New Enantioselective Routes to Nitrogen Containing Compounds: Catalytic Asymmetric aza-Michael and aza-Henry Reactions.

Ph. D. Thesis

By

Rajkumar Halder

San Sebastián, 2006

Universidad del País Vasco Euskal Herriko Unibertsitatea

AUTORIZACION DEL/LA DIRECTOR/A DE TESIS

PARA SU PRESENTACION

Dr. Claudio Palomo Nicolau como Director/a de la Tesis Doctoral: "*New Enantioselective Routes to Nitrogen Containing Compounds: Catalytic Asymmetric aza-Michael and aza-Henry Reactions*" realizada en el Departamento/Instituto Química Orgánica I, Facultad de Química, Universidad del País Vasco, San Sebastián, por el Doctorando Don Rajkumar Halder autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En San Sebastián a 25 de octubre de 2006

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Universidad del País Vasco Euskal Herriko Unibertsitatea

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Dr. Mikel Oiarbide Garmendia como Director/a de la Tesis Doctoral: "*New Enantioselective Routes to Nitrogen Containing Compounds: Catalytic Asymmetric aza-Michael and aza-Henry Reactions"* realizada en el Departamento/Instituto Química Orgánica I, Facultad de Química, Universidad del País Vasco, San Sebastián, por el Doctorando Don Rajkumar Halder autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

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El Consejo del Departamento/Instituto de Química Orgánica I, Facultad de Química, Universidad del País Vasco, San Sebastián en reunión celebrada el día 25 de octubre de 2006 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: "*New Enantioselective Routes to Nitrogen Containing Compounds: Catalytic Asymmetric aza-Michael and aza-Henry Reactions*" dirigida por el/la Dr. Claudio Palomo y Dr. Mikel Oiarbide y presentada por Don Rajkumar Halder ante este Departamento/Instituto.

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ACTA DE GRADO DE DOCTOR

ACTA DE DEFENSA DE TESIS DOCTORAL

DOCTORANDO DON Rajkumar Halder

TITULO DE LA TESIS "*New Enantioselective Routes to Nitrogen Containing Compounds: Catalytic Asymmetric aza-Michael and aza-Henry Reactions*". El Tribunal designado por la Subcomisión de Doctorado de la UPV/EHU para calificar la Tesis Doctoral arriba indicada y reunido en el día de la fecha, una vez efectuada la defensa por el doctorando y contestadas las objeciones y/o sugerencias que se le han formulado, ha otorgado por_____la calificación de:

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Fdo.: Rajkumar Halder

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Ph. D. Thesis

By

Rajkumar Halder

Director: Prof. Dr. Claudio Palomo

Codirector: Prof. Dr. Mikel Oiarbide

Química Orgánica I
Universidad del País Vasco, San Sebastián,
Spain, 2006

Dedicated to My family

"When you look at yourself from a universal standpoint, something inside always reminds or informs you that there are bigger and better things to worry about".

Albert Einstein

Ackonwledgements

This thesis serves as documentation of my research work during the doctoral study, which has been made from April 2003 to May 2006 under the supervision of Professor Claudio Palomo and Professor Mikel Oiarbide in the Departamento de Química Orgánica–I of Universidad del Pais Vasco, San Sebastián, Spain. The study has been co-funded by Ministerio de Educacion y Ciencia (MEC), and Universidad del Pais Vasco, Spain.

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Rajkumar Halder
Sab Sebastian
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List of abbreviation:

app.	Approximately
Ar	Aryl group
aq.	Aqueous
AQN	Anthraquinone
BLA	Brønsted Acid–Assisted Chiral Lewis Acid
Boc	t-Butoxycarbonyl group
$(Boc)_2O$	di-tertbutylcabonylcarbonateanhydride
Bz	Benzoyl group
CAN	Cerium Ammonium Nitrate
Cat.	Catalyst
Cbz	Benzyloxycarbonyl group
Cp	Cyclopentadienyl group
m-CPBA	m-Chloroperbenzoic acid
CSR	Chemical Shift Reagent
de	diastereomeric excess
DET	Diethyl tatrate
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIPT	Diisopropyl tartrate
DMAP	4-*N*,*N*-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
ee	enantiomeric excess
equiv.	Equivalent
h	Hour (s)
HPLC	High-Performance Liquid Chromatography
IR	Infrared Spectroscopy
KHMDP	$KN(SiMe_3)_2$
L	Ligand
L*	chiral ligand
LDA	Lithium Diisopropylamide
M	Metal
Min	minute(s)

MS	Molecular sieves
Ms	Methanesulfonyl (mesyl group)
NME	*N*-Methylephedrine
NMR	Nuclear Magnetic Resonance
PG	Protecting group
PM3	Parametric model 3
PTC	Phase Transfer Catalyst
R*	Chiral alkyl group
Rf	Flow rate (TLC)
S/C	Substrate-to-Catalyst ratio
TEA	Triethylamine
TES	Triethylsilyl group
Tf	Trifuoromethanesulfonyl group
TMS	Trimethylsilyl group
Ts	Toluenesulfonyl (tosyl group)
Q	Quinine
QD	Quinidine

Index

1. General Introduction

General Introduction

Even before the understanding that carbon was tetravalent, the French physicist Biot established that certain organic compounds rotated the plane of polarization of light.[1] However, it was Pasteur who correlated this phenomenon with an asymmetric grouping of atoms within molecules[2] and realized that

> *"…The universe is dissymmetrical; if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality……Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, in their structure, in their external forms, function of cosmic dissymmetric…".*
>
> *Louis Pasteur*

Kekulé establishing that carbon has four valences[3] and van't Hoff[4] and Le Bel[5] arranging these valences in a tetrahedral fashion set the stage for one of the most profound features of organic molecules and their ability to exist in mirror-image forms. The implications of this fundamental feature of organic molecules are immense. Undoubtedly, the richness of the biological world would not exist without this structural feature. Indeed, the very existence of the biological world is likely to have become possible only because of its exquisite use of this phenomenon.

Chirality

Properties of molecules and molecular arrays depend on chirality. Molecular communication in biological systems emanates from this intrinsic structural feature. Optical and electronic materials exhibit their effects by highly ordered assemblies whose sense of ordering frequently derives from this feature. Bulk properties also derive from this phenomenon, and it is amply seen in the frequently enhanced properties of

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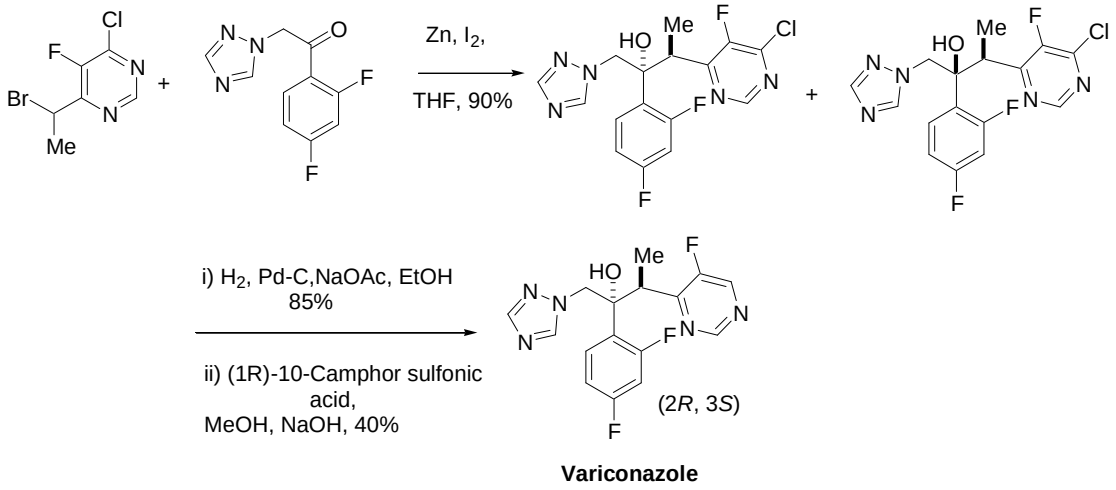
[1] (a) J. B. Biot, *Bull. Soc. Philomath. Paris*, **1815,** 190. (b) J. B. Biot, *Bull. Soc. Philomath. Paris*, **1816**, 125.
[2] G. M. Richardson, *The Foundation of Stereochemistry* (Am. Book Co., New York), Ed. **1901.**
[3] A. Kekule´, *Annals*, **1858,** *106*, 154.
[4] J. H. van't Hoff, *Bull. Soc. Chim. France* **1875**, *23*, 295.
[5] A. J. Le Bel, *Bull. Soc. Chim. France* **1874**, *22*, 337.

stereodefined macromolecules compared with stereo random polymers.[6] Despite this importance, the ability to obtain chiral molecules in enantiopure form remained extremely limited until recently.

Nature provided the richest source of such compounds, providing a limited catalog of enantiomerically pure compounds referred to as the ''chiral pool''.[7] Separating racemates,[8] a procedure introduced by Pasteur,[9] represents the most widespread industrially important method for production of enantiomerically pure products. This is exemplified by the synthesis of voriconazole, a fungistatic agent against *Candida* spp. and *Cryptococcus neoformans.* A diastereoselective Reformatsky reaction was employed to establish the relative stereochemistry followed by camphorsulfonic acid resolution to obtain enantiomerically pure voriconazole (Scheme 1).[10]



Scheme 1: *Synthesis of the enantiomerically pure drug, voriconazole by resolution.*

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[6] (a) G. Natta, *Makromol. Chem.* **1961,** *43*, 68–71. (b) G. Natta, L. Porri, S. Valenti, *Makromol.Chem.* **1963**, *67*, 225–228. (c) G. W. Coates, R. M. Waymouth, *J. Am. Chem. Soc.* **1993**, *115*, 91–98. (d) G. Natta, *Pure. Appl. Chem.* **1966**, *12*, 165–182. (e) G. Natta, *Science*, **1965**, *147*, 261–272. (f) H. H. Brintzinger, D. Fischer, R. Muelhaupt, B. Rieger, R. M. Waymouth, *Angew. Chem. Int. Ed.* **1995**, *34*, 1143–1170.

[7] For reviews; see: (a) S. Hanessian, *Pure Appl. Chem.* **1993**, *65*, 1189–1204. (b) S. Hanessian, J. Franco, B. Larouche, *Pure Appl. Chem.* **1990**, *62*, 1887–1910. (c) S. Hanessian, J. Franco, G. Gagnon, D. Laramee, B. Larouche, *J. Chem. Inf. Comput. Sci.* **1990**, *3*0, 413–425. (d) H. U. Blaser, *Chem. Rev.* **1992**, *92*, 935–952. (e) G. Casiraghi, F. Zanardi, G. Rassu, P. Span, *Chem. Rev.* **1995**, *95*, 1677–1716.

[8] (a) S. H. Wilen, *Top. Stereochem.* **1971**, *6*, 107–176. (b) S. H. Wilen, *Tables of Resolving Agents and Optical Resolutions* (Univ. Notre Dame Press, Notre Dame, IN). **1972**, (c) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions* (Wiley, New York), **1981.**

[9] (a) L. Pasteur, *Ann. Chim. Phys.* **1853**, *38*, 437. (b) L. Pasteur, *C. R. Acad. Sci.* **1853**, *37*, 162. (c) L. Pasteur, *C. R. Acad. Sci.* **1858**, *46*, 615. (e) A. Ladenburg, *Chem. Ber.* **1886**, *19*, 2578.

[10] M. Butters, J. Ebbs, S. P. Green, J. MacRae, M. C. Morland, C. W. Murtiashaw, A. J. Pettman, *Org. Process Res. Dev.*, **2001**, *5*, 28-36.

Because any racemate contains only 50% of the desired enantiomer, the theoretical yield of this strategy is limited to 50%, unless it is possible to convert the opposite enantiomer into the desired one either by a dynamic kinetic resolution or by an alternative synthesis. When a chiral centre is generated later in the synthesis within a more complex substrate it seems that few methods exist that are sufficiently straightforward to be operated economically.

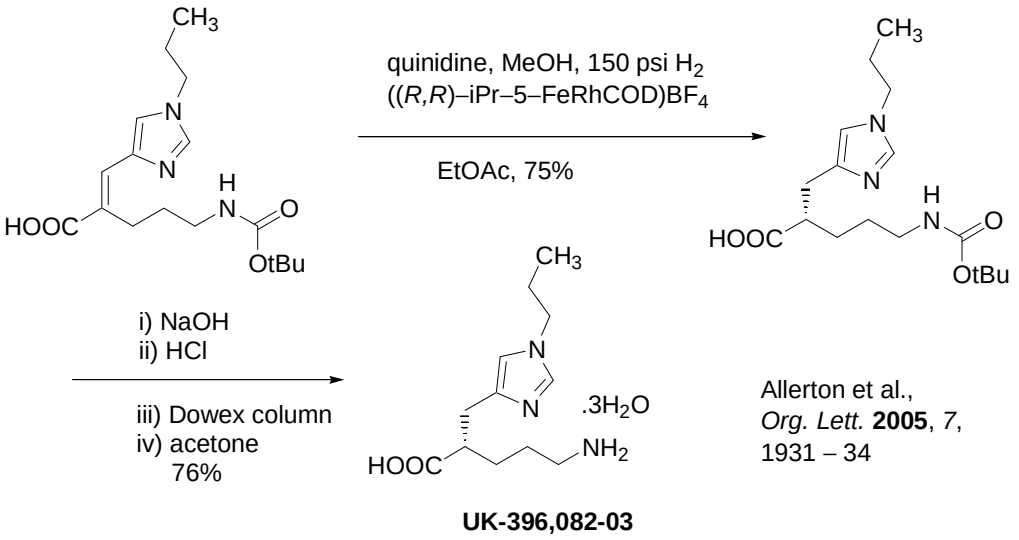
Asymmetric catalysis

The fact that nature already used such methods led to exploitation of nature's asymmetric synthetic machinery,[11] namely the enzymes. Purified enzymes like hydrolases and lipases, which do not require cofactors, have proven to be the most versatile.[12] Asymmetric chemical catalysts have the greatest potential for general asymmetric synthesis since virtually no constraints exist in terms of molecular design, except those imposed by the human designing them, or in terms of what reactions are potentially capable of being performed asymmetrically.[13] Perhaps the earliest example is the utilization of cinchona alkaloids as catalysts for cyanohydrin formation in 1912,[14] a type of catalysis recently dubbed ''organocatalysis''.[15] The use of metal complexes for asymmetric catalysis perhaps dates from efforts in the 1950s to effect asymmetric hydrogenation.[16] Several developments accelerated the growth of defined transition metal complexes for asymmetric catalysis. First, the ability to synthesize and characterize well defined transition metal complexes improved dramatically. Second, access to defined complexes set the stage for understanding the implication of structure for function, which has been got the development of defined transition metal complexes, typically hybrids of organic entities and transition metals, for chemical catalysis. Third, the ability for individuals to wed the understanding that arises by integrating theoretical and physical, organic, and inorganic chemistry with solving complex problems becomes

[11]For details, see: K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis* (Wiley-VCH, Weinheim, Germany), 2nd Ed. **2002**.
[12] (a) R. D. Schmid, R. Verger, *Angew. Chem. Int. Ed.* **1998**, *37*, 1609-1633. (b) Z. Boichem, K. Faber, *Biotransformations in Organic Chemistry*, Springer, Berlin, 4th Ed. **2000**, (c) R. J. Kazlauskas, U. T. Bornscheuer, *Hydrolases in Organic Chemistry*, Wiley-VCH, Weinheim, Germany, **1999**.
[13] (a) E. N. Jacobsen, A. Pflatz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Ed. (Springer, Berlin), **1999**. (b) I. Ojima, *Catalytic Asymmetric Synthesis*, Ed. Wiley-VCH, New York. **2000**.
[14] G. Bredig, P.S. Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7–23.
[15] Recent review: (a) P. I Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. (b) A.Berkessel, H. Groger, *Metal-Free Organic Catalysts in Asymmetric synthesis*, Wiley-VCH, Weinheim, **2004**.
[16](a) S Akabori, S. Sakurai, Y. Izumi, *Nature*, **1956**, *178*, 323-324. (b) Y. Izumi, *Adv. Catal*. **1983**, *32*, 215. (c) A. Tai, T. Harada, *in Thailand Metal Catalysts*, ed. Y. D. Iwasawa, Reidel, Dordrecht,The Netherlands, **1986**, pp. 265-285.

enabling. Probably, the most important strategy to introduce chirality involves the ability of a catalyst to differentiate the enantiotopic faces of a prochiral functional group, notably a π-unsaturation like a carbon–carbon, carbon–oxygen and carbon–nitrogen double bond.

Asymmetric reductions are far more common than oxidations. Catalytic hydrogenation represents the archetypical example involving such a mechanism.[17] In addition, such reactions are among the most important synthetic methods because of their broad scope and efficiency (i.e. selectivity and atom economy). The synthesis of UK396,082-03 which is an anti-thrombotic agent, shown in Scheme 2 is a good example of the use of asymmetric hydrogenation.[18]



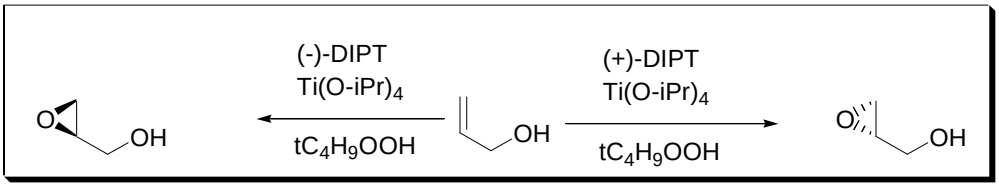
Scheme 2: *Synthesis of UK-396,082-03 by asymmetric hydrogenation.*

Apart from the catalytic hydrogenation, some oxidations such as dihydroxylation of olefins are among the best catalytic asymmetric transformations developed today. The successful asymmetric epoxidation combined a simple tartrate ligand with titanium

[17] See; (a) T. Ohkuma, M. Kitamura, R. Noyori, in *Catalytic Asymmetric Synthesis*, Ed. I. Ojima, Wiley-VCH, New York, **2000**, pp. 1-110. (b) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3069.

[18] C. M. N. Allerton, J. Blagg, M. E. Bunnage, J. Steele, W. O. Pat. Appl., 200214285; I. Appleby, L. T. Boulton, C. J. Cobley, C. Hill, M. L. Highes, P. D. de Koning, I. C. Lennon, C. Praqiuin, J. A. Ramsden, H. J. Samuel, N. Willis, *Org. Lett.* **2005**, *7*, 1931-1934.

(Sharpless asymmetric epoxidation)[19] and has led to early commercialization of both enantiomers of glycidol (Scheme 3), an important chiral building block.[20]



Scheme 3: *Asymmetric epoxidation of allylic alcohol.*

Other types of general organic transformations have been developed to a more limited extent in the context of catalytic and asymmetric versions. In a recent review[21] by principal researchers at three major pharmaceutical companies (Astra Zeneca, GlaxoSmithKline, Pfizer) chemical transformations are broadly classified into two types, constructive and modifying. The constructive categories are: acylations, aromatic heterocycle formation, C–C bond formation, heteroatom alkylation & arylation and some of the miscellaneous. As can be seen from Table 1 the breakdown for reactions that are involved in molecular construction is approximately 48%. The modifying transformations are: deprotection, functional group addition (FGA), functional group interconversion (FGI), oxidation, protection, reduction, resolution and some miscellaneous. From this study, it is concluded that C–C and C–N bond forming reactions are among key transformations (table 1). In the following, some aspects concerning C–C and C–N bond formation are disclosed as well as some previous work in the area developed in our group.

[19] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5974–5976.
[20] (a) J. M. Klunder, T. Onami, K. B. Sharpless, *J. Org. Chem*. **1989**, *54*, 1295–1304. (b) W. P. Shum, M. J. Cannarsa, *Chirality Ind*. **1997**, *2*, 363–380 and references therein.
[21] J. S. Carey, D. Laffan, C. Thomson, T. Williams, *Org. Biomol. Chem*. **2006**, *4*, 2337-2347.

Table 1: *Summary of the reaction categories most used in three pioneer drug companies (Astra Zeneca, GlaxoSmithKline and Pfizer).*

Reaction Category	Astra Zeneca	Glaxo-SmithKline	Pfizer	Total	Percentage of total reactions (%)
Heteroatom alkylation & arylation	87	57	52	196	19
Acylation[a]	41	37	50	128	12
C–C bond forming[a]	31	41	44	116	11
Aromatic heterocycle formation[a]	16	10	26	52	5
Deprotection[b]	54	56	49	159	15
Protection[b]	18	16	27	61	6
Reduction[b]	27	24	43	94	9
Oxidation[b]	17	7	16	40	4
Functional group interconversion[a]	43	34	27	104	10
Fuctional group addition[b]	13	8	12	33	3
Resolution[b]	14	8	8	30	3
Miscellaneous	10	12	4	26	3
Totals	371	310	358	1039	

[a]Reactions used for molecular construction. [b] Modifying reactions.

Asymmetric C-C Bond Formation

The formation of C–C bonds, the basic building blocks of molecules is the most important chemical process in the chemical sciences because of their manufacture of drug candidate molecules and natural product synthesis. This is also true for the biological and material sciences. The C–C bond formation is even more important with simultaneous creation of new stereogenic centers. Among the most fundamental carbon-carbon bond forming reactions are aldol, Mannich, Henry, aza-Henry, Diels-Alder, Michael addition, Suzuki coupling, Heck reaction and Friedel-Crafts reactions among others. To achieve the highest efficiency in catalytic processes in C–C bond formation, first concern is the design of optimum catalysts, either metallic or purely organic molecules. However, there are two additional directions for research: (a) finding the most appropriate reaction conditions (including additives) and (b) finding appropriate achiral templates as reaction substrates. Among the privileged catalysts[22] so far developed are those bearing the chiral ligands depicted below.

[22] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691-1693.

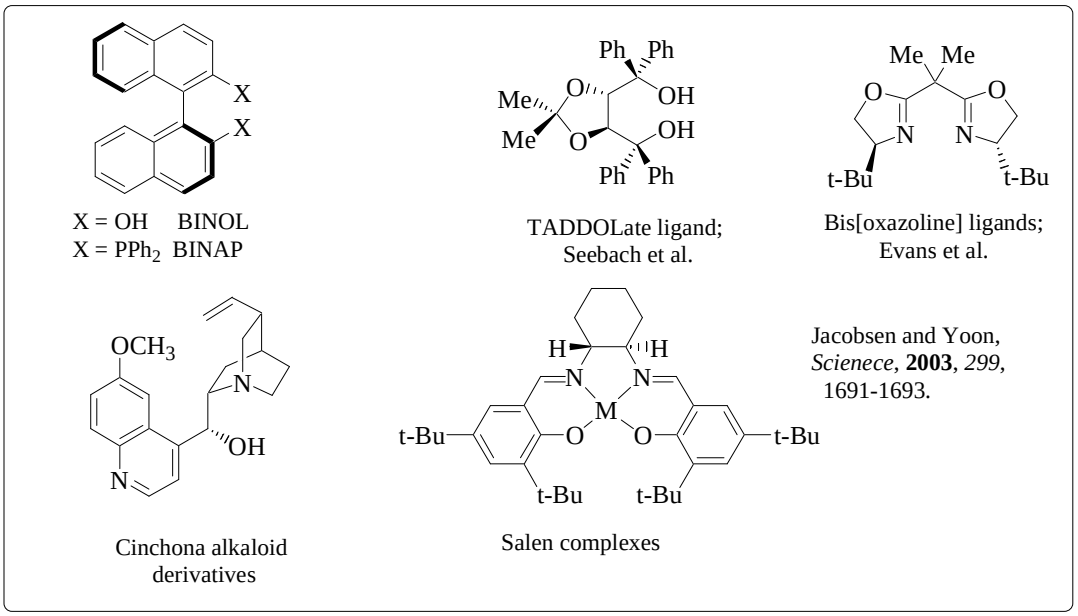


Figure 1: *Most cited ligands in asymmetric synthesis.*[22]

C_2-symmetry bis(oxazolines) are one of the most popular classes of chiral ligands, which have received a great importance as in coordination chemistry[23] and in asymmetric catalysis.[24] According to data reported in reference 24b, the use of chiral C_2-symmetry bis(oxazoline) ligands in asymmetric synthesis for different reactions has increased tremendously, as is shown below, figure 2.

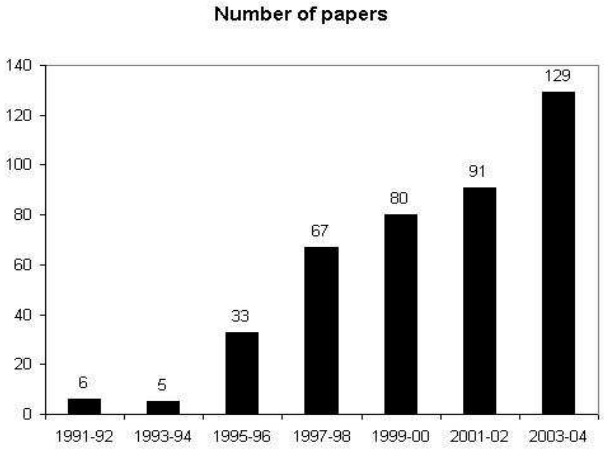


Figure 2: *Number of papers dealing with C_2-symmetric chiral Box Ligands appearing in the literature.*[24b]

[23] For details, see: M. Gomez, G. Muller, M. Rocamora. *Coord. Chem. Rev*. **1999**. *193-195*, 769.
[24] For recent reviews, see: (a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron:Asymmetry* **1998**, *9*, 1. (b) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561-3651. (c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335.

Many carbon-carbon bond-forming reactions employed in organic synthesis are subjected to Lewis acid-promoted rate acceleration.[25] Cycloadditions, conjugate additions, and aldol additions are examples of important processes that strongly respond to Lewis acid activation. When the Lewis acid complex is chiral, the stereochemical course of these catalysed processes may be strongly influenced. The `Holy Grail´ in this area is a chiral Lewis acid that exhibits broad generality for more than one reaction family. Since the demands for each reaction family are quite variable, this realization is not the rule but the exception. The use of previously known chiral catalysts in combination with advanced achiral templates/substrates is another possibility in this respect. The stereoselectivity in these reactions will be established by manipulating the geometry of the reactive complex by judicious choice of simple, readily available, and easily removable achiral templates, in combination with known chiral ligands and Lewis acids. Some widely employed achiral templates are shown in Figure 3. The bidentate templates include α,β–unsaturated N–acyloxazolidinones,[26] α,β–unsaturated malonates (alkylidene malonates),[27] β,γ–unsaturated α–ketoesters,[28] α,β–unsaturated acyl phosphonates,[29] α,β–unsaturated imides,[30] α,β–unsaturated heteroaromatic thioesters,[31] and glyoxalates.[32] The monodentate activated carbonyl compounds are aldehydes,[33] chlorals,[34] fluorals,[35] α,β–unsaturated aldehydes,[36] α,β–unsaturated ketones.[37] It appears

[25] M. Santelli, J. M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press, New York, **1996**.
[26] For Cycloaddition reactions, see: (a) D. A. Evans, S. J. Miller, T.J. Lectka, *J.Am. Chem. Soc.* **1993**, *115*, 6460-6461. (b) D. A. Evans, S. J. Miller, T.J. Lectka, P. von Matt, *J. Am. Chem. Soc*. **1999**, *121*, 7559-7573. (c) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256 and references therein.
[27] For Cycloaddition, Aldol, Michael, and Carbonyl Ene reactions, see: J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335.
[28] (a) For Domino Michael–Aldol reaction, see: N. Halland, P. S. Aburel, K. A. Jøergensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1292-1297. (b) For Friedel–Crafts alkylation, see: K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen. *Angew. Chem. Int. Ed.* **2001**, *40*, 160-163.
[29] (a) For Diels–Alder reactions, see: D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc*. **2000**, *122*, 1635-1636. (b) For Friedel–Crafts alkylation, see: D. A. Evans, K. A. Scheidt, K. R. Frandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc*. **2003**, *125*, 10780-10781.
[30] (a) For conjugate addition of cyanide, see: G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc*. **2003**, *125*, 4442-4443. (b) For Michael additions, see: Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed*. **2005**, *117*, 4100-4103. (c) For formal Hydration reaction, see: E. N. Jacobsen, C. D. Vanderwal, *J. Am. Chem. Soc*. **2004**, *126*, 14724-14725. (d) For radical trapping, see: M. P. Sibi, G. Petrovic, J. Zimmerman, *J. Am. Chem. Soc*. **2005**, *127*, 2390-2391.
[31] For Friedel–Crafts alkylation, see: B. Bandini, A. Melloni, S. Tommasi, A. Umani–Ronchi, *Helv. Chim. Acta* **2003**, *86*, 3753-3763.
[32] For Friedel–Crafts alkylation, see: K. A. Jørgensen, W. Zuang, N. Gathergood, *J. Am. Chem. Soc*. **2000**, *122*, 12517-12522.
[33] Reactions of benzaldehyde, see: S. Itsuno, S. Arima, N. Haraguchi, *Tetrahedron* **2005**, *61*, 12074-12080 and references therein.
[34] Reactions of chloral, see: (a) F. Zhang, N. Su, Y. Gong, *Synlett*, **2006**, 1703-1706. (b) D. A. Evans, D. W. C MacMillan, K. R. Campos, *J. Am. Chem. Soc*.**1997**, *119*, 10859-10860.

that these substrates have become the standard test for new catalyst development, while other achiral templates have been much less investigated.[38]

In this context, α,β–unsaturated carboxylic acids and their surrogates constitute and important type of substrates, given the extreme range of reactions that are susceptible to provide. These achiral templates usually demonstrate good attitudes for catalytic activation and tend to produce well ordered substrate–catalyst complexes. In the case of α,β–unsaturated carbonyl compound surrogates, the properties of an ideal ancillary framework are well known: (a) it must enhance the electrophilicity at β–position, (b) it must include suitable functional groups capable of coordinating to the metal center of a Lewis acid, usually through 5–, 6–membered rings, which are highly effective in obtaining rigid complex conformations, and (c) it must be easy to introduce into the starting material and easy to remove from the product, and possibly recyclable. That is why a whole band of templates such as those shown in the Figure 3 have been described as equivalents of α,β–unsaturated carboxylic acids, some of them monodentate and some bidentate.

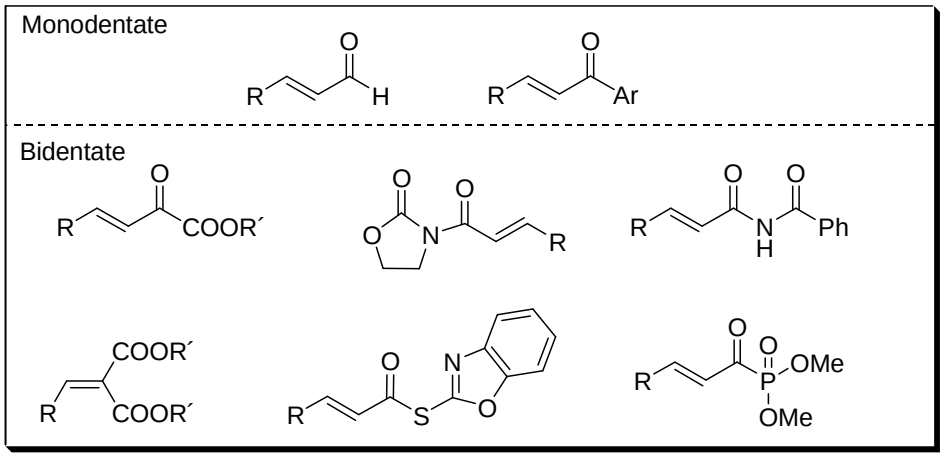


Figure 3: *Available templates for asymmetric catalysis.*

[35] Friedel–Crafts alkylation, see: A.Ishii, V. A. Soloshonok, K. Mikami, *J. Org. Chem*. **2000**, *65*, 1597-1599.

[36] (a) For epoxidation, see: M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc*. **2005**, *127*, 6284-6289. (b) For cyclopropanation, see: R. K. Kunz. D. W. C. MacMillan, *J. Am. Chem. Soc*. **2005**, *127*, 3240-3241. (c) Friedel–Crafts alkylation, see: Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2005**, *127*, 15051-15053.

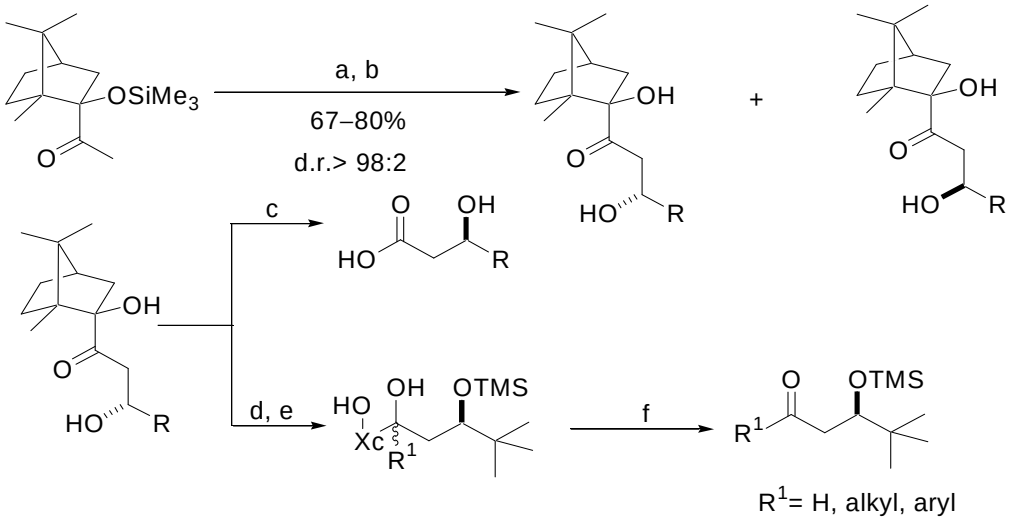
[37] (a) For Michael addition, see: M. Shi, W. L. Duan, G. B. Rong, *Chirality* **2004**, *16*, 642-651. (b) Friedel–Crafts alkylation, see: M. Bandini, M Fagioli, M. Garavelli, M. Melloni, V Trigari, A. Umani–Ronchi, *J. Org. Chem*. **2004**, *69*, 7511-7518.

[38] For the use of acrylic acid-derived hydroxamates in enantioselective Diels–Alder reactions, see: (a) O. Corminboeuf, P. Renaud, *Org. Lett.* **2002**, *4*, 1731-1733.

Despite the remarkable templates available, due to diverse needs of each individual reaction family, quest for new, better performing templates/substrates is still providing a driving force to chemists for innovation.

α'–Hydroxy enones as templates in catalytic C–C bond forming reactions

Three years before this thesis was initiated, our group reported the design and evaluation of a practical camphor based methyl ketone enolate for highly stereoselective ¨acetate¨ aldol reactions[39] (Scheme 4). This was inspired in part, in previous work by Heathcock et al.,[40] and Masamune et al.,[41] in the area of α–hydroxy ketones in aldol transformation and Diels-Alder reaction, repectively. In this instance, the aldol products, upon oxidative cleavage of the ketol moiety, give the desired β–hydroxy carbonyl system, along with recovery of the starting camphor, the source of chiral information.



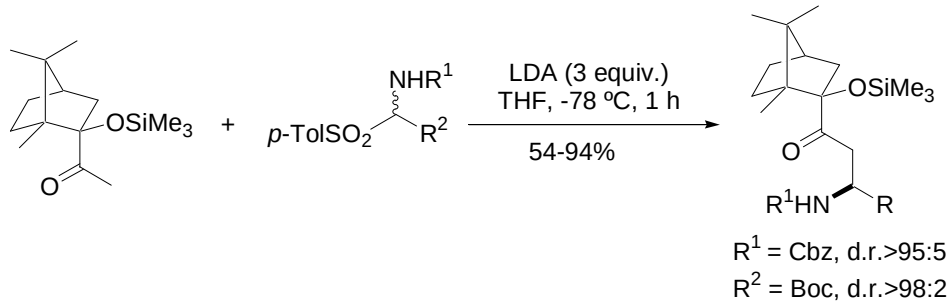
Scheme 4: *Diastereoselective synthesis of α–unsubstituted β–hydroxy carboxylic acids and ketones. Reagents and conditions: (a) LDA (1.2 equiv.), THF, –78 ºC, 0.5 h, then RCHO, 3–7 h. (b) 1 M HCl, MeOH or TBAF (2 equiv.), THF, RT, 5 min. (c) $NaIO_4$, MeOH/H_2O (2/1), RT or reflux, 12–48 h. (d) $ClSiMe_2tBu$, imidazole, DMF, RT, 3 days, 86%. (e) R_1MgBr, $CeCl_3$, THF or Et_2O, 0 ºC, 2 h. or BH_3-THF, Et_2O, 0ºC, 5-6h. (f) $Pb(OAc)_4$ (2 equiv.), C_6H_6, 5 ºC, 2 h.*

[39] (a) C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez, A. Linden, *Angew. Chem. Int. Ed*. **1998**, *37*, 180-182. (b) C. Palomo, M. Oiarbide, A. K. Sharma, M. C. G. –Rego, A. Linden J. M. Garcia, A. Gonzalez, *J. Org. Chem*. **2000**, *65*, 9007-9012.

[40] (a) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, J. E. Sohn, *J. Am. Chem. Soc*. **1979**, *101*, 7077-7079. (b) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, S. D. Young, *J. Org. Chem.* **1981**, *46*, 2290-2300. (c) N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *Ibid.* **1991**, *56*, 2499.

[41] (a) W. Choy, L. A. III Reed, S. Masamune, *J. Org. Chem.* **1983**, *48*, 1137-1139. (b) S. Masamune, L. A. III. Reed, J. T. Davis, W. COI, *Org. Chem*. **1983**, *48*, 4441-4444.

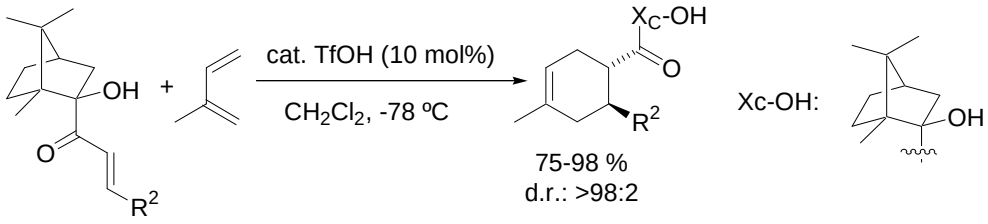
In further development from our laboratory,[42] the Mannich reaction (Scheme 5) of the lithium enolate of camphor derived methyl ketone with α–amido alkyl sulfones was disclosed. In this transformation the corresponding β–amino ketones are generated under an analogous stereochemically controlled event.



Scheme 5: *Mannich reaction of the lithium enolate of a camphor derived α'–hydroxy ketone.*

This idea was further elaborated to the design and synthesis of a novel class of sugar-peptide hybrids by virtue of preparing *C*–linked glyco β–amino acids through a stereoselective "acetate" Mannich reaction.[43] A strategic combination of asymmetric Mannich reaction with a peptide coupling process leading to either β–peptides or α,β–peptides was also demonstrated.

Next to this, the idea was extended to the use of α'–hydroxy enones as equivalents of acrylate in organocatalytic Brønsted acid catalysed Diels–Alder reactions (Scheme 6).[44]



Scheme 6: *Diels–Alder reaction of α'–hydroxy enones catalysed by TfOH.*

[42] C. Palomo, M. Oiarbide, M. C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden, *Angew. Chem. Int. Ed.* **2000**, *39*, 1063-1065.
[43] C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martín-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637-8643.
[44] C. Palomo, M. Oiarbide, J. M. García, A. Gonzalez, A. Lecumberri, A. Linden, *J. Am. Chem. Soc*. **2002**, *124*, 10288-10289.

The remarkable efficiency of these α'–hydroxy enones, even against less reactive dienes, was interpreted on the basis of intermolecular hydrogen bond activation[45] (Figure 4).

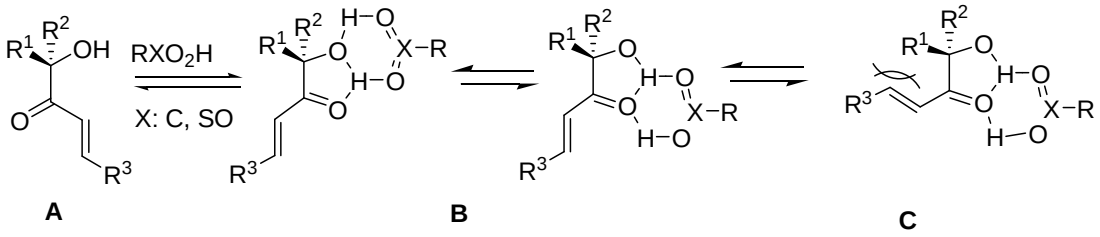


Figure 4: *Working hypothesis that may account for the simultaneous electrophilic activation and rigidification of α'–hydroxy enones by Brønsted acids.*

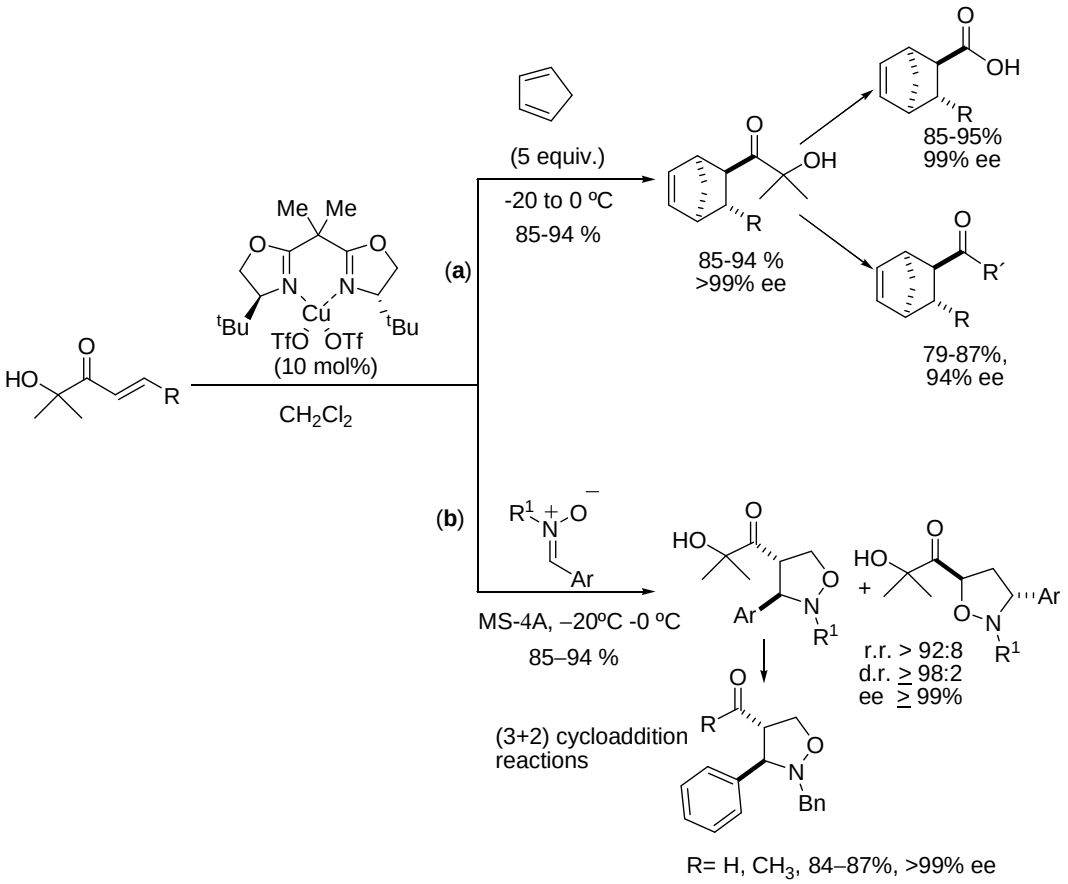
However, these earlier developments from our laboratory are dependent on stoichiometric amounts of camphor based substrates.

As a further step in the same research direction, our group developed an enantioselective variant of the Diels–Alder reaction that uses achiral α'–hydroxy enone templates and Cu(II)–bis(oxazoline) complexes as chiral catalysts[46] for both β–alkyl and β–aryl substituted enones (Scheme 7a) and 1,3–dipolar cycloaddition reaction[47] of nitrones. Excellent diastereoselectivity and enantioselectivity along with regioselectivity were achieved, particularly in the problematic case of β–unsubstituted enoyl systems. The cycloaddition adducts were further transformed into enantioenriched carboxylic acid, aldehyde and ketone derivatives (Scheme 7b). In this approach acetone is the only by product, an additional aspect that is of practical interest.

[45] For Diels–Alder reactions involving hydrogen-bond complexes, see: (a) O. Riant, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403-7406. (b) T. R. Kelly, P. Meghani, V. S. Ekkundi, *Tetrahedron Lett.* **1990**, *31*, 3381-3384. (c) K. Ishihara, H. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930. (d) T. Schuster, M. Kurz, M. W. Gobel, *J. Org. Chem.* **2000**, *65*, 1697-1701. (e) J. C. C. Atherton, S. Jones, *Tetrahedron Lett.* **2001**, *42*, 8239-8241. (f) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217-220. (g) E. J. Corey, T. Shibata, T. N. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808-3809.

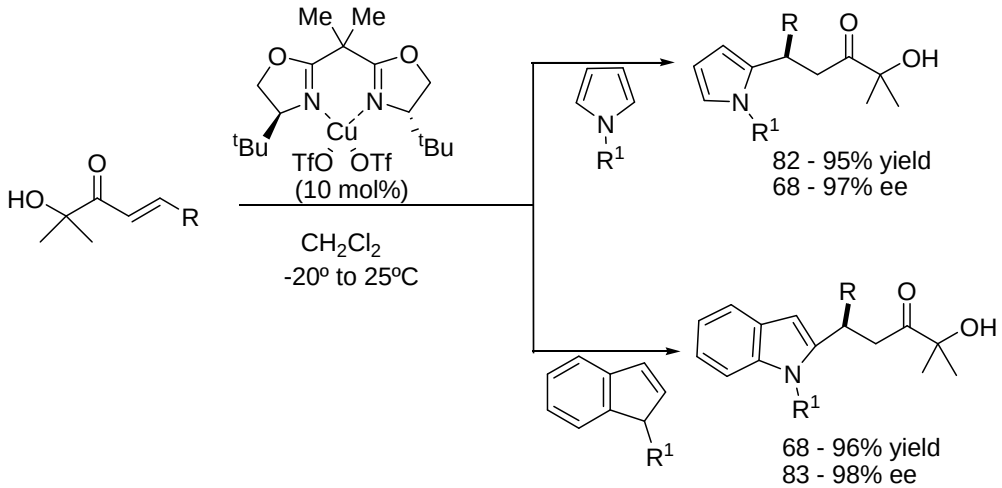
[46] C. Palomo, M. Oiarbide, J. M. Garcia, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003,** *125*, 13942-13943.

[47] C. Palomo, M. Oiarbide, E. Arceo, J. M. Garcia, R. López, A. González, A. Linden, *Angew. Chem. Int. Ed.* **2005**, *44*, 6187-6190.



Scheme 7: *Regio– and stereoselective (a) Diels–Alder reactions of cyclopentadiene and (b)1,3-dipolar cycloadditions of nitrones with α'–hydroxy enones.*

In the same research direction, during the time of this thesis work, our group developed an asymmetric variant of the Friedel-Crafts alkylation (Scheme 8a),[48]



Scheme 8: *Regio– and stereoselective Friedel-Crafts alkylation with α'–hydroxy enones.*

[48] C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc*. **2005**, *125*, 4154-4155

Part of the work presented in this thesis, Chapter I, is a continuation of previous work by our group as shown in Schemes 7-8, and the aim was to demonstrate the great value of the α'–hydroxy enone motif as a surrogate of α, β–unsaturated carboxylic acids, as Michael acceptors in metal catalysed asymmetric transformations.

Nitrogen containing building blocks:

i) β-amino carbonyl compounds

C–N bond formation is another major reaction category, in part because N–containing compounds are widespread in nature and also among the most effective drugs as well as what presently are drug candidates. Within this vast category of compounds, those which present a β-amino carbonyl functionality are prominent. More specially β-amino acids have emerged as important goals for chemical synthesis due to their distinguishing features. Over the last decade there has been a rapid development in the asymmetric synthesis of β-amino acids. As compared to their α-analogs, β-amino acids are not abundant in nature; however, they are present in a wide variety of natural products, such as peptides, cyclopeptides, depsipeptides, glycopeptides, alkaloids ot terpenoids.[49] They are biosynthesized in humans, animals, plants, and marine organisms and are present either in free form or as part of small peptides which exhibit antibiotic, antifungal,[50] cytotoxic[51] and other pharmaceutical properties.[52] β-amino acids are also structural components of important medicinal compounds such as anticancer compound[53] taxol®, where a β-amino acid side chain is essential for its biological

[49] For details, see: (a) F. Von Nussbaum, P. Spiteller, *in β-Amino Acids in Nature in Highlights in Bioorganic Chemistry: Methods and Applications*, C. Schmuck, H. Wennemers, Ed., Wiley-VCH, Weinheim, **2004**, pp. 63. (b) C. N. C. Drey, in *Chemistry and Biochemistry of the Amino Acids*, G. C. Barrets, Chapman and Hall, Ed., Londres, **1985**, p. 25. (c) C. N. C. Drey, in *Chemistry and Biochemistry of the Amino Acids, Peptides and Protines*, B. Weinstein, M. Dekker Ed., New York, **1977**, vol. 4, p. 242. (d) P. Spiteller, F. Von Nussbaum, in *Enantioselective Synthesis of β-Amino Acids*, E. Juaristi, V. Soloshonok, 2nd Ed. Wiley, Hoboken, **2005**.

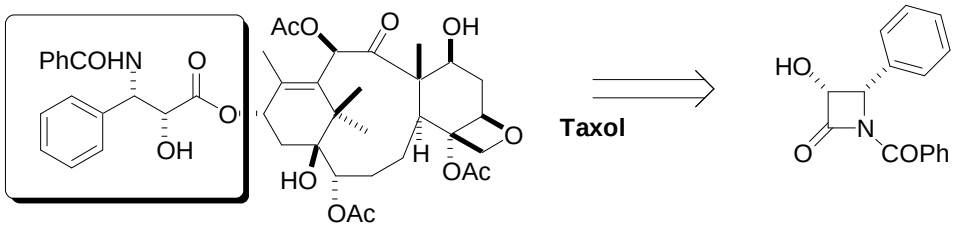
[50] (a) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517-9582. (b) S. Matsunaga, N. Fuestani, *J. Org. Chem*. **1995**, 60, 1177-1181.

[51] G. Trimurtulu, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote, L. Demchik, *J. Am. Chem. Soc.* **1994**, *116*, 4729-4737.

[52] (a) G. L. Helms, R. E. Moore, W. P. Niemczurca, G. M. L. Patterson, K. B. Tomer, M. L. Gross, *J. Org. Chem.* **1988**, 53, 1298-1307. (b) B. E. Maryanoff, M. N. Greco, H. –C. Zhang, P. Andrade-Gordon, J. A. Kaufman, K. C. Nicolau, A. Liu, P. H. Brugs, *J. Am. Chem. Soc.* **1995**, *117*, 1225-1239.

[53] J. M. Villanueva, N. Collignon, A. Guy, P. Savignac, *Tetrahedron* **1983**, *39*, 1299-1305.

activity (Figure 5). Other important β-amino acid derivatives are β-lactams,[54] which are present in antibiotics, human leukocyte elastase inhibitors,[55] and cholesterol uptake inhibitors.[56]



Assignment and structure determination: Wani (1971)[57].

Figure 5: Synthesis: Nicolau (1994),[58] Holton (1994),[59] others.[60]

Moreover, the incorporation of β-amino acids into peptides instead of α-amino acids increases their stability against degradation by mammalian peptides.[61] This enhanced stability is caused by the lack of the enzyme which allows cleavage of peptidic bonds between α-amino acids and β-amino acids.[62] The pioneering works by Seebach et al.,[63a,b] Abele et al.,[63c] and Appella et al.[63d] independently have shown that the oligomeric structure of β-amino acids could fold into defined secondary structures which are analogous to the ones observed in regular proteins. Conformationally constrained β-amino acids (β-AAs) are of great interest in the preparation of oligomers with strong propensity to adopt specific, compact conformations giving rise to

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[54] (a) R. B. Morine, M. Gorman, *Chemistry and Biology of β-Lactum Antibiotics*, Academic, New York, **1982**. (b) G. Lukacs, M. Ohno, *Recent Progress in the chemical Synthesis of Antibiotics and Related Natural products*, Springler-Verlag, Berlin, **1990**.

[55] G. I. Georg, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2135

[56] D. Burnett, M. A. Caplen, H. R. Devis, R. E. Burier, J. Clader, *J. Med. Chem*. **1994**, *37*, 1733.

[57] M. C. Wani, H. L. Taylor, m. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

[58] K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Mantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvennen, E. J. Sorensen, *Nature* **1994**, *367*, 630-634

[59] (a) R. A. Holton, C. Samoza, H. –B. Kim, F. Liang, R. J. Biedigerm, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc*. **1994**, *116*, 1597-1598. (b) R. A. Holton, C. Samoza, H. –B. Kim, F. Liang, R. J. Biedigerm, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc*. **1994**, *116*, 1597-1598.

[60] For total and partial synthesis, see: D. G. I. Kingston, *Chem. Commun*. **2001**, 867-880.

[61] D. L. Steer, R. A. Lew, P. Perlmutter, A. I. Smith, M.-I. Aguilar, *Curr. Med. Chem.* **2002**, *9*, 811-822.

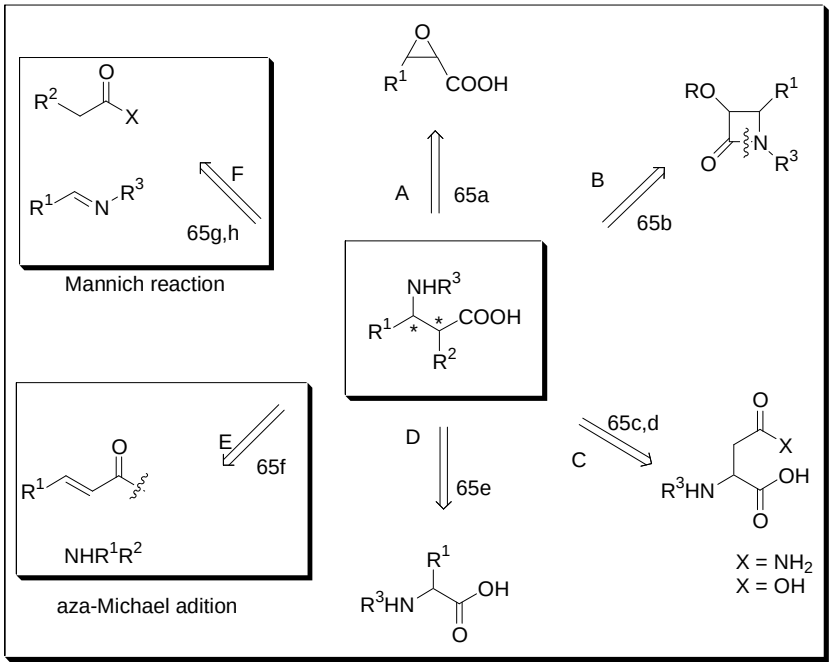
[62] A. Pegova, H. Abe, A. Boldyrev, *Comp. Biochem. Physiol. B*, **2000**, *127*, 443-446.

[63] (a) D. Seebach, M. Overhand, F. N. M. Kuhnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta*, **1996**, *79*, 913. (b) D. Seebach, J. L. Matthews, *Chem. Commun*. **1997**, 2015 (c) S. Abele, K. Vogtil, D. Seebach, *Helv. Chim. Acta*, **1999**, *82*, 1539. (d) D. Appella, L. A Cristianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071-13072.

secondary structures, that is, helixes, turns, sheets.[64] This β-peptides, or foldamers, are relevant in biological studies to investigate the topology of receptors and also are prominent candidates in the development of new drugs.

Therefore β-amino acids are an important tool in the development of drugs capable of withstanding hydrolytic degradation for prolonged periods of time.

The principal synthetic routes towards β-amino acids are shown in the retro synthetic approaches[65] depicted in Scheme 9.



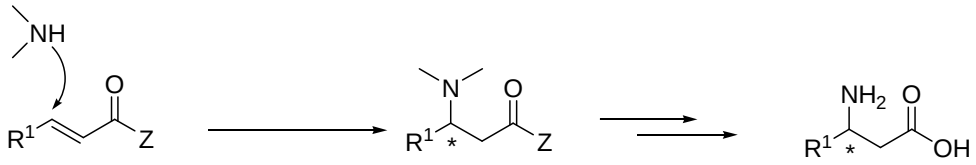
Scheme 9. *Principal retrosynthetic routes to access β-amino acids.*

Among the principal approaches described above, the conjugate addition of amines or related N-centered nucleophiles to α,β-unsaturated carbonyl derivatives

[64]E. Juaristi, D. Quintana, J. Escalante, *Aldrichim. Acta*, **1994**, *27*, 3.

[65] *Enantioselective sinthesis of β-Amino Acids*, E. Juaristi, Ed. Wiley- VCH, New York, **1997**: (a) *Asymmetric Synthesis of β-Amino Acids from catalytic Sharpless Epoxidation*, M. A. Pericas, p. 373. (b) *The Synthesis of β-Amino Acids and their derivativeds from β-Lactams*, C. Palomo et al., p. 279. (c) *Selective Transformation of N, N-Dibenzyl Protected Asparagine and Aspartic Acids Derivatives*, P. Gmeiner, p. 67. (d) *Synthesis of Enantiomerically pure β-Amino Acids Starting from L- and D-Aspartic Acids*, C. W. Jefford, J. McNulty, p. 83. (e) *Preparation of Enantiomerically pure β-Amino Acids from α-Amino Acids Using Arndt Eistert Homologation*, D. Seebach, p. 105. (f) *Asymmetric Addition of Amines to α,β-unsaturated esters and Nitriles in the Enantioselective Synthesis of β-Amino Acids*, E. Juaristi, p. 139. (g) *Synthesis of Nonracemic β-Amino Acids via Chiral Sulfinimines*, F. A. Davis, p. 127. (h) M. Arend, B. Westermann, n. Rish, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044-1070. Book : *"Enantioselective Synthesis of β-Amino Acids"* E. Juaristi, V. Soloshonok, 2nd Ed., Wiley, Hoboken, New Jersey, **2005**.

which is called *aza-Michael addition* (Chapter I), represents an attractive strategy for the synthesis of enantiopure β-amino acids.



Scheme 10: *Asymmetric synthesis of β-amino acids via conjugate addition of amines.*

Three major ways to achieve asymmetric conjugate addition of nitrogen nucleophiles are the use of chiral acceptors[66], chiral amines[67], and chiral catalysts.

In Scheme 11, examples are shown for the the addition of an achiral amine to chiral esters. Thus, Dumas et al. described the highly diastereoselective addition of diphenylmethanamine to 8-phenylmenthol-derived chiral crotonates under high pressure conditions,[68] while Perlmutter and Tabone documented the synthesis of *anti* α-substituted β-amino esters via diastereoselective conjugate addition of $BnNH_2$ to chiral 2-hydroxyalkylpropenoates.[69] Other elegant works have also been reported by others.[70]

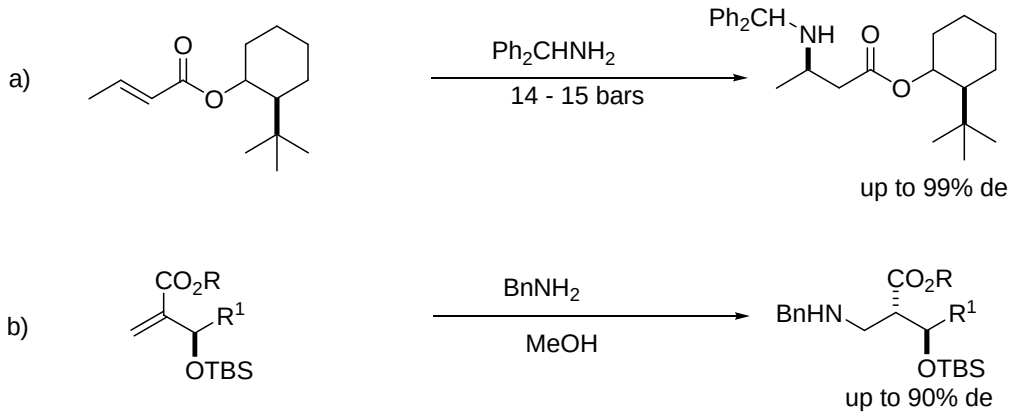
[66] For selected examples of substrate controlled aza-Michael reactions, see: (a) M. Shimano, A. I. Meyers, *J. Am. Chem. Soc*. **1994**, *116*, 6437-6438 and references therein. (b) F Dumas, B. Mezrhab, J. Angelo, *J. Org. Chem.* **1996**, *61*, 2293-2304. referentes therein (c) N. Asao, T. Shimada, T. Sudo, N. Tsukada, K. Yazawa, Y. S. Gyoung, T. Uyehara, Y. Yamamoto, *J. Org. Chem*. **1997**, 62, 6274-6282.

[67] For selected example of reagent controlled aza-Michael reactions, see: (a) M. Furukawa, T. Okawara, Y. Terawaki, *Chem. Pharm. Bull*. **1977**, *25*, 1319-1325. (b) J. M. Hawkins, G. C. Fu, *J. Org. Chem.* **1986**, *51*, 2820-2822. (c) S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, *2*, 183-186. (d) J. G. Rico, R. J. Lindmark, T. E. Rogers, P. R. Bovy, *J. Org. Chem.* **1993**, *58*, 7948-7951. (e) D. Enders, H. Wahl, W. Bettray, W. *Angew. Chem., Int. Ed.* **1995**, *34*, 455-457. (f) N. Sewald, K. D. Hiller, B. Helmreich, *Liebigs Ann.* **1995**, 925-928. (g) M. –L. Leroux, T. Gall, C. Mioskowski, *Tetrahedron: Asymmetry* **2001**, *12*, 1817-1823. (h) S. B. Bull, S. G. Davies, P. M. Bert, E. D. Savory, A. D. Smith, *Tetrahedron* **2002**, *58*, 4629-4642.

[68] F. Dumas, B. Mezrhab, J. d¨ Angelo, C. Riche, A. Chiaroni. *J. Org. Chem*. **1996**, *61*, 2293-2304.

[69] P. Perlmutter, M. J. Tabone, *J. Org. Chem*. **1995**, *60*, 6515-6522 and references therein.

[70] (a) H. Matsuyama, N. Itoh, M. Yoshida, N. Kamigata, S. Sasaki, M. Iyoda, *Chem. Lett*. **1997**, 375-376. (b) T. Ishikawa, K. Nagai, T. Kudoh, S. Saito, *Synlett*, **1995**, 1171-1173, and references therein



Scheme 11: *Conjugate addition to chiral esters: (a) Dumas et al.*[68]*; (b) Perlmutter and Tabone.*[69]

On the other hand, lithium amides, derived from readily available chiral amines (Fig 6), have been extensively used as synthetic equivalents of ammonia in conjugate addition reactions.

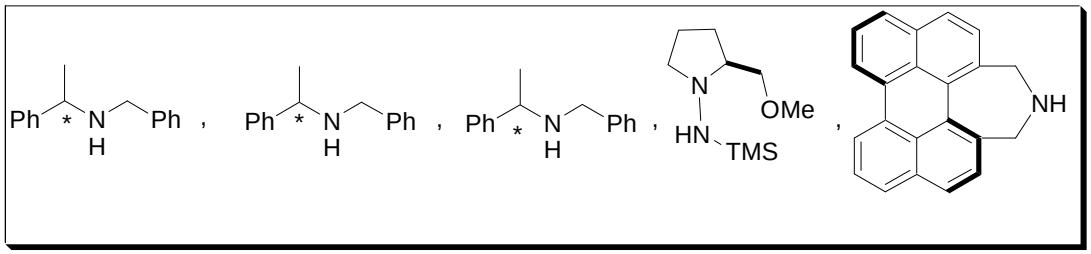


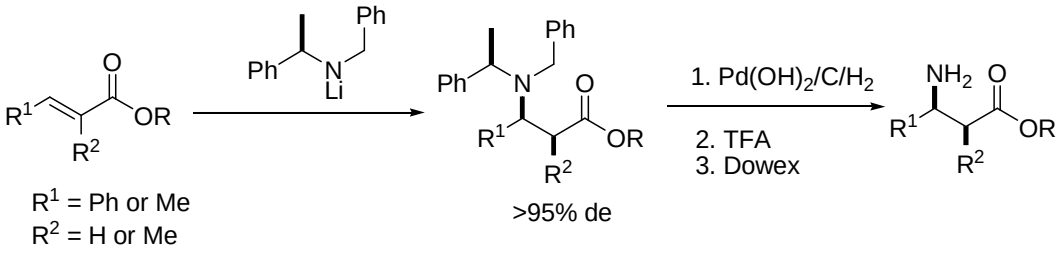
Figure 6. *Privilege chiral amines for conjugate addition.*

In this context, Davies et al.[71] were among the first to demonstrate that lithium N-benzylphenylethylamine, as chiral ammonia equivalent, added to different enoates with high diastereoselectivity. After debenzylation with $Pd(OH)_2$ and subsequent hydrolysis, enantiopure β-amino acids are obtained in good yields (Scheme 12). The conjugate addition of amines has found broad utility in recent years, which was highlighted by some outstanding examples reported by Davies et al.[72] and others[73] in the

[71] (a) D. Enders, H. Wahl, W. Battray, *Angew. Chem. Int. Ed*. **1995**, *34*, 455-457. (b) S. G. Devies, D. R. Fenwick, *J. Chem. Soc. Chem. Commun*. **1995**, 1109-1110

[72] (a) S. G. Devies, D. R. Fenwick, O. Ichihara, *Tetrahedron: Asymmetry* **1997**, *8*, 3387-3391. (b) S. G. Devies, O. Ichihara, *Tetrahedron Lett.* **1999**, *40*, 9313-9316. (c) S. D. Bull, S. D. Devies, S. Delgado-Ballster, G. Fenton, P. M. Kelly, A. D. Smith, *Synlett*, **2000**, 1257-1260. (d) S. D. Bull, S. D. Devies, D. J. Fox, M. Gianotti, P. M. Kelly, C. Pierres, E. D. Savory, A. D. Smith, *J. Chem. Soc. Perkin Trans. 1*. **2002**, 1858-1868.

stereoselective synthesis of many biological interesting β-amino acids as well as natural products.



Scheme 12: *Chiral lithium amide as ammonium equivalent in diastereoselective conjugate addition reactions (TFA = Trifluoroacetic acid)*

In contrast to diastereoselective methods, the catalytic version has been less documented. The body of the work devoted to catalyst-controlled, enantioselective aza-Michael reaction is described in Chapter I.

ii) 1, 2 diamines

Apart from the β-amino carbonyl compounds, 1,2-diamines or vicinal diamines constitute another subset of interesting molecular frameworks because of their presence in many natural products and their use as medicial agents perticularly in Chemotherapy.[74]

Biotin (or vitamim H) which is an essential cofactor to carboxylase-catalyzed reactions, is one of the compounds found in nature that contain the 1,2-diamine moiety in their skeleton.[75] A large number of natural products, specially peptides, contain a *n*,

[73](a) P. J. Coleman, J. H. Hutchinson, C. A. Hunt, P. Lu, E. Delaporte, R. Rushmore, *Tetrahedron Lett.* **2000**, 41, 5803-5806. (b) P. O¨Brien, D. W. Porter, N. M. Smith, *Synlett*, **2000**, 1336-1338. (c) H. Imamura, A. Shimizu, H. Sato, Y. Sugimoto, S. Saturaba, S. Nakajima, S. Abe, K. Mirua, I. Nishimura, K. Yamada, H. Morishima, *Tetrahedron*, **2000**, *56*, 7705-7713. (d)Y. Yamamoto, K. Maeda, K. Tomimoto, T. Mase, *Synlett*, **2002**, 561-563. (e) D. Ma, J. Zhang, *J. Chem. Soc. Perkin Trans 1*. **1999**, 1703-1707. (f) X. Pu, D. Ma, *J. Org. Chem.* **2003**, *68*, 4400-4405. (g) J. M. Langenhan, S. H. Gellman, *J. Org. Chem.* **2003**, *68*, 6440-6443.

[74] For synthesis and application of 1,2-diamine, see: D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem. Int. Ed.***1998**, *37*, 2580-2627.

[75](a) M. A. Eisenberg, in *Escherichia coli and Salmonella typhimurium*, Vol.1 (F. C. Neidhardt), *American Society for Microbiology*, Washington DC, **1987**, pp.544-550. (b) A. Marquet, *Pure Appl. Chem*. **1993**, *65*, 1249-1252.

n+1-diamino carboxylic acid such as 2,3-diaminopropanoic acid, for instance several peptidic antibiotics such as edeines[76] and tuberactomycin derivatives.[77]

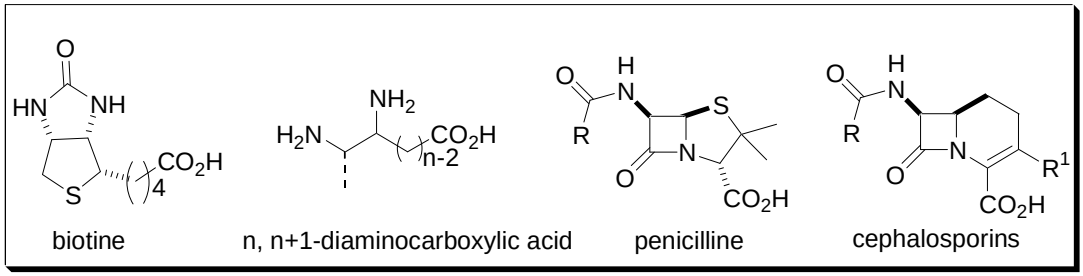


Figure 7: *Selected 1,2-dimaine containing biologically active compounds*

Amphomycene,[78] aspartocin,[79] lavendomycin,[80] glumamycin,[81] antrimycin[82] and cirratiomycin are potent antibacterial peptides incorporating the 2,3-diaminobutanoic acid residue. The well known antibiotics penicillins and cephalosporins also contain a 2,3-diamino carboxylic acid unit, incorporated into the penam and cepham structures, repectively.

The 1,2-diamine functionality can be found in various compounds displaying a broad spectrum of biological activity.[83] For instance, antiarrhythmics,[84] antidepressant agents,[85] antihypertensives, antipsychotics, analgesics, antianxiety agents, anticancer drugs and antiparasitic agents. Antitumor properties of cisplatin (cis-diaminedichloro-platinum (II)) were serendipitously discovered by Rosenberg in the mid 1960s. Among

[76] T. P. Hattinger, L. C. Craig, *Biochemistry* **1970**, *9*, 1224-1232.
[77] H. Yoshioka, T. Aoki, H. Goko, K. Makatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, T. Kaneko, *Tetrahedron Lett.* **1971**, *23*, 2043-2046.
[78](a) M. Bodanzsky, N. C.n. C. Chaturvedi, J. A. Scozzie, R. K. Griffith, A. Bodanzsky, *Antimicrob. Agents Chemother*, **1969**, 135-138. (b) A. Bodanzsky, M. Bodanzshy, *J. Antibiot. Ser. A*, **1970**, *23*, 149-154.
[79]W. K. Hausmann, D. B. Borders, J. E. Lancaster, *J. Antiobiot. Ser. A*, **1969**, *22*, 207-210.
[80] I Uchida, N. Shigematsu, M. Ezaki, M. Hoshimoto, *Chem. Pharm. Bull*. **1985**, *33*, 3053, 3056.
[81] M. Fujino, M. Inoue, J. Ueyanagi, A. Miyake, *Bull. Chem. Soc. Jpn.* **1965**, *38*, 515-517.
[82]K. Morimoto, N. Shimada, H. Naganawa, T. Takita, H. Umezawa, *J. Antiboit.* **1981**, *34*, 1615-1618 and references therein.
[83] E. T. Michalson, J. Szmuszkovics. *Prog. Drug. Res*. **1989**, *33*, 135-149.
[84] Z. Zubovics, L. Toldy, A. Varro, G. Rabloski, M. Kurthy, E. Tomory, *Eur. J. Med. Chim. Ther*. **1986**, *21*. 370-378.
[85](a) D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627. (b) J. Szmuszkovicz, P. F. Von Voigtlander, M. P. Kane, *J. Med. Chem*. **1981**, *24*, 1230-1236.

the 1,2-diaminoplatinum complexes described several posses higher antitumoral activity than cisplatin.[86]

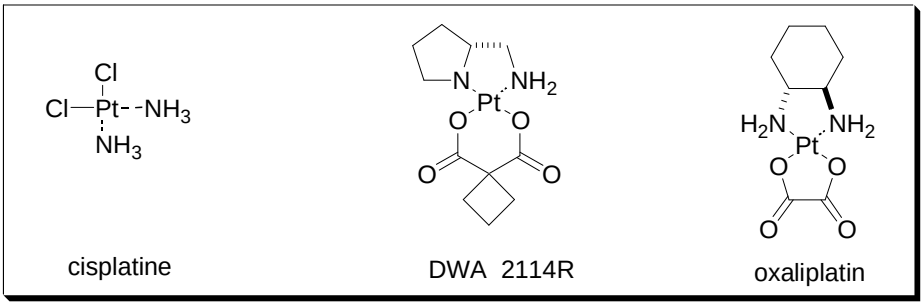


Figure 8: *Cisplatin and some 1,2-diaminoplatinum compounds currently used or evaluated as anticancer drugs.*

1,2-Diamine compounds are valuable synthetic intermediates for the preparation of heterocycles.[87] Diamines such as TMEDA are widely used as additives to stabilize and activate organometallic reagents and inorganic salts.[88] Indeed enantiomerically pure 1,2-diamines and their derivatives are particularly useful chiral auxiliaries or ligands,[89] and they have found tremendous application in stereoselective synthesis. In this field chiral C_2-symmetric 1,2-diamines and their various derivatives offer especially great promise as new reagents for enantioselective synthesis.

Symmetrical vicinal diamines have been used for racemate resolution.[90] For example, (*R*,*R*)-1,2-diaminocyclohexane and (*R*,*R*)-1,2-diphenylethylenediamine (also called stilbenediamine or stein) were used to resolve atropisomeric binaphthols (figure 9).[91] Several chiral auxiliaries derived from 1,2-diamines have been employed in highly stereoselective reactions. They often have C_2 symmetry although early examples

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[86] (a) B. Rosenberg, L. Vanchamp, J. E. Trosko, V. H. Mansour, *Nature*, **1969**, *222*, 385-386. (b) A. Pasini, F. Zunino, *Angew. Chem. Int. Ed*. **1987**, *26*, 615-624. (c) H. Brunner, P. Hankofer, U. Holzinger, H. Schonenberder, *Eur. J. Med. Chem.* **1990**, *25*, 35-44. (d) J. Reedijk, *Chem. Commun.* **1996**, 801-806 and references therein. (e) D. K. Kim, Y. W. Kim, H. T. Kim, K. H. kim, *Bioorg. Med. Chem. Lett*. **1996**, *6*, 643-646.

[87] A. E. A. Popter in *Comprehesive Heterocyclic Chemistry*, *Vol. 3*, (A. R. Katritzky, C. W. Rees Eds., pergamon, Oxford, **1984**, p. 179.

[88] R. K. Haynes, S. C. Vonwiller, in *Encyclopedia of reagents for Organic Synthesis*, *Vol. 7*, L. A. Paquette Eds., Wiley, New York, **1995**, pp. 4811-4815.

[89] Use of 1,2-diamine as chiral auxiliaries, see: J. K. Whitesell, *Chem. Rev*. **1989**, *89*, 1581-1590.

[90] For resolving Chiral aldehydes, See: (a) P. Mangeney, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1998**, *29*, 2677-2680. (b) A. Alexakis, P. mangeney, I. Marek, , E. rose, A, Semra, F. Robert, *J. Am. Chem. Soc*. **1992**, *114*, 8288-8290 and refences therein. For determining the ee of carboxylic acids, see: (a) R. Fulwood, D. Parker, *J. Chem. Soc. Perkin Trans. 2*, **1994**, 57-64. (b) B. Staubach, J. Buddrus, *Angew. Chem. Int. Ed*. **1996**, *108*, 1344-1346.

[91] (a) M. Kawashima, R. Hirata, *Bull. Chem. Soc. Jpn*. **1993**, *66*, 2002-2005.(b) H. Brunner, H. Schiessling, *Angew. Chem. Int. Ed*. **1994**, *33*, 125-126.

described by Mukaiyama involved unsymmetrical auxiliaries.[92] The chiral 1,2-diamine ligands are used often in the field of asymmetric synthesis.

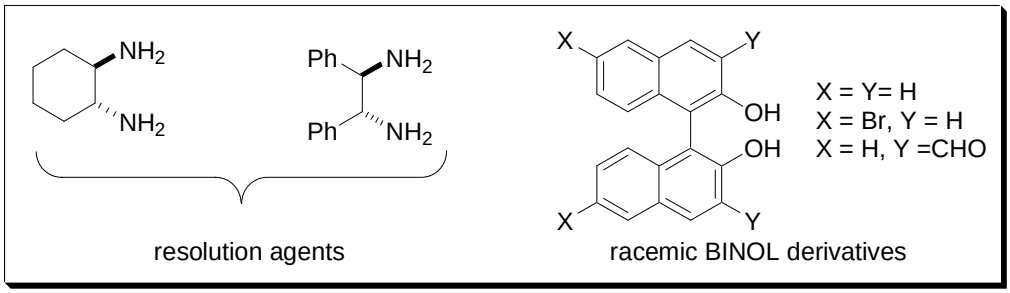
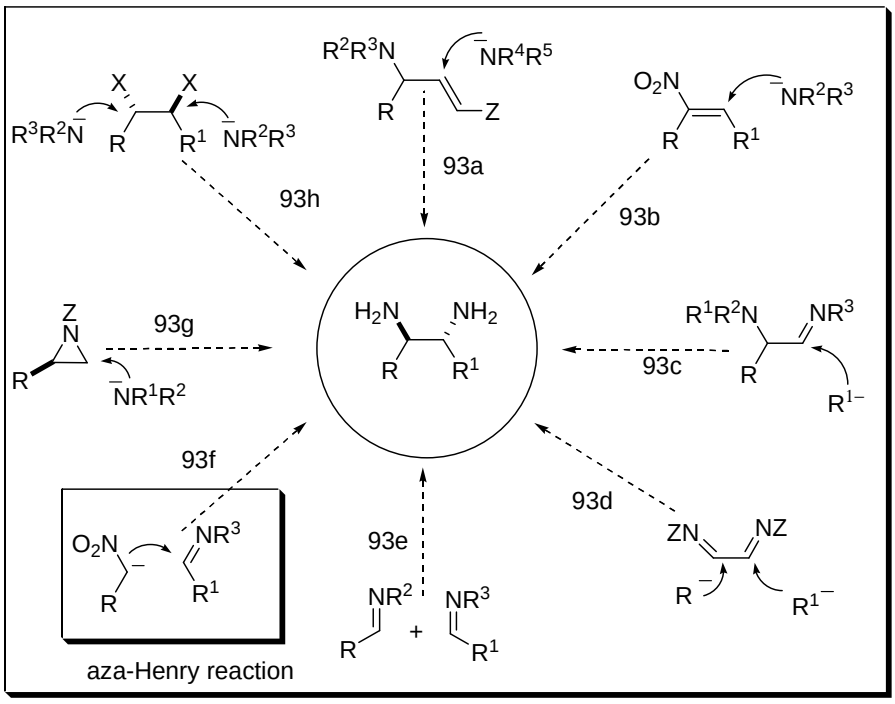


Figure 9: *1,2-diamine used to resolve binapthol atropisomers.*

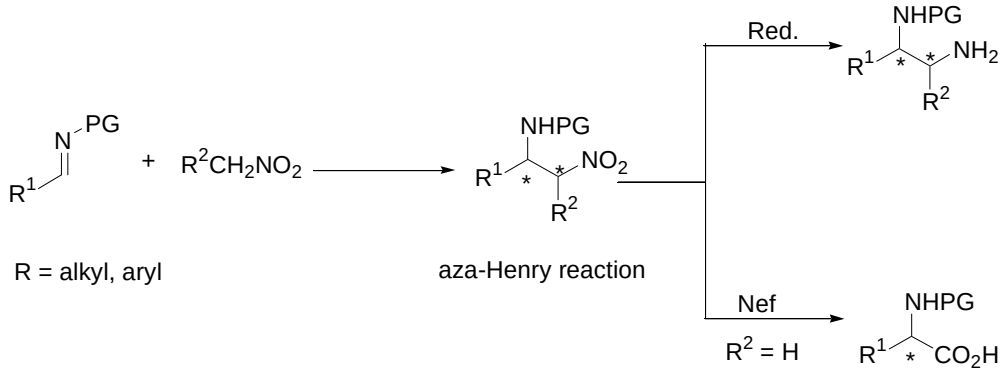


Scheme 13: *Methods for the synthesis of 1,2-disubstituted 1,2-diamines.*[93]

[92] T. Mukaiyama, *Tetrahedron* **1981**, *37*, 4111-4119.

[93] (a) Recent review on the use SAMP and RAMP: D. Enders, M. Klatt, in Encyclopedia of reagents for Organic Synthesis, Vol. 1, L. A. Paqyette Ed. Wiley, New York, **1995**, pp. 178-182. (b) K. Imagawa, E. Hata, T. Yamada, T. Mukaiyama, *Chem. Lett.* **1996**, 291-292 and referentes therein. (c) D. Enders, R. Schiffers, *Synthesis* **1996**, 53-58 and references therein. (d) A. R. Katritzky, W. Q. Fan, C. Fu, *J. Org. Chem*. **1990**, *55*, 3209-3213 and references therein. (e) N. Taniguchi, M. Uemura, *Synlett*, **1997**, 51-53 and references therein. (f) B, Westermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 151-153 and references therein. (g) M. H. Wu, E. N. Jacobsen, *Tetrahedron Lett*. **1997**, *38*, 1693-1696 and references therein. (h) Q. Li, D. T. W. Chu, K. Raye, A. Claiborne, L. Seif, B. Macri, J. J. Plattner, *Tetrahedron Lett*. **1995**, *36*, 8391-8394 and references therein.

From the above approaches, the aza-Henry (nitro Mannich) reaction, that is, nucleophilic addition of nitroalkanes to imines, is a useful C–C bond forming process. The thus-obtained β-nitroamines can be transformed into valuable compounds such as vicinal or 1,2-diamines and α-amino acids by reduction and Nef oxidation of the nitro moiety. Therefore control of the stereochemistry in aza-Henry reaction, wherein up to two new stereogenic centers can be generated, is of prime importance. The Chapter II of this thesis deals with this process. States of the art of asymmetric aza-Henry reaction is discussed and the results of a new practical protocol are disclosed.



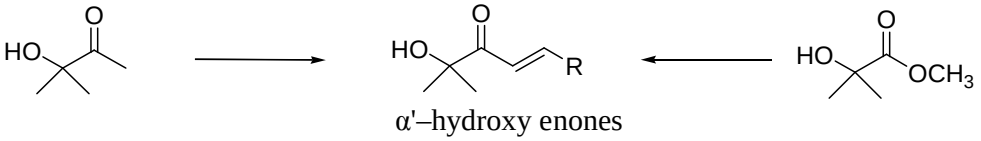
Scheme 14: *General scheme for aza-Henry reaction and subsequent reduction to 1,2-diamines and α-amino acids, (PG = protecting group).*

2. Objectives

Although several methods for the synthesis of β-amino acids and 1,2-diamines have been developed, only recently has the preparation of enantiomerically pure compounds emerged as an important and challenging synthetic endeavor. In the pursuit of this plan, our interest was to evaluate a catalytic asymmetric versions of the Michael reaction of nitrogen nucleophiles. The specific goals at the moment this thesis was initiated were as follows:

Plan 1

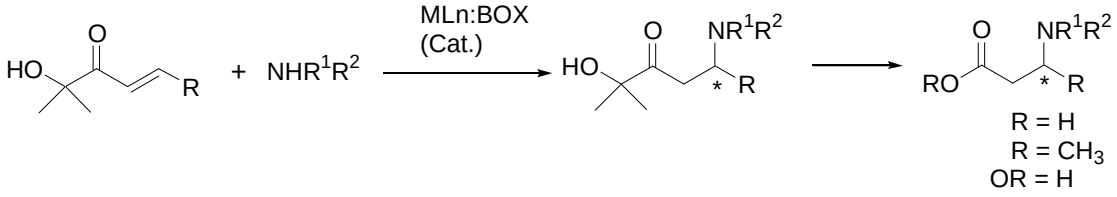
To establish practical conditions for the convenient synthesis of α'–hydroxy enones.



α'–hydroxy enones

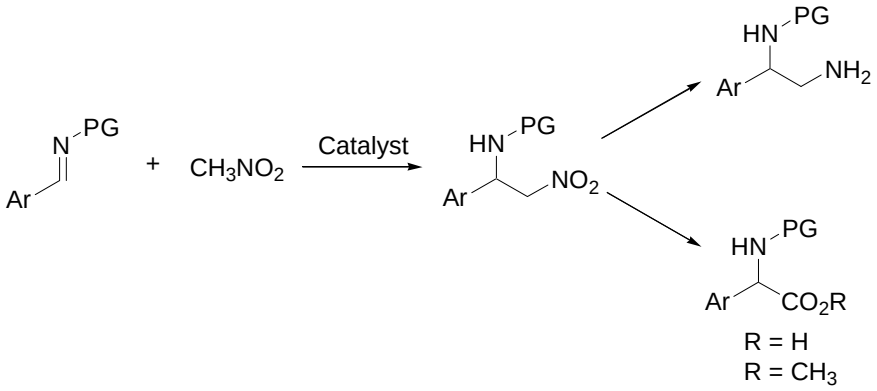
Plan 2

Based on the previous observations from our laboratory and the working hypothesis as described in general introduction, our next goal was the evaluation of α'–hydroxy enones as Michael acceptors in *C—N* bond forming reactions, under the action of Cu(II)−bis(oxazoline) complexes and elaboration of the adducts.



Plan 3

To find out an efficient catalyst system for the asymmetric aza-Henry reaction of nitromethane addition to aldimines and elaboration of the adducts. Extension of the system to other related reactions, such as Mannich reactions.

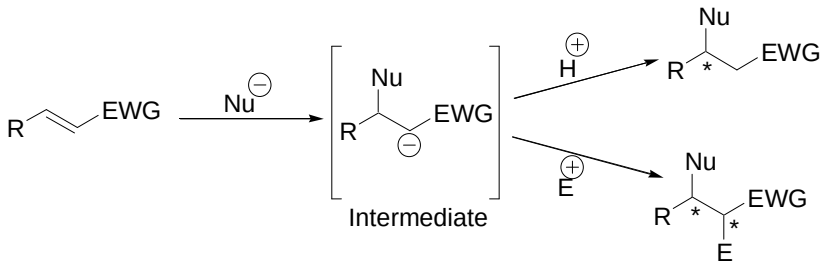


3. Chapter I

aza-Michael reaction

3.1 Introduction

The conjugate addition reaction is regarded as one of the most powerful methods for the preparation of complex molecules.[94] In this transformation, a nucleophile adds to the β-carbon of an electron-deficient olefin which is connected with an electron withdrawing group, giving a stabilized carbanion intermediate which, after protonation or subsequent treatment with another electrophile furnishes the final addition product. The nucleophile can be either carbon or heteroatoms and the acceptors are usually α,β-unsaturated carbonyl compounds (aldehydes, ketones, esters, amides etc.), although other activating groups like nitro, sulphonate, suphoxide, phosphate or phosphonate have also been successfully employed.[95]



Scheme 15: *General addition reaction to electron poor olefins (conjugate addition).*

Owing to simplicity and atom economy, 1,4-addition of a homo- (carbon atom) or hetero- (O, S, N, etc.) nucleophile to the β-carbon attached to an electron withdrawing group, the so-called Michael type reaction, is a very versatile transformation. In addition, by this way remove functionalization of the substrate is possible. Apart from the many types of C–centered nucleophiles suitable for this transformation, when heteronucleophiles are employed, β-thio, β-oxo and β-amino adducts are obtained which are important building blocks in chemical synthesis, specially the later two. Very recently Spencer et. al.[96] and Tamariz et. al.[97] have shown the possibility of the oxa-Michael addition in racemic form. Regarding

[94] P. Perlmutter, *Conjugate addition Reactions in Organic Synthesis*, Pergamon Press. Oxford, **1992**.
[95] Review: (a) X. Li-Wen, X. Chun-Gu, *Eur. J. Org. Chem*. **2005**, 633-639. (b) J. L.Vicario, D. Badia, L. Carrillo, J. Etxebarria, E. Reyes, N. Ruiz, *Organic Preparations and Procedures Int*., **2005**, *37*, 513-538.
[96] For recent progress, see; T. C. Wabnitz, J. –Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484-493 and references therein
[97] P. Bernal, J. Tamariz, *Tetrahedron Lett*. **2006**, *47*, 2905-2909 and references therein.

conjugate addition of S-centered nucleophiles, conjugate additions of thiols have been explored by few groups[98] including our laboratory.[99] The conjugate addition of nitrogen nucleophiles to electron deficient olefins, the called aza-Michael reaction, is a convenient way to introduce an amine-base functionality at the β-carbon attached to an electron-withdrawing group.[100]

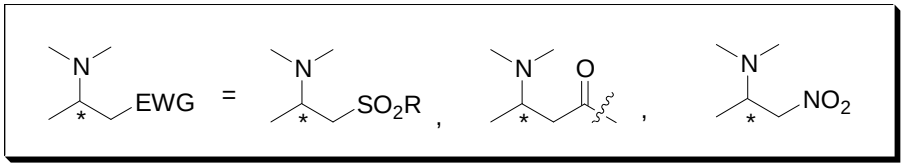


Figure 10: *Privilege Michael adducts.*

Among the Michael adducts, β-amino carbonyl compounds or related derivatives are extremely important molecules not only because of their ubiquitous occurrence as constituents of a plethora of biologically important natural and synthetic products, but also because they have shown to be very versatile intermediates in the synthesis of other nitrogen-containing compounds.[101] Furthermore, the substitution of α-amino acids for β-amino acids in biologically active peptides is a promising tactic to prepare peptide analogues with increased potency and enzymatic stability.[102]

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[98] For leading references, see: (a) M. –J. Wu, C. –C. Wu, T. –C. J. Tseng, *Org. Chem*. **1994**, *59*, 7188-7191. (b) W.-J. Tsai, Y.-T. Lin, B.-J Uang, *Tetrahydron: asymmetry* **1994**, *59*, 1195-1198. (c) K. Tomioka, A. Maraoka, M. Kauai, *J. Org. Chem*. **1995**, *60*, 6188-6190. (d) D. P. Taber, G. J. Gorski, L. M. Liable-Sands, A. L. Rheingold, *Tetrahedron lett*. **1997**, *38*, 6317-6318. (e) O. Miyata, T. Shinada, I. Nynomiya, T. Naito, *Tetrahedron* **1997**, *53*, 2421-2438. (f) C.-H. Lin, K. –S. Yang, J. –P. Pan, K. Chen, *Tetrahedron lett*. **2000**, *41*, 6815-19. (g) M. Node, K. Nashide, Y. Shigeta, H. Shiraki, K. Obata, *J. Am. Chem. Soc*. **2000**, *122*, 1927-1928.

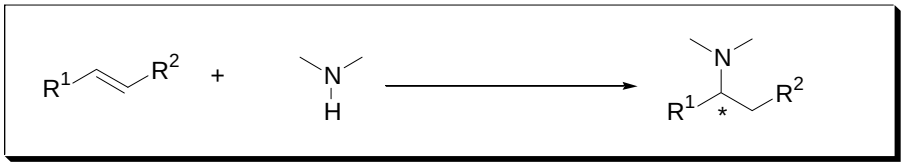
[99] (a) C. Palomo, M. Oiarbide, F. Dias, A. Ortiz, A. Linden, *J. Am. Chem. Soc*. **2001**, *123*, 5602-5603. (b) C. Palomo, M. Oiarbide, F. Dias, R. Lopez, A. Linden, *Angew. Chem. Int. Ed*. **2004**, *43*, 3307-3310.

[100] (a) S. Kobayashi, K. Kakumoto, M. Sugiura, *Org. Lett*. **2002**, *4*, 1319-1322 (b) L. W. Xu, C. G. Xia, *Tetrahedron lett*. **2004**, *45*, 4507-4510. (c) T. C. Wabnitz, J. B. Spencer, *Tetrahedron Lett*. **2002**, *43*, 3891-3894.

[101] a) For reviews, see: *Enantioselctive Synthesis of β-amino acids;* E. Juaristi, Ed.; Wiley-VCH: New York, **1997**. b) J. A. Ma, *Angew. Chem. Int. Ed*. **2003**, *42*, 4290-4299. c) N. Sewald, *Angew. Chem. Int. Ed*. **2003**, *42*, 5794-5795. (d) S. Abele, D. Seebach, *Eur. J. Org. Chem*. **2000**, 1-15. (e) G. Cardillo, C. Tomasini, *Chem. Soc. Rew*., **1996**, *25*, 117-128. (f) D. C. Cole, *Tetrahedron*, **1994**, *50*, 9517-9582.

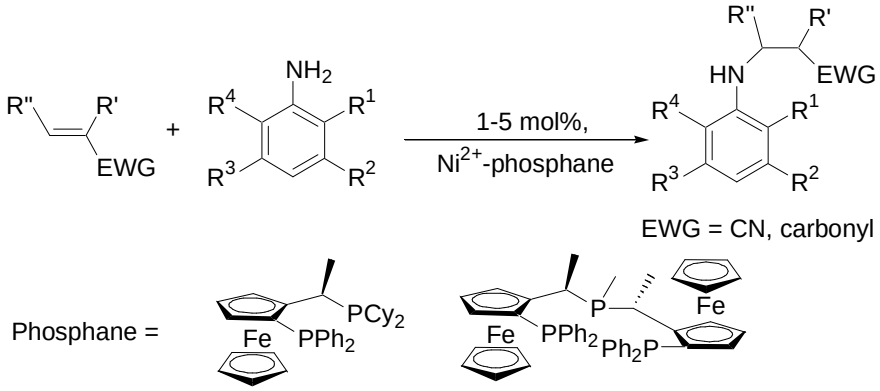
[102](a) R. P. Cheng, S. H. Gellman, W.F. Degrado, *Chem. Rev*, **2001**, *101*, 3219-3232. (b) S. H. Gellman, *Acc. Chem. Res*., **1998**, *31*, 173-180. (c) D. Seebach, S. Abele, J. V.Schreiber, B. Martinoni, A. K. Nussbaum, H. Schild, H. Schulz, H. Hennecke, R. Woessner, F. Bitsch, *Chimia*, **1998**, *52*, 734. (d) D. Seebach, J. L. Mathews, *Chem. Commun*., **1997**, 2015-2022. (e) T. Hintermann, D. Seebach, *Chimia*, **1997**, *50*, 244.

Sometimes, hydroamination of an activated olefin (1,2-addition) is also represented as special aza-Michael reaction. Hydroamination is the direct reaction of an alkene or alkyne with N-H bonds, which is a highly attractive route for the synthesis of nitrogen-containing compounds.[103] It is recognized that metal activation of the olefin /acetylenic bond or the amine is generally required as a preliminary step in catalytic hydroamination reactions.[104]



Scheme 16: *General asymmetric hydroamination reaction.*

In 2003 Togni et al. reported the hydroamination of α,β-unsaturated carbonyl compounds catalysed by Ni^{2+}-phosphane complexes (Scheme 17).[105]



Scheme 17: *Ni^{2+}-phosphane-catalysed hydroamination of α,ß-unsaturated carbonyl compounds with amines*

[103] See, (a) *Review*: T. E. Müller, M. Beller; *Chem. Rev*. **1998**, *98*, 675-703. (b) V. Neff, T. E. Müller, J. A. Lercher, *Chem. Commun.* **2002**, 906-907. (c) P. W. Roesky, T. E. Müller, *Angew, Chem. Int. Ed*. **2003**, *42*, 2708-2710.

