eman ta zabal zazu

Universidad del País Vasco
Euskal Herriko Unibertsitatea

α-KETO AMIDES IN BRØNSTED-BASE MEDIATED STEREOSELECTIVE ALDOL- AND MANNICH-REACTIONS: ACCESS TO CHIRAL POLYFUNCTIONALIZED SCAFFOLDS

DOCTORAL THESIS

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Donostia, 2017

(c)2017 HAIZEA ECHAVE de DOMINGO

*A ti **amatxo**, por cuidarme tanto…por ser mi guía en la oscuridad…por ser la personificación de lo que entiendo por amor verdadero…del amar sin condición …por mostrarme lo que es la conexión con los demás…con mi yo interior… e integrarlo todo ello como el motor de mi vida…*

NO DEJARÉ DE GRITAR EN SILENCIO PARA QUE ME OIGAS…

MAITE ZAITUT

A la ***vida****, que es conocer y reconocer…que es aprender y desaprender…que es creer y es sentir…que es soñar y despertar…es saber que no sé nada…y nadando en un mar de dudas me pierdo en un abismo y me inspiro y me transformo…y soy consciente de mi compañera la inconsciencia…y así creo y siento y tengo la certeza de que sigo viva.*

ESKERRAK

El trabajo descrito en la presente memoria ha sido realizado en el Departamento de Química Orgánica I de la Facultad de Química de Donostia, Universidad del País Vasco (UPV-EHU), bajo la dirección del Dr. Claudio Palomo Nicolau a quien expreso mi gratitud por la oportunidad, la dedicación y el esfuerzo realizados y de la Dra. Rosa Mª López Álvarez, pilar fundamental en el transcurso de este trabajo y a la que estoy sinceramente agradecida por haberme ayudado y apoyado, tanto dentro como fuera del trabajo (¡¡¡Muchísimas gracias!!!).

Debo agradecer, además, la necesaria financiación proveniente de la beca predoctoral del Gobierno Vasco.

Eta orain, barruak astintzeko ordua iritsi zait…izan ere, nahiz eta hurbileko sentitzen zaituztedanekin sentimental jartzen naizen tarteka, aukera hau aprobetxatu nahi dut nire eskerrik berezienak lau haizetara zabaltzeko:

Nire *labokide* kuttunei, lankide izan zinetelako hasieratik pixkanaka denborak eta batez ere, konpartitu dugun guztiak (orduak, orduak eta orduak eta penak eta orduak eta barreak eta orduak eta kristoren barreak eta orduak) lagun min bihurtu gaituelako. Zuen alkimista dohainekin zoritxarrak bizi-poz bilakatu dituzue!!!!!!!

Ene bihotzeko *txutxiak*, mila milioi esker bizitzak dakartzan pozak eta tristurak zuekin konpartitu ahal izanagatik… azken hauek asko izan arren, lagun onekin konpartitzeak izugarri lagundu egiten baitu (lagun-du!)… *"Sasi guztien gainetik eta hodei guztien azpitik…"* zuekin *findelmundo*ra joango nintzake!!

Etxekoei, han-hemenka ibili naizen arren, zuek beti hor izan zaretelako…ikasketa eta lan kontuez piperrik ulertu ez arren, zuek beti hor izan zaretelako...bolada eguzkitsuak eta ekaitz bortitzak bizi arren, zuek beti hor izan zaretelako...eta izango zaretenaren bermea edukitzeak, zorioneko izatea zer den jakitera eraman nauelako.

Finalment però no menys important, Xavier, moltíssimes gràcies per compartir la teva vida amb mi i per acompanyar-me... no sé cap a on vaig però sí que sé que amb tu...Rock & Roll!!

Maite zaituztet!!!!

RESUMEN

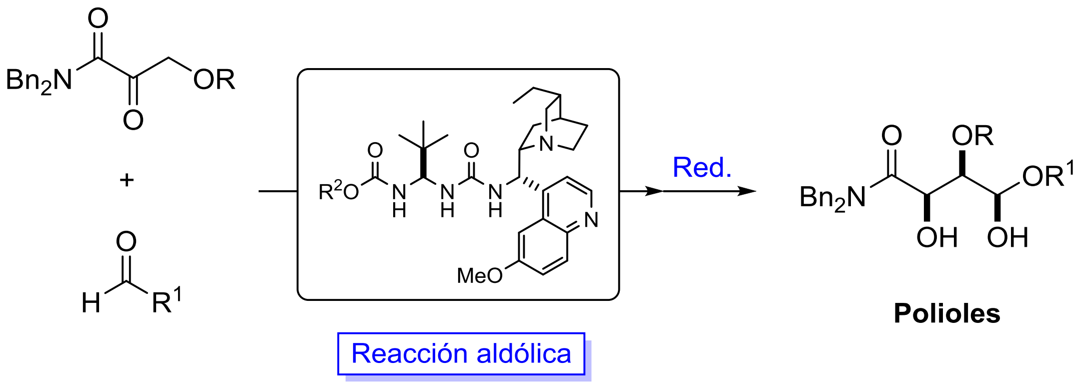
La presente tesis ha tenido como objetivo principal la aplicación de métodos asimétricos organocatalíticos en transformaciones químicas fundamentales como la formación de enlaces carbono-carbono. Las dos líneas de trabajo fundamentales para la consecución de dicho objetivo se han centrado en: a) el diseño, síntesis, caracterización y evaluación de nuevos catalizadores quirales bifuncionales que permitan resolver problemas pendientes relacionados con la eficiencia química, el estereocontrol y la generalidad de los sustratos y b) el diseño de sustratos y plantillas poseedores de características estructurales y funcionales óptimas para la activación por dichos organocatalizadores.

En este contexto, se ha demostrado por vez primera la eficacia de las β-alcoxi-α-ceto amidas como pronucleófilos en la adición asimétrica a aldehídos e iminas catalizada por bases de Brønsted bifuncionales.

En concreto, se ha desarrollado la primera reacción aldólica cruzada catalítica y asimétrica entre β-ceto amidas y aldehídos enolizables que evita reacciones secundarias no deseadas, tales como la reacción homo aldólica, la condensación aldólica y la enolización del aldehído, todas ellas difíciles de controlar en medio básico. El éxito del método reside en la capacidad del organocatalizador de tipo ureidopeptídico de enolizar preferentemente la β-ceto amida de forma estereoselectiva.

Posteriormente, la metodología se ha extendido a la reacción de tipo Mannich obteniéndose en este caso los mejores resultados con bases de Brønsted bifuncionales de tipo escuaramida.

La reducción estereoselectiva de los aductos, tanto de la reacción aldólica como de la reacción de Mannich, ha dado lugar, respectivamente, a la producción de polioles y aminopolioles altamente enantioneriquecidos (Esquema 1).


Bn$_2$N
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Bn$_2$N
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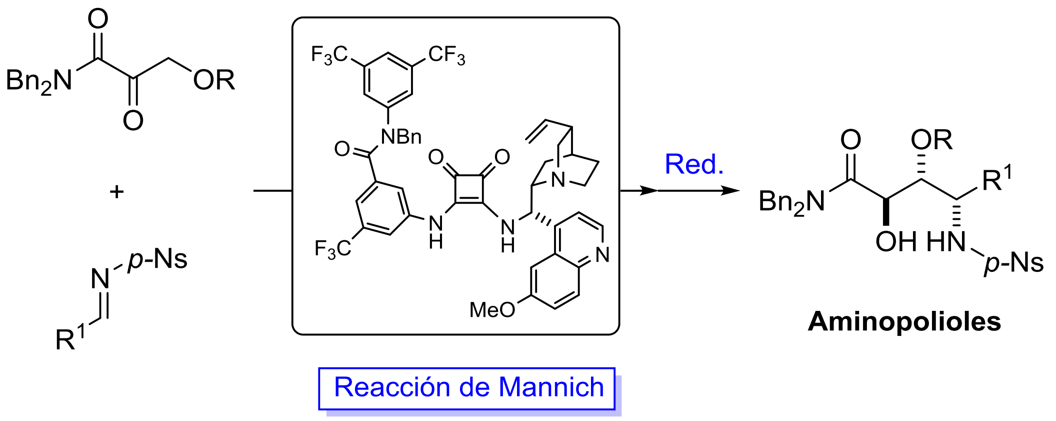
Polioles
Reacción aldólica

Angew. Chem. Int. Ed. **2016**, *55*, 3364–3368


Bn$_2$N
OR
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+
N
p-Ns
R^1
F$_3$C
CF$_3$
NBn
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H
N
H
N
N
MeO
Red.
Bn$_2$N
O
OR
R^1
OH
HN
p-Ns
Aminopolioles
Reacción de Mannich

Esquema 1.

ABBREVIATIONS AND ACRONYMS

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

Å	Amstrong
Ac	Acetyl group
Ar	Aryl group
BB*	Chiral Brønsted base
BINOL	1,1'-Bi-2-naphtol
Bn	Benzyl group
Boc	*tert*-Butyloxycarbonyl group
BOM	Benzyloxymethyl group
Cat.	Catalyst
Cbz	Carboxybenzyl group
calcd.	Calculated
CAN	Cerium Ammonium Nitrate
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl group
d	Days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phtalazinedyil diether
$(DHQ)_2PYR$	Hydroquinine 2,5-diphenyl-4,6-pyridineiyl ether
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylaniline
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

Dpm	Diphenylmethyl group
Dpp	Diphenylphosphinoyl group
dr	Diastereomeric ratio
DMT	Dimethyltryptamine
E	Electrophile
EDG	Electron-donating group
ee	Enantiomeric excess
Et	Ethyl group
Et_3N	Triethylamine
equiv.	Equivalent
Et_2O	Diethyl ether
EWG	Electron-withdrawing group
Fmoc	9-Fluorenylmethoxycarbonyl
h	Hours
HFIP	Hexafluoroisopropanol
i-Bu	*iso*-Butyl group
IBX	2-Iodoxybenzoic acid
i-PrOH	*iso*-Propanol
LDA	Lithium diisopropylamide
Me	Methyl group
min	Minutes
MOM	Methoxymethyl group
MS	Molecular sieves
MW	Microwave irradiation
NeuAc	*N*-Acetylneuraminic acid
NMI	*N*-methyl imidazole
NMP	*N*-methyl pyrrolidone
o-Ns	*ortho*-Nosyl- or *2*-nitrobenzenesulfonyl group

p-Ns	*para*-Nosyl- or *4*-nitrobenzenesulfonyl group
p-TsOH	*para*-Toluenesulfonic acid
PEP	Phosphoenol pyruvate
PG	Protecting group
Ph	Phenyl group
PMB	*para*-Methoxybenzyl group
PMP	*para*-Methoxyphenyl group
Py	Pyridyl group
Red.	Reduction reaction
RT	Room temperature
s-Bu	*sec*-Butyl group
s	Seconds
TIPS	Triisopropyl silyl group
TBS	*tert*-Butyldimethylsilyl group
TBTU	*N,N,N′,N′*-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate
t-Bu	*tert*-Butyl group
Tf	Trifluoromethanesulfonyl group
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TMS	Trimethylsylil group
TBDPS/TBS	*tert*-Butyldiphenylsilyl group
Ts	Tosyl- or *para*-toluenesulfonyl group
Tr	Trityl- or Triphenylmethyl group

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CHAPTER 1

Introduction

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1. INTRODUCTION

Chirality shows itself directly or indirectly in essentially all life processes. In the realm of organic synthesis, the need to obtain enantiomerically pure compounds whenever applicable, is the accepted norm, especially for natural products and drug substances.[1,2] In fact, the strict rules imposed by the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe, and related organizations around the world, regarding the approval of chiral drugs for clinical use has heightened the need to synthesize enantiopure compounds. Among the well known practices toward this objective are optical resolution,[3] microbial and enzymatic transformations,[4] asymmetric chemical synthesis, and the use of enantiopure natural substances.

The enantioselective synthesis of natural products and other organic molecules containing one or more stereogenic carbon atoms requires a plan that includes an asymmetric bond-forming reaction at a predetermined stage.

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[1] For relevant monographs, see: a) R. A. Sheldon, *Chirotechnology,* **1993**, Marcel Dekker, New York; b) *Chirality in Drug Design and Synthesis,* Ed. C. Brown, **1997**, Academic, New York; c) *Chirality in Industry,* Eds. A. N. Collins, G. Sheldrake, J. Crosby, **1997**, Wiley, Chichester; d) *Chirality in Drug Research*, Eds. E. Francotte, W. Lindner, **2006**, Wiley-VCH, Weinheim.

[2] a) *Modern Tools for the Synthesis of Complex Bioactive Molecules*, J. Cossy, S. Arseniyadis, Eds. **2012**, John Wiley and Sons, Hoboken; b) *Design and Strategy in Organic Synthesis*, Eds. S. Hanessian. S. Giroux, B. M. Merner, **2013**, Wiley-VCH, Weinheim.

[3] For general reviews on resolution methods, see: a) N. G. Anderson, *Org. Proc. Res. Dep.* **2005**, *9*, 800–813; b) L. Synoradzki, U. Bernás, P. Ruśkowski, *Org. Prep. Proced. Inc.* **2008**, *40*, 163–200. For general reviews on kinetic dynamic resolution, see: c) B. M. Matute, *An. Quim*. **2006**, *102*, 46–52; d) H. Pellissier, *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge; e) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 659–676; f) H. Pellissier, *Tetrahedron* **2016**, *72*, 3133–3150; g) V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528–4561.

[4] For general reviews on enzyme catalyzed transformations, see: a) A. S. Bommarius, B. R. Riebel*, Biocatalysis: Fundamentals and Applications*, **2007**, Wiley-VCH, Weinheim; b) J.-M. Choi, S.-S. Han, H.-S. Kim, *Biotechnology Advances* **2015**, *33*, 1443–1454; c) A. M. Bezborodov, N. A. Zagustina, *Applied Biochemistry and Microbiology* **2016**, *52*, 237–249.

When considering pure starting materials, a common protocol is to use readily suitable chiral, non-racemic compounds that are available from amino acids, carbohydrates, hydroxy acids, and terpenes (the so called “chiral pool”).[5] Alternatively, starting materials possessing required functionality and stereochemistry can be accessed by chemical asymmetric synthesis.[6] In this case, stereodifferenciation can be achieved by the use of external quiral auxiliaries,[7] chiral reagents[8] or through the influence of a proximal or nearby stereogenic center. Terms such as substrate control and reagent control have been used to describe asymmetric processes.[9] Many innovative contributions have been made in stoichiometric asymmetric synthesis using chiral auxiliaries in particular and applications of asymmetric reactions to the synthesis of preclinical active pharmaceutical compounds have been reviewed.[10] However, the road from bench to market is accompanied by a wide range of difficulties.

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[5] For more information about chiral pool, see: a) H. U. Blaser, D. Seebach, H.-O. Kalinowski, *Nachr. Chem. Tech. Lab*. **1976**, *24*, 415–418; b) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, **1996**, Wiley-VCH, Weinheim; c) K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, **2003**, Wiley-VCH; d) *Handbook of Chiral Chemicals*, Ed. D. Ager, **2006**, CRC Press, Boca Raton; e) V. Alezra, T. Kawabata, *Synthesis* **2016**, 2997–3016

[6] For more information about asymmetric synthesis, see: a) *Asymmetric Synthesis with Chemical and Biological Methods*, Eds. D. Enders, K.-E. Jaeger, **2007**, Wiley-VCH, Weinheim; R. E. Gawley, J. Aube, *Principles of Asymmetric Synthesis* 2nd Edition, **2012**, Pergamon Press, Oxford; V. Šunjić, V. P. Peroković, *Organic Chemistry from Retrosynthesis to Asymmetric Synthesis*, **2016**, Springer International, Cham.

[7] For more information about chiral auxiliaries, see: a) G. Roos, *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York; b) F. Glorious, Y. Gnass, *Synthesis* **2006**, *12*, 1899–1930; c) G. Roos, *Key Chiral Auxiliary Applications* 2nd Edition*,* **2014**, Elsevier, Oxford.

[8] For more information about chiral reagents, see: a) T. Schütz, *Synlett* **2003**, *6*, 901–902; b) *Privileged Chiral Ligands and Catalysts*, Ed. Q.-L. Zhou, **2011**, Wiley-VCH, Weinheim.

[9] For more information about chiral substrates, see: a) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem*. **1985**, 97, 1–31; b) K. Burgess, M. J. Ohlmeyer, *Chem. Rev*. **1991**, 91, 1179–1191; c) A. H. Hoveyda, D. A. Evans, G. C. Fu, *J. Am. Chem. Soc*. **1992**, *114*, 6679–6685.

[10] For reviews and monographs, see: a) J. Crosby, *Tetrahedron* **1991**, *47*, 4789–4846; b) S. Khota, *Tetrahedron* **1994**, *50*, 3639–3662; c) *Asymmetric Catalysis on Industrial Scale*, Eds. H.-U. Blaser, E. Schmidt, **2004**, Wiley-VCH, Weinheim; d) H.-J. Federsel, *Nat. Rev. Drug. Discov.* **2005**, *4*, 685–697; e) V. Farina, J. T. Reeves, C. H. Senayanake, J. Song, *J. Chem. Rev*. **2006**, *106*, 2734–2793.

As a lead compound is recognized as a pre-clinical candidate the usefulness of the synthesis becomes a primordial consideration. Without exception, the original synthesis developed during the discovery phase has to be modified to satisfy cost effectiveness on manufacturing scale. Effectiveness implies the improvement of already existing procedures, or new ones, in terms of sustainability:[11] available starting materials, step-economy, toxicity, use of recyclable reactants, waste production, etc. In this scenario, the phenomenal progress achieved in catalytic asymmetric reactions is modifying synthesis planning. The use of substoichiometric quantities of a chiral enantiopure chemical substance to accelerate the reaction and control the stereochemistry of the products mimics the action of enzymes (biocatalysts), which have been the prime catalysts in academia and industry for over a century, and is greatly contributing to the development of more practical and cost-effective synthesis. In the last decades of 20th century, metal catalysis dominated the field;[12] however, since the beginning of 2000, organocatalysis,[13] which implies the use of small organic molecules to catalyze organic transformations, has become an essential pillar of asymmetric catalysis.

Human´s confidence on Nature for cures and remedies is well known. Plants in particular have been a continuous and rich source of natural products with therapeutic value exhibiting very diverse biological functions: antiviral, antibiotic, antitumor and anti-inflammatory, among others. Today, the number of natural product of various structural complexity increases continuously as new extracts from a variety of sources are analyzed. In spite of modern isolation techniques, including fermentation techniques, the quantities of new natural products can be insufficient for biological tests apart from *in vitro* studies.

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[11] For a recent review on efficiency and environmental sustainability issues on contemporary organic chemistry, see: Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866–880.

[12] For organometallic catalysis, see: a) D. Astruc, *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag, Berlin Heidelberg; b) D. Steinborn, *Fundamentals of Organometallic Catalysis*, **2011**, Wiley-VCH, Weinheim; c) S. H. A. M. Leenders, R. Gramage-Doria, B. de Bruin, J. N. H. Reek, *Chem. Soc. Rev.* **2015**, *44*, 433–448.

[13] For organocatalysis, see: a) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Ed. A. Berkessel, H. Gröger, **2005**, Wiley-VCH, Weinheim; b) *Enantioselective Organocatalysis,* Ed. P. I. Dalko, **2007**, Wiley-VCH, Weinheim; c) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Ed. P. I. Dalko, **2013**, Wiley-VCH, Weinheim.

Modern organic synthesis is definitely linked to the creation of methodologies in order to achieve enantiomerically pure structures. With regard to the search of enantiopure compounds, possessing therapeutic potential, natural products are among the most important targets. A common feature of natural products is that they are usually densely functionalized molecules containing numerous, and frequently, contiguous stereogenic centers. Polyhydroxylated compounds and aminopolyols are illustrative examples of this class of molecules, palytoxin being an impressive representative (Figure 1).

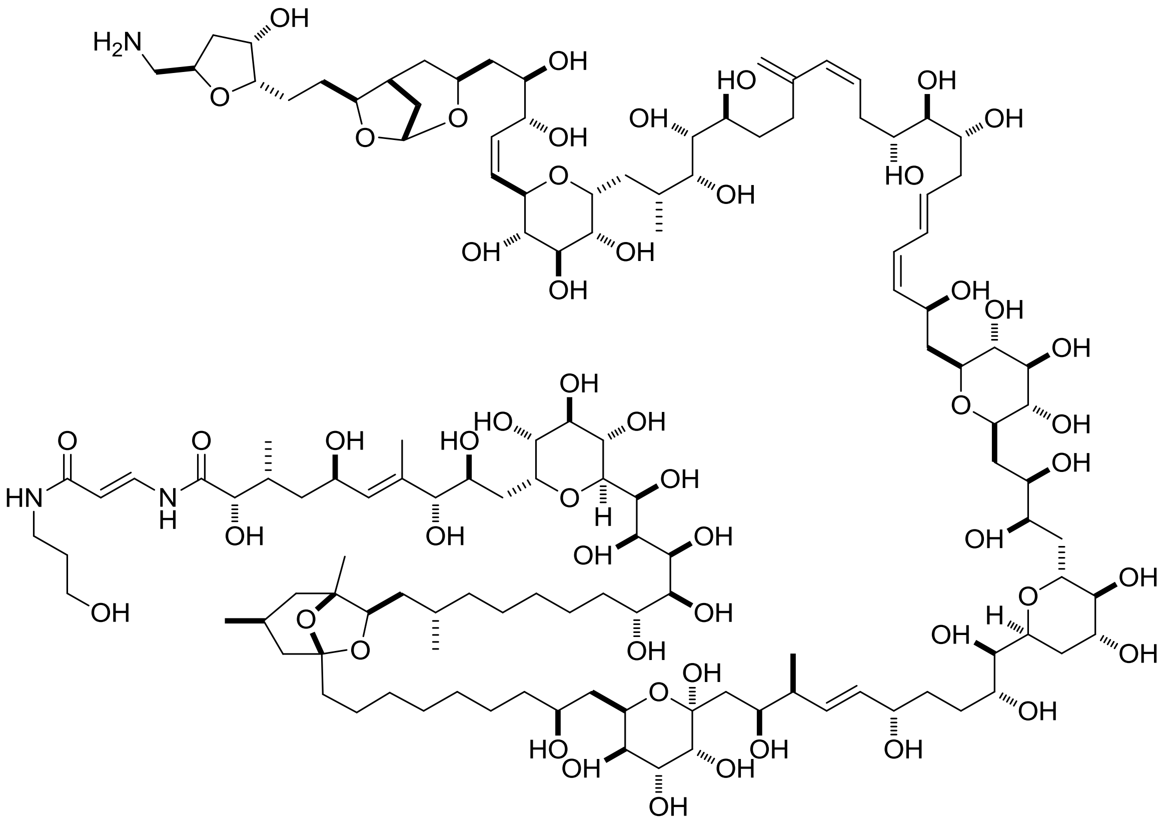

Figure 1. Structure of palytoxin.

Palytoxin, a potent marine toxin that was originally found in soft corals from tropical areas of the Pacific Ocean,[14] is an intense vasoconstrictor,[15] and it is considered to be one of the most toxic non-protein substances known. It is a large, very complex molecule with a long polyhydroxylated and partially unsaturated aliphatic backbone, containing 64 stereogenic centers. This latter feature, coupled with the presence of eight double bonds that are able to exhibit *cis*/*trans*-isomerism means that palytoxin can have more than 10^{21} stereoisomers. It took some time before the complete structure (including stereochemistry) was elucidated. In 1981, this problem was solved almost simultaneously by Moore[16] and Hirata.[17] Palytoxin's structure being established, it took eight years of work, by the group of professor Yoshito Kishi, to complete the total synthesis from eight separate portions of the molecule. First, palytoxin carboxylic acid was synthesized in 1989[18] and in 1994 they succeeded in making palytoxin from this carboxylic acid.[19] The accomplishment of this synthesis has been named "the Mount Everest of organic chemistry, the largest single molecule that anyone has ever even thought about making".[20] The team had two motivations, said professor Kishi: "*to systematically modify portions of the molecule to understand how it interacts with biological systems and to demonstrate what can be done with contemporary organic synthesis*".

The structural diversity of polyhydroxylated products includes from widely known carbohydrates to complex natural products such as alkaloids, macrolides, polyketides, etc. In particular, the polyhydroxylated alkaloids found in plants and micro-organisms are arousing considerable interest as potential therapeutic agents and as a tool used to understand biological recognition processes.[21] The amazing diversity in such small molecules displays a remarkable economy in structural information in Nature. In Figure 2, some naturally occurring polyhydroxylated alkaloids and the synthetic bioactive glycolipid KRN 7000 are shown.

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[14] R. E. Moore, P. J. Scheuer, *Science* **1971**, *172*, 495–498.

[15] The Merck Index: *An Encyclopedia of Chemicals, Drugs and Biologicals*, Ed. S. Budavari, **2001**, Merck.

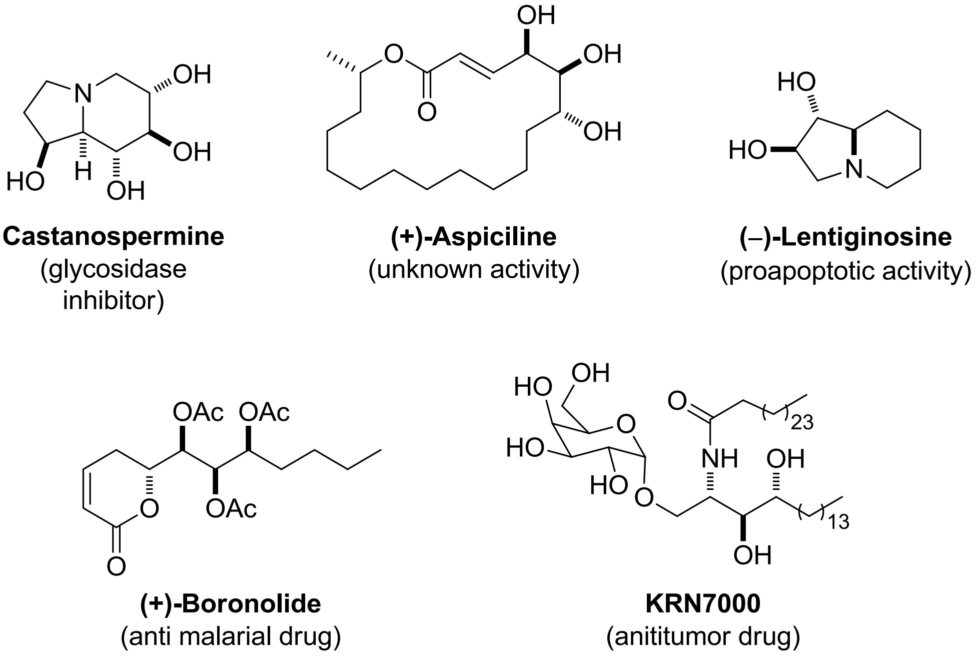
[16] R. E. Moore, G. Bartolini, *J. Am. Chem. Soc.* **1981**, *103*, 2491–2494.

[17] D. Uemura, K. Ueda, Y. Hirata, H. Naoki, T. Iwashita, *Tetrahedron Lett.* **1981**, *22*, 2781–2784.

[18] R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J. Uenishi, J. B. White, M. Yonaga, *J. Am. Chem. Soc.* **1989***, 111,* 7530–7533 and the preceding paper.

[19] E. M. Suh, Y. Kishi, *J. Am. Chem. Soc.* **1994***, 116,* 11205–11206.

[20] M. H. Crawford, *Science*, **1989**, *246*, 34–34.



Castanospermine
(glycosidase inhibitor)

(+)-Aspiciline
(unknown activity)

(–)-Lentiginosine
(proapoptotic activity)

(+)-Boronolide
(anti malarial drug)

KRN7000
(anititumor drug)

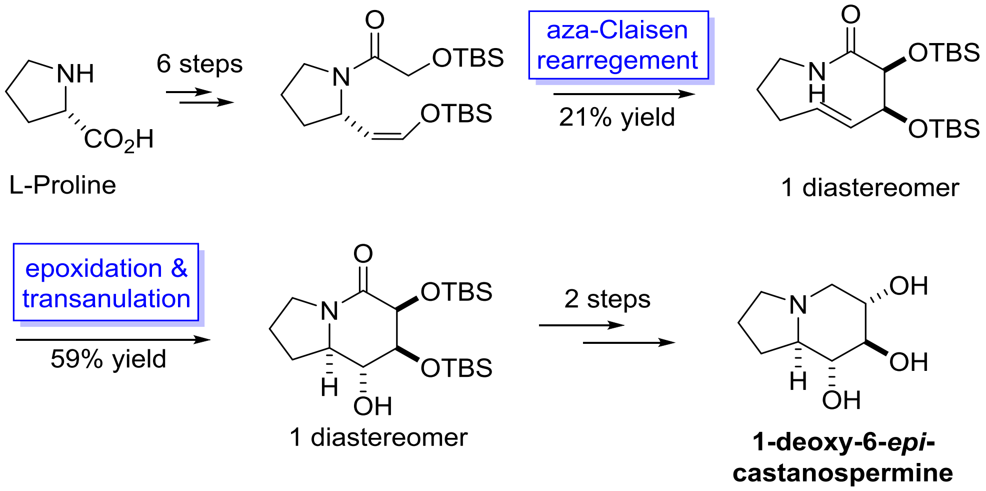
Figure 2. Representative examples of polyhydroxylated molecules with biological activity.

The classical approach towards construction of polyoxyfunctionalized structures is the utilization of the chiral pool.[22] Thereby, quirality from the starting material is used to asymmetrically control bond forming reactions. For instance, Suh and co-workers employed L-proline in the synthesis of castanospermine analogues.[23] L-Proline allowed the highly substrate controlled stereoselective transformations shown in Scheme 1; the stereoselective introduction of the C-3 and C-4 hydroxyl groups utilizing the aza-Claisen rearrangement-induced ring expansion of 1-acyl-2-alkoxyvinyl pyrrolidine and a substrate-controlled stereoselective transannulation of the resulting intermediate.

---

[21] a) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, *Phytochemistry* **2001**, *56*, 265–295; b) Y. Nishimura, *Journal of Antibiotics* **2009**, *62*, 407–423; c) D. S. Alonzi, T. D. Butters, *Chimia* **2011**, *65*, 35–39; c) S. Pal, S. G. Dumbre, *Synlett* **2016**, *272*, 2799–2802.

[22] Recent examples on the stereoselective synthesis based on chiral pool approach: a) K. Gademann, *Asymmetric Synthesis II* **2012**, 317–322; b) N. Chida, T. Sato, *Comprehensive Chirality* **2012**, *2*, 207–239; c) V. Enev, *Comprehensive Chirality* **2012**, *2*, 325–345; d) P. Singh, K. Samanta, S. K. Das, G. Panda, *Org. Biomol. Chem.* **2014**, *12*, 6297–6339; e) S.-M. Paek, M. Jeong, J. Jo, Y. M. Heo, Y. T. Han, H. Yun, *Molecules* **2016**, *21*, 951–964.



Scheme 1. Asymmetric synthesis of 1-deoxy- 6-*epi*-castanospermine.

Another representative example is the total synthesis of (+)-aspicilin reported by Reddy and co-workers.[24] In this case, the authors achieved the objective by combining both the chiral pool and asymmetric catalysis. The key step in this approach is the generation of an enyne intermediate by the coupling of an alkyne with a vinyl iodide, prepared from D-threitol. Conversion of the enyne to the desired macrolide was achieved through Sharpless asymmetric dyhydroxylation and subsequent macrolactonization (Scheme 2).

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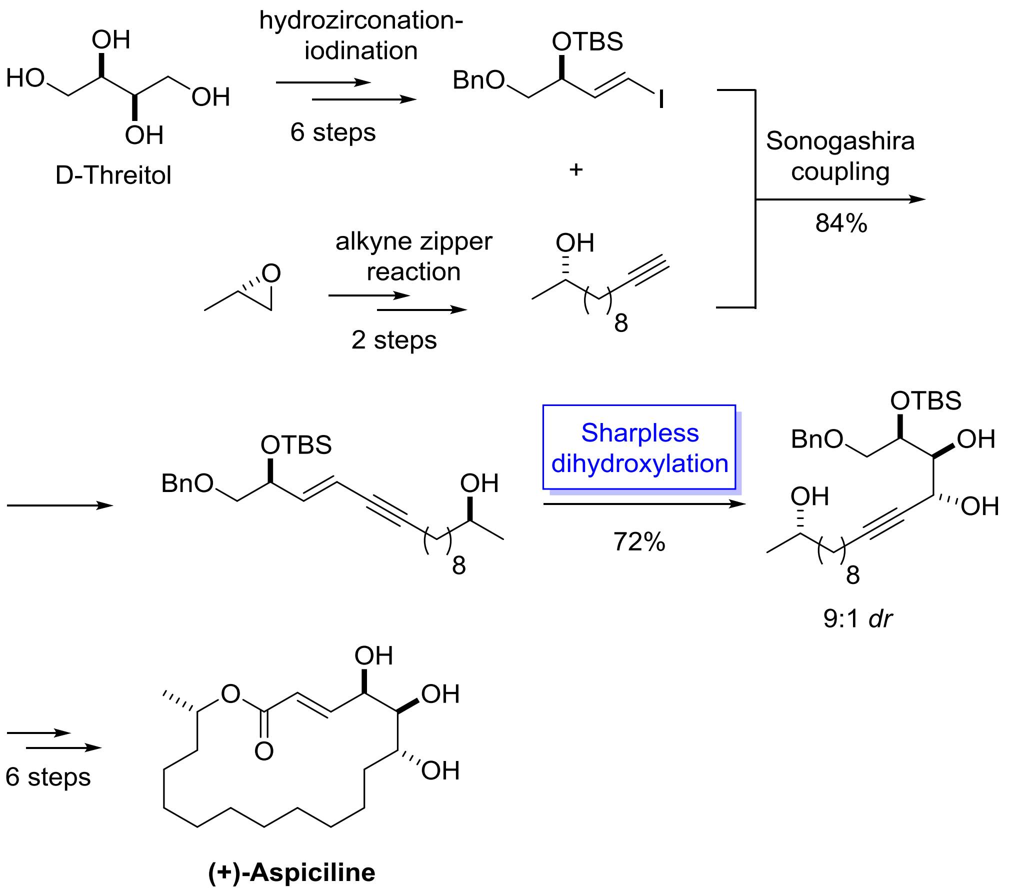
[23] H. Yun, J. Kim, J. Sim, S. Lee, Y. T. Han, D.-J. Chang, D.-D. Kim, Y.-G. Suh, *J. Org. Chem.* **2012**, *77*, 5389–5393.

[24] C. R. Reddy, N. N. Rao, P. Sujitha, C. G. Kumar, *Eur. J. Org. Chem.* **2012**, 1819–1824.


D-Threitol
hydrozirconation-iodination
6 steps
OTBS
BnO
I
+
alkyne zipper reaction
2 steps
OH
8
Sonogashira coupling
84%
Sharpless dihydroxylation
72%
9:1 dr
6 steps
(+)-Aspiciline

Scheme 2. Asymmetric synthesis of (+)-aspiciline.

Nevertheless, *de novo* asymmetric construction of all the stereogenic centers bearing hydroxyl groups within a molecule has been barely explored. An illustrative example is the stereocontrolled synthesis of (+)-boronolide reported by Trost (Scheme 3).[25] In this particular case, the asymmetric synthesis relied on the direct metal catalyzed aldol reaction between 1-(furan-2-yl)-2-hydroxyethan-1-one and varelaldehyde to produce a *syn* aldol intermediate which was stereoselectively reduced, allylated, and further manipulated to afforded (+)-boronolide in twelve steps.

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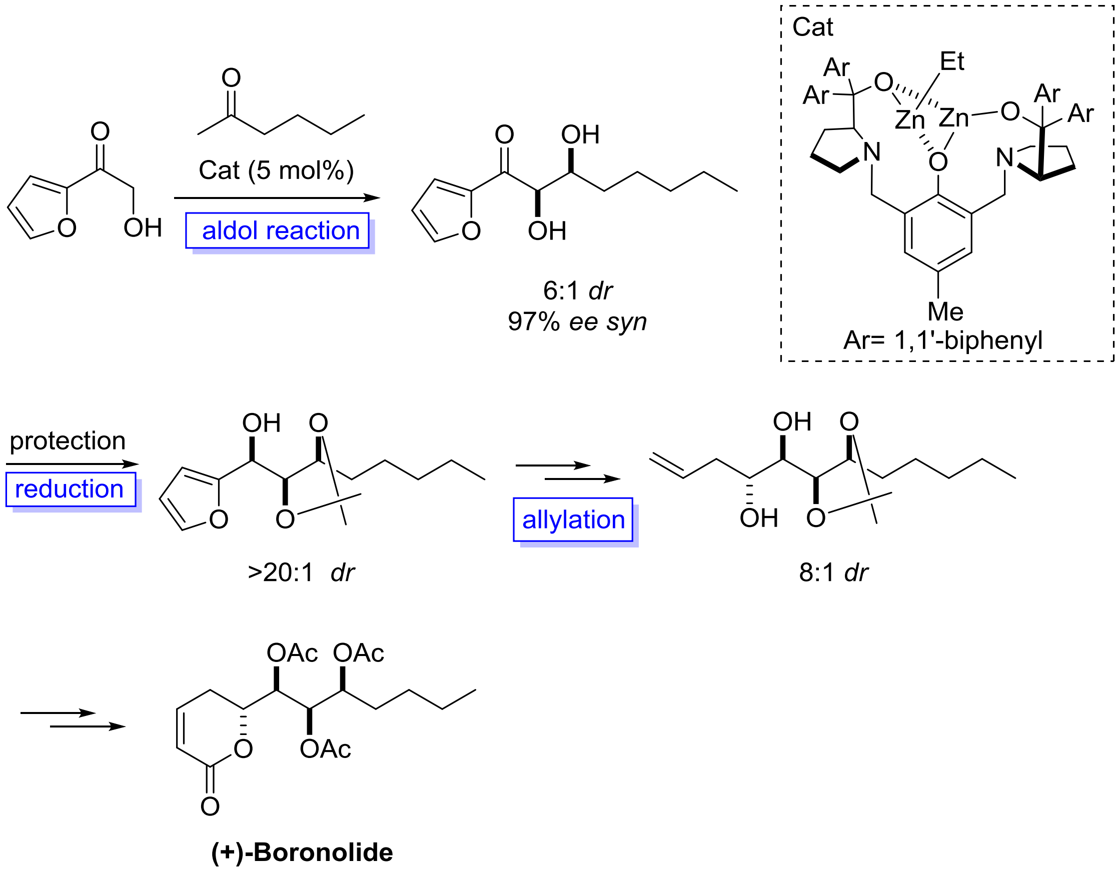
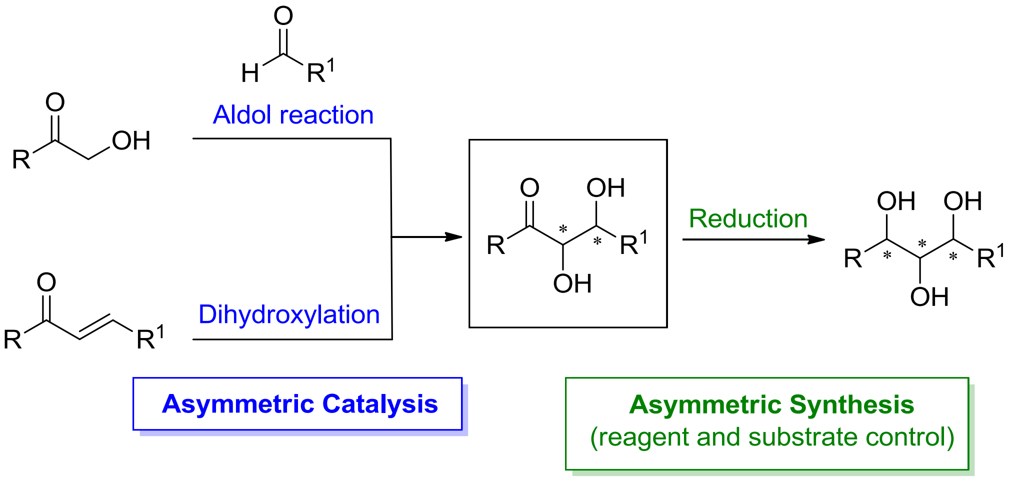
[25] B. M. Trost, V. S. C. Yeh, *Org. Lett.* **2002**, *4*, 3513–3516.


Cat (5 mol%)
aldol reaction
6:1 *dr*
97% *ee syn*
Cat
Ar= 1,1'-biphenyl
protection
reduction
>20:1 *dr*
allylation
8:1 *dr*
(+)-Boronolide

Scheme 3. Stereocontrolled synthesis of (+)-boronolide.

Taking the aforementioned considerations into account, the construction of fragments with high functionalization and adjacent stereogenic centers represents an attractive challenge for scientific community. Definitely, the synthesis of molecular probes and drugs needs to be addressed by the invention of new catalytic procedures, and/or the improvement of known ones, to enhance efficiency in terms of practicality, sustainability and production cost.

In this sense, two of the most direct and atom economical approaches to assemble polyol functionalities appear depicted in Scheme 4: a) the direct catalytic asymmetric aldol reaction of α-hydroxyketones and b) the catalytic asymmetric *cis*-hydroxylation (AD) of α,β-unsaturated carbonyl compounds. Both strategies lead to 1,2-dihydroxylated fragments easily transformable, after steroselective reduction, into enantiomerically enriched polyols.



Scheme 4. Stereocontrolled synthesis of polyol fragments.

The catalyzed asymmetric *cis*-hydroxylation of alkenes is a stereoespecific powerful tool to provide enantiopure diol moieties, being the Sharpless asymmetric alkene dihydroxylation, using OsO_4 (AD-mix), a brand-name procedure.[26] Due to osmium cost and toxicity, notable progress has been achieved for alternative environmentally benign *cis*-dihydroxylations using first-row transition metal catalysts,[27] whereas metal-free methodologies remain underdeveloped.[28] On the other hand, the use of α,β-unsaturated carbonyl compounds has been explored in less extent and, frequently, the efficiency of the asymmetric dihydroxylation is hampered by epimerization and/or retro aldol issues.[29]

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[26] Pioneering report on asymmetric dihydroxylation: a) S. G. Hentges, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265. Pioneering report on asymmetric catalytic dihydroxylation: b) E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. Selected reviews on asymmetric catalytic dihydroxylations: c) H. C. Kolb, M. S. Vannieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; d) M. C. Noe, M. A. Letavic, S. L. Snow, *Organic Reactions,* **2005**, John Wiley & Sons, New Jersey.

[27] Selected review: C. J. R. Bataille, T. Donohoe, *Chem. Soc. Rev.* **2011**, *40*, 114–128.

[28] Review on *cis*-dihydroxylation using either racemic or non-racemic peroxides, hypervalent iodine and selenium- or sulphur reagents: a) M. J. Rawling, N. C. O. Tomkinson, *Org. Biomol. Chem.* **2013**, *11*, 1434–1440. Biocatalytic asymmetric *trans*-dihydroxylations: b) S. Wu, J. Liu, Z. Li, *Synlett* **2016**, 2644–2658.

[29] For successful enantioselective catalytic *cis*-dihydroxylation of electron-deficient alkenes, see: a) T. W.-S. Chow, Y. Liu, C.-M. Che, *Chem. Commun.* **2011**, *47*, 11204–11206; b) C. Zang, Y.

During the last years, contributions in the field of organocatalysis have grown considerably and, nowadays, different methodologies are available to efficiently perform many synthetically useful transformations. In this context soft enolization[30] constitutes an attractive tool for the deprotonation of some carbonyl compounds.[31] In this strategy a relatively weak amine is generally used to reversively deprotonate a relatively acidic substrate. To date, carbonylic compounds such as 1,3-diones, malonates, β-keto esters, α-cyanoacetates, 3-substituted oxindoles and related systems, have been easily deprotonated by relatively weak chiral Brønsted bases and employed as nucleophiles in multiple and diverse carbon-carbon and carbon-heteroatom bond forming reactions. Nonetheless, state of the art in catalytic asymmetric Brønsted-base methodologies still shows important limitations; the range of amenable reactions, constrained to relatively acidic pronucleophile substrates, and the fact that a meaningful bunch of fundamental reactions, i.e. the aldol addition reaction, remains challenging.[32]

The aldol reaction is one of the most powerful procedures for the construction of carbon-carbon bonds.[33] This reaction is also fundamental in the metabolism context, being the most important biochemical process for the naturally occurring carbohydrates. Aldolases are ubiquitous enzymes, belonging

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Liu, Z.-J. Xu, C.-W. Tse, X. Guan, J. Wei, J.-S. Huang, C.-M. Che, *Angew. Chem. Int. Ed.* **2016**, *55*, 10253–10257.

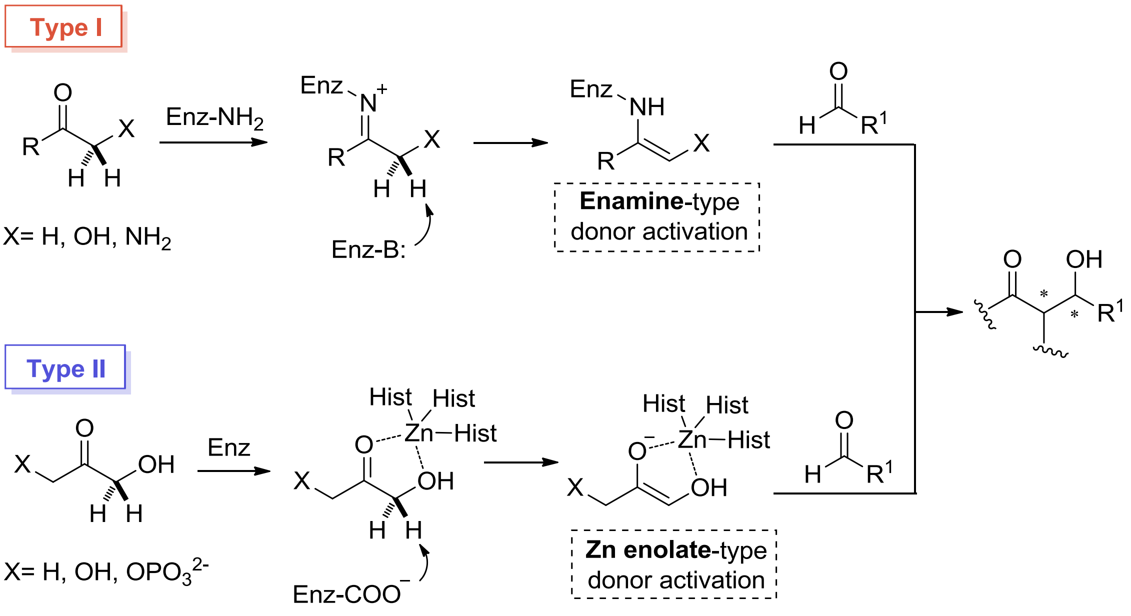
[30] For pioneering examples on soft enolization, see: a) M. W. Rathke, P. J. Cowan, *J. Org. Chem.* **1985**, *50*, 2622–2624; b) M. W. Rathke, M. Nowak, *J. Org. Chem.* **1985**, *50*, 2624–2626; c) R. E. Tirpak, R. S. Olsen, M. W. Rathke, *J. Org. Chem.* **1985**, *50*, 4877–4879.

[31] For selected racemic aldol addition *via* soft enolization, see: a) S. J. Sauer, R. M. Garnsey, D. M. Coltart, *J. Am. Chem. Soc.* **2010**, *132*, 13997–13999; b) J. M. Yost, R. J. Alfie, E. M. Tarsis, I. Chong, D. M. Coltart, *Chem. Commun.* **2011**, *47*, 571–572; c) R. J. Alfie, N. Truong, J. M. Yost, D. M. Coltart, *Tetrahedron Lett.* **2017**, *58*, 185–189.

[32] For catalytic aldol addition *via* soft enolization, see: a) M. Markert, M. Mulzer, B. Schetter and R. Mahrwald, *J. Am. Chem. Soc.* **2007**, *129*, 7258–7259; b) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2007**, *46*, 8666–8669. These two works are commented in section 2.2.2.2.

[33] Selected general reviews on asymmetric aldol reaction: a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36–44; b) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 365–75; c) M. Bartók, *Chem. Rev.* **2010**, *110*, 1663–1705.

to the class of lyases, found in biosynthetic pathways of carbohydrates, keto acids and amino acids, as well in various catabolic pathways for carbohydrates.[34] On a mechanistic basis, aldolases are divided in two groups, depending on the activation mode of the donor carbonyl group (Scheme 5).


Type I
O
R
X
H H
X= H, OH, NH2
Enz-NH2
Enz
N+
R
X
H H
Enz-B:
Enz
NH
R
X
Enamine-type
donor activation
O
H
R1
O
OH
*
*
R1
Type II
O
X
OH
H H
X= H, OH, OPO3 2-
Enz
Hist
Hist
Zn
Hist
O
X
OH
H H
Enz-COO−
Hist
Hist
Zn
Hist
O−
X
OH
Zn enolate-type
donor activation
O
H
R1

Scheme 5. Mechanism of type I and II aldolases.

The reaction mechanism of type I aldolases implies the formation of a Schiff base between the donor substrate and a conserved lysine residue in the active site, which after a deprotonation adds stereospecifically to the carbonyl group of an acceptor. In contrast, type II aldolases utilize a Zn^{2+} ion, coordinated to three histidine nitrogen atoms, to stabilize the enolate intermediate generated after deprotonation. Type I aldolases are found primarily in animals and higher plants, and the type II enzymes are found in microorganisms.

On the other hand, aldolases can be divided in four groups according to the structure of the donor substrate accepted by the enzyme (Table 1). These enzymes generally tolerate a broad range of acceptor substrates but have rigid requirements for donor ones. Generally, stereoselectivity is controlled by the enzyme and does not depend on the structure of the substrates. Besides dihydroxyacetone phosphate (DHAP), pyruvate or phosphoenolpyruvate (PEP), acetaldehyde and glycine can be used by various aldolases as the donor substrate to generate the reactive enolate intermediate.

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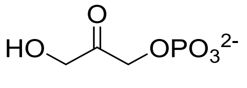
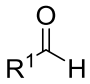
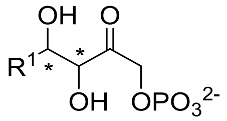
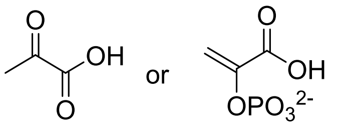
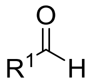
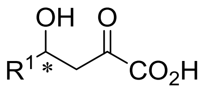
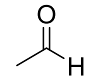
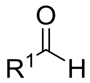
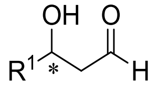
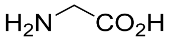
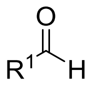
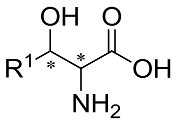
[34] For a comprehensive review on aldolases, see: a) M. Brovetto, D. Gamenara, P. Saenz Mendez, G. A. Seoane, *Chem. Rev.* **2011**, *111*, 4346–4403. For a review on aldolases promoted asymmetric reactions, see: b) N. G. Schmidt, E. Eger, W. Kroutil, *ACS Catal.* **2016**, *6*, 4286–4311.

Table 1. Aldolase classification according to the aldolase-donor structure.

ALDOLASE	DONOR	ACCEPTOR	PRODUCT
Type I	 **DHAP**		
Type II	 **Pyruvate or Phosphoenolpyruvate (PEP)**		
Type III	 **Acetaldehyde**		
Type IV	 **Glycine**		

Insights obtained by the study of the action mechanism and structure of aldolases have been useful not only to design and develop new catalysts but also to create novel catalysts with aldolase activity. In this respect, different types of compounds able to catalyze aldol or retroaldol reactions have been developed in the last years, covering from monoclonal antibodies to small organocatalysts. With no doubt, the extraordinary development of aminocatalysis,[35] in the area of covalent organocatalysis, has been clearly inspired by the fact that enamines generated from carbonyl compounds are some of the most frequent nucleophile counterparts employed by Nature. On the other hand, in order to assemble polyol functionalities, α-hydroxyketones are traditionally the pronucleophiles of choice in direct catalytic asymmetric aldol reactions. In contrast, 1,2-dicarbonyl compounds that present extra reactive centers and offer the opportunity for the construction of highly functionalized fragments have scarcely been employed as pronucleophiles in aldol reactions.

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[35] Selected reviews on aminocatalysis: a) B. List, *Chem. Commun*. **2006**, 819–824; b) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed*. **2006**, *45*, 7876–7880; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; d) C. F. Barbas III, *Angew. Chem. Int. Ed*. **2008**, *47*, 42–47; e) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci*. **2013**, *4*, 2287–2300; f) I. D. Jurberg, I. Chatterjee, R. Tannert, P.

1.1. 1,2-Dicarbonyl compounds

1,2-Dicarbonyl compounds have been used as nucleophiles for thousand years by Nature. Pyruvic acid, one of the simplest 1,2-dicarbonyl compounds, is crucial for the development of living organisms due to fact that numerous biosynthetic routes ramify from pyruvate to produce complex biomolecules.[36] For example, its direct carboxylation to oxaloacetic acid, controlled by pyruvate carboxylases, is the key step in Krebs citric acid cycle.[37] In addition, as previously shown, pyruvate- and phosphoenenolpyruvate-dependent aldolases catalyze the stereoselective addition of pyruvic acid to different aldehydes to produce ulosonic and sialic acids (Scheme 6).[38] These two nine–carbon polyhydroxylated

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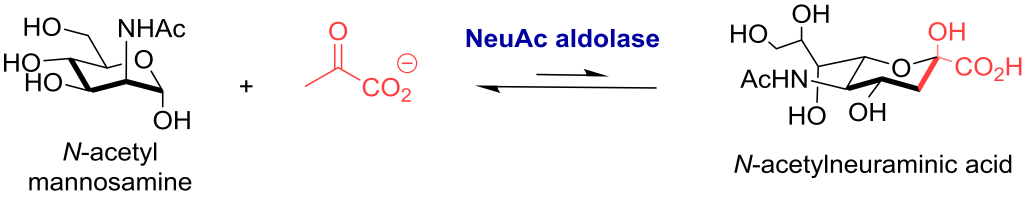
Melchiorre, *Chem. Commun*. **2013**, *49*, 4869–4883; g) L. Albrecht, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2014**, *20*, 358–368; h) B. M. Paz, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2015**, *21*, 1846–1853; i) J. L. Vicario, *Synlett* **2016**, *27*, 1006–1021. For a recent review on primary aminocatalyst incorporating hydrogen bond donating thioureas, see: j) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem*. **2013**, *11*, 7051–7071.

[36] G. D. Cody, N. Z. Boctor, T. R. Filley, R. Mm Hazen, J. H. Scott, A. Sharma, H. S. Yoder Jr., *Science* **2000**, *289*, 1337–1340.

[37] a) M. F. Utter, D. B. Keech, *J. Biol. Chem.* **1963**, *238*, 2603–2608; b) D. Voet, J. G. Voet, in *Biochemistry* 3rd Edition, **2004**, Wiley, New York.

[38] a) D. G. Comb, S. J. Roseman, *J. Am. Chem. Soc.* **1958**, *80*, 497–499; b) D. G. Comb, S. J. Roseman, *J. Biol. Chem.* **1960**, *235*, 2529–2537.

α-keto acids, usually present in glycoconjugates, play major role in cellular recognition in vertebrates.[39]



Scheme 6. NeuAc aldolase catalyzed aldol reaction.

Since Berzelius´s first synthesis of an α-keto acid in 1835,[40] pyruvates have been exploited as a tool in the synthesis of heterocyclic compounds and/or natural product precursors. Their synthetic utility is clearly demonstrated by the increasing number of references (more than 450 in the last 15 years) which employ α-keto esters for preparation of heterocyclic compounds by exploiting their reactivity in a broad variety of reactions.[41] It must be highlighted that the major part of the methodologies reported are stoichiometric and/or racemic versions. Moreover, in the asymmetric contributions, 1,2-dicarbonyl compounds are mainly employed as the electrophilic counterpart due to the increased electrophilic ketone reactivity by the presence of an adjacent carbonyl group.

The use of 1,2-dicarbonyl compounds as nucleophiles (d^2 synthons) remained unexplored until the pioneer work by Enders in which chiral hydrazones derived from 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvates were successfully metalated and alkylated to produce 3-substituted-2-keto esters.[42]

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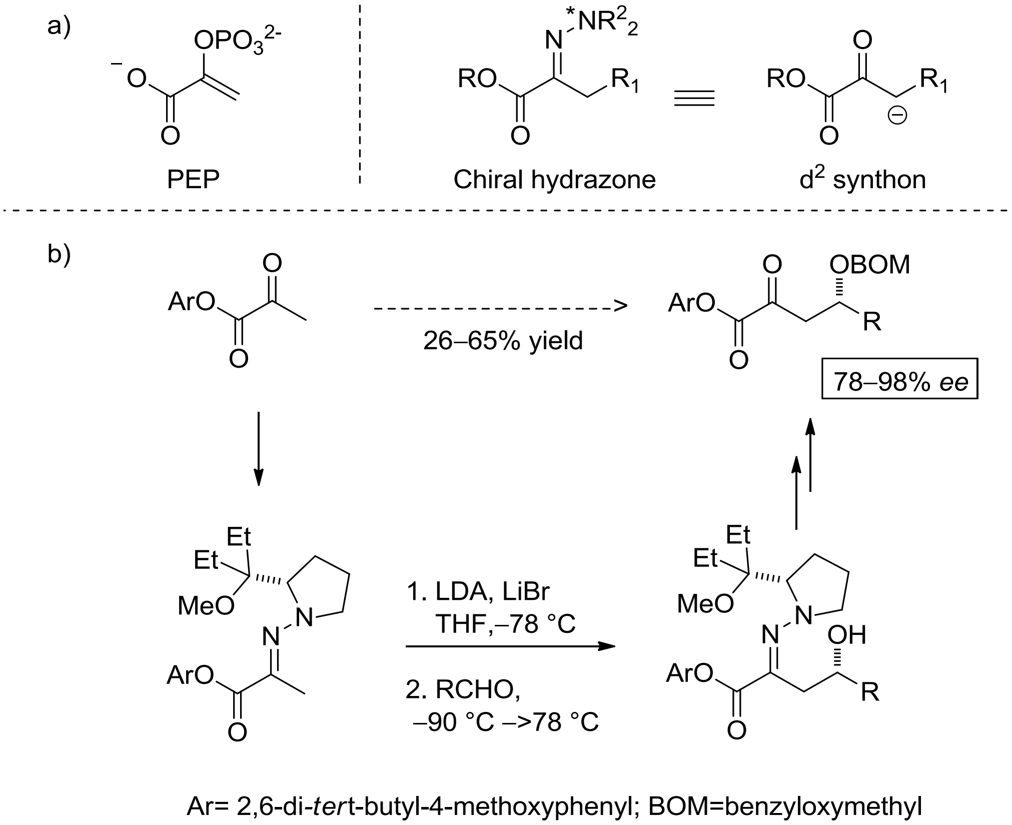
[39] a) L. Warren, H. Felsenfeld, *J. Biol. Chem.* **1962**, *237*, 1421–1431; b) R. Schauer, *Glycobiology* **1991**, *1*, 449–452; c) T. D. Machajewski, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374; d) W. K. Chou, S. Hinderlich, W. Reutter, M. E. Tanner, *J. Am. Chem. Soc.* **2003**, *125*, 2455–2461.

[40] J. J. Berzelius, *Ann. Phys.* **1835**, *36*, 1.

[41] Review on the chemistry of α-keto esters: B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151–264.

[42] a) D. Enders, H. Dyker, G. Raabe, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 618–620. See also: b) D. Enders, H. Dyker, G. Raabe, J. Runsink, *Synlett* **1992**, 901–903.

In the following years, Enders and co-workers extended the chiral hydrazone method to the asymmetric aldol reaction to synthesize 4-hydroxy-2-oxocarboxylic acid esters,[43] as described in Scheme 7, and isotetronic acids.[44]


a)
PEP
Chiral hydrazone
d2 synthon
b)
26–65% yield
78–98% ee
1. LDA, LiBr THF,–78 °C
2. RCHO, –90 °C –>78 °C
Ar= 2,6-di-tert-butyl-4-methoxyphenyl; BOM=benzyloxymethyl

Scheme 7. a) Chiral hydrazones as chemical equivalents of phosphoenolpyruvate (PEP). b) Asymmetric synthesis of 4-hydroxy-2-oxocarboxylic acid esters.

In spite of these works, the use of 1,2-dicarbonyl compounds as pronucleophiles has only grown significantly during the last decade. The main reason for the renewed interest in their nucleophilic character can be attributed mainly to: i) their dense number of reactive centers coupled with their ambident reactivity that can be exploited in sequential reactions and ii) the progress in the selective activation modes to enhance the nucleophilic character of 1,2-dicarbonyls toward cross-condensation instead of their competitive reactivity as electrophiles leading to useless self-condensation. An overview of their pronucleophile potential in asymmetric catalysis is detailed next in order to highlight the state of the art in the field.

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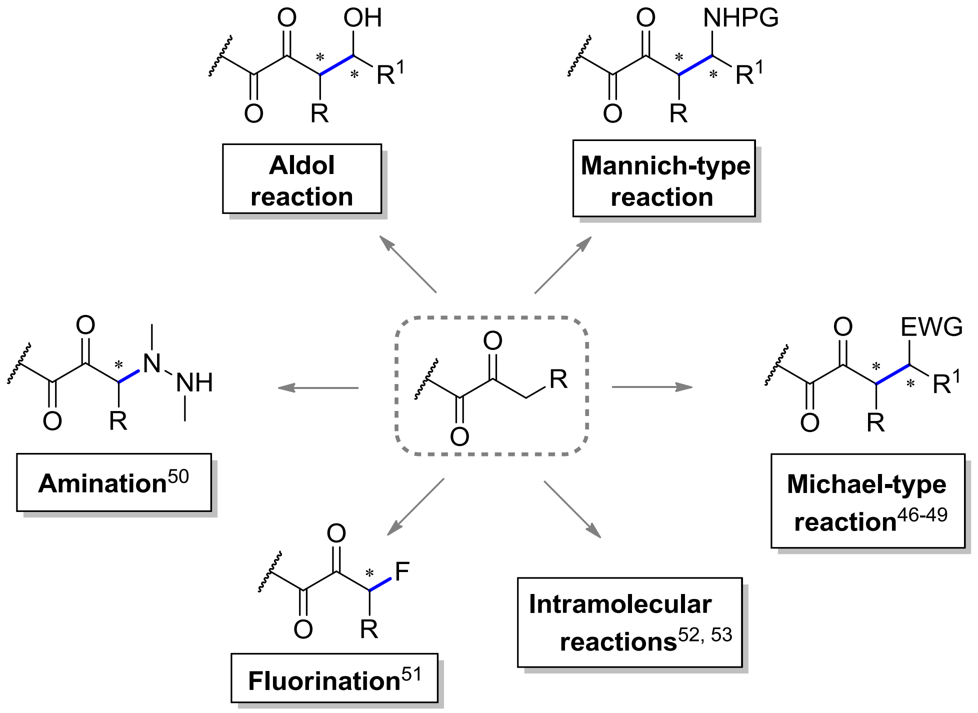
[43] D. Enders, H. Dyker, G. Raabe, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 421–431.

[44] a) D. Enders, H. Dyker, F. R. Leusink, *Chem. Eur. J.* **1998**, *4*, 311–319; b) D. Enders, H. Sun, F. R. Leusink, *Tetrahedron* **1999**, *55*, 6129–6138.

1.2. 1,2-Dicarbonyl compounds as pronucleophiles in asymmetric catalysis

The usefulness of 1,2-dicarbonyl compounds as pronucleophiles has been demonstrated in several either bio-, metal or organocatalytic asymmetric standard transformations as shown in Scheme 8.[45]


Aldol reaction
Mannich-type reaction
Amination[50]
Michael-type reaction[46-49]
Fluorination[51]
Intramolecular reactions[52, 53]
OH
NHPG
EWG
R
R1
F
O

Scheme 8. Asymmetric catalytic transformations of 1,2-dicarbonyl compounds as pronucleophiles.

---

[45] For reviews on the chemistry of 1,2-dicarbonyl compounds as pronucleophiles, see: a) W. Raimondi, D. Bonne, J. Rodriguez, *Chem. Commun.* **2012**, *48*, 6763–6775; b) D. Bonne, T. Constantieux, Y. Coquerel, J. Rodriguez, *Chem. Eur. J.* **2013**, *19*, 2218–2231.

Most examples belong to the Michael-type reaction for which metallo- and organocatalytic approaches have been described using either nitroalkenes[46], α,β-unsaturated aldehydes[47], α,β-unsaturated carboxyl compounds[48] or α,β-unsaturated nitriles[49] as electrophiles. Isolated examples for catalytic asymmetric amination[50], fluorination[51] and intramolecular reactions such as the Claisen rearrangement[52] and the Nazarov cyclization[53] have also been described. Since the overall aim of this investigation, as explained later in detail, is focused on the preparation of enantiomerically pure polyol/aminopolyol fragments, the state of the art in the use of 1,2-dicarbonyl compounds as pronuchleophiles in catalytic asymmetric aldol and Mannich-type reactions is only presented.

---

[46] Metallocatalytic approaches: a) A. Nakamura, S. Leetard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037; b) A. Nakamura, S. Leetard, R. Shimizu, Y. Hamashima, M. Sodeoka, *Tetrahedron: Asymmetry* **2010**, *21*, 1682–1687; c) Y. Xu, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2010**, *12*, 3246–3249; d) D. Shi, Y. Xie, H. Zhou, C. Xia, H. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 1248–1251; e) H. Ouchi, A. Ashina, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, *16*, 1980–1983; f) Q. Liang, J. He, B. Ni, *Tetrahedron: Asymmetry* **2014**, *25*, 1146–1149; g) X. Chen, H. Zhou, H. Huang, *Chin. J. Catal.* **2015**, *361*, 57–67. Organocatalytic approaches: h) O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246–5249; i) W. Raimondi, M. M. Sanchez Duque, S. Goudedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne, J. Rodriguez, *Synthesis* **2013**, 1659–1666; j) W. Raimondi, O. Baslé, T. Constantieux, D. Bonne, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 563–568; k) M. Rueping, A. Kuenkel, R. Fröhlich, *Chem. Eur J.* **2010**, *16*, 4173–4176; l) D. Ding, C.–G. Zhao, Q. Guo, H. Arman, *Tetrahedron* **2010**, *66*, 4423–4427; m) Y. Liu, Y. Wang, H. Song, Z. Zhou, C. Tang, *Adv. Synth. Catal.* **2013**, *355*, 2544–2549.

[47] Organocatalytic approaches: a) M. Rueping, E. Sugiono, E. Merino, *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049; b) A. Lefranc, L. Guénée, A. Alexakis, *Org. Lett.* **2013**, *15*, 2172–2175; c) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem. Int. Ed.* **2009**, *48*, 3699–3702.

[48] Organocatalytic approaches: a) Y. Gao, Q. Ren, Q.-S. Ang, J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 3691–3697; b) Q. Ren, Y. Gao, J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 5297–5302.

[49] Organocatalytic approach: D. Ding, C.-G. Zhao, *Tetrahedron Lett.* **2010**, *51*, 1322–1325.

[50] Metallocatalytic approach: a) K. Jhul, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421. Organocatalytic approach: b) M. Terada, K. Amagai, K. Ando, E. Kwon, H. Ube, *Chem. Eur. J.* **2011**, *17*, 9037–9041.

[51] Metallocatalytic approach: S. Suzuki, Y. Kitamura, S. Lectard, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2012**, 51, 4581–4585.

[52] Metallocatalytic approach: a) L. Abraham, R. Czerwonka, M. Hiersemann, *Angew. Chem. Int. Ed.* **2001**, 40, 4700–4703. Organocatalytic approach: b) C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 9228–9229.

[53] Organocatalytic approach: A. Basak, N. Shimada, W. F. Bow, D. A. Vicic, M. A. Tius, *J. Am. Chem. Soc.* **2010**, *132*, 8266–8267.

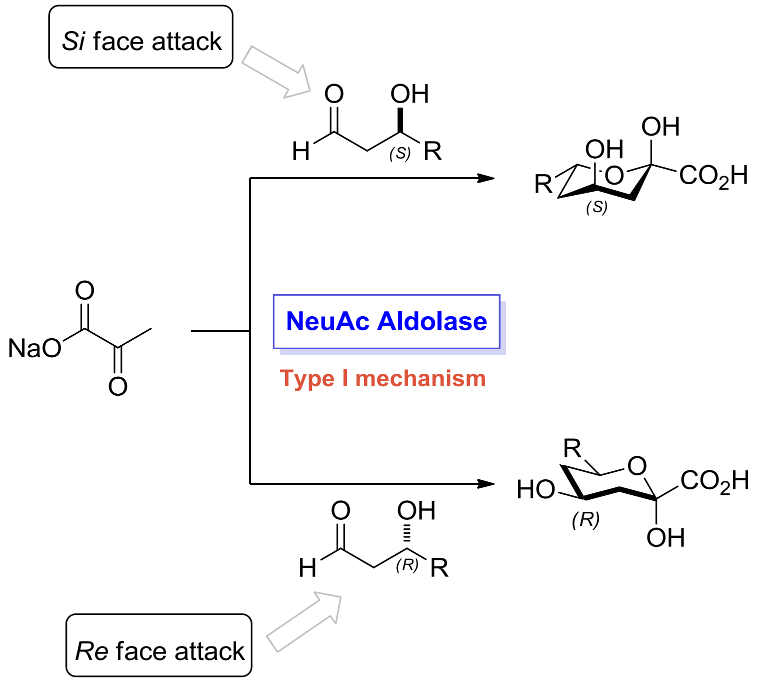
1.2.1. Homo-aldol and cross-aldol reactions

1.2.1.1. Biochemical transformations

In aldol biocatalyzed reactions involving pyruvates as pronucleophiles, the commercially available *N*-acetylneuraminic acid aldolase is the most common aldolase employed due to its high tolerance for aldehyde acceptors.[54] Also, the fact that, in contrast to the majority of aldolases, the induced stereoselectivity also depends on the structure of the sugar derived aldehyde acceptor, makes them very versatile catalysts from a synthetic point of view. As a general trend, in acceptors with the (*S*) configuration at C3, the carbonyl group reacted with sodium pyruvate from the *Si* face, presumably under kinetic contol, whereas acceptors with the opposite configuration suffered the nucleophilic addition from the *Re* face under thermodynamic control (Scheme 9)[54a, 54b]

---

[54] a) C.-H. Lin, T. Sugai, R. L. Halcomb, Y. Ichikawa, C.-H. Wong, *J. Am. Chem. Soc.* **1992**, *114*, 10138–10145; b) W. Fitz, J.-R. Schwark, C.-H. Wong, *J. Org. Chem.* **1995**, *60*, 3663–3670; c) M. Wada, C.-C. Hsu, D. Franke, M. Mitchell, A. Heine, I. Wilson, C.-H. Wong, *Bioorg. Med. Chem.* **2003**, *11*, 2091–2098; d) D. Indurugalla, A. J. Bennet, *Can. J. Chem.* **2008**, *86*, 1005–1009.


Si face attack
O
OH
H
(S)
R
R
OH
OH
O
CO₂H
(S)
NaO
O
O
NeuAc Aldolase
Type I mechanism
R
O
HO
CO₂H
(R)
OH
O
OH
H
(R)
R
Re face attack

Scheme 9. NeuAc aldolase-catalyzed aldol reactions: stereochemical outcome.

Another representative example of NeuAc aldolase mediated synthesis is the preparation of azasugars such as the castanospermine analogue described in Scheme 10.[55] The biocatalyzed addition of pyruvate to the mannosamine derivative followed by reductive amination and further transformations produced 3-(hydroxymethyl)-6-*epi*-castanospermine.

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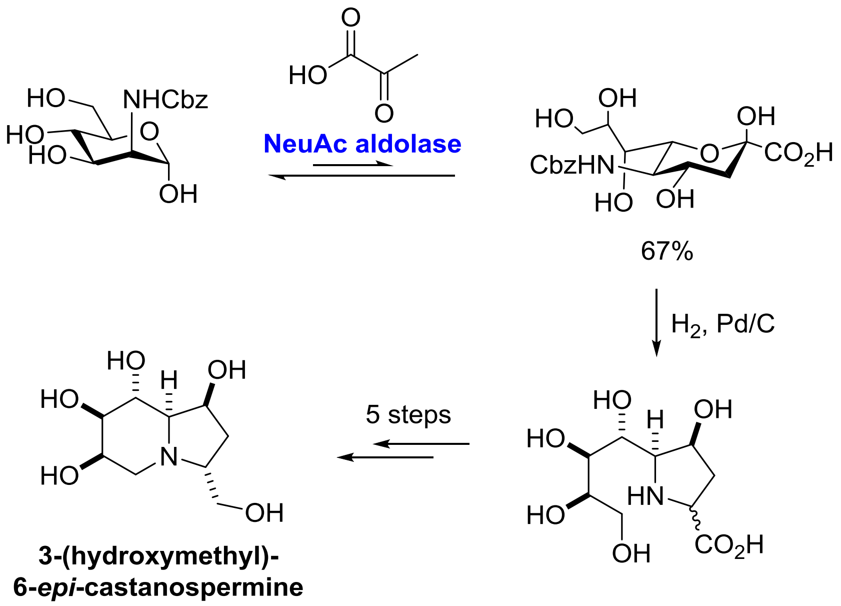
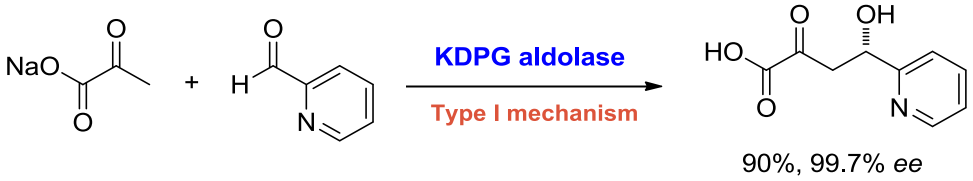
[55] P. Zhou, H. M. Salleh, J. F. Honek, *J. Org. Chem.* **1993**, *58*, 264–266.


NeuAc aldolase
67%
H2, Pd/C
5 steps
3-(hydroxymethyl)-6-epi-castanospermine

Scheme 10. NeuAc aldolase promoted synthesis of azasugars.

Other pyruvate-dependent aldolases such as the 2-keto-3-deoxy-6-phosphogluconate (KPDG) aldolase, was shown to efficiently catalyze the cross-aldol reaction between sodium pyruvate and 2-pyridinecarboxaldehyde (Scheme 11).[56]


KDPG aldolase
Type I mechanism
90%, 99.7% ee

Scheme 11. KPDG aldolase mediated addition to 2-pyridinecarboxaldehyde.

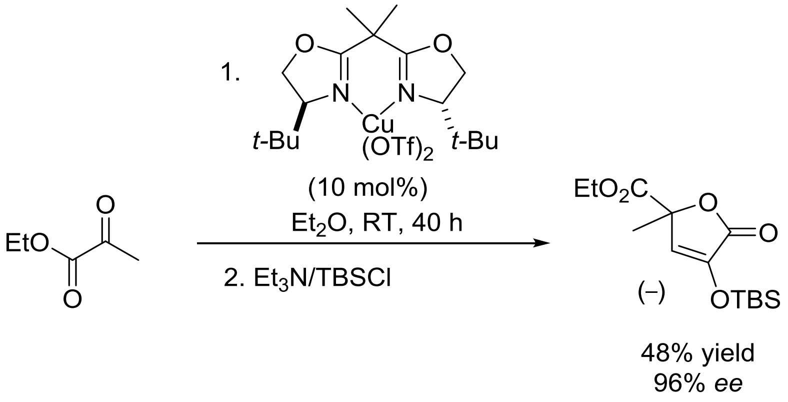
In spite of their relevance in Nature, the synthetic potential of pyruvate dependent aldolases in organic synthesis has encountered only limited applications but it has inspired more general metallo- and organocatalyzed approaches.

---

[56] M. J. Walters, E. J. Toone, *Nat. Protocols* **2007**, 2, 1825–1830.

1.2.1.2. Metallocatalyzed transformations

The first direct catalytic asymmetric transformation using a 1,2-dicarbonyl compound as pronucleophile was described by Jørgensen and co-workers in 2000.[57] The chiral copper(II)-bisoxazoline complex, shown in Scheme 12, efficiently catalyzed the homo-aldol reaction of ethyl pyruvate, by mimicking pyruvate- and phosphoenolpyruvate-dependent type II aldolases. The chiral Lewis acid played a dual role by both promoting the generation of the enol pyruvate and controlling the stereochemistry of the reaction.



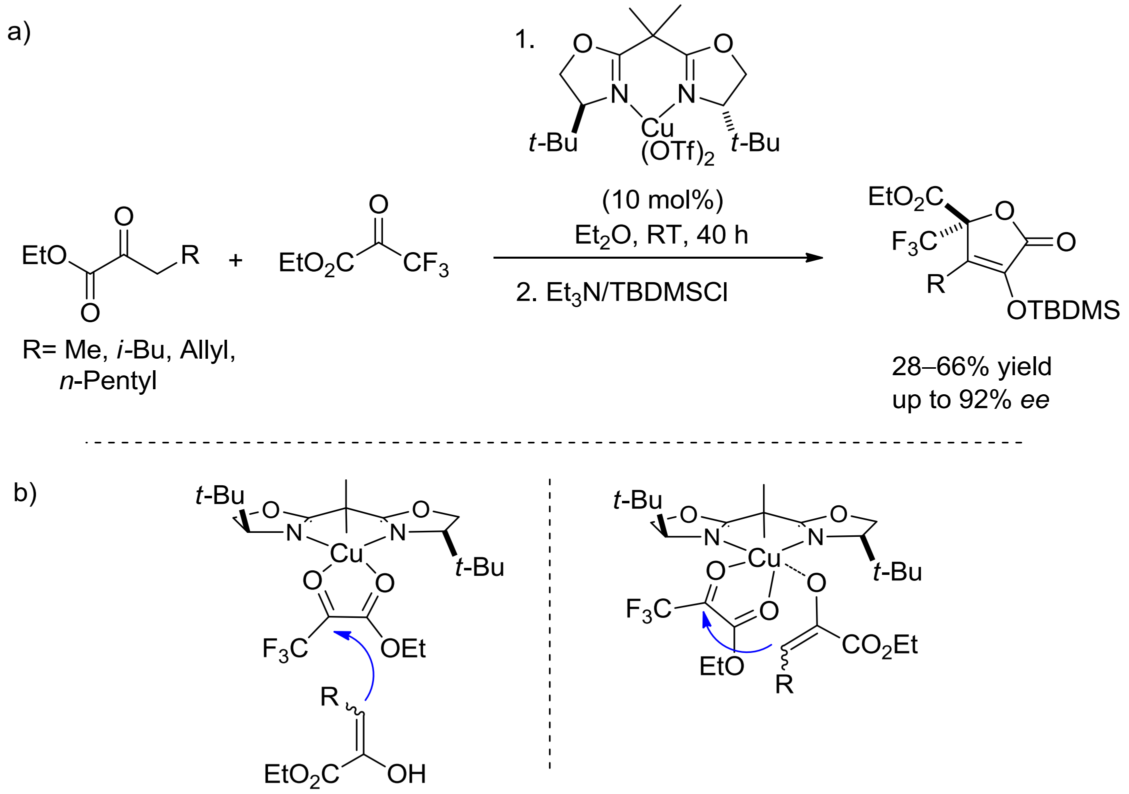
Scheme 12. Chiral Lewis acid catalyzed homo-aldol reaction of ethyl pyruvate.

The same methodology was successfully applied to the cross-aldol reaction when highly activated acceptors, such as ethyltrifluoropyruvate, were employed (Scheme 13).[58] The enantioselectivity induced by the chiral complex was high although diastereoselectivity was negligible. The aldol adducts lactonized to produce the more stable isotetronic acids under hydroxyl protecting conditions.

---

[57] K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 2211–2212.

[58] N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 1077–1085.



Scheme 13. a) Chiral Lewis acid catalyzed cross-aldol reaction of ethyl pyruvates and ethyltrifluoropyruvate. b) Proposed intermediates and approaches for the enolate to the bidentate-coordinated α-keto ester.

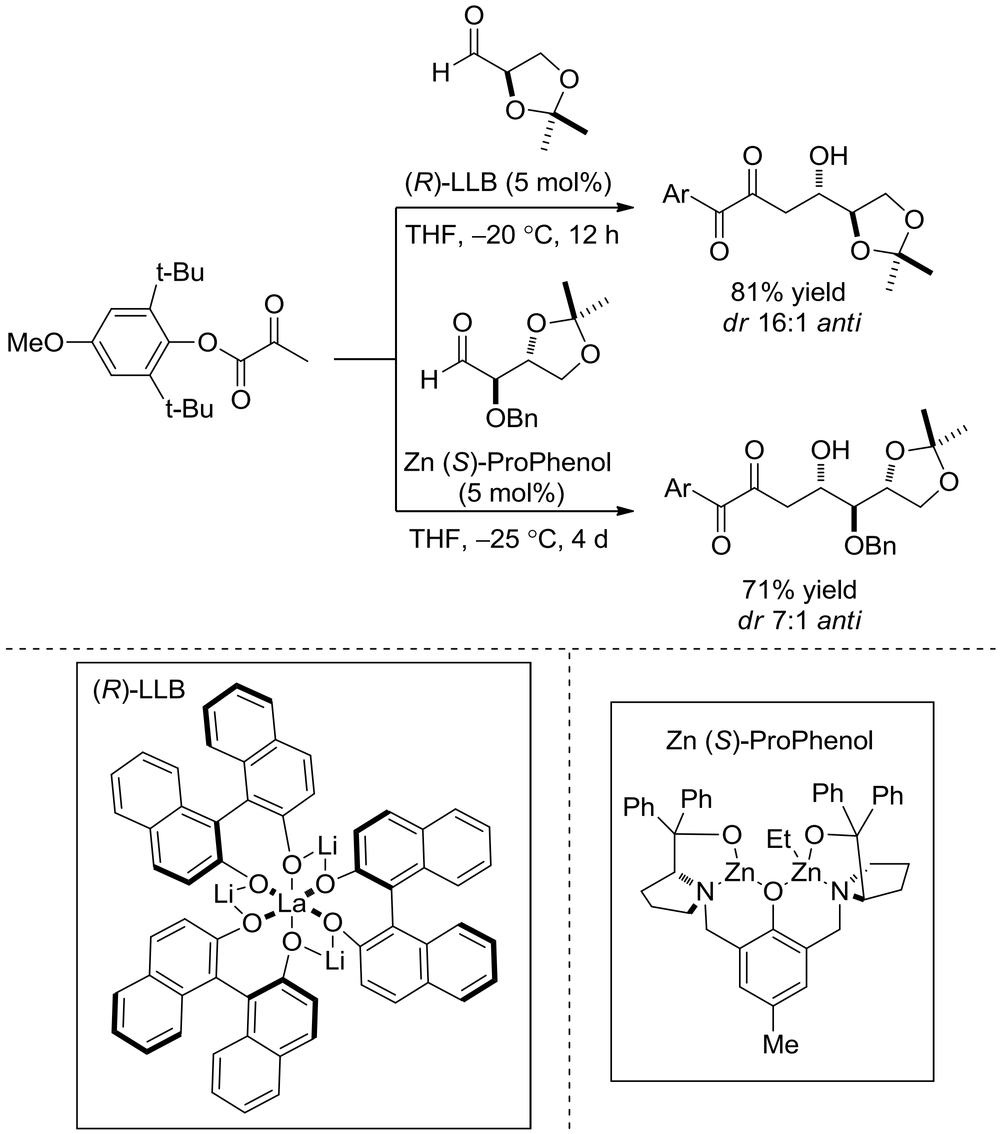
In 2013, Mlynarski and co-workers employed the 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate, previously used by Enders,[42] in the diastereoselective cross-aldol reaction with (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde promoted by the dinuclear lanthanium-lithium-BINOL ((*R*)-LLB) complex shown in Scheme 14 .[59] Two years later, the same group broaden the scope of the reaction by using the dinuclear Zn-(*S*)-ProPhenol complex.[60] Various chiral protected aldehydes such as D-erithrose, D-arabinose, D-mannose and D-glucose, reacted to produce the corresponding *anti*-aldol adducts with moderate to excellent diastereomeric ratios. In particular, the reaction with (*R*)-2-(benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde is shown in

---

[59] O. El-Sepelgy, J. Mlynarski, *Adv. Synth. Catal.* **2013**, *355*, 281–286.

[60] M. A. Molenda, S. Bás, O. El-Sepelgy, M. Stefaniak, J. Mlynarski, *Adv. Synth. Catal.* **2015**, *357*, 2098–2104.

Scheme 14. This methodology provided a new protocol for the stereoselective synthesis of several six-, seven-, eight- and nine-carbon member 3-deoxy-2-ulosonic acids.

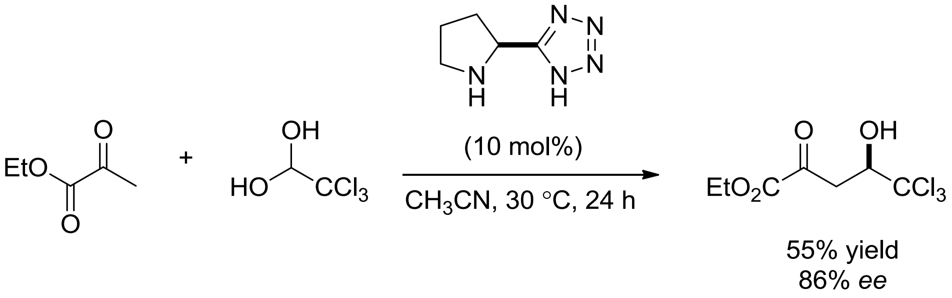

t-Bu
MeO
O
O
O
t-Bu
O
H
O
O
(R)-LLB (5 mol%)
THF, –20 °C, 12 h
Ar
O
OH
O
O
O
81% yield
dr 16:1 anti
H
O
O
O
OBn
Zn (S)-ProPhenol
(5 mol%)
THF, –25 °C, 4 d
Ar
O
OH
O
O
O
OBn
71% yield
dr 7:1 anti
(R)-LLB
Li
O
O
Li
La
O
O
O
O
Li
Zn (S)-ProPhenol
Ph
Ph
Ph
Ph
O
Et
O
Zn
Zn
N
O
N
Me

Scheme 14. Chiral Lewis acid catalyzed diastereoselective cross-aldol reaction of ethyl pyruvates.

1.2.1.3. Organocatalyzed transformations

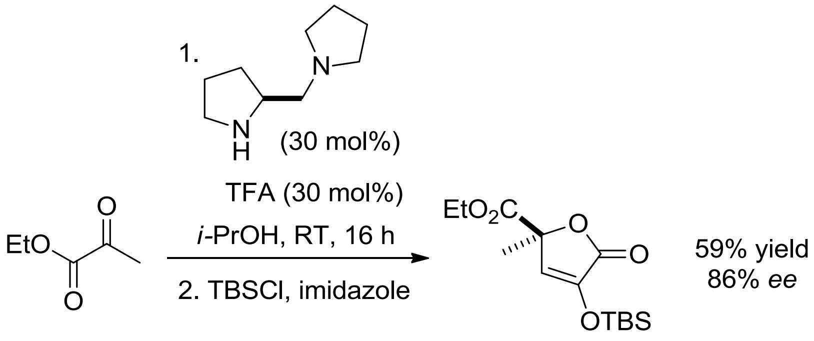
1.2.1.3.1. Covalent organocatalysis

In 2004 Yamamoto and co-workers showed, for the first time, that 1,2-keto esters could be specifically activated *via* enamine activation with a proline-tetrazol catalyst. They described one single example for the cross-aldol reaction of ethyl pyruvate and the highly activated chloral (Scheme 15).[61]


EtO
O
O
+
OH
HO
CCl3
N
H
N
N
N
N
H
(10 mol%)
CH3CN, 30 °C, 24 h
O
OH
EtO2C
CCl3
55% yield
86% ee

Scheme 15. First organocatalyzed cross-aldol reaction of 1,2-dicarbonyl compounds.

One year later, Dondoni and co-workers also shown that aminocatalysis was an effective methodology to produce enantiomerically enriched substituted isotetronic acids by taking advantage of the bidentate reactivity of ethyl pyruvate.[62]


1.
N
H
N
(30 mol%)
TFA (30 mol%)
i-PrOH, RT, 16 h
2. TBSCl, imidazole
EtO
O
O
EtO2C
O
O
OTBS
59% yield
86% ee

Scheme 16. Asymmetric homo-aldol reaction of ethyl pyruvate.

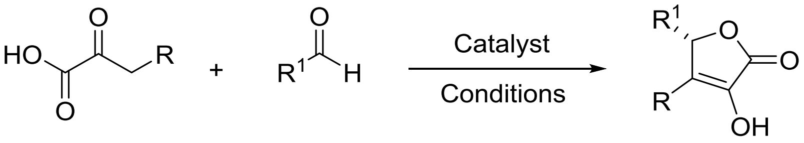
---

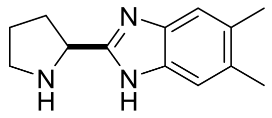
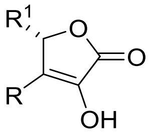
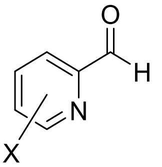
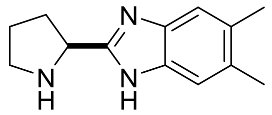
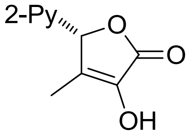
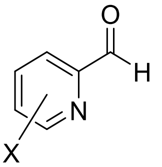
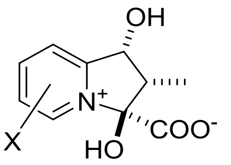
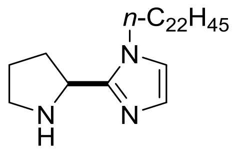
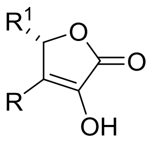
[61] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986.

[62] P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657–4660.

Under aminocatalysis, the domino process cross-aldolization-lactonization was efficiently achieved with aromatic aldehydes by using α-keto acids as pronucleophiles (Table 2). For instance, Vincent, Landais and co-workers reported the reaction between α-keto acids and aromatic aldehydes with a benzimidazole proline-derived organocatalyst.[63]

Table 2. Enantioselective cross-aldolization-lactonization sequence of α-keto acids.



R (Donor)	Acceptor	Catalyst/Conditions	Product	Ref.
Me, Et, Ph	R^1= Aryl, *i*-Pr	 10–30 mol% THF, RT, 4–7 d	 20–90% yield 63–90% *ee*	63
Me	 X= 2-Br, 2-OMe, 3-CN, 3-Br	 10 mol% THF, RT 3 d	 73–84% yield 90–98% *ee*	64
	 X= H, 2-Me, 5-Me, 5-F		 29–77% yield 99% *ee*	
Me, Et, Ph	R^1= Aryl, *i*-Pr, Cy	 10 mol% H_2O, RT, 12 h	 75–94% yield 89–99% *ee*	65

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[63] J.-M. Vincent, C. Margottin, M. Berlande, C. Cavagnat, T. Buffeteau, Y. Landais, *Chem. Commun.* **2007**, 4782–4784.

In 2013, the same group extended the previous methodology to pyridine-2-carbaldehydes.[64] Substitution in the pyridine ring influenced the behaviour of the aldol adducts that were obtained as isotetronic acids or pyridinium salts with moderate to good yields and excellent enantioselectivity (Table 2).

On the other hand, Li´s group introduced a novel amphiphilic imidazole/pyrrolidine catalyst which produced excellent results both in chemical yield and enantioselectivity.[65] Remarkably, the methodology was also highly successful with non-aromatic aldehydes with low tendency to enolization (Table 2).

To explain the stereochemistry obtained with the benzimidazole proline-derived organocatalyst,[63,64] the authors postulated a rigid chair-like transition state where the benzimidazole ring is protonated by the carboxylic acid and the aromatic aldehyde is protonated through hydrogen bonding with the N-H bond of the catalyst. The *E*-enolate approaches the aldehyde from the *Re* face, as exposed in Figure 3.

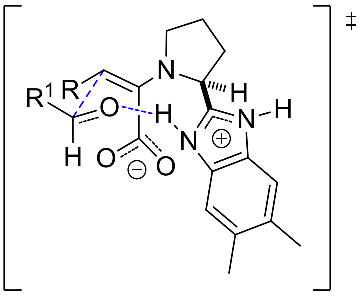


Figure 3. Postulated transition state for the enantioselective cross-aldolization-lactonization.

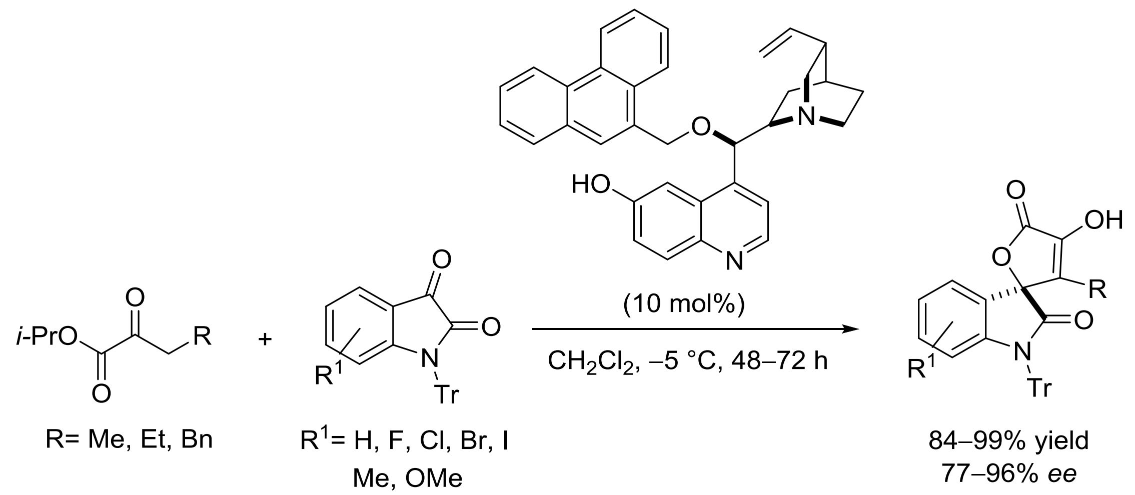
---

[64] V. Liautard, D. Jardel, C. Davies, M. Berlande, T. Buffeteau, D. Cavagnant, F. Robert, J.-M. Vincent, Y. Landais, *Chem. Eur. J.* **2013**, *19*, 14532–14539.

[65] B. Zhang, Z. Jiang, X. Zhou, S. Lu, J. Li, Y. Liu, C. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 13159–13162.

1.2.1.3.2. Non-covalent organocatalysis

Regarding non-covalent organocatalysis, Li and co-workers described in 2014 the first example of a Brønsted-base catalyzed aldol reaction of 1,2-dicarbonyl compounds.[66] The bifunctional 6'-OH *Cinchona* derived catalyst, shown in Scheme 17, enabled the soft enolization of pyruvate and stereoselectively promoted the aldol reaction with highly activated *N*-trityl isatines to produce the corresponding spirooxindole-based isotetronic acids in good yields and high enantioselectivities.

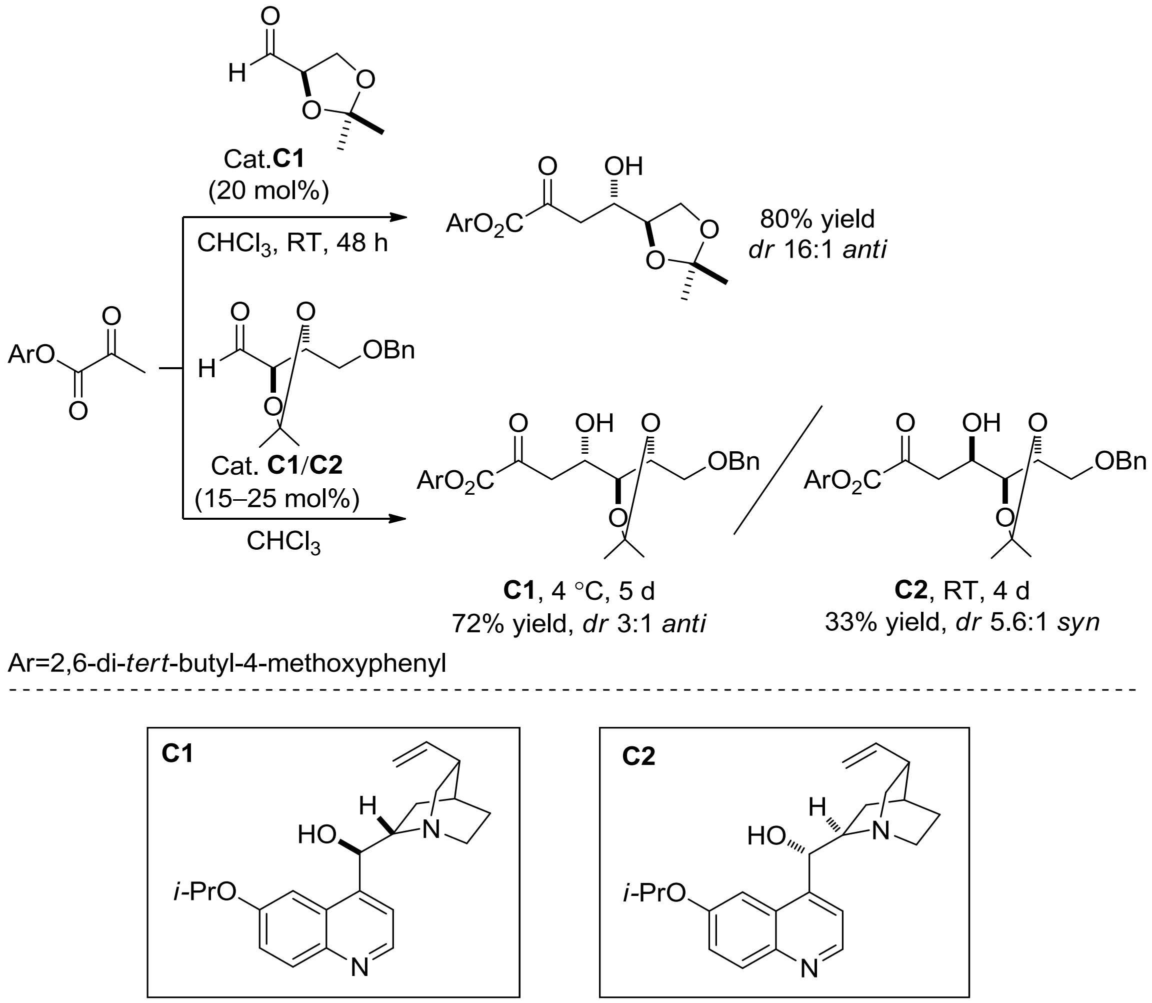


Scheme 17. Asymmetric synthesis of spirooxindole-based isotetronic acids.

In parallel to their work in the metal-catalyzed cross-aldol reaction (Scheme 14, page 34) Mlynarski and co-workers reported a Brønsted-base catalyzed cross-aldol reaction with sugar-derived protected aldehydes promoted by modified *Cinchona* alkaloids. First, with the protected (*R*)-glycerladehyde acetonide to produce the corresponding *anti*-aldol adduct, with identical stereoselectivity obtained in the metal catalyzed approach (16:1 *dr*),[59] (Scheme 14), and later employing protected D-erithrose, D-arabinose, D-mannose and D-glucose derived aldehydes.[67] In general, yields fluctuated from low to moderate and both *anti*- and *syn*-diastereomers were accessible in moderate to good diastereoselectivities by varying the catalyst. As an example, the reaction with protected D-erithrose is shown in Scheme 18.

---

[66] W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu, C. Li, *Chem. Eur. J.* **2014**, *20*, 8545–8550.


Cat.C1
(20 mol%)
CHCl3, RT, 48 h
80% yield
dr 16:1 anti
Cat. C1/C2
(15–25 mol%)
CHCl3
C1, 4 °C, 5 d
72% yield, dr 3:1 anti
C2, RT, 4 d
33% yield, dr 5.6:1 syn
Ar=2,6-di-tert-butyl-4-methoxyphenyl
C1
C2

Scheme 18. *Cinchona* promoted aldol reactions of pyruvates and sugar-derived protected aldehydes. **C1**: quinine derivative. **C2**: quinidine derivative.

The selectivity of these reactions mainly depends on the catalysts configuration, although the conformation of the starting aldehyde seems also to be important. On the basis of the stereochemical outcome of the reactions, the authors presumed that the basic catalyst not only deprotonates the pyruvate ester but also forms an asymmetric environment for the reaction through a network of hydrogen bonds.

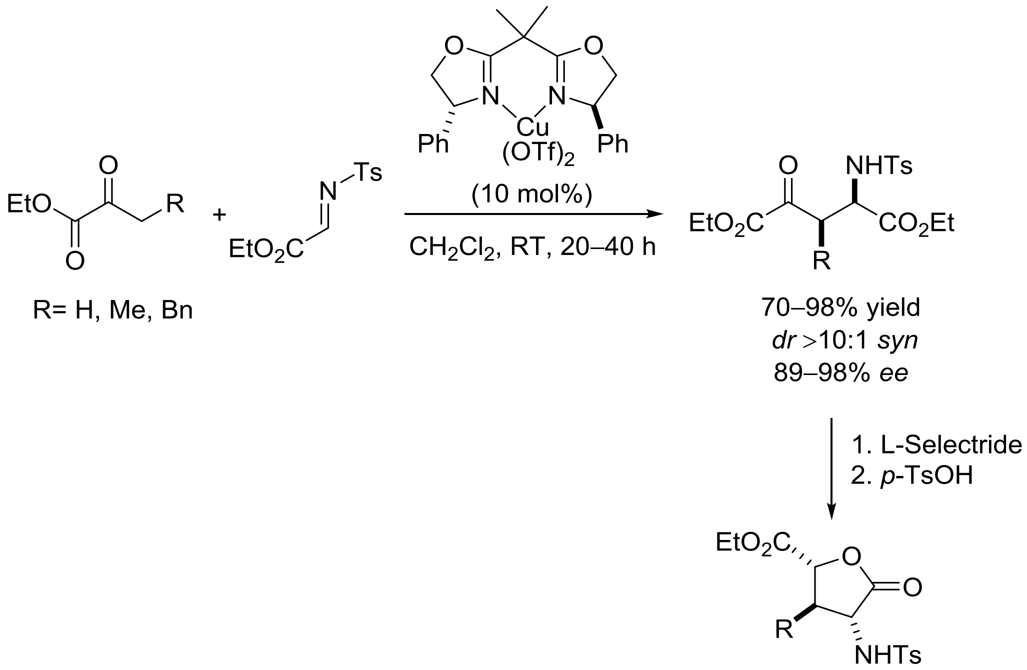
---

[67] M. A. Molenda, S. Bás, J. Mlynarski, *Eur. J. Org Chem.* **2016**, 4394–4403.

1.2.2. Mannich reaction

The Mannich-type reaction of 1,2-dicarbonyl compounds has been scarcely explored and, to the best of our knowledge, only three examples in the context of metallo- and organocatalyzed transformations have been described.

In order to demonstrate the versatility of their protocol for the aldol reaction, in 2001 Jørgensen and co-workers outlined the first direct catalytic asymmetric Mannich-type reaction of α-keto esters with an *N*-tosyl-α-imino ester (Scheme 19).[68] The methodology gave simple access to α-amino acid derivatives, in high yield and in excellent diastereo- and enantioselectivity, which were easily transformed into highly enantioenriched lactones by selective reduction of the 4-oxo moiety. Nevertheless, this important transformation was limited to highly activated *N*-toluensulfoyl glyoxylic imines.

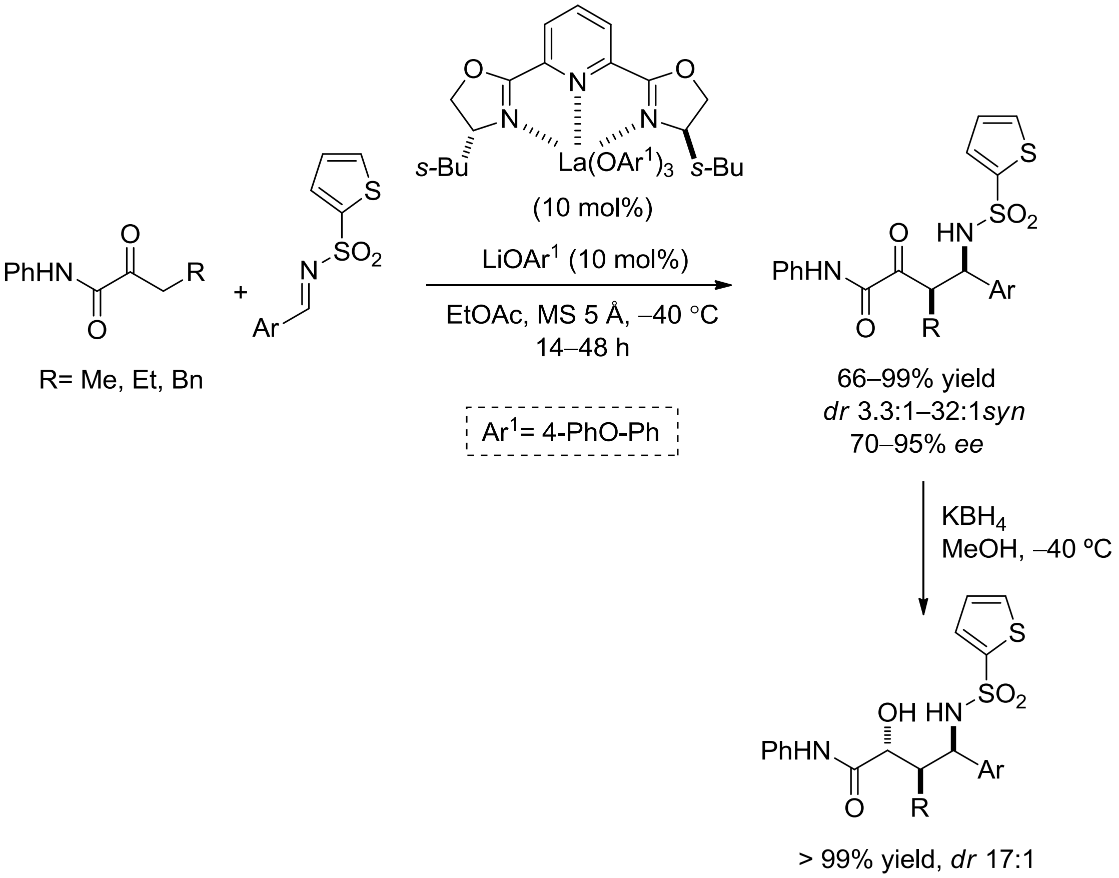

O
N
N
O
Cu
(OTf)2
Ph
Ph
(10 mol%)
CH2Cl2, RT, 20–40 h
EtO
O
O
R
+
N
Ts
EtO2C
R= H, Me, Bn
O
NHTs
EtO2C
CO2Et
R
70–98% yield
dr >10:1 syn
89–98% ee
1. L-Selectride
2. p-TsOH
EtO2C
O
O
R
NHTs

Scheme 19. Chiral Lewis catalyzed Mannich-type reaction of α-keto esters with α-imino esters.

---

[68] K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997.

Several years later Shibasaki and co-workers addressed this drawback by using a chiral heterobimetallic lanthanum aryloxide/lithium aryloxide/pybox complex which promoted the Mannich-type reaction of 1,2-ketoanilides with *N*-thiophenesulfonyl imines to produce enantiomerically enriched γ-amino amides in good yields and also high *syn*-diastereoselectivity (Scheme 20).[69] Highly diastereoselective reduction of the ketone moiety using KBH_4 produced the corresponding β-alkyl-γ-amino-α-hydroxy amides with *anti*/*sin* relationship.


s-Bu
La(OAr¹)₃
s-Bu
(10 mol%)
LiOAr¹ (10 mol%)
EtOAc, MS 5 Å, –40 °C
14–48 h
Ar¹= 4-PhO-Ph
PhHN
R
+
N
SO₂
S
Ar
R= Me, Et, Bn
HN
66–99% yield
dr 3.3:1–32:1syn
70–95% ee
KBH₄
MeOH, –40 °C
OH
> 99% yield, dr 17:1

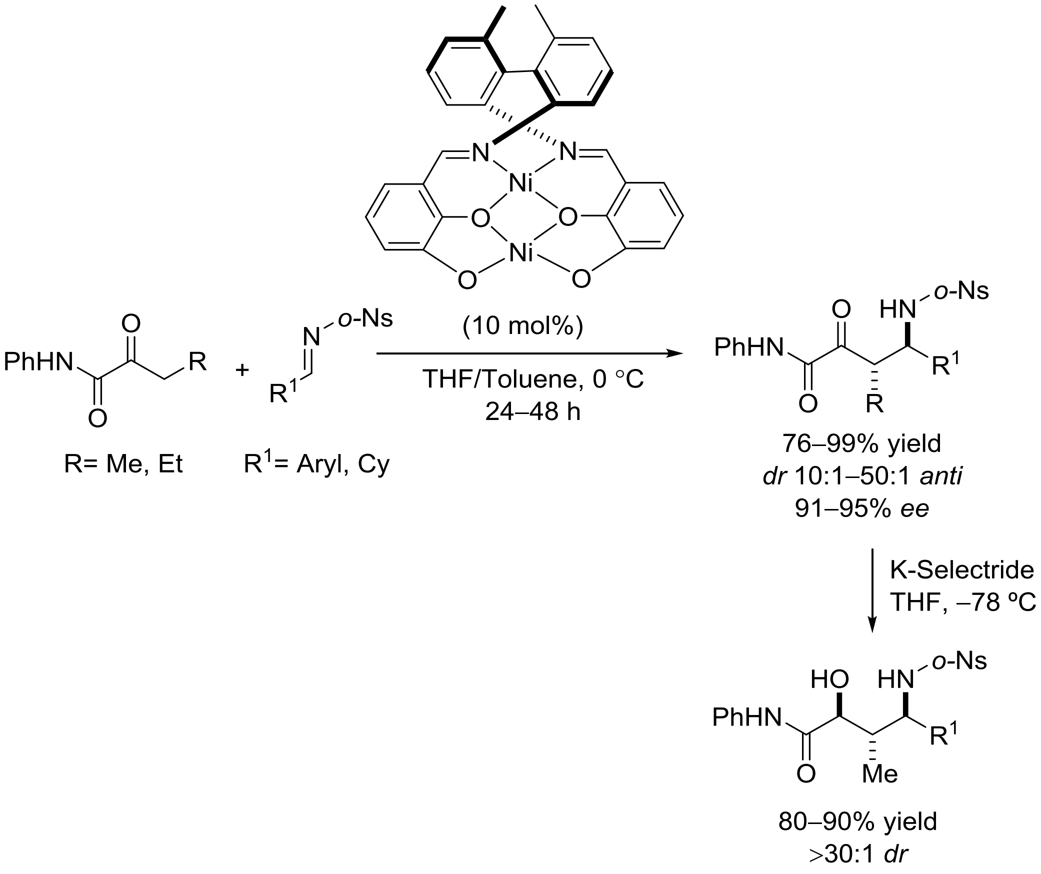
Scheme 20. Chiral Lewis catalyzed *syn*-selective asymmetric Mannich type reaction of α-ketoanilides.

One year later, the same group described the complementary *anti*-selective Mannich-type reaction utilizing the homodinuclear nickel complex shown in Scheme 21 and *N*-*o*-nitrophenyl sulfonyl imines.[70] The stereochemical outcome of the reaction was excellent and the Mannich adducts could be stereoselectively reduced with K-Selectride to afford the corresponding α-hydroxy-β-alkoxyl-γ-amino amides with *anti*/*anti* relative configuration.

---

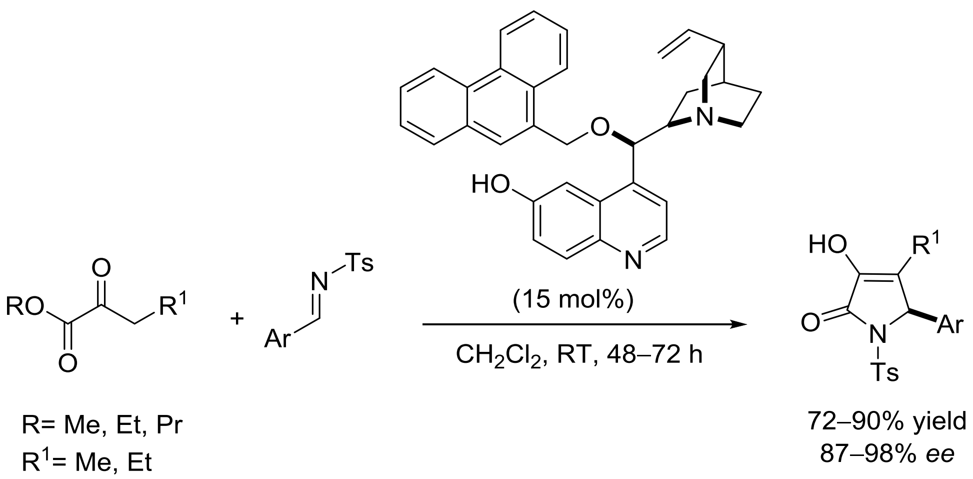
[69] G. Lu, H. Marimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 6847–6850.

[70] Y. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3353–3356.


PhHN
O
R
O
+
N
o-Ns
R1
R= Me, Et
R1= Aryl, Cy
N
Ni
O
O
Ni
(10 mol%)
THF/Toluene, 0 °C
24–48 h
HN
o-Ns
R1
76–99% yield
dr 10:1–50:1 anti
91–95% ee
K-Selectride
THF, –78 ºC
HO
Me
80–90% yield
>30:1 dr

Scheme 21. Chiral Lewis catalyzed *anti*-selective asymmetric Mannich type reaction of α-ketoanilides.

As far as we know, the only organocatalytic Mannich reaction of 1,2-dicarbonyl compounds has been reported by Liu, Li and co-workers in 2014.[66] The 6'-OH *Cinchona* derived catalyst, previously employed in the aldol reaction with *N*-trityl isatins, promoted the transformation with *N*-tosyl imines. Cascade-cyclization of the corresponding Mannich-adducts afforded substituted 5-*1*H-pyrrol-2-ones in good yields and high enantioselectivity (Scheme 22).

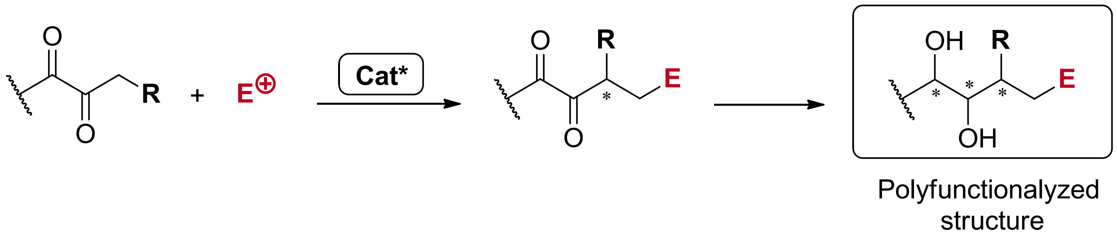


Scheme 22. Organocatalyzed Mannich type reaction of *N*-tosyl imines.

1.3. Objectives

As mentioned in the general introduction, the structural diversity of polyhydroxylated compounds and the arousing interest for their potential as therapeutic agents urge the development of new catalytic methodologies to achieve enantiomerically pure structures by enhancing efficiency, sustainability and production cost. In this sense, one of the most direct and atom economical approaches to assemble polyol functionalities is the direct catalytic asymmetric aldol reaction of α-hydroxyketones followed by stereoselective reduction of the ketone moiety (Scheme 4, page 20).

In order to increase the functionalization of polyol fragments, the use of 1,2-dicarbonyl compounds as pronucleophiles in carbon-carbon bond forming reactions is an appealing approach that has been barely explored. Precedents mentioned in the previous section make clear that the ambiphilic character of these compounds is an advantage for intended cascade reactions but represents an important challenge when the electrophilic counterparts (E^+) are not highly reactive (Scheme 23).



Scheme 23. 1,2-Dicarbonyl compounds as pronucleophiles in catalytic asymmetric carbon-carbon bond forming reactions.

For instance, the most investigated reactions involving pyruvates as donors are the Michael-type reactions which have been successfully effected under either metal or organic catalysis.[71] The usual higher reactivity of the Michael acceptors compared to other potential electrophiles seems to be relevant.

For the less explored cross-aldol reactions main limitations come from the difficulties to avoid the homo-aldol reaction due to the inherently high reactivity of the α,β-dicarbonyl moiety in nucleophilic 1,2-additions. The necessity of using highly reactive aldehydes to effect the cross aldol reaction limits the generality and scope of the metallo- and organocatalyzed methodologies reported so far.[72] On the other hand, aldol adducts also tend to lactonize, which is an important limitation when substituted pyruvates are employed because the cyclization implies loss of a stereogenic center.[73]

In this context, the overall aim of this investigation consists on the development of a Brønsted base catalyzed cross-aldol reaction of 1,2-dicarbonyl compounds with enolizable aldehydes, a reaction that has not yet been realized. Probably, the major reason that justifies this notable deficiency is the difficulty associated with the α-deprotonation of 1,2-dicarbonyl compounds, resulting from the relatively low acidity of the α-carbon atom in this class of pronucleophiles, that may also compete with aldehyde enolization.

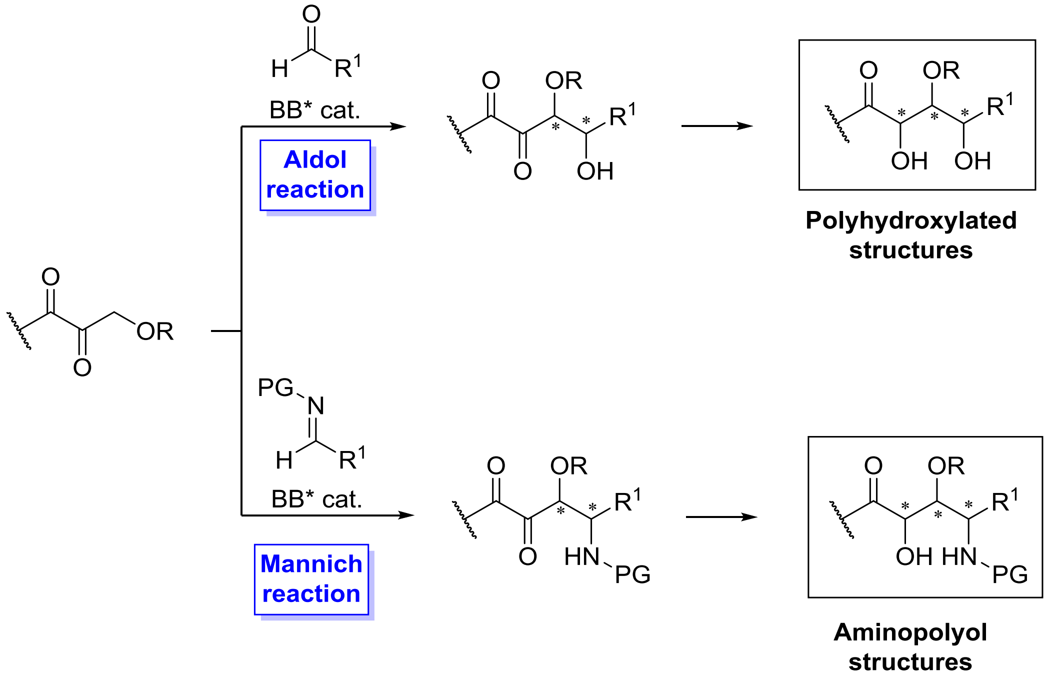
---

[71] See ref. 46–49, page 28.

[72] See pages 33–36 and 38–39.

[73] See pages 33, 34 and 38.

In order to achieve this goal, β-alkoxy-1,2-dicarbonyl compounds were chosen towards the preparation of enantiomerically pure polyhydroxylated fragments. Subsequently, the knowledge and experience adquired in the cross-aldol reaction will be utilized to perform the analogous Mannich type reaction to generate aminopolyol fragments (Scheme 24).


BB* cat.
Aldol reaction
Polyhydroxylated structures
BB* cat.
Mannich reaction
Aminopolyol structures

Scheme 24. Objectives.

Challenges for each particular objective, work hypothesis, the state of the art of the catalytic asymmetric aldol and Mannich reactions applied to the preparation of these types of fragments along with the results obtained will be presented in two independent chapters:

- Chapter 2: Bifunctional Brønsted base catalyzed asymmetric direct aldol reaction of β-alkoxy-α-keto amides.

- Chapter 3: Bifunctional Brønsted base catalyzed asymmetric direct Mannich-reaction of β-alkoxy-α-keto amides.

CHAPTER 2

Bifunctional Brønsted base catalyzed asymmetric direct aldol reaction of β-alkoxy-α-keto amides

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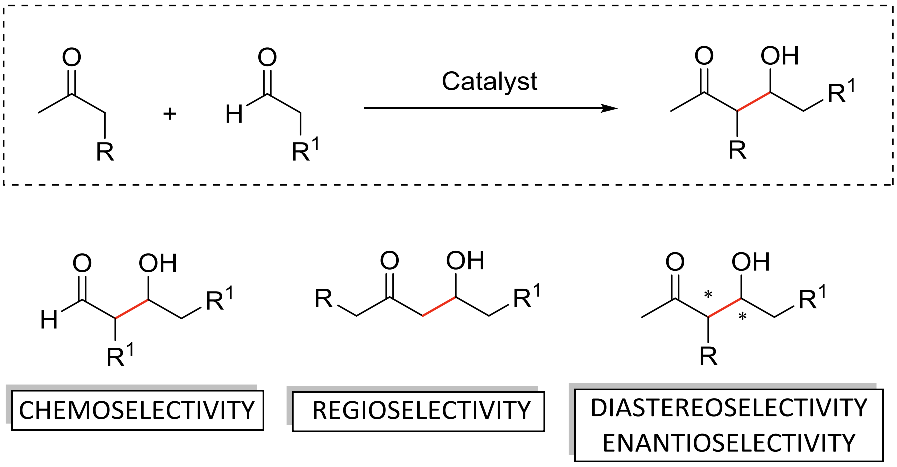
2. Bifunctional Brønsted base catalyzed asymmetric direct aldol reaction of β-alkoxy-α-keto amides

2.1. Asymmetric aldol reaction

The asymmetric aldol reaction is one of the most powerful methods, employed in biological systems as well as in chemical synthesis, for the construction of carbon-carbon bonds. The process unites two relatively simple carbonyl units to give chiral β-hydroxy carbonyl compounds with up to two new stereogenic centers. These aldol products are highly valuable intermediates in the synthesis of interesting and biologically important natural products, particularly for polyoxygenated compounds.[74]

The asymmetric cross-aldol reaction represents an iconic transformation to verify the consistency of new concepts and methodologies in asymmetric catalysis. Along with reactivity, issues of chemo-, regio-, diastereo- and enantioselectivity arise and challenge the synthetic community towards the development of more efficient strategies (Scheme 25).



Scheme 25. Typical selectivity challenges in asymmetric cross-aldol reactions.

---

[74] a) T. D. Machajewsky, C. H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374; b) T. Brodmann, M. Lorenz, R. Schäckel, S. Simsek, M. Kalesse, *Synlett* **2009**, 174–192; c) J. Li, D. Menche, *Synthesis* **2009**, 2293–2315; d) A. K. Ghosh, Z. L. Dawson, *Synthesis* **2009**, 2992–3002; e) M. Bhanushali, C.-G. Zhao, *Synthesis* **2011**, 1815–1830; f) Y. Wu, *Synlett* **2013**, 1623–1636.

Since Wurtz first discovery,[75] many strategies have been developed throughout the years in order to control the challenges associated to selectivity in cross-aldol reactions (Figure 4).

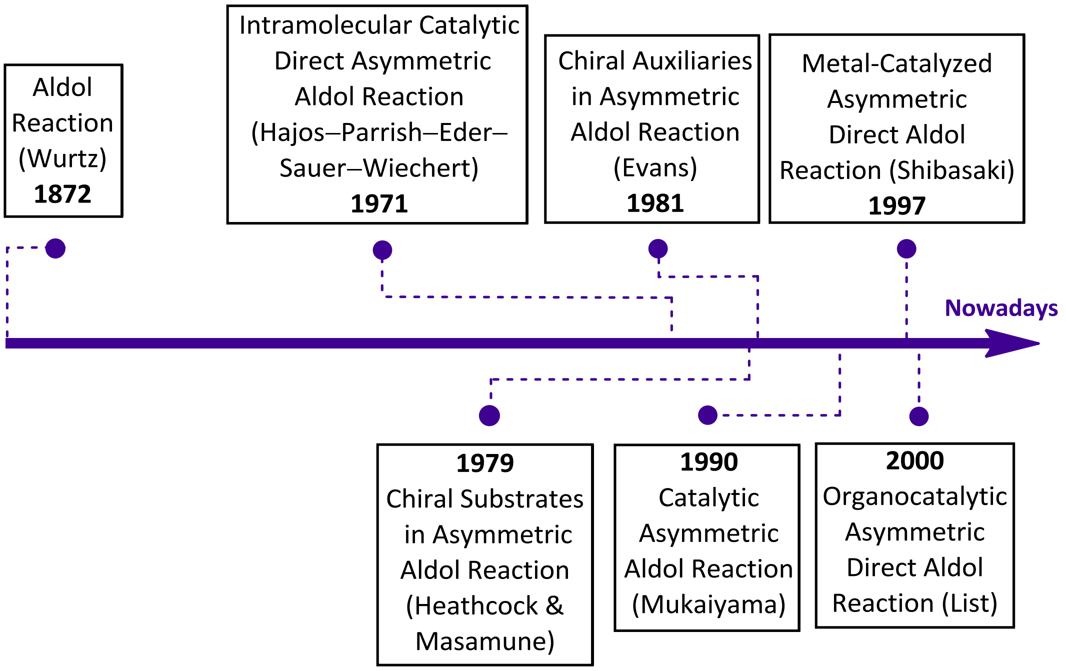

Aldol Reaction (Wurtz) 1872
Intramolecular Catalytic Direct Asymmetric Aldol Reaction (Hajos–Parrish–Eder–Sauer–Wiechert) 1971
Chiral Auxiliaries in Asymmetric Aldol Reaction (Evans) 1981
Metal-Catalyzed Asymmetric Direct Aldol Reaction (Shibasaki) 1997
Nowadays
1979 Chiral Substrates in Asymmetric Aldol Reaction (Heathcock & Masamune)
1990 Catalytic Asymmetric Aldol Reaction (Mukaiyama)
2000 Organocatalytic Asymmetric Direct Aldol Reaction (List)

Figure 4. Chronologically ordered historic milestones regarding selectivity in the asymmetric cross-aldol reaction.

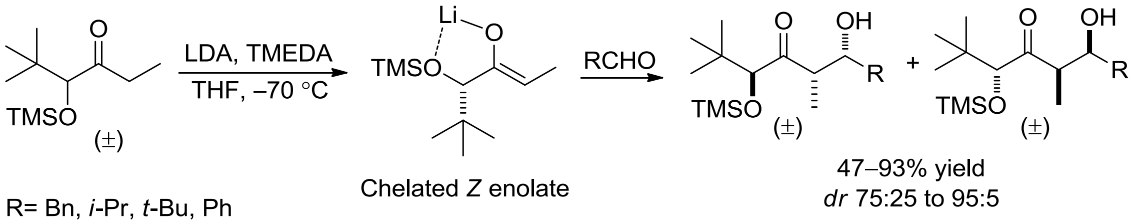
In the late 1970s and early 1980s, the groups of Heathcock[76] and Masamune[77] reported the efficiency of acyclic α-hydroxy ketones to promote highly diastereocontrolled aldol reactions. In his pioneering work, Heathcock attributed the high *syn* diastereoselectivity observed to the preferential formation of the more stabilized *Z* lithium enolate in which the bulky *tert*-butyl group prevented the approach of the aldehyde to the less hindered *Si* face of the enolate (Scheme 26).

---

[75] A. Wurtz, *Bull. Soc. Chim. Fr.* **1872**, *17*, 436–442.

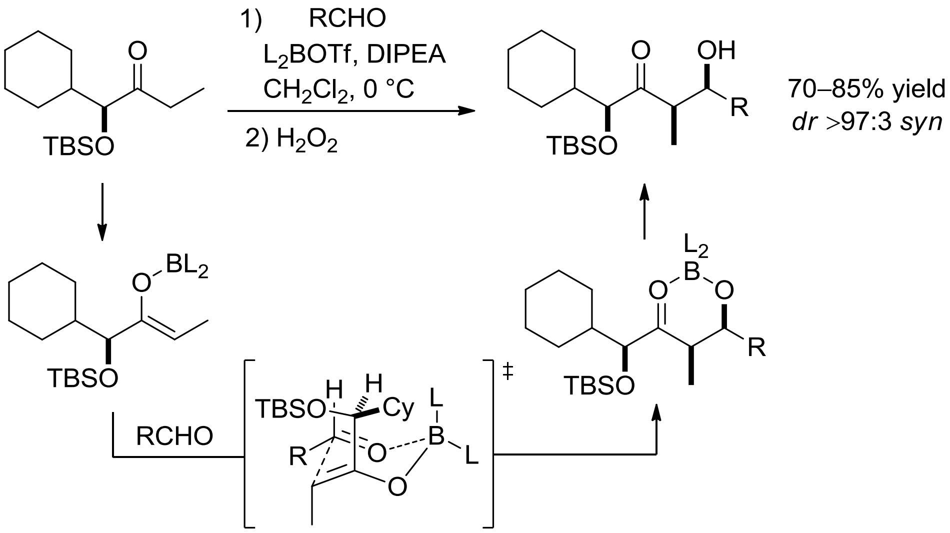
[76] a) C. T. Buse, C. H. Heathcock, *J. Am. Chem. Soc.* **1977**, *99*, 8109–8110; b) C. H. Heathcock, C. T. White, *J. Am. Chem. Soc.* **1979**, *101*, 7076–7077; c) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, J. E. Sohn, *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079.

[77] S. Masamune, W. Choy, F. A. J. Kerdesky, B. Imperiali, *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568.


LDA, TMEDA
THF, −70 °C
TMSO
(±)
Li
TMSO
Chelated Z enolate
RCHO
O
OH
R
+
47–93% yield
dr 75:25 to 95:5
R= Bn, i-Pr, t-Bu, Ph

Scheme 26. Heathcock´s preliminary studies on the substrate-controlled aldol reaction of protected α-hydroxy ethyl ketone.

On the other hand, Masamune reported highly stereoselective aldol reactions from an enantiomerically pure α-silyloxy ethyl ketone. Dialkyl boron triflates produced the chelated *Z* boron enolates to afford the *syn*-adducts as single diastereomers (Scheme 27). The remarkable stereocontrolled transformation was assumed to proceed through a cyclic chair-like transition-state which minimized electrostatic and steric interactions.[78] Many were the contributions that followed these preliminary works that relied on the substrate-control approach to deal with the diastereoselectivity issue associated to the carbon-carbon bond formation in the aldol reaction.[79]


1) RCHO
L2BOTf, DIPEA
CH2Cl2, 0 °C
2) H2O2
TBSO
O
OH
R
70–85% yield
dr >97:3 syn
BL2
RCHO
TBSO
H
H
Cy
L
B
L
R
O
‡
L2
B
O
O
R

Scheme 27. Masamune´s pioneering contribution on substrate-controlled aldol reaction. BL_2= 9-BBN, $B(n\text{-}Bu)_2$, $B(c\text{-}C_5H_9)_2$.

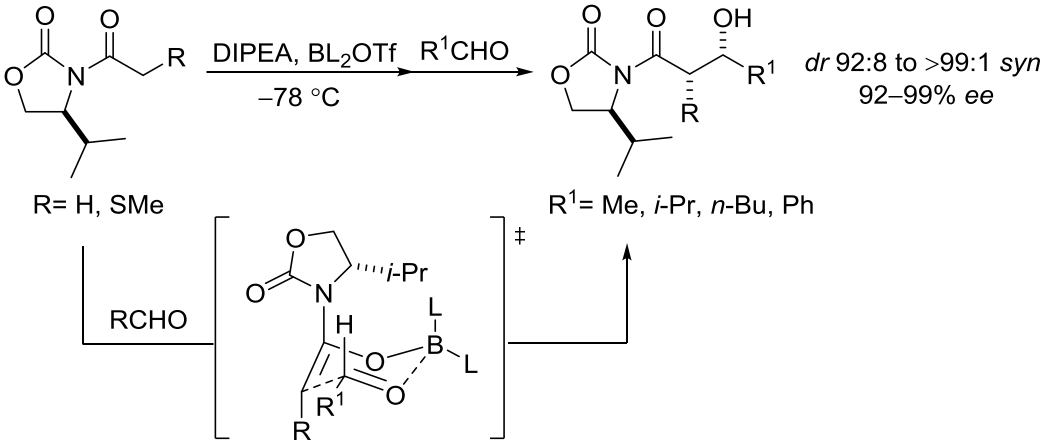
---

[78] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

[79] Review on the substrate-controlled asymmetric aldol reactions: G. Aullón, P. Romea, F. Urpí, *Synthesis* **2017**, *49*, 484–503.

In 1981, Evans and co-workers introduced oxazolidin-2-ones as useful recyclable chiral auxiliaries in order to address the enantioselectivity issue. By combining the previously mentioned diastereoselectivity control, induced by metal enolates, and the chiral auxiliary, aldol adducts were produced with extremely high *syn*-selectivity and enantioselectivity upon subsequent removal of the auxiliary (Scheme 28).[80]

In the next decades, the field became considerably fruitful since numerous chiral auxiliaries were synthesized[81] and evaluated in asymmetric aldol reactions.[82]



Scheme 28. Evans´ acyl oxazolidinone method.

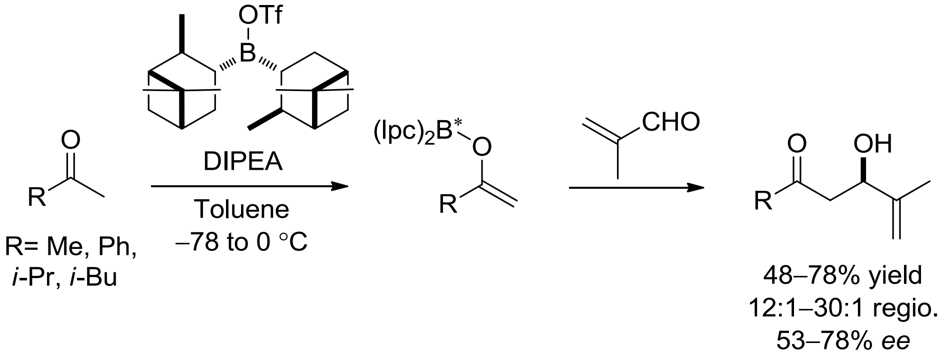
---

[80] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

[81] Selected reports on the synthesis and application of chiral auxiliaries in asymmetric aldol reaction: a) W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772; b) M. A. Wlaker, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 5747–5750; c) A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *1192*, 2586–2587; d) M. T. Crimmins, B. W. King, E. A. Tabet, *Tetrehedron* **1997**, *119*, 7883–7884; e) D. A. Evans, J. S. Tedrow, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392–393; f) D. M. Casper, J. R. Burgenson, J. M. Esken, G. M. Ferrence, S. R. Hitchcock, *Org. Lett.* **2002**, *4*, 3739–3742; g) S. G. Davies, I. A. Hunter, R. L. Nicholson, P. M. Roberts, E. D. Savory, A. D. Smith, *Tetrahedron* **2004**, *60*, 7553–7557.

[82] Selected reviews on the use of oxazolidinones in asymmetric aldol reaction applied to total synthesis: a) M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2013**, *24*, 1149–1188; M. M. Heravi, V. Zadsirjan, B. Farajpour, *RSC Advances* **2016**, *6*, 30498–30551.

In parallel, between 1989 and 1996, stoichiometric amounts of chiral Lewis acids (CLAs), especially boron CLAs, were also explored towards the asymmetric version of the aldol reaction.[83] This chiral reagent method provided a valuable alternative to the use of a chiral auxiliary attached to the boron enolate. As a representative example, in Scheme 29 is depicted Paterson´s pioneering approach for the aldol reaction of methylketones and methacrolein using (−)-B-diisopinocampheyltriflateborane. The methodology offered high regioselectivity control for α-branched unsymmetrical ketones.



Scheme 29. Aldol reaction of methylketones using chiral boron reagents.

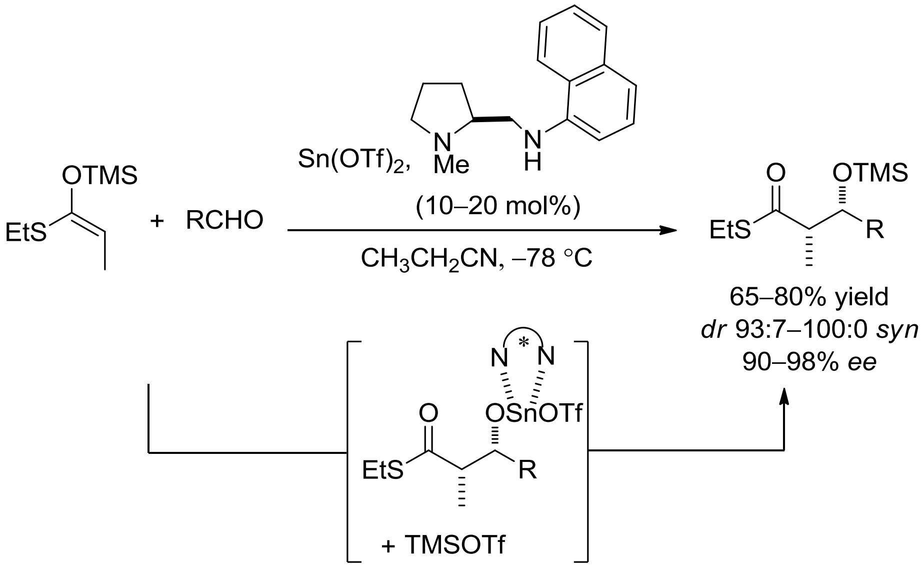
On the other hand, Mukaiyama´s discovery of the directed aldol reaction of silyl enol ethers promoted by Lewis acids[84,85] represented a major milestone that, after subsequent development, had an impressive application in organic synthesis.[86] Silyl enol ethers utilized as enolate equivalents addressed the issues of regio- and chemoselectivity by allowing an unambiguous identification of which carbonyl compound plays the role of the nucleophile or electrophile in the bond-forming event.[87] In 1990, Mukayaima and co-workers reported the first catalytic enantioselective version of the asymmetric aldol reaction. A wide variety of aldehydes including aromatic, aliphatic and α,β-saturated aldehydes reacted with silyl enol ether of S-ethyl propanethionate by use of a chiral diamine coordinated tin (II) triflate as catalyst (Scheme 30).[88] Authors proposed as key step the metal exchange reaction of the initially produced aldol-type adduct with trimethylsilyltriflate (metal exchange from tin(II) to silicon).

---

[83] Selected reports on the boron derived-CLAs directed asymmetric aldol reactions: a) I. Paterson, J. M. Goodman, *Tetrahedron Lett.* **1989**, *30*, 997–1000; b) M. A. Blanchette, M. S. Malamas, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, S. Masamune, *J. Org. Chem.* **1989**, *54*, 2817–2825; c) E. J. Corey, H.-C. Huang, *Tetrahedron Lett.* **1989**, *39*, 5235–5238; d) C. Gennare, A. Vulpetti, M. Donghi, N. Mongelli, E. Vanotti, *Angew. Chem. Int. Ed.* **1996**, *35*, 1723–1725; d) M. Dieckmann, D. Menche, *Org. Lett.* **2013**, *15*, 228–231; P. Nuhant, C. Allais, W. P. Roush, *Angew. Chem. Int. Ed.* ***2013**, 52, 8703*–8707.

[84] T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011–1014.

[85] T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.



Scheme 30. Mukaiyama ´s first catalytic asymmetric aldol reaction.

---

[86] Selected reviews on Mukaiyama aldol reaction: a) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52,* 9086–9096. b) S. B. J. Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108; c) J.-I. Matsuo, M. Murakami, *Angew. Chem. Int. Ed*. **2013**, *52,* 9109–9118; *d*) T. Kitanosono, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 3095–3118; e) S. Kobayashi, Y. Yamashita, W.-J. Yoo, T. Kitanosono, J.-F. Soulé, *Comprehensive Organic Synthesis Vol. 2,* **2014**, Elsevier B.V., Amsterdam.

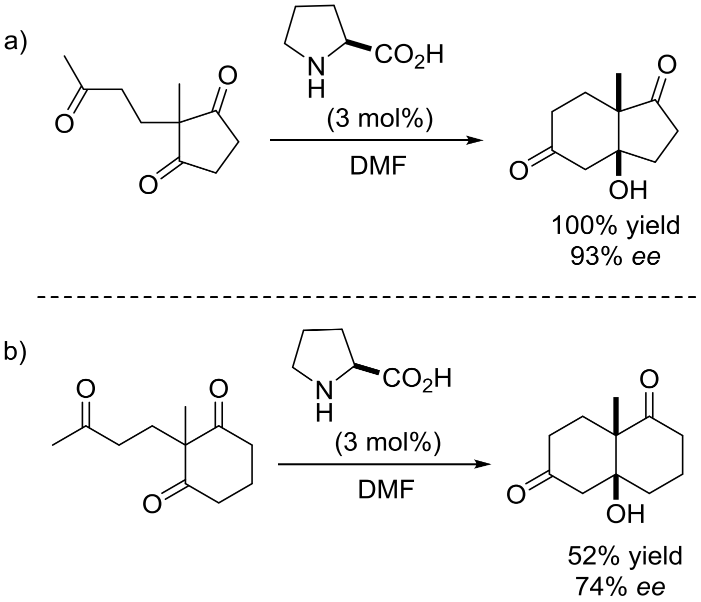
[87] T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331.

[88] a) T. Mukaiyama, S. Kobayashi, H. Uchiro, I. Shina, *Chem. Lett.* **1990**, 129–132; b) S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem. Lett.* **1990**, 1455–1458.

This successful methodology have inspired many subsequent contributions on the addition of diverse preformed directing enolates such as, *O*-, *N*- or *S*- derived silyl ketene acetals to aldehydes or related electrophiles under either Lewis acid or Lewis base catalysis.[89]

2.2. Catalytic asymmetric direct aldol reaction

The first catalytic direct asymmetric aldol reaction was reported by Hajos–Parrish[90] and Eder–Sauer–Wiechert in 1971.[91] This intramolecular aldol cyclization proceeded with very low catalyst loading and the aldol adducts were obtained in very good to excellent yields and enantioselectivities (Scheme 31).



Scheme 31. a) Hajos–Parrish intramolecular aldol reaction. b) Eder–Sauer–Wiechert intramolecular aldol reaction.

---

[89] Selected review on Mukaiyama-type reactions catalytic in silicon: a) J. M. García, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2011**, *50*, 8790–8792.

[90] Z. G. Hajos, D. R. Parrish, *German Pat.*, DE 2102623, 1971.

[91] U. Eder, G. R. Sauer, R. Wiechert, *German Pat.*, DE 2014757, 1971.

Despite the impressive results, particularly for the synthesis of steroids, the present transformation was not further investigated; probably, due to the fact that proline was not appreciated as a broadly applicable catalyst for many years. In contrast, it took decades for the catalytic asymmetric aldol reaction employing non-modified carbonyl-units to emerge. Starting in the 2000, the development of catalytic methods to avoid the production of stochiometric by-products, while maintaining the high level of control available from stoichiometric processes, supposed a breakthrough in terms of atom economy.[92] Certainly numerous asymmetric direct aldol reactions have been described under either biocatalysis[93] or small molecule catalysis (metallic catalysis and organocatalysis).[94] In this context, an outline of the direct asymmetric aldol reaction focusing on small molecule catalysis is described below. Due to the profusion of literature on the topic, only pioneering works are commented and special emphasis is made for methodologies in which 1,2-diol fragments are accessed due to their utility towards the synthesis of polyoxygenated frameworks. Examples involving 1,2-dicarbonyl compounds are omitted as they have been commented in Chapter 1.

---

[92] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

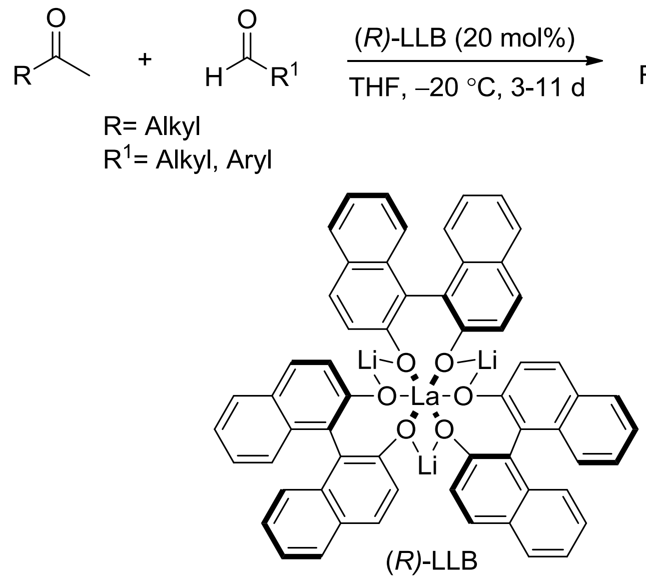
[93] Selected examples: a) W.-D. Fessner, *Asymmetric Organic Synthesis with Enzymes* **2008**, 275–318; b) W.-D. Fessner, *Enzyme Catalysis in Organic Synthesis* 3rd Edition **2011**, *2*, 857–917; c) E. Busto, *ChemCatChem* **2016**, *8*, 2589–2598; d) N. G. Schmidt, E. Eger, W. Kroutil, *ACS Catal.* **2016**, *6*, 4286–4311.

[94] Selected reviews on organocatalyzed asymmetric aldol reaction: a) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; b) S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.* **2009**, *78*, 737–784; c) U. Scheffler, R. Mahrwald, *Synlett* **2011**, 1660–1667; d) M. M. Heravi, S. Asadi, *Tetrahedron: Asymmetry* **2012**, *23*, 1431–1465; e) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541–24580. Selected review on metallocatalyzed asymmetric aldol reaction: f) T. Tsubogo, Y. Yamashita, S. Kobayashi, *Top. Organomet. Chem.* **2013**, *45*, 243–270. Selected review on both organocatalyzed and metallocatalyzed asymmetric aldol reaction: g) B. M. Trost, C. S. Brindle, *Chem. Soc Rev.* **2010**, *39*, 1600–1632.

2.2.1. Metallocatalyzed aldol reaction

A variety of metal-catalyzed processes have been reported that can be compared mechanistically to the type II aldolases, which employ a zinc ion to increase acidity at the α-carbon of the pronucleophile to form an enolate. Many of these catalysts, that function by dual activation of the donor and acceptor, are classified as bifunctional catalysts.[95]

The first enantioselective direct cross-aldol reaction was described by Shibasaki and co-workers for simple ketones using the lanthanum-lithium-BINOL complex shown in Scheme 32.[96] In this reaction $LaLi_3$ tris(binaphthoxide) (LLB) imitates the function of enzymes by displaying both Lewis acidity and Brønsted basicity.



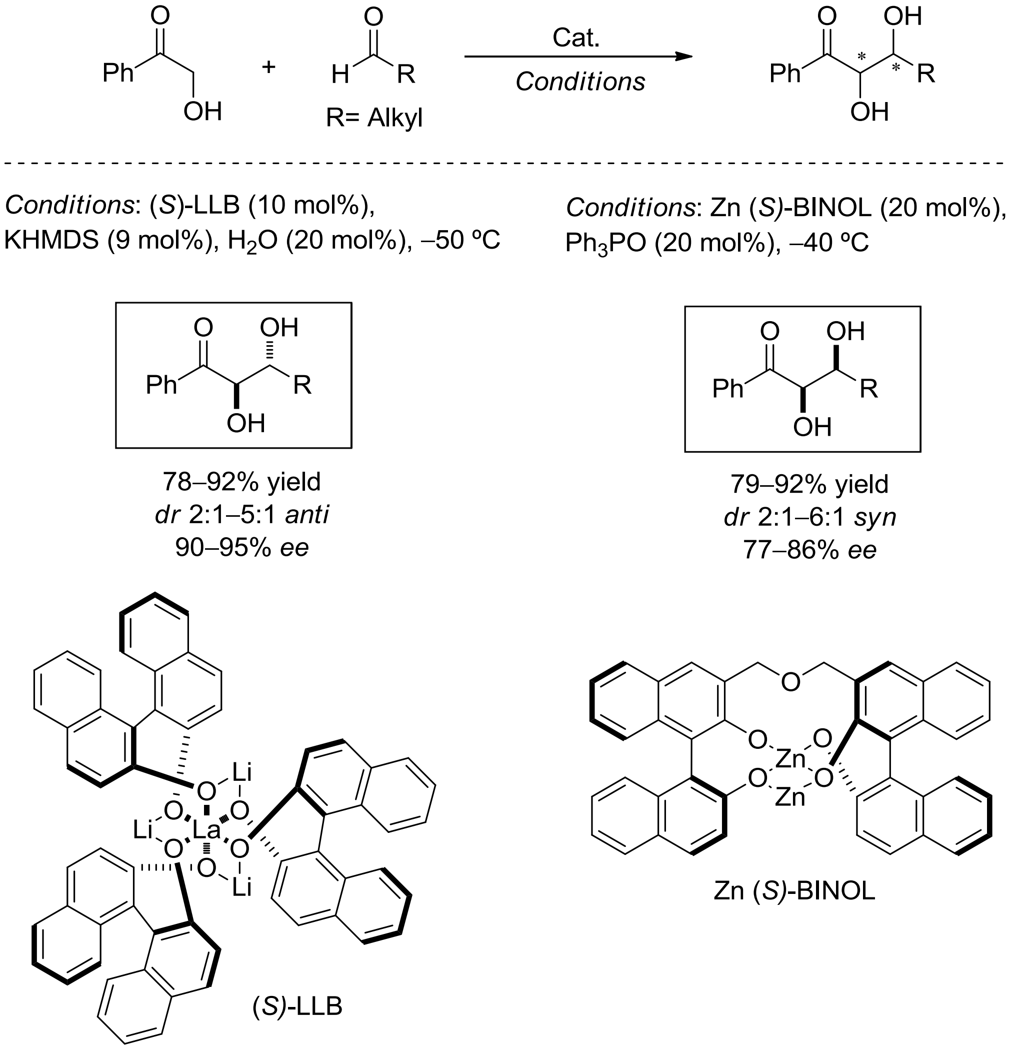
Scheme 32. First enantioselective metallocatalyzed direct cross-aldol reaction.

---

[95] Reviews: a) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3–15; b) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279.

[96] Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873.

Short after, the first examples regarding the entry to 1,2-diols were reported in parallel by the groups of Shibasaki and Trost. On the one hand, Shibasaki using 2-hydroxy-1-phenylethanone as pronucleophile enabled the access to both *anti*- and *syn*-diols by promoting the reaction with either (*S*)-LLB in the presence of KHMDS or the dinuclear Zn (*S*)-BINOL complex in the presence of triphenylphosphine oxide as represented in Scheme 33.[97,98] Both sets of conditions were applicable to α-unbranched aldehydes, a substrate class that usually gives poor results under amine catalysis.


Ph
OH
+
H
R
R= Alkyl
Cat.
Conditions
Ph
OH
OH
R
Conditions: (S)-LLB (10 mol%), KHMDS (9 mol%), H2O (20 mol%), –50 °C
Conditions: Zn (S)-BINOL (20 mol%), Ph3PO (20 mol%), –40 °C
78–92% yield
dr 2:1–5:1 anti
90–95% ee
79–92% yield
dr 2:1–6:1 syn
77–86% ee
Li
La
(S)-LLB
Zn
Zn (S)-BINOL

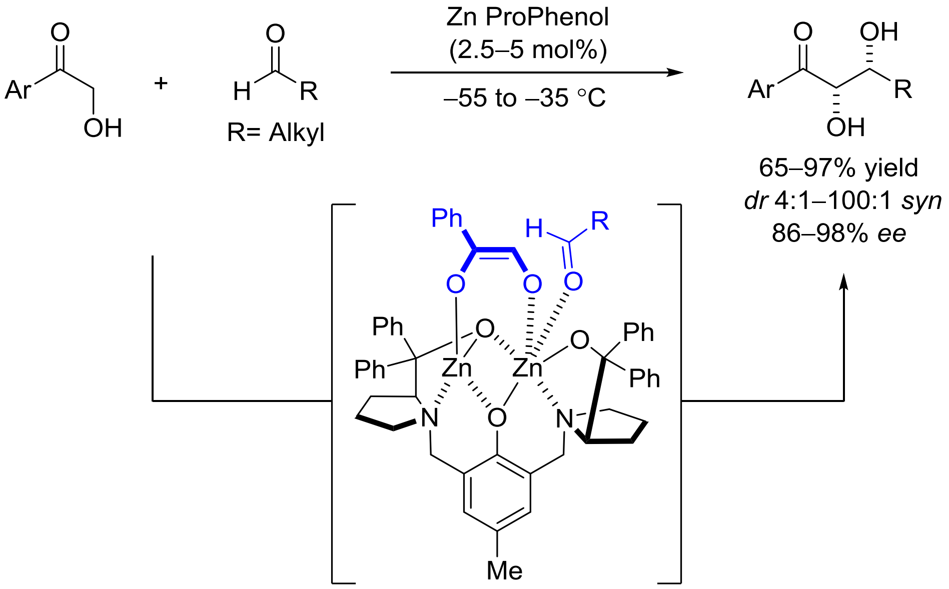
Scheme 33. BINOL-based catalysts for the aldol reaction of 2-hydroxy-1-phenylethanone.

---

[97] N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Oshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467.

[98] N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556–2565.

On the other hand, Trost´s methodology enabled the synthesis of 1,2-diols using the dinuclear Zn ProPhenol-catalyst (Scheme 34).[99] The low catalyst loading, small excess of the donor and commercial availability of the ProPhenol ligand make this reaction an interesting choice for the synthesis of highly enantioenriched *syn*-diols. Chelation of the α-hydroxyketone, by acting as a bidentate ligand, might account for both increased reactivity and selectivity.



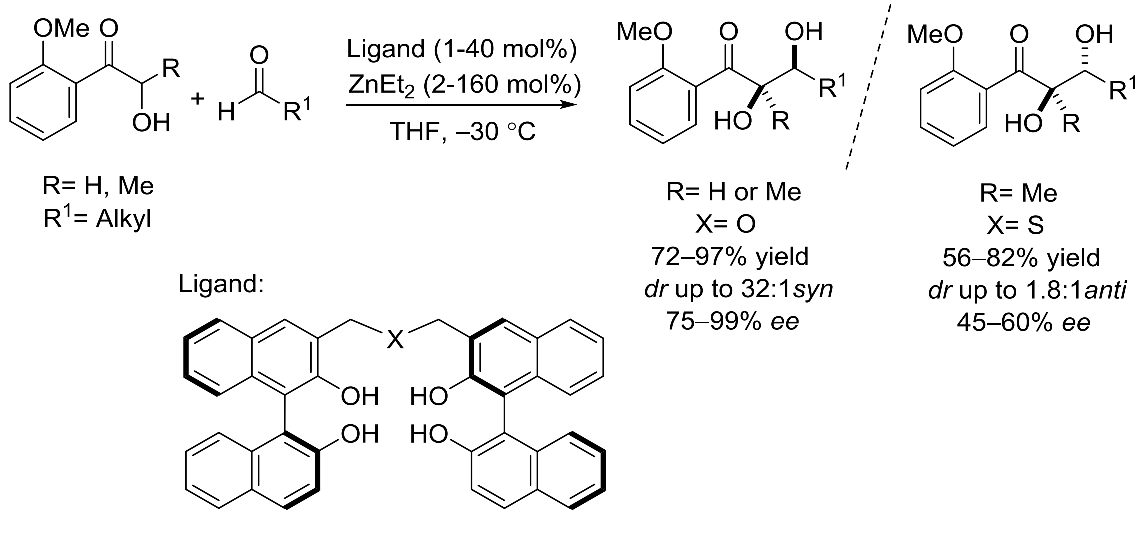
Scheme 34. Dinuclear zinc ProPhenol-catalyzed aldol reaction for the synthesis of *syn*-diols.

In subsequent works, Shibasaki reported the use of previous BINOL-linked ligands towards the synthesis of *syn-* and *anti*-1,2-diols employing substituted α-hydroxyacetophenones.[100] Among all the examples described, it is worth to mention the reaction with α-substituted α-hydroxyketones (R= Me) to produce tetrasubstituted stereogenic centers and the effect of the linker atom (X) in the diastereoselectivity of the process (Scheme 35). [101]

---

[99] a) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368. Application of this methodology in the stereocontrolled synthesis of (+)-boronolide: See ref. 25 and Scheme 3, page 19.

[100] a) N. Kumagai, S. Matsunaga, N. Yoshikawa, M. Shibasaki, *Org. Lett.* **2001**, *3*, 1539–1542; b) Yoshikawa, M. Shibasaki, *Tetrahedron* **2001**, *57*, 2569–2579; c) N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556–2565; d) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178.


OMe O
R
OH
+
O
H
R1
Ligand (1-40 mol%)
ZnEt2 (2-160 mol%)
THF, –30 °C
MeO O OH
R1
HO R
MeO O OH
R1
HO R
R= H, Me
R1= Alkyl
R= H or Me
X= O
72–97% yield
dr up to 32:1syn
75–99% ee
R= Me
X= S
56–82% yield
dr up to 1.8:1anti
45–60% ee
Ligand:
X
OH
OH
HO
HO

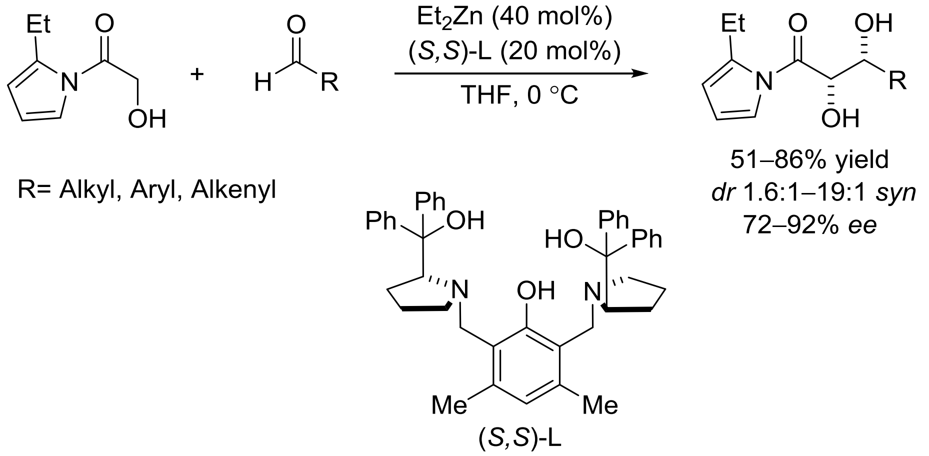
Scheme 35. Linked-BINOL zinc-catalysts for the synthesis of 1,2-diols.

Several years later, Trost and co-workers reported an enantioselective α-hydroxyacetate aldol reaction that employs *N*-acetyl pyrroles as activated ester equivalents.[102] The dinuclear Zn ProPhenol-catalyzed transformation proceeded with high enantioselectivity for a wide range of aldehydes, being the resulting α,β-dihydroxy esters versatile intermediates for the synthesis of carboxylic acid derivatives including amides, esters and unsymmetrical ketones (Scheme 36).

---

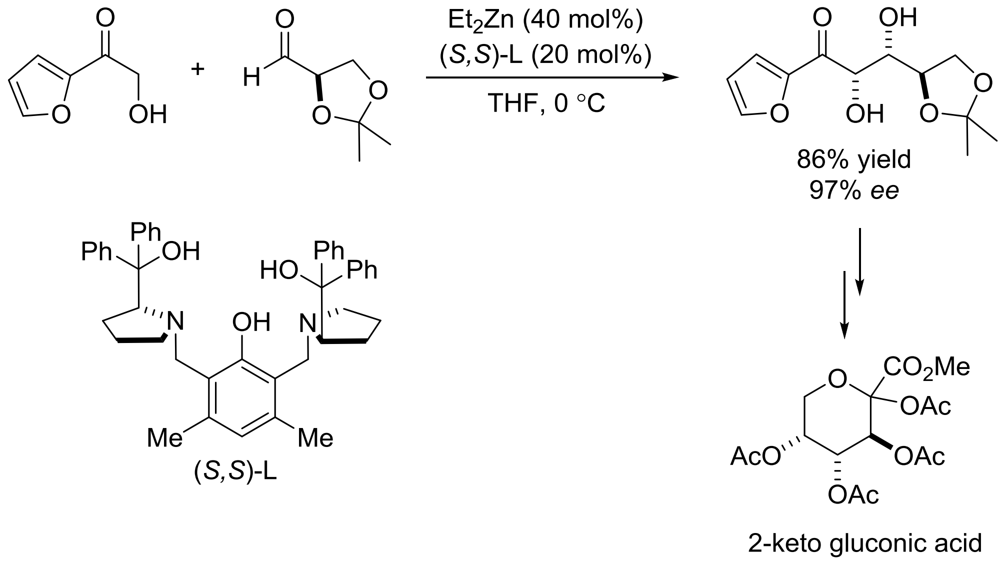
[101] N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178.

