PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS

Zeynep Inci Günler

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PhD Thesis

by

Zeynep Inci Günler

Supervised by:

Dr. Ciril Jimeno and Prof. Miquel A. Pericàs

DEPARTMENT OF ANALYTICAL AND ORGANIC CHEMISTRY (URV)

INSTITUTE OF CHEMICAL RESEARCH OF CATALONIA (ICIQ)

AND

INSTITUTE OF ADVANCED CHEMISTRY OF CATALONIA (IQAC-CSIC)

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2016

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

CERTIFY, that the present Doctoral Thesis entitled **"PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS"** presented by **Zeynep Inci Günler** to obtain the degree of Doctor, has been carried out under our supervision in the Institute of Advanced Chemistry of Catalonia (IQAC) and Institute of Chemical Research of Catalonia (ICIQ) and fulfills all the requirements to be awarded with the "International Doctor" Mention.

Tarragona, July 6, 2016

PhD Thesis Supervisor

Dr. Ciril Jimeno

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Barcelona, July 2016

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Acronyms and Abbreviations

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of the ACS *''Guidelines for authors'' J. Org. Chem.* **2008**, 73, 23A-24A.

http://pubs.acs.org/paragonplus/submission/joceah/joceah_authguide.pdf

List of Publications

This PhD Thesis is based on the following publications:

- *"Deciphering the Roles of Multiple Additives in Organocatalyzed Michael Additions"* Z. Inci Günler, Xavier Companyó, Ignacio Alfonso, Jordi Burés, Ciril Jimeno and Miquel A. Pericàs. *Chem. Commun.,* **2016**, 52, 6821-6824.
- *"A Concentration Effect in the Asymmetric Michael Addition of Acetone to Nitrostyrenes Catalyzed by Primary Amine Thioureas"* Z. Inci Günler, Ignacio Alfonso, Ciril Jimeno and Miquel A. Pericàs. Submitted to *The Journal of Organic Chemistry*
- *"Polymer supported primary amine-thiourea organocatalysts: application to the asymmetric Michael and Mannich reactions"* Z. Inci Günler, Ciril Jimeno and Miquel A. Pericàs. Submitted to *RSC Advances.*

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CHAPTER I

General Introduction

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1. GENERAL INTRODUCTION

1.1. ASYMMETRIC CATALYSIS

The demand for chiral generally enantiomerically pure compounds has increased drastically in the last decades, principally by the demands of pharmaceutical industry, but also agriculture, flavors, and fragrances, food and cosmetic industries as well as in materials science.

The pharmacological value of these compounds stems from the recognition of chiral molecules in the human body. All biological receptors have a chiral, non-racemic structure. As a consequence of enantiomer recognition in our body, the two enantiomers of a chiral compound cause different responses and accordingly different physiological effects.[1] A dramatic example of this fact would be the Thalidomide disaster that happened in the early 1960s. Thalidomide, a drug used for the treatment of morning sickness symptoms in pregnant women, appeared in the markets as its racemic form and caused more than 10.000 birth defects as a result of its consumption.[2] It was later discovered that the (S) enantiomer of thalidomide shows teratogenic activity while the (R) enantiomer acts as a sedative. However, the problem would not be solved even the pure (R) enantiomer was used instead since it racemizes *in vivo* due to the acidic hydrogen at the chiral center. Similarly, the (R) enantiomer of ibuprofen is inactive while the (S) enantiomer is an active pain killer **(Figure 1.1.)**. Accordingly, two-third of the prescription drugs are chiral, the majority being single enantiomers.

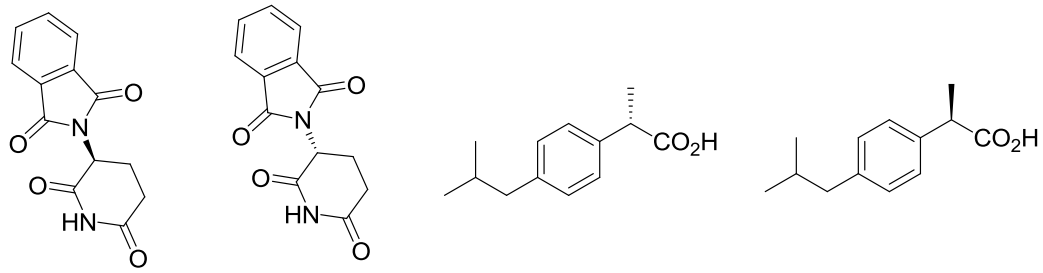


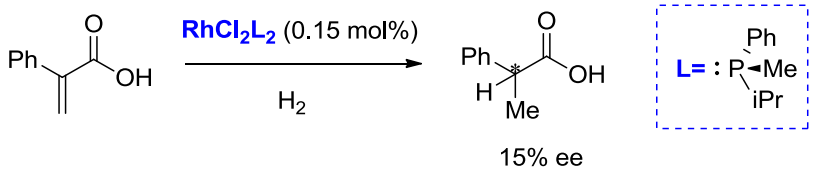
Figure 1.1. Structure and biological effects of enantiomers of some chiral compounds.

The extensive demand for chiral compounds triggered an intensive research to discover methods for synthesizing such compounds. In nature, the synthesis of enantiopure compounds is catalyzed by enzymes. However, historically, the way to reach these compounds was either through the chemical transformations of the natural chiral pool or by

[1] (a) Cushny A. R. *J. Physiol.* **1903**, *30*, 176-194. (b) Cushny A. R.; Peebles A.R. *J. Physiol.* **1905**, *32*, 501-510.
[2] Mcbride, W.G. *The Lancet* **1961,** *278*, 1358.

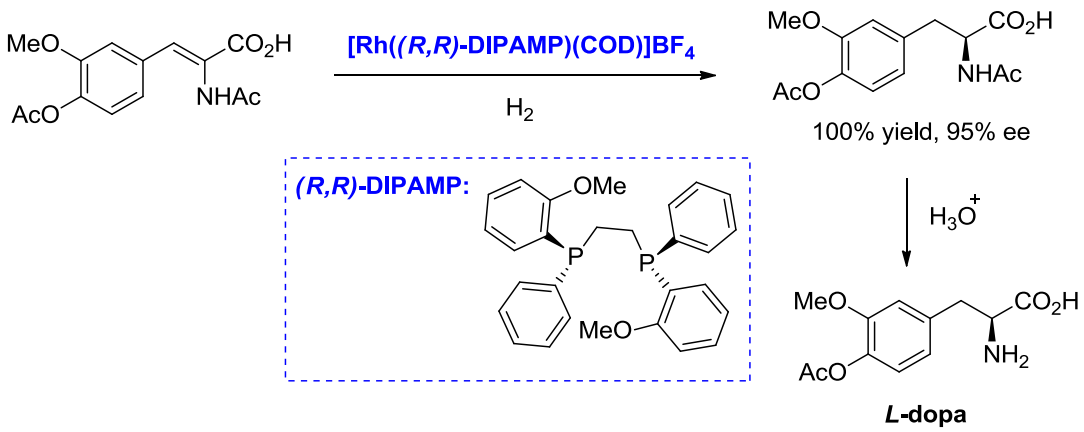
resolving an equimolar mixture of enantiomers (racemate) which yields up to only 50% of the desired pure enantiomer.

In asymmetric catalysis, a chiral enantiopure catalyst directs the formation of a chiral compound favoring one of the stereoisomers. Since the catalyst is continually regenerated, using a small amount of chiral catalyst, a large amount of chiral compound can be produced which makes this method advantageous over the other methods. The major breakthrough to achieve asymmetric catalysis with a synthetic catalyst, occurred in 1968. William Knowles *et al.* demonstrated the enantioselective hydrogenation of prochiral olefins with the asymmetric catalyst which they synthesized by replacing the achiral triphenylphosphine units in Wilkinson's catalyst [$RhCl(PPh_3)_3$], with chiral ones **(Scheme 1.1)**.[3]



Scheme 1.1. Knowles's asymmetric hydrogenation.

This result spurred the research in chiral phosphines. Shortly afterward, this process was commercialized to produce the anti-Parkinson drug *L*-dopa using a chiral diphosphine, followed by many other industrial and laboratory scale applications **(Scheme 1.2)**.[4]

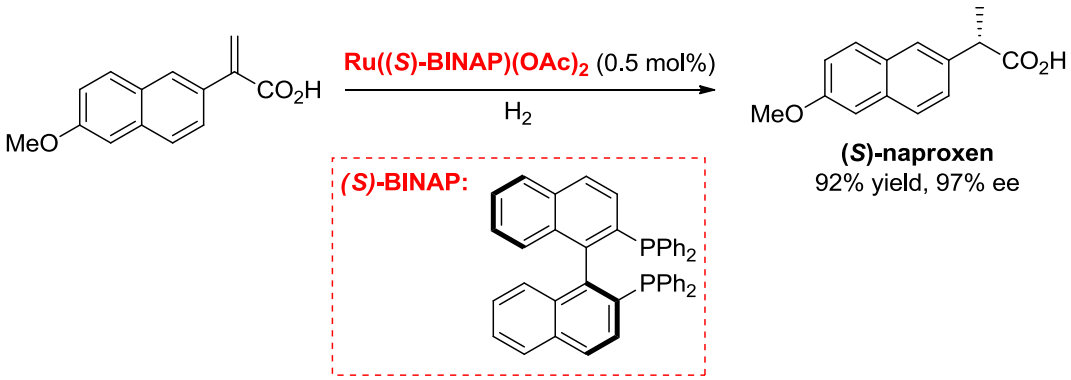


Scheme 1.2. Synthesis of *L*-dopa, industrial application of Knowles's asymmetric hydrogenation.

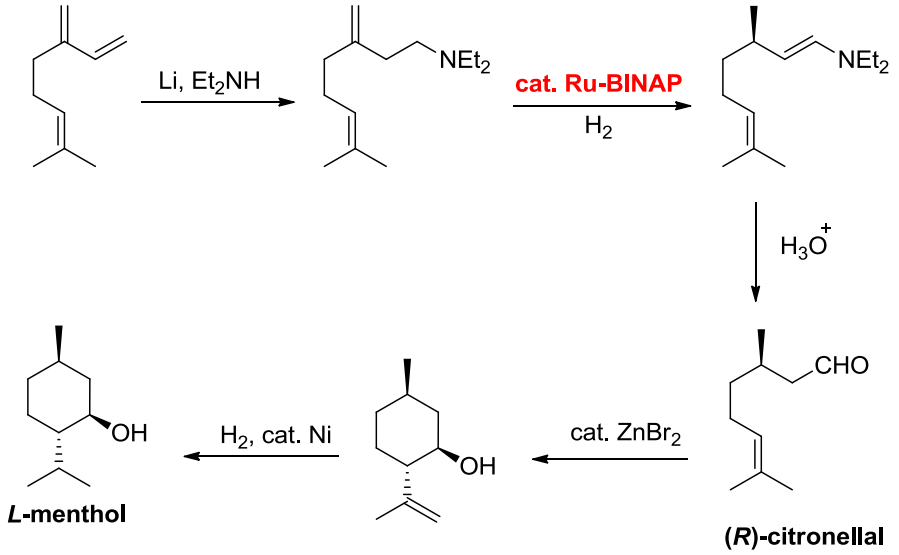
With this discovery, Knowles shared one-half of the 2001 Nobel Prize in chemistry with Ryoji Noyori[5] who also worked on asymmetric hydrogenations using Ru(II)-BINAP

[3] (a) Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445-1446. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J Am. Chem. Soc.* **1977**, *99*, 5946-5952. (c) Knowles, William S. (Nobel Lecture) *Angew. Chem. Int. Ed*. **2002**, *41*, 1998-2007.
[4] Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *US Patent* 4 005 127, **1977**.

complexes, likely the most general chiral complexes for asymmetric hydrogenation. Noyori's method gave access to the synthesis of pharmaceutically important compounds such as (*S*)-naproxen, a nonsteroidal anti-inflammatory drug **(Scheme 1.3)**. It was also applied to industrial scale by flavor and fragrance company Takasago (Japan), for the production of 1500 tons per year of (−)-menthol **(Scheme 1.4)**.[6]



Scheme 1.3. Noyori's asymmetric hydrogenation.



Scheme 1.4. Industrial application of Noyori's asymmetric hydrogenation.

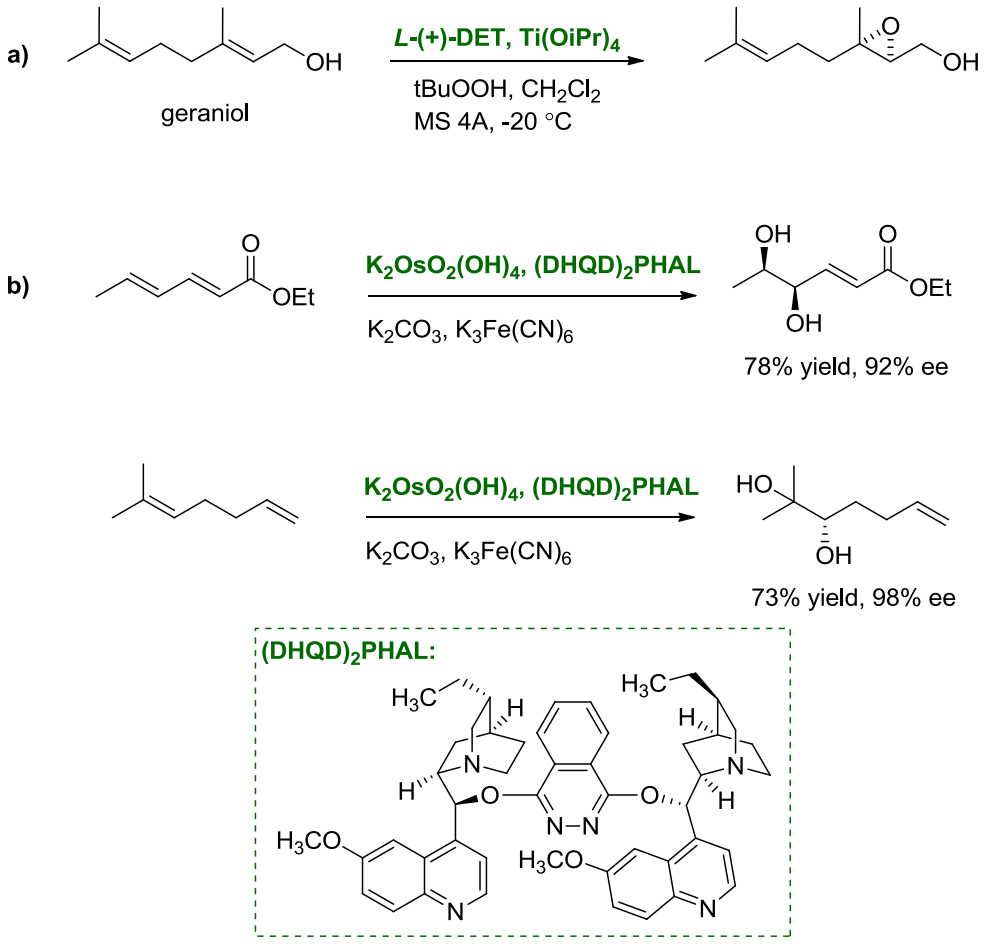
The other half of the Nobel prize was given to K. Barry Sharpless for his work on asymmetric catalytic oxidations. Sharpless introduced asymmetric epoxidation as an efficient method for the synthesis of chiral epoxides from a variety of primary and secondary allylic alcohols **(Scheme 1.5.a)**.[7]

---

[5] (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.
[6] Akutagawa, S. *Top. Catal.* **1997**, 271-274.
[7] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

Chiral epoxides are very important intermediates for the synthesis of natural products since they can be easily converted to diols, amino alcohols, and ethers. As an application of this reaction, Sharpless group generated intermediates of various natural products: methymycin, erythromycin, leukotriene C-1, and (+)-disparlure.[8]

Another discovery of Sharpless is the asymmetric dihydroxylation reaction in which an alkene forms a vicinal diol with potassium osmate(VI) dihydrate in the presence of a chiral quinine ligand **(Scheme 1.5.b)**.[9] In this reaction, osmium tetroxide is regenerated by potassium ferricyanide allowing the use of catalytic amounts of toxic and very expensive osmium tetroxide. This method reduces the cost of this reaction by 99.9% compared to the stoichiometric use of osmium.



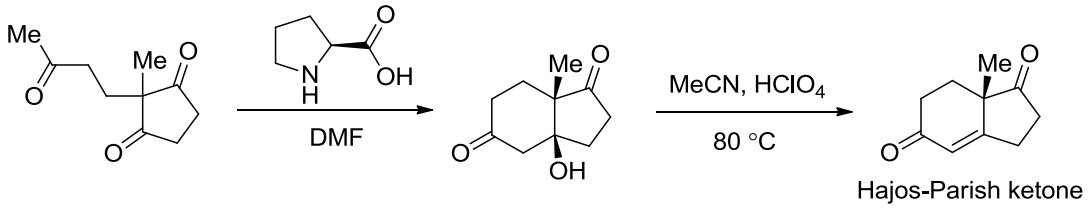
Scheme 1.5. Sharpless oxidations **a)** asymmetric epoxidation **b)** asymmetric dihydroxylation.

[8] Rossiter, B.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464-465.
[9] Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.

1.2. ORGANOCATALYSIS: DEFINITION AND HISTORY

Organocatalysis is a field of catalysis which studies the use of chiral or achiral small organic molecules to catalyze organic transformations. The use of organic molecules for asymmetric catalysis has been overlooked until the beginning of 21st century. As a general idea, enzymatic catalysis and organometallic catalysis were accepted to be the two main branches of catalysis for the efficient enantioselective synthesis of organic compounds.

In 1971 two independent industrial research groups of principal investigators Hajos and Parrish from Hoffmann-La Roche and Eder, Sauer and Wiechert from Schering AG set a milestone for asymmetric organocatalysis. Their work comprised the use of simple, natural amino acid *L*-Proline as the catalyst with extraordinary enantioselectivity for the synthesis of bicyclic ketols from triketones through intramolecular aldol reaction **(Scheme 1.6)**. Acid catalyzed dehydration of the aldol product furnished enediones which have been widely used in industry as building blocks to manufacture steroids on multi-kilogram scales **(Figure 1.2)**.[10]



Scheme 1.6. Hajos-Parrish-Eder-Sauer-Wiechert reaction.

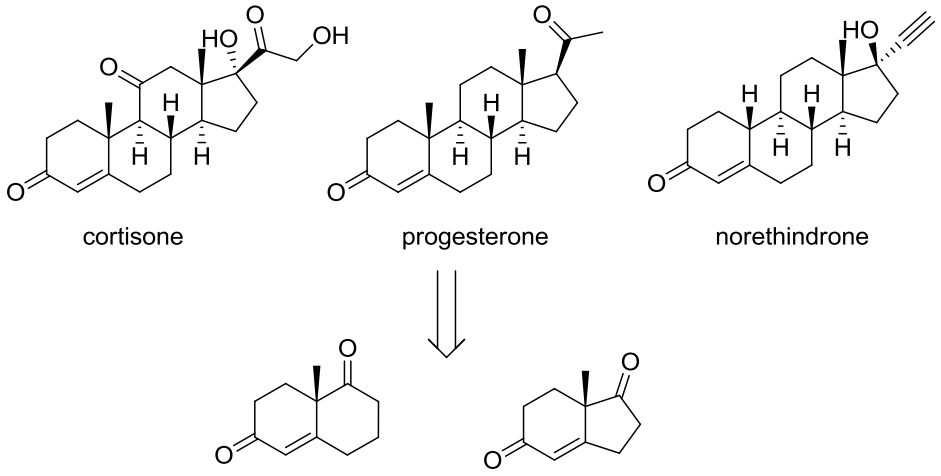
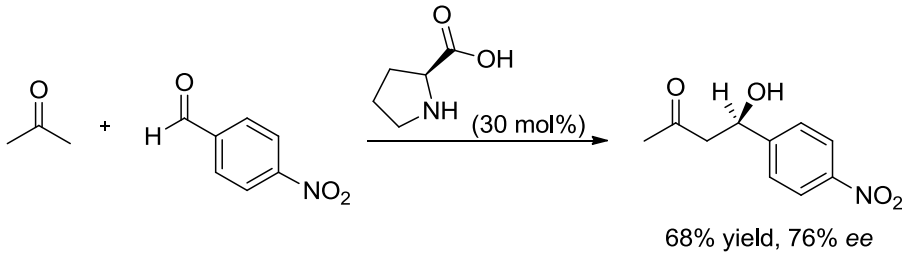


Figure 1.2. Industrial application of Hajos-Parrish-Eder-Sauer-Wiechert reaction in relevant commercialized steroids.

[10] (a) Hajos, Z. G.; Parrish, D. R. *German Patent* DE 2102623, **1971**. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *9*, 1615-1621. (c) Eder, U.; Sauer, G.; Wiechert, R. *German Patent* DE 2104757, **1971** (d) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.

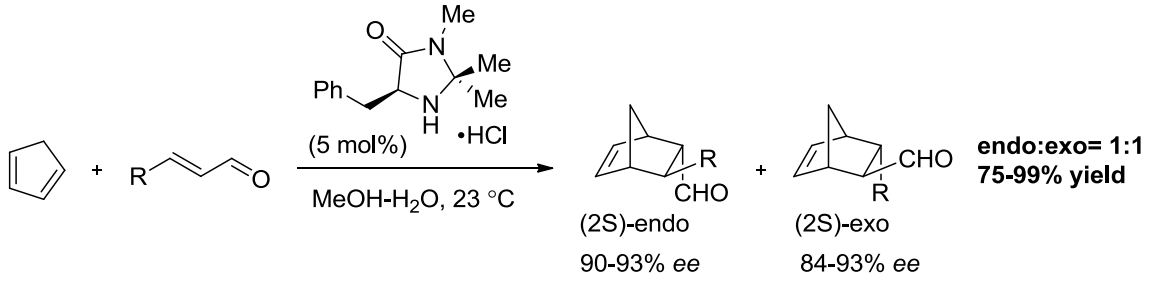
Although these impressive results drew the attention of the chemical synthesis community, they were taken as individual catalysts for unique reactions rather than comprising a general activation of a variety of substrates for many catalytic transformations. Also the potential benefits of using organocatalysts were not emphasized in these early publications.

In the year 2000, Barbas, Lerner, and List disclosed their pioneering studies on intermolecular aldol reactions catalyzed by *L*-proline. This work was substantial because it was shown that a small organic molecule like *L*-proline can do the same work of a complex enzyme through similar mechanisms. Moreover, it was pointed out that the Hajos-Parrish reaction can be extended to many other useful reactions **(Scheme 1.7).** [11]



Scheme 1.7. *L*-Proline catalyzed intermolecular aldol reaction.

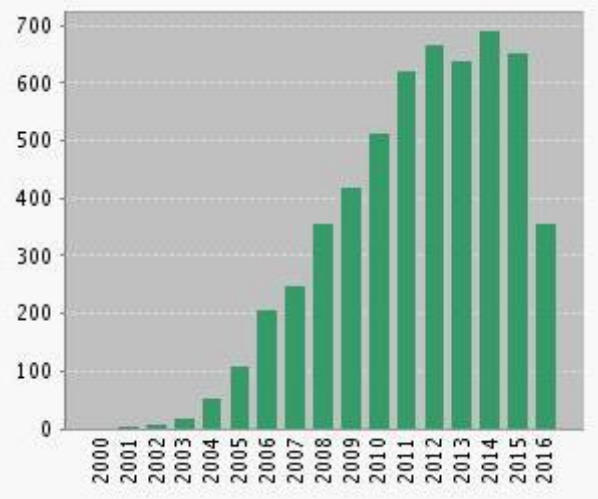
Almost simultaneously, MacMillan *et al.* published their work on iminium catalysis through an asymmetric Diels-Alder reaction (**Scheme 1.8**).[12] A generic mode of activation that can be applied to a wide range of organocatalytic reactions was introduced with this report, as well as the concept of organocatalysis. Following the introduction of the concept of ''organocatalysis'' and ''organocatalysts'', it became a rapidly expanding field for the enantioselective synthesis **(Figure 1.3)**. Indeed, the identification of general activation strategies has led to the design of 130 enantioselective organocatalytic reactions since then.[13]



Scheme 1.8. First highly enantioselective organocatalytic Diels–Alder reaction.

[11] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000***, 122*, 2395-2396.
[12] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000***, 122*, 4243-4244. (b) Jen, W. S; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 9874-9875. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458-2460.
[13] MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.

Organocatalysis has gained popularity as a synthetic philosophy also for its various advantages including the easy preparation of catalysts or their availability from biological sources, easy handling for being robust and inert towards air and moisture, easy scale-up, non-toxicity and their relatively low cost. They generally operate under mild conditions, and also the possibility of immobilizing them on solid supports makes the recovery and recycling possible, which make organocatalysts attractive for the industry and also for academic institutions both from green chemistry and economical point of views.[14]



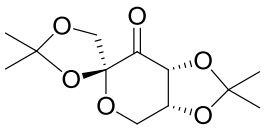
Web of Science, keyword: organocatalysis

Figure 1.3. The number of publications on organocatalysis per year.

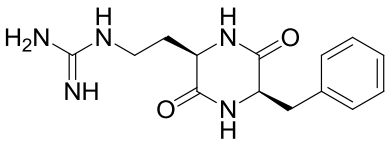
Up to the present, numerous novel small organic catalysts have been discovered. In **Figure 1.4.** some of these organocatalysts are shown.[15]

[14] Shaikh, I. R. *Journal of Catalysts* **2014**, 1-35.

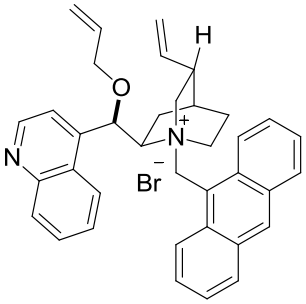
[15] (a) Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807. (b) Iyer, M.; Gigstad K. M.; Namdev N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911. (c) Corey, E. J.; Xu F.; Noe M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415. (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. (e) Corey, E. J.; Grogan, M. J.*Org. Lett.* **1999**, *1*, 157-160. (f) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244. (g) Chen, Y.; Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543. (h) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215. (i) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304. (j) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (k) Akiyama T.; Itoh J.; Yokota K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568. (l) Rueping M.; Sugiono E.; Azap C.; Theissman T.; Bolte M. *Org. Lett.* **2005**, 3781-3783. (m) Hoffman S., Seayad A. M., List B., *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427. (n) Storer, R. I.; Carrera, D. E.; Ni Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84-86. (o) Stephan J. Zuend, S.J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen E. N. *Nature* **2009**, *461*, 968-970. (p) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358-15374.



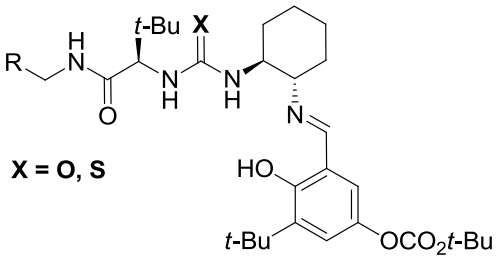
D-fructose derived chiral ketone
Shi 1996[15a]



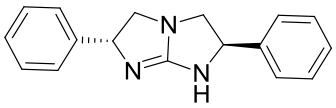
cyclopeptide catalyst
Lipton 1996[15b]



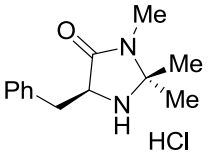
cinchonidine-derived
phase transfer catalyst
Corey 1997[15c]



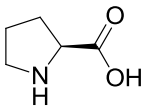
Schiff-base (thio)urea catalyst
Jacobsen 1998[15d]



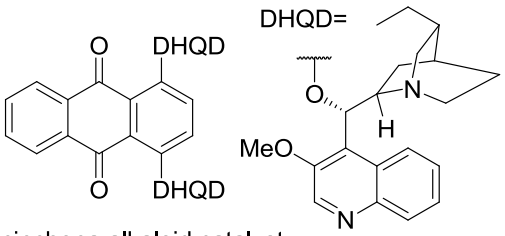
chiral bicyclic guanidine
Corey 1999[15e]



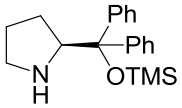
imidozolidinone
MacMillan 2000[15f]



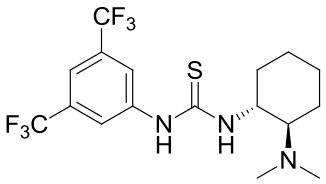
L-proline
List, Barbas, Lerner 2000[11]



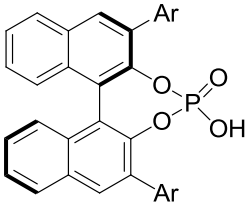
cinchona alkaloid catalyst
Deng 2000[15g]



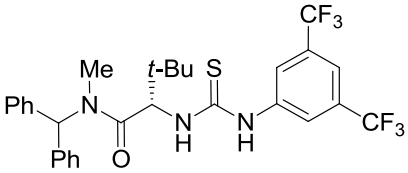
diphenyl prolinol
Hayashi-Jørgensen 2005[15h,i]



tertiary amine-thiourea catalyst
Takemoto 2003[15j]



chiral binaphthol-derived phosphoric
acid catalyst
Akiyama 2004[15k]
Rueping 2005[15l]
List 2005[15m]
MacMillan 2006[15n]



amido-thiourea derivative
Jacobsen 2009[15o,p]

Figure 1.4. Selected examples of chiral organocatalysts developed by different research groups.

1.3. ORGANOCATALYSIS CLASSIFICATION

There are several approaches for the classification of organocatalysis. One of these approaches is the classification according to the *catalyst-substrate interaction* involved in the substrate activation. Following this approach, organocatalysis can be divided into two main groups: covalent and non-covalent catalysis as shown in **Figure 1.5.** This Thesis is based on amine and hydrogen bonding organocatalysis, thus, these two classes will be specifically elaborated.

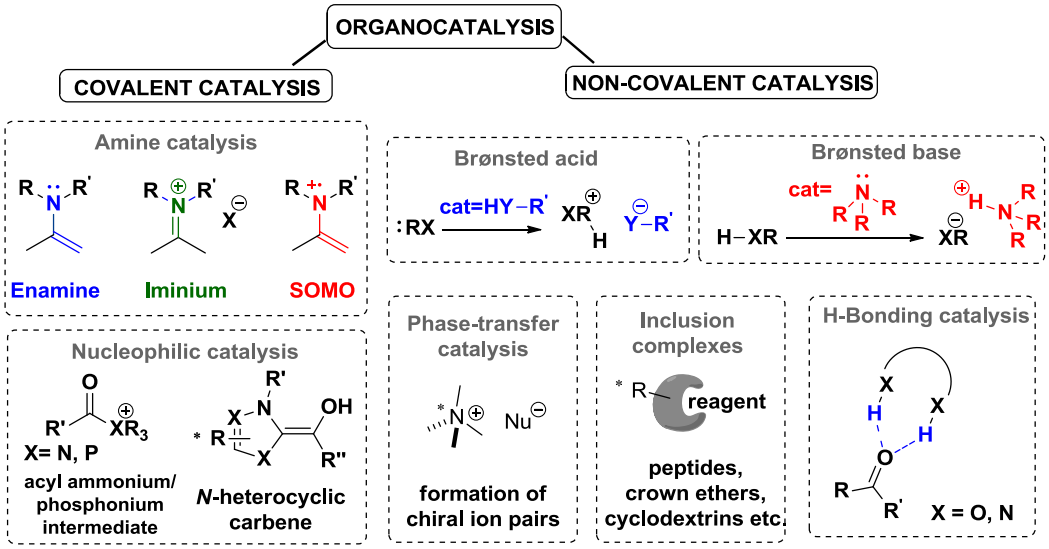


Figure 1.5. Organocatalysis classification according to the catalyst-substrate interaction.

1.3.1. AMINE CATALYSIS

In covalent catalysis, the strong interaction between the catalyst and the substrate leads to the formation of a reversible covalent bond between them within the catalytic cycle. Amine catalysis forms a significant class of this type and operates through diverse mechanisms to convert substrates to either activated nucleophiles or electrophiles.

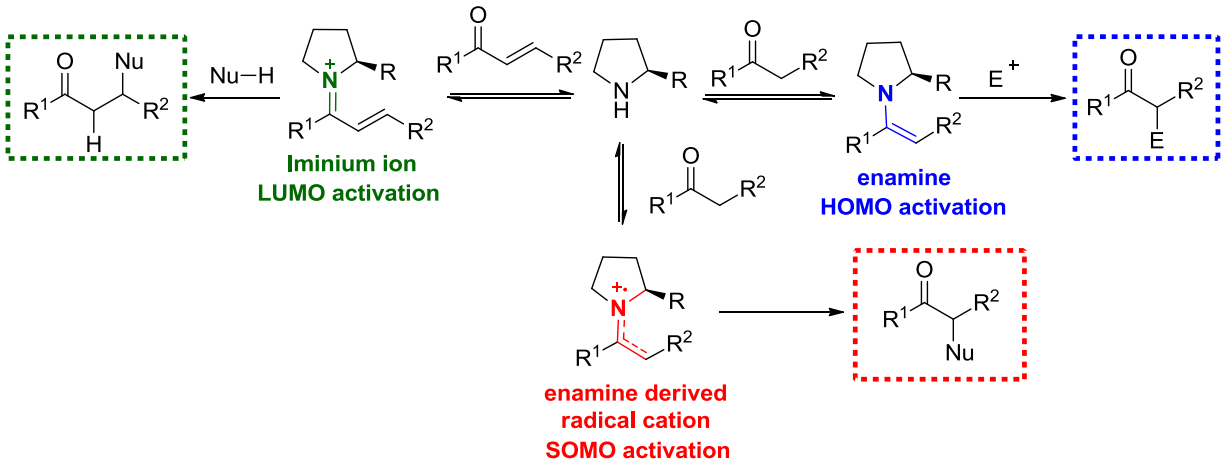


Figure 1.6. Generic activation modes of amine catalysis.

The amine catalysis class can be further divided into subclasses according to the activation modes: HOMO (enamine), LUMO (iminium ion) and SOMO activation **(Figure 1.6)**.

Enamine catalysis provides the activation of ketones and aldehydes towards nucleophilic attack to the proper electron acceptors by raising their HOMO (Highest Occupied Molecular Orbital). The activation occurs through the reversible condensation of an amine catalyst with an enolizable carbonyl compound to form an iminium ion intermediate which then deprotonates to its enamine form **(Figure 1.7).** A general catalytic cycle for enamine activation is depicted in **Scheme 1.9.**[13]

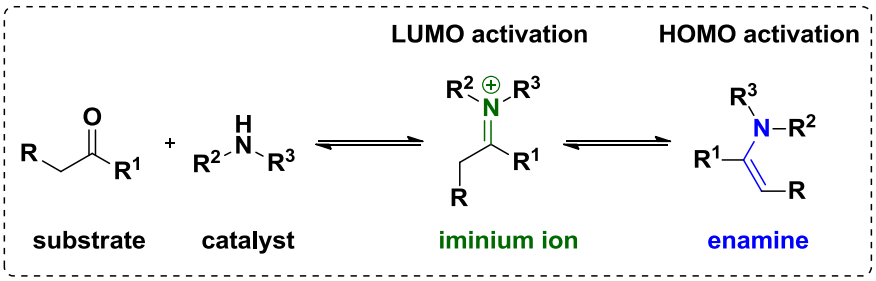
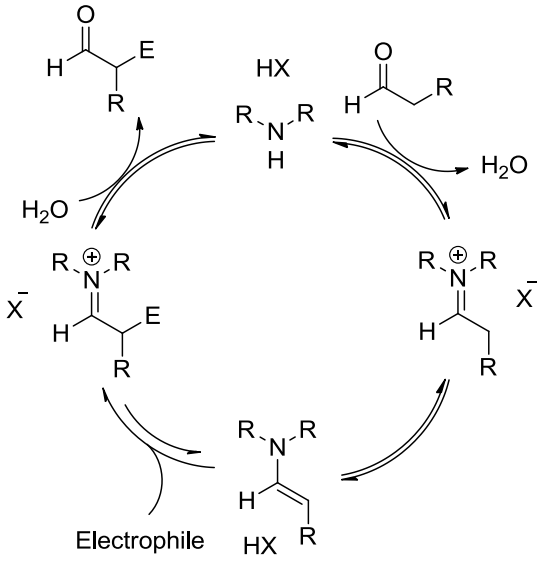


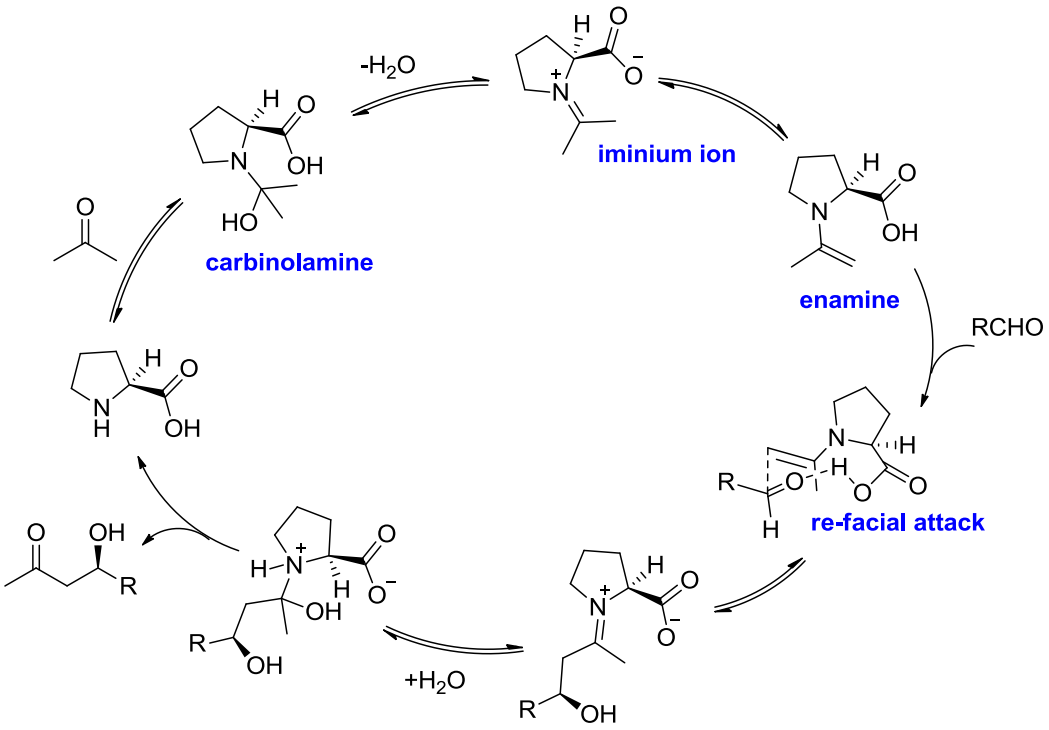
Figure 1.7. Activation through enamine formation.



Scheme 1.9. General catalytic cycle of enamine activation mode.

The first example of the enantioselective enamine-catalyzed process is the aforementioned Hajos-Parrish-Eder-Sauer-Wiechert reaction, an intramolecular aldol reaction catalyzed by the simple amino acid *L*-proline **(Scheme 1.6).**[10] However, the use of secondary amines has gained great popularity since the pioneering work by List, Lerner and Barbas where they used *L*-proline for the intermolecular direct aldol reaction between acetone and a variety of aldehydes **(Scheme 1.7)**. The originally proposed mechanism of this reaction based on nature's class **I** aldolase-mechanism is shown in **Scheme 1.10**.[11]

The catalytic cycle is initiated by the nucleophilic attack of the pyrrolidine moiety to the ketone forming a carbinolamine followed by the dehydration to iminium ion intermediate which then deprotonates to its enamine form. Due to the higher energy HOMO (Highest Occupied Molecular Orbital) of the enamine, its reactivity increases. The enamine then attacks the electrophile (carbon-carbon bond forming step) which in this case is an aldehyde. The approach to the aldehyde is controlled by the hydrogen bonding stabilization of the transition state, which leads to preferred *re*-face attack. The last step is the hydrolysis to afford the enantiomerically enriched product and release the catalyst for the next cycle.



Scheme 1.10. Originally proposed mechanism for the proline-catalyzed aldol reaction.

After this work, many new types of proline catalysts were developed for enamine catalysis and efficiently used in various asymmetric reactions such as aldol, Mannich, Michael, α-amination, intramolecular α-alkylation, α-halogenation etc.[16]

[16] (a) For a review on enamine catalysis: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569. (b) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991-993. (c) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703-3706. (d) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450-451. (e) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285-9289. (f) Jiang, M.; Zhu, S.-F.; Yang, Y.; Gong, L.-Z.; Zhou, X.-G.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 384-387. (g) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263. (h) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321-5323.

Iminium catalysis was developed by MacMillan *et al.* in 2000. Currently, with contributions of Karl Anker Jørgensen[15i,17] and many other research groups, it is used in more than 50 highly enantioselective protocols **(Figure 1.8)**.[12, 13]

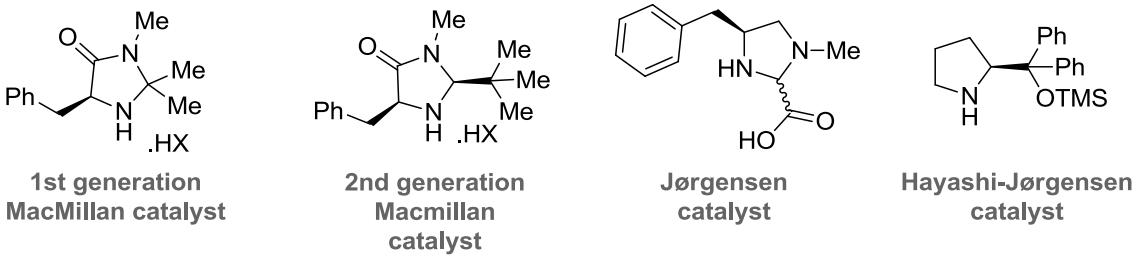


Figure 1.8. Some important organocatalysts developed for iminium catalysis.

This method is considered an organocatalytic alternative to the traditional Lewis acid activation of α,β-unsaturated carbonyl compounds **(Figure 1.9)**.

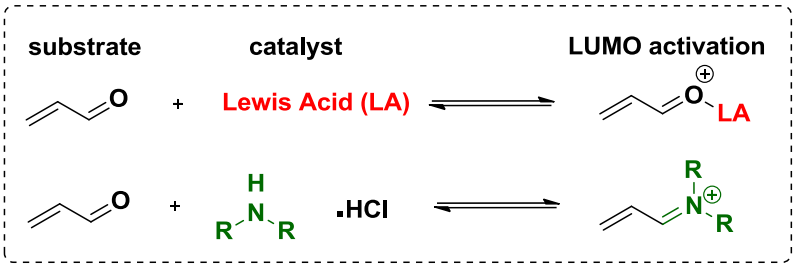
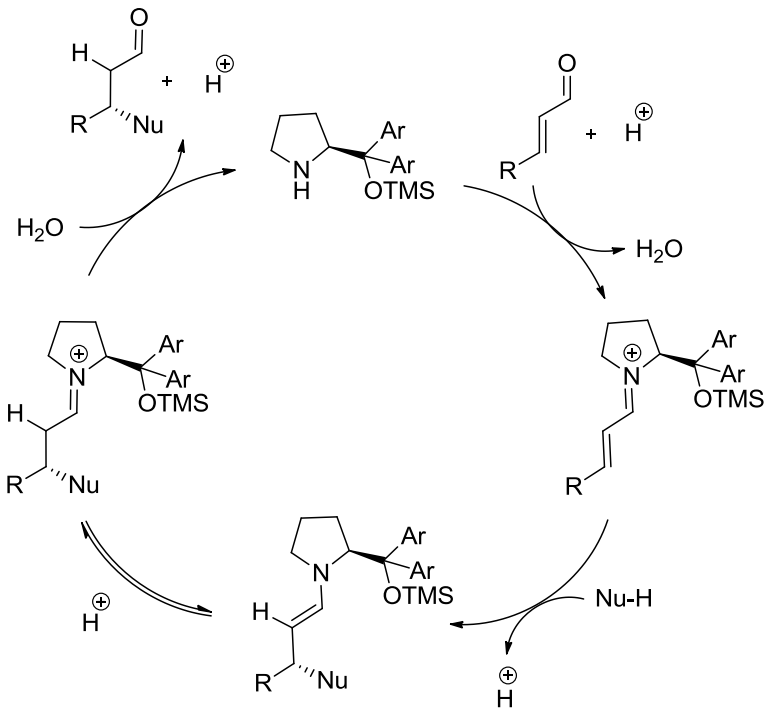


Figure 1.9. Design of iminium catalysis strategy.

The generic activation strategy comprises the activation of the substrate by lowering the LUMO (Lowest Unoccupied Molecular Orbital) through the reversible formation of an iminium ion between α,β-unsaturated carbonyl compounds, and the amine catalyst, thus increasing the reactivity towards nucleophilic attack. Following the nucleophilic attack, the iminium ion hydrolyzes to give the product and release the catalyst for the next catalytic cycle **(Scheme 1.11)**.

[17] (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797. (b) For a review: Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012,** *45*, 248-264. (c) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860-13874. (d) Diner, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983-1987. (e) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 15710-15711. (f) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.*, **2002**, 67, 8331-8338.



Scheme 1.11. Mechanism of β-functionalization of iminium activated α,β-unsaturated aldehydes with Jørgensen catalyst.

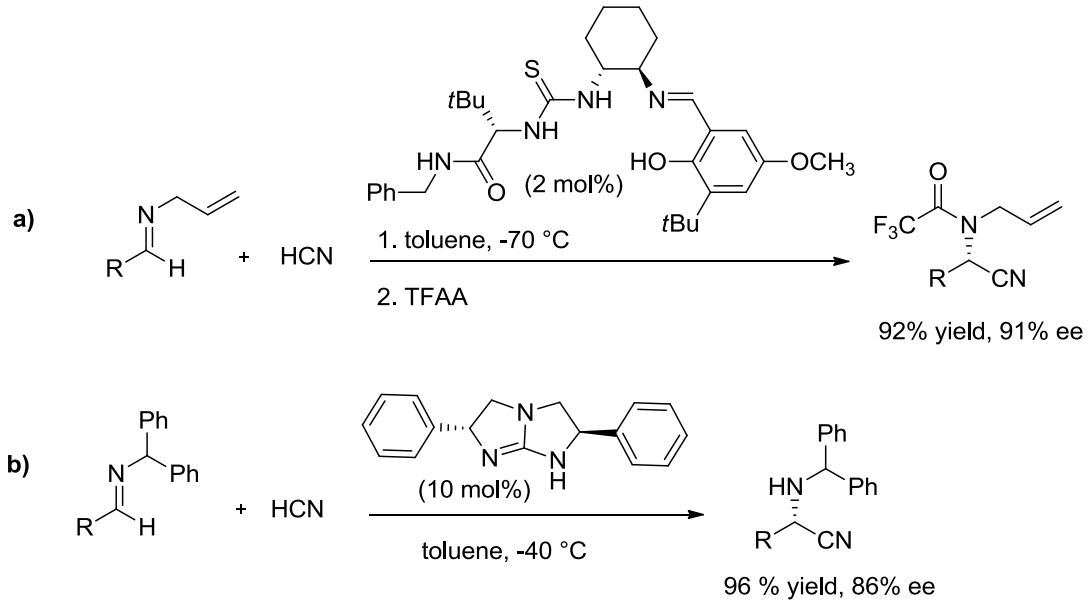
This strategy provides excellent enantio- and chemoselectivities, and therefore, it has found many applications such as the Michael reaction of α,β-unsaturated ketones, Diels-Alder, Friedel-Crafts alkylation, cyclopropanation, Mukaiyama-Michael reactions displaying excellent results.[18]

[18] (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371. (b) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482-5487. (c) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509-2511. (d) Zhao, G. L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 7417-7421. (e) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894-7895. (f) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu,D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437-3440.

1.3.2. HYDROGEN BONDING CATALYSIS

Unlike covalent catalysis, in non-covalent catalysis, weak intermolecular interactions such as hydrogen bonding and ionic interactions are employed. Research on hydrogen bonding in small-molecule chiral organocatalysis has emerged very recently. Early studies on this field implied the H-bonding between the catalyst and the electrophile that leads to the activation of the electrophile and the transition-state organization.[19]

Although early discoveries were well appreciated, the awareness of H-bonding as a key activation mode and its importance on the design of small-molecule chiral organocatalysts grew much later when Jacobsen[15d,20] and Corey[15e] independently reported on the highly enantioselective Strecker reaction, where the activation of imine substrates was achieved *via* H-bonding interactions with the catalyst **(Scheme 1.12).** The principle of hydrogen bonding activation is based on the simultaneous sharing of a hydrogen atom by the substrate (H-bond acceptor) and the catalyst (H-bond donor) which serves to decrease the electron density of the electrophilic substrate, thus, activating it toward nucleophilic attack.



Scheme 1.12. Enantioselective Strecker reactions **a)** Jacobsen's work **b)** Corey's work.

[19] (a) Oku, J.-I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229-230. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181-185. (c) Jackson, W. R.; Jayatilake, G. S.; Matthews, B. R.; Wilshire, C. *Aust. J. Chem.* **1988**, *41*, 203.(d) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (e) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710-4711.

[20] (a) Wenzel, A. G., Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett*. **2000**, *2*, 867-870. (d) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281.

Following these pioneering examples, chiral ureas, thioureas, guanidinium, and amidinium ions, squaramides, and diols became widely used catalysts performing through this type of activation **(Figure 1.10)**.[21]

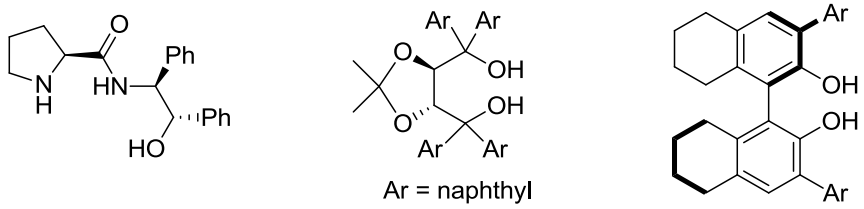


Figure 1.10. Some examples of hydrogen bonding organocatalysts.

1.4. BIFUNCTIONAL ORGANOCATALYSIS

In nature, enzymes catalyze chemical reactions with complete stereoselectivity and high efficiency. These biocatalysts bind reactants using covalent and non-covalent interactions. A notable example is the biological process of amide hydrolysis by the enzyme serine protease where serine is deprotonated by the nitrogen of neighboring histidine and acts as the nucleophilic amino acid attacking the carbonyl carbon of the peptide bond of the substrate. The resulting tetrahedral intermediate bearing a negatively charged alkoxide is stabilized through hydrogen bonding with amide protons in the oxyanion hole of the enzyme. Stabilizing the transition state lowers the activation energy necessary for the reaction thus, promotes the catalysis **(Figure 1.11.a)**.[22]

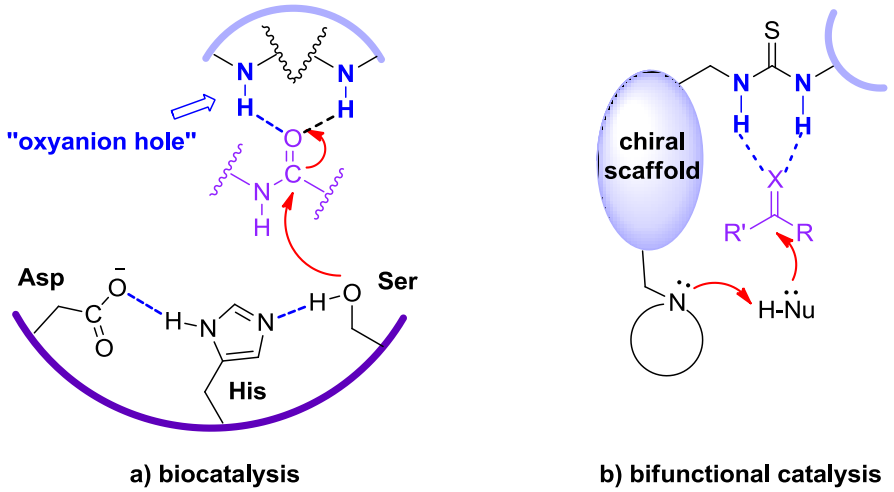


Figure 1.11. Comparison between biocatalysis and chemical catalysis.

[21] (a) Schuster, T.; Bauch, M.; DJrner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179-181. (b) Huang, Y.; Rawal, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662-9663. (c) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424,* 146. (d) Tang, Z.; Jiang, J.; Yu, L. -T.; Cui, X.; Gong, L. -Z.; Mi, A. -Q.; Jiang, Y. -Z.; Wu, Y. -D. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263. (d) McDougal, N. T.; Schaus, S. E.; *J. Am. Chem. Soc.* **2003**, *125*, 12094-12095.

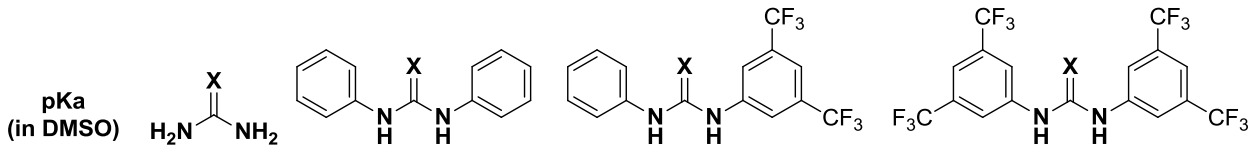
[22] Iván, G.; Szabadka,O.; Ordög, R.; Grolmusz, V.; Náray-Szabó, G. *Biochem. Biophys. Res. Commun.* **2009**, *383*, 417-420. b) Erez, E.; Fass, D.; Bibi, E. *Nature* **2009**, *459*, 371-378.

This bifunctional behavior of nature inspired chemists for the design of similar small molecule organic catalysts. The design comprises the incorporation of a basic or nucleophilic scaffold to the catalyst structure in addition to a hydrogen bond donor functionality. These two functional groups operate synergistically to activate both electrophilic and nucleophilic reaction partners **(Figure 1.11.b)**.

1.4.1. (THIO)UREAS AS BIFUNCTIONAL ORGANOCATALYSTS

(Thio)urea catalysts are interesting in the field of organocatalysis for their capability of double hydrogen bonding, inexpensive synthesis, their stability under air and easy storage. Additionally, small amounts of these catalysts can be very active.

Studies carried out with urea and thiourea organocatalysts showed that thioureas are more active catalysts that ureas. This can be explained in different ways. Thioureas have smaller pKa values than ureas, thus, they are more acidic. An increase in acidity of N-H protons leads to stronger hydrogen bonding with an electrophilic reactant. The acidity of N-H protons can be further increased by introducing electron withdrawing substituents on (thio)ureas **(Figure 1.12)**. Another aspect is that oxygen atom has higher electronegativity which facilitates dimerization while there is less possibility for thiourea molecules to self-associate.[23]



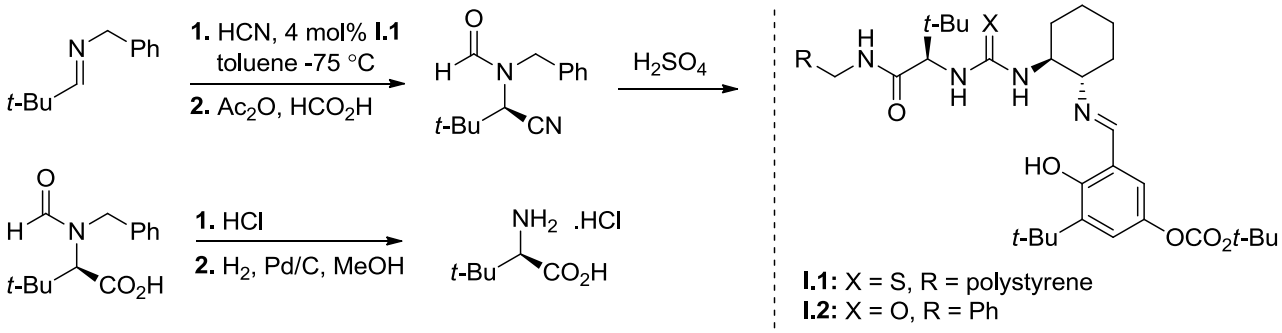
X= O	29.6	18.7	16.1	13.8
X= S	21.1	13.4	10.7	8.5

Figure 1.12. pKa values of ureas and thioureas in DMSO as the solvent.

Until date, numerous derivatives of this type of catalysts have been developed by research groups. Some important examples will be demonstrated in this section.[24]

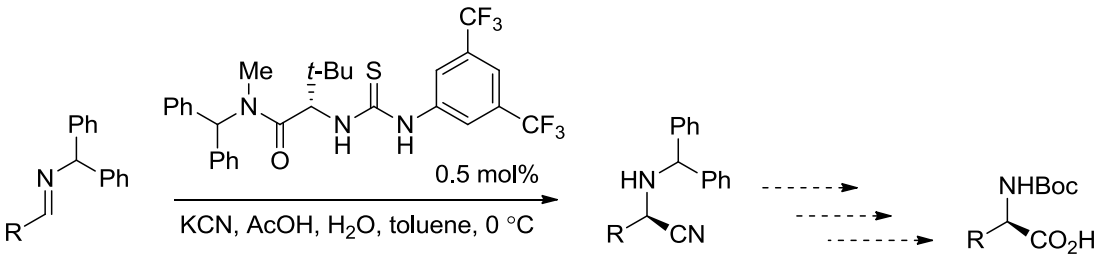
[23] (a) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.*, **1991**, *113*, 8398-8401. (b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.*, **2012**, *14*, 1724-1727.
[24] For reviews on (thio)urea organocatalysts: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299-4306. (b) Connon, S. J. *Chem. Eur. J*. **2006**, *12*, 5418-5427.

The leading example of this type of catalyst was reported in 1998 by Jacobsen and co-workers.[15d] They developed the amino acid derived (thio)urea Schiff base homogeneous and polystyrene-bound catalysts for the asymmetric Strecker synthesis of *tert*-leucine **(Scheme 1.13)**. Although this synthesis provides (*R*)-*tert*-leucine in high yield and enantiomeric excess, it requires cryogenic temperatures and uses hazardous trimethylsilyl cyanide (TMSCN)/methanol or HCN as the cyanide source. These factors have limited the application of this method towards preparative-scale synthesis.



Scheme 1.13. First generation thiourea-catalyzed Strecker synthesis of *tert*-leucine.

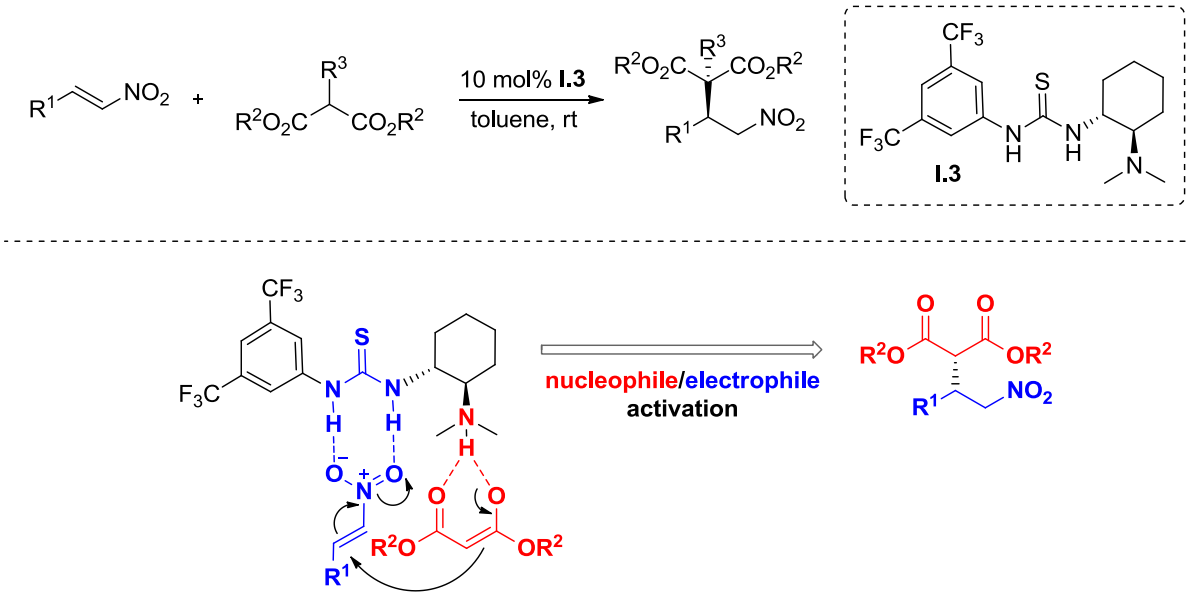
Later on, Jacobsen group discovered the efficient use of simpler amido-thiourea derivatives lacking diamino cyclohexane moiety. These catalysts proved effective and highly enantioselective for the hydrocyanation of imines derived from alkyl, aryl, heteroaryl and alkenyl aldehydes. The reactions could be run in the presence of water using inexpensive and easy to handle potassium cyanide (KCN) and sodium cyanide (NaCN) salts as alternative cyanide sources without the need of cryogenic temperatures and in larger scales (25-100 mmol) **(Scheme 1.14)**. [15o,p]



Scheme 1.14. Potassium cyanide mediated Strecker synthesis.

Jacobsen hydrocyanation reaction is now being exploited commercially by the pharmaceutical company Rhodia ChiRex. The Rhodia ChiRex concept allows the efficient large scale synthesis of chiral amino nitriles which are useful building blocks for transformation into natural and unnatural α-amino carboxylic acids quickly and smoothly and in bulk.