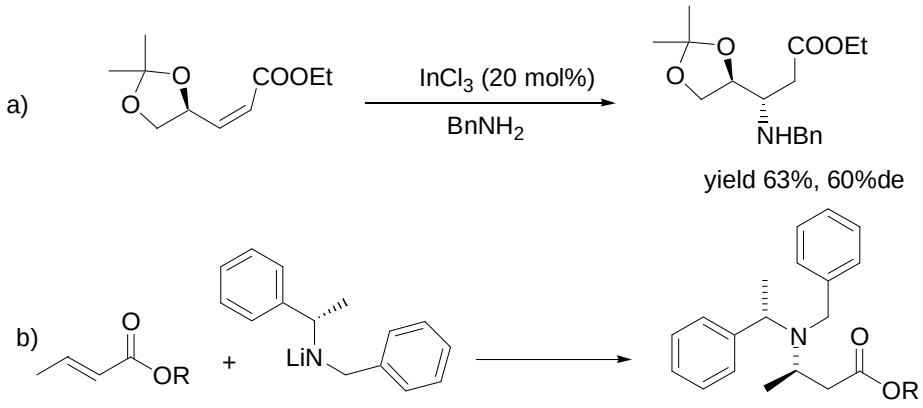
[104] (a) M. R. Gagné, c. L. Stern, T. J. Marks, *J. Am. Chem. Soc*. **1992**, *114*, 275-294. (b) R. Dorta, P. Egli, F. Zuercher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*,10857-10858. (c) S. Burling, L.D. Field, B. A. Messerle, *Organometallics* **2000**, *19*, 87-90. (d) U. Nettekoven, J. F. Hartwig, *J. Am. Chem. Soc*. **2002**, *124*, 1166-1167. (e) F. Pohlki, S. Doye, *Chem. Soc. Rev*. **2003**, **32**, 104-114. for recent development, see: K. Li, P. H. Phua, K. K. Hii, *Tetrahedron*, **2005**, *61*, 6237-6242 and references therein.

[105] L. Fadini, A. Togni, *Chem. Commun*. **2003**, 30–31.

In the aza-Michael reaction, single transition metal based Lewis acids, which coordinate with α,β-unsaturated carbonyl compounds (activated olefins), are often competitively displaced by the amine[106] and because of this reason, it is very difficult to get β-amino carbonyl compounds with high enantioselectivity.

In the last few years, the development of novel and efficient synthetic methods leading to chiral β-amino ketones and β-amino acids and their derivatives has attracted much attention in organic synthesis.[107] There are different strategies employed in order to achieve the desired high stereocontrol in aza-Michael reactions, (a) the use of Michael acceptors covalently attached/bond to chiral auxiliaries that can be easily removed from the final adduct, (b) the use of chiral nitrogen nucleophiles, (c) performing the reaction in the presence of a stoichiometric amount of a chiral ligand and (d) asymmetric catalysis.

The impressive achievements in the asymmetric aza-Michael reaction made to date rely principally on the use of chiral auxiliaries as the main controllers of the stereochemistry. The chiral acceptor and chiral amine controlled aza-Michael reaction are shown in Scheme 18 as an example. However, the accessibility of the chiral amine nucleophiles or Michael acceptors is somehow limited.

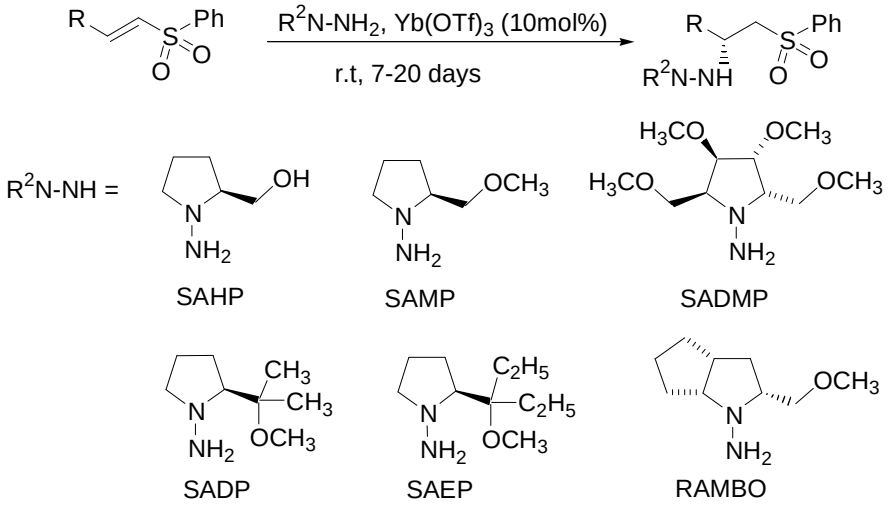


Scheme 18: *Asymmetric aza-Michael reaction of amines to enoates with chiral auxiliaries.*

[106] a) M. Kabatsura, J. F. Hartwig, *Organometallics* **2001**, *20*, 1960-1964; b) L. W. Xu, C. G. Xia, X. X. Hu, *Chem. Commun.* **2003**, 2570-2571.
[107] a) E. Juaristi, H. Lopez-Ruiz, *Curr. Med. Chem*. **1999**, *6*, 983-1004. (b) S. Abele, D. Seebach, *Eur. J.Org. Chem.* **2000**, 1-15. c) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991-8035. (d) J. You, H. J. Drexler, S. Zhang, C. Fischer, D. Heller, *Angew. Chem. Int. Ed*. **2003**, *42*, 913-916. (e) F. Fringuelli, F. Pizzo, M. Rucci, L. Vaccaro, *J. Org. Chem.* **2003**, *68*, 7041-7045. (f) F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603-1624.

The enantioselective synthesis of β-amino carbonyl and related compounds uses classical stoichiometric aza-Michael reactions with chiral auxiliaries or enantiomerically pure starting materials, as shown by the large number of reports.[108]

One remarkable advance in the chiral amine controlled aza-Michael reaction was achieved by Enders and coworkers.[109] This group developed the aza-Michael reaction of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and its derivatives with alkenyl sulphones to afford the corresponding β-amino sulphones with high diastereomeric excess (up to 96% de)(Scheme 19).



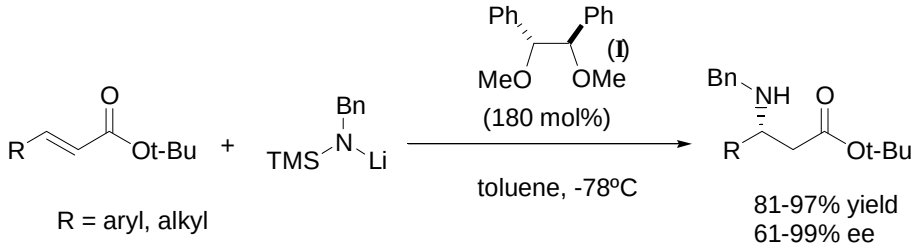
Scheme 19: *aza-Michael reaction of proline-derived hydrazines to electron poor alkenyl sulphones.*

[108] For selected examples, see: (a) H. Matsunaga, T. Sakamaki, H. Nagaoka, *Tetrahedron Lett.* **1983**, *24*, 3009-3012. (b) J. d'Anglo, J. Maddaluno, *J. Am. Chem. Soc.* **1986**, *108*, 8112-8114. (c) J. M. Hawkins, T. A.Lewis, *J. Org. Chem.* **1992**, *57*, 2114 -2121. (d) T. P. Toh, L. L. Wei, *Synlett,* **1998**, 975-977. (e) S. D. Bull, S. G. Davies, S. Delgado-Ballester, G. Fenton, P. M. Kelly, A. D. Smith, *Synlett* **2000**, 1257-1260. (f) G. V. M. Sharma, V. G. Reddy, A.S. Chander, K. R. Reddy, *Tetrahedron: Asymmetry* **2002**, *13*, 21-24. (g) G. Cardillo, L. Gentilucci, V. D. Matteis, *J. Org. Chem.* **2002**, *67*, 5957-5962. (h) M. Sani, L. Bruche, G. Chiva, S. Fustero, J. Piera, A. Voloterio, M. Zanda, *Angew. Chem. Int. Ed.* **2003**, *42*, 2060-2063. (i) A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 10677-10683.

[109] a) D. Enders, S. F. Müller, G. Raabe, *Angew. Chem. Int. Ed.* **1999**, *38*, 195-197. (b) D. Enders, S. Wallert, *Synlett*, **2002**, 304-306. (c) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253-2329. (d) D. Enders, S. Wallert, J. Runsink, *Synthesis* **2003**, 1856-1868.

In a similar manner, Davies and Fenwick[110] have explored the use *N*-trimethylsilyl-(*S*)-2-methoxymethyl-1-aminopyrrolidine (TMS-SAMP) as neucleophile in the aza-Michael addition process to α,β-unsaturated esters.

Tomioka and coworkers[111] have developed efficient chiral-ether-mediated enantioselective conjugate addition of lithium amides to alkyl enoates in the presence of 180 mol% of chiral ligand **I**, which provides a powerful entry into optically active β-amino carbonyl moieties with high enantioselectivity (91-99% ee) (Scheme 20).



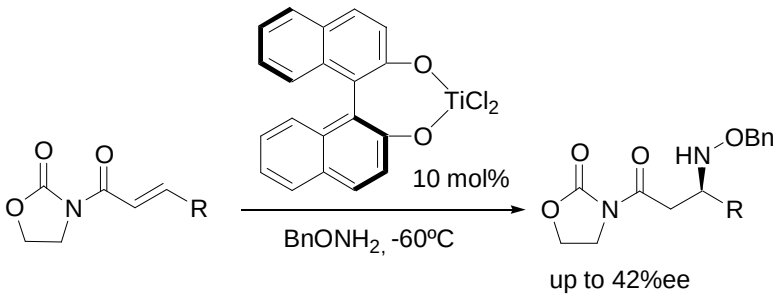
Scheme 20: *Chiral-ether-controlled enantioselective aza-Michael addition of lithium amides to enoates.*

The amount of lithium amide used was one of the crucial factors in determining the efficiency of the reaction. Lowering the amount of lithium amide from 3.0 equiv. to 1.5 equiv. produced Michael adducts with a drop in enantioselectivity from 93 to 82% and yield 92 to 81%.

The examples above illustrate the availability of asymmetric variants of the aza-Michael reaction under stoichiometric compsumption of the chiral inductor. However, the development of efficient chiral catalysts for the aza-Michael reaction remains a significant challenge because the most elegant and most economically attractive way to introduce chirality into a molecule is by using a catalytic amount of a chiral controller.

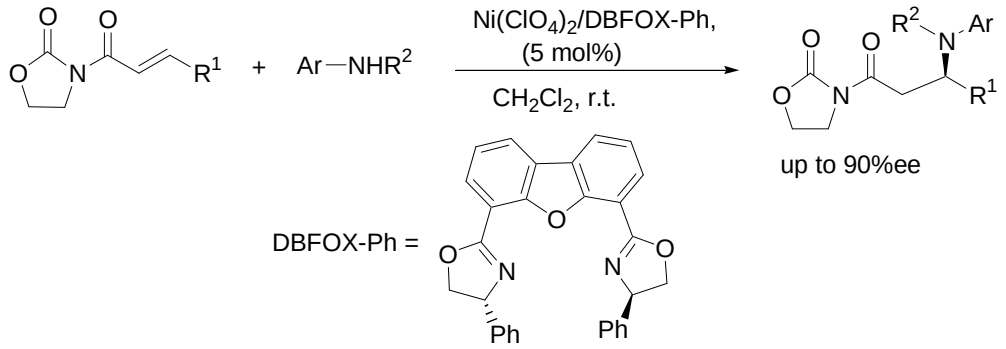
The first example of catalytic enantioselective aza-Michael addition of *O*-benzylhydroxylamine to *N*-enoyl oxazolidinones was reported by Jørgensen and coworkers in 1996[112](Scheme 21).

[110] S. G. Davies, D. R. Fenwick, *J. Chem. Soc. Chem. Commun.* **1995**, 1109-1110.
[111] H. Doi, T. Sakai, M. Iguchi, K. Yamada, K. Tomioka, *J. Am. Chem. Soc.* **2003**, *125*, 2886-2887.
[112] L. Falborg, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans. 1*, **1996**, 2823-8363.



Scheme 21: *Chiral Ti-BINOL- catalyzed aza-Michael addition of amine.*

From the same group it has been documented that secondary aromatic amines can be good nucleophiles for asymmetric aza-Michael addition. The reaction of *N*-methylaniline with *N*-alkenoyl oxazolidinones proceeds well in the presence of $Ni(ClO_4)_2.6H_2O$/DBFOX-Ph[113] as the Lewis acid catalyst, with enantioselectivity up to 90% (Scheme 22).[114]



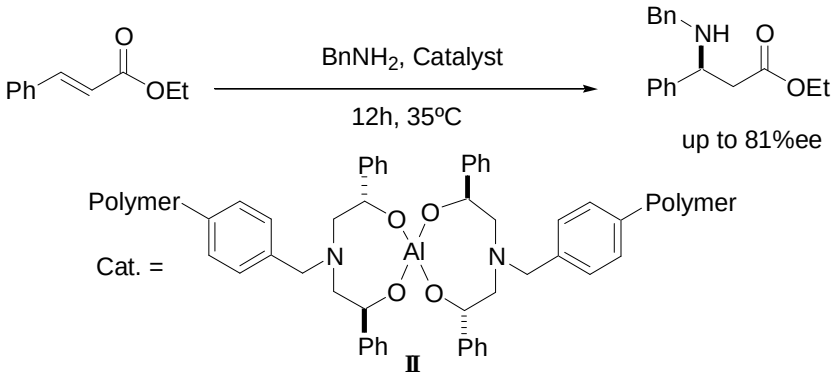
Scheme 22: *Chiral Ni-complex catalyzed conjugate addition of aromatic amines.*

The selectivity and chemical efficiency were found to be dependent on the reaction conditions, including solvents, catalyst, and other metal-salt-based Lewis acids.

Sundararajan and Prabagaran have utilized a novel polymer-supported Al-chiral catalyst **II** in the aza-Micheal addition of $BnNH_2$ to ethylcinnamate for the synthesis of chiral β-aryl-β-amino esters with high enatioselectivity (up to 81% ee) (Scheme 23).

[113] For catalyst, see: (a) S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, H. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074-3075. (b) S. Kanemasa, Y. Oderaotoshi, E. Wada, *J. Am. Chem. Soc.* **1999**, *121*, 8675-8676.

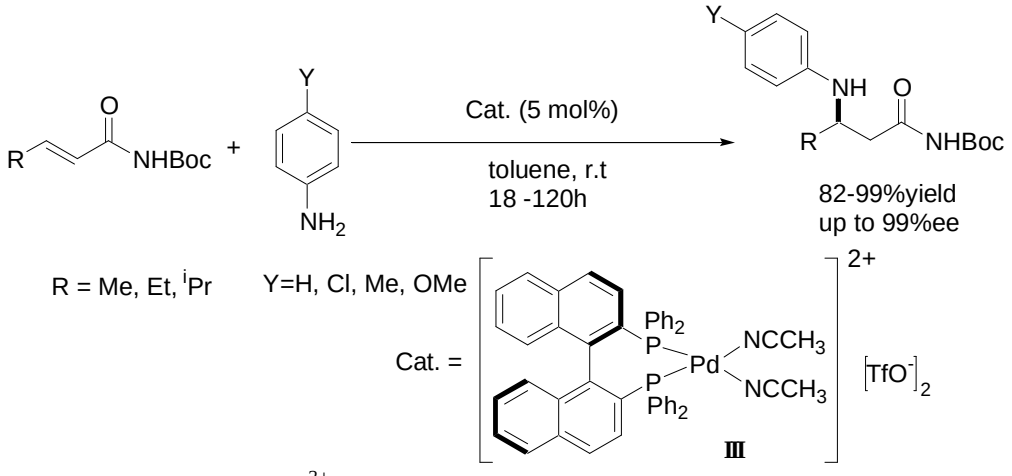
[114] W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Chem. Commun*. **2001**, 1240-1241.



Scheme 23: *Polymer-supported Al-catalyst-mediated aza-Michael reaction of benzyl amine.*

It should be noted that only simple filtration was needed for purification of the final product, and the catalyst could be easily recovered by washing with 1N HCl and reactivated by reacting with lithium aluminum hydride.[115]

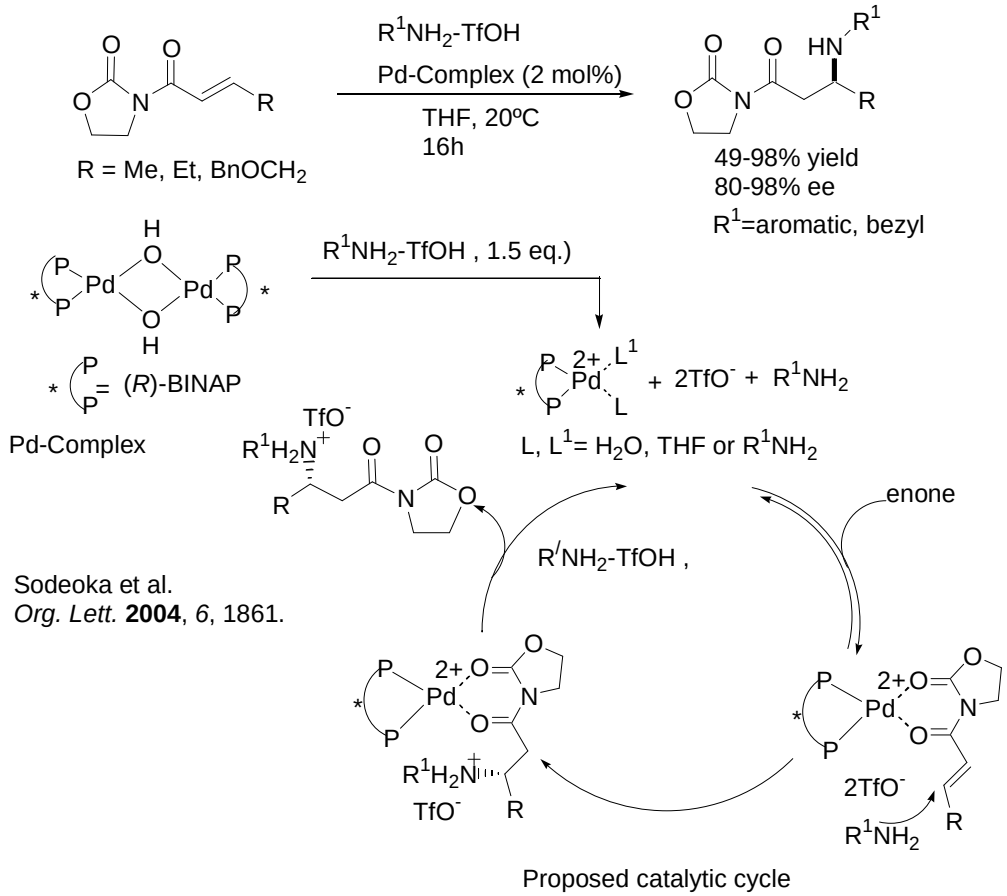
Later in 2003, Hii and coworkers have reported excellent enantioselectivity using $(CH_3CN)_2Pd^{2+}$-BINAP **III** for the addition of aromatic amines (Scheme 24).[116] Hii found that the reaction with electron rich amines did not achieve a synthetically useful level. These phenomena may be due to the basic character of amines, which causes deactivation of the Lewis acid catalysts by coordination to the metal centre and results in uncontrolled reactions.



Scheme 24: (*$CH_3CN)_2$ Pd^{2+}-BINAP –catalysed enantioselective Michael addition of anilines.*

[115] G. Sundararajan, N. Prabagaran, *Org. Lett.* **2001**, *3*, 389-392.
[116] (a)K. Li, K. K. Hii, *Chem. Commun*. **2003**, 1132-1133. (b) K. Li, X. Cheng, K. K. Hii, *Eur. J. Org. Chem.* **2004**. 959-964.

In 2004, Sodeoka and coworkers[117] introduced more robust, binuclear Pd catalyst for such progresses (Scheme 25). In this reaction, appropriate regulation of the amino functionality was achieved by the combined use of aq. Pd-BINAP and an amine salt (RNH_2, TfOH).



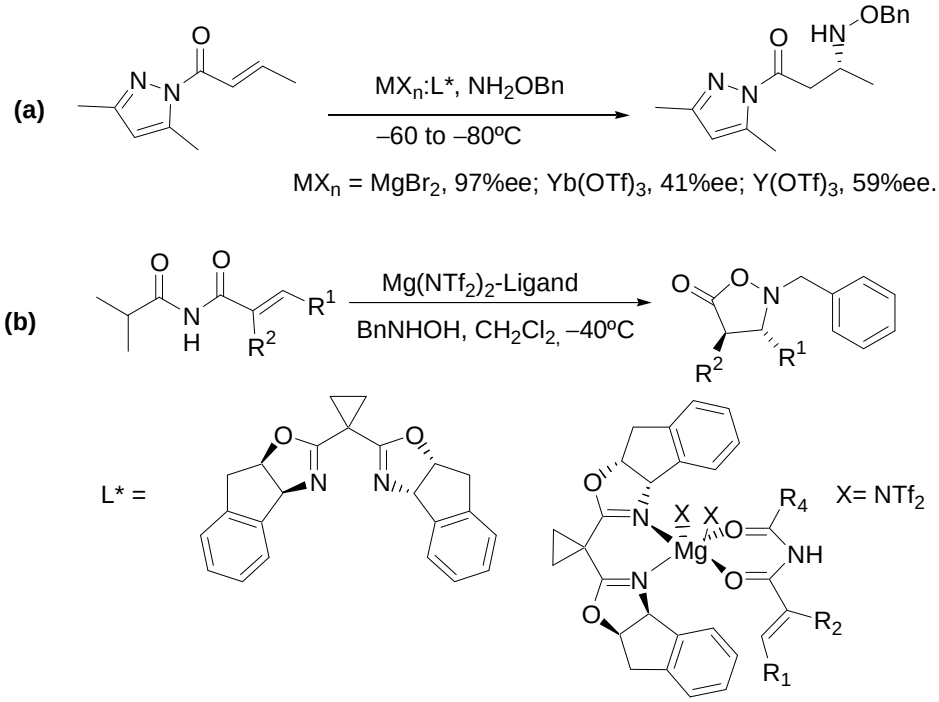
Scheme 25: *Aq.Pd-BINAP-catalysed aza-Michael reaction of amines in the presence of TfOH.*

As a result, both decomposition of the catalyst by amine and the uncontrolled spontaneous reactions were considerably suppressed. Furthermore, the reported aza-Michael reactions with both aromatic and alkyl amines were not so sensitive to either air or water and could be conducted without particular precautions. Although reaction mechanism has not been established, authors speculated that the monomeric Pd complex could activate alkenoyl oxazolidinones in a bidentate fashion, and then the concomitantly formed free amine would attack the activated double bond. Because the *Re*-face of the double bond is blocked preferentially by one of the phenyl groups of

[117] Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett*. **2004**, *6*, 1861-1864.

(*R*)-BINAP, the addition of amine proceeds from the si-face in a highly enantioselective manner to give the Pd enolate. Subsequent protonation of this Pd enolate, followed by dissociation of the product as the salt, would complete the catalytic cycle. In this step, protonation of the product might contribute to preventing the product from coordinating to the metal center.

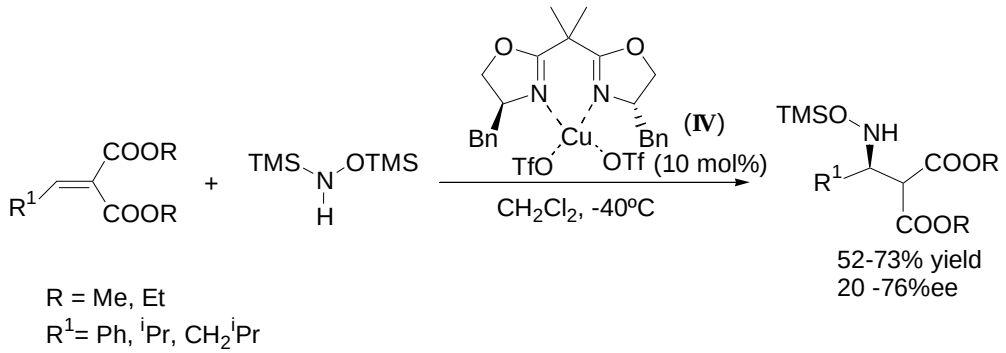
In a similar manner, Sibi and coworkers,[118] have recently developed a highly enantioselective protocol for the aza-Michael addition of *O*-benzylhydroxylamine to 3,5-dimethylpyrazole-derived enoates using catalytic amounts of $MgBr_2.OEt_2$:bisoxazoline complex (Scheme **26a**). Later, the same group has developed a Mg-BOX catalyst for the aza-Michael addition of BnNHOH to pyrazolidinone-derived acceptors.[119] Very recently the substrate scope was extended to α,β-disubstituted imide derivatives as acceptors which provide 96% ee in the presence of the same chiral ligand with magnesium triflimide (Scheme **26b**).[120]



Scheme 26: *Enantioselective conjugate addition of $BnONH_2$.*

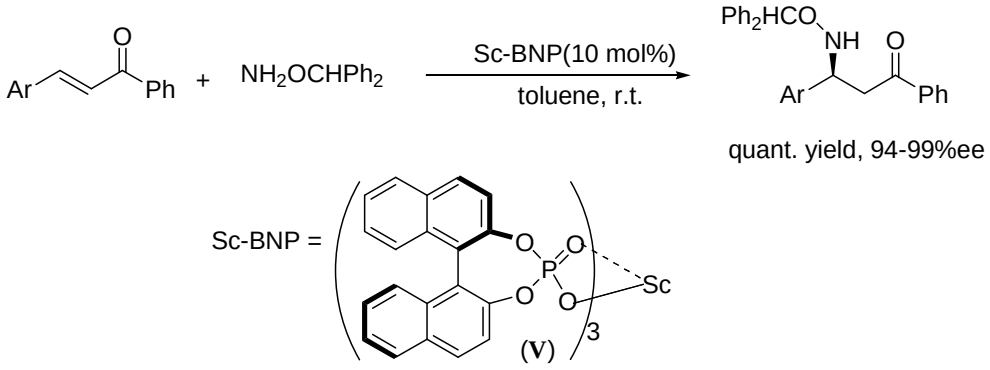
[118] (a) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc*. **1998**, *120*, 6615-6616. (b) M. P. Sibi, U. Grikunti, M. Liu, *Tretrahedron* **2002**, *58*, 8357-8363.
[119] M. P. Sibi, M. Liu, *Org. Lett*. **2001**, *3*, 4181-4183.
[120] M. P. Sibi, N. Pradagaran, S. G. Ghorpade, C. P. Jasperse, *J. Am. Chem. Soc*. **2003**, *125*, 11796-11797.

Independently, Cardillo and coworkers[121] reported that a bulkier amine nucleophile, (*N,O*-bis(trimethylsilyl)hydroxylamine), in the presence of the Cu^{II}-box complex **IV** provides selectivities in the range 20-76% with alkylidene malonates as acceptors (Scheme 27).



Scheme 27. *Cu(II)-box-catalysed aza-Michael addition of N, O-bis(trimethylsilyl) hydroxylamine derivatives with alkylidene malonates.*

Jin and coworkers[122] have shown that in the presence of chiral rare-earth-metal complexes as catalysts, O-alkylhydroxylamine can be reacted with α,β-unsaturated ketones to afford the corresponding β-amino ketones (Scheme 28).

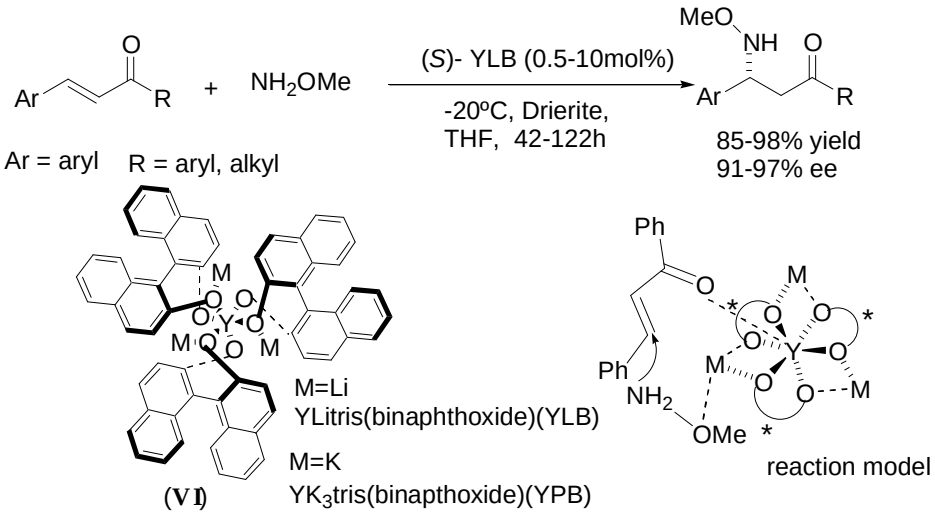


Scheme 28: *Sc^{III}- catalysed asymmetric aza-Michael reaction of O-alkylhydroxylamines to β-aryl enones.*

[121] a) G. Cardillo, L. Gentilucci, M. Gianotti, H. Kim, *Tetrahedron: Asymmetry* **2001**, *12*, 2395-2398. (b) G. Cardillo. S. Fabbroni, L. Gentilucci, M. Gianotti, R. Perciaccante, A. Tolomelli, *Tetrahedron: Asymmetry* **2002**, *13*, 1407-1410.
[122] X. L. Jin, H. Sugihara, K. Daikai, H. Tateishi, Y. Z. Jin, H. Furuno, J. Inanaza, *Tetrahedron* **2002**, *58*, 8321-8329.

The use of the Sc-BNP catalyst **V** and O-(diphenylmethyl)hydroxylamine as a nitrogen source under optimized conditions was found to provide the desired product with quantitative yield and up to 99% ee.

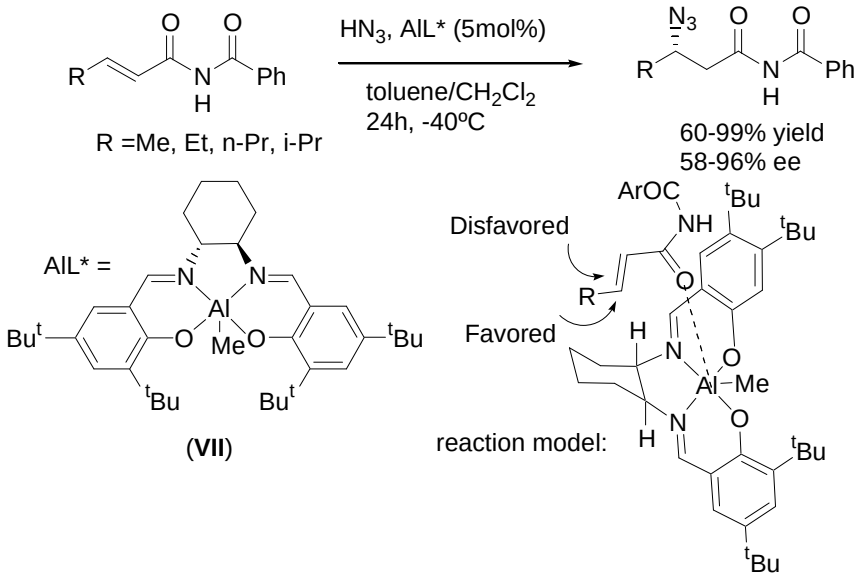
Shibasaki and coworkers[123] have developed an interesting heterobimetallic catalyst that contains rare-earth and alkali metals for the aza-Michael addition of O-alkylhydroxylamine to enones. The YLi_3tris(binaphthoxide) species **VI**, which contains chiral chelating binapthyl groups in their coordination spheres, give the best reactivity and enantioselectivity up to 99% ee, although substrate scope is somewhat limited (Scheme 29). Apart from *N*-akyl, *O*-alkyl hydroxyl amines, and aromatic amines other *N*- centered neucleophiles have also been used in aza-Michael processes.



Scheme 29: *Y-M heterobimetallic catalysis for the enantioselective aza-Michael reaction of O-alkylhydroxylamines to enones.*

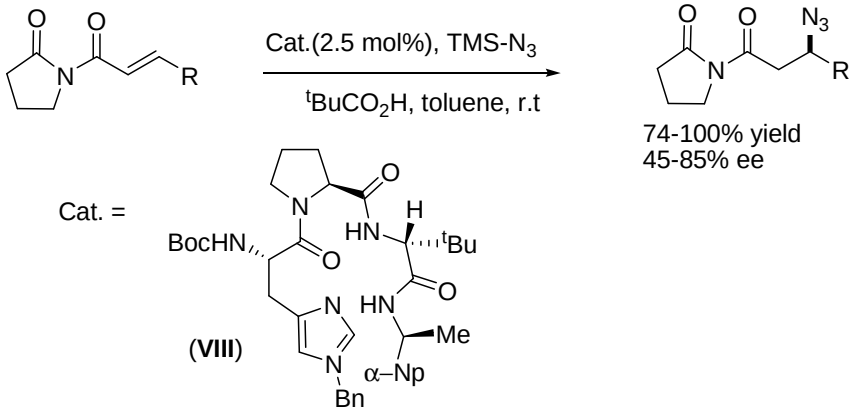
Jacobsen and coworkers[124] have found that the chiral salen Al^{III} complex **VII** catalyses the aza-Michael reaction of hydrazoic acid (HN_3) with α,β-unsaturated imides. This procedure provides access to a variety of enantiopure β-alkyl-β-azido compounds (Scheme 30).

[123] N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc*. **2003**, *125*, 16178-16179.
[124] J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc*. **1999**, *121*, 8959-8960.



Scheme 30: *Asymmetric aza-Michael reaction of hydrazoic acid with a,ß-unsaturated carbonyl compounds promoted by AlL* catalyst.*

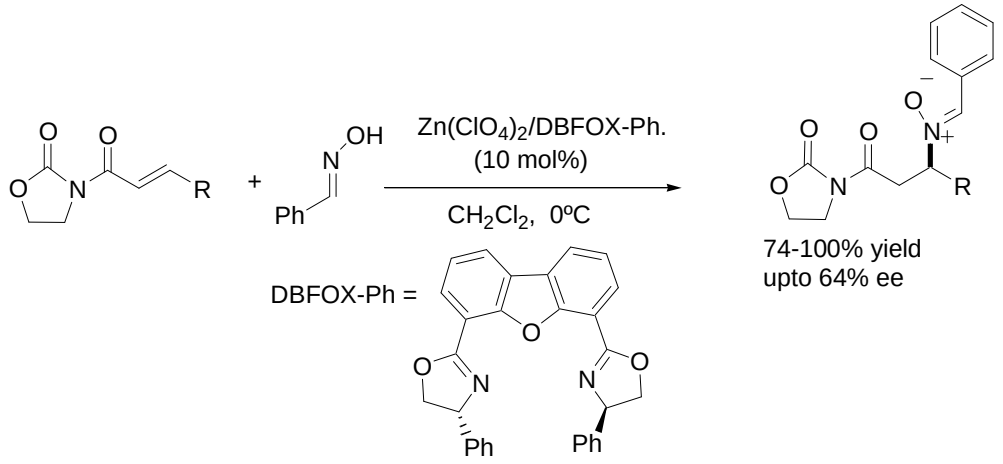
Recently Miller and coworkers[125] have developed a milder, metal free version of this aza-Michael or azidation reaction in which the azide nucleophile is generated from trimethylsilyl azide and 2,2-dimethyl-propionic acid ($^{t}BuCO_2H$) in toluene. Simple β-tripeptide **VIII** mediated aza-Michael of azide to enoates yields β-azido acids derivatives in up to 85% ee. The optimal catalyst was found to have a β-turn conformation, appended with a π-(benzyl)histidine residue to enhance the catalytic activity (Scheme 31).



Scheme 31: *Peptide promoted enantioselective conjugate addition of hydrazoic acid.*

[125] a) T. E. Horsemann, D. J. Guerin, S. J. Miller, *Angew. Chem.. Int. Ed.* **2000**, *39*, 3635-3638. (b) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc*. **2002**, *124*, 2134-2136.

The aza-Michael adition reactions of aldoximes can be accelerated by a catalytic amount of Lewis acid when imides are used as acceptors. The aqua complex derived from (*R,R*)-DBFOX-Ph and zinc(II) perchlorate hexahydrate is an specially active catalyst which afforded enantioselectivities up to 67% ee.[126] This work presents a new nitrone-forming reaction by *N*-alkylation through the aza-Michael reaction of aldoxime to α,β-unsaturated carbonyl compounds in the presence of Lewis acid catalyst although enantioselectivies are only modest (Scheme 32).

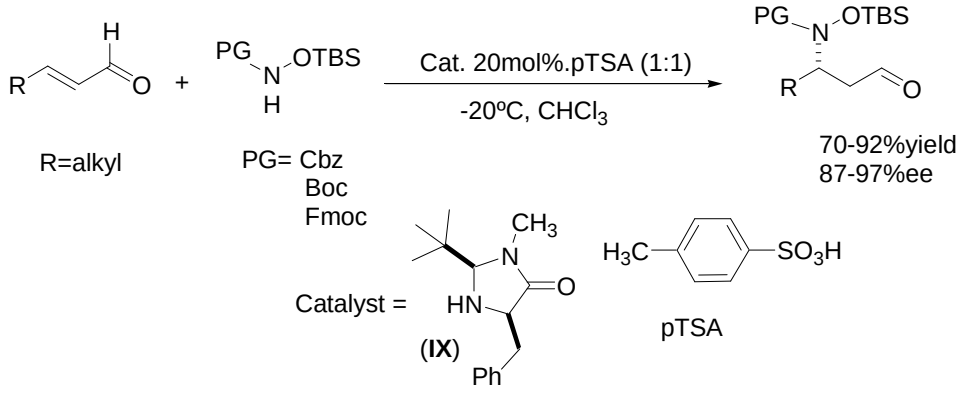


Scheme 32: *Zn:DBFOX- catalysed aza-Michael reaction of aldoximes.*

Catalytic activation of α,β-unsaturated carbonyls towards reaction with weaker nitrogen nucleophiles such as carbamates had, however, proven to be more difficult, and indeed it was only very recently that this reaction coud be realized catalytically through the use of certain Brønsted[127] and Lewis acids.[128] While these recent methods directly afforded useful N-protected β-aminocarbonyl adducts, asymmetric versions of this reaction, which are of potencially great practical importance, remained elusive.

[126] K. Nakama, S. Seki, S. Kanemasa, *Tetrahedron Lett.* **2002**, *43*, 829-832.
[127] T. C. Wabnitz, J. B. Spencer, *Org. Lett.* **2003**, *5*, 2141-2144
[128] (a) $Pd(CH_3CN)_2Cl_2$ and $[Pd(CH_3CN)_4](BF_4)_2$: J. M. Gaunt, J. B. Spencer, *Org. Lett.* **2001**, 3, 25-28. (b) T. C. Wabnitz, J. B. Spencer, *Tetrahedron Lett.* **2002**, *43*, 3891-3894. (c) T. C. Wabnitz, J. –Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484-493. (c) $RhCl_3$,$3H_2O$, $ReCl_5$ and other transition metal salts: S. Kobayashi, K. Kakumoto, M. Sugiura, M. *Org.Lett.* **2002**, *4*, 1319-1322. (d) $Bi(NO_3)_3$: N. Srivastava, B. K. Banik, *J. Org. Chem.* **2003**, *68*, 2109-2114. (e) $FeCl_3$ -Me_3SiCl: L. W. Xu, C. –Gu. Xia, X. –X. Hu, *Chem. Commun.* **2003**, 2570-2571. (f) $R_4N^+X^-/BF_3$,OEt_2: L- W. Xu, L. Li, C. -G Xia, S. –L. Zhou, J. W. Li, X. –X. Hu, *Synlett* **2003**, 2337-2340.

Very recently, after our research work, MacMillan and coworkers[129] have shown that carbamate derivatives act as good nucleophiles for the conjugate addition to α,β-unsaturated aldehydes promoted by organocatalysts. In particular, the chiral secondary amine **IX** in combination with para-toluene sulphonic acid (pTSA) in chloroform, afforded moderate to good yields (70-92%) and high selectivities (87-97%) (Scheme 33).



Scheme 33: *Carbamates conjugate addition to α,β-unsaturated aldehydes by organo catalysis.*

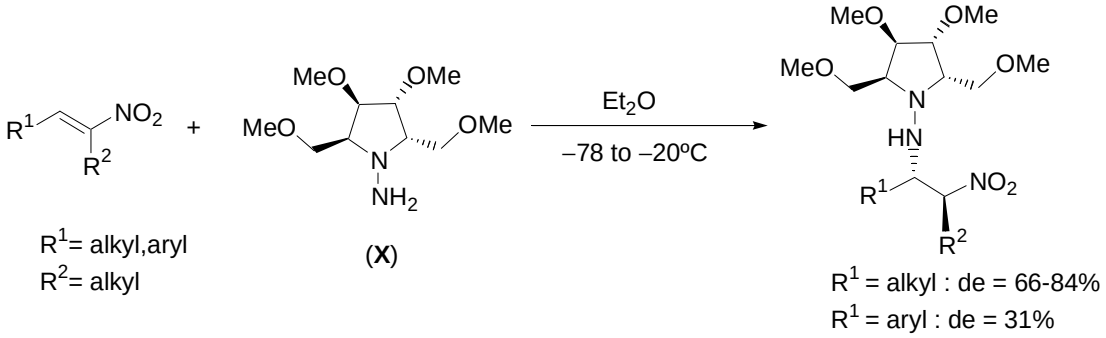
This method presents some limitations: (1) unprotected carbamates do not work and active nucleophiles such as PG-NHOTBS (PG = Cbz, Boc, Fmoc) need to be prepared; (2) β-aryl substituted enones are not tolerated and (3) in addition, to get good selectivities, 20 mol% catalyst is needed.

The 1,4-addition of chiral nitrogen nucleophiles to nitro olefins can also provide vicinal diamines or α-amino acids depending on the transformation of the nitro group.

Enders and coworkers[130] reported an auxiliary-controlled diastereo- and enantioselective synthesis of 1,2-diamines by an aza Michael reaction applying (–)-(*2S,3R,4R,5S*)-1-amino-3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine (ADMP)

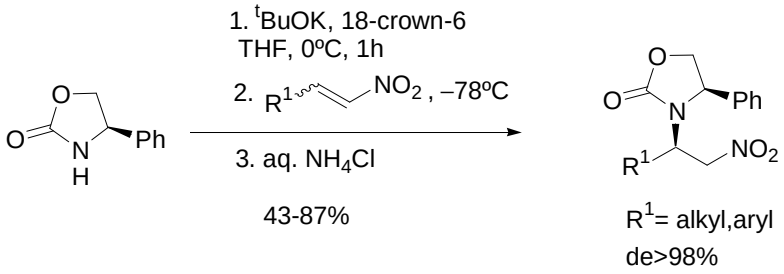
[129] Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2006**, *128*, 9328-9329.
[130] D.Enders, J. Weidemann, *Synthesis* **1996**, 1443-1450.

X as a chiral equivalent of ammonia (Scheme 34). Allowing ADMP to react with nitroalkenes provided the Michael adducts in good yields and diastereoselectivities.



Scheme 34: *Enantioselective conjugate addition of (–)-(2S,3R,4R,5S)-1-amino3,4-dimethoxy-2,5-bis(methoxymethyl)pyrrolidine (ADMP) to nitroalkenes.*

Mioskowski and coworkers[131] have used the potassium salt of (*R*)-and (*S*)-4-phenyl-2-oxazolidinone as enantiopure nucleophile in the aza Michael reaction. Deprotonation of the chiral amine with ^{t}BuOK in the presence of 18-crown-6 provided the 1,4-adducts in good yield as a single diastereomer regardless of the enantiomer of the oxazolidinone used. Interestingly, when (E)/(Z) mixtures of nitroalkenes were applied, a single product was still obtained (Scheme 35).

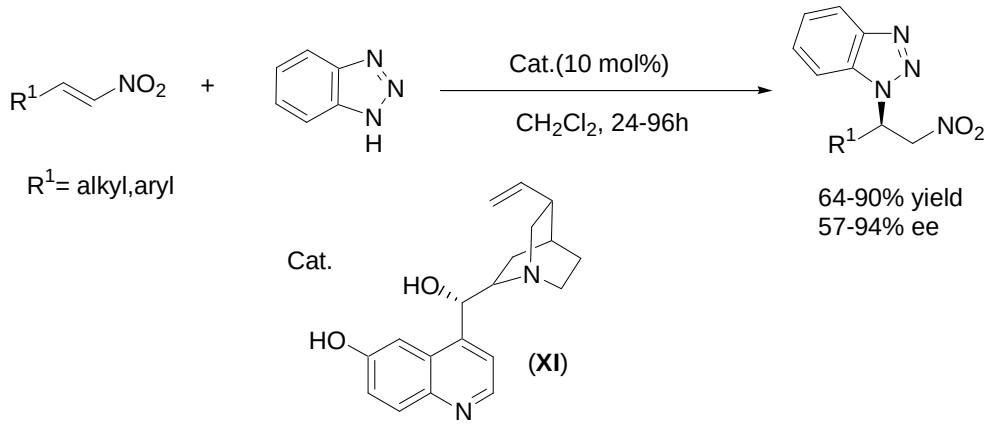


Scheme 35: *Diastereoselective conjugate addition of (R)- and (S)-4-phenyl-2-oxazolidinone to nitroalkenes.*

Very recently Wang and coworkers[132] have described the asymmetric version of the conjugate addition reaction of nitrogen heterocycles with a variety of nitroolefins under 10 mol% catalyst **XI** at -20ºC in dichloromethane. The results

[131] M.-L. Leroux, T. Le Gall, C. Mioskowski, *Tetrahedron: Asymmetry* **2001**, *12*, 1817-1823 and references therein.
[132] J. Wang, H. Li, L. Zu, W. Wang, *Org. Lett.* **2006**, *8*, 1391-1394.

showed that in general the reactions took place efficiently (64-90%) with moderate to excellent levels of enantioselectivity (57-94%)(Scheme 36).



Scheme 36: *Enantioselective heterocyclic aza nucleophile addition to nitroalkenes.*

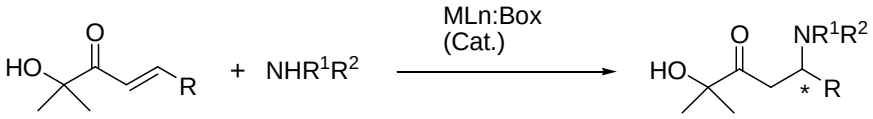
Overall, the conjugate addition of *N*-centered nucleophiles to electron deficient olefins under catalytic control has not found a general solution yet. It has been postulated that a major obstacle to the development of Lewis acid-catalysed enantioselective conjugate additions of carbamates is the possibility for alternative nonselective pathways to be catalysed by Brønsted acids (protons) resulting from the hydrolysis of Lewis acids in reaction media.[133]

The examples shown herein are certainly only the beginning and have limited applications. Our aim and research interest was the search for efficient and flexible aza-nucleophiles which can show high efficiency in terms of enantioselectivity and reactivity in the presence of known Cu(II)–bis(oxazoline) complexes as chiral catalysts. Acceptors such as achiral α'–hydroxy enone templates and nitroalkenes were selected and elaboration of the adducts to the corresponding β-amino acids and 1,2-diamines was another subject of interest.

[133] For detailed on this subject, see: T. C. Wabnitz, J.-Q Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484-493.

3.2 Results and discussion

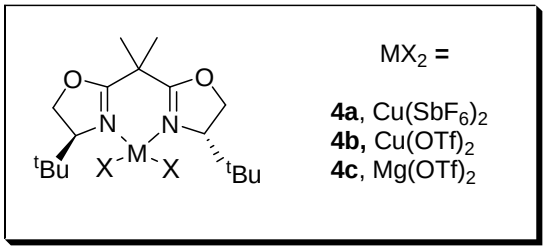
Based on the previous results (described in general introduction) by our group on the use of α'–hydroxy enones as templates in the asymmetric Diels-Alder reaction,[134] we set out to establish the validity of α'–hydroxy enones as Michael acceptors against *N*-nucleophiles under the pertinent catalyst system. We selected for first trials the metal-bisoxazoline systems as the catalyst, and a series of *N*-nucleophiles were tested (Scheme 37).



1a-h

Scheme 37. *Proposed reaction for screening of reagents and conditions.*

The catalysts employed for initial test are depicted below,



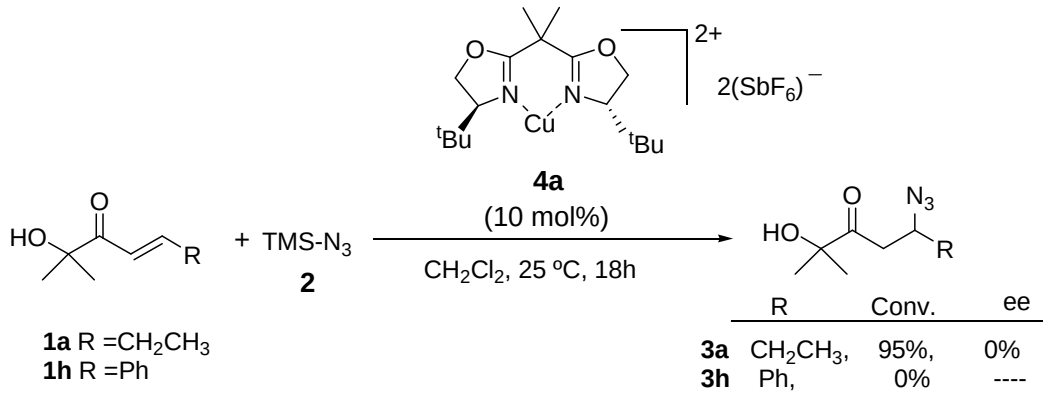
3. 2. 1 Preliminary results with

(i) Trimethylsilyl azide (TMS-N_3)

For the initial studies β–ethyl–α'–hydroxy enone **1a** and β–phenyl–α'–hydroxy enone **1h** were employed as testing bench and research was focused on the use of trimethylsilyl azide (TMS-N_3) as the *N*-centered neucleophile under catalytic action of $Cu(SbF_6)_2$: ^{t}BuBox (Scheme 38). The reaction protocol consisted of *in situ* preformation of the catalyst **4a** by admixing $Cu(SbF_6)_2$ and chiral ligand (2,2-isopropylidenebis[(4*S*)-4-tertbutyl-2-oxazoline) in CH_2Cl_2 for 3h at room temperature. To the catalyst green solution at the specified temperature addition of enone **1a**, stirring for 30 mins, and subsequent addition of trimethylsilyl azide was carried out. The reaction progress was

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

easily monitored by TLC analysis, and conversion was calculated by ^{1}H NMR (500 MHz).



Scheme 38: *Preliminary experiment: aza-Michael addition of TMS-N_3 (**2**) to enones **1a** and **1h** conducted by catalyst **4a**.*

In the first run at room temperature for 18h, aza-Michael adduct **3a** was obtained in 70% conversion with 0% enantiomeric excess.[135] The 1,4-addition of azide was the only product of the reaction with substrate **3a** and conversions were generally good without selectivity. In an attempt to get some enantioselectivity, we considered to reduce the reaction temperature down to −20ºC. However, at this temperature, the reaction rate was very slow (after 20h, 70% conversion) and there was no improvement on selectivity. Later on, the reaction of β-phenyl substituted enone **1h** was evaluated. Moreover, it was observed that there was no reaction even at higher temperature.

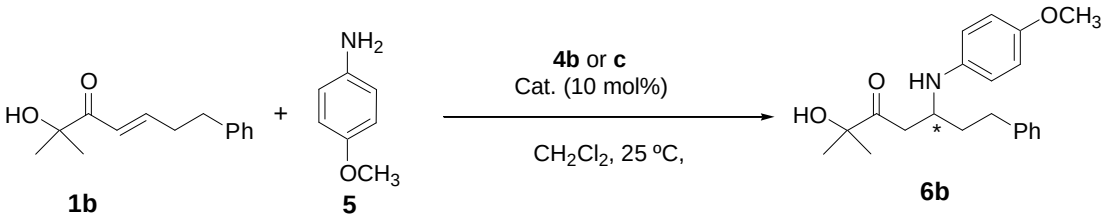
Unfortunately no enantioselectivity was observed in any of the reactions employing chiral ligands, possibly because of the reasonably fast background reaction, which occurs in the absence of catalyst to get racemic product.

(ii) *p*-anisidine

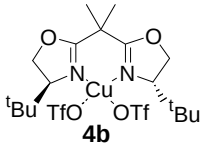
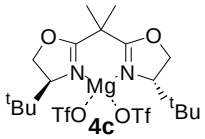
In a second stage, we turned down to the use of *p*-anisidine as the N-nucleophilic species. Accordingly, the reaction of β–phenylethyl–α'–hydroxy enone **1b** and *p*-anisidine was studied under different conditions as shown in table 2.

[135]Note: For this particular case, determination of the ee by chiral stationary phase HPLC was unsuccessful and instead NMR using Europium tris [3-trifluoromethylhydroxymethylene)-(+)-camphor] as chiral shift reagent was employed. Reaction did not work with Lewis acid $Cu(OTf)_2$.

Table 2. *Reaction between p-anisidine and enone **1b** conducted by catalyst **4b** and **4c**.*



1b **5** **6b**

Entry	Catalyst	Time(h)	Conv. (%)[a]	(ee),%[b]
1	----	6.5	0.0	---
2	$Cu(OTf)_2$	8	>95	---
3	$Mg(OTf)_2$	7.5	>95	---
4	 **4b**	15	>95	0
5		18	63	0[c]
6	 **4c**	4.5	95	0

[a]Conversions were determined by ^{1}H NMR (500 MHz). [b]Determined by HPLC chiralcel OD column (Hex: IPA)(90:10), 0.5 mL/min. R_t = 36.1min, 44.5min. [c]Reaction was ran at 0ºC.

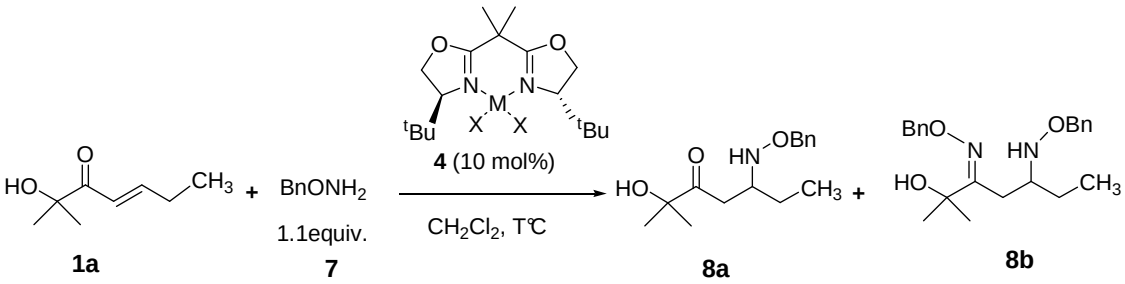
In most cases, studied at 25ºC, the observed conversions to the desired 1,4–addition product **6b** were almost quantitative, but enantioselectivity was 0%. By running the reaction at 0ºC (entry 5) no improvement of ee was detected and the conversion diminished. Reasons for the lack of the enantioselectivity observed in this reaction can be suggested. Firstly, $Cu(OTf)_2$ and $Mg(OTf)_2$ both significantly catalyze the reaction without any ligand being present (entry 2, 3). For reactions with chiral ligands there may be equilibrium at play in which free metal species are present and catalysing the racemic reaction. Also, *p*-anisidine itself has strong coordinating power and may be interacting with the metal forming achiral complexes capable of catalysing the racemic conversion. These considerations moved us to shift to other N-centered nucleophiles.

(iii) *O*-benzylhydroxylamine ($BnONH_2$)

The disappointing results observed with TMS-N_3 and *p*-anisidine as *N*–nucleophile reagents turned our attention towards the use of hydroxylamine derivatives. The first option was the use of *O*-benzylhydroxylamine **7** and the β–ethyl–α'–hydroxy enone **1a** in the presence of catalysts **4b** and **4c**, and the results are shown in Table 3.

In general, this reaction was inefficient at room temperature because of the presence of multiple products. When reaction temperature was reduced to 0ºC, the desired 1,4-addition product **8a** was obtained along with the side double addition product **8b**. The reaction generally did not reach completion and multiple spots were present on TLC.

Table 3. *aza-Michael addition of **7** to enone **1a** promoted by catalysts **4b** and **4c**.*[a]



Entry	Catalyst		TºC	Time(h)	**8a**[b](ee%)	**8b**[c]
	Comp.	MX_2				
1	**4b**	$Cu(OTf)_2$	0	5	84	n.d
2	**4b**	$Cu(OTf)_2$	-20	21	52	n.d
3	**4b**	$Cu(OTf)_2$	-40ºC	90	72	n.d
4	**4c**	$Mg(OTf)_2$	0	5	13	n.d

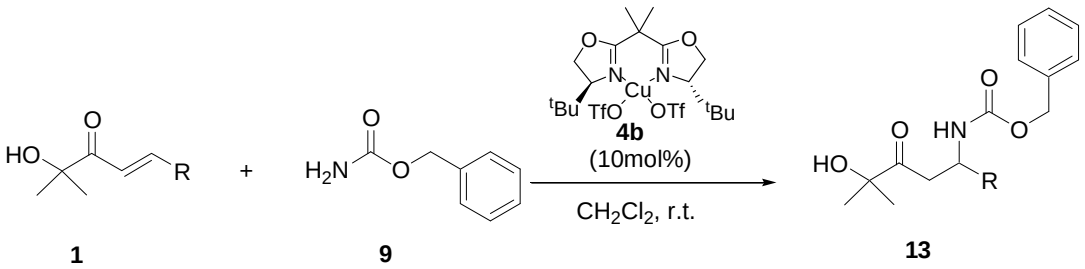
[a] All reactions were conducted at 0.5 mmol scale, reaction time specified, with mole ratio of enones : O-benzylhydoxylamine : catalyst = 1:1.1:0.1; Conversion was not determined.[b]ee was determined Chiralcel OD column, (90:10) hexane: IPA, 0.5 mL/min., 210 nm, Rt = 11.0 min. major, 13.1 min. minor. [c]**8b** was observed in all entries but quantity was not determined.

The major problem was the production of the 1,2- and 1,4-double addition product (**8b**), even at low temperature with decreasing ee (table 3, entry, 2, 3). It is possible that after formation of the 1,4-product in the reaction, the ketone carbonyl subsequently becomes activated towards further 1,2-addition through hydrogen bonding. This reaction was abandoned due to these inherent problems.

(iv) Carbamates

Next we turned our attention to carbamates as nucleophiles. Carbamates are presumed to posses more attenuated nucleophilicity, which might preclude form over addition products. Furthermore, eventual deprotection of the *N*- atom could be performed under very smooth conditions in adducts when derived. We started initial exploration with easily accessible β–phenylethyl α'–hydroxy enone **1b** (table 4, entry 2) and commercially available benzylcarbamate, **9** in the presence of catalyst **4b**. The estimation of reaction progress was easily monitored by TLC analysis, while purification of the crude product was effected by flash column chromatography.

Table 4: *aza-Michael addition of **9** to enones **1a**,**b**,**e** catalysed by **4b**.*[a]



Entry	Substrate **1**	R	Time(h)	Pdt **13**	Yield(%)[b]	ee(%)[c]
1	**a**	CH_2CH_3	66	**a**	83	96
2	**b**	CH_2CH_2Ph	72	**b**	86	96
3	**e**	$CH(CH_3)_2$	67	**e**	53	98

[a]All reactions were conducted at 2.0 mmol scale, reaction time specified, with mole ratio of enones : benzylcarbamate : catalyst =1:2:0.1. [b] Isolated yield after column chromatography. [c]ee was determined by HPLC.

In the first run, at room temperature for 66 h, the aza-Michael adducts **13a** was obtained in 83% isolated yield with 96% ee. Similar results were also obtained with

enones **1b** and **1e** which led to corresponding product **13b** in 86% isolated yield with 96% ee (entry 2) and **13e** in 53% isolated yield with 98% ee (entry 3) respectively.

Based on these preliminary experiments with catalyst **4b**, other catalysts and metal salts were screened. With other bis(oxazoline) ligands as shown in Fig. 11, another different metal salts $Mg(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$ were also used. In this regard, many structural variants are available for the BOX ligand category. In particular, it is well reported that the bis(oxazoline) ligands can be modified by changing the substituents on bridging methylene (2, 2´–position) and oxazoline ring (4, 4´–position).

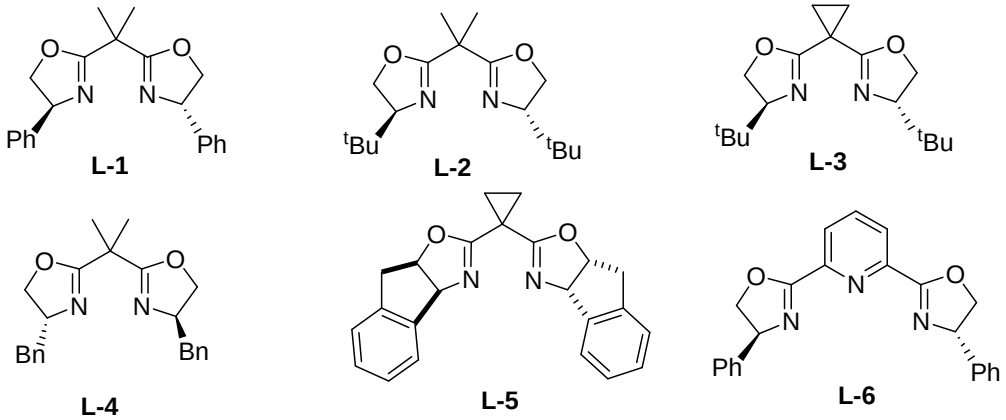
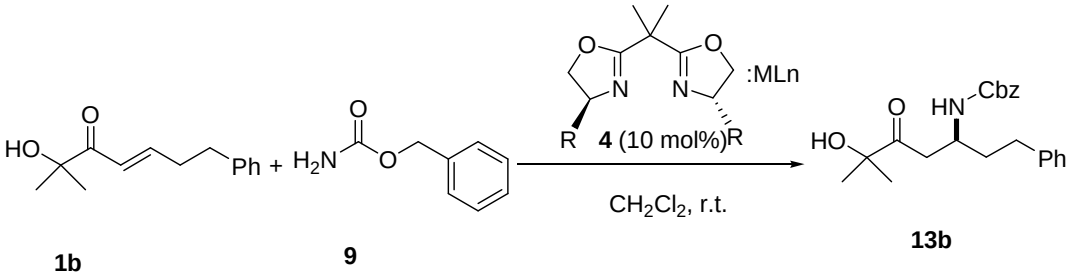


Figure 11: *Box-type chiral ligands evaluated in the aza-Michael reaction of carbamates.*

To this purpose, the $Cu(SbF_6)_2$ salt was preformed from $CuCl_2$ and $Ag(SbF_6)_2$ according to described protocol[136]and then the same sequence of addition of reagents as above described was employed. Unfortunately catalyst **4a** (^{t}BuBox : $Cu(SbF_6)_2$) was unable to promote the reaction (table 5, entry 1, 2).

[136] D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc*. **2000**, *122*, 1635-1649.

Table 5: *Asymmetric aza-Michael addition of benzyl carbamate **9** with α'–hydroxy enone **1b** promoted by metal-box complexes **4**.*[a]



1b **9** **13b**

Entry	catalyst		Solvent	Time(h)	Yield (%)[b]	ee (%)[c]
	Comp, MLn	R				
1	**4a**, $Cu(SbF_6)_2$	^{t}Bu	CH_2Cl_2	48	0[d]	---
2				44	0[f]	---
3	**4b**, $Cu(OTf)_2$	^{t}Bu	Et_2O	72	99	99
4			THF	72	05[d]	---
5			CH_3CN	72	0[d]	---
6			CH_2Cl_2	72	86	96
7	**4c**, $Mg(OTf)_2$	^{t}Bu	CH_2Cl_2	144	0[d]	---
8	**4d**, $Zn(OTf)_2$	^{t}Bu	CH_2Cl_2	144	0[d]	---
9	**4e**, $Cu(OTf)_2$	Ph	CH_2Cl_2	72	49[e]	83
10	**4f**, $Cu(OTf)_2$	Bn	CH_2Cl_2	72	0[d]	---

[a]All reactions were conducted at 0.5 mmol scale, reaction time specified, with mole ratio of enones : benzylcarbamate (**9**):catalyst =1:2:0.1. [b] After column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on the NMR of the crude product after specified time. [e]Reaction time was not optimized.[f]Reaction ran with enone **1e**.

Although copper metal has been used for preliminary reactions, based on previously reported results, other metals were also considered. Fpr example, the aza-Michael addition reaction using catalyst **4c** prepared from ligand **L-2** and $Mg(OTf)_2$,

resulted in no conversion (entry 7). Catalyst **4d** prepared admixing chiral ligand **L–2** and $Zn(OTf)_2$, was unable to promote the reaction too (entry 8).

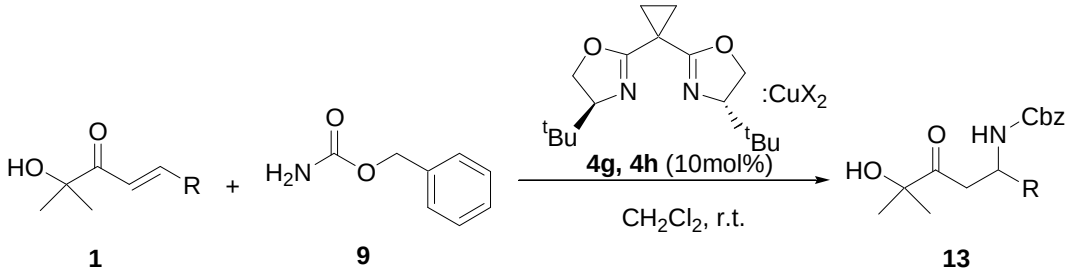
Another possibility that we examined was the effect of the substituents at 4, 4´–positions of the Box ligands. While catalyst **4e** resulted in 83% ee (entry 9), catalyst **4f** was unable to promote the reaction (entry 10).

Among the other solvents tested, neither THF nor acetonitrile led to any significant reaction conversion (entry 4, 5), while Et_2O led to a remarkable 99% conversion and 99% ee (entry 3).

In the next step, structurally modified box ligands were studied. Work by Denmark had demonstrated that changes at the methylene bridge in the bis(oxazoline) ligands can enhance the selectivity. To get the beneficial effect of modifying the ligands bite angle in bis(oxazoline) ligands bridging dimethyl moiety of ligand **L–2** has been substituted by a cyclopropyl ring, as reported by Denmark, Sibi, Pfaltz and Davies independently.[137] The cyclic bridged bis(oxazoline) ligand (spiro-box) (**L–3**) was prepared starting from the commercially available 2,2´–methylene bis(oxazoline) and 1,2–dibromoethane (see experimental section). Hence, catalyst **4g** was prepared using this chiral ligand 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane (**L–3**) and $Cu(OTf)_2$.

[137](a) S. E. Denmark, C. M. Stiff, *J. Org. Chem*. **2000**, 65, 5875-5878. (b) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615-6616. (c) D. Muller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232-240. (d) I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Chem. Commun.* **1996**, 1753-1754.

Table 6: *aza-Michael reaction of carbamate **9** with enones promoted by catalyst **4g** and **4h**.*



1 **9** **13**

Entry	Subs.**1**	R	Cat.	CuX_2	Time(h)	Product **13**	Yield(%)[b]	ee(%)[c]
1	**a**	CH_2CH_3	**4g**	$Cu(OTf)_2$	48	**13a**	98	92 (*S*)
2	**b**	CH_2CH_2Ph	**4g**	$Cu(OTf)_2$	40	**13b**	92	98 (*S*)
3					44	**13b**	50	94[d] (*S*)
4					20	**13b**	83	98[e] (*S*)
5			**4h**	$Cu(SbF_6)_2$	48	**13b**	38	>98(*R*)
6	**e**	$CH(CH_3)_2$	**4g**	$Cu(OTf)_2$	42	**13e**	31	94 (*S*)

[a]All reactions were conducted at 0.5 mmol scale, reaction time specified, with mole ratio of enones : benzylcarbamate (**9**):catalyst =1:2:0.1. [b] After column chromatography. [c] Determined by chiral HPLC. [d]Reaction conducted with 1.0 equiv. of **9**. [e]Reaction conducted with 4.0 equiv. of **9**.

The reaction carried out by using catalyst **4g** with different enones **1a**, **1b** and **1e,** resulted in comparatively same enantioselectivity i.e. **13a**, obtained with 98% isolated yield and 92% ee (table 6, entry 1); **13b**, 92% yield with 98% ee (entry 2**)** and **13e**, 31% yield with 94% ee (entry 6) respectively. But when catalyst **4h** was prepared and reaction conducted with substrate **1b**, after 48h at 25ºC, **13b** was isolated in 38% conversion and >98% ee of the opposite enantiomer (entry 6). In order to avoid time consumption and seeking for economy during preparation of the chiral ligand, like in the case of **L-3**, we selected **L-2** ligand as most practical for our asymmetric aza-Michael reaction.

On the other, the amount of benzylcarbamate **9** seemed not to influence enantioselectivity. For instance, when carbamate **9** loading was changed from 2 equiv. to 4 equiv., after 20h, **13b** was obtained in 83% chemical yield and 98% ee (entry 4) and with 1.0 equiv. of carbamate, after 44h, **13b** was obtained with 94% ee in 50% chemical yield (entry 3).

3. 2. 2 Substrate Scope

After screening reaction conditions and catalyst for the conjugate addition of benzylcarbamate **9** to enones **1a**, **1b** and **1e**, it was obvious that catalyst **4b** was the most convenient for further development. Substrate scope included on the variation of the R substituant at C_β of the α'-hydroxy enone as well as R' group on the carbamate counterpart. About variation on the carbamates, benzylcarbamate was used for initial screening but other carbamates like tert-butyl carbamate **10,** methyl carbamate **11**, and ethyl carbamate **12**, which are commercially available, were also checked. Results are uniformly satisfactory for a series of β-alkyl substituted enones **1a-g** (table 7). Thus linear as well as branched chain alkyl derivatives gave high range of selectivity. With alkyl groups branched at the β-carbon, 20 mol% catalyst was needed in order to avoid long reaction time (entry 10, 11). For enone **1g** bearing the bulky tert-butyl group, refluxing conditions were required (entry 13). Interesting, no detrimental effect on enantioselectivity was observed in this instance.

Regarding the carbamate counterpart, as seen from the table, the reaction tolerates well carbamates **9** and **10** while carbamates **11**-**12** provided poor yield but good selectivity and needed longer reaction times (table 7, entry 4, 5). On the other hand, more sterically hindered carbamates, *N*-benzylbenzylcarbamate (BnHNCOOBn) **17** and *N*-benzyltertbutylcarbamate (BnHNCOOtBu) **18** were prepared using known procedures (see experimental part) and showed to be inert with enone **1b** under the described reaction conditions.

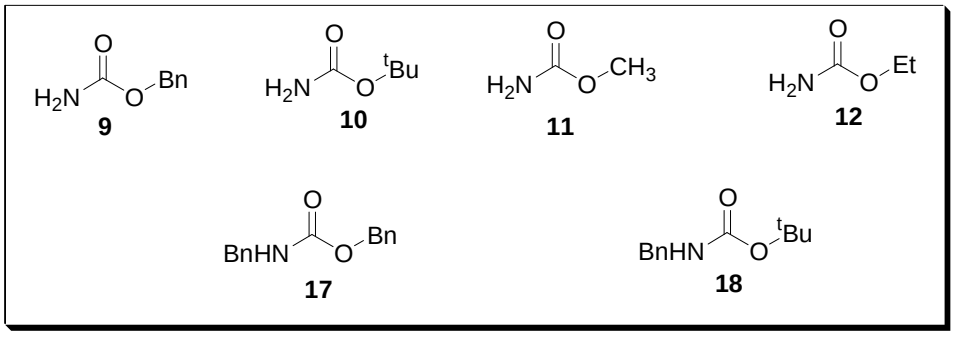
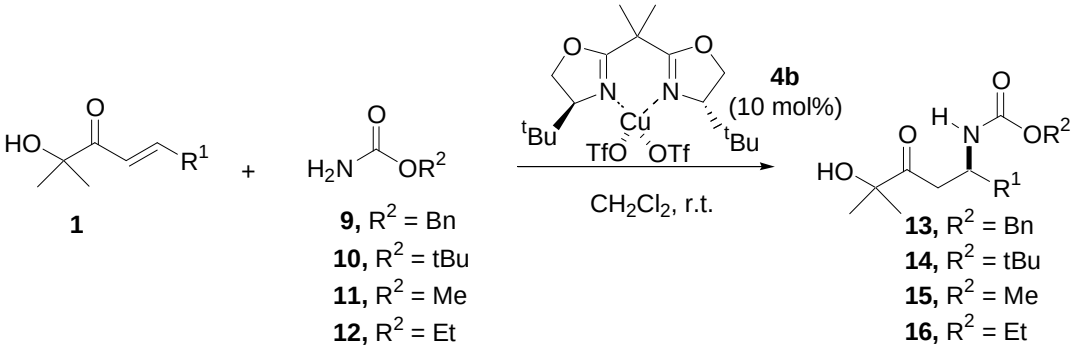


Figure 12: *Selected carbamates.*

Table 7: *Aza-Michael addition of carbamates* ***9-12*** *with various α'–hydroxy enones* ***1a-g*** *promoted by catalyst* ***4b***.



1

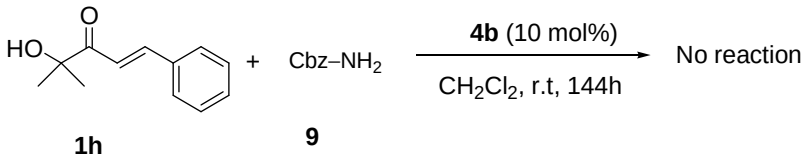
9, R^2 = Bn
10, R^2 = tBu
11, R^2 = Me
12, R^2 = Et

13, R^2 = Bn
14, R^2 = tBu
15, R^2 = Me
16, R^2 = Et

Entry	α'-hydroxy enone **1**		Carbamate		Time,h	Product	Yield,%[b]	ee,%[c]
	Comp.	R^1	Comp.	R^2				
1	**a**	CH_2CH_3	**9**	Bn	46	**13a**	89	92
2	**b**	CH_2CH_2Ph	**9**	Bn	71	**13b**	86	96
3			**10**	^{t}Bu	18	**14b**	92	88
4			**11**	Me	118	**15b**	51[d]	99
5			**12**	Et	142	**16b**	74	96
6	**c**	$(CH_2)_5CH_3$	**9**	Bn	62	**13c**	66	92
7			**10**	^{t}Bu	18	**14c**	76	96
8	**d**	$CH_2CH(CH_3)_2$	**9**	Bn	68	**13d**	71	96
9			**10**	^{t}Bu	22	**14d**	87	98
10	**e**	$CH(CH_3)_2$	**9**[e]	Bn	67	**13e**	53	98
11	**f**	*c*-C_6H_{11}	**9**[e]	Bn	96	**13f**	57	94
12			**10**	^{t}Bu	100	**14f**	85	91
13	**g**	$C(CH_3)_3$	**9**[f]	Bn	96	**13g**	65	94

[a]Reactions performed on 2 mmol scale with a ratio 1:carbamate:4b; 1:2:0.1. [b] Isolated yield after column chromatography. [c] Determined by HPLC using Chiralpak AD, AS, and Chiralcell OD columns. [d] Volatile compound. [e] 20 mol% of catalyst was used. [f] Reaction carried out at refluxing conditions.

From the very beginning, it was observed that β-aryl substituted hydroxy enones performed less satisfactorily. For instance, easily accessible β–phenyl α'–hydroxy enone **1h** did not react with carbamate **9** (Scheme 39) in the presence of catalyst **4b** in dichloromethane. After 144h, starting material was recovered.



Scheme 39: *Unsuccessful reaction between carbamate **9** and enone **1h**.*

Consequently, other catalysts and reaction conditions were screened for β-aryl substituted substrates. We decided to evaluate few more members of bis(oxazoline) ligand category catalysts for the reaction shown in Scheme 39. Accordingly, **4i, 4j** and **4k** were tested with benzylcarbamate **9** and tertbutylcarbamate **10** in the aza-Michael addition to enone **1h**, but after 144h, 0% conversion was detected in both cases. These unsuccessful results turned our attention to select some stronger nucleophiles, like *N*-hydroxybenzylcarbamate (HOHNCOOBn) **19** and *N*-hydroxy-tert-butylcarbamate (HOHNCOOtBu) **20,** which were again unable to promote the aza-Michael addition reaction (Fig. 13). Unfortunately, enones bearing β-aryl substituents proved to be unreactive even under forcing conditions.

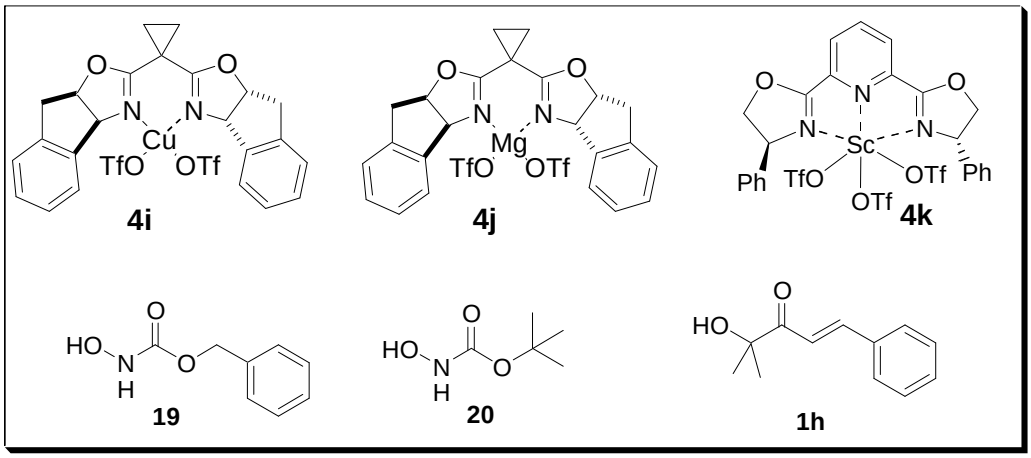
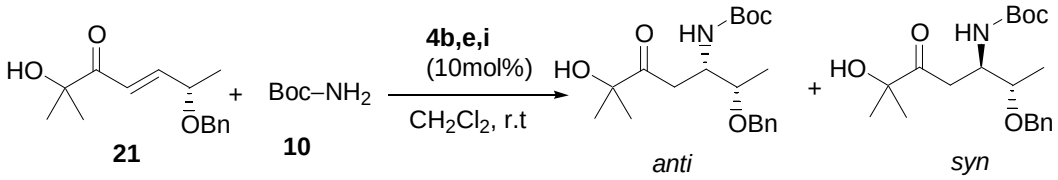
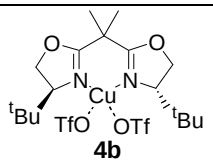
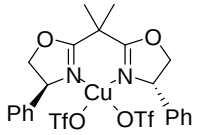
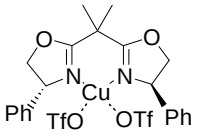


Figure 13: *Catalsyts **4i, j, k** tested in the reaction of enone **1h** and nucleophiles **19** and **20**.*

To evaluate to which extent the reaction stereocontrol could be governed by the chiral catalyst or the chiral substrate acceptor where both components are chiral, one example of double asymmetric induction was conducted. Chiral α'–hydroxy enone **21** was selected, since it could be easily prepared from methyl lactate (for preparation, see experimental part). The reaction of tert-butylcarbamte **10** with **21** promoted by catalyst **4b** under previously optimised conditions led to a mixture of diastereomers in 70:30 ratios with 80% crude yield (table 8, entry 1).

Table 8: *Diastereosective aza-Michael addition of carbamate **10** with chiral enone **21** in the presence of catalysts **4b, e, i**.*



Entry	Enone	Catalyst	Time(h)	Yield[a] (%)	dr,%,[b] *syn:anti or anti:syn*
1	**21**	 **4b**	24	80	70**:**30
2	**21**	 **4e**	112	99	69**:**31
3	**21**	 **4i**	112	99	69**:**31

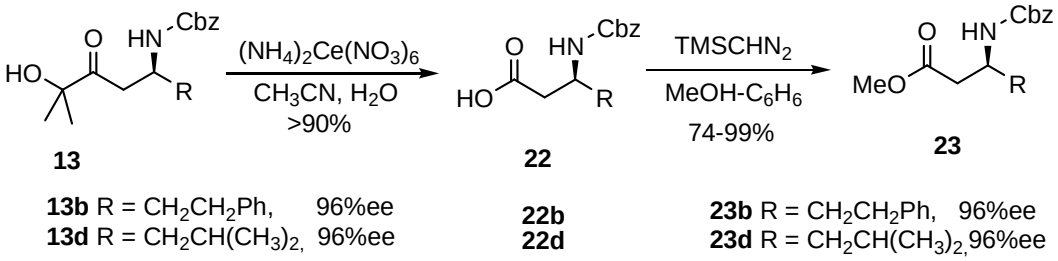
Unless otherwise stated, all reactions were conducted at 1.0 mmol scale, reaction time specified, with mol ratio of enones : 10 : catalyst = 1:2:0.1. [a]Conversion was determined by ^{1}H NMR. [b]dr was determined by ^{1}H NMR (500 MHz).

In a subsequent reaction carried out with **4e**, after 112h, conversion was >99% with a mixture of diastereomers in 69:31 ratio (entry 2). Finally, by using the enantiomeric catalyst **4i**, essentially identical result was obtained. Because of the lack of selectivity, we didn´t proceed to optimize conditions and *syn* or *anti* configurations were not assigned.

3. 2. 3 Elaboration of the aza-Michael adducts

The potential of the catalytic aza-Michael reaction is best demonstrated by the elaboration of the adducts into β-amino acids in high enantiomeric purity. Indeed, the ketol moiety could be smoothly oxidised to either a carboxylic acid or an aldehyde group thus affording N-protected β-amino acids and aldehydes.

On the one hand, treatment of the Cbz-derivatives **13b** and **13d** with ammonium cerium nitrate (CAN) in acetonitrile gave the corresponding *N*-Cbz-protected β-amino carboxylic acids **22b** and **22d** in good chemical yield >91% after column chromatography (Scheme 40). These products were treated with trimethylsilyldiazomethane in the methanol-benzene solvent system, affording the corresponding methyl esters **23b**, **d** without loss of optical integrity.

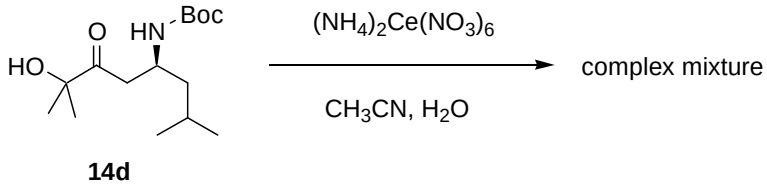


Scheme 40: *Scission of the ketol moiety of aza-Michael adducts.*

Comparison of the specific rotation of **22d**, (observed $[\alpha]_D^{25}$= - 28.7º (c= 2.9, $CHCl_3$)), with literature values reported for *R*-isomer ($[\alpha]_D^{25}$= + 29.5º (c= 2.9, $CHCl_3$)[138]) allowed assignment of the absolute configuration of adducts.

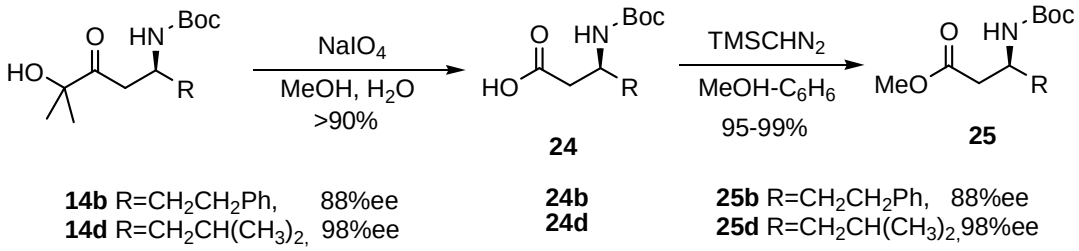
When the same reaction conditions were used for the *N*-Boc-protected aza-Michael adduct **14d**, unexpected products were obtained which were not identified (Scheme 41).

[138] A. E. Marini, M. L. Roumestant, P. Viallefont, D. Razafindramboa, M. Bonato, M. Follet, *Synthesis* **1992**, 1104-1108.



Scheme 41: *Unsuccessful oxidation of N-Boc-protected aza-Michael adducts by Cerium Ammonium Nitrate (CAN).*

To overcome the problem with *N*-Boc adducts, alternative oxidation conditions were tried. For instance, oxidation of *N*-Boc protected aza-Michael adducts **14b** and **14d** with $NaIO_4$ in methanol-water at room temperature, after 24-26h, resulted in formation of carboxylic acids **24**, (>90% yield) (Scheme 42). These acids were transformed into the corresponding methyl esters **25b** and **25d** by trimethylsilyldiazomethane ($TMSCHN_2$) in the MeOH-benzene solvent system at room temperature, with excellent chemical yields (95-99%).



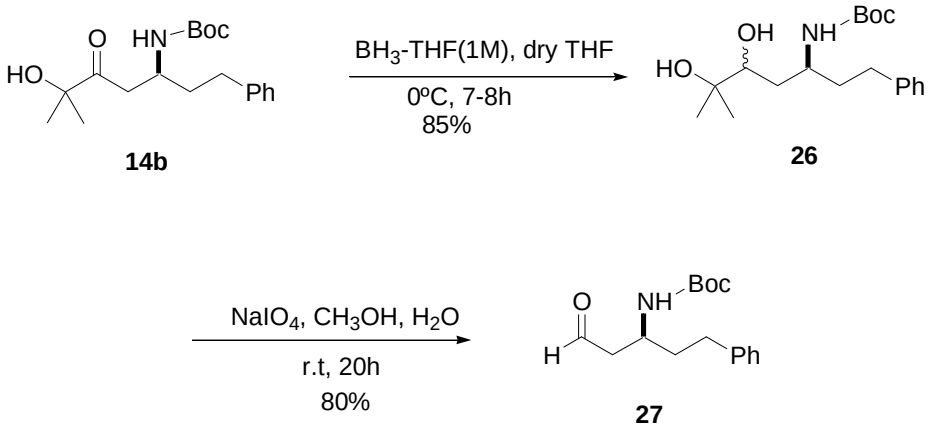
Scheme 42: *Oxidation of N-Boc-protected aza-Michael adducts by sodium periodate followed by esterification.*

Optical intrigity of the final products was assessed by measurement of the specific rotation of **25b.** The observed value ($[\alpha]_D^{20}$ = – 8.7º (c = 1.8, $CHCl_3$)) was compared with the described literature value for the *R*-isomer ($[\alpha]_D^{20}$ = + 7.2º (c = 1.8, $CHCl_3$))[139] indicating that in this aza-Michael reaction the (*S*)-isomer is obtained with 97.3% optical purity.

[139] S. Abele, G. Guichard, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2141-2156.

In addition, oxidation of *N*-Cbz-protected adducts by treatment with $NaIO_4$ instead of CAN (Scheme 40), resulted to be equally efficient in terms of both chemical yield and ee´s.

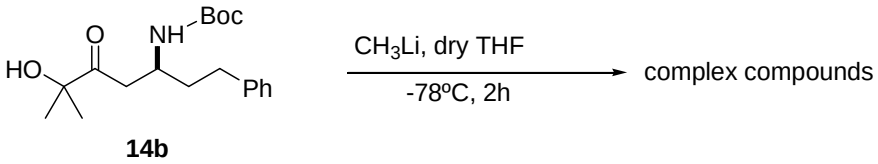
Next we investigated the transformation of the ketol moiety into the aldehyde group. The ketol moiety of **14b** was reduced to diol **26**, by simple treatment with borane–THF for 7-8 h at 0 ºC, in 85% isolated yield (Scheme 43). The subsequent oxidation of the1,2-diol with $NaIO_4$ in methanol-water at room temperature afforded the desired aldehyde product **27** with 80% isolated yield.



Scheme 43. *Transformation of aza-Michael adduct **14b** into the aldehyde **27.***

Compound **27** is unstable and because of this reason specific rotation and enantioselectivity were not determined. Without optimizing the reduction conditions for other substrates, we looked for other elaborations.

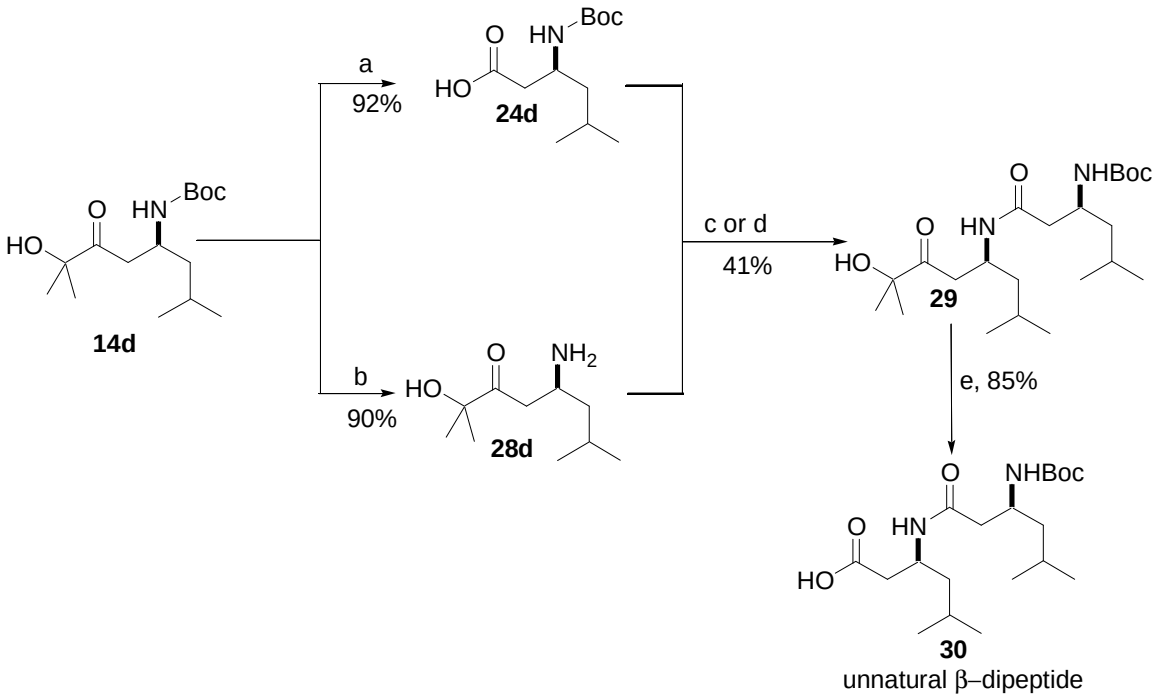
A third option for elaboration of the aza-Michael adduct consists of the nucleophilic addition of alkyl and aryl lithium reagents to the ketone carbonyl and subsequent diol cleavage (Scheme 44). Unfortunately, the reaction did not work.



Scheme 44. *Unsuccessful reduction of aza-Michael adduct by methyl- lithium.*

3. 2. 4. Practical applications: Synthesis of a β-dipeptide

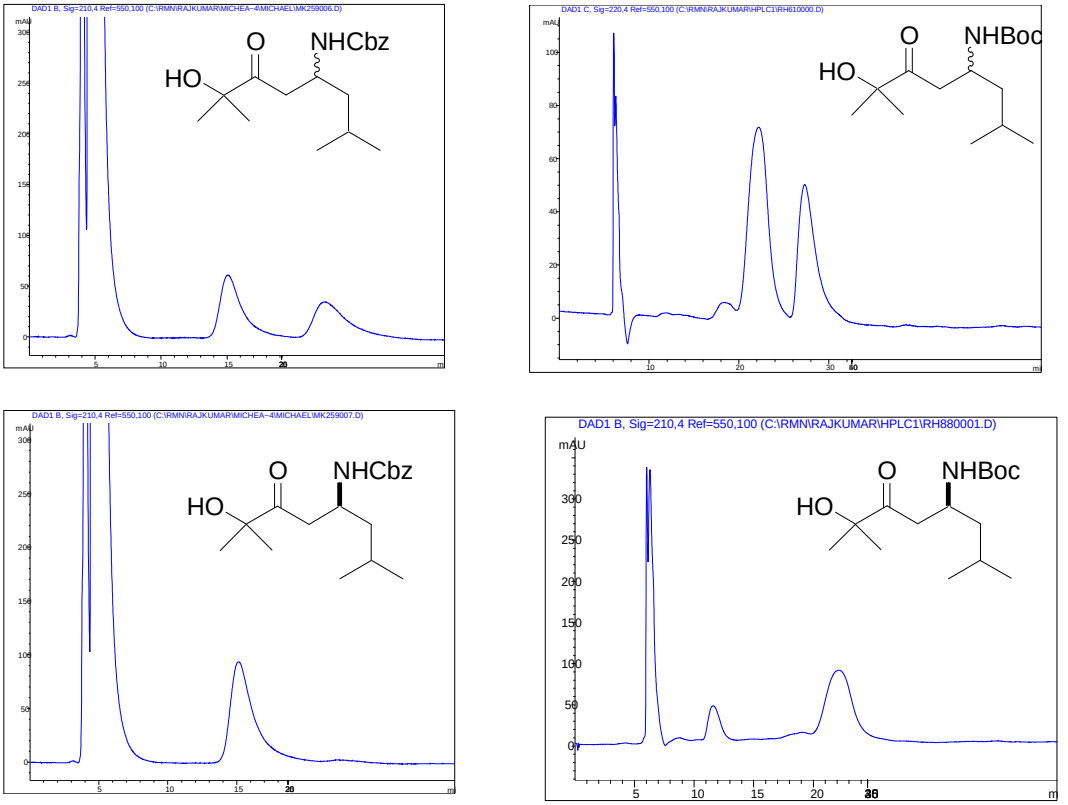
As we proved, ketol moiety in the aza-Michael adducts can be conveniently transformed into other functionality like carboxylic acids and aldehydes. This feature makes the ketal as a masking carboxylic group that may have further applications in the context of peptide synthesis. In this respect, we explored the possibility of integrating this aza-Michael methodology with an amide forming (peptide coupling) process. As an example we performed deprotection of the *N*-Boc protected aza-Michael adduct **14d** by trifluoroacetic acid in dichloromethane at 0ºC, which furnished chiral β-amino carbonyl compound **28d** in 90% crude yield (Scheme 45). The coupling of the free amine **28d** with **24d** under standard peptide coupling conditions (EDC, HOBt in dichloromethane at 0ºC), afforded the corresponding adduct **29** in 41% chemical yield. Oxidation of the adduct **29** by treatment with $NaIO_4$ in a methanol-water system at room temperature, after 22h, give rise to the unnatural β-dipeptide **30** in 85% chemical yield. Chemical yield of the coupling, between **24d** and **28d** was unchanged by using the cyanurilfluoride, *N*-methylmorpholine system in dichloromethane at 0ºC to room temperature.



Scheme 45. *Synthesis of an unnatural β-dipeptide from an aza-Michael adduct. Reagents and conditions: (a)* ***14d****, $NaIO_4$ (10 equiv.), MeOH-H_2O (2:1), 24-26h, 92%; (b)****14d****, TFA (10 equiv.), CH_2Cl_2, 0ºC 5h, 90% (c)* ***24d, 28d****, EDC (1.4 equiv.), HOBt (1.0 equiv.), CH_2Cl_2, 20-24h, 41%; (d) (i)* ***24d, 28d****, cyanuril fluoride(5 equiv.), CH_2Cl_2, -20ºC. 84% (ii) NMM, CH_2Cl_2, 20-24h, 41%; (e)* ***29****, $NaIO_4$ (10 equiv.), MeOH-H_2O (2:1), 24-26h, 85%.*

3. 2. 5 Assignment of the configuration

To properly access the absolute configuration of both Cbz- and Boc-derived adducts, chromatographic correlation was perused. Surprisingly, however, HPLC chromatograms of the Cbz and the Boc adducts showed in all cases a reversal elution pattern for the major enantiomer obtained. For instance, in next Fig. 14 the HPLC chromatograms of adducts **13d**, **14d** are displaced with eluting systems. So we decided to carry out chemical correlation to confirm this aspect (Scheme 46/47).



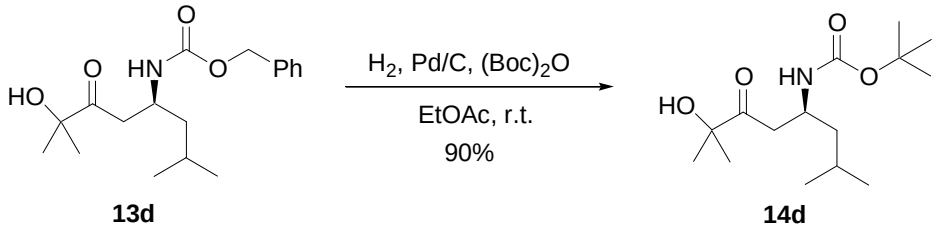
13d, Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 210 nm) Rt_{major} = 15.1 min, Rt_{minor} =22.4 min, 96 % e.e

14d, Chiralpak AD column; iPrOH:hexane 4:96; 0.5 mL/min, 210 nm, Rt_{major} = 22.22 min, Rt_{minor} =19.08 min, 96 % e.e.