[102] B. M. Trost, D. J. Michaelis, M. I. Truica, *Org. Lett.* **2013**, *15*, 4516-4519.


Et
O
N
OH
+
O
H
R
Et$_2$Zn (40 mol%)
(S,S)-L (20 mol%)
THF, 0 °C
Et
O
OH
N
R
OH
51–86% yield
dr 1.6:1–19:1 syn
72–92% ee
R= Alkyl, Aryl, Alkenyl
Ph
Ph
OH
Ph
HO
Ph
N
OH
N
Me
Me
(S,S)-L

Scheme 36. Enantioselective α-hydroxyacetate aldol reaction with activated ester equivalents.

More recently, Mlynarski and collaborators reported a specific diastereoselective example using Trost´s derived dinuclear catalyst towards the synthesis of D- and L-a*rabino*-hex-2-ulosonic acids (Scheme 37).[103]


O
O
OH
+
O
H
O
O
Et$_2$Zn (40 mol%)
(S,S)-L (20 mol%)
THF, 0 °C
O
OH
O
OH
O
O
86% yield
97% ee
Ph
Ph
OH
Ph
HO
Ph
N
OH
N
Me
Me
(S,S)-L
O
CO$_2$Me
OAc
AcO
OAc
OAc
2-keto gluconic acid

Scheme 37. Synthesis of 2-keto-D- and L-gluconic acids.

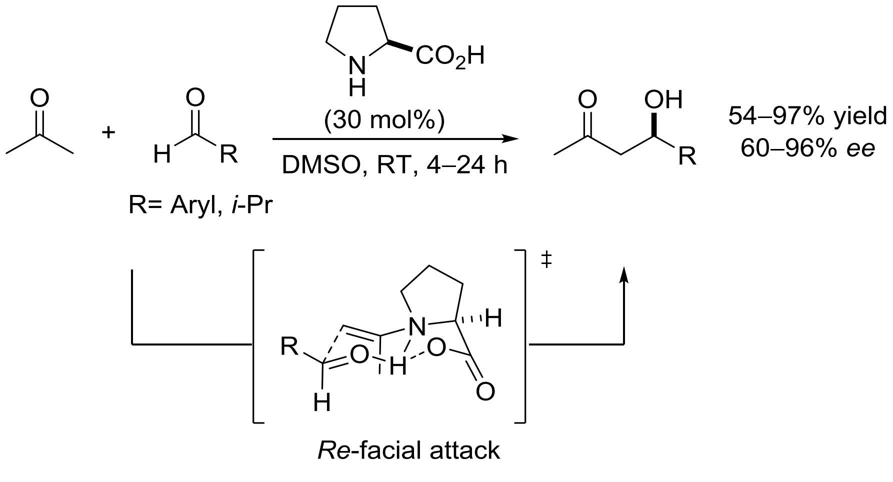
---

[103] S. Bàs, J. Mlynarski, *J. Org. Chem.* **2016**, *81*, 6112–6117.

2.2.2. Organocatalyzed aldol reaction

2.2.2.1. *Covalent organocatalysis*

Inspired by the action of type I aldolases, List, Lerner and Barbas III developed the first amine-catalyzed intermolecular asymmetric direct aldol reaction between ketone and aldehydes (Scheme 38).[104] Aryl aldehydes were good substrates though branched aliphatic aldehydes gave the highest yields and enantioselectivities. A great effort has been made to clarify the mechanism of the proline-catalyzed aldol reaction.[105] The accepted mechanism begins with rate-limiting enamine formation followed by carbonyl addition, which is activated by the carboxylic acid of proline, and hydrolysis of the iminium ion. The tricyclic hydrogen bonded framework ensures the enantiofacial selectivity.



Scheme 38. L-Proline catalyzed direct aldol reaction and proposed transition state.

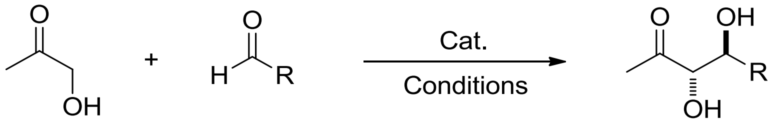
---

[104] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.

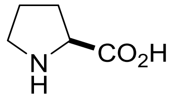
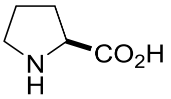
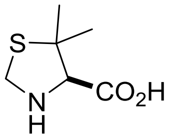
[105] For representative works, see: a) B. List, *Acc. Chem. Res.* **2004**, 37, 548–557; b) C. Alleman, R. Gordillo, F. R. Clemente, P.H. Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569; c) M. Klussmann, A. J. R. White, A. Amstrong, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2006**, *45*, 7985–7989; d) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, *Helv. Chim. Acta*, **2007**, *90*, 425–471.

Also in 2000 the group of List reported a pioneer regio- and stereoselective entry to a*nti* 1,2-diols by using α-hydroxyacetone as pronuclephile in the direct aldol reaction promoted by L-proline (Table 3).[106] Independently, in 2001, Barbas III and co-workers compared the activity of L-proline with that of a 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) (Table 3).[107] The additional *S*-heteroatom together with the dimethyl substitution present in the catalyst enhanced the *ee* values for aromatic aldehydes although yields were in general lower than under L-proline catalysis.

Table 3. L-Proline and 5,5-dimethyl thiazolidinium-4-carboxilate (DMTC) catalyzed *anti*-aldol reaction of α-hydroxyacetone.



***anti*-1,2-diol**

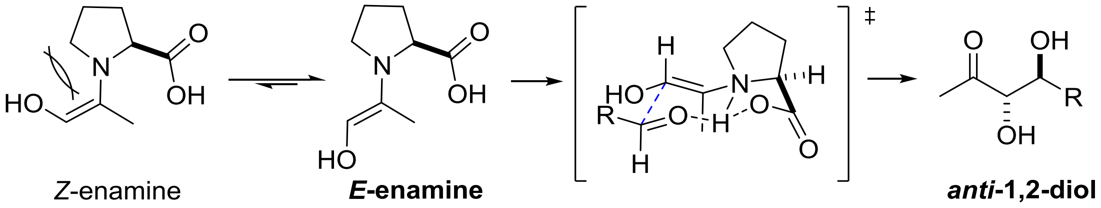
R	Catalyst/Conditions	Results	Ref.
Ph, *o*-Cl-Ph, α-branched alkyl	 20–30 mol% DMSO, RT, 24–72 h	51–95% yield *dr* 1.5:1–20:1 *anti* 67–99% *ee*	**List[106]** **2000**
Ph, *o*-Cl-Ph, Naphtyl, *i*-Pr, Cy, *t*-Bu	 20 mol% DMSO, RT, 24–48 h	38–95% yield *dr* 1:1–20:1 *anti* 67–99% *ee*	**Barbas III[107]** **2001**
Ph, *o*-Cl-Ph, Naphtyl, Cy	 20 mol% DMSO, 37 ^{o}C, 24–48 h	45–60% yield *dr* 1:1–20:1 *anti* 91–95% *ee*	

---

[106] W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

[107] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

The enantiofacial selectivity for the aldehyde in these reactions is identical to that obtained using acetone as the aldol donor. Accordingly, the *Si*-face of the hydroxyacetone *E*-enamine attacks the *Re*-face of the aldehyde to give the *anti*-product through a six member chair-like transition state (Scheme 39).



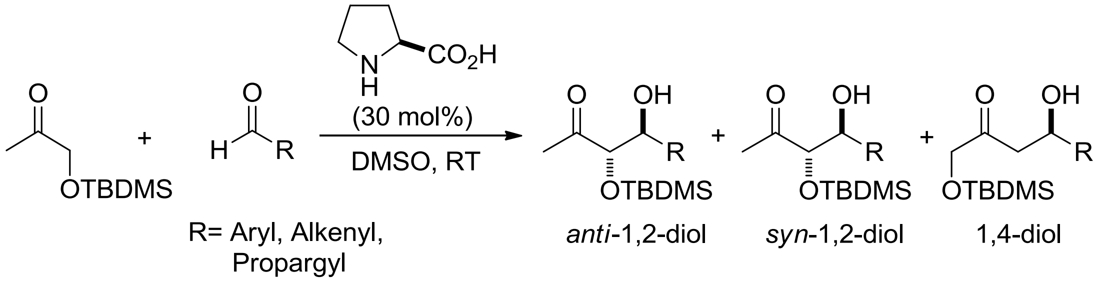
Scheme 39. Plausible mechanism for the production of *anti*-1,2-diols.

In 2003, Li and co-workers extended the proline-catalyzed asymmetric direct aldol reaction to TBDMS protected hydroxyacetone.[108] This donor provided a ready access to optically active monoprotected 1,2-diol units, although regioselectivity (1,2-diol *vs.* 1,4-diol) and diastereoselectivity were highly dependent on aldehyde structure (Scheme 40).[109]

---

[108] H. Liu, L. Peng, T. Zhang, Y. Li, *New J. Chem.* **2003**, *27*, 1159–1160.

[109] For asymmetric aldol reactions affording 1,4-diols, see: a) Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Org. Lett.* **2004**, *6*, 2285–2287; b) S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5321–5323; c) X.-H. Chen, S.-W. Luo, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Chem. Eur.* **2007**, *13*, 689–701; d) L.-Y. B. Wang, Y. Zhu, W.-X. Chang, J. Li, *Tetrahedron: Asymmetry* **2013**, *24*, 533–542.



up to 80% yield (*anti*-1,2-diol)
up to 90:7:3 (*anti*:*syn*:1,4)
43–95% *ee* (*anti*-1,2-diol)

Scheme 40. L-Proline catalyzed asymmetric aldol reaction of TBDMS protected hydroxyacetone.

Despite the utility of proline, a great effort has been exerted for the development of new catalysts. The long reaction times, high catalyst loading and the poor results with certain substrates led to the development of more reactive catalysts as well as the design of catalysts that will not undergo oxazolidinone formation, which is one of the major catalyst deactivation pathways. Several families of proline derivatives have been synthesized for their use in aldol additions: hydroxyprolines, proline esters, prolinamines and –amides, proline tetrazols, prolinols and proline sulfonamides.[110] On the other hand, non-proline secondary and primary chiral amines have been prepared and enabled improvements in substrate scope and stereoselectivity in the direct aldol reaction.[111] Representative examples for the estereoselective preparation of 1,2-diols regarding these new catalysts are shown in the following paragraphs.

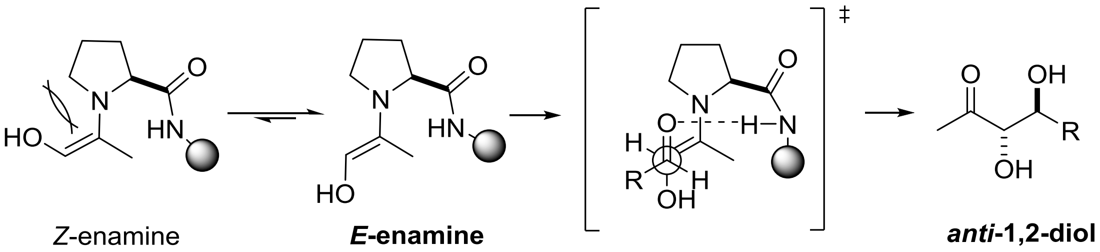
---

[110] Selected reviews on the use of proline-derived catalysts in asymmetric aldol reaction: a) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948; b) S. K. Pandai, *Tetrahedron: Asymmetry* **2013**, *22*, 1817–1847; c) J. Liu, L. Wang, *Synthesis* **2017**, *49*, 960–972.

[111] Selected examples on the use of non-proline derived secondary amines in asymmetric aldol reaction: a) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 3055–3057; b) T. Kano, O. Tokuda, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 7423–7426; c) T. Kano, Y. Yamaguchi, Y. Takana, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 1738–1740.

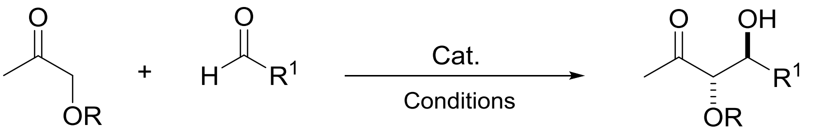
As depicted in Table 4, BINAM-L-prolinamide derivatives promoted the aldol reaction with either free or protected α-hydroxyacetones to mainly produce *anti*-1,2-diols (Nájera, Benaglia and Latanzzi groups).[112–115] In general, lower catalyst loadings were required, compared to L-proline and the *anti* adducts were produced with variable diastereo- and enantioselectivities. As a limitation, the reaction scope is restricted to aromatic aldehydes bearing electron-withdrawing groups. Also, L-prolinethioamides were reported to efficiently promote the aldol reaction, with free or protected α-hydroxyacetones, improving the diastereo- and enantioselectivity of the process (Nájera, Alonso and Li groups).[116,117]

The stereochemical outcome of the reaction could be explained by the N-H group playing the same role as the carboxylic acid in the L-proline catalyzed aldol reactions (Scheme 41).

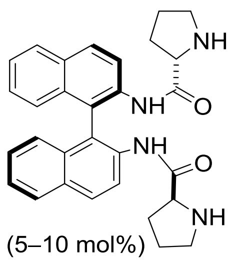


Scheme 41. Plausible mechanism for the production of *anti*-1,2-diols.

Table 4. *Anti*-selective aldol reaction of free and/or protected α-hydroxyacetones promoted by secondary amine catalysts.



***anti*-1,2-diol**

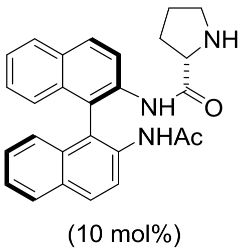


Nájera[113] 2006

R= Me/R^1= EWG-Aryl
77–99% yield
dr 5:1–7:1 *anti*
73–97% *ee*

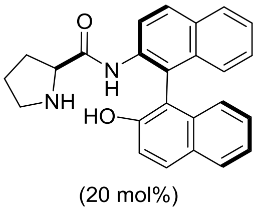
Nájera[114a] 2007

R= H,Bn,Me/R^1= *p*-NO_2Ph
76–92% yield
dr 3:1–6:1 *anti*
16–60% *ee*



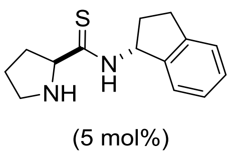
Benaglia[112] 2006

R=Me/R^1=*p*-NO_2Ph
88% yield
dr >49:1 *anti*
91% *ee*



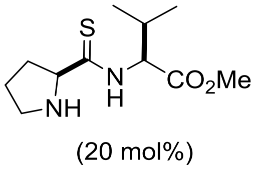
Latanzzi[115] 2007

R=Me/R^1= *p*-NO_2Ph
62% yield
dr 5.2:1 *anti*
84% *ee*



Nájera, Alonso[116] 2008

R= Bn/R^1= *p*-NO_2Ph
90% yield
dr 8:1 *anti*
91% *ee*



Li[117] 2013

R= H/R^1= EWG-Aryl
76–86% yield
dr 7:1–8:1 *anti*
83–97% *ee*

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[112] S. Guizzetti, M. Benaglia, L. Pignataro, A. Puglisi, *Tetrahedron: Asymmetry* **2006**, 1*7*, 2754–2760.

[113] G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, 1*7*, 1027–1031.

[114] a) G. Guillena, M. C. Hita, C. Nájera, S. F. Viózquez, *Tetrahedron: Asymmetry* **2007**, 1*8*, 2300–2308; b) F. J. N. Moles, A. Bañón-Caballero, G. Guillena, C. Nájera, *Tetrahedron: Asymmetry* **2014**, 25, 1323–1330.

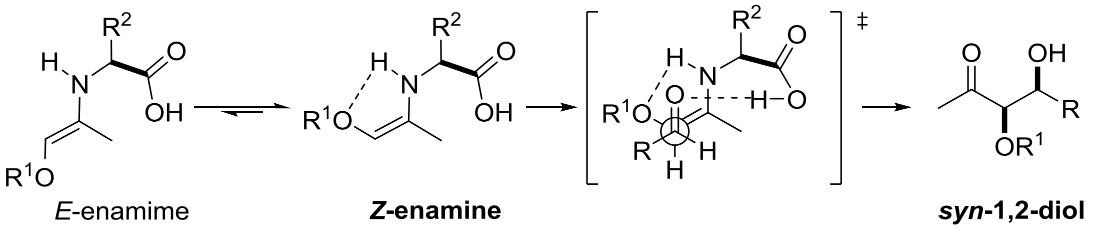
[115] A. Russo, G. Botta, A. Latanzzi, *Tetrahedron* **2007**, 63, 11886–11892.

[116] D. Almaşi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.* **2008**, *350*, 2467–2472.

[117] L.-Y. B. Wang, Y. Zhu, W.-X. Chang, J. Li, *Tetrahedron: Asymmetry* **2013**, 24, 533–542.

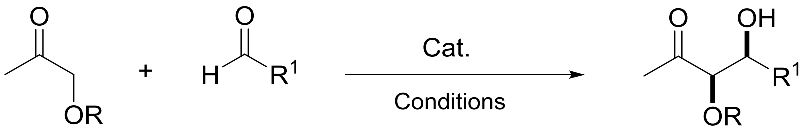
First effective *syn*-selective aldol reactions of α-hydroxyacetones were reported by the groups of Barbas III and Lu in 2007 using primary amines derived from L-threonine.[118–120] As shown in Table 5, the highest diastereoselectivity was achieved with free α-hydroxyacetone, even though the scope was restricted to aromatic aldehydes bearing electron-withdrawing groups. In subsequent works, the groups of Cheng[121,123] and Singh[124] performed *syn*-selective aldol reactions employing chiral primary-tertiary diamine catalysts which helped to improve diastereoselectivity. Interestingly, in 2009, Wu, Zhao and co-workers[122] employed a peptide based primary amine catalyst to promote direct aldol reactions of hydroxyacetone and unactivated aliphatic aldehydes with good to excellent yields and enantioselectivities. In contrast, aromatic aldehydes were obtained with moderate enatioselectivity. Other groups (Chimni,[125] Córdova-Ibrahem,[126] Fu,[127] and Mlynarski[128]) synthesized several catalysts to perform the *syn* selective reaction with aromatic aldehydes. Nonetheless, the stereochemical results did not substantially improve.

For aldol reactions of α-hydroxyketones, promoted by chiral primary amines, *Z*-enamine should predominate over *E*-enamine due to the stabilization conferred by intramolecular hydrogen bonding (Scheme 42). These primary amine catalysts mimic the action of Type I aldolases, in which the lysine is the catalytic residue, to afford *syn*-adducts.



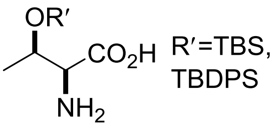
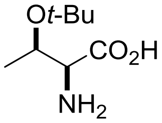
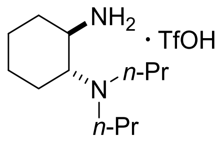
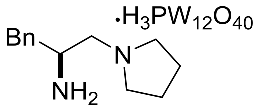
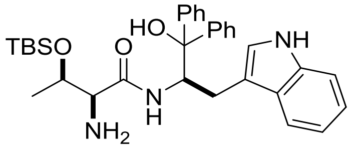
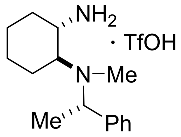
Scheme 42. Plausible mechanism for the production of *syn*-1,2-diols.

Table 5. *Syn*-selective aldol reaction of the free and/or protected α-hydroxyacetones promoted by primary amine catalysts.



O
OR
+
O
H
R^1
Cat.
Conditions
O
OH
R^1
OR

***syn*-1,2-diol**

 OR′ CO_2H NH_2 R′=TBS, TBDPS (2-10 mol%) **Lu**[120] **2007** R= TBS/R^1= EWG-Aryl 76–95% yield *dr* 3:1–8:1 *syn* 91–98% *ee*	 O*t*-Bu CO_2H NH_2 (20 mol%) **Barbas III**[118,119] **2007** R= H/R^1= EWG-Aryl 69–95% yield *dr* 7:1–18:1 *syn* 92–98% *ee* R= TBS, Bn, Me/R^1=*p*-NO_2Ph 79–82% yield *dr* 3:1–5:1 *syn* 92–95% *ee*	 NH_2 · TfOH N *n*-Pr *n*-Pr (10 mol%) **Cheng**[121] **2008** R= H/R^1= Aryl 50–99% yield *dr* 7:1–99:1 *syn* 88–96% *ee*
 $\cdot H_3PW_{12}O_{40}$ Bn N NH_2 (10 mol%) **Cheng**[123] **2009** R= H/R^1= EWG-Aryl, α-branched alkyl 55–97% yield *dr* 3:1–10:1 *syn* 80–95% *ee*	 Ph HO Ph TBSO O NH N H NH_2 (2-8 mol%) **Wu, Zhao**[122] **2009** R= H/R^1= EWG-Aryl 68–99% yield *dr* 4:1–9:1 *syn* 76–83% *ee* R =H/R^1= Alkyl 87–98% yield *dr* 10:1–30:1 *syn* 96–98% *ee*	 NH_2 · TfOH N–Me Me Ph (10 mol%) **Singh**[124] **2009** R= H/R^1= EWG-Aryl 79–89% yield *dr* 19:1–49:1 *syn* 91–99% *ee*

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[118] S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288–289.

[119] N. Utsumi, M. Imai, F. Tanaka, S. S. V. Ramasastry, C. F. Barbas III, *Org. Lett.* **2007**, *9*, 3445–3448.

[120] X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812–816.

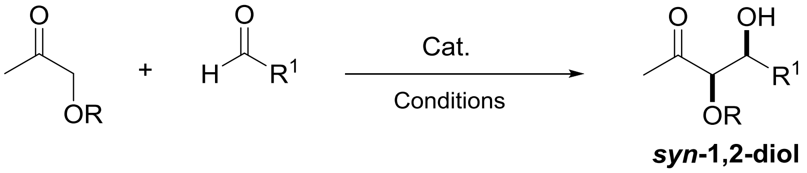
[121] S. Luo, H. Xu, L. Zhang, J. Li, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 653–656.

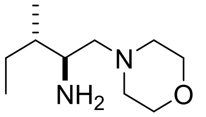
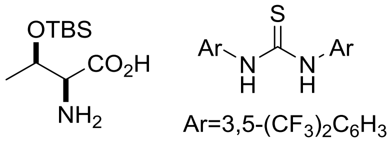
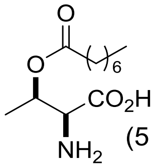
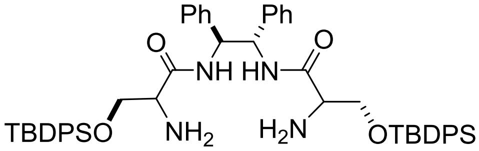
[122] X. Wu, Z. Ma, Z. Ye, S. Qian, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 158–162.

[123] J. Li, S. Luo, J.-P. Cheng, *J. Org. Chem.* **2009**, *74*, 1747–1750.

[124] M. Raj, G. S. Parashari, V. K. Singh, *Adv. Synth. Catal.* **2009**, *351*, 1284–1288.

(Continued)



 (10 mol%) **Chimni[125] 2011** R= TBS/R^1= Aryl 65–94% yield *dr* 2.1:1–13:1 *syn* 83–97% *ee*	 (10 mol%) **Córdova, Ibrahem[126] 2011** R= H/R^1= EWG-Aryl, Cy 56–96% yield *dr* 7:1–32:1 *syn* 91–98% *ee*
 (5 mol%) **Fu[127] 2011** R= H/R^1= Aryl 56–96% yield *dr* 4:1–49:1 *syn* 90–99% *ee*	 (5-10 mol%) **Mlynarski[128] 2012** R= H/R^1= EWG-Aryl, α-branched alkyl 35–95% yield *dr* 3:1–13:1 *syn* 82–99% *ee*

In the same context, dihydroxyacetone (DHA) is also an useful building block for the synthesis of polyhydroxylated scaffolds either in Nature[129] or in the laboratory. On one hand, the pronucleohile incorporates an extra hydroxyl group and, on the other hand, the regioselectivity problem (1,2-diols *vs.* 1,4 diols) is avoided due to the symmetry of the molecule.

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[125] A. Kumar, S. Singh, V. Kumar, S. S. Chimni, *Org. Biomol. Chem.* **2011**, 9, 2731–2742.

[126] G. Ma, A. Bartoszewicz, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2011**, *353*, 3114–3122.

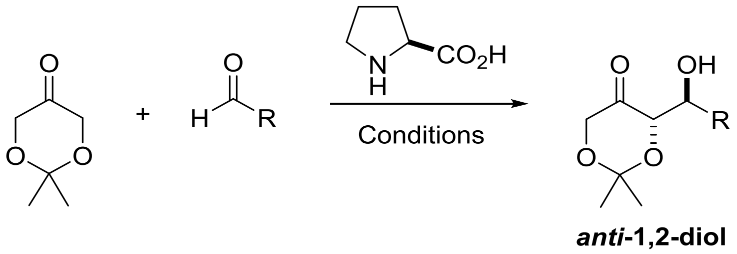
[127] C. Wu, X. Fu, S. Li, *Tetrahedron: Asymmetry* **2011**, 22, 1063–1073.

[128] J. Paradowska, M. Pasternak, B. Gut, B. Gryzlo, J. Mlynarski, *J. Org. Chem.* **2012**, *77*, 173–187.

[129] See Scheme 5, page 22 and Table 1, page 23.

In 2005, the groups of Enders[130] and Barbas III[131] described simultaneously the cross aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one and a variety of aldehydes promoted by L-proline. In spite of the long reaction times required, the corresponding *anti*-1,2-diols were achieved in good yields and excellent stereoselectivities. Cyclic protected DHAs are appropriate substrates for the *anti*-selective aldol reaction promoted by L-proline due to the intrinsic restriction towards the formation of the *E*-enamine.

Table 6. L-Proline catalyzed *anti*-aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one.



R	L-Proline/Conditions	Results	Ref.
i-Pr, Cy, CH_2OBn, chiral α-branched alkyl	30 mol% DMF, 2 °C 6 d	31–97% yield *dr* 16:1–49:1 *anti* 90–98% *ee*	**Enders**[130a] **2005**
i-Bu, Cy, CH_2OAc, chiral α-branched alkyl, *p*-NO_2Ph	20 mol% DMF, 4 °C 72 h	40–89% yield *dr* 6:1–99:1 *anti* 93–98% *ee*	**Barbas III**[131] **2005**

In the following years numerous chiral primary amines, along with a secondary amine, were examined in this transformation. Examples represented in Table 7 highlight the efficacy of this substrate-dependent reaction system since stereochemical results as well as yields were excellent. Nevertheless, the scope of the reaction is highly limited and only particular examples have been explored. Cheng´s study, although being the most extensive, was only applied to aromatic aldehydes containing electron-withdrawing groups.[121]

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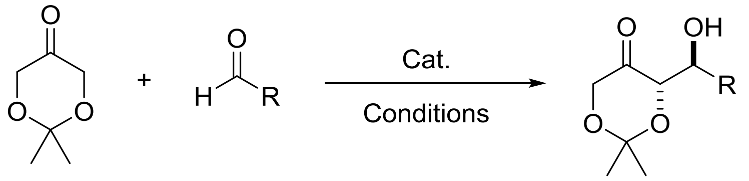
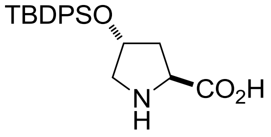
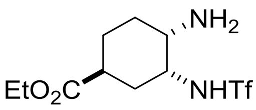
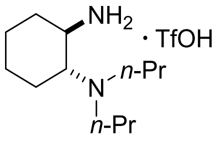
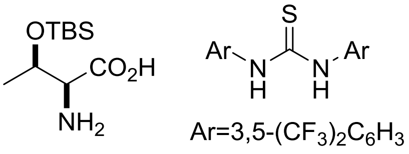
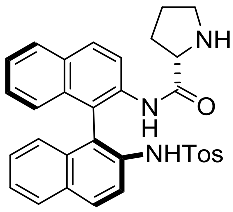
[130] a) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212; for the application of the methodology in the stereoselective synthesis of orthogonal protected aldopentoses and derivatives, see: b) C. Grondal, D. Enders, *Adv. Synth. Catal.* **2007**, *349*, 694–702.

[131] J. T. Dhevalapally, B. Ramachary, Barbas III, *Org. Lett.* **2005**, *7*, 1383–1385.

Table 7. *Anti*-selective aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one under amine catalysts.



***anti*-1,2-diol**

L-Val-L-Phe (30 mol%) **Córdova[132] 2005** R= *p*-NO_2Ph 83% yield *dr* 15:1 *anti* 99% *ee*	 (10 mol%) **Hayashi[133] 2007** R= Ph 77% yield *dr* 14:1 *anti* 95% *ee*	 (5 mol%) **Maruoka[134] 2008** R= *p*-NO_2Ph 99% yield *dr* 9:1 *anti* 98% *ee*
 (10 mol%) **Cheng[121] 2008** R= EWG-Aryl, CH_2OBn 76–86% *dr* 4:1–10:1 *anti* 80–97% *ee*	 Ar=3,5-$(CF_3)_2C_6H_3$ (10 mol%) **Córdova, Ibrahem[126] 2011** R= *p*-NO_2Ph 88% yield *dr* 24:1 *anti* 99% *ee*	 (10 mol%) **Nájera, Guillena[114b] 2014** R= $CH(OMe)_2$ 68% yield *dr* 49:1 *anti* 92% *ee*

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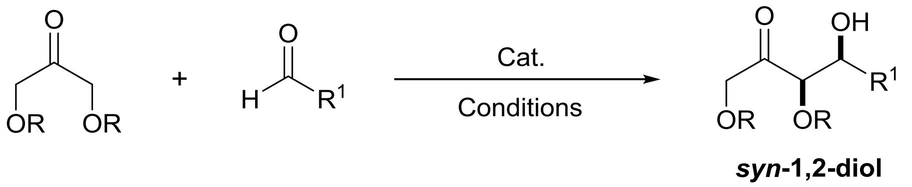
[132] P. Dziedzic, W. Zou, J. Háfren, A. Córdova, *Org. Biomol. Chem.* **2006**, 4, 38–40.

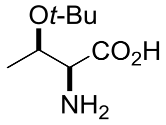
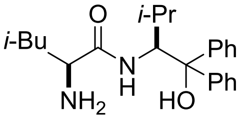
[133] S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246–10256.

[134] K. Nakayama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 17666–17667.

In contrast, acyclic α-dihydroxyacetone was explored more widely as donor in the *syn*-selective aldol addition promoted by chiral primary amine catalysts (Table 8). The high *syn*-selectivity obtained in most of the procedures described is comparable with the aforementioned for primary amine catalyzed aldol reaction of α-hydroxyacetones and can be explained through the same mechanism.[135]

Table 8. *Syn*-selective aldol reaction of free and protected acyclic α-dihydroxyacetones promoted by primary amine catalysts.



L-Val-L-Phe (30 mol%)	 (20 mol%)		 (20 mol%)
Córdova[132] 2006	**Barbas III[136,119] 2007**		**Gong[137] 2008**
R= H/R^1= *p*-NO_2Ph 51% yield *dr* 1:1 70% *ee syn*	R= H/R^1=EWG-Aryl, CH_2CH_2Ph 28–92% yield *dr* 7:1–33:1 *syn* 92–99% *ee*	R= Bn, TBS/R^1= EWG-Aryl, -CO-R' 29–94% yield *dr* 1:1–7:1 *syn* 24–97% *ee*	R= H/R^1= EWG-Aryl 65–90% yield *dr* 14:1–20:1 *syn* 92–99% *ee*

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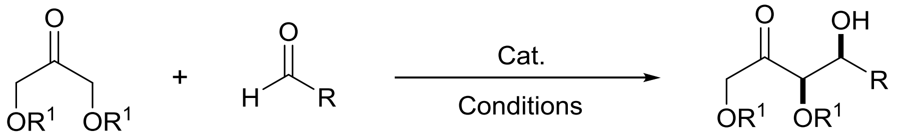
[135] See Scheme 42, page 70.

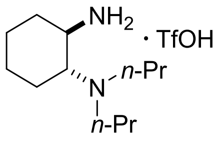
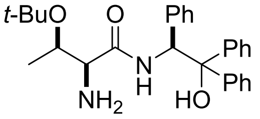
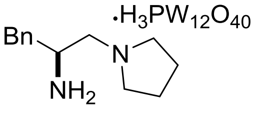
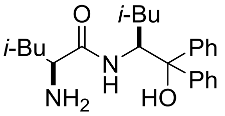
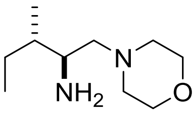
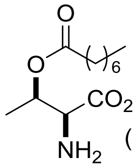
[136] S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 5572–5575.

[137] M.-K. Zhu, X.-Y. Xu, L.-Z. Gong, *Adv. Synth. Catal.* **2008**, *350*, 1390–1396.

(Continued)



***syn*-1,2-diol**

 (10 mol%) **Cheng[121] 2008**	 (15 mol%) **Barbas III[138] 2008**		 (10 mol%) **Cheng[123] 2009**
R= H/R^1= Aryl 43–97% yield *dr* 49:1–99:1 *syn* 84–99% *ee*	R= H/R^1= EWG-Aryl, Alkyl 62–78% yield *dr* 2:1–8:1 *syn* 92–>99% *ee*	R=TBS/R^1= Alkyl, -CO-R' 55–99% yield *dr* 3:1–11:1 *syn* 94–98% *ee*	R= H/R^1= EWG-Aryl 59–97% yield *dr* 8:1–30:1 *syn* 84–99% *ee*
 + 2,4-dinitrophenol (20 mol%) **Da[139] 2009**	 (10 mol%) **Chimni[125] 2011**		 (5 mol%) **Fu[127] 2011**
R= H R^1= EWG-Aryl 48–77% yield *dr* 3:1–12:1 *syn* 91–99% *ee*	R= Bn, TBS/R^1= *p*-NO$_2$Ph 87–93% yield *dr* 4.3:1–5.2:1 *syn* 86–95% *ee*		R= H/R^1= *p*-NO$_2$Ph 96% yield *dr* 32:1 *syn* 99% *ee*

Clearly, α-hydroxyacetone and dihydroxyacetone (DHA) are the most popular donors in the asymmetric direct cross-aldol reaction as they are key building-blocks for the synthesis of polyhydroxylated fragments. Nevertheless, other pronucleophiles have been investigated towards more elaborated structures, although in less extent. The use of aldehydes as donors in enamime-base cross-aldol reactions requires the employment of non- or hardly enolizable carbonylic compounds as acceptors. The groups of Jørgensen[140] and MacMillan[141] described simultaneously L-proline catalyzed additions of aldehydes to either highly activated carbonyl acceptors or aromatic aldehydes and α-branched aldehydes, respectively (Scheme 43). Two years later, MacMillan and co-workers documented the first homo-aldol reaction of protected α-hydroxyaldehydes as a preliminary protocol for the synthesis of carbohydrates (Scheme 44a)[142] which was later applied in the cross-aldol reaction with α-thioacetal aldehydes (Scheme 44b). [143]

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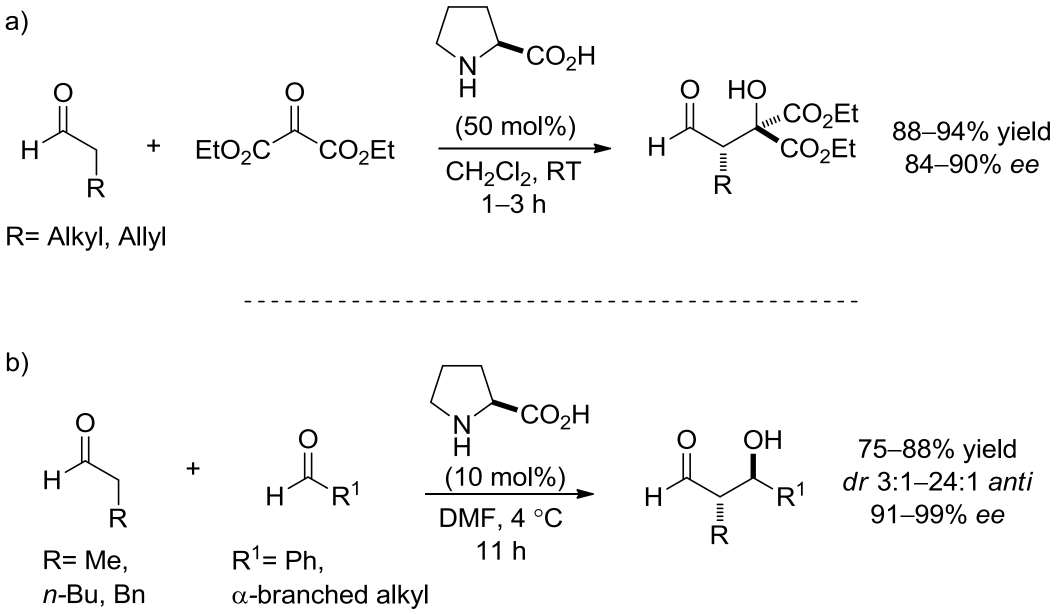
[138] S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, C. F. Barbas III, *Org. Lett.* **2008**, *10*, 1621–1624.

[139] C.-S. Da, L.-P. Che, Q.-P. Guo, F.-C. Wu, X. Ma, Y.-N. Jia, *J. Org. Chem.* **2009**, *74*, 2541–2546.


a)
H
O
R
+
EtO2C
O
CO2Et
N
H
CO2H
(50 mol%)
CH2Cl2, RT
1–3 h
O
HO
CO2Et
CO2Et
H
R
88–94% yield
84–90% ee
R= Alkyl, Allyl
b)
H
O
R
+
H
O
R1
N
H
CO2H
(10 mol%)
DMF, 4 °C
11 h
O
OH
H
R1
R
75–88% yield
dr 3:1–24:1 anti
91–99% ee
R= Me,
n-Bu, Bn
R1= Ph,
α-branched alkyl

Scheme 43. L-Proline catalyzed cross-aldol reaction of aldehydes.

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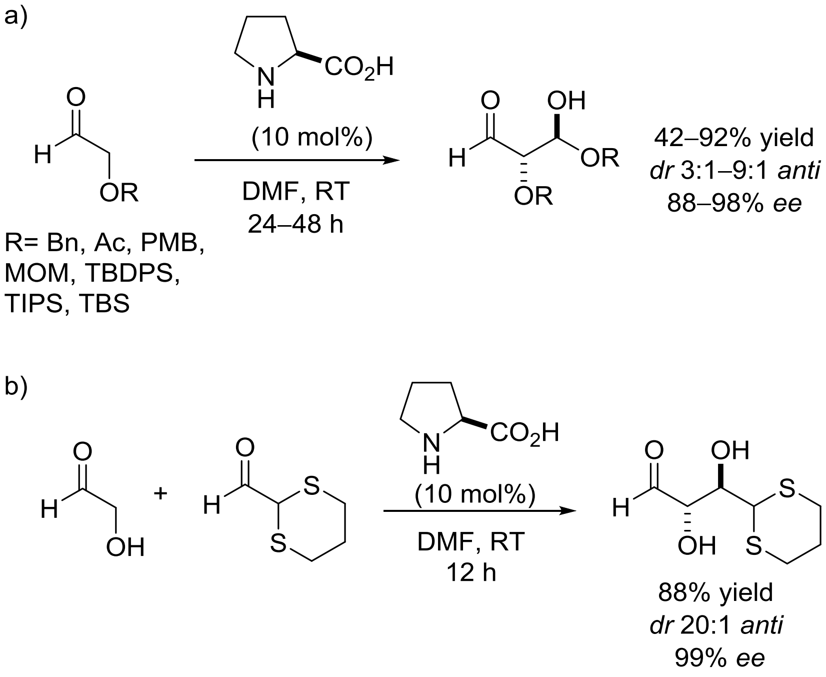
[140] A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620–621.

[141] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

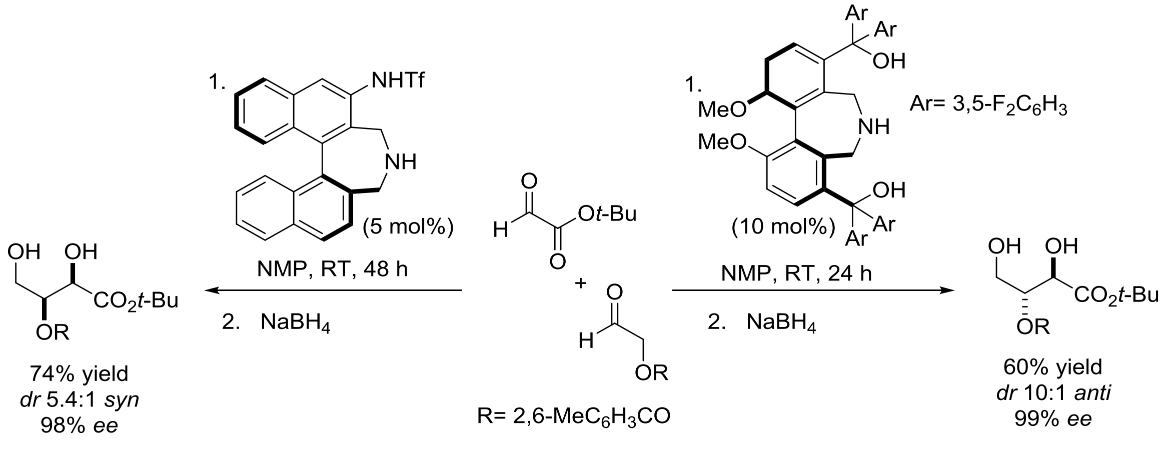
[142] A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154.

[143] R. I. Storer, D. W. C. MacMillan, *Tetrahedron* **2004**, 60, 7705–7714.


a)
(10 mol%)
DMF, RT
24–48 h
R= Bn, Ac, PMB,
MOM, TBDPS,
TIPS, TBS
42–92% yield
dr 3:1–9:1 anti
88–98% ee
b)
(10 mol%)
DMF, RT
12 h
88% yield
dr 20:1 anti
99% ee

Scheme 44. L-Proline catalyzed homo- and cross-aldol reaction of α-hydroxy aldehydes.

More recently, Maruoka and co-workers have reported secondary amine-catalyzed asymmetric cross-aldol reactions of heterofunctionalized acetaldehydes with highly activated *tert*-butyl-2-oxo-acetate.[144] Particular examples for α-hydroxy protected aldehydes were included to produce either *syn*- or *anti*- 1,2-diols by using the appropriate secondary amine catalyst (Scheme 45).

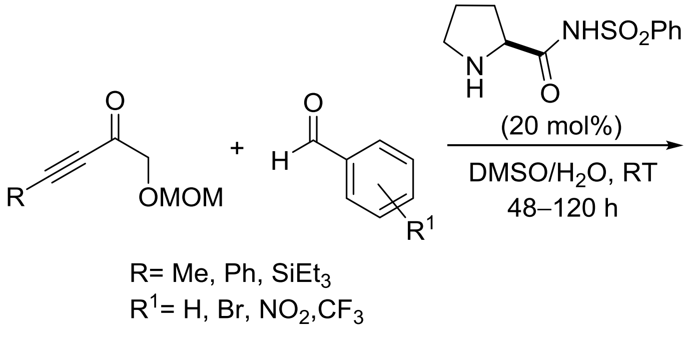

1.
(5 mol%)
NMP, RT, 48 h
2. NaBH4
74% yield
dr 5.4:1 syn
98% ee
R= 2,6-MeC6H3CO
1.
(10 mol%)
Ar= 3,5-F2C6H3
NMP, RT, 24 h
2. NaBH4
60% yield
dr 10:1 anti
99% ee

Scheme 45. *Syn*-and *anti*-selective cross-aldol reaction of α-hydroxy aldehydes.

---

[144] T. Kano, R. Sakamoto, K. Maruoka, *Org. Lett.* **2014**, *16*, 944–947.

On the other hand, Gouverneur and coworkers employed protected α-hydroxy ynones to access more structurally versatile 1,2-diols.[145] The reaction promoted by a proline-based acyl sulfonamide proceeded with electron-deficient aromatic aldehydes to afford *anti*-adducts in moderate to high yields and excellent diastereo- and enantioselectivities (Scheme 46). The aldol adducts were either reduced to afford enantioenriched unsaturated *anti,anti*-triols or cyclized.



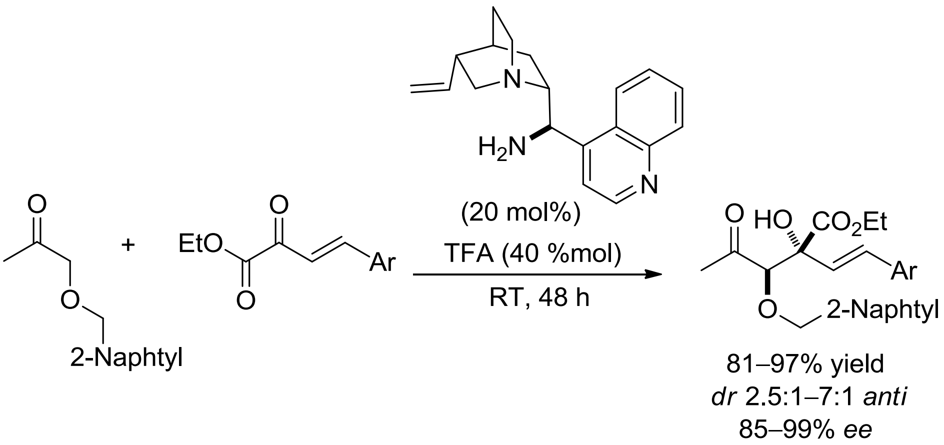
Scheme 46. Enantioselective organocatalytic aldol reaction of protected α-hydroxy ynones.

To the best of our knowledge, there is only one example regarding direct cross-aldol reaction between two ketones. The group of Lu described the cross-aldol addition of protected α-oxyacetones and β,γ-unsaturated α-keto esters promoted by a cinchonine-derived primary amine catalyst enabling the access to *anti*-1,2-diols bearing a tetrasubstituted quaternary center (Scheme 47).[146]

---

[145] F. Silva, M. Sawicki, V. Gouverneur, *Org. Lett.* **2006**, *8*, 5417–5419.

[146] C. Liu, X. Dou, Y. Lu, *Org. Lett.* **2011**, *13*, 5248–5251.



Scheme 47. Enantioselective organocatalytic aldol reaction of protected α-hydroxyacetone and β,γ-unsaturated α-keto esters.

2.2.2.2. *Non-covalent organocatalysis*

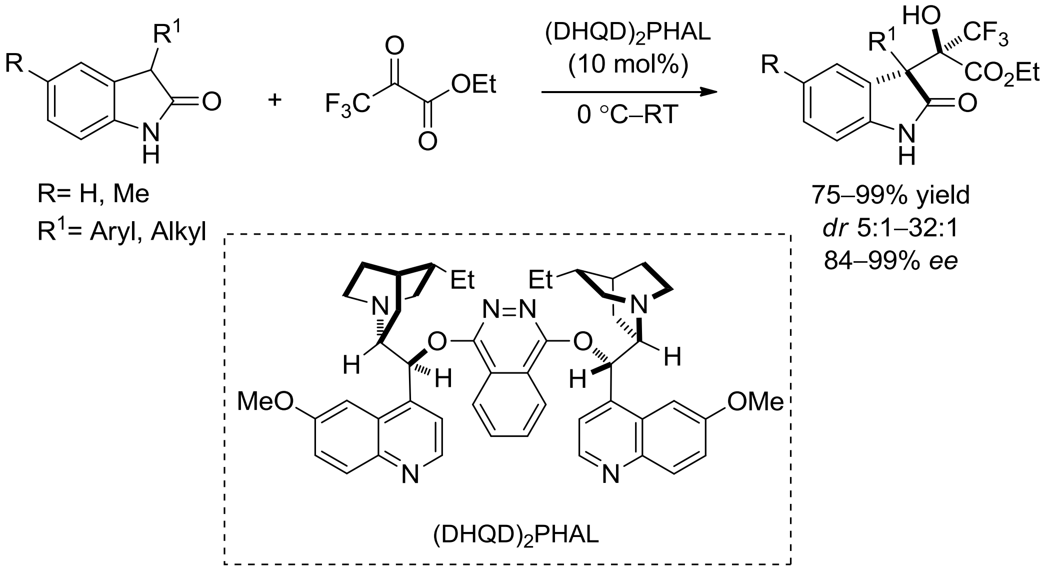
As seen in the previous section, the primary/secondary amine catalyzed cross-aldol reaction of unactivated carbonyls *via* the enamime pathway has been profusely studied. In contrast, the analogous organocatalytic asymmetric aldol reaction *via* enolate intermediates is rather difficult to address due to the low acidity of the carbonyl compounds. The enol pathway is also not easy since the acidity of Brønsted acids is not as high as that of Lewis acids.

In 2010, Blanchet and co-workers described for the first time a *syn*-selective aldol reaction between ketones and by H_8-BINOL-derived phosphoric acids.[147] Nevertheless, as far as we know, this Brønsted acid based methodology has not been explored with α-hydroxy carbonyls or analogous donors.

---

[147] a) G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden, J. Blanchet, *Org. Lett.* **2010**, *12*, 3582–3585. For reviews on chiral Brønsted acids, see: b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; c) M. Terada, *Synthesis* **2010**, 1929–1982.

In 2007, the group of Shibata and Toru described the first asymmetric Brønsted base catalyzed aldol reaction.[148] As shown in Scheme 48, pseudoenantiomeric *Cinchona* alkaloids were employed to access both enantiomeric products for the particular reaction between highly activated oxindoles and ethyl trifluoropyruvate in high yields and excellent diastereo- and enantioselectivities (up to 97:3 *dr* and 99% *ee*).


R
R¹
O
N
H
+
F₃C
O
OEt
(DHQD)₂PHAL
(10 mol%)
0 °C–RT
HO
CF₃
CO₂Et
R= H, Me
R¹= Aryl, Alkyl
75–99% yield
dr 5:1–32:1
84–99% ee
Et
N=N
MeO
OMe
H
(DHQD)₂PHAL

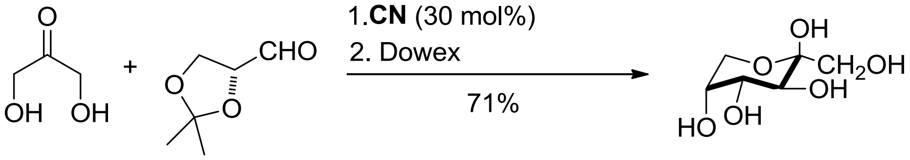
Scheme 48. Direct aldol type reaction of oxindoles and ethyl trifluoropyruvate.

Simultaneously, Mahrwald and co-workers reported a DBU-catalyzed *syn*-selective addition of α-hydroxyacetone to aldehydes that included the first example of an asymmetric Brønsted base catalyzed aldol reaction of α-hydroxy ketones; the cinchonine-catalyzed aldol reaction of DHA with isopropylidene-(*R*)-glyderaldehyde (Scheme 49).[149]

---

[148] S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2007**, *46*, 8666–8669.

[149] M. Market, M. Mulzer, B. Schetter, R. Mahrwald, *J. Am. Chem. Soc.* **2007**, *129*, 7258–7259.



Scheme 49. Cinchonine-catalyzed aldol reaction of DHA and isopropylidene-(*R*)-glyderaldehyde (**CN**: cinchonine).

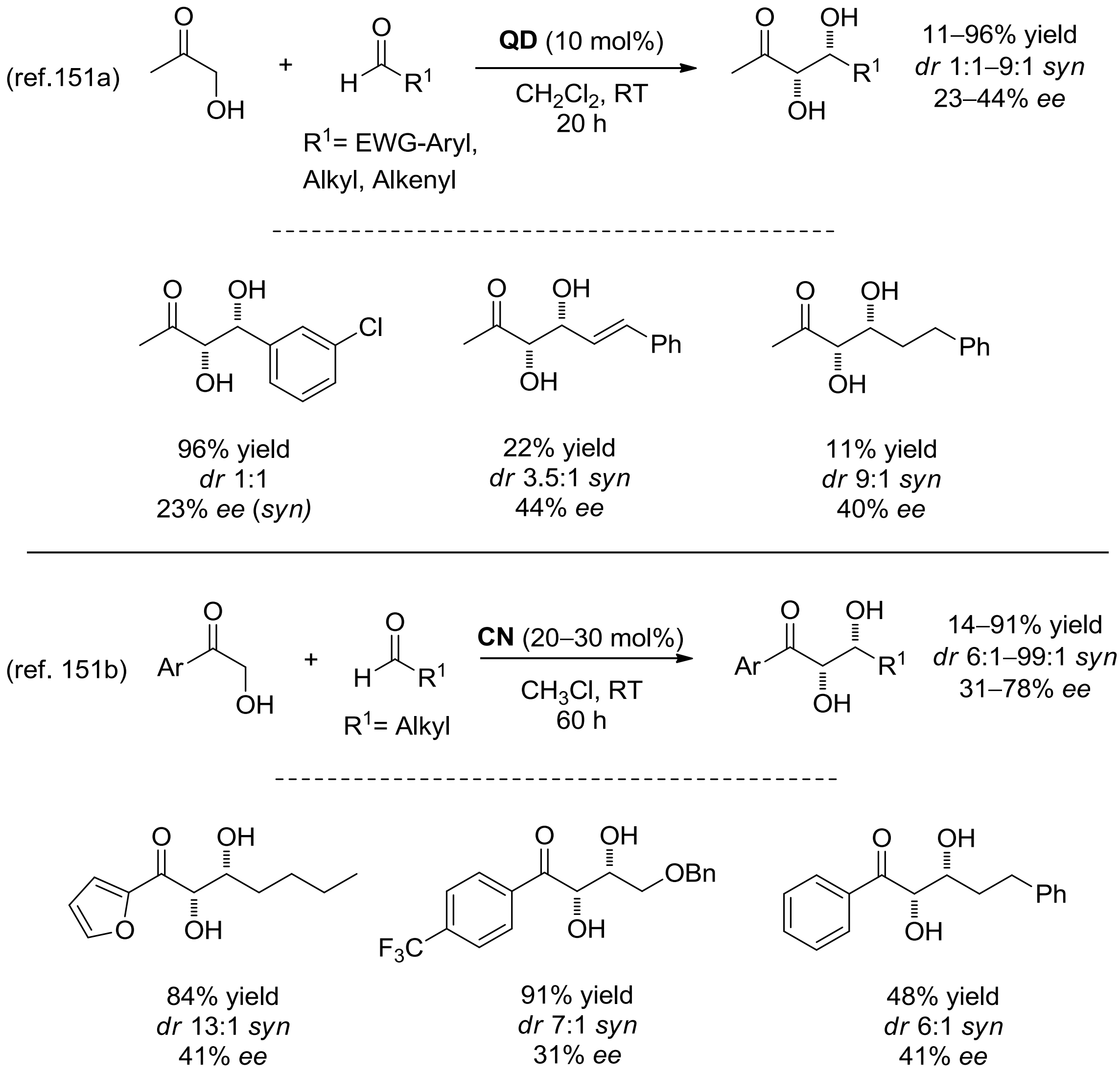
A catalytic asymmetric version of the Mahrwald´s aldol reaction has been more recently studied by Mlynarski and co-workers. They have addressed, in several works, the direct asymmetric aldol reaction of DHA[150] and α-hydroxyketones[151] promoted by *Cinchona* alkaloids and applied the methodology to the synthesis of 2-keto-D- and L-gluconic acids.[152] These studies, carried out between 2009 and 2016, reflect an improvement of the reaction scope and diastereoselectivity. Nevertheless, low yields and poor enantioselectivities were usually achieved, being moreover highly dependent on substrate structure (Scheme 50).

---

[150] O. Popik, M. Pasternak-Suder, K. Leśniak, M. Jawiczuk, M. Górecki, J. Frelek, J. Mlynarski, *J. Org. Chem.* **2014**, *79*, 5728–5739.

[151] a) J. Paradowska, M. Rogozińska, J. Mlynarski, *Tetrahedron Lett.* **2009**, 50, 1639–1641; b) S. Bás, L. Woźniak, J. Cygan, J. Mlynarski, *Eur. J. Org. Chem.* **2013**, 6917–6923. For homo-aldol reaction of α-hydroxy aldehydes, see: c) B. Gut, J. Mlynarski, *Eur. J. Org. Chem.* **2015**, 5075–5078.

[152] S. Bás, J. Mlynarski, *J. Org. Chem.* **2016**, *81*, 6112–6117.


(ref.151a)
QD (10 mol%)
CH2Cl2, RT
20 h
R1= EWG-Aryl, Alkyl, Alkenyl
11–96% yield
dr 1:1–9:1 syn
23–44% ee
96% yield
dr 1:1
23% ee (syn)
22% yield
dr 3.5:1 syn
44% ee
11% yield
dr 9:1 syn
40% ee
(ref. 151b)
CN (20–30 mol%)
CH3Cl, RT
60 h
R1= Alkyl
14–91% yield
dr 6:1–99:1 syn
31–78% ee
84% yield
dr 13:1 syn
41% ee
91% yield
dr 7:1 syn
31% ee
48% yield
dr 6:1 syn
41% ee

Scheme 50. Selected examples for aldol reactions of α-hydroxyketones promoted by *Cinchona* alkaloids (**QD**: quinidine, **CN**: cinchonine).

Interestingly, Misaki, Sugimura and co-workers employed 5*H*-oxazol-4-ones as pronucleophiles in the direct aldol reaction promoted by chiral bicyclic guanidines to access chiral α,β-dihydroxycarboxylates.[153] The transformation proceeded smoothly with high enantioselectivity using bicyclic guanidines bearing a hydroxy group at the appropriate position, and various combinations of 5*H*-oxazol-4-ones and aldehydes (Scheme 51).

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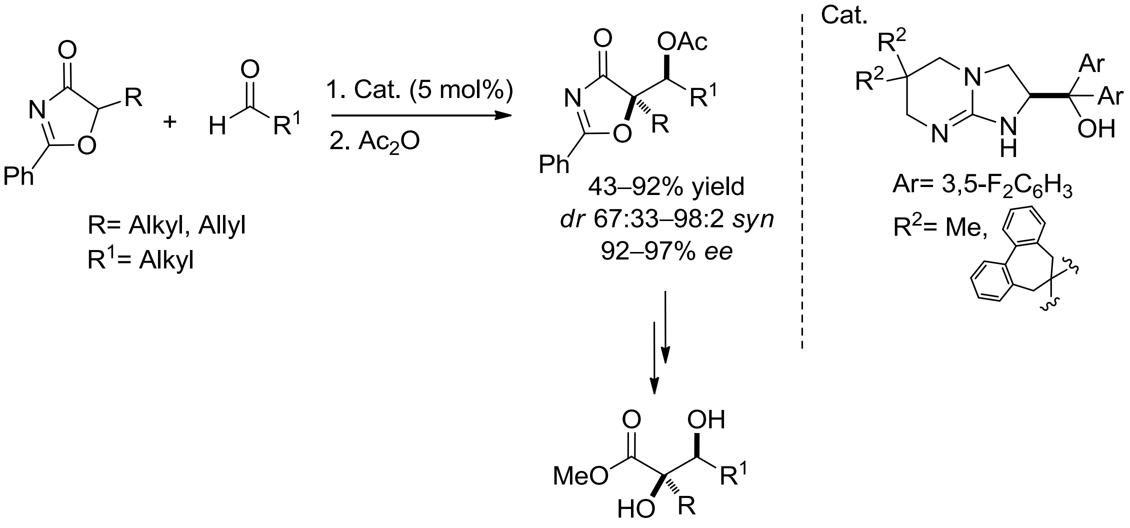
[153] T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.



Scheme 51. Direct asymmetric aldol reaction of 5*H*-oxazol-4-ones with aldehydes.

As shown heretofore, the catalytic asymmetric aldol reaction is a powerful and robust methodology to produce enantiomerically enriched 1,2-diol frameworks. In the particular case of metallocatalyzed cross-aldol reactions, an excellent control over the diastereo- and enantioselectivity has been achieved for the production of both *anti*- and *syn*-diols. In general, methodologies are restricted to the use of α-hydroxyacetophenones as pronucleophiles which are compatible with a wide variety of either aliphatic or aromatic aldehydes.

On the other hand, the stereoselective construction of 1,2-diols *via* covalent organocatalysis has been deeply investigated. A profusion of chiral amines have demonstrated to efficiently promote the cross aldol reaction of α-hydroxyacetones and DHAs with aromatic aldehydes with high regio- (1,2-diols *vs*. 1,4-diols) and diastereoselectivity. Both *anti*- and *syn*- diols are produced by the use of primary or secondary amine catalysts, respectively, and enantioselectivities are usually high. Nevertheless, in spite of the high development that aminocatalysis has experienced during the last years, main limitations arise from the electrophilic counterpart; reaction scope is mainly limited to aromatic and α-branched aldehydes.[154]

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[154] See section 2.2.2.1., pages 64–79.

In contrast, non-covalent organocatalysis is an approach that still remains underexplored. The use of 5*H*-oxazol-4-ones, as pronucleophiles, in the direct aldol reaction promoted by chiral bicyclic guanidines is the only successful methodology to date. Isolated examples concerning the use of *Cinchona* alkaloids as Brønsted base catalysts, in the aldol reaction of α-hydroxyacetones and aliphatic aldehydes, appeared during the development of this work, but chemical and stereochemical efficiencies were very poor.[155]

Clearly, the enamine aldol technology would be nicely complemented in terms of product scope and reaction mechanism if a Brønsted base catalyzed approach would be available.

2.3. Working hypothesis and objectives

As mentioned in the introduction of this chapter, the asymmetric cross-aldol reaction faces two important issues; reactivity and selectivity (regio-, diastereo- and enantioselectivity) that become more complicated to address when using Brønsted bases as catalysts in direct aldol reactions.

First, main difficulties arise from the inherent low acidity of carbonyl compounds which clearly hampers enolate generation. In this strategy a relatively weak amine is generally used to reversively deprotonate a relatively acidic substrate. However, to date, the carbonyl compounds for these reaction are restricted to 1,3-diones, β-keto esters, malonates, α-cyanoacetates, 3-substituted oxindoles and related systems; all of them being easily deprotonated by relatively weak chiral Brønsted bases.[156, 157] On the other hand, for the particular case of using 1,2-dicarbonyl compounds as pronucleophiles, the need of highly reactive acceptors seems to be mandatory to avoid competition with the homo aldol reaction, as shown in section 1.2. Also, a troublesome case is the cross-aldol reaction with enolizable acceptors under Brønsted base catalysis.

---

[155] See Scheme 50, page 83.

[156] pK_a Range for these compounds is 11.1–18.7 according to the acidities measured in DMSO: F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.

[157] For reviews on Brønsted base catalysis, see: a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; b) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200; c) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis,* Ed. K. Maruoka, **2012**, Thieme, Stuttgart; d) *Comprehensive Enantioselective Organocatalysis,* Ed. P. Dalko, **2013**, Wiley-VCH, Weinheim.

Secondly, under Brønsted base catalysis, aldol adducts may undergo undesirable side reactions such as aldol condensation and epimerization, when tertiary stereogenic centers are created.

With regard to stereoselectivity, an appropriate design of the Brønsted-base catalyst is essential to control the enolate configuration and the enolate-acceptor approach in order to induce high diastereo- and enantioselectivities.

The intrinsic non-directional nature of electrostatic interactions in ion pairing complexes, generated with this type of catalysis, makes difficult predicting the sense of stereoinduction. Catalysts that combine a site with Brønsted base character and another site with hydrogen-bond donor ability (ambifunctional catalyst) are best suited to overcome this problem. Namely, the catalyst can anchor both nucleophilic and electrophilic components in the transition state. As a result of this synergic action, more active catalysts are obtained, since both the nucleophilic and the electrophilic components are concurrently activated. In addition, the higher degree of stereochemical order in the transition state usually results in better and more predictable asymmetric induction. Various nitrogen-containing functionalities have been used for the design of chiral Brønsted base catalysts.

Among them, tertiary amines,[158] imidazoles, amidines and guanidines,[159] are the most prominent though other superbases such phosphacenes[160] and cyclopropenimines[161] are arising (Figure 5). In this context, alkaloids, particularly those of the *Cinchona* family, are a straightforward source of enantiopure Brønsted base catalysts. Other principal routes towards chiral Brønsted base catalysts are the corresponding enantiopure α–amino acids or, from non natural sources, synthetic 1,2–diamines and binaphtols. In the last decades a tremendous effort has been made in order to improve reaction efficiency and selectivity employing bifunctional Brønsted bases and, so far, (thio)urea[162] and squaramide[163] functionalities have emerged as the most general and effective units with hydrogen bond donor ability (Figure 5).

---

[158] Selected reviews on the use of *Cinchona* alkaloids in asymmetric transformations: a) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279; b) L. A. Bryant, R. Fanelli, A. J. A. Cobb, *Beilstein E. J. Org. Chem.* **2016**, *12*, 429–443. *Cinchona* alkaloids as "privileged chiral catalyst": c) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693; d) *Privileged Chiral Ligands and Catalysts,* Ed. Q.-L- Zhou, **2011**, Wiley-VCH, Weinheim; e) C. Quigley, Z. Rodríguez-Docampo, S. J. Connon, *Chem. Commun.* **2012**, *48*, 1443.

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[159] Selected reviews on the use of guanidines in asymmetric transformations: a) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752; b) D. Leow, C.-H. Tan, *Synlett* **2010**, 1589–1605; c) X. Fu, C.-H. Tan, *Chem. Commun.* **2011**, *47*, 8210–18222; d) P. Selig, *Synthesis* **2013**, *45*, 703–718.

[160] Selected example on the use of phosphacenes in asymmetric transformations: H. Krawczyk, M. Dzęgielewski, D. Deredas, A. Albrecht, L. Albrecht, *Chem. Eur. J.* **2015**, *218*, 10268–10277.

[161] Selected examples on the use of cyclopropenimines in asymmetric transformations: a) J. S. Bandar, T. H. Lambert, *J. Am. Chem. Soc.* **2012**, *134*, 5552–5555; b) V. H. Lauridsen, L. Ibsen, J. Blom, K. A. Jørgensen, *Chem. Eur. J.* **2016**, *22*, 3259–3263.

[162] Selected reviews on the use of (thio)ureas in asymmetric transformations: a) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; b) X. Fang, C. J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197.

[163] Selected reviews on the use of squaramides in asymmetric transformations: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; b) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, *Adv. Synth. Catal.* **2015**, *357*, 253–281; c) B.-L. Zhao, J.-H. Li, D.-M. Du, *Chem. Rec.* **2017**, *17*, 1–27.

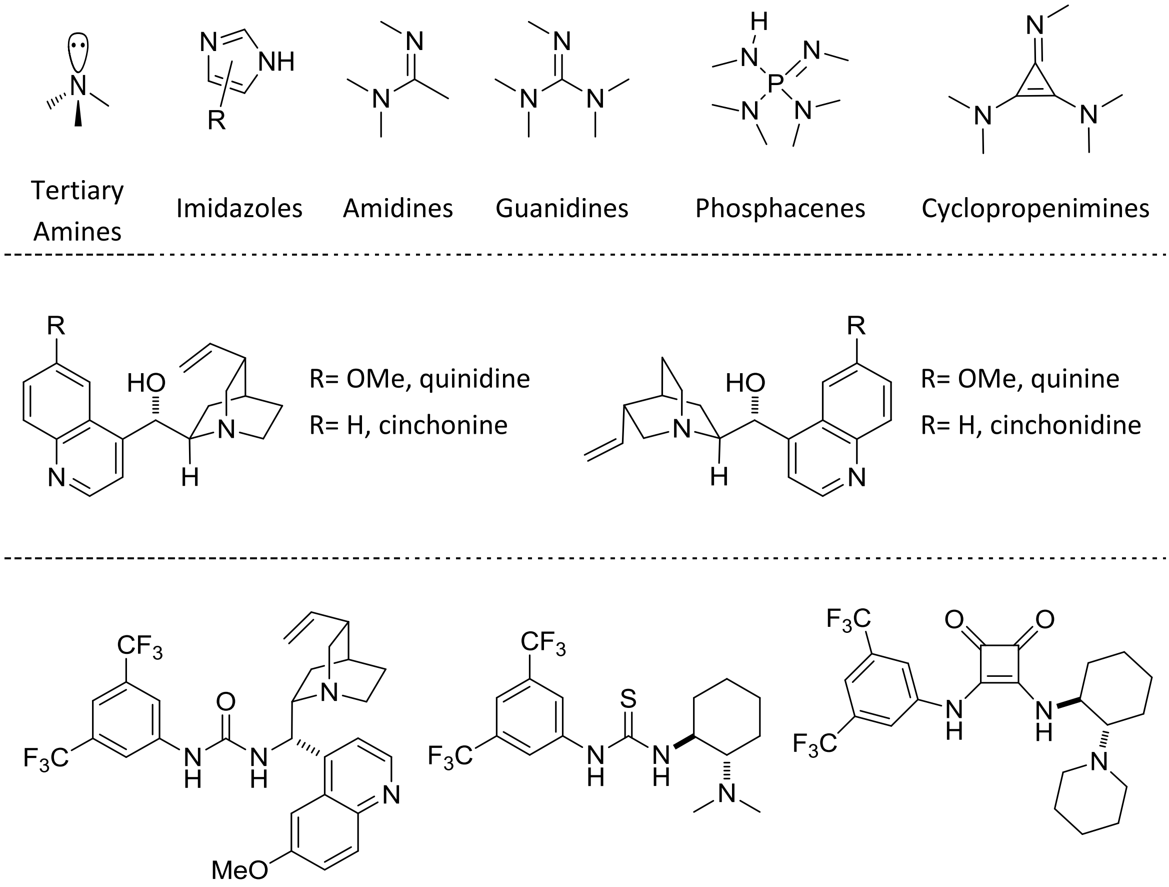

Tertiary Amines
Imidazoles
Amidines
Guanidines
Phosphacenes
Cyclopropenimines
R= OMe, quinidine
R= H, cinchonine
R= OMe, quinine
R= H, cinchonidine

Figure 5. Basic core functions ordered according to decreasing occurrence (top). Alkaloids from the *Cinchona* family (middle). Some representative bifunctional chiral Brønsted bases (below).

Taking into account the previous considerations, in order to address the overall aim of this investigation, we first focused on the design of the 1,2-dicarbonylic compound to be used as pronucleophile in the Brønsted base catalyzed cross-aldol reaction with enolizable aldehydes. As stated in chapter 1, main difficulties associated to the use of 1,2-dicarbonylic compounds as pronucleophiles derive from the relatively low acidity of the α-carbon atom compared to 1,3-dicarbonyl compounds. Nevertheless, the presence of an extra carbonyl group decreases the corresponding pK_a (16.6 for pyruvic acid)[164] to a value somehow compatible with Brønsted base catalysis[165] (Figure 6).

---

[164] a) Y. Chiang, A. J. Kresge, P. Pruszynski, *J. Am. Chem. Soc.* **1992**, *114*, 3103–3107; b) J. Ho, M. L. Coote, *J. Chem. Theory Comput.* **2009**, *5*, 295–306.

[165] The pK_a´s of (thio)urea organocatalysts in DMSO are in the range of 8.5–21.1: a) X. Li, H. Deng, B. Zhang, J. Li, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur.* **2010**, *16*, 450–455; b) G. Jakab, C.

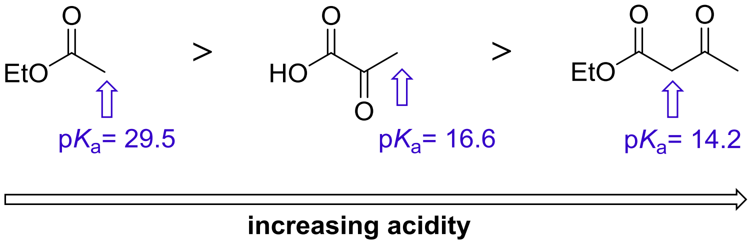
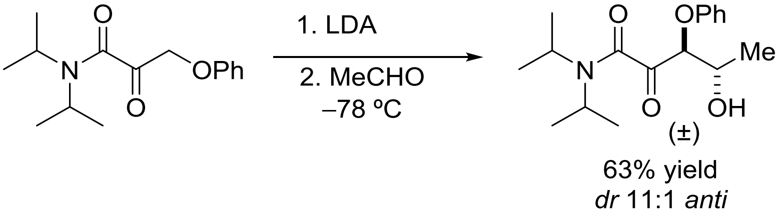


Figure 6. pK_a Values for ethyl acetate,[166] pyruvic acid and ethyl acetoacetate.[166]

We hypothesized that β-alkoxy-α-keto amides could be good candidates to behave as good pronucleophiles in cross-aldol reactions. On one hand, the α-keto amide motif is widely found in natural products and bioactive molecules[167] and the extra oxygen increases the functionalization towards polyol fragments. On the other hand, and most important, β-alkoxy-α-keto amides had been previously employed in racemic aldol reactions in which the corresponding adducts were obtained as stable fragments that did not lactonize;[168] an important limitation observed for substituted pyruvates because the cyclization implies loss of a stereogenic center (Scheme 52).



Scheme 52. Aldol reaction of *N,N*-diisopropyl-2-oxo-3-phenoxypropanamide.

Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724–1727; the pK_a´s of squaramide-based organocatalysts in DMSO are in the range of 8.4–14.5: c) X. Ni, Z. Wang, J.-P. Cheng, *Org. Lett.* **2014**, *16*, 1786–1789.

[166] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.

[167] For synthesis of α-keto amides, see: a) C. De Risi, G. P. Pollini, V. Zanirato, *Chem. Rev.* **2016**, *116*, 3241–3305; b) A. de la Torre, D. Kaiser, N. Maulide, *J. Am. Chem. Soc.* **2017**, *139*, 6578–6581.

[168] E. R. Koft, P. Dorff, R. Kullnig, *J. Org. Chem.* **1989**, *54*, 2936–2940.

We also believed that the introduction of an extra oxygen in the pronucleophile might contribute to decrease the pK_a of the α-carbon atom facilitating Brønsted-base promoted soft activation. Furthermore, given their bidentate character, activation through multiple hydrogen-bonding interactions might also facilitate deprotonation to give an α-keto enolate with a specific configuration (Figure 7).

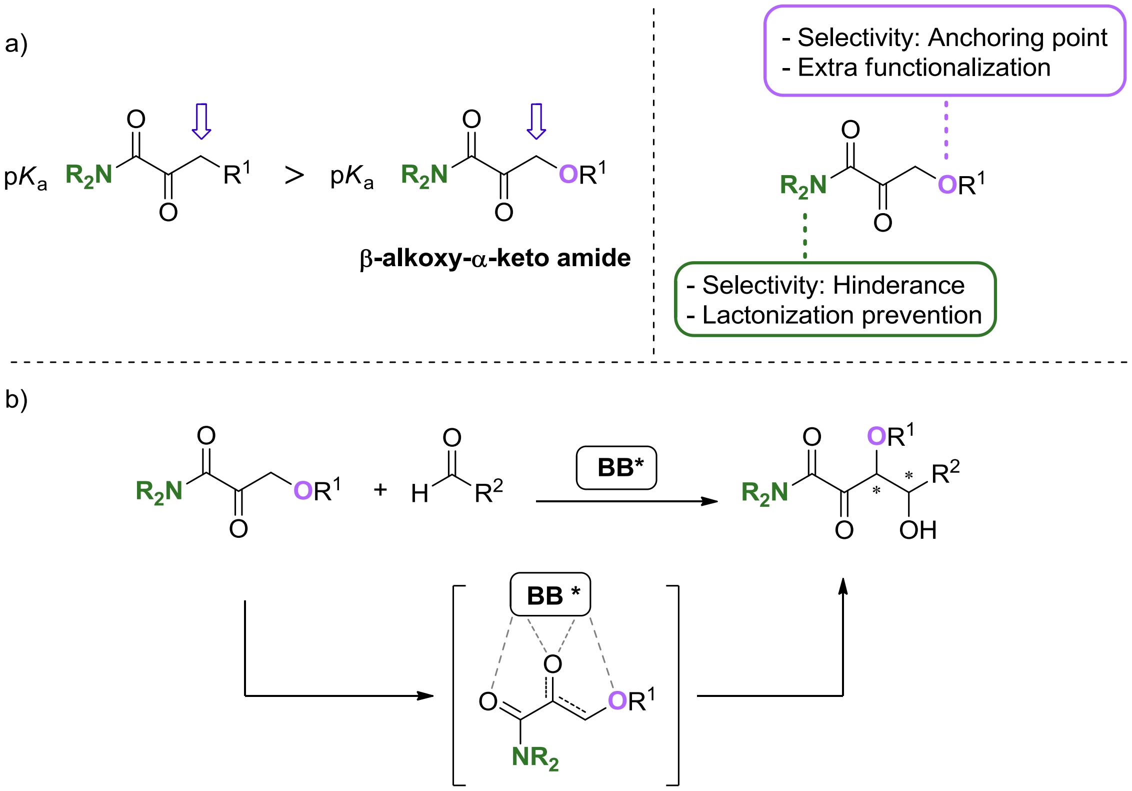

a)
pK_a
R$_2$N
R^1
>
pK_a
R$_2$N
OR^1
β-alkoxy-α-keto amide
- Selectivity: Anchoring point
- Extra functionalization
R$_2$N
OR^1
- Selectivity: Hinderance
- Lactonization prevention
b)
R$_2$N
OR^1
+
H
R^2
BB*
R$_2$N
OR^1
R^2
OH
BB *
NR$_2$
OR^1

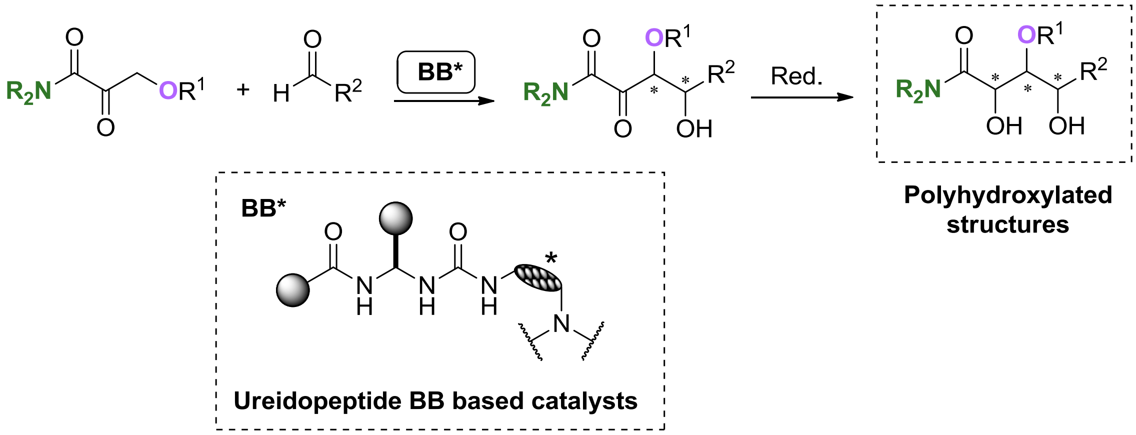
Figure 7. a) Design of 1,2-dicarbonyl pronucleophiles. b) Brønsted base promoted cross-aldol reaction of β-alkoxy-α-keto amides.

Regarding the strong catalyst-substrate dependence of Brønsted base catalyzed direct asymmetric C-C bond forming reactions, catalyst design was the other critical issue to address in order to achieve our goal. Recently, our group has developed ureidopeptide-based Brønsted bases as a new sub-family of organocatalysts. These compounds are distinguished by the presence of an *N,N*-diacylaminal unit and an urea moiety as hydrogen-bond donors and have demonstrated their efficiency in several transformations,[169] providing experimental evidence of their potential scope (more detailed information about these organocatalysts is provided in next section).

---

[169] Catalytic enantioselective synthesis of tertiary thiols: a) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–

In accordance with the aforementioned hypothesis, we envisaged developing a general asymmetric Brønsted-base catalyzed direct cross-aldol reaction of β-alkoxy-α-keto amides valid for the challenging enolizable aldehydes that could be also extensible to non-enolizable ones (Scheme 53). Classical bifunctional Brønsted bases along with ureidopeptide-based Brønsted bases were chosen to control the two main challenges associated to cross-aldol reactions: chemoselectivity (cross- *versus* homo-aldol reaction) and stereoselectivity. Finally, enantiomerically enriched polyhydroxyl fragments, which were the main aim of this work, could be directly obtained after stereoselective reduction of the keto functionality in the aldol adducts.



Scheme 53. Objetive of this work: BBs catalyzed cross aldol reaction of β-alkoxy-α-keto amides: stereoselective synthesis of polyhydroxylated structures.

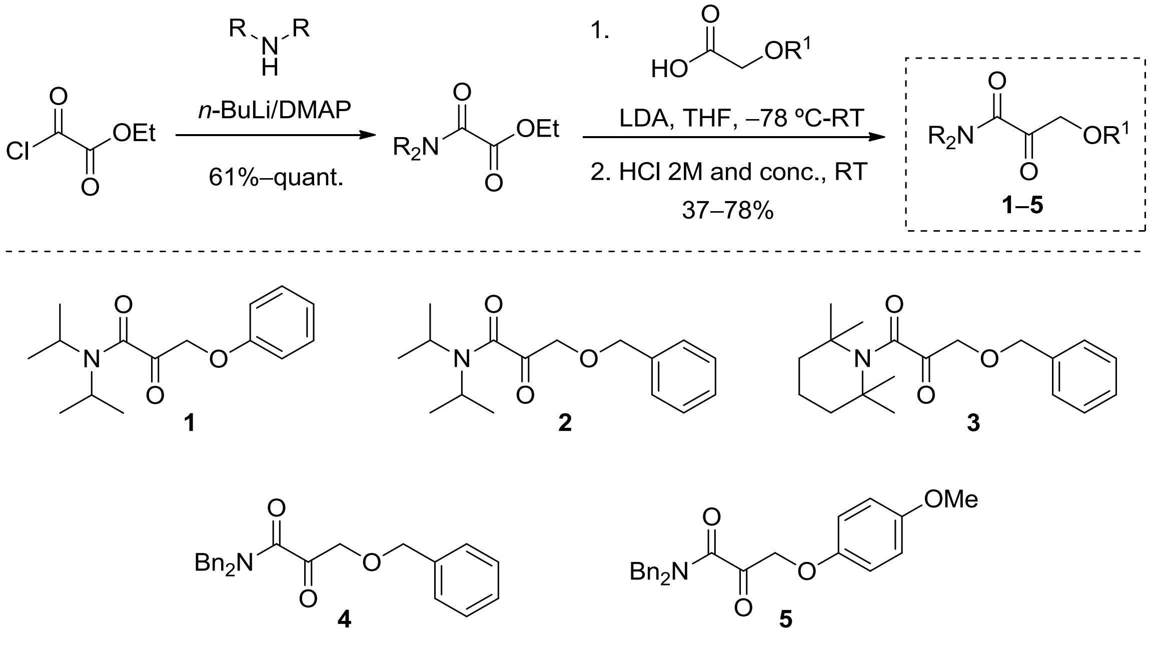
11851. Catalytic enantioselective synthesis of β-amino nitriles: b) S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.

2.4. Results and discussion

2.4.1. Synthesis of β-alkoxy-α-keto amides

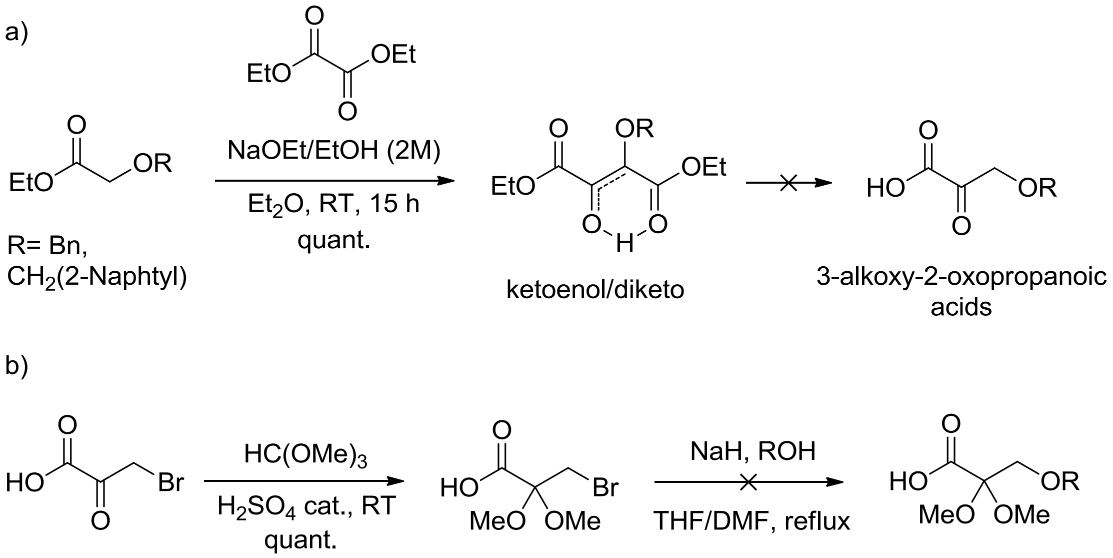
Along with catalyst design, there is an increasingly interest for the elaboration of pronucleophiles that can act as privileged templates in the area of organocatalysis. For this reason we first focused our efforts in the development of a general and efficient methodology to obtain a great variety of β-alkoxy-α-keto amides since the nature of substituents at nitrogen and oxygen atoms in the pronucleophile might strongly affect the interaction with the catalyst.

The selected strategy consisted in the reaction of 2-alkoxy acetic acids with the appropriate ethyl-2-(dialkylamine)-2-oxoacetate, easily prepared from ethyl 2-chloro-2-oxoacetate, followed by *in situ* decarboxylation of the resultant β-keto acid (Scheme 54). The corresponding β-alkoxy-α-keto amides **1**–**5**, with different alkyl and aromatic substituents, were produced in moderate yields. Although we were able to install phenyl and benzyl groups at the oxygen atom, attempts to introduce more hindered groups failed.



Scheme 54. Synthesis of β-alkoxy-α-keto amides **1**–**5** by *in situ* decarboxylation of β-keto acids.

A different approach for the synthesis of β-alkoxy-α-keto amides might consist in the preparation of 3-alkoxy-2-oxopropanoic acids that could be subsequently transformed into the corresponding β-keto amides. For that purpose, we performed the reaction between diethyl oxalate and the corresponding ethyl 2-oxyacetates (Scheme 55a).[170] Nevertheless, decarboxylative saponification of the ketoenol/diketo adducts was not achieved in spite of using a variety of reaction conditions. On the other hand, nucleophilic substitution reactions of 3-bromo-2,2-dimethoxypropanoic acid were also fruitless (Scheme 55b).


a)
EtO
OEt
O
NaOEt/EtOH (2M)
Et$_2$O, RT, 15 h
quant.
OR
R= Bn,
CH$_2$(2-Naphtyl)
ketoenol/diketo
HO
3-alkoxy-2-oxopropanoic acids
b)
Br
HC(OMe)$_3$
H$_2$SO$_4$ cat., RT
quant.
MeO
OMe
NaH, ROH
THF/DMF, reflux

Scheme 55. Unsuccessful preparation of 3-alkoxy-2-oxopropanoic acids.

As a different alternative, we considered to prepare α-keto amides bearing a free hydroxyl group which could be further tuned with diverse protecting groups. Unfortunately, we found that *N,N*-dibenzyl-3-hydroxy-2-oxopropanamide, although detected after catalytic hydrogenation, was very unstable and decomposed during isolation. On the other hand, catalytic hydrogenation of the benzyl protected α-keto amide was efficiently performed but deprotection of the carbonyl group under acidic conditions was not accomplished (Scheme 56).

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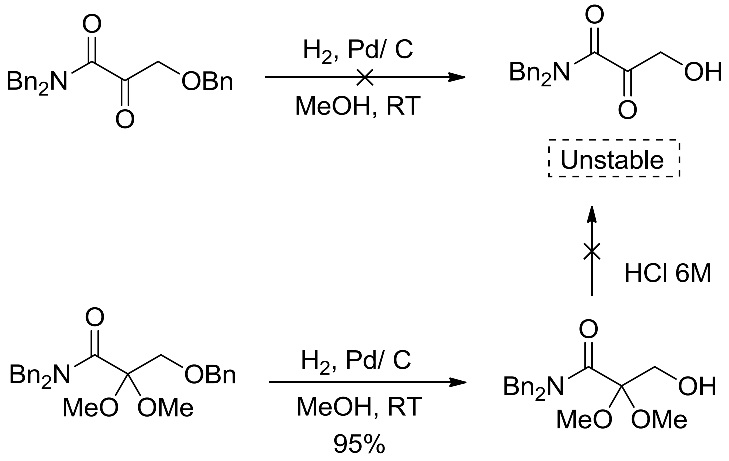
[170] Adapted from: C. Maurin, F. Bailly, P. Cotelle, *Tetrahedron* **2004**, *60*, 6479–6486.



Scheme 56. Unsuccessful preparation of *N,N*-dibenzyl-3-hydroxy-2-oxopropanamide.

Finally, we found that the most efficient and general approach for the synthesis of β-alkoxy-α-keto amides consisted in the protection of the α-carbonyl group in the 3-bromo-2-oxopropanoic acid, followed by preparation of the corresponding amide, under peptide-coupling conditions,[171] subsequent nucleophilic substitution of the suitable alcohol[172] and finally carbonyl group deprotection[173] (Scheme 57). Following this methodology β-alkoxy-α-keto amides **6**–**9**, that included variations at both nitrogen and oxygen atoms, were prepared.[174]

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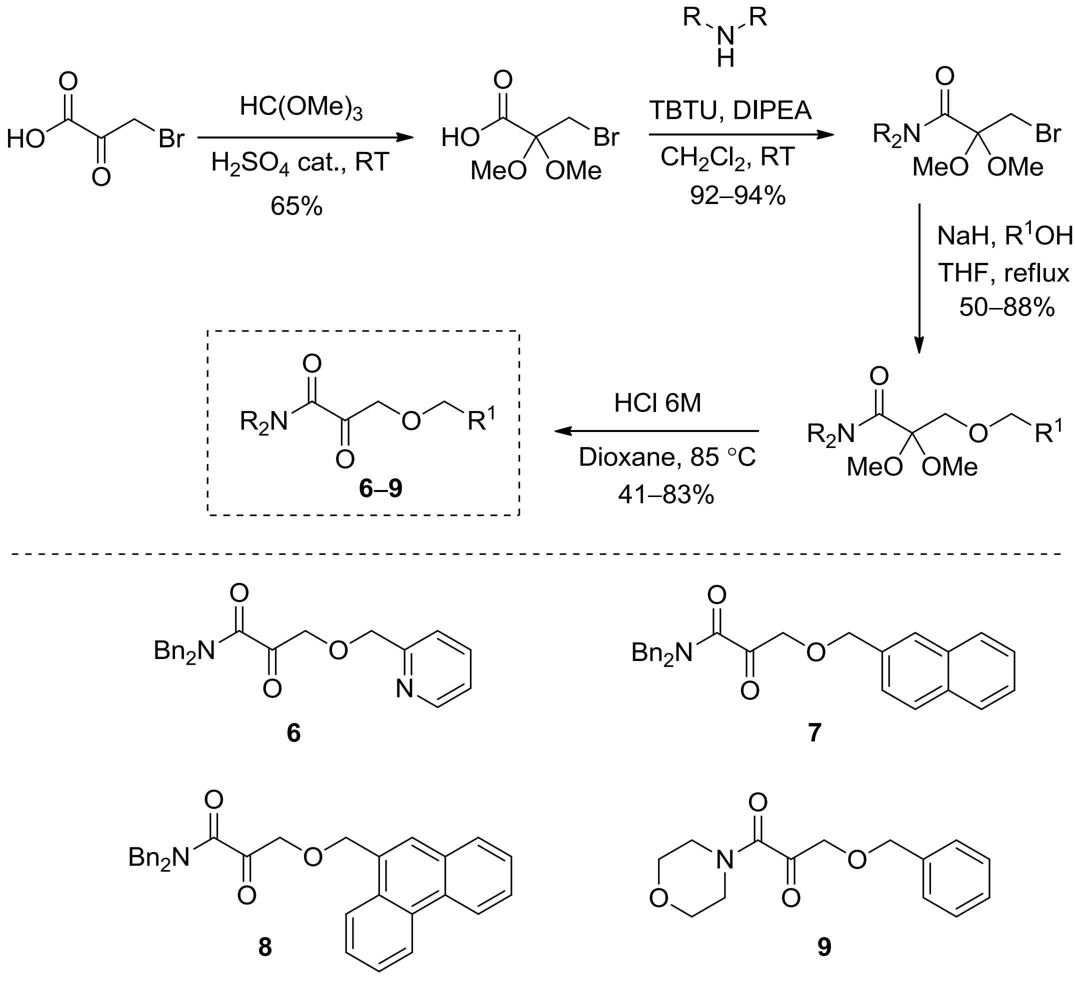
[171] M. R. Davis, E. K. Singh, K. Erinprit, H. Wahyudi, L. D. Alexander, J. B. Kunicki, L. A. Nazarova, K. A. Fairweather, A. M. Giltrap, K. A. Jolliffe, S.R. McAlpine, *Tetrahedron* **2012**, *68* , 1029–1051.

[172] Adapted from: Q. Huang, B. Zheng, Q. J. Long, *J. Chem. Sci.* **2010**, *122*, 203–207.

[173] Adapted from: G. Neef, U. Eder, *Tetrahedron Lett.* **1977**, *32*, 2825–2828.

[174] β-Alkoxy-α-keto amide **4** was also prepared following this methodology.


HC(OMe)3
H2SO4 cat., RT
65%
TBTU, DIPEA
CH2Cl2, RT
92–94%
NaH, R1OH
THF, reflux
50–88%
HCl 6M
Dioxane, 85 °C
41–83%
6–9
6
7
8
9

Scheme 57. Synthesis of β-alkoxy-α-keto amides **6**–**9**.

2.4.2. Catalyst design

In the past decades, scientific community has made great efforts in order to develop chiral bifunctional Brønsted bases capable of activating substrates through non-covalent weak interactions. In this context, the 3,5-bis(trifluoromethyl)phenyl group, present in most of (thio)urea and squaramide-based bifunctional Brønsted bases, seems to be a key structural motif for the success of this type of catalysis. The 3,5-bis(trifluoromethyl)phenyl group was first introduced by Schreiner and Wittkopp in 2002.[175] Later, the groups of

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[175] a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; c) M. Kotice, P. R. Schreiner, *Hydrogen Bonding in Organic Synthesis* **2007**, Ed. P. M. Pihko, 141–351.

Zhong[176] and Schreiner,[177] as a result of an exhaustive study based on NMR- and IR- spectroscopy, mass-spectrometry together with DFT calculations, suggested that the success of this family of catalysts may be a consequence of the participation of three contiguous H-bond donors, both *N*-H bonds in (thio)urea unit and the *ortho* C-H bond of the aryl group, during the electrophile activation event (Figure 8).

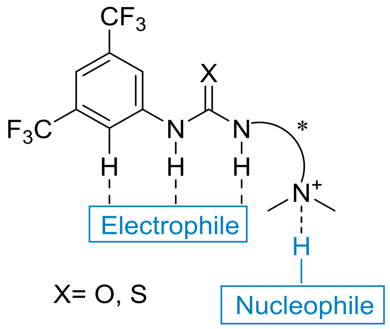

Figure 8. Activation mode proposal.

Based on these appreciations and given the proved efficacy of flexible synthetic peptides for fine-tuning of reactivity and selectivity of several synthetic transformations,[178] our group has recently developed ureidopeptide-based Brønsted bases as a new subfamily of organic catalysts. These compounds are distinguished by the presence of an *N*,*N*-diacylaminal unit in place of the bis(trifluoromethyl)phenyl group, and an urea moiety as hydrogen bond donors, and both in close proximity to an additional stereodirecting group. This type of structures closely resembles to ureidopeptides, Figure 9, which have been recognized for their ability to develop hydrogen bond interactions.[179] It was expected that the replacement of the α-amino acid (aa) terminus by a moiety bearing a tertiary amine in ureidopeptides should result in new bifunctional Brønsted base catalysts with several sites amenable for structural modification.

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[176] B. Tan, Y. Lu, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682–2685.

[177] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919–5927.

[178] Selected review: E. A. C. Davie, S. M. Mennen, Y. Xu. J. M. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812.

[179] a) F. S. Schoonbeek, J. H. vanEsch, R. Hulst, R. M. Kellog, B. L. Feringa, *Chem. Eur. J.* **2000**, *6*, 2633–2643; b) V. Semetey, D. Rognan, C. Hemmerlin, R. Graff, J.-P. Briand, M. Marraud, G. Guichard, *Angew. Chem. Int. Ed.* **2002**, *41*, 1893–1895; c) A. C. Myers, J. A. Kowalski, M. A. Lipton, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222; d) V. V. Sureshbabu, B. S. Patil, R. Venkataramanarao, *J. Org. Chem.* **2006**, *71*, 7697–7705.

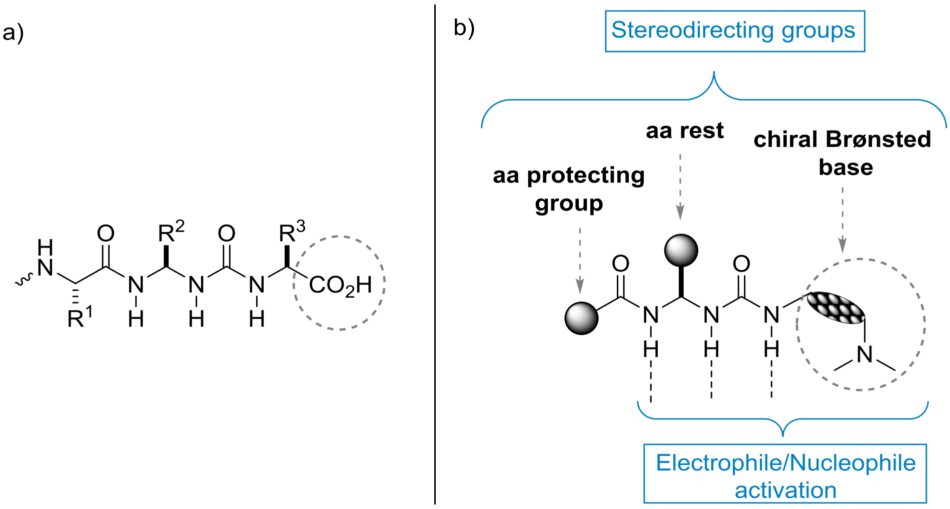

Figure 9. a) Ureidopeptide structures. b) Design for ureidopeptide-based Brønsted bases.

The first synthesis and subsequent optimization of these catalysts were carried out by Diosdado[180] in our research group. The proposed general synthetic sequence involves carbamate protection of the α-amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base to produce the ureidopetide-based Brønsted base catalysts (Scheme 58).

From a synthetic point of view, these structures can be easily tuned in several sites facilitating the modulation of catalyst properties.

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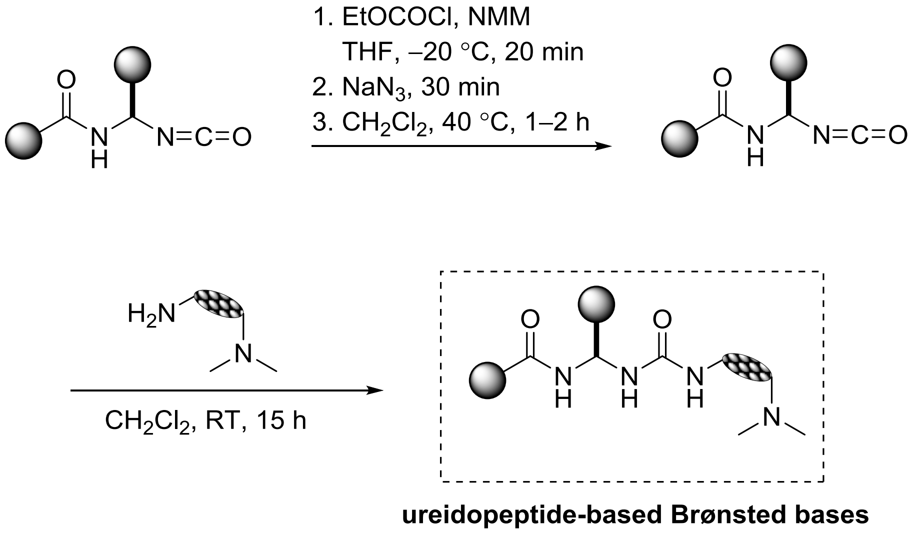
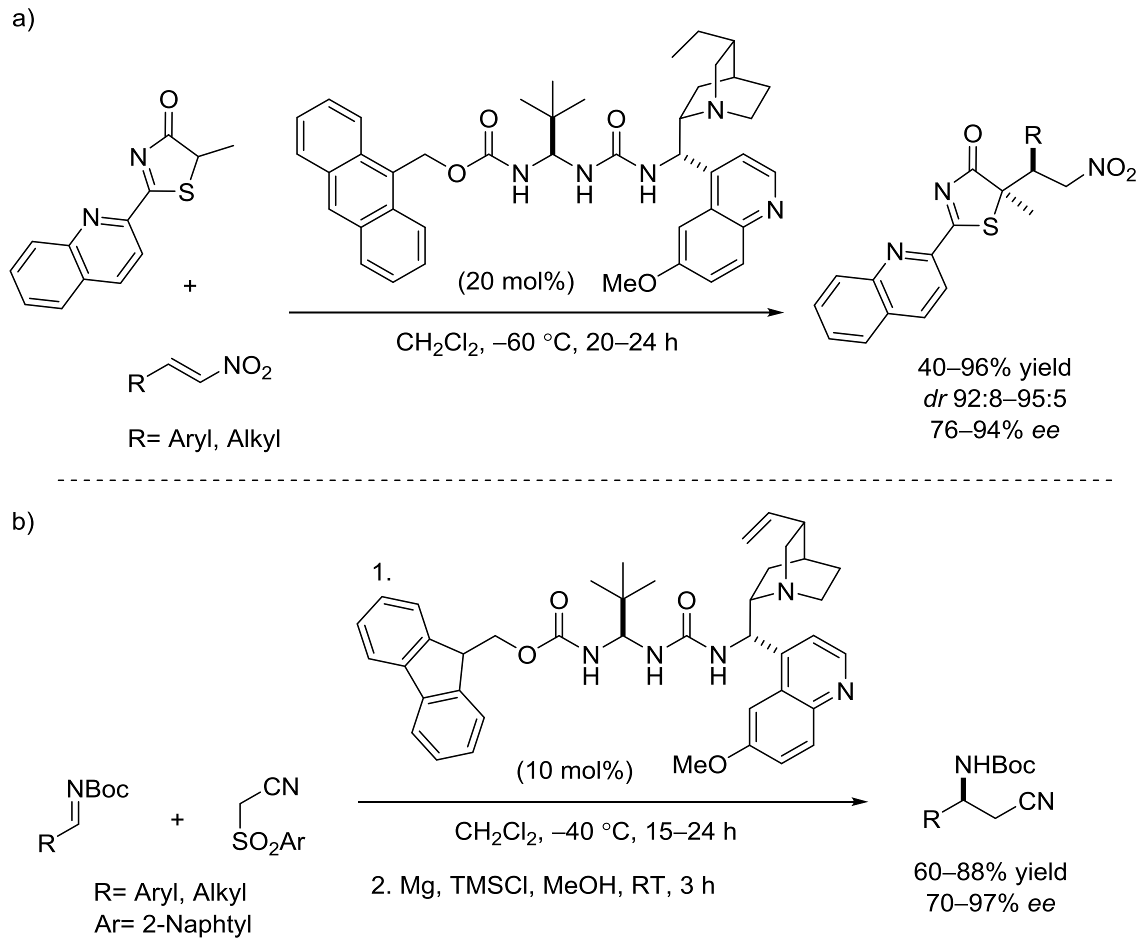
[180] Saioa Diosdado Migeltorena, PhD. Dissertation, EHU/UPV, 2014. http://www.ehu.eus/es/web/gicas/tesiak


1. EtOCOCl, NMM
THF, –20 °C, 20 min
2. NaN3, 30 min
3. CH2Cl2, 40 °C, 1–2 h
O
N
H
N=C=O
H2N
N
CH2Cl2, RT, 15 h
ureidopeptide-based Brønsted bases

Scheme 58. Ureidopeptide-based Brønsted bases: Catalysts preparation.

To date, bifunctional ureidopeptide-based Brønsted bases derived from *tert*-leucine and 9-amino-(9-deoxy)*epi*quinine alkaloid have shown to be very effective in promoting the stereocontrolled synthesis of tertiary thiol derivatives[169a] and β-amino nitriles[169b] (Scheme 59a and Scheme 59b, respectively).


a)
+
R= Aryl, Alkyl
(20 mol%)
CH2Cl2, –60 °C, 20–24 h
40–96% yield
dr 92:8–95:5
76–94% ee
b)
1.
(10 mol%)
CH2Cl2, –40 °C, 15–24 h
2. Mg, TMSCl, MeOH, RT, 3 h
R= Aryl, Alkyl
Ar= 2-Naphtyl
60–88% yield
70–97% ee

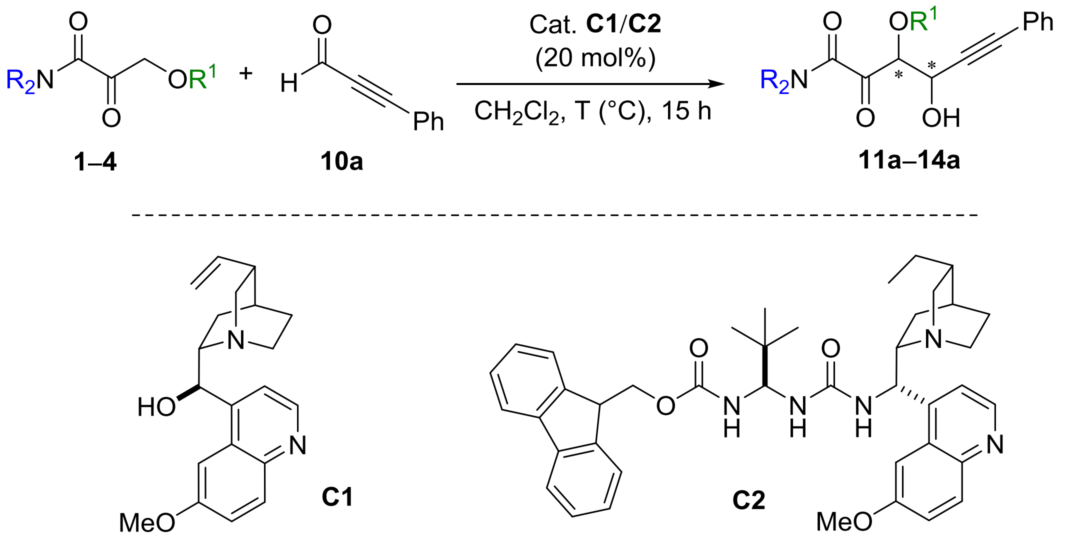
Scheme 59. a) Stereoselective Michael-type reaction of 5*H*-thiazol-4-ones. b) Stereoselective Mannich-type reaction of (arylsulfonyl)acetonitriles.

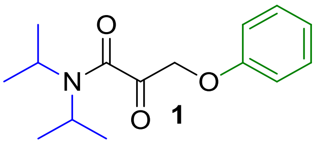
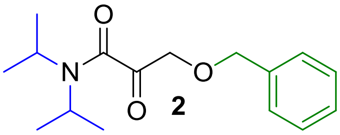
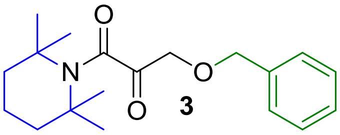
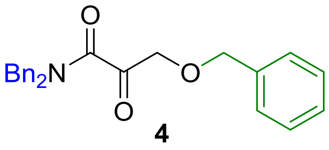
2.4.3. Initial experiments and optimizations

Given the observations noted above, we first decided to study the aldol reaction between β-alkoxy-α-keto amides and propargylic aldehydes, instead of the more challenging enolizable ones. In order to check the viability of our hypothesis, we thought that, as first approach, it could be easier to deal exclusively with reactivity (enolate generation) and selectivity issues avoiding side-reactions resulting from aldehyde enolization.

Initial experiments were carried out using α-keto amides **1**–**4** and 3-phenylpropiolaldehyde (**10a**). For comparative purposes the commercially available quinine (**C1**) and the ureidopeptide-based Brønsted base **C2** were initially tested as promoters of the reaction (Table 9). First of all, we were satisfied to confirm that β-alkoxy-α-keto amides were reactive substrates under Brønsted base catalysis. The production of the corresponding cross-aldol adducts was observed for all the combinations employed albeit reactivity was highly dependent on the type of substitution in the amide moiety and the catalyst. In addition, aldol condensation was not observed at any of the reaction conditions explored. As shown in Table 9, the lower reactivity of the system using quinine (**C1**) required to perform the reactions at room temperature (entries 1,3,5 and 7). Regarding the stereoselectivity of the process, diastereo- and enantioselectivities were moderate and it is worth to notice that quinine (**C1**) and the ureidopeptide **C2** induced opposite diastereoselectivity. Although the cyclic α-keto amide **3** provided the highest diastereoselectivity (98:2 *dr*, entry 6), a better balance reactivity/selectivity was observed for α-keto amide **4** which produced the corresponding aldol adduct **14a** with a 79:21 diastereomeric ratio and 66% *ee* for the major diastereomer (entry 8).

Table 9. Initial experiments for the cross-aldol reaction between α-keto amides **1–4** and **10a**. [a–d]



Ent.	R, R^1	Cat	T (°C)	Conv. (%)^b	Prod.	*dr*^{c}	*ee* (%)^d
1	 **1**	**C1**	RT	>95	**11a**	40:60	n.d.
2		**C2**	–40	>95	**11a**	75:25	40
3	 **2**	**C1**	RT	>95	**12a**	41:59	<10
4		**C2**	–40	80	**12a**	88:12	44
5	 **3**	**C1**	RT	50	**13a**	10:90	30
6		**C2**	–40	75	**13a**	98:2	55
7	 **4**	**C1**	RT	>95	**14a**	37:63	32
8		**C2**	**–40**	**>95**	**14a**	**79:21**	**66**

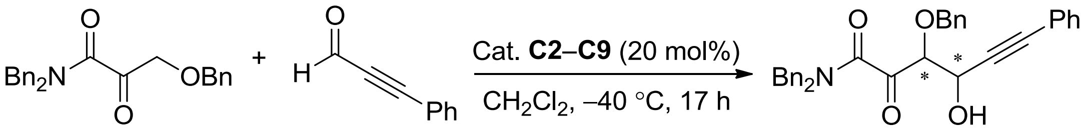
[a] Reaction conditions: **1–4** (0.2 mmol) and **10a** (1 equiv., 0.2 mmol) in CH_2Cl_2 (1 mL). [b] Conversions into the corresponding adducts were determined by ^{1}H-RMN spectroscopy. [c] The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. [d] The *ee* values were determined for the major diastereomer by chiral HPLC.

With these preliminary results in hand, we next evaluated several classical Brønsted bases, using α-keto amide **4**, under same reaction conditions (Table 10).

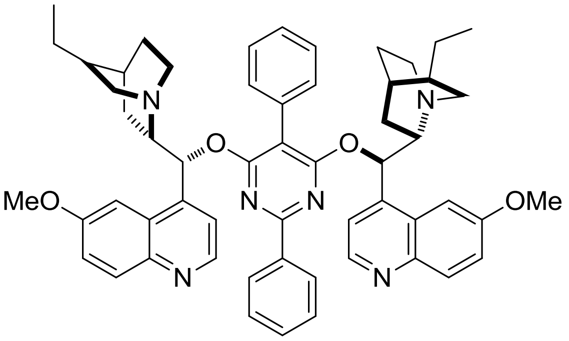
The results clearly illustrated that bifunctional Brønsted base catalysts with recognized hydrogen bond donor ability efficiently promoted the cross aldol reaction at –40 ^{o}C. Complete conversion into the corresponding adduct **14a** was observed when chiral bases such as quinine-squaramide derivative **C4**, Takemoto´s thiourea **C5** and quinine-thiourea derivative **C6** were employed. In contrast, the alkaloid dimer $(DHQ)_2PYR$ (**C3**) performed very poorly in terms of reactivity and selectivity.

Regarding the stereochemical outcome of the reaction, diastereoselectivities were in general moderate for thiourea and squaramide-catalyst (**C4**–**C6**), although the enantiomeric excess for the major diastereomer significantly improved up to 80% with catalyst **C6.** *tert*-Leucine based ureidopeptide catalysts **C7**, **C8** and **C9** exerted a better control over diastereoselectivity, compared with the initially tested **C2**, whereas enantiomeric excesses were still moderate and poorer for the catalyst bearing *tert*-butyl carbamate (**C9**).

Table 10. Catalyst screening for the addition of α-keto amide **4** to aldehyde **10a**.[a]

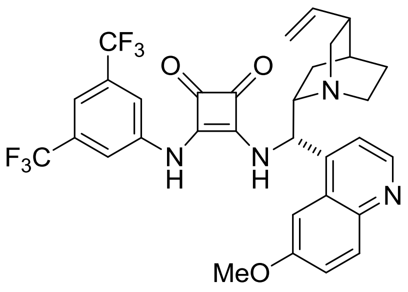

Bn$_2$N
OBn
+
H
Ph
Cat. **C2**–**C9** (20 mol%)
CH$_2$Cl$_2$, –40 °C, 17 h
OBn
Ph
Bn$_2$N
*
*
OH

4 **10a** **14a**


MeO
N
N
N
O
O
N
OMe
N
N

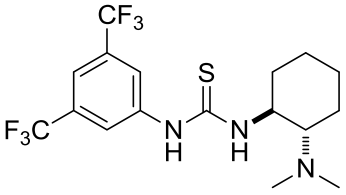
C3

conv. 50%, 63:37 *dr*, <10% *ee*


CF$_3$
O
O
F$_3$C
N
H
N
H
N
N
MeO

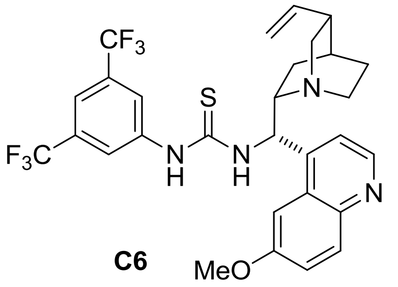
C4

conv. >95%, 35:65 *dr*, 31% *ee*


CF$_3$
S
F$_3$C
N
H
N
H
N

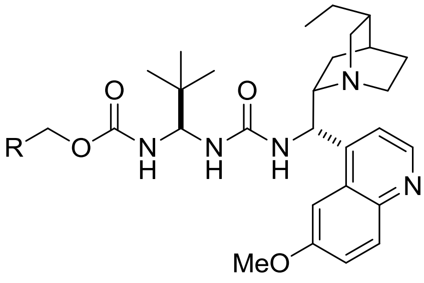
C5

conv. >95%, 68:32 *dr*, 72% *ee*

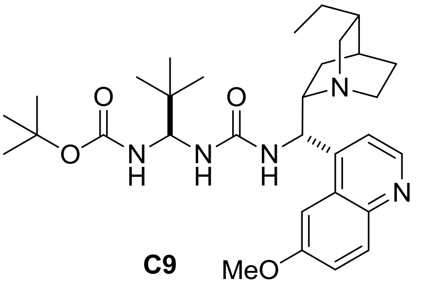

CF$_3$
S
F$_3$C
N
H
N
H
N
N
MeO

C6

conv. >95%, 76:24 *dr*, 80% *ee*


R
O
O
O
N
H
N
H
N
H
N
N
MeO

C2 R= Fluorenyl, conv. >95%, 79:21 *dr*, 66% *ee*
C7 R= Ph, conv. >95%, 90:10 _dr_, 64% _ee_
C8 R= Antracenyl, conv. >95%, 87:13 *dr*, 67% *ee*


O
O
O
N
H
N
H
N
H
N
N
MeO

C9

conv. >95%, 90:10 *dr*, 50% *ee*

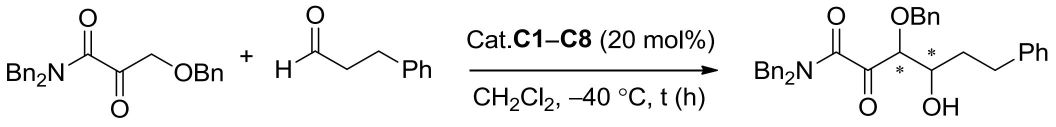
[a] Reaction conditions: **4** (0.2 mmol) and **10a** (1 equiv., 0.2 mmol) in CH$_2$Cl$_2$ (1 mL). Conversions into the corresponding adduct determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

2.4.3.1. Initial experiments with enolizable aldehydes

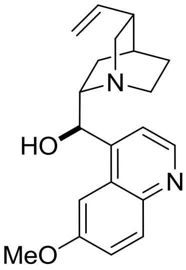
In parallel, we investigated the performance of the system with enolizable aldehydes. With this purpose, we chose α-keto amide **4**, which performed the best in the reaction with 3-phenylpropiolaldehyde (**10a**), and hydrocinnamaldehyde **11a**. In order to compensate the lower reactivity of aliphatic aldehydes, compared to propargylic ones, excess of aldehyde (1.2 equiv.) was employed and solvent volume was reduced. As results in Table 11 shown, the predicted lower reactivity was confirmed by the fact that, neither quinine (**C1**) nor non-bifunctional catalyst **C3** promoted the reaction after 24 hours even at room temperature. Bifunctional squaramide **C4** was ineffective in terms of reactivity and selectivity whereas thioureas **C5** and **C6** displayed a high control over both diastereoselectivity and enantioselectivity. As a drawback, full conversion into the aldol adduct was not reached with neither of these catalysts after long reaction times.

A remarkable increased reactivity was observed for ureidopeptide based catalysts **C2**, **C7** and **C8** confirming our hypothesis about the beneficial effect of multiple hydrogen-bonding interactions on pronucleophile activation. Complete conversions into the aldol adduct **15a** were accomplished after 36–48 hours at –40 ^{o}C. Under these reaction conditions, these catalysts seemed to promote the exclusive generation of the α-keto amide enolate which reacted with the aldehyde without the generation of side-products resulting from dehydration, α-keto amide self-condensation, aldehyde enolization, and cyclization towards isotetronic acid formation.

Table 11. Catalyst screening for the addition of α-keto amide **4** to hydrocinnamaldehyde (**11a**).[a]

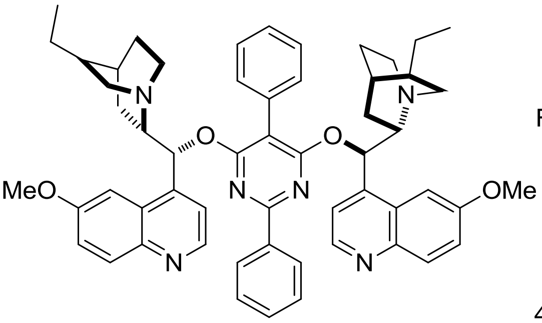

Bn2N
OBn
+
H
Ph
Cat.C1–C8 (20 mol%)
CH2Cl2, –40 °C, t (h)
Bn2N
OBn
OH
Ph
*
*

4 **11a** **15a**



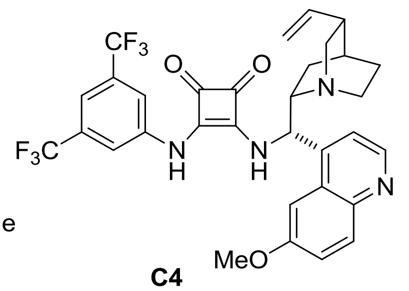
C1

24 h, RT, NR


N
O
O
N
N
MeO
OMe
N
N
N

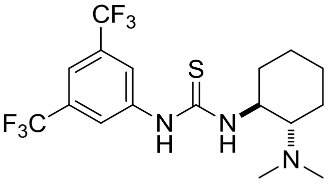
C3

24 h, RT, NR


CF3
O
O
F3C
N
H
N
H
N
N
MeO

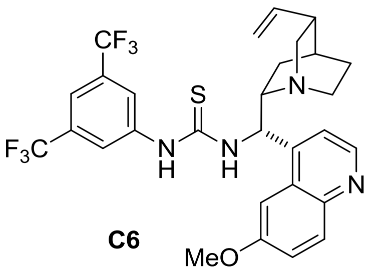
C4

48 h, conv. 30%, 44:56 *dr*, 64% *ee*


CF3
S
F3C
N
H
N
H
N

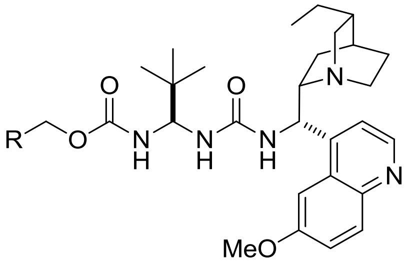
C5

48 h, conv. 30%, 83:17 *dr*, 90% *ee*
96 h, conv. 50%, 85:15 *dr*, 92% *ee*


CF3
S
F3C
N
H
N
H
N
N
MeO

C6

48 h, conv. 30%, 87:13 *dr*, 92% *ee*
96 h, conv. 80%, 96:4 *dr*, 94% *ee*


R
O
O
O
N
H
N
H
N
H
N
N
MeO

C2 R= Fluorenyl, 48 h, conv. >95%, 79:21 *dr*, 94% *ee*
C7 R= Ph, 36 h, conv. >95%, 86:14 *dr*, 92% *ee*
C8 R= Antracenyl, 48 h, conv. >95%, 75:25 *dr*, 92% *ee*

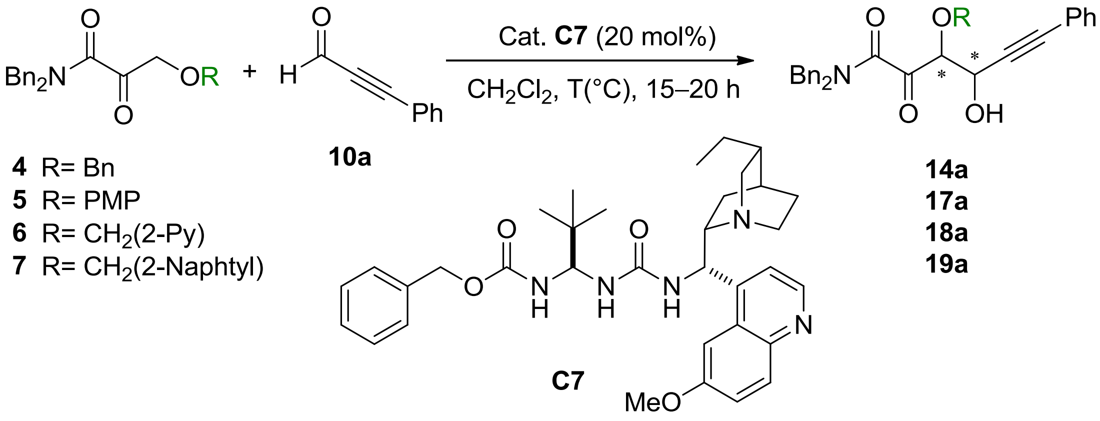
[a] Reaction conditions: **4** (0.2 mmol) and aldehyde **11a** (1.2 equiv., 0.24 mmol) in CH_2Cl_2 (0.5 mL). Conversions into the corresponding adduct determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

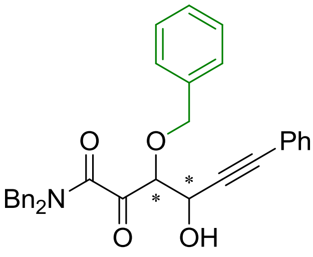
2.4.3.2. Substituent screening at the oxygen atom in the α-keto amide

Next, we decided to study the impact on selectivity of the substituent at the oxygen atom in the β-alkoxy α-keto amide in more detail; specially, for the case of 3-phenylpropiolaldehyde (**10a**) in which the enantioselectivity reached with ureidopeptide-based catalyst **C7** was moderate (64% *ee*, Table 10). Results obtained are summarized in Table 12.

The higher reactivity displayed by propargylic aldehydes allowed to carry out the transformation with the α-keto amide **4** at –60 °C giving rise to a slight improvement in enantioselectivity (68% *ee versus* 64% *ee* at –40 °C). Reactions were then carried out with the other α-keto amides at –60 °C and the best results were obtained with α-keto amide **7**; complete conversion to the aldol adduct **19a** after 17 hours with a diastereomeric ratio 90:10 and 80% *ee*.

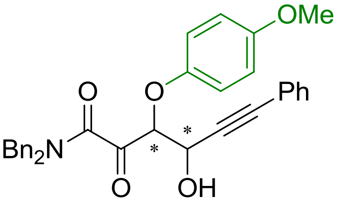
Table 12. β-Alkoxy α-keto amide screening in the reaction with **10a** promoted by catalyst **C7**.[a]


Bn2N
OR
O
O
+
H
O
Ph
Cat. C7 (20 mol%)
CH2Cl2, T(°C), 15–20 h
Bn2N
O
O
OR
OH
Ph
*
*
10a
4 R= Bn
5 R= PMP
6 R= CH2(2-Py)
7 R= CH2(2-Naphtyl)
C7
MeO
N
N
14a
17a
18a
19a



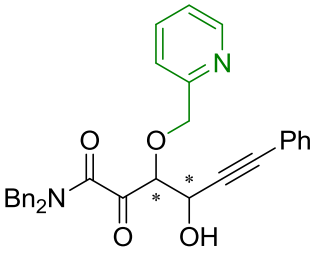
14a

–40 °C, conv. >95%, 90:10 *dr*, 64% *ee*
–60 °C, conv. >95%, 90:10 *dr*, 68% *ee*



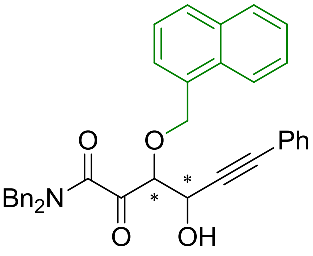
17a

–60 °C, conv. >95%, 50:50 *dr*, <10% *ee*



18a

–60 °C, conv. >95%, messy crude



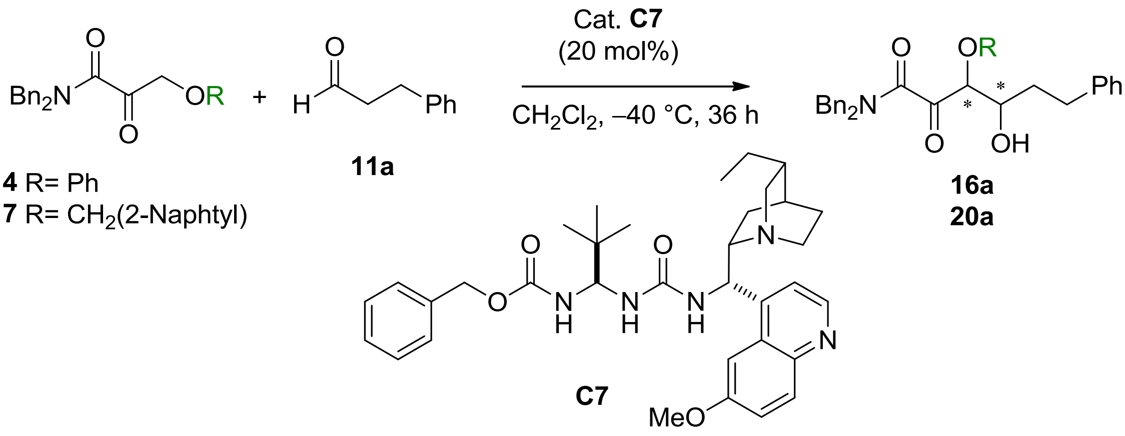
19a

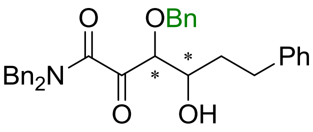
–60 °C, conv. >95%, 90:10 *dr*, 80% *ee*

[a] Reaction conditions: **4–7** (0.2 mmol) and **10a** (1 equiv., 0.2 mmol) in CH_2Cl_2 (1 mL). Conversions into the corresponding adducts determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

The presence of the 2-naphtyl group in α-keto amide **7** significantly improved the enantioselectivity of the addition to 3-phenylpropiolaldehyde (**10a**). Therefore, we decided to evaluate the behavior of **7** in the reaction with hydrocinnamaldehyde (**11a**) employing the same catalyst (**C7**). Results shown in Table 13 revealed that increasing the aromatic character of the substituent in the α-keto amide was also benefitial in the reaction with the aliphatic aldehyde. The diastereomeric ratio of the reaction raised up to 90:10.

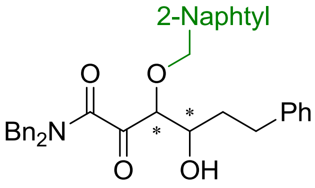
Table 13. α-Keto amide screening for the addition to aliphatic aldehyde **11a** promoted by catalyst **C7**.[a]


Bn2N
OR
O
+
H
Ph
Cat. C7
(20 mol%)
CH2Cl2, –40 °C, 36 h
4 R= Ph
7 R= CH2(2-Naphtyl)
11a
16a
20a
C7
MeO
N


Bn2N
OBn
O
OH
Ph

16a

conv. >95%, 86:14 *dr*, 92% *ee*


2-Naphtyl
Bn2N
O
OH
Ph

20a

conv. >95%, 90:10 *dr*, 92% *ee*

[a] Reaction conditions: **4/7** (0.2 mmol) and **11a** (1.2 equiv., 0.24 mmol) in CH_2Cl_2 (0.5 mL). Conversions into the corresponding adducts determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

2.4.3.3. *Catalyst reassessment*

Once α-keto amide **7** was confirmed as the most promising pronucleophile, we decided to perform a more detailed study on the influence of variations of the ureidopeptide-based catalyst structure in the aldol reaction with 3-phenylpropiolaldehyde (**10a**). For this purpose, catalysts with increased aromatic character in the carbamate protecting group and structurally diverse chiral Brønsted base moieties were examined (Table 14). Substitution of the benzyl carbamate by the phenantrenyl one provoked a beneficial effect in the enatioselectivity of the process that afforded adduct **19a** in 88% *ee* albeit with a decreased diastereoselectivity (85:15). On the other hand, substitution of the 9-9-amino-(9-deoxy)*epi*quinine fragment by other chiral 1,2-diamino cyclohexyl fragments revealed the importance of the proper choice of the fragment responsible of the Brønsted base action. Catalyst **C10**–**C13** promoted the aldol reaction of α-keto amide **7** and aldehyde **10a** with moderate to good selectivities, but with a remarkable lower reactivity related also with the poor solubility of these catalysts. As already uncovered for previous asymmetric transformations, the 9-amino-(9-deoxy)*epi*quinine fragment appears as an essential moiety for the high performance of ureidopeptide-based Brønsted base catalysts.[181]

Attempts to improve diastereo- and enantioselectivity of the process by decreasing reaction temperature with catalyst **C10** also failed due to solubility problems: at –80 °C, conversion after 17 hours was 70%, and adduct **19a** was produced in 75:25 diastereomeric ratio and 70% *ee* for the major diastereomer.

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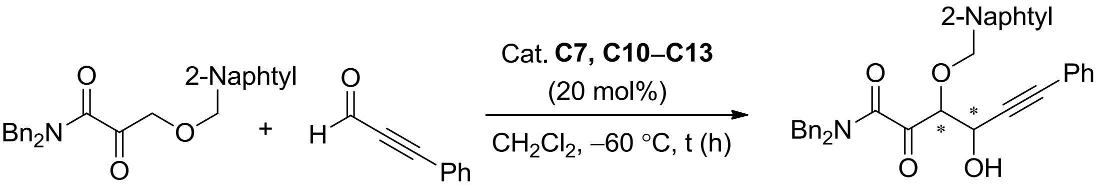
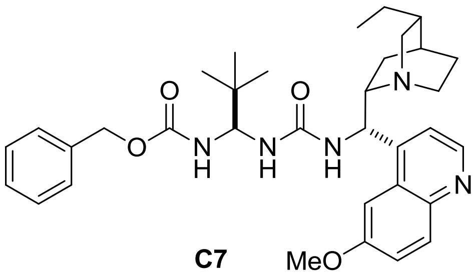
[181] See Scheme 59, page 99.

Table 14. Catalyst screening for the addition of α-keto amide **7** to **10a**.[a]

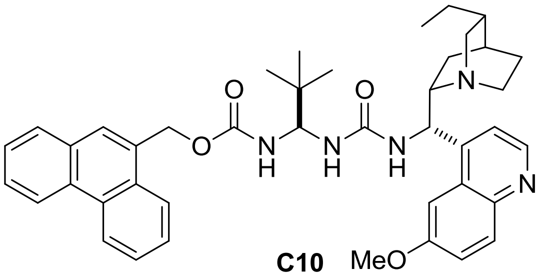

2-Naphtyl
O
Bn_2N
O
O
+
H
O
Ph
Cat. **C7, C10–C13**
(20 mol%)
CH_2Cl_2, –60 °C, t (h)
2-Naphtyl
O
O
Ph
Bn_2N
*
*
O
OH

7 **10a** **19a**



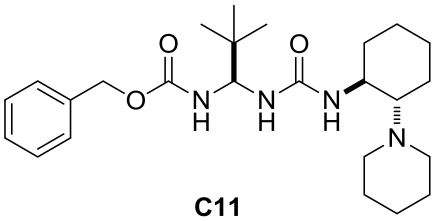
C7

17 h, conv. >95%, 90:10 *dr*, 80% *ee*



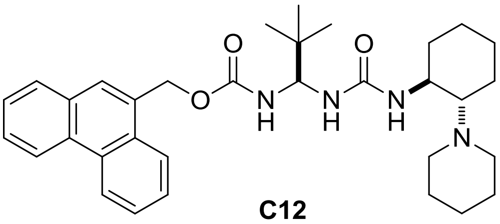
C10

17 h, conv. >95%, 85:15 *dr*, 88% *ee*



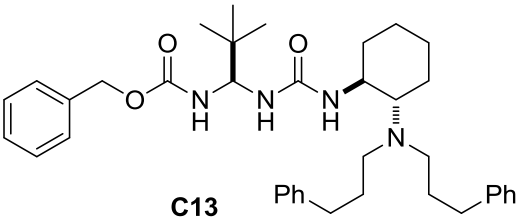
C11

17 h, conv. 40%, 92:8 *dr*, 82% *ee*



C12

60 h, conv. 50%, 94:6 *dr*, 72% *ee*



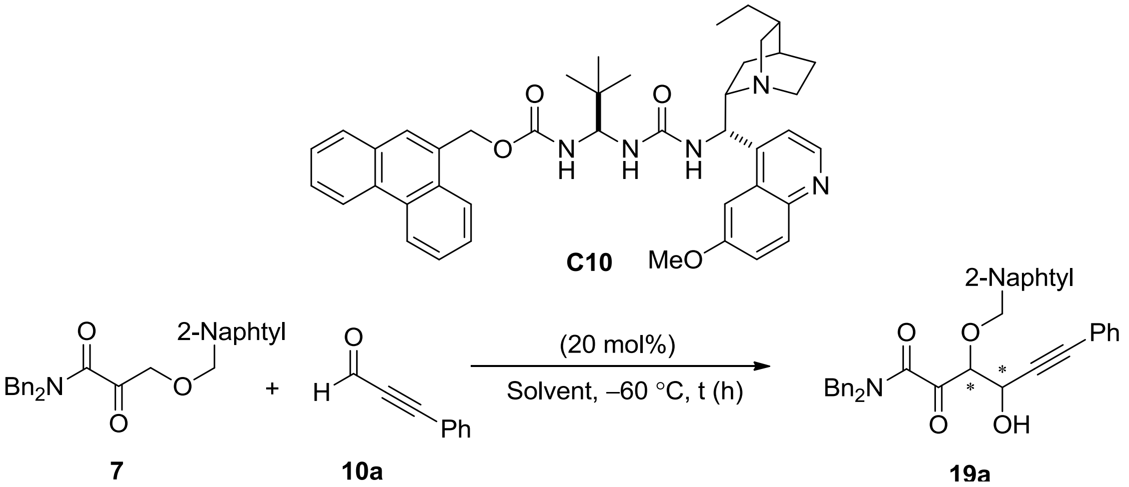
C13

40 h, conv. 50%, 89:11 *dr*, 78% *ee*

[a] Reaction conditions: **7** (0.2 mmol) and **10a** (1 equiv., 0.24 mmol) in CH_2Cl_2 (1 mL). Conversions into the corresponding adduct determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

To complete the screening of the reaction conditions, several solvents were tested in the reaction of α-keto amide **7** and aldehyde **10a** promoted by catalyst **C10**, observing that the initially used solvent for the reaction, dichloromethane, was the optimum (Table 15).

Table 15. Solvent screening for the addition of α-keto amide **7** to aldehyde **10a** promoted by catalyst **C10**.[a]



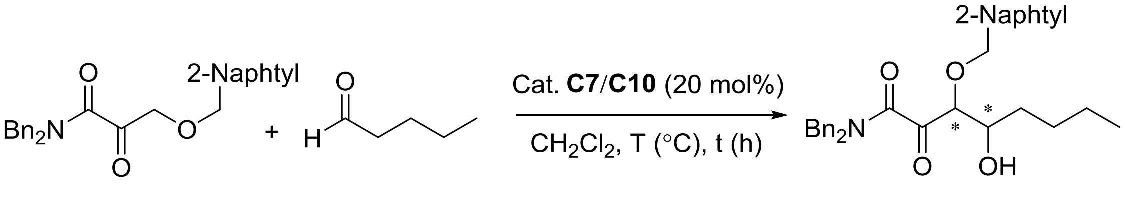
Solvent	t (h)	Conv. (%)[b]	*dr*[c]	*ee* (%)[d]
CH_2Cl_2	17	>95	85:15	88
$CHCl_3$	17	>95	85:15	80
THF	17	85	83:17	86
Et_2O	17	<10[e]	---	---
Toluene	48	85 [e]	60:40	78

[a] Reaction conditions: **7** (0.2 mmol) and **10a** (1 equiv., 0.24 mmol) in the coresponding solvent (1 mL). [b] Conversions into the corresponding adduct determined by ^{1}H-RMN spectroscopy. [c] The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. [d] The *ee* values were determined for the major diastereomer by chiral HPLC. [e] Poor solubility of catalyst **C10** in the solvent.

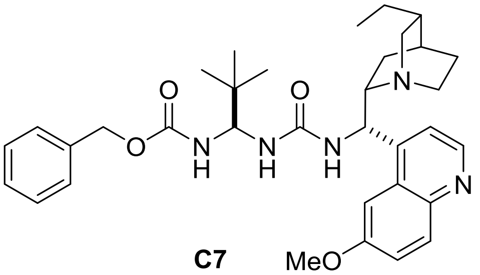
Once catalyst **C10** and reaction conditions (dichloromethane at –60 °C) were established for the aldol reaction of α-keto amide **7** with propargylic aldehydes, a final comparison of the performance of catalyst **C7** and **C10** in the reaction with enolizable aldehydes was made. For this particular case, pentanal

(**11b**) was employed (Table 16). Results revealed that catalyst **C7** afforded the best balance between reactivity and selectivity for aliphatic aldehydes at –20 °C. The stereochemical outcome with **C7** was excellent at –60 °C but reactivity diminished considerably.

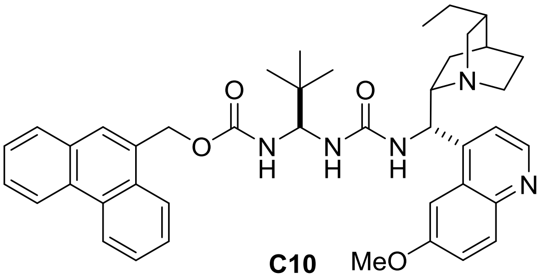
Table 16. Catalysts **C7/C10** comparison for the addition of α-keto amide **7** to pentanal (**11b**).[a]



7 **11b** **20b**



C7



C10

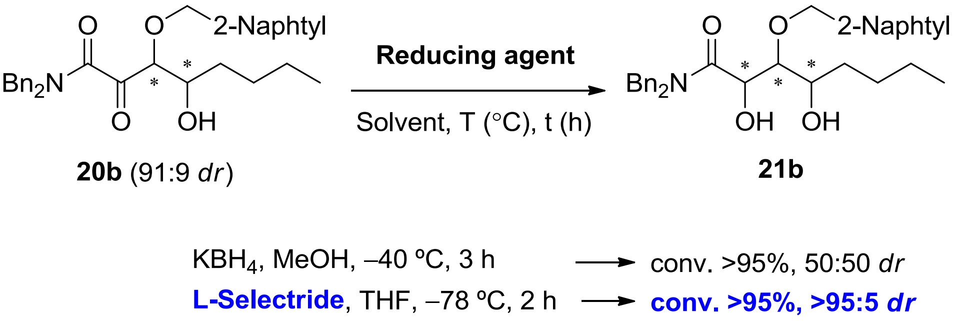
–20 °C, 40 h, conv. >95% **81:19 *dr*, 92% *ee***	–20 °C, 64 h, conv. 90% 81:19 *dr*, 96% *ee*
–60 °C, 7 d, conv. 90% 91:9 *dr*, 96% *ee*	–40 °C, 5 d, conv. 75% 85:15 *dr*, 98% *ee*

[a] Reaction conditions: **7** (0.2 mmol) and **11b** (3 equiv., 0.6 mmol) in CH$_2$Cl$_2$ (0.5 mL). Conversions into the corresponding adduct determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

Given all the observations noted above, α-keto amide **7** and catalyst **C7** were selected as the optimum combination to perform the cross-aldol reaction with enolizable aldehydes in dichloromethane at –20 °C.

2.4.3.4. Stereoselective reduction of aldol adducts

Although the reaction conditions employed were able to avoid non-desirable side reactions such epimerization and dehydration, attempts to isolate pure aldol adducts were unsuccessful. Isolation techniques led to variable amounts of epimerized aldol adducts and products from aldol condensation. For that reason we decided to submit each crude reaction mixture to reduction. Taking into account previous works reported by the groups of Jørgensen[182] and Shibasaki[183] in related systems, we tried KBH_4 and L-Selectride in the reduction of aldol adduct **20b** (Scheme 60). We were very gratified to observe that when L-Selectride was employed, the triol **21b** was obtained as only one detectable diastereomer.[184]



20b (91:9 *dr*)

21b

KBH_4, MeOH, –40 ºC, 3 h ⟶ conv. >95%, 50:50 *dr*

L-Selectride, THF, –78 ºC, 2 h ⟶ **conv. >95%, >95:5 *dr***

Scheme 60. Stereoselective reduction of adduct **20b**.

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[182] See Scheme 19, page 40.

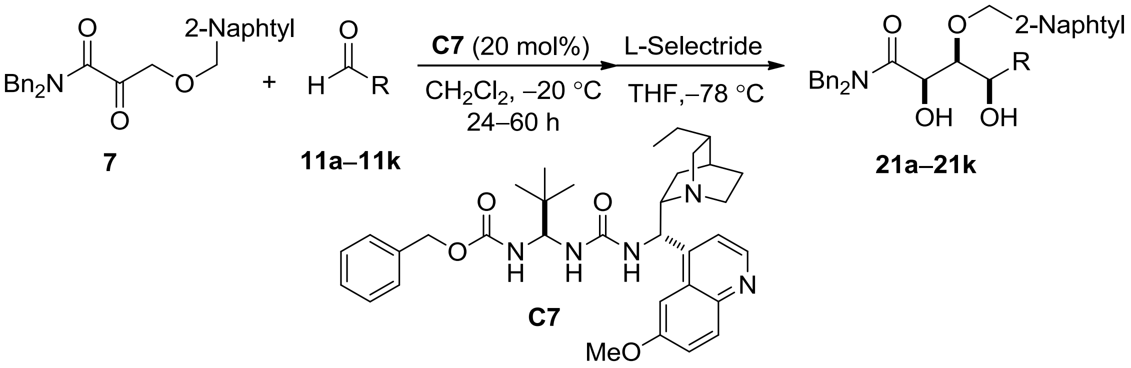
[183] See Scheme 20, page 41.

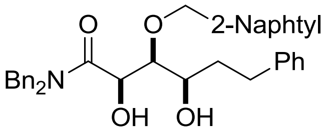
[184] The one-pot version (aldol reaction-reduction) was tried but irreproducible results were obtained.

2.4.4. Reaction scope

With optimized reaction conditions for the catalytic stereoselective direct aldol reaction and subsequent reduction in hand, the scope and limitations of the system were investigated. As our main objective was the development of an asymmetric aldol reaction valid for enolizable aldehydes, the reaction between α-keto amide **7** and a representative selection of aliphatic aldehydes, promoted by catalyst **C7,** was first studied (Table 17). Reactions were generally performed at –20 °C using 3 equivalents of aldehyde, in order to mitigate the characteristic low reactivity of this class of aldehydes, and each crude reaction mixture for aldol adduct **20** was submitted to reduction with L-Selectride. We were very pleased to observe that the reduction proceeded cleanly at –78 °C and with essentially complete stereoselectivity to give the corresponding *syn,syn* 1,2,3-triols **21a**–**21k** in 60–72% yields, upon isolation after two steps. The aldol reaction was carried out at –60 °C for selected aldehydes, such as hydrocinamaldehyde (**11a**) and 2-(benzyloxy)acetaldehyde (**11h**), for which reactivity and solubility were not compromised. As the data in Table 17 show, results were very gratifying since short alkyl chain aldehydes (e.g., propanal), longer chain aldehydes (e.g., hexanal and heptanal), β-branched isovaraldehyde, and even aldehydes bearing side chains with functional groups (e.g., alkene, ester, carbamate and ether) participate satisfactorily, thus giving enantiomeric excesses up to 96%. In contrast, diastereomeric ratios seemed to decrease as the length of the alkyl chain in the aldehyde increased (compare **21b**, **21c**, and **21d**), and with the presence of α-substitution (**21j** and **21k**) while maintaining high enantiomeric excesses. In addition, 3 mmol scale reactions proceeded without any detrimental effect in the reaction outcome (**21f**).

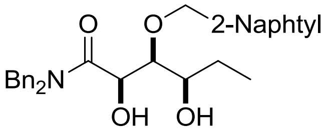
Table 17. Scope of the catalytic aldol reaction of α-keto amide **7** and enolizable aldehydes.[a-e]





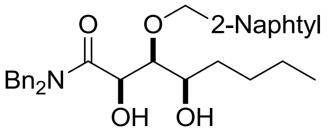
21a

65%, 94:6 *dr*, 92% *ee*[b]



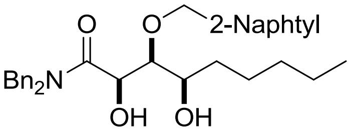
21c

64%, 83:17 *dr*, 92% *ee*



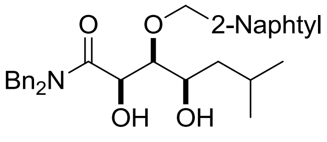
21b

70%, 81:19 *dr*, 92% *ee*
91:9 *dr*, 96% *ee* (–60 °C, 7 d)



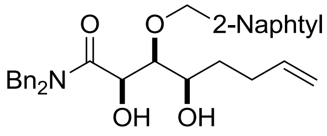
21d

58%, 76:24 *dr*, 92% *ee*



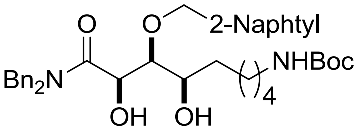
21e

65%, 94:6 *dr*, 96% *ee*



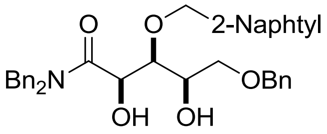
21f

70%, 91:9 *dr*, 94% *ee*[d]



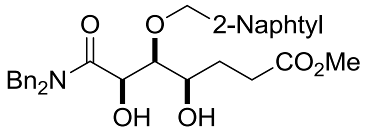
21g

70%, 75:25 *dr*, 96% *ee*[c][e]



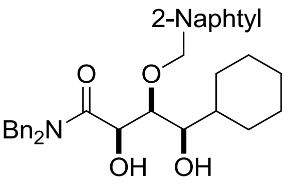
21h

72%, 98:2 *dr*, 95% *ee*[b]



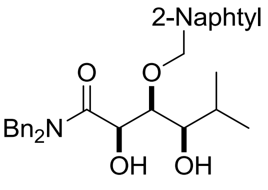
21i

60%, 89:11 *dr*, 90% *ee*[c]



21j

70%, 60:40 *dr*, 90% *ee*[e]

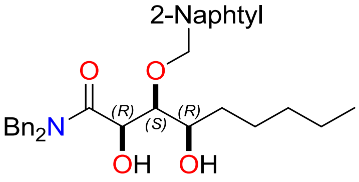


21k

61%, 65:35 *dr*, 90% *ee*[e]

[a] Reaction conditions: **7** (0.6 mmol) and aldehyde (3 equiv., 1.2 mmol) in CH_2Cl_2 (1.5 mL). Yields refer to isolated adducts after two steps. The *dr* values were determined by chiral HPLC and corroborated by ^{1}H-RMN analysis, before reduction. The *ee* values determined for the major diastereomer by chiral HPLC, before reduction. [b] Reactions conducted at –60 °C. [c] For aldehydes **11g** and **11i** the mol ratio of **7**:aldehyde, 1:1.5. [d] Reaction performed at 3 mmol scale. [e] Combined yield of *syn,syn* and *anti,syn* products.

The relative and absolute configurations of the major *syn,syn* enantiomer were determined by X-ray crystallographic analysis of **21d** and a uniform reaction mechanism for the aldol reaction was assumed (Figure 10).



21d

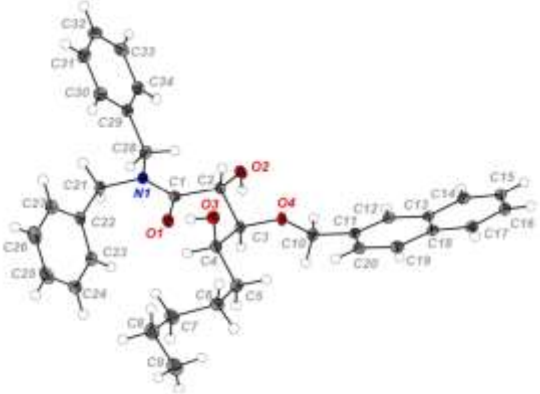
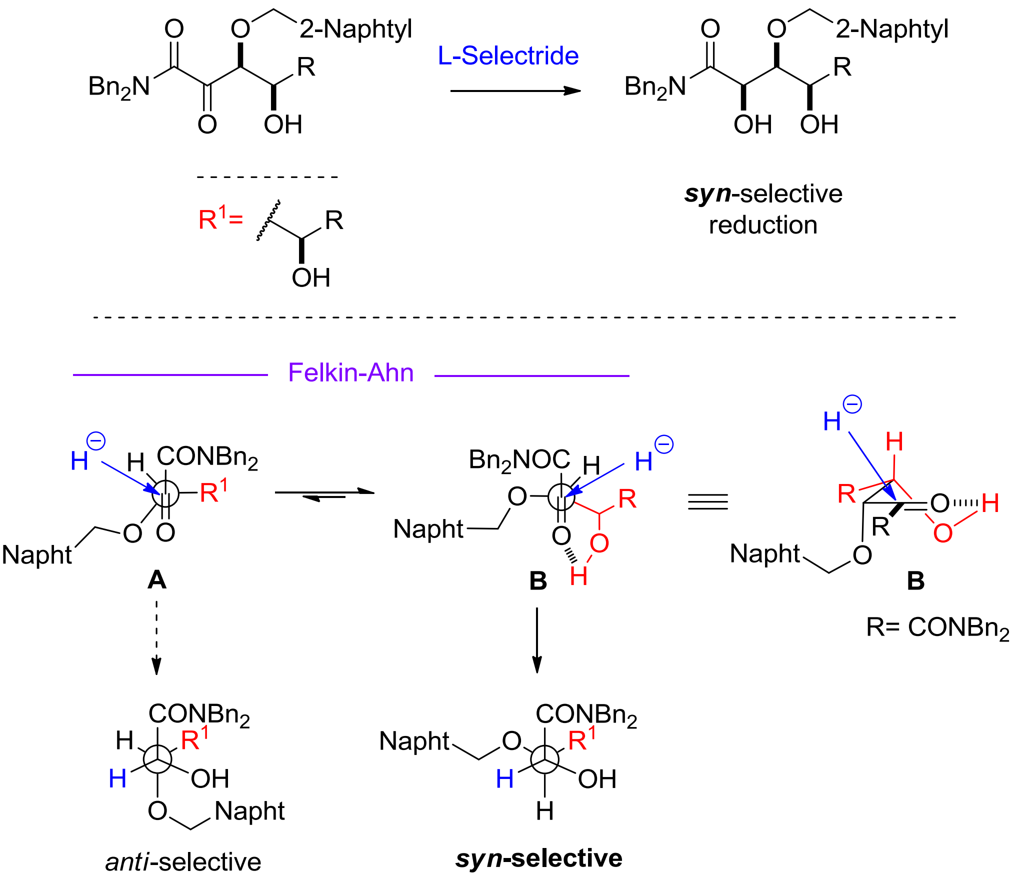


Figure 10. ORTEP diagram for compound **21d**. Thermal ellipsoids shown at 50% probability.

Noteworthy, the highly *syn*-selective reduction of the keto functionality in *syn* aldol adducts using L-Selectride could be explained by the Felkin-Ahn model for internal 1,2-asymmetric induction in nuclephilic additions to carbonyls.[185] As depicted in Scheme 61, the reaction mechanism could proceed through transition states **A** or **B**, in which steric repulsions are minimized and the external hydride (L-Selectride) approaches from the less hindered face. Along with the steric effect, another reason to explain the clear preferential *syn*-selectivity could be an extra stabilizing interaction. Indeed, in conformer **B** an intramolecular hydrogen bond between hydroxyl group and keto functionality could be produced resulting in the observed stereochemical outcome (Scheme 61).

---

[185] Examples on L-Selectride reduction of ketones *via* Felkin-Ahn model: a) H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1986**, *51*, 3769–3771; b) K. C. Nicolau, R. A. Daines, T. K. Chakraborty, Y. Ogaya, *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696; c) A.-M. Faucher, C. Brochu, S. R. Landry, I. Duchesne, S. Hantos, A. Roy, A. Myles, C. Legault, *Tetrahedron Lett.* **1998**, *39*, 8425–8428; d) B. M. Trost, V. S. C. Yeh, *Org. Lett.* **2002**, *4*, 3513–3516.

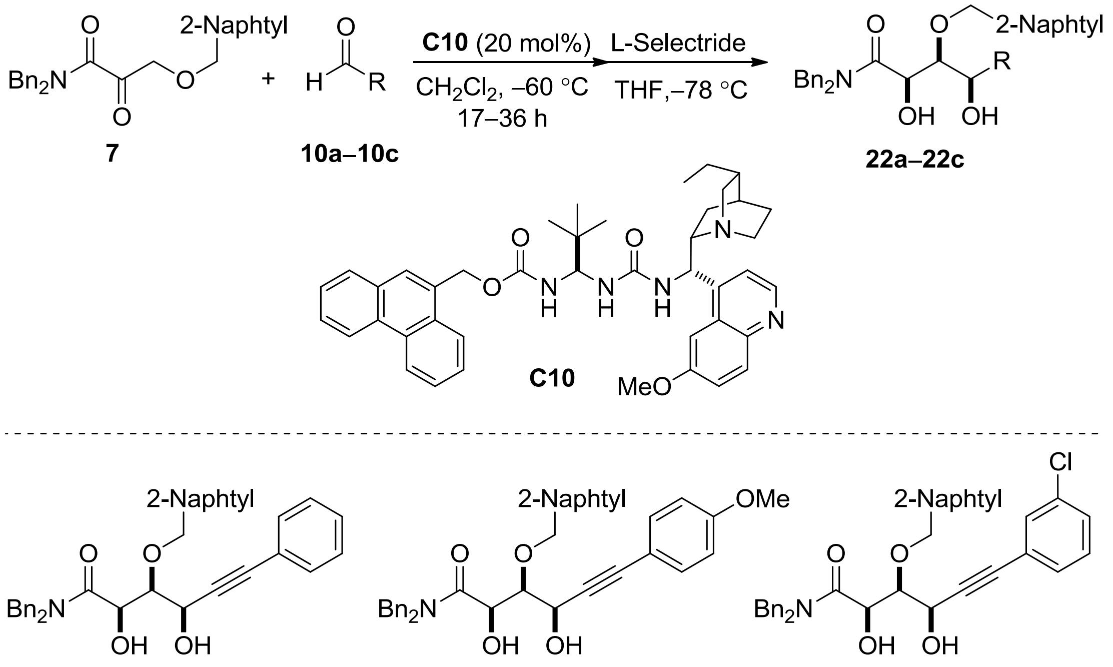


Scheme 61. Plausible model that might explain the observed *syn*-selective reduction.

It should be noted that this study represents the first enantioselective direct cross-aldol reaction of α-keto amides with enolizable aldehydes, mediated by Brønsted base catalysis, capable of providing stereodefined *syn*-aldol adducts without self-condensation, competitive aldehyde enolization, aldol dehydration, and lactonization products, which are usually observed when using α-keto esters as donor partners.

According to the main objective, our goal was to develop a general asymmetric Brønsted base catalyzed direct cross aldol reaction of α-keto amides also extensible to non-enolizable aldehydes. During the initial experiments and optimization of the reactions conditions, 3-phenylpropialdehyde (**10a**) was utilized to search for the most suitable combination of α-keto amide and ureidopeptide-based Brønsted base catalyst; phenanthrenyl-derived catalyst **C10** turned out to be the most appropriate to achieve high stereoselectivities in dichloromethane at –60 °C. Under these reaction conditions, electronically diverse substituted aromatic ynals were tested to produce, after stereoselective reduction of the resulting aldol adducts **19**, the corresponding *syn,syn* propargylic alcohols **22** in good yields and diastereoselectivities though enantiomeric excess were moderate (Table 18).[186]

Table 18. Scope of the catalytic aldol reaction of α-keto amide **7** and propargylic aldehydes.[a]



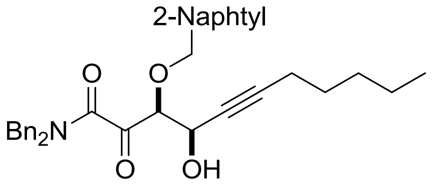
22a	**22b**	**22c**
68%, 85:15 *dr*, 88% *ee*	61%, 85:15 *dr*, 76% *ee*	59%, 90:10 *dr*, 84% *ee*

[a] Reaction conditions: **7** (0.2 mmol) and aldehyde (1.2 eq., 0.24 mmol) in CH_2Cl_2 (0.5 mL). Yields refer to isolated adducts after stereoselective reduction. The *dr* values were determined by chiral HPLC and corroborated by ^{1}H-RMN analysis, before reduction. The *ee* values determined for the major diastereomer by chiral HPLC, before reduction.

---

[186] Propargylic alcohols are attractive compounds resulting from the rich chemistry of the triple bond. For enamine aldol pathways to propargylic alcohols and further uses, see: a) E. Gómez-Bengoa, J. M. García, S. Jiménez, I. Lapuerta, A. Mielgo, J. M. Odriozola, I. Otazo, J. Razkin, I. Urruzuno, S. Vera, M. Oiarbide, C. Palomo, *Chem. Sci.* **2013**, *4*, 3198–3204; b) Y. Hayashi, M. Kojima, Y. Yasui, Y. Kanda, T. Mukaiyama, *ChemCatChem* **2013**, *5*, 2887–2892; c) J. M. García, J. M. Odriozola, J. Razkin, I. Lapuerta, A. Odriozola, I. Urruzuno, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 15543–15554.

Nevertheless, when aliphatic substituted ynals were submitted to the same reaction conditions, a noticeably diminish in enantiomeric excesses was observed. For instance, 2-octynal (**10d**) produced the corresponding aldol adduct **19d** with a diastereomeric ratio 86:14 and 69% *ee* for the major diastereomer. The crude mixture was not submitted to reduction (Figure 11).



19d

–60 ºC, 36 h, >95% conv.
86:14 *dr*, 68% *ee*

Figure 11. Aldol adduct obtained in the reaction with 2-octynal.

On the other hand, absolute configuration for the adduct **22c** was also determined by X-ray crystallographic analysis, Figure 12, thus confirming a uniform reaction mechanism for the aldol reaction with both aliphatic and propargylic aldehydes.

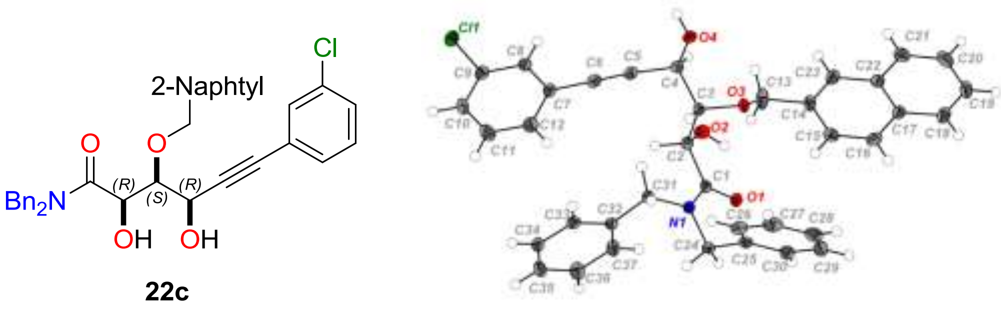
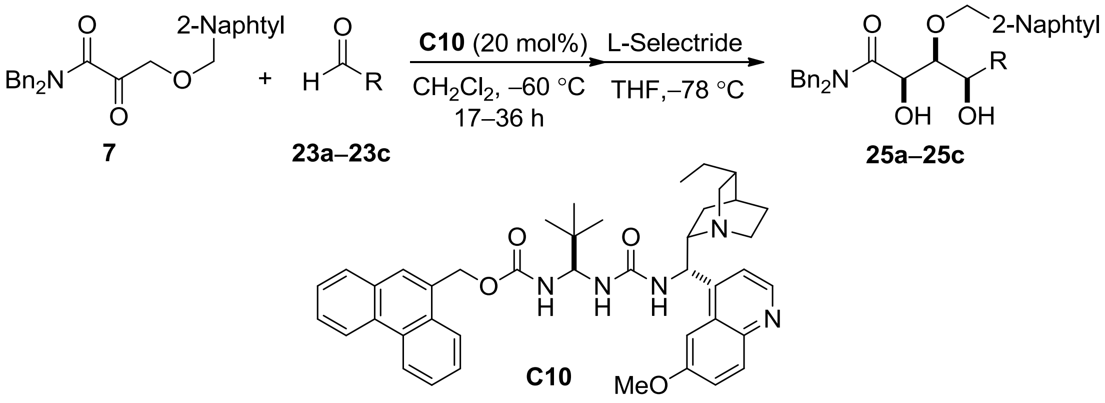


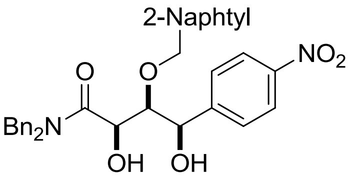
Figure 12. ORTEP diagram of compound **22c**. Thermal ellipsoids shown at 50% probability.