After Jacobsen's initial thiourea catalysts, Takemoto and co-workers successfully designed a biomimetic small molecule as the first representative of thiourea bifunctional organocatalyst family. This bifunctional catalyst is built on a *trans*-1,2-diaminocyclohexane scaffold as the source of chirality. It consists of a basic tertiary amine for the activation of the nucleophile and a double hydrogen bond donor thiourea group (p*K*a= 13.8 in DMSO)[25] for the simultaneous activation of the electrophile and a phenyl group attached to the thiourea moiety bearing trifluoromethyl groups which enhance H-bonding due to its electron-withdrawing ability. Takemoto's catalyst **I.3** was initially used efficiently in Michael additions of 1,3-dicarbonyl compounds to nitroolefins **(Scheme 1.15)**.[15j]

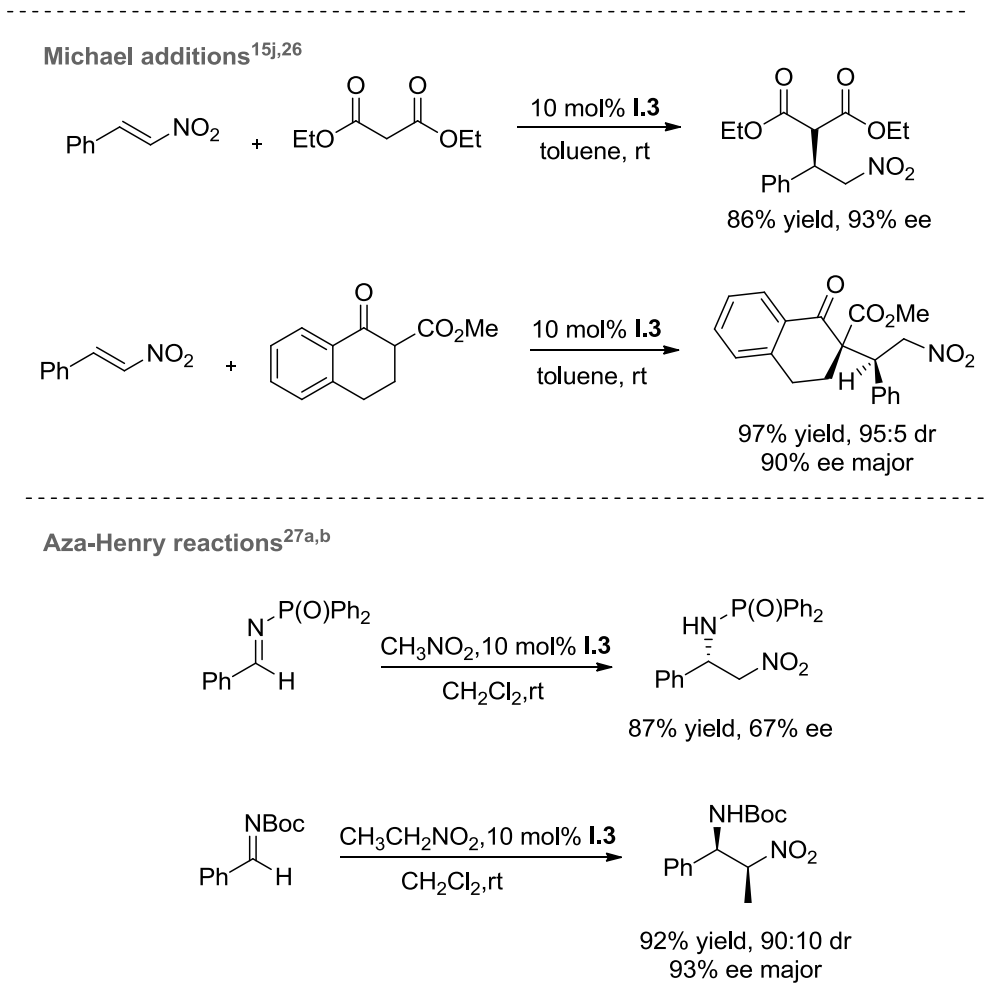


Scheme 1.15. Simultaneous activation of nucleophile/electrophile proposed by Takemoto.

Subsequent investigations were conducted to reveal the structure-reactivity-selectivity relationships. In the case of attaching the basic unit to a flexible alkyl chain, lack of activity and selectivity was observed, showing that the rigidity from the cyclohexane ring is crucial for high activity and selectivity. Similarly, replacing the thiourea group with a monodentate H-bond donor led to poorer results underlining the necessity of double H-bonding thiourea groups. Changing the substituents on phenyl ring also slightly affected the outcome of the reaction due to the influence of electronic effects on the H-bond ability of the thiourea group. [26]

[25] Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner P. R. *Org.Lett.* **2012**, *14*, 1724-1727.
[26] Okino, T.; Hoashi, Y.; Furukawa. T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

Takemoto's thiourea has found many applications since its discovery. It displayed high activity and selectivity in many asymmetric reactions **(Scheme 1.16)**.[27] It was also utilized in the synthesis of natural products such as *R*-(−)-baclofen[26],(−)-lycoramine, (−)-epibatidine[27c], (−)-galanthamine and (+)-lunarine.[27d]



Scheme 1.16. Selected examples for the application of Takemoto's catalyst.

[27] (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto Y. *Org. Lett.* **2004***, 6*, 625-627. (b) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466-476. (c) Hoashi, Y.; Yabuta, Y.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365-374. (d) Chen, P.; Bao, X.; Zhang, L. F.; Ding, M.; Han, X. J.; Li, J.; Zhang, G. B.; Tu, Y. Q.; Fan, C. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8161-8166. (e) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413-9419. (f) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y.; *Synthesis* **2007**, 2571-2575. (g) Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y.; *Synthesis* **2006**, 3295-3300.(h) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137-140. (i) Hoashi, Y.; Okino, T.; Takemoto, Y.; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032-4035.

After Takemoto's leading bifunctional catalyst design **(Scheme 1.15)**[15j], cinchona alkaloids drew the attention for being potential bifunctional structures since they are inexpensive starting materials and exist in both pseudo enantiomeric forms. The general activation mode is similar to that of Takemoto catalyst: the thiourea moiety binds the electrophile while quinuclidine ring activates the nucleophile by deprotonation **(Figure 1.13)**.

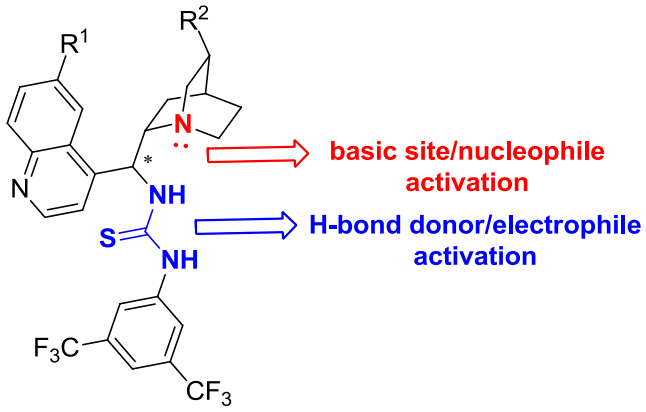
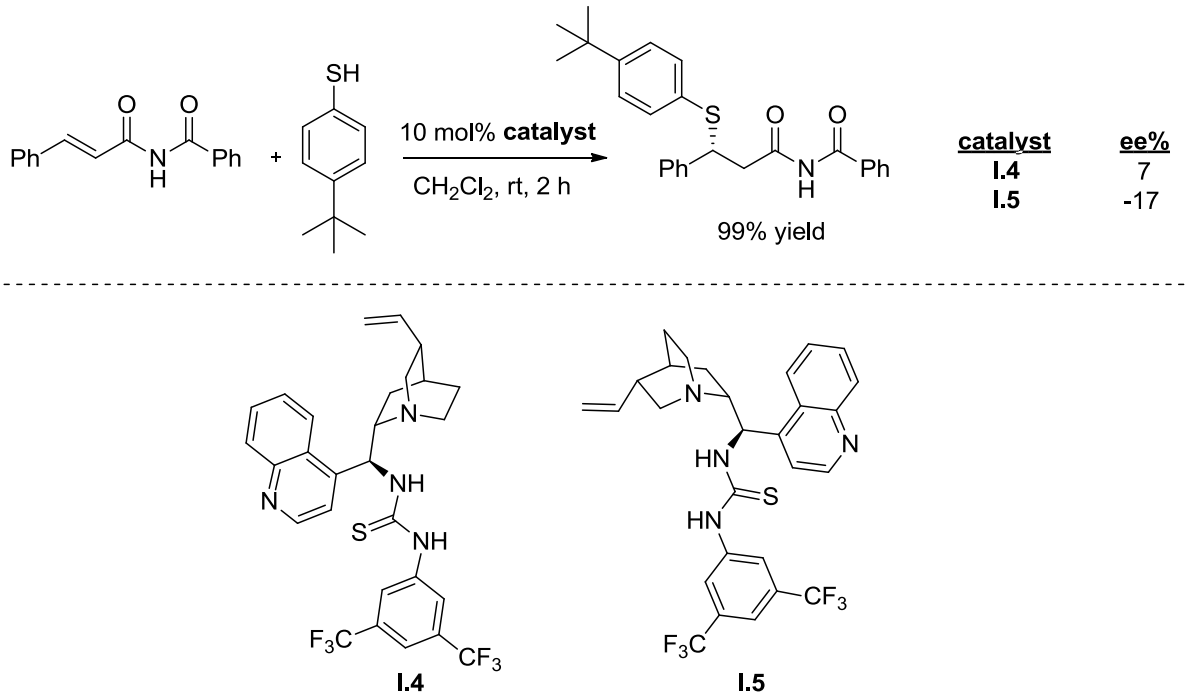


Figure 1.13. The general structure of bifunctional cinchona alkaloid-derived catalyst.

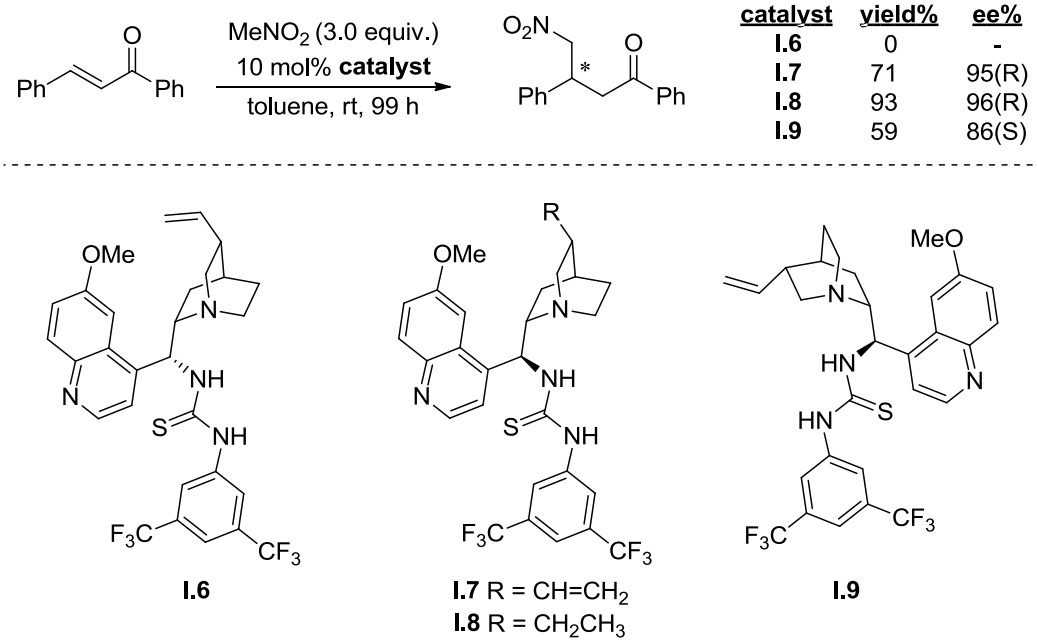
Thus, four research groups began independently working on the design of thiourea-modified cinchona alkaloid bifunctional catalysts. The first report came from Chen and co-workers on highly active catalysts for Michael addition of thiophenols to α,β-unsaturated imides. However, the reaction proceeded with low enantioselectivity **(Scheme 1.17).**[28]



Scheme 1.17. The first report of thiourea-modified cinchona catalysts by Chen *et al.*

[28] Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding L. S.; Wu, Y. *Synlett* **2005**, 603-606.

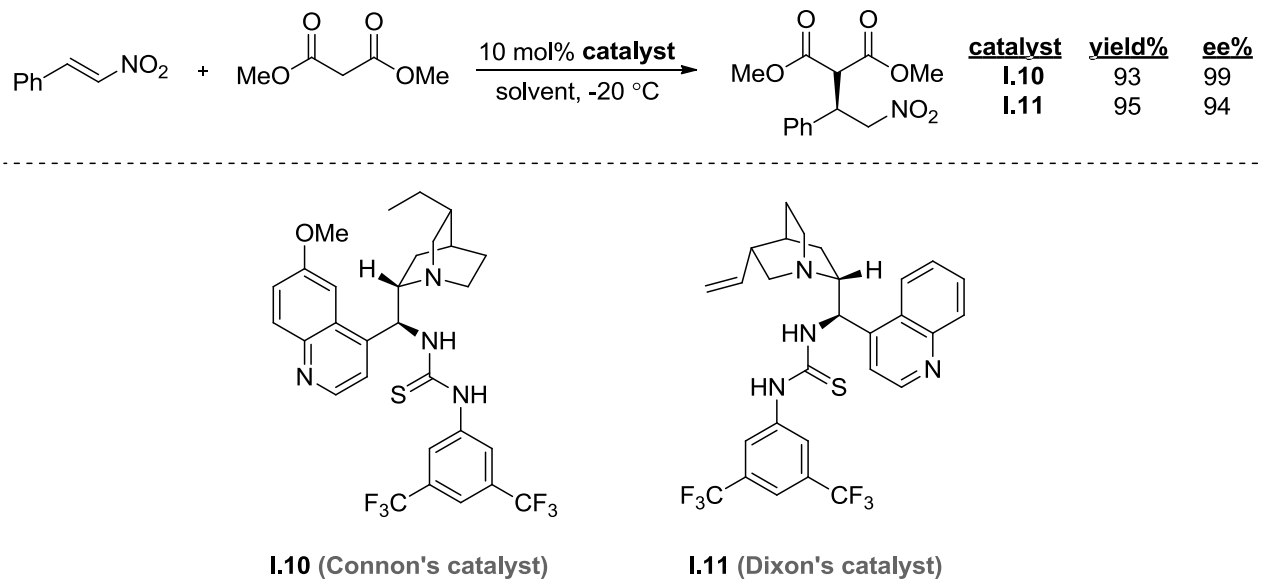
Soós and co-workers developed quinine/quinidine derived thiourea-substituted cinchona alkaloids to be used for the enantioselective addition of nitromethane to chalcones. Surprisingly, thiourea derivative **I.6**, of natural stereochemistry at C-9 was found to be inactive just as quinine itself while derivatives **I.7, I.8,** and **I.9** with opposite stereochemistry at C-9, showed high selectivity. The relation between the reactivity and the relative orientation of thiourea and quinuclidine moieties supports the bifunctional mechanism of this system **(Scheme 1.18)**.[29]



Scheme 1.18. Thiourea-modified cinchona catalysts developed by Soós and co-workers for nitromethane addition to chalcone.

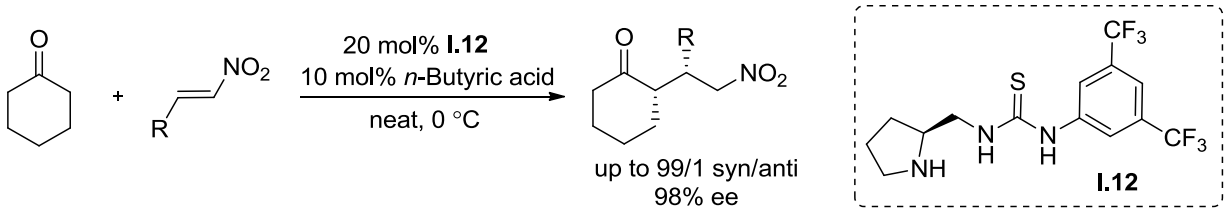
Connon and Dixon and their co-workers independently reported the efficient use of similar catalytic systems for the Michael addition reactions of dimethyl malonate to nitroalkenes **(Scheme 1.19)**.[30] Soon after the first remarkable examples, these compounds have proven to be excellent catalysts for asymmetric conjugate additions of acidic pronucleophiles to a variety of substrates.[31]

[29] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967-1969.
[30] (a) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed*. **2005**, *44*, 6367-6370. (b) Ye, J.; Dixon, D. J.; Hynes, P.S. *Chem. Commun.* **2005**, 4481-4483.
[31] (a) For a review: Connon, S. J. *Chem. Commun.* **2008**, 2499-2510. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mazzanti, A.; Sambri, L.; Melchiorre, P. *Chem. Commun.* **2007**, 722-724. (c) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107-2110. (d) Liu, T. Y.; Cui, H. L.; Chai, Q.; Long, J.; Li, B. J.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Chem. Commun.* **2007**, 2228-2230. (e) Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3646-3648.



Scheme 1.19. Evaluation of Connon's and Dixon's catalysts.

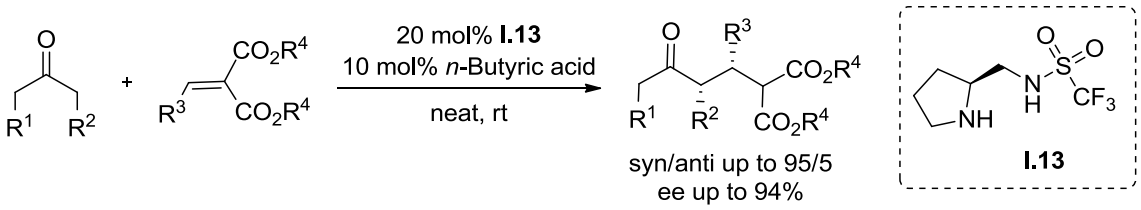
L-Proline is a widely used chiral scaffold in organocatalysts. The combination of pyrrolidine and thiourea functionalities was initially used by Tang and coworkers. Starting from *L*-proline, in two steps they synthesized pyrrolidine-thiourea derivatives which combine the enamine-iminium (secondary amine) and hydrogen bonding (thiourea) activation modes. Derivatives of this structure have been tested in the Michael addition of cyclohexanone to nitroalkenes in the presence of a Brønsted acid additive with high efficiency and selectivity **(Scheme 1.20).**[32]



Scheme 1.20. Pyrrolidine-thiourea catalyzed Michael reaction.

[32] Cao, C.; Ye, M.; Sun, X.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901-2904.

The same research group also reported the use of another *L*-proline derivative, *N*-(pyrrolidin-2-ylmethyl)trifluoromethane sulfonamide in the Michael addition of ketones to alkylidene malonates with moderate to good yields and good to high diastereoselectivities and enantioselectivities. The good performance of this monodentate catalyst demonstrated that double hydrogen bond interactions might not always be essential **(Scheme 1.21)**.[33]



Scheme 1.21. Pyrollidine-sulfonamide catalyzed Michael reaction.

Later on, other examples of pyrrolidine derived thioureas were developed by other research groups for Michael additions[34], *anti*-Mannich reactions,[35] and α-chlorination of aldehydes.[36] Structures of these catalysts are depicted in **Figure 1.14.**

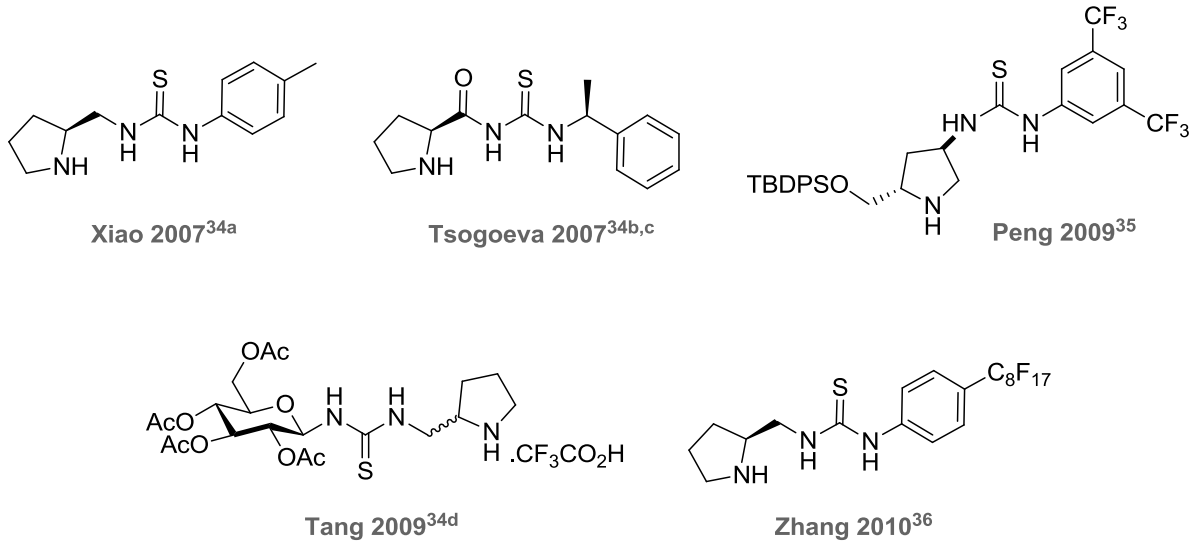
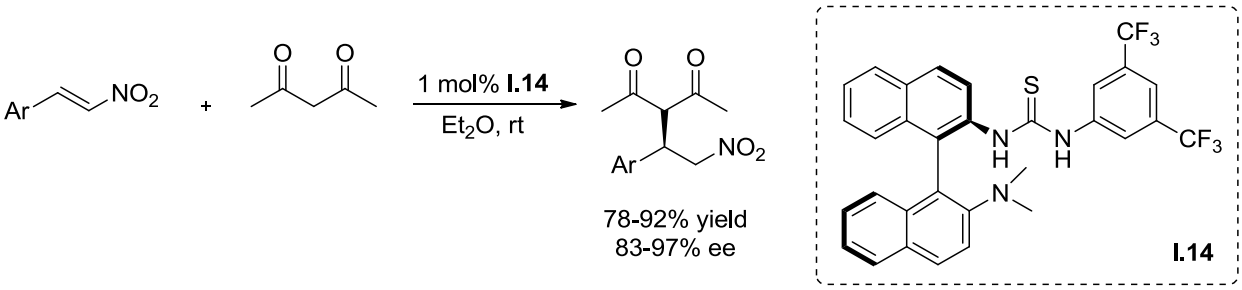


Figure 1.14. Examples of pyrrolidine-thiourea organocatalysts used in literature.

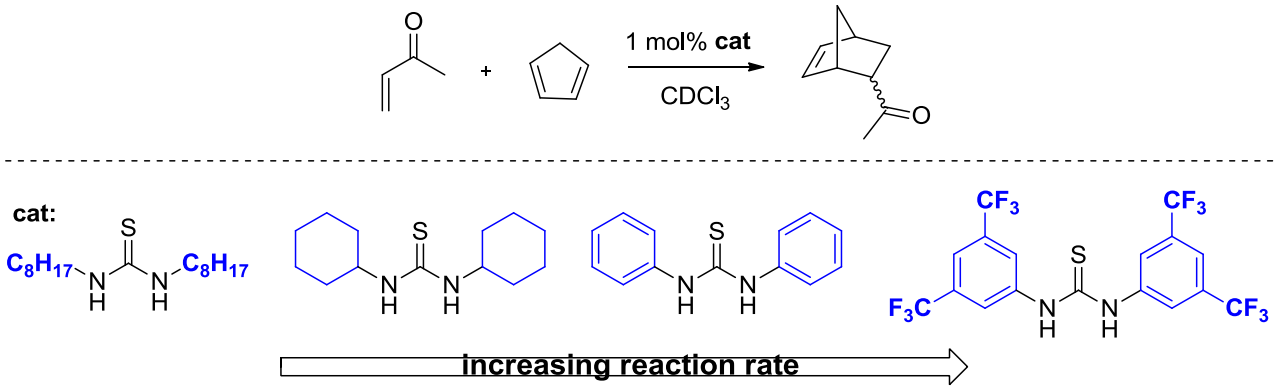
[33] Cao, C.; Ye, M.; Sun, X.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 4073-4076.
[34] (a) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Lia, Y. J.; Xiao, W. J. *Tetrahedron Lett.* **2007**, *48*, 21-24. (b) Tsogoeva, S. B.; Wei, S. *Chem. Commun*. **2006**, 1451-1453. (c) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, C. *Catalysis Today* **2007**, *121*, 151-157. (d) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141-3147.
[35] Zhang, H.; Chuan, Y.; Li, Z.; Peng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2288-2294.
[36] Wang, L.; Cai, C.; Curran, D. P.; Zhang, W. *Synlett* **2010**, *3*, 433-436.

All the above chiral (thio)urea organocatalysts possess at least one stereogenic center to induce chirality. Wang and co-workers followed a different approach by introducing axially chiral binaphthyl amine catalysts. The design comprises a tertiary amine basic functionality and a double hydrogen bond donor thiourea functionality similar to Takemoto and cinchona derived thiourea catalysts. However, Wang's catalyst showed superior activity and selectivity compared to Takemoto and cinchona catalysts even at 1 mol% catalyst loading. This behavior can be attributed to the higher acidity of this thiourea compared to other catalysts (p*K*a = 10.72 in DMSO) leading to stronger H-bonding donating ability **(Scheme 1.22)**.[37]



Scheme 1.22. Michael reaction catalyzed by Wang's thiourea.

Schreiner *et al.* discovered that simple, neutral thioureas act similarly to Lewis acids due to their bidentate hydrogen bond donating ability and increase the reaction rates and stereoselectivities of some organic reactions. For instance, they activate unsaturated carbonyl dienophiles through hydrogen bonding and facilitate Diels-Alder reactions in a similar way to Lewis acids like $AlCl_3$ and $TiCl_4$. In a model reaction, it was observed that the rate of the reaction depends mostly on the substituents, which affect the hydrogen bond donor ability of the thiourea moiety **(Scheme 1.23)**.[38]



Scheme 1.23. Schreiner's hydrogen bonding thioureas utilized in Diels-Alder reaction.

[37] Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett*. **2005**, *7*, 4713-4716.
[38] Wittkopp, A.; Schreiner, P. R., *Chem. Eur. J.* **2003**, 407-414.

Nagasawa *et al.* combined thiourea and guanidine functional groups to develop a new bifunctional catalyst for the asymmetric Henry reaction. This catalyst employs guanidine and thiourea groups for the activation of nitromethane and aldehyde respectively. Optimization of reaction conditions using α-branched aldehydes as substrates led to 70-91% yield and 82-92% ee in the presence of 10 mol% catalyst **(Figure 1.15.a)**.[39]

Ricci *et al.* developed a thiourea bearing an additional hydroxy group for the catalytic enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes. In this system, the proposed bifunctional mode of action of the catalyst takes place by the two thiourea hydrogen atoms activating the nitroalkene, whereas the free hydroxy functionality directs the nucleophilic attack of indole to the nitroolefin **(Figure 1.15.b)**.[40]

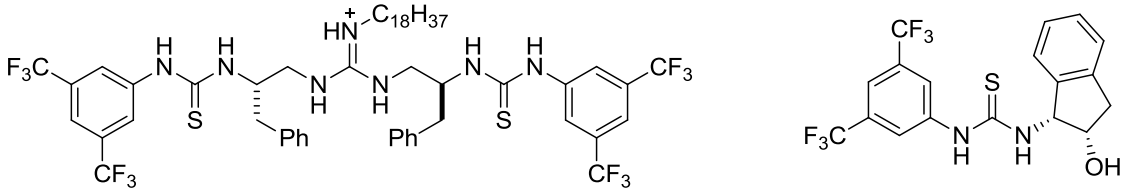


Figure 1.15. Thiourea derivatives developed by Nagasawa and Ricci.

In 2006, primary amine-thiourea organocatalysts were introduced for the first time by the Jacobsen[41] and Tsogoeva groups[42] **(Figure 1.16)**. Since then significant progress has been made regarding this class and their applications in various asymmetric organic transformations. This Thesis is based on the thiourea organocatalysts developed by Tsogeova's group. Recent progress and mechanistic studies on primary amine-thioureas will be illustrated in detail in Chapter 2.

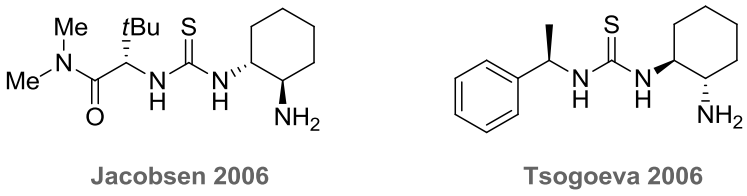


Figure 1.16. Primary amine-thiourea organocatalysts developed by the Jacobsen and Tsogoeva groups.

[39] Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643-1648.
[40] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci A., *Angew. Chem. Int. Ed.* **2005**, *44*, 6576-6579.
[41] Huang, H.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171.
[42] Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451-1453.

1.5. OBJECTIVES OF THE THESIS

This thesis focuses on chiral primary amine-thiourea organocatalysts (PATs).

CHAPTER II:

The beneficial effects of water and acid additives in PAT catalysis are well recognized, however, the effects of these additives on Michael additions of ketones have not been addressed exhaustively. Therefore in this chapter, the simultaneous effects of acid and water on the PAT catalyzed Michael addition of acetone to *trans*-β-nitrostyrene will be studied in detail. The effect of concentration on this reaction will be explored as well. Using the data that we obtain from these studies we wish to optimize the reaction conditions in a rational way.

CHAPTER III:

The immobilization of primary amine-thioureas has not been performed until now. Thus, we aimed at the design and synthesis of polystyrene-supported PATs and their evaluation in different asymmetric carbon-carbon bond forming reactions.

CHAPTER II

Asymmetric Michael Addition Reactions to Nitroalkenes Catalyzed by Primary Amine-Thioureas

UNIVERSITAT ROVIRA I VIRGILI
PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS
Zeynep Inci Günler

CONTENTS

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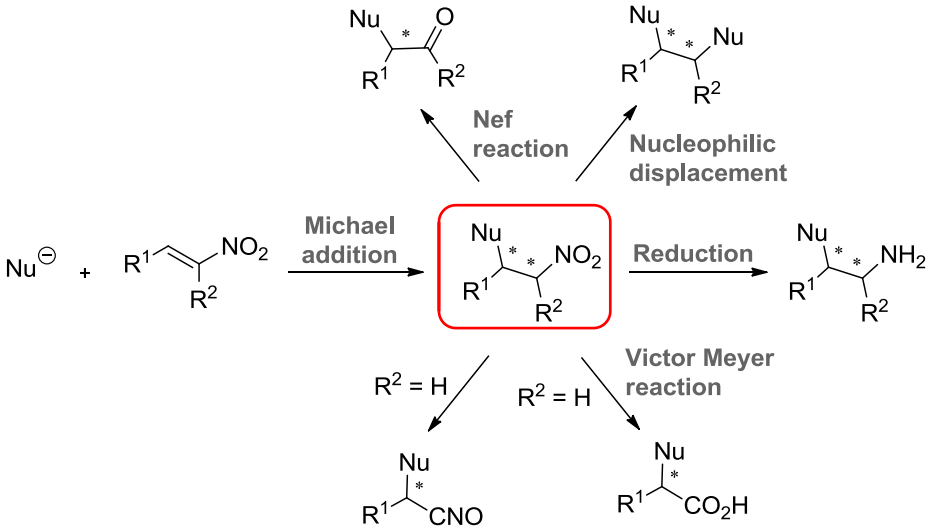
2. ASYMMETRIC MICHAEL ADDITION REACTIONS TO NITROALKENES CATALYZED BY PRIMARY AMINE THIOUREAS

2.1. INTRODUCTION

Asymmetric Michael addition reactions to nitroolefins give access to synthetically useful C-C, C-N, and C-O, C-S and C-P bond-formations, leading to enantioenriched and highly functionalized building blocks for the total synthesis of biologically active compounds and natural products.[1] Nitroalkenes are very attractive Michael acceptors among others because the nitro group is a highly electron withdrawing group making these substrates highly reactive and its versatility allows the transformation to many other functionalities after the addition reaction takes place.[2] Some examples of the possible transformations that nitro groups can undergo are shown in **Scheme 2.1.**



Scheme 2.1. Possible transformations of nitro groups.

Moreover, the nitro group is well recognized by the thiourea moiety through strong hydrogen bonding which makes nitroolefins popular substrates for thiourea based amine organocatalysts. It was proven that tertiary and secondary amine-thioureas successfully catalyze conjugate addition reactions to nitroalkenes.[3] Besides these recent developments, primary amine-thiourea (abbreviated PAT) organocatalysts have also been recognized to

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[1] (a) Fuji, K.; Node, M. *Synlett* **1991**, 603-610. (b) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901-7903. (c) Node, M.; Hao, X. J.; Fuji K. *Chem. Lett.* **1991**, 57-60. (d) Fuji, K.; Zheng, S. Z.; Node, M.; Hao, X. J. *Chem. Pharm. Bull.* **1991**, *39*, 202-203. (e) Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612-615.

[2] (a) Nef, J. U.; *Justus Liebigs Ann. Chem.* **1894**, *280*, 263-291. (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434. (c) Loyd, D. H.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294-4298. (d) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356-1361. (e) Meyer, V.; Wurster, C. *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 1168-1172. (f) Mukayama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.

[3] (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.*, **2004**, *126*, 9558-9559. (b) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.*, **2004**, *126* , 9906-9907. (c) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed*. **2010**, 157-160.

activate carbonyl compounds similar to enzymes such as type I aldolases containing catalytic lysine residues.[4] Thioureas of this type were first introduced in 2006 by the Jacobsen[5] and Tsogeova groups.[6] The demonstration of the usage of PATs as efficient catalysts triggered the development of new PAT catalysts for enantioselective transformations by different research groups. Some of these catalysts are represented in **Figure 2.1**.[7]

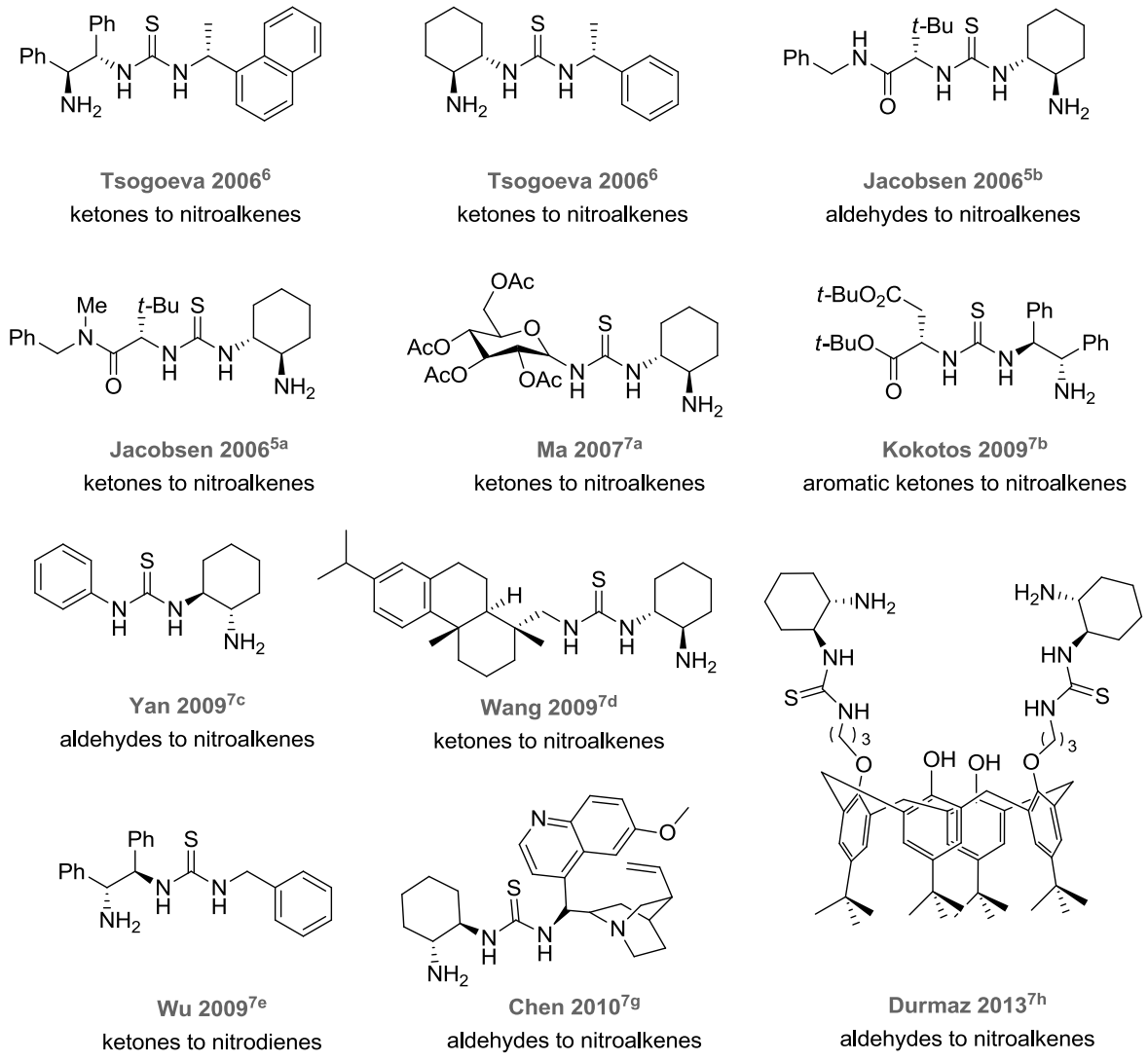


Figure 2.1. Selection of PAT organocatalysts developed for Nitro Michael additions.

[4] Gefflaut, T.; Blonski, C.; Perie, J.; Willson, M. *Prog. Biophys. Mol. Biol.*, **1995**, *63*, 301-340.

[5] (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171. (b) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 6366-6370.

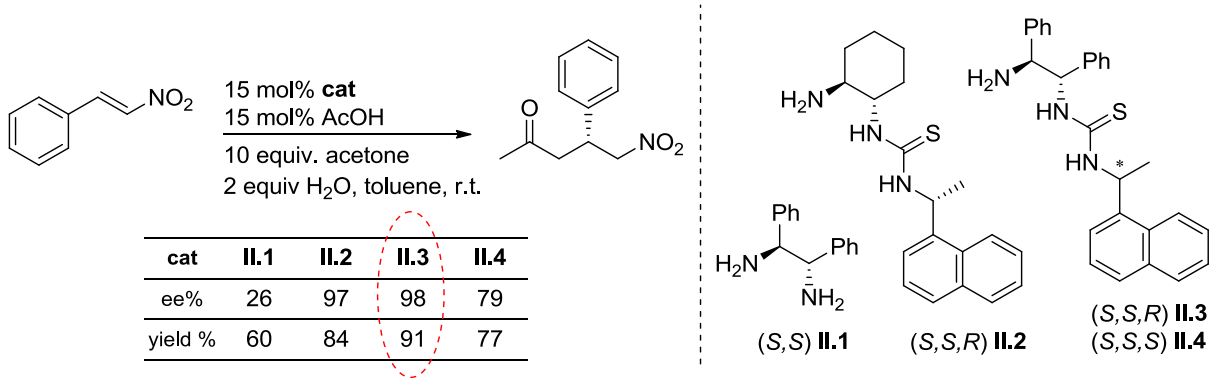
[6] (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun*. **2006**, 1451-1453. (b) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826-832. (c) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151-157.

[7] (a) Liu, K.; Cui, H. F.; Nie, J.; Dong, K. Y.; Li, X. J.; Ma, J. A. *Org. Lett*. **2007**, *9*, 923-925. (b) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355-1362. (c) Zhang, X. J.; Liu, S. P.; Lao, J. H.; Du, G. J.; Yan, M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 1451-1458. (d) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett*. **2009**, *11*, 153-156. (e) He, T.; Qian, J.-Y.; Song, H.-L.; Wu, X.-Y. *Synlett* **2009**, 3195-3197. (f) He, T.; Wu, X.-Y. *Synth. Commun.* **2012**, *42*, 667-677. (g) Chen, J. R.; Zou, Y. Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W. J. *Tetrahedron* **2010**, *66*, 5367-5372. (h) Durmaz, M.; Sirit, A. *Supramol. Chem.* **2013**, *25*, 292-301.

2.2. ADDITION OF KETONES TO NITROALKENES

Organocatalytic asymmetric Michael addition of ketones to nitroolefins had been previously reported using *L*-proline and pyrrolidine-based catalytic systems with poor to moderate enantioselectivities.[8] Therefore this particular reaction has been considered a challenging task.

In 2006, Tsogoeva *et al.* designed a new catalyst structure for this reaction. Their design comprised the hydrogen bond donor thiourea moiety in combination with a primary amine group. Initial studies involved the optimization of the Michael reaction of acetone with *trans*-β-nitrostyrene using thioureas **II.2-II.4** in the presence of AcOH and H_2O as additives. Optimization studies led to their final catalytic system in toluene/AcOH/water furnishing the Michael adduct in 98% yield and 91% ee using 15 mol% of catalyst **II.3 (Scheme 2.2)** [6a]



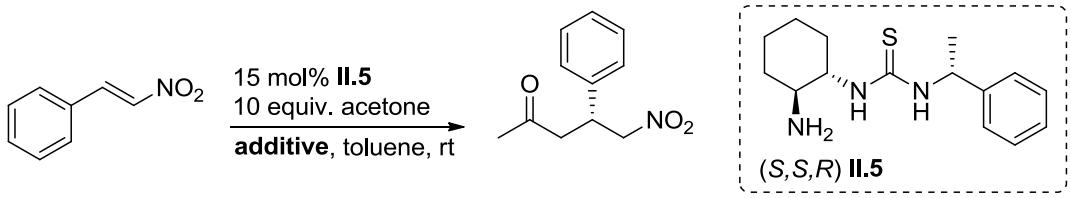
cat	II.1	II.2	II.3	II.4
ee%	26	97	98	79
yield %	60	84	91	77

Scheme 2.2. Seminal work by Tsogoeva group.

It was found out that opposite diastereomers **II.3** and **II.4** gave the same enantiomer of the product. However, the (*S,S,R*) diastereomer **II.3** provided better results, being the optimal catalyst (matched case). This catalyst was then tested in the Michael addition of aliphatic and cyclic ketones to a variety of aromatic nitroolefins delivering products in high yields (84-99%) and enantioselectivities (90-99%). Under the optimized reaction conditions, the usage of diamine **II.1** as catalyst gave poorer results confirming that the thiourea functionality neighboring the stereogenic carbon centers is essential for high yield and enantioselectivity.[6a]

[8] (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267. (b) List, Pojarliev, P. B.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423-2425. (c) Enders, D.; Seki, A. *Synlett* **2002**, 26. (d) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611-3614. (e) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am*. *Chem. Soc*. **2004**, *126*, 9558-9559. (f) Cobb, A. J. A.; Longbottom,D. A.; Shaw D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808-1809. (g) Cobb; A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold; J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96. (h) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147-1168.

After these successful results, they reported a more detailed investigation on the nature of solvent and additives and the mechanism of the same model reaction using a new catalyst **II.5 (Table 2.1)**.[6b]



entry	additive	time (h)	yield%	ee%
1	-	72	55	86
2	H_2O (1 equiv.)	47	59	85
3	H_2O (2 equiv.)	32	78	86
4	**H_2O: AcOH (2: 0.15 equiv.)**	**16**	**86**	**86**

Table 2.1. Effect of different additives on the Michael reaction catalyzed by **II.5**.

The best results were obtained in toluene, which was attributed to its non-polar nature allowing strong hydrogen bonding interactions. The screening of chiral and achiral weak acids in combination with water as additives showed that the highest reaction rates were obtained in the presence of the combination 0.15 equiv. AcOH/2 equiv. H_2O **(Table 2.1, entry 4)**. Although no further investigation was carried out to find out the actual roles of additives, it was assumed that these additives accelerate the reaction by facilitating the interconversion of reaction intermediates on the catalytic cycle **(Scheme 2.3)**.[6b]

The Michael reaction with different ketones and nitroolefins gave mostly ***R*** product. To explain this predominant formation of ***R*** enantiomer, they determined the transition state structures for both enantiomers computationally. These calculations suggested that the ***R*** TS is more compact and the second nitro group oxygen points towards the reactive center while in the ***S*** TS, the same oxygen points away from this center and causes repulsive interactions with the phenyl ring of the catalyst **(Figure 2.2)**.[6b]

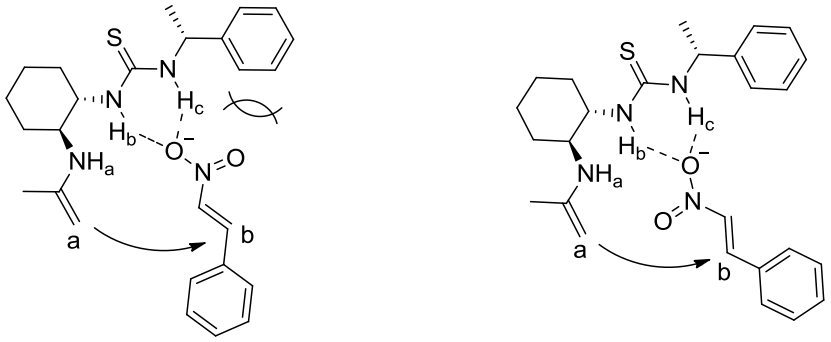
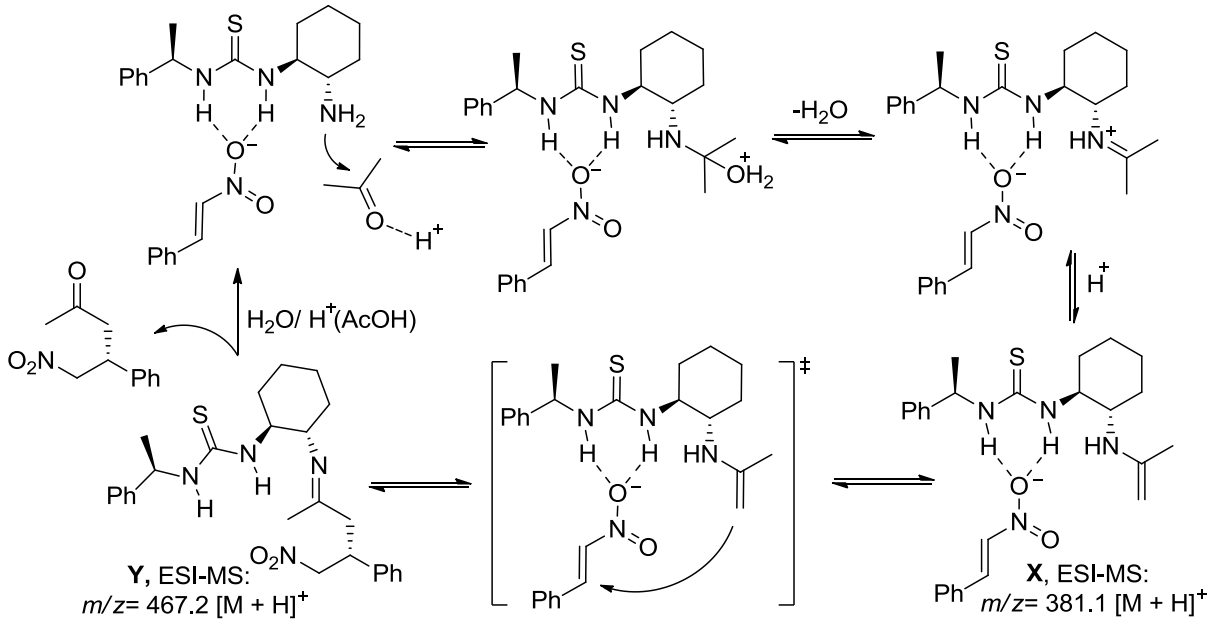


Figure 2.2. Transition state structure for the formation of the ***R*** (right) and ***S*** (left) enantiomers.

Furthermore, these computational calculations gave evidence that only one oxygen atom is involved in hydrogen bonding with thiourea moiety. They showed mass spectroscopic data as evidence for the existence of the intermediates catalyst-enamine **X** and catalyst-product imine **Y**.[6b]

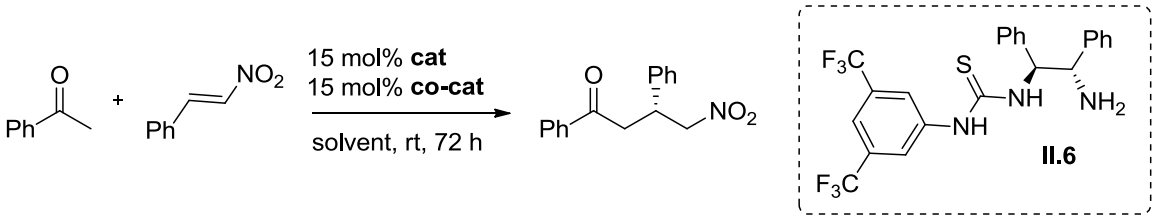
Based on these observations, the proposed reaction mechanism is shown in **Scheme 2.3.**



Scheme 2.3. Proposed reaction mechanism by Tsogoeva *et al.*

Following this development, in 2010 Xu *et al.* reported on the mechanism of the same reaction using aromatic ketones instead of aliphatic and cyclic ketones as Michael donors. However, their catalytic system did not comprise the use of water. It was observed that in the absence of any acidic cocatalyst the reaction did not proceed **(Table 2.2, entry 1)**. Similarly to the Tsogoeva group they attributed this behavior to the acid assisted interconversion of reaction intermediates in the catalytic cycle. Accordingly, they used *p*-nitrobenzoic acid (abbreviated PNBA) as the only additive to achieve catalytic activity, which gave slightly better results than AcOH **(Table 2.2, entry 2 vs 3)**. Best performance was obtained in THF using catalyst **II.6** and cocatalyst PNBA giving the product in 97% yield and 99% ee after 72 h **(Table 2.2, entry 4)**.[9]

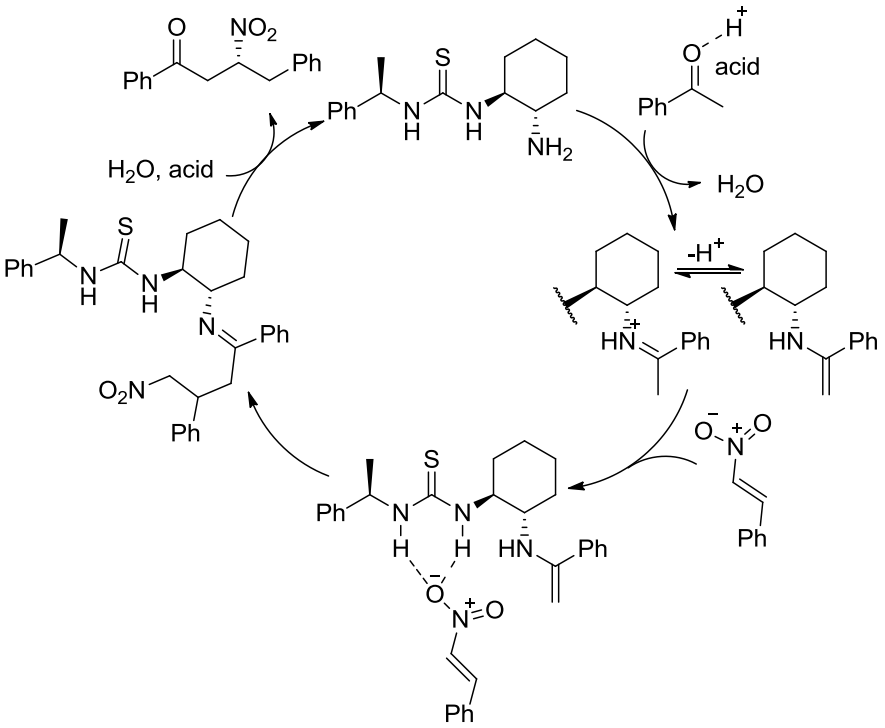
[9] Li, B. L.;Wang, Y. F.; Luo, S. P.; Zhong, A. G.; Li, Z. B.; Du, X. H.; Xu, D. Q. *Eur. J. Org. Chem.* **2010**, 656-662.



entry	catalyst	solvent	co-catalyst	yield%	ee%
1	**II.6**	CH_2Cl_2	-	-	-
2	**II.6**	CH_2Cl_2	AcOH	85	84
3	**II.6**	CH_2Cl_2	PNBA	90	85
4	**II.5**	**THF**	**PNBA**	**97**	**99**

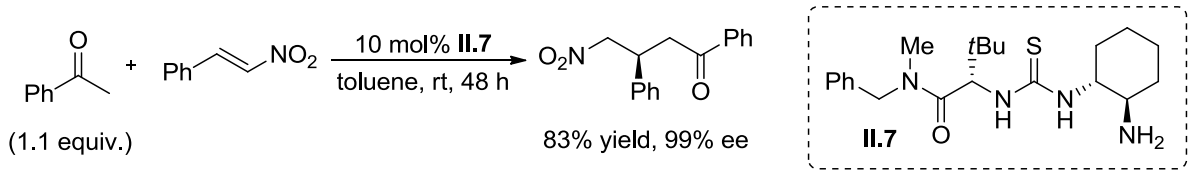
Table 2.2. Acid and solvent effect on the Michael reaction catalyzed by **II.6**.

In addition, they used ESI-MS spectroscopy to detect the iminium/enamine intermediates under relevant reaction conditions and ^{1}H NMR spectroscopic analysis to confirm hydrogen bonding between thiourea functionality of the catalyst and nitro group of nitrostyrene. Taking into consideration these results, they proposed a similar catalytic mechanism to that of Tsogoeva's **(Scheme 2.4)**.[9]



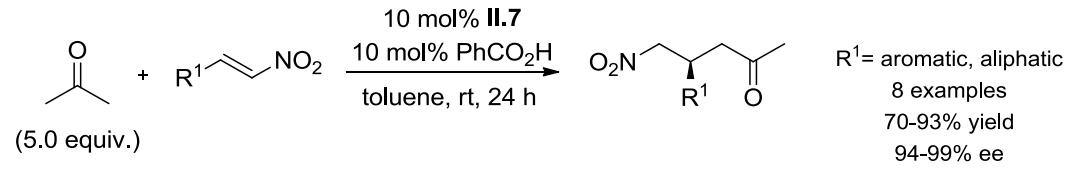
Scheme 2.4. The proposed mechanism by Xu *et al.*

Concomitantly to Tsogoeva's report, Jacobsen *et al.* reported the highly enantioselective conjugate addition of ketones to nitroalkenes catalyzed by amino acid derived primary amine-thiourea catalyst **II.7**. They undertook the addition of acetophenone to *trans*-β-nitrostyrene as a model reaction. Increasing the initial concentration of nitrostyrene to 5 M allowed the use of a small excess of acetophenone (1.1 equiv.) and delivered the Michael product in 83% yield and 99% ee **(Scheme 2.5)**.[5a]



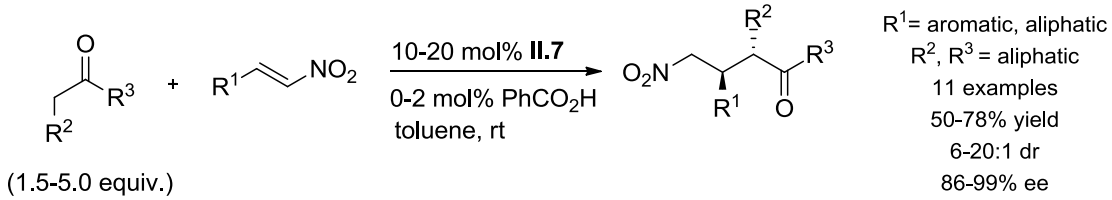
Scheme 2.5. The model reaction

However, when acetone was used as the nucleophilic substrate, the Michael product was obtained in 99% ee but with low yield (40% yield) due to the formation of bis alkylation product. At this point, catalytic amounts of benzoic acid had to be used as the additive to suppress the formation of this side reaction and increase the product yield without loss of enantioselectivity. Under these conditions, the reaction proceeded in high yields and enantioselectivities for a range of aromatic and aliphatic nitroalkenes **(Scheme 2.6)**.[5a]



Scheme 2.6. Enantioselective addition of acetone to nitroalkenes.

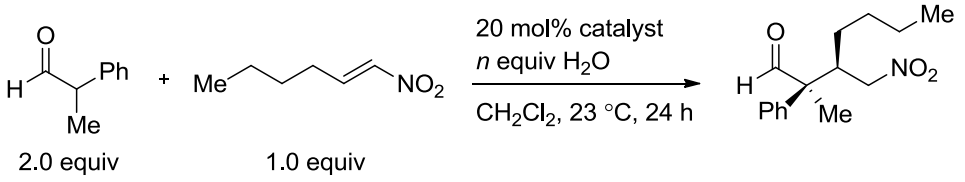
Catalyst **II.7** was also tested for the activation of ethyl ketones, which allows the formation of a range of branched products bearing contiguous tertiary stereocenters. The products were obtained in good regio- and diastereoselectivity favoring the *anti*-isomers and high enantioselectivities (86-99% ee). However, the product yields were moderate (50-65%) in most cases. The authors attributed the moderate yields to the formation of insoluble polymeric materials since no soluble side products were observed **(Scheme 2.7)**.[5a]

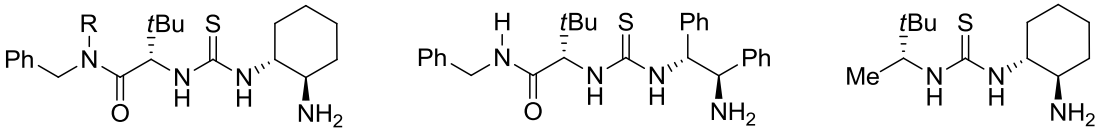


Scheme 2.7. The regio- and diastereoselective asymmetric addition of ethyl ketones to nitroalkenes.

2.3. ADDITION OF ALDEHYDES TO NITROALKENES

After the successful application of PAT catalyst **II.7** to the Michael addition of ketones to nitroalkenes, Jacobsen and co-workers also investigated the PAT catalyzed enantio- and diastereoselective conjugate addition of racemic α,α-disubstituted aldehydes to β-substituted nitroalkenes generating tertiary and quaternary stereogenic centers. For the optimization studies, they selected the reaction between 1-nitrohex-1-ene, a β-alkyl-substituted nitroalkene and 2-phenylpropionaldehyde.[5b]





II.7 R = Me
II.8 R = H

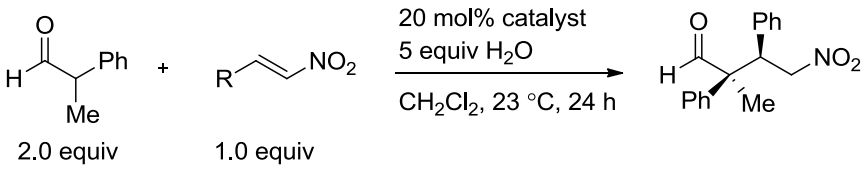
II.9

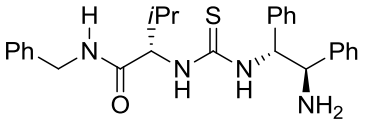
II.10

entry	catalyst	H_2O (equiv)	yield%	d.r. (syn/anti)	ee%
1	**II.8**	0	34	>10:1	96
2	**II.8**	2.0	56	>10:1	96
3	**II.8**	5.0	64	>10:1	96
4	**II.8**	10	54	>10:1	96
5	**II.7**	5.0	31	>10:1	96
6	**II.10**	5.0	<5	-	-
7	**II.9**	0	93	>10:1	99
8	**II.9**	**5.0**	**100**	**>10:1**	**99**

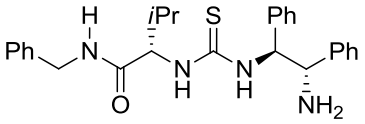
Table 2.3. Effect of water on the addition of 2-phenylpropionaldehyde to 1-nitrohex-1-ene.

Modification of standard reaction parameters like temperature, solvent, reagent ratios, concentration, catalyst loading failed to improve the product yield. At this point, authors emphasize the benefits of added water for the reaction outcome. The addition of controlled amounts of water gave rise to improvements in product yields **(Table 2.3, entry 1 vs 2-4, 7 vs 8)**. Catalysts bearing an *N*-monosubstituted amide gave better results than their *N,N*-disubstituted amide analog **(Table 2.3, entries 3, 8 vs. 5)** while the catalyst lacking amide group was actually inactive **(Table 2.3, entry 6)**. Under optimized conditions, for a variety of α,α-disubstituted aldehyde/nitroalkene combinations, excellent enantioselectivities and yields and useful levels of diastereoselectivities were obtained using catalyst **II.9**.[5b]





II.11



II.12

entry	R	catalyst	yield%	d.r.(syn/anti)	ee% (syn/anti)
1	Ph	**II.8**	100	1.2:1	67:3
2	Me	**II.8**	91	23:1	99(syn)
3	Ph	**II.9**	86	8.6:1	97:24
4	Ph	**II.11**	84	11.9:1	97:32
5	Ph	**II.12**	35	6.9:1	71:40

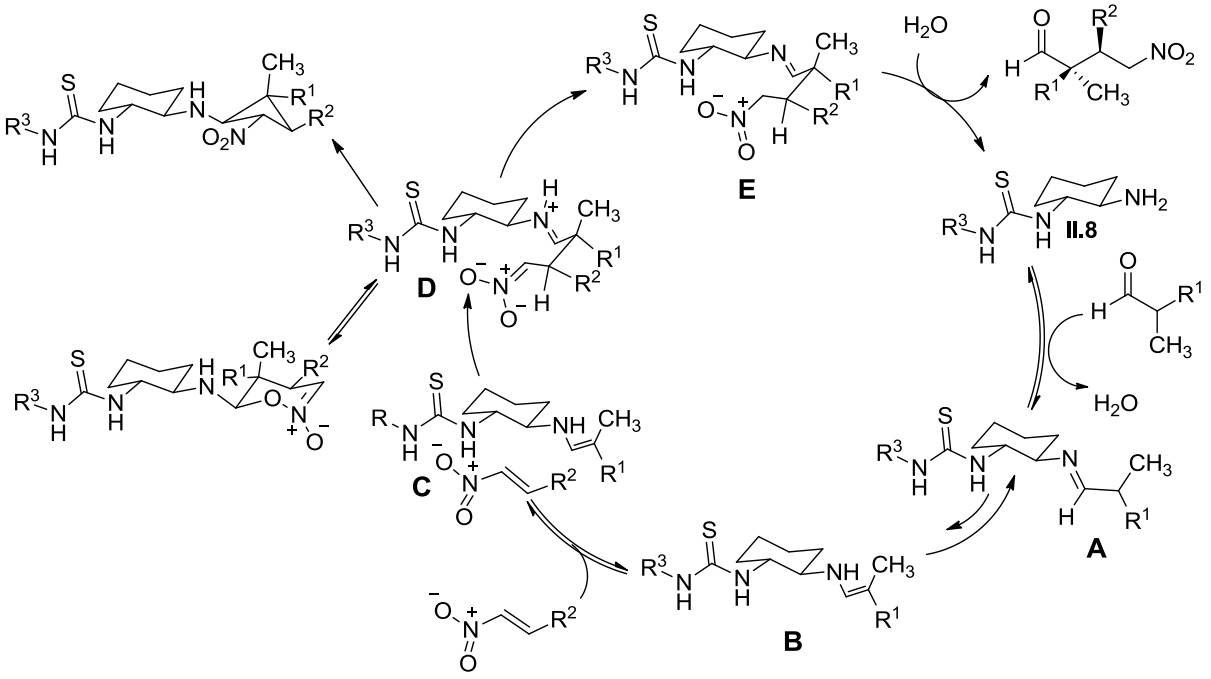
Table 2.4. The use of valine derived PAT catalysts in asymmetric addition of 2-phenylpropionaldehyde to *trans*-β-nitrostyrene.