Figure 14: *HPLC chromatograms of Boc and Cbz protected aza-Michael adducts.*

Functional group interchange (FGI) could bea good alternative. First, *N*-Cbz protected adduct **13d** was transformed into Boc-protected adduct by hydrogenolysis (H_2, Cat. Pd/C) carried out in the presence of $(Boc)_2O$. Thus obtained product **14d** showed

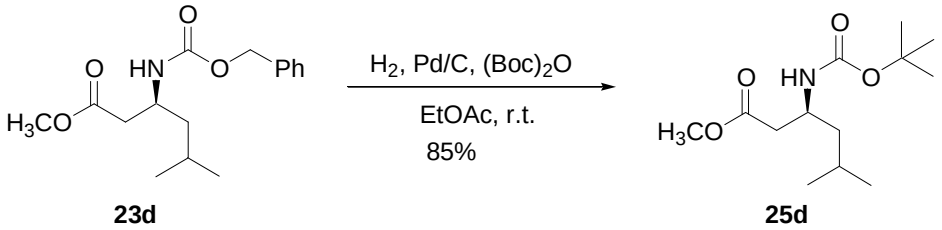
identical elution pattern on HPLC and same sign of optical rotation to those of the *N*-Boc adduct prepared from the aza-Michael reaction.



13d **14d**

Scheme 46: *Functional group interchange of **13d** into **14d**.*

A parallel correlation was done with compound **23d** to corresponding **25d** (Scheme 47). Again, HPLC and optical rotation measurements of the latter were favourable compared with those of products **25d** obtained from scission of Boc-adducts. Thus, a major reaction mechanism for the aza-Michael reaction of both Cbz and Boc carbamates was concluded.



23d **25d**

Scheme 47: *Functional group interchange ester compound.*

For the remaining adducts, it was assumed a uniform reaction mechanism and indicative of the assigned stereochemistry.

3. 2. 7 Mechanistic aspects and stereochemical model

A rationale that would explain the catalytic activation mode of reactants as well as the stereochemical course of the reaction was seeked. The catalytic cycle we propose is depicted in Figure 15. Enone β-carbon is activated by chelation of ketol moiety to the Cu(II) center in such a manner that *Re* face is less accessible for nuecleophile approaching. Subsequent decomplexation affords the product and concomitantly

regenerates the catalyst **4b**. Hence, the stereomodel that correctly predicts the sense of asymmetric induction observed in the aza-Michael reactions considers a Cu(II) metal center adopting a distorted square planar geometry, as previously disclosed in the literature for other Cu(II)-bidentate substrates.[140]

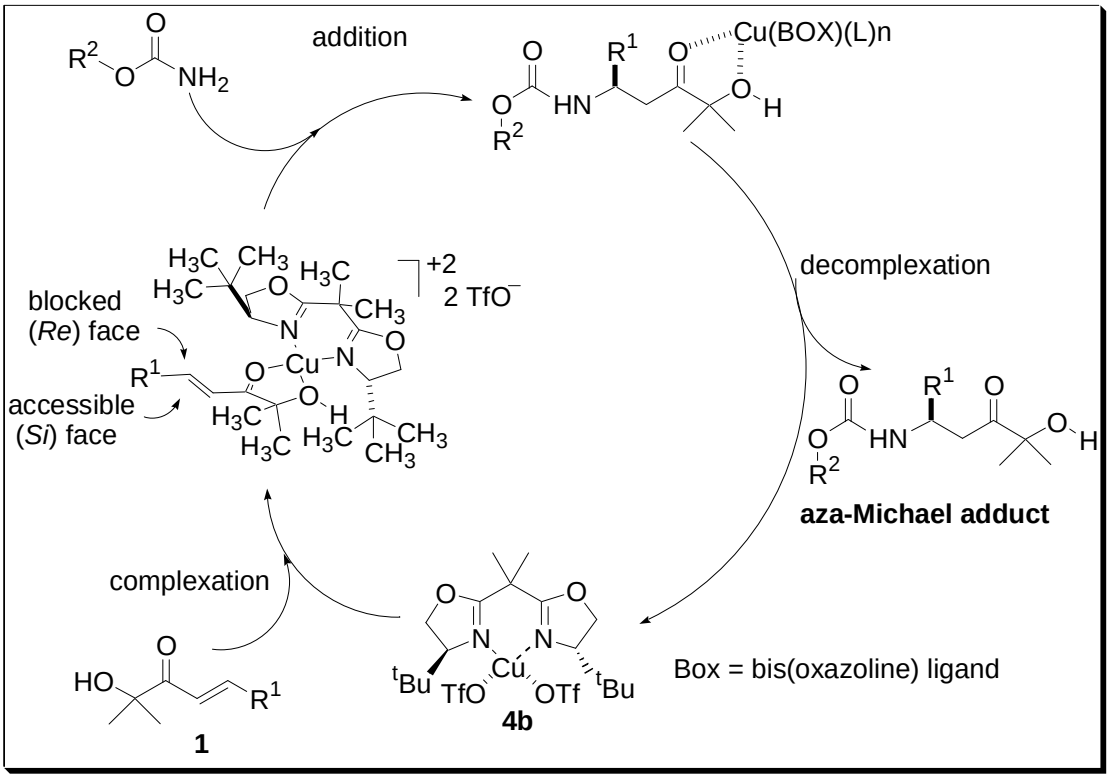


Figure 15: *Plausible reaction mechanism.*

A PM3 geometry optimisation for such a complexes geometry provides a nice stereoview for the preferred attack of the carbamate to less shielded *Si*– face of α'–hydroxy enone (Fig. 16).

[140] (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335 and references therein. (b) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888-1898. (c) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561-3651.

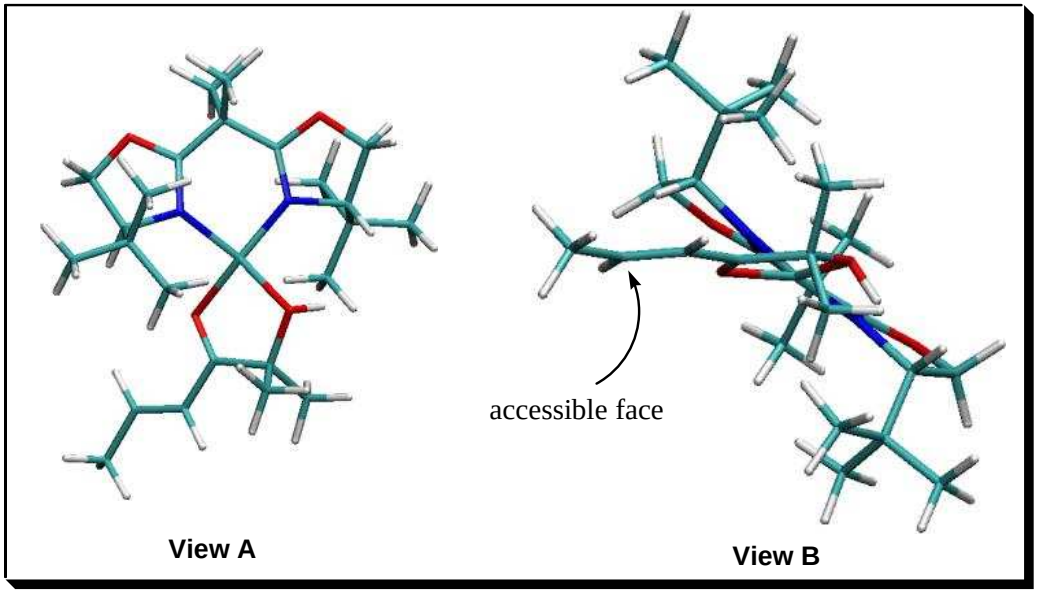
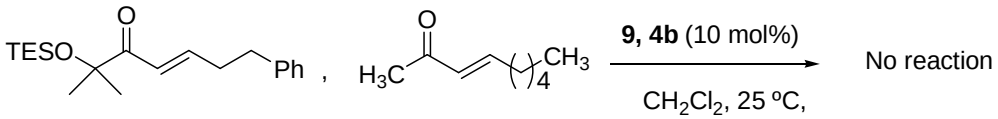


Figure 16: *PM3 geometry optimization.* Two stereoviews of the PM3 minimized structure of the enone-chiral catalyst complex (R = CH_3) showing the more accessible Si- face for carbamate attack.

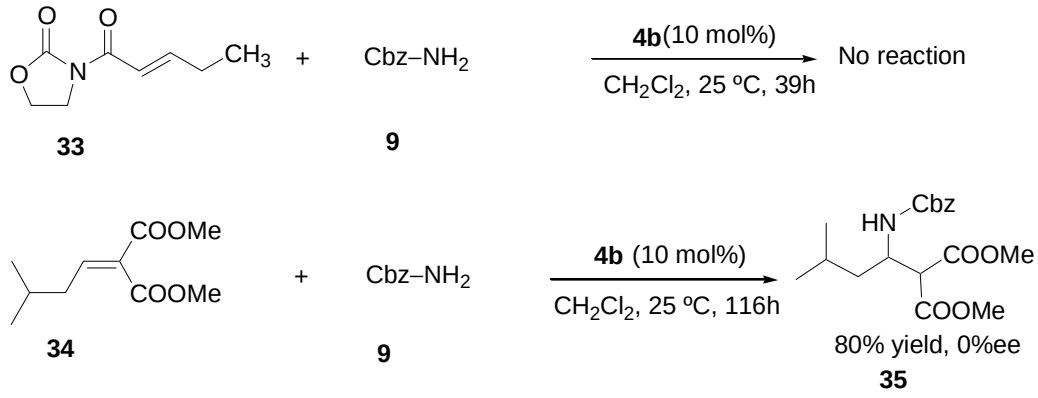
Further evidence of the effective 1,4–metal binding chelated structure that α'–hydroxy enones and Cu(II) adopt, was obtained from comparison of the results obtained with free –OH α'–hydroxy enones, *O*-protected α'–hydroxy enones and simple enones, repectively. Thus, the reaction of triethylsilyloxy enone **31** with benzylcarbamate **9** under the optimised conditions did not proceed at all, and unreacted starting materials were recovered. No reaction was also observed when simple enone **32** was employed. Apparently, the greatly diminished capability of the trimethylsilyloxy group for metal chelation affects adversely to the substrate activation, and indirectly proves the need for substrate chelation as a key element of the present methodology (Scheme 48).



31 **32**

Scheme 48: *Unsuccessful aza-Michael reaction with simple enones **31**, **32**.*

On the other hand, the unique properties of α'–hydroxy enone templates can be reflected by failure of the aza-Michael reaction when *N*–enoyl oxazolidinone **33**[141] was employed instead of α'–hydroxy enone (Scheme 49). In addition, when alkylidene malonate **34** was employed as the acceptor template under otherwise identical conditions to those employed with α'-hydroxy enones, Michael adduct **35** was indeed obtained in 80% chemical yield, but in essentially racemic form.

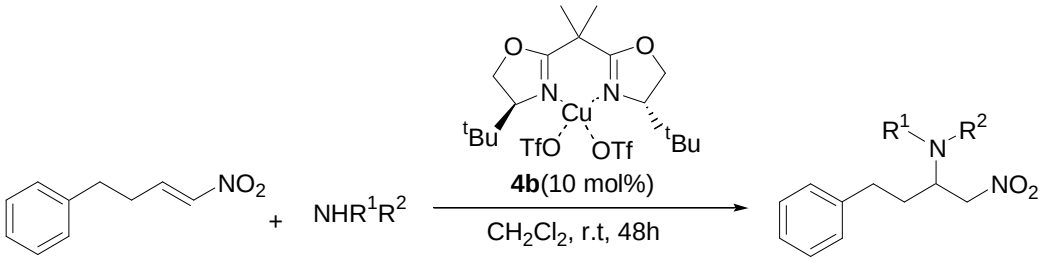


Scheme 49: *aza-Michael addition reaction where enone **33**, **34** was employed*

[141] Template **30** have been widely used as bidentate templates in the context of catalytic asymmetric transformation. See: (a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335. (b) C. Chaozhong, V. A. Soloshonok, V. J. Hruby, *J. Org. Chem.* **2001**, *66*, 1339-1350.

3.3 Preliminary results with nitroalkenes

From our previous aza-Michael addition results, we eyed on the finding of new Michael acceptors towards establishing the validity of this catalyst with carbamate nucleophiles (Scheme 50).



36

9, R^1 = Cbz, R^2 = H
19, R^1 = Cbz, R^2 = OH
20, R^1 = Boc, R^2 = OH

37, R^1 = Cbz, R^2 = H
38, R^1 = Cbz, R^2 = OH
39, R^1 = Boc, R^2 = OH

Scheme 50. *aza-Michael addition reaction to nitroalkene **36.***

For the initial studies nitroalkene **36** was employed as testing bench and research was focused on the use of benzylcarbamate **9**. The reaction protocol consisted of *in situ* preformation of the catalyst **4b** in CH_2Cl_2 according to the method described previously.Siquencial addition of nitroalkene **36** and carbamate **9** following usual experimental conditions did not afford the expected product after 48h stirring (Table 9, entry 1). The same result was observed with catalyst **4j** (see structure on page 60). We decided to explore the reaction with the same catalytic system and stronger aza-nucleophiles, such as, *N*-hydroxybenzylcarbamate **19** and *N*-hydroxytert-butyl carbamate **20**.

With the stronger selected nucleophiles, the reactions worked perfectly with excellent conversion, but selectivity was 0%ee in all entries (table 9, entry 2, 3). Even there was no selectivity improvement while reaction temperature down to -60ºC.

Table 9: *Conversion and ee of aza-Michael addition of aza nucleophiles **9, 19, 20** to nitroalkene **36** in the presence of catalyst **4b**.*[a]

Entry	NHR^2R^3			Product	Yield(%)[b]	ee(%)[c]
	Comp.	R^2	R^3			
1	**9**	Cbz	H	**37**	0	---
2	**19**	Cbz	OH	**38**	99	0
3	**20**	Boc	OH	**39**	99	0

[a]Reactions performed on 1 mmol scale with a ratio 36:carbamate:4b; 1:2:0.1. [b] Reaction conversion. [c]ee determined by chiral HPLC.

Based on the preliminary unsuccessful results with catalyst **4b**, subsequently, we decided to evaluate the effect of thiourea derivatives for the aza-Michael addition. In this regard, many structural variants of thiourea derivatives are available. In particular, it is well reported that the indanol- and BINAP- derivatized thioureas (**40, 41**) (Fig. 17) are easy to prepare (see experimental part) and these were selected for the aza-Michael addition.

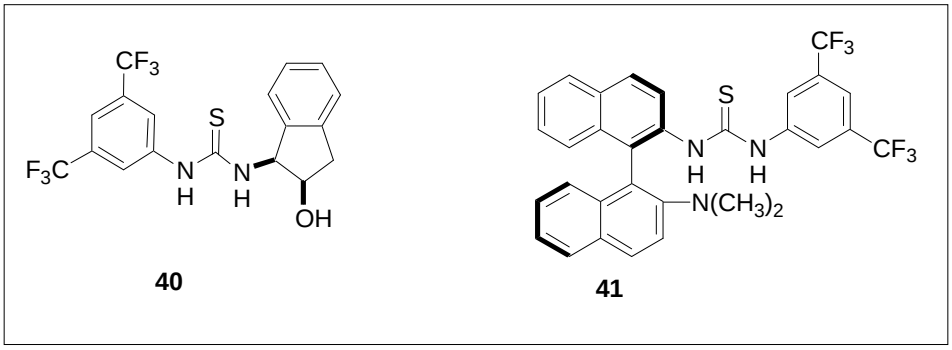


Figure 17: *Organocatalysts based on thiourea derivatives.*

For the initial studies β-nitrostyrene **45** was employed as testing bench for these catalysts. Catalyst **40** and **41** (10 mol %) were unable to promote the reaction with nucleophile **9,** whereas, the addition of nucleophiles **42** and **43** (Fig. 18) to **45** in the presence of catalysts **40** and **41**, resulted in excellent conversion (>99%) with 0% ee in both cases. Selectivity was not improved within the temperature range from 25ºC to −60ºC. Nucleophile phthalimide **44** was also inert to react (table 10).

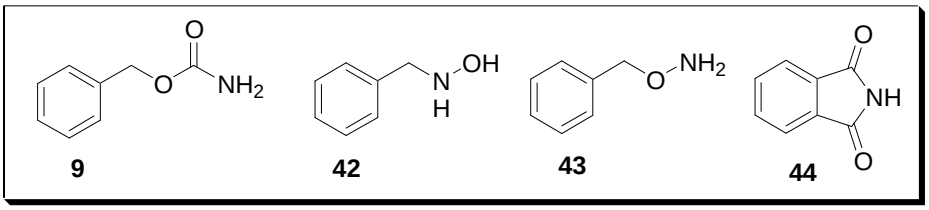
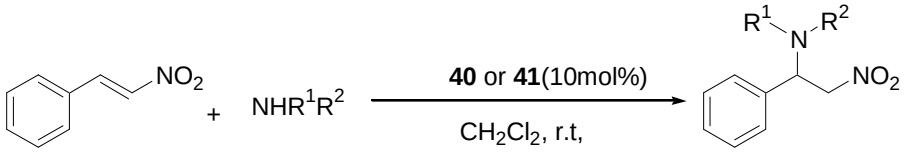


Figure 18: N*ucleophiles **9**, **42**, **43**, **44***.

Table 10: *aza-Michael addition reaction between **9, 42, 43, 44** and β-nitrostyrene **45** catalysed by thiourea derivatives **40** or **41**.*[a]



45

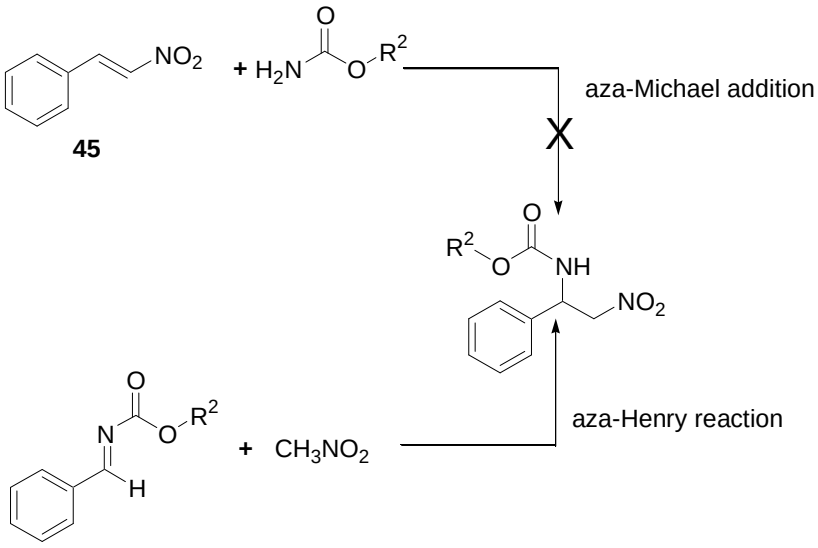
9, $CbzNH_2$
42, BnNHOH
43, $BnONH_2$
44, phthalimide

NR^2R^3=
46, CbzNH
47, BnNOH
48, BnONH
49, phthalimide

Entry	NHR^2R^3	TºC	Time(h)	Product	Conv. (%)[b]	ee(%)[c]
1	**9**, Cbz-NH_2	25	48	**46**	----	----
2	**42**, BnNHOH	25	5	**47**	>99	0
3		-30	24	**47**	>99	0
4		-60	48	**47**	60	0
5	**43**, $BnONH_2$	25	5	**48**	>99	0
6		-30	24	**48**	>99	0
7		-60	48	**48**	70	0
8	**44**, phthalimide			**49**	----	----

[a]Reactions performed on 1 mmol scale with a ratio nitroalkene: catalyst: nucleophile; 1:0.1:1. [b]Reaction conversion was determined by ^{1}H NMR (500MHz). [c]Determined by HPLC. Nucleophiles **19**, **20** and $(Boc)_2NH$ were also unreactive in the above condition.

In view of the unsuccessful results of the aza-Michael addition of aza nucleophiles to β-nitrostyrene, we considered the aza-Henry reaction as alternative pathway to get β-nitroamines (Scheme 51). The results are described in the following chapter (Chapter II).



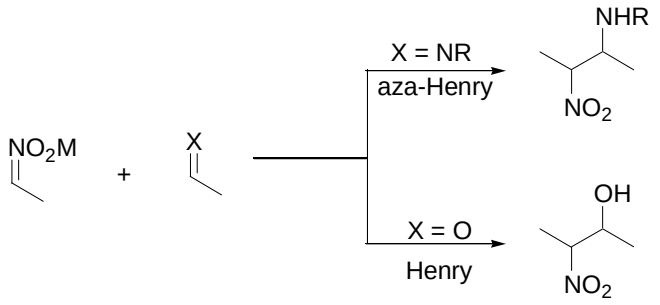
Scheme 51. *Alternative path to β-nitroamines.*

4. Chapter II

aza-Henry reaction

4.1. Introduction

Bearing close resemblance to three of the most fundamental carbon-carbon bond forming reactions (aldol, Mannich and Henry), nitro-Mannich or aza-Henry reaction allows access to synthetically useful β-nitroamines (Scheme 52).[142]



Scheme 52: *General aza-Henry and Henry reaction.*

The β-amino nitroalkane structure can be derivatized in a number of ways, principally, *via* simple reduction[143] of the nitro function to yield 1,2-diamines,[144] α-amino acids, *via* Meyer oxidation,[145] Nef oxidation,[146] conversion to nitrile oxide,[147] nucleophilic substitution[148] and replacement of the nitro function by hydrogen leading to the corresponding monoamino derivatives[149] (Scheme 53). The 1,2-diamine structural motif is important in biologically active natural products,[150] in medicinal chemistry,[151]

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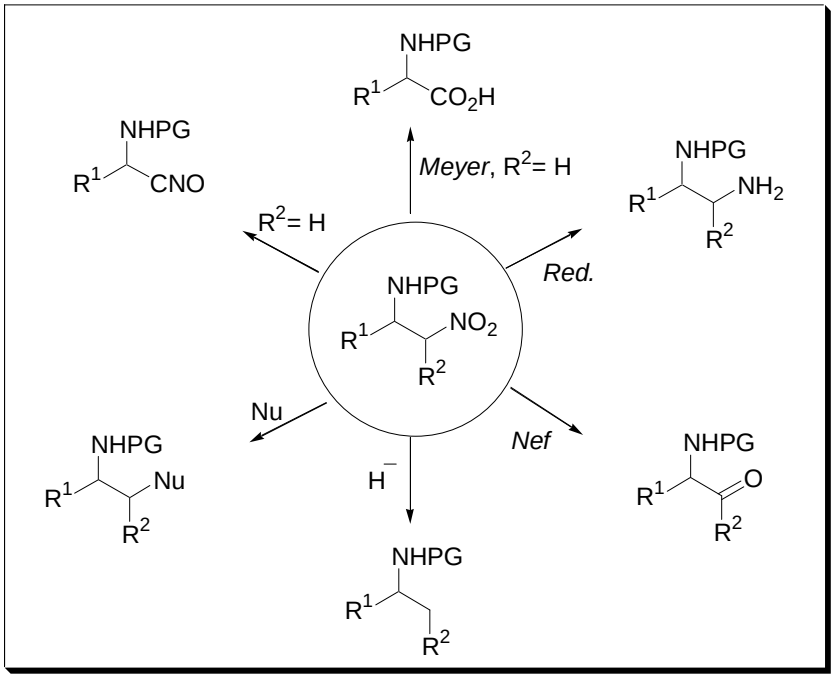
[142] Highlight: N. Westermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 151-153.
[143] See, for instance: P. H. O´Brien, D. R. Sliskovic, C. J. Blankley, B. Roth, M. W. Wilson, K. L. Hamelehle, B. R. Krause, R. L. Stanfield, *J. Med. Chem.* **1994**, *37*, 1810-1822.
[144] For a review on 1,2-diamines, see: D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627.
[145](a) V. Mayer, C. Wurster, *Ber. Dtsch. Chem. Ges*, **1873,** *6*, 1168-1172. (b) K. J. Kamlet, L. A. Kaplan, J. C. Dacons. *J. Org. Chem*. **1961**, *26*, 4371-4375.
[146] For Nef oxidation, See: Reviews, (a) H. W. Pinnick, *Org. React.* **1990**, *38*, 655-792. (b) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017-1047. For the application of this approach to the synthesis of optically active α-amino acids, see: (c) E. Foresti, G. Palmieri, M. Petrini, R. Profeta, *Org. Biol. Chem.* **2003**, *1*, 4275-4281.
[147] T. Mukayama, T. Hoshino, *J. Am. Chem. Soc*. **1960**, *82*, 5339-5342.
[148] R. Tamura, A. Kamimura, N. Ono, *Sínthesis*, **1991**, 423-434.
[149] (a) N. Ono, *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**. (b) N. Ono, *In Nitro Compounds: Recent advances in Synthesis and Chemistry*; H. Feuer, A. Nielsen, T. A. Eds., VCH: New York **1990**, 1-135.
[150] (a) A. Pasini, F. Zunino, *Angew. Chem. Int. Ed*. **1987**, *26*, 615-624. (b) M. Otsuka, T. Masuda, A. Haupt, M. Ohno, T. Shiraki, Y. Sugiura, K. Maeda, *J. Am. Chem. Soc*. **1990**, *112*, 838-845.

and more recently in their use in chiral auxiliaries and chiral ligands for asymmetric catalysis.[152]



Scheme 53. *Transformation of the nitro group.*

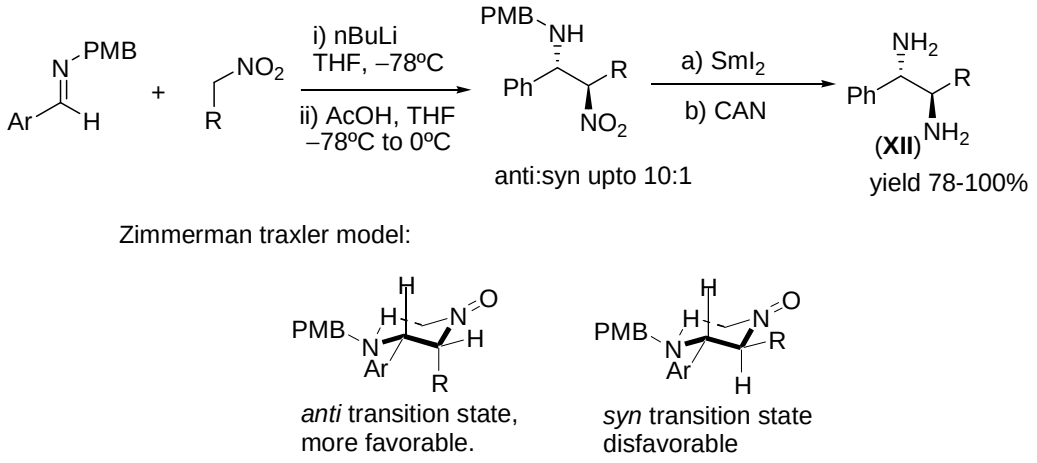
While a number of intriguing reports have appeared detailing the stereoselective generation of 1,2-diamines, the diastereoselective synthesis of 1,2-disubstituted 1,2-diamines to date relies upon the conversion of alkenes *via* diols and diazides[153] or aziridines,[154] aza-pinacol-type coupling of two imines,[155] conversion of enantiomerically pure naturally occurring amino acids,[156] the addition of alkyl-nitrogen carbanions to imines,[157] and the use of chiral auxiliaries.[158] The scope of these methods

[151](a) E. T. Michalson, J. Smuszkovicz, *Prog. Drug. Res.* **1989**, *33*, 135. (b) J. Reedijk, *J. Chem. Soc. Chem. Commun.* **1996**, 801-806.
[152](a) H.-U. Blaser, *Chem. Rev*. **1992**, *92*, 935-952. (b) E. N. Jacobsen, in *Catalytic Asymmetric Synthesis*; I. Ojima, Ed. VCH: Weinheim, **1993**, p 159. (c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev*. **1994**, *94*, 2483-2547 and references therein.
[153] D. Pini, A. Iuliano, C. Rosini, P. Salvadori, *Synthesis* **1990**, 1023-1024.
[154](a) M. Meguro, N. Asao, Y. Yamamoto, *Tetrahedron Lett*. **1994**, *35*, 7395-7398. (b) W.-H. Leung, M.-T. Yu, M.-C. Wu, L.-L. Yeung, *Ibid*. **1996**, 37, 891-892.
[155](a) M. Shimizu, T. Iida, T. Fujisawa, *Chem. Lett.* **1995**, 609-610 and references therein. (b) N. Taniguchi, M. Uemura, *Synlett* **1997**, 51-53.
[156] M. T. Reetz, R. Jaeger, R. Drewlies, M. Hübel, *Angew. Chem., Int. Ed.* **1991**, *30*, 103-106.
[157](a) N. Kise, K. Kashiwagi, M. Watanabe, J. Yoshida, *J. Org. Chem*. **1996**, *61*, 428-9. (b) Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757-3758 and references therein.
[158](a) D. Enders, J. Wiedemann, *Synthesis* **1996**, 1443-1450. (b) G. Alvaro, F. Grepioni, D. Savoia, *J. Org. Chem.* **1997**, *62*, 4180-4182 and references therein.

is limited due to the variability in diastereoselectivity and, where appropriate, the availability of enantiomerically pure starting materials, the nature of the chiral auxiliary, or in many cases the basicity of the reaction conditions[159].

Organometallic methodologies with potential catalytic variations are known, but often they are hampered by very narrow substrate-specificity or have limited application for the synthesis of chiral, nonracemic products.

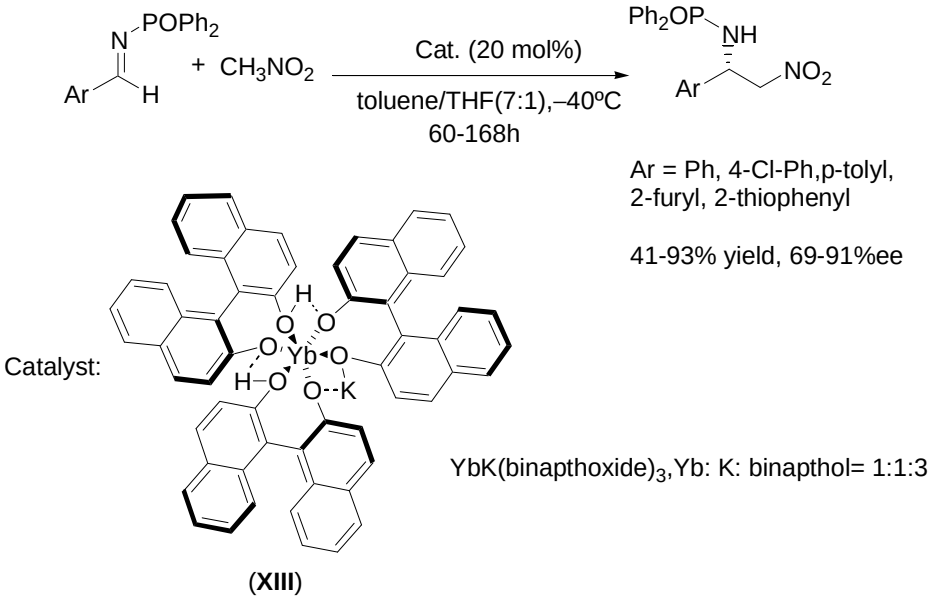
Anderson and coworkers[160] reported an interesting diastereoselective aza-Henry reaction providing β-nitroamines in racemic form (Scheme 54). To avoid retro-addition, these intermediates were then reduced to the corresponding diamine with SmI_2 and *p*-methoxybenzyl (PMB) group was deprotected by ceric-ammonium nitrate (CAN). The vicinal diamine **XII** could be thus obtained in moderate to high yields and with good diastereoselectivities (upto 1:10, syn:anti). The predominate formation of *anti* isomer over *syn* isomer has been explained on the basis of a six membered, Zimmerman-Traxler model. Hydrogen bonding between the vicinal NH and ON-O groups in anti is energetically favourable. More recently, the same author has found that the reaction can proceed faster and with better selectivity if Lewis acid catalysts like BF_3 and $Sc(OTf)_3$ are employed.[161] Thus, the stage was set for developing the catalytic, asymmetric variants of this sequence.



Scheme 54: *Diastereoselective aza-Henry reaction of imines with nitronates promoted by Lewis acids.*

[159] For a recent review see: D. Lucet, T. LeGall, C. Mioskowski, *Angew. Chem., Int. Ed.* **1998**, *37*, 2580-2627 and references therein.
[160] H. Adams, J. C. Anderson, S. Peace, A. M. K. Pennell, *J. Org. Chem.* **1998**, *63*, 9932-9935.
[161] J. C. Anderson, S. Peace, S. Pih, *Synlett*, **2000**, 850-852.

Pioneering contribution to the asymmetric, catalytic aza-Henry reaction was made by Shibasaki and coworkers[162] who developed the asymmetric aza-Henry reaction conducted with the heterobimetallic catalyst **XIII** (Scheme 55). Since the catalyst contains both Brønsted basic and Lewis acidic functionalities, both the electrophile and the nucleophile can be activated concurrently. In the case of usual imines such as *N*-benzylimines, only unsatisfactory results were obtained, whereas *N*- phosphinoylimines which have coordinating power of O-atom of P=O with heterometallic complexes, gave moderate to good enantioselectivity (69-91%) with variable chemical yields (41-93%).

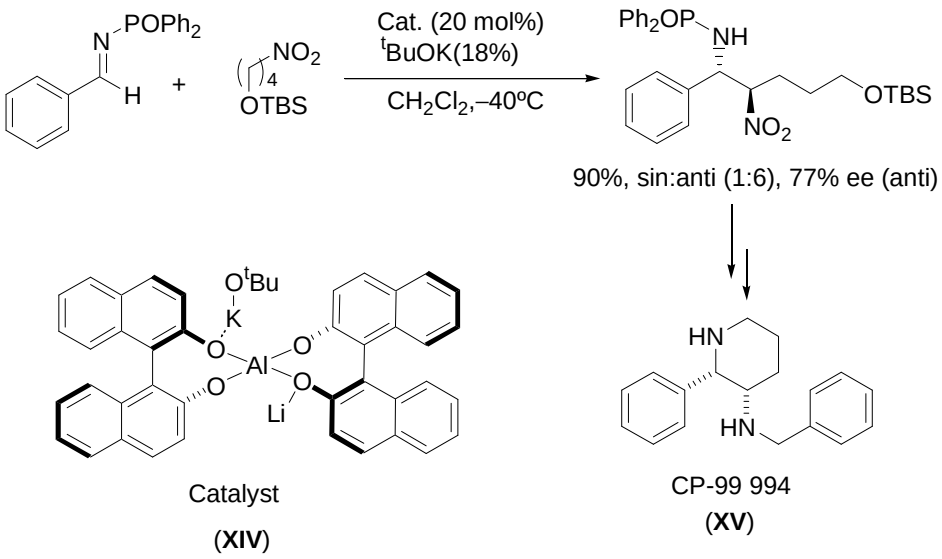


(**XIII**)

Scheme 55: *Asymmetric aza-Henry reaction of nitromethane to arylimines promoted by heterobimetallic catalyst.*

Later from the same group a new heterodimetallic catalyst **XIV** (Scheme 56) based on Al and Li metal centres has been documented. For high selectivities it appears mandatory to include anchor groups in the imine component (P=O bonds), which provide additional complexation and orientation elements in the transition state. Under optimized conditions the adducts could be obtained in 70-90% yield (*sin:anti* > 1:6) with an enantiomeric excess >80%. Among the disadvantages are the limited number of suitable nitroalkanes, the restriction to *N*-phosphinoylimines, and the large amount of catalyst (20 mol%, which corresponds to 40 mol% chiral ligand BINOL).

[162] (a)K. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem. Int. Ed*. **1999**, *38*, 3504-3506. (b) K. Yamada, G. Moll, M. Shibasaki, *Synlett,* **2001**, 980-982.

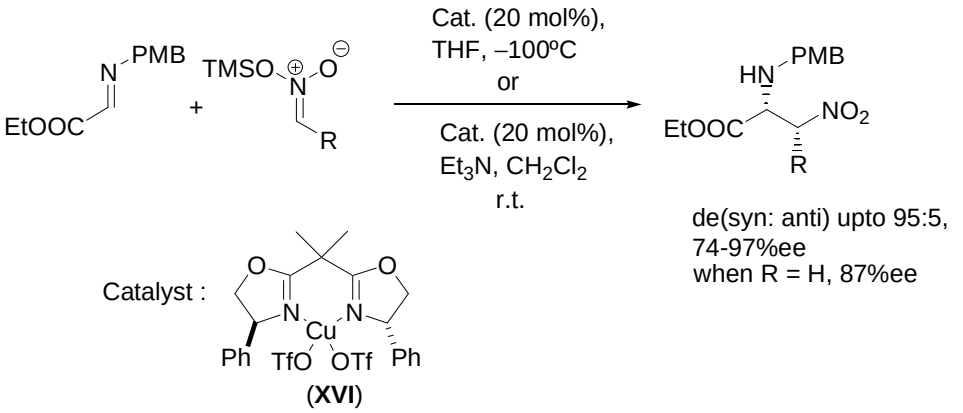


Scheme 56: *Asymmetric aza-Henry reaction of arylimines with nitroalkanes conducted by heterobimetallic catalyst.*

One point in favour of this methodology is that vicinal diamines can be obtained easily by reduction of the nitro group with SmI_2 and cleavage of the phosphinoyl group by 6M HCl. The effectiveness of this method has been demonstrated recently in the synthesis of the potent antagonist of substance P, CP-99994 (**XV**).[163]

Jørgensen and coworkers achieved an interesting method in terms of handling, substrate variety, and practicability.[164] They showed that application of Cu(II)-chiral bis(oxazolines) complexes **XVI** (20 mol %) to the addition of silyl nitronates to imino esters can afford aza-Henry products with high diastereo and enantioselectivities (Scheme 57). After reduction of the nitro moiety, the aza-Henry adduct can be transformed into very valuable building blocks like α, β-diaminocarboxylicacids.

[163] N. Tsuritani, K. Yamada, N. Yoshikawa, M. Shibasaki, *Chem. Lett.* **2002**, 276-277.
[164](a) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843-5844. (b) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, A*ngew. Chem. Int. Ed*. **2001**, *40*, 2992-2994.



Scheme 57: *Asymmetic aza-Henry reaction catalysed by Ph-Box-Cu(OTf)$_2$ complex*.

Under these reaction conditions the aza-Henry adducts are stable and can be isolated. Owing to the high reactivity of the silylated nitronates, the reaction proceeds uncatalyzed even at –78ºC. A practical drawback is that very low reaction temperatures (–100ºC) were required to achieve high diastereoselectivities (*syn:anti* > 25:1) and high enantioselectivities (> 95% ee for the syn product).

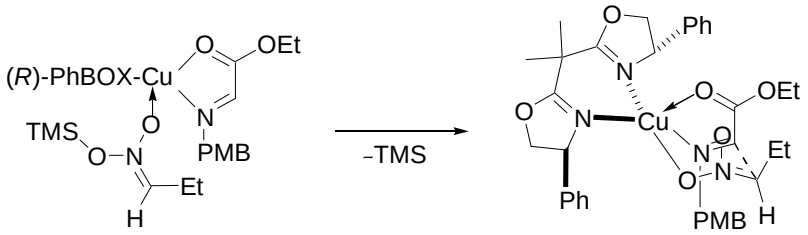
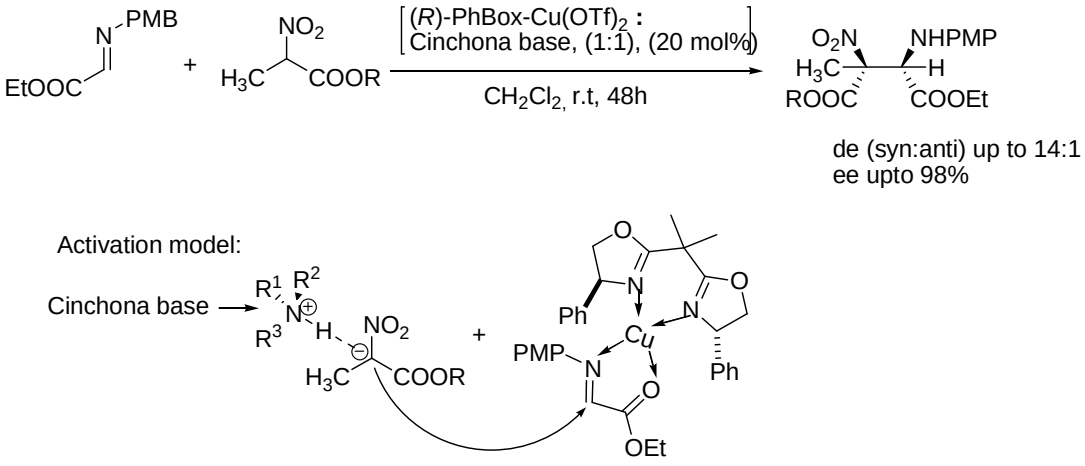


Figure 19: *Possible reaction model*

This limitation can be overcome and the reaction can be conducted at room temperature when amines (Et_3N has been the amine of choice) are added to the less reactive nitro compounds. The resulting stereoselectivities and yields are generally very high (syn:anti >92:8; >93% ee for the syn product, >80%ee for the anti product; 60-87% yield). All these features make this sequence amenable to technical applications. Decreasing the temperature to 0ºC, which is easily accomplished, increased selectivities but prolonged reaction times were needed. The solvent used (CH_2Cl_2) does not need further purification and drying, and inert gas atmosphere can be avoided. The reaction

with nitromethane, however, afforded only moderate enatioselectivity (87% ee) and catalyst loading is considerably high (20 mol %).

Later the same group[165] extended their catalytic system to create quaternary stereogenic centers in the reaction between both prochiral imine and nitronate species (Scheme 58). The approach is based on chiral molecular recognition by the combination of chiral Lewis acids [Cu(II): bis(oxazoline)] (20 mol%) and chiral organocatalysis (cinchona base) for the formation of optically active quarternary centers in the aza-Henry reaction. The procedure leads to products with up to 98%ee and a diastereomeric ratio of 14:1 in excellent yields with catalyst loadings of 5 mol%.



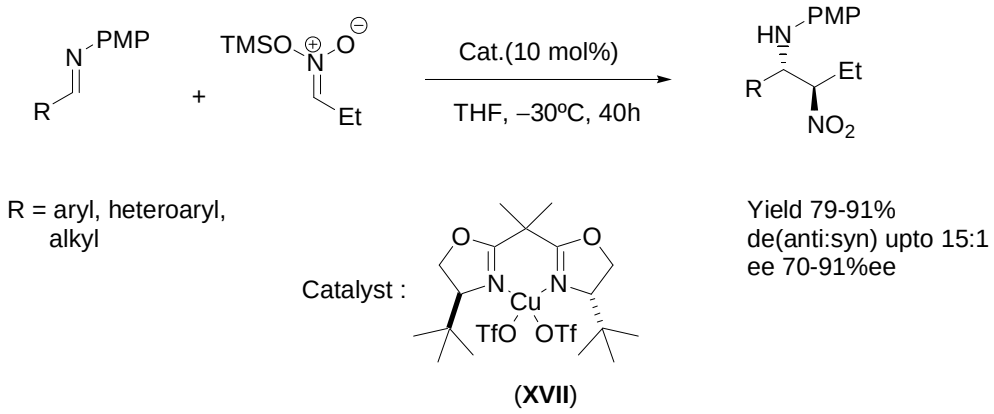
Scheme 58: *Construction of optically active quaternary centres by aza-Henry reaction catalysed by Ph-BOX-Cu(OTf)$_2$ complex and cinchona base.*

In classic chiral Lewis-acid catalysis, the chiral ligand will screen one of the *Re*- or *Si*-faces of the electrophile from attack. In a situation where the nucleophile is a chiral tertiary anion the catalyst must, in order to attain good diastereoselectivity, also distinguish between the two easily interchangeable enantiomeric or enantiotopic faces of the anion. Here, a single activation strategy might fail, affording the product in high enantioselectivity, but with low (or no) diastereoselectivity. For controlling the assembly of tertiary nucleophiles with electrophiles a chiral Lewis acid catalyst, which was prepared admixing (*R*)-PhBox and Cu(OTf)$_2$, is used to activate the electrophile and organocatalysis (Cinchona alkaloid base) is used to activate the nucleophile thereby

[165] K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362-1364.

generating a diastereomeric pair (Scheme 58). To obtain excellent level of enantiomeric excess imine component was restricted only to imino-ester substrate.

Anderson and coworkers[166] developed a protocol that overcome this limitation on imine scope for the enantioselective aza-Henry reaction between alkyl, aryl, and heterocyclic *p*-methoxybenzylimines and trimethylsilylnitropropionate catalyzed by a chiral tBu-BOX Cu(II) complex **XVII** (Scheme 59).



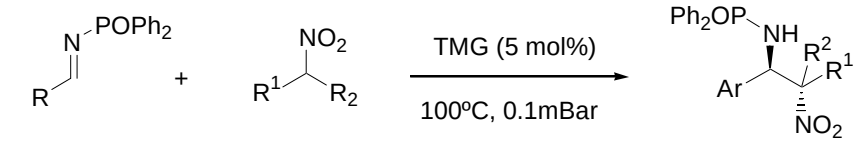
(**XVII**)

Scheme 59: *Diastereoselective and enantioselective aza-Henry reaction of silyl nitronate catalysed by ^{t}Bu-BOX-Cu(OTf)$_2$ complex **XVII**.*

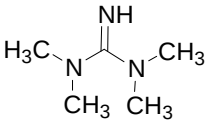
The resultant β-nitroamines are obtained in 70-94% enantiomeric excess in good yield and can be readily reduced to synthetically useful 1,2-diamines.

Over the past few years, significant interest has been focused on the development of new protocols for environmentally processes that are both economically and technologically feasible, an important area called green chemistry. Ricci and coworkers[167] have developed organocatalysed solvent-free aza-Henry reaction (Scheme 60).

[166] J. C. Anderson, G. P. Howell, R. M. Lawrence, C. S. Wilson, *J. Org. Chem*. **2005**, *70*, 5665-5670.
[167] L. Bernardi, B. F. Bonini, E. Capito, G. Dessole, M. Comes-Franchini, M. Fochi, A. Ricci, *J. Org. Chem*. **2004**, *69*, 8168-8171.



R = aryl, hetaroaryl.



1,1,3,3-tetramethylguanidine (TMG)

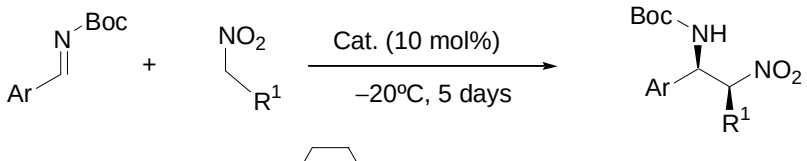
(**XVIII**)

90-96% yield
upto 98:2(anti:syn)

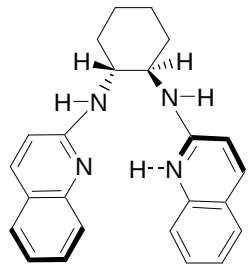
Scheme 60: *Highly diastereroselective synthesis by achiral base 1,1,3,3-tetramethylguanidine (TMG)* ***XVIII****.*

A nitrogen containing superbase 1,1,3,3-tetramethylguanidine (TMG) **XVIII** was found to be an effective organocatalyst for the reaction between *N*-diphenylphosphinoyl imines and nitroalkanes to obtain the corresponding adduct in its racemic form bearing tertiary and quaternary stereogenic centres. Exploiting a protocol that avoids the use of solvent also during workup procedure, the synthesis of a series of β-nitroamines in excellent yields (90-96%) and high diastereomeric ratios ((anti:syn) upto >98:2%) was described.

Johnston and coworkers[168] have developed a "chiral proton" model that promotes the diastereoselective aza-Henry reaction (Scheme 61).



Catalyst:



(**XIX**)

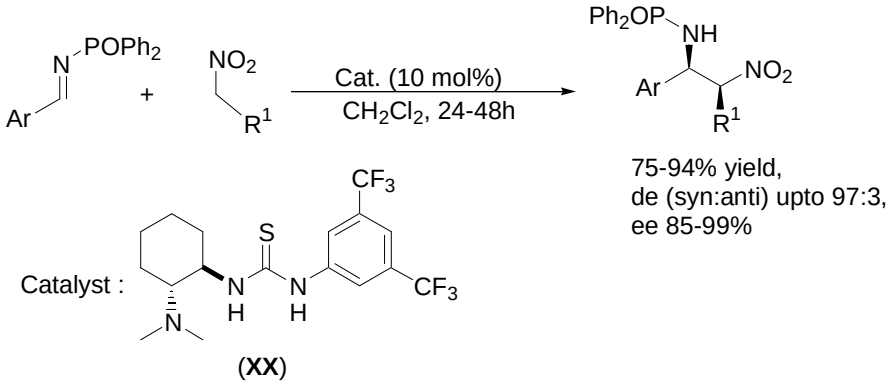
50-69% yield,
de(syn:anti) upto 95:5,
ee 59-90%

Scheme 61: *Chiral proton* ***XIX*** *catalysed asymmetric aza-Henry reaction of N-Boc arylimines.*

[168] B. M. Nugent, R. A. Poder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418-3419.

With 10 mol% of the protonated C_2 amidine ligand chiral **XIX** at −20ºC for 5 days, moderate isolated yields enantio- and diastereoselectivities were obtained. Under these reaction conditions nitromethane didn´t afford good enantioselectivities.

Takemoto and coworkers[169] have developed a bifunctional thiourea catalyst for the highly selective aza-Henry reaction of *N*-phosphorylimines. Typically 10 mol% of catalyst **XX** is used in dichloromethane with nitromethane, and after 24-48h, moderate yields (57-91%) and ee´s (63-76%) were obtained (Scheme 62).



Scheme 62: *Asymmetric aza-Henry reaction of N-POPh₂ arylimine with nitroalkanes promoted by chiral thiourea derivative **XX**.*

The same author obtained better enantioselectivity when N-Boc-imines were used instead, with 10 mol% of the same catalyst at −20ºC, high enantioselectivities (85-99%ee) and diastereoselectivities (upto *syn:anti*, 97:3) with excellent chemical yields were observed.

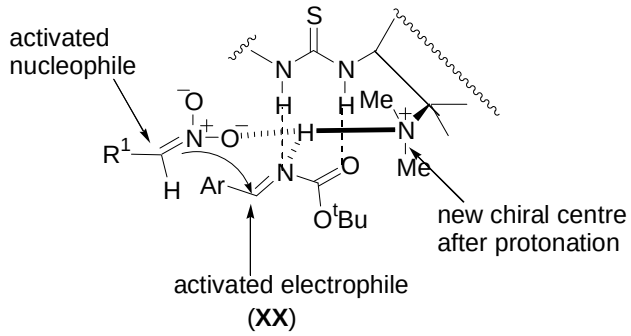
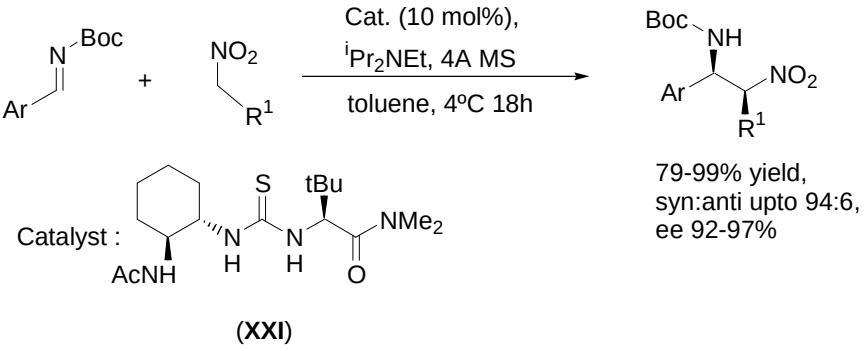


Figure 20: *Model for substrate activation catalysed by **XX**.*

[169] X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466-476.

The proposed reaction model implies a bifunctional catalyst **XX** (Figure 20) where a tertiary nitrogen atom acts as base. After nitronate formation, the protonated amine can increase the electrophilicity of the imine carbon through hydrogen bonding.

With a similar catalyst design, Jacobsen and coworkers[170] have developed a more efficient catalytic model for the asymmetric aza-Henry reaction (Scheme 63).



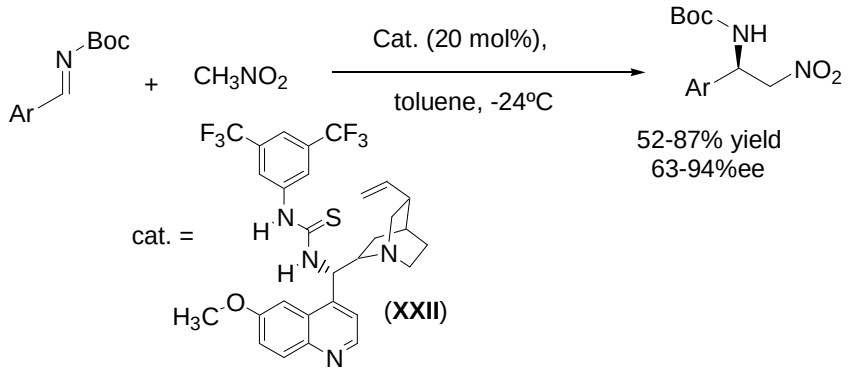
(**XXI**)

Scheme 63: *Highly asymmetric aza-Henry reaction of N-Boc arylimines with nitroalkanes promoted by chiral thiourea derivative **XXI** and triethylamine as base.*

In this catalytic system, the thiourea catalyst **XXI** alone is unable to promote the reaction because its nitrogen atoms are not enough basic. Consequently, to promote the reaction, triethylamine, which acts as external base, is required; and after 18h at 4ºC, good chemical yields (79-99%) with high selectivities (*syn:anti*, 94:6 and 92-97%ee) are obtained. With this catalytic system, the reaction with nitromethane showed good enantioselectivity but imine scope is somewhat limited.

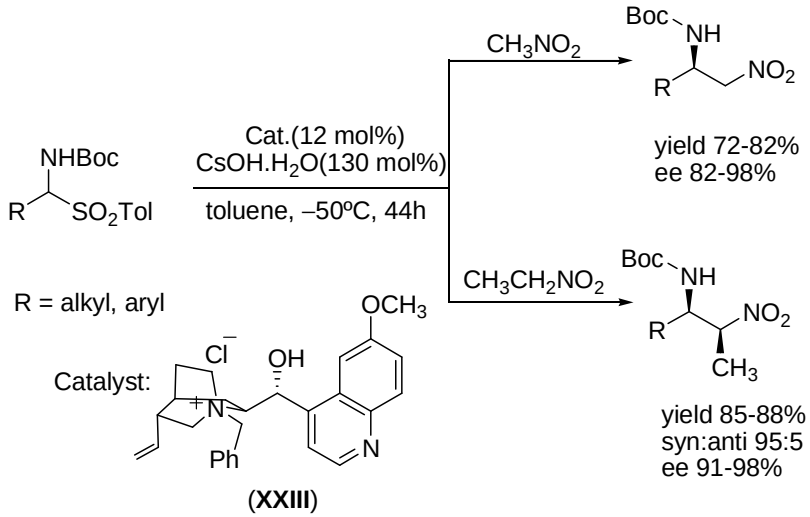
After our research work, another thiourea catalyst derived from cinchona alkaloids was developed by Ricci and coworkers.[171] Using 20 mol% of catalyst **XXII**, the reaction with *N*-Boc imines are achieved in reasonable time and good chemical yields with moderate to high enantioselectivity (63-94%ee) (Scheme 64).

[170] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466-468.
[171] L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, Alfredo, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375-380.



Scheme 64: *Enantioselective aza-Henry reaction promoted by cinchona alkaloid thiourea derivative (**XXII**).*

Very recently, independent but related methods employing PTC and α-amido sulfones as imine precursors have been documented. On one hand work developed in our laboratory by A. Laso and R. Lopez[172] and on the other hand, work by L. Bernardi et al.[173] have described the aza-Henry reaction of substituted nitroalkanes using α-Boc-amidoaryl sulfones as *N*-Boc-imino equivalents (Scheme 65). In these cases, 12 mol% of phase transfer catalyst (PTC) **XXIII** was used with 130 mol% $CsOH.H_2O$ base. Base promoted elimination of *p*-toluenesulfinic acid from the *N*-Boc-amidoaryl sulfones leads to the corresponding *N*-Boc imines in situ that react with the the nitroalkane, affording the aza-Henry adducts in good yields and high selectivity.



Scheme 65: *Asymmetric aza-Henry reaction by phase transfer catalyst using α-amido sulfones.*

[172] C. Palomo, M. Oiarbide, A. Laso, R. Lopez, *J. Am. Chem. Soc*. **2005**, *127*, 17622-17623.
[173] L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Angew. Chem. Int. Ed*. **2005**, *45*, 7975-7978.

Despite the above mentioned impressive progress, many challenges remain unaddressed for the catalytic asymmetric aza-Henry reactions, notably with regard to extension of substrate scope, selectivity and reactivity.

Our specific new finding is that cooperative activation[174]of nitrocompounds and aldimines towards the aza-Henry reaction can be effected by a combination of a Lewis acid, a chiral amino alcohol ligand,[175] and a tertiary amine base, to obtain highly enantioselective aza-Henry adducts, thus providing a new entry to enantioenriched aryl glycines upon final Nef oxidation.

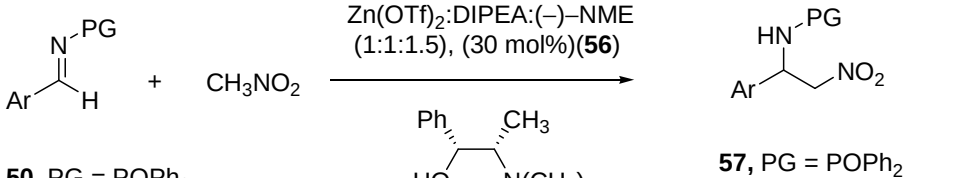
[174] Recent reviews on cooperative activation of nucleophiles (or pronucleophiles) and electrophiles: (a) J.-A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 4566-4583. (b) S. Kanemasa, K. Ito, *Eur. J. Org. Chem*. **2004**, 4741-4753.

[175] For other recent uses of *N*-methylephedrine, see: Addition of acetylides to aldehydes: (a) N. K. Anand, E. M. Carreira, *J. Am. Chem. So*c. **2001**, *123*, 9687-9688. (b) D. E. Frautz, R. Fässler, E.M. Carreira, *J. Am. Chem. Soc*. **2000**, *122*, 1806-1807. Imino-Reformatsky Reaction; c) P. G. Cozzi, E. Rivalta, *Angew. Chem. Int. Ed*. **2005**, *44*, 3600-3603.

4. 2 Results and discussion

4. 2. 1 Selection of the protecting group

Our initial concern was to identify the best suited *N*-protecting group in the imine component in terms of both reaction conversion and enantioselection. Initial screening reactions were carried out using commercially available nitromethane (distilled in presence of $MgSO_4$, kept on molecular sieves) with *N*-phosphinoylimine under the combination of $Zn(OTf)_2$, diisopropylamine (DIPEA), and the chiral amino alcohol *N*–methylephedrine ((–)-NME) promoting system **56** (Scheme 66). *N*–Methylephedrine ((–)-NME) and $Zn(OTf)_2$ were selected, because this chiral Lewis acid complex showed good reactivity and selectivity in other type of reactions.[176] The reaction protocol consisted of *in situ* preformation of the catalyst by admixing $Zn(OTf)_2$ and diisopropylamine (DIPEA) in nitromethane for 1h at room temperature, from which a nonhomogeneous yellow colored solution is formed. Then (–)-(*1R, 2S*)-*N*-methylephedrine (45 mol %) was added and after stirring the mixture for an additional 2h, the imine was added at the same temperature. After 19h, the reaction was quenched with 0.1M HCl and β-nitroamine **57** was obtained with >99% conversion. Unfortunately the crude product showed 0%ee (table 11, entry1).



50, PG = $POPh_2$
51, PG = *p*-$CH_3OC_6H_4$
52, PG = $C_6H_4CH_2$
53, PG = *p*-$C_6H_4SO_2$
54, PG = Cbz
55, PG = Boc

57, PG = $POPh_2$
58, PG = *p*-$CH_3OC_6H_4$
59, PG = $C_6H_4CH_2$
60, PG = *p*-$C_6H_4SO_2$
61, PG = Cbz
62, PG = Boc

Scheme 66: *aza-Henry reaction between imines **50-55** and nitromethane, PG=protecting group.*

When reaction temperature was decreased to –20ºC, there was only 10% conversion after 48h and ee determination was excluded (table 11, entry 2). Imines

[176] T. F. Knöpfel, D. Boyall, E. M. Carreira, *Org. Lett*, **2004**, *6*, 2281-2283.

from *p*-anisidine (entry 3) and benzyl amine (entry 4) which correspond to *p*-methoxyphenyl and benzyl protected *N*-atom did not react under the conditions described.

Table 11: *Effect of the imine substituent (PG) on yield and enantioselectivity*.

Entry	Imine	PG	T°C	Product	Yield(%)[a]	ee(%)[c]
1	**50**	Ph_2PO	r.t.[d]	**57**	>99	0
2	**50**	Ph_2PO	–20°C	**57**	10	---
3	**51**	*p*-$CH_3OC_6H_4$	r.t.[d]	**58**	---	---
4	**52**	$C_6H_5CH_2$	–20°C	**59**	---	---
5	**53**	*p*-$CH_3C_6H_4SO_2$	–20°C	**60**	>99	30
6	**54**	Cbz	–20°C	**61**	82[b]	82
7	**55a**	Boc	–20°C	**62a**	80[b]	94

Otherwise noted: Reactions conducted on a 1 mmol scale in nitromethane (2 mL) using imine: $Zn(OTf)_2$:*i*Pr_2EtN:(–)-NME in a 1:1:1:1.5 molar ratios at specified temperature. [a] Reaction conversion. [b] After column chromatography [c] Determined by HPLC. [d]r.t. is defined as room temperature.

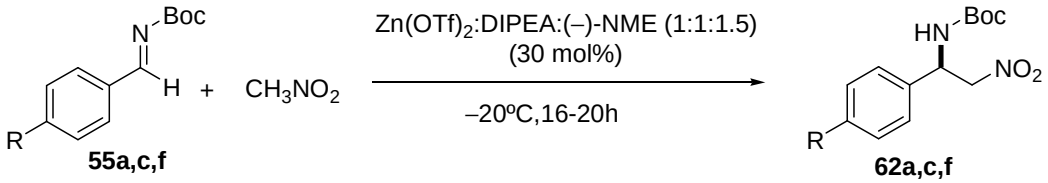
The reaction conducted with *N*-Ts protected imine **53** led**,** after 15h at –20°C, to the corresponding β-nitroamine **60** obtained in >99% conversion, with poor enantioselectivity (30% ee, entry 5).

Results changed drastically when *N*-Boc and *N*-Cbz imines were used. Thus the aza-Henry reaction of *N*-Cbz protected benzaldehyde imine **54** led, after 18h to adduct **61**, which was obtained in 82% isolated yield after column chromatography with a promising 82% ee (entry 6). More encouraging, *N*-Boc protected imine **55a** produced after 15h at the described temperature, the corresponding β-nitroamine adduct **62a** in 80% isolated yield after flash column chromatography and with 94% ee (entry 7). Enantiomeric excess for this reaction was determined by using chiralpak IA column on chiral HPLC (see experimental part). Strikingly, however, the selectivity was not consistent and results were varying in different runs from 20% ee to 94% ee.

4. 2. 2 Reaction condition optimization

As a first hypothesis for this large fluctuation, we thought that moisture coming from either reactant might be the cause. To prove our thought, reaction was conducted with 40 μL water on 1 mmol scale. After 20h, >99% conversion with 0% ee were obtained (table 12, entry 6), thus indicating the deleterious effect of water on the selectivity. Subsequently, several reaction conditions were tested in order to establish the most consistent ones. In a similar manner, when hexafluoro-2-propanol ($(CF_3)_2CHOH$) was used as additive, selectivity was reduced too (64%) (entry 5). To avoid moisture, we envisaged that some beneficial effect may arise from performing the reactions in the presence of molecular sieves. Firstly MS-4Å, previously dried under vacuum at 160ºC for 72h, was used, leading after 15h at –20ºC, to aza-Henry adduct **62a** in 80% isolated yield and with 97% ee (entry 3). Consistent yields and ee´s were obtained under these conditions in several runs.

Table 12: *Effect of additives on the reaction between N-Boc imine **55a** and nitromethane under catalytic conditions.*



55a,c,f **62a,c,f**

Entry	Imine	R	Additive[a]	Product	Yield(%)[b]	ee(%)[d]
1	**55a**	H	…..	**62a**	80	94
2	**55a**	H	MS-3Å	**62a**	78	84
3	**55a**	H	MS-4Å	**62a**	80	97
4	**55a**	H	MS-5Å	**62a**	83	96
5	**55a**	H	$(CF_3)_2CHOH$	**62a**	>99[c]	64
6	**55a**	H	H_2O(40μL)	**62a**	>99[c]	0
7	**55c**	CH_3	……	**62c**	90	91
8	**55c**	CH_3	MS-4Å	**62c**	91	92
9	**55f**	Cl	……	**62f**	96	84
10	**55f**	Cl	MS-4Å	**62f**	97	96

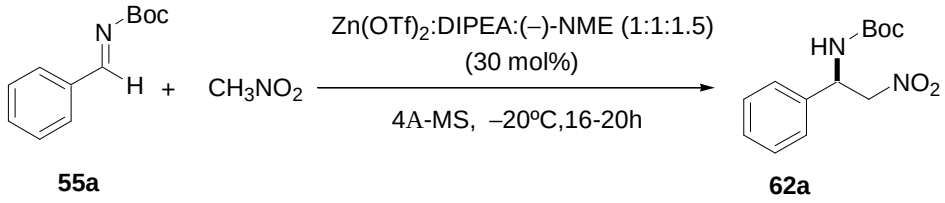
[a] Additives were used (100 mg/mmol). [b] After column chromatography. [c] Reaction conversion. [d] Determined by HPLC.

Among the other often employed sieves, MS-5Å performed similarly (80% yield, 96% ee) (entry 4), while the efficiency of MS-3Å was apparently inferior (80%

yield, 84% ee)(entry 2). To ensure general applicability of these conditions, reactions with imines **55c, f** were also conducted, leading to consistent yields/ee´s of 91/92 and 97/96, respectively.

After getting consistent results from above reaction conditions, we next explored the influence of catalyst loading and temperature. Reactions were conducted at temperatures variable within the range of –20 ºC to 25 ºC. For example, in the case of *N*-Boc-imine **55a**, temperature variation from –20 ºC to –10ºC resulted in >99% conversion with lower enantioselectivity (88% ee, Table 13, entry 2). At room temperature, after 3h, conversion was >99% with 87% ee (entry 1) whereas reactions are temperature tolerant within the range of –20 ºC to –60 ºC.

Table 13: *Temperature and catalyst loading effect on the enantioselectivity in the aza-Henry reaction of nitromethane with imine **55a**.*



55a **62a**

Entry	$Zn(OTf)_2$ (mol%)	DIPEA (mol%)	(–)NME (mol%)	MS-4Å 100mg/mmol	T(ºC)	t(h)	ee[a] (%)
1	30	30	45	100mg	25	3	87
2	30	30	45	-------	–10	14	88
3	30	30	45	100mg	–20	16	97
4	20	20	30	100mg	–20	18	87
5	10	10	15	100mg	–20	22	72

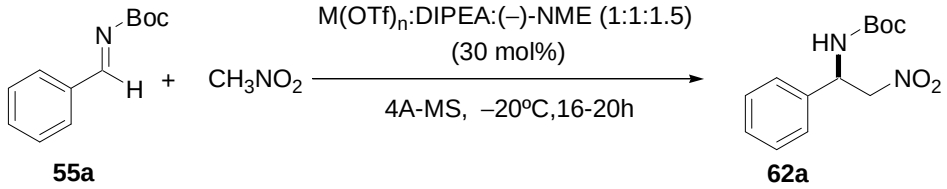
Reaction conversion were >99% in all entries [a] Determined by HPLC.

On the other hand, selectivity was reduced with lower catalyst loadings. For instance, in the case of 20 mol% catalyst, at –20ºC, after 18h, selectivity fell from 97% to 87% ee (entry 4) and with catalyst loading of 10 mol%, enantioselectivity was only 72% ee (entry 5).

Although initially we chose zinc metal, the preliminary inconsistent results forced us to consider other metals too. Hence $Mg(OTf)_2$, $Cu(OTf)_2$, $Ba(OTf)_2$, and

$Yb(OTf)_3$ Lewis acids were selected but none of them could provide selectivity above 14% ee, though >99% conversions were obtained in all entries (Table 14, entry 2-5).

Table 14: *Effect of the Lewis acids on the aza-Henry reaction between N-Boc imine* ***55a*** *and nitromethane.*



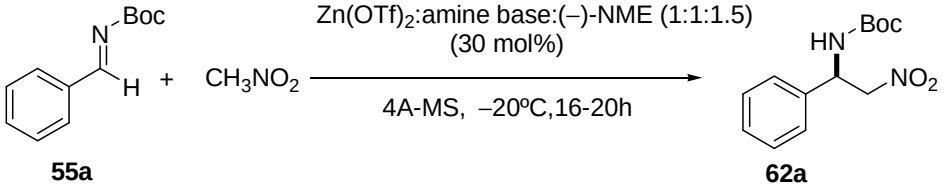
55a **62a**

Entry	$M(OTf)_n$	Conv.(%)[a]	ee(%)[b]
1	$Zn(OTf)_2$	>99	97
2	$Cu(OTf)_2$	>99	14
3	$Mg(OTf)_2$	>99	7
4	$Ba(OTf)_2$	>99	13
5	$Yb(OTf)_3$[c]	>99	0

[a]Conversion determined by ^{1}H NMR (500 MHz). [b]Determined by HPLC. [c] Reaction time only 5h.

Regarding the base, although other amines were also useful in promoting the aza-Henry reaction with good level of chemical and stereochemical efficiency (Table 15), DIPEA was the best option.

Table 15: *Effect of the amine base on the reaction of nitromethane with N-Boc imine* ***55a****.*



55a **62a**

Entry	Base	Conv.(%)	ee(%)
1	DIPEA	>99	97
2	Et_3N	>99	92
3	Bu_3N	>99	95
4	DBU	>99	84
5	P2-Et	>99	77

[a]Conversion determined by ^{1}HNMR (500MHz). [b]Determined by HPLC

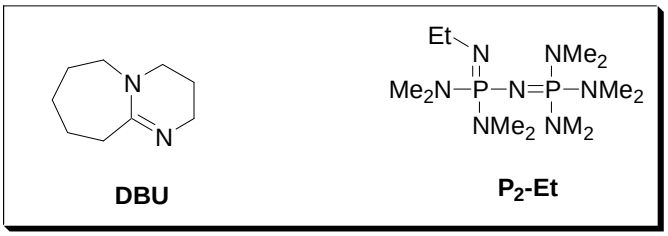
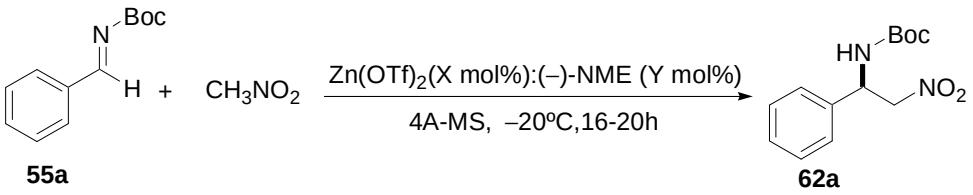


Figure 21. *BDU and P_2-Et bases.*

When triethylamine and tributylamine were used, in both cases conversions were >99% after 16-20h with 92% ee (entry 2) and 96% ee (entry 3) respectively. Stronger bases, like DBU and P_2-Et, afforded >99% conversion and led to with lower selectivities after 16-18h; 84% ee and 77% ee respectively (entry 4, 5).

On the other hand, the mol unit ratio of the three components of the triggering system ($Zn(OTf)_2$: DIPEA: (–)-NME) was shown to be crucial for both high yield and selectivity. In this sense, NME alone was unable to impart any asymmetric induction, although the reaction took place (entry 1, table 16). The combination of 45% (–)-NME with 30% $Zn(OTf)_2$ resulted in slow reaction rate with 40% conversion after 22h and 0% ee (entry 2).

Table 16: *Effect of the relative amount of (–)-NME and $Zn(OTf)_2$ on the enantioselectivity of the reaction of nitromethane with imine **55a**.*



55a **62a**

Entry	X(mol%)	Y(mol%)	Conv.(%)[a]	ee(%)[b]
1	0	45	60	0
2	30	45	40	0
3	30	60	>99	38
4	30	75	>99	97
5	30	90	>99	95
6	30	100	>99	88

[a] Conversion determined by ^{1}H NMR (500 MHz). [b] Determined by HPLC.

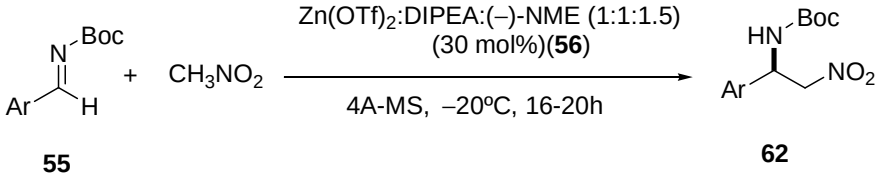
Combinations of $Zn(OTf)_2$ and(–)-NME in a mol ratio of 30:75 or higher (entries 4-6) led to high enantioselectivities, again. These results demonstrate that the

presence of base is key for success and suggest that the amino alcohol ligand, when used in excess, may play a dual role, as base and as chiral inductor. In addition, the reaction conducted with $Zn(OTf)_2$ (30mol%) and (−)-(1*R*,2*S*)-*N*-methylephedrine (45%) without DIPEA (entry 2), resulted sluggish, with racemic product formed in only 40% conversion after 20h.

4. 2. 3 Substrate scope of the reaction

Having established the best reaction conditions and catalyst composition for the reaction of nitromethane and imine **55a**, the validity of the method for other imines, was explored. As the results in Table 17 show, the preliminary evaluation of the reaction scope was carried out by using a survey of *N*-Boc aryl imines which vary in electronic character. Imines **55a-m** bearing electron-rich, electron-neutral, and electron-poor aryl substituents were well tolerated to give *N*-Boc β-nitroamines **62a-m** in generally good chemical yields and high levels of stereocontrol. Apparently, heteroaromatic *N*-Boc imines are less suited substrates for the reaction. For instance, using the furfuraldehyde corresponding *N*-Boc imine **62n**, the aza-Henry adduct was obtained in 96% yield, but with a poor 66% ee. The standard reaction conditions involved nitromethane as solvent, but other solvent systems, such as mixtures of nitromethane and methylene chloride or toluene (50/50 v/v), can be equally used. A practical aspect of the method is that a single recrystallization from hexane and or mixtures of ethyl acetate and hexane of the crude β-nitroamine can provide products of increased enantiomeric purity.

Table 17: *Enantioselective aza-Henry reaction of nitromethane with different N-Boc arylimines promoted by catalyst* ***56.***



55 **62**

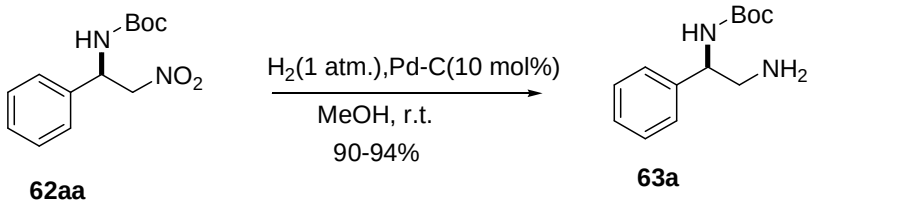
Imine **55**	Ar	Product **62**	Yield(%)[a]	ee(%)[b]
a	C_6H_5	**a**	81	97
b	*o*-$CH_3C_6H_4$	**b**	75	99
c	*p*-$CH_3C_6H_4$	**c**	90	92(94)
			92	88[c]
			85	86[d]
d	*m*-$CH_3OC_6H_4$	**d**	80	90(99)
			86	88[c]
e	*p*-$CH_3OC_6H_4$	**e**	73	91
f	*p*-ClC_6H_4	**f**	97	96[e](98)
g	*p*-$F_3CC_6H_4$	**g**	98	92(94)
h	*m*-$NO_2C_6H_4$	**h**	59	90(92)
i	*p*-$NO_2C_6H_4$	**i**	65	87
j	*p*-$CH_3O_2CC_6H_4$	**j**	78	94
k	1-Naphthayl	**k**	95	94(98)
l	2-Naphthayl	**l**	70	93
m	3,5-Cl_2,4-$MeOC_6H_2$	**m**	66	87[d](95)
n	2-furfural	**n**	96	66

[a]Isolated yield after column chromatography. [b]Determined by HPLC after removal of traces of (–)-NME by column chromatography. The number in parentheses refers to the product after a single crystallization from hexane/ethyl acetate. [c]Using $Zn(OTf)_2$(20%); DIPEA (20%); (–)-NME (30%). [d] Using $Zn(OTf)_2$ (30%); (–)-NME (75%). [e]In the absence of 4Å molecular sieves, 84% ee was attained.

4. 2. 4 Chemical elaboration of aza-Henry adducts

To demonstrate the synthetic utility of the method, elaboration of the adducts into orthogonally protected vicinal diamines was undertaken first. For example, reduction of the nitro group of **62a** by hydrogen in the presence of Pd-C, led to the

known monoprotected diamine **63a** with 90-94% chemical yield. This allowed to correlate the absolute configuration of adducts[177] (Scheme 67).

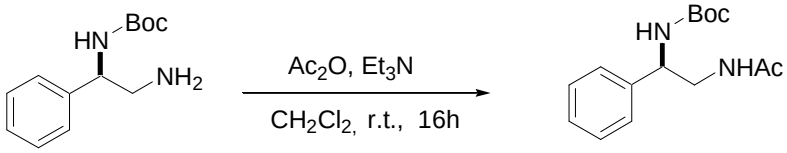


62aa **63a**

$[\alpha]_D^{20}$ = – 43.6 (c 1.1%, $CHCl_3$)
Lit.$[\alpha]_D^{20}$ = – 44.0 (c 1.1%, $CHCl_3$)

Scheme 67: *Reduction of the nitro group to amine group.*

Further acetylation of **63a** by acetic anhydride and triethylamine in dichloromethane to the known **64a** allowed establishing the optical purity. After single crystallisation with hot hexane, the product was isolated with >99% ee.



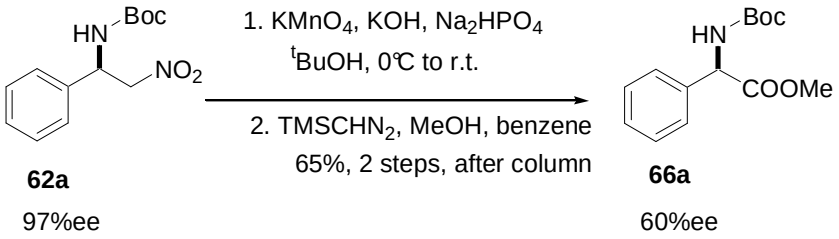
97%ee 97%ee
63a **64a**

Scheme 68: *Acylation of the primary amine by acetic anhydride*

The second option explored was the Nef oxidation of the C–NO_2 group to the carboxy group, which will led to the corresponding *N*-Boc-α-amino acid. We selected for that the oxidation of the nitro group by $KMnO_4$ developed by Profeta and coworkers (Scheme 69).[178] The oxidation of adduct **62a** (97% ee) under potassium permanganate ($KMnO_4$) with potassium hydroxide (KOH) and disodium

[177] P. H. O'Brien, D. R. Sliskovic, C. J. Blankley, B. Roth, M. W. Wilson, K. L. Hamelehle, B. R. Krause, R. L. Stanfield, *J. Med. Chem*. **1994**, *37*, 1810-1822.
[178] E. Foresti, G. Palmieri, M. Petrini, R. Profeta. *Org. Biomol. Chem*. **2003**, *1*, 4275-4281

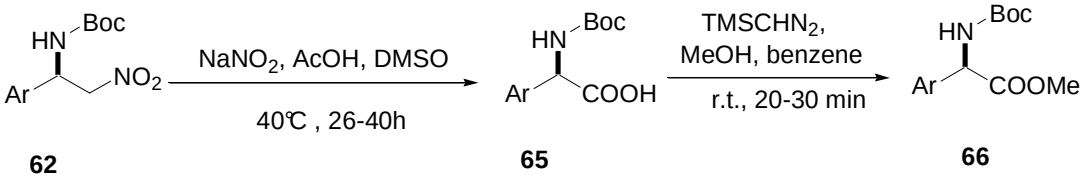
monohydrogen phosphate (Na_2HPO_4), originated **65a,** which upon methylation afforded **66a** in 65% yield after two steps. This compound showed a 60% ee thus indicating that partial racemisation took place during Nef oxidation.



62a 97%ee **66a** 60%ee

Scheme 69: *Oxidation of the nitro group by $KMnO_4$.*

To overcome the racemisation problem, we selected the oxidation conditions developed by Mioskowski and coworkers.[179] The *N*-Boc-β-nitroamine adducts **62a-c** upon treatment with sodium nitrite and acetic acid in dimethylsulfoxide at 40ºC, afforded the corresponding *N*-Boc protected aryl glycines **65a-c** in good yield (Scheme 70). Subsequently, esterification with trimethylsilyldiazomethane yielded the *N*-Boc-arylglycine methyl esters **66a-c** without apparent loss of optical integrity (Table 18). Specific rotation of **66a**, ($[\alpha]_D^{25}$ = –104.9º (c = 0.65, CH_3OH) resulted to be opposite sign as compared with authentic material prepared from commercially available (*S*)–methylphenylglycine ($[\alpha]_D^{25}$ = +104.9º (c = 0.65, CH_3OH) and also described literature value $[\alpha]_D^{25}$ = +104.9º; c = 0.65, CH_3OH).[180]



62 **65** **66**

Scheme 70: *Oxidation of the nitro group onto carboxylic acid, followed by esterification.*

[179] a) C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234-235. b) B. M. Trost, V. S. C. Yeh, *Angew. Chem. Int. Ed.* **2002**, *41*, 861-863.
[180] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.

Table 18: *Effect of the Nef oxidation on yield and enantioselectivity*.

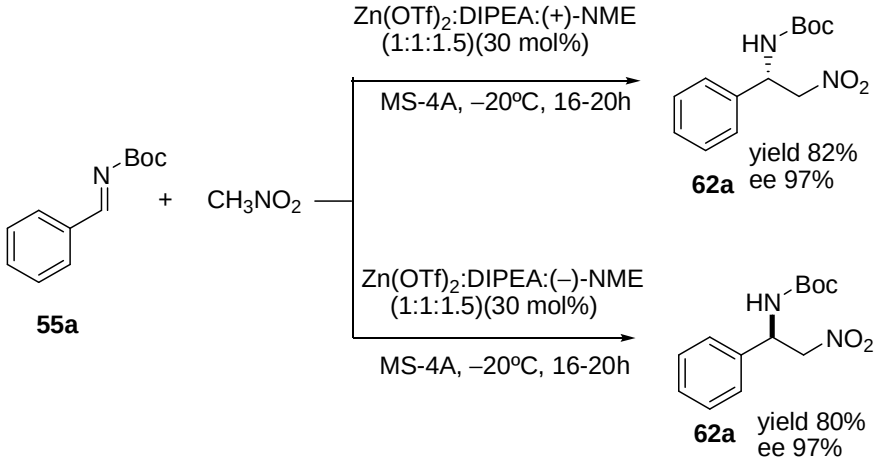
Adduct **62**		ee(%)of	Product	Yield(%)[a]	Product	Yield(%)[a]	ee(%)[b]
Compd.	Ar.	adduct **62**	**65**	of **65**	**66**	of **66**	of **66**
a	C_6H_5	97	**a**	90	**a**	80	97
b	*o*-MeC_6H_5	99	**b**	77	**b**	75	99
c	*p*-MeC_6H_5	92	**c**	70	**c**	65	93
m	3,5-Cl_2,4-$MeOC_6H_2$	95	**m**	85	**m**	72	33

[a] Yield of isolated product. [b] Determined by chiral HPLC.

Nef oxidation with sodium nitrite was not supporting when β-nitroamine adduct is attached with electron withdrawing groups. For instance, adduct **62m** (95% ee) subjected upon the same conditions afforded **66m** in good yield, but with important detrimental in ee (33% ee).

4. 2. 5 Practical advantages of this method are:

(i) The availability of the chiral ligand in both enantiomeric forms (Scheme 20) and as a results both enantiomers of β-amino nitro compounds can be obtained. For example, aldimine **55a** was treated with (+)-NME in optimized conditions, and after 16-20h, **62a** was obtained as opposite isomers in 82% yield with 97% ee (Scheme 71).



Scheme 71: *Formation of both enantiomers of the aza-Henry adducts using chiral ligand (+) - or (–) –NME (45 mol %), DIPEA (30 mol %) and Zn(OTf)₂ (30 mol %).*

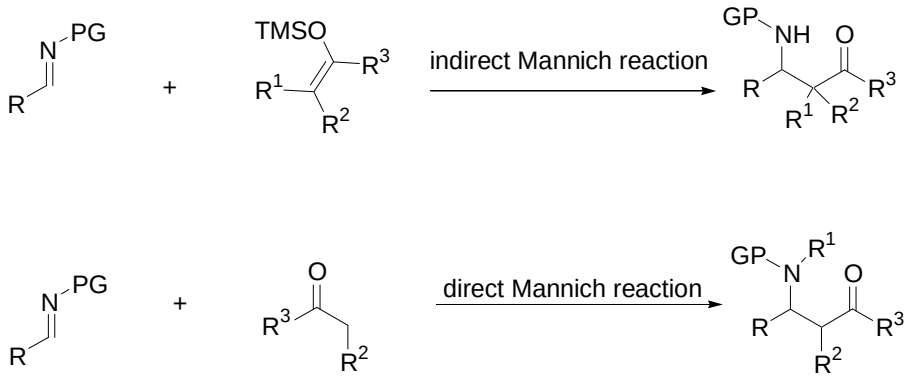
(ii) The essentially total recovery of (-)-NME. (-)-NME was not recovered by simple aqueous worked up with 0.1 M HCl because it remained in the organic phase. So, NME was recovered by following ways: from the late fractions of the column, (1*S*, 2*R*)-*N*-methylephedrine was recovered 32%. Recovery of the chiral ligand that remained in the acidic aqueous phase was carried out by drop-wise addition of a solution of NaOH 65%. Combined yield of chemically and optically pure (−)-NME ligand (97%).

5. Chapter III

Mannich Reaction

5. 1 Introduction

Enantioselective Mannich reactions[181] are of fundamental importance for the synthesis of optically active chiral amines and β-amino acids. Control over the asymmetric Mannich reaction constitutes one of the main challenges. Impressive achievements have recently been demontrated, in particular in asymmetric catalysis, with regard to the versatility of this reaction. Catalytic direct and indirect enantioselective methodologies have been developed. While the direct Mannich reaction requires unmodified ketone donors, amines and aldehydes, the indirect Mannich reaction uses performed enolate eqivalents and /or imines (Scheme 72).



Scheme 72: *General Scheme for direct and indirect Mannich reaction.*

Many catalytic asymmetric Mannich methods have been reported over the last few years. Excellent indirect catalytic methods, which involve the addition of enolates to imines in the presence of metal catalysts, have been reported by Kobayashi,[182] Sodeoka,[183] Lectka,[184] and Jacobsen[185] research groups who used chiral

[181] For reviews, See: (a) A. Cordova, *Acc. Chem. Res.* **2004**, *37*, 102-112. (b) S. Kobayashi, M. Ueno, In *Comprehensive Asymmetric Catalysis Supplement I*., Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, Berline, **2003**, Chapter 29.5. (c) S. Kobayashi, H. Ishitani, *Chem. Rev*. **1999**, *99*, 1069-1094 and references therein

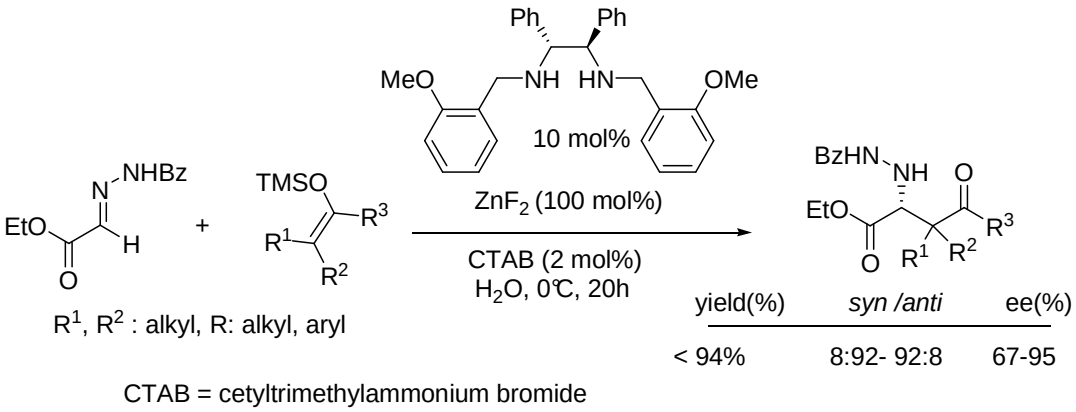
[182] a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc*. **1997**, *119*, 7153-7154. (b) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc*. **2002**, *124*, 5640-5641. (c) H. Ishitani, S. Ueno, S. Kobayashi, *J. Am. Chem. Soc*. **2000**, *122*, 8180-8186.

[183] (a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am Chem. Soc*. **1998**, *120*, 2474-2475. (b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am Chem. Soc*. **1999**, *121*, 545-556.

[184] (a) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc*. **1998**, *120*, 4548-4549. (b) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. III, Drury, L. Ryzhkov, T. Taggi, T. Lectka, *J. Am Chem. Soc*. **2002**, *124*, 67-77 and references therein.

[185] A.G. Wenzel, E. N. Jacobsen, *J. Am Chem. Soc*. **2002**, *124*, 12964-12965

zirconium/binol, palladium(II)/binap, copper(I)/binap complexes and thiourea respectively. Recently Kobayashi and coworkers[186] developed an efficient catalytic, enantioselective and diastereoselective Mannich type reaction of a hydrazone ester with silicon enolates using water as the solvent (Scheme 73).



Scheme 73: *Indirect Mannich reaction using water as solvent.*

It should be noted that this method provides access to either the syn or anti adducts stereospecifically from (*E*) or (*Z*)-enolates.

However, a disadvantage of these stereoselective Mannich reactions can be the preparation and instability of the preformed enolates used. The most effective and atom-economic asymmetric Mannich reaction would be a catalytic process that involves the same number of equivalents of imine and unmodified carbonyl donor, a process which is so-called direct Mannich reaction.[187] The transformations are catalyzed by both organometallic complexes and metal-free organic catalysts.

Recently, Shibasaki et al. reported that the Et_2Zn/ linked-BINOL (**XXIV**) complex is an excellent catalyst for the direct asymmetric Mannich-type reaction.[188]

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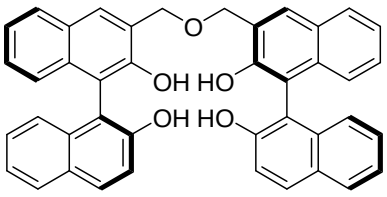
[186] T. Hamda, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc*. **2004**, *126*, 7768-7769.
[187] B.M Trost, The Atom Economy: *A Search for Synthetic Efficiency*. *Science* **1991**, *254*, 1471-1477.
[188] (a) S. Matsunaga, N Kumagai, N. Harada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712-4713. (b) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1871-1873 and references therein. (c) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168-4178. (d) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466-2467. (e) D. Sawada, M. Shibasaki, *Angew. Chem., Int. Ed.* **2000**, *39*, 209-213. (f) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307-310.

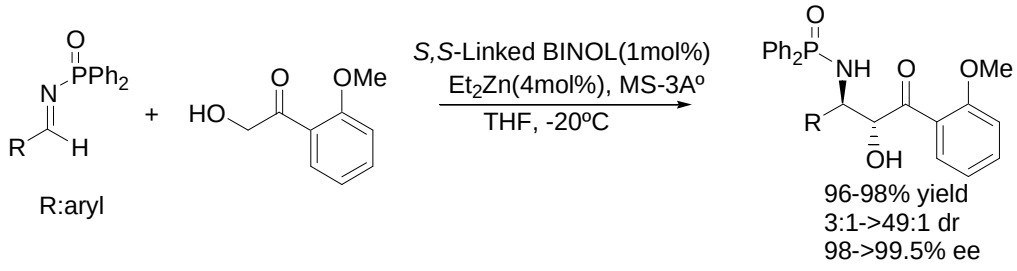


(*S,S*)-Linked BINOL complex (**XXIV**)

Figure 22: *(S,S)-linked-BINOL complex*

The Et_2Zn/linked-BINOL complex was investigated as catalyst due to its high selectivity in direct asymmetric *syn*-selective aldol reactions and Michael reactions with aryl hydroxyketones as the donors.[189]

Mannich reactions between imines with various *N*-protecting groups, hydroxyaceto-2-methoxyphenone, and Et_2Zn/linked-BINOL (**XXIV**) complex revealed that N-diphenylphosphinoyl (Dpp) protected imines were the most promising with regard to stereoselectivity. Thus, *N*-Dpp-protected imines are employed as acceptors, and the corresponding Mannich adducts are isolated in high yield (96 – 98%) and excellent enantioselectivity (98 -99 % ee) (Scheme 74).

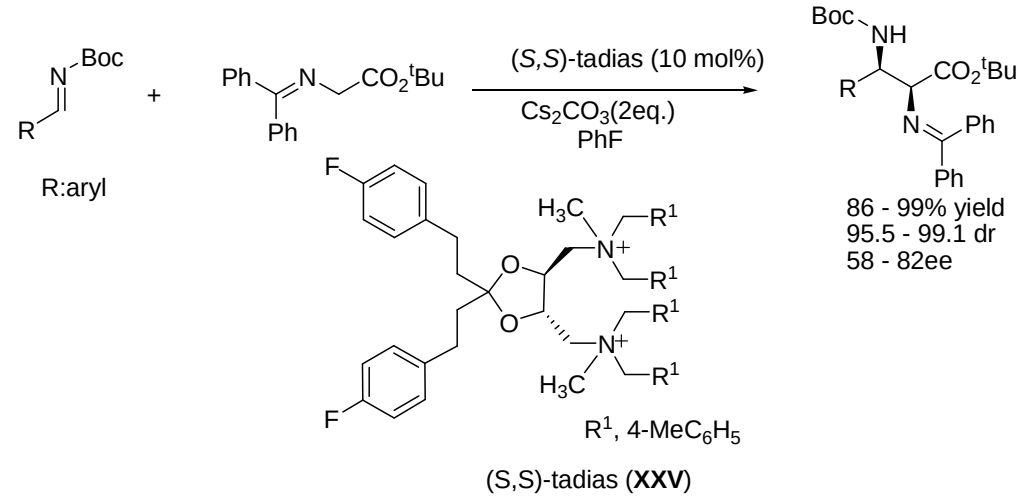


Scheme 74: *Mannich reaction of α-hydroxy ketone to imines using BINOL derivatives (**XXIV**) and Et_2Zn.*

Recently the same group, has reported a highly efficient *syn*-selective enantio- and diastereoselective catalytic Mannich type reaction of a glycine Schiff

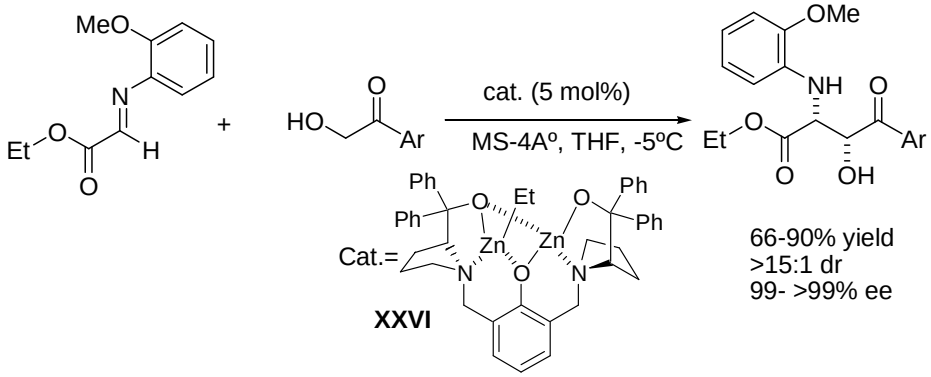
[189] (a) S. Matsunaga, J. Das, J. Roels, E. M. Vogel, N. Yamomoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc*. **2000**, *122*, 6506-6507. (b) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc*. **2003**, *125*, 2169-2178 and references therein. (c) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc*. **2003**, *125*, 2582-2590 and references therein.

base using the chiral two-centre phase transfer catalyst (*S,S*)-tadias (**XXV**) (Scheme 75).[190]



Scheme 75: *Mannich reaction using the phase transfer catalyst (S,S)-tadias **XXV**.*

Trost and co-workers reported that dinuclear zinc complexes catalysed Mannich reactions with unmodified aromatic hydroxy ketones as donors with excellent enantioselectivity.[191] Mannich-type reactions between *N*-*o*-methoxyphenyl-protected α-ethyl glyoxylate and hydroxyacetophenone in the presence of a catalytic amount (5 mol%) of catalyst chiral Lewis acid (aminoalcohol and diethylzinc) **XXVI** afford the desired *N*-PMP protected amino acid derivative in 76% yield, with a dr of 7:1 and 95% ee (Scheme 76).

