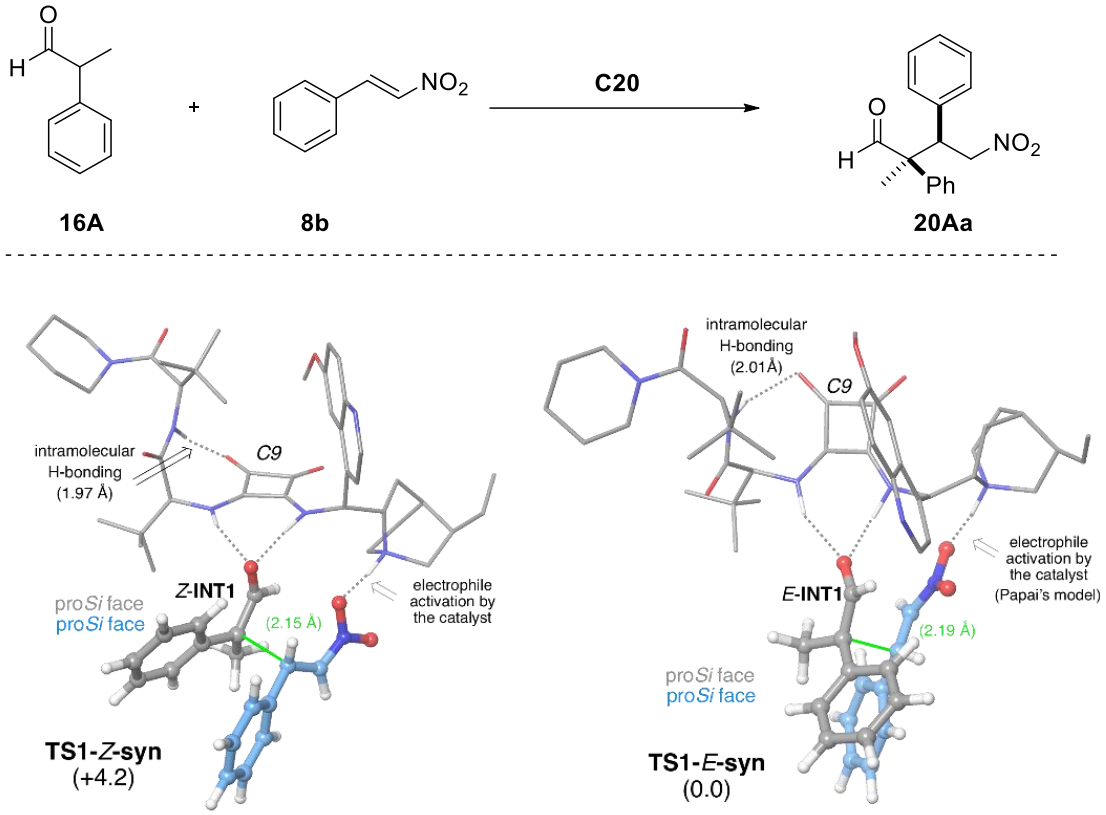
23Ca
C9: 64 h, %90eko konb., %68ko etekina 85:15 *dr*, %46 *ee*

[a] Erreakzioak 0 ºC-tan burutu ziren 0.2 mmol eskalan eta 0.6 mL CH_2Cl_2-tan (nitroolefina/ aldehido/katalizatzaile mol ratioa 3:1:0.1). Konbertsioa hasierako aldehidoaren desagerpenarekin zehaztu zen. Isolatutako bi diastereoisomeroen etekina. *dr*-a ^{1}H-RMN analisiaren bidez erreakzio gordinean zehaztua. Enantiomero soberakina HPLC kiral bidez zehaztua.

16A (±)-fenil propionaldehidoaren eta **8b** nitroestirenoaren arteko erreakzioa eskala handiagoan burutu daiteke, 4 mmol arte erabiliz, **20Ab** aduktua %82ko etekinean, 96:4 *dr* eta *syn* isomeroa %95eko *ee*-arekin lortuz. Esperimentu honetan, **C20** katalizatzailea %87ko etekinarekin berreskuratu zen.