When *trans*-β-nitrostyrene was used as the electrophilic substrate, catalyst **II.9** displayed reasonably higher enantio- and diastereoselectivities than catalyst **II.8 (Table 2.4, entry 1 vs 3)**. Further modification of the catalyst structure showed that valine derived catalyst **II.11** gave identical results to *tert*-leucine derived catalyst **II.9 (Table 2.4, entries 3 and 4)**. Significant drop in yield and ee values with mismatched catalyst **II.12** demonstrates the cooperative role of the stereochemistry between both amino acid and diamine in defining catalyst activity and selectivity **(Table 2.4, entry 5)**.[5b]

Methyl substitution in the nitroalkene substrate led to significantly higher selectivities compared to phenyl substituted nitroalkene **(Table 2.4, entry 2 vs 1)**. This difference of the outcome for different nitroalkenes was explored by Blackmond *et al.* by the use of successful NMR techniques to probe the kinetics and structures of organocatalytic intermediates. Their mechanistic investigations revealed that the reaction is subject to two selection levels: the formation of *E* and *Z* aldehyde-enamine from the imine and the addition of the electrophile to form the second stereogenic center. Different enantio- and diastereoselectivities for different catalyst-substrate combinations are attributed to the degree of reversibility in each level. Lower selectivity is associated with greater ease of reversibility with phenyl compared with methyl substitution in the nitroalkene substrates.[10]

[10] Ji, Y.; Blackmond, D. G. *Catal. Sci. Technol.* **2014**, *4*, 3505-3509.

The Jacobsen group proposed the catalytic cycle shown in **Scheme 2.8** consistent with their experimental results. In this catalytic cycle, imine **A**, resulting from the condensation of catalyst **II.8** and aldehyde, tautomerizes to form *E* or *Z* enamine. Considering the observed diastereoselectivities, the preferred formation of thermodynamically favorable enamine **B** is proposed. Formation of intermediate **C** through hydrogen bonding between thiourea moiety and only one of the oxygens of nitroalkene allows the enamine to reach close proximity for carbon-carbon bond formation to occur. Proton transfer converts **D** to **E**, which then hydrolyzes to yield the product and regenerate the catalyst for the next cycle.[5b]

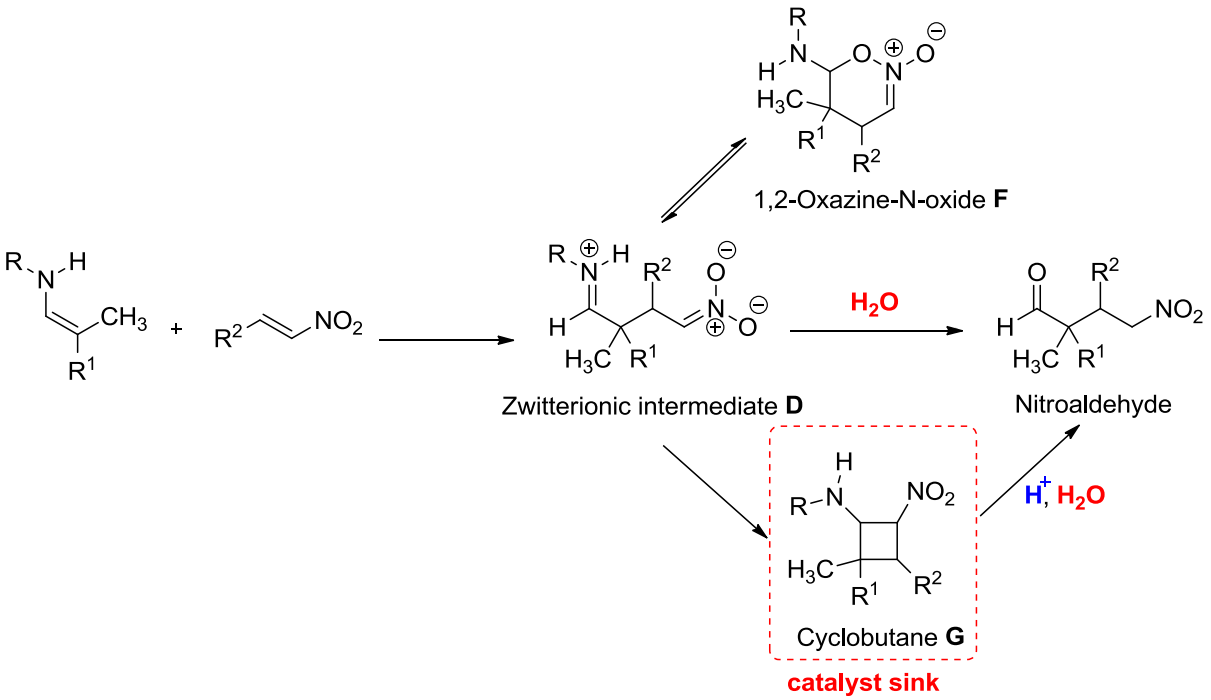


Scheme 2.8. Proposed mechanism for the addition of α,α-disubstituted aldehydes to nitroalkenes catalyzed by **II.8**.

The authors performed several experiments to explore catalyst deactivation. Incubation of the catalyst and the aldehyde for 12 hours prior to nitroalkene addition had no effect on the product yield whereas, incubation of the catalyst and the nitroalkene for 12 hours prior to aldehyde addition resulted in lower product yield. The authors attribute this to the primary amine-catalyzed nitroalkene polymerization which, they claim would not lead to catalyst deactivation. Monitoring the reaction of 2-phenylpropionaldehyde with 1-nitrohex-1-ene catalyzed by **II.8** (20 mol%) showed that substrate conversion stopped after 24 hours and both starting substrates could be recovered as well as the product. Based on these observations two possible scenarios were suggested: product inhibition or catalyst deactivation. Experiments run in the absence and presence of added Michael adduct to the reaction mixture gave similar yields ruling out product inhibition. On the other hand, catalyst deactivation might occur either by poisoning or decomposition pathways. Addition of a second 20 mol% catalyst to the stalled reaction mixture led to complete conversion after 24

hours and Michael product could be isolated in 92% yield revealing that catalyst was not deactivated by build-up poisons.[5b]

Therefore, it was postulated that decomposition of an intermediate in the catalytic cycle was responsible for the catalyst deactivation. Zwitterionic intermediate **D** may undergo hydrolysis to nitro aldehyde product or collapse to 1,2-oxazine-*N*-oxide **F** or cyclobutane **G** intermediates. However, 1,2-oxazine-*N*-oxides such as **F**, have been shown to undergo hydrolysis under atmospheric moisture while cyclobutanes analogous to **G** require strong aqueous acidic conditions such as 1 M HCl **(Scheme 2.9)**.[11] Regarding this, the beneficial role of water in the catalytic cycle is interpreted as *''increasing turnover by eliminating potential catalyst sink formation of **F** and accelerating imine **E** hydrolysis''*.[5b]



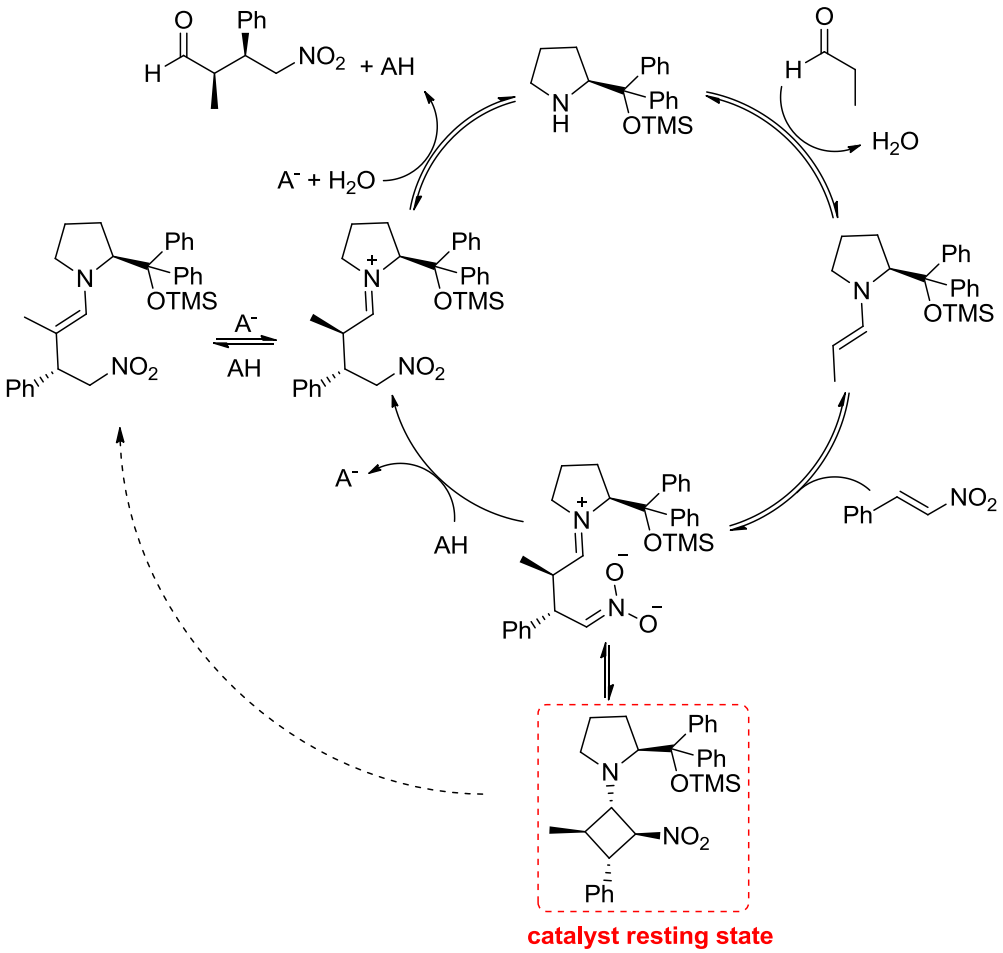
Scheme 2.9. Possible deactivation pathway suggested by Jacobsen.

Whereas under these catalytic conditions cyclobutane **G** is unlikely to undergo hydrolysis thus, its irreversible formation is assumed to be responsible for catalyst deactivation. In addition, mass spectral analysis of the only isolated side product was consistent with the cyclobutane intermediate **G** although NMR analysis of this side product was not informative due to peak broadening caused by hydrogen bonding.[5b]

[11] (a) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162-172. (b) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2331-2335.

However, Blackmond *et al.* based on their aforementioned mechanistic studies on the same reaction (see page 43), disagree this postulate. In their report, it is stated that the lack of NMR spectroscopic evidence especially for the C-H proton on the cyclobutane ring connected to the NO_2 group argues its presence. Moreover, mass spectroscopic evidence that Jacobsen *et al.* showed is questionable since the mass of the cyclobutane **G** is the same as the product imine **E**.[10]

In another mechanistic study reported by Blackmond *et al.,* in the conjugate addition of propanal to nitrostyrene catalyzed by diaryl prolinol ethers, a similar cyclobutane intermediate was identified by *in situ* monitoring of reaction by NMR spectroscopy. Further detailed NMR studies confirmed that unlike Jacobsen's postulate, cyclobutane formation from this catalyst and linear aldehydes is a reversible step and easily converts to product enamine after the limiting substrate is fully reacted and therefore it is not an irreversible sink. It is the reversibly formed catalyst resting state and acts as a key intermediate in the maintenance of high stereoselectivity. The catalytic cycle proposed is shown in **Scheme 2.10.**[12]



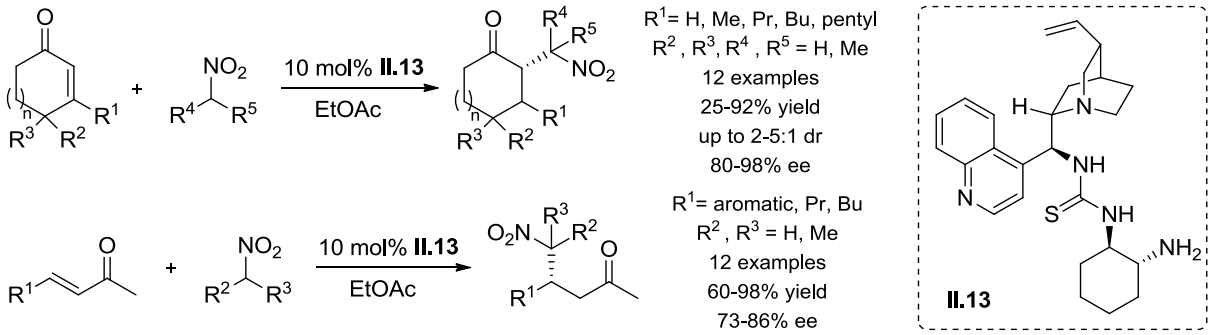
Scheme 2.10. Proposed catalytic cycle for the addition of linear aldehyde to nitrostyrene.

[12] Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822-8825.

2.4. OTHER ACCEPTORS IN PAT CATALYZED MICHAEL ADDITION REACTIONS

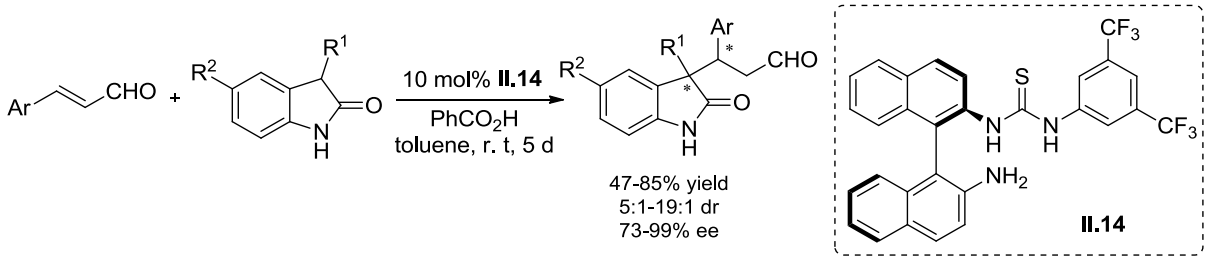
- **α,β-Unsaturated ketones and aldehydes as acceptors**

In 2008, Liang, Ye and co-workers used multifunctional primary amine thiourea catalyst **II.13** derived from cinchona alkaloid and 1,2-diaminocyclohexane in the Michael addition of nitroalkanes to cyclic and acyclic enones **(Scheme 2.11)**. The authors propose a multifunctional activation mode: tertiary amine deprotonates the pronucleophile, thiourea moiety arranges the nucleophile *via* hydrogen bonding and primary amine activates the enone by the formation of iminium ion. [13]



Scheme 2.11. Asymmetric conjugate addition of nitroalkanes to enones.

In 2009 for the first time, Melchiorre and coworkers applied primary amine-thiourea catalysts for iminium ion activation of α,β-unsaturated aldehydes. The asymmetric conjugate addition of oxindoles to enals generating chiral products with quaternary and tertiary stereocenters with high efficiency and stereo control was demonstrated (**Scheme 2.12)**. However, without acidic additive, the reaction was not efficient (39% yield, 97% ee).[14]



Scheme 2.12. Melchiorre's primary amine thiourea and its application.

A plausible bifunctional activation mode was suggested where the thiourea moiety activated the oxindole by stabilizing its enol form while the primary amine functionality activated the unsaturated aldehyde through iminium ion formation.[14]

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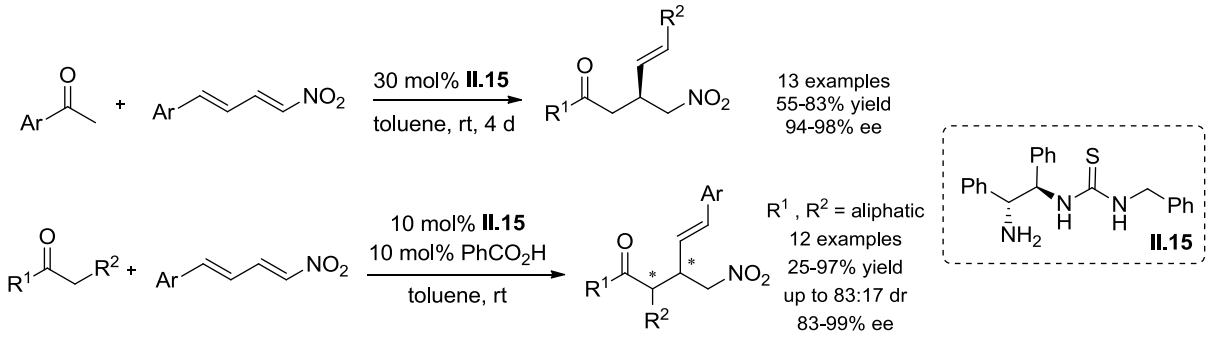
[13] Li, P.; Wang, Y.; Liang, X.; Jinxing, Y. *Chem. Commun.* **2008**, 3302-3304.

[14] Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2009**, *15*, 7846-7849.

- **Nitro dienes as acceptors**

Wu and co-workers applied for the first time primary amine-thioureas for Michael addition reaction of aryl methyl ketones to aromatic nitro dienes. This reaction required high catalyst loadings (30 mol%) and prolonged reaction times to give the adduct in moderate to high yields (55-83%) and in excellent enantioselectivities (94-98%).[7e]

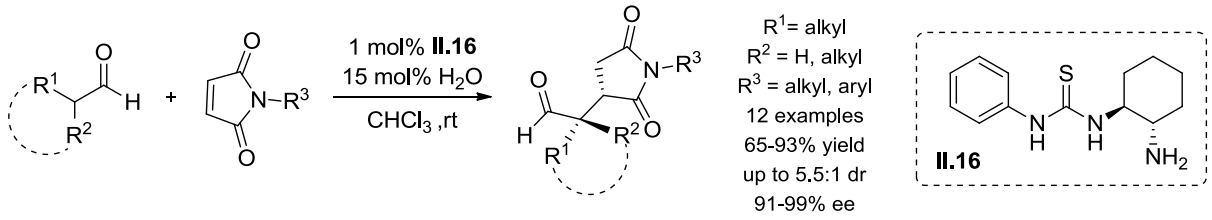
Later on, the same research group extended this application to the use of aliphatic ketones as pronucleophiles in the presence of benzoic acid. The use of benzoic acid as co-catalyst improved the catalyst performance allowing to reduce the catalyst loading from 30 to 10 mol% . Enantioselectivities up to 99% and yields up to 97% were obtained **(Scheme 2.13)**.[7f]



Scheme 2.13. The PAT catalyzed conjugate addition of ketones to nitro dienes.

- **Maleimides as acceptors**

In 2010, Wang and coworkers were the first to develop the conjugate addition of α,β-unsaturated aldehydes to maleimides catalyzed by a simple primary amine-thiourea. The use of only 1 mol% catalyst in combination with water additive (15 mol%) afforded biologically useful chiral α-branched succinimides bearing two contiguous quaternary and/or tertiary stereogenic centers in high yields and excellent enantioselectivities **(Scheme 2.14)**. [15]

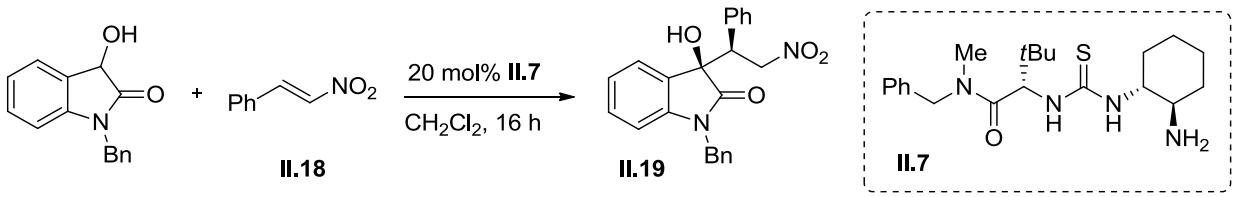


Scheme 2.14. Conjugate addition of α,β-unsaturated aldehydes to maleimides.

[15] Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979-7982.

2.5. EFFECT OF CONCENTRATION IN (THIO)UREA CATALYSIS

Jacobsen's primary amine thiourea catalyst **II.7** was used by the Melchiorre group for the asymmetric Michael addition of dioxindoles to β-substituted nitroalkenes. However, an unusual correlation was observed between reaction temperature, concentration and enantioselectivity: *ee* values of the product **II.19** decreased at lower temperatures and higher concentrations. This behavior was then rationalized by self-aggregation of the catalyst **II.7** according to DOSY (diffusion ordered spectroscopy) and ^{1}H dilution NMR spectroscopy experiments.[16]



[II.18]$_0$ M	[II.7] M	dr (syn/anti)	ee% (major)	ee% (minor)	D (10^{-10}m^{2}s^{-1})
1	0.2	1.6:1	63	23	**3.23**
0.25	0.05	2.5:1	89	43	**9.74**
0.05	0.01	4:1	94	57	**12.02**

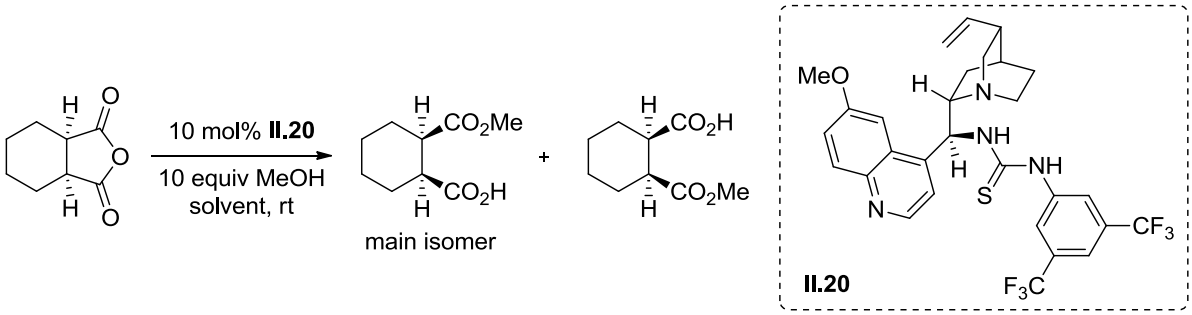
Table 2.5. DOSY NMR spectroscopy experiments.

^{1}H NMR dilution experiments of **II.7** were carried out in CH_2Cl_2. Upon dilution (0.2 to 0.01 M), concentration dependencies were observed for the chemical shifts of –C(=S)N(H) proton and $–NH_2$ protons. Additionally, DOSY NMR spectroscopy experiments showed that the diffusion coefficients (D) of the catalyst **II.7** significantly decreased upon increasing concentration which correlates with *ee* values **(Table 2.5)**. This indicated that the self-association of the catalyst plays an important role in determining the stereoselectivity, and in turn, that under more diluted reaction conditions the catalyst monomeric form is favored which is the most selective species. According to these results, more diluted reaction conditions (**[II.18]$_0$**= 0.05 M) were selected as optimal conditions to further examine the scope of this Michael addition by screening a variety of substrates.[16]

Similarly, the Song group investigated the methanolysis of *meso*-cyclic anhydrides with a quinine derived bifunctional thiourea organocatalyst **II.20** and observed unusual effects of concentration, temperature, and solvent on enantioselectivity. For the enantioselective methanolysis reaction shown in **Scheme 2.15**, when the amount of reaction solvent was increased from 2.5 mL to 80 mL, keeping all other conditions the same, the enantioselectivity increased from 82% to 96% **(Figure 2.3)**. Moreover, enantioselectivity increased (77% to 82% *ee*) upon raising the reaction temperature from -20 to 25 °C. Under dilute conditions with aprotic hydrogen bond accepting solvents (THF, dioxane, Et_2O) highest

[16] Retini, M.; Bergonzini, G.; Melchiorre, P. *Chem. Commun.* **2012**, *48*, 3336-3338.

enantioselectivities were obtained while with toluene lower enantioselectivities were observed.[17]



Scheme 2.15. Enantioselective methanolysis of *meso*-cyclic anhydride.

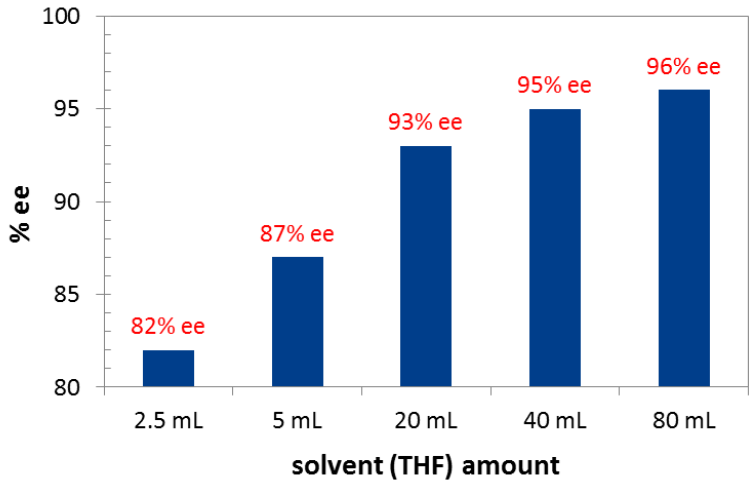
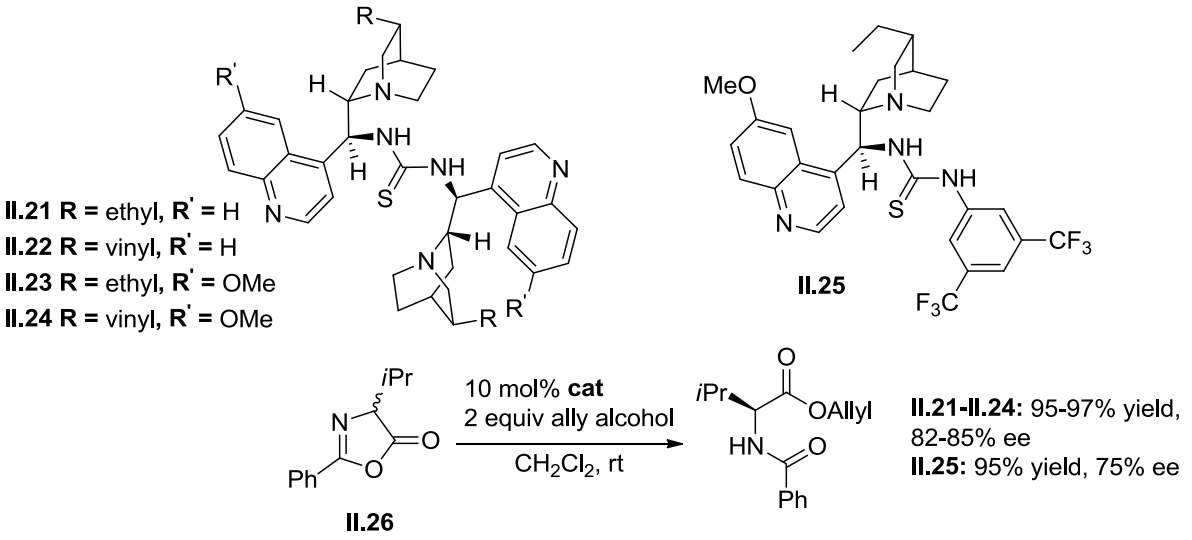


Figure 2.3. Effect of concentration on the enantioselective methanolysis.

In the light of these experimental results, the authors suggest that catalyst **II.20** may exist mainly in dimeric (or higher) form at high concentrations, low temperatures and with non-coordinating solvents like toluene. On the other hand, under dilute conditions, ambient temperature and with coordination solvents like THF the catalyst mainly may exist as the monomeric form which is responsible for the high enantioselectivities. This hypothesis was supported by ^{1}H NMR dilution experiments of the catalyst **II.20** in d_8-toluene which showed concentration dependencies for the chemical shift of –C(=S)N(H)-Ar proton upon dilution (212 mM to 10 Mm). [17]

[17] Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun*. **2008**, 1208-1210.

A fine example of prevention of catalyst aggregation would be another investigation conducted by the Song group, in which self-association free dimeric bifunctional thiourea organocatalysts **II.21-II.24** were reported to achieve concentration independent enantioselectivity in dynamic kinetic resolution (DKR) of racemic azlactones **(Scheme 2.16)**.[18]



Scheme 2.16. Enantioselective DKR reaction of racemic azlactone.

They performed the DKR of **II.26** in the presence of dimeric catalyst **II.21** and the corresponding monomeric catalyst **II.25** at various concentrations ($[\mathbf{II.26}]_0$ = 0.1-1.0 M). As depicted in **Figure 2.4**, the enantioselectivity of the dimeric catalyst **II.21** was not dependent on concentration and even under highly concentrated conditions ($[\mathbf{II.26}]_0$ = 1.0 M) the enantioselectivity could be maintained high while monomeric catalyst **II.25** displayed lowered enantioselectivities at increased concentrations.[18]

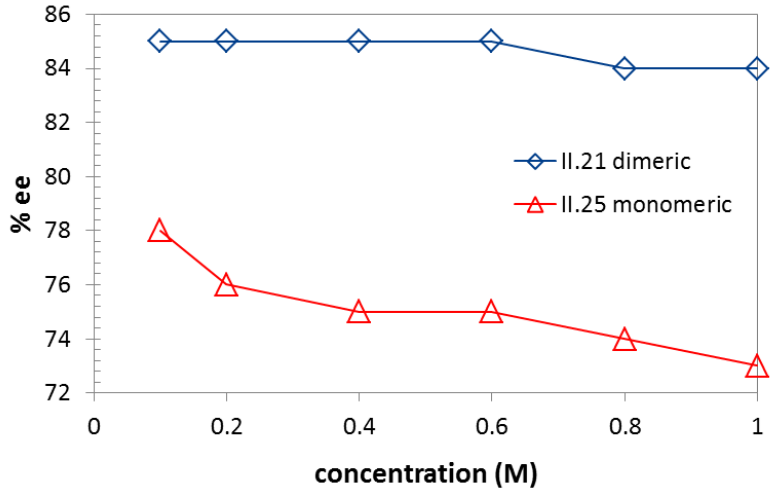


Figure 2.4. Effect of concentration on the enantioselectivity in the DKR reaction.

[18] Oh, J. S.; Lee, J. W.; Ryu, T.H.;Lee, J. H.; Song, C. E. *Org. Biomol. Chem.* **2012**, *10*, 1052-1055.

These results together with ^{1}H NMR dilution experiments of catalyst **II.21**, showing no concentration dependencies for the chemical shift of the thiourea proton upon dilution (1.0 to 0.1 M), demonstrated that the catalyst does not self-aggregate to any appreciable extent in solution. Moreover, single crystal X-Ray analysis showed that also in solid state there is no hydrogen bonding interaction between the thiourea NH protons and the thiourea sulfur atom.[18]

As a summary, urea and thiourea based bifunctional organocatalysts may suffer from self-aggregation due to their hydrogen bonding ability. This type of molecules can form dimers or even higher aggregates in solution which act as distinct catalyst species than the monomer, therefore, showing a strong dependence of stereoselectivity and reactivity on concentration, temperature as well as the reaction solvent. Understanding the self-association phenomena would make it possible to optimize the reaction conditions (temperature, solvent, concentration, catalyst loading etc.) and to well-design the catalyst structure which might suppress or even prevent the catalyst aggregation and eventually improve the catalyst performance.

2.6. AIM OF OUR STUDY

The examples presented in this introduction demonstrate that additives (acid and water) play an important role in Michael additions catalyzed by chiral primary amine thioureas (PATs). However, the role of these additives in this type of reactions has not been studied in detail and remains elusive. In this work, we aimed to reveal the mechanistic roles of water and acetic acid in the catalytic system AcOH/water/toluene developed by the Tsogoeva's group (see section 2.2). Quantitative ^{1}H NMR was chosen as the tool for the continuous monitoring of the reaction. **(Paper A)**

In the second section of this chapter, we aimed at exploring the effect of concentration on PAT catalyzed Michael addition reaction to *trans*-β-nitrostyrene in the context of our mechanistic study, and trying to develop a practical method for PAT catalyzed Michael additions. **(Paper B)**

PAPER A

Deciphering the Roles of Multiple Additives in Organocatalyzed Michael Additions

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Paper A- Part of the kinetic studies were performed at the Department of Chemistry, Imperial College London under the supervision of Dr. Jordi Burés in the course of a short stay research visit.

UNIVERSITAT ROVIRA I VIRGILI
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Zeynep Inci Günler

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Deciphering the roles of multiple additives in organocatalyzed Michael additions†

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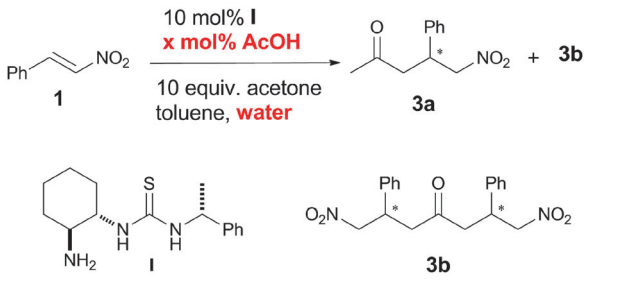
The synergistic effects of multiple additives (water and acetic acid) on the asymmetric Michael addition of acetone to nitrostyrene catalyzed by primary amine-thioureas (PAT) were precisely determined. Acetic acid facilitates hydrolysis of the imine intermediates, thus leading to catalytic behavior, and minimizes the formation of the double addition side product. In contrast, water slows down the reaction but minimizes catalyst deactivation, eventually leading to higher final yields.

Organocatalyzed asymmetric Michael additions are widely employed in organic synthesis and are useful benchmarks for the development of new catalysts.[1] Among thiourea-based bifunctional organocatalysts, primary amine-thioureas (PAT) gain popularity because of their easy preparation, versatility and effectiveness.[2] Moreover, the presence of primary amines in the active sites of many enzymes (such as class I aldolases and pyridoxal phosphate dependent enzymes, among many others) contributes to the general interest in this kind of catalysis.[3] To highlight the importance of PAT, it is worth mentioning that after the seminal work by Tsogoeva[4] and Jacobsen[5] in 2006, a great variety of catalyst structures and reaction conditions have been described using ketones as nucleophiles, which had remained challenging substrates up to then.[2a]

We hypothesized that besides the basic, catalytic scaffold (the chiral primary amine-thiourea), reaction conditions and additives would play a fundamental role in the catalytic event, definitely contributing to the yield and stereoselectivity.[6] For example, the role of water in proline-catalyzed aldol reactions has long been recognized to have a deep impact on yield, affecting both on-cycle and off-cycle equilibria.[7] Acid additives have also been found to be effective, and often essential, in many organocatalyzed reactions.[8] In this respect, the beneficial effect of acid additives and the presence of water in PAT catalysis were recognized from the beginning too, especially when dealing with more challenging substrates like ketones or α,α-disubstituted aldehydes. Hence, Tsogoeva developed an AcOH/water/toluene system,[4a] whereas Jacobsen used benzoic acid in toluene at high concentration of nitrostyrene (2–5 M) to achieve similar results with ketones.[5a] However, in the addition of α,α-disubstituted aldehydes, the use of 10 equiv. of water was required, without adding acid.[5b]

Altogether, the simultaneous effect of acid and water on organocatalyzed Michael additions of ketones has not been addressed exhaustively and remains an elusive question from a mechanistic point of view, although it is clear that both additives have a fundamental impact on the catalytic outcome (Scheme 1). Studying in detail the roles of multiple additives used simultaneously in a catalytic asymmetric reaction is both a challenge and a requirement to understand the catalytic system as a whole.

There are few mechanistic studies on PAT catalyzed Michael additions. The role of reversibility in the reactions of α,α-disubstituted aldehydes with nitrostyrenes mediated by PAT was assessed recently.[9] Some theoretical studies leading to the characterization



Scheme 1 Conjugate addition of acetone to nitrostyrene catalyzed by 10 mol% of PAT catalyst **I**.

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† Electronic supplementary information (ESI) available: Characterization of products and intermediates, detailed quantitative ^{1}H NMR analyses, and additional kinetic data. See DOI: 10.1039/c6cc01026a

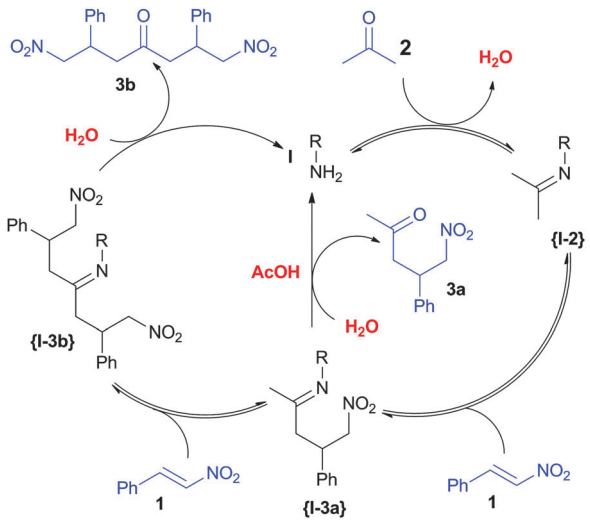
of transition states in combination with MS studies to identify potential intermediates in the catalytic cycle have been carried out too.[4b,10] We disclose in this Communication our findings on how added water and acid have a decisive effect on the stability and turnover of PAT catalysts.

We selected for this study Tsogoeva's PAT catalyst **I**. Under the originally developed conditions, which comprise 15 mol% catalyst loading, 15 mol% of AcOH and 2 equiv. of water, it affords adduct **3a** in 86% yield and 86% ee.[4b] We devised three sets of experimental conditions to prove our hypothesis and clarify the roles of water and acid: performing the reaction (A) without adding acid or water, (B) adding acetic acid but no water, and (C) adding acid and water. We then performed a careful re-examination of the outcome of Michael additions with catalyst **I** by monitoring the reactions by quantitative ^{1}H NMR. Nitrostyrene **1**, the Michael adduct **3a**, the double addition side product **3b**, and several imine-catalyst intermediates were characterized and their concentrations determined under conditions A, B and C. Our proposed catalytic cycle is shown in Scheme 2.

In the absence of added water and AcOH (conditions A), the catalyst reacted indeed with the substrates and a certain amount of nitrostyrene (*ca.* the molar amount of the catalyst) was consumed very fast. Following this event, some double addition imine intermediate **{I-3b}** was formed. Under these conditions, we detected product **3a** at even lower concentration, as well as traces of imine **{I-2}**. Overall, the reaction was sluggish and the concentration of all the species detected remained constant after 16 hours (see the ESI,† pages S11 and S14–S24). These data are important because they show that reaction intermediates indeed form rapidly without the addition of either acid or water. In fact, the C–C bond forming reaction has already occurred at this point.

However, no hydrolysis of intermediates **{I-3a}** and **{I-3b}** took place at a significant rate, and thus the formation of free products and catalyst turnover were minimal. Nevertheless, turnover occurred just upon addition of acetic acid in the absence of added water (conditions B). In contrast, with 1 equivalent of water added but without AcOH, essentially only the formation of imine intermediate **{I-3b}** and traces of free product **3a** could be detected (see the ESI,† page S32), as in the experiment under conditions A. It is clear that the main role of acetic acid is to facilitate hydrolysis of **{I-3a}** and therefore turnover.[11] A minimum amount of AcOH is essential for the Michael addition to take place, 5 mol% being the optimal amount (see the ESI,† pages S8–S10, S12 and S25–S33). Finally, upon addition of 1 equivalent of water besides AcOH (conditions C), the reaction took place smoothly and **3a** was isolated in high yield. Reaction monitoring by ^{1}H NMR was able to detect the presence of intermediates **{I-2}**, **{I-3a}** and **{I-3b}** as well, albeit at concentration much lower than under conditions B. In this sense it is worth mentioning that the total concentration of the detected catalytic intermediates for conditions B varies from 0.014 to 0.006 M, whereas it stays between 0.005 and 0.003 M for conditions C (see the ESI,† pages S12 and S13).

In Fig. 1A, the concentration of nitrostyrene **1** and product **3a** *vs.* time is shown for experiments run under conditions B and C (1 equiv. of water added). At the beginning there was a sharp decrease in the concentration of **1** in all cases. This regime corresponds to the initial reaction of the catalyst with the substrates to form stable intermediates as under conditions A. Afterwards, a second regime dominated the process throughout the rest of the reaction.



Scheme 2 Interrelated processes in the asymmetric Michael addition of acetone to **1** catalyzed by PAT **I**: (1) the regular catalytic cycle leading to **3a**; (2) the extended catalytic cycle leading to **3b**.

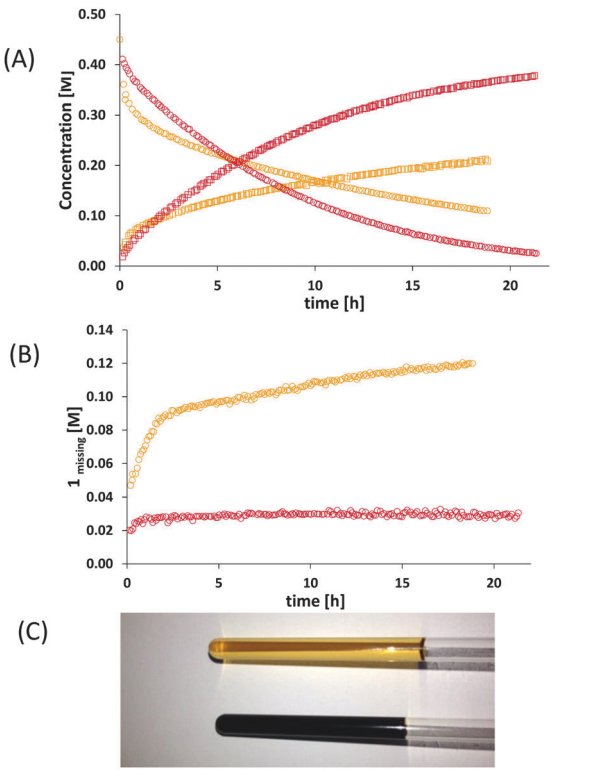


Fig. 1 Michael addition of acetone to nitrostyrene at $[\mathbf{1}]_0$ = 0.45 M using 10 mol% catalyst **I**, 5 mol% AcOH, and 10 equiv. acetone, in toluene at rt, (A) reactions run under conditions B (orange) and C (1 equiv. added water, red). [**1**], circles; [**3a**], squares. (B) "Missing" nitrostyrene concentration *vs.* time, under conditions B (orange) and C (red). (C) Picture showing the final appearance of reactions run under conditions B (bottom tube) and C (upper tube).

It was also apparent that water had an inhibiting effect on the initial regime that, at least in part, we attributed to a shift of the equilibrium of the formation of acetone imine **{I-2}**. However, the formation of product **3a** was clearly superior to the rest of the reaction under conditions C (Fig. 1A). Therefore, since higher conversion was achieved at the end of the reaction in the presence of added water, it was suggested that catalyst deactivation or product inhibition could take place in its absence. Nevertheless, product inhibition was discarded as a potential source of loss of catalytic activity (see the ESI,† page S37). We hypothesized then that nitrostyrene being a strong Michael acceptor could lead to undesirable side reactions and catalyst deactivation through the formation of polymers initiated by a catalytic intermediate.[12,13]

The formation of side product **3b** was minimal under both conditions B and C (always below 4 mol% formation), and depended essentially on the amount of AcOH present. Increasing amounts of AcOH decreased the formation of **3b** under both conditions B and C, as it is shown in the ESI† (page S10). Finally, as a result of this evaluation, our optimized reaction conditions comprise the use of 10 mol% of catalyst **I**, 5 mol% of AcOH and 1 equiv. of water. Adduct **3a** can be then isolated in 94% yield and 90% ee. Enantiomeric excess does not change along the reaction (see the ESI,† pages S4 and S5).

We then performed the mass balance for nitrostyrene to quantify the total amount of catalytic species in the cycles (eqn (1)). This approach has the advantage that all the species (detectable and not detectable) can be analyzed globally. The "missing" nitrostyrene concentration was plotted *vs.* time (Fig. 1B), showing the pre-steady-state regime, and afterwards a steady-state regime where the concentration of intermediates (which would include deactivated catalytic species by nitrostyrene) was essentially constant under conditions C. In the absence of added water, though (conditions B), a slight but constant increase in the total concentration of intermediates was appreciated, which can be attributed to the continuous formation of deactivated species containing nitrostyrene. Remarkably, the concentration of catalytic intermediate species that contain nitrostyrene was near four times smaller in the presence of "added water".

$$[\text{intermediates}] \approx [\mathbf{1}]_{\text{missing}} = [\mathbf{1}]_0 - [\mathbf{1}]_t - [\mathbf{3a}]_t - 2*[\mathbf{3b}]_t \quad (1)$$

In the presence of "added water" (conditions C), the concentration of "missing" nitrostyrene was smaller than the total concentration of the catalyst (*ca.* 0.028 M *vs.* $[\mathbf{I}]_0$ = 0.045 M), thus showing that up to 38% of the overall catalyst is present as free catalyst and acetone imine **{I-2}** (more precisely, catalytic species that do not contain nitrostyrene). This can occur because the hydrolysis of product imine **{I-3a}** is favored, the formation of imine **{I-2}** is disfavored, or both simultaneously. In contrast, high concentration of intermediate species containing nitrostyrene, actually slightly higher than twice the total catalyst concentration, was observed under conditions B. This suggested that several molecules of **1** might be involved in those intermediates, in accordance with its tendency to polymerize.[12,13] Finally, we must add that under "added water" conditions (conditions C), the reaction mixture remained a pale yellow solution, whereas a dark, turbid solution appeared throughout the time when no extra water was added, indicating the formation of some unknown side product (Fig. 1C and ESI,† page S34). In any case, all our attempts to isolate and characterize the deactivated species through NMR and MS techniques failed, likely due to its oligo- or polymeric nature.

The stabilizing effect of water was further checked by running a reaction under conditions C. Upon completion (*ca.* 21 h), nitrostyrene was added and its concentration was re-adjusted to 0.45 M.[14] A pre-steady-state regime leading to a sharp decrease in the concentration of **1** was observed again, proving the presence of a free, fully operative catalyst at the end of the reaction. However, catalyst deactivation was still observed since the consumption of nitrostyrene **1** was slower than in the first reaction run (Fig. 2A).

We then pre-treated catalyst **I** with nitrostyrene for 3 hours before acetone was added, performing the reaction in the presence of added water and AcOH (conditions C). The reaction behaved as in the regular experiments, showing an identical reaction profile (see Fig. 2B). Since higher catalyst deactivation did not take place, we can ascertain that the free catalyst does not get deactivated by reaction with nitrostyrene, and that deactivation must then take place through some of the other catalytic intermediates of our proposed catalytic cycle depicted in Scheme 2 (see also the ESI,† pages 35 and 36).

As a result of this interplay, under optimal conditions (5 mol% AcOH and 1 equiv. of added water), 38% of the overall catalyst in the reaction medium exists as catalytic species that do not contain nitrostyrene, since the formation of **{I-2}** slows down

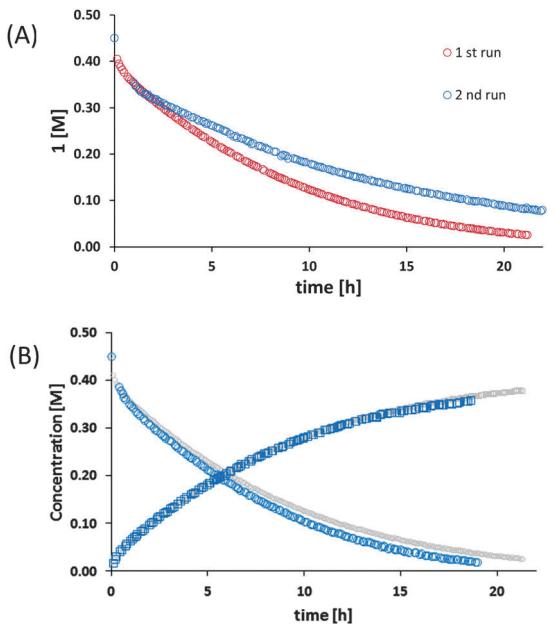


Fig. 2 Michael addition of acetone to nitrostyrene at $[\mathbf{1}]_0$ = 0.45 M using 10 mol% catalyst **I**, 5 mol% AcOH, 10 equiv. acetone and 1 equiv. water, in toluene at rt, (A) time-adjusted profile after addition of nitrostyrene up to the initial concentration (blue) after 21 hours of reaction (red). (B) Catalyst **I** pre-treated with **1** for 3 hours before addition of acetone ([**1**], blue circles, [**3a**], blue squares). In grey, original reaction profiles without pre-treatment (see also Fig. 1A).

and the hydrolysis of **{I-3a}** accelerates. At the same time, competitive deactivation of the catalyst is minimized. This situation is indeed similar to the case of proline-catalyzed aldol reactions, where parasitic off-cycle catalyst deactivation reactions were minimized by water, while the relative concentration of catalytic species decreased by shifting the equilibria towards proline.[7a,15]

In summary, we have determined the roles of acetic acid and water in the asymmetric Michael addition of acetone to nitrostyrene. Acetic acid provides turnover to the PAT catalyst by facilitating the hydrolysis of imine intermediate **{I-3a}**. If not present, the PAT catalyst ends up as the catalyst-double addition product imine **{I-3b}**, and little hydrolysis to product **3a** takes place. According to this, AcOH is also essential to minimize the double addition side product **3b**. On the other hand, the presence of water in the reaction medium is even more important: although it slows down the reaction, water minimizes irreversible catalyst deactivation by nitrostyrene and stabilizes the productive reaction pathway. This reaction becomes a fine example of minimization of catalyst deactivation, which leads eventually to higher conversion. Water and AcOH affect the on-cycle and off-cycle reactions present in PAT catalysis in a subtle but decisive way, and, therefore, must be carefully controlled. Studies on synthetic applications of PAT catalysts are underway in our laboratories and will be reported in due course.

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ELECTRONIC SUPPLEMENTARY INFORMATION

Deciphering the Roles of Multiple Additives in Organocatalyzed Michael Additions**

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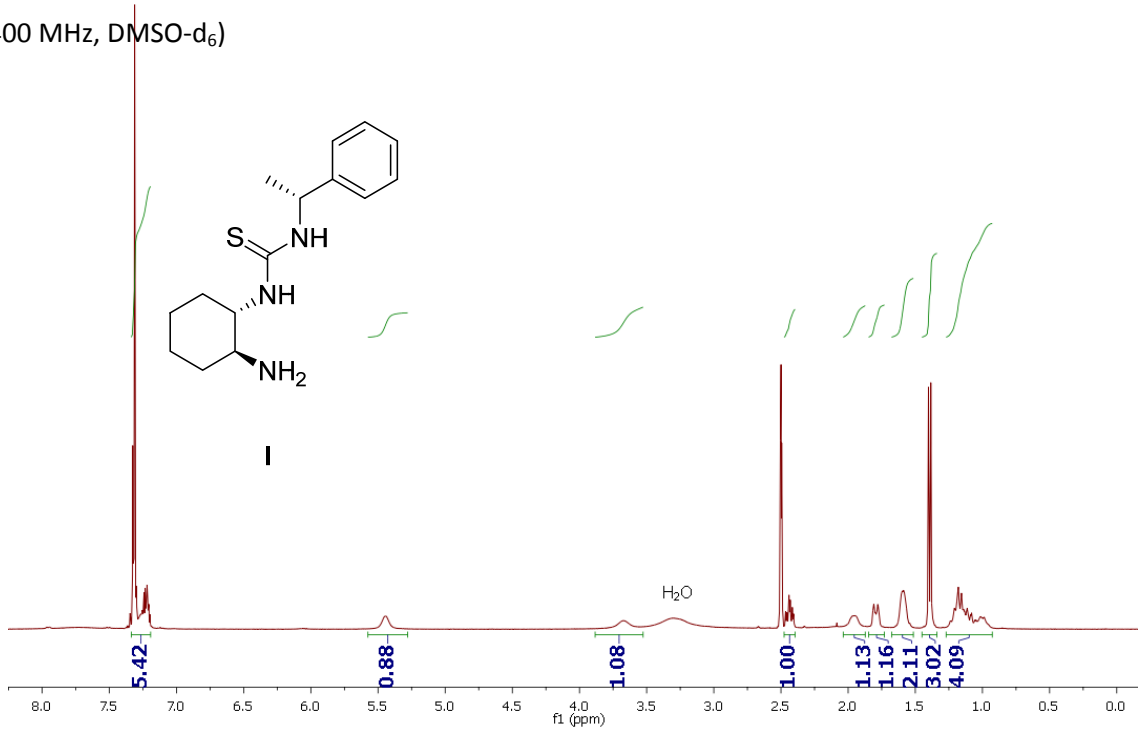
1. General

All the reagents were purchased from Aldrich or TCI and used without any further purification. The solvents were directly used from bottle unless otherwise is indicated. Anhydrous solvents were obtained from a Solvent Purification System. TLC chromatography was performed on silica gel 60 F_{254} aluminum sheets. Flash chromatography was performed using silica gel P60 (200-500 mesh). HPLC analyses were performed using a Shimadzu Prominence modular equipment with autosampler and UV-Vis detector. The characterization of products by NMR was performed on an automated Varian VNMRS 400 MHz equipped with a One NMR Probe. ^{1}H NMR kinetic experiments were recorded on Bruker DRX-400 MHz equipped with a BBFO 5 mm Prove or Bruker 500 MHz equipped with a cryoprobe.

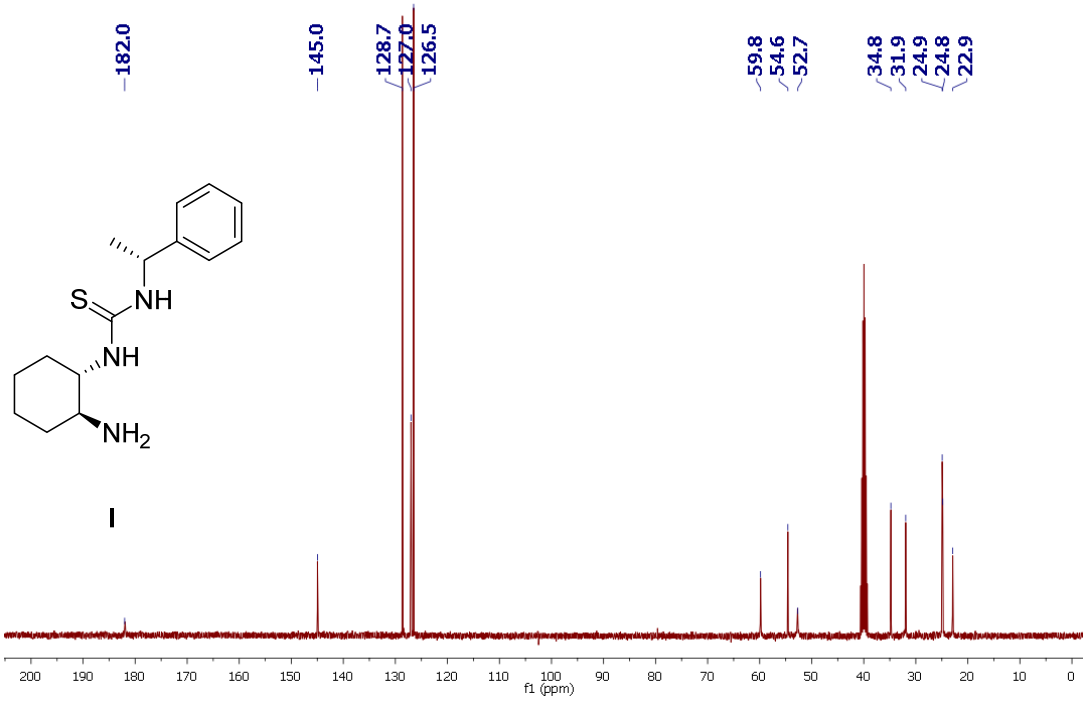
2. Preparation and NMR spectra of catalyst I

Catalyst **I** was prepared according to a described procedure and matches literature data.[1] Unprotected (*1S,2S*)-diaminocyclohexane was used instead of the mono Boc-protected diamine to avoid potential acid contamination during the deprotection step.

(400 MHz, DMSO-d_6)

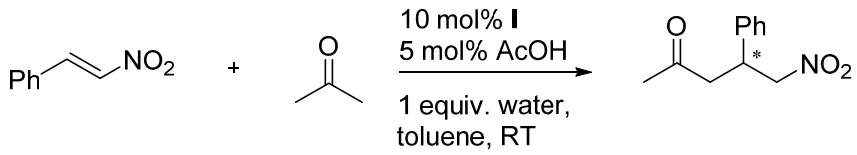


(100 MHz, DMSO-d_6)



[1]S. B. Tsogoeva, S. W. Wei;*Chem. Commun.*,**2006**, 1451-1453.

3. EnantioselectiveMichael addition of acetone to nitrostyrene

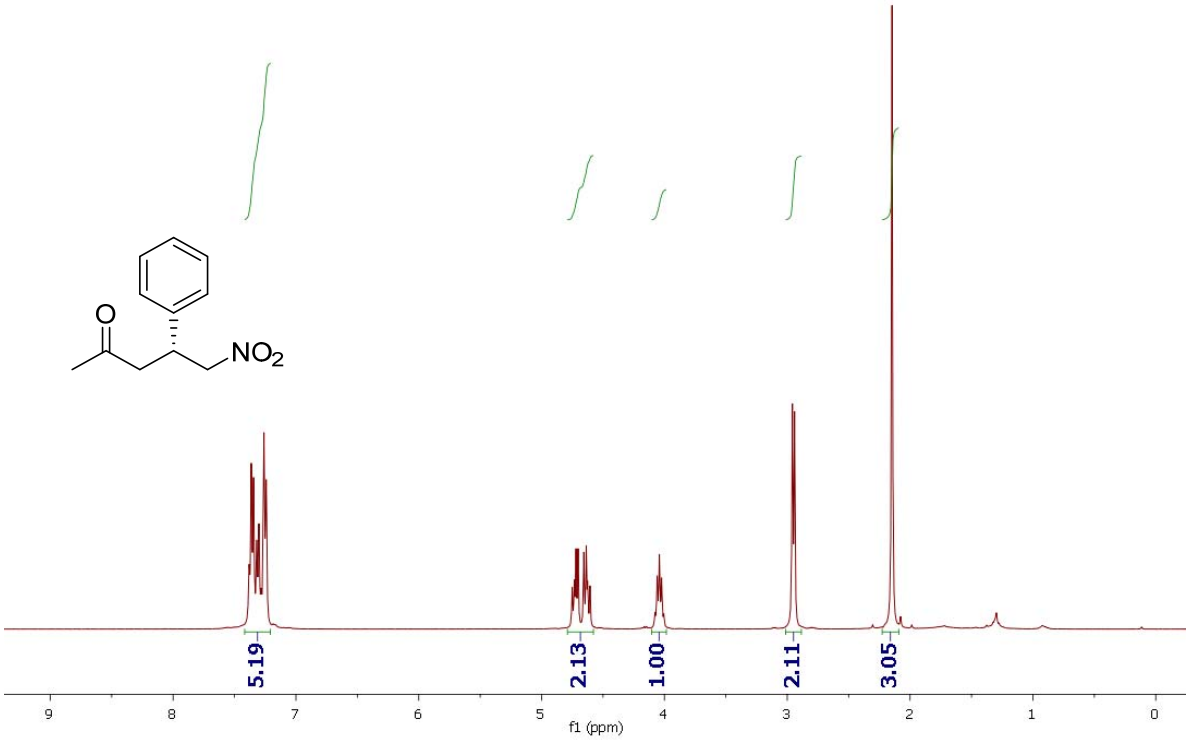


$[1]_0$ = 0.15 M **2** **3a**

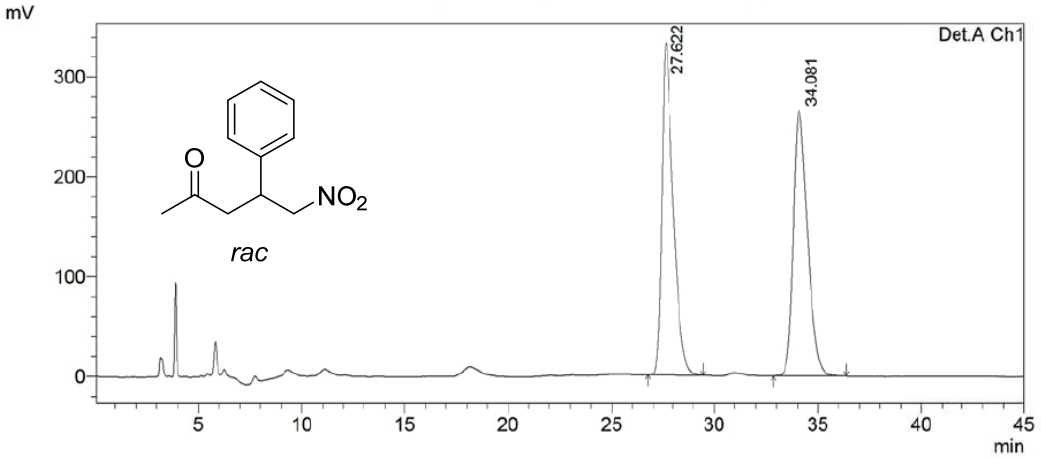
In a vial, catalyst **I** (0.1 equiv., 0.0335 mmol, 9.3 mg) and nitrostyrene **1** (1 equiv., 0.335 mmol, 50 mg) were weighed and dissolved in 1.9 mL of toluene. To this clear solution, 0.05 equiv. of AcOH was added (using 100 µL of a stock solution of 0.168 mmol, 10 µL AcOH in 1 mL toluene). Finally, 1 equiv. of water and 10 equiv. of acetone were added (using 0.25 mL of a stock solution of 0.335 mmol, 24 µL water in 1 mL acetone). The reaction was stirred at room temperature for 24 hours. To quench the reaction, water was added to the reaction vial and the organic phase was extracted with EtOAc(x3). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude mixture was directly analyzed by ^{1}H NMR to determine the conversion. Purification by flash chromatography (EtOAc:Hexane= 1:4) afforded the product **3a**. Enantiomeric excess was determined by HPLC by comparison with the authentic racemic compounds (Phenomenex Lux 5u-Amylose-2 column,Hexane:*i*PrOH= 90:10, 1 mL/min, 209 nm). HPLC samples were directly prepared from the crude reaction mixture.