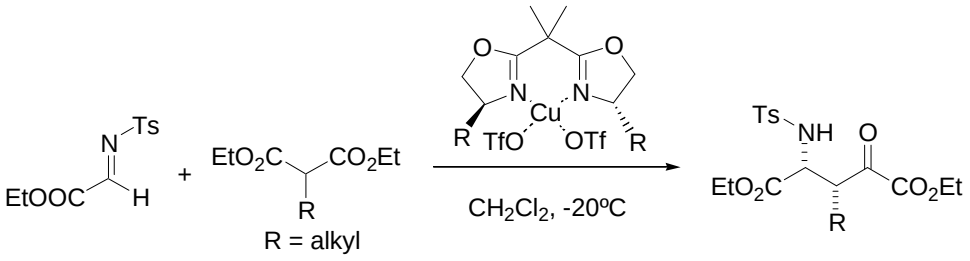


Scheme 76: *Mannich reaction of α-hydroxy ketone to imines in the presence of chiral amino alcohol and Et_2Zn.*

[190] A. Okada, T. shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4564

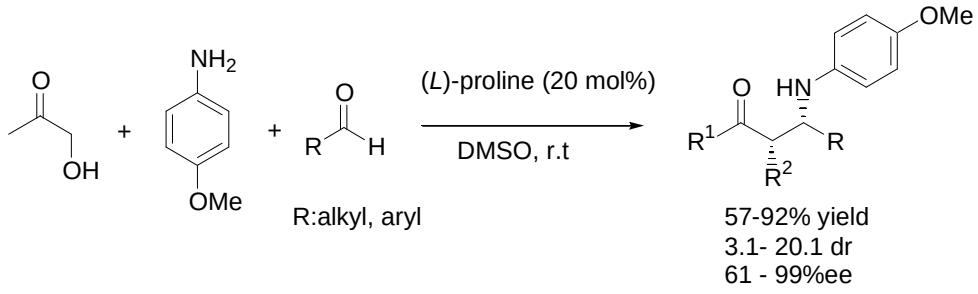
[191] B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc*. **2003**, *125*, 338-339.

Jørgensen and coworkers have disclosed the first chiral Cu(II)/Box complex-catalyzed direct asymmetric Mannich reaction of activated carbonyl compounds and α-imino esters.[192] The chiral $Cu(OTf)_2$/Box complexes are also catalysts for the asymmetric Mannich-type additions of unmodified malonates and β-ketosters to activated *N*-tosyl-α-imino esters.[193] Reactions with substituted diethyl malonates in the presence of a catalytic amount of $Cu(OTf)_2$/Box complexes proceed smoothly at -20 °C, giving Mannich adducts in good yield with 61-87% ee (Scheme 77).



Scheme 77: *Enantioselective Mannich reaction of active methylenes to α-imino esters in the presence of Cu-Box complexes.*

Scheme 78 shows the first direct aminocatalytic asymmetric Mannich reaction which has been reported by List.[194]



Scheme 78: *Direct Mannich organocatalytic reaction using proline.*

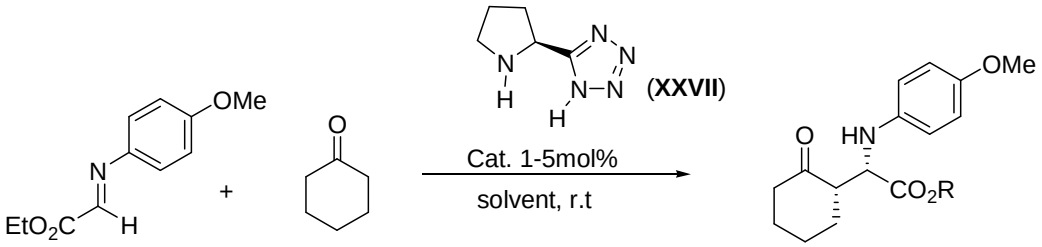
[192] (a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2995-2997. (b) K. Juhl, N. Gathergood, K. A. Jørgensen,. *Chem. Commun*. **2000**, 2211-2212. (c) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc*. **2002**, *124*, 2420-2421.

[193] M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem.-Eur. J*. **2003**, *9*, 2359-2367.

[194] (a) B.List, *J. Am. Chem. Soc*. **2000**, *122*, 9336-9337. (b) B.List, P. Porjalev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc*. **2002**, *124*, 827-833.

The Mannich reaction is regiospecific for oxygen-substituted ketones, providing one single regioisomer in good yield with high ee. The highest selectivity is observed when aromatic imines with electron-withdrawing groups are used as acceptors. Similar model reactions are described by Barbas and coworkers[195] and others.[196]

More recently Ley and coworkers screened new catalysts and solvent for the catalytic asymmetric Mannich reaction.[197] Among the catalysts tested, a new catalyst tetrazole derivative **XXVII** was found to catalyze the asymmetric Mannich reaction of ketone and *N*-PMP-protected α-imino ethyl glyoxylate with high enantioselectivity and high yield (Scheme 79).



Scheme 79: *Mannich reaction in the presence of pyrrolidine-tetrazole catalyst **XXVII**.*

Despite the above mentioned impressive progress, many challenges remain unaddressed for the catalytic asymmetric Mannich reactions, notably with regard to substrate scope, selectivity and reactivity.

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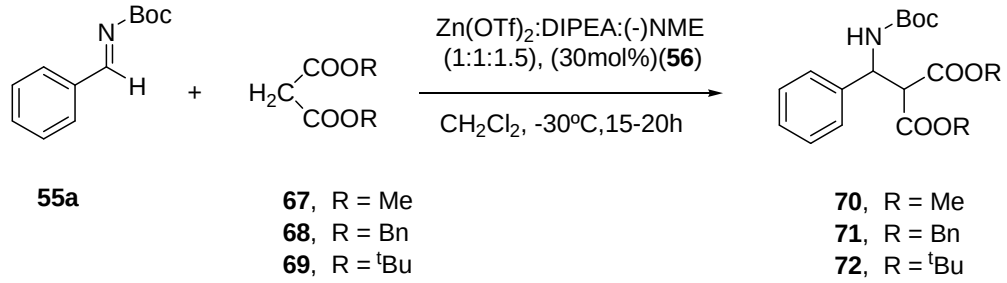
[195] W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199-201.

[196](a) A. Cordova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301-303. (b) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620-621. (b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799. (c) N. S. Chowdari, D. B. Ramachary, A. Co´rdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591-9595. (d) A. Co´rdova, W. Notz, C. F Barbas III, *Chem.Commun.* **2002**, *67*, 3024-3025. (e) A.Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2002**, *41*, 1790-1793. (f) B. List, *J. Am. Chem.Soc.* **2002**, *124*, 5656-5657. (g) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254-6255. (h) T. D. Machajewski, C.-H. Wong, *Angew. Chem., Int. Ed.* **2000**, *39*, 1352-1374 and references therein. (k) A. Co´rdova, S. Watanabe, F.Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866-1867.

[197] A. J. A. Cobb, D. M. Shaw, D. A. Long-Bottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84.

5.2 Results and discussion

Mannich reaction is a well known and a good tool to make C-C bond formation. To get the asymmetric version, we first thought to extend the catalytic system of the chiral Lewis acid complex ($Zn(OTf)_2$ (30mol%), DIPEA(30mol%), (–) NME (45mol%)) which shown the best results for the aza-Henry reaction, to other active methylene nucleophiles. Our initial screening reactions were carried out using commercially available dimethylmalonate (was used as recieved) with N-Boc-phenylimine under the $Zn(OTf)_2$, DIPEA, (-)NME (1:1:1.5) (30 mol%) catalytic,[198] conditions that showed good performance in aza-Henry reactions (previous chapter). The reaction protocol was as follows: dimethyl malonate (300 mol%) was added into a solution of $Zn(OTf)_2$ (30 mol%) and diisopropylethylamine (DIPEA) (30 mol%) in dichloromethane (2 mL) at room temperature and stirred for 1h at the same temperature. Then chiral ligand (-) (*1R, 2S*)-*N*-methylephedrine (45 mol %) was added and stirred for an additional 2h. After that the colorless reaction mixture was kept at -30ºC for 10 min and imine **55a** was added. The reaction was quenched after 19h and **70** was obtained in 95% conversion with 36% ee (table 19, entry 1).



Scheme 80: *Asymmetric Mannich reaction of dialkylmalonate to imine **55a**.*

Next, our concern was to identify the best suited alkyl group (R) in the malonate component in terms of both reaction conversion and enantioselectivity.

[198] C. Palomo, M. Oiarbide, R. Halder, A. Laso, R. Lopez, *Angew. Chem. Int. Ed.* **2006**, *45*, 117-120.

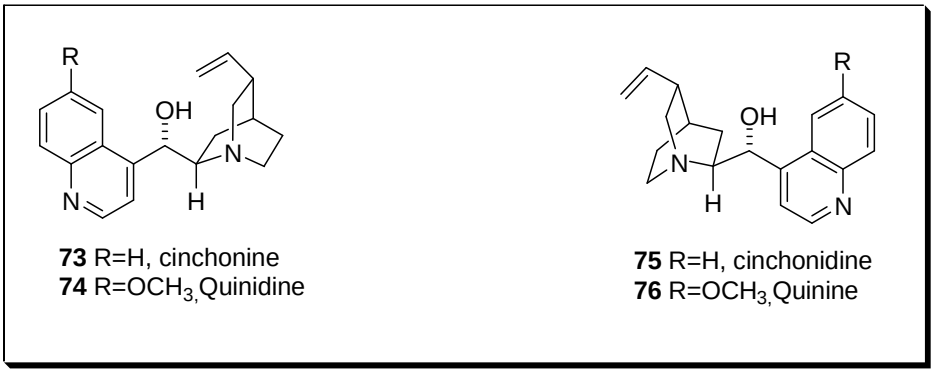
Table 19: *Conversion and enantioselectivty of the Mannich reaction of malonate to imine **55a**.*

Entry	Malonate		Product	Yield(%)[a]	ee(%)[b]
	Comp.	R			
1	**67**	Me	**70**	95	36
2	**68**	Bn	**71**	90	47
3	**69**	^{t}Bu	**72**	95	72

Reactions conducted on a 1 mmol scale (1-5) in dialkylmalonate (3.0 equiv.) using imine: $Zn(OTf)_2$:*i*Pr_2EtN:(–)-NME in a 1:1:1:1.5 molar ratio at specified temperature. [a] Reaction conversion was determined by ^{1}H NMR (500 MHz). [b] Determined by HPLC.

For example, when dibenzylmalonate and ditertbutylmalonate were used, after 16-20h, conversion were >90-95% and stereoselectivities 47%ee (entry 2) and 72%ee (entry 3) respectively.

As the chiral aminoalcohol-Lewis acid complex shoowed somewhat limited results in the initial attempts, we thought about switching to homologue commercially available and cheap chiral aminoalcohol cinchona alkaloids (**73, 74, 75** and **76**) without changing the nucleophiles and acceptor. During our work, Schaus and coworkers[199] shown that cinchona alkaloids act as good bifunctinal catalysts to promote the Mannich reaction of β-ketoesters to imines. Our interest was to use the same catalytic system with soft nucleophiles like dialkylmalonates in the addition to imines, a reaction which was still undeveloped.



73 R=H, cinchonine
74 R=OCH_3, Quinidine

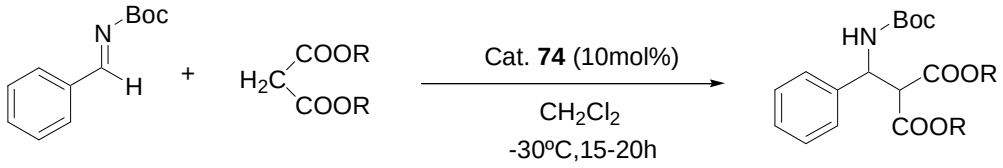
75 R=H, cinchonidine
76 R=OCH_3, Quinine

Figure 23: *Cinchona alkaloids used in Mannich reaction.*

[199] S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc*. **2005**, *127*, 11256-11257.

In the initial testing reaction, diethylmalonate addition to imine **55a** in the presence of quinidine **74** (10 mol%) at –30ºC was performed and after 16h, adduct **70** was obtained with 99% conversion and 80%ee (table 20, entry1).

Table 20: *Dialkylmalonate addition to imine **55a** in the presence of organocatalyst quinidine **74**.*



55a

67, R = Me
68, R = Bn
69, R = tBu

70, R = Me
71, R = Bn
72, R = tBu

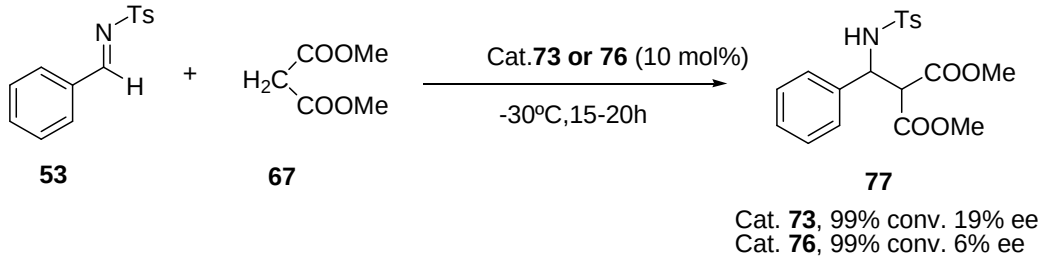
Entry	Malonate	Catalyst	Solvent	product	Conversion[a]	ee(%)[b]
1		**74**	CH_2Cl_2		99%	80[d]
2	**67**	**74**	Toluene	**70**	90	68
3		**74**	THF		95	33
4		**74+ (*R*)MA**[c]	CH_2Cl_2		20	24
5			CH_2Cl_2		94	89
6			$CHCl_3$		99	67
7			EtOH		81	29
8	**68**	**74**	MeOH	**71**	34	05
9			CH_3CN		55	77
10			Et_2O		67	88
11			^tBuOMe		76	72
12	**69**	**74**	CH_2Cl_2	**72**	40	52

(a) Reaction conversion determined by ^{1}HNMR (500MHz). (b) ee determined on chiral HPLC. [c]MA is defined as Mendelic acid, used 10 mol% as additive. [d]Reaction was also ran with cinchonidine **75**, 78% ee of opposite isomer was obtained.

We thought changing the solvent system could be detrimental for selectivity. When reactions were conducted in toluene and THF, Mannich adduct **70** was obtained in >90% conversion and lower selectivity; 68% ee and 33% ee respectively (entry 2,

3). Addition of an additive, says mandelic acid, also reduced the reaction rate as well as selectivity 24% ee (entry 4). However dibezylmalonate reacted to imine in better selectivity (89% ee) with good conversion (94%, Table 20, entry 5).Changing the solvent system, did not enhance the selectivity at all (entries 5-11). Reaction with ditertbutylmalonate showed poor reactivity (40% conversion) and selectivity 52% (table 20, entry 12). Next, our concern was to identify the best suited *N*-protecting groups in the imine component.

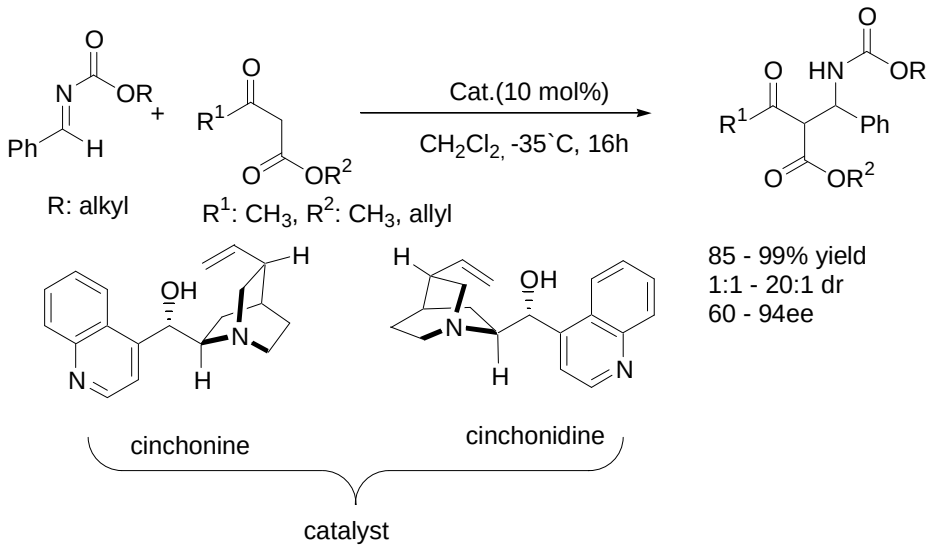
Our second selection was N-tosyl protected benzaldehyde aldimine **53**. The reaction conducted with this imine and dimethylmalonate **67** in the presence of catalyst **73** in dichloromethane, after 20h, afforded **77** in excellent conversion (99%) and 19% ee. Catalyst **76**, however, showed less selectivity (6% with 99% conversion).



Scheme 81: *Dimethylmalonate addition to N- tosylaldimine promoted by catalyst **73** or **76**.*

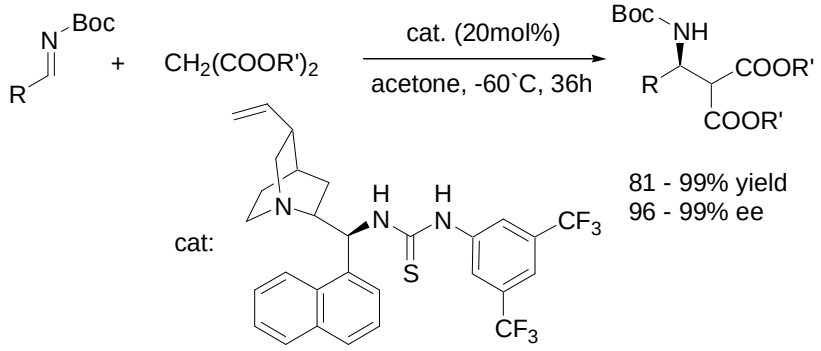
During our work, Schaus and coworkers[200] showed that the cinchonine- and cinchonidine promoted asymmetric Mannich reaction of β-ketoesters with acyl imines proceeds with chemical and stereochemical efficiency (Scheme 82).

[200] S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc*. **2005**, *127*, 11256-11257.



Scheme 82: *Enantioselective Mannich reaction promoted by cinchona alkaloids*.

Very recently, Deng and coworkers also reported that thiourea derivatives of cinchona alkaloids were efficient bifunctional catalyst for Mannich reaction of malonates with N-Boc imines (Scheme 83).[201]



Scheme 83: *Thiourea induced Mannich reaction of malonates to imines.*

Addition of less nucleophile malonates with imines in the presence of 20 mol% thiourea based on cinchona alkaloids provided good chemical yield (81-99%) and excellent enantioselectivity (96-99%) under mild, moisture- and air-compatible conditions. The above mentioned partially developed Mannich reactions of active methylene compounds with imines, which were reported during our own work, turned our attention to find out better organocatalysts.

[201] J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc*. **2006**, *128*, 6048-6049.

As mentioned in the introduction of the second chapter (aza-Henry reaction), our group presented a new asymmetric aza-Henry technology with broad substrate scope based on the use of α-amido sulfone substrates and phase transfer catalysis (PTC). Therefore, we considered the application of these conditions to the Mannich reaction of dialkylmalonates.

The initial screen of several chiral quaternary ammonium salts **78-82** and inorganic bases CsOH, H_2O (120 mol %) for the reaction of α-amido sulfone **83** and dimethylmalonate **67** in toluene as solvent was informative. After 48h, good conversion 90% was obtained and 0% ee as shown in Table 21 (entry 1). Similar results were obtained with tosyl-protected α-amido sulfone, whereas Cbz-protected α-amido sulfone showed the highest selectivity (41% ee) and good conversion (99%).

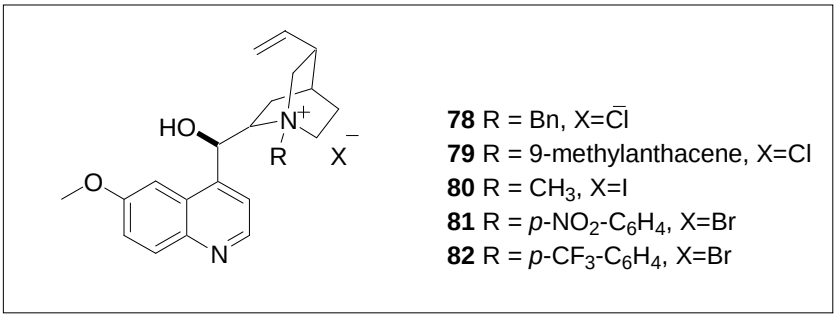
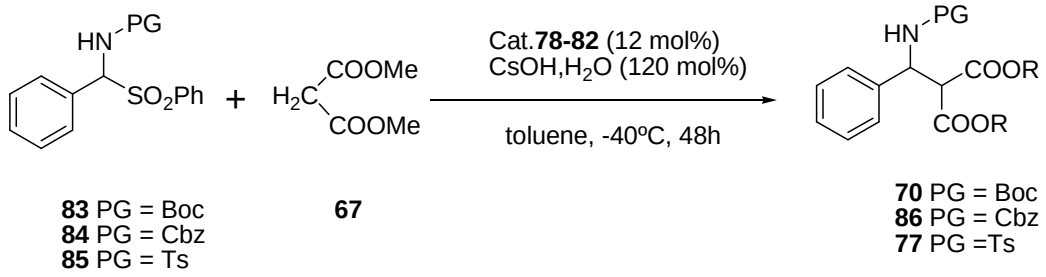


Figure 24: *Quaternary ammonium salts of chinchona alkaloids.*

Table 21: *Screening of quaternary ammonium salts in the reaction of amino sulfones **83-85** with dimethylmalonate **67**.*



83 PG = Boc
84 PG = Cbz
85 PG = Ts

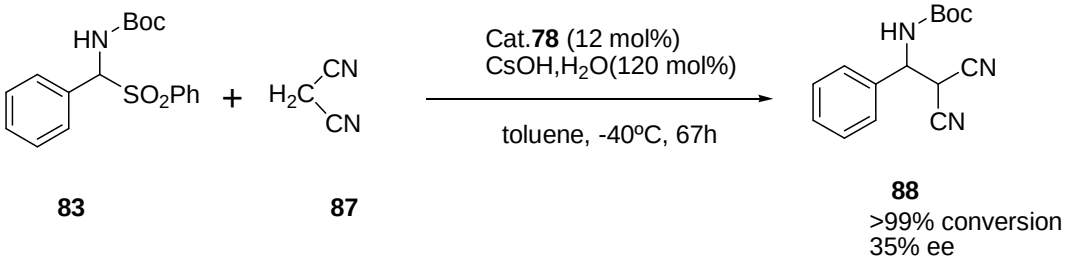
67

70 PG = Boc
86 PG = Cbz
77 PG =Ts

Entry	α-amido sulfone	Ammonium salt	Product	Conv.(%)[a]	ee (%)[b]
1	**83**	**78**	**70**	90	0
2		**79**		10	06
3		**80**		99	0
4		**81**		99	17
5		**82**		50	30
6	**84**	**78**	**86**	99	41
7	**85**	**78**	**77**	60	0

[a]Conversion was determined by NMR (500MHz).[b]ee determined on chiral HPLC.

As selectivities were not higher than 41%, we considered other different nucleophiles and among them malononitrile. Reaction of malononitrile with the α-amido sulfone **83** in the presence of $CsOH.H_2O$ (120 mol %) and catalyst **78** (12 mol %) in toluene at -40ºC, after 67h, afforded Mannich adduct **88** in >99% conversion and 35% ee (Scheme 84).



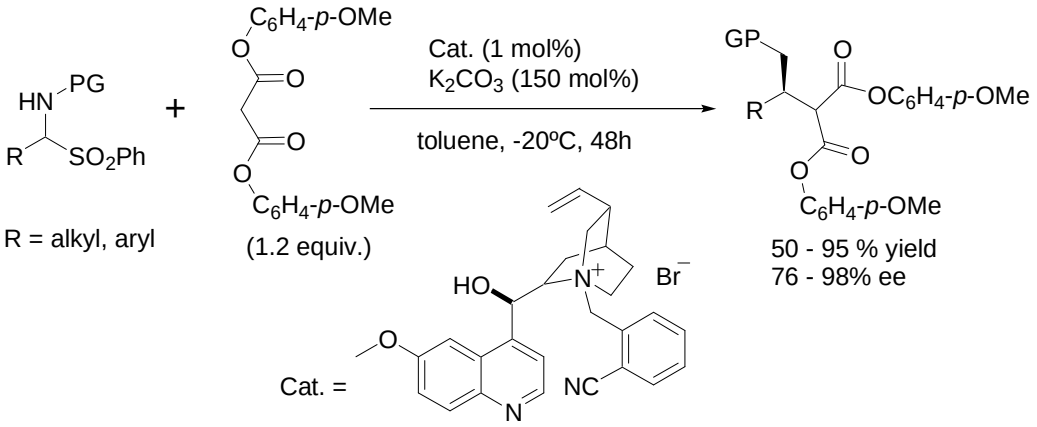
83

87

88
>99% conversion
35% ee

Scheme 84: *Mannich reaction of malononitrile **87** to α-amido-sulfone **83**.*

In the mean time, Ricci and coworkers have demonstrated the enantioselective reaction between in situ generated Cbz-protected azomethines and malonates in the presence of 150 mol% of potassium carbonate (50% v/v) and 1 mol% of quinine-derived quaternary ammonium bromides as phase transfer organocatalysts (Scheme 85).



Scheme 85: *Mannich reaction between α-amido sulfones and malonate promoted by organo-phase transfer catalysts.*

Under these conditions and with 1 mol% catalyst the reported selectivities were moderate to good. However this method presents some limitations: (i) Selected active methyl compound which is not commercially available is essencial to obtain high selectivity; (ii) Base loading is very high.

The published results by other groups as mentioned above turned our attention to look for other new catalytic systems which could provide better selectivity and broader substrate scope.

Thus, the quest for the best catalysts is still remained.

6. Conclusions

The field of asymmetric catalysis is a lively, fascinating and highly competitive research field in organic chemistry. The continuous need for novel asymmetric reactions as well as the demands for cheaper and more environmentally friendly catalytic processes is a challenge for all chemists in this filed. The work presented in this thesis has focused on the development of novel asymmetric reactions as well as contributing to the field of asymmetric catalysis by the development and successful application of novel catalysis.

A new asymmetric aza-Michael methology has been implemented. Highly enantioselective conjugate addition of carbamates has been achieved by using α'–hydroxy enones as the Michael acceptors and Cu(II)–bis(oxazoline) catalysis. The bidentate ketol moiety plays a key role, likely through efficient 1,4-metal binding chelation with the catalytic metal since other widely appreciated Michael acceptors such as *N*-enoyl oxazolidinones, alkylidene malonates do not react at all and/or give poor selectivity. Importantly, while the method gives high selectivity (ee up to 99%) with β-alkyl substituted enones, the counterpart β-aryl substituted substrates resulted inactive even under forcing conditions. The method resulted quite general with repect to the nature of the carbamates. Further elaboration of the resulting adducts through oxidation cleavage of the ketol unit opens a new entry into enantioenriched β-amino carboxylic acids and aldehydes.

A new practical and asymmetric aza-Henry methodology has been implemented based on the use of combined Lewis acid/Brønsted base/Chiral ligand as the catalytic trigger of the reaction. The best catalytic system is comprised of $Zn(OTf)_2$ / DIPEA / NME (in a 0.3:0.3:0.45 ratio) and yields in a 59-96% range and ee´s in a 66 – 99% range are observed for the reaction of nitromethane with an array of *N*-Boc aryl imines. The method uses readily available commercial materials as the catalyst components and tolerates well a wide range of electronically and structurally distinct aryl imines.

These results, along side previously described results in Henry reaction (A. Laso´s Doctoral Thesis, Donostia 2006), indicates the Lewis acid/Brønsted

base/Chiral ligand system bears considerable potential as ambifunctional catalysis in a broader context.

Finally, a preliminary study has been carried out of the Mannich reaction between malonates and imines (either preformed or in situ formed from α-amido sulfone precursors) under PTC catalysis. Using 10-12 mol% chiral ammonium salts derived from cinchona and $CsOH.H_2O$ as stoichiometric base, selectivities upto 89% ee are attained. New work in this direction is still needed to properly address malonate scope, imine scope and projection.

7. Experimental part

7. 1 General

All reactions were carried out under an atmosphere of nitrogen in flame/oven dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2), acetonitrile were dried by distilling over CaH_2. THF and diethyl ether were dried by distilling over sodium metal. Commercially available HPLC grade ethanol, isopropyl alcohol, and hexane were used without distillation. Diisopropylamine was dried by refluxing over KOH and after distillation, stored with MS–4Å (1.6 mm pellets). Toluene was dried in the presence of sodium metal. Methanol, benzene, dimethyl sulphoxide (DMSO) were used as reagent grade. Nitromethane was destilled at 760 mm Hg over anhydrous $MgSO_4$ before use and stored over 4Å molecular sieves. The 4Å molecular sieves was received from Aldrich and activated by heating to 150 ºC in high vacuum for 3 days before use.

Commercial $Cu(OTf)_2$, $Sc(OTf)_3$, $Mg(OTf)_2$, $Ba(OTf)_2$ and $Yb(OTf)_3$) were used without purification. Zinc triflate ($Zn(OTf)_2$) was heated at 130 ºC for 4 to 5 hours before use. LiCl was dried by heating at 150 ºC for 24 h under vacuum. Chiral ligands 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline, (*S*)-(-)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) were purchased from Aldrich Chemical. (-)-(1*R*,2*S*)-*N*-Methylephedrine was dried over phosphorous pentoxide before use. Aliphatic aldehydes were distilled prior to use. Sodium nitrite ($NaNO_2$), glacial acetic acid were used as reagent grade. Organocatalyst cinchona alkaloids (quinine, quinidine, cinchonine, chinchonidine) and diphenyl-pyrrolidin-2-yl-methanol were used as received from Aldrich. Benzylquininiumchloride, 3-Hydroxy-3-methyl-2-butanone and tertbutyl acetate were used as received. Active methylene compounds: dimethyl malonates, ditertbutyl malonates, dibenzyl malonates, malono nitrile were also used as received from Aldrich.

Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water, ammonium molibdate (21 g), cerium sulphate (1 g) and concentrated sulphuric acid (31

mL), followed by heating. Melting points were measured with a Büchi SMP–20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200, Bruker Avance-DPX-300, and Bruker Avance-500 spectrometers and are reported in ppm from internal tetramethylsilane (TMS) or chloroform. Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on Waters 600E and Hewlett Packard series 1050 chromatographs, equipped with a diode array UV detector, using Daicel Chiralpak IA, AD, AS, and Chiralcel OD, OJ columns.

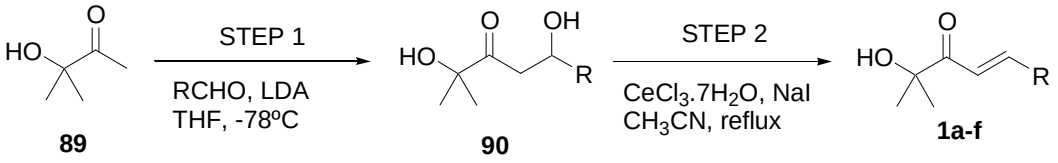
7. 2 Preparation of α'–hydroxy enones

Various α'–hydroxy enone derivatives, varying in their β–substituents, were prepared by two alternative routes using commercially available starting materials. β–Alkyl α'–hydroxy enones **1a**-**h** were prepared by two step methodology involving aldol reaction of commercially available 3-hydroxy-3-methyl-2-butanone (**89**) with corresponding aliphatic aldehyde and subsequent dehydration of aldol adduct by cerium(III)chloride heptahydrate ($CeCl_3$, $7H_2O$). β–Phenyl-α'–hydroxy enones **1h** was prepared in one step procedure from commercially available 3-hydroxy-3-methyl-2-butanone (**89**) and corresponding aromatic benzaldehyde using LiOH/methanol-water system. Synthesis of β–isopropyl α'–hydroxy enone **1e** was found problematic by aldol methodology, hence, the Horner-Eadsworth-Emmons reaction using (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester (**93**) was employed according to reported procedure.[202]

[202] Prepared in two steps (92% overall yield) from commercially available methyl 2-hydroxyisobutyrate, according to: (a) P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem.* **1986**, *51*, 2525-2529. (b) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll, S. E. Lawrence, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3667-3675.

7. 2. 1 Route I: From 3-hydroxy-3-methyl-2-butanone

General Procedure A: From commercial 3-hydroxy-3-methyl-2-butanone



89 **90** **1a-f**

To an oven or flame-dried 3-neck round bottom flask fitted with a low temperature thermometer and a dropping funnel loaded with n-BuLi (2.5 M solution in hexanes, 80 mL, 200 mmol) under nitrogen was added dry THF (200 mL) and diisopropylamine (28 mL, 200 mmol). The solution was cooled to -78°C and n-BuLi added dropwise such that the temperature remained below -70°C. After the addition, the mixture was allowed to stir at -78°C for 1 h before adding 3-hydroxy-3-methyl-2-butanone (8.8 mL, 80 mmol) dropwise (again keeping the temperature below -78°C). After complete addition, the mixture was allowed to stir at -78°C for a further 1 h before dropwise addition over a 45 min period of a solution of the corresponding aldehyde (240 mmol, 3 equiv.) in dry THF (30 mL). The mixture was stirred at -78°C and the reaction monitored by TLC (7:3 Hexane:EtOAc, product). After 2-3 h, the reaction was quenched with sat. NH_4Cl and then extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$ and concentrated. The crude product was flash chromatographed (SiO_2) using a hexane: ethyl acetate gradient from 5:1 to 1:1. Dehydration was carried out by slight modification of known procedure.[203] $CeCl_3 \cdot 7H_2O$ (1.5 mmol per 1 mmol substrate aldol) and NaI (1.5 mmol per 1 mmol substrate aldol) were successively added to a suspension of the aldol intermediate thus obtained in CH_3CN (10 mL/mmol) and the mixture was stirred at reflux for 3 h. After cooling at room temperature, the reaction was diluted with ether (200 mL) and washed with 0.5 M HCl (50 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the EtOAc extracts were combined, successively washed with 20 % $NaHSO_3$ (30 mL), $NaHCO_3$ (30 mL) and brine (30 mL), and dried over $MgSO_4$. Evaporation of solvent under reduced pressure gave a crude product which was flash chromatographed (SiO_2) using 9:1 hexane:ethyl acetate as eluent.

[203] G. Bartoli, M. C. Bellucci, M. Petrini, E. Marcantoni, L. Sambri, E. Torregiani, *Org. Lett.* **2000**, 2, 1791-1793.

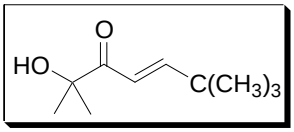
Table 22: Yields of α'–hydroxy enones 1a–f after two steps.

Enone	R	Yield (%)[a]
1a	CH_3-CH_2-	56
1b	$PhCH_2$-CH_2-	42
1c	CH_3-$(CH_2)_5$-	64
1d	$(CH_3)_2$-CH_2-	55
1e	$(CH_3)_2$-CH-	80
1f	Cyclohexyl-	43

[a] Isolated yields after column chromatography

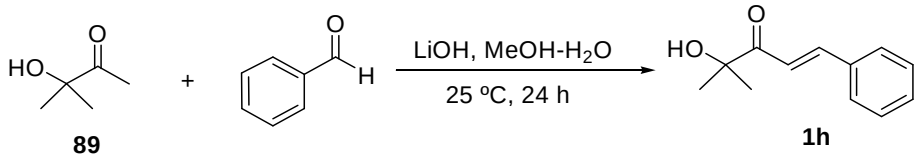
Preparation of compound 2-Hydroxy-2,6,6-trimethyl-hept-4-en-3-one (1g)

(Procedure is not optimized) 3-Hydroxy-3-methyl-2-butanone **89** (5.0 g, 49 mmol) was



dissolved in a mixture of MeOH (120 mL) and H_2O (40 mL). Freshly distilled *tert*-pentanal (7.5 g, 87.5 mmol) was then added followed by $LiOH.H_2O$ (10.28 g, 245 mmol)The reaction was stirred at reflux for 3 h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$ and concentrated. The crude product was flash chromatographed (SiO_2) using a 4:1 hexane:ethyl acetate mixture as eluent to get the title compound **1g**. Yield 2.3 g (18%). IR ($CHCl_3$, cm-1) δ 3456, 2940, 1705, 1602, 1065; 1H NMR (200 MHz, $CDCl_3$) δ 7.07 (d, 1H, J=15.6 Hz), 6.28 (d, 1H, J=15.8 Hz), 4.06 (br s, 1H), 1.3 (s, 6H), 1.0 (s, 9H); 13C NMR (50 MHz, CDCl3) δ 203.0, 160.4, 117.2, 75.4, 34.1, 28.6, 26.4.

Preparation of 4-Hydroxy-4-methyl-1-phenyl-pent-1-en-3-one (1h)



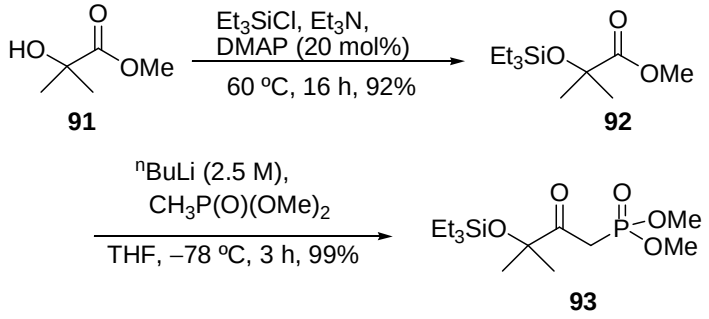
3-Hydroxy-3-methyl-2-butanone **87** (11.1 mL, 100 mmol) was dissolved in methanol-water (3:1 ratio, 400 mL) and benzaldehyde (11 mL, 110 mmol), $LiOH.H_20$

(842 mg, 20 mmol) were added successively. The reaction mixture was stirred at room temperature for around 24h until TLC analysis (7:3 hexane:ethyl acetate) or NMR analysis (if needed) indicated disappearance of starting ketone. (Reaction time can be reduced to 5 hrs by using 9.24 g (220 mmol) of $LiOH.H_2O$ instead of 20 mmol). After completion of reaction, methanol was removed in vacuo. The residue was diluted with water (250 mL) and extracted by dichloromethane (3 x 125 mL). Organic layer was washed with water (3 x 75 mL) and dried over MgSO4. Evaporation of solvent under reduced pressure and subsequent purification of crude product by flash column chromatography using hexane:ethyl acetate (95:5) as eluent yielded the title compound **(1h).** Yield 16 g (84%). IR ($CHCl_3$, cm^{-1}) 3464, 2976, 1690, 1607, 1076; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, *J*= 15.0 Hz), 7.60–7.41 (m, 5H), 7.10 (d, 1H, *J*= 15.3 Hz), 4.06 (bs, 1H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 145.4, 134.3, 130.9, 128.9, 128.6, 118.5, 75.6, 26.4.

7. 2. 2 Route II: For β-Alkyl-α'–hydroxy enones

Step 1:

Preparation of (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester (According to: (a) P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem.* **1986**, *51*, 2525-2529. (b) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll, S. E. Lawrence, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3667-3675).

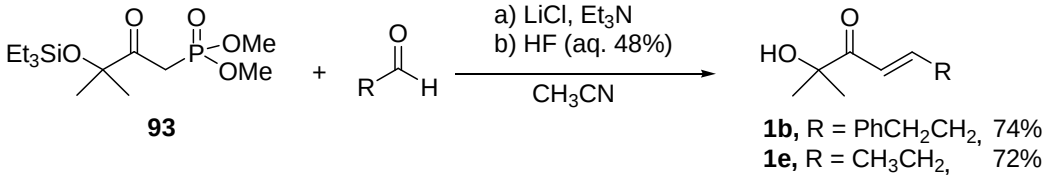


Methyl 2-hydroxyisobutyrate **91** (6.9 mL, 60 mmol) was added under a nitrogen atmosphere to a solution of *N,N*–dimethylamino pyridine (DMAP) (1.22 g, 10 mmol), triethylamine (6.8 mL, 50 mmol) and triethylchlorosilane (8.5 mL, 50 mmol) in 50 mL dichloromethane. The reaction mass was stirred at 60ºC for 16h. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1

x 50 mL). Evaporation of solvent under reduced pressure yielded compound **92**. Yield: 12.6 g (92%). No further purification is needed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 1.45 (s, 6H), 0.95 (q, 6H, *J* = 4.0 Hz), 0.59 (m, 9H).

Commercially available dimethyl methyl phosphonate (13.8 mL, 130 mmol) in dry THF (40 mL) was added dropwise to a cold solution of n-BuLi (1.6 M in hexanes, 79 mL, 130 mmol) in dry THF (80 mL) at –78°C under nitrogen atmosphere. After stirring the resulting solution for 30 min, a solution of the crude triethylsilyl ether **92** (12 g, 51 mmol) in dry THF (100 mL) was added dropwise at –78 °C. The mixture was stirred at the same temperature (–78 ºC) for 3 h and then quenched at this temperature with sat. NH_4Cl (200 mL). Reaction mass was extracted with diethyl ether (3 x 250 mL), dried over $MgSO_4$. Evaporation of solvent under reduced pressure yielded the title compound **93**. Yield: 17 g (99%). It was used for the next step without purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.77 (s, 3H), 3.39 (d, 2H, *J*= 11.0 Hz), 1.35 (s, 6H), 0.96 (t, 9H, *J*= 8.0 Hz), 0.63 (q, 6H, *J*= 8.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.2, 80.1, 52.87, 34.3, 33.2, 26.9, 7.0, 6.5).

Step 2: Preparation of enones **1e** by Horner-Eadsworth-Emmons reaction[204]

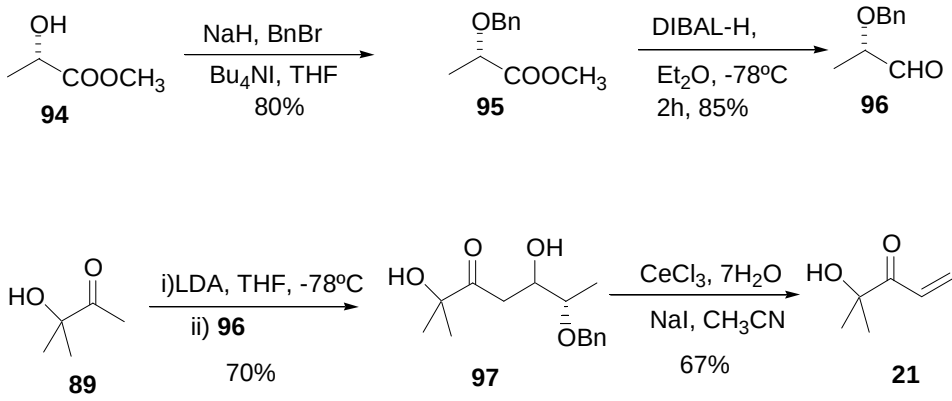


Dried LiCl (1.05 g, 23.75 mmol) and triethylamine (3.3 mL, 22.85 mmol) were added successively to a solution of (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester **93** (7.0 g, 21.6 mmol) in dry acetonitrile (50 mL). The resulting milky suspension was stirred for 15 min at room temperature and the corresponding aldehyde (21.5 mmol) was added dropwise. The mixture was stirred for 48 h, diluted with water (150 mL) and extracted with diethyl ether (3 x 75 mL). Evaporation of the solvent gave an oil which was dissolved in acetonitrile (120 mL) and HF acid (48% aqueous, 1.2 mL) was added dropwise. The mixture was stirred at

[204] H-E-E reaction developed by M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

25 ºC for 3 h, diluted with dichloromethane (250 mL), washed with brine (3 x 75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column cromatography (hexane:ethyl acetate, 90:10) of the crude residue gave corresponding pure title α'–hydroxy enones. **1b** (R = $PhCH_2CH_2$) (74%), **1e** (R = CH_3CH_2) (72%).

7. 2. 3 Preparation of chiral enone 6-Benzyloxy-2-hydroxy-2-methyl-hept-4-en-3-one (21)



Benzylation of (*S*)-methyllactate

To a solution of NaH (washed with toluene(2 x 10mL) (80% dispersion in mineral oil, 2.55g, 85 mmol) in THF (50 mL) was added *S*-methyl lactate **94** (5mL, 52 mmol), benzyl bromide(6 ml, 50mmol) and tetrabutylammonium bromide (18.5g, 50 mmol) at 0ºC under N_2 atm. Then reaction mixture was stirred for 18h at ambient temperature. Reaction was quenched with saturated NH_4Cl (30 mL) at 0ºC and extracted with hexane (3 x 100mL). Collected organic phase was dried over $MgSO_4$, evaporated under reduced pressure to get oil methyl O-benzyl lactate **95** which was purified by flash column chromatography using eluent ethylacetate/hexane (2:8). Yield 80%.

Reduction of methyl ester

To a solution of methyl ester **95** (8.75 g, 45 mmol) in diethyl ether (45 mL) was added dropwise diisobutylaluminiumhydride (DIBAL-H) (1M in hexane, 67.5 mL, 67.5 mmol) during 1.5h at -78ºC under N_2 atm. After 2h at same temperature, water (7 mL) was added dropwise and allowed the reaction to get room temperature.

The reaction was filtrated off and washed with diethyl ether. Collected organic phase was dried over $MgSO_4$, evaporated under reduced pressure to get crude aldehyde **96** which was purified by flash column chromatography. Yield 6.2 g, 85%.

Aldol condensation

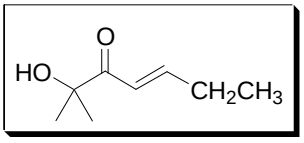
The aldol product **97** was obtained using the general procedure A (Route 1, step 1) from aldehyde **96** (30 mmol). Yield 70% after column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (br. s, 5H), 7.01 (dd, 1H, J=9.1, 8.9Hz), 6.63 (d, 1H, 15Hz), 4.77 (dd,1H, *J*=8.5, 7.5Hz), 4.6 (d, 1H, *J*=8.0Hz), 4.3 (br. 1H), 1.36 (s, 6H), 1.25 (dd, 3H, *J*=7.5, 8.2Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 205.3, 144.4, 142.1, 128.6, 128.5, 126.3, 123.2, 82.8, 76.8, 72.5, 27.2, 26.3.

Enone 21:

The enone **21** was prepared using the general dehydration procedure A (Route 1, step 2) from aldol adduct **97** (20 mmol). Yield 67% after column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.77 (dd,1H, *J*=8.5, 7.5Hz), 4.44 (d, 1H, *J*=8.0Hz), 4.1(br. 1H), 3.8 (d, 1H, *J* = 12Hz), 3.0 (br. 2H), 2.8 (br. 1H), 1.36 (s, 6H), 1.25 (dd, 3H, *J*=7.5, 8.2Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 202.3, 144.4, 128.6, 128.5, 126.3, 82.8, 76.8, 75.3, 72.5, 34.5, 24.2, 22.3.

2-Hydroxy-2-methyl-hept-4-en-3-one (1a)

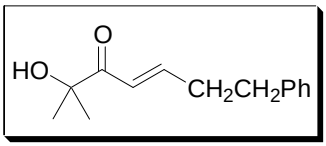
The general procedure (Route I, method A) was followed using n-propanaldehyde (17.5 mL, 240 mmol). Yield 6.6g (56%). IR ($CHCl_3$, cm^{-1}): 3390, 2950, 1635, 1169, 974; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (m, 1H), 6.38 (d, 1H, *J* =15Hz), 4.0 (s, 1H), 2.27 (m, 2H), 1.36 (s, 6H), 1.08 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 152.3, 121.4, 75.2, 26.4, 25.9, 12.2



.

2-Hydroxy-2-methyl-7-phenyl-hept-4-en-3-one (1b)

The general procedure (Route I, Method A) was followed using hydrocinnamaldehyde (31.6 mL, 240 mmol). Yield 7.7g (42%). IR ($CHCl_3$, cm^{-1}): 3446, 2973, 1677, 1630; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.21 (m, 6H), 6.41 (d,1H, *J* =15.5Hz), 3.98 (s, 1H),

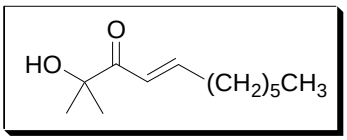


2.8 (t, 2H, *J* = 8Hz), 2.59 (m, 2H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 149.4, 140.6, 128.6, 128.5, 126.3, 123.1, 75.3, 34.5, 34.3, 26.3.

Using General Procedure (Route II) from hydrocinnamaldehyde (0.221g, 1.65 mmol), 0.270 g (74%) of the title compound was obtained.

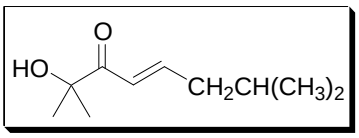
2-Hydroxy-2-methyl-undec-4-en-3-one (1c)

The general procedure (Route I, method A) was followed using n-heptanal (33.5 mL, 240 mmol). Yield 10.6g (64%). IR ($CHCl_3$, cm^{-1}): 3465, 2959, 1677, 1630, 1475; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.0 (m,1H), 6.35 (d,1H, *J* = 16.2Hz), 4.04 (br s, 1H), 2.13 (q, 2H, *J* =7.2 Hz), 1.36-1.32 (m, 2H), 1.25 (s, 6H), 1.17 (br s, 6H), 0.76 (t, 3H, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.3, 150.8, 122.3, 75.2, 32.7, 31.5, 28.8, 27.9, 26.3, 22.5, 14.0.



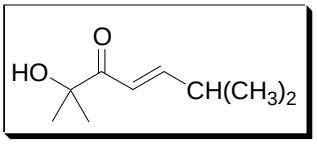
2-Hydroxy-2, 7-dimethyl-oct-4-en-3-one (1d)

The general procedure (Route I, method A) was followed using isopentanaldehyde (25.7 mL, 240 mmol). Yield 7.78g (55%). IR ($CHCl_3$, cm^{-1}): 3465, 2940, 1696, 1621, 1456; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.32 (d,1H, *J*=15.2 Hz), 3.98 (br s, 1H), 1.98 (t, 2H, *J*= 8.5 Hz), 1.61 (m, 1H), 1.20 (s, 6H), 0.75 (d, 6H, *J*= 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 149.93, 123.5, 75.1, 41.9, 27.8, 26.2, 22.3.



2-Hydroxy-2,6-dimethyl-hept-4-en-3-one (1e)

The general procedure (Route I, method B) was followed using isobutyraldehyde (1.65 mL, 18.2 mmol). Yield 2.3 g (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, 1H, *J* = 15.3 Hz, *J'*= 8.5 Hz), 6.35 (d,1H, *J*= 15.4 Hz), 4.0 (s, 1H), 2.5 (m, 1H), 1.4 (s, 6H),

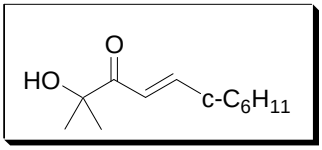


1.1 (d, 6H, *J*= 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.70, 157.07, 119.27, 75.18, 31.44, 26.36, 21.20.

Using General Procedure (Route II) from isobutadehyde. 72% title compound was obtained.

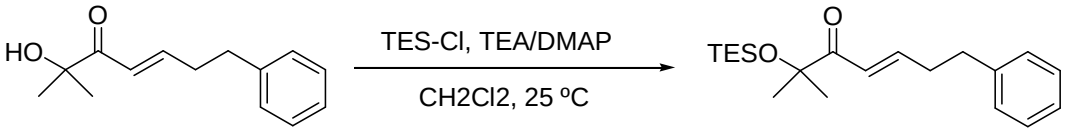
1-Cyclohexyl-4-hydroxy-4-methyl-pent-1-en-3-one (1f)

The general procedure (Route I, Method A) was followed using



cyclohexylcarbaldehyde (29 mL, 240 mmol). Yield 7.0g (43%). IR ($CHCl_3$, cm^{-1}): 3456, 2940, 2846, 1696, 1621, 1475; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 (dd,1H, *J*=15.4 Hz, *J'*= 6.8 Hz), 6.27 (d,1H, *J*= 15.4 Hz), 4.04 (s, 1H), 2.0 (m, 1H), 1.60 (m, 4H), 1.17 (s, 6H), 1.1 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.6, 155.2, 119.9, 75.2, 40.8, 31.6, 26.2, 25.8, 25.6.

6. 2. 4 Preparation of TES–protected enone (31)



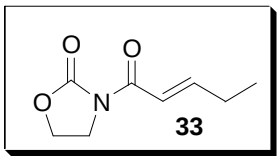
1b **31**

Under N_2 atmosphere, α'–hydroxy enone **1b** (218 mg, 1 mmol) was dissolved in 10 mL dichloromethane. To this solution *N*,*N*–dimethylamino pyridine (DMAP) (24 mg, 0.2 mmol), triethylamine (208 μL, 1.5 mmol) were added. Reaction mass was cooled to 0 ºC and triethylsilylchloride (252 μL, 1.5 mmol) was added dropwise over a period of 5 min. The reaction mass was warmed to room temperature and stirred until TLC analysis indicated the reaction completion (about 12 h). Reaction was quenched with sat. NH_4Cl (25 mL), and extracted with dichloromethane (3 x 30 mL). Organic layer was washed with brine (1 x 30 mL) and water (1 x 30 mL). Evaporation of solvent under reduced pressure and subsequent purification by flash column chromatography using hexane:EtOAc (95:5) as eluents yielded the pure

product **31** as colourless oil. Yield: 310 g (95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 7.00 (q, 1H, *J* = 7.0 Hz), 6.80 (d, 1H, *J* =16.0 Hz), 2.80 (t, 2H, *J* = 7.5 Hz), 2.56 (dd, 2H, *J*= 7.5 Hz), 1.34 (s, 6H), 0.96 (t, 9H, *J* = 8.0 Hz), 0.60 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.7, 146.9, 141.0, 128.4, 128.3, 126.1, 124.5, 78.8, 34.48, 34.40, 27.2, 7.0, 6.6.

Preparation 3-Pent-2-enoyl-oxazolidin-2-one[205] (33)

To a solution of oxazolidin-2-one (0.74 g, 8.4 mmol) in dry THF (8 mL) was added



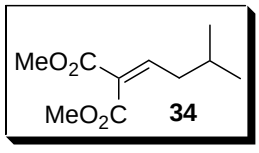
33

sodium hydride (60%, 0.502 g, 12.6 mmol) with THF (15 mL) as emulsion at 0ºC temperature and stirred for 30 min.Then trans-pentenoylchloride (1.19 g) in THF (10 mL) was added and stirred for another two hours at same temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure to get the crude product which was purified by flash column chromatography using eluent ethylacetate and hexane (1:5). The title compound **33** was obtained as an oil. Yield (1.1 g, 77%).

2-(3-Methyl-butylidene)-malonic acid dimethyl ester (34)

The title compound was prepared accordingly Cardillo et al.[206]

A solution of isovaleraldehyde (2.58 g, 3.2 mL, 30 mmol) in dry DMSO (10 mL) with



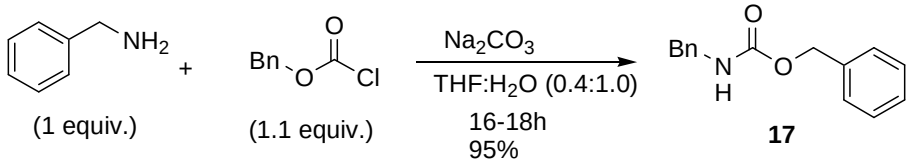
34

10 mol% proline (0.35 g) was stirred for 5 min. Then dimethylmalonate (7.92g, 6.86 mL, 60 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was diluted with ethylacetate (30 mL) and washed twice with water (30 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under vaccum to afford 2-(3-methylbutylidene) malonic acid dimethyl ester **34** which was purified by flash column chromatography using eluent ethylacetate/hexane (1:5). (Yield 5.52gm, 92%).

[205] C. Chaozhong, V. A. Soloshonok, V. J. Hruby, *J. Org. Chem.* **2001**, *66*, 1339-1350.
[206] G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti, A. Tolomelli, *Syn. Comm.* **2003**, *33*, 1587-1594.

7. 3 Preparation of carbamates

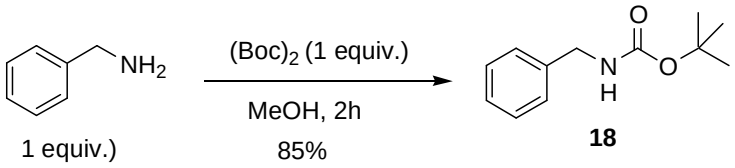
Benzyl-carbamic acid benzyl ester (17)



(1 equiv.) (1.1 equiv.) **17**

The title compound was prepared according to Smith et al.[207]

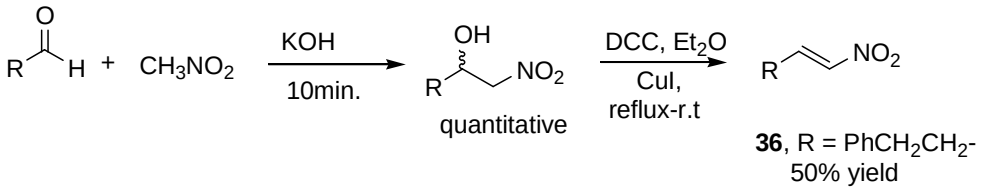
Benzyl-carbamic acid tert-butyl ester (18)



1 equiv.) **18**

The title compound was prepared according to Chen et al.[208]

Preparation of (4-Nitro-but-3-enyl)-benzene (36)



quantitative **36**, R = $PhCH_2CH_2$-
50% yield

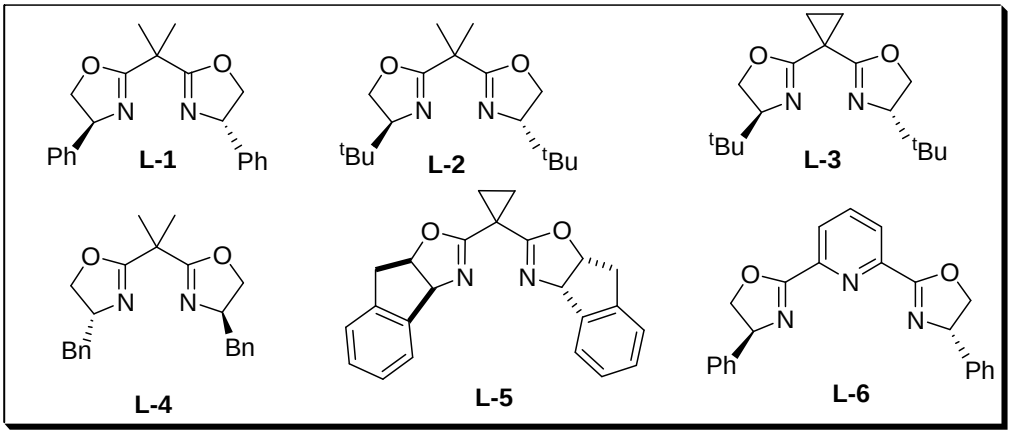
The title compound was prepared according to Mioskowski et al.[209]

[207] S. E. Gibson, M. H. Smith, *Org. Biomol. Chem*, **2003**, *1*, 676-683
[208] C. T. Chen, J. H. kou, V. D. Pawar, Y. S. Munot, S. S. Weng, C. H. Ku, C. Y. Liu, *J. Org. Chem.* **2005**, *70*, 1188-1197
[209] D. Lucet, S. Sabelle, O. Kostelitz, T.-L, Gall, C. Mioskowski, *Eur. J. Org. Chem.* **1999**, 2583-2591.

7.4 aza-Michael Reaction

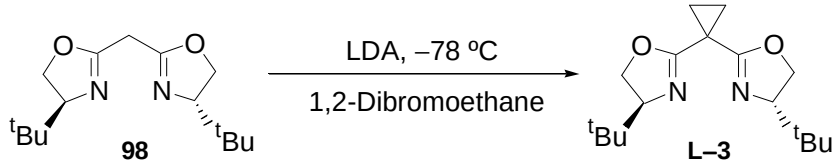
7. 4. 1 Preparation of chiral ligands and catalysts

Chiral ligands (*S*)-(-)-2,2'-isopropylidene bis(4-phenyl-2-oxazoline) (**L–1**), 2,2'-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline (**L–2**), (*S*)-(-)-2,2'-isopropylidene bis(4-benzyl-2-oxazoline)(**L–4**), 2,6-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)pyridine (**L–6**) were purchased from Aldrich chemical. Chiral ligand 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane (**L–3**) was prepared according to procedure reported by Denmark (see below). Chiral ligand {3a*S*-[2(3'a*R**, 8'aα), 3aα, 8aα]}-2,2´-(cyclopropylidene)-bis{3a, 8a-dihydro-8H-indeno[1,2-*d*]-oxazole} (**L–5**) was synthesized according to Sibi (see below).



Preparation of chiral ligands

Preparation of chiral ligand (L-3)[210]

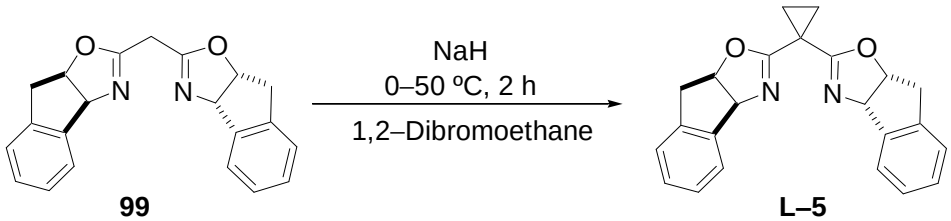


Chiral ligand **L–3**, 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane, was prepared according to the procedure repoted by Denmark and co-

[210] Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875—5878.

workers as follows: Under N_2 atmosphere, to a solution of commercially available 2,2'-methylene bis[(4*S*)-4-tert-butyl-2-oxazoline)] (**L-2**) **98** (1.0 g, 3.75 mmol) in dry THF (100 mL), was added *N*,*N*-tetramethylethylene diamine (TMDA) (1.13 mL, 7.5 mmol) and diisopropyl amine (DIPA) (533 µL, 3.75 mmol). Reaction mass was cooled to –75 ºC and n-BuLi (5.0 mL, 1.5 M soln in n-hexane, 7.5 mmol) was added keeping temperature at –75 ºC. Reaction mass was warmed to –20 ºC and stirred for 30 min. and again cooled to –75 ºC. 1,2–Dibromoethane (324 µL, 3.75 mmol) was added slowly to the reaction in about 10 min. Then reaction mass was allowed to warm to room temperature and stirred at the same temperature for 16 h. The yellow reaction mass was quenched with sat. NH_4Cl (40 mL) and extracted with diethyl ether (3 x 100 mL). Combined organic layers were washed with water (3 x 75 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using ethyl acetate:methanol (98:2) eluents and further crystallisation using hexane/ethyl acetate yielded white solid with yellow tinch as pure product **L–3** in 30% yield (330 mg).

Preparation of chiral ligand (L-5)[211]



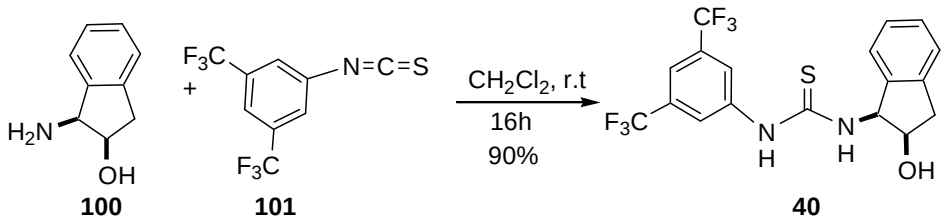
99 **L–5**

The title compound was prepared according to process repoted by Sibi and co-workers as follows: Under N_2, to a solution of commercially available dihydro bisoxazoline **99** (400 mg, 1.2 mmol) in dry THF (6 mL), at 0 ºC, was added sodium hydride (145 mg, 3.6 mmol, 60% in mineral oil) in 3 lots at 10 min interval between each. Reaction mass was stirred for 30 min at 0 ºC. 1,2–Dibromoethane (125 µL, 1.4 mmol) was added slowly to the reaction. Then reaction mass was then warmed to 50 ºC till reaction completion indicated by TLC analysis (around 2 h). The reaction was quenched with sat. NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 100 mL). Combined organic layers were washed with water (3 x 75 mL), dried over $MgSO_4$.

[211] M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615—6616.

Evaporation of solvent and subsequent purification by flash column chromatography using ethyl acetate: methanol (98:2) eluents and further crystallisation using hexane:ethyl acetate (90:10) yielded white solids as pure product **L–5** in 80% yield (340mg).

1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2-hydroxy-indan-1-yl)-thiourea (40)

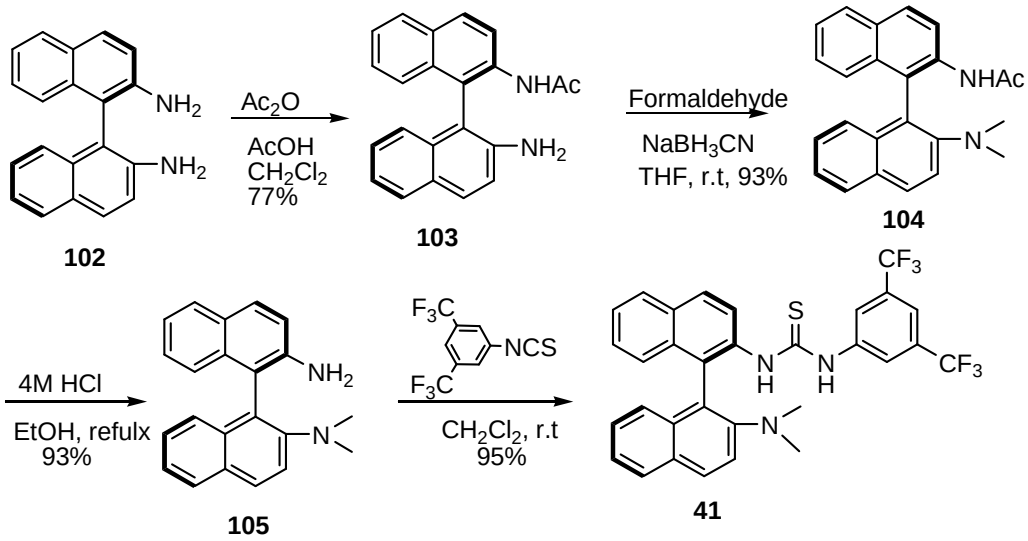


100 **101** **40**

The title compound was prepared according to Ricci et al.[212]**:**

To a stirred solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (5 mmol) in CH_2Cl_2 (10 mL), (1*R*, 2*S*)-cis-1-amino-2-indanol (5 mmol) was added in one portion. After stirring the resulting solution at room temperature for 16h, the solvent was evaporated under reduced pressure and white solid purified by crystallisation (hexane/acetone), afforded **40** as a white solid in 90% yield.

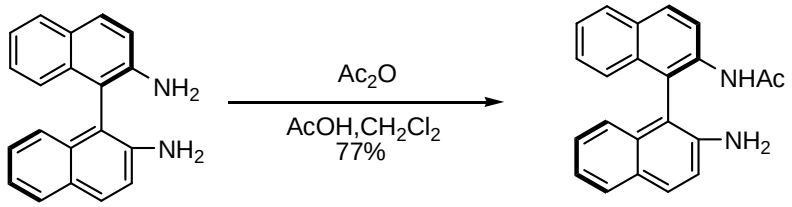
Preparation of 1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2'-dimethylamino-[1,1']binaphthalenyl-2-yl)-thiourea (41)



102 **103** **104** **105** **41**

[212] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576-6579.

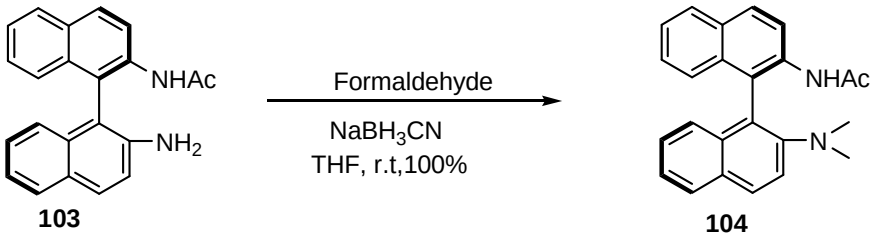
Preparation of compound (*R*)-*N*-(1-(2-Aminonaphthalen-1-yl)naphthalen-2-yl)acetamide (103)[213]



102 **103**

To a solution of (*R*)-(+)-1,1´-Binaphthyl-2,2´-diamine **102** (284 mg, 1.0 mmol) and acetic acid (0.6 mL, 10 mmol) in 10 mL of dried CH_2Cl_2 was added acetic anhydride (104 μL, 1.0 mmol) at 0ºC under nitrogen atmosphere. The resulting solution was stirred for overnight at room temperature, then 2M NaOH aqueous solution was added to adjust the solution to pH ~7. The reaction mixture was extracted by CH_2Cl_2 (3 x 20 mL) and combined rganic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (ethylacetate/hexane; 2:1) to afford the colorless oil in 80% yield.

Preparation of compound (*R*)-*N*-(1-(2-Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide (104)[214]



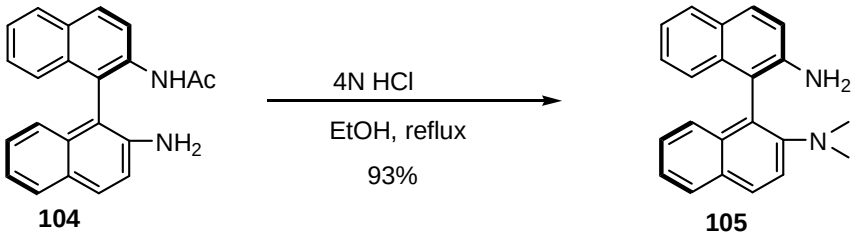
103 **104**

To a solution of (*R*)-*N*-(1-(2-Aminonaphthalen-1-yl)naphthalen-2-yl)acetamide (**103**) (0.25 g, 0.77 mmol) and aqueous formaldehyde (37%, 0.75 mL, 9.0 mL) in 10 mL of THF was stirred for 15 min. Then NaBH3CN (200 mg, 5.3 mmol) was added and stirred for further 15 min, following by addition of AcOH (1.0 mmol).

[213] S. Pieraccini, G. Gottarelli, R. Labruto, S. Masiero, O. Pandoli, G. D. Spada, *Chem. Eur. J.* **2004**, *10*, 5632.
[214] C. –J. Wang, M. Shi, *J. Org. Chem*. **2003**, *68*, 6229.

The resulting solution was stirred for overnight at room temperature, then 2M NaOH aqueous solution was added to adjust the solution to pH ~7. The reaction mixture was extracted by CH_2Cl_2 (3 x 30 mL) and combined rganic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (ethylacetate/hexane; 1:5) to afford a brown powder quantitative 100% yield (272 mg, 0.77 mmol).

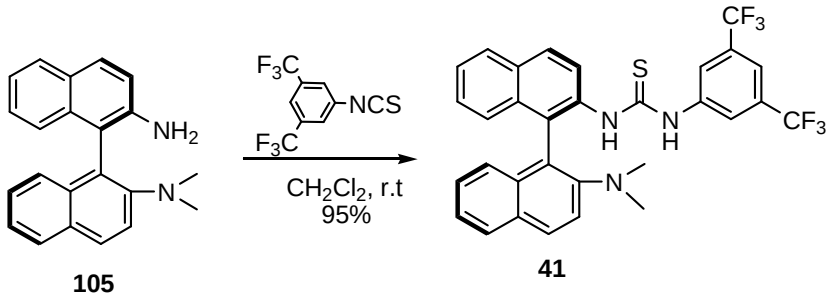
Preparation of compound (*R*)-*N*-(1-(2-Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)-2-amine (105)[214]



104 **105**

To a solution of (*R*)-*N*-(1-(2-Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide **104** (0.18 g, 0.51 mmol)in 15 mL of EtOH was added 4m HCl (6 mL). The resulting solution was stirred under reflux for 18h, then 1M MaOH aqueous solution was added to adjust the solution to pH ~ 7. The reaction mixture was extracted by CH_2Cl_2 (3 x 30 mL) and combined rganic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (ethylacetate/hexane; 1:10) to afford a colorless oilin 93% yield (148 mg, 0.47 mmol).

Preparation of 1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2'-dimethylamino-[1,1']binaphthalenyl-2-yl)-thiourea (41)



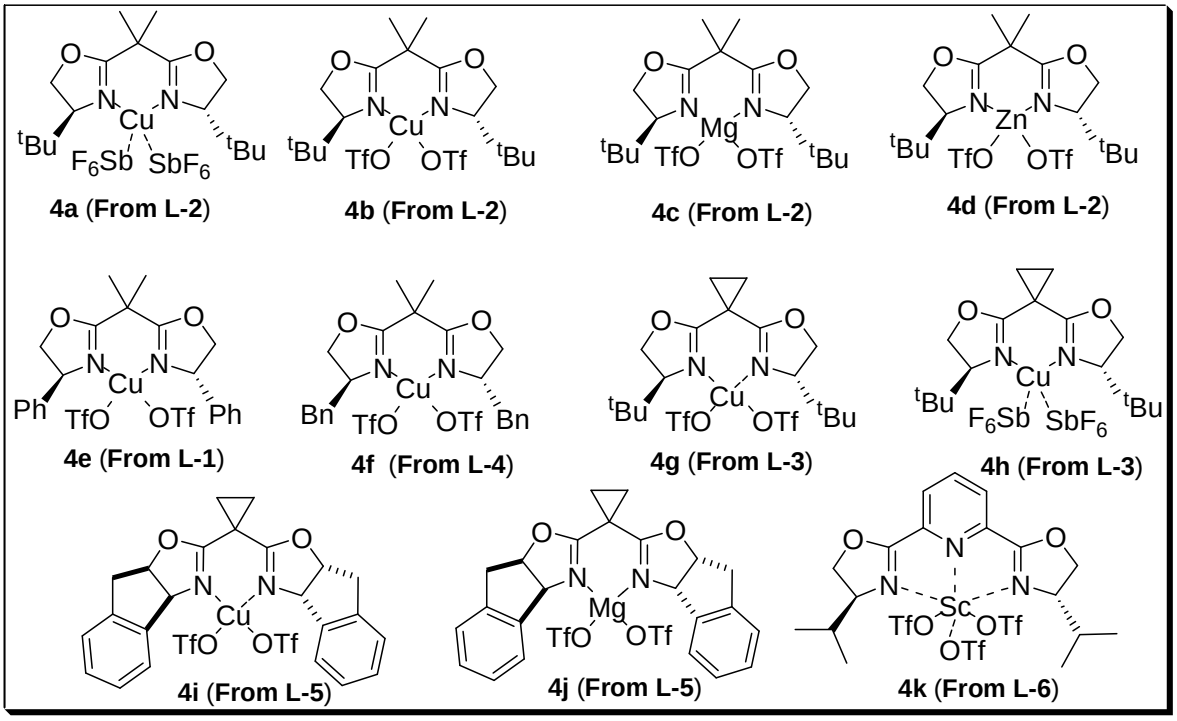
105 **41**

The title compound was prepared according to Wang et al.[215]

To a solution of (*R*)-*N*-(1-(2-Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)-2-amine **105** (36 mg, 0.12 mmol) in 2 mL of dried CH_2Cl_2 was added 3,5-bis(trifluromethyl)phenylisothiocyanate(22.0 mg, 0.132 mmol) at 0ºC under nitrogen atm. The resulting solution was stirred for overnight at room temperature. The reaction mixture was concentrated in Vacuo and then the crude product was purified ny flash column chromatography to afford the slight yellow solid in 95% yield (68 mg). $[\alpha]_D^{25}$ = 8.5 (c = 0.5, $CHCl_3$).

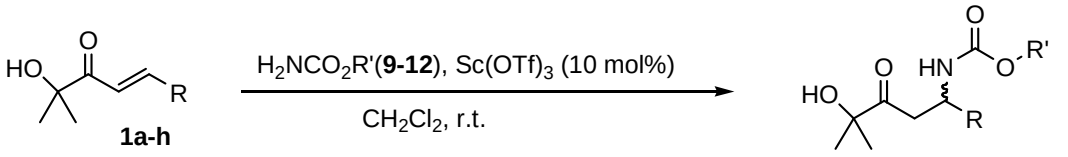
[215] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett*. **2005**, *7*, 4713-4716.

General procedure for preparation of catalyst complexes 4a-k



At room temperature, under an N_2 atmosphere, corresponding bis(oxazoline) ligand **L–1** to **L–6** (0.075 mmol) and corresponding metal salt (0.05 mmol) were admixed in stated solvent and stirred for 3 h. Then this solution was subjected to the specified condition for aza-Michael addition.

7. 4. 2 Preparation of racemic adducts: General procedure for the reaction of α´-hydroxy enones with carbamates 9-12 catalysed by $Sc(OTf)_3$[216]



9, R^1 = Bn; **11**, R^1= Me
10, R^1 = tBu; **12**, R^1= Et

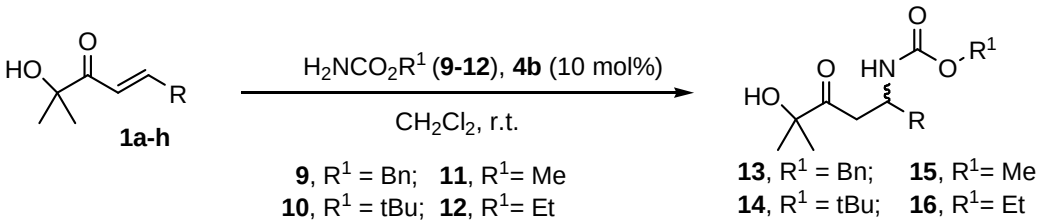
13, R^1 = Bn; **15**, R^1= Me
14, R^1 = tBu; **16**, R^1= Et

The corresponding enone **1** (0.5 mmol) was weighted into an oven or flame-dried flask and placed under N_2. The corresponding carbamate **9-12** (1 mmol) was then added by rinsing with dry CH_2Cl_2 (0.5 mL) from a weighting boat directly into the

[216] S. Kobayashi, K. Kakumoto, M. Sugiura, *Org. Lett*. **2002**, *4*, 1319-1322.

reaction flask. $Sc(OTf)_3$ (0.024 g, 0.05 mmol) was then added by rinsing with dry CH_2Cl_2 (1.0 mL) from a weighting boat directly into the reaction flask. The resulting solution was stirred at room temperature until disappearance of starting material as monitored by TLC. The mixture was then diluted with 0.1 M HCl (10 ml) and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 layers were combined, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography using gradient mixtures of ethyl acetate/dichloromethane as eluent.

7. 4. 3 Preparation of asymmetric adducts: General procedure for asymmetric 1,4-conjugate additions of carbamates *9-12* to α´-hydroxy enones 1a-h.

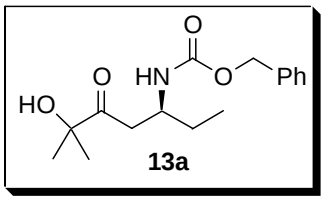


2,2´-Isopropylidene bis[(4*S*)-4-tert-butyl-2-oxazoline] (tBu-BOX) (or the corresponding chiral ligand) (0.22 mmol) was weighted in a flame-dried flask and placed under N_2. $Cu(OTf)_2$ (72.3 mg, 0.2 mmol) was then added by rinsing with dry CH_2Cl_2 (3.0mL) from a weighting boat directly into the reaction flask. After stirred at room temperature for 3 h, a solution of the corresponding α´-hydroxy enone **1a-h** (2 mmol) in dry CH_2Cl_2 (1.5 mL) was cannulated into the solution followed by a 1.5 mL rinse, and the resulting mixture was stirred for a further 30 min at room temperature. This solution was cannulated into a solution of the corresponding carbamate **9-12** (4 mmol) in dry CH_2Cl_2 (2.0 mL) followed by a 1.0 mL rinse, and the mixture was stirred at room temperature under N_2 for the stated time. The resulting reaction mixture was diluted with 0.1 M HCl (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The CH_2Cl_2 layers were combined, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by column chromatography on SiO_2 eluting first with CH_2Cl_2 until total elution of the excess carbamate and then successively with 2%, 5% and 10% EtOAc in CH_2Cl_2 to yield pure compounds **13-16**. The ee was determined by chiral HPLC analyses as stated below.

Characterisation data

***N*-(1-Ethyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid *O*-benzyl ester (13a)**

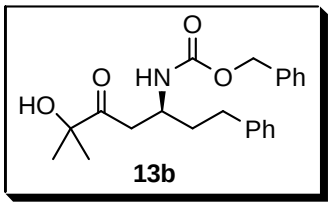
The title compound was prepared according to the general procedure starting from enone **1a** (0.284 g, 2 mmol). Yield 488 mg (83 %). Clear oil; $[\alpha]_D^{25}$ = -20.6 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3419, 3334, 1687, 1532; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.14 (d, 1H, *J* = 6.5Hz), 5.07 (q, 2H, *J*=13Hz), 3.97-3.90 (m, 1H), 3.66 (br.s, 1H), 2.85 (dd, 1H, *J* = 17.0Hz, *J´*=5.3Hz), 2.77 (dd, 1H, *J* = 17.0Hz, *J´* = 4.3Hz), 1.58 (dq, 2H, *J*=7.5Hz, *J´* = 6.5Hz), 1.33 (s, 3H), 1.32 (s, 3H), 0.93 (t, 3H, *J* = 7.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 156.0, 136.4,128.5, 128.1, 128.0, 76.5, 66.7, 49.8, 40.1, 27.3, 26.3, 26.2, 10.0; Elemental analysis calcd (%) for $C_{16}H_{23}NO_4$ (293.36): C 65.51, H 7.90, N 4.77; found: C 65.35, H 8.19, N 4.70; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 5:95; 0.8 mL/min, 210 nm) Rt_{major} = 17.1 min, Rt_{minor} =24.6 min, 96 % e.e.



13a

***N*-(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid *O*-benzyl ester (13b)**

The title compound was prepared according to the general procedure starting from enone **1b** (0.436 g, 2 mmol).Yield 633 mg (86 %); white waxy solid which crystallizes to form clear rods from CH_2Cl_2/hexane; m.p. 61-63°C; $[\alpha]_D^{25}$ = –15.0 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3408, 3325, 1701, 1536. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, *J* = 7.5Hz), 7.15 (d, 1H, *J* = 7Hz), 5.23 (d, 1H, *J* = 7.5Hz), 5.09 (d, 2H, *J* = 12.7Hz), 4.07-4-01 (m, 1H), 3.58 (br.s, 1H), 2.89 (dd, 1H, *J* = 17.0Hz, *J´*=5.3Hz), 2.80 (dd, 1H, *J* = 17.0Hz, *J´* = 4.5Hz), 2.75-2.69 (m, 1H), 2.65-2.59 (m, 1H), 1.99-1.93 (m, 1H), 1.85-1.78 (m, 1H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 155.9, 141.1, 136.4, 128.5, 128.4, 128.3, 128.2, 128.1, 126.1, 76.5, 66.7, 48.0, 40.4, 35.9, 32.7, 26.3, 26.2; Elemental analysis calcd (%) for $C_{22}H_{27}NO_4$ (369.45): C 71.52, H 7.37, N 3.79; found: C 73.18, H 7.32, N 3.94.

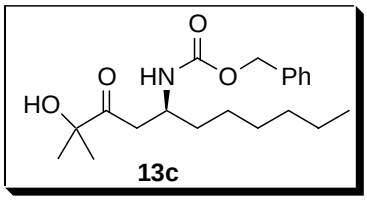


13b

Chiral HPLC (Chiralpak AS column; iPrOH:hexane 5:95; 0.8 mL/min, 210 nm) Rt_{major} = 25.4 min., Rt_{minor} =34.2 min., 96 % e.e.

_N_-[1-(3-Hydroxy-3-methyl-2-oxo-butyl)-heptyl]-carbamic acid _O_-benzyl ester (13c)

The title compound was prepared according to the general procedure starting from

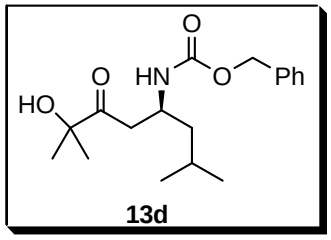


13c

enone **1c** (0.099 g, 0.5 mmol) and benzyl carbamate (0.151 g, 1.0 mmol). Yield 115 mg (66%); white solid. m.p. 46-48ºC (hexane:ethyl acetate); $[\alpha]_D^{25}$ = –18.6 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3477, 3334, 2910, 1718, 1571. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.15 (d, 1H, *J* = 2.9Hz), 5.08 (s, 2H), 4.02-4.00 (m, 1H), 3.67 (br s, 1H), 2.8-2.79 (m, 2H), 1.53-1.52 (m, 2H), 1.34-1.33 (m, 8H), 1.29-1.26 (m, 6H), 0.89-0.86 (t, 3H, *J*=5.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 156.0, 136.6, 128.6, 128.2, 128.1, 76.6, 66.7, 48.4, 40.5, 34.4, 31.7, 29.0, 26.4, 26.3, 22.6, 14.1; Elemental analysis calcd (%) for $C_{20}H_{31}NO_4$ (349.46): C 68.74, H 8.94, N 4.01; found: C 69.84, H 8.36, N 4.14; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.5 mL/min, 210 nm) Rt_{major} = 17.7 min, Rt_{minor} = 27.9 min, 92 % e.e.

_N_-(4-Hydroxy-1-isobutyl-4-methyl-3-oxo-pentyl)-carbamic acid _O_-benzyl ester (13d)

The title compound was prepared according to the general procedure starting from



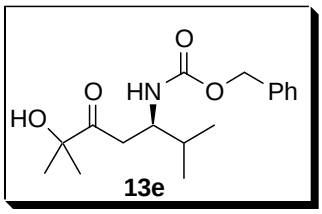
13d

enone **1d** (0.340 g, 2 mmol). Yield 456 mg (71 %). Clear oil; $[\alpha]_D^{25}$ = –27.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3409, 3344, 1696, 1536; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.11 (d, 1H, *J* = 8.0Hz), 5.07 (s, 2H), 4.13-4.06 (m, 1H), 3.66 (br s, 1H), 2.83 (dd, 1H, *J* = 17.3 Hz, *J´* = 5.3 Hz), 2.77 (dd, 1H, *J* = 17.3 Hz, *J´*= 4.7 Hz), 1.67-1.60 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.32-1.25 (m, 1H), 0.91 (t, 6H, *J* = 7.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 155.9, 136.4, 128.5, 128.1, 128.0, 76.4, 66.7, 46.4, 43.4, 40.8, 26.3, 26.1, 25.0, 23.0, 21.9; Elemental analysis calcd (%) for $C_{18}H_{27}NO_4$

(321.41): C 67.26, H 8.47, N 4.36; found: C 67.22, H 7.85, N 4.51; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 210 nm) Rt_{major} = 15.1 min, Rt_{minor} =22.4 min, 96 % e.e.

_N_-(4-Hydroxy-1-isopropyl-4-methyl-3-oxo-pentyl)-carbamic acid _O_-benzyl ester (13e)

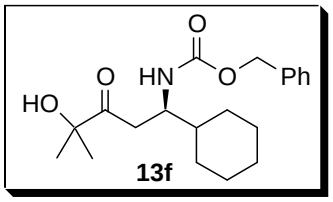
The title compound was prepared according to the general procedure starting from enone **1e** (0.312g, 2 mmol). Yield 323 mg (53 %). Pale yellow oil; $[\alpha]_D^{25}$ = –20.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3437, 3344, 1701, 1541; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.10 (d, 1H, *J* = 6.5Hz), 5.07 (s, 2H), 3.88-3.82 (m, 1H), 3.66 (br s, 1H), 2.80 (d, 2H, *J* = 6Hz), 1.95-1.86 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 0.92 (t, 6H, *J* = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 156.2, 136.4, 128.5, 128.1, 128.0, 76.6, 66.7, 53.7, 38.3, 31.3, 26.4, 26.3, 19.5, 18.5; Elemental analysis calcd (%) for $C_{17}H_{25}NO_4$ (307.38): C 66.43, H 8.20, N 4.56; found: C 66.14, H 8.48, N 4.58; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 210 nm, Rt_{major} = 16.3 min, Rt_{minor} =20.7 min, 98 % ee.



13e

(1-Cyclohexyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid benzyl ester 13f

The title compound was prepared according to the general procedure starting from enone **1f** (0.98 g, 0.5 mmol) and benzyl carbamate (0.302 g, 2 mmol). Yield 100mg (57.6%). White solid; M.p. 88-89ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = –7.4 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}); 3370, 3328, 2935, 1710, 1560; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H), 5.15 (d, 1H, *J* = 9.2 Hz), 5.07 (s, 2H), 3.87 (m, 1H), 3.71 (br s, 1H), 2.83 (d, 2H, *J* = 5.6 Hz), 1.7 (m, 6H), 1.35-1.18 (br s, 6H), 1.18 (m, 3H), 1.0 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 156.2, 136.6, 128.6, 128.2, 128.1, 76.7, 66.8, 53.0, 41.0, 38.0, 30.2, 29.2, 26.5, 26.4, 26.2, 26.1, 26.0; Elemental analysis calcd (%) for $C_{20}H_{29}NO_4$ (347.45): C 69.14, H 8.41, N 4.03; found: C 70.27, H 8.32, N 4.21; Chiral HPLC

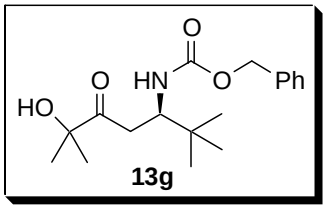


13f

(Chiralcel OD column; iPrOH:hexane 10:90; 0.5 mL/min, 220 nm, Rt_{major} = 34.8 min, Rt_{minor} =42.4 min, 94 % e.e

(1-tert-Butyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid benzyl ester (13g)

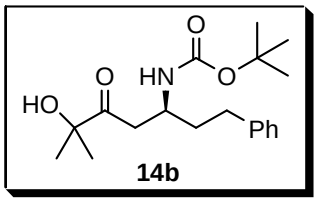
The title compound was prepared according to the general procedure starting from enone **1g** (0.075 g, 0.44 mmol) and benzyl carbamate (0.133 g, 0.88 mmol). Yield 64mg (45%). White solid; m.p.118-119ºC ; $[\alpha]_D^{25}$ = −1.4 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) δ 3267.5, 2967.5, 1726, 1677, 1541; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H), 5.1 (s, 2H), 4.85 (d, 1H, *J* = 8.2 Hz), 4.08 (br s, 1H), 3.7 (s, 1H), 2.89 (dd, 1H, *J* = 3.6 Hz, *J'*= 14.8 Hz), 2.5 (dd, 1H, *J* = 10.6 Hz, *J'*= 15.6 Hz), 1.34 (d, 6H, *J* = 8.6 Hz), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 156.4, 136.3, 128.4, 127.9, 77.4, 66.9, 56.3, 37.3, 34.7, 26.6; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.5 mL/min, 220 nm, Rt_{major} = 17.06 min, Rt_{minor} =21.06 min, 94 % e.e.



13g

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid tert-butyl ester (14b)

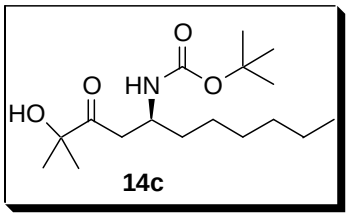
The title compound was prepared according to the general procedure starting from enone **1b** (0.109 g, 0.5 mmol) and tert-butyl carbamate (0.117 g, 1 mmol). Yield 154 mg (92%). White solid, M.p. 93-94ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = −18.4 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3390, 3259, 1710, 1668. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3-7.2 (m, 5H), 4.9 (s, 1H,), 4.0 (br s, 1H), 3.7 (br s, 1H), 2.8 (br s, 2H), 2.7 (m, 1H), 2.6 (m, 1H), 1.9-1.8 (m, 2H), 1.45 (s, 9H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 155.7, 141.2, 128.8, 126.1, 79.6, 47.9, 41.1, 36.4, 32.8, 28.6, 26.4; Elemental analysis calcd (%) for $C_{19}H_{29}NO_4$ (335.41): C 68.03, H 8.71, N 4.18; found: C 68.07, H 8.70, N 4.11; Chiral HPLC (Chiralcel OD column; iPrOH:hexane 10:90; 0.5 mL/min, 220 nm, Rt_{major} = 13.1 min, Rt_{minor} =11.6 min, 90 % e.e.



14b

[1-(3-Hydroxy-3-methyl-2-oxo-butyl)-heptyl]-carbamic acid tert-butyl ester (14c)

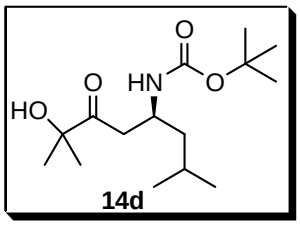
The title compound was prepared according to the general procedure starting from enone **1c** (0.099 g, 0.5 mmol) and tert-butyl carbamate (0.117 g, 1 mmol). Yield 120 mg (76%). White waxy solid; M.p. 49-50ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = - 21.6 (*c* 0.5, CH_2Cl_2). IR (KBr, cm^{-1}) 3477, 3334, 2910, 1718, 1571; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (br s, 1H), 3.87 (m, 2H), 2.78 (br s, 2H), 1.54 (br s, 2H), 1.42 (s, 9H), 1.34 (br s, 8H), 1.27 (br s, 6H), 0.88 (t, 3H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 155.6, 79.4, 48.0, 41.0, 34.7, 31.7, 28.9, 28.3, 26.2, 22.5, 14.0; Elemental analysis calcd (%) for $C_{17}H_{33}NO_4$ (315.45): C 64.73, H 10.54, N 4.44; found: C 65.60, H 9.77, N 4.50; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 3:97; 0.5 mL/min, 220 nm, Rt_{major} = 30.0 min, Rt_{minor} =75 min, 96.5 % e.e.



14c

(4-Hydroxy-1-isobutyl-4-methyl-3-oxo-pentyl)-carbamic acid tert-butyl ester (14d)

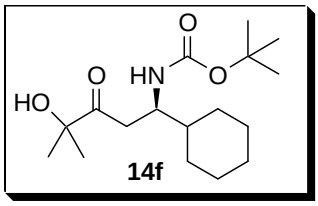
The title compound was prepared according to the general procedure starting from enone **1d** (0.510 g, 3 mmol) and tert-butyl carbamate (0.702 g, 6 mmol). Yield 746 mg (86.6%). White solid; m. p. 63-64ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = -29.0 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3287.5, 2987.5, 1696, 1677, 1541; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.83 (d, 1H, *J*= 8.8 Hz), 4.06 (m, 1H), 3.9 (s, 1H), 2.8 (m, 2H), 1.6 (m, 1H), 1.43 (s, 9H), 1.36 (s, 6H), 0.92 (d, 6H, *J*= 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 155.6, 79.4, 46.2, 43.7, 41.5, 28.4, 26.2, 25.0, 22.95, 22.94; Elemental analysis calcd (%) for $C_{15}H_{29}NO_4$ (287.40): C 62.69, H 10.17, N 4.87; found: C 62.66, H 9.39, N 4.80; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 4:96; 0.5 mL/min, 210 nm, Rt_{major} = 22.22 min, Rt_{minor} =19.08 min, 96 % e.e.



