APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES

Esther Alza Barrios

Dipòsit Legal: T. 1351-2011

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PhD THESIS PRESENTED BY

Esther Alza Barrios

Supervised by

Prof. Miquel A. Pericàs and Dr. Sonia Sayalero

DEPARTMENT OF ANALYTICAL AND ORGANIC CHEMISTRY (URV)
AND INSTITUTE OF CHEMICAL RESEARCH OF CATALONIA (ICIQ)

TARRAGONA, 2011

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Institut Català d'Investigació Química

Av. Països Catalans, 16
43007 Tarragona
Tel. 977 920 200
Fax. 977 920 222

Universitat Rovira i Virgili

Departament De Química Analítica
I Química Orgànica
C/ Marcel.lí Domingo s/n
Campus Sescelades
43007 Tarragona
Tel. 34 977 55 97 69
Fax 34 977 55 84 46

Prof. MIQUEL A. PERICÀS, Group Leader of Research Group and Director of the Institute of Chemical Research of Catalonia (ICIQ) and,

Dr. SONIA SAYALERO, Researcher at ICIQ and Consolider-INTECAT project coordinator,

CERTIFY, that the present Doctoral Thesis entitled: "**APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES**", presented by ESTHER ALZA BARRIOS to receive the degree of Doctor, has been carried out under our supervision, in the Institute of Chemical Research of Catalonia (ICIQ) and fulfils all the requirements to be awarded with the "Doctor Europeus" Mention.

Tarragona, 26th April 2011

PhD Thesis Supervisor

Prof. Miquel A. Pericàs

PhD Thesis Co-supervisor

Dr. Sonia Sayalero

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LIST OF PUBLICATIONS

This PhD Thesis is based on the following publications:

Esther Alza, Xacobe C. Cambeiro, Ciril Jimeno, and Miquel A. Pericàs
Title: **Highly Enantioselective Michael Additions in Water Catalyzed by a PS-Supported Pyrrolidine**
Org. Lett. **2007,** *9* (19), 3717-3720

Esther Alza, Amaia Bastero, Susanna Jansat and Miquel A. Pericàs
Title: **Aqueous Asymmetric Transfer Hydrogenation Using Modular Hydrophobic Aminoalcohols**
Tetrahedron: Asymmetry **2008,** *19*, 374-378

Esther Alza, Carles Rodríguez-Escrich, Sonia Sayalero, Amaia Bastero, and Miquel A. Pericàs
Title: **A Solid-Supported Organocatalyst for Highly Stereoselective, Batch, and Continuous-Flow Mannich Reactions**
Chem. Eur. J. **2009**, *15*, 10167-10172

Esther Alza, and Miquel A. Pericàs
Title: **A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior**
Adv. Synth. Catal. **2009**, *351*, 3051-3056

Esther Alza, Sonia Sayalero, Xacobe C. Cambeiro, Rafael Martín-Rapún, Pedro O. Miranda, Miquel A. Pericàs
Title: **Catalytic Batch and Continuous Flow Production of Highly Enantioenriched Cyclohexane Derivatives with Polymer-Supported Diarylprolinol Silyl Ethers**
Synlett **2011**, *4*, 464-468.

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One never notices what has been done;
one can only see what remains to be done.

Marie Sklodowska Curie. Chemist & physicist (1867-1934)

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ABBREVIATIONS

Boc	*tert*-butoxycarbonyl
br	broad
brd	broad doublet
brm	broad multiplet
$CDCl_3$	deuterated chloroform
$(CD_3)_2SO$	deuterated dimethyl sulfoxide
conv	conversion
d	doublet
DCM	dichloromethane
dd	double doublet
DiMePEG	polyethylene glycol dimethyl ether
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	double triplet
DVB	divinylbenzene
ee	enantiomeric excess
e.g.	*exempli gratia* ("for example")
eq.	Equivalents
et al.	*et alii* ("and others")
Et_3N	triethylamine
f	resin functionalization level
h	hours
KOH	potassium hydroxide
m	multiplet
Me	methyl
MeOH	methanol
min	minutes
MPEG	polyethylene glycol methyl ether
NaH	sodium hydride
PEG	polyethylene glycol
ppm	parts per million

PS	polystyrene
py	pyridine
rt	room temperature
s	singlet
t	triplet
td	triple doublet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	tetrametylsilane
t_r	retention time

The rest of abbreviations and acronyms: '*Guidelines for authors*' *J. Org. Chem*. **2008**, *73*, 23A-24A.

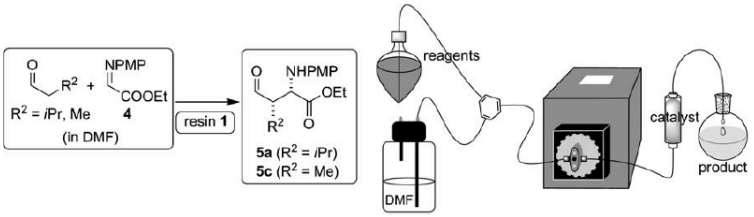
GRAPHICAL ABSTRACTS

CHAPTER I – General Introduction

OBJECTIVES

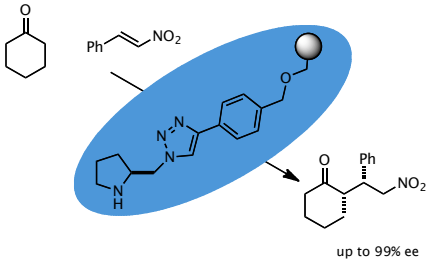
CHAPTER II-A

Stereoselective Mannich Continuous-Flow Mannich Reactions reactions of aldehydes and ketones with the *N*-(*p*-methoxyphenyl) ethyl glyoxylate imine are efficiently catalyzed by a functionalized polystyrene resin. For aldehydes, the reactions have been implemented in a flow system (see figure); continuous synthesis of the enantiomerically and diastereomerically pure adducts was achieved in just minutes at room temperature.

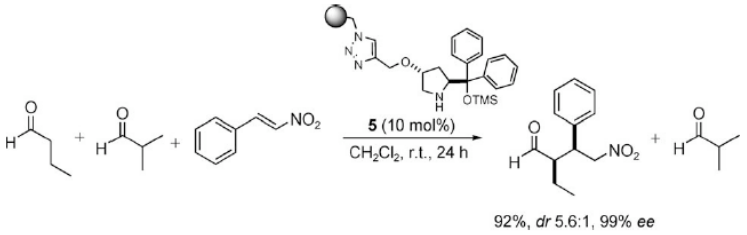


CHAPTER II-B

The development of a highly efficient, polymer-supported organocatalyst for the Michael addition of ketones to nitroolefins is described. A 1,2,3-triazole ring, constructed through a click 1,3-cycloaddition, plays the double role of grafting the chiral pyrrolidine monomer onto the polystyrene backbone and of providing a structural element, complementary to pyrrolidine, key to high catalytic activity and enantioselectivity. Optimal operation in water and full recyclability make the triazole linker attractive for the immobilization of organocatalysts.

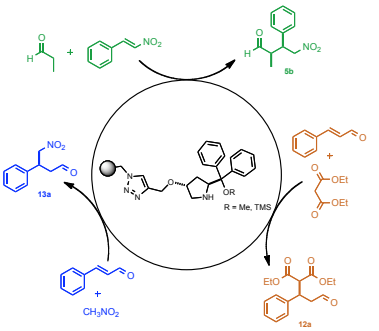


A polymer-supported α,α-diarylprolinol silyl ether displays catalytic activity and enantioselectivity comparable to the best homogeneous catalysts in the Michael addition of aldehydes to nitro-olefins. Above all, the combination of polymer backbone, triazole linker, and catalytic unit confers to it an unprecedented substrate selectivity in favor of linear, short-chain aldehydes.



CHAPTER III

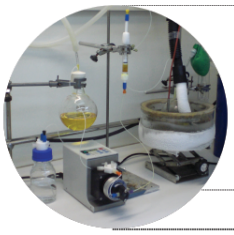
A highly selective α,α-diphenylprolinol silyl ether anchored to a polystyrene resin has been developed. The catalytic activity and enantioselectivity displayed by this catalytic system are comparable to the best homogeneous catalysts in the addition of aldehydes to nitroolefins and both malonates and nitromethane to α,β-unsaturated aldehydes. The combination of the catalytic unit, the triazole linker and the polymeric matrix provided an unprecedented substrate selectivity in favor of linear, short-chain aldehydes when the organocatalyzed reaction proceeds via enamine mechanism besides high versatility in reactions catalyzed via iminium ion intermediate. Polystyrene-supported α,α-diphenyl prolinol methyl ether is also presented and evaluated in some asymmetric Michael addition reactions. The immobilization approach offers important operational advantages as easy recovery of catalytic systems from the reaction mixture by simple filtration and its reuse.

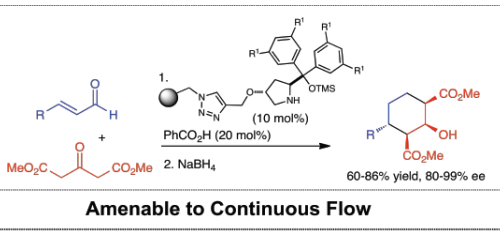


All the experimental work herein presented respect to supported (*S*)-α,α-diphenylprolinol methyl ether was carried out by Pinar Kasaplar in Prof. M. A. Pericàs Group at ICIQ.

CHAPTER IV

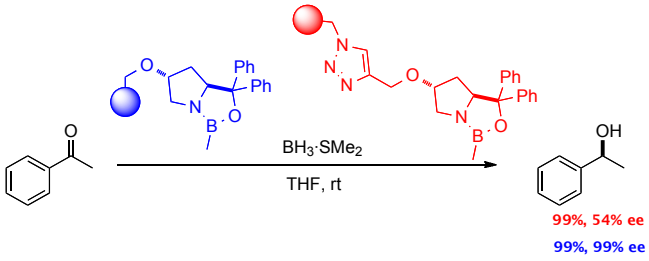
Diarylprolinol silyl ethers immobilized onto polystyrene have been employed as catalysts in the enantioselective domino Michael–Knoevenagel reaction of dimethyl 3-oxoglutarate and 3-substituted acrolein derivatives, including aliphatic ones. The best catalyst allows the preparation of highly functionalized cyclohexane derivatives in a straightforward and efficient manner, both under batch and continuous flow conditions.





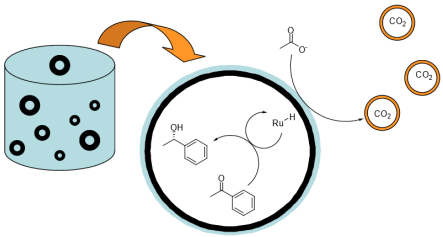
CHAPTER V

The asymmetric reduction of ketones with borane mediated by oxazaborolidine-type supported catalysts was studied. The use of CBS-derivatives anchored onto polymers by CuAAC or by direct nucleophilic substitution on a Merrifield resin represents a great difference in the selectivity of such reductions. Thus, preliminary results showed that the triazole ring formed by CuAAC anchoring strategy is deletereous for the enantioselectivity of the reaction.



CHAPTER VI

A series of new modular Ru/aminoalcohol systems were used as enantioselective catalysts in the asymmetric transfer hydrogenation reaction in both water and 2-propanol. The catalytic behavior exhibited in these two media follows different tendencies regarding the tunable ligand structure. Additionally, cationic, anionic, and neutral surfactants do not improve the catalytic behavior in water.



CONCLUSIONS AND OUTLOOK

Chapter I

UNIVERSITAT ROVIRA I VIRGILI
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GENERAL INTRODUCTION

Asymmetry is present in every part of the Nature. In fact, in Tarragona you can admire the beauty of the asymmetry (subjectively talking) contemplating in the Modern Art Museum of the city, a join work of Joan Miró and Josep Royo called "*The Tarragona Tapestry*" (Fig. 1.1). As starts one of the books of Frank Close[1], "The world is an asymmetrical place full of asymmetrical beings" and the importance of asymmetry is present on many fields, and specifically in chemistry.

Figure 1.1. "The Tarragona Tapestry" – Joan Miró/Josep Royo 1970.[2]

At the microscopic level, the three-dimensional structural asymmetry present in the molecules plays a key role in science and technology. The chirality (from Greek χειρ (cheir), meaning "hand") is defined[3] as the geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image (Fig. 1.2). The term

[1] F. Close, *Lucifer's Legacy: The Meaning of Asymmetry*, Oxford: Oxford Press, London, **2000**.
[2] Picture reproduced with the kind permission of Cruz Roja, owner of the work, and Museu d'Art Modern de Tarragona.
[3] IUPAC, Compendium of Chemical Terminology, 2nd ed. (the "Gold Book") (**1997**). Online corrected version: (**2006-**)

and the definition of chirality was used the first time in a lecture of Lord Kelvin[4] in 1884. Although in that period the scientific discipline of stereoselective synthesis has its origins with the studies of Fischer about structural characterization of carbohydrates and the work of Pasteur about enzymatic decarboxylative kinetic resolution of racemic solution of ammonium tartrate,[5] is nowadays when the obtaining of chiral compounds represents one of the most important and challenging fields in organic synthesis.[6]

Figure 1.2. The city of Salamanca (Spain) reflected in the Tormes River.[7]

Two molecules that are mirror image each other and non-superposable are known as enantiomers. Chirality is a fundamental property of biological systems and reflects the underlying asymmetry of matter. The difference between two stereoisomers is crucial in pharmaceuticals, flavours or fragrance industry since two enantiomers have different flavour, smell and more important, different activity, toxicology or interaction against the same target. This behaviour is caused by the fact that most important constituents present in the living systems are one of the enantiomers of chiral molecules like for instance amino acids or sugars. One interesting example to illustrate

[4] W. T. Kelvin, *The second Robert Boyer lecture*, J. Oxford Univ. Junior Sci. Club 18: 25, **1884**.
[5] L. Pasteur, *Compt Rend. Acad. Sci.* **1858**, *46*, 15.
[6] a) P. D. Ritchie, *Asymmeric Synthesis and Asymmetric Induction*, Oxford University Press, London, New York, **1933**. b) E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**.
[7] Picture reproduced with the permission of www.minube.com and the author, Ángel L. Taranilla.

that concept can be the odorant receptors. Most of them are composed by L-amino acids and for that reason our sense of smell is sensitive to the chirality of the odorant molecules, among other characteristics, as Louise Pasteur suggested long time ago.[8] For instance, the (+)-enantiomer of the compound androstenone (Fig. 1.3) is produced by male-humans and, although many people described it as unpleasant and urinous smell, this compound has been marketed as a human female sex attractant. The (-)-enantiomer apparently is no detectable for the olfactory humans sense and a drawback in the use of this compound as a sexual attractant is the fact that close to 50% of the people cannot smell either enantiomer.[9]

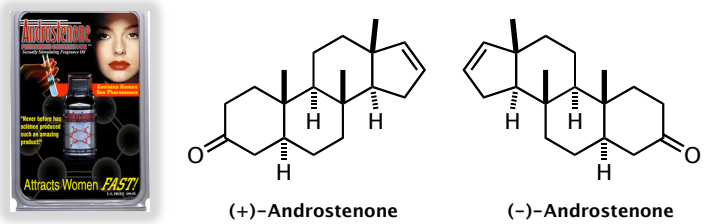

Figure 1.3. Package of commercially available (+)-Androstenone and molecular structures of (+)-Androstenone and (-)-Androstenone.

More important is the different activity that can present both enantiomers of a determinate synthetic drug. Interactions of drugs with receptors, enzymes or binding sites have long been known to be stereoselective, and both pharmacodynamic and pharmacokinetic events contribute to the overall clinically observed stereoselectivity. The most common different effects observed are when the eutomer (the active enantiomer of a chiral molecule) is significantly more active than the distomer (the less active enantiomer) or when this last one is totally inactive. The problems in the administration of the drugs as racemate (equimolar mixture of a pair of enantiomers) appear when both enantiomers act as eutomers and have independent therapeutic effects, like in the case of quinine used as antimalarial and quinidine that is an anti-arrhythmic agent or even worse,

[8] L. Pasteur, *Memoire sur la fermentation appelee lactique*, Comptes Rend. Acad. Sci. Paris 46:615, **1858**.
[9] J. P. Riehl, *Mirror-Imatge Asymmetry: an Introduction to the Origin and Consequence of Chirality*, Wiley-VCH, New Jersey, Canada, **2010**.

when the distomer has harmful or undesirable effects. One example of this last type is the enantiomers of 3-methoxy-17-methylmorphinan (methorphan) (Fig. 1.4).[10] The D-isomer, common known as dextromethorphan, is used as a cough suppressant (antitussive) and it is one of the active ingredients in many over-the-counter medicines, such as Bisolvon Antitusivo® (brand name in Spain). On the other hand, Levomethorphan is an opioid narcotic.

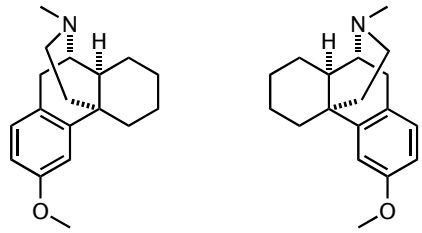

Figure 1.4. D- and L-isomers of methorphan.

Other well-known example but with terrible consequences is the thalidomide.[11] In the 1960s, this drug was administrated as racemic mixture to calm the nauseas during early pregnancy when only the (*R*)-isomer presents this activity and the (*S*)-one has teratogenic effect in foetus. The impact of this incident, that caused more than 10,000 birth defects worldwide, was the reason to change the regulatory laws for new-drugs approval. The United States Food and Drug Administration (FDA) ordered to test the pharmacological and toxicological activities of both enantiomers present in all racemic drugs as well as interconversion of enantiomers in animals and humans and forcing to the pharmaceutical companies to justify rigorously its use as racemate. This fact also had its impact in the scientific community because of the demand of highly efficient methods of asymmetric synthesis to obtain enantiomerically pure compounds. Although nowadays there are quite a lot of biologically active compounds used as racemic mixture like ibuprofen (in this case because ibuprofen racemizes in

[10] A. K. Peepliwal, S. B. Bagade, C. G. Bonde, *J. Biomed. Sci. and Res.* **2010**, *2*, 29.
[11] R. Brynner, T. Stephens, *Dark Remedy: the Impact of Thalidomide and its Revival as a Vital Medicine*, Perseus Publishing, Cambridge MA, **2001**.

the body), the production of enantiomerically pure drugs is increasing not only because of the important reasons explained above, but also because the cost of production of a single enantiomer is in most of the cases lower than the cost of the work necessary to elucidate the toxicological and pharmacokinetic profile of the undesired enantiomer.[12]

The requirements for practical asymmetric synthesis include high stereoselectivity, high rate and productivity, cost efficiency, operational simplicity, atom economy[13] and environmental friendliness with low energy consumption. Among the different strategies of asymmetric synthesis, the enantioselective catalysis is the one with more advantages, compared with the rest of them. For instance, the resolution of a racemate, even being a good method when both enantiomers are desired, is a wasteful synthetic way when only one isomer is needed with lower atom economy compared with catalytic methodologies. The use of chiral auxiliaries involves additional steps of their attachment and detachment and in the case of using enantiopure starting materials from the chiral pool, its availability is limited. For that reasons the use of chiral catalysts[14] in asymmetric synthesis is a highly valuable method for preparing optically active compounds.

1.1. ASYMMETRIC CATALYSIS

Catalytic asymmetric synthesis is one of the most important areas in organic synthesis and the design and development of new high-performance catalysts for applications in asymmetric catalytic reactions is one of the most interesting challenges for organic chemists. According to a promotional brochure from the chemical company BASF, more than 80% of globally produced chemicals are made using catalytic processes.[15] The use of (ideally)

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[12] V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**. *106*, 2734.
[13] B. M. Trost, *Angew. Chem.* **1995**, 107, 285; Angew. *Chem. Int. Ed.* **1995***, 34*, 259.
[14] a) *Catalytic Asymmetric Synthesis*, I. Ojima, Ed., VCH Publishers, Cambridge, **1993**. b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1999**. c) *Comprehensive Asymmetric Catalysis*, Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, New York, **1999**. d) P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, **2009**.
[15] R. Noyori, *Nature Chemistry* **2009**, *1*, 6.

very small amount of a chiral catalyst produces a large amount of chiral product because one molecule of catalyst is able to transfer the chirality to a multiple molecules of prochiral or achiral substrate through a catalytic cycle.

Nowadays, asymmetric catalysis can be divided in three main blocks: biocatalysis or enzymatic catalysis, metal catalysis and organocatalysis (the use of low-molecular weigh organic molecules to catalyze organic transformations) (Fig. 1.5). This division is relatively new because for decade was generally accepted that only enzymes or metallic complexes could be efficient asymmetric catalysts. However, due to the explosion of the organocatalysis field in the last ten years has been made mandatory include it as one of the big branch of the asymmetric catalysis.

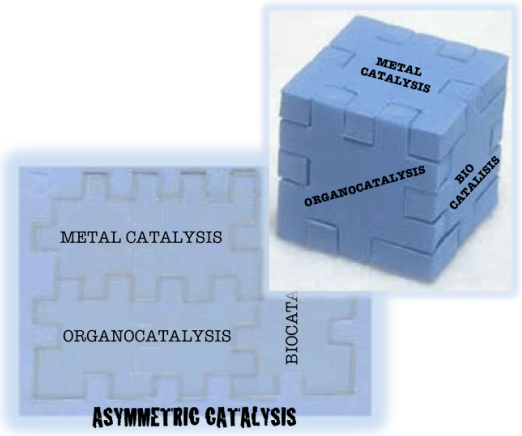


Figure 1.5. Field of asymmetric catalysis represented as a composite of three blocks: bio-, metal- and organo-catalysis.

The present work is focused mainly in supported-organocatalysts that mediate organic transformations and two chiral metal-complexes catalyzed processes. Therefore, due to that enzymatic catalysis is beyond the scope of this PhD dissertation, will not be mentioned.

1.1.1. METAL CATALYSIS

Despite the impressive growth of the organocatalytic processes in the last years, the use of chiral complexes based on transition metals or main group elements is one of the most general strategies used in asymmetric synthesis.

High proportion of asymmetric catalysts developed are organometallic compounds, where the catalytic activity is basically originated from the central metal and the stereoselectivity is due to the chiral ligands. In addition, the reactivity of complexes bearing a chiral ligand is enhanced in comparison to that with nonchiral ligand, due to the so-called "ligand acceleration effect".[16] In Figure 1.6 is illustrated a typical catalytic cycle where the catalyst formed by a metallic element and chiral organic ligands activates the achiral substrates A and B to transform them in the chiral product A-B.[17]

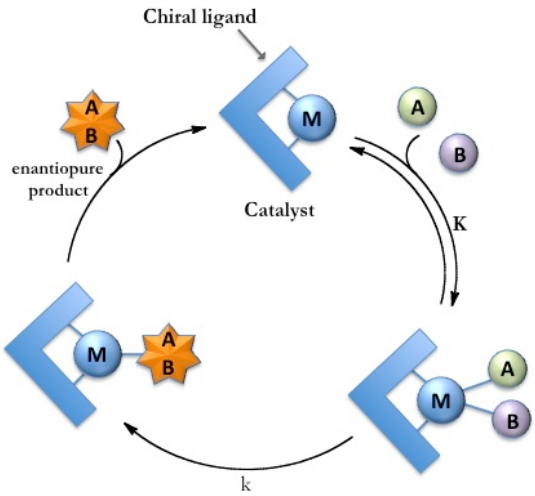
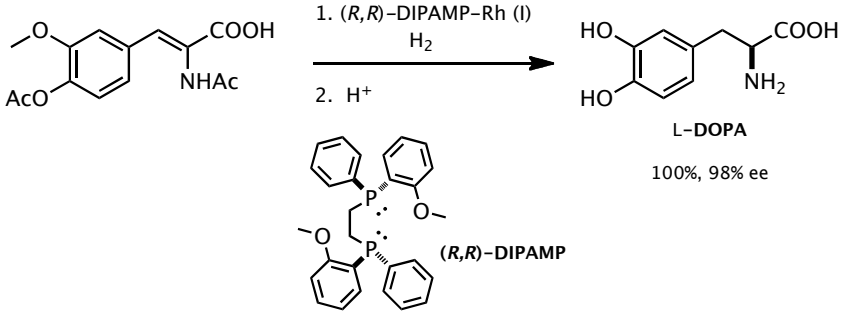


Figure 1.6. General representation of a catalytic cycle involving a chiral organometallic catalyst.

[16] a) E. N. Jacobsen, I. Marko, M. B. France, J. S. Svendsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 737. b) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.
[17] R.Noyori, M. Kitamura, T. Ohkuma, *PNAS* **2004**, *101*, 5356.

The first industrial catalytic asymmetric synthesis was the production of (L)-DOPA ((L)-3-(3,4-dihydroxyphenyl)alanine). This process was able due to the discovery by William S. Knowles in 1968 of a chiral rhodium (Rh) complex to catalyze asymmetric hydrogenation reactions[18] or in other words, he discovered the use of a metal complex as chiral catalyst. Before that, the industrial synthesis of the anti-Parkinsonian amino acid L-DOPA was carried out by Hoffman-LaRoche. There, they started the synthesis from vanillin to obtain racemic D,L-DOPA followed by its resolution and deprotection to give enantiopure L-DOPA. As is explained in the Nobel Lecture of Prof. Knowles,[19] Monsanto Company was custom-manufacturing the racemic intermediate to Hoffman-LaRoche. When Knowles and co-workers patented the (*R,R*)-DIPAMP-Rh(I) complex for the asymmetric hydrogenation of the enamide precursor of the amino acid, the known as Monsanto's process (Scheme 1.1) was the only way to produce L-DOPA in 100% yield and 98% ee. The process has been also used for the production of more other α-amino acids as L-phenylalanime (96% ee) or L-triptophan (93% ee) and employed for other companies including Hoffman-LaRoche.



Scheme 1.1. Monsanto L-DOPA process of synthesis.

The Nobel Prize award in 2001 to Prof. William S. Knowles and Prof. Ryoji Noyori "for their work on chirally catalyzed hydrogenation reactions" and Prof. Sharpless "for his work on chirally catalyzed oxidation

[18] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445.
[19] W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.

reactions",[20] is the best illustration of the importance of metal complexes-mediated asymmetric catalysis. As a curiosity, one year before, in 2000, the Swedish scientist Arvid Carlsson, join with Paul Greengard and Eric R. Kandel, was awarded with the Nobel Prize in Physiology or Medicine for his studies of dopamine neurotransmitters and how the administration of L-DOPA (the precursor of dopamine) alleviate the symptoms of Parkinson's disease.[21]

A large number of synthetic catalysts have been developed since then and there are some of them, called 'privileged chiral catalysts' (Fig 1.7),[22] that are enantioselective for a wide range of organic reactions with different mechanisms.

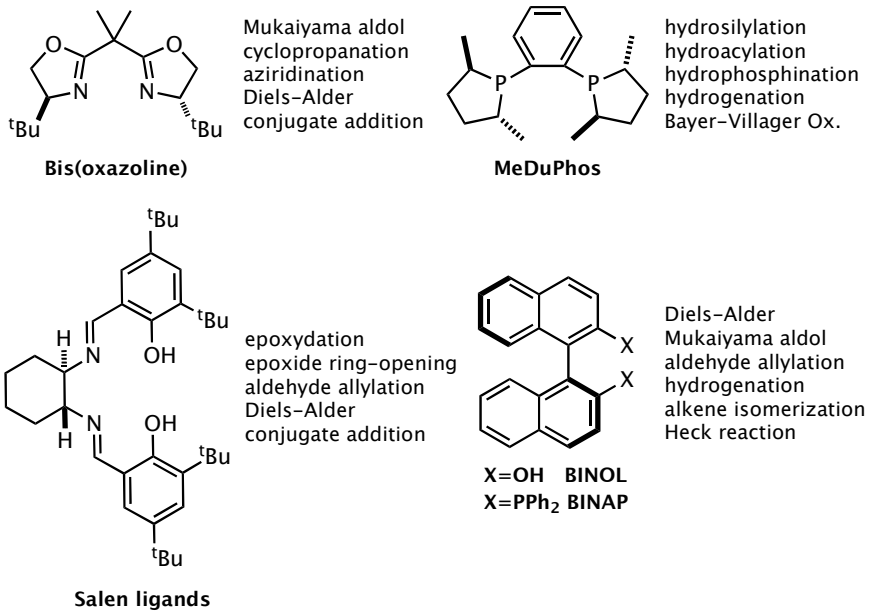


Figure 1.7. Some examples of 'privileged' chiral ligands and catalysts.

[20] Nobel lectures: a) Ref. 14. b) R. Noyori, *Angew. Chem.* **2002**, *114*, 2106; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. c) K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2112; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.
[21] From *Nobel Lectures, Physiology or Medicine 1996-2000*, Ed. Hans Jörnvall, World Scientific Publishing Co., Singapore, **2003**.
[22] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691.

One recent example that displays the powerful utility of metal-asymmetric catalysis is the synthesis of fostriecin.[23] The synthesis is carried out through one enantio- and three diastereoselective reactions all using chiral catalysts and one different catalyst to establish each individual stereogenic unit (Fig. 1.8). Fostriecin is an antitumor drug that because of its instability, the clinical trials were interrupted in phase I. However, there is still a great interest in routes to synthesize it and analogous those are more stable and that could have the same biological activity as fostriecin.[24]

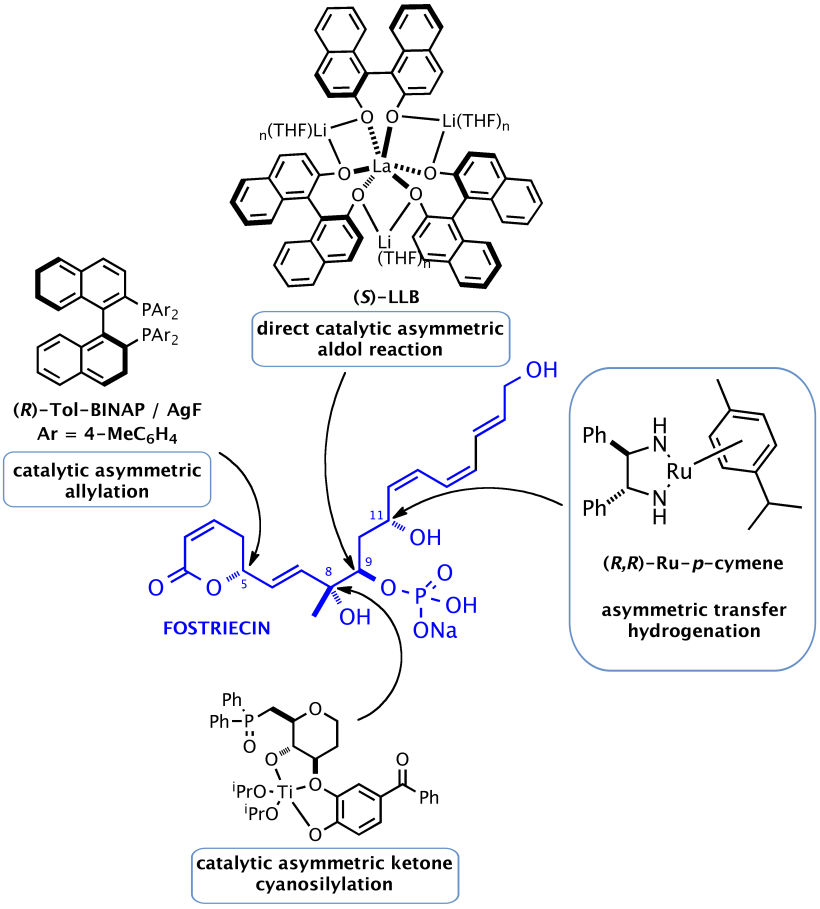
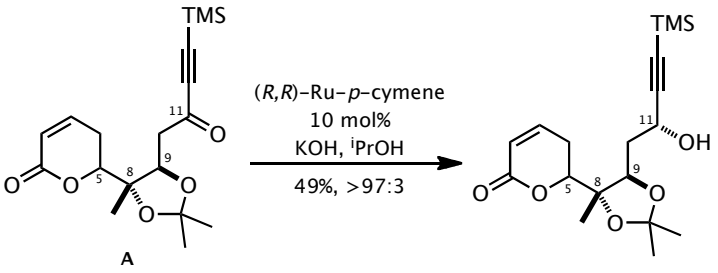


Figure 1.8. Chiral catalysts used in the asymmetric synthesis of fostriecin.

[23] K. Fujii, K. Maki, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 733.
[24] D. Gao, G. A. O'Doherty, *Org. Lett.* **2010**, *12*, 3752.

In the final stereochemical step of the mentioned synthesis, a Ruthenium (Ru)-*p*-cymene complex was used as precatalyst for the highly diastereoselective asymmetric reduction of the ynone A (Scheme 1.2), providing a >97:3 ratio of diastereomers.



Scheme 1.2. Noyori reduction step in the synthesis of fostriecin.

This asymmetric transfer hydrogenation reaction, also known as Noyori reduction,[25] is the reaction object of study in the Chapter VI of the present dissertation where is commented in more detail.

1.1.2. ORGANOCATALYSIS

By definition, organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound in absence of a metal element.[26] As already has been mentioned, in the last ten years has being an exponential increase in the publications about this filed taking into account that in 2001 there were 5 publications about organocatalysis whereas in 2010 were reported 509 and in the first quarter of 2011 there are already 154 publications (Fig. 1.9).[27] The fundamental advantages of organocatalysis are mainly related with the easier experimental procedures required with mild conditions. That involves low levels of chemical waste that means savings in time and energy and also in cost because usually organocatalysts are relatively inexpensive, compared with organometallic species.

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[25] K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738.
[26] P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248*; Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
[27] Data from *ISI Web of Knowledge-Web of Science Database.*

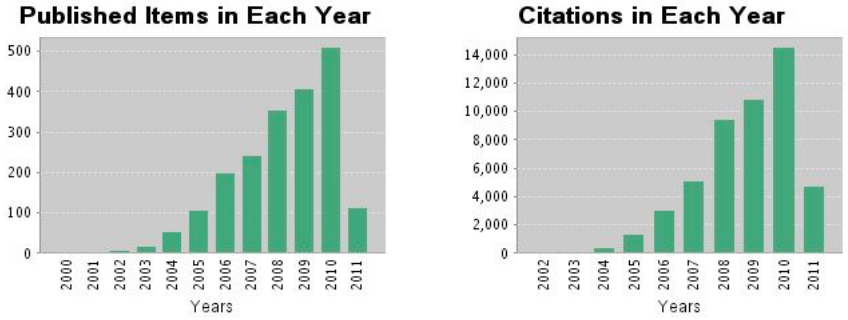
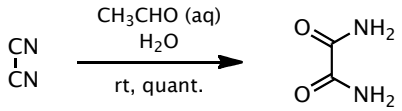


Figure 1.9. Graph illustration of the number of publications and citations per year of organocatalysis topic.

In spite of the relative novelty of organocatalysis, organic molecules have been used as catalysts from the early age of synthetic chemistry.[28] In 1932, Wolfgang Lagenbeck coined the term 'Organic Catalyst' ('Organische Katalysatoren'),[29] although was in the middle of 19th century when Justus von Liebig described the first organocatalytic reaction.[30] This reaction was the transformation of dicyan into oxamide in the presence of an aqueous solution of acetaldehyde (Scheme 1.3).

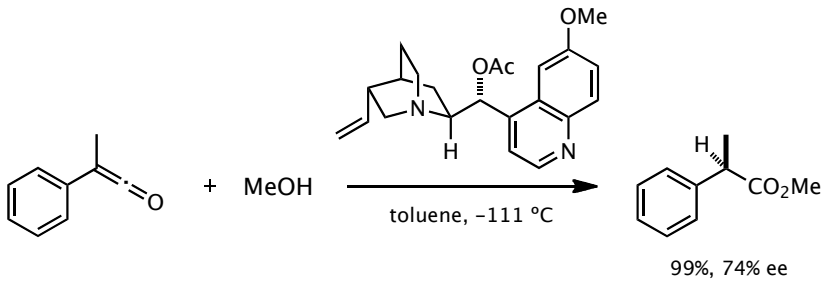


Scheme 1.3. Organocalytic oxamide synthesis.

One century after that, it was reported the first asymmetric organocatalyzed reaction with acceptable level of enantioselectivity.[31] In the work of Pracejus, a cinchona derivative (*O*-acetylquinine) catalyzed the methanolysis of a ketene with 74% ee (Scheme 1.4).

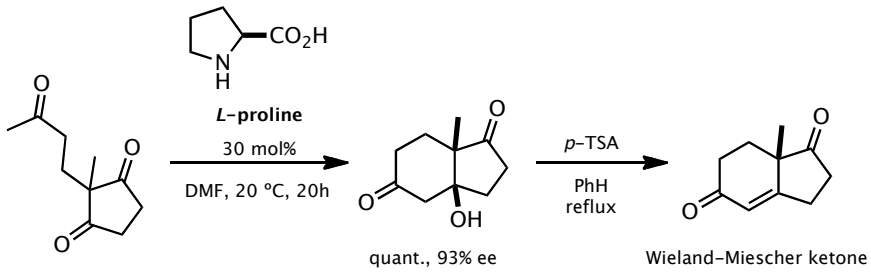
---

[28] P. I. Dalko, *Enantioselective Organocatalysis*, Wiley VCH, Weinheim, **2007**.
[29] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley VCH, Weinheim, **2005**. b) W. Lagenbeck, *Angew. Chem.* **1932**, *45*, 97.
[30] J. von Liebig, *Justus Ann. Chem. und Pharmacie*, **1860**
[31] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.



Scheme 1.4. Organocalytic methanolysis by *O*-acetylquinine.

In the 1970s, two independent groups from Schering Berlin[32a] and Hoffmann-LaRoche[32b] reported the L-proline-catalyzed asymmetric Robison annulation that provided key intermediates for the synthesis of natural products[32] as well as a practical route to obtain the Wieland-Miescher ketone in enantioselective way (Scheme 1.5).[33]



Scheme 1.5. Enantioselective L-proline catalyzed Robison annulation followed by the formation of Wieland-Miescher ketone.

This intramolecular aldol reaction also so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction marked a turning point in the field of organocatalysis and since then, high efficient organocatalysts and organocatalytic reactions have been described.

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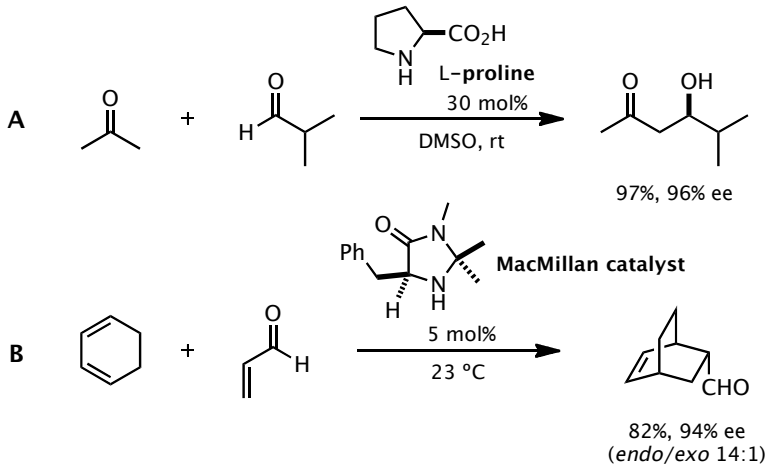
[32] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492*; Angew. Chem. Int. Ed.* **1971**, *10*, 496. b) Z. G. Hajos, D. R. Parrish, *Asymmetric synthesis of optically active polycyclic organic compounds*. German patent DE 2102623, **1971**. c) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[33] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951.

Since late 1990s articles on organocatalysis were more focused in the reaction *per se* that in the benefits of the catalysis by a small organic molecule. From then on, important contributions to this field have been described. The work of Yian Shi about enantiomeric epoxydation of a wide range of *trans*-olefins mediated by a chiral ketone derived from D-fructose using persulfate as O_2 source is a good example,[34] or the asymmetric Strecker reaction catalyzed by Schiff bases or by chiral bicyclic guanidine in the works of Eric Jacobsen[35] and Elias Corey[36] groups respectively, being the first examples of hydrogen-bonding catalysis. The simultaneous appearance in 2000 of two articles about catalytic reactions promoted by chiral secondary amines, *via* enamine from the group of Carlos Barbas III (Scheme 1.6A),[37] and *via* iminium ion by the group of David MacMillan[38] (Scheme 1.6B) was the starting point for the organocatalysis boom, the conceptualization of the field[39] and the discovery of new efficient organocatalysts as well as new modes of catalyst activation.



Scheme 1.6. L-proline catalyzed intermolecular asymmetric aldol reaction (A) and asymmetric Diels-Alder reaction using MacMillan catalyst (B).

[34] Y. Tu, Z. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806.
[35] M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.
[36] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157.
[37] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[38] K. A Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[39] D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

The molecular structures of the mentioned organocatalysts and some additional representative ones are shown in Figure 1.10.

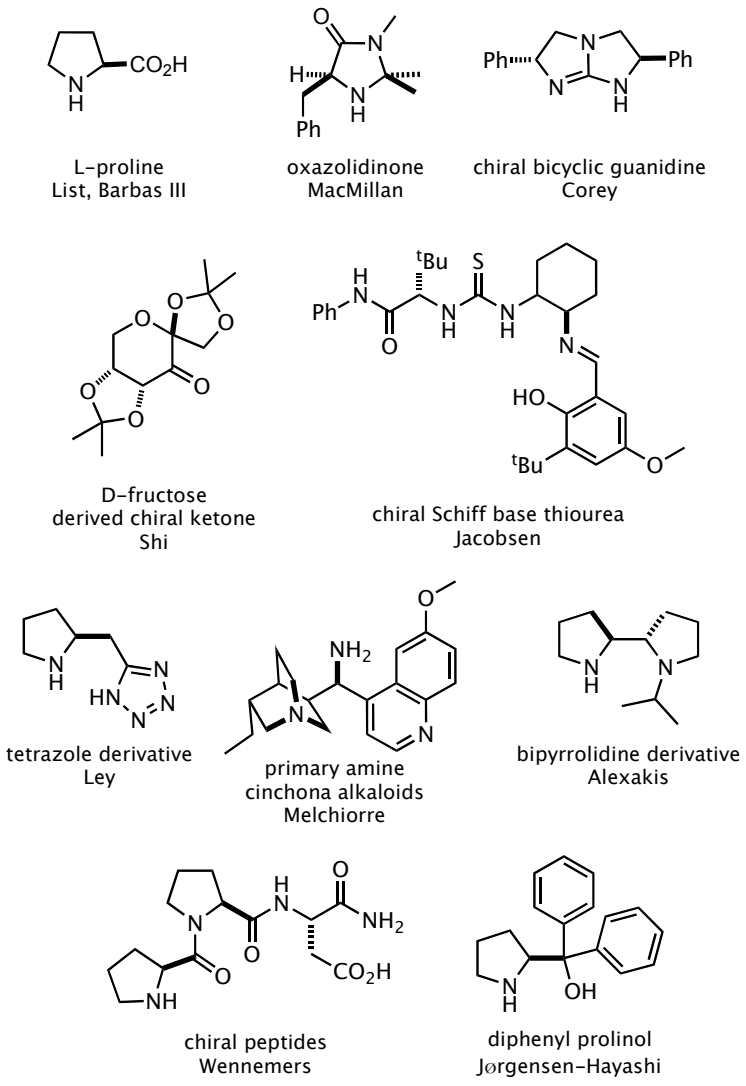


Figure 1.10. Molecular structure of some representative organocatalysts.

1.1.2.1. ORGANOCATALYSTS CLASSIFICATION

There are two main ways of classifying organocatalysts depending on the interaction catalyst-substrate[29a] (Fig. 1.11) or according to their acid/base reactivity[40] (Fig. 1.12).

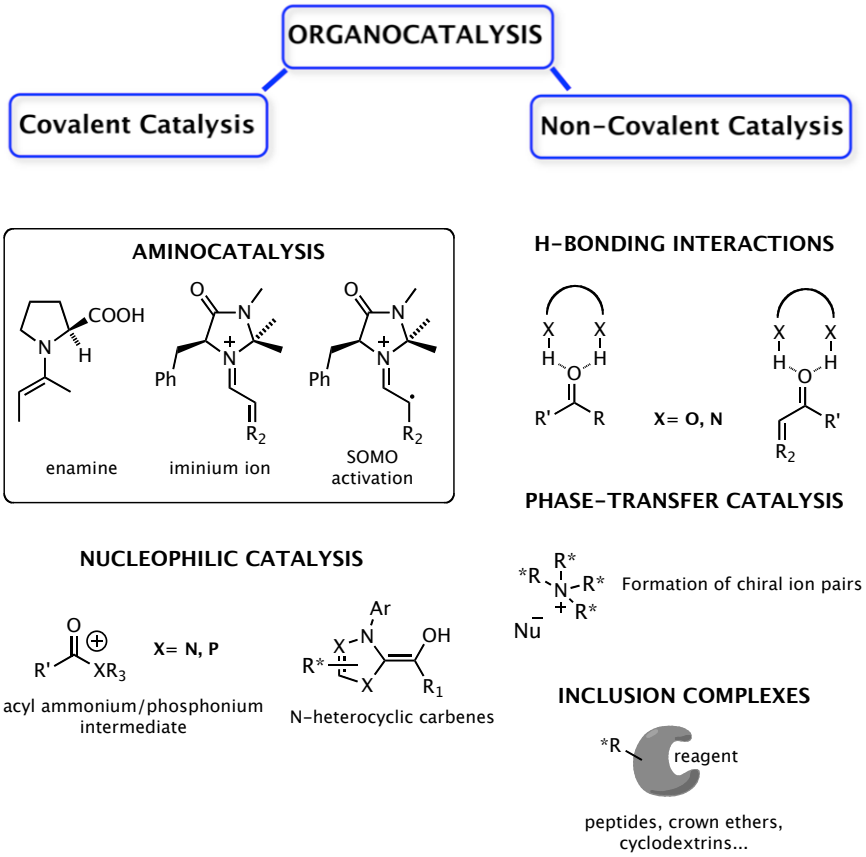


Figure 1.11. Organocatalysts classification into 'Covalent catalysis' or 'non-covalent catalysis'.

[40] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.

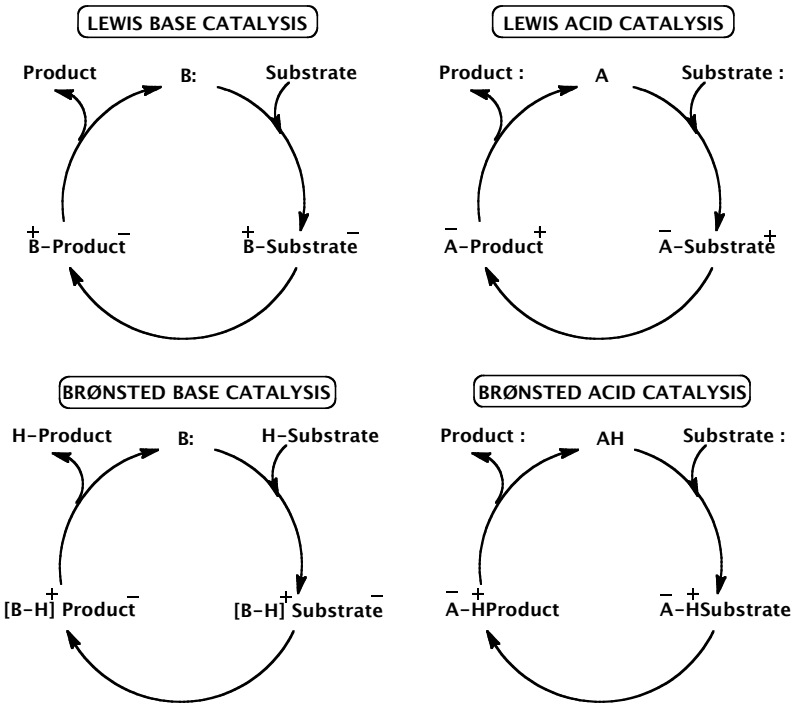


Figure 1.12. Organocatalytic cycles according to the organocatalysts acid/base reactivity classification.

Brønsted Base Catalysis

Using a Brønsted base organocatalyst,[41] the catalytic cycle (bottom-left Fig. 1.12) is initiated via a (partial) deprotonation of a pro-nucleophile substrate (H-Substrate) to render a new species with enhanced nucleophilicity (Substrate$^-$) due to the formation of a ion-pair that maintains the chiral environment during the reaction (in the case of chiral Brønsted bases).

Due to this ion-pair formation, this type of catalysis is *"non-covalent"*. The most common chiral Brønsted bases used in organocatalysis are terciary amines, imidazols, amidines, guanidines or alkaloids such as cinchona (Fig.

[41] For a recent review, see: C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632.

1.13-left).[42] The use of chiral Brønsted bases is in most cases as a part of Brønsted base-hydrogen bonding bifuctional catalyst, which activates the pro-nucleophile by deprotonation while the substrate is activated by hydrogen-bond interactions (Fig. 1.13-righ).[43]

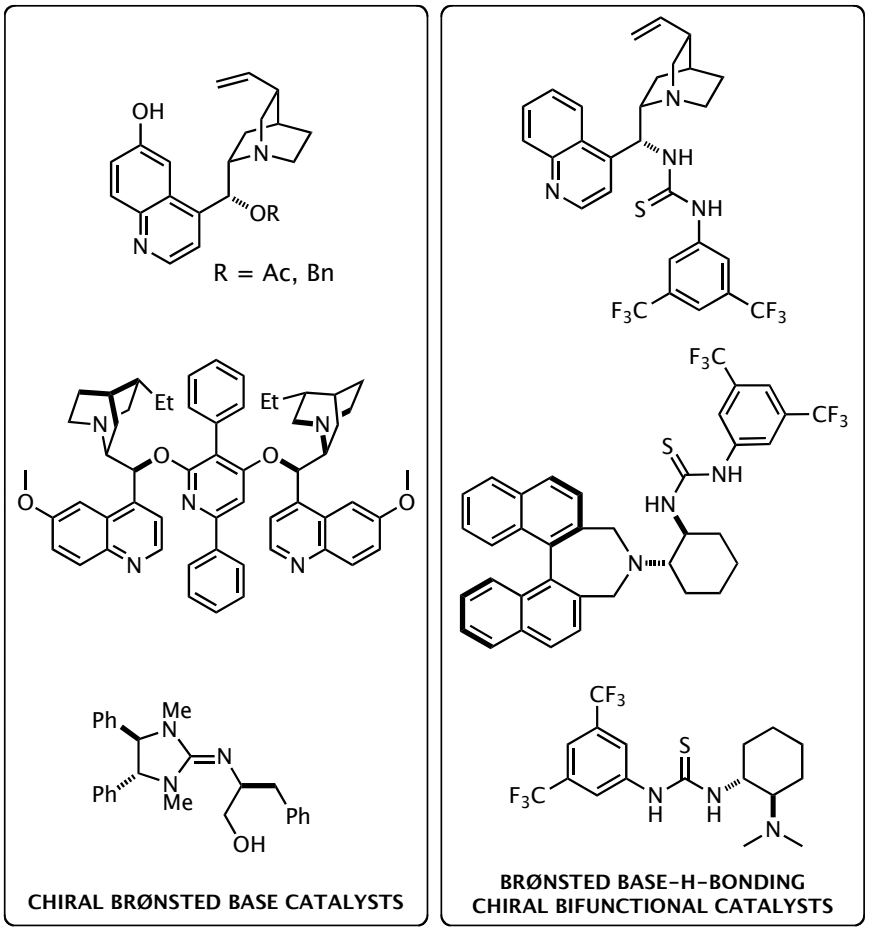


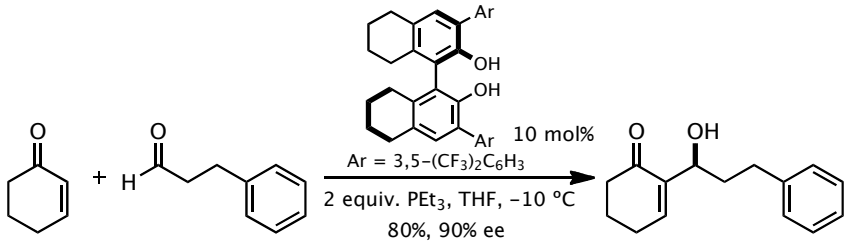
Figure 1.13. Examples of Brønsted base chiral organocatalysts.

[42] For reviews focused on cinchona alkaloid-derived catalysts, see: a) Y.-C. Chen, *Synlett*, **2008**, *13*, 1919. b) G. Bartoli, P. Melchiorre, *Synlett*, **2008**, *12*, 1759. c) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.*, **2011**, DOI: 10.1039/C0CY00096E.

[43] For some examples of Brønsted base-H-bonding bifuctional catalysts, see: a) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713. b) F.–Z. Peng, Z.–H. Shao, B.–M. Fan, H. Song, G.–P. Li, H.–B. Zhang, *J. Org. Chem.* **2008**, *73*, 5202. c) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753.

Brønsted Acid Catalysis

In this case, the activation of this type of *non-covalent* catalysis is though the protonation of the substrate or via hydrogen bonding interactions (Fig. 1.12 bottom-right). These interactions activate the nucleophilic attack lowering the electronic density of the electrophile. This kind of catalysis by H-bonding has becoming a powerful methodology for asymmetric transformations and there are described a large of number of efficient organocatalysts.[44] The catalysts commonly used are ureas, thioureas, diols or chiral amides and carboxylic acids. Recently, has been demonstrated the efficiency and highly selectivity showed by relatively strong chiral Brønsted acid catalysts like binaphthol-derived phosphoric acids.[45] To form hydrogen bonds that allow the asymmetric catalysis, these catalysts have modest acidity (pK_a ~ 30-5), low dimerization potential and induce directionality within the substrate. There are many asymmetric reactions mediated by chiral Brønsted acid organocatalysts as Mannich, Michael, Henry or Diels-Alder among others. As example, in catalytic enantioselective Morita-Baylis-Hillman reaction (Scheme 1.7),[46] BINOL-derived Brønsted acid promotes the conjugate addition step and remains hydrogen-bonded to the resulting enolate in the enantioselectivity-determining aldehyde addition step.



Scheme 1.7. Enantioselective reaction catalyzed by BINOL-derived Brønsted acid.

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[44] For reviews about Brønsted acids, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713. b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. c) H. Yamamoto, D. Nakashima, *Acid Catalysis in Modern Organic Synthesis, Vol, 1*, Wiley-VCH, Weinheim, **2008**. d) A. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187. e) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science*, **2010**, *327*, 986.

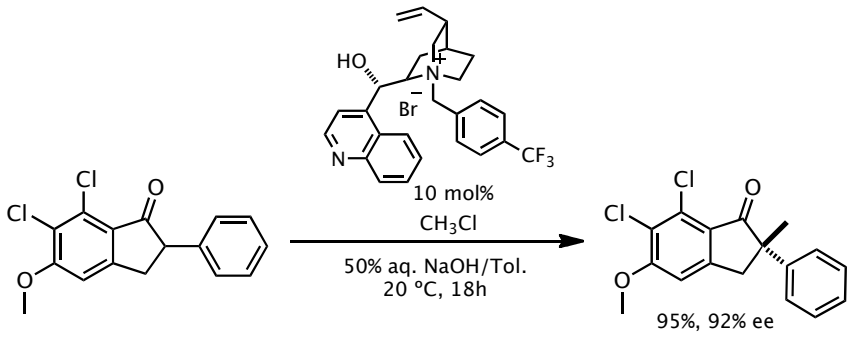
[45] a) T. Akiyama, J. Itoh, K.Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592. b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356. c) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356. d) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, Eur. *J. Org. Chem.* **2011**, *11*, 2209.

[46] N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094.

Lewis Acid Catalysis

Although is the common activation associated to metal catalysis, there are also organic catalysts that can be considered Lewis acids that activates nucleophilic substrates.[40] The most important organocatalytic Lewis acids are phase-transfer catalysts and the catalysis is also *non-covalent*, although the mechanism of phase-transfer catalyst is unique because promotes reactivity altering the properties of the reactants but also involves transport phenomenon. There are several enantioselective phase transfer catalyzed reactions as α-alkylation of glycine derivatives or aldol or Michael reactions.[47]

The first application of a chiral-transfer catalyst with good enantioselective results was developed in Merck in 1984 (Scheme 1.8).[48] The catalyst was a *N*-benzyl cinchoninium salt for the asymmetric α-methylation of indanones.



Scheme 1.8. Asymmetric phase-transfer catalyzed reaction.

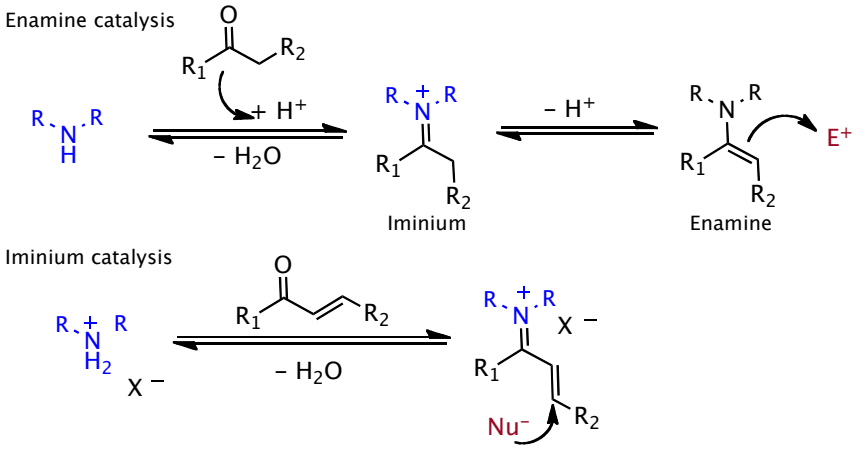
[47] For reviews and publications on Lewis acid organocatalysis, see: a) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103,* 3013. b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506. c) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488. d) D. Yang, *Acc. Chem. Res.* **2004**, *37*, 497. e) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46,* 4222. f) O. Sereda, S. Tabassum, R. Wilhelm, *Topics Current Chem.* **2009**, *291*, 86. g) X. Wang, Q. Lan, S. Shirakawa, K. Maruoka, *Chem. Commun.* **2010**, *46*, 321.

[48] U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *118*, 446.

Lewis Base Catalysis

As Lewis base (B: in top-left Fig. 1.12), the organocatalysts activates the substrate by attaching to it via nucleophilic addition or substitution (on top-left Fig. 1.12). Therefore, the Lewis bases are included in the *covalent-catalysis* classification of the organocatalysts and depending on the Lewis base, the different modes of activation convert the substrates either into activated nucleophiles or electrophiles. The use of Lewis bases in organocatalysis are the most widely studied strategy to date and implies the reversible attach of the catalyst to the substrate and final product allowing high turnover number of the catalyst. Chiral amines are the Lewis bases more used in organocatalysis, so-called *aminocatalysis*, and activate the substrate though different modes as *enamine catalysis, iminium ion catalysis* or by *iminium ion radicals*, also called *SOMO* (Singly Occupied Molecular Orbital) *catalysis*).

In **enamine catalysis**[49] the nucleophile chiral amine reacts with an enolizable carbonyl compound forming a chiral enamine that is a more nucleophile compound. This can be considered as HOMO (Highest Occupied Molecular Orbital) activation.



Scheme 1.9. Enamine and iminium ion catalysis.

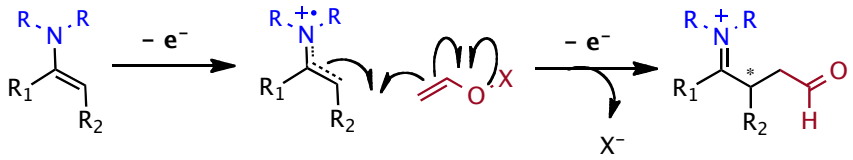
[49] For reviews on enamine catalysis, see: a) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580. b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123. c) S. Murkherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471. d) T. Kano, K. Maruoka, *Chem. Comm.* **2008**, 5465.

On the other hand, as LUMO (Lowest Unoccupied Molecular Orbital) activation, in **iminium catalysis**[50] an α,β-unsaturated carbonyl compound form an iminium ion with the chiral amine, which acts as the electrophile. The iminium ion is a much better electrophile than the aldehyde itself, so the reaction is accelerated respect to the non catalyzed one as in the case of enamine formation (Scheme 1.9).

Enamine and iminium ion catalysis are two of the generic modes of activation more used in aminocatalysis. These two methodologies of activation are central theme in the work related to organocatalysis of this thesis, and will be analyzed in more detail in Chapter II and III.

The **SOMO catalysis**[51] is a quite recent mode of activation introduced by the MacMillan's research group in 2006 and consists in the selective generation of a reactive radical cation with three π-electrons by one-electron oxidation of an electron-rich (chiral) enamine. The electrophilicity of the singly occupied molecular orbital of that intermediate allows the reaction with weakly carbon nucleophiles at the α-carbon of the parent enamine (Scheme 1.10).[39]

SOMO catalysis



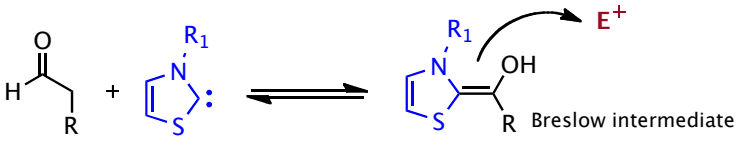
Scheme 1.10. SOMO activation mode.

[50] For reviews on iminium-ion catalysis, see: a) G. Lelais, D. W. C. Macmillan, *Aldrichimica Acta* **2006**, *39*, 79. b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

[51] First SOMO catalysis application and first use as generic mode of activation: a) H-Y Young, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc* **2007**, *129*, 7004. For other important publications and highlights about SOMO catalysis, see: b) T. D Beeson, A. Mastracchio, J.-B. Hong, A. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582. c) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 7500; *Angew. Chem. Int. Ed.* **2007**, *46,* 7356. d) P. Renaud, P. Leong, *Science* **2008**, *322*, 55. e) D. A. Nicewicz, D. W. C MacMillan, *Science* **2008**, *322,* 77. f) P. Melchiorre, *Angew. Chem.* **2009**, *121*, 1386; *Angew. Chem. Int. Ed.* **2009**, *48,* 1360.

The SOMO activation requires that catalyst should undergo efficient and reversible enamine formation with high levels of control of enamine geometry and selective discrimination of olefin π-face. It is also important that the enamine undergoes selective oxidation in the presence of an amine catalyst, aldehyde or iminium ion. Despite to be a novel activation mode, the SOMO mechanism has been employed with success in a variety of enantioselective transformations, even avoiding drawbacks of some of them like in the intermolecular α-alkylations of aldehydes where low reactivity of alkyl halides is improved by SOMO activation.[51f]

The **nucleophilic catalysis** is also inside the covalent-activation group and can be promoted by tertiary chiral amines or phosphines via the corresponding ylides,[52] acylamonium salts or chiral DMAP derivatives.[53] Another important group of these catalysts are *N*-heterocyclic carbenes.[54] Generally, in carbene catalysis the carbene catalyst reacts with the aldehyde forming the nucleophilic Breslow intermediate (Scheme 1.11) and facilitating thus the addition to an electrophile.



Scheme 1.11. Carbene catalysis.

The heterogenization or immobilization of active compounds on supports or carriers are the best strategies to combine the properties of these catalysts showed with the possibility of its easy separation from the product solution and recycle maintaining their catalytic properties.

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[52] For reviews, see: a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103,* 2985. b) M. J. Gaunt, C. C. C. Johanson, *Chem. Rev.* **2007**, *107,* 5596. c) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107,* 5656. d) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107,* 5841.

[53] a) J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601. b) R. P. Wurz *Chem. Rev.* **2007**, *107,* 5570.

[54] About chiral carbenes catalysis, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534. b) J. S. Johnson, *Angew. Chem.* **2004**, *116*, 1348; *Angew. Chem. Int. Ed.* **2004**, *43,* 1326. c) D. Enders, O. Niemerier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606. d) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46,* 2988.

1.2. SUPPORTED CATALYSTS

As has been mentioned at the beginning of the present general introduction, the high increase of demand for enantiopure chiral chemicals have led in the last decades to the development of a huge amounts of chiral metal complexes for the homogeneous asymmetric catalysis of great number of organic reactions. But although the asymmetric catalysts are every time more used in industrial processes, there is still a limited use of them because of the high economical cost of metals and chiral ligands as well as the cost in energy and waste in separation of metal complexes from reaction mixture. Another drawback is the no-tolerated presence of any metal traces especially in the production of fine chemicals and pharmaceuticals. For a large scale or industrial asymmetric processes, the stability of the catalyst join its easy separation from the products and the possibility of reuse are important aspects to be considered. The immobilization of catalytic species on a solid support represents a solution for these problems.[55] That characteristic is enhanced when organocatalysts are used since their non-metallic nature confers less toxicity and more economic costs to the industrial, as well as allows the use of mild reaction conditions and prevents the possible leaching (or coming off) of toxic metal to the organic product.

The term catalyst immobilization can be defined as a 'transformation of a homogeneous catalyst in a heterogeneous one, which is able to be separated from the reaction mixture and preferably be reused for multiple times'.[55e] The desirable properties of a supported catalyst are the combination of the positive aspects of homogeneous catalyst like high activity and reproducibility, and those of heterogeneous catalyst for instance the stability and reusability. The principal objectives to immobilize a catalyst onto a support are a simple reaction work-up, easy recovery and its possible recycle, although other reasons can lead to support a catalytic compound.

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[55] For reviews, see: a) D. E. De Vos, I. F. J. Van-kelecom, P. A. Jacobs, *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, **2000**. b) R. A. Sheldon, H. Bekkum, *Fine Chemicals through heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2001**. c) J. A. Gladysz, *Chem. Rev. Special Issue: Recoverable Catalysts and Reagents* **2002**, *102*, 3215. d) P. McMorn, G. Hutchings, *Chem. Soc. Rev.* **2004**, *33*, 108. e) K. Ding, Y. Uozumi, *Handbook of Asymmetric Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2008**. f) P. Barbaro, F. Liguari, *Heterogenized Homogeneous Catalysts for Fine Chemicals Production Catalysis by Metal Complexes*, Springer, Heidelberg, Vol. 33, **2010**.

To improve the stability during the reaction or better reactivity or selectivity due to the change in structure can be good examples. In principle, it is expected that the heterogenized catalysts will be less reactive compared with the homogeneous counterpart because of the increase in the steric hindrance caused by the support making the active sites less accessible, but not always is the case.[56] If the chemically modified homogeneous ligand has been properly designed, the supporting process does not perturb the reaction site and the target catalytic process can take place in an essentially homogeneous environment.[55f] The linker or spacer also takes an important role solving problems of reactivity not only related to accessibility. It can create a microenvironment around the active site of the catalyst more beneficial to reactivity than the provided only by the support (Fig. 1.14).[57]

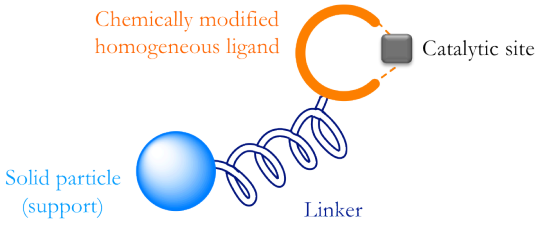

Figure 1.14. Schematic representation of supported catalytic species.

The choice of the support is crucial because its properties can influence in the catalyst behaviour. The solubility profile, cost, commercial availability, degree of functionalization and the possible participation of the support backbone in the reaction are important features of the support to take into account.[58] The strategies of immobilization of an asymmetric catalyst depend on whether the modifications are made on the reaction medium (*multiphase catalysis on nonconventional media*) or on the catalyst structure (*catalyst heterogenization*).

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[56] For some reported examples where the immobilized catalyst has better performance than the non-supported one, see: a) M.S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901. b) M.S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336*; Angew. Chem. Int. Ed.* **2000**, *39*, 1279. c) R. Annunciata, M. Benaglia, M. Cinquini, F. Cossi, G. Tocco, *Org. Lett.* **2000**, *2*, 1737. d) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012. e) S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941.

[57] For first publication demonstrating the importance of the spacer in polymer supported catalysis, see: P. L. Anelli, B. Czech, F. Monatarani, S. Quici, *J. Am. Chem. Soc.* **1984**, *106*, 861.

[58] F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367.

1.2.1. IMMOBILIZATION OF ASYMMETRIC HOMOGENEOUS CATALYSTS IN NON-CONVENTIONAL MEDIA

In this case, the system is formed by the catalyst and some non-conventional reaction medium, as can be fluorous phase, ionic liquid or supercritical carbon dioxide ($scCO_2$).[59] Aqueous phase is also included in this group of systems that act as mobile carrier. That methodology presents a 'green' advantage because normally these mediums are environmentally benign solvents. The catalysis can be carried out in monophasic conditions but also under biphasic combinations as for instance aqueous or fluorous/organic, with different effects in the reaction. Usually it is formed a biphasic system where the organic product is immiscible in one of the phases being easily isolated and recovered by phase separation.

The catalyst immobilization in water[60] has experimented a great interest in recent years because water is abundant, nontoxic and cheap and due it low miscibility with most of organic compounds is very useful in biphasic catalysis. Furthermore, the incorporation of anionic groups such as sulphonates, cationic groups as quaternary ammonium ions (Fig. 1.15) or neutral hydrophilic groups as polyethers make the chiral ligands soluble in water favouring its catalytic performance and avoiding the inconvenient poor water compatibility of catalyst and organic substrates.

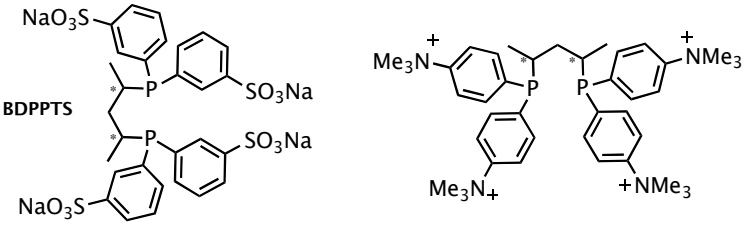

Figure 1.15. Water-soluble versions of bisdiphenylphosphinopentane (BDPP)

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[59] a) B. E. Hanson, Liquid biphasic enantioselective catalysis, pp. 81-96 in *Chiral Catalyst Immobilization and Recycling*, Eds. D. E. De Vos, I. F. J. Van-kelecom, P. A. Jacobs, Wiley-VCH, Weinheim, **2000**. b) R. T. Baker, S. Kobayashi, W. Leitner, *Adv. Synth. Catal. Special Issue: Multiphase Catalysis, Green Solvents and Immobilization* **2006**, *348 (12 + 13)*, 1371.

[60] For reviews, see: a) U. M. Lindstroem, *Chem. Rev.* **2002**, *102*, 2751. b) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095. c) C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68. d) C. J. Li, T.–H. Chan, *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, Hoboken, **2007**.

In the approach using fluorous phase-separation techniques,[61] the perfluorous solvents used are chemically inert an immiscible with most organic solvents and also water at ambient temperature, but the miscibility increase with the temperature. This thermotropic solubility feature allows a monophasic reaction increasing the temperature followed by a two-phase separation when gets cool. Similar with the use of water, the catalyst has to be modified in order to be soluble in the fluorous phase and therefore easily separated and reused after reaction. This goal can be achieved incorporating fluorocarbon moieties (called 'fluorous ponytails') to the structure of the homogeneous catalyst. The most common fluorous ponytails used are linear or branched perfluoroalkyl C_6-C_{12} chains that may contain other heteroatoms. (Fig. 1.16)[62]

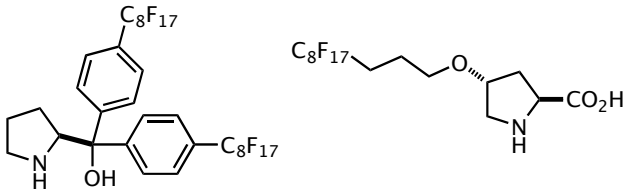

Figure 1.16. Fluorous modifications in common pyrrolidine structures.

Enantioselective catalysis in ionic liquids[63] and in supercritical fluids (SCF)[64] has generated a considerable interest during the last years. Ionic liquids are salts with a melting point below 100 ºC and no vapour pressure. Their structure (Fig. 1.17) is composed by organic cations with weakly coordinated inorganic anions. Physical or chemical properties of the ionic

[61] For representative examples, see: a) I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72. b) E. Wolf, G. Van Koten, B. J. Deelman, *Chem. Soc. Rev.* **1999**, *28*, 37. c) I. T. Horváth, Immobilization by Other Liquids: Fluorous Phases, in *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **2002**. d) G. Pozzi, I. Shepperson, *Coord. Chem. Rev.* **2003**, *242*, 115.

[62] a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986. b) F. Fache, O. Piva, *Tetrahedron Asymmetry* **2003**, *14*, 139.

[63] For reviews, see: a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071. b) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.* **2002**, *102*, 3667. c) H. Zhao, S. V. Malhotra, *Aldrichimica Acta* **2002**, *35*, 75. d) J. Muzart, *Avd. Synth. Catal.* **2006**, *348*, 275. e) V. I. Parvulescu, C. Hardacre, *Chem. Rev.* **2007**, *107*, 2615.

[64] For reviews, see: a) R. Noyori, Supercritical fluids, *Chem. Rev. Thematic Issue* **1999**, *99*, 353. b) G. Musie, M. Wei, B. Subramaniam, D. H. Busch, *Coord. Chem. Rev.* **2001**, *219-221*, 789. c) D. J. Cole-Hamilton, *Adv. Synth. Catal.* **2006**, *348*, 1341.

liquid can be fine-tuned by changing its structural constituents. They belong to highly polar solvents being immiscible with nonpolar ones. Just like the two methodologies explained above, the reactions in ionic liquids can be performed in one or two phases. In the case of biphasic way, generally the catalyst remains dissolved in the ionic liquid during the separation and both can be reused again.

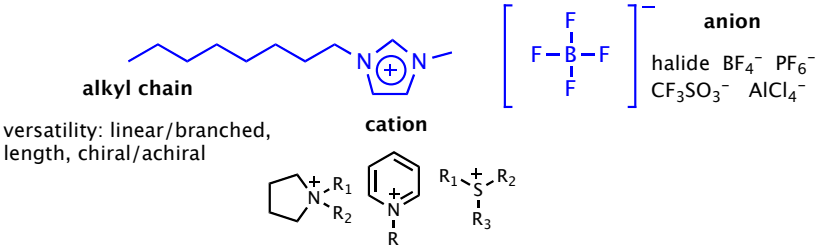

Figure 1.17. Structure of [omim]BF_4^- ionic liquids (in blue).

In the case of SCF, the main advantage is the excellent miscibility with gases being suitable for reactions involving gases such as hydrogenation or hydroformylation reactions where the solubility of the gaseous reactant can be rate limiting. A SCF is a state of a certain compound above the critical point, whereupon it demonstrates properties like a gas and like a liquid in as a homogeneous phase (Fig. 1.18). At this point the matter is a liquid-like gas. In the case of $scCO_2$, above its critical point that is at T_c = 31.1 ºC and P_c = 73.8 bar, both liquid and gas carbon dioxide coexist. The solubility of organic substrates and products in $scCO_2$ is high but, on the other hand, organometallic catalysts have low solubility in $scCO_2$ and that allows to the easy separation of the catalyst to the reaction mixture.

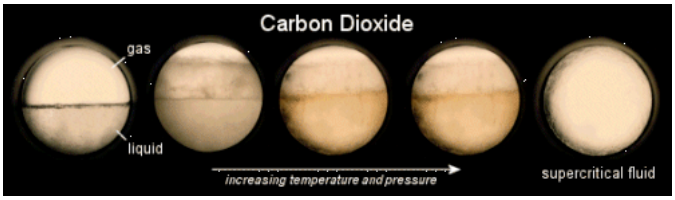

Figure 1.18. (From left to right): A chamber containing carbon dioxide as liquid and gas (two phases visible). Increasing the temperature and pressure the two phases merge to become a supercritical fluid.

1.2.2. IMMOBILIZATION OF CHIRAL HOMOGENEOUS CATALYSTS: CATALYST HETEROGENIZATION

The immobilization of a chiral catalyst can be done by covalent or non-covalent attachment of a ligand, preassembled complex or organocatalyst to the support. Nevertheless, during the immobilization process can occur numerous problems affecting the performance of the catalyst. That includes undesired interactions between the support and the catalyst, the distortion of the optimal geometry of the catalyst by the support, limited accessibility of the active sites, or a weak linkage between support and catalyst or, in the case of organometallic complexes, the metal and supported ligand.[65]

An optimal solid support should have some important features[66] as:

- be mechanically robust,
- stable to temperature variations,
- with accessible sites to the reagents,
- acceptable loadings,
- acceptable bead size, when is applicable, to facilitate its separation by filtration and,
- be stable in diverse media.

The anchoring of homogeneous asymmetric catalyst by non-covalent immobilization is an attractive approach from synthetically point of view due to the unnecessary modifications in the structure of the homogeneous specie. However the poor linkage obtained by *adsorption* or *ion-pair formation* through van der Waals interactions and their sensibility to solvent effects limits their use as immobilization strategies. Silica or mesoporous silicates materials such as MCM-41 or clays as montmorillonite are common used supports for this type of immobilization. Other interesting strategy that can be included in the non-covalently support of a catalyst is the *encapsulation* or 'ship in a bottle' method. It consists in the assembling of the catalyst in the pores of mesoporous material or the entrapping of the complex by polymerization in a sol-gel process or in a polydimethylsiloxane (PDMS)

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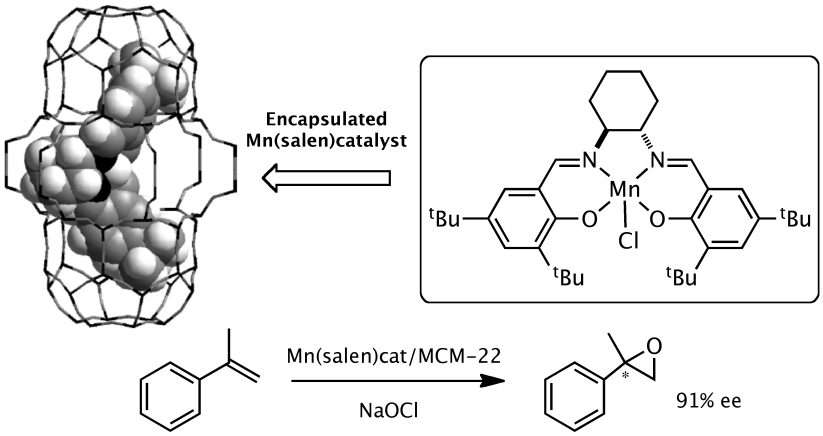
[65] M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732.
[66] J. Tulla-Puche, F. Albericio, *The Power of Functional Resins in Organic Synthesis*, Wiley-VCH, Weinheim, **2008**.

film. Mesoporous materials and zeolites are the usual supports employed. To avoid leaching, it is important that the openings of the pores of the support are smaller than the enclosed complex but, at the same time, if the pores are too small, difficult the access to the active sites compromising the good reactivity of the catalyst. Despite this, there are exceptions and in some cases the encapsulated complex leads to a better selectivity in comparison with the reaction performed in homogeneous way. For example, the encapsulation of Jacobsen catalyst in the zeolite MCM-22[67] results in an enhancement of the enantioselectivity in the epoxidation reaction of α-methylstyrene with sodium hypochlorite from 51% ee in homogeneous phase[68] to a 91% ee (Scheme 1.12). In this case, the heterogenization of this catalyst not only was beneficial in terms of less expensive catalyst separation and recovery but in the enhancement in stability, activity and selectivity.



Scheme 1.12. Enantioselective epoxidation of α-methylstyrene catalyzed by encapsulated Jacobsen catalyst.