3.1. ^{1}H NMR spectrum of Michael adduct 3a

(400 MHz, $CDCl_3$)

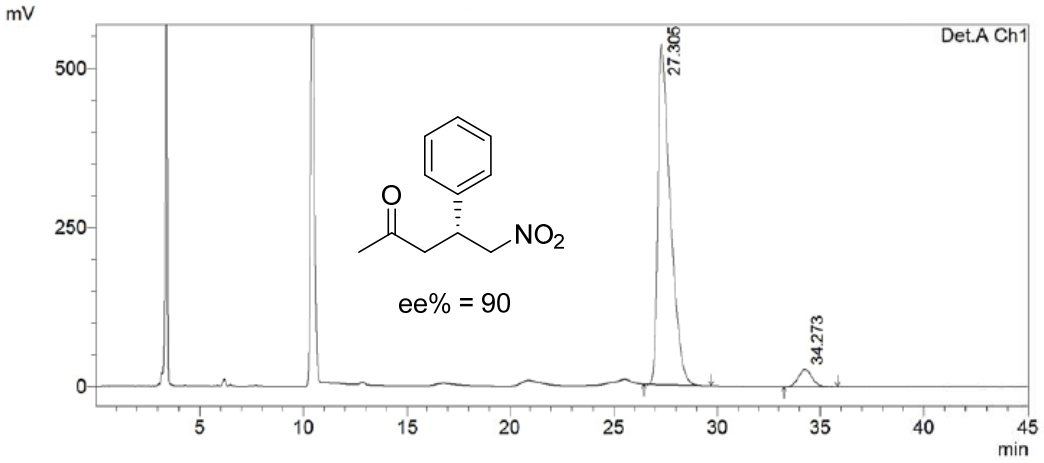


3.2. HPLC chromatograms of Michael adduct 3a



Detector A Ch1 209nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.622	13392042	332685	51.396	55.601
2	34.081	12664406	265661	48.604	44.399
Total		26056448	598346	100.000	100.000



Detector A Ch1 209nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.305	22544256	535394	94.879	95.185
2	34.273	1216824	27084	5.121	4.815
Total		23761079	562479	100.000	100.000

The *ee* value was measured along the reaction. It stays constant over time.

time (h)	ee%
1.3	90
3	90
5	90
24	90

4. Quantitative ^{1}H NMR kinetic analysis

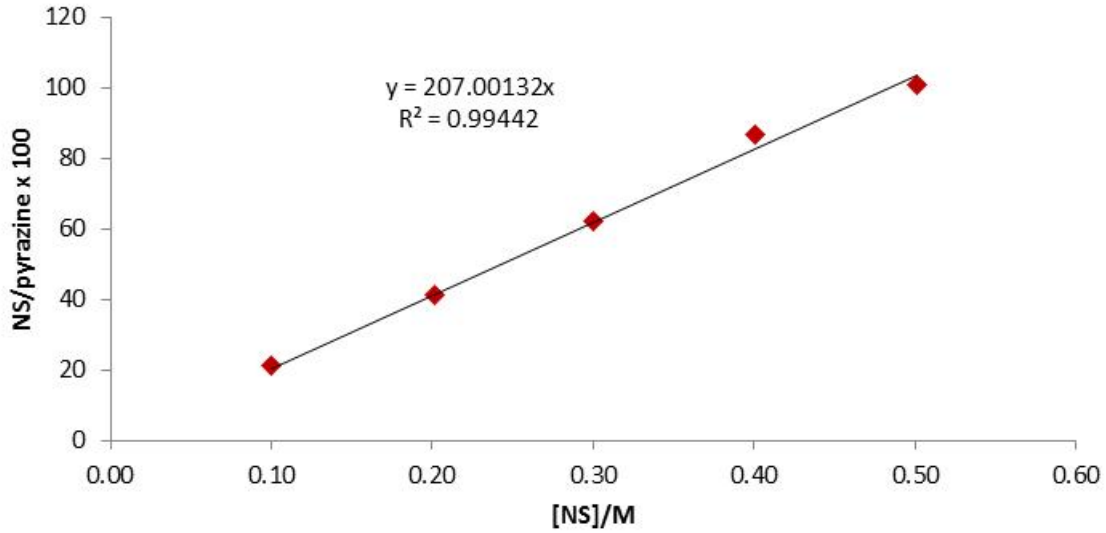
4.1. Materials and general procedure for NMR kinetic experiments

D_8-toluene (D % 99.6 ampoules of 1 mL) was purchased from Sigma-Aldrich. NMR spectra were recorded on Bruker DRX-400 MHz equipped with a BBFO 5 mm Prove. A capillary with pyrazine (δ= 7.90 ppm) was used as an external standard to quantify the concentration of the different species. To achieve quantitative data for all the species we measured the 90 degree flip angle (P1/4) and the longitudinal relaxation time (T1) for pyrazine as 7.5 s (all the species had a relaxation time lower than pyrazine). Relaxation delay (D1) was calculated as 37.5 s (7.5 s x 5) and used in all kinetic experimeriments.

4.2. Calibration curve for qNMR

To calibrate the pyrazine capillary five different solutions of known concentration of nitrostyrene **1** (NS) were prepared.^{1}H NMR of each solution with the capillary of pyrazine was recorded with ns= 8.The signals of pyrazine and NS (δ= d, 7.74 ppm) were integrated and the ratios of areas were plotted vs. the concentration of nitrostyrene.

Concentration of NS [M]	(AreaNS/Area pyrazine)×100
0.0998	21.18
0.2018	41.47
0.3004	62.40
0.4003	86.54
0.5008	100.62

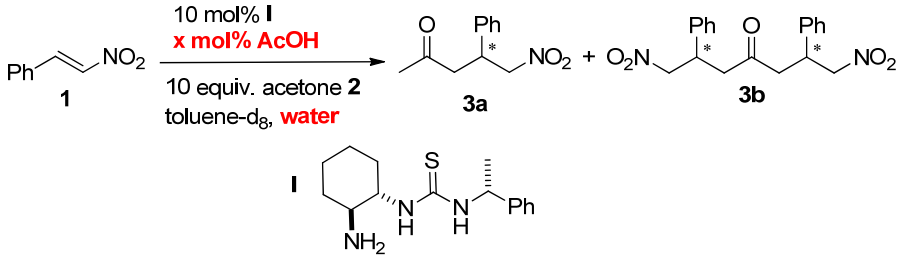


4.3. General procedure for kinetic experiments

7.5 mg (0.027 mmol) of catalyst **I** was weighed directly into NMR tube. The other reagents were added from common stock solutions in the indicated order below in function of experiment required. The reaction starting time was recorded just after the addition of the nitrostyrene (last reagent added). The shimming was done as fast as possible using the same reaction tube once the reaction was setted up (4 min approximately).

- **Stock solution A (nitrostyrene):** 201.4 mg (1.35 mmol) nitrostyrene in 1 mL d_8-toluene
- **Stock solution B (AcOH):**
  - **for 10 mol% AcOH:** 162.4 mg (155.5 µL, 2.7mmol) of acetic acid in 1 mLd_8-toluene. 0.1 mL of this solution was diluted to 1 mL d_8-toluene.
    Final solution: 0.27 mmol AcOH / mL solution
  - **for 5 mol% AcOH:** 81.2 mg (77.4 µL, 1.35mmol) of acetic acid in 1 mL d_8-toluene. 0.1 mL of this solution was diluted to 1 mLd_8-toluene.
    Final solution: 0.135 mmol AcOH / mL solution
  - **for 2.5mol% AcOH:** 40.5 mg (38.7 µL, 0.675 mmol) of acetic acid in 1 mL d_8-toluene. 0.1 mL of this solution was diluted to 1 mL d_8-toluene.
    Final solution: 0.0675 mmol AcOH / mL solution
- **Stock solution C (H_2O):**
  - **for 1 equiv. H_2O:** 24.3 µL H_2O (1.35 mmol) in 1 mL acetone.
  - **for 0.5 equiv. H_2O:** 24.3 µL H_2O (1.35 mmol) in 2 mL acetone.

Reagent addition order for the different experiments



i. **''no extra water added'' reactions (conditions B):**
   + 100 µL toluene- d_8
   + 200 µL acetone
   + 100 µL stock soln. B
   + 200 µL stock soln. A

ii. **''added water'' reactions (conditions C):**
   + 100 µL toluene- d_8
   + 200 µL stock soln. C
   + 100 µL stock soln. B
   + 200 µL stock soln. A

4.4. Concentration *vs* time plots at different AcOH and water amounts

The same colors and different symbols are used for the same acid and different water amount sets.

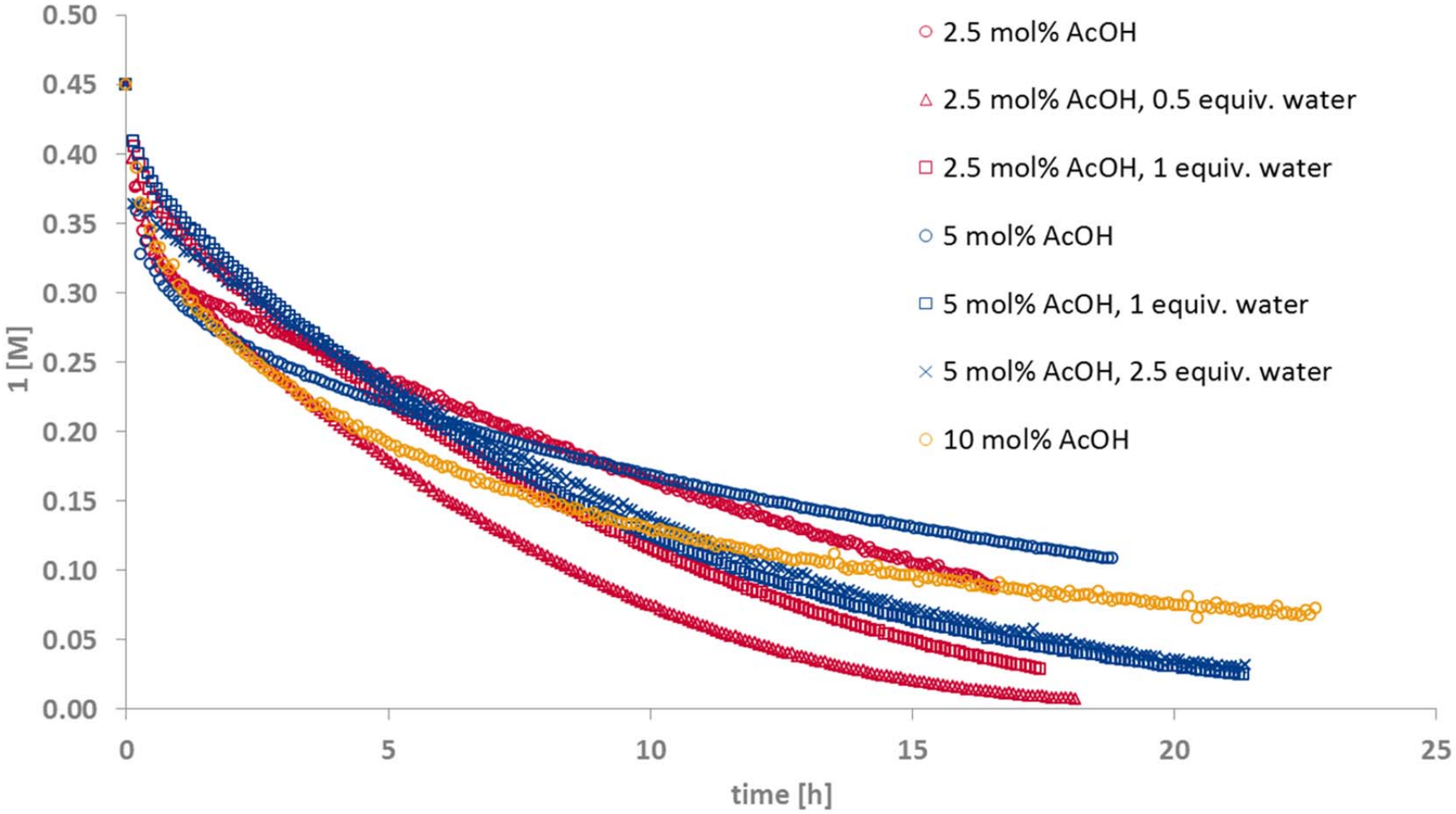


Figure 1. Consumption of nitrostyrene **1** over time under different conditions

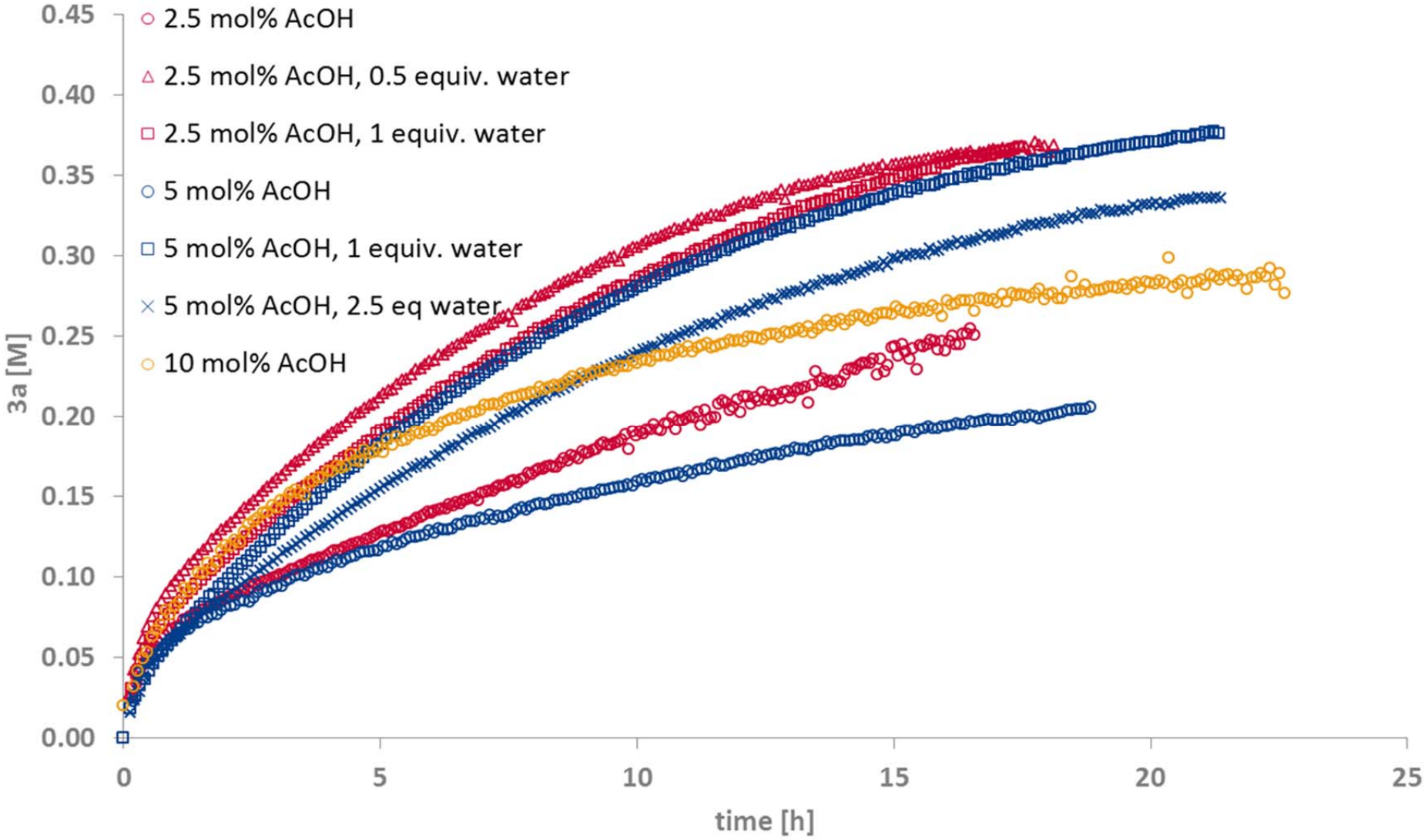


Figure 2. Formation of addition product **3a** over time under different conditions

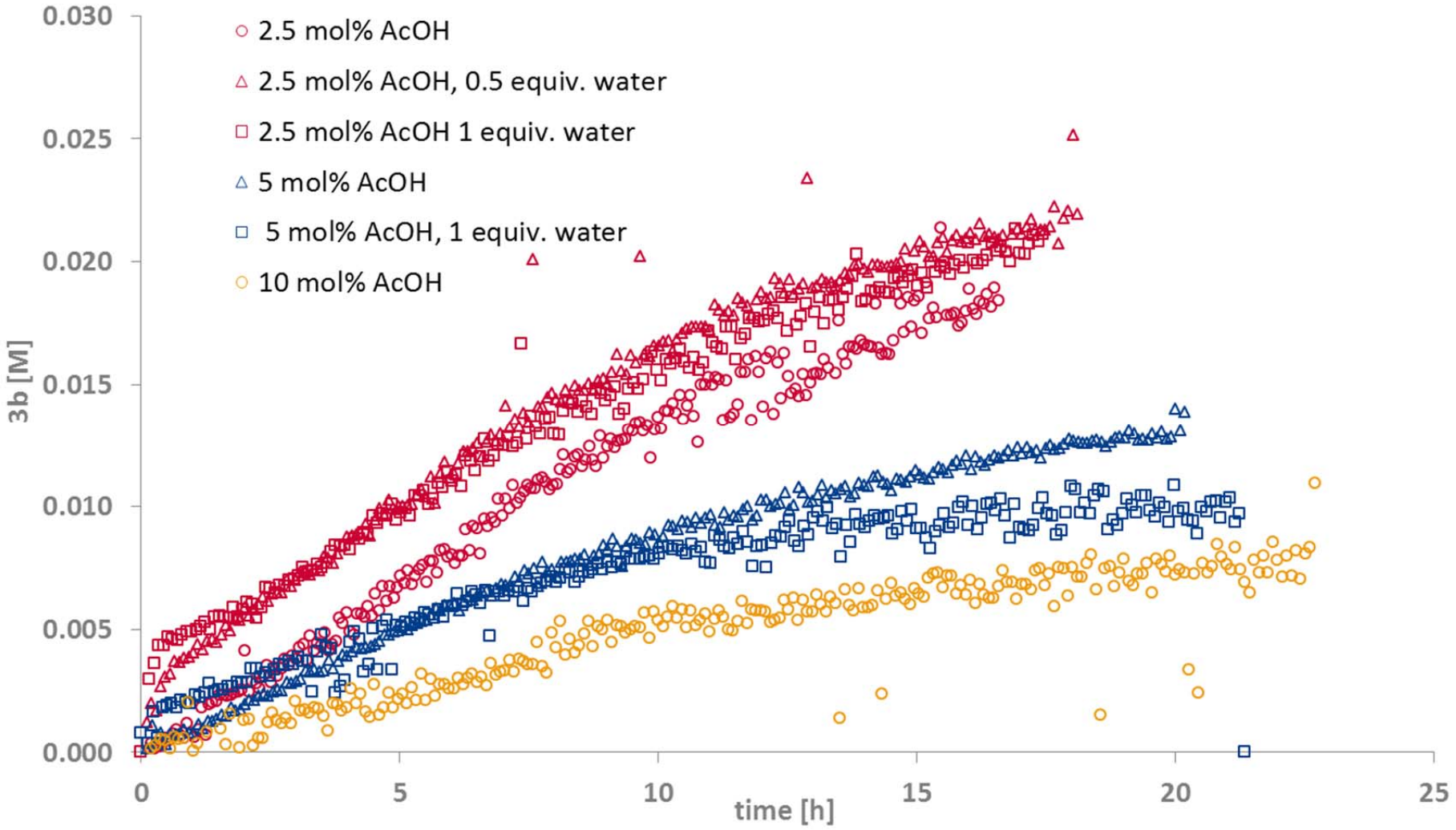


Figure 3. Formation of double addition side product **3b** over time under different conditions

4.5 Catalytic species profile over the reaction course (Conditions A):

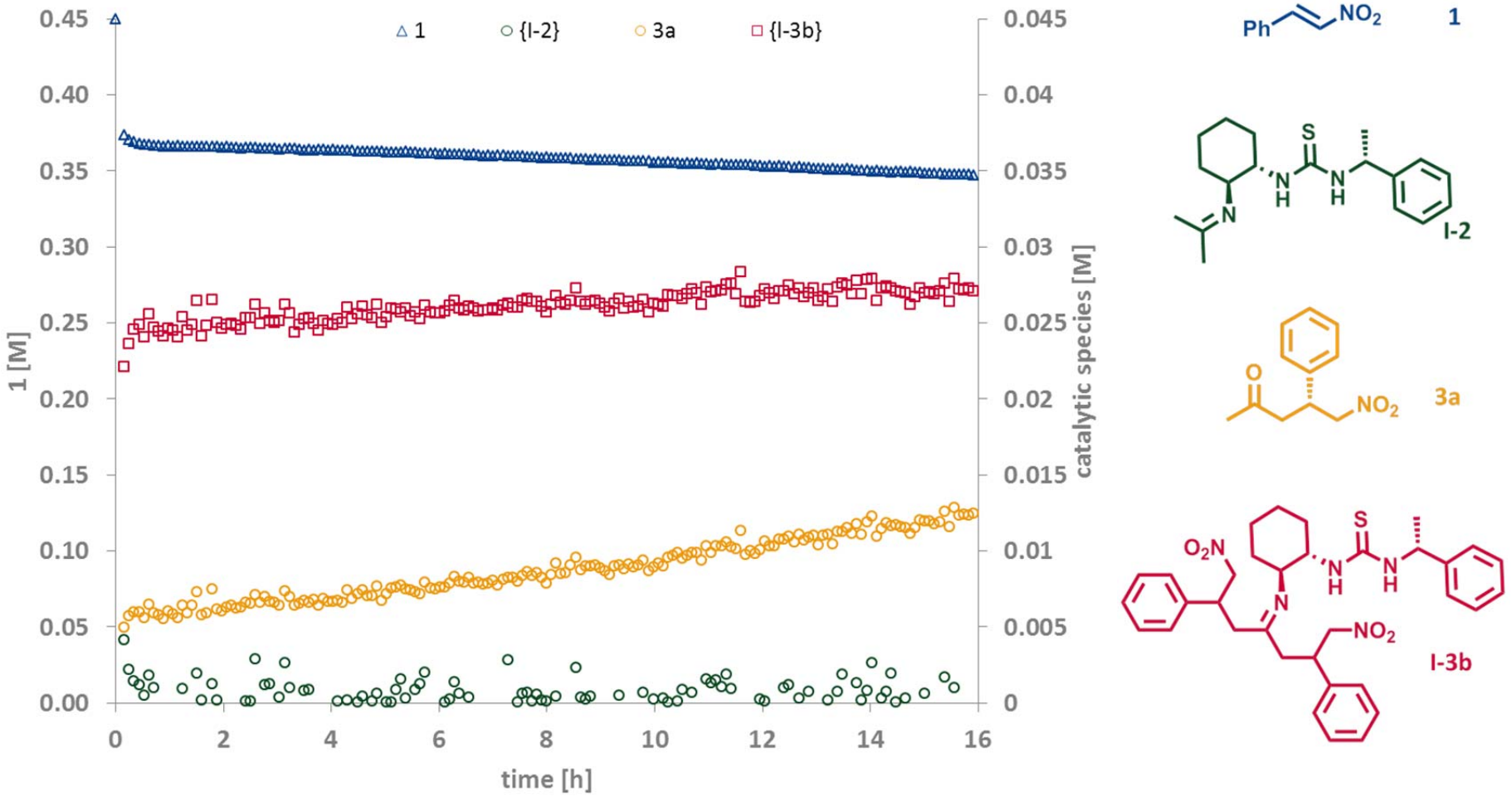
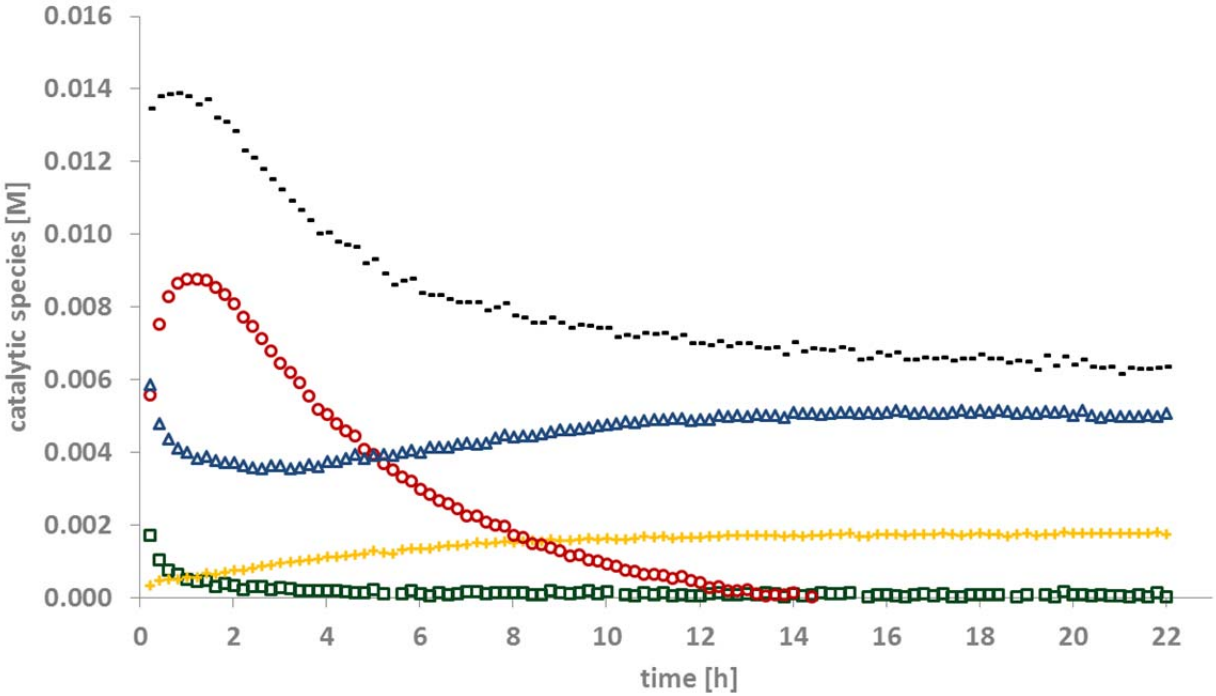
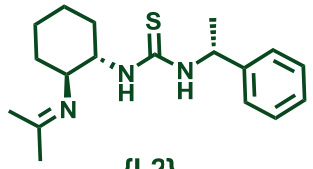
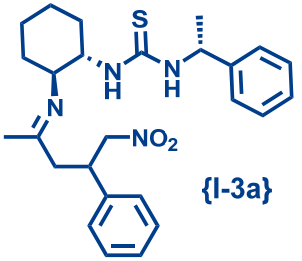


Figure 4. Reaction profile under ''no extra water added, no AcOH'' conditions (Conditions A), $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I**. Nitrostyrene concentration is shown in the left Y axis. Catalytic species and the addition product **3a** concentrations are shown in the right Y axis. Recorded on a Bruker Avance 600 MHz equipment.

4.6 Catalytic species profile over the reaction course (Conditions B):







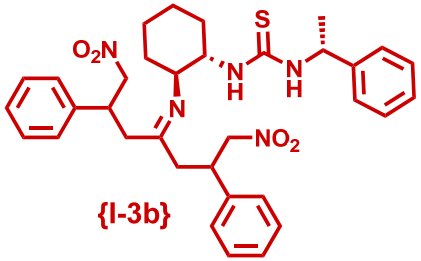
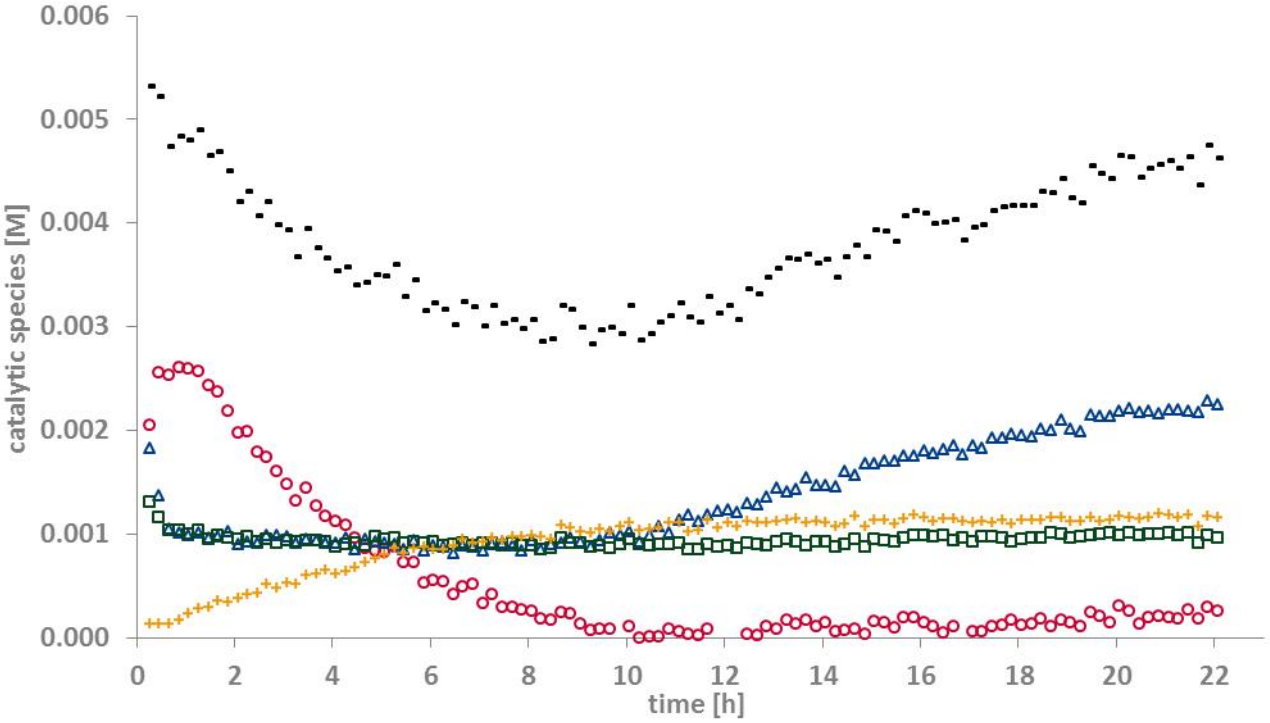
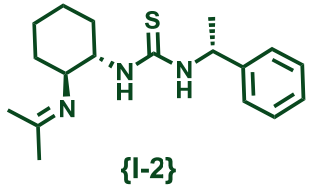


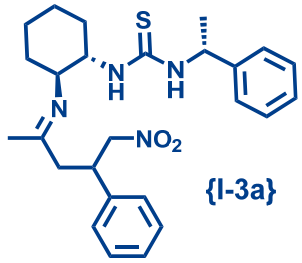
Figure 5. Catalytic species profile determined by ^{1}H NMR during the reaction under ''no extra water added' conditions (Conditions B). [**1**]$_0$=0.45 M, 5 equiv. acetone, 10 mol% **I**, 5 mol% AcOH. **{I-2}**, green; **{I-3a}**, blue; **{I-3b}**, red; unknown species, yellow; total concentration of *detected* catalytic species, black hyphen. Recorded on a Bruker 500 MHz spectrometer equipped with a cryoprobe.

The concentration of catalyst-acetone imine {**I-2**} decreases fast from the beginning of the reaction and then stays at a very low level (green squares). Catalyst-product imine {**I-3a**} concentration (blue triangles) also decreases at the beginning but after the reaction is *ca*. 50% conversion its concentration increases again slowly and remains constant thereafter. In contrast, concentration of the catalyst-double addition product imine {**I-3b**} increases along the reaction up to a maximum at *ca*. 0.009 M, and then decreases down to very low concentrations at the end of the reaction (red circles). This behavior suggests an equilibrium between **{I-3a}** and **{I-3b}**. ^{1}H NMR signals corresponding to unknown species that we attribute to catalyst decomposition products (yellow crosses) are initially at very low intensity, but the concentration of these species increases constantly with time. The total concentration of *detected* catalytic species decreases constantly along the reaction, from 0.014 M to 0.006 M (black hyphens).

4.7 Catalytic species profile over the reaction course (Conditions C):







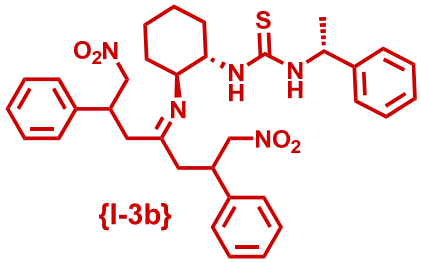
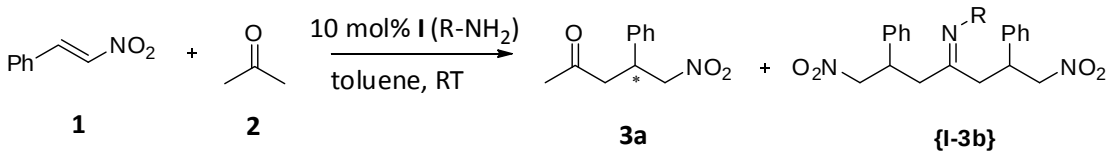


Figure 6. Catalytic species profile determined by ^{1}H NMR during the reaction under acid and water added (Conditions C).[**1**]$_0$=0.45 M, 5 equiv. acetone, 10 mol% **I**, 5 mol% AcOH, 1 equiv. water. **{I-2}**, green; **{I-3a}**, blue; **{I-3b}**, red; unknown species, yellow; total concentration of *detected* catalytic species, black hyphen. Recorded on a Bruker 500 MHz spectrometer equipped with a cryoprobe.

The concentration of catalyst-acetone imine {**I-2**} decreases fast from the beginning of the reaction and then stays at a very low but appreciable level (*ca*. 0.001 M, green squares). Catalyst-product imine {**I-3a**} concentration (blue triangles) decreases fast at the beginning but afterwards stabilizes at ca. 0.001 M, and after 10 hours its concentration increases again slowly. In contrast, concentration of the catalyst-double addition product imine {**I-3b**} increases fast at the beginning up to a maximum at *ca*. 0.003 M, and then decreases down slowly to very low concentrations at the end of the reaction (red circles). This behavior suggests an equilibrium between **{I-3a}** and **{I-3b}**. ^{1}H NMR signals corresponding to unknown species that we attribute to catalyst decomposition products (yellow crosses) are initially at very low intensity, but the concentration of these species increases up to 0.001 M and stays constant after 6 hours. The total concentration of *detected* catalytic species decreases constantly along the reaction, from 0.005 M to 0.003 M, at around 8-10 hours. Afterwards the total concentration increases slowly to the original level (black hyphens).

4.8. Characterization of intermediate species



In the absence of added water and AcOH (Conditions A, $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I**), the catalyst-double addition imine intermediate **{I-3b}** and the product **3a** formed cleanly and could be fully characterized by NMR.

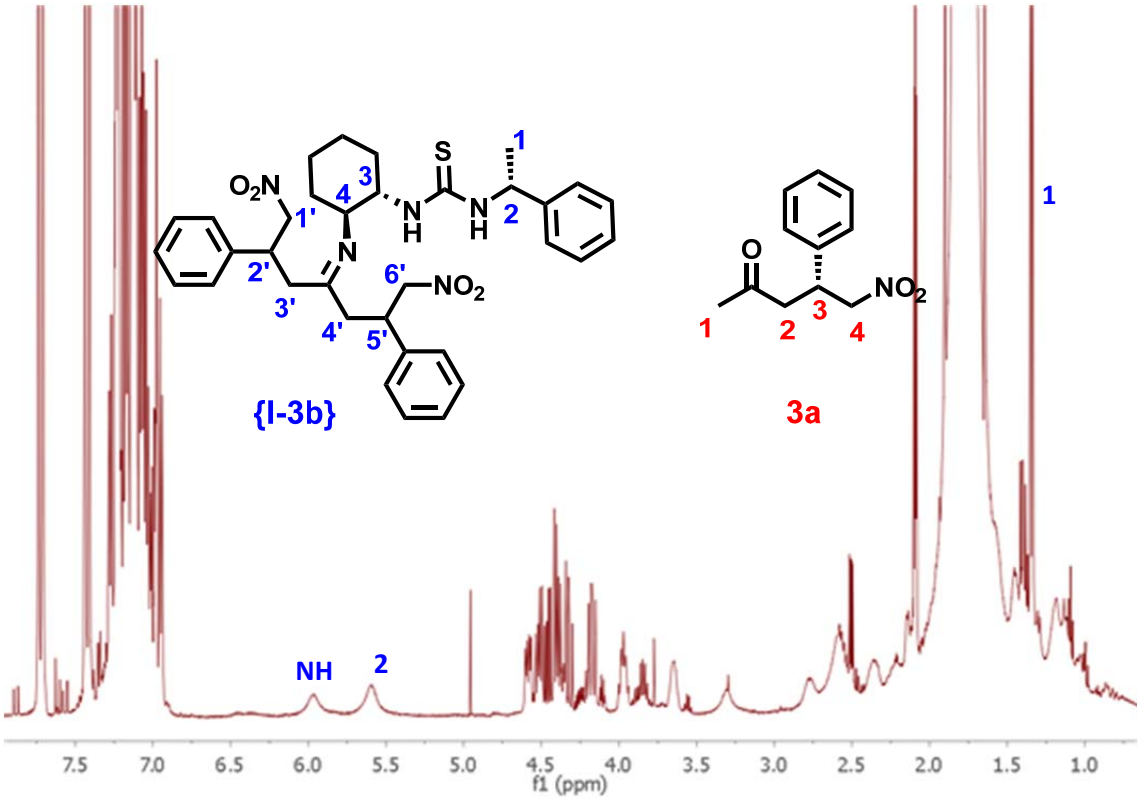


Figure 7. ^{1}H NMR characterization of the catalytic species **{I-3b}** and product **3a**. Performed in the absence of added water and AcOH (Conditions A).

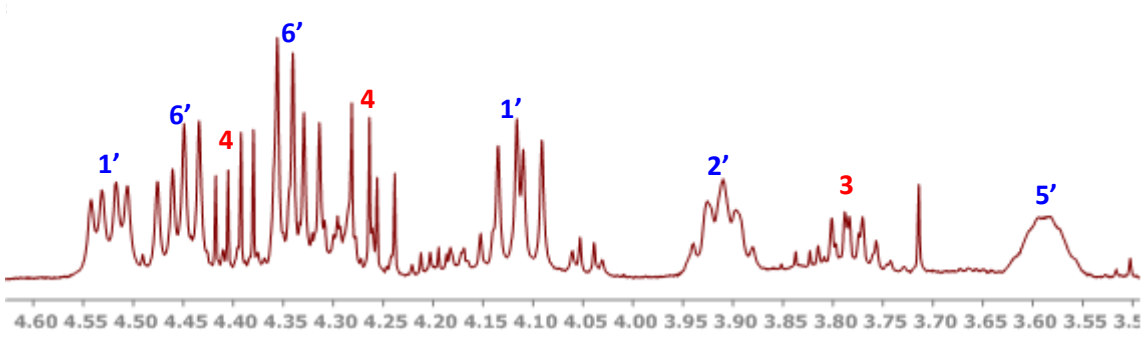


Figure 8. Expansion of ^{1}H NMR spectrum range 3.50-4.75 ppm

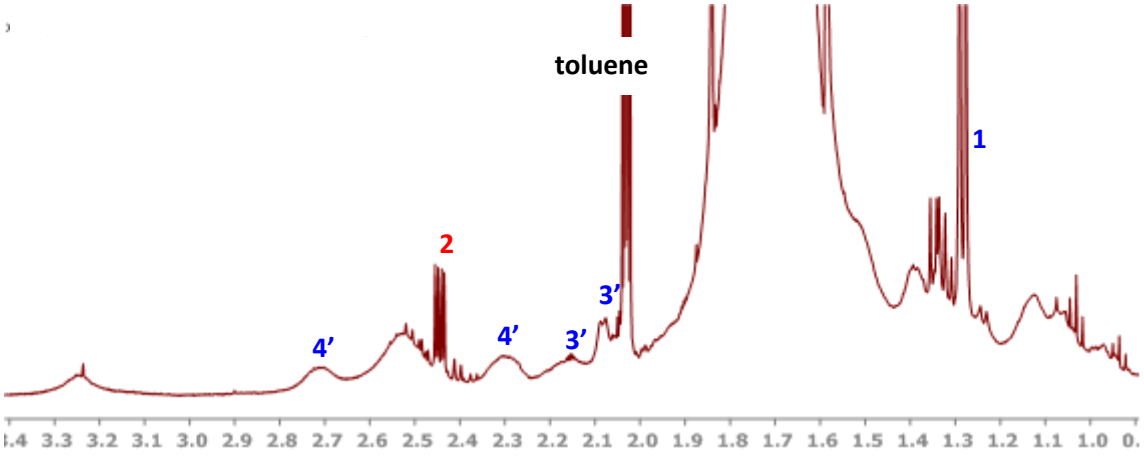


Figure 9. Expansion of ^{1}H NMR spectrum range 1.0-3.4 ppm

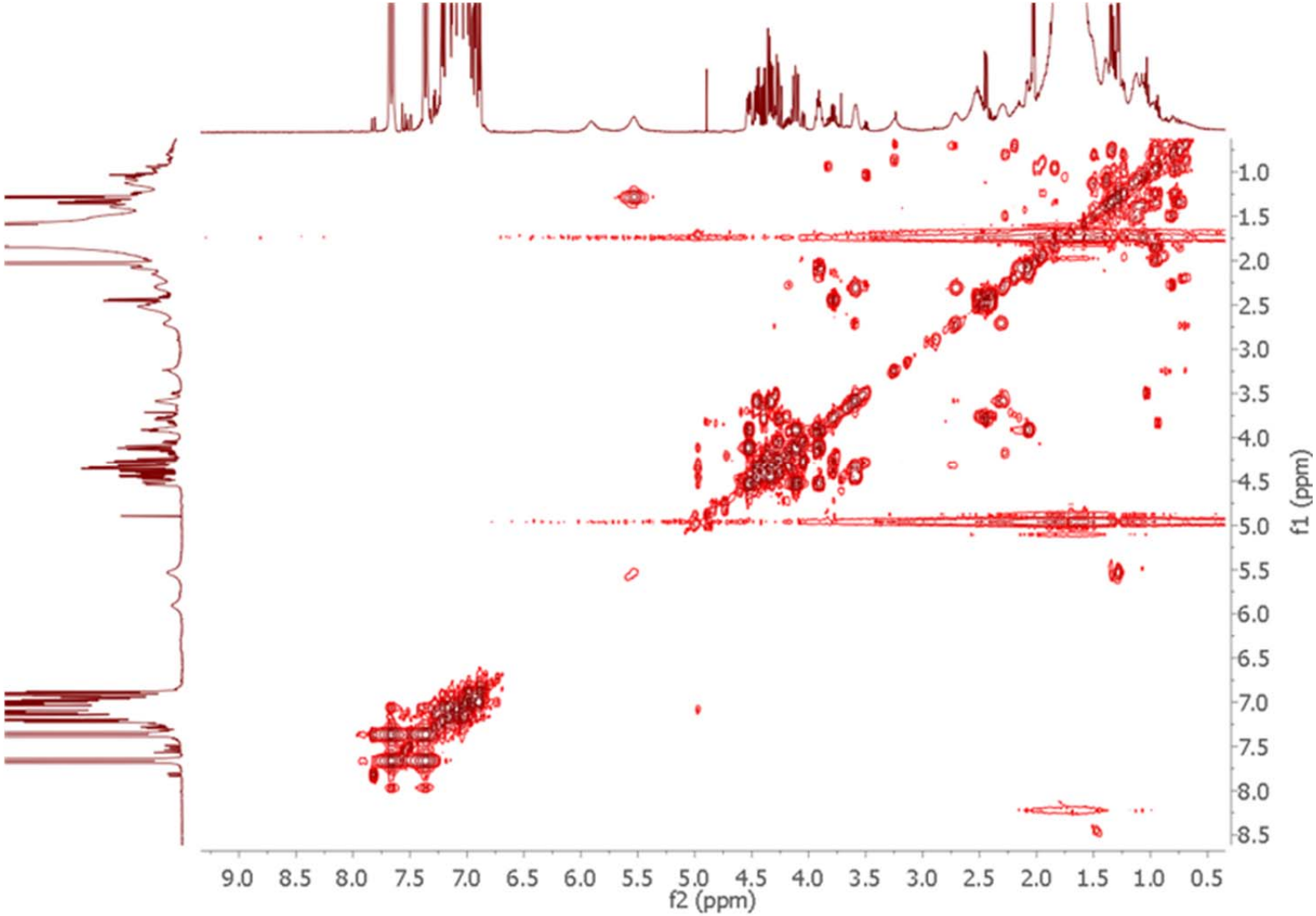


Figure 10. Full COSY NMR Spectrum in the absence of added water and AcOH (Conditions A).

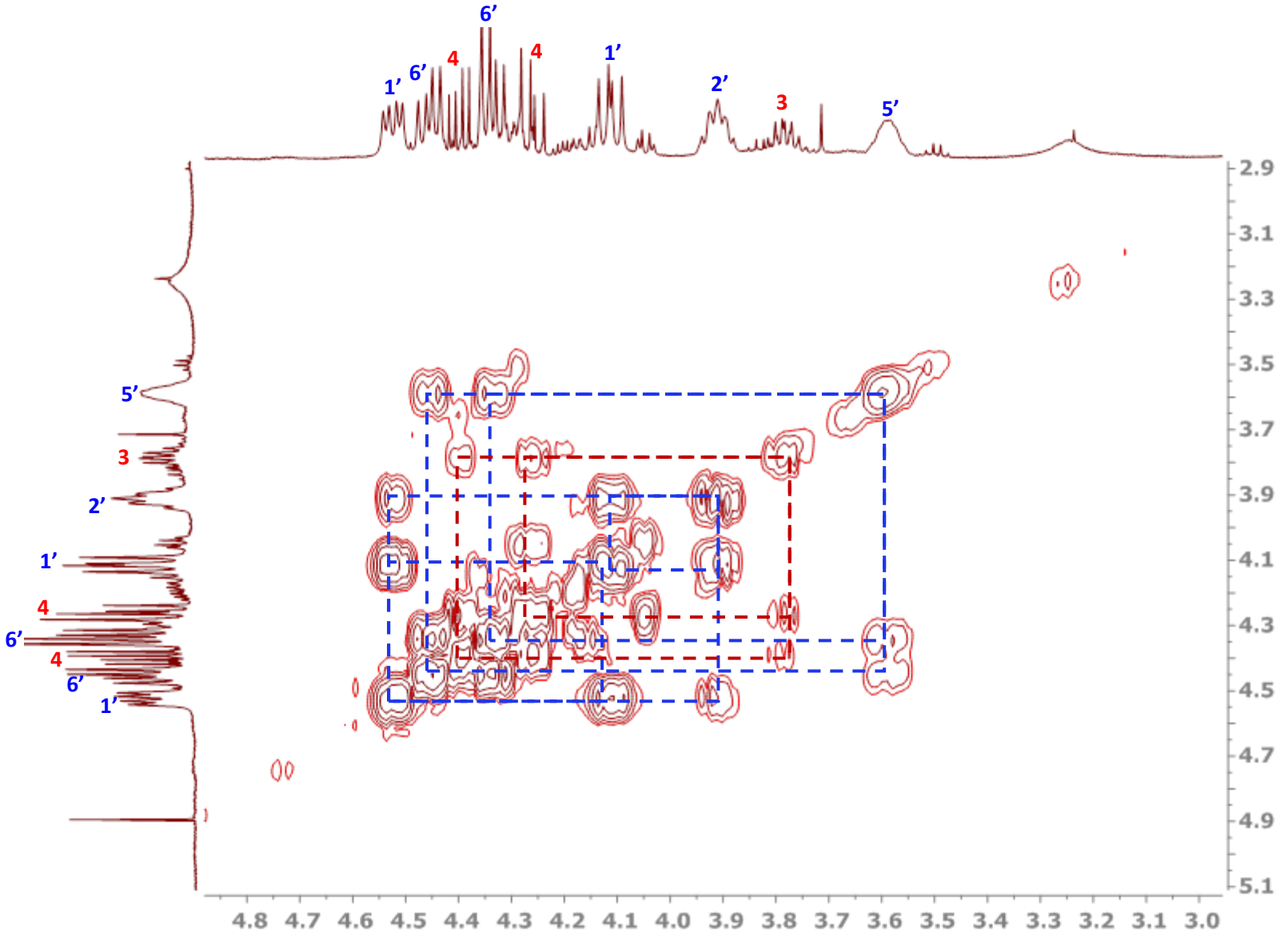


Figure 11. COSY cross peaks on the range 1.5-4.5 ppm

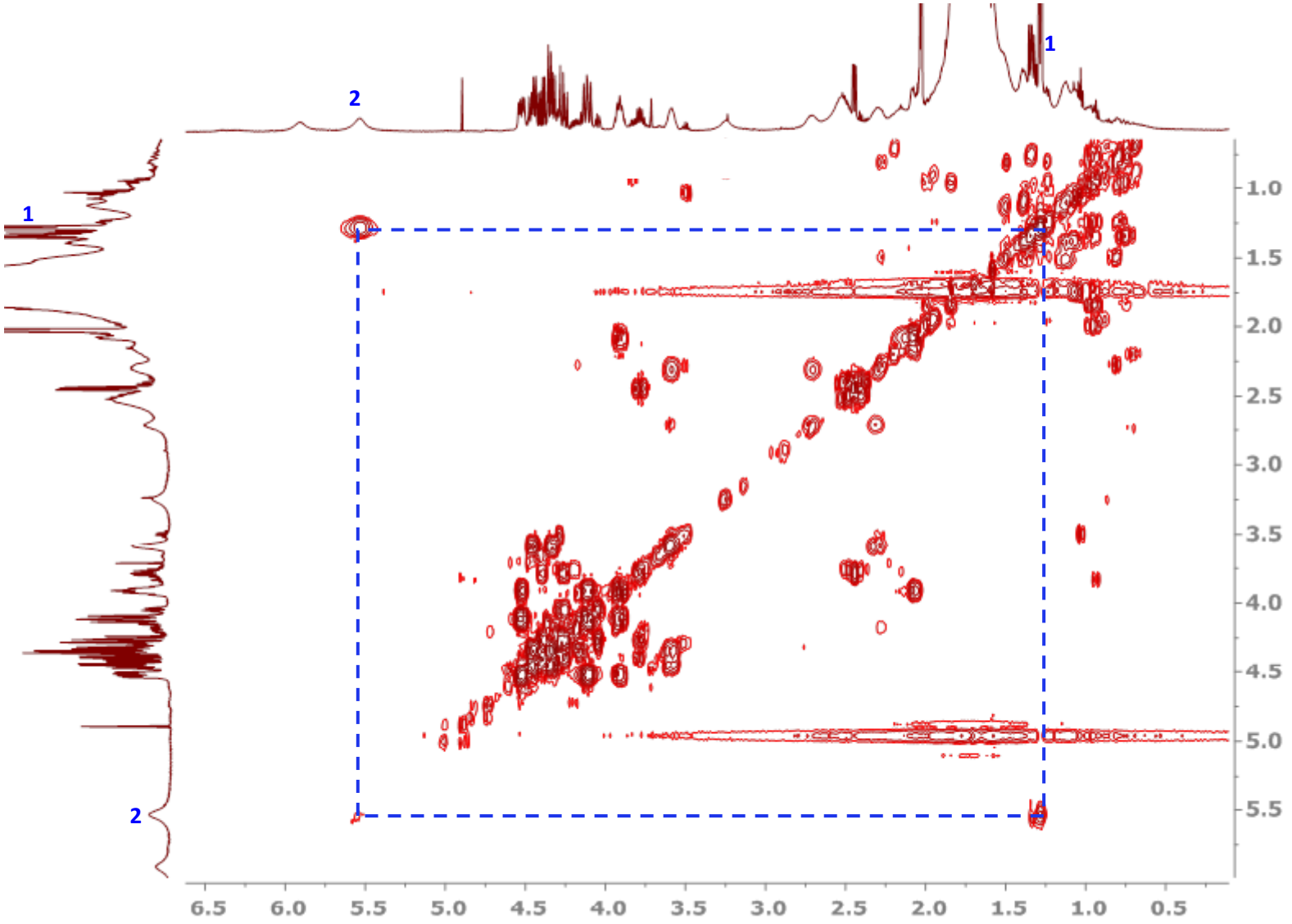


Figure 12. COSY cross peak between protons 1 and 2 of compound **{I-3b}**

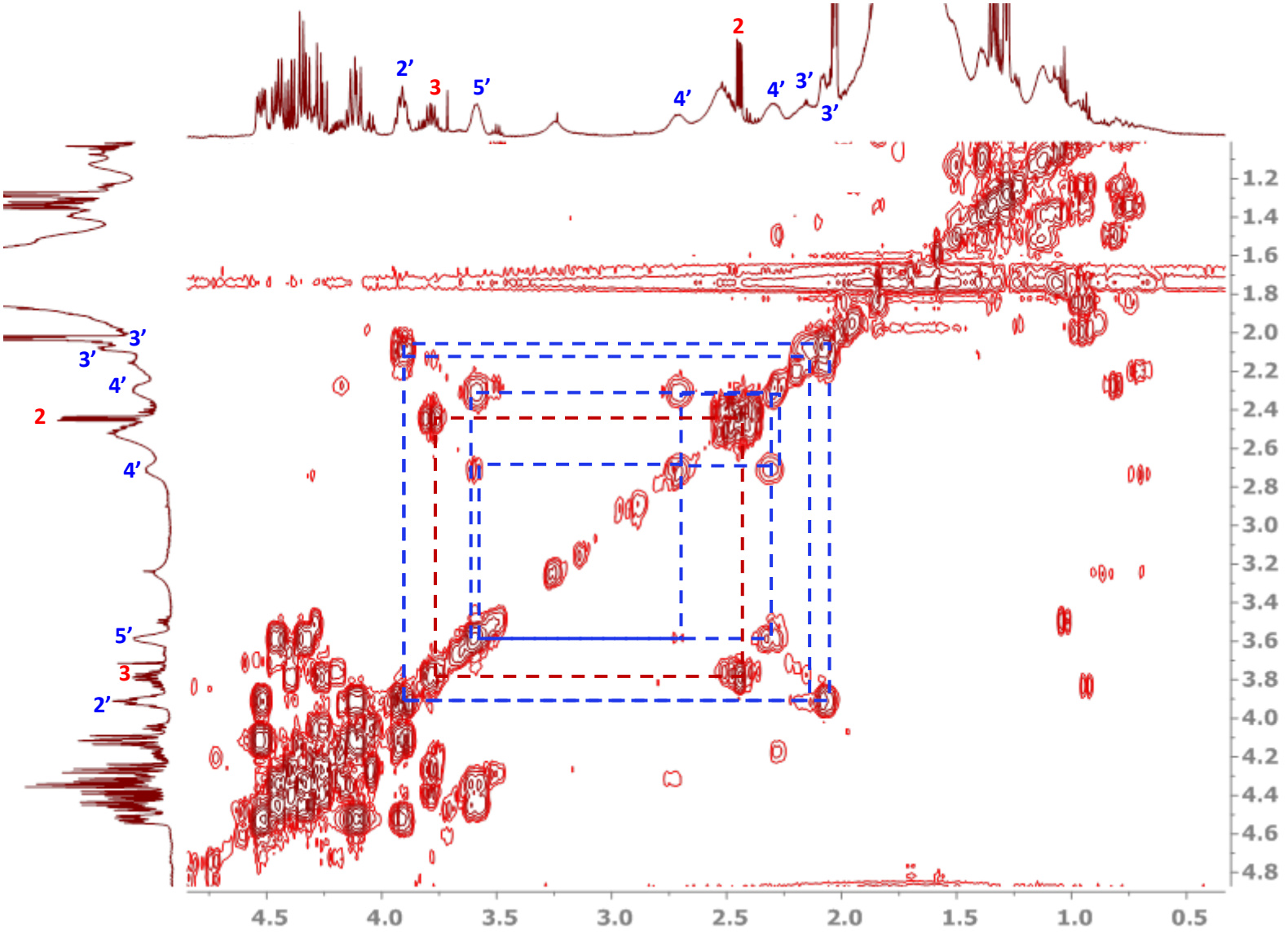


Figure 13. COSY cross peaks on the range 1.5-4.5 ppm

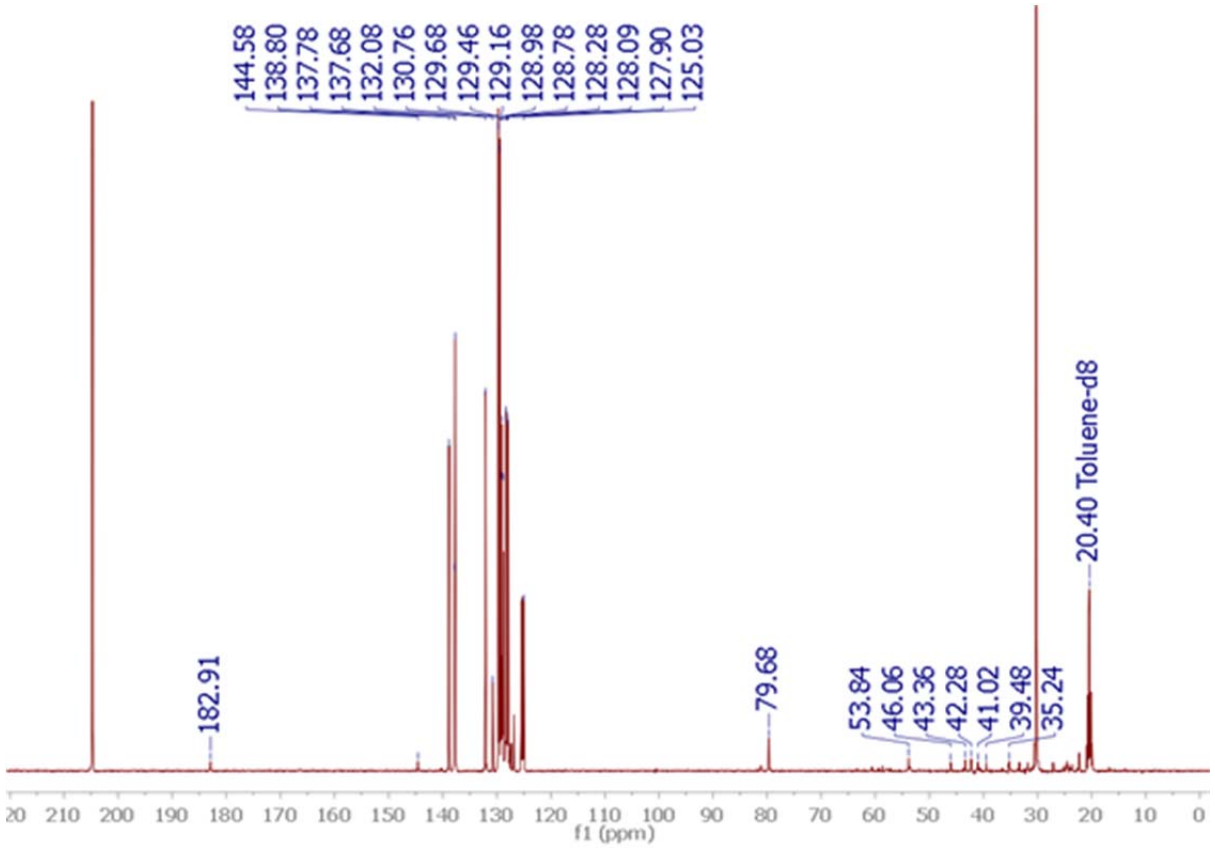


Figure 14. ^{13}C NMR characterization of the catalytic species **{I-3b}** and product **3a**. Performed in the absence of added water and AcOH (Conditions A).