14d

(1-Cyclohexyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid tert-butyl ester (14f)

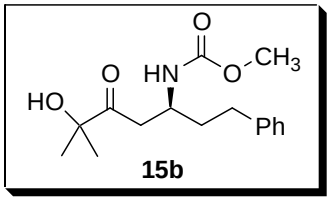
The title compond was prepared according to the general procedure starting from enone **1f** (0.180 g, 0.51 mmol) and tert-butyl carbamate (0.120 g, 1.02 mmol). Yield 135 mg (85%); White solid; M. p. 96-97ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = -16.8 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3387, 3365, 2912, 1725, 1660; ^1H NMR (200 MHz, $CDCl_3$) δ 4.9-4.8 (d, 1H, *J* = 7.6 Hz), 3.9 (br s, 1H), 3.8 (br s, 1H), 2.7 (m, 2H), 1.7 (m, 6H), 1.42 (s, 9H), 1.4 (s, 6H), 1.2 (s, 3H), 0.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 155.8, 79.4, 52.6, 41.2, 38.6, 30.0, 29.6, 29.126.3, 26.0; Elemental analysis calcd (%) for $C_{17}H_{31}NO_4$ (313.43): C 65.14, H 9.97, N 4.47; found: C 66.17, H 9.84, N 4.61; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 5:95; 0.5 mL/min, 210 nm, Rt_{major} = 17.2 min, Rt_{minor} =22.3 min, 91 % e.e.



14f

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid methyl ester (15b)

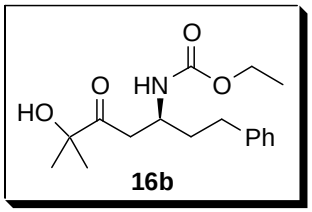
The title compound was prepared according to the general procedure starting from enone **1b** (0.150 g, 0.688 mmol) and methyl carbamate (0103 g, 1.38 mmol). Yield 103 mg (51%); White waxy solid; m. p. 45-46ºC (ethyl acetate/hexane); $[\alpha]_D^{25}$ = –9.8 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3475, 3362, 2950, 1710, 1527; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3-7.17 (m, 5H), 5.20 (d, 1H, *J*= 7.4Hz), 4.05 (br s, 1H), 3.67 (s, 3H), 2.9-2.7 (m, 4H), 1.86 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 156.7, 141.3, 128.6, 126.2, 76.5, 52.2, 48.1, 40.5, 36.1,32.8, 26.3; Elemental analysis calcd (%) for $C_{16}H_{23}NO_4$ (293.16): C 65.51, H 7.90, N 4.77; found: C 66.43, H 8.04, N 4.88; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 220 nm, Rt_{major} = 30.7 min, Rt_{minor} =41.2 min, >99 % e.e.



15b

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid ethyl ester (16b)

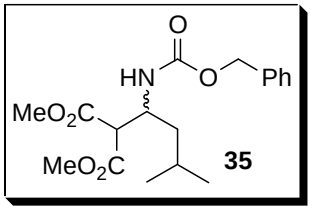
The title compound was prepared according to the general procedure starting from enone **1b** (0.050 g, 0.229 mmol) and urethane (0.41 g, 0.46 mmol). Yield 52 mg (74%). Colorless oil; $[\alpha]_D^{25}$ = –12.2 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3409, 2987, 1705, 1545; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 -7.19 (m, 5H), 5.23 (d, 1H, *J*= 3.4 Hz), 4.1 (m, 3H), 2.87 (t, 2H, *J*= 7.3 Hz), 2.7-2.59 (m, 2H), 2.2-1.8 (m, 2H), 1.35 (s, 6H), 1.3-1.2 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.7, 155.5, 141.3, 128.5, 126.0, 61.0, 48.0, 40.7, 36.2, 32.8, 26.4, 14.7; Elemental analysis calcd (%) for $C_{17}H_{25}NO_4$ (307.18): C 66.43, H 8.20, N 4.56; found: C 64.66, H 8.11, N 4.11; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 220 nm, Rt_{major} = 21.9 min, Rt_{minor} =30.6 min, 96 % e.e.



16b

2-(1-Benzyloxycarbonylamino-3-methyl-butyl)-malonic acid dimethyl ester (35)

The title compound was prepared following the general procedure applied to α-hydroxy enones starting from alkylidene malonate **34** (0.050 g, 0.25 mmol) and benzyl carbamate (0.076 g, 0.5 mmol). Yield 70 mg (80%); Colorless liquid; IR ($CHCl_3$, cm^{-1}) 3448, 2968, 1738.8, 1513; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.6 (d, 1H, *J* = 10Hz), 5.08 (d, 2H, *J* =1.2 Hz), 4.4 (m, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.65 (d, 1H, *J* = 6.3 Hz), 1.64 (m, 1H), 1.30 (m, 2H), 0.94 (t, 6H, *J* = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 168.2, 155.9, 136.7, 128.5, 66.7, 55.2, 52.7, 49.1, 42.6, 25.0, 23.1, 21.9; Chiral HPLC (Chiralpak OD column; iPrOH:hexane 3:97; 0.5 mL/min, 220 nm, Rt_{major} = 28.1 min, Rt_{minor} =30.7 min, ~00 % e.e.

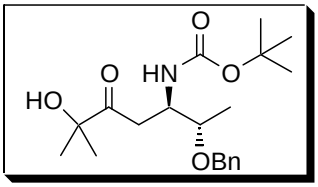


35

[1-(1-Benzyloxy-ethyl)-4-hydroxy-4-methyl-3-oxo-pentyl]-carbamic acid tert-butyl ester

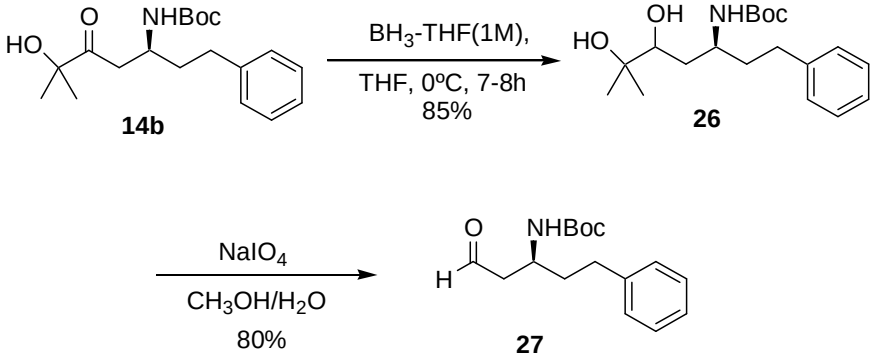
The title compond was prepared according to the general procedure starting from enone **21** (0.127 g, 0.51 mmol) and tert-butyl carbamate (0.120 g, 1.02 mmol). Crude yield 149 mg (80%).The title compound was not purified and the optical rotation was

not measured. ^{1}H NMR (500 MHz, $CDCl_3$) (major isomer) δ 7.35-7.32 (m, 5H), 4.9 (d, 1H, *J* = 8.5Hz), 4.64 (d, 2H, *J* = 18Hz), 4.32 (d, 1H, *J* = 11.5), 2.99-2.8 (br, 2H), 1.44 (s, 9H), 1.30 (t, 6H, *J* = 7.5, 6.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 213.7, 156.2, 140.2,137.7,128.8, 127.6, 127.4, 127.2, 126.9, 79.6, 76.3, 75.7, 70.6, 51.7, 38.5, 29.2, 27.9, 27.7, 26.6, 25.8, 16.1.



7. 4. 4 Elaboration of the adducts

A) To aldehyde (27)



Step 1

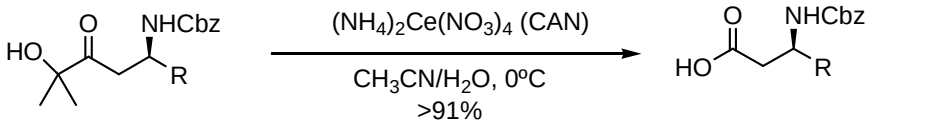
To a solution of (4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid tert-butyl ester **14b** (335 mg, 1mmol) in THF (3 mL) was added boron hydride (1M solution in THF) at 0ºC and stirred for 7-8h at same temperature. Then reaction was quenched with methanol and allowed to get room temperature. Solvent was evaporated under reduced pressure and white solid was washed with ethylacetate to give the title compound **26**, which was purified by flash column chromatography. Yield 286 mg, 85%.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3-7.2 (m, 5H), 4.5-4.34 (m, 2H), 3.9-3.73 (br, 2H), 3.49-3.40 (br s, 1H), 2.8 (br s, 2H), 2.7 (m, 1H), 2.6 (m, 1H), 1.9-1.8 (m, 2H), 1.45 (s, 9H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 155.7, 142.2, 128.8, 127.1, 126.1, 79.6, 47.9, 48.2, 41.1, 36.4, 32.8, 28.6, 26.4.

Step 2

A solution of sodium periodate (1.50 g, 7 mmol) in H_2O (10 mL) was added to a solution of the corresponding vicinal diol **26** (337 mg, 1 mmol) in methanol (1 mL) and after complete addition the reaction was stirred at room temperature until starting material disappeared as monitored by TLC (several hours). Methanol was then removed under reduced pressure and the reaction mixture extracted several times with CH_2Cl_2. The organic layers were combined, washed with brine and then dried over anhydrous $MgSO_4$ and concentrated. Corresponding unstable aldehyde **27** was obtained in 80% (221 mg) yield. Optical rotation was not determined. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.7 (s, 1H), 7.4-7.3 (m, 5H), 4.4-4.34 (m, 1H), 3.9-3.73 (br, 1H), 3.49-3.40 (br s, 1H), 2.8 (br s, 1H), 2.7 (m, 1H), 2.6 (m, 1H), 1.9-1.8 (m, 2H), 1.45 (s, 9H).

B) To acids and esters

(i) Method A: With Cerium Ammonium Nitrate (CAN)

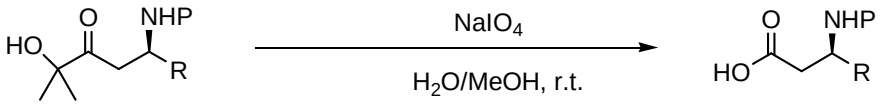


13b, R = CH_2CH_2Ph
13d, R = $CH_2CH(CH_3)_2$

22b, R = CH_2CH_2Ph
22d, R = $CH_2CH(CH_3)_2$

The corresponding α'-hydroxyketone (1.0 eq, 0.81 mmol,) was dissolved in CH_3CN (9.0 mL) and cooled to 0°C. A solution of cerium(IV) ammonium nitrate (3.0 eq., 2.43 mmol, 1.33 g) in H_2O (4.5 mL) was then added dropwise and after complete addition the reaction was stirred at 0°C for 45 min. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and added to a separating funnel where it was shaken with 0.1 M HCl (40 mL). The organic layer was separated and the aqueous layer extracted further with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, washed with brine (15 mL) and then dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on SiO_2 eluting with 2% acetic acid in CH_2Cl_2. The purified product was then triturated with pentane to yield upon drying the pure (*S*)-β-amino acid as a white solid.

(ii) Method B: With sodium periodate ($NaIO_4$)



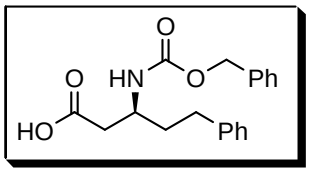
13b, R = $PhCH_2CH_2$, P = Cbz
13d, R = $(CH_3)_2CHCH_2$, P = Cbz
14b, R = $PhCH_2CH_2$, P = Boc
14d, R = $(CH_3)_2CHCH_2$, P = Boc

22b, R = $PhCH_2CH_2$, P = Cbz
22d, R = $(CH_3)_2CHCH_2$, P = Cbz
24b, R = $PhCH_2CH_2$, P = Boc
24d, R = $(CH_3)_2CHCH_2$, P = Boc

A solution of sodium periodate (1.50 g, 7 mmol) in H_2O (10 mL) was added to a solution of the corresponding α-hydroxy ketone (0.7 mmol) in methanol (1 mL) and after complete addition the reaction was stirred at room temperature until starting material disappeared as monitored by TLC (several hours). Methanol was then removed under reduced pressure and the reaction mixture extracted several times with CH_2Cl_2. The organic layers were combined, washed with brine and then dried over anhydrous $MgSO_4$ and concentrated.

3-Benzyloxycarbonylamino-5-phenyl-pentanoic acid (22b)

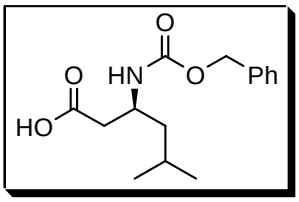
The compound **22b** was prepared using general Method A, starting from **13b** (0.258 g, 0.7 mmol). Yield 0.208 g (91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.2 (br. 1H), 7.38-7.31 (m, 4H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, *J* = 7.5Hz), 7.15 (d, 1H, *J* = 7Hz), 5.23 (d, 1H, *J* = 7.5Hz), 5.09 (d, 2H, *J* = 12.7Hz), 4.07-4-01 (m, 1H), 3.58 (br.s, 1H), 2.89 (dd, 1H, *J* = 17.0Hz, *J´*= 5.3Hz), 2.80 (dd, 1H, *J* = 17.0Hz, *J´* = 4.5Hz), 2.75-2.69 (m, 1H), 2.65-2.59 (m, 1H), 1.99-1.93 (m, 1H), 1.85-1.78 (m, 1H).



The compound **22b** was prepared using general Method B, starting from **13b** (0.369 g, 1.0 mmol). Yield 0.314 g (96%)

3-Benzyloxycarbonylamino-5-methyl-hexanoic acid (22d)

The compound **22d** was prepared using general Method A, starting from **13d** (0.225 g, 0.7 mmol). Yield 0.177g (91%). The obtained compound showed identical physical

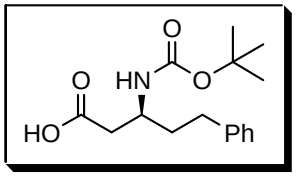


and spectroscopic data to those reported.[217] $[\alpha]_D^{25}$ = −28.7 (*c* = 2.9, $CHCl_3$) [Lit. data for *R* isomer: $[\alpha]_D^{25}$ = + 29.5 (*c* 2.5, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5(s, 5H), 5.45-5.15(d, 1H, J= 8Hz), 5.15(s, 2H), 4.33-4.0 (m, 1H), 2.66-2.5 (m, 2H), 1.6-1.33 (m, 3H), 0.92 (d, 6H, *J*= 5.8 Hz).

The compound **22d** was prepared using general Method B, starting from **13d** (0.321 g, 1.0 mmol). Yield 0.301 g (94%).

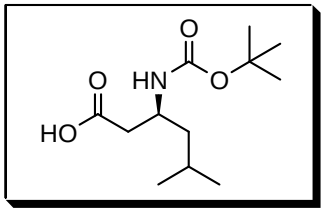
3-tert-Butoxycarbonylamino-5-phenyl-pentanoic acid (24b)

The compound **24b** was prepared using general Method B, starting from **14b** (0.335 g, 1.0 mmol). Yield 0.331 g (99%). The compound showed the identical published spectroscopy data.[218] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 5.84 (br.1H,), 4.9 (br. 1H), 3.96 (br, 1H), 2.89 (dd, 1H, *J*=17.0Hz, *J´*=5.3Hz), 2.80 (dd, 1H, *J*=17.0Hz, *J´*=4.5Hz), 2.75-2.69 (m, 1H), 2.65-2.59 (m, 1H), 1.99-1.72 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 155.6, 141.4, 128.5, 128.4, 126.0, 79.7, 47.4, 39.3, 36.4, 32.6, 28.4.



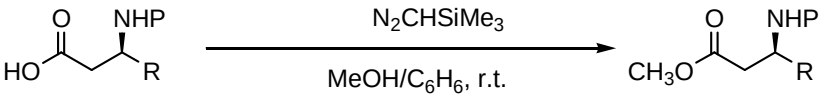
3-tert-Butoxycarbonylamino-5-methyl-hexanoic acid (24d)

The compound **24d** was prepared using general Method B, starting from **14d** (0.287 g, 1.0 mmol). Yield 0.264 g (92%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.83 (d, 1H, *J*= 8.8 Hz), 4.06 (m, 1H), 3.9 (s, 1H), 2.8 (m, 2H), 1.6 (m, 1H), 1.43 (s, 9H), 0.92 (d, 6H, *J*= 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 158.6, 74.7, , 49.4, 46.3, 42.2, 27.4, 26.3.



[217] El Marini, A.; Roumestant; Viallefont, P., Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.
[218] Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141-2156.

Transformation of acids into methyl esters



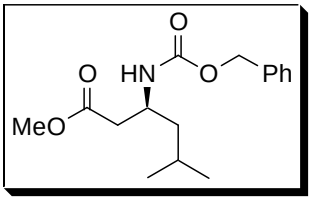
22b, R = $PhCH_2CH_2$, P = Cbz
22d, R = $(CH_3)_2CHCH_2$, P = Cbz
24b, R = $PhCH_2CH_2$, P = Boc
24d, R = $(CH_3)_2CHCH_2$, P = Boc

23b, R = $PhCH_2CH_2$, P = Cbz
23d, R = $(CH_3)_2CHCH_2$, P = Cbz
25b, R = $PhCH_2CH_2$, P = Boc
25d, R = $(CH_3)_2CHCH_2$, P = Boc

Trimethylsilyl diazomethane (2M solution in hexanes, 0.165 mL, 0.33 mmol) (**explosive**) was added dropwise to a solution of acid **22**/**24** (0.3 mmol) in benzene (5 mL) and methanol (0.5 mL) at room temperature. After 20 min of stirring, solvents were removed under reduced pressure to get the corresponding crude ester, which was purified by flash column chromatography (gradient eluent: ethyl acetate/hexane).

3-Benzyloxycarbonylamino-5-methyl-hexanoic acid methyl ester (23d)

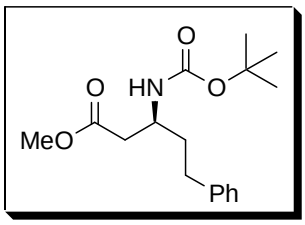
The compound **23d** thous obtained from **22d** (360 mg, 1.28 mmol). Yield 270 mg (74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5-7.33 (m, 5H), 5.45-5.15 (d, 1H, *J* = 8Hz), 5.15(s, 2H), 4.33-4.0 (m, 1H), 3.8 (s, 3H), 2.62-2.52 (m, 2H), 1.5-1.33 (m, 3H), 0.92 (d, 6H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 157.6, 141.4, 128.5, 128.4, 126.0, 72.7, 50.5, 45.4, 43.3, 36.4, 24.2, 22.9. This compound was transformed into **25d** by *N*-deprotection and subsequent Boc-protection thus confirming identity and configuration.



3-tert-Butoxycarbonylamino-5-phenyl-pentanoic acid methyl ester (25b)

The compound thus obtained from **24b** (85 mg, 0.29 mmol) showed identical physical and spectroscopic data than that published.[219] Yield 88 mg (98%). $[\alpha]_D^{25}$ = −8.7 (*c*=1.8, $CHCl_3$) [Lit. data for *R* isomer: $[\alpha]_D^{25}$ = +7.2 (*c*=1.8, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.2 (m, 5H), 5.74 (br.1H), 4.85 (br. 1H), 3.96 (br., 1H), 3.8(s, 3H) 2.89

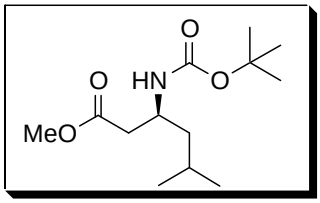
[219] M. Alcon, M. Canas, M. Poch, A. Mayono, M. A. pericas, A. Riera, *Tetrahedron Lett*, **1994**, *35*, 1589-1592.



(dd, 1H, *J* = 17.0Hz, *J´* = 5.1Hz), 2.75 (dd, 1H, *J* = 17.0Hz, *J´* = 4.5Hz), 2.75-2.69 (m, 1H), 2.60-2.55 (m, 1H), 1.90-1.75 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 154.6, 142.4, 128.5, 128.4, 126.0, 79.7, 50.5, 47.4, 39.3, 36.4, 32.6, 28.4.

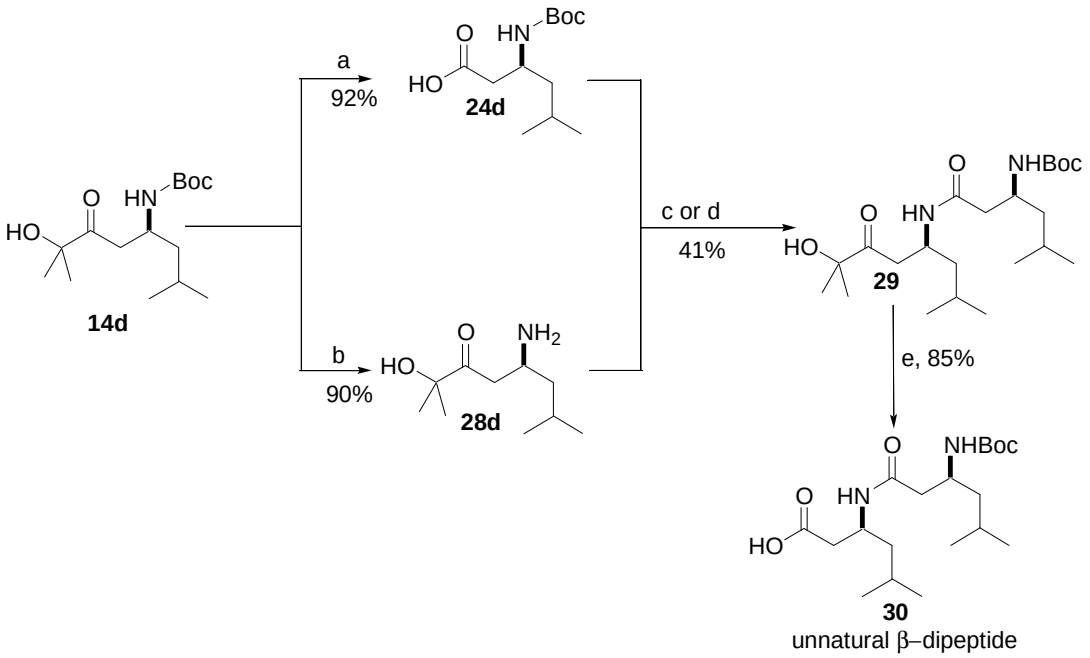
3-tert-Butoxycarbonylamino-5-methyl-hexanoic acid methyl ester (25d)

The compound thus obtained from **24d** (149 mg, 0.6 mmol) showed identical physical and spectroscopic data than that published**.** Yield 150 mg (95%). $[\alpha]_D^{25}$ = − 21.9 (*c* 1.47, CH_3OH) [Lit.[220] $[\alpha]_D^{25}$ = −22.8 (*c*=1.47, CH_3OH)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33-5.15 (d, 1H, J= 8Hz), 4.33-4.0 (m, 1H), 3.65 (s, 3H), 2.62 (d, 2H, J= 6Hz), 1.5-1.33 (m, 3H), 1.43(s, 9H), 0.92 (d, 6H, *J*= 7.2 Hz). ^{13}CNMR (125 MHz, $CDCl_3$) δ 172.0, 157.6, 70.7, 50.5, 48.4, 44.3, 40.2, 28.4, 27.3.



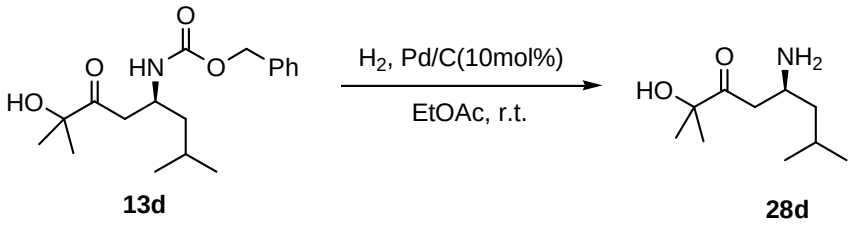
[220] El Marini, A.; Roumestant; Viallefont, P., Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.

7. 4. 5 Synthesis of an unnatural β-dipeptide



Reagents and conditions: (a) $NaIO_4$ (10 equiv.), MeOH-H_2O (2:1), 24-26h, 92%; (b) TFA (10 equiv.), CH_2Cl_2, 0ºC 5h, 90% (c) EDC (1.4 equiv.), HOBt (1.0 equiv.), CH_2Cl_2, 20-24h, 41%; (d) (i) cyanuril fluoride (5 equiv.), CH_2Cl_2, -20ºC, 84% (ii) NMM, CH_2Cl_2, 20-24h, 41%; (e) $NaIO_4$ (10 equiv.), MeOH-H_2O (2:1), 24-26h, 85%.

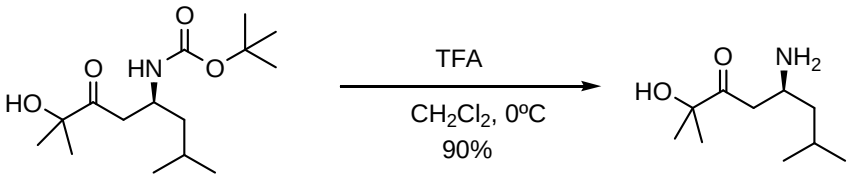
Deprotection of Cbz group of 13d



To a solution of adduct **13d** (174 mg, 0.54 mmol) in ethyl acetate (5.0 mL) was added 10% activated Pd on charcoal and the mixture was kept under hydrogen atmosphere at room temperature for several hours till the starting material was disappeared. Then the suspension was filtered through a pad of celite and evaporated under reduced pressure. The crude product was used in next step without further purification. Yield 95% (95 mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (s, br. 2H), 4.83

(d, 1H, *J* = 8.8 Hz), 4.06 (m, 1H), 3.9 (s, 1H), 2.8 (m, 2H), 1.6 (m, 1H), 1.36 (s, 6H), 0.92 (d, 6H, *J* = 6.8 Hz);

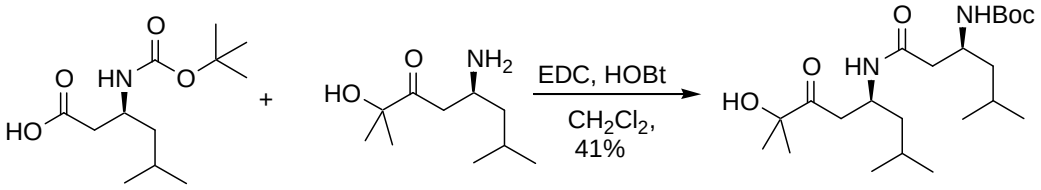
Deprotection of Boc group 14d



14d **28d**

To a solution of corresponding N-Boc adduct (189 mg, 0.59 mmol) in dry dichloromethane (6 mL) cooled to 0ºC was added trifluoroacetic acid (1.2 mL, 18 mmol). The resulting solution was stirred at the same temperature for 5-6h. Then dichloromethane (4 mL) was added and the organic solution was washed with saturated aqueous solution of $NaHCO_3$ (3 x 15mL). The combined organic layer were dried over MgSO4, filtered, and concentrated under vacuum to give the unprotected amine.Crude yield 90% (99 mg). The crude compound was used in the next step without further purification.

Carboxylic acid and amine couplings.

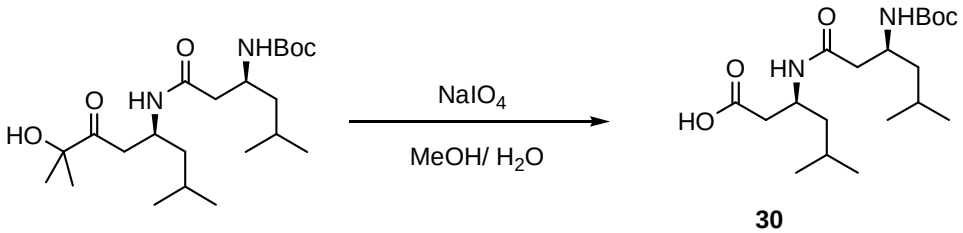


24d **28d** **29**

A solution of the corresponding amine **28d** (0.3 g, 1.7 mmol), the corresponding carboxylic acid **24d** (0.4 g, 1.7 mmol), EDC (0.45g, 2.3 mmol) and

HOBt (0.23g, 1.7 mmol) in dry dichloromethane (26 mL) was stirred at 0ºC for 1h, and at room temperature for additional 16h. The resulting mixture was diluted with dichloromethane (50 mL) and washed with 0.1 N $KHSO_4$ (3 x 20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the coupling product **29**, which was purified by flash column chromatography (eluent hexane:ethylacetate). Yield 41%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.3 (br.s, 1H), 5.07 (d, 2H, *J* = 8Hz), 4.37 (br. s, 2H), 3.9-3.87 (br. m, 2H), 2.8-2.5(m, 3H), 2.36 (br. s, 2H), 1.61(m, 2H), 1.45 (s, 9H), 1.35 (m, 6H), 0.92 (d, 12H, *J* = 7.2 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 213.9, 174.3, 171.1, 155.9, 79.2, 77.8, 54.1, 46.5, 44.8, 43.7, 43.4, 41.8, 41.4, 39.4, 28.4, 26.2, 25.0, 23.04, 23.0, 22.08, 21.95.

Oxidative scission of the ketol moiety 29

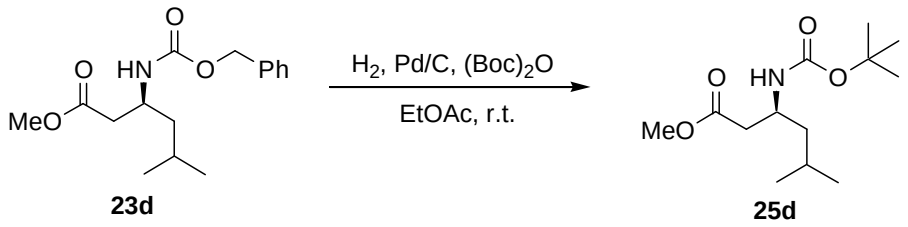


29 **30**

The coupling adduct **29** (1mmol) was oxidised by general oxidation pathway using $NaIO_4$ in methanol and water system as described above. Unnatural β-dipeptide **30** was obtained in 80% yield, as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.5 (br.s, 1H), 5.1 (br s, 2H,), 4.34 (br. s, 2H), 4.2-3.8 (m, 2H), 2.57-2-43 (m, 3H), 1.61 (m, 2H), 1.45 (s, 9H), 1.27 (m, 2H), 0.93 (m, 12H).

7. 4. 6 Chemical correlations:

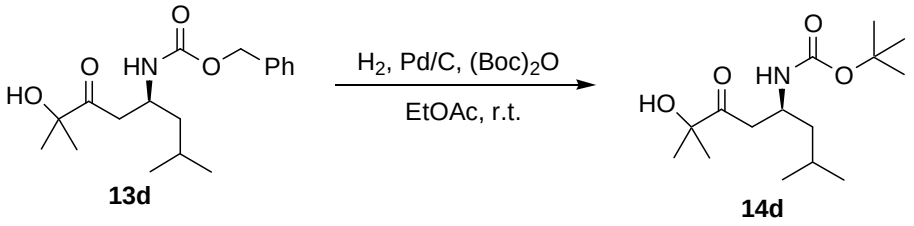
i) between 23d and 25d



23d **25d**

To a solution of adduct **23d** (174 mg, 0.59 mmol) and $(Boc)_2O$ (259 mg, 1.18 mmol) in ethyl acetate (5.0 mL) was added 10% activated Pd on charcoal and the mixture was kept under hydrogen atmosphere at room temperature for several hours till the starting material was disappeared. Then the suspension was filtered through a pad of celite and evaporated under reduced pressure. The residue was purified by column chromatography (gradient eluent of Hexane: ethyl acetate) to get the title ester compound **25d**. Yield 0.130 g (85%). The compound thus obtained showed identical physical and spectroscopic data than that published. $[\alpha]_D^{25}$ = −21.9 (*c* = 1.47, Methanol) [Lit. $[\alpha]_D^{25}$ = −22.8 (*c*=1.48, Methanol)].

ii) between Cbz adduct 13d and Boc adduct 14d



13d **14d**

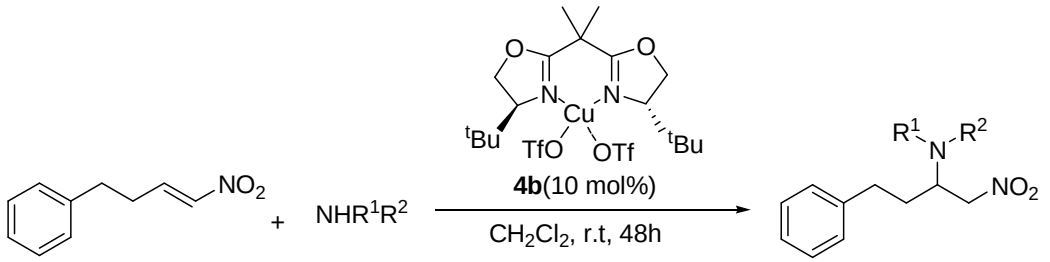
To a solution of **13d** (0.030 g, 0.093 mmol) and $(Boc)_2O$ (0.041 g, 0.186 mmol) in ethyl acetate (3 mL) was added activated Pd on charcoal (10%, 3 mg) and the mixture was kept under hydrogen atmosphere at room temperature for several hours till the starting material disappeared. Then the suspension was filtered through a pad of celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (eluent, ethyl acetate/hexane) to get the title compound which showed identical physical and spectroscopic data than authentic **14d**. Yield 0.024 g (90%).

7. 5 aza-Michael addition to nitroalkene

7. 5. 1 Preparation of asymmetric adducts:

General procedure:

Method A: 1,4-conjugate addition of aza-nucleophiles to nitroalkene 36 with catalyst 4b.



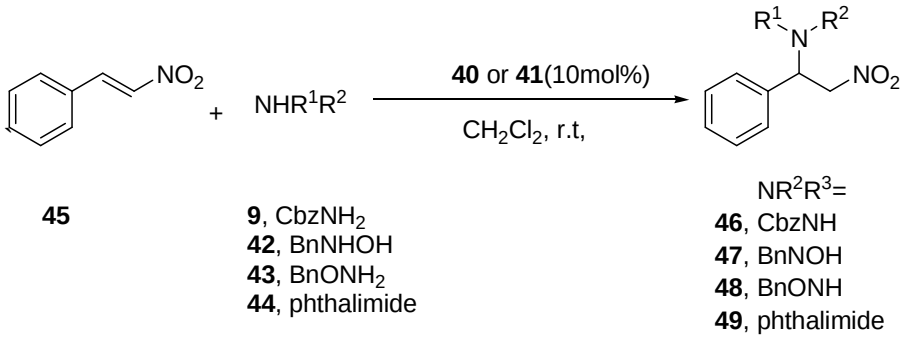
36

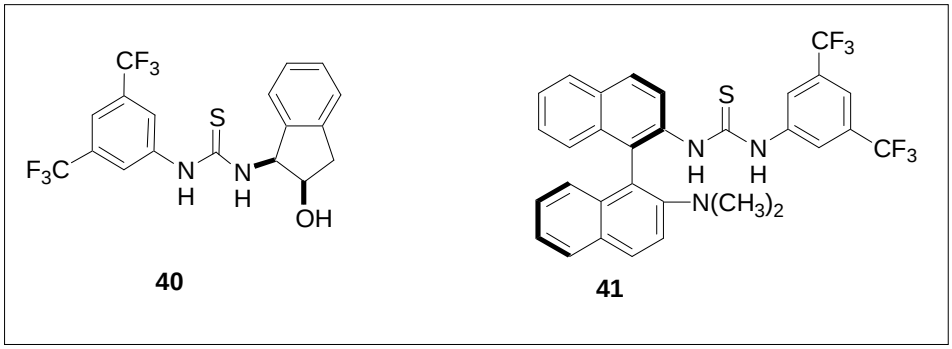
9, R^1 = Cbz, R^2 = H
19, R^1 = Cbz, R^2 = OH
20, R^1 = Boc, R^2 = OH

37, R^1 = Cbz, R^2 = H
38, R^1 = Cbz, R^2 = OH
39, R^1 = Boc, R^2 = OH

2,2´-Isopropylidene bis[(4*S*)-4-tert-butyl-2-oxazoline] (tBu-BOX) (0.11 mmol) was weighted in a flame-dried flask and placed under N_2. $Cu(OTf)_2$ (36 mg, 0.1 mmol) was then added by rinsing with dry CH_2Cl_2 (1.5 mL) from a weighting boat directly into the reaction flask. After stirred at room temperature for 3 h, nitroalkene **36** (1 mmol) was added, and the resulting mixture was stirred for a further 30 min at room temperature. Then aza-nucleophile (2 mmol) was added and the mixture was stirred at room temperature under N_2 for the stated time. The resulting reaction mixture was diluted with 0.1 M HCl (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The CH_2Cl_2 layers were combined, dried over anhydrous $MgSO_4$ and concentrated. The crude product was not purified by column chromatography. Conversion and ee´s were determined by NMR (500 MHz) and chiral HPLC repectively.

Method B:

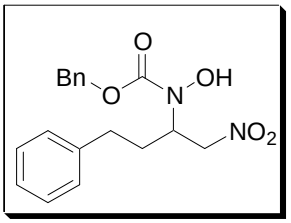




To a solution of β-nitro styrene **45** (1 mmol) in dichloromethane was added catalyst **40** or **41** (10 mol%) at room temperature and stirred for 1h. Then aza nucleophile was added (1 mmol) and the resulting solution was stirred for 5-48h at specified temperature. Then after reaction was quenched with 0.1M HCl (3 mL) and extracted with dichloromethane. The organic phase was dried over $MgSO_4$, evaporated under reduced pressure to give the crude product which was not purified. Conversion and ee´s were determined by NMR (500 MHz) and chiral HPLC repectively.

(1-Nitromethyl-3-phenyl-propyl)-N-hydroxycarbamic acid benzyl ester (38)

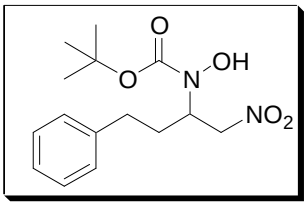
The title compound was prepared following above described procedure A, using



carbamate **19** (2 mmol), nitroalkene **36** (177 mg, 1 mmol) and catalyst **4b** (0.1 mmol). Conversion >99%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.31 (m, 10H), 5.43 (br s, 1H), 5.2(m, 1H), 5.1 (d, 2H, *J* = 2.0 Hz), 4.88 (br s, 1H), 4.65 (d, 1H, *J* = 8 Hz) 2.75-2.69 (m, 1H), 2.65-2.59 (m, 1H), 1.99-1.93 (m, 1H), 1.85-1.78 (m, 1H). Chiral HPLC (Chiralcel AS column; 97:3 hexane: iPrOH, 0.6 mL/min, 220 nm, Rt_{major} = 22.1 min, Rt_{minor} =32.7 min, ~00 % e.e.

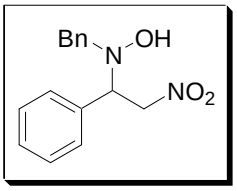
(1-Nitromethyl-3-phenyl-propyl)-N-hydroxycarbamic acid tert-butyl ester (39)

The title compound was prepared following above described procedure A, using carbamate **20** (2 mmol), nitroalkene **36** (177 mg, 1mmol) and catalyst **4b** (0.1 mmol). Conversion >99%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 5.41 (br s, 1H), 5.32(m, 1H), 4.78 (br s, 1H), 4.62 (m, 1H), 2.75-2.69 (m, 2H), 1.99-1.72 (m, 2H), 1.46 (s, 9H); Chiral HPLC (Chiralpak OD column; 96:4 hexane: iPrOH, 0.5 mL/min, 220 nm, Rt_{major} = 28.1 min, Rt_{minor} =30.7 min, ~00 % e.e.



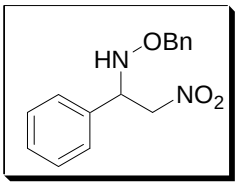
N-Benzyl-N-(2-nitro-1-phenyl-ethyl)-hydroxylamine (47)

The title compound was prepared following above described procedure B, using *N*-benzylhydroxylamine **42** (123 mg, 1 mmol), nitroalkene **45** (149 mg, 1mmol) and catalyst **40** or **41** (0.1 mmol). Conversion >99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.40 (m, 5H), 7.30-7.28 (m, 5H), 5.1 (m, 1H,), 4.88 (m, 2H), 3.6 (m, 2H); Chiral HPLC (Chiralpak IA column; hexane:iPrOH 95:5; 0.5 mL/min, 220 nm, Rt = 33.1 min, Rt=36.0 min, ~00 % e.e.



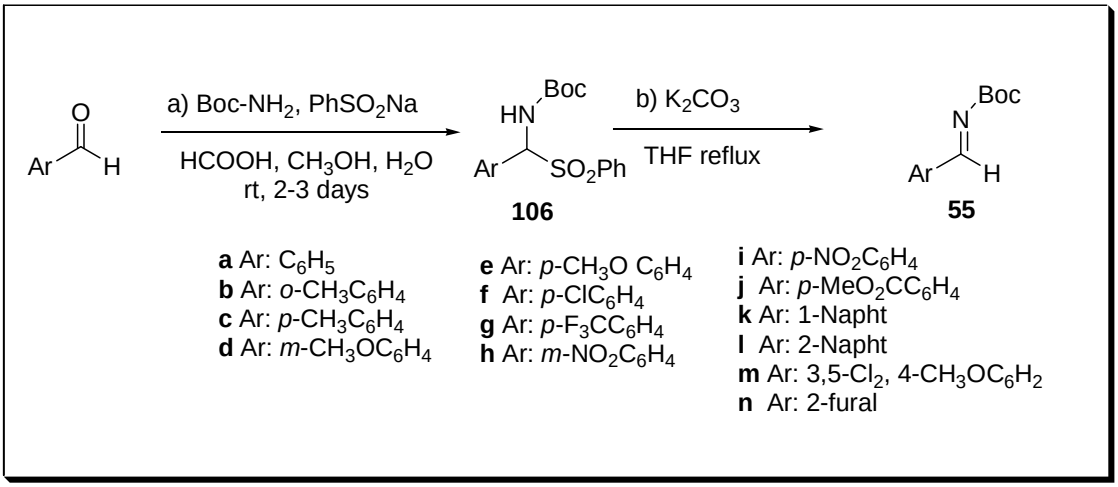
O-Benzyl-N-(2-nitro-1-phenyl-ethyl)-hydroxylamine (48)

The title compound was prepared following above described procedure B, Uding *O*-benzylhydroxylamine **43** (123 mg, 1 mmol), nitroalkene **45** (149 mg, 1 mmol) and catalyst **40** or **41** (0.1 mmol). Conversion >99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4-7.30 (m, 10H), 5.29(m, 1H), 5.2 (br s, 1H), 4.99 (m, 2H), 4.88 (br s, 1H), 4.65 (d, 1H, *J* = 8 Hz); (Chiralpak IA column; hexane: iPrOH, 98:2; 0.5 mL/min, 220 nm, Rt = 33.1 min, Rt = 36.0 min, ~00 % e.e.



7. 6 Preparation of imines

7. 6. 1 Two-step preparation of *N*-Boc aldimines 55. [221]



General Procedure: (According to Jacobsen´s procedure) [222]

Step 1.

t-Butyl carbamate (2.93 g, 25 mmol) and benzenesulfinic acid sodium salt (8.2 g, 50 mmol) were taken into a 250 mL round bottom flask and dissolved in a mixture of methanol (25 mL) and water (50 mL). The corresponding benzaldehyde[223] (50 mmol) was then added, followed by formic acid (1.9 mL) and the reaction mixture was stirred for 3 days at room temperature. The resulting white solid was filtered off and washed with water and ether, redissolved in dichloromethane, dried over $MgSO_4$, and concentrated under reduced pressure to afford the respective α-amido benzenesulfone as white solid.

Step 2.

An oven dried round bottom flask was charged with anhydrous potassium carbonate (16g) and dry THF (10 mL/mmol) under nitrogen atmosphere. Then, the

[221] (a) A. M. Kanazawa, J.-N. Denis, A. E. Greene, *J. Org. Chem.* **1994**, *59*, 238-1240 (b) B. M. Nugent, R. A. Yoder , J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418-3419.

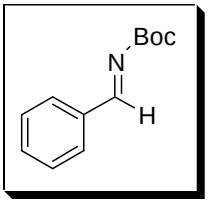
[222] A. G. Wenzel, E. N. Jacobsen, *J.Am.Chem.Soc.* **2002**, *124*, 12964-12965

[223] All aldehydes used are commercial except 3,5-dichloro-4-methoxybenzaldehyde. For its preparation, see: T. Kousaka, K. Mori, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 697-701. Commercially available methyl 3,5-dichloro-4-methoxybenzoate was treated with sodiumborohydride ($NaBH_4$) in EtOH at 0ºC, to obtain corresponding alcohol which was oxidised by PCC to get the tilte compound 3,5-dichloro-4-methoxybenzaldehyde.

respective α-amido benzenesulphone (19.4 mmol) was added and the mixture was heated to reflux with stirring under a nitrogen atmosphere for 17 h. The mixture was then cooled to room temperature, filtered through a short pad of celite and concentrated under reduced pressure. The residue was redissolved in dichloromethane, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding *N*-Boc aldimine **55a-n** which was kept under high vacuum at RT for several hours before use. It is important to note that compound is moisture sensitive. Aldimines were stored at -30ºC to avoid decomposition.

***N*-Benzylidene carbamic acid tert-butyl ester (55a)**

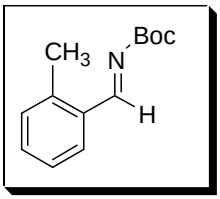
The aldimine **55a** was prepared from adduct α-amidosulfone**106a** (6.73 g, 19.4 mmol)



using general protocol as above described to get the pure compound as oil. Yield (3.9 g, 98%). IR (thin film, cm^{-1}) 2960, 1730, 1640,1210. ^1H NMR (200 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.0-7.93 (m, 2H), 7.6-7.49 (m, 3H), 1.65 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 168.9, 163.0, 134.0, 133.4, 129.9, 128.4, 81.8, 27.8.

***N*-(2-Methyl-benzylidene)-carbamic acid tert-butyl ester (55b)**

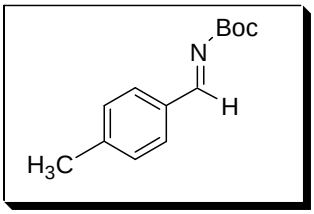
The aldimine **55b** was prepared from adduct α-amidosulfone **106b** (9.6 mmol) using



general protocol as above described to get the pure compound as white solid (1.5g, 98%), IR(thin film, cm^{-1}) 2945, 1730, 1654, 1210; ^1H NMR (200MHz, $CDCl_3$) δ 8.84 (1H, s) 8.10-7.96 (m, 1H), 7.57-7.41 (m, 1H), 7.37-7.25 (m, 2H), 2.58 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 169.0, 163.8, 139.2, 133.6, 132.9, 130.4, 129.3, 127.4 , 82.2, , 27.8, 19.4.

***N*-(4-Methyl-benzylidene)-carbamic acid tert-butyl ester (55c)**

The aldimine **55c** was prepared from adduct α-amidosulfone **106c** (36 mmol) using

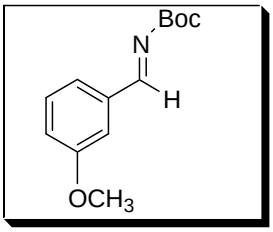


general protocol as above described to get the pure compound as white solid (7g, 89%), IR (thin film, cm^{-1}) 2930, 1634, 1340; ^1H NMR (200MHz, $CDCl_3$) δ 8.90 (s,

1H) 7.41-7.30 (m, 2H), 7.28–7.16 (m, 2H), 2.36 (s, 3H) 1.51 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 171.0, 162.8, 142.2, 132.9, 132.3, 129.3, 82.0, 28.8, 20.3.

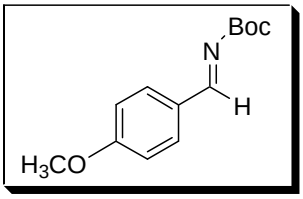
***N*-(3-Methoxy-benzylidene)-carbamic acid tert-butyl ester (55d)**

The aldimine **55d** was prepared from adduct α-amidosulfone **106d** (4.8 mmol) using general protocol as above described to get the pure compound as waxy solid. (1.1 g, 98%), IR (thin film, cm^{-1}) 2991, 1725, 1610, 1245, ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.87 (s, 1H) 7.53 (s, 1H), 7.43 (d, 1H, *J* = 6.8Hz), 7.28 (d, 1H, *J* = 6.8 Hz), 7.14 (m, 1H) 3.8 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 169.4, 163.8, 162.2, 132.7, 126.3, 114.0 , 82.1, , 55.9, 27.6.



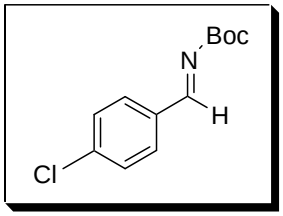
***N*-(4-Methoxy-benzylidene)-carbamic acid tert-butyl ester (55e)**

The aldimine **55e** was prepared from adduct α-amidosulfone **106e** (21 mmol) using general protocol as above described to get the pure compound as white solid (5.0 g, 100%), IR (thin film, cm^{-1}) 2930, 1713, 1590, 1340; ^{1}H NMR (200MHz, $CDCl_3$) δ 8.90 (s, 1H) 7.93-7.91 (d, 2H, *J* = 8.4Hz), 6.98 (d, 2H *J* = 8.4Hz), 2.90 (s, 3H) 1.61 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 169.4, 163.8, 162.2, 132.7, 126.3, 114.0 , 82.1, 55.9, 27.



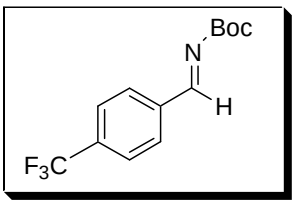
***N*-(4-Chloro-benzylidene)-carbamic acid tert-butyl ester (55f)**

The aldimine **55f**was prepared from adduct α-amidosulfone **106f** (13 mmol) using general protocol as above described to get the pure compound as white solid (3.0g, 98%), IR (thin film, cm^{-1}) 2978, 1720, 1451; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.85 (s, 1H) 7. 90 (d, 2H, J = 6Hz), 7.49 (d, 2H, *J* = 5Hz), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 162.8, 141.2, 132.9, 131.3, 129.3, 81.3, 28.



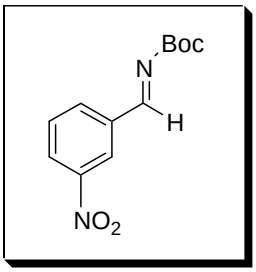
***N*-(4-Trifluoromethyl-benzylidene)-carbamic acid tert-butyl ester (55g)**

The aldimine **55g** was prepared from adduct α-amidosulfone **106g** (15 mmol) using general protocol as above described to get the pure compound as white solid (3.5 g, 97%), IR (thin film, cm^{-1}) 3315, 2981, 1723, 1634, 1320 ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.07 (d, 2H, *J* = 8.1Hz), 7.78 (d, 2H, *J* = 8.4Hz), 2.36 (s, 3H) 1.62 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 167.5, 162.8, 137.2, 134.5, 130.3, 126.3, 126.1, 82.9, 28.2.



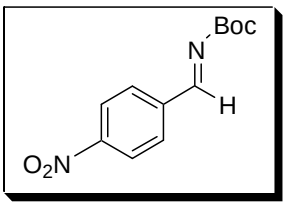
***N*-(3-Nitro-benzylidene)-carbamic acid tert-butyl ester (55h)**

The aldimine **55h** was prepared from adduct α-amidosulfone **106h** (17.8 mmol) using general protocol as above described to get the pure compound as yellow oil. (4.5 g, 100%), IR (thin film, cm^{-1}) 2990, 1717, 1534, 1330 ^{1}H NMR (500MHz, $CDCl_3$) δ 8.90 (s, 1H) 8.78-8.77 (m, 1H), 8.44–7.16 (m, 2H), 2.36 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 171.0, 162.8, 142.2, 132.9, 132.3, 129.3, , 82.0, , 28.8, 20.3.



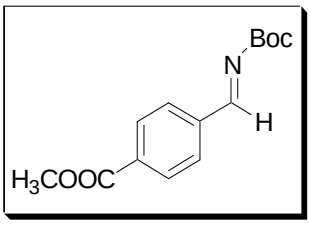
***N*-(4-Nitro-benzylidene)-carbamic acid tert-butyl ester (55i)**

The aldimine **55i**was prepared from adduct α-amidosulfone **106i** (10.2 mmol) using general protocol as above described to get the pure compound as yellow solid (2.5 g, 100%), IR(thin film, cm^{-1}) 2939, 1724, 1478, 1340 ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.37 (d, 2H, *J*= 9Hz), 8.12 (2H, d, *J*= 8.7Hz), 1.63 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 166.4, 162.8, 140.0, 130.9, 124.3, 123.3, , 83.0, 28.5.



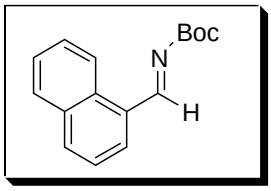
***N*-(4-methoxycarbonylbenzylidene) carbonic acid tert-butyl ester (55j)**

The aldimine **55j** was prepared from adduct α-amidosulfone **106j** (5 mmol) using general protocol as above described to get the pure compound as waxy solid. (1.16 g, 90%), IR (thin film, cm^{-1}) 2971, 1697, 1630, 1340, ^{1}H NMR (200 MHz, $CDCl_3$) δ



8.89 (s, 1H), 8.18 (d, 2H, *J* = 8.1Hz), 7.9 (d, 2H, *J* = 8.2Hz), 3.9 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ δ 168.2, 166.2, 162.3, 137.8, 34.2, 130.06, 129.98, 129.61, 82.85, 52.6, 28.01.

***N*-Naphthalene-1-ylmethylene-carbamic acid tert-butyl ester (55k)**

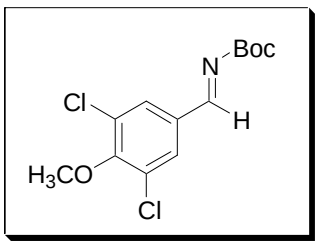


The aldimine **55k** was prepared from adduct α-amidosulfone **106k** (3.5 mmol) using general protocol as above described to get the pure compound as yellow oil (0.87 g, 97%), IR (thin film, cm^{-1}) 2971,1697, 1630,1340, ^{1}H NMR (200MHz, $CDCl_3$) δ 9.96 (s, 1H) 8.9 (d, 1H, *J* = *8.*25Hz), 8.2 (d, 1H, *J* = 7.2Hz), 8.1 (d, 1H, *J* = 8.25Hz), 7.9 (d, 1H, *J*= 8.3Hz), 7.65 (m, 5H), 1.66 (s, H); ^{13}C NMR (50MHz, $CDCl_3$) δ 169.12, 162.99, 134.4, 133.8, 132.1, 132.0, 129.37, 129.2, 128.99, 128.24, 126.24, 126.6, 125.2, 124.98, 124.04, 82.35, 28.12.

***N*-Naphthalene-2-ylmethylene-carbamic acid tert-butyl ester (55l)**

The aldimine **55l**was prepared from adduct α-amidosulfone **106l** (6.2 mmol) using general protocol as above described to get the pure compound as white solid (1.5 g, 95%), IR (thin film, cm^{-1}) 2980, 1710, 1634, 1345 ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.35 (s, 1H), 8.10 (dd, 1H, *J* = 1.9, 9.0 Hz), 7.94 (m, 1H), 7.87 (m, 2H), 7.66-7.56 (m, 2H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 162.8, 136.2, 134.4, 132.6, 131.4,129.3, 128.6, 128.4, 127.9, 126.7,124.0, 82.0, , 27.8.

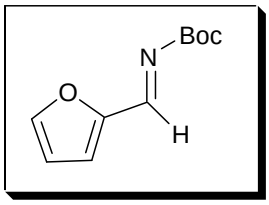
***N*-(3,5-Dichloro-4-methoxy-benzylidene)-carbamic acid tert-butyl ester (55m)**



The aldimine **55m**was prepared from adduct α-amidosulfone **106m** (5 mmol) using general protocol as above described to get the pure compound as white

solid (1.4 g 96%); IR (film, cm^{-1}) 3040, 1704, 1629, 1435**.** ^1H NMR (200 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.89 (s, 1H), 3.99 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.49, 161.8, 156.37, 131.28, 130.35, 126.68, 82.9, 61.09, 27.96.

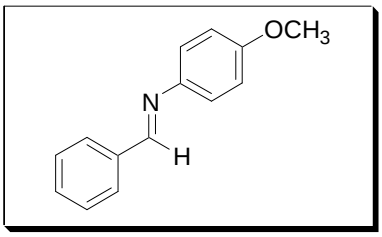
_N_-Furan-2-ylmethylene-carbamic acid tert-butyl ester (55n)



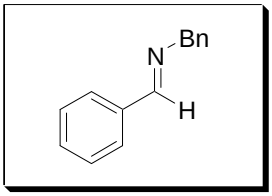
The aldimine **55m**was prepared from adduct α-amidosulfone **106m** (15 mmol) using general protocol as above described to get the pure compound as yellow oil (2.7 g, 95%), IR (thin film, cm^{-1}) 2990, 1715, 1634, 1245 ^1H NMR (500MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.65 (s, 1H), 7.21 (d, 1H, *J* = 3.9Hz), 6.64 (dd, 1H, *J* = 1.56, J= 3.5 Hz), 1.56 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 162.8, 157.5, 150.8, 148.0, 121.0, 113.4, 82.1, 27.6.

Benzylidene-(4-methoxy-phenyl)-amine (51)

To a solution of benzaldehyde (1.0 mL, 10 mmol) in dichloromethane (10 mL) was added *p*-anisidine (1.2 g, 10 mmol) and $MgSO_4$ (1.0 g) The mixture was stirred for 3h at room temperature and then filtered through celite. The filtrate was concentrated under reduced pressure to give corresponding imine which was recrystalized from dichloromethane/hexane solution to give colorless needles in 2 g (98%) yield. ^1H NMR (500 MHz, $CDCl_3$) δ 8.7 (s, 1H), 7.53-7.45 (m, 2H), 7.33-7.20 (m, 5H), 6.8-6.72 (m, 2H), 3.7 (s, 3H); ^{13}C NMR (50MHz, $CDCl_3$) δ 165.4, 161.8, 145.2, 132.7, 129.4, 126.3, 123.1, 114.0, 55.9.



Benzyl-benzylidene-amine (52)

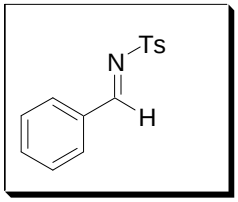


The title compund was prepared following the same procedure described for **51**, using benzyl amide (1 mmol). Yield 185mg (95%). ^1H NMR (500MHz, $CDCl_3$) δ 8.6 (s, 1H) 7.63-7.57 (m, 2H), 7.29-7.20 (m, 5H), 7.14-7.05 (m,

3H), 4.8 (s, 3H); ^{13}C NMR (50MHz, $CDCl_3$) δ 163.4, 137.8, 132.7, 129.4, 125.3, 123.1, 59.0.

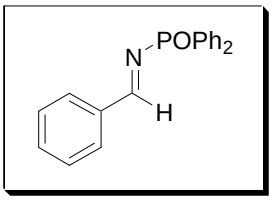
_N_-Benzylidene-4-methylbenzenesulfonamide (53)[224]

Titanium tetrachloride (1.05 mL, 9.5 mmol)) in dry dichloromethane (10 mL) was added dropwise to a stirred, ice-cooled solution of benzaldehyde (19 mmol), *p*-toluenesulfonamide (19 mmol), and triethylamine (5.76 g, 57 mmol) in dry dichloromethane (40 mL). After the addition was completed, the mixture was stirred for 30 min. The titanium dioxide was removed by suction filtration through celite and washed with dichloromethane (20 mL). Evaporation of the solvent under reduced pressure afforded a white solid which was broken up by refluxing in dry diethyl ether (75 mL) for 15 min. The residual trimethyl amino hydrochloride salt was removed by filtration and the filtrate was concentrated under reduced pressure to afford the crude imine. Purificaton by crystallization (hexane/dichloromethane) afforded **1** as a white solid (3.4 g , 70%); m.p 110-111ºC (Lit 109ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.96-7.92 (m, 4H), 7.64 (t, 1H, *J* = 7.5 Hz), 7.48 (t, 1H, *J* = 7.4 Hz), 7.30 (d, 2H, *J* =8.8 Hz), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 144.2, 134.8, 131.2, 130.2, 128.6, 21.0.



_P,P_-Diphenyl-_N_-(phenylmethylene)phosphinic amide (50)

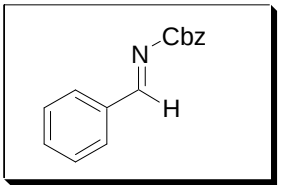
The title compund was prepared accordingly Gennings et al., following the same procedure described for **53**, using diphenylphosphinic amide (2.5 g, 11.5 mmol). Purification of **50** was effected by crystallization from a mixture of hexane /dichloromethane. Yield 2.1 g (60%); m.p 143-144 ºC (lit 139-140 ºC). All spectroscopic data matched those described in literature.



[224] W. B. Jennings, C. J. Lovely, *Tetrahedron* **1991**, *47*, 5561-5568.

Benzylidene-carbamic acid benzyl ester (57)

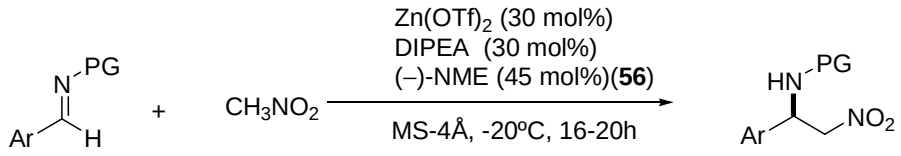
The title compound was prepared according to the general procedure described for *N*-



Boc aldimines (vide infra) using benzylcarbamate (6.5 mmol) instead of *tert*-butylcarbamate. Yield 1.5 g (95%); oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H) 8.35 (s, 1H), 8.10 (dd, 1H, *J* =1.9, 9.0 Hz), 7.94 (m, 1H), 7.87 (m, 2H), 7.66-7.56 (m, 2H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 162.8, 136.2, 134.4, 132.6, 131.4, 129.3, 128.6, 128.4, 127.9, 126.7, 124.0, 82.0, 27.8.

7. 7 aza-Henry reaction

7. 7. 1 General procedure for the asymmetric aza-Henry reaction with arylimines



50, PG = $POPh_2$
51, PG = *p*-$CH_3OC_6H_4$
52, PG = $C_6H_4CH_2$
53, PG = *p*-$C_6H_4SO_2$
54, PG = Cbz
55, PG = Boc

57, PG = $POPh_2$
58, PG = *p*-$CH_3OC_6H_4$
59, PG = $C_6H_4CH_2$
60, PG = *p*-$C_6H_4SO_2$
61, PG = Cbz
62, PG = Boc

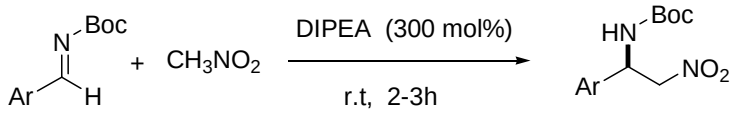
Diisopropylethylamine (0.054 mL, 0.3 mmol) was added dropwise to a solution of previously dried $Zn(OTf)_2$ (0.109 g, 0.3 mmol) in anhydrous CH_3NO_2 (2 mL) under a nitrogen atmosphere and the mixture was stirred at 25-30 ºC for 1h. The reaction mixture became yellow, and after addition of (-)-(1*R*, 2*S*)-*N*-methylephedrine (0.081 g, 0.45 mmol) and MS 4 Å (0.1 g), the resulting mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was then kept for 10 min at -20°C, and subsequently the corresponding aromatic aldimine (1 mmol) was added and the reaction mixture stirred for 16-18 h at that temperature. The reaction was quenched with 0.1M HCl (3 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate/hexane mixtures as the eluant.

***Recovery of the aminoalcohol ligand*:**

From the late fractions of the column, part of (1*S*,2*R*)-*N*-methylephedrine was recovered. Recovery of the aminoalcohol ligand that remained in the acidic aqueous phase was carried out by drop-wise addition of a solution of NaOH (20% w/v) until pH≥10. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer was dried over $MgSO_4$ and evaporated to afford additional quantities of (—)-NME. Combined yield of chemically and optically pure (—)-NME recovered were regularly within the 90-97% range.

7. 7. 2 Preparation of racemic adducts

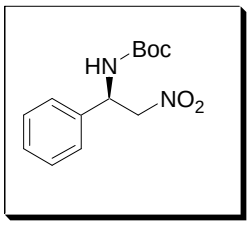
Racemic aza-Henry adducts were prepared by treatment of the corresponding aryl aldimine (1 mmol) in nitromethane (solvent, 2.0 mL) with diisopropylethylamine (300 mmol%) at RT for 2-3 hours. Then reaction mixture was washed with water, organic layer was extracted with dichloromethane (3 x 5), evaporated under reduced pressure to get the title crude compound which was used in next step without further purification.



rac 62a-n

(*R*)-*N*-(2-Nitro-1-phenyl-ethyl)-carbamic acid *tert*-butyl ester (62a)

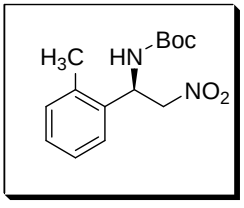
The title compound was prepared according to the general procedure starting from



imine **55a** (0.20 g, 1 mmol). 0.22 g (81%); white solid; m.p. 105-106 ºC (Lit.[2b]: mp 116-118 ºC, 60% *ee*); $[\alpha]_D^{25}$ = – 28.2 (*c*=1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3330, 2988, 1675, 1550; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 1H, *J* = 7 Hz), 7.36 (d, 1H, *J* = 7.5 Hz), 7.32 (d, 2H, *J* = 7.0 Hz), 7.26 (br s, 1H), 5.38 (br s, 1H), 5.29 (br s, 1H), 4.86 (br s, 1H), 4.72 (t, 1H, *J* = 4.5 Hz), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 136.9, 129.0, 128.5, 126.3, 78.7, 52.7, 28.11; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220 nm) Rt_{major} = 13.06 min, Rt_{minor} =12.27 min, 97% *ee*; Anal. calcd. for $C_{13}H_{18}N_2O_4$ (266.29): C, 58.63; H, 6.81; N, 10.52. Found: C, 58.62; H, 6.81; N, 10.53.

(*R*)-*N*- (2-Nitro-1-*o*-tolyl-ethyl)-carbamic acid *tert*-butyl ester (62b)

The title compound was prepared according to the general procedure starting from

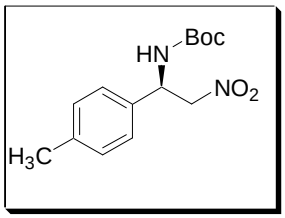


imine **55b** (0.22 g, 1 mmol). Yield 0.21 g (75%); white solid; m.p. 123-125 ºC $[\alpha]_D^{25}$ = – 47.0 (c 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3351, 2945, 1715, 1510; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (br s, 4H), 5.67 (d, 1H, *J* = 5.6 Hz), 5.19 (br s, 1H), 4.70 (d, 1H, *J* = 5.2 Hz), 2.48 (s, 3H), 1.44 (s, 9H);

^{13}C NMR (125MHz, $CDCl_3$) δ 154.7, 136.02, 136.0, 131.36, 128.69, 126.86, 125.02, 78.8, 49.5, 28.3, 19.19; Chiral HPLC (chiralcel OD column; hexane : iPrOH; 90:10; 1.0 mL/min 220nm) Rt_{major} = 18.37 min ,Rt_{minor} =34.31 min, 99% *ee*; Anal.calcd.$C_{14}H_{20}N_2O_4$ (280.32): C, 59.99; H, 7.19; N, 9.99. Found C, 59.97; H, 7.18; N 9.94.

(*R*)-*N*- (2-Nitro-1-*p*-tolyl-ethyl)-carbamic acid *tert*-butyl ester (62c)

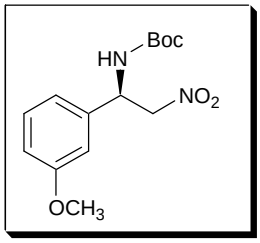
The title compound was prepared according to the general procedure starting from



imine **55c** (0.22 g, 1 mmol). Yield 0.25 g (90%); white solid; m.p. 99-100 ºC; $[\alpha]_D^{25}$ = – 30.4 (*c* =1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3320, 2998, 1698, 1578; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (br s, 2H), 7.19 (br s, 2H), 5.33 (br s, 1H), 5.21 (br s, 1H), 4.8 (m, 1H), 4.68 (m, 1H), 2.37 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 138.5, 133.8, 129.7, 126.1, 80.4, 78.8, 52.5, 28.4, 21.0; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220 nm) Rt_{major} = 12.01 min, Rt_{minor} =11.14 min, 92% *ee* (after crystallization from hexane 94% *ee*); Anal. calcd. for $C_{14}H_{22}N_2O_4$ (280.32): C, 59.99; H, 7.19; N, 9.99. Found: C, 59.98; H, 7.21; N, 10.00.

(*R*)-*N*-[3-Methoxy-phenyl)-2-nitro-ethyl]-carbamic acid *tert*-butyl ester (62d)

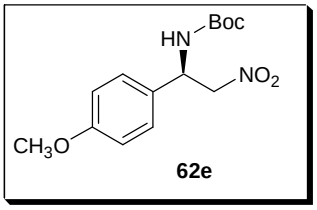
The title compound was prepared according to the general procedure starting from



imine **55d** (0.24 g, 1 mmol). Yield 0.237g (80%); White solid; m.p 99-100^{0}C; $[\alpha]_D^{25}$ = - 22.9 (c = 1.0, acetone); ^1H NMR (500MHz, $CDCl_3$) δ 7.3 (t, 1H, *J* =7.9 Hz), 6.89-6.82 (m, 3H), 5.3 (d, 1H, *J*=5.9 Hz), 5.23 (br s,1H), 4.82 (m, 1H), 4.68 (dd, 1H, *J*=5.5, 12.5 Hz), 3.70 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (300MHz, $CDCl_3$) δ 160.2, 154.7, 138.5, 130.3, 118.3, 112.4, 80.7, 78.8, 55.3, 52.8, 28.2; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10, 1.0mL/min, 220 nm) (R)t_r = 23.5 min, (S)t_r =16 min, 90% *ee* (after crystallization from hexane, 99% *ee*); Anal. calcd. For $C_{14}H_{20}N_2O_5$ (296.14): C, 56.7; H, 6.8; N, 9.45. Found: C, 57.1; H, 6.8; N, 9.3%.

(*R*)-*N*-[1-(4-Methoxy-phenyl)-2-nitro-ethyl]-carbamic acid *tert*-butyl ester (62e)

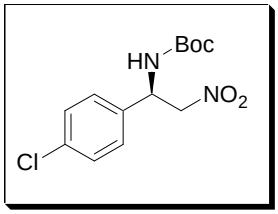
The title compound was prepared according to the general procedure starting from imine **55e** (0.24 g, 1 mmol). Yield 0.27 g (91%); white solid; m.p. 115-116 ºC, $[\alpha]_D^{25}$ = -15.3 (*c* =0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3320, 2945, 1689, 1548; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 2H, *J* =8.5 Hz), 6.89 (d, 2H, *J* =8.6 Hz), 5.29 (br s, 1H), 4.84 (br s, 1H), 5.65 (m, 1H), 4.47 (m, 1H), 3.8 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 154.2, 127.5, 114.4, 81.5, 78.8, 55.1, 28.1; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 0.8 mL/min 220nm) Rt_{major} = 19.88 min, Rt_{minor} =17.98 min, 91% *ee*; Anal. calcd. for $C_{14}H_{20}N_2O_5$ (296.32): C, 56.75; H, 6.80; N, 9.45. Found: C, 56.73; H, 6.82; N, 9.45.



62e

(*R*)-*N*-[1-(4-Chloro-phenyl)-2-nitro-ethyl]-carbamic acid *tert*-butyl ester (62f)

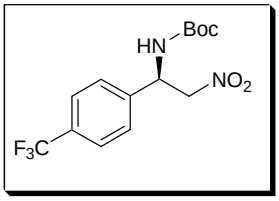
The title compound was prepared according to the general procedure starting from imine **55f** (0.24 g, 1 mmol). Yield 0.29 g (97%); white solid; m.p. 121-123 ºC; $[\alpha]_D^{25}$ = – 25.0 (*c* =0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3368, 2956, 1704, 1540; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, 2H, *J* = 1.5 Hz), 7.37 (br s, 1H), 7.30 (br s, 2H), 5.43 (m, 1H), 4.85 (m, 1H), 4.74 (m, 1H), 4.68 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 135.5, 134.7, 129.4, 127.9, 81.0, 78.8, 52.3, 28.3; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220 nm) Rt_{major} = 15.54 min, Rt_{minor} = 11.8 min, 96% (after crystallization from hexane 98% *ee*); Anal. calcd. for $C_{13}H_{17}ClN_2O_4$ (300.75): C, 59.92; H, 5.70; N, 9.30. Found: C, 59.94; H, 5.68; N, 9.32.



(*R*)-*N*-[2-Nitro-1-(4-trifluoromethyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (62g)

The title compound was prepared according to the general procedure starting from imine **55g** (0.27 g, 1 mmol). Yield 0.33 g (98%); white solid (ethyl acetate/hexane); m.p. 121-123 ºC; $[\alpha]_D^{25}$ = –13.2 (c=1.0, acetone); IR (KBr, cm^{-1}) 3368, 2896, 1658,

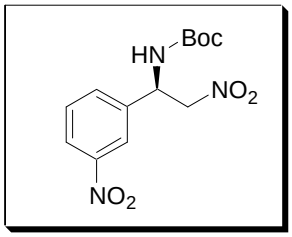
1540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* =8.2 Hz), 7.45 (d, 2H, *J* = 8.1 Hz),



5.5 (br s,1H), 5.45 (br s, 1H), 4.87 (m, 1H), 4.73 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 141.0, 126.8, 126.4, 126.2, 81.1, 78.6, 52.3, 28.2; Chiral HPLC (chiralpak AD column; hexane:iPrOH 90:10; 1.0 mL/min, 220nm) Rt_{major} = 16.59 min, Rt_{minor} =13.32 min, 92% *ee* (after crystallization from hexane 94% *ee*); Anal. calcd. for $C_{14}H_{17}F_3N_2O_4$ (334.11): C, 50.3; H, 5.1; N, 8.4. Found: C, 50.8; H, 5.3; N, 8.0.

(*R*)-*N*-2-Nitro-1-(3-nitro-phenyl)-ethyl-carbamic acid tert-butyl ester (62h)

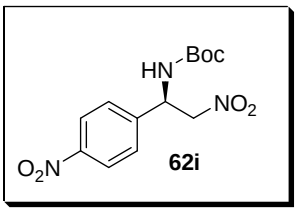
The title compound was prepared according to the general procedure starting from



imine **55h** (0.25 g, 1 mmol). Yield 0.18 g (59%); white solid; m.p. 134-135 ºC $[\alpha]_D^{25}$ = – 29.2 (*c* = 1.0, acetone) (Lit. m.p: 140-142ºC, 95% *ee*); IR (KBr, cm^{-1}) 3346, 2899, 1670, 1560; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23–8.21 (m, 2H), 7.70 (d, 2H, *J* = 7.8 Hz), 7.60 (dd, 1H. *J* = 7.8, 8.5 Hz), 5.60 (d, 1H, *J* =7.5 Hz), 5.48 (d, 1H, *J* =5.4 Hz), 4.89 (m, 1H), 4.80 (dd, 1H, *J* =13.3, 4.3 Hz), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 148.3, 139.5, 132.5, 130.8, 123.5, 121.6, 81.5, 78.4, 52.4, 28.4; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220nm) Rt_{major} = 44.12 min , Rt_{minor} = 28.25 min, 90% *ee* (92% *ee* after crystallization from hexane); Anal. calcd. for $C_{13}H_{17}N_3O_6$ (311.29): C, 50.16; H, 5.50; N, 13.50. Found: C, 50.16; H, 5.51; N, 13.50.

(*R*)-*N*-2-Nitro-1-(4-nitro-phenyl)-ethyl-carbamic acid tert-butyl ester (62i)

The title compound was prepared according to the general procedure starting from

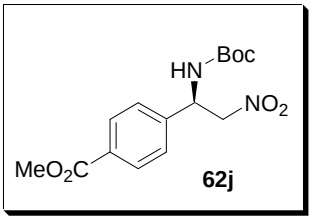


imine **55i** (0.25 g, 1 mmol). Yield 0.20 g (65%); yellow solid; m.p. 133-134 ºC $[\alpha]_D^{25}$ = –16.5 (*c*=1.0, acetone) (Lit.[3] m.p. 132-134 ºC, 82% *ee*); IR (KBr, cm^{-1}) 3323, 2978, 2798, 1709, 1568; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, 2H, *J* = 8.5 Hz), 7.54 (d, 2H, *J*= 8.5 Hz,), 5.55 (br s, 1H), 5.43 (br s, 1H), 4.89 (m, 1H), 4.76 (dd, 1H, *J* =13.0, 4.3 Hz), 1.43 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 144.3, 127.0, 124.5, 81.5, 78.4, 52.7, 28.3; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220nm) Rt_{major} = 46.5 min, Rt_{minor} = 21.27 min, 87% *ee*; Anal. calcd. for $C_{13}H_{17}N_3O_6$ (311.29): C, 50.16; H, 5.50; N, 13.50. Found: C, 50.17; H, 5.50; N, 13.49.

(*R*)-*N*-4-(1-tert-Butoxycarbonylamino-2-nitro-ethyl)-benzoic acid methyl ester (62j)

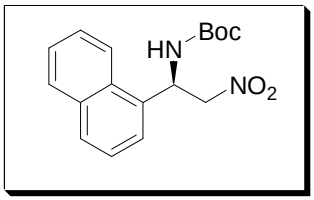
The title compound was prepared according to the general procedure starting from imine **55j** (263 mg, 1mmol). Yield 205 mg (78%); white solid; m.p 166-168 ^{0}C (ethyl acetate/hexane); $[\alpha]_D^{25}$ = – 28.6 (c=0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3220, 2941, 1682, 1670, 1548; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, 2H, *J* = 8.0 Hz), 7.4 (d, 2H, *J* = 8.5 Hz), 5.4 (br s, 2H), 4.86 (br s, 1H), 4.74 (d, 1H, *J* = 12.5 Hz), 3.92 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 155.1, 142.3, 130.9, 130.8, 126.8, 81.4, 78.9, 52.6, 28.6. Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220nm) Rt_{major} = 24.06 min, Rt_{minor} = 18.05 min, 94%ee; Anal. calcd. for $C_{15}H_{20}N_2O_6$ (324.13): C, 55.55; H, 6.22; N, 8.64. Found: C, 55.53; H, 6.21; N, 8.62.



62j

(*R*)-*N*- (1-Naphthalen-1-yl-2-nitro-ethyl)-carbamic acid *tert*-butyl ester (62k)

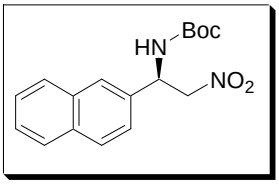
The title compound was prepared according to the general procedure starting from imine **55k** (0.25 g, 1 mmol). Yield 0.15 g (95%); white solid; m.p. 153-154 ºC $[\alpha]_D^{20}$ = -11.6 (*c* =0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3360, 2917, 1709, 1549; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, 1H, *J* =8.2 Hz), 7.9-7.85 (m, 2H), 7.68-7.53 (m, 2H), 7.48 (d, 2H, *J* =5 Hz), 6.32 (m, 1H), 5.43 (d, 1H, *J* =7.8 Hz), 4.90 (d, 2H, *J* =5.8 Hz), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 134.1, 132.6, 130.3, 129.6, 129.3, 127.3, 126.4, 125.3, 123.3, 122.2, 80.8, 78.4, 49.3, 28.3; Chiral HPLC (chiralpak IA column; hexane:iPrOH 90:10; 1.0 mL/min, 220nm) Rt_{major} = 19.28 min, Rt_{minor} =13.58 min, 94% *ee* (after



crystallization from hexane, 98% *ee*); Anal. calcd. for $C_{17}H_{20}N_2O_4$ (316.35): C, 65.54; H, 6.37; N, 8.86. Found: C, 65.49; H, 6.36; N, 8.86.

(*R*)-*N*- (1-Naphthalen-2-yl-2-nitro-ethyl)-carbamic acid *tert*-butyl ester (62l)

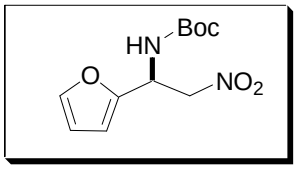
The title compound was prepared according to the general procedure starting from



imine **55l** (0.25 g, 1 mmol). Yield 0.24 g (70%); white solid; m.p 141-143 ºC $[\alpha]_D^{25}$ = -46.8 (*c* = 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3348, 2970, 1728, 1498; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.88-7.79 (m, 2H), 7.56-7.44 (m, 2H), 7.40 (d, 1H, *J* = 4 Hz), 5.56 (m, 1H), 5.53 (br s, 1H), 4.96-4.84 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 134.3, 133.3, 133.2, 129.3, 128.1, 127.8, 126.8, 126.7, 125.7, 123.9, 80.8, 78.9, 53.1, 28.3; Chiral HPLC (chiralcel OD column; hexane:iPrOH; 80:20; 1.0 mL/min, 220nm) Rt_{major} = 46.78 min, Rt_{minor} = 35.38 min, 93% *ee*; Anal. calcd. for $C_{17}H_{20}N_2O_4$ (316.35): C, 65.54; H, 6.37; N, 8.86. Found: C, 65.55; H, 6.38; N, 8.87.

(*R*)-*N*- (1-Furan-2-yl-2-nitro-ethyl)-carbamic acid tert-butyl ester (62n)

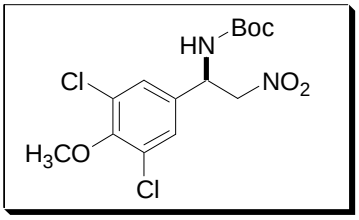
The title compound was prepared according to the general procedure starting from



imine **55n** (0.2 g, 1 mmol). Yield 0.25 g (96%); white solid; IR (KBr, cm^{-1}) 3323, 2978, 2798, 1709, 1568; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.2. (d, 1H, *J* = 8.5 Hz), 6.26-6.06 (m, 2H), 5.55 (br s,1H), 5.43 (br s, 1H), 4.89 (m, 1H), 4.76 (dd, 1H, *J* =13.0, 4.3 Hz), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160, 140.2, 110.3, 105.0, 81.5, 78.4, 50.7, 28.3; Chiral HPLC (chiralpak OD column; hexane:iPrOH 85:15; 1.0 mL/min, 220nm) Rt_{major} = 26.5 min, Rt_{minor} =33.8 min, 66% *ee*; Anal. calcd. for $C_{11}H_{16}N_2O_5$ (256.26): C, 51.56; H, 6.29; N, 10.93. Found: C, 51.17; H, 6.50; N, 11.

(*R*)-*N*- [1-(3,5-Dichloro-4-methoxy-phenyl)-2-nitro-ethyl]-carbamic acid *tert*-butyl ester (62m)

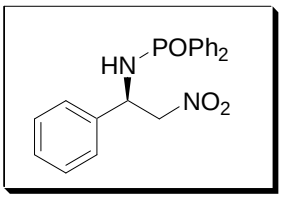
The title compound was prepared according to the general procedure starting from the



imine **55m** (0.30 g, 1 mmol). Yield 0.24 g (66%); white solid; m.p. 153-155 ºC $[\alpha]_D^{25}$ = – 24.2 (c, 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3248, 2900, 1704, 1445; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 2H), 5.6 (br s, 1H), 5.3 (br s, 1H), 4.7 (m, 2H), 3.8 (s, 3H),1.44 (s, 9H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 152.4, 134.7, 130.16, 127.04, 126.59, 81.2, 80.95, 60.85, 28.3; Chiral HPLC (chiralcel OD column; hexane : iPrOH; 90:10; 1.0 mL/min 220nm) Rt_{major} = 10.5 min ,Rt_{minor} =8.29 min, 87% *ee* (after single crystallization from ethylacetate/hexane, 95% *ee*); Analysis calc. for $C_{14}H_{18}Cl_2N_2O_5$ (365.21): C, 46.04; H, 4.97; N, 7.67. Found: C, 46.0; H, 4.99; N 7.68.

(*R*)-*N*- (2-Nitro-1-phenyl-ethyl)- *P,P*-Diphenyl- phosphinic amide (57)

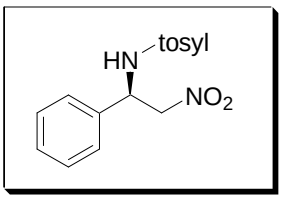
The title compound was prepared according to the general procedure starting from the



imine **50** (0.30 g, 1 mmol) at room temperature. Yield >99% conversion. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93-7.67 (m, 4H), 7.59-7.67 (m, 11H), 4.97-4.77 (m, 3H), 4.36 (dd, 1H, *J*=8.2, 7.3Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.9, 132.4, 132.36, 132.3, 131.8, 131.7, 131.3, 130.8, 129.1, 128.7, 128.6, 128.5, 126.4, 80.8, 80.7, 53.3, 53.2. Chiral HPLC (chiralcel OD column; hexane : iPrOH; 90:10; 1.0 mL/min 220nm) Rt_{major} = 10.5 min ,Rt_{minor} =8.29 min, 0% *ee*

(*R*)-*N*-4-Methyl-N-(2-nitro-1-phenyl-ethyl)-benzenesulfonamide (60)

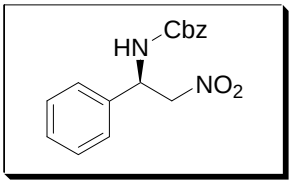
The title compound was prepared according to the general procedure starting from



imine **53** (0.26 g, 1 mmol). Yield 0.31 g (97%); off-white solid. m. p 155-157ºC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J*= 8.3Hz), 7.27-7.24 (m, 5H), 7.10 (d, 2H, *J* = 8.3 Hz), 5.5 (d, 1H, *J* = 7.4 Hz), 4.99 (m, 1H), 4.84 (dd, 1H, *J*=13.1, 6.6Hz), 4.66 (dd, 1H, J=13.1Hz, 6.34Hz), 2.40 (s, 3H); 30% *ee*

(*R*)-*N*- (2-Nitro-1-phenyl-ethyl)-carbamic acid benzyl ester (61)

The title compound was prepared according to the general procedure starting from

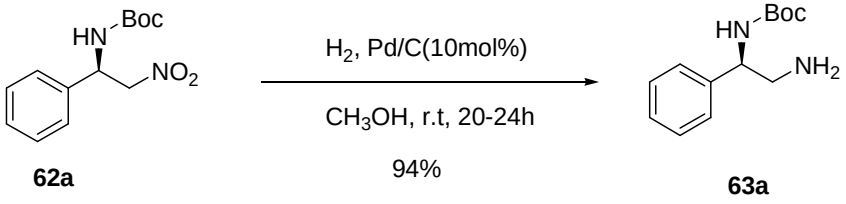


imine **54** (0.24 g, 1 mmol). Yield 0.26g (86%); white solid; m.p. 67-70 ºC $[\alpha]_D^{25}$ = -9.2 (*c* =1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3368, 2987, 1704, 1529; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.31 (m, 10H), 5.9 (d, 1H, *J* = 7.5 Hz), 5.48 (d, 1H, *J* =6.0 Hz), 5.1 (d, 2H, *J* =2.0 Hz), 4.88 (br s, 1H), 4.65 (d, 1H, *J*= 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 136.7, 135.9, 129.2, 129.05, 128.7, 128.6, 128.3, 128.1, 126.4, 125.8, 78.5, 67.4, 53.3. Chiral HPLC (chiralpak IA column; hexane:iPrOH 85:15; 1.0 mL/min, 220nm) Rt_{major} = 23.01 min, Rt_{minor} = 17.1min, 82% *ee*; Anal. calcd. for $C_{16}H_{16}N_2O_4$ (300.35): C, 63.99; H, 5.39; N, 9.33. Found: C, 63.94; H, 5.40; N, 9.32.

7. 7. 3 Elaboration of the aza-Henry adducts

A) To 1, 2-diamine

(2-Amino-1-phenyl-ethyl)-carbamic acid *tert*-butyl ester



62a **63a**

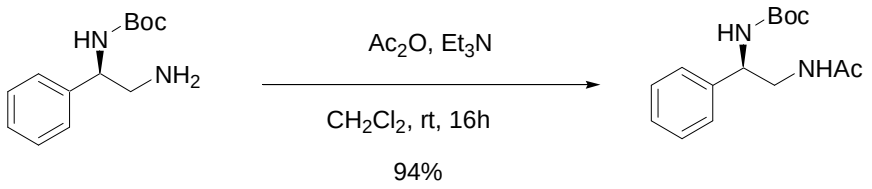
According to procedure developed by Stanfield and coworkers (Ref. below): To a solution of **62a** (0. 27 g, 1 mmol) in methanol (3 mL) was added activated Pd(C) (10%, 0.027 g) and the mixture was kept under hydrogen atmosphere at RT until the starting material dissapeared. The resulting suspension was filtered through a short pad of celite, and the solution concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate/hexane mixtures as the eluant. Yield 0.222 g (94%); Yellow oil; $[\alpha]_D^{25}$ = – 43.6 (*c* =1.1, $CHCl_3$), [Lit.[225] $[\alpha]_D^{25}$ = – 44 (*c* =1.1, $CHCl_3$)]. ^1H NMR (200 MHz, $CDCl_3$) δ 7.33-7.29 (m, 5H),

[225] P. H O'Brien, D. R. Sliskovic, C. J. Blankley, B. Roth, W. Wilson, K. L. Hamelehle, B. R. Krause, R. L. Stanfield, *J. Med. Chem*. **1994**, *37*, 1810-1822.

6.10 (br s, 1H), 5.43 (br s, 1H), 4.8 (br s,1H), 3.60 (m, 2H), 2.01 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.1, 139.7, 128.8, 128.5, 127.8, 126.4, 79.8, 55.3, 45.5, 29.7, 28.3, 23.1; All other spectroscopic data were coincident with published data.

Acetylation :

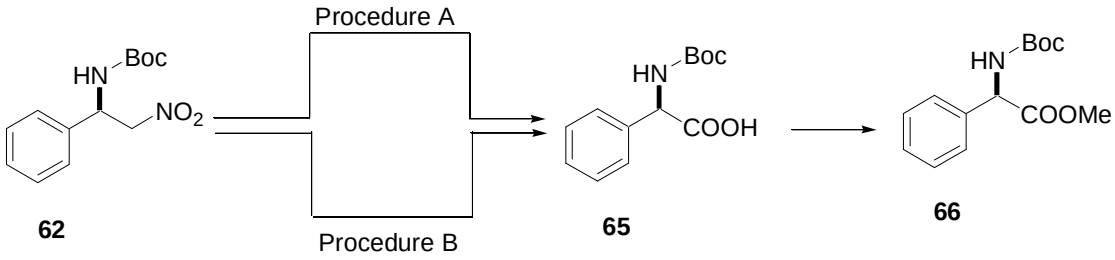
(2-Acetylamino-1-phenyl-ethyl)-carbamic acid *tert*-butyl ester (64a)



63a **64a**

To a solution of *N*-Boc diamine **63a** (0.12 g, 0.5 mmol) in dichloromethane (1 mL) were successively added acetic anhydride (0.08 mL, 0.7 mmol) and triethylamine (0.12 mL, 0.8 mmol). The resulting solution was stirred for 16 h at room temperature under a nitrogen atmosphere, quenched with 0.1M HCl (2 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography using ethyl acetate/hexane mixtures as the eluant, and recrystallisation from hexane/dichloromethane afforded the title compound **64a**. Yield 0.13 g (94%); m.p. 180-181 ºC; $[\alpha]_D^{20}$ = -49.4 (*c* =1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.33-7.29 (m, 5H), 6.10 (br s,1H), 5.43 (br s, 1H), 4.8 (br s, 1H), 3.60 (m, 2H), 2.01 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.1, 139.7, 128.8, 128.5, 127.8, 126.4, 79.8, 55.3, 45.5, 29.7, 28.3, 23.1; Chiral HPLC (chiralpak IA column; hexane:iPrOH 95:05; 0.5 mL/min, 220nm) Rt_{major} = 27.4 min, Rt_{minor} =23.6 min, 97% *ee* (>99% *ee* after washing with hot hexane); Anal. calcd. for $C_{15}H_{22}N_2O_3$ (278.35): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.73; H, 7.96; N, 10.1.

B) To Acids and esters



Procedure A.

The method developed by Petrini was employed:[226]

Nitroderivative **62a** (1 mmol, 97%ee) dissolved in ^{t}BuOH(8mL) was treated with aqueous buffered KOH (0.5 M in KOH and 1.25 M in K_2HPO_4, 6mL) at room temperature. The mixture was stirred for 5mins and then aqueous $KMnO_4$ (0.5 M, 2 mL, 4 mmol) was added dropwise mailtaineing the temperature below 25ºC by occasional cooling. After cooling at room temperature for 1h the mixture was cooled by ice bath and then saturated Na_2SO_3 (10 mL) was added. The mixture was then acidified with 2M HCl until pH~5 and then extracted with ethylacetate (4 x 15 mL). The crude carboxylic acid **65a** was dissolved in a mixture of methanol (0.84 mL) and benzene (8.4 mL), and the resulting solution was treated with trimethylsilyl diazomethane (2M solution in hexane, 0.5 mL, 1 mmol) and stirred for 20min at room temperature. The solution was concentrated under reduced pressure to get compound N-Bocphenylglycine **66a** which was purified by flash column chromatography (eluent: ethyl acetate/hexane). Yield 65% with 60% ee.

Procedure B:

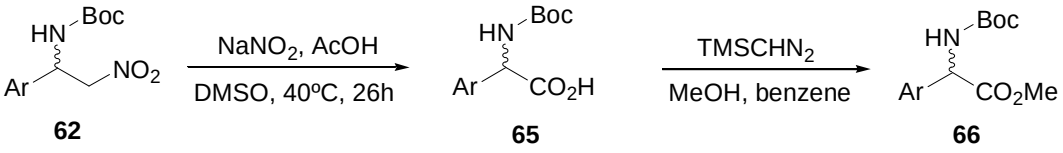
The method of Mioskowski[227] was employed: A solution of nitro compound **62** (0.67 mmol), sodium nitrite (2.0 mmol), and acetic acid (0.4 mL, 10 mmol) in DMSO (5 mL) was heated at 40ºC for 24h. After cooling at RT, 1N HCl (10 mL) was added and the aqueous phase was extracted with dichloromethane, dried over $MgSO_4$,

[226] E. Foresti, G. Palmieri, M Petrini, R. Profeta, *Org. Biomol. Chem.*, **2003**, *1*, 4275-4281.
[227] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234-235

and concentrated under reduced pressure. The crude carboxylic acid **65** was dissolved in a mixture of methanol (0.84 mL) and benzene (8.4 mL), and the resulting solution was treated with trimethylsilyl diazomethane (2M solution in hexane, 0.5 mL, 1 mmol) and stirred for 20min at RT. The solution was concentrated under reduced pressure to get compound **66**, which was purified by flash column chromatography (eluent: ethyl acetate/hexane).

Preparation of racemic samples

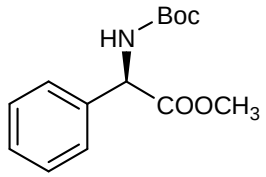
Racemic compound **66** was prepared from the corresponding racemic adduct **62** according to the general procedure described in B.



62 **65** **66**

tert-Butoxycarbonylamino-phenyl-acetic acid methyl ester (66a)

The title compound was prepared following general procedure **B** starting from **62a**

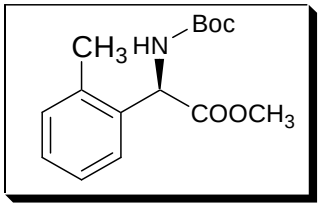


(266mg, 1 mmol, 97%ee).Yield 212 mg (80%); white solid; mp-101-103ºC; IR (KBr, cm^{-1}) 2980, 1705, 1680, 1560; $[\alpha]_D^{25}$ = –104.9 (*c* = 0.65, CH_3OH) (optical rotation of authentic material prepared from commercial (*S*)–phenylglycine: $[\alpha]_D^{25}$ = + 104.46 (*c* =0.65, CH_3OH)); ^1H NMR (200 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.68 (br s, 1H), 5.36 (br s, 1H), 3.7 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (50MHz, $CDCl_3$) δ 171.7, 154.9, 136.9, 128.9, 128.7, 128.5, 127.2, 80.2, 57.7, 52.8, 28.4; Chiral HPLC (Chiralcel OD, hexane:iPrOH, 99:01, 0.4 mL/min, 210nm), Rt_{major} = 21.56min, Rt_{minor} = 26.21min, 97% *ee* (after one recrystallisation from hot hexane, *ee*>99%). [Lit[228] m.p. 102-103ºC, $[\alpha]_D^{20}$ = - 105.0º (*c* =1.09, CH_3OH)].