The most common method to immobilize a chiral homogeneous catalyst is to anchor it covalently to a suitable support. This *covalent linkage* implies a modification in the structure of the chiral ligand or monomeric

[67] G. Gbery, A. Zsigmond, K. J. J. Balkus, *Catal. Lett.* **2001**, *74*, 77.
[68] E. N. Jacobsen, W. Zhang, A.R. Muci, J. R. Ecker and L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063.

organocatalysts in order to create an anchoring position usually as far away as possible from the active site of the catalyst, in such a way that the support does not perturb the reaction site. The choice of the appropriate linker and support is essential to achieve minimal levels of undesired interactions and provide the same opportunities for selectivity control than homogeneous catalysts. Nowadays, the most used supports for covalent immobilization of monomeric catalytic species are inorganic oxides as silicas or zeolites,[69] nanostructures as nanotubes or nanoparticles[70] (which are at its very peak) and organic polymers, in which is focused the present work.

[69] For selected reviews and articles about immobilization on silica and related materials, see: a) J. M. Fraile, J. A. Mayoral, J. Serrano, M. A. Pericàs, Ll. Solà, D. Castellnou, *Org. Lett.* **2003**, *5*, 4333. b) A. Corma, *Cat. Rev.* **2004**, *46*, 369. c) C. Li, *Catal. Rev.* **2004**, *46*, 419P. d) McMorn, G. J. Hutchings, *Chem. Soc. Rev.* **2004**, *33*, 108. e) D. Moelans, P. Cool, J. Baeyens, E. F. Vansant, *Catal. Commun*. **2005**, *6*, 307. f) J. M. Fraile, J. I. García, J. A. Mayoral, *Coord. Chem. Rev.* **2008**, *252*, 624. g) Y. Yang, B. Beele, J. Bluemel, *J. Am. Chem. Soc.* **2008**, *130*, 3771. h) N. Puretskiy, L. Ionov, *Langmuir*, **2011**, *27*, 3006.

[70] For selected publications about nanotubes, see: a) G. G. Wildgoose, C. E. Banks, R. G. Compton, *Small* **2006**, *2*, 182. b) S. Nakagaki, F. Wypych, *J. Colloid and Interface Science* **2007**, *315*, 142. c) E. V. Rybak-Akimova, O. E. Voronina, J. Wikstrom, *Chem. Carbon Nanotubes* **2008**, *2*, 81. For reviews about supporting on metallic-nanoparticles, see: a) D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem.* **2005**, *117*, 8062; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852. b) A.-H. Lu, E. L. Salabas, F. Schueth, *Angew. Chem.* **2007**, *119*, 1242; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222. c) M. A. Newton, *Chem. Soc. Rev.* **2008**, *37*, 2644. d) R. J. White, R. Luque, V. L. Budarin, J. H. Clark, D. J. MacQuarrie, *Chem. Soc. Rev.* **2009**, *38*, 481. e) A. Schaetz, O. Reiser, W. J. Stark, *Chem. Eur. J*. **2010,** *16*, 8950.

1.2.2.1. POLYMER-SUPPORTED CHIRAL CATALYSTS

The field of polymer-supported chiral catalysis[71] has become popular during the last decades with great importance due mainly to the easy separation and reuse of such species. The important work on solid-phase synthesis[72] published by Robert Bruce Merrifield in the 1960s (importance recognized with the Nobel Prize in 1984), was the start point for the developing of high number of catalytic compounds supported onto polymers, either insoluble or soluble. It is hardly surprising that the Merrifield's publication in the Journal of American Chemical Society is inside the Top 20 Most Cited articles published by the journal in all its history.[73]

The use of polymeric supports sometimes involves a lowering in the activity of the immobilized catalysts compared with its non-supported version because the heterogeneous nature of the supported catalyst leads to a poor interaction with the substrates in solution. Nevertheless, a great number of polymer-supported catalyst have been developed showing excellent activity and selectivity. In some cases, the environment created by the polymer, linker and catalyst leads to a better results in asymmetric transformations in comparison with the homogeneous counterpart.[71h,j]

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[71] For reviews about polymer-supported catalyst, see: a) J. Clark, D. Mcquarrie, *Handbook of Green Chemistry* & *Technology*, Blackwell Publ, London, **2002**. b) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217. c) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275. d) M. R. Buchmeiser, *Polymeric materials in organic synthesis and catalysis,* Wiley-VCH, Weinheim, **2003**. e) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401. f) R. Haag, S. Roller, *Immobilized Catalysts*, in *Topics in Current Chemistry*, ed. A. Kirsching, Springer, Heidelberg, **2004**. g) B. M. L. Dioos, I. F. J. Vankelecom, P. A. Jacobs, *Adv. Synth. Catal.* **2006**, *348*, 1413. h) S. Itsuno, N. Haraguchi, *Heterogeneous Enantioselective Catalysis Using Organic Polymeric Supports* in, *Handbook of Asymmetric Heterogeneous Catalysis*, eds. K. Ding, Y. Uozumi, Wiley-VCH, Weinheim, **2008**. i) M. Benaglia, *Recoverable and Recyclable Catalysts*, John Wiley & Sons, Chichester, **2009**. j) C. Jimeno, S. Sayalero, M. A. Pericàs, *Covalent Heterogenization of Asymmetric Catalysts on Polymers and Nanoparticles* in, *Heterogenized Homogeneous Catalysts for Fine Chemicals Production Catalysis by Metal Complexes*, eds. P. Barbaro, F. Liguari, Springer, Heidelberg, Vol. 33, **2010**.

[72] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149.

[73] From searching for 'most cited articles' in 'all time' in the web of *J. Am. Chem. Soc.*

Soluble Polymer-Bound Catalysts

The immobilization of catalytic species onto *soluble polymers* is a useful strategy because combine the easy recovery by precipitation and subsequent filtration of the supported catalyst with the homogeneous environment present during the reaction. It also allows the analysis of the supported catalysts by common methodologies in solution as NMR, MS, TLC, which is generally not possible with insoluble supports as inorganic solids or insoluble organic polymers.[71i] Despite the mentioned advantages, some problems are associated with the use of soluble polymers. One of them is related to the recovery of the supported catalyst. Usually, large amount of solvent are necessary to obtain a quantitative recovery of it and in some cases sticky mixtures are achieved making difficult its recovery and reuse. In the case of supported organometallic complexes, the recovery process enhance the probability of metal leaching during the washing cycles and co-precipitation of by-products that contaminate the recovered catalyst and reduce its activity. The soluble polymers generally used as supports, are polyethylene glycol (PEG)-type as $MeOPEG_{5000}$ and non-crosslinked polystyrene (PS).

Insoluble Polymer-Bound Catalysts

Insoluble resins are widely used as polymeric supports to heterogenize homogeneous catalysts. That supports are mainly polystyrene-based cross-linker polymers. High degree of cross-linking (more than 5%) usually leads to better mechanical stability although compromise the accessibility of reagents to the active sites because low-swelling properties. Moreover, these macroporous resins have also a low loading capacity.[71i] On the other hand, the microporous resins, also known as gel-type resins have a cross-linked degree about a 1-2%. These gel-type supports are flexible polymeric networks that can expand or exclude solvent to accommodate the growing molecules present within the gel. The solvation of the resin (if it is well swelled) is crucial for rapid and complete transformations. When the resin beads are not well swollen in solvents, this can result in poor reaction site

accessibility and diminished reaction rates. The so-called Merrifield resin and its derivatives are the most widely used gel-type resin.

Merrifield resin is a divinylbenzene (DVB) crosslinked polystyrene matrix functionalized with chloromethylene groups (Fig. 1.19A). This chlorine at the benzylic position can be substituted *via* nucleophilic reactions by many functional groups, as for instance a phenylmethanol group (Wang resin, Fig. 1.19B), thiol, amide or crown ether group, and also chiral molecules that act as organocatalysts or chiral ligands. These resins swell in non-protic solvents such as THF and DMF, halogenated and aromatic hydrocarbons, whereas do not swell properly in apolar aprotic solvents as alkanes and polar protic solvents as alcohols and water.[74]

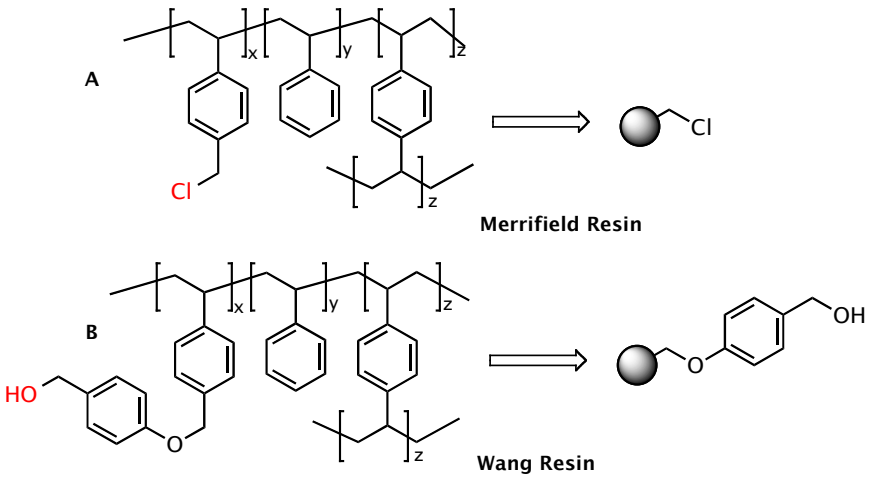


Figure 1.19. Structure and representation of Merrifield (A) and Wang resins (B).

To solve this lack of swelling property, Toy and Janda introduced a longer tetrahydrofuran-derived crosslinker making more flexible the polymer chains.[75] This kind of resins are commercial available, called JandaJel® (Figure 1.20A) and can also be functionalized. Furthermore, the swelling in polar solvents of cross-linked PS resins can be enhanced introducing groups more compatible with such solvents. The easier way is incorporating a PEG

[74] R. Santini, M. C. Griffith, M. Qi, *Tetrahedron Lett.* **1998**, *39*, 8951.
[75] P. H. Toy, K. D. Janda, *Tetrahedron Lett.* **1999**, *40*, 6329.

backbone (TentaGel®, Fig 1.20B) that can be also derivatized to obtain diverse sort of resins.[76] In this case, the PEG moiety is anchored to a preformed PS matrix resin but, alternatively, this group can be incorporated cross-linking PEG with PS resin (similar to JandaJel® but with PEG as cross-linker). The swelling degree in polar solvents of these amphiphilic PS-PEG resins is larger compared with the PS ones,[77] enhancing the catalytic activity of active species supported onto PS-PEG resins in such solvents.[78]

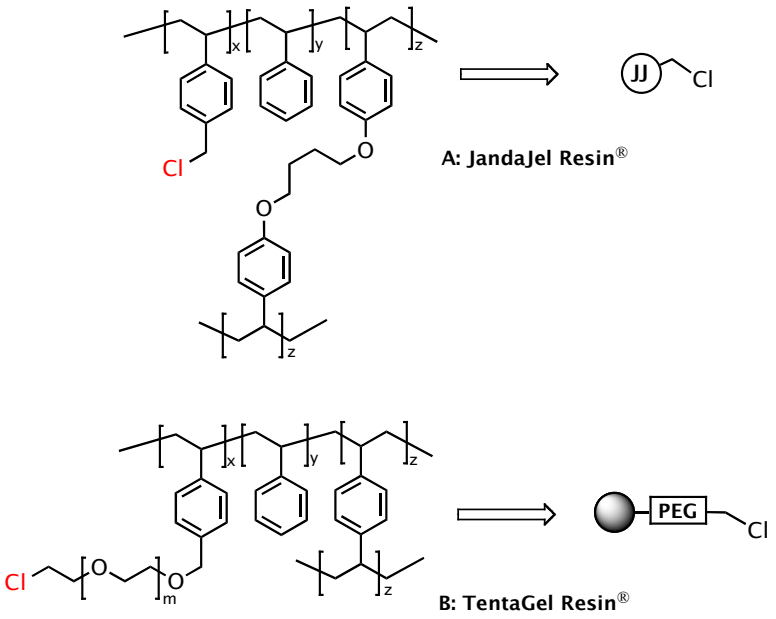


Figure 1.20. Structure and representation of JandaJel (A) and TentaGel resins (B).

[76] W. Rapp in, *Combinatorial Peptide and Nonpeptide Libraries, A Handbook*, Ed. G. Jung, Wiley-VCH, Weinheim, **1996**.
[77] M. Grøtli, C. H. Gotfredsen, J. Rademann, J. Buchhardt, A. J. Clark, J. Ø. Duus, M. Meldal, *J. Comb. Chem.* **2000**, *2*, 108.
[78] For PS-supported Pd-catalyst for Suzuki cross-coupling reaction see: a) J.-H. Kim, B.-H. Jun, J.-W. Byun, Y.-S. Lee, *Tetrahedron Lett.* **2004**, *45*, 5827. For amphiphilic resin supporting Pd-catalyst for Suzuki cross-coupling reactions see: b) J.-W. Kim, J.-H. Kim, D.-H. Lee, Y.-S. Lee, *Tetrahedron Lett.* **2006**, *47*, 4745.

In our research group, there is a large experience in developing polystyrene-supported ligands for organometallic reactions (Fig. 1.21).[79] Most of these PS-supported ligands have been used in the asymmetric addition of alkyl and aryl zinc to aldehydes. Moreover, we have described the development of high number of pyrrolidine derivatives anchored onto polystyrene supports and their application as organocatalysts (Fig. 1.22).[80] The synthesis and evaluation of some of those supported ligands and organocatalysts are aims of the present dissertation and will be explained in more detail in the following chapters.

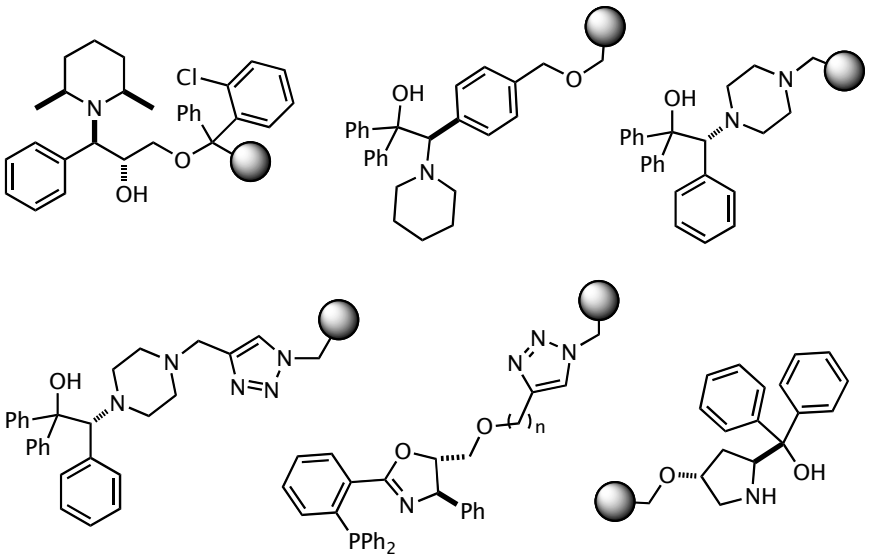


Figure 1.21. Structure of PS-supported ligands developed by our group.

[79] a) A. Vidal-Ferran, N. Bampos, A. Moyano, M. A. Pericàs, A. Riera, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 6309. b) M. A. Pericàs, D. Castellnou, I. Rodríguez, A. Riera, Ll. Solà, *Adv. Synth. Catal.* **2003**, *345*, 1305. c) D. Castellnou, Ll. Solà, C. Jimeno, J. M. Fraile, J. A. Mayoral, A. Riera, M. A. Pericàs, *J. Org. Chem.* **2005**, *70*, 433. d) D. Castellnou, M. Fontes, C. Jimeno, D. Font, Ll. Solà, X. Verdaguer, M. A. Pericàs, *Tetrahedron* **2005**, *61*, 12111. e) A. Bastero, D. Font, M. A. Pericàs, *J. Org. Chem* **2007**, *72*, 2460.

[80] a) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653. b) D. Font, A. Bastero, S. Sayalero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 1943. c) E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717. d) D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337. e) E. Alza, C. Rodriguez-Escrich, S. Sayalero, A. Bastero, M. A. Pericàs, *Chem. Eur. J.* **2009**, *15*, 10167. f) E. Alza, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 3051. g) E. Alza, S. Sayalero, X. C. Cambeiro, R. Martín-Rapún, P. O. Miranda, M. A. Pericàs, *Synlett* **2011**, *4*, 464.

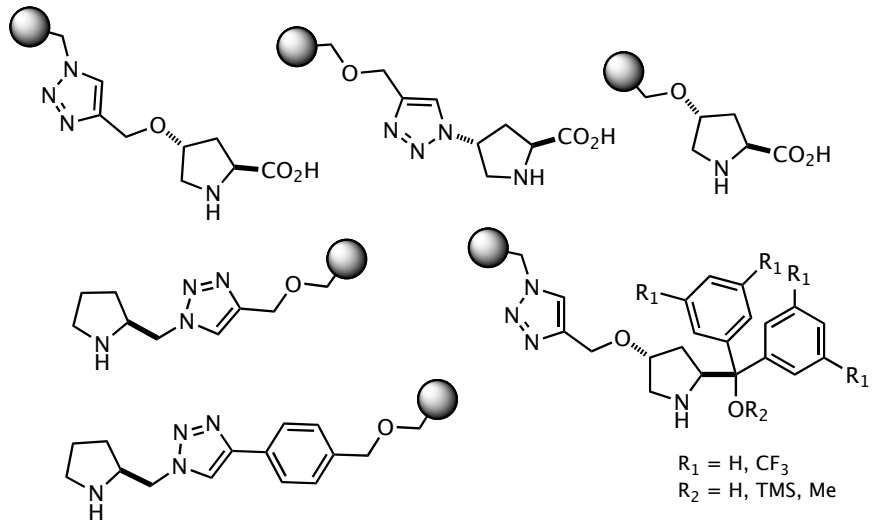


Figure 1.22. Structure of PS-supported organocatalysts developed by our group.

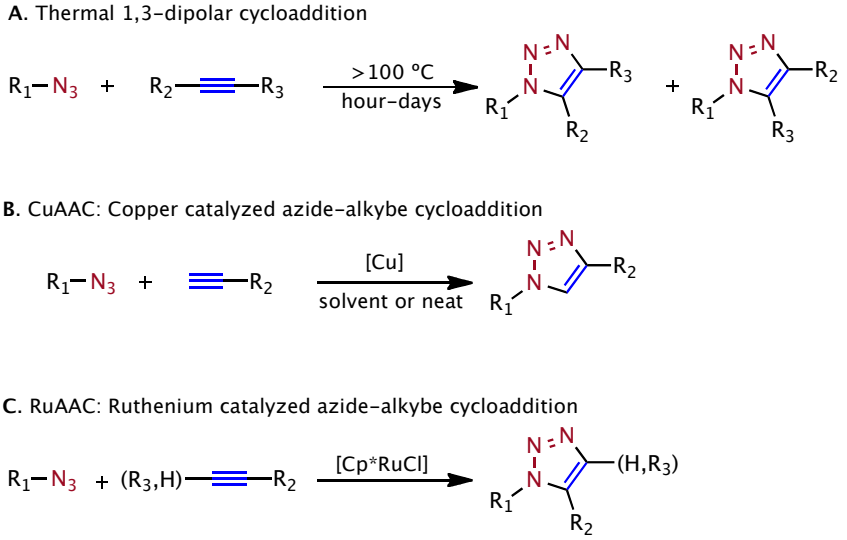
1,2,3-Triazole Moiety As Linker For Covalent Immobilization Of Catalytic Units

"Click chemistry" is a term introduced by Sharpless *et. al.* in 2001, that describes the approach of chemistry processes to generate substances quickly and reliably by joining small units together.[81] This 'philosophy' is inspired by the fact that nature also generates substances by joining small modular units. Inside the features of such processes are including the modularity of the reactions and very high yield obtained, because of thermodynamic stability. Moreover, the reaction has to be applicable to a broad scope of substrates and has to be stereospecific and ideally must generate inoffensive byproducts that can be removed by non-chromatographic methods. The chemical transformations involving carbon-heteroatom bond formation are the most common examples of click chemistry. Cycloadditions of unsaturated species, ring-opening reactions of strained heterocyclic electrophiles, carbonyl chemistry of the non-aldol type,

[81] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

or additions to carbon-carbon multiple bonds, are some examples of click reactions.

Azide-alkyne Huisgen dipolar cycloaddition reaction[82] is the most popular click reaction and consists in Cu(I)-catalyzed reaction (CuAAC) to form regioselectively only 1,4-disubstituted-1,2,3-triazoles. The reaction can take place also by thermal activation that results in a mixture of 1,4 and 1,5 regioisomers. When the reaction is catalyzed by Ru(II) (RuCAAC), can proceed with both terminal and internal alkynes and gives 1,5-disubstituted and fully 1,4,5-trisubstituted-1,2,3-triazoles (**A**, **B** and **C** in Scheme 1.13).[83]

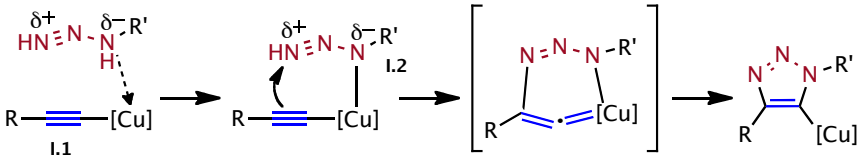


Scheme 1.13. 1,3-dipolar cycloadditions to form different substituted triazole rings.

[82] a) R. Huisgen, "Centenary Lecture - 1,3-Dipolar Cycloadditions". *Proceedings of the Chem. Soc. London* **1961**, 357. b) R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, **1984**.

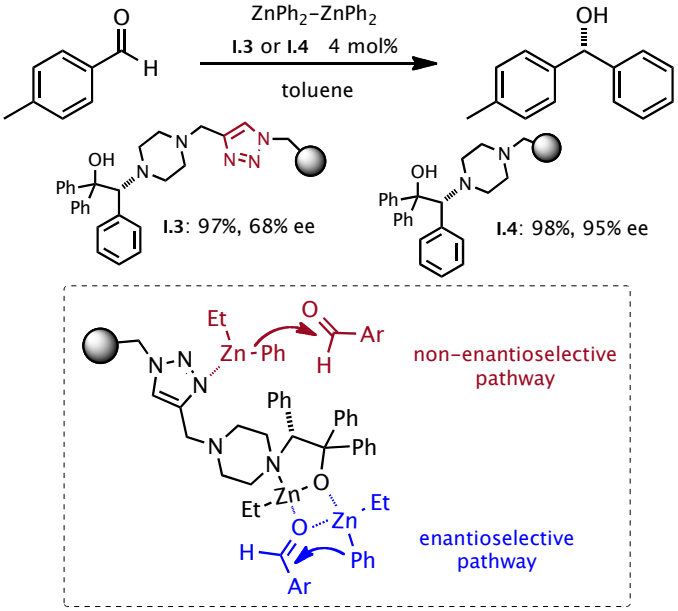
[83] a) C. W. Tornøe, M. Meldal, in *Proc. Second Intl. and seventeenth Amer. Peptide Soc. Symp.*, pp 263-264, Eds. M. Lebl, R. A. Houghten, American Peptide Society and Kluwer Academic Press, San Diego, **2001**. b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057. c) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. For a recent review, see: d) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302.

The simplify mechanism of CuAAC is showed in Scheme 1.14. The key C–N bond-forming event takes place between the nucleophilic, vinylidene-like b-carbon of Cu(I) acetylide **I.1** and the electrophilic terminal nitrogen of the coordinated organic azide **I.2** Finally, the triazole is released from Cu upon protonation of the terminal carbon, and the catalyst is regenerated.[84]



Scheme 1.14. Mechanism of 1,3-dipolar cycloaddition CuAAC.

The effect of the triazole linker in metal-based supported catalysts is attributed to its ability to form coordination complexes with metals, thus interfering in the normal reaction pathway (Scheme 1.15).[79e]



Scheme 1.15. Performance of chiral amino alcohol ligands immobilized by direct substitution or by CuAAC in the phenylation reaction of aldehydes.

[84] For more complex mechanistic details, see reference 83d.

In organocatalysis, on the other hand, the triazole group has been shown to be fundamental for high performance of the catalysts in water. The data suggest the creation of a polar microenvironment inside the large hydrophobic backbone that the polymer constitutes (Fig. 1.23).[80d]

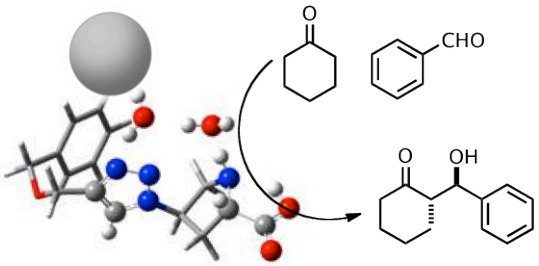


Figure 1.23. Representation of proline supported PS-resin as organocatalysts for aldol reaction in water with an aqueous microenvironment.

The immobilization of catalysts onto insoluble resins not only makes possible their recovery by simple filtration, recycle and re-use but also they can be efficiently employed in continuous flow processing.

1.3. CONTINUOUS FLOW METHODOLOGY

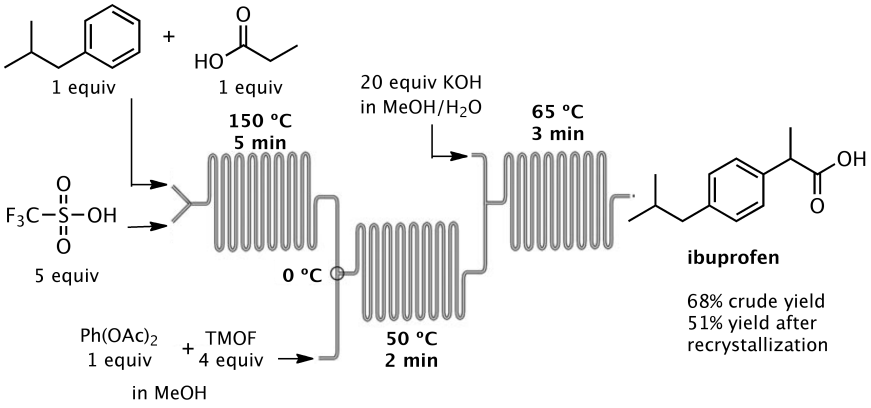
Although the synthesis in the laboratory is commonly carried out in standardised glassware in batch transformations, the use of continuous processes using flow reactors is being established every time more as an attractive methodology, not just exclusive for industrial context.[85]

The processes under continuous flow are generally more efficient than batch ones and offer much higher throughput per unit volume and per unit

[85] For relevant reviews on continuous flow processes, see: a) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972. b) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300. c) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, 1655. d) A. Kirschning, Chemstry in Flow Systems: Thematic Issue in, *Beilstein J. Org. Chem.* **2009**, *5*, 15. e) S. V. Luis, E. Garcia-Verdugo, *Chemical Reactions and Processes Under Flow Conditions*, RSC, Cambridge, **2010**. f) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583.

time. Reactants are introduced continuously, reacting on maximum contact in a smaller reaction space, and the product emerge and is removed continuously from the reaction space. There is better control of process variables and the risk of side reactions is reduced. The reactor volume is determined by the flow rate and residence time of the materials rather than vice versa; therefore, vessels can be smaller and heat transfer and mixing are easier to control and waste levels are generally also lower.[85e]

One of the best features of these continuous flow systems is that using a series of different coupled packed-beds or *chips* (in the case of the micro flow reactors), multistep reactions can be arranged in a continuous sequence,[86] with facile automation, reproducibility and safe conditions as the production of ibuprofen showed in Scheme 1.16.[86c]



Scheme 1.16. The three-step, continuous-flow synthesis of ibuprofen using microreactors.

The benefits increase with the combination of miniaturized continuous flow systems with heterogenized catalysts for the study of chemical reactions because there is a simultaneous catalytic reaction and separation of

[86] For recent examples, see: a) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450. b) I. R. Baxendale, S. V. Ley, A. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017. c) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. Tyler McQuade *Angew. Chem.* **2009**, *121*, 8607; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547. d) D. Webb, T. F. Jamison, *Chem. Science,* **2010**, 6, 675. e) A. Sniady, M. W. Bedore, T. F. Jamison, *Angew. Chem.* **2011**, *123,* 9; *Angew. Chem. Int. Ed.* **2011**, *50,* 9.

the catalyst from the reaction media. The introduction of the catalyst within the reactor allows the pass of the reagents though the supported-catalyst bed providing a far higher catalyst to substrate ratio at any given time, not possible under batch conditions.[55f]

Several solid supports have been applied in continuous flow processes as clays or silica-based materials and ionic liquids or polymers supports, which are being used every time more in this methodology.[87] The cross-linking degree in polymer immobilized catalysts is important in order to avoid pressure problem, thus to control the volume of the swollen polymer is a parameter to have in account.

Nowadays, thinking about an industrial application and for enhancing the efficiency of continuous flow reactors, the trend goes towards the design of structure beds based on a nano-scale up to the macro-geometry to overcome the drawbacks associated to the existing continuous flow systems using solid supports as stagnation zones, broad residence time distribution or blocked reactors and monolithic supports are the best structured materials known for this purpose.[88]

Recently, in our research group, it has been developed the application of several continuous flow systems in metal catalysis[89] and also organocatalysis, these last group are part of the present thesis (chapters IIA and IV). In the first system (showed in Scheme 1.17), a vertical fritted and jacket-thermostated Omnifit glass column (10 mm of bore size and 70 mm of

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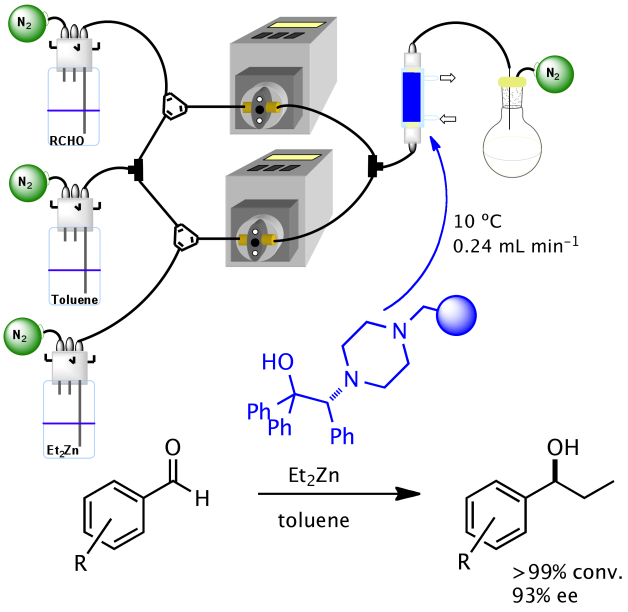
[87] S. Ceylan, A. Kirsching, *Organic Synthesis with Mini Flow Reactors Using Immobilized Catalysts* in, *Recoverable and Recyclable Catalysts*, ed. M. Benaglia, John Wiley & Sons, Chichester, **2009**.

[88] For some representative examples using monolithic supports and its application in flow chemisty, see: a) R. M. Heck, S. Gulati, R. J. Farratu, *Chem. Eur. J.* **2001**, *82*, 149. b) S. Zalusky, R. Olayo-Valles, C. J. Taylor, M. A. Hillmyer, *J. Am. Chem. Soc.* **2001**, *123*, 1519. c) U. Kunz, A. Kirschning, H.-L. Wen, W. Solodenko, R. Cecilia, C. O. Kappe, T. Turek, *Catal. Today* **2005**, *105,* 318. d) M. I. Burguete, A. Cornejo, E. Garcia-Berdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martinez-Merino, M. Sokolova, *J. Org. Chem.* **2007**, *72*, 4344. e) K. Mennecke, R. Cecilia, T. N. Glasnov, S. Gruhl, C. Vogt, A. Feldhoff, M. A. Larrubia Vargas, C. O. Kappe, U. Kunz, A. Kirschning, *Adv. Synth. Catal.* **2008**, *350*, 717.

[89] For applications developed by our research group in continuous flow processes of PS-supported organometallic complexes, see: a) M. A. Pericàs, C. I. Herrerías, Ll. Solà, *Adv. Synth. Cat.* **2008**, *350*, 927. b) D. Popa, R. Marcos, S. Sayalero, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Cat.* **2009**, *351*, 1539. c) J. Rolland, X. C. Cambeiro, C. Rodríguez-Escrich, M. A. Pericàs, *Belstein J. Org. Chem.* **2009**, *5*, 56.

maximum bed height) with a volume of 5.5 mL was used, which was loaded with the functionalized piperazine-based aminoalcohol supported on Merrifield resin for its use in the enantioselective alkylation of arylaldehydes.[89a] After pumping a solution of the corresponding aldehyde and diethyl zinc in toluene through the reactor, the products were obtained in 13.0 mmol h^{-1} per gram of resin with excellent enantioselectivities. Compared with the reaction in batch conditions, the use of continuous flow process mean a 24-fold reduction of time reaction with the advantage of possible regeneration of the catalyst with a simple washing protocol and its use in several consecutive alkylation reactions.



Scheme 1.17. Schematic representation of continuous flow system used in the asymmetric addition of Et_2Zn to aldehydes.

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

1.4. OBJECTIVES

The present thesis project is focused in the immobilization of catalytic systems derived from pyrrolidines onto crosslinked polystyrene resins allowing the formation of carbon-carbon and carbon-heteroatom bonds through enantioselective procedures with improved sustainability characteristics in the organocatalysis field. The approach introduced by our group combines the optimization of the catalytic properties of the ligands, which is greatly facilitated by their modular nature, with a design principle consisting in performing the anchoring to the polymer through auxiliary functional groups, positioned on the ligand molecule for minimal perturbation of the catalytic site. In this manner, we have been able to develop polymer-supported catalysts that do not show any decrease in catalytic activity or in enantioselectivity with respect to their homogeneous counterparts. The usual anchoring strategy used is the Cu-catalyzed azide/alkyne 1,3 dipolar cycloaddition.

In this context, the particular aims of this work are:

1. The synthesis of PS-supported organocatalysts containing (*S*)-proline moiety and its evaluation in the enantioselective Mannich reactions of aldehydes and ketones with preformed imines. The ultimate goal would be the implementation of a single-pass, continuous-flow process, for the production of diastereo- and enantiomerically pure Mannich adducts in minutes at room temperature with the use of less amount of catalyst with respect to the batch process (**Chapter II-A, Article 1**).

2. Observing the efficiency of systems bearing highly nitrogen-rich substituent such as tetrazoles and 1,2,3-triazoles and also diphenylprolinol derivatives in different transformations, as a general aim, we wanted to implement the copper-mediated 1,3-dipolar cycloadditions as a general immobilization for the synthesis of new immobilized and recyclable organocatalysts onto a insoluble support to evaluate them in several transformations like *via* enamine catalysis as the Michael reaction of ketones and aldehydes with nitroolefins (**Chapter II-B, Articles 2 and 3**).

3. The development of the polystyrene-supported, enantiopure (S)-α,α-diphenylprolinol trimethylsilyl ether as a recyclable organocatalyst for asymmetric Michael reactions taking place through enamine and iminium mechanisms led to its evaluation in the asymmetric Michael reaction of malonates and nitromethane with α,β-unsaturated aldehydes (**Chapter III, Article 4**).

4. The use of polystyrene-supported (S)-α,α-diphenylprolinol trimethylsilyl ether in cascade reactions to obtain highly functionalized products in a straightforward and efficient manner, and be able to perform this kind of reactions under continuous flow conditions (**Chapter IV, Article 5**).

Despite the thesis are centred on organocatalytic processes, asymmetric catalysis mediated by metal complexes also has been investigated during the present research work. In this case, the objectives are:

5. The study of the asymmetric reduction of ketones with borane and oxazaborolidine type catalysts, with the synthesis of different polystyrene-supported (S)-α,α-diphenylprolinol species paying attention to the different linkers to anchor the catalytic unit onto the polymeric backbone and its influence in the performance of the catalysts. (**Chapter V, Article-manuscript 6**).

6. The synthesis of a series of new modular chiral aminoalcohols to form ruthenium complexes, their evaluation as enantioselective catalysts in the asymmetric transfer hydrogenation reaction of ketones in both water and 2-propanol and its possible immobilization on polymer supports (**Chapter VI, Article 7**).

Chapter II

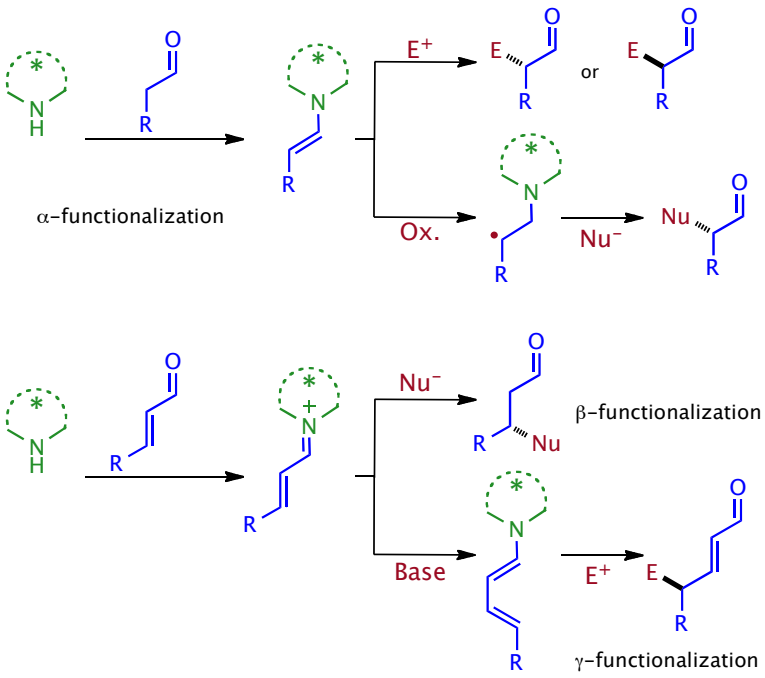
UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

ENANTIOSELECTIVE AMINOCATALYSIS *via* ENAMINE

Catalytic asymmetric transformations of carbonyl compounds mediated by chiral amines (asymmetric aminocatalysis) represent one of the most active areas within the field of organocatalysis.[1] Recent investigations on amino acids and primary amines[2] and, mainly on the use of chiral secondary amines, have contribute with the great development of aminocatalysis during last years, being one of the methods of choice for many chemoselective and asymmetric functionalization of carbonyl compounds. In particular, the pyrrolidine moiety is present in numerous organocatalysts structures. The α-, β- and γ-functionalization of carbonyl compounds have been explored and applied in asymmetric synthesis of, especially, aldehydes and α,β-unsaturated aldehydes, as well as more complex domino, cascade and tandem reactions. These reactions have been applied also in the synthesis of important molecules with biological activity. The main aminocatalytic pathways for carbonyl functionalization are shown in Scheme 2.1.[1j]

[1] For reviews on aminocatalysis, see: a) the concept of "aminocatalysis" was first mentioned in 2001: B. List, *Synlett* **2001**, 1675. b) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904. c) B. List, *Chem. Commun.* **2006**, *42*, 819. d) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, *42*, 2001. e) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, *43*, 3123. f) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267. g) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. h) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178. i) M. Marigo, P. Melchiorre, *Chem. Cat. Chem.* **2010**, *2*, 621. For recent review about mechanisms in aminocatalysis, see: j) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632.

[2] For reviews on amino acids and primary amines in organocatalysis, see: a) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047. b) Y.-C. Chen, *Synlett* **2008**, 1919. c) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, *45*, 1807. d) Q. Zhu, Y. Lu, *Chem. Commun.* **2010**, *46*, 2235. e) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.* **2011**, DOI: 10.1039/C0CY00096E.



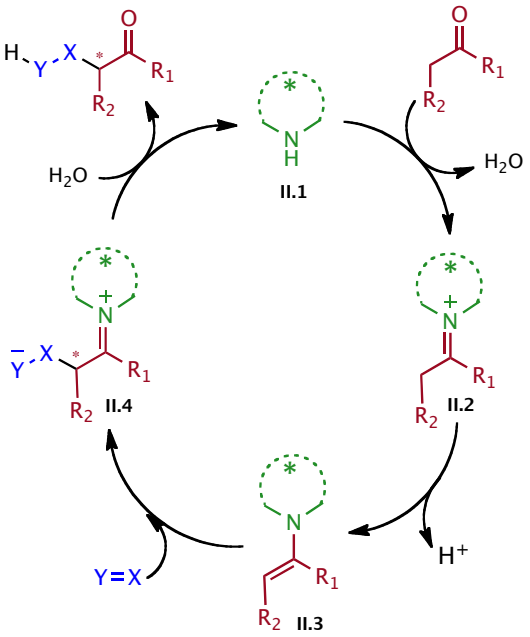
Scheme 2.1. Aminocatalytic pathways for carbonyl functionalization (E^+ = electrophile, Ox. = oxidant and Nu^- = nucleophile).

The catalysis *via* enamine formation is one of the most common, efficient and simple mechanisms to activate the α-position in ketones and aldehydes to form carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds by nucleophilic addition or nucleophilic substitution.[3]

The general catalytic cycle for nucleophilic addition by enamine catalysis is shown in Scheme 2.2. It starts with the formation of the iminium ion **II.2** by condensation of the chiral amine catalyst **II.1** with the donor carbonyl compound. After fast deprotonation of such iminium intermediate as a result of the increase in the acidity of proton in the α-C caused by the low energy of its LUMO orbital, the enamine **II.3** is formed. This key

[3] For reviews on enamine catalysis, see: a) B. List, *Tetrehedron* **2002**, *58*, 5573. b) B. List, *Acc. Chem. Res.* **2004**, *37*, 548. c) S. Mukherjee, J. Woon, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471-5569. d) F. Tanaka, C. F. Barbas III, *Enamine Catalysis* in, *Enantioselective Organocatalysis, Reactions and Experimental Procedures*, ed. P. I. Dalko, Wiley-VCH, Weinheim, **2007**. e) P. M. Pihko, I. Majander, A. Erkkila, *Top. Curr. Chem.* **2010**, *291*, 29.

intermediate is able to react with divers electrophiles with π-orbitals such as for instance aldehydes (aldol reaction), electro-poor alkenes (Michael reaction) or imines (Mannich reaction), to form the corresponding C-C or C-X bond.[1] This reactivity is produced because the enamine is activated as nucleophile due to enhance the energy of its HOMO orbital. Finally, the hydrolysis of the resulting iminium ion **II.4** affords the product and restores the aminocatalyst for a new catalytic cycle. Some limitation of catalyst turnover observed could be produced due to the availability of the amine catalyst prone to be trapped by the electrophilic substrate.[1e]

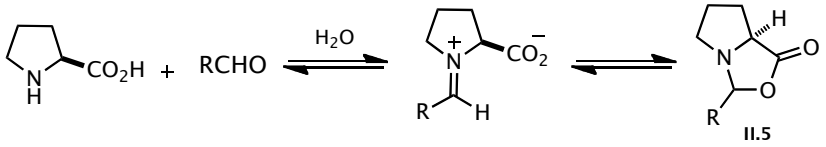


Scheme 2.2. Generally accepted enamine catalytic cycle in nucleophilic addition.

Although this work is focused on nucleophilic addition, it has to be mentioned that also single bond containing electrophiles such alkyl halides reacts by nucleophilic substitution reaction of the enamine intermediate taking place α-heterofunctionalization reactions.[1d]

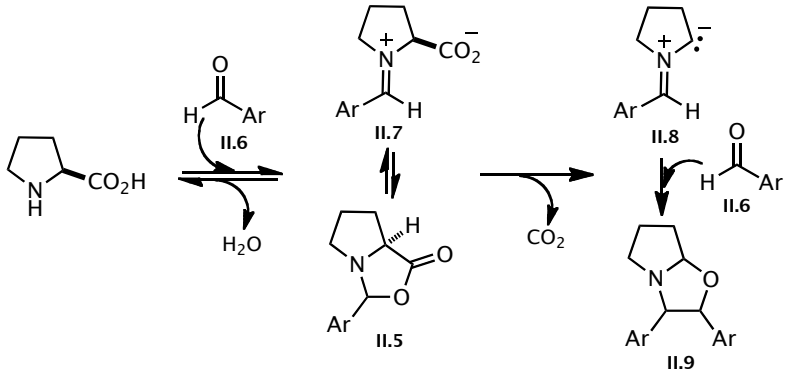
Some mechanism consideration in enamine catalysis mediated by proline derivatives should be pointed out. Oxazolidinones **II.5**, obtained from proline and aldehydes or ketones (Scheme 2.3), have been detected during

the enamine intermediate formation in α-functionalization reactions and that process has been investigated in order to determine the effect in the catalytic performance of such catalyst.[1j,4]



Scheme. 2.3. Formation of oxazolidinones **II.5** from L-proline and aldehydes.

The oxazolidinone formation is reversible and can be suppressed in the presence of water due to the shift of the equilibrium from the iminium-ion to free proline and carbonyl compound mainly for electron-rich aldehydes. Irreversible deactivation of proline in the absence of added water occurs as it is shown in Scheme 2.4. With electrondeficient aromatic aldehydes such as **II.6** the iminium species **II.7** may undergo decarboxylation to form the azomethine ylide **II.8** that may then react with a further aldehyde molecule to form the oxazole **II.9**.[4c]



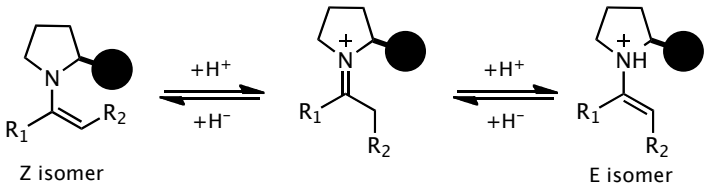
Scheme 2.4. Reactions of L-proline with aromatic aldehydes.

[4] a) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770. b) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5839. c) N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100. d) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425. e) I. Komstantinov, L. J. Broadbelt, *Top Catal.* **2010**, *53*, 1031. f) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem.* **2010**, *122*, 5117; *Angew. Chem. Int. Ed.* **2010**, *49*, 4997. g) A. K. Sharma, R. B. Sunoj, *Angew. Chem.* **2010**, *122*, 6493; *Angew. Chem., Int. Ed.* **2010**, *49*, 6373.

Although initially, oxazolidinones were proposed as a "parasitic specie" being not able to promote the desired addition reaction during the enamine catalytic cycle,[4b] it has been shown (currently, at least for aldol-type reactions) that within the currently adopted catalytic cycle for the L-proline-promoted reactions, the formation of oxazolidinones is a kinetically and thermodynamically favorable process.[4e] Moreover, there are examples were oxazolidinones act as catalysts where the aldol products were obtained in 72-82% yield and from 66% to more than 99% of ee.[5]

Stereochemical Induction By Chiral Enamine Formation

The enamine intermediate has two possible isomers: the E and Z originate for the two possible configurations of the double bond in the enamine (Scheme 2.5). In general, the E enamine is favored thermodynamically for both aldehydes ketone, unless other specific binding interactions, as may be hydrogen bonding, favoring the enamine Z. Furthermore, each isomer has two possible conformers: the enamine *anti* or *syn* (respect the double bond and the bulky group in α-position to the nitrogen of the pyrrolidine moiety) when double bond is positioned *anti* or *syn* relative to the chiral group in the pyrrolidine ring.

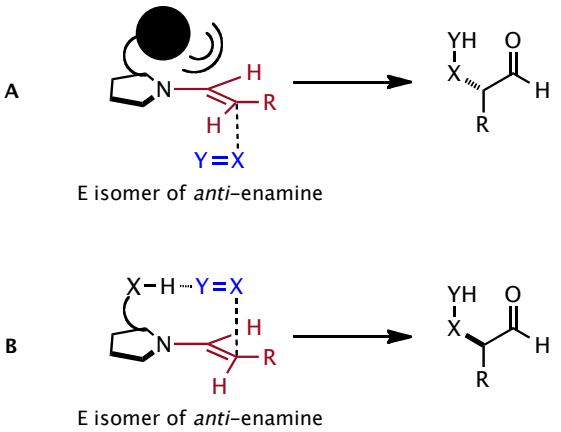


Scheme 2.5. Representation of Z/E-isomers of *syn*-enamine.

Then, the approximation of the acceptor to the enamine can be performed by both sides of the enamine, as shown in Scheme 2.6. This approximation can be controlled by steric factors or electronic effects. In the first case, one face of the enamine is shielded by the steric bulk present in the catalyst and favours the approach of the electrophile from the

[5] C. Isart, J. Burés, J. Vilarrasa, *Tetrahedron Lett.* **2008**, *49*, 5414.

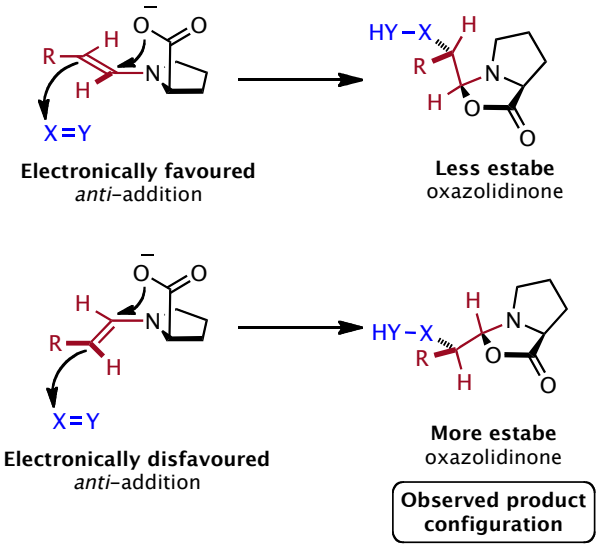
opposite face (attack from "below", Scheme 2.6-A). In the second case, catalysts like proline or bifunctional catalysts direct the electrophile to approach from one side of the enamines via electronic interactions (attack from "above", Scheme 2.6-B).



Scheme 2.6. Modes of stereochemical control in aminocatalysts. **A**) Induction by steric effects. The approximation of the electrophile (X=Y) occurs by the *Si*-face of the enamine. **B**) Induction by electronic effects. The approximation of the electrophile is by the *Re*-face of the enamine.

While the explanation for the sterically directing organocatalysts is commonly accepted, the stereochemical induction by electronic effects has recently been the subject of some debate.[1j] The mode presented above is the known as Houk-List model where the approach of the electrophile from the "upper side" is facilitated by the acid moiety of the catalyst.[6] In 2007, Seebach *et al.* introduced an alternative proposal in which oxazolidinones play a key role in the catalytic cycle.[4d] In this case, the stereochemical obtained for the product was explained by the formation of the more thermodynamic stable oxazolidinone, rather than the kinetic product which is favoured according to stereoelectronic reasons (Scheme 2.7).

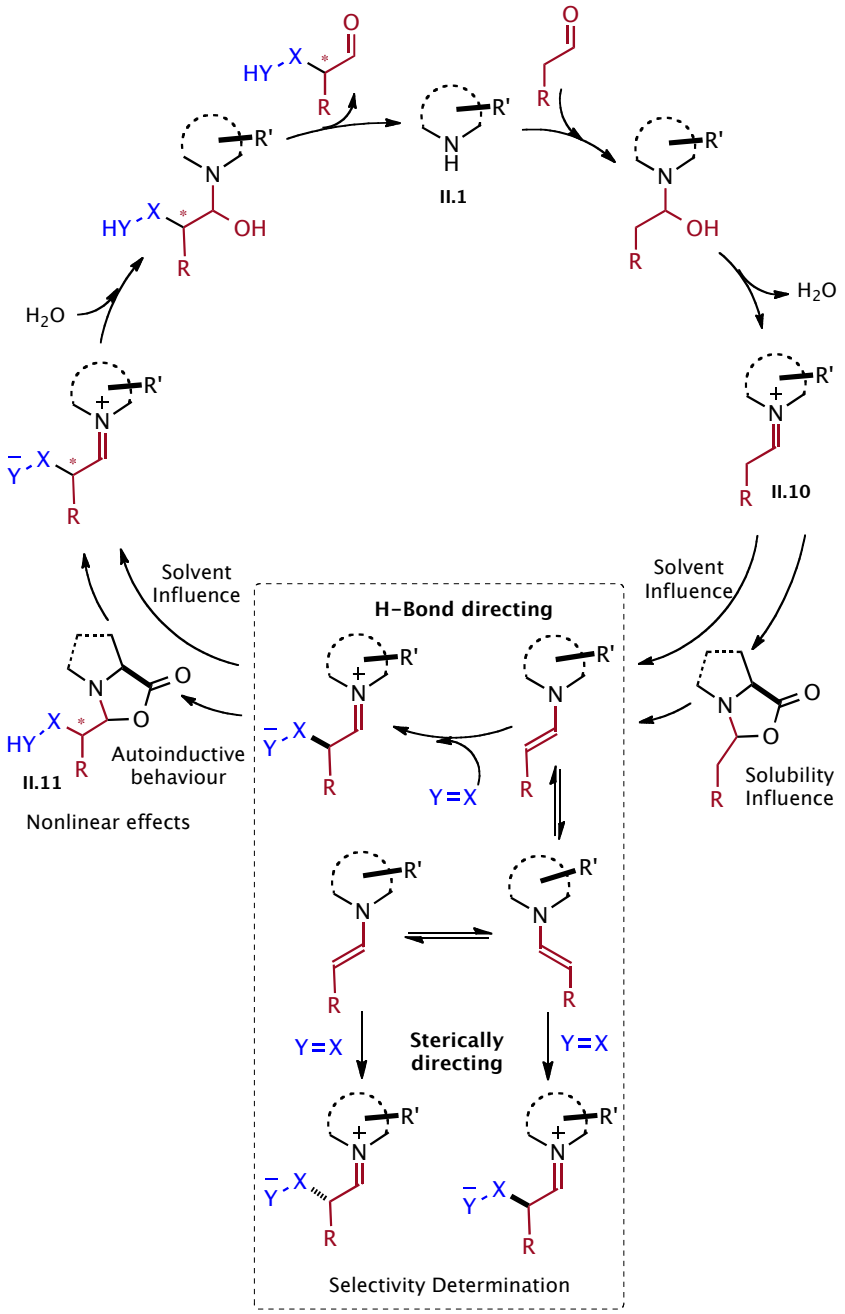
[6] S. Bahmayar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem Soc.* **2003**, *125*, 2475.



Scheme 2.7. Seebach-model proposal for proline catalyzed reactions.

As result, Jørgensen and co-workers have described a catalytic cycle of α-functionalizations with electrophiles mediated by secondary amine catalysts including much more intermediates than usually drawn in general catalytic cycles that is represented in Scheme 2.8.[1j]

After the formation of the iminium-ion **II.10** *via* a hemiacetal, the tautomerization to the enamine follows different pathways depending on the solvent and the catalyst employed. As a result, the stereoselectivity of the nucleophilic addition is determined by the nature of the aminocatalyst. The addition products can be directly hydrolysed to the free catalyst **II.1** and the functionalised aldehyde or remain connected like **II.11** and contribute to further catalytic cycles adopting additive or catalyst roles. In the Scheme 2.8 is not accounted the Seebach-mechanism for electronic interactions effects in stereoselectivity showed above.



Scheme 2.8. Catalytic cycle of the α-functionalization including mechanistic details.

After the introduction of the stoichiometric use of enamines as nucleophiles in organic chemistry by Stork in 1963,[7] the enamine catalysis has become a powerful strategy within modern organocatalysis field. Since the intramolecular aldol reaction catalyzed by proline (Hajos-Parish-Eder-Sauer-Wiechert reaction) and its revival as intermolecular version in 2000 by List and Barbas, asymmetric amine catalysis is becoming increasingly important.

L-Proline is one of the organocatalysts more employed in enamine aminocatalysis. However, a large number of different compounds have shown also high efficiency in such kind of activation, most of them derived from pyrrolidine structure. Some representative examples are shown in Figure 2.1.

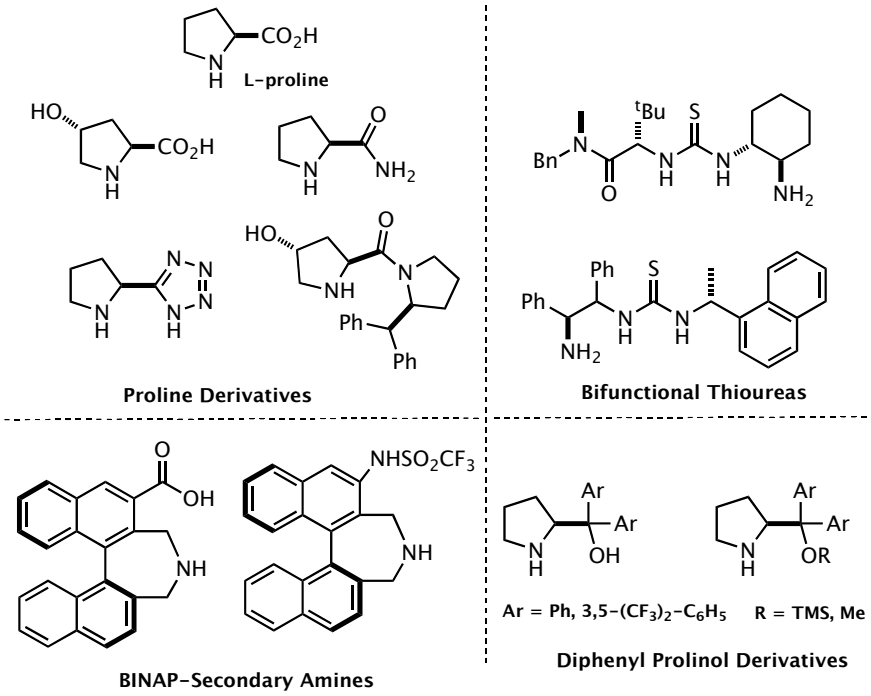
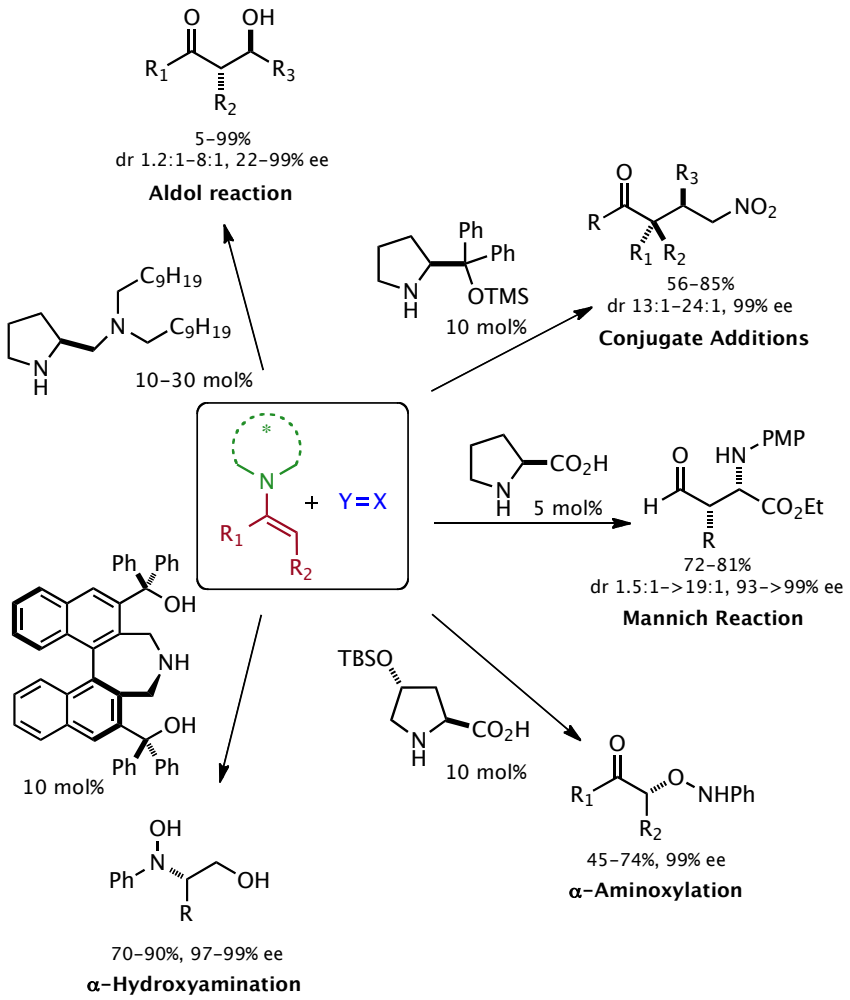


Fig. 2.1. Representative organocatalysts used in reactions *via* enamine catalysis.

[7] a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207. b) Z. Rappoport, *The Chemistry of Enamines*, Wiley, New York, **1994**.

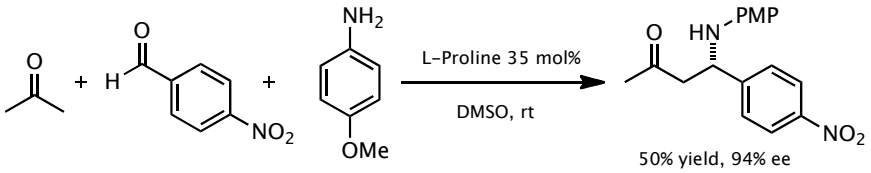
The enamine activation has been applied to a wide variety of reactions (Scheme 2.9). In this chapter the attention is focused to the *Mannich reaction* of aldehydes and ketones with *N*-protected imino ethylglyoxylate (**Chapter IIA – Article 1**) and in the *Michael reaction* of ketones and aldehydes with nitroolefins (**Chapter IIB – Articles 2 and 3**).



Scheme. 2.9. Some examples of asymmetric organocatalyzed nucleophilic additions *via* enamine mechanism.

A SOLID-SUPPORTED ORGANOCATALYST FOR HIGHLY STEREOSELECTIVE, BATCH, AND CONTINUOUS-FLOW MANNICH REACTIONS

Enantioselective organocatalytic Mannich reaction is a highly useful and widely recognized as the most straightforward route toward diastereomerically and enantiomerically enriched β-amino carbonyl compounds (named Mannich bases), precursors to a variety of bioactive molecules. Several organocatalytic systems have been described for enantioselective Mannich transformations.[8] This reaction is named after Carl Mannich, who reported in 1912 the first condensation reaction of formaldehyde with ammonia to form the corresponding iminium ion and the subsequent addition of a carbon nucleophile (enol) to provide the pertinent Mannich base.[9] More recently, List and coworkers reported the first example of three component asymmetric Mannich reaction using L-proline as organocatalyst (Scheme 2.10) to obtain the desired β-aminoketones with excellent enantioselectivities.[10]



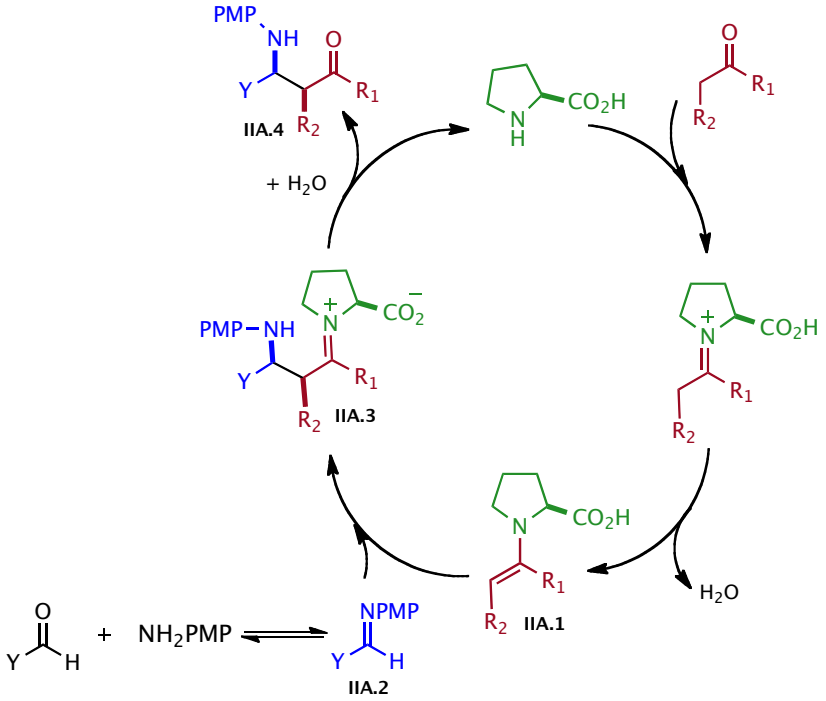
Scheme 2.10. Proline-catalyzed asymmetric three-component Mannich reaction of acetone with *p*-anisidine and *p*-nitrobenzaldehyde.

[8] For reviews on organocatalytic Mannich reactions, see: a) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 2531; *Angew. Chem. Int. Ed.*, **2001**, *40*, 529. b) A. Córdova, *Acc. Chem. Res.*, **2004**, *37*, 102. c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.*, **2004**, *37*, 580. d) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. e) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348. f) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797. g) J. M. M. Verkade, J. C. v. H. Lieke, P. J. L. M. Quadflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29. h) P. S. Bhadury, B.-A. Song, *Current Org. Chem.* **2010**, *14*, 1989.

[9] C. Mannich, W. Krosche *Arch. Pharm.* **1912**, *250*, 647.

[10] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336.

A simplified version of the catalytic cycle for Mannich reaction is shown in Scheme 2.11. Analogous to proline-catalyzed direct aldol reaction, also it involves hydrogen-bonding activation mode between the enamine intermediate formed and the electrophile imine substrate that can be preformed or generated *in situ* from a primary amine and an aldehyde. The imine **IIA.2** is attacked by the nucleophilic enamine **IIA.1** to form an iminium ion intermediate **IIA.3** which contains two stereocenters, that can give raise to two diastereomeric pairs of enantiomers.[8h] This intermediate **IIA.3** is then hydrolyzed providing the Mannich product **IIA.4** stereoselectively.



Scheme 2.11. Catalytic cycle of L-proline-catalyzed Mannich reaction.

2A.1. STEREOCHEMISTRY AND MECHANISTIC FACTORS IN PROLINE-CATALYZED ASYMMETRIC *SYN*-SELECTIVE MANNICH REACTIONS

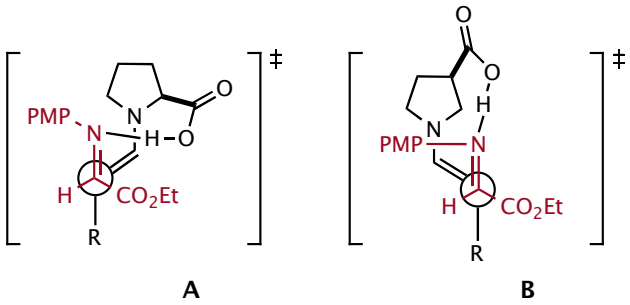
The L-proline-catalyzed Mannich reaction leads to products with *syn*-stereochemistry in high diastereoselectivity in most cases.[8,10] As has been mentioned, the proposed mechanism of Mannich reaction is analogous to the conventional aldol reaction. However, the transition state in proline-catalyzed addition of aldehydes to aldimines features complete proton transfer from the carboxyl group of the catalyst to the imine nitrogen atom.[1j] This interaction determines the facial selection of the addition, since the *syn* addition of the imine to the carbonyl group of the proline enamine is the rate-determining step. With the position of the imine molecule fixed by the carboxylic acid of the catalyst, also important for the high enantioselectivity, the enamine conformation is which determines the diastereomeric outcome of the reaction. For that reason, L-proline leads to *syn*-Mannich adducts whereas 3-pyrrolidinecarboxylic acid promotes the *anti*-Mannich reaction.[11]

The transition states calculated to determine the stereochemistry in the Mannich reaction[12] of an aldehyde and *N*-(*p*-methoxyphenyl)ethyl glyoxylate imine (aldimine used also in our research project) are showed in Scheme 2.12 (with proline **A**, with 3-pyrrolidinecarboxylic acid **B**). The *p*-methoxyphenyl (PMP)-protected imino ethylglyoxylate has been observed to be an E-aldimine, which explains the preferred diastereo- and enantioselectivities obtained in organocatalytic Mannich reactions. Thus, using proline as catalyst, the enamine formed by condensation with the corresponding aldehyde attacks the E-aldimine on its *Si*-face, because the

[11] For selected examples on the aminocatalytic asymmetric *anti*-Mannich reactions, see: a) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408. b) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040. c) T. Kano, Y. Yamaguchi, K. Maruoka, *Angew. Chem.* **2009**, *121*, 1870; *Angew. Chem. Int. Ed.* **2009**, *48*, 1838. d) T. Kano, Y. Yamaguchi, K. Maruoka, *Chem. Eur. J.* **2009**, *15*, 6678.

[12] H. Zhang, S. Mitsumori, N. Utsumi, M. Imari, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2008**, *130*, 875.

Re-face is blocked by steric interactions between the aromatic ring of the PMP group and the proline ring, to give the *syn*-selective product.



Scheme 2.12. Transition states leading to *syn*- (**A**) and *anti*- (**B**) Mannich products.

These mechanism explanations are similar for the case of ketone-nucleophiles since the carboxyl group of proline (and proline isomers) marks the transition state due to the crucial proton transfer process.

The preference for the *syn*-Mannich products is maintained when chiral proline is used as catalyst, independently of the configuration of its C2 carbon. Of the two possible *syn* adducts, the reactions is also eanatioselective towards the enantioner (*S,S*) when L-proline is used while using D-proline, the other enantiomer *syn* (*R,R*) is predominantly obtained.[8h]

FULL PAPER

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A Solid-Supported Organocatalyst for Highly Stereoselective, Batch, and Continuous-Flow Mannich Reactions

Esther Alza,[a] Carles Rodríguez-Escrich,[a] Sonia Sayalero,[a] Amaia Bastero,[a] and Miquel A. Pericàs*[a, b]

Abstract: The fast and highly stereoselective Mannich reaction of aldehydes and ketones with the *N*-(*p*-methoxyphenyl) ethyl glyoxylate imine catalyzed by polystyrene resins functionalized with (2*S*,4*R*)-hydroxyproline is reported. The effect of the nature of the linker connecting proline with the polymeric backbone has been studied, and a 1,2,3-triazole linker constructed from azidomethyl polystyrene and *O*-propargyl hydroxyproline turns out to be optimal for catalytic activity and enantioselectivity. With aldehyde donors, fast reactions leading to complete conversion in 1–3 h are recorded in DMF. With ketone donors, the reactions tend to be slower, but can be efficiently accelerated (six-membered ring cycloalkanones) by low-power microwave irradiation. This approach, which greatly facilitates product isolation since the catalyst is removed by simple filtration, has allowed the implementation of the reactions of aldehyde substrates in a continuous-flow, single-pass system. In this manner, the continuous synthesis of the enantiomerically and diastereomerically pure adducts (*syn*/*anti* > 97:3; *ee* > 99%) has been achieved at room temperature with residence times of 6.0 min. This methodology has allowed for the preparation of up to 7.8 mmol of the desired Mannich adduct through the use of 0.46 mmol of catalytic resin (5.9 mol%), in a greatly simplified experimental protocol that avoids purification steps.

Keywords: aldehydes · asymmetric catalysis · flow reactors · Mannich reactions · organocatalysis

Introduction

As sustainability concerns have begun to influence almost every aspect of daily life, many of the aspirations that the chemical community formulated at the outset of this century[1] have evolved into peremptory needs. Among these aspirations, that of performing complex reactions or reaction sequences in a completely selective manner, without the need to resort to special reaction conditions and avoiding wasteful isolation/purification steps remains a key challenge for the future of chemical industry. For an increasing number of reactions, organocatalytic approaches provide high selectivity at low control level, thus allowing very simple reaction setups.[2] However, it is not unusual that the high polarity of organocatalysts and reaction products renders the isolation processes wasteful and tedious. Immobilization of catalysts onto solid or readily separable supports[3] represents an attractive alternative to separation processes, but is usually accompanied by important decreases in catalytic activity. Thus, the development of supported, yet very active (organo)catalytic species appears to be a desirable goal in light of its simultaneous solution to the selectivity/control/isolation problem.[4]

We herein report the full achievement of these goals for the Mannich reaction of aldehydes and ketones with preformed imines,[5] ultimately leading to the implementation of a single-pass, continuous-flow process[6,7] for the production of diastereo- and enantiomerically pure Mannich adducts in minutes at room temperature with the use of threefold decreased amounts of catalyst with respect to the batch process.

Enantioselective organocatalytic Mannich reactions are now widely recognized as the most straightforward routes toward the diastereomerically and enantiomerically enriched 3-aminocarbonyl compounds that are precursors to a variety

[a] E. Alza, Dr. C. Rodríguez-Escrich, Dr. S. Sayalero, Dr. A. Bastero, Prof. Dr. M. A. Pericàs
Institute of Chemical Research of Catalonia (ICIQ)
Avinguda dels Països Catalans 16, 43007 Tarragona (Spain)
Fax: (+34) 977-920-222
E-mail: mapericas@iciq.es

[b] Prof. Dr. M. A. Pericàs
Departament de Química Orgànica
Universitat de Barcelona (UB), 08028 Barcelona (Spain)

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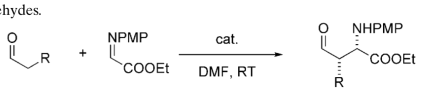
of bioactive molecules.[5c,d] When glyoxylate imines are used as electrophiles in the reaction, the process becomes a most convenient approach to enantiopure α-amino acids bearing additional stereocenters at the β and (potentially) γ positions.

As a general fact, Mannich adducts are highly polar, rather labile substances. It is not unusual that rather clean reaction crudes suffer important degradation in their diastereomerical and even chemical composition during chromatographic processes aimed at removing soluble catalysts used for their synthesis. With this in mind, important advantages can be expected from the use in the Mannich reaction of polymer-supported, insoluble catalysts that can be separated from reaction products by simple filtration. In spite of that, no approaches to this synthetically important reaction involving immobilized catalysts have been reported up to date in the literature.

Results and Discussion

Given that proline itself is an optimal catalyst for *syn*-selective Mannich reactions,[8] polystyrene (PS)-supported proline derivatives **1**, **2**, and **3**, originally developed for aldol reactions,[4] were tested in batch conditions in the reaction between two model aldehydes (isovaleraldehyde and heptanal) and preformed *N*-(*p*-methoxyphenyl) (*N*-PMP) ethyl glyoxylate imine **4** in DMF (Table 1). For both aldehyde donors, **3** displayed poor catalytic activity (Table 1, entries 3 and 6), whereas both **1** and **2** gave excellent stereoselectivities (Table 1, entries 1, 2, 4, and 5). Interestingly, these results replicate those recorded with the same catalyst set for aldol reactions in water, thus confirming the beneficial role of the 1,2,3-triazole linker on the catalytic behavior of these supported species.[4a,c] Since the more readily available catalyst **1** was also slightly more active, it was selected as the catalyst of choice for the rest of the study.

Table 1. Catalyst screening in batch conditions for the reaction of **4** with aldehydes.

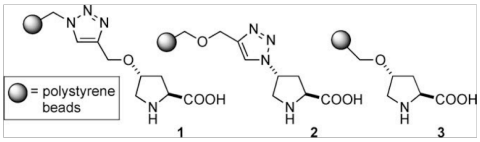


4

5a (R = *i*-C_3H_7)
5b (R = *n*-C_5H_{11})

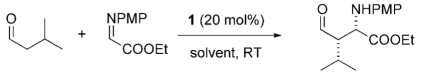
Entry	Product	Cat. ([mol %])[a]	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**5a**	**1** (20)	2	79	>97:3	>99
2	**5a**	**2** (15)	2	62	94:6	99
3	**5a**	**3** (20)	2	37	93:7	73
4	**5b**	**1** (20)	1	65	94:6	96
5	**5b**	**2** (15)	1	55	95:5	96
6	**5b**	**3** (20)	1	53	92:8	72

[a] The functionalization of the resins, determined by elemental analysis, was 0.46, 0.56, and 0.55 mmol g^{-1} for **1**, **2**, and **3**, respectively. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis.



When polymer-supported catalysts are used, careful attention has to be paid to the nature of the solvents. Besides its possible role in the preferential stabilization of a given transition state, which is key to the achievement of high diastereo- and enantioselectivity, its ability to swell the polymer matrix has also to be considered. This is key to overcoming mass-transfer limitations and has a deep effect on reaction rates. For these reasons, a broad range of polar solvents was evaluated for the reaction. For the solvent screening, again in batch conditions, the optimal resin **1** was used as the catalyst, with isovaleraldehyde as the donor substrate. In sharp contrast with previous reports on proline-catalyzed Mannich reactions[5a,8] and with our own experience[4] with resins **1** and **2**, the range of suitable solvents for this transformation turned out to be very narrow (Table 2). Indeed, only solvents containing an amide function in their structures (DMF, *N*,*N*-dimethylacetamide (DMAC), and *N*-methylpyrrolidone (NMP)) led to high conversions in short reaction times (Table 2, entries 1, 6, and 7). With other polar aprotic solvents such as DMSO and dioxane (Table 2, entries 2 and 4) the reaction was unacceptably slow. Protic solvents such as isopropyl alcohol or water (Table 2, entries 3 and 5), in turn, exclusively led to the decomposition of **4** in spite of the high activity exhibited by **1** (and **2**) in aldol reactions in aqueous medium.[4a,c] A close comparison of the amide-containing solvents revealed that reactions were much faster in DMF. Bearing in mind the development of a continuous-flow process as our ultimate goal, the kinetics of the transformation was deemed crucial and DMF was used for the rest of the study.

Table 2. Solvent screening in batch conditions for the reaction of **4** with isovaleraldehyde mediated by resin **1**.



4 **5a**

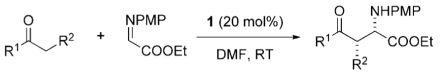
Entry	Solvent	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	DMF	2	79	>97:3	>99
2	DMSO	72	18	n.d.	n.d.
3	*i*PrOH	72	–[d]	–	–
4	dioxane	72	5	n.d.	n.d.
5	water[e]	1	–[d]	–	–
6	Me_2NCOCH_3	5	80	96:4	>99
7	NMP	5	75	96:4	>99

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by chiral HPLC analysis. [d] Decomposition of **4** was observed. [e] In this entry, **2** was used as the catalyst.

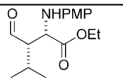
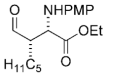
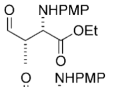
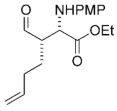
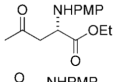
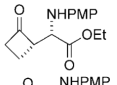
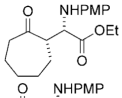
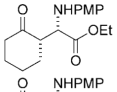
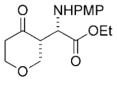
Next, the scope of the reaction with respect to the donor was studied. With this purpose, a representative set of aldehydes and ketones was reacted with imine **4** under the optimized batch conditions (resin **1**, DMF). The results of this study have been summarized in Table 3.

Gratifyingly, a fast reaction leading to the corresponding *syn* adducts in a highly stereocontrolled manner was observed at room temperature with aldehyde donors (Table 3, entries 1–4). For these substrates, resin **1** compares favorably to the most efficient homogeneous organocatalysts previously used in the same reaction from the perspectives of both catalytic activity and stereoselectivity.[5c,d] With ketone donors (Table 3, entries 5–9) excellent stereoselectivities were also observed, but substantially longer reaction times were required. Looking for practical solutions to this problem, we were most pleased to find that, at least for six-membered cyclic ketones, low-power microwave (MW) irradiation efficiently accelerated reactions with the PS-supported catalyst **1**, while the macroscopic temperature of the reaction mixture remained almost unaffected. In this manner, when the reactions leading to **5h** and **5i** were performed at 1 W power in a MW reactor, the reaction times were significantly shortened (Table 3, entries 8 and 9, data in parentheses), while the enantioselectivities and diastereoselectivities matched those recorded under the standard reaction conditions. In these experiments, the temperature of the reaction mixture increased from room temperature (ca. 23 °C) to approximately 30 °C. A plausible explanation for this behavior is that heat accumulated by the resin beads results in increased polymer chain mobility and more efficient catalyst–substrate contact, thus overcoming mass-transfer limitations.[9]

Table 3. Substrate scope in the Mannich reaction catalyzed by the PS-supported proline derivative **1** in batch conditions.