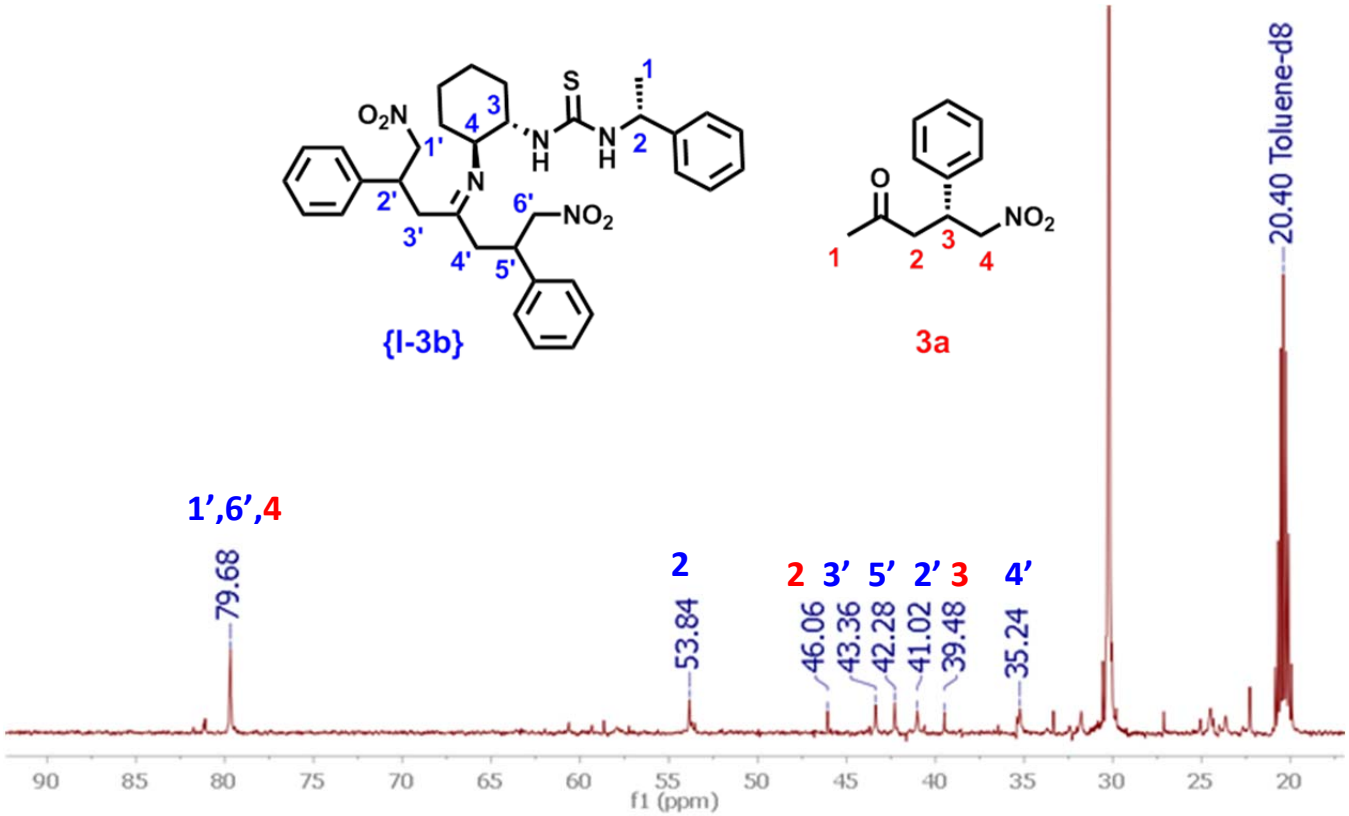


Figure 15. Expansion of ^{13}C NMR spectrum range 20-90 ppm

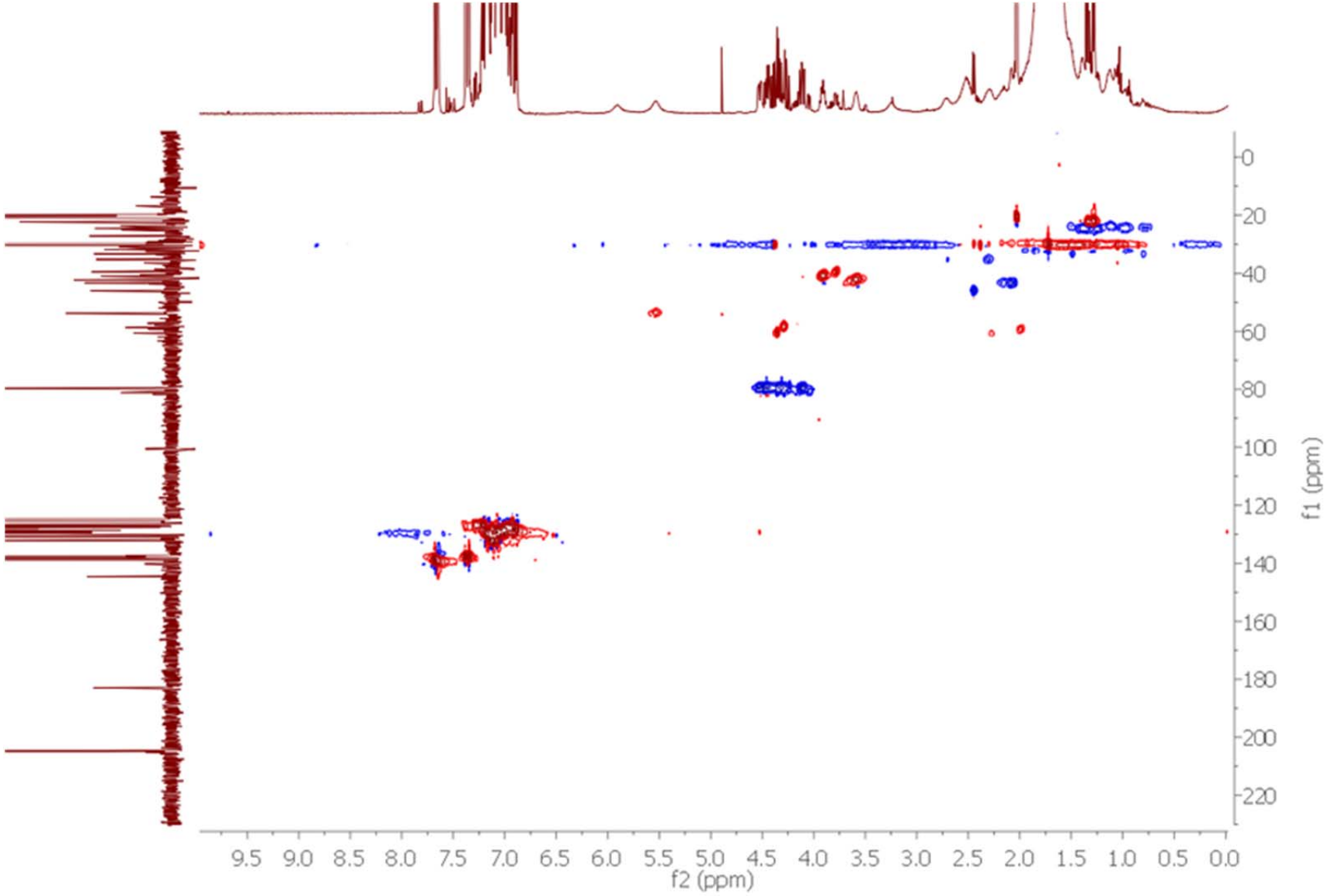


Figure 16. Full HSQC Spectrum in the absence of added water and AcOH (Conditions A).

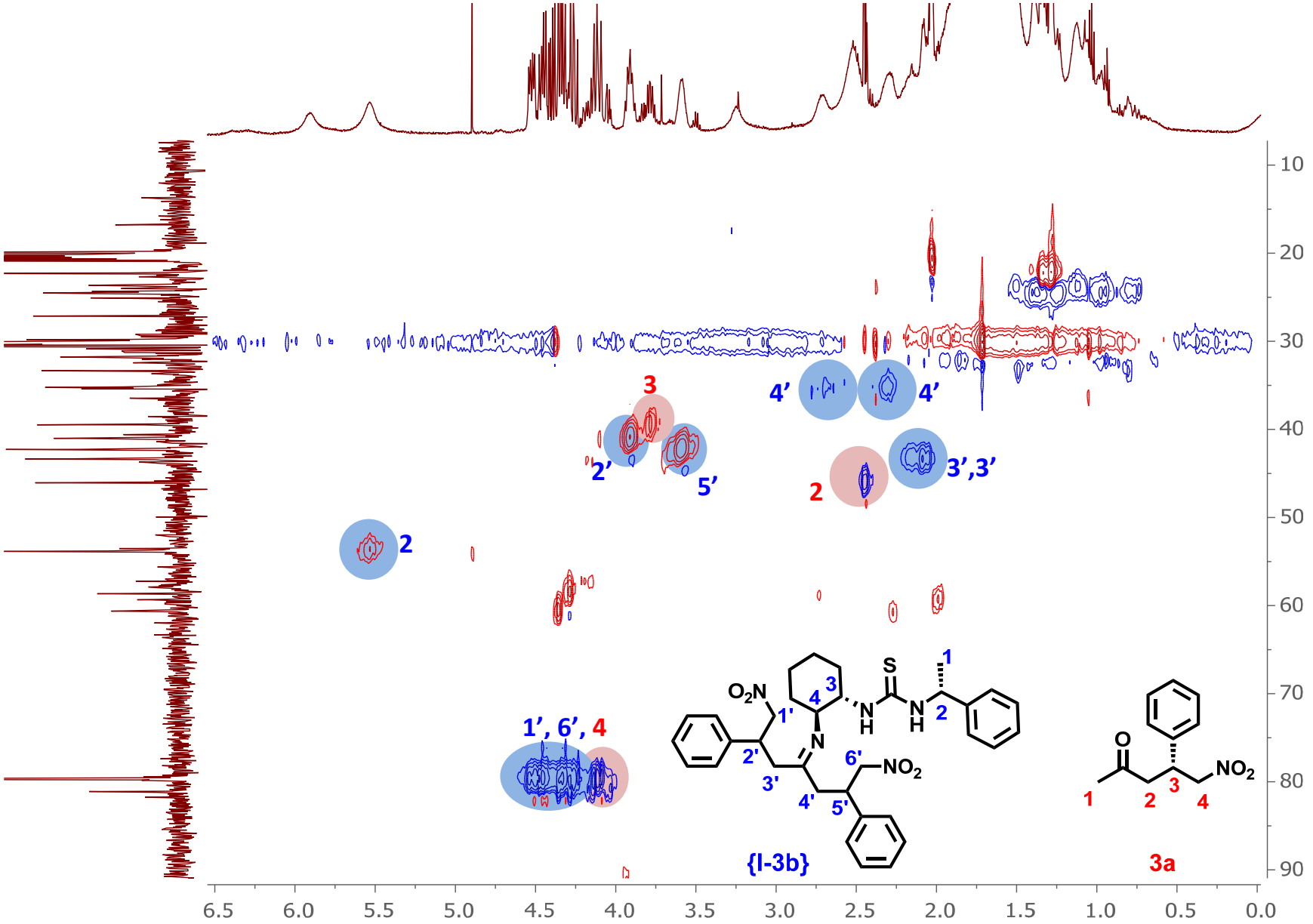


Figure 17. Expansion of HSQC spectrum range 0.0-6.5 ppm

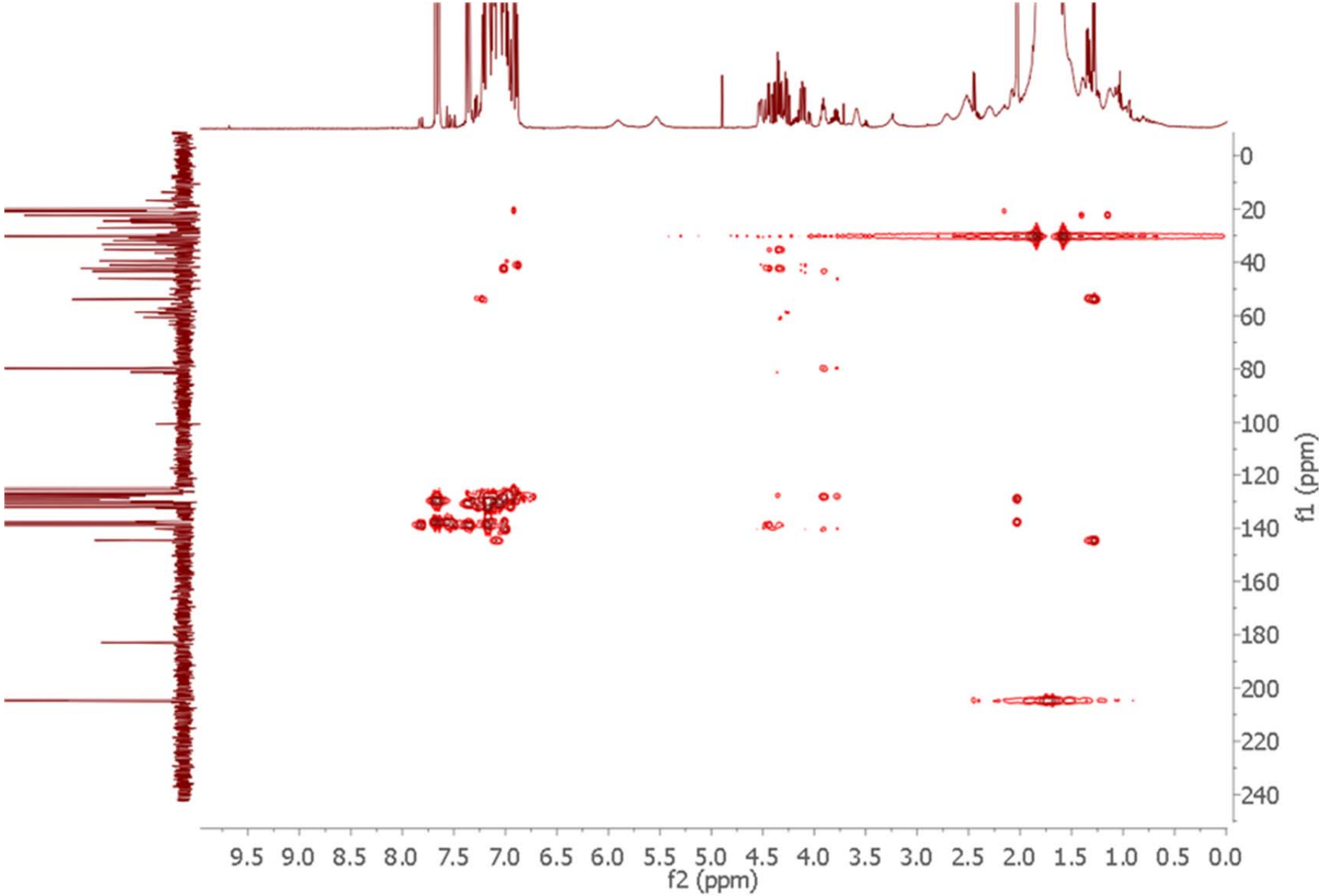


Figure 18. Full HMBC Spectrum in the absence of added water and AcOH (Conditions A).

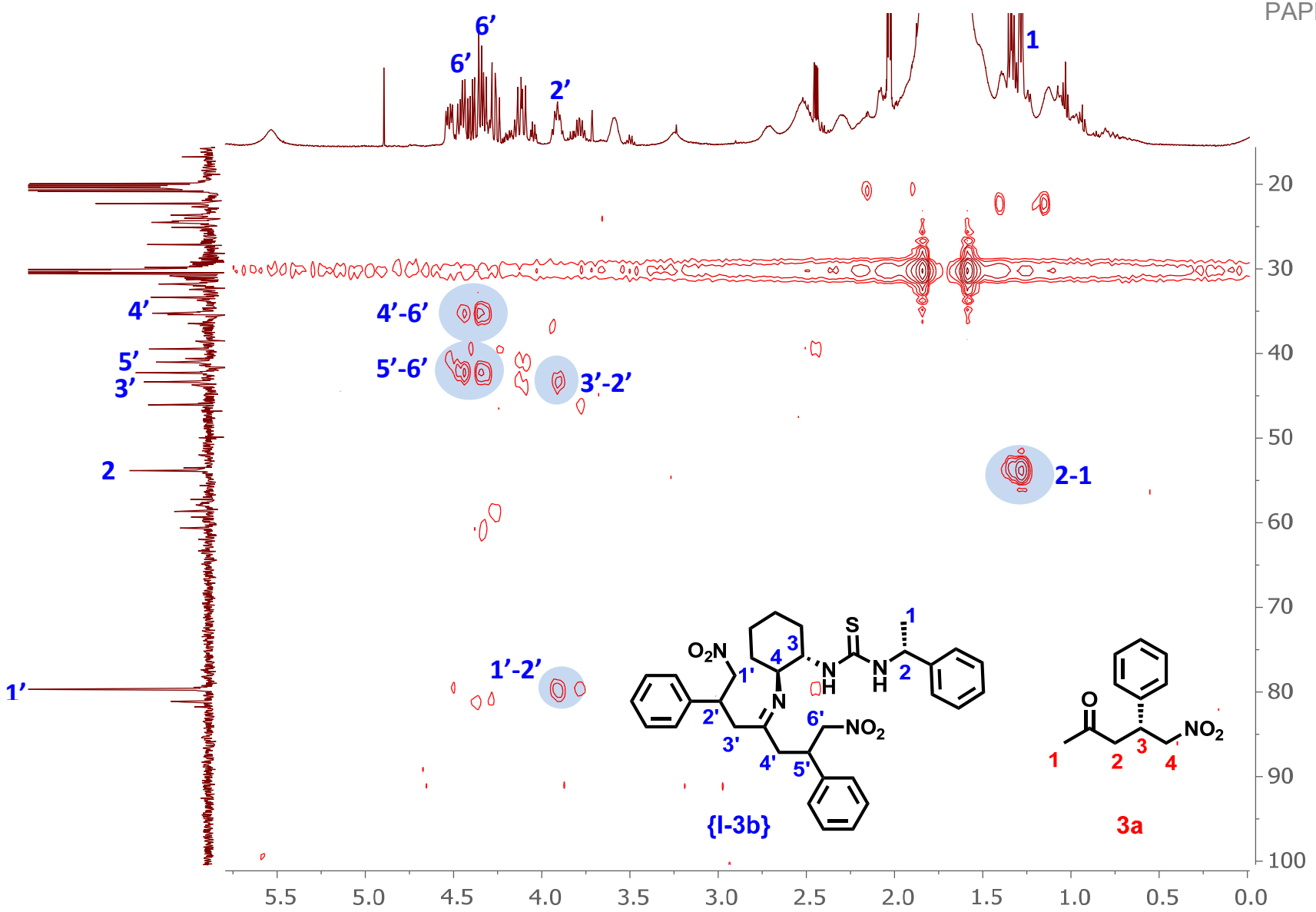


Figure 19. Expansion of HMBC Spectrum range 0.0-5.5 ppm

When the Michael addition was performed in the presence of 10 mol% AcOH and no added water (Conditions B, $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I,** 10 mol% AcOH), in the beginning of the reaction (up to 30 min), catalyst-product imine intermediate **{I-3a}** could be characterized by NMR.

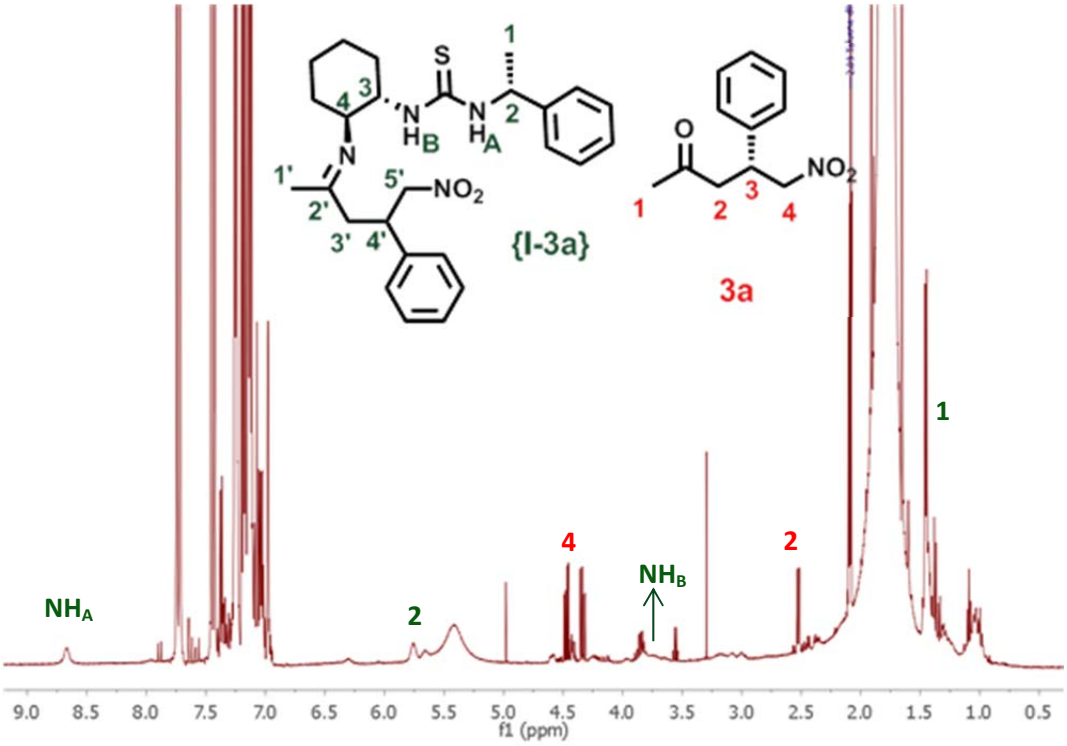


Figure 20. ^{1}H NMR characterization of the catalytic species **{I-3a}** and product **3a** (Conditions B).

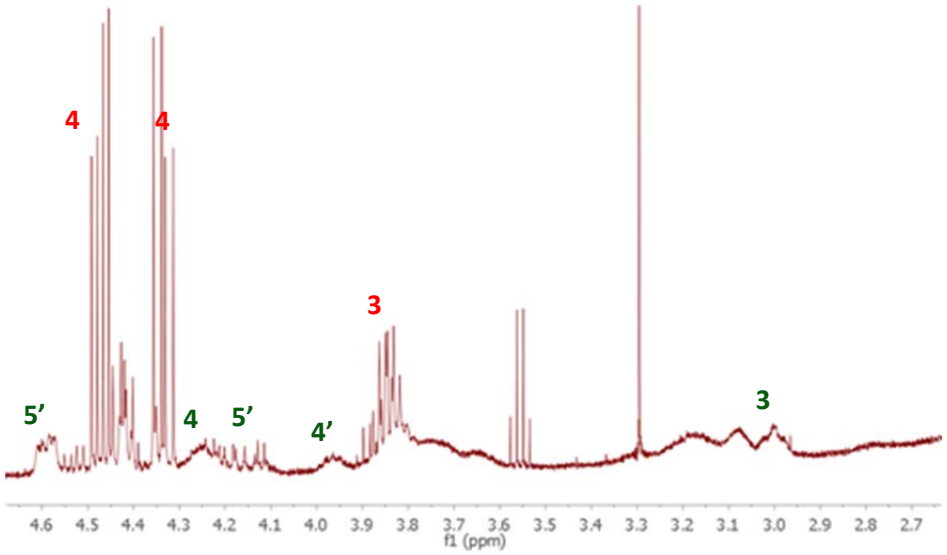


Figure 21. Expansion of ^{1}H NMR spectrum range 2.7-4.6 ppm.

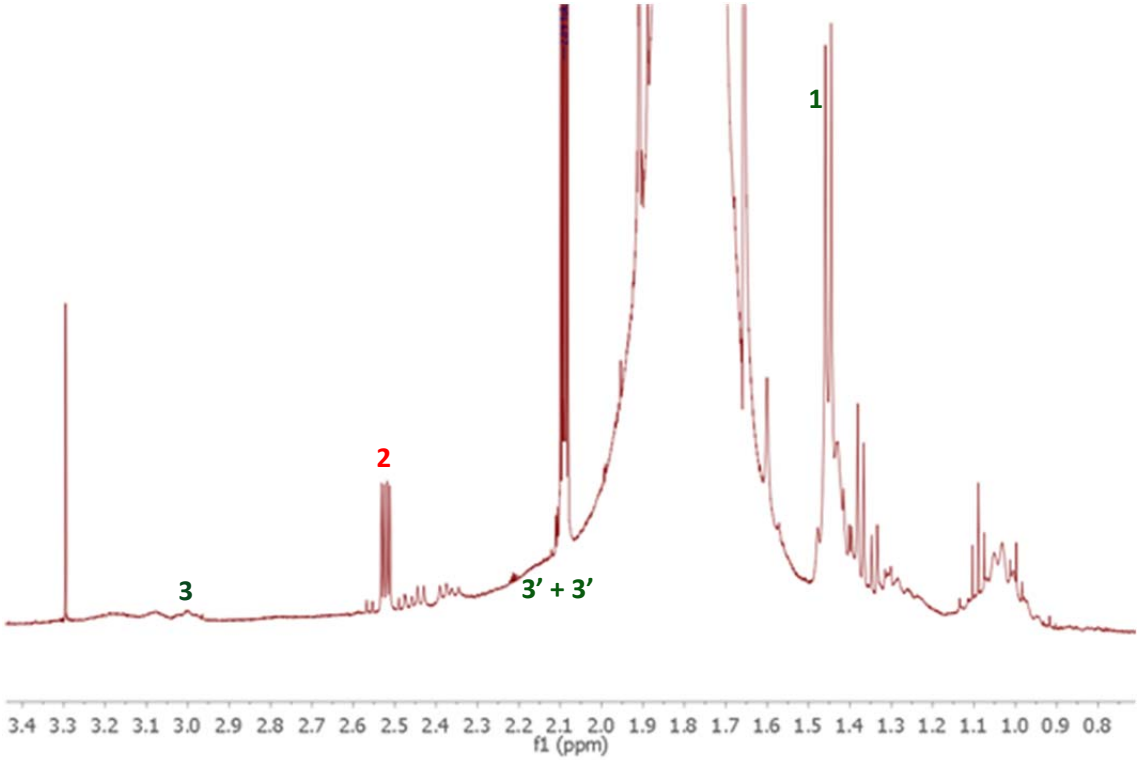


Figure 22. Expansion of ^{1}H NMR spectrum range 1.0-3.5 ppm.

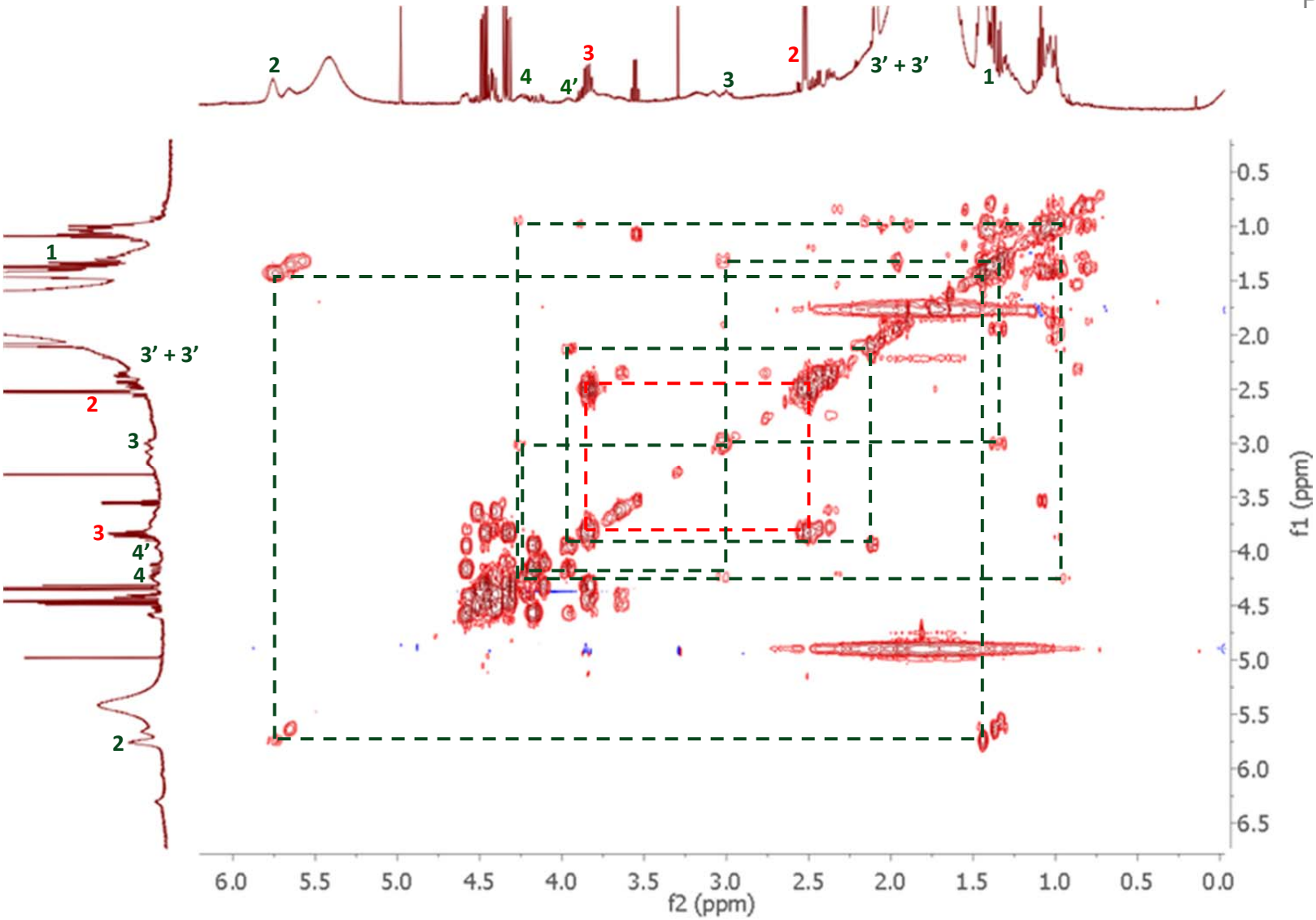


Figure 23. COSY cross peaks on the range 0.5-6.0 ppm

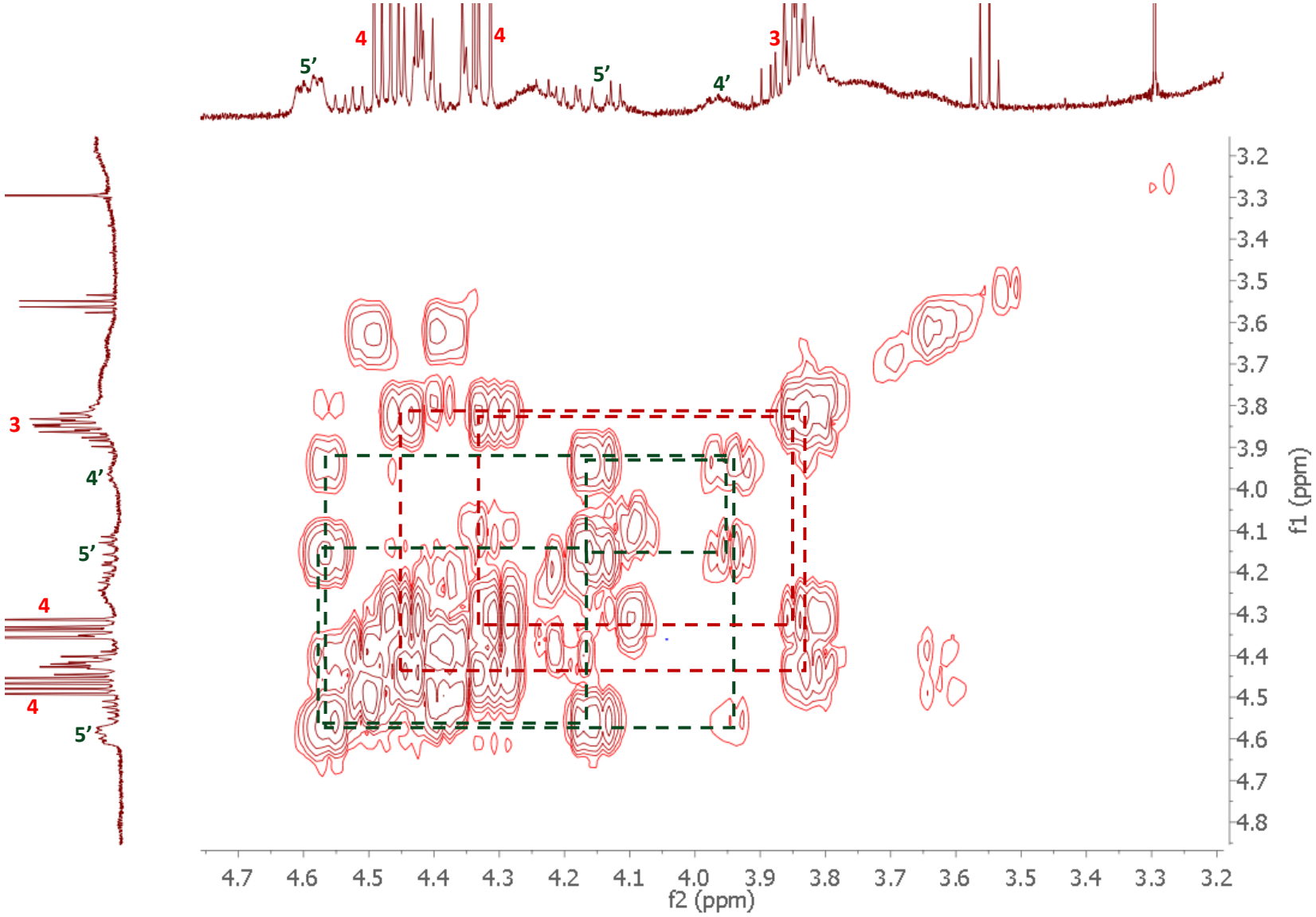


Figure 24. COSY cross peaks on the range 3.5-4.8 ppm

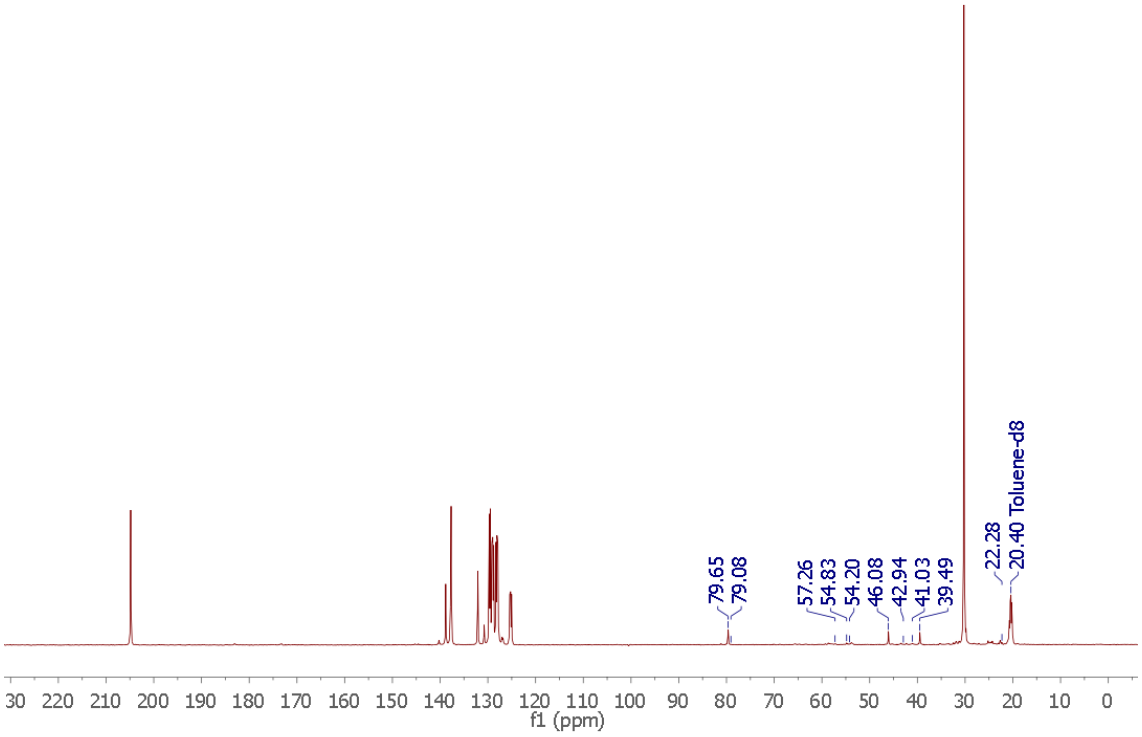


Figure 25. ^{13}C NMR characterization of the catalytic species **{I-3a}** and product **3a** under Conditions B. $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I**, 10 mol% AcOH.

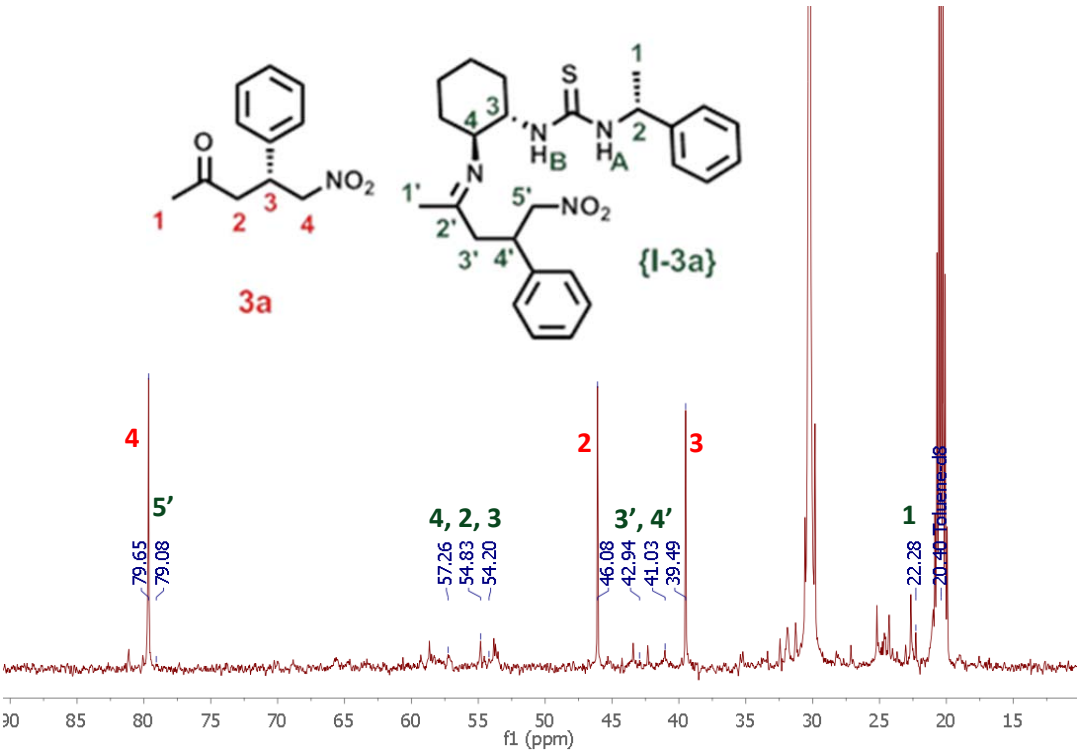


Figure 26. Expansion of ^{13}C NMR spectrum range 20-90 ppm

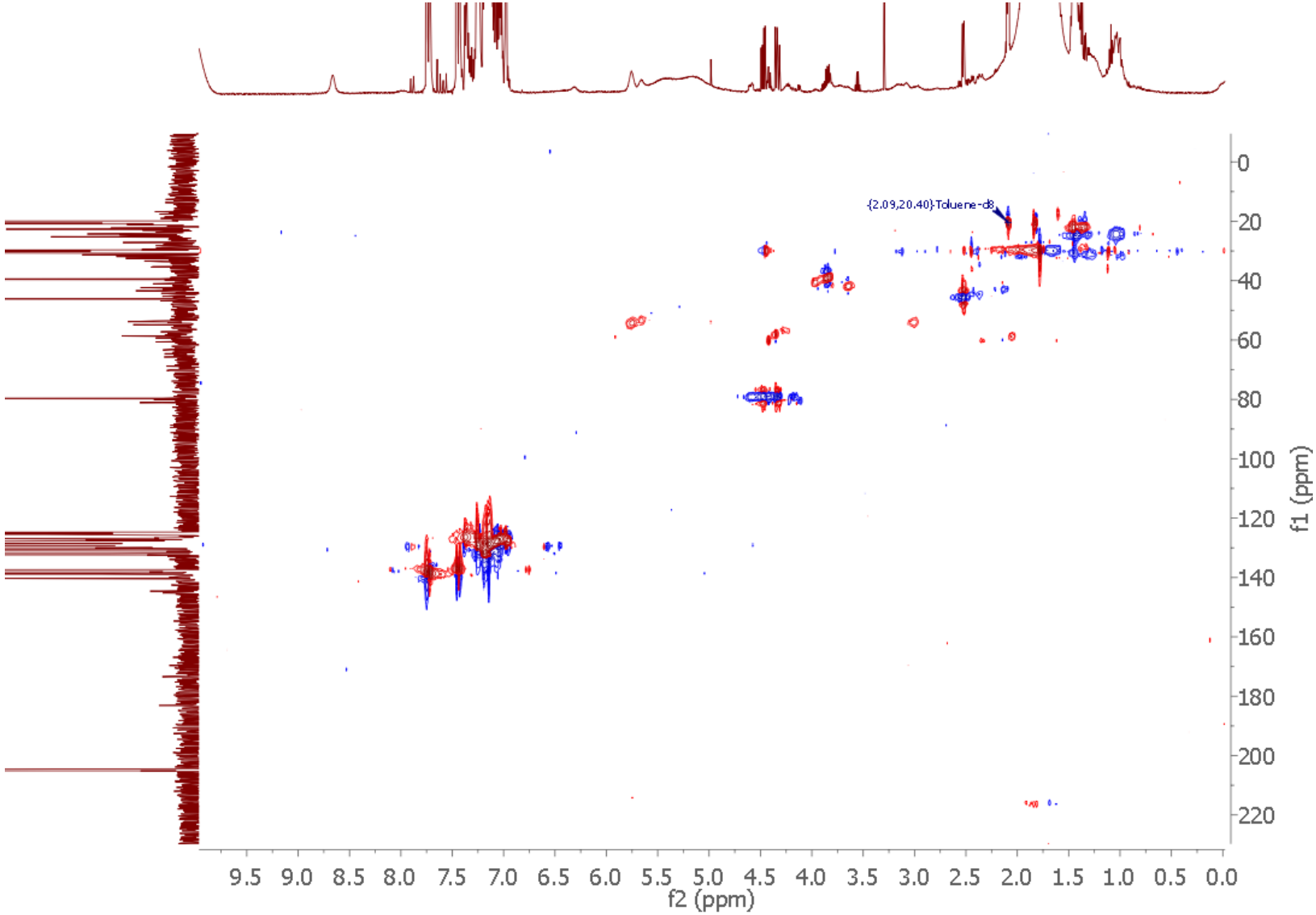


Figure 27. Full HSQC Spectrum under Conditions B. $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I**, 10 mol% AcOH.

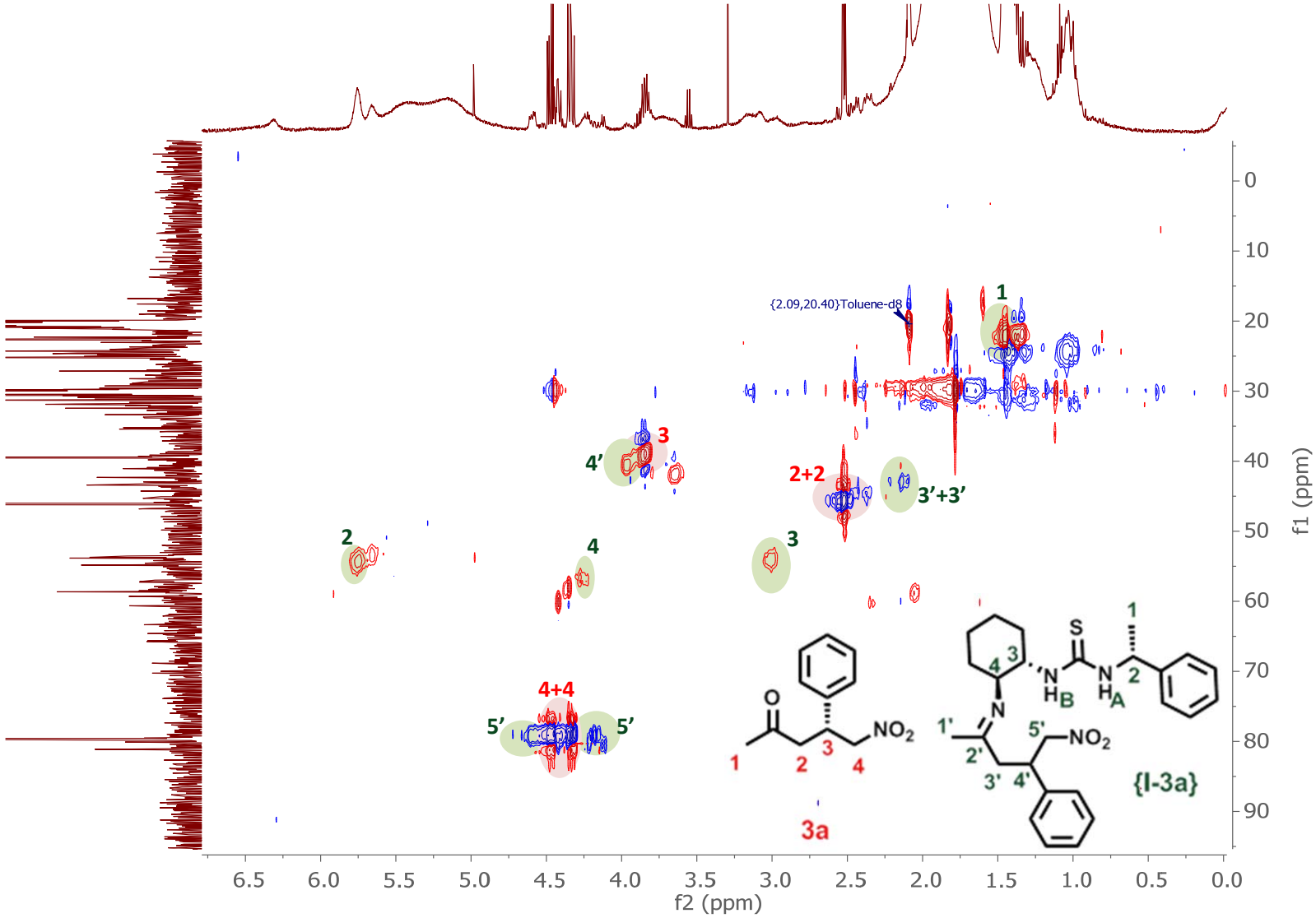
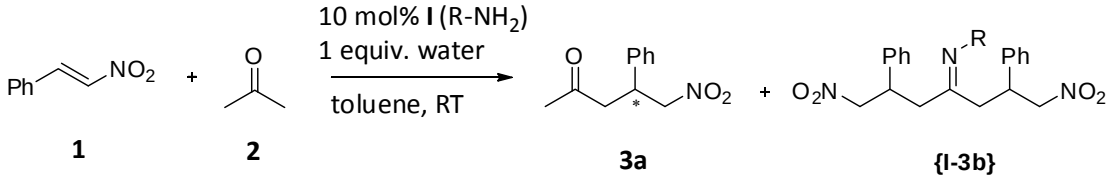


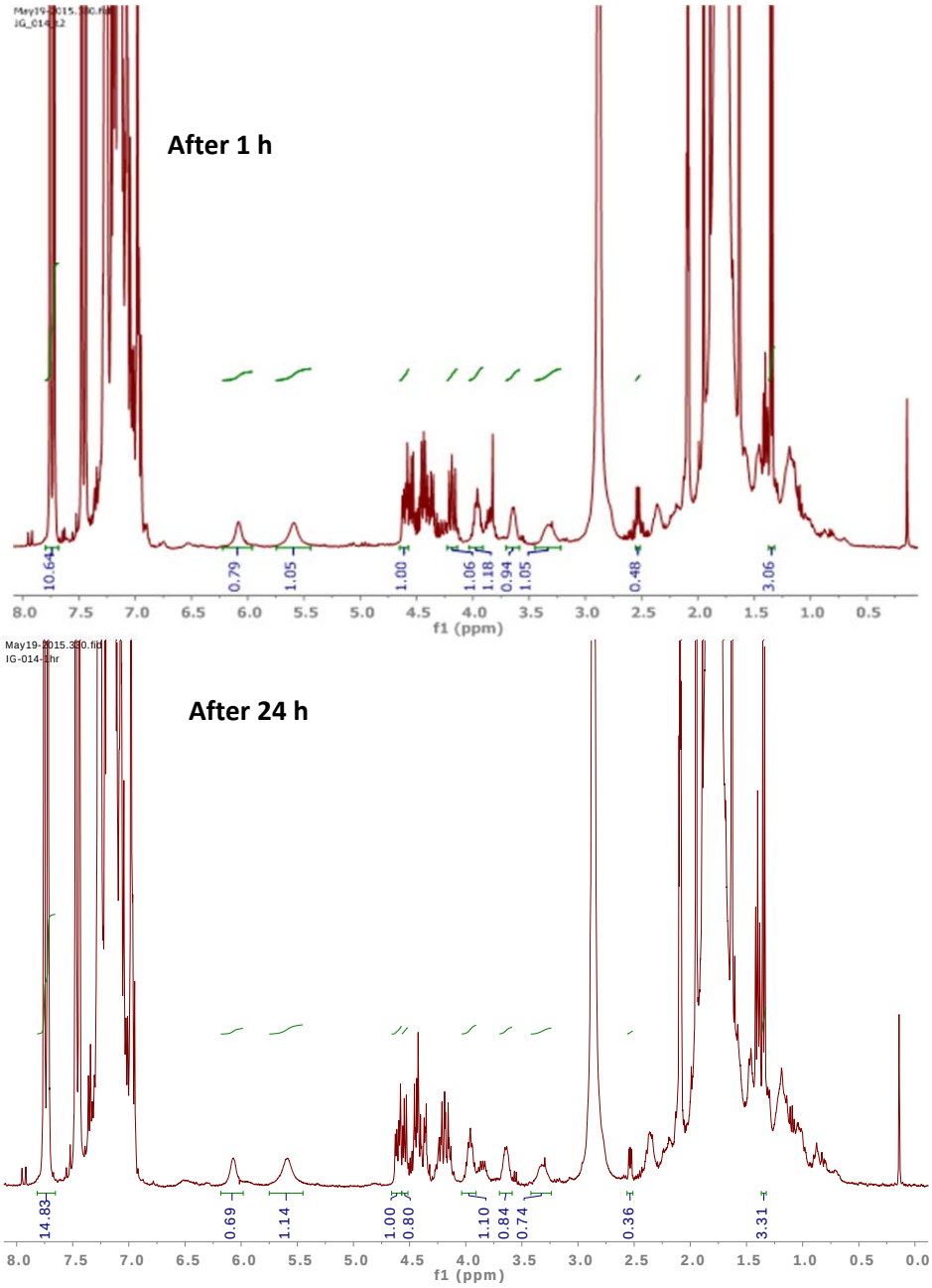
Figure 28. Expansion of HSQC Spectrum range 0.0-6.5 ppm.

4.9. ^{1}H NMR spectra for the reaction run with 1 equivalent of water added but no AcOH

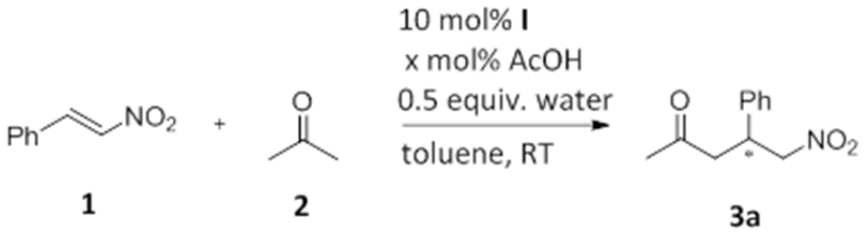


1 **2** **3a** **{I-3b}**

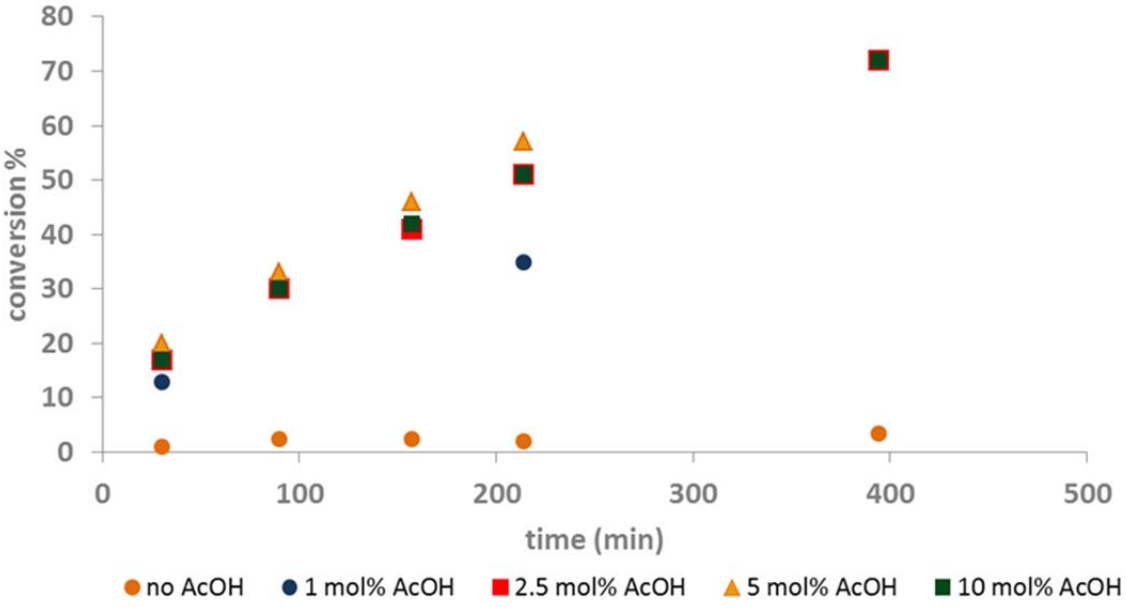
Under acid-free conditions but adding 1 equiv. of water ($[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% **I**, 1 equiv. water) double addition product imine **{I-3b}** and product **3a** were formed (See Section 7.6). After 24 hours the concentration of the two species remained constant.



4.10. Effect of the amount of AcOH



Effect of AcOH amount in the Michael addition of acetone to nitrostyrene was tested under Conditions C. $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% catalyst **I**, x mol% AcOH, 0.5 equiv. water in toluene at rt.



4.11. Dissapearence of nitrostyrene due to the formation of products, intermediates and side-products

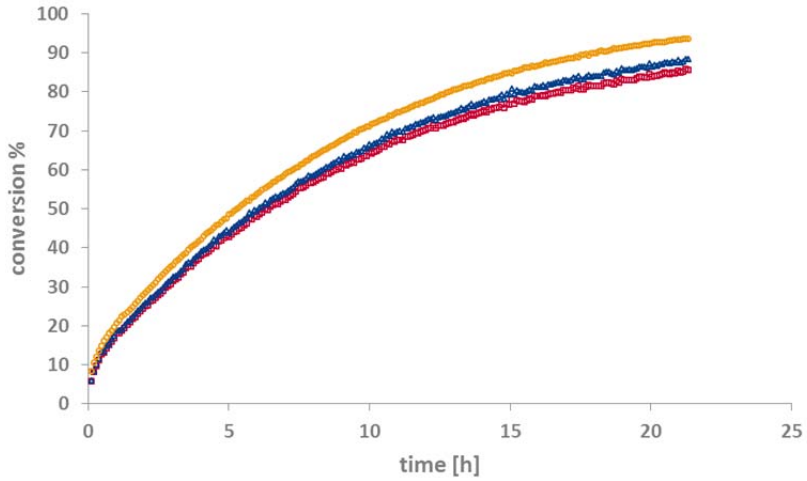


Figure 29. Conversion *vs.* time under ''added water'' conditions (Conditions C). $[\mathbf{1}]_0$= 0.45 M, 10 equiv. acetone, 10 mol% catalyst **I**, 5 mol % AcOH, 1 equiv. water.

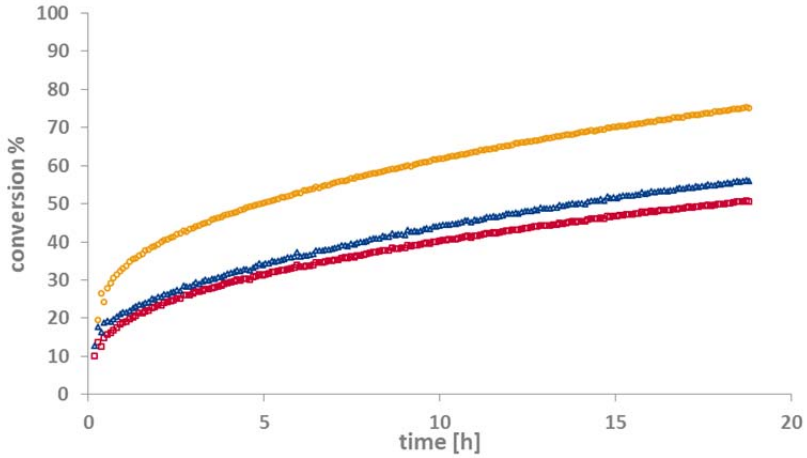


Figure 30. Conversion *vs.* time under ''no extra water added'' conditions (Conditions B). $[\mathbf{1}]_0$= 0.45 M, 10 mol% catalyst **I**, 5 mol % AcOH.

Red squares: conversion calculated based on product **3a** formation

$$conversion\ \% = \frac{[\mathbf{3}\boldsymbol{a}]}{[\mathbf{1}]_0}.\mathbf{100}$$

blue triangles: conversion based on product **3a** plus double-addition side product **3b** formation

$$conversion\ \% = \frac{[\mathbf{3}\boldsymbol{a}] + [\mathbf{3}\boldsymbol{b}]}{[\mathbf{1}]_0}.\mathbf{100}$$

yellow circles: conversion based on nitrostyrene disappearance

$$conversion\ \% = \frac{[\mathbf{1}]_0 - [\mathbf{1}]\boldsymbol{t}}{[\mathbf{1}]_0}.\mathbf{100}$$

4.12. Proof of the ''free catalyst'' does not deactivate

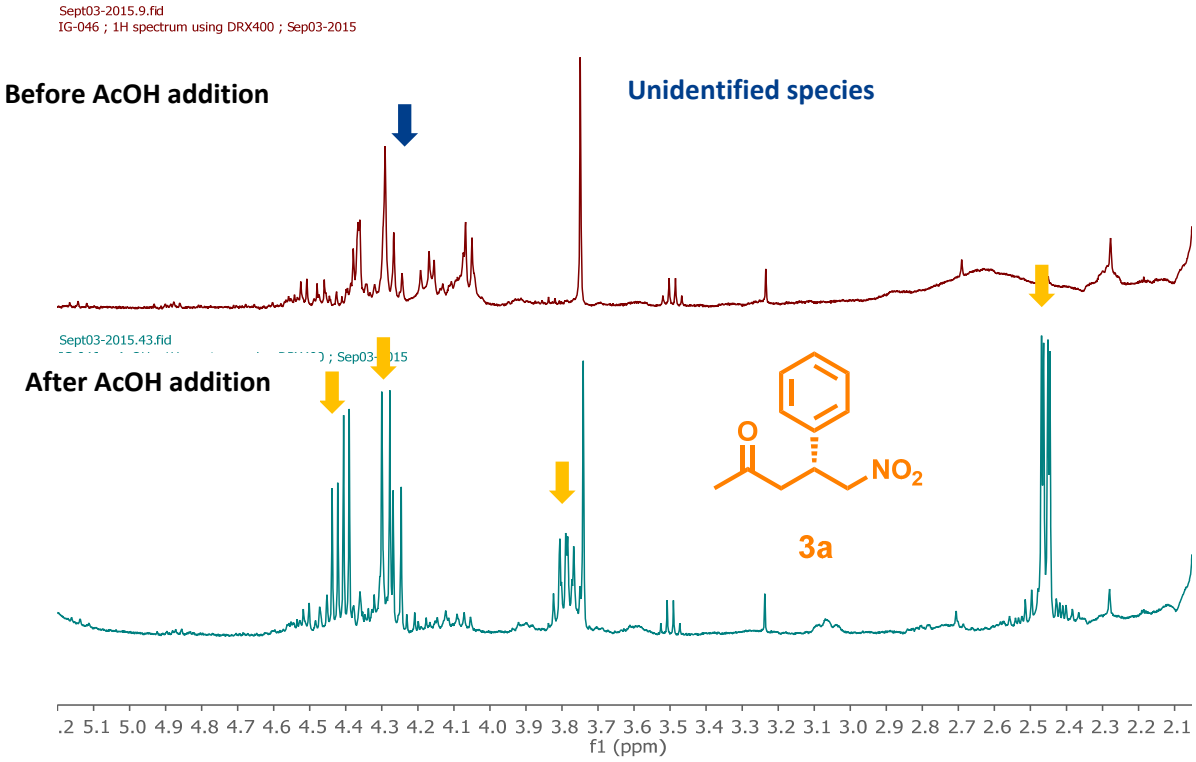
The reactions were carried out under three different sets of reaction conditions (Conditions A-C). For all three sets of reactions, $[\mathbf{1}]_0$= 0.45 M, 10 equiv. acetone and 10 mol% catalyst **I** were used. First, the catalyst (7.5 mg, 0.027 mmol) was weighed directly into the NMR tube, and then the reagents were added from common stock solutions in the indicated order. The catalyst was exposed to nitrostyrene for 3 hours prior to acetone addition. The reaction was then recorded continuously by NMR.

- **Stock solution A (nitrostyrene):** 201.4 mg (1.35 mmol) nitrostyrene in 1 mL d_8-toluene
- **Stock solution B (AcOH):** 81.2 mg (77.4 µL, 1.35mmol) of acetic acid in 1 mL d_8-toluene. 0.1 mL of this solution was diluted to 1 mL d_8-toluene.