[228] N. Matsunaga, H. Harada, T. Aoyama, T. Shioiri, *Heterocycles* **1992**, *33*, 235-255.

tert-Butoxycarbonylamino-o-tolyl-acetic acid methyl ester (66b)

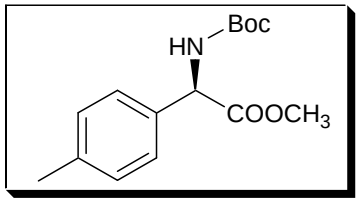
The title compound was prepared following general procedure **B** starting from **62b**



(69 mg, 0.25 mmol, 99%ee). yield: (45 mg, 75%), IR (KBr, cm-1) 2970, 1710, 1685,1530; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.15 (m, 4H), 5.65(d, 1H, *J* =15Hz), 5.4 (d, 1H, J=15Hz), 3.75 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 156.1, 137.6, 134.4, 128.8, 127.2, 80.2, 57.7, 52.8, 28.7, 21.5. Chiral HPLC (chiralpak IA column; hexane : iPrOH 98:02; 0.5 mL/min 220nm) Rt_{major} = 22.54 min ,Rt_{minor} = 26.08 min, 99%ee.

tert-Butoxycarbonylamino-p-tolyl-acetic acid methyl ester (66c)

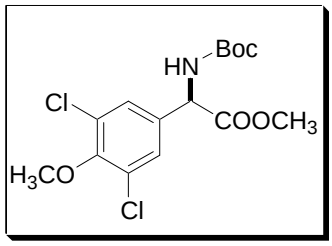
The title compound was prepared following general procedure **B** starting from **62c**



(69mg, 0.25mmol, 92%ee). yield: (39mg, 65%), IR (KBr, cm-1) 2980, 1705, 1680, 1560 ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.15 (m, 4H), 5.55 (d, 1H, *J* = 13.5Hz), 5.3 (d, 1H, *J* = 17Hz), 3.72 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.2, 155.2, 138.6, 134.4, 129.8, 127.2, 80.2, 57.7, 52.8, 28.7, 21.5. Chiral HPLC (chiralpak IA column; hexane:iPrOH 98:02; 0.5 mL/min 220nm) Rt_{major} = 29.57 min, Rt_{minor} = 27.42 min, 93% ee.

tert-Butoxycarbonylamino-(3,5-dichloro-4-methoxy-phenyl)-acetic acid methyl ester (66m)

The title compound was prepared following general procedure **B** starting from **62m**

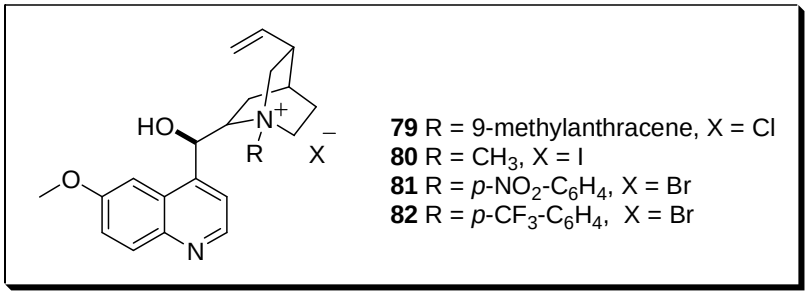


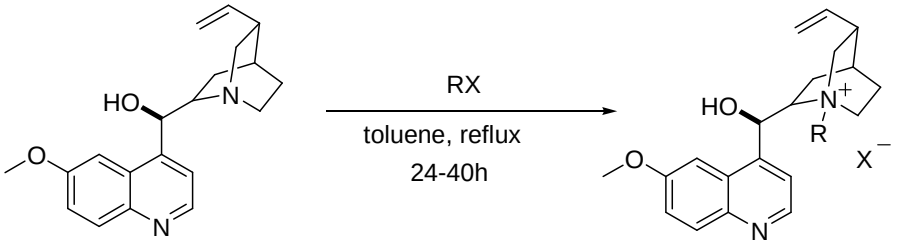
(70 mg, 0.19 mmol, 95%ee).Yield 50 mg, 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 2H), 5.59 (br s, 1H), 5.16 (br s, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.7, 162.2, 157.9, , 134.6, 129.7, 127.2, 80.2, 59.7, 53.1, 52.2 28.4. Chiral HPLC (Chiralcel OD, hexane: iPrOH, 99:01, 0.4 mL/min 220nm), 30%ee.

7. 8 Mannich reaction

7. 8. 1 Preparation of organocatalysts

(According to the described method by Shioiri and coworkers) [229]





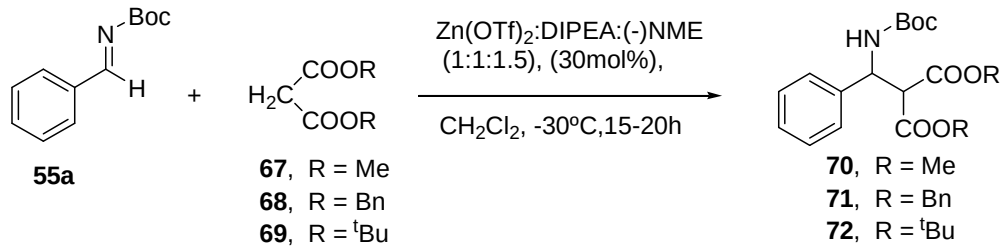
A mixture of quinine (3.24 g, 10 mmol) and the corresponding benzyl halide (10 mmol) in THF (40 mL) was refluxed. The precipitated solid was filtered, washed with benzene and recrystallised from methanol to give the pure compound.

The compound thus obtained showed identical physical and spectroscopic data that published.[230]

[229] (a) S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shioiri, *Tetrahedron*, **2002**, *58*, 1623-1630.
[230] (a) T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hebrault, *Org. Lett.***2000**, *2*, 2959-2962; (b) B.lygo, P. G. Wainwright, *Tetrahedron Lett*. **1998**, *39*, 1599-1602; (c) T. Ooi, M. Kameda, k. Maruoka, *J. Am. Chem. Soc*. **2003**, *125*, 5139-5155.

7. 8. 2 General procedures for asymmetric Mannich reaction

Procedure A:



55a

67, R = Me
68, R = Bn
69, R = ^{t}Bu

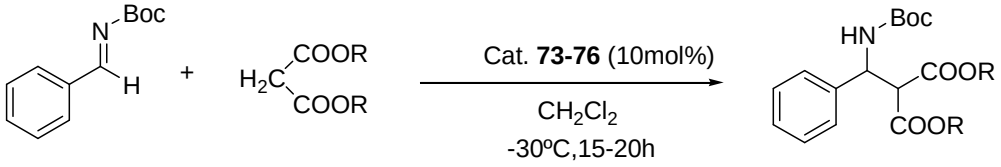
70, R = Me
71, R = Bn
72, R = ^{t}Bu

Diisopropylethylamine (0.054 mL, 0.3 mmol) was added dropwise to a solution of previously dried $Zn(OTf)_2$ (0.109 g, 0.3 mmol) and dialkyl malonate (3 mmol) in anhydrous CH_2Cl_2 (2 mL) under a nitrogen atmosphere and the mixture was stirred at 25-30 ºC for 1h. The reaction mixture after addition of (-)-(1*R*, 2*S*)-*N*-methylephedrine (0.081 g, 0.45 mmol), the resulting mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was then kept for 10 min at -30°C, and subsequently the corresponding aromatic aldimine (1 mmol) was added and the reaction mixture stirred for 16-20 h at that temperature. The reaction was quenched with 0.1M HCl (3 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Reaction Conversion was determined by NMR and the crude product was used for ee determination.

The compound thus obtained showed identical spectroscopic data than that published.[231]

[231] J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc*. **2006**, *128*, 6048-6049.

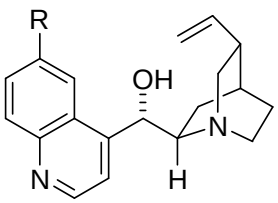
Procedure B:



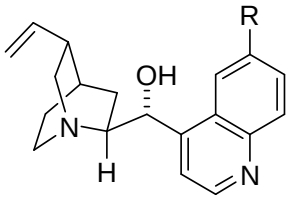
55a

67, R = Me
68, R = Bn
69, R = tBu

70, R = Me
71, R = Bn
72, R = tBu



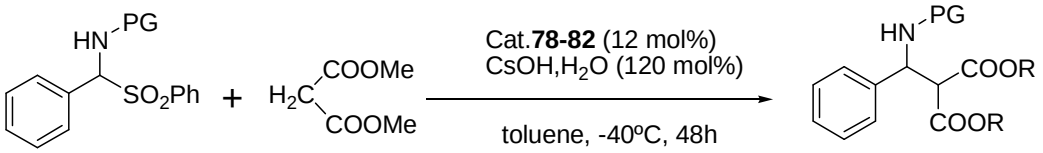
73 R=H, cinchonine
74 R=OCH_3,Quinidine



75 R=H, cinchonidine
76 R=OCH_3,Quinine

To a solution of the corresponding dialkyl malonate or malononitrile compound (300 mmol%) in dichloromethane (2 mL) under a nitrogen atmosphere was added cinchona alkaloid catalyst (10 mol %) and stirred at 25-30 ºC for 30min. The reaction mixture was then kept for 20 min at -30ºC, and subsequently imine **55a** was added and the reaction mixture stirred for 40-48 h at that temperature. The reaction was quenched with 0.1M HCl (3 mL), extracted with dichloromethane (3 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Reaction Conversion was determined by NMR and ee was determined on the crude product using a chirlpak IA column.

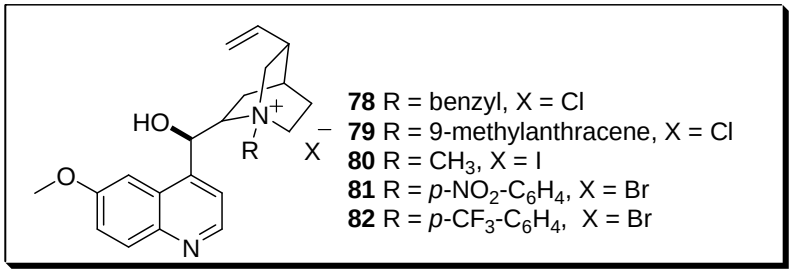
Procedure C:



83 PG = Boc
84 PG = Cbz
85 PG = Ts

67

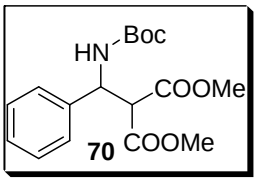
70 PG = Boc
86 PG = Cbz
77 PG =Ts



78 R = benzyl, X = Cl
79 R = 9-methylanthracene, X = Cl
80 R = CH_3, X = I
81 R = *p*-NO_2-C_6H_4, X = Br
82 R = *p*-CF_3-C_6H_4, X = Br

To a solution of the corresponding dialkyl malonate or active methylene compounds (3 mmol) in anhydrous toluene (3 mL) under a nitrogen atmosphere was added the corresponding α-amido sulfone (1mmol) and the corresponding catalyst (**78-82**) (12 mol %) and stirred at 25-30 ºC for 30min. The reaction mixture was then kept for 20 min at -40°C, and subsequently base CsOH, H_2O (120 mmol%) was added and the reaction mixture stirred for 40-48 h at -40ºC temperature. The reaction was quenched with 0.1M HCl (3 mL), extracted with dichloromethane (3 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Reaction Conversion was determined by NMR and ee was determined on the crude product using a chirlpak IA column.

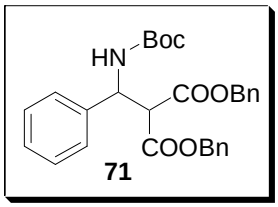
2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester (**70**)



70

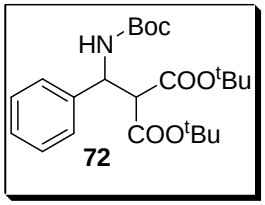
The title compound was obtained using general procedure B. Conversion >99%. Chiral HPLC (Chiralpak IA column; iPrOH:hexane 30:70; 0.6 mL/min, 210 nm, Rt = 19.9 min, Rt =16.5 min, ee 79%.

2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid dibenzyl ester (**71**)



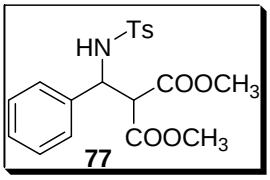
The title compound was obtained using general procedure B. Conversion >94%.Chiral HPLC (Chiralpak IA column; iPrOH:hexane 20:80; 0.6 mL/min, 210 nm, Rt = 34.06 min, Rt =41.05 min, ee 89%.

2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid ditertbutyl ester (**72**)



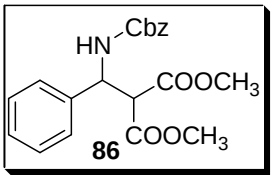
The title compound was obtained using general procedure A. Conversion >95%.Chiral HPLC (Chiralpak IA column; iPrOH:hexane 20:80; 0.5 mL/min, 210 nm, Rt = 14.8 min, Rt = 24.89 min, ee 72%

2-[Phenyl-(toluene-4-sulfonylamino)-methyl]-malonic acid dimethyl ester (**77**)



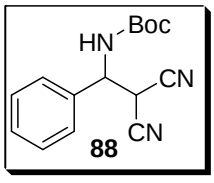
The title compound was obtained using general procedure C. Conversion >99%.Chiral HPLC (Chiralpak IA column; iPrOH:hexane 10:90; 0.5 mL/min, 210 nm, Rt = 49.6 min, Rt = 55.8 min, ee 41%.

2-(Benzyloxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester (**86**)



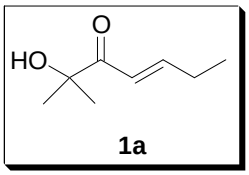
The title compound was obtained using general procedure B. Conversion 60%.Chiral HPLC (Chiralpak IA column; iPrOH:hexane 25:75; 1.0 mL/min, 210 nm, Rt = 19.8 min, Rt = 28.59 min, ee 0%.

(2,2-Dicyano-1-phenyl-ethyl)-carbamic acid tert-butyl ester (**88**)



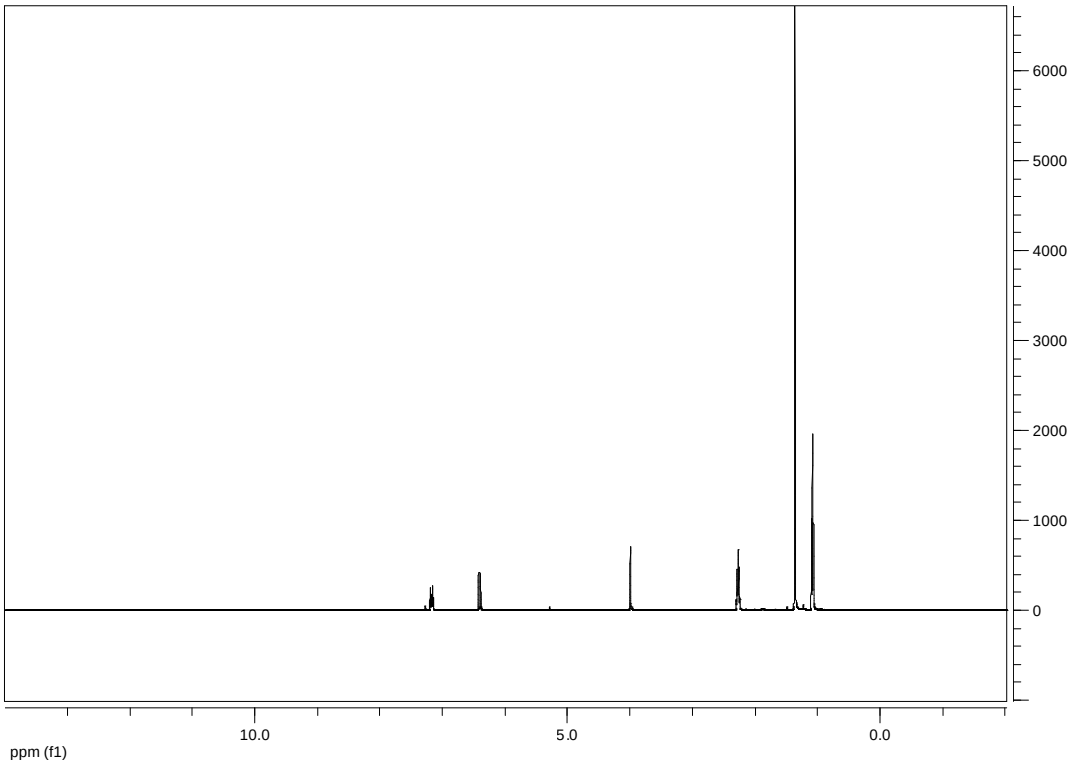
The title compound was obtained using general procedure C. Conversion >99%.Chiral HPLC (Chiralcel OD column; iPrOH:hexane 10:90; 1.0 mL/min, 210 nm, Rt = 18.1 min, Rt = 35.8min, ee 35%.