Considering the shortage of effective direct Brønsted base catalyzed asymmetric cross-aldol reactions, we also explored the ability of aromatic aldehydes to participate in the reaction with α-keto amides.

As shown in Table 19, aromatic aldehydes bearing electron withdrawing groups also participate in aldol process under the same aforementioned reaction conditions. After stereoselective reduction of the aldol adducts **24** with L-Selectride, the corresponding s*yn,syn* 1,2,3-triols **25** were isolated in good 54–61% yields and generally good diastereo- (71:29–97:3 *dr*) and enantioselectivities (88–92% *ee*).

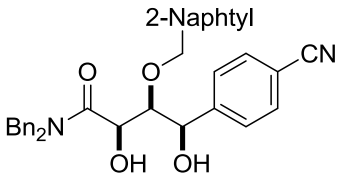
Table 19. Scope of the catalytic aldol reaction of α-keto amide **7** and aromatic aldehydes.[a]


2-Naphtyl
Bn2N
O
O
7
+
H
R
23a–23c
C10 (20 mol%)
CH2Cl2, –60 °C
17–36 h
L-Selectride
THF,–78 °C
2-Naphtyl
R
Bn2N
OH OH
25a–25c
C10
MeO
N
H


2-Naphtyl
NO2
Bn2N
OH OH

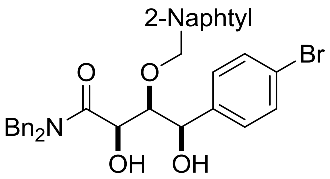
25a

60%, 97:3 *dr*, 92% *ee*


2-Naphtyl
CN
Bn2N
OH OH

25b

61%, 96:4 *dr*, 88% *ee*

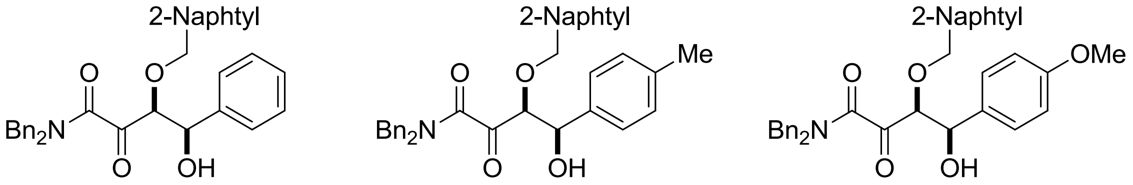

2-Naphtyl
Br
Bn2N
OH OH

25c

54%, 71:29 *dr*, 90% *ee*

[a] Reaction conditions: **7** (0.2 mmol) and aldehyde (1.2 eq., 0.24 mmol) in CH_2Cl_2 (0.5 mL). Yields refer to isolated adducts after stereoselective reduction. The *dr* values were determined by chiral HPLC and corroborated by ^{1}H-RMN analysis, before reduction. The *ee* values determined for the major diastereomer by chiral HPLC, before reduction.

Unfortunately, disappointing results were obtained with electronically diverse aromatic aldehydes. For instance, a diminished reactivity and, more important, absence of diastereoselectivity were observed for benzaldehyde; a trend that was confirmed for other electron rich aromatic aldehydes such as 4-methylbenzaldehyde and 4-methoxybenzaldehyde (Figure 13). Attempts to improve asymmetric induction by using catalyst **C7** led to analogous results. At this point, we have no evidence for the unsatisfactory performance of these aldehydes under the present Brønsted base catalyzed aldol methodology.[187]



24d
–40 ºC, 60 h, >95% conv.
57:43 *dr*, 88/98% *ee*

24e
–20 ºC, 96 h, 85% conv.
65:35 *dr*, 44/88% *ee*

24f
–20 ºC, 60 h, 30% conv.
64:36 *dr*, *ee not determined*

Figure 13. Aldol adducts obtained in the reaction with benzaldehyde, 4-methylbenzaldehyde and 4-methoxybenzaldehyde.

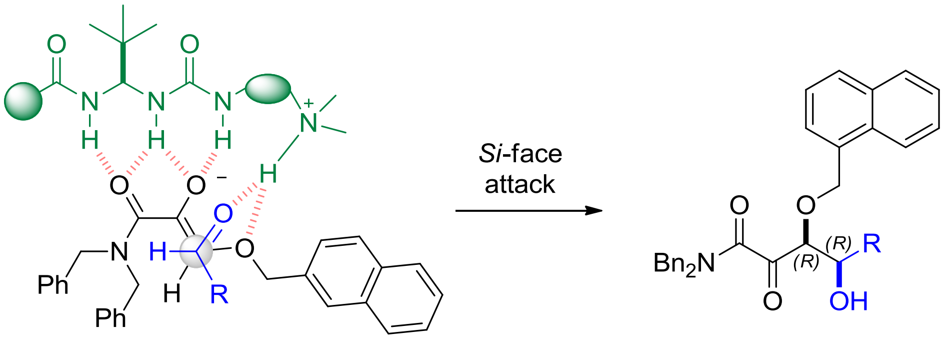
2.4.5. Model proposal

The description of a reaction model which would accurately explain the outcome of the reaction was our next matter of interest. The difference of the results obtained concerning reactivity and selectivity when thioureas and squaramides were employed, made clear that the extra H-bond donor moiety of ureidopeptide-based catalysts was involved in the process.

According to the diastereo- and enantioselectivities observed, the capacity of these catalysts to mainly induced *syn*-configured aldol adducts might be consistent with the generation, as a result of electrostatic and hydrogen-bonding interactions, of a more stabilized *Z* enolate which preferentially approaches de *Si* face of the aldehyde (Figure 14).

---

[187] The use of electron rich aromatic aldehydes is also a limitation in amino-catalyzed asymmetric aldol reactions of α-hydroxy carbonyls (see section 2.2.2.1)

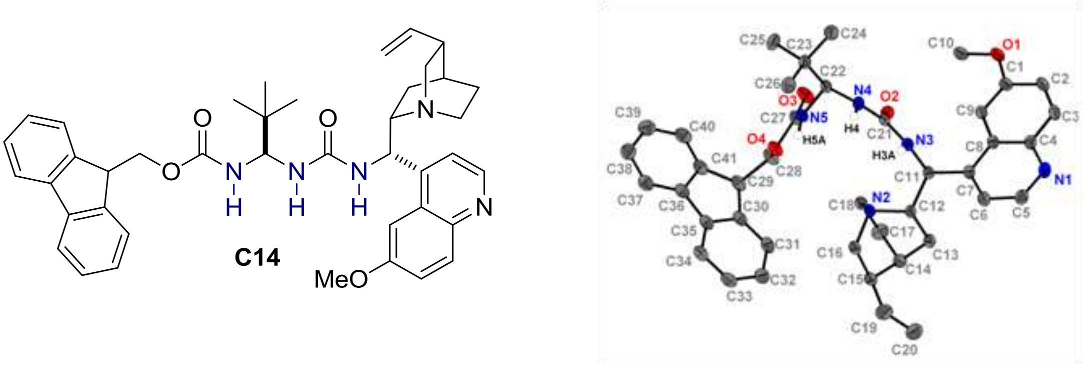


Z-enolate

syn-aldol adducts

Figure 14. Proposed model that might account for the observed preference of *syn*- over *anti*-aldol adduct formation.

In general, these ureidopeptide-based catalysts were solids and Dr. Diosdado from our group obtained a single crystal of **C14** that was analyzed by X-ray. The analysis revealed that, in the solid state, the N-H groups, in the *N,N*-diacyl aminal and the urea moiety, are oriented in the same direction and neither of them display an apparent tendency to develop intramolecular hydrogen bonds (Figure 15). Nevertheless, this orientation could differ in solution. At present, not conclusive results are attained from computational studies due to the flexibility of these rather large catalysts which would require an extensive number of reaction modes to be examined.

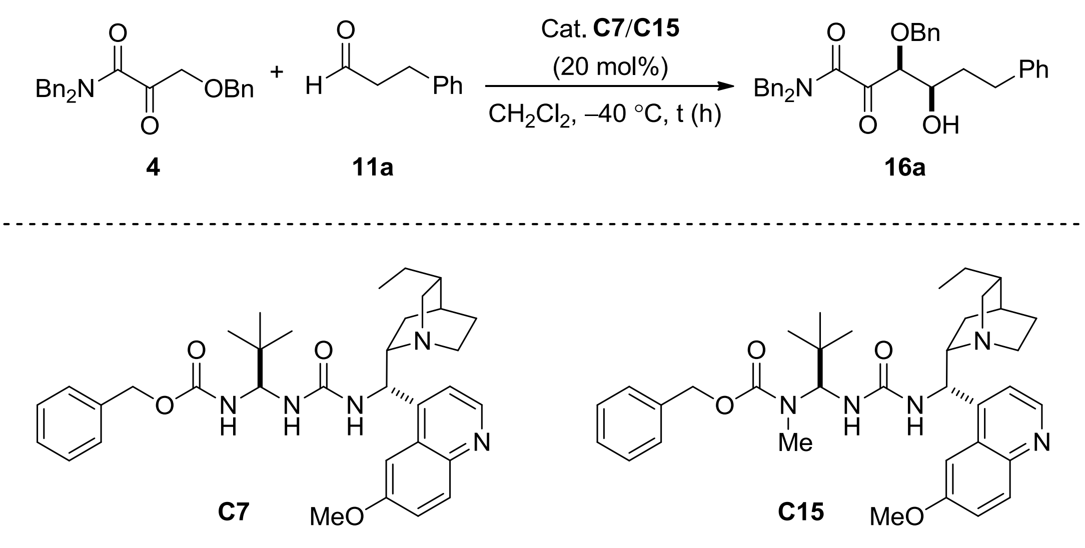


C14

Figure 15. ORTEP diagram of compound **C14**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

Although we still have no evidence of the actual mode of substrate-catalyst interaction,[188] the fact that reaction with common Brønsted base catalysts (see Table 11, page 105) as well as with the *N*-methylated **C15** were significantly less efficient, supports the beneficial effect of multiple H-bonding to boost reactivity (Table 20).

Table 20. Catalysts **C7/C15** comparison for the aldol reaction of α-keto amide **7** and **11a**.



36 h, conv. >95%, 86:14 *dr*, 92% *ee*

48 h, conv. >30%, 75:25 *dr*, 86% *ee*

[a] Reaction conditions: **4** (0.2 mmol) and **11a** (1.2 equiv., 0.24 mmol) in CH_2Cl_2 (0.5 mL).

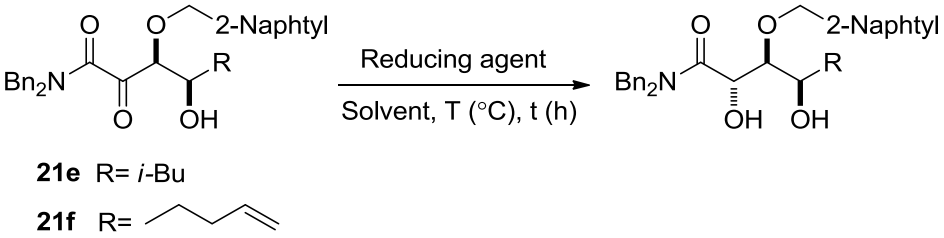
2.4.6. Elaboration of adducts

The chemical manipulation of aldol adducts was briefly investigated to illustrate the synthetic potential of this approach to assembly highly enantiopure polyol fragments. First of all, we were interested in inverting the stereochemical outcome of the L-Selectride reduction of the *syn* aldol adducts to access *anti*,*syn*-triols. For that purpose, several reducing agents were assayed under diverse reaction conditions with aldol adducts **21e** and **21f** following described procedures (Table 21).

---

[188] For transition-state variants promoted by bifunctional thiourea- and squaramide-Brønsted base catalysts under proton-transfer conditions, see: B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631–5639.

Table 21. Screening of reaction conditions for the steroselective carbonyl reduction aldol adducts **21e** and **21f**.



Adduct	Red. agent	Solvent	T (°C)	t (h)	Conv. (%)	***anti,syn:syn,syn***
21f	Red-Al[189]	CH_2Cl_2	–78	2	>95	30:70
21e	$Zn(BH_4)_2$[190]	THF	–20	2	65	60:40
21e	BH_3.THF	THF	–78	2	>95	18:82
21e	$Et_3B/NaBH_4$[191]	THF	–78	2	>95	55:45
21e	$Bu_3B/NaBH_4$[191]	THF	–78	2	>95	70:30

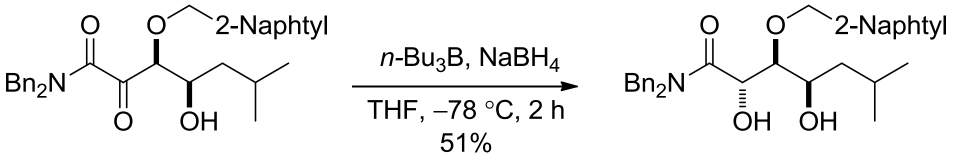
Among all reduction conditions explored, only the system *n*-$Bu_3B/NaBH_4$ was suitable to invert the stereoselectivity of the reduction. These reaction conditions applied to aldol adduct **21e** produced a 70:30 mixture of *anti, syn/syn,syn* diastereomers from which the major *anti,syn* adduct **26e** was isolated in reasonable yield (Scheme 62).

---

[189] N. Bajwa, M. P. Jennings, *J. Org. Chem.* **2008**, *73*, 3638–3641.

[190] See ref. 168, page 89.

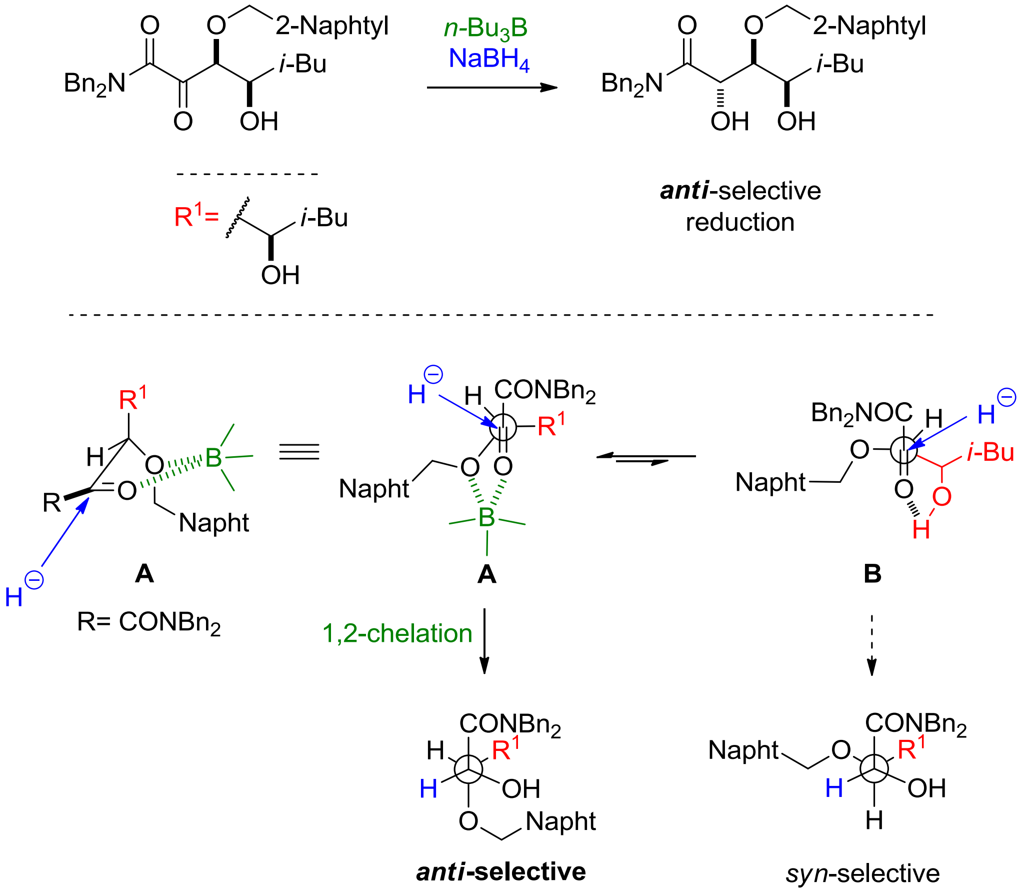
[191] K. Narasaka, F.-C. Pai, *Tetrahedron* **2008**, *40*, 2233–2238.


2-Naphtyl
Bn2N
O
OH
n-Bu3B, NaBH4
THF, −78 °C, 2 h
51%
2-Naphtyl
Bn2N
OH
OH

21e **26e**

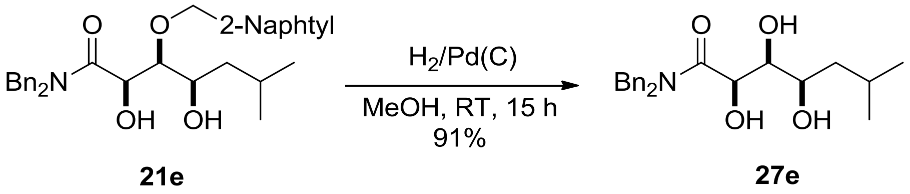
Scheme 62. Stereoselective reduction of aldol adduct **21e**.

The preference for the *anti*-selective reduction could be explained in this case by a chelated-model. The chelating character of the tributylborane could favor a five-member cyclic 1,2-chelated intermediate which would suffer the approach of the extern hydride ($NaBH_4$) from the less hindered face, as shown in Scheme 63.


2-Naphtyl
i-Bu
Bn2N
OH
n-Bu3B
NaBH4
2-Naphtyl
i-Bu
Bn2N
OH
OH
R1=
i-Bu
OH
anti-selective
reduction
R1
H
R
B
Napht
H
A
R= CONBn2
H
H
CONBn2
R1
Napht
B
A
1,2-chelation
Bn2NOC
H
H
i-Bu
Napht
O
H
B
CONBn2
H
R1
H
OH
Napht
anti-selective
Napht
CONBn2
R1
H
OH
H
syn-selective

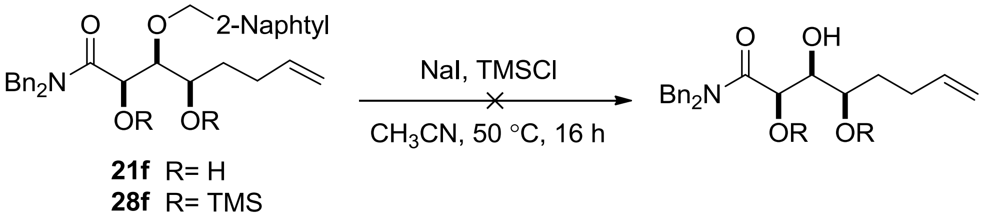
Scheme 63. Tentative model that might explain the observed *anti*-selective reduction.

On the other hand, cleavage of the 2-naphtyl auxiliary *via* catalytic hydrogenation of the *syn*,*syn*-adduct **21e** proceeded efficiently to give the free triol **27e** in excellent 91% yield (Scheme 64).


Bn2N
2-Naphtyl
OH
21e
H2/Pd(C)
MeOH, RT, 15 h
91%
27e

Scheme 64. Preparation of triol **27e**.

Above described conditions for the deprotection of the 2-naphtyl auxiliary, were unsuitable for aldol adducts produced in the reaction with ynals since complete hydrogenation of the triple bond was detected prior deprotection went to completion. Other strategies for the cleavage of related ethers[192] such as treatment with sodium iodide failed; complex mixtures were obtained for either aldol adduct **21f** and protected **28f** (Scheme 65).

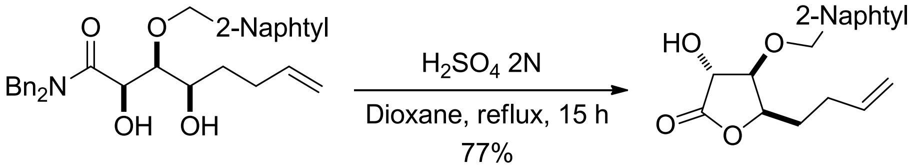

Bn2N
2-Naphtyl
OR
21f R= H
28f R= TMS
NaI, TMSCl
CH3CN, 50 °C, 16 h
OH

Scheme 65. Unsuccessful deprotection of adducts **21f** and **28f**.

---

[192] For the particular deprotection of 2-nahptylyden ethers, see: X. Xu, Y. Qian, L. Yang, W. Hu, *Chem. Commun.* **2011**, *47*, 797–799.

Interestingly, enantiopure lactones were readily available under acidic conditions[193] without loss of any stereogenic center (Scheme 66).

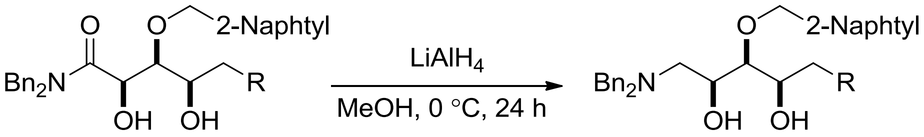


21f

29f

Scheme 66. Acid- promoted lactone formation of adduct **21f**.

Finally, reduction of the amide group using lithium aluminium hydride opened the possibility to access stereodefined aminotriol units which are interesting building blocks for hydroxylated pyrrolidine-containing iminosugars and related products.[194] Aldol adducts **21c** and **21h** produced the corresponding aminotriols **30c** and **30h**, respectively, in reasonable yields under standard reaction conditions (Scheme 67).



21c R= Me
21h R= OBn

30c R= Me, 68%
30h R= OBn, 72%

Scheme 67. Reduction of the amide group in aldol adducts **21c** and **21h**.

---

[193] Adapted from: E. Reyes, L. Carrillo, J. L. Vicario, D. Badía, *Lett. Org. Chem.* **2004**, *1*, 331–334.

[194] B. L. Stocker, E. M. Dangerfield, A. L. Win-Mason, G. W. Haslett, M. S. M. Timmer, *Eur. J. Org. Chem.* **2010**, 1615–1637.

CHAPTER 3

Bifunctional Brønsted base catalyzed asymmetric direct Mannich-reaction of β-alkoxy-α-keto amides

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3. Bifunctional Brønsted base catalyzed asymmetric Mannich-reaction of β-alkoxy-α-keto amides

3.1. Asymmetric Mannich reaction

The asymmetric Mannich-type reaction[195] is one of the most powerful methods for the construction of chiral nitrogen containing molecules.[196] In general, it consists of the reaction between an enolizable carbonyl unit, an aldehyde and an amine component to produce an enantioenriched β-amino carbonyl compound (Mannich base) with up to two new stereogenic centers. It is generally assumed that the aldehyde and the amine condensate to form an imine (or an iminium salt) which subsequently suffers the nucleophilic attack of the enol resulting from the carbonyl unit (Scheme 68).

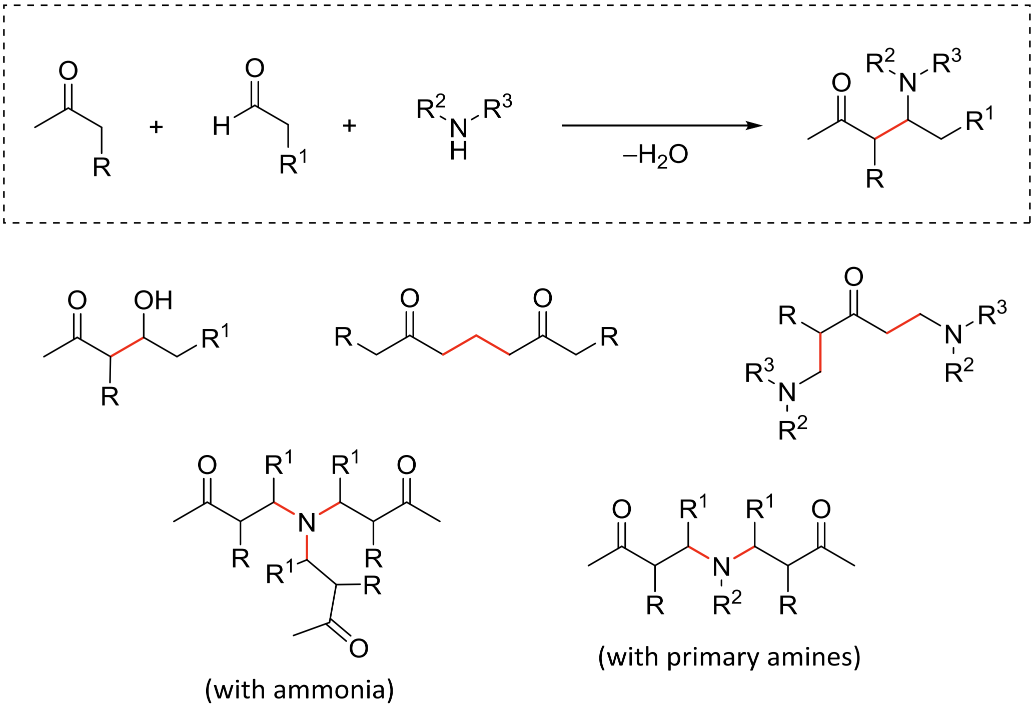
The classical intermolecular reaction, first developed by Carl Mannich,[197] presents a number of serious disadvantages. Indeed, due to the drastic reaction conditions as well as the long reaction times usually required, many side-products are normally obtained (Scheme 68). For instance, compounds derived from the homo-aldol reaction and bis-ketones, by deamination of the Mannich adducts, among others. Also, when ammonia or primary amines are employed, all the H atoms on the nitrogen can be replaced.

---

[195] For general reviews on the asymmetric Mannich reaction, see: a) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; b) M. Syamala, *Org. Prep. Procc. Int.* **2009**, *41*, 1–68; c) S. J. Greco, V. Lacerda, R. Bezerra dos Santos, *Aldrichimica Acta* **2011**, *44*, 15–23; d) P. S. Bhadury, B.-A. Song, *Curr. Org. Chem.* **2010**, *14*, 1989–2006; d) C. Xiao-Hua, G. Hui, X. Bing, *Eur. J. Chem.* **2012**, *3*, 258–266.

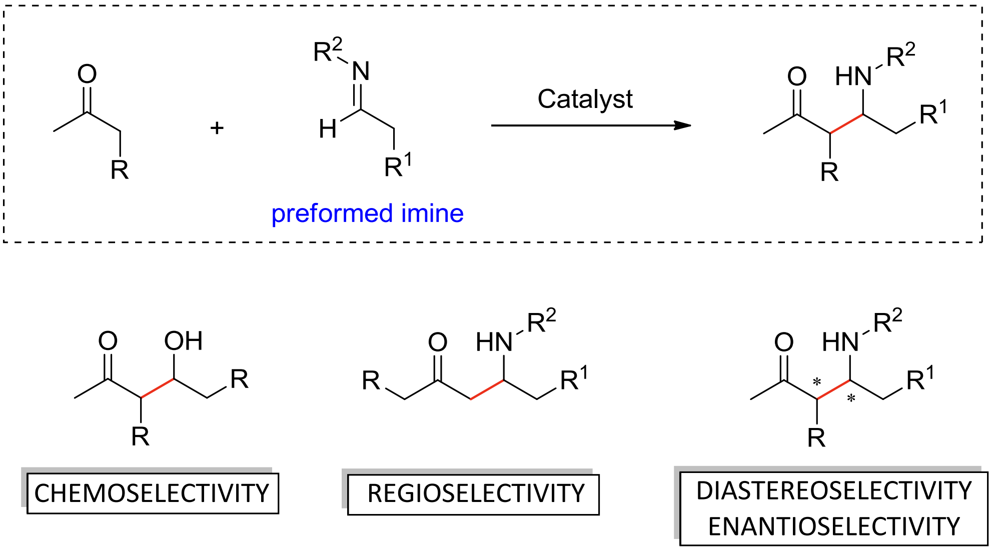
[196] a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99,* 1069–1094; b) S. Hata, K. Tomioka, *Tetrahedron* **2007**, *63*, 8514–8520; c) S. G. Subramaniapillai, *J. Chem. Sci.* **2013**, *125,* 467–482.

[197] C. Mannich, W. Krosche, *Arch. Pharm.* **1912**, *250*, 647–667.



Scheme 68. Three-component Mannich-reaction and some representative side-products derived from the drastic reaction conditions.

Due to the attractive nature of the β-amino carbonyl compounds, there have been many attempts to avoid the severe drawbacks of the classical procedure. Modern versions of the Mannich reaction usually allow a simpler entry into Mannich bases through the use of preformed nucleophiles (enolates, enol ethers, and enamines) and electrophiles (e.g. iminium salts or imines). In the particular case of the catalytic asymmetric Mannich reaction, key to success has been the use of preformed electrophiles. The formation of the azomethine component in a previous step guarantees a higher concentration of the electrophile, leading to lower reaction temperatures and much shorter reaction times; conditions that undoubtedly have helped to address selectivity issues in the catalytic asymmetric version (Scheme 69).


O
R
+
R2
N
H
R1
preformed imine
Catalyst
O
HN
R2
R1
R
O
OH
R
R
CHEMOSELECTIVITY
O
HN
R2
R
R1
REGIOSELECTIVITY
O
HN
R2
R1
R
DIASTEREOSELECTIVITY
ENANTIOSELECTIVITY

Scheme 69. Typical selectivity challenges in two component asymmetric Mannich-type reactions.

Among the most representative electrophilic substrates are iminium salts,[198] imines[199] and/or their precursors, such as aminals,[200] *N,O*-acetals[201] or α-amidosulfones[202] from which the corresponding imines can be generated *in situ* (Figure 16).

---

[198] Selected examples on the use of iminium salts in diastereoselective Mannich-type reactions: a) M. Arend, N. Risch, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2639–2640; b) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352; c) P. Wu, T. E. Nielsen, *Chem. Rev.* **2017**, DOI: 10.1021/acs.chemrev.6b00806. Selected reviews on the use of *N*-acyl iminium salts in diastereoselective transformations: d) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368; e) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541. Selected review on the use of *N*-acyl iminium salts in organocatalytic enantioselective transformations: f) Y. S. Lee, M. M. Alam, R. S. Keri, *Chem. Asian J.* **2013**, *8*, 2906–2919.

[199] Selected examples on the use of *N*-sulfinyl imines in asymmetric Mannich reactions: a) G. Q. Lin, M. H. Xu, Y. W. Zhong, X. W. Sun, *Acc. Chem. Res.* **2008**, *41*, 831–840; b) F. Ferreira, C. Botuha, F. Chemla, A. Perez-Luna, *Chem. Soc. Rev.* **2009**, *38*, 1162–1186; c) C. Xie, W. Sha, Y. Zhu, J. Han, V. A. Soloshonok, *RSC Adv.* **2017**, *7*, 5679–5683. Selected examples on the use of *N*-sulfonyl imines in asymmetric catalytic Mannich reactions: d) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588–9589; e) E. Gómez-Bengoa, M. Maestro, A. Mielgo, I. Otazo, C. Palomo, I. Velilla, *Chem. Eur. J.* **2010**, *16*, 5333–5342; f) J. Guang, S. Rout, M. Bihani, A. J. Larson, H. D. Arman, J. C.-G. Zhao, *Org. Lett.* **2016**, *18*, 2648–2651. Selected examples on the use of *N*-phosphinoyl imines in asymmetric catalytic Mannich reactions: g) S. M. Weinreb, R. K. Orr, *Synthesis* **2005**, 1205–1227; h) Z. Sun, K. Weidner, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2015**, *21*, 17574–17577. Selected reviews on the use of *N*-acyl and *N*-carbamoyl imines in asymmetric catalytic transformations: i) M. Petrini, E. Torregiani, *Synthesis* **2007**, 159–186; j) J. Vesely, R. Rios, *Chem. Soc. Rev.* **2014**, *43*,

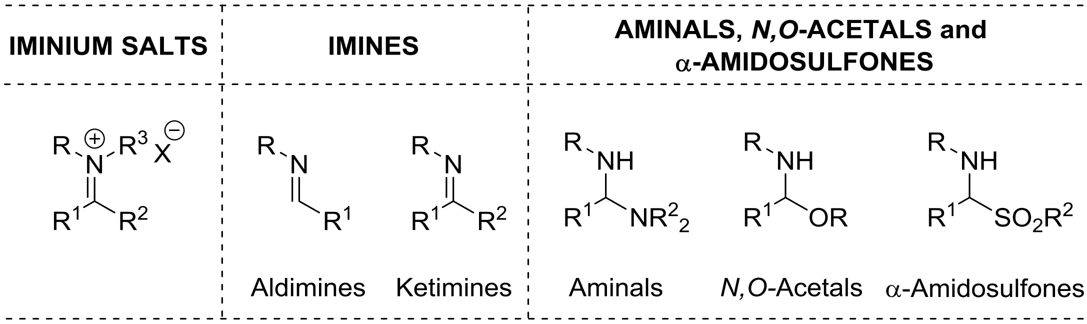


Figure 16. Representative electrophiles in the Mannich type reaction.

611–630; k) E. Marcantoni, M. Petrini, *Adv. Synth. Catal.* **2016**, *358*, 3657–3682. Selected examples on the use of *N-p*-methoxyphenyl imines in asymmetric catalytic Mannich reactions: l) A. Córdova, *Synlett* **2003**, 1651–1654; m) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680; n) L. Q. Li, M. Y. Han, M. X. Xiao, Z. X. Xie, *Synlett* **2011**, 477–480. Selected examples on the use of ethyl glyoxylate imines in asymmetric catalytic Mannich reactions: o) A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; p) S.-I. Watanabe, A. Córdova, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2002**, *4*, 4519–4522; q) M. Marigo, A. Kjaesgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367; r) W. Wang, J. Wang, H. Li, *Synthesis* **2010**, 1205–1208; s) M. Wasa, R. Y. Liu, S. P. Roche, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, *136*, 12872–12875.

[200] Selected examples on the use of *N*-Boc aminals in asymmetric catalytic Mannich-type reactions: a) T. Kano, R. Kobayashi, K. Maruoka, *Angew. Chem. Int. Ed.* **2015**, *54*, 8471–8474; b) T. Yurino, Y. Aota, D. Asakawa, T. Kano, K. Maruoka, *Tetrahedron* **2016**, *72*, 3687–3700. Selected example on the use of *N*-benzotriazol aminals in asymmetric Mannich reactions: c) H. Brice, D. M. Gill, L. Goldie, P.S. Keegan, W. J. Keer, P. H. Svensson, *Chem. Commun.* **2012**, *48*, 4836–4838.

[201] Selected review on the use of *N,O*-acetals in asymmetric catalytic transformations: Y.-Y. Huang, C. Cai, X. Yang, Z.-C. Lv, U. Schneider, *ACS Catal.* **2016**, *6*, 5747–5763.

[202] Selected review on the use of α-amidosulfones in asymmetric catalytic transformations: B. Yin, Y. Zhang, L.-W. Xu, *Synthesis* **2010**, 3583–3595.

Iminium salts are among the most common reagents employed because they are more electrophilic than imines, aminals, and *N*,*O*-acetals. Aminals and *N*,*O*-acetals resemble imines in terms of electrophilicity. They must normally be activated by Lewis acids, in order to react with nucleophiles. Likewise, imines are generally much less electrophilic than the corresponding aldehyde, drawback that can often be overcome by using Lewis or Brønsted acids and the introduction of activating groups at either or both the nitrogen and the iminic carbon (Figure 17). On the other hand, imines derived from enolizable aldehydes have been barely employed due to their inherent instability and tendency to imine/enamine isomerization.[203]

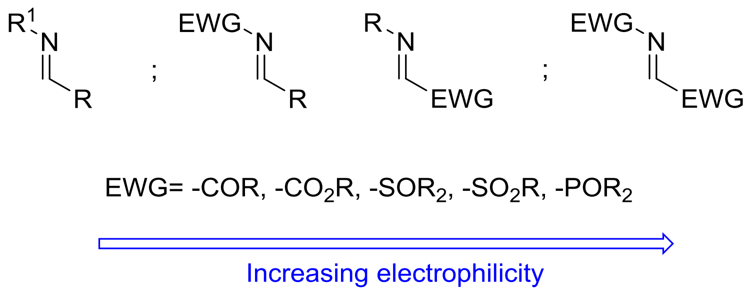

R^1
N
R
;
EWG
N
R
R
N
EWG
;
EWG
N
EWG
EWG= -COR, -CO_2R, -SOR_2, -SO_2R, -POR_2
Increasing electrophilicity

Figure 17. Representative imines used in the Mannich reaction classified according to reactivity.

Since Mannich first report, many strategies have been developed towards efficient direct catalytic asymmetric reactions. Figure 18 summarizes the pioneer contributions from the initial indirect versions, using stoichiometric chiral inductors, to the posterior more efficient direct catalytic versions.

---

[203] For more information about the tendency of aliphatic imines to decomposition or isomerization, see: a) A. R. Katritzky, P. A. Harris, *Tetrahedron* **1990**, *46*, 987–996; b) E. G. Nolen, A. Allocco, A. M. Broody, A. Zuppa, *Tetrahedron Lett.* **1991**, *32*, 73–74; c) C. M. Marson, A. Fallah, *Chem. Commun.* **1998**, 83–84.

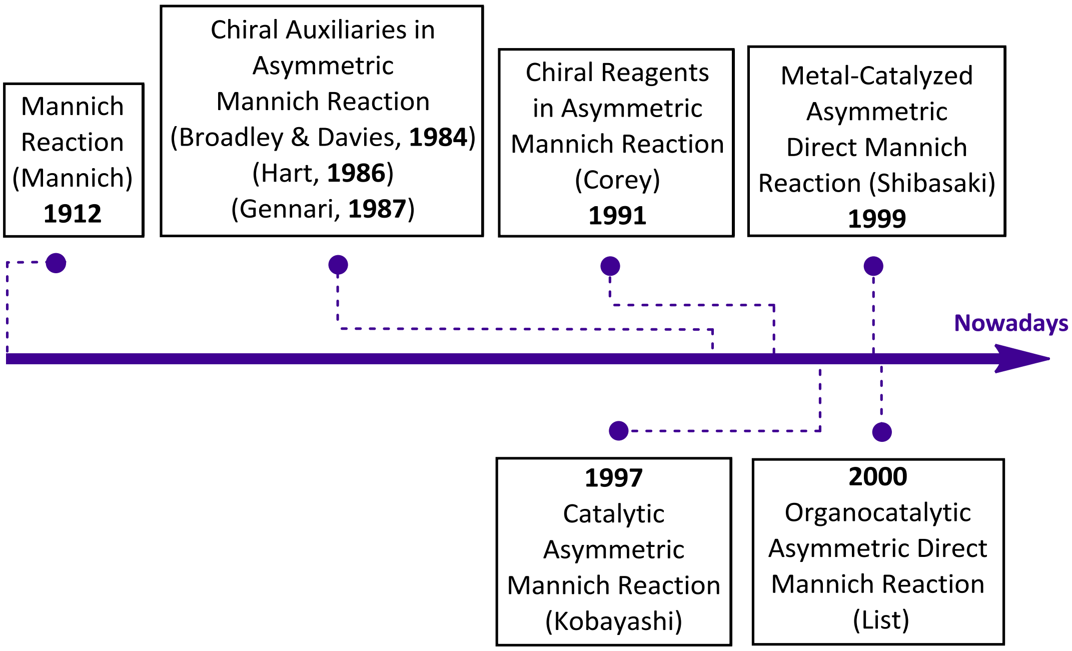
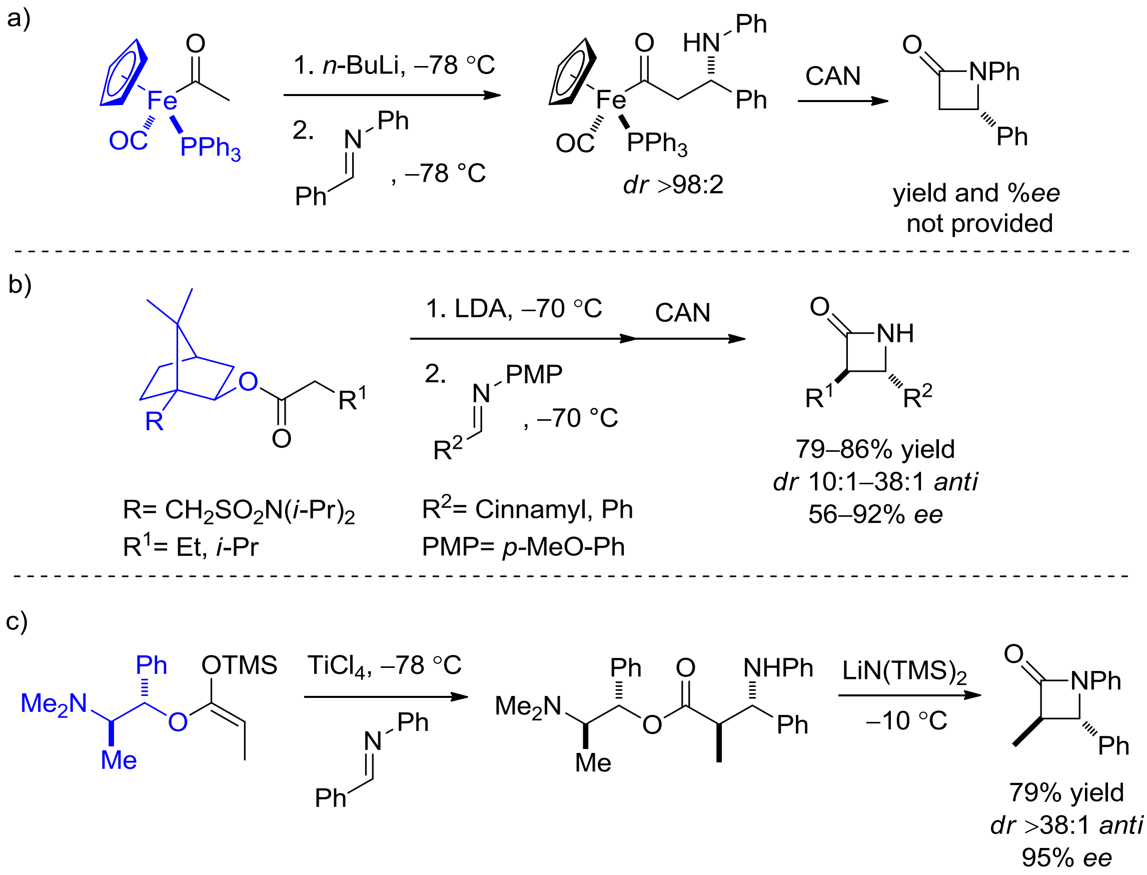

Mannich Reaction (Mannich) 1912
Chiral Auxiliaries in Asymmetric Mannich Reaction (Broadley & Davies, 1984) (Hart, 1986) (Gennari, 1987)
Chiral Reagents in Asymmetric Mannich Reaction (Corey) 1991
Metal-Catalyzed Asymmetric Direct Mannich Reaction (Shibasaki) 1999
Nowadays
1997 Catalytic Asymmetric Mannich Reaction (Kobayashi)
2000 Organocatalytic Asymmetric Direct Mannich Reaction (List)

Figure 18. Chronologically ordered historic landmarks regarding selectivity in the asymmetric Mannich-type reaction.

In 1980 decade, the first examples of the asymmetric Mannich reaction were reported, based on the use of chiral auxiliaries. In Scheme 70 are depicted some representative approaches in which chiral enolates bearing inductors of different nature reacted with the corresponding imine to produce, after cyclization, enantioenriched β-lactams.[204, 205, 206]


a)
Fe
OC
PPh3
O
1. n-BuLi, –78 °C
2. N Ph, Ph, –78 °C
HN Ph
Ph
dr >98:2
CAN
NPh
yield and %ee not provided
b)
R
O
R1
1. LDA, –70 °C
2. N PMP, R2, –70 °C
CAN
NH
R1
R2
79–86% yield
dr 10:1–38:1 anti
56–92% ee
R= CH2SO2N(i-Pr)2
R1= Et, i-Pr
R2= Cinnamyl, Ph
PMP= p-MeO-Ph
c)
Me2N
Ph
OTMS
Me
TiCl4, –78 °C
N Ph, Ph
NHPh
LiN(TMS)2
–10 °C
NPh
79% yield
dr >38:1 anti
95% ee

Scheme 70. Some representative stereoselective Mannich approaches using different chiral auxiliaries: a) chiral iron complex.[204] b) chiral sultam.[205] c) (1*S*,2*R*)-*N*-methylephedrine.[206]

In the early 1990s, Corey and co-workers described the first diastereo- and enantioselective Mannich type reaction by using chiral boron enolates.[207] The reaction of *S*-*tert*-butyl thiopropionate with *N*-benzyl and *N*-allyl imines promoted by the chiral *S,S*-diazaborolidine, shown in Scheme 71, produced the corresponding β-amino thioesters with excellent diastereo- and enantiocontrol.

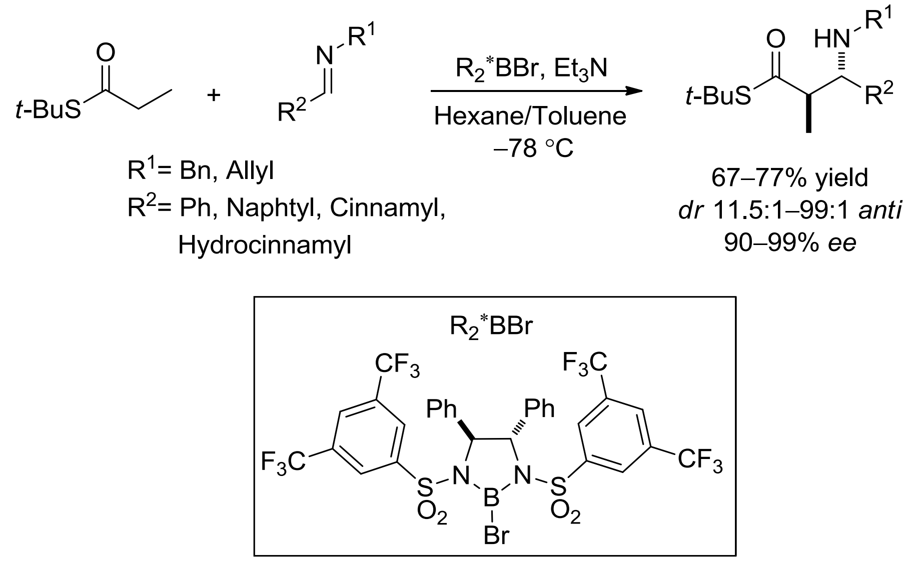
---

[204] Asymmetric Mannich reaction using a chiral iron complex: K. Broadley, S. G. Davies, *Tetrahedron Lett.* **1984**, *25*, 1743–1744.

[205] Asymmetric Mannich reaction using a chiral sultam: D. J. Hart, C.-S. Lee, *J. Am. Chem. Soc.* **1986**, *108*, 6054–6056.

[206] Asymmetric Mannich reaction using chiral *N*-methylephedrine: C. Gennari, I. Venturini, G. Gilson, G. Shimperna, *Tetrahedron Lett.* **1987**, *28*, 227–230.

[207] E. J. Corey, C. P. Decicco, R. C. Newbold, *Tetrahedron Lett.* **1991**, *32*, 5287–5290.


t-BuS
O
+
N
R1
R2
R2*BBr, Et3N
Hexane/Toluene
−78 °C
O
HN
R1
t-BuS
R2
R1= Bn, Allyl
R2= Ph, Naphtyl, Cinnamyl,
Hydrocinnamyl
67–77% yield
dr 11.5:1–99:1 anti
90–99% ee
R2*BBr
CF3
F3C
Ph
Ph
F3C
CF3
S
N
B
N
S
O2
O2
Br

Scheme 71. Corey´s pioneer enantioselective Mannich reaction using chiral boron enolates.

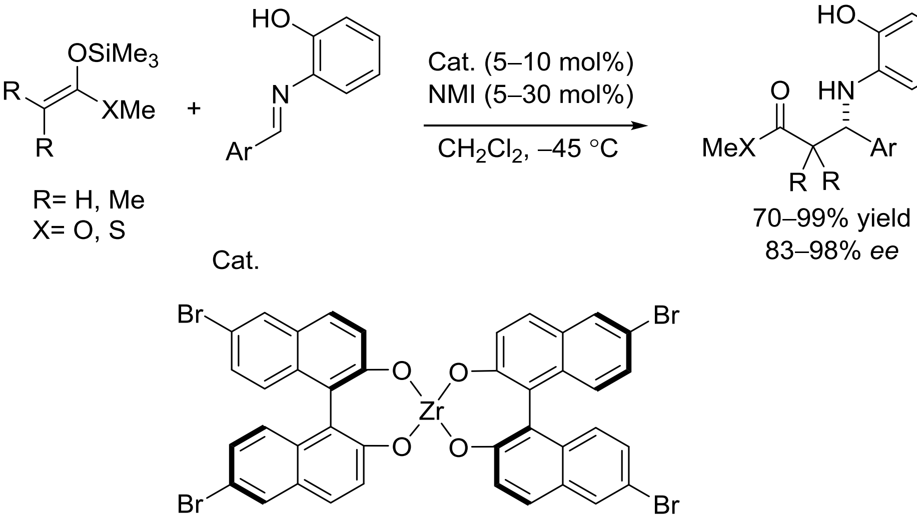
In the following years, many were the efficient methodologies that followed these pioneering works; most of them founded on the use of chiral auxiliaries and strategies that had previously succeeded in the cross-aldol reaction.[208]

On the other hand, Kobayashi and co-workers described in 1997, the first catalytic enantioselective Mannich-reaction between silyl enol ethers and aryl aldimines promoted by a chiral zirconium catalyst derived from (*R*)-BINOL (Scheme 72).[209]

---

[208] For selected examples on the use of chiral sultams, see: a) W. Oppolzer, *Pure & Appl. Chem.* **1988**, *60*, 39–48; b) W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* **1989**, *308*, 5603–5606. For an example on the use of chiral oxazolidinones, see: b) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. For an example on the use of chiral 1,3-dithiane-1-oxide, see: c) P. C. B. Page, S. M. Allin, E. W. Collington, R. A. E. Carr, *J. Org. Chem.* **1993**, *58*, 6902–6904. For an example on the use of chiral hydrazones, see: d) D. Enders, D. Ward, J. Adam, G. Raabe, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 981–984. For an example on the use of camphor, see: e) C. Palomo, M. Oiarbide, M. C. González-Rego, A. K. Sharma, J. M. Garcia, C. Landa, A. Linden, *Angew. Chem. Int. Ed.* **2000**, *39*, 1063–1065.

[209] H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154.



Scheme 72. Kobasashi´s first catalytic asymmetric Mannich reaction. (NMI: *N*-methylimidazole)

The authors assumed a catalytic cycle in which the catalyst coordinates the aldimine to form the zirconium complex (Scheme 73). The silyl enolate attacks the aldimine to produce an intermediate, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with the regeneration of the catalyst. The final Mannich adduct, shown in Scheme 73, is obtained after acidic treatment.

This work inspired many subsequent catalytic non-direct examples in which either the metal center, the chiral ligands or the nature of the catalyst were modified.[210]

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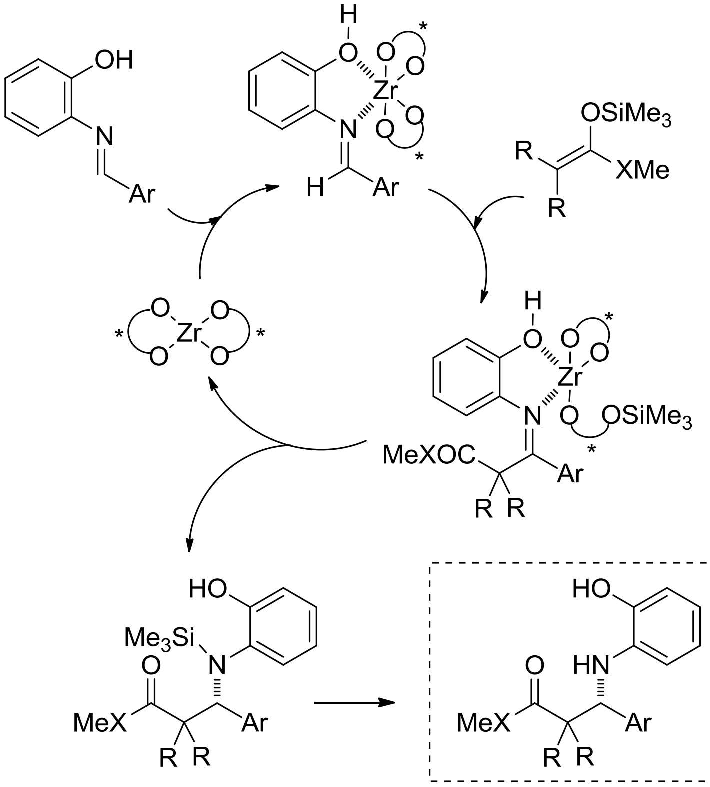
[210] For examples on the use of metal catalysis, see: a) D. Ferraris, B. Young, T. Dudding, T. Lecta, *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549; b) A. Fuji, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458; c) S. Nakamura, H. Sano, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Tetrahedron Lett.* **2007**, *48*, 5565–5568. For an example on the use of organocatalysis, see: d) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965. For an example on the use of ternary complex ligand, see: d) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061.



Scheme 73. Assumed catalytic cycle.

3.2. Catalytic asymmetric direct Mannich reaction

The first catalytic asymmetric Mannich-type reactions, with unmodified ketones, were introduced by Shibasaki[211] and List[212] under metal- and organo-catalysis, respectively. Since these pioneering works, several asymmetric Mannich type reactions have been described under either metallic catalysis or organocatalysis employing either preformed imines or the three-component variant (ketone, aldehyde and amine).[213]

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[211] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307–310.

[212] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

[213] Selected reviews on metallocatalyzed approaches: a) M. Shibasaki, S. Matsunaga, *J. Organomet. Chem.* **2006**, *691*, 2089–2100; b) U. Kazmaier, *Angew. Chem Int. Ed.* **2009**, *48*, 5790–5792; c) M. Hatano, K. Ishihara, *Synthesis* **2010**, 3785–3801; d) T. Tsubogo, Y. Yamashita, S. Kobayashi, *Top. Organomet. Chem.* **2013**, *45*, 243–270; e) B. Karimi, D. Enders, E. Jafari, *Synthesis* **2013**, 2769–2812. Selected reviews on organocatalyzed approaches: f) W. Notz, F.

In this context, a brief summary of the catalytic asymmetric Mannich reaction is described below, with special emphasis for early works and methodologies in which 1,2-amino alcohols are produced due to their prevalence as precursors for the synthesis of chiral aminopolyol fragments.[214] Reports employing 1,2-dicarbonyl compounds as pronucleophiles in the Mannich reaction have been previously commented in Chapter 1.[215]

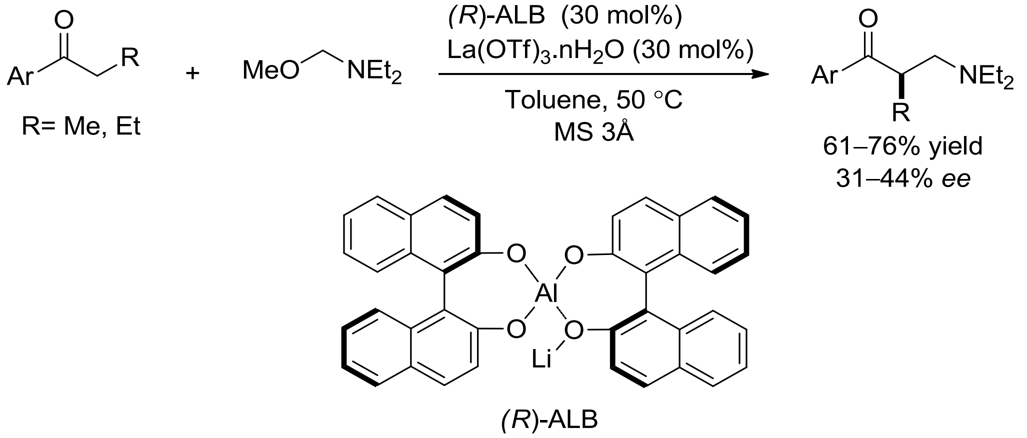
3.2.1. Metallocatalyzed Mannich reaction

The first direct catalytic asymmetric Mannich-type reaction was described by Shibasaki and co-workers using unmodified ketones with aminomethyl ether.[211] As shown in Scheme 74, the reaction was promoted by cooperative catalysis of a heterobimetallic chiral complex AlLibis(binapthtoxide) (ALB) and La(OTf)$_3$. Although the enantiomeric excesses obtained were moderate, the present work constituted the basis for the rapid growth experienced by the field.

Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624–9634; g) M. M. B. Marques, *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; h) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797–5815; i) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41; j) X.-H. Cai, B. Xie, *Arkivoc* **2013**, *1*, 264–293; k) Y. Hayashi, *J. Synth. Org. Chem.* **2014**, *72*, 1228–1238. Selected reviews on both metallocatalyzed and organocatalyzed approaches: l) A. Córdova, *Acc. Chem. Rev.* **2004**, *37*, 102–112; m) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *387*, 1940–1948; n) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626–2704.

[214] For selected examples on the synthesis of several aminopolyol structures with therapeutic potential, see: a) T. A. Y. Génisson, M. Baltas, *Org. Biomol. Chem.* **2005**, *3*, 2626–2631; b) A. Banchet-Cadeddu, E. Hénon, M. Dauchez, J.-H. Renault, F. Monneaux, A. Haudrechy, *Org. Biomol. Chem.* **2011**, *9*, 3080–3104; c) E. D. D. Calder, A. M. Zaed, A. Sutherland, *J. Org. Chem.* **2013**, *78*, 7223–7233.

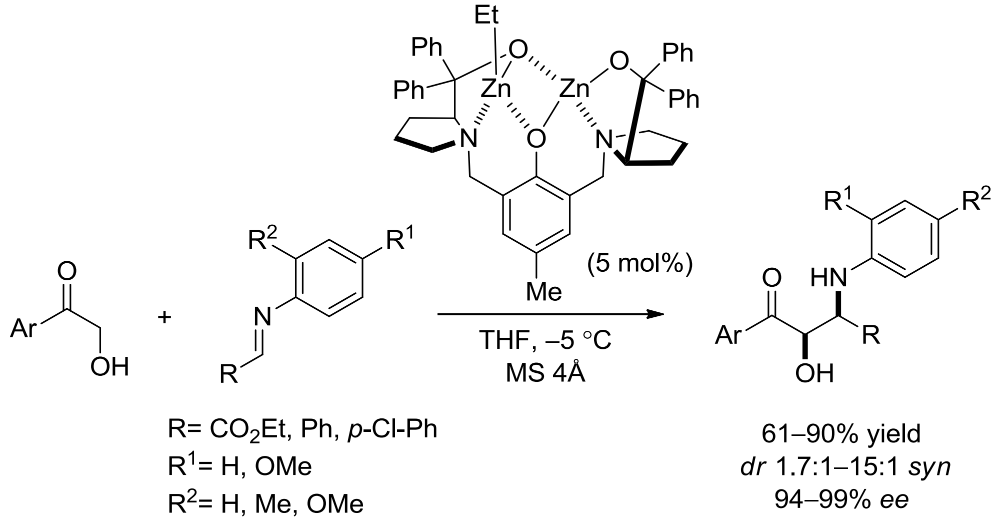
[215] Chapter 1, pages 40–43.



(R)-ALB (30 mol%)
La(OTf)3.nH2O (30 mol%)
Toluene, 50 °C
MS 3Å
Ar
R
MeO
NEt2
R= Me, Et
61–76% yield
31–44% ee
Al
Li
(R)-ALB

Scheme 74. First enantioselective metallocatalyzed direct Mannich reaction.

Several years later, the groups of Trost and Shibasaki simultaneously reported the first approaches for the preparation of vicinal amino alcohols through a Mannich type reaction. On one hand, Trost and coworkers documented the *syn*-selective addition of α-hydroxyacetophenone to glyoxalate imines and aldimines in the presence of the dinuclear Zn ProPhenol catalyst.[216] As illustrated in Scheme 75, *syn*-1,2-amino alcohols were produced in excellent yield and stereoselectivities.



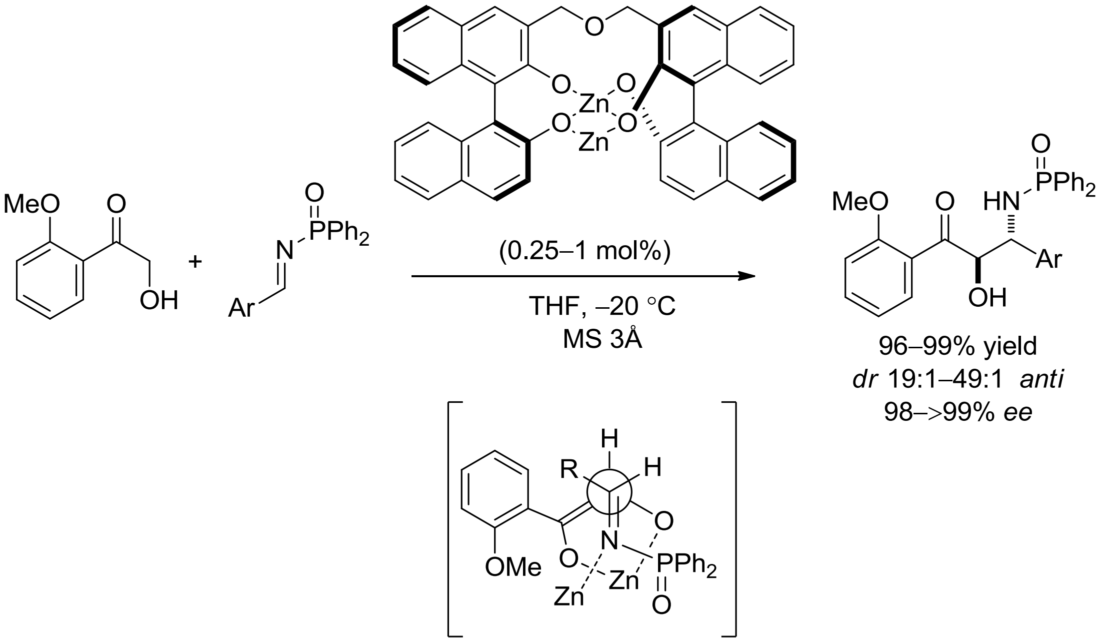
Et
Ph
Zn
Me
(5 mol%)
THF, –5 °C
MS 4Å
Ar
OH
R
R1
R2
HN
R= CO2Et, Ph, p-Cl-Ph
R1= H, OMe
R2= H, Me, OMe
61–90% yield
dr 1.7:1–15:1 syn
94–99% ee

Scheme 75. Dinuclear zinc ProPhenol-catalyzed Mannich reaction for the synthesis of *syn*-1,2-amino alcohols.

---

[216] B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

On the other hand, Shibasaki took advantage of the Et_2Zn/linked-BINOL complex, previously described for the aldol reaction, to promote the reaction between α-hydroxy-2-methoxyacetophenone and diphenylphosphinoyl *N*-protected imines to afford the corresponding *anti*-Mannich adducts in excellent yield and stereoselectivity (Scheme 76).[217] The authors speculated that the *anti*-selectivity would be provoked by the bulky diphenylphosphinoyl group in the imine nitrogen. To avoid steric repulsion, the Mannich-type reaction could proceed *via* the transition state shown in Scheme 76.


MeO
O
OH
+
O
PPh2
N
Ar
O
Zn
O
O
Zn
O
(0.25–1 mol%)
THF, –20 °C
MS 3Å
MeO
O
HN
PPh2
Ar
OH
96–99% yield
dr 19:1–49:1 anti
98–>99% ee
H
R
H
O
N
OMe
O
Zn
PPh2
Zn
O

Scheme 76. *Anti*-selective Mannich reaction catalyzed by dinuclear zinc-BINOL complex and proposed transition state model.

Short after, the same group developed a protocol which enabled the access to both *anti*- and *syn*-1,2-amino alcohols in good diastereomeric ratios, yields and excellent enantiomeric excesses using the same dinuclear Zn (*S*)-

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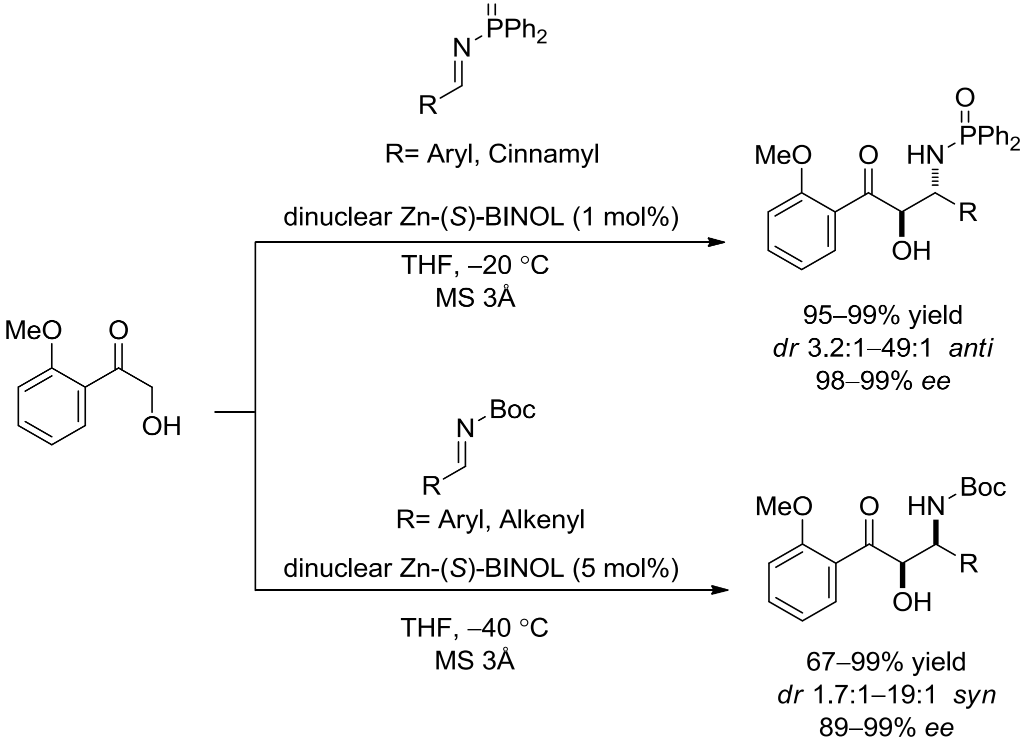
[217] S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713.

BINOL catalyst, by choosing the proper protective groups on imine nitrogen (Scheme 77).[218, 219]


R= Aryl, Cinnamyl
dinuclear Zn-(*S*)-BINOL (1 mol%)
THF, –20 °C
MS 3Å
95–99% yield
dr 3.2:1–49:1 *anti*
98–99% *ee*
R= Aryl, Alkenyl
dinuclear Zn-(*S*)-BINOL (5 mol%)
THF, –40 °C
MS 3Å
67–99% yield
dr 1.7:1–19:1 *syn*
89–99% *ee*

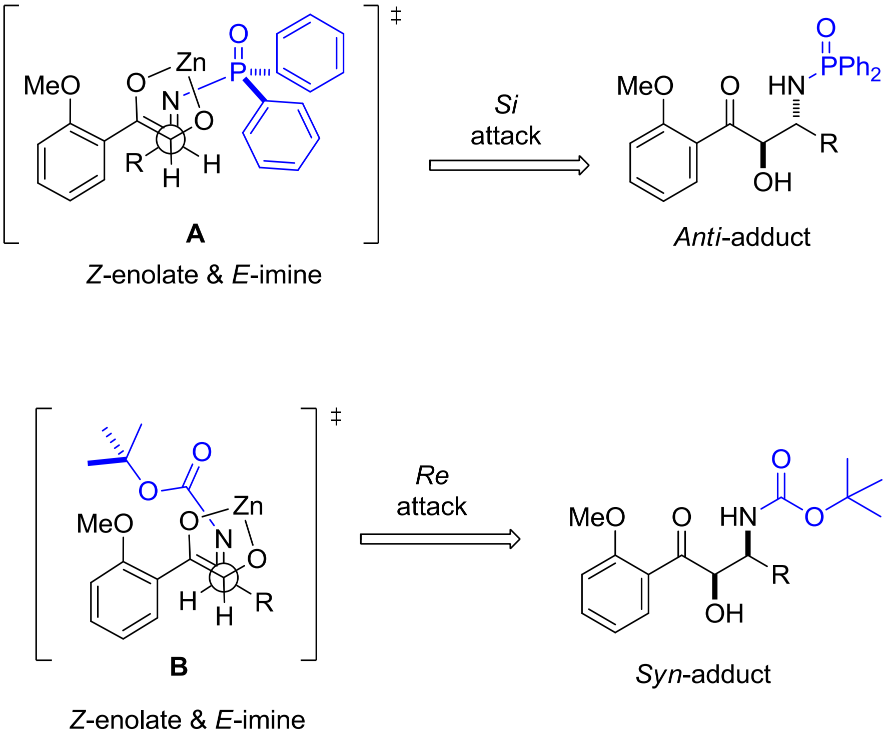
Scheme 77. Dinuclear zinc-BINOL complex catalyzed *anti*- and *syn*-Mannich type reaction.

The authors explained the stereochemical course of the reaction by the preferential formation of the more stabilized *Z*-enolate which approached the less hindered face of the *N*-protected imine: the approach in the presence of the bulky diphenylphosphinoyl group would proceed *via* transition state **A**, as previously proposed, whereas for the less bulky *N*-Boc protected imine would advance *via* transition state **B** (Scheme 78).

---

[218] S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785.

[219] For an additional approach to the *anti*-selective Mannich reaction employing a non-C_2-symmetric catalyst, see: T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 3470–3474.


‡
MeO
O
Zn
O
P
N
O
R
H
H
A
Z-enolate & E-imine
Si
attack
MeO
O
HN
PPh2
O
R
OH
Anti-adduct
‡
O
O
MeO
O
Zn
N
O
H
H
R
B
Z-enolate & E-imine
Re
attack
MeO
O
HN
O
O
R
OH
Syn-adduct

Scheme 78. Proposed transition states models to rationalize the observed selectivities.

Two years later, Trost and co-workers corroborated the influence of the imine protection on the *anti*/*syn* selectivity using their dinuclear Zn ProPhenol catalyst. The catalyst efficiently promoted the Mannich reaction of alkyl and α-branched aliphatic *N*-protected imines, although the stereochemical induction was slightly inferior (Scheme 79).[220]

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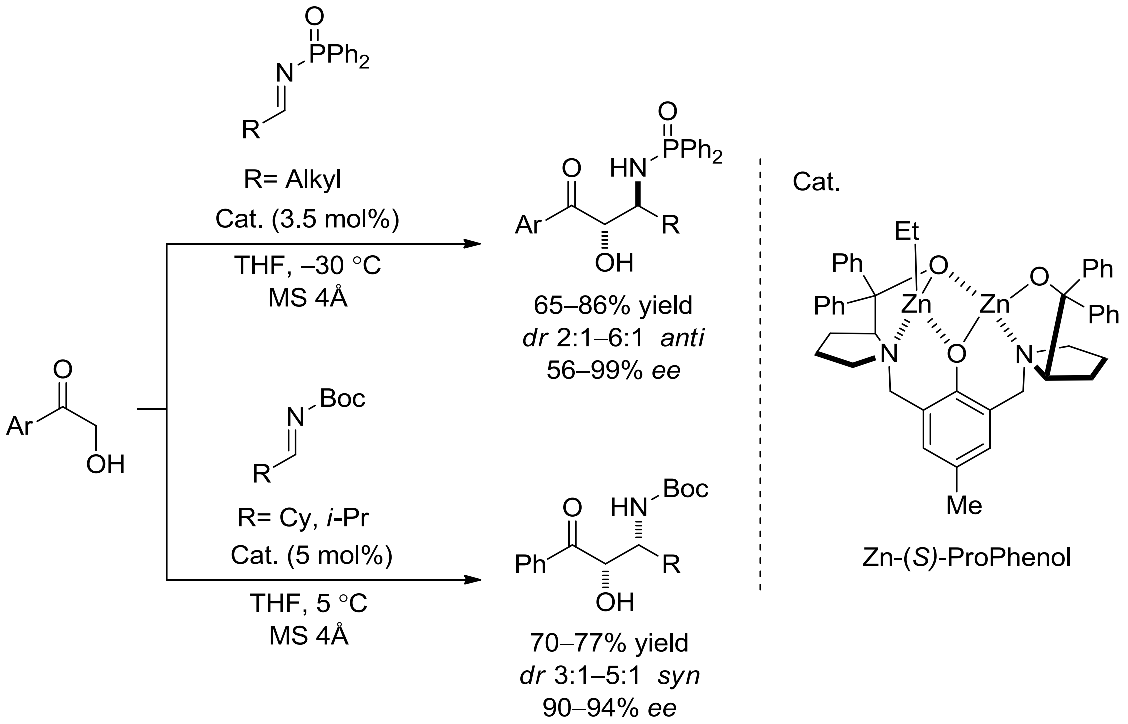
[220] B. M. Trost, J. Jaratjaroonphong, V. Reutrakul, *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779.


R= Alkyl
Cat. (3.5 mol%)
THF, –30 °C
MS 4Å
65–86% yield
dr 2:1–6:1 anti
56–99% ee
R= Cy, i-Pr
Cat. (5 mol%)
THF, 5 °C
MS 4Å
70–77% yield
dr 3:1–5:1 syn
90–94% ee
Cat.
Zn-(S)-ProPhenol

Scheme 79. Dinuclear Zn ProPhenol catalyzed *anti*- and *syn*-Mannich type reaction of aliphatic imines.

Also, Shibasaki´s group described a *syn*-Mannich type reaction between *N*-diphenylphosphinoyl imines derived from aliphatic aldehydes promoted by Et_2Zn/linked-BINOL complex.[221] The reaction proceeded with high chemical efficiency (up to 92%) and enantioselectivity (up to 99% *ee*) but with poorer control over diastereoselectivity (*dr* 1:1.9–4.5:1 *anti*/*syn*). The authors said that the diastereoselectivity was strongly dependent on the imine alkyl substituent and attributed the low diastereocontrol to the low facial selectivity of imines.

Towards the search of more versatile pronucleophiles, Shibasaki and co-workers demonstrated the effectiveness of *N*-(2-hydroxyacetyl)pyrrole as an ester-equivalent donor in the Mannich type reaction assisted by a chiral complex composed of In(O*i*-Pr)$_3$ and (*S*,*S*)-linked BINOL.[222] The reaction of *o*-

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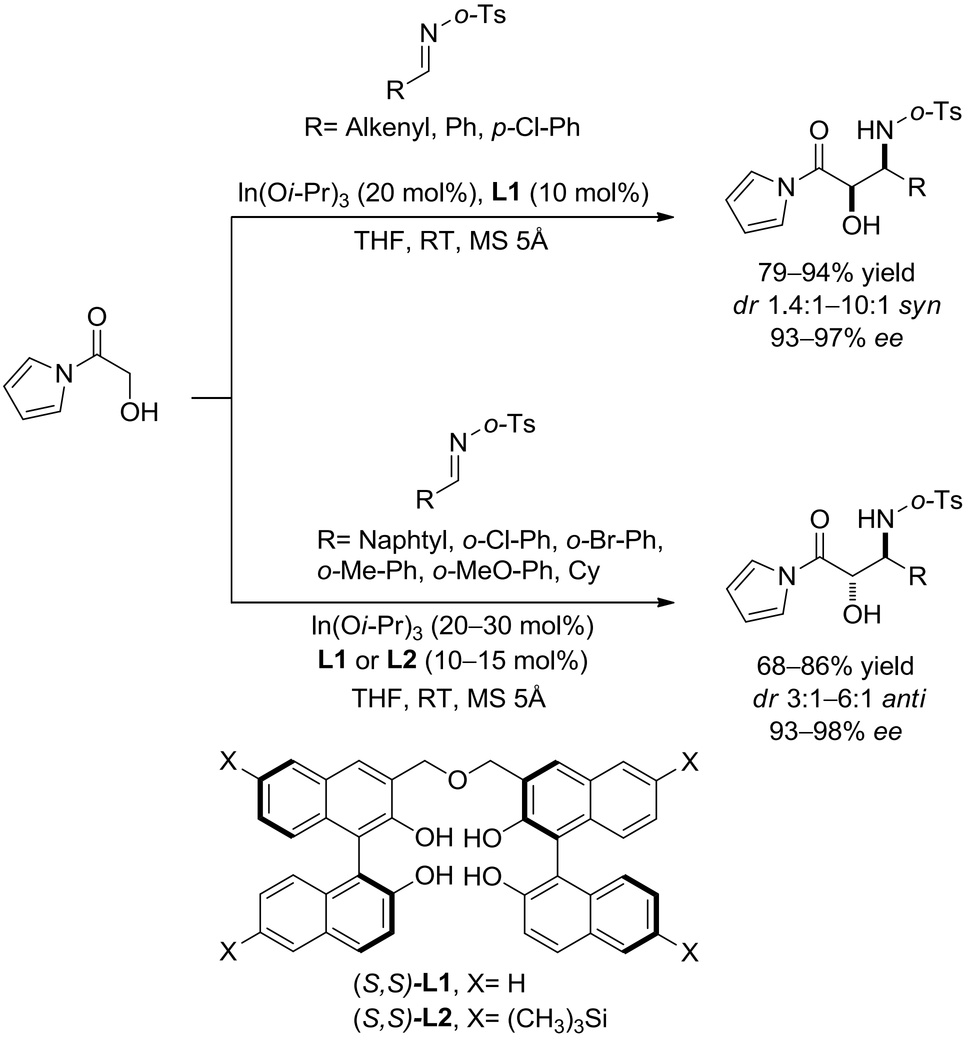
[221] A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 3985–3989.

[222] S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368.

tosyl *N*-protected imines underwent with opposite diastereoselection depending on the R substituent of the imine (Scheme 80). Alkenyl and aryl imines led to *syn*-β-amino-α-hydroxy adducts with variable diastereomeric ratios and excellent enantioselectivity. In contrast, more hindered *o*-substituted imines rendered *anti*-adducts with also variable diastereoselectivity and excellent enantiocontrol. In all examples, the *syn* and the *anti* adducts were obtained with the same absolute configuration at the β position (*S*), implying that selection of the imine enantioface is identical.


N
o-Ts
R
R= Alkenyl, Ph, p-Cl-Ph
In(Oi-Pr)3 (20 mol%), L1 (10 mol%)
THF, RT, MS 5Å
O
HN
o-Ts
N
R
OH
79–94% yield
dr 1.4:1–10:1 syn
93–97% ee
O
N
OH
N
o-Ts
R
R= Naphtyl, o-Cl-Ph, o-Br-Ph,
o-Me-Ph, o-MeO-Ph, Cy
In(Oi-Pr)3 (20–30 mol%)
L1 or L2 (10–15 mol%)
THF, RT, MS 5Å
O
HN
o-Ts
N
R
OH
68–86% yield
dr 3:1–6:1 anti
93–98% ee
X
O
X
OH HO
OH HO
X
X
(S,S)-L1, X= H
(S,S)-L2, X= (CH3)3Si

Scheme 80. *Syn*- and *anti*-Mannich catalyzed reactions of *N*-(2-hydroxyacetyl)pyrrole.

In Figure 19, proposed models for the acyclic *anti*-periplanar transition state are shown, based on that steric repulsion between imine substituents R and the pyrrol ring in the indium enolate would become more predominant for non-planar or *ortho*-substituted aromatic rings, thus following model **B**.

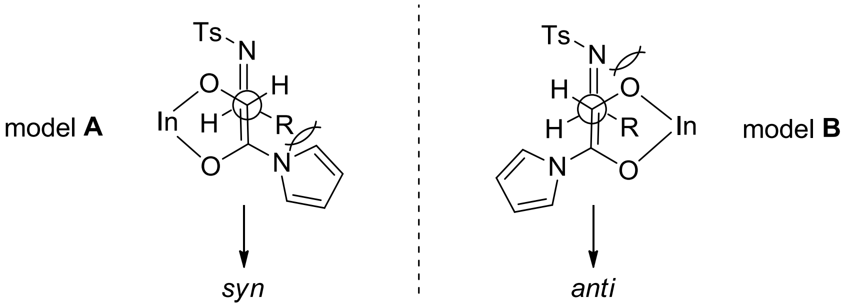


Figure 19. Postulated transition-state model.

More recently, in 2012, Wang and co-workers addressed the access to α-alkyl-α-hydroxy β-amino acid derivatives by using 5*H*-oxazol-4-ones as donor templates (Scheme 81).[223] Excellent enantioselectivities and diastereoselectivities were achieved with a series of *N*-diphenylphosphinoyl protected imines and the catalytic system formed by dinuclear Zn (*S*)-ProPhenol complex and diethyl phosphoramidate, exhibited excellent yield, diastereo- and enantioselectivities. To the best of our knowledge, this example represents the only approach to vicinal amino alcohols bearing a tetrasubstituted stereogenic center.

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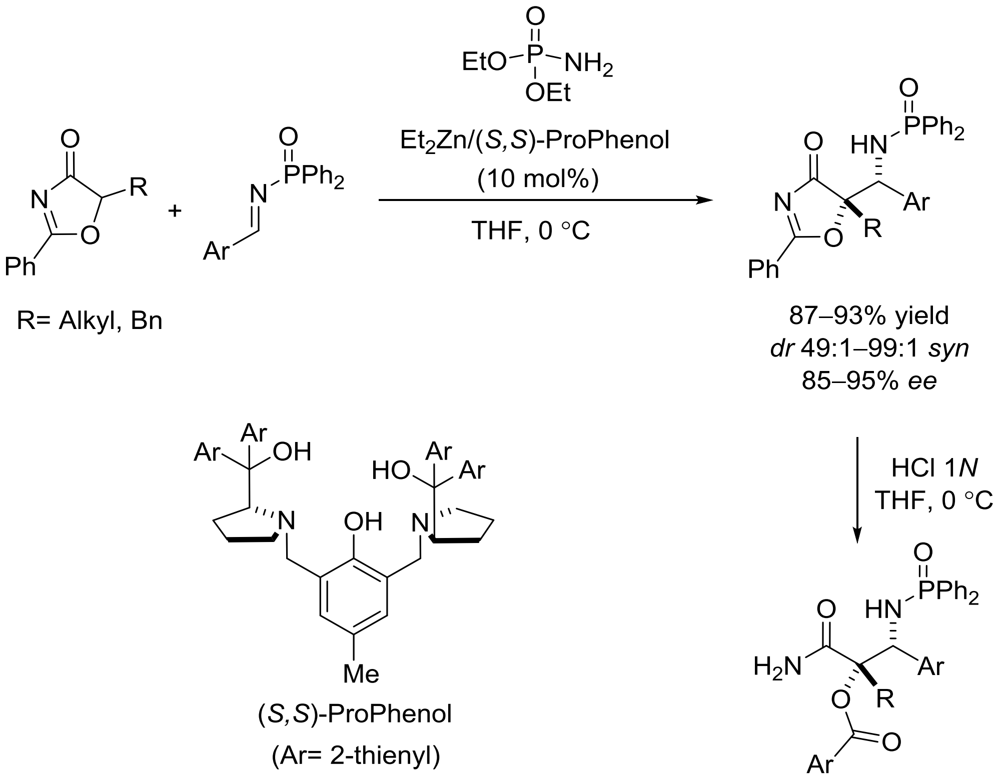
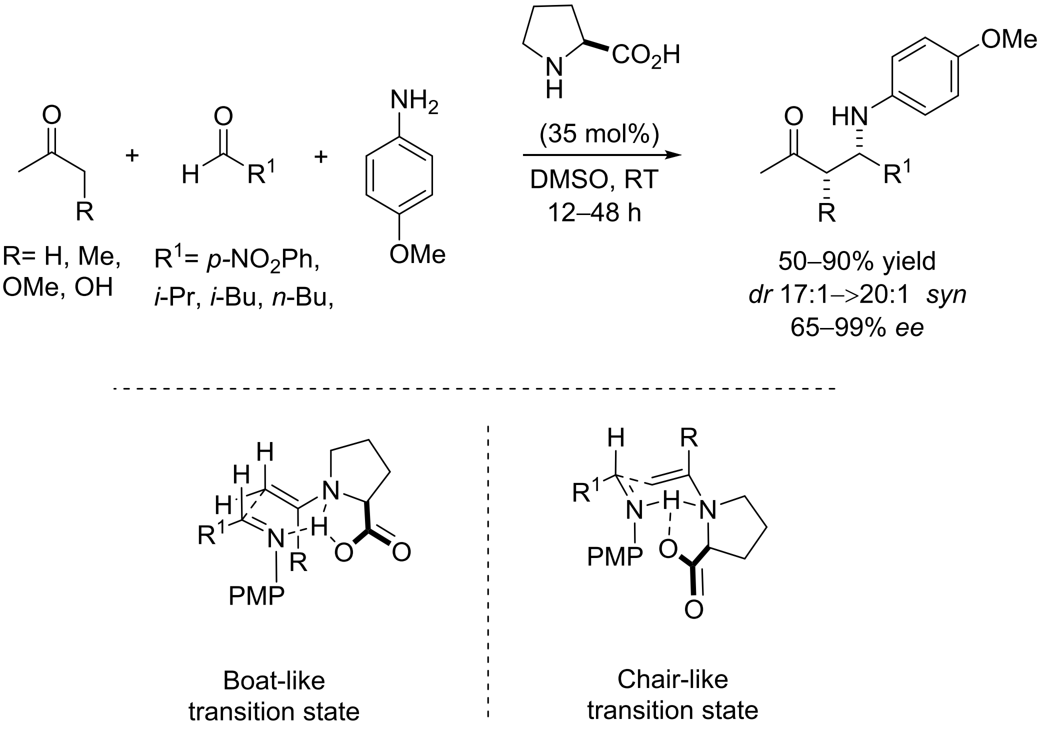
[223] D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem.Int. Ed.* **2012**, *51*, 7523–7527.


EtO–P(O)(OEt)–NH$_2$
Et$_2$Zn/(S,S)-ProPhenol
(10 mol%)
THF, 0 °C
R= Alkyl, Bn
87–93% yield
dr 49:1–99:1 syn
85–95% ee
HCl 1N
THF, 0 °C
(S,S)-ProPhenol
(Ar= 2-thienyl)

Scheme 81. Catalytic asymmetric Mannich reaction *of* 5*H*-oxazol-4-ones.

3.2.2. Organocatalyzed transformations

In 2000, List disclosed the first proline-catalyzed asymmetric three-component Mannich reaction of enolizable ketones and aldehydes in the presence of 4-methoxy aniline as the primary amine. As illustrated in Scheme 82, the corresponding *syn* Mannich adducts were produced with good to excellent yields and stereoselectivities.[212] The stereochemical outcome of the reaction was preliminarily explained through an enamine mechanism which involved either boat-like or chair-like transition states (Scheme 82). Both transition states included a *Z* imine to account for the observed *Si*-facial enantioselectivity, in contrast to the *Re*-facial enantioselectivity usually observed in proline-catalyzed aldol reactions (See ref. 104 and Scheme 38, page 64).


R= H, Me, OMe, OH
R1= p-NO2Ph, i-Pr, i-Bu, n-Bu,
(35 mol%)
DMSO, RT
12–48 h
50–90% yield
dr 17:1–>20:1 syn
65–99% ee
Boat-like transition state
Chair-like transition state
PMP

Scheme 82. List pioneering report on L-proline catalyzed asymmetric direct three-component Mannich-reaction (above). Proposed transition states that might explain the observed stereochemical outcome (below). PMP: *para*-methoxy phenyl.

Soon after, List and co-workers applied the proline-catalyzed three component Mannich strategy to the highly enantioselective synthesis of *syn* 1,2-amino alcohols.[224] The addition of α-hydroxyacetone, promoted by L-proline, produced the corresponding *syn*-Mannich adducts in high chemo-, regio-, diastereo-, and enantioselectivities and in good yields. It must be underlined that the lowest selectivities corresponded to aromatic aldehydes bearing electron-donating substituents. Afterwards, Barbas III and co-workers extended the reaction scope to aliphatic aldehydes affording *syn*-1,2-amino alcohols with similar levels of selectivity (Table 22).[225]

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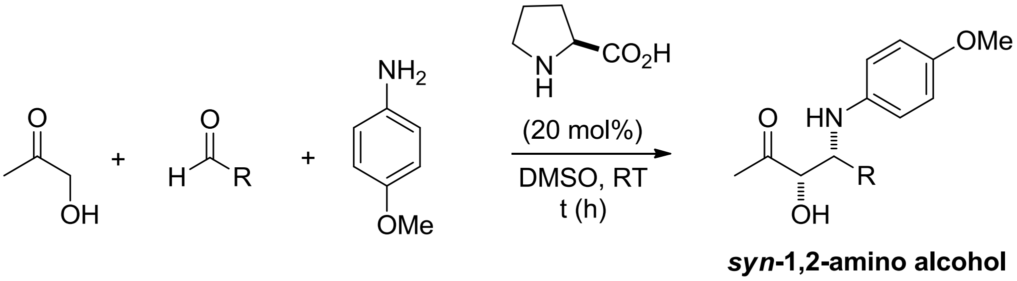
[224] B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

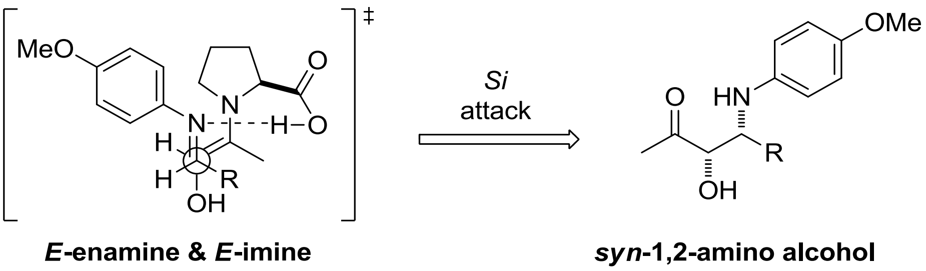
[225] W. Notz, S.-I. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131–1140.

Table 22. L-Proline catalyzed *syn*-Mannich reaction of α-hydroxyacetone.


NH2
CO2H
(20 mol%)
DMSO, RT
t (h)
OMe
OH
H
R
syn-1,2-amino alcohol

R	t (h)	Results	Ref.
Aryl, *i*-Pr	3–24	57–92% yield *dr* 3:1–20:1 *syn* 61–99% *ee*	**List**[224] **2002**
Ph, Naphtyl, *i*-Bu, Pentyl, CH_2OBn	24–48	46–91% yield *dr* 2.6:1–20:1 *syn* 86–94% *ee*	**Barbas III**[225] **2004**

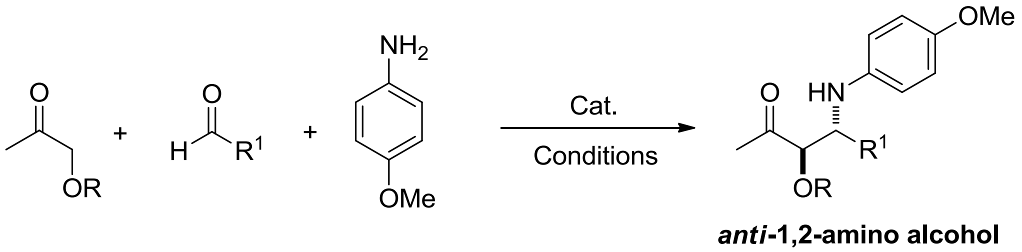
Although originally the authors employed *Z* imines to explain enantioselectivity, typically they are present in only low equilibrium concentrations. Then, they assumed (*E*)-configurations for both the enamine and the imine. The *Si*-face of the imine is selectively attacked by the enamine to allow for protonation of its lone pair and compensation of negative charge formation. Attack of the imine *Re*-face, would result in steric interactions between the aromatic ring and pyrrolidine; interactions that do not exist in the aldol reaction (Scheme 83).[224]

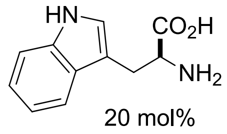
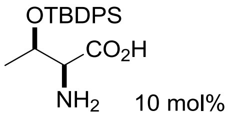
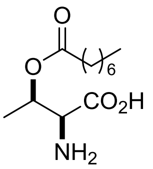
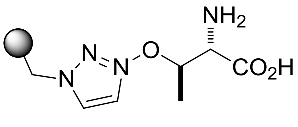

MeO
O
N
N
H–O
H
H
R
OH
‡
Si
attack
OMe
O
HN
R
OH
E-enamine & E-imine
syn-1,2-amino alcohol

Scheme 83. Plausible mechanism for the production of *syn*-1,2-amino alcohols.

In the following years, the *anti*-selective three-component Mannich reaction of either free or protected α-hydroxyacetone was accomplished by the use of primary amines as catalysts (Table 23).

Table 23. *Anti*-selective Mannich reaction of free and/or protected α-hydroxyacetone promoted by primary amine catalysts.



R	R^1	Catalyst	Conditions	Results	Ref.
H	Aryl	 20 mol%	DMF, 4 °C 16–20 h	72–95% yield *dr* 1.3:1–10:1 *anti* 53–95% *ee*	**Barbas III**[226] **2007**
Bn	Aryl, alkyl	 10 mol%	H_2O, RT 5–36 h	50–98% yield *dr* 1.5:1–20:1 *anti* 62–97% *ee*	**Lu**[227] **2007**
H	Aryl	 20 mol%	NMP, 0 °C 4–12 h	75–93% yield *dr* 1:1–11.5:1 *anti* 70–>99% *ee*	**Fu**[228] **2011**
H, Bn	Aryl, *i*-Bu	 20 mol%	DMF/CH_2Cl_2, RT 4–38 h	52–94% yield *dr* 1.1:1–7.3:1 *anti* 49–90% *ee*	**Pericàs**[229] **2014**

Barbas III and co-workers, described the L-triptophane catalyzed reaction between α-hydroxy acetone and aryl imines to afford *anti*-amino alcohols in good yields and variable selectivities.[226] Same year, Lu´s group widened the reaction scope regarding the imine component, describing the addition of protected α-benzyloxyacetone to both aliphatic and aromatic aldehydes in the presence of a L-threonine derived catalyst.[227] Comparable levels of reactivity and selectivity were reported by Fu and co-workers, with structurally similar catalyst.[228] More recently, the group of Pericàs has reported the continuous flow enantioselective three-component *anti*-Mannich reaction of α-benzyloxyacetone and α-hydroxyacetone catalyzed by a polymer-supported threonine derivative.[229]

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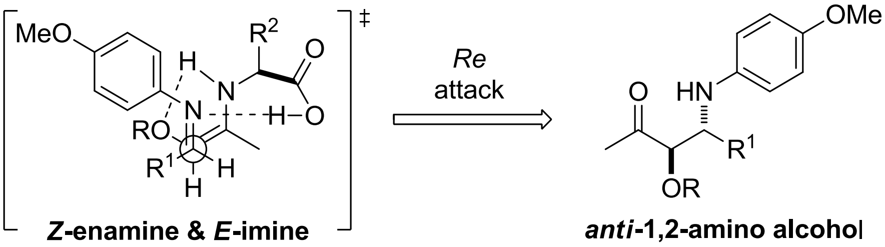
[226] S. S. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288–289.

Anti- and absolute configurations, obtained for the Mannich reaction promoted by chiral primary amines, were reasoned by the predominant formation of the *Z*-enamine *via* H-bond stabilization and subsequent attack to the *in situ* generated *E*-imine from the *Re*-face (Scheme 84).[226,227]



Scheme 84. Plausible mechanism for the production of *anti*-1,2-amino alcohols.

On the other hand, based on the homologous organocatalytic aldol reaction for the synthesis of carbohydrates,[230] the groups of Westermann,[231] Enders[232] and Córdova[233] utilized the protected cyclic α-dihydroxyacetone (DHA) as the donor in the three-component *syn*-selective Mannich reaction catalyzed by L-proline for the preparation of amino sugars (Table 24).

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[227] L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018–1020.

[228] C. Wu, X. Fu, S. Li, *Tetrahedron: Asymmetry* **2011**, *22*, 1063–1073.

[229] C. Ayats, A. H. Henseler, E. Dibello, M. A. Pericàs, *ACS Catal.* **2014**, *4*, 3027–3033.

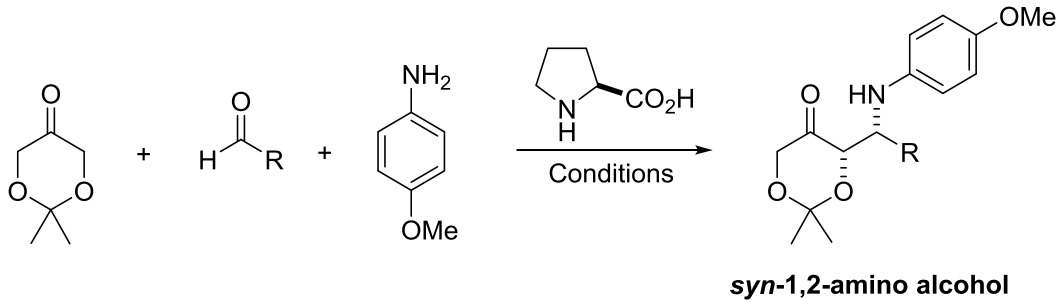
[230] See Chapter 2, pages 73–76.

[231] B. Westermann, C. Neuhaus, *Angew. Chem. Int. Ed.* **2005**, *44*, 4077–4079.

[232] D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083.

[233] I. Ibrahem, W. Zou, Y. Xu, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 211–222.

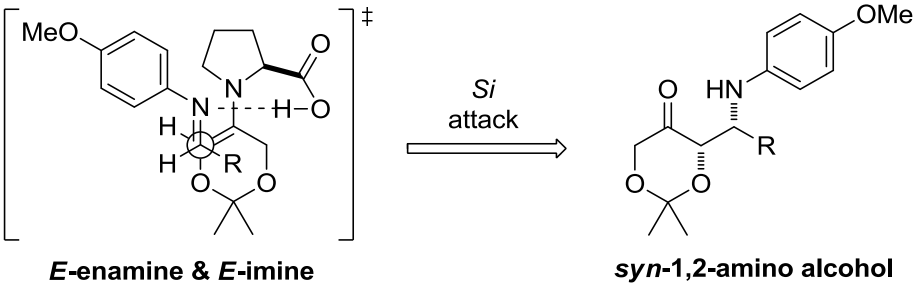
Table 24. L-Proline catalyzed *syn*-Mannich reaction of the protected cyclic α-dihydroxyacetone (DHA).



R	Conditions	Results	Ref.
CO_2Et	20 mol% cat. 2,2,2-trifluoroethanol RT, 20 h	30% yield *dr* 9:1 *syn* 94% *ee*	**Westermann**[231] **2005**
CO_2Et, CH_2OBn, $CH(OMe)_3$, α-substituted chiral substrates, Py, *o*-Cl-Ph	10–30 mol% cat. 0–4 equiv. H_2O DMF; NMP; MeCN 2 °C, 2–5 d	57–94% yield *dr* 1.5:1–99:1 *syn* 51–98% *ee*	**Enders**[232] **2005**
H, CO_2Et, CH_2OBn, Ph, *i*-Pr, α-substituted chiral substrates	30 mol% cat. 5 equiv. H_2O DMSO RT, 24 h	40–84% yield *dr* 3:1–16:1 *syn* 48–99% *ee*	**Córdova**[233] **2006**

Westermann and co-workers described the proline-catalyzed addition of 2,2-dimethyl-1,3-dioxan-5-one to the glyoxylate derived imine, under the action of microwaves, to provide the corresponding *syn* 1,2-amino alcohol in low yield but high stereoselectivity. The methodology developed by the group of Enders, was compatible with a wide variety of aldehydes, though long reaction times were required. On the other hand, reaction conditions developed by Córdova and co-workers were able to efficiently decrease reaction times while maintaining from moderate to good selectivities. It is remarkable the fact that the reaction between DHA and aryl aldehydes in general and with *i*-propyl aldehyde, in particular, produced the corresponding *syn*-1,2-amino alcohols with a considerable decrease in both *ee* and *dr* values. The beneficial effect of a small amount of water is associated to a faster hydrolysis of intermediates in the catalytic cycle which might favor the turnover and diminished catalyst inhibition.[233]

The stereoselectivity observed was justified according to the aforementioned L-proline catalyzed Mannich reaction of α-hydroxyacetone; the *E*-enamine attacks the *Si*-face of the *E*-imine, as shown in Scheme 85.[232,233]



Scheme 85. Plausible mechanism for the production of *syn*-1,2-amino alcohols.

In contrast to the examples of secondary/primary amine catalyzed Mannich reactions described for the synthesis of vicinal amino alcohols, to the best of our knowledge, there is only one regarding non-covalent organocatalysis. In 2013, Zhao and co-workers reported a highly stereoselective three-component direct Mannich reaction between aromatic aldehydes, *p*-toluenesufonamide and ketones through an enolate mechanism promoted by a bifunctional quinidine thiourea catalyst.[234] The methodology included a few examples of protected α-hydroxyacetophenones which produced, under Brønsted base catalysis, the corresponding *syn*-1,2-amino alcohols in high yields and excellent diastereo- and enantioselectivities (Scheme 86).

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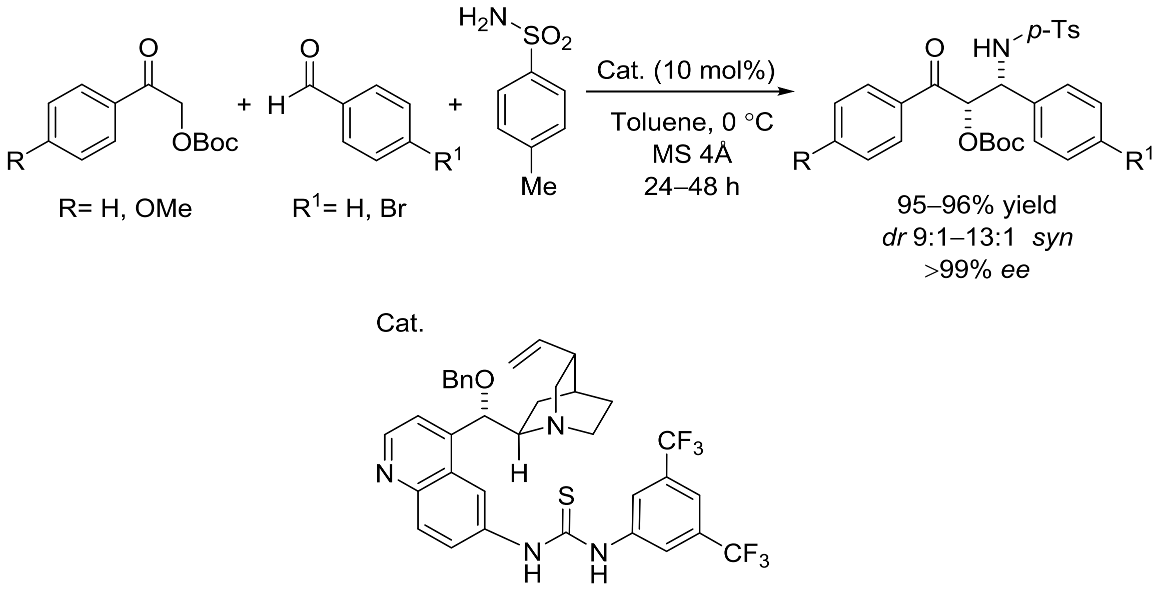
[234] Q. Guo, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 508–511.



Scheme 86. Bifunctional Brønsted base catalyzed three-component Mannich reaction.

As shown in this brief outlook, the development of catalytic asymmetric Mannich reactions towards the production of enantiomerically enriched 1,2-amino alcohol frameworks is far from the progress achieved in the analogous catalytic asymmetric aldol reaction for the preparation of enantiopure 1,2-diols.

Metal catalysis has demonstrated its effectiveness to address selectivity issues. The use of α-hydroxyacetophenones on one hand, and preformed imines on the other hand, enabled to solve regioselectivity and chemoselectivity problems, respectively. High control over *syn*/*anti* selectivity and enantioselectivity has been achieved in general, although reaction scope regarding the azomethine component is more limited for the *syn*-Mannich reaction (i.e. only α-branched aliphatic amines performed well).[235]

Covalent organocatalysis mediated by chiral amines supposed an important breakthrough towards the stereoselective three-component Mannich reaction. The role of each component is well defined enabling a total control over chemoselectivity whereas the use of secondary or primary chiral amines give access to *syn*- or *anti*- adducts, respectively. Nevertheless, the scope of the reaction regarding the electrophilic counterpart is clearly improvable. Particularly, electron-donating group containing aryl imines are still challenging substrates since reaction with these electrophiles underwent with moderate yield and stereoselectivities.[236]

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[235] See pages 144, 146, 148 and 149.

On the other hand, the production of enantiopure 1,2-amino alcohols through non-covalent catalytic Mannich reactions is an unexplored field which reveals the difficulties associated with the establishment of the role of each reactant in the three component version and the diminished reactivity of azometine groups, compared to aldehydes, for the two component version of the Mannich reaction.[237]

Finally, as shown in Chapter 1, the use of 1,2-dicarbonyl compounds as pronucleophiles in the catalytic asymmetric Mannich reaction is also a barely investigated area which would represent a straightforward approach for the synthesis of enantiomerically pure aminopolyol fragments.[238]

3.3. Working hypothesis and objectives

In this context, we questioned whether our successful system, based on the use of β-alkoxy-α-keto amides as pronucleophiles and ureidopeptidic Brønsted bases as catalysts for the estereoselective catalytic direct cross-aldol reaction, might be also effective in the reaction with azomethine groups. If successful, the Mannich adducts obtained could be stereoselectively reduced, as in the prior project, and provide a new entry to enantiomerically enriched aminopolyol skeletons bearing up to three new stereogenic centers (Scheme 87).

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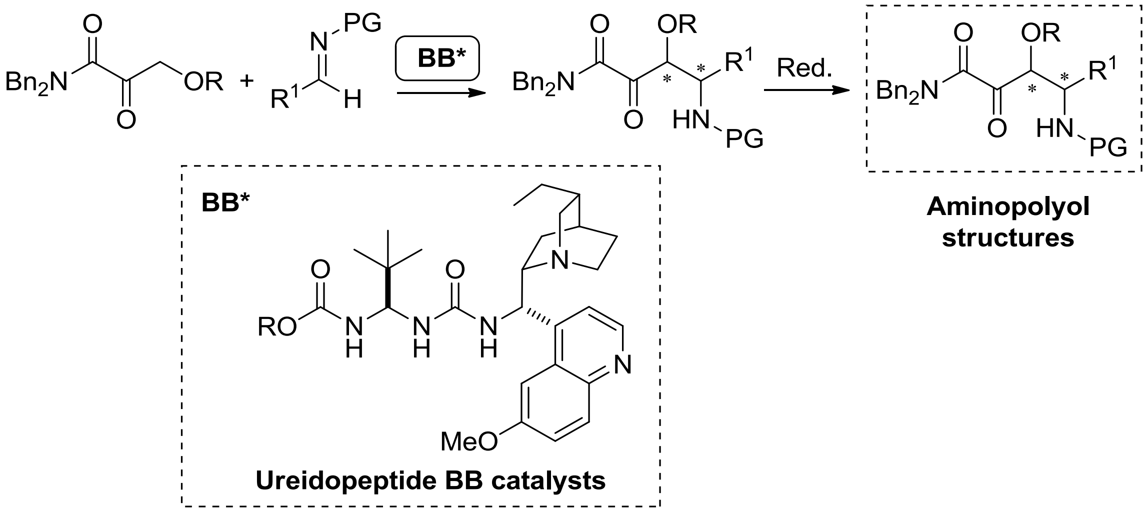
[236] See pages 153, 154 and 156.

[237] See page 158.

[238] See pages 40–43.



Scheme 87. Objetive of this work: Ureidopeptide BBs catalyzed asymmetric Mannich reaction of β-alkoxy-α-keto amides: access to enantioenriched aminopolyol structures.

3.4. Results and discussion

3.4.1. Initial experiments and optimizations

Initial experiments were aimed at verifying the suitability of the Brønsted base catalyzed methodology described for the aldol reaction, in promoting the Mannich one. With this purpose, α-keto amides **4** and **7** were chosen as the pronucleophile counterparts of the reaction and ureidopeptides **C7** and **C10**, as the initial catalysts, due to their high performance in the aldol reaction with non-enolizable- and enolizable aldehydes, respectively. In addition, several *N*-protected imines were prepared to evaluate the initial reactivity of the system in dichloromethane (Table 25).

First of all, as results in Table 25 reflect, the protecting/activating group at the nitrogen of the azomethine had a great impact in reactivity. For instance, a complete absence of reaction was observed with *N*-Boc protected imine **31a** and catalyst **C10** even after 72 hours at 0 °C (entry 1). This was clearly an unexpected result since carbamoyl protected imines had participated with high efficiency in the Mannich type reaction, promoted by bifunctional ureidopeptide-based Brønsted bases, to produce β-amino nitriles (Scheme 59b).[239] With sulfonyl protected imines, a diverse behavior was observed; the pyridyl sulfonyl **32a** did not promote the reaction (entry 2) whereas tosyl and nosyl *N*-protected imines performed well in terms of reactivity. Importantly, side-reactions such substrate self-condensation or cyclization of the Mannich adducts were not detected. The best results were achieved with *ortho*-nosyl (**34a**) and *para*-nosyl (**35a**), being the latter the most efficient, as full conversion into the corresponding Mannich adduct was observed after 8 hours at –20 °C (entry 5). Nevertheless, although the diastereoselectivity induced by catalyst **C10** was excellent (94:6), enantioselectivity was very poor (30%). In order to improve this disappointing result, α-keto amide **7,** with an increased aromatic character and catalyst **C7** were also assayed. Even so, despite the excellent diastereoselectivity (up to 99.1), similar enantiocontrol for both nosyl *N*-protected imines was attained at –20 °C (entry 7) and –60 °C (entries 6 and 8).

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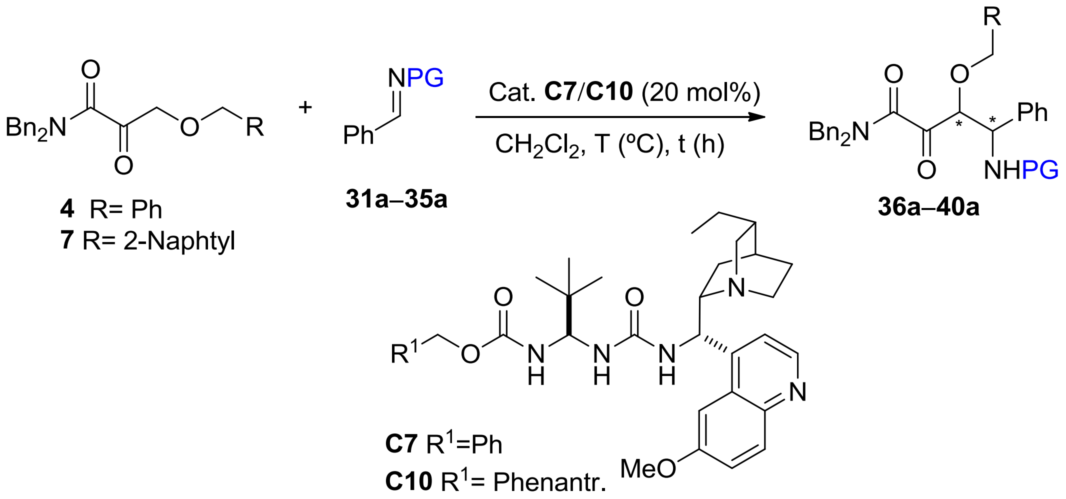
[239] S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531.

Table 25. Initial experiments for the Mannich reaction of α-keto amides **4** and **7** promoted by **C7** and **C10**.[a]



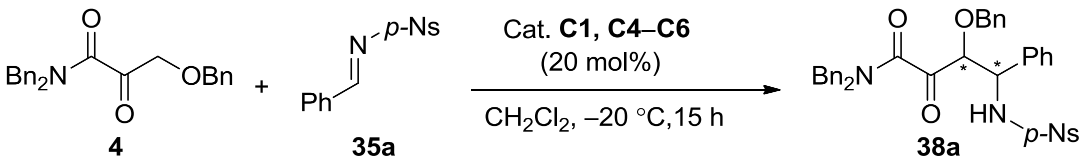
	α-keto	PG, imine	Cat.	T (°C)	T (h)	Conv. (%)	Product	*dr*	*ee* (%)
1	**4**	Boc/**31a**	**C10**	–20	20	N.R.	-	-	-
				0	72	N.R.	-	-	-
2	**4**	SO$_2$Py/**32a**	**C10**	–20	120	N.R.	-	-	-
3	**4**	*p*-Ts/**33a**	**C10**	–20	120	80	**36a**	85:15	34
4	**4**	*o*-Ns/**34a**	**C10**	–20	15	71	**37a**	82:18	28
5	**4**	*p*-Ns/**35a**	**C10**	–20	8	>95	**38a**	94:6	30
6	**7**	*o*-Ns/**34a**	**C7**	–60	45	75	**39a**	99:1	44
7	**7**	*p*-Ns/**35a**	**C7**	–20	8	>95	**40a**	93:7	30
8	**7**			–60	45	90		99:1	40

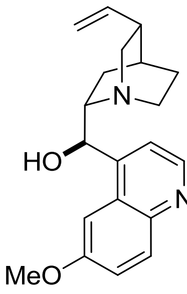
[a] Reaction conditions: α-keto amide (0.1 mmol) and imine (1.5 equiv., 0.15 mmol) in CH$_2$Cl$_2$ (0.5 mL). Adducts were not isolated. Conversions determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by chiral HPLC and compared to ^{1}H-RMN on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

These unsatisfying results contrast with those obtained in the aldol reaction for which ureidopeptide-based Brønsted base catalysts provided the highest levels of chirality transfer. In our initial plan, we considered that the bidentate character of the pronucleophile could hypothetically guaranteed, on one hand, a higher reactivity and on the other hand, a higher selectivity based on the formation of tight transition states. Nevertheless, the flexibility displayed by these type of catalysts along with the greater number of interaction sites in nosyl *N*-protected imines, compared to aldehydes, could lead to the generation of analogous transition states in terms of energy. Thus, we turned our attention into more rigid squaramide and thiourea based Brønsted bases, which also present a strong hydrogen bond donor capability, and we studied the reaction with α-keto amide **4** an imine **35a**. For comparison, also quinine **C1** was tested (Table 26).

As shown in Table 26, quinine **C1**, thioureas **C5** and **C6** promoted the addition of α-keto amide **4** with excellent diastereoselectivity (90:10–96:4 *dr*) but with very poor enantiocontrol (22–48% *ee*). In contrast, squaramide **C4** produced the Mannich adduct **38a** with excellent enantiomeric excess (88%). It is remarkable the high reactivity displayed by combinations formed by nosyl *N*-protected imines and bifunctional Brønsted bases and the fact that quinine-based squaramide **C4** and quinine derived thiourea **C6** induced opposite enantioselectivity.

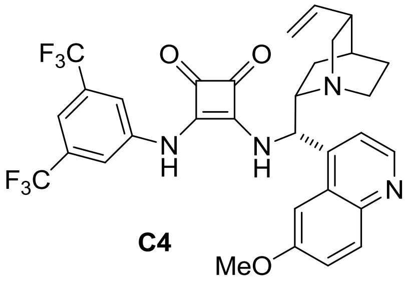
Table 26. Catalyst screening for the reaction of α-keto amide **4** and imine **35a**.[a]





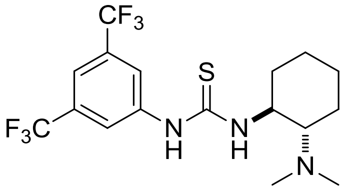
C1

conv. 80%
90:10 *dr*, –22% *ee*



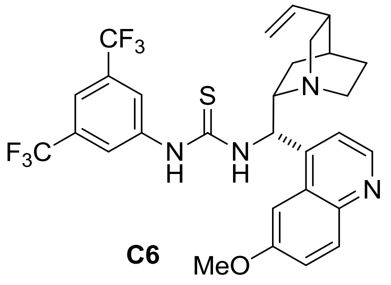
C4

conv. >95%
95:5 *dr*, 88% *ee*



C5

conv. >95%
96:4 *dr*, –48% *ee*



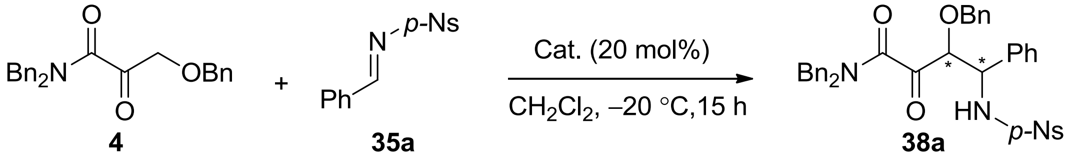
C6

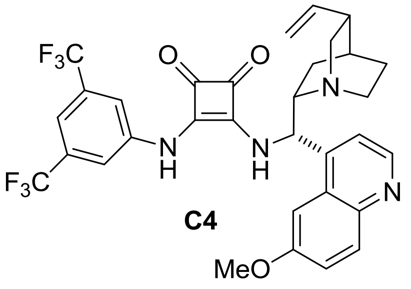
conv. >95%
95:5 *dr*, –48% *ee*

[a] Reaction conditions: **4** (0.1 mmol) and imine **35a** (1.5 equiv., 0.15 mmol) in CH_2Cl_2 (0.5 mL). Adduct was not isolated. Conversions determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by chiral HPLC and compared to ^{1}H-RMN on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

With this notable result in hand, we decided to test some squaramide-based catalysts bearing diverse structural modifications, under the same reaction conditions (Table 27).

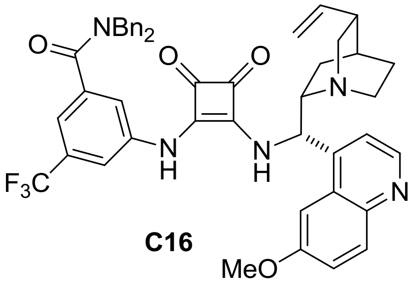
Table 27. Squaramide-based catalyst screening.[a]





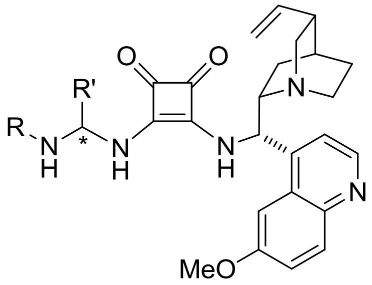
C4

conv. >95%
95:5 *dr*, 88% *ee*

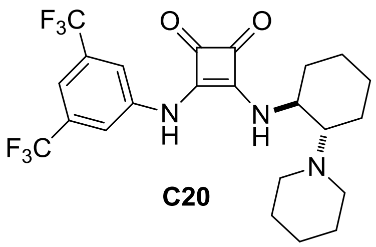


C16

conv. >95%
90:10 *dr*, 80% *ee*

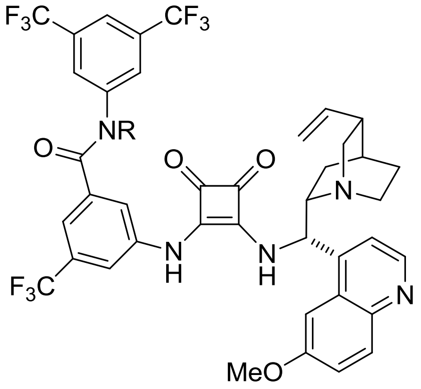


C17 R=COPh, R'= *i*-Pr(L), 15 h, conv. >95%, 85:15 *dr*, 42% *ee*
C18 R=COPh, R'= *i*-Pr(D), 72 h, conv. 65%, 87:13 *dr*, 22% *ee*
C19 R=Cbz, R'= *t*-Bu(L), 64 h, conv. 81%, 87:13 *dr*, 10% *ee*



C20

conv. 50%
91:9 *dr*, 62% *ee*



C21 R= H, conv. >95%, 87:13 *dr*, 64% *ee*
C22 R= Me, conv. >95%,95:5 *dr*, 92% *ee*
C23 **R= Bn, conv.>95%, 97:3 *dr*, 92% *ee***
C24 R= Pr, conv. >95%, 99:1 *dr*, 88% *ee*

[a] Reaction conditions: **4** (0.1 mmol) and imine **35a** (1.5 equiv., 0.15 mmol) in CH_2Cl_2 (0.5 mL). Adduct was not isolated. Conversions determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by chiral HPLC and compared to ^{1}H-RMN on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

Squaramide-based catalyst **C16**, in which the dibenzyl amide moiety replaces the trifluoromethyl group, rendered the Mannich adduct with slightly reduced selectivity. Squaramide-aminal combining catalysts **C17**–**C19** were not effective neither in terms of selectivity nor reactivity. Next, the substitution of the 9-amino-(9-deoxy)*epi*quinine fragment by the (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine moiety (**C20**) had a detrimental effect in reactivity and enantioselectivity. At this point, despite the good results obtained with catalyst **C4**, we decided to focus in a way to further improve the stereocontrol of the reaction. Recently, based on the β-turn structures found in peptides,[240] our group designed and synthesized catalyst **C21** which promoted the Michael addition of of 1-*H*-imidazol-4(5*H*)-ones to α-silyloxyenones very efficiently.[241,242] Nevertheless, when using catalyst **C21** both diatereomeric ratio and enantioselectivity diminished (87:13 *dr*, 64% *ee*). Once again, the possibility of establishing multiple hydrogen-bonding interactions seemed to be detrimental for enantioselectivity. In contrast, protection of the NH group in the amide moiety (catalysts **C22**–**C24**) had a good impact in stereoselectivity. In particular, the benzyl substituted catalyst **C23** afforded the Mannich adduct **38a** in 97:3 *dr* and 92% *ee*.

With these excellent results in hand, the effect of temperature and solvent were next studied and compared with those obtained in dichloromethane at –20 °C (Table 28). A rise in temperature up to 0 °C or room temperature deteriorated significantly both the diastereo- and enantioselectivity (entries 3 and 4). On the other hand, the solvent study revealed that chloroform was the most suitable since diastereoselectivity raised up to 99:1 (entry 8).

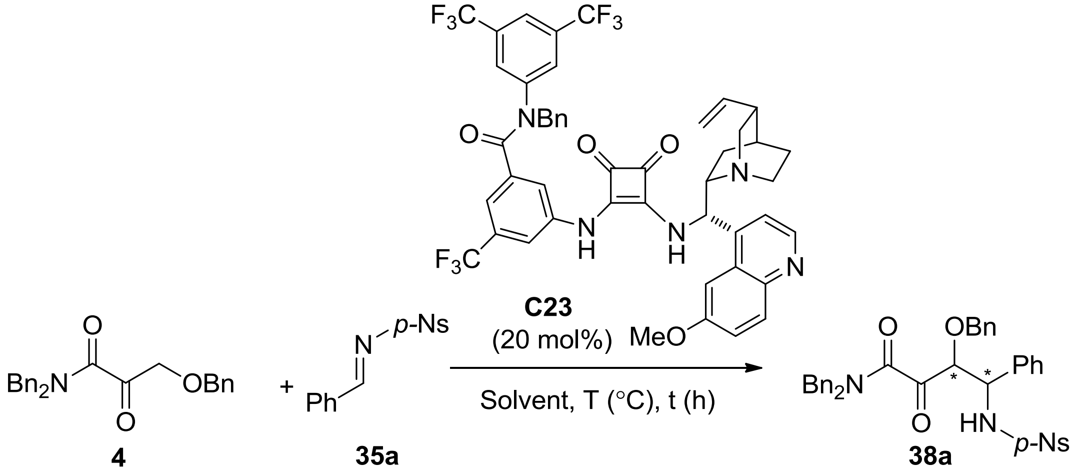
---

[240] Selected examples on structure and catalytic activity of β-turn peptides: a) A. J. Metrano, N. A. Abascal, B. Q. Mercado, E. K. Paulson, A. E. Hurtley, S. J. Miller, *J. Am. Chem. Soc.* **2017**, *139*, 492–516; b) C. E. Grünenfelder, J. K. Kisunzu, N. Trapp, R. Kastl, H. Wennemers, *Peptide Science* **2017**, *108*. DOI: 10.1002/bip.22912.

[241] J. Etxabe, J. Izquierdo, A. Landa, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.

[242] Julen Etxabe Telleria, PhD. Dissertation, EHU/UPV, 2016.
http://www.ehu.eus/es/web/gicas/tesiak

Table 28. Temperature and solvent screening for the Mannich reaction promoted by **C23**.[a]



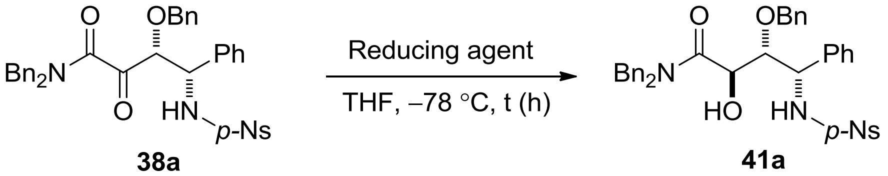
Entry	Solvent	T (°C)	t (h)	Conv. (%)	*dr*	*ee* (%)
1	CH_2Cl_2	–40	24	95	97:3	92
2		–20	15	95	97:3	92
3		0	6	95	96:4	80
4		RT	4	95	79:21	70
5		–40	24	95	97:3	92
6	THF	–20	30	80	95:5	90
7	DCE	–20	30	95	98:2	84
8	$CHCl_3$	–20	15	95	99:1	92

[a] Reaction conditions: **4** (0.1 mmol) and imine **35a** (1.5 equiv., 0.15 mmol) in solvent (0.5 mL). Adduct was not isolated. Conversions determined by ^{1}H-RMN spectroscopy. The *dr* values were determined by chiral HPLC and compared to ^{1}H-RMN on the reaction crude. The *ee* values were determined for the major diastereomer by chiral HPLC.

In some experiments, throughout all the optimization process, we observed partial decomposition of the *p*-nosyl *N*-protected imine **35a**, specially for those that required long reaction times. From then on, reactions were performed under the presence of molecular sieves (3Å) to avoid the addition of imine in excess.

As in the previously described aldol reaction, attempts to isolate pure Mannich adducts were unsuccessful. Consequently, we evaluated diverse reducing agents in order to produce stereoselectively the corresponding amino polyol fragments (Table 29). In spite of the effectiveness of L-Selectride in the *syn*-stereoselective reduction of aldol adducts, same reaction conditions applied to Mannich adduct **38a** produced **41a** in a moderate 72:28 diastereomeric ratio (*anti,syn:syn,syn*) and with less chemical efficiency. Based on the precedents for the stereoselective reduction of similar compounds, we also evaluated other reductive systems but only K-Selectride[244] induced good diastereoselectivity. Although absolute configuration for **41a** was not determined by the time we performed the experiments, it has been indicated in the scheme to improve clarity. A rationalization of the stereochemical outcome will be outlined later.

Table 29. Screening of reaction conditions for the stereoselective carbonyl reduction of **38a**.[a]



Entry	Reducing agent	t (h)	Conv. (%)	***anti,syn:syn,syn***
1	L-Selectride	3	n.d.[b]	72:28
2[243]	$Zn(BH_4)_2$	2	n.d.[b]	67:33
3[244]	$LiBHEt_3$	3	n.d.[b]	54:46
4[245]	KBH_4	2	>95	40:60
5	K-Selectride	5	70	92:8

[a] Reaction conditions: **38a** (0.1 mmol) and reducing agent (3 equiv., 0.3 mmol) in THF (1 mL). The *dr* values were determined by ^{1}H-RMN spectroscopy. [b] Not determined due to the crude complexity.

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[243] See ref. 168, page 89.

[244] See ref. 69, page 41.

[245] See ref. 70, page 41.

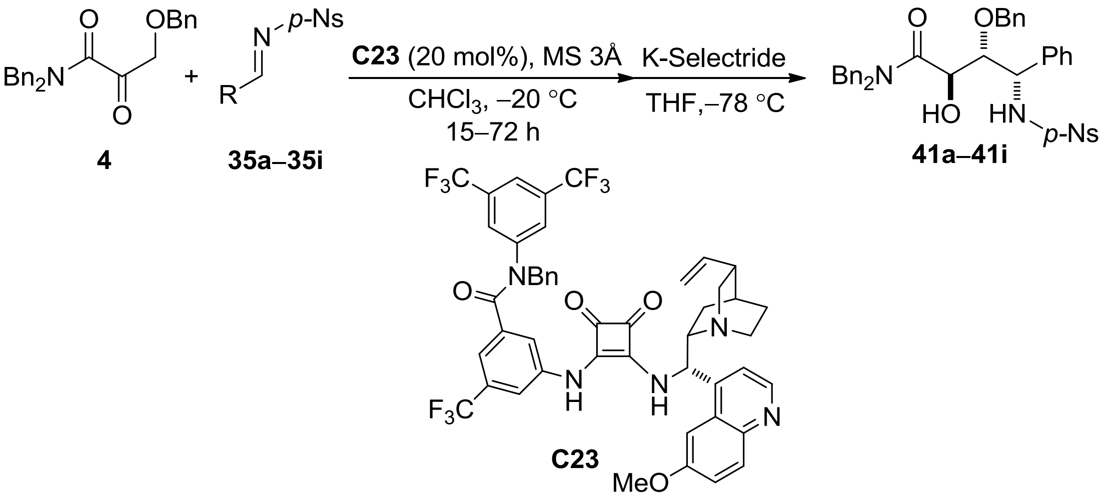
3.4.2. Reaction scope

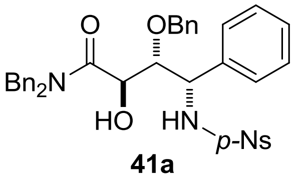
With the optimized reaction conditions in hand, we then focused on the scope of the reaction with the aim of evaluating the generality of this asymmetric route respect to the imine component. The Mannich reaction between α-keto amide **4** and a representative selection of *p*-nosyl *N*-protected aromatic imines assisted by **C23** was evaluated (Table 30). Reactions were performed in chloroform at –20 °C in the presence of molecular sieves and each crude reaction mixture was submitted to reduction with K-Selectride.

As the results in Table 30 show, excellent diastereo- and enantioselectivities were generally obtained for all *p*-nosyl *N*-protected imines assayed, regardless the electronic character of the aromatic group. As an exception, both diastereo- and enantioselectivity for adduct **41g** diminished considerably (70:30 *dr*, 58% *ee*).

The reaction was also performed at 3 mmol scale (adduct **41a**) with no detrimental effect on the stereochemical outcome. In addition, when catalyst loading was lowered to 5 mol% the reaction underwent with identical levels of selectivity although longer reaction times were normally required (adducts **41a**, **41e** and **41f**).

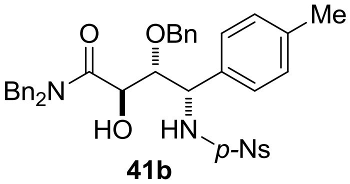
Table 30. Scope of the Mannich reaction of α-keto amide **4** and *p*-Ns-*N*-protected aromatic imines.[a]


Bn2N
O
OBn
O
4
+
N
p-Ns
R
35a–35i
C23 (20 mol%), MS 3Å
CHCl3, –20 °C
15–72 h
K-Selectride
THF,–78 °C
HO
HN
p-Ns
Ph
41a–41i
F3C
CF3
NBn
N
H
N
H
N
N
MeO
C23



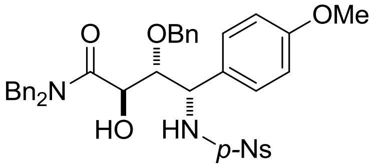
41a

72 h, 68%, 99:1 *dr*, 92% *ee*
3 mmol scale, **C23** (5 mol%)



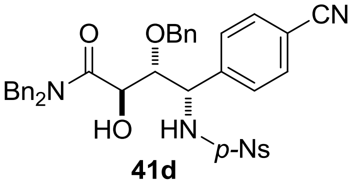
41b

40 h, 58%, 97:3 *dr*, 92% *ee*



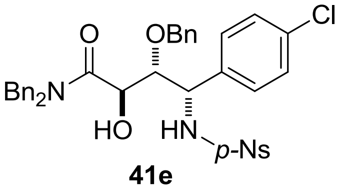
41c

72 h, 59%, 97:3 *dr*, 88% *ee*



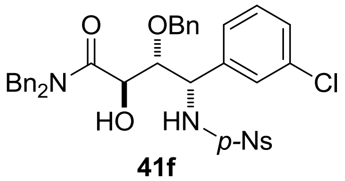
41d

15 h, 60%, 97:3 *dr*, 92% *ee*



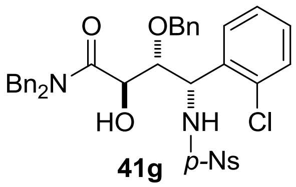
41e

60 h, 61%, 99:1 *dr*, 92% *ee*
C23 (5 mol%)



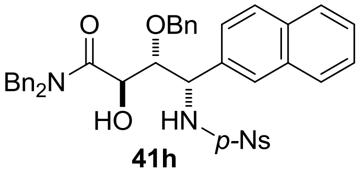
41f

72 h, 64%, 98:2 *dr*, 88% *ee*
C23 (5 mol%)



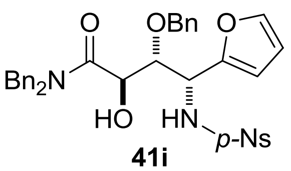
41g

24 h, 44%, 70:30 *dr*, 58% *ee*



41h

15 h, 57%, 98:2 *dr*, 88% *ee*



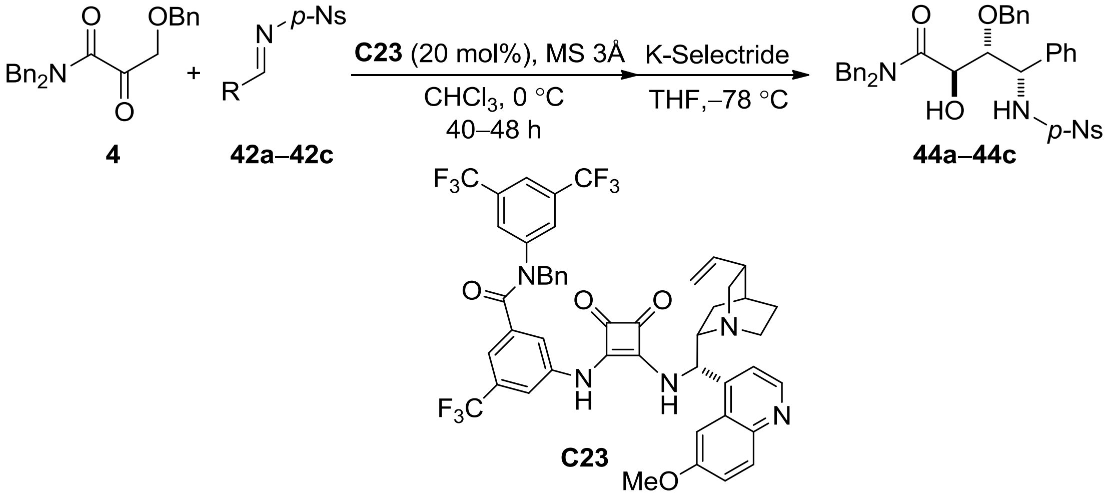
41i

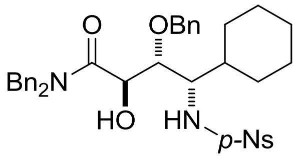
15 h, 53%, 99:1 *dr*, 80% *ee*

[a] Reaction conditions: **4** (0.15 mmol) and imine (1.5 equiv., 0.23 mmol) in $CHCl_3$ (1.5 mL), unless otherwise stated. Yields refer to isolated adducts after stereoselective reduction. The *dr* values were determined by chiral HPLC and corroborated by ^{1}H-RMN analysis, before reduction. The *ee* values determined for the major diastereomer by chiral HPLC, before reduction.

We also studied the Mannich reaction between α-keto amide **4** and a representative selection of imines derived from aliphatic aldehydes. In this particular case, reactions were carried out at 0 °C using 3 equivalents of imine to compensate their typical low reactivity.[246]

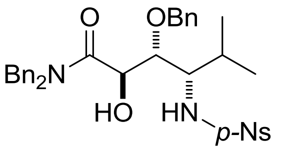
Table 31. Scope of the Mannich reaction of α-keto amide **4** and *p*-Ns-*N*-protected aliphatic imines.[a]


O
OBn
Bn$_2$N
O
4
+
N
p-Ns
R
42a–42c
C23 (20 mol%), MS 3Å
CHCl$_3$, 0 °C
40–48 h
K-Selectride
THF,–78 °C
O
OBn
Ph
Bn$_2$N
HO
HN
p-Ns
44a–44c
F$_3$C
CF$_3$
NBn
O
O
O
N
H
N
H
N
N
F$_3$C
C23
MeO


O
OBn
Bn$_2$N
HO
HN
p-Ns

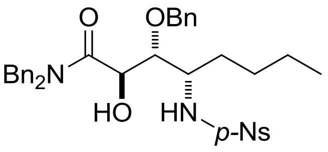
44a

40 h, 56%, 99:1 *dr*, 86% *ee*


O
OBn
Bn$_2$N
HO
HN
p-Ns

44b

48 h, 51%, 97:3 *dr*, 80% *ee*


O
OBn
Bn$_2$N
HO
HN
p-Ns

44c

40 h, 45%, 86:14 *dr*, 56% *ee*

[a] Reaction conditions: **4** (0.15 mmol) and imine (3 equiv., 0.45 mmol) in CHCl$_3$ (1.5 mL). Yields refer to isolated adducts after stereoselective reduction. The *dr* values were determined by chiral HPLC and corroborated by ^{1}H-RMN analysis, before reduction. The *ee* values determined for the major diastereomer by chiral HPLC, before reduction.

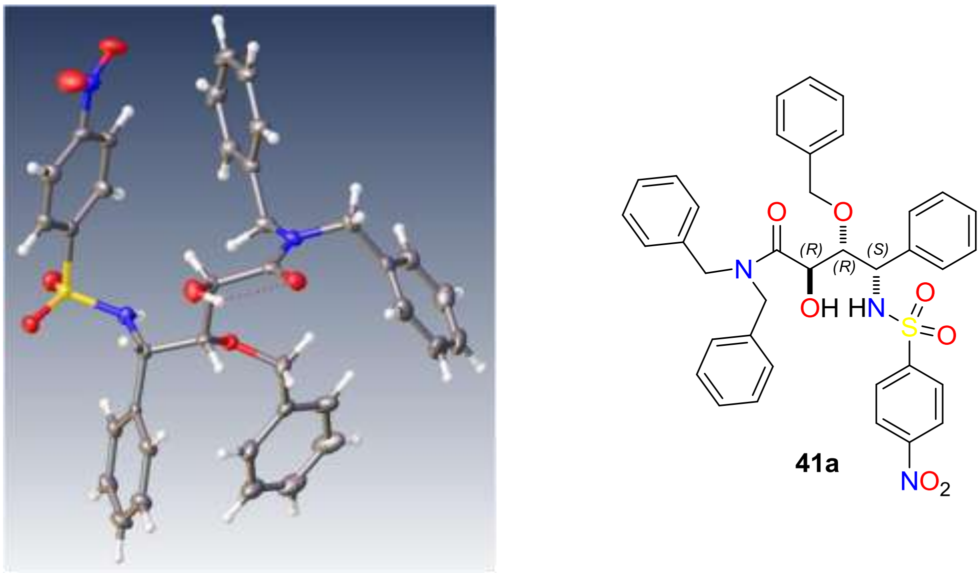
As shown in Table 31, reactions underwent with full conversion. Mannich reaction with imines derived from α-branched alkyl aldehydes **42a** and **42b** produced the corresponding Mannich adducts **43a** and **43b**, respectively, in high enantiomeric excesses and excellent diastereomeric ratios. After stereoselective reduction, pure aminodiols **44a** and **44b** were isolated in reasonable yield.

---

[246] Reactions did not proceed at lower temperatures.

Nevertheless, poor control over the enantioselectivity of the reaction was observed for adduct **44c**. Remarkably none of the possible competitive side-reactions (α-keto amide self-condensation and cyclization) were detected.

The relative and absolute configurations of the major enantiomer were determined by X-ray crystallographic analysis of *anti,syn*-aminodiol **41a** and a uniform mechanism for the Mannich reaction was assumed (Figure 20).



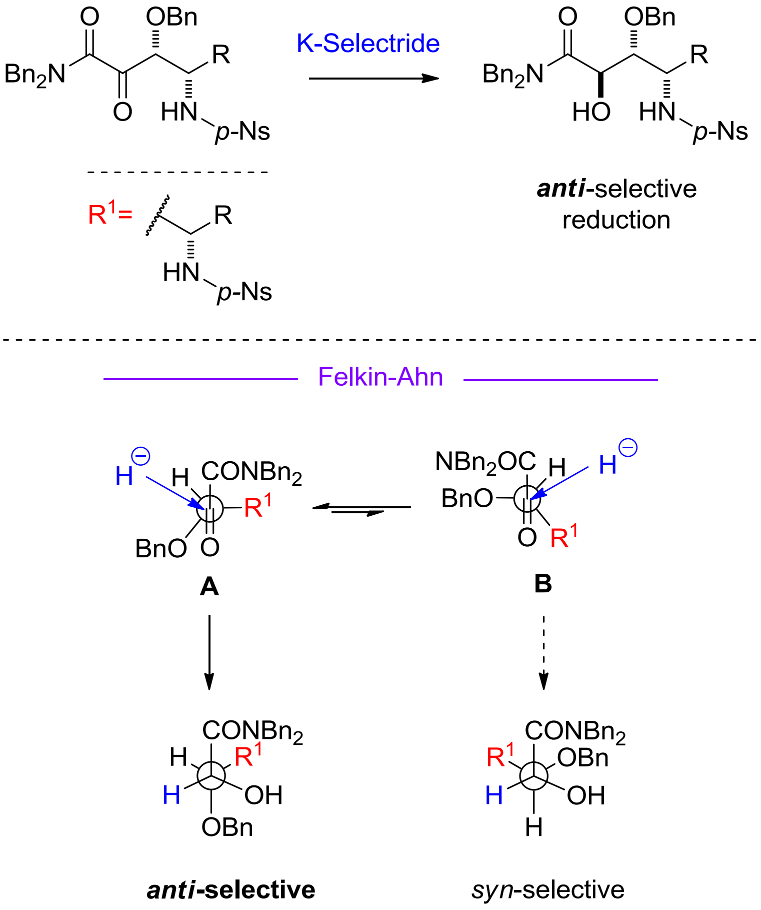
41a

Figure 20. ORTEP diagram for compound **41a**. Thermal ellipsoids shown at 50% probability.

According to the diastereo- and enantioselectivities obtained, the capacity of the catalyst to mainly induced *syn*-configured Mannich adducts could be consistent with the generation of a more stabilized Z enolate which preferentially approaches the *Re* face of the imine. Nevertheless, at this point we have no evidence of the actual mode of substrate-catalyst interaction. On one hand, most of the bifunctional Brønsted base catalysts, tested in the initial screening for the Mannich reaction, performed with a high degree of diastereoselection, but only a specific type of squaramide-based catalysts bearing the 9-amino-(9-deoxy)*epi*quinine fragment (cat. **22**, **23** and **24**) induced high enantioselectivity. Therefore, the role of multiple H-bonding *versus* other structural features such as steric hindrance together with the fact that nosyl *N*-

protected imines display a higher number of coordinating groups, compared to aldehydes, makes very difficult to predict the most favorable interactions and to propose a model.

On the other hand, the *anti*-selectivity observed in the reduction of the Mannich adducts could be explained by assuming the Felkin-Ahn model. As depicted in Scheme 88, the reaction presumably proceeds through conformer **A**, in which the bulkiest group appears perpendicular to the carbonyl group. It must be highlighted that the observed stereoinduction is in agreement with previous works including related systems.[247]


Bn2N
O
OBn
R
HN
p-Ns
K-Selectride
HO
anti-selective reduction
R1=
Felkin-Ahn
H
CONBn2
BnO
A
NBn2OC
B
OH
anti-selective
syn-selective

Scheme 88. Model proposal that might explain the *anti*-selective reduction.

---

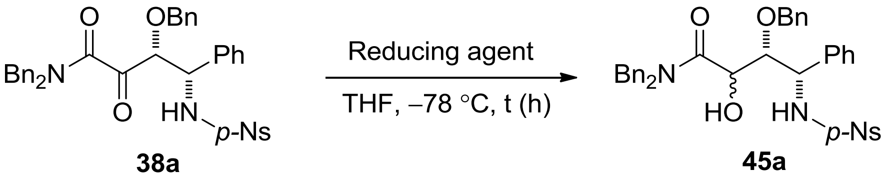
[247] See ref. 69 and 70, page 41.

3.4.3. Elaboration of adducts

Our next concern was the elaboration of the Mannich adducts taking advantage of the versatility of the diverse functional groups at the *N*-nosyl-γ-amino-β-alkoxy-α-keto amides.

As for the aldol reaction, we explored the possibility of inverting the stereochemical outcome of the reduction, and we tested diverse reducing agents as summarized in Table 32.[248] *Syn*-selective reduction was observed for sodium borohydride in polar non protic THF and for the combined systems alkylboranes/sodium borohydride.

Table 32. Screening for the stereoselective carbonyl reduction in adduct **38a**.



Reducing agent	Solvent	t (h)	Conv. (%)	***anti,syn:syn,syn***
$NaBH_4$	THF	2	>95	20:80
$NaBH_4$	MeOH	2	>95	75:25
BH_3.THF	THF	3	>95	50:50
DIBAL-H	THF	2	>95	50:50
$Et_3B/NaBH_4$	THF	2	>95	12:88
$Bu_3B/NaBH_4$	THF	2	>95	14:86

[a] Reaction conditions: **38a** (0.1 mmol) and reducing agent (3 equiv., 0.3 mmol) in THF (1 mL). The *dr* values were determined by ^{1}H-RMN spectroscopy.

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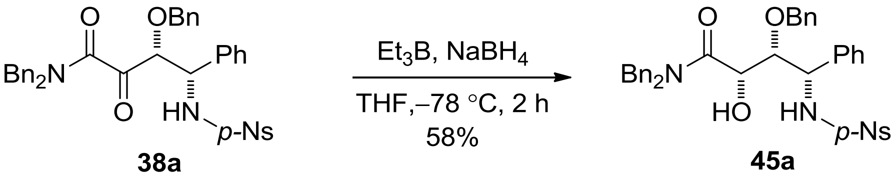
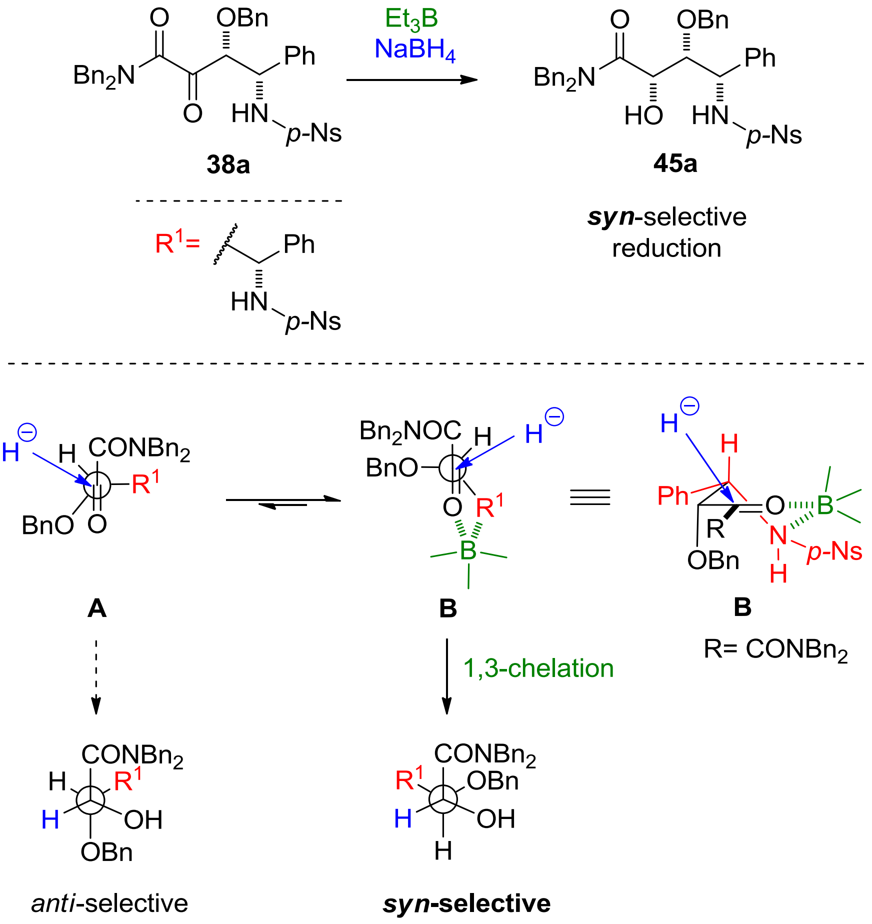
[248] See Table 21, page 124.

The reduction of adduct **38a** with the system Et_3B /$NaBH_4$ in THF at low temperature afforded the *syn,syn*-aminodiol **45a** in good yield (Scheme 89).


O
OBn
Bn2N
Ph
O
HN
p-Ns
38a
Et3B, NaBH4
THF,–78 °C, 2 h
58%
O
OBn
Bn2N
Ph
HO
HN
p-Ns
45a

Scheme 89. Stereoselective reduction of Mannich adduct **38a**.

The *syn*-selectivity obtained might be explained by the chelating character of the triethylborane that could favor a six-member cyclic 1,3-chelated intermediate[249] which would suffer the approach of the extern hydride ($NaBH_4$) from the less hindered face, as shown in Scheme 90.

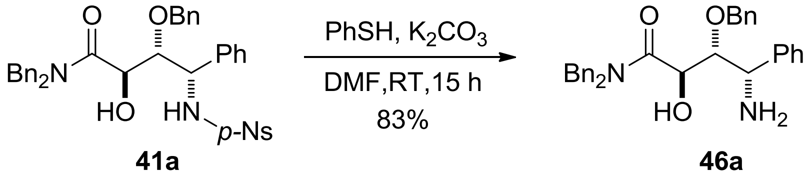

O
OBn
Bn2N
Ph
O
HN
p-Ns
38a
Et3B
NaBH4
O
OBn
Bn2N
Ph
HO
HN
p-Ns
45a
syn-selective
reduction
R1=
Ph
HN
p-Ns
H
H
CONBn2
R1
BnO
O
A
Bn2NOC
H
H
BnO
O
R1
B
Ph
H
O
B
R
N
p-Ns
H
OBn
B
R= CONBn2
1,3-chelation
CONBn2
H
R1
H
OH
OBn
anti-selective
CONBn2
R1
OBn
H
OH
H
syn-selective

Scheme 90. Proposed model for the *syn*-selective reduction.

---

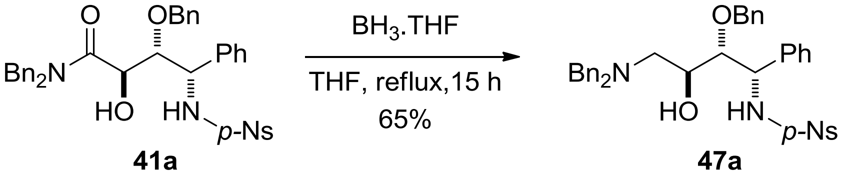
[249] N. Yamazaki, C. Kibayashi, *J. Am. Chem. Soc.* **1989**, *111*, 1396–1408.

The cleavage of *p*-nosyl protecting group was efficiently promoted in the presence of thiophenol and potassium carbonate, to afford the corresponding amino polyol fragment **46a** in high yield (Scheme 91).[250]


Bn2N
O
OBn
Ph
HO
HN
p-Ns
41a
PhSH, K2CO3
DMF,RT,15 h
83%
Bn2N
O
OBn
Ph
HO
NH2
46a

Scheme 91. Deprotection of the amine in adduct **41a**.

On the other hand, the reduction of the amide group was carried out using the borane tetrahydrofurane complex to produce **47a** in good yield (Scheme 92).[251]


Bn2N
O
OBn
Ph
HO
HN
p-Ns
41a
BH3.THF
THF, reflux,15 h
65%
Bn2N
OBn
Ph
HO
HN
p-Ns
47a

Scheme 92. Reduction of the amide group in adduct **41a**.

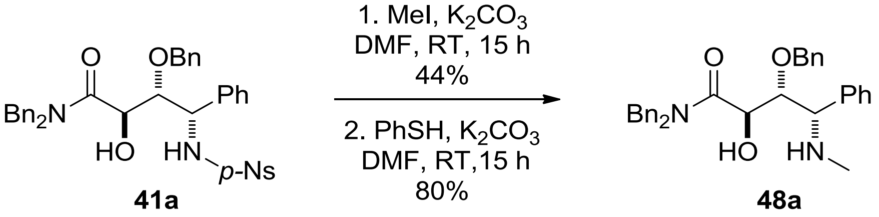
An interesting feature of nosyl protected amines is that they can be easily transformed in secondary amines through alkylation followed by deprotection.[252] Methylation of adduct **41a**, and subsequent *p*-nosyl cleavage,[252a] produced the corresponding secondary amine **48a**, as shown in Scheme 93. This approach highlights the structural versatility of catalytic Mannich reaction, since the nosyl group allows the access to either primary or secondary amines.

---

[250] Adapted from: N. Kato, T. Shirai, Y. Yamamoto, *Chem. Eur. J.* **2016**, *22*, 7739–7742.

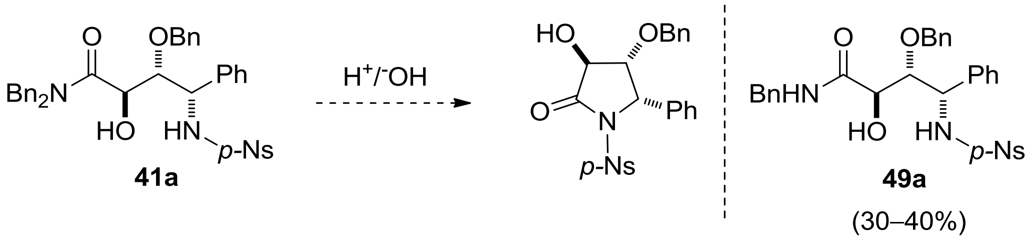
[251] Adapted from: B. Ramalingam, M. Neuburger, *Synthesis* **2007**, 572–582.

[252] Selected examples on the use of nosyl group for the selective alkylation of amines: a) T. Kan, T. Fukuyuma, *Chem. Commun.* **2004**, 353–359; b) F. Cardullo, D. Donati, V. Fusillo, G. Merlo, A. Paio, M. Salaris, A. Solinas, M. Taddei, *J. Comb. Chem.* **2006**, *8*, 834–840. For a recent example on alkylation of *N*-sulfonyl imines, see: J. N. Naoum, K. Chandra, D. Shemesh, R. B. Gerber, C. Gilon, M. Hurevich, *Beilstein J. Org. Chem.* **2017**, *13*, 806–816.



Scheme 93. Preparation of secondary amines.

Disappointingly, attempts to transform the Mannich adducts into γ-lactams were unsuccessful.[253] Mannich adduct **41a** under acidic or basic treatment, regardless of reaction conditions (acid/base concentration and temperature), systematically led to complex mixtures in which only the byproduct **49a** resulting from loss of a benzyl group could be identified (Scheme 94).



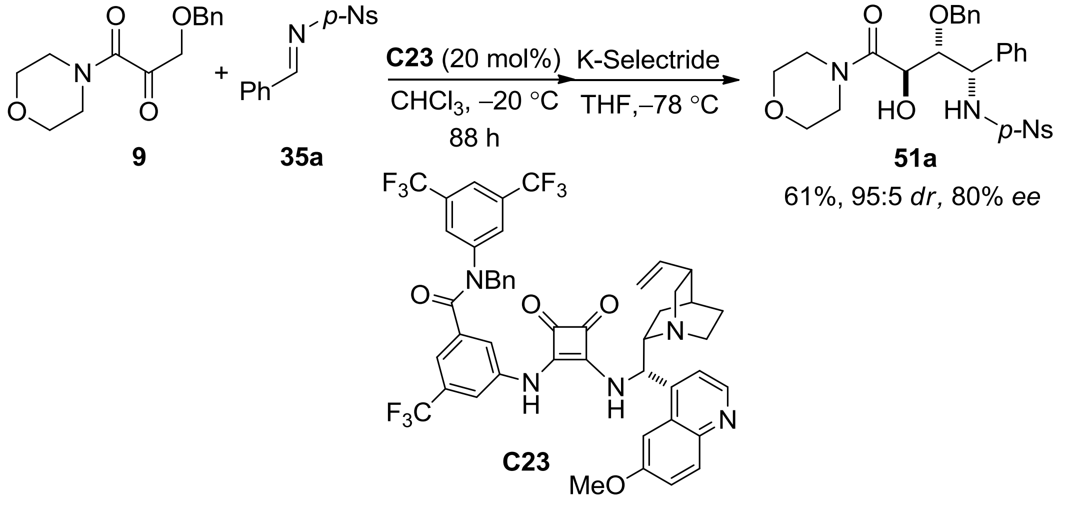
Scheme 94. Unsuccessful production of γ-lactams.

In order to obtain more versatile adducts, we performed the Mannich reaction using morpholine-derived α-keto amide **9** since morpholine-derived amides are recognized as efficient carbonyl surrogates.[254] Under the aforementioned optimized reaction conditions for the Mannich reaction and subsequent reduction of the Mannich adduct **50a**, *anti,syn*-aminodiol **51a** was isolated in good yield and excellent diastereo- and enantioselectivity (Scheme 95).

---

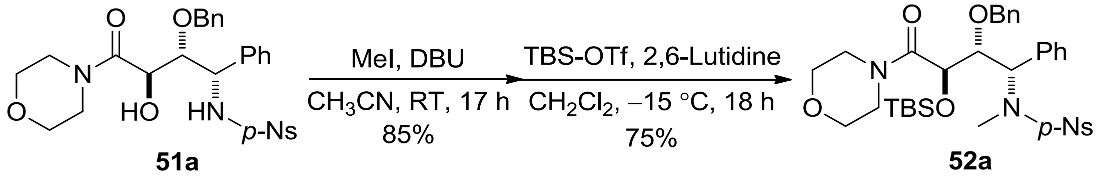
[253] Acidic treatment of aldol adduct gave the corresponding lactone. See Scheme 66, page 127.

[254] Selected examples on the use of morpholine-derived amides as carbonyl surrogate: a) S. E. Denmark, J. R. Heemstra Jr., *J. Am. Chem. Soc.* **2006**, *128*, 1038–1039; b) A. Olivella, C. Rodríguez-Escrich, F. Urpí, J. Vilarrasa, *J. Org. Chem.* **2008**, *73*, 1578–1581.



Scheme 95. Mannich type reaction of α-keto amide **9**.

Adduct **51a** was submitted to standard reaction conditions using phenyl lithium[255] and phenyl magnesium bromide,[256] to produce the corresponding ketone, but complex mixtures were obtained instead. At this point, we considered protecting both the amino- and hydroxyl groups to avoid undesired reactions. Nitrogen alkylation with methyl iodide, followed by silylation of the alcohol in **51a** rendered **52a** in good yield (Scheme 96). But, to our disappointment, all efforts towards the production of the corresponding ketone have been fruitless so far.



Scheme 96. Protection of adduct **51a**.

---

[255] T. Kaku, S. Tsujimoto, N. Matsunaga, T. Tanaka, T. Hara, M. Yamaoka, M. Kusaka, A. Tasaka, *Bioorg. Med. Chem.* **2011**, *19*, 2428–2442.

[256] A. Tasaka, N. Tamura, Y. Matsushita, K. Teranishi, R. Hayashi, K. Okonogi, K. Itoh, *Chem. Pharm. Bull.* **1993**, *41*, 1035–1041.

CHAPTER 4

Conclusions

4. CONCLUSIONS

The potential of β-alkoxy-α-keto amides as pronucleophiles in asymmetric Brønsted base catalyzed carbon-carbon bond forming reactions has been disclosed.

Specifically, the first enantioselective direct cross-aldol reaction of α-keto amides with aldehydes, mediated by a bifunctional ureidopeptide-based Brønsted base catalyst, has been described. The system promoted the exclusive generation of the α-keto amide enolate which reacted with either enolizable or non-enolizable aldehydes to produce highly enantioenriched polyoxygenated aldol adducts without side-products resulting from dehydration, α-keto amide self-condensation, aldehyde enolization and cyclization. Moreover, additional stereoselective reduction of aldol adducts allowed the access to easily modulable enantiopure polyfunctionalized scaffolds containing three contiguous stereocenters.