  Final solution: 0.135 mmolAcOH / mL solution

Conditions A, in the absence of added water and AcOH:

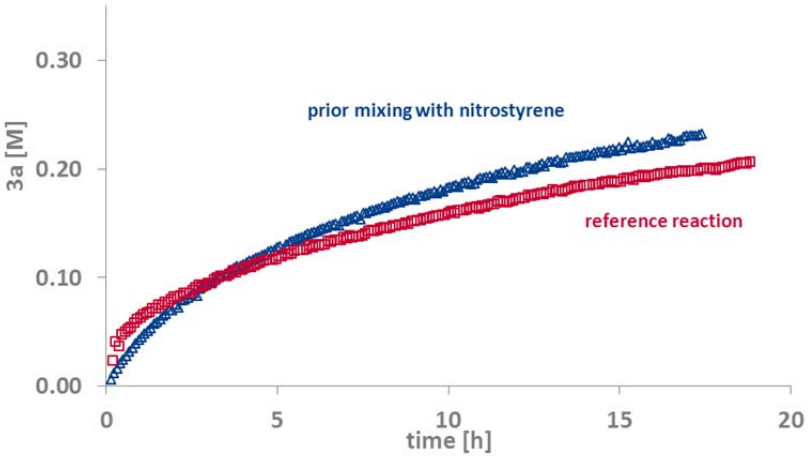
+ 200 µL d_8-toluene
+ 200 µL stock soln. A
Wait 3 hours
+ 200 µL acetone
Wait 1 hour
+ 100 mL stock soln. B



Conditions B, with 5 mol% AcOH and no extra water added:

+100 µL toluene-d_8
+ 100 µL stock soln. B
+ 200 µL Stock soln. A
Wait 3 hours
+ 200 µL acetone

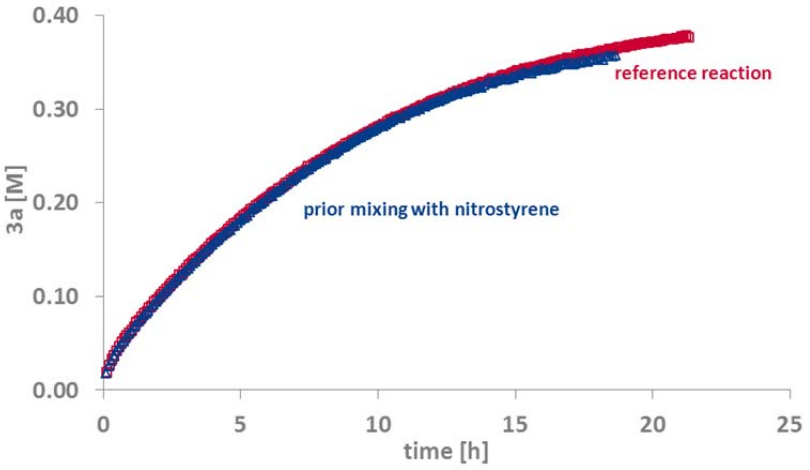
Formation of product **3a** was observed similarly to a reference reaction without catalyst pre-mixing with NS.



Conditions C, with 5mol% AcOH and water added (1 equiv.):

+100 µL d_8-toluene
+ 100 µL Stock soln B
+ 200 µL Stock soln A
+ 4.86 µL H_2O
Wait 3 hours
+ 200 µL acetone

Formation of product **3a** was observed identical to a reference reaction without catalyst pre-mixing with nitrostyrene.



4.13. Proof of no product inhibition

An initial kinetic experiment by ^{1}H NMR (red squares) was repeated under identical conditions (Conditions B, [**1**]$_0$=0.45 M, 10 equiv. acetone, 10 mol% catalyst **I** and 5 mol% AcOH) and recorded continuously by NMR. The amount of product formed during the first 2.5 hours (yellow circles) was calculated as 0.114 M (15 mg, 0.0684 mmol). Another experiment was carried out under identical conditions adding the calculated amount of product at the beginning of the reaction. The overlay of these two traces (product added experiment and the reference experiment) concludes there is *no product inhibition* responsible for this reaction.

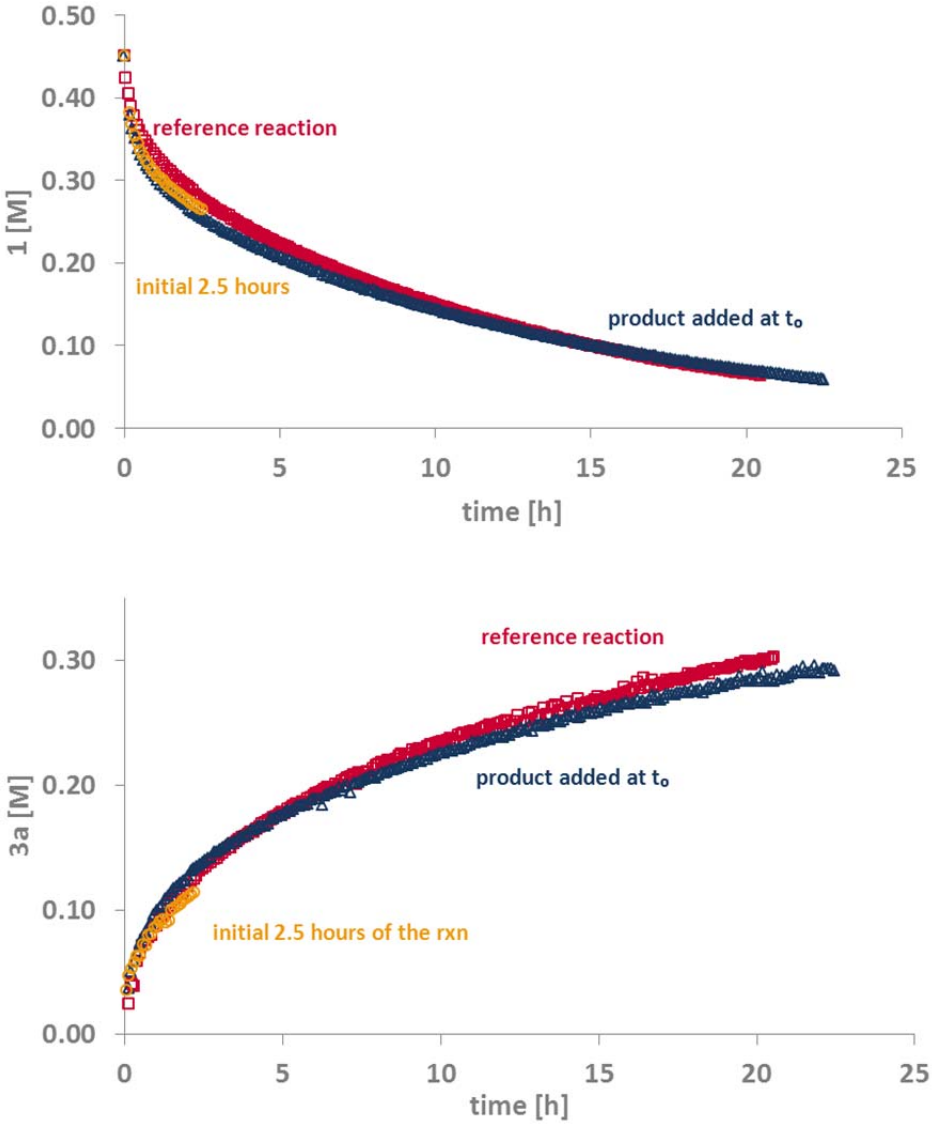


Figure 31. Proof of no product inhibition by carrying out reaction with and without addition of product at t_0.

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Zeynep Inci Günler

PAPER B

A Concentration Effect in the Asymmetric Michael Addition of Acetone to Nitrostyrenes Catalyzed by Primary Amine Thioureas

Submitted to The Journal of Organic Chemistry (Notes)

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PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS
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A Concentration Effect in the Asymmetric Michael Addition of Acetone to Nitrostyrenes Catalyzed by Primary Amine Thioureas

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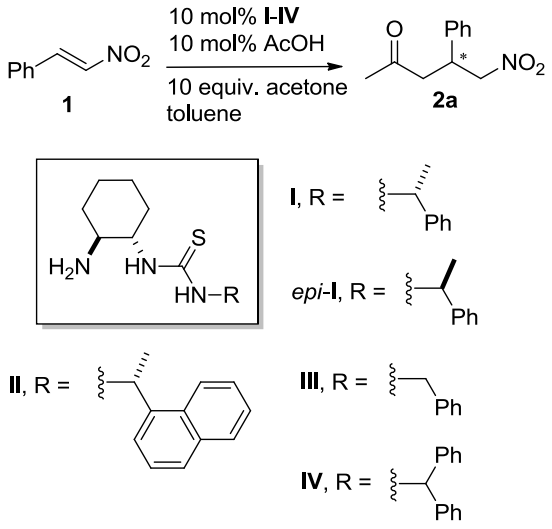
Abstract: Bifunctional primary amine thiourea organocatalysts (PAT) show remarkable improvement in enantioselectivity with high catalytic activity for the asymmetric Michael addition of acetone to nitrostyrenes upon dilution. We attribute this behavior to the complex mechanism of the reaction, which includes off-cycle catalyst deactivation, rather than to aggregation phenomena. Work at lower concentrations (≤ 0.2 M in nitrostyrene) must lead to the minimization of such side reaction and thus to the enhancement in yield and ee of the desired product.

The bifunctional primary amine thioureas (PAT) developed by Tsogoeva[1] and Jacobsen[2] in 2006 represented the first truly effective organocatalysts for asymmetric Michael addition of challenging substrates like ketones and hindered aldehydes to α,β-unsaturated nitro compounds. Indeed, the use of additives (water and/or organic acids) was found to be crucial for the development of efficient and highly enantioselective Michael additions of those challenging substrates. Since then, many examples have been described in the literature due to the interest of the asymmetric Michael addition in organic synthesis and as a benchmark for the development of new catalysts.[3, 4] Likewise, the occurrence of primary amines in the active site of enzymes such as class I aldolases and pyridoxal phosphate dependent enzymes, among many others, has also contributed to stimulate the interest in this kind of catalysts.[5] Furthermore, this type of catalysts can perform efficiently in other reactions besides a large variety of 1,4-type additions, such as Mannich, α-alkylation of aldehydes, cyclizations and cycloadditions, vinilogous aldol, and multicomponent Biginelli reactions.[3a, 3b]

During the mechanistic analysis of the catalytic system comprising **I**, we disclosed the subtle yet decisive effects that acetic acid and water exert over PAT catalysts in the asymmetric Michael addition of acetone to nitrostyrene (Scheme 1).[6] These additives modify the reaction mechanism: water minimizes catalyst deactivation by nitrostyrene,

and acetic acid, which provides the catalyst turnover, the formation of an undesired double addition side product. Although water actually slows down the reaction rate, the overall result is an enhancement in the yield of the desired Michael adduct **2a**.[6]



Scheme 1. Michael addition of acetone to nitrostyrene catalyzed by bifunctional PAT **I**-**IV**.

In continuation of our efforts in asymmetric organocatalysis in general and Michael additions in particular,[7] in this Note we will show how PAT catalysis presents significant changes in conversion and enantioselectivity upon concentration changes. Essentially, dilution leads consistently to higher ee's of the Michael adducts. This behavior was found to be identical for the five PAT catalysts studied herein (Scheme 1). Finally, we will show how under these new reaction conditions, catalyst **IV** behaves as a simple yet efficient PAT catalyst for the Michael addition of acetone to nitrostyrenes.

Several PAT organocatalysts were synthesized according to literature methods and evaluated under the reaction conditions of Scheme 1. Notice that no water was added to the reaction, since the presence of sufficient water was secured by adventitious traces present in solvents, reagents and the atmosphere.[8] Catalysts **I**, *epi*-**I** and **II** were successfully developed for this reaction by Tsogoeva *et al.*[1] Catalyst **III**, developed initially by Yan *et al.*, lacks additional stereocenters and therefore can be considered a simplified version of **I** and *epi*-**I**.[9] Finally, catalyst **IV**, at first designed and tested for asymmetric hydrocyanation reactions by Jacobsen *et al.*, with little success,[10] provided a bulkier benzhydryl side moiety with no additional stereocenters either (Scheme 1).

Hence, acetic acid was used as the only controlled additive to promote the Michael addition. The amount of AcOH was re-optimized for catalyst **I**. Indeed, Figure 1 shows that it is important not to surpass 10 mol% of AcOH; above this value a decrease in conversion takes place. We also observed that ee remained unaffected by the amount of acid (83-86% ee). Therefore the optimal amount of AcOH must be set in a narrow range of 5-10 mol%. Altogether, in this work we decided to use thereafter a 10 mol% of AcOH to ensure that there was always enough acid, but being especially accurate not to surpass that amount (Figure 1).

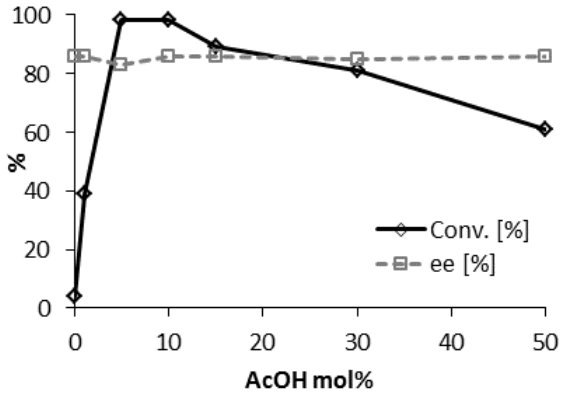


Figure 1. Effect of the AcOH amount in the Michael addition of acetone to nitrostyrene, using 10 mol% catalyst **I**, $[\mathbf{1}]_0$= 0.45 M and 10 equiv. of acetone, in toluene at rt.

Then the benchmark Michael addition was studied at several concentrations with PAT catalysts **I**-**IV**, using 10 mol% catalyst and 10 mol% AcOH. In all cases, a clear improvement in ee was observed upon dilution, the amount of solvent being the only variable. For reactions using 0.335 mmol of nitrostyrene, enantioselectivity increased asymptotically for all catalysts studied (Figure 2) from experiments at high concentration (toluene volume of 0.15 ml plus acetone volume of 0.25 ml, $[\mathbf{1}]_0$ = 0.84 M) to experiments at low concentration (toluene volume of 5 ml plus acetone volume of 0.25 ml, $[\mathbf{1}]_0$ = 0.06 M). For catalyst **I**, the increase of ee was of 14%, whereas for *epi*-**I** it was of 24%. Catalyst **II** exhibited an improvement of 14% ee too. For catalyst **III**, it was of 17% ee, and for catalyst **IV**, up to 15% ee. Clearly the stereoselectivity of the Michael adduct underwent a significant increase, reaching above 90% ee for most catalysts under the more diluted conditions (5 ml toluene added, $[\mathbf{1}]_0$ = 0.06 M). Further dilution below 0.06 M (not shown) led to poorer results, though, likely due to a decrease of catalytic efficiency (Figure 2). The analogous results for *epi*-**I** can be found in the SI.

Regarding conversion, it was also clear that higher concentrations (0.15 ml toluene, $[\mathbf{1}]_0$ = 0.84 M) were not suitable to run this reaction for none of the catalysts studied. Dilution improved the conversion as well, best results being obtained for an initial concentration of nitrostyrene around 0.3 M (1 ml toluene added). Further dilution led, in general, to a slight but still acceptable decrease in conversion. Eventually, conversion ≥95% can be safely achieved for all five catalysts **I**-**IV** in the range of $[\mathbf{1}]_0$ = 0.06 - 0.30 M (1-5 ml of toluene added, Figure 2).

In this way, these experiments showed the importance of optimizing the reactants concentration as a key parameter in PAT catalysis. For the catalysts studied herein, a compromise between the optimal reagents concentration for enantioselectivity and conversion must be decided. An initial concentration of nitrostyrene of 0.15 M seems a good choice in view of our results (2 ml of toluene used plus acetone for 0.335 mmol nitrostyrene), and this value was used thereafter as optimal conditions to test the synthetic utility and substrate scope of catalyst **IV** (*vide infra*). Our data also suggest that the side moiety of the thiourea in PAT catalysts might not be so important in determining activity and enantioselectivity, once a catalytic scaffold, like enantiopure *trans*-1,2-diaminocyclohexane, has been set. Reaction conditions, including additives and concentration, might play a much more important role in defining the final results of PAT-based catalytic systems.

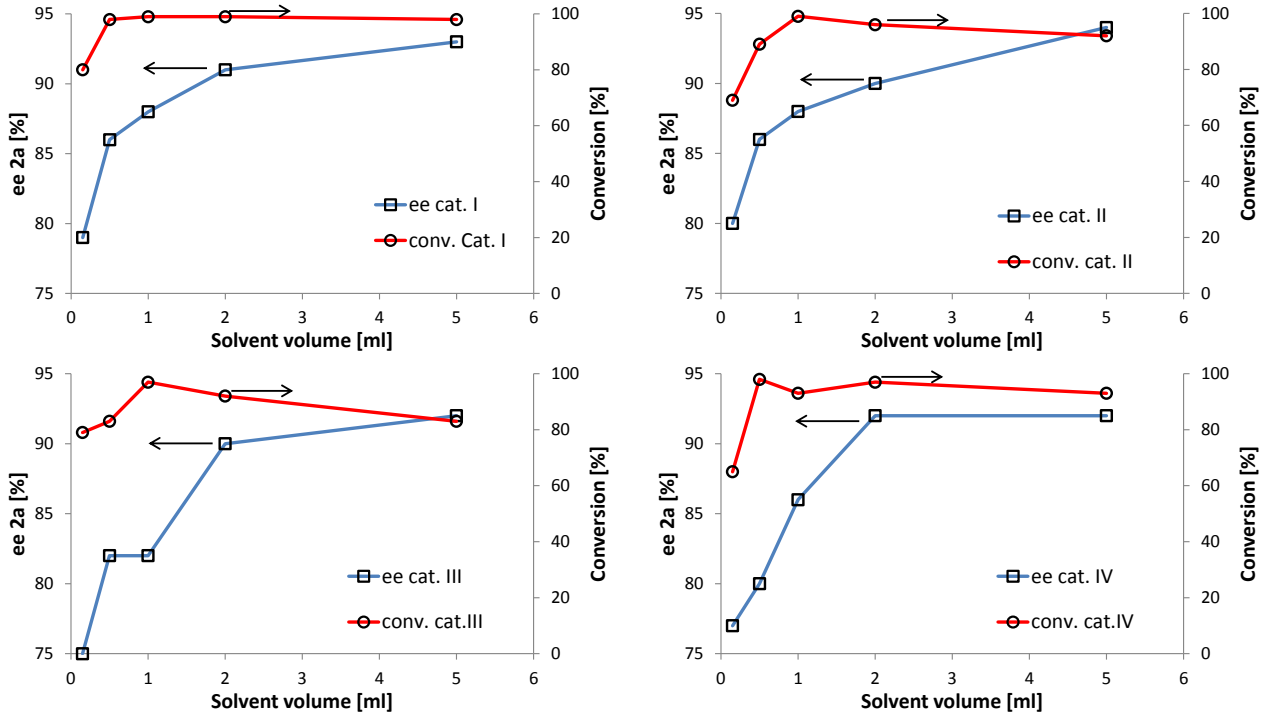
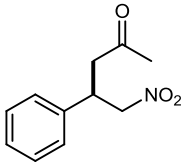
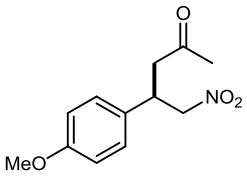
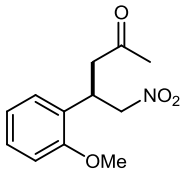
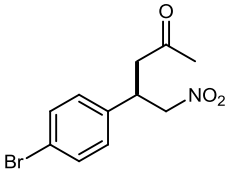
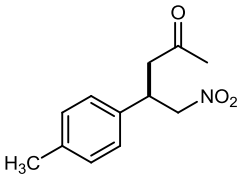
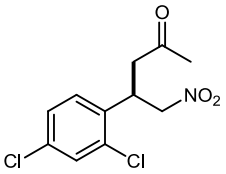
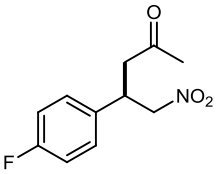
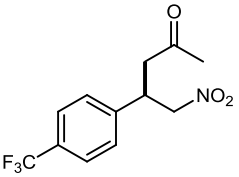


Figure 2. Effect of reactants concentration in ee (left y axis) and conversion (right y axis) for the addition of acetone to nitrostyrene (50 mg, 0.335 mmol) catalyzed by **I**-**IV**, plotted as the amount of toluene added to the reaction. 10 mol% catalyst, 10 mol%. AcOH and 10 equiv. of acetone in toluene, after 24 h reaction. Conversion determined by ^{1}H NMR in the crude samples. ee determined by HPLC on a chiral stationary phase.

Then, we checked the substrate scope under the optimal concentration (Initial concentration of nitrostyrene of 0.15 M, 10 mol% catalyst **IV** and 10 mol% AcOH), as shown in Table 2. High isolated yields and enantioselectivities in the range 84 - 96% ee were obtained for a variety of substituted nitrostyrenes, bearing electron-donating (EDG, entries 2 - 3 and 5) or electron-withdrawing (EWG, entries 4 and 6 - 8) groups. No particular dependence for enantioselectivity was observed on electronic effects. These results prove that **IV** is a simple yet reliable catalyst for this particular reaction.

Table 2. Asymmetric Michael addition of acetone to substituted nitrostyrenes at $[\mathbf{1}]_0$ = 0.15 M, using 10 mol% catalyst **IV** and 10 mol% AcOH, in toluene at rt for 24 h.

Entry	Product	Yield [%][a]	*ee* [%][b]
1		72	93
2		76	96
3		80	91
4		81	89
5		55	87
6		77	92
7		80	92
8		54	84

[a] Isolated yield after purification by flash chromatography on silica gel. [b] Determined by chiral phase HPLC.

We are aware that catalyst self-aggregation phenomena could be an explanation for this behavior since some thioureas and squaramides are known to undergo concentration-dependent aggregation that have a deep impact in their performance as asymmetric catalysts.[11, 12] High aggregation phenomena because of gelation can even lead to inversion of stereoselectivity.[13] In these compounds aggregation usually takes place through the establishment of intermolecular hydrogen bonds between thiourea (or squaramide) groups. However, we have discarded catalyst aggregation phenomena in PAT catalysis because NMR dilution experiments on **I** proved specifically that no aggregation took place in solution in the presence of AcOH, although a weak dimerization constant (K_{dimer} = 25 M^{-1} at 25 ºC) can be associated to the acid-free catalyst in solution (See SI for details). Moreover, the absence on non-linear effects in the asymmetric Michael addition catalyzed by **IV** (See SI), in the same way that Takemoto's catalyst (a tertiary amine thiourea catalyst) supported this observation too.[14]-Finally, we were able to obtain single crystals of **IV**·AcOH suitable for X-rays diffraction analysis (Figure 3). No thiourea-thiourea contacts were observed in the solid state either. Instead, thiourea-acetate and thiourea-ammonium hydrogen bonding were the norm.

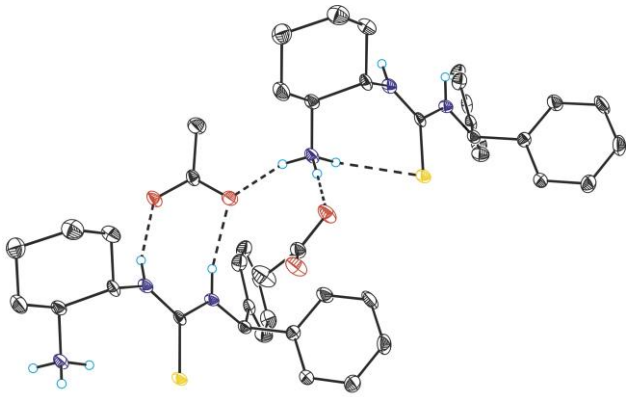


Figure 3. Unit cell of **IV**·AcOH showing intra and intermolecular hydrogen bonding. Sulfur, yellow; nitrogen, blue; oxygen, red; carbon, grey. Non H-bonding hydrogen atoms have been omitted for clarity. Elipsoid probability level set at 50%.

Reaction reversibility, which has a decisive impact in yield and stereoselectivity of Michael addition of α,α-disubstituted aldehydes to nitro-olefins,[15] must be of negligible importance for the Michael addition of acetone since, for example, ee stays constant over time with catalyst **IV**. Likewise, we never detected product inhibition nor a backwards reaction of the addition product with the free PAT catalyst (See SI).[6]

It could be argued that these changes in conversion and enantioselectivity can be due to changes in pH due to different concentrations of AcOH that might affect a non-asymmetric background reaction. However, it can be calculated, assuming an aqueous

solution, that pH would only decrease from 3.5 to 2.9 when going from the most diluted conditions to the most concentrated ($[\mathbf{1}]_0$ = 0.06 M to 0.84 M). Therefore, the most likely explanation for the observed concentration effect relies on the very mechanism of PAT catalysis: Catalyst deactivation by nitrostyrene is an off-cycle process in direct competition with the main catalytic cycle leading to the Michael adduct.[6] If dilution makes this process kinetically disfavored (For example, a second order reaction like nitrostyrene polymerization should be disfavored upon dilution in front of a first order reaction),[16] more active catalyst is available for the main cycle and TOF increases. Hence, yields remain very high in all cases. The increase in ee can be simply attributed to this increase in TOF of the catalytic asymmetric process in front of the non-asymmetric background reaction. The conclusion is that running the reaction under diluted conditions can keep under control the side reactions hampering the Michael addition and achieve an efficient process.

To sum up, we have found a remarkable and general concentration effect in the asymmetric Michael addition of acetone to nitrostyrenes catalyzed by PAT. When decreasing the reactants concentration (dilution), ee's increase significantly while conversion remains high. Under the optimal concentration ($[\mathbf{1}]_0$ = 0.15 M) excellent results can be obtained. Finally, we have successfully applied catalyst **IV** to the asymmetric Michael addition of acetone to nitrostyrenes for the first time. It thus becomes apparent that, in this Michael addition catalyzed by PAT, reaction concentration plays a fundamental role and must be thoroughly optimized to ensure the highest performance of the catalyst.

Experimental Section

All reagents were purchased and used without any further purification. 4-Trifluoromethyl-β-nitrostyrene was synthesized according to the literature procedure.[17] The solvents were directly used from the bottle unless otherwise indicated. Unless otherwise stated, all reactions were performed in air. Column chromatography and TLC were performed on silica gel using UV light and/or indicated stains to visualize the products. ^{1}H and ^{13}C NMR spectra were measured in the indicated deuterated solvent at 25 °C on a 400 or 500 MHz spectrometer. Chemical shifts are reported in ppm downfield and upfield from tetramethylsilane and referenced to solvent resonances. High resolution mass spectra were performed with a LC-MS spectrometer equipped with a TOF analyzer.

General Michael addition procedure for dilution studies: In a vial, the catalyst (0.1 equiv., 0.0335 mmol) and nitrostyrene (1 eq., 0.335 mmol, 50 mg) were weighed and dissolved in 2 ml toluene (varied for other reaction concentrations). To this solution 0.1 equiv. of AcOH was added (using 10 µl of a stock solution of 200 µl, 3.5 mmol AcOH in 1 ml toluene). Finally 10 equiv. of acetone (3.35 mmol, 250 µl) was added and the reaction was stirred at room temperature for 24 hours. To quench the reaction, water was added and the organic phase was extracted with EtOAc and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the crude mixture was analyzed by ^{1}H NMR to determine the conversion. HPLC samples were prepared from crude reaction mixture and analyzed in a Phenomenex Lux 5u-Amylose-2 column (Hexane: ^{i}PrOH= 90:10, 1 ml/min, 209 nm).

General preparative Michael addition procedure ($[nitroalkene]_0$ = 0.15 M): In a 10 ml flask, catalyst **IV** (0.1 equiv., 0.1 mmol, 34 mg) and the corresponding nitroalkene (1 equiv., 1 mmol) were weighed and dissolved in 6 ml toluene. To this solution AcOH (0.1 equiv., 0.1 mmol, 5.7 µl) and acetone (10 equiv., 10 mmol, 0.75 ml) were added. The reaction was stirred at room temperature for 24 hours. Then, water was added to the reaction and that mixture was taken to a separation funnel. The organic phase was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the crude mixture was purified by chromatography on silica gel (1:4 EtOAc:Hexane). HPLC samples were prepared from pure products and analyzed in a Phenomenex Lux 5u-Amylose-2 column (Hexane: ^{i}PrOH= 90:10, 1 mL/min, 209 nm).

Associated content

The Supporting Information is available free of charge on the ACS Publications website at.

NMR spectra of catalysts **I**-**IV** and Michael adducts. Chiral HPLC traces of Michael adducts. NMR titration spectra and fitting to a dimerization model. Non-linear effects plots. X-rays diffraction data. Conversion and ee vs concentration plot for catalyst *epi*-**I** (PDF).

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Notes

The authors declare no competing financial interest.

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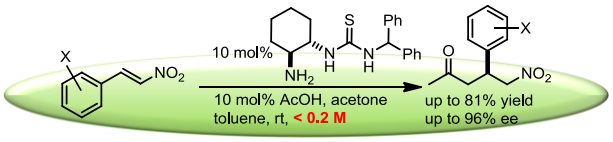

SUPPORTING INFORMATION

A concentration effect in the asymmetric Michael addition of acetone to nitrostyrenes catalyzed by primary amine thioureas

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1. NMR spectra of catalysts I-IV

NMR Spectra for catalyst I

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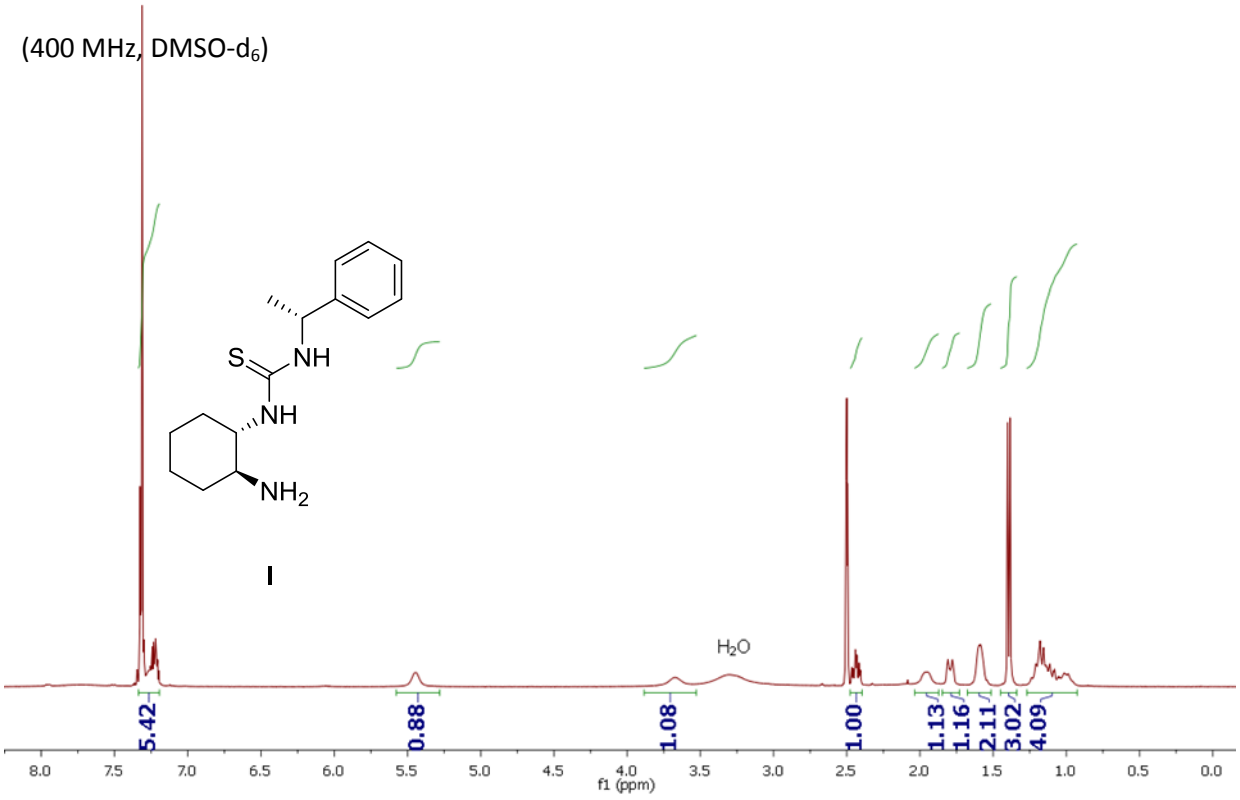

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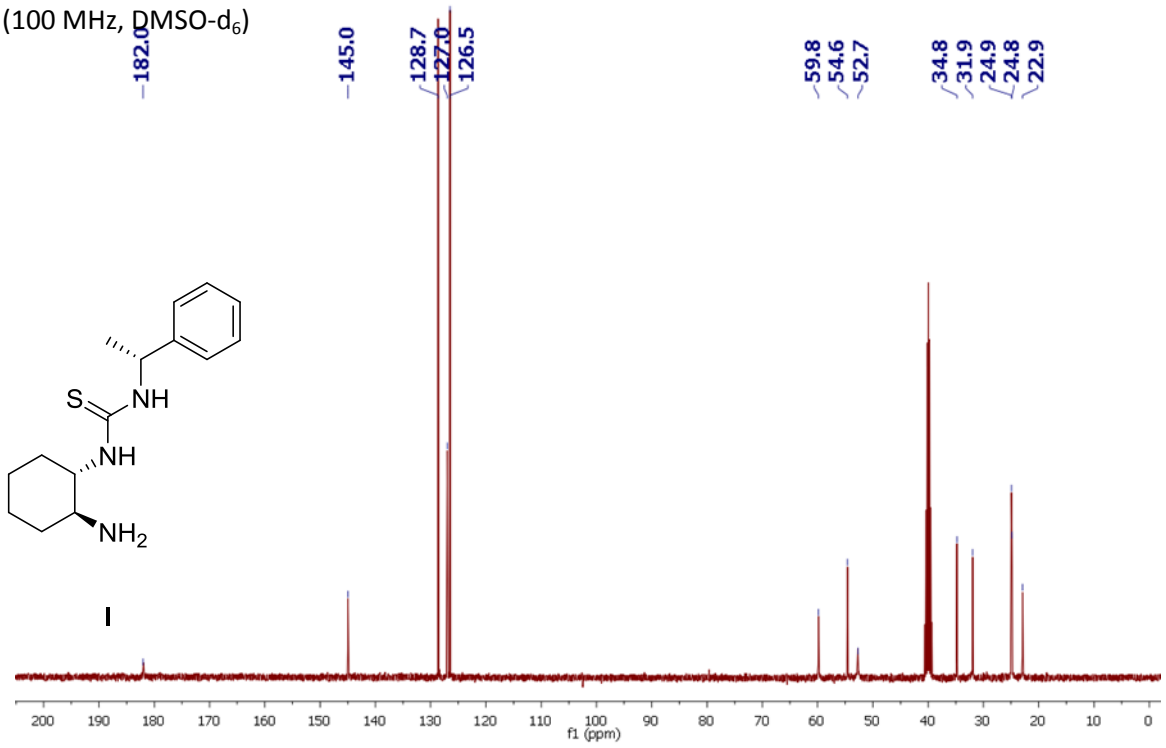
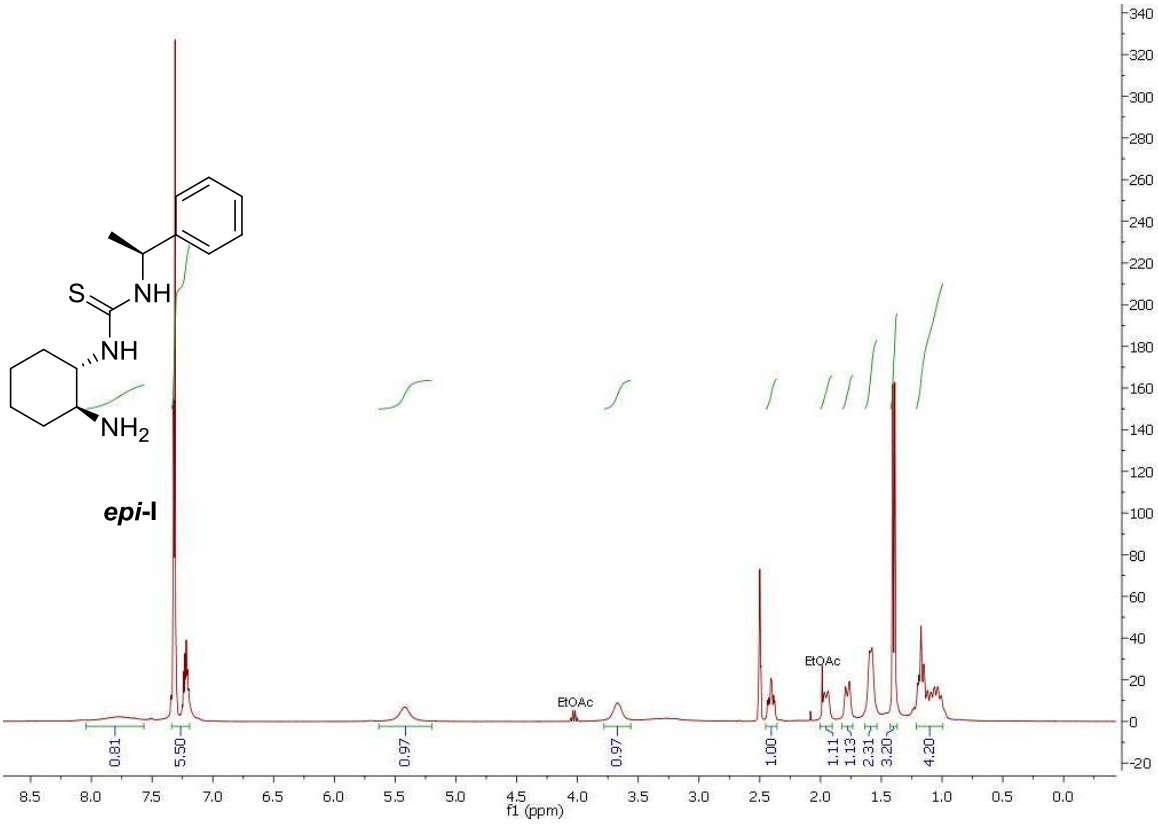


NMR Spectra for catalyst *epi*-I

(400 MHz, DMSO-d_6)



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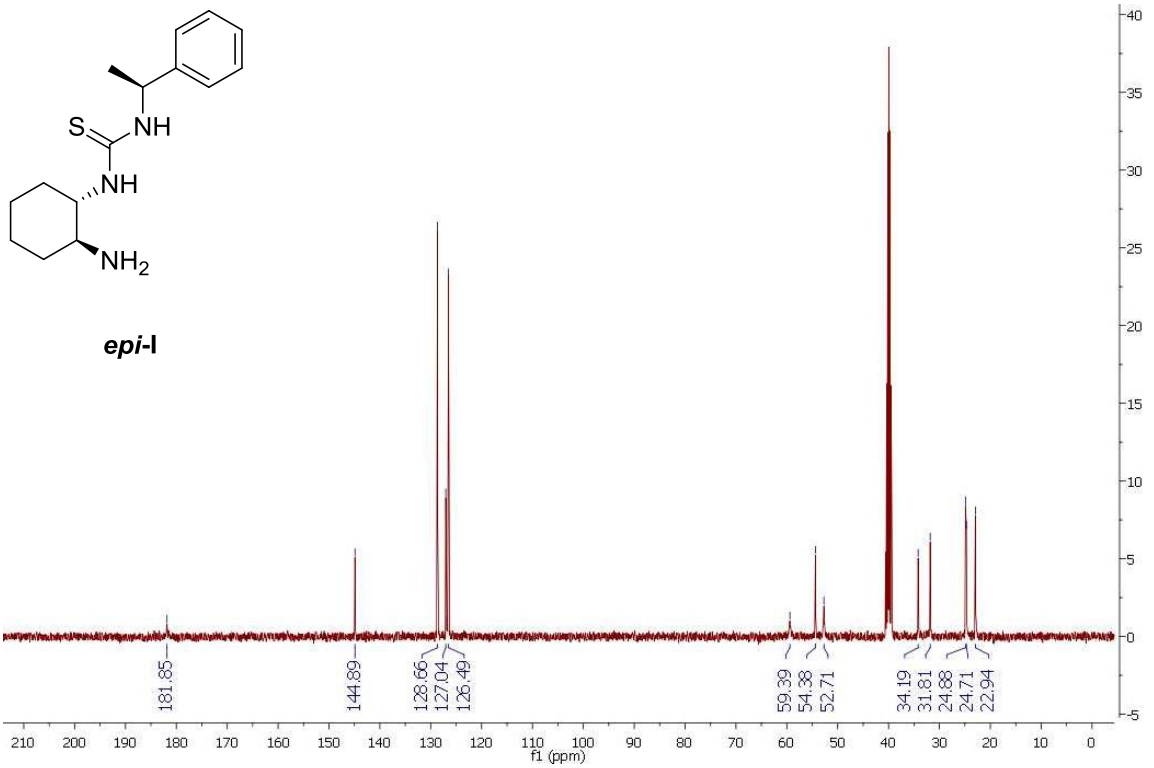

NMR Spectra for catalyst II

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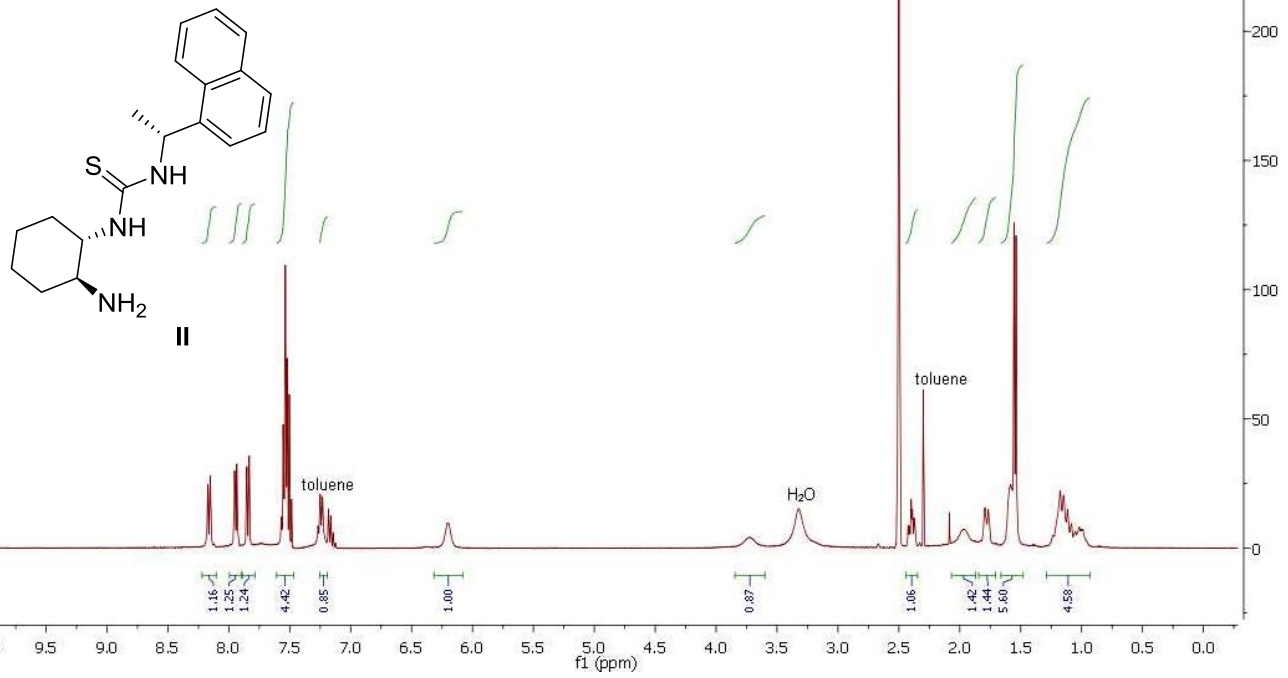

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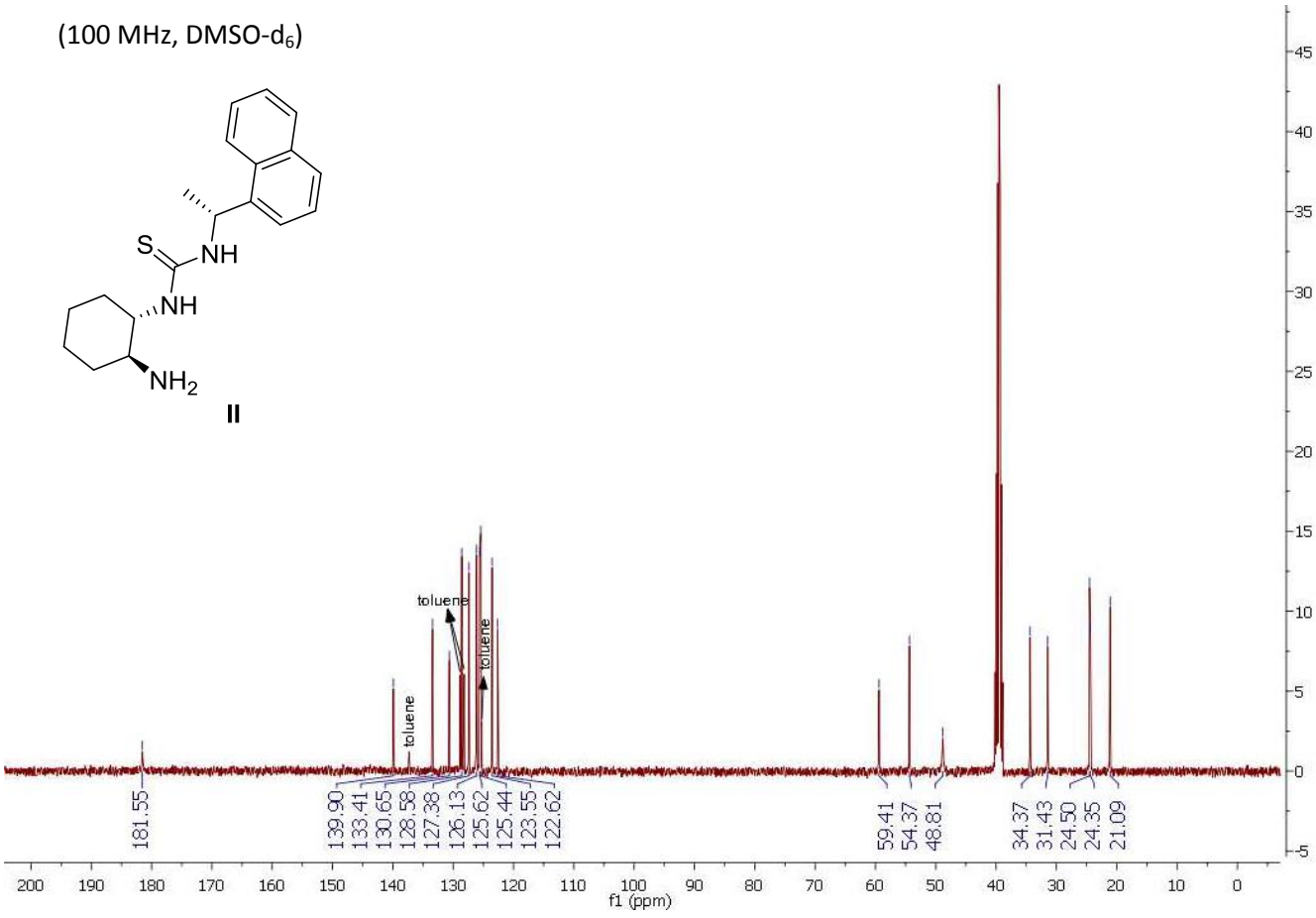

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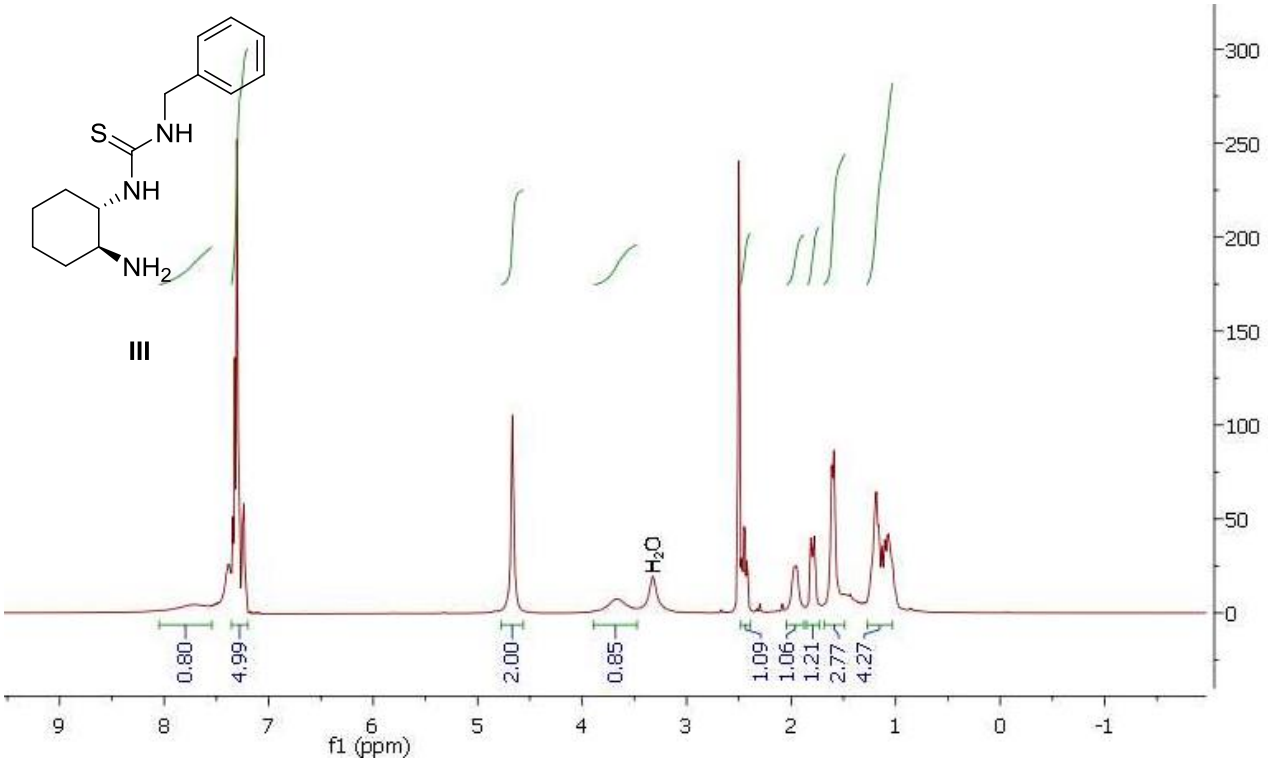

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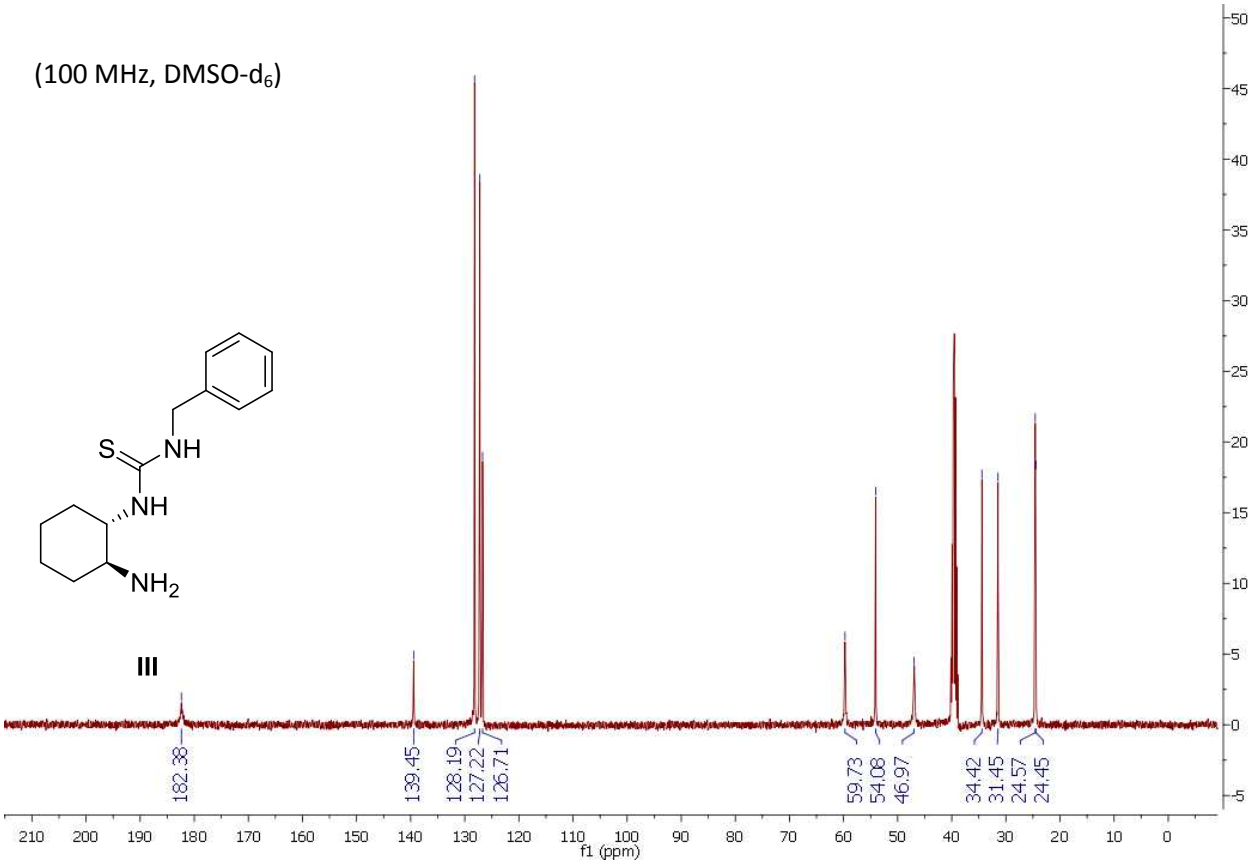

NMR Spectra for catalyst IV

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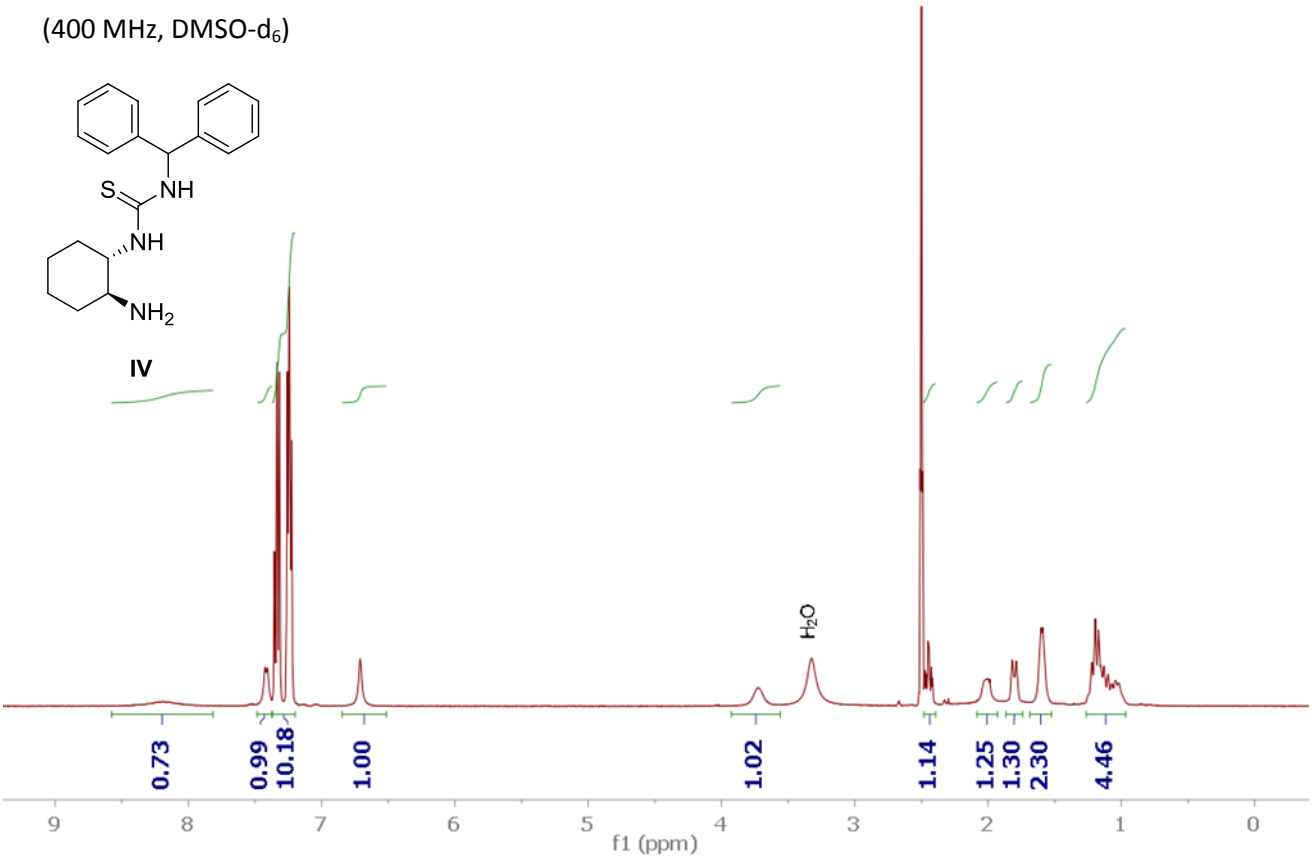

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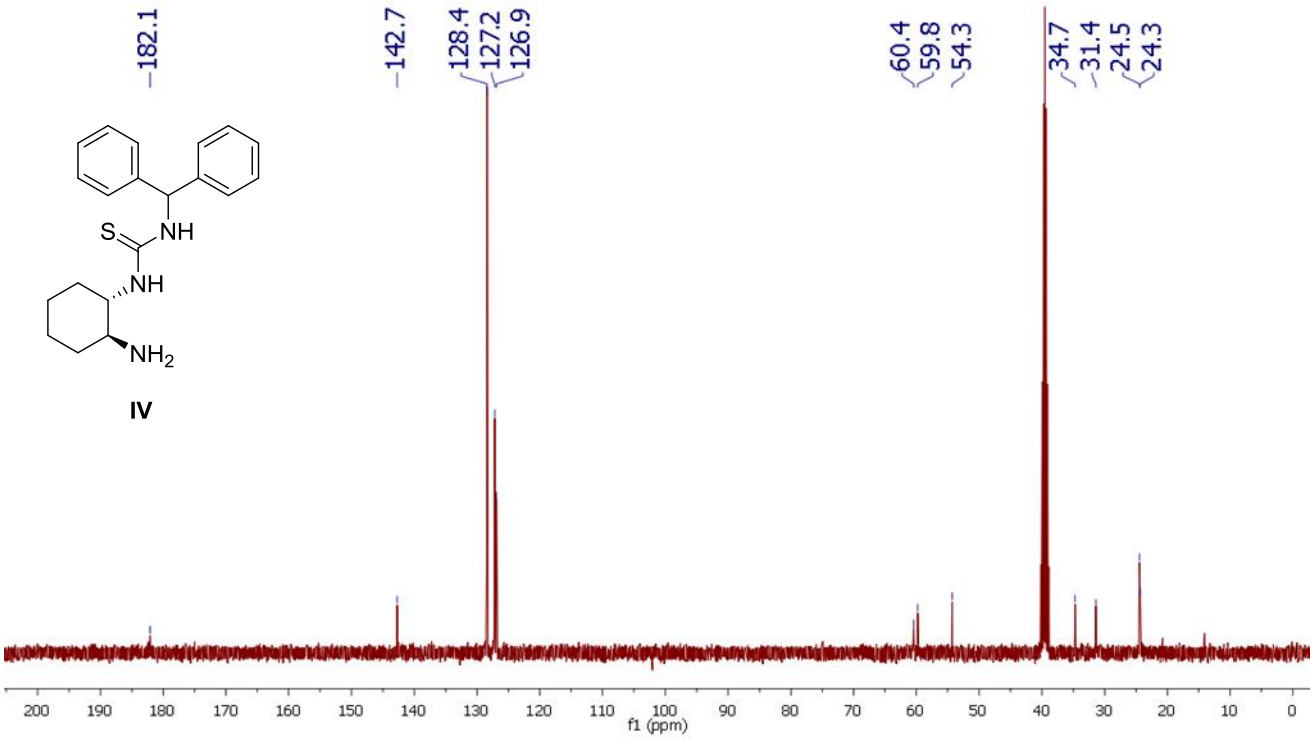