Apendix I

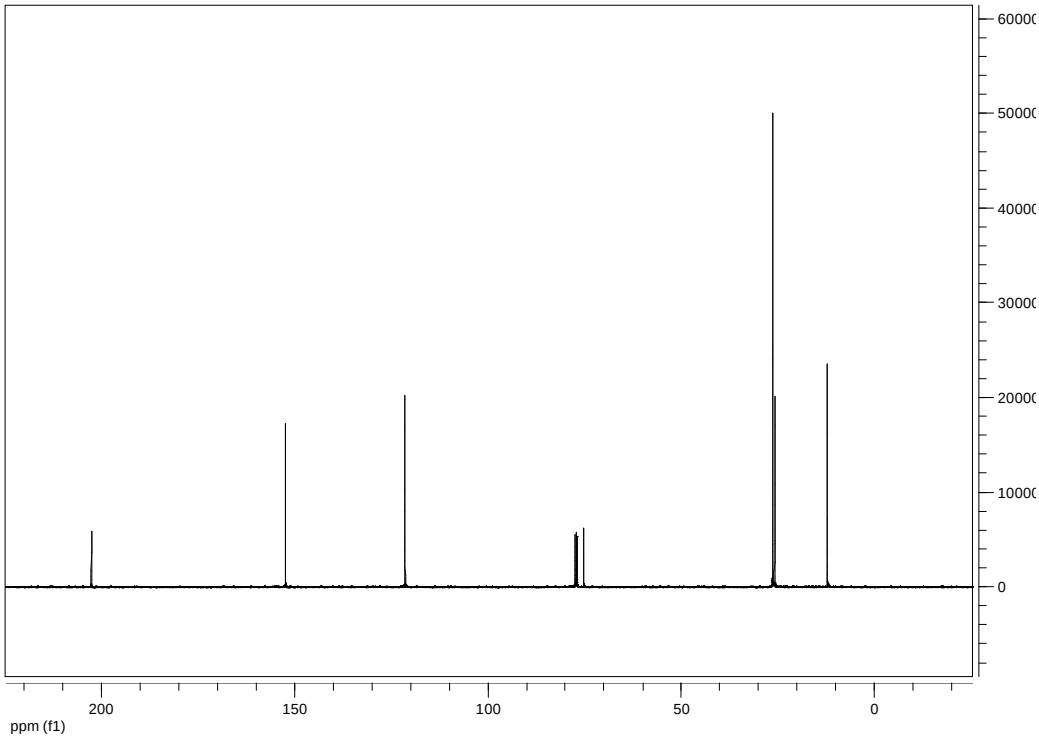


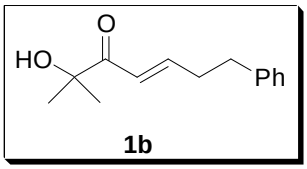
1a

^{1}H NMR



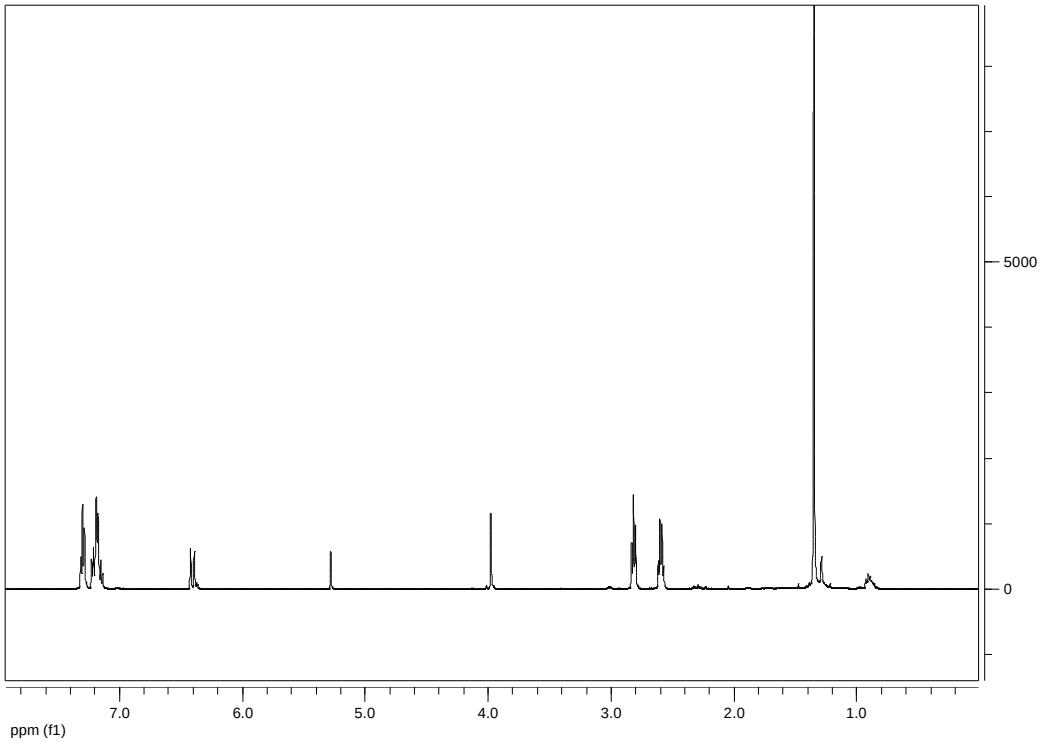
^{13}C NMR



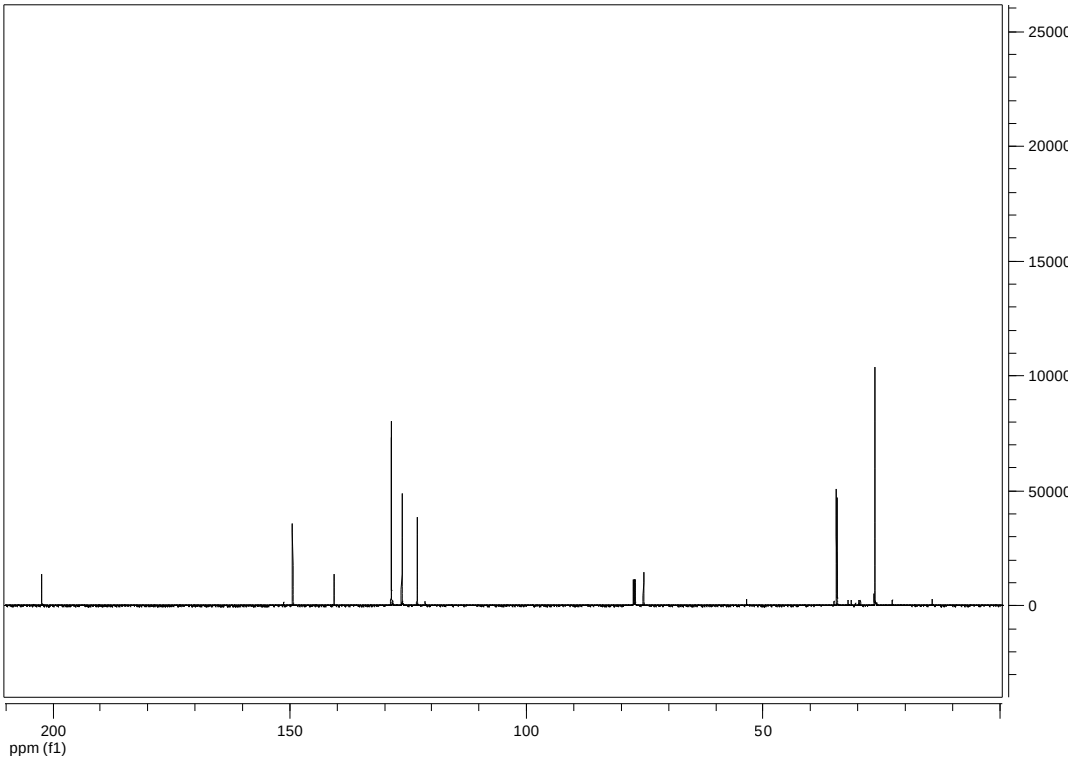


1b

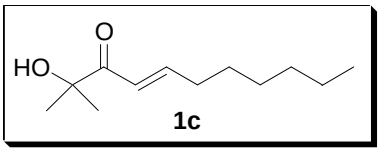
^{1}H NMR



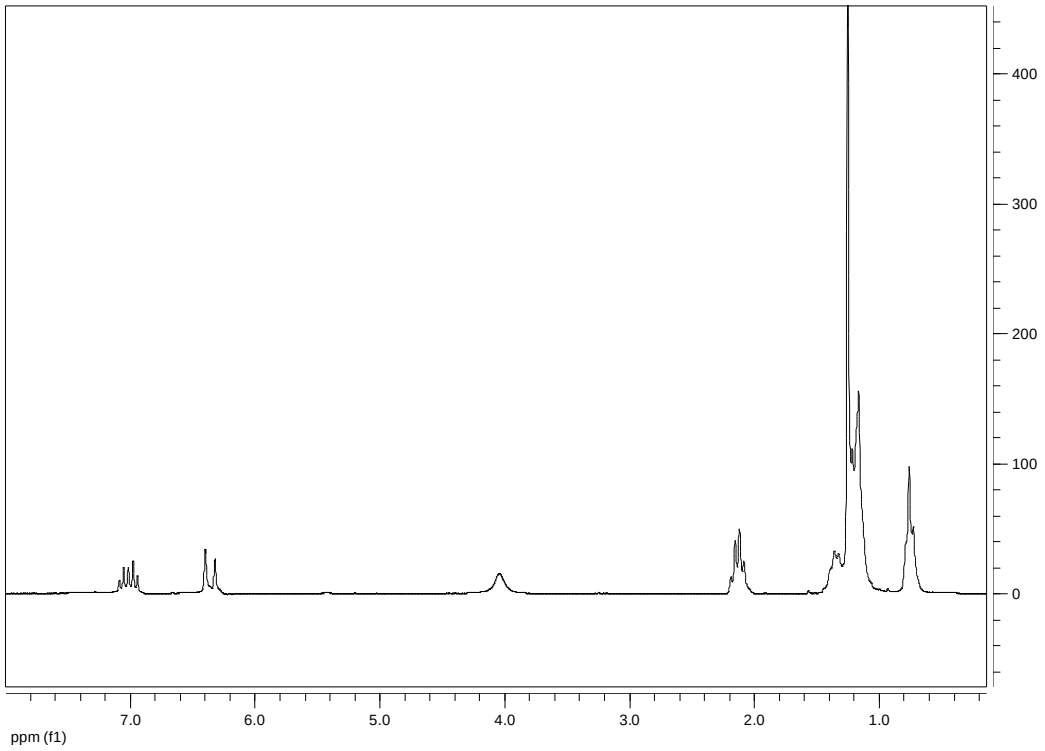
^{13}C NMR



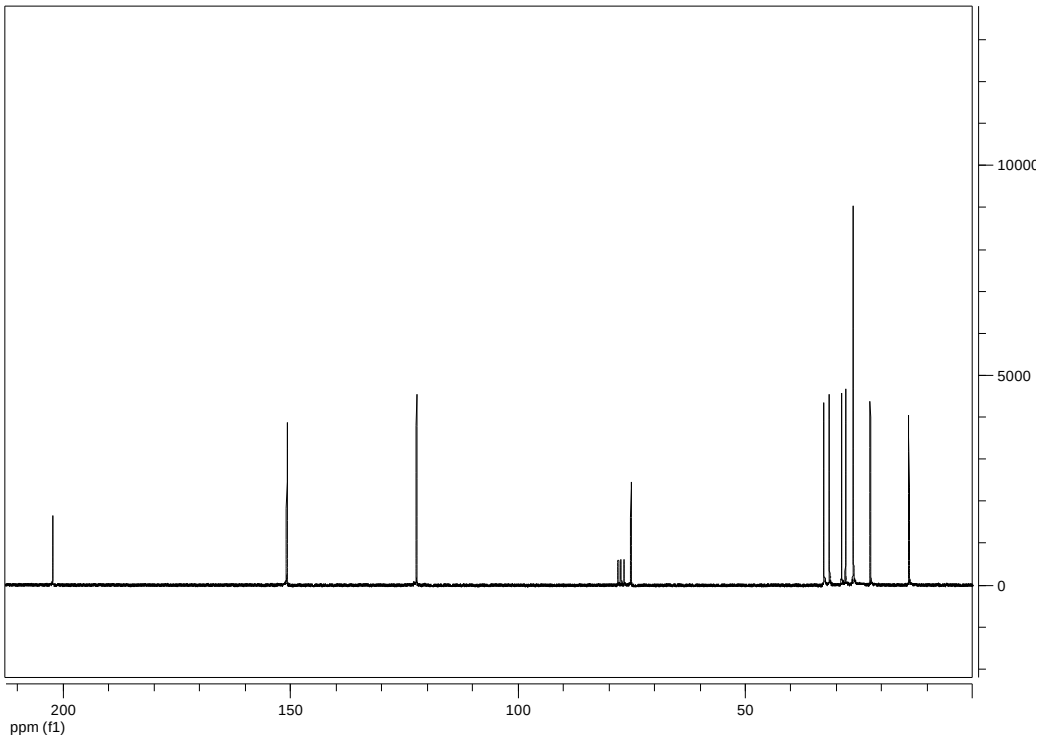
^{1}H NMR

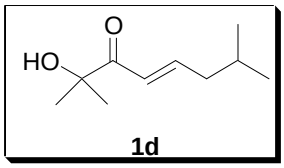


1c



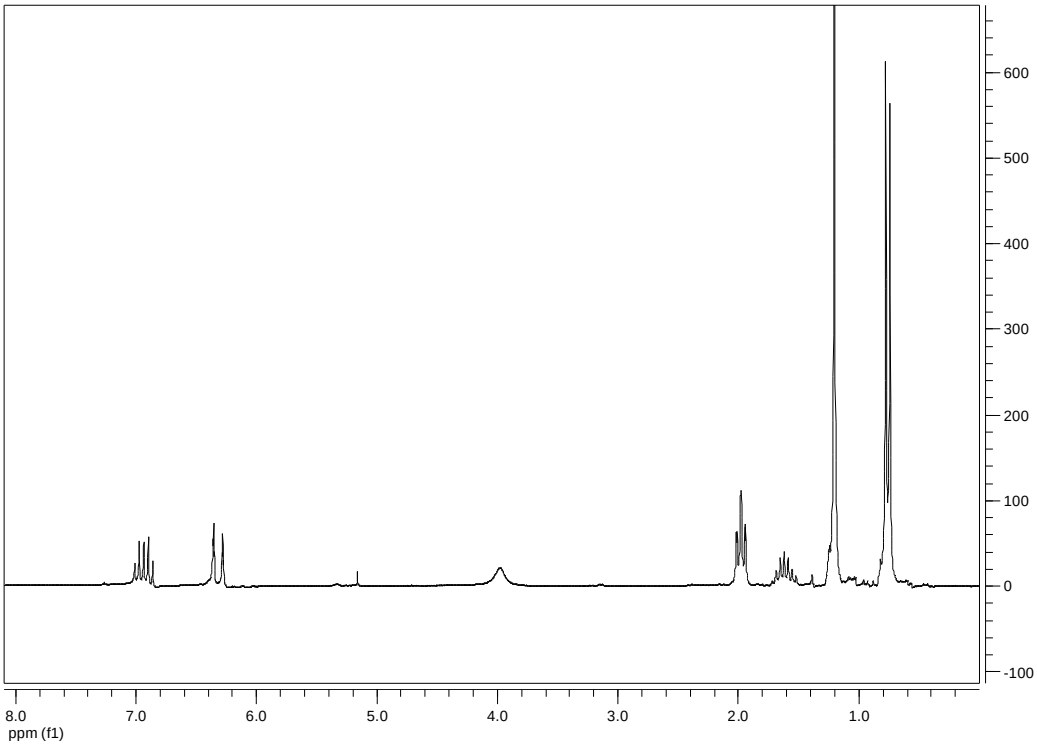
^{13}C NMR



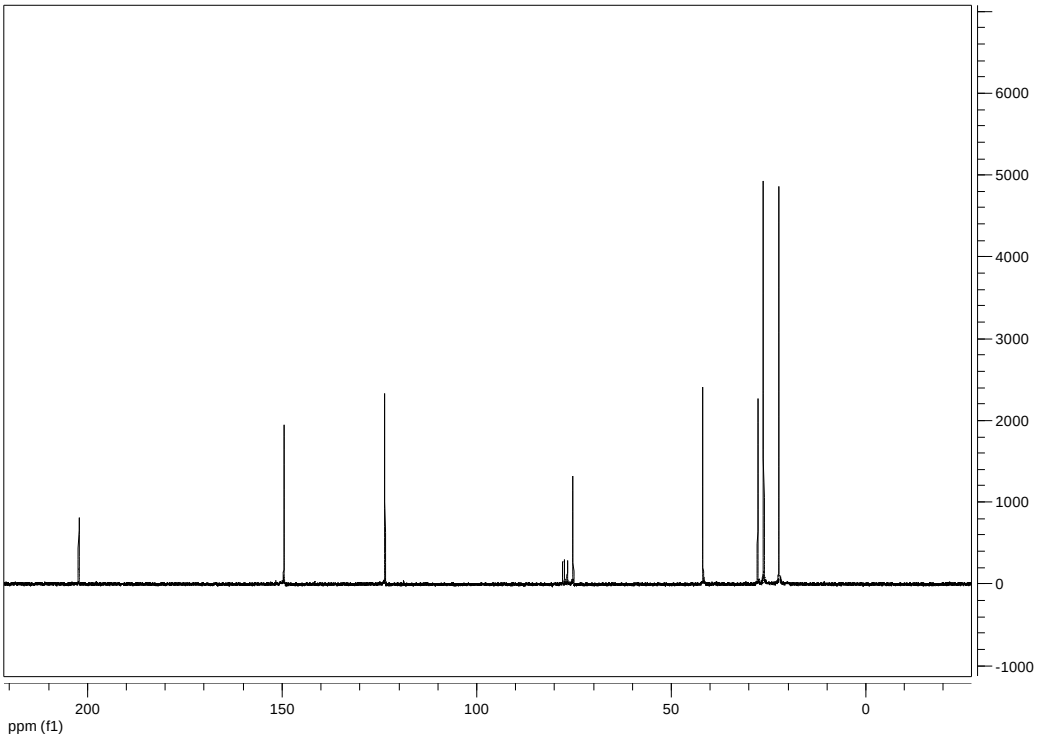


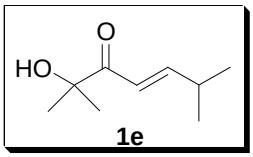
1d

^{1}H NMR



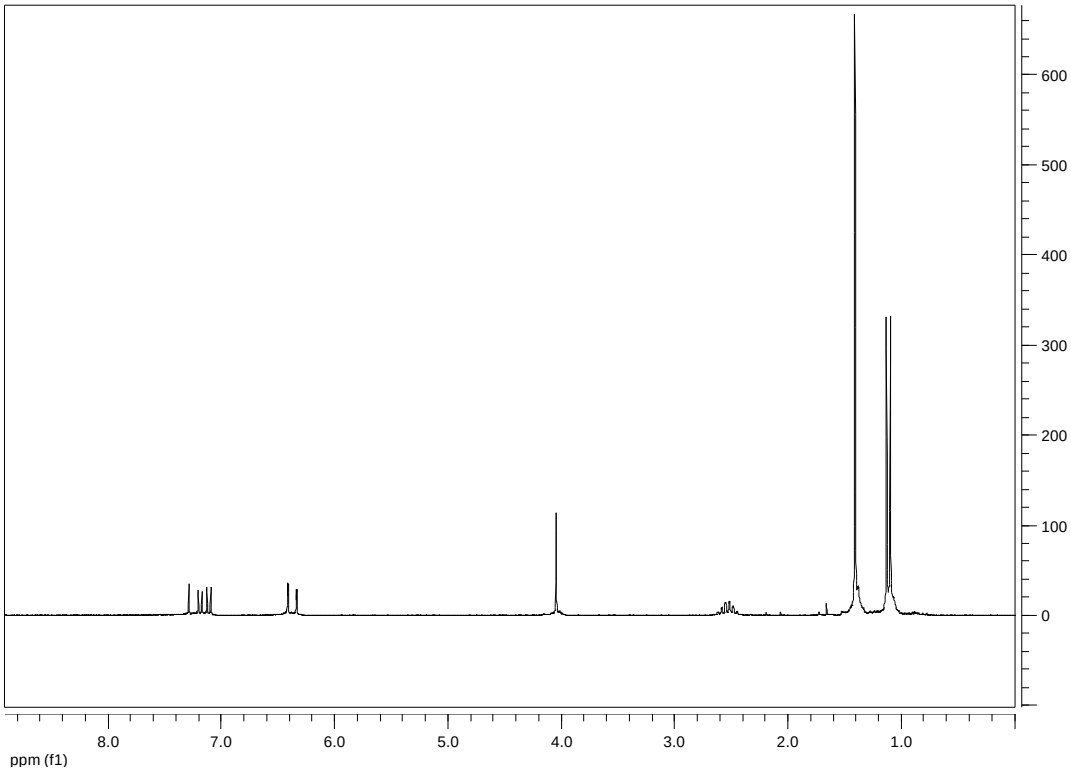
^{13}C NMR



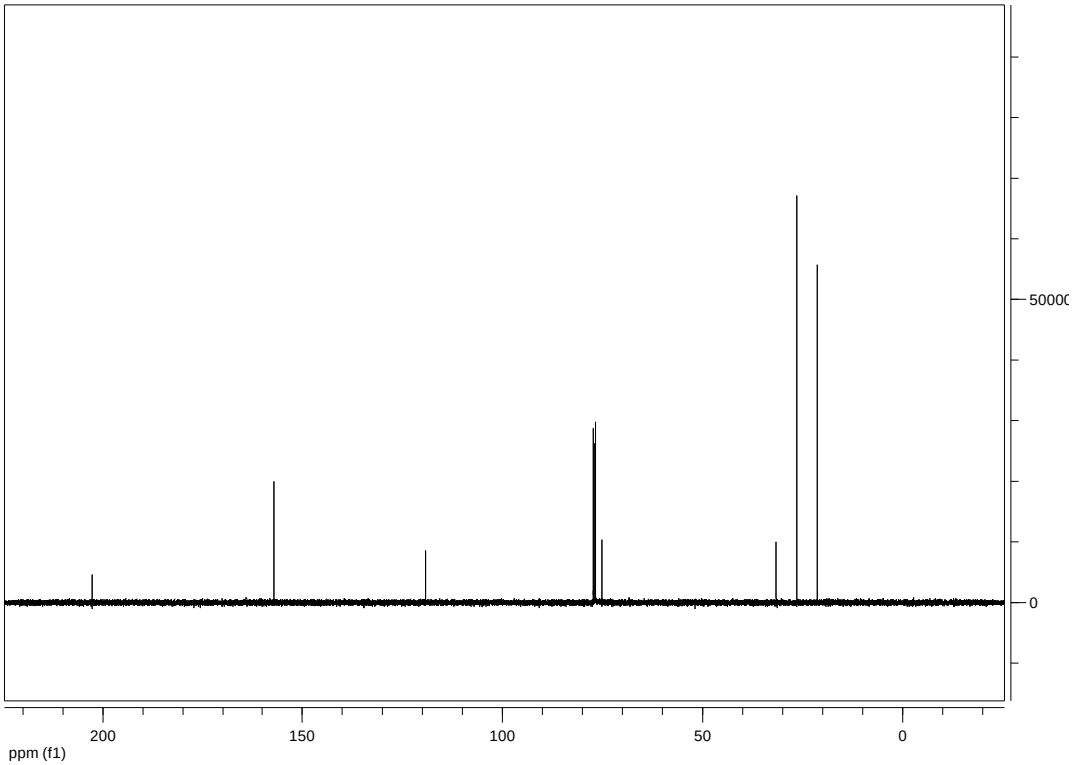


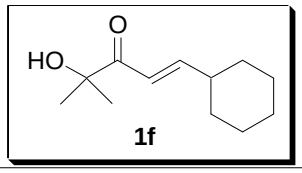
1e

^{1}H NMR



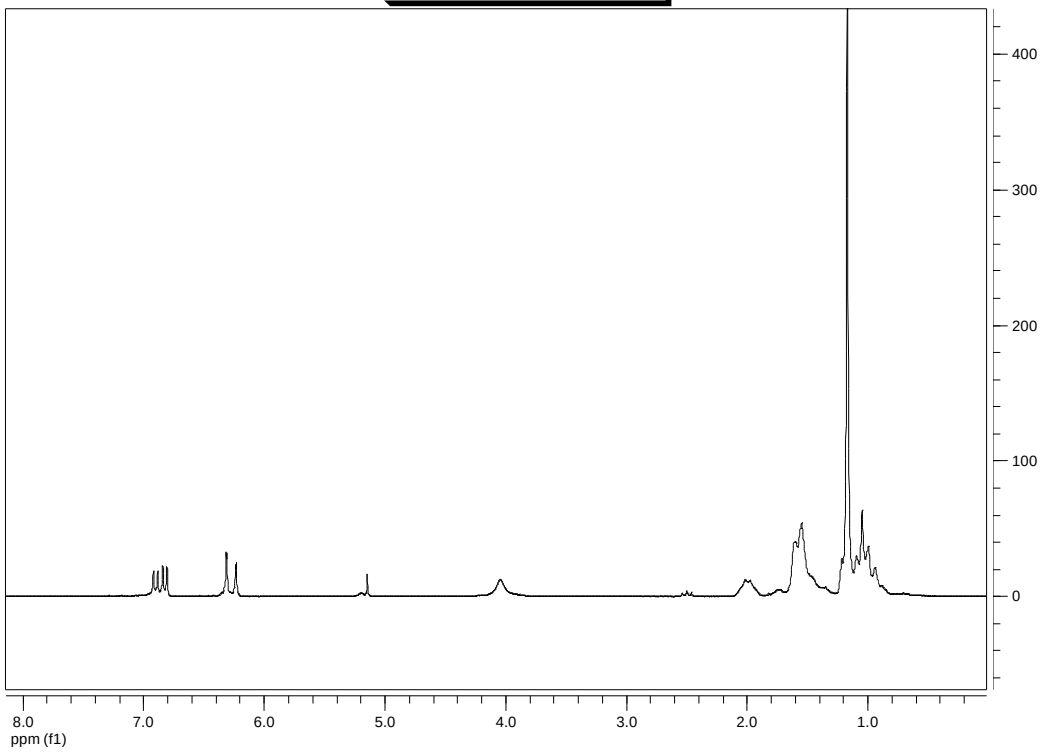
^{13}C NMR



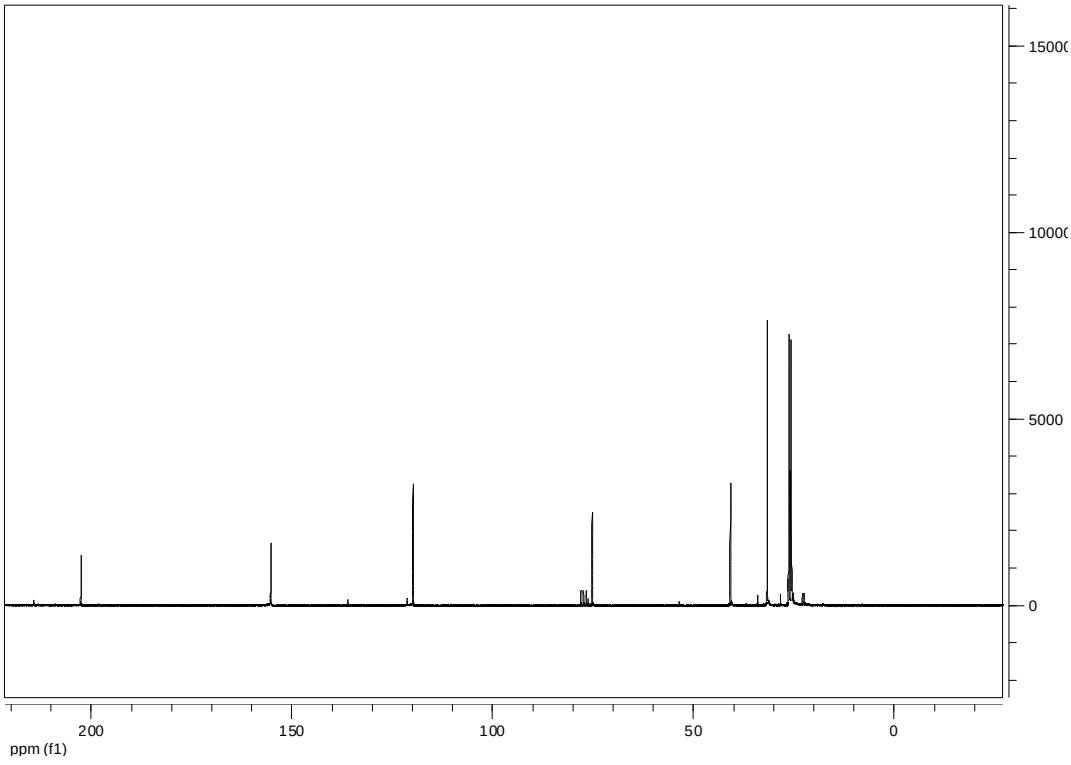


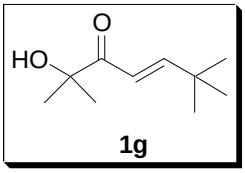
1f

^{1}H NMR



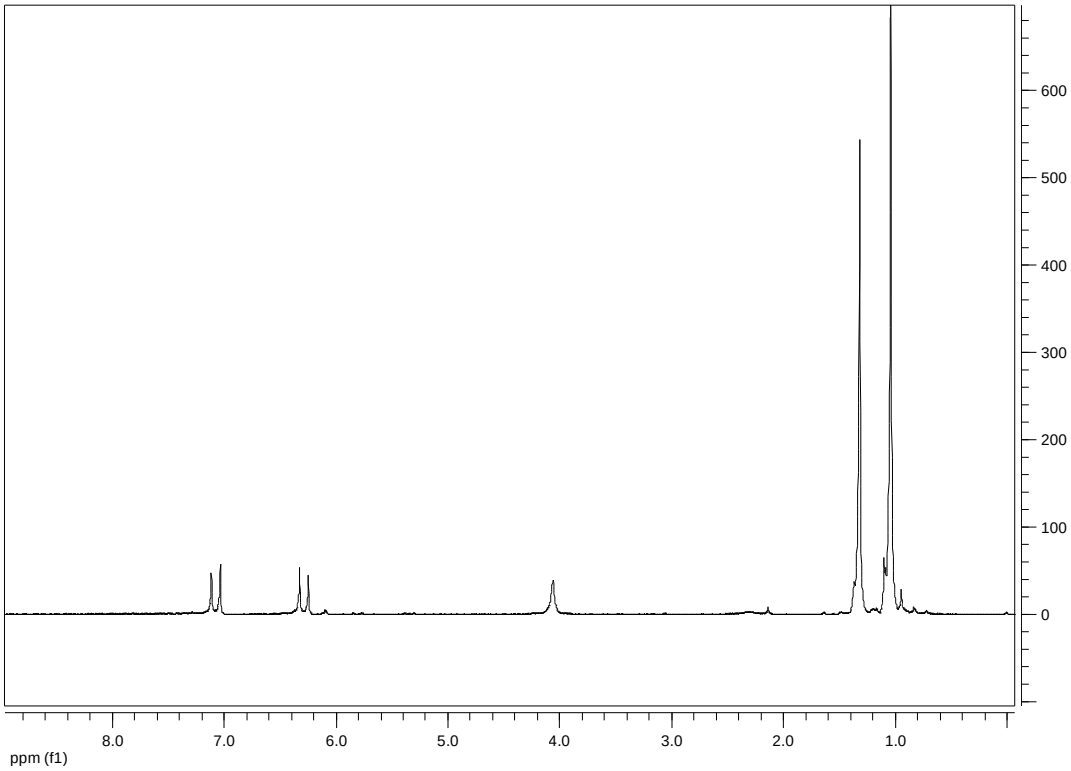
^{13}C NMR



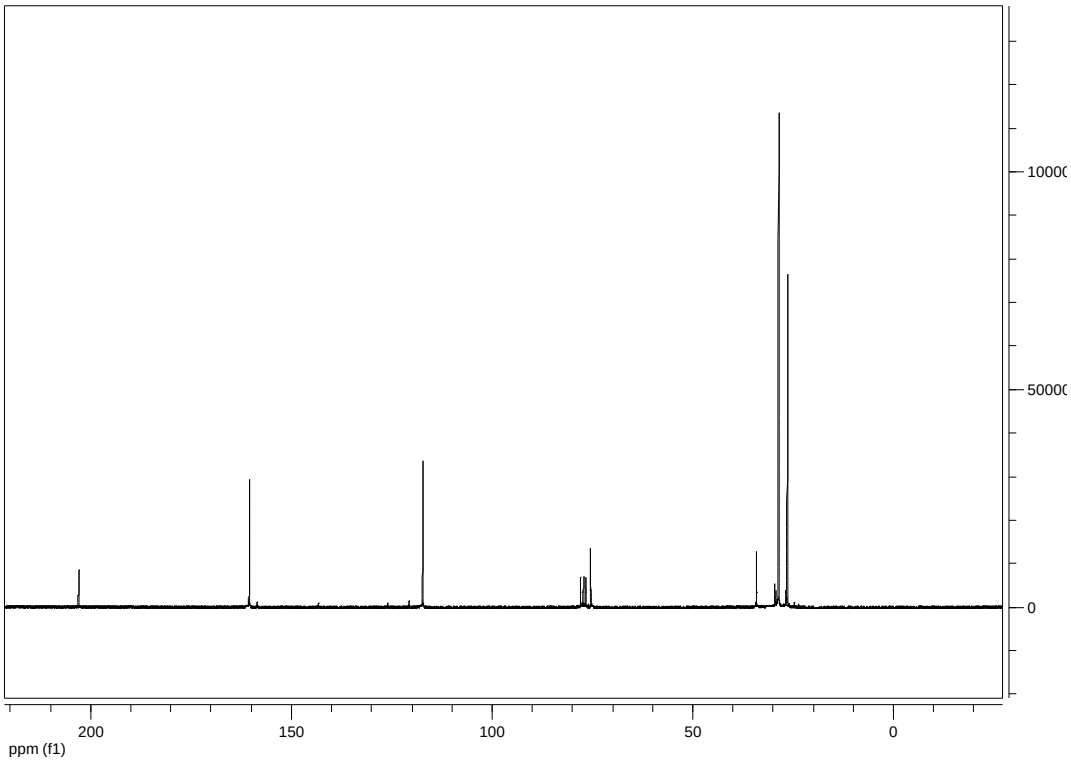


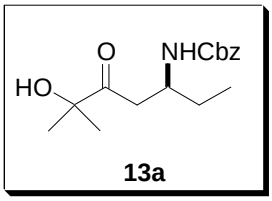
1g

^{1}H NMR



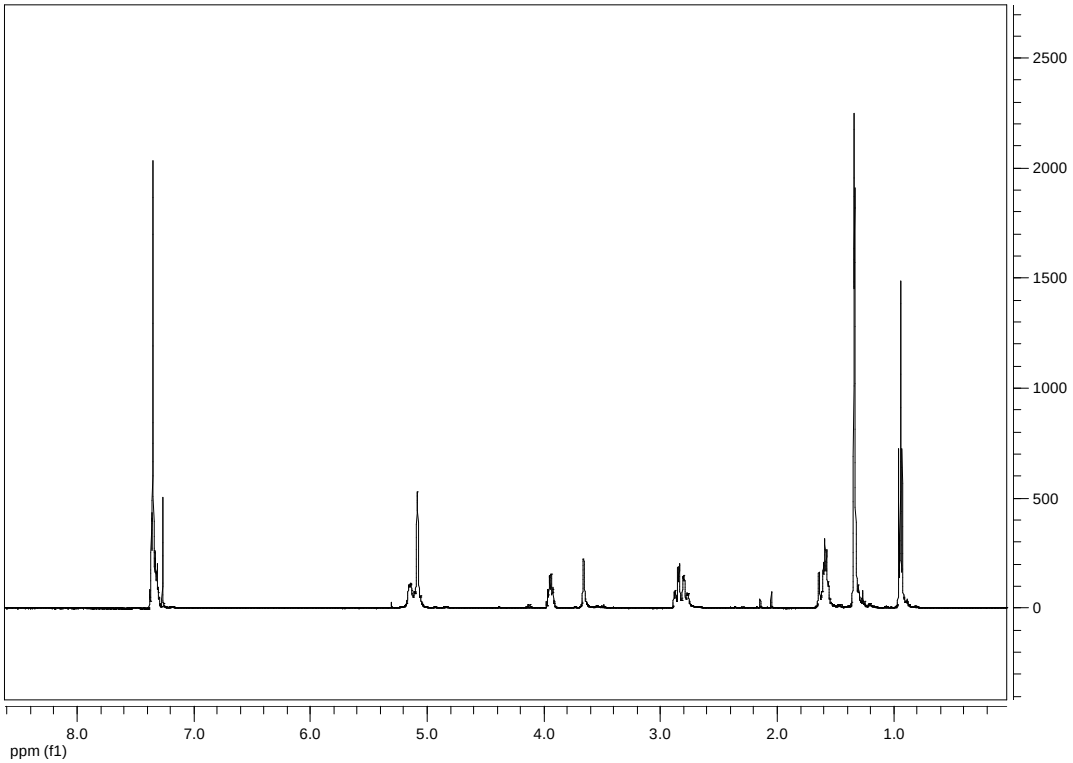
^{13}C NMR



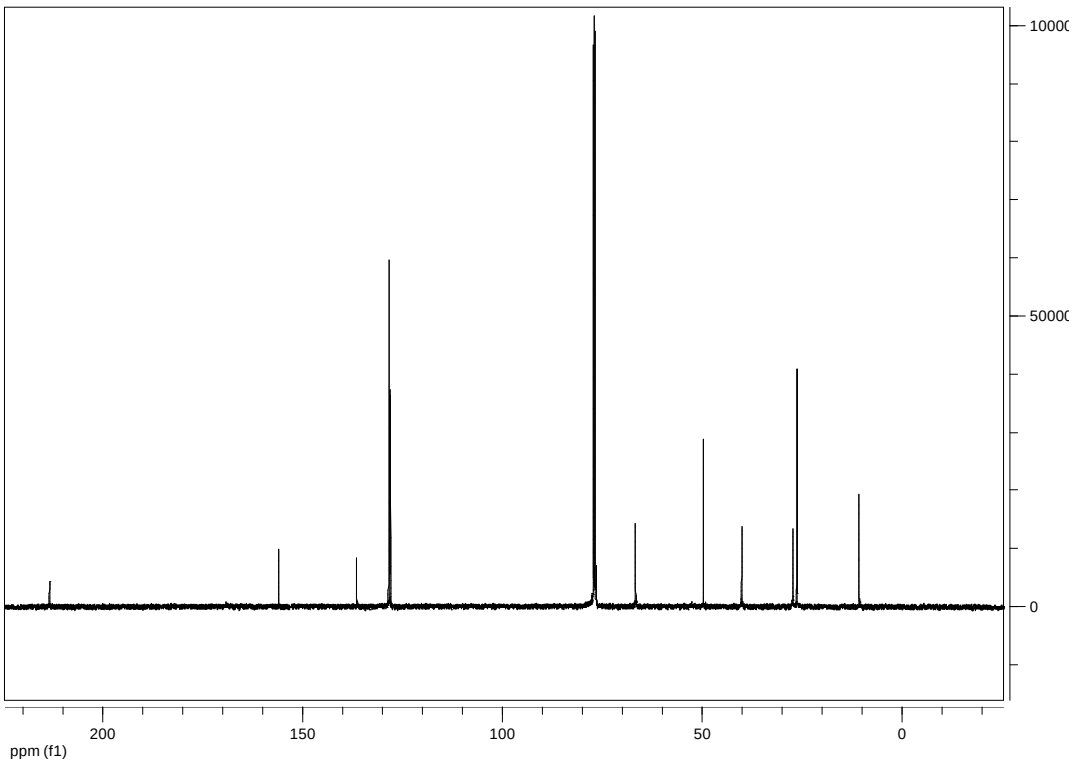


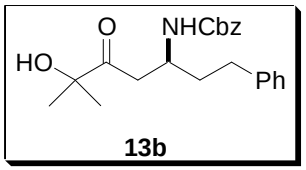
13a

^{1}H NMR



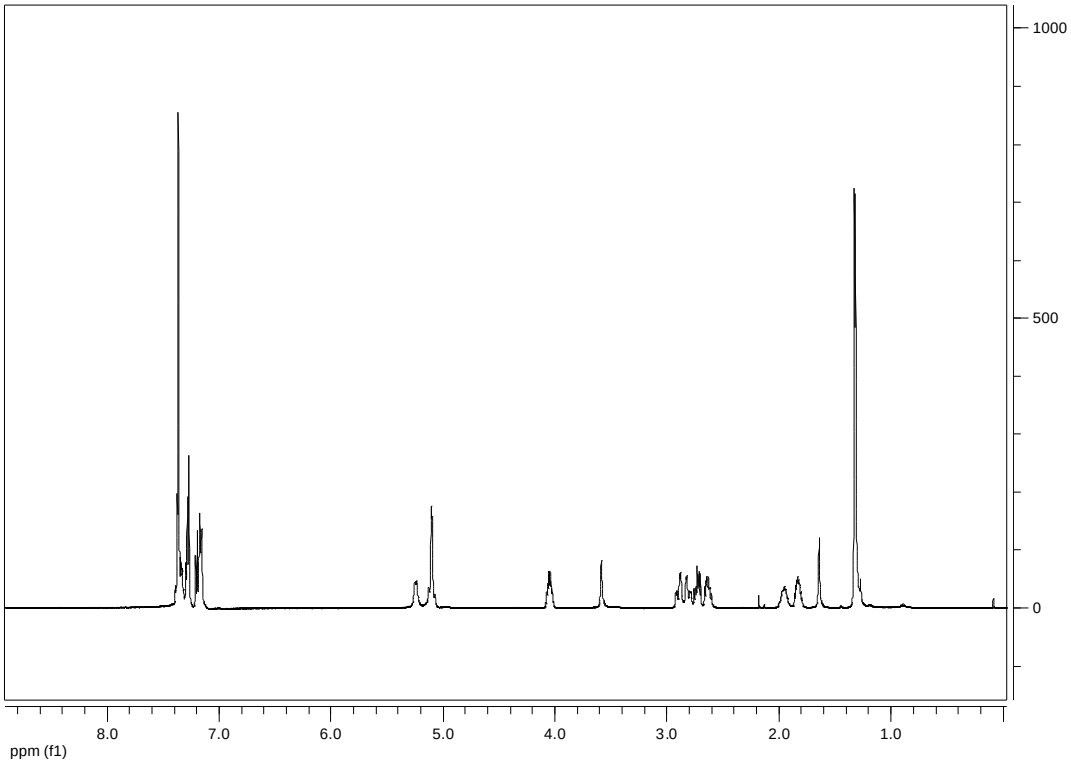
^{13}C NMR



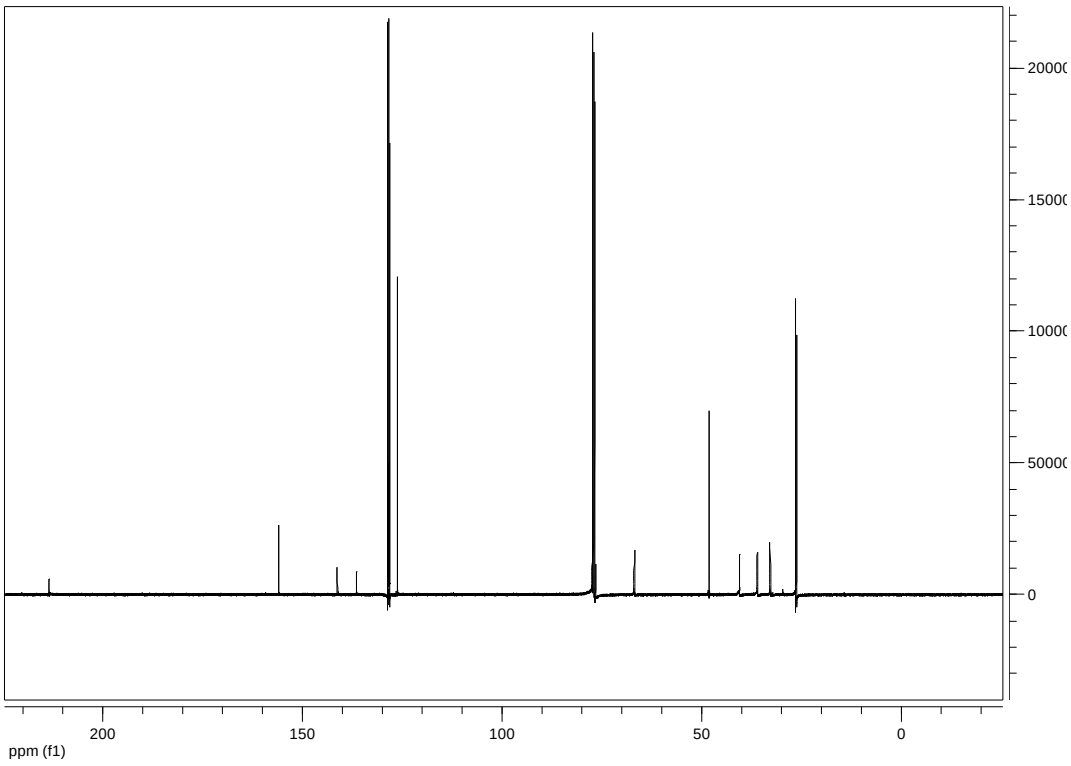


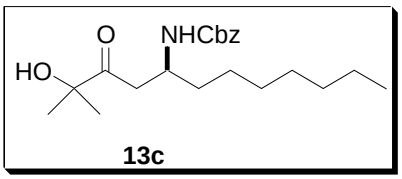
13b

^{1}H NMR



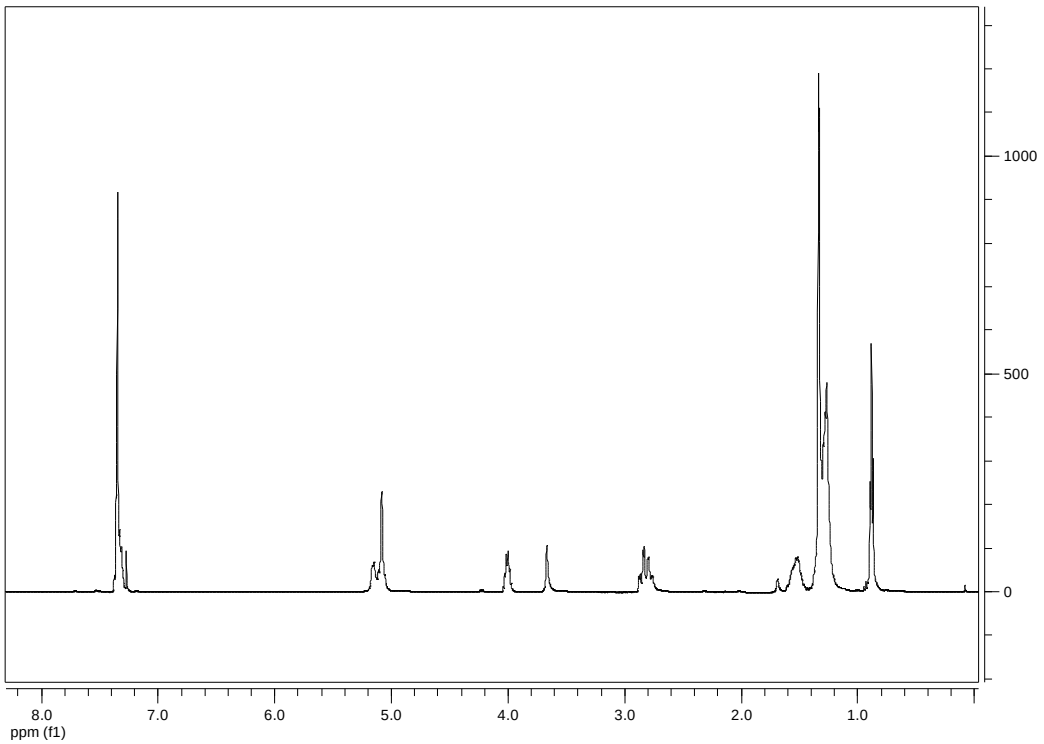
^{13}C NMR



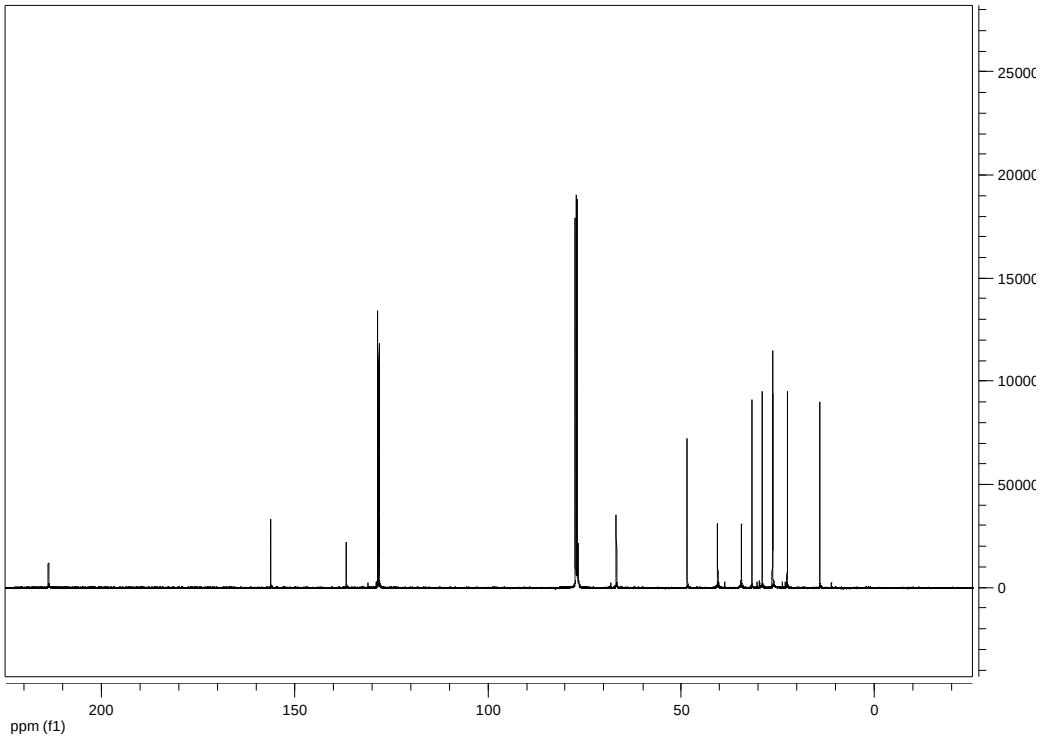


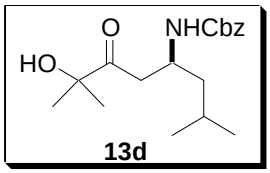
13c

^{1}H NMR



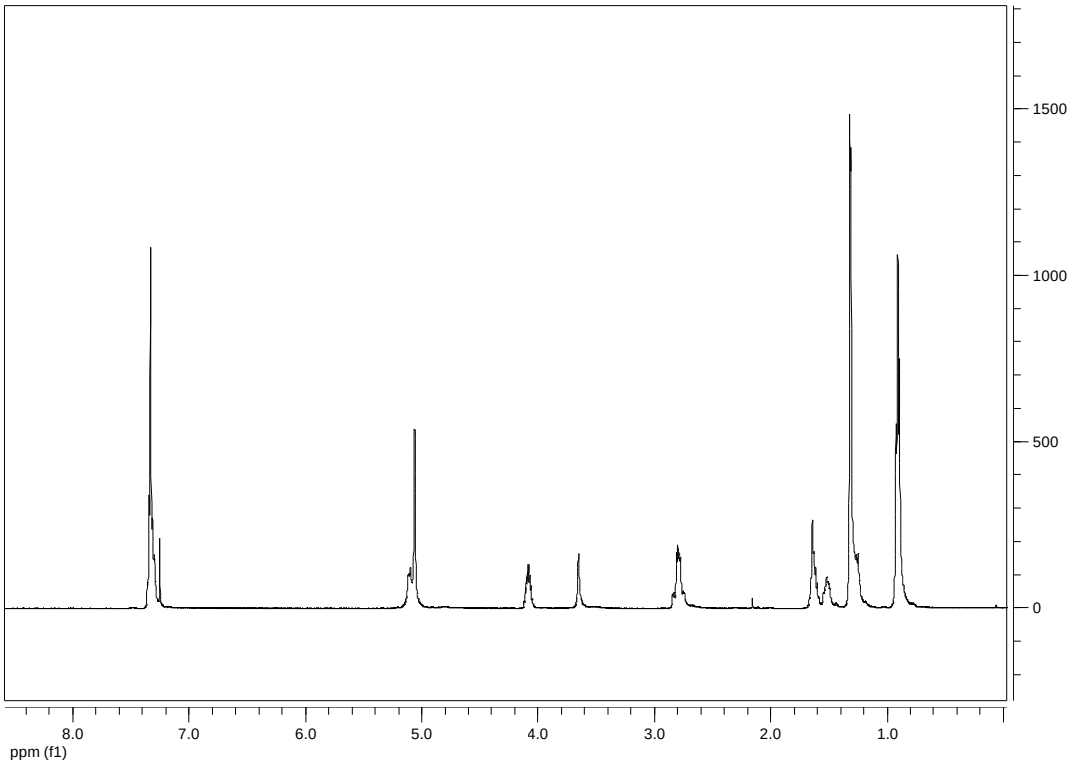
^{13}C NMR



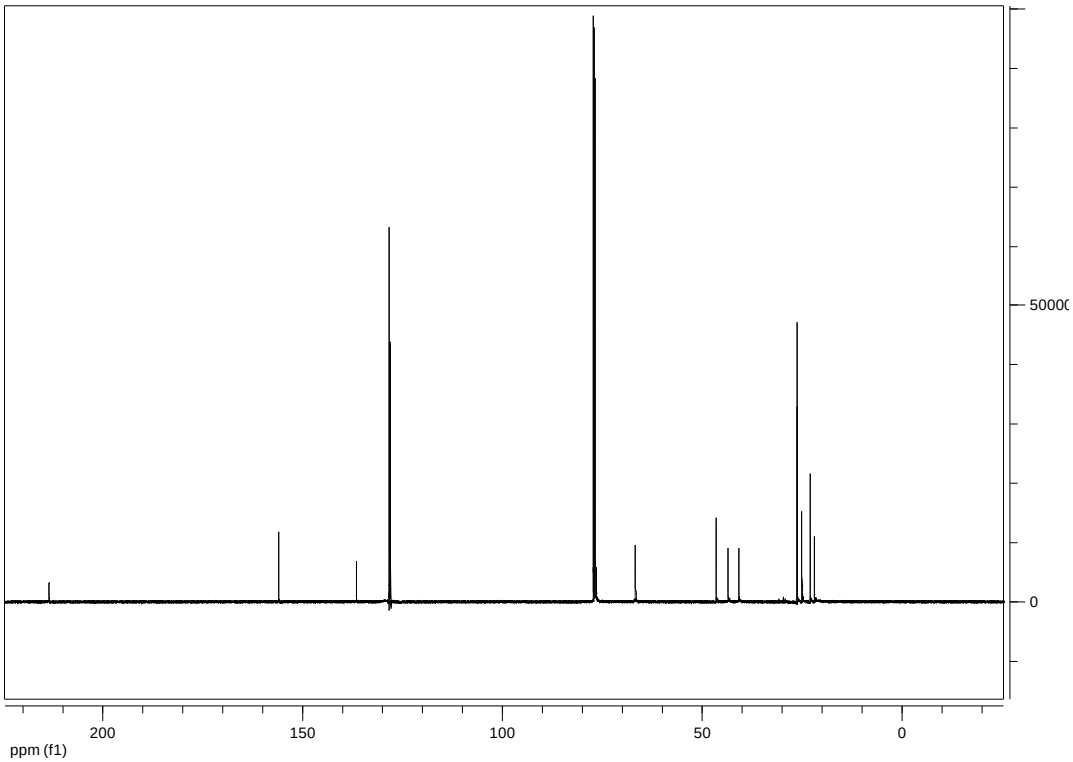


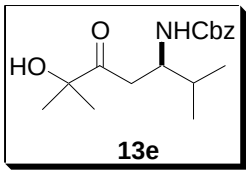
13d

^{1}H NMR



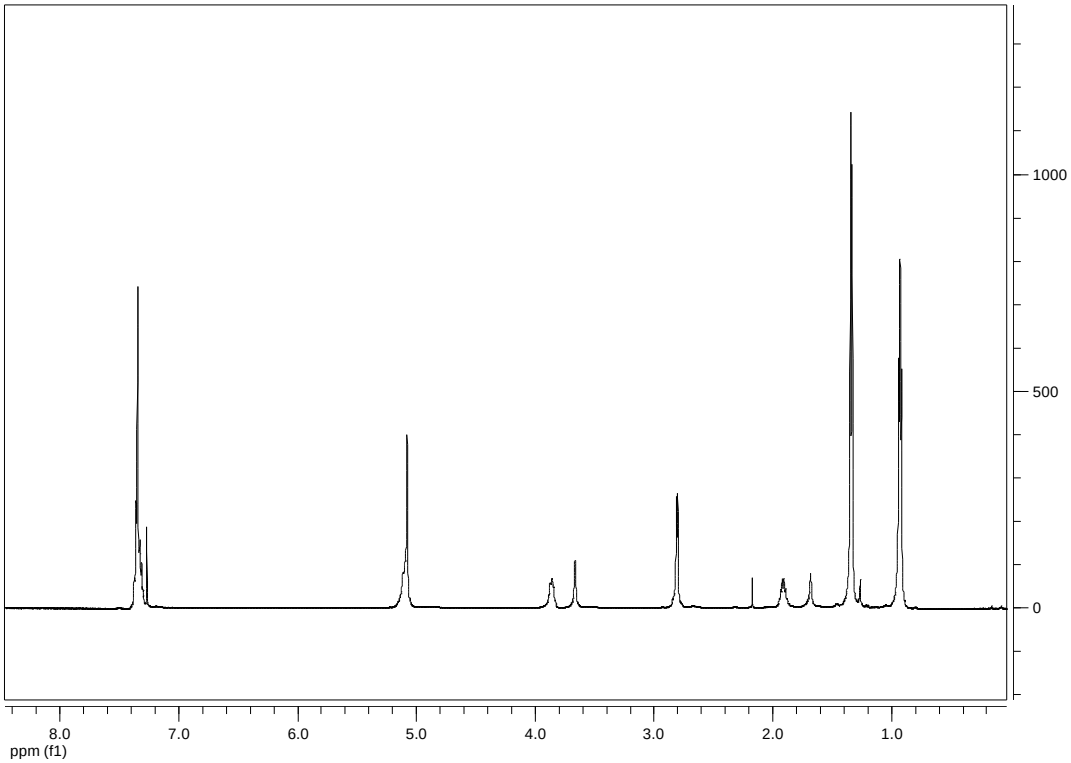
^{13}C NMR



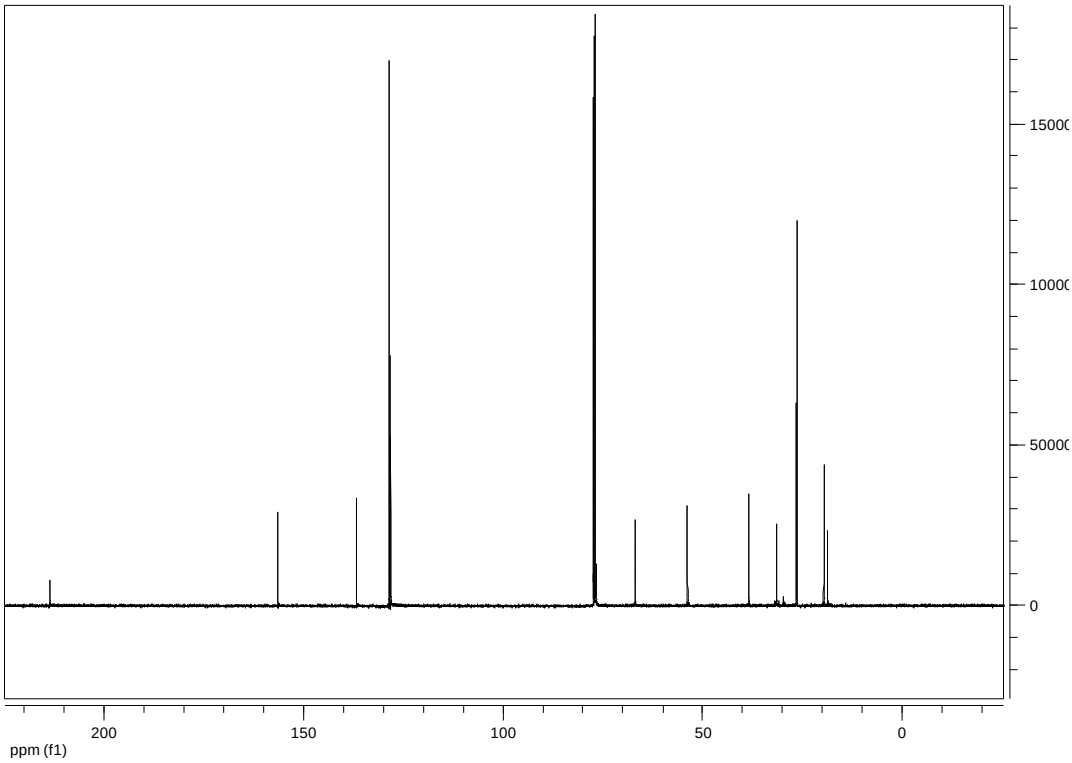


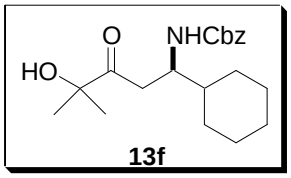
13e

^{1}H NMR



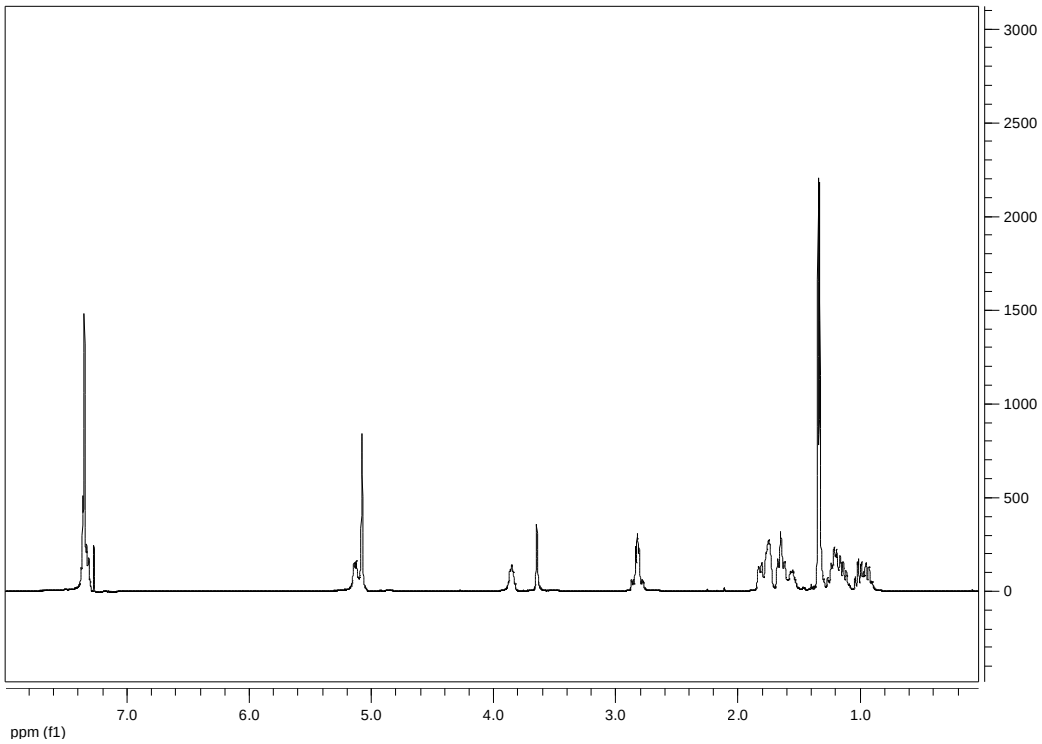
^{13}C NMR



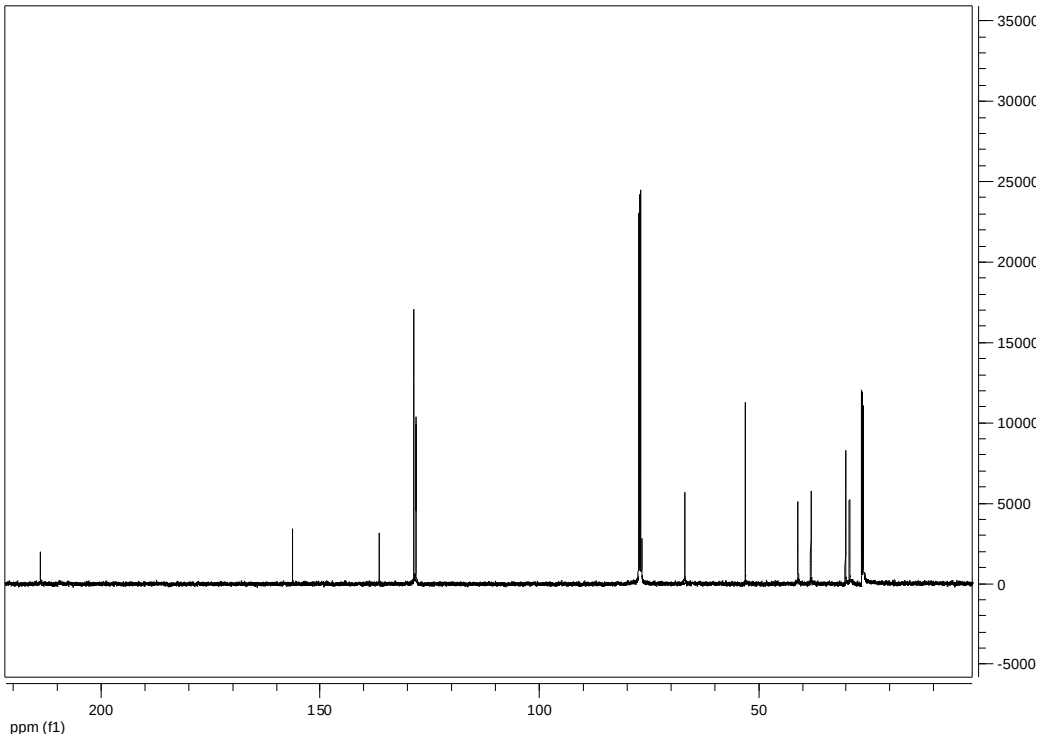


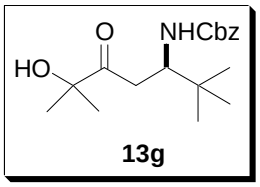
13f

^{1}H NMR



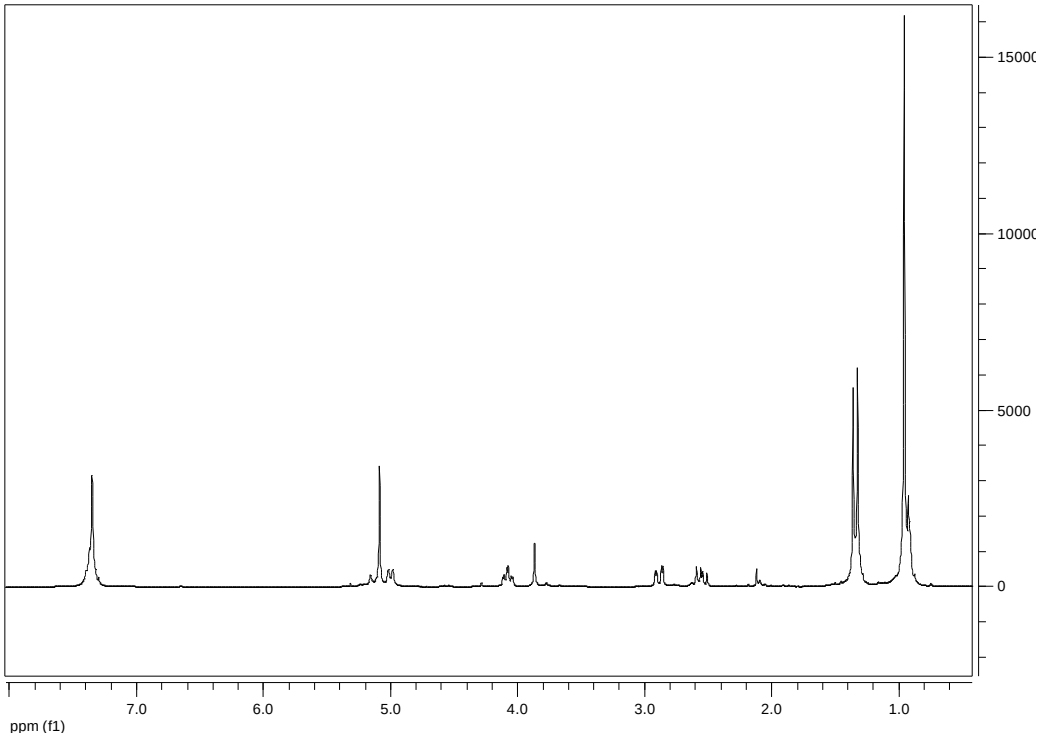
^{13}C NMR



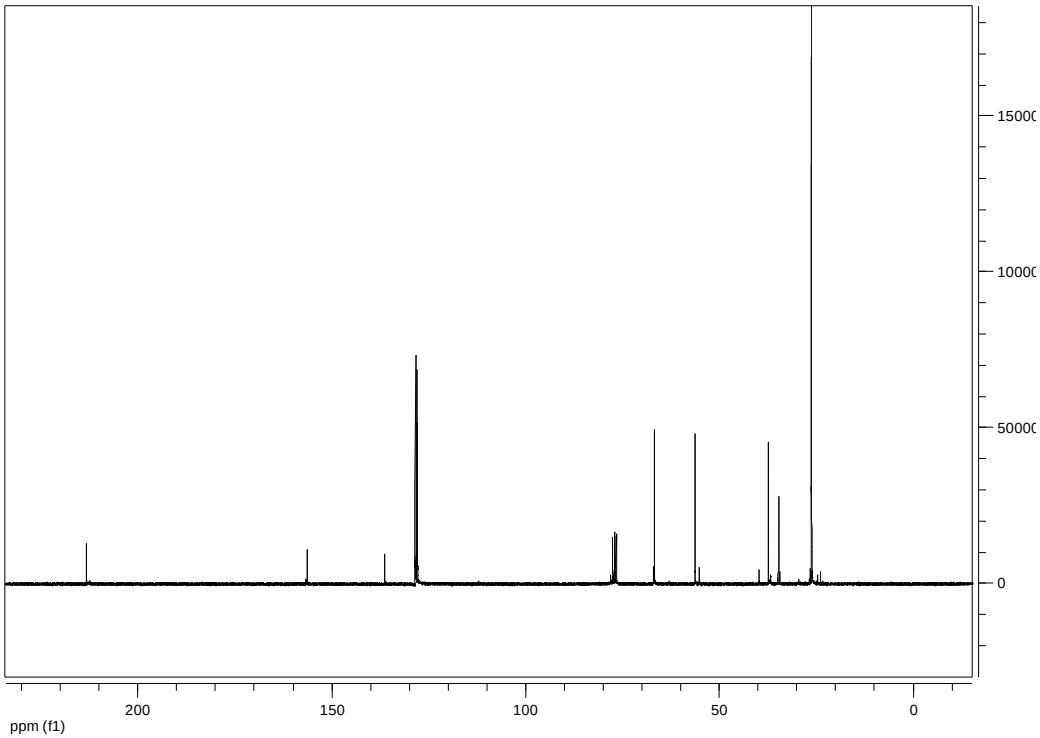


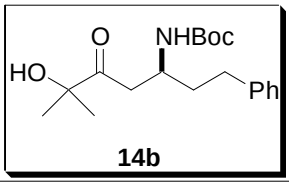
13g

^{1}H NMR



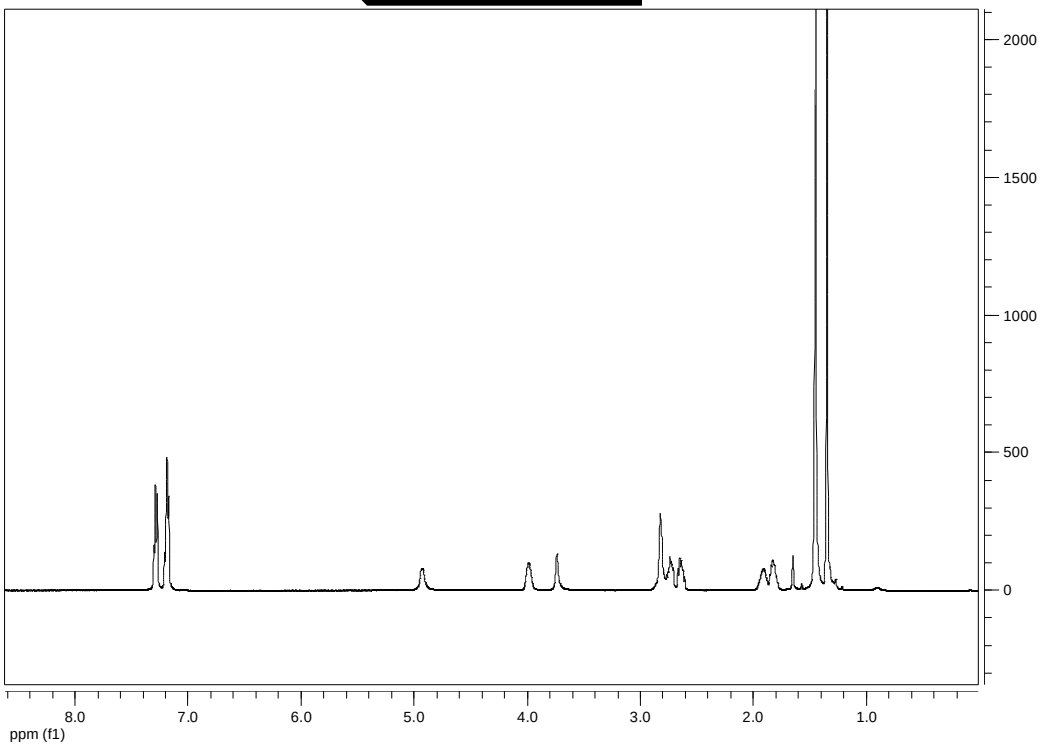
^{13}C NMR



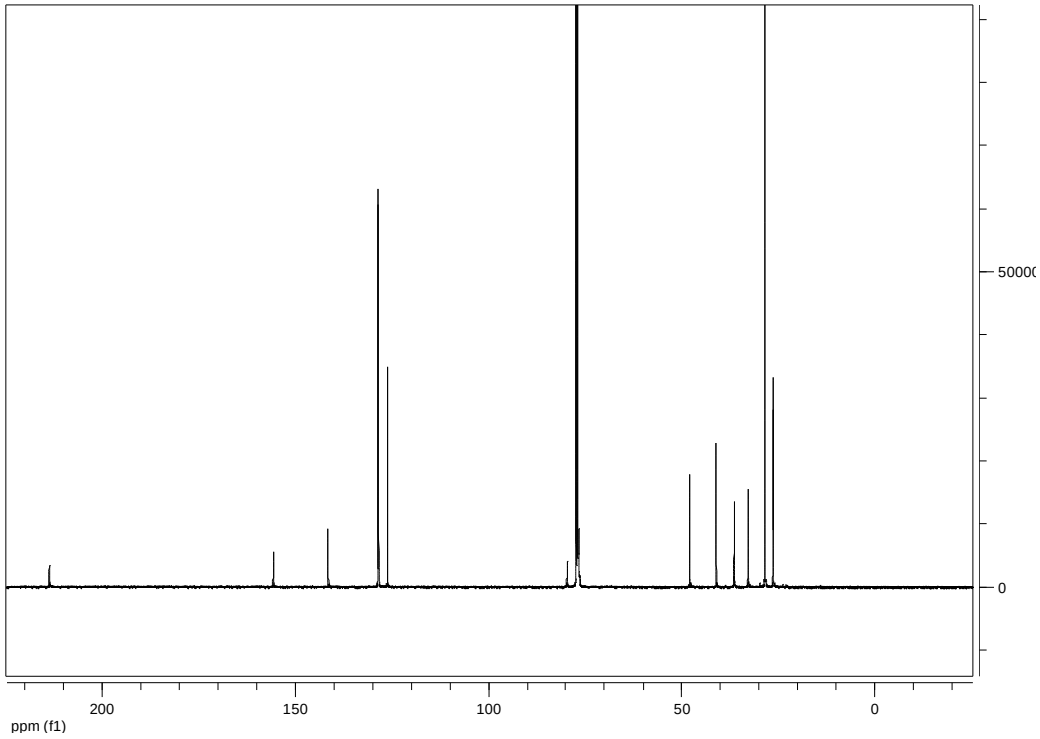


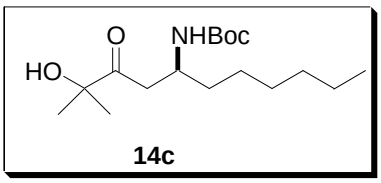
14b

^{1}H NMR



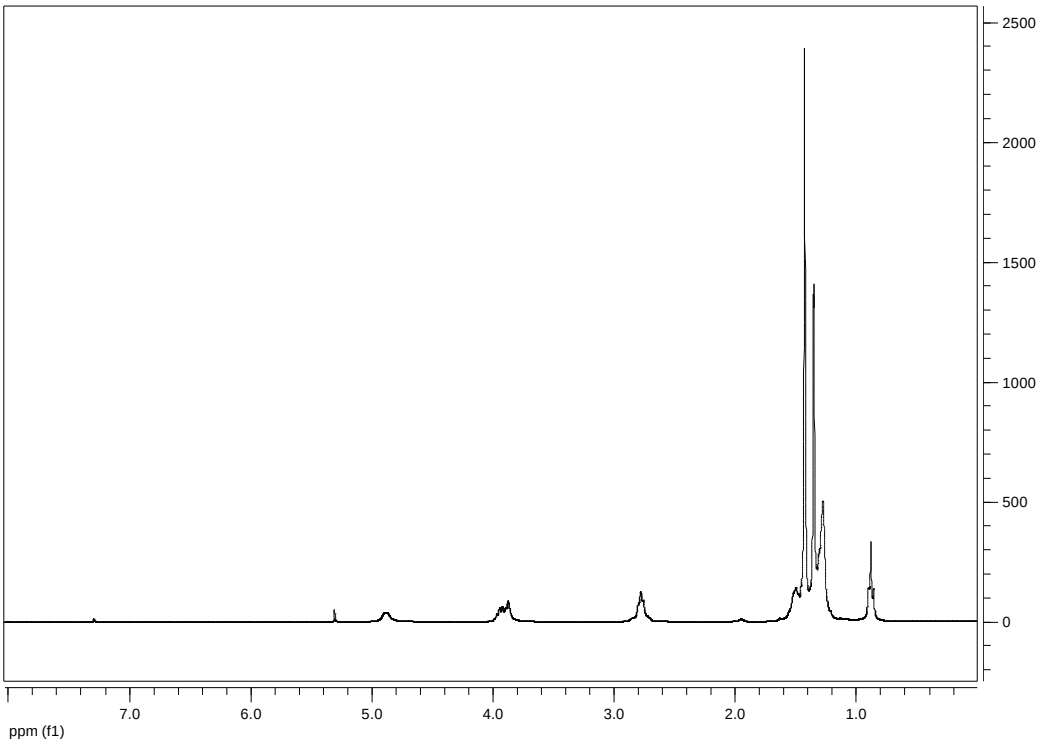
^{13}C NMR



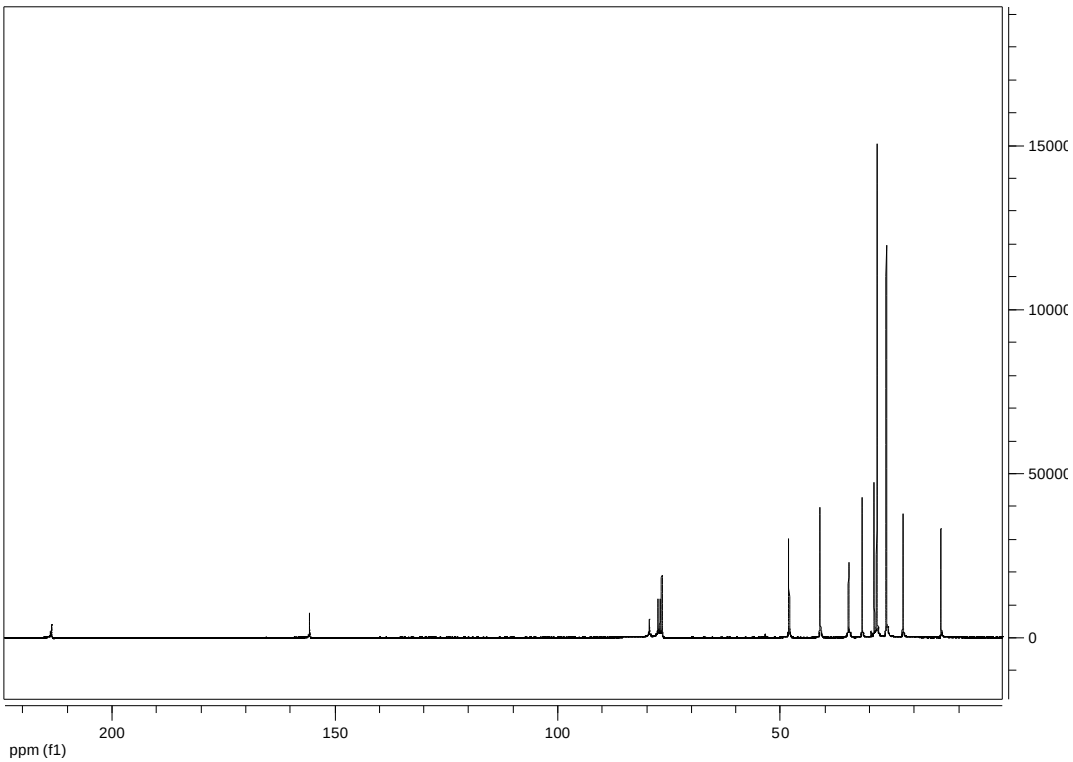


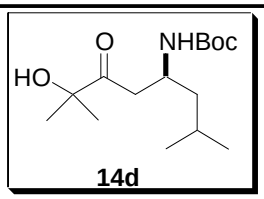
14c

^{1}H NMR



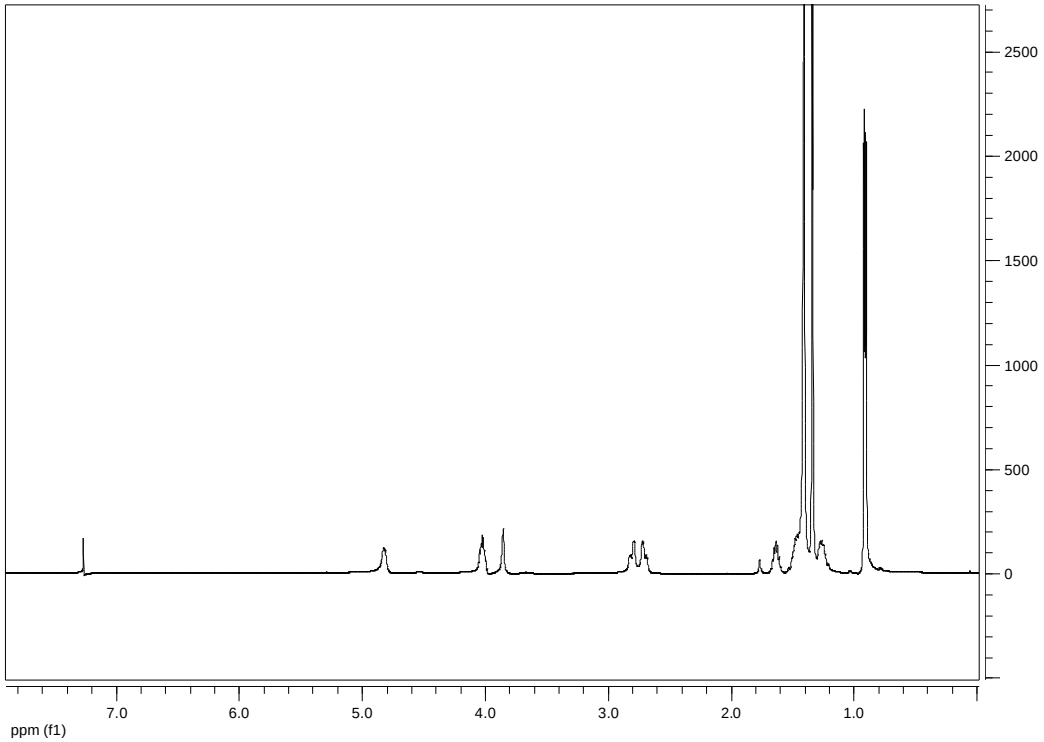
^{13}C NMR



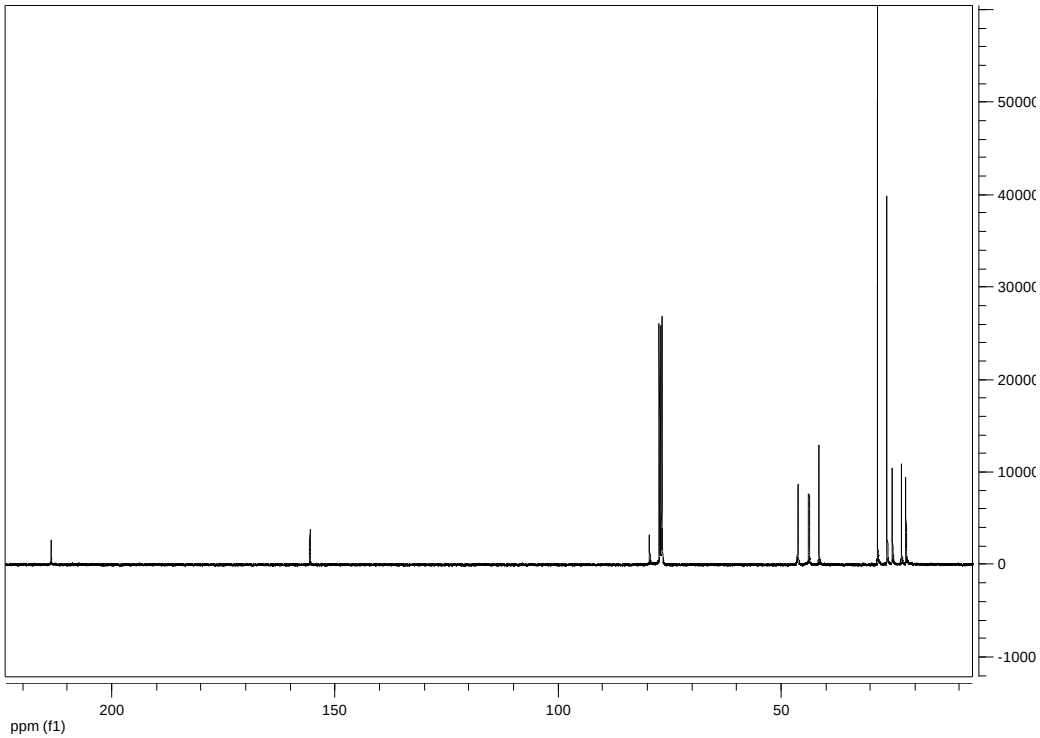


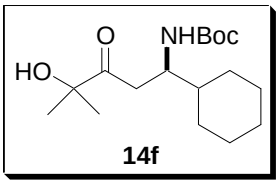
14d

^{1}H NMR



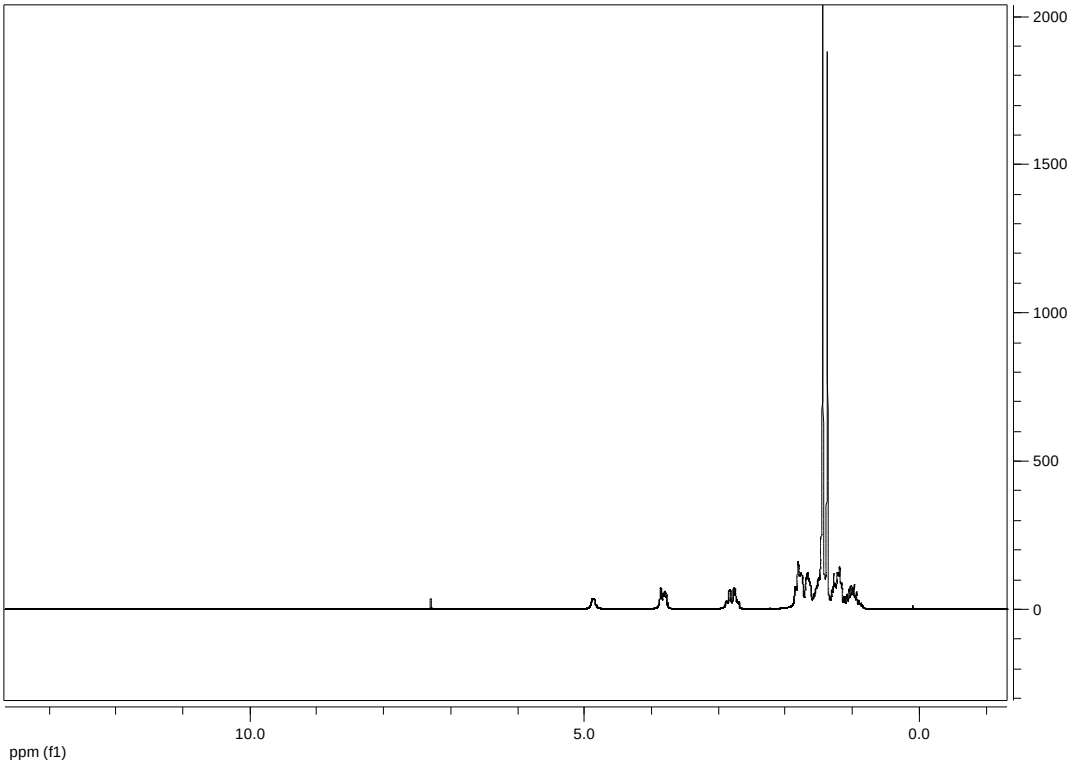
^{13}C NMR



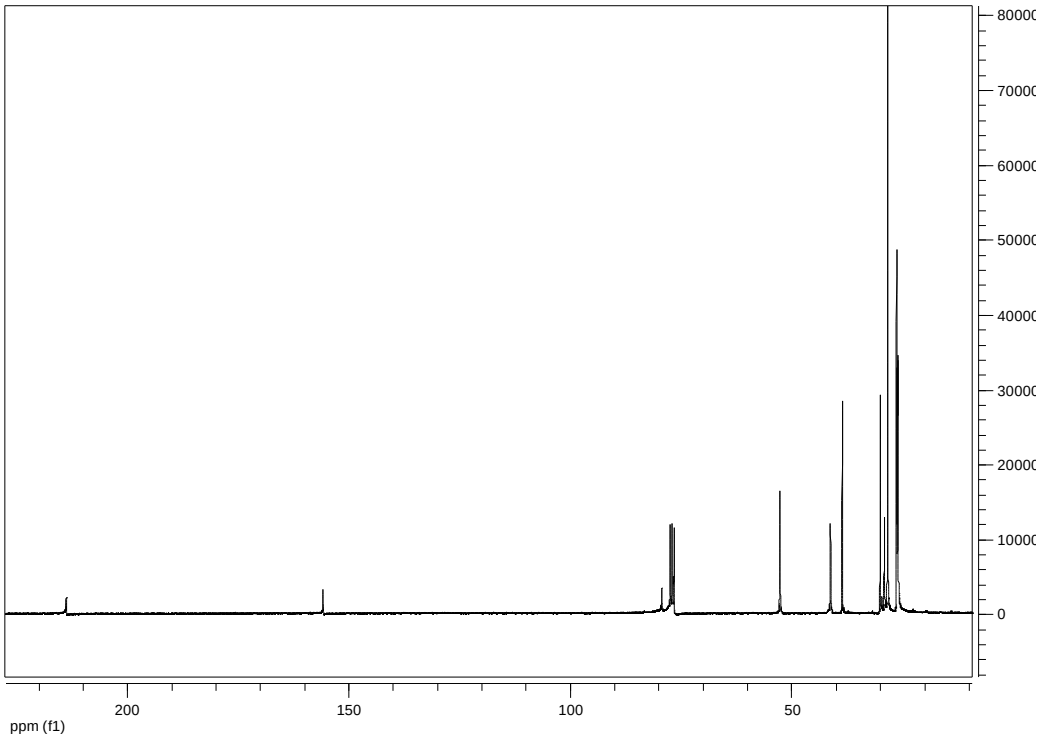


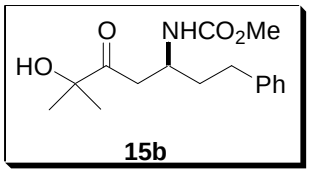
14f

^{1}H NMR



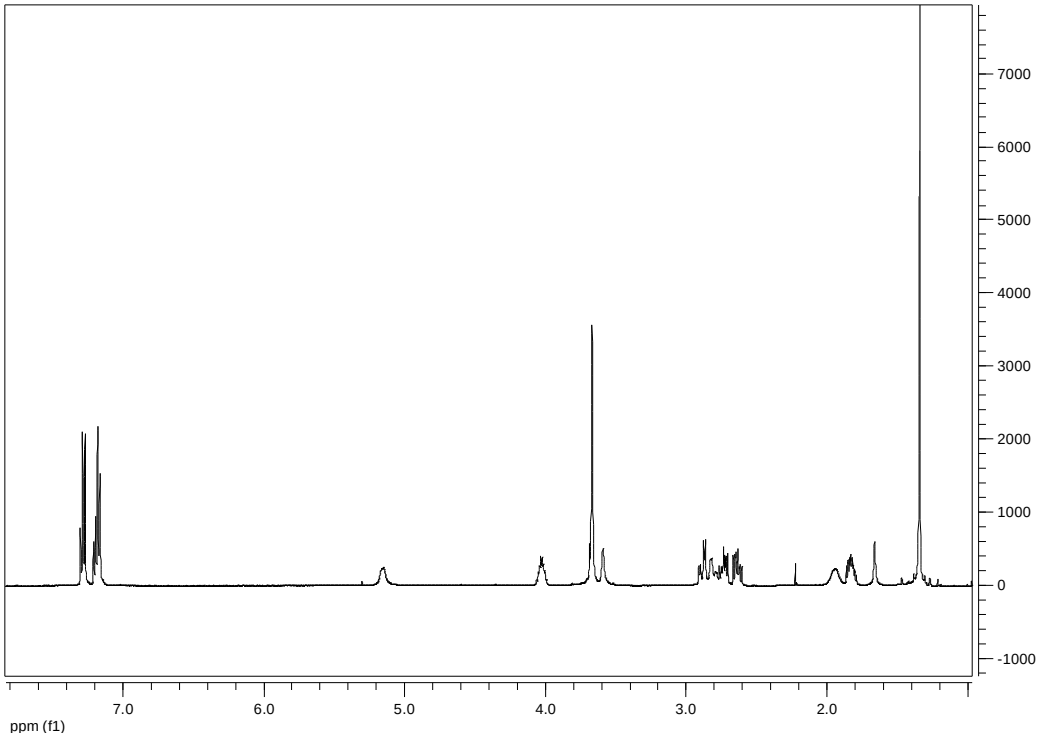
^{13}C NMR



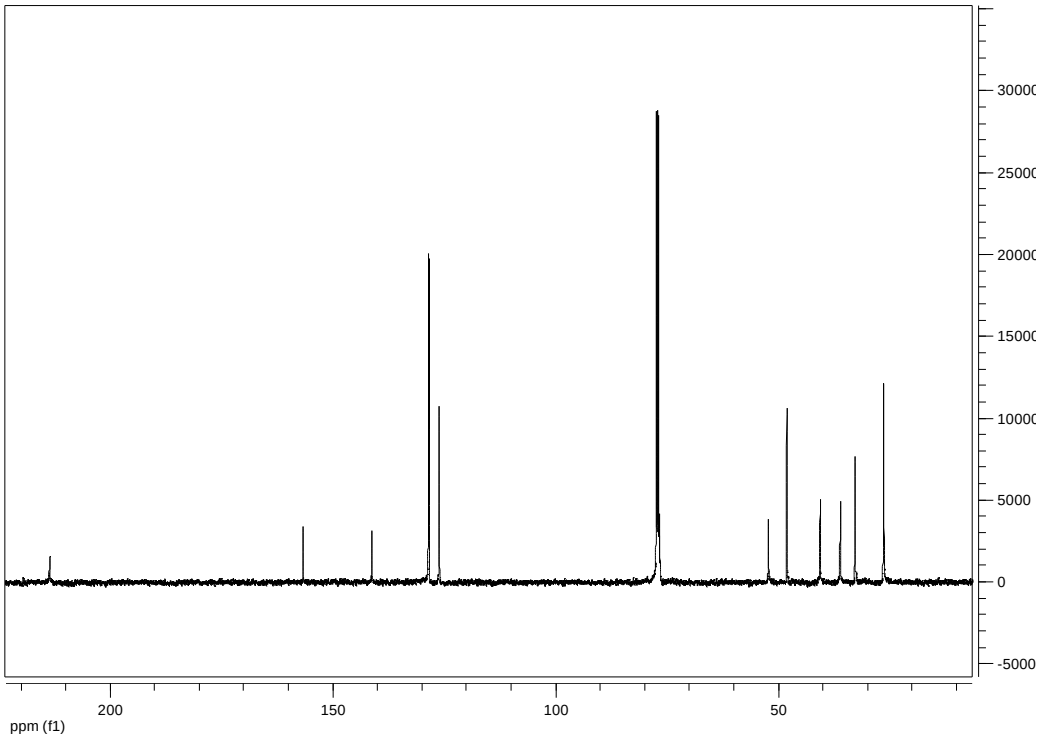


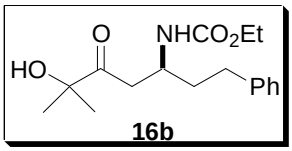
15b

^{1}H NMR



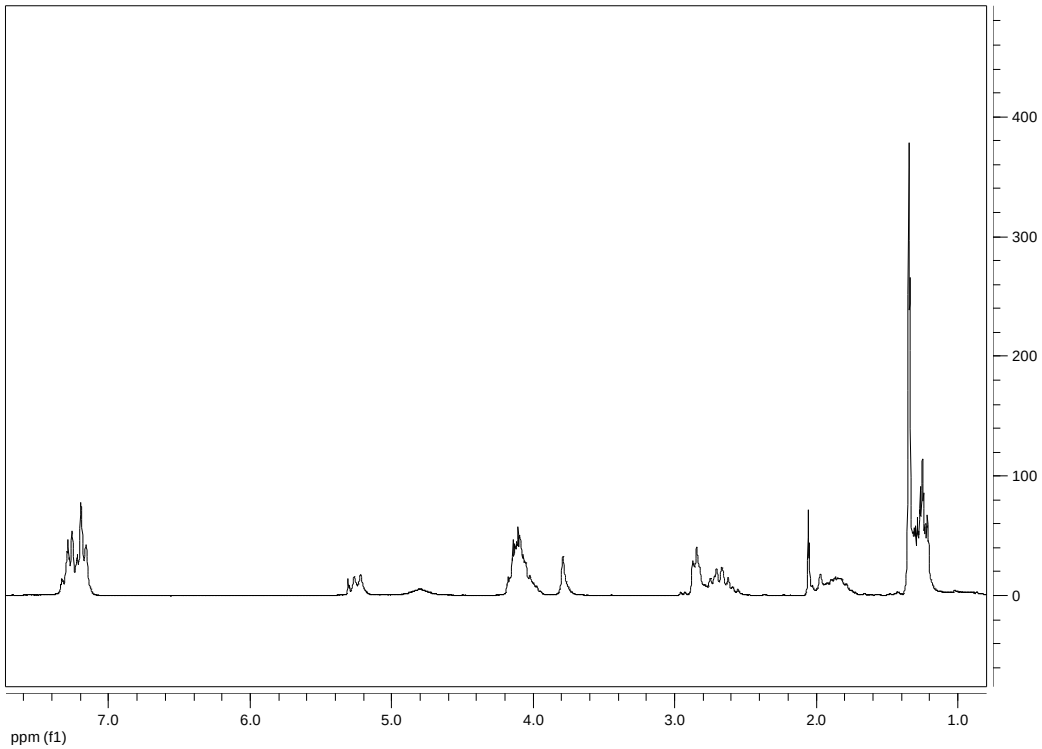
^{13}C NMR



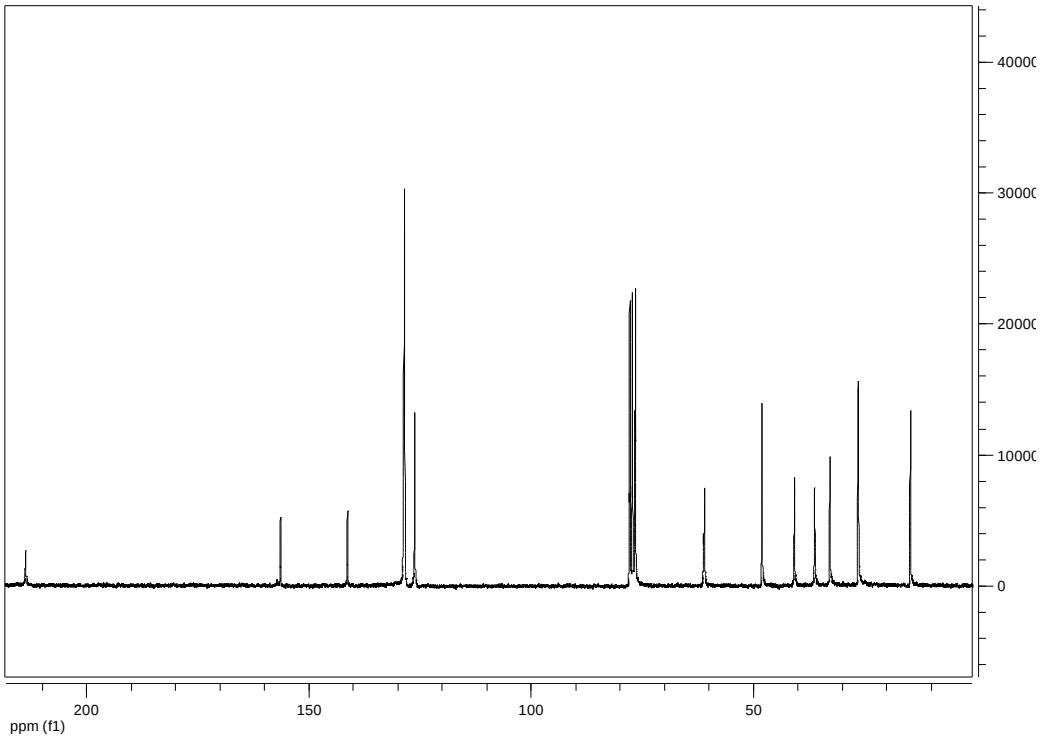


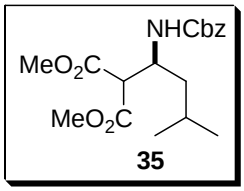
16b

^{1}H NMR



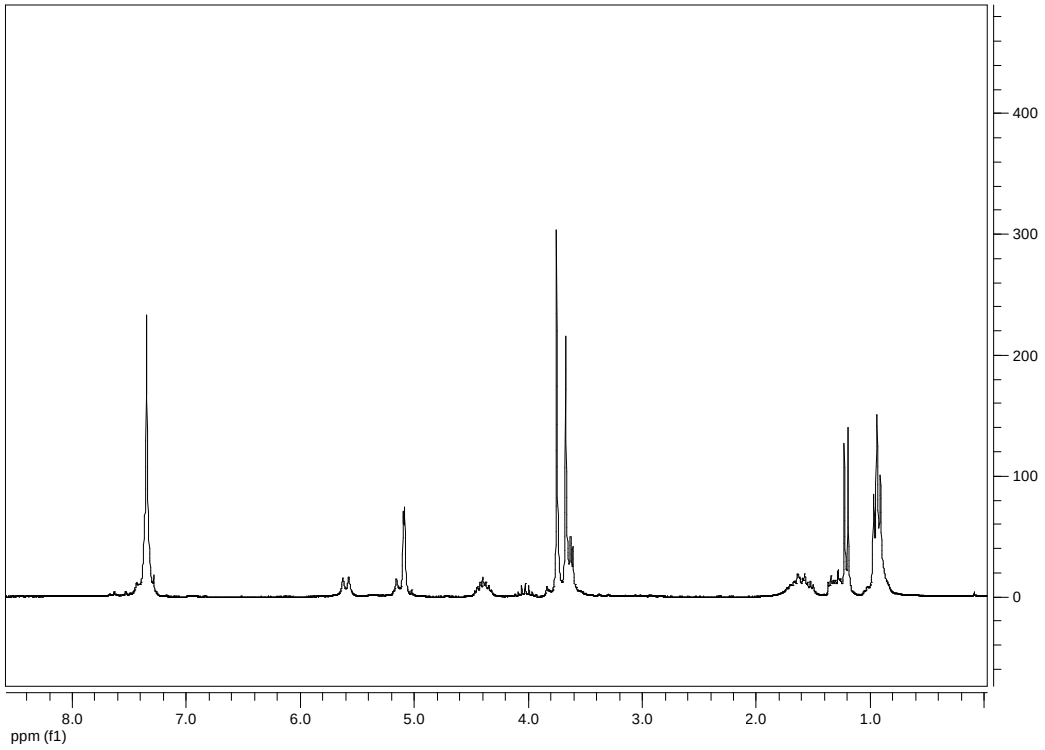
^{13}C NMR



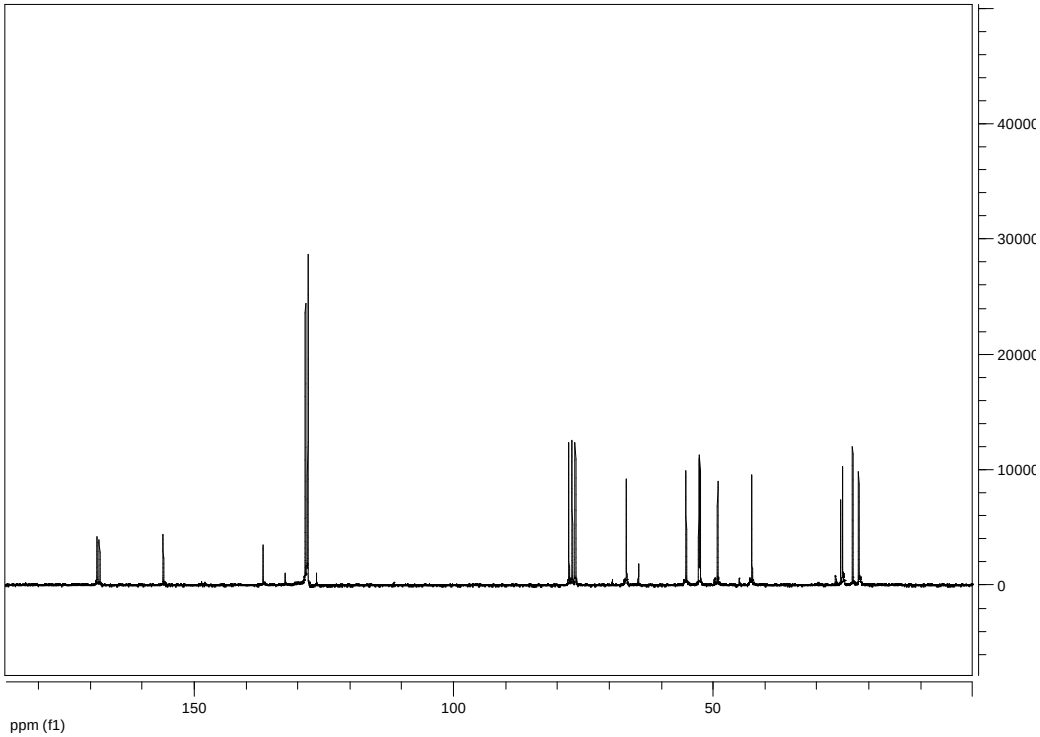


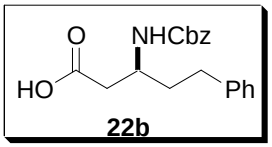
35

^{1}H NMR



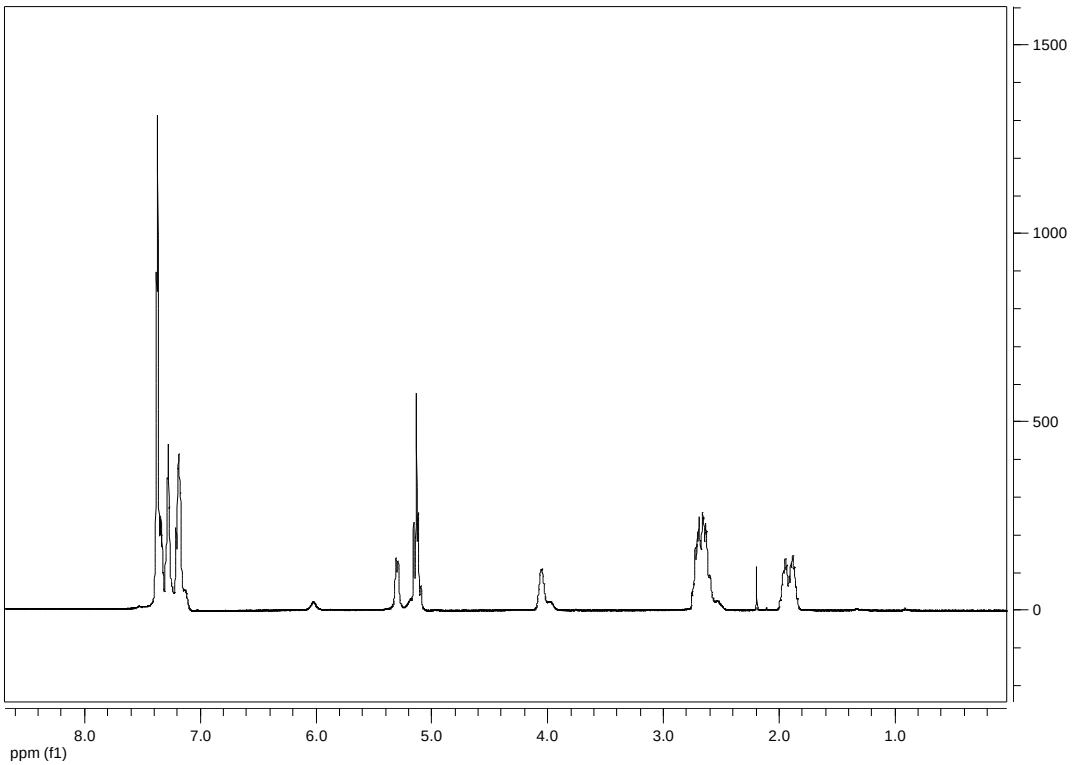
^{13}C NMR



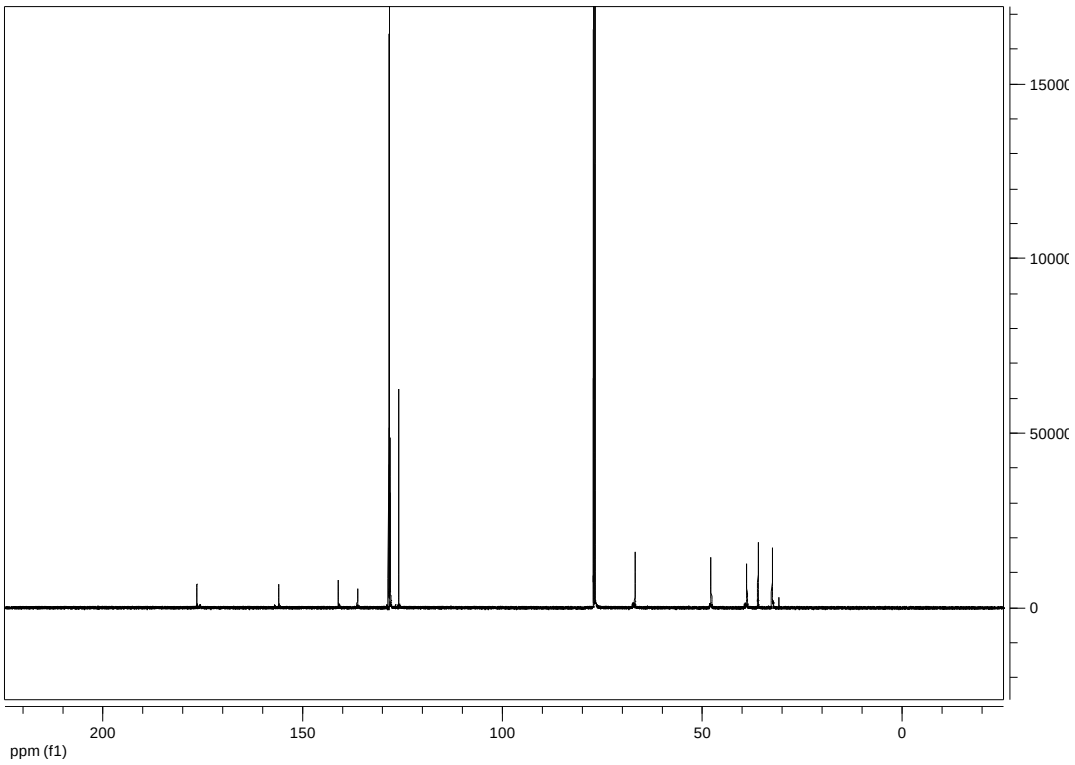


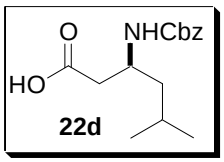
22b

^{1}H NMR



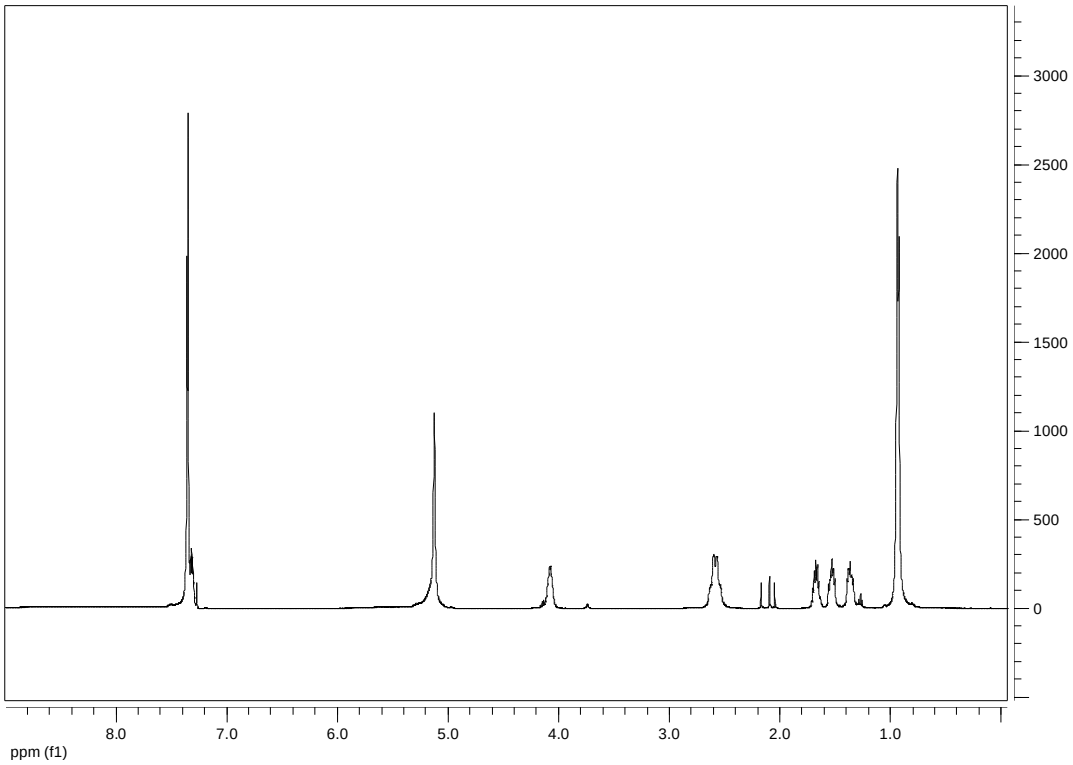
^{13}C NMR



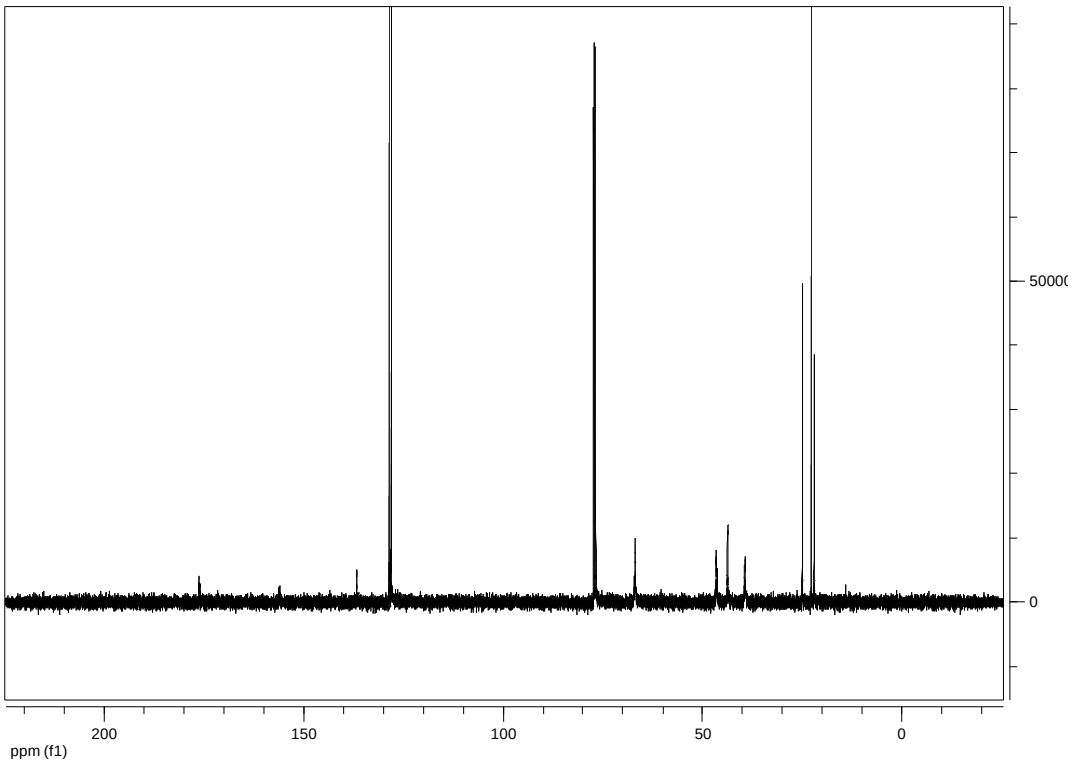


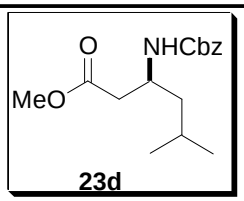
22d

^{1}H NMR



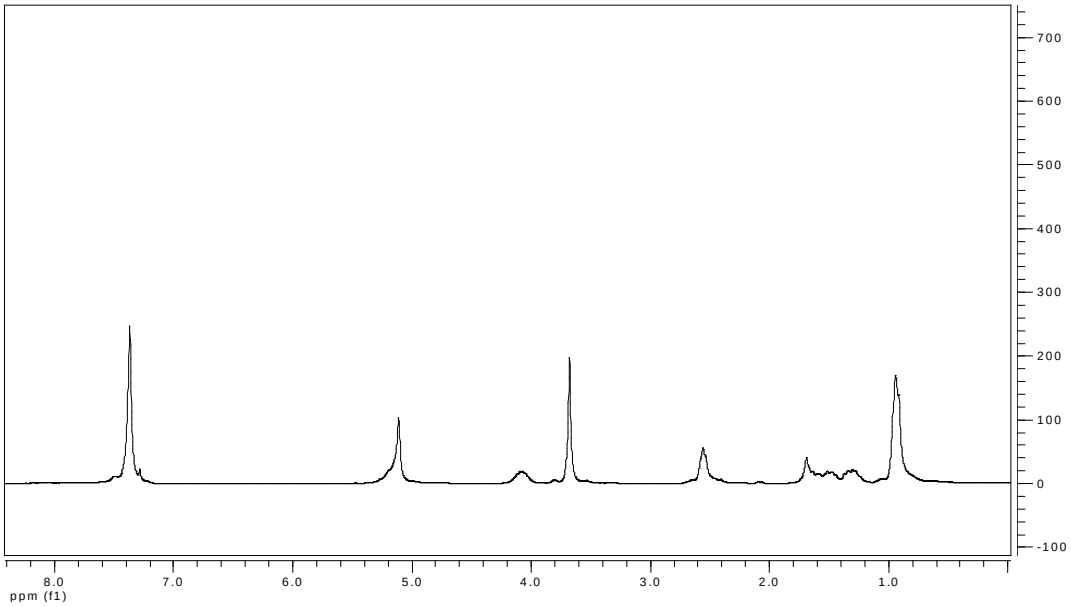
^{13}C NMR

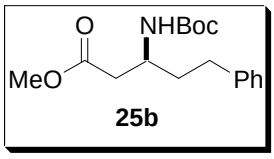




23d

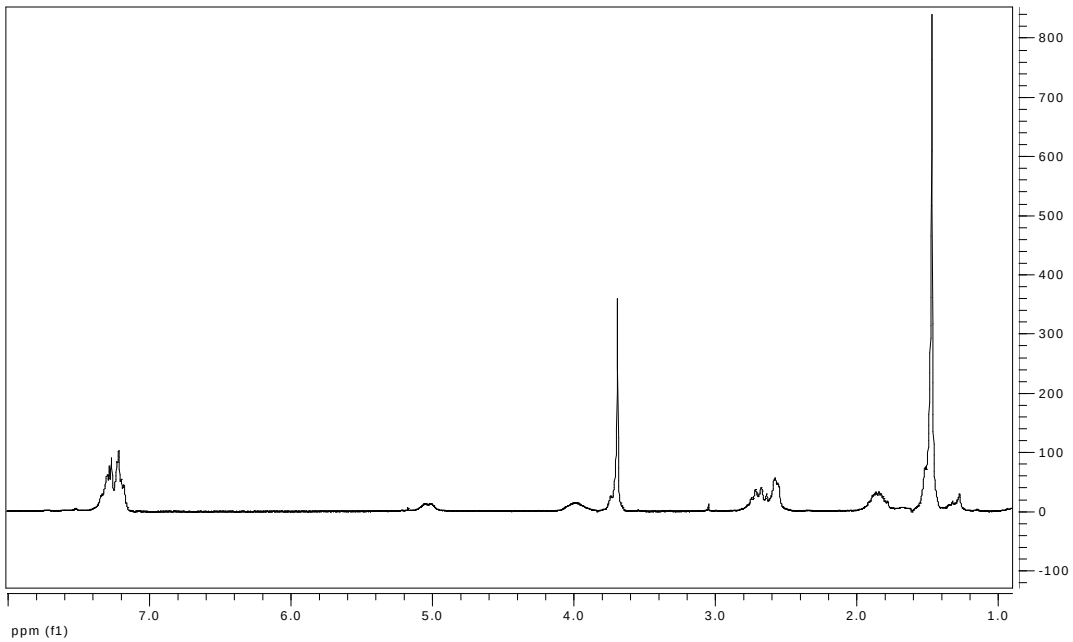
^{1}H NMR



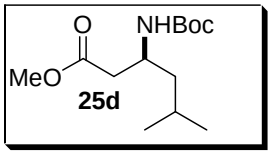


25b

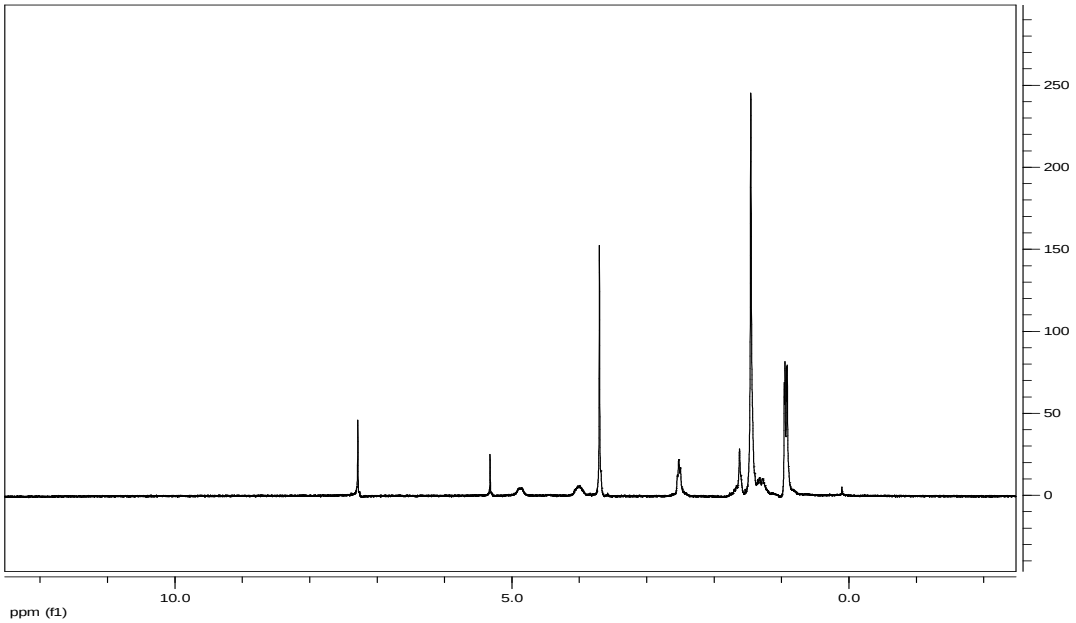
^{1}H NMR



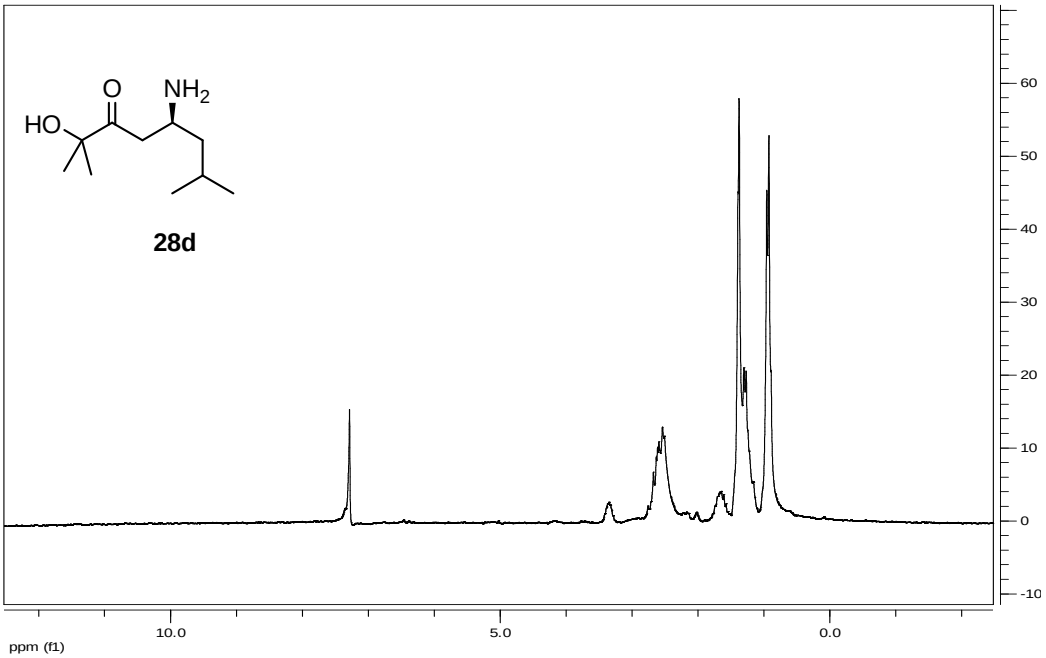
^{1}H NMR



25d

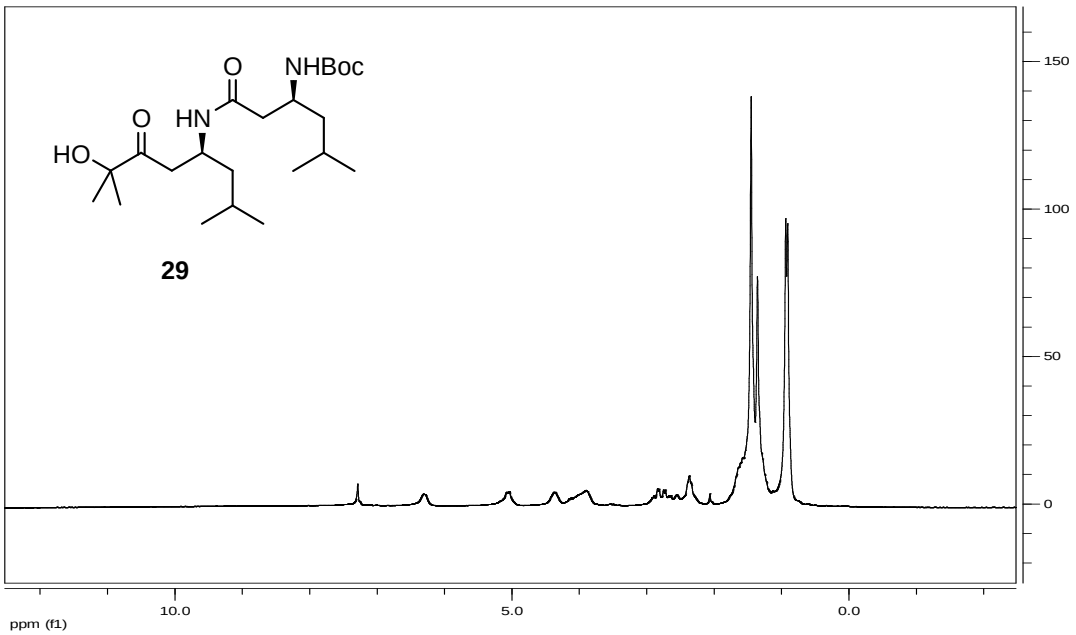


^{1}H NMR

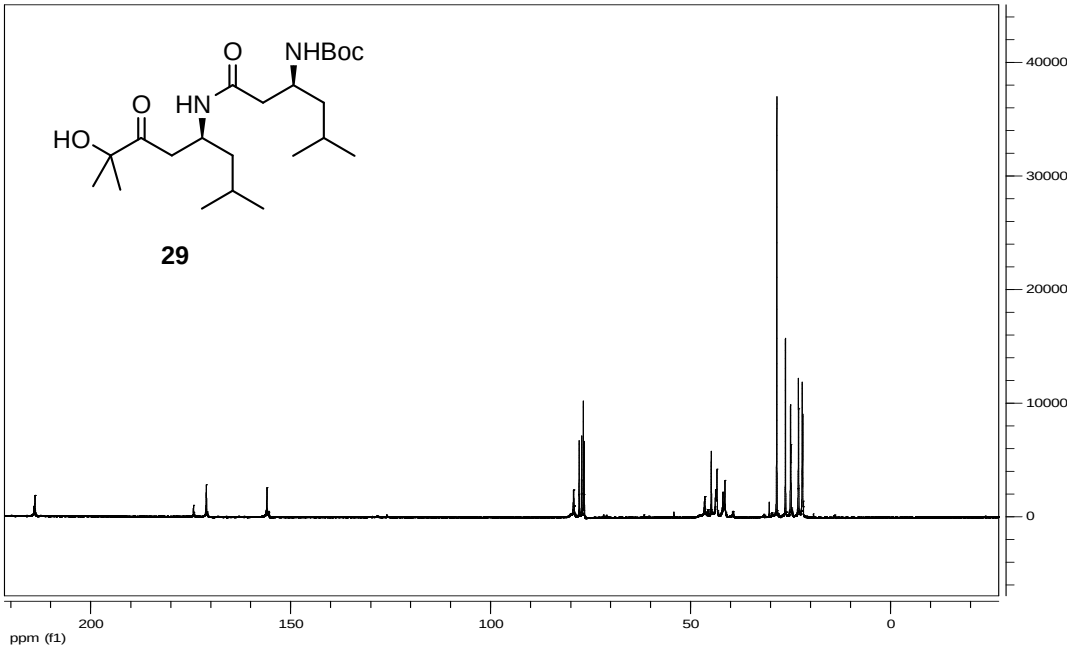


28d

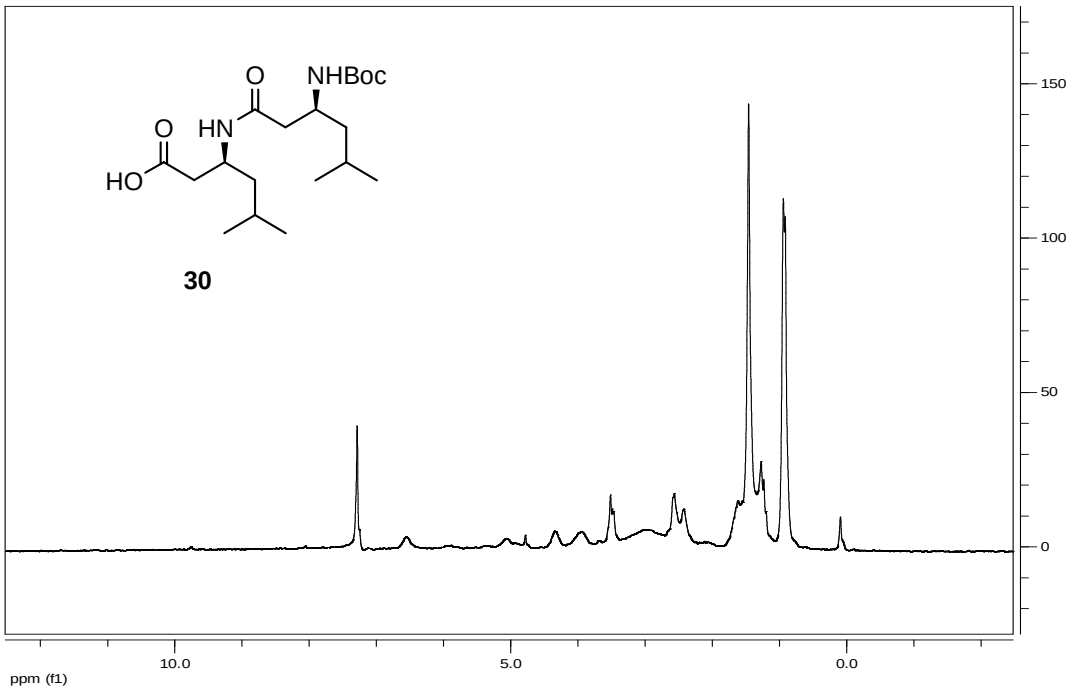
^{1}H NMR



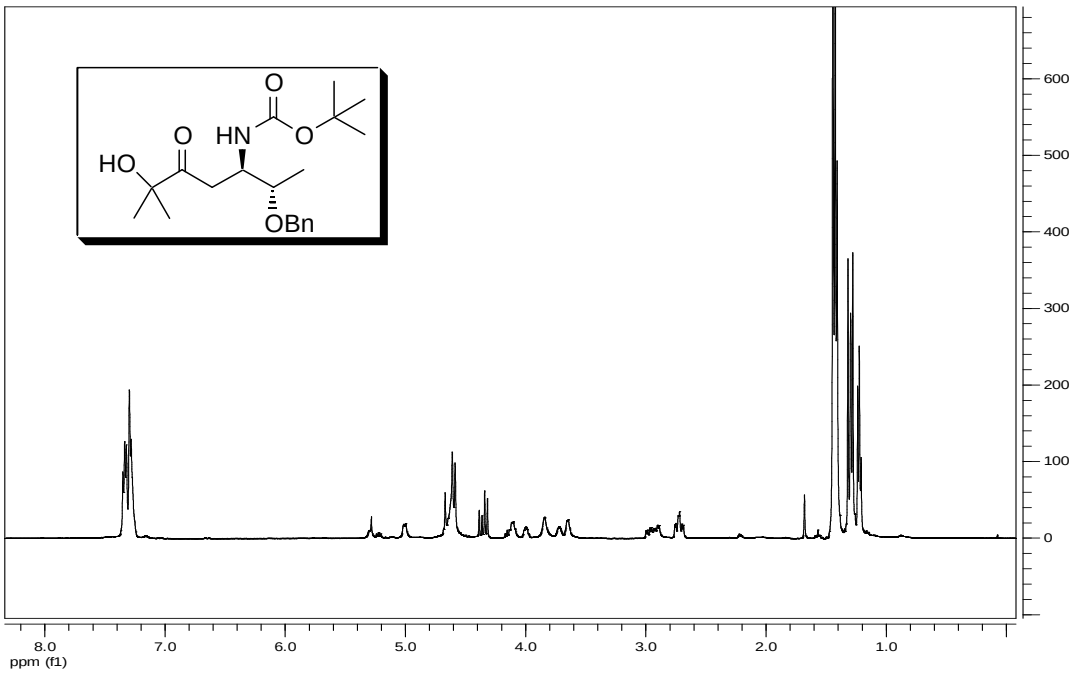
^{13}C NMR



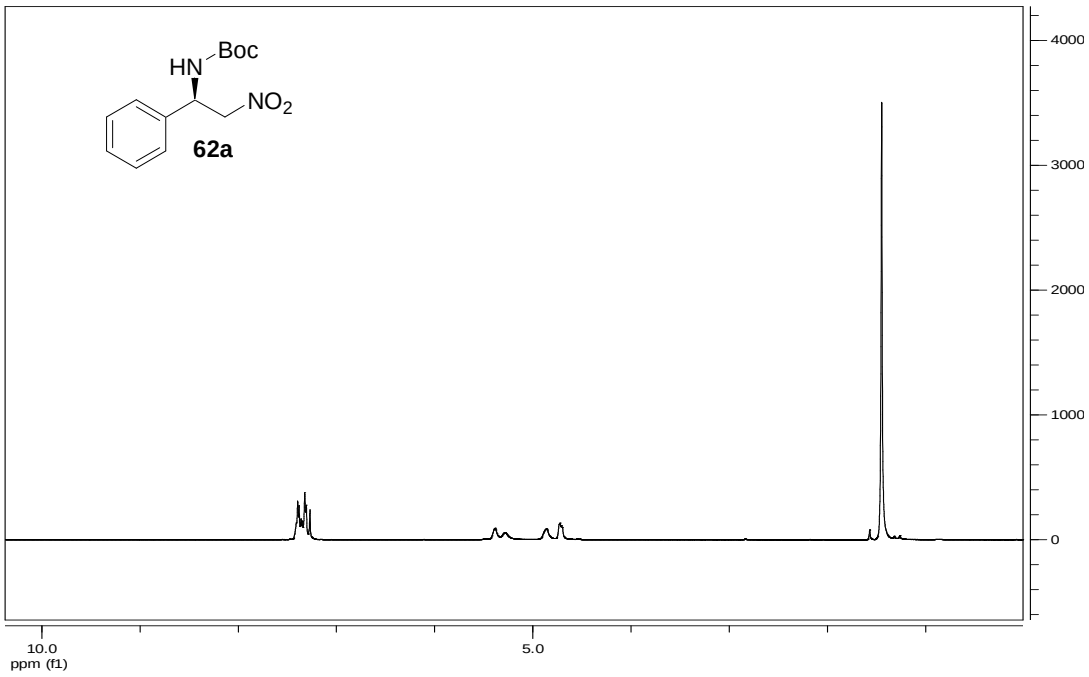
^{1}H NMR


O
NHBoc
O
HN
HO
30
150
100
50
0
10.0
5.0
0.0
ppm (f1)

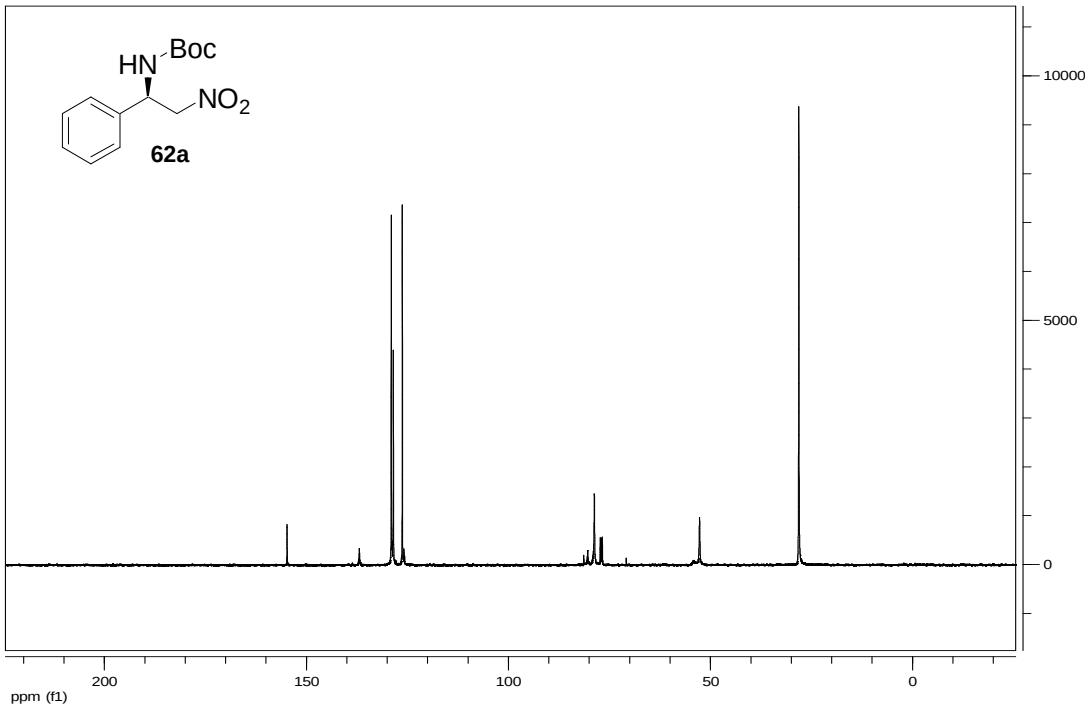
^{1}H NMR


O
O
HN
O
HO
OBn
600
500
400
300
200
100
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

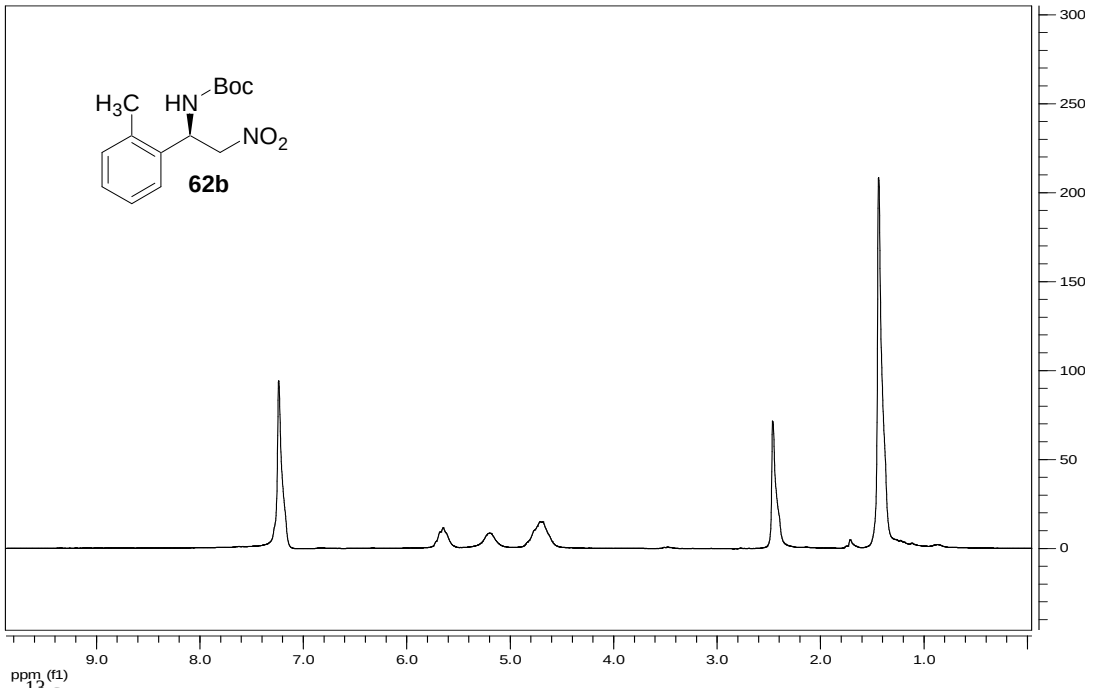
^{1}H NMR



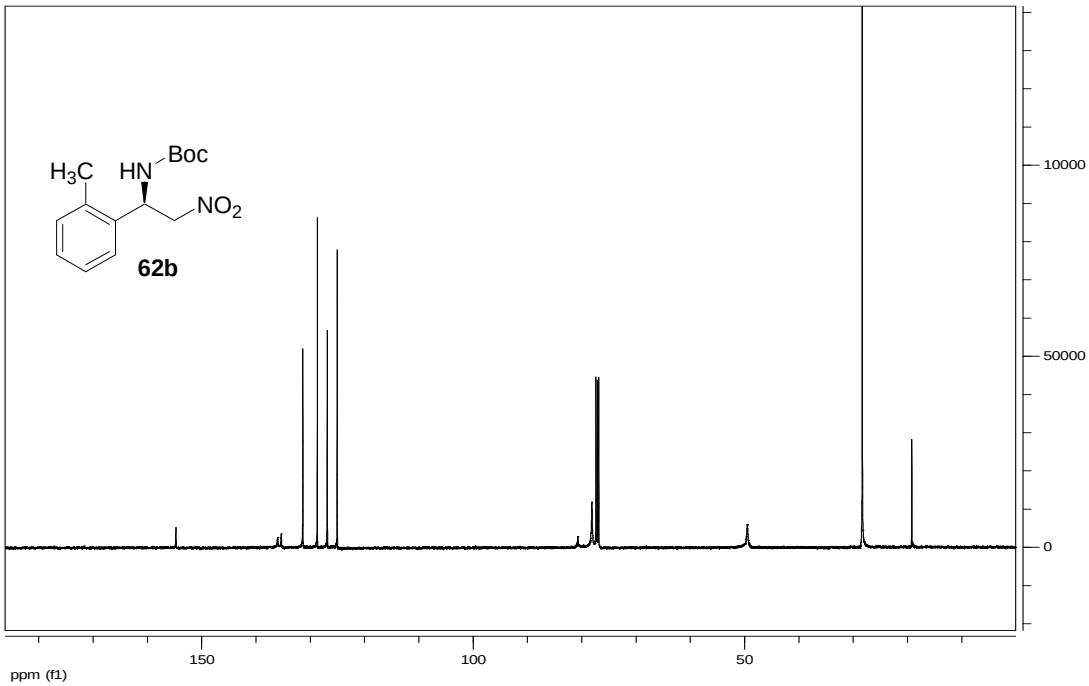
^{13}C NMR



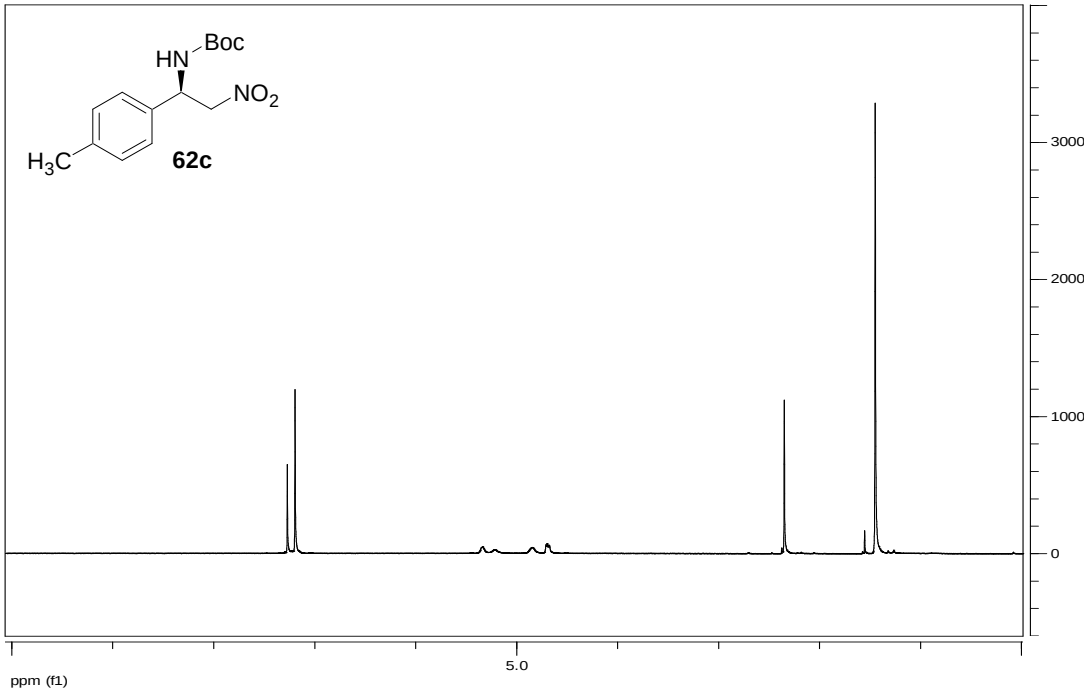
^{1}H NMR



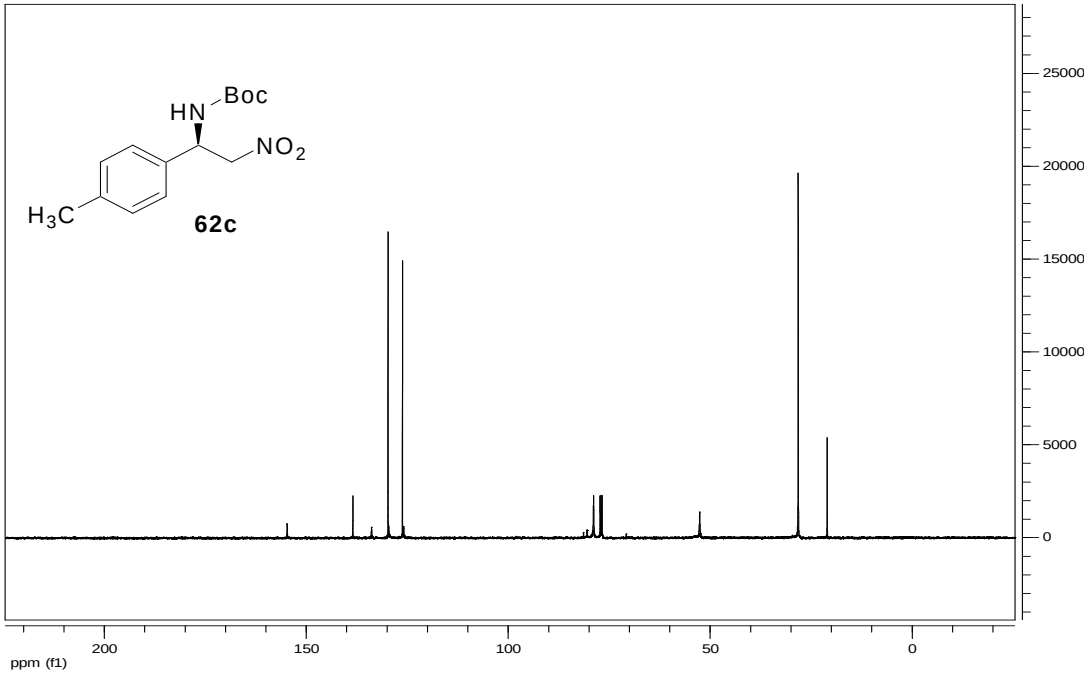
^{13}C NMR



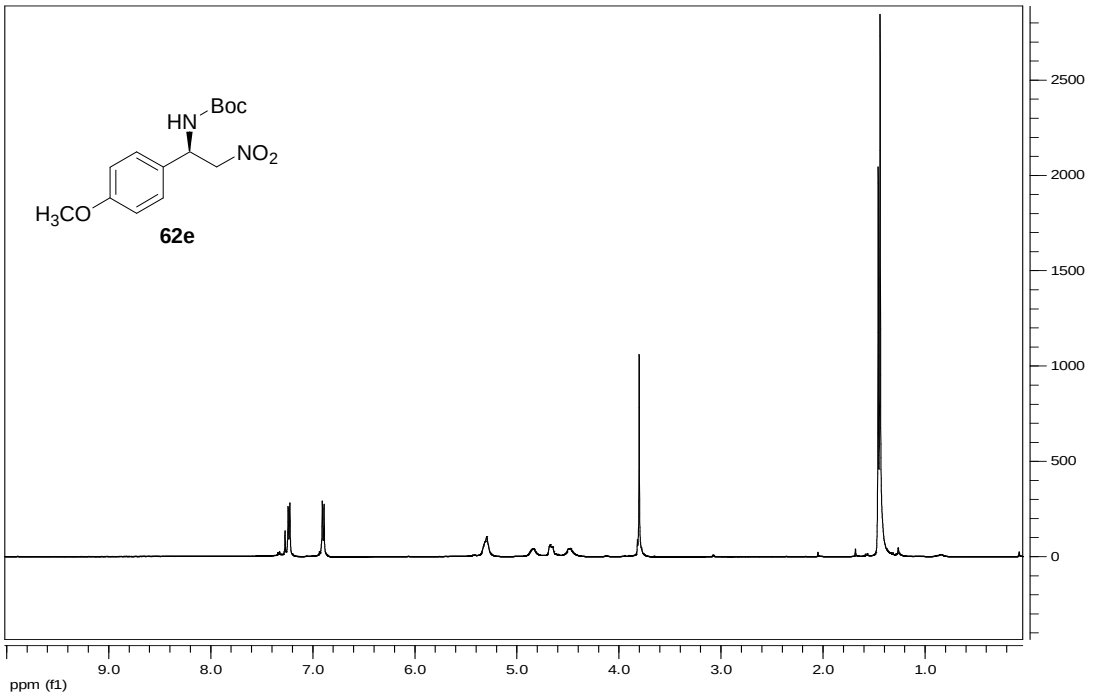
^{1}H NMR



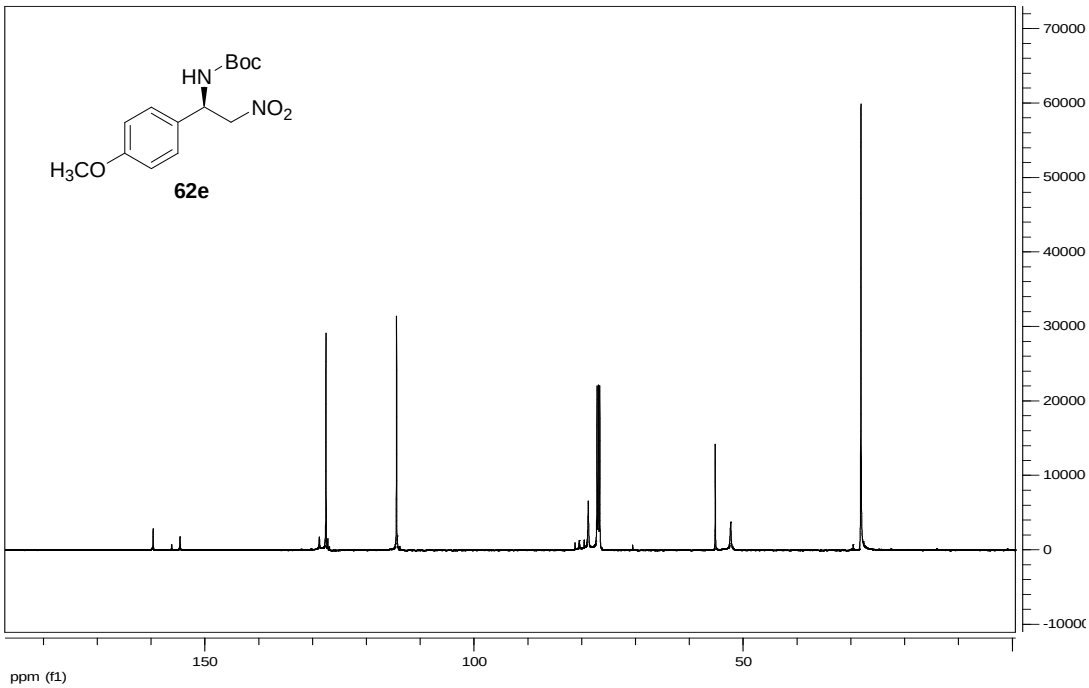
^{13}C NMR



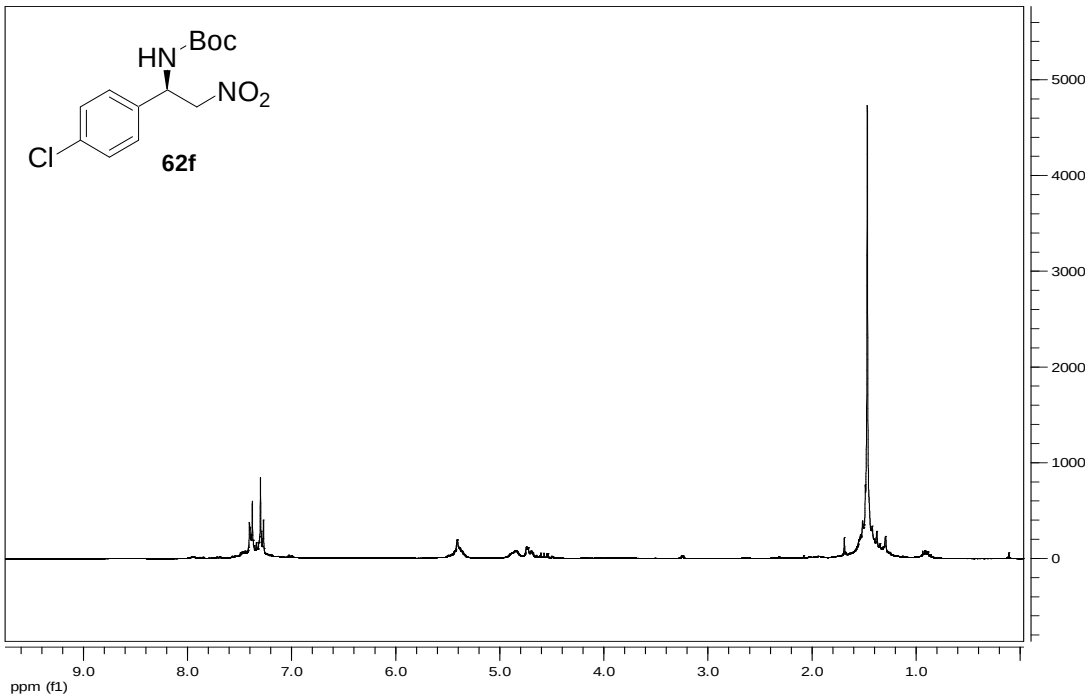
^{1}H NMR



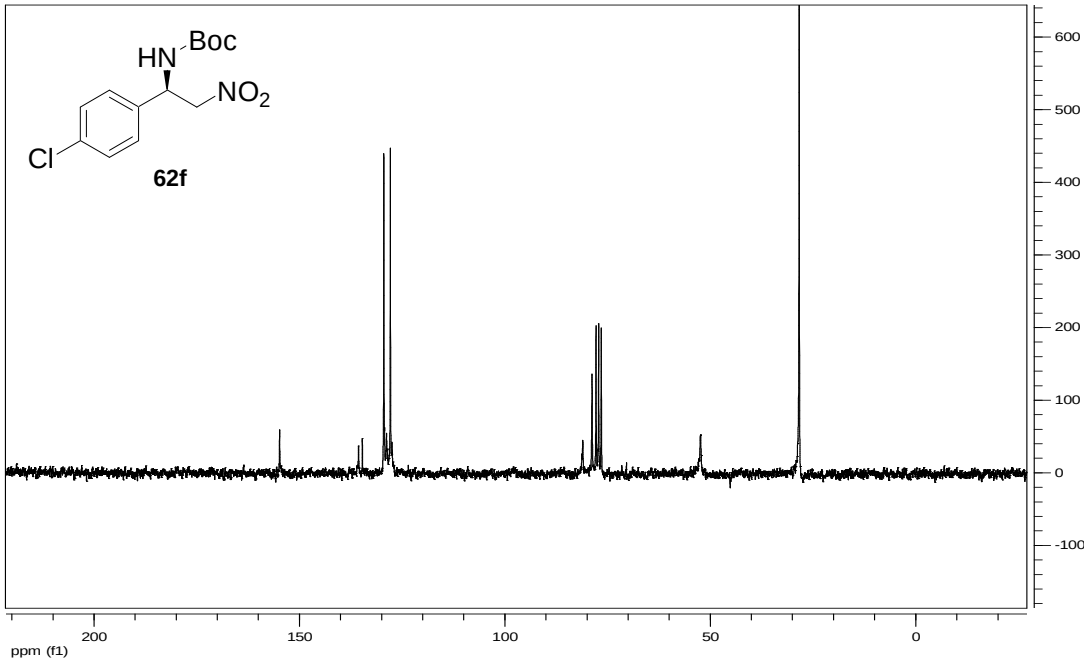
^{13}C NMR



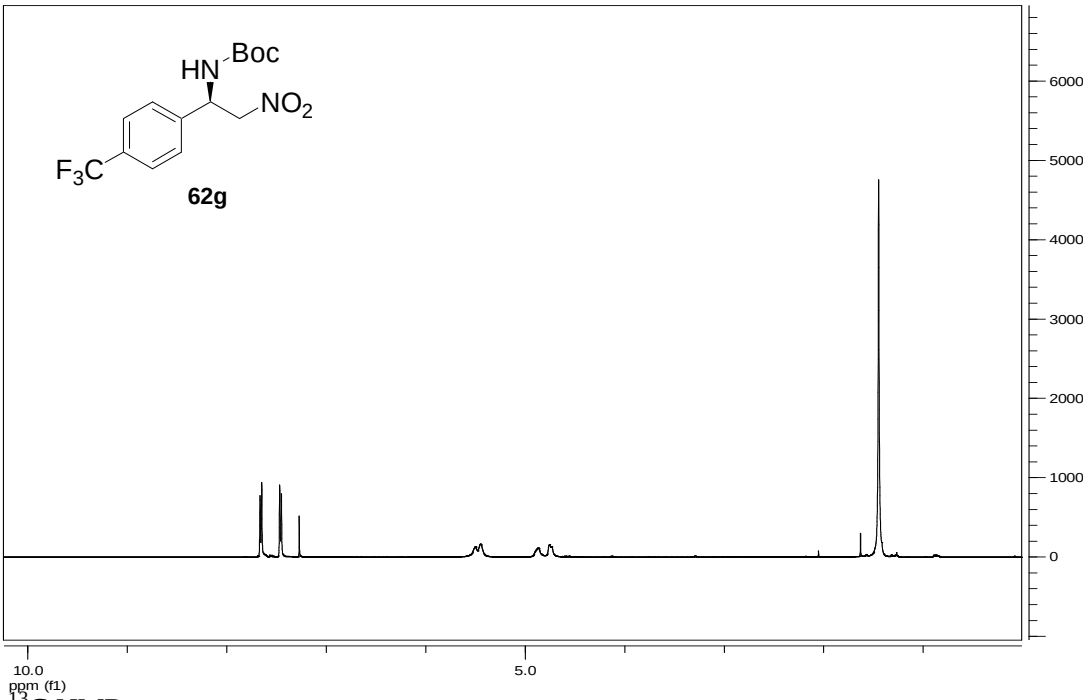
^{1}H NMR



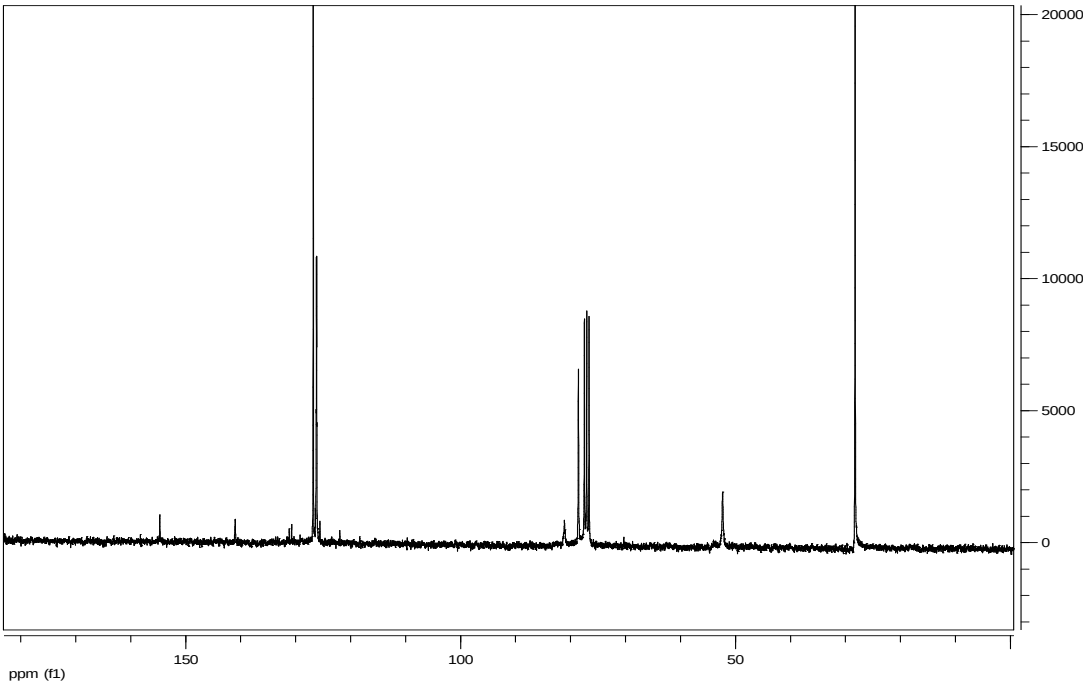
^{13}C NMR



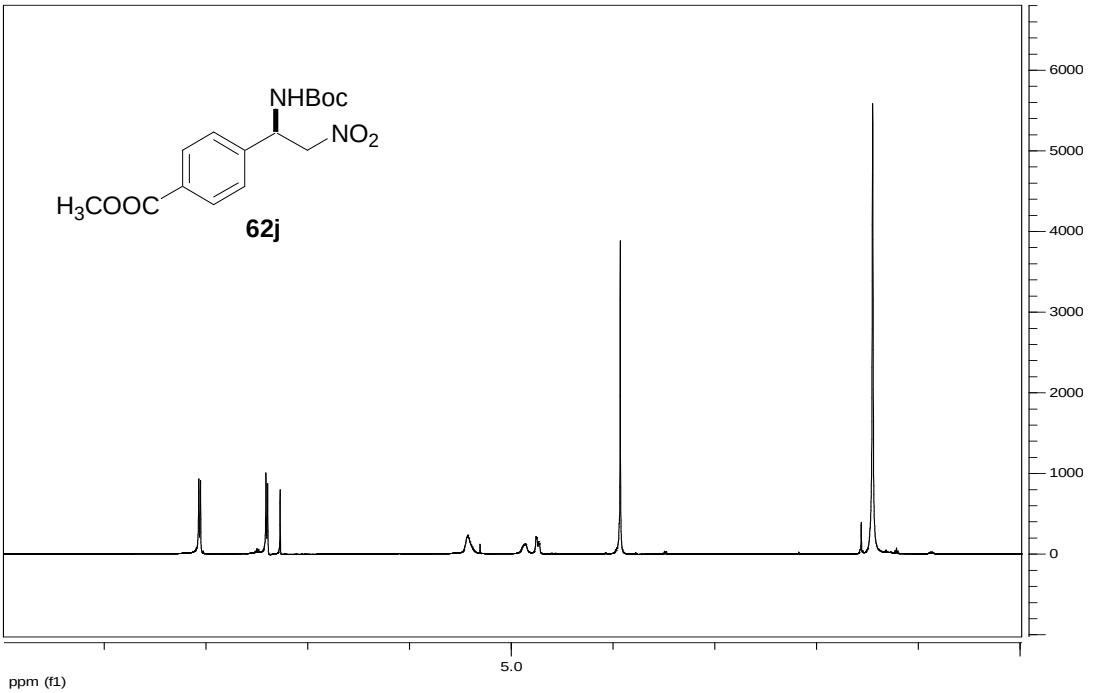
^{1}H NMR



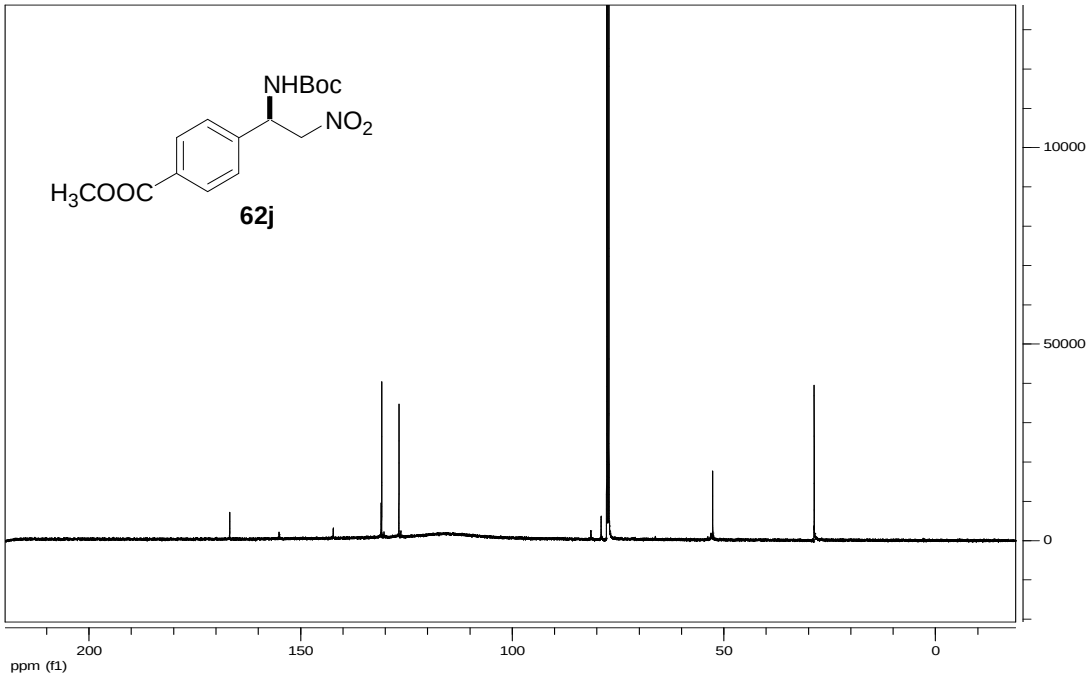
^{13}C NMR



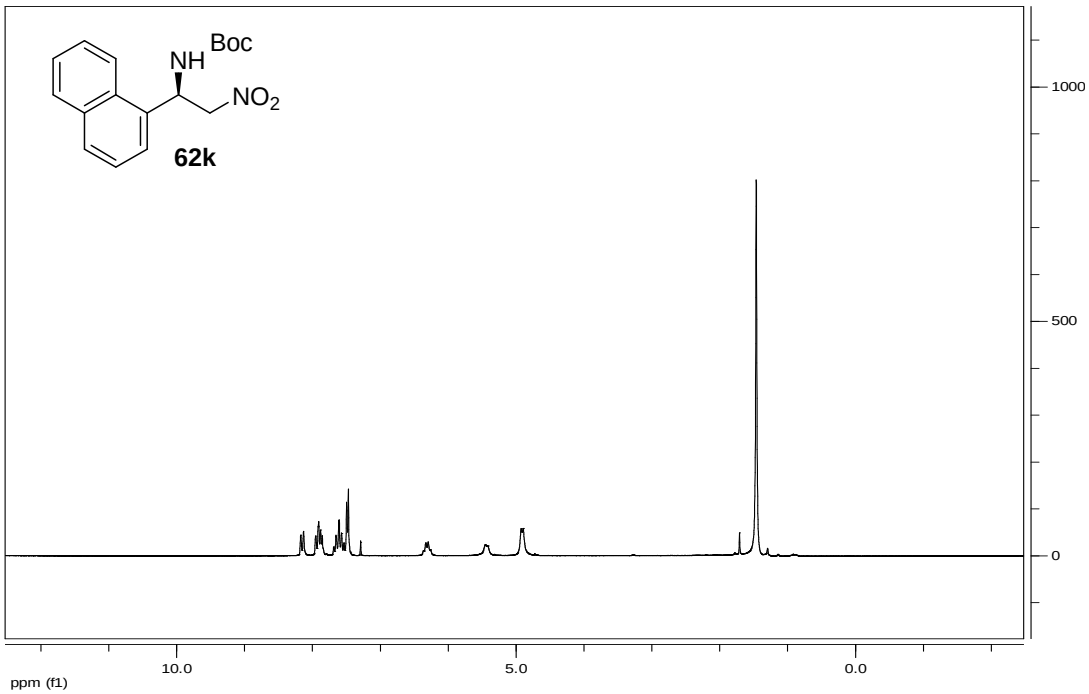
^{1}H NMR


NHBoc
NO2
H3COOC
62j
6000
5000
4000
3000
2000
1000
0
5.0
ppm (f1)

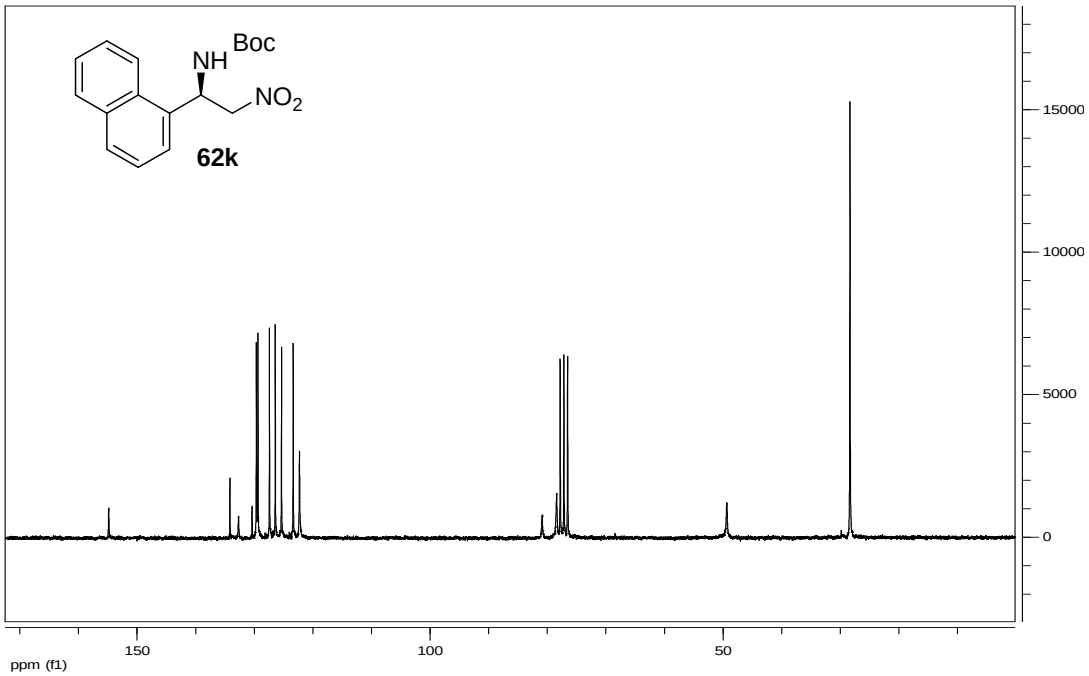
^{1}C NMR


NHBoc
NO2
H3COOC
62j
10000
50000
0
200
150
100
50
0
ppm (f1)