4 **5a–i**

Entry	Product		t [h][a]	Yield [%][a,b]	*syn*/*anti*[c]	*ee* [%][d]
1		**5a**	2	79	>97:3	99
2		**5b**	1	65	94:6	96
3		**5c**	1	72	>97:3	97
4		**5d**	3	45	88:12	96
5		**5e**	24	46	–	76
6		**5f**	48	45	>97:3	99
7		**5g**	24	40	91:9	99
8		**5h**	24 (3)	95 (86)	>96:4	99
9		**5i**	48 (4)	83 (87)	87:13	88

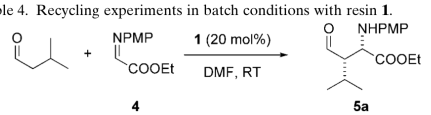
[a] The results of the experiments under MW irradiation are shown in parentheses. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis.

The robustness of the catalytic resin **1** is illustrated by the possibility of extending its use by simple recovery and recycling. Thus, in three consecutive runs with isovaleraldehyde, the excellent stereochemical performance of resin **1** remains intact, while catalytic activity shows only marginal erosion (Table 4).[10]

In view of the short reaction times required for the reactions to proceed under batch conditions, a simple device was assembled to test the possibility of performing the reactions under single-pass, continuous-flow conditions. The experimental setup (Figure 1) consisted in a jacketed omnifit column loaded with the PS-supported proline derivative **1** and connected to a single-piston pump used to feed the reactor with a solution of both reagents in DMF (no reaction takes place in the absence of catalyst).

Operating this device at room temperature with a loading of 1.0 g of **1** (functionalization (f) = 0.46 mmol g^{-1}) and using isovaleraldehyde as substrate, a simple flow-rate optimization showed that conversion was still complete when the reagent mixture (Scheme 1) was pumped at 0.20 mL min^{-1}. To our delight, the stereoselectivity of the batch process was exactly replicated in the flow

Table 4. Recycling experiments in batch conditions with resin **1**.



4 **5a**

Run	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	2	79	>97:3	>99
2	2	74	>97:3	>99
3	2	68	>97:3	>99

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by chiral HPLC analysis.

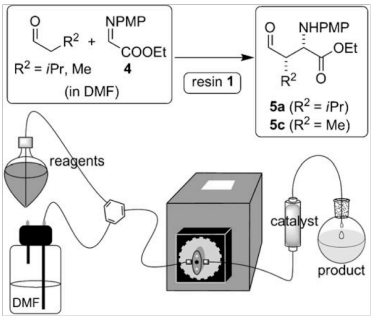
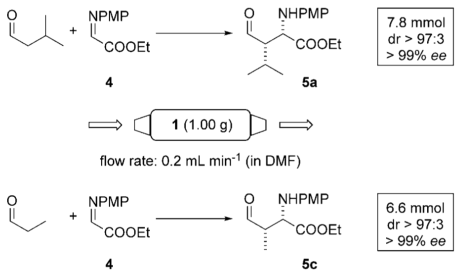


Figure 1. Schematic representation of the continuous-flow system used in this study.



Scheme 1. Continuous production of Mannich adducts of aldehydes.

process. The experiment was limited to 5.5 h, when all the reagent solution (8.65 mmol of **4**, 17.31 mmol of aldehyde) was consumed. It should be mentioned that at the end of this period instant conversion was still >95%. Since the aldehyde donor is volatile, the process is experimentally friendly because the chemically and stereochemically pure target compound **5a** is delivered after a trivial workup involving no purification. Important parameters of this reaction are a 6.0 min residence time[11] and a productivity of 1.42 mmol h^{-1} per gram of **1**. Taking the batch process as a reference, the continuous-flow process allows for a fourfold reduction of the catalyst amount without any deterioration in its performance.

In a parallel manner, the Mannich reaction of propanal was also studied under flow conditions. Working with the same catalyst loading as in the previous experiment and similar flow rate (0.22 mL min^{-1}), 6.6 mmol of chemically and stereochemically pure **5c** were produced in a 5.5 h run. To preserve the stereochemical integrity of **5c**, the product was collected and kept at −30 °C until workup.

It is worth mentioning here that when the production of this manuscript was in the final stages, a report by Odedra and Seeberger appeared in which aldol and Mannich reactions are performed in a continuous-flow manner in a microfluidic device.[12] These examples, besides involving longer residence times and elevated temperatures, are carried out by pumping a mixture of reagents and catalyst, so that the advantages derived from the use of an immobilized support (simplified workup and easy product isolation) cannot be exploited.

Conclusion

In summary, a catalytic system for the highly stereoselective Mannich reaction allowing purification-free, continuous operation has been developed. To the best of our knowledge, this is the first example of a Mannich reaction involving a solid-supported catalyst, and one of the first flow processes involving immobilized catalysts allowing the fast and enantiopure production of chiral targets.[13] The development of modified catalysts with extended lifecycle and the application of the same principles to the development of continuous-flow versions of other synthetically important reactions is currently underway.

Experimental Section

General methods: Resins **1**–**3** were prepared by reported procedures.[4a,c,14] A slightly cross-linked (1% 1,4-divinylbenzene) Merrifield resin with a functionalization of 0.6–0.8 mmol g^{-1} (100–200 mesh) was used as starting material. In each case, the extent of the supporting process and the functionalization of the final resin was determined by elemental analysis (% Cl for the starting Merrifield resin and % N for the functional resins **1**–**3** and their precursors). The incorporation of the monomers onto the resins was in all cases >95%.[15] All flash chromatography purifications were carried out using 60 mesh silica gel and dry-packed columns. The experiments under microwave irradiation were carried out using a CEM Discover microwave reactor operated in power control mode. NMR spectra were recorded using a Bruker Avance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature operating at 400.13 MHz (^{1}H) and 100.63 MHz (^{13}C{^{1}H}). ^{1}H NMR spectroscopy chemical shifts are quoted in ppm relative to internal tetramethylsilane (TMS) and ^{13}C NMR spectra to $CDCl_3$. Enantiomeric excess (*ee*) values were determined by HPLC using Agilent 1100 Series chromatographs with a UV detector. Elemental analyses (C, H, N, Cl) were performed by Servei de Microanalisi, CSIC, Barcelona, Spain.

General procedure 1 (GP1)—A representative protocol for the Mannich reaction of aldehydes in batch conditions: The resin **1**[4a] (typically 0.45–0.70 mmol g^{-1}; bead size ca. 120 mesh; 20 mol% according to the func-

tionalization) and the imine **4**[16] (0.125 mmol) were placed in a vial. DMF (1 mL, nondried, nondistilled) was added, followed by the aldehyde (1.5 equiv), and then the mixture was shaken at 25 °C until **4** was consumed. Then the resin was filtered, rinsed with DMF (3 mL), and the filtrate was diluted with water (30 mL). The mixture was extracted with Et_2O (2×15 mL) and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

General procedure 2 (GP2)—A representative protocol for the Mannich reaction of ketones in batch conditions: The resin **1**[4a] (typically 0.45–0.70 mmol g^{-1}; bead size ca. 120 mesh; 20 mol% according to the functionalization) and the imine **4**[16] (0.125 mmol) were placed in a vial. DMF (1 mL, nondried, nondistilled) was added, followed by the ketone (20 equiv), and then the mixture was shaken at 25 °C for the indicated time (see Table 1). Then the resin was filtered, rinsed with DMF (3 mL), and the filtrate was diluted with water (30 mL). The mixture was extracted with hexanes (2×15 mL), and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

General procedure 3 (GP3)—A representative protocol for the Mannich reaction of ketones in batch conditions under MW irradiation (CEM Discover microwave system): The resin **1**[4a] (typically 0.45–0.70 mmol g^{-1}; bead size ca. 120 mesh; 20 mol% according to the functionalization) and the imine **4**[16] (0.125 mmol) were placed in a MW tube. DMF (1 mL, nondried, nondistilled) was added, followed by the ketone (20 equiv), and then the mixture was irradiated at 1 W for the indicated time. Throughout the whole experiment the temperature remained below 33 °C, as determined both by the built-in IR sensor or (under open-vessel conditions) using an OpSens optical fiber temperature probe. Then the resin was filtered, rinsed with DMF (3 mL), and the filtrate was diluted with water (30 mL). The mixture was extracted with hexanes (2×15 mL) and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

Ethyl (2*S*,3*S*)-3-formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate[17] (5a): Following GP1, the title compound was obtained in 79% yield (29.0 mg, 0.0988 mmol). HPLC: AS-H (hexanes/*i*PrOH 99:1; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 27.6 min; t_R(minor) = 43.9 min.

Ethyl (2*S*,3*S*)-3-formyl-2-(*p*-methoxyphenylamino)octanoate[17] (5b): Following GP1, the title compound was obtained in 65% yield (26.1 mg, 0.0812 mmol). HPLC: AS-H (hexanes/*i*PrOH 99:1; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 25.1 min; t_R(minor) = 32.7 min.

Ethyl (2*S*,3*S*)-3-formyl-2-(*p*-methoxyphenylamino)butanoate[17] (5c): Following GP1, the title compound was obtained in 72% yield (23.9 mg, 0.0901 mmol). HPLC: AS-H (hexanes/*i*PrOH 99:1; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 32.1 min; t_R(minor) = 45.9 min.

Ethyl (2*S*,3*S*)-3-formyl-2-(*p*-methoxyphenylamino)-5-hexenoate[18] (5d): Following GP1, the title compound was obtained in 45% yield (16.4 mg, 0.0563 mmol). HPLC: AS-H (hexanes/*i*PrOH 99:1; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 47.7 min; t_R(minor) = 73.4 min.

Ethyl (2*S*,3*S*)-2-(*p*-methoxyphenylamino)-4-oxopentanoate[8a] (5e): Following GP2, the title compound was obtained in 46% yield (15.3 mg, 0.0575 mmol). HPLC: AS (hexanes/*i*PrOH 99:1; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 26 min; t_R(minor) = 21 min.

Ethyl (2*S*,1′*S*)-2-(*p*-methoxyphenylamino)-2-(2′-oxocyclobut-1′-yl)acetate[19] (5f): Following GP2, the title compound was obtained in 45% yield (15.6 mg, 0.0563 mmol). HPLC: OD (hexanes/*i*PrOH 95:5; 1.0 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 14 min; t_R(minor) = 19 min.

Ethyl (2*S*,1′*S*)-2-(*p*-methoxyphenylamino)-2-(2′-oxocycloheptyl-1′-yl)acetate[16] (5g): Following GP2, the title compound was obtained in 40% yield (16.0 mg, 0.0501 mmol). HPLC: AS (hexanes/*i*PrOH 94:6; 0.7 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 20 min; t_R(minor) = 26 min.

Ethyl (2*S*,1′*S*)-2-(*p*-methoxyphenylamino)-2-(2′-oxocyclohex-1′-yl)acetate[8a] (5h): Following GP2, the title compound was obtained in 95% yield (36.3 mg, 0.1189 mmol). When GP3 was followed for 3 h the yield was 86% (32.8 mg, 0.1074 mmol). HPLC: AS (hexanes/*i*PrOH 94:6; 0.7 mL min^{-1}; λ_{max} = 254 nm); t_R(major) = 23 min; t_R(minor) = 27 min.

Ethyl (2*S*,1′*S*)-2-(*p*-methoxyphenylamino)-2-(6′-oxo-3′-oxan-1′-yl)acetate[20] (5i): Following GP2, the title compound was obtained in 83% yield (32.0 mg, 0.104 mmol). When GP3 was followed for 4 h the yield was 87% (33.4 mg, 0.1087 mmol). HPLC: OD-H (hexanes/*i*PrOH 95:5; 1.0 mL min^{-1}; λ_{max} = 240 nm); t_R(major) = 33.8 min; t_R(minor) = 30.6 min.

Description of the experimental setup for the continuous-flow process: A piston pump was connected (using HPLC-type connectors) to a bottle of DMF and to a flask containing a mixture of the reagents in appropriate proportions through a three-way connector that allows switching between channels. The pump outlet was connected to an omnifit column of 10 mm internal diameter and 100 mm length, previously packed with resin **1**, and at the end of the column the solution containing the product was collected in an open flask. Under these conditions, and working with 1.0 g of resin **1**, the dead volume was determined to be 2.2 mL when the process was slow enough as to allow maximal swelling of the resin. The total packed bed volume (swollen resin) was 3.1 mL.

Continuous-flow experiment with isovaleraldehyde: The column was filled with previously swollen resin **1** (1.0 g; 0.46 mmol g^{-1} functionalization) in DMF and then the same solvent was flushed for about 30 min at an effective flow rate of 0.20 mL min^{-1}. When the resin has been conditioned, the solvent channel was switched to the reagents and a solution containing **4** (1.79 g, 8.65 mmol) and isovaleraldehyde (1.86 mL, 17.31 mmol) in DMF (66 mL) was pumped at a flow rate of 0.20 mL min^{-1}. After 5.5 h, the reagent solution was consumed and the channel was switched again to the solvent to wash the system. Instant conversion (determined by ^1H NMR spectroscopy) was >95% at the end of the reaction. The collected yellow solution was diluted with water (400 mL) and extracted with hexanes (3×150 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and evaporated to furnish the desired compound **5a** as a yellow solid in 90% yield (2.30 g, 7.82 mmol).

Continuous-flow experiment with propanal: The same procedure as described above for isovaleraldehyde was followed for a solution containing **4** (1.85 g, 8.93 mmol) and propanal (1.30 mL, 18.02 mmol) in DMF (68 mL). Due to the instability of **5c**, the solution was collected in a closed flask immersed in a cooling bath (−30 °C). The collected yellow solution was diluted with water (400 mL) and extracted with diethyl ether (3×150 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and evaporated at low temperature to furnish the desired compound **5c** as a yellow oil in 74% yield (1.75 g, 6.60 mmol).

Acknowledgements

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[11] The residence time was determined by pumping a solution of methyl red through the system and measuring the time elapsed between the first contact of the dye with the resin and the moment when red color appears at the column output.

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[13] For some examples, see: a) M. A. Pericàs, C. I. Herrerías, L. Solà, *Adv. Synth. Catal.* **2008**, *350*, 927; b) W. Solodenko, G. Jas, U. Kunz, A. Kirschning, *Synthesis* **2007**, 583; c) F. Bonfils, I. Cazaux, P. Hodge, C. Caze, *Org. Biomol. Chem.* **2006**, *4*, 493; d) P. Stephenson, B. Kondor, P. Licence, K. Scovell, S. K. Ross, M. Poliakoff, *Adv. Synth. Catal.* **2006**, *348*, 1605.

[14] K. Kondo, T. Yamano, K. Takemoto, *Makromol. Chem.* **1985**, *186*, 1781.

[15] Yield of incorporation calculated as $100f/f_{max}$, in which f (mmol ligand per gram resin) is the functionalization calculated from the nitrogen elemental analysis, and f_{max} (mmol ligand per gram resin), the maximal ligand functionalization level, is calculated as described in the following: A. Vidal-Ferran, N. Bampos, A. Moyano, M. A. Pericàs, A. Riera, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 6309.

[16] J. A. Cobb, D. M. Shaw, D. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84.

[17] A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1866.

[18] A. Córdova, C. F. Barbas, *Tetrahedron Lett.* **2003**, *44*, 1923.

[19] J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558.

[20] W. Wang, J. Wang, H. Li, *Tetrahedron Lett.* **2004**, *45*, 7243.

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Supporting Information for:

A Solid-Supported Organocatalyst for Highly Selective, Continuous Flow Mannich Reactions

Esther Alza, Carles Rodríguez-Escrich, Sonia Sayalero, Amaia Bastero, Miquel A. Pericàs

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

GENERAL INDEX

1. General Procedures used in the course of the present study

– General Procedure 1 (*GP1*). Representative protocol for the Mannich reaction of aldehydes in batch conditions:

The resin **1**[1] (20 mol% according to the functionalization) and the imine **4**[2] (0.125 mmol) were placed in a vial. DMF (1 mL, non-dried, non-distilled) was added, followed by the aldehyde (1.5 equiv) and then the mixture was shaken at 25 ºC until **4** was consumed. Then the resin was filtered, rinsed with DMF (3 mL) and the filtrate was diluted with water (30 mL). The mixture was extracted with Et_2O (2 × 15 mL) and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

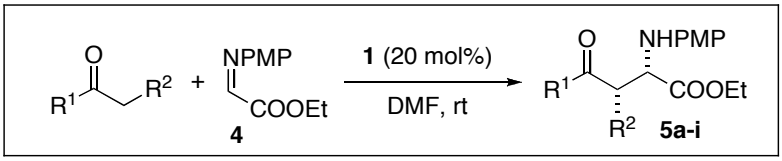
– General Procedure 2 (*GP2*). Representative protocol for the Mannich reaction of ketones in batch conditions

The resin **1**[1] (20 mol% according to the functionalization) and the imine **4**[2] (0.125 mmol) were placed in a vial. DMF (1 mL, non-dried, non-distilled) was added, followed by the ketone (20 equiv) and then the mixture was shaken at 25 ºC for the indicated time (see Table 1, main text). Then the resin was filtered, rinsed with DMF (3 mL) and the filtrate was diluted with water (30 mL). The mixture was extracted with hexanes (2 × 15 mL) and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

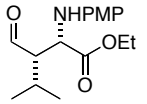
– General Procedure 3 (*GP3*). Representative protocol for the Mannich reaction of ketones in batch conditions under MW irradiation.

The resin **1**[1] (20 mol% according to the functionalization) and the imine **4**[2] (0.125 mmol) were placed in a MW tube. DMF (1 mL, non-dried, non-distilled) was added, followed by the ketone (20 equiv) and then the mixture was irradiated at 1 W for the indicated time. Then the resin was filtered, rinsed with DMF (3 mL) and the filtrate was diluted with water (30 mL). The mixture was extracted with hexanes (2 × 15 mL) and the combined organic extracts were washed with water (20 mL) and dried over Na_2SO_4. Solvent removal afforded the desired product. Flash chromatography was used to purify the product when necessary.

2. Mannich Reactions of Several Aldehydes and Ketones with *N*-PMP-Protected α-Imino Ethyl Glyoxylate 4



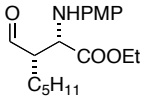
Ethyl (2*S*,3*S*) 3-formyl-2-(*p*-methoxyphenylamino)4-methylpentanoate[3] (**5a**):



Following *GP1* the title compound was obtained in 79% yield (29.0 mg, 0.0988 mmol).

HPLC: AS-H (hexanes/^{i}PrOH 99:1; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 27.6 min; t_R minor = 43.9 min.

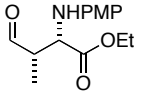
Ethyl (2*S*,3*S*) 3-formyl-2-(*p*-methoxyphenylamino)octanoate[3] (**5b**):



Following *GP1* the title compound was obtained in 65% yield (26.1 mg, 0.0812 mmol).

HPLC: AS-H (hexanes/^{i}PrOH 99:1; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 25.1 min; t_R minor = 32.7 min.

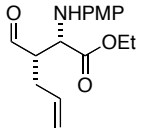
Ethyl (2*S*,3*S*) 3-formyl-2-(*p*-methoxyphenylamino)butanoate[3] (**5c**):



Following *GP1* the title compound was obtained in 72% yield (23.9 mg, 0.0901 mmol).

HPLC: AS-H (hexanes/^{i}PrOH 99:1; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 32.1 min; t_R minor = 45.9 min.

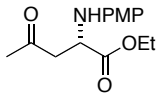
Ethyl (2*S*,3*S*) 3-formyl-2-(*p*-methoxyphenylamino)-5-hexenoate[4] (**5d**):



Following *GP1* the title compound was obtained in 45% yield (16.4 mg, 0.0563 mmol).

HPLC: AS-H (hexanes/^{i}PrOH 99:1; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 47.7 min; t_R minor = 73.4 min.

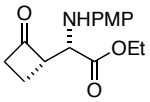
Ethyl (2*S*,3*S*) 2-(*p*-methoxyphenylamino)-4-oxopentanoate[5] (**5e**):



Following *GP2* the title compound was obtained in 46% yield (15.3 mg, 0.0575 mmol).

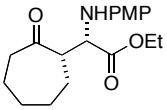
HPLC: AS (hexanes/^{i}PrOH 99:1; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 26 min; t_R minor = 21 min.

Ethyl (2*S*,1'*S*)-2-(*p*-methoxyphenylamino)-2-(2'-oxocyclobut-1'-yl)-acetate[6] (**5f**):



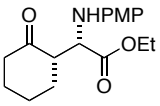
Following *GP2* the title compound was obtained in 45% yield (15.6 mg, 0.0563 mmol).
HPLC: OD (hexanes/^{i}PrOH 95:5; 1.0 mL·min^{-1}; l_{max} = 254 nm) t_R major = 14 min; t_R minor = 19 min.

Ethyl (2*S*,1'*S*)-2-(*p*-methoxyphenylamino)-2-(2'-oxocyclohept-1'-yl)-acetate[2] (**5g**):



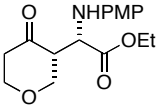
Following *GP2* the title compound was obtained in 40% yield (16.0 mg, 0.0501 mmol).
HPLC: AS (hexanes/^{i}PrOH 94:6; 0.7 mL·min^{-1}; l_{max} = 254 nm) t_R major = 20 min; t_R minor = 26 min.

Ethyl (2*S*,1'*S*)-2-(*p*-methoxyphenylamino)-2-(2'-oxocyclohex-1'-yl)-acetate[5] (**5h**):



Following *GP2* the title compound was obtained in 95% yield (36.3 mg, 0.1189 mmol).
When *GP3* was followed for 3 h the yield was 86% (32.8 mg, 0.1074 mmol).
HPLC: AS (hexanes/^{i}PrOH 94:6; 0.7 mL·min^{-1}; l_{max} = 254 nm) t_R major = 23 min; t_R minor = 27 min.

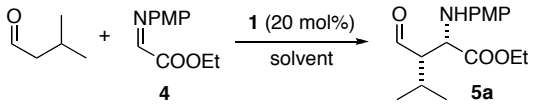
Ethyl (2*S*,1'*S*)-2-(*p*-methoxyphenylamino)-2-(6'-oxo-3'-oxan-1'-yl)-acetate[7] (**5i**):



Following *GP2* the title compound was obtained in 83% yield (32.0 mg, 0.104 mmol).
When *GP3* was followed for 4 h the yield was 87% (33.4 mg, 0.1087 mmol).
HPLC: OD-H (hexanes/ ^{i}PrOH 95:5; 1.0 mL·min^{-1}; l_{max} = 240 nm) t_R major = 33.8 min; t_R minor = 30.6 min.

3. Screening of the solvent

The following table summarizes the results obtained after screening different solvents in the Mannich reaction catalyzed by **1** and using isovaleraldehyde as the donor.

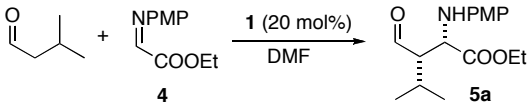


Entry	Solvent	t [h]	Yield [%][a]	*syn*/*anti*[b]	ee [%][c]
1	DMF	2	79	>97:3	>99
2	DMSO	72	18	nd	nd
3	^{i}PrOH	72	–[d]	–	–
4	dioxane	72	5[d]	nd	nd
5[e]	H_2O	1	–[d]	–	–
6	$(CH_3)_2NCOCH_3$	5	80	96:4	>99
7	NMP	5	75	96:4	>99

a) Isolated Yield. b) Determined by ^{1}H NMR of the reaction crude after workup. c) Determined by HPLC on a chiral stationary phase. d) Decomposition of the starting imine. e) Catalyst **2**

4. Recycling experiments using isovaleraldehyde as the donor

The following table shows several runs with the same batch of PS-supported catalyst, reused after simply washing the resin with DMF.



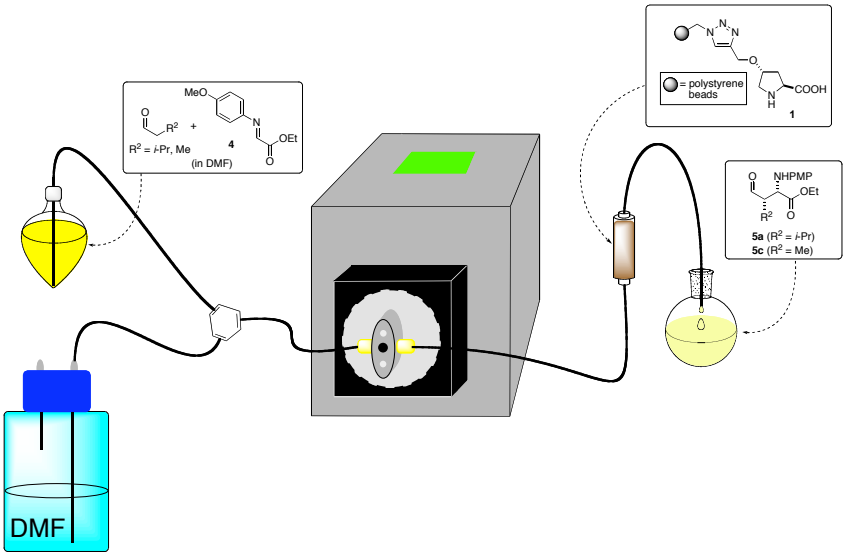
Run	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	ee [%][c]
1	2	79	>97:3	>99
2	2	74	>97:3	>99
3	2	68	>97:3	>99

a) Isolated Yield. b) Determined by ^{1}H NMR of the reaction crude after work-up. c) Determined by HPLC on a chiral stationary phase.

5. Continuous flow experiments

5.1. Description and scheme of the experimental setup

A piston pump is connected (using HPLC-type connectors) to a bottle of DMF and a mixture of the reagents through a three-way connector that allows to switch between channels. The pump outlet is connected to an omnifit column of 10 mm internal diameter, previously packed with resin **1**, and at the end of the column the solution containing the product is collected in an open flask.



5.2. Continuous flow experiment with isovaleraldehyde

The column is filled with 1.0 g of previously swollen resin **1** (0.46 mmol·g^{-1} functionalization) in DMF and then the same solvent is flushed for about 30 min at an effective flow rate of 0.20 mL·min^{-1}. When the resin has been conditioned, the solvent channel is switched to the reagents and a solution containing 1.79 g of **4** (8.65 mmol) and 1.86 mL of isovaleraldehyde (17.31 mmol) in 66 mL of DMF is circulated at a flow rate of 0.20 mL·min^{-1}.

After 5.5 h the reagents solution is consumed and the channel is switched again to the solvent to wash the system. Instant conversion (determined by ^{1}H NMR) is > 95% at the end of the reaction.

The collected yellow solution is diluted with 400 mL water and extracted with hexanes (3 × 150 mL). The combined organic extracts are washed with brine (200 mL), dried over Na_2SO_4 and evaporated to furnish the desired compound **5a** as a yellow solid in 90% yield (2.30 g, 7.82 mmol).

5.3. Continuous flow experiment with propanal

The same procedure described above for isovaleraldehyde is followed for a solution containing 1.85 g of **4** (8.93 mmol) and 1.30 mL of propanal (18.02 mmol) in 68 mL of DMF. Due to the instability of **5c**, the solution is collected in a closed flask immersed in a cooling bath (–30 ºC).

The collected yellow solution is diluted with 400 mL water and extracted with diethyl ether (3 × 150 mL). The combined organic extracts are washed with brine (200 mL), dried over Na_2SO_4 and evaporated at low temperature to furnish the desired compound **5c** as a yellow oil in 74% yield (1.75 g, 6.60 mmol).

6. References for the Supporting Information:

[1] (a) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2006**, *8*, 4653. (b) For PS-supported catalysts **2** and **3**, see: Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 337.

[2] Cobb, J. A.; Shaw, D. M.; Longbottom, D.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem*. **2005**, *3*, 84.

[3] Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas III, C. F. *J. Am. Chem. Soc*. **2002**, *124*, 1866.

[4] Córdova, A.; Barbas III, C. F. *Tetrahedron Lett*. **2003**, *44*, 1923.

[5] Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc*. **2002**, *124*, 1842.

[6] Cobb, J. A.; Shaw, D. M.; Ley, S. V. *Synlett*, **2004**, 558.

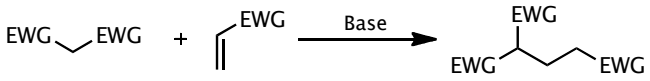
[7] Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett*. **2004**, *45*, 7243.

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

HIGHLY ENANTIOSELECTIVE MICHAEL ADDITIONS *via* ENAMINE CATALYZED BY PS-SUPPORTED PYRROLIDINE DERIVATIVES

The organocatalytic asymmetric conjugate addition[1e,13] is one of the most powerful bond-forming reaction to construct enantioenriched, highly functionalised carbon skeletons for the total synthesis of natural and biologically active compounds. In particular, the Michael addition has been subjected to a spectacular development in recent years.

The Michael reaction is the conjugate addition of resonance-stabilized carbon nucleophiles to electron-poor species (Scheme 2.13). The reaction is named after its discoverer Arthur Michael in the 19th century.[14]



Scheme 2.13. General equation for the Michael reaction.

Among the Michael acceptors in reactions via enamine pathway, nitroalkenes are very attractive, because the nitro group is the most electron-withdrawing group known.[15] In particular *trans*-β-nitrostyrene can act as a reactive electrophile and is therefore an attractive Michael acceptor.

The general mechanism of the Michael addition of carbonyl compounds to nitroolefins *via* enamine catalysis is shown in Scheme 2.14.

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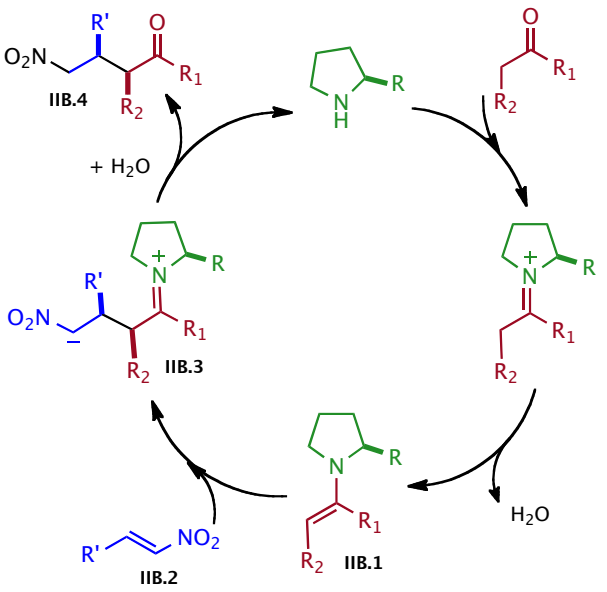
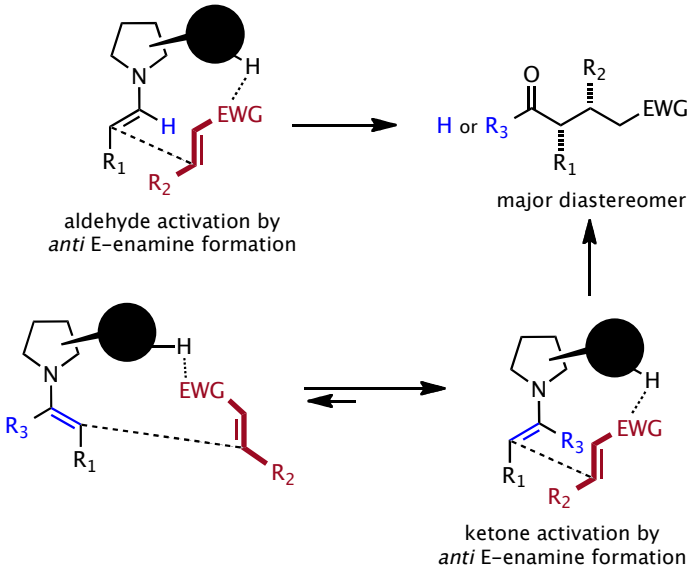
[13] For reviews, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701. b) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron Asymmetry* **2007**, *18*, 299. c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065. e) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions*, RCS Publishing, Cambridge, **2010**.
[14] A. Michael, *J. Prakt Chem.* **1887**, *36*, 349.
[15] N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.



Scheme 2.14. Catalytic cycle of Michael reaction of carbonyl compounds and nitroolefins.

The stereochemistry of the conjugate additions of aldehydes or ketones to electron-deficient olefins is determined by the structure of the catalyst. As before mentioned, according to steric hindrance, the thermodynamically favourable E-enamine from aldehydes and ketones is preferably formed unless other specific electronic interactions would favour the Z-enamine. As also the substituent of the catalyst determine the shift of the equilibrium between enamine rotamers, influencing the face selectivity. The relative size of both sides of the enamine depends on the carbonyl compounds. Thus, the smallest group in aldehydes is the hydrogen and leads to the formation of the *Re*-rotamer (E-enamine *anti*), whereas in the case of ketones it is the double bond giving the *Si*-rotamer (E-enamine *syn*). After that, the *syn*-diastereoselectivity observed in the case of pyrrolidine-derived organocatalysts for Michael reaction *via* enamine is explained though a

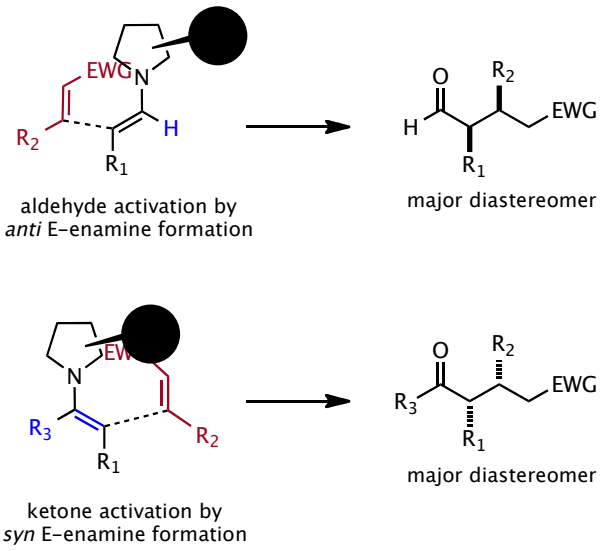
synclinal acyclic transition state, proposed by Seebach and Golinski[16] in the attack of the nucleophilic E-enamine to the Michael acceptor. When in the catalyst are present substituents able to form H-bonds interactions, such in the case of L-proline, tetrazole or thiourea catalysts, the approximation of the acceptor would arise from the same face as the chiral substituent (Scheme 2.15). In the case of ketones, repulsive steric interactions could force the E-enamine to adopt the disfavoured *anti*-conformation.



Scheme 2.15. Electronic transition states in the organocatalyzed Michael addition of aldehydes and ketones to electron-deficient olefins.

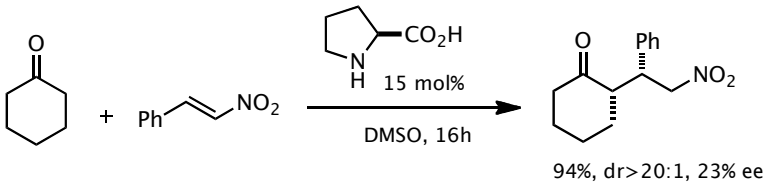
On the other hand, the steric impediments constrain the attack from the opposite side of the chiral substituent. Therefore, the less hindered *Si, Si* transition state though *anti*-enamine is favoured for aldehydes (Scheme 2.16 up) while for ketones is the *Re, Re*-approach *via syn*-enamine (Scheme 2.16 down).

[16] a) D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413. b) S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, *116*, 2250. c) D. Seebach, M. Missbach, G. Calderari, M. Eberle, *J. Am. Chem. Soc.* **1990**, *112*, 7625.



Scheme 2.16. Steric effects controlling transition states in the organocatalyzed Michael addition of aldehydes and ketones to electron-deficient olefins.

Initial studies of the L-proline catalyzed 1,4-addition of cyclohexanone to nitrostyrene revealed that this reaction proceed smoothly to furnish the Michael adduct in high yield and diastereoselectivity, but even with a 15 mol% of catalyst loading the observed enantioselectivity remained very low (Scheme 2.17).[17] This first example highlights the need for more optimized catalysts for these reactions.

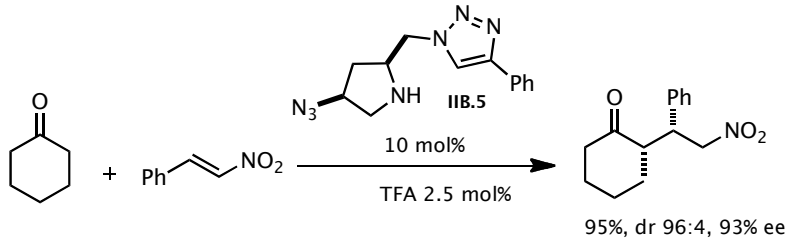


Scheme 2.17. L-Proline catalysed Michael reaction of cyclohexanone and nitrostyrene.

[17] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423.

Accordingly, the development of efficient catalysts for enantioselective Michael reactions has become a highly sought-after goal in organocatalysis. Simple 2-substituted cyclic amines (mostly pyrrolidines) have been developed and often used very successfully since the side chain acts as steric controller that directs the reactivity towards the less hindered diastereotopic face of the intermediate enamine.

Within this category, systems bearing highly nitrogen-rich substituent such as tetrazoles and 1,2,3-triazoles have shown good activity-selectivity profiles in the asymmetric Michael reactions.[18] In line with the work presented in the **Article 2**, Lou and co-workers synthesized a library of 1,2,3-triazoles, 4-substituted pyrrolidine-type compounds as organocatalysts for the asymmetric Michael addition of ketones to nitroolefins, showing good catalytic activity and stereoselectivity (Scheme 2.18).[19]



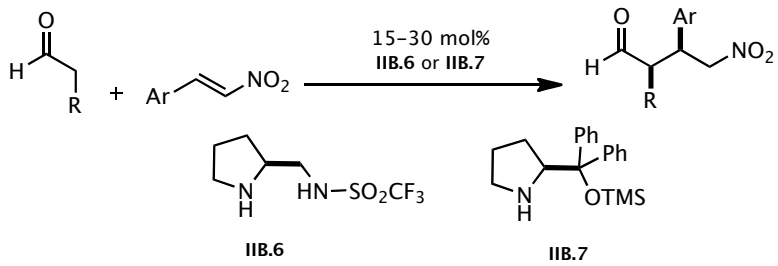
Scheme 2.18. Michael addition reaction organocatalyzed by **IIB.5**.

There are many examples for the catalytic enantioselective Michael addition of carbonyl compounds to nitrostyrenes in the literature and the development of asymmetric reactions that proceed under environmentally benign conditions has grown into an extensively investigated field.[1e] The use in this reaction of organocatalysts in non-organic solvent as water,[20] or brine,[21] and recyclable catalysts as soluble polymers[22] or ionic liquids[23] have

[18] a) Z. Yan, Y. Niu, H. Wei, L. Wu, Y. Zhao, Y. Liang, *Tetrahedron: Asymmetry* **2007**, *17*, 3288. b) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Comm.* **2004**, *16*, 1808. c) C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, *4*, 611.
[19] S. Luo, H. Xu, X. Mi, J. Li, X. Zheng, J. Cheng, *J. Org. Chem.* **2006**, *71*, 9244.
[20] L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077.
[21] N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966.
[22] L. Gu, Y. Wu, Y. Zhang, G. Zhao, *J. Mol. Catal. A* **2007**, *263*, 186.

been reported, but until the work presented in **Article 2** no examples had been known on the use of insoluble, polymer-supported organocatalysts in this process.

When aldehydes are used as Michael acceptors, the most active catalysts described for this reaction where the pyrrolidine derivative **IIB.6** developed by Wang[24] (Scheme 2.19) and the (*S*)-α,α-diaryprolinol silyl ethers introduced by Hayashi (Scheme 2.19, **IIB.7**).[25] The latter was reported, in parallel by the group of Jørgensen for the α-sulphenylation of aldehydes.



Scheme 2.19. Michael addition of aldehydes to nitroolefins catalyzed by **IIB.6-7**.

The generally accepted mechanism for organocatalyzed Michael addition of aldehydes to nitro alkenes, has been recently revised by the groups of Seebach and Hayashi.[26] The mechanistic investigations of this reaction catalyzed by diphenylprolinol trimethyl silyl ether conclude that knowing that the reaction is acid-catalyzed, the *p*-nitrophenol (weak acid with pK_a 7.15) is the most effective additive in terms of activity (does not affect the enantioselectivity) allowing to reduce the amount of catalyst to 1 mol%.

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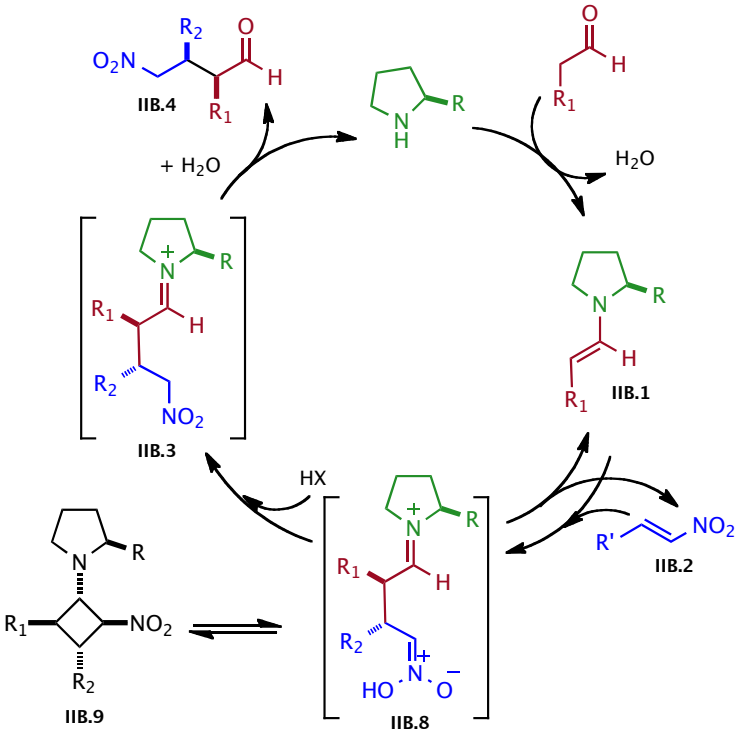
[23] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J. Cheng, *Angew. Chem.* **2006**, *118*, 3165; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093.
[24] a) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Et.* **2005**, *44*, 1369. b) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *8,* 4321.
[25] For reviews on α,α-diarylprolinols silyl ethers, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, 118, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876. b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922. c) A. Lattanzi, *Chem. Commun.* **2009**, 1452. For the first reports on the use of such catalyst, see: d) Y. Hayashi, H. Gotoh, T. Hayasi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. e) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
[26] K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719.

The fast formation of amino-nitro-cyclobutane intermediates **IIB.9** has been confirmed by NMR studies. This specie results from the reaction between the enamine **IIB.1** with the nitroolefins. Therefore, the authors suggest a revised mechanism that it is shown in Scheme 2.20. The important aspects to highlight are that the cyclobutanes **IIB.9** can be considered as 'parasitic' components like off-cycle species, in which the catalyst is taken out of the catalytic cycle, and that the zwitterions **IIB.8** are the 'key players' of the process, which are protonated to afford finally the addition products.[27]



Scheme 2.20. Revised mechanism of the amine-catalyzed Michael addition of aldehydes to nitroolefins (compared with Scheme 2.14).

[27] For more specific details, see ref. 26.

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APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
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Highly Enantioselective Michael Additions in Water Catalyzed by a PS-Supported Pyrrolidine

Esther Alza,[†] Xacobe C. Cambeiro,[†,‡] Ciril Jimeno,[†] and Miquel A. Pericàs*[,†,‡]

Institute of Chemical Research of Catalonia (ICIQ), Avda. Països Catalans, 16, 43007 Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

mapericas@iciq.es

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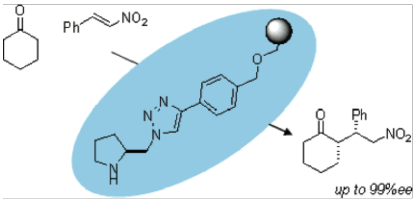
ABSTRACT



The development of a highly efficient, polymer-supported organocatalyst for the Michael addition of ketones to nitroolefins is described. A 1,2,3-triazole ring, constructed through a *click* 1,3-cycloaddition, plays the double role of grafting the chiral pyrrolidine monomer onto the polystyrene backbone and of providing a structural element, complementary to pyrrolidine, key to high catalytic activity and enantioselectivity. Optimal operation in water and full recyclability make the triazole linker attractive for the immobilization of organocatalysts.

C−C bond-forming reactions occupy the central position in the playground of organic synthesis because they are key to the construction of molecular frameworks of increasing complexity. In recent times, a growing interest has arisen in achieving this goal in an enantioselective manner through the use of purely organic, metal-free catalysts. As a result, different catalytic systems (quite often based on proline) have been developed providing very useful solutions for almost every reaction involving classical carbonyl chemistry.[1]

Organocatalytic processes are generally considered as environmentally benign because the use of metals is avoided. However, their catalytic efficiency is usually lower than in metal-catalyzed processes in terms of turnover number. To circumvent this difficulty, the development of immobilized, easily recoverable, and reusable catalysts appears as one of the most promising strategies.[2]

For optimal performance, ligands to be supported must be designed to allow anchoring through positions remote from the catalytic sites because, in this way, interference by the bulky polymer backbone is avoided. Working according to this principle, we have developed polystyrene-supported ligands for organometallic reactions which keep intact the catalytic activity and enantioselectivity of their homogeneous counterparts.[3] Quite recently, we have shown that *trans*-4-hydroxyproline can be properly immobilized onto polystyrene (PS) resins through copper-mediated 1,3-dipolar cycloaddition between azides and alkynes (*click chemistry*)[4] and that the resulting resins show improved catalytic properties over homogeneous counterparts in the direct aldol

[†] ICIQ.
[‡] UB.

(1) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley VCH: New York, 2005.

(2) For reviews on immobilized organocatalysts, see: (a) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401. (b) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367.

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reaction in water[5] and in the α-aminoxylation of ketones and aldehydes,[6] while offering important operational advantages.[7]

In the context of our efforts toward the implementation of copper-mediated 1,3-dipolar cycloadditions as a general immobilization strategy for organocatalysis, we turned our attention to the catalytic enantioselective Michael addition of ketones to nitrostyrenes.[8] This reaction is a powerful synthetic tool that provides access to synthons of many interesting types[9] and has been studied from the perspective of organocatalysis following two different approaches: (i) the use of bifunctional catalysts that simultaneously activate the ketone and nitroolefin partners[10] and (ii) the use of simple 2-substituted cyclic amines (mostly pyrrolidines), where the side chain is believed to act as a steric controller that directs the reactivity toward the less hindered diastereotopic face of the intermediate enamine.[11] Within this category, systems bearing highly nitrogen-rich substituents such as tetrazoles and 1,2,3-triazoles have shown promising activity−selectivity profiles in the asymmetric Michael reactions.[11d,e,g,h]

However, in spite of the interest of the reaction, the first efforts toward the development of recyclable catalysts have only been published quite recently,[12] and nothing has been known until now on the use of insoluble, polymer-supported organocatalysts in this process.

In this paper, we report on the preparation of new immobilized organocatalysts (Figure 1) through Cu-catalyzed

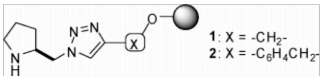
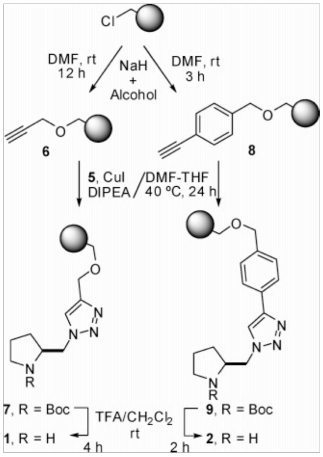


Figure 1. Structure of the supported catalysts.

1,3-dipolar cycloadditions between (*S*)-2-azidomethylpyrrolidine and alkynyl-functionalized Merrifield resins and on the development of optimal conditions for the use of these resins as highly efficient catalysts for the asymmetric Michael addition.

The catalysts were prepared by a straightforward route as shown in Scheme 1 and the Supporting Information. Azi-

Scheme 1. Functionalization of the PS Resin



domethylpyrrolidine **5** was prepared from L-proline by reduction with lithium aluminum hydride and subsequent protection of the unstable aminoalcohol with di-*tert*-butyl dicarbonate. The alcohol **3** was then activated as a tosylate, and azide was introduced via S_N2 substitution.[13]

On the other hand, a Merrifield resin (1% DVB, $f_o = 0.74$ mmol/g) was treated with propargyl alcohol under basic

(3) (a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (b) Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, Ll. *Adv. Synth. Catal.* **2003**, *345*, 1305. (c) Fraile, J. M.; Mayoral, J. A.; Serrano, J.; Pericàs, M. A.; Solà, Ll.; Castellnou, D. *Org. Lett.* **2003**, *5*, 4333. (d) Castellnou, D.; Solà, L.; Jimeno, C.; Fraile, J. M.; Mayoral, J. A.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2005**, *70*, 433. (e) Castellnou, D.; Fontes, M.; Jimeno, C.; Font, D.; Solà, L.; Verdaguer, X.; Pericàs, M. A. *Tetrahedron* **2005**, *61*, 12111.

(4) (a) Tornøe, C. W.; Meldal, M. In *Proc. Second Intl. and Seventeenth Amer. Peptide Soc. Symp.*; Lebl, M., Houghten, R. A., Eds.; American Peptide Society and Kluwer Academic Press: San Diego, 2001; pp 263−264. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Rostovtsed, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. For a review on the concept of click chemistry, see: (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

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(8) For a review, see: Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

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(10) (a) Cao, C.; Ye, M.; Sun, X.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (b) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151. (c) Liu, K.; Cui, H.; Nie, J.; Dong, K.; Li, X.; Ma, J. *Org. Lett.* **2007**, *9*, 923.

(11) (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (c) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (d) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J. *J. Org. Chem.* **2006**, *71*, 9244. (e) Yan, Z.; Niu, Y.; Wei, H.; Wu, L.; Zhao, Y.; Liang, Y. *Tetrahedron: Asymmetry* **2007**, *17*, 3288. (f) Vishnumaya; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. For examples of pyrrolidine-type catalysts with protic groups: (g) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, *16*, 1808. (h) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, *4*, 611. (i) Prieto, A.; Halland, N.; Jorgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (j) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966.

(12) Approaches to recyclable organocatalysts for Michael additions, Soluble polymers: (a) Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A* **2007**, *263*, 186. Ionic liquids: (b) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (c) Kotrusz, P.; Toma, S.; Schmalz, H.; Adler, A. *Eur. J. Org. Chem.* **2004**, *7*, 1577. Fluorous catalysts: (d) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077.

(13) (a) Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2661. (b) Koh, D. W.; Coyle, D. L.; Mehta, N.; Ramsinghani, S.; Kim, H.; Slama, J. T.; Jacobson, M. K. *J. Med. Chem.* **2003**, *46*, 4322.

conditions (NaH in DMF) to provide the alkyne-functionalized resin **6**. Azide **5** was grafted onto this resin by a Cu-catalyzed Huisgen cycloaddition to afford, upon deprotection with TFA, the immobilized catalyst **1**. In a similar manner, catalyst **2** was prepared from the same Merrifield resin, through intermediate functionalization with 4-ethynylbenzyl alcohol (resin **8**).

Both resins were tested as catalysts for the Michael addition of cyclohexanone to β-nitrostyrene in a variety of solvents (Table 1). As a general trend, resin **1** was clearly more active but less enantioselective than **2**.

Table 1. Optimization of the Reaction Conditions*

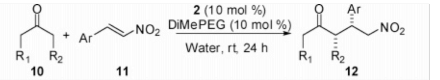
entry	catalyst	solvent	additive	% conv[e]	d.r.[e,f]	% ee[g]
1[a]	**1**	–	TFA[c]	80	94:6	67
2[a]	**1**	H_2O	TFA[c]	55	96:4	60
3[a]	**1**	DMF	TFA[c]	31	97:3	75
4[a]	**1**	THF	TFA[c]	67	93:7	67
5[a]	**1**	toluene	TFA[c]	72	93:7	62
6[a]	**1**	H_2O	–	27	93:7	79
7[b]	**1**	H_2O	–	66	95:5	77
8[b]	**2**	H_2O	–	35	94:6	85
9[b]	**2**	brine	–	19	95:5	84
10[b]	**2**	–	TFA[c]	42	94:6	82
11[b]	**2**	DMF	TFA[c]	17	97:3	76
12[b]	**2**	H_2O	TFA[c]	84	95:5	87
13[b]	**2**	H_2O	DiMePEG[d]	87	95:5	89
14[b]	**2**	H_2O	TFA[c] + DiMePEG[d]	77	90:10	87
15[b]	**2**	toluene[h]	–	15	95:5	85
16[b]	**2**	toluene[i]	TFA[c]	19	91:9	83
17[b]	**2**	toluene[j]	DiMePEG[d]	23	93:7	84

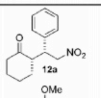
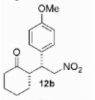
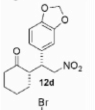
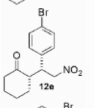
* All reactions performed with 0.5 mmol of nitrostyrene and 6 mol % of catalyst in 2 mL of solvent. [a] 5 equiv of cyclohexanone. [b] 20 equiv of cyclohexanone. [c] 2.5 mol %. [d] 10 mol %. [e] Determined by ^{1}H NMR of the crude material. [f] Diastereomeric ratio, anti/syn. [g] Determined by HPLC. [h] 79 ppm of water. [i] 579 ppm of water. [j] 560 ppm of water.

The best conversion with resin **1** was achieved with trifluoroacetic acid (TFA) as an additive under neat conditions (entry 1).[14] In turn, the highest ee was recorded when water (no TFA) was used as the solvent (79% ee, entry 6), although conversion was significantly lower under these conditions. Quite interestingly, conversion increased to 66% by simply increasing the amount of cyclohexanone employed in the reaction (compare entries 6 and 7). It is thus strongly suggested that the role of TFA in these reactions is limited to facilitating the formation and hydrolysis of the intermediate enamine and that 2-triazolylmethylpyrrolidines do not behave as bifunctional catalysts.[15]

As already mentioned, resin **2** behaved as much more enantioselective in the considered process, and water (no TFA additive) turned out to be the solvent of choice for the reactions where it was used. In sharp contrast with what is

Table 2. Michael Addition of Ketones to Nitrostyrenes*



entry	product	% conv[a] (yield[b])	*syn:anti*[a]	% ee[c]
1	 12a	>99 (85)	95:5 100:0[d]	90 99.9[d]
2	 12b	>99 (84)	95:5	>99
3	 12c	>99 (83)	95:5	91
4	 12d	>99 (77)	93:7	94
5	 12e	>99 (84)	96:4	90
6	 12f	98 (78)	95:5	92
7	 12g	94 (76)	>99:1	95
8	 12h	>99 (81)	98:2	93
9	 12i	>99 (80)	90:10	79
10	 12j	98 (62)	94:6	85
11	 12k	91 (40[e])	-	26
12	 12l	>99 (64[f])	89:11	70

* All reactions performed with 0.25 mmol of the nitroolefin, 20 equiv of the ketone, 10 mol % of DiMePEG, and 10 mol % of catalyst **2** in 1 mL of water, at room temperature for 24 h. [a] Determined by ^{1}H NMR of the crude products. [b] Isolated yield. [c] Determined by HPLC. [d] After a single recrystallization. [e] 19% of the double addition product also observed. [f] 31% of attack by the primary carbon also observed.

(14) For a review, see: Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758.

(15) The configuration of the chiral center in the cyclohexanone ring of **9a** indicates that attack to β-nitrostyrene by the intermediate enamine takes place by the face opposite to the triazolylmethyl substituent.

observed with **1**, the use of organic solvents was deleterious for conversion with this resin (compare entries 1/10, 3/11, and 5/16).

The catalytic performance of resin **2** in water could be improved by addition of two different additives. On one hand, and in contrast with **1**, addition of TFA (2.5 mol %) led to increased catalytic activity without deterioration in enantioselectivity (compare entries 2 and 6 for **1**, and 8 and 12 for **2**). On the other hand, the use of DiMePEG as an additive in the reactions led to an even greater improvement both in conversion and in ee (entry 13). Those were in fact the conditions of choice for the reaction because the simultaneous use of both additives, TFA and DiMePEG (entry 14), did not lead to any synergistic effect. Results for the test reaction in water (entries 12−14) are particularly remarkable when compared with the corresponding ones in toluene (entries 15−17) because resin **2** swells in toluene but not in water.

When the structures of resins **1** and **2** are compared, the *p*-phenylene group present in the linker in resin **2** possesses increased size and hydrophobicity with respect to the corresponding linker in **1**. Hence, the presence in **2** of a single, small hydrophilic moiety (the pyrrolidine−triazole system) embedded in a vast hydrophobic domain (the polymer backbone and the linker) appears to be key to the high enantioselectivity shown by this resin in the presence of water.

This is the same phenomenon already observed for a PS-supported hydroxyproline catalyst[5] and suggests the presence of combined hydrophobic−hydrophilic effects that might stabilize the transition states leading to products, thus speeding up the reaction. We suggest that the combination of both effects might be a general activation mode in organocatalysis and particularly important with polymer-supported organocatalysts.

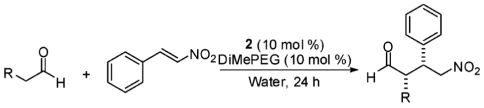
To establish the scope of the reaction with resin **2**, a series of substrates (nitroolefins and ketones) were tested under the optimized reaction conditions (Table 2).

β-Nitrostyrenes with different substitution patterns on the phenyl ring, including electron-releasing and electron-withdrawing groups, were tested as Michael acceptors. All the addition products where obtained in good yields and with excellent diastereo- and enantioselectivities, with no significant dependence on the electronic or steric properties of the substrate (entries 1 to 8). Recycling of the catalyst was tested with the reagent combination of entry 2. After three consecutive uses, no decrease was observed in the isolated yield of adduct **12b** or in the stereoselectivity parameters.

When major structural changes were introduced on the Michael acceptor (entry 9), a slight decrease was observed in diastereo- and enantioselectivity, whereas the reaction yield remained high. On the other hand, use of ketones other than cyclohexanones had a detrimental effect on the performance of the catalyst. Thus, the use of acetone as a Michael donor (entry 11) resulted in a dramatic drop in both yield and ee, a mixture of the single and double addition products being obtained. With 2-butanone (entry 12), in turn, a mixture of regioisomers was obtained. The regioisomer arising from the most substituted enamine could be isolated in 64% yield and with 70% ee.

The resin was also tested in the Michael addition of aldehydes to nitrostyrene (Scheme 2). High conversions and diastereoselectivities were obtained for linear aldehydes, although ee's were only moderate. A *β*-branched aldehyde such as isovarelaldehyde gave poor conversion and ee. Cyclohexanecarbaldehyde, in turn (α-branched), did not react at all.

Scheme 2. Michael Addition of Aldehydes to Nitrostyrene



R = Me[a]	> 99% conv. (81% yield)	96:4 *syn:anti*	62 % ee
R = Pr[b]	90% conv. (90% yield)	87:13 *syn:anti*	48 % ee

[a] At 4 °C. [b] At rt.

In summary, a highly efficient, polymer-supported organocatalyst for the highly diastereo- and enantioselective Michael addition of nitroolefins to ketones has been developed. This catalytic system, constructed through the use of *click chemistry*, represents the first insoluble mediator for this reaction and approaches the performance of referable, soluble catalysts for the same process. The exact role of water and the hydrophobic polymer backbone in the reaction is being studied, and results will be reported in due course.

Acknowledgment. We thank MEC (Grant CTQ2005-02193/BQU), DURSI (Grant 2005SGR225), Consolider Ingenio 2010 (Grant CSD2006-0003), and ICIQ Foundation for financial support. X.C.C. thanks MEC for a predoctoral fellowship. E.A. thanks ICIQ Foundation for a predoctoral fellowship.

Supporting Information Available: Experimental procedures and preparation and characterization of resins **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071366K

Supporting Information

Highly Enantioselective Michael Additions in Water Catalyzed by a PS-Supported Pyrrolidine

*Esther Alza, Xacobe C. Cambeiro, Ciril Jimeno and Miquel A. Pericàs.**

Institute of Chemical Research of Catalonia (ICIQ), Avda Països Catalans, 16, 43007, Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 080208, Barcelona, Spain.

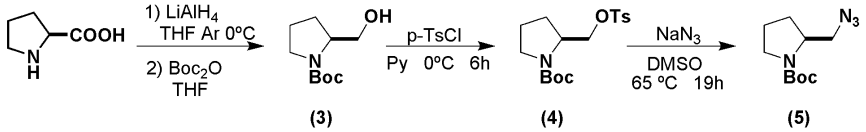
mapericas@iciq.es

General Information:

All commercial reagents were used as received, and all reactions were carried out directly under open air, unless otherwise stated. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer, at room temperature and in $CDCl_3$. TMS was used as internal standard for ^{1}H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded in a Tensor 27 Bruker FT-IR. Elemental analyses were performed in a Carlo Erba - ThermoQuest Model 1108. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak AD-H and IA columns (with AD-H pre-columns). Racemic standard products were prepared using DL-proline as catalyst in order to establish HPLC conditions. In cases when peak assignation was ambiguous, it was confirmed by the UV spectrum obtained using a diode array detector.

Synthesis of the immobilyzed catalysts:

Synthesis of *N*-Boc-2-azidomethylpyrrolidine



(3) (4) (5)

N-Boc-L-prolinol (3):

A modification of a reported procedure was used[1], avoiding isolation of the unstable L-prolinol: 12.9 g (322 mmol) of lithium aluminium hydride were placed in a Labmax 2 L automatic reactor, which had been previously flushed with nitrogen at 110 ºC and then cooled to 0 ºC. Then, 400 mL of dry THF were added and, after the temperature became stable again at 0 ºC, 25 g of L-proline (215 mmol) were introduced portionwise as a solid. The resulting mixture was stirred for one hour at 0 ºC and one more while warming it up to 25 ºC. After this time, 50 mL of 20% aqueous KOH solution were carefully added, and the mixture was filtered through celite and anhydrous sodium sulphate, under inert atmosphere.

The resulting colourless solution was diluted to 600 mL with additional dry THF and then a solution with 71.7 g (322 mmol) of Boc_2O in 150 mL of THF was added. The solution was stirred overnight at room temperature. Then, aqueous saturated $NaHCO_3$ solution was added. The layers were separated, the aqueous one was extracted with diethyl ether and the combined organic phases were washed with brine, dried with anhydrous sodium sulphate, filtered and concentrated under vacuum, yielding a clear oil.

The product was purified by flash chromathography through deactivated silica (2.5% Et_3N v/v) eluting with hexane-ethyl acetate mixtures. After removal of the solvents, 39.1 g of the title product were obtained as a white solid (overall yield: 91%).

All the spectroscopic data of the product matched those reported in the literature.[1]

^{1}H-NMR ($CDCl_3$, 400 MHz): d (ppm) 1.48 (s, 9H), 1.53 to 1.60 (1H), 1.73 to 1.90 (m, 2H), 1.98 to 2.06 (m, 1H), 3.29 to 3.35 (m, 1H), 3.44 to 3.49 (m, 1H), 3.57 to 3.67 (m, 2H), 3.89 to 3.98 (brm), 4.76 (brd, J = 5.8 Hz, 1H). **^{13}C-NMR** ($CDCl_3$, 100 MHz, PENDANT): d (ppm) 24.0 (CH_2), 28.4 (CH), 28.7 (CH_2), 47.5 (C), 60.2 (CH_3), 67.7 (CH_2), 80.2 (CH_2), 157.1 (C=O).

O-tosyl-*N*-Boc-prolinol[1] (4):

In a 25 mL round-bottom flask, *N*-Boc-L-prolinol **(3)** (606 mg, 3 mmol) was dissolved in 3 mL of pyridine, and cooled down to 0 ºC. Then, *p*-toluenesulfonyl chloride (696 mg, 3.6 mmol) was added and the mixture was stirred at 0 ºC for 6 h. After this time, the reaction mixture was diluted with 150 mL of diethyl ether and washed with 1M HCl, saturated $NaHCO_3$ and, finally, water. The organic layer was dried with sodium sulfate, filtered and concentrated under reduced pressure, yielding a colourless oil.

The crude product was purified by flash chromathography through deactivated silica (2.5% Et_3N v/v) eluting with hexane-ethyl acetate 3:1. After evaporation of the solvents, the title product was obtained as a colourless oil (704 mg, 66%).

All the spectroscopic data of the product matched with those reported in the literature.[1]

^{1}H-NMR (400 MHz, CDCl3): d (ppm) 1.37 (s, 9H), 1.84 (br, 4H), 2.44 (s, 3H), 3.28 (br, 2H), 3.93 (br, 2H), 7.33 (br, 2H), 7.76 (d, 2H, *J* = 8.18 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$, PENDANT): d (ppm) 21.9 (CH_2), 28.5 (CH_2), 47.1 (CH_3), 55.8 (CH_2), 69.9 (CH_3), 128.1 (CH_2), 130.0 (CH_2).

***N*-Boc-2-azidomethylpyrrolidine[1] (5):**

Tosylate **(4)** (703.5 mg, 1.9 mmol) was dissolved in DMSO (21 mL) and sodium azide (776 mg, 12 mmol) was added and the resulting mixture was heated to 65 ºC for 19 h. Then, it was allowed to cool to room temperature, diluted with diethyl ether (50 mL), washed with H_2O (3x30 mL) and brine (20 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the title product was obtained as a colourless oil. (355 mg, 80%). It was not further purified and was stored in the refrigerator until used.

All the spectroscopic data of the product matched with those reported in the literature.[1]

^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 373 K): δ (ppm) 1.49 (s, 9H), 1.77 (m, 2H), 1.88 (m, 1H), 2.01 (m, 1H), 3.25 (m, 1H), 3.37 (m, 2H), 3.49 (dd, 1H, *J* = 12.29, 6.42 Hz). **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$, DEPTQ-135, 373 K): d (ppm) 22.3 (CH_2), 27.6 (CH_3), 28.1 (CH_2), 45.9 (CH_2), 52.7 (CH_2), 55.7 (CH).

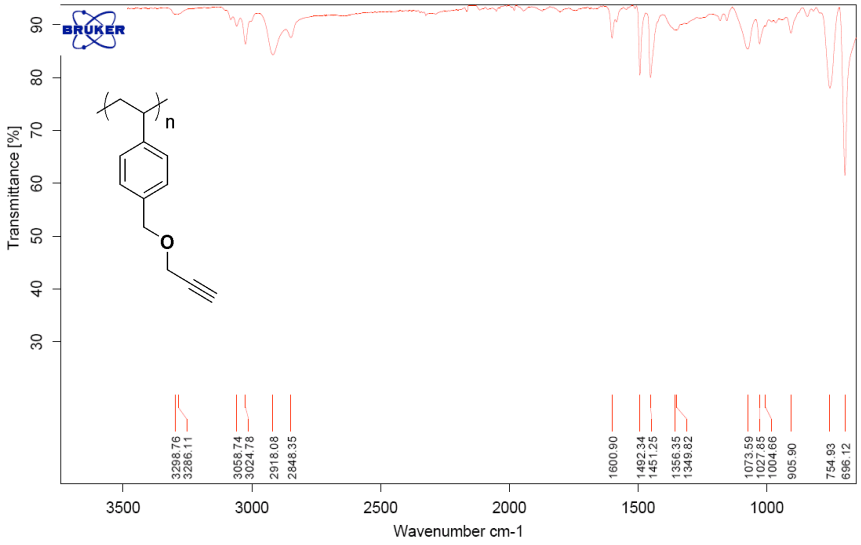
[(2-propyn-1-yl)-oxymethyl] polystyrene (6):

A solution of propargyl alcohol (0.24 mL, 4.0 mmol) in dry DMF (7 mL) was added *via canula* into a suspension of sodium hydride (163 mg, 4.1 mmol) in dry DMF (10 mL) at -20 ºC under N_2. The resulting mixture was stirred for 20 min and it was transferred onto a suspension of Merrifield resin (3 g, 1% DVB, f_o = 0.74 mmol/g) swelled with DMF (18 mL). The reaction mixture was shake at room temperature, while monitored by the appearance of the terminal alkyne signal in the ATR-FTIR spectrum, until it was judged to be complete (12 h).

After that, it was quenched with MeOH and the resin was washed sequentially with water (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250

mL) and THF again (250 mL). The solid was dried under vacuum for 24 h at 40 ºC.

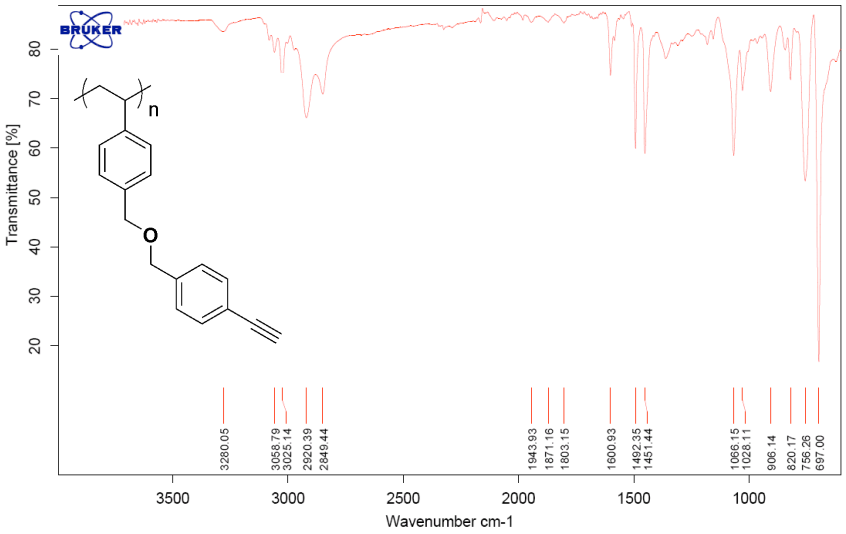
IR (ATR): ν = 3298 (≡C-H), 3058, 3024, 2918, 2848, 1600, 1492, 1451 cm^{-1}.



(4-ethynylbenzyloxymethyl)polystyrene (7):

The same procedure described for product **(6)** was followed, using 4-ethynylbenzyl alcohol (539.2 mg, 4.08 mmol) and Merrifield resin (3 g, 1% DVB, f_o = 0.74 mmol/g). The reaction was complete in 3 h.

IR (ATR) = 3280 (≡C-H), 3058, 3025, 2920, 2849, 1600, 1492, 1451 cm^{-1}.



1-(*N*-Boc-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-ylmethoxy polystyrene (8):

tert-Butyl-2-(azidomethyl)pyrrolidine-1-carboxylate **(5)** (150 mg, 0.66 mmol), *N,N*-diisopropylethylamine (1.2 mL, 6.6 mmol) and copper (I) iodide (6 mg, 0.03 mmol) were added to a suspension of propargylated resin **(6)** (650 mg, f = 0.788 mmol/g) in DMF:THF 1:1 (20 mL), and the mixture was shake at 40 ºC, while monitoring the disappearance of the IR-signal of the terminal alkyne. When it was complete (24h), the resin was isolated by filtration and washed sequencially with water (250 mL), DMF (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL), and then it was dried under vacuum for 24 hours at 40 ºC.

IR (ATR) = 3063, 3024, 2919, 2853, 1689 (C=O), 1596, 1489, 1447 cm^{-1}.

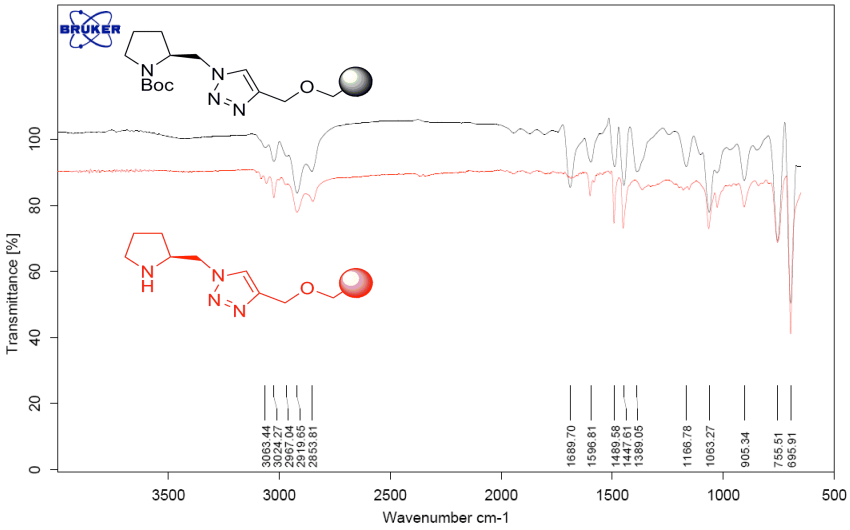
Elemental analysis (%) = N 2.35, C 87.32, H 7.90. $\boldsymbol{f}$ = 0.42 mmol/g.

1-(Pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-ylmethoxy polystyrene (1):

Trifluoroacetic acid (10 mL) was added on a suspension of resin **(8)** (0.7 g, *f* = 0.42 mmol/g) swelled with 5 mL of CH_2Cl_2 and the mixture was shake at room temperature, while monitoring the evolution of the deprotection by ATR-FTIR. After complete disappearance of the IR-signal corresponding to *tert*-butyl and carbonyl groups (2 h), the resin was filtered and washed sequentially with Et_3N solution (2% in THF, 200 mL), water (200 mL), THF (200 mL), THF-MeOH 1:1 (200 mL), MeOH (200 mL) and THF (200 mL). The solid was dried under vacuum for 24 hours at 40 ºC.

IR (ATR) = 3063, 3024, 2919, 2853, 1596, 1489, 1447 cm^{-1}.

Elemental analysis (%) = N 2.26, C 83.83, H 7.76. ***f*** = 0.404 mmol/g.



4-[1-(*N*-Boc-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl]phenylmethoxy polystyrene (9):

The same procedure described for product **(8)** was used, employing *tert*-Butyl-2-(azidomethyl)pyrrolidine-1-carboxylate **(5)** (250 mg, 1.1 mmol), *N,N*-diisopropylethylamine (2.5 mL, 14.5 mmol), copper (I) iodide (17 mg, 0.09 mmol) and (4-ethynylbenzyloxymethyl)polystyrene **(7)** (1.5 g, f = 0.69 mmol/g) in DMF:THF 1:1 (20 mL). The solid was dried under vacuum for 24 hours at 40 ºC.

IR (ATR) = 3025, 2972, 2921, 2850, 1686 (C=O), 1600, 1492, 1451 cm^{-1}.

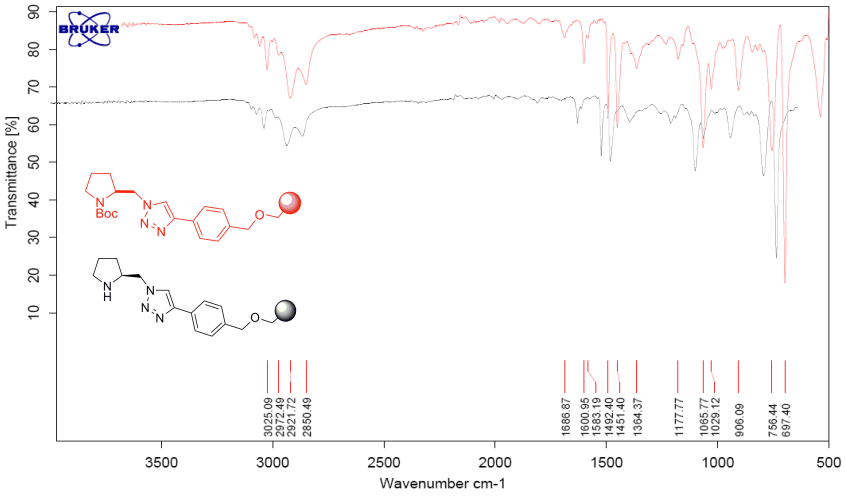
Elemental analysis (%) = N 2.60, C 85.29, H 7.55. $\boldsymbol{f}$ = 0.464 mmol/g.

4-[1-(*N*-Boc-pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl]phenylmethoxy polystyrene (2):

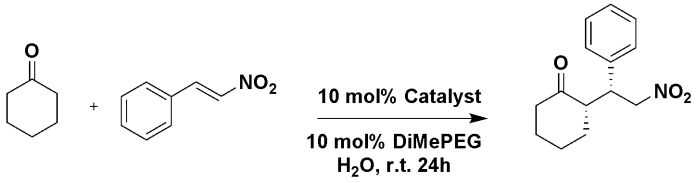
The same procedure described for product **(1)** was followed, employing resin **(9)** (1.665 g, f = 0.464 mmol/g) and trifluoroacetic acid (23 mL). The reaction was complete after 4 h.

IR (ATR) = 3025, 2972, 2921, 2850, 1686 (C=O), 1600, 1492, 1451 cm^{-1}.

Elemental analysis (%) = N 2.35, C 86.04, H 7.54. $\boldsymbol{f}$ = 0.42 mmol/g.



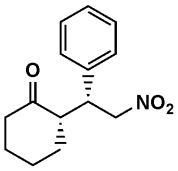
Typical procedure for the Michael reaction.



Trans-β-nitrostyrene (37 mg, 0.25 mmol), catalyst **2** (59.5 mg, 10 mol%) and DiMePEG (50 mg, 10 mol%) were mixed with cyclohexanone (0.52 mL, 5 mmol) and water (1 mL). The suspension was stirred at room temperature for 24 h and then directly filtered. The solid resin was washed with ethyl acetate and the organic filtrate was concentrated under reduced pressure. A ^{1}H-NMR spectrum was registered to calculate conversion (>99%) and diasteromeric ratio (syn/anti = 95:5), and the product was purified by flash chromatography on silica gel (EtOAc/Hexane) to afford the Michael adduct (52.5 mg, 85%) as a white solid. The enantiomeric excess was determined by HPLC on a chiral phase chiralpak AD-H column (90% ee).

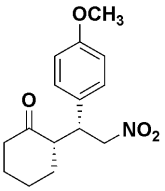
Spectroscopic and chromathographic data of the Michael adducts:

***(S)*-2-(*(R)*-2-nitro-1-phenylethyl)cyclohexanone[4] (12a):**



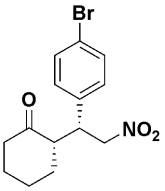
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.34-7.25 (m, 3H), 7.17 (d, 2H, *J* = 7.3 Hz), 4.94 (dd, 1H *J* = 12.4, 4.5 Hz), 4.64 (dd, 1H *J*= 12.3, 10 Hz), 3.76 (dt, 1H, *J* = 9.9, 4.4 Hz), 2.73-2.66 (m, 1H), 2.51-2.46 (m, 1H), 2.43-2.32 (m, 1H), 2.12-2.05 (m, 1H), 1.82-1.70 (m, 4H), 1.29-1.19 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak IA column (hexane-ethanol 90:10, 1 mL·min^{-1}, λ_{max} 206 nm): t_R = 11.9 min (minor, *syn*), 13.4 min (minor, *anti*), 18.9 min (major, *anti*), 19.9 min (major, *syn*).

***(S)*-2-(*(R)*-1-(4-methoxyphenyl)-2-nitroethyl)cyclohexanone[4] (12b):**



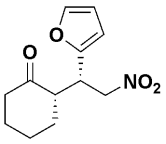
^{1}H NMR (400 MHz, CDCl3): d (ppm) 7.08 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 4.90 (dd, 1H, *J* = 12.2, 4.6 Hz), 4.58 (dd, 1H, *J* = 12.2, 9.7 Hz), 3.78 (s, 3H), 3.71 (dt, 1H, *J* = 9.8, 4.7 Hz), 2.68-2.61 (m, 1H), 2.50-2.44 (m, 1H), 2.41-2.34 (m, 1H), 2.10-2.04 (m, 1H), 1.81-1.56 (m, 4H), 1.28-1.18 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 975:25, 1 mL·min^{-1}, λ_{max} 203 and 224 nm): t_R = 31.2 min (major, *anti*), 32.3 min (minor, *syn*), 39.5 min (major, *syn*), 40.5 min (minor, *anti*).