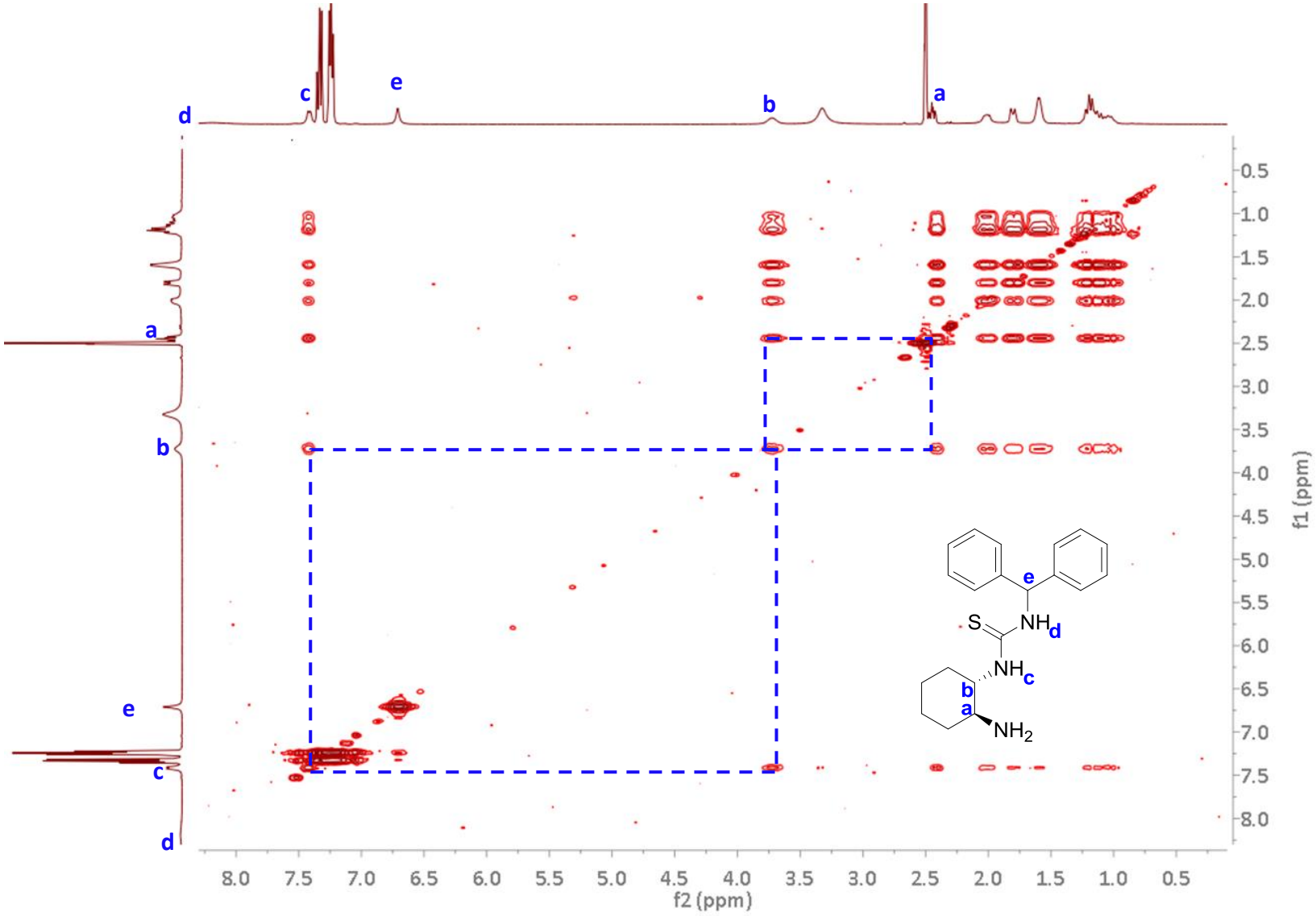
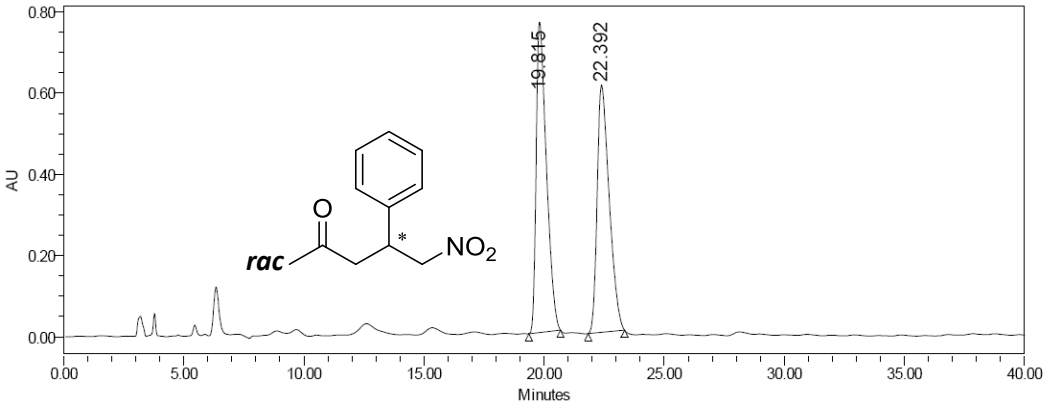


Figure 1. TOCSY cross peaks for catalyst **IV**

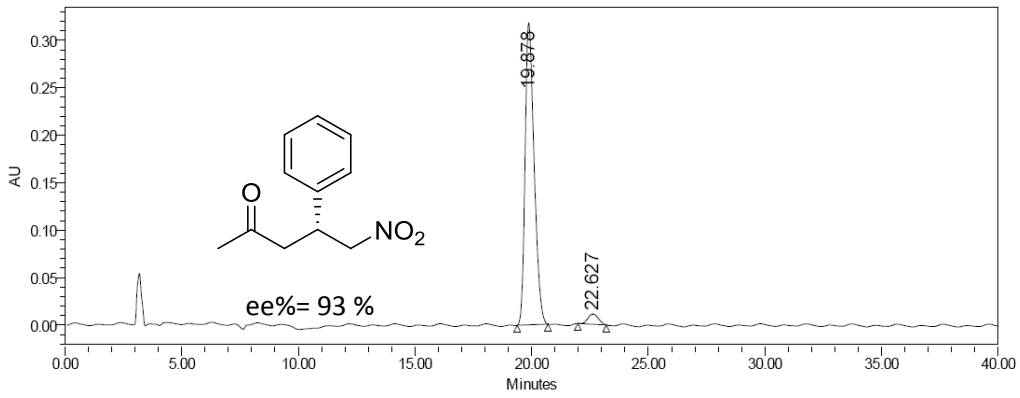
2. Enantioselective Michael addition of acetone to nitroalkenes

2.1. Synthesis of racemic Michael addition products: In a vial, DL-Proline (0.1 eq., 0.075 mmol, 8.65 mg) and nitroalkene (1 eq., 0.5 mmol) were dissolved in 2 mL DMSO. Acetone (10 eq., 5 mmol) was added and the reaction was stirred overnight. Water was added to the reaction and the mixture was taken to a small separation funnel. Organic phase was extracted with ethyl acetate and concentrated *in vacuo*. The crude mixture was purified over silica using 1:4 EtOAc:Hexane as eluent. HPLC analysis was performed to determine the retention times of each enantiomer (Phenomenex Lux 5u-Amylose-2 column, Hexane:*i*PrOH, 90:10, 1 mL/min, 209 nm). The same HPLC conditions were used for all chiral products. Absolute configuration of addition product was determined by optical rotation and comparison with literature data.[3]

2.2. Chiral HPLC Chromatograms of Michael adducts

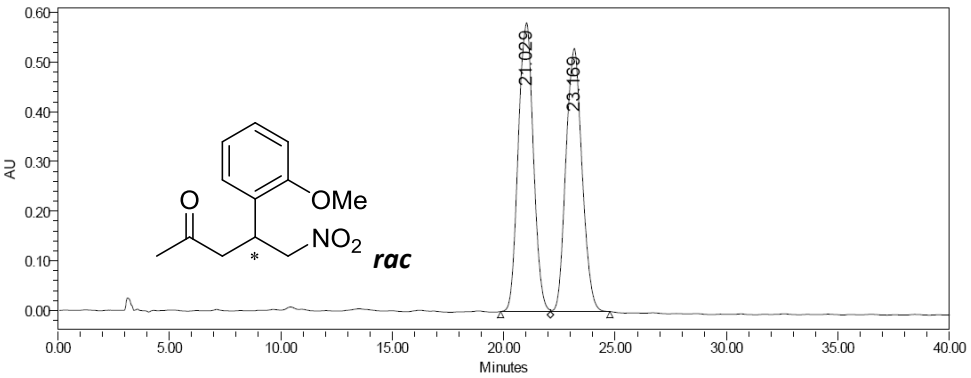


	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	19.815	22554926	51.50	764212
2	22.392	21237472	48.50	608730



$[\alpha]^{20}_{D}$ = -6.75° (c = 0.4, $CHCl_3$)

	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	19.878	8568885	96.23	318261
2	22.627	335895	3.77	10822



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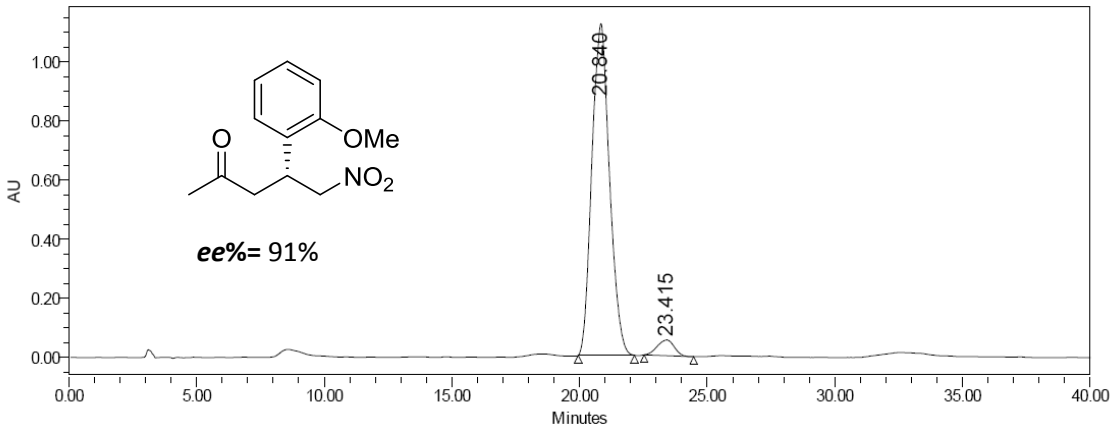
2	23.169	26646170	49.29	529539



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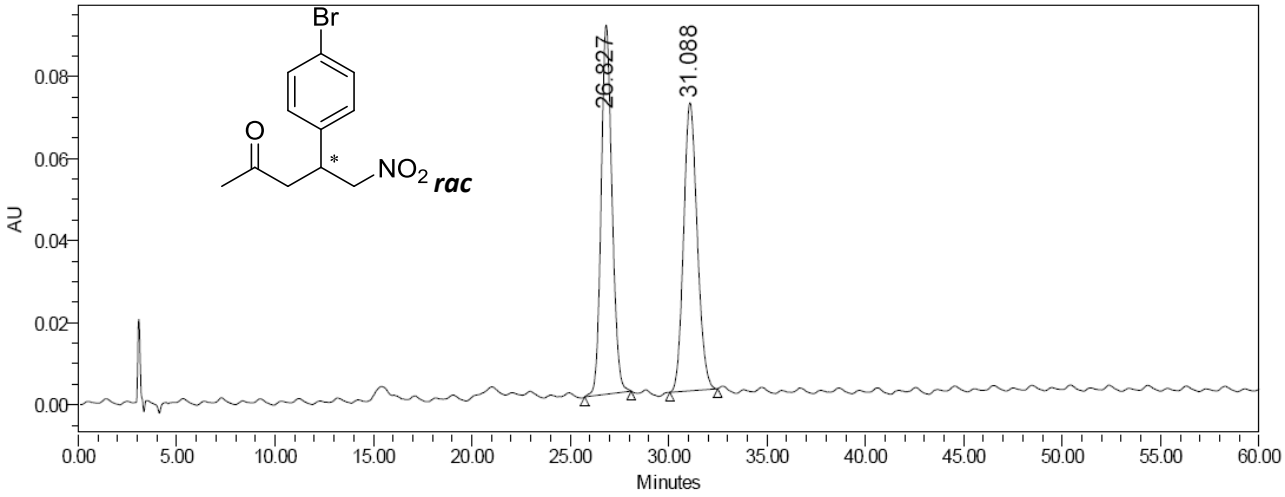
1	20.840	53926669	95.63	1123283
2	23.415	2461592	4.37	53226



	RT (min)	Area (μV*sec)	% Area	Height (μV)
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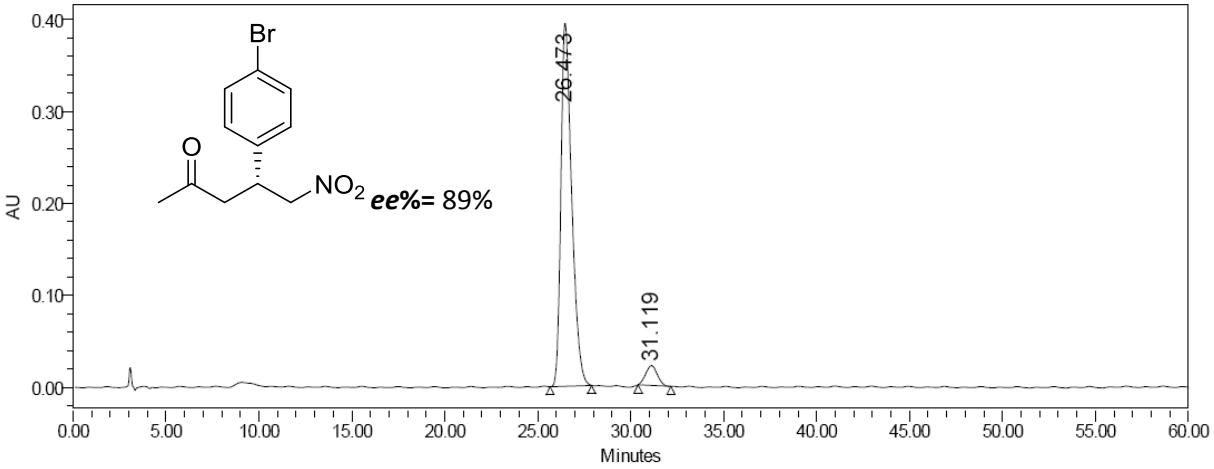
2	31.088	3382969	49.45	70189



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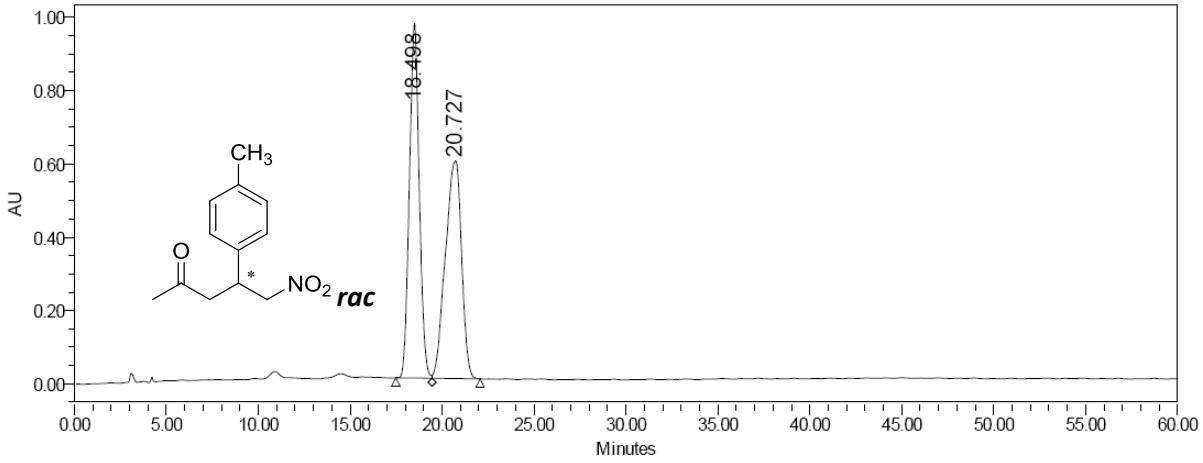
2	31.119	928985	5.51	21567



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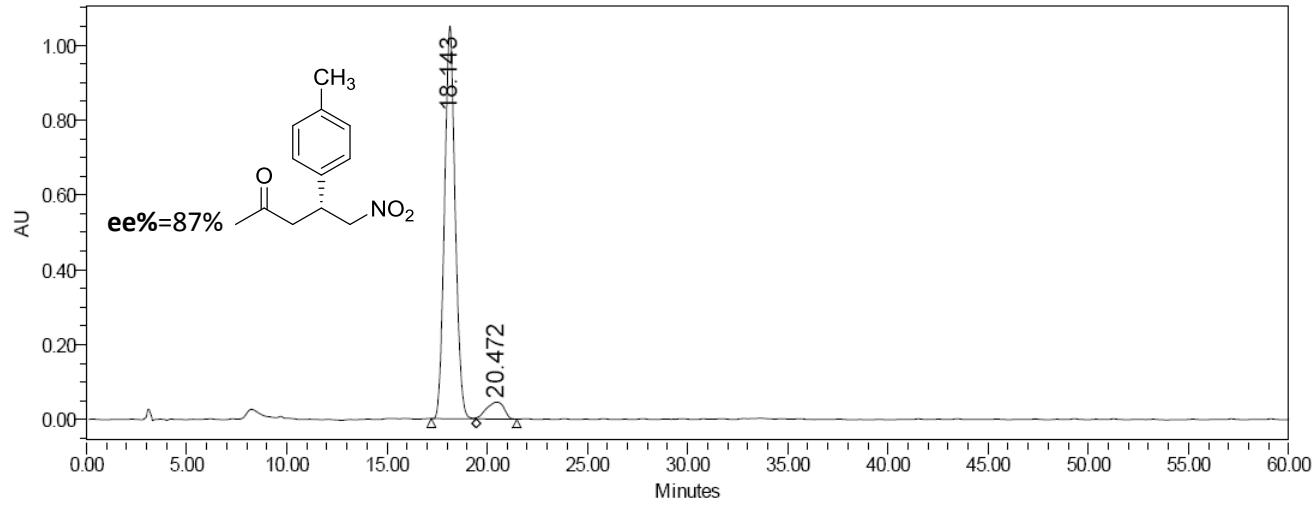
2	20.727	36287663	50.21	593370



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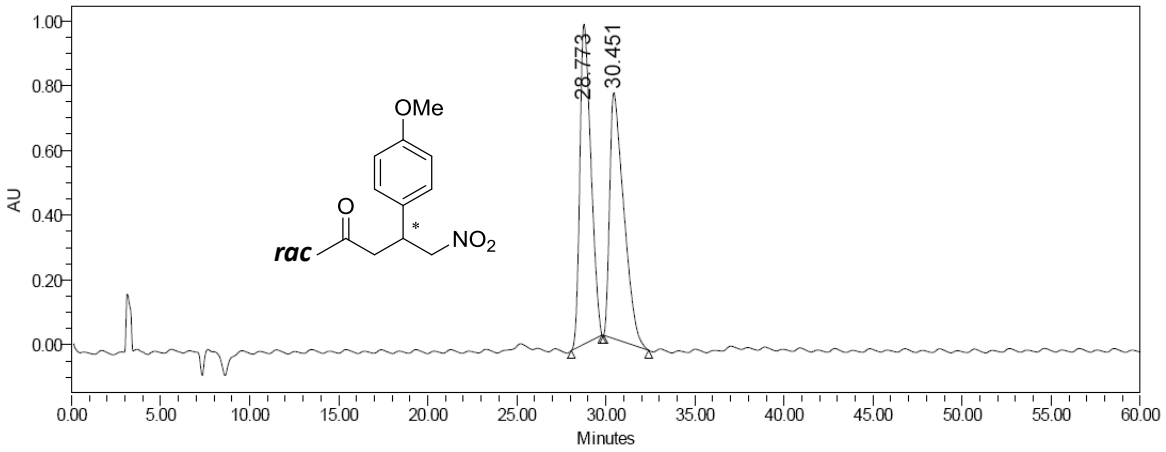
2	20.472	2757748	6.65	45173



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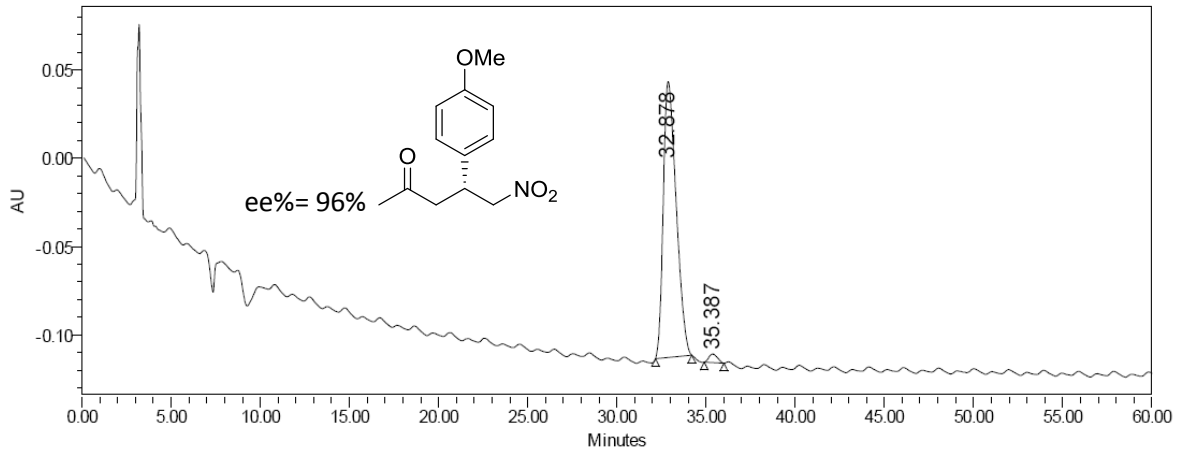
2	30.451	41955117	49.60	759016



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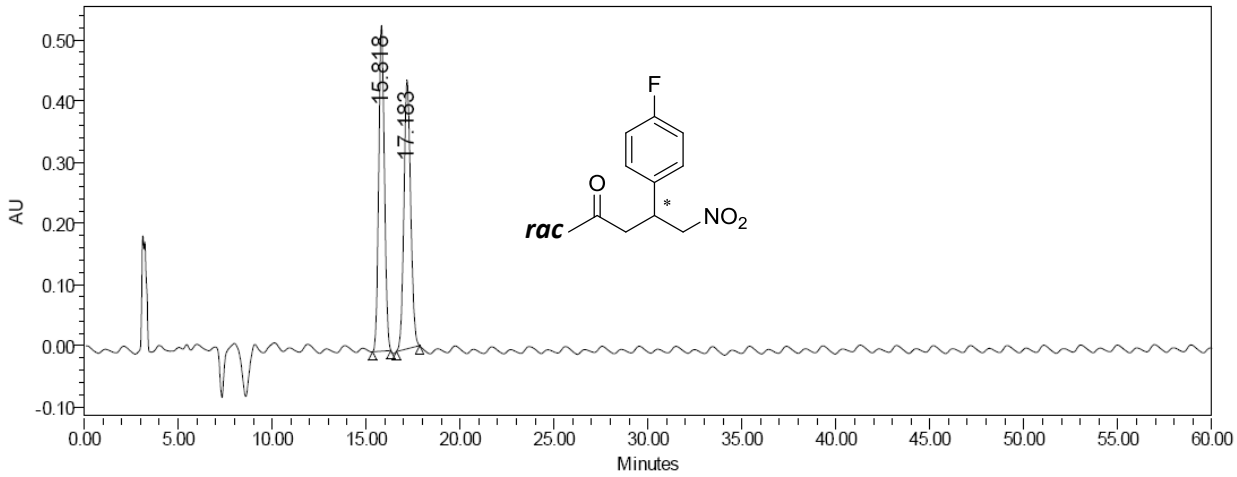

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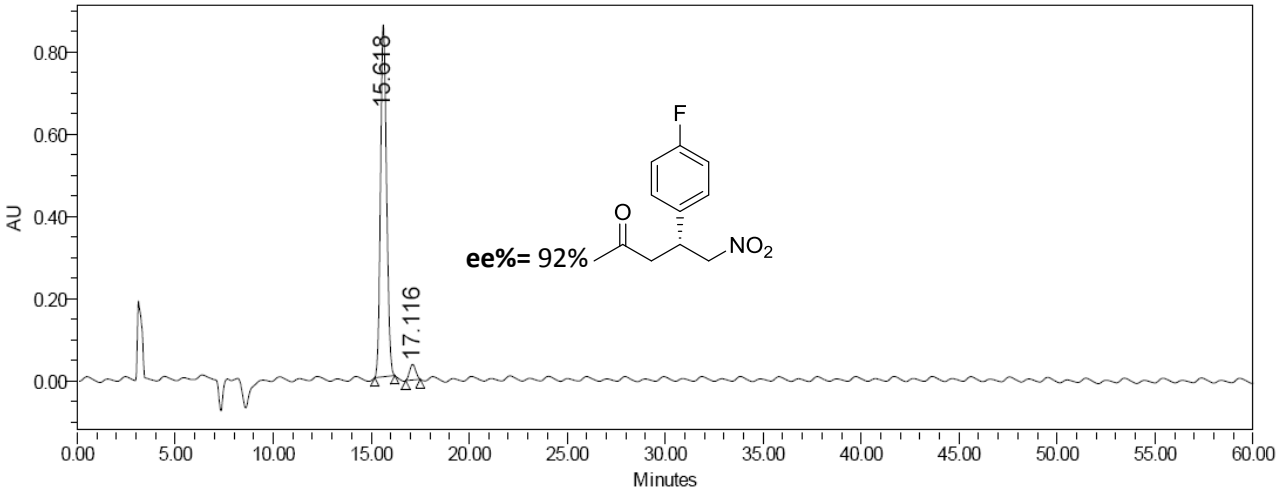

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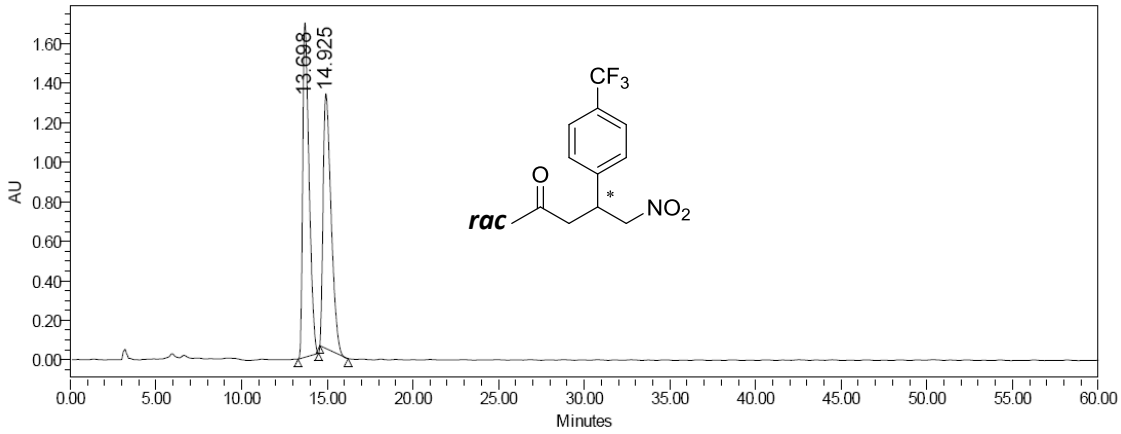
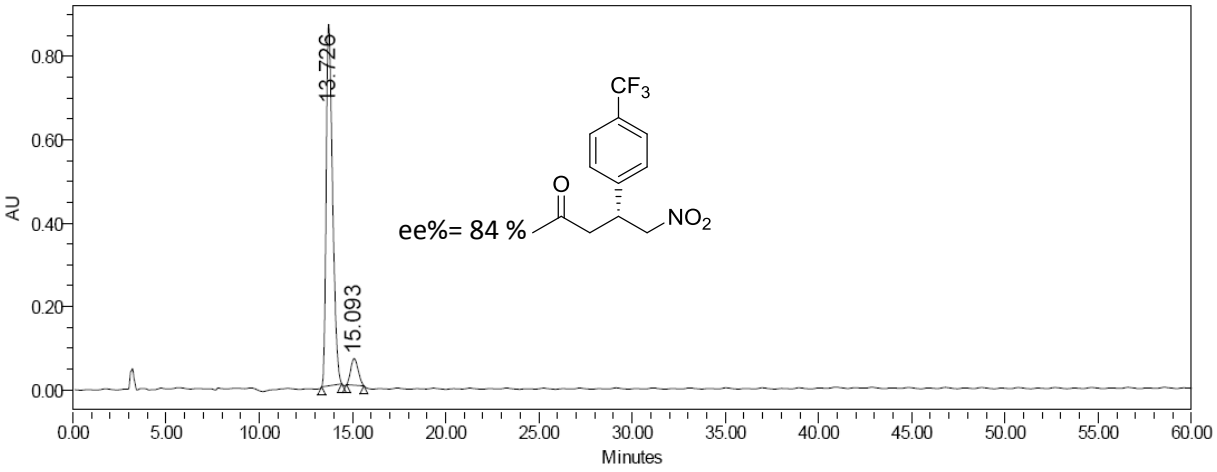
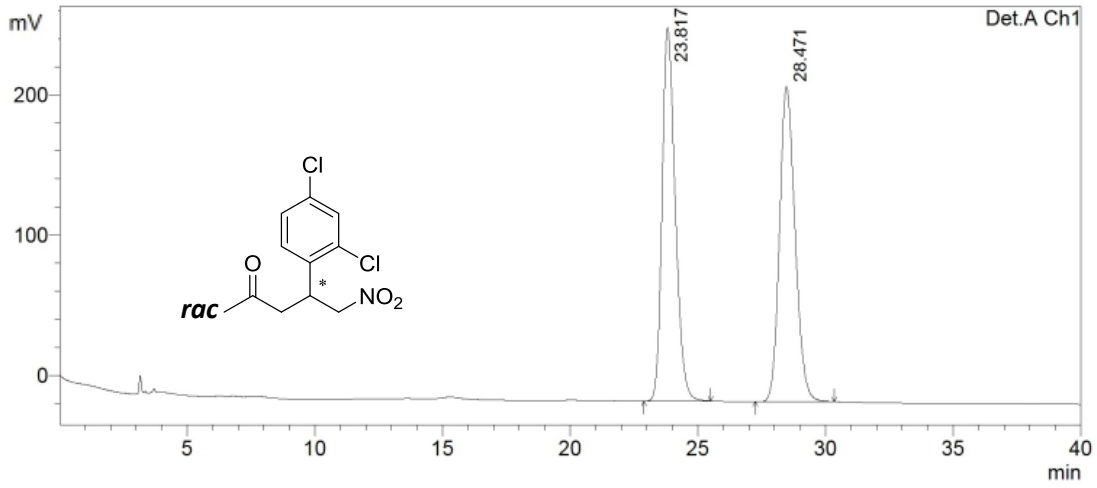
1	15.618	18228822	95.70	854343
2	17.116	819680	4.30	37838



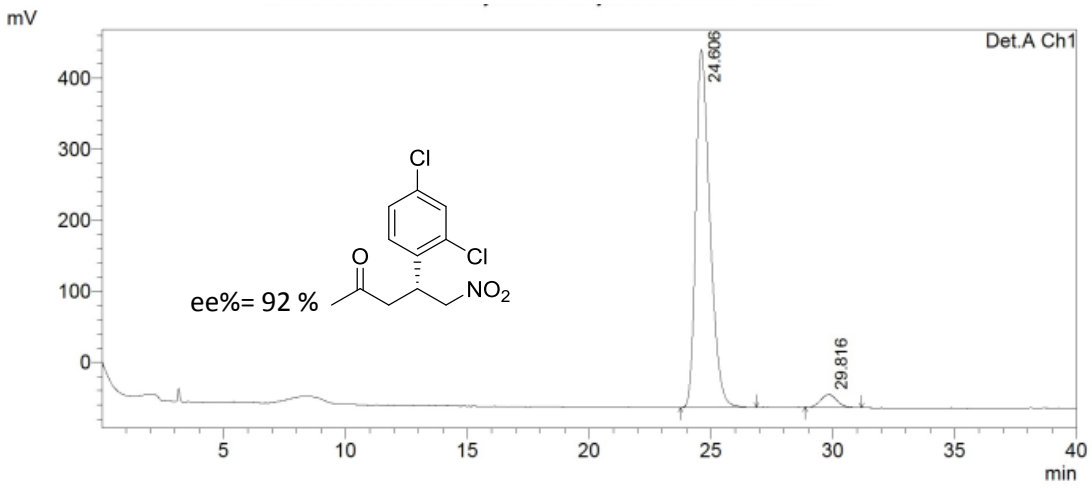
	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	13.698	43836841	51.17	1692744
2	14.925	41824771	48.83	1289722



	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	13.726	20714645	92.14	868875
2	15.093	1766880	7.86	63884



Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.817	9512226	266276	49.903	54.214
2	28.471	9549021	224883	50.097	45.786
Total		19061247	491159	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.606	20286579	503673	96.133	96.560
2	29.816	816085	17946	3.867	3.440
Total		21102664	521619	100.000	100.000

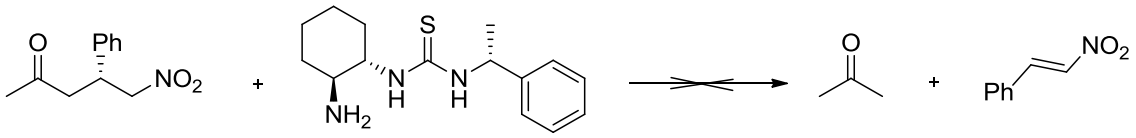
2.3. Enantioselectivity *vs.*time for the reaction leading to 2a

The *ee* value was measured by sampling along the Michael addition of acetone to nitrostyrene for two different concentrations (0.45 m and 0.15 M). It stays constant over time. Experiments were performed using Catalyst **IV**

time hr	ee % (0.45 M Nitrostyrene)	ee % (0.15 M Nitrostyrene)
0.5	81	92
1	81	93
2	81	93
3	80	92
20	80	92

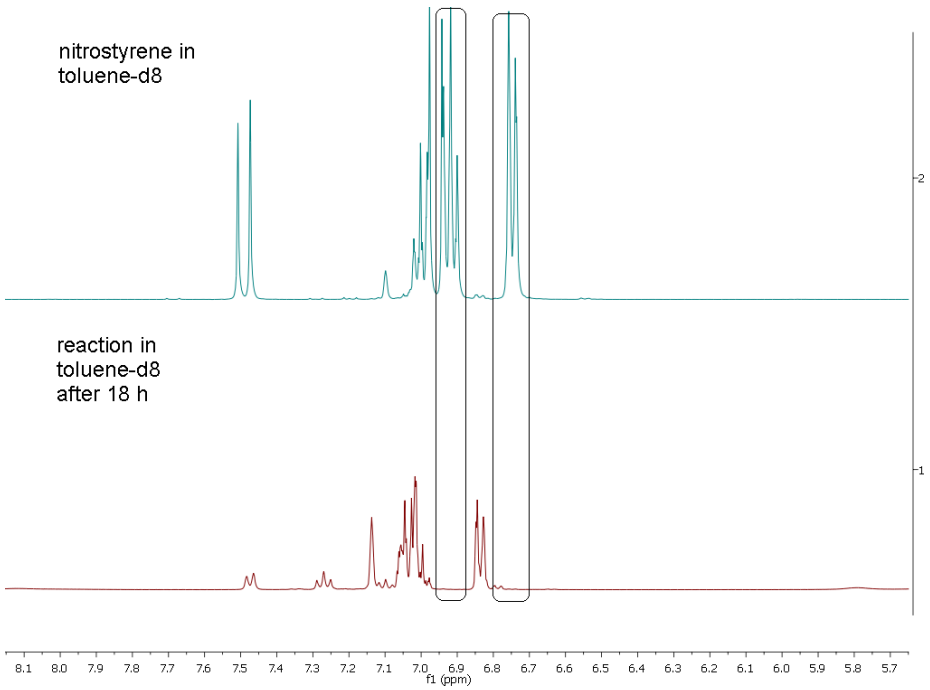
2.4. Proof of no backwards reaction

A solution of catalyst **I** (0.017 mmol, 4.7 mg) in toluene-d_8 was prepared. Enantioenriched addition product **2a** (0.085 mmol, 17.6 mg) and AcOH (0.017 mmol, 1 µL) were added to this solution. ^{1}H NMR recording over time showed the absence of nitrostyrene.



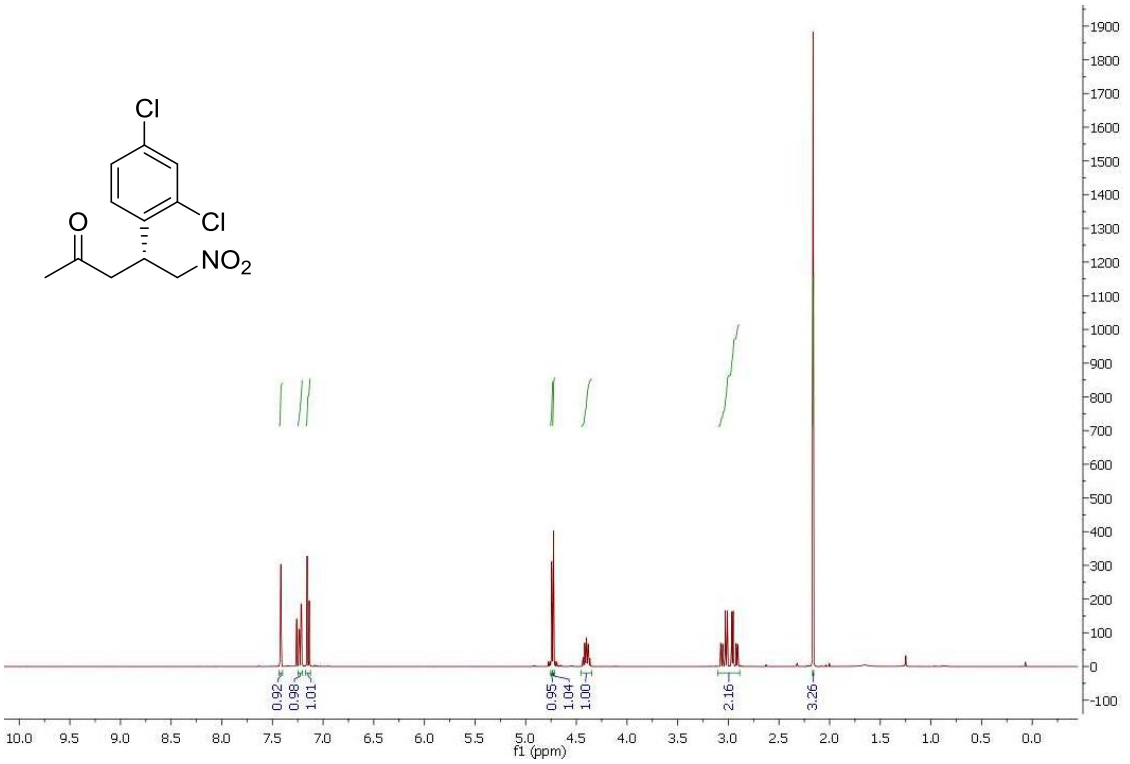
0.085 mmol 0.017 mmol

^{1}H NMR spectra after 18 hours overlayed with nitrostyrene in toluene-d_8:

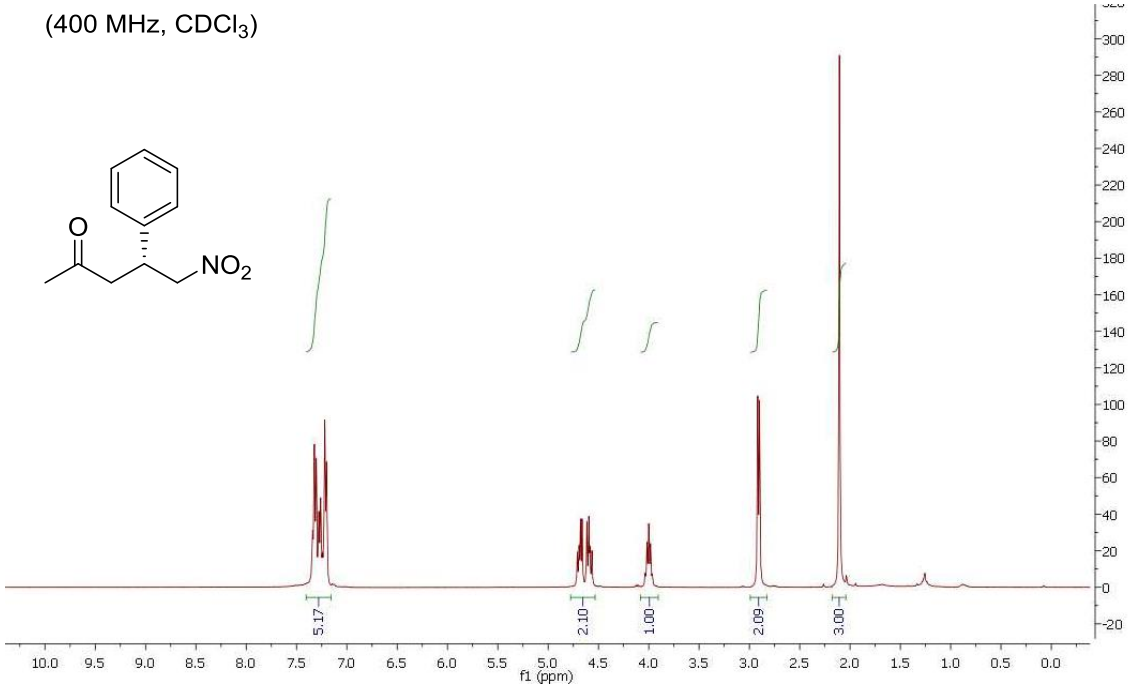


2.5. ^{1}H NMR spectra of Michael addition products

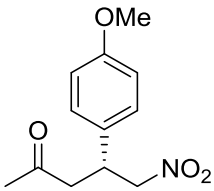
(400 MHz, $CDCl_3$)



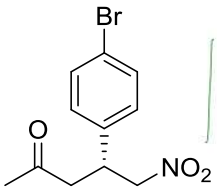
(400 MHz, $CDCl_3$)



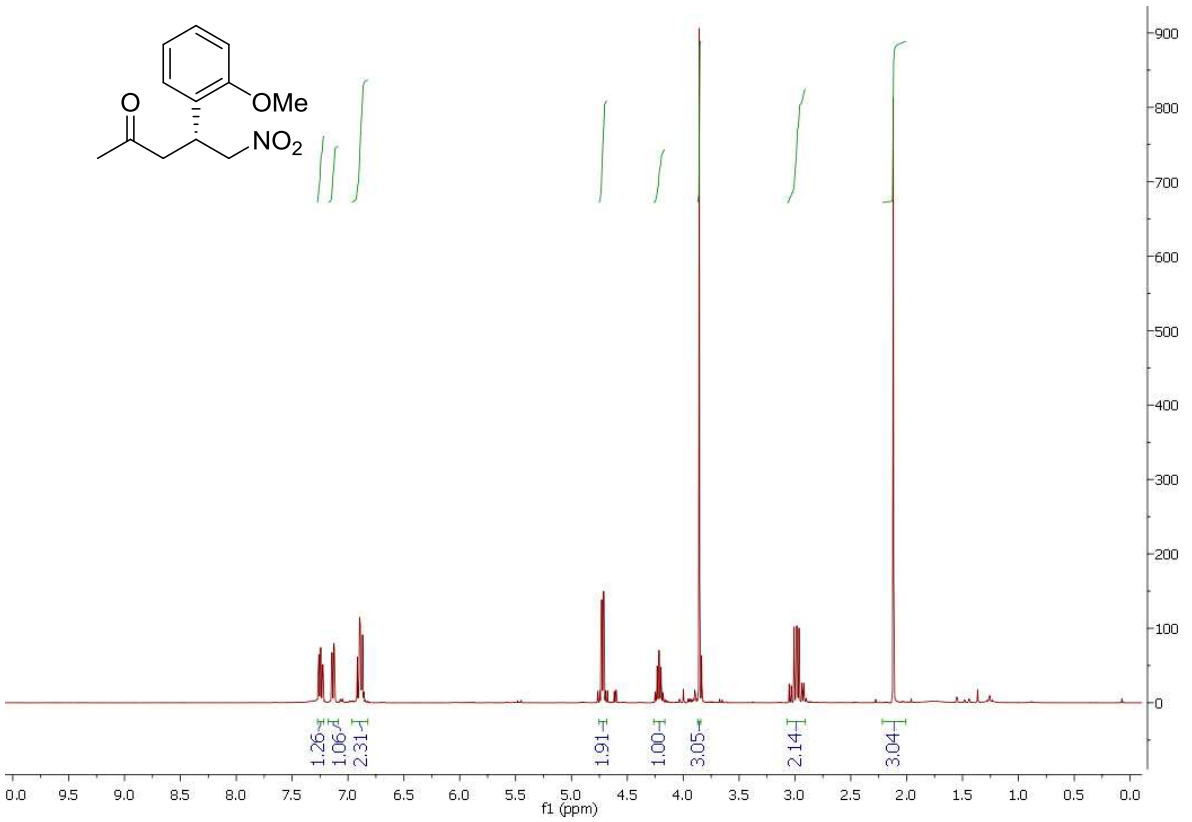
(400 MHz, $CDCl_3$)



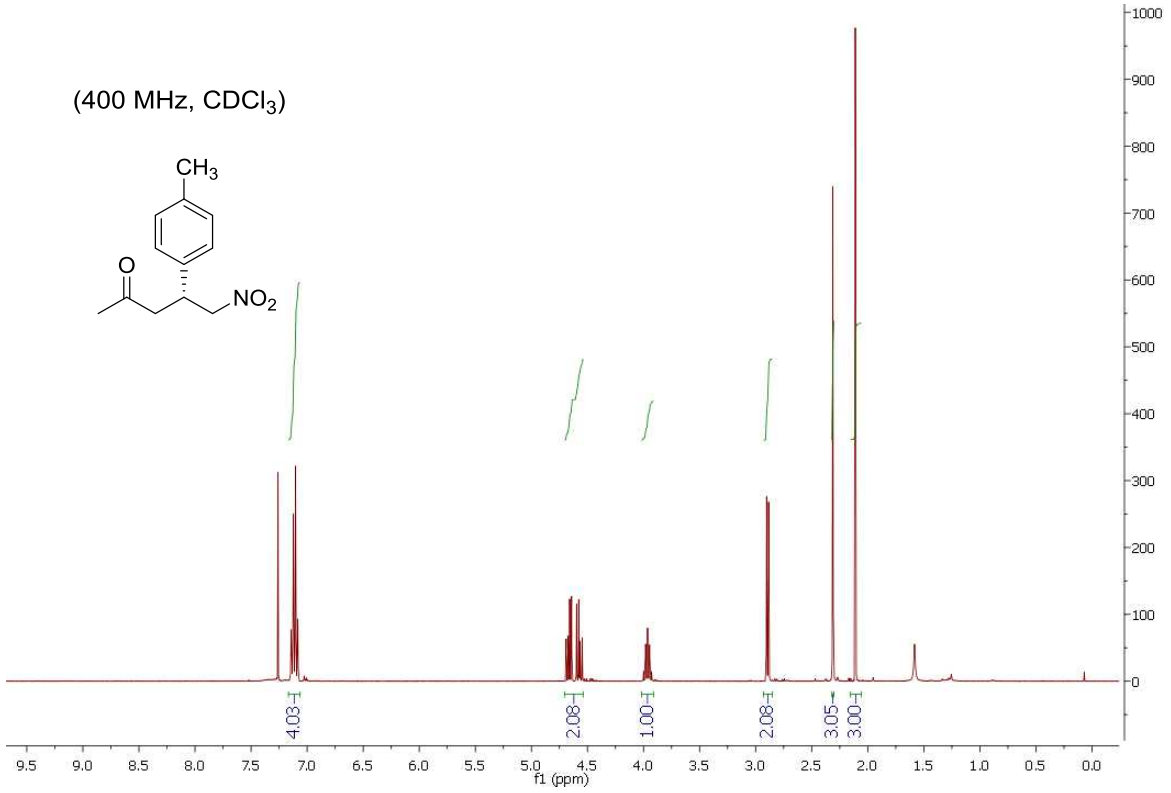
(400 MHz, $CDCl_3$)



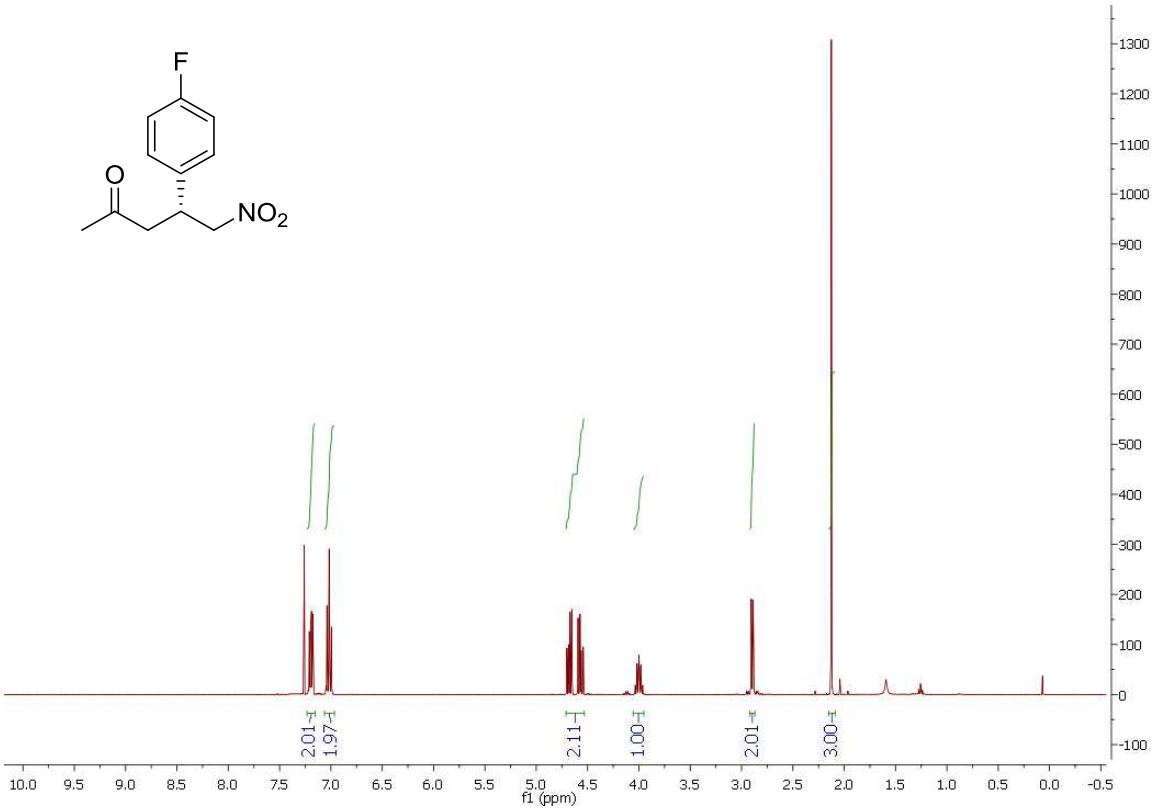
(400 MHz, $CDCl_3$)



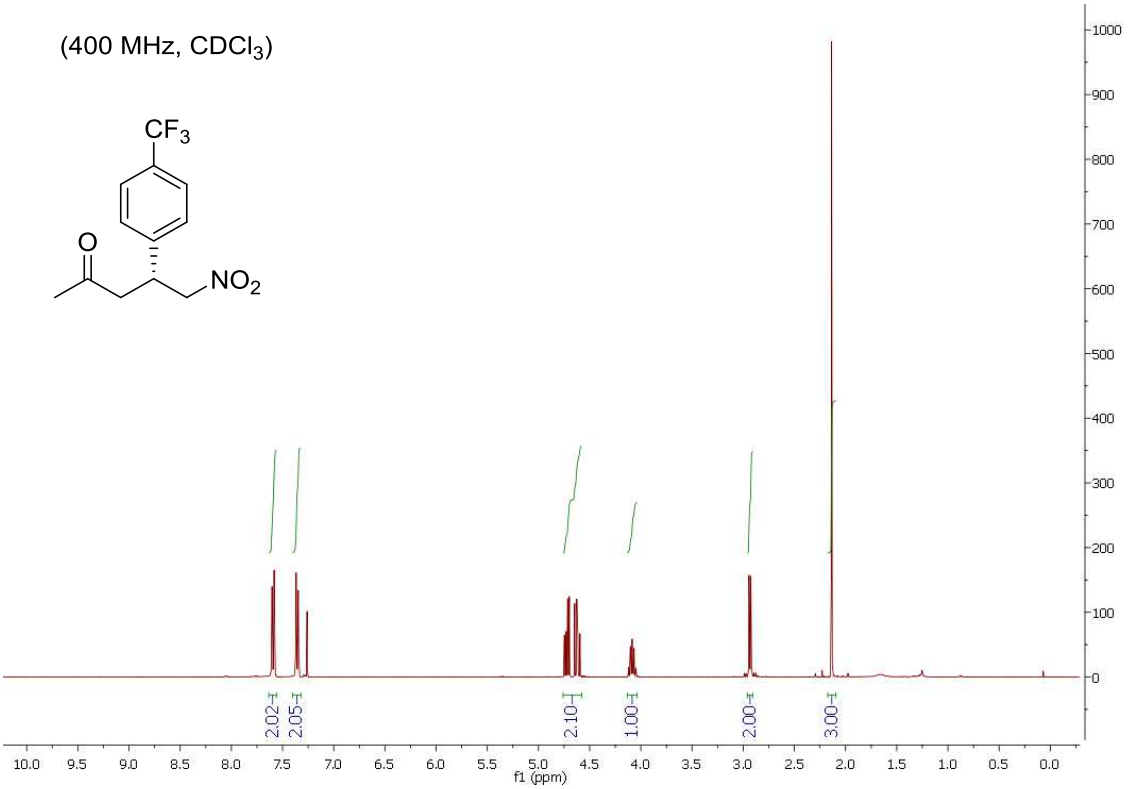
(400 MHz, $CDCl_3$)



(400 MHz, $CDCl_3$)



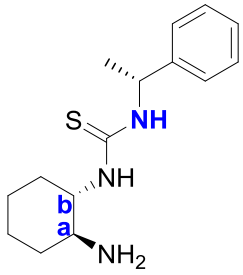
(400 MHz, $CDCl_3$)

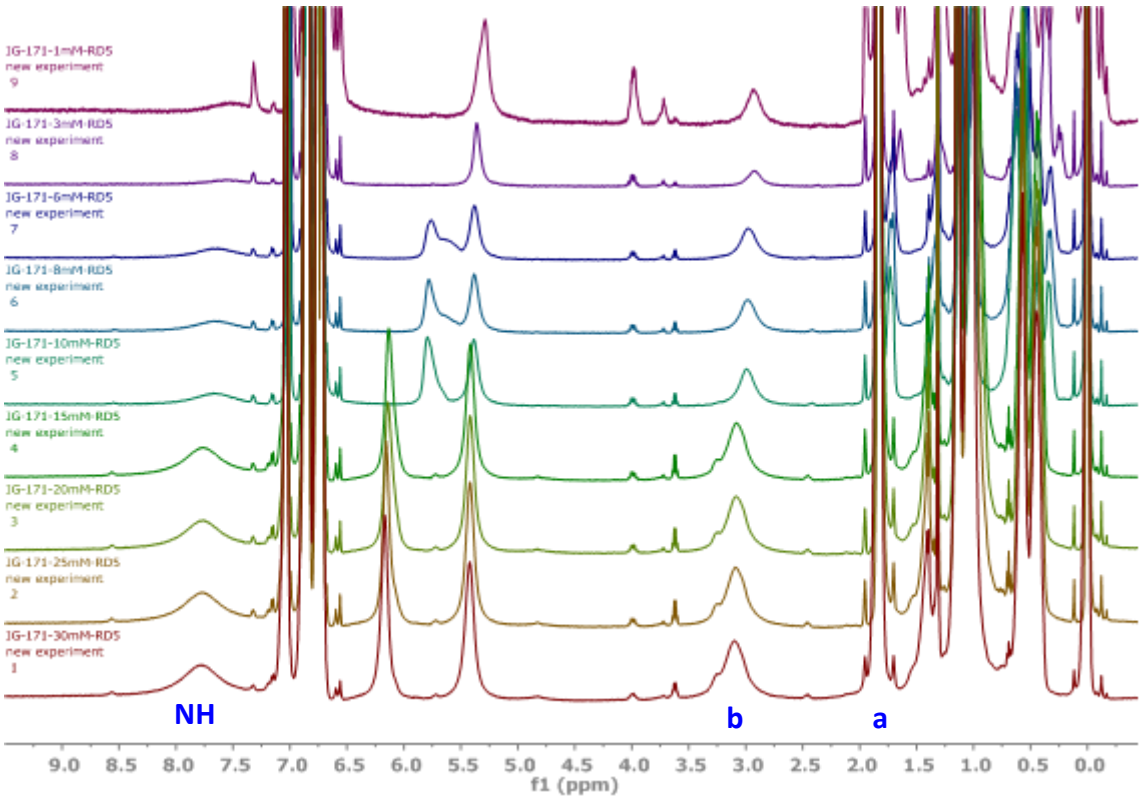


3. ^{1}H NMR dilution studies of catalyst I

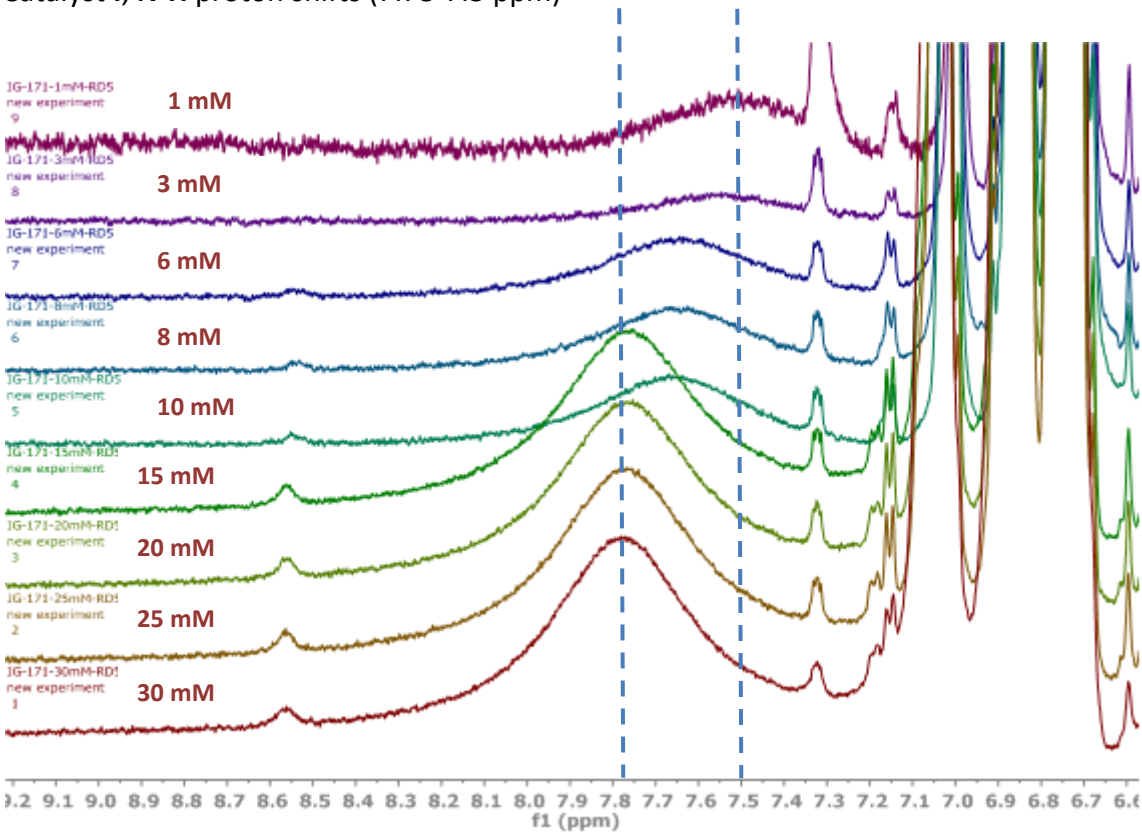
3.1. ^{1}H NMR dilution studies of catalyst I in the absence of AcOH and fitting to a dimerization model

^{1}H NMR dilution studies on catalyst **I** were perfomed at room temperature in toluene-d_8 and recorded on a Varian 500 MHz spectrometer. Tetrakis(trimethylsilyl)silane was added to each sample to be used as reference signal. Neither acid nor any additive were added to the solution. The change in the chemical shift of the protons **a**, **b** and **–NH** (from the thiourea group) upon dilution (30 mM to 1 Mm) were modeled by HypNMR2008 using a dimerization model (Figure 2)