2.3.2.3. Mekanismoaren behaketak eta froga teorikoak

Michael adizio katalitiko hauen mekanismoa hobeto ulertzeko helburuarekin Dr. Abel de Cózar gure lankideak DFT kalkuluak burutu zituen, **16A** (±)-fenil propionaldehidoaren eta **8b** nitroestirenoaren arteko erreakzioa eredutzat hartuz. Hasiera batean, A (Takemoto), B (Pápai) eta C (Wang) ereduak (8 Irudia) kalkulatu ziren, baina α-amino aldehidoen erreakziorako bezala, Wang-en eredua jarraitzen zuten saiakera guztiek A eredura zeramaten, eta beraz, C eredu hau albo batera utzi zen. Kasu honetan ere Curtin-Hammett zinetika onartu zen, non produktuen proportzioak trantsizio egoeren arteko Gibbs energia askeen desberdintasunak zehazten dituen.

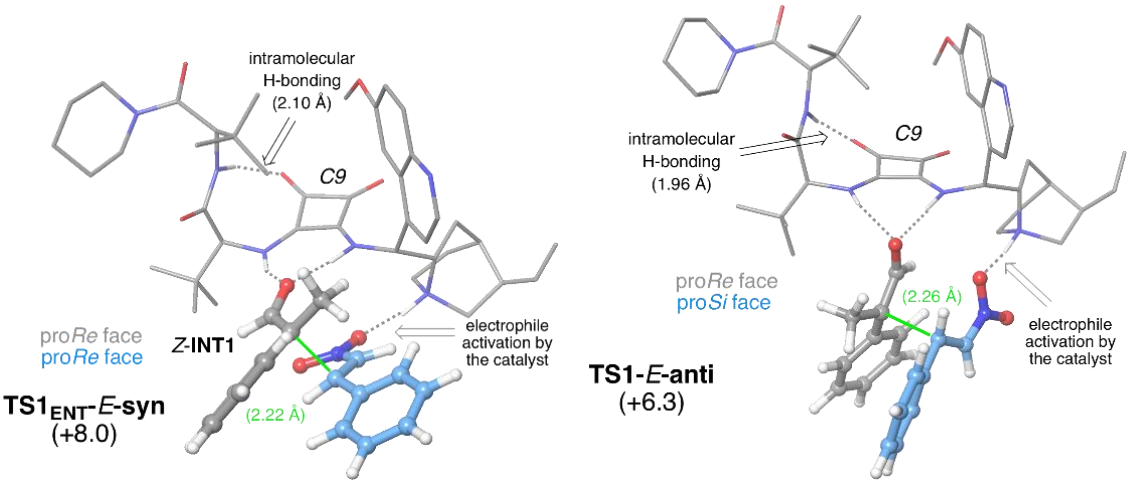


*37 Eskema. **C20**-rekin katalizatutako **16A** nukleozalearen eta **8b** nitroestirenoaren arteko erreakziorako, energia gutxieneko **TS1** trantsizio egoeren Gibbs-en energia aske erlatiboak eta ezaugarri geometriko nagusiak, **20Ab** aduktuaren E- eta Z-enolatoen formazioa kontutan hartuz. Hidrogeno atomo batzuk ezkutatu dira irudia argiago ikusteko. Energia balioak (kcal mol^{-1}-etan) B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K)-rekin kalkulatu dira. Aldehidoaren eta nitroalkenoaren aurpegi prokiral erreaktiboak grisez eta urdinez irudikatu dira, hurrenez hurren.*

Kalkuluen arabera, trantsizio egoera energetikoki egonkorrenak (**TS1**) Pápai-ren aktibazio eredua jarraitzen du, non protonatutako aminoa tertziarioa elektroizalearen nitro taldearekin koordinatzen den eta aldehidoaren karboniloak bi H-lotura osatzen dituen eskuaramidaren NH taldeekin. Enolatoaren konfigurazioari dagokionez, **TS1-*E*-syn** *Z*-enolatoa duen bere baliokidea baino 4.2 kcal/mol egonkorragoa da (37 Eskema),