***(S)*-2-(*(R)*-1-(4-bromophenyl)-2-nitroethyl)cyclohexanone[5] (12e):**



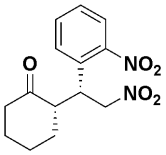
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.45 (d, 2H, *J* = 8.5 Hz), 7.05 (d, 2H, *J* = 8.5 Hz), 4.92 (dd, *J* = 12.6, 4.7 Hz, 1H), 4.60 (dd, *J* = 12.6, 10 Hz, 1H), 3.74 (dt, *J* = 9.8, 4.6 Hz, 1H), 2.68-2.61 (m, 1H), 2.50-2.45 (m, 1H), 2.41-2.32 (m, 1H), 2.12-2.06 (m, 1H), 1.83-1.78 (m, 1H), 1.75-1.56 (m, 3H), 1.28-1.17 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 90:10, 1 mL·min^{-1}, λ_{max} 204 and 218 nm): t_R = 12.7 min (minor, *syn*), 13.7 min (minor, *anti*), 16.3 min (major, *anti*), 20.5 min (major, *syn*).

***(S)*-2-(*(S)*-1-(furan-2-yl)-2-nitroethyl)cyclohexanone[4] (12i):**



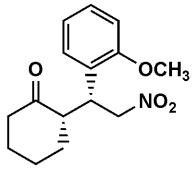
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.34 (d, 1H, *J* = 1.2 Hz), 6.28 (dd, 1H, *J* = 2.8, 2.1 Hz), 6.17 (br-dd, 1H), 4.78 (dd, 1H, *J* = 12.5, 4.8 Hz), 4.67 (dd, 1H, *J* = 12.5, 9.2 Hz), 3.97 (dt, 1H, *J* = 9.1, 4.7 Hz), 2.78-2.71 (m, 1H), 2.49-2.44 (m, 1H), 2.40-2.32 (m, 1H), 2.13-2.07 (m, 1H), 1.86-1.82 (m, 1H), 1.79-1.73 (m, 1H), 1.71-1.61 (m, 2H), 1.33-1.23 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 98:2, 1 $mL \cdot min^{-1}$, λ_{max} 210 nm): t_R = 22.1 min (minor, *anti*), 23.1 min (major, *syn*), 28.4 min (minor, *syn*), 29.4 min (major, *anti*).

***(S)*-2-(*(R)*-2-nitro-1-(2-nitrophenylethyl)cyclohexanone[5] (12h):**



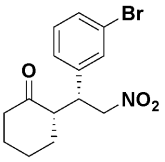
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.84 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.46-7.41 (m, 2H), 4.98-4.88 (m, 2H), 4.31 (dt, *J* = 4.2, 9.0 Hz, 1H), 2.97-2.91 (m, 1H), 2.50-2.45 (m, 1H), 2.42-2.31 (m, 1H) 2.14-2.08 (m, 1H), 1.85-1.61 (m, 5H). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane-ethanol 95:5, 1 $mL \cdot min^{-1}$, λ_{max} 208 nm), t_R = 28.9 min (minor, *syn*), 29.4 min (minor, *anti*), 24.2 min (major, *anti*), 43.2 min (major, *syn*).

***(S)*-2-(*(R)*-1-(2-methoxyphenyl)-2-nitroethyl)cyclohexanone[4] (12c):**



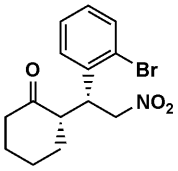
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.22 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.08 (dd, 1H, *J* = 7.3, 1.5 Hz), 6.90-6.85 (m, 2H), 4.86-4.77 (m, 2H), 3.95 (dt, 1H, *J* = 9.7, 5.3 Hz), 3.84 (s, 3H), 3.0-2.93 (m, 1H), 2.49-2.44 (m, 1H), 2.42-2.31 (m, 1H), 2.09-2.04 (m, 1H), 1.89-1.83 (m, 1H), 1.79-1.61 (m, 3H), 1.26-1.15 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane-ethanol 90:10, 1 $mL \cdot min^{-1}$, λ_{max} 206 and 280 nm): t_R = 7.2 min (major, *anti*), 7.9 min (minor, *anti*), 8.2 min (major, *syn*), 8.4 min (minor, *syn*).

***(S)*-2-(*(R)*-1-(3-bromophenyl)-2-nitroethyl)cyclohexanone [6] (12f):**



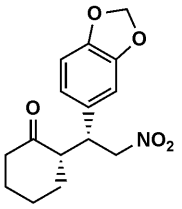
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.41 (d, 1H, *J* = 7.9 Hz), 7.33 (s, 1H), 7.20 (t, 1H, *J* = 7.8 Hz), 7.12 (d, 1H, *J* = 7.6 Hz), 4.93 (dd, 1H, *J* = 12.9, 4.4 Hz), 4.62 (dd, 1H, *J* = 12.6, 10 Hz), 3.77-3.71 (m, 1H), 2.69-2.62 (m, 1H), 2.51-2.46 (m, 1H), 2.42-2.32 (m, 1H), 2.13-2.07 (m, 1H), 1.76-1.57 (m, 4H), 1.30-1.20 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 98:2, 1 mL·min^{-1}, λ_{max} 204 nm): t_R = 22.4 min (minor, *anti*), 25.7 min (major, *anti*), 26.9 min (minor, *syn*), 29.0 min (major, *syn*).

***(S)*-2-(*(R)*-1-(2-bromophenyl)-2-nitroethyl)cyclohexanone[5] (12g):**



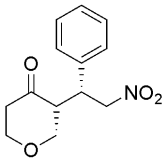
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.57 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.31-7.20 (m, 2H), 7.14-7.10 (m, 1H), 4.96-4.84 (m, 2H), 4.33-4.27 (m, 1H), 2.91 (m, 1H), 2.50 -2.45 (m, 1H), 2.42 -2.32 (m, 1H), 2.13-2.07 (m, 1H), 1.88-1.70 (m, 4H), 1.43 -1.32 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 98:2, 1 mL·min^{-1}, λ_{max} 206 nm): t_R = 21.3 min (minor, *anti*), 22.5 min (minor, *syn*), 27.2 min (major, *anti*), 38.5 min (major, *syn*).

***(S)*-2-(*(R)*-1-(benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)cyclohexanone[5] (12d):**



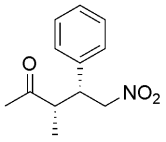
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 6.74 (d, 1H, *J* = 7.9 Hz), 6.65 (d, 1H, *J* = 1.8 Hz), 6.62 (dd, 1H, *J* = 7.9, 1.8 Hz), 5.95 (s, 2H), 4.90 (dd, 1H, *J* = 12.5, 4.5 Hz), 4.55 (dd, 1H, *J* = 12.5, 10.1 Hz), 3.71-3.66 (m, 1H), 2.64-2.57 (m, 1H), 2.50-2.44 (m, 1H), 2.41-2.32 (m, 1H), 2.12-2.04 (m, 1H), 1.83-1.59 (m, 4H), 1.30-1.19 (m, 1H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 95:5, 1 mL·min^{-1}, λ_{max} 208 nm): t_R = 26.8 min (major, *anti*), 28.0 min (minor, *syn*), 29.2 min (minor, *anti*), 33.2 min (major, *syn*).

***(R)*-tetrahydro-3-(*(R)*-2-nitro-1-phenylethyl)pyran-4-one[4] (12j):**

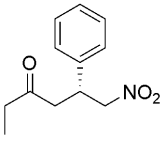


^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.25-7.28 (m, 3H), 7.18 (d, 2H, *J* = 7.3 Hz), 4.93 (dd, 1H, *J* = 12.7, 4.5 Hz), 4.64 (dd, 1H, *J* = 12.6, 10 Hz), 4.17 -4.11 (m, 1H) 3.86-3.74 (m, 2H), 3.69 (dd, 1H, *J* = 11.7, 5.0 Hz), 3.27 (dd, 1H, *J* = 11.4, 9.1 Hz), 2.91-2.84 (m, 1H), 2.70-2.63 (m, 1H), 2.56 (dt, 1H, *J*= 13.8, 4.0 Hz). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 95:5, 1 mL·min^{-1}, λ_{max} 206 nm): t_R = 26.3 min (minor, *anti*), 27.1 min (minor, *syn*), 31.1 min (major, *anti*), 56.5 min (major, *syn*).

***(3S,4R)*-3-methyl-5-nitro-4-phenylpentan-2-one[5] (12l):**

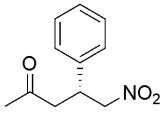


^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.35-7.28 (m, 3H), 7.18-7.15 (m, 2H), 4.68-4.60 (m, 2H), 3.68 (dt, 1H, *J* = 9.2, 5.1 Hz), 3.02-2.94 (m, 1H), 2.23 (s, 3H), 0.98 (d, 3H, *J* = 7.3 Hz). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 99:1, 1 mL·min^{-1}, λ_{max} 206 nm): t_R = 23.7 min (major, *anti*), 29.7 min (major, *syn*), 31.8 min (minor, *anti*), 38.7 min (minor, *syn*).

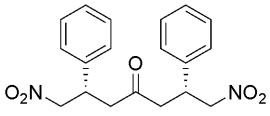


The known product of reaction by the less substituted carbon was also observed. Its spectroscopic data matched those previously described.[5].

***(R)*-5-nitro-4-phenylpentan-2-one[5] (12k)**

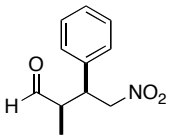


^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 7.35-7.12 (m, 5H), 4.72-4.59 (m, 2H), 4.04-3.94 (m, 1H), 2.92 (d, 2H, *J* = 7.0 Hz), 2.12 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane-IPA 90:10, 1 mL·min^{-1}, λ_{max} 206 nm): t_R = 9.6 min (minor), 10.3 min (major).



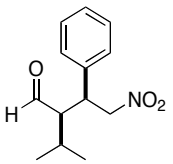
The known double addition product was also observed. Its spectroscopic data matched those previously described.[7] **^{1}H NMR** (400 MHz, $CDCl_3$): d (ppm) 7.33-7.26 (m. 3H), 7.23-7.20 (m, 2H), 4.74-4.54 (m, 2H), 4.08-3.98 (m, 1H), 2.88 (d, *J* = 7.2 Hz, 2H), 2.43-2.33 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H).

***(2S,3R)*-2-methyl-4-nitro-3-phenylbutanal[9] (12m)**



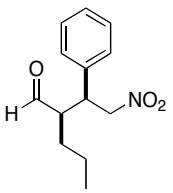
^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 9.71 (d, 1H, *J* = 1.8 Hz), 7.36-7.15 (m, 5H), 4.79 (dd, 1H, *J* = 12.8, 5.4 Hz), 4.67 (dd, 1H, *J* = 12.6, 9.4 Hz), 3.80 (td, 1H, *J* = 9.2, 5.7 Hz), 2.81-2.73 (m, 1H), 0.99 (d, 3H, *J* = 7.3 Hz). The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane-IPA 91:9, 1 mL·min^{-1}, λ_{max} 210 nm): t_R = 26.1 min (*anti*), 22.2 min (minor, *syn*), 28.6 min (*anti*), 31.5 min (major, *syn*).

***(2S,3R)*-2-isopropyl-4-nitro-3-phenylbutanal[10] (12n)**



^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 9.93 (d, 1H, *J* = 2.3 Hz), 7.37-7.18 (m, 5H), 4.67 (dd, 1H, *J* = 12.5, 4.5 Hz), 4.58 (dd, 1H, *J* = 12.6, 9.9 Hz), 3.89 (td, 1H, *J* = 10.3, 4.6 Hz), 2.79-2.75 (m, 1H), 1.09 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 6.7 Hz). The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane-IPA 97:3, 0.7 mL·min^{-1}, λ_{max} 220 nm): t_R = 25.6 min (*anti*), 30.5 min (major, *syn*), 32.3 min (minor, *syn*), 44.4 min (*anti*).

***(2S,3R)*-2-nitro-1-phenylethyl)pentanal[10] (12o)**



^{1}H NMR (400 MHz, $CDCl_3$): d (ppm) 9.72 (d, 1H, *J* = 2.6 Hz), 7.38-7.18 (m, 5H), 4.72 (dd, 1H, *J* = 13.1, 5.4 Hz), 4.66 (dd, 1H, *J* = 12.0, 10.0 Hz), 3.82-3.76 (m, 1H), 3.57-3.55 (m, 1H), 2.75-2.55 (m, 1H), 0.97-0.89 (m, 6H). The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane-IPA 90:10, 1 mL·min^{-1}, λ_{max} 220 nm): t_R = 13.8 min (*anti*), 16.3 min (minor, *syn*), 17.8 min (*anti*), 19.8 min (major, *syn*).

Recycling of catalyst 2 in the preparation of *(S)*-2-(*(R)*-1-(4-methoxyphenyl)-2-nitroethyl)cyclohexanone

All experiments were performed using the general method, with the resin recovered from the previous run and simply washed with water, MeOH, THF and dried before the reaction.

Cycle	Conv. (Yield) (%)	syn:anti	ee (%)
1	>99 (84)	95:5	>99
2	>99 (83)	94:6	>99
3	93 (83)	94:6	>99
4	92 (72)	94:6	>99

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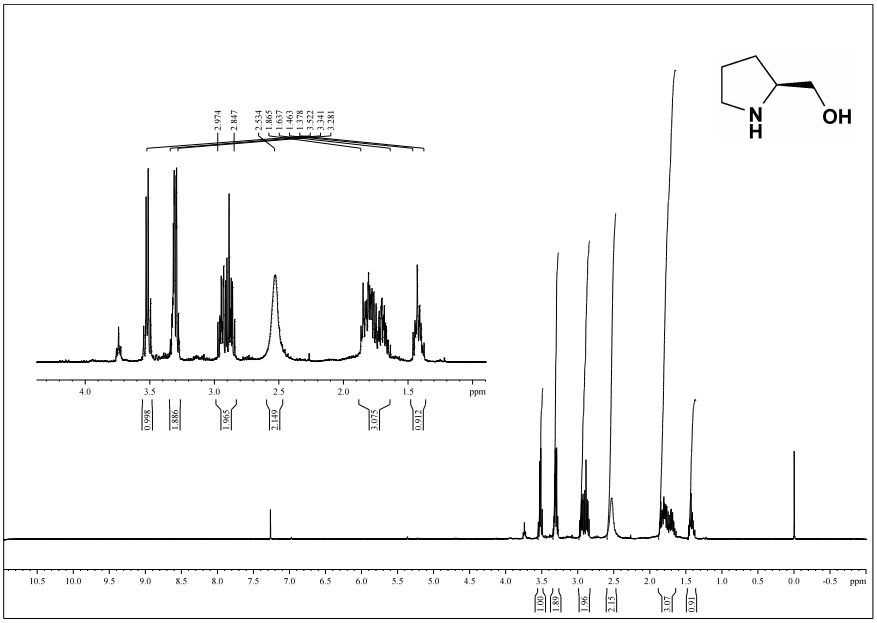
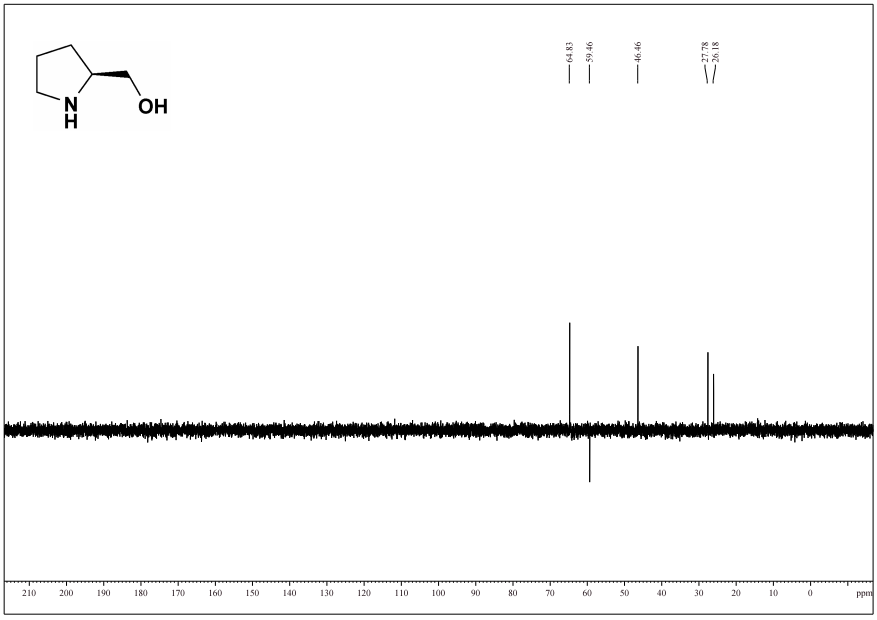
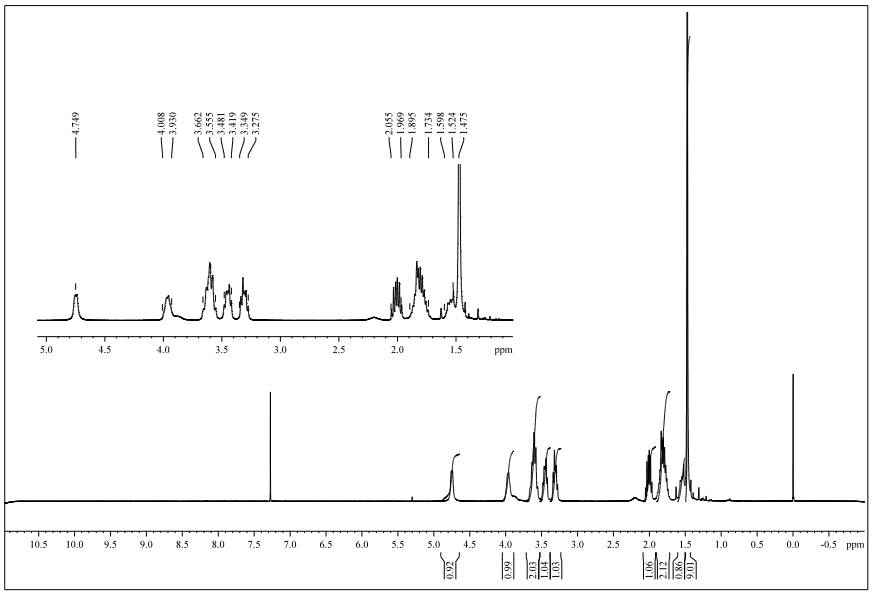


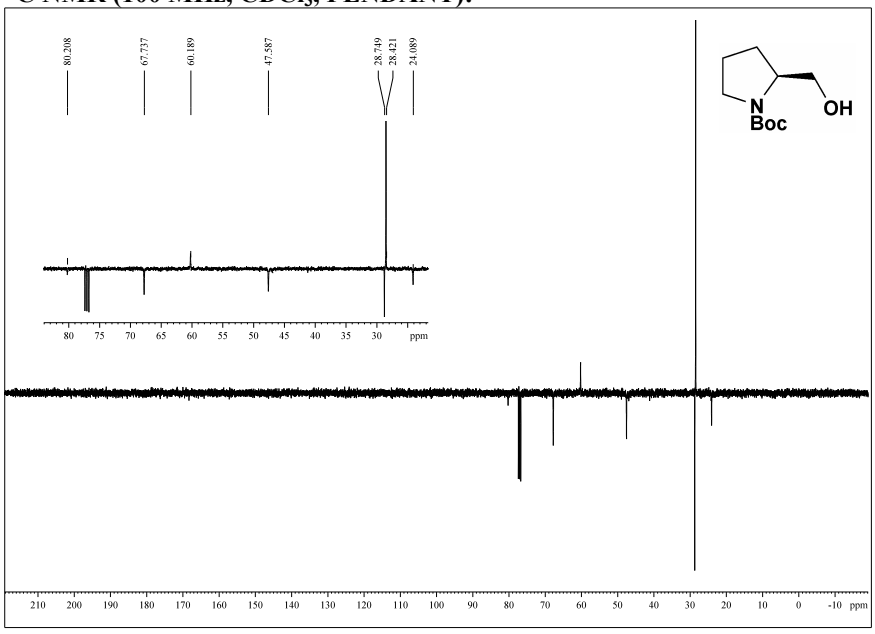
^{13}C NMR (100 MHz, $CDCl_3$, PENDANT):



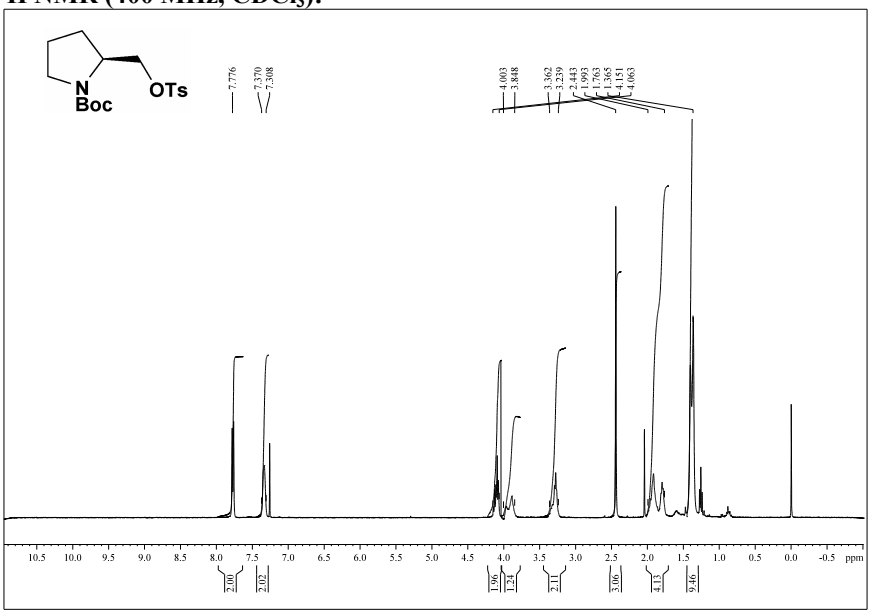
H NMR (400 MHz, $CDCl_3$):



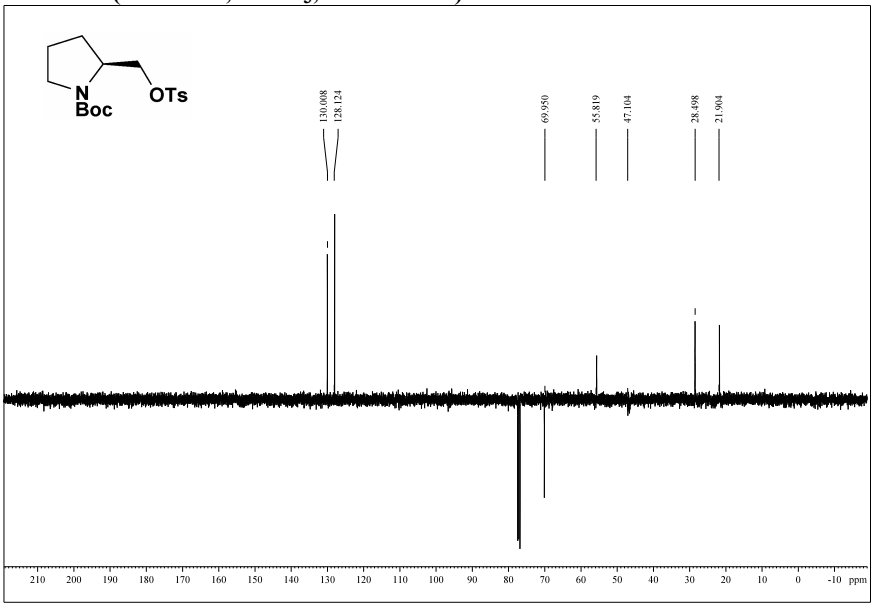
^{13}C NMR (100 MHz, $CDCl_3$, PENDANT):



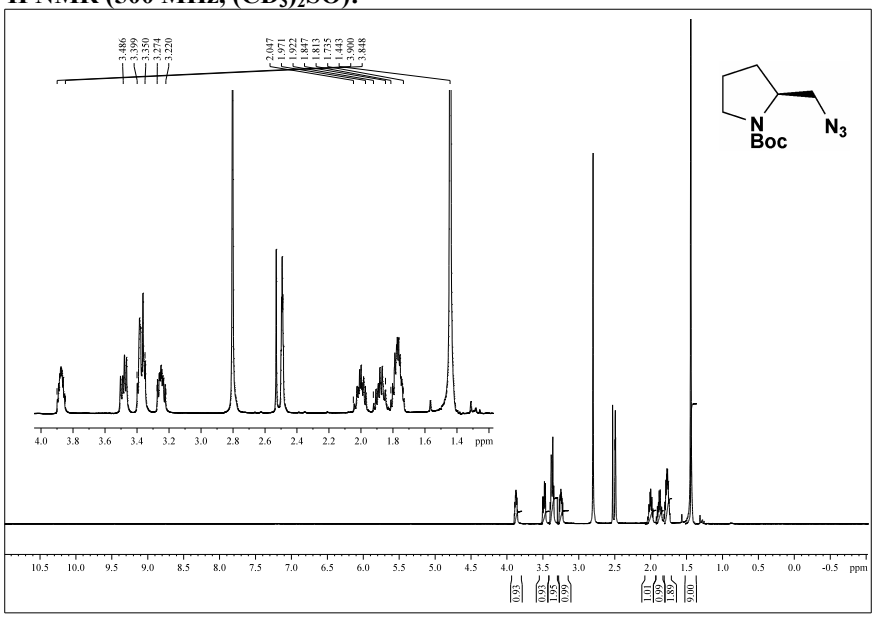
^{1}H NMR (400 MHz, $CDCl_3$):



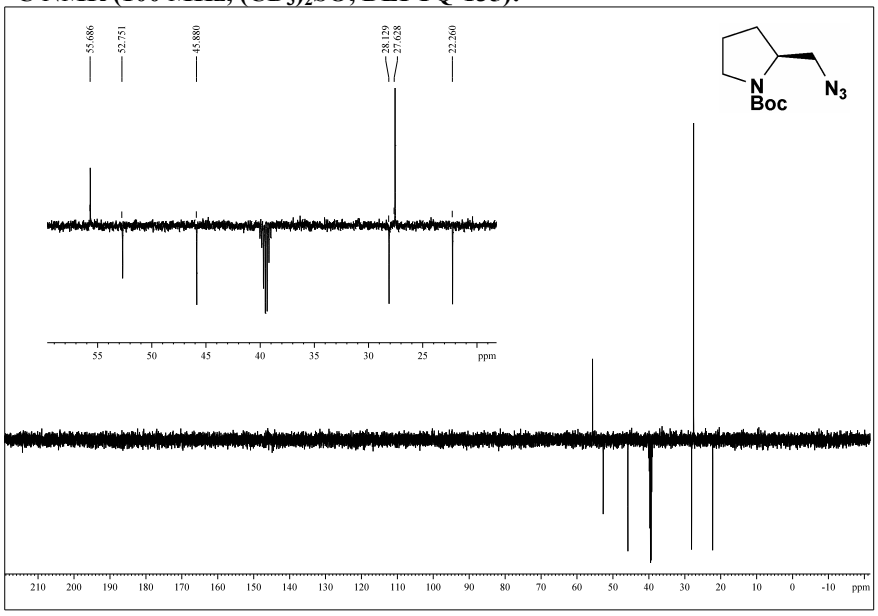
^{13}C NMR (100 MHz, $CDCl_3$, PENDANT):



^{1}H NMR (500 MHz, $(CD_3)_2SO$):



^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPTQ-135):

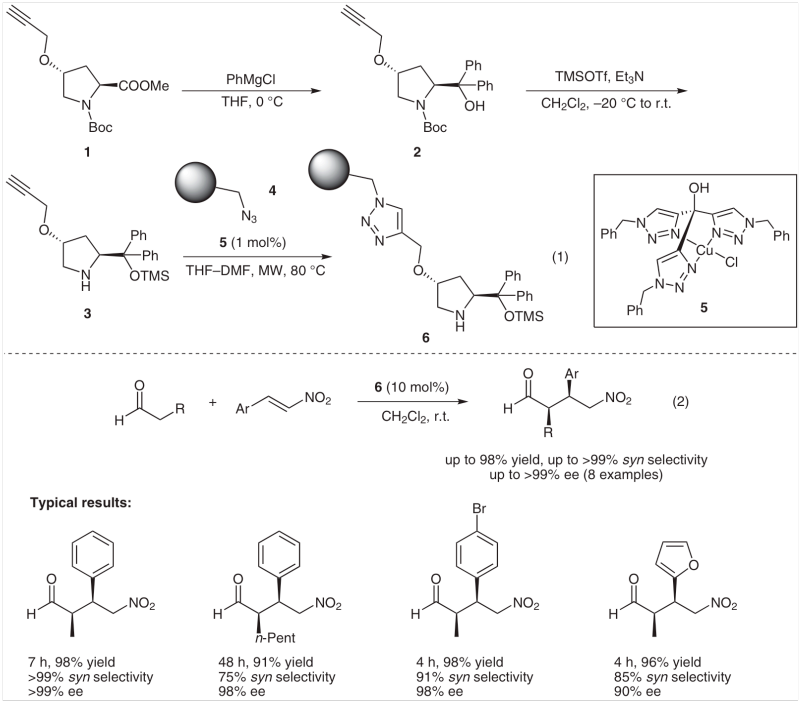


UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

E. ALZA, M. A. PERICÀS* (INSTITUTE OF CHEMICAL RESEARCH OF CATALONIA, TARRAGONA AND UNIVERSITAT DE BARCELONA, SPAIN)

A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior
Adv. Synth. Catal. **2009**, *351*, 3051-3056.

Michael Addition with a Polymer-Supported Organocatalyst



Significance: A polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**6**) was prepared from **1** via the Grignard alkylation, silylation with the concomitant carbamate deprotection, and the Huisgen 1,3-dipolar cycloaddition with azidomethylpolystyrene **4** (eq. 1). The polystyrene-supported organocatalyst **6** promoted the Michael addition of aldehydes to nitroolefins to give the corresponding adducts in up to 98% yield with up to >99% *syn* selectivity and up to >99% ee (8 examples, eq. 2).

Comment: The authors previously reported that the copper complex **5** efficiently catalyzed the Huisgen 1,3-dipolar cycloaddition (*Org. Lett.* **2009**, *11*, 4680). In the Michael addition of propanal to 4-bromo-β-nitrostyrene, the polystyrene-supported organocatalyst **6** was reused six times after recovery by simple filtration and reactivation with trimethylsilyl *N*,*N*-dimethylcarbamate (6th reuse run: 89% yield, 92% *syn* selectivity, 97% ee).

SYNFACTS Contributors: Yasuhiro Uozumi, Takao Osako
Synfacts 2010, 3, 0369-0369 Published online: 18.02.2010
DOI: 10.1055/s-0029-1219288; **Reg-No.:** Y01010SF

Category
Polymer-Supported Synthesis

Key words
polystyrenes
organocatalysis
Michael addition
nitroolefins

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

COMMUNICATIONS

DOI: 10.1002/adsc.200900817

A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior

Esther Alza[a] and Miquel A. Pericàs[a,b,*]

[a] Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain
Fax: (+34)-977-920-222; e-mail: mapericas@iciq.es
[b] Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

Received: September 29, 2009; Revised: November 24, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900817.

Abstract: A polymer-supported α,α-diarylprolinol silyl ether displays catalytic activity and enantioselectivity comparable to the best homogeneous catalysts in the Michael addition of aldehydes to nitroolefins. Above all, the combination of polymer backbone, triazole linker, and catalytic unit confers to it an unprecedented substrate selectivity in favor of linear, short-chain aldehydes.

Keywords: asymmetric catalysis; Michael addition; nitroolefins; organocatalysis; synthetic enzymes

The design and preparation of immobilized catalysts[1] that keep intact the characteristics (activity and selectivity) of their homogeneous counterparts represents a major goal in view of more efficient chemical production. When enantioselective processes are concerned,[1c] the opportunities offered by this approach (recovery and reuse of expensive catalytic species, highly simplified work-up, implementation of continuous flow processing) become even more evident.

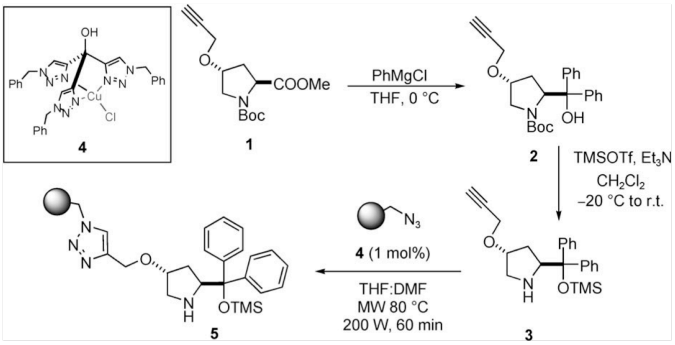
In a continued effort towards this goal, we have shown that a variety of organocatalytic processes can be most efficiently mediated by proline derivatives supported onto polystyrene resins through 1,2,3-triazole linkers.[2] Synergistic effects between polymer backbone, triazole linker and catalytic unit leading to very high catalytic activity and enantioselectivity have been observed.[2a,d] Most remarkably, the behavior of some of these catalytic resins is reminiscent of that of polypeptides with enzyme activity.[2d] The Michael addition of carbon nucleophiles to nitroolefins is a convenient entry to versatile synthetic intermediates.[3] The reaction has been widely used as the first step in cascade processes,[4] and the most successful enantioselective versions of it are based on organocatalytic approaches.[5] Among them, those mediated by enantiopure pyrrolidines bearing a bulky C-2 substituent have found wide application[6] and, in particular, (*S*)-α,α-diarylprolinol silyl ethers (Jørgensen–Hayashi catalysts) exhibit optimal performance for a variety of donors and acceptors.[7]

Herein we report the preparation of a polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**5**) displaying high catalytic activity and enantioselectivity in the Michael addition of aldehydes to nitroolefins with unprecedented, enzyme-like substrate selectivity.

The preparation of **5** from commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester *via* its propargyloxy derivative (**1**) is shown in Scheme 1 (see Supporting Information for details).

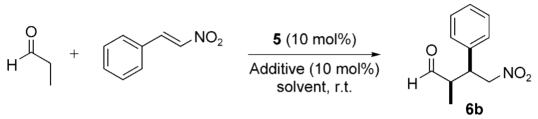
The silylation with concomitant carbamate deprotection of **2** leads to the key intermediate **3**, already containing the functional arrangement of the target catalyst. The immobilization of **3** onto azidomethylpolystyrene using click chemistry, in turn, posed an important synthetic challenge, since common catalysts for the cycloaddition were deactivated by the free amino group in the substrate. Gratifyingly enough, the recently developed tris(triazolyl)methanol-copper complex **4**[8] efficiently catalyzed the immobilization reaction, thus allowing the easy and highly reproducible synthesis of the catalytic resin **5**.

The Michael addition[9] of propanal to β-nitrostyrene was selected as a model for the evaluation of **5** and was studied under a variety of experimental conditions (Table 1). In the initial set of experiments (entries 1–4) a ten-fold excess of aldehyde donor was used, according to the usual practice in this organocatalytic process with homogeneous catalysts.[7b] Under these conditions, dichloromethane proved itself as the optimal solvent, reactions in it being faster and more stereoselective in the absence of additives (entry 2). Quite interestingly, the use of a much more conven-



Scheme 1. Synthesis of the polymer-supported organocatalyst **5**.

Table 1. Screening of reaction conditions for the Michael addition of propanal to (*E*)-β-nitrostyrene.[a]



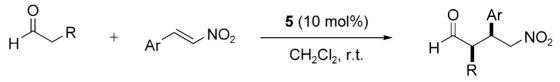
Entry	Solvent	Additive[b]	*t* [h]	Conversion [%][c]	*syn/anti*[c]	*ee* [%][d]
1[e]	hexane:THF	none	36	40	97:3	97
2[e]	CH_2Cl_2	none	7	>99	96:4	>99
3[e]	CH_2Cl_2	DMAP	24	>99	81:19	99
4[e]	CH_2Cl_2	PhCOOH	24	>99	77:23	97
5	CH_2Cl_2	none	7	>99	>99:1	>99
6	CH_2Cl_2	DMAP	23	>99	86:14	>99
7	CH_2Cl_2	PhCOOH	2	>99	87:13	99
8	H_2O	DiMePEG	24	97	96:4	99
9	CH_2Cl_2	TFA	48	none	–	–

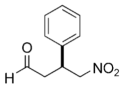
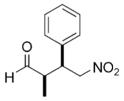
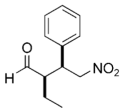
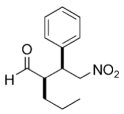
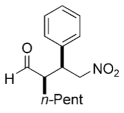
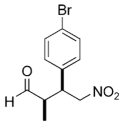
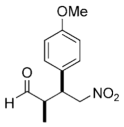
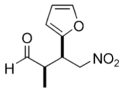
[a] All reactions performed with 0.2 mmol of (*E*)-β-nitrostyrene, 0.3 or 2.0 mmol of propanal, and 0.02 mmol of **5** in 1 mL of solvent at room temperature.
[b] 0.02 mmol.
[c] Determined by ^{1}H NMR of the reaction crude.
[d] Determined by chiral HPLC analysis.
[e] 2 mmol of propanal were used.

ient 1.5:1 propanal to β-nitrostyrene ratio (entries 5–9) led to cleaner reaction crudes (aldehyde self-aldol reaction was efficiently suppressed) with increased diastereoselectivity. The straightforward isolation of the Michael adducts in the absence of additives, simply involving catalyst separation by filtration and concentration of the reaction crude (entry 5), strongly favors these reaction conditions. On the other hand, it is worth noting that **5** is also able to induce a highly enantioselective Michael addition in water (entry 8), and this represents the first example of an insoluble catalyst successfully dealing with aldehydes in this solvent.[2c]

The scope of the Michael addition mediated by **5** was next investigated. The results of this study have been summarized in Table 2. As a general trend, diastereo- and enantioselectivities achieved with **5** compare well with those recorded with the most efficient homogeneous organocatalysts. Quite unexpectedly, the catalytic activity of resin **5** was remarkably dependent on the aldehyde donor. Thus, a fast reaction was observed for linear, short chain aldehydes like propanal and butanal (entries 2 and 3), while further increases in the chain length (entries 4 and 5) resulted in significant extension of reaction time. In all these cases, yield and enantioselectivity of the major *syn* adducts were excellent. Branching in the β position of the aldehyde (**6i** and **6j**, Figure 1) is deletereous for conversion, while α-branching (**6k**, Figure 1) completely blocks the reaction. Ketones like acetone and

Table 2. Scope of the Michael addition of aldehydes to nitroolefins catalyzed by **5**.[a]



Entry	Product		t [h]	Conversion[b] [%] (Yield [%])[c]	*syn/anti*[b]	*ee*[d] [%]
1		**6a**	72	50 (44)	–	96
2		**6b**	7	>99 (98)	>99:1	>99
3		**6c**	5	>99 (93)	90:10	>99
4		**6d**	27	>99 (98)	82:18	99
5		**6e**	48	99 (91)	75:25	98
6		**6f**	4	>99 (98)	91:9	98
7		**6g**	8	>99 (94)	89:11	99
8		**6h**	4	>99 (96)	85:15	90

[a] All reactions performed with 0.2 mmol of nitroolefin, 0.3 mmol of aldehyde, and 0.02 mmol of **5** in 1 mL of CH_2Cl_2 at room temperature.
[b] Determined by ^1H NMR of the reaction crude.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

cyclohexanone, in turn, are completely unreactive. With respect to Michael acceptors, nitroethylenes bearing β-aryl or hetaryl substituents with different electronic characters were studied, the corresponding *syn*-adducts being obtained in excellent yields and selectivities after short reaction times (Table 2, entries 6–8). Finally, resin **5** was also tested in the more demanding Michael addition of acetaldehyde to β-nitrostyrene (Table 2, entry 1), with results comparable to those reported in the literature for homogeneous

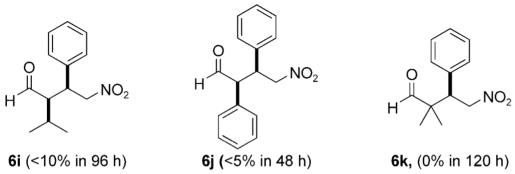
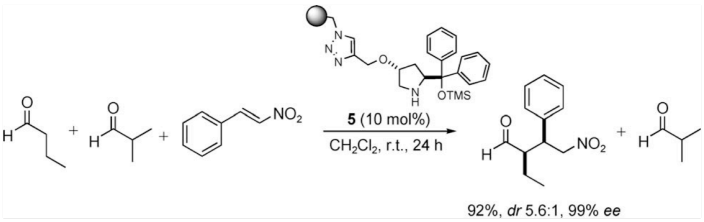


Figure 1. Michael adducts whose formation is not efficiently mediated by resin **5**.

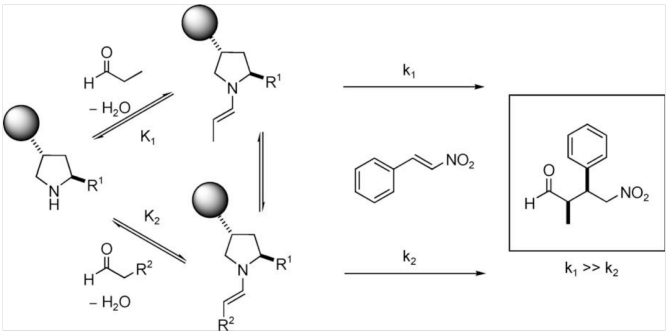
catalysts,[10] but using in the present case a much smaller excess of acetaldehyde and half catalyst loading.[10b]

In view of the high substrate selectivity exhibited by resin **5**, we envisaged a possible application in the discrimination between linear and α-branched aldehyde donors for Michael additions. To test this possibility, the 1.6:1 mixture of butanal and 2-methylpropanal obtained in the Rh-catalyzed hydroformylation of propene[11] was treated with β-nitrostyrene in the presence of **5** (**5**/β-nitrostyrene/butanal/2-methylpropanal: 0.1/1/2.4/1.5; see Scheme 2). Under these conditions, *only the linear aldehyde underwent Michael addition*. While the enantioselectivity of the reaction with butanal alone was preserved (99%, see Table 2, entry 3), the reaction time required for complete conversion (92% isolated yield) was substantially extended (24 *vs.* 5 h), and this suggested that unproductive enamines involving 2-methylpropanal can be formed during the reaction. The suggestion that substrate selectivity in reactions mediated by **5** finds its origin in the different reactivity of equilibrating enamine intermediates is reinforced by the results of an experiment where an equimolar mixture of pentanal and cyclohexanone is treated with β-nitrostyrene (see Supporting Information for details). As anticipated, cyclohexanone did not participate in the addition process, but its presence in the reaction media extended the required time for complete conversion from 27 h to 55 h. When the cyclohexanone:pentanal ratio was changed to 13:1, the reaction time increased to 7 days.

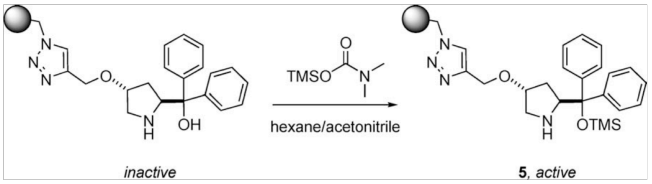
We have summarized in Scheme 3 our interpretation on the origin of the selectivity in the reactions mediated by resin **5**. First, the observed *syn* selectivity and the sign of enantioselection are indicative of the intermediacy of conformationally biased enamines, with the bulky R^1 substituent on the pyrrolidine blocking one of the enamine faces. With respect to substrate selectivity, the retardant effect of bulky aldehydes (or ketones) is strongly indicative of the participation of these reagents in the reversible forma-



Scheme 2. Selective Michael addition of butanal to β-nitrostyrene in the presence of 2-methylpropanal catalyzed by **5**.



Scheme 3. Origin of the substrate-selectivity in the Michael addition of aldehydes to β-nitrostyrene catalyzed by **5**.



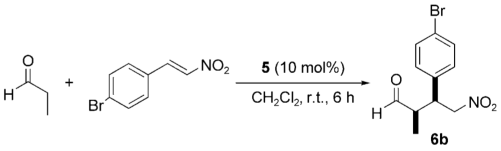
Scheme 4. Reconditioning conditions for supported organocatalyst **5.**

tion of unreactive enamine intermediates. The reason why even very similar enamines based on resin **5** could exhibit so strikingly different reactivities in front of β-nitrostyrene must result from the topology of the reaction cavity defined by the combination of polymer backbone, triazole linker, and catalytic unit. Thus, the enzyme-like selectivity exhibited by **5** would obey to restrictions in the achievement of the required transition state geometry for C–C bond formation whenever a *bulky* aldehyde is involved in the formation of the putative enamine intermediate.

As already mentioned, one of the main advantages associated to heterogenized catalysts is the possibility of its easy recovery and reuse. While recovery can be easily achieved by simple filtration when insoluble polymers are employed, the possibility of catalyst reuse is normally limited by deactivation processes. In the case of α,α-diarylprolinol silyl ethers, deactivation is triggered by hydrolysis of the labile silyl ether.[9r] More precisely, we have observed that a resin analogous to **5**, but bearing free hydroxy substituents instead of trimethylsilyl ethers is completely inactive in the considered Michael reactions. We accordingly devoted some effort to the development of a simple procedure for *error correction* on resin **5**. After testing a variety of silylating agents, we found that a brief treatment of an inactive diphenylprolinol-type resin with trimethylsilyl *N,N*-dimethylcarbamate[12] in hexane/acetonitrile leads to the selective protection of the hydroxy groups with full recovery of catalytic activity (Scheme 4). From a practical point of view, the re-conditioning process leaves dimethylamine as the only by-product, so that the resin can be immediately reused after washing out any excess of silylating agent. In practice, the intercalation of catalytic and re-conditioning cycles leads to complete preservation of the catalytic activity and stereoselectivity, thus allowing effective reuse over six consecutive runs (Table 3).

In summary, a highly efficient, polymer-supported organocatalyst for Michael additions of aldehydes to nitroolefins (**5**) has been prepared. Besides very high catalytic activity and enantioselectivity, comparable to those depicted by the best homogeneous catalysts in the same process, **5** displays unprecedented substrate selectivity that allows, in practice, inducing the completely selective reaction of a linear aldehyde in the presence of its α-branched regioisomer. Extension of the use of **5** to tandem processes is currently underway in our laboratories.

Table 3. Recycling experiments of catalyst **5** in the Michael addition of propanal to 4-bromo-β-nitrostyrene.[a]



Cycle	Conversion[b] [%] (Yield [%])[c]	*syn:anti*[b]	*ee* [%][d]
1	>99 (98)	93:7	99
2	>99 (96)	93:7	99
3	98 (96)	92:8	97
4	96 (94)	92:8	97
5	94 (92)	93:7	98
6	91 (89)	92:8	97

[a] All the experiments were performed using the general method with the resin recovered from the previous run and reconditioned before its use with trimethylsilyl *N,N*-dimethylcarbamate in 0.1 M hexane solution.
[b] Determined by ^{1}H NMR of the reaction crude.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

Experimental Section

Typical Experimental Procedure

Propionaldehyde (22 μL, 0.3 mmol) was added to a mixture of *trans*-β-nitrostyrene (30 mg, 0.2 mmol) and **5** (46 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The suspension was stirred for 7 h and then directly filtered off. The solid resin was washed with CH_2Cl_2 and the organic filtrate was concentrated under reduced pressure. The Michael adduct **6b** was obtained without further purification as a clear oil; yield: 40.2 mg (98%); *syn/anti* 99:1 (by ^{1}H NMR spectroscopy), 99% *ee* by HPLC on a chiral phase (Chiralpak IC column, λ = 214 nm, ethanol/hexane 95:5, 0.8 mL min^{-1}): t_R = 30.7 min (minor, *syn*), 36.8 min (major, *syn*).

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Supporting Information

A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior

*Esther Alza and Miquel A. Pericàs**

Institute of Chemical Research of Catalonia (ICIQ), Avda Països Catalans, 16, 43007, Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 080208, Barcelona, Spain.

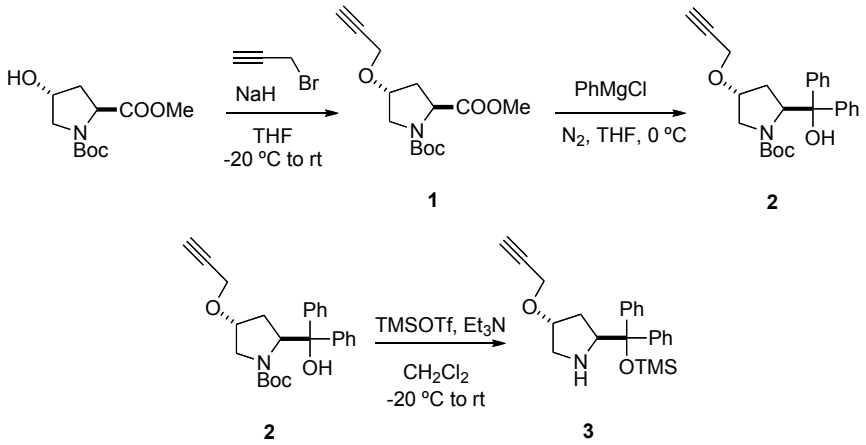
mapericas@iciq.es

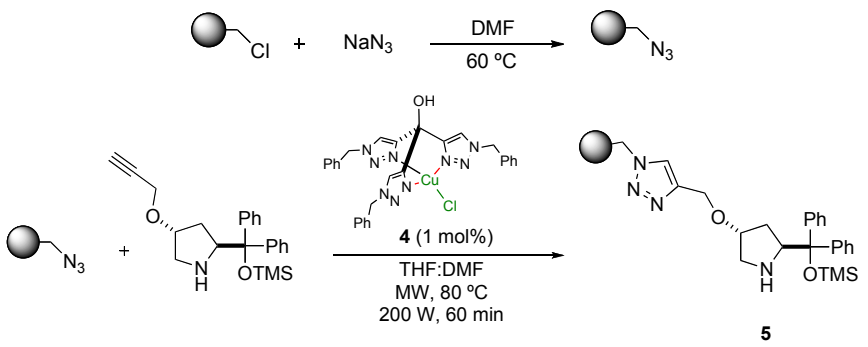
General Methods:

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol Cl g–1 resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns.

NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz (^1H) and 100.63 MHz ($^{13}C\{1H\}$). TMS was used as internal standard for ^1H-NMR and CDCl3 for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses (C; H; N) were performed in a Carlo Erba - ThermoQuest Model 1108 by Servei de Microanalisi, Consell Superior d'Investigacions Científiques, Barcelona, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak AD-H, IC and IA columns using guard columns. Racemic standard products were prepared using DL-proline as catalyst in order to establish HPLC conditions.

Synthesis of the immobilized catalysts:





(2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-(prop-2-ynyloxy) pyrrolidine-1,2-dicarboxylate[1] (1)

A solution of *N*-Boc-*trans*-4-hydroxy-*L*-proline methyl ester (2 g, 7.9 mmol) in anhydrous THF (20 mL) was added *via canula* to a suspension of sodium hydride (475 mg, 11.8 mmol) in anhydrous THF (35 mL) at -20 ºC under N_2. The resulting mixture was stirred for 20 min and then a solution of propargyl bromide (1.3 mL, 11.8 mmol) in THF was added. The reaction mixture was stirred at -20 ºC for 1 h and then was allowed to reach room temperature and stirred overnight. After the reaction was completed, 10 mL of MeOH were added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude was purified by flash chromathography through deactivated silica (2.5% Et_3N v/v) eluting with hexanes-ethyl acetate 2:1. After evaporation of the solvents, the title product was obtained as an orange oil (1.8 g, 80% yield).

^{1}H-NMR ($CDCl_3$): *d* = 1.44 (s, 9H), 2.04 - 2.12 (m, 1H), 2.24 - 2.46 (m, 2H), 3.47 - 3.65 (m, 2H), 3.68 - 3.74 (brs, 3H), 4.11 - 4.17 (m, 2H), 4.28 - 4.45 (m, 2H). **^{13}C-NMR** ($CDCl_3$, 328 K): *d* = 28.4 (CH_3), 36.6 (CH_2), 51.3 (CH_2), 52.0 (CH_3), 56.5 (CH_2), 57.8 (CH), 74.8 (CH), 75.9 (CH), 79.4 (C), 80.1 (C), 153.8

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(C=O), 173.4 (C=O).
HRMS (ESI+): *m/z* = 306.1306, calcd. for $C_{14}H_{21}NO_5Na$ $[M+Na]^+$: 306.1317.
$[\alpha]_D^{27}$ = -7.1 (*c* 0.997 in CH_2Cl_2)

(2*S*,4*R*)-*tert*-butyl 2-(hydroxydiphenylmethyl)-4-(prop-2-ynyloxy) pyrrolidine-1-carboxylate (2)
To a solution of **(1)** (1.3 g, 4.6 mmol) in 20 mL of anhydrous THF was added dropwise by an addition funnel a solution of phenyl magnesium chloride 2M in THF (11.5 mL, 22.9 mmol) at 0 ºC under argon atmosphere and drop wise by addition funnel. After the addition was completed, the reaction mixture was stirred for 6 h and then was quenched with 10 mL of saturated aqueous solution of NH_4Cl. The resulting solution was diluted with Et_2O (150 mL) and the organic layer was washed with a saturated aqueous solution of NH_4Cl. (80 mL x 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure, yielding a colourless oil. The crude product was purified by flash chromathography through deactivated silica (2.5% Et_3N v/v) eluting with hexanes-ethyl acetate 2:1. The title product was obtained after the evaporation of the solvents as a colorless oil (704 mg, 66% yield).

^{1}H-NMR ($CDCl_3$): mixture of rotamers: *d* = 1.28 (s, 9H), 1.94 - 2.15 (m, 2H), 2.28 -2.38 (m, 1H), 2.91 (br, OH), 3.56 (br, 2H), 3.96 – 4.30 (3H), 4.93 - 5.03 (1H), 7.15 - 7.57 (m, 10H). **^{13}C-NMR** ($CDCl_3$, 328 K): mixture of rotamers: *d* = 28.2, 28.5, 35.9, 36.5, 53.1, 53.2, 56.3, 57.1, 65.3, 65.4, 74.5, 75.2, 76.7, 79.1, 79.8, 80.2, 80.9, 81.2, 81.8, 126.9 - 128.1, 143.8, 145.4, 145.9, 157.3
HRMS (ESI+): *m/z* = 430.1981, calcd. for $C_{25}H_{29}NO_4Na$ $[M+Na]^+$: 430.1994
$[\alpha]_D^{27}$ = -44.1 (*c* 0.992 in CH_2Cl_2).

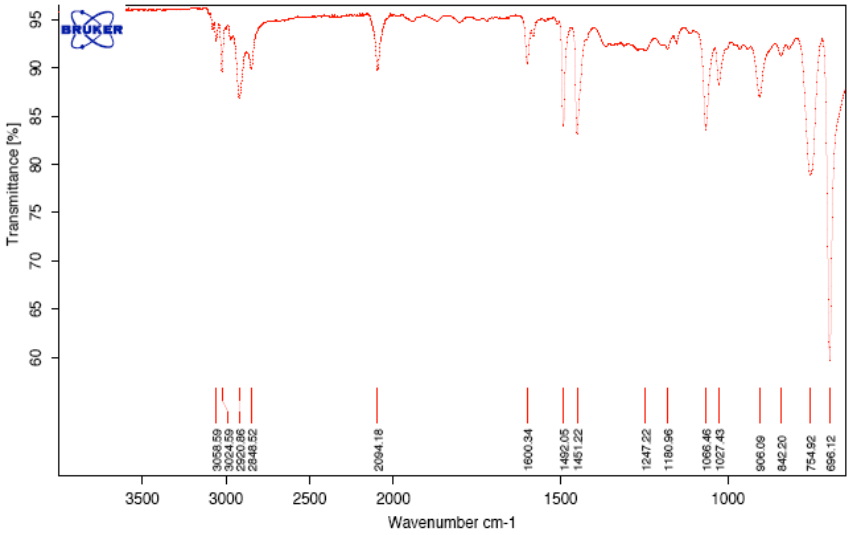
(2*S*,4*R*)-2-(diphenyl(trimethylsilyloxy)methyl)-4-(prop-2-ynyloxy)pyrrolidine (3)
To a solution of **(2)** (460.3mg, 1.13 mmol) in 25 mL of CH_2Cl_2 at -20 ºC was added triethylamine (0.31 mL, 2.15 mmol) and trimethylsilyl trifluoromethanesulfonate (0.39 mL, 2.15 mmol). The solution was then allowed to reach 0 ºC and was stirred for 3 h at this temperature. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash

chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford the desired product as a pale yellow oil (288.4 mg, 68% yield).

^{1}H-NMR ($CDCl_3$): d = -0.11 (s, 9H), 1.67 - 1.70 (m, 2H), 1.74 (br, NH), 2.36 (t, J = 2.39 Hz, 1H), 2.79 (dd, J = 11.82, 4.85 Hz, 1H), 2.95 (dd, J = 11.82, 2.42 Hz, 1H), 3.91 to 3.95 (m, 1H), 4.05 (dd, J = 2.35, 1.23 Hz, 2H), 4.32 (t, J = 7.94 Hz, 1H), 7.18 - 7.47 (m, 10H). **^{13}C-NMR** ($CDCl_3$): d = 2.3 (CH_3), 34.2 (CH_2), 52.8 (CH_2), 56.2 (CH_2), 63.7 (CH), 74.1 (CH), 79.4 (CH), 80.2 (C), 83.0 (C), 127.0 - 128.6 (CH, Ar), 145.5 (C, Ar), 146.8 (C, Ar).
HRMS (ESI+): m/z = 380.2036, calcd. for $C_{23}H_{30}NO_2Si$ 380.2046 $[M+H]^+$.
$[\alpha]_D^{27}$ = -56.5 (c 0.996 in CH_2Cl_2).

(Azidomethyl)polystyrene[2]
Sodium azide (0.83 g, 54 mmol) was added to a suspension of 4 g of (Chloromethyl)polystyrene (f = 0.53 mmol g^{-1}) in 40 mL of DMF. The mixture was shaken (orbital shaker) at 60 ºC for 19 h. After cooling, the suspension was filtered and the resin was sequentially washed with water (500 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried in vacuo for 24 h at 40 ºC.
IR (ATR): n = 2094.18 cm^{-1}
A 98% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.21; found: N 2.17, C 89.45, H 7.74; f = 0.517 mmol g^{-1}.

[2] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653.



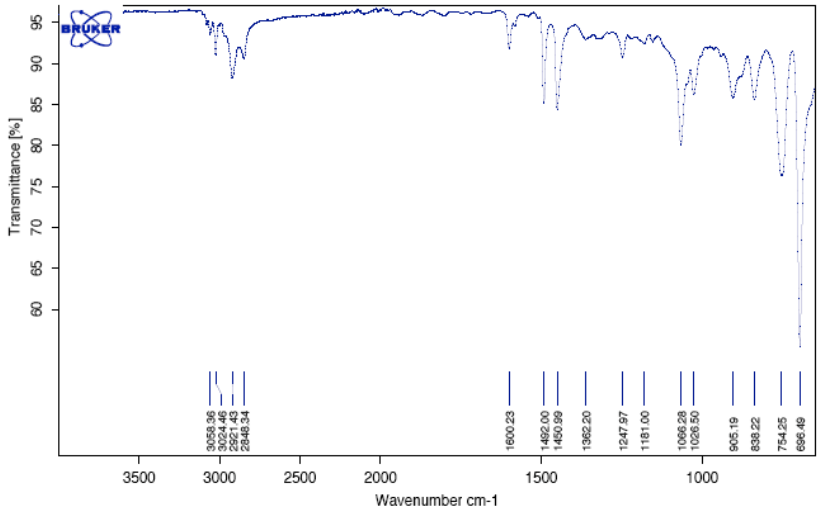
4-(((3*R*,5*S*)-5-(diphenyl(trimethylsilyloxy)methyl)pyrrolidin-3-yloxy)methyl)-1H-1,2,3-triazolmethyl polystyrene (5)

Pyrrolidine derivative **3** (118 mg, 0.31 mmol), resin **4** (500 mg), 3 mL of DMF, 3 mL of THF and tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst (1.6 mg, 0.0026 mmol, 1 mol%) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC (setting temperature) for 50 min under microwave irradiation of 200 W without stirring.

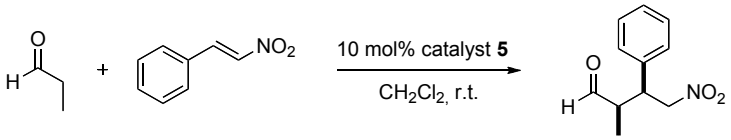
After the cycloaddition reaction was complete, the resin was filtered and washed with CH_2Cl_2 (100 mL) and THF (100 mL) and was dried in vacuo at 40 ºC .

IR (ATR): *n* = 3058.36, 2848.34, 1600.23, 1492.00, 1450.99, 1247.97, 1066.28 cm^{-1}

A 99% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.43; found: N 2.42, C 85.52, H 7.68; f = 0.432 mmol g^{-1}.



Typical procedure for the Michael reaction

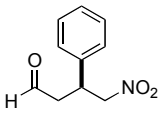


Trans-b-nitrostyrene (30 mg, 0.2 mmol) and catalyst **5** (46.1 mg, 10 mol%) were mixed with propionaldehyde (22 mL, 0.3 mmol) in CH_2Cl_2 (1.0 mL). The suspension was stirred at room temperature for 7 h and then directly filtered. The solid resin was washed with CH_2Cl_2 and the organic filtrate was concentrated under reduced pressure. A ^{1}H-NMR spectrum was registered to calculate conversion and diasteromeric ratio and in this case, the product was obtained without further purification due to the volatility of the aldehyde. When the purification was required it was done by flash chromatography on silica gel (EtOAc/Hexanes) to afford the Michael adduct. The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak IC column and IC guard column).

Physical and spectroscopical data of the Michael products:

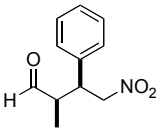
All the products are known and all the spectroscopic data matched those reported in the literature.

(*S*)-4-Nitro-3-phenylbutanal[3] (6a):



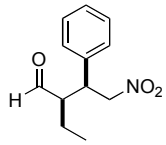
Title compound was prepared from *trans*-β-nitrostyrene and acetaldehyde according to General Procedure. The enantiomeric excess was determined by GLC with a Supelco Chiraldex G-TA column (100 to 170 °C, 1 ºC /min gradient, 1.5 mL/min): tR = 64.2 min (minor), 67.8 min (major)

(2*R*, 3*S*)-2-Methyl-4-nitro-3-phenylbutanal[4] (6b):



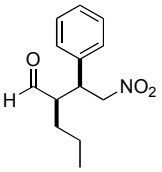
Title compound was prepared from *trans*-β-nitrostyrene and propionaldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an IC column (hexanes-ethanol 95:5, 0.8 mL·min^{-1}, 214 nm): tR = 30.7 min (minor, *syn*), 36.8 min (major, *syn*).

(2*R*, 3*S*)-2-Ethyl-4-nitro-3-phenylbutanal[4] (6c):



Title compound was prepared from *trans*-β-nitrostyrene and butanal according to General Procedure. The enantiomeric excess was determined by HPLC with an IA column (hexanes-IPA 99:1, 0.5 mL·min^{-1}, 214 nm): tR = 41.1 min (major, *syn*), 55.1 min (minor, *syn*), 44.8 min (major, *anti*), 50.4 (minor, *anti*).

(2*R*)-((*S*)-2-Nitro-1-phenylethyl)-pentanal[4] (6d):



Title compound was prepared from *trans*-β-nitrostyrene and valeraldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an IA column (hexanes-ethanol 95:5, 0.8 mL·min^{-1}, 214 nm): tR = 21.5 min (minor, *syn*), 23.1 min (major, *syn*), 15.7 min (minor, *anti*), 19.7 (major, *anti*).

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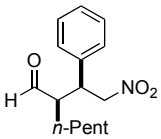
[3] Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800; *Angew. Chem. Int. Ed.* **2008**, *46*, 4722.

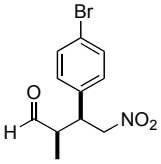
[4] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

(2*R*)-((*S*)-2-Nitro-1-phenylethyl)-heptanal[5] (6e):



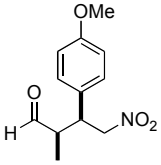
Title compound was prepared from *trans*-β-nitrostyrene and heptaldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an IA column (hexanes-IPA 99:1, 0.75 mL·min^{-1}, 254 nm): tR = 18.3 min (major, *syn*), 20.1 min (minor, *syn*), 22.6 min (minor, *anti*), 23.6 (major, *anti*).

(2*R*, 3*S*)-(4-Bromophenyl)-2-methyl-4-nitrobutyraldehyde[4] (6f):



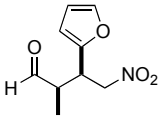
Title compound was prepared from *trans*-4-bromo-b-nitrostyrene and propionaldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an AD-H column (hexanes-IPA 99:1, 1 mL·min^{-1}, 240 nm): tR = 25.8 min (major, *syn*), 36.1 min (minor, *syn*), 31.1 min (major, *anti*), 34.1 (minor, *anti*).

(2*R*, 3*S*)-2-Methyl-4-nitro-3-(4-methoxyphenyl)-butanal[4] (6g):



Title compound was prepared from *trans*-4-methoxy-b-nitrostyrene and propionaldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an IC column (hexanes-ethanol 80:20, 1 mL·min^{-1}, 254 nm): tR = 11.3 min (major, *syn*), 12.7 min (minor, *syn*), 9.2 min (major, *anti*), 13.3 (minor, *anti*).

(2*R*, 3*S*)-3-Furyl-2-methyl-4-nitrobutyraldehyde[4] (6h):



Title compound was prepared from 2-(2-nitrovinyl)-furan and propionaldehyde according to General Procedure. The enantiomeric excess was determined by HPLC with an IC column (hexanes-IPA 95:5, 1 mL·min^{-1}, 230 nm): tR = 30.1 min (minor, *syn*), 41.9 min (major, *syn*), 61.4 min (*anti*), 69.9 (*anti*).

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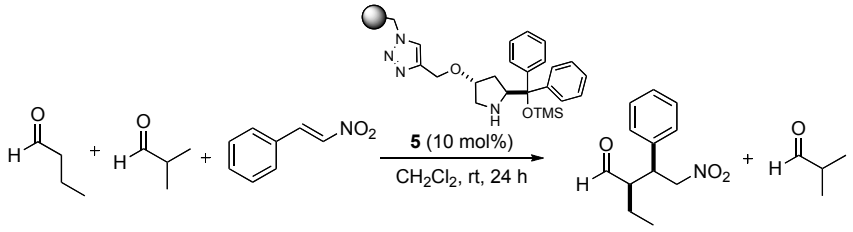
[5] C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984.

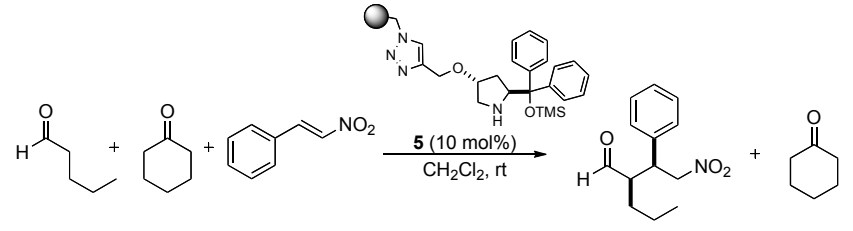
Kinetic resolution of a mixture of butanal and 2-methylpropanal



6c

A mixture of isobutyraldehyde (31 mL, 0.35 mmol) and butanal (50 mL, 0.55 mmol) was added to a suspension of *trans*-b-nitrostyrene (35 mg, 0.23 mmol) and catalyst **5** (53 mg, 0.023 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 24 h when the almost totally disappearance of nitrostyrene was confirmed by TLC. The resin was then directly filtered and was washed with CH_2Cl_2 . The organic filtrate was concentrated under reduced pressure. A ^{1}H-NMR spectrum was registered to calculate conversion observed only for butanal (96%) and diasteromeric *syn:anti* ratio (5.6:1) and the crude of the reation was then purified by flash chromatography on silica gel (EtOAc/Hexanes 4:1) to afford the Michael adduct **6c** (47 mg, 92%). The enantiomeric excess (99%) was determined by HPLC on a chiral stationary phase Chiralpak IA column (hexanes/*i*PrOH 99:1, 0.5 mL·min^{-1}, 214 nm).

Michael addition of pentanal to trans-β-nitrostyrene in the presence of cyclohexanone



6d

a) 1:1 mixture of pentanal and cyclohexanone

Pentanal (32 mL, 0.3 mmol) and cyclohexanone (31 mL, 0.3 mmol) were added to a mixture of *trans*-b-nitrostyrene (30 mg, 0.2 mmol) and catalyst **5** (46 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL). The reaction suspension was stirred at room temperature for 55 h when the almost totally disappearance of nitrostyrene was confirmed by TLC. The resin was then directly filtered and was washed with CH_2Cl_2 . The organic filtrate was concentrated under reduced pressure. A ^{1}H-NMR spectrum was registered to calculate conversion observed only for pentanal (97%) and diasteromeric *syn:anti* ratio (2.6:1) and the crude of the reation was then purified by flash chromatography on silica gel (EtOAc/Hexanes 4:1) to afford the Michael adduct **6d** (41 mg, 87%). The enantiomeric excess (97%) was determined by HPLC on a chiral stationary phase Chiralpak IA column (hexanes-ethanol 95:5, 0.8 mL·min^{-1}, 214 nm).

b) 1:13 mixture of pentanal and cyclohexanone

The same procedure as above was realiced. The amounts used in this case were: pentanal (32 mL, 0.3 mmol), cyclohexanone (0.41 mL, 3.9 mmol), *trans*-b-nitrostyrene (30 mg, 0.2 mmol) and catalyst **5** (46 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 7 days to achieve 80% of conversion to only Michael product **6d** (31 mg, 67%). *syn:anti* ratio of 3.2:1 and 98% of enantiomeric excess.

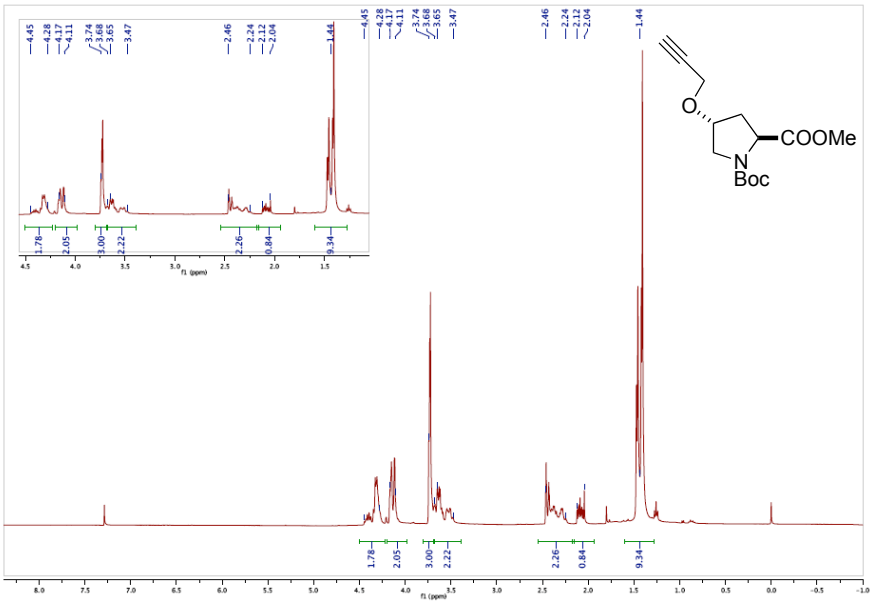
Recycling of Catalyst 5 in the formation of (2*R*, 3*S*)-(4-bromophenyl)-2-methyl-4-nitrobutyraldehyde:

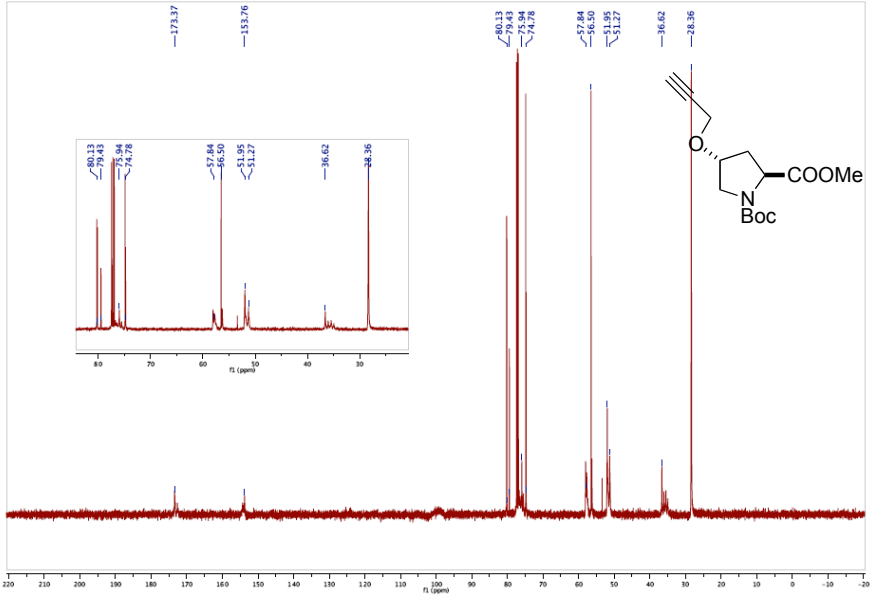
All the experiments were performed using the general method with the resin recovered from the previous run and reconditioned before its use with trimethylsilyl *N,N*-dimethylcarbamate[6] in 0.1 M hexane solution (0.5 mL of solution for each 50 mg of resin) and swelling the resin with a little amount of acetonitrile (0.15 mL/50 mg resin). The mixture is stirred for 2 h and the resin is filtered off, washed with hexane and THF, dried and another portion of reactants is added (general amounts: *trans*-4-bromo-b-nitrostyrene (45 mg, 0.2 mmol), propionaldehyde (22 mL, 0.3 mmol) and **5** (46 mg. 0.02 mmol) in CH_2Cl_2 (1.0 mL)).

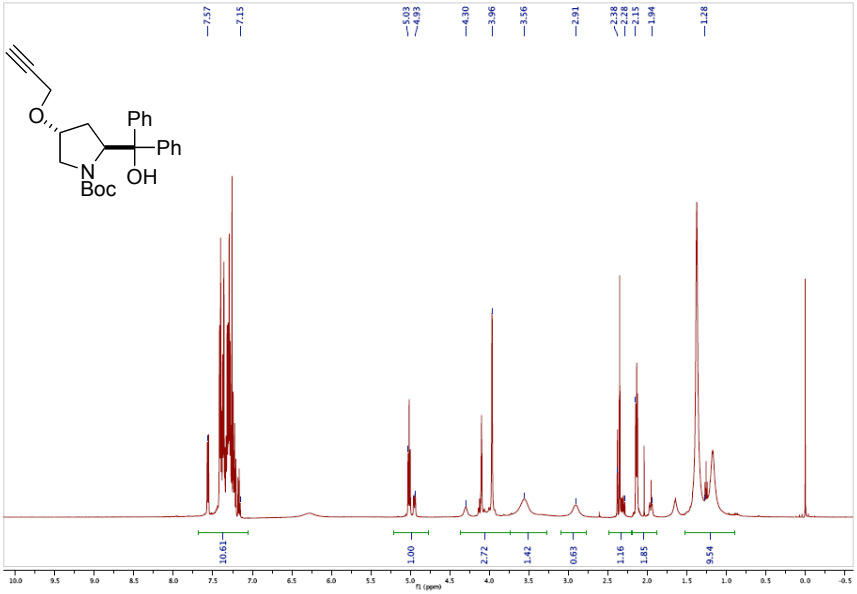
Cycle	t (h)	Conv. (Yield) (%)	syn:anti	ee (%)
1	4	>99 (98)	93:7	99
2	6	>99 (95)	92:8	97
3	6	93 (90)	92:8	96
4	6	92 (85)	92:8	97

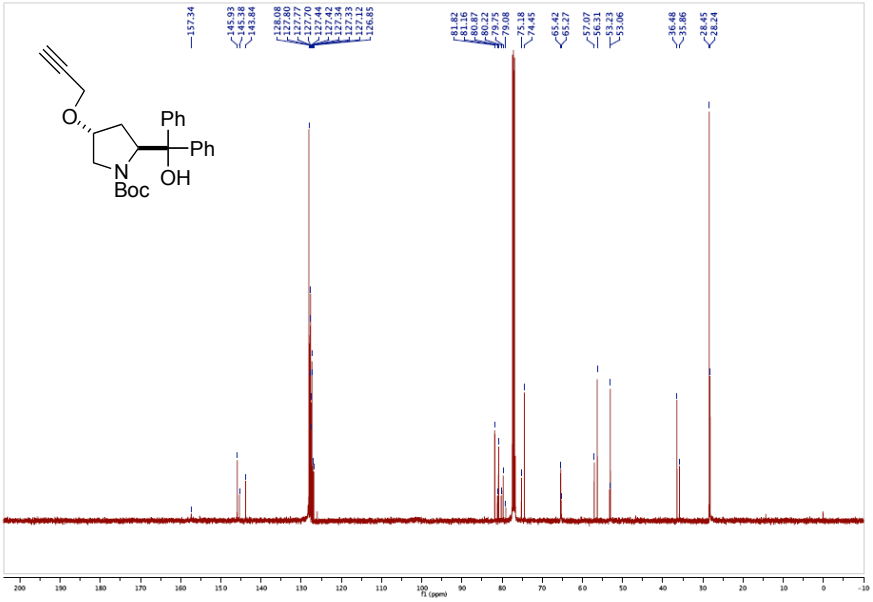
[6] a) D. Knausz, A. Meszticzky, L. Szakacs, B. Csakvari, K. D. Ujszaszy, *J. Organomet. Chem.* **1983**, *256*, 11; b) D. Knausz, A. Meszticzky, L. Szakacs, B. Csakvari, *J. Organomet. Chem.* **1984**, *268*, 207.

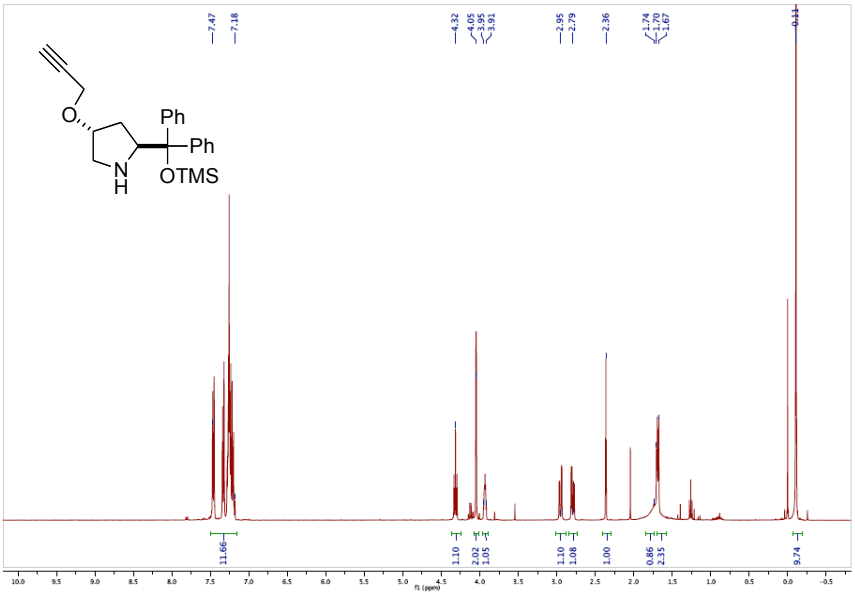
Compilation of NMR spectra:

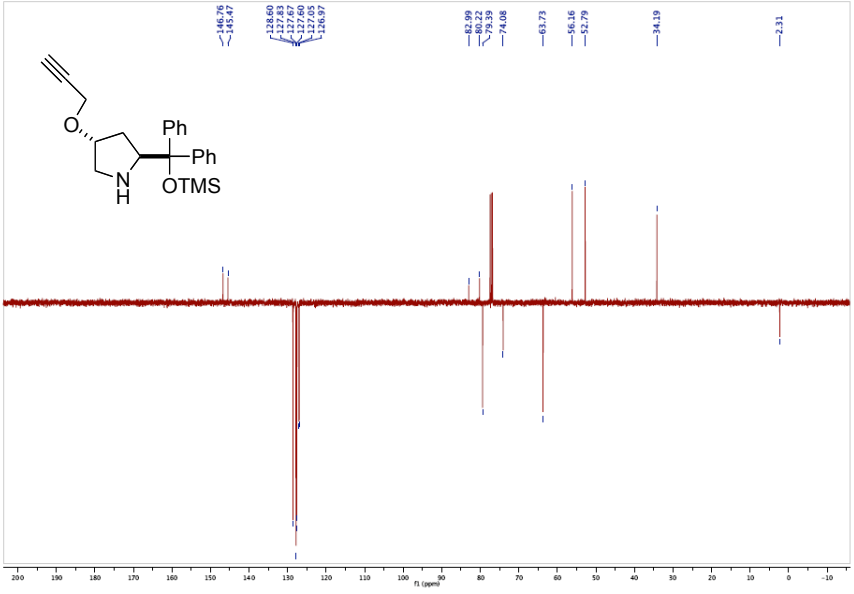





7.57
7.15
5.03
4.93
4.30
3.96
3.56
2.91
2.38
2.28
2.15
1.94
1.28
Ph
Ph
OH
N
Boc
O
10.61
1.00
2.72
1.42
0.63
1.16
1.85
9.54


157.34
145.93
145.38
143.84
128.08
127.80
127.77
127.70
127.44
127.42
127.34
127.33
127.12
126.85
81.82
81.16
80.87
80.72
80.35
79.08
75.18
74.45
65.42
65.27
57.07
56.31
53.33
53.06
36.48
35.86
28.45
28.24
Ph
Ph
OH
N
Boc
O





UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

Chapter III

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

ENANTIOSELECTIVE AMINOCATALYSIS *via* IMINIUM ION

Iminium catalysis[1] was the first organocatalytic activation mode observed and introduced as a general strategy for asymmetric organic synthesis. It is based in the formation of iminium ions from primary or secondary amines and α,β-unsaturated aldehydes or ketones, which are more electrophiles than the corresponding carbonyl compound through lowest-unoccupied molecular orbital (LUMO)-lowering activation of the carbonyl component toward nucleophilic attack (Fig. 3.1).