Likewise, β-alkoxy-α-keto amides have been used as pronucleophiles in the enantioselective direct Mannich type reaction with *p*-nosyl imines. The addition promoted, in this case, by a squaramide-base Brønsted-base catalyst provided an entrance to highly versatile enantioenriched aminopolyols which could be useful intermediates in the synthesis of hydroxylated γ–lactams and pyrrolidines.

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5. EXPERIMENTAL SECTION

5.1. Materials and general techniques

5.1.1. Solvents and reagents

Unless otherwise specified, reagents were obtained from commercial sources (Sigma-Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, etc.), stored as suppliers indicated and used without purification.

When anhydrous solvents were required, they were dried following established protocols. Dichloromethane and acetonitrile were dried over CaH_2. Toluene was dried over sodium. *N,N*-dimethylformamide and dimethyl sulfoxide were dried over MS (3Å). Tetrahydrofuran and diethyl ether were dried by filtration through activated alumina (Sigma-Aldrich).

Triethylamine and *N*,*N*-diisopropylethylamine were purified by distillation.

Aldehydes **10a**–**10d**, **11a**–**11k** and **23a**–**23f** were washed with aqueous saturated $NaHCO_3$ prior to its use. Liquid ones were further purified by distillation before its use and stored in the fridge at –30 °C.

After purification, ureidopeptidic catalysts **C2**, **C7**–**C13** and **C15** and squaramide-based catalysts **C4** and **C16**–**C24** were basified with aqueous saturated $NaHCO_3$ before usage.

Imines **35a**–**35i** and **42a**–**42c** were crushed with hexane before its utilization and stored in the fridge at –30 °C. They decompose over time to give off the corresponding aldehydes and 4-nitrobenzenesulfonamide.

5.1.2. General experimental

All non-aqueous reactions were performed under argon atmosphere in flame dried glassware with efficient magnetic stirring.

Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise specified.

5.1.3. Chromatography

Reactions were monitored by either ^{1}H-NMR analysis of reaction aliquots or thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Ficher Bioblock lamp VL-4LC, λ= 254 and 365 nm. Visualization of TLC was accomplished with a solution of potassium permanganate (1 g) in 100 mL of water (limited lifetime), followed by heating.

Purification of reaction products was carried out by flash column chromatography using ROCC silica gel 60 (40-63 µm, 230-400 mesh).

Non acid silica gel was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 h and subsequent evaporation of water in an oven at 80 °C for 72 hours.

5.1.4. Melting point

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

5.1.5. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported.

5.1.6. Mass spectra

MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) and on an UPLC-DAD-QTOF spectrometer (Ultra High Performance Liquid Chromatograph-Mass spectrometer; Waters UPLC ACQUITY, Waters PDA Detector, Waters Synapt G2). Mass-spectrometry analyses were performed in the General Research Service (SGIKer) of the University of the Basque Country (EHU-UPV).

5.1.7. NMR spectra

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 300 MHz or 500 MHz and 75 MHz or 125 MHz, respectively. The chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak, $CDCl_3$ (δ = 7.26), CD_3OD (δ = 3.31, 4.87), DMSO-d_6 (δ = 2.50) and acetone- d_6 (δ = 2. 05) for ^{1}H NMR and relative to $CDCl_3$ (δ = 77.0), CD_3OD (δ = 49.2), DMSO- d_6 (δ = 39.5) and acetone-d_6 (δ = 206.7) for ^{13}C NMR. Registered spectra process and edition were done using MestReNova MNova 8.1 program. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. The coupling constans (*J*) are reported in Hertz (Hz).

5.1.8. Determination of enantiomeric excesses

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

5.1.9. Optical rotations

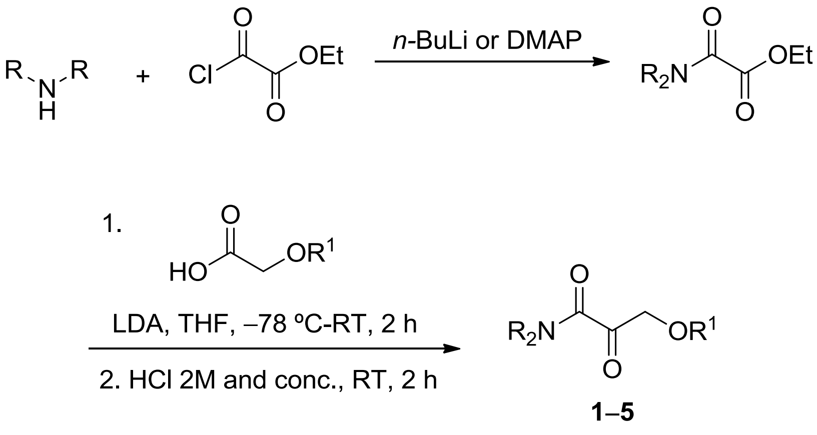
Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotations (SR) ($[\alpha]_D$) are reported in 10^{-1} deg·cm^{2}·g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degree Celsius (°C).

5.1.10. X-Ray diffraction analysis

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

5.2. General procedure for the synthesis of β-alkoxy-α-keto amides 1–9

5.2.1. General procedure for the synthesis of β-alkoxy-α-keto amides 1–5[257]

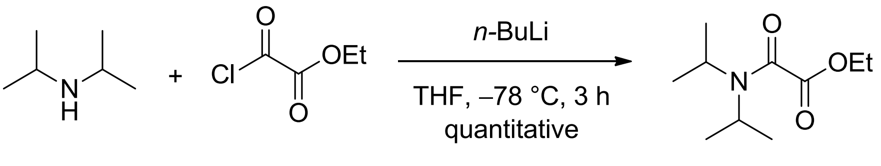

n-BuLi or DMAP
OEt
Cl
R
N
H
R₂N
1.
HO
OR¹
LDA, THF, –78 °C-RT, 2 h
2. HCl 2M and conc., RT, 2 h
O

1–5

5.2.1.1. Preparation of ethyl 2-amino-2-oxoacetates

5.2.1.1.1. Procedure A using n-BuLi

Ethyl 2-(diisopropylamino)-2-oxoacetate

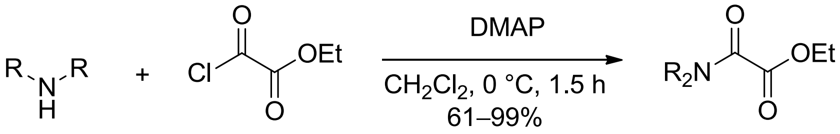

n-BuLi
THF, –78 °C, 3 h
quantitative
N
H
Cl
OEt
O

To a cooled solution of diisopropylamine (2 equiv., 10 mmol, 1.40 mL) in THF (25 mL), *n*-BuLi 1.6M (2 equiv., 10 mmol, 6.25 mL) was added at –78 °C and the reaction mixture was stirred for 30 minutes. Then, ethyl oxalyl chloride (1 equiv., 5 mmol, 0.57 mL) was added dropwise at the same temperature and stirred for another 3 hours. The reaction was then quenched with NH_4Cl (10 mL) and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the crude product which was used in the next step without further purification. Orange oil. Yield: 1.01 g, (quantitative). ^{1}H-RMN (500 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.1, 1H), 4.30 (q, *J* = 7.1, 2H), 3.69 (dt, *J* = 13.2, 6.6, 1H), 3.49 (dt, *J* = 13.6, 6.8, 1H), 1.45 (d, *J* = 6.8, 6H), 1.23 (d, *J* = 6.6, 6H).

---

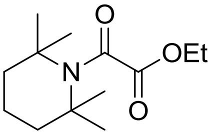
[257] E. R. Koft, P. Dorff, R. Kullnig, *J. Org. Chem.* **1989**, *54*, 2936–2940.

5.2.1.1.2. Procedure B using DMAP



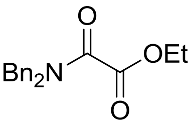
To a cooled solution of the corresponding amine (1 equiv., 5 mmol, 0.99 mL) in CH_2Cl_2 (10 mL), DMAP (1.2 equiv., 6 mmol, 0.73 g) was added at 0 °C and stirred for 1 hour. Then, ethyl oxalyl chloride (2 equiv., 10 mmol, 1.14 mL) was added dropwise and the mixture was stirred for another 1.5 hours. The reaction mixture was quenched with water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic phase was washed with water (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the crude product which was used in the next step without further purification.

Ethyl 2-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yl)acetate



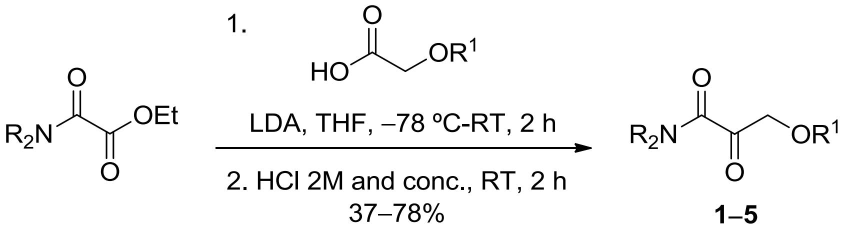
The title compound was prepared from 2,2,6,6-tetramethylpiperidine according to general procedure B. Yellow oil. Yield: 0.74 g, (61%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.2, 2H), 1.73 (s, 6H), 1.48 (s, 12H), 1.35 (t, *J* = 7.2, 3H).

Ethyl 2-(dibenzylamino)-2-oxoacetate



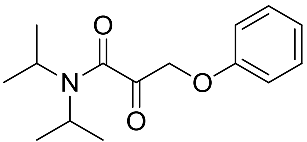
The title compound was prepared from dibenzyl amine and DMAP according to general procedure B. White solid. Yield: 1.48 g, (99%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 10H), 4.50 (s, 2H), 4.34 (p, *J* = 7.2, 4H), 1.32 (t, *J* = 7.1, 3H).

5.2.1.2. Preparation of β-alkoxy-α-keto amides 1–5



To a cooled solution of DIPA (3 equiv.) in THF (7 mL/1 mmol), *n*-BuLi 1.6M (3 equiv.) was added dropwise at –78 °C and the mixture was stirred for 1 hour. Then, the corresponding oxyacetic acid (1.5 equiv.) was added dropwise at the same temperature. After 1 hour, a solution of the corresponding ethyl 2-amino-2-oxoacetate (1 equiv.) in THF (3 mL/1 mmol) was added dropwise and the mixture was stirred for 30 minutes at –78 °C and left up to room temperature for another 2 hours. Then, HCl 2N and HCl conc. were added dropwise (until color changing and bubbling were observed) and the reaction mixture was stirred for 2 hours. Water (20 mL) and diethyl ether (40 mL) were added and the organic phase was successively washed with water (3 x 40 mL), NaOH 2M (3 x 40 mL) and brine (3 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the corresponding 3-alkoxy-2-oxopropanamide that was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10).

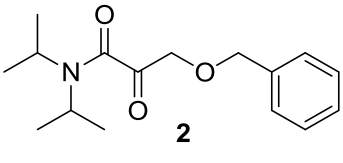
N,N-Diisopropyl-2-oxo-3-phenoxypropanamide (1)



1

The title compound was prepared from phenyloxyacetic acid and ethyl 2-(diisopropylamino)-2-oxoacetate according to the general procedure. Colourless oil. Yield: 0.78 g, (59%). All data were consistent with those previously reported.[257] ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 3H), 7.05 – 6.97 (m, 2H), 4.92 (s, 2H), 3.81 (dt, *J* = 13.3, 6.6, 1H), 3.53 (dt, *J* = 13.7, 6.9, 1H), 1.46 (d, *J* = 6.8, 6H), 1.19 (d, *J* = 6.6, 6H).

3-(Benzyloxy)-N,N-diisopropyl-2-oxopropanamide (2)

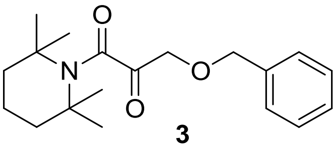


2

The title compound was prepared from benzyloxyacetic acid and ethyl 2-(diisopropylamino)-2-oxoacetate according to the general procedure.

Yellow oil. Yield: 0.53 g, (47%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.65 (s, 2H), 4.39 (s, 2H), 3.74 (dt, *J* = 13.2, 6.5, 1H), 3.50 (dt, *J* = 13.6, 6.9, 1H), 1.44 (d, *J* = 6.8, 6H), 1.18 (d, *J* = 6.6, 6H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 207.1, 198.7, 166.7, 137.2, 128.6, 128.2, 128.2, 74.2, 73.1, 50.1, 46.1, 31.1, 20.8, 20.3. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1763.

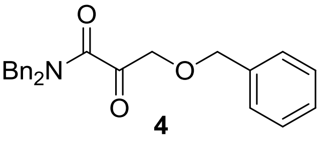
3-(Benzyloxy)-1-(2,2,6,6-tetramethylpiperidin-1-yl)propane-1,2-dione (3)



3

The title compound was prepared from benzyloxyacetic acid and ethyl 2-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yl)acetate according to the general procedure. Yellow oil. Yield: 1.24 g, (78%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 4H), 4.68 (s, 2H), 4.47 (s, 2H), 1.74 (s, 6H), 1.47 (s, 12H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 196.3, 170.7, 137.5, 128.5, 128.0, 73.9, 72.3, 57.1, 37.2, 29.5, 14.9. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{19}H_{28}NO_3$ 318.2069, found 318.2076.

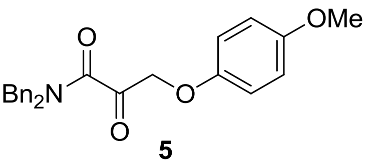
***N,N*-Dibenzyl-3-(benzyloxy)-2-oxopropanamide (4)**



4

The title compound was prepared from benzyloxyacetic acid and ethyl 2-(dibenzylamino)-2-oxoacetate according to the general procedure. Yellow oil. Yield: 1.01 g, (54%). ^{1}H-RMN (300 MHz, $CDCl_3$) 7.38 – 7.17 (m, 15H), 4.65 (s, 2H), 4.52 (s, 2H), 4.49 (s, 2H), 4.36 (s, 2H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 198.6, 166.8, 128.9, 128.7, 128.5, 128.3, 128.3, 128.2, 128.2, 127.9, 74.2, 73.5, 47.0, 46.9. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{24}H_{24}NO_3$ 374.1756, found 374.1754.

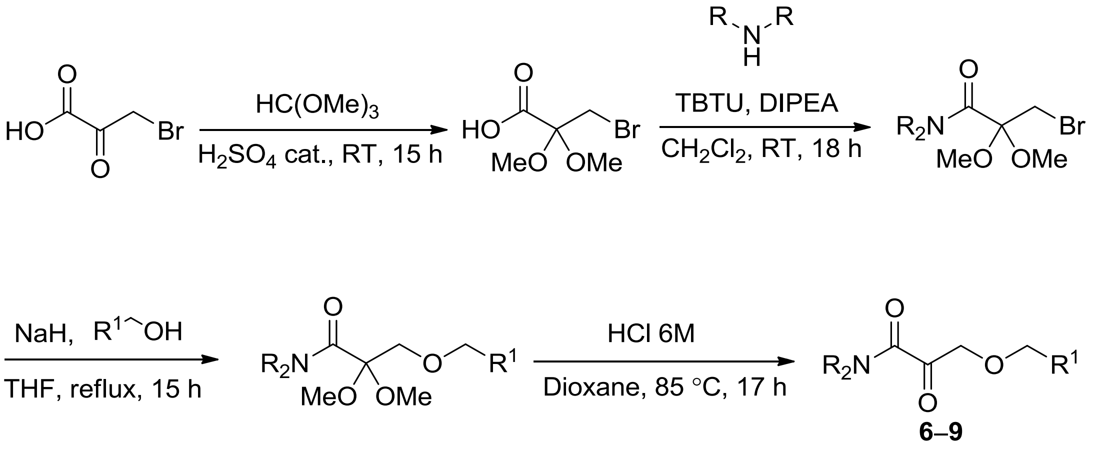
***N,N*-Dibenzyl-3-(4-methoxyphenoxy)-2-oxopropanamide (5)**



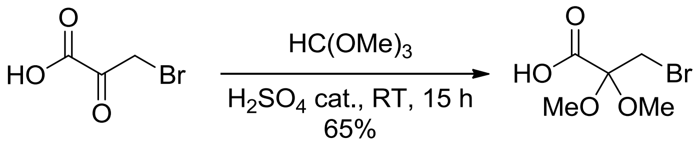
5

The title compound was prepared from 2-(4-methoxyphenoxy)acetic acid and ethyl 2-(dibenzylamino)-2-oxoacetate according to the general procedure. Yellow oil. Yield: 0.58 g, (37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 10H), 6.90 – 6.81 (m, 4H), 4.99 (s, 2H), 4.58 (s, 2H), 4.41 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 166.1, 154.7, 151.8, 135.5, 135.1, 128.9, 128.8, 128.5, 128.2, 128.0, 127.9, 115.8, 114.8, 71.9, 55.7, 49.8, 46.9. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{24}H_{23}NO_4$ 390.1705, found: 390.1711.

5.2.2. General procedure for β-alkoxy-α-keto amides 6–9


HC(OMe)3
H2SO4 cat., RT, 15 h
TBTU, DIPEA
CH2Cl2, RT, 18 h
NaH, R1⌒OH
THF, reflux, 15 h
HCl 6M
Dioxane, 85 °C, 17 h
6–9

5.2.2.1. Preparation of 3-bromo-2,2-dimethoxypropanoic acid[258]


HC(OMe)3
H2SO4 cat., RT, 15 h
65%

To a cooled solution of bromopyruvic acid (20 mmol, 3.34 g) in sulfuric acid (0.25 equiv., 5 mmol, 0.28 mL), trimethyl orthoformate (3 equiv., 60 mmol, 6.56 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 15 hours. Work-up was done by adding HCl 3M (20 mL) and extracting the aqueous phase with CH_2Cl_2 (5 x 10 mL). After back extraction of organic phase with HCl 4M (5 x 10 mL) in order to wash trimethyl orthoformate traces, another back extraction was done with CH_2Cl_2 (10 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford bromoketal acid which was used in the next step without further purification.

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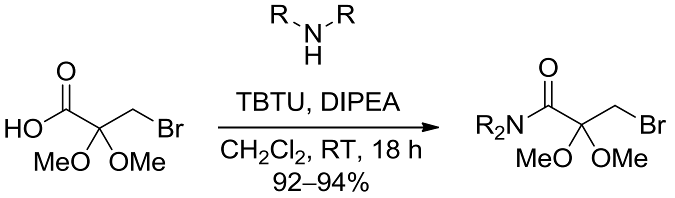
[258] Adapted from: M. R. Davis, E. K. Singh, H. Wahyudi, L. D. Alexander, J. B. Kunicki, L. A. Nazarova, K. A. Fairweather, A. M. Giltrap, K. A. Jolliffe, S. R. McAlpine, *Tetrahedron* **2012**, *68*, 1029–1051.

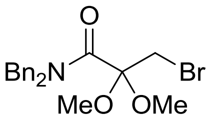
White solid. Yield: 2.78 g (65%). All data were consistent with those previously reported. ^{1}H RMN (300 MHz, $CDCl_3$) δ 3.62 (s, 2H), 3.37 (s, 6H).

5.2.2.2. Preparation of 3-bromo-2,2-dimethoxypropanamides[258]



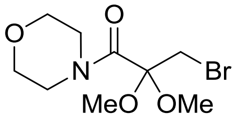
To a solution of 3-bromo-2,2-dimethoxypropanoic acid (1 equiv., 13 mmol, 2.78 g) in CH_2Cl_2 (130 mL), were added the corresponding amine (1.1 equiv, 14.3 mmol), DIPEA (4 equiv., 52 mmol, 9.06 mL) and TBTU (1.1 equiv., 14.3 mmol, 4.59 g). The reaction mixture was stirred at room temperature for 15 hours. Another 0.25 equiv. of TBTU were added and the reaction mixture was stirred for additional 3 hours. Then, the mixture was washed with HCl 3M (2 x 100 mL), the organic layer dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 80:20) to afford the corresponding 3-bromo-2,2-dimethoxypropanamide.

N,N-Dibenzyl-3-bromo-2,2-dimethoxypropanamide



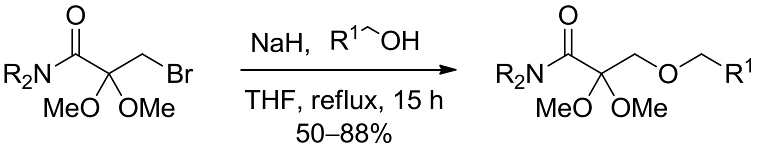
The title compound was prepared from dibenzyl amine according to the general procedure. White solid. Yield: 4.69 g (92%). White solid. m.p.= 60–62°C. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 10H), 4.92 (s, 2H), 4.57 (s, 2H), 3.81 (s, 2H), 3.33 (s, 6H).

3-Bromo-2,2-dimethoxy-1-morpholinopropan-1-one



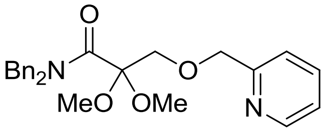
The title compound was prepared from morpholine according to the general procedure. Orange oil. Yield: 3.45 g, (94%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 4.02 (brs, 2H), 3.72 (s, 2H), 3.70 (brs, 6H), 3.33 (s, 6H).

5.2.2.3. *Preparation of 3-alkoxy-2,2-dimethoxypropanamides*



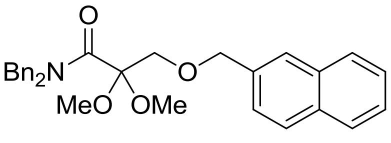
To a suspension of NaH (5 equiv.) in THF (40 mL), the corresponding alcohol (2 equiv.) was added at 0 °C. The reaction mixture was stirred at reflux for 1 hour. At room temperature, a solution of the corresponding 3-bromo-2,2-dimethoxypropanamide derivative (1 equiv.) in THF (20 mL) was added and the mixture was stirred at reflux for another 15 hours. The reaction temperature was then lowered to room temperature and the reaction was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding ethers. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10–60:40) to afford the corresponding 3-alkoxy-2,2-dimethoxypropanamide.

N,N-dibenzyl-2,2-dimethoxy-3-(pyridin-2-ylmethoxy)propanamide



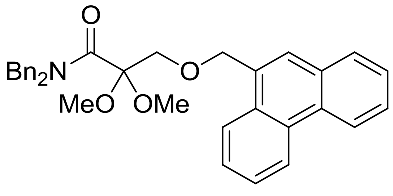
The title compound was prepared from *N*,*N*-dibenzyl-3-bromo-2,2-dimethoxypropanamide and pyridin-2-ylmethanol according to the general procedure. Yellow oil. Yield: 2.84 g, (52%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.8, 1.6, 0.8, 1H), 7.57 (td, *J* = 7.7, 1.8, 1H), 7.35 – 7.13 (m, 12H), 4.86 (s, 2H), 4.65 (s, 2H), 4.53 (s, 2H), 3.89 (s, 2H), 3.33 (s, 6H).

N,N-Dibenzyl-2,2-dimethoxy-3-(naphthalen-2-ylmethoxy)propanamide



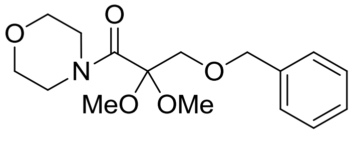
The title compound was prepared from naphthalen-2-ylmethanol and *N*,*N*-dibenzyl-3-bromo-2,2-dimethoxypropanamide according to the general procedure. Yellow oil. Yield: 5.13 g, (84%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.87 – 7.67 (m, 4H), 7.51 – 7.46 (m, 3H), 7.34 – 7.24 (m, 10H), 4.86 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 3.83 (s, 2H), 3.30 (s, 6H).

N,N-Dibenzyl-2,2-dimethoxy-3-(phenanthren-9-ylmethoxy)propanamide



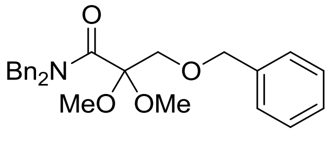
The title compound was prepared from phenanthren-9-ylmethanol and *N,N*-dibenzyl-3-bromo-2,2-dimethoxypropanamide according to the general procedure. Orange solid. Yield: 3.38 g, (50%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 13.2, 8.1, 1H), 8.66 (d, *J* = 8.0, 1H), 8.10 (d, *J* = 8.2, 1H), 7.83 – 7.78 (m, 1H), 7.69 – 7.48 (m, 5H), 7.21 (m, 10H), 5.02 (s, 2H), 4.85 (s, 2H), 4.52 (s, 2H), 3.89 (s, 2H), 3.22 (s, 6H).

3-(Benzyloxy)-2,2-dimethoxy-1-morpholinopropan-1-one



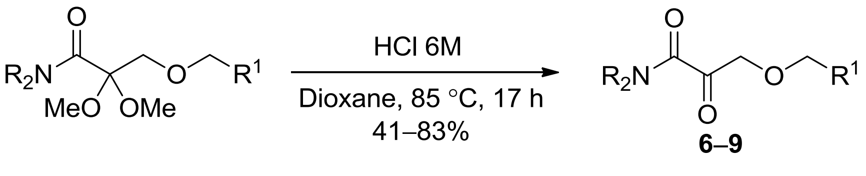
The title compound was prepared from benzyl alcohol and 3-bromo-2,2-dimethoxy-1-morpholinopropan-1-one according to the general procedure. Yellow pale oil. Yield: 2.73 g, (68%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 4.52 (s, 2H), 3.87 (brs, 2H), 3.68 (s, 2H), 3.65 (brs, 4H), 3.47 (d, *J* = 6.5, 2H), 3.29 (s, 6H).

N,N-Dibenzyl-3-(benzyloxy)-2,2-dimethoxypropanamide



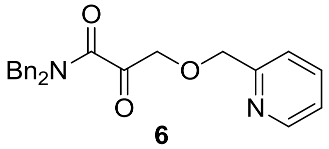
The title compound was prepared from *N,N*-dibenzyl-3-bromo-2,2-dimethoxypropanamide and benzyl alcohol according to the general procedure. Yellow oil. Yield: 4.80 g, (88%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 15H), 4.84 (s, 2H), 4.52 (s, 2H), 4.51 (s, 2H), 3.79 (s, 2H), 3.31 (s, 6H).

5.2.2.4. Preparation of β-alkoxy-α-keto amides 6–9



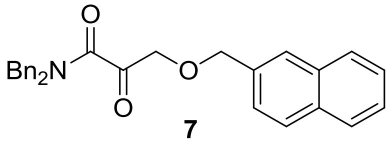
To a solution of the corresponding 3-alkoxy-2,2-dimethoxypropanamide obtained in the previous step in dioxane (2 mL/mmol), HCl 6M was added (2 mL/mmol) and the mixture was stirred at 85 °C for 17 hours. At room temperature, water (2 mL/mmol) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL/mmol). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford the corresponding β-alkoxy-α-keto amide.

***N*,*N*-Dibenzyl-2-oxo-3-(pyridin-2-ylmethoxy)propanamide (6)**


6

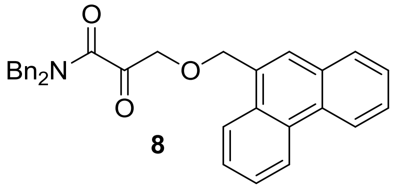
The title compound was prepared from *N*,*N*-dibenzyl-2,2-dimethoxy-3-(pyridin-2-ylmethoxy)propanamide according to the general procedure. Before work-up was done as described in the general procedure, pH was adjusted up to 8–9 by adding a solution of $NaHCO_3$ (sat.). Orange oil. Yield: 1.32 g, (83%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.0, 1H), 7.68 (td, *J* = 7.7, 1.7, 1H), 7.44 – 7.28 (m, 7H), 7.25 – 7.17 (m, 5H), 4.75 (s, 2H), 4.61 (s, 2H), 4.53 (s, 2H), 4.41 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 166.6, 149.4, 148.8, 137.0, 135.7, 135.3, 129.6, 129.1, 129.0, 128.7, 128.4, 128.2, 128.0, 122.9, 121.9, 74.9, 74.1, 50.0, 47.1. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{23}H_{23}N_2O_3$ 375.1709, found 375.1712.

***N*,*N*-Dibenzyl-3-(naphthalen-2-ylmethoxy)-2-oxopropanamide (7)**


7

The title compound was prepared from *N*,*N*-dibenzyl-2,2-dimethoxy-3-(naphthalen-2-ylmethoxy)propanamide according to the general procedure. Yellow oil. Yield: 3.24 g, (70%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.89 – 7.76 (m, 4H), 7.48 (m, 3H), 7.33 – 7.17 (m, 10H), 4.81 (s, 2H), 4.53 (s, 2H), 4.52 (s, 2H), 4.36 (s, 2H). 13C RMN (75 MHz, $CDCl_3$) δ 198.5, 166.8, 135.7, 135.3, 134.5, 133.4, 129.0, 128.9, 128.6, 128.6, 128.3, 128.2, 128.0, 127.9, 127.3, 126.4, 126.3, 126.1, 74.4, 73.5, 49.9, 46.9. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{28}H_{26}NO_3$ 424.1913, found 424.1915.

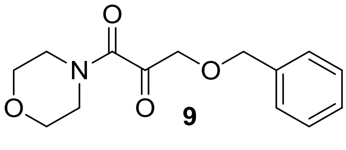
N,N-dibenzyl-2-oxo-3-(phenanthren-9-ylmethoxy)propanamide (8)



8

The title compound was prepared from *N*,*N*-dibenzyl-2,2-dimethoxy-3-(phenanthren-9-ylmethoxy)propanamide according to the general procedure. Yellow solid. Yield: 1.85 g, (60%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.74 (d, J = 7.9, 1H), 8.69 (d, *J* = 8.3, 1H), 8.21 (dd, *J* = 8.1, 1.0, 1H), 7.87 (dd, *J* = 7.8, 1.3, 1H), 7.77 (s, 1H), 7.72 – 7.55 (m, 4H), 7.21 (m, 10H), 5.15 (s, 2H), 4.59 (s, 2H), 4.51 (s, 2H), 4.32 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 166.8, 135.6, 135.2, 131.3, 130.9, 130.9, 130.6, 129.0, 128.9, 128.6, 128.5, 128.3, 128.1, 127.9, 127.3, 127.1, 127.0, 126.9, 125.0, 123.2, 122.7, 73.3, 73.2, 50.0, 46.9. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{32}H_{48}NO_3$ 474.2069, found 474.2064.

3-(Benzyloxy)-1-morpholinopropane-1,2-dione (9)



9

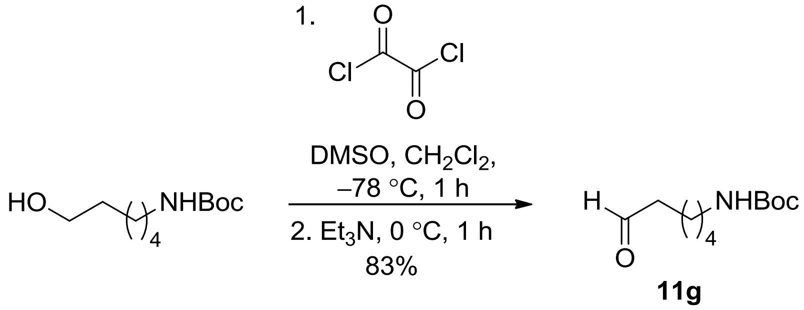
The title compound was prepared from 3-(benzyloxy)-2,2-dimethoxy-1-morpholinopropan-1-one and the mixture was stirred at 50 °C for 5 h, according to the general procedure. Before work-up was done as described in the general procedure, pH was adjusted up to 8–9 by adding a solution of $NaHCO_3$ (sat.). Yellow pale oil. Yield: 0.95 g, (41%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 5H), 4.62 (s, 2H), 4.46 (s, 2H), 3.70 – 3.57 (m, 6H), 3.49 – 3.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 164.1, 136.9, 128.6, 128.3, 128.2, 74.1, 73.2, 66.8, 66.6, 46.0, 42.0.UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1237.

5.3. General procedure for the synthesis of aldehydes

Propargylic aldehydes **10a** and **10d**, aliphatic aldehydes **11a**–**11f, 11h, 11j** and **11k** and aromatic aldehydes **23a**–**23f** are commercially available and were purchased from commercial suppliers.

5.3.1. General procedure for the synthesis of aliphatic aldehydes 11g and 11i

***tert*-Butyl (6-oxohexyl)carbamate[259] (11g)**



To a cooled solution of oxalyl chloride (1.6 equiv., 16 mmol, 1.40 mL) in dichloromethane (20 mL) a solution of DMSO (3.2 equiv., 32 mmol, 2.27 mL) in dichloromethane (10 mL) was added at –78 °C and stirred for 5 minutes. Then, a solution of *tert*-butyl (6-hydroxyhexyl)carbamate (1 equiv., 10 mmol, 2.17 g) in dichloromethane (20 mL) was added dropwise and stirred for another hour at the same temperature. Subsequently, triethylamine (4.8 equiv., 48 mmol, 6.68 mL) was added and the solution was allowed to reach 0 °C and stirred for an additional hour. The mixture was poured into water (40 mL) and diluted with Et_2O (80 mL). The organic phase was separated and washed with brine (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduce pressure to afford the crude product which was purified by flash column chromatography on silica gel to afford aldehyde **11g** as a colourless oil. Yield: 1.78 g, (83%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7, 1H), 4.52 (s, 1H), 3.11

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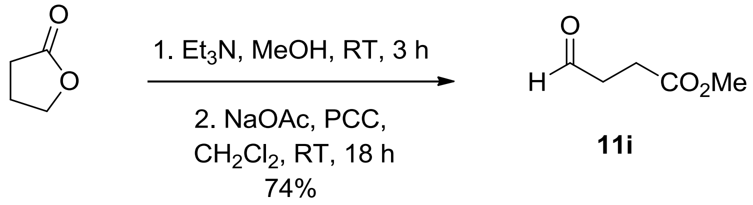
[259] X. Xiao, S. Antony, G. Kohlhagen, Y. Pommier, M. Cushman, *Bioorg. Med. Chem.* **2004**, *126*, 5147–5160.

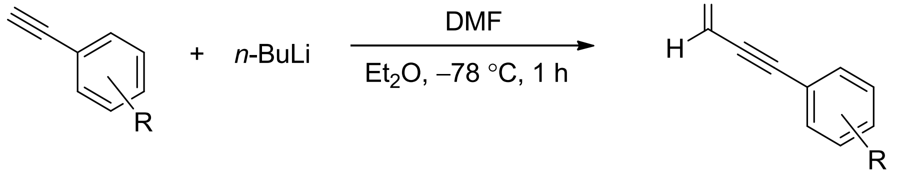
(dd, *J* = 13.1, 6.6, 2H), 2.43 (td, *J* = 7.3, 1.7, 2H), 1.71 – 1.57 (m, 2H), 1.50 (dd, *J* = 11.2, 4.0, 3H), 1.43 (s, 9H), 1.36 (ddd, *J* = 12.8, 7.1, 2.5, 2H).

Methyl 4-oxobutanoate (11i)


1. Et$_3$N, MeOH, RT, 3 h
2. NaOAc, PCC, CH$_2$Cl$_2$, RT, 18 h
74%
H
CO$_2$Me
11i

To a solution of γ-butyrolactone (1 equiv., 10 mmol, 0.77 mL) in MeOH (10 mL), was added triethylamine (6 equiv., 60 mmol, 8.40 mL) and the reaction mixture was stirred at room temperature until the dissapearance of the starting material (progress was monitorized by infrared spectra). After solvent evaporation, the residue was dissolved in CH_2Cl_2 (20 mL) and sodium acetate (0.32 equiv., 3.2 mmol, 0.26 g) and pyridinium chlorochromate (1.5 equiv., 15 mmol, 3.23 g) were added. The mixture was stirred at room temperature for 18 hours and then was filtered off through silica gel with CH_2Cl_2 (20 mL). After solvent removal under vacuum, the residue was purified by flash column chromatography on silica gel to afford aldehyde **11i** as a colourless oil. Yield: 0.86 g, (74%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.81 (s, 1H), 3.69 (s, 3H), 2.80 (t, *J* = 6.6, 2H), 2.63 (t, *J* = 6.4, 2H).

5.3.2. General procedure for the synthesis of propargylic aldehydes 10b and 10c[260]



10b R= 4-OMe, 48%
10c R= 3-Cl, 69%

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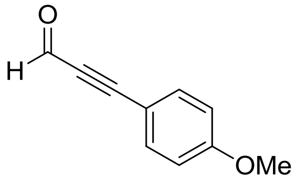
[260] E. Gómez-Bengoa, M. Maestro, A. Mielgo, I. Otazo, C. Palomo, I. Velilla, *Chem. Eur. J.* **2010**, *16*, 5333–5342.

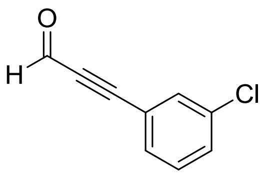
To a cooled solution of *n*-BuLi 1.6M (1 equiv., 6 mmol, 3.75 mL) in Et_2O (6 mL) at to –78 °C, was added dropwise the corresponding alkyne (1 equiv., 6 mmol). The reaction mixture was stirred at this temperature for 30 minutes after which DMF (1.25 equiv., 7.5 mmol, 0.58 mL) was added slowly. The resulting mixture was warmed slowly to room temperature and stirred for 20 minutes. Then, the reaction mixture was poured slowly into a cold solution of water (25 mL) and HCl 4M (4 mL) and basified with a solution of saturated $NaHCO_3$ until pH 6–7. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude product was purified by flash column chromatography on silica gel to afford the corresponding aldehyde.

3-(4-Methoxyphenyl)propiolaldehyde (10b)



The title compound was prepared from 1-ethynyl-4-methoxybenzene according to the general procedure. White solid. Yield: 0.47 g, (48%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.63 – 7.49 (m, 2H), 6.96 – 6.86 (m, 2H), 3.85 (s, 3H).

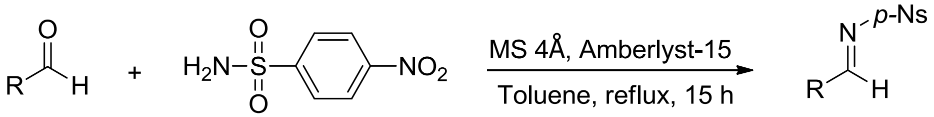
3-(3-Chlorophenyl)propiolaldehyde (10c)



The title compound was prepared from benzaldehyde according to the general procedure. Orange oil. Yield: 0.68 g, (69%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.64 – 7.26 (m, 4H).

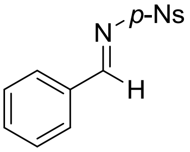
5.4. General procedure for the synthesis of *p*-Ns-imines

5.4.1. General procedure for the synthesis of aromatic *p*-Ns-imines 35a–35i[261]



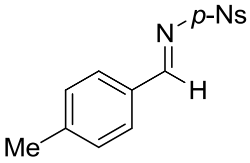
A sealed tube containing stirrer, molecular sieves 4Å (400 mg/mmol, 4 g) and Amberlyst-15 (35 mg/mmol, 0.35 g) was flamed. At room temperature, dry toluene (10 ml) was added. Then, 4-nitrobenzenesulfonamide (1 equiv., 10 mmol) and benzaldehyde (1.1 equiv., 11 mmol) were added followed by the addition of more dry toluene (10 ml). The suspension was stirred at reflux for 15 hours. At room temperature, the mixture was filtered through celite, washed with CH_2Cl_2 (2 x 20 mL) and concentrated in vacuo. The resulting solid was crushed with hexane (to remove aldehyde excess), filtered off and washed with hexane (2 x 15 mL) to afford the corresponding *p*-nosyl imines **35a**–**35i** which were used in asymmetric reactions without further purification.

(*E*)-*N*-Benzylidene-4-nitrobenzenesulfonamide (35a)



The title compound was prepared from benzaldehyde according to the general procedure. Brown pale solid. Yield: 2.06 g, (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.43 – 8.36 (m, 2H), 8.26 – 8.19 (m, 2H), 8.00 – 7.92 (m, 2H), 7.53 (t, *J* = 7.6, 2H).

(*E*)-*N*-(4-Methylbenzylidene)-4-nitrobenzenesulfonamide (35b)



The title compound was prepared from 4-methylbenzaldehyde according to the general procedure. Brown pale solid. Yield: 1.88 g, (62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.38 (d, *J* = 9.0, 2H), 8.20 (d, *J* = 9.0, 2H), 7.84 (d, *J* = 8.2, 2H), 7.33 (d, *J* = 8.0, 2H), 2.45 (s, 3H).

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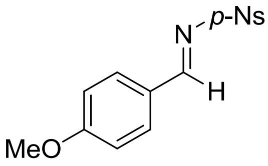
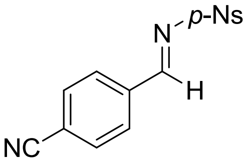
[261] J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 629–633.

(*E*)-*N*-(4-Methoxybenzylidene)-4-nitrobenzenesulfonamide (35c)



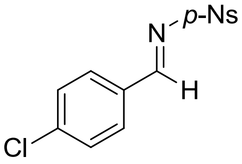
The title compound was prepared from 4-methoxybenzaldehyde according to the general procedure. Brown pale solid. Yield: 2.43 g, (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.38 (d, *J* = 9.0, 2H), 8.19 (d, *J* = 9.0, 2H), 7.92 (d, *J* = 8.9, 2H), 7.00 (d, *J* = 8.9, 2H), 3.91 (s, 3H).

(*E*)-*N*-(4-Cyanobenzylidene)-4-nitrobenzenesulfonamide (35d)



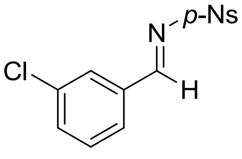
The title compound was prepared from 4-formylbenzonitrile according to the general procedure. Yellow pale solid. Yield: 2.43 g, (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.42 (d, *J* = 8.8, 2H), 8.23 (d, *J* = 8.8, 2H), 8.06 (d, *J* = 8.4, 2H), 7.82 (d, J = 8.4, 2H).

(*E*)-*N*-(4-Chlorobenzylidene)-4-nitrobenzenesulfonamide (35e)



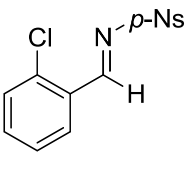
The title compound was prepared from 4-chlorobenzaldehyde according to the general procedure. Brown pale solid. Yield: 2.42 g, (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.45 – 8.36 (m, 2H), 8.25 – 8.17 (m, 2H), 7.94 – 7.85 (m, 2H), 7.55 – 7.48 (m, 2H).

(*E*)-*N*-(3-Chlorobenzylidene)-4-nitrobenzenesulfonamide (35f)



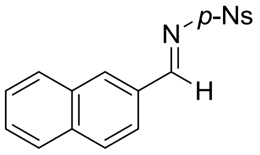
The title compound was prepared from 3-chlorobenzaldehyde according to the general procedure. Brown pale solid. Yield: 2.46 g, (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.41 (d, *J* = 9.0, 2H), 8.22 (d, *J* = 9.0, 2H), 7.96 (t, *J* = 1.8, 1H), 7.84 – 7.79 (m, 1H), 7.63 (ddd, *J* = 8.0, 2.1, 1.1, 1H), 7.48 (t, *J* = 7.9, 1H).

(*E*)-*N*-(2-Chlorobenzylidene)-4-nitrobenzenesulfonamide (35g)



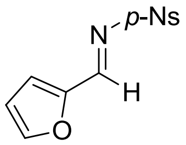
The title compound was prepared from 2-chlorobenzaldehyde according to the general procedure. Brown pale solid. Yield: 2.59 g, (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.47 – 8.37 (m, 2H), 8.27 – 8.19 (m, 2H), 8.15 (dd, *J* = 7.8, 1.5, 1H), 7.63 – 7.48 (m, 2H), 7.38 (dd, *J* = 7.8, 7.2, 1H).

(*E*)-*N*-(Naphthalen-2-ylmethylene)-4-nitrobenzenesulfonamide (35h)



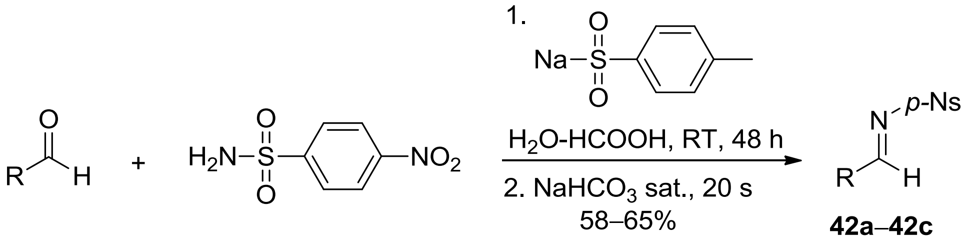
The title compound was prepared from 2-naphthaldehyde according to the general procedure. Brown pale solid. Yield: 2.45 g, (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.40 (dt, *J* = 10.7, 5.4, 4H), 8.30 – 8.21 (m, 2H), 8.06 – 7.96 (m, 2H), 7.91 (dd, *J* = 8.3, 4.1, 2H), 7.72 – 7.57 (m, 2H).

(*E*)-*N*-(Furan-2-ylmethylene)-4-nitrobenzenesulfonamide (35i)



The title compound was prepared from furan-2-carbaldehyde according to the general procedure. Orange solid. Yield: 1.96 g, (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.38 (d, *J* = 8.8, 2H), 8.19 (d, *J* = 8.7, 2H), 7.81 (s, 1H), 7.44 (d, *J* = 3.7, 1H), 6.70 (dd, *J* = 3.6, 1.6, 1H).

5.4.2. General procedure for the synthesis of aliphatic *p*-Ns-imines 42a–42c[262]



A suspention of the corresponding aldehyde (1 equiv., 10 mmol), 4-nitrobenzenesulfonamide (1 equiv., 10 mmol) and sodium *p*-toluenesulfinate (1 equiv., 10 mmol) in formic acid (15 mL) and water (15 mL) was stirred vigorously for 48 hours. The resulting white precipitate was filtered off and washed with water (3 x 15 mL) and hexane (2 x 15 mL). The precipitate was dissolved in CH_2Cl_2 (50 mL) and the organic phase was rapidly washed with saturated $NaHCO_3$ (10 mL). (**NOTE:** the time of this step is very important. The separatory funnel must be vigorously shaken for at most 20 seconds). The organic layer was rapidly dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the corresponding *p*-nosyl imines **42a**–**42c** which were used in asymmetric reactions without further purification.

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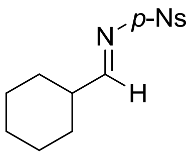
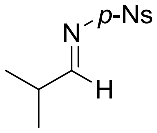
[262] Z. Cui, H.-J. Yu, R.-F. Yang, W.-Y. Gao, C.-G. Feng, G.-Q. Lin, *J. Am. Chem. Soc.* **2011**, *133*, 12394–12397.

(*E*)-*N*-(Cyclohexylmethylene)-4-nitrobenzenesulfonamide (42a)



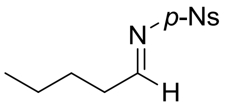
The title compound was prepared from cyclohexanecarbaldehyde according to the general procedure. White solid. Yield: 1.72 g, (58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.3, 1H), 8.44 – 8.33 (m, 2H), 8.18 – 8.10 (m, 2H), 2.48 (dt, *J* = 7.4, 5.3, 1H), 1.95 – 1.66 (m, 6H), 1.33 (t, *J* = 10.1, 4H).

(*E*)-*N*-(2-Methylpropylidene)-4-nitrobenzenesulfonamide (42b)



The title compound was prepared from isobutyraldehyde according to the general procedure. White solid. Yield: 1.54 g, (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.0, 1H), 8.38 (d, *J* = 8.9, 2H), 8.13 (d, *J* = 8.9, 2H), 2.84 – 2.66 (m, 1H), 1.17 (d, *J* = 6.9, 6H).

(E)-4-Nitro-N-pentylidenebenzenesulfonamide (42c)



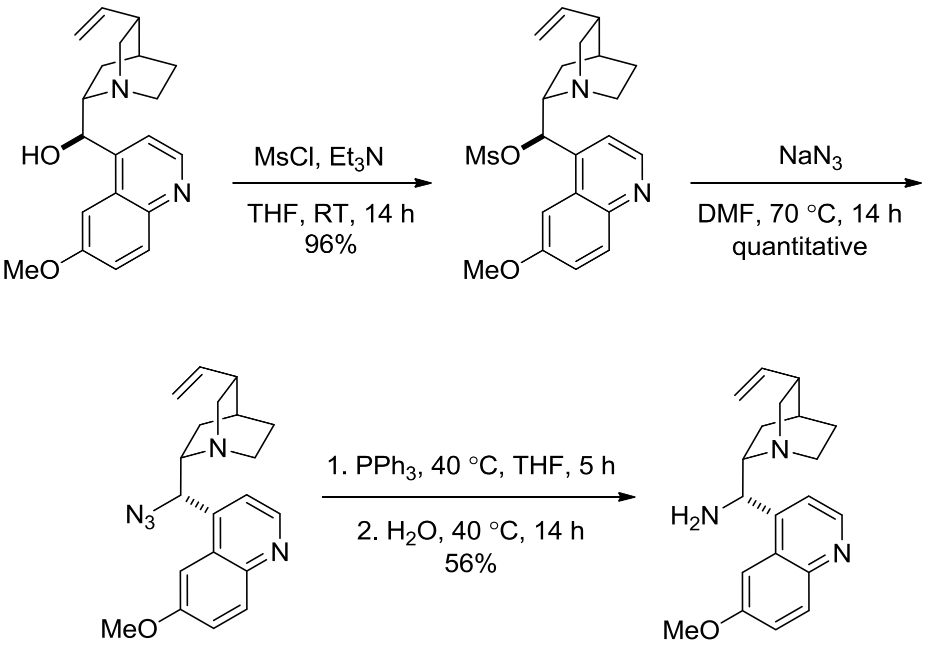
The title compound was prepared from pentanal according to the general procedure. White solid. Yield: 1.75 g, (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (t, *J* = 4.5, 1H), 8.43 – 8.33 (m, 2H), 8.21 – 8.11 (m, 2H), 2.58 (td, *J* = 7.4, 4.5, 2H), 1.63 (dt, *J* = 20.5, 7.4, 2H), 1.38 (dt, *J* = 14.8, 7.3, 2H), 0.91 (t, *J* = 7.3, 3H).

5.5. General procedure for the synthesis of catalysts

Quinine **C1**, $(DHQ)_2PYR$ **C3** and thiourea **C5** were purchased from commercial suppliers. All bifunctional catalysts employed in this work include a chiral amine as Brønsted-base fragment. The synthesis of these amines is first described in the following section.

5.5.1. Preparation of chiral amines

5.5.1.1. Preparation of 9-amino-(9-deoxy)epiquinine[263]


HO
N
N
MeO
MsCl, Et3N
THF, RT, 14 h
96%
MsO
N
N
MeO
NaN3
DMF, 70 °C, 14 h
quantitative
N3
N
N
MeO
1. PPh3, 40 °C, THF, 5 h
2. H2O, 40 °C, 14 h
56%
H2N
N
N
MeO

1st step:[264] A mixture of quinine (1 equiv., 50 mmol, 16.2 g) and triethylamine (3.6 equiv., 180 mmol, 25.1 mL) in dry THF (250 mL) was cooled to 0 °C and then methanesulfonyl chloride (1.8 equiv., 90 mmol, 7.0 mL) was added dropwise. The mixture was stirred at room temperature for 14 hours. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with water (30 mL) and saturated $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude product (96% yield) which was used in the next step without further purification.

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[263] Adapted from: H. Brunner, J. Büegler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.

[264] Adapted from: M. Zielinska-Blajet, M. Kucharska, J. Skarzewski, *Synthesis* **2006**, 4383–4387.

2nd step:[265] The crude mesylate (1 equiv., 48 mmol, 19.3 g) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and sodium azide (2 equiv., 96 mmol, 6.2 g) was added portionwise. The mixture was stirred at 70 °C for 16 hours and after this time the reaction mixture was quenched with water (80 mL) and diluted with EtOAc (150 mL). The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude azide in quantitative yield which was used in the next step without further purification.

3rd step:[265] The crude azide was dissolved in THF (250 mL) and PPh_3 (1 equiv., 48 mmol, 12.6 g) was added. The reaction mixture was heated to 40 °C and stirred until gas evolution ceased (ca. 5 hours). Then, water (8 mL) was added and the mixture was stirred at 40 °C for 14 hours. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with CH_2Cl_2 (2 x 100 mL). Then, the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH (40%). The aqueous phase was then extracted with CH_2Cl_2 (3 x 150 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give pure 9-amino-(9-deoxy)*epi*quinine. Brown foam. Yield: 8.7 g (56%). All data were consistent with those previously reported.[266] ^1H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36 – 8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02 – 3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26 – 1.63 (m, 4H), 0.80 (m, 1H).

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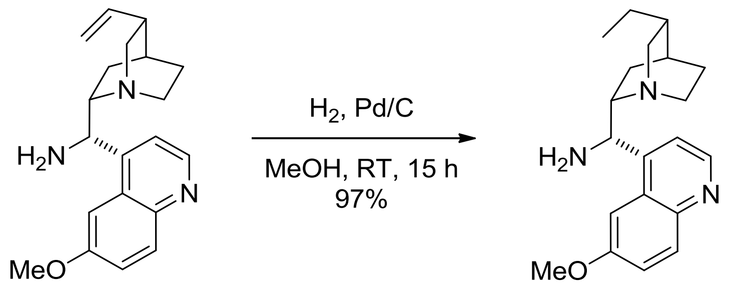
[265] Adapted from: U. Sudermeier, C. Döbler, G. M. Mehlretter, W. Baumann, *Chirality* **2003**, *15*, 127–134.

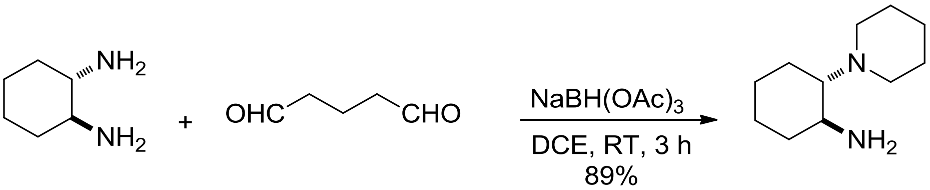
[266] W. He, P. Liu, B. L. Zhang, X. L. Sun, S. Y. Zhang, *Appl. Organometal. Chem.* **2006**, *20*, 328–334.

5.5.1.2. Preparation of 9-amino-(9-deoxy)epihydroquinine



To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 30 mmol, 9.6 g) in methanol (30 mL), Pd/C was added (Pd 10% in activated carbon, 10% in weight, 0.96 g) and stirred for 15 hours under H_2 atmosphere. Then, the reaction mixture was filtered over celite and concentrated under reduced pressure to afford pure 9-amino-(9-deoxy)*epi*hydroquinine. Brown foam. Yield: 9.47 g (97%). All data were consistent with those previously reported.[267] ^{1}H-RMN (300 MHz, CD_3OD) δ 8.69 (d, *J* = 4.7, 1H), 7.97 (d, *J* = 9.3, 1H), 7.69 (brs, 1H), 7.61 (d, *J* = 4.7, 1H), 7.45 (d, *J* = 9.3, 2.6, 1H), 4.72 (d, *J* = 11.0, 1H), 4.00 (s, 3H), 3.36 – 3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9, 1H), 3.16 (q, *J* = 10.7, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3, 1H), 1.62 – 1.58 (m, 1H), 1.60 (d, *J* = 13.3, 10.4, 1H), 1.58 – 1.47 (m, 4H), 0.85 (t, *J* = 7.3, 3H).

5.5.1.3. (1S,2S)-2-(piperidin-1-yl)cyclohexanamine[268]



To a mixture of (1*S*,2*S*)-cyclohexane-1,2-diamine (1 equiv., 10 mmol, 1.14 g) and $NaBH(OAc)_3$ (4 equiv., 40 mmol, 8.50 g) in $ClCH_2CH_2Cl$ (60 mL), glutaraldehyde (1.04 equiv., 50 wt% in H_2O, 10.4 mmol, 1.9 mL) was added dropwise at room temperature and stirred for 3 hours. The mixture was quenched with NaOH 6M aq solution (30 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine which was used in next step without further purification. Yellow oil. Yield: 1.62 g (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 – 2.68 (m, 1H), 2.67 – 2.49 (m, 3H), 2.41 – 2.19 (m, 2H), 2.16 –1.92 (m, 2H), 1.88 – 1.34 (m, 8H), 1.31 – 0.97 (m, 4H).

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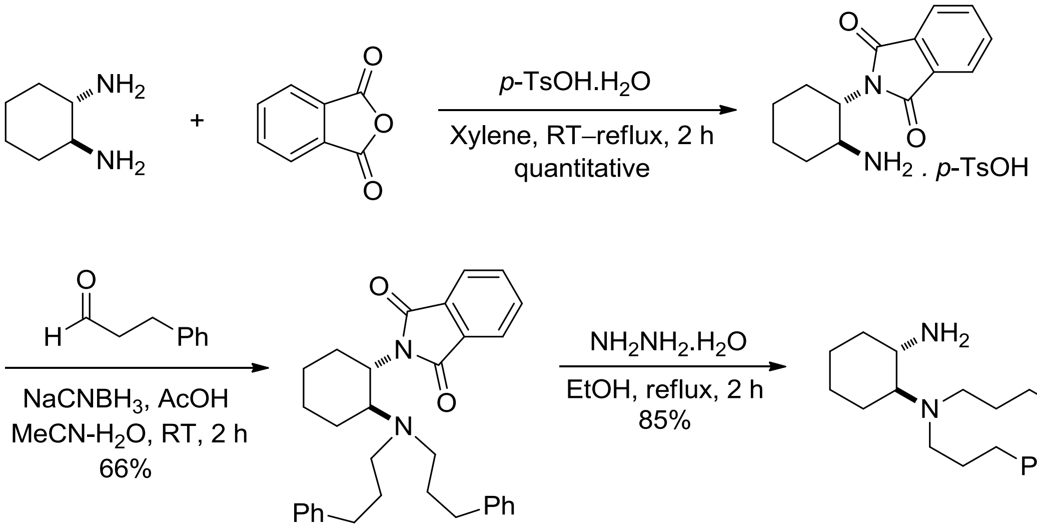
[267] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967–1969.

[268] Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed*. **2010**, *49*, 153–156.

5.5.1.4. (1S,2S)-N^1,N^1-bis(3-phenylpropyl)cyclohexane-1,2-diamine[269]



1st step: A solution of *p*-toluenesulfonic acid monohydrate (1 equiv., 8 mmol, 1.55 g) in xylene (40 mL) was heated to reflux for 2 hours using a Dean-Stark. At room temperature, (1*S*,2*S*)-cyclohexane-1,2-diamine (1 equiv., 8 mmol, 0.91 g) and phtalic anhydride (1 equiv., 8 mmol, 1.18 g) were added and heated to reflux until the mixture became homogeneous. Later, the desired product precipitated. The precipitate was filtered off and washed with xylene and hexane to afford 2-((1*S*,2*S*)-2-aminocyclohexyl)isoindoline-1,3-dione which was used in next step without further purification. Brown pale salt. Yield: 3.35 g (quantitative). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.55 (dd, *J* = 5.5, 3.0, 2H), 7.42 (dd, *J* = 5.5, 3.0, 2H), 7.33 (d, *J* = 8.1, 2H), 7.00 (d, *J* = 8.0, 2H), 4.19 (td, *J* = 11.9, 4.0, 1H), 3.96 (dd, *J* = 11.1, 7.4, 1H), 2.13 – 1.23 (m, 8H).

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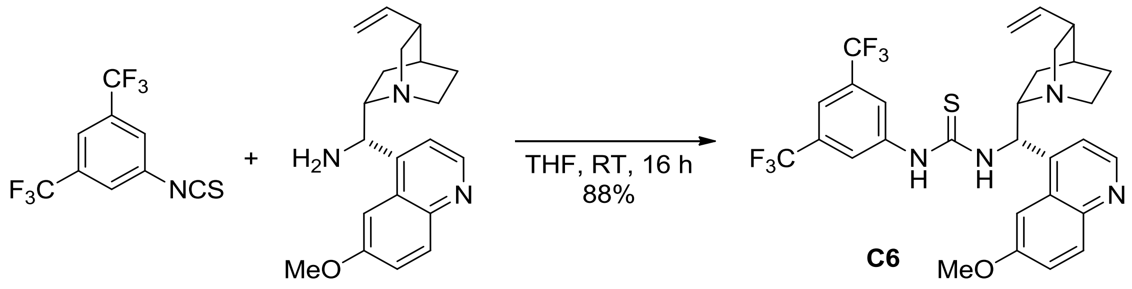
[269] T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759.

2nd step: A suspension formed by 2-((1*S*,2*S*)-2-aminocyclohexyl)isoindoline-1,3-dione (1 equiv., 8 mmol, 3.35 g), hydrocinnamaldehyde (5 equiv., 10 mmol, 1.32 mL) and water (0.27 mL/ 1 mmol) in CH_3CN (44 mL) was stirred for 15 minutes. $NaCNBH_3$ (2.1 equiv., 16.8 mmol, 1.12 g) was added and, after another 15 minutes, acetic acid (0.27 mL/ 1 mmol) was also added and the reaction was stirred for 3 hours. The mixture was concentrated under reduced pressure, diluted with EtOAc (80 mL) and washed with NaOH 1M (2 x 80 mL) and brine (2 x 80 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc, 99:1–80:20) to afford 2-((1*S*,2*S*)-2-(bis(3-phenylpropyl)amino)cyclohexyl)isoindoline-1,3-dione as yellow pale oil. Yield: 1.59 g (85%). All data were consistent with those previously reported. ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.67 (brs, 4H), 7.34 – 6.95 (m, 10H), 4.18 (td, *J* = 11.7, 3.8, 1H), 3.37 (td, *J* = 11.2, 3.2, 1H), 2.97 (t, *J* = 7.5, 1H), 2.79 (t, *J* = 7.6, 1H), 2.53 – 2.24 (m, 9H), 2.00 – 1.78 (m, 4H), 1.56 – 1.23 (m, 8H).

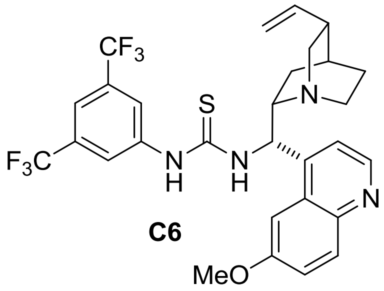
3rd step: A solution of 2-((1*S*,2*S*)-2-(bis(3-phenylpropyl)amino)cyclohexyl)isoindoline-1,3-dione (1 equiv., 6 mmol, 2.88 g) and hydrazine monohydrate (0.03 mL/1mmol) in EtOH (3.0 mL) were heated to reflux and stirred for 2 hours. At room temperature, the reaction mixture was diluted with Et_2O and precipitates were removed by filtration. The filtrate was concentrated under reduced pressure to afford (1*S*,2*S*)-N^1,N^1-bis(3-phenylpropyl)cyclohexane-1,2-diamine which was used in the next step without further purification. Yellow pale oil. Yield: 1.39 g (66%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.39 – 7.00 (m, 10H), 2.74 – 2.62 (m, 2H), 2.61 – 2.48 (m, 4H), 2.38 (ddd, J = 13.0, 7.9, 5.1, 2H), 2.22 – 2.04 (m, 3H), 2.00 (d, J = 12.2, 1H), 1.86 – 1.61 (m, 6H), 1.18 – 1.05 (m, 4H).

5.5.2. Preparation of thiourea-based Brønsted base catalyst C6[267]



To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 5 mmol, 1.6 g) in dry THF (7.5 mL) at 0 °C, a solution of bis(trifluoromethyl)phenyl isocyanate (1.1 equiv., 5.5 mmol, 1.5 g) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under vacuum. The residue was purified by flash column chromatography on non acid silica gel (Hex/EtOAc, 80:20–EtOAc) to afford **C6**.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (C6)

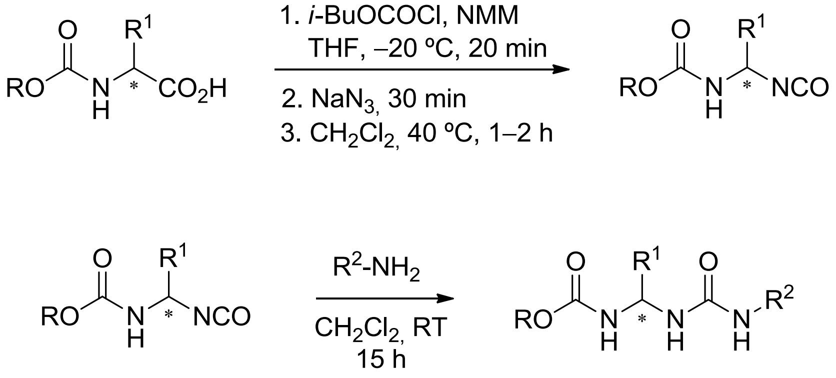


C6

White solid. Yield: 2.6 g, (88%). All data were consistent with those previously reported.[267] ^{1}H NMR (300 MHz, CD$_3$OD) δ ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38–2.35 (m, 1H), 1.71–1.68 (m, 2H), 1.64–1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

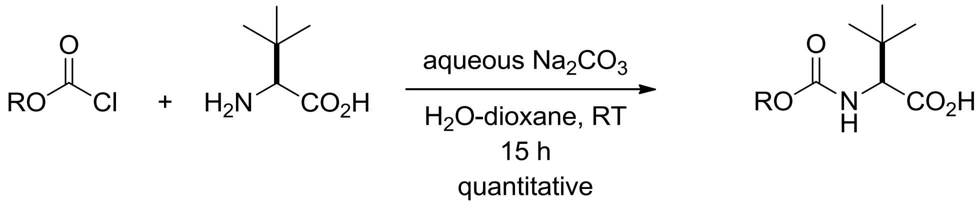
5.5.3. Preparation of ureidopeptide-based Brønsted base catalysts C2, C7–C13 and C15

Ureidopeptide-based Brønsted base catalysts were prepared according to the following general scheme:


1. i-BuOCOCl, NMM
THF, –20 ºC, 20 min
2. NaN3, 30 min
3. CH2Cl2, 40 ºC, 1–2 h
R2-NH2
CH2Cl2, RT
15 h

5.5.3.1. Preparation of carbamate N-protected α-amino acids

5.5.3.1.1. Procedure A using chloroformates [270]


aqueous Na2CO3
H2O-dioxane, RT
15 h
quantitative

To a stirred solution of L-*tert*-leucine (1 equiv., 10 mmol, 1.31 g) in 10% aqueous Na_2CO_3 (26 mL) and dioxane (10 mL), was slowly added at 0 °C a solution of the corresponding chloroformiate (1 equiv., 10 mmol) in dioxane (30 mL). The mixture was stirred in an ice bath for 1 hour and then allowed to warm to room temperature and subsequently stirred at the same temperature for 15 hours, poured into water (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the corresponding *N*-protected L-*tert*-leucine which was used in the next step without further purification.

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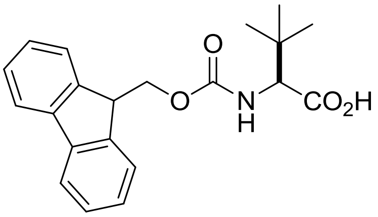
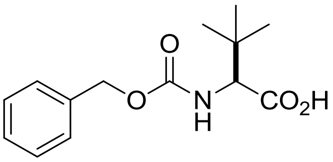
[270] J. D. Bain, D. A. Wacker, E. E. Kuo, A. R. Chamberlin, *Tetrahedron* **1991**, *47*, 2389–2400.

(*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3,3-dimethylbutanoic acid



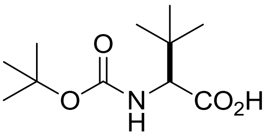
The title compound was prepared from (9H-fluoren-9-yl)methyl chloroformate according to the general procedure. White solid. Yield: 3.39 g, (95%). ^{1}H-RMN (300 MHz, CD_3OD) δ 7.78 (d, *J* = 7.5, 2H), 7.68 (d, *J* = 6.7, 2H), 7.39 (t, *J* = 7.5, 2H), 7.30 (dt, *J* = 7.5, 1.0, 2H), 4.50 (s, 2H), 4.39 – 4.33 (m, 2H), 4.23 (t, *J* = 6.9, 1H), 4.05 (d, brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

(*S*)-2-(((Benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid



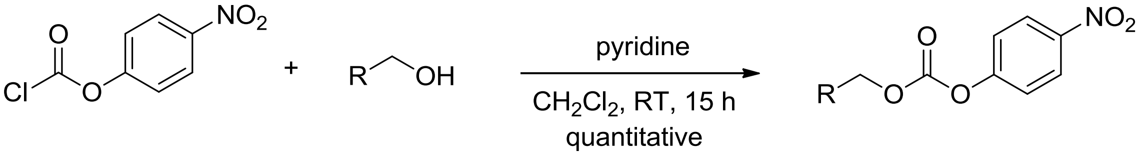
The title compound was prepared from benzyl chloroformate according to the general procedure. White solid. Yield: 2.38 g, (91%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.33 (d, *J* = 9.6, 1H), 5.12 (s, 2H), 4.21 (d, *J* = 9.5, 1H), 1.02 (s, 9H).

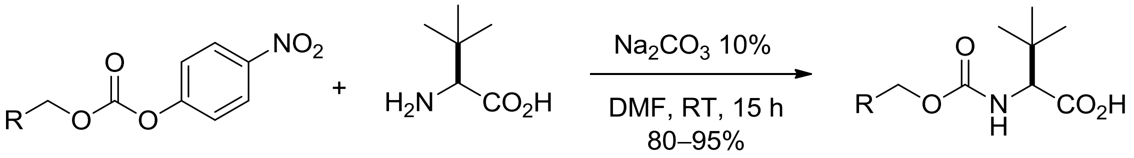
(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanoic acid



The title compound was prepared from *tert*-butyl chloroformate according to the general procedure. White solid. Yield: 2.29 g, (99%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 5.07 (d, *J* = 8.5, 1H), 4.18 – 4.07 (m, 1H), 1.45 (s, 9H), 1.02 (s, 9H).

5.5.3.1.2. *Procedure B using 4-nitrophenyl carbonates*[271]





1st step: To a stirred solution of *p*-nitrophenylchloroformate (1.1 equiv., 2.2 g, 11 mmol) in CH_2Cl_2 (13.6 mL) was added pyridine (1.1 equiv., 11 mmol, 0.9 mL). The formed white slurry was cooled to 0 °C, and the corresponding alcohol (1 equiv., 10 mmol) was added in several portions to keep the temperature at 0 °C. After complete addition, the yellow mixture was allowed to warm to room temperature and stirred for 15 hours. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and subsequently washed with 1 N HCl (20 mL), water (20 mL) and brine (20 mL), dried with $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

2nd step: To a stirred solution of L-*tert*-leucine (1 equiv., 10 mmol, 1.31 g) in 10% aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0 °C a solution of the corresponding 4-nitrophenyl carbonate (1 equiv., 10 mmol) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 hour and then allowed to warm to room temperature and subsequently stirred at the same temperature for 15 hours, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc, 80:20) to afford the corresponding *N*-protected L-*tert*-leucine.

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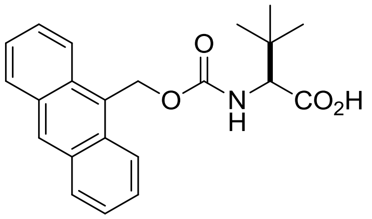
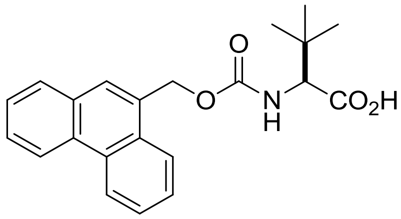
[271] P. Lan, J. A. Porco Jr., M. S. South, J. J. Parlow, *J. Comb. Chem.* **2003**, *5*, 660–669.

(*S*)-2-(((Antracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid



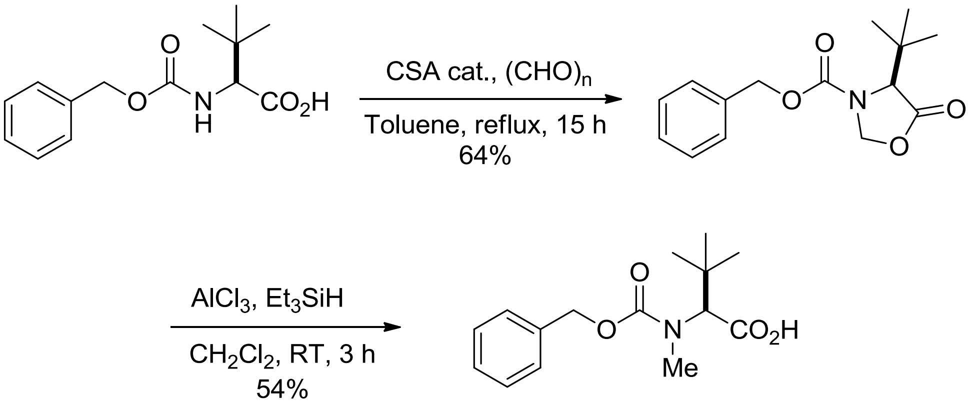
The title compound was prepared from anthracen-9-ylmethanol according to the general procedure. White solid. Yield: 3.21 g, (88%). All data were consistent with those previously reported. ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.38 (d, *J* = 8.9, 2H), 8.04 (d, *J* = 8.7, 2H), 7.65 – 7.54 (m, 2H), 7.53 – 7.46 (m, 2H), 6.18 (q, *J* = 12.1, 2H), 5.24 (d, *J* = 10.4, 1H),4.28 (d, *J* = 10.2, 1H), 1.01 (s, 9H).

(*S*)-3,3-Dimethyl-2-(((phenanthren-9-ylmethoxy)carbonyl)amino)butanoic acid



The title compound was prepared from phenanthren-9-ylmethanol according to the general procedure. White solid. Yield: 2.74 g, (75%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 7.5, 1H), 8.66 (d, J = 8.0, 1H), 8.07 (d, *J* = 7.0, 1H), 7.88 (d, *J* = 7.5, 1H), 7.81 (s, 1H), 7.61 (dd, *J* = 18.5, 10.7, 4H), 5.63 (q, *J* = 12.4, 2H), 5.37 (d, *J* = 9.4, 1H), 4.26 (d, *J* = 9.5, 1H), 1.02 (s, 9H).

5.5.3.1.3. Preparation of N-Cbz-N-Me-L-tert-Leucina



1st step:[272] A solution of *N*-Cbz-L-*tert*-Leucina (1 equiv., 3.20 g, 12 mmol), camphorsulfonic acid (0.1 equiv., 0.28 g, 1.2 mmol) and *p*-formaldehyde (10 equiv., 3.60 g, 120 mmol) in toluene (160 mL) was heated to reflux for 15 hours using a Dean-Stark. At room temperature the reaction mixture was diluted with EtOAc and washed with $NaHCO_3$ aq (5 x 120 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc, 80:20) to afford (*S*)-benzyl 4-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate as a colorless oil. Yield: 2.12 g (64%). ^1H-RMN (300 MHz, $CDCl_3$) δ 7.54 – 7.29 (m, 5H), 5.71 (brs, 1H), 5.25 – 5.07 (m, 4H), 1.07 (s, 9H).

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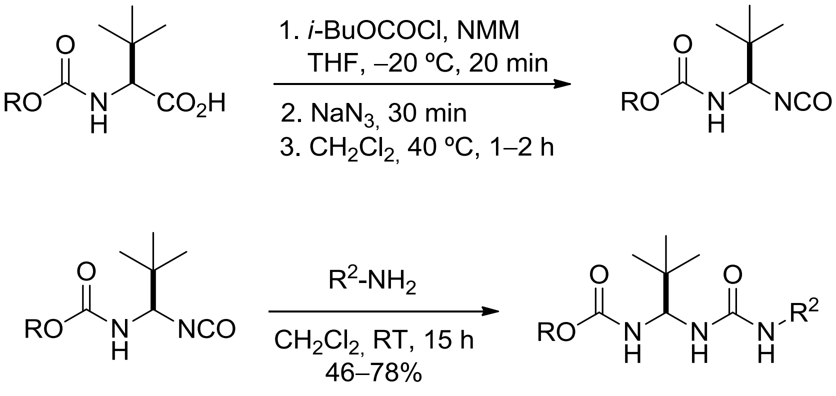
[272] L. Aurelio, J. S. Box, R. T. C. Brownlee, A. B. Hughes, M. M. Sleebs, *J. Org. Chem.* **2003***, 68,* 2652–2667.

2^{nd} step:[273] To a solution of the cycled product obtained in the previous step (1 equiv., 2.12 g, 7.68 mmol) in CH_2Cl_2 (140 mL), triethylsilane (2 equiv., 2.44 mL, 15.36 mmol) and aluminium chloride (2 equiv., 2.04 g, 15.36 mmol) were added. After 3 hours, the mixture was washed with HCl 1M (120 mL). After drying over $MgSO_4$ and concentrating under vacuum, the residue was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford (*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3,3-dimethylbutanoic acid as a white solid. Yield: 0.96 g (54%). ^1H-RMN (300 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 5H), 5.23 – 5.08 (m, 2H), 4.82 (s, 1H), 3.04 (s, 3H), 1.12 (s, 9H).

5.5.3.2. Preparation of α-amino acid derived isocyanates and coupling with amines[274]



C2, C7–C13, C15

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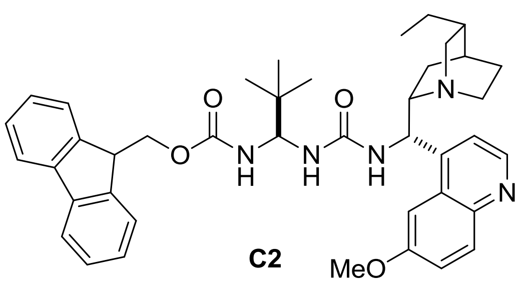
[273] A. B. Hughes, M. M. Sleebs, *Helvetica Chimica Acta* **2006***, 89,* 2611–2619.

[274] Procedure adapted from: V. V. Suresh Babu, B. S. Patil, R. Venkataramanarao, *J. Org. Chem.* **2006***, 71,* 7697–7705.

To a cooled solution of the corresponding *N*-protected α-amino acid (1 equiv., 5 mmol) in dry THF (20 mL), were added isobutyl chloroformate (1 equiv., 5 mmol, 0.65 mL) and *N*-methylmorpholine (1 equiv., 5 mmol, 0.6 mL) at –20 °C and the mixture was stirred for 20 minutes. Then, a suspension of NaN_3 (1.5 equiv., 7.5 mmol, 0.48 g in 5 mL of H_2O) was added and the reaction mixture was stirred at the same temperature. After 30 minutes, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil which was redissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 °C under nitrogen for 1-2 hours. The reaction was monitored by infrared analysis until disappearance of the isocyanate band. After completion, the corresponding amine was added (0.7 equiv., 3.5 mmol) and the reaction mixture was stirred at room temperature for 15 hours. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2–CH_2Cl_2/MeOH, 80:20) or by non acid silica gel (Hex/EtOAc, 80:20–EtOAc) to afford the desired catalysts **C2**, **C7**–**C13** and **C15**.

(9H-fluoren-9-yl)methyl ((*S*)-1-(3-((S)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C2)



C2

The title compound was prepared from (*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3,3-dimethylbutanoic acid and 9-amino-(9-deoxy)*epi*hydroquinine according to the general procedure. White solid. Yield: 1.37 g, (58%). All data were consistent with those previously reported.[275] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.0, 1H), 7.97 (d, *J* = 9.2, 1H), 7.76 (d, *J* = 7.5, 2H), 7.70 (d, *J* = 1.7, 1H), 7.55 (t, *J* = 8.1, 2H), 7.43 – 7.24 (m, 6H), 6.35 (s, 1H), 5.25 (s, 1H), 5.17 – 4.90 (m, 3H), 4.40 (dd, *J* = 10.5, 7.2, 1H), 4.30 (dd, *J* = 10.5, 6.8, 1H), 4.18 (d, *J* = 6.5, 1H), 3.93 (s, 3H), 3.21 (dd, *J* = 16.5, 6.7, 2H), 3.03

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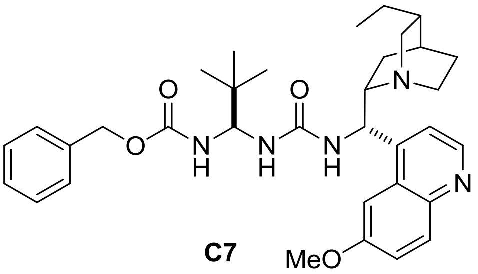
[275] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

(s, 1H), 2.76 – 2.59 (m, 1H), 2.44 (d, *J* = 11.5, 1H), 1.64 – 1.15 (m, 8H), 0.86 (s, 9H), 0.78 (t, *J* = 7.3, 3H).

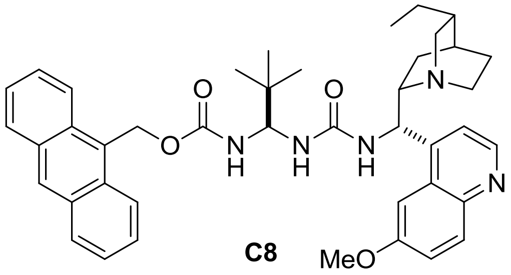
Benzyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C7)



C7

The title compound was prepared from (*S*)-2-(((benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid and and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. White solid. Yield: 1.44 g, (70%). m.p.= 105–136 °C. $[\alpha]_D^{25}$ = –29.3 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.4, 1H), 8.00 (d, *J* = 9.2, 1H), 7.72 (s, 1H), 7.41 – 7.26 (m, 8H), 6.34 (brs, 1H), 5.29 – 5.19 (m, 1H), 5.12 – 4.77 (m, 6H), 3.97 (s, 3H), 3.22 (dt, *J* = 24.3, 12.3, 2H), 3.01 (dd, *J* = 16.9, 9.8, 1H), 2.75 – 2.63 (m, 1H), 2.53 – 2.41 (m, 1H), 1.74 (s, 9H), 0.87 (s, 9H), 0.82 (t, *J* = 7.3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 157.9, 156.5, 147.7, 145.0, 131.8, 128.7, 128.5, 122.1, 102.2, 67.1, 66.9, 60.3, 57.4, 56.0, 41.3, 35.5, 27.3, 25.6, 25.2, 12.0. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{34}H_{46}N_5O_4$ 588.3550, found 588.3565.

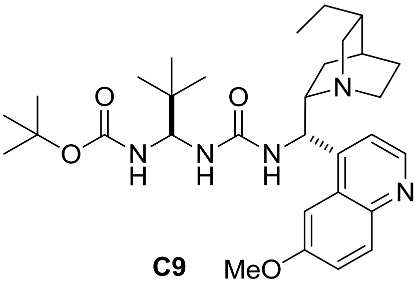
Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C8)



C8

The title compound was prepared from (*S*)-2-(((antracen-9-ylmethoxy)carbonyl)amino)-3,3-dimethylbutanoic acid and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. White solid. Yield: 1.88 g, (78%). All data were consistent with those previously reported.[275] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1H NMR (300 MHz, $CDCl_3$), δ 8.77 – 8.44 (m, 3H), 8.15 – 7.52 (m, 10H), 7.39 – 7.29 (m, 1H), 7.16 (s, 1H), 5.55 (s, 4H), 5.09 (s, 1H), 3.91 (s, 3H), 3.14 (s, 3H), 2.63 – 2.31 (m, 2H), 1.63 – 1.10 (m, 8H), 0.85 (dt, *J* = 22.4, 8.4, 15H).

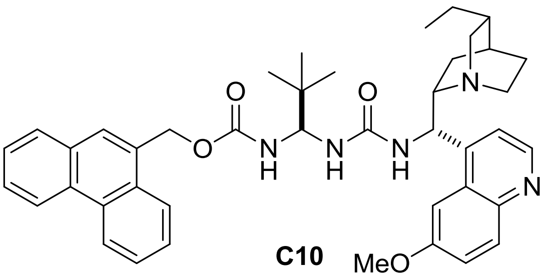
tert-Butyl ((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C9)



C9

The title compound was prepared from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. White solid. Yield: 1.30 g, (67%). m.p.= 117–150 °C. $[\alpha]_D^{25}$ = –27.5 (c=0.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5, 1H), 7.98 (d, *J* = 9.2, 1H), 7.73 (d, *J* = 2.0, 1H), 7.34 (dd, *J* = 5.9, 3.6, 2H), 6.48 (brs, 1H), 5.29 (brs, 1H), 5.06 (d, *J* = 6.8, 1H), 4.92 – 4.75 (m, 2H), 3.96 (s, 3H), 3.21 (dd, *J* = 13.5, 9.8, 2H), 3.01 (dd, *J* = 17.5, 9.1, 1H), 2.76 – 2.62 (m, 1H), 2.53 – 2.32 (m, 2H), 1.52 (d, *J* = 32.4, 2H), 1.37 (d, *J* = 18.5, 9H), 1.24 (ddd, *J* = 10.2, 8.7, 5.2, 3H), 0.89 – 0.72 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 157.5, 155.9, 147.5, 144.7, 131.5, 128.7, 121.67, 119.07, 102.07, 79.9, 66.1, 60.4, 57.5, 55.6, 41.1, 37.4, 35.2, 28.7, 28.3, 27.5, 25.9, 25.3, 12.0. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{31}H_{48}N_5O_4$ 554.3706, found 554.3721.

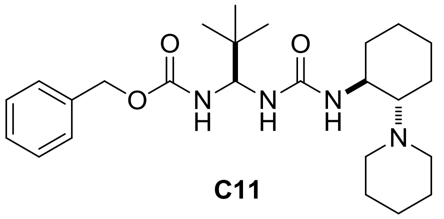
Phenanthren-9-ylmethyl ((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C10)



C10

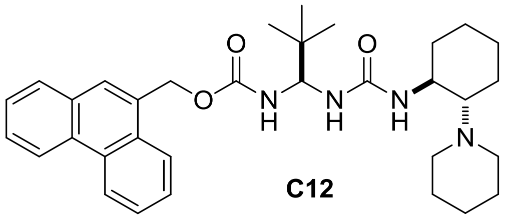
The title compound was prepared from (*S*)-3,3-dimethyl-2-(((phenanthren-9-ylmethoxy)carbonyl)amino)butanoic acid and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. White solid. Yield: 1.66 g, (69%). m.p.= 132–175 °C. $[\alpha]_D^{25}$ = –8.7 (c=1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 21.2, 8.1, 2H), 8.53 (s, 1H), 8.05 – 7.49 (m, 9H), 7.37 – 7.31 (m, 1H), 7.21 (s, 1H), 6.35 (s, 1H), 5.55 (t, *J* = 10.6, 2H), 5.11 (dd, *J* = 28.1, 15.1, 4H), 3.93 (s, 3H), 3.24 – 3.06 (m, 2H), 2.99 (s, 1H), 2.56 (s, 1H), 2.42 (d, J = 11.1, 1H), 2.21 (s, 1H), 1.36 (dd, *J* = 58.1, 27.4, 7H), 0.92 – 0.72 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 157.6, 156.7, 147.7, 146.5, 144.9, 131.8, 131.5, 131.2, 129.2, 126.8, 125.3, 124.2, 121.8, 119.4, 102.3, 66.7, 60.6, 59.6, 57.8, 55.8, 41.1, 37.5, 35.6, 28.8, 27.6, 25.9, 25.4, 21.2, 14.4, 12.2. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{42}H_{50}N_5O_4$ 688.3863, found 688.3863.

Benzyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C11)


C11

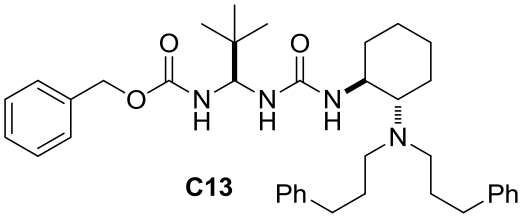
The title compound was prepared from (*S*)-2-(((benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine according to the general procedure. White solid. Yield: 0.93 g, (60%). m.p.= 158–174 °C. $[\alpha]_D^{25}$ = –9.7 (c=1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.25 (m, 5H), 5.86 (s, 1H), 5.18 (d, *J* = 12.2, 1H), 5.03 (d, *J* = 12.3, 2H), 4.98 – 4.84 (m, 1H), 4.69 (d, *J* = 7.2, 1H), 3.40 (t, *J* = 14.8, 1H), 2.59 (s, 2H), 2.31 (s, 3H), 2.16 – 2.05 (m, 1H), 1.88 – 1.72 (m, 3H), 1.66 – 1.35 (m, 8H), 1.23 – 1.10 (m, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.4, 136.3, 128.5, 128.2, 128.1, 68.1, 66.9, 51.0, 49.4, 35.4, 33.6, 27.0, 25.6, 25.0 , 24.7, 23.6. UPLC (DAD-QTOF [M+H]+) calcd for $C_{25}H_{41}N_4O_3$ 445.3179, found 445.3193.

Phenanthren-9-ylmethyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C12)


C12

The title compound was prepared from (*S*)-3,3-dimethyl-2-(((phenanthren-9-ylmethoxy)carbonyl)amino)butanoic acid and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine according to the general procedure. White solid. Yield: 1.03 g, (54%). m.p.= 195–197 °C. $[\alpha]_D^{25}$ = 14.2 (c=0.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 – 8.70 (m, 1H), 8.67 (d, *J* = 8.2, 1H), 8.10 – 8.05 (m, 1H), 7.85 (d, *J* = 14.9, 2H), 7.72 – 7.57 (m, 4H), 5.83 (s, 1H), 5.62 (dd, *J* = 32.2, 12.5, 3H), 5.07 (d, *J* = 7.2, 1H), 5.00 – 4.87 (m, 1H), 4.62 (d, J = 7.7, 1H), 3.33 (s, 1H), 2.55 (s, 2H), 2.29 (s, 4H), 1.68 (s, 2H), 1.45 (d, J = 11.6, 8H), 1.21 – 1.09 (m, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.4, 131.2, 130.7, 130.3, 130.1, 128.8, 128.5, 127.1, 127.0, 126.8, 126.6, 124.3, 68.1, 67.0, 65.8, 50.8, 49.3, 35.4, 33.5, 26.8, 25.6, 25.4, 24.6, 23.6. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{33}H_{45}N_4O_3$ 545.3492, found 545.3497.

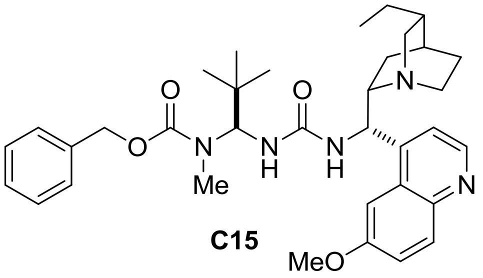
Benzyl ((*S*)-1-(3-((1*S*,2*S*)-2-(bis(3-phenylpropyl)amino)cyclohexyl)ureido)-2,2-dimethylpropyl)carbamate (C13)



C13

The title compound was prepared from (*S*)-2-(((benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid and (1*S*,2*S*)-*N*^{1},*N*^{1}-bis(3-phenylpropyl)cyclohexane-1,2-diamine according to the general procedure. White solid. Yield: 0.99 g, (46%). m.p.= 162–164 °C. $[\alpha]_D^{25}$ = 5.1 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 15H), 5.81 (s, 1H), 5.12 (d, *J* = 12.2, 1H), 5.02 (d, *J* = 12.2, 2H), 4.85 (t, *J* = 8.7, 1H), 4.56 (d, *J* = 8.3, 1H), 3.57 – 3.42 (m, 1H), 2.74 – 2.48 (m, 5H), 2.46 – 2.17 (m, 4H), 1.86 – 1.67 (m, 5H), 1.60 (d, *J* = 11.1, 1H), 1.33 – 1.11 (, 3H), 1.01 – 0.89 (m, 1H), 0.85 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 156.5, 142.6, 136.3, 128.5, 128.3, 128.2, 128.1, 128.0, 125., 66.9, 66.6, 64.0, 51.2, 49.8, 35.2, 33.7, 31.2, 25.6, 25.4, 24.8, 24.4.UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{38}H_{53}N_4O_3$ 613.4118, found 613.4127.

Benzyl ((*S*)-1-(3-((S)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)(methyl)carbamate (C15)

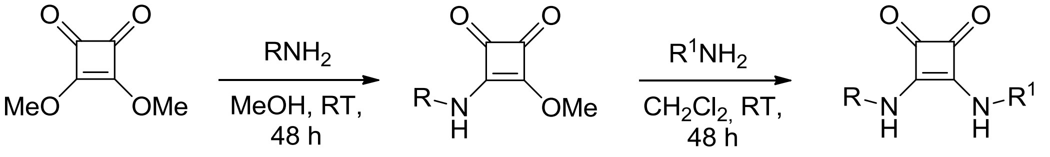


C15

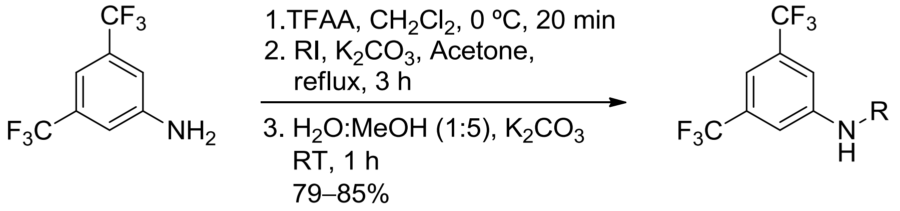
The title compound was prepared from (*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3,3-dimethylbutanoic acid and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. White solid. Yield: 1.31 g, (62%). m.p.= 90–96 °C. $[\alpha]_D^{25}$ = –40.1 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 39.6, 1H), 7.99 (t, *J* = 8.5, 1H), 7.65 (s, 1H), 7.34 (d, *J* = 3.5, 6H), 6.22 (s, 1H), 5.63 – 4.98 (m, 4H), 3.93 (s, 3H), 3.27 – 3.02 (m, 2H), 3.01 – 2.80 (m, 2H), 2.65 (dd, *J* = 16.9, 7.5, 1H), 2.54 – 2.23 (m, 3H), 1.69 – 1.11 (m, 9H), 0.76 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 157.6, 147.6, 144.8, 136.9, 131.7, 128.7, 128.3, 128.0, 121.8, 102.1, 67.5, 67.2, 60.5, 57.6, 55.8, 41.0, 37.4, 28.7, 27.6, 26.5, 25.9, 25.4, 12.1. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{35}H_{48}N_5O_4$ 602.3706, found 602.3699.

5.5.4. Preparation of squaramide-based Brønsted base catalysts C4, C16–C24

Squaramide-based Brønsted base catalysts were prepared according to the following general scheme:


MeO
OMe
RNH2
MeOH, RT, 48 h
R
N
H
OMe
R1NH2
CH2Cl2, RT, 48 h
R1

5.5.4.1. *Preparation of anilines*[276]


CF3
F3C
NH2
1.TFAA, CH2Cl2, 0 °C, 20 min
2. RI, K2CO3, Acetone, reflux, 3 h
3. H2O:MeOH (1:5), K2CO3 RT, 1 h
79–85%
R
N
H

To a cooled solution of bis(trifluoromethyl)phenyl aniline (1 equiv., 5 mmol, 0.78 mL) in CH_2Cl_2 (10 mL), trifluoroacetic anhydride (3 equiv., 15 mmol, 2.09 mL) was added and the reaction mixture was stirred at 0 °C. After 20 minutes, solvent and excess of trifluoroacetic anhydride were evaporated and the residue was dissolved in acetonitrile (10 mL). Potassium carbonate (2 equiv., 10 mmol, 1.38 g) and the corresponding alkyl iodide were added and the solution was stirred at mild reflux for 3 hours. At room temperature, a solution of potassium carbonate (1 equiv., 5 mmol, 0.69 g) in MeOH:H_2O (25:5 mL) was added to the mixture and stirred for another hour. Solvents were partially evaporated and the residue was dissolved in water (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under vacuum to afford the corresponding alkylated anilines which were used in the next step without further purification.

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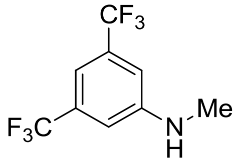
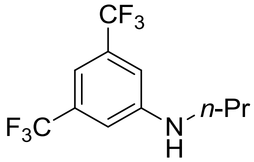
[276] A. O. Kataja, A. M. P. Koskinen, *Arkivoc* **2010**, 205–223.

N-Methyl-3,5-bis(trifluoromethyl)aniline



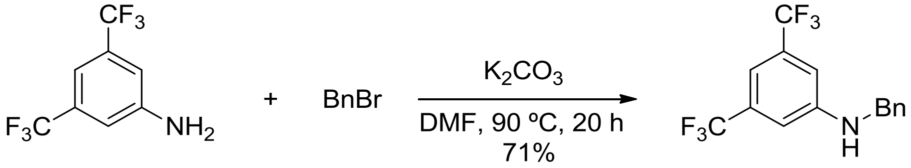
The title compound was prepared from methyl iodide (3 equiv., 15 mmol, 0.93 mL) according to the general procedure. Yellow oil. Yield: 1.03 g, (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.92 (s, 2H), 4.16 (s, 1H), 2.91 (t, *J* = 5.2, 3H).

N-Propyl-3,5-bis(trifluoromethyl)aniline



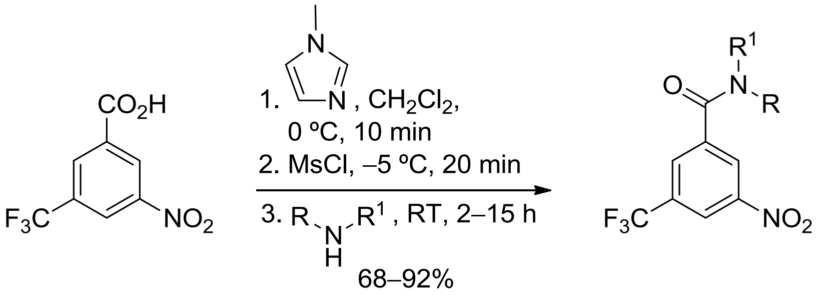
The title compound was prepared from *n*-propyl iodide (5 equiv., 25 mmol, 2.44 mL) according to the general procedure. Yellow oil. Yield: 1.06 g, (79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.92 (s, 2H), 4.07 (s, 1H), 3.13 (td, *J* = 7.0, 5.5, 2H), 1.76 – 1.60 (m, 2H), 1.03 (t, *J* = 7.4, 3H).

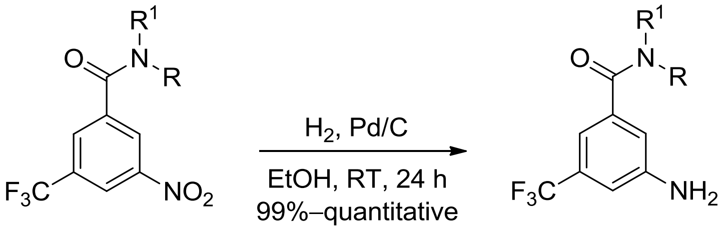
N-Benzyl-3,5-bis(trifluoromethyl)aniline



A solution of 3,5-bis(trifluoromethyl)phenyl aniline (1 equiv., 10 mmol, 1.56 mL), benzyl bromide (1 equiv., 10 mmol, 1.18 mL) and potassium carbonate (1 equiv., 10 mmol, 1.38 g) in DMF (10 mL) was stirred at 90 °C for 20 hours. At room temperature, the mixture was diluted with EtOAc and the organic phase was washed with brine (6 x 40 mL). Drying ($MgSO_4$), filtration and evaporation gave the corresponding crude that was purified by flash column chromatography on silica gel (hexane/EtOAc, 99:1–95:5) to afford the desired product as a yellow pale oil. Yield: 1.13 g, (71%). ^{1}H-RMN (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.98 (s, 2H), 4.45 (d, *J* = 4.3, 1H), 4.38 (d, *J* = 5.3, 2H).

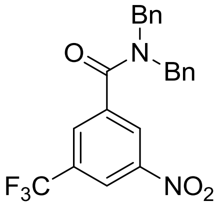
5.5.4.2. Preparation of 3-amino-5-(trifluoromethyl)benzamides





1st step:[277] To a cooled slurry of 3-nitro-5-(trifluoromethyl)benzoic acid (1 equiv., 10 mmol, 2.36 g) in CH_2Cl_2 (30 mL), 1-methylimidazole (2.5 equiv., 25 mmol, 1.99 mL) was added at 0 °C and the mixture was stirred for 10 minutes. Then, MsCl (1.5 equiv., 15 mmol, 1.16 mL) in CH_2Cl_2 (2 mL) was added to the mixture under –5 °C. The resulting mixture was stirred under that temperature for 20 minutes and then, the corresponding aniline/amine (1 equiv., 10 mmol) was added. The mixture was stirred at room temperature for 2 hours. H_2O (40 mL) was then added and a solid precipitated which was dissolved in EtOAc (300 mL). The organic layer was washed with brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. The residue was purified by flash column chromatography on silica gel (hexane/ EtOAc, 99:1–90:10) to afford the corresponding benzamide.

N,N-Dibenzyl-3-nitro-5-(trifluoromethyl)benzamide



The title compound was prepared from dibenzyl amine according to the general procedure. Yellow pale foam. Yield: 3.32 g, (80%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 – 8.44 (m, 1H), 7.99 (d, J = 0.5, 1H), 7.49 – 6.96 (m, 11H), 4.78 (s, 2H), 4.38 (s, 2H).

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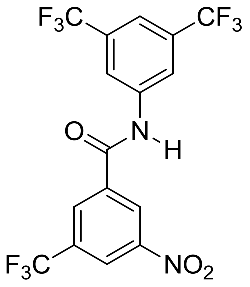
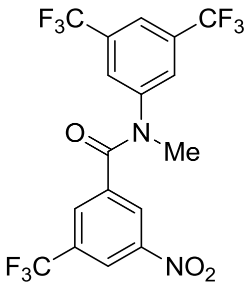
[277] Adapted from: L. Mao, Z. Wang, Y. Li, X. Han, W. Zhou, *Synlett* **2011**, *1*, 129–133.

N-(3,5-Bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide



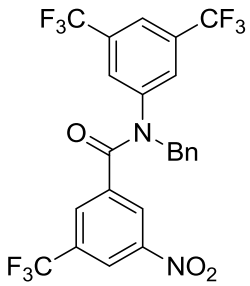
The title compound was prepared from 3,5-bis(trifluoromethyl)aniline according to the general procedure. White solid. Yield: 3.97 g, (89%). ^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (s, 1H), 8.72 (s, 2H), 8.43 (s, 2H), 7.72 (s, 1H).

N-(3,5-Bis(trifluoromethyl)phenyl)-*N*-methyl-3-nitro-5-(trifluoromethyl)benzamide



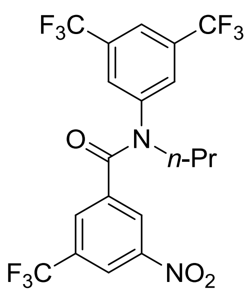
The title compound was prepared from *N*-methyl-3,5-bis(trifluoromethyl)aniline according to the general procedure. White solid. Yield: 4.23 g, (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.12 (m, 2H), 7.71 (s, 1H), 7.67 – 7.60 (m, 1H), 7.55 (s, 2H), 7.49 (t, *J* = 7.9 Hz, 1H), 3.58 (s, 3H).

N-Benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide



The title compound was prepared from *N*-benzyl-3,5-bis(trifluoromethyl)aniline according to the general procedure. White solid. Yield: 3.64 g, (68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.34 (s, 1H), 7.82 (s, 1H), 7.71 (s, 1H), 7.41 – 7.29 (m, 5H), 7.24 (dd, *J* = 6.7, 2.9, 2H), 5.17 (s, 2H).

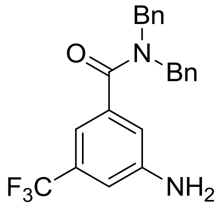
N-(3,5-Bis(trifluoromethyl)phenyl)-3-nitro-*N*-propyl-5-(trifluoromethyl)benzamide



The title compound was prepared from *N*-propyl-3,5-bis(trifluoromethyl)aniline according to the general procedure. White solid. Yield: 3.31 g, (68%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.42 (s, 1H), 8.33 (s, 1H), 7.80 (s, 1H), 7.76 (s, 1H), 7.53 (s, 2H), 4.06 – 3.83 (m, 2H), 1.80 – 1.60 (m, 2H), 1.00 (t, *J* = 7.4, 3H).

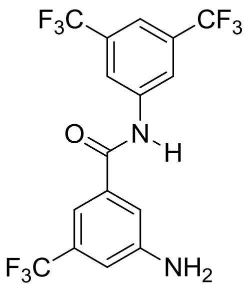
2nd step: To a solution of the corresponding benzamide (5 mmol) in EtOH (2 mL/1 mmol) and under inert atmosphere, Pd/C was added (Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H$_2$ atmosphere (1 atm) at room temperature for 24 hours. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the corresponding hydrogenated product which was used in next step without further purification.

3-Amino-*N,N*-dibenzyl-5-(trifluoromethyl)benzamide



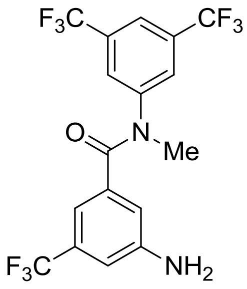
The title compound was prepared from *N,N*-dibenzyl-3-nitro-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 1.93 g, (quantitative). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43 – 7.21 (m, 8H), 7.13 (s, 2H), 7.04 (s, 1H), 6.89 (s, 2H), 4.69 (s, 2H), 4.38 (s, 2H), 3.96 (s, 2H).

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



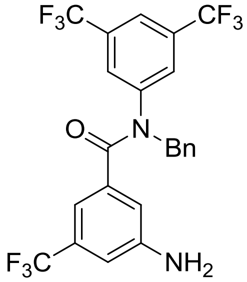
The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide according to the general procedure. Yellow oil. Yield: 2.06 g, (99%). ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.40 (s, 2H), 7.77 (s, 1H), 7.68 (s, 1H), 7.49 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 7.12 (s, 1H).

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-methyl-5-(trifluoromethyl)benzamide



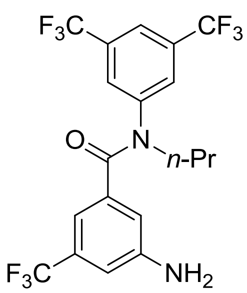
The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-methyl-3-nitro-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 2.08 g, (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.53 (s, 2H), 6.87 (s, 1H), 6.83 (s, 1H), 6.69 (s, 1H), 3.92 (s, 2H), 3.53 (s, 3H).

3-Amino-*N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



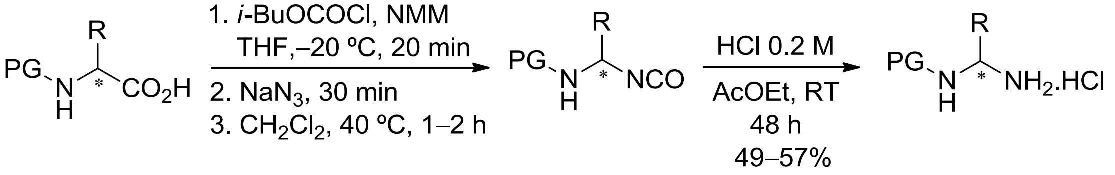
The title compound was prepared from *N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 2.51 g, (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.40 – 7.20 (m, 7H), 6.87 (s, 1H), 6.78 (s, 1H), 6.67 (s, 1H), 5.13 (s, 3H), 3.90 (brs, 1H).

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-propyl-5-(trifluoromethyl)benzamide



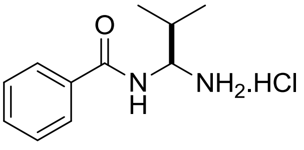
The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-*N*-propyl-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 2.27 g, (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.49 (s, 2H), 6.84 (s, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 3.92 – 3.87 (m, 4H), 1.65 (dq, *J* = 14.9, 7.4, 2H), 0.95 (t, *J* = 7.4, 3H).

5.5.4.3. *Preparation of N-(1-aminoalkyl) amides and N-(1-aminoalkyl) derived amides*[278]



To a cooled solution of the corresponding *N*-protected α-amino acid (1 equiv., 5 mmol) in dry THF (20 mL), were added isobutyl chloroformate (1 equiv., 5 mmol, 0.65 mL) and *N*-methylmorpholine (1 equiv., 5 mmol, 0.6 mL) at –20 °C and the mixture was stirred for 20 minutes. Then, a suspension of NaN_3 (1.5 equiv., 7.5 mmol, 0.48 g in 5 mL of H_2O) was added and the reaction mixture was stirred at the same temperature. After 30 minutes, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 °C under nitrogen for 1-2 hours. The reaction was monitored by infrared analysis until disappearance of the isocyanate band. After completion, HCl 0.2M was added (5 mL/1 mmol) and the reaction mixture was stirred at room temperature for 48 hours. The solvents were evaporated under reduced pressure to afford the corresponding salt which was used in next step without further purification.

(*S*)-*N*-(1-Amino-2-methylpropyl)benzamide hydrochloride



The title compound was prepared according to the general procedure. The starting *N*-amide amino acid was prepared following procedure A[279] using benzoyl chloride and L-valine. White foam. Yield: 0.65 g, (57%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.16 (d, *J* = 8.3, 1H), 8.37 (brs, 3H), 7.92 (d, *J* = 8.0, 2H), 7.52 (t, *J* =

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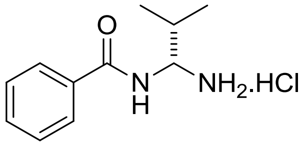
[278] Adapted from: a) G. M. Loudon, M. R. Almond, J. N. Jacob, *J. Am. Chem. Soc.* **1981**, *103*, 4508–4515; b) M. M. Campbell, B. C. Ross, G. Semple, *Tetrahedron Letters* **1989**, *30*, 6749–6752.

[279] See ref. 270, page 215.

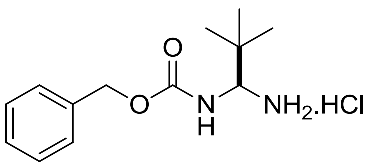
7.3, 3H), 4.83 (ddd, *J* = 11.1, 7.8, 4.7, 1H), 2.31 – 2.16 (m, 1H), 1.03 (d, *J* = 6.7, 3H), 0.97 (d, J = 6.7, 3H).

(*R*)-*N*-(1-Amino-2-methylpropyl)benzamide hydrochloride



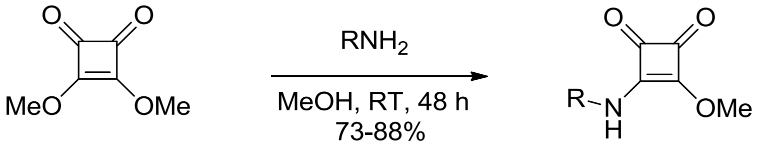
The title compound was prepared according to the general procedure. The starting *N*-amide amino acid was prepared following procedure A[279] using benzoyl chloride and D-valine. White foam. Yield: 0.64 g, (56%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (d, J = 8.4, 1H), 8.34 (brs, 2H), 7.92 (d, *J* = 7.6, 2H), 7.52 (t, *J* = 7.5, 3H), 4.91 – 4.78 (m, 1H), 2.29 – 2.16 (m, 1H), 1.03 (d, *J* = 6.7, 3H), 0.97 (d, *J* = 6.6, 3H).

(*S*)-Benzyl (1-amino-2,2-dimethylpropyl)carbamate hydrochloride[278]



The title compound was prepared from (*S*)-2-(((benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid according to the general procedure A. White solid. Yield: 0.67 g, (49%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 9.2, 3H), 7.41 – 7.30 (m, 5H), 5.13 (s, 2H), 4.64 – 4.54 (m, 1H), 0.97 (s, 9H).

5.5.4.4. *Sequential synthesis of **C4, C16** and **C20–C24*** [280]



1st step: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 5 mmol) in MeOH (2 mL/ 1 mmol) was added the corresponding primary amine (1 equiv., 5 mmol) and the reaction mixture was stirred for 48 hours. The formed precipitate was filtered and dried in vacuo to give the desired product which was used in next step without further purification.

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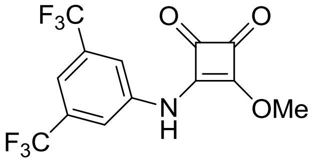
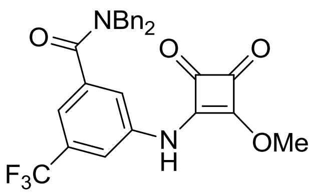
[280] Adapted from: a) Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004–3006; b) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453; c) W. Yang, D.-M. Du, *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



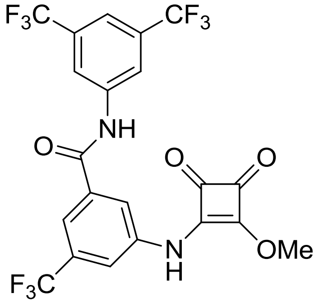
The title compound was prepared from 3,5-bis(trifluoromethyl)phenyl aniline according to the general procedure. Yellow solid. Yield: 1.24 g, (73%). All data were consistent with those previously reported.[280b] ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

N,N-Dibenzyl-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide



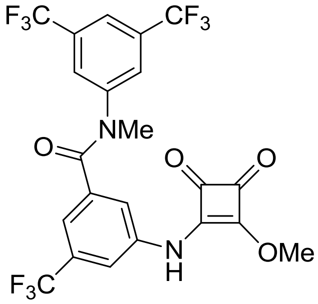
The title compound was prepared from 3-amino-*N,N*-dibenzyl-5-(trifluoromethyl)benzamide according to the general procedure. Yellow pale solid. Yield: 2.08 g, (84%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (s, 1H), 7.57 (s, 2H), 7.47 – 7.23 (m, 10H), 7.12 (s, 2H), 4.75 (s, 2H), 4.44 (s, 3H), 4.40 (s, 2H).

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



The title compound was prepared from 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 2.31 g, (88%). ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.71 (s, 1H), 10.52 (s, 1H), 8.03 (s, 2H), 7.73 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.39 (s, 1H), 3.96 (s, 3H).

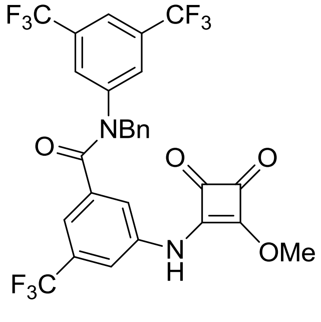
N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-methyl-5-(trifluoromethyl)benzamide



The title compound was prepared from 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-methyl-5-(trifluoromethyl)benzamide according to the general procedure. White solid. Yield: 2.24 g, (83%). ^{1}H NMR

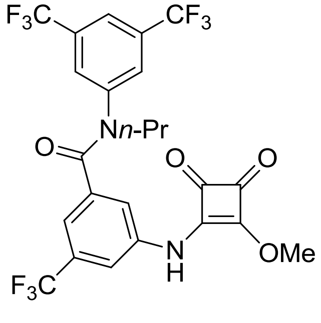
(300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 5.0 Hz, 2H), 7.57 (s, 2H), 7.51 (s, 1H), 7.18 (s, 1H), 4.52 (s, 3H), 3.58 (s, 3H).

N-Benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide

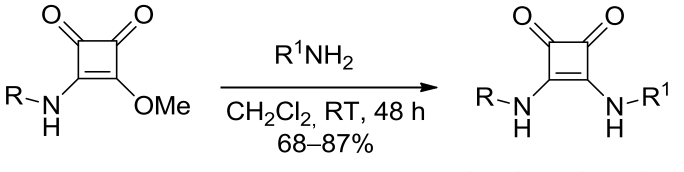


The title compound was prepared from 3-amino-*N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide according to the general procedure. Yellow pale solid. Yield: 2.56 g, (83%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.40 – 7.19 (m, 8H), 7.16 (s, 1H), 5.17 (s, 2H), 4.48 (s, 3H).

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



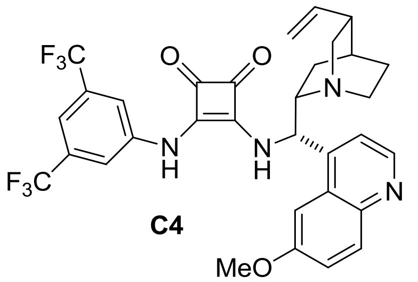
The title compound was prepared from 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-propyl-5-(trifluoromethyl)benzamide according to the general procedure. Yellow pale solid. Yield: 1.47 g, (86%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 – 8.60 (m, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 7.53 (d, J = 6.1, 3H), 7.13 (s, 1H), 4.51 (s, 3H), 4.02 – 3.87 (m, 2H), 1.68 (dq, J = 14.9, 7.4, 3H), 0.97 (t, J = 7.4, 3H).



C4, **C16, C20–C24**

2nd step: To a suspension of the squarate (1 equiv., 3 mmol) in CH_2Cl_2 (5 mL/ 1 mmol) was added the corresponding amine (1 equiv., 3 mmol) at room temperature and the reaction mixture was stirred vigorously for 48 hours. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2–CH_2Cl_2/MeOH, 90:10) to afford the desired catalysts **C4**, **C16** and **C20**–**C24**.

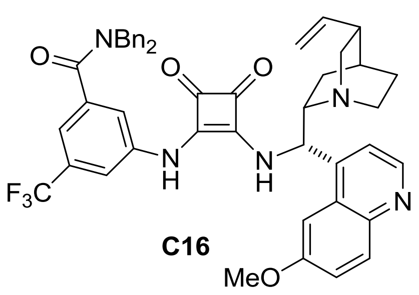
3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C4)



C4

The title compound was prepared from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow pale solid. Yield: 1.64 g, (87%). All data were consistent with those previously reported.[280b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (brs, 1H), 8.81 (d, *J* = 3.5 Hz, 1H), 8.47 (d, *J* = 6.5 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.57 (s, 2H), 7.29 (s, 2H), 7.15 (s, 2H), 6.38 − 6.35 (m, 1H), 5.89 − 5.81 (m, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 3.56 − 3.53 (m, 1H), 3.16–3.12 (m, 1H), 2.98–2.81 (m, 3H), 2.25 (brs, 1H), 1.66 (s, 1H), 1.53 (brs, 2H), 1.16 − 1.14 (m, 1H), 1.04 (brs, 1H).

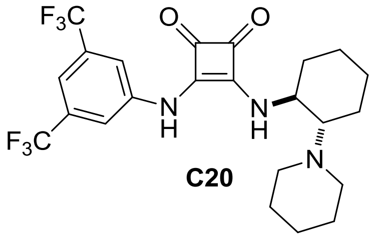
N,*N*-Dibenzyl-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C16)



C16

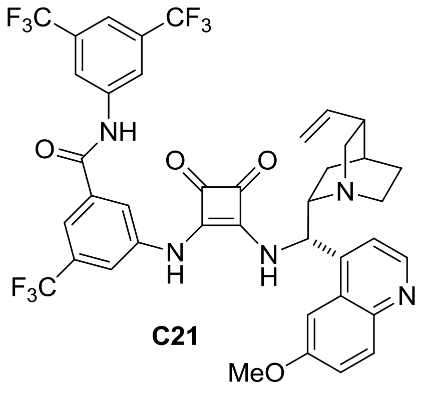
The title compound was prepared from *N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow pale solid. Yield: 1.77 g, (75%). m.p.= 179–184 °C. $[\alpha]_D^{25}$ = –40.1 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.2, 1H), 7.97 (d, *J* = 9.2, 1H), 7.79 (s, 1H), 7.57 (s, 1H), 7.45 – 7.03 (m, 17H), 6.95 (d, *J* = 5.9, 3H), 6.22 (brs, 1H), 5.88 – 5.70 (m, 1H), 5.06 – 4.91 (m, 3H), 4.73 – 4. 57 (m, 2H), 4.50 – 4. 36 (m, 3H), 3.99 (s, 4H), 3.44 (s, 2H), 3.18 (t, *J* = 11.2, 1H), 2.72 (s, 1H), 2.29 (s, 1H), 1.76 – 1.42 (m, 4H), 0.75 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 180.9, 171.2, 169.0, 159., 147.6, 144.9, 139.4, 137.8, 135.9, 135.4, 131.8, 129., 127.9, 127.5, 121.0, 117.8, 116.2, 115.0, 101.2, 60.5, 56.2, 53.6, 52.6, 48.0, 41.0, 39.5, 27., 26.2. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{46}H_{43}N_5O_4F_3$ 786.3267, found 786.3270.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (C20)



The title compound was prepared from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine according to the general procedure. Yellow solid. Yield: 1.04 g, (71%). All data were consistent with those previously reported.[280c] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (s, 2H), 7.42 (s, 1H), 4.00 (s, 1H), 2.62 (brs, 2H), 2.35 − 2.27 (m, 3H), 2.18 − 2.16 (m, 1H), 1.89 − 1.87 (m, 1H), 1.78 (d, *J* = 10.5Hz, 1H), 1.70 (d, *J* = 11.0 Hz, 1H), 1.40 − 1.12 (m, 10H).

N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C21)



The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow solid. Yield: 1.67 g, (68%). All data were consistent those previously reported.[281] ^{1}H NMR (300 MHz, DMSO-d_6) 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 3H), 2.85 – 2.55 (m, 2H), 2.28 (q, *J* = 8.0, 7.2 Hz, 1H), 1.84

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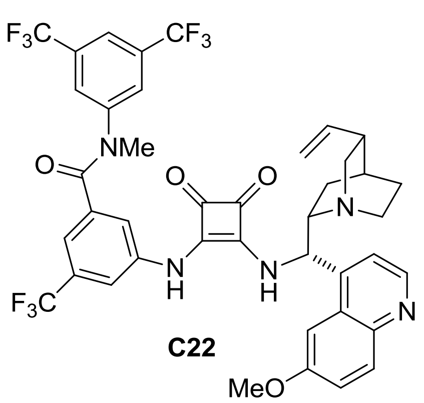
[281] Eider Badiola Aramendi, PhD. Dissertation, EHU/UPV, 2016. http://www.ehu.eus/es/web/gicas/tesiak

– 1.34 (m, 4H), 0.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3, 143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.8, 55.7,40.2, 39.4, 38.3, 38.0, 27.3, 26.0. UPLC (DAD-QTOF [M+H]$^+$) calcd for $C_{40}H_{33}N_5O_4F_9$ 818.2389, found: 818.2398.

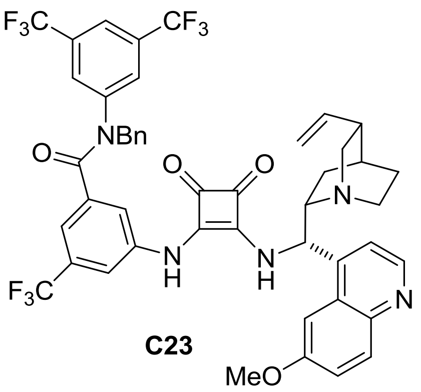
***N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-methyl-5-(trifluoromethyl)benzamide (C22)**



C22

The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-methyl-5-(trifluoromethyl)benzamide and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow solid. Yield: 1.92 g, (77%). m.p.= 165–170 °C. $[\alpha]_D^{25}$ = –59.6 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.96 (d, *J* = 9.1, 1H), 7.87 – 7.16 (m, 8H), 6.90 (s, 1H), 6.19 (s, 1H), 5.87 – 5.66 (m, 1H), 5.15 – 4.82 (m, 2H), 3.96 (s, 3H), 3.45 (s, 4H), 3.21 (d, *J* = 19.8, 2H), 2.73 (s, 2H), 2.31 (s, 1H), 1.75 – 1.36 (m, 4H), 0.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 181.2, 169.0, 163.5, 159.1, 147.6, 145.2, 144.9, 143.2, 140.6, 140.1, 137.0, 133.1, 133.1, 132.7, 132.0, 131.8, 128.1, 127.1, 124.9, 124.5, 123.0, 121.2, 120.9, 118.9, 117.3, 116.6, 115.4, 101.2, 77.6, 77.4, 77.2, 76.8, 60.2, 56.2, 55.8, 53.9, 41.1, 39.2, 38.6, 27.4, 26.0. UPLC (DAD-QTOF [M+H]$^+$) calcd for 831.2593, found: 831.2596.

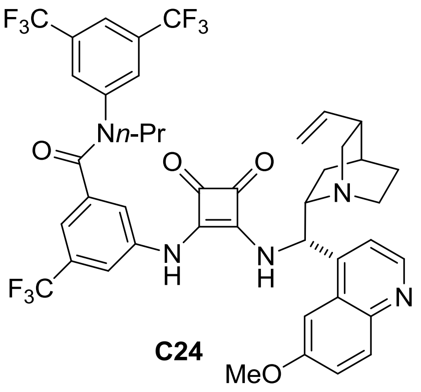
N-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C23)



C23

The title compound was prepared from *N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow pale solid. Yield: 2.12 g, (78%). m.p.= 155–168 °C. $[\alpha]_D^{25}$ = –47.2 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.02 – 7.66 (m, 3H), 7.57 (s, 1H), 7.43 – 7.02 (m, 10H), 6.85 (s, 1H), 6.17 (s, 1H), 5.81 – 5.62 (m, 1H), 5.05 – 4.91 (m, 4H), 3.93 (s, 3H), 3.63 – 3.30 (m, 2H), 3.13 (s, 1H), 2.78 (s, 1H), 2.66 (s, 1H), 2.30 (s, 1H), 1.63 (brs, 4H), 0.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 181.1, 168.9, 163.5, 159.0, 147.6, 144.8, 143.8, 137.0, 135.7, 129.1, 128.4, 122.8, 121.6, 121.1, 120.7, 119.2, 117.1, 116.5, 115.2, 101.4, 60.6, 56.1, 55.9, 54.2, 41.1, 39.3, 27.4, 26.0. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{47}H_{39}N_5O_4F_9$ 908.2858, found 908.2855.

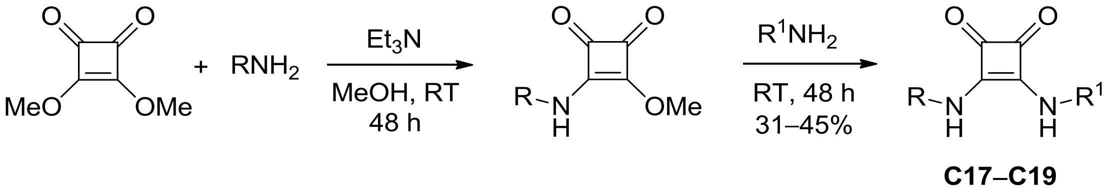
N-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-propyl-5-(trifluoromethyl)benzamide (C24)



C24

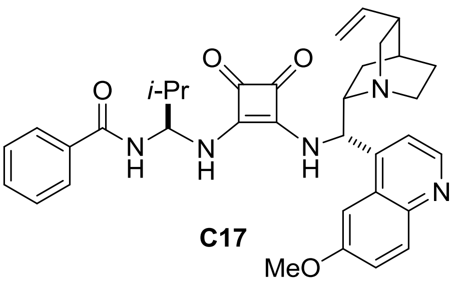
The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-propyl-5-(trifluoromethyl)benzamide and 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow pale solid. Yield: 1.83 g, (71%). m.p.= 168–173 °C. $[\alpha]_D^{25}$ = –48.2 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.95 (d, *J* = 9.0, 1H), 7.73 (s, 1H), 7.66 (s, 2H), 7.52 (s, 2H), 7.36 (d, *J* = 8.9, 2H), 7.18 (s, 1H), 6.85 (s, 1H), 6.17 (s, 1H), 5.90 – 5.68 (m, 1H), 5.18 – 4.89 (m, 2H), 3.94 (d, *J* = 10.7, 3H), 3.92 – 3.72 (m, 2H), 3.44 (d, *J* = 6.9, 2H), 3.16 (d, *J* = 10.2, 1H), 2.92 – 2.60 (m, 2H), 2.33 (s, 1H), 1.89 – 1.42 (m, 5H), 0.90 (t, *J* = 7.2, 3H), 0.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 181.4, 169.1, 168.8, 159.1, 147.5, 144.8, 144.0, 139.9, 137.5, 133.2, 132.8, 131.6, 128.2, 124.8, 124.4, 122.9, 121.5, 121.1, 120.8, 119.1, 117.2, 116.5, 115.0, 101.4, 60.2, 56.1, 52.3, 41.0, 39.6, 27.6, 26.2, 21.2, 11.2. (DAD-QTOF $[M+H]^+$) calcd for $C_{43}H_{39}N_5O_4F_9$ 860.2858, found 860.2842.

*5.5.4.5. One-pot synthesis of **C17–C19***



To a solution of the corresponding amine (1 equiv., 2 mmol) and triethylamine (3 equiv., 15 mmol) in MeOH (5 mL/1 mmol), 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 5 mmol) was added and the reaction mixture was stirred at room temperature for 48 hours. Subsequently, the corresponding second amine was added (1 equiv., 5 mmol). The suspension was stirred at room temperature for another 48 hours. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2–CH_2Cl_2/MeOH, 90:10) to afford the desired catalysts **C17**–**C19**.

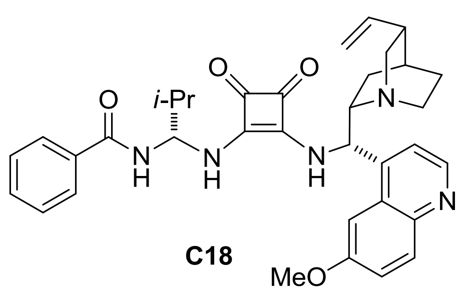
***N*-((*S*)-1-((2-(((S)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-2-methylpropyl)benzamide (C17)**



C17

The title compound was prepared from (*S*)-*N*-(1-amino-2-methylpropyl)benzamide hydrochloride and subsequent addition of 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow solid. Yield: 1.16 g, (39%). m.p.= 177–185 °C. $[\alpha]_D^{25}$ = –20.8 (c=1, CH_3OH). ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.02 – 8.71 (m, 2H), 8.83 – 8.68 (m, 1H), 7.96 (dd, *J* = 9.2, 3.1, 2H), 7.81 (d, J = 9.1, 2H), 7.63 – 7.37 (m, 4H), 6.13 – 5.77 (m, 2H), 5.35 (s, 1H), 5.12 – 4.89 (m, 2H), 3.93 (s, 3H), 3.18 (dd, *J* = 9.9, 3.3, 1H), 2.76 – 2.55 (m, 2H), 2.27 (s, 1H), 2.22 – 2.10 (m, 1H), 1.93 – 1.74 (m, 2H), 1.66 – 1.37 (m, 4H), 0.87 (dd, *J* = 12.3, 4.9, 6H), 0.60 (s, 1H). ^{13}C NMR (75 MHz, DMSO- *d*$_6$) δ 182.5, 181.5, 167.0, 166.2, 157.8, 147.8, 147.5, 144.3, 143.8, 143.5, 142.0, 133.7, 131.5, 128.4, 127.4, 121.9, 121.3, 119.1, 114.4, 102.2, 101.5, 65.9, 59.9, 59.0, 55.9, 55.7, 55.4, 42.4, 39.1, 27.2, 26.0, 18.7, 18.4. UPLC (DAD-QTOF [M+H]$^+$) calcd for $C_{35}H_{40}N_5O_4$ 594.3080, found 594.3099.

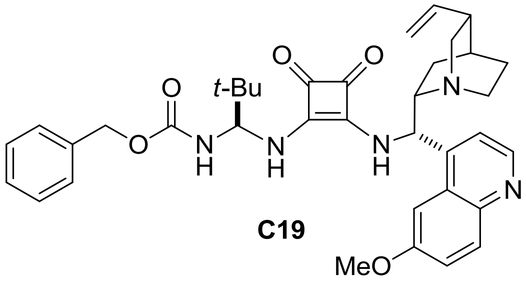
***N*-((*R*)-1-((2-(((S)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-2-methylpropyl)benzamide (C18)**



C18

The title compound was prepared from (*R*)-*N*-(1-amino-2-methylpropyl)benzamide hydrochloride and subsequent addition of 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow solid. Yield: 0.53 g, (45%). m.p.= 202–205 °C. $[\alpha]_D^{25}$ = –40.4 (c=1, CH_3OH). ^{1}H NMR (300 MHz, DMSO- *d*$_6$) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.56 (s, 1H), 7.94 (dd, *J* = 9.2, 5.3, 1H), 7.82 (s, 2H), 7.65 (dd, *J* = 9.3, 4.2, 1H), 7.59 – 7.34 (m, 4H), 6.03 (s, 1H), 5.93 – 5.72 (m, 1H), 5.46 (s, 1H), 5.06 – 4.85 (m, 2H), 3.94 (s, 3H), 3.37 – 3.25 (m, 7H), 3.17 (dd, *J* = 13.0, 10.1, 1H), 2.64 (s, 2H), 2.25 (s, 1H), 2.19 – 2.05 (m, 1H), 1.75 (d, *J* = 10.9, 1H), 1.51 (d, *J* = 6.4, 3H), 0.98 – 0.71 (m, 6H), 0.57 (s, 1H).^{13}C NMR (75 MHz, , DMSO- *d*$_6$) δ 182.5, 181.5, 167.1, 167.0, 166.5, 166.0, 157.9, 157.1, 147.8, 147.5, 144.3, 143.9, 143.6, 141.9, 133.8, 131.6, 131.5, 131.2, 128.4, 127.4, 126.7, 121.9, 121.2, 119.1, 114.6, 114.4, 102.3, 101.5, 65.9, 65.7, 60.2, 59.0, 55.8, 55.7, 55.4, 42.1, 39.1, 27.2, 26.0, 18.7, 18.3. UPLC (DAD-QTOF [M+H]$^+$) calcd for $C_{35}H_{40}N_5O_4$ 594.3080, found 594.3082.

Benzyl ((*S*)-1-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-2,2-dimethylpropyl)carbamate (C19)

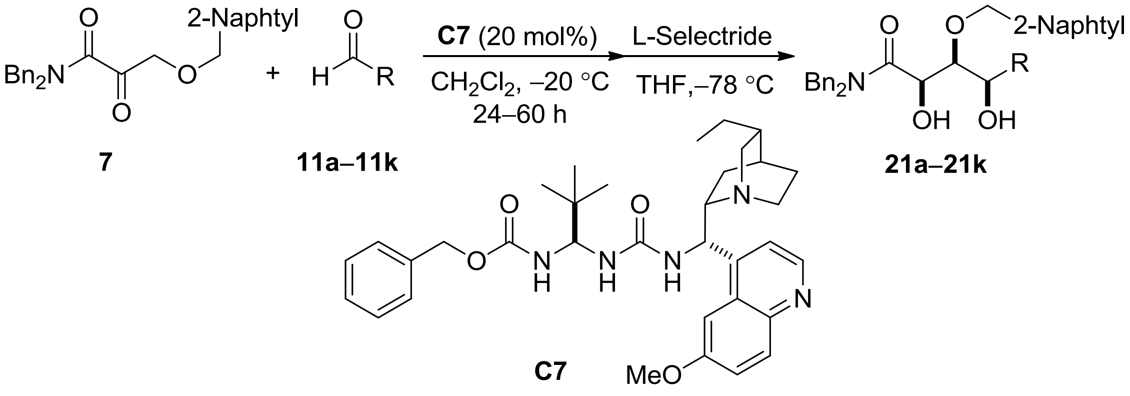


C19

The title compound was prepared from (*S*)-benzyl (1-amino-2,2-dimethylpropyl)carbamate hydrochloride and subsequent addition of 9-amino-(9-deoxy)*epi*quinine according to the general procedure. Yellow solid. Yield: 0.40 g, (31%). m.p.= 188–200 °C. $[\alpha]_D^{25}$ = –30.0 (c=0.5, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 8.68 (d, *J* = 4.7, 1H), 7.95 (s, 1H), 7.90 (d, *J* = 10.7, 1H), 7.70 (d, *J* = 4.6, 1H), 7.41 (dd, *J* = 9.2, 2.5, 1H), 7.21 (s, 4H), 6.32 (s, 1H), 5.89 (ddd, *J* = 17.5, 10.1, 7.7, 1H), 5.51 (s, 1H), 5.04 (dd, *J* = 18.4, 13.9, 4H), 3.98 (s, 3H), 3.74 (s, 1H), 3.67 – 3.47 (m, 1H), 3.42 – 3.32 (m, 1H), 3.05 – 2.76 (m, 2H), 2.44 (s, 1H), 1.71 – 1.57 (m, 4H), 0.92 (s, 9H), 0.75 (dd, *J* = 9.8, 6.2, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 183.9, 183.2, 169.3, 168.1, 160.6, 158.1, 148.6, 145.4, 138.0, 131.8, 129.5, 129.1, 129.0, 124.4, 121.0, 115.8, 115.5, 102.4, 71.0, 67.9, 61.0, 56.9, 56.6, 54.7, 41.9, 40.2, 37.0, 28.8, 25.6. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{37}H_{44}N_5O_5$ 638.3342, found 638.3356.

5.6. General procedure for the asymmetric direct aldol reaction of β-alkoxy-α-keto amides

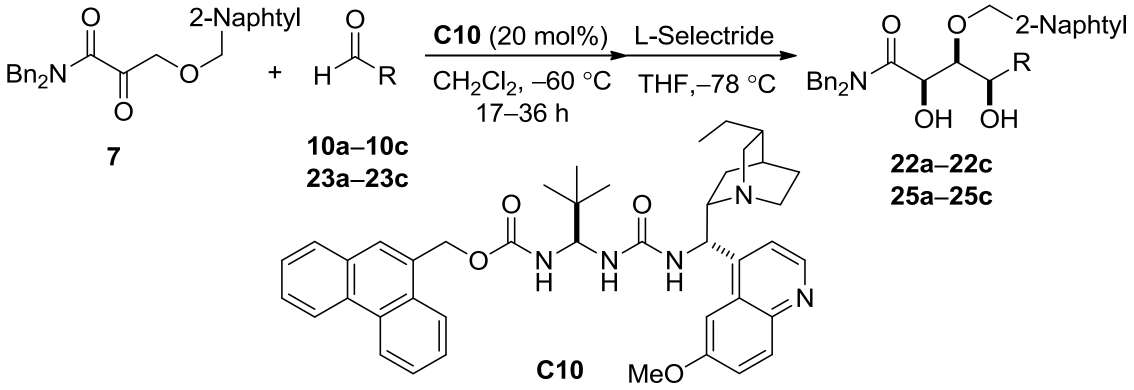
5.6.1. Asymmetric addition to aliphatic aldehydes


Bn2N
2-Naphtyl
7
+
H
R
11a–11k
C7 (20 mol%)
CH2Cl2, –20 °C
24–60 h
L-Selectride
THF,–78 °C
2-Naphtyl
Bn2N
R
OH
OH
21a–21k
MeO
C7

To a cooled solution of α-keto amide **7** (1 equiv., 0.6 mmol, 0.254 g) and the ureidopetide-based catalyst **C7** (0.02 equiv., 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added the corresponding aldehyde (3 equiv.) at –20 °C. The resulting solution was stirred at the same temperature until complete disappearance of **7**. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude aldol adduct which was directly reduced following the procedure described below.

The diastereoselectivity and enantioselectivity of the process were determined by HPLC analysis of aldol adducts before reduction

5.6.2. Asymmetric addition to propargylic and aromatic aldehydes



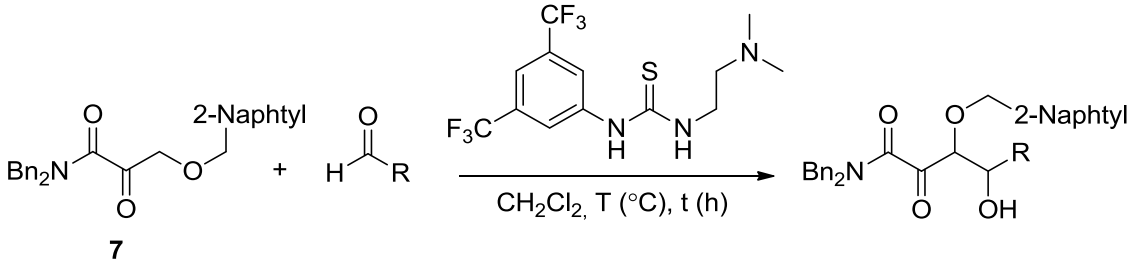
To a cooled solution of α-keto amide **7** (0.6 mmol, 0.254 g) and the ureidopetide-based catalyst **C10** (0.02 equiv., 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added the corresponding aldehyde (1.2 equiv) at –60 °C. The resulting solution was stirred at the same temperature until complete disappearance of **7**. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude aldol adduct which was directly reduced following the procedure described below.

The diastereoselectivity and enantioselectivity of the process were determined by HPLC analysis of aldol adducts before reduction

5.6.3. Stereoselective reduction

To a cooled solution of the corresponding crude aldol adducts in THF (6 mL) was added L-Selectride (1M THF, 2-3 equiv.) at –78 °C. After stirring for 1.5 hours, water (0.4 mL) and EtOH (0.8 mL) were successively added, followed by H_2O_2 (30% , 0.8 mL) five minutes later. The reaction temperature was allowed to rise to room temperature and the mixture was stirred for 10 additional minutes. Then, it was diluted with EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (Hex/ EtOAc, 80:20) to afford pure compound.

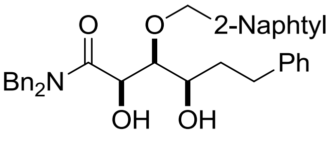
5.6.4. Racemic reaction



To a solution of α-keto amide **7** (1 equiv., 0.2 mmol) and the achiral catalyst 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea (0.02 equiv., 0.04 mmol) in CH_2Cl_2 (1 mL) was added the corresponding aldehyde (3 equiv. for enolizable aldehydes; 1.2 equiv. for ynals and aromatic aldehydes). The reaction mixture was carried out at 40 °C for enolyzable aldehydes and from –20 °C to room temperature for ynals and aromatic aldehydes. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude aldol adduct which was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford the corresponding aldol adduct.

5.6.5. Characterization data for compounds 21

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)-6-phenylhexanamide (21a)



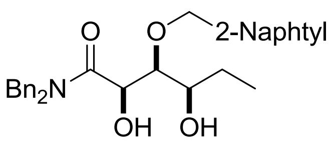
21a

The title compound was prepared from hydrocinnamaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 72 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21a**. Yield: 0.218 g (65%). Yellow pale oil. $[\alpha]_D^{25}$= 28.9 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.81 (m, 3H), 7.70 (s, 1H), 7.47 (m, 3H), 7.38 – 7.09 (m, 15H), 5.07 (d, *J* = 14.5, 1H), 4.87 (dd, *J* = 16.8, 14.3, 2H), 4.71 (dd, *J* = 11.5, 6.1, 2H), 4.34 (d, *J* = 16.9, 1H), 4.13 (d, *J* = 14.5, 1H), 3.85 (d, *J* = 8.0, 1H), 3.78 (s, 1H), 3.68 (t, *J* = 3.7, 1H), 2.85 – 2.74

(m, 1H), 2.56 (dd, *J* = 14.1, 8.8, 1H), 2.53 (s, 1H), 1.89 – 1.78 (m, 2H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.3, 141.9, 136.5, 135.8, 135.2, 133.4, 133.3, 129.2, 128.9, 128.6, 126.9, 126.4, 126.3, 126.2, 126.0, 83.2, 75.1, 70.9, 69.4, 49.5, 48.9, 35.9, 32.4. UPLC (DAD-QTOF [M+H]+) calcd. for $C_{37}H_{38}NO_4$ 560.2801, found 560.2818.

Data for aldol addut **21a**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.50 mL/min, 220 nm). *syn* isomer t_r (major)= 64.6 min, t_r (minor)= 109.2 min; *anti* isomer t_r (major)= 70.0 min, t_r (minor)= 97.1 min. Isomers ratio as determined by HPLC: *syn:anti* 94:6; 92% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)hexanamide (21c)

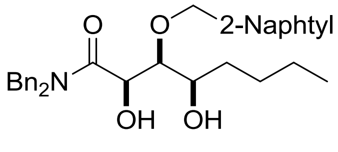


21c

The title compound was prepared from propanal according to general procedure. The catalytic aldol reaction was performed at –20 °C for 24 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21c**. Yield: 0.186 g (64%). White foam. $[\alpha]_D^{25}$= 32.7 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.87 – 7.77 (m, 3H), 7.73 (s, 1H), 7.53 – 7.43 (m, 3H), 7.39 – 7.25 (m, 8H), 7.20 – 7.12 (m, 2H), 5.11 (d, *J* = 14.5, 1H), 4.92 (dd, *J* = 13.9, 10.3, 2H), 4.76 (d, *J* = 11.3, 2H), 4.74 (s, 1H), 4.34 (d, *J* = 16.9, 1H), 4.16 – 4.09 (d, 1H), 3.93 (s, 1H), 3.69 (t, *J* = 3.6, 1H), 3.63 (s, 1H), 2.51 (s, 1H), 1.64 – 1.51 (m, 2H), 0.94 (t, *J* = 7.4, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.4, 136.6, 135.8, 135.3, 133.3, 133.2, 129.1, 129.1, 128.8, 128.4, 128.1, 127.9, 127.8, 126.9, 126.3, 126.2, 83.2, 75.1, 72.7, 69.6, 49.4, 48.8, 27.1, 10.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{31}H_{34}NO_4$ 484.2488, found 484.2485.

Data for aldol addut **21c**: Chiral HPLC (Chiralpak AD-H column; hexane:EtOH 80:20; 1.00 mL/min, 220 nm). *syn* isomer t_r (major)= 20.6 min, t_r (minor)= 30.6 min; *anti* isomer t_r (major)= 16.9 min, t_r (minor)= 35.6 min. Isomers ratio as determined by HPLC: *syn:anti* 83:17; 92% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)octanamide (21b)

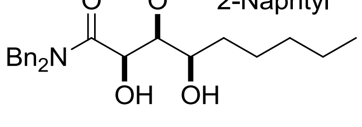


21b

The title compound was prepared from pentanal according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21b**. Yield: 0.215 g (70%). White foam. $[\alpha]_D^{25}$= 35.4 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.88 – 7.77 (m, 3H), 7.73 (s, 1H), 7.53 – 7.43 (m, 3H), 7.41 – 7.23 (m, 8H), 7.19 – 7.12 (m, 2H), 5.12 (d, *J* = 14.5, 1H), 4.92 (dd, *J* = 14.1, 9.6, 2H), 4.75 (d, *J* = 11.5, 1H), 4.73 – 4.68 (m, 1H), 4.34 (d, *J* = 16.9, 1H), 4.13 (d, *J* = 14.5, 1H), 3.79 (d, *J* = 8.1, 1H), 3.74 – 3.63 (m, 2H), 2.36 (d, *J* = 6.0, 1H), 1.58 – 1.16 (m, 6H), 0.85 (t, *J* = 7.0, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 136.6, 135.9, 135.3, 133.4, 133.3, 129.2, 128.9, 128.5, 128.1, 127.9, 127.2, 126.9, 126.3, 83.3, 75.2, 71.3, 69.7, 49.5, 48.9, 33.9, 28.2, 22.8, 14.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{33}H_{38}NO_4$ 512.2801, found 512.2807.

Data for aldol addut **21b**: Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm). *syn* isomer t_r (major)= 40.5 min, t_r (minor)= 81.1 min; *anti* isomer t_r (major)= 49.4 min, t_r (minor)= 45.5 min. Isomers ratio as determined by HPLC: *syn:anti* 81:19; 92% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)nonanamide (21d)

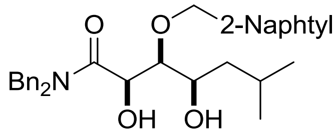


21d

The title compound was prepared from hexanal according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21d**. Yield: 0.182 g (58%). White foam. $[\alpha]_D^{25}$= 37.2 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 3H), 7.73 (s, 1H), 7.53 – 7.43 (m, 3H), 7.41 – 7.24 (m, 8H), 7.20 – 7.12 (m, 2H), 5.13 (d, *J* = 14.5, 1H), 4.93 (dd, *J* = 14.0, 9.9, 2H), 4.79 – 4.69 (m, 2H), 4.35 (d, *J* = 16.9, 1H), 4.13 (d, *J* = 14.5, 1H), 3.82 (d, *J* = 7.6, 1H), 3.74 – 3.62 (m, 2H), 2.39 (s, 1H), 1.58 – 1.36 (m, 3H), 1.31 – 1.16 (m, 5H), 0.87 (t, *J* = 6.8, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173. 5, 136.6, 135.9, 135.3, 133.4, 133.3, 129.2, 128.9, 128.5, 128.1, 128.1, 127.9, 127.9, 127.2, 126.9, 126.4, 126.3, 126.3, 83.3, 75.2, 71.3, 69.7, 49.5, 48.9, 34.2, 31.9, 25.7, 22.7, 14.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{34}H_{40}NO_4$ 526.2957, found 526.2969.

Data for aldol addut **21d**: Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm). *syn* isomer t_r (major)= 40.2 min, t_r (minor)= 85.2 min; *anti* isomer t_r (major)= 49.4 min, t_r (minor)= 46.7 min. Isomers ratio as determined by HPLC: *syn:anti* 76:24; 92% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-6-methyl-3-(naphthalen-2-ylmethoxy)heptanamide (21e)

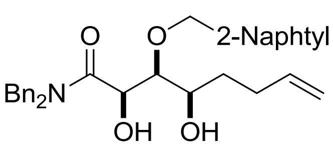


21e

The title compound was prepared from isovaleraldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 40 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21e**. Yield: 0.200 g (65%). Yellow pale oil. $[\alpha]_D^{25}$= 46.2 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 3H), 7.75 (s, 1H), 7.54 – 7.45 (m, 3H), 7.42 – 7.25 (m, 8H), 7.21 – 7.14 (m, 2H), 5.14 (d, *J* = 14.5, 1H), 4.95 (dd, *J* = 14.1, 5.8, 2H), 4.80 – 4.68 (m, 2H), 4.35 (d, *J* = 16.9, 1H), 4.12 (d, *J* = 14.5, 1H), 3.82 (dd, *J* = 14.2, 5.6, 2H), 3.64 (t, *J* = 3.8, 1H), 2.34 (d, *J* = 6.6, 1H), 1.76 (dq, *J* = 19.9, 6.6, 1H), 1.54 (ddd, *J* = 14.5, 9.4, 5.3, 1H), 1.28 (ddd, *J* = 16.7, 9.1, 4.0, 1H), 0.91 (d, *J* = 6.7, 3H), 0.86 (d, *J* = 6.5, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 136.6, 135.9, 135.3, 133.4), 133.3, 129.2, 128.9, 128.9, 128.5, 128.1, 128.1, 127.9, 127.2, 126.9, 126.3, 126.3, 126.2, 75.4, 69.7, 69.3, 49.5, 48.9, 43.2, 24.7, 23.6, 22.0. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{33}H_{38}NO_4$ 512.2807, found 512.2801.

Data for aldol addut **21e**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.50 mL/min, 220 nm). *syn* isomer t_r (major)= 46.6 min, t_r (minor)= 81.9 min; *anti* isomer t_r (major)= 51.1 min. Isomers ratio as determined by HPLC: *syn:anti* 94:6; 96% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)oct-7-enamide (21f)

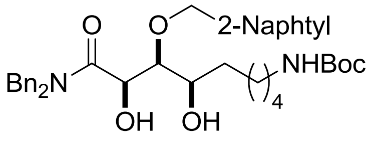


21f

The title compound was prepared from pent-4-enal according to general procedure. The catalytic aldol reaction was performed at –20 °C for 24 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21f**. Yield: 0.211 g (70%). Yellow pale oil. $[\alpha]_D^{25}$= 33.2 (c= 1, CH_2Cl_2). ^1H RMN (300 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 3H), 7.74 (s, 1H), 7.56 – 7.44 (m, 3H), 7.42 – 7.24 (m, 8H), 7.21 – 7.12 (m, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.6, 1H), 5.12 (d, *J* = 14.5, 1H), 5.06 – 4.85 (m, 4H), 4.75 (dd, *J* = 11.8, 8.1, 2H), 4.36 (d, *J* = 16.9, 1H), 4.18 (s, 1H), 3.88 (d, *J* = 7.8, 1H), 3.77 (d, *J* = 5.2, 1H), 3.68 (t, *J* = 3.8, 1H), 2.50 (d, *J* = 4.0, 1H), 2.31 – 2.15 (m, 1H), 2.15 – 2.01 (m, 1H), 1.74 – 1.55 (m, 2H).^{13}C RMN (75 MHz, $CDCl_3$) δ 173.4, 138.2, 136.6, 135.8, 135.2, 133.4, 133.3, 129.2, 128.9, 128.5, 128.1, 128.1, 127.9, 127.9, 127.2, 126.9, 126.4, 126.3, 115.2, 83.3, 75.1, 70.8, 69.5, 49.5, 48.9, 33.3, 30.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{33}H_{36}NO_4$ 510.2644, found 510.2651.

Data for aldol addut **21f**: Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm). *syn* isomer t_r (major)= 47.2 min, t_r (minor)= 91.2 min; *anti* isomer t_r (major)= 56.3 min, t_r (minor)= 52.4 min. Isomers ratio as determined by HPLC: *syn:anti* 91:9; 94% *ee* (*syn*).

***tert*-Butyl ((6*R*,7*S*,8*R*)-9-(dibenzylamino)-6,8-dihydroxy-7-(naphthalen-1-ylmethoxy)-9-oxononyl)carbamate (21g)**

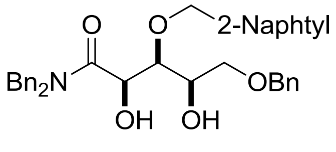


21g

The title compound was prepared from *tert*-butyl (6-oxohexyl)carbamate **11g** according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21g**. Yield: 0.269 g (70%). Yellow pale oil. $[\alpha]_D^{25}$= 18.9 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.80 (td, *J* = 10.2, 5.6, 3H), 7.70 (s, 1H), 7.45 (ddd, *J* = 10.1, 7.2, 2.2, 3H), 7.38 – 7.27 (m, 6H), 7.25 – 7.07 (m, 4H), 5.07 (d, *J* = 14.4, 1H), 4.88 (t, *J* = 12.9, 2H), 4.71 (t, *J* = 8.5, 2H), 4.34 (d, *J* = 16.9, 1H), 4.13 (d, *J* = 14.4, 1H), 3.81 (d, *J* = 8.0, 1H), 3.62 (dd, *J* = 7.2, 4.4, 2H), 3.03 (d, *J* = 6.2, 3H), 2.44 (d, *J* = 4.1, 1H), 1.59 – 1.50 (m, 2H), 1.44 (s, 9H), 1.39 – 1.30 (m, 4H), 1.22 – 1.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 156.2, 136.6, 135.8, 135.3, 133.3, 133.2, 129.2, 128.8, 128.4, 128.1, 128.0, 127.9, 127.8, 127.2, 126.9, 126.3, 126.2, 83.0, 75.0, 71.1, 69.5, 49.5, 48.8, 40.5, 33.9, 32.7, 30.0, 28.6, 26.7, 25.6. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{39}H_{48}N_2O_6$ 640.3512, found 640.3492.

Data for aldol addut **21g**: Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 90:10; 0.50 mL/min, 220 nm). *syn* isomer t_r (major)= 61.9 min, t_r (minor)= 136.1 min; *anti* isomer t_r (major)= 94.1 min, t_r (minor)= 58.7 min. Isomers ratio as determined by HPLC: *syn:anti* 75:25; 96% *ee* (*syn*)

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-5-(benzyloxy)-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)pentanamide (21h)

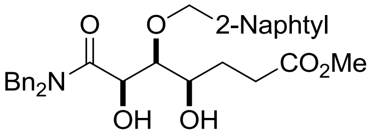


21h

The title compound was prepared from 2-(benzyloxy)acetaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 68 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21h**. Yield: 0.252 g (73%). Yellow pale oil. $[\alpha]_D^{25}$= 24.5 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 3H), 7.68 (s, 1H), 7.51 (dd, *J* = 6.1, 3.4, 3H), 7.33 (ddd, *J* = 16.4, 7.1, 3.1, 11H), 7.23 – 7.17 (m, 2H), 7.15 – 7.08 (m, 2H), 5.12 (d, *J* = 14.4, 1H), 4.84 (d, *J* = 15.8, 1H), 4.77 (d, *J* = 8.1, 2H), 4.68 (d, *J* = 11.5, 1H), 4.45 (s, 2H), 4.29 (d, *J* = 16.7, 1H), 4.09 (d, *J* = 14.5, 2H), 4.00 (d, *J* = 5.3, 1H), 3.92 (dd, *J* = 4.6, 2.5, 1H), 3.65 (td, *J* = 9.7, 4.9, 2H), 2.75 (s, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.2, 137.9, 136.6, 135.7, 135.4, 133.4, 133.3, 129.2, 129.0, 128.9, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.0, 126.3, 126.2, 126.1, 80.3, 74.6, 73.7, 71.3, 70.8, 68.5, 49.3, 48.7. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{38}NO_5$ 576.2750, found 576.2750.

Data for aldol addut **21h**: Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 90:10; 0.80 mL/min, 220 nm). *syn* isomer t_r (major)= 41.8 min, t_r (minor)= 34.9 min; *anti* isomer t_r (major)= 38.5 min. Isomers ratio as determined by HPLC: *syn:anti* 98:2; 95% *ee* (*syn*).

Methyl (4*R*,5*S*,6*R*)-7-(dibenzylamino)-4,6-dihydroxy-5-(naphthalen-2-ylmethoxy)-7-oxoheptanoate (21i)



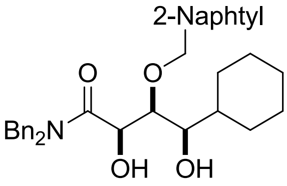
21i

The title compound was prepared from methyl 4-oxobutanoate **11i** according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21i**. Yield: 0.195 g (60%). Yellow pale oil. $[\alpha]_D^{25}$= 25.5 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 9.0, 4.5, 3H), 7.69 (s, 1H), 7.45 (ddd, *J* = 15.9, 7.2, 2.6, 3H), 7.32 (s, 4H), 7.25 – 7.06 (m, 6H), 5.09 – 5.02 (m, 1H), 4.86 (dd, *J* = 14.1, 9.6, 2H), 4.73 (d, *J* = 11.4, 2H), 4.37 – 4.29 (m, 1H), 4.16 (s, 1H), 3.85 – 3.72 (m, 2H), 3.64 (s, 3H), 2.73 (s, 1H), 2.42 (dd, *J* = 16.2, 7.4, 2H), 1.86 (dt, *J* = 12.2, 5.1, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 173.4, 136.6, 135.8, 135.2, 133.4, 133.3, 129.3, 128.9, 128.6, 128.2, 128.1, 128.0, 127.9, 127.2, 127.0, 126.4, 126.3, 126.2, 83.0, 75.0, 70.9, 69.1, 51.9, 49.5, 48.9, 30.9, 29.0. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{33}H_{36}NO_6$ 542.2543, found 542.2546.

Data for aldol addut **21i**: Chiral HPLC (Chiralpak AD-H column; hexane:EtOH 50:50; 1.0 mL/min, 220 nm). *syn* isomer t_r (major)= 36.7 min, t_r (minor)= 52.3 min; *anti* isomer t_r (major)= 21.1 min, t_r (minor)= 125.4 min. Isomers ratio as determined by HPLC: *syn:anti* 89:11; 90% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-4-cyclohexyl-2,4-dihydroxy-3-(naphthalen-2-ylmethoxy)butanamide (21j)

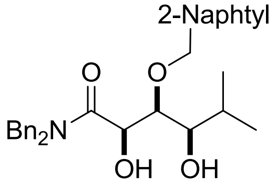


21j

The title compound was prepared from cyclohexanecarbaldehyde according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21j**. Yield: 0.226 g (70%). From this mixture pure *syn, syn* **21j** was isolated and characterized: Yellow pale oil. $[\alpha]_D^{25}$= 35.4 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.82 (td, *J* = 9.1, 4.3, 3H), 7.72 (s, 1H), 7.52 – 7.42 (m, 3H), 7.39 – 7.23 (m, 8H), 7.19 – 7.12 (m, 2H), 5.16 (d, *J* = 14.4, 1H), 4.98 (dd, *J* = 14.1, 9.4, 2H), 4.77 (d, *J* = 11.3, 1H), 4.75 – 4.70 (m, 1H), 4.30 (d, *J* = 17.0, 1H), 4.06 (d, *J* = 14.5, 1H), 3.86 (dd, *J* = 5.0, 2.2, 1H), 3.73 (d, *J* = 8.1, 1H), 3.25 (td, *J* = 7.9, 1.8, 1H), 2.27 (d, *J* = 8.1, 1H), 1.89 (d, *J* = 12.6, 1H), 1.75 – 1.55 (m, 3H), 1.46 (t, *J* = 12.3, 2H), 1.17 – 1.01 (m, 3H), 0.99 – 0.82 (m, 2H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.6, 136.7, 136.0, 135.4, 133.4, 133.3, 129.2, 128.9, 128.9, 128.5, 128.2, 128.0, 127.9, 127.9, 127.3, 126.9, 126.4, 126.3, 80.7, 75.4, 75.0, 70.5, 49.5, 48.9, 40.6, 29.83, 28.9, 26.5, 26.1, 26.0. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{35}H_{40}NO_4$ 538.2957, found 538.2961.