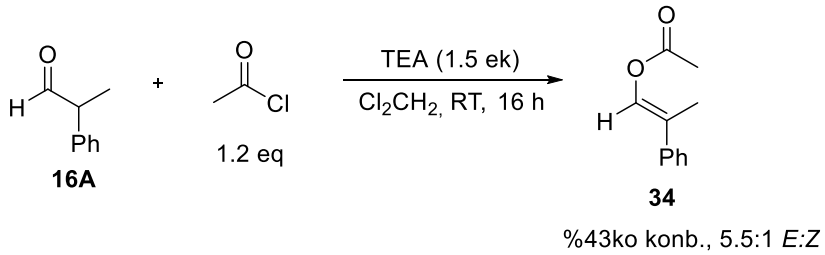
seguruenik aldehidoaren oxigeno eta fenil taldeek, eragozpen esterikoaren ondorioz, aldentzeko joera dutelako.

α-Amino aldehidoen erreakziorako **C7** katalizatzailean gertatzen zen bezala, **C20**-ean ere molekulabarneko hidrogeno lotura bat osatzen da eskuaramidaren karbonilo baten eta aminoazidoaren NH-aren artean. Elkarrekintza honek katalizatzailearen konformazioa finkatzen denez, **TS1$_{ENT}$-*E*-syn** eta **TS1-*E*-anti** egituretan katalizatzaile eta substratuen arteko interakzioak ez dira hain optimoak (13 Irudia). Horregatik, *syn*-**20Ab** aduktuaren sintesia dakarren **TS1-*E*-syn** da egoera energetikoki hobetsiena (37 Eskema). Kalkulu teorikoek aurresaten dituzten % 99ko *ee* eta >99:1 *dr*-a bat datoz esperimentalki lortutako datuekin.



13 Irudia. ***C20****-rekin katalizatutako* ***16A*** *nukleozalearen eta* ***8b*** *nitroestirenoaren arteko erreakziorako, energia gutxieneko TS1 trantsizio egoeren Gibbs-en energia aske erlatiboak eta ezaugarri geometriko nagusiak. Hidrogeno atomo batzuk ezkutatu dira irudia argiago ikusteko. Energia balioak (kcal mol^{-1}-etan) B3LYP-D3(PCM)/6-311+G(d,p)//B3LYP-D3/6-31G(d) level (298 K)-rekin kalkulatu dira. Aldehidoaren eta nitroalkenoaren aurpegi prokiral erreaktiboak grisez eta urdinez irudikatu dira, hurrenez hurren.*

Enolato egonkorrena isolatzeko burututako esperimentuak ere bat datoz DFT kalkuluekin. Izan ere, **16A** (±)-2 fenil propionaldehidoa trietilamina (1.5 eq) eta azetil kloruroaren (1.2 eq) presentzian 16 orduz irabiatzerakoan **34** produktuaren *E*/*Z* nahaste bat lortzen da 5.5:1 proportzioan (38 Eskema).



38 Eskema. ***34*** *E/Z enol azetatoen prestakuntza* ***16A*** *(±)-2 fenil propionaldehidotik hasita, trietilamina eta azetil kloruroaren presentzian*

Laburbilduz, α-amino eta α-aril aldehidoen nitroolefinetarako Michael adizioa modu eraginkor batean katalizatu da lehenengo aldiz Brønsted base bat erabiliz, zehazki, DFT kalkuluen bidez baieztatutako molekulabarneko H-lotura bat duen aminoazido batetik eratorritako eskuaramida katalizatzaile bat. α-Amino aldehidoak erabiltzerakoan *anti* aduktuak eskuratu dira, eta aldiz *syn* aduktuak α-aril α-metil azetaldehidoetatik hasita presta daitezke, bi kasuetan enantio- eta diastereoselektibitate bikainekin.

3. KAPITULUA

ONDORIOAK

3. Ondorioak

Peptido laburretatik eratorritako BB katalizatzaileen bi familia berri garatu dira Tesi honetan, bat eskuaramida unitate bata daramana eta bestea ureidoaminal unitatea duena, eta beraien eraginkortasun maila altua frogatu ahal izan da oraindaino erronkatzat har daitezkeen Michael motako erreakzioetan.