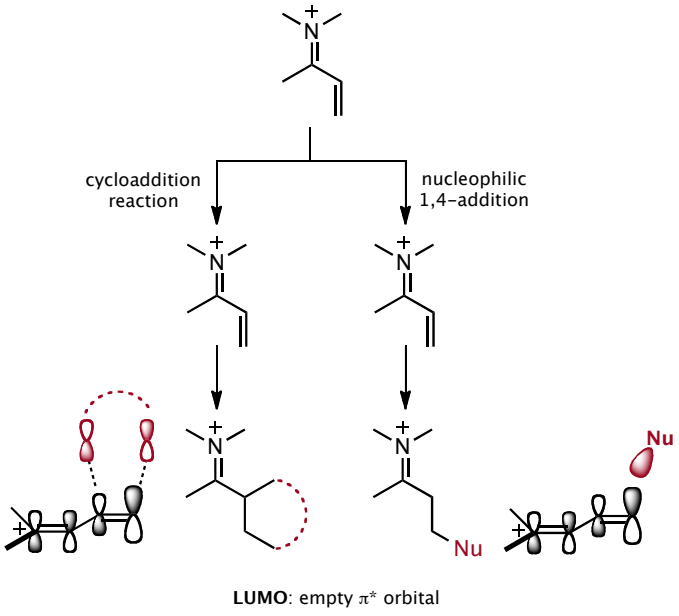
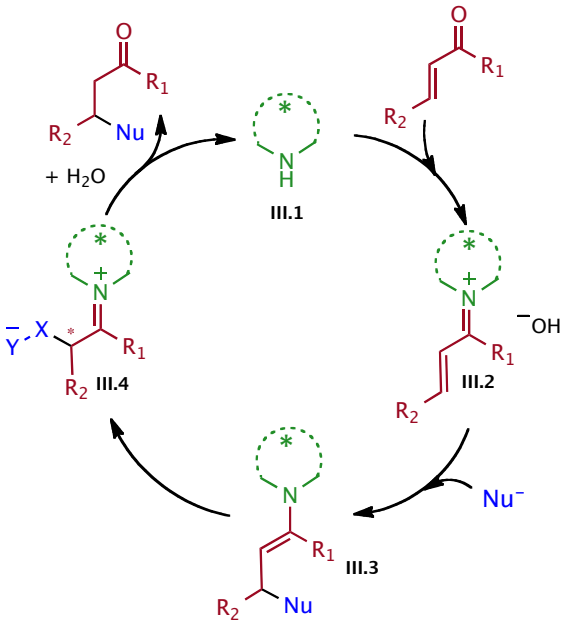


Figure 3.1. Modes of activation of iminium ion formed of a secondary amine and an α,β-unsaturated carbonyl compound.

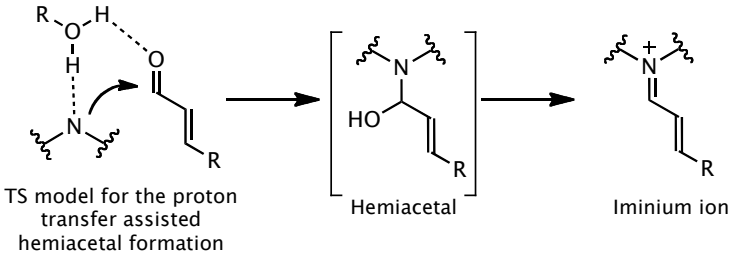
[1] For reviews on iminium ion catalysis, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79. b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

The generally accepted catalytic cycle is represented in Scheme 3.1 and starts with the formation of the iminium intermediate **III.2** from an α,β-unsaturated carbonyl compound and catalyst **III.1**. Iminium ions are ambident electrophiles but, in analogy to the carbonyl compound, the largest coefficient of the LUMO is at the β-position, which is then attacked by the nucleophile leading to the intermediate **III.3**. This resulting enamine is in tautomeric equilibrium with the corresponding iminium-ion **III.4**. In this step, the presence of a water molecule can accelerate this tautomerization reaction by lowering the energy barrier of the proton transfer, decreasing the transition state energy. Thus, a proton-donor additive seems to imply a very important role in the catalytic cycle. Then this intermediate **III.3** is hydrolyzed to obtain the product and regenerating the catalyst. It has to be noted that the enamine **III.3** can also react with an electrophile allowing a cascade process, which is tackled in the Chapter IV of the present work.



Scheme 3.1. General iminium ion catalytic cycle.

Theoretical studies[2] have found that also at the beginning of the catalytic cycle, an assisted-proton transfer in the formation of an hemiacetal intermediate lowers the calculated activation barriers significantly, explaining thus the enhance in the reaction rate when water or acidic additives are present in the reaction media (Scheme 3.2).



Scheme 3.2. Iminium ion formation *via* hemiacetal intermediate.

In Figure 3.2 are shown some relevant organocatalysts for iminium-ion activation, like imidazolidinones (**III.5** and **III.6**), secondary amines, especially derived from pyrrolidine (**III.7**, **III.8** and **III.9**) or primary amines (**III.10** and **III.11**).

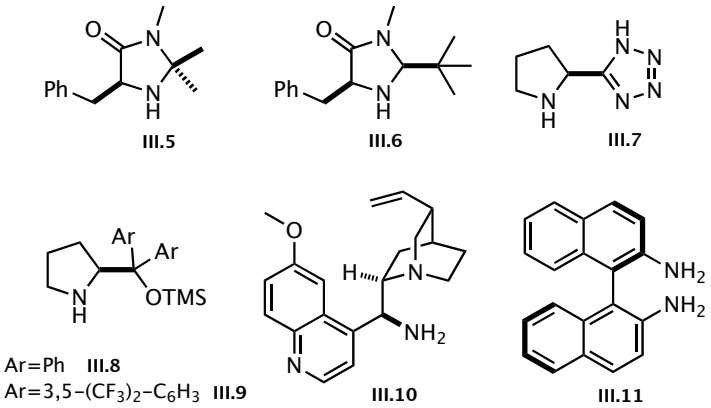


Figure 3.2. Some representative catalysts used in iminium ion catalysis.

[2] M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632.

MacMillan was the pioneer in determining the requirements for building widely versatile catalysts for processes by iminium ion pathway introducing the application of imidazolidinone-type organocatalysts for such reactions.[3] These catalysts have been applied in a large number of transformations like Friedels-Crafts, epoxidation, cycloaddition, conjugate addition or cascade reactions among others.[4]

Another important type of organocatalysts used in iminium ion activation are the Jørgensen-Hayashi diphenylprolinol derivatives. Studies on stereochemical aspects of TMS-protected diarylprolinol performance by calculations and based on NMR observations and crystal structures have been reported by several groups.[2,5] It has been found that in iminium-ions formed from TMS-protected diarylprolinol catalysts with α,β-unsaturated aldehydes, the conformer having the nitrogen atom and the TMS-group in a *sc-exo* relationship on the exocyclic C–C bond is the most stable one (Fig. 3.3).[2] This implies that the sterical blocking of the *Re*-face of the iminium-ion is due to the TMS-group and not the aryl moiety.

---

[3] a) A. Kateri, C. Abrendt, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172.

[4] For examples on the use of imidazolidinone organocatalysts, see: a) T. Poisson, *Synlett* **2008**, *11*, 147. In Friedels-Crafts reactions: b) N. A. Para, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370. c) Reference 3b. d) K. C. Nicolaou, R. Reingruber, D. Serlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, *131,* 2086. e) Y.-C. Guo, D.-P. Li, Y.-L. Li, H.-M. Wang, W.-J. Xiao, *Chirality* **2009**, *21*, 777. In epoxidations, see: f) S. Lee, D. W. C. MacMillan, *Tetrahedron* **2006**, *62*, 11413. In cycloaddition reactions, see: g) Reference 3a. h) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124,* 2458. i) M. Harmata, S. K. Ghosh, X. C. Hong, S. Wacharasindh, P. A. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058. In conjugate additions, see: j) M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 4048; *Angew. Chem. Int. Ed.* **2004**, *43*, 3958. k) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *125*, 1192. l) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328. m) S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *1295*, 1536. In cascade reactions, see: n) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051. o) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, *10*, 1477.

[5] a) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983. b) R. Cordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175. c) I. Ibrahem, P. Hammer, J. Vesely, R. Rios, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2008**, *350*, 1875. d) D. Seebach, U. Groselj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999. e) U. Groselj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2009**, *92*, 1225.

On the other hand, in *meta*-substituted phenyl groups, as for instance 3,5-$(CF_3)_2C_6H_3$, this substituent is a major contributor to the sterical hindrance and the good performance of the organocatalysts. In this case, the stereochemistry outcome of the iminium-ion has been attributed to the *meta*-bulkier substitution (Fig. 3.3).[2]

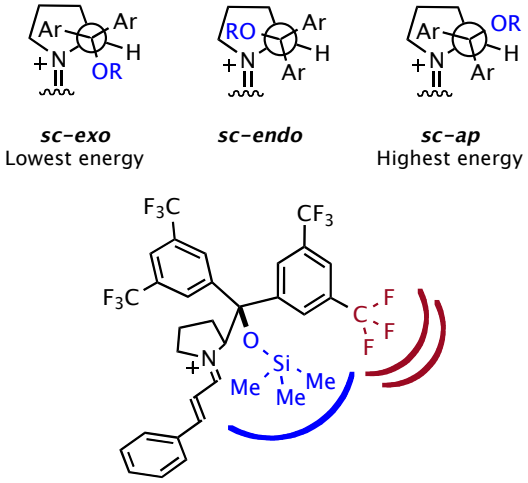
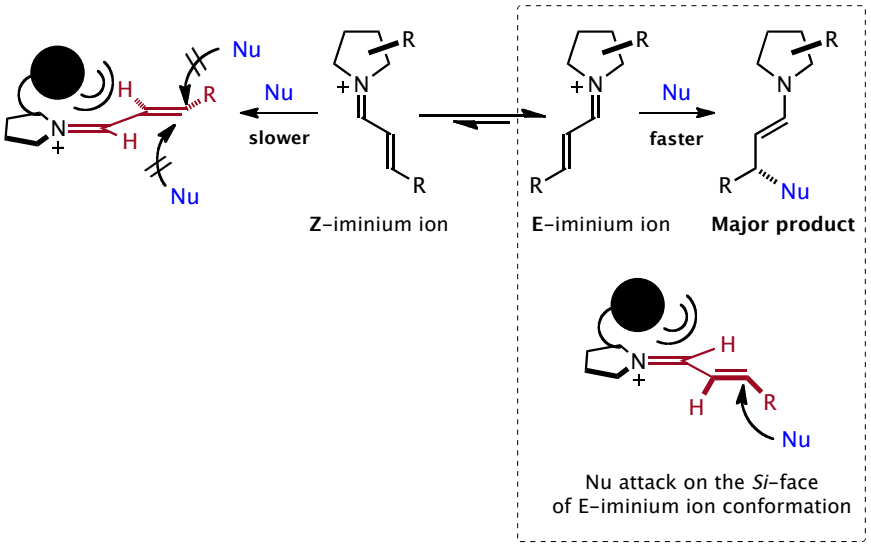


Figure 3.3. Conformations of the iminium-ions derived from 3,5-$(CF_3)_2C_6H_3$ substituted diarylprolinol and cinnamaldehyde.

As well as in the case of rections *via* enamine, the stereoselectivities of the final product depend on the E or Z configuration of the intermediate. Although both isomers of iminium ion are in equilibrium, it has been observed that the E-configuration of the iminium ion is more stable in terms of energy difference between them (Scheme 3.3).[5a] The energy of the *cis*-conformation of the C-C bond between the two double bonds of the iminium ion is higher than the *trans*-one, therefore it is not consider as plausible active intermediate. Other important point for stereoselectivity determining is the nucleophilic attack on the iminium ion. This attack is highly disfavoured if it is on the Z-configuration because of the steric repulsions present in the transition state (Scheme 3.3). Thus, the nucleophilic attack on the *Si*-face (less sterically hindered one) of the E-configuration of the iminium ion has been found the most favoured process.

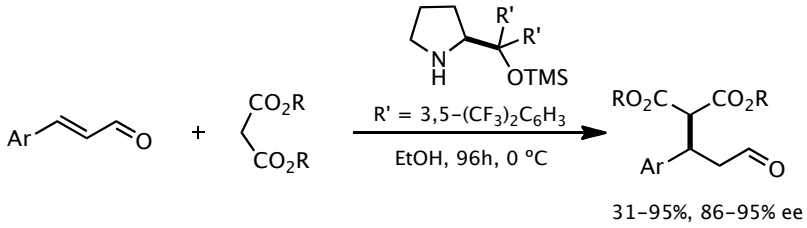


Scheme 3.3. E/Z-equilibrium and preferential attack on the E-iminium ion.

3.1. 1,4-ADDITION OF ACTIVE METHYLENE COMPOUNDS TO α,β-UNSATURATED ALDEHYDES.

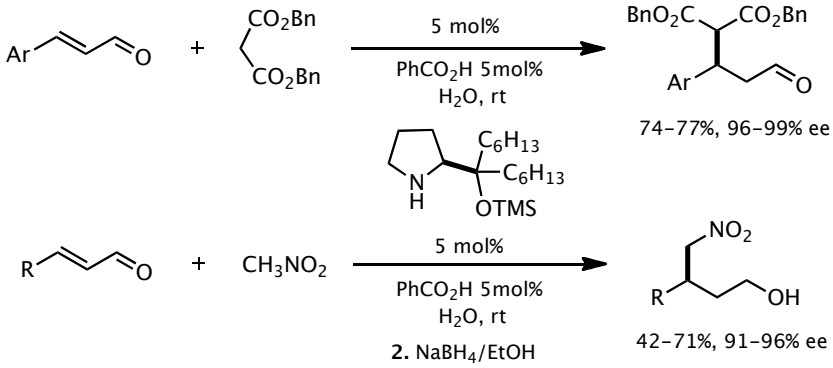
Conjugate addition of malonates to enones has led to high levels of selectivity using several organocatalysts.[6] However, until the work of Jørgensen and co-workers in 2006 there was no any effective catalyst for this reaction with α,β-unsaturated aldehydes.[7] They successfully applied the described diphenylprolinol catalyst in the Michael addition of malonates to enals (Scheme 3.4) achieving the corresponding products in good enantioselectivity although long reaction times were required.

[6] a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661. b) G. Bartoli, P. Melchiorre, *Synlett* **2008**, *12*, 1759. The first catalytic addition of malonates to enones: c) A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805.
[7] S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305.



Scheme 3.4. First highly selective 1,4-addition of malonates to α,β-enals.

Using TMS-protected diphenylprolinol silyl ether, Ma and co-workers were able to obtain high yields and enantioselectivities when the reaction was performed in water with acetic acid as additive even with alkyl- and alkenyl-substituted enals in general in short reaction times.[8] Moreover, several catalysts have been development to be optimal under the reaction conditions employed. One example of that are the water-compatible catalysts, introduced by the group of Palomo.[9] They consist in prolinol derivative compounds bearing bulky silyl groups and hydrophobic alkyl chains. The use of this catalysts for addition of malonates and nitromethane to α,β-unsaturated aldehydes in water as unique solvent and with benzoic acid as additive resulted in an active and high enantioselective Michael process (Scheme 3.5).

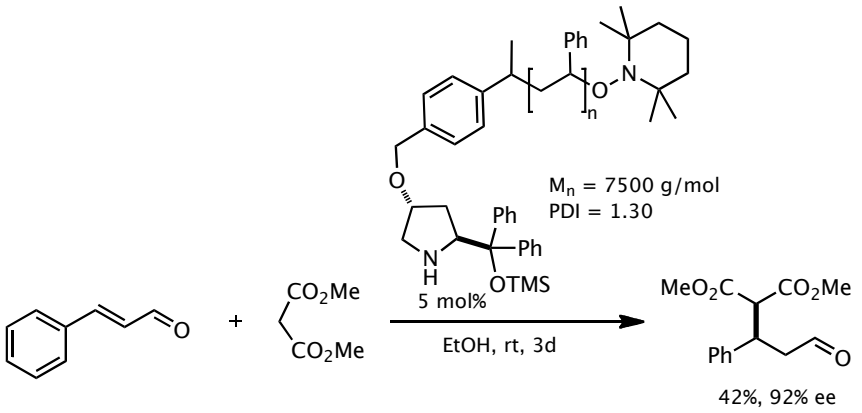


Scheme 3.5. Michael addition of malonates and nitromethane to α,β-enals in water.

[8] A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075.
[9] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431.

Ye and co-workers described the improvement of the catalytic reactivity and turnover in those Michael additions with a Lewis base–Brønsted base bifunctional catalysis that combines both HOMO-raising and LUMO-lowering mechanisms.[10] A Lewis base such as a chiral amine catalyst was used to activate the α,β-unsaturated carbonyl compound and induce the chirality of the reaction by the iminium mechanism and a Brønsted base such as basic lithium salt was used to activate the nucleophilic reagent by deprotonation or hydrogen-bond interaction. This approach was used also in **Article 4** of the present work.

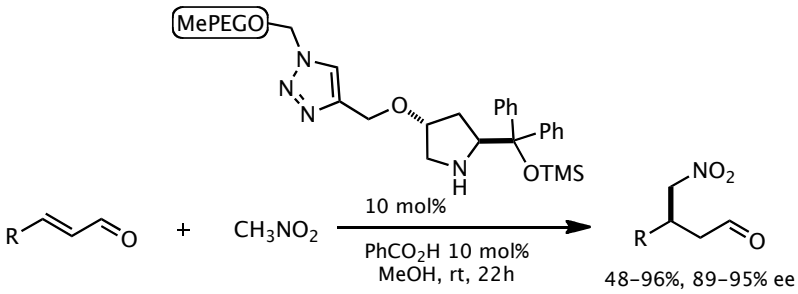
In terms of polymer-supported diarylprolinol silyl ethers as catalysts for this kind of reactions, the group of Studer synthesized a diphenylprolinol derivative bound to oligostyrene, which was then immobilized onto a polystyrene matrix to give fibre systems.[11] These fibres were tested in the Michael addition of dimethyl malonate to cinnamaldehyde in EtOH (Scheme 3.6). Although the selectivity obtained was more or less identical to those obtained by the homogeneous counterpart, the chemical yield was only 42%, compared to 84% for the monomeric catalyst. The catalyst was recycle nine times however, the activity of the catalyst decreased during the third run.



Scheme 3.6. Michael addition of dimethyl malonate to cinnamaldehyde catalyzed by fibre supported *O*-TMS-diphenylprolinol.

[10] Y. Wang, P. Li, X. Liang, J. Ye, *Adv. Synth. Catal.* **2008**, *350*, 1383.
[11] C. Röben, M. Stasiak, B. Janza, A. Greiner, J. H. Wendorff, A. Studer, *Synthesis* **2008**, 2163.

Jørgensen-Hayashi type catalyst has been also supported onto PEG and tested in the asymmetric Michael addition of nitromethane to cinnamaldehydes in MeOH, giving excellent chemical yields and enantioselectivities (Scheme 3.7).[12] This immobilized catalyst could be recycled for five reaction cycles without any change in the selectivity, but the product yields dropped significantly.



Scheme 3.7. Michael addition of dimethyl malonate.

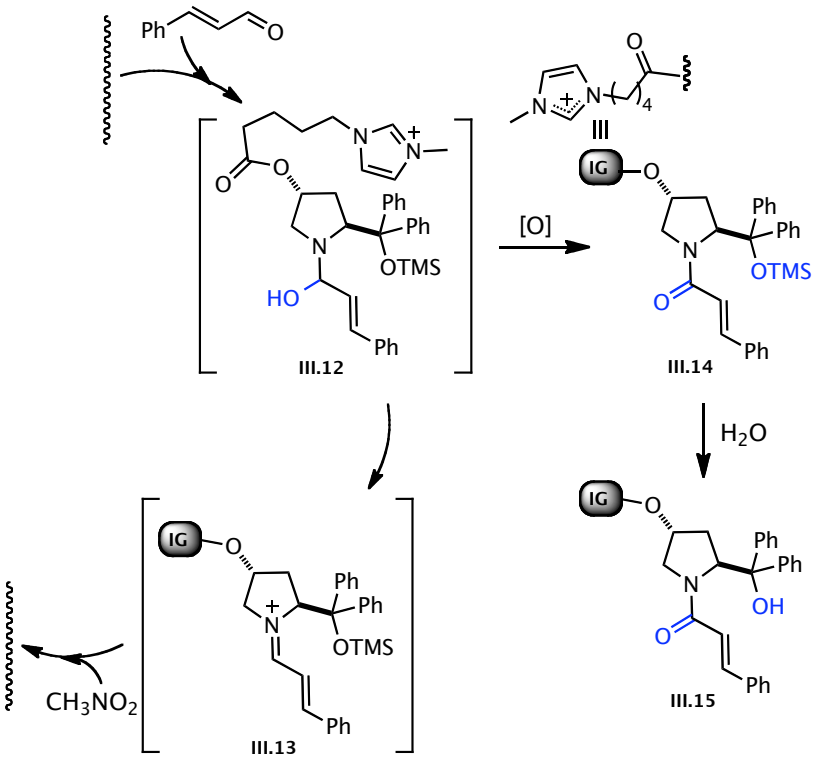
As can be observed, in most cases supported diarylprolinol silyl ethers become much less active after the first recycling runs whereas the enantioselectivity remains, as we have also observed in our work (**Articles 3** and **4**). That deactivation appears to be more accentuated when long reaction times are necessary. As we have discussed in the previous chapter, in our particular case we attributed this deactivation to the hydrolysis of the O-Si bond since we were able to recover the activity after treating the resin with a silylating agent ($Me_2NCO_2SiMe_3$). However, as has been observed, similar loss in the activity is obtained using OMe-diphenylprolinols.[13]

This fact suggests the existence of side reactions that deactivate the supported organocatalysts mentioned. Very recently, the group of Zlotin have published an interesting study about the deactivation pathways of Jørgensen-Hayashi type catalyst in asymmetric Michael reactions of α,β-enals and C- or N-nucleophiles.[13] They present a diphenylprolinol organocatalyst modified with an ionic liquid fragment to mediate such reactions and identify by ESI-MS (electrospray ionization mass

[12] I. Mager, K. Zeitler, *Org. Lett.* **2010**, *12*, 1480.
[13] O. V. Maltsev, A. O. Chizhov, S. G. Zlotin, *Chem. Eur. J.* **2011**, *17*, 6109.

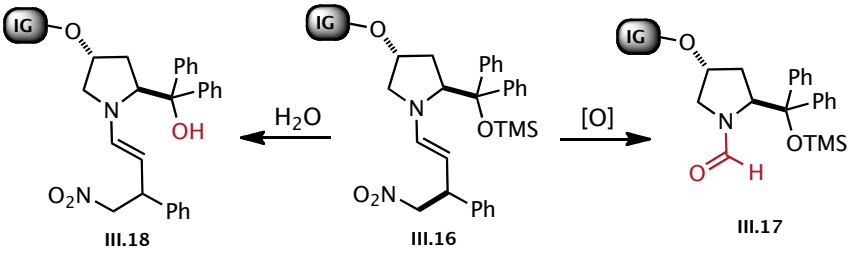
spectrometry) 'parasitic' transformations and undesirable cation intermediates that poison the catalyst.

One interesting intermediate detected in the asymmetric addition of nitromethane to *trans*-cinnamaldehyde was the hemiaminal **III.12** (Fig. 3.4). This specie is formed at the beginning of the catalytic cycle before its transformation to the iminium cation **III.13**. The cationic intermediate **III.12** can react with nucleophiles or with oxidizing agents (presumably air oxygen) to afford addition, desilylation or oxidation side products (as **III.14** and **III.15** in Scheme 3.8).



Scheme 3.8. First intermediates in the catalytic cycle *via* iminium ion determined by ESI-MS (+).

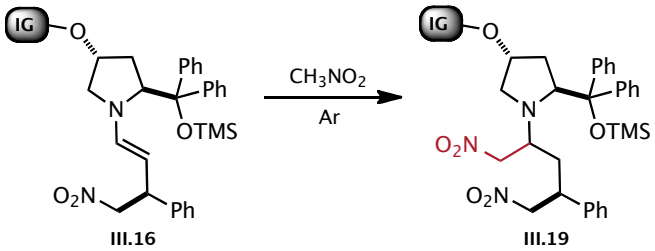
The consequent enamine **III.16** formed underwent also oxidation and hydrolysis reactions affording thus catalytically inactive *N*-formyl-pyrrolidine **III.17** and deprotected-prolinol **III.18**. This last specie, as it is known, is able to catalyze the Michael reaction in less efficient way than *O*-TMS-protected catalyst (Scheme 3.9).



Scheme 3.9. Oxidation and hydrolysis transformations of enamine **III.16**.

Analogous enamine cations, as well as oxidation and hydrolysis products were also detected in other Michael reactions of *trans*-cinnamaldehyde with dimethylmalonate and with *N*-carbobenzyloxy-hydroxylamine as nucleophiles, mediated by the same catalyst.

The 'parasitic' products of oxidation and hydrolysis seem to be the responsible for the deactivation of supported diarylprolinol silyl ether catalysts and the formations of such compounds are probably due to atmospheric oxygen. For that reason, the same addition reaction of nitromethane to cinnamaldehyde was examined under oxygen-free conditions. The major compounds observed in this case were the active enamine **III.16** and the dinitro-**III.19**, product of reversible Michael/Henry tandem reactions of iminium intermediate **III.13** with nitromethane, formed only under oxygen-free conditions (Scheme 3.10). The poisoning side products observed when the reaction was performed in air were almost absent.



Scheme 3.10. Dinitro-compound formed under oxygen-free reaction conditions.

The inhibition of hydrolysis process under reduced atmosphere is attributed to the cinnamic acid formed from oxidation of cinnamaldehyde by atmospheric oxygen that accelerates the O-Si bond cleavage of the catalyst.

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Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type reactions

Esther Alza,[a] Sonia Sayalero,[a] Pinar Kasaplar,[a] Diana Almaşi,[a] and Miquel A. Pericàs*[a][b]

Abstract: α,α-Diphenylprolinol ethers (methyl and trimethylsilyl) anchored onto a polystyrene resin through CuAAC reactions have been prepared. The catalytic activity and enantioselectivity displayed by the OTMS derivative are comparable to those exhibited by the best homogeneous catalysts in the addition of aldehydes to nitroolefins and of both malonates and nitromethane to α,β-unsaturated aldehydes. The combination of the catalytic unit, the triazole linker and the polymeric matrix provided an unprecedented substrate selectivity in favor of linear, short-chain aldehydes when the organocatalyzed reaction proceeds via enamine mechanism, together with high versatility in reactions catalyzed via iminium ion intermediate. The catalytic behavior of polystyrene-supported α,α-diphenyl prolinol methyl ether has also been evaluated in some asymmetric Michael addition reactions. As a general trend, the CuAAC-based immobilization of diarylprolinol ethers onto insoluble polystyrene resins offers important operational advantages such as high catalytic activity, easy recovery from the reaction mixture by simple filtration and the possibility of extended reuse.

Keywords: asymmetric catalysis • Michael addition • organocatalysis • aldehydes • polymer supported catalysts

Introduction

The covalent immobilization of chiral catalytic species onto polymer supports has become an important research area over the last decade,[1] mainly due to the inherent properties of the polymer backbone that allows easy recovery by simple filtration, recycling and reuse and even its application in continuous flow processes. However, this strategy sometimes leads to a decrease of catalytic activity with respect to monomeric species due to a deficient interaction between reactants and the supported catalyst, and to a decrease in enantioselectivity, due to perturbation of the transition state of the enantiodetermining step by the polymer chain. An appropriate design and preparation of the heterogeneous catalytic systems is thus essential to achieve catalytic activities and selectivities comparable to those provided by their homogeneous counterparts. Besides a proper selection of the anchoring point on the molecule of the homogeneous catalyst (the synthesis of these chemically modified structures can be in some cases an important source of complexity), the nature of the polymer support plays also a fundamental role. The more widely used supports when homogeneous conditions have to be approached are highly swellable, yet insoluble resins made of slightly cross-linked polystyrene-based polymers, which are easily available, can be readily functionalized in a variety of manners and present high chemical inertness.[2] Among them, Merrifield resins and their derivatives are ideal carriers for catalytic species due to their easy handling, optimal physical properties and modularity.[3]

The continued and ever-growing interest on organocatalysis over the past two decades has led to the development of many different types of organocatalyzed reactions providing enantiomerically pure compounds through very simple reaction setups.[4] However, many of these reactions lead to rather polar products, so that isolation and purification becomes the most important source of solvent consumption and waste generation. Taking into account factors such as separation and recovery of catalyst and ease of purification of reaction products, the immobilization of organocatalytic species appears as a promising strategy.

In a continued effort towards the development of chemical processes with improved sustainability characteristics, we have introduced a variety of organocatalysts synthesized from pyrrolidine derivatives and anchored onto insoluble polystyrene resins[5] by copper-mediated azide-alkyne 1,3-dipolar cycloaddition.[6] The nature of the catalytic species, the presence of the triazole linker and the environment provided by the polymer

[a] E. Alza, Dr. S. Sayalero, P. Kasaplar, Dr. D. Almasi, Prof. Dr. M. A. Pericàs
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans, 16, 43007 Tarragona (Spain)
Fax: (+34) 977920222
E-mail: mapericas@iciq.es

[b] Prof. Dr. M. A. Pericàs
Departament de Química Orgànica
Universitat de Barcelona (UB), 08028 Barcelona (Spain)

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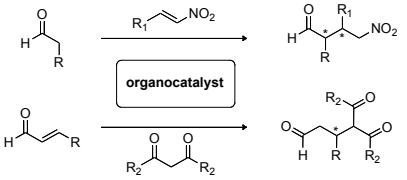
backbone have shown synergistic effect leading to remarkably high catalytic activity and enantioselectivity.[5]

Catalysis mediated by primary or secondary amines include reactions taking place through enamine and iminium ion intermediates.[7] Among these processes, Michael reactions[8] represent a most powerful synthetic tool for the assembly of 1,5-difunctional organic synthons (Scheme 1). Within the wide application range of these chemical transformations, their use as the first step in cascade processes[9] or the combination of the two catalysis mechanisms in tandem sequences has aroused a great deal of interest, since it allows the construction of complex molecular frameworks in simple, one-pot operations.

Of particular interest are catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers,[10] independently introduced by Jørgensen and Hayashi for the enantioselective organocatalyzed α-sulfenylation of aldehydes and for the asymmetric Michael addition of aldehydes to nitroalkenes, respectively.[11] The steric effect caused by the bulky substituent placed at C-2 on the pyrrolidine ring very efficiently controls the enantioselectivity of the reactions.



Scheme 1. Michael reaction of aldehydes with nitroolefins and malonates via enamine and iminium ion intermediates, respectively.

We have recently reported[5f] the development of a new polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**4**) which displays an unprecedented selectivity in favor of linear, short-chain aldehyde donors in the highly enantioselective Michael addition to nitroolefins. Herein, we report a full account of the design and synthesis of polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether, the chemical modification of this specie for the seek of extended life cycle, and its use in a variety of Michael reaction involving aldehydes, malonates or nitromethane as donors and nitroolefins or α,β-unsaturated aldehydes as acceptors.

Results and Discussion

Design and synthesis of a polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether, and evaluation in the Michael addition of aldehydes to nitroolefins. The asymmetric organocatalytic Michael addition[12] has emerged as one of the most important carbon-carbon bond forming reactions and aldehydes have turned out to be very reactive and convenient donors in this process. Catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers have provided excellent results in terms of activity and selectivity for aminocatalytic enantioselective Michael reactions. For the design of a widely applicable polymer-supported Jørgensen-Hayashi-type organocatalyst, we reasoned that the strategy of immobilization should imply the functionalization these systems of the remotest position from the catalytic active amine moiety and the chiral C-2 atom, in order to avoid perturbation of the enantiodetermining transition states by the linker and the polymeric backbone (Figure 1).

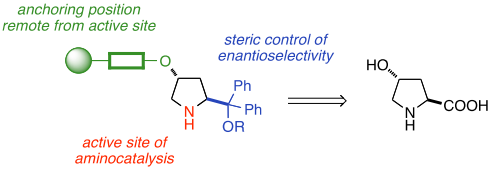
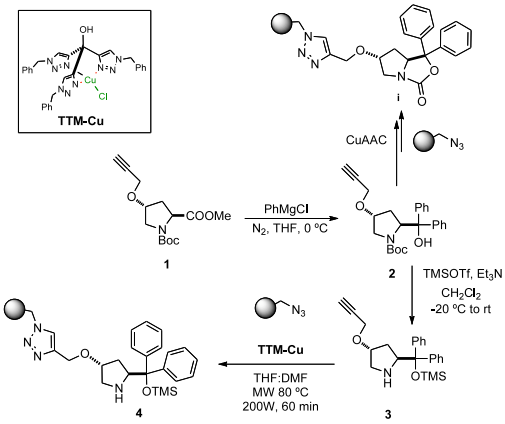


Figure 1. Supported organocatalyst design.

We selected natural hydroxyproline as our starting material and, to carry out the initial idea, we chose the CuAAC reaction as the covalent strategy for the anchoring of the pyrrolidine moiety onto a Merrifield resin. This well-established atom-economic immobilization approach[5] required some synthetic effort to prepare the key intermediate **3** from propargyloxy derivative **1** of commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester. The silylation with concomitant carbamate deprotection of **2** affords the desired intermediate **3**,[5f] which is ready for support through the selected methodology. The CuAAC conjugation step represented an important synthetic challenge, since common Cu(I) catalysts employed for the cycloaddition were incompatible with the free amino group present in the substrate (Scheme 2). Notably, the immobilization of **3** onto azidomethylpolystyrene was efficiently catalyzed by the tris(triazolyl)methanol-copper complex **TTM-Cu**[13] allowing the easy and highly reproducible synthesis of the catalytic resin **4**.



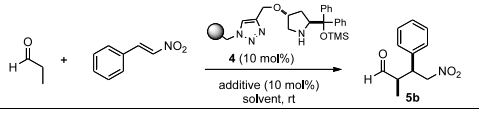
Scheme 2. Immobilization reaction for the obtention of the polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether **4**.

It is to be noted that when the immobilization was performed at an early stage (**2**, leading to resin **i**) the unavoidable formation of a cyclic carbamate was observed. While hydrolysis of this class of intermediates is feasible in homogeneous phase, it posed severe experimental difficulties on polymer substrates.

In recent times, significant progress in the development of organocatalyzed Michael reaction has been achieved through the

introduction of a variety of catalytic species and reaction conditions. These include work in aqueous media or in less conventional environments such as ionic liquids.[14] In this context, the Michael addition of propionaldehyde to β-nitrostyrene was selected as a model reaction for the use of **4** and was employed for the optimization of reaction conditions (Table 1). It was soon established that DCM was the optimal solvent for the reaction. Although different additives were tested (entries 2-4 and 6-8), optimal results were recorded with the use of 10 mol% catalyst in the absence of any additive (entry 5). Noteworthy, these optimal conditions involve the use of a 1.5:1 aldehyde:nitrostyrene molar ratio, much more convenient than the usually employed 10:1 one. Indeed, Michael adducts were obtained in this manner with better diastereoselectivity and from cleaner reaction crudes due to the suppression of aldehyde self-aldol reactions. When volatile substrates were used, the direct isolation of the pure products was possible after a simple filtration of the catalyst and evaporation of the solvent. In any case, it is also important to emphasize the excellent performance of **4** in water, being the first example of an insoluble organocatalyst successfully dealing with aldehydes in this solvent.[5c]

Table 1. Screening of reaction conditions for the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]

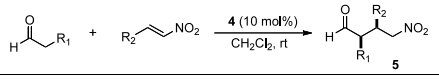


Entry	Solvent	Additive[b]	t [h]	conv [%][c]	syn/ anti[c]	ee [%][d]
1[e]	Hex:THF	none	36	40	97:3	97
2[e]	CH_2Cl_2	none	7	>99	96:4	>99
3[e]	CH_2Cl_2	DMAP	24	>99	81:19	99
4[e]	CH_2Cl_2	PhCOOH	24	>99	77:23	97
5	CH_2Cl_2	none	7	>99	>99:1	>99
6	CH_2Cl_2	DMAP	23	>99	86:14	>99
7	CH_2Cl_2	PhCOOH	2	>99	87:13	99
8	H_2O	DiMePEG	24	97	96:4	99
9	CH_2Cl_2	TFA	48	none	-	-

[a] All reactions performed with 0.2 mmol of (*E*)-β-nitrostyrene, 0.3 or 2.0 mmol of propionaldehyde, and 0.02 mmol of **5** in 1 mL of solvent at room temperature. [b] 0.02 mmol [c] Determined by ^{1}H NMR of the reaction crude. [d] Determined by chiral HPLC analysis. [e] 2 mmol of propionaldehyde was used.

The scope of the Michael addition between aldehydes and nitroolefins mediated by **4** was next studied. Results are presented in Table 2. As a general trend, the *syn*-type Michael products **5** were obtained with excellent diastereo- and enantioselectivity. Even in the challenging Michael reaction of acetaldehyde with β-nitrostyrene (Table 2, entry 1) resin **4** compares favorably with α,α-diphenylprolinol trimethylsilyl ether, avoiding in the present case the use of a large excess of acetaldehyde and employing half catalyst loading.[15] Thus, adduct **5a** can be prepared in 96% ee and this deserves special comment given the interest of α-unsubstituted γ-nitroaldehydes like **5a** (Figure 2) and the general interest of organocatalytic reactions of acetaldehyde.[15],[16]

Table 2. Screening of substrates in the Michael addition of aldehydes to nitroolefins catalyzed by **4**.[a]



Entry	R_1	R_2	**5**	t [h]	Conv.[b] [%] (Yield[c] [%])	d.r.[b]	ee[d] [%]
1	H	Ph	**a**	72	50 (44)	-	96
2	Me	Ph	**b**	7	>99 (98)	>99:1	>99
3	Et	Ph	**c**	5	>99 (93)	90:10	>99
4	Pr	Ph	**d**	27	>99 (98)	82:18	99
5	n-Pent	Ph	**e**	48	99 (91)	75:25	98
6	*i*Pr	Ph	**f**	96	<10	n.d.	n.d.
7	Ph	Ph	**g**	48	<5	n.d.	n.d.
8	$(CH_3)_2$	Ph	**h**	120	0	n.d.	n.d.
9	Me	4-BrC_6H_4	**i**	4	>99 (98)	91:9	98
10	Me	4-MeOC_6H_4	**j**	8	>99 (94)	89:11	99
11	Me	2-furyl	**k**	4	>99 (96)	85:15	90
12	Me	$(CH_2)_2C_6H_5$	**l**	24	>99 (94)	81:19	95
13	Me	C_6H_{11}	**m**	64	>99 (89)	70:30	97
14	Me	*i*Pr	**n**	96	88 (84)	70:30	99

[a] Reactions carried out at room temperature with 0.2 mmol of nitroolefin, 0.3 mmol of aldehyde, and 0.02 mmol of **4** in 1 mL of solvent. [b] Determined by ^{1}H NMR of the crude reaction. [c] Isolated yield. [d] Determined by chiral HPLC analysis. n.d. (not determined)

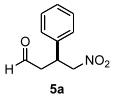
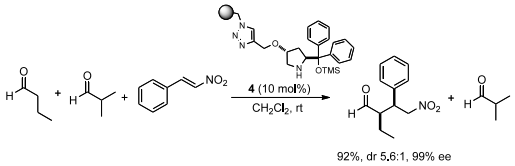


Figure 2. Michael adduct from Michael addition of acetaldehyde to β-nitrostyrene.

On the other hand, the catalytic activity of **4** showed a remarkable dependency on the structure of the aldehyde donor. Thus, fast reactions were observed for linear, short chain aldehydes like propionaldehyde and butanal (Table 2, entries 2 and 3), while the reaction time increases significantly with chain length (Table 2, entries 4 and 5). In all these cases, yield and enantioselectivity of the major *syn* products were excellent. Branching at the β position of the aldehyde had a detrimental effect on reaction rate (Table 2, entries 6 and 7) while α-branching (Table 2, entry 8) completely blocked the reaction. Ketones like acetone and cyclohexanone were also tested as Michael donors, although they were found to be completely unreactive.

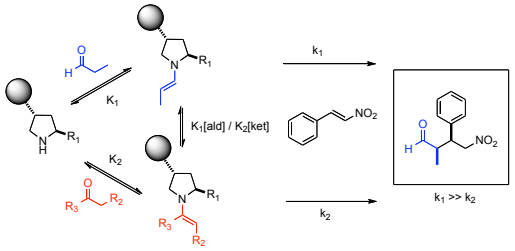
With respect to Michael acceptors, various substituted nitroolefins were tested. Under the optimized conditions, the addition of propionaldehyde to β-aromatic nitroalkenes gave the corresponding *syn*-adducts in excellent yields and enantioselectivities after short reaction times, independently of the electronic properties of the aryl or hetaryl substituent (Table 2, entries 9-11). Reaction time increased notably when a present aromatic substituent is not conjugated with the nitroolefin (Table 2, entry 12) and for aliphatic nitroolefins, although the Michael products **5m-n** were obtained in high yield and excellent enantioselectivity.

To ascertain if selectivity for linear aldehydes could be achieved in the presence of branched ones, we tested resin **4** in the Michael reaction of a mixture of butanal and 2-methylpropanal with the composition resulting from the Rh-catalyzed hydroformylation of propene and β-nitrostyrene in the presence of **4** (**4**/β-nitrostyrene/butanal/2-methylpropanal: 0.1/1/2.4/1.5; see Scheme 4). Very gratifyingly, under these conditions, *only the linear aldehyde underwent Michael addition* with no decrease in enantioselectivity (99%, see Table 2, entry 3).



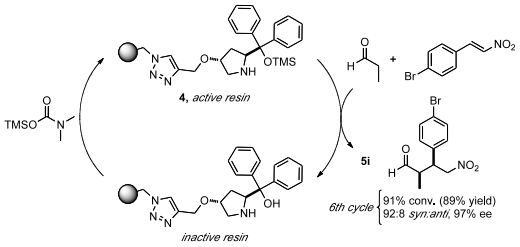
Scheme 4. Selective Michael addition of butanal to β-nitrostyrene in the presence of 2-methylpropanal catalyzed by **4**.

However, the reaction time required for complete conversion (92% isolated yield) under these conditions was substantially extended (24 *vs.* 5 h), and this suggested that unproductive enamines involving 2-methylpropanal could be formed during the reaction, leading to a decrease in the concentration of the viable enamine intermediate. This suggestion is reinforced by the results of competition experiments involving pentanal and cyclohexanone. When an equimolar mixture of these substrates was treated with β-nitrostyrene, the required time for the complete conversion of pentanal extended from 27 to 55 h. Even more notably, when the cyclohexanone:pentanal ratio was changed to 13:1, the reaction time increased to 7 days. The retarding efect exerted by bystander branched aldehydes or ketones can be rationalized through the equilibria represented in Scheme 5.



Scheme 5. Origin of the substrate-selectivity in the Michael addition of aldehydes to β-nitrostyrene catalyzed by **4**.

As already mentioned, the insoluble nature of the polymer allows the catalyst recovery by a simple filtration. However, the recycling process can be limited by deactivation effects and in the case of α,α-diphenylprolinol silyl ethers, the lability of the silyl ether group towards hydrolysis[12r] makes the reuse of the organocatalyst sometimes difficult. In our case, the complete absence of catalytic activity in the considered Michael reaction of a resin bearing free hydroxy groups in the α,α-diphenylprolinol moiety was observed.

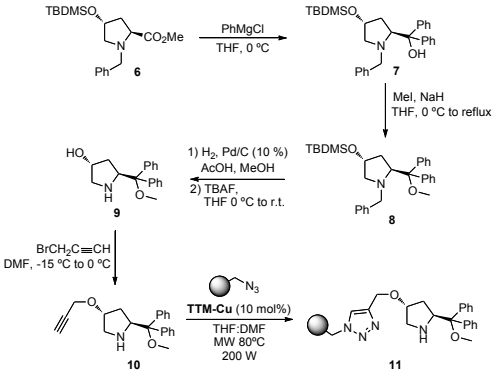


Scheme 6. Cycle of reconditioning and reuse of the active resin **4**.

After extensive experimentation, we were able to revert the deactivation problem of catalyst **4** by selectively reprotecting the hydroxy groups of inactive diphenylprolinol-type resins through a brief treatment with trimethylsilyl *N,N*-dimethylcarbamate[17] in hexane/acetonitrile. This simple procedure leads to full recovery of the catalytic activity of the supported organocatalyst **4** and makes possible its reuse. Thus, in six consecutives cycles of reaction/reaconditioning process, the excellent performance of resin **4** in Michael addition of propionaldehyde to 4-bromo-β-nitrostyrene remains intact (Scheme 6). Interestingly, the reactivation procedure does not represent any important inconvenient from a practical point of view. Since the only by-product formed in the process is dimethylamine, the reactivated resin can be directly reused after washing out any excess of silylating reagent.

Synthesis and evaluation in the Michael reaction of aldehydes and nitroalkenes of a polystyrene-supported version of (*S*)-α,α-diphenylprolinol methyl ether. Even though the origin of the deactivation of resin **4** could be elucidated and properly solved, we were interested in the possibility of developing more robust polymer-supported diphenylprolinol-type catalysts with the ultimate goal of performing the present reaction in a continuous flow manner. Therefore, we set-up to prepare and evaluate a polymer-supported diphenylprolinol methyl ether, which should be stable under the standard reaction and recycling conditions, do not showing hydrolytic deactivation. The synthesis of resin **11** has been explained in detail in the Supporting Information and it is summarized in Scheme 7.

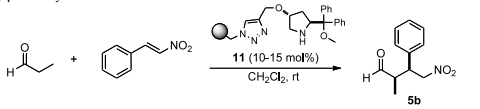
To avoid the difficulties associated to the preparation at small scale of a nonsupported counterpart,[18] our synthetic approach started with the preparation of compound **6** by selective protection of commercially available (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride. Grignard addition and subsequent methylation of the resulting tertiary alcohol provided the intermediate **8**, which was sequentially deprotected giving the key 4-hydroxy diphenylprolinol methyl ether **9**. Propargylation of **9** led to required derivative **10** suitable for *click* reaction with azidomethyl-polystyrene mediated by the **TTM-Cu** catalyst.



Scheme 7. Synthesis of the polymer-supported organocatalyst **11**.

The resin **11** was evaluated in the model Michael addition of propionaldehyde to (*E*)-β-nitrostyrene (Table 3). Under the conditions previously optimized for **4** (Table 3, entry 1), the reaction proceeded slowly and with lower selectivity than with the silylated resin **4**. The addition of a cocatalyst such as benzoic acid (Table 3, entry 2) led to a slight improvement in the activity of catalyst **11**, although deactivation was observed (after *ca.* 48 h) before full conversion could be achieved.

Table 3. Evaluation of organocatalyst **11** in the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]



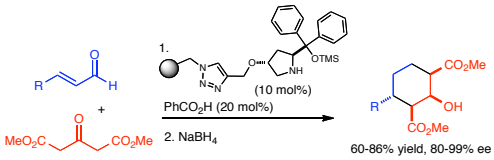
Entry	additive (10 mol %)	t [h]	Yield[b] [%]	d.r.[c]	ee[d] [%]
1	-	96	51	80:20	85
2	PhCOOH	48	63	79:21	92
3[e]	PhCOOH[f]	48	53	82:18	90
4	4-NO_2PhCOOH	48	35	2:1	82
5[g]	PhCOOH	48	55	93:7	93
6[h]	PhCOOH	60	72	95:5	93

[a] Reactions performed at room temperature on a 0.2 mmol scale using 1.5 equiv of propionaldehyde and 10 mol % of catalyst **11**. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction. [d] Determined by chiral HPLC analysis. [e] Reaction carried out with 15 mol % of catalyst **11**. [f] 15 mol % of additive. [g] Reaction carried out using 1.5 equiv of (*E*)-β-nitrostyrene. [h] Reaction carried out using 3 equiv of (*E*)-β-nitrostyrene.

On the other hand, the addition of benzoic acid had a positive effect in the enantioselectivity of the process, which increased from 85% to 92% *ee*, while the diastereoselectivity did not experience any change. The addition of an additional 5 mol % of catalyst and cocatalyst did not change significantly the results (Table 3, entry 3). The addition of more acidic *p*-nitrobenzoic acid, in turn, had a negative effect on both conversion and stereoselectivity (Table 3, entry 4). At the light of recently published kinetic studies revealing that, in the case of peptide-organocatalyzed conjugate addition reactions between aldehydes and nitroolefins, the rate limiting steps are both the reaction of the enamine with the electrophile and the hydrolysis of the resulting imine,[19] we decided to perform the Michael addition of propanal to (*E*)-β-nitrostyrene using 1:1.5 and 1:3 molar ratios of aldehyde to nitroolefin (Table 3, entries 8 and 6 respectively). In these cases, the excess of nitrostyrene led to the corresponding Michael adduct with good enantioselectivity and highly improved diastereoselectivity in comparison with the previous results. Reaction rate also increased, although complete conversion was not achieved. Based on these initial experiments, we can envisage that polystyrene-supported (*S*)-α,α-diphenylprolinol methyl ether **11**, although does not present the problem of ether cleavage under mild reaction conditions, would show worse performance as catalyst in the Michael addition of aldehydes to nitroolefins in comparison with **4**. This demonstrates once again the crucial role exerted by the *O*-sylyl protection pattern in the control of catalytic activity and selectivity of diarylprolinol ether derivatives.

Conjugate Additions of Malonates to α,β-Unsaturated Aldehydes catalyzed by 4. As it is known, secondary amines readily experience condensation reactions with aldehydes or ketones to form intermediate iminium cations. These species are characterized by a low-lying LUMO, and can often by trapped by nucleophiles before a proton loss converts them into imines (primary amines) or into enamines (secondary amines). This nucleophilic trapping is the fundamental event in iminium-type aminocatalysis. Focusing on conjugate addition reactions, a broad range of nucleophilic intermediates such as nitroalkanes, nitroesters, malonates or ketoesters among others have been used for conjugate addition to α,β-unsaturated systems via iminium-type aminocatalyis.[20] The modularity of the products arising from this process made them valuable building blocks in organic chemistry. Chiral secondary amines such as imidazolidinone derivatives and *O*-TMS protected diarylprolinols have shown high efficiency as catalysts by activating α,β-unsaturated systems through iminium-type mechanisms. Through the use of recoverable organocatalysts, this synthetic efficiency could be complemented by economical and environmental aspects.

In this context, we have recently reported the suitability of the immobilized catalyst **4** for iminium activation in the first step of the Michael-Knoevenagel domino reaction of 3-substituted acrolein derivatives and dimethyl 3-oxoglutarate (Scheme 8).[5g]

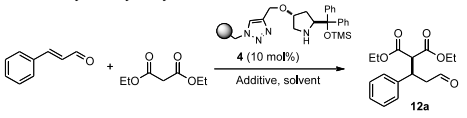


Scheme 8. Domino reaction of 3-substituted acrolein derivatives and dimethyl 3-oxoglutarate catalyzed by **4**.

In view of these results, w decided to test the polymer supported α,α-diphenylprolinol trimethylsilyl ether **4** in the reaction of α,β-unsaturated aldehydes with dialkyl malonates.[21] The addition of diethyl malonate to cinnamaldehyde was selected as a model reaction, and the results for the preliminary screening of reaction conditions are shown in Table 4. Initially, we chose methylene chloride as the solvent because of its good swelling properties for resin **4** and the optimal performance of this catalyst in the Michael addition of aldehydes to nitroalkenes discussed above. When the reaction was performed in the absence of additives, poor activity

was recorded, with only 24% of conversion after 4 days reaction (Table 4, entry 1), although enantioselectivity was high (90% ee). Benzoic acid, a commonly employed acidic cocatalyst for iminium catalysis, was tested as an additive to favor conversion (Table 4, entry 2) but no improvement was observed by adding 30 mol % of this substance. As an alternative, we attempted to increase the activity of catalyst **4** by Lewis base-Brønsted base bifunctional catalysis.[21c] Thus, lithium acetate was used as Brønsted base to activate the malonate reagent, and complete conversion was recorded after 36 h reaction while enantioselectivity was preserved (Table 4, entry 3). To investigate the effect of the ratio between the amount of aldehyde and malonate in the reaction, we tried the same reaction using 1.0 equivalents of diethyl malonate and 1.5 equivalents of cinnamaldehyde and 10 mol % of lithium acetate (Table 4, entry 4). Whereas no change in enantioselectivity was observed, conversion suffered a dramatic and only 25% conversion was achieved after 24 h. Tetrahydrofuran was tested as a solvent for the optimal swelling of 4 in this solvent but, surprisingly, resulted in total loss of catalytic activity (Table 4, entry 5). Water was also tested as solvent, but after 4 days of reaction the conversion was only 49% and the ee decreased to 53% (Table 4, entry 6). Thus, the possible environmental advantages presented by this solvent are overbalanced by its probable negative effect on iminium formation and on malonate reactivity. Finally, in order to mitigate the requirement of long reaction times and according to our previous experience in other reactions organocatalyzed by polystyrene supported secondary amines, we decided to perform the reaction under low-power microwave (MW) irradiation. Very gratifyingly, a notable acceleration of the reaction was observed in this manner (Table 4, entry 7).

Table 4. Screening of conditions in the asymmetric addition of diethyl malonate to cinnamaldehyde catalyzed by **4**.[a]



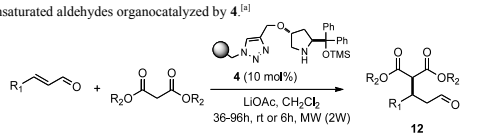
Entry	Solvent	additive (30 mol %)	t [h]	Conv.:[b] [%]	ee[c] [%]
1	CH_2Cl_2	-	96	24	90
2	CH_2Cl_2	PhCOOH	24	8	nd
3	CH_2Cl_2	LiOAc	36	>99	90
4[d]	CH_2Cl_2	LiOAc[e]	24	25	90
5	THF	LiOAc	48	0	nd
6	H_2O	LiOAc	96	49	53
7[f]	CH_2Cl_2	LiOAc	6	93	90

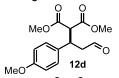
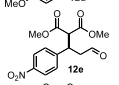
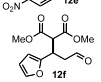
[a] Reactions performed at room temperature on a 0.2 mmol scale using 3 equiv of diethyl malonate, 10 mol % of catalyst **4** and 1 mL of solvent. [b] Determined by ^1H NMR of the crude reaction. [c] Determined by chiral HPLC analysis. [d] Reaction carried out with 1.5 equiv of aldehyde respect to the malonate. [e] 10 mol%. [f] Reaction carried out at 2 W power MW irradiation in 0.3 mL of CH_2Cl_2.

Under 2 W power microwave irradiation the reaction temperature increased from 23 to 30 ºC and the reaction time was reduced by a factor of six for the same conversion, while no change in enantioselectivity was noticed. Under these optimized conditions, the scope of the reaction was studied. A series of dialkyl malonates and α,β-unsaturated aldehydes were tested and the results are presented in Table 5.

The addition of different dialkyl malonates such as methyl, ethyl or isopropyl esters to cinnamaldehyde was studied at room temperature and under microwave irradiation (2W, 6 h), leading in all cases to the corresponding products with full conversion and high (90-99% ee) enantioselectivities (Table 5, entries 1-3). Branching in the alkyl moiety of the malonate ester (entry 3) resulted in extended reaction time for complete conversion. Given the excellent enantioselectivity recorded with dimethyl malonate (entry 2), we evaluated its addition to a small family of α,β-unsaturated aldehydes. Good yields and high enantioselectivities were obtained with cinnamaldehyde derivatives bearing either an electron withdrawing or an electron donating group in the *para* position of the ring (Table 5, entries 4 and 5).

Table 5. Substrate scope in the asymmetric addition of dialkyl malonates to α,β-unsaturated aldehydes organocatalyzed by **4**.[a]



Entry	Product	t [h]	Yield[b,c] [%]	ee[b,d] [%]
1	 12a	36	81 (88)	91 (90)
2	 12b	36	86 (80)	99 (99)
3	 12c	72	85 (63)	90 (90)
4	 12d	96	87 (85)	94 (92)
5	 12e	36	90 (89)	92 (90)
6	 12f	96	75 (82)	77 (78)
7	 12g	96	85 (76)	79 (83)

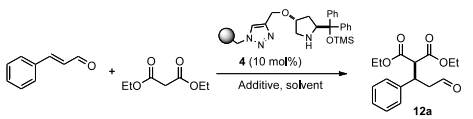
[a] Reactions performed at room temperature on a 0.2 mmol scale using 3 equiv of malonate, 30 mo% of LiOAc, 10 mol % of catalyst **4** in 0.3M CH_2Cl_2 solution. [b] The results of the experiments under MW irradiation are shown in parentheses (6h, 2W). [c] Isolated yield. [d] Determined by chiral HPLC analysis.

In the case of the addition of dimethyl malonate to heterocyclic α,β-unsaturated aldehydes such as 3-(2-furyl)acrolein, full conversion was again observed but enantioselectivity was substantially lower (Table 5, entry 6). To exemplify enals lacking extended conjugation, 2-heptenal was also tested as an electrophile in the reaction (Table 5, entry 7) providing the addition product in good yield and enantioselectivity. As a general observation, the results obtained in this screening showed that the bifunctional catalyst system **4**-lithium acetate is highly efficient for the addition of malonates to α,β-unsaturated aldehydes with the advantage of easy separation of the supported catalyst from the obtained products. From the point of view of experimental conditions, activation of the reactions with low-power microwave irradiation (2

W) is clearly advantageous over performing the reactions at room temperature.

The possibility of recycling and reusing resin **4** was next studied. As it is shown in Table 6, conversion decreased considerably when the catalytic system resin **4**:LiOAc was directly reused after separation of the reaction mixture and simply washed with dichloromethane (Table 6, cycle 2). Addition of fresh LiOAC in the next cycle did not improve the catalytic activity (Table 6, cycle 3); nevertheless, enantioselectivity remained unchanged over the three runs. As already mentioned, we could reactivate resin **4** in the Michael addition of aldehydes to nitroolefines by reprotecting inactive polymer-supported diphenylprolinol with trimethylsiyl *N,N*-dimethylcarbamate.[17] In this particular case, however, such a treatment (albeit positive) did not lead to complete recovery of the catalytic activity of **4** (Table 6, cycle 4).

Table 6. Recycling experiments of catalyst **4** in the asymmetric addition of diethyl malonate to cinnamaldehyde.[a]



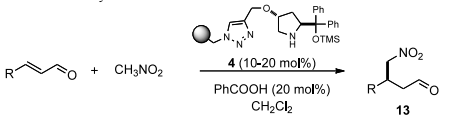
Cycle	t [h]	Conv[b] [%]	ee[c] [%]
1	6	93	90
2	6	73	90
3[d]	6	53	90
6[e]	6	77	90

[a] Reactions performed at room temperature on a 0.2 mmol scale using 3 equiv of malonate, 30 mo% of LiOAc, 10 mol % of catalyst **4** and in 0.3M CH_2Cl_2 solution under 2 W power MW irradiation. [b] Determined by ^{1}H NMR of the crude reaction. [c] Determined by chiral HPLC analysis. [d] Additional 30 mol % of LiOAc was added. [e] Re-conditioned resin by treating it with trimethylsilyl *N,N*-dimethylcarbamate.[5f]

In order to test the performance of polystyrene-supported (*S*)-α,α-diphenylprolinol methyl ether **11** in reactions taking place *via* iminium intermediates, **11** was also tested as catalyst in the addition of diethyl malonate to cinnamaldehyde at 10 mol % catalyst loading and in the presence of 30 mol % of LiOAc in CH_2Cl_2, using 2W MW irradiation during 6h. The yield obtained was only 27% with 86% of enantiomeric excess, confirming again the lower efficiency of **11** with respect to **4**.

Addition of Nitromethane to α,β-Unsaturated Aldehydes catalyzed by 4. Further proof of the effectiveness of resin **4** in reactions taking place *via* iminium activation could be obtained from its notable performance in the iminium-catalyzed enantioselective synthesis of γ-nitro aldehydes via a Henry-type reaction of nitromethane with α,β-unsaturated aldehydes.[22] Preliminary experiments in the addition of nitromethane to cinnamaldehyde under the optimal reaction conditions reported for α,α-diphenylprolinol-type catalysts[22a,c] (MeOH, 10 mol % catalyst and 10-20 mol % benzoic acid as cocatalyst) resulted in poor conversion. Much better results were obtained with dichloromethane, an optimal swellling media for **4**, which was adapted as the solvent for this study (Table 7). On the other hand, the use of 20 mol % LiOAc as a cocatalyst in the model addition of nitromethane to cinnamaldehyde resulted in a significant reduction in activity, so that its use was no longer considered. Thus, the selected reaction conditions involved the use of **4**/benzoic acid in dichloromethane.

Table 7. Evaluation of organocatalyst **4** in the Michael addition of nitromethane to α,β-unsaturated aldehydes.[a]



Entry	Product	T [ºC]	t [h]	Conv.[b] [%] (Yield[c] [%])	ee[d] [%]
1[e]		rt	65	75 (52)	96
2		rt	56	>99 (86)	96
3	13a	45	20	83 (75)	95
4[e]		45	30	64 (51)	93
5[f]		45	6	>99 (61)	96
6[f]	13b	45	6	>99 (80)	91
7[f]	13c	45	6	>99 (88)	90
8[f]	13d	45	6	>99 (85)	90
9[f]	13e	45	6	>99 (31)	94
10[f]		30	7	85 (52)	95

[a] Reactions performed on a 0.2 mmol scale using 3 equiv of nitromethane, 20 mol % of PhCOOH, 20 mol % of catalyst **4** in 0.5 mL of CH_2Cl_2. [b] Determined by ^{1}H NMR of the crude reaction. [c] Isolated yield. [d] Determined by chiral GC or HPLC analysis. [e] 10 mol % of catalyst **4**. [f] Reaction performed in a MW reactor (7 W power, except entry 10 that was at 3 W).

When 10 mol % **4** and 20 mol% benzoic acid were used to promote the reaction at room temperature, only moderate conversion was recorded after 65 h (entry 1). Enantioselectivity, however, compared very favorably with that recorded with soluble α,α-diphenylprolinol trimethylsilyl ethers.[22] Increasing catalyst loading to 20 mol % was enough to achieve complete conversion, high yield and excellent enantiomeric excess after reasonable reaction time (entry 2). We also found that heating the reaction mixture at 45 ºC importantly accelerates the reaction, but compromising both yield and enantioselectivity (entries 3-4). Interestingly, when the reaction was performed at this temperature, but in a microwave reactor at 7 W power irradiation, we were able to reduce significantly reaction time and to achieve total conversion of cinnamaldehyde without any deterioration in enantioselection (entry 5). The observed decrease in isolated yield under these conditions can be attributed to sensitivity of the aldehyde product.[22b]

The beneficial effect of microwave activation in this reaction was additionally confirmed when a representative selection of α,β-unsaturated aldehydes was evaluated under these conditions. High yields and selectivities were recorded with both electron poor or electron rich substituted cinnamaldehydes (Table 7, entries 6-8).

With 3-(2-furylacrolein (Table 7, entries 9-10) the reaction proceeded better when was run under MW irradiation at 30 ºC, giving the corresponding γ-nitro aldehyde in moderate yield but excellent enantioselectivity.

Conclusion

In summary, an insoluble polystyrene-supported diarylprolinol silyl ether (**4**) has been prepared and used as a highly efficient, reusable organocatalyst for Michael additions taking place under both enamine or iminium catalysis. In reactions taking place via enamine intermediates, **4** exhibits a remarkable preference for linear aldehyde donors, that can be used in practice for the differentiation between linear and branched aldehydes in their reactions with nitroolefins. In reactions taking place via iminium intermediates, **4** efficiently mediates the addition of dialkyl malonates and nitromethane to α,β-unsaturated aldehydes. As a general observation, **4** exhibits a catalytic performance comparable or superior to monomeric or soluble diarylprolinol silyl ethers while offering the additional advantages of simplified reaction work-up, easy catalyst recovery, and possibility of reuse. In an attempt to extend the life cycle of **4** in view of repeated use, a polystyrene-supported diarylprolinol methyl ether (**11**) has also been prepared and evaluated. However, the catalytic characteristics of this species lie far below those of **4**.

Experimental Section

General procedure for the Michael addition of aldehydes to nitroolefines catalyzed by 4 or 11 (GP1): The corresponding nitroolefin (0.2 mmol) and catalyst **4** (46.1 mg, 10 mol %, f = 0.462 mmol g^{-1}) or **11** (45.1 mg, 10 mol %, f = 0.443 mmol g^{-1}) were mixed with the aldehyde (0.3 mmol) in CH_2Cl_2 (1.0 mL). The suspension was stirred at room temperature for the time mentioned in Table 2 and then directly filtered off. The solid resin was washed with CH_2Cl_2 and the organic filtrate was concentrated under reduced pressure. A ^{1}H-NMR spectrum was registered to calculate conversion and diasteromeric ratio. In the case of volatility of the starting aldehyde, the Michael adduct was obtained without further purification. When the purification was required it was done by flash chromatography on silica gel (EtOAc/hexanes) to afford the Michael adduct. The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak IB and Chiralcel AD-H columns and their respective guard columns).
All the products are known and spectroscopic data of all products obtained are in agreement with the published data. The products **5a-k** have been previously described.[5f]
Starting nitroolefins *E*-(4-nitrobut-3-en-1-yl)benzene, *E*-(2-nitrovinyl)cyclohexane and *E*-3-methyl-1-nitrobut-1-ene were prepared according to the literature procedure. [23]

(2*R*, 3*R*) 2-Methyl-3-nitromethyl-5-phenyl-pentanal[24] **(5l)**:
Title compound was prepared from *E*-(4-nitrobut-3-en-1-yl)benzene and propionaldehyde according to GP1 in 94% yield (44.2 mg, 0.188 mmol) as mixture of two inseparable diastereomers. 95% *ee* by HPLC: IB (hexane/*i*PrOH 95:5, 1.0 mLmin^{-1}, λ = 220 nm); t_R(major) = 18.6 min, t_R(minor) = 21.3 min.

(2*R*, 3*R*)-3-Cyclohexyl-2-methyl-4-nitrobutyraldehyde[12c] **(5m):**
Title compound was prepared from *E*-(2-nitrovinyl)cyclohexane and propionaldehyde according to GP1 in 89% yield (38 mg, 0.178 mmol) as mixture of two inseparable diastereomers. 97% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 1.0 mLmin^{-1}, λ = 213 nm); t_R(major) = 13.3 min, t_R(minor) = 16.7 min.

(2*R*, 3*R*)-2,4-Dimethyl-3-nitromethylpentanal[25] **(5n):**
Title compound was prepared from *E*-3-methyl-1-nitrobut-1-ene and propionaldehyde according to GP1 in 84% yield (29 mg, 0.168 mmol) as mixture of two inseparable diastereomers. 99% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 0.8 mLmin^{-1}, λ = 210 nm); t_R(major) = 12.6 min, t_R(minor) = 13.9 min.

General procedure for the addition of malonates to α,β-unsaturated aldehydes (in batch conditions) (GP2): The resin **4** (10 mol % according to the functionalization, f = 0.462 mmol g^{-1}) and lithium acetate (30 mol%) were placed in a vial. 1 mL of CH_2Cl_2 was added, followed by the corresponding α,β-unsaturated aldehyde (0.2 mmol) and malonate (0.6 mmol). The mixture was stirred at room temperature for the time indicated in Table 4 until total conversion was confirmed by NMR. Then the resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography on silica gel using hexanes:diethyl ether (10:1) as eluent.

General procedure for the addition of malonates to α,β-unsaturated aldehydes (under MW irradiation) (GP3): To the resin **4** (10 mol %, f = 0.462 mmol g^{-1}) and lithium acetate (30 mol %) placed in a MW tube with 0.3 mL of CH_2Cl_2, were added the corresponding α,β-unsaturated aldehyde (0.2 mmol) and malonate (0.6 mmol) were added. The mixture was irradiated at 2 W (30 ºC) during 6 h. Then the resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography using hexanes:diethyl ether (10:1) as eluent.
All the products are known compounds and its spectroscopic data are in agreement with the published data.[21c,g-26]

(*R*)-diethyl 2-(3-oxo-1-phenylpropyl)malonate[21c] **(12a):**
The title compound was obtained from (*E*)-cinnamaldehyde and diethyl malonate with catalyst **4** after 36 h in 81% yield (47.4 mg, 0.162 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 88% yield (51.5 mg, 0.176 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mLmin^{-1}, l = 210 nm); t_R(major) = 17.5 min, t_R(minor) = 21.9 min.

(*R*)-dimethyl 2-(3-oxo-1-phenylpropyl)malonate[21c] **(12b):**
The title compound was obtained from (*E*)-cinnamaldehyde and dimethyl malonate with catalyst **4** after 36 h in 86% yield (45.5 mg, 0.172 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 80% yield (42.3 mg, 0.16 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mLmin^{-1}, l = 210 nm); t_R(major) = 20.4 min, t_R(minor) = 23.8 min.

(*R*)-diisopropyl 2-(3-oxo-1-phenylpropyl)malonate[21c] **(12c):**
The title compound was obtained from (*E*)-cinnamaldehyde and diisopropyl malonate with catalyst **4** after 72 h in 85% yield (54.5 mg, 0.17 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 63% yield (40.3 mg, 0.126 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mLmin^{-1}, l = 210 nm); t_R(major) = 14.4 min, t_R(minor) = 17.6 min.

(*R*)-2-isopropyl 3-methyl 2-((*R*)-1-(4-methoxyphenyl)-3-oxopropyl)malonate[21g] **(12d):**
The title compound was obtained from (*E*)-3-(4-methoxyphenyl) acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 87% yield (56 mg, 0.174 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 85% yield (54.8 mg, 0.17 mmol). HPLC: AD-H (hexane/*i*PrOH 90:10, 0.8 mLmin^{-1}, l = 210 nm); t_R(major) = 25.3 min, t_R(minor) = 27.1 min.

(*R*)-1-isopropyl 3-methyl 2-((*R*)-1-(4-nitrophenyl)-3-oxopropyl)malonate[21g] **(12e):**
The title compound was obtained from (*E*)-3-(4-nitrophenyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 36 h in 90% yield (61 mg, 0.18 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 89% yield (60 mg, 0.178 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mLmin^{-1}, l = 210 nm); t_R(major) = 23.8 min, t_R(minor) = 25.4 min.

(*R*)-1-isopropyl 3-methyl 2-((*R*)-1-(furan-2-yl)-3-oxopropyl)malonate[21g] **(12f):**
The title compound was obtained from (*E*)-3-(2-furyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 75% yield (42.7 mg, 0.15 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 82% yield (46.3 mg, 0.164 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mLmin^{-1}, l = 210 nm); t_R(minor) = 20.3 min, t_R(major) = 22.2 min.

(*R*)-1-isopropyl 3-methyl 2-((*R*)-1-oxoheptan-3-yl)malonate[26] **(12g):**
The title compound was obtained from (*E*)-hept-2-enal and dimethyl malonate with catalyst **4** after 96 h in 85% yield (46.3 mg, 0.17 mmol) following **GP2**. When it was synthesized via **GP3** was obtained in 76% yield (41.4 mg, 0.152 mmol). HPLC: IC (heptane/*i*PrOH 90:10, 1 mLmin^{-1}, mass-APCI(-)); t_R(major) = 13.3 min, t_R(minor) = 14.1 min.

General procedure for the Michael addition of nitromethane to cinnamaldehyde (GP4): Catalyst **4** (10-20 mol %, f = 0.462 mmolg^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a vial. CH_2Cl_2 (0.5 mL), cinnamaldehyde (0.2 mmol, 25 μL), and nitromethane (0.6 mmol, 32 μL) were added successively. The mixture was stirred at the indicated temperature for the time that appears in Table 7. Then the resin was filtered and rinsed with CH_2Cl_2. Solvent removal afforded the desired product, which was purified by flash chromatography (silica gel, hexanes/EtOAc 10:1).

General procedure for the Michael addition of nitromethane to α,β-unsaturated aldehydes under MW irradiation (GP5): Catalyst **4** (86.6 mg, 0.04 mmol, f = 0.462 mmolg^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a MW tube. CH_2Cl_2 (0.5 mL), the **α,β**-unsaturated aldehyde (0.2 mmol), and nitromethane (0.6 mmol, 32

μL) were added successively. The mixture was irradiated at 7 W for 6 h at 45 ºC. Then the resin was filtered and rinsed with CH_2Cl_2. Solvent removal afforded the desired product, which was purified by flash chromatography (silica gel, hexanes/EtOAc 10:1). All the products are known compounds and its spectroscopic data are in agreement with the published data.[22a,c]

(*S*)-4-Nitro-3-phenylbutanal[22a] **(13a)**: Title compound was obtained from cinnamaldehyde in 86% yield following GP4, and in 61% yield via GP5. GC-MS: Chiraldex Γ-TA (130 ºC isotherm, 1.5 mLmin^{-1}); t_R(minor) = 133.4 min, t_R(major) = 139.4 min.

(*S*)-3-(4-Methoxyphenyl)-4-nitrobutanal[22a] **(13b)**: Title compound was obtained from 3-(4-methoxyphenyl)propenal in 80% yield following GP5. HPLC: IB (hexane/*i*PrOH 85:15, 1.0 mLmin^{-1}, λ = 254 nm); t_R(minor) = 11.9 min, t_R(major) = 12.5 min.

(*S*)-4-Nitro-3-(4-nitrophenyl)butanal[22a] **(13c)**: Title compound was obtained from 3-(4-nitrophenyl)propenal in 88% yield following GP5. HPLC: IC (hexane/*i*PrOH 90:10, 1.0 mLmin^{-1}, λ = 254 nm); t_R(minor) = 41.3 min, t_R(major) = 44.4 min.

(*S*)-3-(4-Chlorophenyl)-4-nitrobutanal[22a] **(13d)**: Title compound was obtained from 3-(4-chlorophenyl)propenal in 85% yield following GP5. HPLC: IC (hexane/*i*PrOH 10:1, 1.0 mLmin^{-1}, λ = 240 nm); t_R(minor) = 18.9 min, t_R(major) = 20.8 min.

(*S*)-3-(2-Furyl)-4-nitrobutanal[22a] **(13e)**: Title compound was obtained from 3-furyl-propenal in 52% yield following GP5 but under irradiation at 3 W for 7 h. GC-MS: Chiraldex Γ-TA (130 ºC isotherm, 1.5 mLmin^{-1}); t_R(minor) = 49.9 min, t_R(major) = 54.0 min.

For full details on instruments used and data obtained of synthesis and characterization of **11**, please see Supporting Information.

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Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type reactions

Esther Alza, Sonia Sayalero, Pinar Kasaplar, Diana Almaşi and Miquel A. Pericàs*

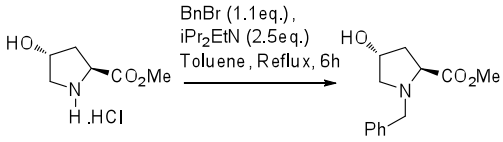
Institute of Chemical Research of Catalonia (ICIQ), Avda Països Catalans, 16, 43007, Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 080208, Barcelona, Spain.

1. General remarks:

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol of Cl g^{-1} resin) was purchased from Novabiochem. In each case the extent of the supporting process and the functionalization of the final resin was determined by elemental analysis (%Cl for the starting Merrifield resin and %N for the functional resins **2**, **4** and **11**). The incorporation of the monomers onto the resins was in all cases >95%.[1] All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz (^1H) and 100.63 MHz ($^{13}C\{1H\}$). TMS was used as internal standard for ^1H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatograph (Serie1200), using Chiralcel AD-H, Chiralpak IA, IB and IC columns and guard columns. GC-MS was performed on Agilent Technologies chromatograph (Model 6890N), equipped with a mass Selective Detector 5973 Inert using Chiraldex G-TA (30 m x 0.25 mm, 0.12 mm) column. Racemic standard products were prepared using the same general procedures but using 10 mol% of (R,S)-α,α-diphenyl-2-pyrrolidinemethanol tert-butyldimethylsilyl ether as catalyst according to reported procedures in order to establish HPLC or GC conditions.

2. Synthesis of polystyrene-supported (*S*)-a,a-diphenylprolinol methyl ether (11):

(2*S*,4*R*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate [2]



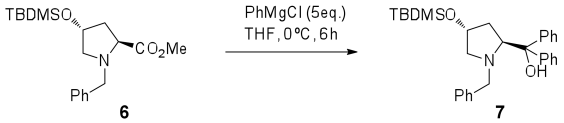
To a solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester hydrochloride (1.7 g, 9.4 mmol) in toluene (20.0 mL) were added *i*-PrNEt (4.1 ml, 23.6 mmol) and benzyl bromide (1.2 mL, 10.4 mmol) and the mixture was heated at reflux (110 ºC) for 6 h. Within this time the reaction mixture was turned into dark orange biphasic clear solution. After 6 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). The organic materials were extracted with EtOAc (3x30 mL) and dried over Na_2SO_4. The product was obtained in 99% yield after solvent removal and used in the next step without any further purification. R_f = 0.17 (EtOAc/hexanes 9:1); $[\alpha]_D^{26}$ = -55.6 (*c* =1.29 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 - 7.26 (m, 5H), 4.47 - 4.44 (m, 1H), 3.90 (d, *J* = 12.92 Hz, 1H), 3.68 - 3.59 (m, 2H), 3.65 (s, 3H), 3.32 (dd, *J* =10.16, 5.60 Hz, 1H), 2.47 (dd, *J* =10.18, 3.78 Hz, 1H), 2.29 - 2.22 (m, 1H), 2.11 - 2.04 (m, 1H), 1.80 - 1.76 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 138.1, 129.1, 128.3, 127.2, 70.3, 63.6, 61.1, 58.1, 51.7, 39.6; IR (ATR): ν = 3401, 3054, 2952, 2811, 1734, 1453, 1437, 1265 cm^{-1}.