Data for aldol addut **21j**: Chiral HPLC (Chiralpak IC column; hexane:*i*-PrOH 95:5; 1.00 mL/min, 220 nm). *syn* isomer t_r (major)= 28.2 min, t_r (minor)= 95.6 min; *anti* isomer t_r (major)= 39.8 min, t_r (minor)= 26.6 min. Isomers ratio as determined by HPLC: *syn:anti* 60:40; 90% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-5-methyl-3-(naphthalen-2-ylmethoxy)hexanamide (21k)



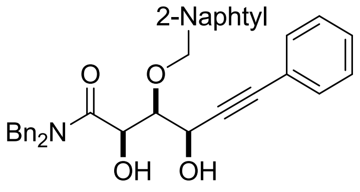
21k

The title compound was prepared from isobutyraldehyde according to general procedure. The catalytic aldol reaction was performed at –20 °C for 60 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **21k** (*syn, syn/ syn, anti* mixture, 65:35). Yield: 0.182 g (61%). From this mixture pure *syn, syn* **21k** was isolated and characterized: White foam. $[\alpha]_D^{25}$= 44.0 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.80 (td, *J* = 9.9, 3.6, 3H), 7.71 (s, 1H), 7.51 – 7.40 (m, 3H), 7.39 – 7.21 (m, 8H), 7.18 – 7.11 (m, 2H), 5.15 (d, *J* = 14.5, 1H), 4.97 (dd, *J* = 14.0, 9.4, 2H), 4.77 (d, *J* = 11.2, 1H), 4.75 – 4.69 (m, 1H), 4.29 (d, *J* = 17.0, 1H), 4.05 (d, *J* = 14.5, 1H), 3.84 (dd, *J* = 4.8, 2.5, 1H), 3.76 (d, *J* = 8.0, 1H), 3.24 (td, *J* = 7.8, 2.3, 1H), 2.32 (d, *J* = 7.9, 1H), 1.81 (dq, *J* = 13.6, 6.8, 1H), 0.94 (d, *J* = 6.7, 3H), 0.85 (d, *J* = 6.7, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 136.7, 135.9, 135.3, 133.4, 133.3, 129.2, 128.9, 128.9, 128.5, 128.2, 128.1, 127.9, 127.9, 127.2, 126.9, 126.4, 126.3, 81.5, 76.3, 75.1, 70.4, 49.5, 48.9, 31.1, 19.7, 18.6. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{32}H_{36}NO_4$ 498.2644, found 498.2653.

Data for aldol addut **21k**: Chiral HPLC (Chiralpak IC column; hexane:*i*-PrOH 95:5; 1.00 mL/min, 220 nm). *syn* isomer t_r (major)= 26.8 min, t_r (minor)= 98.9 min; *anti* isomer t_r (major)= 58.8 min, t_r (minor)= 21.6 min. Isomers ratio as determined by HPLC: *syn:anti* 65:35; 90% *ee* (*syn*).

5.6.6. Characterization data for compounds 22

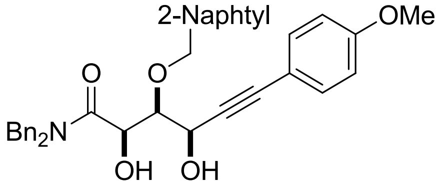
(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-1-ylmethoxy)-6-phenylhex-5-ynamide (22a)


22a

The title compound was prepared from 3-phenylpropiolaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 15 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **22a**. Yield: 0.227 g (68%). Orange foam. $[\alpha]_D^{25}$= –26.1 (c= 1, CH_2Cl_2). ^1H RMN (300 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 3H), 7.75 (s, 1H), 7.53 – 7.46 (m, 3H), 7.33 – 7.16 (m, 13H), 7.08 (dd, *J* = 7.0, 2.0, 2H), 5.06 (d, *J* = 14.5, 1H), 4.95 – 4.87 (m, 4H), 4.82 (d, *J* = 16.8, 1H), 4.42 (d, *J* = 16.8, 1H), 4.18 (d, *J* = 14.5, 1H), 3.97 – 3.89 (m, 2H), 2.99 (s, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 172.7, 136.5, 135.4, 135.0, 133.4, 133.4, 131.8, 129.2, 128.9, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.3, 126.8, 126.4, 126.3, 126.2, 122.0, 86.9, 75.4, 68.6, 63.7, 49.4, 48.8. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{34}NO_4$ 556.2488, found 556.2493.

Data for aldol addut **22a**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210 nm). *syn* isomer t_r (major)= 67.3 min, t_r (minor)= 99.3 min; *anti* isomer t_r (major)= 82.9 min, t_r (minor)= 56.7 min. Isomers ratio as determined by HPLC: *syn:anti* 85:15; 88% *ee* (*syn*).

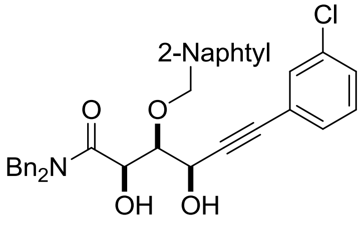
(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-6-(4-methoxyphenyl)-3-(naphthalen-1-ylmethoxy)hex-5-ynamide (22b)


22b

The title compound was prepared from 3-(4-methoxyphenyl)propiolaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 15 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **22b**. Yield: 0.214 g (61%). White foam. $[\alpha]_D^{25}$= –23.6 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 3H), 7.75 (s, 1H), 7.55 – 7.45 (m, 3H), 7.34 – 7.22 (m, 8H), 7.15 – 7.06 (m, 4H), 6.71 (d, *J* = 8.8, 2H), 5.06 (d, *J* = 14.5, 1H), 4.94 – 4.87 (m, 3H), 4.83 (d, *J* = 16.8, 1H), 4.42 (d, *J* = 16.8, 1H), 4.18 (d, *J* = 14.5, 1H), 3.93 (dd, *J* = 6.8, 2.2, 2H), 3.79 (s, 3H), 2.98 (s, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 172.8, 160.0, 136.5, 135.4, 135.1, 133.4, 133.3, 129.2, 128.9, 128.6, 128.2, 128.1, 128.0, 127.9, 127.2, 126.9, 126.4, 126.3, 126.2, 114.1, 114.0, 87.1, 85.5, 83.4, 75.4, 68.5, 63.8, 55.4, 49.4, 48.8. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{38}H_{36}NO_5$ 586.2593, found 586.2598.

Data for aldol addut **22b**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210 nm). *syn* isomer t_r (major)= 92.9 min, t_r (minor)= 118.5 min; *anti* isomer t_r (major)= 110.1 min, t_r (minor)= 79.8 min. Isomers ratio as determined by HPLC: *syn:anti* 85:15; 76% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-6-(3-chlorophenyl)-2,4-dihydroxy-3-(naphthalen-1-ylmethoxy)hex-5-ynamide (22c)



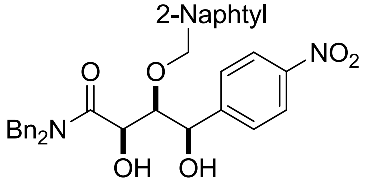
22c

The title compound was prepared from 3-(3-chlorophenyl)propiolaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 15 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **22c**. Yield: 0.209 g (59%). White foam. $[\alpha]_D^{25}$= –28.4 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, CDCl3) δ 7.83 (d, *J* = 8.5, 3H), 7.72 (s, 1H), 7.54 – 7.44 (m, 3H), 7.32 – 7.03 (m, 14H), 5.06 (d, *J* = 14.4, 1H), 4.92 – 4.75 (m, 5H), 4.42 (*d*, *J* = 16.8, 1H), 4.18 (*d*, *J* = 14.5, 1H), 3.93 (dd, *J* = 6.4, 2.6, 1H), 3.86 (d, *J* = 7.2, 1H), 2.87 (s, 1H).^{13}C RMN (75 MHz, $CDCl_3$) δ 172.6, 136.5, 135.3, 134.9, 134.3, 133.4, 133.9, 131.6, 130.0, 129.7, 129.3, 129.2, 128.9, 128.7, 128.2, 128.1, 127.9, 127.3, 126.7, 126.4, 126.4, 126.1, 123.7, 88.2, 85.5, 83.1, 75.3, 68.6, 63.5, 49.4, 48.9. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{33}NO_4Cl$ 590.2098, found 590.2107.

Data for aldol addut **22c**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210 nm). *syn* isomer t_r (major)= 56.2 min, t_r (minor)= 97.0 min; *anti* isomer t_r (major)= 80.2 min, t_r (minor)= 51.9 min. Isomers ratio as determined by HPLC: *syn:anti* 89:11; 84% *ee* (*syn*).

5.6.7. Characterization data for compounds 25

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-1-ylmethoxy)-4-(4-nitrophenyl)butanamide (25a)

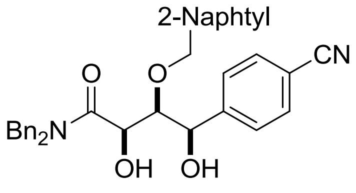


25a

The title compound was prepared from 4-nitrobenzaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 72 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 70:30) to afford pure **25a**. Yield: 0.207 g (60%). White foam. $[\alpha]_D^{25}$= –20.0 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.02 – 7.94 (m, 1H), 7.84 – 7.45 (m, 7H), 7.38 – 7.19 (m, 10H), 6.98 (dd, *J* = 6.3, 2.9, 2H), 4.99 (s, 1H), 4.94 (d, *J* = 14.5, 1H), 4.68 (d, *J* = 11.2, 1H), 4.47 (dd, *J* = 20.8, 14.1, 3H), 4.31 (dd, *J* = 15.7, 5.7, 2H), 3.93 (d, *J* = 7.2, 1H), 3.82 (t, *J* = 3.8, 1H), 3.51 (s, 1H).^{13}C RMN (75 MHz, $CDCl_3$) δ 172.8, 148.3, 143.5, 136.3, 135.4, 134.3, 133.3, 132.8, 129.3, 128.9, 128.8, 128.5, 128.2, 128.1, 127.9, 127.5, 126.5, 126.5, 126.1, 122.7, 121.5, 83.8, 75.1, 72.6, 68.7, 49.6, 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{35}H_{33}N_2O_6$ 577.2339, found 577.2347.

Data for aldol addut **25a**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 85:15; 0.60 mL/min, 220 nm). *syn* isomer t_r (major)= 38.4 min, t_r (minor)= 64.9 min; *anti* isomer t_r (major)= 34.9 min, t_r (minor)= 34.9 min. Isomers ratio as determined by HPLC: *syn:anti* 97:3; 92% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-4-(4-cyanophenyl)-2,4-dihydroxy-3-(naphthalen-1-ylmethoxy)butanamide (25b)

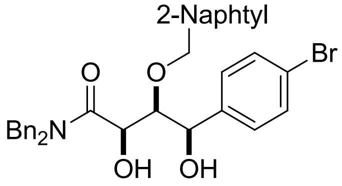


25b

The title compound was prepared from 4-formylbenzonitrile according to general procedure. The catalytic aldol reaction was performed at –60 °C for 40 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 70:30) to afford pure **25b**. Yield: 0.204 g (61%). Orange oil. $[\alpha]_D^{25}$= –17.3 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 6.1, 3.4, 1H), 7.77 – 7.62 (m, 3H), 7.53 – 7.19 (m, 14H), 6.95 (dd, *J* = 6.4, 2.9, 2H), 4.93 (d, *J* = 14.4, 2H), 4.67 (d, *J* = 11.3, 1H), 4.46 (d, *J* = 11.2, 1H), 4.43 – 4.37 (m, 2H), 4.28 (dd, *J* = 15.7, 8.9, 2H), 3.86 (d, *J* = 7.7, 1H), 3.80 (dd, *J* = 4.3, 3.5, 1H), 3.39 (d, *J* = 4.0, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 172.7, 146.6, 136.3, 135.3, 134.4, 133.3, 132.4, 132.2, 129.3, 128.9, 128.8, 128.6, 128.2, 128.1, 127.9, 127.4, 127.3, 127.2, 126.5, 126.5, 126.0, 118.8, 111.6, 83.9, 75.1, 72.9, 68.6, 64.3, 49.5, 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{36}H_{33}N_2O_4$ 557.2440, found 557.2449.

Data for aldol addut **25b**: Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 85:15; 0.60 mL/min, 220 nm). *syn* isomer t_r (major)= 45.1 min, t_r (minor)= 98.2 min; *anti* isomer t_r (major)= 34.3 min. Isomers ratio as determined by HPLC: *syn:anti* 96:4; 88% *ee* (*syn*).

(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-3-(naphthalen-1-ylmethoxy)-4-(4-bromo)butanamide (25c)



25c

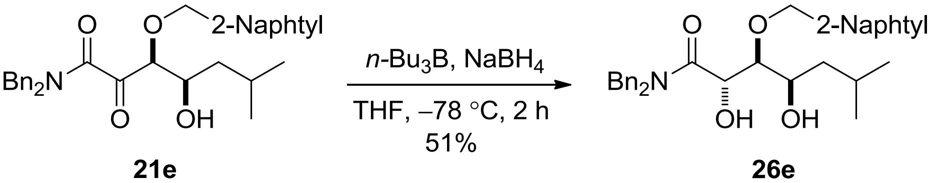
The title compound was prepared from 4-bromobenzaldehyde according to general procedure. The catalytic aldol reaction was performed at –60 °C for 96 hours. After ketone reduction, the crude was was purified by flash column chromatography (Hex/EtOAc, 70:30) to afford pure **25c**. Yield: 0.198 g (54%). White foam. $[\alpha]_D^{25}$= –13.5 (c= 0.4, CH_2Cl_2). ^{1}H RMN

(300 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 3H), 7.60 (s, 1H), 7.53 – 7.45 (m, 2H), 7.38 – 7.24 (m, 13H), 7.18 (d, *J* = 8.4, 2H), 6.94 – 6.86 (m, 2H), 4.93 (d, *J* = 14.5, 1H), 4.88 – 4.83 (m, 1H), 4.72 (d, *J* = 11.2, 1H), 4.53 (d, *J* = 11.2, 1H), 4.34 – 4.17 (m, 4H), 3.81 (d, *J* = 8.3, 1H), 3.73 (dd, *J* = 5.7, 2.7, 1H), 3.13 (d, *J* = 3.7, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.0, 139.8, 136.5, 135.4, 134.8, 133.4, 131.8, 129.3, 129.0, 128.9, 128.7, 128.6, 128.2, 128.1, 127.9, 127.4, 1265, 126.1, 122.1, 84.5, 75.2, 73.2, 68.2, 49.5, 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{35}H_{33}NO_4Br$ 610.1593, found 610.1588.

Data for aldol addut **25c**: Chiral HPLC (Chiralpak IA column; hexane: *i*-PrOH 85:15; 0.50 mL/min, 220 nm). *syn* isomer t_r (major)= 39.6 min, t_r (minor)= 80.0 min; *anti* isomer t_r (major)= 32.9 min, t_r (minor)= 28.6 min. Isomers ratio as determined by HPLC: *syn:anti* 71:29; 90% *ee* (*syn*).

5.6.8. Elaboration of adducts

5.6.8.1. *Anti-selective reduction of adduct **21e***[282]



(2*S*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,4-dihydroxy-6-methyl-3-(naphthalen-2-ylmethoxy) heptanamide (26e)

To a solution of the crude aldol addut **21e** (0.15 mmol, 0.076 g) and tributylborane (1M THF, 1.1 equiv., 0.15 mL) in THF (1 mL) was bubbled a small amount of air and the reaction mixture was stirred for 2 hour at room temperature. The solution was then cooled to –78 °C, $NaBH_4$ (0.33 mmol, 2.2 equiv., 0.012 g) was added and the reaction stirred for 2 hours. After quenching with phosphate buffer pH=7 (1.0 mL), EtOH (1.5 mL) and H_2O_2 (30%, 0.75 mL) the mixture was diluted with CH_2Cl_2 (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This procedure was repeated twice to completely decompose borane derivatives. The crude product was obtained as an *anti:syn* mixture 70:30 from which the *anti* **26e** was isolated as pure diastereoisomer after flash column chromatography on silica gel (Hex/EtOAc 80:20). Yield: 0.038 g (50%). White solid. m. p.=154 – 157°C. $[\alpha]_D^{25}$= –52.1 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 6.0, 3.4, 1H), 7.72 (dd, *J* = 7.0, 4.2, 2H), 7.48 (dd, *J* = 6.2, 3.3, 2H), 7.39 – 7.20 (m, 9H), 7.17 – 7.06 (m, 3H), 5.24 (d, *J* = 14.2, 1H), 4.95 (d, *J* = 17.1, 1H), 4.77 (s, 1H), 4.51 (s, 2H), 4.10 (d, *J* = 17.1, 1H), 4.06 – 3.97 (m, 1H), 3.93 (d, *J* = 14.3, 1H), 3.74 – 3.64 (m, 1H), 3.51 (dd, *J* = 8.6, 1.6, 1H), 2.23 – 2.11 (m, 1H), 1.85 – 1.70 (m, 1H), 1.55 (s, 1H), 1.28 (s, 1H), 0.91 (d, *J* = 6.7, 3H), 0.87 (d, *J* = 6.5, 3H).^{13}C RMN (75 MHz, $CDCl_3$) δ 174.5, 136.7, 135.8, 135.0, 133.3, 133.2, 129.5, 129.2, 128.9, 128.4, 128.1, 127.9, 127.0, 126.8, 126.4, 126.3, 126.0, 83.6, 74.6, 69.5, 67.9, 49.6, 49.0, 43.2, 24.9, 23.6, 22.2.UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{33}H_{38}NO_4$ 512.2801, found 512.2804.

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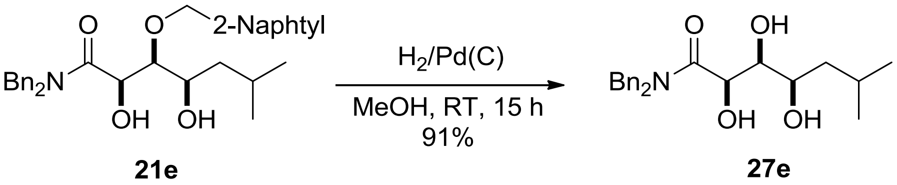
[282] K. Narasaka, F.-C. Pai, *Tetrahedron* **2008**, *40*, 2233–2238.

5.6.8.2. *Catalytic hydrogenation of adduct* ***21e***

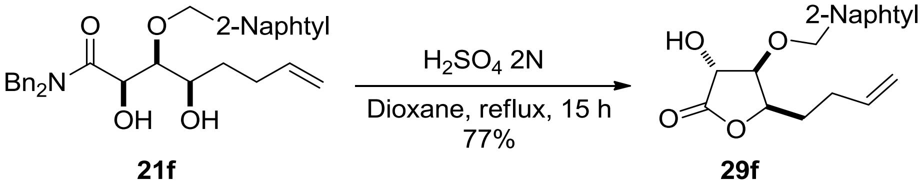


(2*R*,3*S*,4*R*)-*N*,*N*-Dibenzyl-2,3,4-trihydroxy-6-methylheptanamide (27e)

To a solution of aldol **21e** (0.15 mmol, 0.076 g) in MeOH (0.5 mL) was added Pd/C (0.008 g, 10% w/w) and the mixture was stirred at room temperature under hydrogen atmosphere for 15 hours. Then, the mixture was filtered through celite and concentrated *in vacuo*. The crude compound was purified by flash column chromatography on silica gel (Hex/EtOAc, 70:30) to afford pure **27e**. Yield: 0.051 g (91%). Yellow pale oil. $[\alpha]_D^{25}$= 33.9 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.04 (m, 10H), 4.90 (d, *J* = 14.8, 1H), 4.68 (d, *J* = 16.7, 1H), 4.62 (d, *J* = 3.1, 1H), 4.36 (d, *J* = 6.6, 1H), 4.31 (d, *J* = 4.5, 1H), 3.89 –

3.81 (m, 1H), 3.60 (t, *J* = 2.8, 1H), 2.95 (s, 2H), 1.80 – 1.65 (m, 1H), 1.55 (ddd, *J* = 14.5, 9.3, 5.4, 1H), 1.28 – 1.14 (m, 2H), 0.89 (d, *J* = 3.1, 3H), 0.86 (d, *J* = 3.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 136.3, 135.5, 129.3, 129.0, 128.5, 128.3, 128.0, 127.0, 73., 71.1, 70.3, 49.4, 48.7, 42.7, 24.5, 23.6, 22.0.UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{22}H_{30}NO_4$ 372.2182, found 372.2175.

5.6.8.3. *Acidic treatment of adduct **21f***[283]



(2*R*,3*S*,4*R*)-2,4-Dihydroxy-3-(naphthalen-2-ylmethoxy)oct-7-enoic acid (29f)

A solution of aldol **21f** (0.3 mmol, 0.153 g) and H_2SO_4 2N (3 mL) in dioxane (3 mL) was heated to reflux for 15 hours. Water (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 5mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude compound was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford pure **29f**. Yield: 0.076 g (77%). Yellow oil. $[\alpha]_D^{25}$= 41.2 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.90 – 7.76 (m, 4H), 7.54 – 7.42 (m, 3H), 5.77 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.12 – 4.98 (m, 2H), 4.94 (d, *J* = 12.0, 1H), 4.77 (d, *J* = 12.0, 1H), 4.63 – 4.53 (m, 2H), 4.30 (t, *J* = 7.1, 1H), 3.65 (s, 1H), 2.27 (dt, *J* = 11.3, 7.5, 1H), 2.20 – 2.06 (m, 1H), 1.96 (dddd, *J* = 12.8, 9.2, 7.1, 3.7, 1H), 1.78 – 1.65 (m, 1H).^{13}C RMN (75 MHz, $CDCl_3$) δ 175.5, 137.1, 134.7, 133.4, 133.3, 128.6, 128.1, 127.9, 127.0, 126.5, 126.4, 125.8, 116.1, 80.3, 79.4, 72.7, 72.2, 29.8, 29.0. Anal. calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.07; H, 6.67.

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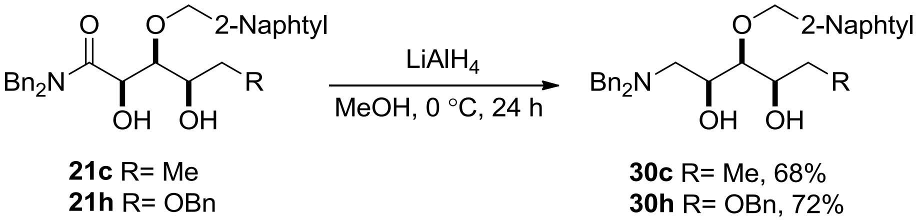
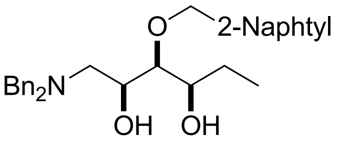
[283] Adapted from: E. Reyes, L. Carrillo, J. L. Vicario, D. Badía, *Lett. Org. Chem.* **2004**, *1*, 331–334.

*5.6.8.4. General procedure for the reduction of the amide group in adducts **21c** and **21h*** [284]



To a cooled solution of the corresponding aldol **21** in THF (5mL/mmol) was added LiAlH$_4$ (1M THF, 2-3 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 24 hours. Then, the mixture was quenched by adding $Na_2SO_4.10H_2O$ until bubbling stopped, filtered trough celite and concentrated *in vacuo*. The crude compound was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford the corresponding pure aminotriol **30**.

(2*R*,3*S*,4*R*)-1-(Dibenzylamino)-3-(naphthalen-2-ylmethoxy)hexane-2,4-diol (30c)



30c

The title compound was prepared according to general procedure starting from **21c** (0.26 mmol, 0.125 g). Yield: 0.083 g (68%). Yellow oil. $[\alpha]_D^{25}$= –13.0 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.86 – 7.77 (m, 3H), 7.68 (s, 1H), 7.51 – 7.45 (m, 2H), 7.37 – 7.20 (m, 11H), 4.68 (d, *J* = 11.4, 1H), 4.62 (d, *J* = 11.4, 1H), 4.01 – 3.91 (m, 1H), 3.71 (d, *J* = 13.4, 2H), 3.60 – 3.52 (m, 3H), 3.33 (t, *J* = 4.0, 1H), 2.94 – 2.78 (m, 1H), 2.67 (ddd, *J* = 17.9, 12.7, 6.7, 3H), 1.59 – 1.46 (m, 2H), 0.94 (t, *J* = 7.4, 3H).^{13}C NMR (75 MHz, CDCl$_3$) δ 138.6, 135.7, 133.40, 133.2, 129.4, 128.7, 128.4, 128.1, 127.6, 126.9, 126.3, 126.2, 82.5, 75.1, 73.5, 69.1, 58.9, 56.5, 27.1, 10.5.UPLC (DAD-QTOF [M+H]$^+$) calcd. for $C_{31}H_{36}NO_3$ 470.2695, found 470.2708.

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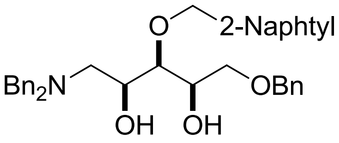
[284] B. L. Stocker, E. M. Dangerfield, A. L. Win-Mason, G. W. Haslett, M. S. M. Timmer, *Eur. J. Org. Chem.* **2010**, 1615–1637.

(2*R*,3*S*,4*R*)-1-(Dibenzylamino)-3-(naphthalen-2-ylmethoxy)hexane-2,4-diol (30h)

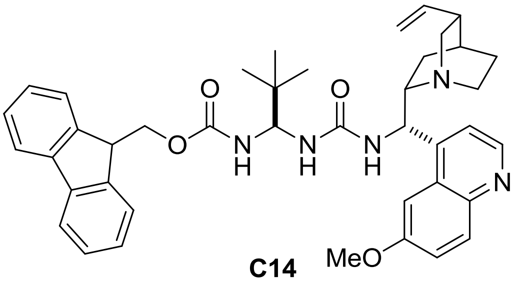

2-Naphtyl
O
Bn2N
OBn
OH
OH

30h

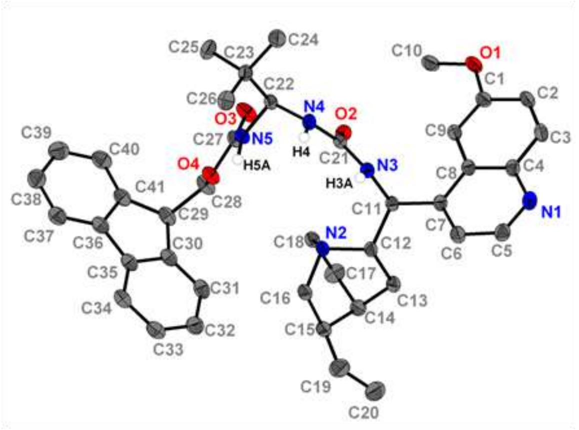
The title compound was prepared according to general procedure starting from **21h** (0.10 mmol, 0.057 g). Yield: 0.040 g (72%). Yellow oil. $[\alpha]_D^{25}$= –12.1 (c= 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0, 2H), 7.62 (s, 1H), 7.47 (dd, *J* = 6.1, 3.4, 2H), 7.40 – 7.26 (m, 17H), 4.67 (d, *J* = 11.5, 1H), 4.57 (d, *J* = 11.4, 1H), 4.47 (d, *J* = 1.3, 1H), 3.94 (dt, *J* = 9.5, 4.9, 2H), 3.79 – 3.75 (m, 2H), 3.68 (d, *J* = 13.4, 2H), 3.63 – 3.59 (m, 2H), 3.59 – 3.55 (m, 1H), 3.54 (d, *J* = 2.8, 2H), 3.50 (d, *J* = 10.7, 1H), 2.71 (dd, *J* = 12.6, 8.7, 1H), 2.56 (dd, *J* = 12.7, 4.9, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.2, 135.8, 133.4, 133.2, 129.4, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 127.0, 126.4, 126.3, 126.2, 73.6, 73.5, 71.6, 71.4, 70.9, 68.8, 62.2, 58.8, 56.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{40}NO_4$ 562.2957, found 562.2954.

5.6.9. ORTEP diagram of C14 and compounds 21d and 22c

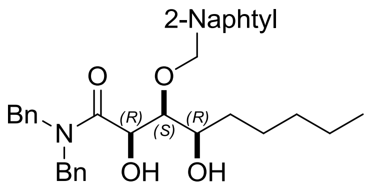
CCDC 947275 contains the supplementary crystallographic data for the structural analysis of **C14**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


O
O
N
H
N
H
N
H
N
N
MeO

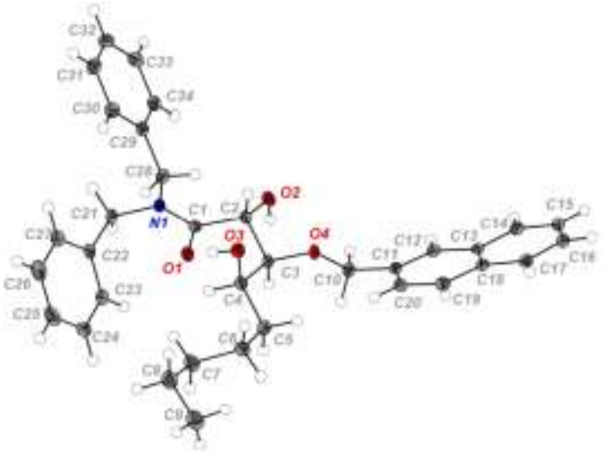
C14

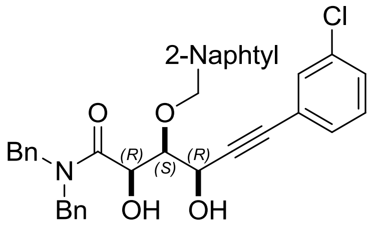

C25
C23
C24
C10
O1
C26
C22
C1
C2
O3
N4
O2
C39
C27
N5
C9
C3
C40
H4
C21
H5A
N3
C4
O4
H3A
C8
C41
C11
C38
C29
C28
N1
C7
C37
C36
C30
N2
C18
C12
C6
C5
C17
C35
C31
C16
C13
C34
C14
C15
C32
C33
C19
C20

CCDC 1434756 contains the supplementary crystallographic data for the structural analysis of **21d** and **22c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

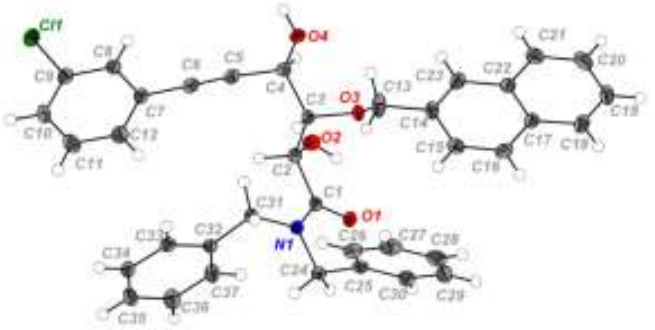

2-Naphtyl
O
O
Bn
N
Bn
(R)
(S)
(R)
OH
OH

21d


C32
C33
C31
C34
C30
C29
C28
C21
N1
C1
C2
O2
O3
O4
O1
C3
C4
C5
C6
C7
C8
C9
C10
C11
C12
C13
C14
C15
C16
C17
C18
C19
C20
C22
C23
C24
C25
C26
C27

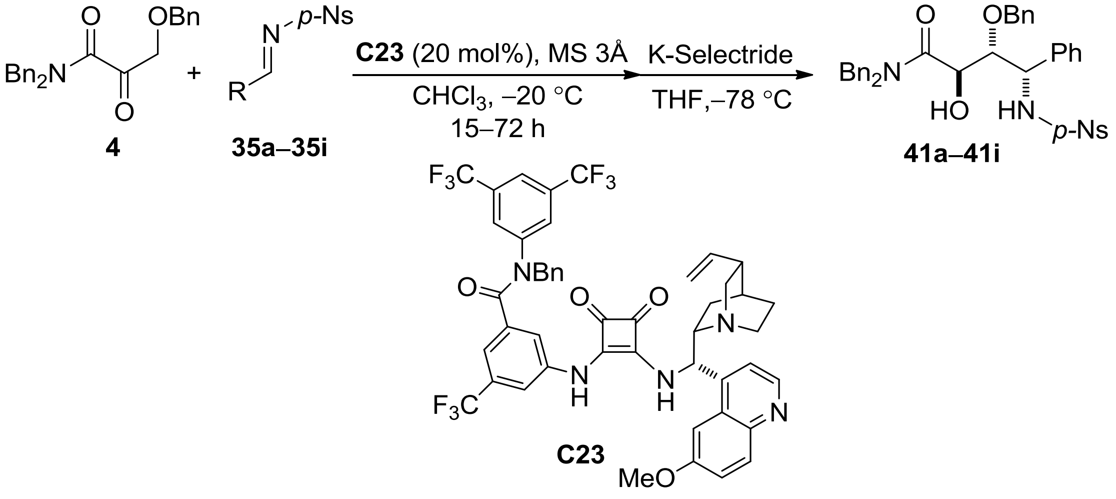

Cl
2-Naphtyl
O
O
Bn
N
Bn
(R)
(S)
(R)
OH
OH

22c


Cl1
C8
C9
C10
C11
C12
C7
C6
C5
O4
C4
C3
O3
C13
C14
C15
C16
C17
C18
C19
C20
C21
C22
C23
O2
C2
C1
O1
N1
C31
C32
C33
C34
C35
C36
C37
C24
C25
C26
C27
C28
C29
C30

5.7. General procedure for the asymmetric direct Mannich-reaction of β-alkoxy-α-keto amides

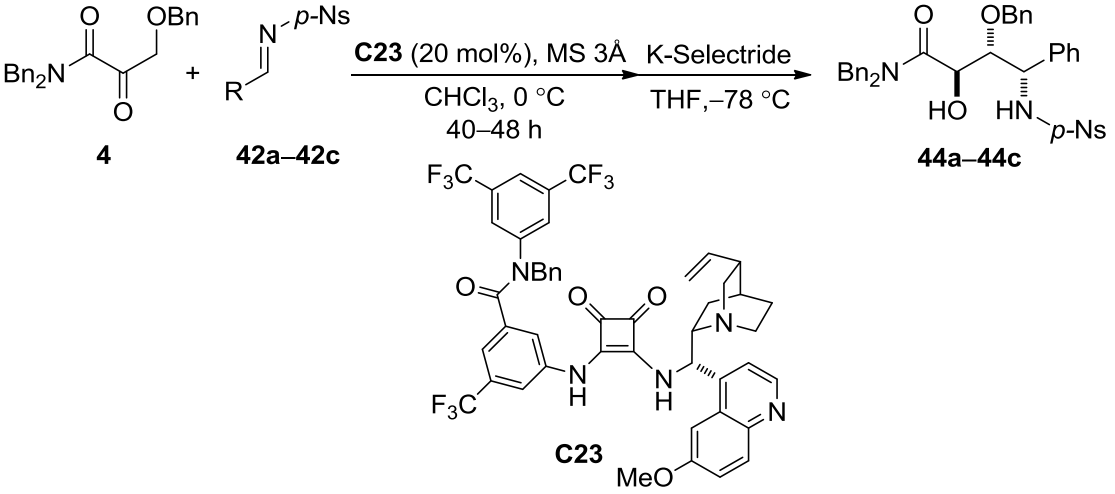
5.7.1. Asymmetric addition to aromatic imines 35a–35i


O
OBn
Bn_2N
O
4
+
N
p-Ns
R
35a–35i
C23 (20 mol%), MS 3Å
$CHCl_3$, –20 °C
15–72 h
K-Selectride
THF,–78 °C
O
OBn
Bn_2N
Ph
HO
HN
p-Ns
41a–41i
F_3C
CF_3
NBn
O
O
O
N
H
N
H
F_3C
N
N
C23
MeO

To a cooled solution of α-keto amide **4** (1 equiv., 0.15 mmol, 0.056 g), squaramide-based catalyst **C23** (0.02 equiv., 0.03 mmol) and molecular sieves (pellets, 3Å) in $CHCl_3$ (1.5 mL) was added the corresponding imine (1.5 equiv., 0.23 mmol) at –20 °C. The resulting solution was stirred at the same temperature until complete disappearance of **4**. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude Mannich adduct which was directly reduced following the procedure described below.

The diastereoselectivity and enantioselectivity of the process were determined by HPLC analysis of aldol adducts before reduction.

5.7.2. Asymmetric addition to aliphatic imines 42a–42c



To a cooled solution of α-keto amide **4** (1 equiv., 0.15 mmol, 0.056 g), squaramide-based catalyst **C23** (0.02 equiv., 0.03 mmol) and molecular sieves (pellets, 3Å) in CH_2Cl_2 (1.5 mL) was added the corresponding imine (3 equiv., 0.45 mmol) at 0 °C. The resulting solution was stirred at the same temperature until complete disappearance of **4**. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude Mannich adduct which was directly reduced following the procedure described below.

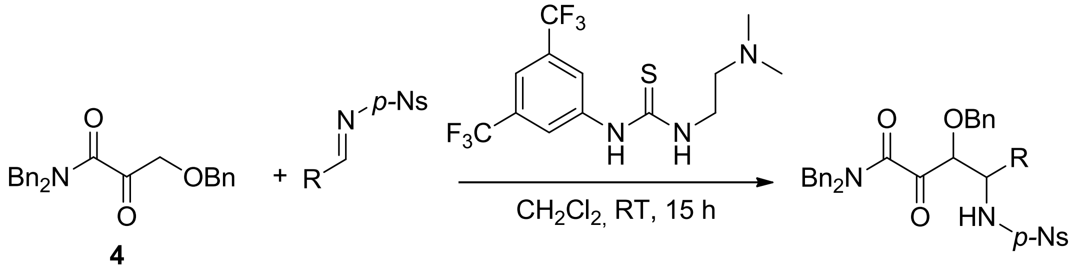
The diastereoselectivity and enantioselectivity of the process were determined by HPLC analysis of aldol adducts before reduction.

5.7.3. Stereoselective reduction

To a cooled solution of the corresponding crude Mannich adduct in THF (1.5 mL) was added K-Selectride (1M THF, 3-4 equiv.) at –78 °C. After stirring for 2 h, phosphate buffer pH=7 (0.5 mL) and EtOH (1.0 mL) were successively added, followed by H_2O_2 (30% , 0.8 mL) five minutes later. The reaction temperature was allowed to rise to room temperature and the mixture was stirred for 10 additional min. Then, it was diluted with EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo.

The crude product was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford the corresponding pure compound.

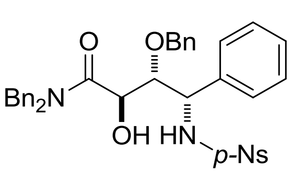
5.7.4. Racemic reaction



To a solution of α-keto amide **4** (1 equiv., 0.1 mmol) and the achiral catalyst 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea (0.04 equiv., 0.04 mmol) in CH_2Cl_2 (1 mL) was added the corresponding imine (3 equiv. for enolizable imines; 1.5 equiv. for aromatic imines) and stirred at room temperature for 15 hours. The reaction mixture was quenched with HCl 0.1M (5 mL), the organic layer was washed with HCl 0.1M (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the corresponding crude aldol adduct which was purified by flash column chromatography on silica gel (Hex/EtOAc, 90:10) to afford the corresponding Mannich adduct.

5.7.5. Characterization data for compounds 41

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(4-nitrophenylsulfonamido)-4-phenylbutanamide (41a)



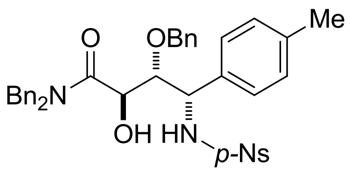
41a

The title compound was prepared from imine **35a** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41a**. Yield: 0.068 g (68%).White solid. m.p. 190–192 °C. $[\alpha]_D^{25}$= 46.1 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9, 2H), 7.72 (d, *J* = 8.9, 2H), 7.20 (d, *J* = 11.9, 16H), 6.95 (dd, *J* = 6.5, 2.7, 2H), 6.67 – 6.58 (m, 2H), 5.89 (d, *J* = 9.9, 1H), 5.23 (d, *J* =

14.2, 1H), 5.06 (d, *J* = 9.1, 1H), 4.64 (d, *J* = 17.3, 1H), 4.16 (t, *J* = 9.1, 1H), 4.08 (d, *J* = 10.3, 1H), 4.01 (d, *J* = 17.3, 1H), 3.89 – 3.80 (m, 2H), 3.75 (dd, *J* = 9.3, 1.6, 1H), 3.59 (d, *J* = 9.0, 1H).^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 149.8, 146.5, 138.2, 136.5, 135.4, 129.4, 129.2, 129.0, 128.7, 128.6, 128.3, 128.3, 128.2, 128.2, 128.1, 126.8, 126.6, 124.1, 85.5, 75.0, 67.3, 57.3, 49.5. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{36}N_3O_7S$ 666.2274, found 666.2274.

Data for Mannich addut **41a**: Chiral HPLC (Chiralpak IB column; hexane:EtOH 90:10; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 36.2 min, t_r (minor)= 13.7 min; *anti* isomer t_r (major)= 18.2 min, t_r (minor)= 19.3 min. Isomers ratio as determined by HPLC: *syn:anti* 98:2; 94% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(4-nitrophenylsulfonamido)-4-(*p*-tolyl)butanamide (41b)



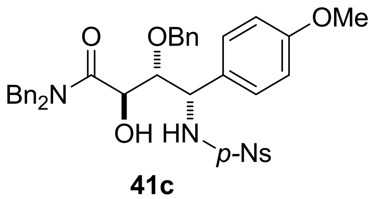
41b

The title compound was prepared from imine **35b** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41b.** Yield: 0.059 g (58%). Brown pale solid. m.p. 167–172 °C. $[\alpha]_D^{25}$= 20.7 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8, 2H), 7.71 (d, *J* = 8.8, 2H), 7.38 – 7.13 (m, 12H), 7.07 – 6.90 (m, 6H), 6.65 (d, *J* = 7.0, 2H), 5.90 (d, *J* = 9.4, 1H), 5.22 (d, *J* = 14.2, 1H), 5.01 (d, *J* = 8.3, 1H), 4.63 (d, *J* = 17.4, 1H), 4.17 (t, *J* = 8.9, 1H), 4.09 (d, *J* = 10.3, 1H), 4.00 (d, *J* = 17.3, 1H), 3.93 – 3.81 (m, 2H), 3.77 – 3.71 (m, 1H), 3.60 (d, *J* = 8.9, 1H), 2.26 (s, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 149.7, 146.6, 137.8, 136.6, 136.5, 135.4, 135.0, 129.3, 129.2, 129.0, 128.5, 128.2, 126.8, 126.6, 124.0, 85.4, 74.9, 67.3, 57.1, 49.5, 49.4, 21.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{38}H_{38}N_3O_7S$ 680.2430, found 680.2426.

Data for Mannich addut **41b**: Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 25.9 min, t_r

(minor)= 59.6 min; *anti* isomer t_r (major)= 29.3 min, t_r (minor)= 21.1 min. Isomers ratio as determined by HPLC: *syn:anti* 97:3; 92% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(4-methoxyphenyl)-4-(4-nitrophenylsulfonamido)butanamide (41c)

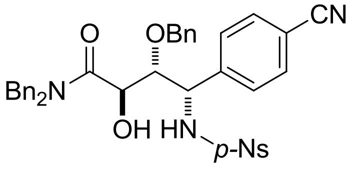


41c

The title compound was prepared from imine **35c** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 72 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41c**. Yield: 0.062 g (59%). Yellow pale solid. m.p. 146–151 °C. $[\alpha]_D^{25}$= 58.8 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9, 2H), 7.72 (d, *J* = 8.9, 2H),, 7.35 – 7.13 (m, 11H), 7.05 (d, *J* = 8.6, 2H), 6.94 (dd, *J* = 6.6, 2.7, 2H), 6.73 – 6.62 (m, 4H), 5.92 (d, *J* = 9.8, 1H), 5.22 (d, *J* = 14.2, 1H), 4.99 (d, *J* = 9.4, 1H), 4.63 (d, *J* = 17.4, 1H), 4.16 (s, 1H), 4.11 (d, *J* = 10.3, 1H), 4.00 (d, *J* = 17.3, 1H), 3.93 (d, *J* = 10.4, 1H), 3.85 (d, *J* = 14.3, 1H), 3.73 (s, 3H), 3.70 (d, *J* = 1.6, 1H), 3.64 (d, *J* = 8.8, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 159.4, 149.7, 146.6, 136.6, 136.5, 135.4, 129.9, 129.3, 129.2, 129.0, 128.6, 128.2, 128.2, 128.1, 128.0, 126.6, 124.0, 114.0, 85.3, 74.8, 67.4, 56.8, 55.5, 49.5. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{38}H_{38}N_3O_8S$ 696.2380, found 696.2380.

Data for Mannich addut **41c:** Chiral HPLC (Chiralpak IA column; hexane: EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 34.7 min, t_r (minor)= 68.5 min; *anti* isomer t_r (major)= 27.4 min, t_r (minor)= 32.1 min. Isomers ratio as determined by HPLC: *syn:anti* 97:3; 88% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-4-(4-cyanophenyl)-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (41d)

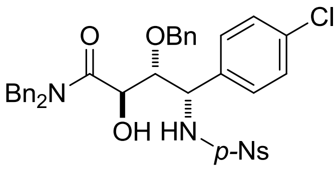


41d

The title compound was prepared from imine **35d** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41d**. Yield: 0.062 g (60%). White solid. m.p. 192–194 °C. $[\alpha]_D^{25}$= 39.5 (c= 0.5, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.9, 2H), 7.75 (d, *J* = 8.9, 2H), 7.57 – 7.13 (m, 15H), 6.93 (dd, *J* = 6.3, 2.8, 2H), 6.59 (d, *J* = 7.0, 2H), 5.90 (d, *J* = 6.7, 1H), 5.26 (d, *J* = 14.2, 1H), 5.00 (d, *J* = 6.8, 1H), 4.61 (d, *J* = 17.6, 1H), 4.07 (d, *J* = 10.9, 1H), 3.92 (t, *J* = 8.6, 1H), 3.82 (d, *J* = 14.1, 1H), 3.75 (d, *J* = 10.5, 1H), 3.65 (dd, *J* = 9.2, 1.5, 1H), 3.55 (d, *J* = 8.4, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.1, 150.0, 146.2, 140.6, 136.2, 135.8, 135.1, 131.6, 131.2, 130.5, 129.6, 129.5, 129.4, 129.1, 128.8, 128.8, 128.5, 128.4, 128.1, 126.3, 124.3, 118.3, 113.0, 84.9, 75.1, 67.2, 56.8, 49.7, 49.3. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{38}H_{35}N_4O_7S$ 691.2226, found 691.2226.

Data for Mannich addut **41d**. Chiral HPLC (Chiralpak IA column; hexane: EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 29.2 min, t_r (minor)= 39.0 min; *anti* isomer t_r (major)= 24.7 min, t_r (minor)= 19.8 min. Isomers ratio as determined by HPLC: *syn:anti* 97:3; 92% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-4-(4-chlorophenyl)-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (41e)



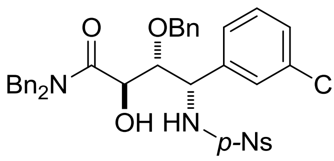
41e

The title compound was prepared from imine **35e** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41e**. Yield: 0.064 g

(61%). Orange solid. m.p. 181–183 °C. $[\alpha]_D^{25}$= 37.2 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9, 2H), 7.74 (d, *J* = 8.9, 2H), 7.41 – 7.08 (m, 15H), 6.92 (dd, *J* = 6.5, 2.6, 2H), 6.63 (d, *J* = 7.0, 2H), 5.91 (d, *J* = 9.6, 1H), 5.25 (d, *J* = 14.2, 1H), 4.99 (d, *J* = 9.4, 1H), 4.60 (d, *J* = 17.4, 1H), 4.09 (d, *J* = 10.4, 1H), 4.01 (dd, *J* = 11.8, 6.5, 2H), 3.87 (d, *J* = 6.3, 1H), 3.83 (d, *J* = 10.1, 1H), 3.69 (dd, *J* = 9.3, 1.6, 1H), 3.58 (d, *J* = 8.9, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.3, 146.4, 137.0, 136.4, 136.2, 135.3, 134.0, 129.4, 129.3, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 126.4, 124.2, 85.1, 74.9, 67.3, 56.8, 49.7, 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{35}N_3O_7S$ 700.1884, found 700.1884.

Data for Mannich addut **41e**: Chiral HPLC (Chiralpak IA column; hexane: EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 26.6 min, t_r (minor)= 44.9 min; *anti* isomer t_r (major)= 19.8 min, t_r (minor)= 22.3 min. Isomers ratio as determined by HPLC: *syn:anti* 98:2; 92% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-4-(3-chlorophenyl)-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (41f)

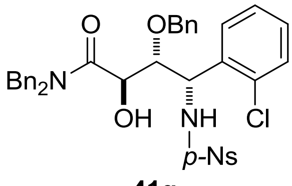


41f

The title compound was prepared from imine **35f** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41f**. Yield: 0.067 g (64%). Orange solid. m.p. 165–168 °C. $[\alpha]_D^{25}$= 19.9 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.9, 2H), 7.72 (d, *J* = 8.9, 1H), 7.38 – 7.12 (m, 8H), 7.08 (t, *J* = 3.9, 0H), 6.96 (dd, *J* = 6.4, 2.6, 0H), 6.61 (d, *J* = 6.9, 0H), 5.88 (d, *J* = 9.7, 1H), 5.25 (d, *J* = 14.1, 1H), 5.00 (d, *J* = 9.5, 1H), 4.65 (d, *J* = 17.3, 1H), 4.17 – 4.00 (m, 3H), 3.83 (t, *J* = 12.0, 2H), 3.70 (dd, *J* = 9.3, 1.4, 1H), 3.58 (d, *J* = 8.9, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 149.9, 146.3, 140.4, 136.4, 136.1, 135.3, 134.8, 130.0, 129.5, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.1, 126.5, 125.2, 124.1, 85.2, 75.2, 67.2, 56.9, 49.6 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{35}N_3O_7S$ 700.1884, found 700.1891

Data for Mannich addut **41f**: Chiral HPLC (Chiralpak OD-H column; hexane:EtOH 90:10; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 52.7 min, t_r (minor)= 16.4 min; *anti* isomer t_r (major)= 26.1 min, t_r (minor)= 23.1 min. Isomers ratio as determined by HPLC: *syn:anti* 98:2; 88% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-4-(2-chlorophenyl)-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (41g)

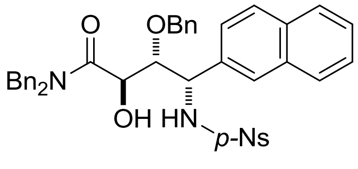


41g

The title compound was prepared from imine **35g** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 24 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41g**. Yield: 0.046 g (44%). White solid. m.p. 210–213 °C. $[\alpha]_D^{25}$= 6.2 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0, 2H), 7.76 (d, *J* = 9.0, 1H), 7.39 – 7.07 (m, 9H), 7.02 (dd, *J* = 6.4, 2.8, 1H), 6.53 (d, *J* = 7.0, 1H), 5.77 (d, *J* = 9.6, 1H), 5.49 (d, *J* = 9.0, 1H), 5.21 (d, *J* = 14.1, 1H), 4.73 (d, *J* = 17.4, 1H), 4.16 – 4.04 (m, 2H), 4.01 (d, *J* = 9.9, 1H), 3.83 (dd, *J* = 16.1, 7.6, 2H), 3.61 (d, *J* = 9.9, 1H), 3.37 (d, *J* = 9.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 149.9, 146.0, 136.5, 136.3, 136.2, 135.4, 132.4, 130.2, 129.6, 129.4, 129.3, 129.0, 128.5, 128.4, 128.2, 127.0, 126.5, 124.2, 83.3, 75.6, 67.4, 54.2, 49.4, 49.4. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{35}N_3O_7S$ 700.1884, found 700.1885.

Data for Mannich addut **41g**: Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 17.4 min, t_r (minor)= 22.7 min; *anti* isomer t_r (major)= 46.0 min, t_r (minor)= 15.2 min. Isomers ratio as determined by HPLC: *syn:anti* 70:30; 58% *ee* (*syn*)

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(naphthalen-2-yl)-4-(4-nitrophenylsulfonamido)butanamide (41h)

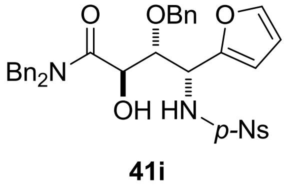


41h

The title compound was prepared from imine **35h** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41h**. Yield: 0.061 g (57%). White solid. m.p. 180–183 °C. $[\alpha]_D^{25}$= 20.7 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.86 – 7.40 (m, 10H), 7.34 – 7.06 (m, 12H), 6.89 (d, *J* = 6.6, 2H), 6.61 (d, *J* = 7.0, 2H), 6.07 (d, *J* = 9.8, 1H), 5.22 (t, *J* = 12.1, 2H), 4.64 (d, *J* = 17.3, 1H), 4.21 (d, *J* = 9.1, 1H), 4.11 (d, *J* = 10.3, 1H), 4.02 (d, *J* = 17.3, 1H), 3.91 – 3.81 (m, 3H), 3.69 (d, *J* = 9.0, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.5, 149.6, 146.5, 136.4, 136.4, 135.4, 135.2, 133.0, 132.9, 129.4, 129.2, 129.0, 128.6, 128.6, 128.2, 128.2, 128.1, 127.8, 126.8, 126.6, 126.5, 126.2, 124.7, 123.9, 85.3, 75.0, 67.4, 57.5, 49.6, 49.5. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{41}H_{38}N_3O_7S$ 716.2430, found 716.2429.

Data for Mannich addut **41h**: Chiral HPLC (Chiralpak IB column; hexane:EtOH 90:10; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 32.4 min, t_r (minor)= 18.3 min; *anti* isomer t_r (major)= 21.4 min, t_r (minor)= 25.1 min. Isomers ratio as determined by HPLC: *syn:anti* 98:2; 90% *ee* (*syn*).

(2*R*,3*R*,4*R*)-*N,N*-dibenzyl-3-(benzyloxy)-4-(furan-2-yl)-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (41i)



41i

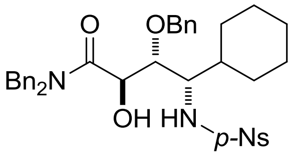
The title compound was prepared from imine **35i** according to general procedure. The catalytic Mannich reaction was performed at –20 °C for 15 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **41i**. Yield: 0.052 g (53%). White solid. m.p. 159–164 °C. $[\alpha]_D^{25}$= 47.0 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz,

$CDCl_3$) δ 8.02 (d, *J* = 8.8, 2H), 7.79 (d, *J* = 8.9, 2H), 7.37 – 7.13 (m, 12H), 7.03 – 6.93 (m, 2H), 6.69 – 6.62 (m, 2H), 6.23 (dd, *J* = 3.2, 1.8, 1H), 6.17 (d, *J* = 3.3, 1H), 5.73 (d, *J* = 10.1, 1H), 5.24 (d, *J* = 14.2, 1H), 5.11 (d, *J* = 10.0, 1H), 4.70 (d, *J* = 17.3, 1H), 4.21 (t, *J* = 9.2, 1H), 4.11 (d, *J* = 10.1, 1H), 4.01 (d, *J* = 17.3, 1H), 3.95 – 3.86 (m, 2H), 3.84 (d, *J* = 14.3, 1H), 3.59 (d, *J* = 9.2, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.4, 151.6, 149.8, 146.3, 142.4, 136.6, 136.6, 135.4, 129.4, 129.2, 129.0, 128.6, 128.3, 128.2, 126.6, 124.1, 111.0, 108.5, 83.4, 74.6, 67.0, 52.2, 49.4, 49.3. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{35}H_{34}N_3O_8S$ 656.2067, found 656.2071.

Data for Mannich addut **41i**: Chiral HPLC (Chiralpak IA column; hexane: EtOH 70:30; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 20.3 min, t_r (minor)= 30.9 min; *anti* isomer t_r (major)= 25.1 min. Isomers ratio as determined by HPLC: *syn:anti* 99:1; 80% *ee* (*syn*).

5.7.6. Characterization data for compounds 44 and 51a

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-4-cyclohexyl-2-hydroxy-4-(4-nitrophenylsulfonamido)butanamide (44a)

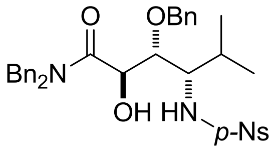


44a

The title compound was prepared from imine **42a** according to general procedure. The catalytic Mannich reaction was performed at 0 °C for 40 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **44a**. Yield: 0.056 g (56%). White solid. m.p. 151–156 °C. $[\alpha]_D^{25}$= 17.0 (c= 1, CH_2Cl_2). ^1H RMN (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9, 2H), 7.85 (d, *J* = 9.0, 2H), 7.32 – 7.18 (m, 11H), 6.91 (dd, *J* = 6.5, 2.6, 2H), 6.79 (dd, *J* = 7.7, 1.6, 2H), 5.11 (d, *J* = 14.0, 1H), 4.92 (d, *J* = 9.8, 1H), 4.60 (d, *J* = 17.3, 1H), 4.17 (s, 2H), 3.96 (d, *J* = 17.3, 1H), 3.87 (t, *J* = 8.2, 1H), 3.80 (d, *J* = 14.1, 1H), 3.67 (d, *J* = 9.3, 2H), 3.33 (d, *J* = 8.5, 1H), 1.80 – 1.55 (m, 7H), 1.10 – 0.93 (m, 4H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.8, 149.7, 147.4, 136.9, 136.2, 135.0, 129.7, 129.2, 129.0, 128.7, 128.4, 128.3, 128.2, 128.0, 126.5, 124.1, 80.6, 74.63, 66.8, 60.0, 49.2, 49.0, 40.3, 30.8, 30.6, 26.4, 26.3. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{42}N_3O_7S$ 672.2743, found 672.2737.

Data for Mannich addut **44a**: Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 40.4 min, t_r (minor)= 37.2 min; *anti* isomer t_r (major)= 34.7 min, t_r (minor)= 24.0 min. Isomers ratio as determined by HPLC: *syn:anti* 99:1; 86% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N,N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-5-methyl-4-(4-nitrophenylsulfonamido)hexanamide (44b)

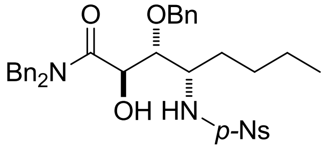


44b

The title compound was prepared from imine **42b** according to general procedure. The catalytic Mannich reaction was performed at 0 °C for 48 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **44b**. Yield: 0.048g (51%). White solid. m.p. 147–150 °C. $[\alpha]_D^{25}$= –11.5 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9, 2H), 7.87 (d, *J* = 8.9, 2H), 7.38 – 7.15 (m, 11H), 6.99 – 6.88 (m, 2H), 6.83 – 6.72 (m, 2H), 5.12 (d, *J* = 14.1, 1H), 5.01 (d, *J* = 10.0, 1H), 4.63 (d, *J* = 17.3, 1H), 4.26 (d, *J* = 10.7, 1H), 4.20 (d, *J* = 10.6, 1H), 4.04 – 3.89 (m, 2H), 3.83 (d, *J* = 14.1, 1H), 3.67 (d, *J* = 9.1, 1H), 3.62 (d, *J* = 9.1, 1H), 3.36 (d, *J* = 9.2, 1H), 1.85 (dq, *J* = 13.6, 6.8, 1H), 0.95 (dd, *J* = 6.7, 3.8, 6H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.8, 149.7, 147.4, 136.9, 136.2, 135.1, 129.7, 129.2, 129.0, 128.6, 128.4, 128.0, 128.0, 126.5, 124.2, 81.0, 74.6, 66.9, 60.8, 49.2, 49.0, 31.1, 20.5, 20.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{34}H_{38}N_3O_7S$ 632.2430, found 632.2438.

Data for Mannich addut **44b**: Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 41.1 min, t_r (minor)= 34.8 min; *anti* isomer t_r (major)= 50.6 min, t_r (minor)= 32.0 min. Isomers ratio as determined by HPLC: *syn:anti* 97:3; 80% *ee* (*syn*).

(2*R*,3*R*,4*S*)-*N*,*N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(4-nitrophenylsulfonamido)octanamide (44c)

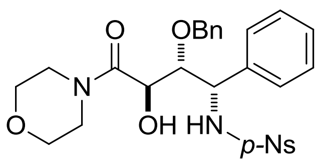


44c

The title compound was prepared from imine **42c** according to general procedure. The catalytic Mannich reaction was performed at 0 °C for 40 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **44c**. Yield: 0.043g (45%). White solid. m.p. 135–138 °C. $[\alpha]_D^{25}$= 9.7 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.8, 2H), 7.85 (d, *J* = 8.8, 2H), 7.39 – 7.17 (m, 11H), 7.05 – 6.92 (m, 2H), 6.85 (d, *J* = 6.3, 2H), 5.21 (d, *J* = 14.2, 1H), 5.12 (d, *J* = 10.1, 1H), 4.75 (d, *J* = 17.4, 1H), 4.21 (s, 2H), 4.09 – 3.97 (m, 2H), 3.81 (d, *J* = 14.2, 1H), 3.78 – 3.69 (m, 1H), 3.52 – 3.37 (m, 3H), 1.55 (dd, *J* = 14.0, 6.8, 2H), 1.30 – 1.15 (m, 4H), 0.81 (t, *J* = 6.9, 3H).^{13}C RMN (75 MHz, $CDCl_3$) δ 173.8, 149.8, 147.1, 136.9, 136.4, 135.3, 129.5, 129.2, 129.0, 128.7, 128.4, 128.3, 128.2, 128.1, 126.5, 124.3, 81.9, 74.8, 67.0, 55.0, 49.3, 49.2, 32.9, 28.4, 22.5, 14.0. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{35}H_{40}N_3O_7S$ 646.2587, found 646.2598.

Data for Mannich addut **44c**: Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 62.7 min, t_r (minor)= 33.3 min; *anti* isomer t_r (major)= 13.8 min. Isomers ratio as determined by HPLC: *syn:anti* 86:14; 56% *ee* (*syn*).

N-((1*S*,2*R*,3*R*)-2-(Benzyloxy)-3-hydroxy-4-morpholino-4-oxo-1-phenylbutyl)-4-nitrobenzenesulfonamide (51a)



51a

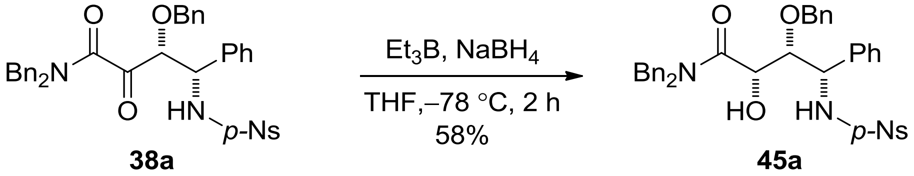
The title compound was prepared from α-keto amide **9** and imine **35a** according to general procedure. The catalytic Mannich reaction was performed in 0.3 mmol scale at –20 °C for 88 hours. After ketone reduction, the crude was purified by flash column chromatography (Hex/EtOAc, 80:20) to afford pure **51a**. Yield: 0.101 g (61%). White solid. m.p. 108–115 °C. $[\alpha]_D^{25}$= 25.6

(c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.9, 2H), 7.79 (d, *J* = 8.9, 2H), 7.41 – 6.94 (m, 10H), 6.12 (d, *J* = 6.9, 1H), 5.06 (d, *J* = 6.6, 1H), 4.42 (t, *J* = 8.5, 1H), 4.26 (d, *J* = 10.9, 1H), 4.20 (d, *J* = 10.9, 1H), 3.73 (dd, *J* = 17.8, 4.6, 2H), 3.65 (dd, *J* = 9.1, 1.8, 1H), 3.62 – 3.50 (m, 2H), 3.43 (ddd, *J* = 10.2, 6.9, 3.9, 2H), 3.35 – 3.21 (m, 2H), 3.18 – 3.03 (m, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 171.4, 149.8, 146.5, 137.0, 136.5, 128.8, 128.7, 128.4, 128.3, 128.1, 127.0, 124.0, 85.9, 75.0, 66.6, 66.3, 57.6, 46.2, 43.2. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{27}H_{30}N_3O_8S$ 556.1754, found 556.1761.

Data for Mannich addut **51a**: Chiral HPLC (Chiralpak IC column; hexane:EtOH 90:10; 1.00 mL/min, 210 nm). *syn* isomer t_r (major)= 28.7 min, t_r (minor)= 26.5 min; *anti* isomer t_r (major)= 37.5 min, t_r (minor)= 31.5 min. Isomers ratio as determined by HPLC: *syn:anti* 95:5; 80% *ee* (*syn*).

5.7.7. Elaboration of adducts

5.7.7.1. *Syn-selective reduction of adduct* ***38a***[285]



(2*S*,3*R*,4*S*)-*N*,*N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(4-nitrophenylsulfonamido)-4-phenylbutanamide (45a)

To a solution of the crude Mannich-adduct **38a** (1 equiv., 0.15 mmol, 0.072 g) and triethylborane (1M THF, 1.1 equiv., 0.16 mmol, 0.16 mL) in THF (1.5 mL) was bubbled a small amount of air and the reaction mixture was stirred for 2 hours at room temperature. The solution was then cooled to –78 °C, $NaBH_4$ (2.2 equiv., 0.33 mmol, 0.012 g) was added and the reaction stirred for 2 hours.

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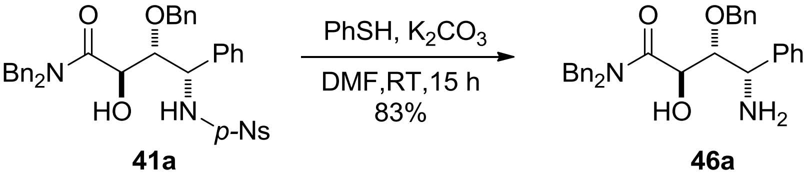
[285] See ref. 282, page 257.

After quenching with phosphate buffer pH=7 (0.5 mL), EtOH (1.0 mL) and H_2O_2 (30%, 0.8 mL) the mixture was allowed to rite to room temperature, diluted with CH_2Cl_2 (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This procedure was repeated twice to completely decompose borane derivatives. The crude product was obtained as a *anti:syn* mixture 88:12 from which the *syn* **45a** was isolated as pure diastereoisomer after flash column chromatography on silica gel (Hex/EtOAc, 80:20). Yield: 0.058 g (58%). White foam. $[\alpha]_D^{25}$= 44.1 (c= 1, CH_2Cl_2). ^1H RMN (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7, 2H), 7.60 (d, *J* = 8.9, 2H), 7.46 – 6.88 (m, 20H), 5.79 (d, *J* = 5.9, 1H), 4.77 (d, *J* = 14.6, *1*H), 4.71 (t, *J* = 5.7, 1H), 4.51 (d, *J* = 10.8, 1H), 4.36 (d, *J* = 14.6, 1H), 4.28 (dd, *J* = 7.6, 3.9, 3H), 4.18 (d, *J* = 10.8, 1H), 3.84 (dd, *J* = 5.2, 4.1, 1H), 3.48 (d, *J* = 7.4, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 171.5, 149.5, 146.1, 137.0, 136.7, 136.2, 135.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 127.4, 126.7, 123.6, 82.5, 75.0, 68.1, 58.8, 49.4, 48.7. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{36}N_3O_7S$ 666.2274, found 666.2272.

*5.7.7.2. Cleavage of p-Ns protecting group in **41a***[286]



(2*R*,3*R*,4*S*)-4-amino-*N*,*N*-dibenzyl-3-(benzyloxy)-2-hydroxy-4-phenylbutanamide (46a)

To a solution of **41a** (1 equiv., 0.10 mmol, 0.067 g) in DMF (1.5 mL), tiophenol (2 equiv., 0.20 mmol, 0.021 mL) and potassium carbonate (2.5 equiv., 0.25 mmol, 0.035 g) were added and the solution was stirred at room temperature for 15 hours. The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was washed with NaOH 1M (5 mL) and brine (5 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) affording pure **46a** as a white foam. Yield: 0.040 g (83%). $[\alpha]_D^{25}$= 19.7 (c= 1, CH_2Cl_2). ^1H RMN (300 MHz, $CDCl_3$) δ 7.40 – 7.09 (m, 18H), 6.79 (dd, *J* = 7.6, 1.7, 2H), 5.02 (d, *J* = 14.5, 1H), 4.81 – 4.70 (m, 2H), 4.53 (d, *J* = 1.3, 1H), 4.19 (d, *J* = 17.1, 1H), 4.14 (d, *J* = 9.4, 1H), 4.10 (d, *J* = 12.9, 1H), 3.87 (d, *J* = 10.9, 1H), 3.79 (dd, *J* = 7.1, 1.7, 1H), 2.63 (brs, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 174.1, 143.8, 137.6, 136.9, 136.2, 129.1, 129.0, 128.9, 128.6, 128.4, 128.0, 127.9, 127.8, 127.1, 126.7, 84.4, 74.1, 69.1, 55.6, 49.7, 48.7. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{31}H_{33}N_2O_3$ 481.2491, found 481.2490.

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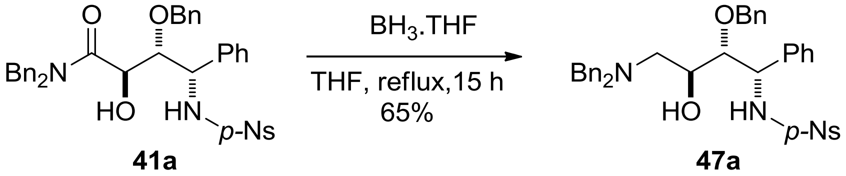
[286] Adapted from: N. Kato, T. Shirai, Y. Yamamoto, *Chem. Eur. J.* **2016**, *22*, 7739–7742.

*5.7.7.3. Reduction of the amide group in adduct **41a***[287]



_N_-((1_S_,2_R_,3_S_)-2-(Benzyloxy)-4-(dibenzylamino)-3-hydroxy-1-phenylbutyl)-4-nitrobenzenesulfonamide (47a)

To a solution of **41a** (1 equiv., 0.10 mmol, 0.067 g) in THF (1 mL) borane.THF complex (5 equiv., 1M THF, 0.50 mmol, 0.50 mL) was added dropwise. Once ceased bubbling, the solution was heated to reflux and stirred for 15 hours. Once corroborated starting material disappearance, the mixture was cooled cooled to –60 °C and quenched with phosphate buffer pH=7 (0.5 mL), EtOH (1.0 mL) and H_2O_2 (30%, 0.8 mL) and the mixture was allowed to rise to room temperature. The mixture was then diluted with CH_2Cl_2 (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on

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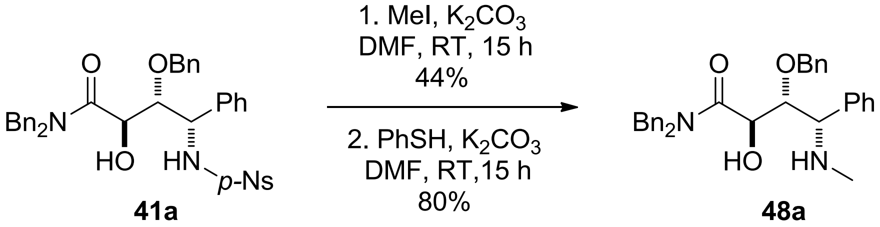
[287] Adapted from: B. Ramalingam, M. Neuburger, *Synthesis* **2007**, 572–582.

silica gel (hexane/EtOAc, 80:20) affording pure **47a** as a white foam. Yield: 0.042 g (64%). $[\alpha]_D^{25}$= – 25.5 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8, 2H), 7.70 (d, *J* = 8.8, 2H), 7.36 – 7.03 (m, 20H), 6.25 (s, 1H), 4.86 (s, 1H), 4.32 (d, *J* = 11.2, 1H), 4.26 (d, *J* = 11.2, 1H), 3.72 (d, *J* = 13.4, 2H), 3.50 – 3.40 (m, 1H), 3.36 (dd, *J* = 7.8, 3.1, 1H), 3.28 (d, *J* = 13.4, 2H), 2.60 (dd, *J* = 12.5, 3.1, 1H), 2.39 (dd, *J* = 12.5, 10.3, 1H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 149.6, 147.0, 138.2, 137.4, 137.1, 129.2, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 123.8, 83.2, 73.8, 66.4, 58.5, 57.8, 56.3. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{37}H_{38}N_3O_6$ S 652.2481, found 652.2487.

*5.7.7.4. Methylation of the amino group and subsequent cleavage of p-Ns protecting group in adduct **41a***



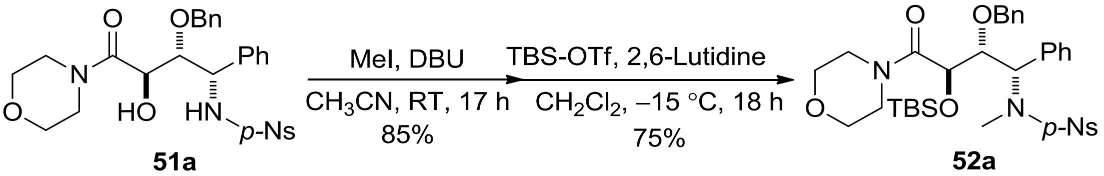
(2*R*,3*R*,4*S*)-*N*,*N*-Dibenzyl-3-(benzyloxy)-2-hydroxy-4-(methylamino)-4-phenylbutanamide (48a)

1st step: A solution of **41a** (1 equiv., 0.10 mmol, 0.067 g), iodomethane (3.6 equiv., 0.36 mmol, 0.022 mL) and potassium carbonate (3 equiv., 0.30 mmol, 0.041 g) in DMF (1 mL) was stirred at room temperature for 15 hours. The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was washed with brine (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 95:5) affording pure methylated product as a white foam. Yield: 0.030 g (44%). ^{1}H RMN (300 MHz, $CDCl_3$) 8.03 (d, *J* = 8.9, 2H), 7.83 (d, *J* = 8.9, 2H), 7.33 – 7.10 (m, 16H), 7.07 – 6.93 (m, 2H), 6.62 – 6.53 (m, 2H), 5.71 (d, *J* = 3.2, 1H), 5.05 (d, *J* = 14.2, 1H), 4.75 (d, *J*

= 17.4, 1H), 4.22 (dt, *J* = 8.7, 5.5, 4H), 4.08 (d, *J* = 14.2, 1H), 3.94 (d, *J* = 10.4, 1H), 3.69 (d, *J* = 8.5, 1H), 3.02 (s, 3H).

2nd step: To a solution of previously methylated adduct (1 equiv., 0.04 mmol, 0.030 g) in DMF (0.4 mL), tiophenol (2 equiv., 0.08 mmol, 0.010 mL) and potassium carbonate (2.5 equiv., 0.10 mmol, 0.014 g) were added and the solution was stirred at room temperature for 15 hours. The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was washed with NaOH 1M (5 mL) and brine (5 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) affording pure **48a** as a white foam. Yield: 0.016 g (80%). $[\alpha]_D^{25}$= 19.8 (c= 1, CH_2Cl_2). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.48 – 7.11 (m, 18H), 7.00 (dd, *J* = 6.4, 3.0, 2H), 4.94 – 4.78 (m, 2H), 4.62 (d, *J* = 16.8, 1H), 4.42 – 4.27 (m, 4H), 4.13 (d, *J* = 11.2, 1H), 3.87 (d, *J* = 4.1, 1H), 3.75 (brs, 2H), 2.36 (s, 3H). ^{13}C RMN (75 MHz, $CDCl_3$) δ 173.6, 139.4, 137.7, 137.0, 136.5, 129.0, 128.8, 128.7, 128.4, 128.0, 127.8, 127.7, 127.2, 82.5, 73.6, 69.8, 64.4, 49.7, 48.4, 33.6. UPLC (DAD-QTOF $[M+H]^+$) calcd. for $C_{32}H_{35}N_2O_3$ 495.2648, found 495.2653.

5.7.7.5. *Protection of amino- and hydroxyl groups in adduct **51a***



1st step: To a solution of adduct **51a** (1 equiv., 0.18 mmol, 0.100 g) in acetonitrile (1.8 mL) were added DBU (2 equiv., 0.36 mmol, 0.054 mL) and MeI (3 equiv., 0.54 mmol, 0.034 mL) and the solution was stirred at room temperature for 17 hours. The reaction mixture was diluted with dichloromethane (5 mL) and the organic phase was washed with HCl 1M (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford methylated adduct as a white foam which was used in next step

without further purification. Yield: 0.088 g (85%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.9, 2H), 7.87 (d, *J* = 8.9, 2H), 7.32 – 7.16 (m, 8H), 7.07 (dd, *J* = 6.6, 2.9, 2H), 5.58 (d, *J* = 4.7, 1H), 4.66 (t, *J* = 6.4, 1H), 4.38 (d, *J* = 10.9, 1H), 4.25 (d, *J* = 11.0, 1H), 4.03 (dd, *J* = 7.1, 4.7, 1H), 3.78 (d, *J* = 6.8, 2H), 3.59 – 3.36 (m, 6H), 3.30 – 3.14 (m, 2H), 3.09 (s, 3H).

2nd step:[288] To a cooled solution of methylated adduct crude (1 equiv., 0.15 mmol, 0.088 g) in dichloromethane (1.5 mL) were added dropwise 2,6-lutidine (2.4 equiv., 0.37 mmol, 0.043 mL) and TBSOTf (2 equiv., 0.30 mmol, 0.071 mL) at –15 °C and the solution was stirred at that temperature for 18 hours. The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was washed with $NaHCO_3$ (5 mL), $CuSO_4$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hex/EtOAc, 80:20) affording pure silylated product **52a** as a white foam. Yield: 0.077 g (75%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.9, 2H), 7.70 (d, *J* = 8.9, 2H), 7.29 – 7.22 (m, 8H), 7.15 (dd, *J* = 6.6, 3.0, 2H), 5.42 (d, *J* = 7.7, 1H), 4.69 (d, *J* = 4.7, 1H), 4.60 (d, *J* = 10.5, 1H), 4.42 (d, *J* = 10.4, 1H), 4.29 (dd, *J* = 7.6, 4.7, 1H), 3.62 – 3.28 (m, 8H), 2.91 (s, 3H), 0.97 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H).

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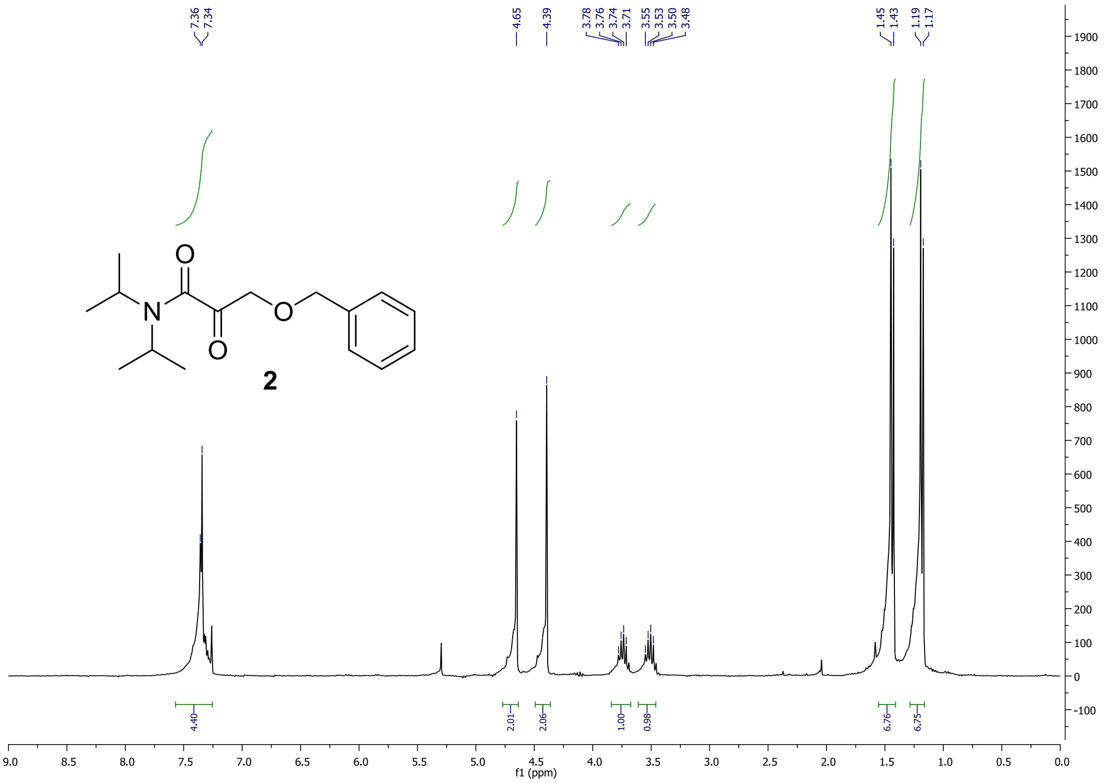
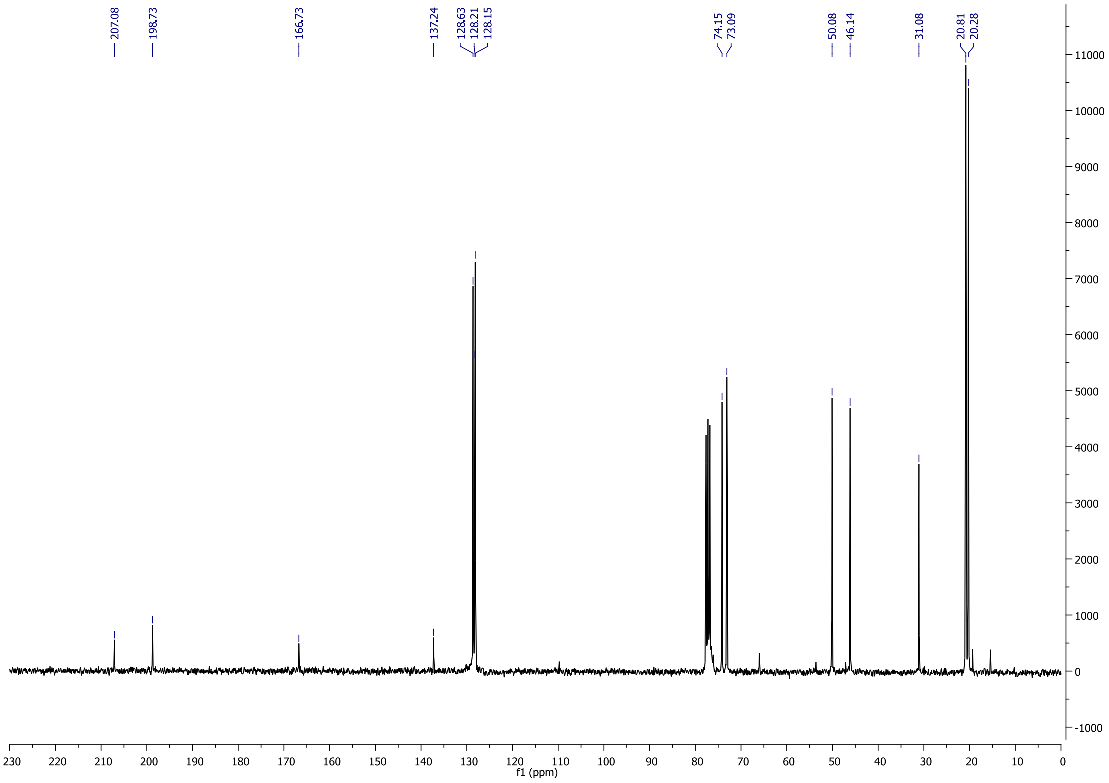
[288] M. A. McGowan, C. P. Stevenson, M. A. Schiffler, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2010**, *49*, 6147–6150.

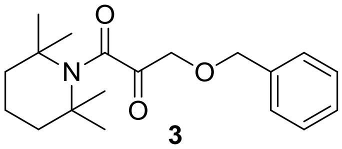
5.8. Representative NMR espectra

5.8.1. β-alkoxy-α-keto amides 2–9



2

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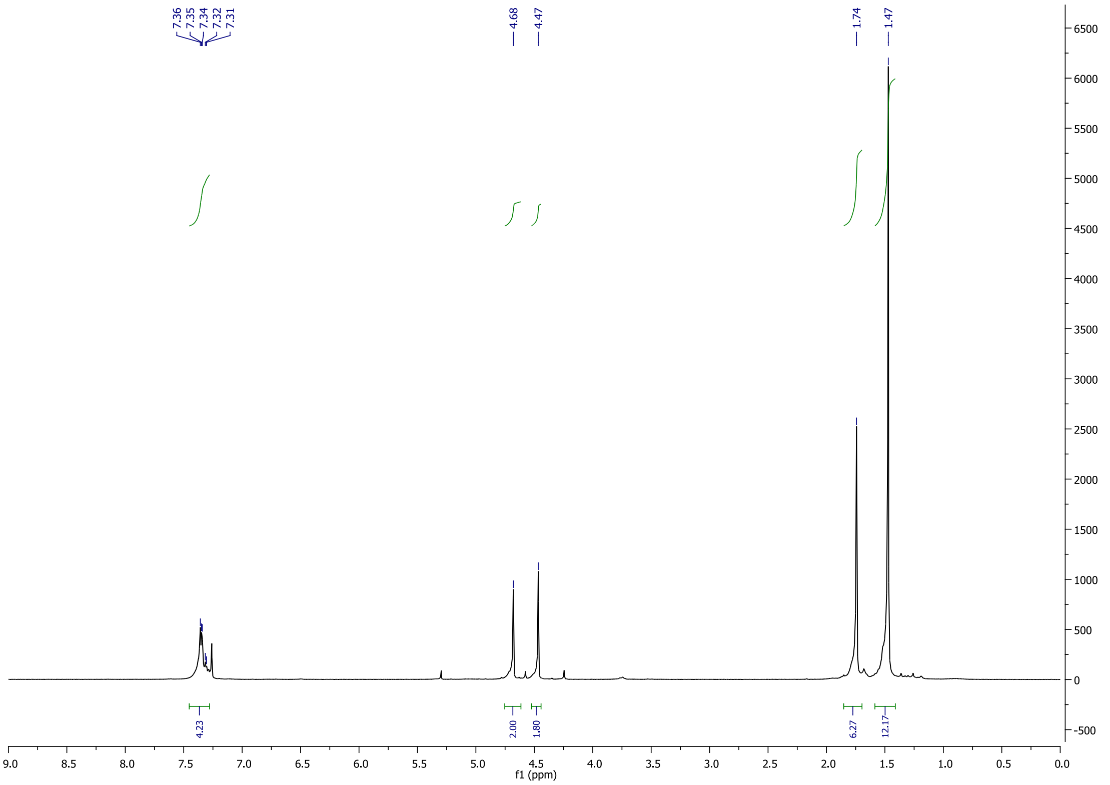
N
O
O

3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1.74
1.47
4.23
2.00
1.80
6.27
12.17
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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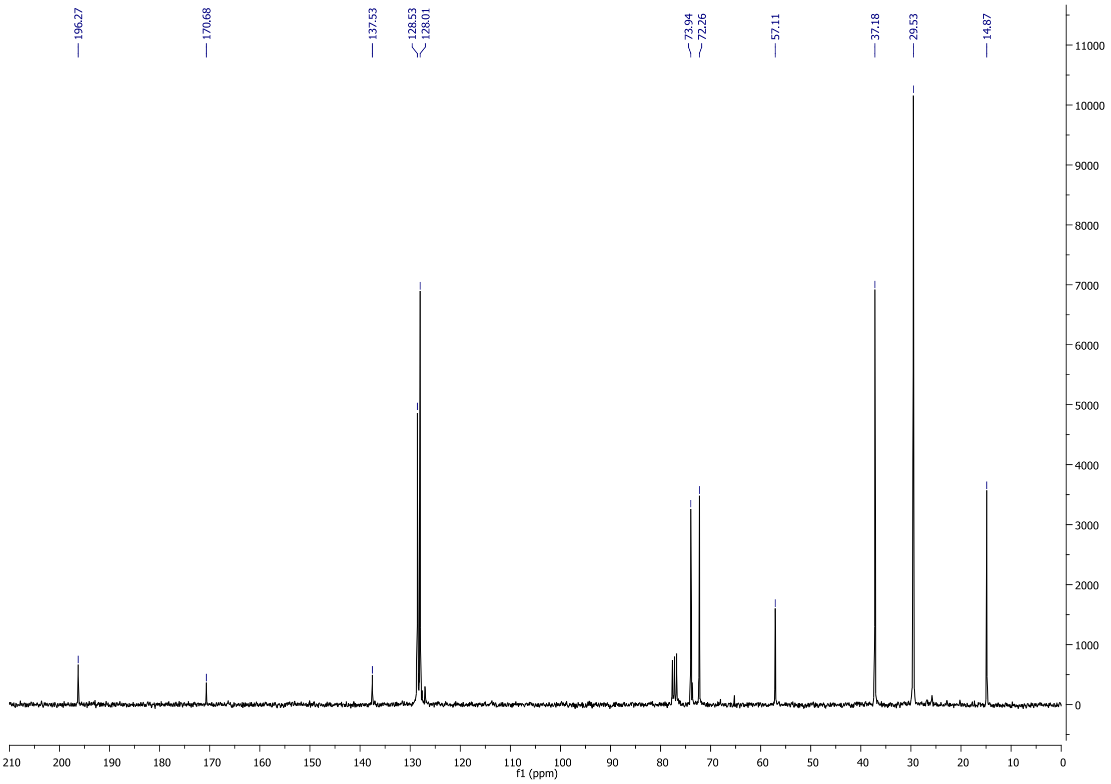
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210
200
190
180
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110
100
90
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50
40
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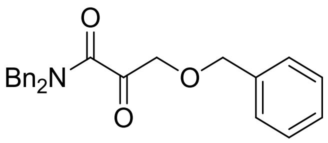
f1 (ppm)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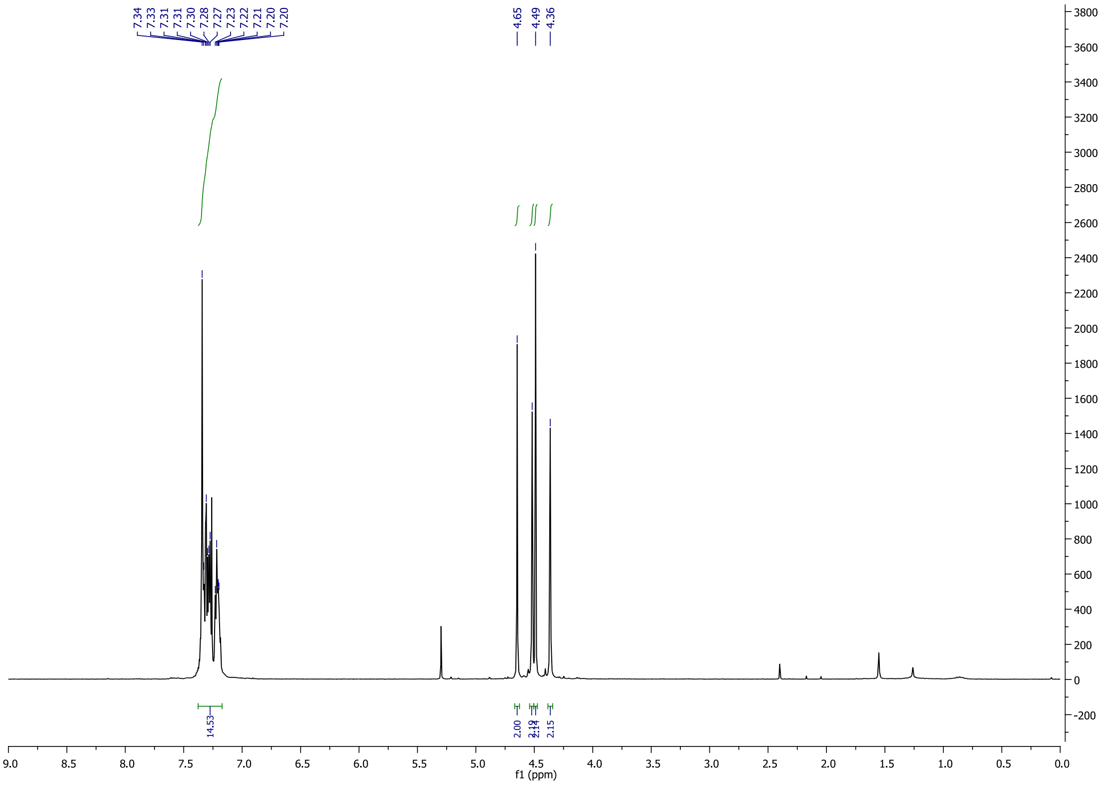
Bn$_2$N
O
O

4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4.49
4.36
14.53
2.00
2.19
2.14
2.15
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3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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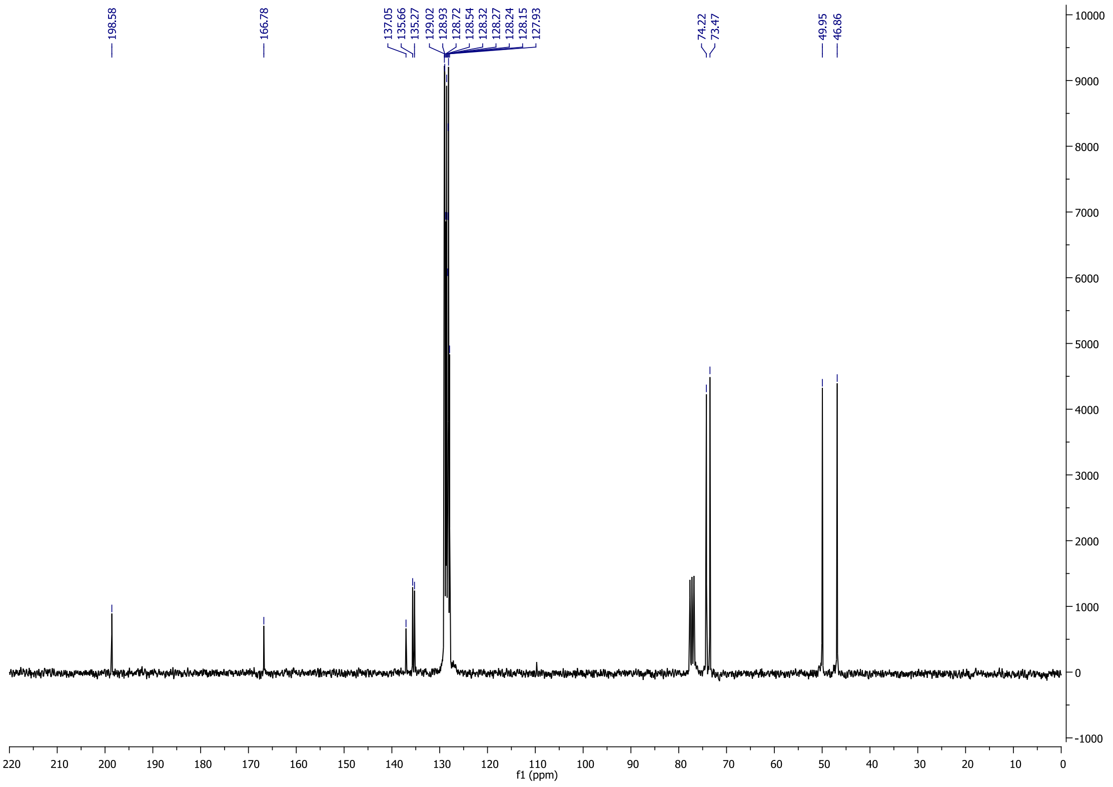
f1 (ppm)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128.15
127.93
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73.47
49.95
46.86
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8000
7000
6000
5000
4000
3000
2000
1000
0
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180
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50
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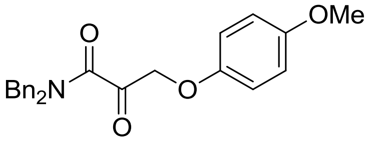
f1 (ppm)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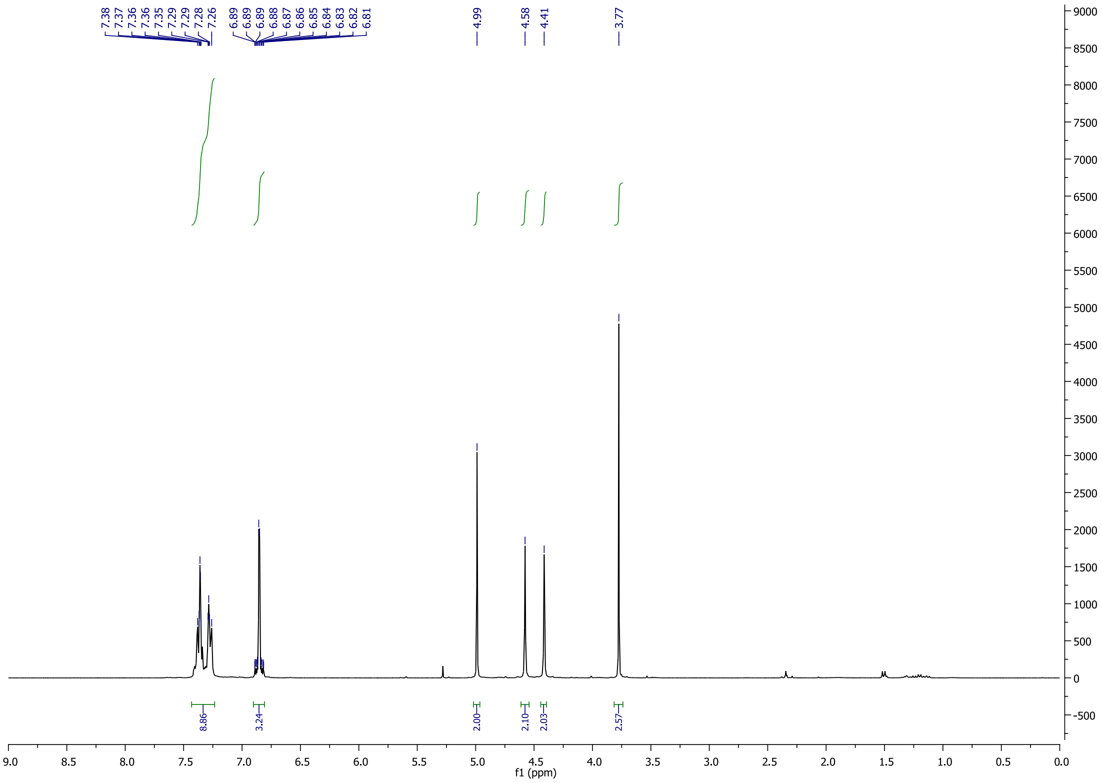
5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6.84
6.83
6.82
6.81
4.99
4.58
4.41
3.77
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3.24
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2.10
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9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
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6.0
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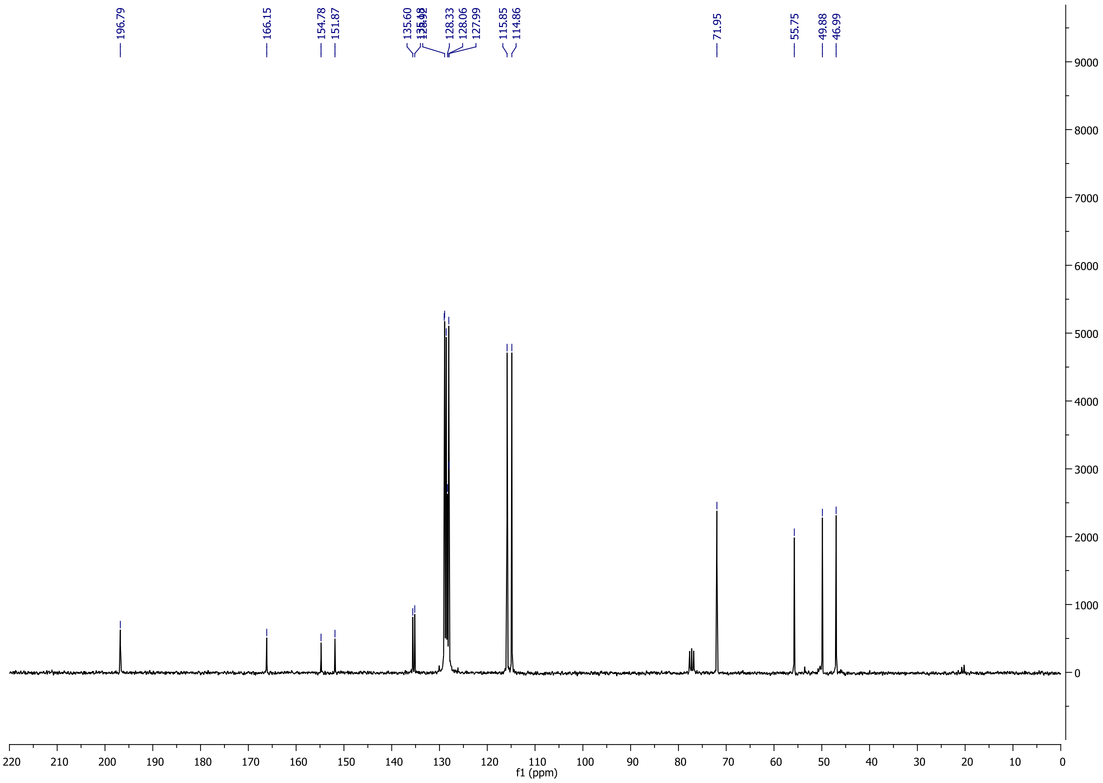
f1 (ppm)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49.88
46.99
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7000
6000
5000
4000
3000
2000
1000
0
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210
200
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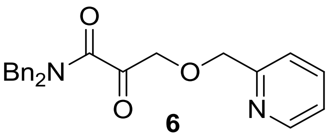
Bn2N
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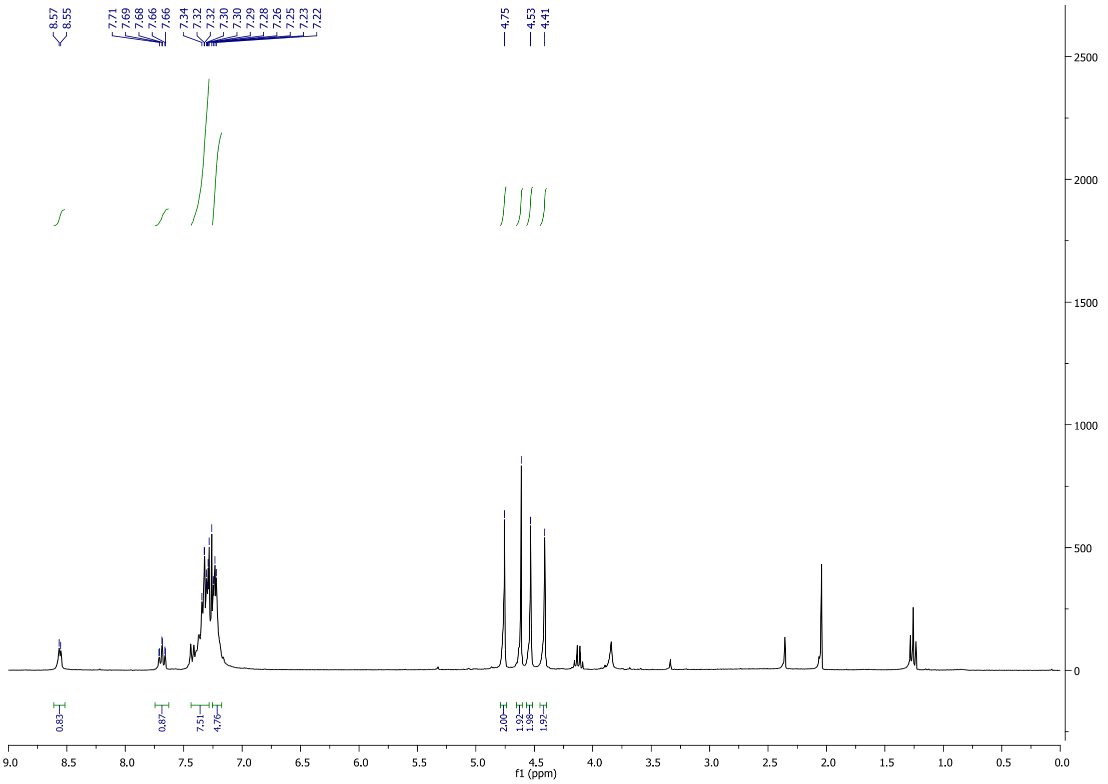
O
O
N

6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7.29
7.28
7.26
7.25
7.23
7.22
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4.76
2.00
1.92
1.98
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2000
1500
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500
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1.0
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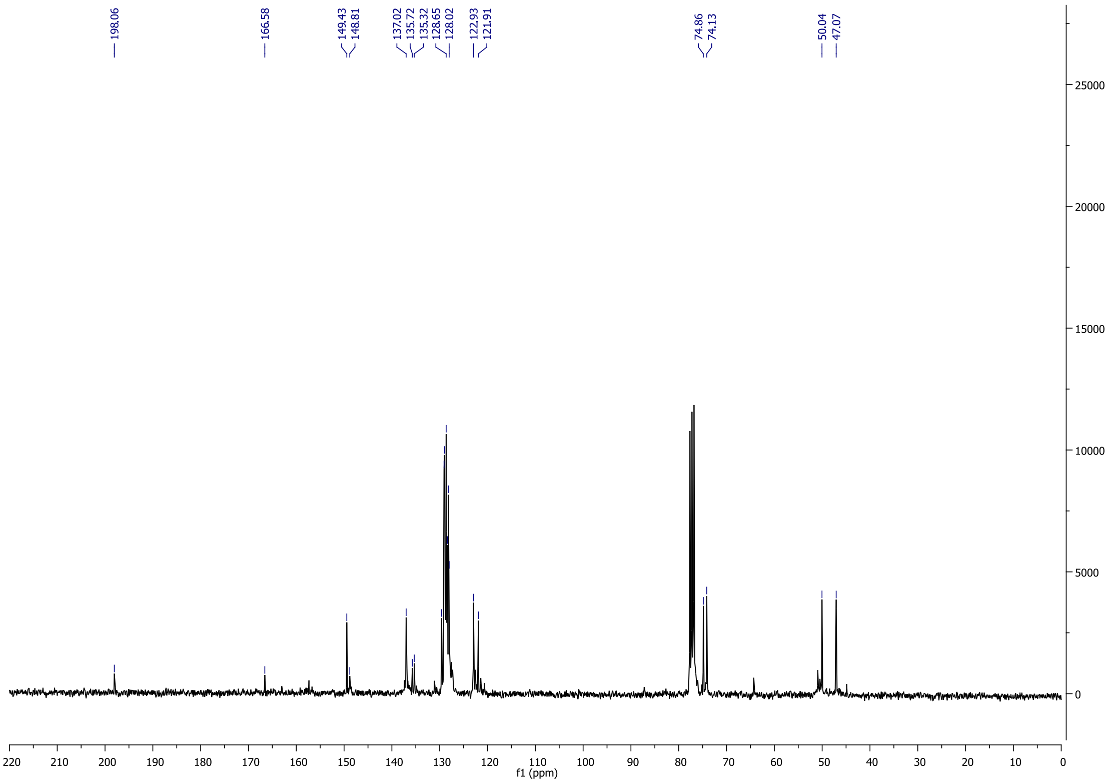
f1 (ppm)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128.02
122.93
121.91
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74.13
50.04
47.07
25000
20000
15000
10000
5000
0
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210
200
190
180
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110
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50
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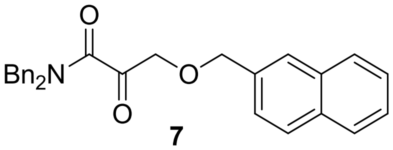
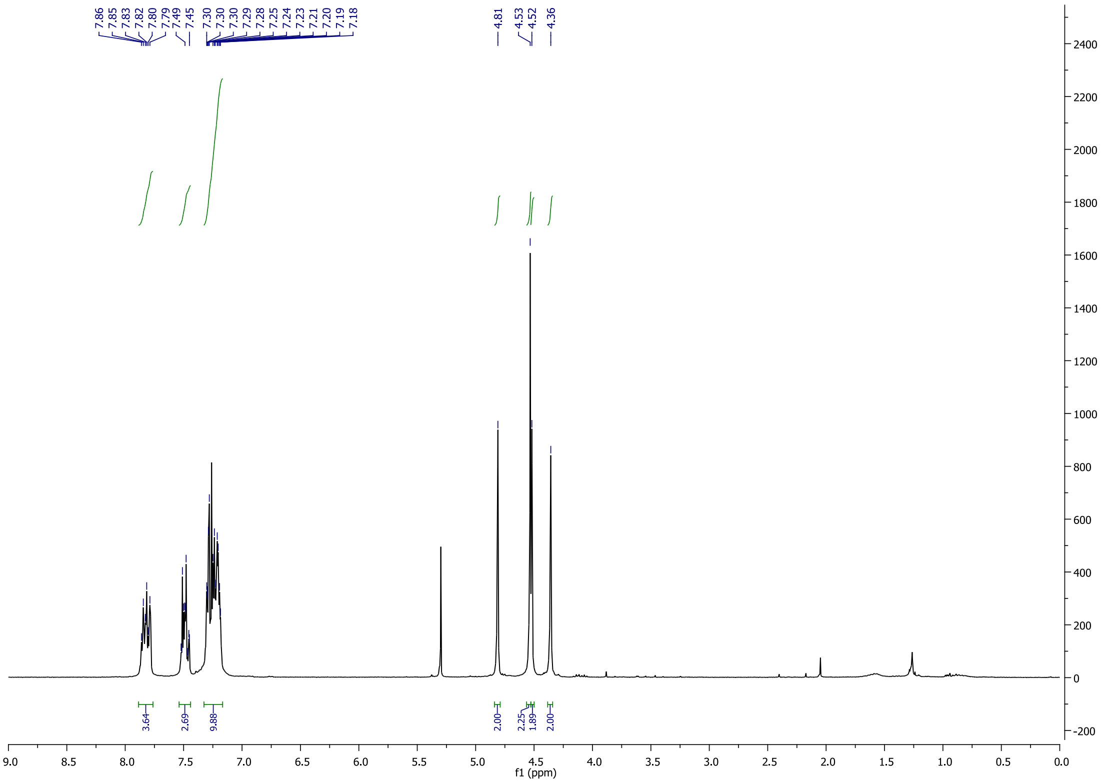
f1 (ppm)


Bn2N
O
O
O

7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7.20
7.19
7.18
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3.64
2.69
9.88
2.00
2.25
1.89
2.00
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2000
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1600
1400
1200
1000
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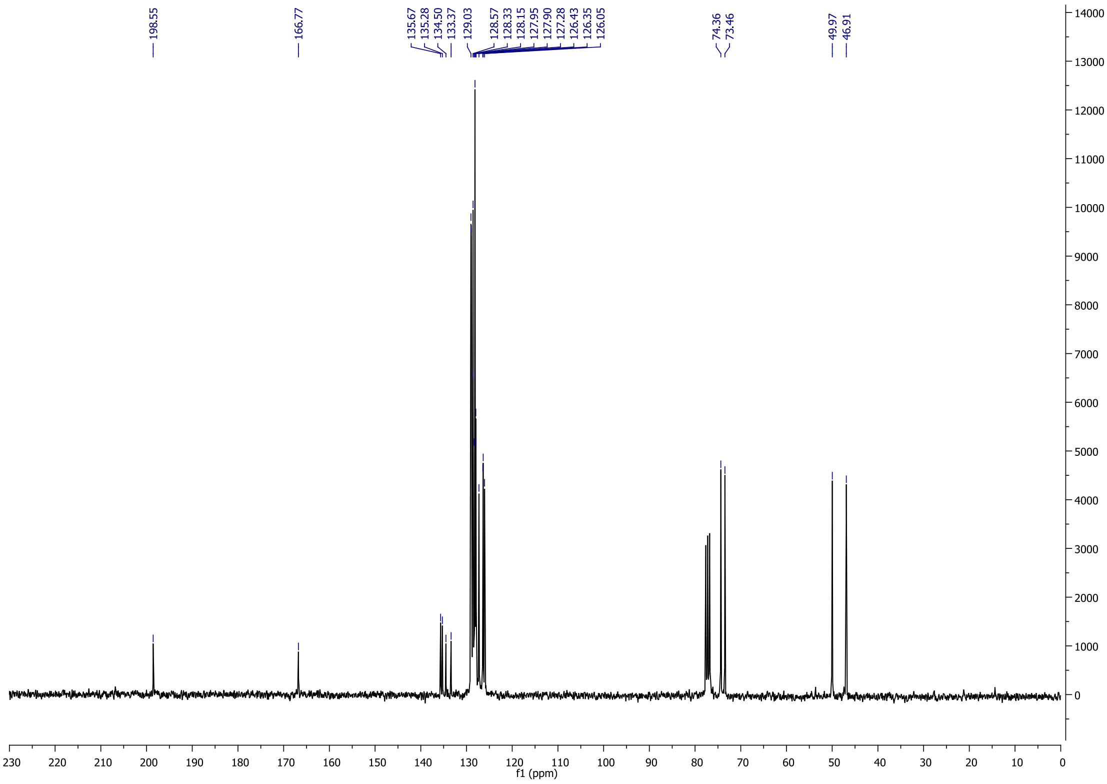
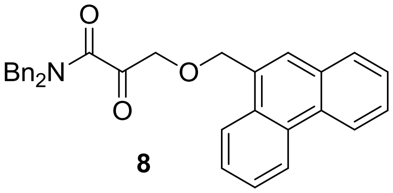
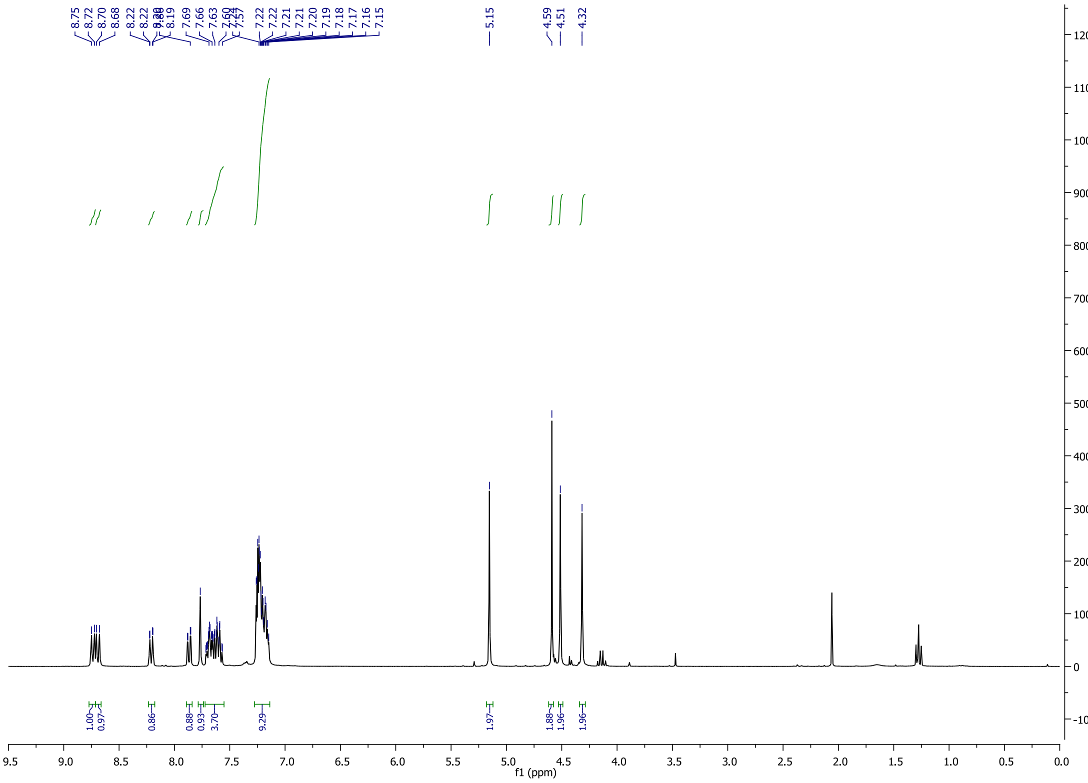
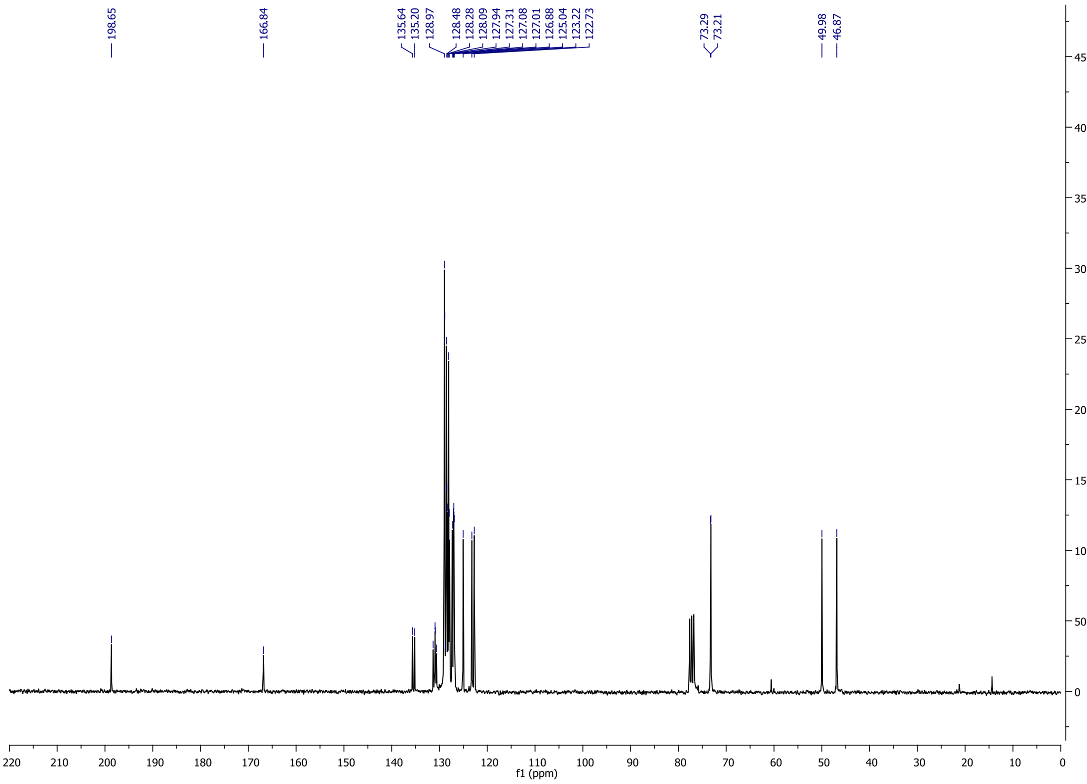
400
200
0
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

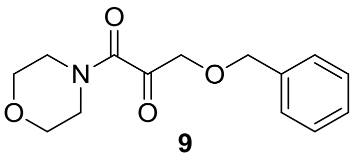

198.55
166.77
135.67
135.28
134.50
133.37
129.03
128.57
128.33
128.15
127.95
127.90
127.28
126.43
126.35
126.05
74.36
73.46
49.97
46.91
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Bn$_2$N
O
O
O

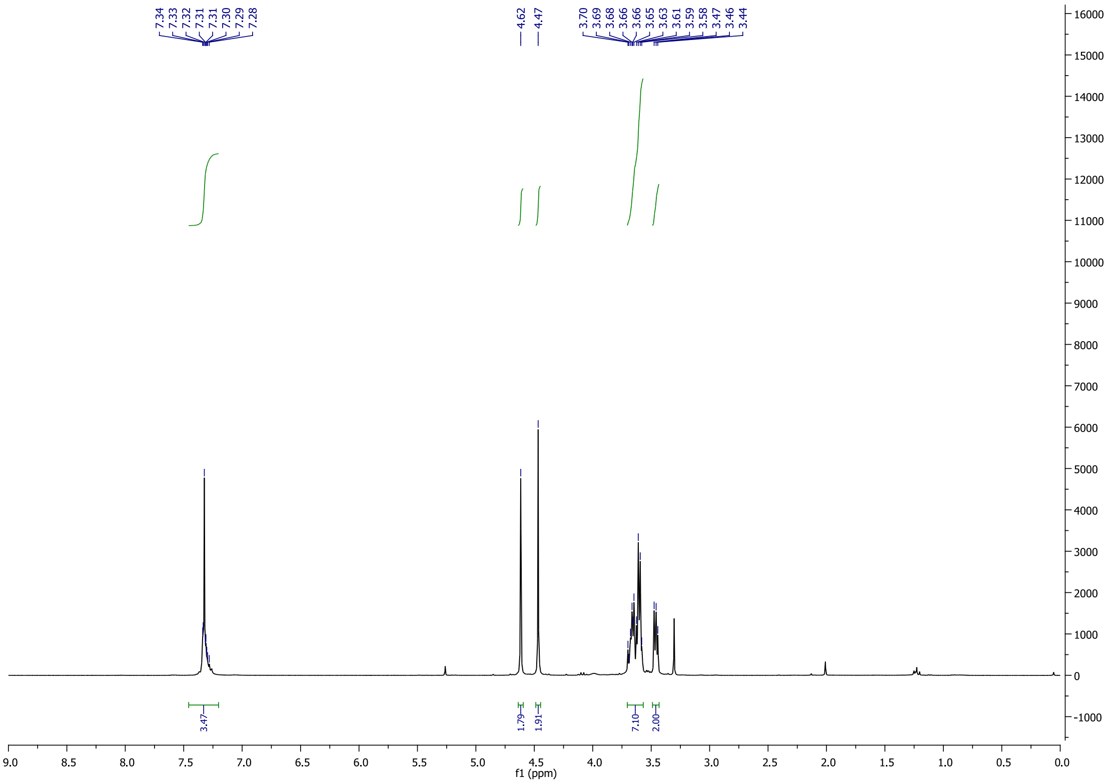
8

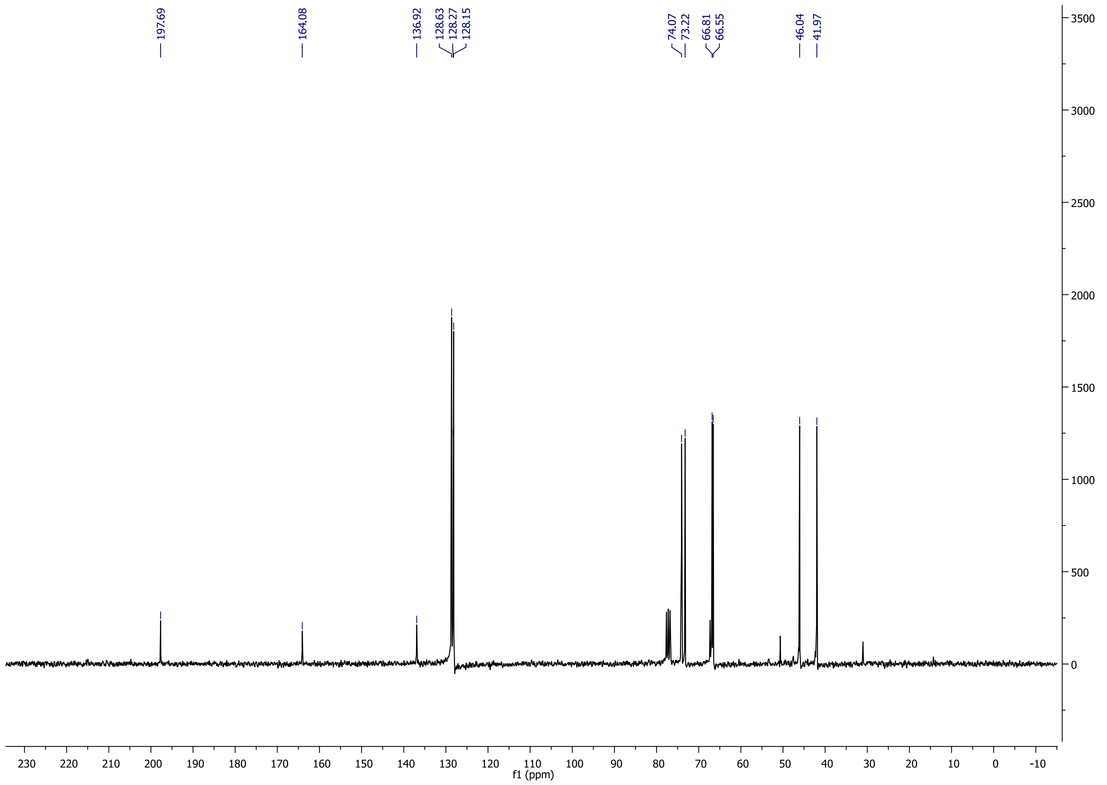

8.75
8.72
8.70
8.68
8.22
8.22
8.19
7.69
7.66
7.63
7.57
7.22
7.22
7.21
7.21
7.20
7.19
7.18
7.17
7.16
7.15
5.15
4.59
4.51
4.32
1.00
0.97
0.86
0.88
0.93
3.70
9.29
1.97
1.88
1.96
1.96
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


198.65
166.84
135.64
135.20
128.97
128.48
128.28
128.09
127.94
127.31
127.08
127.01
126.88
125.04
123.22
122.73
73.29
73.21
49.98
46.87
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

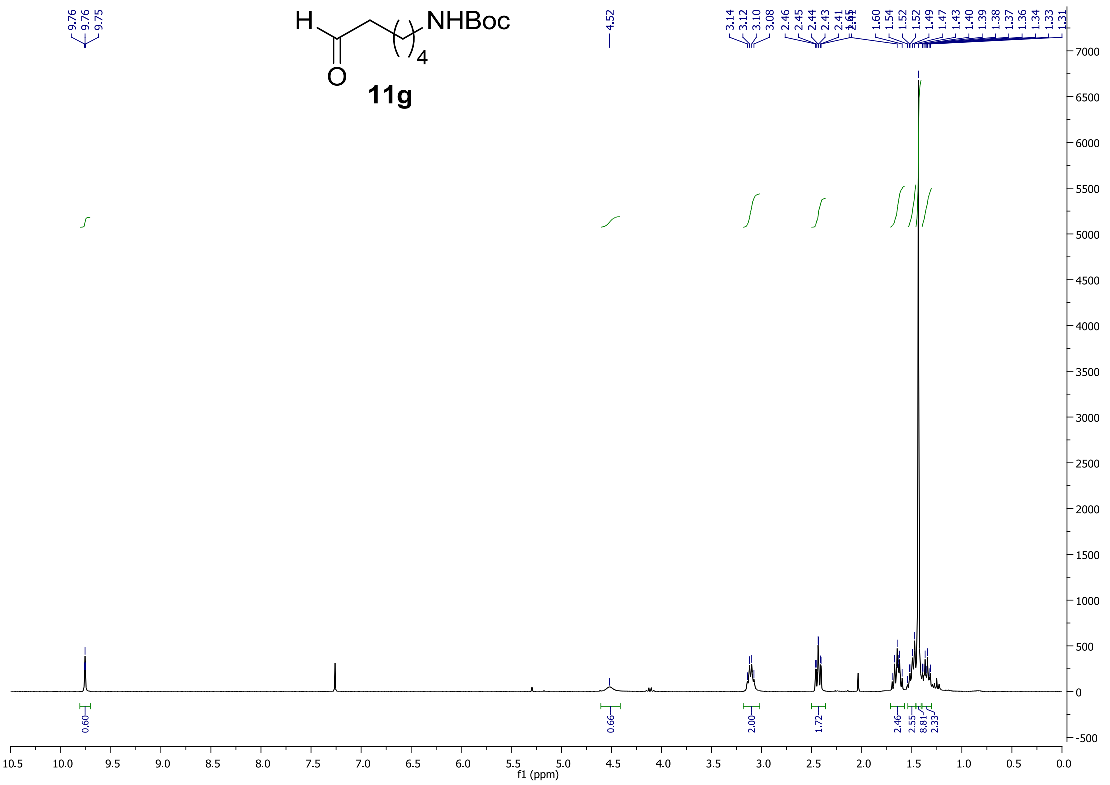

O
N
O
O
O

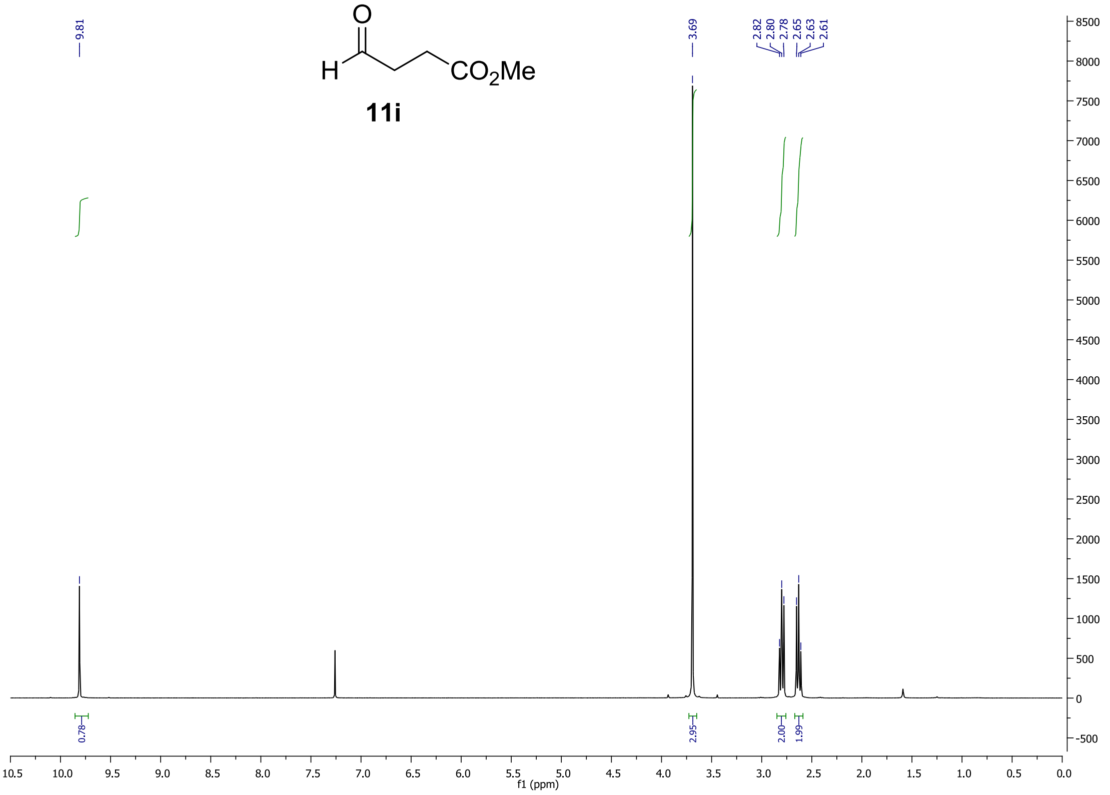
9

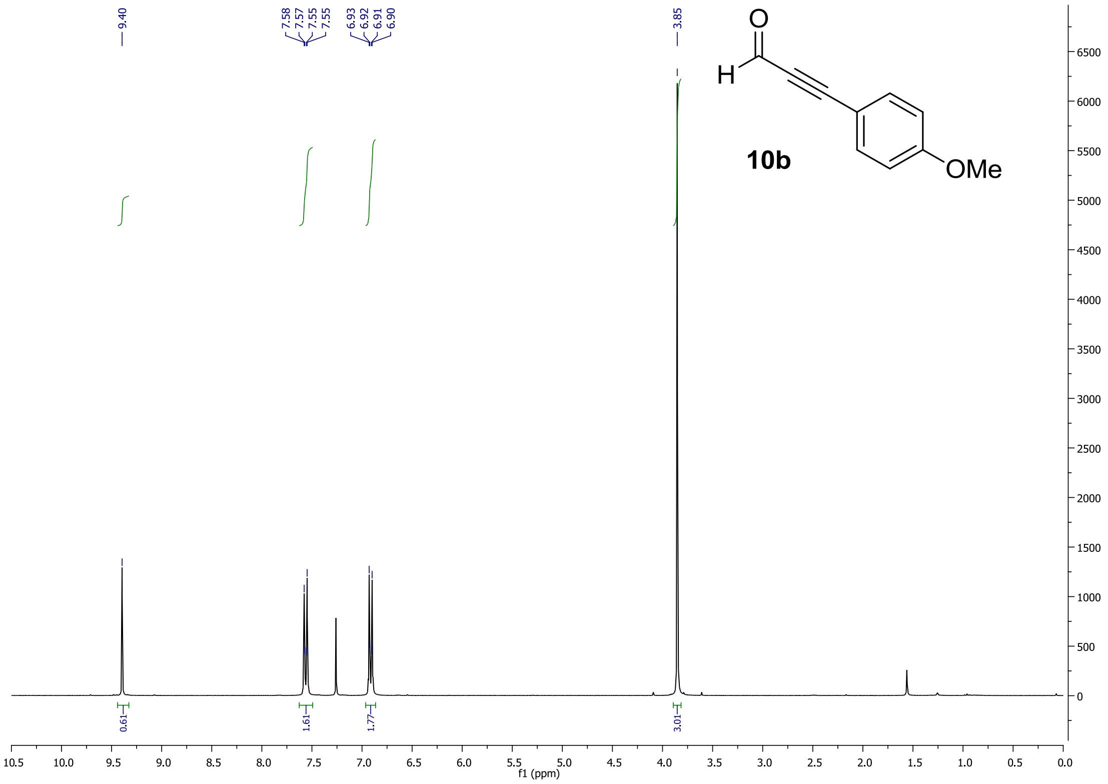

7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.28
4.62
4.47
3.70
3.69
3.68
3.66
3.66
3.65
3.63
3.61
3.59
3.58
3.47
3.46
3.44
3.47
1.79
1.91
7.10
2.00
f1 (ppm)


197.69
164.08
136.92
128.63
128.27
128.15
74.07
73.22
66.81
66.55
46.04
41.97
f1 (ppm)

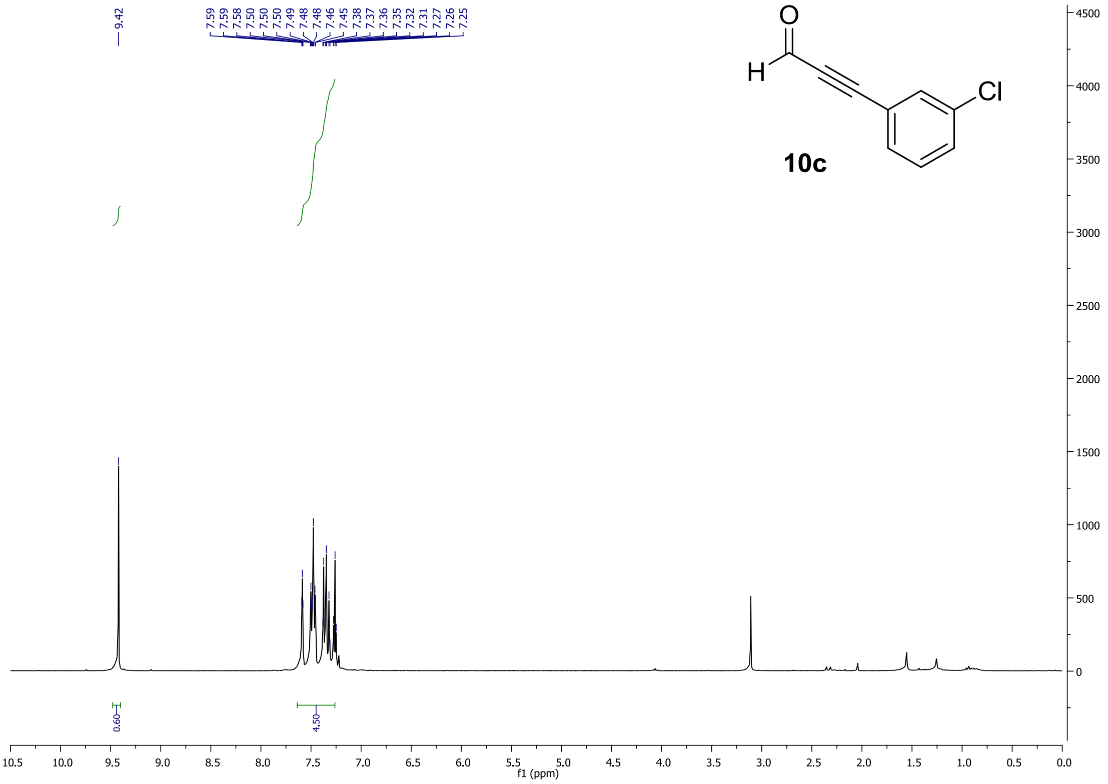
5.8.2. Aldehydes 11g, 11i, 10b and 10c





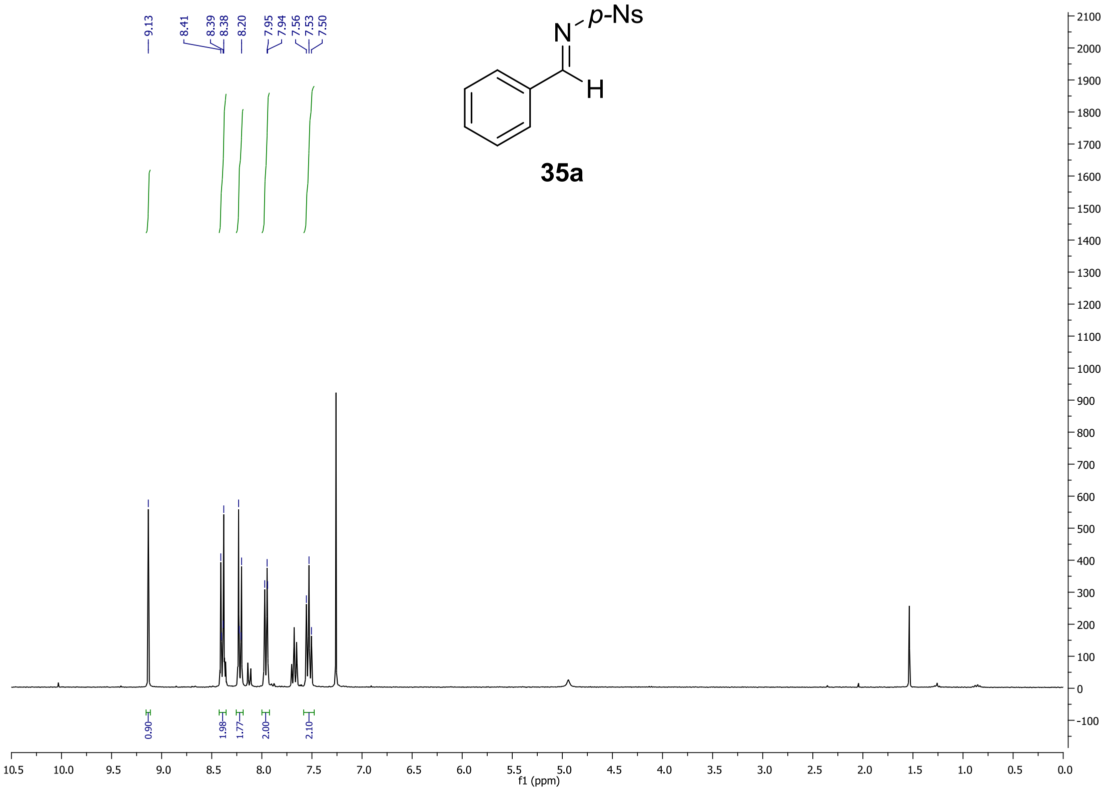

9.40
7.58
7.57
7.55
7.55
6.93
6.92
6.91
6.90
3.85
0.61
1.61
1.77
3.01
O
H
OMe
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0

10b

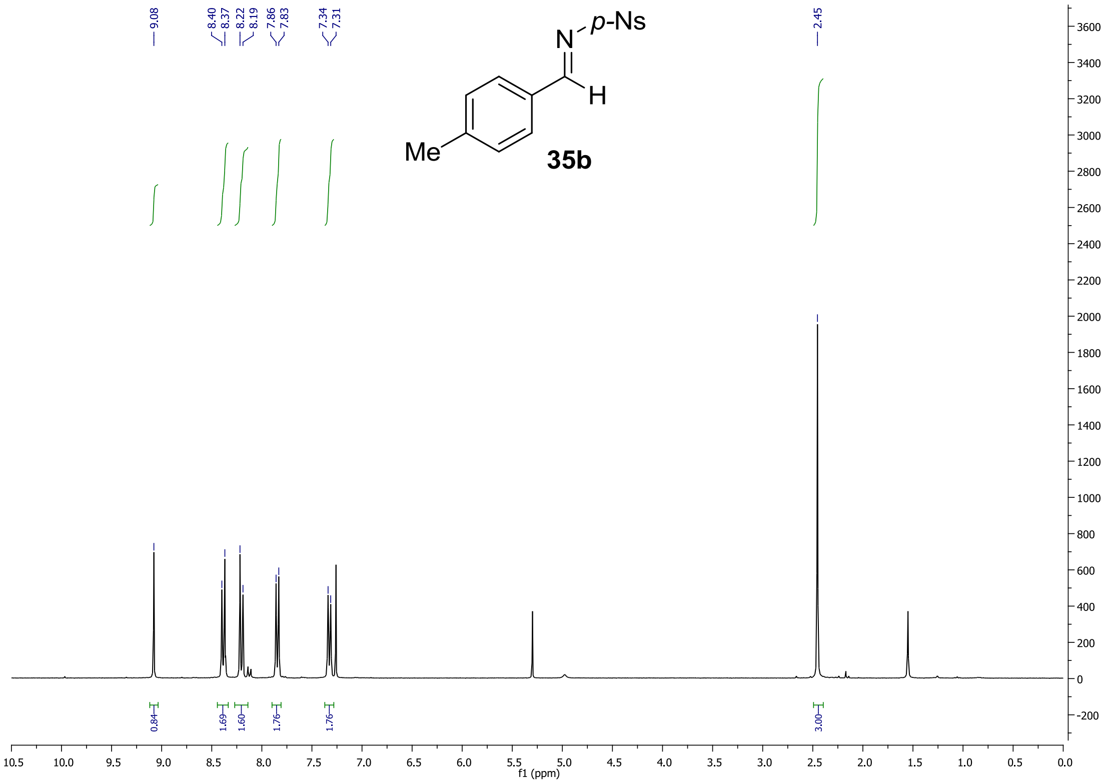

9.42
7.59
7.59
7.58
7.50
7.50
7.50
7.49
7.48
7.48
7.46
7.45
7.38
7.37
7.36
7.35
7.32
7.31
7.27
7.26
7.25
0.60
4.50
O
H
Cl
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
4500 4000 3500 3000 2500 2000 1500 1000 500 0

10c

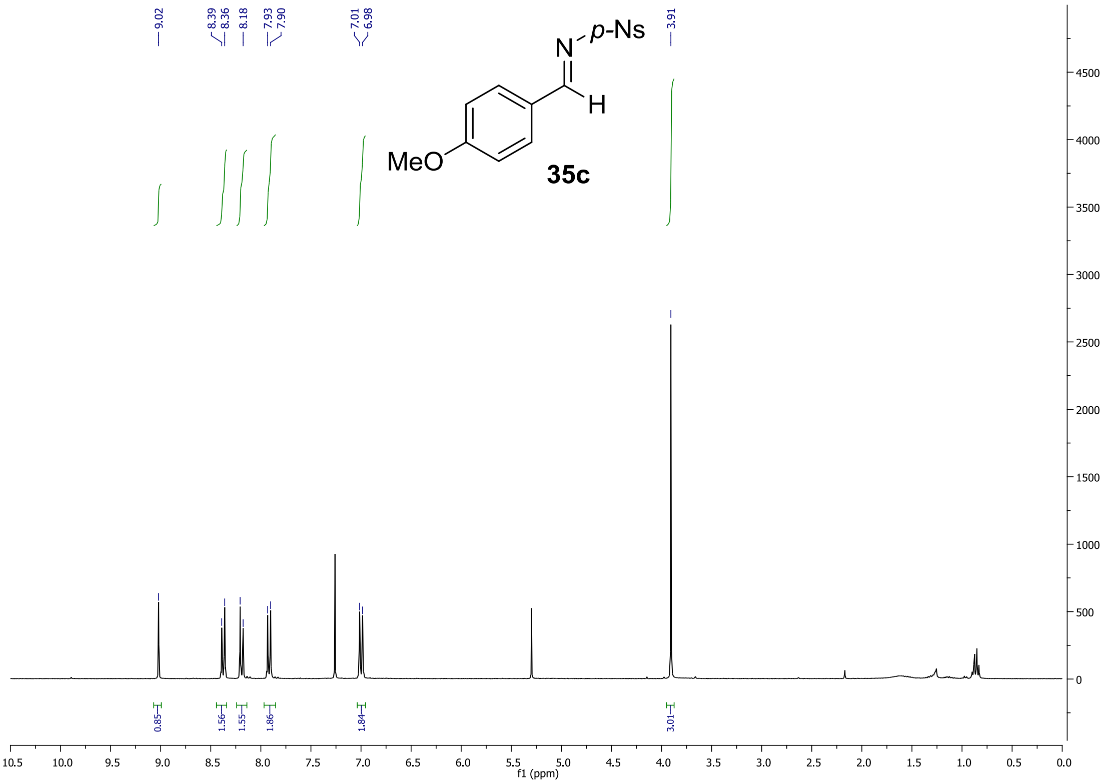
5.8.3. Imines 35 and 42

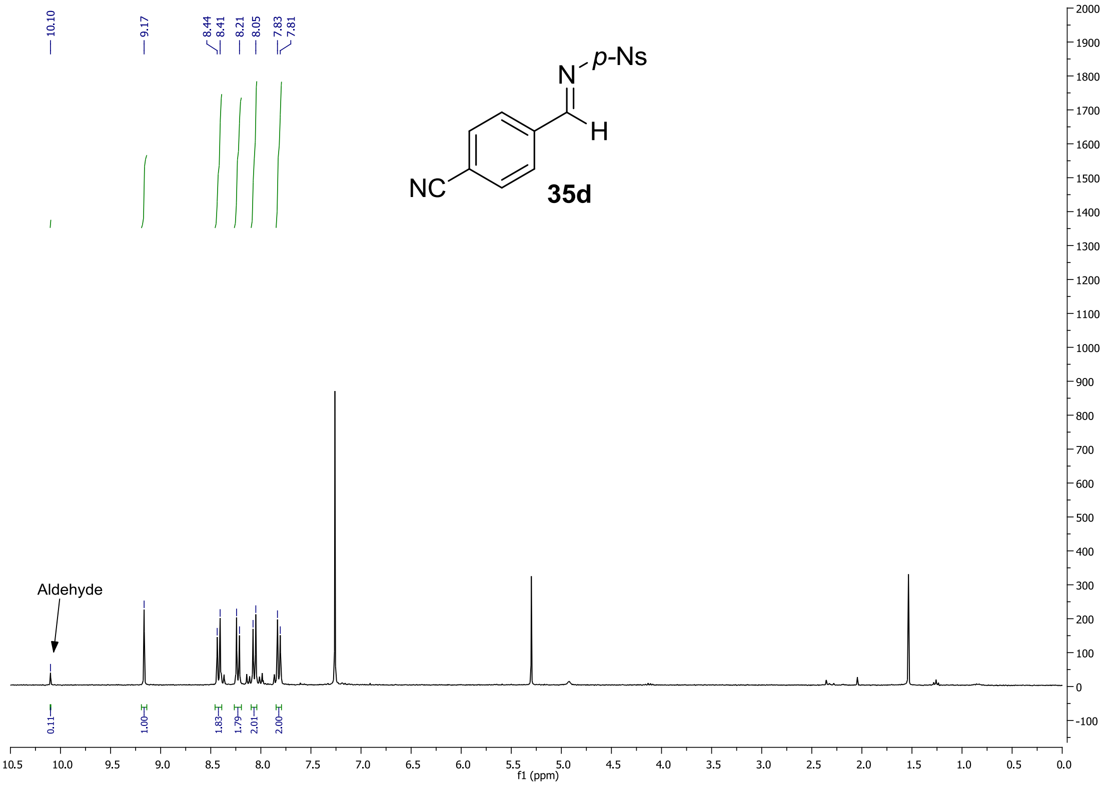


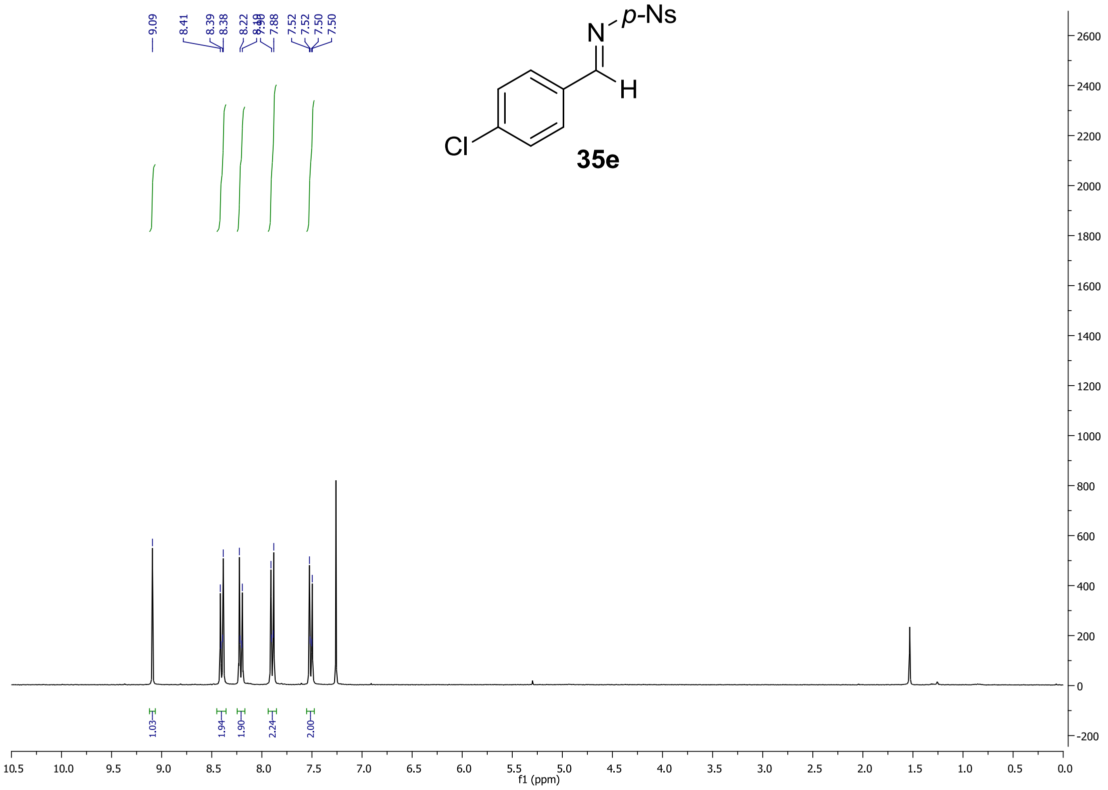
35a

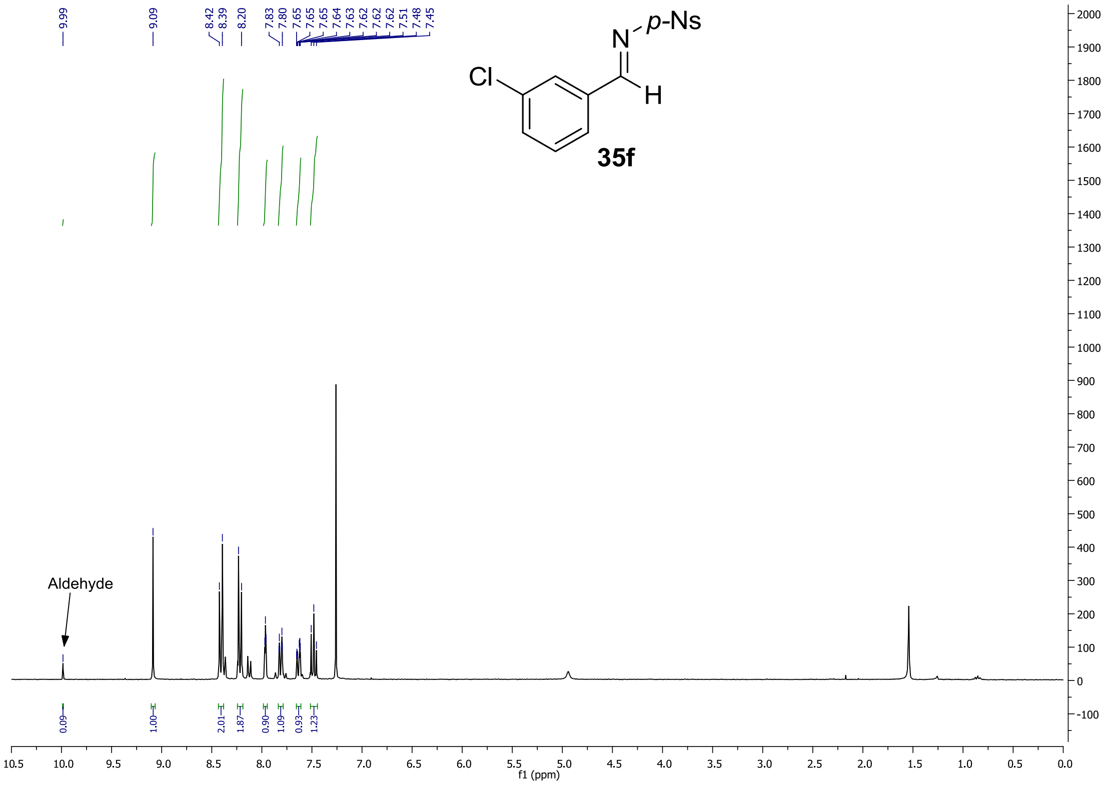


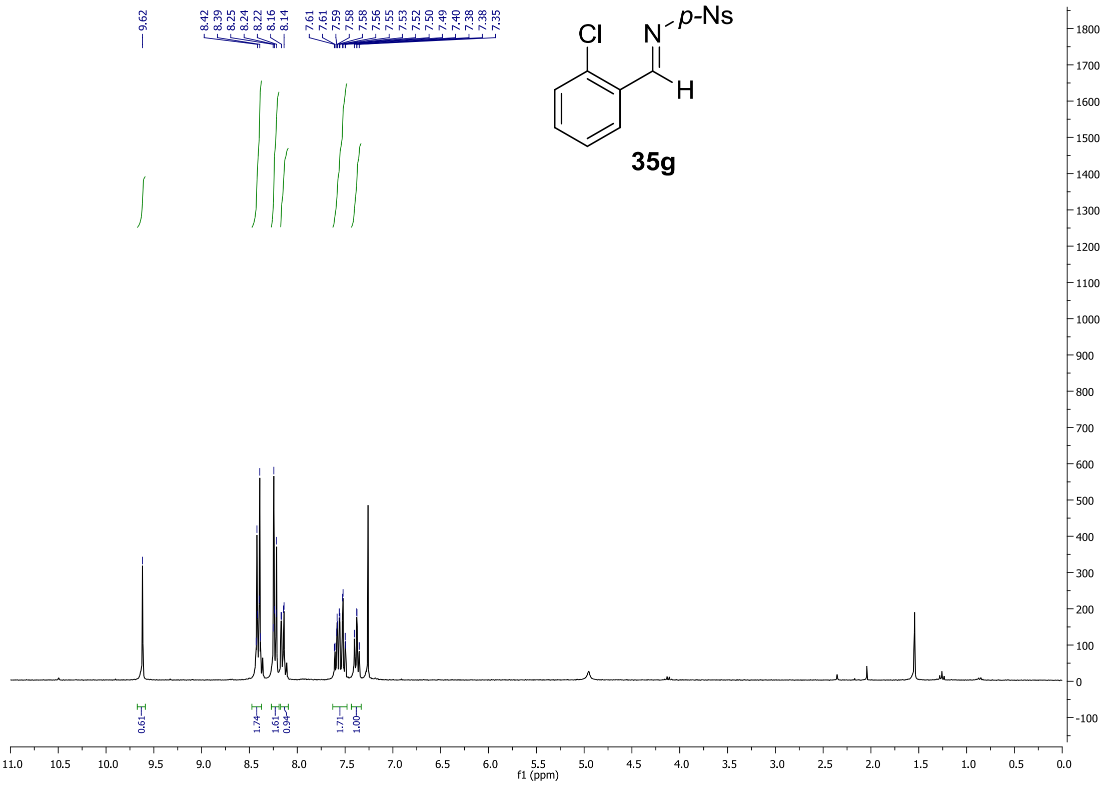
35b

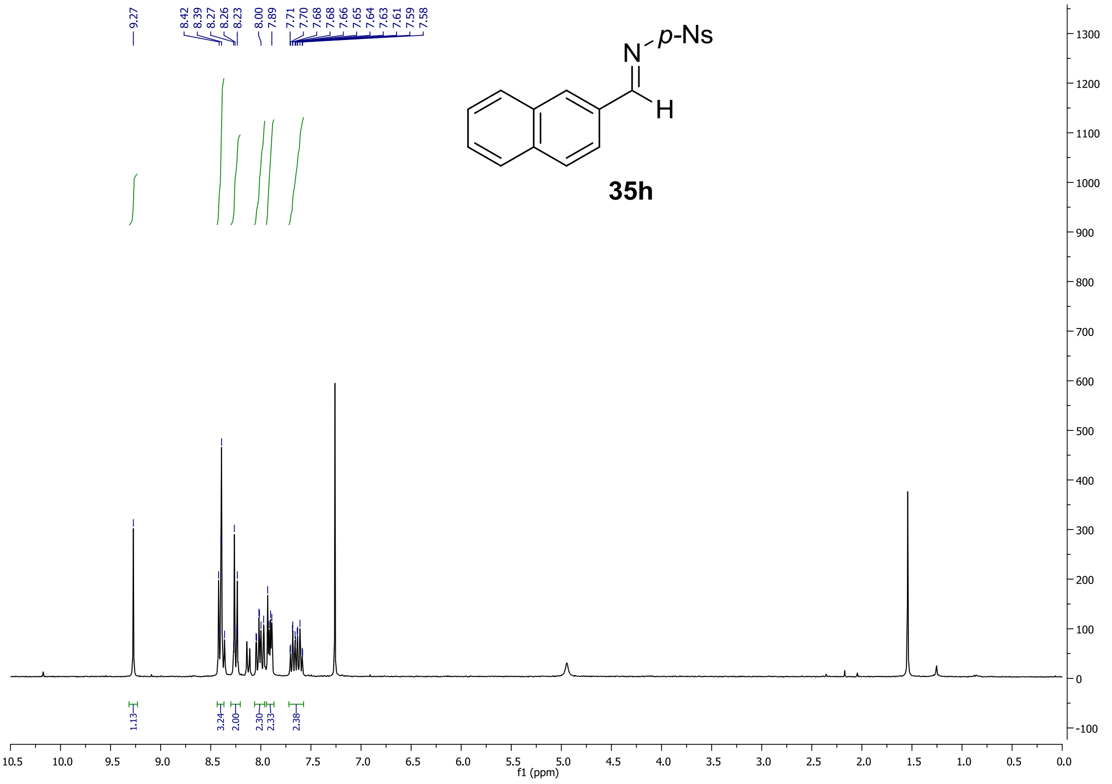

9.02
8.39
8.36
8.18
7.93
7.90
7.01
6.98
3.91
N
p-Ns
H
MeO
35c
0.85
1.56
1.55
1.86
1.84
3.01
f1 (ppm)

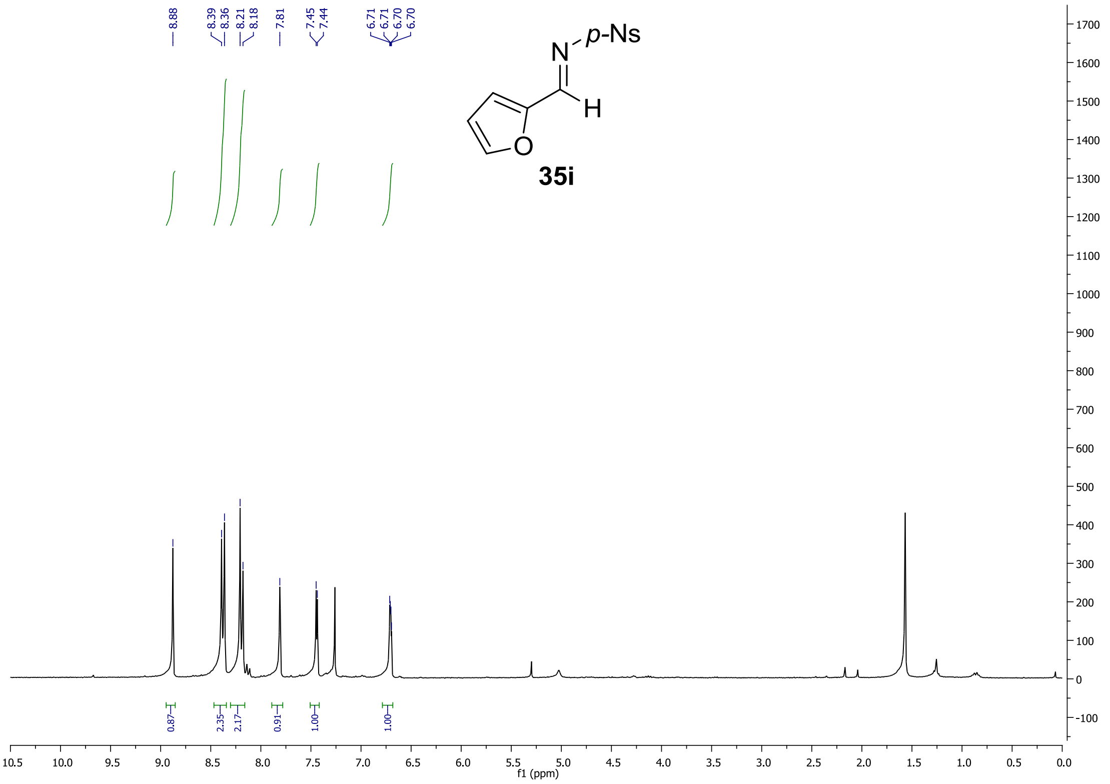

10.10
9.17
8.44
8.41
8.21
8.05
7.83
7.81
N
p-Ns
H
NC
35d
Aldehyde
0.11
1.00
1.83
1.79
2.01
2.00
f1 (ppm)