Alde batetik, α-ordezkatutako aldehidoak pronukleozale bezala lehenengo aldiz erabiliak izan dira modu arrakastatsuan BB bidez katalizatutako erreakzioetan. Bai α-amino aldehidoen, bai α-aril azetaldehidoen eta nitroolefinen arteko Michael errakzioa modu eraginkor batean burutu dira katalizatzaile moduan peptido laburretatikik eratorritako eskuaramida-BBak erabiliz. α-Amino aldehidoen kasuan, hauek *N*-Boc, *N*-Cbz, *N*-Fmoc eta *N*-azil bezala babestuak erabil daitezke modu eraginkorrean. Era berean, α-ordezkatzaile desberdinetako aldehidoak erabil daitezke erreakziorako, *tert*-butil edo *iso*-propil bezalako albo kate eragotziak izan ezik. Bestalde, ordezkapen patroi desberdinak dituzten nitroestirenoak eta alkenil eta alkinil ordezkatzaileak dituzten nitroolefinak erreakzioaren bateragarriak gertatu dira kasu guztietan, Michael aduktuak estereoselektibitate eta etekin bikainekin lortuz. Metodoaren erabilgarritasuna azaleratzearren, aduktu hauek tetraordezkatutako α-aminoazidoetan eta funtzionalizazio maila handiko alilaminetan bihurtu dira urrats sintetiko bakarrean. Azkenik, erreakzio aduktuetatik hasita “one-pot” Michael-Michael-Henry tandem erreakzio bat burutuz guztiz ordezkatutako estereozentro kuaternario bat duten ziklohexilaminak ere prestatu dira, 64 diastereoisomero posibleetatik bi bakarrik lortuz, oso proportzio eta etekin onean.

Ondoren, α-ordezkatutako aril azetaldehidoen eta nitroolefinen arteko erreakzio katalitikoa aztertu da peptido laburretatik eratorritako eskuaramida motako BB katalizatzaileak erabiliz eta ikusi, orokorrean, α-metil α-aril azetaldehidoetatik abiatuta prestatutako aduktuak oso etekin eta estereoselektibitate altuan lor daitezkeela, β-aril zein β-alkil ordezkatutako nitroolefinekin. Alfa posizioan metilo ez den beste ordezkatzaile handiagoak dituzten aril azetaldehidoen kasuan, erreakzio-denbora luzeagoak behar izan dira eta *dr* eta *ee* balio aldakorragoak lortu dira, ordezkatzailearen arabera.

Eraldaketa hauetarako burututako DFT kalkuluek erreakzioaren mekanismoa ulertzen lagundu dute eta bertan H-loturek erreaktibotasunean eta estereoselektibitatean duten papera, bai α-amino aldehidoetan baita peptido laburretatik eratorritako katalizatzaileetan ere.

Beste aldetik, aktibatu gabeko α-ordezkatutako nitroalkanoen eta α-hidroxi enonen arteko Michael adizioa ere peptido laburretatik eratorritako ureidopeptido motako BBak erabiliz kataliza daitekeela frogatu da lehen aldiz. Hiru amino azido arte dituzten katalizatzaileak aztertu dira erreakzioan, baina emaitza hoberenak amino azido

bakarretik eratorritako BB bifuntzionala erabiliz lortu dira. Kiralitate desberdinetako unitateak erabiliz osatutako katalizatzaileak alderatu dira eta ondoriozta daiteke “matched” egoera (*L*)-*tert*-Leuzinaren eta kinidina deribatuaren konbinaketari dagokiola. Hare gehiago, kate peptidikoan kiralitatea izatea estereoselektibitatea induzitzeko ezinbestekoa dela ikusi da.

Alfa posizioan benzil edo 2-naftil bezalako ordezkatzaile handiagoak dituzten α-hidroxi enonak erabiliz enantioselektibitatea hobetzen dela hauteman da. Azkenik, α-hidroxi enonak Michael hartzaile egokiagoak suertatu diren arren, akrilato eta tioakrilato esterrak erabiliz egindako esperimentuek erakutsi dute metodo hau beste Michael hartzaile batzuetara ere zabal litekeela, katalizatzailean edo erreakzio baldintzetan moldaketa batzuk egitea beharrezkoa bada ere. Hala ere, α-hidroxi enonak bai erreaktibotasunari bai estereoselektibitateari dagokionez eraginkorragoak direla ikusi da, elektroizale hauen erabilgarritasuna berretsiz.