(2*S*,4*R*)-methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy) pyrrolidine-2-carboxylate (6) [3]

To a stirred solution of (2*S*,4*R*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate (2.2 g, 9.3 mmol) in DMF (105 mL), imidazole (1.9 g, 27.9 mmol), *tert*-butyldimethylsilyl chloride (2.8 g, 18.6 mmol) and 4-dimethylaminopyridine (0.34 g, 2.8 mmol) were added in this order. The reaction mixture was stirred at room temperature for 18 h. After quenching with MeOH (20 mL), the reaction mixture was diluted with EtOAc (50 mL) and washed with water (3x30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column

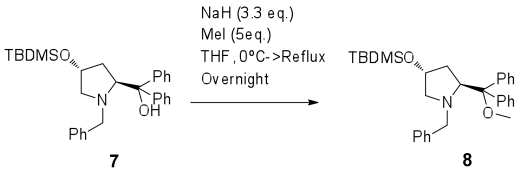
chromatography using EtOAc:hexanes (1:19) as eluent. The product was obtained as colourless oil in 88 % yield. R_f= 0.26 (EtOAc/Hexanes 1:8); $[\alpha]_D^{26}$ = - 30.6 (*c* = 1.25 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 - 7.24 (m, 5H), 4.42 - 4.39 (m, 1H), 3.91 (d, *J* = 12.80 Hz, 1H), 3.64 (s, 3H), 3.59 (d, *J* =12.80 Hz, 1H), 3.53 (t, *J*= 8.16 Hz, 1H), 3.26 (dd, *J* = 9.72, 5.76 Hz, 1H), 2.37 (dd, *J* = 9.72, 5.16 Hz, 1H), 2.22 - 2.15 (m, 1H), 2.05 - 1.99 (m, 1H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 138.1, 129.2, 128.2, 127.1, 70.5, 64.4, 61.7, 59.4, 51.8, 39.6, 25.8, 18.0, -4.8; IR (ATR): ν = 2951, 2929, 2856, 2802, 1748, 1735, 1494, 1470, 1454, 1251, 1094 cm^{-1}.

((2*S*,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl)diphenylmethanol (7)



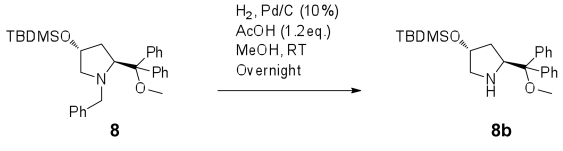
(2*S*,4*R*)-Methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate **(6)** (2.8 g, 8.0 mmol) was dissolved in dry THF (60 mL) under N_2 and cooled at 0 ºC. PhMgCl (20.0 mL, 2 M solution in THF) was added dropwise within 20 min. The reaction mixture was stirred for 6 h, and then quenched with saturated aqueous NH_4Cl. THF was removed under reduced pressure to give a milky residue which was partitioned between CH_2Cl_2 and 1 N HCl solution. The organic layers were collected, washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (EtOAc/Hexanes 1:19) to give the product as slight yellow solid in 92 % yield. R_f= 0.38 (EtOAc/Hexanes 1:6); $[\alpha]_D^{27}$ = + 29.4 (*c* = 1.49 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.36 Hz, 2H), 7.59 (d, *J* = 7.16 Hz, 2H), 7.32 - 7.09 (m, 9H), 7.04 (d, *J* = 7.16 Hz, 2H), 4.97 (s, 1H), 4.36 (t, *J* = 7.84 Hz, 1H), 4.20 - 4.16 (m, 1H), 3.32 (d, *J* = 16.96 Hz, 2H), 2.96 (dd, *J* = 10.90, 4.38 Hz, 1H), 2.50 (dd, *J* = 10.90, 4.02 Hz, 1H), 1.85 - 1.83 (m, 1H), 0.89 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.9, 146.1, 139.9, 128.5, 128.2, 128.1, 128.0, 126.8, 126.5, 126.3, 125.7, 125.5, 71.5, 70.9, 62.2, 61.5, 39.0, 25.8, 17.9, -4.7, -4.8; IR (ATR): ν = 3346, 2952, 2928, 2855, 2802, 1494, 1471, 1252, 1028 cm^{-1}. HRMS (ESI+): *m/z* = 474.2817, calcd. for $C_{30}H_{40}NO_2Si$ $[M+H]^+$: 474.2828.

(2*S*,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxydiphenylmethyl)pyrrolidine (8)



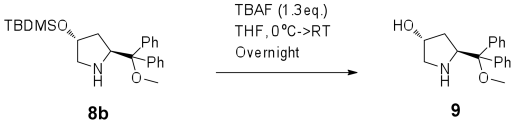
((2*S*,4*R*)-1-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl) diphenylmethanol **(7)** (1.7 g, 3.5 mmol) was dissolved in dry THF (25 mL) and transferred via cannula over NaH (95%, 0.294 g, 11.6 mmol), which was cooled in an ice bath. After stirring this mixture half an hour in an ice bath, MeI (1.1 mL, 17.6 mmol) was added. Then reaction mixture was allowed to warm to room temperature and hydrogen gas evolution was completed. Then, reflux started and reaction continued overnight. The reaction was quenched with aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. Combined organic layers were dried (MgSO4) and concentrated under reduced pressure. Product was obtained as colorless oil in 98 % yield without further purification. R_f= 0.32 (EtOAc/ Hexanes 1:10); $[\alpha]_D^{27}$ = -73.7 (*c* = 1.41 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.61 (m, 4H), 7.38 - 7.23 (m, 9H), 7.07 (d, *J* = 7.32 Hz, 2H), 4.14 - 4.05 (m, 2H), 3.54 (d, *J* = 12.69 Hz, 1H), 2.95 - 2.88 (m,1H), 2.92 (s, 3H), 2.43 (dd, *J* = 5.44, 9.44 Hz, 1H), 2.12 (dd, *J* = 6.82, 9.38 Hz, 1H), 1.93 - 1.89 (m, 2H), 0.75 (s, 9H), -0.18 (s, 3H), -0.2 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.8, 140.3, 138.8, 130.3, 130.2, 128.6, 128.0, 127.3, 127.2, 127.1, 126.4, 87.3, 70.6, 62.4, 61.0, 52.0, 37.9, 25.8, 17.9, -4.9, -5.1; IR (ATR): ν = 3059, 3026, 2950, 2928, 2825, 1600, 1493, 1470, 1462, 1448, 1251, 1072 cm^{-1}; HRMS (ESI+) *m/z* = 488.2970, calcd. for $C_{31}H_{41}NO_2Si$ $[M+H]^+$: 488.2985.

(2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxydiphenylmethyl)pyrrolidine (8b)



To (2*S*,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxydiphenylmethyl)pyrrolidine **(8)** (1.27 g, 2.6 mmol) in a flame-dried flask was added Pd on activated charcoal (10 %). The mixture was submitted to hydrogenolysis in MeOH (10 mL) in the presence of AcOH (0.18 mL, 3.1 mmol), under H_2 atmosphere. The reaction was continued overnight. After that, the reaction mixture was filtered through a short bed of celite and the solution was evaporated under reduced pressure. The saturated aqueous solution of $NaHCO_3$ (30 mL) was added over residue and extracted with Et_2O (3x30 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using EtOAc:Hexanes (1:19) as an eluent. The product was obtained as colourless oil in 85 % yield. R_f= 0.16 (EtOAc/Hexanes 1:2); $[\alpha]_D^{27}$ = + 11.8 (*c* = 1.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 - 7.41 (m, 4H), 7.32 - 7.26 (m, 6H), 4.45 (t, *J* = 7.58 Hz, 1H), 3.74 - 3.71 (m, 1H), 3.07 (s, 3H), 2.60 (dd, *J* = 11.38, 3.50 Hz, 1H), 2.45 (dd, *J* = 11.40, 4.80 Hz, 1H), 2.03 (br, 1H), 1.80 - 1.75 (m, 2H), 0.84 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 141.6, 129.2, 129.1, 127.7, 127.3, 127.2, 127.0, 85.0, 72.6, 60.7, 55.4, 51.4, 37.6, 25.9, 18.1, -4.7, -4.8; IR (ATR): ν = 3087, 2950, 2928, 2855, 1599, 1492, 1360, 1069 cm^{-1}; HRMS (ESI+) *m/z* = 398.2537, calcd. for $C_{24}H_{36}NO_2Si$ $[M+H]^+$: 398.2515

(3*R*,5*S*)-5-(methoxydiphenylmethyl)pyrrolidin-3-ol (9)

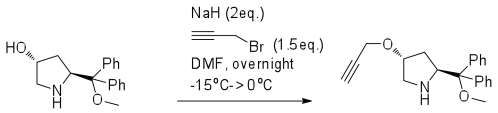


8b **9**

To a solution of (2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxydiphenylmethyl)pyrrolidine **(8b)** (0.9 g, 2.3 mmol) in dry THF (38 mL) was added tetra-*n*-butylammonium fluoride (3 mL, 3 mmol) at 0 ºC under inert atmosphere. Then the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with CH_2Cl_2 (2x50 mL). Combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2:MeOH (99:1 to 90:10) as an eluent. The product was obtained as slight yellow solid in 72 % yield. R_f= 0.22

(MeOH/CH_2Cl_2 1:8); $[\alpha]_D^{27}$ = - 19.2 (*c* = 0.92 in MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 - 7.39 (m, 4H), 7.31 - 7.26 (m, 6H), 4.50 (t, *J* = 15.80 Hz, 1H), 4.01 - 3.98 (m, 1H), 3.07 (s, 3H), 2.71 - 2.67 (m, 1H), 2.49 - 2.45 (br, 2H), 2.34 (dd, *J* = 11.64, 4.24 Hz, 1H), 1.91 - 1.79 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6, 141.3, 129.2, 128.9, 127.7, 127.5, 127.3, 127.2, 85.1, 72.4, 60.3, 55.0, 51.4, 37.4; IR (ATR): ν = 3343, 3087, 2938, 2826, 1492, 1445, 1073 cm^{-1}; HRMS (ESI+) *m/z* = 284.1651, calcd. for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651.

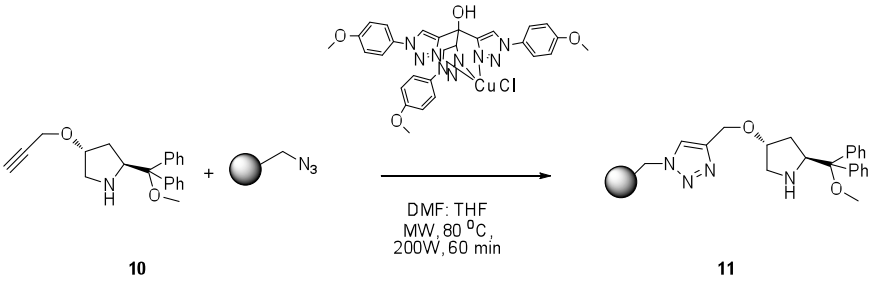
(2*S*,4*R*)-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (10)



9 **10**

NaH (124 mg, 60% dispersion in mineral oil) was placed in a flame-dried flask under argon, washed with 2x10 mL portions of dry hexanes and dried. Then dry DMF (5 mL) was added and the mixture cooled to -15 ºC. A solution of **(9)** (0.44 g, 1.6 mmol) in dry DMF (10 mL) was added to the NaH suspension via cannula. The solution was stirred under inert atmosphere for half an hour, and evolution of H_2 was observed. A solution of 80% propargyl bromide in toluene (0.26 mL, 2.33 mmol) was promptly added and the reaction mixture turned brown colored. The reaction was warmed to 0 ºC and stirred overnight. The reaction was quenched with 5 mL of methanol. Then 100 mL of water were added over the reaction mixture and it was extracted with 3x50 mL of CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The product was purified by flash column chromatography using CH_2Cl_2:MeOH (99:1 to 90:10) as eluent. The product was obtained as brown oil in 60% yield. R_f= 0.31 (MeOH/CH_2Cl_2 1:8); $[\alpha]_D^{28}$ = - 8.61 (*c* = 0.45 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 - 7.24 (m, 10H), 4.41 (dd, *J* = 7.38, 8.46 Hz, 1H), 4.05 (d, *J* = 2.40 Hz, 2H), 3.82 - 3.78 (m, 1H), 3.07 (s, 3H), 2.86 - 2.82 (m, 1H), 2.41 (dd, *J* = 12.16, 4.56 Hz, 1H), 2.37 (t, *J* = 2.42 Hz, 1H), 2.02 - 1.96 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 141.5, 129.9, 129.2, 129.0, 128.3, 127.7, 127.3, 127.2, 127.1, 84.9, 80.1, 79.5, 74.0, 60.8, 56.1, 52.1, 51.5, 34.0; IR (ATR): ν = 3286, 3087, 2935, 2855, 2113, 1658, 1596, 1491, 1444, 1072 cm^{-1}. HRMS (ESI+) *m/z* = 322.1796, calcd. for $C_{21}H_{23}NO_2$ $(M+H)^+$: 322.1807.

4-((((3*R*,5*S*)-5-(methoxydiphenylmethyl)pyrrolidin-3-yl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazole polystyrene (11)



(2*S*,4*R*)-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine **(10)** (122 mg, 0.38 mmol), azidomethylpolystyrene resin[4] (610 mg, f = 0.517 mmol g^{-1}), 3 mL of DMF, 3 mL of THF and *tris*(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst[5] (20.5 mg, 0.03 mmol, 10 mol %) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 50 min under microwave irradiation of 200 W without stirring. After the reaction was completed, the resin was filtered and washed with CH_2Cl_2 (200 mL) and THF (200 mL) and was dried overnight in vacuo at 40 ºC. IR (ATR): ν = 3082, 3059, 2918, 1600, 1492, 1451, 1265, 1248, 1066 cm^{-1}; A 99% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.52; found: C 88.06, H 7.41, N 2.48; f = 0.443 mmol g^{-1}.

3. References for the Supporting Information:

[1] Yield of incorporation calculated as $100f/f_{max}$, in which f (mmol ligand per gram resin) is the fuctionalization calculated from the nitrogen elemental analysis, and f_{max} (mmol ligand per gram resin), the maximal ligand functionalization level, is calculated as described in the following: Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309.

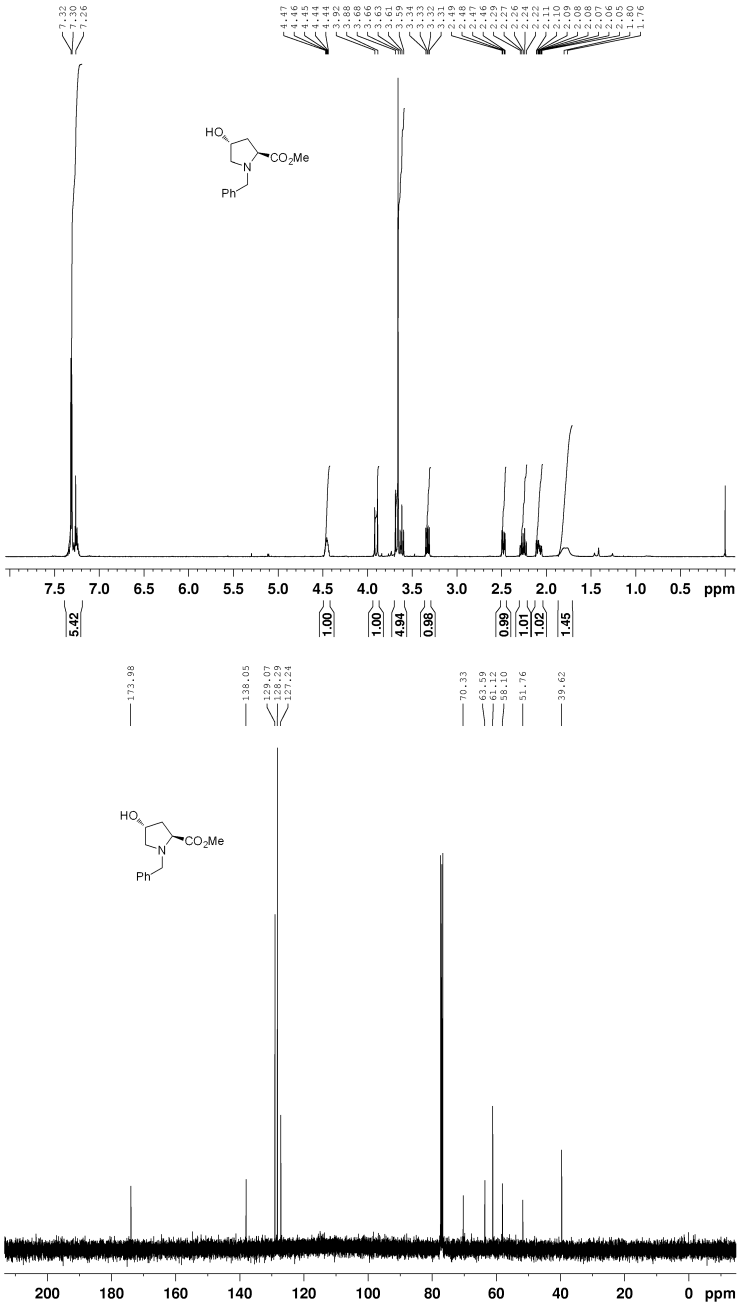
[2] Rosen, T; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis* **1988**, *1*, 40.

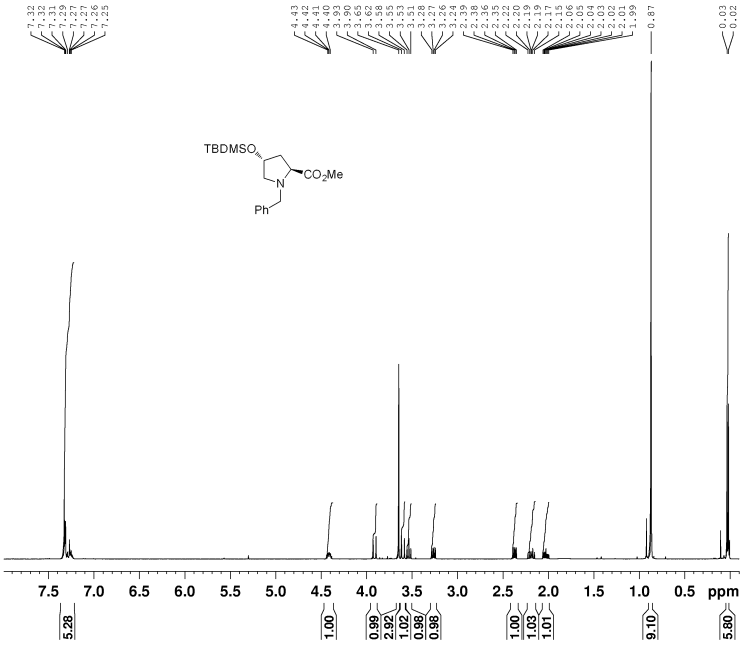
[3] Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; and Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598.

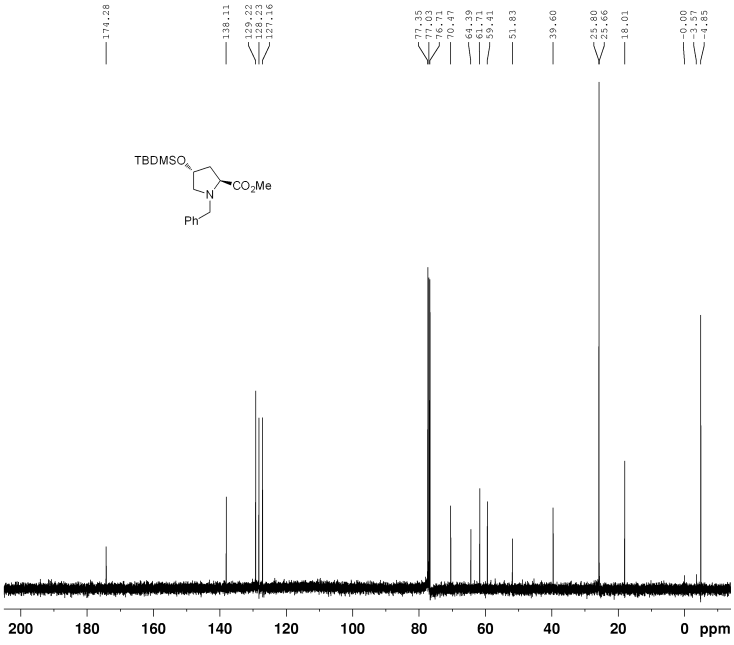
[4] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653

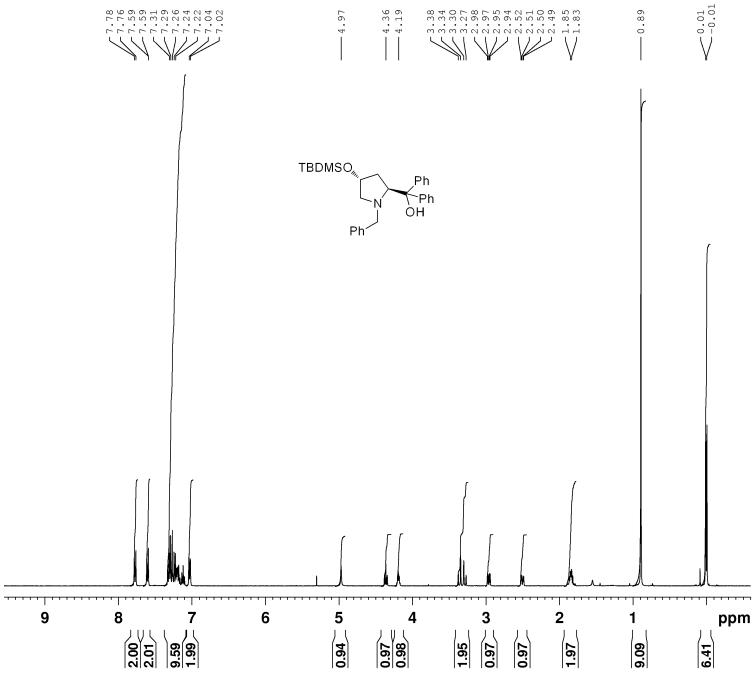
[5] Özcubukcu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680.

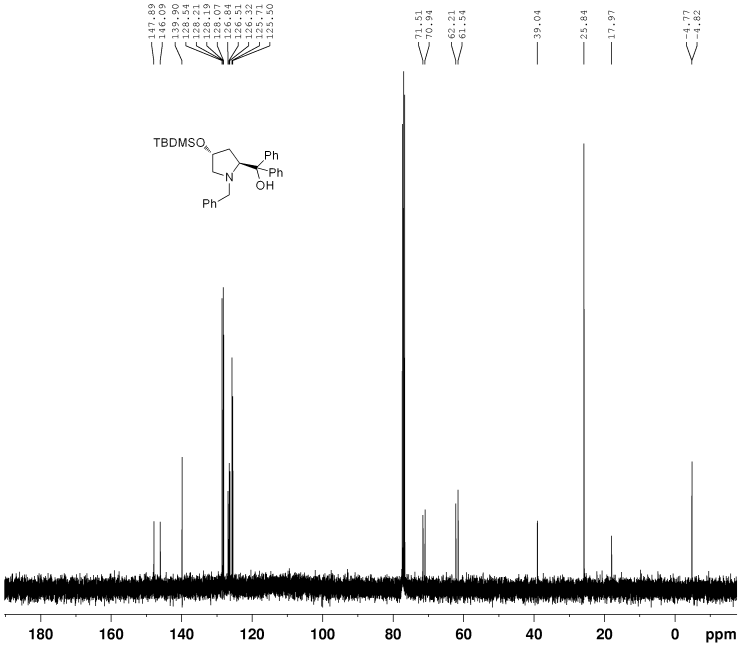
4. Compilation of NMR spectra of new compounds

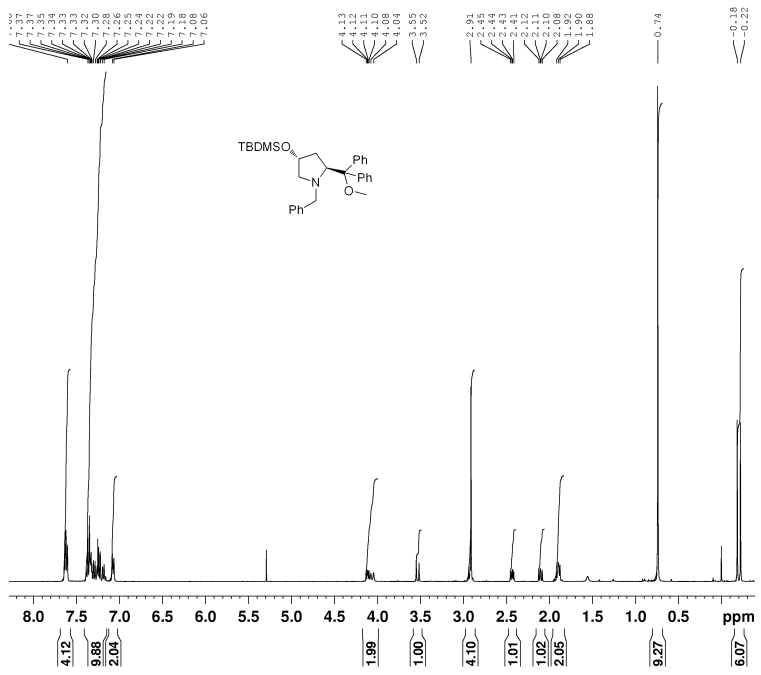








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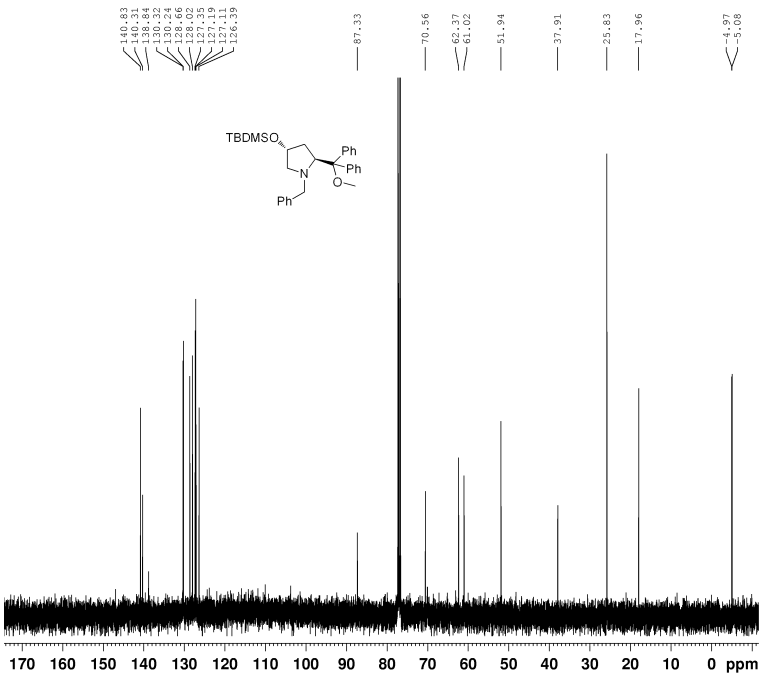
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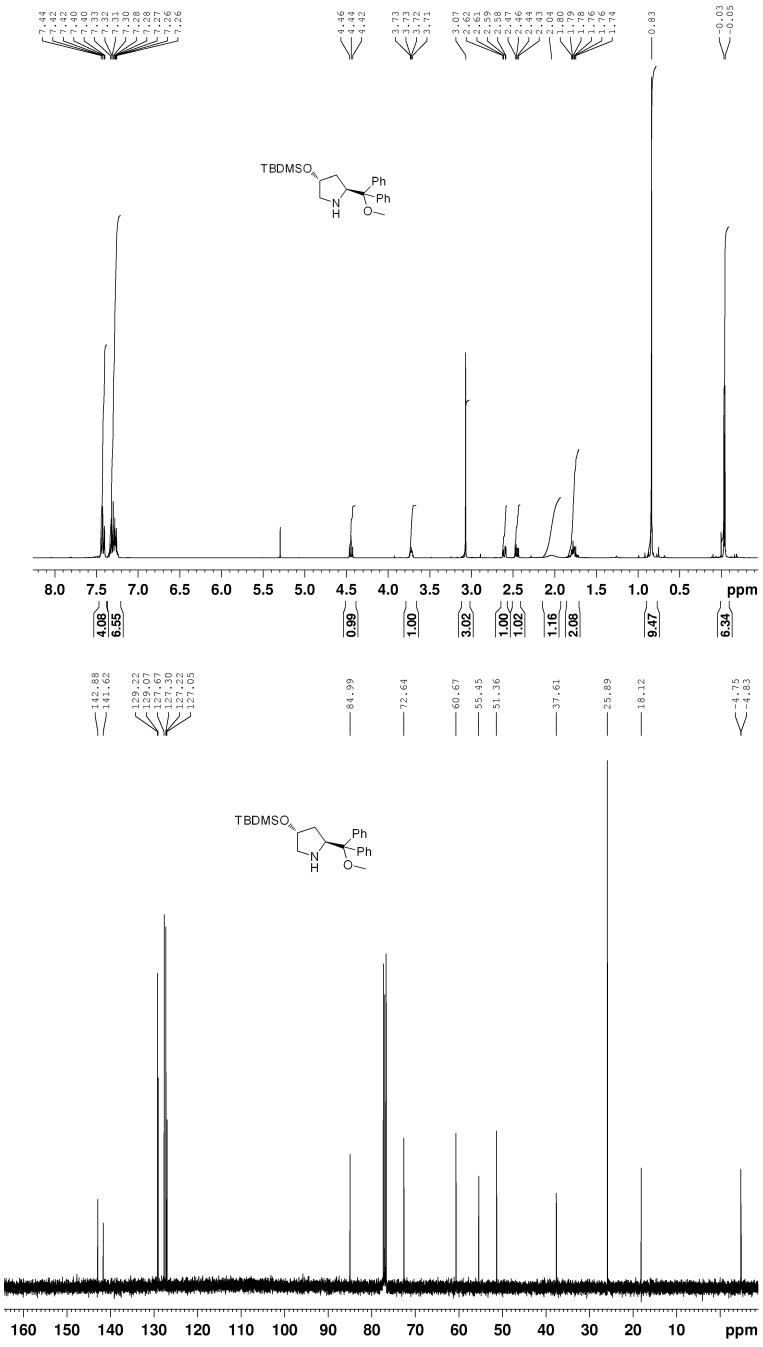
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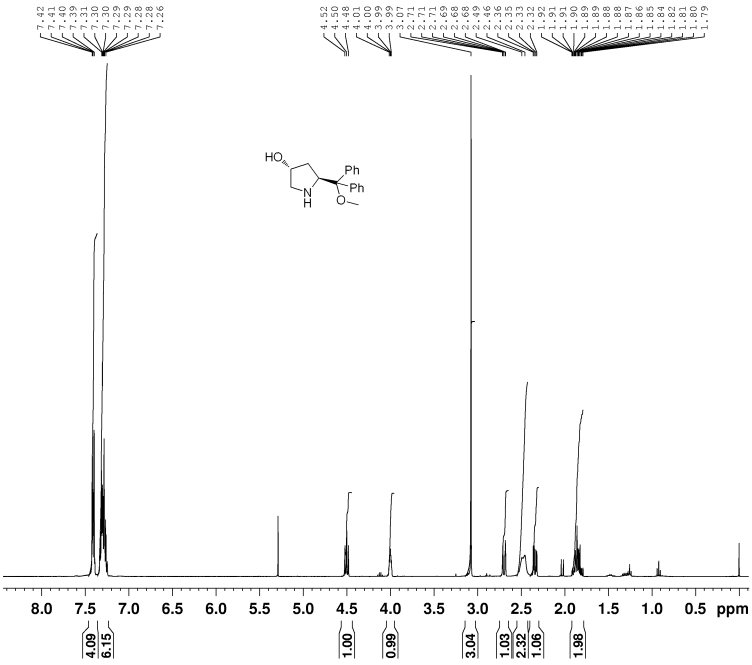
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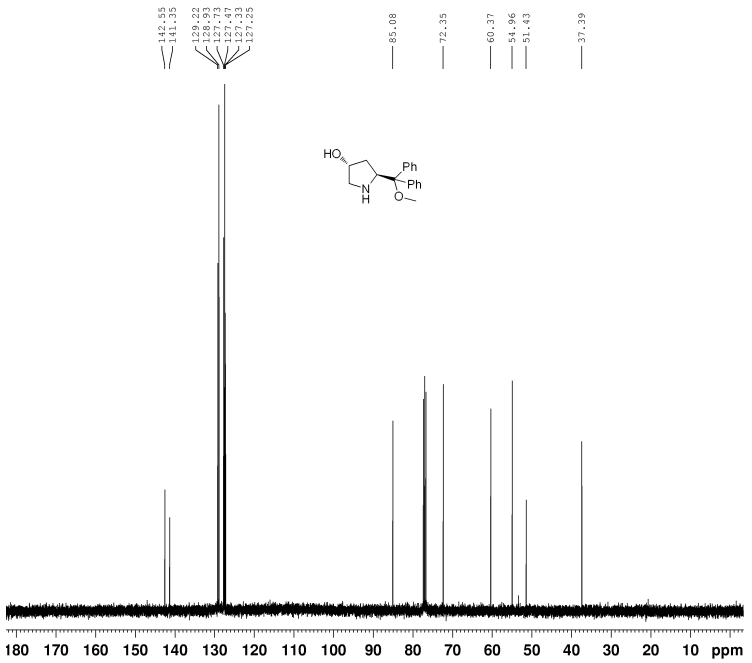
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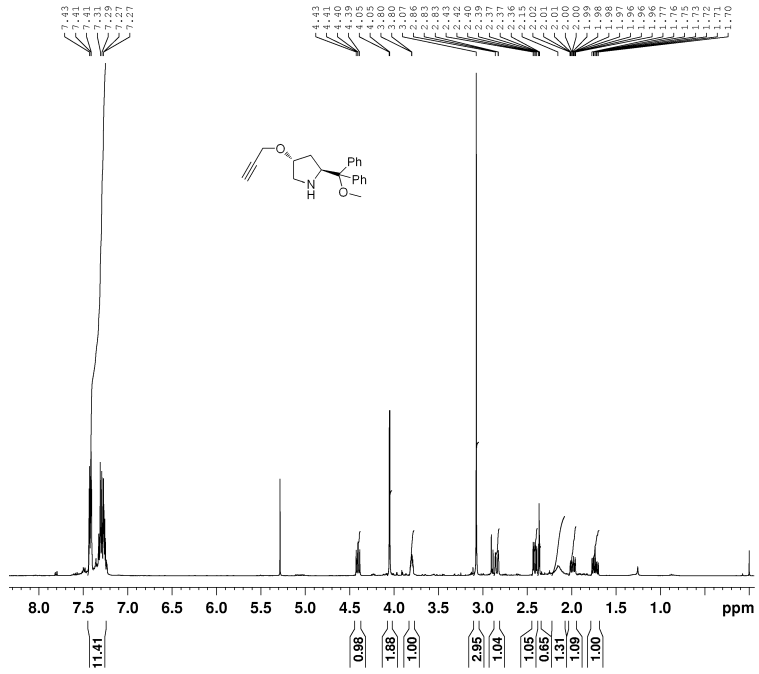

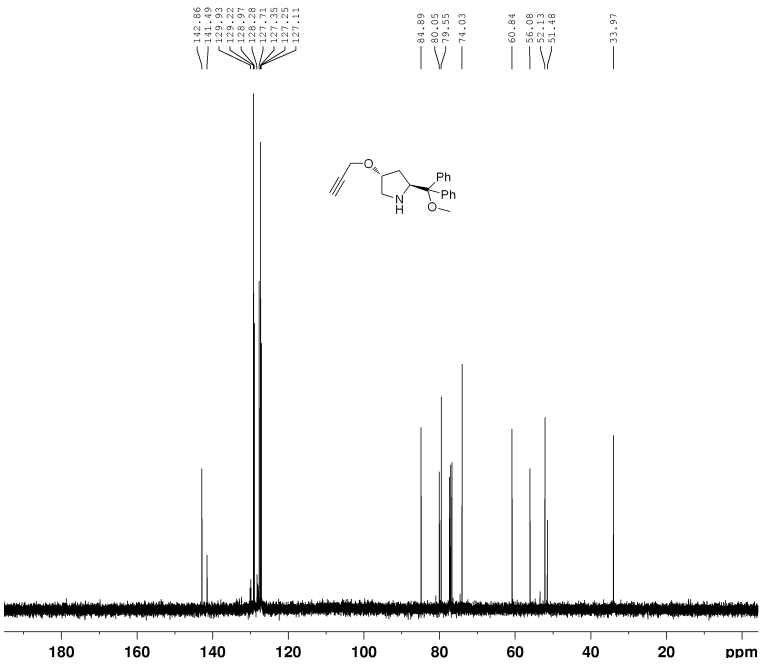

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APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

Chapter IV

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DL:T. 1351-2011

CATALYTIC CASCADE REACTION WITH POLYMER-SUPPORTED DIARYLPROLINOL SILYL ETHERS

The development of new types of chemical reactions for the synthesis of complex and structural diverse natural products has enabled synthetic chemists to assemble almost every discovered natural product over the past few decades. A main driving force for these huge synthetic efforts is the important biological activities of natural products, with high impact on our society. Currently, in the field of total synthesis, cascade reactions[1], and specially organocascade reactions, have an important role in the efficient and rapid generation of complex architectures. One of the big advantages of such domino reactions over classical synthesis is that at least two reactions are carried out in a single operation under the same reaction conditions,[1a] avoiding time-consuming, costly protecting-group manipulations as well as the isolation of reaction intermediates. In this way molecular complexity is achieved quickly, often accompanied by high levels of stereoselectivity. Although Nicolaou noted that the descriptors *domino*, *cascade*, *tandem*, and *sequential* are often used indistinguishably from one another in the literature,[1b] there are several opinions about how these type of reactions should be classified. We consider in this work a domino (or cascade) reaction as a process in which two or more bond-forming transformations occur based on functionalities formed in the previous step and no additional reagents, catalysts, or additives are added to the reaction vessel, without any change in reaction conditions. There are tandem reactions that are not cascades, which involve the isolation of intermediates, a change in reaction conditions, or the addition of reagents or coupling partners.

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[1] For reviews, see: a) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Chemistry*, Wiley-VCH, Weinheim, **2006**. b) K.C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. c) D. Enders, C. Grondal, M. R. M. Huettl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. d) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477. e) H. M. Davies, E. J. Sorensen, *Chem. Soc. Rev.* **2009**, *38*, 2981. f) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993. g) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167. h) B. Westermann, M. Ayaz, S. S. van Berkel, *Angew. Chem.* **2010**, *122*, 858; *Angew. Chem. Int. Ed.* **2010**, *49*, 846. i) D. Bonne, Y. Coquerel, T. Constantieux, J. Rodriguez, *Tetrahedron Asymmetry* **2010**, *21*, 1085.

Organocatalysts are attractive candidates for catalytic cascade reactions because they allow distinct modes of activation, which can be easily combined. As have been mentioned in chapters I and II of the present report, the use of LUMO-lowering iminium ion activation and HOMO-raising enamine activation are the most studied mechanisms in organocatalysis. The combinations of both activation modes in a single operation in an organocatalysed cascade reaction represent an important area of amine-catalysis. Several ways have been explored to combine enamine and iminium catalysis. This concept is limited not only to simple tandem processes, but also to triple-cascade extensions and very recently, quadruple-cascades have also been elaborated.[2] The number of reactions for each activation mode and the exponential increase of combinations for double, triple and quadruple processes lead to new reaction combinations and rapid and efficient synthesis of complex and valuable synthetic building blocks (Fig. 4.1).[3]

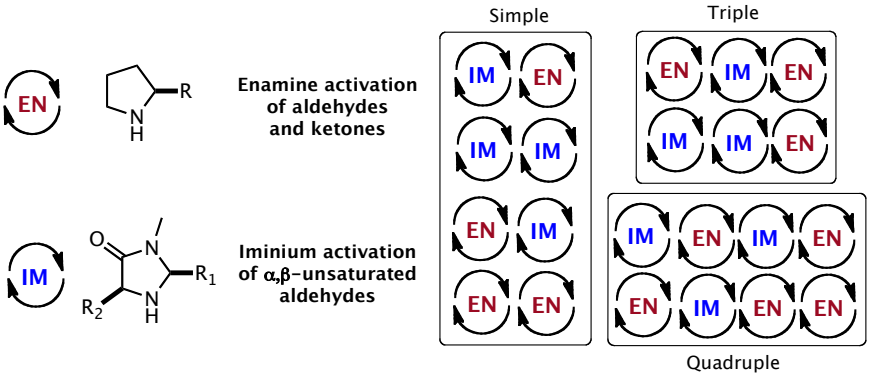


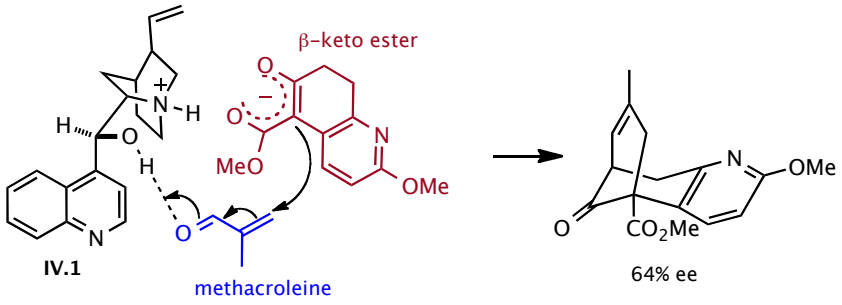
Fig. 4.1. Different combinations of activation for organocascade reactions.

[2] a) F.-L. Zhang, A.-W. Xu, Y.-F. Gong, M.-H. Wei, X.-L. Yang, *Chem. Eur. J.* **2009**, *15*, 6815. b) P. Kotame, B.-C Hong, J.-H. Liao, *Tetrahedron Lett.* **2009**, *50*, 704. c) D. Enders, C. Wang, M. Mukanova, A. Greb, *Chem. Commun.* **2010**, *46*, 2447. d) K. Jiang, Z.-J. Jia, X. Yin, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 2766. e) M. Rueping, K. L. Haack, W. Ieawsuwan, H. Sunden, M. Blanco, F. R. Schoepke, *Chem. Commun.* **2011**, *47*, 3828.

[3] For examples with different activation modes, see ref. 1g.

4.1. ORGANOCATALYTIC MICHAEL/ALDOL TYPE DOMINO PROCESSES.

The Robinsson annulation[4] is a classical cascade reaction consisting of a Michael addition followed by a ring closing aldol reaction. It can be seen as preceding new catalytic asymmetric domino reaction initiated by Michael addition. In 1996, was reported a catalytic asymmetric Michael domino reaction mediated by an heterobimetallic complex.[5] Afterwards, in 1998 an organocatalyzed by cinchona-derivative **IV.1** domino Michael/aldol cascade reaction was applied in the synthesis of the natural product (-)-huperzine A from a β-keto ester and methacrolein (Scheme 4.1).[6]



Scheme 4.1. Intermediate ionic complex in a Michael/aldol cascade reaction.

Since then, the asymmetric organocatalytic domino strategy[1,7] has been deeply investigated and has led to the development of a large number of reactions. In the last year, diaryl-prolinol silyl ethers have been the most

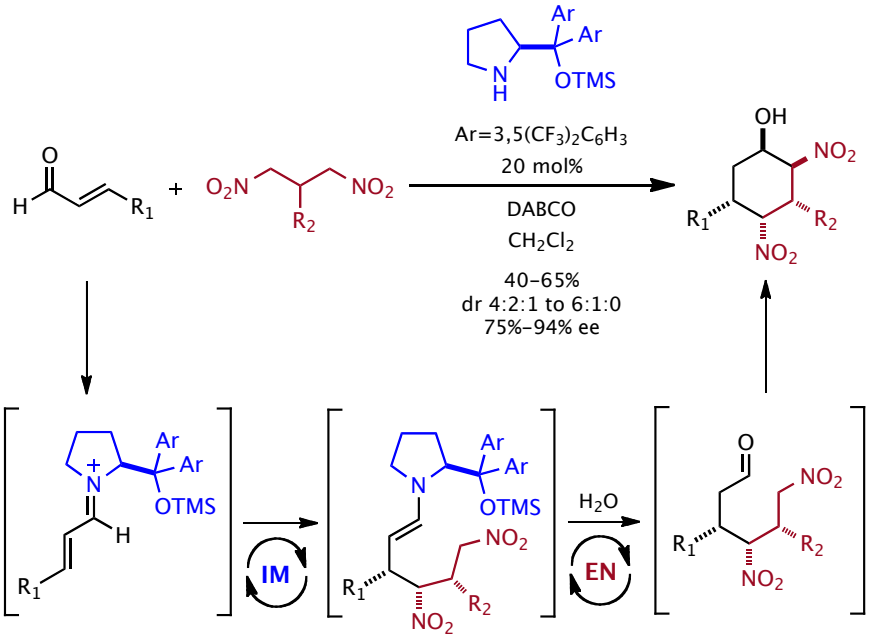
[4] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285. Using proline as catalyst: a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615. b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496. c) B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[5] T. Arai, H. Sasai, K.-I. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* **1996**, *108*, 103; *Angew. Chem. Int. Ed.* **1996**, *35*, 104.

[6] S. Kaneko, T. Yoshino, T. Katoh, S. Terashima, *Tetrahedron* **1998**, *54*, 5471.

[7] For reviews on asymmetric organocatalytic domino reactions, see: a) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619. b) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143. c) N. Ismabery, R. Lavila, *Chem. Eur. J.* **2008**, *14*, 8444. d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. e) X. Yua, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037. f) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions*, RSC Publishing, Cambridge, **2010**. g) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, RSC Publishing, Cambridge, **2010**.

used organocatalysts for asymmetric domino Michael additions to carbon-nucleophiles.[7e] Among them, the iminium-enamine combination is one of the most used strategies. One of the best examples of the powerful iminium/enamine cascade reaction catalyzed by an α,α-diarylprolinol trimethyl silyl ether derivative is the nitro-Michael/nitroaldol cascade between dinitroalkanes and α,β-unsaturated aldehydes to form 2,4-dinitrocyclohexanols containing five stereogenic centers and one major diastereomer of the 32 possible (Scheme 4.2).[8]

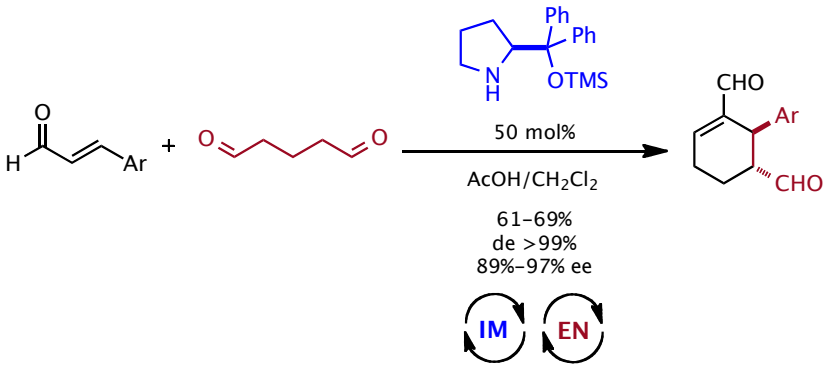


Scheme 4.2. Nitro-Michael/nitroaldol cascade reaction.[7f]

The domino Michael addition/aldol process between a 1,5-dicarbonyl compound like glutaraldehyde and α,β-unsaturated aldehydes can also be catalyzed by α,α-diphenylprolinol trimethyl silyl ether (Jørgensen-Hayashi catalyst).[9] The cyclohexene dicarbaldehydes obtained are highly

[8] E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202.
[9] B.-C. Hong, R. Y. Nimje, A. A. Sadani, J.-H. Liao, *Org. Lett.* **2008**, *10*, 2345.

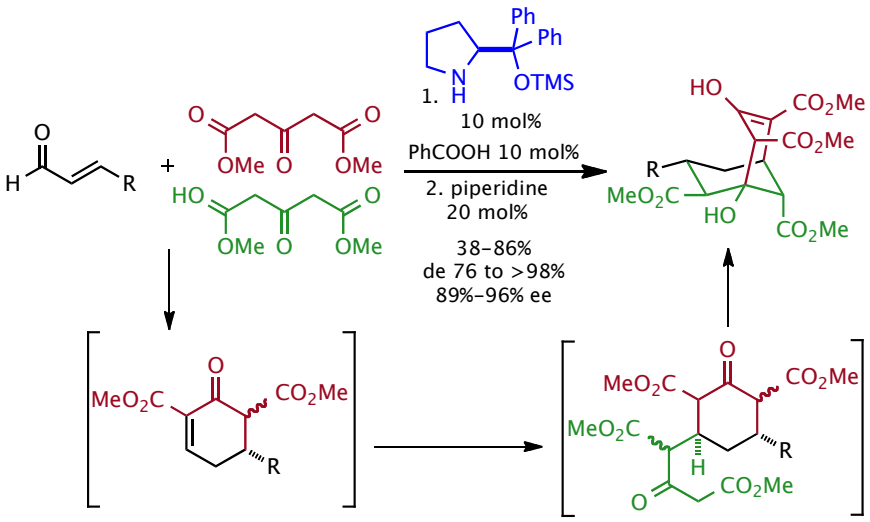
functionalised and with excellent diastereo- and enantioselectivities although in the presence of high catalyst loading (Scheme 4.3).



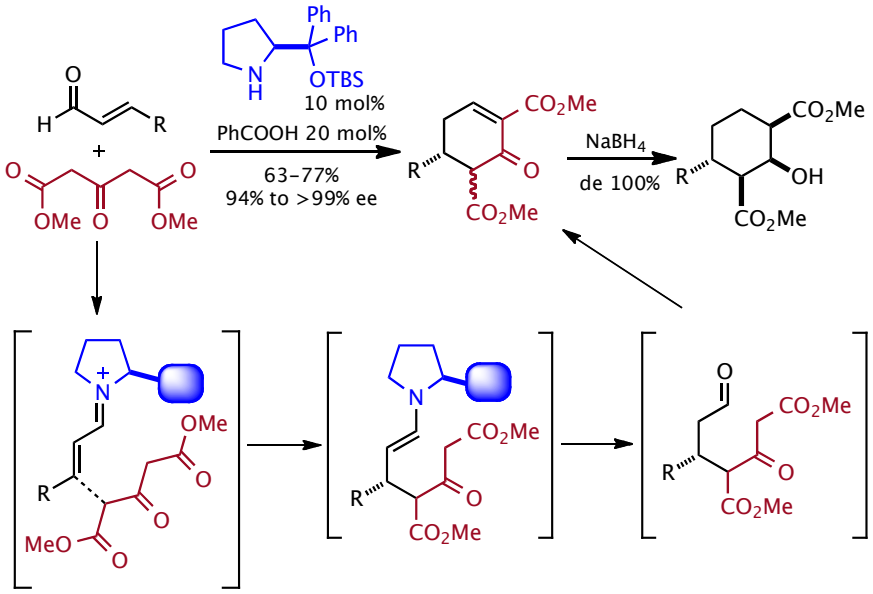
Scheme 4.3. Michael/aldol cascade reaction.

The same catalyst was also employed by the group of Jørgensen to mediate the cascade reaction of a tricarbonyl compound (dimethyl 3-oxo-pentanedioate) and α,β-unsaturated aldehydes. This reaction led to the formation of optically active bicyclo-compounds though two cascade reactions in one-pot procedure, first a cascade Michael/intramolecular aldol condensation followed by a second one promoted by piperidine (Scheme 4.4).[10] This double cascade reaction allows the selective formation of 4 new carbon–carbon bonds, providing 6 new stereocenters in a fully diastereo- and enantioselective way, leading to the controlled synthesis of 1 out of 64 possible stereoisomers by mixing two simple molecules. Subsequently, the group of Hayashi reported the formation of chiral substituted cyclohexenone derivatives by a Michael/Knoevenagel cascade process also between α,β-unsaturated aldehydes and dimethyl 3-oxo-pentanedioate but using in this case only one equivalent (specifically, 1.1 equivalent) of the 1,3,5-tricarbonyl compound to avoid the formation of the bicyclic products (Scheme 4.5).[11] The reaction was catalyzed by *O*-silylated diphenylprolinol and the cyclohexenone products, generated in highly enantioselective manner, are useful synthetic intermediates with several functional groups that allows diverse transformations.

[10] S. Bertelsen, R. L. Johansen, K. A. Jørgensen, *Chem. Commun.* **2008**, 3016.
[11] Y. Hayashi, M. Toyoshima, H. Gotoh, H. Ishikawa, *Org. Lett.* **2009**, *11*, 45.



Scheme 4.4. Organocatalytic asymmetric two-component reaction leading to bicyclo[3.3.1]non-2-enes.



Scheme 4.5. Organocatalytic cyclohexanes formation by domino Michael addition/Knoevenagel reaction.

This cascade process involves an asymmetric Michael reaction by iminium activation of the enal, followed by an intramolecular condensation after release of the catalyst. Further one-pot reactions with other reagents can be performed, which can construct complex cyclohexanones via formation of several bonds in a single pot.[11]

As has been shown and is collected in many reviews and books,[1,7] the imine/enamine activated cascade reactions enable the obtaining of a large number of carbo- or hetero-cyclic complex molecules containing multiple stereogenic centers that are achieved in highly diastereo- and enantioselective processes. Although excellent results are obtained in domino reactions by diverse organocatalysts like, for instance, cinchona alkaloids derivatives,[12] *O*-silylated diarylprolinols are one of the most employed chiral organocatalysts for this type of reactions.[13]

4.2. DOMINO REACTIONS MEDIATED BY SUPPORTED ORGANOCATALYSTS.

There are only few examples in the use of supported organocatalysts in domino reaction,[14] and since the work collected in the present chapter, there is not any precedent reported about the use of supported organocatalysts in continuous flow conditions involving a domino process.

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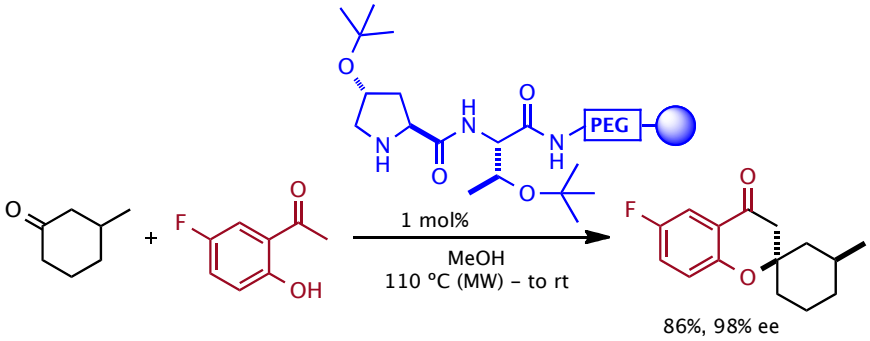
[12] For selected examples of domino reactions organocatalyzed by cinchona alkaloids, see: a) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437. b) B. Tan, P. J. Chua, X. L. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2008**, *10*, 3489. c) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200. d) F. De Vincentiis, G. Bencivenni, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Galzerano, P. Melchiorre, *Chem. Asian J.* **2010**, *5,* 7. e) N. Holub, H. Jiang, M. W. Paixão, C. Tiberi, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16,* 14.

[13] For selected examples of enantioselective domino reactions catalyzed by diarylprolinol silyl ethers, see ref. 10 in **Article E** of the present PhD dissertation.

[14] a) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322. b) R. D. Carpenter. J. C. Fettinger, K. S. Lam, M. J. Kurth, *Angew. Chem.* **2008**, *120*, 6507; *Angew. Chem. Int. Ed.* **2008**, *47*, 6407. c) V. Rodionov, H. Gao, S. Scroggins, D. A. Unruh, A.-J. Avestro, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2010**, *132*, 2570.

The soluble star polymers with highly branched non-interpenetrating cores able to encapsulate catalysts, developed by Fréchet *et. al.*, allows the iminium, enamine, and hydrogen-bond domino process between *N*-methyl indole, 2-hexenal and methyl vinyl ketone in the presence of four incompatible catalysts.[14a] The cascade products were obtained in good yield and diastereoselectivities with more than 99% ee. However, recycle and reuse of the catalyst are not mentioned in the paper. Otherwise, in the case of the hydroxyprolylthreonine derivatives immobilized onto insoluble TentaGel® resin developed by the group of Kurth, optical active chromanones are obtained with excellent ee and high yields and the catalyst can be reused over 40 times without loss of efficiency (Scheme 4.6).[14b]



Scheme 4.6. Chiral Chromanones synthesis through domino reaction mediated by TentaGel-bound organocatalyst.

Catalytic Batch and Continuous Flow Production of Highly Enantioenriched Cyclohexane Derivatives with Polymer-Supported Diarylprolinol Silyl Ethers

Esther Alza,[a] Sonia Sayalero,[a] Xacobe C. Cambeiro,[a] Rafael Martín-Rapún,[a] Pedro O. Miranda,[a] Miquel A. Pericàs*[a,b]

[a] Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

[b] Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain
Fax +34(977)920222; E-mail: mapericas@iciq.es

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Abstract: Diarylprolinol silyl ethers immobilized onto polystyrene have been employed as catalysts in the enantioselective domino Michael–Knoevenagel reaction of dimethyl 3-oxoglutarate and 3-substituted acrolein derivatives, including aliphatic ones. The best catalyst allows the preparation of highly functionalized cyclohexane derivatives in a straightforward and efficient manner, both under batch and continuous flow conditions.

Key words: asymmetric organocatalysis, domino process, Michael addition, Knoevenagel condensation, flow reactors

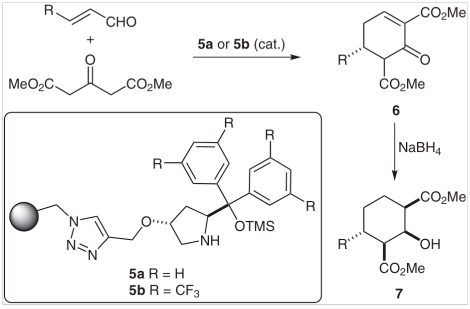
Domino processes[1] are gaining progressive interest for their enormous potential in the synthesis of complex molecules. More specifically, catalytic enantioselective domino reactions[2] not involving the use of metals have potential for importantly modifying the scenario of the synthesis of active pharmaceutical ingredients.

From a practical perspective, the optimal catalytic enantioselective domino process should be performed in such a manner that catalyst separation would not introduce any complexity[3] and, desirably, should be amenable to continuous flow operation.[4,5]

Domino processes involving the combination of Michael and aldol-type reactions (Michael initiated ring closure reactions, MIRC)[6] represent one of the most efficient, convergent approaches to cyclic compounds. Of particular interest are processes where a single catalytic species, like an enantiomerically pure amine, is able to catalyze the enantiodifferentiating step and to mediate the final cyclization thus allowing the formation of enantiomerically pure products.[7] In this context, Hayashi and co-workers[8] and Jørgensen and co-workers[9] have recently reported the use of diarylprolinol silyl ethers as catalysts for enantioselective domino processes involving amine-catalyzed Michael and aldol reactions.[10]

In the context of a research project devoted to the development of chemical processes with improved sustainability characteristics, we have studied the immobilization of organocatalytic species onto polymers[11] using the copper-catalyzed alkyne-azide cycloaddition (CuAAC).[12,13] This strategy has led to supported species with catalytic activities and enantioselectivities similar to or even better than those of their homogeneous counterparts, and has allowed the implementation of single-pass, continuous flow processes for enantioselective Mannich reactions.[11e]

As a part of this project, we have recently reported the preparation and use in Michael reactions of polystyrene-supported diphenylprolinol trimethylsilyl ether (**5a**)[11f] and we thought that this class of catalysts (Scheme 1) could be suitable for the direct synthesis of highly functionalized cyclohexane derivatives in enantiopure form through a domino process.



Scheme 1 Enantioselective synthesis of highly functionalized cyclohexane derivatives with polystyrene-immobilized catalysts **5**

We wish to report in this communication the preparation of a new polystyrene-supported diarylprolinol trimethylsilyl ether catalyst [aryl: 3,5-bis(trifluoromethyl)phenyl, **5b**], the evaluation of **5a** and **5b** for the domino Michael–Knoevenagel process, the recycling and reuse of the optimal resin (**5a**), and the implementation of a flow process allowing the continuous production of highly enantioenriched cyclohexane derivatives from substituted acrolein derivatives and dimethyl 3-oxoglutarate with the same catalyst.

Supporting diarylprolinol trimethylsilyl ethers onto a Merrifield resin using copper-catalyzed alkyne–azide cycloaddition (CuAAC)[12] was easily achieved from commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester via its propargyloxy derivative **1**.[11f] As shown in Scheme 2, Grignard alkylation followed by silylation with concomitant carbamate deprotection of **2** provided the key intermediate **3**, which was subjected to copper(I)-catalyzed azide-alkyne cycloaddition with azi-

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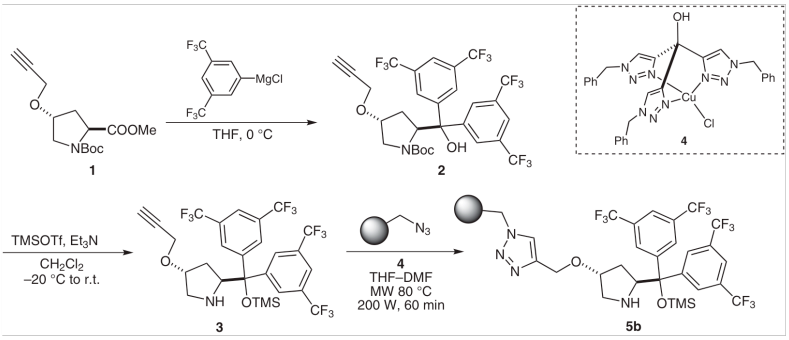


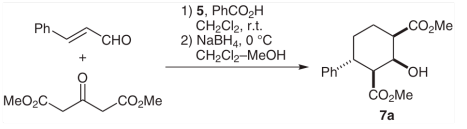
Scheme 2 Synthesis of the polystyrene-supported catalyst **5b**

domethylpolystyrene. The tris(triazolyl)methanol copper complex **4**[14] was an effective catalyst for the 'click' cycloaddition due to its compatibility with free amino groups in the substrate. In this manner, the polymer-supported organocatalyst **5b** can be prepared with high reproducibility in four simple steps.[15]

According to previously reported results[8] and to the swelling properties of resin **5a**,[11f] dichloromethane was selected as the solvent for this study. Moreover, it has been also reported that a small excess of dimethyl 3-oxoglutarate (1.1 equiv) increases the yield of the reaction and prevents the formation of side products.[8]

Taking these considerations into account, organocatalysts **5** were examined in a first series of experiments in the reaction of dimethyl 3-oxoglutarate and *trans*-cinnamaldehyde, with the results summarized in Table 1. It was found that the use of benzoic acid as an additive increased the yield of the domino process, providing alcohol **7a** as a single isomer with good yield over the two steps, in a remarkably shorter reaction time (2 h) and with excellent enantioselectivity (entries 1 and 2). Interestingly, the use of 5 mol% of **5a** and 10 mol% of benzoic acid was enough to induce the complete conversion of cinnamaldehyde in four hours without compromising the enantioselectivity of the process (entry 3). The catalyst loading could be reduced even further to 1 mol%, although the reaction turned somewhat sluggish (entry 4). In the presence of resin **5b** the reaction also proceeded efficiently allowing isolation of **7a** in similar yield and with only a slight erosion in enantioselectivity (entry 5). However, the considerable increase recorded in the reaction time makes apparent the better performance of catalyst **5a**.

Table 1 Optimization of the Reaction Conditions



Entry	Catalyst/$PhCO_2H$ (mol%)	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	**5a** (10)	12	60	96
2	**5a** (10)/(20)	2	73	98
3	**5a** (5)/(10)	4	72	98
4	**5a** (1)/(2)	50[d]	49	98
5	**5b** (10)/(20)	48	71	93

[a] Total conversion to cyclohexenone intermediate **6a** was obtained in all cases, as determined by ^1H NMR of the crude mixture.
[b] Isolated yield of **7a** after reductive workup.
[c] Determined by HPLC (see Supporting Information).
[d] An 84% conversion was obtained in this case.

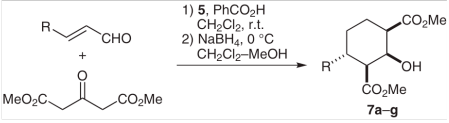
Under the optimized reaction conditions [resin **5a** (10 mol%), benzoic acid (20 mol%) in dichloromethane at room temperature][16] the generality of the process was investigated with a representative set of α,β-unsaturated aldehydes (Table 2).

As shown in the Table 2, the process is compatible with the presence of different functional groups on the aryl ring in substituted cinnamaldehyde substrates (entries 1–6). For these substrates, reactions with catalyst **5a** proceeded smoothly to completion in short reaction times (less than 2 h) to afford the products in good yield and excellent enantioselectivity (97% to >99% ee), regardless of the electronic nature of the substituent in the aryl ring. A similar behavior was observed with other aromatic and heteroaromatic substrates (entries 7–9), although with a moderate decrease in the enantioselectivity for 3-furylacrolein (entry 9). With catalyst **5b** the reaction was in all the cases slower than that with **5a** and slightly less enantioselective (entries 2, 4 and 8).

Noteworthy, the reaction also worked well with an aliphatic substrate such as *trans*-2-heptenal (entry 10), in contrast with previous reports.[8]

Gratifyingly enough, resin **5a** compares favorably with the most efficient homogeneous organocatalyst described so far for the same reaction and substrates, from the perspectives of both catalytic activity and enantioselectivity.[8,9] Moreover, the relative configuration of the four

Table 2 Scope of the Domino Michael–Knoevenagel Process of α,β-Unsaturated Aldehydes and Dimethyl 3-Oxoglutarate



Entry	Product	R	Catalyst	Time (h)	Yield (%)[a]	ee (%)[b]
1	**7a**	Ph	**5a**	2	73	98
2	**7a**	Ph	**5b**	48	71	93
3	**7b**	4-MeOC$_6$H$_4$	**5a**	1.5	86	97
4	**7b**	4-MeOC$_6$H$_4$	**5b**	96	nd[c]	nd
5	**7c**	4-O$_2$NC$_6$H$_4$	**5a**	2	69	99
6	**7d**	4-ClC$_6$H$_4$	**5a**	2	73	>99
7	**7e**	2-naphthyl	**5a**	1	59	>99
8	**7e**	2-naphthyl	**5b**	96	nd[d]	nd
9	**7f**	2-furyl	**5a**	1.5	63	80
10	**7g**	*n*-butyl	**5a**	3	68	87

[a] Isolated yield of **7** after reductive workup.
[b] Determined by HPLC (see Supporting Information).
[c] A 25% conversion into **6b** was obtained as determined by ^{1}H NMR of the crude mixture.
[d] A 5% conversion into **6e** was obtained as determined by ^{1}H NMR of the crude mixture.

stereocenters in the final cyclohexanes could be confirmed in the present instance by X-ray diffraction analysis of **7b** (Figure 1),[17] which was consistent with the diastereoselective, substrate-controlled reduction by borohydride.

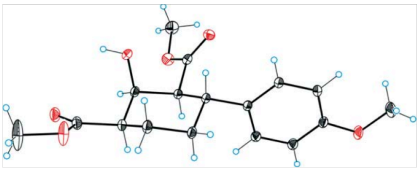


Figure 1 ORTEP plot of substituted cyclohexanol **7b**

As a further step towards our ultimate goal of developing a continuous flow process, we next explored the possibility of a repeated use of samples of **5a**. Very interestingly, in six consecutive runs with *trans*-cinnamaldehyde, the excellent stereochemical performance of the resin remained intact, while the catalytic activity started decreasing after the third run (Table 3).[18] In any case, samples of partially deactivated **5a** could be fully reactivated by treatment with trimethylsilyl *N*,*N*-dimethylcarbamate.[11f]

Table 3 Recycling Experiments in the Reaction between *trans*-Cinnamaldehyde and Dimethyl 3-Oxoglutarate Leading to **7a**, Catalyzed by **5a**

Run	Time (h)	Conv. (%)[a]	Yield (%)[b]	ee (%)[c]
1	2	>99	73	98
2	2	>99	71	98
3	2	>99	68	98
4	4	>99	70	98
5	8	>99	65	98
6	12	82	54	98

[a] Conversion into cyclohexenone **6a** was determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield of **7a** after reductive workup.
[c] Determined by HPLC (see Supporting Information).

In view of the high catalytic activity exhibited by **5a**, we considered that the process could be adapted to continuous flow operation. For this purpose, a system was built up as depicted in Scheme 3, sharing the design principle with previously described systems for similar processes.[11e] Namely, the setup for continuous flow experiments consisted of a glass column filled with the supported catalyst **5a** as the central element. Upstream from the column, a pump and a flask containing a solution with all the reagents were placed and, finally, downstream from the column, a receiving flask. The column was filled with 900 mg of the supported catalyst, and a 0.12 mL/min flow rate (equivalent to ca. 10 min residence time) and 0.1 M concentration for the aldehyde (limiting reagent) were used.

Direct translation of the reaction conditions used in batch to the continuous flow system (1.1 equiv dimethyl 3-oxoglutarate, 0.2 equiv benzoic acid) resulted in low conversion (ca. 10%). However, this initial drawback could be overcome by simply increasing the amount of benzoic acid in the feed mixture, with 64% conversion being achieved with one equivalent of benzoic acid.

Gratifyingly enough, **5a** showed an excellent stability under these conditions, as illustrated by the results recorded in continuous flow operation for 72 hours (Table 4).

In this experiment, in order to avoid deterioration of the reaction product, the receiving flask was flushed with argon and kept at –40 °C during operation. Workup involving borohydride reduction of the cyclohexenone product allowed isolation of cyclohexanol **7b**. After continuous flow operation for 72 hours, 8.7 g of pure **7b** were isolated without any deterioration of the enantioselectivity during the process (97% ee). The use of continuous flow conditions, thus, allowed achieving a TON of 66 (referred to the product formed), meaning an approximately tenfold increase with respect to batch conditions, in an easy and practical manner. Noteworthy, this experiment was carried out with a sample of repeatedly used resin **5a**, which was resilylated (see above) for this purpose.

Table 4 Continuous Flow Production of **7b** from 3-(4-Methoxyphenyl)acrolein and Dimethyl 3-Oxoglutarate Catalyzed by **5a**

Entry	Time (h)	Conv. (%)[a]	ee (%)[b]
1	1	64	–
2	2	64	–
3	3	63	–
4	4	65	–
5	5	65	–
6	24	64	97
7	48	62	97
8	72	62	97

[a] Instant conversion into cyclohexenone, determined by ^{1}H NMR of the crude mixture.
[b] The ee value of isolated **7b** was determined by HPLC (see Supporting Information).

In conclusion, we have shown the suitability of the immobilized catalyst **5a** for the Michael–Knoevenagel domino reaction of 3-substituted acrolein derivatives and dimethyl 3-oxoglutarate. Catalyst **5a** allows repeated recycling under batch conditions, and offers the possibility of easy re-conditioning. Under flow conditions, **5a** exhibits a remarkable robustness, which allows its use for three consecutive days without any appreciable deterioration of its performance (activity and enantioselectivity) for the continuous production of highly substituted cyclohexane derivatives.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was funded by the MICINN (Grant CTQ2008-00947/BQU), the DIUE (Grant 2009SGR623), the Consolider Ingenio 2010 (Grant CSD2006-0003) and the ICIQ Foundation. E.A. thanks the ICIQ Foundation for a predoctoral fellowship. The authors gratefully acknowledge M. Martínez Belmonte and J. Benet-Buchholz, as well as G. Gómez Castresana for their invaluable help with X-ray diffraction and NMR techniques, respectively.

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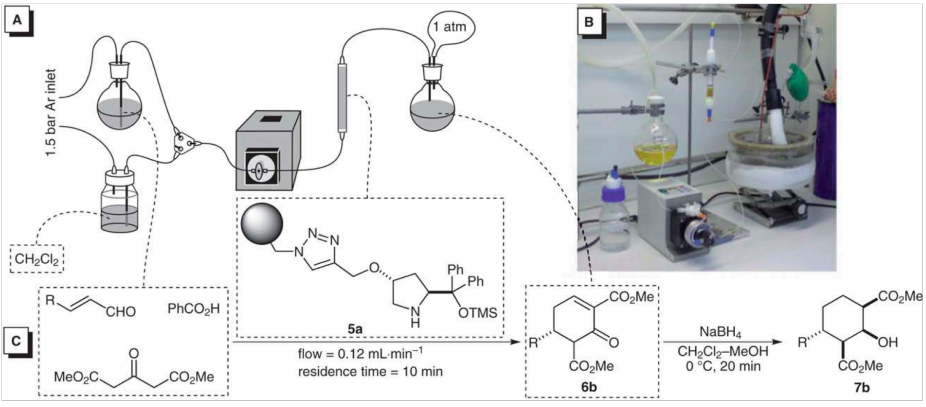

Scheme 3 Schematic representation of the build up for continuous flow operation

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(15) See Supporting Information for details.

(16) **General Procedure for the Domino Michael–Knoevenagel Process of α,β-Unsaturated Aldehydes and Dimethyl 3-Oxopentanedioate**: Benzoic acid (0.05 mmol), the corresponding aldehyde (0.25 mmol) and dimethyl 3-oxopentanedioate (0.275 mmol) were added to catalyst **5** (0.025 mmol) previously swollen in CH_2Cl_2 (1 mL). The suspension was shaken at r.t. for the time indicated in Table 2 and then directly filtered. The resin was rinsed with CH_2Cl_2 (3 × 1 mL) and the organic filtrate was concentrated under reduced pressure. MeOH (1 mL) and $NaBH_4$ (0.25 mmol) were added to a solution of the resulting crude in CH_2Cl_2 (0.5 mL) at 0 °C, which was stirred at that temperature for 20 min. After addition of the pH 7 phosphate buffer, the organic materials were extracted with CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2–EtO_2) to afford **7**.

(17) The deposition number at the Cambridge Crystallographyc Data Centre is CCDC 804763.

(18) These recycling experiments show the results obtained in six consecutive runs. After each run, the reaction mixture was filtered and the solid-supported catalyst was washed with CH_2Cl_2 and directly reused.

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

Supporting Information

Catalytic Batch and Continuous Flow Production of Highly Enantioenriched Cyclohexane Derivatives with Polymer-Supported Diarylprolinol Silyl Ethers

Esther Alza, Sonia Sayalero, Xacobe C. Cambeiro, Rafael Martín-Rapún, Pedro O. Miranda, Miquel A. Pericàs*

Institute of Chemical Research of Catalonia (ICIQ), Avda Països Catalans, 16, 43007, Tarragona, Spain, and Departament de Química Orgànica, Universitat de Barcelona (UB), 080208, Barcelona, Spain.

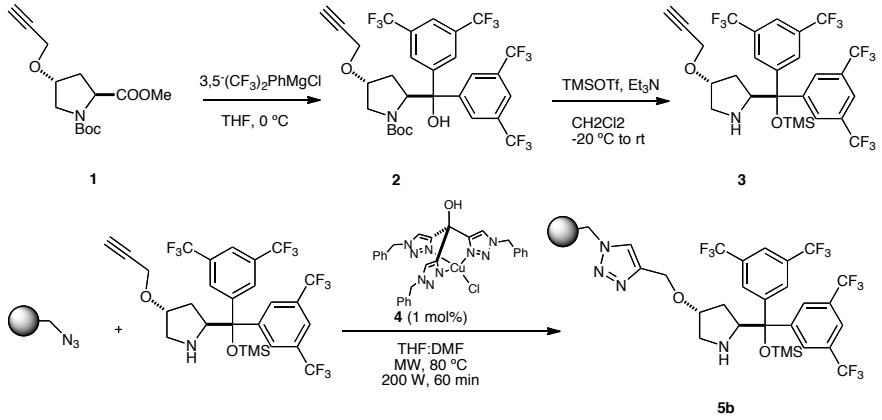
mapericas@iciq.es

1. General Methods:

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol of Cl · g^{-1} resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz (^1H) and 100.63 MHz ($^{13}C\{1H\}$) and 282 MHz ($^{19}F\{1H\}$). TMS was used as internal standard for ^1H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. ^1H, ^{13}C and ^{19}F NMR experiments of resin **5b** were performed with a Bruker Avance spectrometer operating at a frequency of 500.13 MHz using a Bruker 4 mm 1H/13C/2H gradient and ^{19}F HR-MAS probe. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. Melting points were determined using a Büchi melting point apparatus. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Serie1200), using Chiralpak IA column and guard columns.

Crystal structure determination was carried out using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with Mo_{Ka} radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = 100 K). Full-sphere data collection was used with w and j scans. Programs used: Data collection APEX-2[i], data reduction Bruker Saint[ii] V/.60A and absorption correction SADABS[iii]. Structure Solution and Refinement were carried out using the SHELXTL[iv] program.

2. Synthesis of the immobilized catalysts:



(2*S*,4*R*)-*tert*-butyl 2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (2)

To a solution of **1**[1] (1.1 g, 3.8 mmol) in anhydrous THF (15 mL) was added dropwise by an addition funnel a solution of 3,5-bis(trifluoromethyl)phenyl magnesium bromide 0.5M in THF (22.9 mL, 11.5 mmol) at 0 ºC under argon atmosphere. After the addition was completed, the reaction mixture was stirred for 6 h and then was quenched with 10 mL of saturated aqueous solution of NH_4Cl and diluted with Et_2O (150 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (80 mL x 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromathography through deactivated silica (2.5% Et_3N v/v) eluting with hexanes-ethyl acetate 2:1. The title product was obtained after the evaporation of the solvents as light brown solid (790 mg, 30% yield).

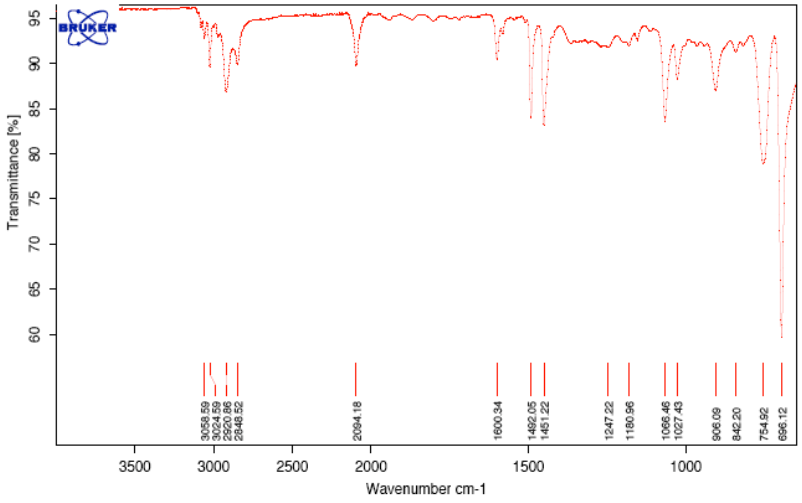
^{1}H-NMR (400 MHz, $CDCl_3$): *d* (ppm) = 7.91 (s, 3H), 7.84 (s, 1H), 7.81 (s, 2H), 4.94 (t, *J* = 8.4 Hz, 1H), 4.04 (qd, *J* = 16.1, 2.4 Hz, 2H), 3.86 (br, 1H), 3.73 (d, *J* = 12.7 Hz, 1H), 2.89 (dd, *J* = 12.7, 4.2 Hz, 1H), 2.39 (t, *J* = 2.4 Hz, 1H), 2.14 - 2.08 (m, 1H), 1.91 - 1.84 (m, 1H), 1.35 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$): *d* (ppm) = 157.8, 146.5, 145.0, 132.1, 131.8, 131.7, 131.4, 127.8, 127.6, 124.7, 124.6, 122.2, 122.0, 121.9, 82.4, 80.6, 79.1, 77.5, 77.2, 76.8, 75.5, 75.1, 66.2, 56.3, 53.4, 36.9, 28.1. **^{19}F-NMR** (376 MHz, $CDCl_3$): *d* (ppm) = -62.92, -62.96. **HRMS (ESI+):** *m/z* = 702.1514, calcd. for $C_{29}H_{25}NO_4F_{12}Na$ $[M+Na]^+$: 702.1490 $[\alpha]_D^{27.5}$ = +10.0 (*c* 1.00 in CH_2Cl_2).