9.09
8.41
8.39
8.38
8.22
8.19
7.90
7.88
7.52
7.52
7.50
7.50
N
p-Ns
H
Cl
35e
1.03
1.94
1.90
2.24
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200

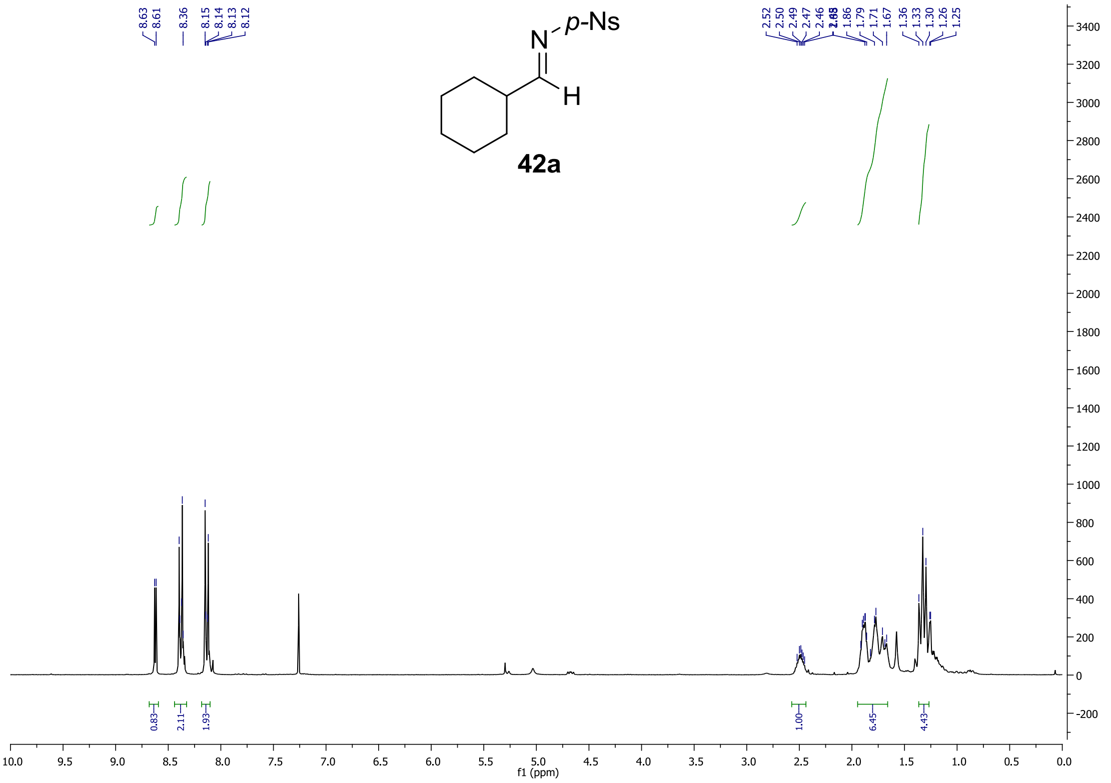

9.99
9.09
8.42
8.39
8.20
7.83
7.80
7.65
7.65
7.65
7.64
7.63
7.62
7.62
7.62
7.51
7.48
7.45
N
p-Ns
Cl
H
35f
Aldehyde
0.09
1.00
2.01
1.87
0.90
1.09
0.93
1.23
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100


9.62
8.42 8.39 8.25 8.24 8.22 8.16 8.14
7.61 7.61 7.59 7.58 7.58 7.56 7.55 7.53 7.52 7.50 7.49 7.40 7.38 7.38 7.35
Cl
N
p-Ns
H
35g
0.61
1.74
1.61
0.94
1.71
1.00
f1 (ppm)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

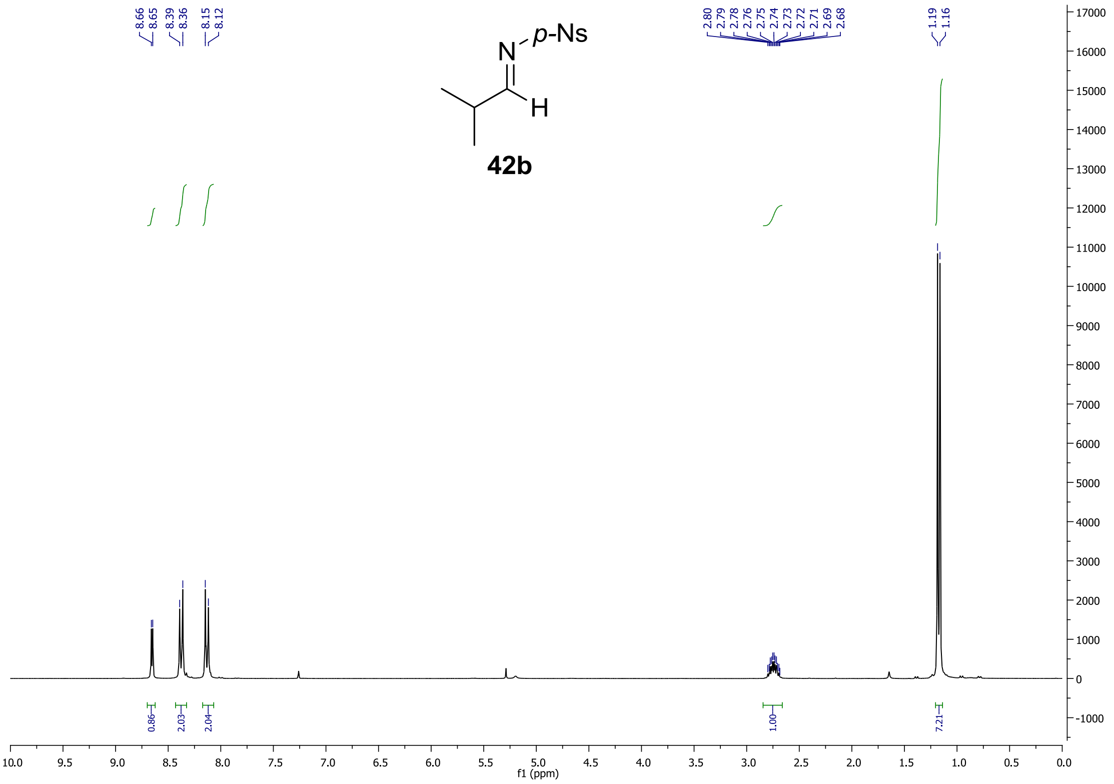

9.27
8.42 8.39 8.27 8.26 8.23
8.00 7.89
7.71 7.70 7.68 7.66 7.65 7.64 7.63 7.61 7.59 7.58
N
p-Ns
H
35h
1.13
3.24
2.00
2.30
2.33
2.38
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100


8.88
8.39
8.36
8.21
8.18
7.81
7.45
7.44
6.71
6.71
6.70
6.70
N
p-Ns
H
O
0.87
2.35
2.17
0.91
1.00
1.00
f1 (ppm)

35i

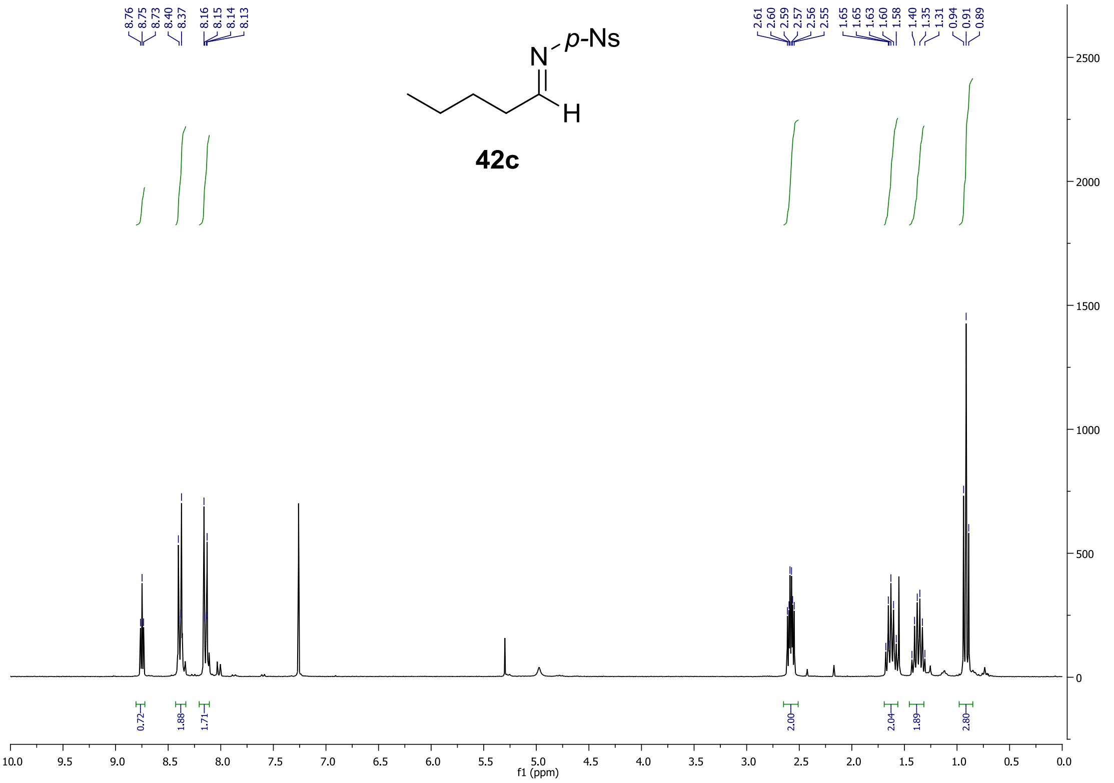

8.63
8.61
8.36
8.15
8.14
8.13
8.12
2.52
2.50
2.49
2.47
2.46
1.86
1.79
1.71
1.67
1.36
1.33
1.30
1.26
1.25
N
p-Ns
H
0.83
2.11
1.93
1.00
6.45
4.43
f1 (ppm)

42a



42b

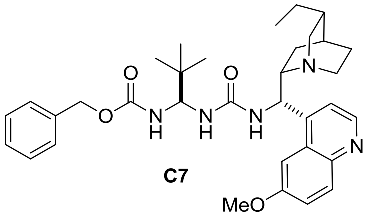
8.66
8.65
8.39
8.36
8.15
8.12
2.80
2.79
2.78
2.76
2.75
2.74
2.73
2.72
2.71
2.69
2.68
1.19
1.16
N
p-Ns
H
0.86
2.03
2.04
1.00
7.21
f1 (ppm)



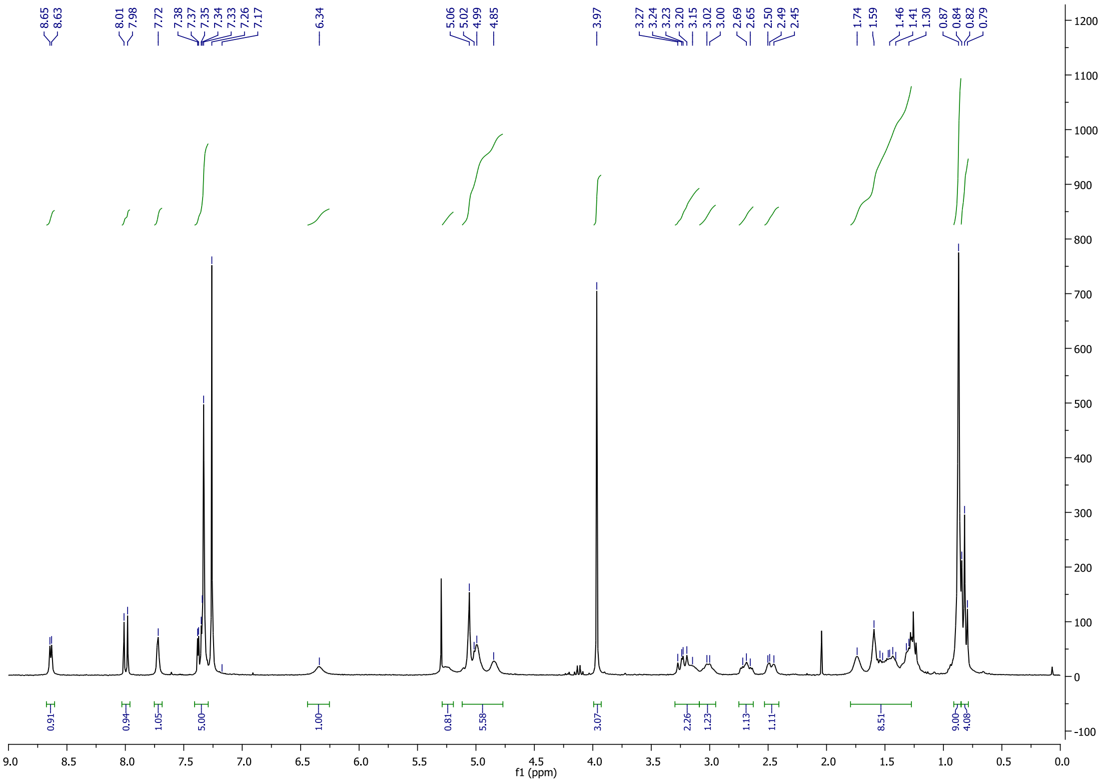
42c

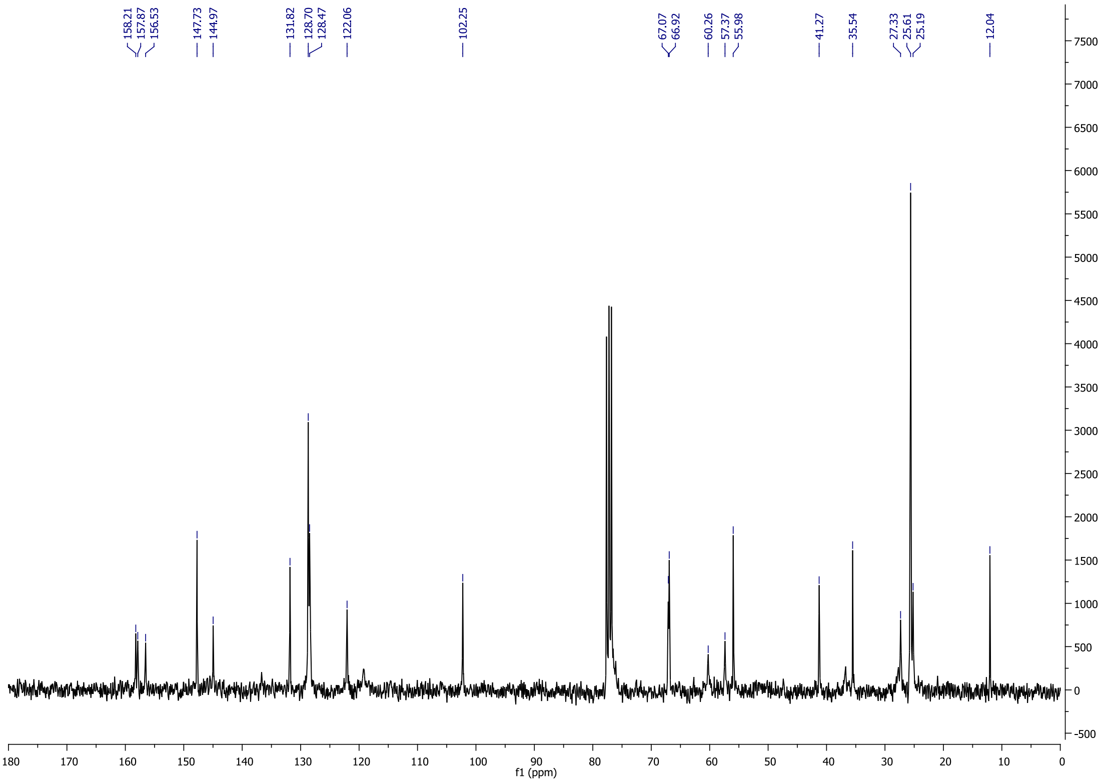
8.76
8.75
8.73
8.40
8.37
8.16
8.15
8.14
8.13
2.61
2.60
2.59
2.57
2.56
2.55
1.65
1.65
1.63
1.60
1.58
1.40
1.35
1.31
0.94
0.91
0.89
N
p-Ns
H
0.72
1.88
1.71
2.00
2.04
1.89
2.80
f1 (ppm)

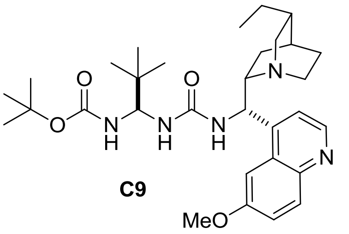
5.8.4. Ureidopeptidic catalysts C7 and C9–C13 and C15


O
O
O
N
H
N
H
N
H
N
N
MeO

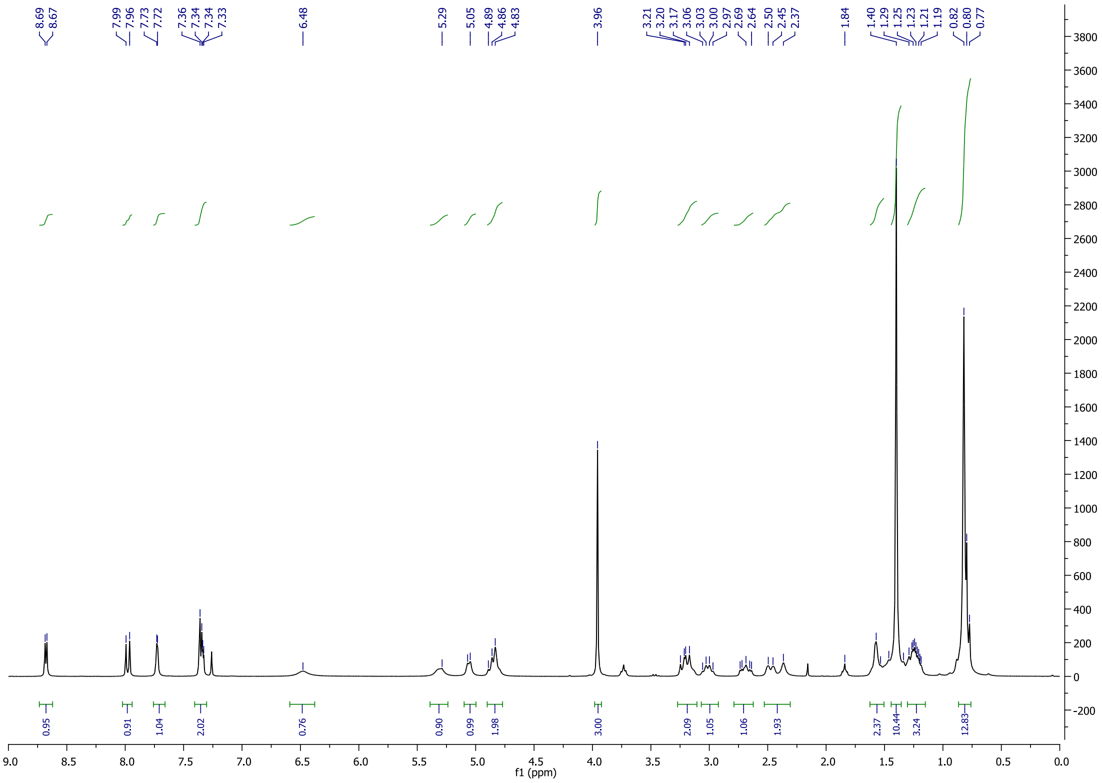
C7

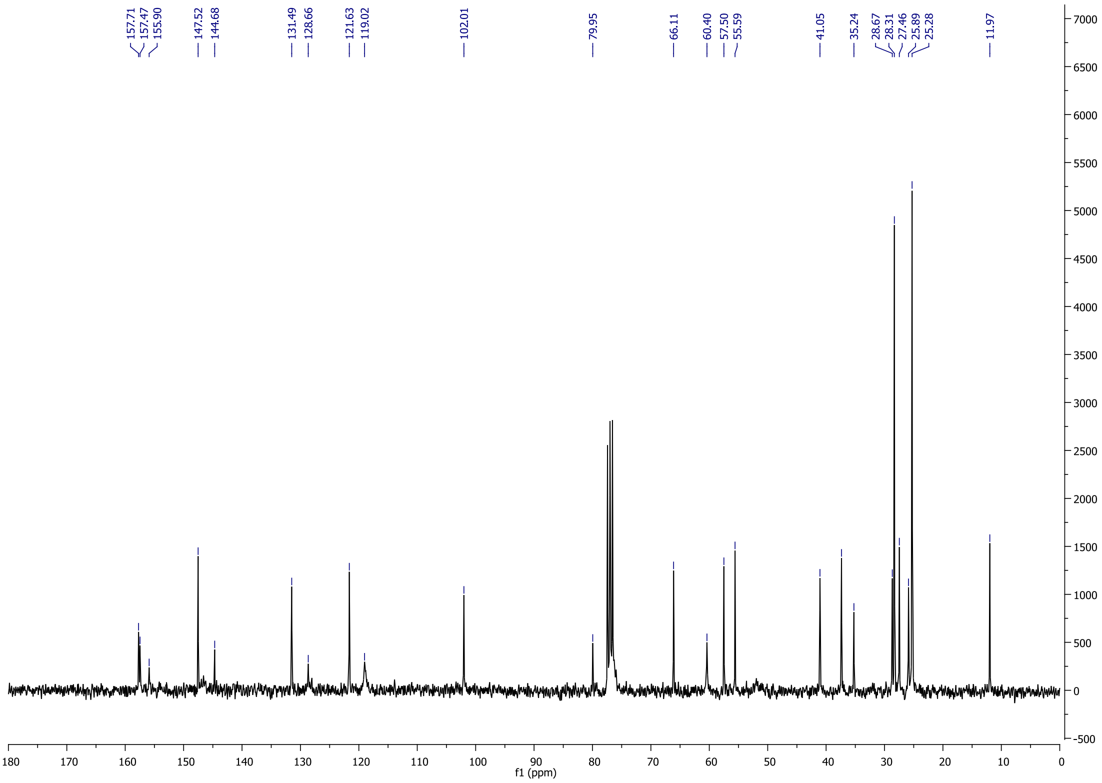


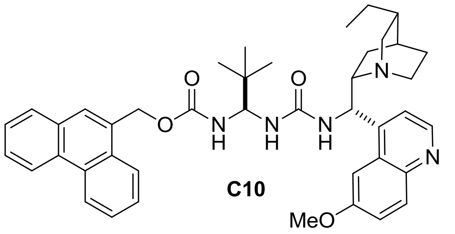




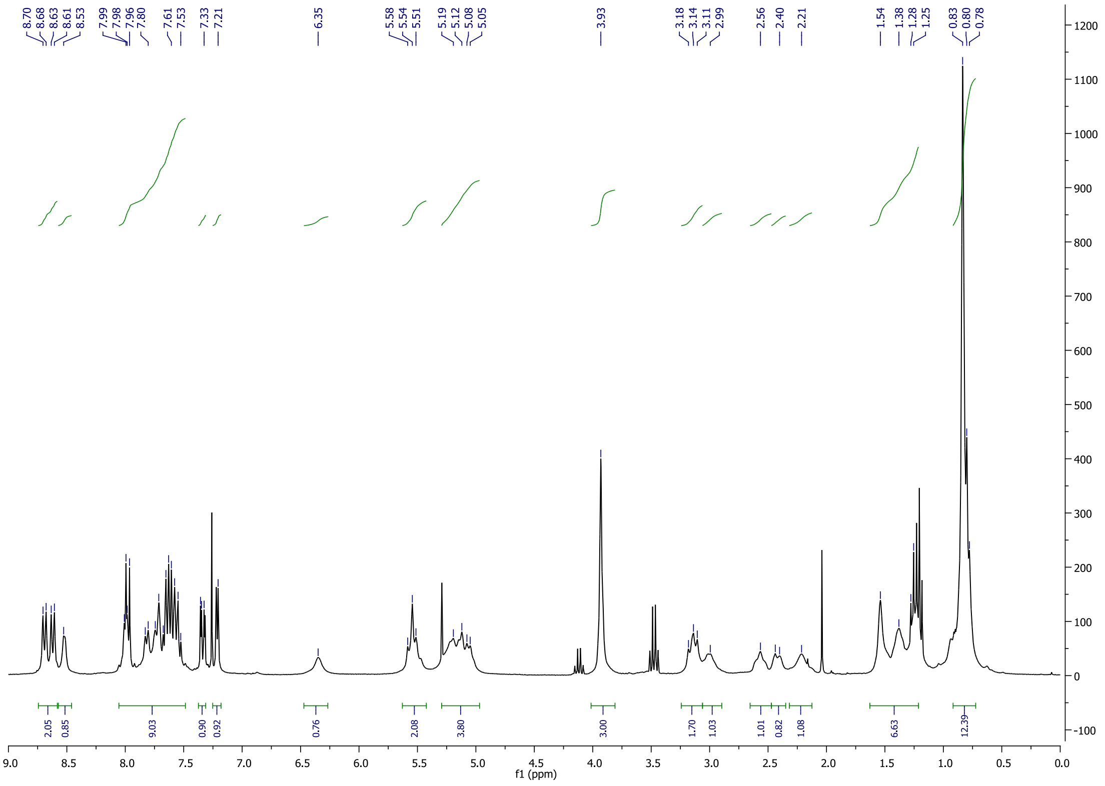
C9

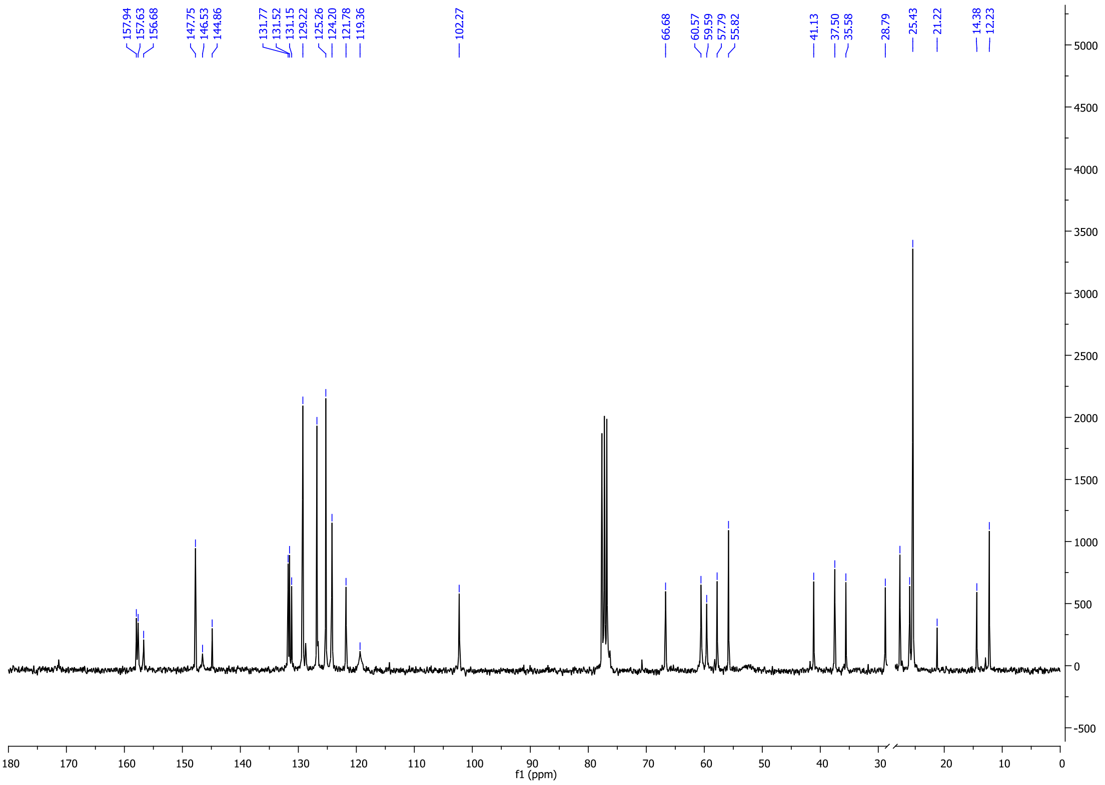

8.69
8.67
7.99
7.96
7.73
7.72
7.36
7.34
7.34
7.33
6.48
5.29
5.05
4.89
4.86
4.83
3.96
3.21
3.20
3.17
3.06
3.03
3.00
2.97
2.69
2.64
2.50
2.45
2.37
1.84
1.40
1.29
1.25
1.23
1.21
1.19
0.82
0.80
0.77
0.95
0.91
1.04
2.02
0.76
0.90
0.99
1.98
3.00
2.09
1.05
1.06
1.93
2.37
10.44
3.24
12.83
f1 (ppm)

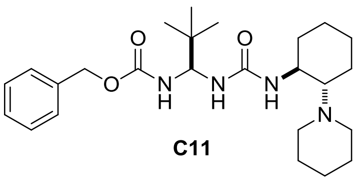

157.71
157.47
155.90
147.52
144.68
131.49
128.66
121.63
119.02
102.01
79.95
66.11
60.40
57.50
55.59
41.05
35.24
28.67
28.31
27.46
25.89
25.28
11.97
f1 (ppm)


O
O
N
H
N
H
N
H
O
N
N
MeO

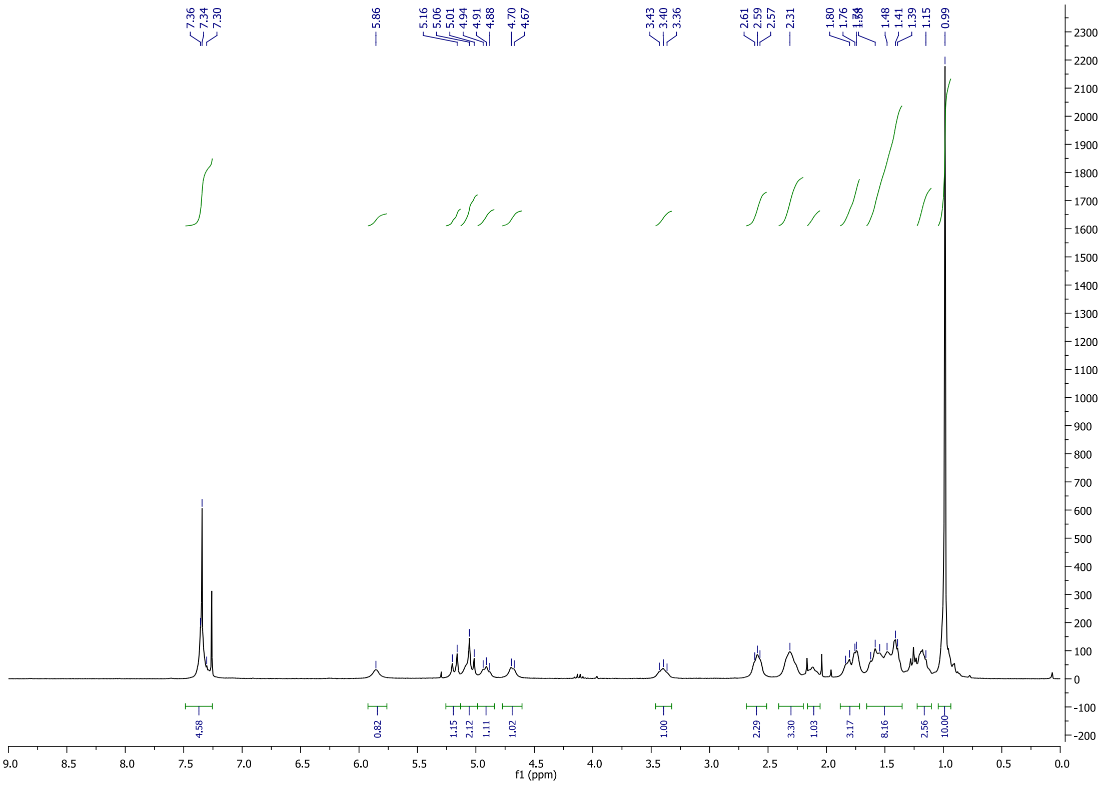
C10

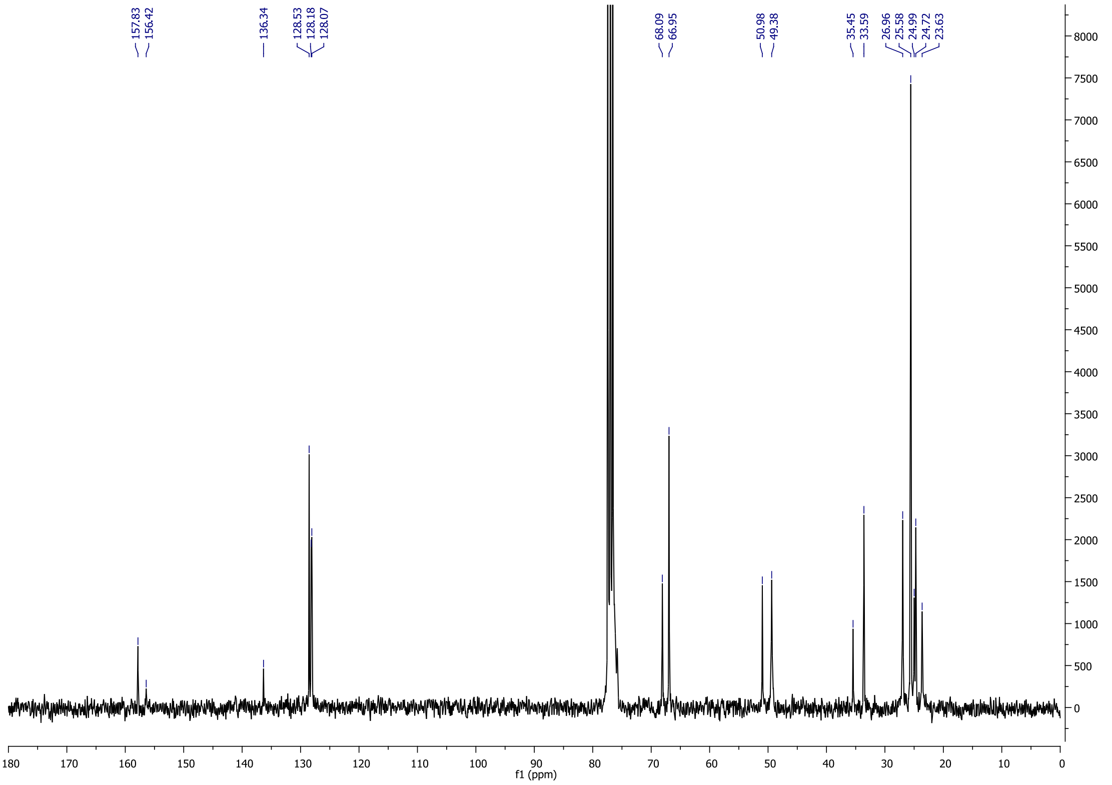

8.70
8.68
8.63
8.61
8.53
7.99
7.98
7.96
7.80
7.61
7.53
7.33
7.21
6.35
5.58
5.54
5.51
5.19
5.12
5.08
5.05
3.93
3.18
3.14
3.11
2.99
2.56
2.40
2.21
1.54
1.38
1.28
1.25
0.83
0.80
0.78
2.05
0.85
9.03
0.90
0.92
0.76
2.08
3.80
3.00
1.70
1.03
1.01
0.82
1.08
6.63
12.39
f1 (ppm)

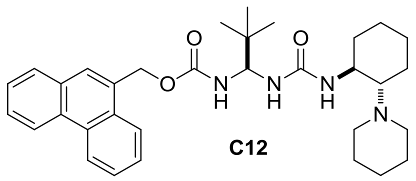

157.94
157.63
156.68
147.75
146.53
144.86
131.77
131.52
131.15
129.22
125.26
124.20
121.78
119.36
102.27
66.68
60.57
59.59
57.79
55.82
41.13
37.50
35.58
28.79
25.43
21.22
14.38
12.23
f1 (ppm)


O
O
N
H
N
H
O
N
H
N

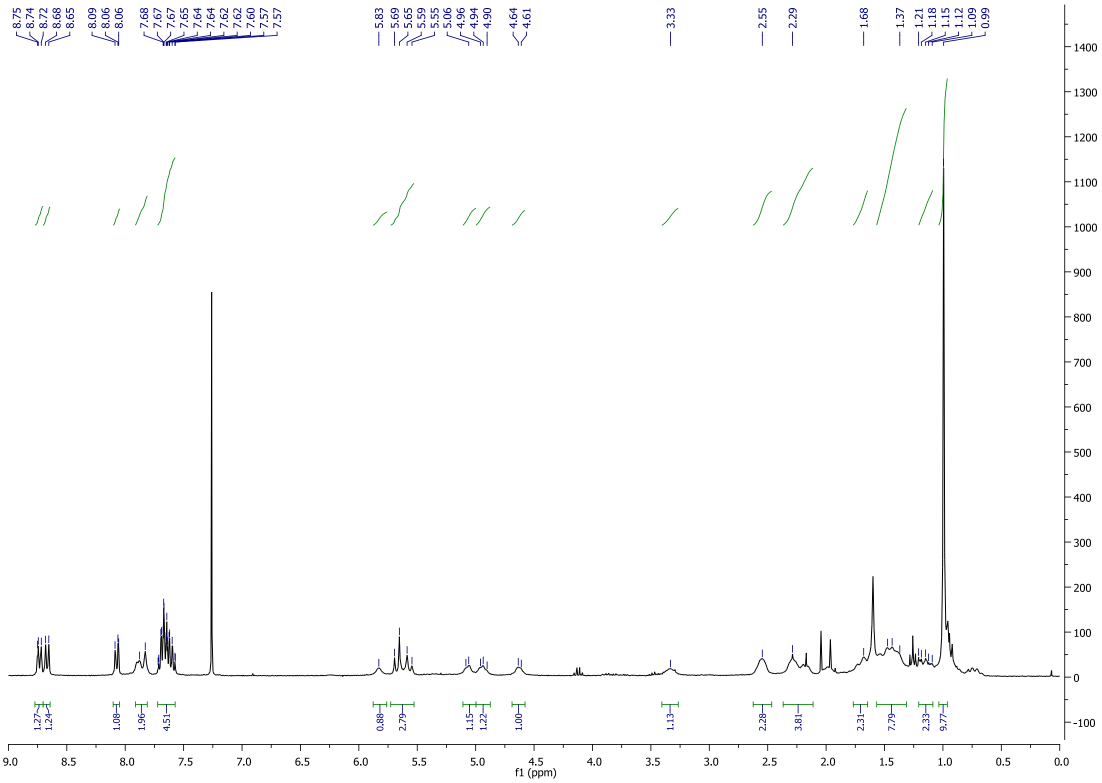
C11

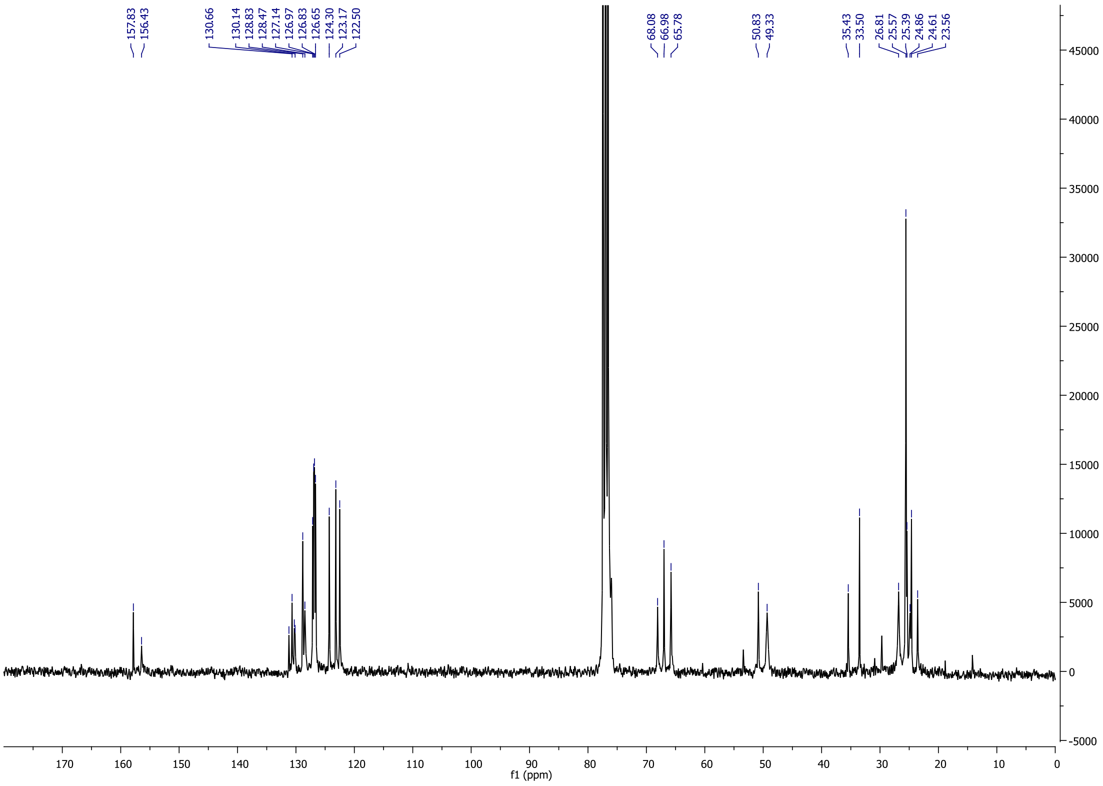

7.36
7.34
7.30
5.86
5.16
5.06
5.01
4.94
4.91
4.88
4.70
4.67
3.43
3.40
3.36
2.61
2.59
2.57
2.31
1.80
1.76
1.74
1.58
1.48
1.41
1.39
1.15
0.99
4.58
0.82
1.15
2.12
1.11
1.02
1.00
2.29
3.30
1.03
3.17
8.16
2.56
10.00
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

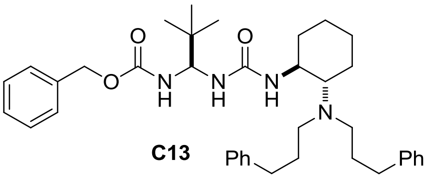

157.83
156.42
136.34
128.53
128.18
128.07
68.09
66.95
50.98
49.38
35.45
33.59
26.96
25.58
24.99
24.72
23.63
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
N
H
N
H
O
N
H
N

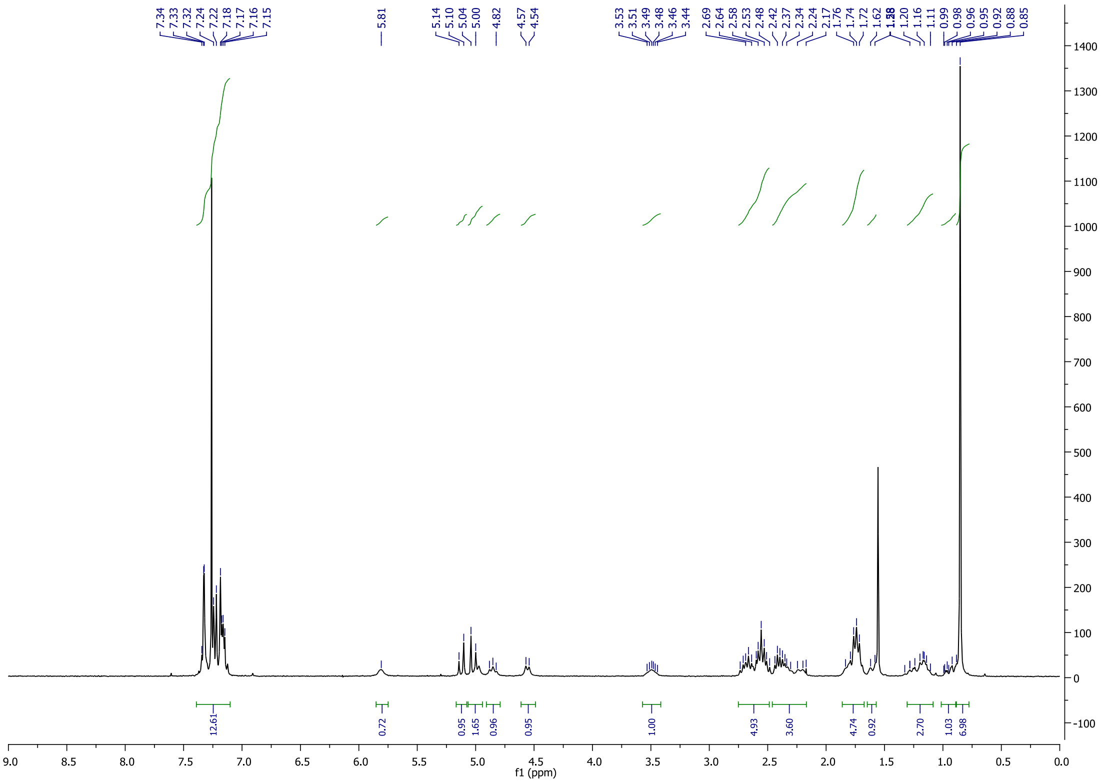
C12

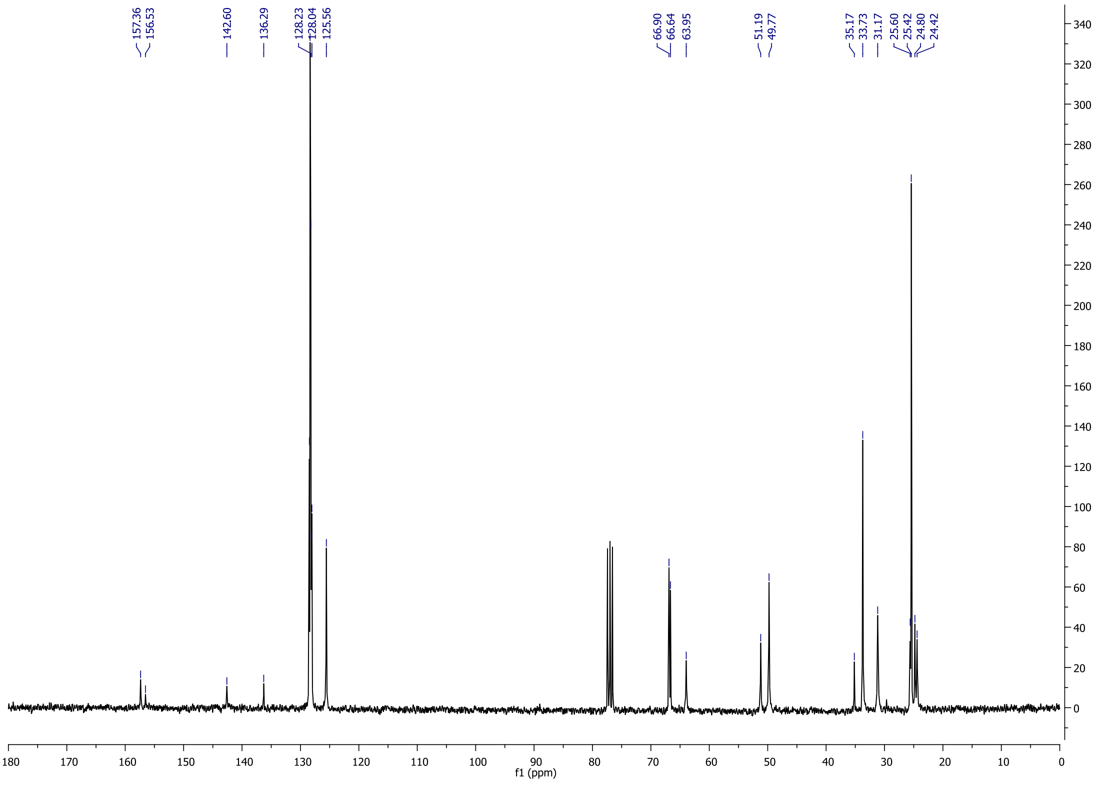

8.75
8.74
8.72
8.68
8.65
8.09
8.06
8.06
7.68
7.67
7.67
7.65
7.64
7.64
7.62
7.62
7.60
7.57
7.57
5.83
5.69
5.65
5.59
5.55
5.06
4.96
4.94
4.90
4.64
4.61
3.33
2.55
2.29
1.68
1.37
1.21
1.18
1.15
1.12
1.09
0.99
1.27
1.24
1.08
1.96
4.51
0.88
2.79
1.15
1.22
1.00
1.13
2.28
3.81
2.31
7.79
2.33
9.77
f1 (ppm)

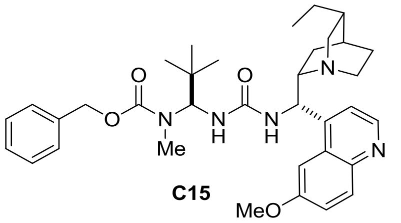

157.83
156.43
130.66
130.14
128.83
128.47
127.14
126.97
126.83
126.65
124.30
123.17
122.50
68.08
66.98
65.78
50.83
49.33
35.43
33.50
26.81
25.57
25.39
24.86
24.61
23.56
f1 (ppm)


O
O
O
N
H
N
H
N
H
N
Ph
Ph

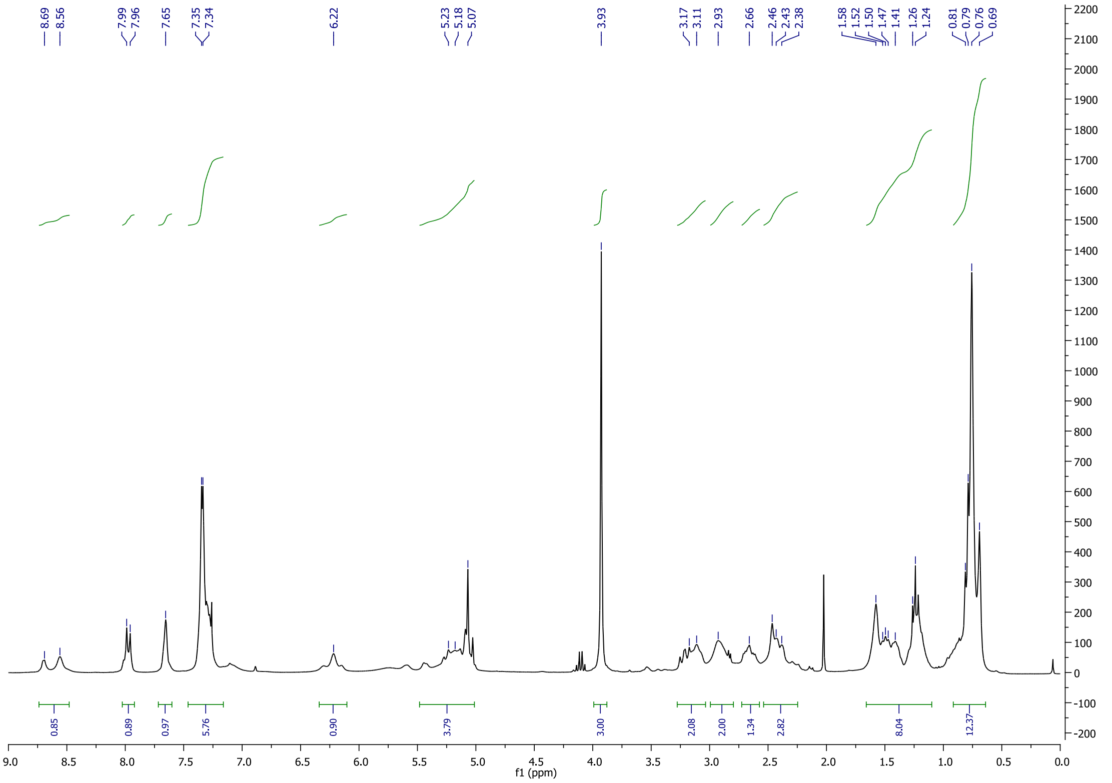
C13

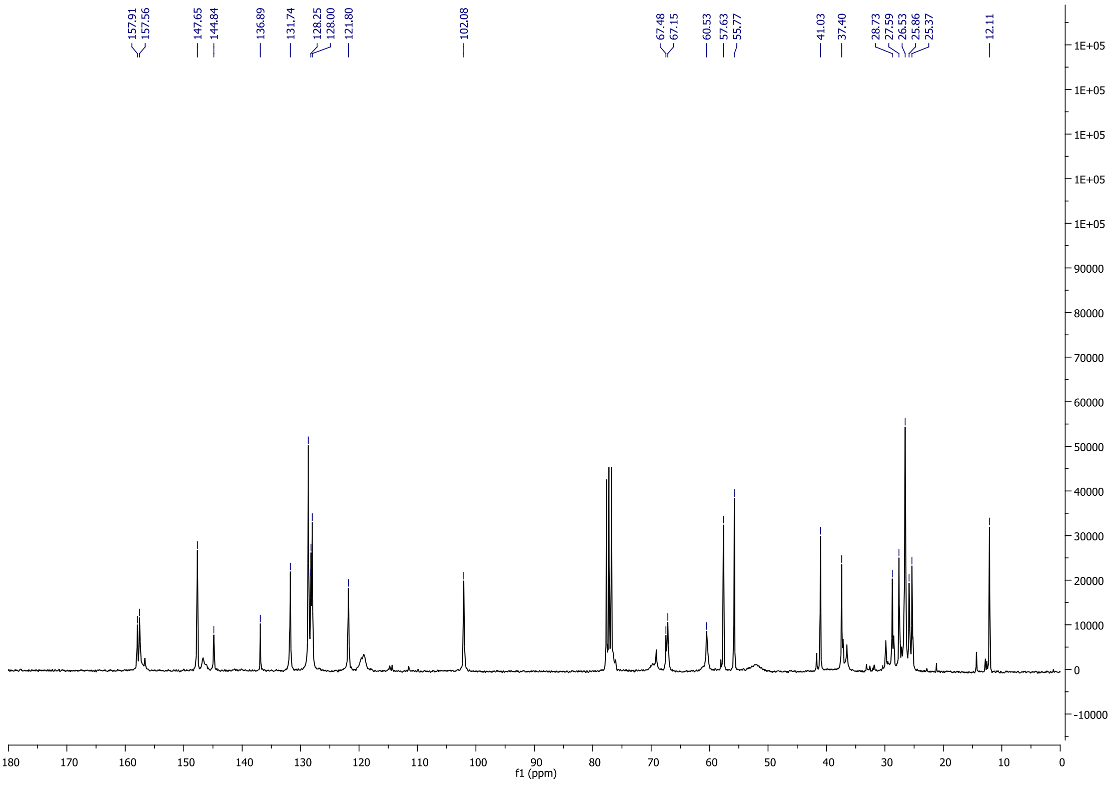

7.34
7.33
7.32
7.24
7.22
7.18
7.17
7.16
7.15
5.81
5.14
5.10
5.04
5.00
4.82
4.57
4.54
3.53
3.51
3.49
3.48
3.46
3.44
2.69
2.64
2.58
2.53
2.48
2.42
2.37
2.34
2.24
2.17
1.76
1.74
1.72
1.62
1.58
1.20
1.16
1.11
0.99
0.98
0.96
0.95
0.92
0.88
0.85
12.61
0.72
0.95
1.65
0.96
0.95
1.00
4.93
3.60
4.74
0.92
2.70
1.03
6.98
f1 (ppm)


157.36
156.53
142.60
136.29
128.23
128.04
125.56
66.90
66.64
63.95
51.19
49.77
35.17
33.73
31.17
25.60
25.42
24.80
24.42
f1 (ppm)

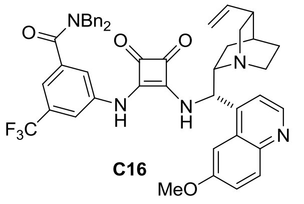

O
O
N
Me
N
H
O
N
H
N
N
MeO

C15

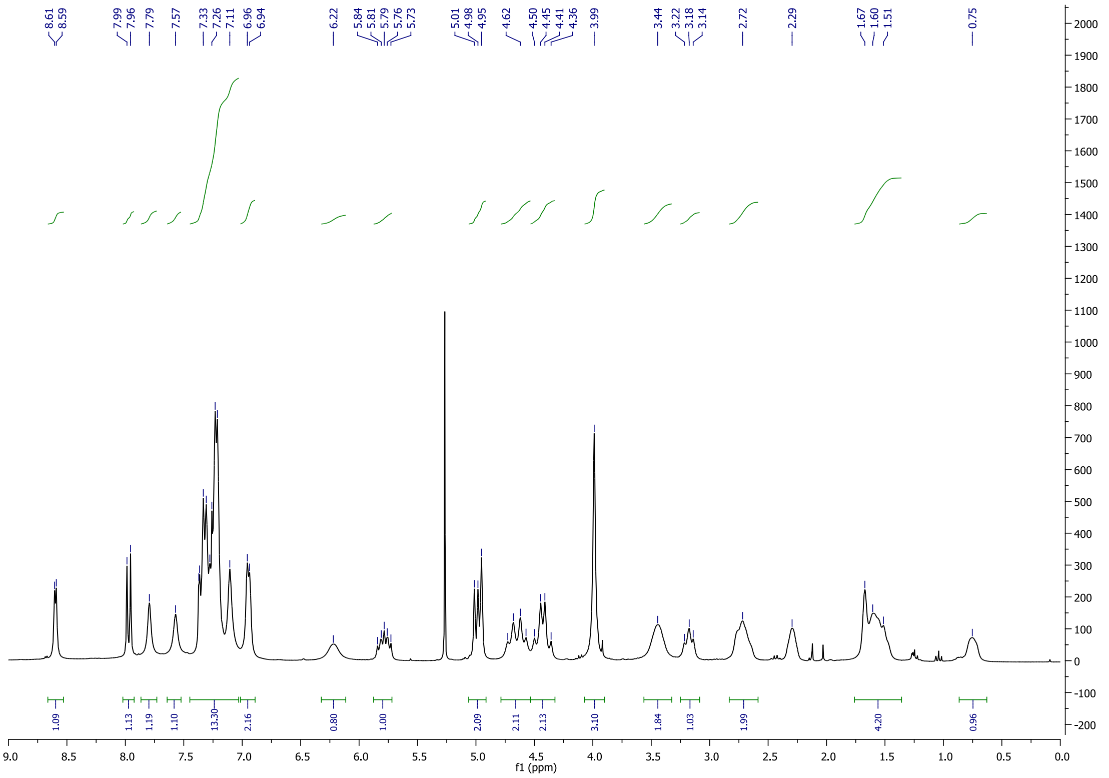

8.69
8.56
7.99
7.96
7.65
7.35
7.34
6.22
5.23
5.18
5.07
3.93
3.17
3.11
2.93
2.66
2.46
2.43
2.38
1.58
1.52
1.50
1.47
1.41
1.26
1.24
0.81
0.79
0.76
0.69
0.85
0.89
0.97
5.76
0.90
3.79
3.00
2.08
2.00
1.34
2.82
8.04
12.37
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

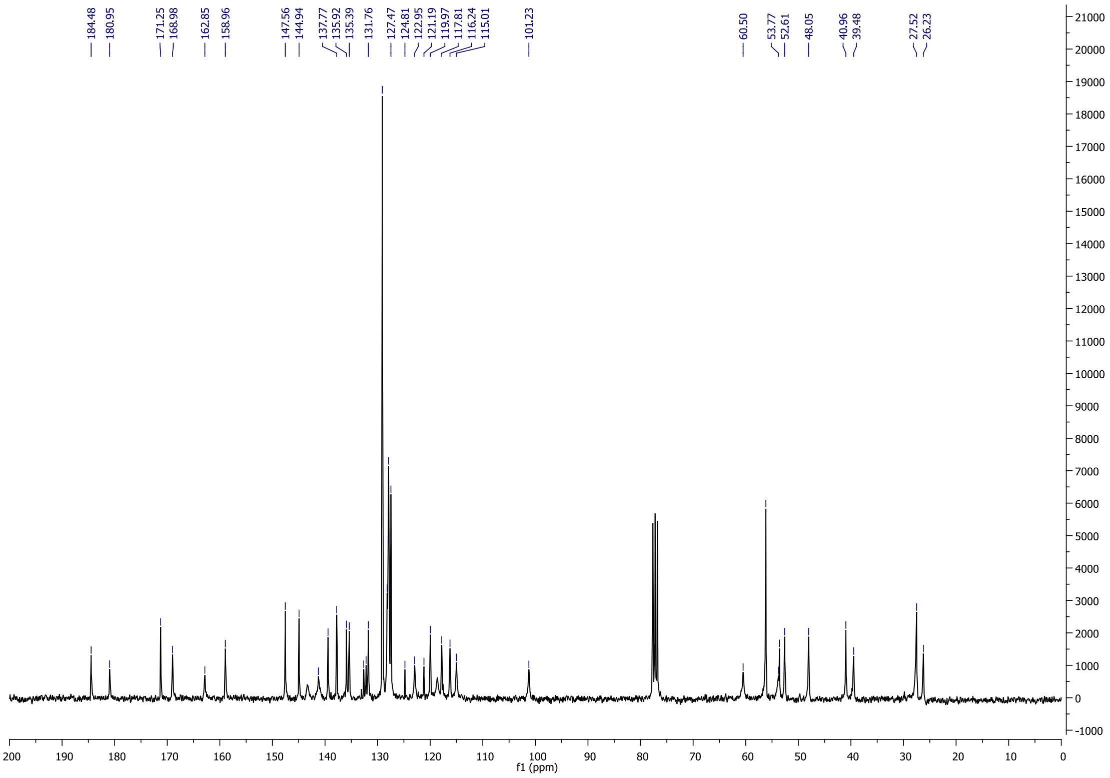

157.91
157.56
147.65
144.84
136.89
131.74
128.25
128.00
121.80
102.08
67.48
67.15
60.53
57.63
55.77
41.03
37.40
28.73
27.59
26.53
25.86
25.37
12.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
1E+05
1E+05
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000

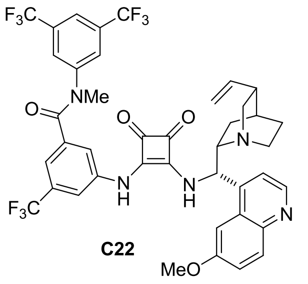
5.8.5. Squaramide-based catalysts C16–C19 and C22–C24


NBn2
O
O
O
N
F3C
N
H
N
H
N
MeO

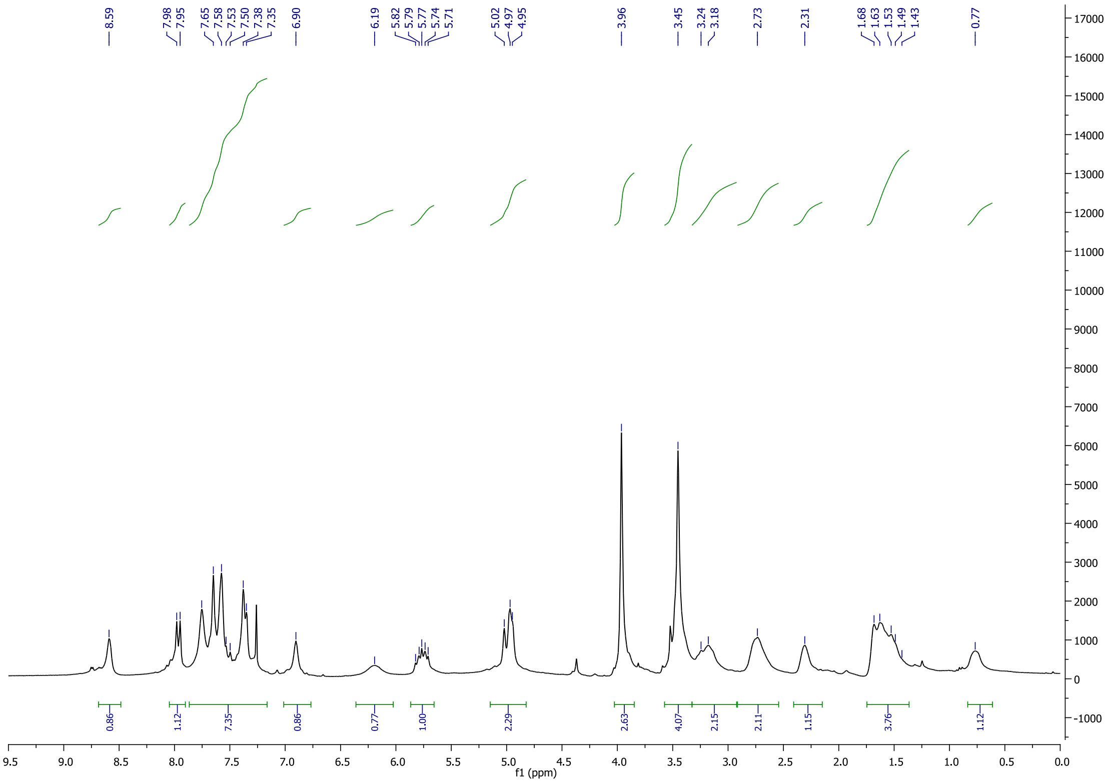
C16

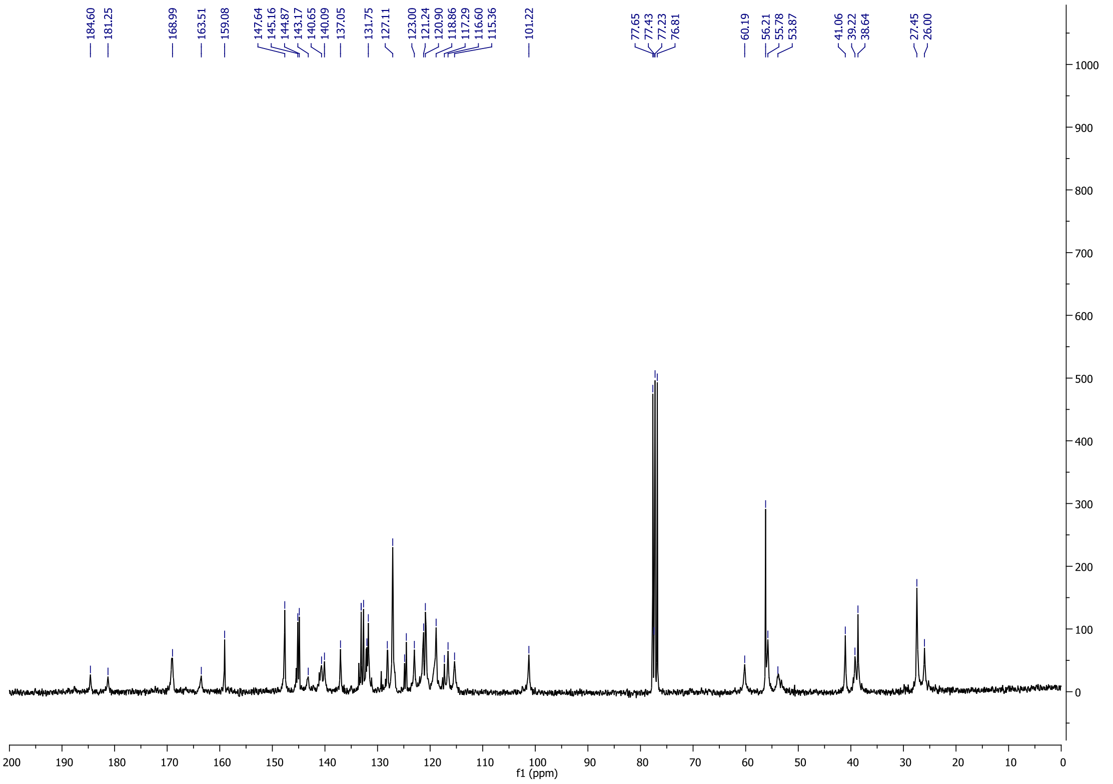


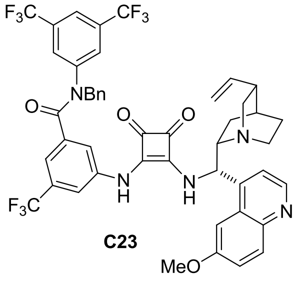



F$_3$C
CF$_3$
O
NMe
O
O
N
H
N
H
N
N
F$_3$C
MeO

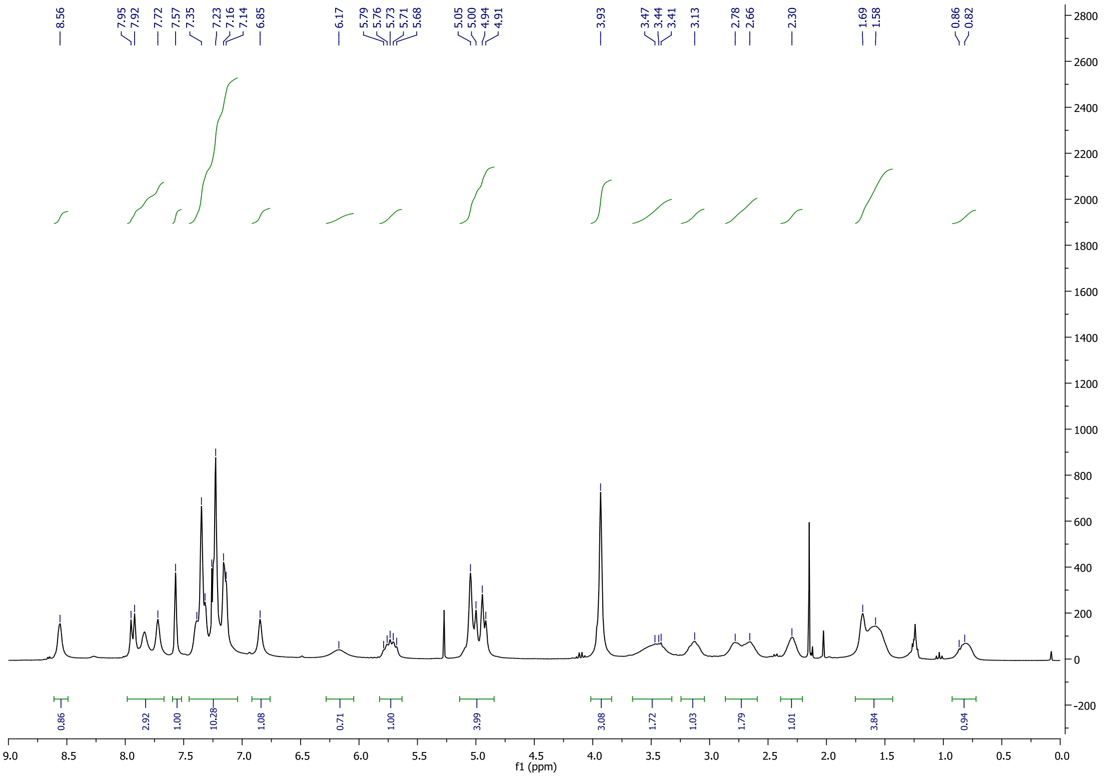
C22

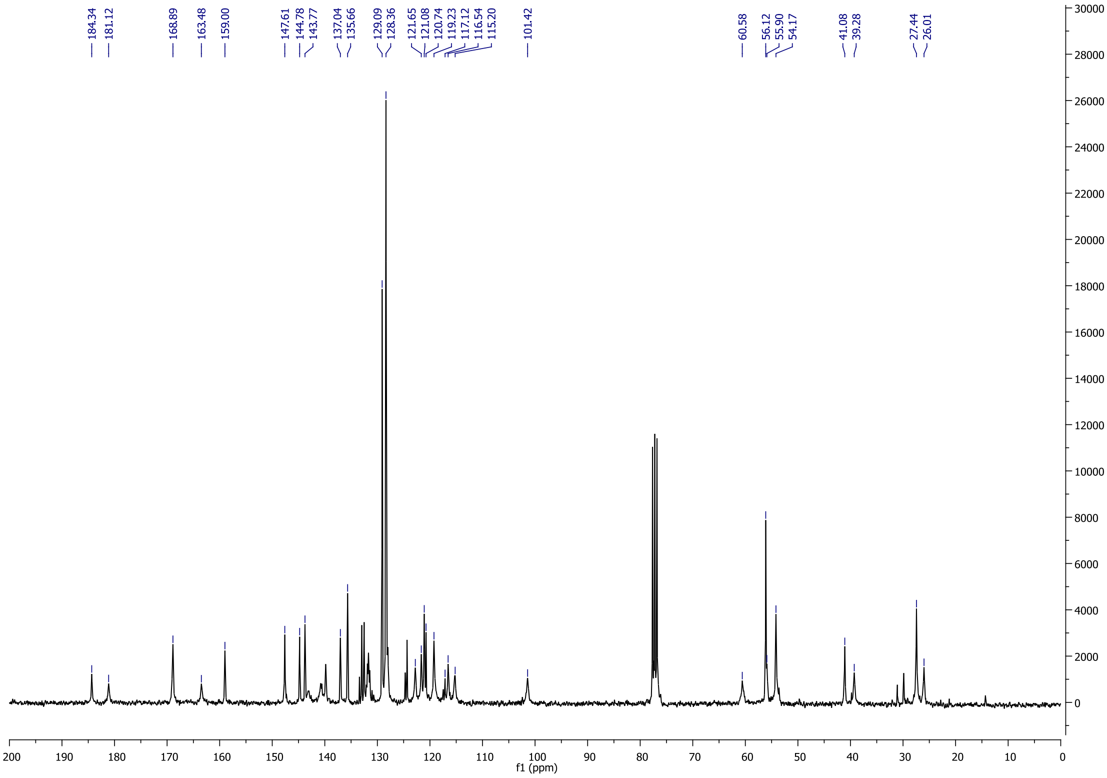

8.59
7.98
7.95
7.65
7.58
7.53
7.50
7.38
7.35
6.90
6.19
5.82
5.79
5.77
5.74
5.71
5.02
4.97
4.95
3.96
3.45
3.24
3.18
2.73
2.31
1.68
1.63
1.53
1.49
1.43
0.77
0.86
1.12
7.35
0.86
0.77
1.00
2.29
2.63
4.07
2.15
2.11
1.15
3.76
1.12
f1 (ppm)

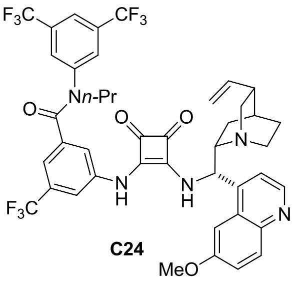

184.60
181.25
168.99
163.51
159.08
147.64
145.16
144.87
143.17
140.65
140.09
137.05
131.75
127.11
123.00
121.24
120.90
118.86
117.29
116.60
115.36
101.22
77.65
77.43
77.23
76.81
60.19
56.21
55.78
53.87
41.06
39.22
38.64
27.45
26.00
f1 (ppm)


F3C
CF3
NBn
O
O
O
N
H
N
H
N
N
F3C
MeO

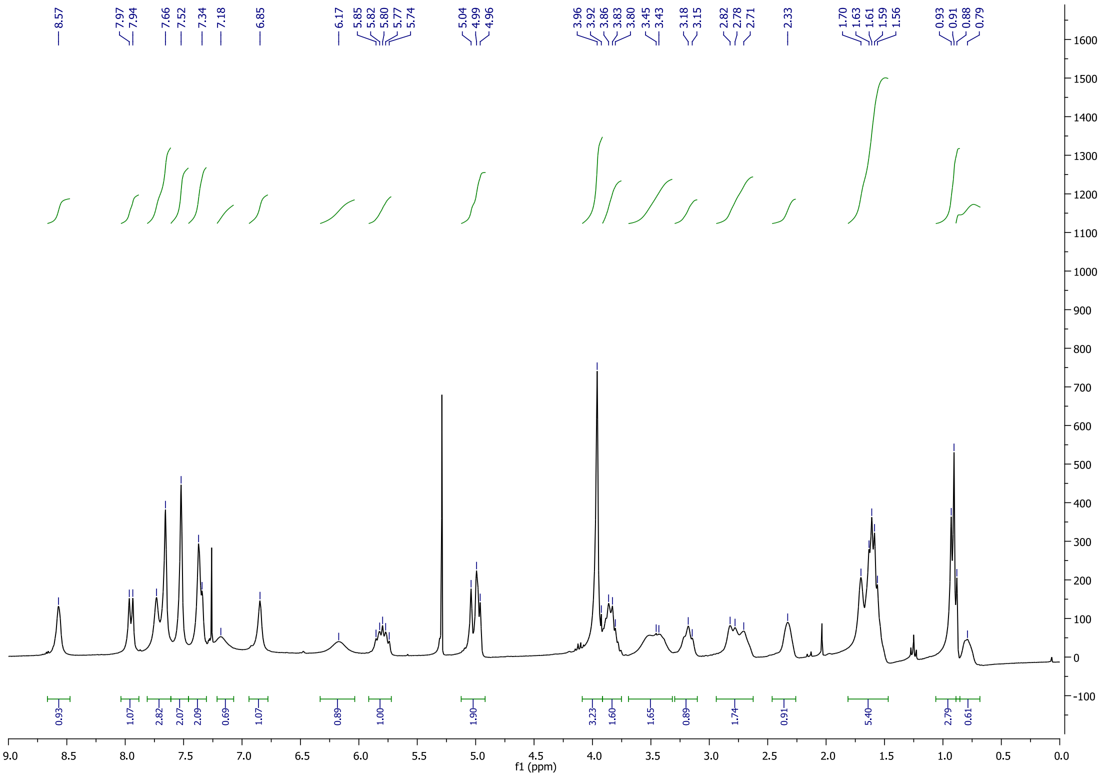
C23

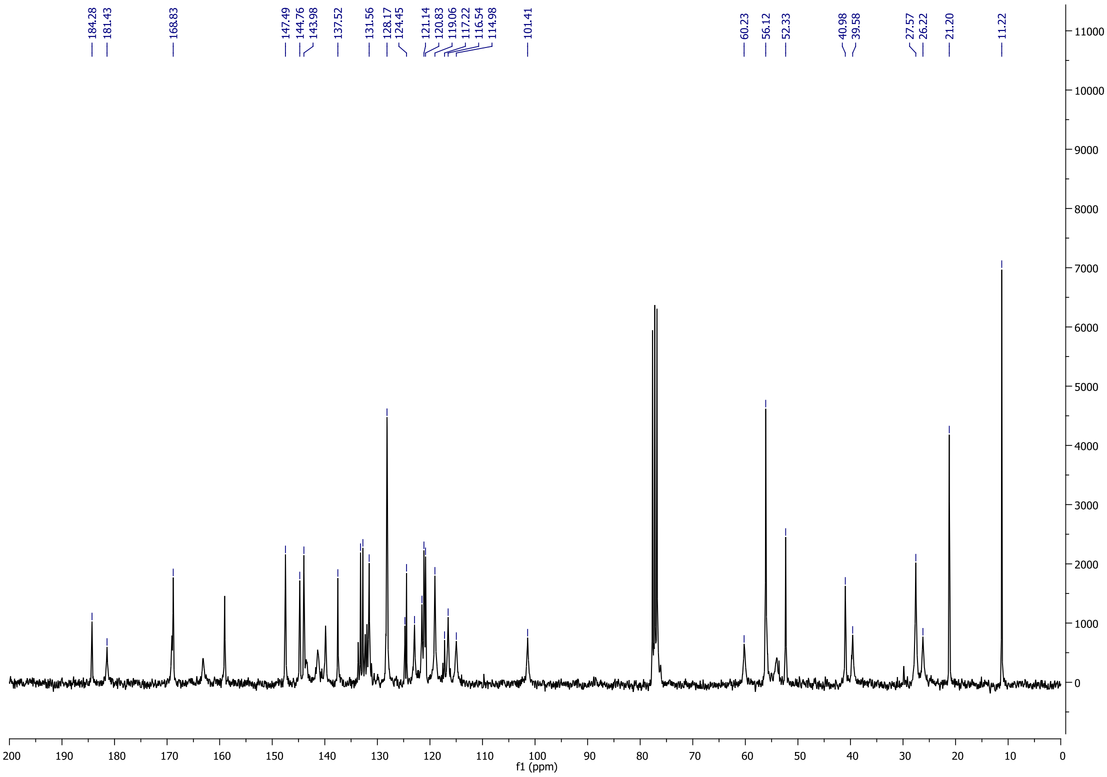

8.56
7.95
7.92
7.72
7.57
7.35
7.23
7.16
7.14
6.85
6.17
5.79
5.76
5.73
5.71
5.68
5.05
5.00
4.94
4.91
3.93
3.47
3.44
3.41
3.13
2.78
2.66
2.30
1.69
1.58
0.86
0.82
0.86
2.92
1.00
10.28
1.08
0.71
1.00
3.99
3.08
1.72
1.03
1.79
1.01
3.84
0.94
f1 (ppm)

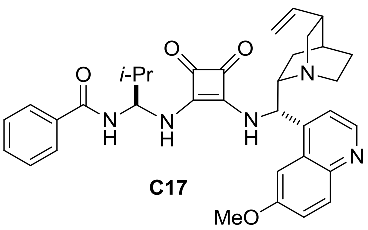

184.34
181.12
168.89
163.48
159.00
147.61
144.78
143.77
137.04
135.66
129.09
128.36
121.65
121.08
120.74
119.23
117.12
116.54
115.20
101.42
60.58
56.12
55.90
54.17
41.08
39.28
27.44
26.01
f1 (ppm)


F3C
CF3
Nn-Pr
O
O
O
N
N
H
N
H
F3C
N
MeO

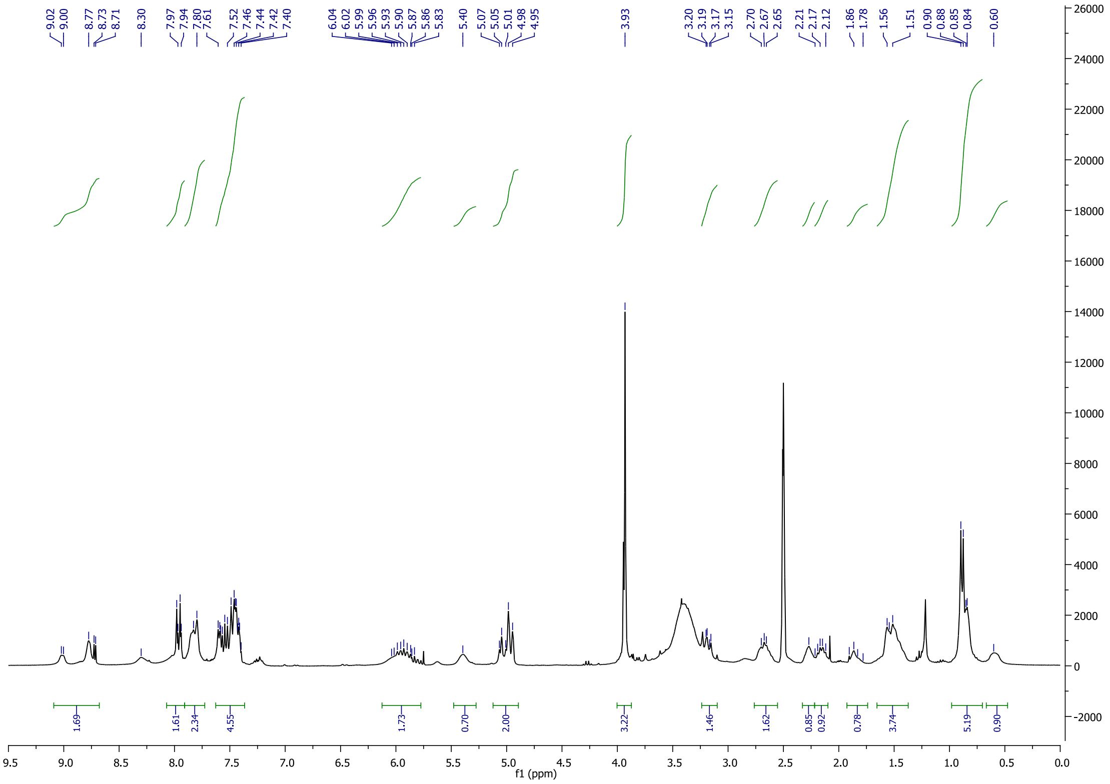
C24

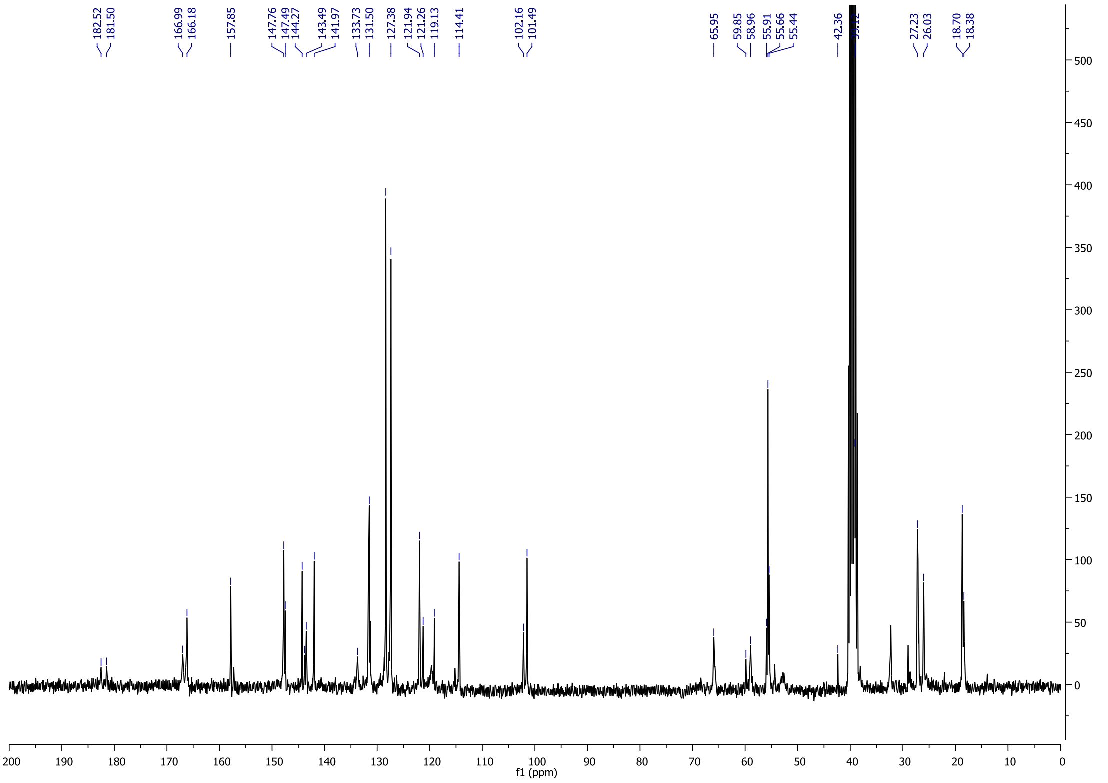

8.57
7.97
7.94
7.66
7.52
7.34
7.18
6.85
6.17
5.85
5.82
5.80
5.77
5.74
5.04
4.99
4.96
3.96
3.92
3.86
3.83
3.80
3.45
3.43
3.18
3.15
2.82
2.78
2.71
2.33
1.70
1.63
1.61
1.59
1.56
0.93
0.91
0.88
0.79
0.93
1.07
2.82
2.07
2.09
0.69
1.07
0.89
1.00
1.90
3.23
1.60
1.65
0.89
1.74
0.91
5.40
2.79
0.61
f1 (ppm)

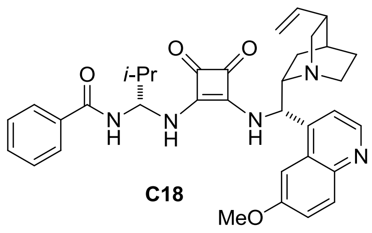

184.28
181.43
168.83
147.49
144.76
143.98
137.52
131.56
128.17
124.45
121.14
120.83
119.06
117.22
116.54
114.98
101.41
60.23
56.12
52.33
40.98
39.58
27.57
26.22
21.20
11.22
f1 (ppm)


O
i-Pr
O
O
N
H
N
H
N
H
N
N
MeO

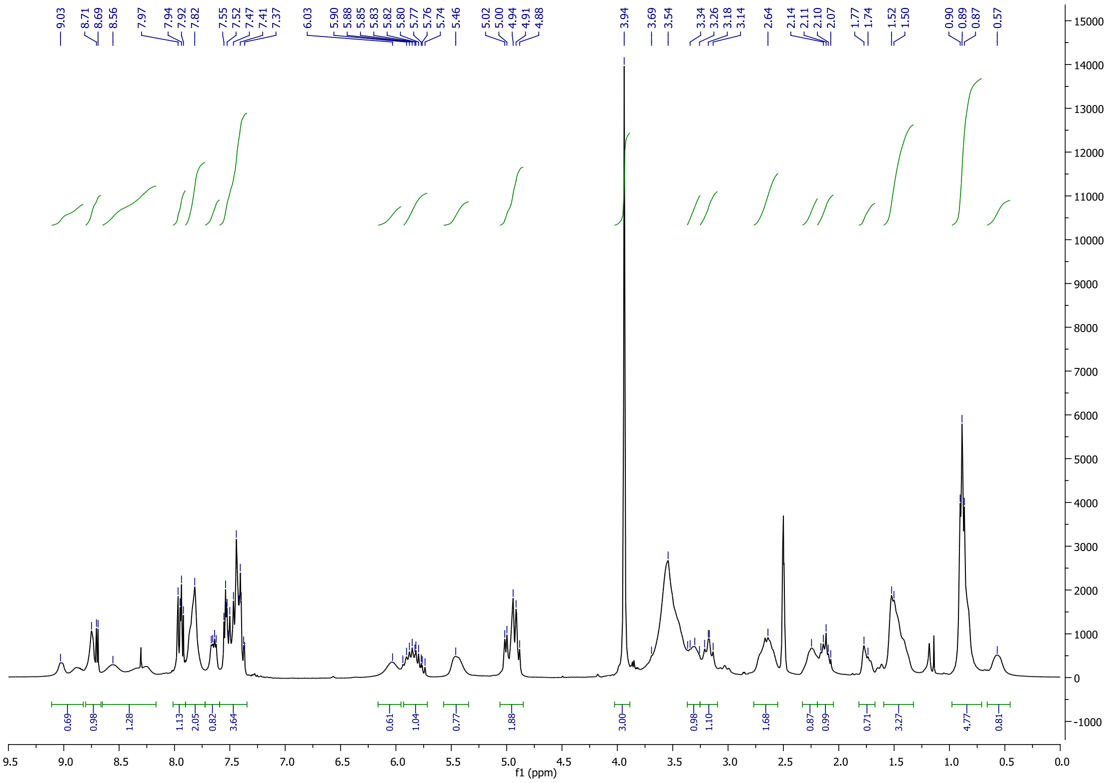
C17

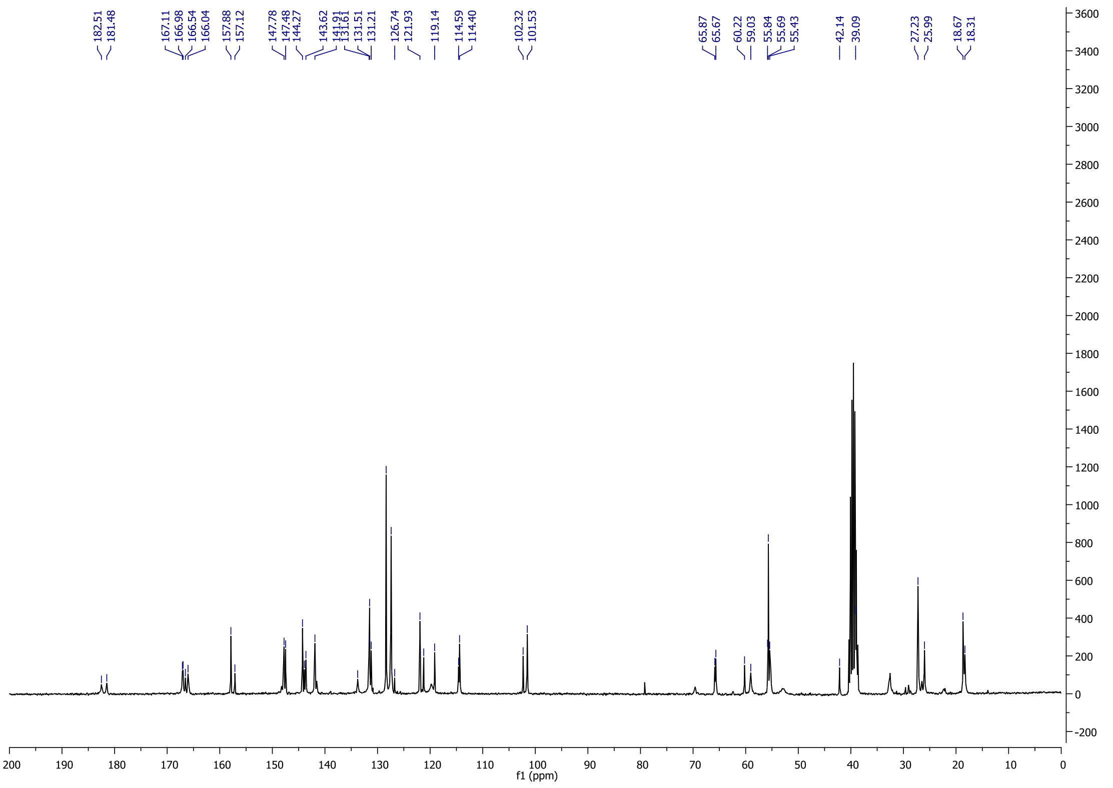

9.02
9.00
8.77
8.73
8.71
8.30
7.97
7.94
7.80
7.61
7.52
7.46
7.44
7.42
7.40
6.04
6.02
5.99
5.96
5.93
5.90
5.87
5.86
5.83
5.40
5.07
5.05
5.01
4.98
4.95
3.93
3.20
3.19
3.17
3.15
2.70
2.67
2.65
2.21
2.17
2.12
1.86
1.78
1.56
1.51
0.90
0.88
0.85
0.84
0.60
1.69
1.61
2.34
4.55
1.73
0.70
2.00
3.22
1.46
1.62
0.85
0.92
0.78
3.74
5.19
0.90
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

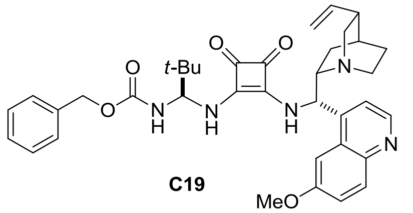

182.52
181.50
166.99
166.18
157.85
147.76
147.49
144.27
143.49
141.97
133.73
131.50
127.38
121.94
121.26
119.13
114.41
102.16
101.49
65.95
59.85
58.96
55.91
55.66
55.44
42.36
27.23
26.03
18.70
18.38
500
450
400
350
300
250
200
150
100
50
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
i-Pr
O
O
N
H
N
H
N
H
N
N
MeO

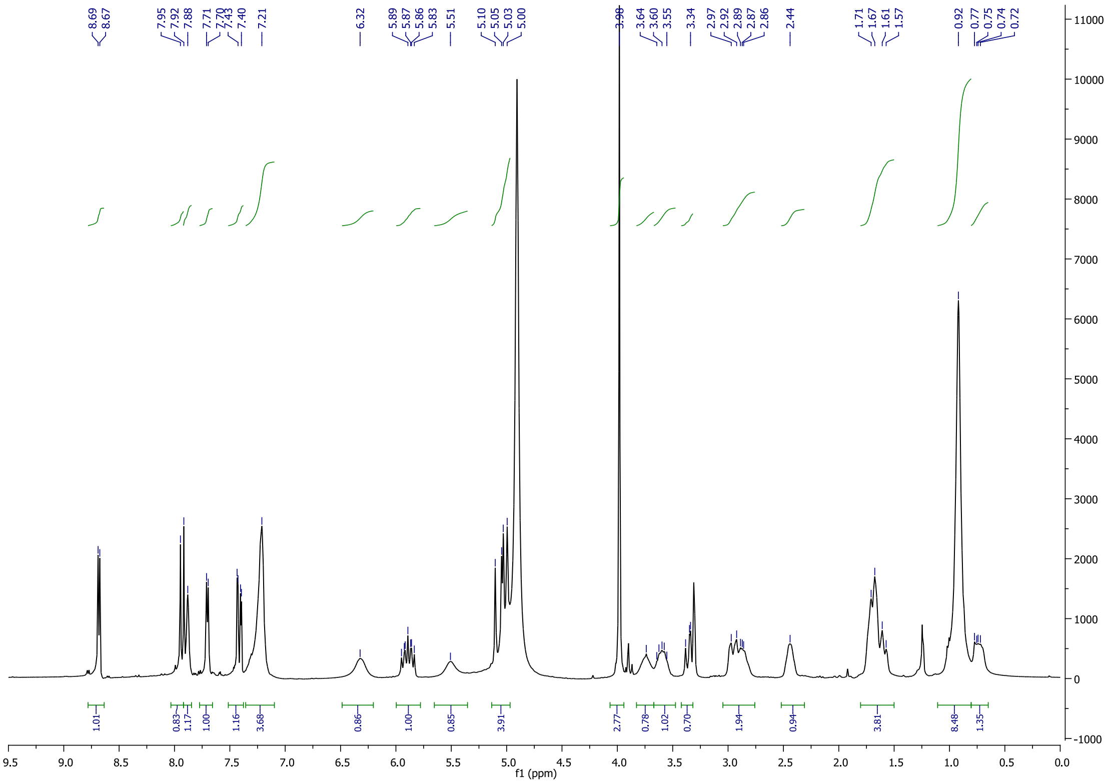
C18

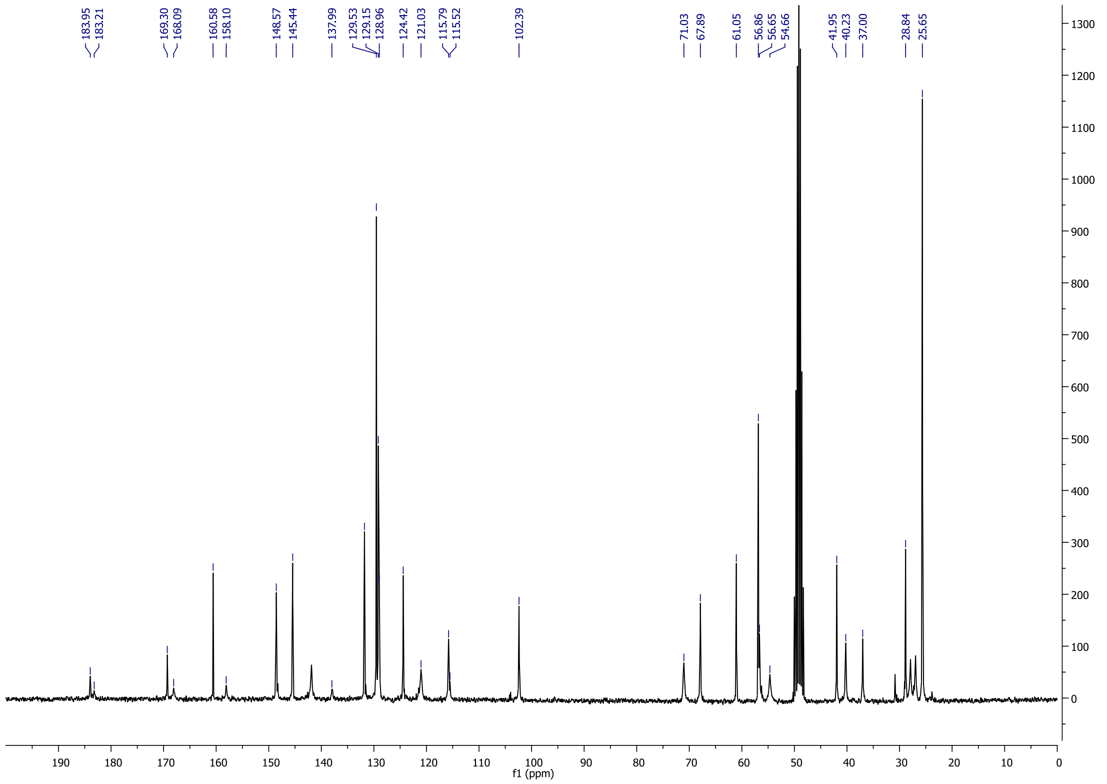

9.03
8.71
8.69
8.56
7.97
7.94
7.92
7.82
7.55
7.52
7.47
7.41
7.37
6.03
5.90
5.88
5.85
5.83
5.82
5.80
5.77
5.76
5.74
5.46
5.02
5.00
4.94
4.91
4.88
3.94
3.69
3.54
3.34
3.26
3.18
3.14
2.64
2.14
2.11
2.10
2.07
1.77
1.74
1.52
1.50
0.90
0.89
0.87
0.57
0.69
0.98
1.28
1.13
2.05
0.82
3.64
0.61
1.04
0.77
1.88
3.00
0.98
1.10
1.68
0.87
0.99
0.71
3.27
4.77
0.81
f1 (ppm)


182.51
181.48
167.11
166.98
166.54
166.04
157.88
157.12
147.78
147.48
144.27
143.62
141.91
131.61
131.51
131.21
126.74
121.93
119.14
114.59
114.40
102.32
101.53
65.87
65.67
60.22
59.03
55.84
55.69
55.43
42.14
39.09
27.23
25.99
18.67
18.31
f1 (ppm)

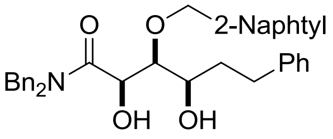

O
t-Bu
O
O
N
H
N
H
N
H
N
N
MeO

C19

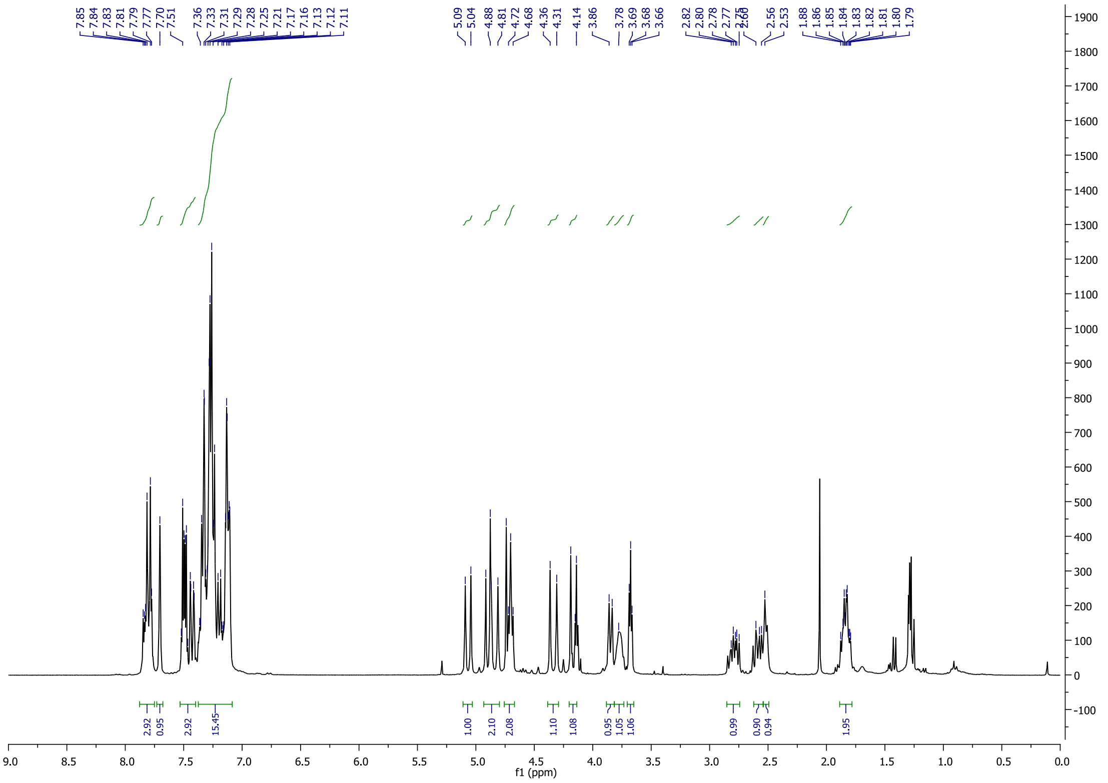

8.69
8.67
7.95
7.92
7.88
7.71
7.70
7.43
7.40
7.21
6.32
5.89
5.87
5.86
5.83
5.51
5.10
5.05
5.03
5.00
3.98
3.64
3.60
3.55
3.34
2.97
2.92
2.89
2.87
2.86
2.44
1.71
1.67
1.61
1.57
0.92
0.77
0.75
0.74
0.72
1.01
0.83
1.17
1.00
1.16
3.68
0.86
1.00
0.85
3.91
2.77
0.78
1.02
0.70
1.94
0.94
3.81
8.48
1.35
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

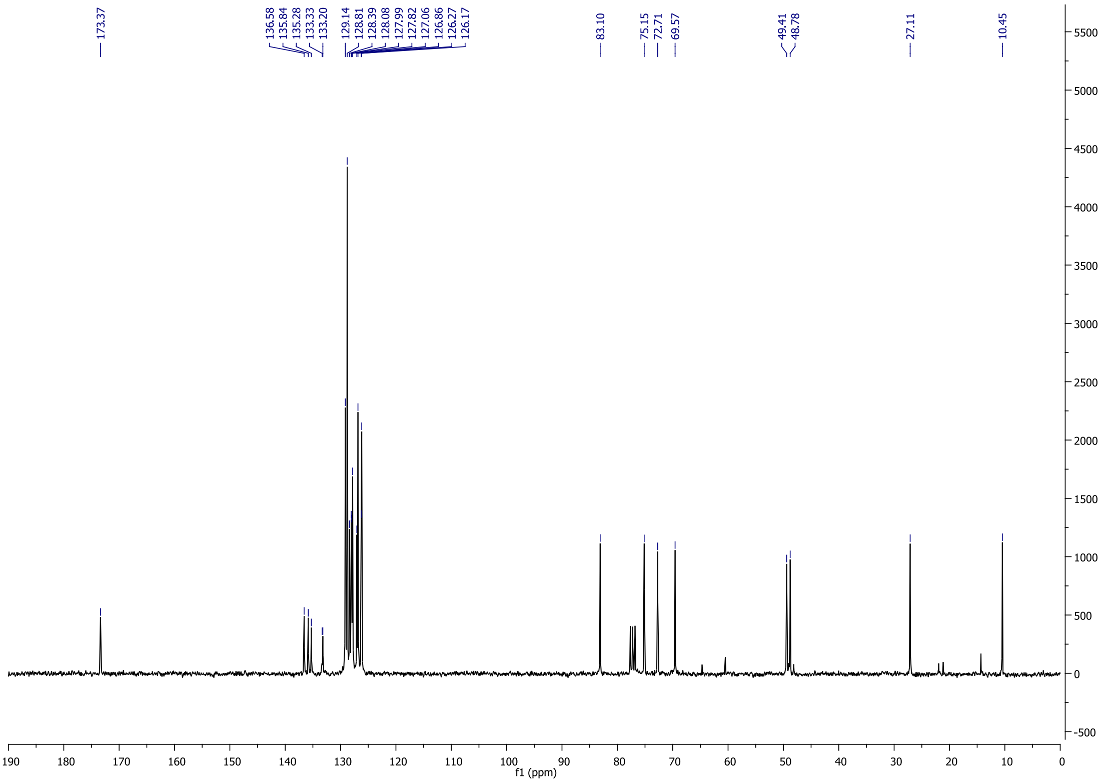

183.95
183.21
169.30
168.09
160.58
158.10
148.57
145.44
137.99
129.53
129.15
128.96
124.42
121.03
115.79
115.52
102.39
71.03
67.89
61.05
56.86
56.65
54.66
41.95
40.23
37.00
28.84
25.65
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0

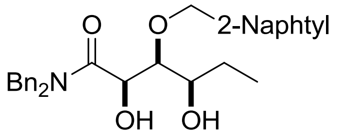
5.8.6. Aldol adducts 21


O
O
2-Naphtyl
Ph
Bn2N
OH
OH

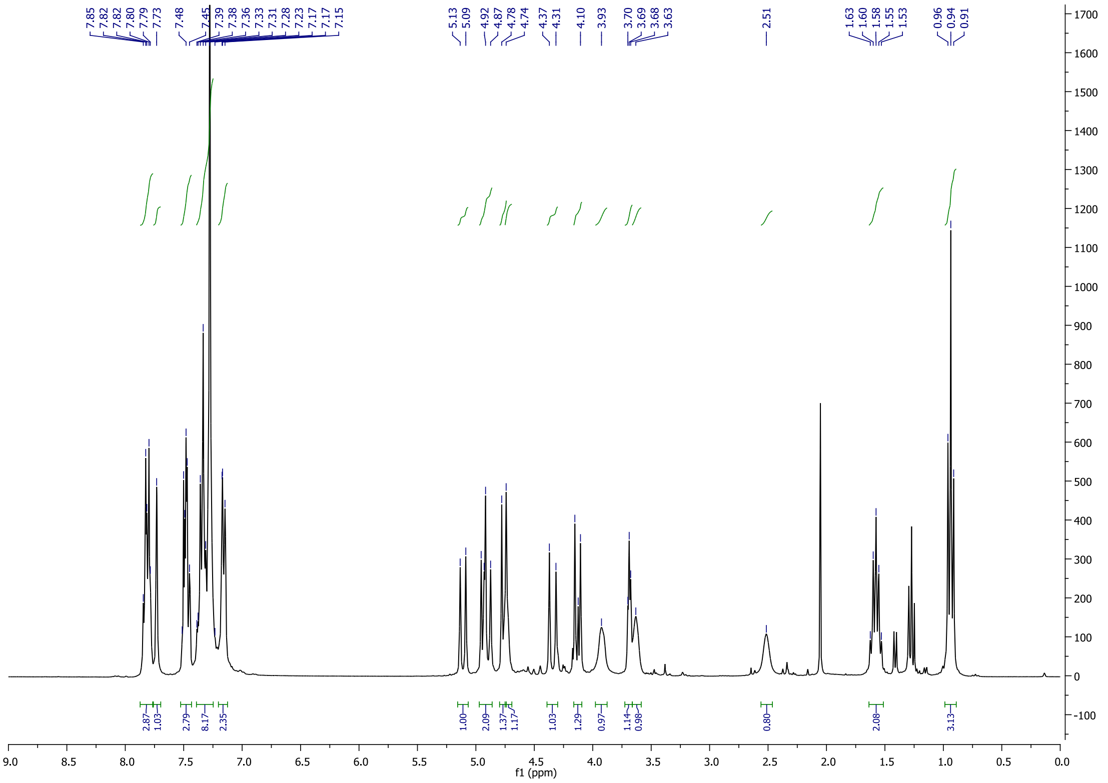
21a

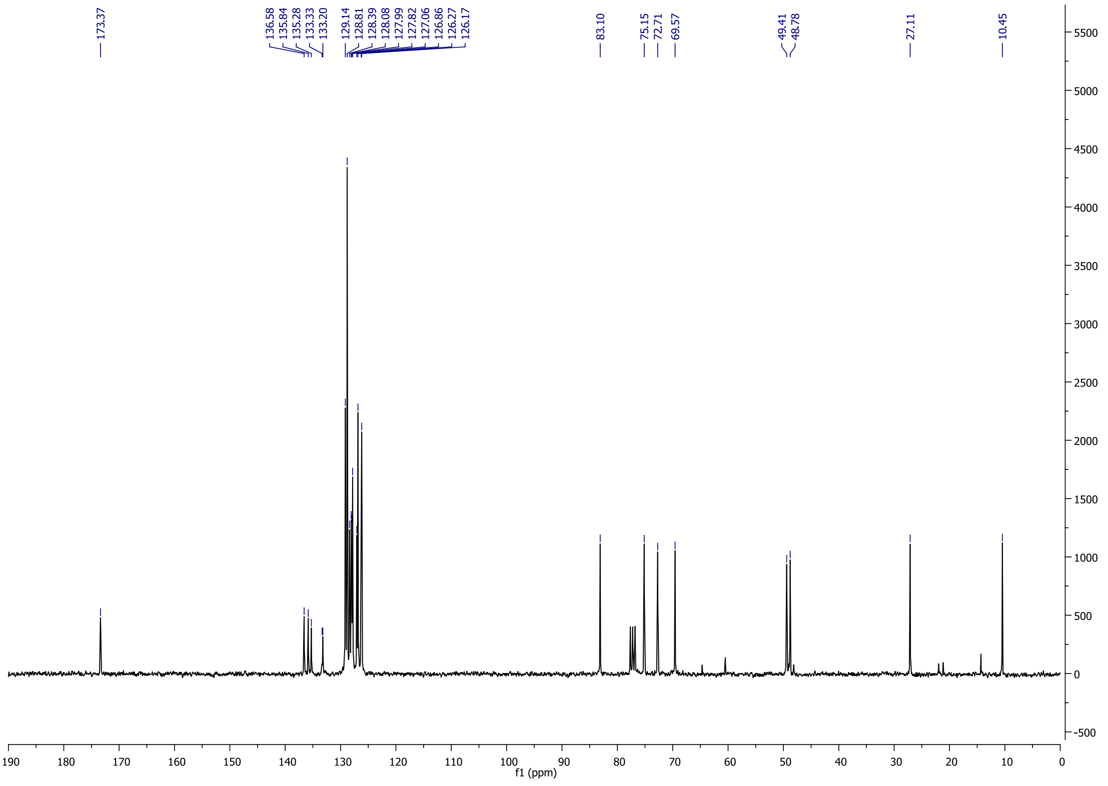


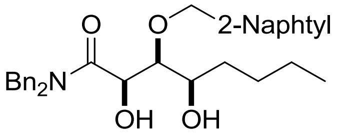



O
O
2-Naphtyl
Bn2N
OH
OH

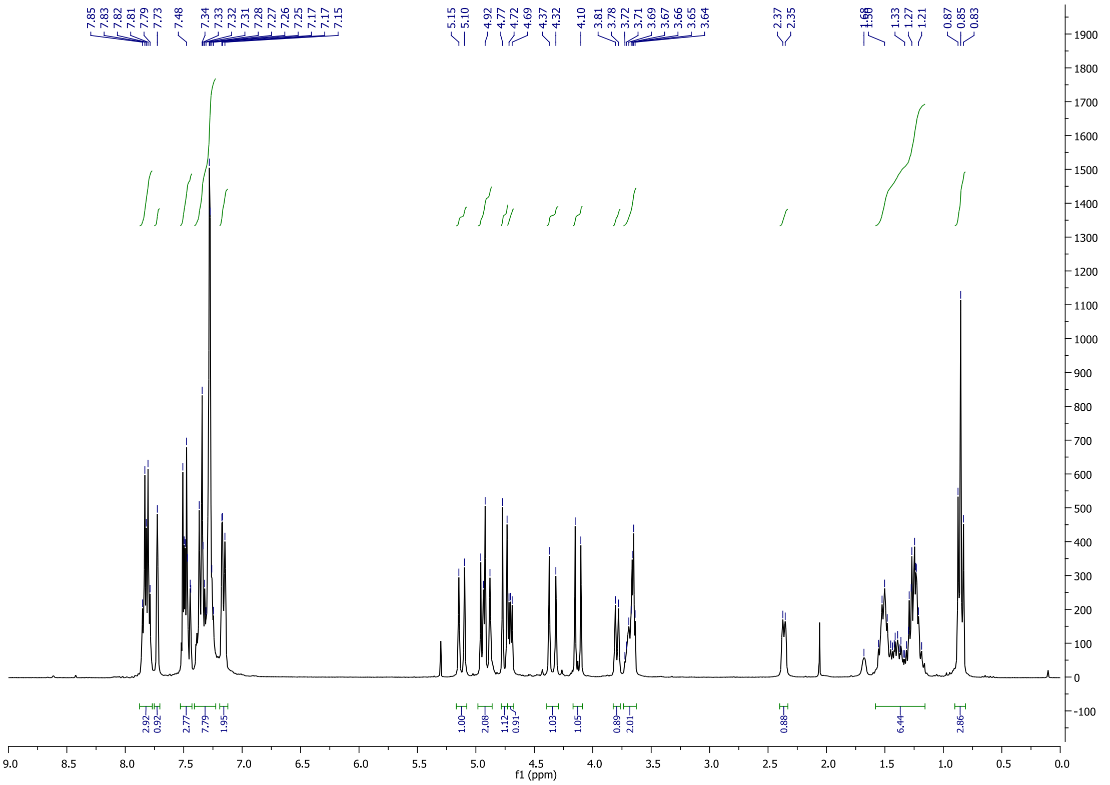
21c

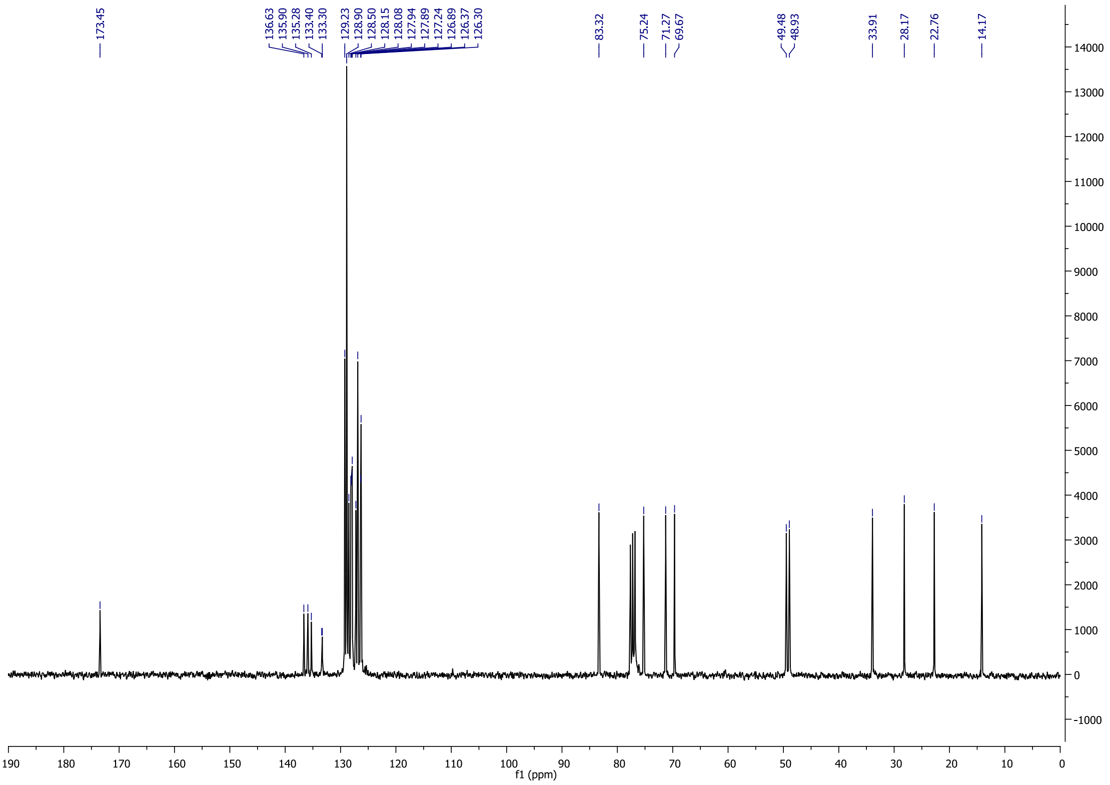

7.85
7.82
7.82
7.80
7.79
7.73
7.48
7.45
7.39
7.38
7.36
7.33
7.31
7.28
7.23
7.17
7.17
7.15
5.13
5.09
4.92
4.87
4.78
4.74
4.37
4.31
4.10
3.93
3.70
3.69
3.68
3.63
2.51
1.63
1.60
1.58
1.55
1.53
0.96
0.94
0.91
2.87
1.03
2.79
8.17
2.35
1.00
2.09
1.37
1.17
1.03
1.29
0.97
1.14
0.98
0.80
2.08
3.13
f1 (ppm)

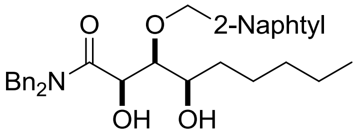

173.37
136.58
135.84
135.28
133.33
133.20
129.14
128.81
128.39
128.08
127.99
127.82
127.06
126.86
126.27
126.17
83.10
75.15
72.71
69.57
49.41
48.78
27.11
10.45
f1 (ppm)


O
O
2-Naphtyl
Bn2N
OH
OH

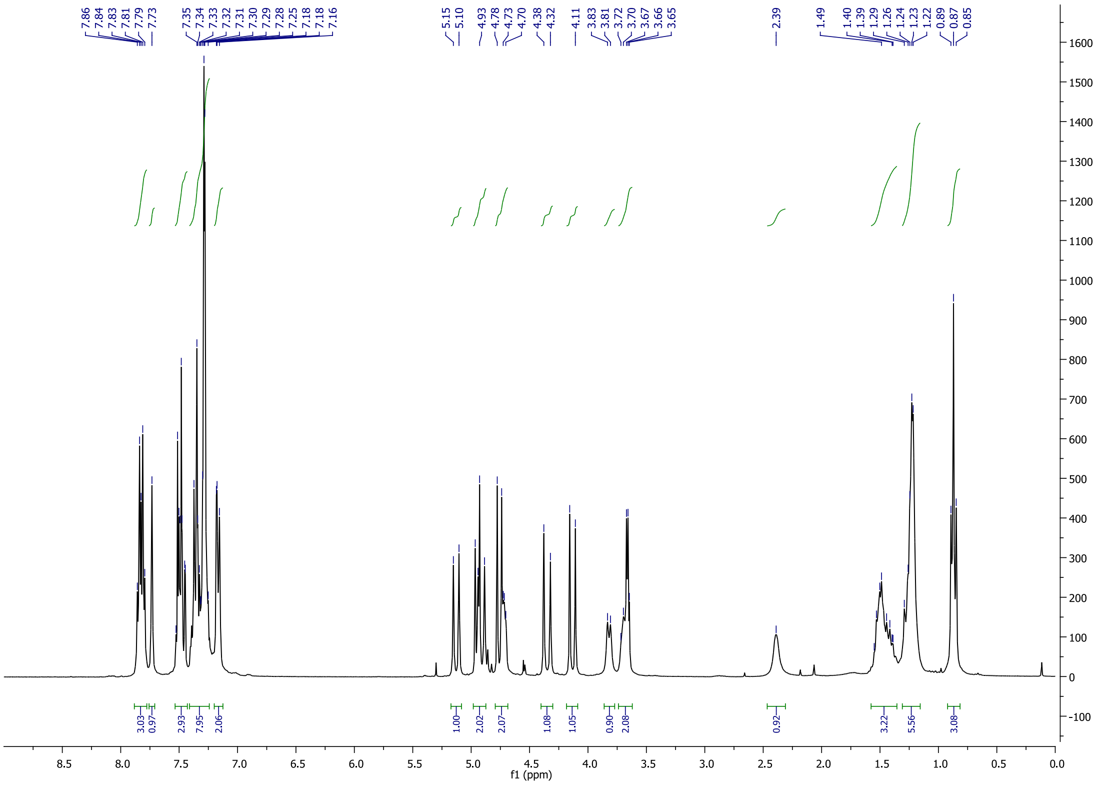
21b

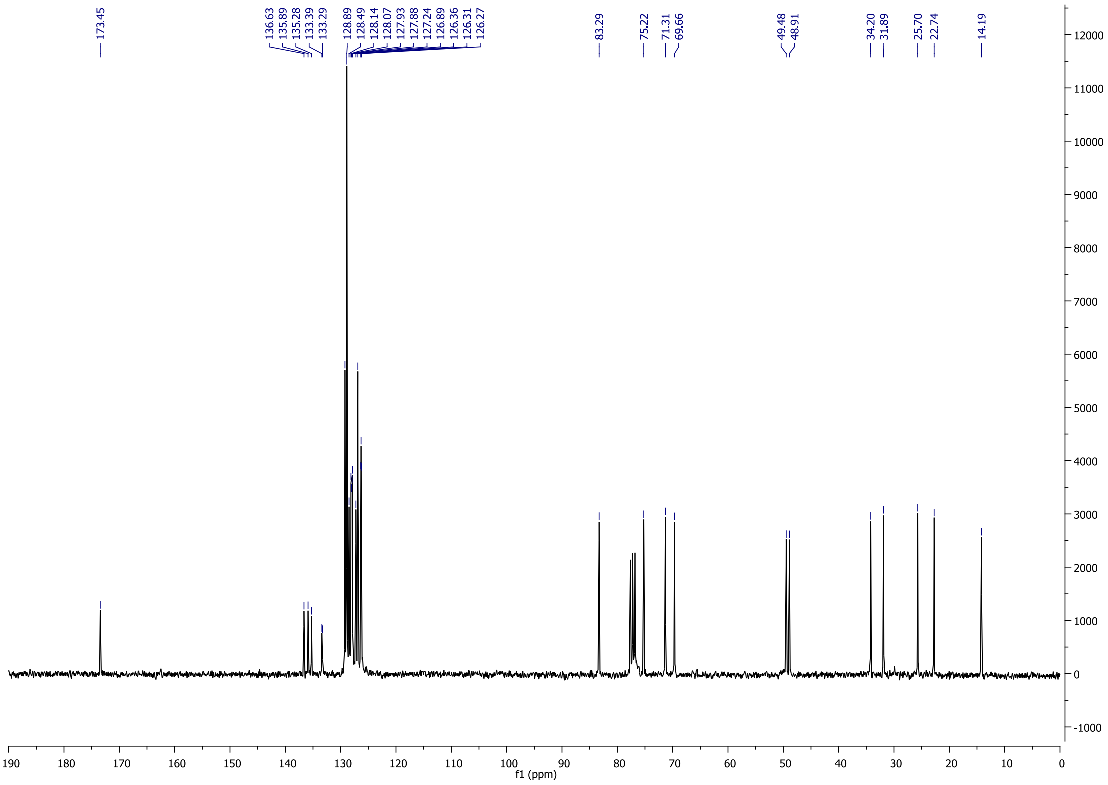

7.85
7.83
7.82
7.81
7.79
7.73
7.48
7.34
7.33
7.32
7.31
7.28
7.27
7.26
7.25
7.17
7.17
7.15
5.15
5.10
4.92
4.77
4.72
4.69
4.37
4.32
4.10
3.81
3.78
3.72
3.71
3.69
3.67
3.66
3.65
3.64
2.37
2.35
1.68
1.50
1.33
1.27
1.21
0.87
0.85
0.83
2.92
0.92
2.77
7.79
1.95
1.00
2.08
1.12
0.91
1.03
1.05
0.89
2.01
0.88
6.44
2.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

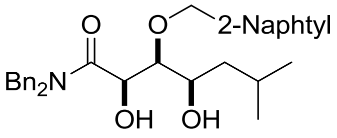

173.45
136.63
135.90
135.28
133.40
133.30
129.23
128.90
128.50
128.15
128.08
127.94
127.89
127.24
126.89
126.37
126.30
83.32
75.24
71.27
69.67
49.48
48.93
33.91
28.17
22.76
14.17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


O
O
2-Naphtyl
Bn2N
OH
OH

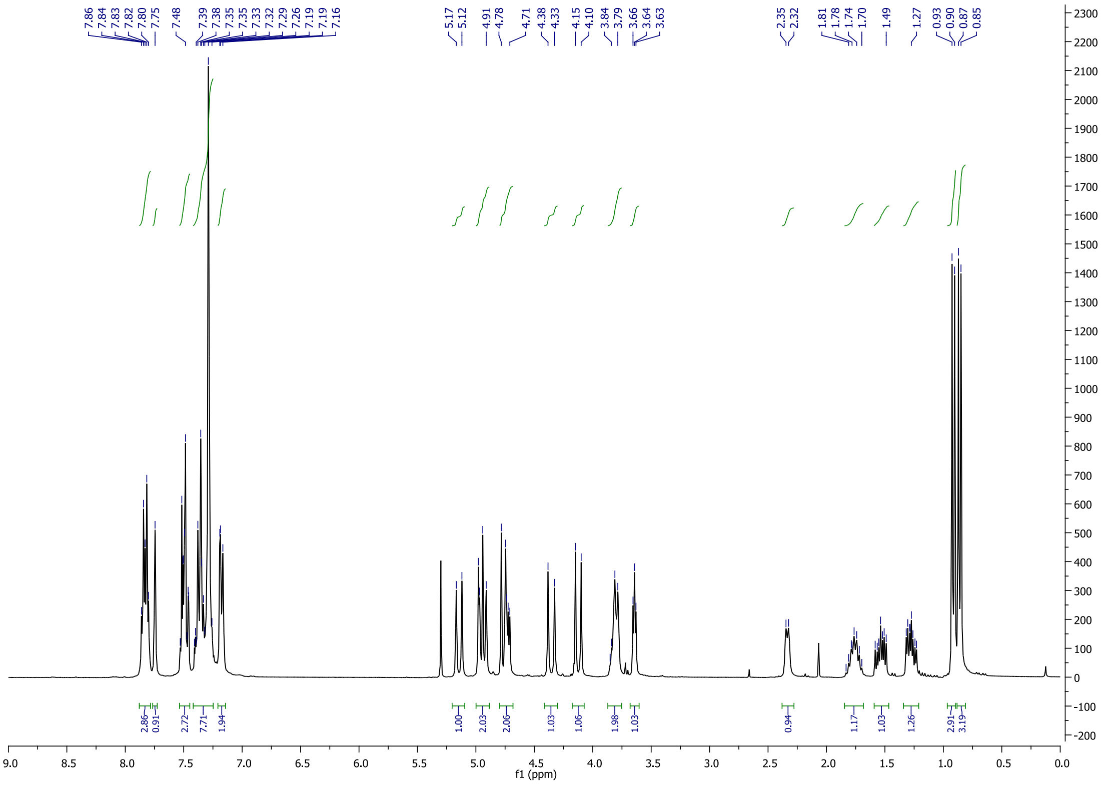
21d

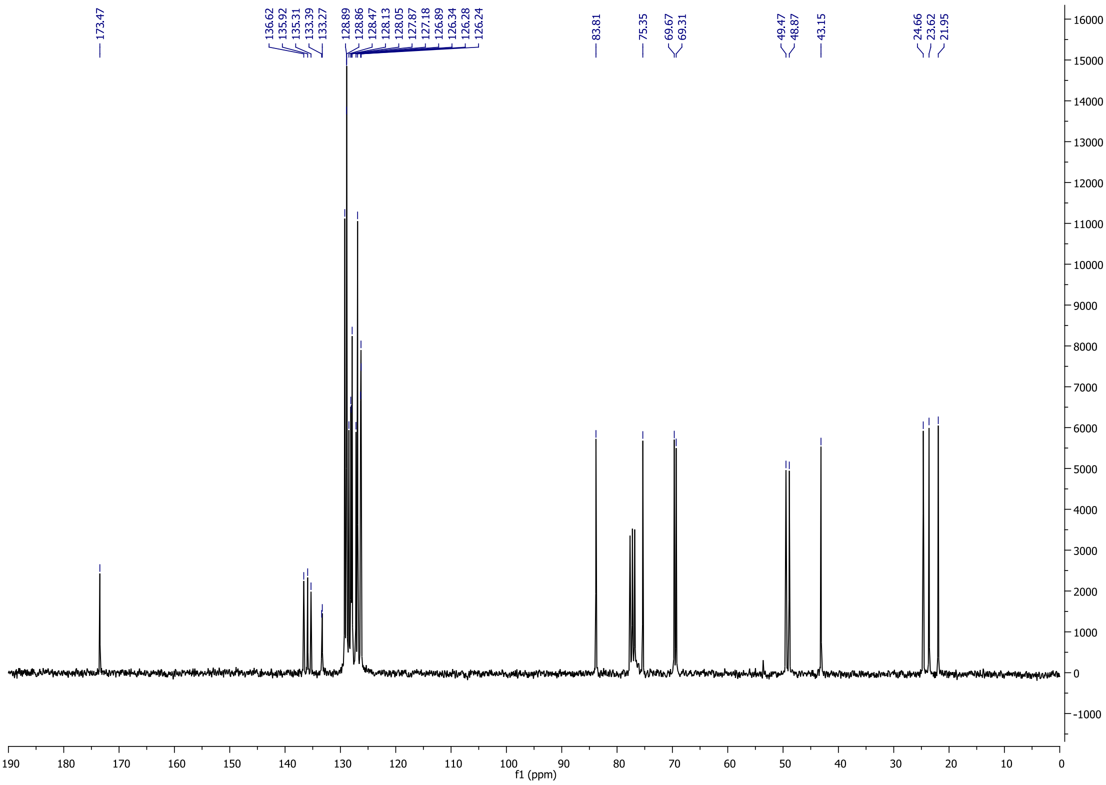

7.86
7.84
7.83
7.81
7.79
7.73
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.25
7.18
7.18
7.16
5.15
5.10
4.93
4.78
4.73
4.70
4.38
4.32
4.11
3.83
3.81
3.72
3.70
3.67
3.66
3.65
2.39
1.49
1.40
1.39
1.29
1.26
1.24
1.23
1.22
0.89
0.87
0.85
3.03
0.97
2.93
7.95
2.06
1.00
2.02
2.07
1.08
1.05
0.90
2.08
0.92
3.22
5.56
3.08
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

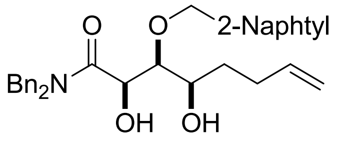

173.45
136.63
135.89
135.28
133.39
133.29
128.89
128.49
128.14
128.07
127.93
127.88
127.24
126.89
126.36
126.31
126.27
83.29
75.22
71.31
69.66
49.48
48.91
34.20
31.89
25.70
22.74
14.19
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
2-Naphtyl
Bn2N
OH
OH

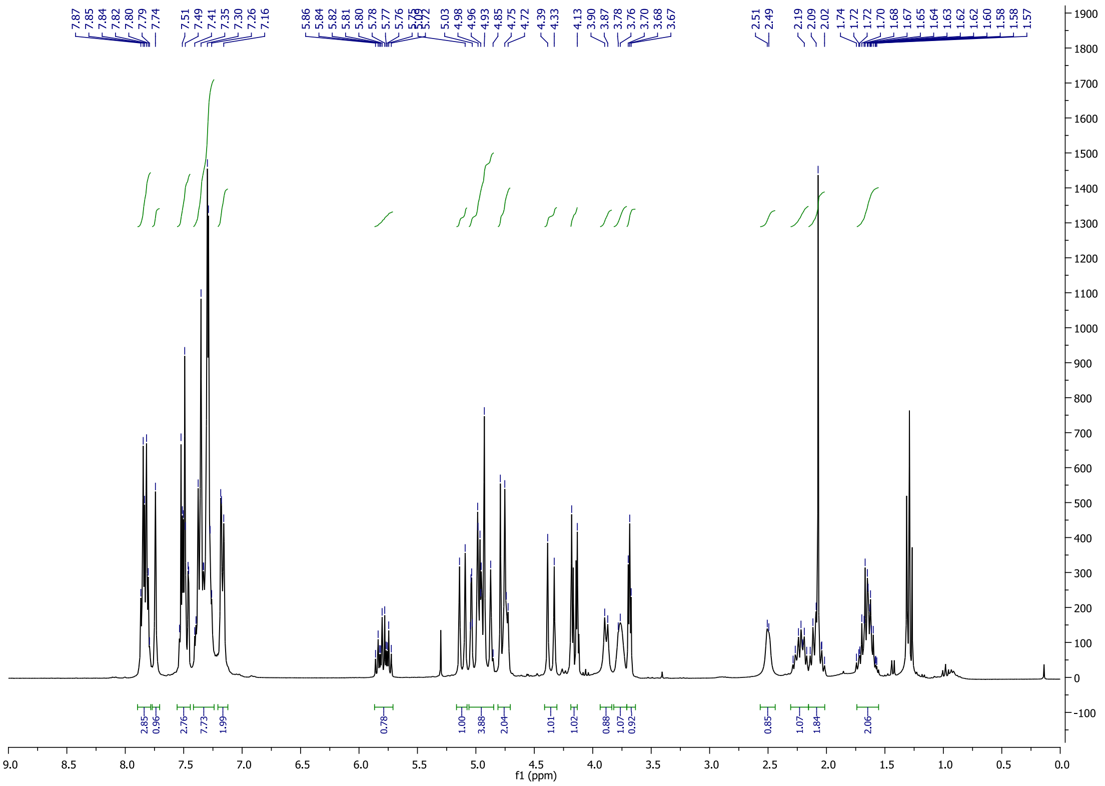
21e

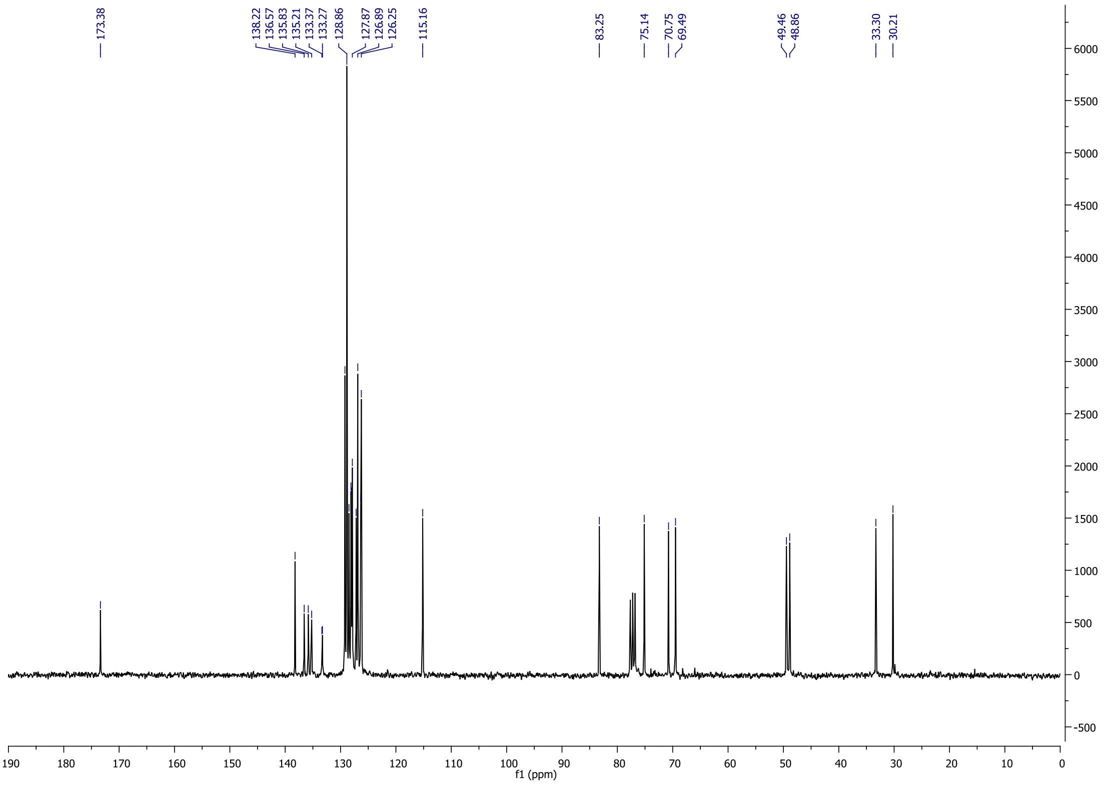

7.86
7.84
7.83
7.82
7.80
7.75
7.48
7.39
7.38
7.35
7.35
7.33
7.32
7.29
7.26
7.19
7.19
7.16
5.17
5.12
4.91
4.78
4.71
4.38
4.33
4.15
4.10
3.84
3.79
3.66
3.64
3.63
2.35
2.32
1.81
1.78
1.74
1.70
1.49
1.27
0.93
0.90
0.87
0.85
2.86
0.91
2.72
7.71
1.94
1.00
2.03
2.06
1.03
1.06
1.98
1.03
0.94
1.17
1.03
1.26
2.91
3.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

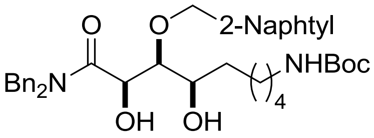

173.47
136.62
135.92
135.31
133.39
133.27
128.89
128.86
128.47
128.13
128.05
127.87
127.18
126.89
126.34
126.28
126.24
83.81
75.35
69.67
69.31
49.47
48.87
43.15
24.66
23.62
21.95
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


O
O
2-Naphtyl
Bn2N
OH
OH

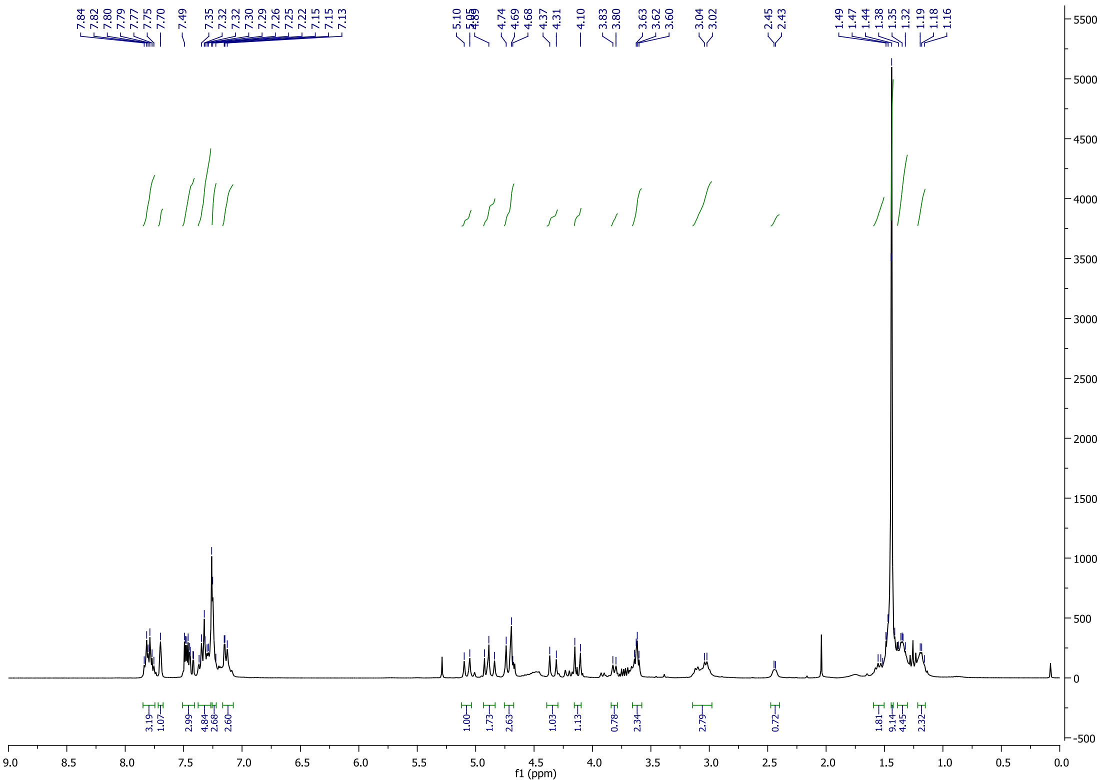
21f

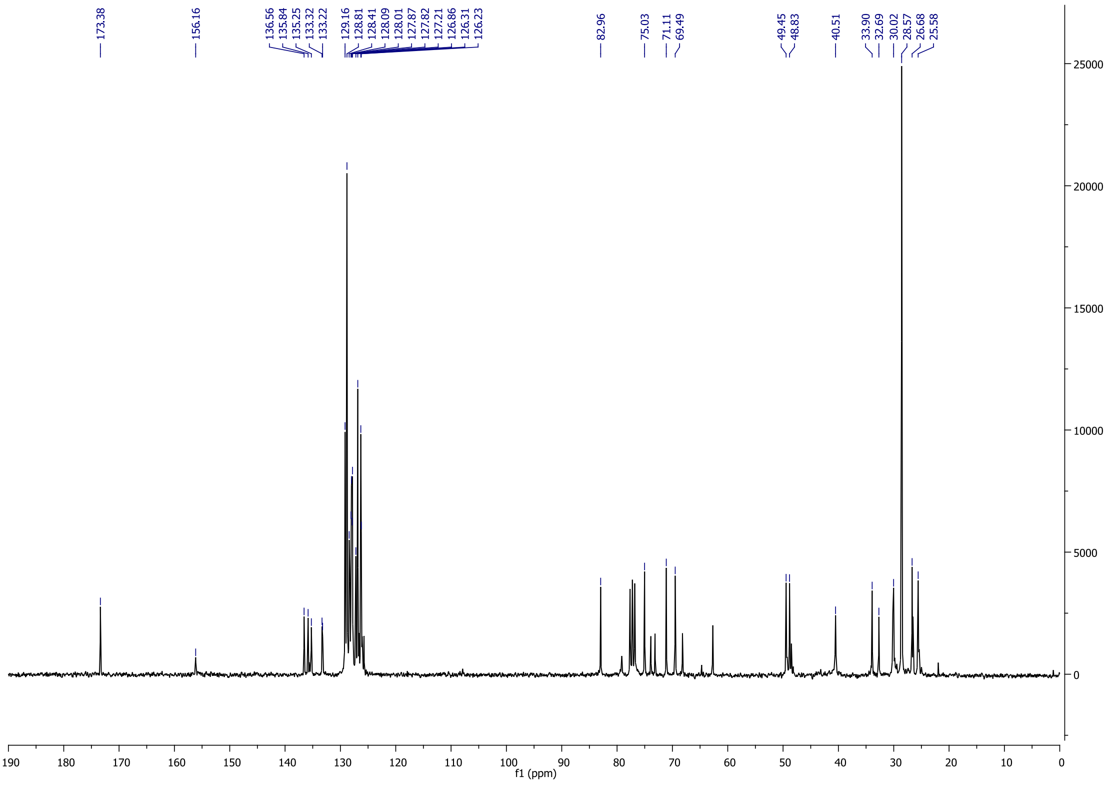

7.87
7.85
7.84
7.82
7.80
7.79
7.74
7.51
7.49
7.41
7.35
7.30
7.26
7.16
5.86
5.84
5.82
5.81
5.80
5.78
5.77
5.76
5.75
5.73
5.72
5.03
4.98
4.96
4.93
4.85
4.75
4.72
4.39
4.33
4.13
3.90
3.87
3.78
3.76
3.70
3.68
3.67
2.51
2.49
2.19
2.09
2.02
1.74
1.72
1.72
1.70
1.68
1.68
1.67
1.65
1.64
1.63
1.62
1.62
1.60
1.58
1.58
1.57
2.85
0.96
2.76
7.73
1.99
0.78
1.00
3.88
2.04
1.01
1.02
0.88
1.07
0.92
0.85
1.07
1.84
2.06
f1 (ppm)

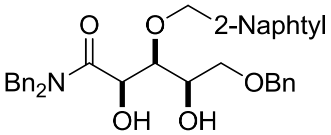

173.38
138.22
136.57
135.83
135.21
133.37
133.27
128.86
127.87
126.89
126.25
115.16
83.25
75.14
70.75
69.49
49.46
48.86
33.30
30.21
f1 (ppm)


O
O
2-Naphtyl
NHBoc
Bn2N
OH
OH
4

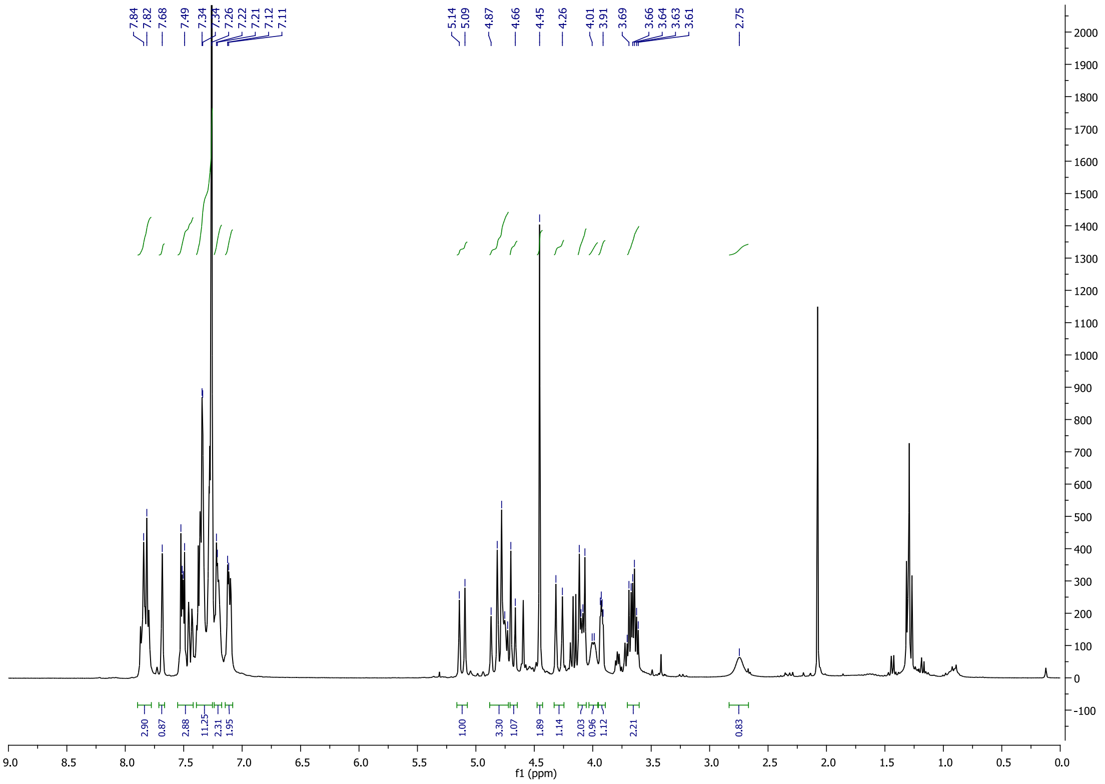
21g

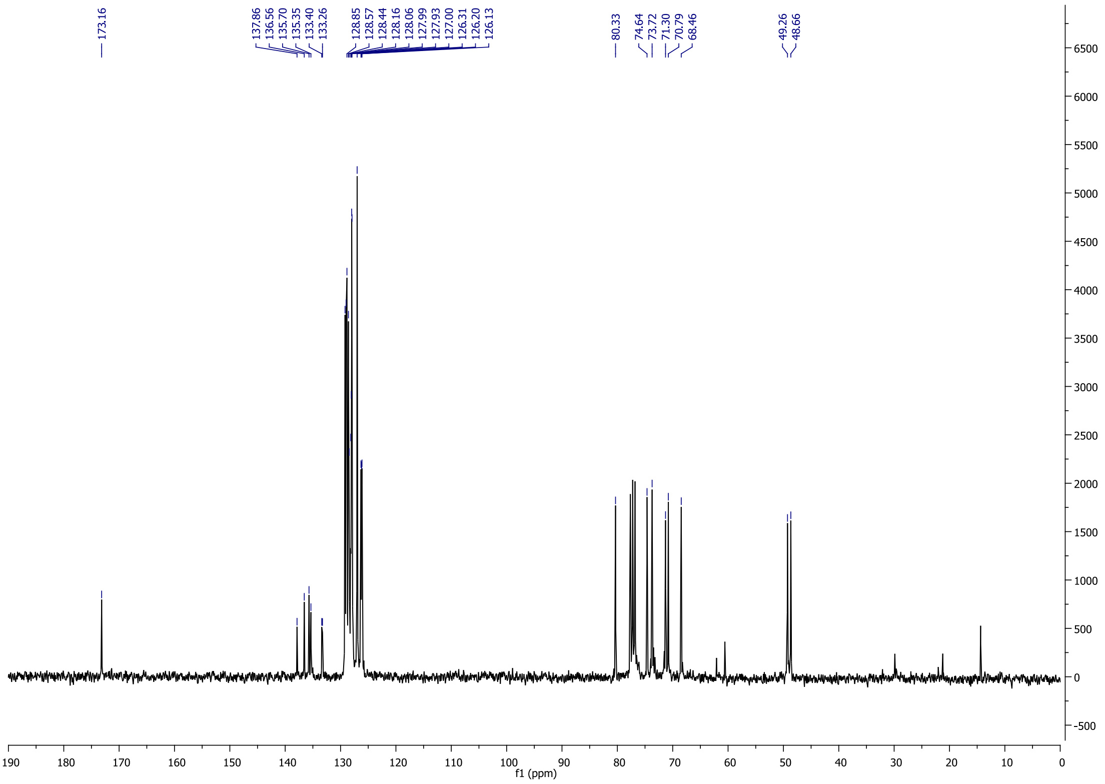

7.84
7.82
7.80
7.79
7.77
7.75
7.70
7.49
7.35
7.32
7.32
7.30
7.29
7.26
7.25
7.22
7.15
7.15
7.13
5.10
5.05
4.99
4.74
4.69
4.68
4.37
4.31
4.10
3.83
3.80
3.63
3.62
3.60
3.04
3.02
2.45
2.43
1.49
1.47
1.44
1.38
1.35
1.32
1.19
1.18
1.16
3.19
1.07
2.99
4.84
2.68
2.60
1.00
1.73
2.63
1.03
1.13
0.78
2.34
2.79
0.72
1.81
9.14
4.45
2.32
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

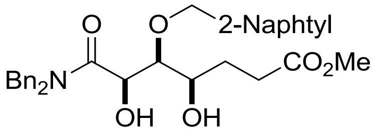

173.38
156.16
136.56
135.84
135.25
133.32
133.22
129.16
128.81
128.41
128.09
128.01
127.87
127.82
127.21
126.86
126.31
126.23
82.96
75.03
71.11
69.49
49.45
48.83
40.51
33.90
32.69
30.02
28.57
26.68
25.58
25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
2-Naphtyl
Bn2N
OBn
OH
OH

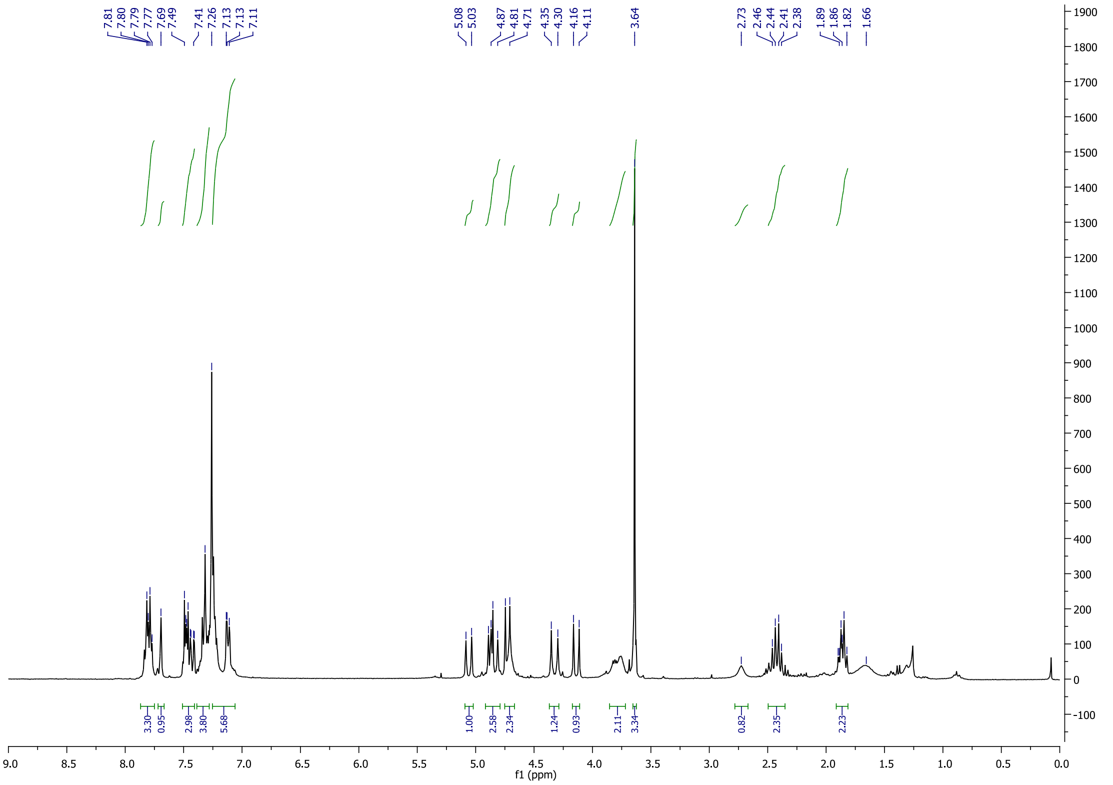
21h

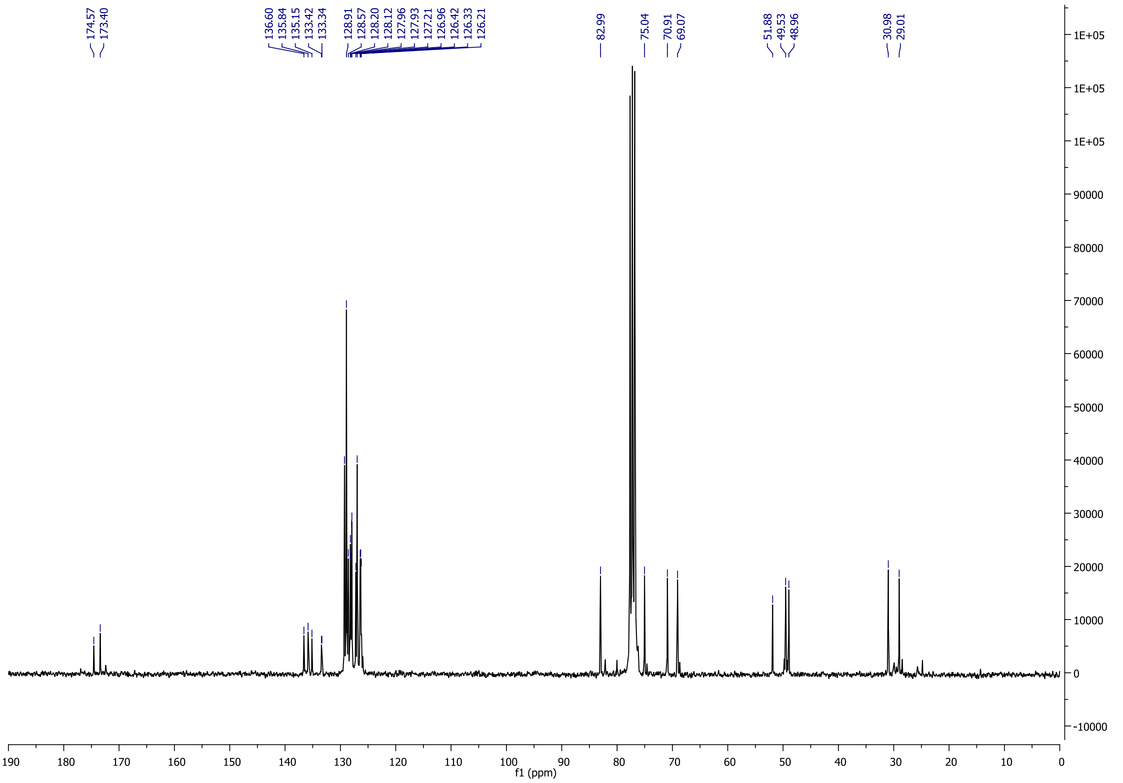

7.84
7.82
7.68
7.49
7.34
7.34
7.26
7.22
7.21
7.12
7.11
5.14
5.09
4.87
4.66
4.45
4.26
4.01
3.91
3.69
3.66
3.64
3.63
3.61
2.75
2.90
0.87
2.88
11.25
2.31
1.95
1.00
3.30
1.07
1.89
1.14
2.03
0.96
1.12
2.21
0.83
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

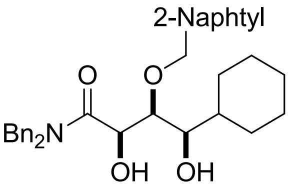

173.16
137.86
136.56
135.70
135.35
133.40
133.26
128.85
128.57
128.44
128.16
128.06
127.99
127.93
127.00
126.31
126.20
126.13
80.33
74.64
73.72
71.30
70.79
68.46
49.26
48.66
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