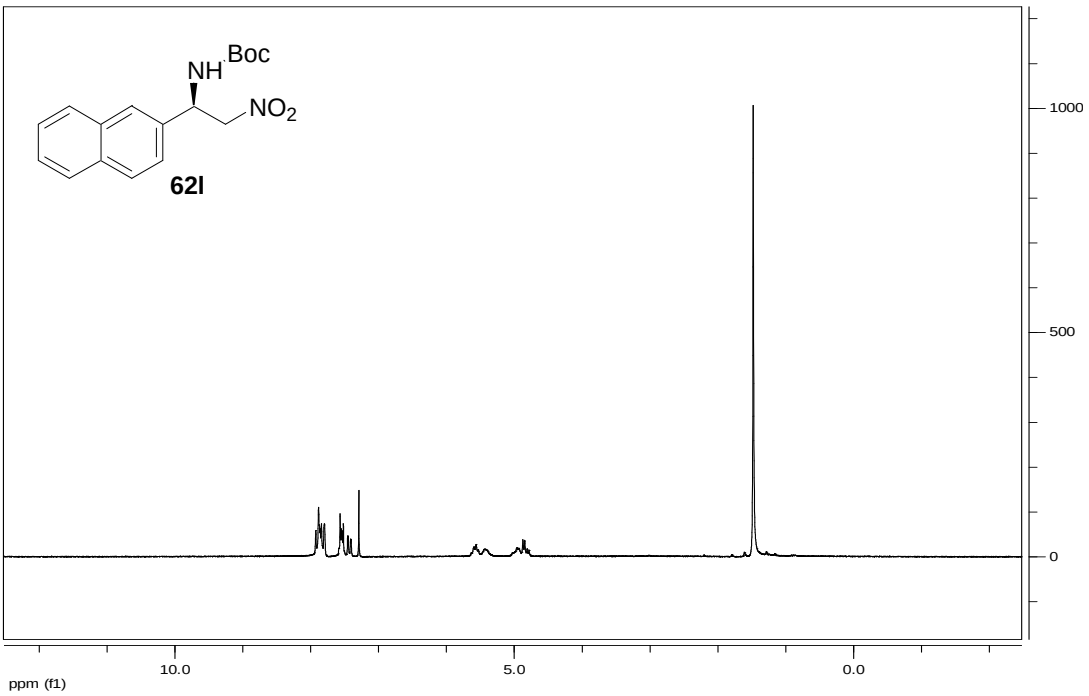
^{1}H NMR



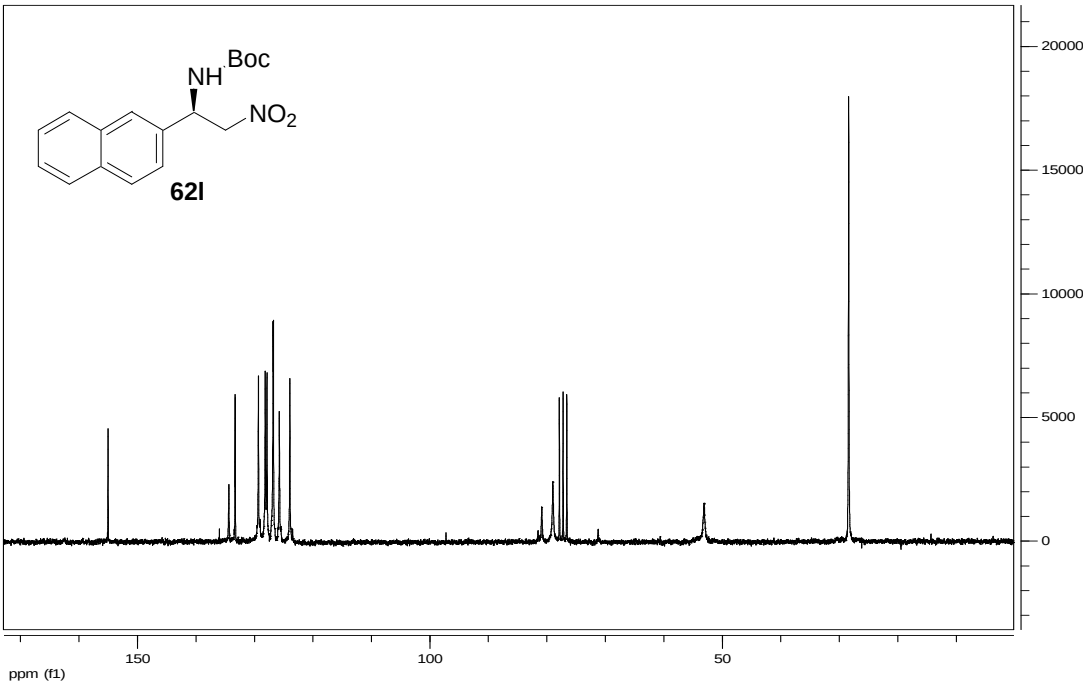
^{13}C NMR



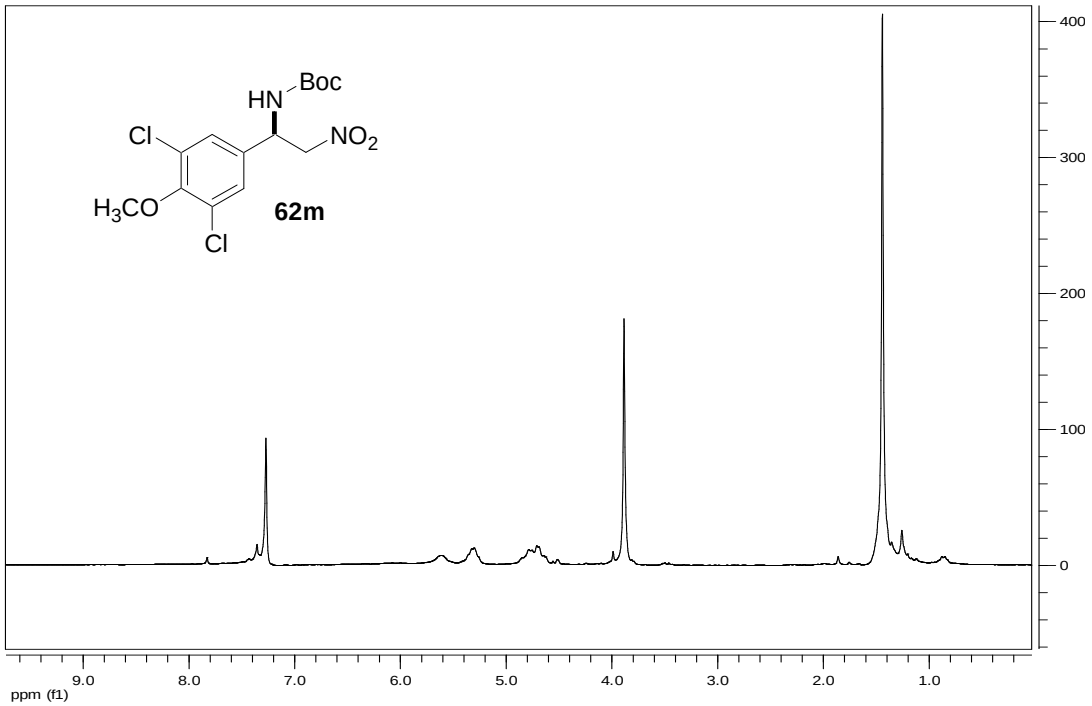
^{1}H NMR



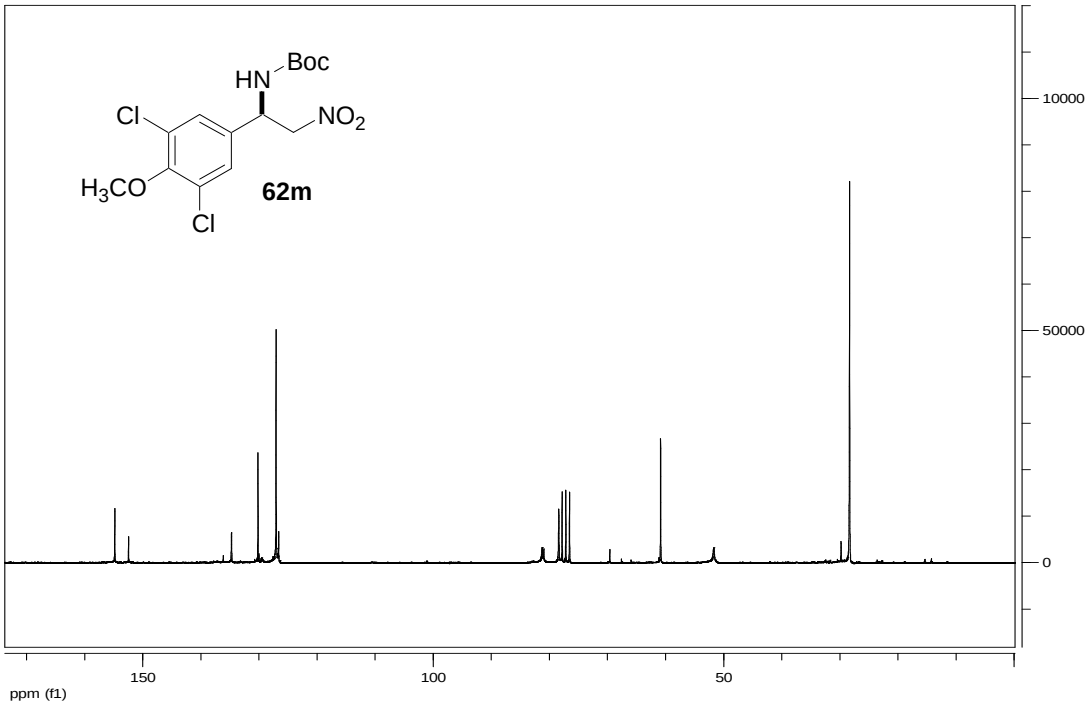
^{13}C NMR



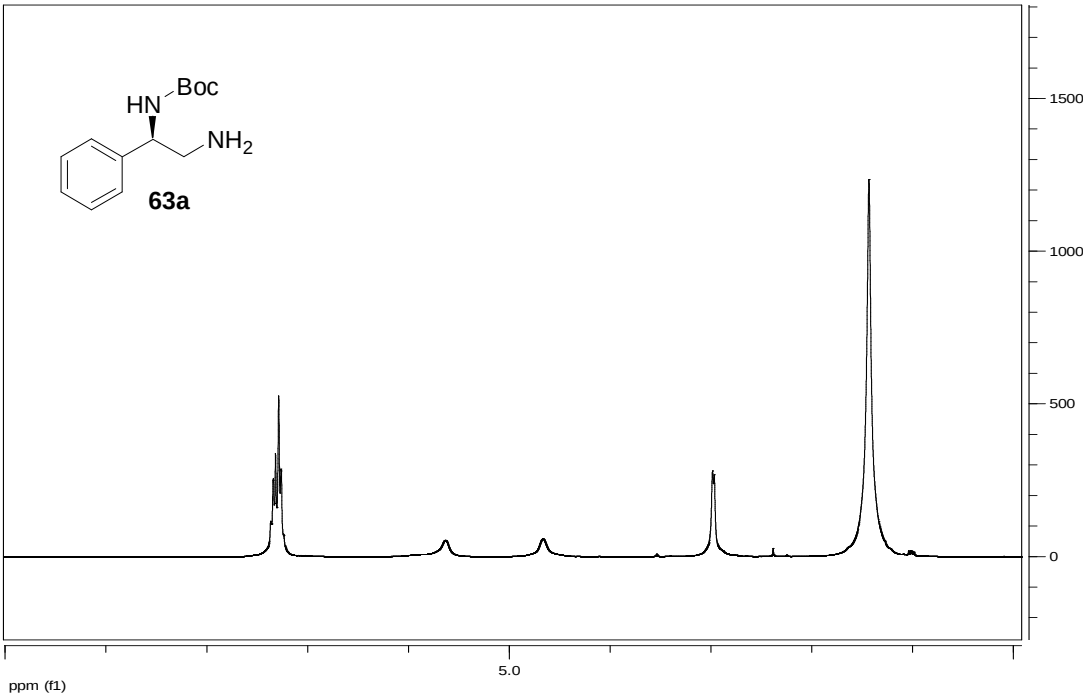
^{1}H NMR



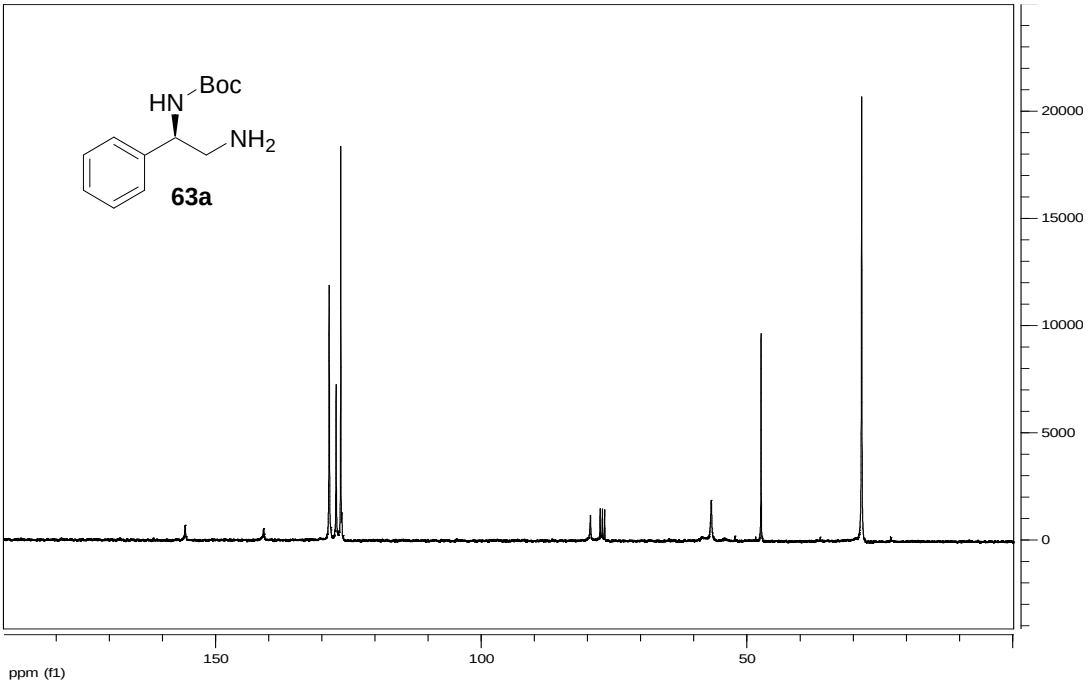
^{13}C NMR



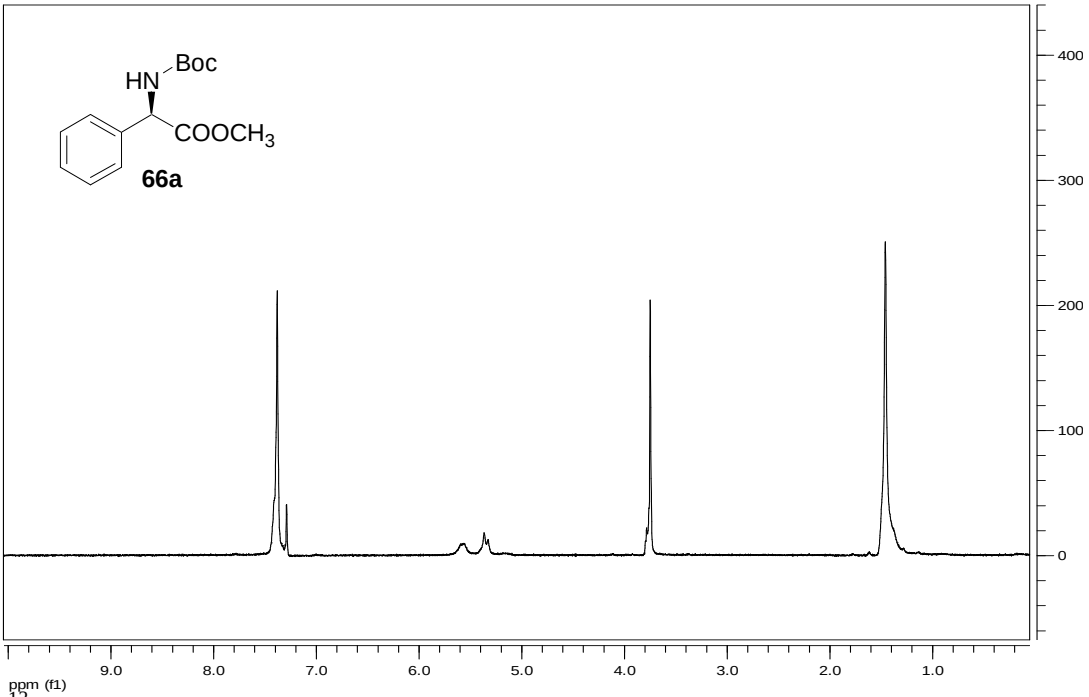
^{1}H NMR



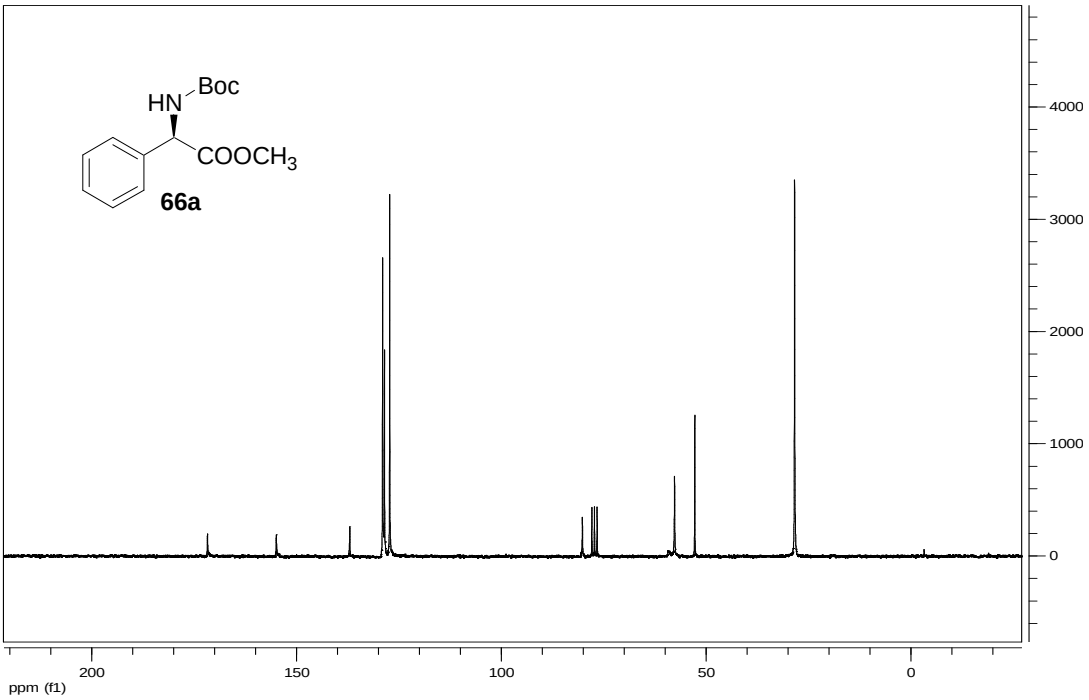
^{13}C NMR



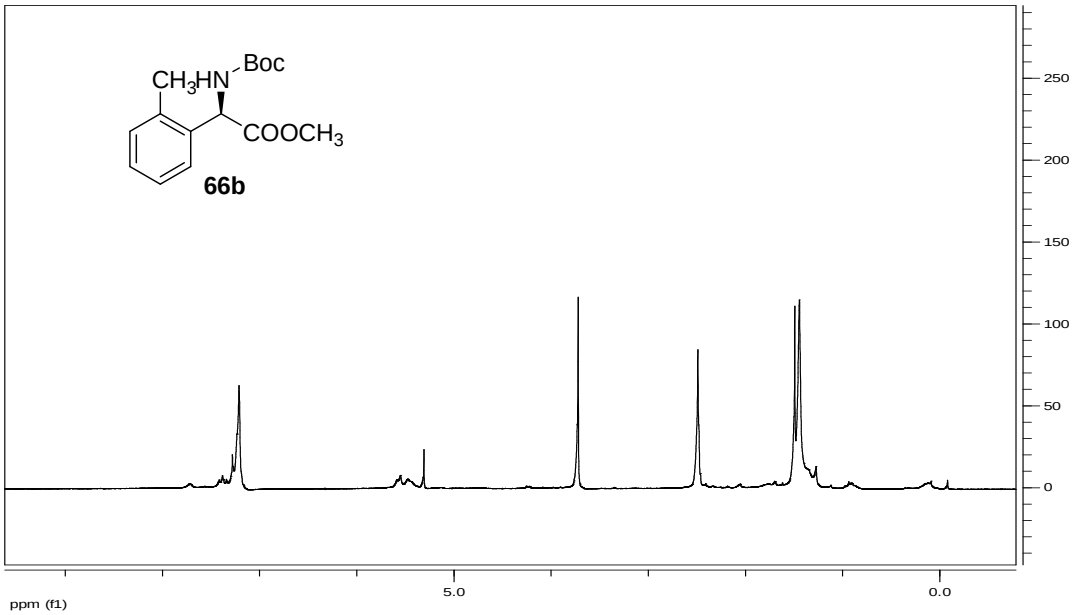
^{1}H NMR



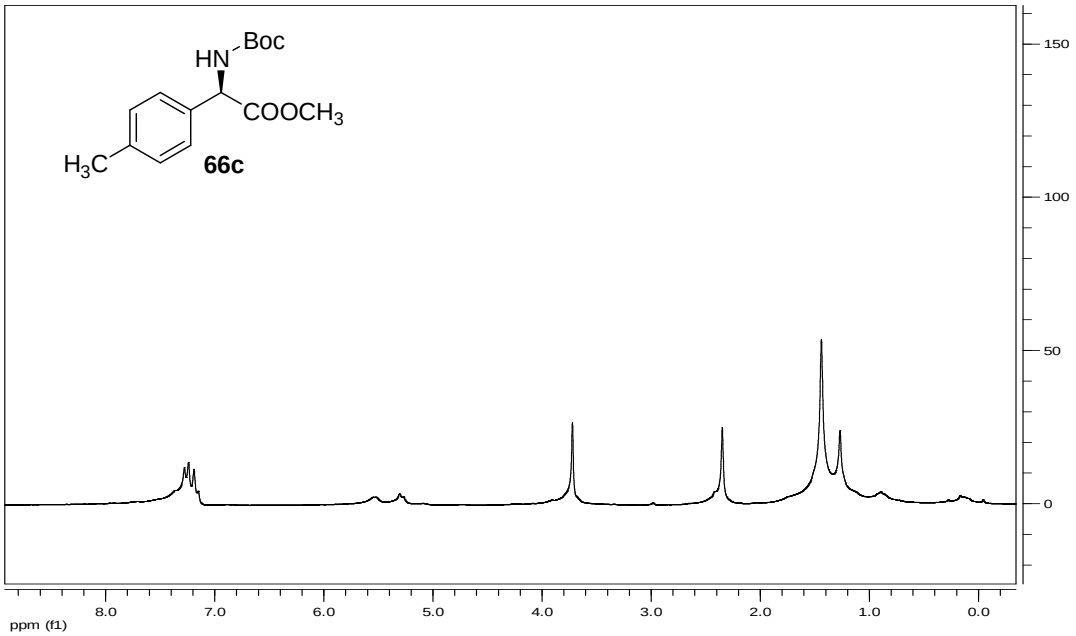
^{13}C NMR



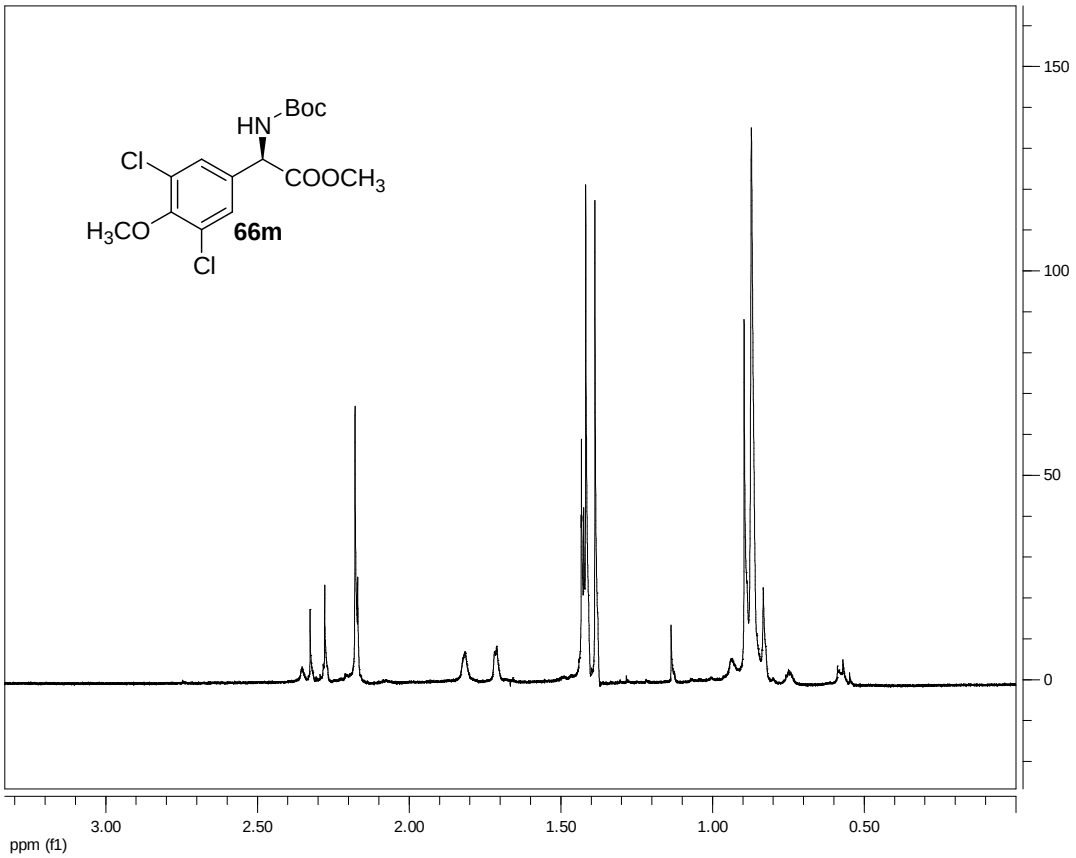
^{1}H NMR


CH3HN
Boc
COOCH3
66b
250
200
150
100
50
0
5.0
0.0
ppm (f1)

^{1}H NMR

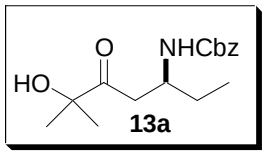

HN
Boc
COOCH3
H3C
66c
150
100
50
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

^{1}H NMR


HN
Boc
Cl
COOCH3
H3CO
66m
Cl
150
100
50
0
3.00
2.50
2.00
1.50
1.00
0.50
ppm (f1)

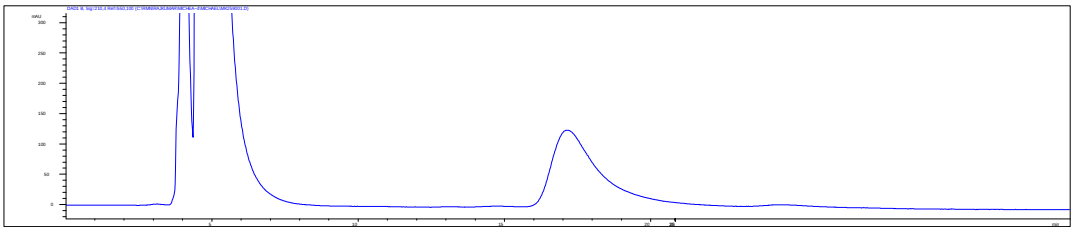
Apendix II

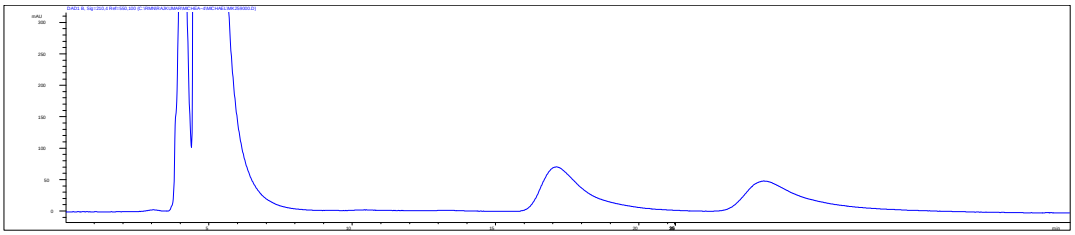
Chiralpak AS, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm



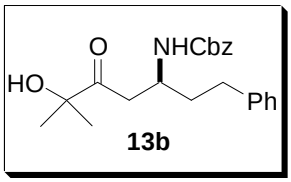
13a

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.146	MM	1.9395	1.47286e4	126.56786	97.6234
2	24.624	MM	1.7084	358.55582	3.49790	2.3766



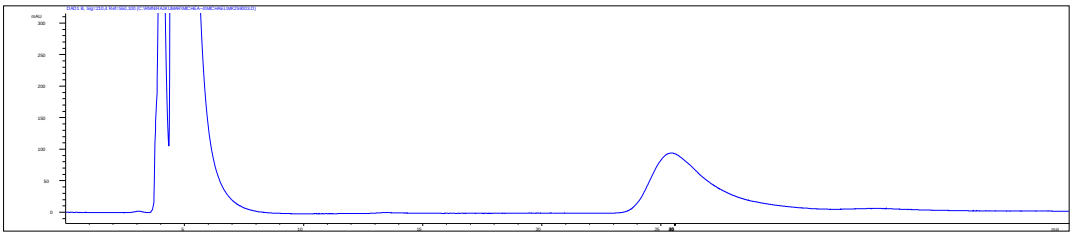


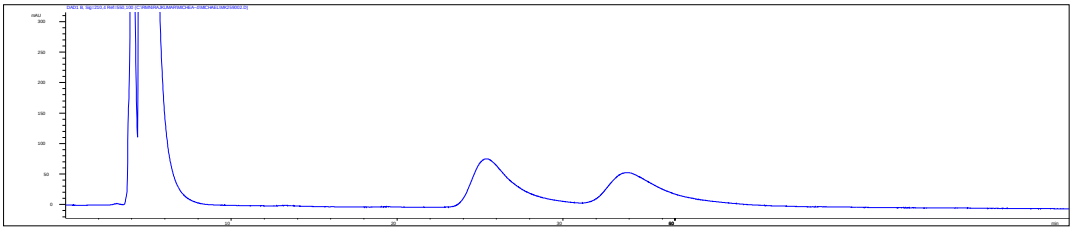
Chiralpak AS, 95:5 (hexane:iPrOH), 0.8mL/min, λ=210nm



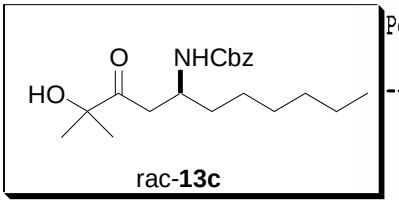
13b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.436	MM	2.9519	1.66433e4	93.96838	98.1968
2	34.205	MM	2.3225	305.61594	2.19311	1.8032

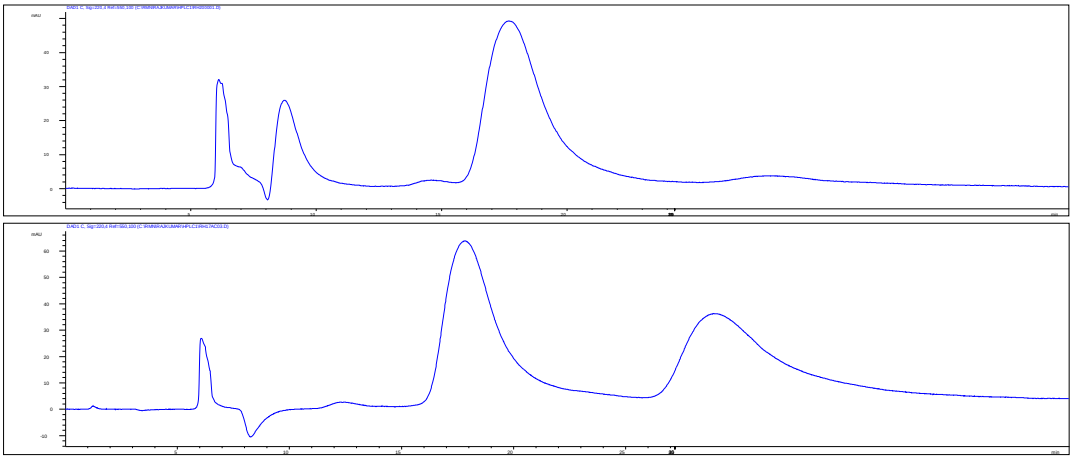




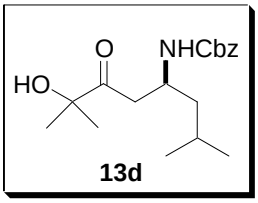
Chiralpak AS, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm



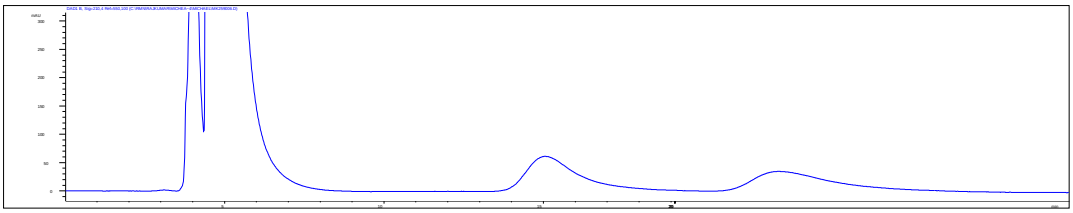
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.694	MM	2.6588	7477.41455	46.87159	95.8491
2	27.873	MM	2.8419	323.82446	1.89910	4.1509

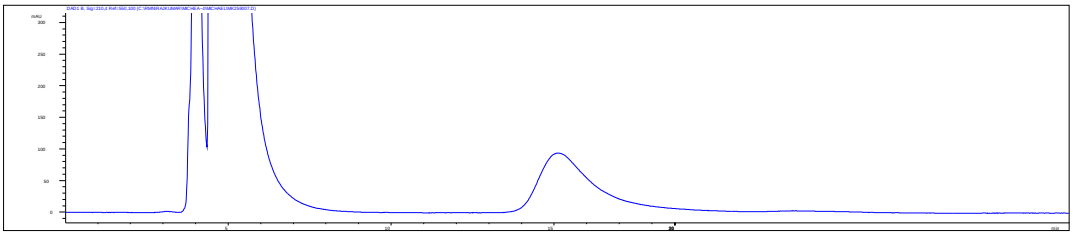


Chiralpak AS, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm

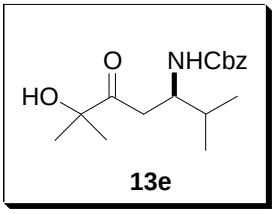


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.125	MM	2.0383	1.15045e4	94.06971	97.5042
2	22.408	MM	2.2875	294.47495	2.14552	2.4958



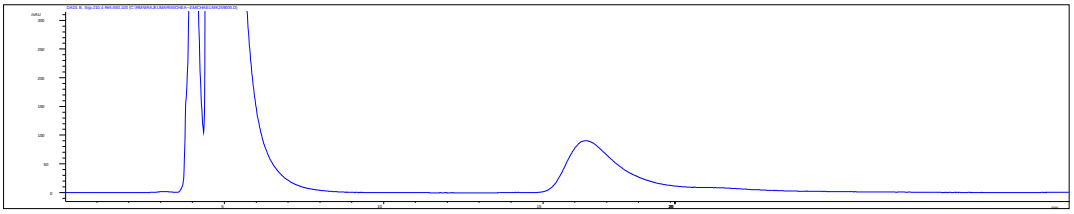


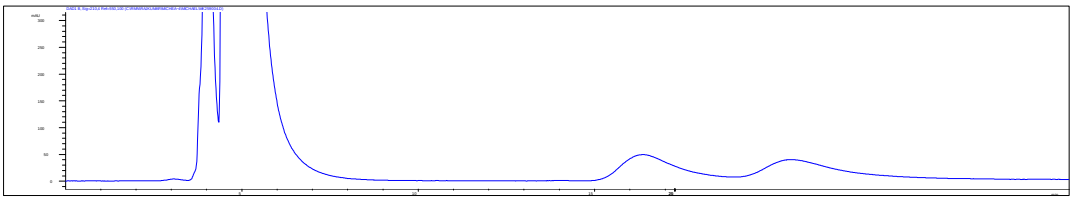
Chiralpak AS, 95:5 (hexane:iPrOH), 0.8mL/min, λ=210nm



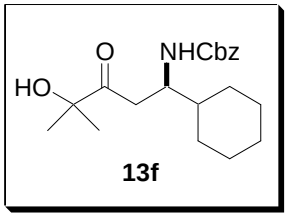
13e

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.336	MM	1.8388	9658.24414	87.54135	98.9665
2	20.693	MM	1.2916	100.85738	1.30144	1.0335



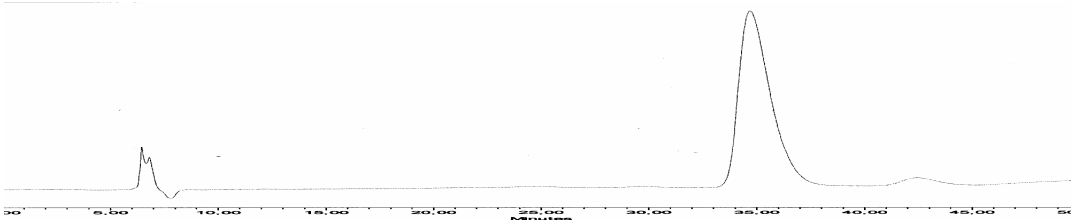


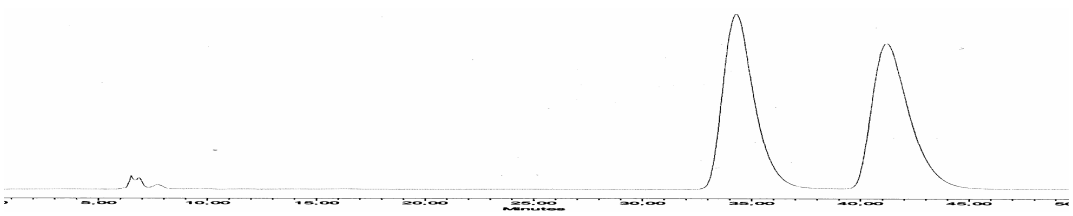
Chiralpak AS, 96:4 (hexane:iPrOH), 0.8mL/min, λ=210nm



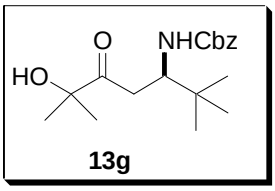
13f

Retention Time (min)	Area	% Area	Height
34,809	12977659	97,00	127364
42,425	400944	3,00	4460



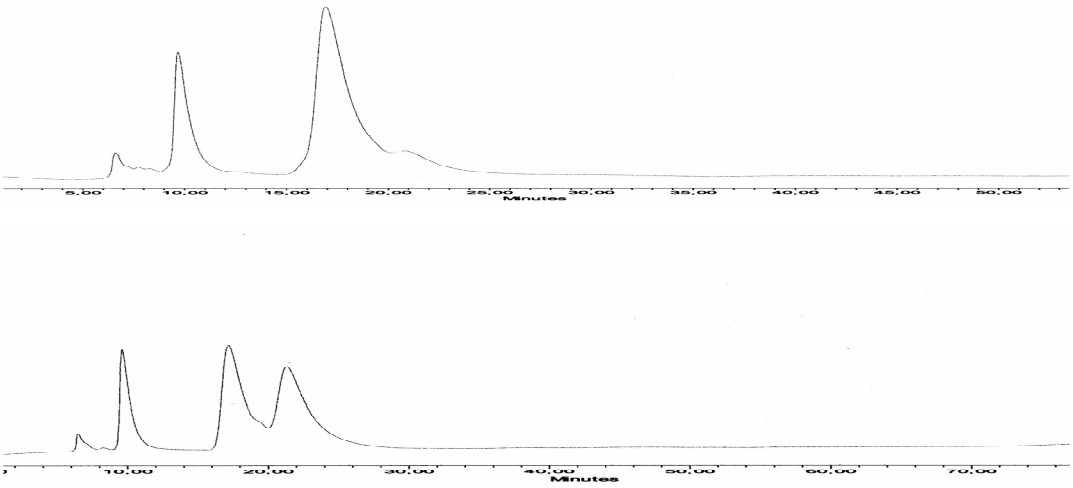


Chiralpak AS, 96:4 (hexane:iPrOH), 0.8mL/min, λ=210nm

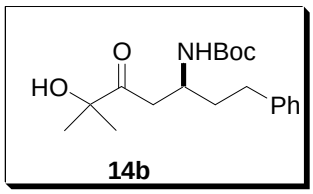


13g

Retention Time (min)	Area	% Area	Height
17,076	24005579	96,92	235024
21,067	763498	3,08	7900

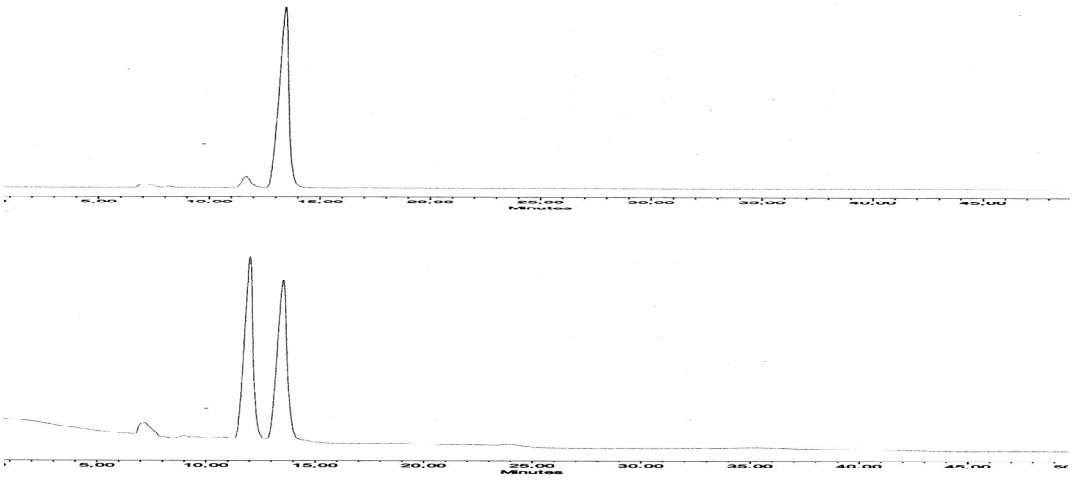


Chiralcel OD, 90:10 (hexane:iPrOH), 0.5mL/min, λ=220nm

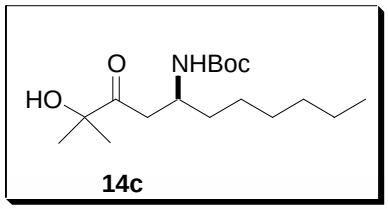


14b

Retention Time (min)	Area	% Area	Height
11,615	631146	4,90	24219
13,110	12250728	95,10	400790

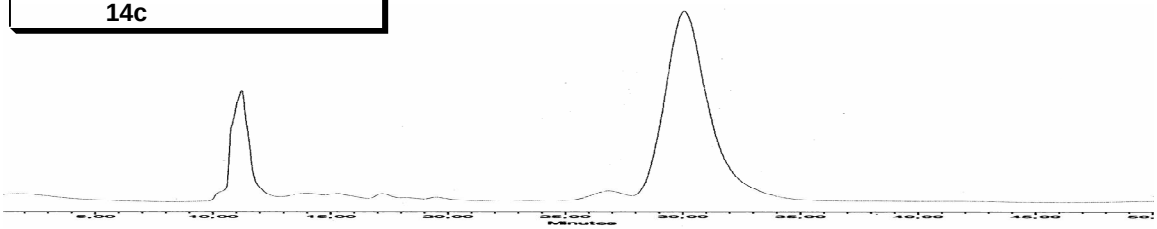


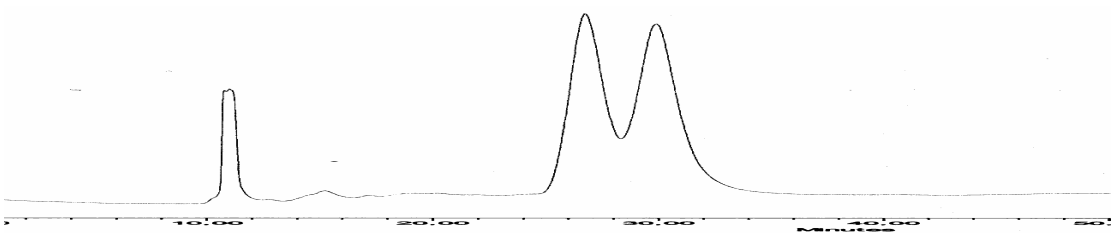
Chiralpak AD, 97:3 (hexane:iPrOH), 0.5mL/min, λ=220nm



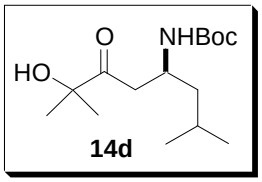
14c

Retention Time (min)	Area	% Area	Height
26,750	104631	1,78	1436
30,046	5785131	98,22	45163



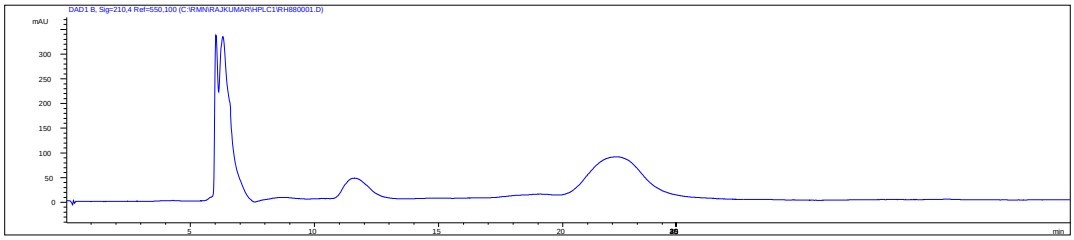


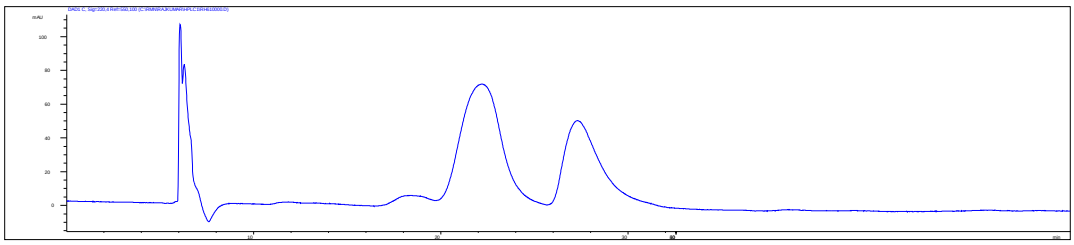
Chiralpak AD, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm



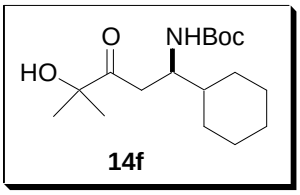
14d

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.089	MM	1.5875	242.23987	2.54318	1.9252
2	22.223	MM	2.5295	1.23404e4	81.30984	98.0748



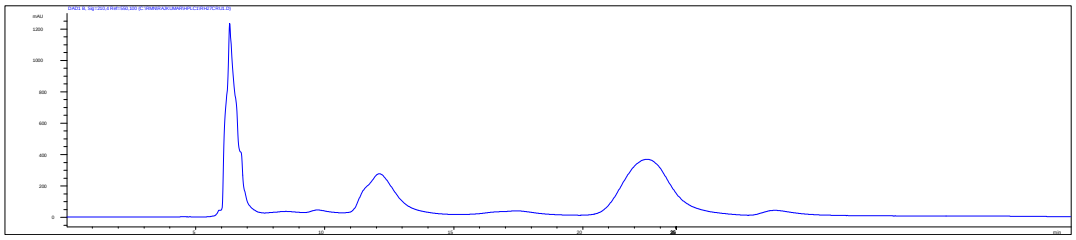


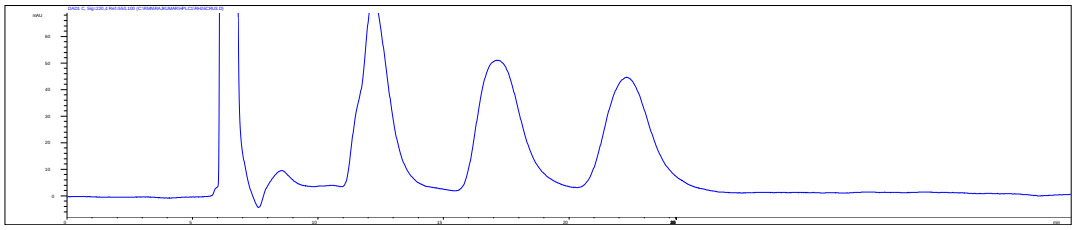
Chiralpak AD, 95:5 (hexane:iPrOH), 0.5mL/min, λ=210nm



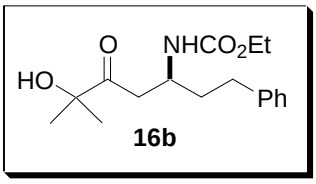
14f

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.245	MM	1.7430	668.27991	6.39004	4.4651
2	22.334	VV	1.6275	1.42985e4	104.03514	95.5349



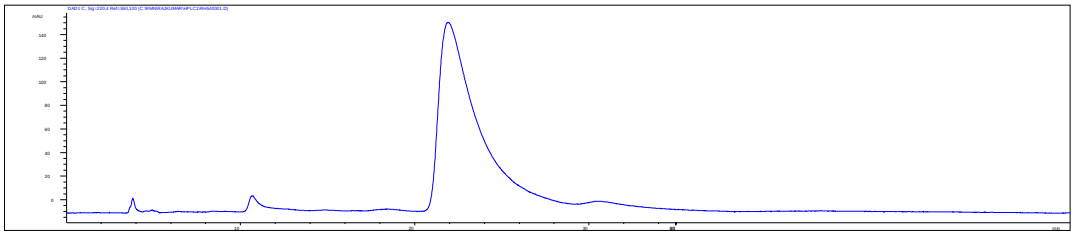


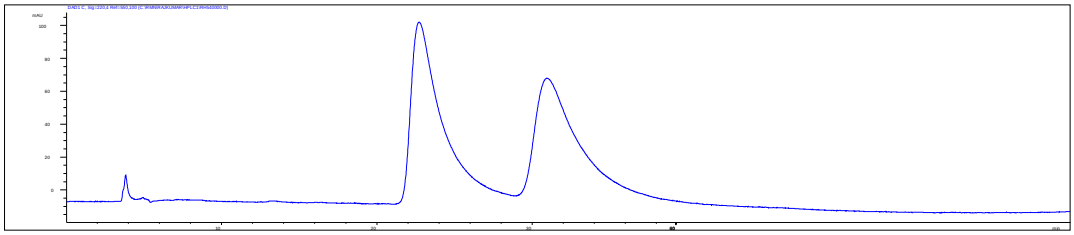
Chiralpak AS, 96:4 (hexane:iPrOH), 0.8mL/min, λ=220nm



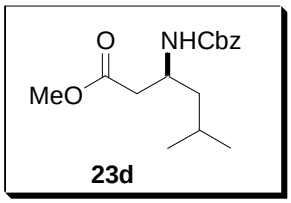
16b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.923	MM	2.6171	2.50359e4	159.43698	98.0971
2	30.610	MM	2.1385	485.65616	3.78506	1.9029



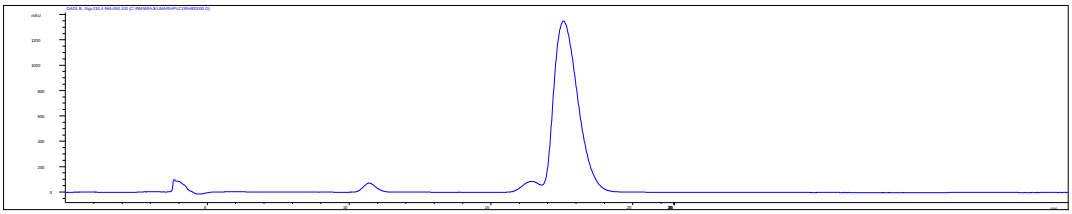


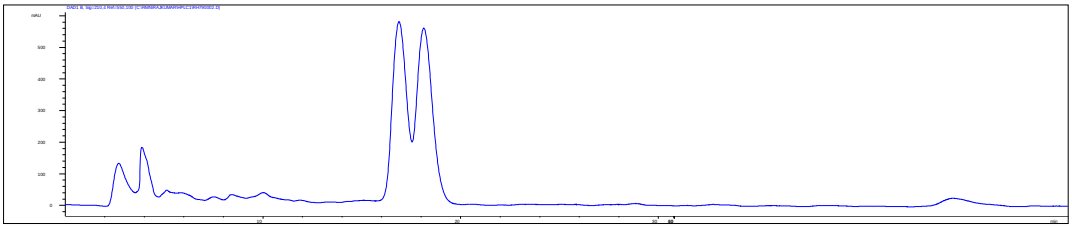
Chiralcel AD, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm



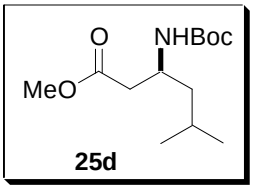
23d

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.437	MM	0.5841	1704.13281	48.62803	2.2017
2	17.562	MM	0.9636	7.56983e4	1309.35278	97.7983



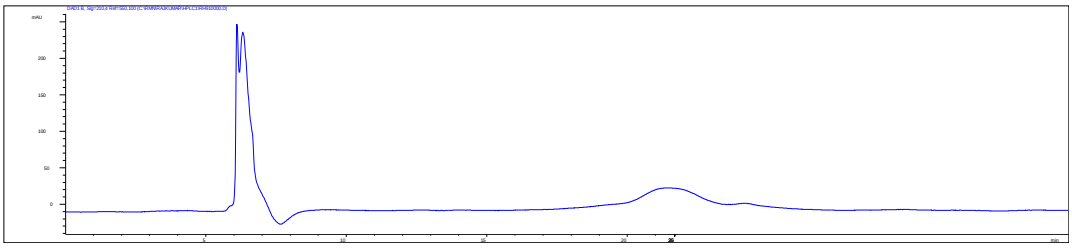


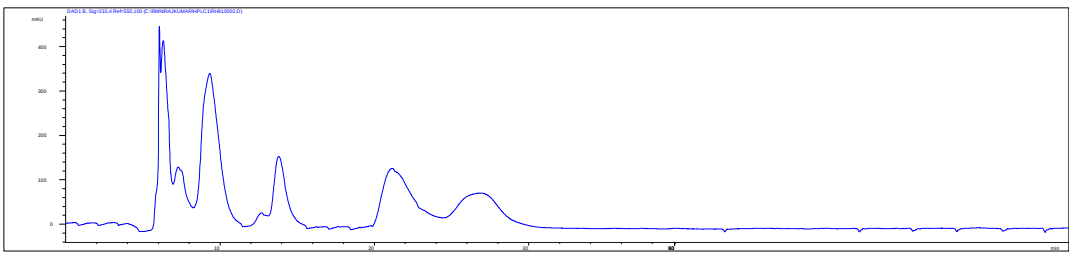
Chiralpak AD, 96:4 (hexane:iPrOH), 0.5mL/min, λ=210nm



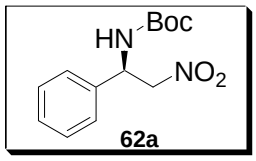
25d

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.927	MM	1.8223	528.91943	4.83756	3.2768
2	22.097	MM	2.7113	1.56125e4	95.97194	96.7232





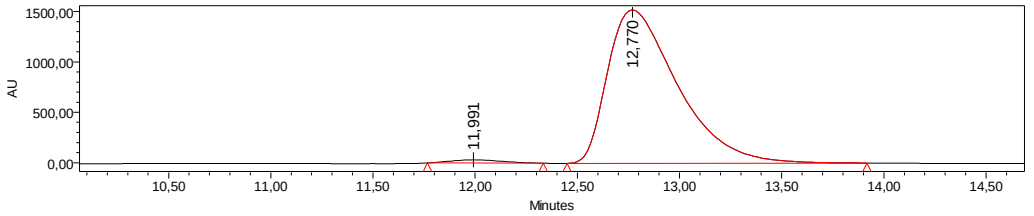
CHIRALPAK IA, 90:10(hexane:iPrOH),1.0mL/min, λ=210nm

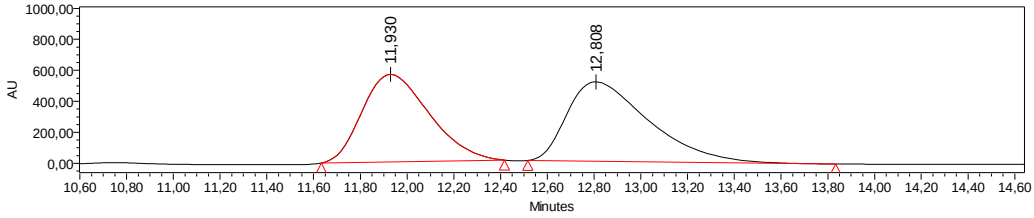


62a

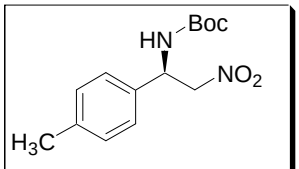
Processed Channel Descr.: 210

	Processed Channel Descr.	RT	Area	% Area	Height
1	210	12,289	279398	1,38	16639
2	210	13,055	19985916	98,62	790943





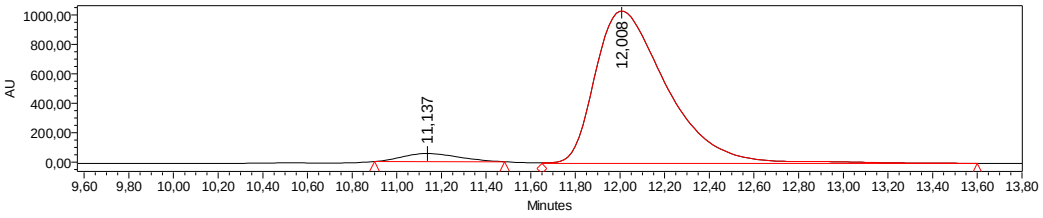
CHIRALPAK IA, 90:10(hexane: iPrOH), 1.0mL/min, λ=220nm (alter column chromatography)

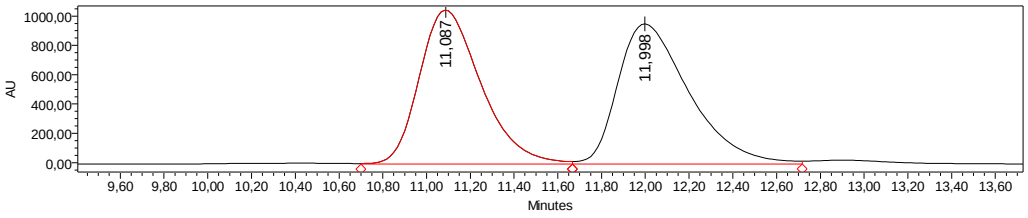


62c

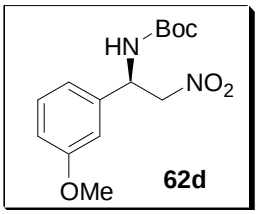
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	11,137	966445	4,02	55398
2	220	12,008	23067898	95,98	1035187



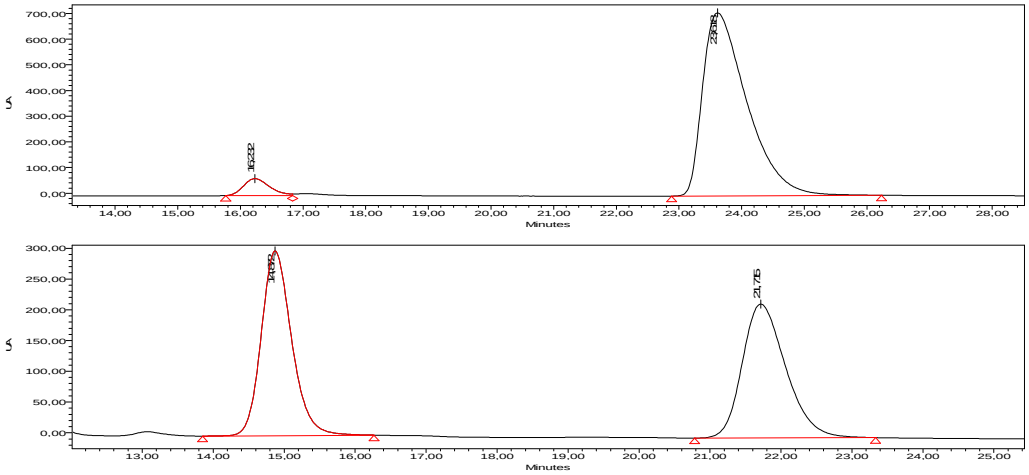


Chiralpak IA 90:10 hex : iPrOH, 90:10, 1.0mL/min

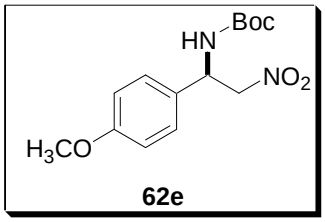


Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	16,232	1905502	5,17	65848
2	@210nm	23,618	34975867	94,83	713200

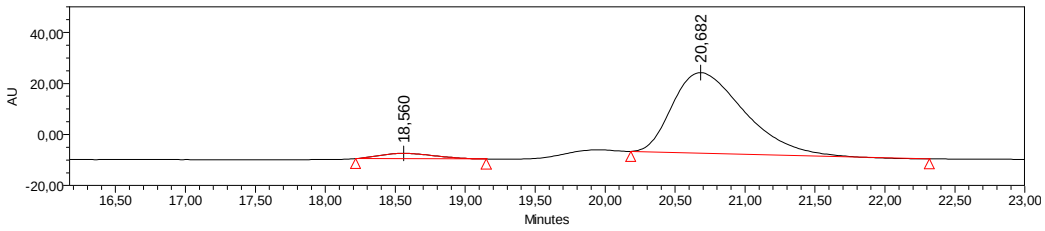


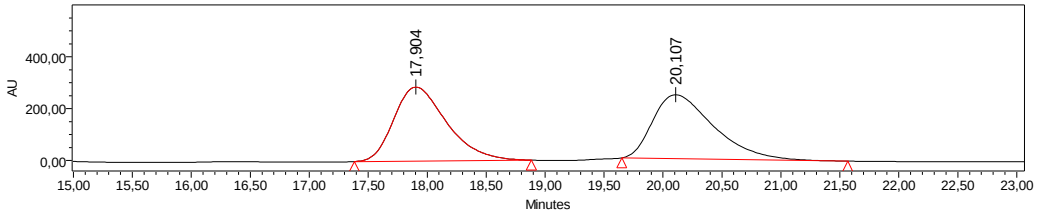
Chiralpak IA, hexane:iPrOH (90:10), 0.8 mL/min, λ=210nm



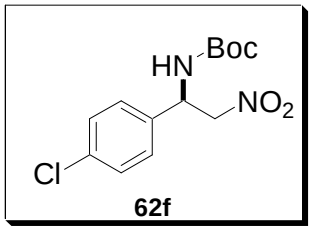
Processed Channel Descr.: 210

	Processed Channel Descr.	RT	Area	% Area	Height
1	210	18,559	60926	4,17	2216
2	210	20,682	1401338	95,83	33674





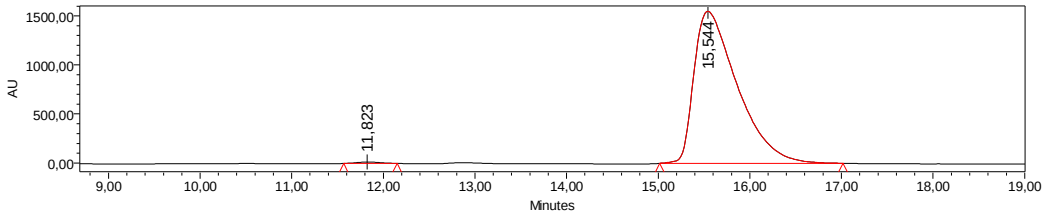
CHIRALPAK IA, 90:10(hexane:iPrOH),1.0mL/min, λ=220nm (after crystallization 99%, before 96%)

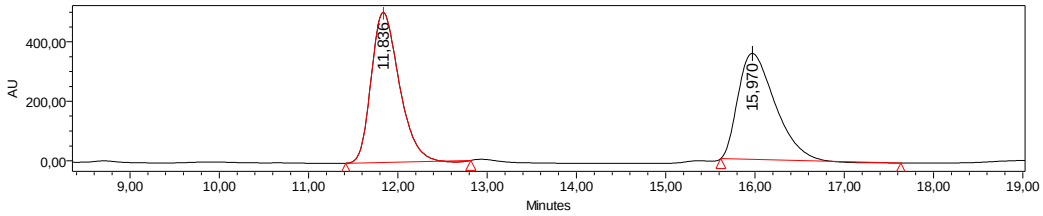


62f

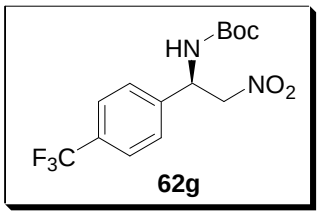
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	11,823	269660	0,53	14349
2	220	15,544	50917060	99,47	1551381





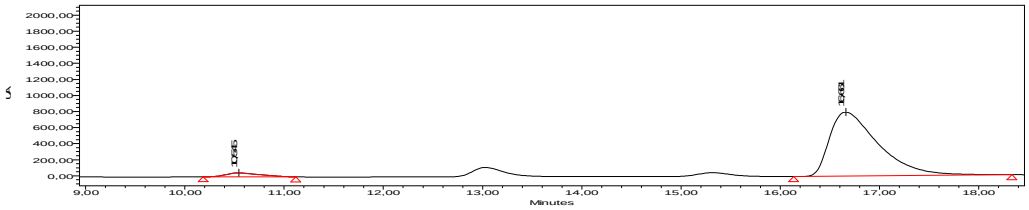
Chiralpak IA 90:10 hex : iPrOH, 90:10, 1.0mL/min

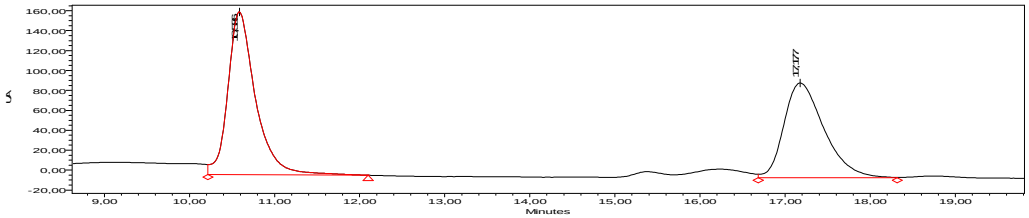


62g

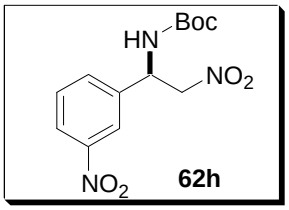
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	14,311	23709055	95,29	811629
2	@210nm	22,570	1172298	4,71	30929



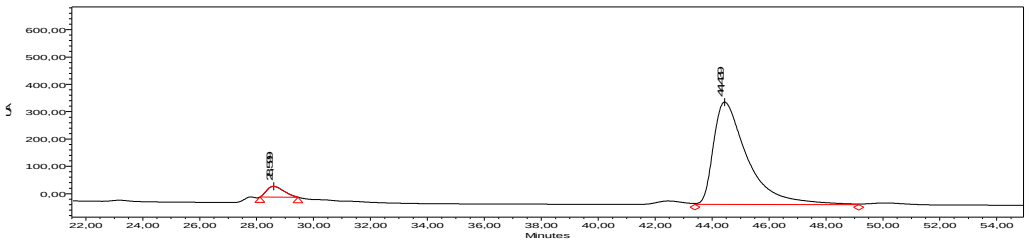


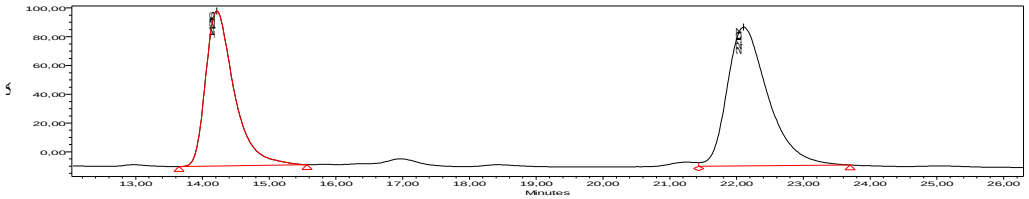
Chiralpak IA 90:10 hex : iPrOH, 90:10, 1.0mL/min



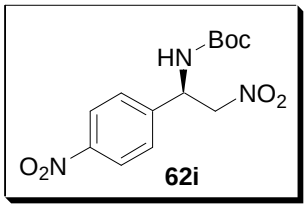
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	28,599	1636863	4,99	39477
2	@210nm	44,439	31137261	95,01	374634



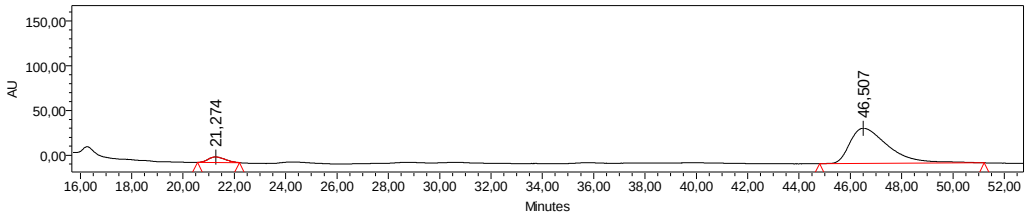


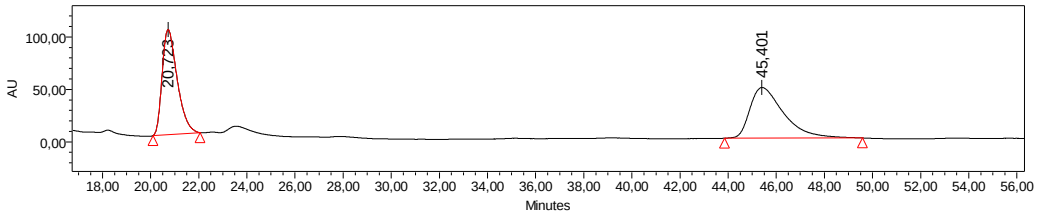
CHIRALPAK IA, 90:10(hexane:iPrOH),1.0mL/min, λ=220nm



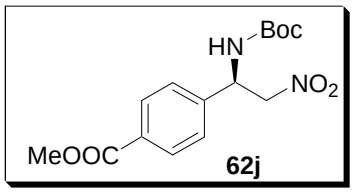
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	21,274	287350	6,55	6273
2	220	46,507	4098032	93,45	39416



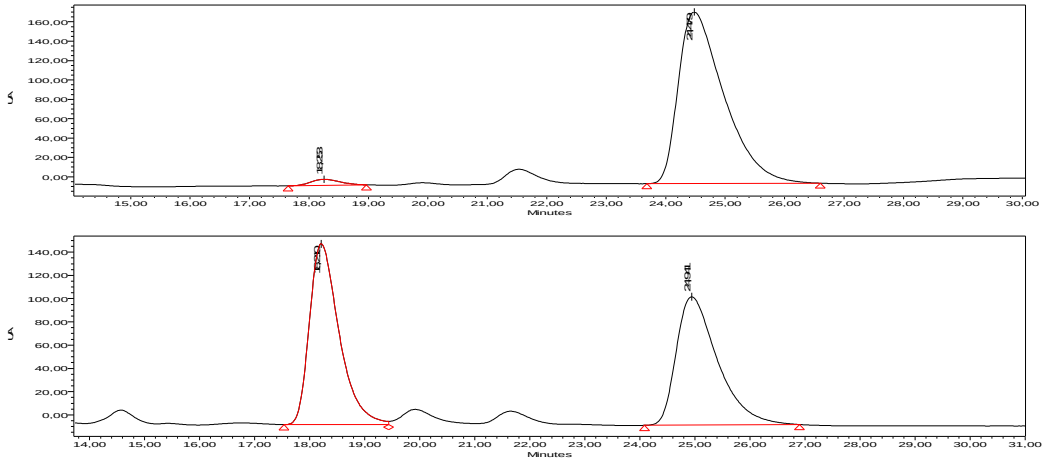


CHIRALPAK IA, 90:10(hexane:iPrOH),1.0mL/min, λ=220nm

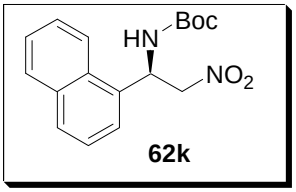


Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	28,599	1636863	4,99	39477
2	@210nm	44,439	31137261	95,01	374634

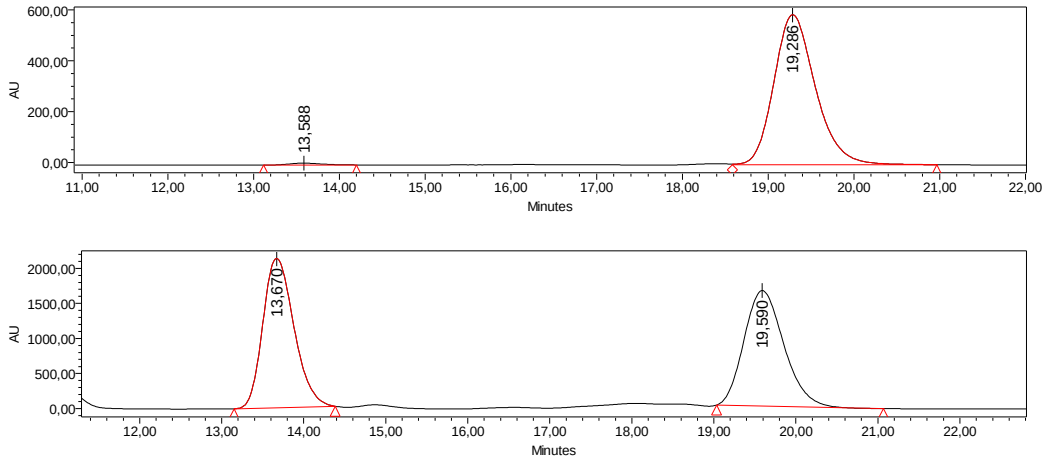


CHIRALPAK IA, 90:10(hexane:iPrOH),1.0mL/min, λ=220nm(after crystalisation 98%, before crystalisation 94%)

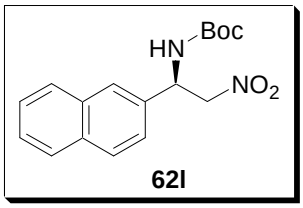


Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	13,588	186542	0,93	7348
2	220	19,286	19860547	99,07	590180

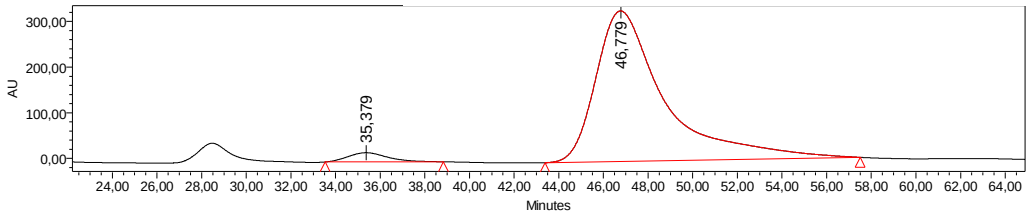


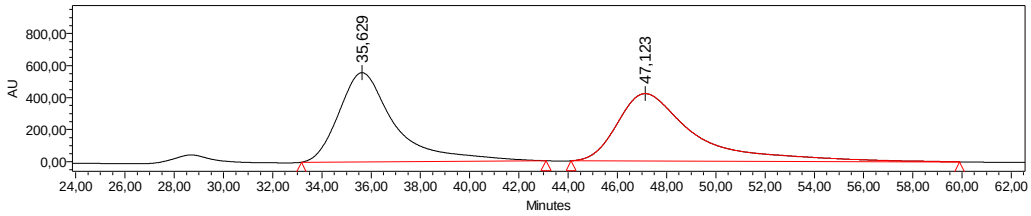
ChiralcelOD, 80:20(hexane:iPrOH),1.0mL/min, λ=220nm



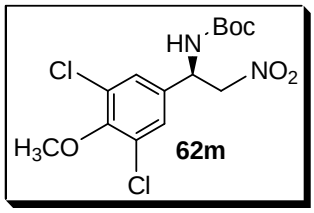
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	35,379	2482155	3,40	20162
2	220	46,779	70433524	96,60	329369

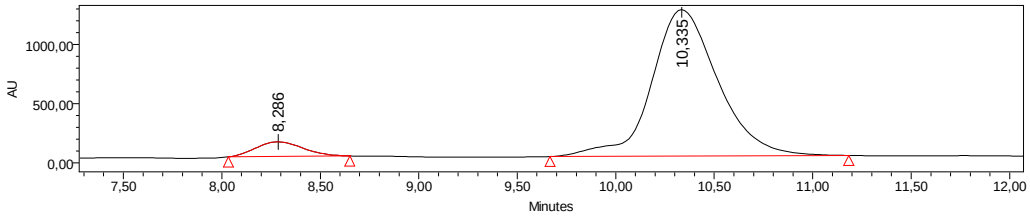


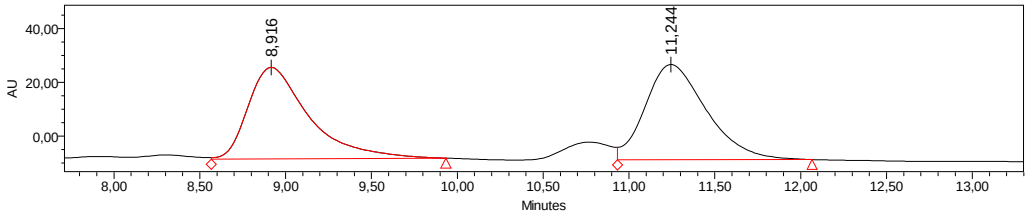


CHIRALPAK IA, 90:10 (hexane:iPrOH),1.0mL/min, λ=220nm(after crystalisation 95%, before crystalisation 87%)

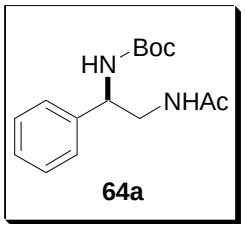


Area	% Area	Height	Retention Time
2070701	6,68	123908	8,286
28935805	93,32	1238493	10,335





Chiralcel IA, 95:5 (hexane:iPrOH), 0.5mL/min, λ=220nm



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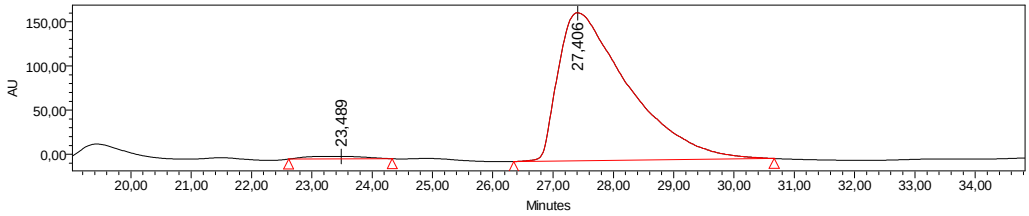
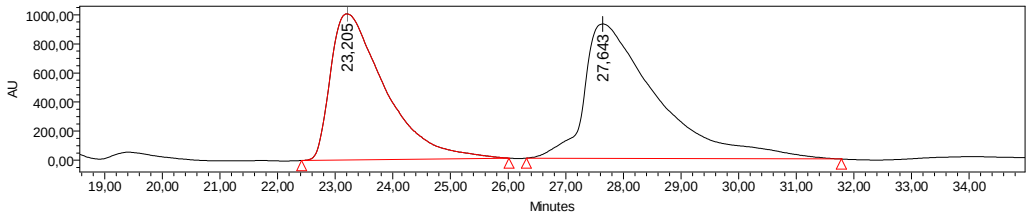
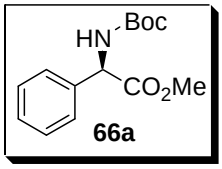
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	23,489	195862	1,42	2733
2	220	27,406	13589371	98,58	167674





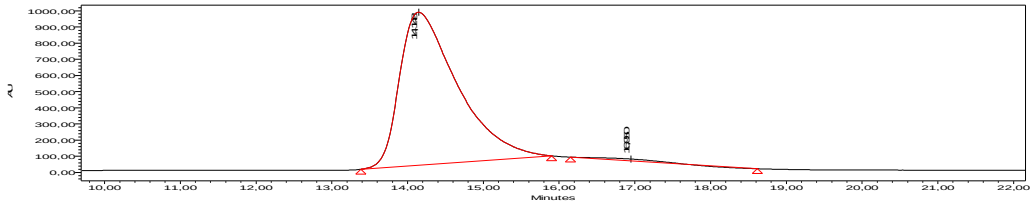
Chiralcel OD, 98:2 (hexane:iPrOH),0.5mL/min, λ=220nm

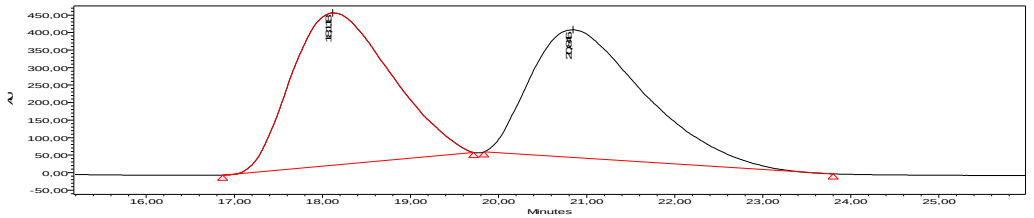


66a

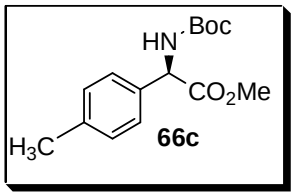
Processed Channel Descr.: 220

	Processed Channel Descr.	RT	Area	% Area	Height
1	220	14,148	50270576	98,48	947426
2	220	16,950	775184	1,52	11587

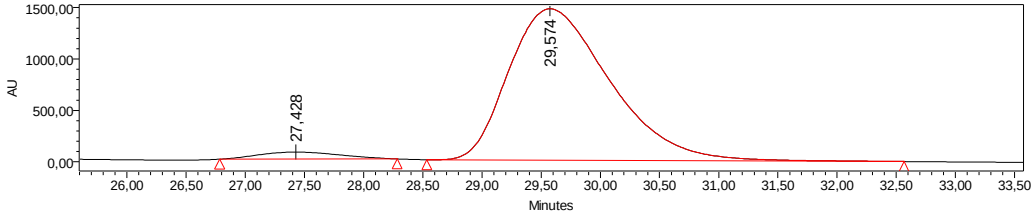


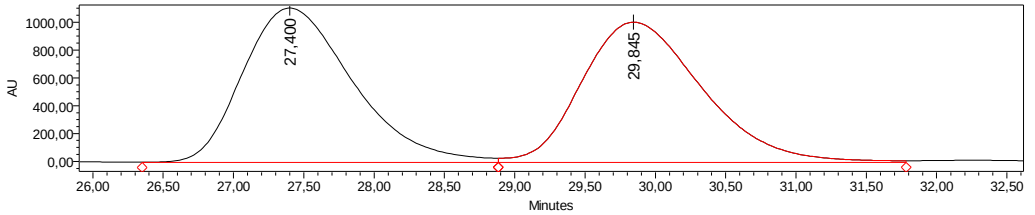


Chiralpak IA, 98:2 (hexane:iPrOH),0.5mL/min, λ=220nm

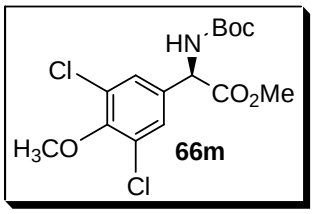


Area	% Area	Height	Retention Time
3247751	3,58	68355	27,428
87468273	96,42	1472575	29,574

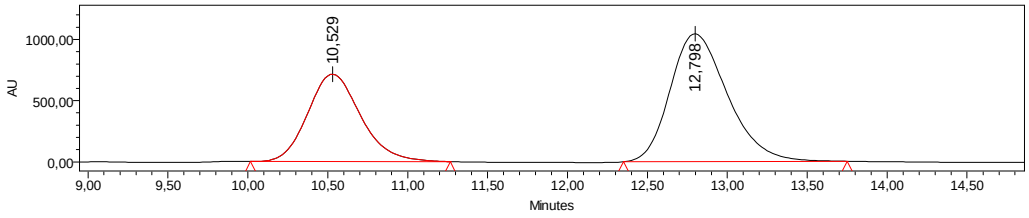


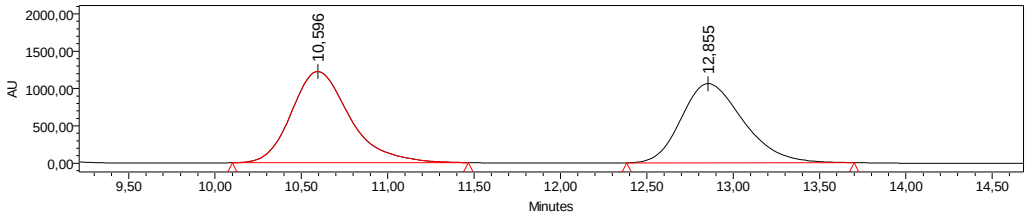


Chiralpak IA, 98:2 (hexane:iPrOH),0.5mL/min, λ=220nm

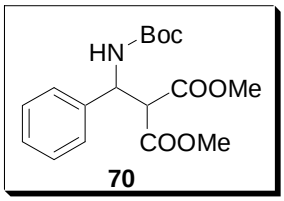


Area	% Area	Height	Retention Time
16418352	38,64	713741	10,529
26072104	61,36	1045447	12,798





Chiral HPLC (Chiralpak IA column; iPrOH:hexane 30:70; 0.6 mL/min, 210 nm, Rt = 19.9 min, Rt =16.5 min.



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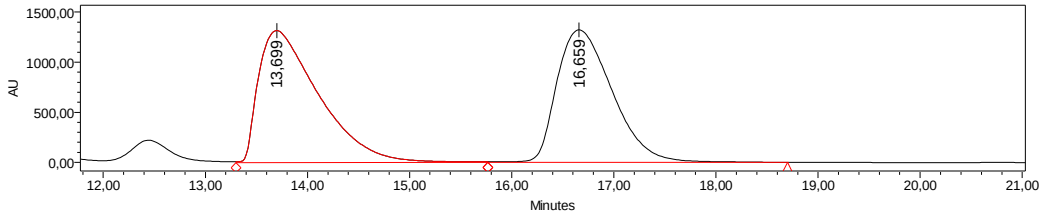
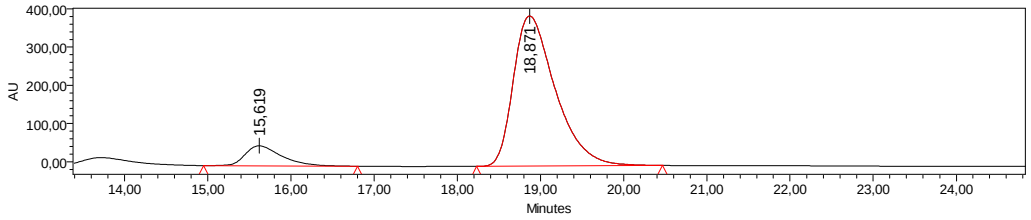
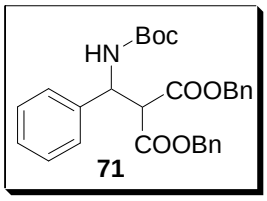
Retention Time	Area	% Area	Height
15,619	1588215	10,33	52366
18,871	13786695	89,67	393037





Chiral HPLC (Chiralpak IA column; iPrOH:hexane 20:80; 0.6 mL/min, 210 nm, Rt = 34.06 min, Rt =41.05 min



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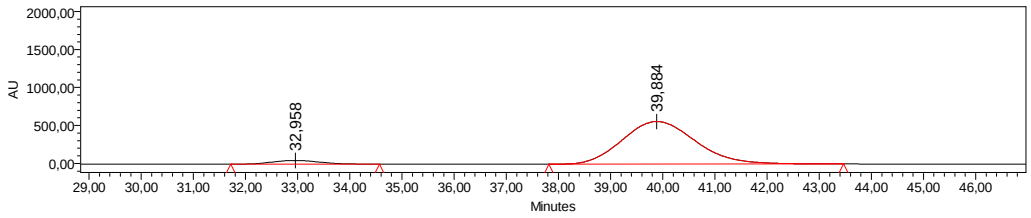
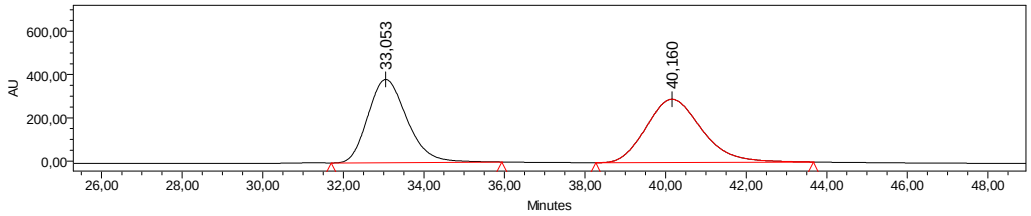
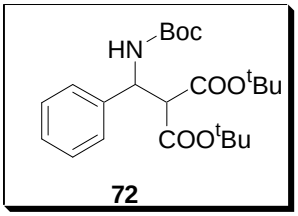
Retention Time	Area	% Area	Height
32,958	3155938	5,43	49244
39,884	54999916	94,57	561287

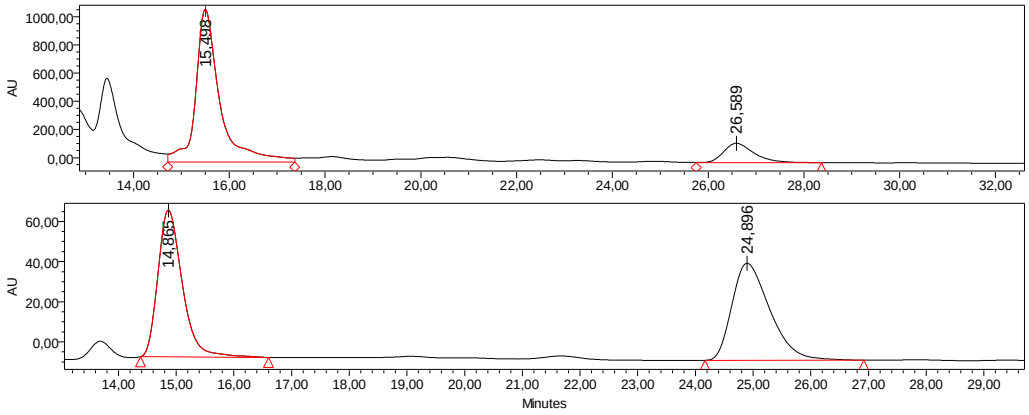




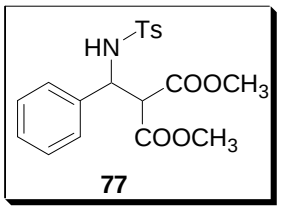
Chiral HPLC (Chiralpak IA column; iPrOH:hexane 20:80; 0.5 mL/min, 210 nm, Rt = 14.8 min, Rt = 24.89 min

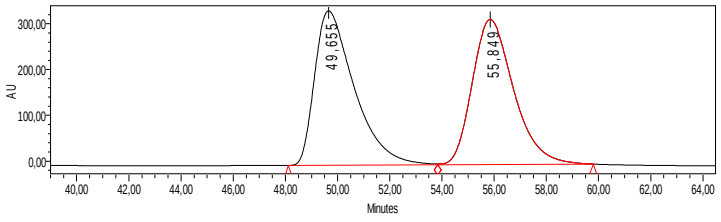


Area	% Area	Height	Retention Time
37893397	86,22	1082195	15,498
6056883	13,78	137227	26,589

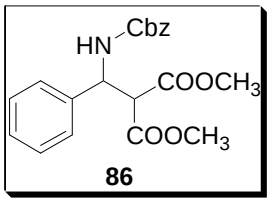


Chiral HPLC (Chiralpak IA column; iPrOH:hexane 10:90; 0.5 mL/min, 210 nm, Rt = 49.6 min, Rt = 55.8 min





Chiral HPLC (Chiralpak IA column; iPrOH:hexane 25:75; 1.0 mL/min, 210 nm, Rt = 19.8 min, Rt = 28.59 min



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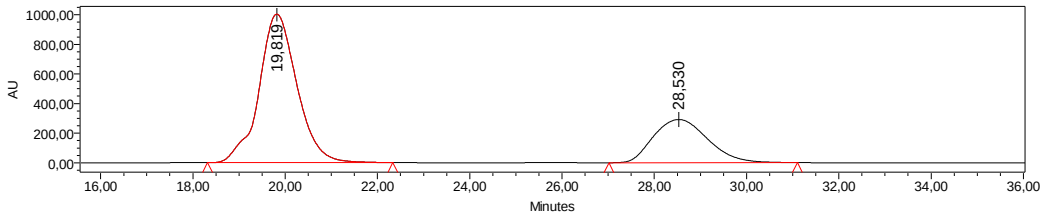
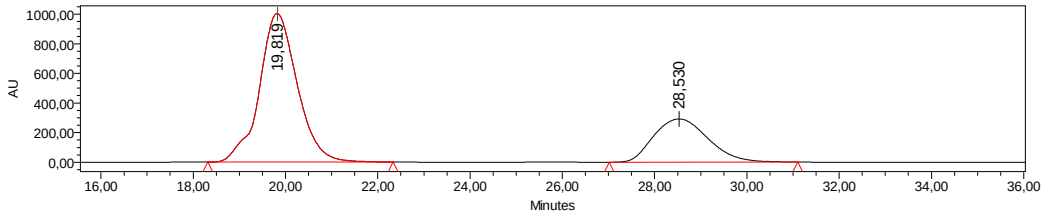
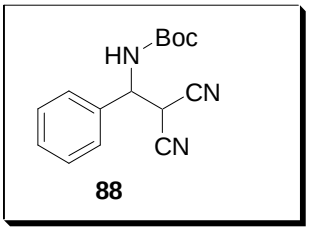
Retention Time	Area	% Area	Height
19,819	57095022	70,53	1003339
28,530	23859303	29,47	291750





Chiral HPLC (Chiralcel OD column; iPrOH:hexane 10:90; 1.0 mL/min, 210 nm, Rt = 18.1 min, Rt = 35.8 min



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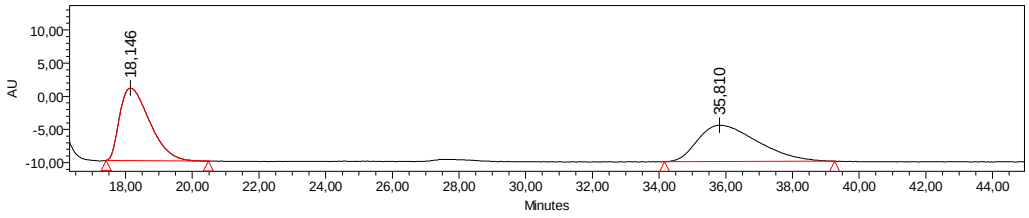
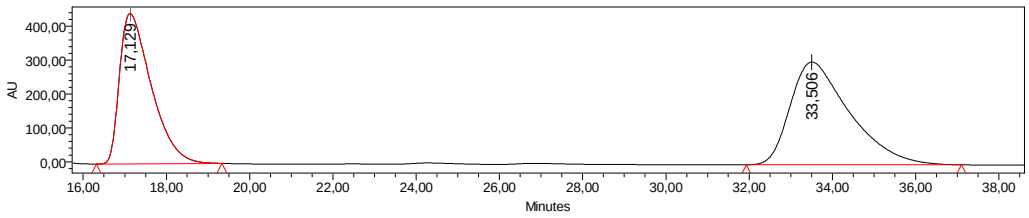
Retention Time	Area	% Area	Height
17,129	23429607	43,83	443657
33,506	30025233	56,17	303075





Publication