IR (ATR): *n* = 3323.06, 3190.32, 1661.06, 1402.86, 1367.20, 1120.86, 900.47cm^{-1}
m.p = 129.1 ºC

(2*S*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (3)
To a solution of **2** (790 mg, 1.17 mmol) in 30 mL of CH_2Cl_2 at -20 ºC was added triethylamine (0.21 mL, 1.52 mmol) and trimethylsilyl trifluoromethanesulfonate (0.27 mL, 1.52 mmol). The solution was then allowed to reach 0 ºC and was stirred for 2 h at this temperature. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford the desired product as a colorless oil (242 mg, 32% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): *d* (ppm) = 8.01 (s, 2H), 7.84 (s, 2H), 7.76 (s, 2H), 4.47 (dd, *J* = 8.6, 7.5 Hz, 1H), 4.08 (d, *J* = 2.3 Hz, 2H), 3.88 (br, 1H), 3.01 (d, *J* = 12.6 Hz, 1H), 2.40 (t, *J* = 2.4 Hz, 1H), 2.20 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.98 - 1.93 (m, 1H), 1.45 - 1.38 (m, 1H), -0.09 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$): *d* (ppm) = 148.2, 146.1, 145.4, 131.6, 131.2, 130.9, 128.7, 128.3, 124.8, 124.6, 121.7, 79.7, 74.5, 63.0, 56.2, 34.4, 2.0. **^{19}F-NMR** (376 MHz, $CDCl_3$): *d* (ppm) = -62.82, -62.86.
HRMS (ESI+): *m/z* = 652.1559, calcd. for $C_{27}H_{26}NO_2F_{12}Si$ 652.1541 $[M+H]^+$.
$[\alpha]_D^{23.9}$ = -659.1 (*c* 0.99 in CH_2Cl_2).
IR (ATR): *n* = 3323.06, 3190.32, 1661.06, 1402.86, 1367.20, 1120.86, 900.47cm^{-1}

Azidomethylpolystyrene[2]
IR (ATR): *n* = 2094.18 cm^{-1}
A 98% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.21; found: N 2.17, C 89.45, H 7.74; *f* = 0.517 mmol g^{-1}.



4-((((3R,5S)-5-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidin-3-yl)oxy)methyl)-1-ethyl-1H-1,2,3-triazol (5b)

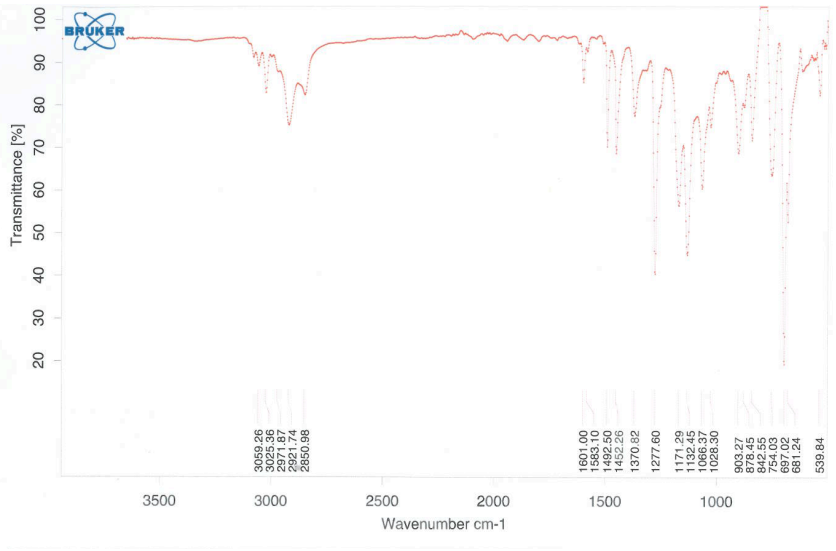
Pyrrolidine derivative **3** (121 mg, 0.19 mmol), azidomethylpolystyrene resin *f* = 0.517 mmol/g (300 mg), 2 mL of DMF, 2 mL of THF and tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst[3] (1 mg, 1.56 mmol, 1 mol%) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC (setting temperature) for 1 hour under microwave irradiation of 200 W without stirring.

After the cycloaddition reaction was completed, the resin was filtered and washed with CH_2Cl_2 (75 mL) and THF (75 mL) and was dried over night in vacuo at 40 ºC.

^{13}C-NMR HR-MAS (126 MHz, CD_2Cl_2) δ (ppm) = 148.6, 146.5, 82.4, 80.0, 67.9, 63.0, 62.1, 52.6, 40.6, 34.5, 25.7, 1.7. **^{19}F-NMR** (376 MHz, $CDCl_3$): *d* (ppm) = -63.19, -63.21.

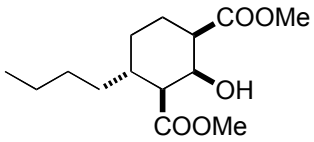
IR (ATR): *n* = 3025.36, 2921.74, 2850.98, 1601.00, 1583.10, 1492.50, 1370.82, 1277.60, 1066.37, 697.02 cm^{-1}

A quantitative yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.21, C 80.66, H 6.74; *f* = 0.395 mmol g^{-1}.



3. Physical and spectroscopical data of the products:

(1*R*,2*R*,3*S*,4*R*)-dimethyl 4-butyl-2-hydroxycyclohexane -1,3-dicarboxylate (7g)



Title compound was prepared from (*E*)-hept-2-enal and dimethyl 1,3-acetonedicarboxylate according to General Procedure.

^{1}H-NMR (400 MHz, CDCl3): d (ppm) = 4.47 (sbr, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.32 - 3.31 (m, 1H), 2.36 - 2.32 (m, 1H), 2.20 (dd, *J* = 11.6, 2.1 Hz, 1H), 2.05 - 1.90 (m, 3H), 1.86 - 1.79 (m, 1H), 1.34 - 1.18 (m, 6H), 1.09 - 0.94 (m, 1H), 0.87 (t, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$): *d* (ppm) = 175.24, 174.36, 67.69, 53.22, 52.05, 51.93, 47.01, 34.20, 32.26, 31.07, 30.03, 28.63, 22.95, 21.66, 14.14.

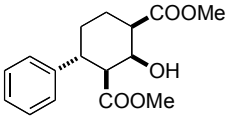
HRMS (ESI+): *m/z* = 295.1516, calcd. for $C_{14}H_{24}O_5Na$ 295.1521 $[M+Na]^+$.

$[\alpha]_D^{25.3}$ = -7.6 (*c* 0.15 in CH_2Cl_2).

The product was converted to the corresponding trimethylsilylether derivative with TMSOTf and triethylamine and enantiomeric excess was determined by HPLC using a Chiralpack IA column, hexane-ethanol 95:5, 0.8 mL·min^{-1}, 220 nm): tR = 14.3 min (major), 15.6 min (minor).

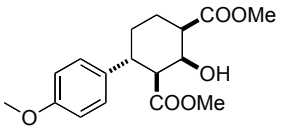
The rest of compounds are known and all the spectroscopic data matched those reported in the literature.[4]

(1*R*, 2*R*, 3*S*, 4*R*)-dimethyl-2-hydroxy-4-phenylcyclohexane-1,3-dicarboxylate (7a):



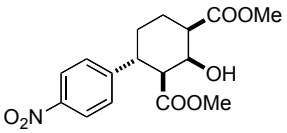
Title compound was prepared from *trans*-cinnamaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) = 7.29 - 7.26 (m, 2H), 7.20 - 7.17 (m, 3H), 4.64 (sbr, 1H), 3.75 (s, 3H), 3.46 (s, 1H), 3.43 (s, 3H), 3.28 (td, *J* = 12.3, 3.6 Hz, 1H), 2.74 (dd, *J* = 12.1, 2.2 Hz, 1H), 2.55 – 2.50 (m, 1H), 2.13 (qd, *J* = 13.0, 3.4 Hz, 1H), 2.01 - 1.89 (m, 2H), 1.58 - 1.48 (m, 1H). **^{13}C-NMR** (101 MHz, DEPTQ-135, $CDCl_3$): *d* (ppm) = 174.4, 174.0, 143.7, 128.6, 127.4, 126.8, 67.7, 53.1, 52.2, 51.8, 46.8, 39.5, 33.4, 31.1, 22.2.
The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 6.9 min (major), 10.8 min (minor)

(1*R*, 2*R*, 3*S*, 4*R*)-dimethyl-2-hydroxy-4-(4-methoxyphenyl)cyclohexane-1,3-dicarboxylate (7b):



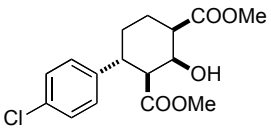
Title compound was prepared from *trans*-p-methoxy cinnamaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) = 7.11 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.62 (sbr, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.45 (s, 3H), 3.23 (td, *J* = 12.3, 3.5 Hz, 1H), 2.68 (dd, *J* = 12.1, 2.2 Hz, 1H), 2.53 – 2.48 (m, 1H), 2.17 - 2.06 (m, 1H), 1.98 - 1.88 (m, 2H), 1.55 - 1.43 (m, 1H). **^{13}C-NMR** (101 MHz, DEPTQ-135, $CDCl_3$): *d* (ppm) = 176.2, 174.1, 135.7, 128.3, 113.9, 67.7, 55.3, 53.4, 52.2, 51.8, 46.7, 38.7, 33.7, 22.2.
The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 8.8 min (major), 15.5 min (minor).

(1*R*, 2*R*, 3*S*, 4*R*)-dimethyl 2-hydroxy-4-(4-nitrophenyl)cyclohexane-1,3 dicarboxylate (7c):



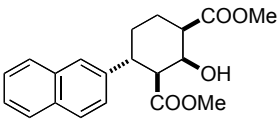
Title compound was prepared from (*E*)-3-(4-nitrophenyl) acrylaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) = 8.15 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 4.70 (sbr, 1H), 3.76 (s, 3H), 3.49 (s, 3H), 3.34 (m, 1H), 2.78 (dd, *J* = 12.1, 2.2 Hz, 1H), 2.58 – 2.54 (m, 1H), 2.17 - 2.07 (m, 1H), 2.01 - 1.94 (m, 2H), 1.55 - 1.46 (m, 1H). The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 11.6 min (minor), 15.7 min (major).

(1*R*, 2*R*, 3*S*, 4*R*)-dimethyl 4-(4-chlorophenyl)-2-hydroxycyclohexane-1,3-dicarboxylate (7d):



Title compound was prepared from (*E*)-3-(4-chlorophenyl) acrylaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) = 7.25 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.64 (sbr, 1H), 3.75 (s, 3H), 3.47 (s, 3H), 3.40 (d, *J* = 1.5, 1H), 3.28 (td, *J* = 12.3, 3.6 Hz, 1H), 2.70 (dd, *J* = 12.1, 2.2 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.15 - 2.06 (m, 1H), 1.98 - 1.89 (m, 2H), 1.47 (qd, *J* = 13.6, 4.1 Hz, 1H). **^{13}C-NMR** (101 MHz, DEPTQ-135, $CDCl_3$): *d* (ppm) = 174.3, 173.6, 142.4, 132.4, 128.8, 128.7, 67.6, 53.0, 52.2, 51.9, 46.7, 38.8, 33.4, 31.1, 22.2.
The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 7.4 min (major), 8.4 min (minor).

(1*R*, 2*R*, 3*S*, 4*R*)-dimethyl-2-hydroxy-4-(naphthalen-2-yl)cyclohexane-1,3-dicarboxylate (7e):

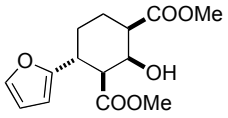


Title compound was prepared from (*E*)-3-(naphthalen-2-yl)acrylaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) =

7.80 - 7.76 (m, 3H), 7.63 (s, 1H), 7.46 - 7.34 (m, 3H), 4.69 (sbr, 1H), 3.77 (s, 3H), 3.49 (s, 1H), 3.38 (s, 3H), 2.88 (dd, *J* = 12.1, 2.1 Hz, 1H), 2.60 – 2.55 (m, 1H), 2.20 - 2.12 (m, 1H), 2.07 - 1.94 (m, 2H), 1.62 (qd, *J* = 13.3, 3.7 Hz, 1H). **^{13}C-NMR** (101 MHz, DEPTQ-135, $CDCl_3$): *d* (ppm) = 174.3, 173.9, 141.3, 133.6, 132.6, 128.2, 127.8, 127.7, 126.0, 126.0, 125.8, 125.6, 67.7, 53.00, 52.2, 51.8, 46.8, 39.5, 33.5, 22.2.

The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 7.7 min (major), 13.3 min (minor).

1*R*, 2*R*, 3*S*, 4*R*)-dimethyl-2-hydroxy-4-(naphthalen-2-yl)cyclohexane-1,3-dicarboxylate (7f):



Title compound was prepared from (*E*)-3-(furan-2-yl)acrylaldehyde and dimethyl 1,3-acetonedicarboxylate according to General Procedure. **^{1}H-NMR** (400 MHz, CDCl3): d (ppm) = 7.28 (d, *J* = 1.1 Hz, 1H), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.02 (d, *J* = 3.1 Hz, 1H), 4.61 (sbr, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 3.41 (td, *J* = 12.4, 3.8 Hz, 1H), 2.72 (dd, *J* = 12.0, 2.1 Hz, 1H), 2.49 – 2.44 (m, 1H), 2.14 - 2.04 (m, 1H), 1.94 - 1.88 (m, 2H), 1.64 – 1.54 (m, 1H). **^{13}C-NMR** (101 MHz, DEPTQ-135, $CDCl_3$): *d* (ppm) = 174.2, 174.1, 157.0, 141.3, 110.2, 105.0, 67.3, 52.2, 52.1, 51.4, 46.5, 33.1, 31.1, 30.4, 21.5.

The enantiomeric excess of the trimethylsilylether derivative was determined by HPLC with a Chiralpack IA column, hexane-isopropanol 98:2, 1 mL·min^{-1}, 240 nm): tR = 7.8 min (major), 8.6 min (minor).

X-Ray of (1*R*, 2*R*, 3*S*, 4*R*)-dimethyl-2-hydroxy-4-(4-methoxyphenyl) cyclohexane-1,3-dicarboxylate[5]

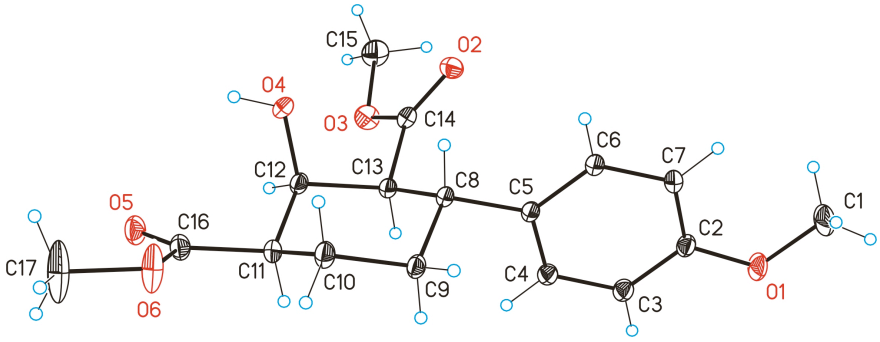


Table 1. Crystal data and structure refinement for EA527_0m.

Identification code	EA527_0m
Empirical formula	C17 H22 O6
Formula weight	322.35
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 26.0264(12) Å α= 90.00° b = 5.5628(2) Å β = 106.125(2)° c = 11.8300(6) Å γ = 90.00°
Volume	1645.36(13) $Å^3$
Z	4
Density (calculated)	1.301 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	688
Crystal size	0.30 x 0.10 x 0.02 mm^3
Theta range for data collection	1.63 to 36.35°.
Index ranges	-38 <=h<=43 ,-9 <=k<=9 ,-19 <=l<=13
Reflections collected	6592
Independent reflections	6034 [R(int) = 0.0253]
Completeness to theta =36.35°	0.917 %
Absorption correction	Empirical
Max. and min. transmission	0.9951 and 0.9664
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6592 / 1 / 212
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0429 , wR2 = 0.1146
R indices (all data)	R1 = 0.0488 , wR2 = 0.1246
Absolute Structure Flack parameter	x =-0.4(6)
Largest diff. peak and hole	0.584 and -0.304 $e.Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for EA527_0m.

Bond lengths----	
C1-O1	1.4293(17)
O1-C2	1.3745(12)
C2-C3	1.3912(16)
C2-C7	1.3960(14)
O2-C14	1.2078(13)
C3-C4	1.3920(14)
O3-C14	1.3442(15)
O3-C15	1.4486(16)
C4-C5	1.4072(13)
O4-C12	1.4252(13)
C5-C6	1.3871(14)
C5-C8	1.5188(13)
O5-C16	1.2034(16)
C6-C7	1.3990(14)
O6-C16	1.3371(15)
O6-C17	1.4490(16)
C8-C13	1.5378(16)
C8-C9	1.5444(14)
C9-C10	1.5310(14)
C10-C11	1.5212(17)
C11-C16	1.5122(14)
C11-C12	1.5330(15)
C12-C13	1.5458(13)
C13-C14	1.5186(14)
Angles----------	
C2-O1-C1	116.77(9)
O1-C2-C3	116.04(9)
O1-C2-C7	124.17(10)
C3-C2-C7	119.79(9)
C2-C3-C4	120.25(9)
C14-O3-C15	115.24(10)
C3-C4-C5	121.11(10)
C6-C5-C4	117.42(9)
C6-C5-C8	121.12(8)

C4-C5-C8	121.33(9)
C5-C6-C7	122.43(9)
C16-O6-C17	115.16(11)
C2-C7-C6	118.99(10)
C5-C8-C13	112.83(8)
C5-C8-C9	109.60(8)
C13-C8-C9	110.33(8)
C10-C9-C8	111.75(9)
C11-C10-C9	109.10(9)
C16-C11-C10	115.29(9)
C16-C11-C12	109.01(9)
C10-C11-C12	111.60(9)
O4-C12-C11	111.01(8)
O4-C12-C13	108.02(8)
C11-C12-C13	111.14(8)
C14-C13-C8	110.94(8)
C14-C13-C12	107.25(8)
C8-C13-C12	114.06(8)
O2-C14-O3	123.33(10)
O2-C14-C13	125.47(11)
O3-C14-C13	111.19(9)
O5-C16-O6	123.41(10)
O5-C16-C11	123.88(10)
O6-C16-C11	112.68(10)

Table 3. Torsion angles [°] for EA527_0m.

C1-O1-C2-C3	178.87(13)
C1-O1-C2-C7	-0.98(18)
O1-C2-C3-C4	179.01(11)
C7-C2-C3-C4	-1.13(17)
C2-C3-C4-C5	0.22(17)
C3-C4-C5-C6	0.97(16)
C3-C4-C5-C8	-174.95(11)
C4-C5-C6-C7	-1.29(17)
C8-C5-C6-C7	174.63(10)
O1-C2-C7-C6	-179.34(11)

C3-C2-C7-C6	0.82(17)
C5-C6-C7-C2	0.41(17)
C6-C5-C8-C13	127.09(11)
C4-C5-C8-C13	-57.14(13)
C6-C5-C8-C9	-109.54(11)
C4-C5-C8-C9	66.23(13)
C5-C8-C9-C10	-179.68(9)
C13-C8-C9-C10	-54.85(11)
C8-C9-C10-C11	60.32(11)
C9-C10-C11-C16	174.95(9)
C9-C10-C11-C12	-59.98(11)
C16-C11-C12-O4	62.85(12)
C10-C11-C12-O4	-65.64(11)
C16-C11-C12-C13	-176.89(9)
C10-C11-C12-C13	54.62(11)
C5-C8-C13-C14	-66.26(10)
C9-C8-C13-C14	170.78(7)
C5-C8-C13-C12	172.51(8)
C9-C8-C13-C12	49.55(10)
O4-C12-C13-C14	-50.97(11)
C11-C12-C13-C14	-172.98(9)
O4-C12-C13-C8	72.30(11)
C11-C12-C13-C8	-49.71(11)
C15-O3-C14-O2	-4.87(14)
C15-O3-C14-C13	173.92(9)
C8-C13-C14-O2	-9.01(13)
C12-C13-C14-O2	116.15(11)
C8-C13-C14-O3	172.23(8)
C12-C13-C14-O3	-62.61(10)
C17-O6-C16-O5	2.2(2)
C17-O6-C16-C11	-175.73(16)
C10-C11-C16-O5	166.15(11)
C12-C11-C16-O5	39.74(15)
C10-C11-C16-O6	-15.92(14)
C12-C11-C16-O6	-142.33(11)

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4. Continuous flow experiment:

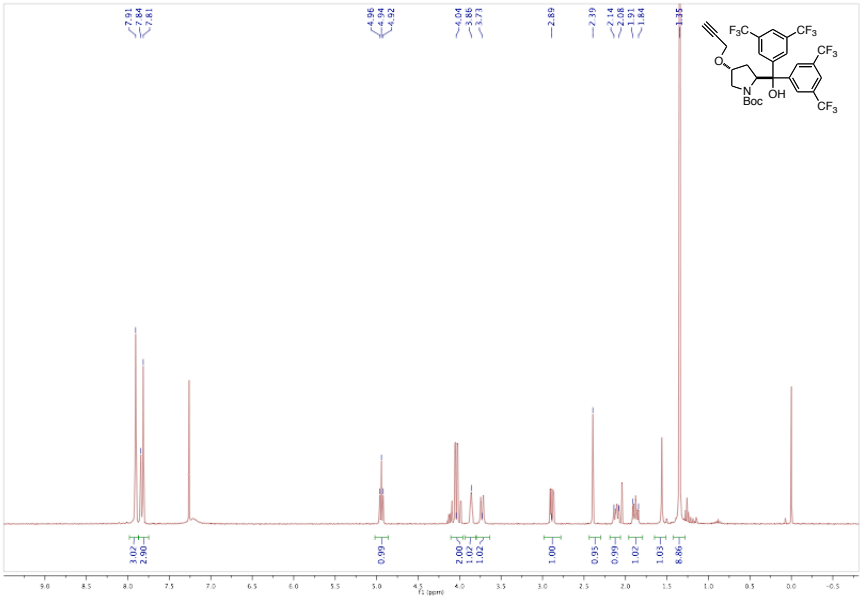
General method for the Michael-Knoevenagel domino reaction under continuous flow conditions.

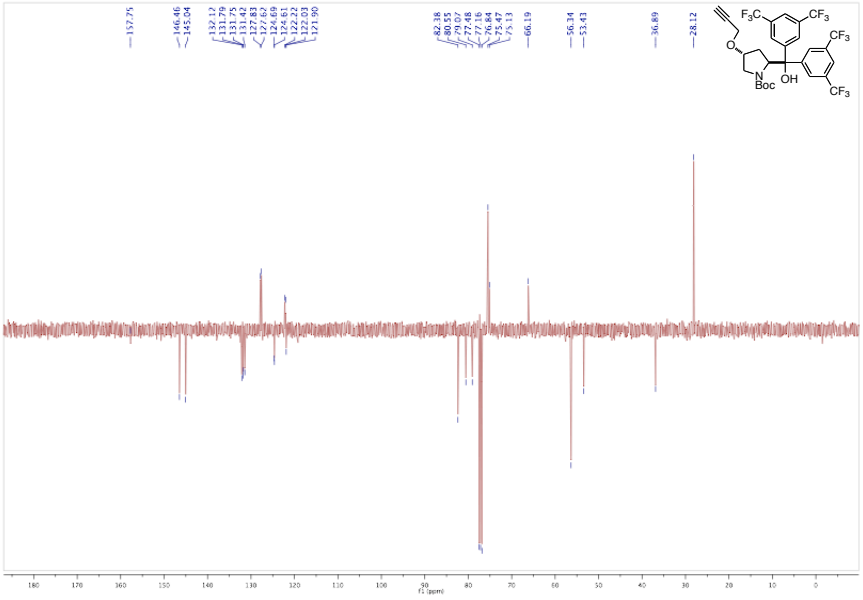
A solution containing trans-3-(4-methoxyphenyl)acrolein (0.1 M), dimethyl 2-oxoglutarate (0.11 M) and benzoic acid (0.1 M) in dichloromethane was pumped at 0.12 mL·min-1 through a glass column filled with 900 mg (2.38 mmol) of immobilized catalyst **5a**. The eluent was collected in a cooled flash at –40 ºC. Conversion at a given time was determined by 1H NMR analysis of a simple taken directly from the column eluent, without any work up. After 72 h of continuous operation, the collecting flash was removed and allowed to warm up to 0 ºC. Then, MeOH (ca. 250 mL) was added, followed by sodium borohydride (3.92 g) in small portions. After stirring for 20 min, a pH 7 phosphate buffer was added (250 mL) and the organic layer separated. The aqueous layer was washed twice with ethyl acetate (150 mL) and the combined organic extracts were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was the purified by flash chromatography through silica gel, eluting with 95:5 dichloromethane:diethyl ether mixture to yield, after removal of the solvents, cyclohexanol **7b** as a white solid (8.7 g).

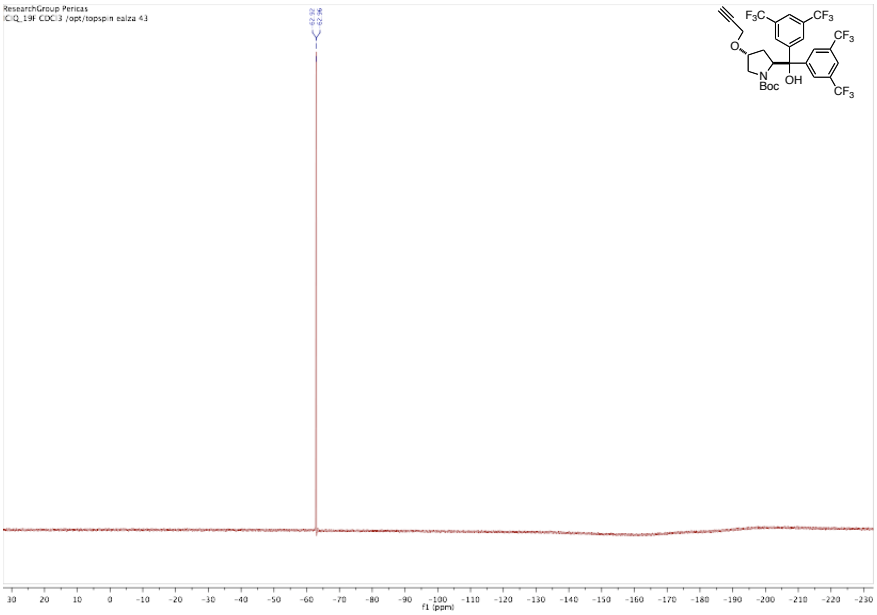
5. References for the Supporting Information:

[i] Data collection with APEX II v2009.1-02. Bruker (2007). Bruker AXS Inc., Madison, Wisconsin, USA.
[ii] Data reduction with Bruker SAINT V7.60A. Bruker (2007). Bruker AXS Inc., Madison, Wisconsin, USA.
[iii] SADABS: V2008/1 Bruker (2001). Bruker AXS Inc., Madison, Wisconsin, USA. Blessing, Acta Cryst. (1995) A51 33-38.
[iv] Sheldrick, G.M. Acta Cryst. 2008 A64, 112-122. SHELXTL V6.14.
[1] Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051.
[2] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2006**, *8*, 4653.
[3] Özçubukçu, S.; Özkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680.
[4] Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45.
[5] Deposition number at Cambridge Crystallographic Data Centre CCDC 804763.

6. Compilation of NMR spectra of new compounds:



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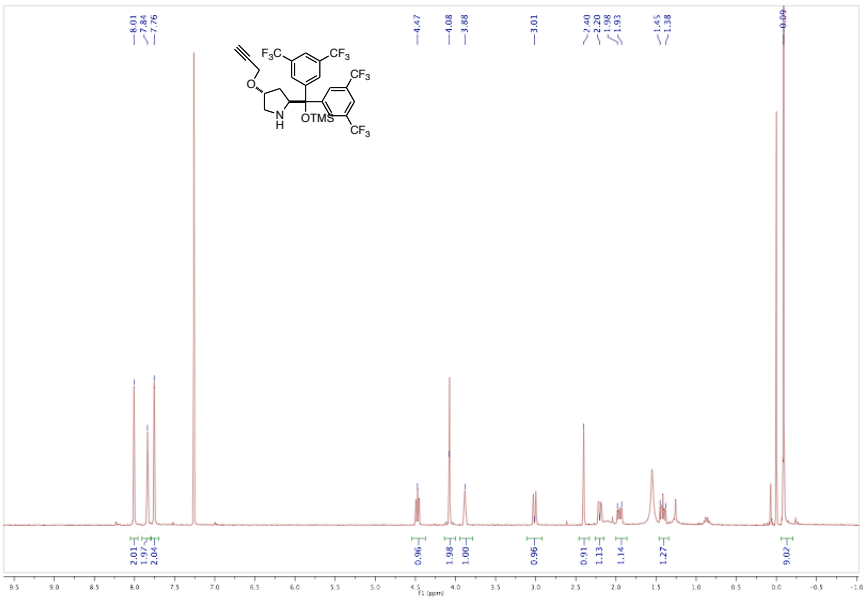
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CF3
CF3
CF3
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N
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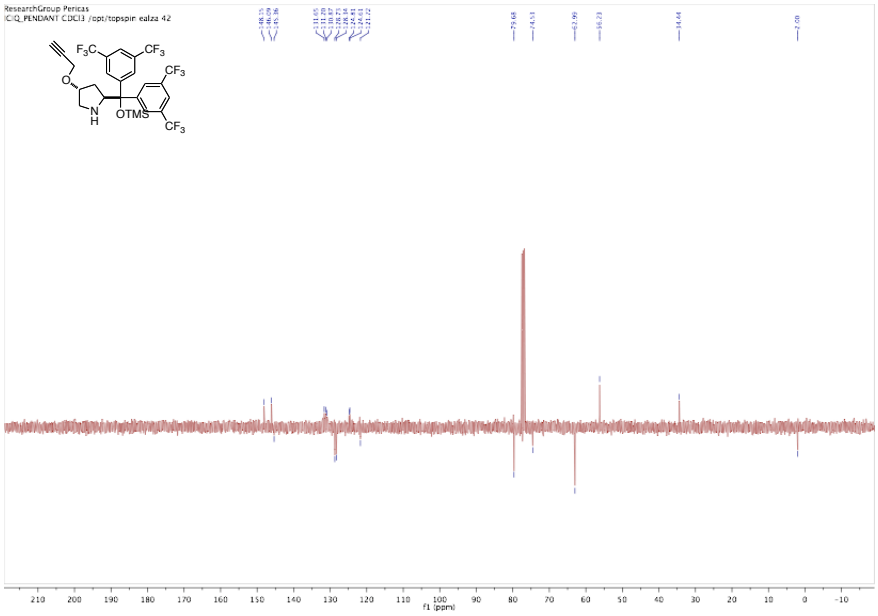
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CF3
O
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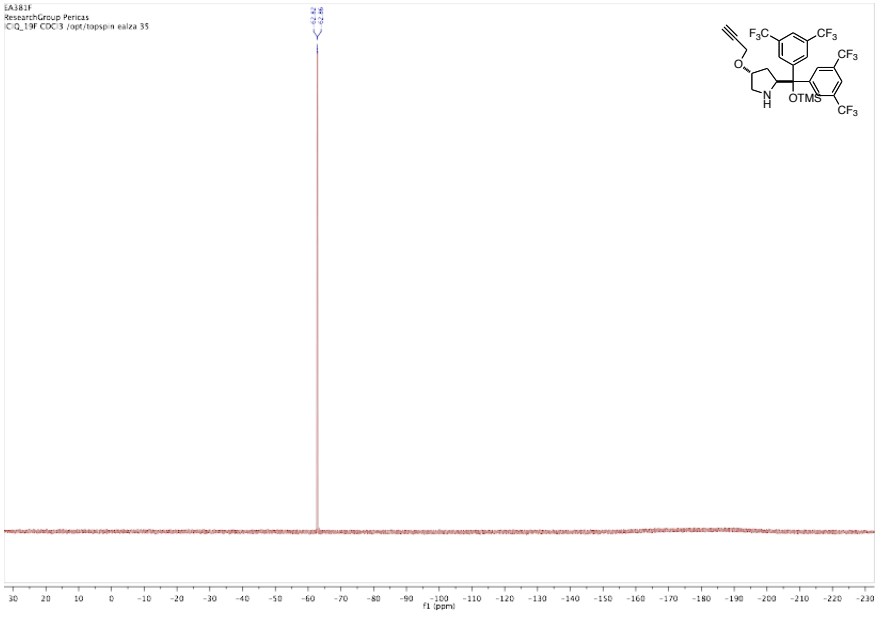
H
OTMS
CF3
f1 (ppm)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ResearchGroup Pericas
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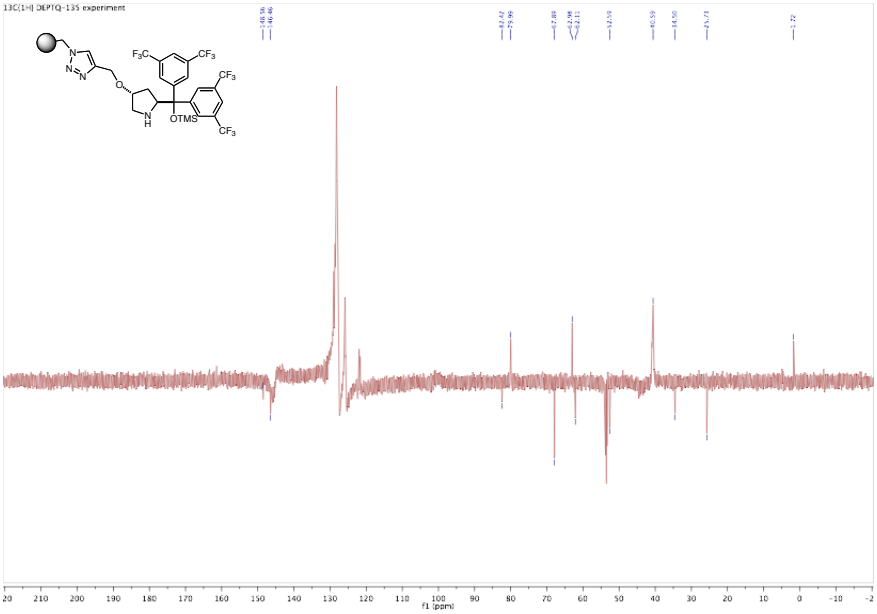
f1 (ppm)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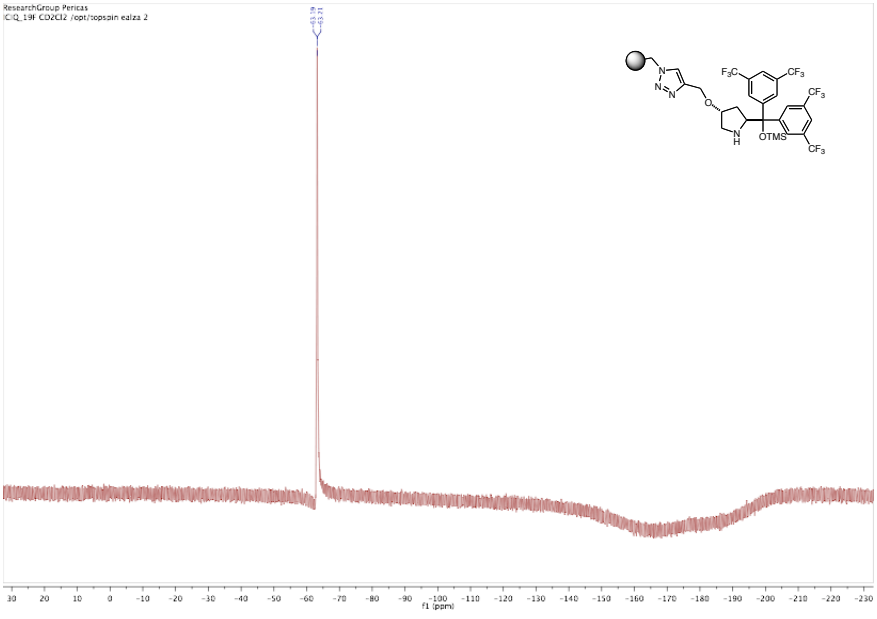
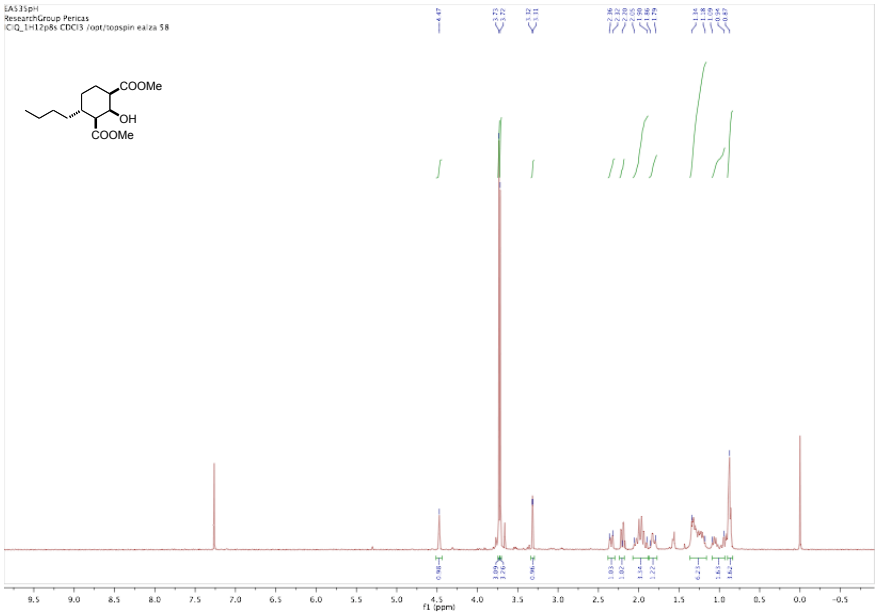
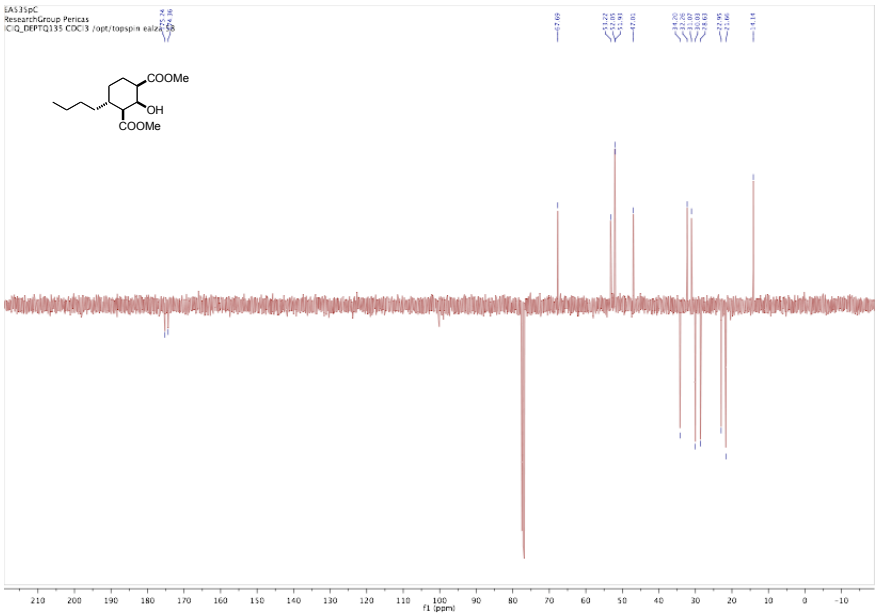
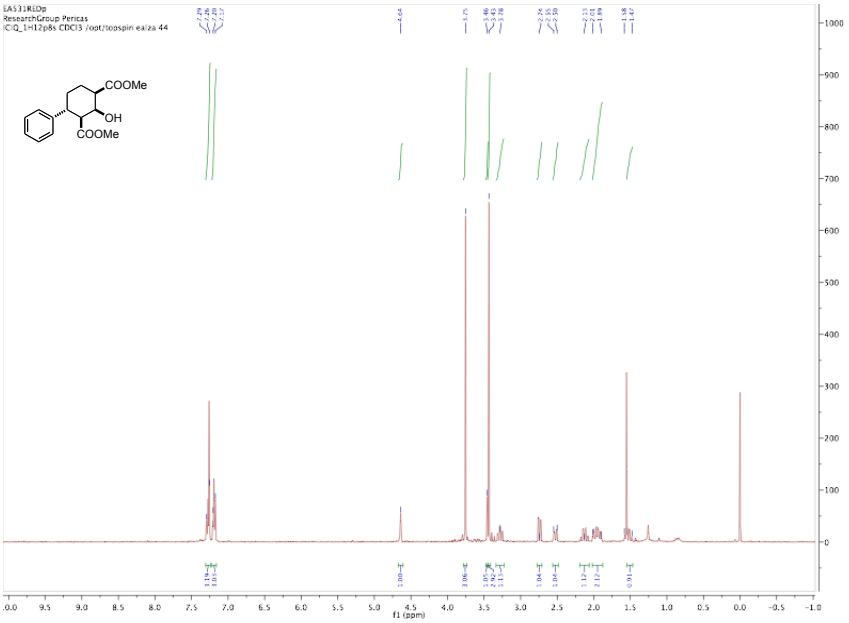
f1 (ppm)


ResearchGroup Pericas
f1 (ppm)



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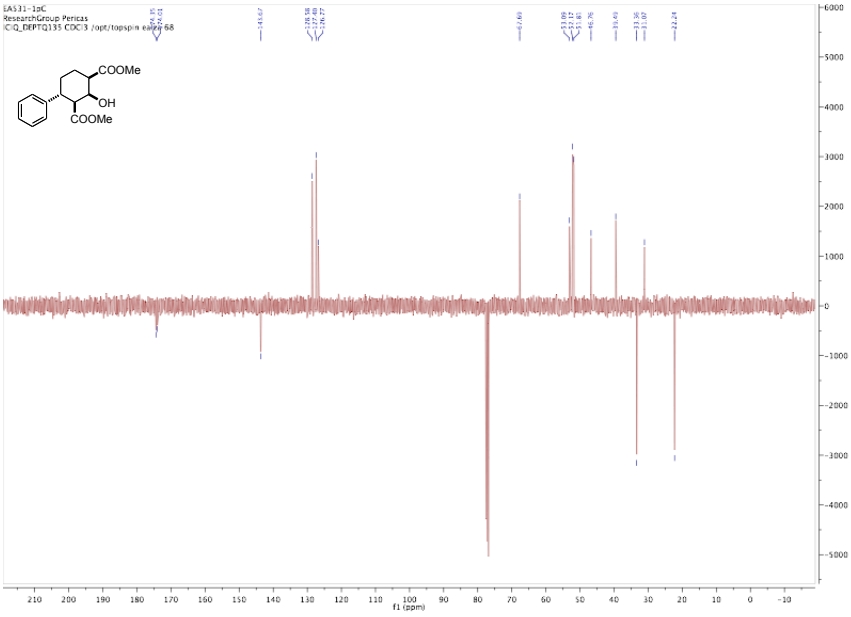
COOMe
f1 (ppm)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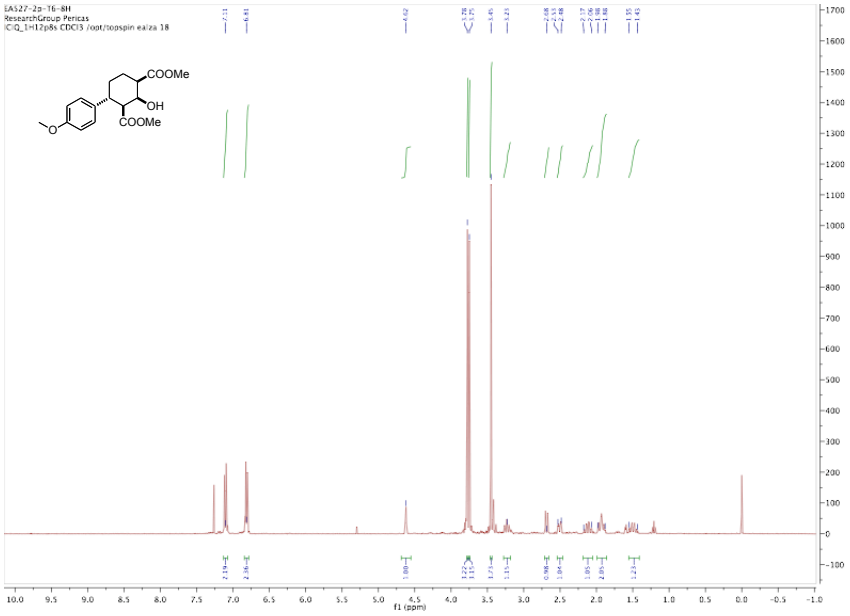
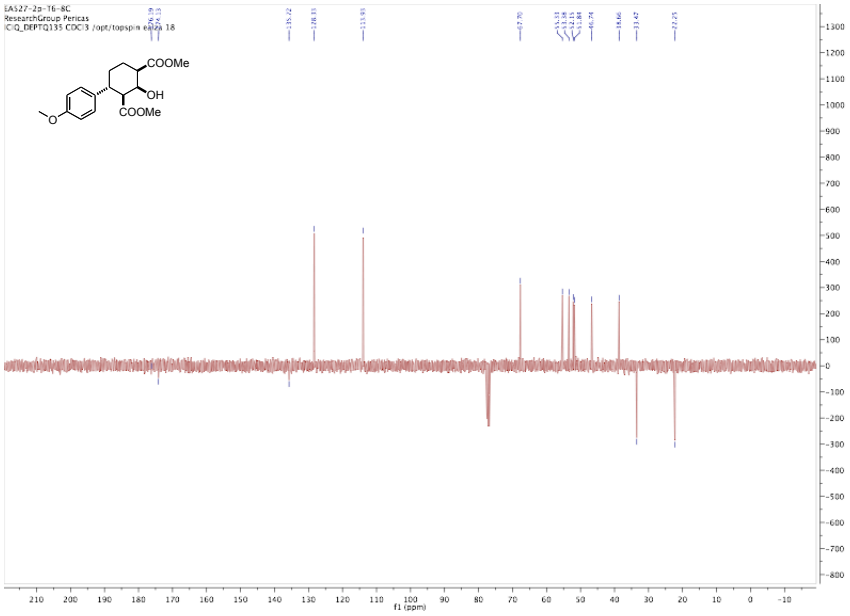
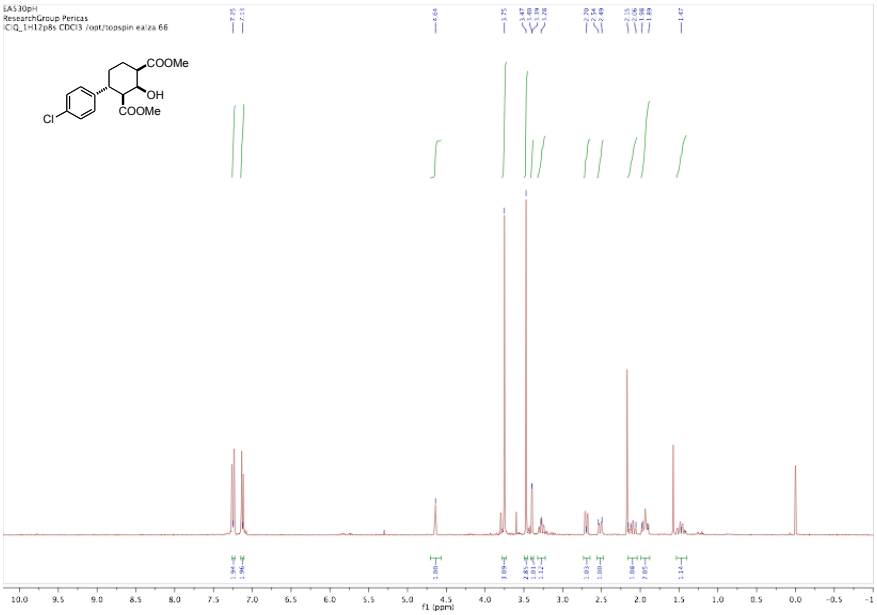
OH
COOMe
f1 (ppm)



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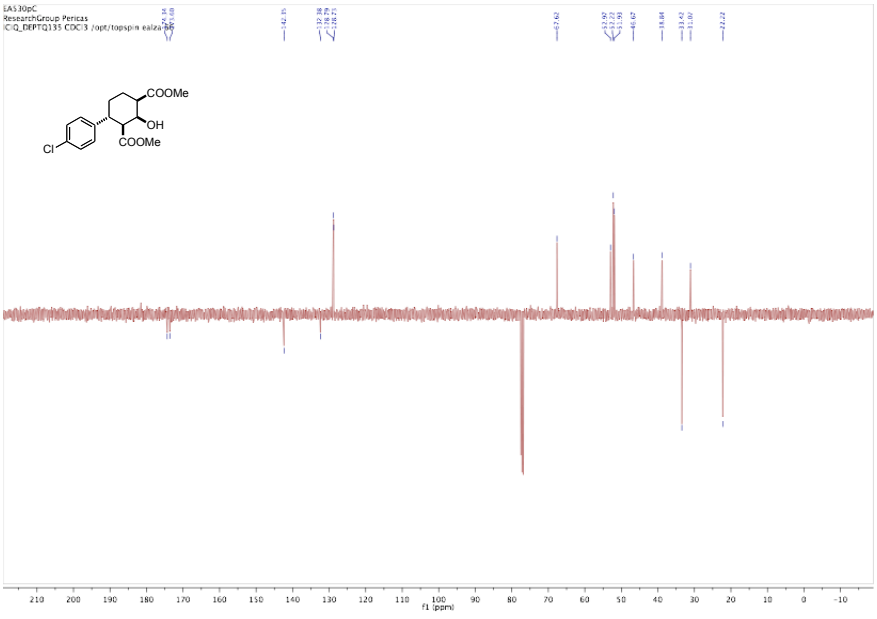
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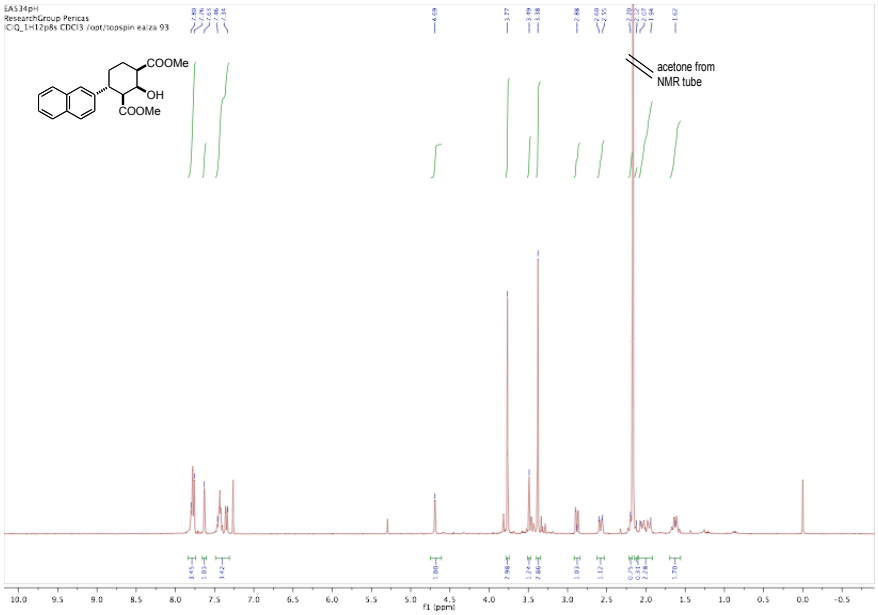
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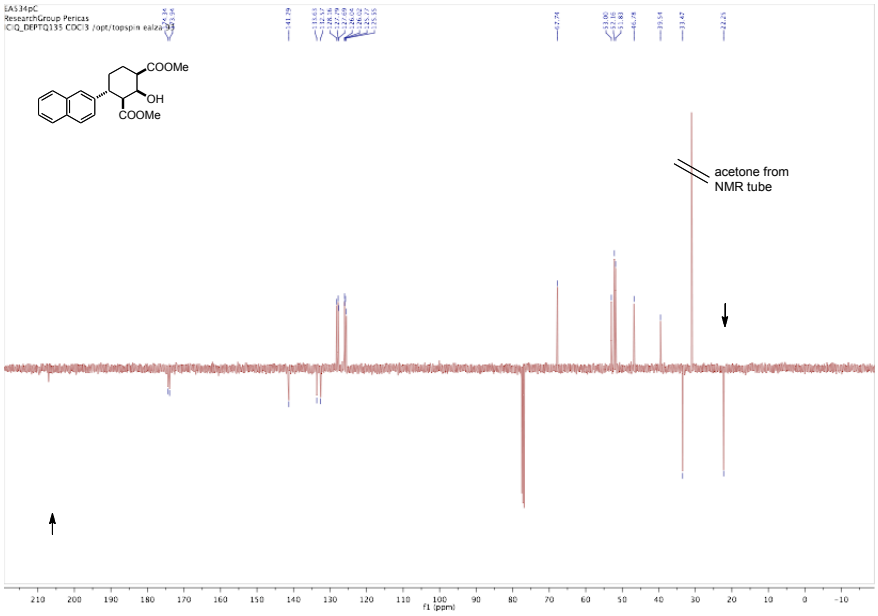
OH
COOMe
acetone from
NMR tube
f1 (ppm)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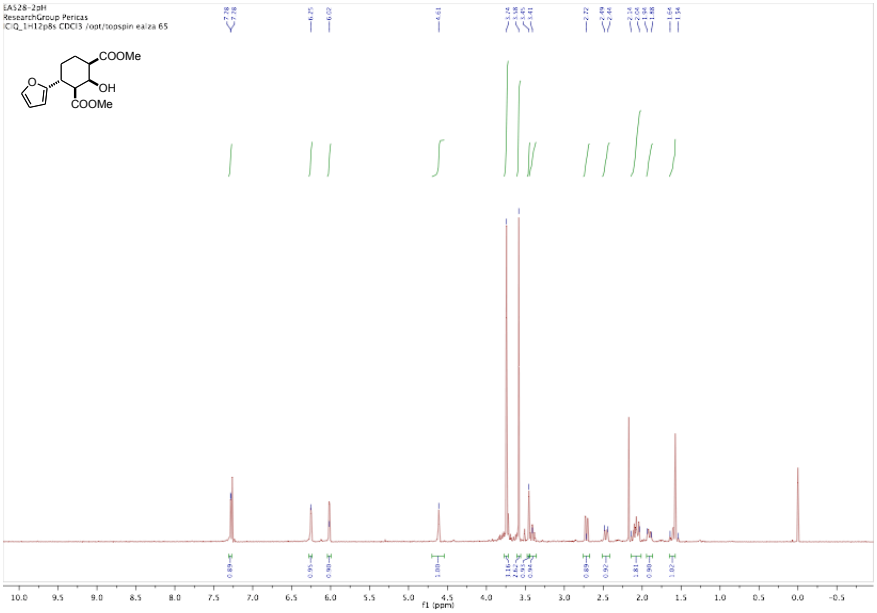
OH
COOMe
acetone from
NMR tube
f1 (ppm)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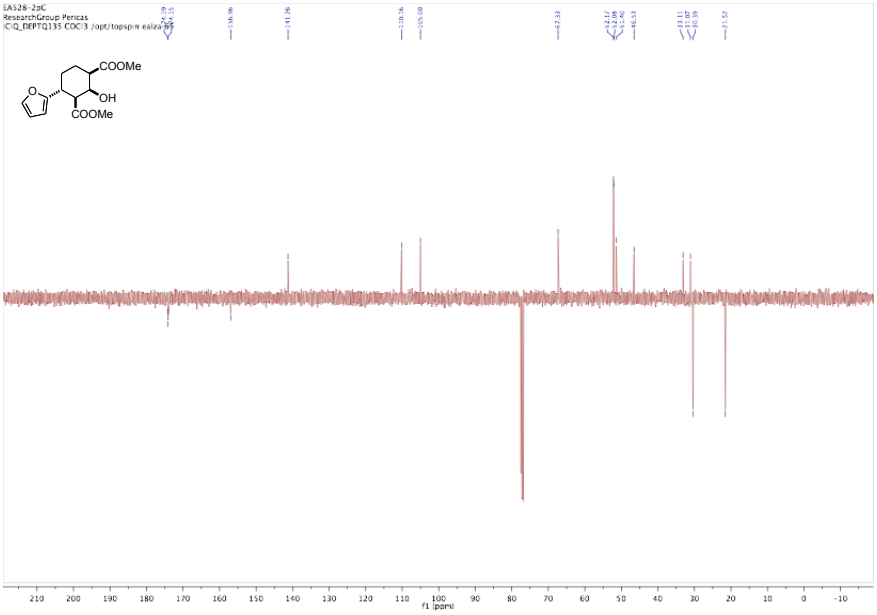
ResearchGroup Pericas
COOMe
OH
COOMe
f1 (ppm)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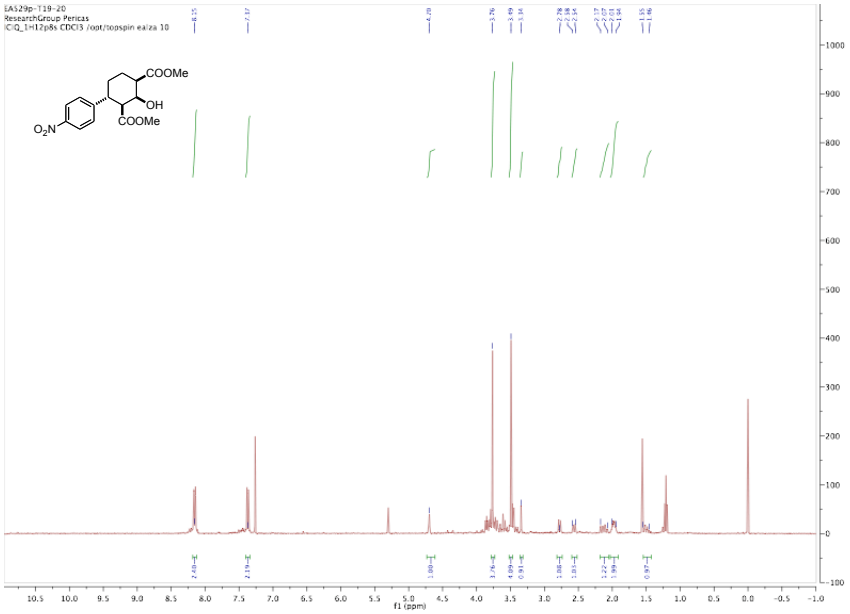
COOMe
OH
COOMe
f1 (ppm)



UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

Chapter V

UNIVERSITAT ROVIRA I VIRGILI
APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
Esther Alza Barrios
DL:T. 1351-2011

ENANTIOSELECTIVE REDUCTION OF KETONES WITH BORANE CATALYZED BY POLYMER SUPPORTED OXAZABOROLIDINES

There is a considerable interest in the development of highly efficient routes to obtain enantiomerically pure alcohols because are useful chiral building blocks in organic synthesis, and can be used as key intermediates in the synthesis of many biologically active synthetic targets.[1] One of the simplest and most useful methods for the preparation of such compounds is the asymmetric reduction of prochiral ketones.

In 1981, Itsuno and co-workers[2] described the first enantioselective oxazaborolidine (OAB)-based system for the reduction of ketones with borane reagents as hydride source.[3] The authors reported the novel reduction of achiral ketones to chiral secondary alcohols using a mixture of chiral amino alcohols and $BH_3 \cdot THF$ in nearly quantitative yield with enantiomeric excesses in the range of 10-73% ee. After screening of numerous amino alcohols, it was discovered that a tertiary amino alcohol derived from (*S*)-valine together with two equivalents of $BH_3 \cdot THF$ converted acetophenone in to (*R*)-1-phenylethanol with 94% enantiomeric excess (Scheme 5.1).

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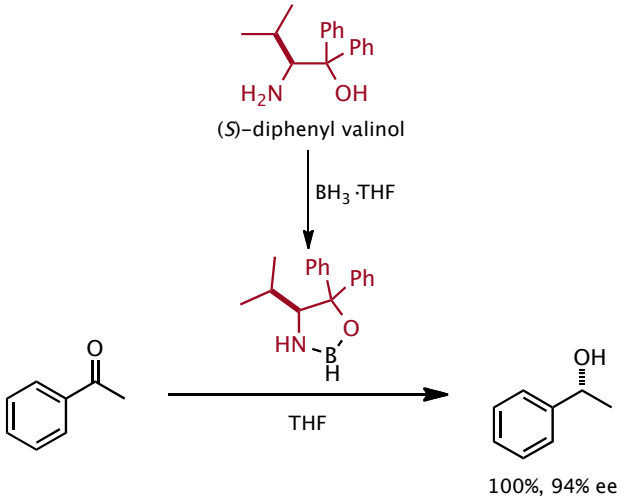
[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**.
[2] a) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315. b) S. Itsuno, A. Hirao, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1673.
[3] For reviews, see: a) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475. b) V. K. Singh, *Synthesis* **1992**, 605. c) L. Deloux, M. Srebnik, *Chem. Rev.* **1993**, *93*, 763. d) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1986. e) S. Itsuno, in *Comprehensive Asymmetric Catalysts*, *1*, 289, eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, New York, **1999**. f) B. T. Cho, *Oxazaborolidines as Asymmetric Inducers for the Reduction of Ketones and Ketimines*, in *Boronic Acids: Preparation and Applications in Organic Synthesis*; ed. D. G. Hall, Wiley-VCH, Weinheim, **2005**. g) B. T. Cho, *Tetrahedron* **2006**, *62*, 7621. h) R. T. Stemmler, *Synlett* **2007**, *6*, 997. i) B. T. Cho, *Chem. Soc. Rev.* **2009**, *38*, 443.



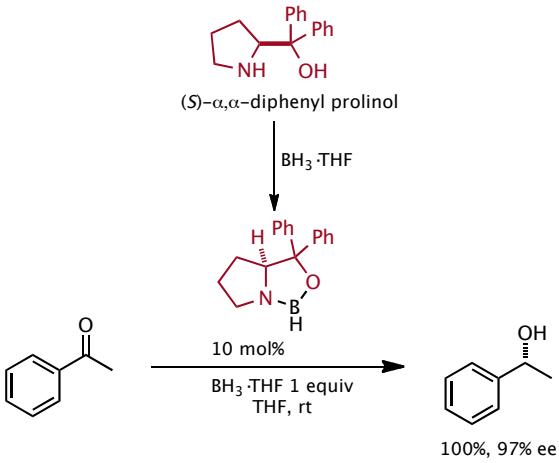
Scheme 5.1. Enantioselective reduction reported by Itsuno.

The concept developed by Itsuno *et al.* was further rationalized by mechanistic studies some years after by Corey and co-workers.[4] The authors found that the reaction of (*S*)-diphenyl valinol with two equivalents of BH_3 in THF at 35 ºC produced two equivalents of hydrogen gas and the requisite oxazaborolidine, which was obtained in pure form after sublimation. In the absence of the oxazaborolidine, the reduction of acetophenone was relatively slow with $BH_3 \cdot$ THF at room temperature. The rate acceleration in the presence of the oxazaborolidine immediately suggested to the authors that substoichiometric quantities of it could induce the asymmetric reduction of a ketone. Thus, using 2.5 mol% of the oxazaborolidine and 1.2 equivalents of $BH_3 \cdot$ THF, the reduced product (*R*)-1-phenylethanol was obtained in 95% ee.

The demonstration of the catalytic activity of the OAB formed from the (*S*)-valine derivative and valuable mechanistic considerations,[5] led to the formation of a new reducting systems from proline-derived aminoalcohol

[4] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.*, **1987**, *109*, 5551.
[5] a) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925. b) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861.

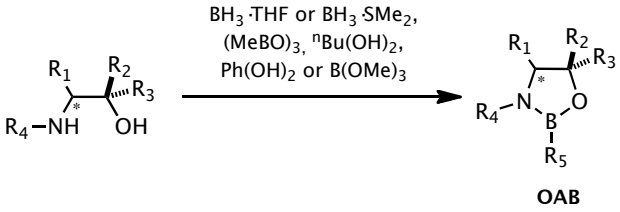
((*S*)-2,2-diphenylhydroxymethylpyrrolidine) that resulted superior to valine-derived one (Scheme 5.2).



Scheme 5.2. Enantioselective CBS-reduction.

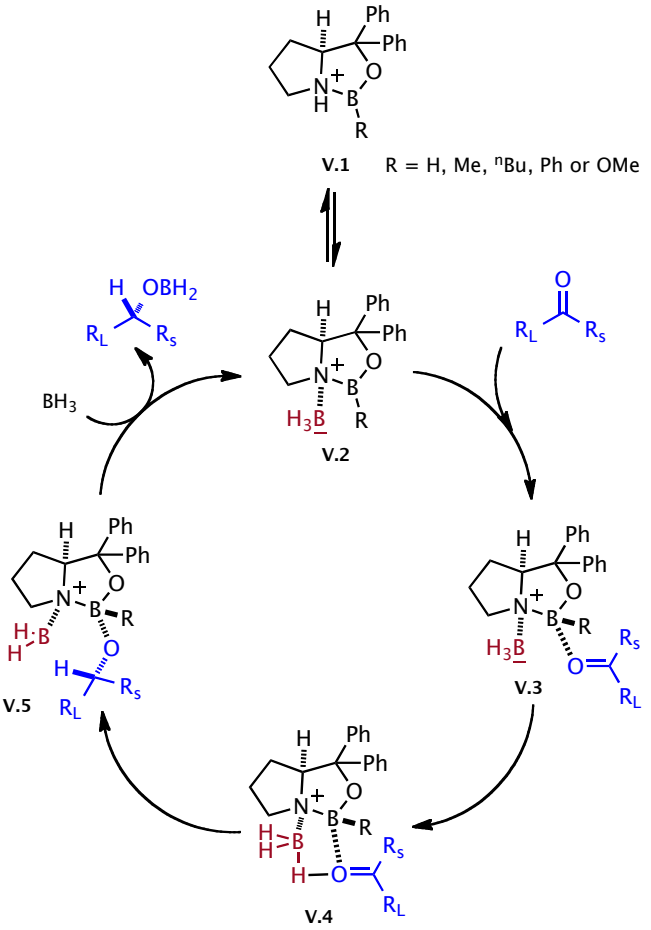
This approach, named CBS reduction, after its founders Corey, Bakshi and Shibata, has become one of the most versatile and successful asymmetric reducing systems known to date.

Chiral OABs are commonly prepared by the reaction of enantiopure 1,2-aminoalcohols with borane-THF ($BH_3 \cdot THF$), borane-dimethyl sulfide (BMS), alkyl or aryl boronic acids, trimethylboroxine or trialkylborates (Scheme 5.3).[3i]



Scheme 5.3. General preparation of oxazaborolidines (OAB).

OAB-catalyzed asymmetric borane reduction of prochiral ketones is a well-studied reaction.[6] The most widely mechanism accepted mechanism it is showed in Scheme 5.4 (for (*S*)-CBS-oxazaborolidine catalyzed ketone reduction).



Scheme 5.4. General mechanism proposed for the asymmetric reduction of ketones mediated by CBS-catalyst.

[6] a) G. Alagona, C. Ghio, M. Persico, S. Tomasi, *J. Am. Chem. Soc.* **2003**, *125*, 10027. b) J. Xu, T. Wei, Q. Zhang, *J. Org. Chem.* **2004**, *69*, 6860.

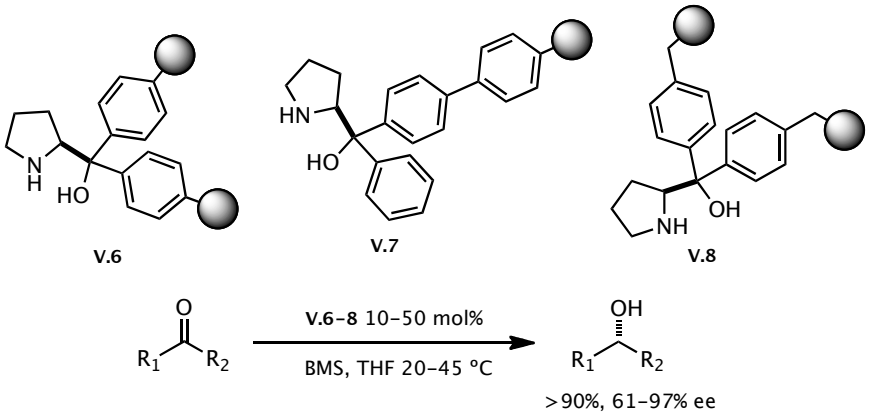
The catalytic cycle start with an *endo* complexation of borane to the nitrogen of the precatalysts **v.1** to the less hindered site of the OAB ring system (**v.2**). This adduct serves to activate BH_3 as a hydride donor and also to increase the Lewis acidity of the boron atom of the OAB ring. As a result, coordination with the carbonyl oxygen of the ketone provides the more stable *anti* form along the direction of the oxygen lone pair.[3i] The *anti*-coordination of the ketone oxygen to the ring boron of the catalysts favours a face-selective hydrogen transfer from the coordinated borane to the carbonyl via a six-membered cyclic transition state **v.4**. The resulting complex provides the reduction product *via* decomposition of the intermediate **v.5** with excess of BH_3, allowing also the regeneration of the catalyst. One important aspect is that OABs themselves do not reduce ketones. They can act as reducing agents only after addition of a second equivalent of borane.

5.1. POLYMER SUPPORTED OAB CATALYSTS.

As already mentioned in the previous chapters of the present dissertation, the use of immobilized diarylprolinol derivatives, as organocatalysts is very recent. However these catalysts were originally developed as supported versions of CBS-catalyst in order to make it suitable for easily separation and recycling. Most of those supported ligands are immobilized onto polymeric resins and derived from diphenylprolinol (Scheme 5.5).[7] The **v.6**[6a,b] and **v.7**[6c] compounds are CBS reagents anchored onto a cross-linked polystyrene, and **v.8**[6d] is attached to a polyethylene polymer. When the reduction was carried out with 10-50 mol% of these ligands, 61-97% ee for aralkyl ketones, α-halo ketones and pinacolone were obtained (Scheme 5.5). In terms of recycling of the catalyst, **v.6** and **v.7** can withstand many reaction cycles and can be reused several times without loss of enantioselectivity for the reduction of acetophenone, while in the case of

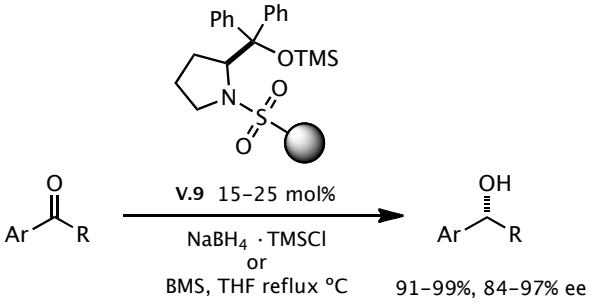
[7] a) M. D. Price, J. K. Sui, M. J. Kurth, N. E. Schore, *J. Org. Chem.* **2002**, *67*, 8086. b) M. C. Varela, S. M. Dixon, M. D. Price, J. E. Merit, P. E. Berget, S. Shiraki, M. J. Kurth, N. E. Schore, *Tetrahedron* **2007**, *63*, 3334. c) R. J. Kell, P. Hodge, P. Snedden, D. Watson, *Org. Biomol. Chem.* **2003**, *1*, 3238. d) S. Degni, C.-E. Wiln, A. Rosling, *Tetrahedron: Asymmetry* **2004**, *15*, 1495.

V.8 the recycling experiments were totally unsuccessful.



Scheme 5.5. Asymmetric reduction mediated by polymer-supported CBS-catalysts.

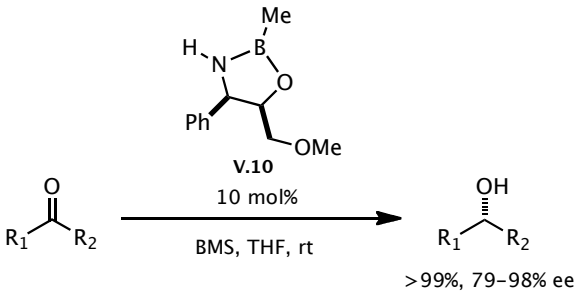
A chiral prolinol-based supported-sulfonamide **V.9** has been also developed from (*S*)-α,α-diphenylprolinol and polymeric sulfonyl chloride.[8] This ligand cannot form an OAB ring structure with borane reagents due to the absence of an N–H group. However, it is highly effective as a catalyst for the borane reduction of aryl methyl ketones, providing high enantioselectivity (84-96% ee) (Scheme 5.6). Furthermore, the catalyst could be reused five times for the reduction of 4-nitroacetophenone with no loss of selectivity (96-97% ee).



Scheme 5.6. Asymmetric borane reduction of ketones catalyzed by chiral polymer-supported sulfonamide.

[8] a) J.-B. Hu, G. Zhao, Z.-D. Ding, *Angew. Chem.* **2001**, *113*, 1143; *Angew. Chem. Int. Ed.* **2001**, *40*, 1109. b) J.-B. Hu, G. Zhao, G.-S. Yang, Z.-D. Ding, *J. Org. Chem.* **2001**, *66*, 303.

In our research group has been developed a family of enantiopure amino alcohol ligands, obtained from readily available enantiopure epoxy alcohols able to mediate the $BH_3.SMe_2$ catalytic reductions of alkyl aryl and dialkyl prochiral ketones in highly stereoselective asymmetric manner (Scheme 5.7).[9]



Scheme 5.7. Catalytic enantioselective reduction of prochiral ketones mediated by chiral oxazaborolidine **V.10**.

The modular nature of these CBS-type ligands, make them suitable for its immobilization onto polymer supports in order to take advantage of its easy separation, efficient recycling, minimization of metal traces in the final product and improved handling and process control.

5.2. RESULTS AND DISCUSSION

In the past several years we have described the synthesis of PS-supported ligands to use them in the asymmetric addition of alkyl and aryl zinc to aldehydes.[10] The anchoring of such ligands was performed by nucleophilic

[9] C. Puigjaner, A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera, A. *J. Org. Chem.* **1999**, *64*, 7902.

[10] a) A. Vidal-Ferran, N. Bampos, A. Moyano, M. A. Pericàs, A. Riera, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 6309. b) M. A. Pericàs, D. Castellnou, I. Rodríguez, A. Riera, Ll. Solà, *Adv. Synth. Catal.* **2003**, *345*, 1305. c) D. Castellnou, Ll. Solà, C. Jimeno, J. M. Fraile, J. A. Mayoral, A. Riera, M. A. Pericàs, *J. Org. Chem.* **2005**, *70*, 433. d) D. Castellnou, M. Fontes, C. Jimeno, D. Font, Ll. Solà, X. Verdaguer, M. A. Pericàs, *Tetrahedron* **2005**, *61*, 12111. e) A. Bastero, D. Font, M. A. Pericàs, *J. Org. Chem* **2007**, *72*, 2460. f) M. A. Pericàs, C. I. Herrerías, Ll. Solà, *Adv. Synth. Cat.* **2008**, *350*, 927. g) J. Rolland, X. C. Cambeiro, C. Rodríguez-Escrich, M. A. Pericàs, *Belstein J. Org. Chem.* **2009**, *5*, 56.

substitution reaction. This strategy have some limitation with respect to the ligand structure and prevents the use of the anchoring step as a source of diversity for the preparation of libraries of supported ligands.

As a guide to this work, we decided to fine-tune the CBS-structure in order to have an appropriate anchoring position (Fig. 5.1).

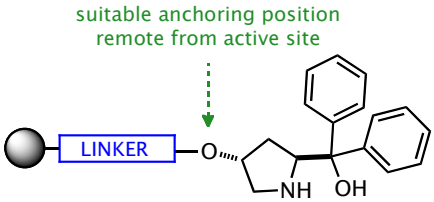
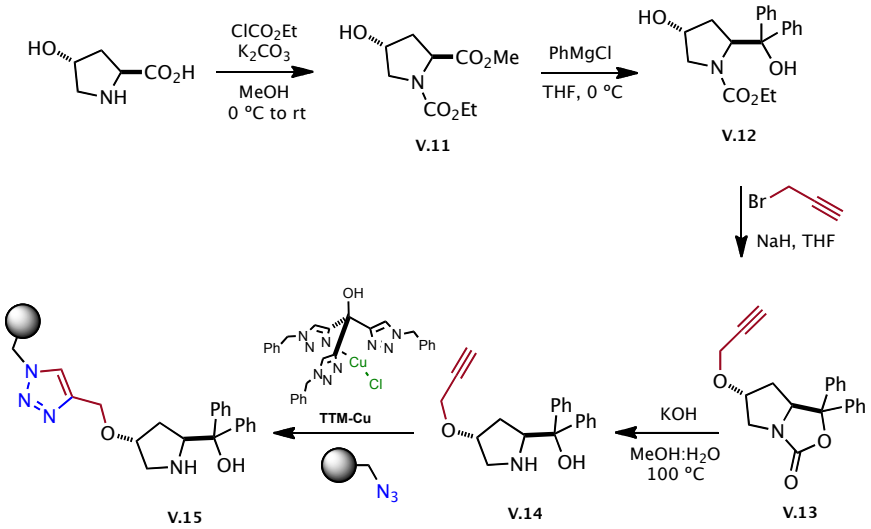


Figure 5.1. Immobilization of aminoalcohol-type ligands.

The CuAAC reaction between an alkyne and an azide was our first choice as immobilization strategy of the chiral prolinol onto Merrifield resins. The synthesis of the supported **V.15** compound is showed in Scheme 5.8.



Scheme 5.8. Synthesis of PS-supported CBS-ligand by CuAAC reaction.

The synthesis of versatile intermediate **V.14** is known[11] and starts from the commercially available 4-hydroxy-L-proline. The esterification of both acid and amine groups leads to **V.11**, which is then transformed in to the diphenylprolinol-derivative **V.12**. The following step was the reaction with propargyl bromide yielding the cyclic compound **V.13**, which is opened under basic conditions to obtain the propargyloxy diphenylprolinol-derivative **V.14**. The immobilization of this diphenylprolinol onto azidomethylpolystyrene[12] was catalyzed by the tris(triazolyl)methanol-copper complex **TTM-Cu**[13] allowing the synthesis of the immobilized ligand **V.15** from free aminoalcohol **V.14**. This anchoring reaction is followed by the disappearance of the azide functionality present in the resin by IR (ca. 2090 cm^{-1}) and elemental analysis confirms quantitative conversions.

The test reaction of choice was the reduction of acetophenone. We decided to employ trimethylborate as boron source. It has been established[14] that an increment in the Lewis acidity of the boron atom could accelerate the catalytic reaction, and consequently, enhance the enantioselectivity. Due to this revelation, the authors reasoned that a B-methoxy-oxazaborolidine should be a more efficient catalyst than its B-methyl analog.

The ketone reduction was performed employing the B-OMe-supported-oxazaborolidine prepared in situ. The treatment of the polymeric resin (0.10 eq) with trimethyl borate (1.2 eq.) in 1 mL of dry THF at room temperature with stirring for 1 hour under inert atmosphere rendered the desired B-OMe-oxazaborolidine. The excess of trimethyl borate was removed by filtration *via* cannula and the resin was rinsed with THF several times (10 mL) with the final addition of 1 mL of THF. For the reduction, BMS (1.0 eq.) was added to the reaction mixture followed by a solution of acetophenone (1.0 eq.) in 1 mL of THF, which was added dropwise during one hour into the reaction mixture. Once the addition of the ketone finish, the reaction mixture is stirred during 30 minutes and quenched in acidic conditions. The product is obtained after separation of the immobilized ligand by filtration, wash with water and evaporation of the solvents.