O
O
2-Naphtyl
CO2Me
Bn2N
OH
OH

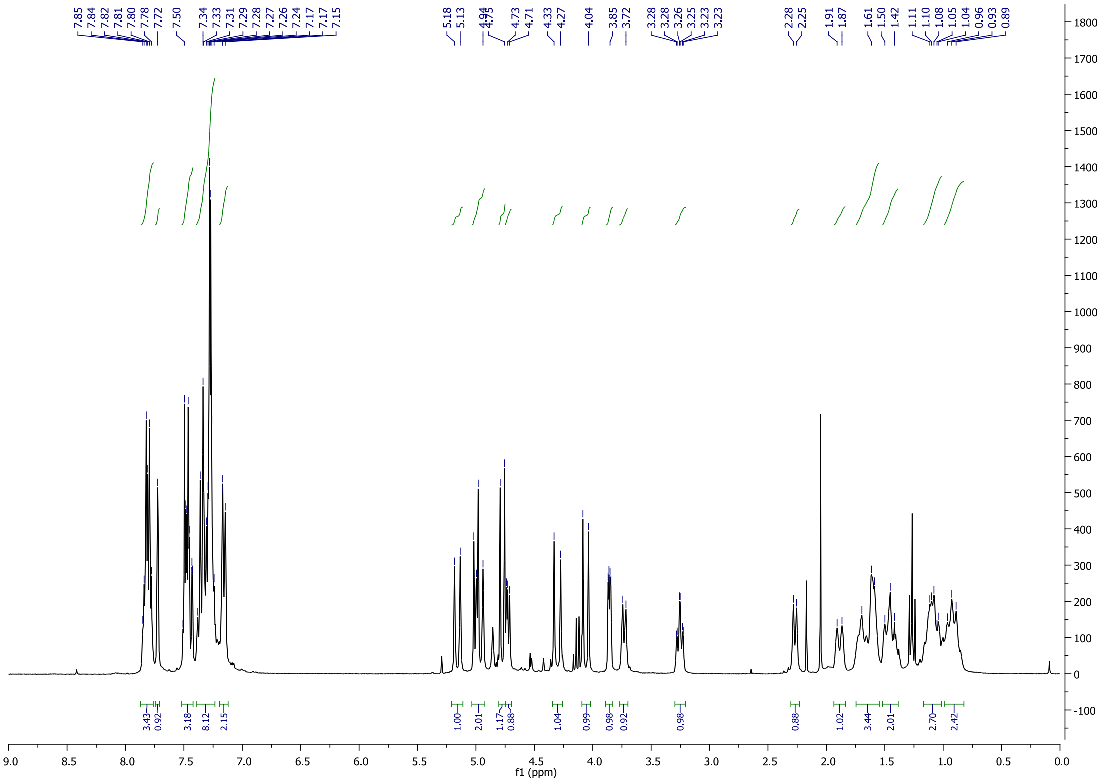
21i

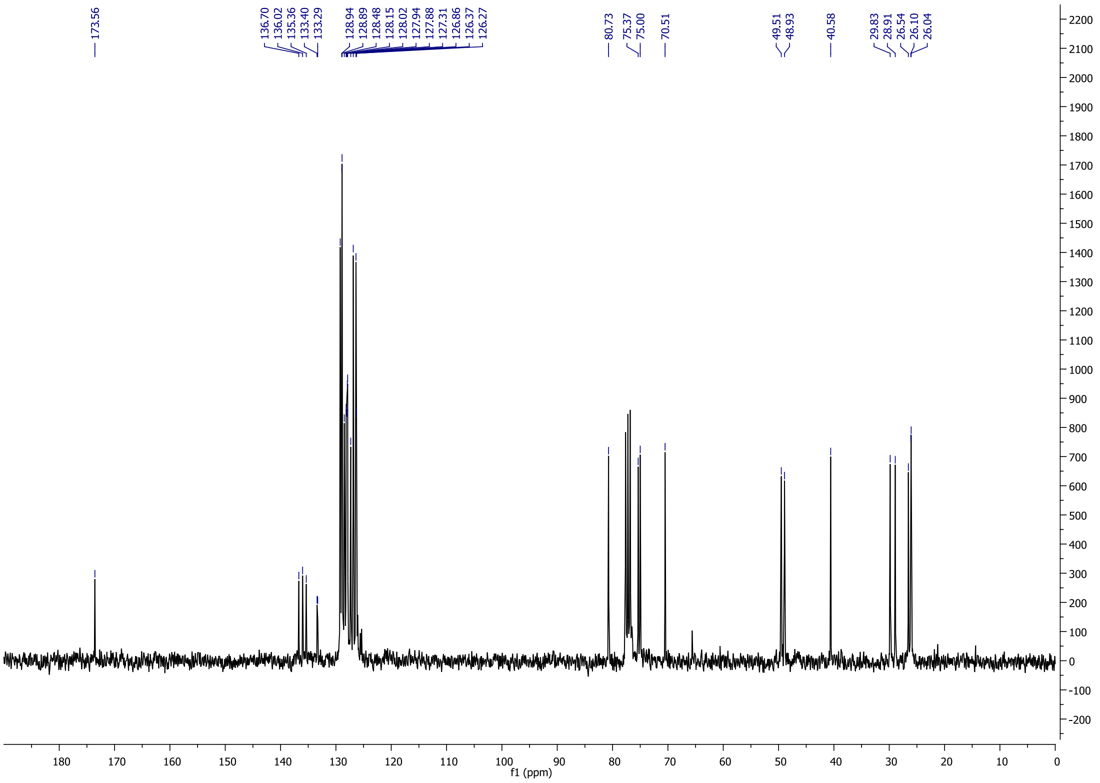

7.81
7.80
7.79
7.77
7.69
7.49
7.41
7.26
7.13
7.13
7.11
5.08
5.03
4.87
4.81
4.71
4.35
4.30
4.16
4.11
3.64
2.73
2.46
2.44
2.41
2.38
1.89
1.86
1.82
1.66
3.30
0.95
2.98
3.80
5.68
1.00
2.58
2.34
1.24
0.93
2.11
3.34
0.82
2.35
2.23
f1 (ppm)

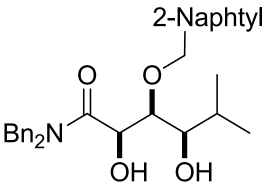

174.57
173.40
136.60
135.84
135.15
133.42
133.34
128.91
128.57
128.20
128.12
127.96
127.93
127.21
126.96
126.42
126.33
126.21
82.99
75.04
70.91
69.07
51.88
49.53
48.96
30.98
29.01
f1 (ppm)


2-Naphtyl
O
O
Bn2N
OH
OH

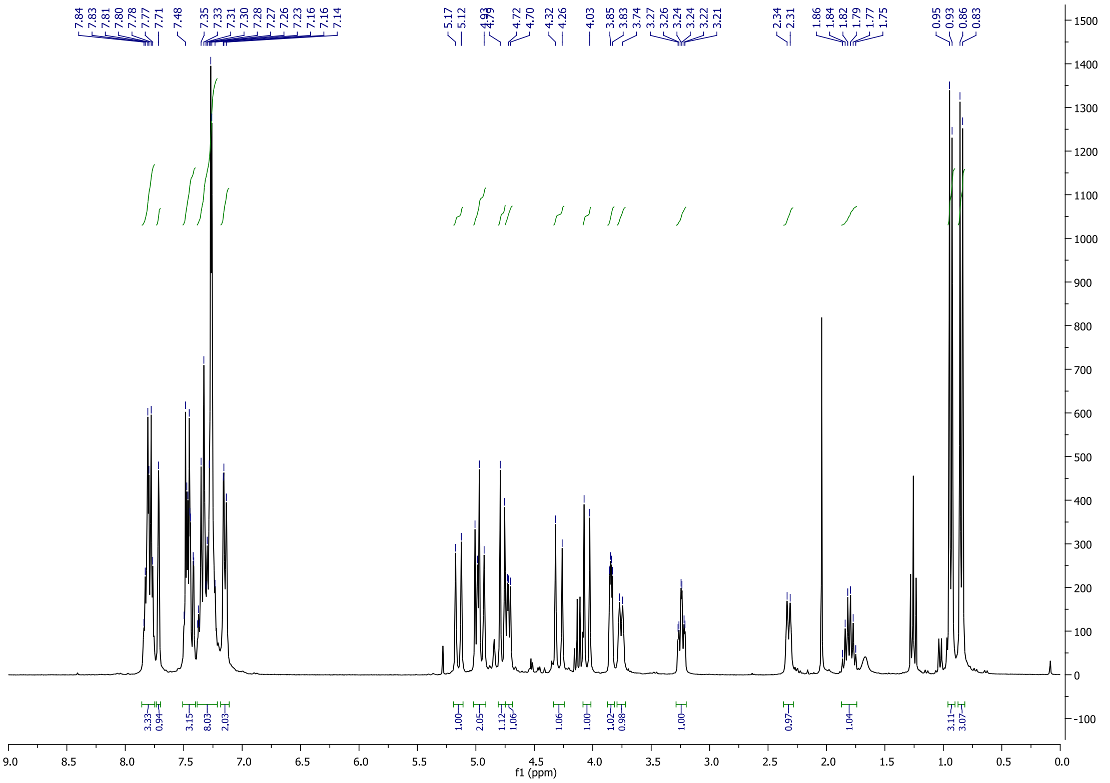
21j

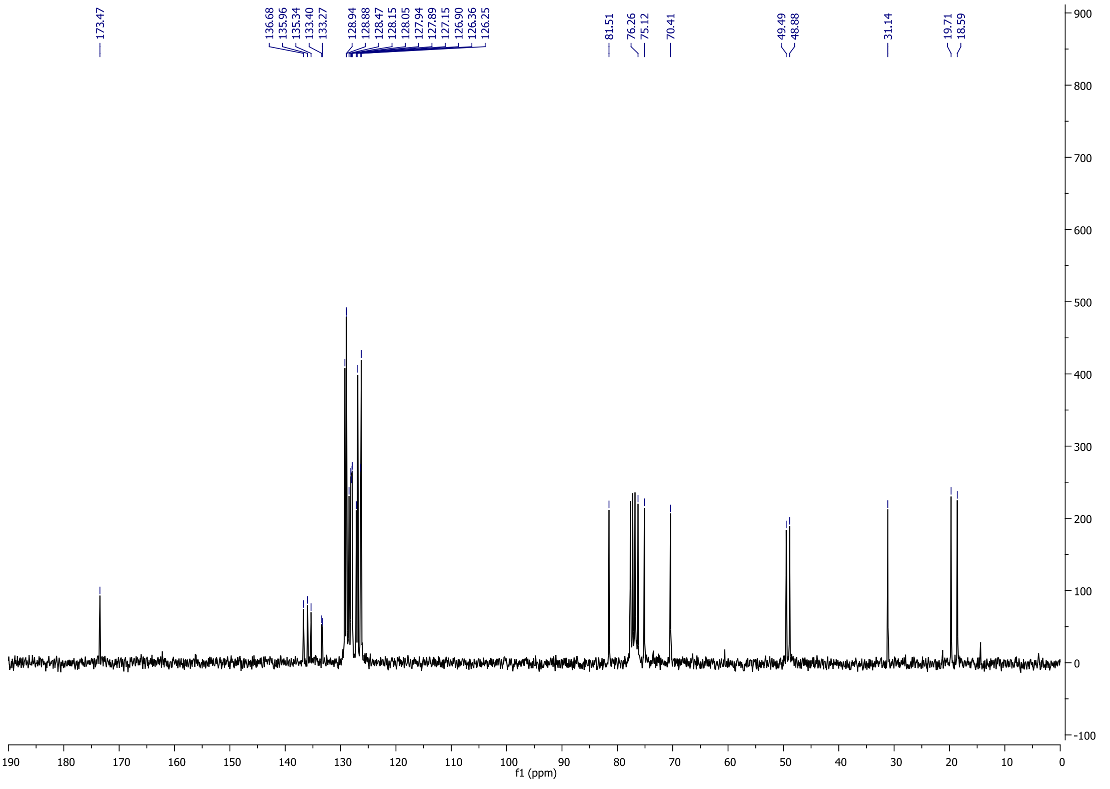

7.85
7.84
7.82
7.81
7.80
7.78
7.72
7.50
7.34
7.33
7.31
7.29
7.28
7.27
7.26
7.24
7.17
7.17
7.15
5.18
5.13
4.94
4.95
4.73
4.71
4.33
4.27
4.04
3.85
3.72
3.28
3.28
3.26
3.25
3.23
3.23
2.28
2.25
1.91
1.87
1.61
1.50
1.42
1.11
1.10
1.08
1.05
1.04
0.96
0.93
0.89
3.43
0.92
3.18
8.12
2.15
1.00
2.01
1.17
0.88
1.04
0.99
0.98
0.92
0.98
0.88
1.02
3.44
2.01
2.70
2.42
f1 (ppm)


173.56
136.70
136.02
135.36
133.40
133.29
128.94
128.89
128.48
128.15
128.02
127.94
127.88
127.31
126.86
126.37
126.27
80.73
75.37
75.00
70.51
49.51
48.93
40.58
29.83
28.91
26.54
26.10
26.04
f1 (ppm)

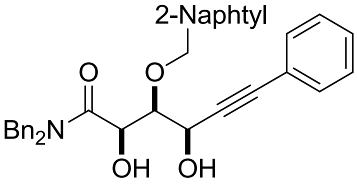

2-Naphtyl
O
O
Bn2N
OH
OH

21k

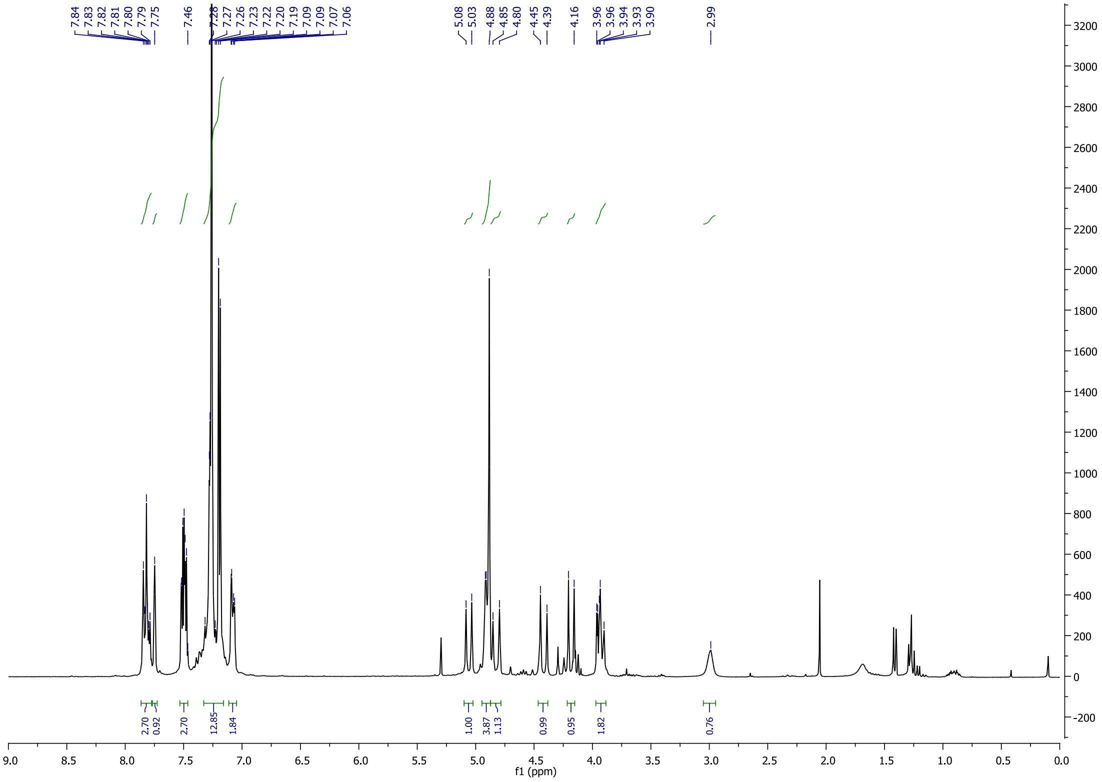

7.84
7.83
7.81
7.80
7.78
7.77
7.71
7.48
7.35
7.33
7.31
7.30
7.28
7.27
7.26
7.23
7.16
7.16
7.14
5.17
5.12
4.93
4.79
4.72
4.70
4.32
4.26
4.03
3.85
3.83
3.74
3.27
3.26
3.24
3.24
3.22
3.21
2.34
2.31
1.86
1.84
1.82
1.79
1.77
1.75
0.95
0.93
0.86
0.83
3.33
0.94
3.15
8.03
2.03
1.00
2.05
1.12
1.06
1.06
1.00
1.02
0.98
1.00
0.97
1.04
3.11
3.07
f1 (ppm)

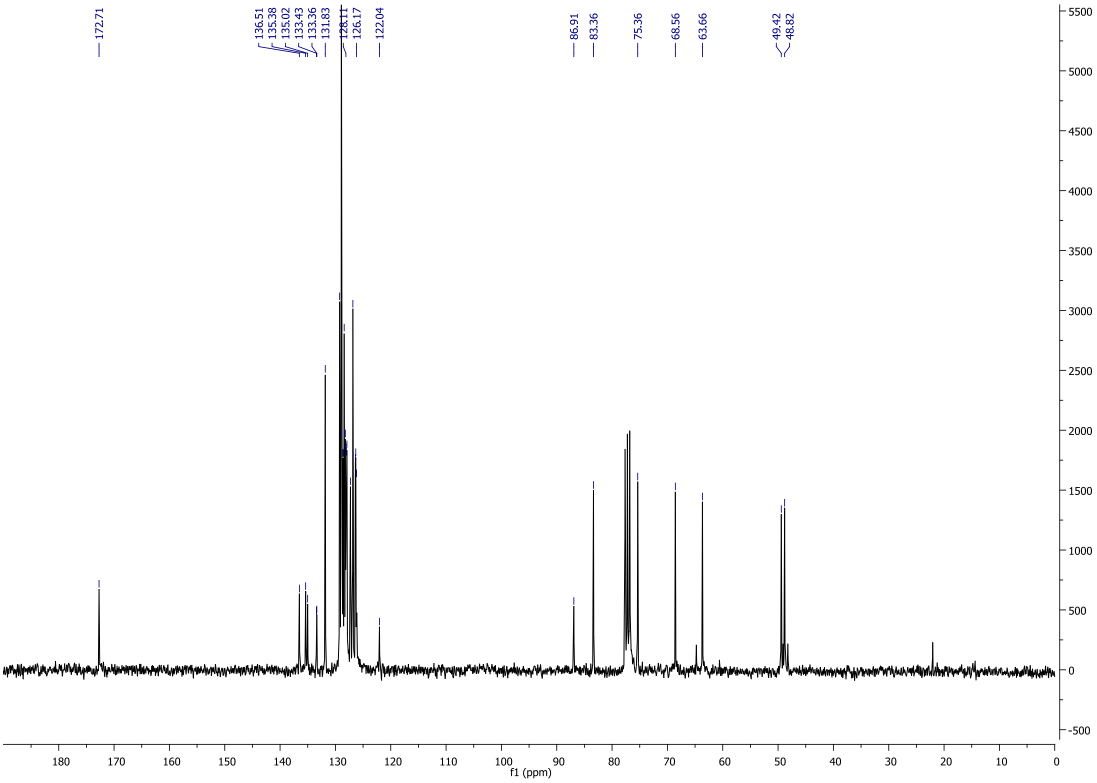

173.47
136.68
135.96
135.34
133.40
133.27
128.94
128.88
128.47
128.15
128.05
127.94
127.89
127.15
126.90
126.36
126.25
81.51
76.26
75.12
70.41
49.49
48.88
31.14
19.71
18.59
f1 (ppm)

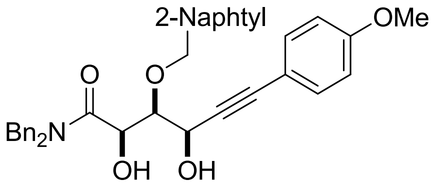
5.8.7. Aldol adducts 22


2-Naphtyl
O
O
Bn$_2$N
OH
OH

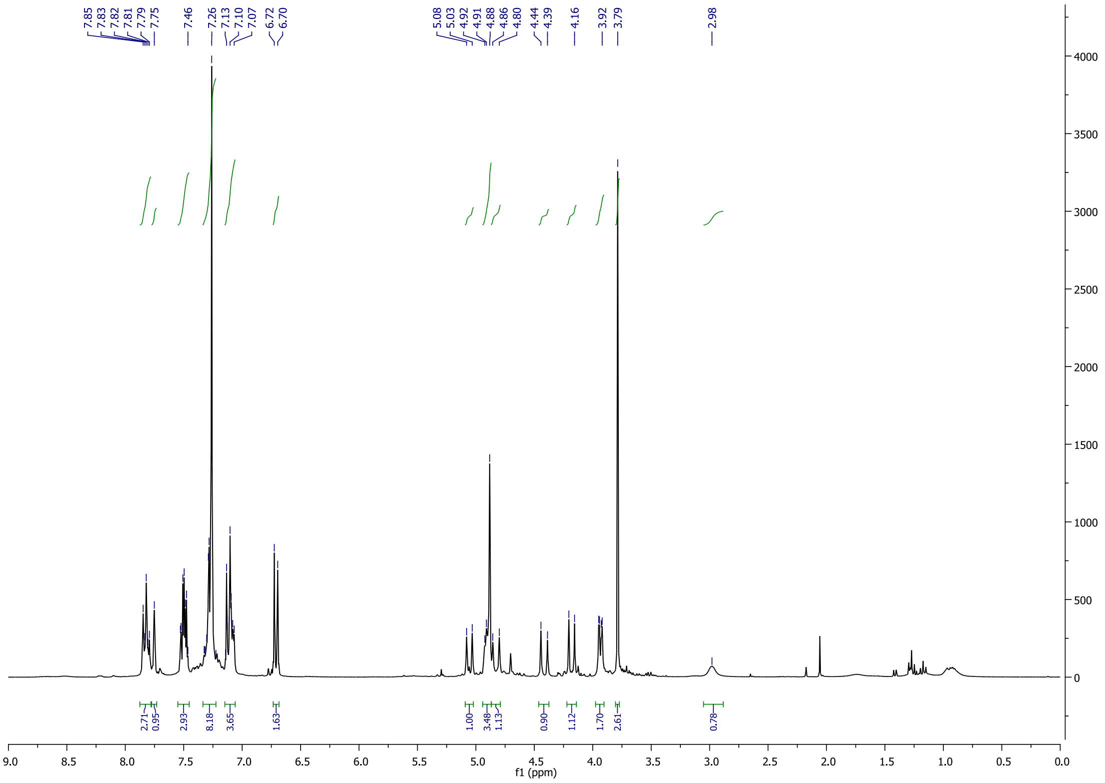
22a

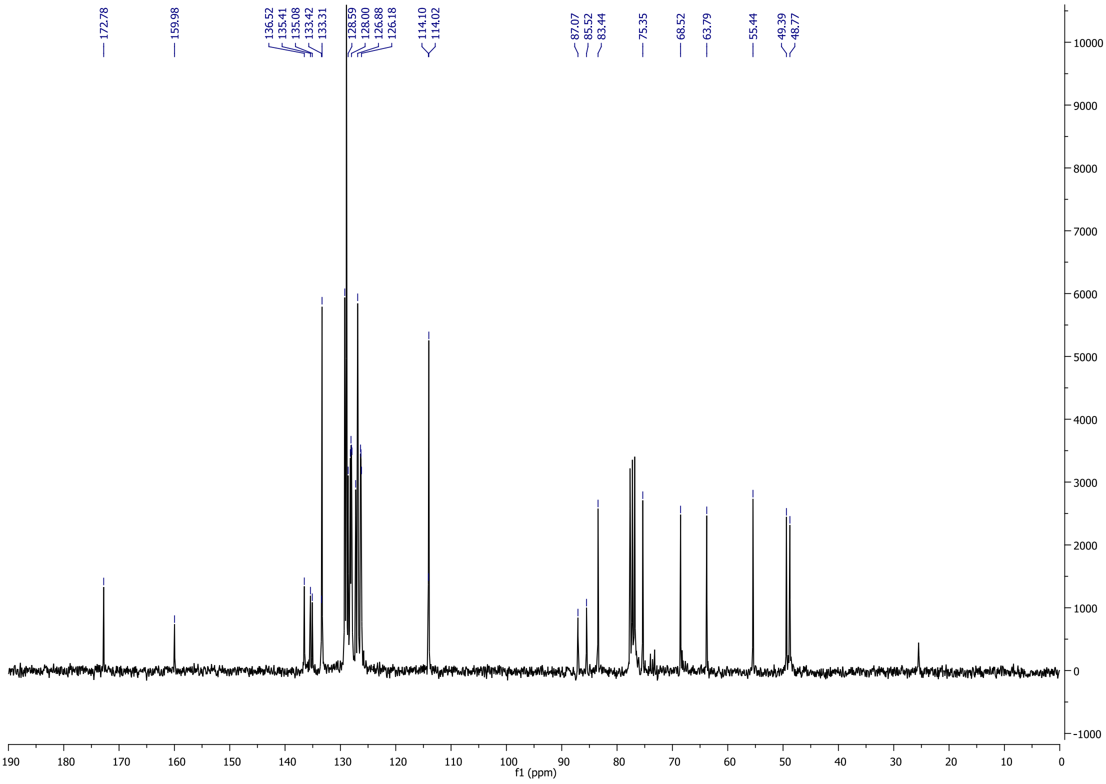


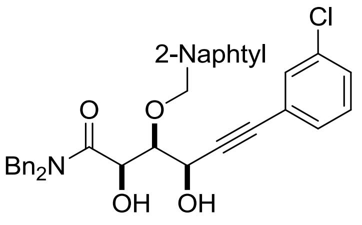



2-Naphtyl
OMe
O
O
Bn$_2$N
OH
OH

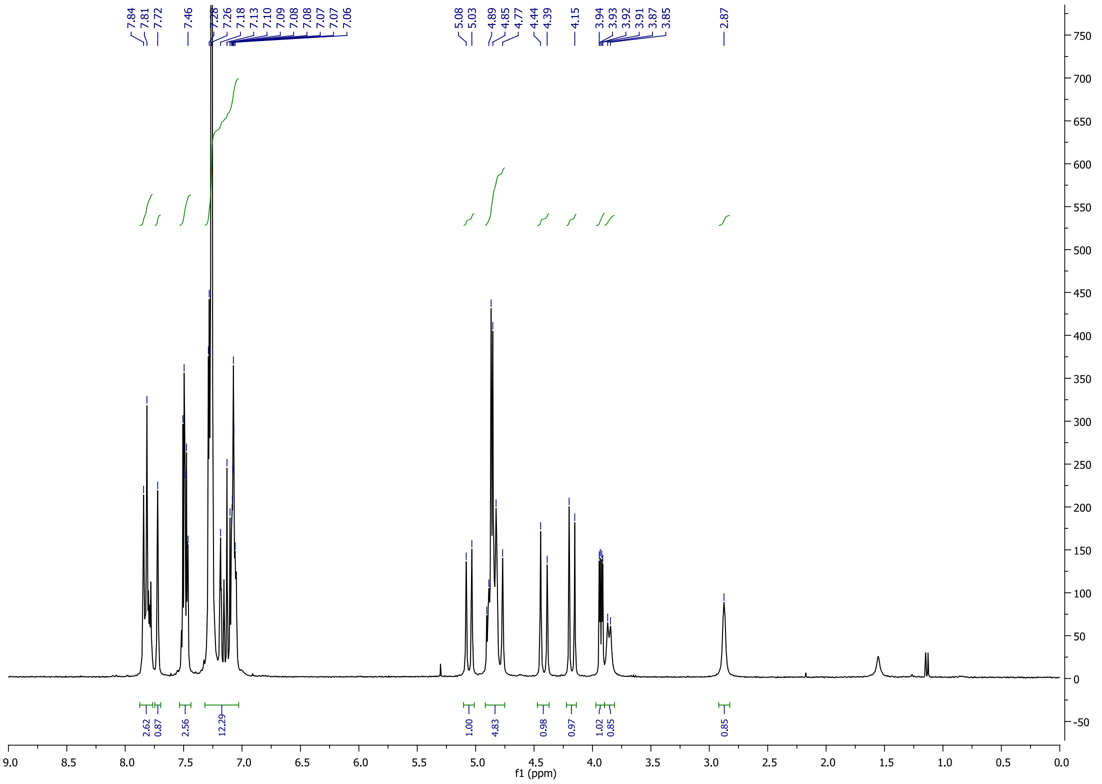
22b

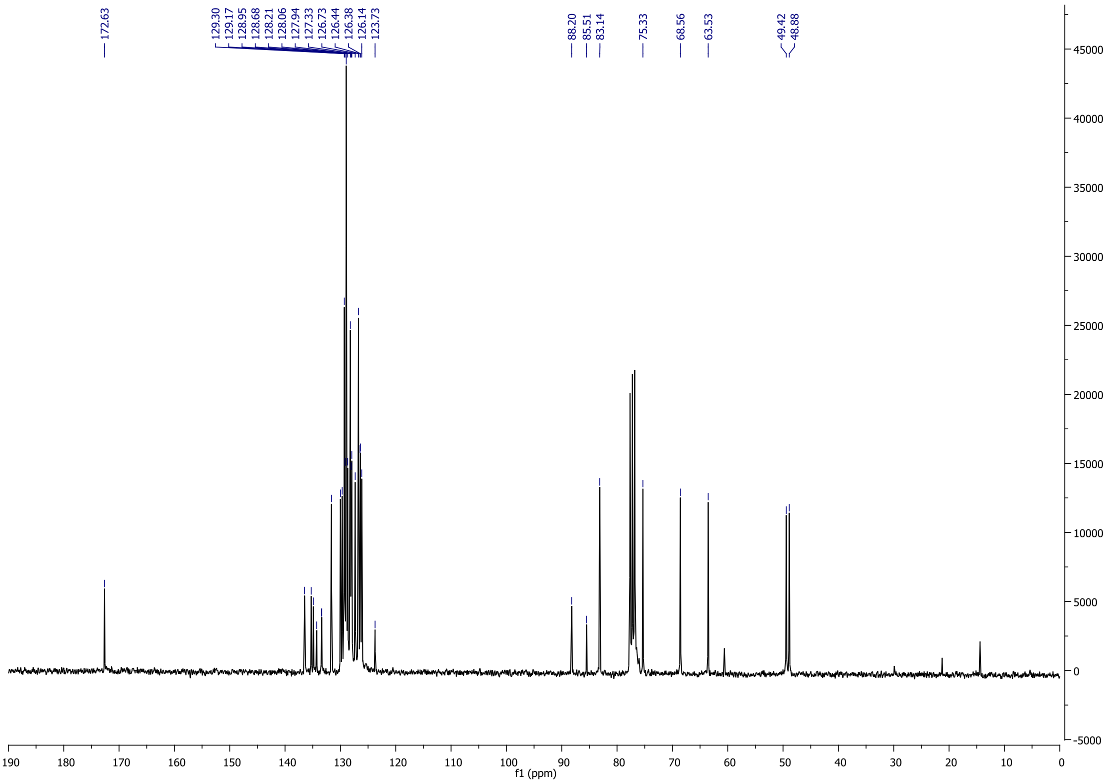

7.85
7.83
7.82
7.81
7.79
7.75
7.46
7.26
7.13
7.10
7.07
6.72
6.70
5.08
5.03
4.92
4.91
4.88
4.86
4.80
4.44
4.39
4.16
3.92
3.79
2.98
2.71
0.95
2.93
8.18
3.65
1.63
1.00
3.48
1.13
0.90
1.12
1.70
2.61
0.78
4000
3500
3000
2500
2000
1500
1000
500
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.78
159.98
136.52
135.41
135.08
133.42
133.31
128.59
128.00
126.88
126.18
114.10
114.02
87.07
85.52
83.44
75.35
68.52
63.79
55.44
49.39
48.77
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

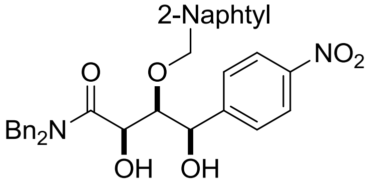

Cl
2-Naphtyl
O
O
Bn2N
OH
OH

22c

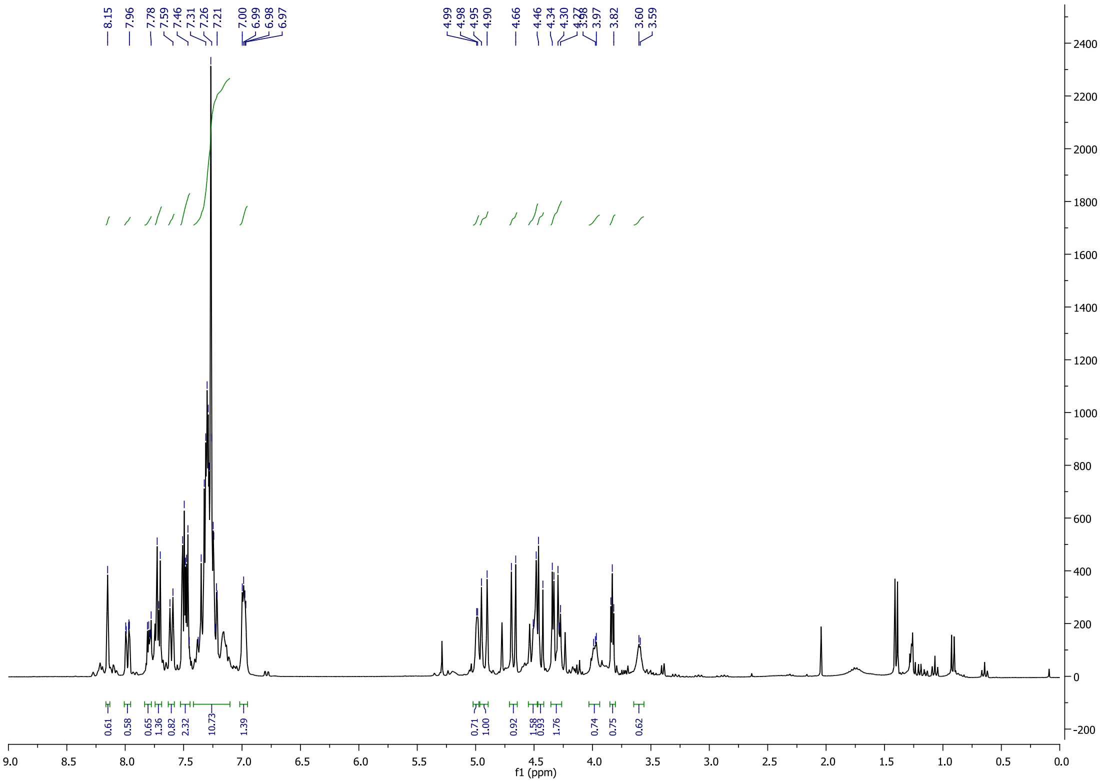

7.84
7.81
7.72
7.46
7.28
7.26
7.18
7.13
7.10
7.09
7.08
7.08
7.07
7.07
7.06
5.08
5.03
4.89
4.85
4.77
4.44
4.39
4.15
3.94
3.93
3.92
3.91
3.87
3.85
2.87
2.62
0.87
2.56
12.29
1.00
4.83
0.98
0.97
1.02
0.85
0.85
f1 (ppm)

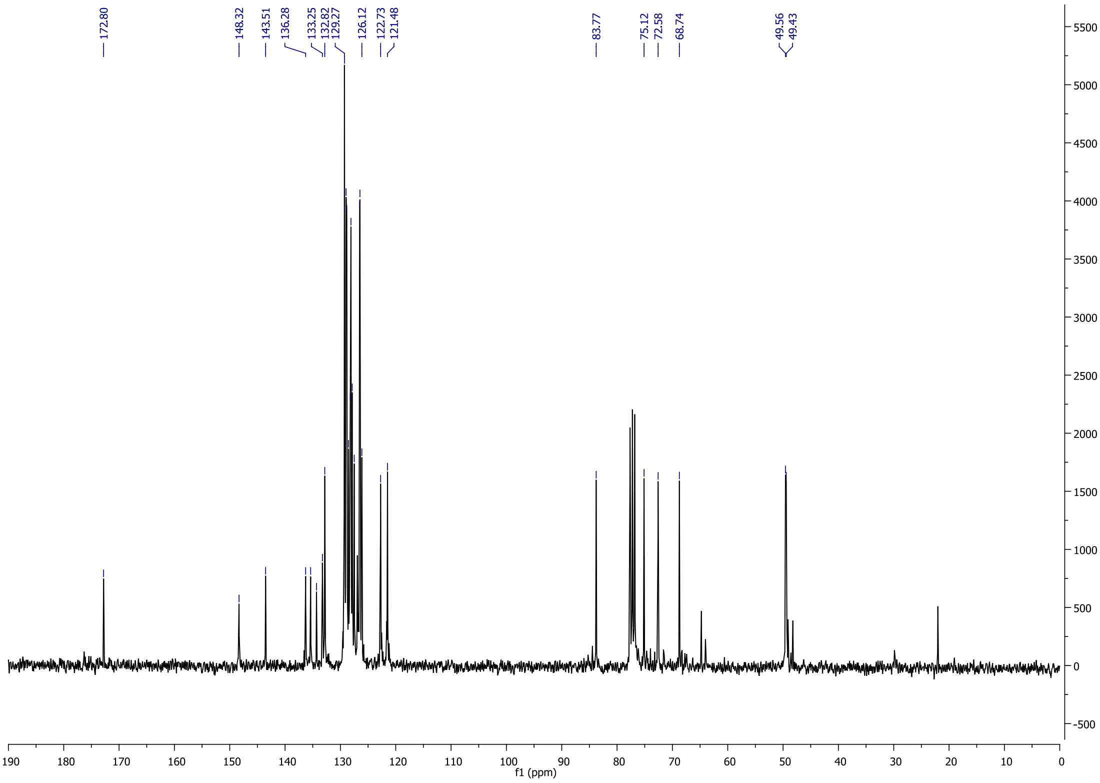

172.63
129.30
129.17
128.95
128.68
128.21
128.06
127.94
127.33
126.73
126.44
126.38
126.14
123.73
88.20
85.51
83.14
75.33
68.56
63.53
49.42
48.88
f1 (ppm)

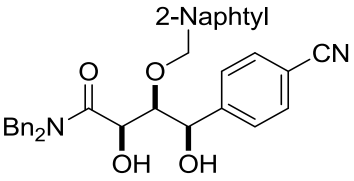
5.8.8. Aldol adducts 25


2-Naphtyl
NO$_2$
O
O
Bn$_2$N
OH
OH

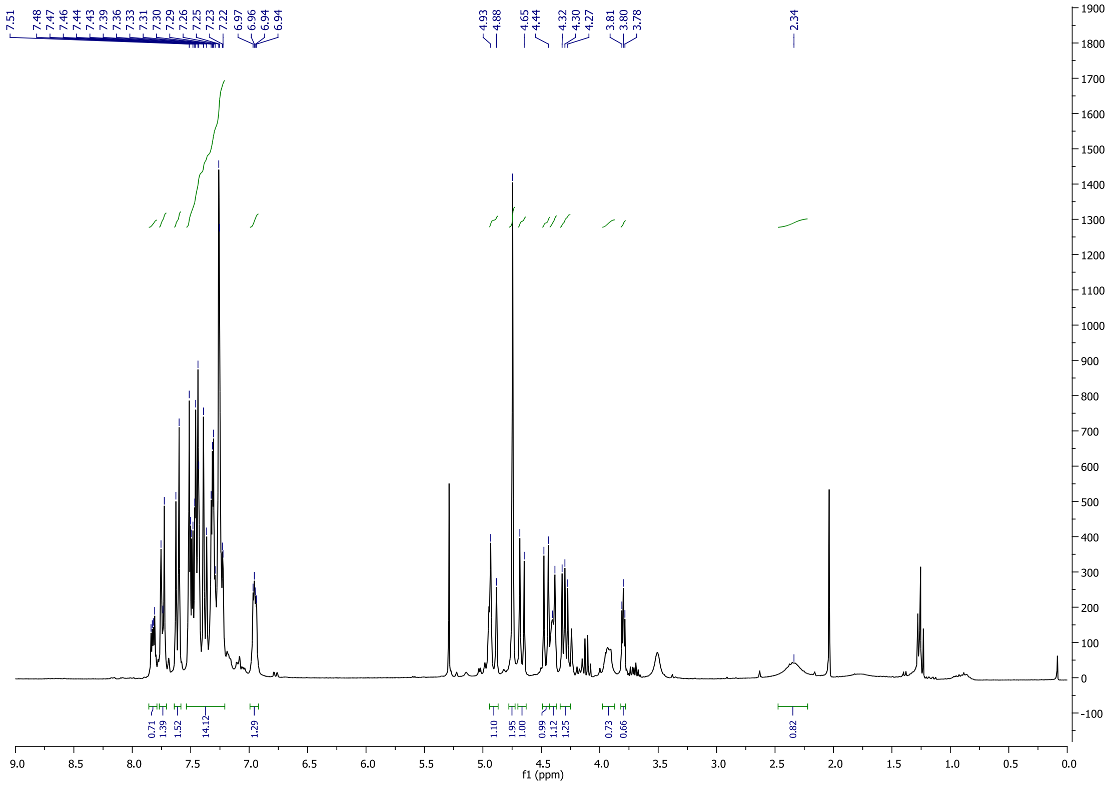
25a

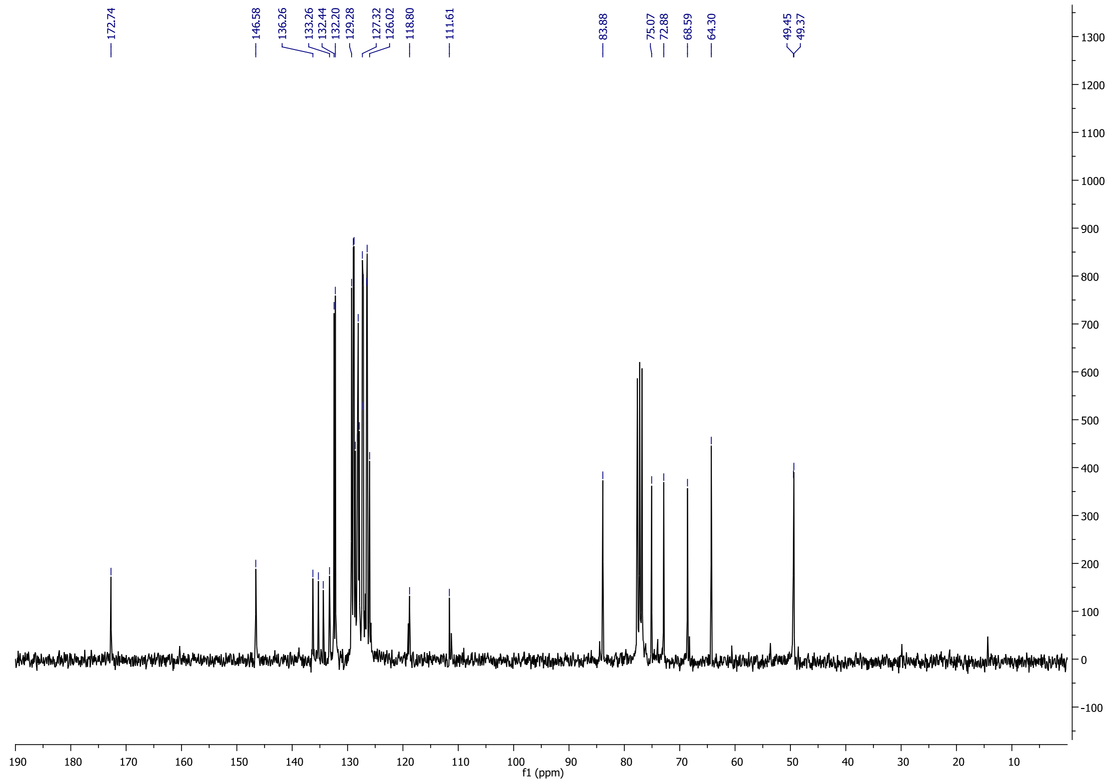


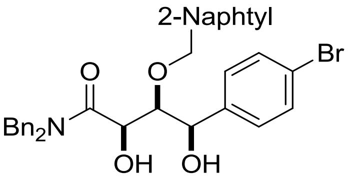



2-Naphtyl
CN
O
O
Bn2N
OH
OH

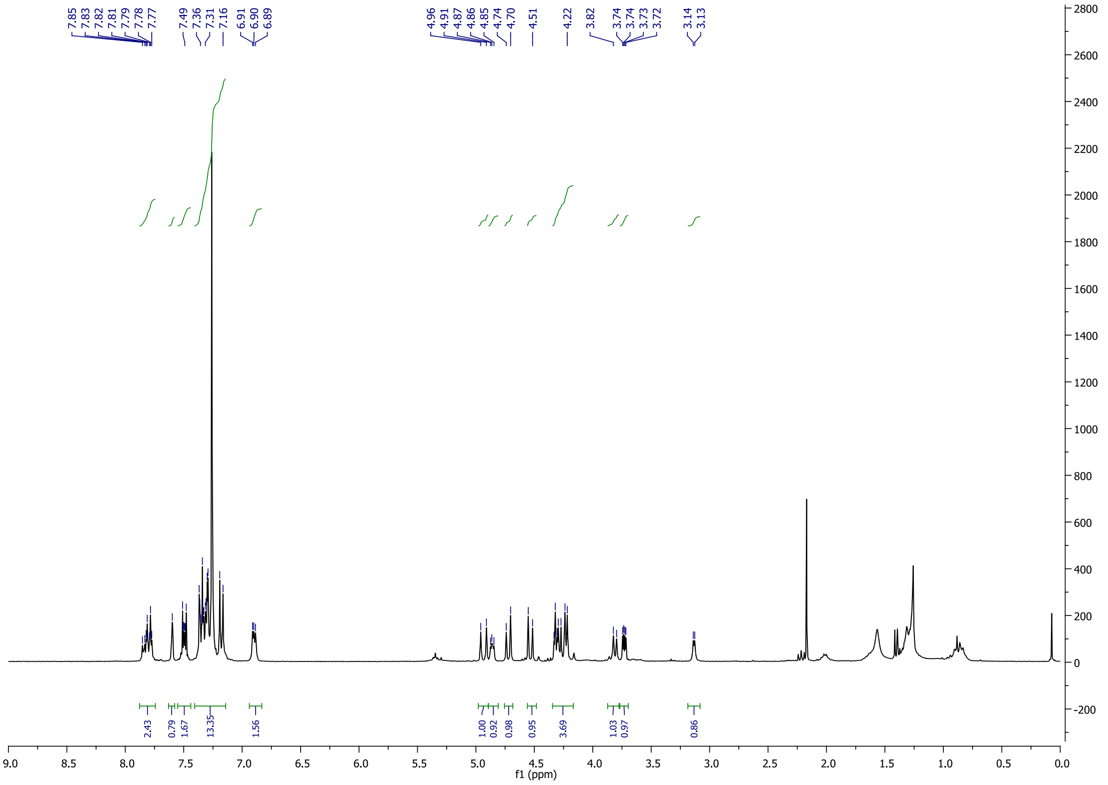
25b

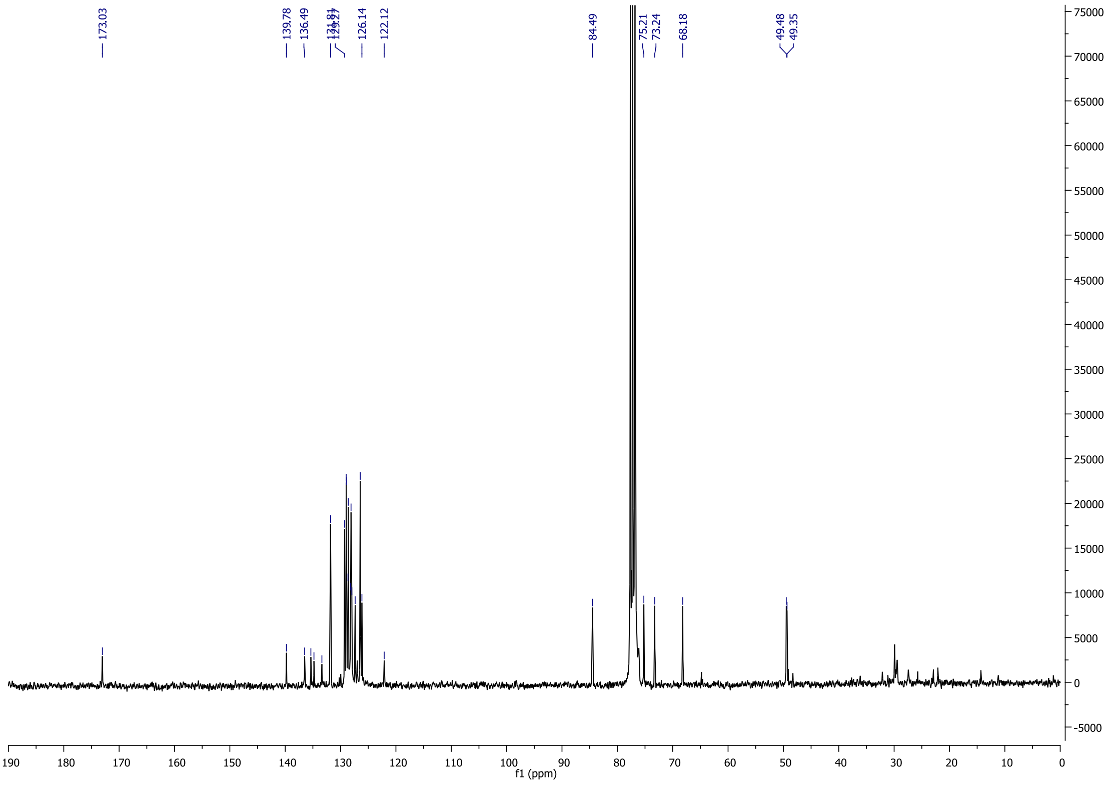

7.51
7.48
7.47
7.46
7.44
7.43
7.39
7.36
7.33
7.31
7.30
7.29
7.26
7.25
7.23
7.22
6.97
6.96
6.94
6.94
4.93
4.88
4.65
4.44
4.32
4.30
4.27
3.81
3.80
3.78
2.34
0.71
1.39
1.52
14.12
1.29
1.10
1.95
1.00
0.99
1.12
1.25
0.73
0.66
0.82
f1 (ppm)


172.74
146.58
136.26
133.26
132.44
132.20
129.28
127.32
126.02
118.80
111.61
83.88
75.07
72.88
68.59
64.30
49.45
49.37
f1 (ppm)

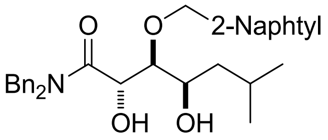

2-Naphtyl
O
O
Br
Bn2N
OH
OH

25c

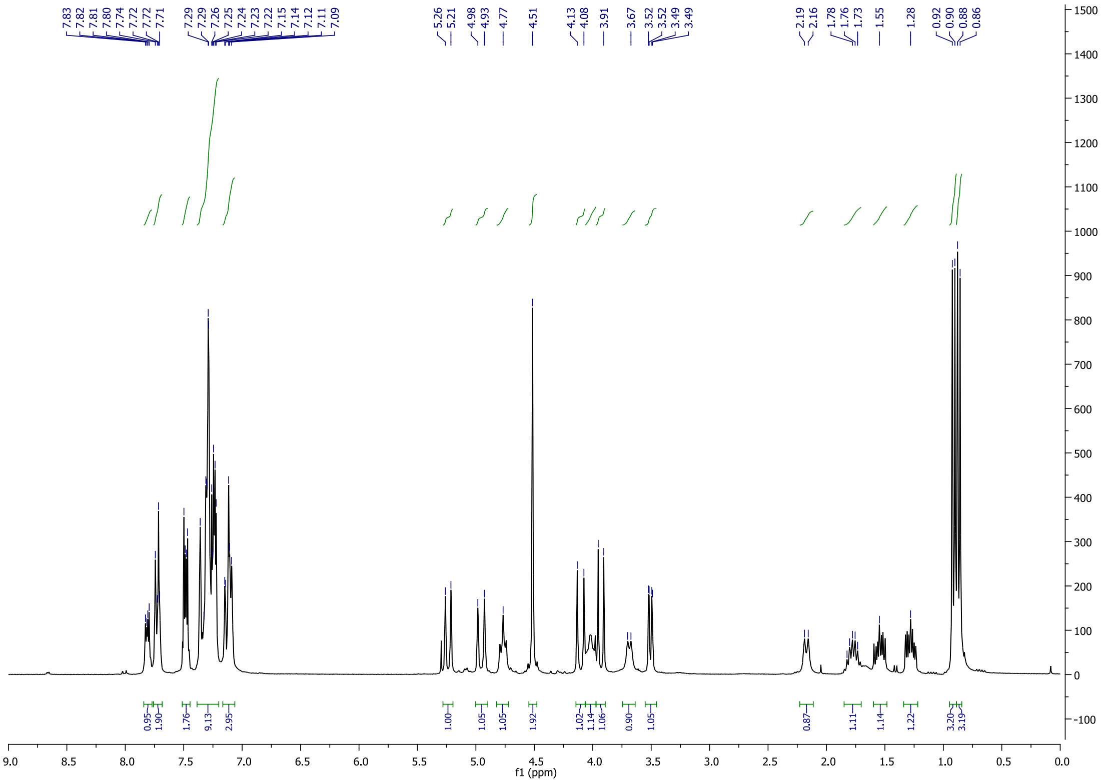

7.85
7.83
7.82
7.81
7.79
7.78
7.77
7.49
7.36
7.31
7.16
6.91
6.90
6.89
4.96
4.91
4.87
4.86
4.85
4.74
4.70
4.51
4.22
3.82
3.74
3.74
3.73
3.72
3.14
3.13
2.43
0.79
1.67
13.35
1.56
1.00
0.92
0.98
0.95
3.69
1.03
0.97
0.86
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

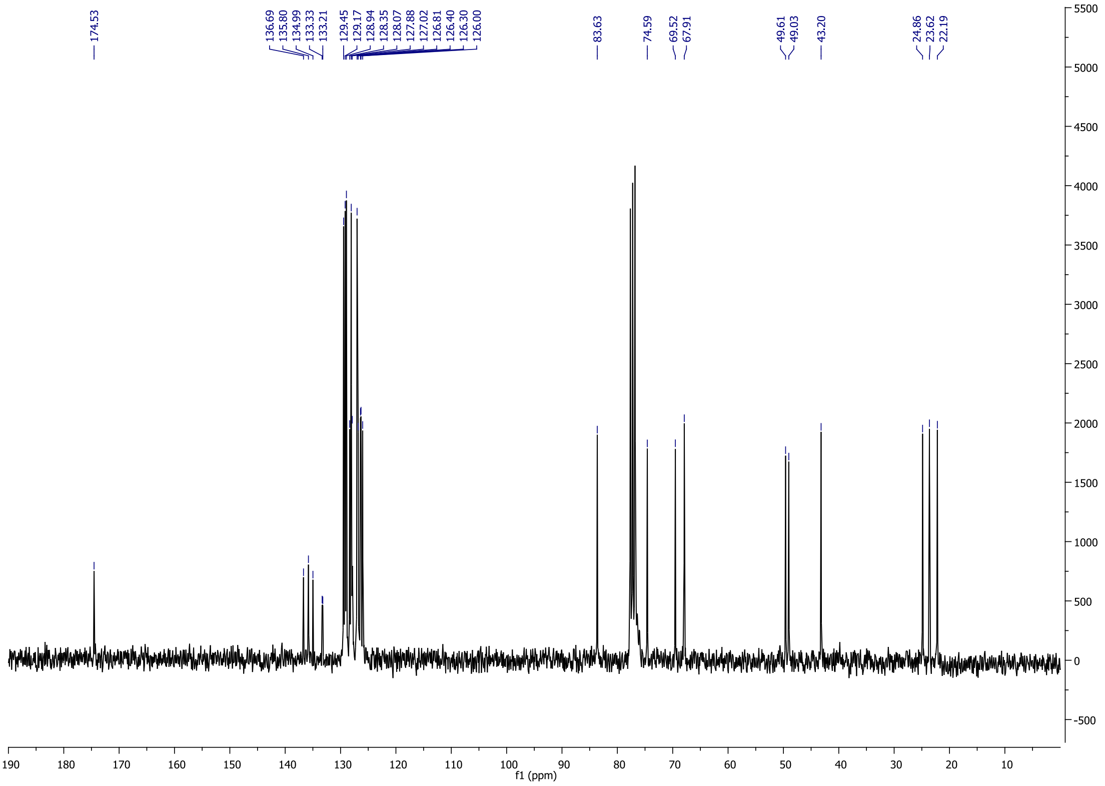

173.03
139.78
136.49
131.81
129.27
126.14
122.12
84.49
75.21
73.24
68.18
49.48
49.35
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

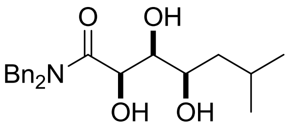
5.8.9. Elaborated adducts 26e, 27e, 29f, 30c and 30h


O
O
2-Naphtyl
Bn2N
OH
OH

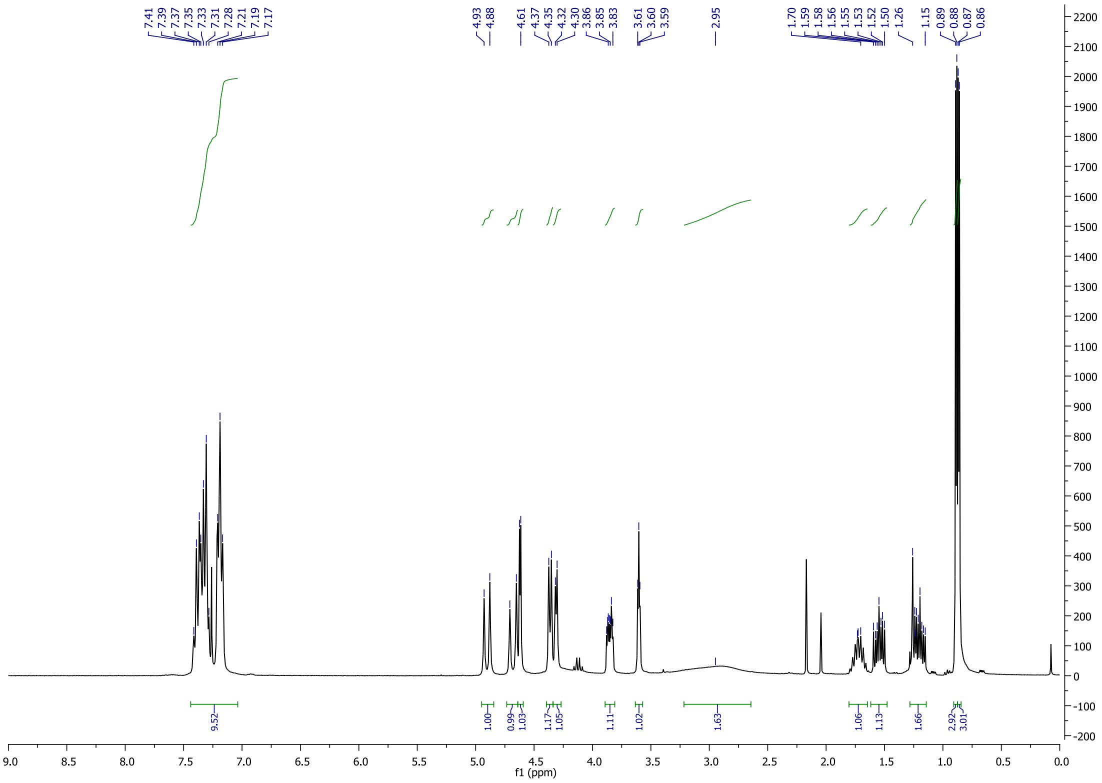
26e

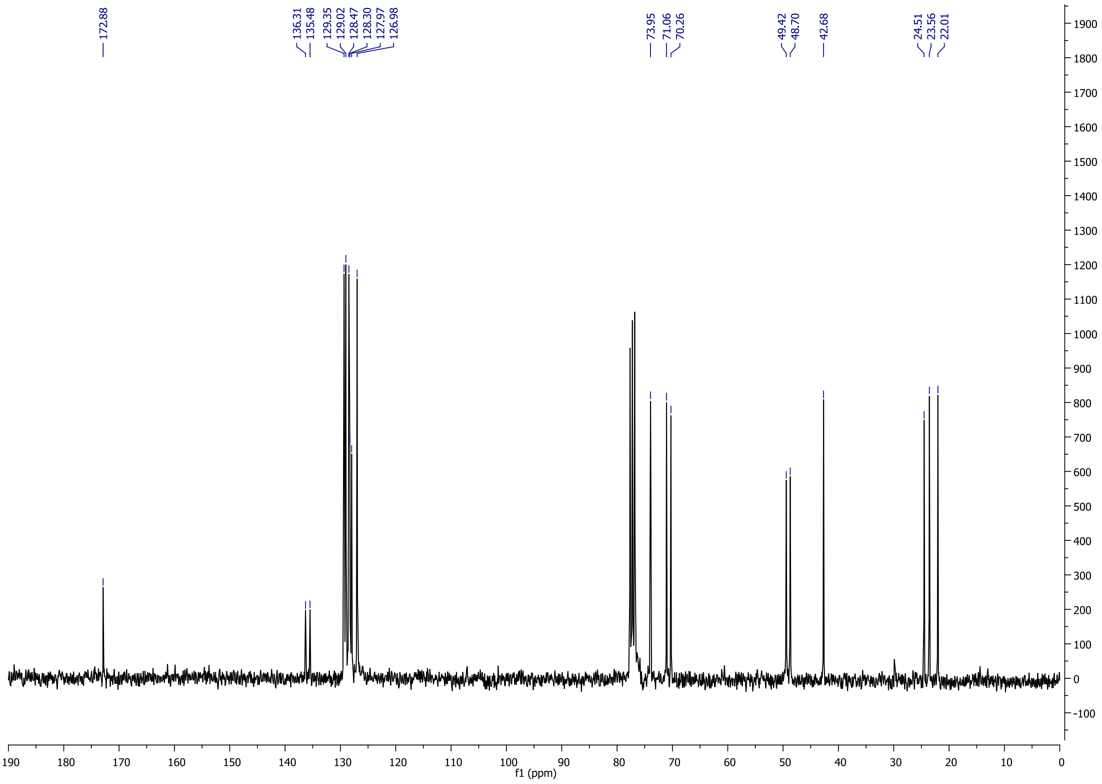


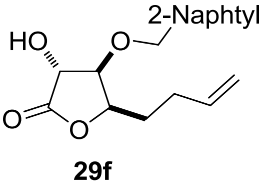



O
OH
Bn2N
OH
OH

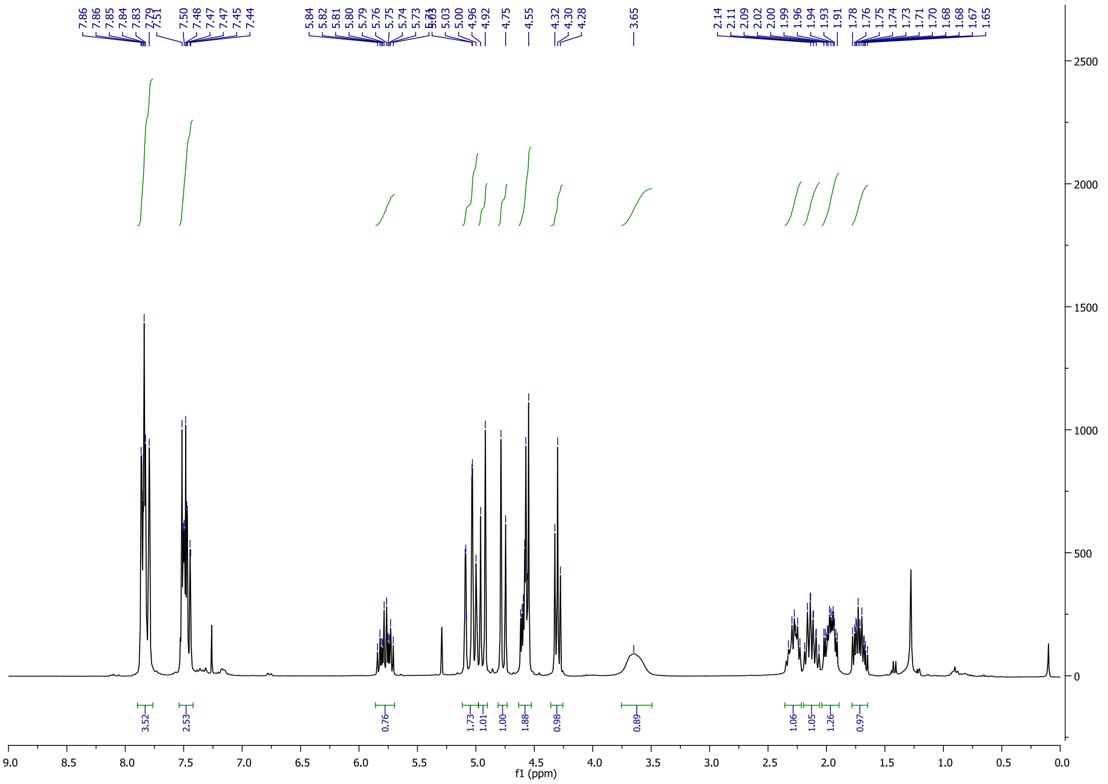
27e

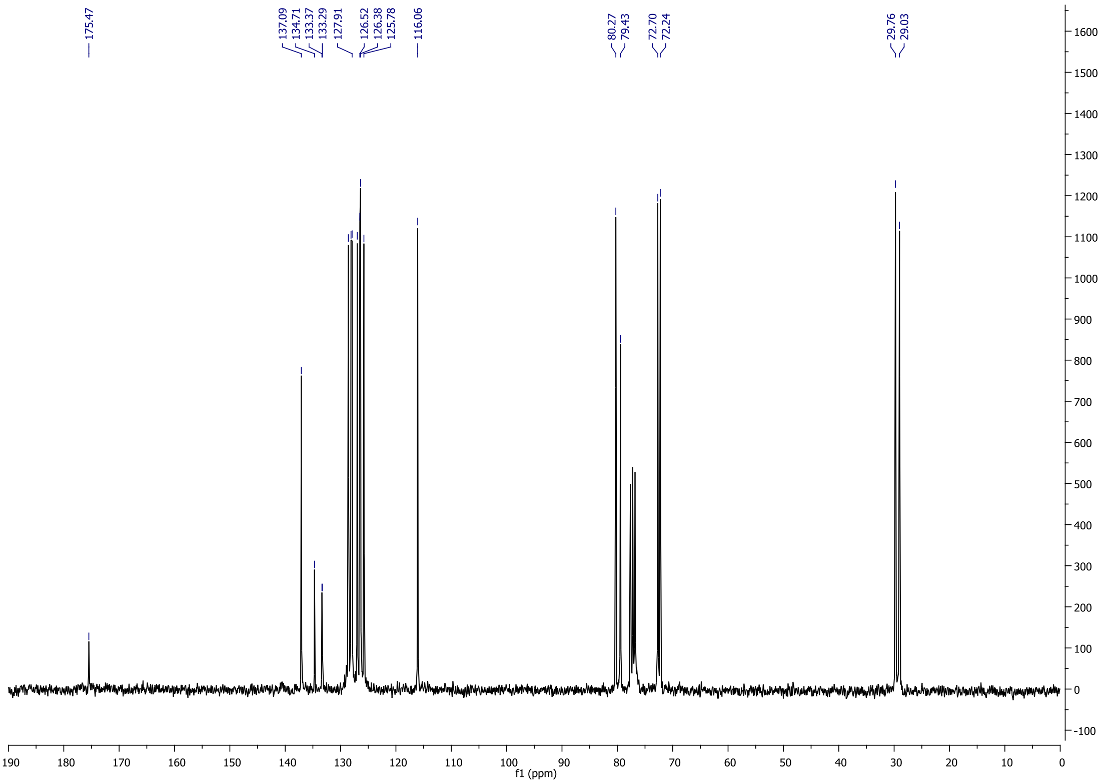

7.41
7.39
7.37
7.35
7.33
7.31
7.28
7.21
7.19
7.17
4.93
4.88
4.61
4.37
4.35
4.32
4.30
3.86
3.85
3.83
3.61
3.60
3.59
2.95
1.70
1.59
1.58
1.56
1.55
1.53
1.52
1.50
1.26
1.15
0.89
0.88
0.87
0.86
9.52
1.00
0.99
1.03
1.17
1.05
1.11
1.02
1.63
1.06
1.13
1.66
2.92
3.01
f1 (ppm)

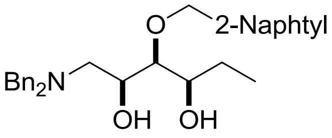

172.88
136.31
135.48
129.35
129.02
128.47
128.30
127.97
126.98
73.95
71.06
70.26
49.42
48.70
42.68
24.51
23.56
22.01
f1 (ppm)


2-Naphtyl
HO
O
O
O

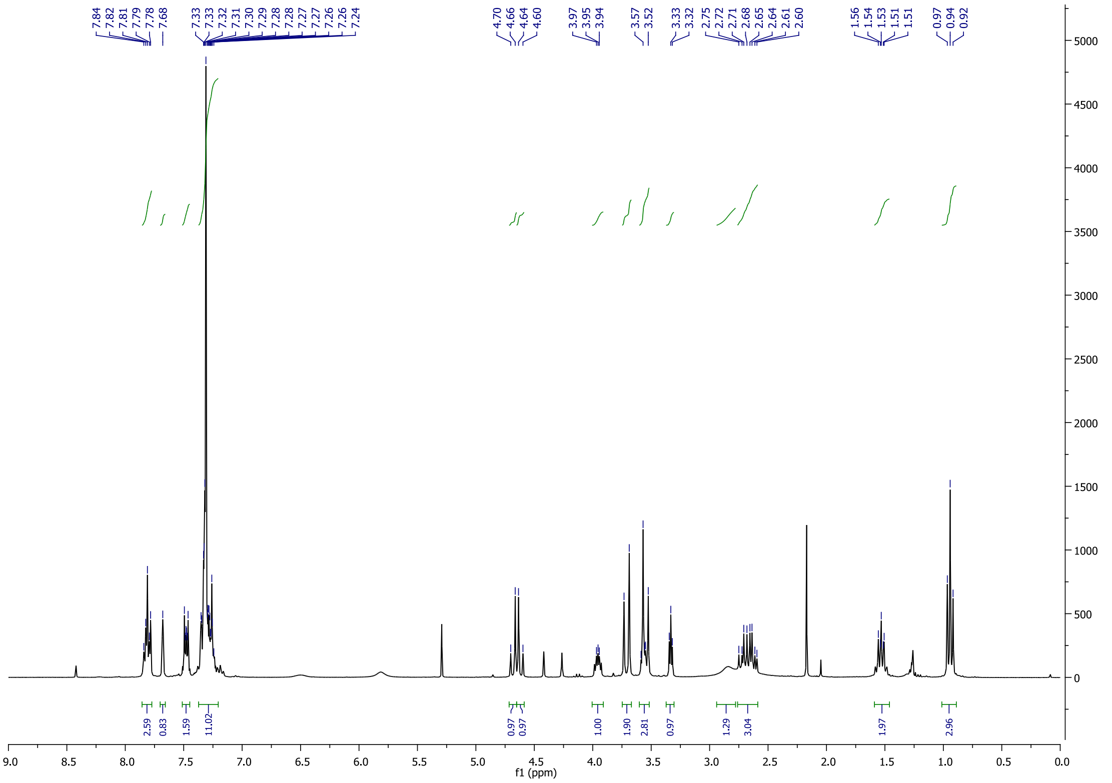
29f

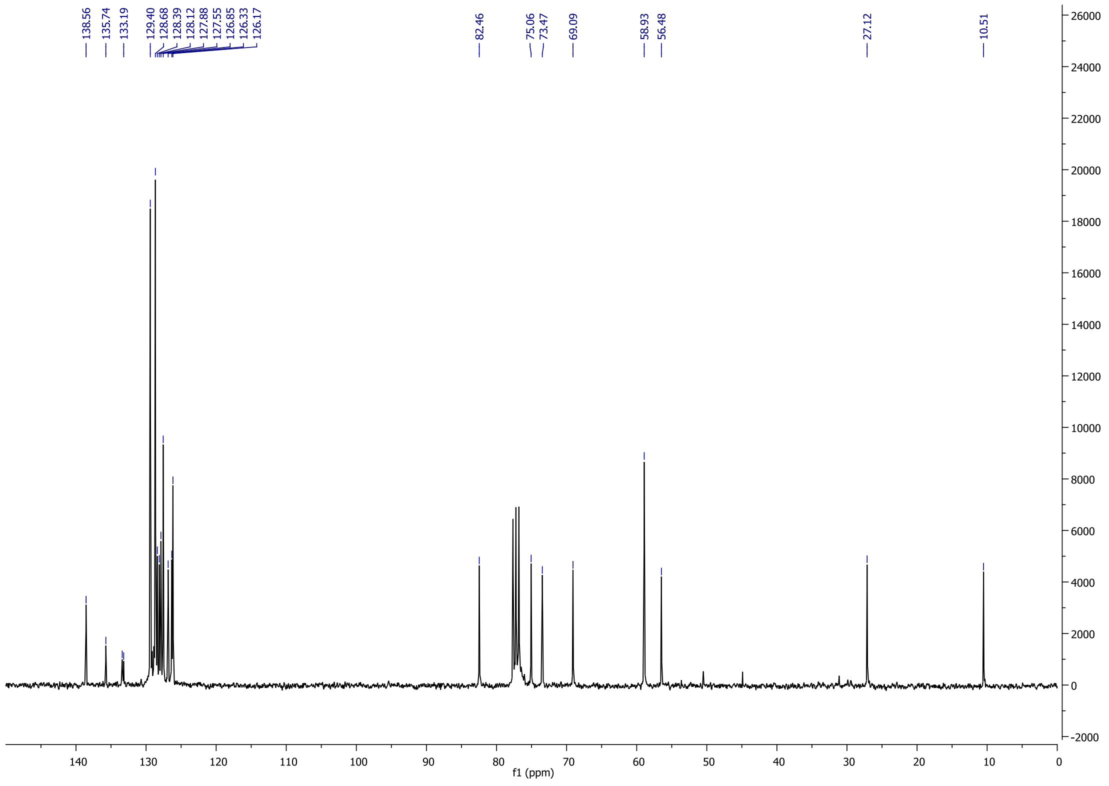

7.86 7.86 7.85 7.84 7.83 7.79 7.51 7.50 7.48 7.47 7.47 7.45 7.44
5.84 5.82 5.81 5.80 5.79 5.76 5.75 5.74 5.73 5.03 5.03 5.00 4.96 4.92 4.75 4.55 4.32 4.30 4.28
3.65
2.14 2.11 2.09 2.02 2.00 1.99 1.96 1.94 1.93 1.91 1.78 1.76 1.75 1.74 1.73 1.71 1.70 1.68 1.68 1.67 1.65
3.52 2.53 0.76 1.73 1.01 1.00 1.88 0.98 0.89 1.06 1.05 1.26 0.97
2500 2000 1500 1000 500 0
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

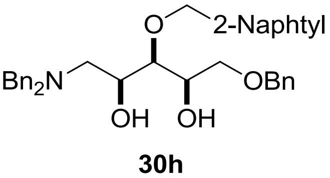

175.47
137.09 134.71 133.37 133.29 127.91 126.52 126.38 125.78
116.06
80.27 79.43 72.70 72.24
29.76 29.03
1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


2-Naphtyl
O
Bn2N
OH
OH

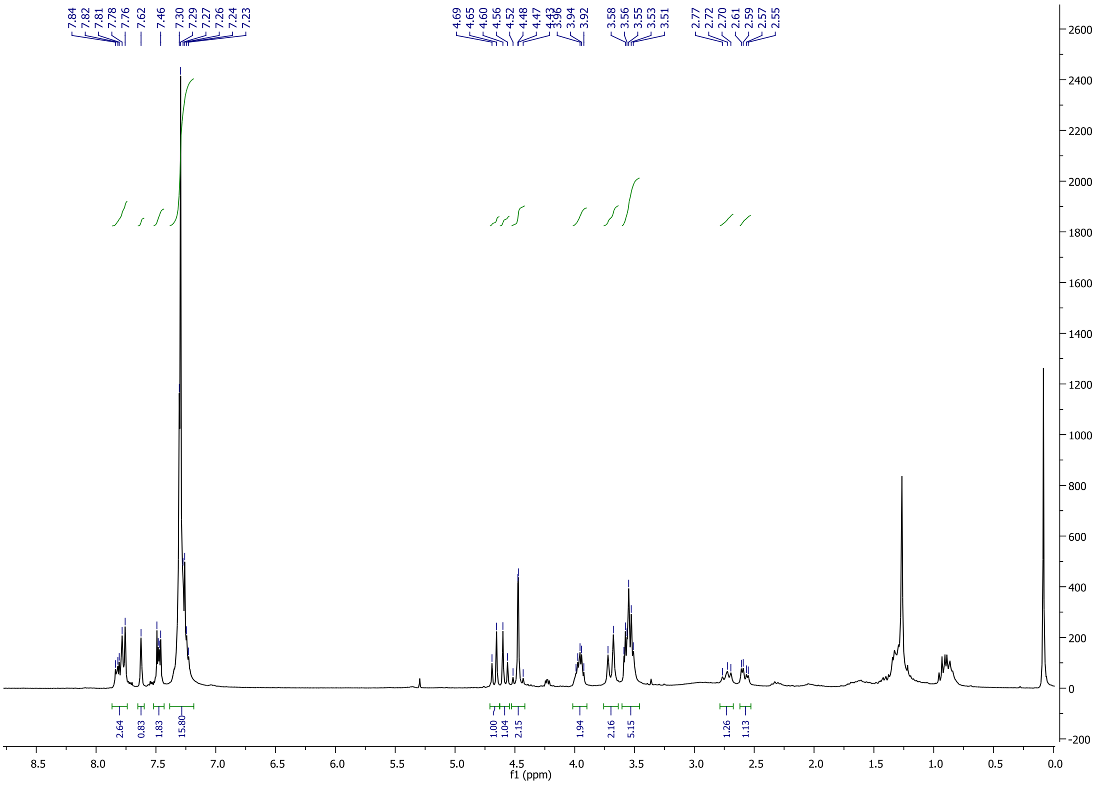
30c

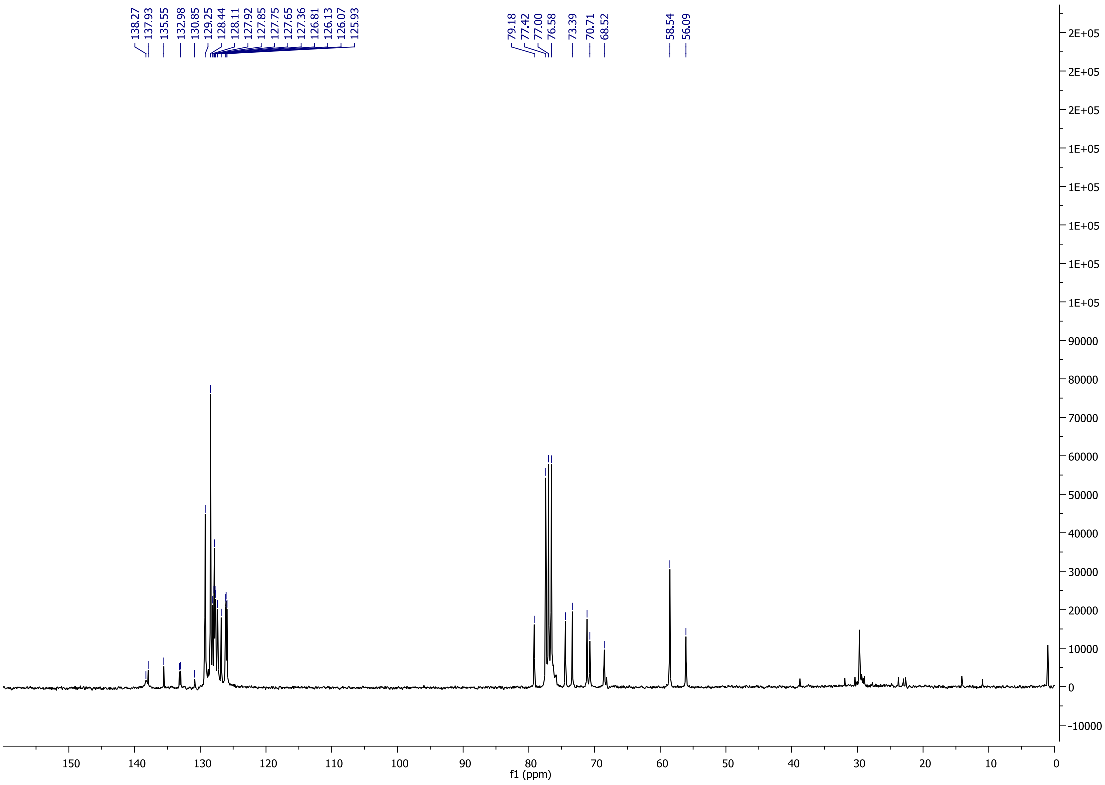

7.84
7.82
7.81
7.79
7.78
7.68
7.33
7.33
7.32
7.31
7.30
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.24
4.70
4.66
4.64
4.60
3.97
3.95
3.94
3.57
3.52
3.33
3.32
2.75
2.72
2.71
2.68
2.65
2.64
2.61
2.60
1.56
1.54
1.53
1.51
1.51
0.97
0.94
0.92
2.59
0.83
1.59
11.02
0.97
0.97
1.00
1.90
2.81
0.97
1.29
3.04
1.97
2.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0


138.56
135.74
133.19
129.40
128.68
128.39
128.12
127.88
127.55
126.85
126.33
126.17
82.46
75.06
73.47
69.09
58.93
56.48
27.12
10.51
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

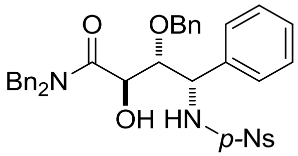

O
2-Naphtyl
Bn2N
OBn
OH
OH

30h

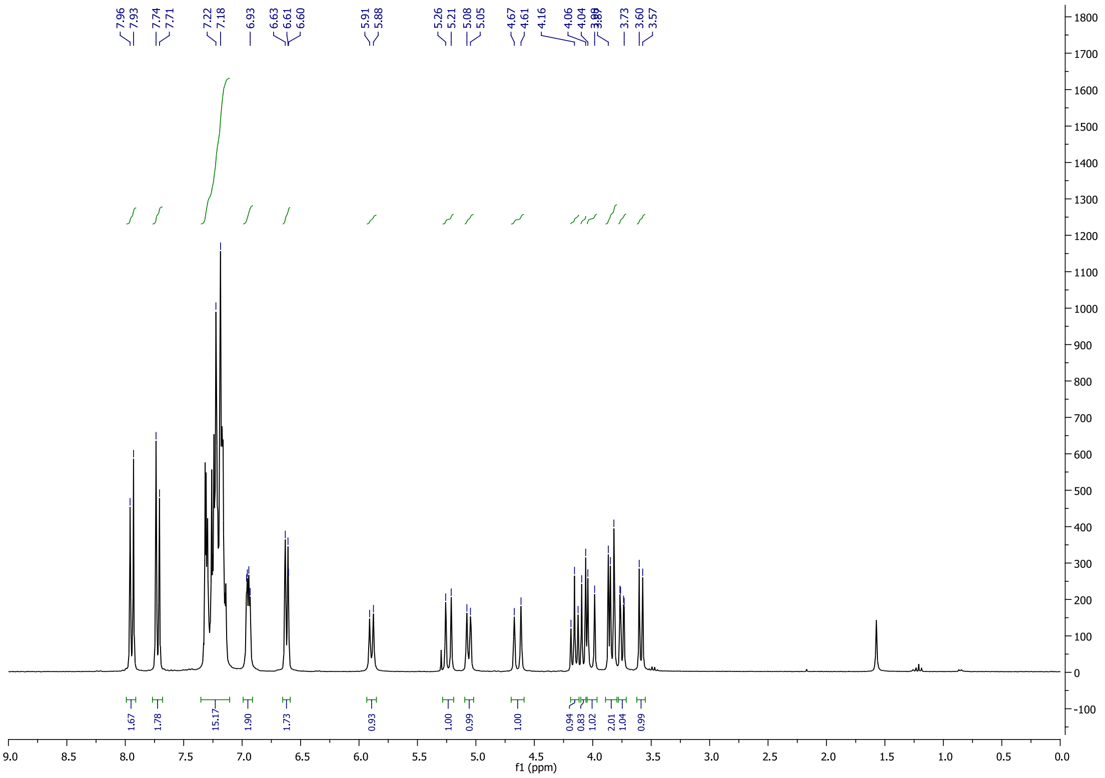

7.84
7.82
7.81
7.78
7.76
7.62
7.46
7.30
7.29
7.27
7.26
7.24
7.23
4.69
4.65
4.60
4.56
4.52
4.48
4.47
4.43
3.96
3.94
3.92
3.58
3.56
3.55
3.53
3.51
2.77
2.72
2.70
2.61
2.59
2.57
2.55
2.64
0.83
1.83
15.80
1.00
1.04
2.15
1.94
2.16
5.15
1.26
1.13
f1 (ppm)

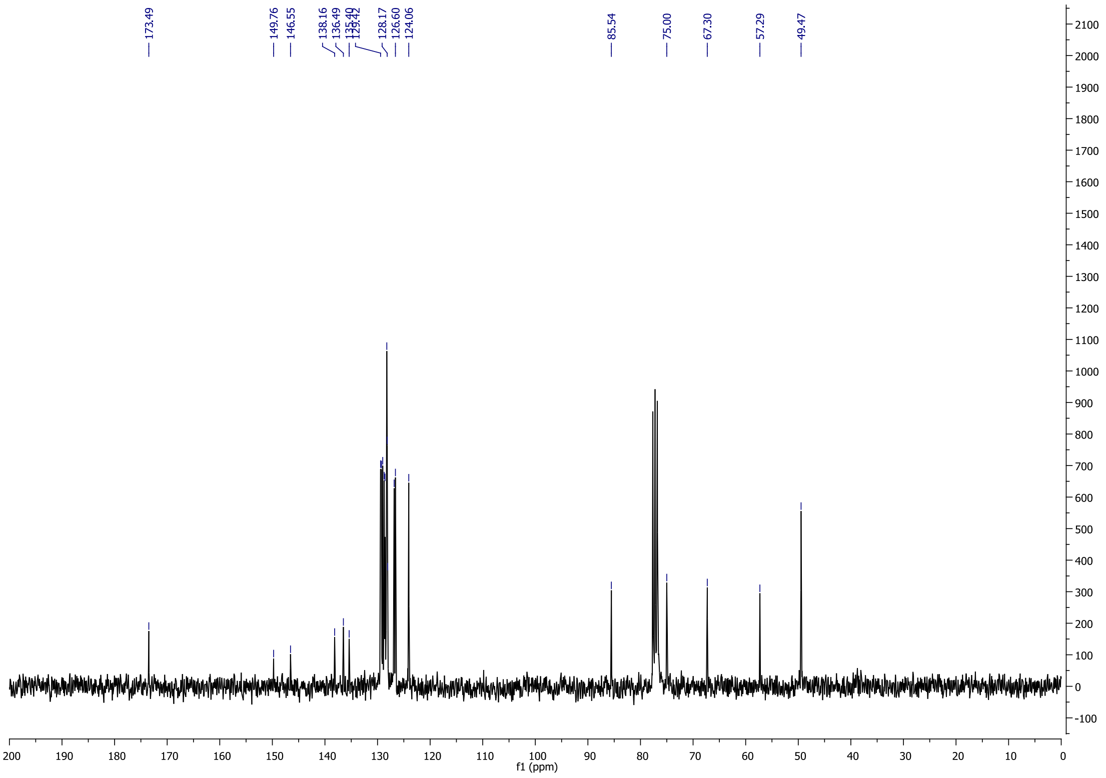

138.27
137.93
135.55
132.98
130.85
129.25
128.44
128.11
127.92
127.85
127.75
127.65
127.36
126.81
126.13
126.07
125.93
79.18
77.42
77.00
76.58
73.39
70.71
68.52
58.54
56.09
f1 (ppm)

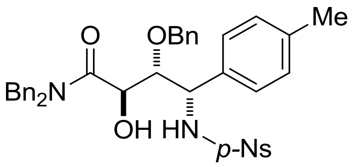
5.8.10. Mannich adducts 41


O
OBn
Bn2N
OH HN
p-Ns

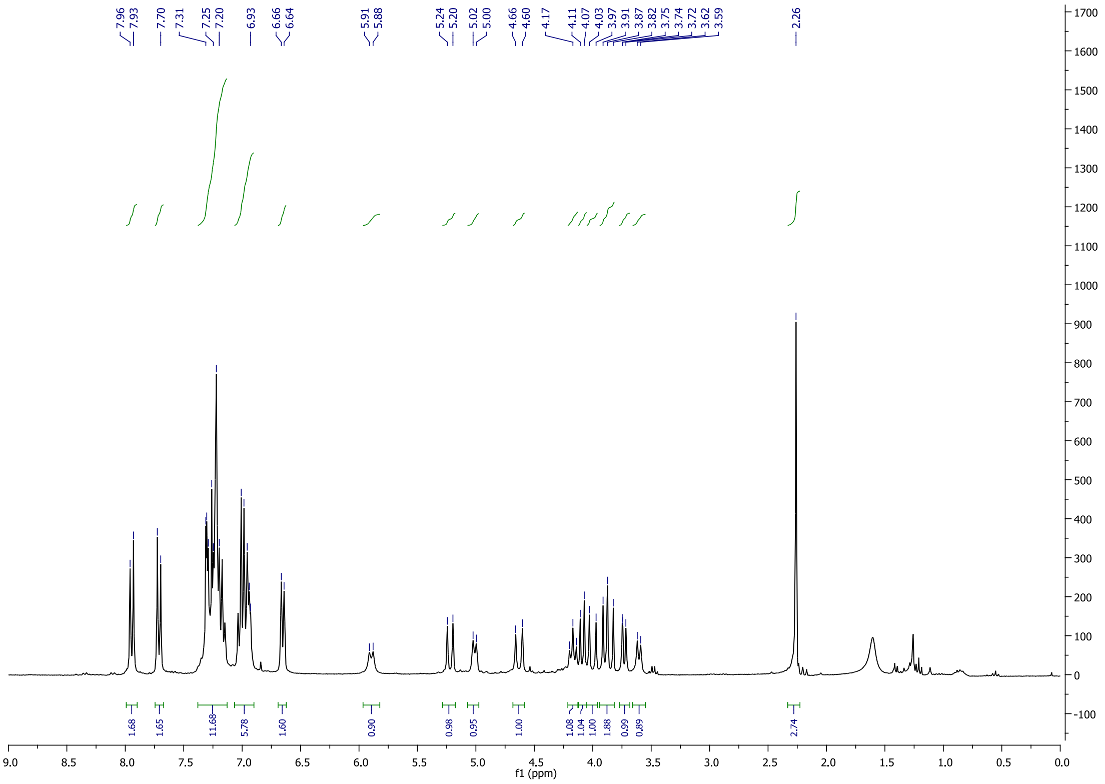
41a

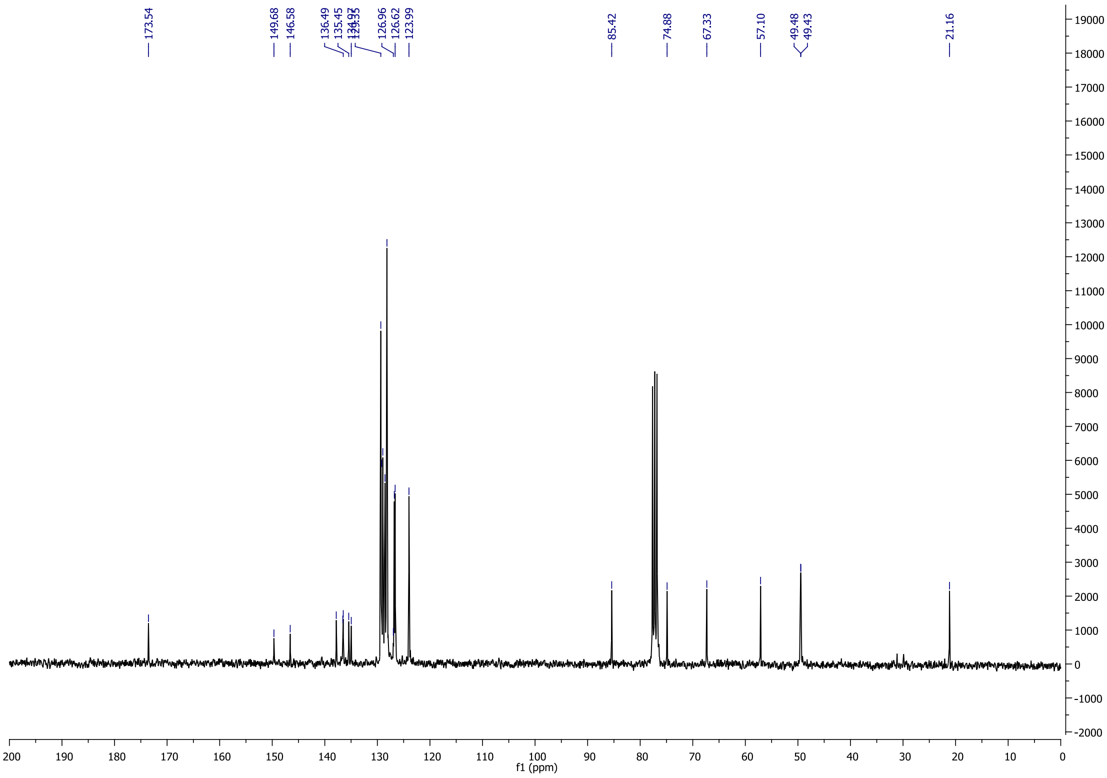


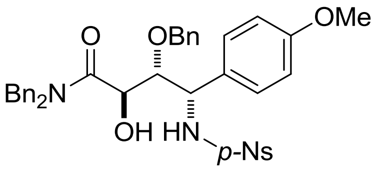



O
OBn
Me
Bn2N
OH
HN
p-Ns

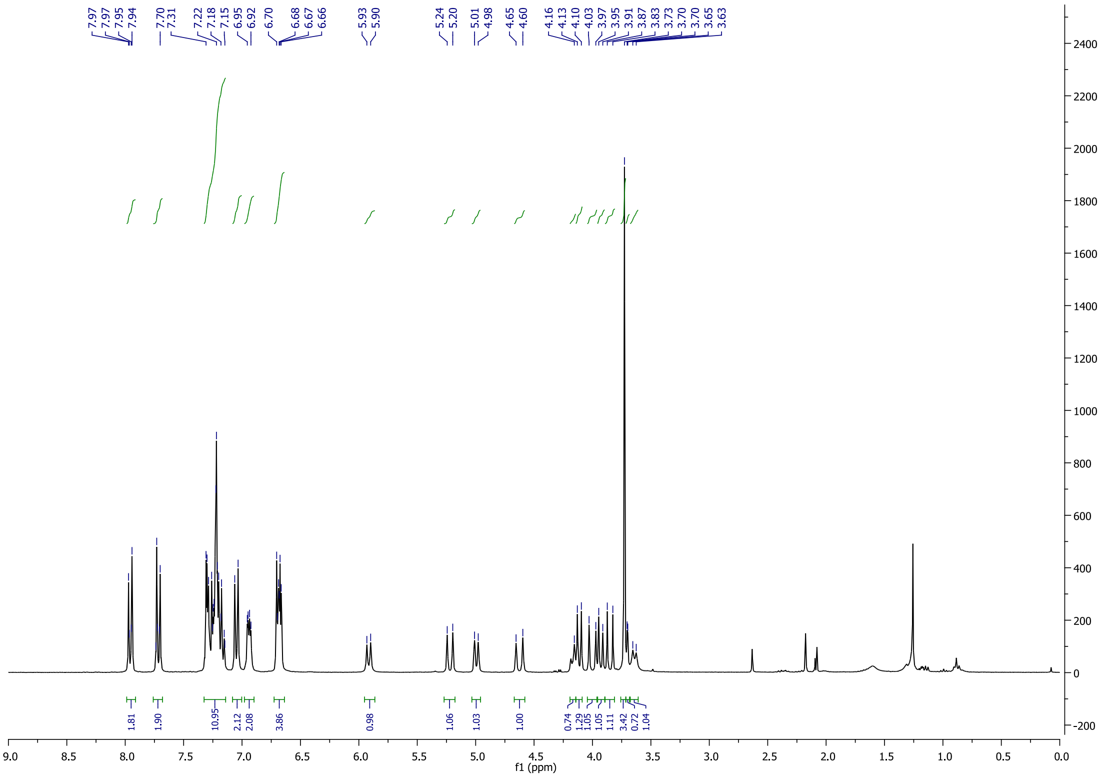
41b

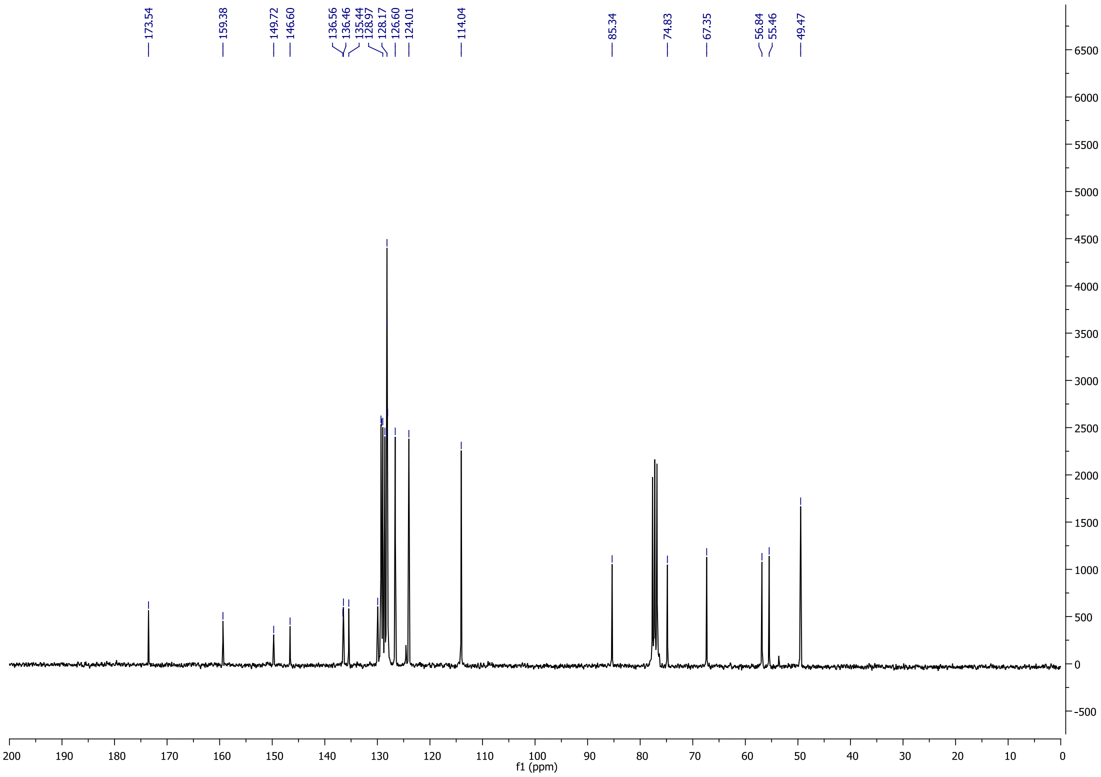

7.96
7.93
7.70
7.31
7.25
7.20
6.93
6.66
6.64
5.91
5.88
5.24
5.20
5.02
5.00
4.66
4.60
4.17
4.11
4.07
4.03
3.97
3.91
3.87
3.82
3.75
3.74
3.72
3.62
3.59
2.26
1.68
1.65
11.68
5.78
1.60
0.90
0.98
0.95
1.00
1.08
1.04
1.00
1.88
0.99
0.89
2.74
f1 (ppm)

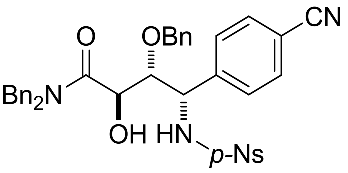

173.54
149.68
146.58
136.49
135.45
134.97
129.35
126.96
126.62
123.99
85.42
74.88
67.33
57.10
49.48
49.43
21.16
f1 (ppm)


O
OBn
OMe
Bn2N
OH HN
p-Ns

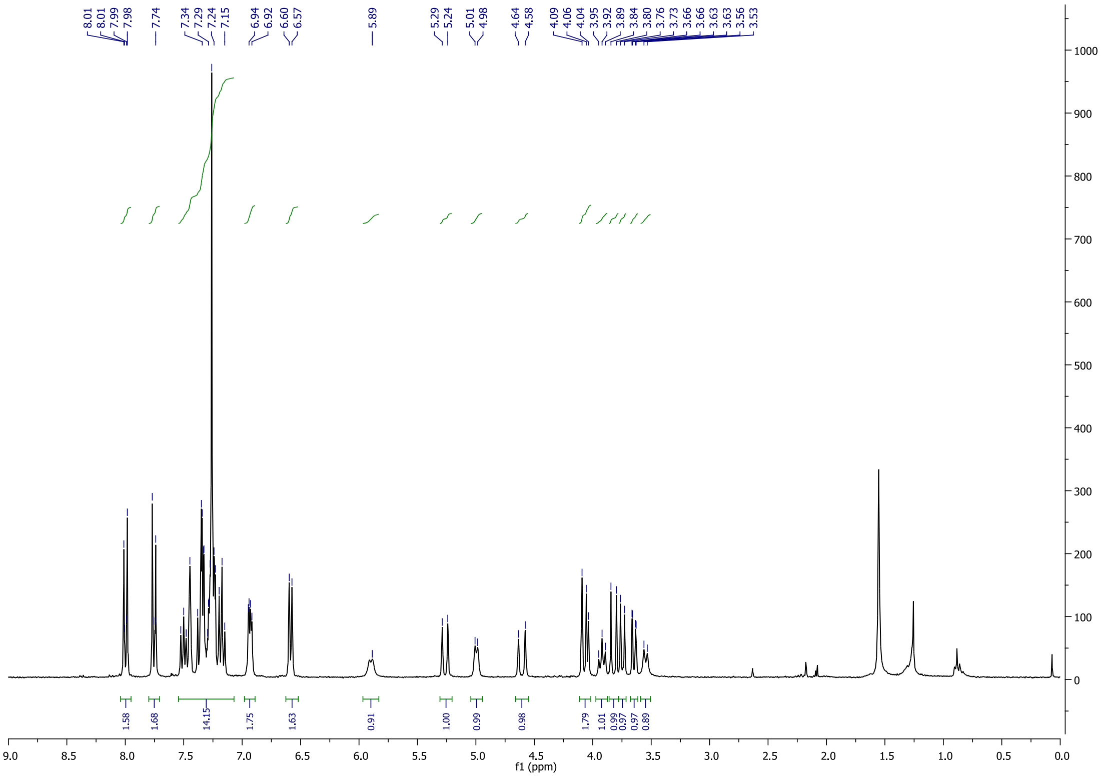
41c

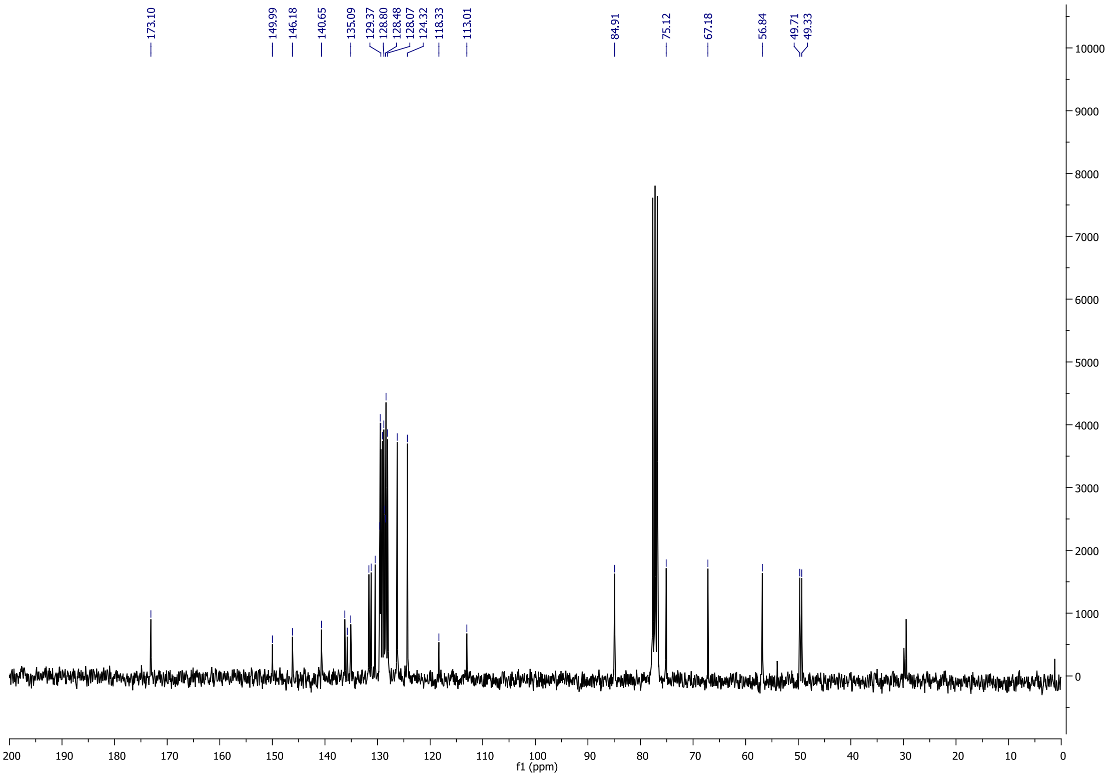

7.97
7.97
7.95
7.94
7.70
7.31
7.22
7.18
7.15
6.95
6.92
6.70
6.68
6.67
6.66
5.93
5.90
5.24
5.20
5.01
4.98
4.65
4.60
4.16
4.13
4.10
4.03
3.97
3.95
3.91
3.87
3.83
3.73
3.70
3.70
3.65
3.63
1.81
1.90
10.95
2.12
2.08
3.86
0.98
1.06
1.03
1.00
0.74
1.29
1.05
1.05
1.11
3.42
0.72
1.04
f1 (ppm)

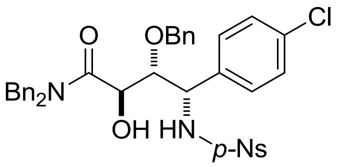

173.54
159.38
149.72
146.60
136.56
136.46
135.44
128.97
128.17
126.60
124.01
114.04
85.34
74.83
67.35
56.84
55.46
49.47
f1 (ppm)


O
OBn
CN
Bn2N
OH
HN
p-Ns

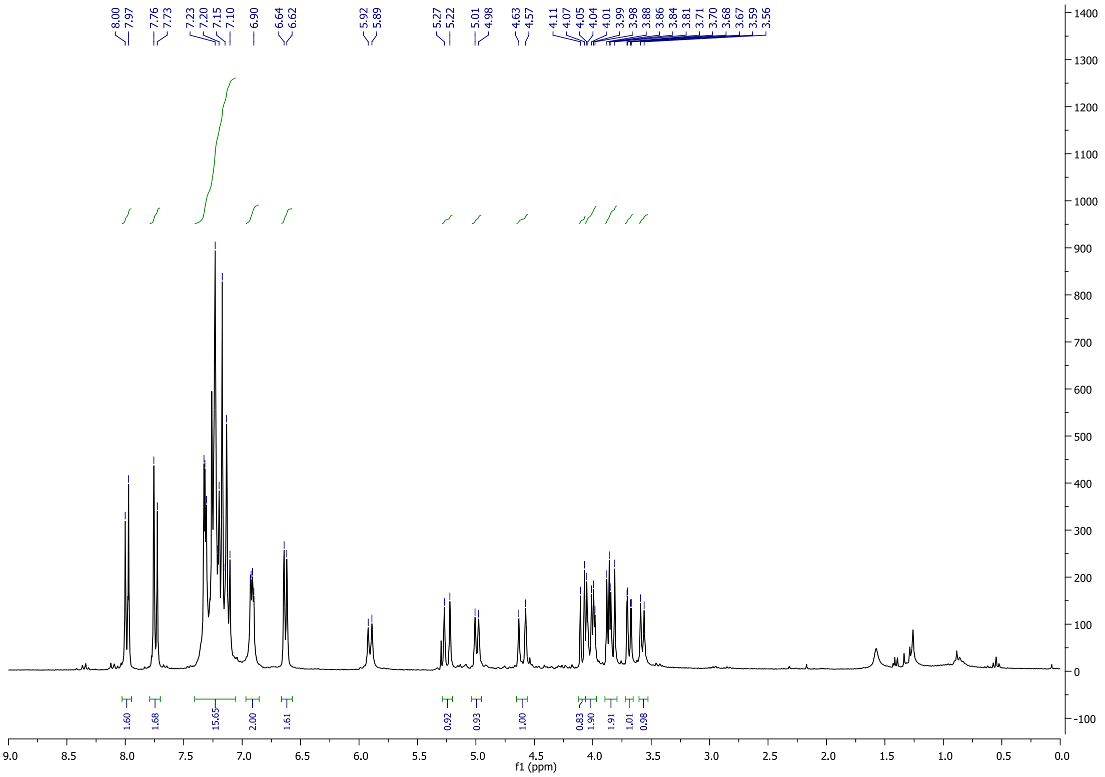
41d

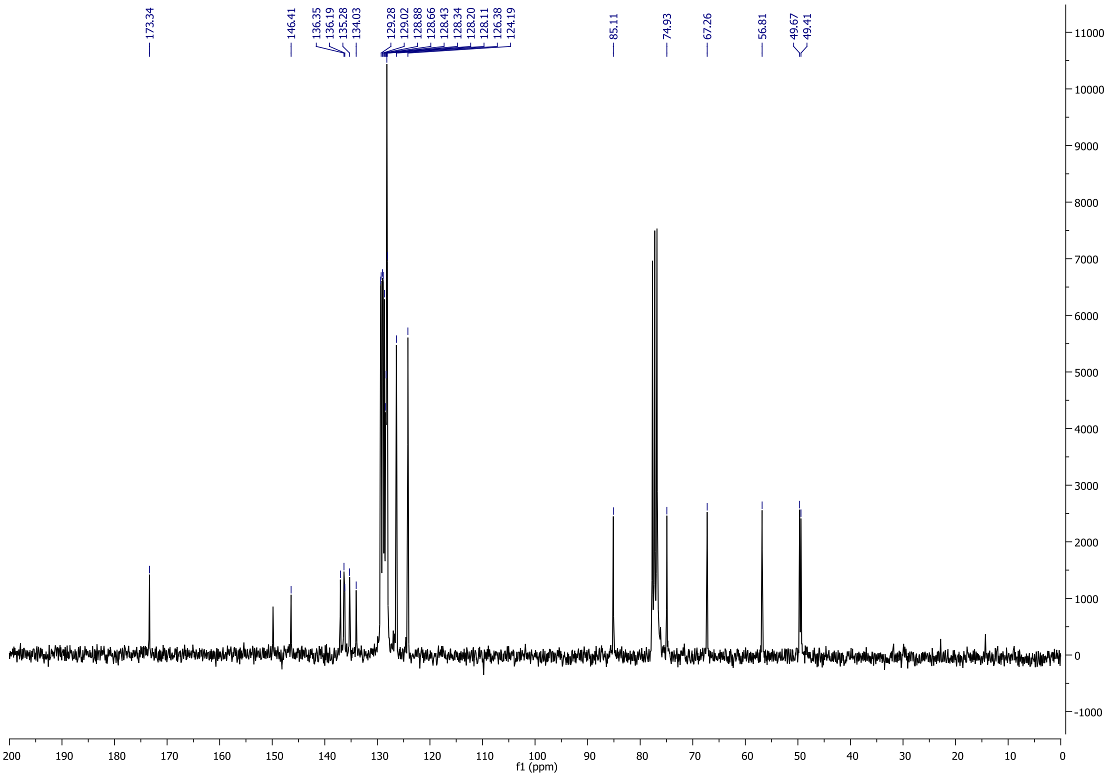

8.01
8.01
7.99
7.98
7.74
7.34
7.29
7.24
7.15
6.94
6.92
6.60
6.57
5.89
5.29
5.24
5.01
4.98
4.64
4.58
4.09
4.06
4.04
3.95
3.92
3.89
3.84
3.80
3.76
3.73
3.66
3.66
3.63
3.63
3.56
3.53
1.58
1.68
14.15
1.75
1.63
0.91
1.00
0.99
0.98
1.79
1.01
0.99
0.97
0.97
0.89
1000
900
800
700
600
500
400
300
200
100
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

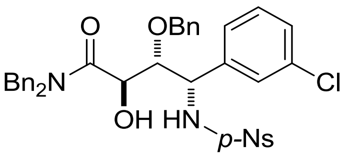

173.10
149.99
146.18
140.65
135.09
129.37
128.80
128.48
128.07
124.32
118.33
113.01
84.91
75.12
67.18
56.84
49.71
49.33
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OBn
Cl
Bn2N
OH
HN
p-Ns

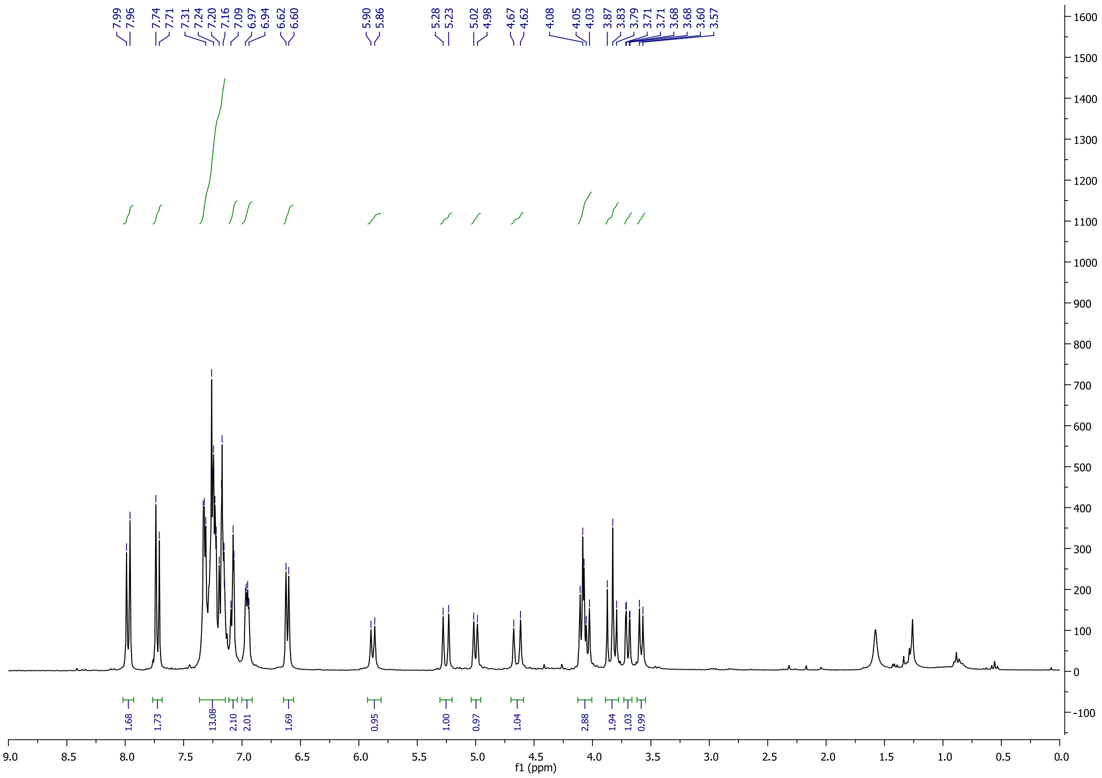
41e

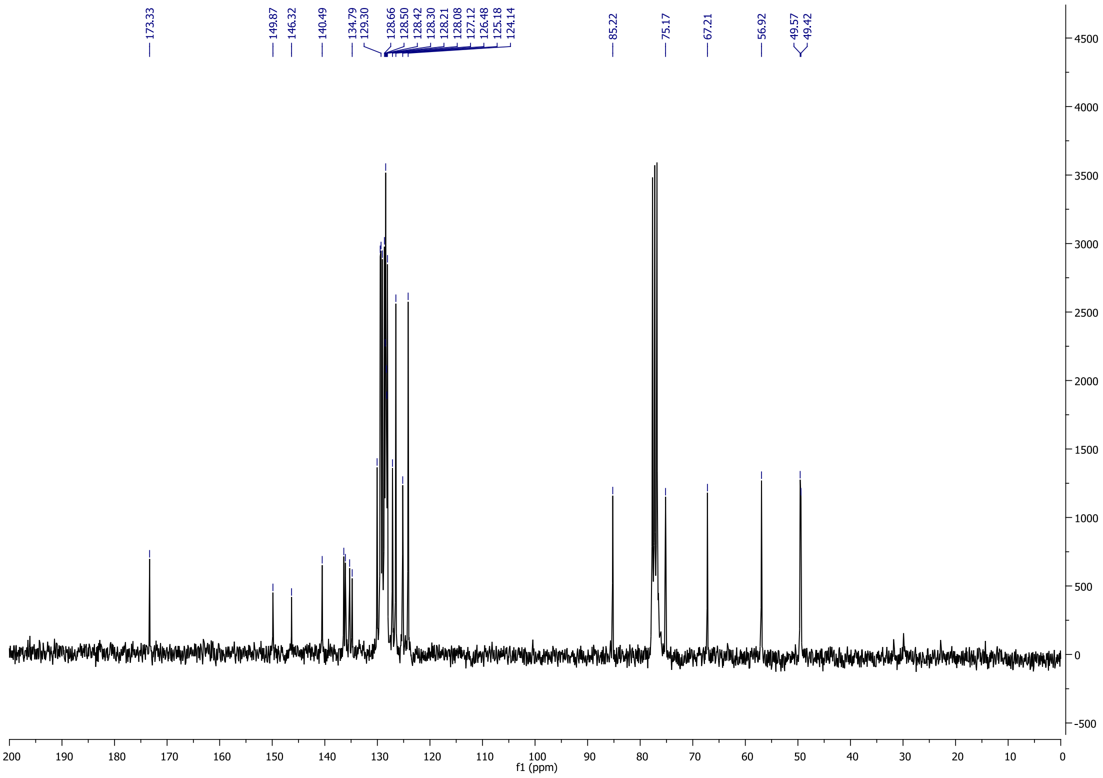

8.00
7.97
7.76
7.73
7.23
7.20
7.15
7.10
6.90
6.64
6.62
5.92
5.89
5.27
5.22
5.01
4.98
4.63
4.57
4.11
4.07
4.05
4.04
4.01
3.99
3.98
3.88
3.86
3.84
3.81
3.71
3.70
3.68
3.67
3.59
3.56
1.60
1.68
15.65
2.00
1.61
0.92
0.93
1.00
0.83
1.90
1.91
1.01
0.98
f1 (ppm)

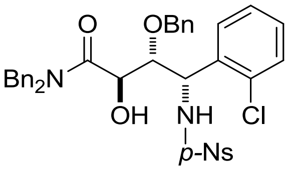

173.34
146.41
136.35
136.19
135.28
134.03
129.28
129.02
128.88
128.66
128.43
128.34
128.20
128.11
126.38
124.19
85.11
74.93
67.26
56.81
49.67
49.41
f1 (ppm)


O
OBn
Bn2N
Cl
OH HN
p-Ns

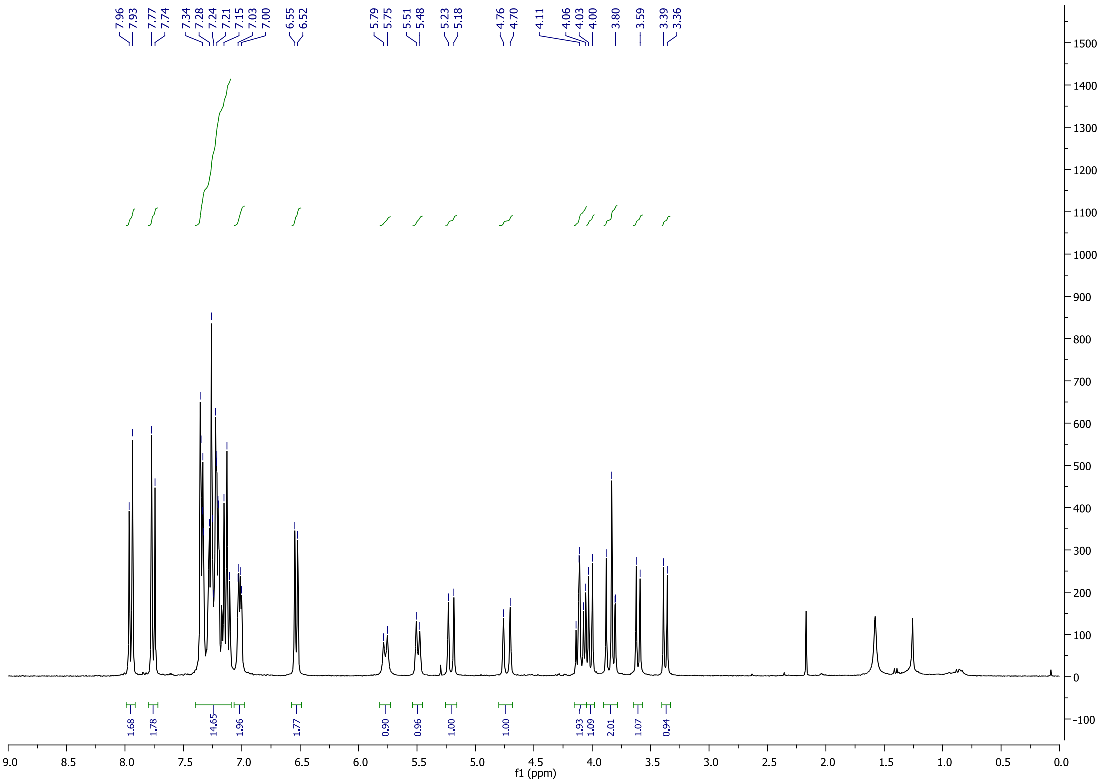
41f

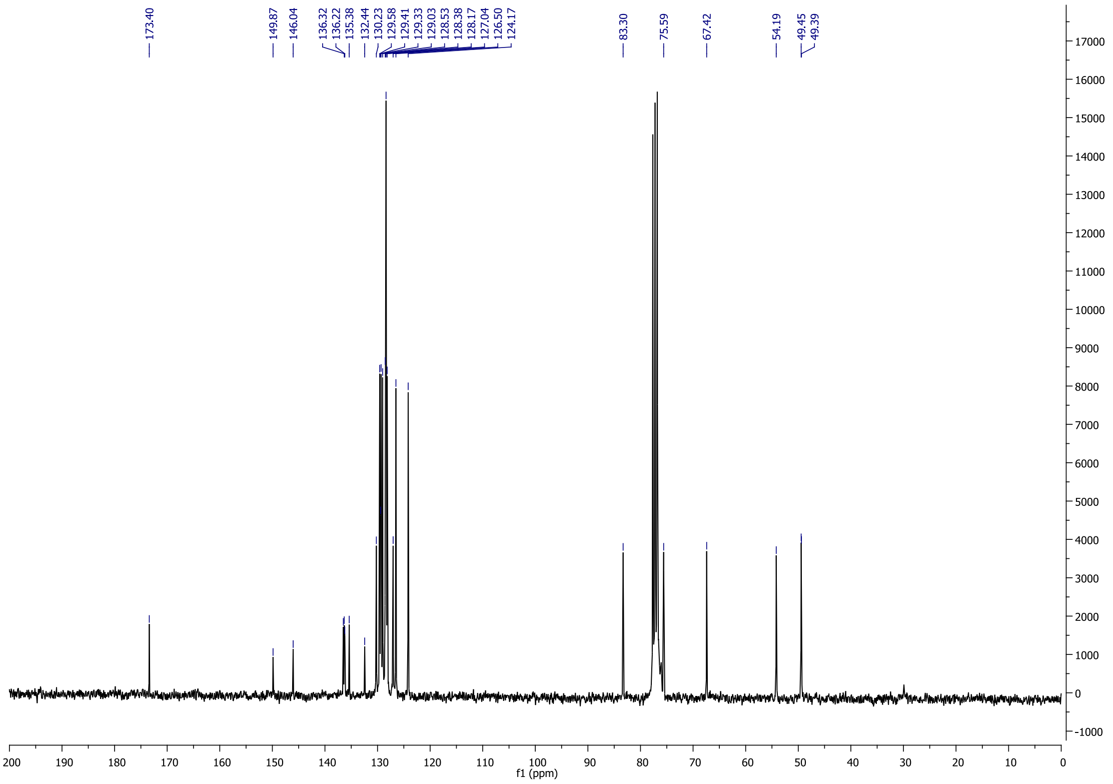

7.99
7.96
7.74
7.71
7.31
7.24
7.20
7.16
7.09
6.97
6.94
6.62
6.60
5.90
5.86
5.28
5.23
5.02
4.98
4.67
4.62
4.08
4.05
4.03
3.87
3.83
3.79
3.71
3.71
3.68
3.68
3.60
3.57
1.68
1.73
13.08
2.10
2.01
1.69
0.95
1.00
0.97
1.04
2.88
1.94
1.03
0.99
f1 (ppm)

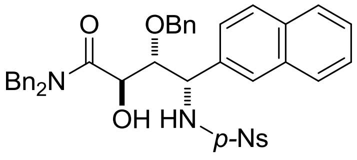

173.33
149.87
146.32
140.49
134.79
129.30
128.66
128.50
128.42
128.30
128.21
128.08
127.12
126.48
125.18
124.14
85.22
75.17
67.21
56.92
49.57
49.42
f1 (ppm)


O
OBn
Bn2N
OH
NH
Cl
p-Ns

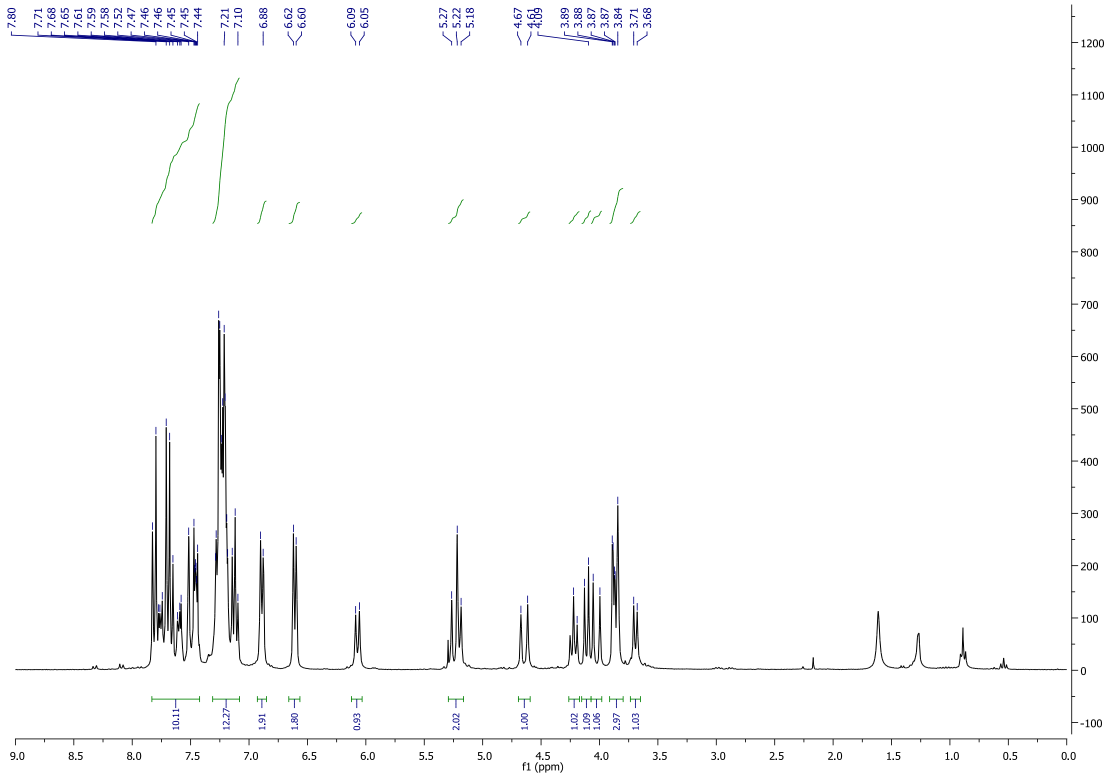
41g

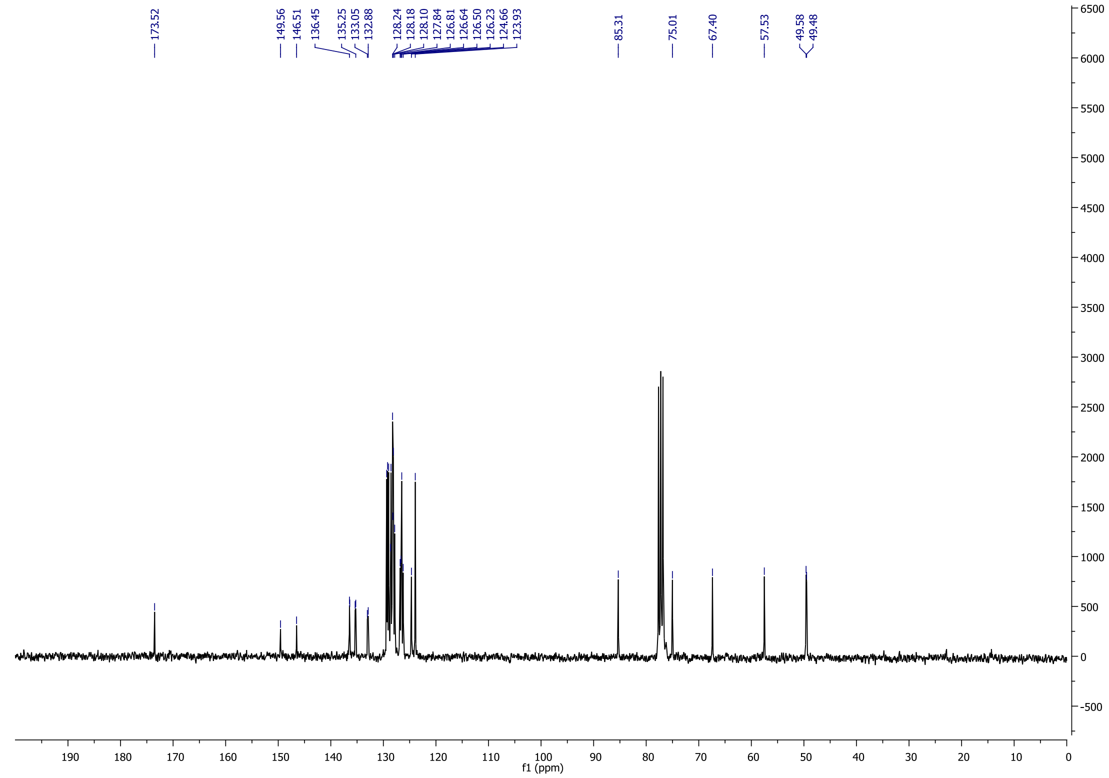

7.96
7.93
7.77
7.74
7.34
7.28
7.24
7.21
7.15
7.03
7.00
6.55
6.52
5.79
5.75
5.51
5.48
5.23
5.18
4.76
4.70
4.11
4.06
4.03
4.00
3.80
3.59
3.39
3.36
1.68
1.78
14.65
1.96
1.77
0.90
0.96
1.00
1.00
1.93
1.09
2.01
1.07
0.94
f1 (ppm)

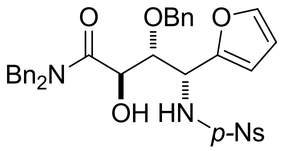

173.40
149.87
146.04
136.32
136.22
135.38
132.44
130.23
129.58
129.41
129.33
129.03
128.53
128.38
128.17
127.04
126.50
124.17
83.30
75.59
67.42
54.19
49.45
49.39
f1 (ppm)


O
OBn
Bn2N
OH
HN
p-Ns

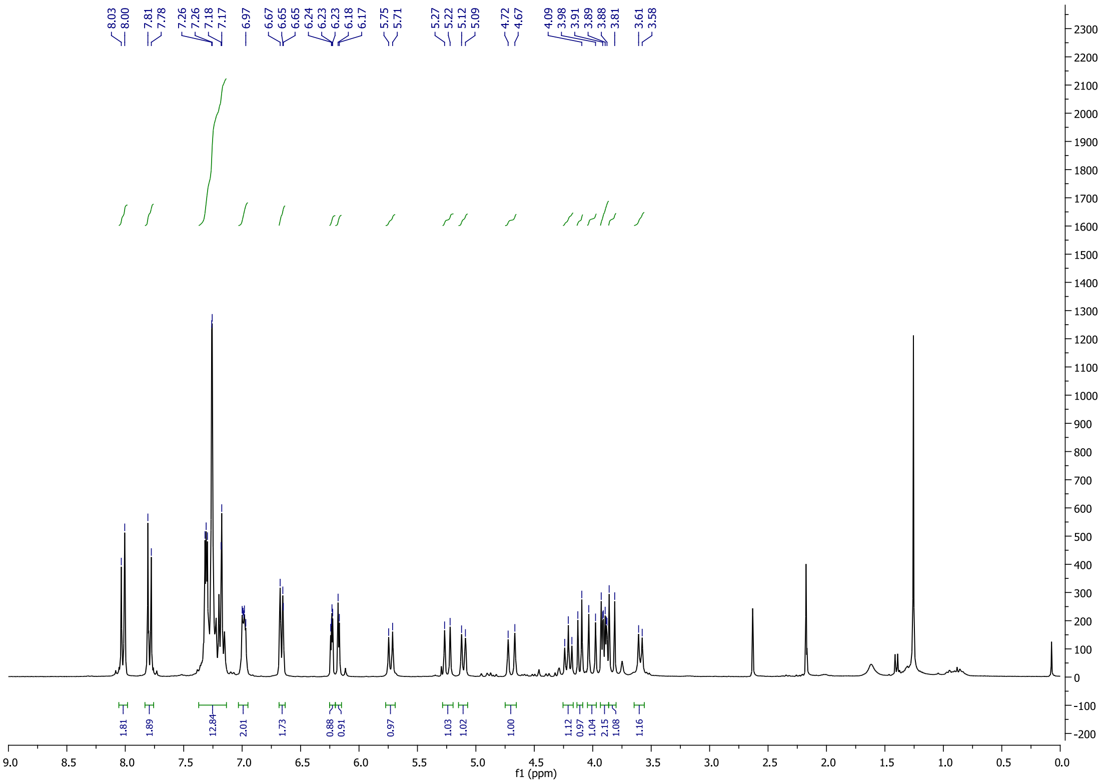
41h

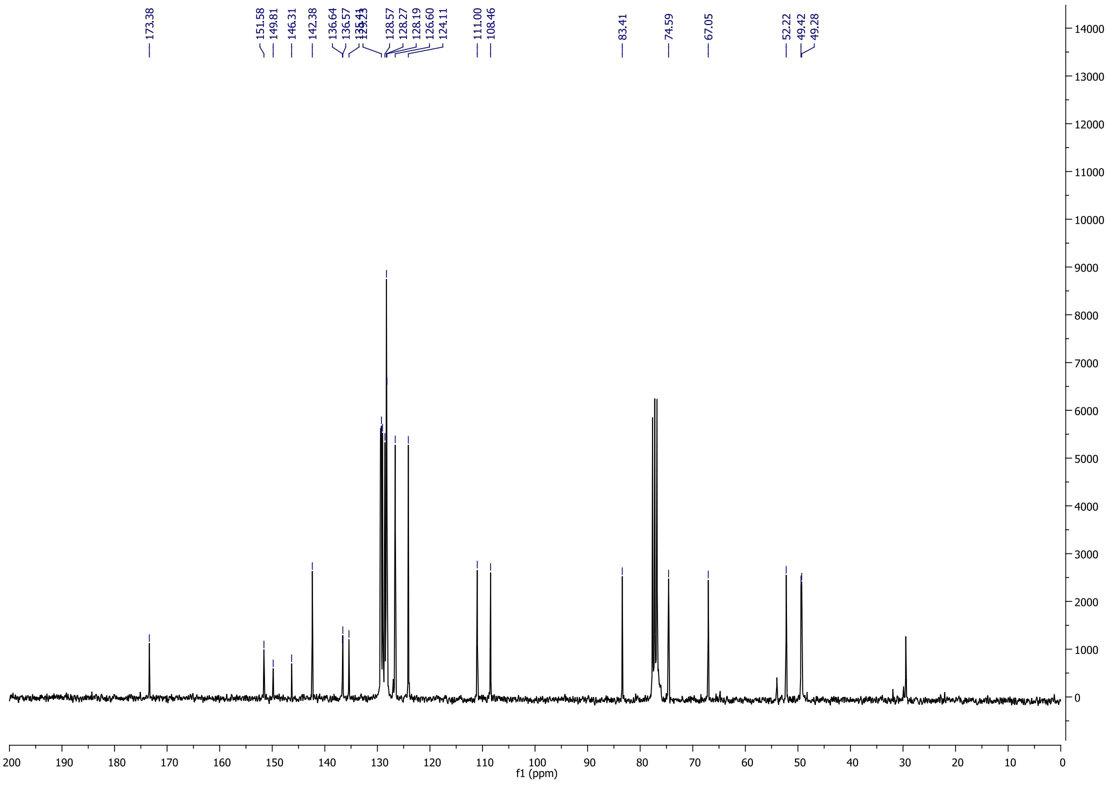

7.80
7.71
7.68
7.65
7.61
7.59
7.58
7.52
7.47
7.46
7.45
7.45
7.44
7.21
7.10
6.88
6.62
6.60
6.09
6.05
5.27
5.22
5.18
4.67
4.61
4.09
3.89
3.88
3.87
3.87
3.84
3.71
3.68
10.11
12.27
1.91
1.80
0.93
2.02
1.00
1.02
1.09
1.06
2.97
1.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100


173.52
149.56
146.51
136.45
135.25
133.05
132.88
128.24
128.18
128.10
127.84
126.81
126.64
126.50
126.23
124.66
123.93
85.31
75.01
67.40
57.53
49.58
49.48
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

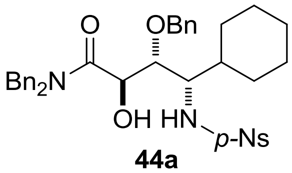

O
OBn
O
Bn2N
OH
HN
p-Ns

41i

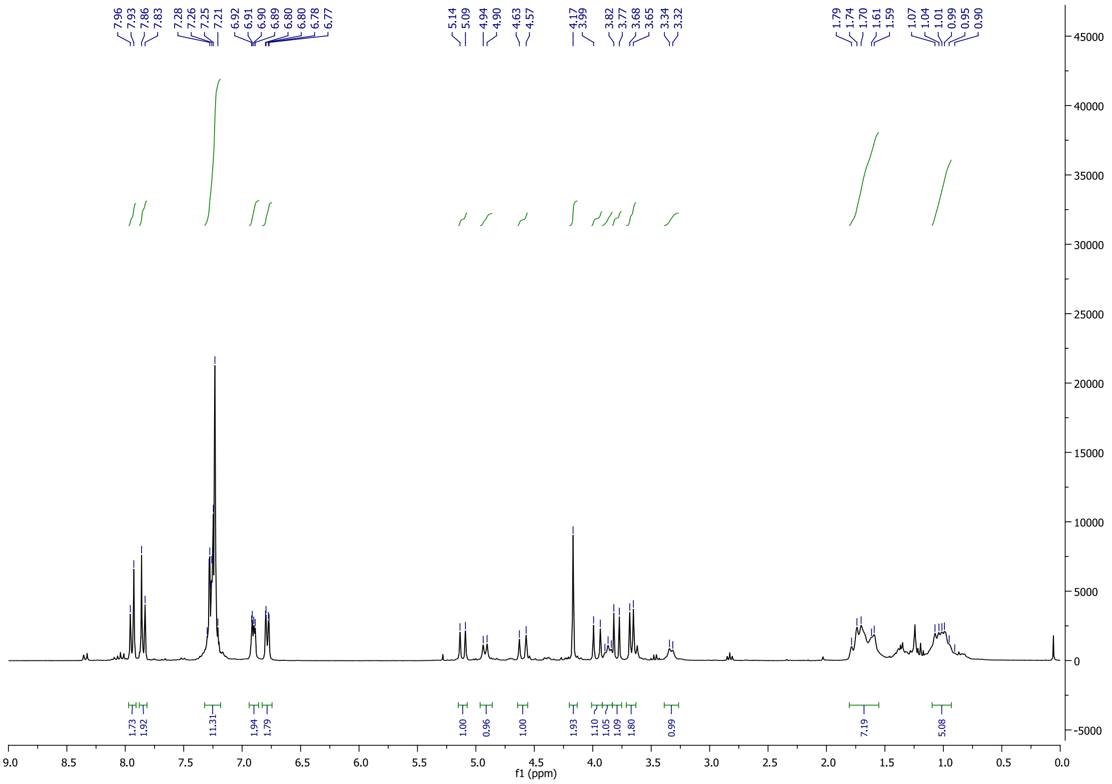

8.03
8.00
7.81
7.78
7.26
7.26
7.18
7.17
6.97
6.67
6.65
6.65
6.24
6.23
6.23
6.18
6.17
5.75
5.71
5.27
5.22
5.12
5.09
4.72
4.67
4.09
3.98
3.91
3.89
3.88
3.81
3.61
3.58
1.81
1.89
12.84
2.01
1.73
0.88
0.91
0.97
1.03
1.02
1.00
1.12
0.97
1.04
2.15
1.08
1.16
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

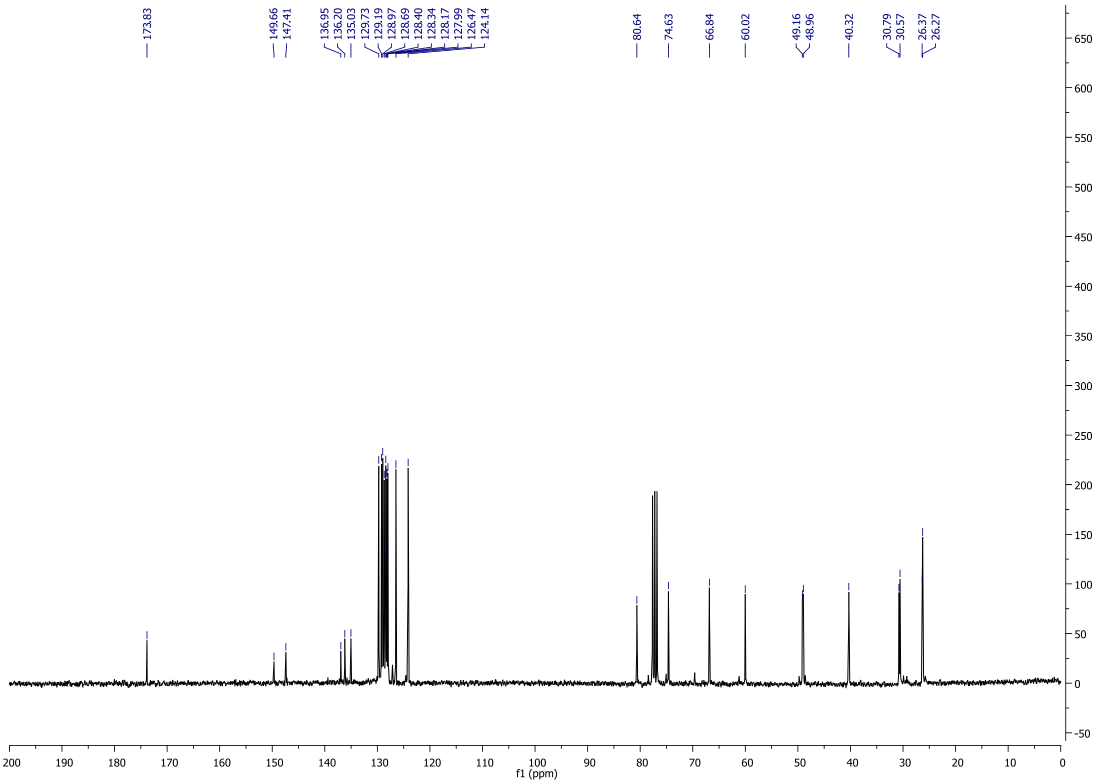

173.38
151.58
149.81
146.31
142.38
136.64
136.57
135.41
129.23
128.57
128.27
128.19
126.60
124.11
111.00
108.46
83.41
74.59
67.05
52.22
49.42
49.28
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0

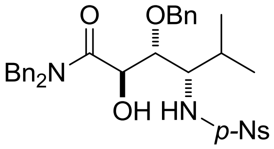
5.8.11. Mannich adducts 44


O
OBn
Bn2N
OH HN
p-Ns

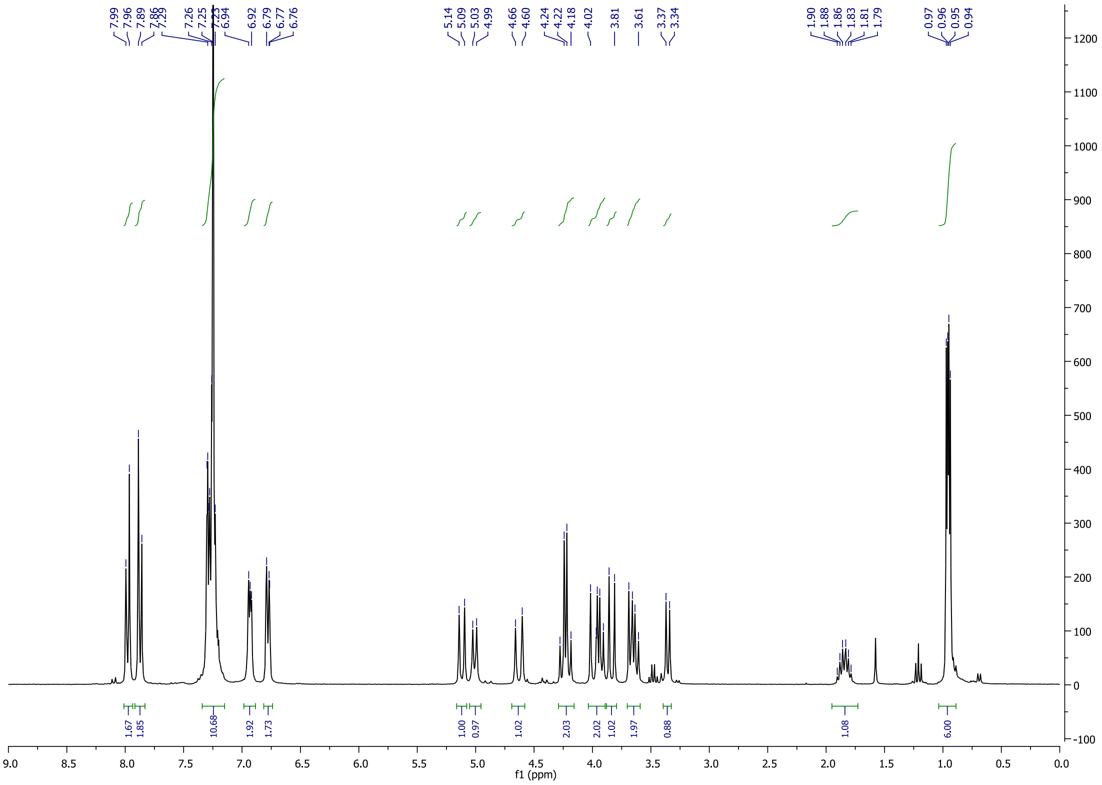
44a

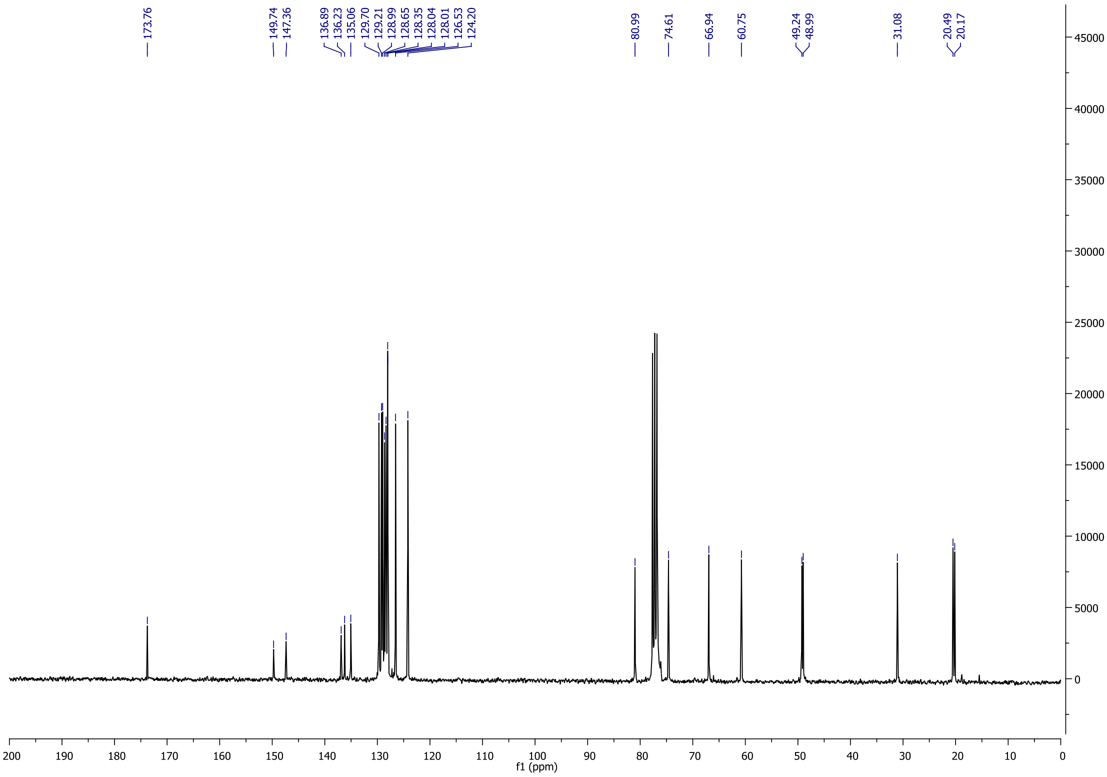


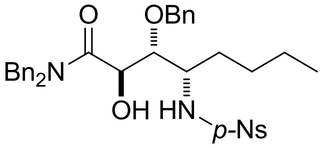



O
OBn
Bn2N
OH
HN
p-Ns

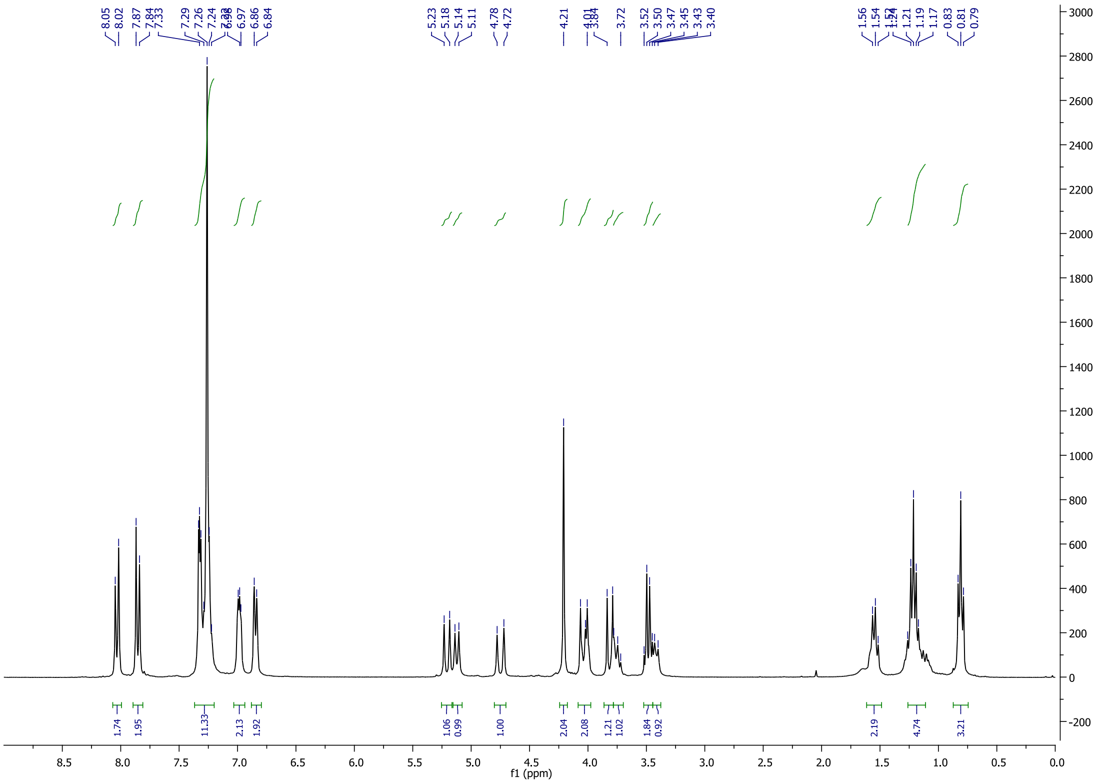
44b

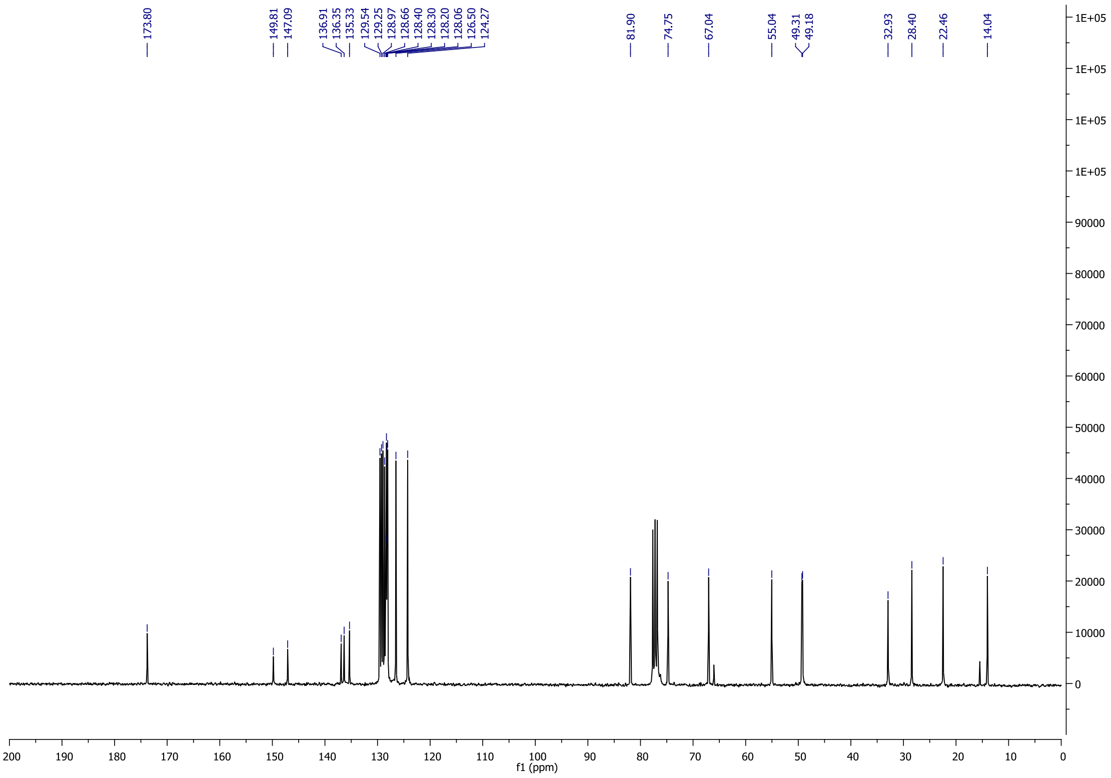

7.99
7.96
7.89
7.86
7.29
7.26
7.25
7.23
6.94
6.92
6.79
6.77
6.76
5.14
5.09
5.03
4.99
4.66
4.60
4.24
4.22
4.18
4.02
3.81
3.61
3.37
3.34
1.90
1.88
1.86
1.83
1.81
1.79
0.97
0.96
0.95
0.94
1.67
1.85
10.68
1.92
1.73
1.00
0.97
1.02
2.03
2.02
1.02
1.97
0.88
1.08
6.00
f1 (ppm)


173.76
149.74
147.36
136.89
136.23
135.06
129.70
129.21
128.99
128.65
128.35
128.04
128.01
126.53
124.20
80.99
74.61
66.94
60.75
49.24
48.99
31.08
20.49
20.17
f1 (ppm)

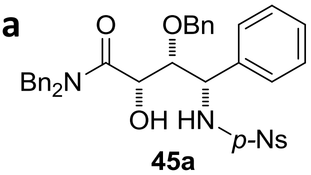

O
OBn
Bn2N
OH
HN
p-Ns

44c

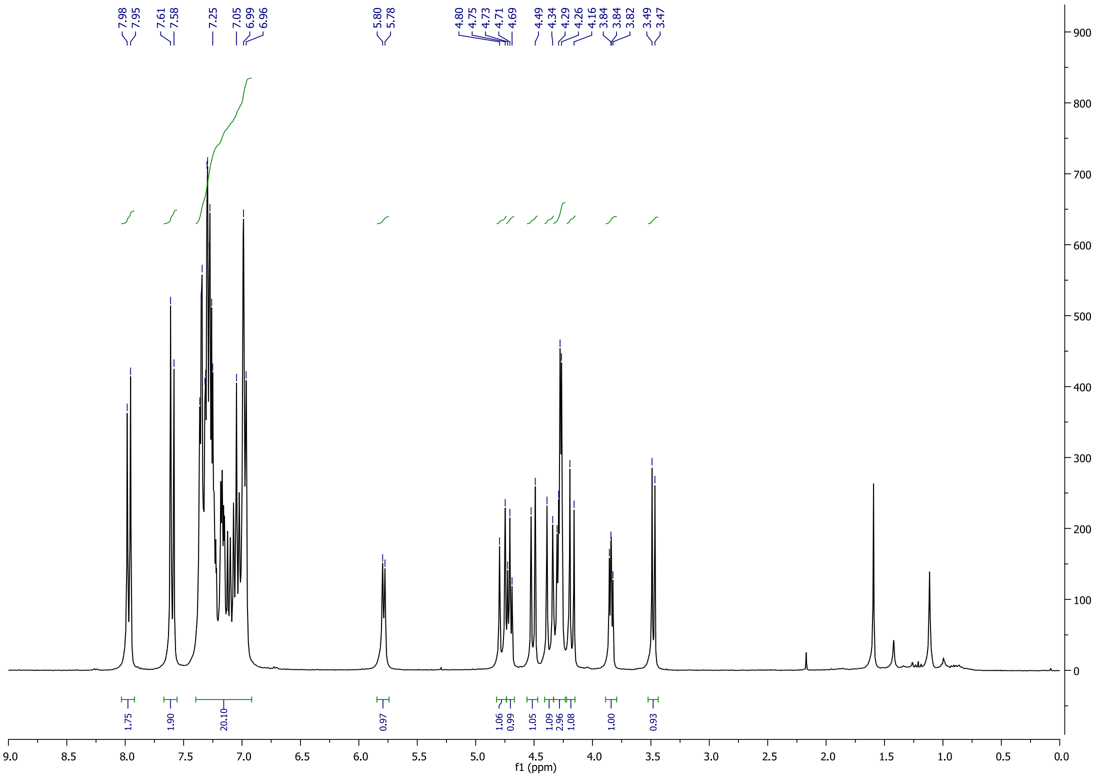

8.05
8.02
7.87
7.84
7.33
7.29
7.26
7.24
6.98
6.97
6.86
6.84
5.23
5.18
5.14
5.11
4.78
4.72
4.21
4.01
3.84
3.72
3.52
3.50
3.47
3.45
3.43
3.40
1.56
1.54
1.52
1.24
1.21
1.19
1.17
0.83
0.81
0.79
1.74
1.95
11.33
2.13
1.92
1.06
0.99
1.00
2.04
2.08
1.21
1.02
1.84
0.92
2.19
4.74
3.21
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

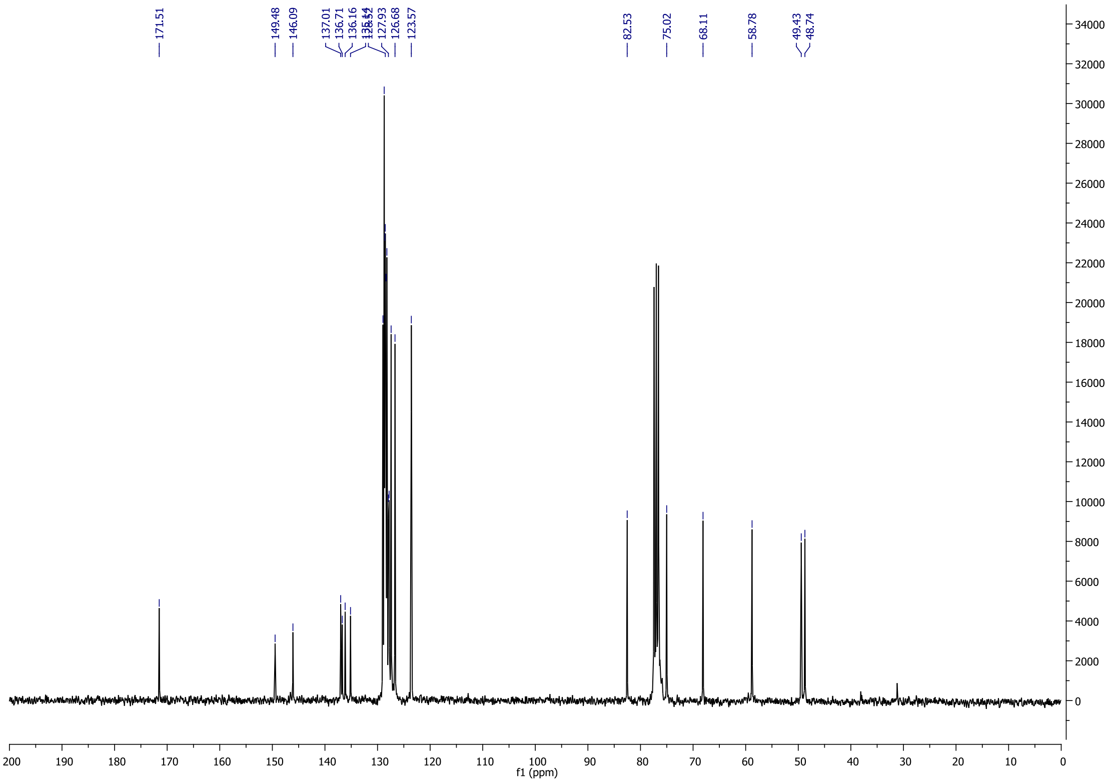

173.80
149.81
147.09
136.91
136.35
135.33
129.54
129.25
128.97
128.66
128.40
128.30
128.20
128.06
126.50
124.27
81.90
74.75
67.04
55.04
49.31
49.18
32.93
28.40
22.46
14.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
1E+05
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0