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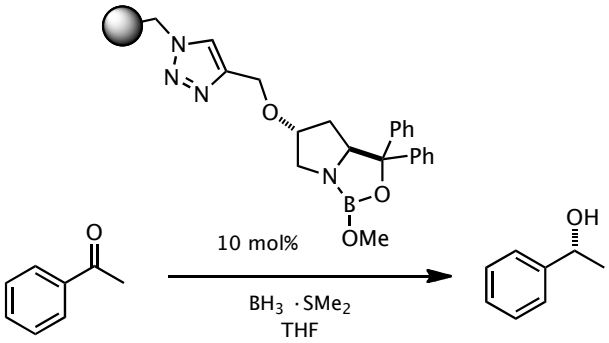
[11] I. Mager, K. Zeitler, *Org. Lett.* **2010**, *12*, 1480.
[12] D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653.
[13] S. Özçubukçu, E. Özkal, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2009**, *11*, 4680.
[14] M. Masui, T. Shioiri, *Synlett* **1997**, 273.

The enantiomeric excess was obtained by GC and resulted in a poor 50% (entry 1, Table 1). The reaction was carried out under different conditions in order to improve this enantioselectivity. The results are showed in Table 1.

Table 1. Reduction of acetophenone mediated by OAB formed with supported-**v.15** ligand.

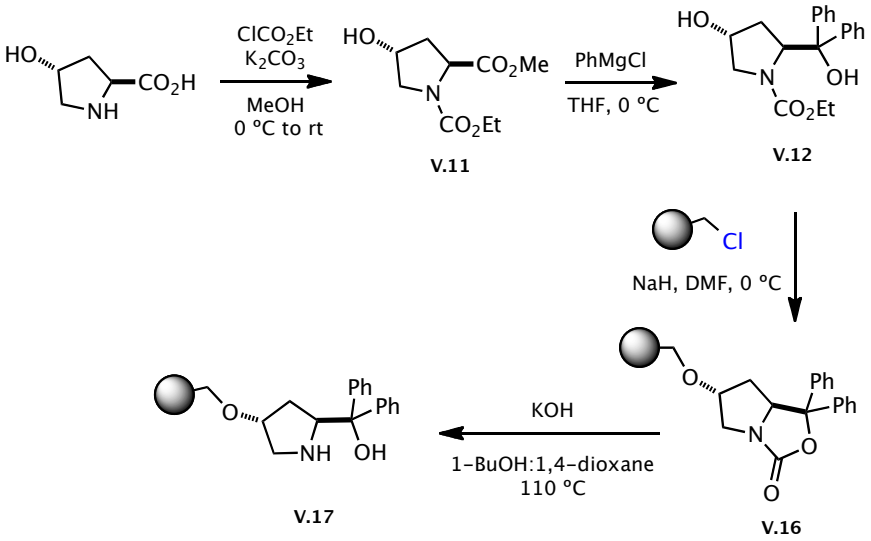


Entry	% mmol cat.	Added in 1h	Conv. %	ee %
1	10	acetophenone	>99	50
2	20	acetophenone	>99	54
3	10	BMS	>99	5
4	10	both	>99	41
5[a]	10	acetophenone	>99	40
6[b]	10	acetophenone	>99	51

a) Formation of oxazaborolidine during 12 h.
b) Using the resin of the previous reaction.

The use of larger catalytic loading (entry 2, Table 1) does not proportionate better results and only a slight increase in the enantiomeric excess was observed. Changing the order of addition was deleterious for the selectivity (entry 3, Table 1) whereas the slow addition of both reagents at the same time has no a considerable effect (entry 4, Table 1). Then we consider the possibility of a slower formation of the oxazaborolidine due to the heterogeneous nature of our ligand. The reaction to form the OAB was

carried out overnight but the selectivity was not enhanced (entry 5, Table 1). The use of reused resin from a previous run resulted in the same enantioselectivity which minds that the immobilized CBS-ligand can be recycled despite is low selectivity. In view of the results obtained, we investigate the possibility that the triazole ring present in the structure of the resin could lead to a non-enantioselective pathway like it was observed for other transformations.[10e] For trying to solve this drawback, a new resin was synthesized avoiding the presence of the triazole as linker. The synthesis of this new ligand is showed in Scheme 5.9. It is analogous to the previous one showed in Scheme 5.8, although in this case, the cyclic carbamate **V.16** is formed during the anchoring step by SN_2 type reaction. The opening of the cycle to obtain the desired ligand **V.17** can be followed by the disappearance of such carbonyl functionality by IR (ca. 1765 cm^{-1}) and confirmed by elemental analysis.



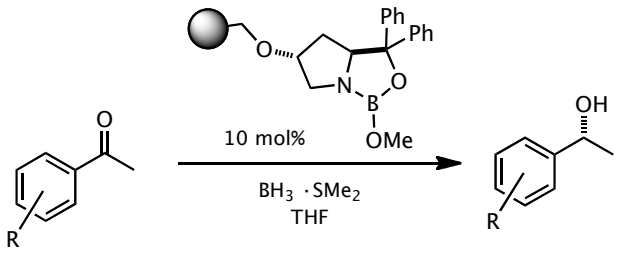
Scheme 5.9. Synthesis of PS-supported CBS-ligand by SN_2 reaction.

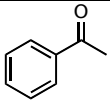
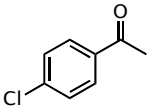
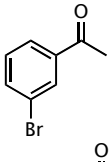
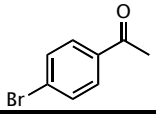
This new resin, which has the α,α-diphenylprolinol directly anchored to the Merrifield resin by the hydroxy group in carbon 4, was also tested in the asymmetric reduction of acetophenone. Gratifyingly, the resulting OMe-oxazaborolidine, which is form in the same conditions than **V.15**, provided

the desired alcohol in 99% ee. This result confirms that the presence of the triazole moiety is deleterious for the enantioselectivity of the process.

The preliminary results for the scope of the supported ligand **V.17** are collected in Table 2.

Table 2. Reduction of aromatic ketones mediated by OAB formed with supported-**V.17** ligand.

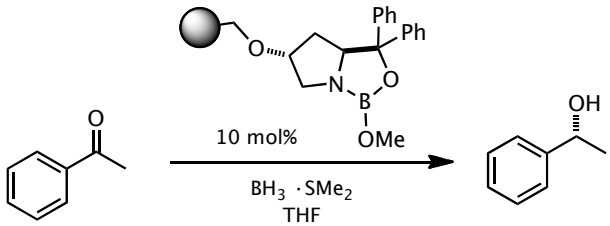


Entry	Substrate	Conv. %	ee %
1		>99	99
2		>99	94
3		>99	99
4		>99	99
5		>99	71

The scope of the reaction will be extended in the very near future because of the promising results obtained with this new CBS-supported derivative. In order to establish the robustness of the ligand, a first recycling

experiments were carried out. The results are showed in Table 3.

Table 3. Recycling experiments of the acetophenone reduction mediated by OAB formed with supported-**v.17** ligand.



Run	mol%	% yield	% ee
1	10	>99	99
2	10	>99	63
3	10	>99	82

The first recycling run was performed rinsing the resin with THF several times (10 mL) under argon atmosphere after collecting the reaction crude. Then BMS (1 eq.) was added, followed by slow addition of the ketone solution (1 eq. in 1 mL of THF) (entry 2, Table 3). The important decrease in the enantioselectivity could be attributed to a partial or total hydrolization of the catalytic OAB specie. For that reason, in the next run, this resin was also rinsing with THF under inert atmosphere, and before the reagents addition, additional $B(OMe)_3$ (1.2 eq.) was added, allowing the formation of the OAB during one hour. After removing the excess of trimethyl borate, the starting materials were added as usual (entry 3, Table 3). In this case, better enantioselectivity than the previous run was achieved, although slightly lower than in the first run.

5.3. SUPPORTING INFORMATION

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resins (1% DVB, f = 0.53 mmol/g resin and 1% DVB, f = 0.8-1.0 mmol/g resin) were obtained from Merck. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz (1H) and 100.63 MHz (13C{1H}). TMS was used as internal standard for 1H-NMR and CDCl3 for 13C-NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses (C, H, N) were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Gas Chromatography (GC) was performed on β-dex column. Racemic standard products were prepared using $NaBH_4$ in order to establish GC conditions.

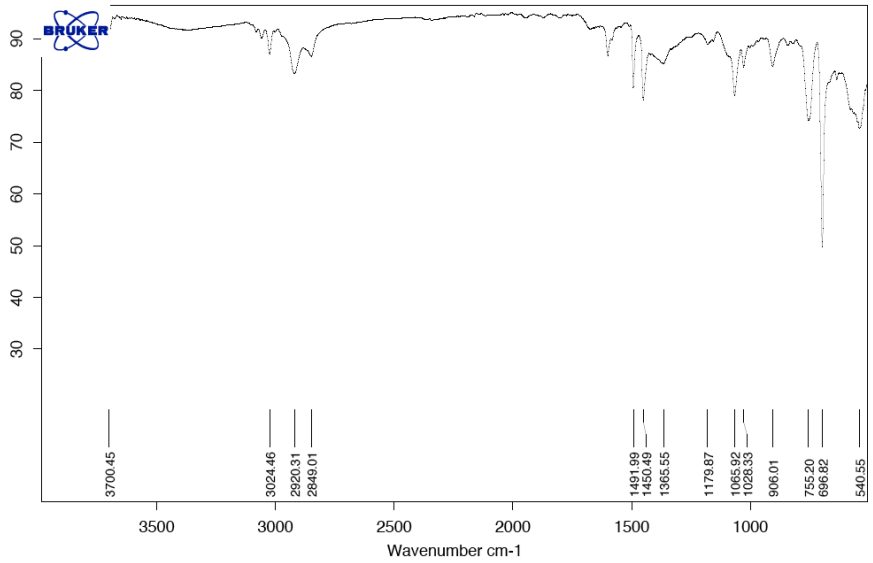
Synthesis of the immobilized catalysts

Triazolyloxy-diphenylprolinol-supported resin (V.15)

Synthetically known aminoalcohol **V.14**[11] (96 mg, 0.31 mmol), azidomethylpolystyrene resin (500 mg, f = 0.517 mmol g^{-1}), 3 mL of DMF, 3 mL of THF and tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol · CuCl (**TTM-Cu**) catalyst (1.6 mg, 1 mol%) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 50 min under microwave irradiation of 200 W, without stirring. When the cycloaddition reaction was completed, the functionalized resin was filtered, washed with water (100 mL), water-THF 1:1 (100 mL) and THF (100 mL), and was dried overnight in vacuo at 40 ºC to afford modified resin **V.15**.

IR (ATR): ν = 3058.90, 3024.87, 2921.08, 2849.63, 1600.47, 1492.26, 1450.77, 1066.04, 1027.85 cm^{-1}.

The functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 4.12; found: N 3.22, C 84.59, H 7.56; *f* =0.57 mmol/g.



(2*S*,4*R*)-1-Ethyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (V.11)
Ethyl chloroformate (6.9 mL, 72.2 mmol) was added dropwise at 0 °C to a mixture of *trans*-4- hydroxyl L-proline (3.06 g, 23.3 mmol) and K_2CO_3 (5.2 g, 37.5 mmol) in MeOH (45 mL), and the resulting mixture was warmed up to room temperature gradually. After completion of the reaction as shown by TLC, the reaction mixture was filtered and the filtrate was concentrated, diluted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography afforded **V.11** as an oil (3.8 g, 14.7 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.20-1.30 (m, 3H), 2.06-2.14 (m, 1H), 2.30-2.35 (m, 1H), 3.52-3.69 (m, 2H), 3.75 (s, 3H), 4.13-4.17 (m, 2H),

4.45-4.52 (m, 1H). **^{13}C-NMR** ($CDCl_3$): δ (ppm) = 14.51, 14.96, 21.38, 38.79, 39.50, 52.55, 52.66, 54.89, 55.40, 57.99, 58.10, 60.76, 61.86, 61.93, 69.72, 70.50, 155.18, 155.63, 173.55, 173.67.

(2*S*,4*R*)-Ethyl 4-hydroxy-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate (V.12)

PhMgBr solution in THF (2 M, 17.7 mL, 35.4 mmol) was added dropwise at 0 °C under argon atmosphere to a solution of **V.11** (1.2 g, 5.9 mmol) in anhydrous THF (40 mL), and the resulting reaction mixture was warmed up to room temperature gradually. After kept stirring for 2 days, the reaction was quenched by MeOH (10 mL), concentrated under reduced pressure, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure and recrystallized from dichloromethane/*n*-heptane to give the pure product as a white solid (0.8 g, 2.4 mmol, 40 % yield).

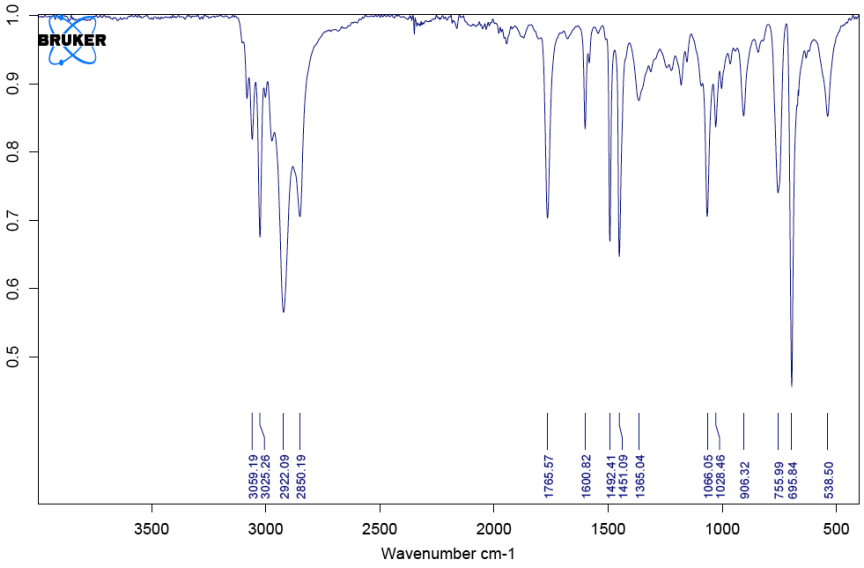
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.15 (t, *J* = 7.1 Hz, 3H), 1.66 (d, *J* = 4.1 Hz, 1H), 2.04 (dddd, *J* = 14.2 Hz, *J* = 8.5 Hz, *J* = 3.4 Hz, *J* = 1.7 Hz, 1H), 2.15 (ddd, *J* = 14.3 Hz, *J* = 6.3 Hz, *J* = 5.8 Hz, 1H), 3.00 (dd, *J* = 12.1 Hz, *J* = 4.4 Hz, 1H), 3.54 (d, *J* = 12.1 Hz, 1H), 3.96-3.84 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 5.09 (dd, *J* = 8.5 Hz, *J* = 6.6 Hz, 1H), 7.44-7.19 (m, 10H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ (ppm) = 14.6, 39.4, 56.2, 62.2, 65.6, 69.9, 81.6, 127.4, 127.4, 127.6, 127.8, 127.9, 128.1, 143.4, 145.6, 158.2.

Oxazolidinone-derived resin (V.16)

A solution of **V.12** (420 mg, 1.2 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (73 mg, 1.8 mmol) in DMF (5 mL) at 0 °C under N_2. The mixture was stirred for 20 min, quickly poured onto a suspension of the Merrifield resin (1.7 g, 0.85 mmol) in DMF (15 mL) at 0 °C, flushed with N_2, and smoothly stirred for 48 h at 0 °C. The functionalized resin was filtered, washed with water (100 mL), water-THF 1:1 (100 mL) and THF (100 mL), and was dried overnight in vacuo at 40 ºC to afford modified resin **V.16** (f_{max} = 0.46 mmolg^{-1}).

IR (ATR): ν = 3059.20, 3025.07, 2921.42, 2849.93, 1765.79, 1600.69, 1492.25, 1450.86, 1364.50, 1066.04 cm^{-1}.

The functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 0.65; found: N 0.54, C 87.72, H 7.79; *f* =0.39 mmol/g.

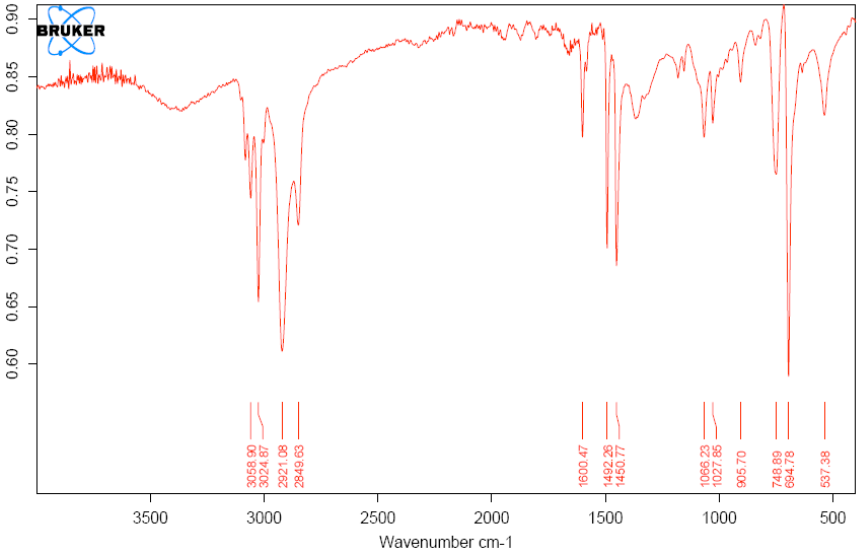


Diphenylprolinol-supported resin (V.17)

The corresponding modified resin **V.16** (0.5 g, *f* = 0.39 mmol g^{-1}), KOH (2.5 M, 15 mmol), and *n*-Buthanol:1,4-dioxane (3:3 mL), were heated in a sealed pressure tube at 110 °C overnight. The mixture was left to reach room temperature and the resin was filtered and washed with water (100 mL), water-THF 1:1 (100 mL) and THF (100 mL) and was dried overnight in vacuo at 40 ºC.

IR (ATR): ν = 3058.90, 3024.87, 2921.08, 2849.63, 1600.47, 1492.26, 1450.77, 1066.04, 1027.85 cm^{-1}.

The functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 0.66; found: N 0.51, C 85.87, H 7.82; *f* =0.36 mmol/g.



Spectroscopic data of secondary alcohols

(*R*)-1-Phenylethanol[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.50 (d, *J* = 6.4 Hz, 3H), 1.83 (br, 1H), 4.90 (q, *J* = 6.4 Hz, 1H), 7.25 to 7.29 (m, 1H), 7.33 to 7.39 (m, 4H). **GC:** β-Dex, isoterm 120 ºC, t_R = 14.6 min (*R*), 16.2 min (*S*)

(*R*)-1-(4-Chlorophenyl)ethanol[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.48 (d, *J* = 6.4 Hz, 3H), 1.83 (br, 1H), 4.88 (q, *J* = 6.4 Hz, 1H), 7.31 (s, 4H). **GC:** β-Dex, isoterm 120 ºC, t_R = 37.9 min (*R*), 41.8 min (*S*).

(*R*)-1-(4-Bromophenyl)ethanol[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.46 (d, *J* = 6.5 Hz, 3H), 2.01 (br, 1H), 4.85 (q, *J* = 6.5 Hz, 1H), 7.22-7.25 (m, 2H), 7.45-7.47 (m, 2H). **GC:** β-Dex, isoterm 120 ºC, t_R = 81.6 min (*R*), 90.3 min (*S*).

[15] D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, E. J. J. Grabowski, *J. Org.Chem.* **1993**, *58*, 2880.

(*R*)-1-(3-Bromophenyl)ethanol[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.47 (d, *J* = 6.4 Hz, 3H), 2.01 (br, 1H), 4.85 (q, *J* = 6.4 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.28 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.52 (d, *J* = 1,6 Hz, 1H). **GC:** β-Dex, isoterm 130 ºC, t_R = 43.8 min (*R*), 46.6 min (*S*).

(*R*)-1-(2-Bromophenyl)ethanol[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.43 (d, *J* = 6 Hz, 3H), 2.07 (br, 1H), 5.23 (q, *J* = 6 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.59 (dd, *J* = 7.6, 2.0 Hz, 1H). **GC:** β-Dex, isoterm 110 ºC, t_R = 11.1 min (*R*), 11.5 min (*S*).

[16] D. Chaplin, P. Harrison, J. P. Henschke, I. C. Lennon, G. Meek, P. Moran, C. J. Pilkington, J. A. Ramsden, S. Watkins, A. Zanotti-Gerosa, *Org. Proc. Research Develop.* **2003**, *7*, 89.

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APPROACHES TO ASYMMETRIC CATALYSIS WITH POLYMER-SUPPORTED PYRROLIDINES
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Chapter VI

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AQUEOUS ASYMMETRIC TRANSFER HYDROGENATION USING MODULAR HYDROPHOBIC AMINOALCOHOLS

Many biologically active compounds, along with important building blocks for the pharmaceutical industry, have stereogenic centers containing alcohol functionality.[1] For that reason, the field of asymmetric reductions has been widely explored. A convenient method for obtaining chiral secondary alcohols is the enantioselective reduction of prochiral ketones, which can be achieved by metal catalysis using chiral ligands. Two different approaches can be employed to perform this transformation, either direct hydrogenation using molecular hydrogen, or via hydrogen transfer from a suitable donor molecule.[2] Alkenes are easily reduced via direct hydrogenation, whereas unsaturated compounds involving heteroatoms like ketones or imines are often reduced by the latter method. Due to their natural availability, it is not surprising that amino acids, or closely related compounds, such as the corresponding amino alcohols are common ligands used for asymmetric catalysis.[3]

TRANSFER HYDROGENATION

Although the first catalytic hydrogen transfer was demonstrated by Knoevenagel and Bergdolt in 1903 who observed the disproportion of dimethyl 1,4-dihydroterephthalate to dimethyl terephthalate and *cis*-hexahydroterephthalate mediated by palladium black,[4] it was in the 1920's when appeared the first examples of reduction of ketones by transfer hydrogenation, reported independently by Meerwein, Verley and Ponndorf

[1] V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734.
[2] J. S. M. Samec, J. E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237.
[3] For a review on the application of β-amino alcohols in asymmetric transformations, see: D. J. Ager, I. Prahash, D. R. Schaad, *Chem. Rev.* **1996,** *96*, 835.
[4] E. Knoevenagel, B. Bergdolt, *Chem. Berg.* **1903**, *36*, 2857.

(MPV-reduction)[5], where stoichiometric amount of aluminum isopropoxide allowed the reversible transfer of hydrogen from 2-propanol to a ketone, forming a secondary alcohol and acetone. In 1967 Herbest published the first example of transition metal-catalyzed transfer hydrogenation, employing an Ir-DMSO-complex.[6] Although the fist transfer hydrogenation reactions catalyzed by Ru-complexes were reported a few years later,[7] the addition of base to the reaction mixture using a Ru (II)-complex as catalyst reported by Bäckvall in 1991, was a crucial contribution to high accelerate the rate of the reaction.[8]

6.1. ASYMMETRIC TRANSFER HYDROGENATION (ATH)

The reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst is known as catalytic asymmetric transfer hydrogenation and the most widely used catalysts are transition metals in combination with chiral ligands.[9] Transfer hydrogenation has the advantages of operational simplicity. Since no hydrogen pressure is used, no special equipment is required and in addition, no hazardous waste is produced.

The first ATH was reported by the groups of Ohkubo and Sinou in the 1970s using as catalytic specie $[RuCl_2(PPh_3)_3]$ in the presence of either a chiral monophosphine or a chiral hydrogen donor.[10] Since then, a wide range of metal complexes has been explored to catalyze the ATH of olefins and ketones. Among the most active and selective catalysts reported so far are those containing the diphosphonite,[11] diamine-based,[12] pyridine

[5] a) H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, *444*, 221; b) A. Verley, *Bull. Soc. Fr.* **1925**, *37*, 537; c) W. Ponndorf, *Angew. Chem.* **1926**, *39*, 138.
[6] Trocha-Grimshaw, J.; Henbest, H. B. *Chem. Commun.* **1967**, 544.
[7] a) Y. Sasson, J. Blum, *Tetrahedron Lett.* **1971**, 2167. b) Y. Sasson, J. Blum, *J. Org. Chem.* **1975**, *40*, 1887.
[8] R.L.Chowdhury, J. E. Bäckvall, *Chem. Commun.* **1991**, 1063.
[9] S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226.
[10] K. Ohkubo, K. Hirata, K. Yoshinaga, M. Okada, *Chem. Lett.* **1976**, 183. b) G. Descotes, D. Sinou, *Tetrahedron Lett.* **1976**, *17*, 4083.
[11] M. T. Reetz, X. Li, *J. Am. Chem. Soc.* **2006**, *128*, 1044.

derivatives,[13] or aminoalcohol ligands,[14] (**A**, **B**, **C** and **D** respectively in Figure 6.1). Phosphorated and pyridine ligands in combination with ruthenium, iridium and rhodium complexes have providen low enantiomeric excesses and the reactions required high temperatures for a reasonable turn over frequency. It was demonstrated that the addition of a base increases the rate of hydrogen transfer considerably and since today, a base is commonly used as co-catalyst.[15]

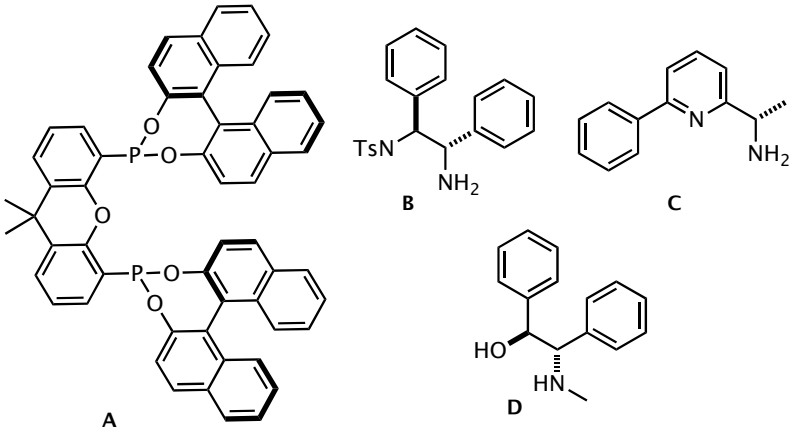


Fig. 6.1. Ligands selection for catalytic asymmetric transfer hydrogenation.

$[RuCl_2(arene)]_2$-complexes in combination with a chiral amino alcohol or monotosylated diamine as ligand were developed by Noyori and coworkers as catalysts for the transfer hydrogenation of aromatic ketones resulting in excellent enantioselectivity and reaction rates.[16] The reported complex Ru-TsDPEN (where DPEN = 1,2-diphenylethylenediamine, **B** in Fig. 6.1) is

[12] a) J.Hannedouche, G. J.; Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986. b) A.M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318. c) F. K.Cheung, A. M. Hayes, J. Hannedouche, A. S. Y. Yim, M. Wills, *J. Org. Chem* **2005**, *70*, 3188.
[13] W. Baratta, F. Benedetti, A. Del Zotto, L. Fanfoni, F. Felluga, S. Magnolia, E. Putignano, P. Rigo, *Organometallics* **2010**, *29*, 3563.
[14] J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya, R. Noyori, *J. Chem. Soc. Chem. Commun.* **1996**, 233.
[15] a) S. Gladiali, G. Chelucci, G. Chessa, G. Delogue, F. Soccolini, *J. Organometal. Chem.* **1987**, 327. b) R. L. Chowdhury, J. E. Bäckvall, *Chem. Commun.* **1991**, 1063.
[16] a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562. b) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521. c) For a review, see : R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.

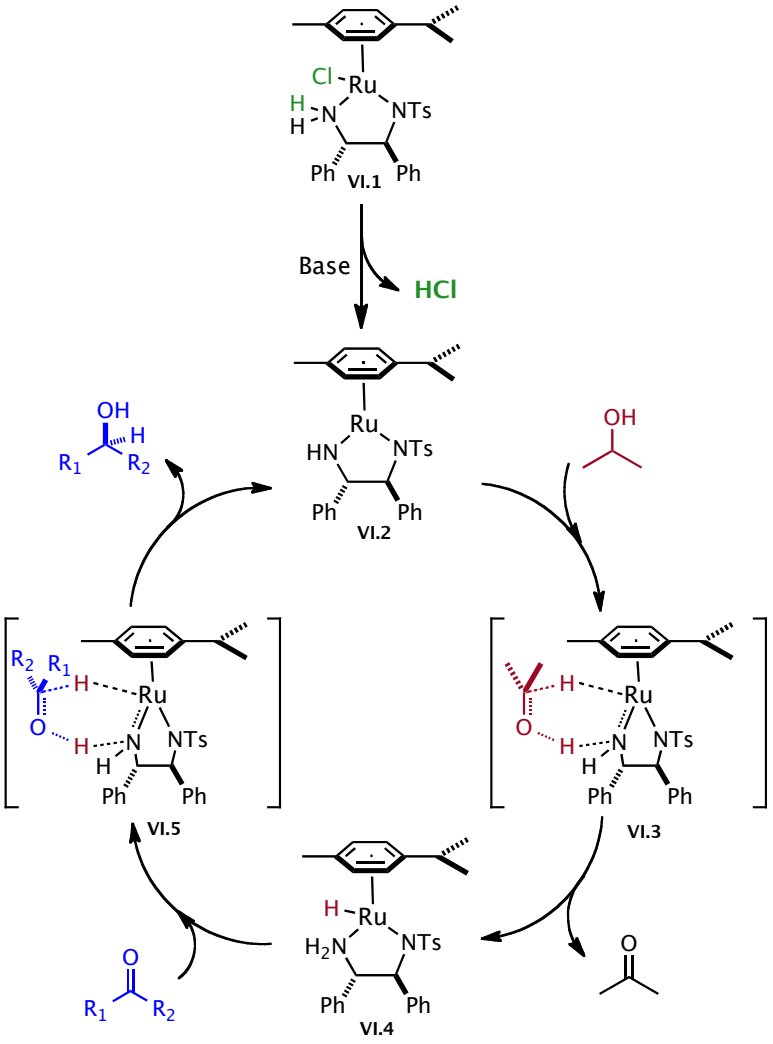
until now the most well-known and successful catalyst for asymmetric transfer hydrogenation.

The mechanism of the ATH described by Noyori is shown in Scheme 6.1. When transition metals are involved, the mechanism of ATH reaction proceeds though a hydridic route with the formation of a metal hydride obtained from a β-hydride elimination from a donor such as 2-propanol. The hydrogen is then transferred from the metal to the acceptor (for instance a ketone) by a six-member transition state formed with the concerted delivery of a proton from the ligand and a hydride from ruthenium. In this metal-ligand bifunctional catalysis the ketone is reduced without coordination to the metal.[17] The role of the base is to generate a 16 electron-complex **VI.2** that is reduced to the active 18 electron-complex **VI.4.**

Compared with phosphine ligands, nitrogen based ones are most favourable and commonly used in ATH, since they usually are cheaper to synthesize and more stable towards oxidation. Concerning the hydrogen donors, the most widely used reaction media is 2-propanol which is non-hazardous, cheap, stable and acetone is the only by-product of the reaction.[18] One of the drawbacks of this reaction is the large excess of 2-propanol required to obtain high conversions and to avoid the reverse process towards the carbonyl compound that decreases the enantiomeric excess. The 2-propanol conditions often include alkaline isopropoxide as base and the equilibrium can be shifted towards the product by distilling off acetone throughout the reaction. Other popular hydrogen source is the azeotrope of formic acid and triethylamine (triethyl ammonium formate, TEAF, in formic acid). Despite TEAF could be a more convenient hydrogen donor, because of the irreversible formation of carbon dioxide upon hydrogen donation, only a limited number of catalysts are compatible

[17] a) K-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297; *Angew. Chem. Int. Ed.* **1997**, *36*, 285. b) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931.
[18] a) F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng, Y. Jiang, *J. Org. Chem.* **2005**, *70*, 9424. b) X. Wu, D. Vinci, T. Ikariya, J. Xiao, *Chem. Commun.* **2005**, 4447. c) D. S. Matharu, D. J. Morris, C. J. Clarkson, M. Wills, *Chem. Commun.* **2006**, 3232.

with the formic acid conditions,[19] as the strong interactions between the donor and the catalyst can result in inhibition or even decomposition of the catalyst.



Scheme 6.1. Concerted ATH mechanism *via* six-member cyclic transition state.

[19] S. Gladiali, R. Taras, in *Modern Reduction Methods*; eds. P. G. Andersson, I. J. Munslow, Wiley-VCH, Weinheim, **2008**.

In our research group has been studied the ATH of ketones mediated by diverse catalytic species.[20] In this context, the aim of this project was the study of ATH in water catalyzed by aminoalcohol based metal-complexes and depending on the results obtained, their structural modification to make them suitable for immobilization onto a polymeric support[21] and their application on aqueous ATH under the same reaction conditions.

6.1.1. ATH IN WATER

As a result of the increasing demand for more environmental benign chemical processes, nowadays water has been widely used as green solvent in asymmetric transfer hydrogenation, affording fast reaction rate, high enantioselectivity and good chemoselectivity. In recent years, it has become popular to perform asymmetric transfer hydrogenation reactions in water using alkaline formate salts as the hydrogen source.[22] When the ATH-reaction is performed in water, the use of aqueous micellar catalysis[23] often accelerates the reaction and can moreover give rise to enhance the selectivity. Another approach is improving the hydrophilicity of the catalyst to perform aqueous catalysis using catalysts soluble in water assembled through the use of water-soluble ligands.[24] One example are the

[20] a) M. Pastó, A. Riera, M. A. Pericàs, *Eur. J. Org. Chem.* **2002**, 2337. b) S. Ferrer, M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron: Asymmetry* **2003**, *14*, 1747. c) F. Michalek, A. Lagunas, C. Jimeno, M. A. Pericàs, *J. Mater. Chem.* **2008**, *18*, 4692. d) S. Rodríguez-Escrich, L. Solà, C. Jimeno, C. Rodríguez-Escrich, M. A. Pericàs, *Adv. Synth. Catal.* **2008**, *350*, 2250. e) X. C. Cambeiro, M. A. Pericàs, *Adv. Synth. Catal.* **2011**, *353*, 113. f) R. Marcos, C. Jimeno, M. A. Pericàs, *Adv. Synth. Catal.* **2011**, in press.

[21] For examples on ATH of ketones in organic solvent using polymer-supported chiral catalysts, see: a) D. J. Bayston, C. B. Travers, M. E. C. Polywka, *Tetrahedron: Asymmetry* **1998**, *9*, 2015. b) X. Li, W. Chen, W. Hems, F. King, J. Xiao, *Tetrahedron Lett.* **2004**, *45*, 951. c) P. N. Liu, P. M. Gu, F. Wang, Y. Q. Tu, *Org. Lett.* **2004**, *6*, 169.

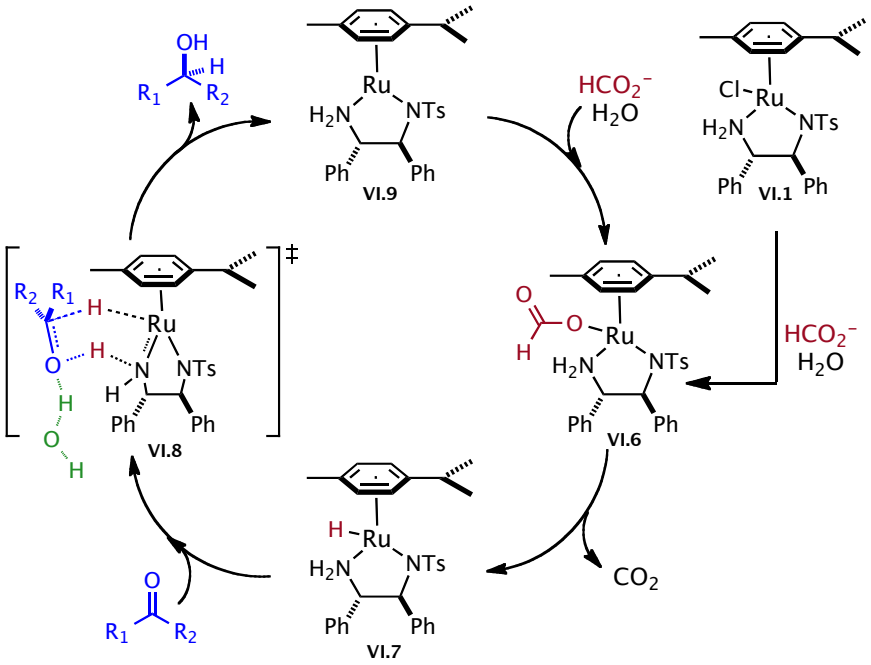
[22] a) B. Cornils, W. A. Herrmann, *Aqueous Phase Organometallic Catalysis*, Wiley-VCH, Weinheim, **2004**. b) X. Wu, J. Xiao, *Chem. Commun.* **2007**, 2449.

[23] U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751.

[24] a) T. Thorpe, J. Blacker, S. M. Brown, C. Bubert, J. Crosby, S. Fitzjohn, J. P. Muxworthy, J. M. J. Williams, *Tetrahedron Lett.* **2001**, *42*, 4041. b) C. Bubert, J. Blacker, S. M. Brown, J. Crosby, S. Fitzjohn, J. P. Muxworthy, T. Thorpe, J. M. J. Williams, *Tetrahedron Lett.* **2001**, *42*, 4037. c) Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. Deng, *Org. Lett.* **2003**, *5*, 2103. d) Z. Zhou, Y. Sun, *Catal. Commun.* **2009**, *10*, 1685. e) Z. Zhou, Q. Ma, Y. Sun, A. Zhang, L. Li, *Heteroat. Chem.* **2010**, *21*, 505. f) A. Barrón-Jaime, O. F. Narvaez-Garayzar, J. González, V. Ibarra-Galván, G. Aguirre, M. Parra-Hake, D. Chávez, R. Somanathan, *Chirality* **2011**, *23*, 178.

monosulfonylated derived diamine ligands.[25]

The mechanism of ATH in water proceeds also by six-member transition state, like in the general catalytic cycle described by Noyori, with the formate in this case as the hydrogen source (Scheme 6.2). The intermediates ruthenium–hydride **VI.7** and oxidized-**VI.9** are active species in ATH in water, as well as in the catalytic cycle of ATH in organic media (**VI.2** and **VI.4** in Scheme 6.1). The chloride **VI.1** is a precatalyst, which is instantly converted into **VI.6** upon the introduction of formate. DTF calculations confirm that in the transition state **VI.8**, water acts as a hydrogen bond donor interacting with the ketone oxygen lone pair during hydrogen transfer. This interaction lowers the reaction barrier of hydrogen transfer to acetophenone by about 4 kcal mol^{-1} with respect to the transition state **VI.5**, showed for ATH in organic media.[26]



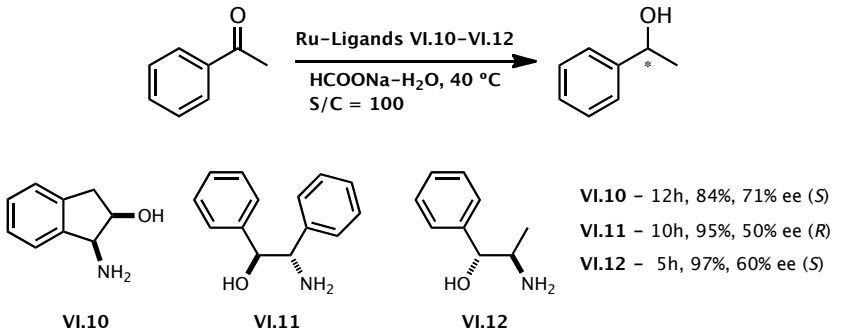
Scheme 6.2. Mechanism of ATH in water.

[25] J. Canivet, G. Süss-Fink, *Green Chem.* **2007**, *9*, 391.
[26] X. Wu, J. Liu, D. Di Tommaso, J. A. Iggo,C. R. A. Catlow, J. Bacsa, J. Xiao, *Chem. Eur. J.* **2008**, *14*, 7699.

The role of water appears not to be only related to the transition state **VI.8** but involved in the whole catalytic cycle. Also, it acts as a base to assist the dechlorination of precatalyst **VI.1** and it presumably facilitates the decarboxylation of the formate intermediate **VI.6** to form the hydride **VI.7**.

Generally, water-soluble catalysts act in biphasic systems. The application of this type of catalysts is limited by the rather long syntheses needed to introduce water-solubilising groups in the catalyst structure. A way to overcome this difficulty is the use of stable hydrophobic catalysts directly on water,[27] an approach of interest for reactions taking place at the interphase between an organic substrate and water (reaction "on water").[28]

Few examples employing aminoalcohols as ligands in ATH in water had been reported.[29] The reduction rates enantioselectivities obtained in these cases were much lower than those obtained with the diamines (Scheme 6.3).



Scheme 6.3. ATH in water of acetophenone with Ru-aminoalcohol based catalysts.

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[27] For selected examples, see: a) X. F. Wu, X. G. Li, W. Hems, F. King, J. Xiao, *Org. Biomol. Chem.* **2004**, *2*, 1818. b) X. F. Wu, D. Vinci, T. Ikariya, J. Xiao, *Chem. Commun.* **2005**, 4447. c) X. F. Wu, J. K. Liu, X. H. Li, A. Zanotti-Gerosa, F. Hancock, D. Vinci, J. W. Ruan, J. Xiao, *Angew. Chem.* **2006**, *118*, 6870; *Angew. Chem. Int. Ed.* **2006**, *45*, 6718. d) Y. Xing, J. S. Chen, Z. R. Dong, Y. Y. Li, J. X. Gao, *Tetrahedron Lett.* **2006**, *47*, 4501. e) O. Soltani, M. A. Ariger, H. Vázquez-Villa, E. M. Carreira, *Org. Lett.*, **2010**, *12*, 2893. f) C. Romain, S. Gaillard, M. K. Elmkaddem, L. Toupet, C. Fischmeister, C. M. Thomas, J.-L. Renaud, *Organometallics*, **2010**, *29*, 1992.

[28] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

[29] J. Mao, B. Wan, F. Wu, S. Lu, *Tetrahedron Lett.* **2005**, *46*, 7341. b) X. Wu, X. Li, M. McConville, O. Saisdi, J. Xiao, *J. Mol. Catal. A-Chem.* **2006**, *247*, 153.

In general, commonly used homogeneous catalysts for ATH are expensive and cannot be easily separated from products. For a practical point of view, the development of supported ligands on solid surfaces is really desirable since catalyst separation and recycling are remarkable advantages of this approach (Fig. 6.2).[20c,30]

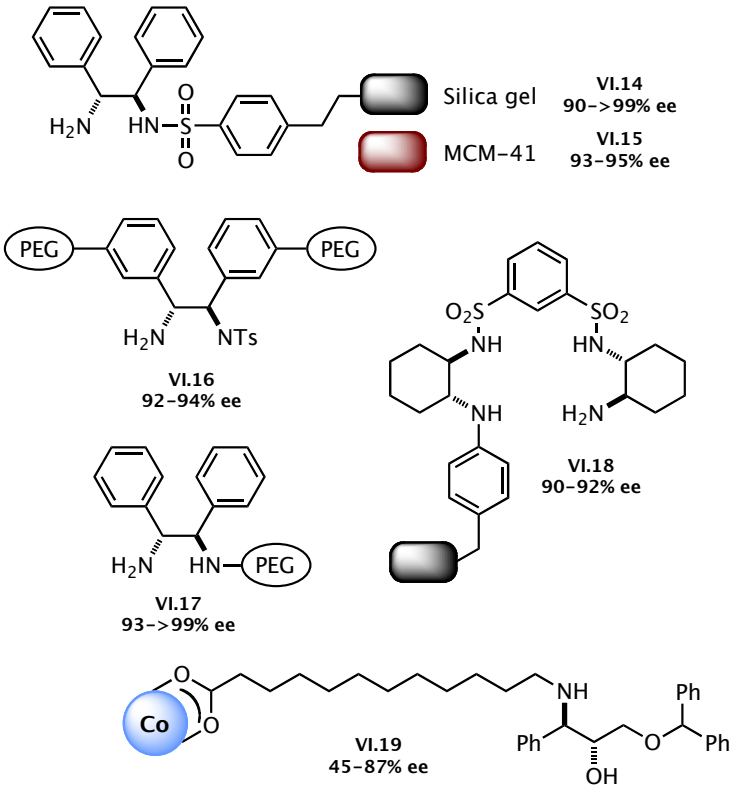

Figure 6.2. Some examples of immobilized ligands for ATH in water.

[30] For selected exemples on ATH in water using supported chiral ligads, see: a) X. G. Li, X. F. Wu, W. P. Chen, F. E. Hancock, F. King, J. Xiao, *Org. Lett.* **2004**, *6*, 3321. b) X. G. Li, W. P. Chen, W. Hems, F. King, J. Xiao, *Tetrahedron Lett.* **2004**, *45*, 951. c) P. N. Liu, J. G. Deng, Y. Q. Tu, S. H. Wang, *Chem. Commun.* **2004**, 2070. d) P. N. Liu, P. M. Gu, J. G. Deng, Y. Q. Tu and Y. P. Ma, *Eur. J. Org. Chem.* **2005**, 221. e) Y. Arakawa, N. Haraguchi, S. Itsuno, *Tetrahedron Lett.* **2006**, *47*, 3239. f) Y. Arakawa, A. Chiba, N. Haraguchi, S. Itsuno, *Adv. Synth. Catal.* **2008**, *350*, 2295. g) N. A. Cortez, G. Aguirre, M. Parra-Hake. R. Somanathan, *Tetrahedron Lett.* **2009**, *50*, 2228. h) Y. Tang, J. Xiang, L. Cun, Y. Wang, J. Zhu, J. Liao, J. Deng, *Tetrahedron Asymmetry* **2010**, *21*, 1900. i) W. Shan, F. Merg, Y. Wu, F. Mao, X. Li, *J. Organometal. Chem.* **2011**, *696*, 1687.

Due to the good performance of TsDPEN ligand in ATH, several derivatives of such ligand have been grafted on different supports (Fig. 6.2, **VI.14**-**VI.17**). For instance, Xiao and co-workers reported the immobilization of TsDPEN monomer onto PEG polymer by the aryl groups providing an example of soluble polymer supported catalyst for ATH in water (Ligand **VI.16** in Fig. 6.2).[30a] The conversion and enantioselectivity afforded is comparable with that of Noyori's homogeneous catalyst with the advantage of recyclability. The PEG-immobilized catalyst could be reused 14 times with no loss in enantioselectivity, demonstrating its excellent recyclability and lifetime under aqueous conditions. The hydrophilic polymers reported by Itsuno *et. al.* having pendant groups of carboxylates or sulfonates have been used as a polymer supports also for TsDPEN ligand and applied in the ATH aromatic ketones in water. The optically active secondary alcohols were obtained with up to 99% ee demonstrating that water-soluble polymers are not always necessary as supports for organic reactions in aqueous phase. Moreover, the catalyst can be recycled several times without loss of its catalytic activity.[30f]

Excellent enantioselectivity and reactivity were also achieved for aromatic ketones with silica gel supported Ru-TsDPEN catalyst **VI.14** (Fig. 6.2).[30c] Particularly, the catalyst could be readily recovered and reused in multiple consecutive catalytic runs (up to 11 runs without recharging Ru) maintaining the enantioselectivity. One feature of this catalytic system operating in aqueous media was the acceleration effect observed (109 TOF) in comparison with the reaction performed in organic solvent (10 TOF).

Novel supports as cobalt nanoparticles (Fig. 6.2 **VI.19**) have been used as magnetically decantable ligands in the Ru-catalyzed ATH of alkyl aryl ketones.[20c] The enantioselectivity obtained is generally higher than those observed with the structurally related monomeric aminoalcohol ligands (**Article 7** of the present chapter). Although the immobilization of the ligand on nanosized particles seems to be favourable, it has the drawback of poor reusability of the functional cobalt nanoparticles because of leaching of the carboxylate ligands.

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Aqueous asymmetric transfer hydrogenation using modular hydrophobic aminoalcohols

Esther Alza,[a] Amaia Bastero,[a] Susanna Jansat[a] and Miquel A. Pericàs[a,b,*]

[a]*Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain*
[b]*Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain*

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Abstract—A series of new modular Ru/aminoalcohol systems were used as enantioselective catalysts in the asymmetric transfer hydrogenation reaction in both water and 2-propanol. The catalytic behavior exhibited in these two media follows different tendencies regarding the tunable ligand structure. While the bulkiness of the R^1 group has a positive effect on the activity for reactions in 2-propanol, ligands with bulky R^1 groups are generally less active in water. Additionally, cationic, anionic, and neutral surfactants do not improve the catalytic behavior in water.

1. Introduction

Sustainability concerns have led in recent times to increased research efforts aimed to decrease the environmental impact of chemical processes. For this reason, the atom economy[1] provided by catalytic reactions becomes crucial. To minimize the catalyst loading or to avoid treatments required for separation or removal from reaction products, different approaches to enantioselective catalysis have focused on the heterogenization of the catalytic system.[2]

On the other hand, the use of water as a solvent or even solvent-free methodologies is the strategy commonly used toward greener chemistry.[3] Water as a reaction medium is highly desirable since it is safe, non-toxic, environmentally friendly, and inexpensive. However, many transition metal catalysts are moisture sensitive, making aqueous catalysis only possible in extremely careful conditions. In addition, the insolubility of many organic compounds in water limits its application in various chemical transformations.

An interesting approach to aqueous catalysis is the use of water-soluble catalysts, which are assembled through the use of water-soluble ligands. Generally, water-soluble catalysts act in biphasic systems, the catalysts being in the aqueous phase and the substrate and product/s in the organic one. These systems present the possibility of catalyst recycling by simple phase separation. However, the application of most of these catalysts is limited by the rather long syntheses needed to introduce water-solubilizing groups in the catalyst structure. A way to overcome this difficulty is the use of stable hydrophobic catalysts directly on water,[4] an approach of interest for reactions taking place at the interphase between an organic substrate and water.

Enantioselective reduction of prochiral ketones to yield enantiopure secondary alcohols is of interest because of the importance of these alcohols as intermediates in the production of pharmaceuticals and advanced materials. Among the different catalytic methods reported to this end, the Asymmetric Transfer Hydrogenation (ATH) is of importance since it avoids the use of flammable hydrogen as a reducing agent.[5] The first successful examples were reported by Noyori et al., with ruthenium-based catalysts bearing monotosylated diamines or 1,2-aminoalcohols as chiral ligands. The most popular solvents for this catalytic reaction are either 2-propanol or the formic acid/triethylamine mixture, which act at the same time as hydrogen donors for the reduction process. Nevertheless, aqueous formate, which is used in nature by enzymes for reduction reactions, has been rarely used until quite recent reports by Xiao and co-workers[6a,b] and by Wills,[6c] who have shown the possibility of performing ATH in water using sodium formate as a hydrogenation agent. Most of the catalytic

* Corresponding author. Tel.: +34 977 920 211; fax: +34 977 920 222; e-mail: mapericas@iciq.es

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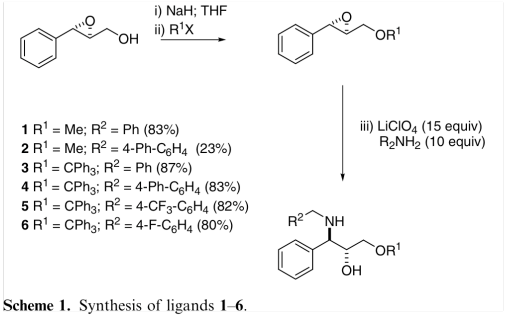
systems reported for the aqueous ATH bear *N*,*N* type ligands (amino-amide,[7] monotosylated[8] or sulfonated[9] diamine ligands, and imino-pyridines[10]). The use of aminoalcohols, which are also important ligands in this reaction, has been only quite recently reported.[11]

Given the interest in conducting this reaction in water, the search for new catalysts, which are active and stable in an aqueous medium, is a significant challenge. We report here on the use of a family of readily accessible chiral 1,2-aminoalcohols (**1**–**6**) as enantioselective ligands for the catalytic aqueous ATH reaction. Their tunable backbone allows for a programmed variation of their hydrophobic nature, and results on their catalytic activity show that reaction occurring at the surface of the organic substrate droplets dispersed in water is faster in some cases than homogeneous reactions in isopropanol mediated by the same catalytic systems (Fig. 1).

2. Results and discussion

It has been recently reported that the asymmetric transfer hydrogenation of aromatic ketones using Noyori's catalyst (Ru-(*R*,*R*)-TsDPEN) can be performed in an open atmosphere using water as a solvent with very good results.[3] Chiral aminoalcohols can in general be readily prepared, while some of them are even commercially available. However, to the best of our knowledge, there are only two reports using commercially available aminoalcohols as ligands for the ATH in water. Among them, (−)-ephedrine[11] gave the best activities, with enantioselectivities up to 78% for the reduction of acetophenone.

We reported some time ago the preparation of a family of modular aminoalcohols from enantiopure Sharpless epoxyalcohols. The steric and electronic properties of these ligands were conveniently tuned for the application in several catalytic processes[12] including ATH in 2-propanol.[12b] For the asymmetric transfer hydrogenation in an aqueous medium, we decided to test related ligands, bearing some structural changes. The general route followed for the synthesis of aminoalcohols **1**–**6** is based on the lithium perchlorate catalyzed,[13a] regioselective and stereospecific ring opening of a protected Sharpless enantiopure epoxide with a primary amine (Scheme 1).[13b] All new ligands are air stable, orange-yellowish oils, which have been characterized by ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, and specific rotation.



Scheme 1. Synthesis of ligands **1**–**6**.

A preliminary screening of the transfer hydrogenation of acetophenone in 2-propanol was conducted with aminoalcohols **1**–**4** (Scheme 2 and Table 1). These ligands showed that the bulkiness of the primary alcohol protecting group R^1 increases dramatically the activity of the catalyst (entries 1 and 2 vs 3 and 4 in Table 1), while enantioselectivity is mainly influenced by the R^2 substituent on the amino group (entries 1 and 3 vs 2 and 4). It is important to note the use of a 4-phenylbenzyl group as an amine substituent (R^2) that improved the selectivity of the process up to 90%. This ee is substantially higher than the previously reported with similar ligands bearing alkyl R^2 substituents as Me or Bu (ee: 76%; 0 °C; R^2: Bu).[12b]

The ATH in aqueous medium was conducted similarly, albeit under air. Formate was chosen as a hydrogen source

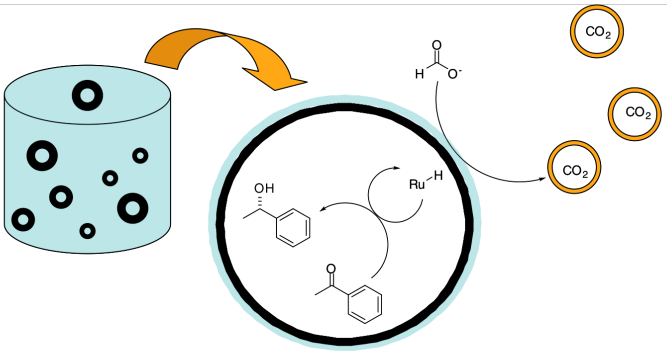
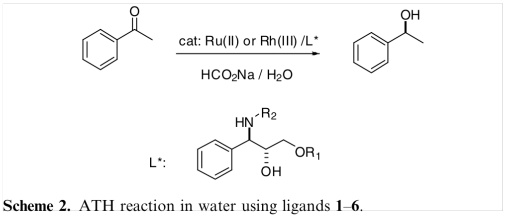


Figure 1. Cartoon representation of the use of hydrophobic catalysts in aqueous medium.



Scheme 2. ATH reaction in water using ligands **1**–**6**.

Table 1. Transfer hydrogenation in 2-propanol using aminoalcohols **1**–**4**

Entry	Ligand	Time (h)	Conversion[a] (%)	ee[a] (%)
1	**1**	6	22	80 (*S*)
2	**2**	24	13	86 (*S*)
3	**3**	4	>99	82 (*S*)
4	**4**	6	51	90 (*S*)

Reaction conditions: $[RuCl(p\text{-cymene})]_2$ (0.004 mmol); ligand (0.016 mmol); 2-propanol (6.8 mL); KOH (0.029 mmol; 0.08 M in 2-propanol); acetophenone (0.4 mmol; 0.5 M in 2-propanol); temperature: 25 °C (see Section 4).
[a] Determined by GC, with a β-DEX 120 column.

because for Ru/aminoalcohol systems reaction rates are faster in basic media (HCOONa, initial pH 7.3; $HCOOH–NEt_3–H_2O$ with $HCOOH/NEt_3 = 1/1.7$, initial pH 5.7).[11b] As a representative procedure, a suspension of the ruthenium precursor and the ligand was stirred in water for 2 h at room temperature. The solution became yellow in color although part of the precursor remained as a solid. Then, formate and acetophenone were directly added and the solution was vigorously stirred or shaken, ensuring a homogeneous emulsion with no phase separation during the whole process. The solution was stirred for 12 or 24 h at room temperature, while the progress of the reaction was followed by GC.

To find the best conditions for the aqueous ATH, we initially studied the reaction performed with the catalytic system containing ligand **1** (Table 2). At 25 °C, conversions of 35% and 60% after 12 h and 24 h, respectively, were recorded. This shows that although less active in water, the catalyst Ru/**1** is stable for hours in this medium. Interestingly, the enantioselectivity was maintained as high as in the reaction performed in 2-propanol (82% ee versus 80% ee). 1-Phenylethanol with the same absolute configuration (*S*) was obtained in water and in isopropanol.

When the temperature was increased to 40 °C, which is the temperature at which other reported systems have been tested,[11b] a decrease in conversion was observed, albeit the ee kept constant, probably indicating a decomposition of the catalyst. The use of $[RhClCp^*]_2$[14] as the catalyst precursor led to a more active catalyst, as reported for diamine-containing systems,[6a] but the enantioselectivity was only moderate (entry 4, 53% ee). An increase in temperature up to 40 °C with the Rh/**1** system led to an important increase in reaction rate but enantioselectivity deteriorated slightly.

Table 2. Aqueous asymmetric transfer hydrogenation using chiral aminoalcohols **1**–**6**

Entry	Ligand	Temp (°C)	Time (h)	Conv.[a] (%)	ee[a] (%)
1	**1**	25	12	35	81 (*S*)
2[b]	**1**	25	12	41	79 (*S*)
3	**1**	25	24	60	82 (*S*)
4	**1**	40	24	47	81 (*S*)
5[c]	**1**	25	12	58	53 (*S*)
6[c]	**1**	40	12	94	48 (*S*)
7[d]	**1**	25	24	14	67 (*S*)
8[e]	**1**	25	24	13	84 (*S*)
9	**2**	25	24	25	83 (*S*)
10	**3**	25	24	52	70 (*S*)
11[b,f]	**3**	25	24	60	60 (*S*)
12[b]	**3**	25	24	72	60 (*S*)
13	**4**	25	24	60	68 (*S*)
14[g]	**4**	25	24	33	61 (*S*)
15	**5**	25	24	49	67 (*S*)
16	**6**	25	24	52	68 (*S*)

Reaction conditions: $[RuCl_2(p\text{-cymene})_2]_2$ (0.0125 mmol); ligand (0.05 mmol); water (2 mL); NaHCOO (6.25 mmol); acetophenone (1.25 mmol); acetophenone/Ru: 50.
[a] Determined by GC with a β-DEX 120 column at 120 °C isotherm.
[b] Shaker.
[c] $[RhCl_2Cp^*]_2$ used as the catalyst precursor.
[d] CTAB added as cationic surfactant (1.25 mmol, 100%).
[e] SDS added as anionic surfactant (1.25 mmol, 100%).
[f] DiMePEG added as neutral surfactant (0.125 mmol, 10%).
[g] SDS added as anionic surfactant (0.025 mmol, 2%).

According to this result, the rest of the experiments in this study were performed using as optimized conditions: 25 °C, $[RuCl_2(p\text{-cymene})]_2$ as the ruthenium source and sodium formate as hydrogen donor in neat water as the only solvent.

Amino alcohols **2**–**6** showed moderate activities (up to 60% of conversion) after 24 h (entries 9–13 in Table 2) working at a 1/50 Ru/substrate ratio, thus suggesting possible mass transfer limitations at the organic-aqueous interphase. Anionic, cationic, and neutral surfactants as SDS, CTAB, and DiMePEG, respectively, were added to increase the miscibility of reactants in the water phase and/or interphase (entries 7 and 8) and, hence, to improve the catalytic behavior of the system.[15] Surprisingly, a negative effect in conversion was observed with both the ionic surfactants. This could be due to the existence of interactions between the surfactant molecules and the ruthenium species at the droplet surface, with the consequence of the catalytic sites being partially blocked. The enantioselectivity did not change when using SDS, indicating that the catalytically active species is the same. With CTAB, in turn, a slight decrease in enantioselectivity is observed. Effect of the neutral agent DiMePEG was limited to a small decrease of catalytic activity.

Additionally, electronic effects on the ligand backbone were analyzed by placing electron-withdrawing groups (fluoride and trifluoromethyl) in the *para*-position of the aromatic ring in the R^2 substituent in the structure of ligand **3** (ligands **5** and **6**). This had no effect on the catalytic activity or the enantioselectivity (entries 10 vs 15 and 16 in Table 2).

3. Conclusion

In summary, a series of new modular aminoalcohols **1**–**6** have been prepared in good yields from enantiopure phenylglycidol and used as ligands in the ruthenium-catalyzed ATH both in water and in 2-propanol as reacting media. The tunable structure of **1**–**6** allows for a programmed variation of their hydrophobic nature. Results on ATH show that, for some of the ligands studied, reaction in aqueous media is faster than in isopropanol. In isopropanol, acetophenone is reduced with enantioselectivities up to 90%. Quite significantly, the catalytic behaviors of these systems in water and in isopropanol follow different trends regarding the structure of the chiral ligand (bulkiness of the R^1 substituent) which has different effects in isopropanol versus water: while bulky R^1 substituents dramatically accelerate reductions in isopropyl alcohol, an opposite effect is observed in water. This fact suggests that bulky groups prevent proper access of the substrate to the metallic specie at the substrate/water interphase. The enantioselectivity recorded under aqueous conditions in the ATH of acetophenone reaches 83%, only slightly below than in isopropanol. This result opens the possibility of using hydrophobic systems in catalytic reactions performed in water as the only solvent.

4. Experimental

4.1. Ligand 1: (1*R*,2*R*)-1-(Benzylamino)-3-methoxy-1-phenylpropan-2-ol

A mixture of (2*S*,3*S*)-2-(methoxymethyl)-3-phenyloxiran (250 mg, 1.52 mmol), lithium perchlorate (2.4 g, 22.8 mmol) and benzylamine (1.6 mL, 15.2 mmol) in 4 mL of acetonitrile was reacted under nitrogen at 80 °C overnight. After that time, reaction was analyzed by TLC and determined to be complete. Work-up included the addition of water (10 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure. The residual oil was purified by flash chromatography on deactivated silica (2.5% Et_3N v/v) eluting with hexane-ethyl acetate 80:20 to afford the desired aminoalcohol (340.6 mg, 83%), $[\alpha]_D^{24} = -466.3$ (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H, CH_{arom}), 3.98–3.94 (m, 1H, C*H*–NH), 3.91 (d, $J = 4.9$ Hz, 1H, C*H*–OH), 3.87 (br, 2H, CH_2–NH), 3.76 (d, $J = 13.2$ Hz, 1H, CH_2–OMe), 3.57 (d, $J = 13.2$ Hz, 1H, CH_2–OMe), 3.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8–127.2 (CH_{arom}), 73.9 (CH_2–OMe), 72.6 (CH–OH), 64.6 (CH–NH), 59.2 (CH_3), 51.5 (CH_2–NH). ESI +ve for $C_{17}H_{22}NO_2$ [M+H] 272.1651; found 272.1656.

4.2. Ligand 2: (1*R*,2*R*)-1-(Biphenyl-4-ylmethylamino)-3-methoxy-1-phenylpropan-2-ol

See ligand **1** for synthesis. Yield: 23%, $[\alpha]_D^{24} = -4.1$ (*c* 0.96, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.42 (m, 14H, CH_{arom}), 4.22 (d, $J = 13$ Hz, 1H, CH_2–NH), 4.06 (d, $J = 13$ Hz, 1H, CH_2–NH), 4.04 (d, $J = 5.0$ Hz, 1H, C*H*–NH), 4.01–3.98 (m, 1H, C*H*–OH), 3.32 (br dd, 1H, CH_2–OMe), 3.29 (br dd, 1H, CH_2–OMe), 3.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (C), 135.9 (C), 134.0 (C), 132.1 (C), 128.8–124.0 (CH_{arom}), 73.8 (CH_2–OMe), 72.7 (CH–OH), 65.2 (CH–NH), 59.1 (CH_3), 49.5 (CH_2–NH). ESI +ve for $C_{23}H_{26}NO_2$ [M+H] 348.1964; found 348.1978.

4.3. Ligand 3: (1*R*,2*R*)-1-(Benzylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 87%, $[\alpha]_D^{23} = -193.7$ (*c* 0.99, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$) 7.45–7.15 (m, 25H, CH_{arom}), 4.03 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.95-3.89 (m, 1H, C*H*–OH), 3.76 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.58 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.19 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$), 2.96 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 139.9 (C), 139.1 (C), 128.7–127.1 (CH_{arom}), 87.1 (C), 72.7 (CH–OH), 65.2 (CH–NH), 64.6 (CH_2–OCPh$_3$), 51.6 (CH_2–NH). ESI +ve for $C_{35}H_{34}NO_2$ [M+H] 500.2590; found 500.2576.

4.4. Ligand 4: (1*R*,2*R*)-1-(Biphenyl-4-ylmethylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 83%, $[\alpha]_D^{22} = +34.9$ (*c* 1.09, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$) δ 7.96–7.14 (m, 29H, CH_{arom}), 4.01 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.91–3.87 (m, 1H, C*H*–OH), 3.75 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.58 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.19 (dd, $J = 9.9$ Hz, $J = 4.1$ Hz, 1H, CH_2–OCPh$_3$), 2.95 (dd, $J = 9.9$ Hz, $J = 4.1$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 141.2 (C), 140.1 (C), 139.4 (C), 128.9–127.1 (CH_{arom}), 87.1 (C), 73.0 (CH–OH), 65.5 (CH–NH), 64.8 (CH_2–OCPh$_3$), 51.3 (CH_2–NH). ESI +ve for $C_{41}H_{38}NO_2$ [M+H] 576.2903; found 576.2910.

4.5. Ligand 5: (1*R*,2*R*)-1-(4-Fluorobenzylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 82%. $[\alpha]_D^{23} = -221.7$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–6.97 (m, 24 H, CH_{arom}), 3.95 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.88–3.84 (m, 1H, C*H*–OH), 3.68 (d, $J = 13.2$ Hz, 1H, CH_2–NH), 3.50 (d, $J = 13.2$ Hz, 1H, CH_2–NH), 3.18 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$), 2.94 (dd, $J = 9.8$ Hz, $J = 4.2$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (C), 139.2 (C), 136.0 (C), 129.9–115.2 (CH_{arom}), 72.8 (CH–OH), 65.2 (CH–NH), 64.4 (CH_2–OCPh$_3$), 50.9 (CH_2–NH). ESI +ve for $C_{35}H_{33}NO_2F$ [M+H] 518.2495; found 518.2484.

4.6. Ligand 6: (1*R*,2*R*)-1-Phenyl-1-(4-(trifluoromethyl)-benzylamino)-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 80%, $[\alpha]_D^{23} = -193.7$ (*c* 0.99, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$): δ 7.62–7.10 (m, 24H, CH_{arom}), 3.94 (d, $J = 5.0$ Hz, 1H, C*H*–NH), 3.88–3.84 (m, 1H, C*H*–OH), 3.75 (d, $J = 13.5$ Hz, 1H, CH_2–NH), 3.56 (d, $J = 13.5$ Hz, 1H, CH_2–NH), 3.20 (dd, $J = 9.8$ Hz, $J = 4.5$ Hz, 1H, CH_2–OCPh$_3$), 2.96 (dd,

$J = 9.9$ Hz, $J = 4.4$ Hz, 1H, CH_2–$OCPh_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (C), 128.7–125.5 (CH_{arom}), 73.1 (CH–OH), 65.6 (CH–NH), 64.8 (CH_2–$OCPh_3$), 51.4 (CH_2–NH). ESI +ve for $C_{36}H_{33}NO_2F_3$ [M+H] 568.2463; found 568.2455.

4.7. Asymmetric transfer hydrogenation in 2-propanol

The reactions in Table 1 were performed under argon. $[RuCl_2(p\text{-cymene})]_2$ (0.004 mmol) and the aminoalcohol (0.016 mmol) were placed in 2-propanol (6.84 mL) at 80 °C and reacted for 30 min giving a yellow solution. Then the mixture is allowed to reach 25 °C and a solution of KOH (0.029 mmol; 0.08 M in 2-propanol) and of acetophenone (0.4 mmol; 0.5 M in 2-propanol) were added. The reaction proceeded for the reported times at room temperature. After reaction time, the reaction mixture was passed through a silica plug to eliminate metal traces and analyzed by GC with a β-DEX 120 column.

4.8. Aqueous asymmetric transfer hydrogenation

The metal precursor (0.0125 mmol) and the aminoalcohol (0.05 mmol) were placed in 2 mL of distilled water and stirred for 2 h at the corresponding temperature. Then sodium formate (6.25 mmol) and acetophenone (1.25 mmol) were added and the reaction was vigorously stirred (see Table 2 for times and type of agitation). After a suitable reaction time, diethyl ether was added and the organic phase was extracted (3×5 mL). The combined organic phases were dried with $MgSO_4$ and passed through a short silica plug to eliminate metal traces. The sample was analyzed by GC with a β-DEX 120 column.

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Conclusions and Outlook

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CONCLUSIONS AND OUTLOOK

The design and preparation of immobilized catalysts that keep intact the activity and selectivity of their homogeneous counterparts represents a major goal in view of more efficient chemical production. When enantioselective processes are concerned, the opportunities offered by this approach like recovery and reuse of expensive catalytic species, highly simplified work-up, or implementation of continuous flow processing, become even more evident. For that reasons, the main aim of the present thesis research was the synthesis of new supported catalytic species efficient for asymmetric transformations mainly in organocatalytic processes but also in metal catalysis. This goal has been accomplished with the synthesis of the catalysts showed in Figure 7.1.

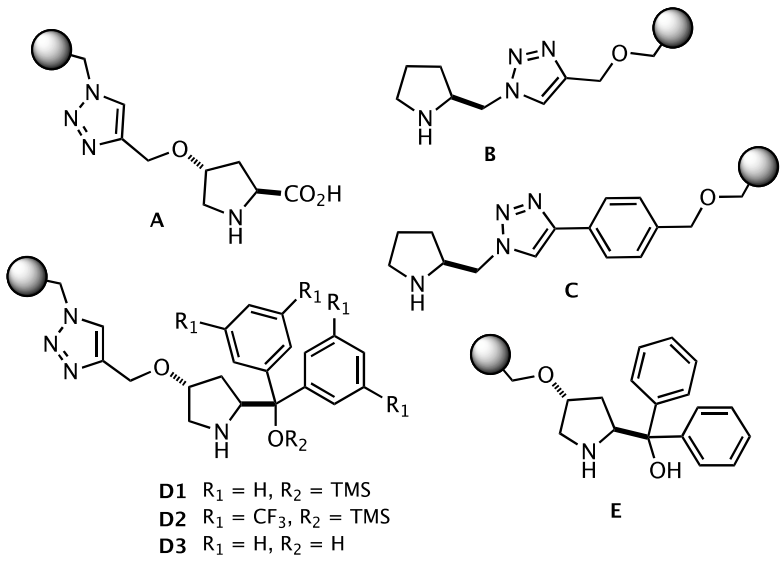


Fig. 7.1. PS-supported pyrrolidine derivative catalysts synthesized in the present research work.

The use of easy to handle immobilization strategies like CuAAC reaction between an azido- and alkynyl-derivatives, largely developed in the course of the present thesis, represents a significant improvement over previously existing supporting methodologies.

In **Chapter IIA**, a catalytic system for the highly stereoselective *syn*-Mannich reaction allowing purification-free, continuous operation has been presented. To the best of our knowledge, this was the first example of a Mannich reaction involving a solid-supported catalyst, and one of the first flow processes involving immobilized catalysts allowing the fast and enantiopure production of chiral targets. The effect of the nature of the linker connecting proline with the polymeric backbone has been studied, and a 1,2,3 triazole linker constructed from azidomethyl polystyrene and *O*-propargyl hydroxyproline turns out to be optimal for catalytic activity and enantioselectivity. With aldehyde donors, fast reactions leading to complete conversion in 1-3 h are recorded in DMF. With ketone donors, the reactions tend to be slower, but can be efficiently accelerated by low-power microwave irradiation. The continuous synthesis of the enantiomerically and diastereomerically pure adducts with a *syn:anti* ratio of more than 97:3 and enantiomeric excess >99%, has been achieved at room temperature with residence times of 6.0 min. This methodology has allowed for the preparation of up to 7.8 mmol of the desired Mannich adduct through the use of 0.46 mmol of catalytic resin (5.9 mol%), in a greatly simplified experimental protocol that avoids purification steps. The use of DMF as optimal solvent also leads to deactivation of catalyst after some cycles. This fact represents a challenge in order to improve the robustness of the immobilized catalyst to allow its continuous use for days or weeks, *en route* to an industrially applicable process. In the future, structural modifications of the catalytic molecule or the use of alternative, more robust supports could be carried out to achieve this goal. Other approach in study is the use of triazolyl-supported catalyst **2** (in Article 1, Chapter IIA) in Mannich reaction in aqueous media. Its known excellent performance for aldol reaction in water would also be expected for other transformations.

In **Chapter IIB**, two different types of catalysts for the Michael addition of ketones (Article 2) and aldehydes (Article 3) to nitroolefins are presented. In one of these catalyst classes (Fig. 7.1 **B** and **C**), a 1,2,3-triazole linker prepared through the use of CuAAC strategy plays the double role of allowing the immobilization of the pyrrolidine unit and of providing a nitrogen-rich, bulky substituent key for enantiocontrol. Catalysts **B** and **C** represented the first insoluble mediators for this reaction, and approach the

performance of referable, soluble catalysts for the same process. The use of water as solvent represents also a big step towards more environmentally benign process. It was observed that the *p*-phenylene group present in the linker that resin **C** possesses, increase its size and hydrophobicity with respect to the corresponding linker in resin **B**. Hence, the presence in **C** of a single, small hydrophilic moiety (the pyrrolidine-triazole system) embedded in a vast hydrophobic domain (the polymer backbone and the linker) appears to be key to the high enantioselectivity shown by this resin in the presence of water. Future applications of these resins are in process.

The preparation of a polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (Fig. 7.1 **D1**) displaying high catalytic activity and enantioselectivity in the Michael addition of aldehydes to nitroolefins with unprecedented, enzyme-like substrate selectivity has also been reported. The use of DCM as solvent, together with the straightforward isolation of the Michael adducts in the absence of additives, which involves simply catalyst separation by filtration and concentration of the reaction crude, are clear advantages associated to the use of this catalyst. A very important substrate selectivity in favour of linear, short-chain aldehydes has been observed. With α-branched aldehydes and ketones the resin **D1** was completely unreactive. For that reason, the application of the developed catalyst in the discrimination between linear and α-branched aldehyde donors for Michael additions was also investigated. It was observed that **D1** is able to induce the highly enantioselective Michael reaction of a linear aldehyde in the presence of a α-branched one. It was also observed that D1 behaves as an efficient catalyst in water. It is thus expected that it can be also used in that media for different transformations.

All the catalysts shown in chapter II are recyclable and reusable maintaining their activity and selectivity for several cycles making them suitable for their use in continuous conditions. Their cooperative use in complex transformations can also be envisaged.

In **Chapter III**, the asymmetric addition of malonates and nitromethane to α,β-unsaturated aldehydes, mediated by **D1** is discussed. In these reactions, taking place *via* iminium intermediates, additives were necessary

for a good performance of the supported catalysts. The beneficial effect of MW activation on these reactions was also confirmed. The use lithium acetate as an additive in these processes confirms the improvement of the catalytic reactivity and turnover of the Michael addition of malonates to α,β-unsaturated aldehydes by a Lewis base-Brønsted base bifunctional catalysis. It is assumable to perform these reactions under oxygen-free conditions to increase the active operation period of the PS-supported diphenylprolinol trimethylsilyl ether catalyst developed in view of the recent results reported by other groups.

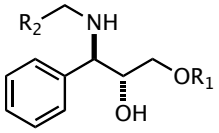
In view of the versatile performance of polystyrene-immobilized (*S*)-α,α-diphenylprolinol trimethylsilyl ether **D1** in both enamine and iminium-ion asymmetric transformations, a logical next step was its application in a cascade process. The successful results achieved in the Michael-Knoevenagel domino reaction of dimethyl 3-oxoglutarate with substituted cinnamaldehydes are collected in **Chapter IV**. Also the synthesis of a new polystyrene-supported diarylprolinol trimethylsilyl ether catalyst (aryl: 3,5-bis(trifluoromethyl)phenyl) (Fig. 7.1 **D2**) has been described. This catalyst was developed with the aim of improving the enantioselectivity of the process through an increased contribution to stereocontrol by the diarylcarbinol moiety. The obtained results, however, were not in agreement with our expectations and the use of **D2** led to slower reactions. Presumably, this decrease in activity could be attributed to a very large steric hindrance to reactivity arising from a combination of meta-substitution of the phenyl group, the triazole linker and the polymer backbone that prevents the approximation of the substrates into bonding distances.

The cascade reaction mediated by resin **D1** presented in Chapter III nicely illustrates the potential of this catalyst for the fast preparation of highly functionalized cyclohexane derivatives. The efficiency of the reaction sequence mediated by **D1** allowed its implementation under continuous flow operation conditions. In this task, the resin exhibited a remarkable robustness, allowing its use for three consecutive days without any appreciable deterioration of its performance (activity and enantioselectivity).

The last two chapters of the present report deal with asymmetric metal-

catalyzed transformations. In **Chapter V**, the asymmetric reduction of ketones with borane mediated by oxazaborolidine-type supported catalysts was studied. The use of diphenylprolinol derivatives anchored onto polymers by CuAAC or by direct nucleophilic substitution on a Merrifield resin represents a great difference in the selectivity of such reductions. Thus, preliminary results showed that the triazole ring formed by CuAAC anchoring strategy is deletereous for the enantioselectivity of the reaction because of the simultaneous operation of a non-enantioselective pathway resulting from borane coordination to the triazole (ee less than 60%). When the triazole ring is not present in the structure of the catalysts, aromatic ketones are reduced with high enantioselectivities (90-99%) and complete conversion after 30 minutes. The yield is quantitative because after the easy removal of the catalyst from the product by filtration, the desired product is obtained without any further purification. The scope of the reaction will be extended and also the recycling experiments will be optimized to lead to a non-stop, diversity-oriented reduction process in which a ketone could be processed immediately after the recovery of the optically pure product of the previous substrate.

Finally, in **Chapter VI**, a series of new modular Ru/amino alcohol systems were developed and used as enantioselective catalysts in the asymmetric transfer hydrogenation reaction (ATH) of ketones in both water and 2-propanol (Fig. 7.2).



F1 R_1 = Me, R_2 = Ph
F2 R_1 = Me, R_2 = 4-Ph-C_6H_4
F3 R_1 = CPh_3, R_2 = Ph
F4 R_1 = CPh_3, R_2 = 4-Ph-C_6H_4
F5 R_1 = CPh_3, R_2 = 4-CF_3-C_6H_4
F6 R_1 = CPh_3, R_2 = 4-F-C_6H_4

Fig. 7.2. Aminoalcohol-type ligands synthesized.

The enantioselectivity recorded under aqueous conditions in the ATH of acetophenone reaches 83%, only slightly below than in 2-propanol. The catalytic behaviour exhibited in these two media follows different tendencies regarding the tuneable ligand structure. While the bulkiness of the ether substituent group has a positive effect on the activity for reactions in 2-propanol, the opposite effect is observed in water. Additionally, cationic, anionic, and neutral surfactants do not improve the catalytic behaviour in water. Due to the rather poor selectivity of these amino alcohols in homogeneous condition reactions, we decided to stop the project in this point and do not support them onto polystyrene resins. However, the idea of immobilizing these ligands onto different supports (hydrophilic, amphiphilic, soluble, etc) can find its opportunity in the near future due to the limited number of immobilized catalytic systems involving aminoalcohols for such reaction in water.

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