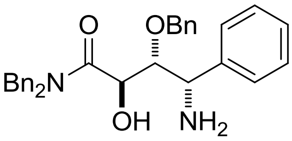
5.8.12. Elaborated adducts 45a, 46a, 47a, 48a, 49a, 51a and 52a


O
OBn
Bn2N
OH
HN
p-Ns

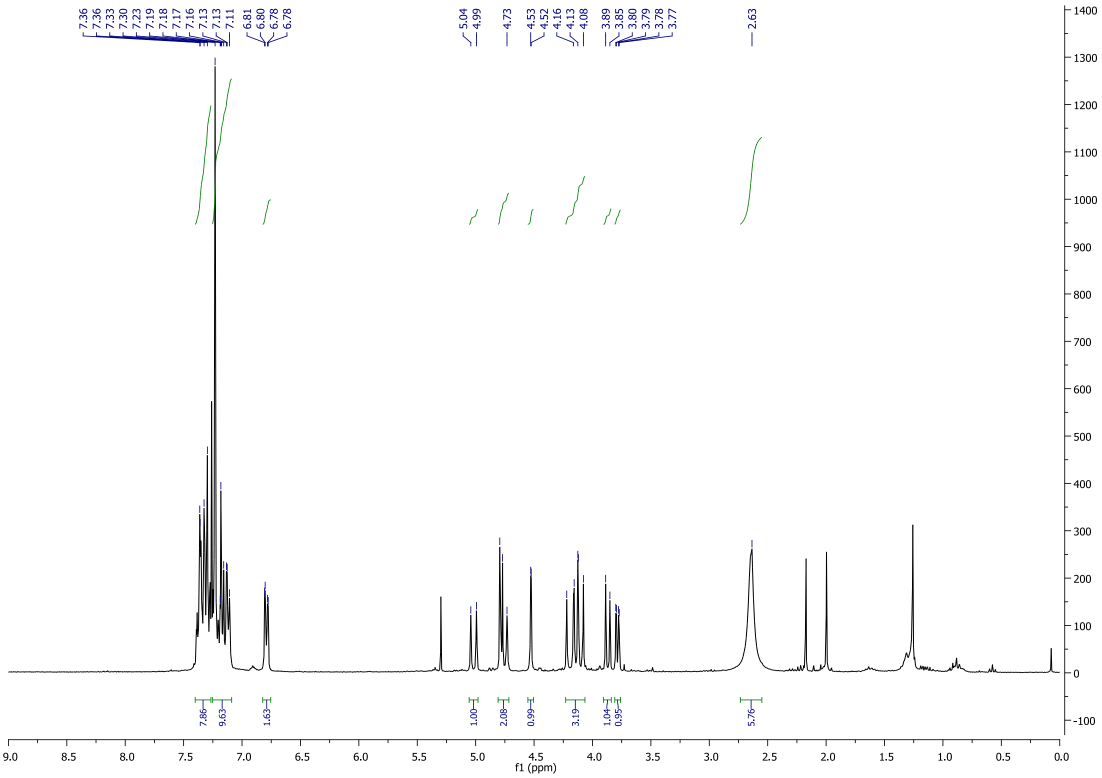
45a

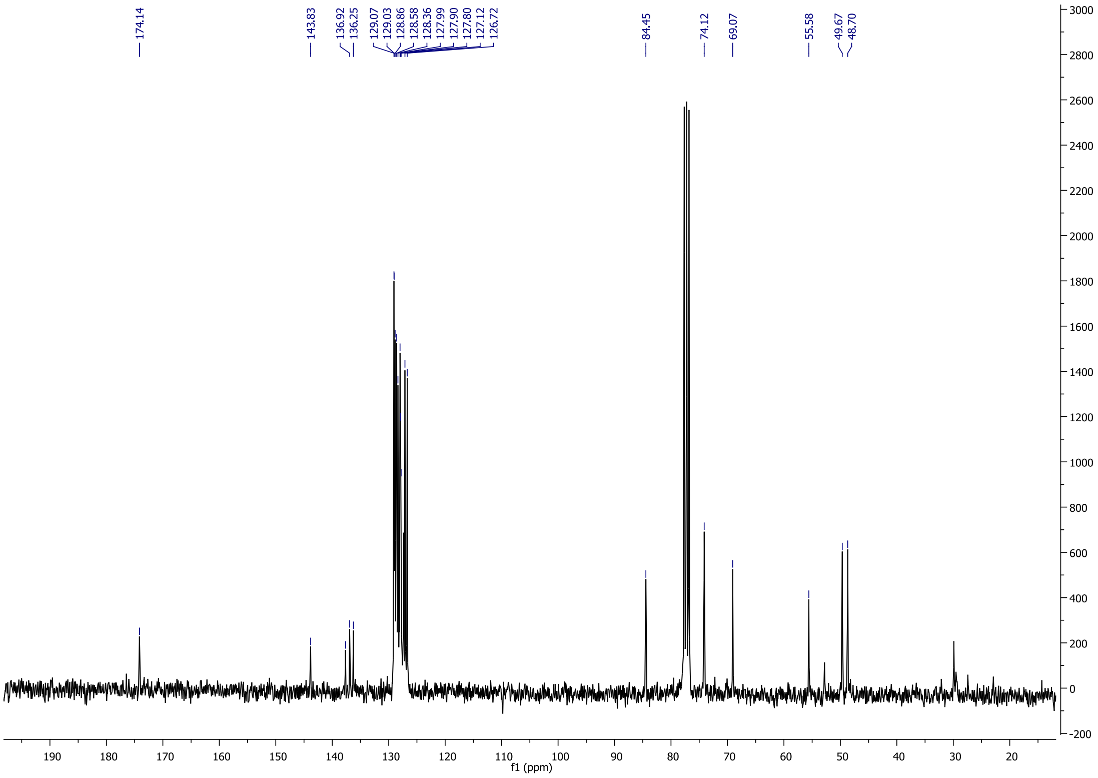


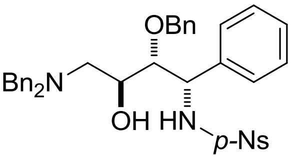



O
OBn
Bn2N
OH
NH2

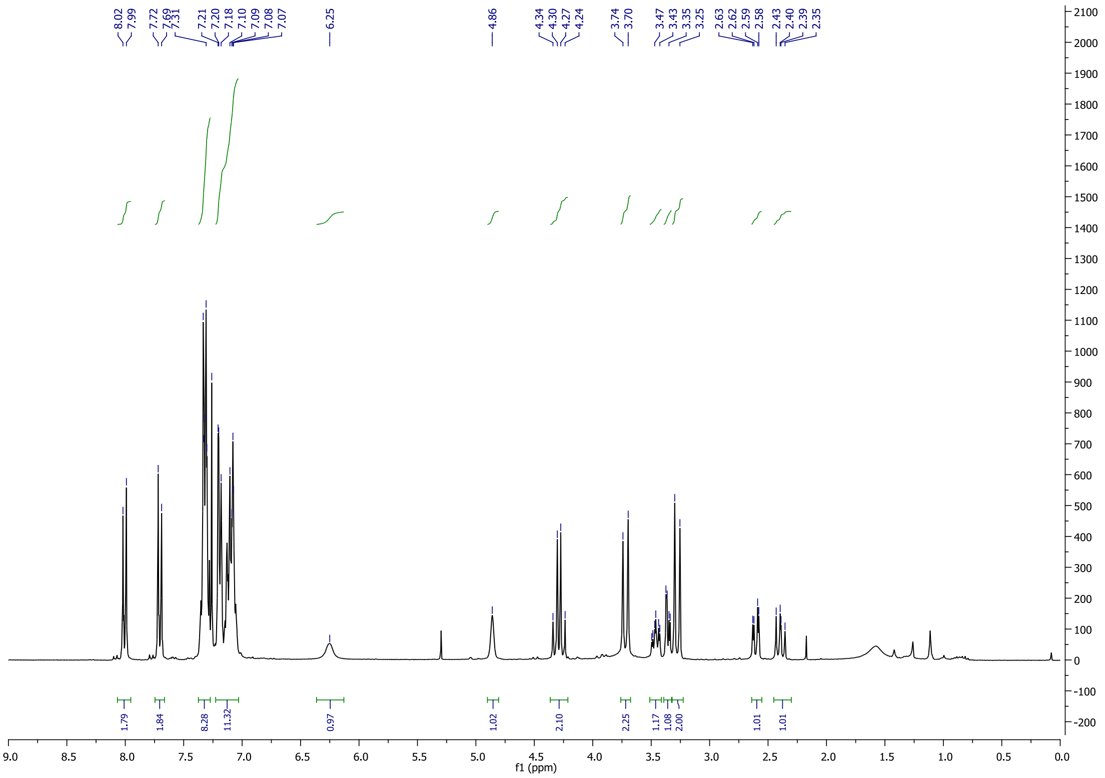
46a

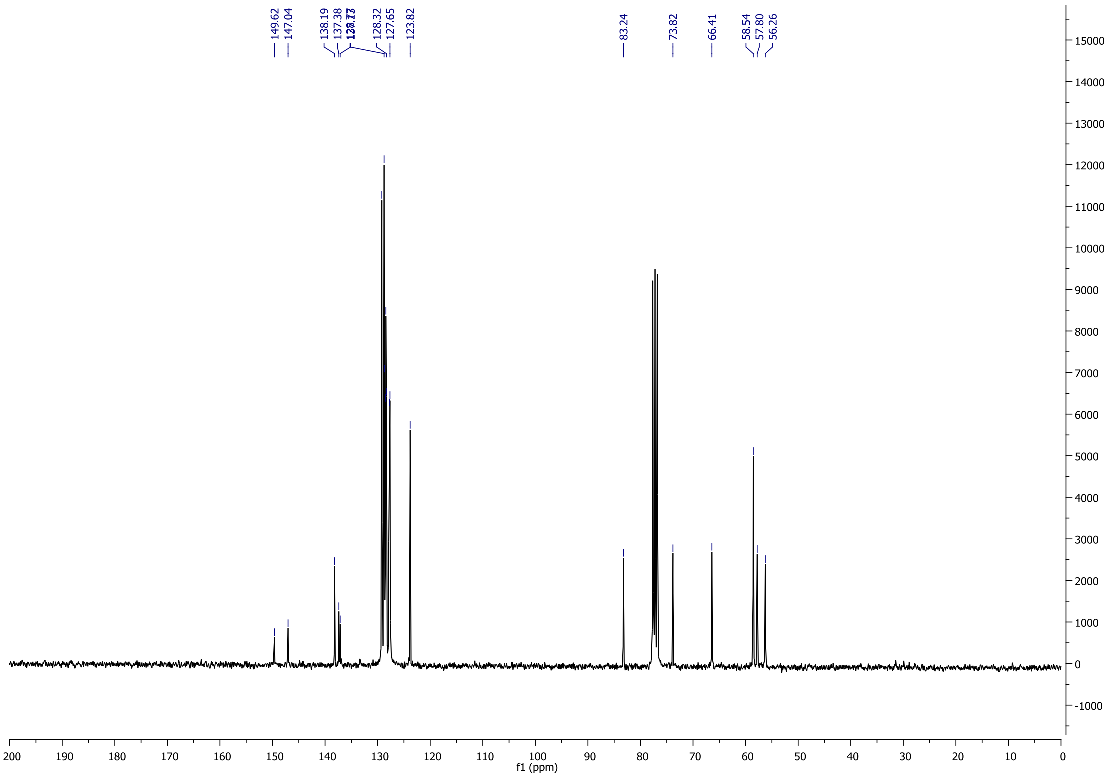

7.36
7.36
7.33
7.30
7.23
7.19
7.18
7.17
7.16
7.13
7.13
7.11
6.81
6.80
6.78
6.78
5.04
4.99
4.73
4.53
4.52
4.16
4.13
4.08
3.89
3.85
3.80
3.79
3.78
3.77
2.63
7.86
9.63
1.63
1.00
2.08
0.99
3.19
1.04
0.95
5.76
f1 (ppm)

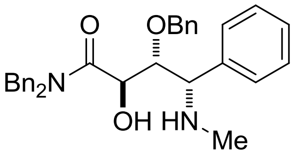

174.14
143.83
136.92
136.25
129.07
129.03
128.86
128.58
128.36
127.99
127.90
127.80
127.12
126.72
84.45
74.12
69.07
55.58
49.67
48.70
f1 (ppm)


OBn
Bn$_2$N
OH
HN
p-Ns

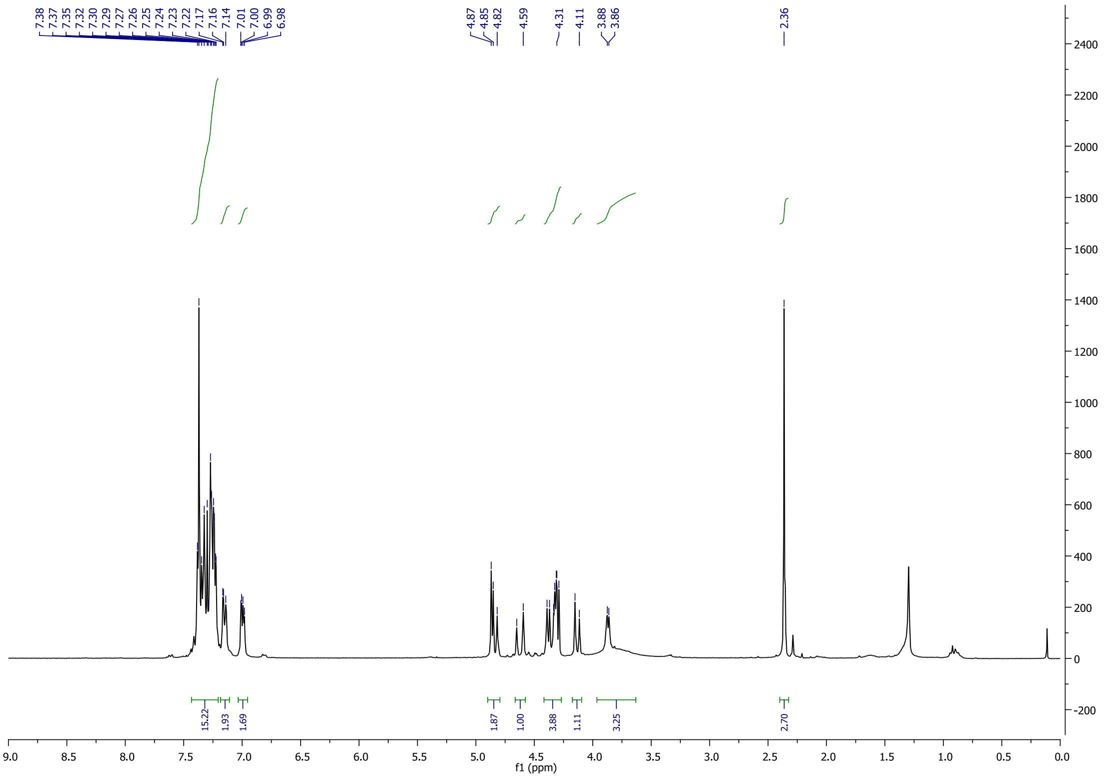
47a

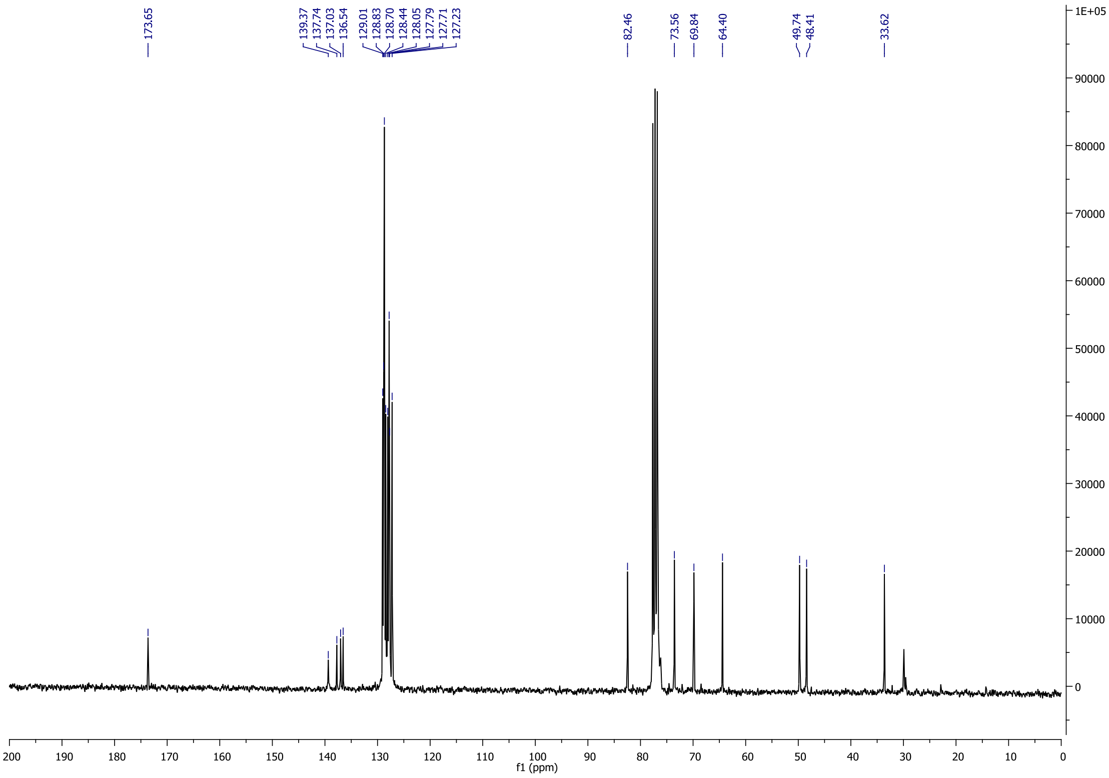

8.02
7.99
7.72
7.69
7.31
7.21
7.20
7.18
7.10
7.09
7.08
7.07
6.25
4.86
4.34
4.30
4.27
4.24
3.74
3.70
3.47
3.43
3.35
3.25
2.63
2.62
2.59
2.58
2.43
2.40
2.39
2.35
1.79
1.84
8.28
11.32
0.97
1.02
2.10
2.25
1.17
1.08
2.00
1.01
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

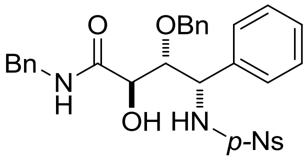

149.62
147.04
138.19
137.38
128.77
128.73
128.32
127.65
123.82
83.24
73.82
66.41
58.54
57.80
56.26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


O
OBn
Bn2N
OH
HN
Me

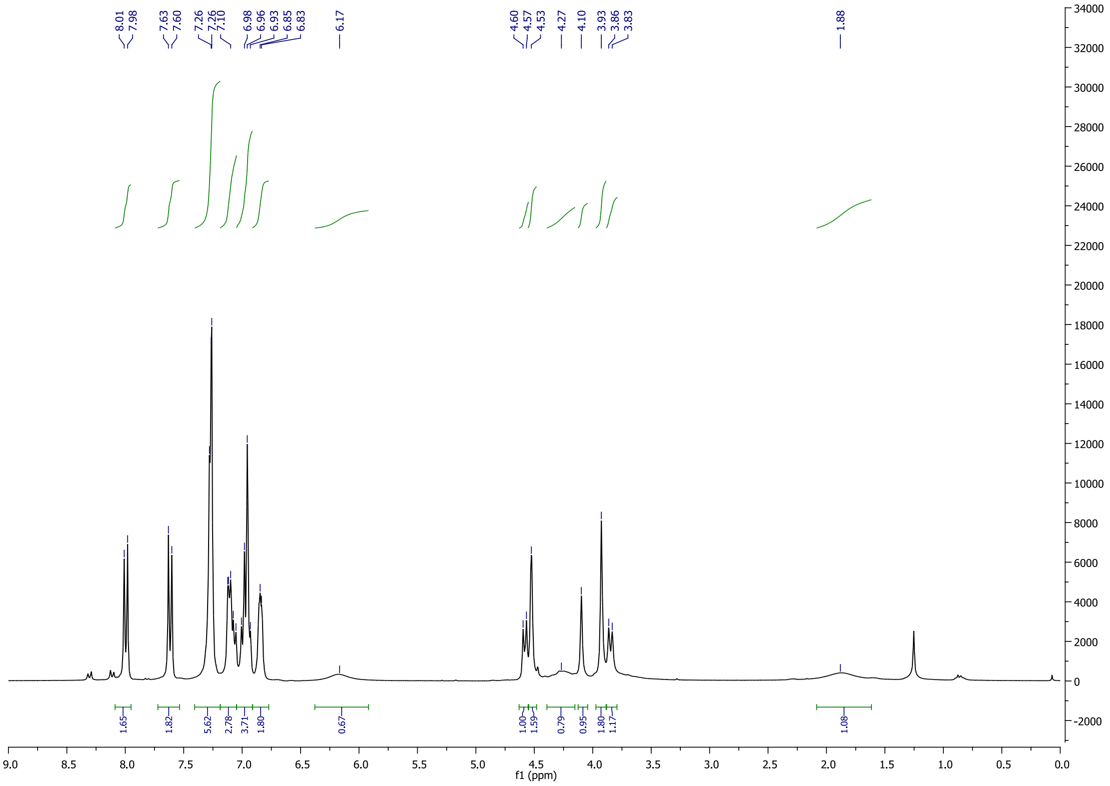
48a

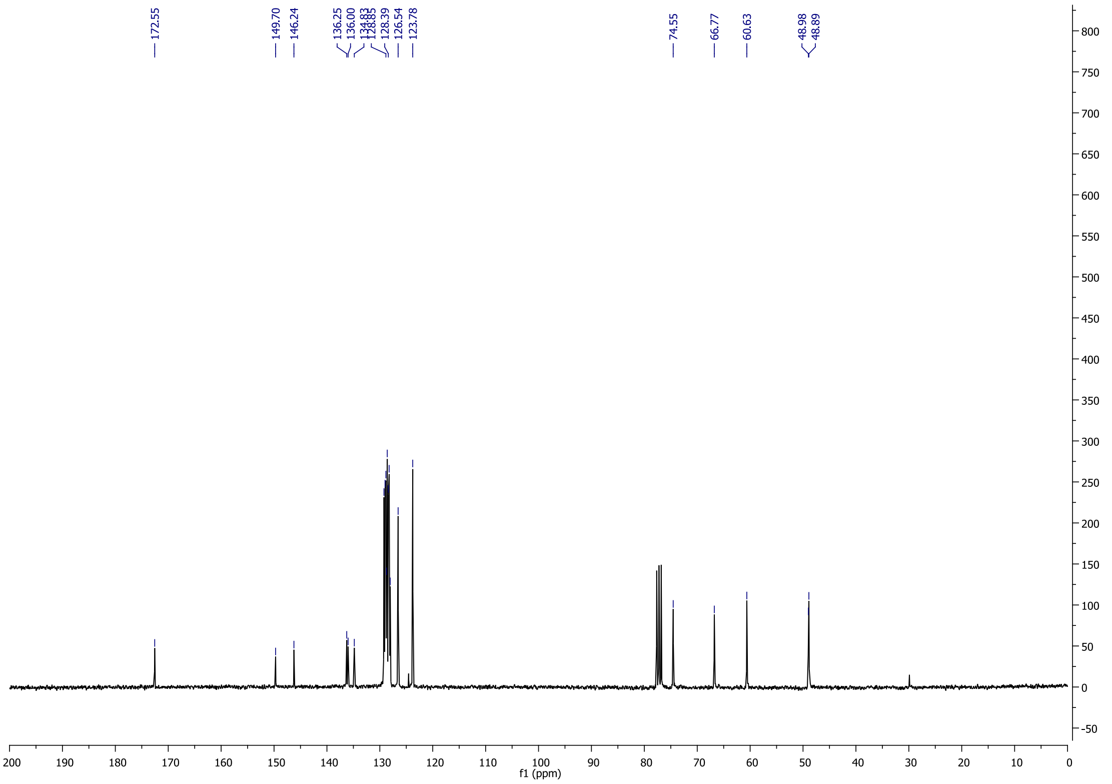

7.38
7.37
7.35
7.32
7.30
7.29
7.27
7.26
7.25
7.24
7.23
7.22
7.17
7.16
7.14
7.01
7.00
6.99
6.98
4.87
4.85
4.82
4.59
4.31
4.11
3.88
3.86
2.36
15.22
1.93
1.69
1.87
1.00
3.88
1.11
3.25
2.70
f1 (ppm)

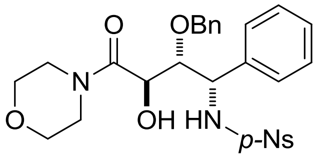

173.65
139.37
137.74
137.03
136.54
129.01
128.83
128.70
128.44
128.05
127.79
127.71
127.23
82.46
73.56
69.84
64.40
49.74
48.41
33.62
1E+05
f1 (ppm)


O
OBn
Bn
N
H
OH
HN
p-Ns

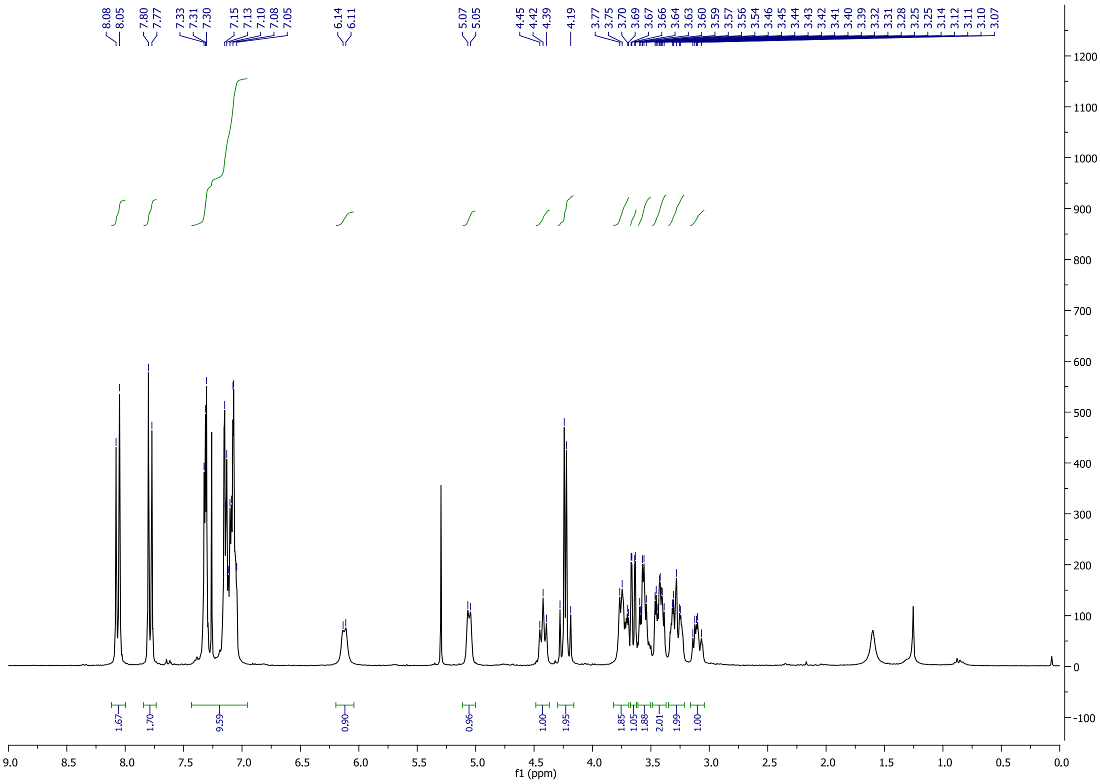
49a

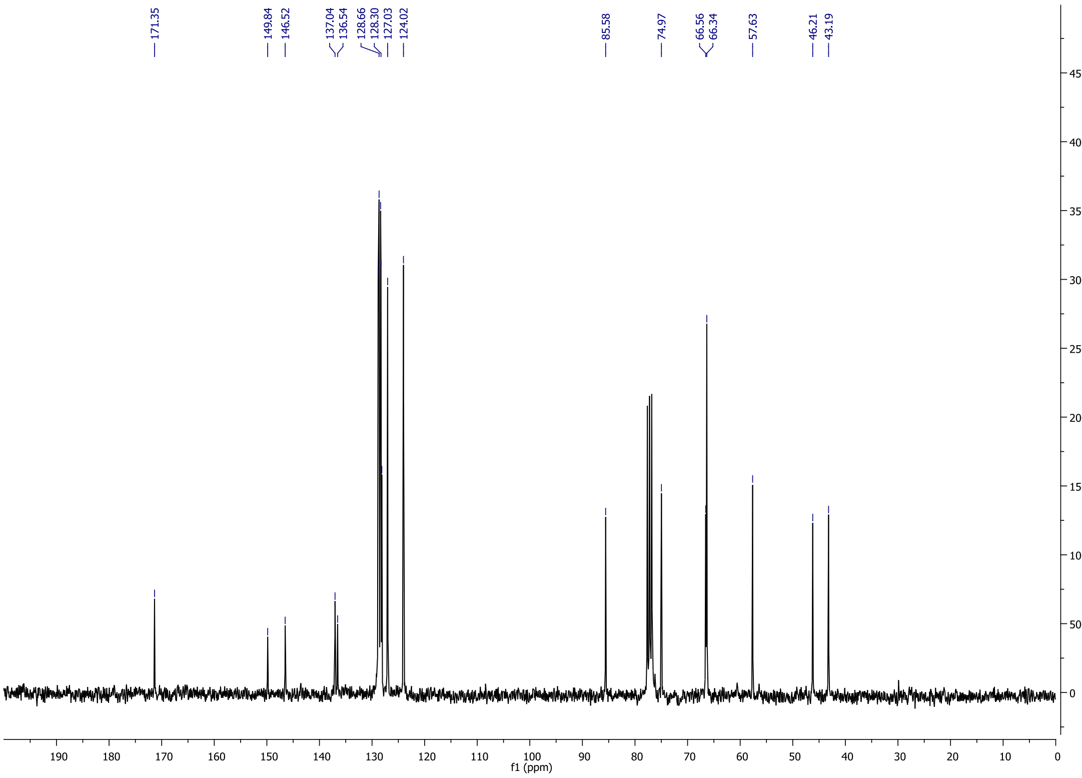

8.01
7.98
7.63
7.60
7.26
7.26
7.10
6.98
6.96
6.93
6.85
6.83
6.17
4.60
4.57
4.53
4.27
4.10
3.93
3.86
3.83
1.88
1.65
1.82
5.62
2.78
3.71
1.80
0.67
1.00
1.59
0.79
0.95
1.80
1.17
1.08
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

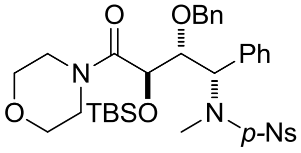

172.55
149.70
146.24
136.25
136.00
134.83
128.85
128.39
126.54
123.78
74.55
66.77
60.63
48.98
48.89
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OBn
N
O
OH
HN
p-Ns

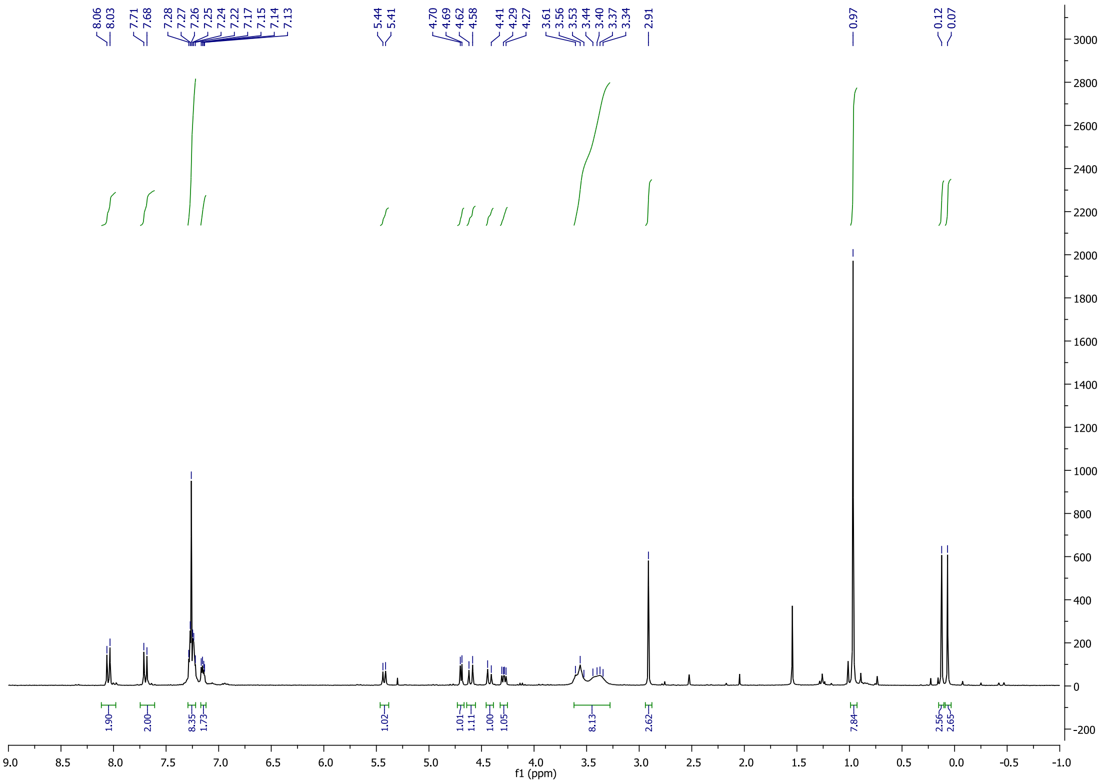
51a


8.08
8.05
7.80
7.77
7.33
7.31
7.30
7.15
7.13
7.10
7.08
7.05
6.14
6.11
5.07
5.05
4.45
4.42
4.39
4.19
3.77
3.75
3.70
3.69
3.67
3.66
3.64
3.63
3.60
3.59
3.57
3.56
3.54
3.46
3.45
3.44
3.43
3.42
3.41
3.40
3.39
3.32
3.31
3.28
3.25
3.25
3.14
3.12
3.11
3.10
3.07
1.67
1.70
9.59
0.90
0.96
1.00
1.95
1.85
1.05
1.88
2.01
1.99
1.00
f1 (ppm)


171.35
149.84
146.52
137.04
136.54
128.66
128.30
127.03
124.02
85.58
74.97
66.56
66.34
57.63
46.21
43.19
f1 (ppm)

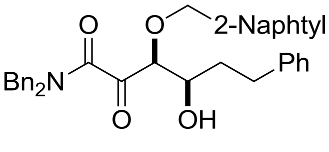

O
OBn
Ph
N
O
TBSO
N
p-Ns

52a


8.06
8.03
7.71
7.68
7.28
7.27
7.26
7.25
7.24
7.22
7.17
7.15
7.14
7.13
5.44
5.41
4.70
4.69
4.62
4.58
4.41
4.29
4.27
3.61
3.56
3.53
3.44
3.40
3.37
3.34
2.91
0.97
0.12
0.07
1.90
2.00
8.35
1.73
1.02
1.01
1.11
1.00
1.05
8.13
2.62
7.84
2.56
2.65
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

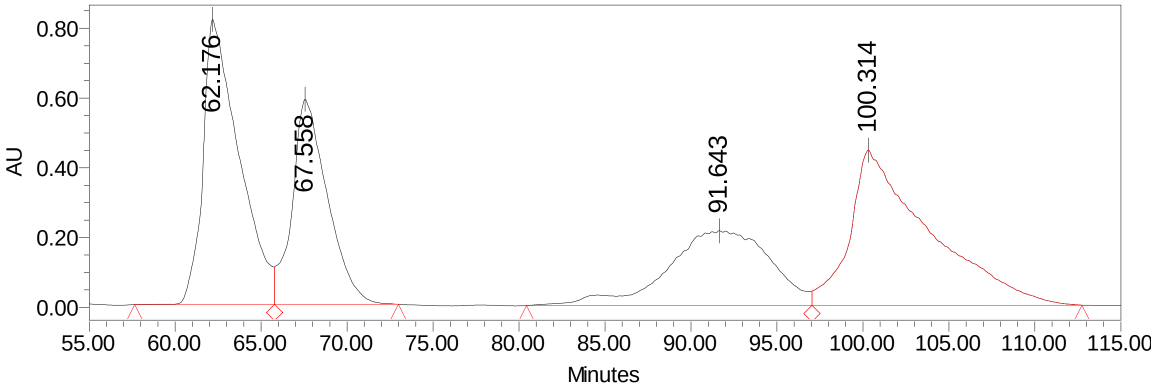
5.9. HPLC Chromatograms

5.9.1. HPLC Chromatograms of aldol adducts 20

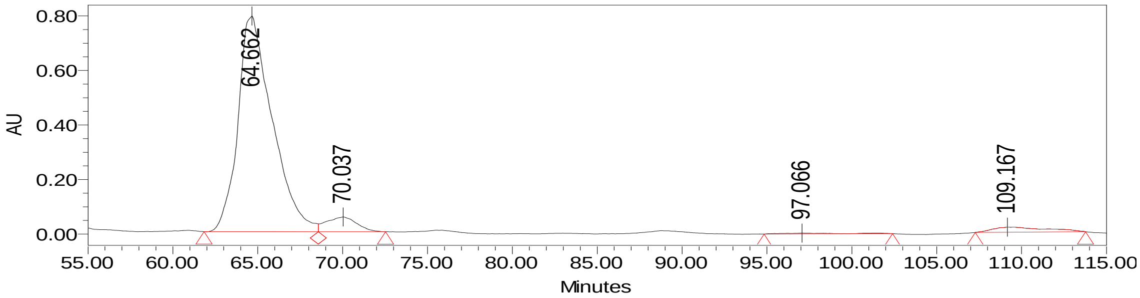


20a

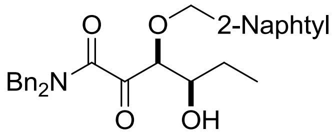
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.50 mL/min, 220 nm).



	Retention Time	% Area
1	62.176	29.80
2	67.558	21.02
3	91.643	19.65
4	100.314	29.52

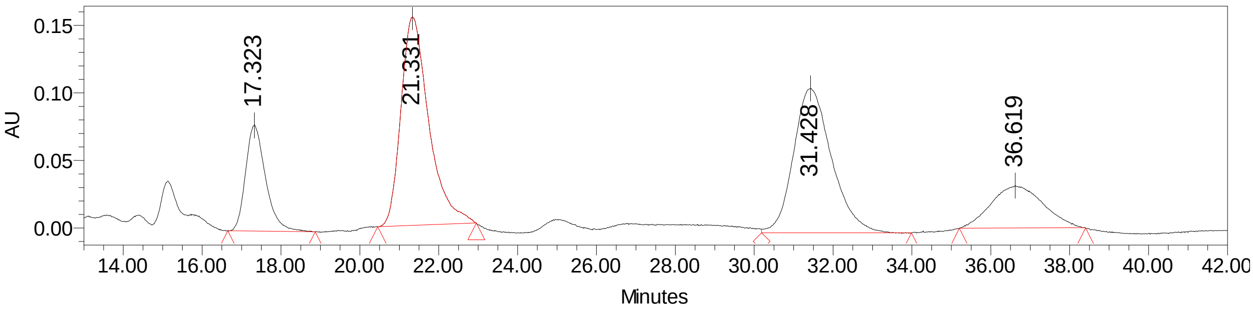


	Retention Time	% Area
1	64.662	90.60
2	70.037	5.46
3	97.066	0.58
4	109.167	3.36

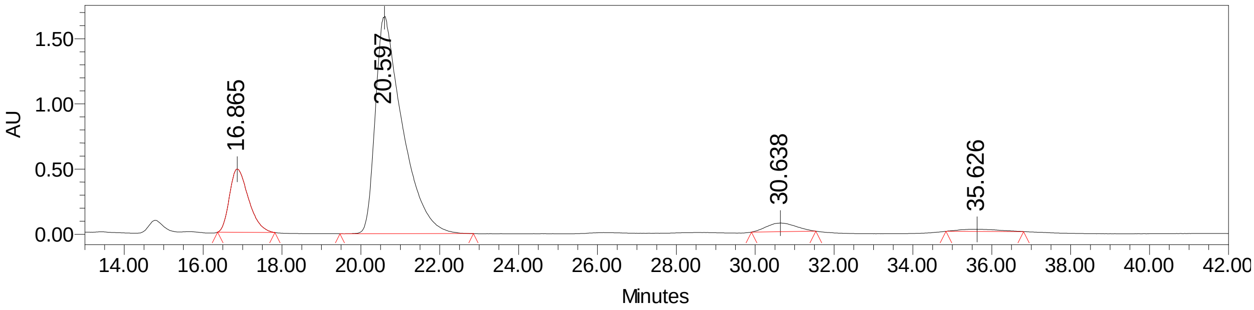


20c

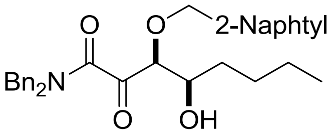
Chiral HPLC (Chiralpak AD-H column; hexane:EtOH 80:20; 1.00 mL/min, 220 nm).



	Retention Time	% Area
1	17.323	13.52
2	21.331	37.18
3	31.428	35.24
4	36.619	14.07

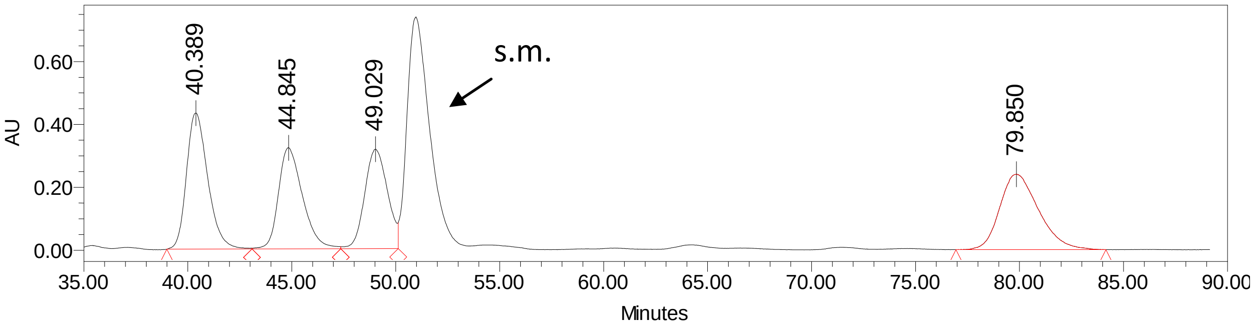


	Retention Time	% Area
1	16.865	16.21
2	20.597	79.22
3	30.638	3.42
4	35.626	1.15

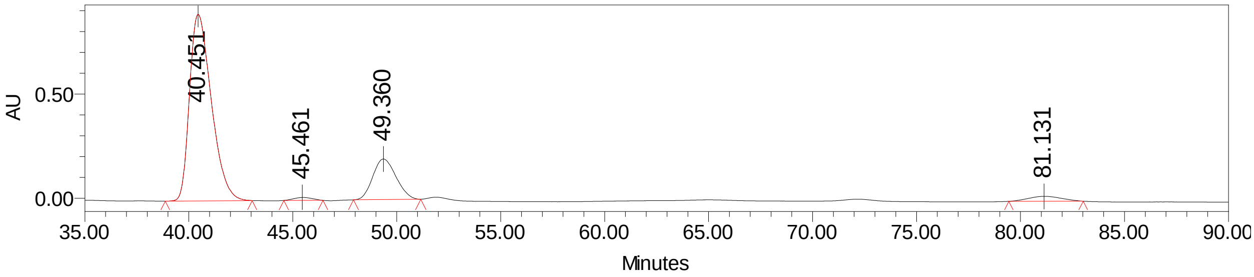


20b

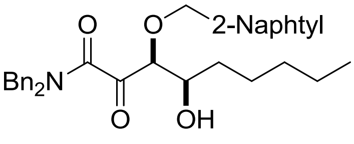
Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm).



	Retention Time	% Area
1	40.389	27.21
2	44.845	22.97
3	49.029	22.48
4	79.850	27.33

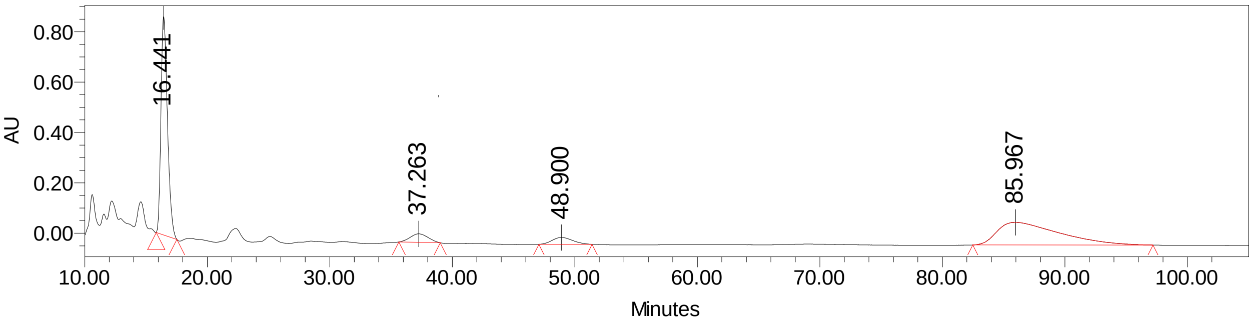


	Retention Time	% Area
1	40.451	78.11
2	45.461	1.04
3	49.360	18.09
4	81.111	2.76

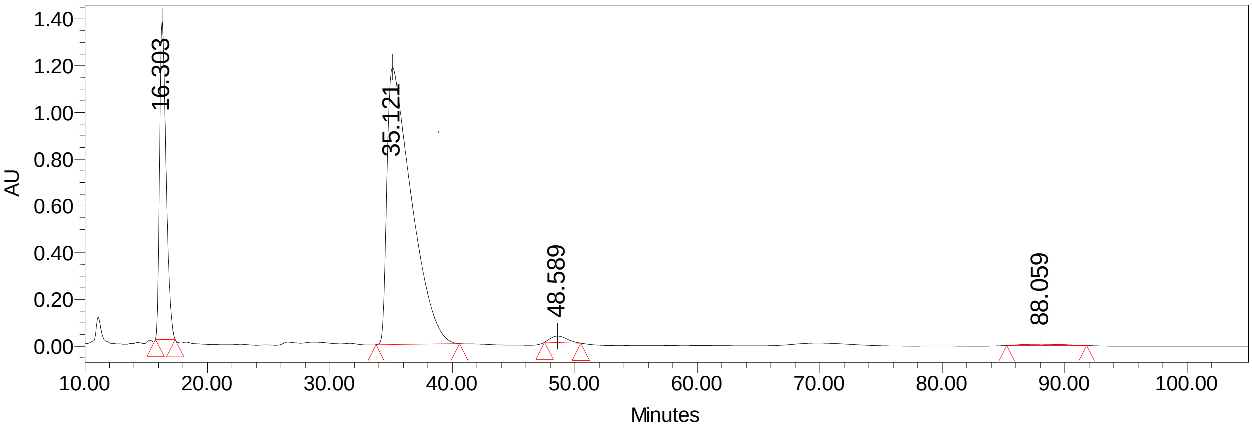


20d

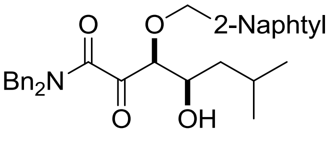
Chiral HPLC (Chiralpak AD-H column; hexane:EtOH 80:20; 1.00 mL/min, 220 nm).



	Retention Time	% Area
1	16.441	45.44
2	37.263	4.91
3	48.900	4.54
4	85.967	45.11

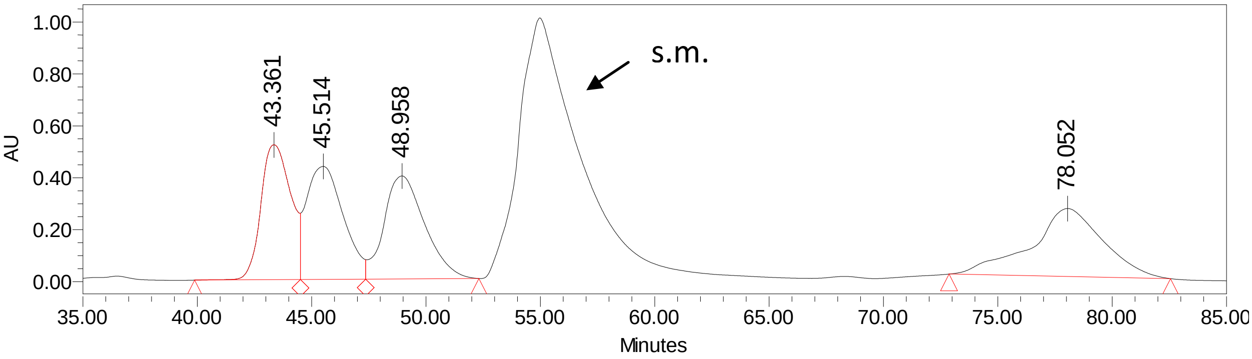


	Retention Time	% Area
1	16.303	22.99
2	35.121	75.24
3	48.589	1.17
4	88.059	0.61

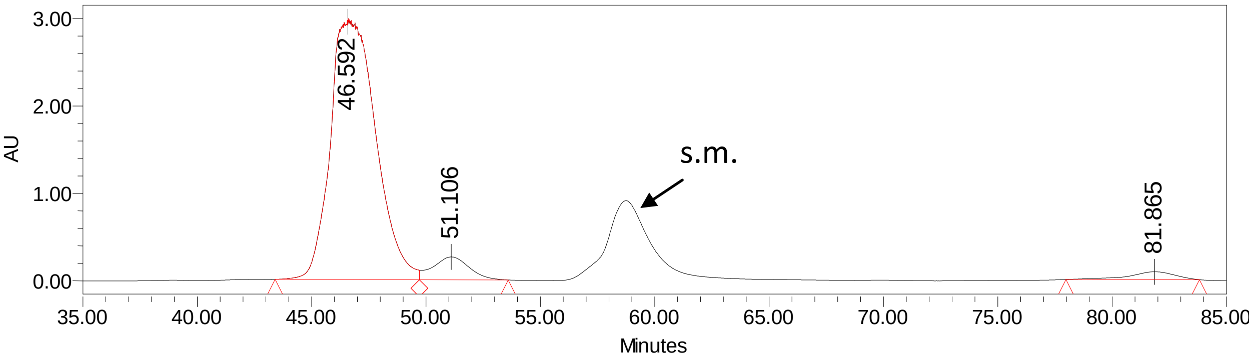


20e

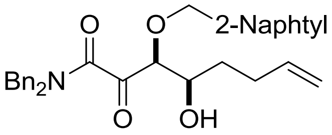
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.50 mL/min, 220 nm).



	Retention Time	% Area
1	43.361	23.33
2	45.514	24.11
3	48.958	24.28
4	78.052	28.28

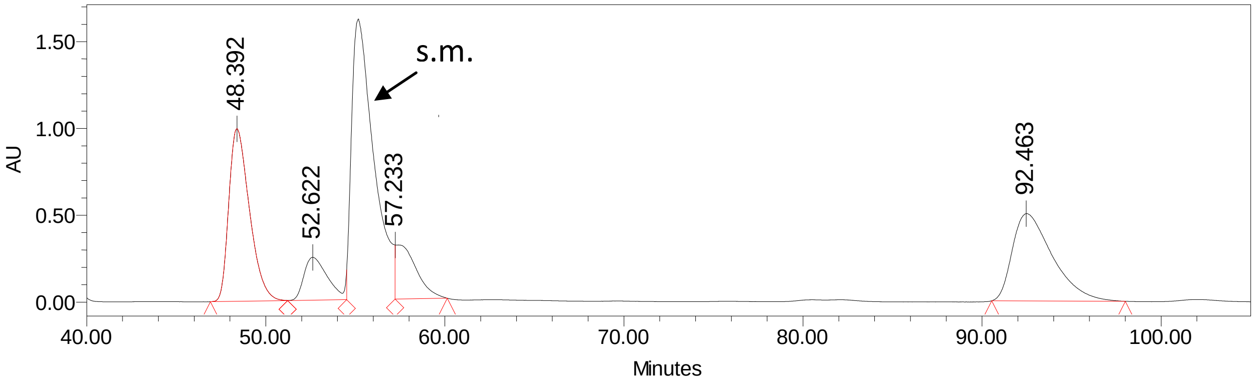


	Retention Time	% Area
1	46.592	90.85
2	51.106	6.39
3	81.865	2.76

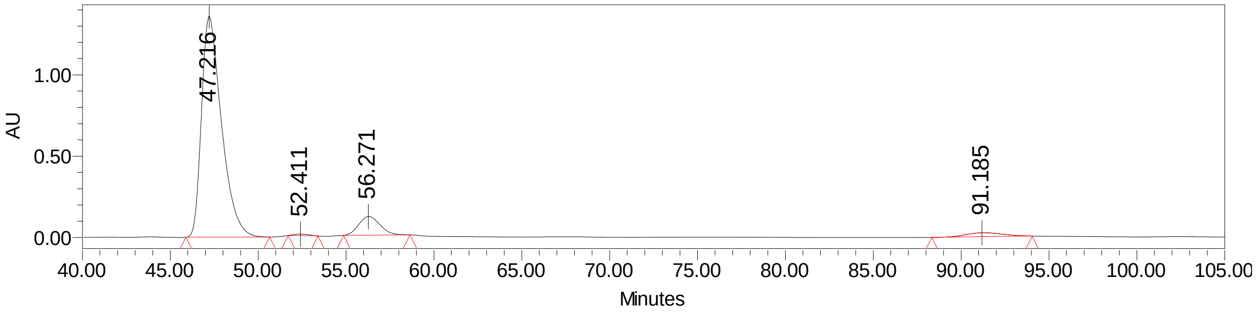


20f

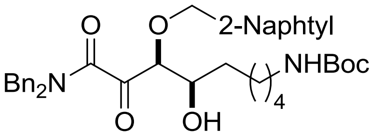
Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm).



	Retention Time	% Area
1	48.392	38.66
2	52.622	11.22
3	57.233	12.17
4	92.463	37.95

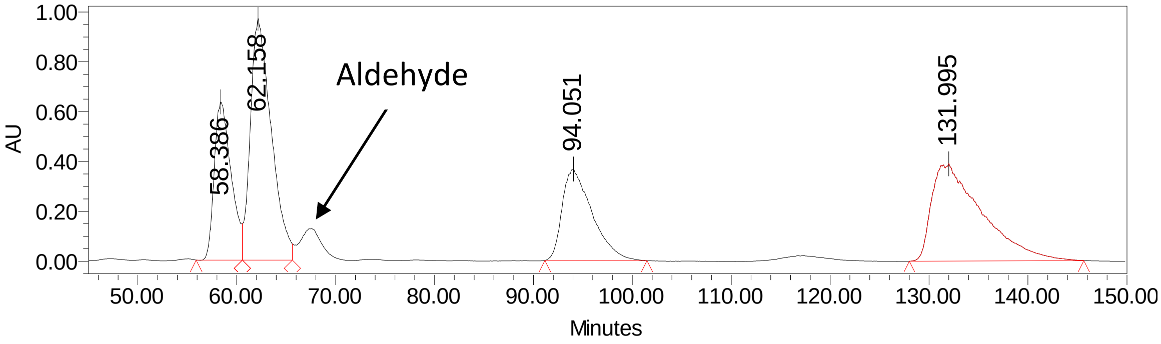


	Retention Time	% Area
1	47.216	88.59
2	52.411	0.52
3	56.271	7.94
4	91.185	2.95

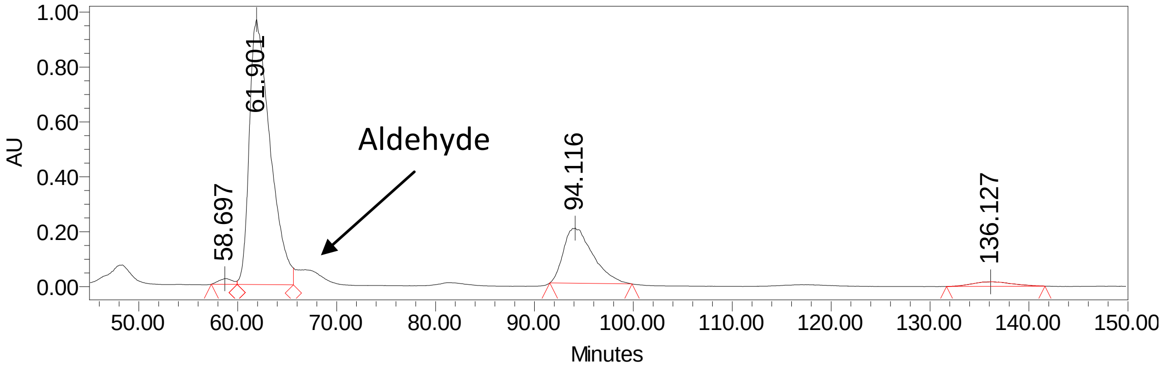


20g

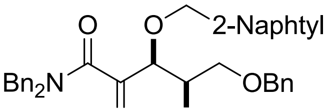
Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 90:10; 0.80 mL/min, 220 nm).



	Retention Time	% Area
1	58.386	17.50
2	62.158	32.83
3	94.051	17.85
4	131.995	31.83

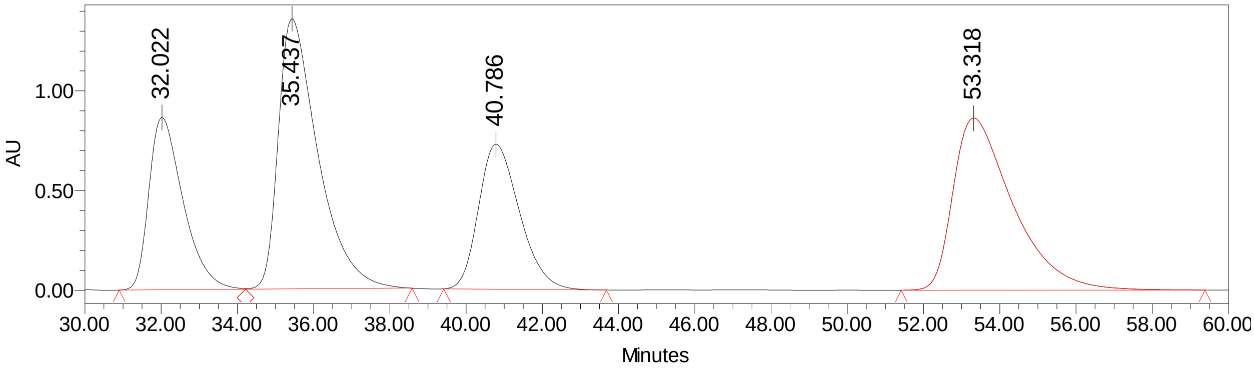


	Retention Time	% Area
1	58.697	1.06
2	61.901	73.39
3	94.116	23.51
4	136.127	2.03

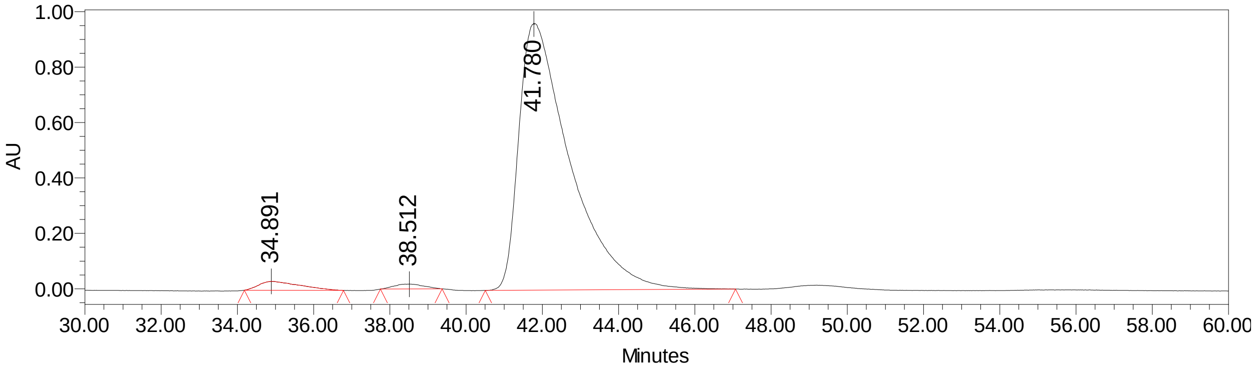


20h

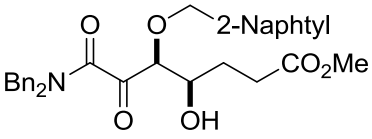
Chiral HPLC (Chiralpak AD-H column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 220 nm).



	Retention Time	% Area
1	32.024	17.38
2	35.434	33.53
3	40.783	17.49
4	53.317	31.60

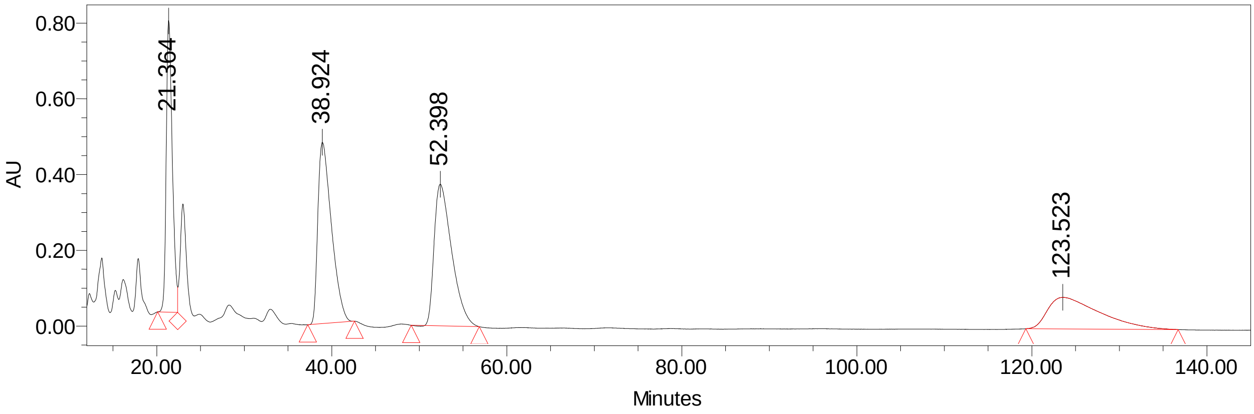


	Retention Time	% Area
1	34.891	2.47
2	38.512	1.18
3	41.780	96.35

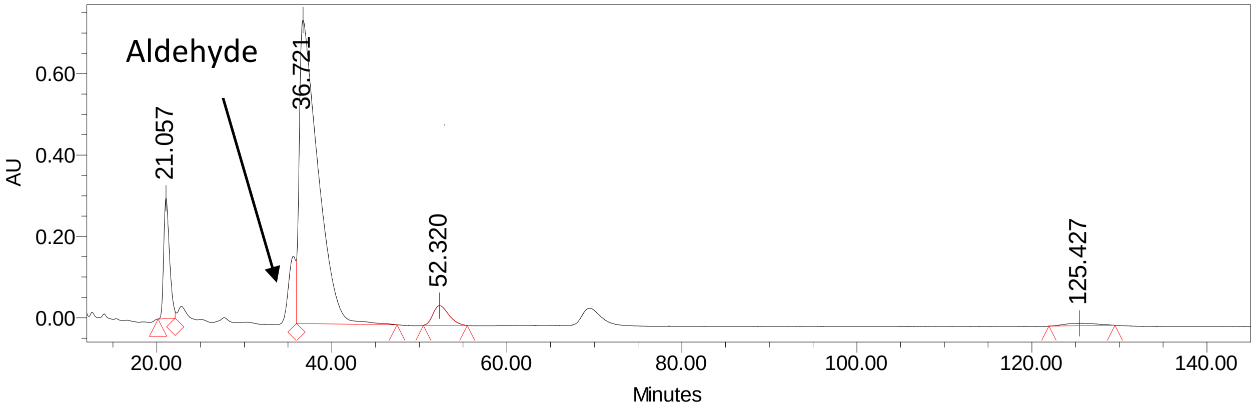


20i

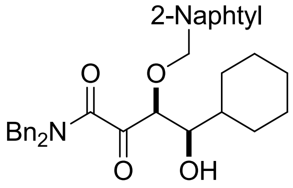
Chiral HPLC (Chiralpak AD-H column; hexane:EtOH 50:50; 1.00 mL/min, 220 nm).



	Retention Time	% Area
1	21.364	21.08
2	38.924	29.53
3	52.398	29.80
4	123.523	19.59

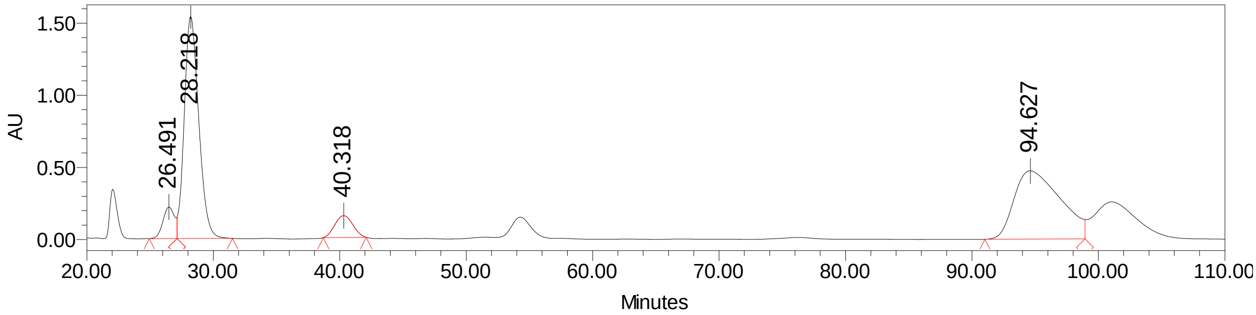


	Retention Time	% Area
1	21.057	10.39
2	36.721	83.81
3	52.320	4.61
4	125.427	1.19

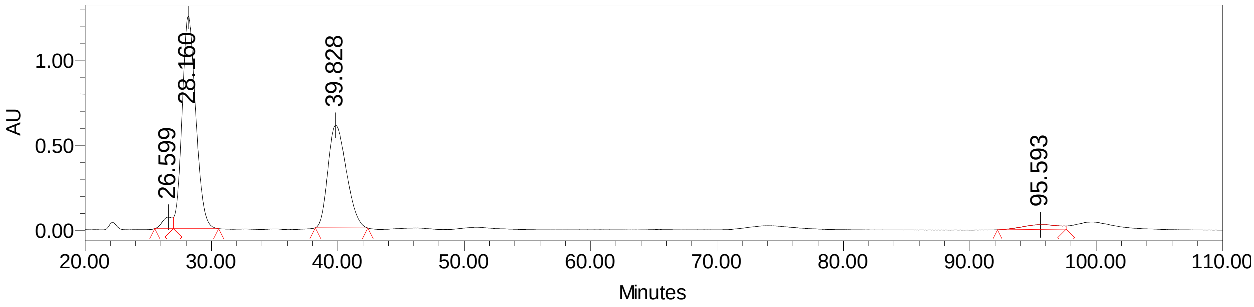


20j

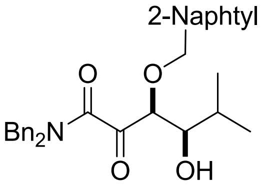
Chiral HPLC (Chiralpak IC column; hexane:*i*-PrOH 95:5; 1.00 mL/min, 220nm).



	Retention Time	% Area
1	26.491	5.17
2	28.218	44.99
3	40.318	5.51
4	94.627	44.33

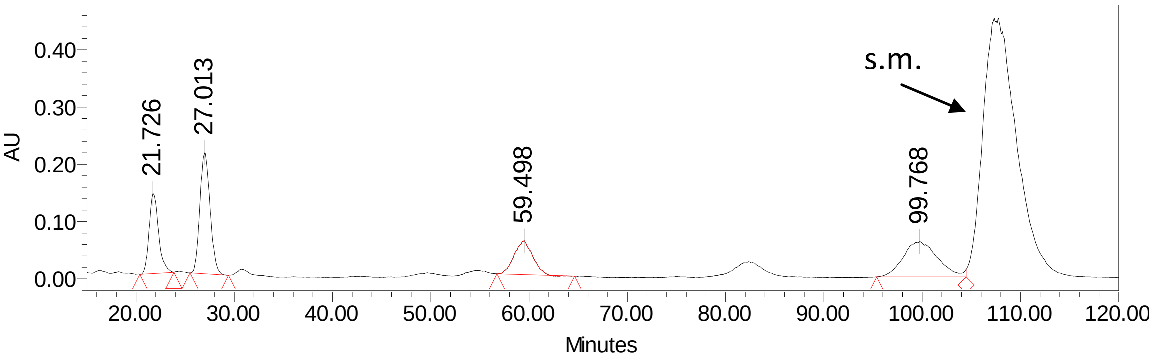


	Retention Time	% Area
1	26.599	2.27
2	28.160	56.92
3	39.828	37.77
4	95.593	3.03

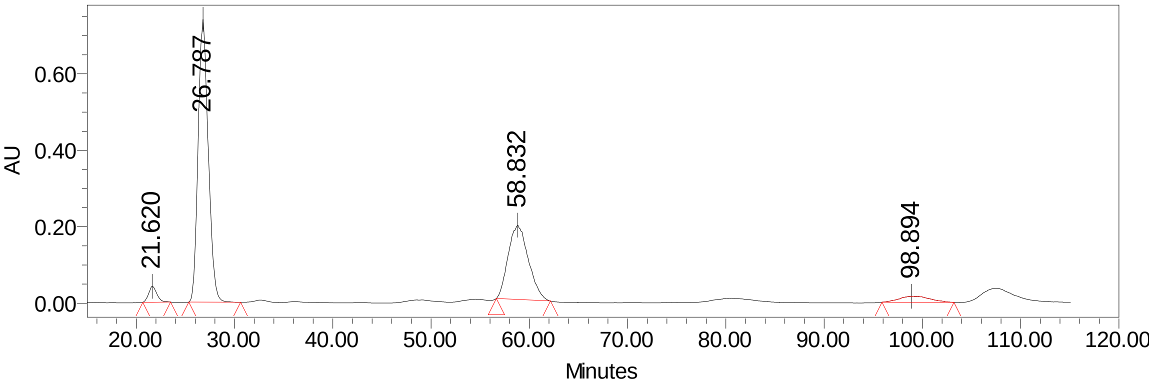


20k

Chiral HPLC (Chiralpak IC column; hexane:*i*-PrOH 95:5; 1.00 mL/min, 220nm).

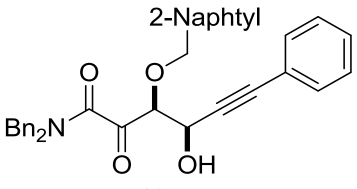


	Retention Time	% Area
1	21.726	19.67
2	27.013	32.17
3	59.498	16.38
4	99.768	31.78



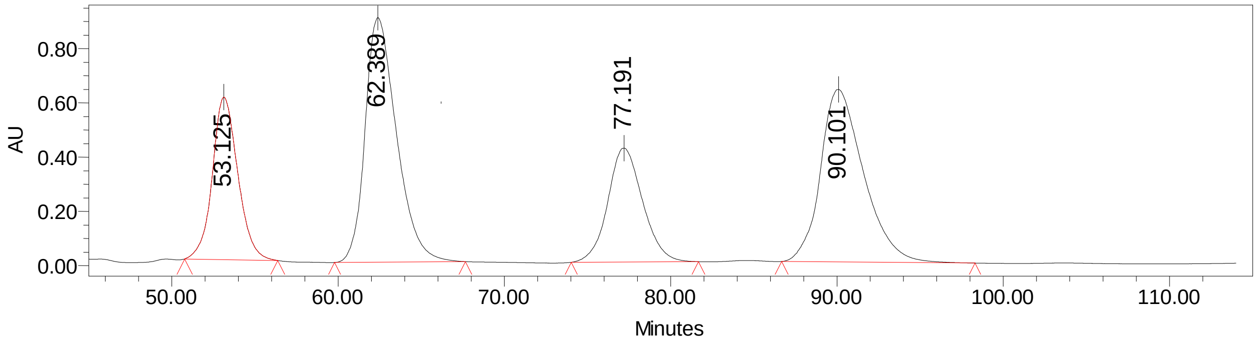
	Retention Time	% Area
1	21.620	2.80
2	26.787	61.27
3	58.832	31.97
4	98.894	3.96

5.9.2. HPLC Chromatograms of aldol adducts 19

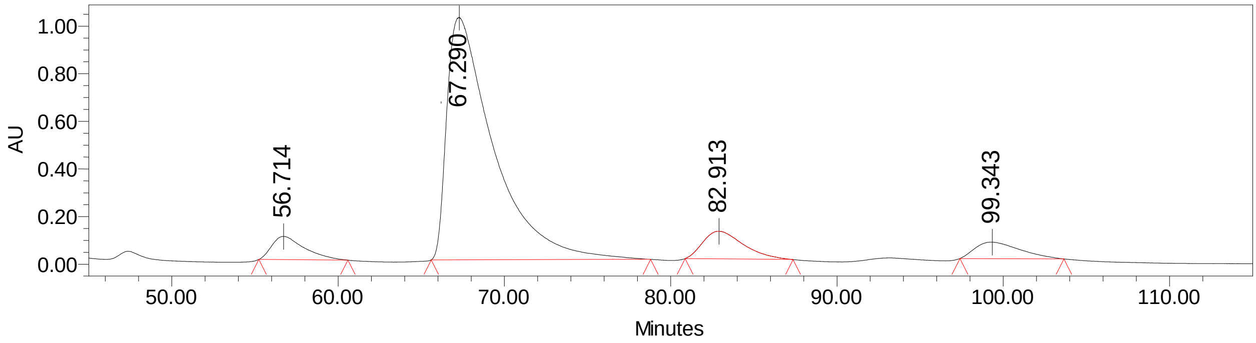


19a

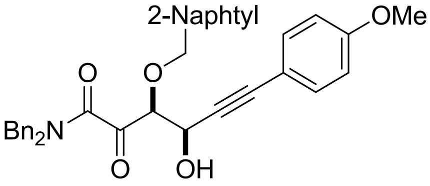
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210nm).



	Retention Time	% Area
1	53.125	17.84
2	62.389	33.12
3	77.191	17.07
4	90.101	31.97

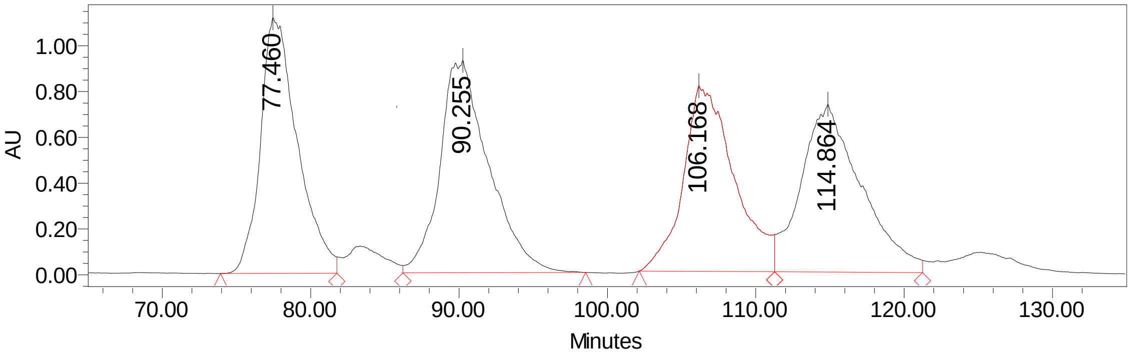


	Retention Time	% Area
1	56.714	5.45
2	67.290	81.18
3	82.913	8.06
4	99.343	5.30

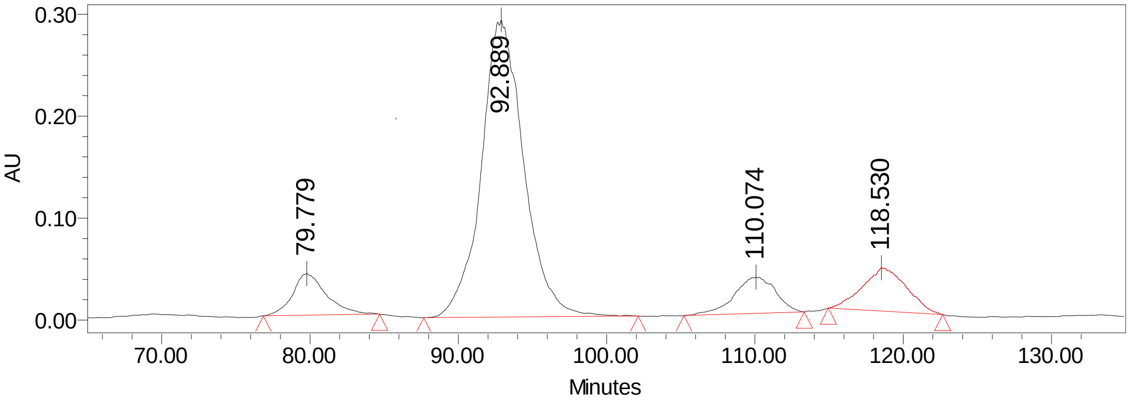


19b

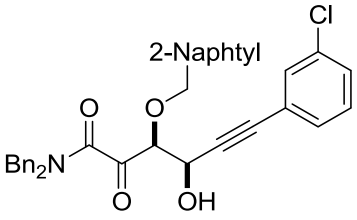
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210nm).



	Retention Time	% Area
1	77.460	24.03
2	90.255	26.37
3	106.168	24.09
4	114.864	25.52

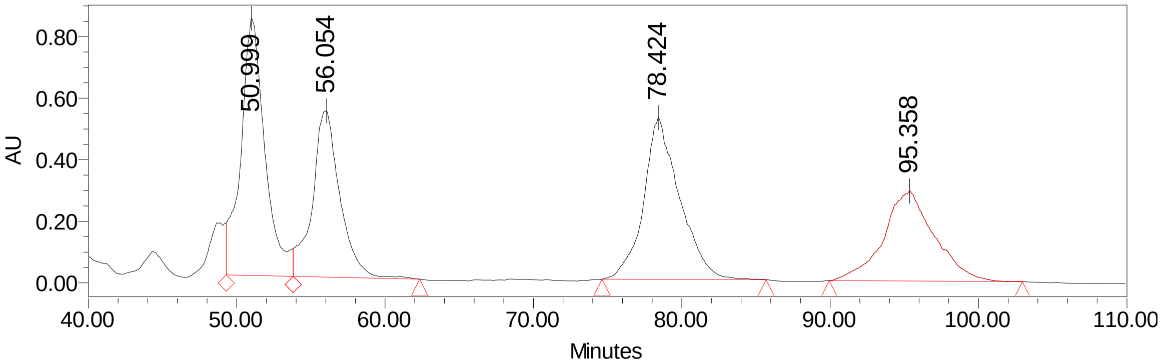


	Retention Time	% Area
1	79.779	7.42
2	92.889	74.34
3	110.074	8.05
4	118.527	10.18

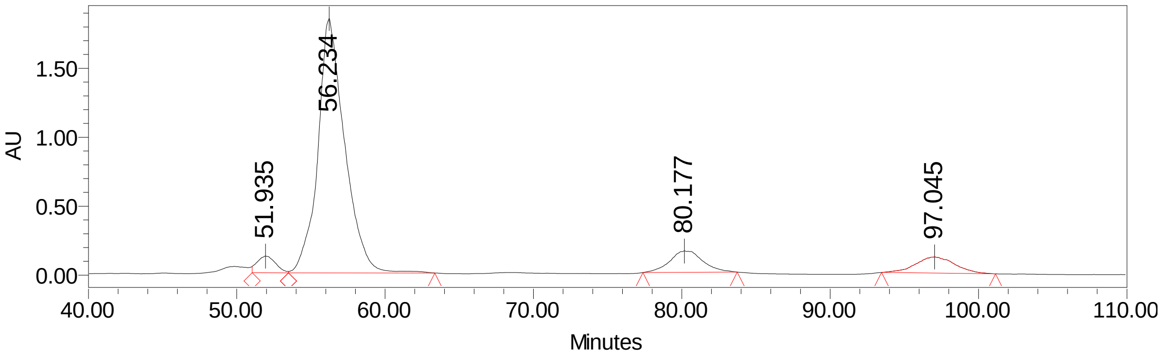


19c

Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 95:5; 0.80 mL/min, 210nm).

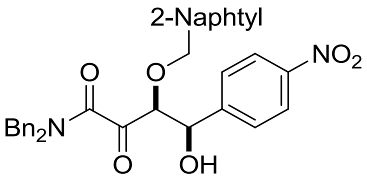


	Retention Time	% Area
1	50.999	29.41
2	56.054	21.67
3	78.424	27.43
4	95.358	21.50



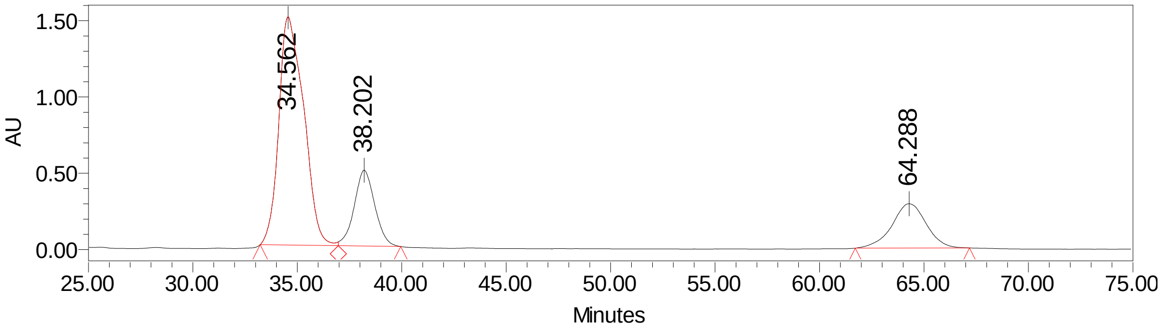
	Retention Time	% Area
1	51.935	3.30
2	56.234	81.70
3	80.178	7.96
4	97.045	7.04

5.9.3. HPLC Chromatograms of aldol adducts 24

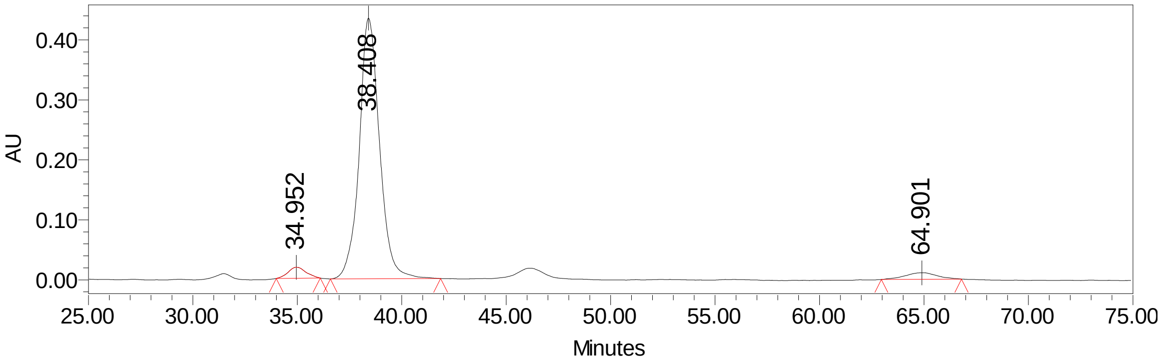


24a

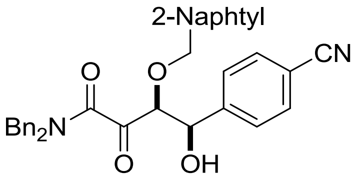
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 85:15; 0.60 mL/min, 220nm).



	Retention Time	% Area
1	34.562	64.85
2	38.202	17.79
3	64.288	17.36

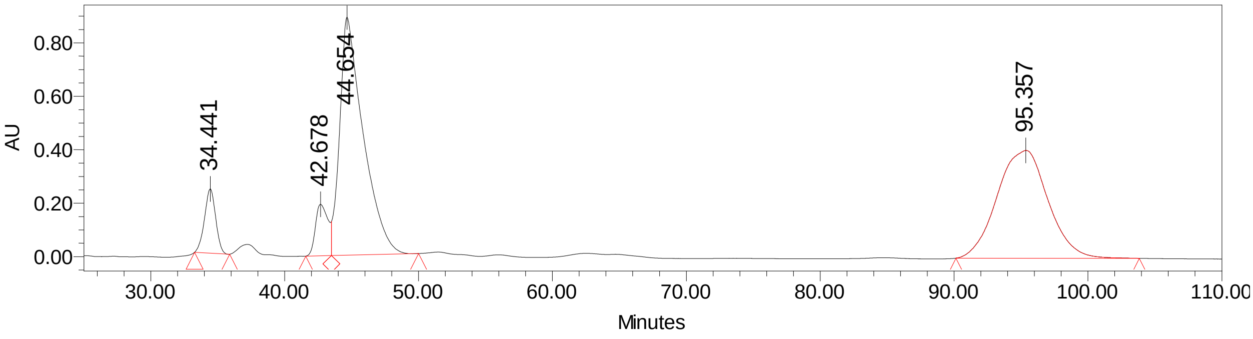


	Retention Time	% Area
1	34.952	3.45
2	38.408	92.87
3	64.901	3.68

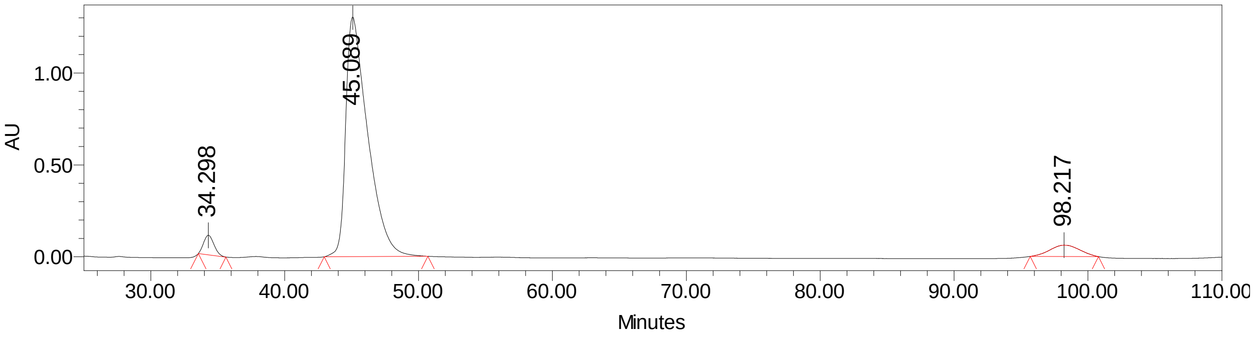


24b

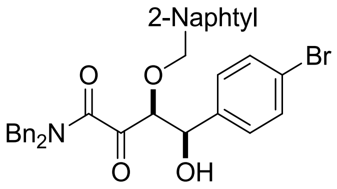
Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 85:15; 0.60 mL/min, 220nm).



	Retention Time	% Area
1	34.441	5.76
2	42.678	5.27
3	44.654	44.86
4	95.357	44.11

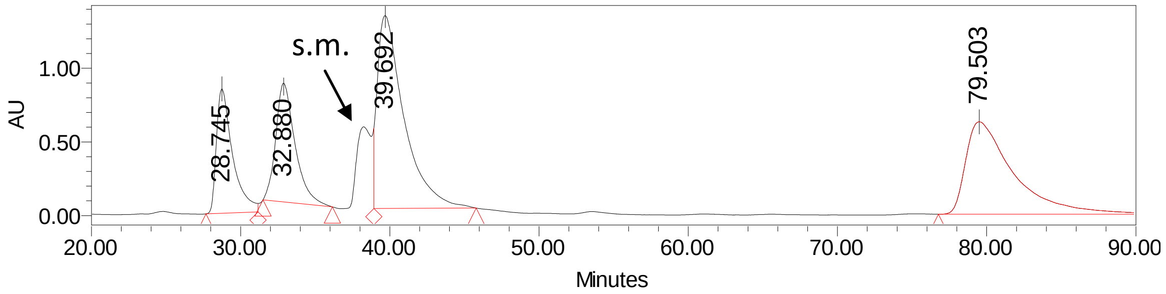


	Retention Time	% Area
1	34.298	3.47
2	45.089	90.73
3	98.217	5.80

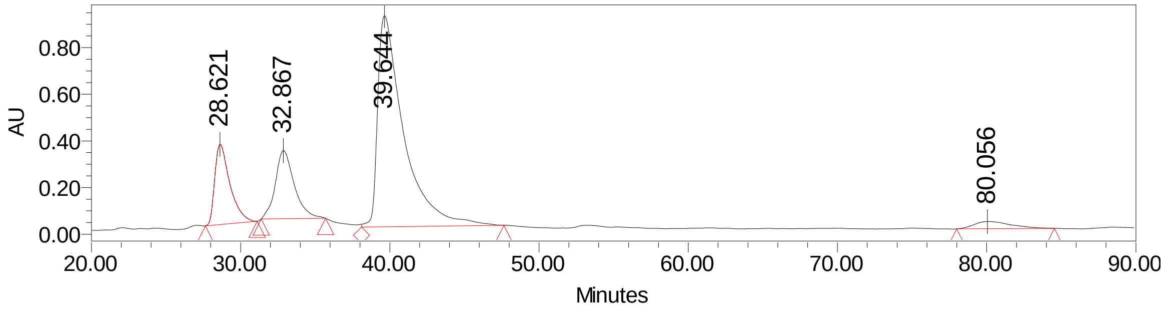


24c

Chiral HPLC (Chiralpak IA column; hexane:*i*-PrOH 85:15; 0.50 mL/min, 220nm).

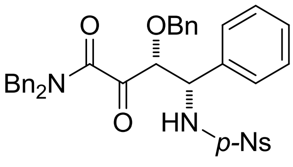


	Retention Time	% Area
1	28.745	14.52
2	32.880	16.51
3	39.692	36.97
4	79.503	32.00



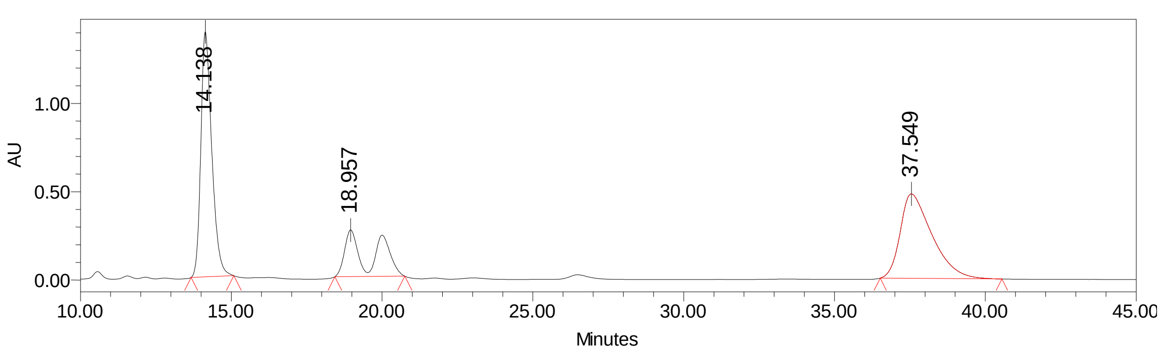
	Retention Time	% Area
1	28.636	12.43
2	32.876	16.69
3	39.647	67.73
4	80.188	3.15

5.9.4. HPLC Chromatograms of Mannich adducts 38

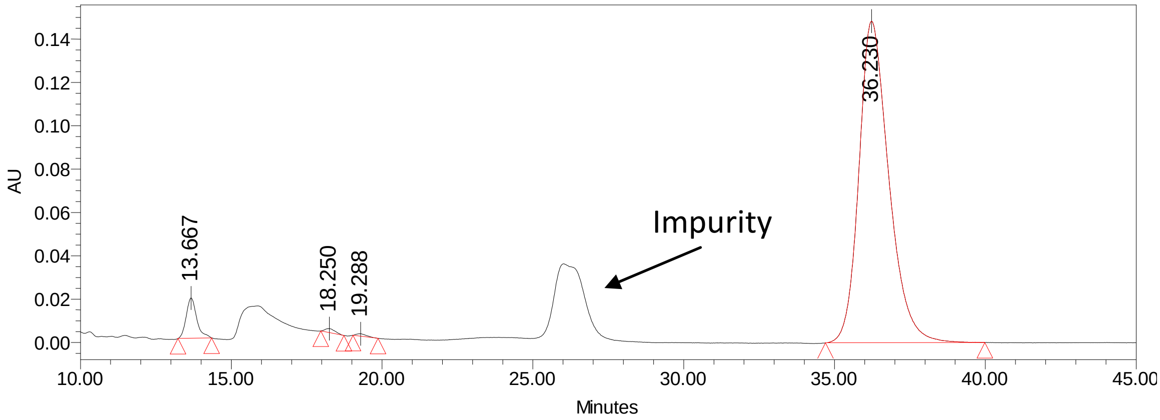


38a

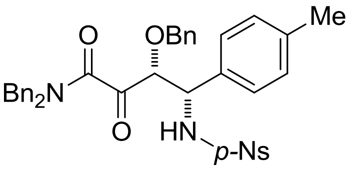
Chiral HPLC (Chiralpak IB column; hexane:EtOH 90:10; 1 mL/min, 210 nm).



	Retention Time	% Area
1	14.138	40.72
2	18.957	9.23
3	20.001	9.12
4	37.549	40.92

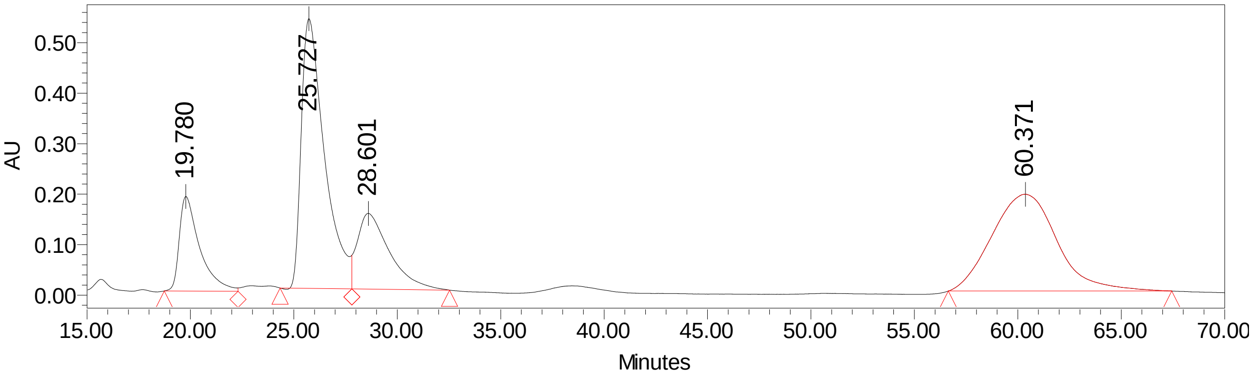


	Retention Time	% Area
1	13.667	4.19
2	18.250	0.37
3	19.288	0.23
4	36.230	95.22

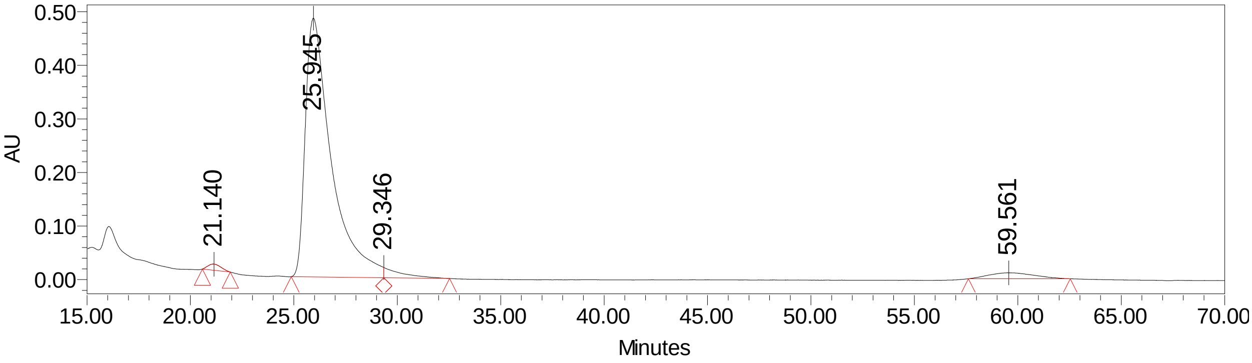


38b

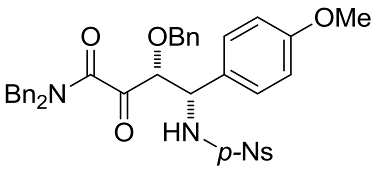
Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).



	Retention Time	% Area
1	19.780	11.37
2	25.727	37.12
3	28.601	14.35
4	60.371	37.15

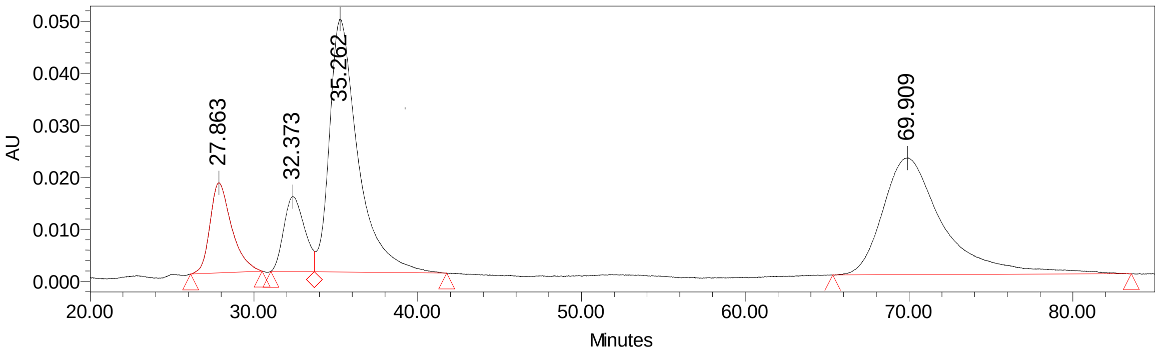


	Retention Time	% Area
1	21.140	1.12
2	25.945	92.66
3	29.346	2.48
4	59.561	3.74

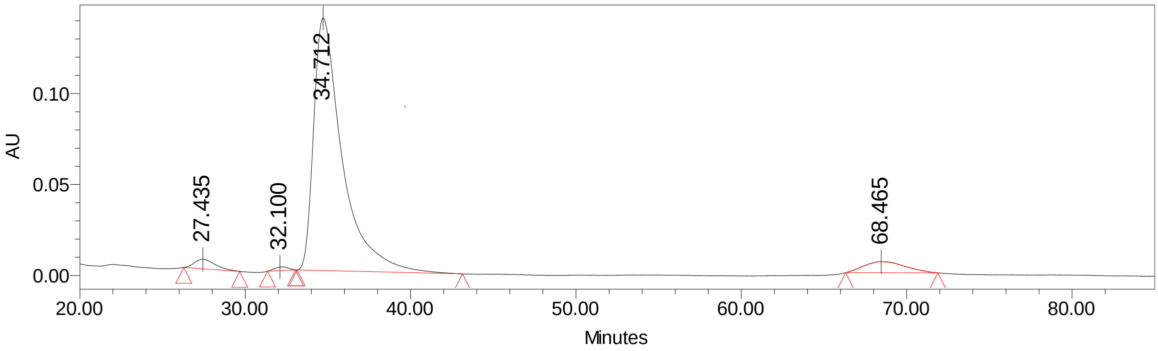


38c

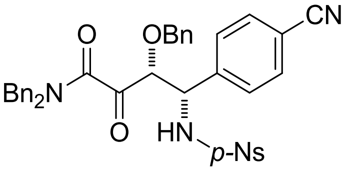
Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).



	Retention Time	% Area
1	27.863	10.98
2	32.373	8.76
3	35.262	40.67
4	69.909	39.60

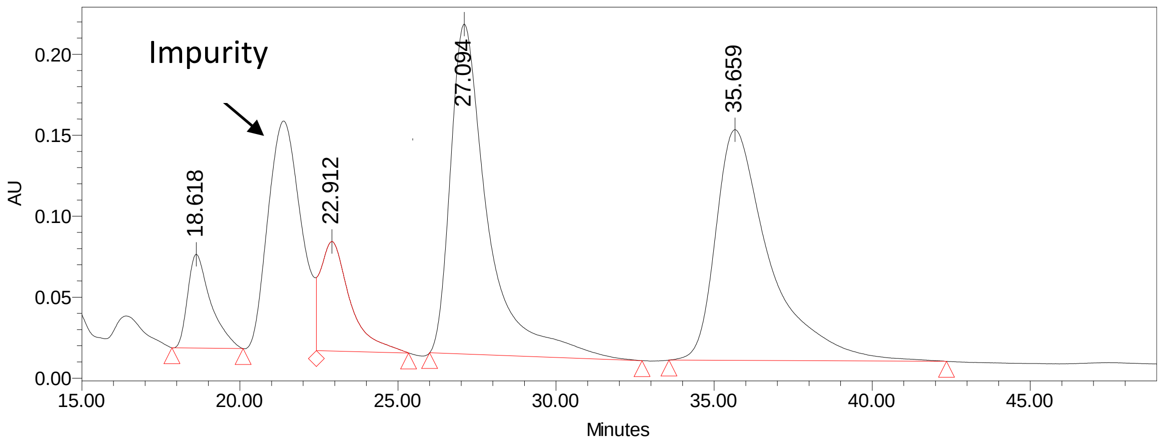


	Retention Time	% Area
1	27.412	2.03
2	32.341	1.01
3	34.713	90.77
4	68.471	6.19

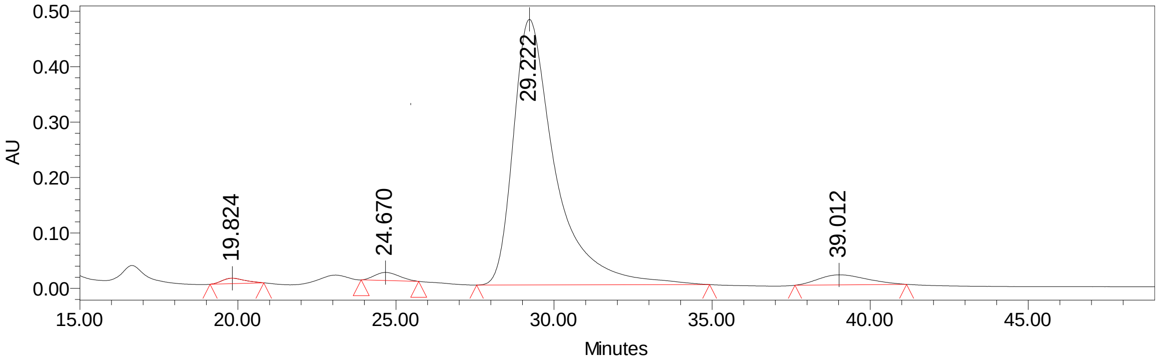


38d

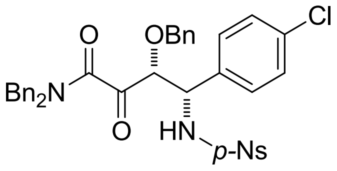
Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).



	Retention Time	% Area
1	18.618	7.15
2	22.912	10.86
3	27.094	40.79
4	35.659	41.21

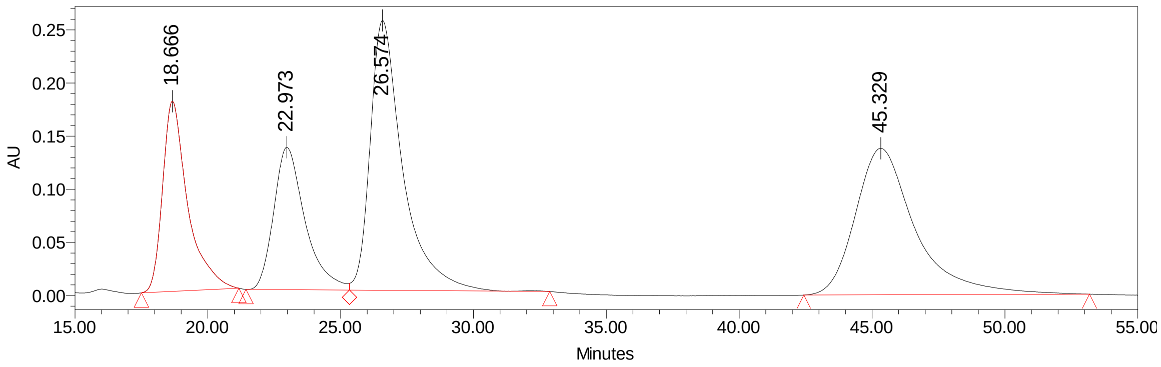


	Retention Time	% Area
1	19.824	1.03
2	24.670	1.65
3	29.222	93.27
4	39.012	4.04

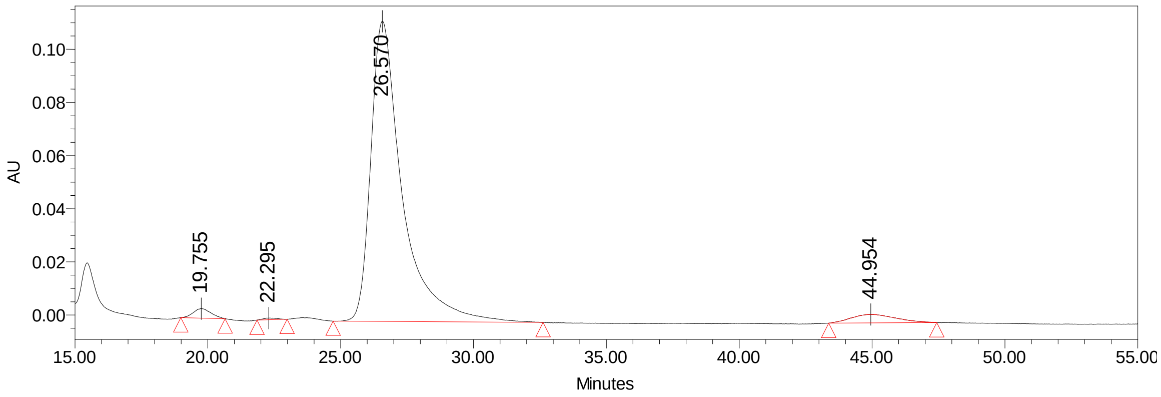


38e

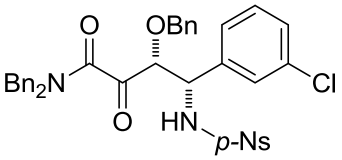
Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).



	Retention Time	% Area
1	18.666	17.80
2	22.973	16.69
3	26.574	32.84
4	45.329	32.67

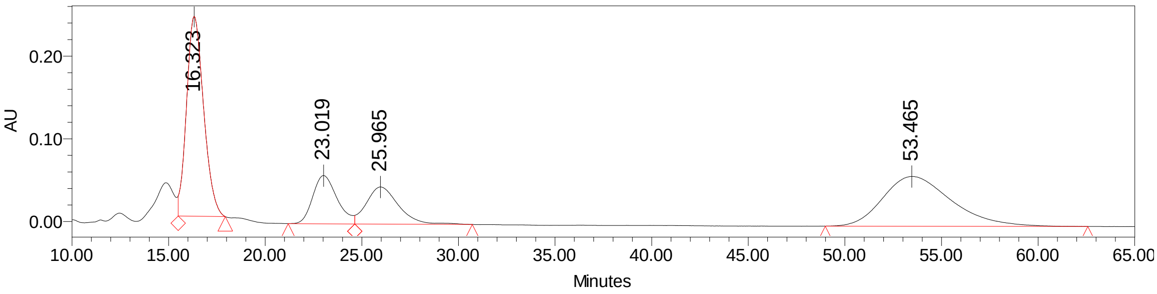


	Retention Time	% Area
1	19.755	1.69
2	22.295	0.23
3	26.570	94.33
4	44.954	3.75

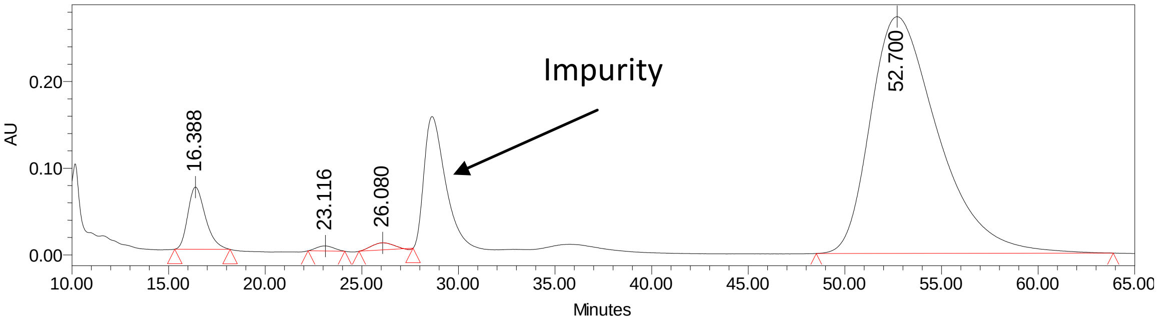


38f

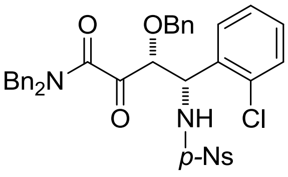
Chiral HPLC (Chiralpak OD-H column; hexane:EtOH 90:10; 1 mL/min, 210 nm).



	Retention Time	% Area
1	16.323	37.10
2	23.019	12.79
3	25.965	12.96
4	53.465	37.16

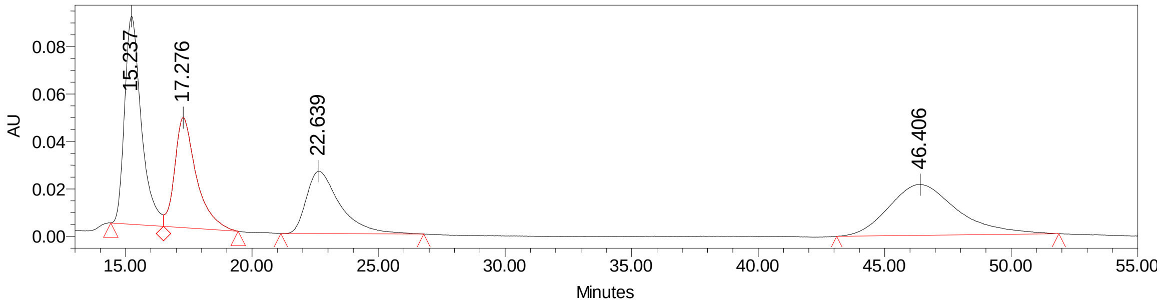


	Retention Time	% Area
1	16.388	6.31
2	23.116	0.51
3	26.080	0.92
4	52.700	92.26

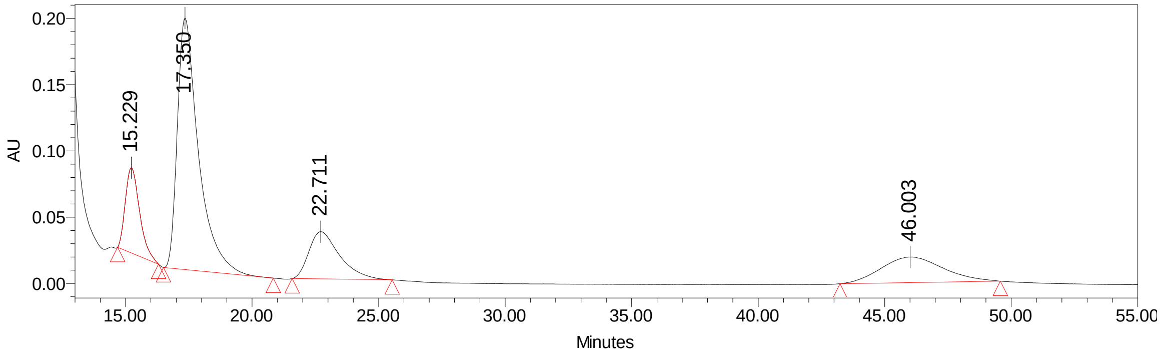


38g

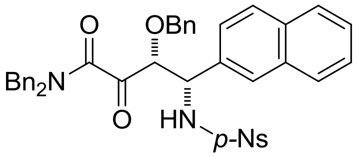
Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).



	Retention Time	% Area
1	15.237	30.29
2	17.276	20.42
3	22.639	18.63
4	46.406	30.65

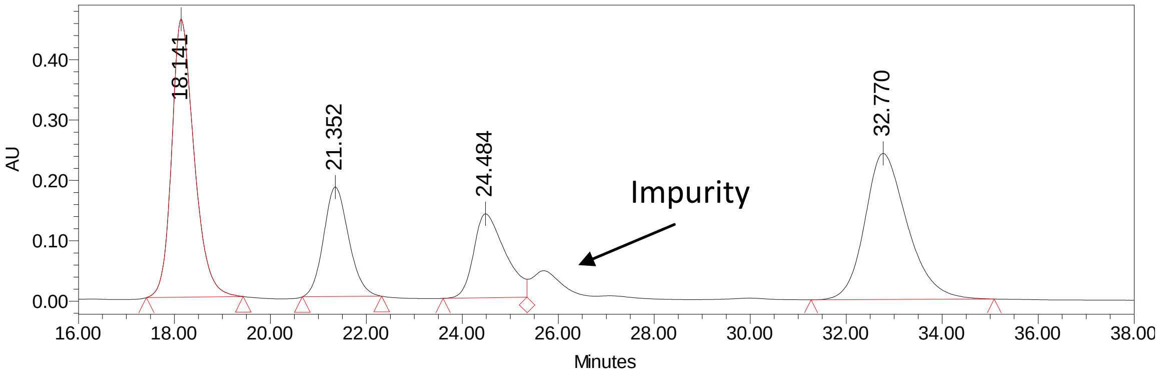


	Retention Time	% Area
1	15.229	12.72
2	17.350	55.50
3	22.711	15.21
4	46.003	16.57

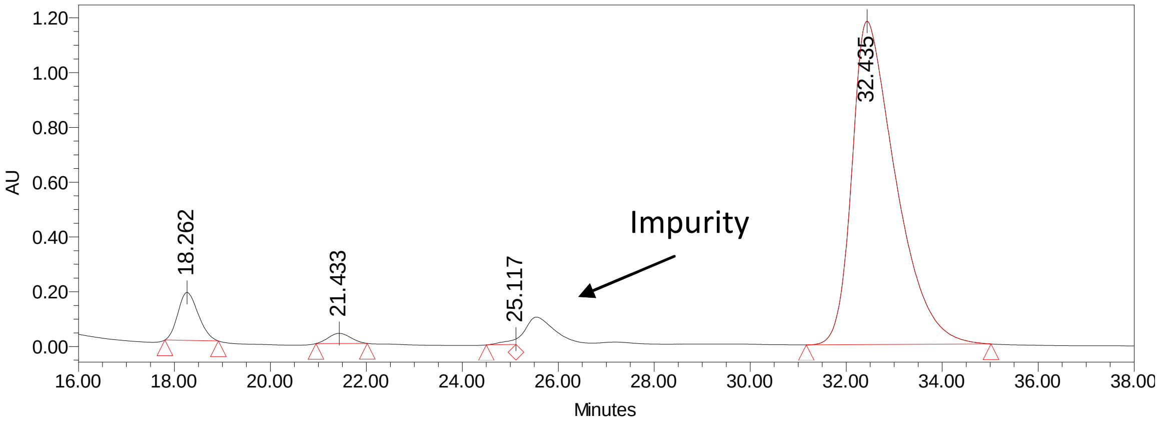


38h

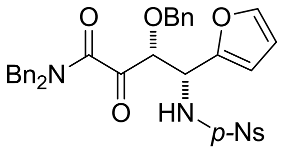
Chiral HPLC (Chiralpak IB column; hexane:EtOH 90:10; 1 mL/min, 210 nm).



	Retention Time	% Area
1	18.141	34.93
2	21.352	15.37
3	24.484	14.90
4	32.770	34.80

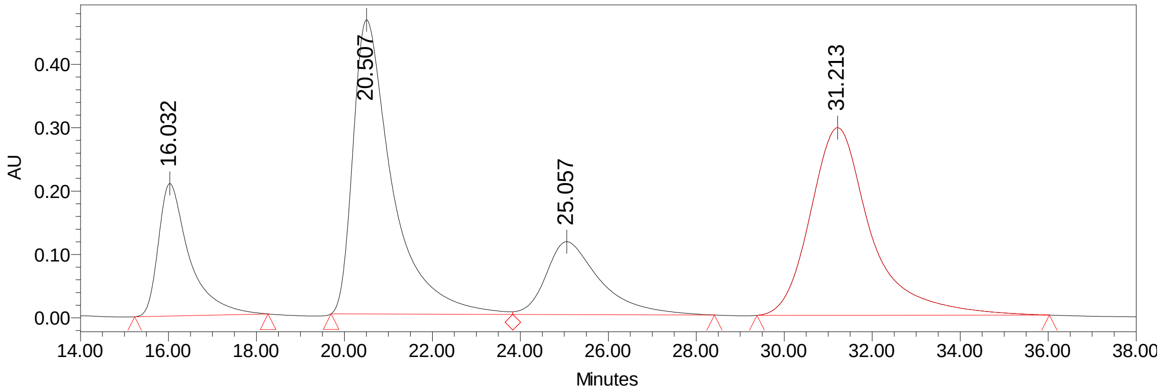


	Retention Time	% Area
1	18.262	6.08
2	21.433	1.57
3	25.183	0.50
4	32.435	91.86

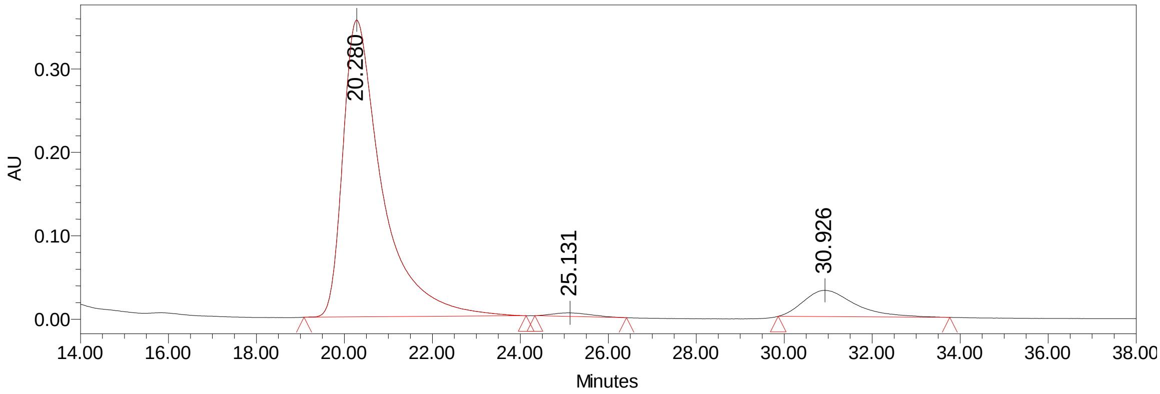


38i

Chiral HPLC (Chiralpak IA column; hexane:EtOH 70:30; 1 mL/min, 210 nm).

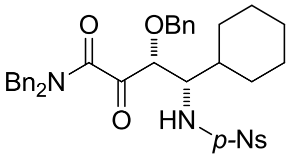


	Retention Time	% Area
1	16.032	13.05
2	20.507	37.03
3	25.057	12.75
4	31.213	37.17



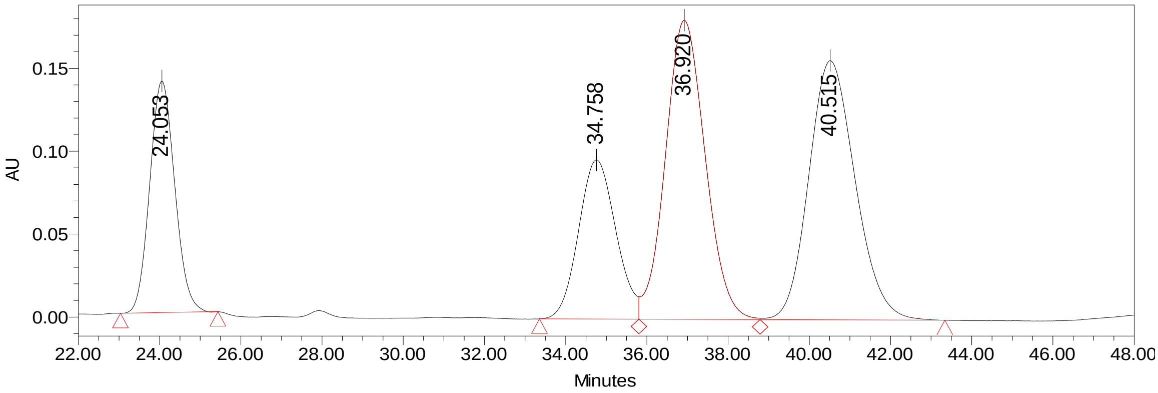
	Retention Time	% Area
1	20.280	88.67
2	25.131	1.05
3	30.926	10.29

5.9.5. HPLC Chromatograms of Mannich adducts 43 and 50a

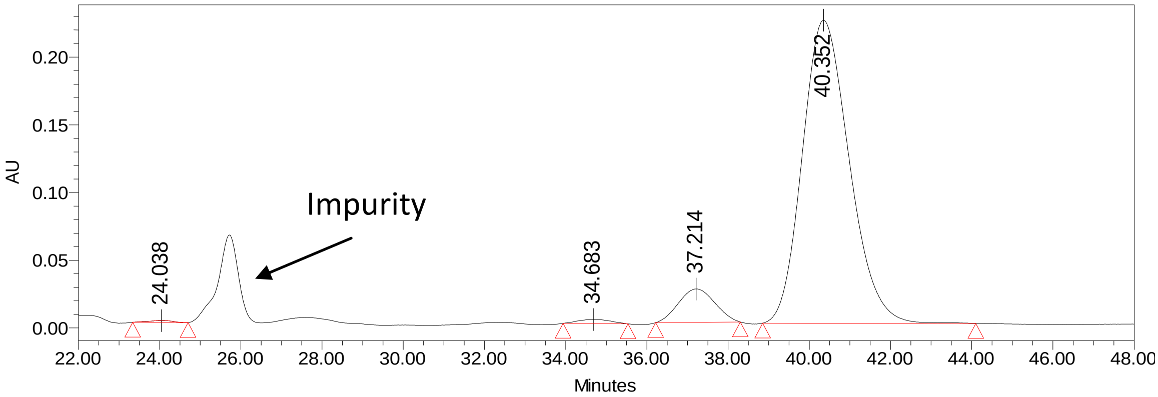


43a

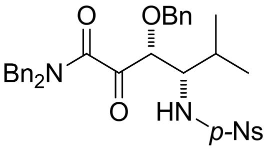
Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1 mL/min, 210 nm).



	Retention Time	% Area
1	24.053	16.51
2	34.758	16.72
3	36.920	33.16
4	40.515	33.60

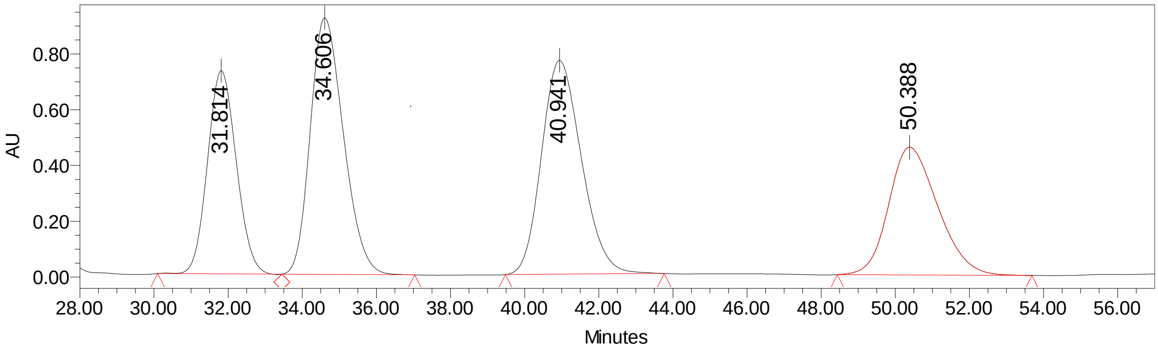


	Retention Time	% Area
1	24.038	0.31
2	34.683	0.86
3	37.214	7.73
4	40.352	91.11

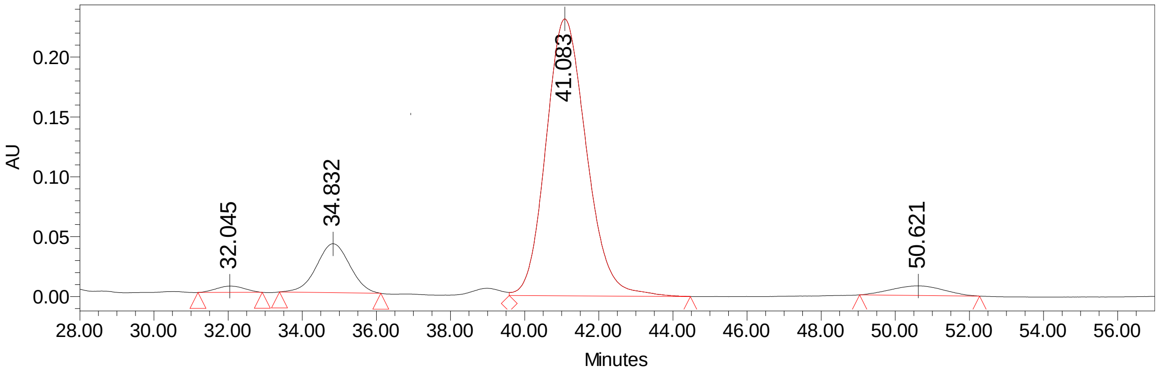


43b

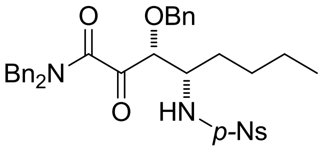
Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1 mL/min, 210 nm).



	Retention Time	% Area
1	31.814	20.03
2	34.606	29.22
3	40.941	29.29
4	50.388	21.46

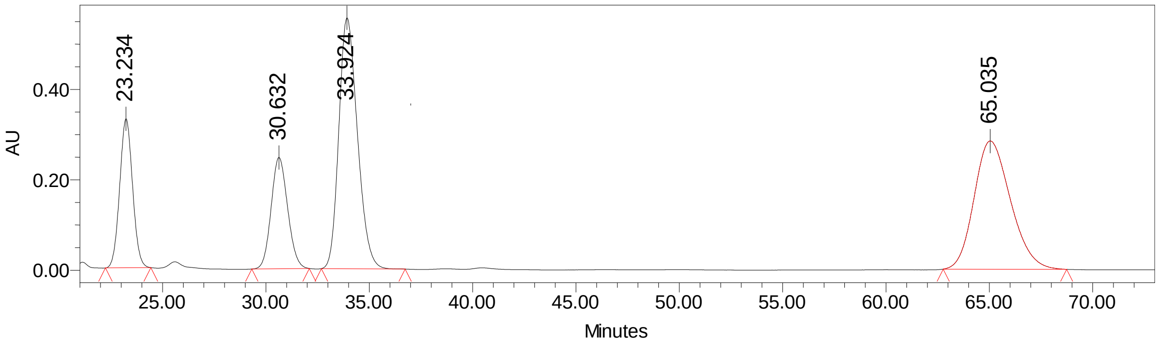


	Retention Time	% Area
1	32.045	1.33
2	34.832	12.05
3	41.083	82.93
4	50.621	3.69

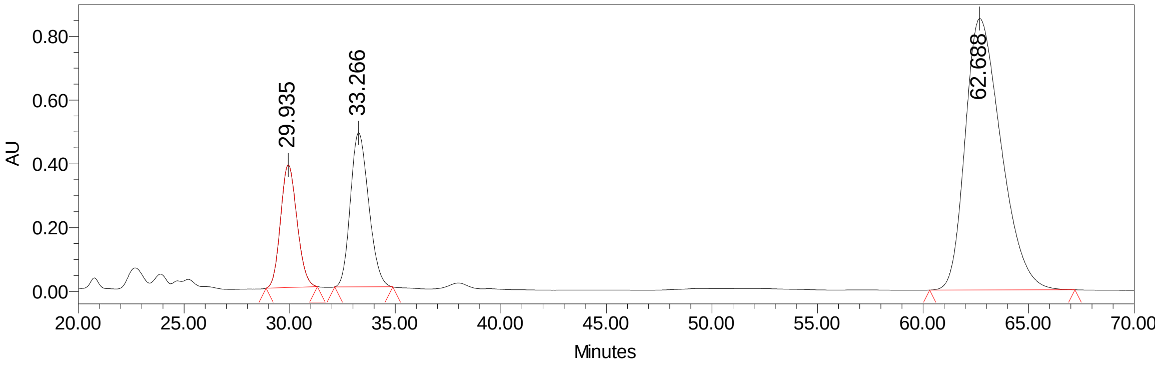


43c

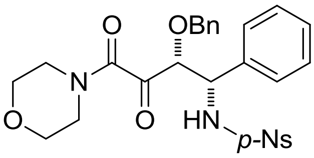
Chiral HPLC (Chiralpak IC column; hexane:EtOH 95:5; 1 mL/min, 210 nm).



	Retention Time	% Area
1	23.234	14.68
2	30.632	14.06
3	33.924	35.63
4	65.035	35.64

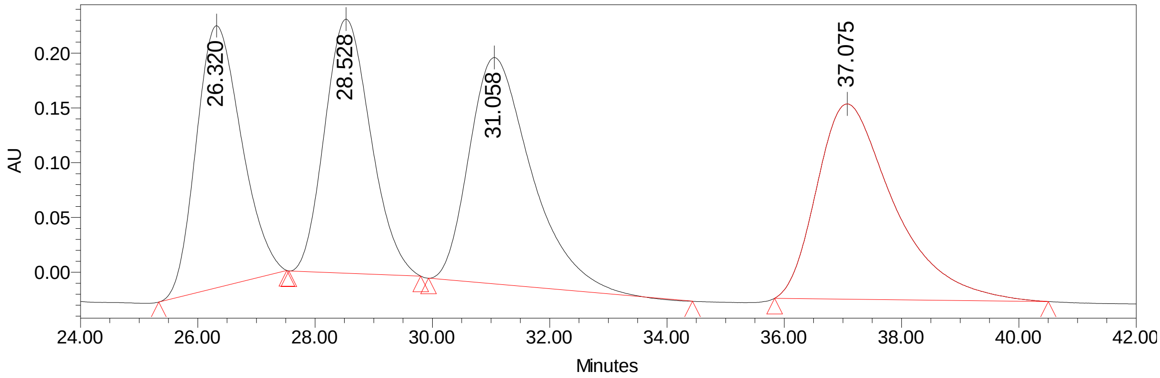


	Retention Time	% Area
1	29.935	13.80
2	33.266	19.30
3	62.688	66.89

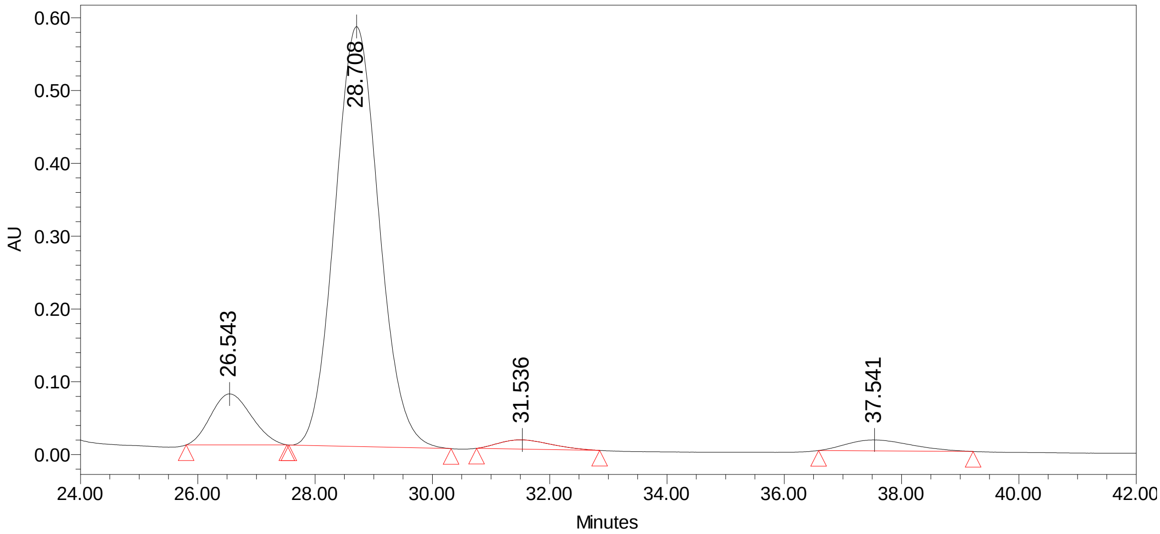


50a

Chiral HPLC (Chiralpak IC column; hexane:EtOH 90:10; 1 mL/min, 210 nm).



	Retention Time	% Area
1	26.320	22.43
2	28.528	22.11
3	31.058	26.89
4	37.075	28.57



	Retention Time	% Area
1	26.543	9.46
2	28.708	85.07
3	31.536	2.21
4	37.541	3.26

Publication

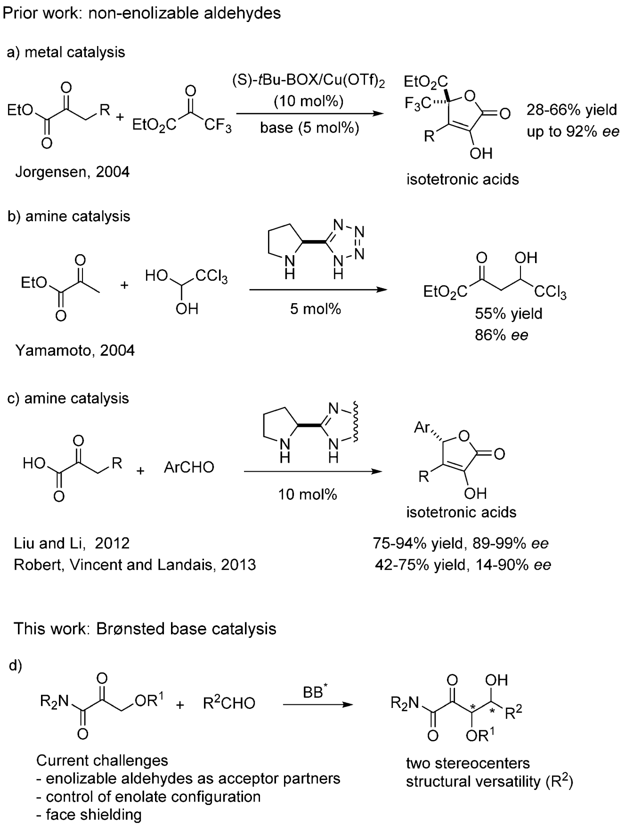
Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201510482
German Edition: DOI: 10.1002/ange.201510482

Bifunctional Brønsted Base Catalyzes Direct Asymmetric Aldol Reaction of α-Keto Amides

*Haizea Echave, Rosa López, and Claudio Palomo**

Abstract: *The first enantioselective direct cross-aldol reaction of α-keto amides with aldehydes, mediated by a bifunctional ureidopeptide-based Brønsted base catalyst, is described. The appropriate combination of a tertiary amine base and an aminal, and urea hydrogen-bond donor groups in the catalyst structure promoted the exclusive generation of the α-keto amide enolate which reacted with either non-enolizable or enolizable aldehydes to produce highly enantioenriched polyoxygenated aldol adducts without side-products resulting from dehydration, α-keto amide self-condensation, aldehyde enolization, and isotetronic acid formation.*


Prior work: non-enolizable aldehydes
a) metal catalysis
EtO
R
EtO2C
CF3
(S)-tBu-BOX/Cu(OTf)2
(10 mol%)
base (5 mol%)
EtO2C
F3C
R
OH
28-66% yield
up to 92% ee
Jorgensen, 2004
isotetronic acids
b) amine catalysis
EtO
HO
CCl3
OH
5 mol%
EtO2C
OH
CCl3
55% yield
86% ee
Yamamoto, 2004
c) amine catalysis
HO
R
ArCHO
10 mol%
Ar
R
OH
isotetronic acids
Liu and Li, 2012
Robert, Vincent and Landais, 2013
75-94% yield, 89-99% ee
42-75% yield, 14-90% ee
This work: Brønsted base catalysis
d)
R2N
OR1
R2CHO
BB*
R2N
OH
R2
OR1
Current challenges
- enolizable aldehydes as acceptor partners
- control of enolate configuration
- face shielding
two stereocenters
structural versatility (R2)

Scheme 1. Cross-aldol reactions of 1,2-dicarbonyl compounds. BB = Brønsted base, Tf = trifluoromethanesulfonyl.

1,2-Dicarbonyl compounds, such as pyruvic acid and phosphoenolpyruvate, are employed as C_3-donor units in the aldolase-promoted biosynthesis of ulosonic acids and sialic acids.[1] Despite the synthetic interest, however, the utilization of pyruvates in the realm of chemical synthesis has been mainly limited to their use as electrophilic counterparts because of the inherently high reactivity of the α,β-dicarbonyl in nucleophilic 1,2-additions.[2] The asymmetric homoaldol reaction of ethyl pyruvate was first described by Jørgensen and co-workers wherein a chiral copper/bisoxazoline complex was used.[3] A few years later, Dondoni and co-workers described the homoaldol reaction of ethyl pyruvate using secondary amine catalysis[4] to produce the more stable isotetronic acids. For pyruvate cross-aldol reactions to be effective highly reactive acceptor carbonyl compounds are usually required (Scheme 1a and 1b),[5] however, the aldol adducts also tend to lactonize, which is an important limitation when substituted pyruvates are employed because the cyclization implies loss of a stereogenic center. This limitation also exists for enamine-based cross-aldol reactions between α-ketoacids and either aromatic aldehydes[6] or substituted pyridine carbaldehydes[7] which also give isotetronic acids (Scheme 1c). In contrast, a masked pyruvate equivalent, such as pyruvic aldehyde dimethyl acetal, has been employed under amine catalysis in the reaction with aromatic aldehydes, to prevent lactonization.[8] Clearly, this enamine aldol technology would be nicely complemented in terms of product scope and reaction mechanism if a Brønsted base catalyzed approach addressing this problem would be available. Mlynarski and co-workers,[9] based upon the observation that esters of bulky phenols prevent pyruvate self-condensation and lactonization,[10] reported a diastereoselective aldol reaction of 2,6-di-*tert*-butyl-4-methoxyphenyl pyruvate with chiral nonracemic α-oxy aldehydes using this approach. Later on Liu, Li, and co-workers[11] documented the reaction of ethyl pyruvate with isatins, a highly electrophilic class of ketones. In this case, however, lactonization occured and, again, isotetronic acids were formed with the loss of a stereogenic center. Despite these advances, Brønsted base catalyzed cross-aldol couplings of α-substituted pyruvates with enolizable aldehydes have not yet been realized. Probably, the major reason that justifies this notable deficiency is the difficulty associated with the α-deprotonation of 1,2-dicarbonyl compounds resulting from the relatively low acidity of the α-carbon atom in this class of pronucleophiles.[12] Not surprisingly, α-substituted pyruvates and related 1,2-dicarbonyl compounds have been employed in Brønsted base mediated reactions involving, as far as we know, only highly reactive acceptors.[11,13] Given their bidentate charac-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201510482.

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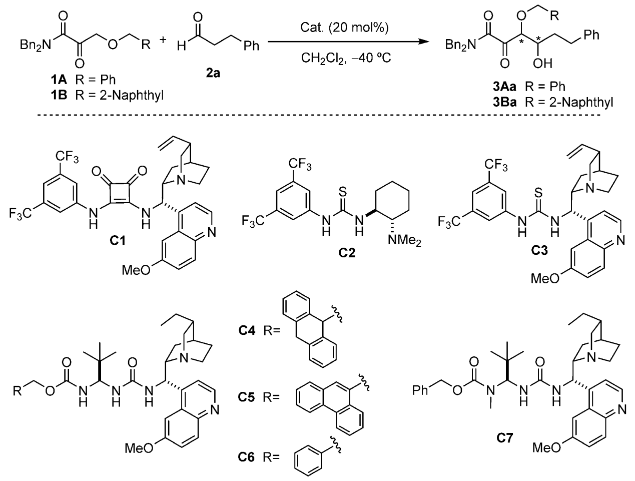
ter, we questioned whether substrate activation through multiple hydrogen-bonding interactions might facilitate deprotonation by a mild Brønsted base to give an α-keto enolate with a specific configuration. Recently, we introduced ureidopeptide-based Brønsted bases as a new subfamily of organic catalysts bearing several hydrogen-bond donors.[14] Herein we report the utility of these newly developed Brønsted bases by documenting the first direct catalytic enantioselective cross-aldol reaction of α-keto amides with either enolizable or non-enolizable aldehydes.[15]

In contrast to the progress achieved in enamine based aldol reactions, cross-aldol couplings mediated by Brønsted bases appear to be more challenging to establish.[16] Probably, the most effective systems to date involve highly electrophilic carbonyl acceptors such as 1,2-dicarbonyl compounds.[17] We initiated this work by evaluating several known Brønsted bases for the reaction of the α-keto amide **1A** and hydrocinnamaldehyde (**2a**; Table 1). The experiments soon revealed that, indeed, the Brønsted base was the key for success. For example, when using quinine, quinidine, and $(DHQ)_2$PYR, no aldol product (**3Aa**) was observed after 24 hours, either at −40 °C or 0 °C. While the squaramide **C1** was also ineffective in terms of reactivity and selectivity (entry 1), the bifunctional thiourea-tertiary amine catalysts **C2** and **C3** provided **3Aa** with good diastereomeric ratios and *ee* values, but the transformations required prolonged reaction times (entries 2–5). We were gratified to observe that ureidopeptide-based Brønsted bases, which might display up to three hydrogen-bonding interactions,[18] promoted this cross-aldol addition most effectively.

Table 1: Catalyst screening for the aldol reaction between **1A** and **2a**.[a]



Entry	1	Cat.	*t* [h]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**1A**	**C1**	48	30[e]	44:56	64
2	**1A**	**C2**	48	40	83:17	90
3	**1A**	**C2**	96	60	85:15	92
4	**1A**	**C3**	48	60	96:4	94
5	**1A**	**C3**	96	80	96:4	94
6	**1A**	**C4**	48	> 95	75:25	92
7	**1A**	**C5**	48	> 95	79:21	90
8	**1A**	**C6**	36	> 95	86:14	92
9	**1B**	**C6**	36	> 95	90:10	92
10	**1A**	**C7**	48	> 30	75:25	86

[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio of **1A**/**2a**, 1: 1.2). [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy and corroborated by HPLC. [d] The *ee* value of the major diastereomer determined by chiral-phase HPLC. [e] 50% conversion after 96 h.

As the results in Table 1 show, the catalysts **C4** and **C5** promoted complete conversion into **3Aa** within 48 hours (entries 6 and 7), whereas the catalyst **C6** achieved a somewhat higher level of stereocontrol in a relatively shorter reaction time (entry 8). Importantly, under these reaction conditions self-condensation of either **1A** or **2a** were not detected. Also, neither dehydrated nor lactonized aldol products were observed. Further experiments revealed an improvement in diastereoselectivity by increasing the aromatic character of the substituent in the α-keto amide. The adduct **3Ba** was produced, with increased diastereoselectivity (90:10 d.r.), whilst maintaining the enantioselectivity (92% *ee*), from the α-keto amide **1B** (entry 9). In addition, the N-methylated catalyst **C7** behaved similarly to both **C2** and **C3**, and provided the aldol **3Aa** in 30% conversion (d.r.75:25, 86% *ee*) after 48 hours.

A representative selection of aldehydes was subjected to the optimized reaction conditions to produce the aldol adducts **3B** for which diastereomeric ratios and enantiomeric excesses were determined (Table 2). To avoid α-epimerization during purification,[19] each crude reaction mixture of the products **3B** was submitted to reduction with L-selectride. The reduction proceeded cleanly at −78 °C and with essentially complete stereoselectivity to give the corresponding *syn,syn* 1,2,3-triols **4B** in 60–72% yields upon isolation after two steps. As the data in Table 2 show, results were consistently good. Short alkyl chain aldehydes (e.g., propanal), longer chain aldehydes (e.g., hexanal and heptanal), β-branched isovareldehyde, and even aldehydes bearing side chains with functional groups (e.g., alkene, ester, carbamate, and ether) participate satisfactorily, thus giving enantiomeric excesses of up to 96%. In contrast, diastereomeric ratios seemed to decrease as the length of the alkyl chain in the aldehyde increased (compare **4Bb**, **4Bc**, and **4Bd**), and with the presence of α-substitution (**4Bj** and **4Bk**) while maintaining high enantiomeric excesses. In addition, 3 mmol scale reactions proceeded without any detrimental effect in the reaction outcome (**4Ba** and **4Bf**).

The relative and absolute configurations of the major *syn,syn* enantiomer were determined by X-ray crystallographic analysis of **4Bd** (Scheme 2a) and a uniform reaction mechanism for the aldol reaction was assumed.[20] Taking into account the diastereo- and enantioselectivity observed, the capacity of the ureidopeptide-based catalysts to mainly produce *syn*-configured adducts might be consistent with the generation, as a result of electrostatic and hydrogen-bonding interactions, of a more stabilized *Z* enolate which preferentially approaches the *Si* face of the aldehyde (Scheme 2b). Although we still have no evidence of the actual mode of substrate–catalyst interaction,[21] the fact that reactions with common Brønsted base catalysts, as well as with **C7**, were significantly less efficient supports the beneficial effect of multiple hydrogen-bonding interactions to boost reactivity.

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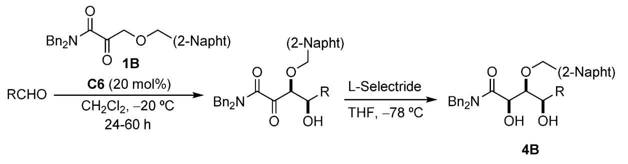
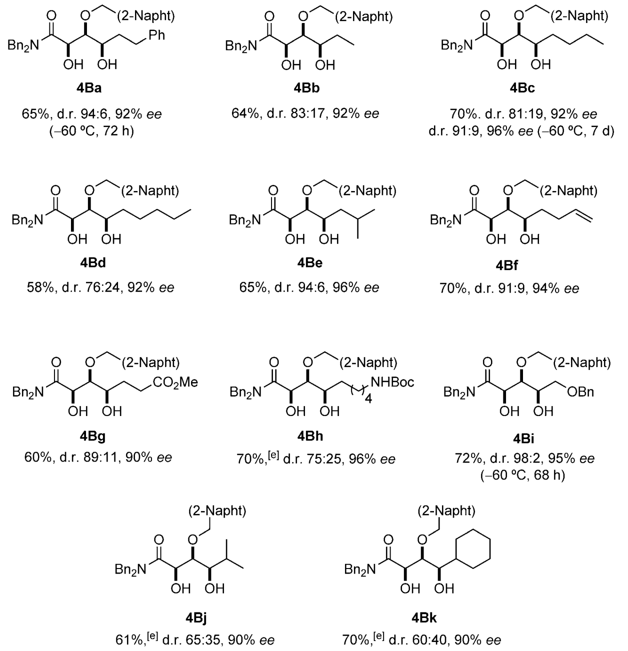
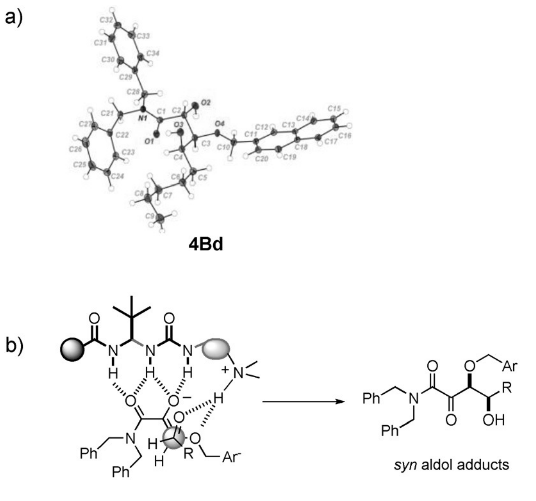
Table 2: Scope of the catalytic aldol reaction of enolizable aldehydes.[a–e]





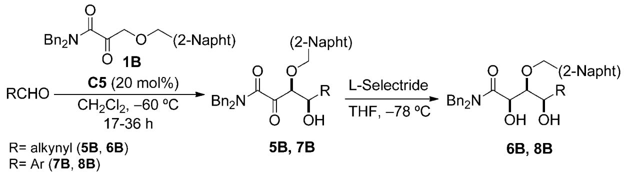
Compound	Result
4Ba	65%, d.r. 94:6, 92% *ee* (–60 °C, 72 h)
4Bb	64%, d.r. 83:17, 92% *ee*
4Bc	70%. d.r. 81:19, 92% *ee* d.r. 91:9, 96% *ee* (–60 °C, 7 d)
4Bd	58%, d.r. 76:24, 92% *ee*
4Be	65%, d.r. 94:6, 96% *ee*
4Bf	70%, d.r. 91:9, 94% *ee*
4Bg	60%, d.r. 89:11, 90% *ee*
4Bh	70%,[e] d.r. 75:25, 96% *ee*
4Bi	72%, d.r. 98:2, 95% *ee* (–60 °C, 68 h)
4Bj	61%,[e] d.r. 65:35, 90% *ee*
4Bk	70%,[e] d.r. 60:40, 90% *ee*

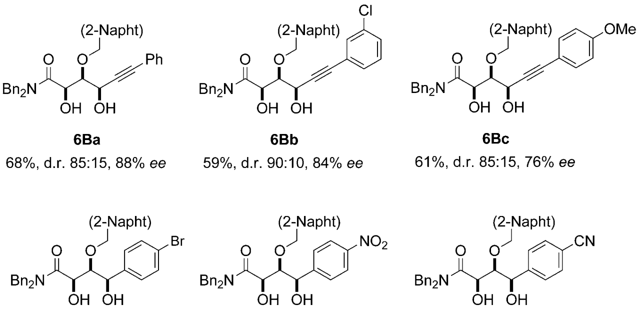
[a] Reactions conducted on a 0.6 mmol scale in 1.5 mL of CH_2Cl_2 (mol ratio of **1 B**/aldehyde, 1: 3. For the aldehydes **2g** and **2h**: mol ratio of **1 B**/ aldehyde = 1: 1.5). [b] Yield of the isolated *syn,syn* adduct **4 B** after aldol reaction and stereoselective reduction. [c] The *syn/anti* ratio determined by ^{1}H NMR spectroscopy and corroborated by HPLC for the aldol adducts **3 B** before stereoselective reduction. [d] The *ee* value of the major diastereomer (*syn* aldol adduct), before reduction, was determined by chiral-phase HPLC. [e] Combined yield of the *syn,syn* and *syn,anti* products. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.



Scheme 2. a) ORTEP representation for **4 Bd**. Thermal ellipsoids shown at 50% probability. b) Proposed model that might account for the observed preference of *syn*- over *anti*-aldol product formation.

Table 3: Scope of the catalytic aldol reaction of propargylic and aromatic aldehydes.[a–d]





Compound	Result
6Ba	68%, d.r. 85:15, 88% *ee*
6Bb	59%, d.r. 90:10, 84% *ee*
6Bc	61%, d.r. 85:15, 76% *ee*
8Ba	54%, d.r. 71:29, 90% *ee*
8Bb	60%, d.r. 97:3, 92% *ee*
8Bc	61%, d.r. 96:4, 88% *ee*

[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio of **1 B**/aldehyde, 1:1.2). [b] Yield of the isolated *syn,syn* adduct after aldol reaction and stereoselective reduction. [c] The *syn/anti* ratio determined by ^{1}H NMR spectroscopy and corroborated by HPLC for the aldol adducts **5 B** and **7 B** before respective stereoselective reduction. [d] The *ee* value of the major diastereomer (*syn* aldol adduct), before reduction, was determined by chiral-phase HPLC.

Considering the shortage of effective direct Brønsted base catalyzed asymmetric cross-aldol reactions, we explored the ability of aromatic, as well as propargylic aldehydes, to participate in the reaction with α-keto amides (Table 3). Once again, ureidopeptide-based catalysts performed well in comparison with other bifunctional thiourea-tertiary amine catalysts,[22] and the highest stereoselectivity was induced by the phenanthrenyl-derived catalyst **C5**. In particular, electronically diverse, substituted ynals produced, after stereoselective reduction of the resulting aldol adducts **5 B**, the corresponding *syn,syn* propargylic alcohols **6 B**, which are attractive compounds for further chemical transformations resulting from the rich chemistry of the triple bond.[23]

The aldol adducts obtained in the cross-aldol reaction of α-keto amides are valuable precursors of several structural motifs with more than two stereocenters (Scheme 3). In this respect, the stereochemical outcome of the stereoselective reduction of the aldol adducts, promoted by L-Selectride, to give *syn,syn*-**4 B** could be inverted to efficiently produce, under treatment with $nBu_3B/NaBH_4$, a 70:30 mixture of *anti,syn*/*syn,syn* diastereomers from which the major *anti,syn* adduct **9** was isolated in reasonable yield. Trivial manipulations such as the cleavage of the 2-naphthyl auxiliary by catalytic hydrogenation and acidic treatment of the *syn,syn* adducts **4 B**, produced either the corresponding free triol **10** or lactone **11**. Significantly, this aldol reaction provides, through simple reduction of the amide function with $LiAlH_4$, a quick entry for construction of stereodefined aminotriol units such

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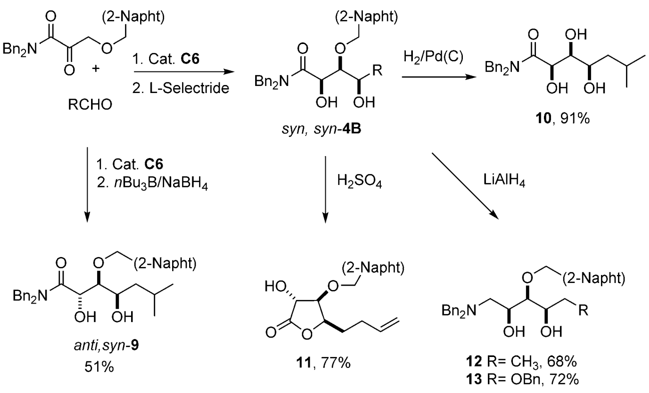

Scheme 3. Selected products synthesized from aldol adducts.

as **12** and **13**, which are interesting building blocks for hydroxylated pyrrolidine-containing iminosugars and related products.[24]

In summary, we have developed the first direct catalytic asymmetric cross-aldol reaction of α-keto amides and it expands the realm of aldol additions promoted by Brønsted bases. Given the occurrence of di- and trihydroxylated fragments in bioactive molecules and their frequent use as intermediates in synthesis, this reaction provides a new tool for their rapid construction. The catalysts employed are distinguished from the known bifunctional Brønsted bases (BBs) in that they comprise three consecutive moieties, an aminal, an urea, and a tertiary amine base, which facilitates direct carbon–carbon bond-forming reactions under proton-transfer conditions. We believe these catalysts to be of great utility for broadening the domain of reactions for catalytic asymmetric BB methodologies.

Experimental Section

To a solution of α-ketoamide **1B** (0.6 mmol, 0.254 g) and the ureidopeptide-based catalyst **C6** (0.02 equiv, 0.12 mmol, 0.071 g) in CH_2Cl_2 (1.5 mL) was added the corresponding aldehyde (3 equiv for enolizable aldehydes) at the indicated temperature. The resulting solution was stirred until complete disappearance of **1B**. The reaction mixture was quenched with HCl 0.1 M (5 mL), the organic layer was washed with HCl 0.1 M (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the corresponding crude reaction mixture containing the aldol adduct, which was subjected to reduction. To a solution of the corresponding crude reaction mixture containing the aldol adduct in THF (6 mL) was added L-Selectride (1 M THF, 2 equiv 1.2 mmol, 1.2 mL) at −78 °C. After stirring for 1.5 hours, water (0.4 mL) and EtOH (0.8 mL) were successively added followed by H_2O_2 (30 %, 0.8 mL) 5 min later. The reaction temperature rose to room temperature and the mixture was stirred for an additional 10 min. Then, it was diluted with AcOEt (5 mL) and water (5 mL). The aqueous phase was extracted with AcOEt (3 × 5 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (Hex/AcOEt) to afford the pure compounds **4B**.

Acknowledgments

Financial support was provided by the University of the Basque Country UPV/EHU (UFI 11/22), Basque Government (Grant No IT-628-13), and Ministerio de Economía y Competitividad (MEC, Grant CTQ2013-47925-C2-1-P), Spain. H.E. thanks Basque Government for a fellowship. We also thank SGIker (UPV/EHU) for providing NMR, HRMS, and X-Ray resources.

Keywords: aldol reaction · asymmetric catalysis · Brønsted bases · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368
Angew. Chem. **2016**, *128*, 3425–3429

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Received: November 11, 2015
Revised: January 8, 2016
Published online: February 2, 2016

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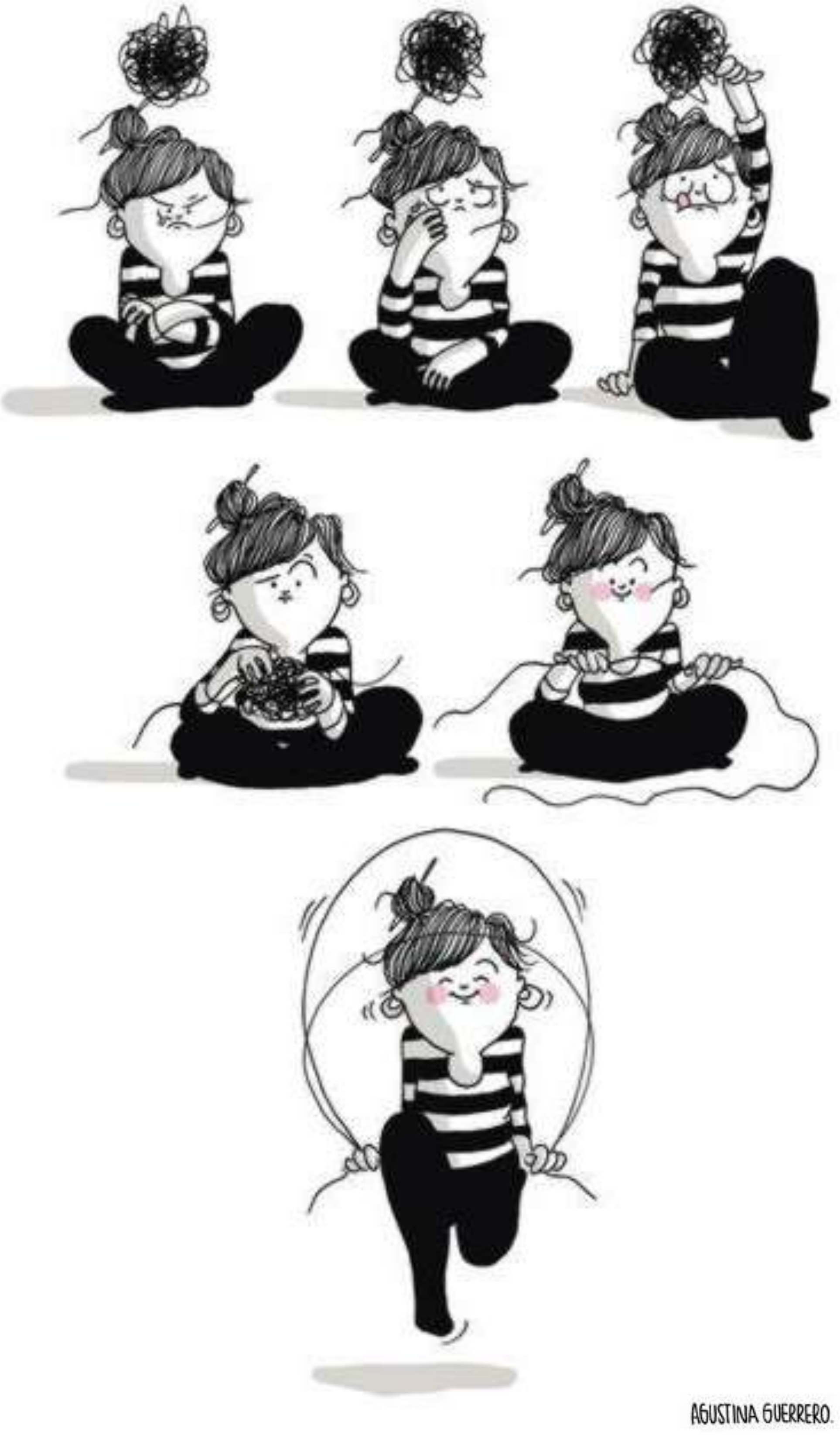
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