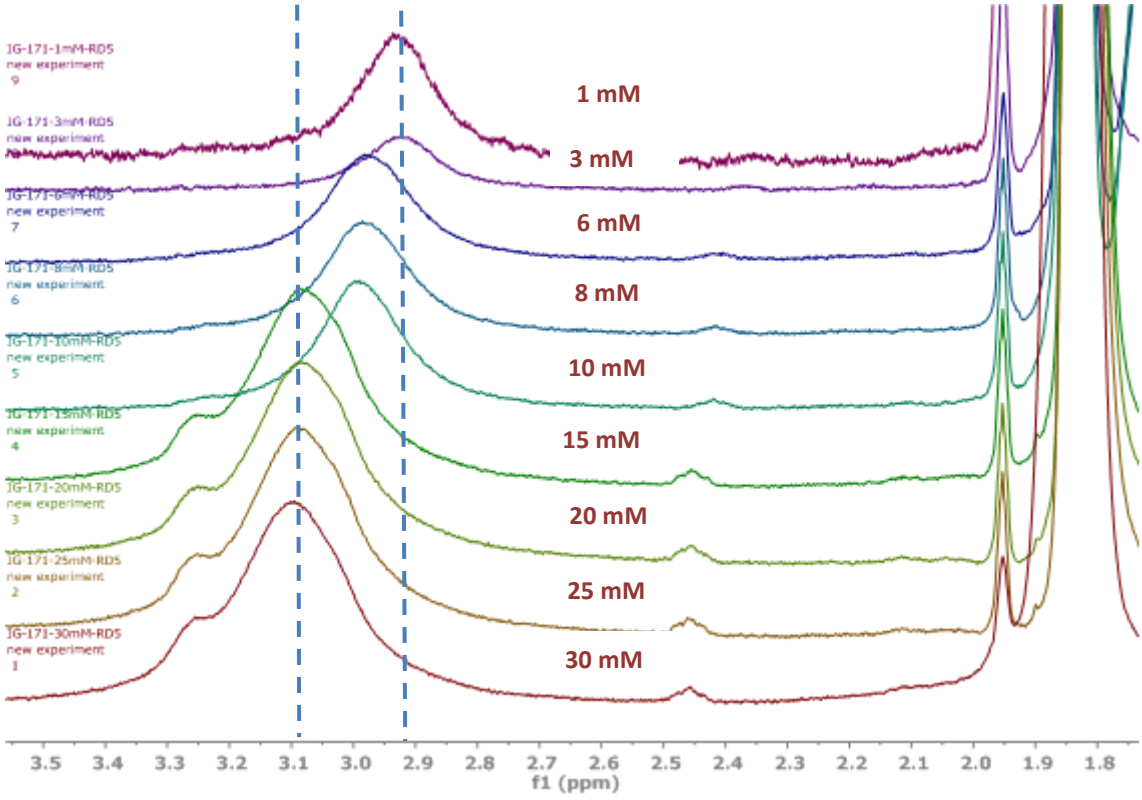




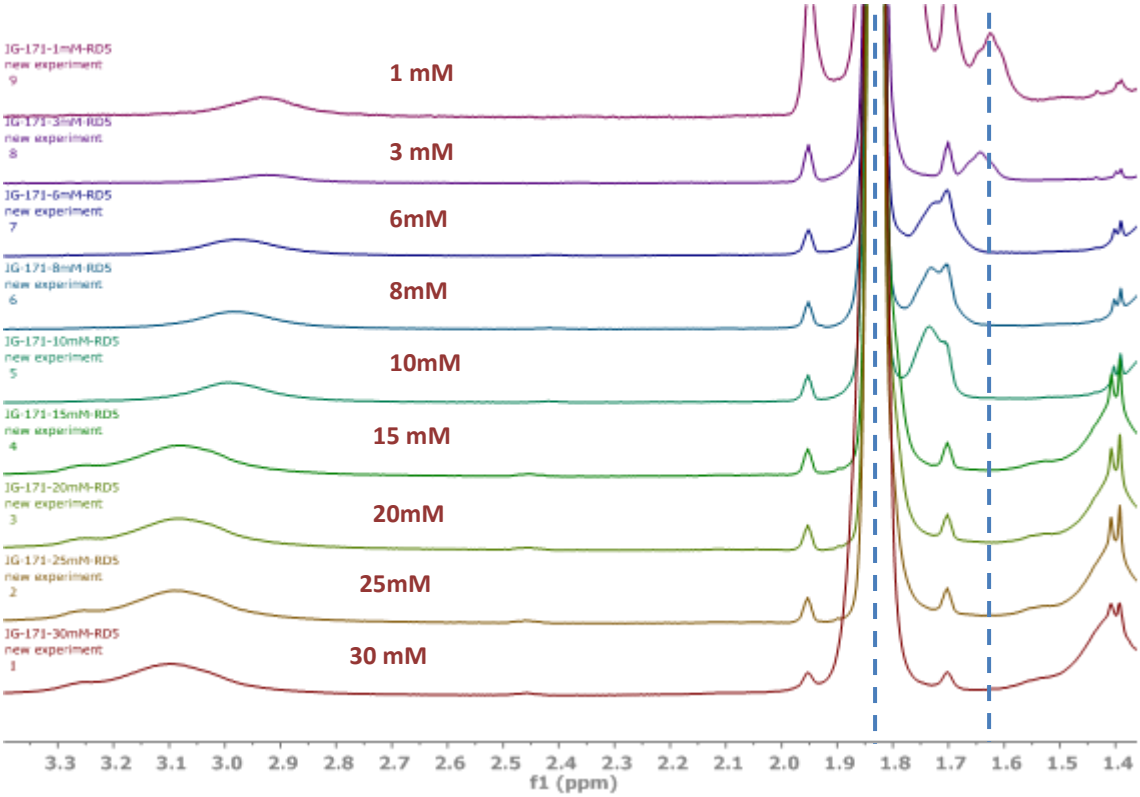
Catalyst **I**, **N-H** proton shifts (7.78-7.5 ppm)



Catalyst **I**, proton **b** shifts (3.10-2.93 ppm)



Catalyst **I**, proton **a** shifts (1.82-1.62 ppm)



Results of HypNMR2008 data fitting

$$2cat \rightleftharpoons cat2 \quad (K_{dimer})$$

$\log K_{dimer} = 1.39 \pm 0.13$

$K_{dimer} = 25 \pm 7\ M^{-1}$

Sigma = 13.9

concentration(M)	δ proton N-H	δ proton a	δ proton b
0.030	7.78	1.82	3.10
0.025	7.77	1.80	3.09
0.020	7.76	1.80	3.08
0.010	7.66	1.73	2.99
0.008	7.63	1.72	2.98
0.006	7.63	1.71	2.98
0.003	7.55	1.64	2.93
0.001	7.50	1.62	2.93

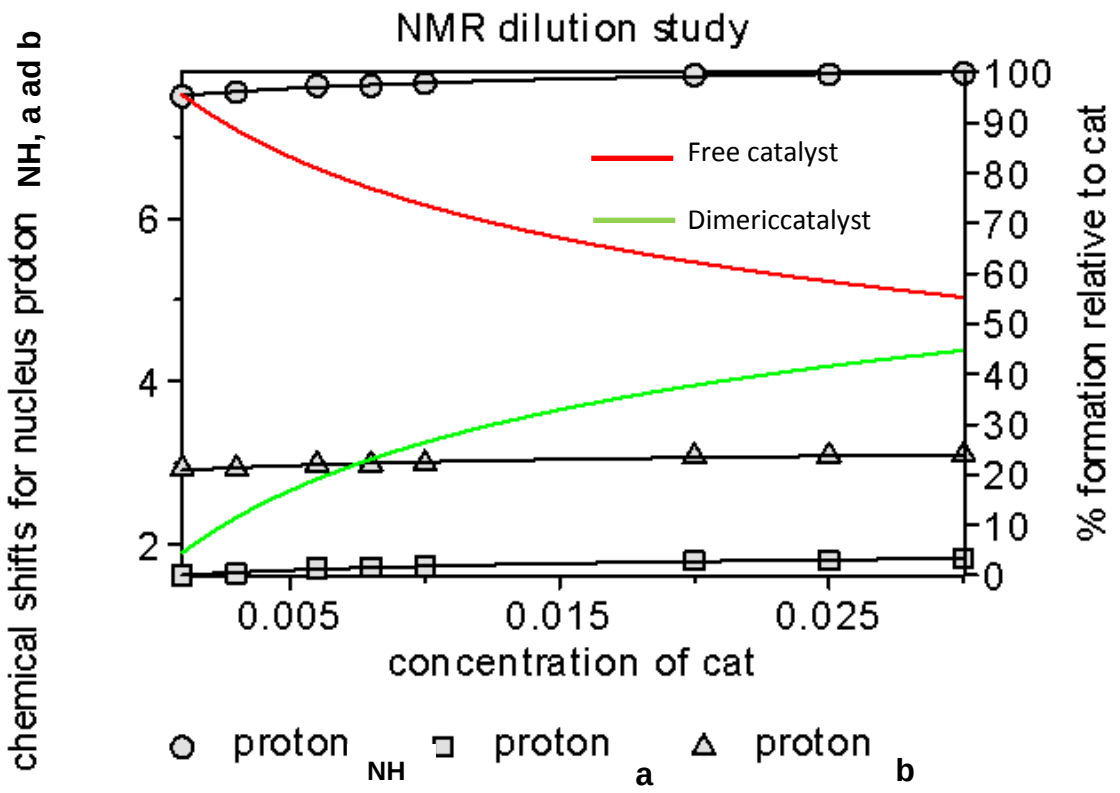
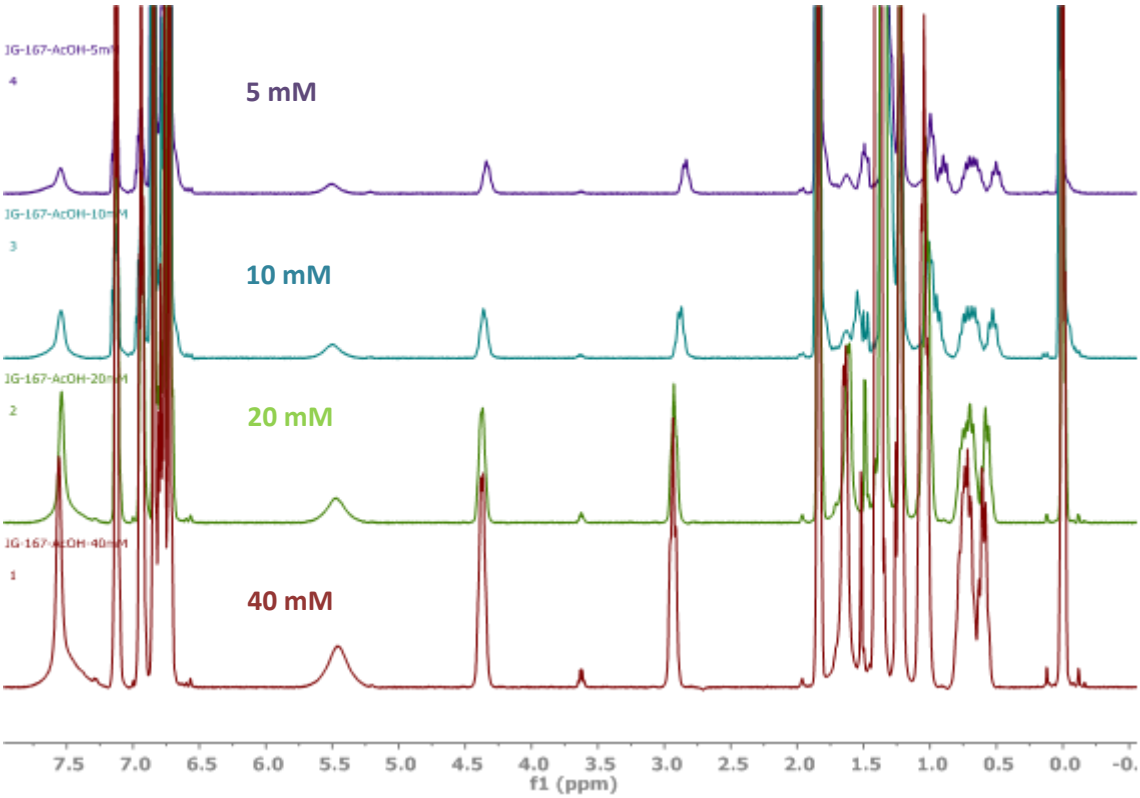


Figure 2. Results of data fitting using HypNMR2008. Symbols represent experimental chemical shifts, black lines represent calculated values.

3.2. ^{1}H NMR dilution studies of catalyst I in the presence of AcOH

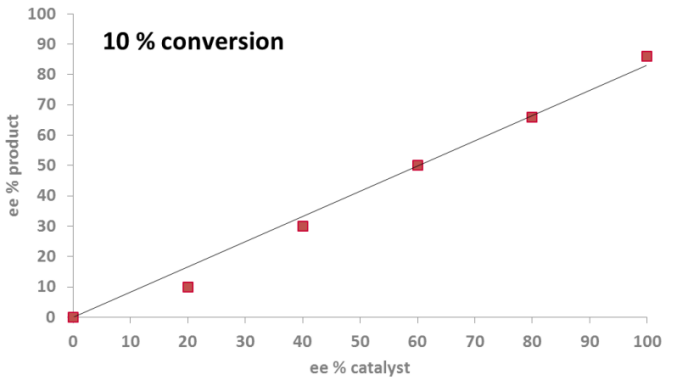
Various solutions of catalyst **I** in d_8-toluene at different concentrations between 5-40 mM were prepared, and in each NMR tube was added 2 µL of AcOH *via* a Hammilton syringe. NMR of each sample was recorded on a Varian 500 MHz spectrometer.

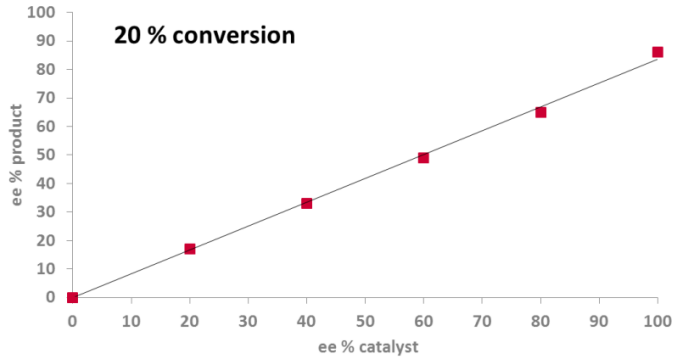


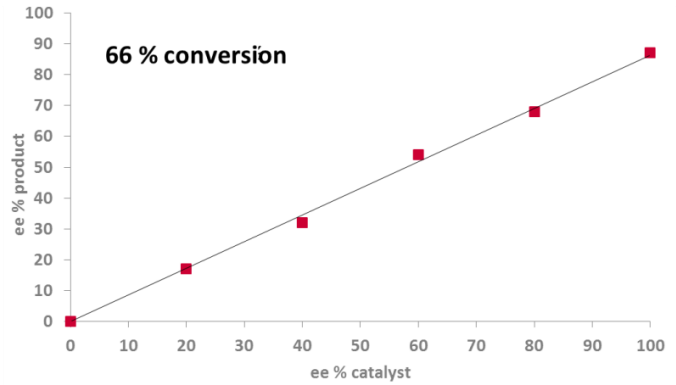
Under these reaction conditions no significant change in chemical shifts could be observed upon dilution.

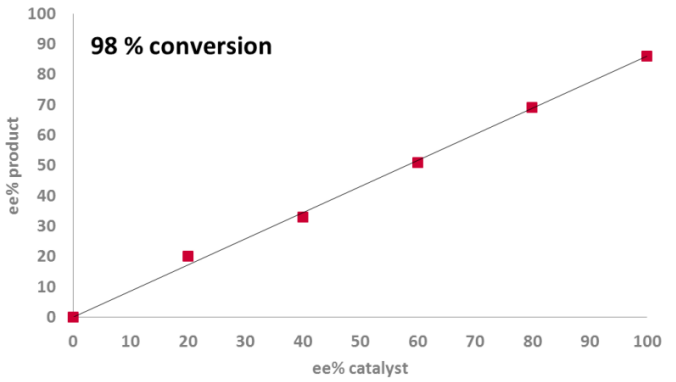
4. Non-Linear Effect (NLE) studies with catalyst IV

Catalyst (*R,R*)-**IV** was synthesized and combined with the enantiomeric catalyst (*S,S*)-**IV**in the appropriate ratios. The Michael addition of acetone to nitrostyrene was performed with these mixtures using procedure in the manuscript. The reactions were sampled at different conversions and analyzed by chiral HPLC to determine the *ee*of addition product **3a**. Conditions: $[\mathbf{1}]_0$=0.45 M, 10 equiv. acetone, 10 mol% catalyst **IV** and 10 mol% AcOH were used in all sets of experiments.



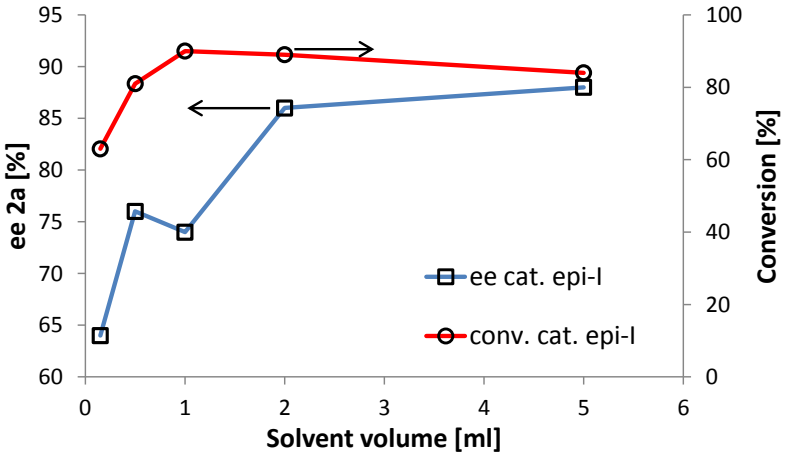






5. Effect of reactants concentration in ee and conversion for the addition of acetone to nitrostyrene catalyzed by *epi*-I.

50 mg, 0.335 mmol nitrostyrene. Plotted as the amount of toluene added to the reaction. 10 mol% catalyst, 10 mol%. AcOH and 10 equiv. of acetone in toluene, after 24 h reaction. Conversion determined by ^{1}H NMR in the crude samples and ee determined by HPLC on a chiral stationary phase.



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CHAPTER III

Immobilization of Primary Amine-Thiourea Organocatalysts for Asymmetric Michael and Mannich-Type Reactions

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3. IMMOBILIZATION OF PRIMARY AMINE THIOUREA ORGANOCATALYSTS FOR ASYMMETRIC MICHAEL AND MANNICH-TYPE REACTIONS

3.1. ASYMMETRIC ORGANOCATALYSTS COVALENTLY IMMOBILIZED ON POLYMERIC RESINS

The field of polymer-supported catalysts roots in the seminal work by R. Bruce Merrifield who pioneered the solid phase synthesis of peptides (Nobel Prize in Chemistry 1984).[1] Merrifield introduced the chloromethylated and 1-2% divinylbenzene (DVB) crosslinked polystyrene (PS) resin, known simply as Merrifield resin, to synthesize peptides in the solid phase. The Wang resin is a phenyl methanol modification of the Merrifield resin.[2] Both resins have favorable swelling properties in non-protic, non-polar organic solvents such as THF and halogenated and aromatic hydrocarbons, which make them suitable supports for the immobilization of catalysts and reagents for organic synthesis **(Figure 3.1)**.

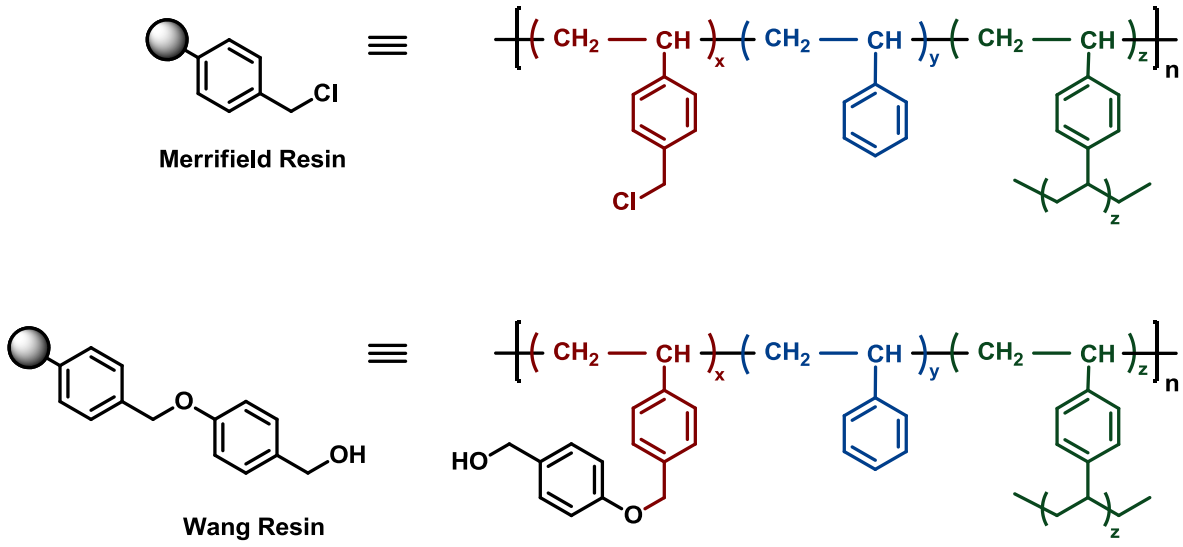


Figure 3.1. Schematic representation of Merrifield and Wang resins.

[1] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
[2] Wang, S. S. *J. Am. Chem. Soc*. **1973**, *95*, 1328-1333.

Swelling is an essential characteristic of resins applied to organic synthesis. If the polymers are not well swelled, the reactive sites can not be accessed properly, therefore causing catalytic activity problems. To overcome the solvent restrictions, a number of modifications were introduced on resins to enhance swelling characteristics by incorporating elements compatible with more polar solvents. Resins with longer and more flexible ether crosslinkers and functionalities were commercialized such as JandaJel® and TentaGel® resins **(Figure 3.2)**.[3]

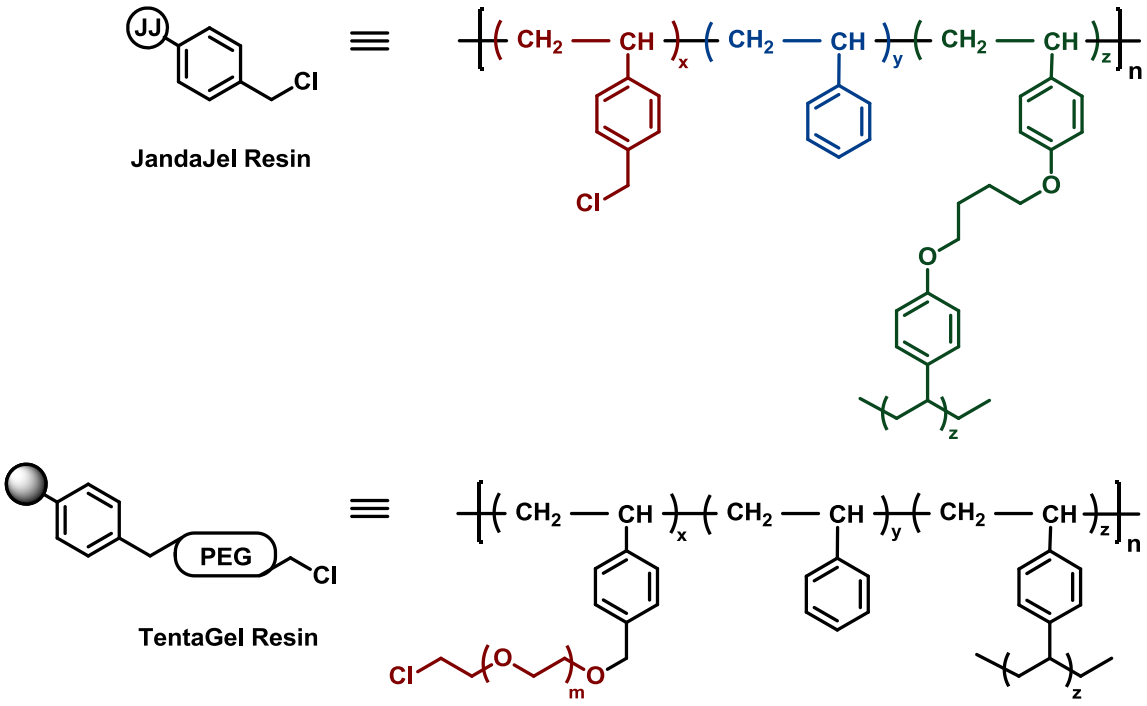


Figure 3.2. Schematic representation of JandaJel® and TentaGel® resins.

Once the type of commercial resin is chosen considering the desired reaction conditions, the degree of functionalization is another important feature to choose for catalyst immobilization. An optimal degree of functional units per mass (mmol. g^{-1}) must be chosen in order to have a proper mass of catalyst for practical use and avoid potentially undesirable catalyst-catalyst interactions.

[3](a) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329-6332. (b) Rapp, W. in:*Combinatorial Peptide and Nonpeptide Libraries, A Handbook* (Ed.: G. Jung), Wiley-VCH, Weinheim, **1996**, 425-464.

Immobilized catalysts may show lower reactivity compared to their homogeneous analogs due to the bulk structure of the polymeric support. To overcome this problem, the interactions between the catalytic unit and the support must be restricted by the use of linker/spacer molecules which are chemically inert under reaction conditions, to ensure optimal distance control between the polymer surface and the catalytically active moiety. A schematic representation of a supported catalyst is depicted in **Figure 3.3**.

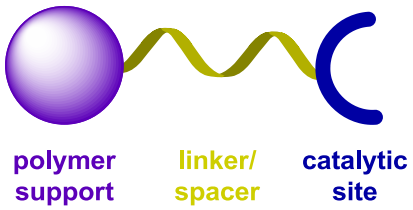


Figure 3.3. General schematic representation of immobilization strategy.

There are many reasons for the immobilization of an organic catalyst.[4] The most important reasons are the advantageous easy isolation of the products from the reaction mixture, the recovery of the catalyst and its expected recyclability. Nevertheless, in continuous flow methods, the catalyst does not need to be removed from the vessel, permanently resides in the reactor where it transforms the entering starting materials into the existing products. In this way, the product separation from the catalyst, catalyst recovery, and recycling are combined in one single operation which saves time, money, and space. Due to its benefits, continuous flow chemistry in both organocatalytic[5a,b,c,d,e] applications and metal catalysis[5f,g,h] has also been studied in our research group.

Economic concerns also justify the catalyst immobilization. It is convenient if the catalyst is expensive, requires complex synthesis or is employed in a large amount. In this case, omitting the cost of the polymer and the linker for a simpler comparison, it is important that the synthesis of the supported catalyst uses a starting material comparable in cost and synthetic complexity to that of the starting material used for the synthesis of the non-supported catalyst.

---

[4] For reviews, see: a) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367-1390. b) Benaglia, M. *New J. Chem.*, **2006**, *30*, 1525-1533. c) Kristensen, T. E.; Hansen T. *Eur. J. Org. Chem.* **2010**, 3179-3204.

[5] (a) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, *24*, 2566-2568. b) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 3668-3671. c) Kasaplar, P.; Rodriguez-Escrich, C.; Pericàs, M. A. *Org. Lett*. **2013**, *15*, 3498-3501. d) Alza, E.; Sayalero, S.; Cambeiro, X. C.; Martin-Rapún, R.; Miranda, P. O.; Pericàs, M. A. *Synlett* **2011**, *4*, 464-468. (e) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, *15*, 10167-10172. (f) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, 351, 1539-1556. (g) Rolland, J.; Cambeiro, X. C.; Rodriguez-Escrich, C.; Pericàs, M. A. *Belstein J. Org. Chem.* **2009**, *5*, 56. (h) Osorio-Planes, L.; Rodriguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 1816-1819.

Despite the possible drawbacks, the advantages of immobilized catalysts still make them desirable in the field. After the explosion in the field of organocatalysis, the design of covalently supported organocatalysts for their use in environmentally friendly green solvents has become popular. For example, our group, and others have been working for a while in developing polymer-supported amphiphilic proline derivatives for asymmetric aldol reactions in water. Our group developed a general click strategy for the immobilization of catalytic units on polystyrene resin through a copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction. This strategy was successfully used to develop proline derivatives.[6] Using the same strategy the immobilization of another important family of amine catalysts, the Jorgensen-Hayashi diaryl prolinols was also reported. The resulting catalyst displayed a comparable result to the homogenous counterparts in the Michael addition of aldehydes to nitroolefins.[7] Likewise, bifunctional hydrogen bonding squaramides have been immobilized on polymer supports and used in a recyclable manner in Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes.[8]

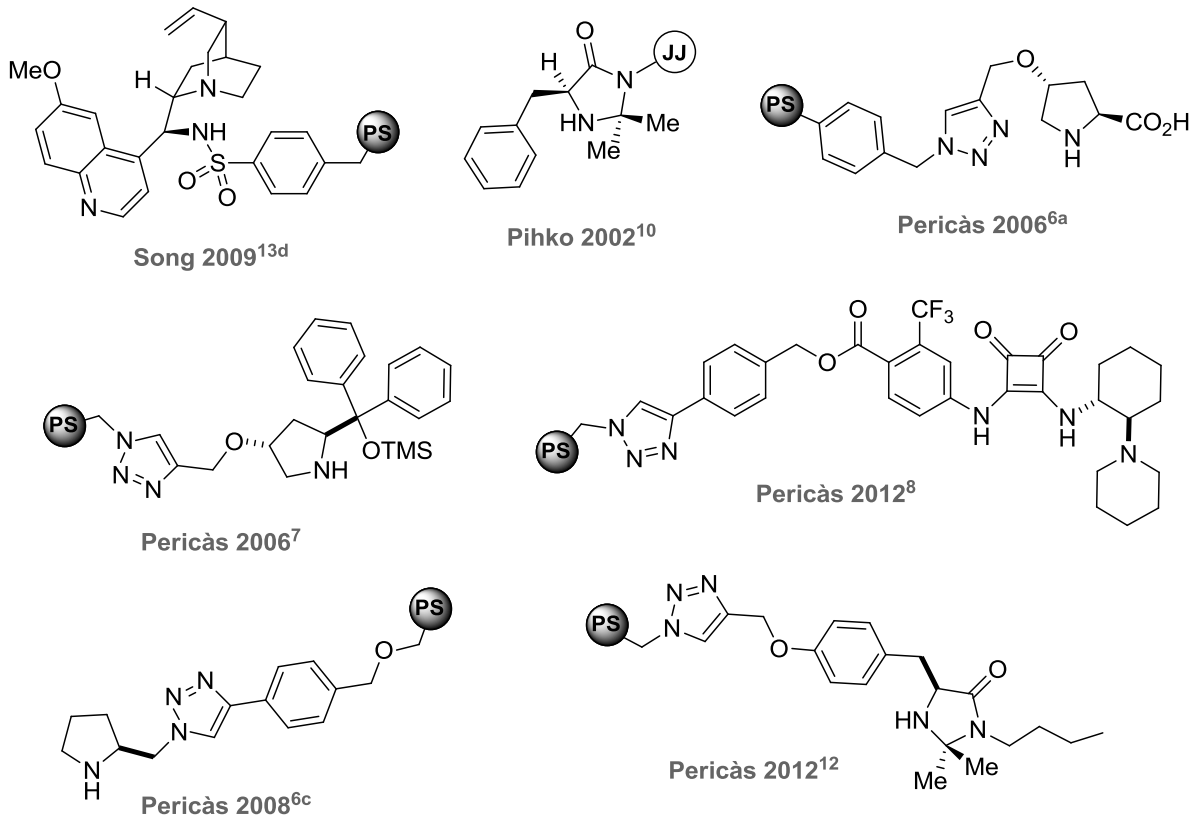


Figure 3.4. Selected examples of polymer supported organocatalysts.

[6] a) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653-4655. b) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 1943-1946. c) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2008**, *10*, 337-340.
[7] Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051-3056.
[8] Kasaplar, P.; Riente, P.; Hartmann, C.; M. A. Pericàs; *Adv. Synth. Catal.* **2012**, *354*, 2905-2910.

Similarly, many other research groups have been working on the immobilization of enamine and iminium organocatalysts. MacMillan imidazolidinones were immobilized by different research groups following different approaches. In 2002, the Cozzi group developed PEG-supported imidazolidinones.[9] At the same time with this report, Pihko and co-workers reported a JandaJel® supported MacMillan imidazolidinone.[10] Both catalysts were tested in Diels-Alder reactions. Hansen *et al.* recently reported the preparation of polymer-supported MacMillan imidazolidinone by acrylic copolymerization.[11] A Merrifield supported version of MacMillan catalyst was developed in our research group as well.[12] Likewise, cinchona derived organocatalysts have enjoyed a history of polymer immobilization starting already in the 1970s.[13] Selected examples of these supported catalysts are depicted in **Figure 3.4**.

However, in spite of their broad applicability, supported versions of (thio)urea organocatalysts are rare in the literature. This thesis chapter will focus on the covalent immobilization of primary amine-thioureas on polystyrene supports. Thus, the related known examples in the literature and their applications will be elaborated in the following section.

[9] a) Benaglia, M.; Celentano, G.; Cinquini, M.; Puglisi, A.; Cozzi, F. *Adv. Synth. Catal.* **2002**, *344*, 149-152; b) Puglisi, A.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Eur. J. Org. Chem.* **2004**, 567-573.
[10] Selkälä, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv.Synth. Catal.* **2002**, *344*, 941-945.
[11] Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 1620-1629.
[12] Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 3668-3671.
[13] (a) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3186-3187.(b) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071-7072 (c) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H. *J. Org. Chem.* **1988**, *53*, 1157-1161 (d) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853-10859. (d) Youk, S. H.; Oh, S. H.; Rho, H. S.; Lee, J. E.; Lee, J. W.; Song, E. C. *Chem. Commun.* **2009**, 2220-2222.

3.1.1. POLYMER SUPPORTED (THIO)UREA ORGANOCATALYSTS

The first polymer-supported (thio)ureas were used by the Jacobsen group in the asymmetric Strecker reaction. The discovery and optimization were approached by screening parallel libraries of resin-bound Schiff base catalyst candidates. They modified the Schiff base ligand structure by replacing the amino alcohol unit with diamines in order to use the second nitrogen as the site for attachment to the polystyrene support. An additional amino acid was added as a diversity element between diamine and the polymer support **(Figure 3.5)**.[14]

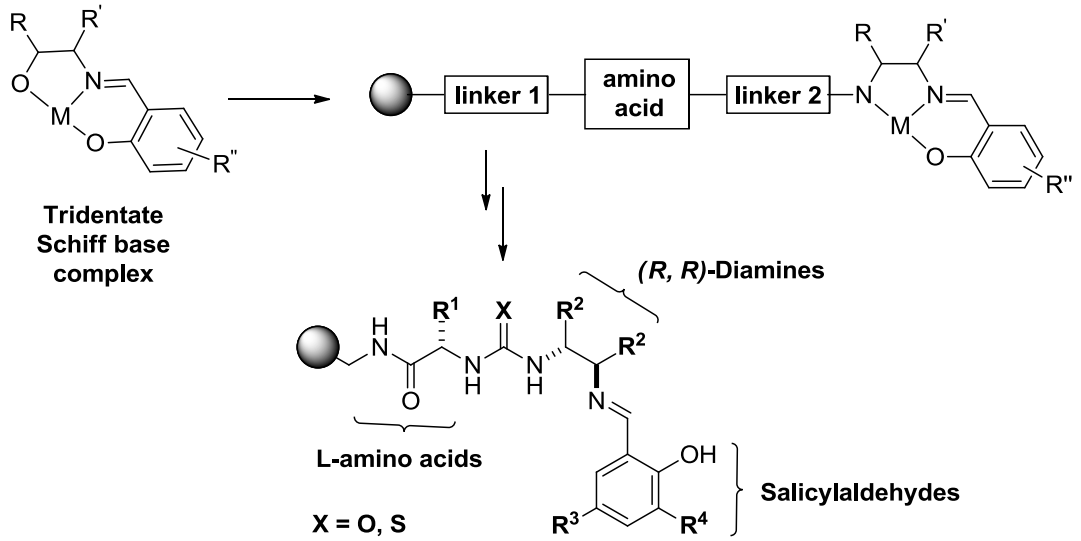


Figure 3.5. Concept for the immobilization of Jacobsen's Schiff base (thio)urea catalysts.

Interestingly, initial screening studies showed that the catalyst gave superior results in the absence of metal. Linker 1 led to poorer results and therefore was removed from the structure. The key elements responsible for high enantioselectivity were the bulky substituents both on the amino acid position (R^1) and 3-position on salicyl imine moiety (R^3, R^4). As a result of the structural optimization, the catalyst bearing *L*-valine and a chiral diamino cyclohexane backbone was found to be the best catalyst. As the conclusion to this work, these catalysts could be used efficiently in asymmetric Strecker reactions either in solution or covalently immobilized on polystyrene resin. Immobilized catalysts could be recycled unlimitedly without loss of reactivity or enantioselectivity.[14]

[14] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120,* 4901-4902. b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1280.

Takemoto *et al.* immobilized their previously designed homogeneous chiral thiourea catalyst **III.1** on different polymers **(Figure 3.6)**. The supporting strategy was designed to use an ester group to attach the catalyst on polymer supports. First, insoluble crosslinked polystyrenes were used as supports using a spacer generated from pentane-1,5-diol. Despite the easy work-up, catalysts **III.3** and **III.4** were not useful since they showed lower activities in Michael and aza-Henry reactions compared to their homogeneous analog **III.2**. [15]

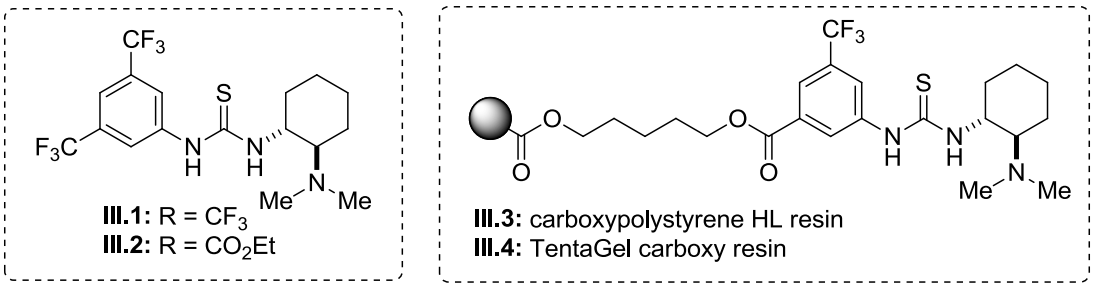
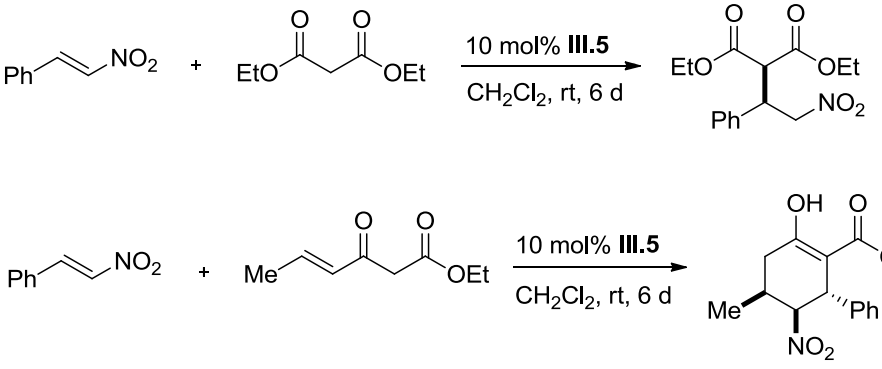


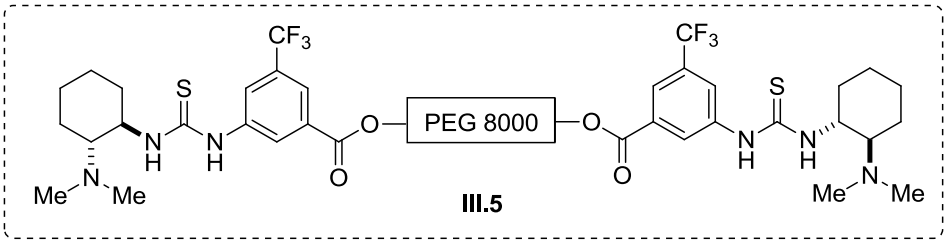
Figure 3.6. Homogeneous and polystyrene supported versions of Takemoto catalyst.

In order to improve these results, non-crosslinked soluble polymer polyethylene glycol (PEG) was used as a support for the synthesis of PEG-bound thiourea **III.5**. This catalyst was applied to Michael and tandem Michael reactions of *trans*-β-nitrostyrene affording the products with good yields and enantioselectivities. Furthermore, the catalyst was recoverable through precipitation by addition of diethyl ether and could be reused repeatedly without further treatment after the recovery by filtration, without loss in the catalytic activity **(Scheme 3.1)**.[15]



cycle	yield%	ee%
1	71	86
2	74	90

cycle	yield%	ee%
1	63	76
2	64	76
3	63	79



Scheme 3.1. Michael and tandem Michael addition using soluble PEG-bound catalyst **III.5**.

[15] Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y. *Synthesis* **2006**, *19*, 3295-3300.

After Jacobsen and Takemoto, only a few more studies have been published on polymer supported (thio)ureas. One of them was from Schreiner *et al.*, reporting an organocatalytic, non-asymmetric, tetrahydropyran and 2-methoxypropene protection of alcohols using polystyrene bound *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thioureas. The catalytic efficiency of these thioureas was remarkable with very high turnover numbers at catalyst loadings down to 0.001 mol% **(Figure 3.7)**.[16]

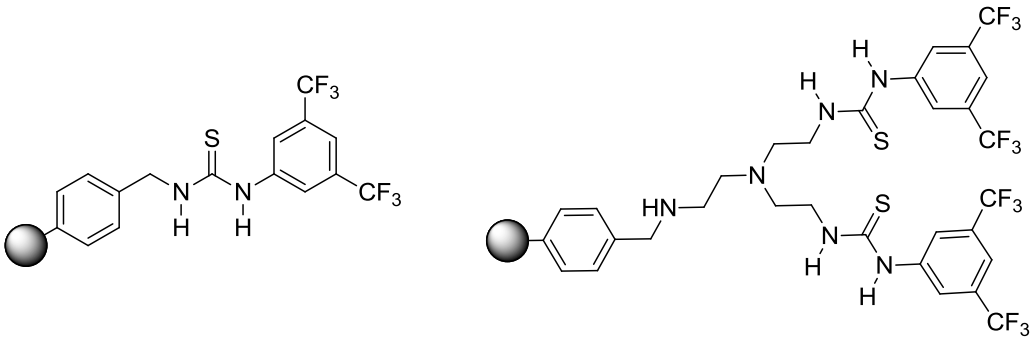
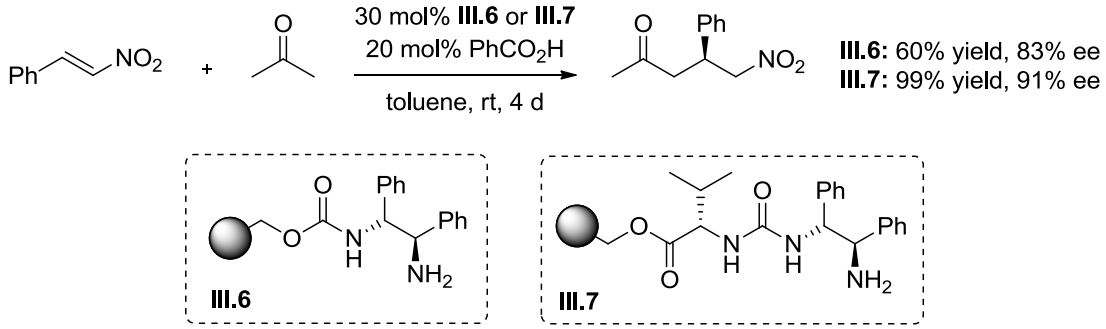


Figure 3.7. Schreiner's polystyrene supported thioureas.

Another example came from the Portnoy research group. They designed a polystyrene supported bifunctional amino carbamate **III.6** which gave moderate results in Michael addition of acetone to *trans*-β-nitrostyrene.[17] Later on, they elaborated the catalyst design to a more active and selective analog **III.7**. The improvement was achieved by introducing another chiral center to a remote position using amino acids as spacers between the catalytic primary amine unit and the Wang linker of the polymer support **(Scheme 3.2)**. The same catalysts were also evaluated in nitro-Michael addition of aldehydes to nitroolefins. Catalyst **III.6** could be recycled 3 times without loss of activity in addition of acetone to *trans*-β-nitrostyrene, however, the activity diminished upon recycling in addition of isobutyraldehyde which the authors attribute to possible irreversible catalyst deactivation [18]



Scheme 3.2. Asymmetric nitro-Michael addition catalyzed by supported catalysts.

[16] Kokte, M.; Schreiner, P. R. *Synthesis* **2007**, 0779-0790.
[17] Tuchman-Shukron, L.; Portnoy, M. *Adv. Synth. Catal.* **2009**, *351*, 541-546.
[18] Tuchman-Shukron, L.; Miller, S. J.; Portnoy, M. *Chem. Eur. J.* **2012**, *18*, 2290-2296.

Peng *et al*. developed insoluble, non-swelling MPS-supported (mesoporous polymer) thiourea organocatalysts to be used efficiently in direct asymmetric Michael addition of ketones and aldehydes to nitrostyrenes in the presence of acid additives. The catalyst could be recycled up to 6 runs without loss in activity and enantioselectivity.[19]

Cui *et al.* developed a group of Merrifield-resin supported *L*-proline derived thiourea organocatalysts. These catalysts were evaluated successfully even at low loadings of 2 mol% in the direct asymmetric aldol reactions of ketones and aromatic aldehydes in water. Moreover, they could be recycled up to 4 cycles with a slight decrease in yields and enantioselectivities.[20] Similarly, Kokotos *et al*. immobilized their tripeptide-like prolinamide-thiourea catalyst on different supports (JandaJel, PS-DVB, ChemMatrix) to be used in direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde. However, polymer supported catalysts gave inferior results compared to their efficient homogeneous analogs.[21]

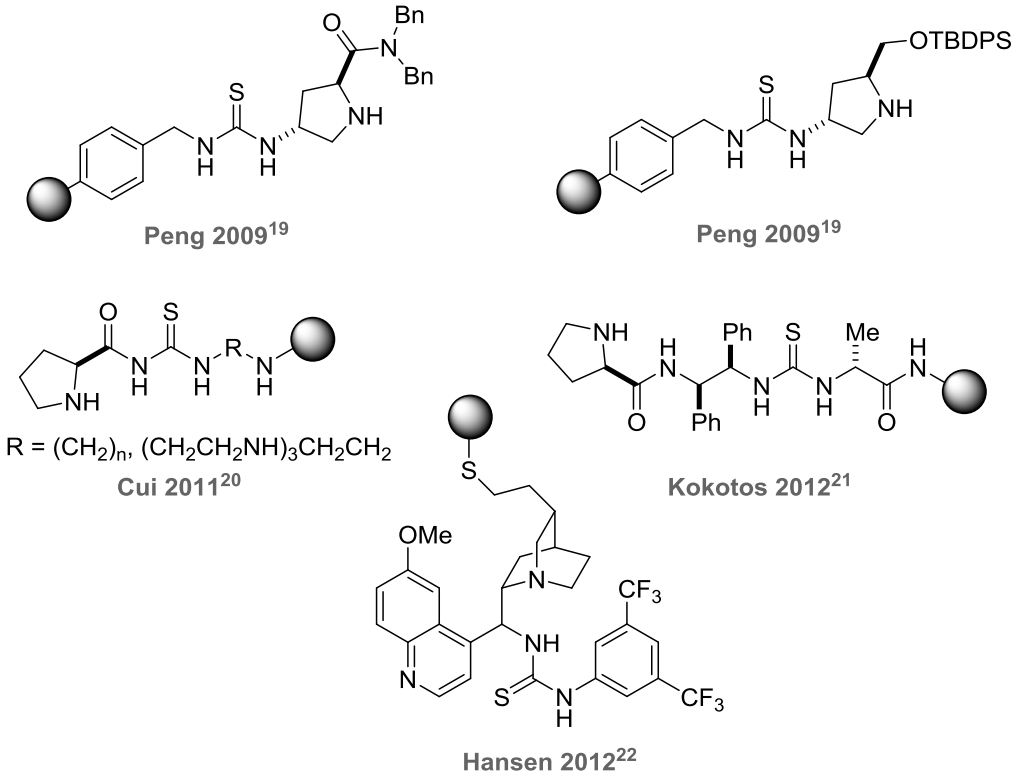
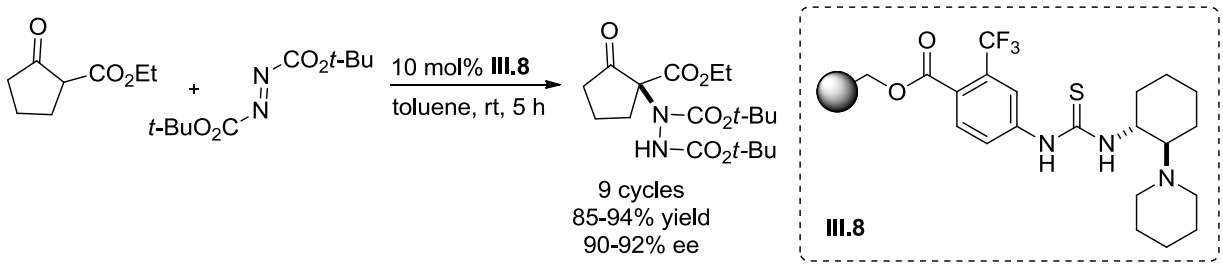


Figure 3.8. Recent examples of polymer supported thioureas.

[19] Chuan, Y.; Chen, G.; Peng, Y. *Tetrahedron Lett* **2009**, *50*, 3054-3058.
[20] Li, J.; Yang, G.; Qin, Y.; Yang, X.; Cui, Y. *Tetrahedron: Asymmetry* **2011**, *22*, 613-618.
[21] Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem.* **2012**, *10*, 5613-5619.

A different supporting strategy was reported by Hansen *et al.* on the immobilization of cinchona organocatalysts: A thiol-ene suspension copolymerization of polyfunctional thiols and alkenes together with the cinchona precursors was used, thus combining bead polymerization and catalyst immobilization in a single step. These supported organocatalysts have been evaluated in several asymmetric transformations. However, recycling gave relatively poor results.[22] The structures of the above-mentioned catalysts can be found in **Figure 3.8**.

More recently, a polymer supported bifunctional tertiary amine-thiourea catalyst was developed and prepared through immobilization onto a Merrifield resin in the Pericàs group. This catalyst has shown high activity and enantioselectivity in the α-amination of 1,3-dicarbonyl compounds with azodicarboxylates and could be reused up to 9 cycles thanks to the reactivation of the catalyst by simple washing with triethylamine between runs. This reaction was also adapted successfully in continuous flow operation **(Scheme 3.3)**.[23]

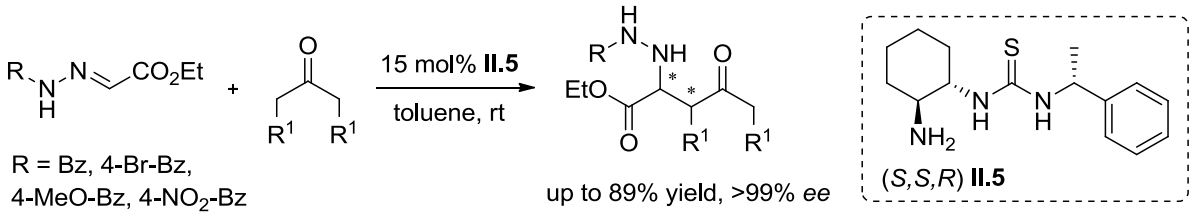


Scheme 3.3. Recycled use of polymer supported thiourea **III.8** in α-amination reaction.

[22] Frediksen, K. A.; Kristensen, T. E.; Hansen, T. *Beilstein J. Org. Chem.* **2012**, *8,* 1126-1133.
[23] Kasaplar, P.; Ozkal, E.; Rodríguez-Escrich, C.; Pericàs, M. A. *Green Chem.* **2015**, *17*, 3122-3129.

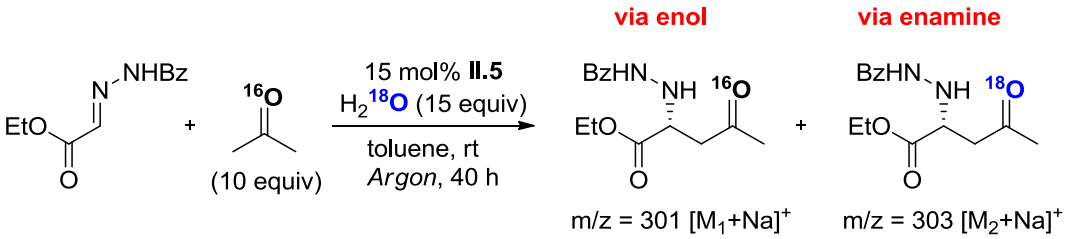
3.2. MANNICH-TYPE REACTIONS CATALYZED BY PRIMARY AMINE-THIOUREAS

Mannich reaction is a powerful tool for preparing β-amino carbonyl compounds. Tsogoeva *et al.* reported the first example of the primary amine thiourea-catalyzed Mannich-type addition of unmodified ketones to *N*-benzoyl hydrazones. They employed their chiral primary amine thioureas **II.2**, **II.3,** and **II.5** aforementioned in section 2.2. The best results were obtained using catalyst **II.5**, providing the product in up to 89% yield and excellent enantioselectivities (up to >99% yield) **(Scheme 3.4)**.[24]



Scheme 3.4. Mannich-type reaction catalyzed by primary amine thioureas.

Based on their DFT calculation and ^{18}O incorporation studies, they suggested evidence for an enol mechanism together with the enamine mechanism responsible for the Mannich-type reaction of acetone with *N*-benzoyl hydrazone. ESI-MS studies indicated the both enol and enamine pathways are active with a predominance of the enamine pathway while computational studies suggested a preference of enol over enamine mechanism **(Scheme 3.5)**.[24]

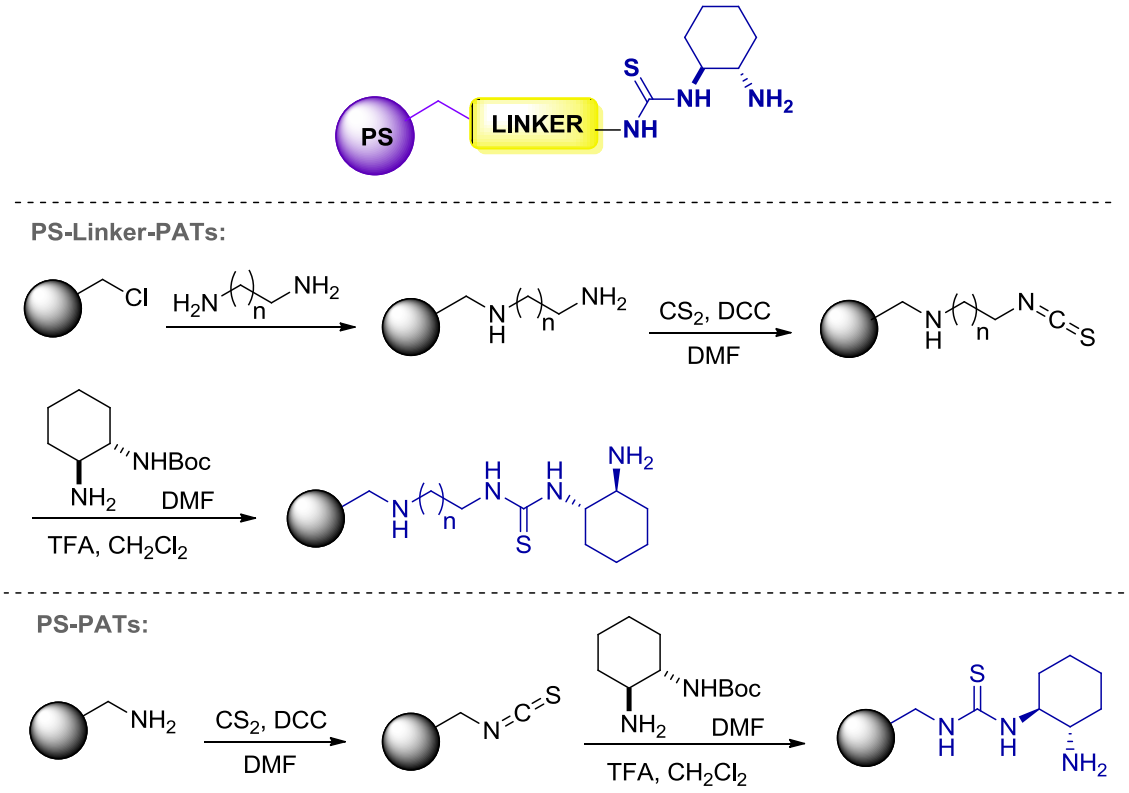


Scheme 3.5. ^{18}O-incorporation experiment studied by ESI-MS methods.

[24] Yalalov, D. A.; Tsogeova, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 6624-6628.

3.3. AIM OF OUR STUDY

These previously published studies show that the immobilization of primary amine-thioureas has not been demonstrated yet. Based on this, we decided to develop immobilization strategies to obtain heterogeneous versions of primary amine thiourea organocatalysts. Our approach starts from the design by the Tsogoeva group for homogeneous catalysts[25] and aims at the direct immobilization of the *trans*-1,2-diaminocyclohexane moiety with concomitant formation of the thiourea through a click chemistry strategy **(Scheme 3.6)**. We have supported these catalysts on polystyrene resins and evaluated them in asymmetric Michael addition of acetone to *trans*-β-nitrostyrene and Mannich type addition of unmodified ketones to *N*-benzoyl hydrazones. These reactions were previously performed successfully using the homogeneous analogs of our catalysts.[24,25]



Scheme 3.6. General design and the immobilization strategy of our polymer supported catalysts.

[25] Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451-1453.

PAPER C

Polymer Supported Primary Amine-Thiourea Organocatalysts:

Application to the Asymmetric Michael and Mannich Reactions

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PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS
Zeynep Inci Günler

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Chiral primary amine thiourea (PAT) organocatalysts have been inmobilized on polystyrene-based resins for the first time through a very simple "click" strategy that renders the thiourea group and the linkage simultaneously. The as-synthesized catalytic polymers have been applied to the asymmetric Michael addition and Mannich reaction of ketones. High enantioselectivities were recorded for the Mannich reaction, whereas the current catalyst design led to moderate ee's in the Michael addition.

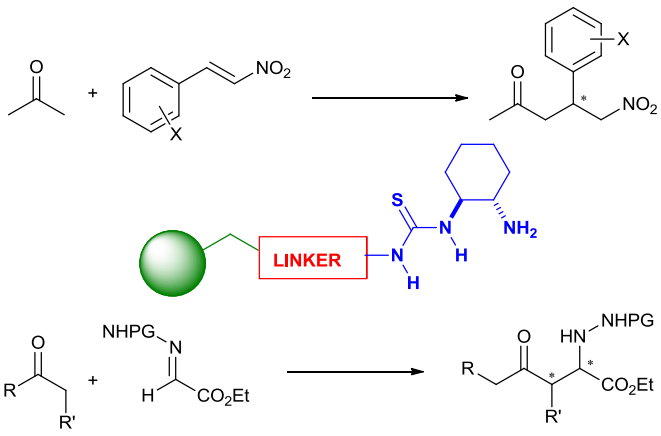
Introduction

Primary amine thiourea (PAT) organocatalysts have gained popularity among the asymmetric organocatalysis community because they are easily synthesized and can be applied to a variety of reactions.[1] They were originally developed by Tsogoeva *et al.*[2, 3] and Jacobsen *et al.*[4, 5] for asymmetric Michael additions, and they showed a remarkable performance in the reaction of ketones and branched aldehyde donors. However, PAT can be also used as efficient and highly asymmetric organocatalysts for many other types of Michael additions, Mannich reactions, α-alkylation of aldehydes, and a variety of cyclizations and cycloadditions, including asymmetric Nazarov, intramolecular [5+2] cycloaddition, and a diversity of Diels-Alder-type reactions.[1]

In view of the synthetic potential of PAT catalysts, it is desirable to develop immobilized versions to facilitate their recovery and recycling. To our knowledge, this task has not been carried out yet. Our group has been recently involved in the development of amine-thiourea[6] and amine guanidine[7] organocatalysts. A recent example from our group of tertiary amine thioureas (TAT) immobilized on polymeric resins has been applied to the enantioselective α-amination of 1,3-dicarbonyl compounds. A continuous flow protocol was eventually established with success.[8]

Before this example, Takemoto had developed an immobilized version of his TAT catalyst on PEG.[9] Cinchona alkaloid derivatives have also been immobilized through cross-linked thiol-ene resins. A TAT derivative was thus successfully applied to the asymmetric Michael addition of malonate to nitrostyrene, although serious loss of catalytic activity was observed in the third cycle.[10] Secondary amine-thioureas have been also immobilized. For example, a pseudo-peptide containing prolinamide and thiourea was bonded to several resins and tested in the asymmetric aldol reaction with little success compared to the free catalyst.[11] Another design using a prolinamido-thiourea linked to a Merryfield resins was more successful and rendered high yield, ee and recyclability in the asymmetric aldol reaction. Diastereoselectivity was low, though.[12] Other authors have favored the sulfonamido moiety in front of the thiourea for these immobilized prolinamide derivatives.[13]

In contrast, no PAT catalysts have been immobilized to our knowledge. Only a primary amine urea (PAU) catalyst was supported onto a polymeric resin affording excellent results in the asymmetric Michael addition of acetone to nitrostyrene, although it suffered from serious catalyst deactivation upon recycling.[14, 15]



Scheme 1. Immobilized PAT organocatalyst design and model reactions.

[a] *Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), c/Jordi Girona 18-24, E08034 Barcelona, Spain.*
[b] *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, E43007 Tarragona, Spain.*
[c] *Dept. Química Orgànica, Universitat de Barcelona, E08080 Barcelona, Spain.*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

As far as we know, these are all the known examples of immobilized bifunctional amine-(thio)urea asymmetric organocatalysts. Therefore the particular task of immobilizing PAT catalysts and studying their catalytic behaviour is of great interest.[16]

We want to report herein on the successful implementation of a simple strategy towards this goal: essentially, we planned to use the isothiocyanate-amine reaction that furnishes thioureas to simultaneously generate one of the catalytic functions and bind the primary amine thiourea organocatalyst to the resin (Scheme 1). The isothiocyanate-amine reaction can be considered a click reaction[17] and hence is an excellent reaction candidate for the immobilization of all sorts of catalysts. As far as we are aware, though, this approach has only been used before by our group to immobilize chiral tertiary amine thioureas[8] and by two more groups to synthesize achiral polymers containing the *N*-3,5-bis(trifluoromethyl) phenylthiourea moiety.[18, 19]

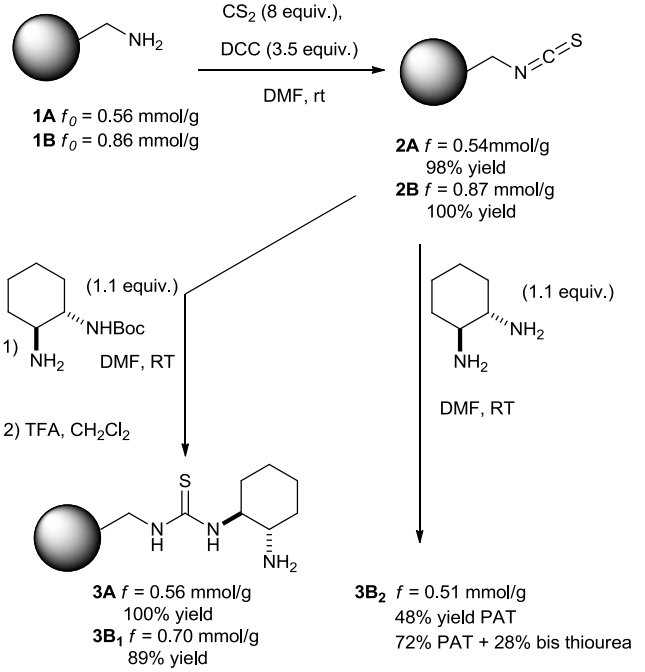
The resulting polymer-supported PAT's were applied to the asymmetric Michael addition of acetone to nitrostyrenes and the Mannich reaction of ketones with activated hydrazones (Scheme 1).[20-23]

Results and discussion

Synthesis of the catalytic resins

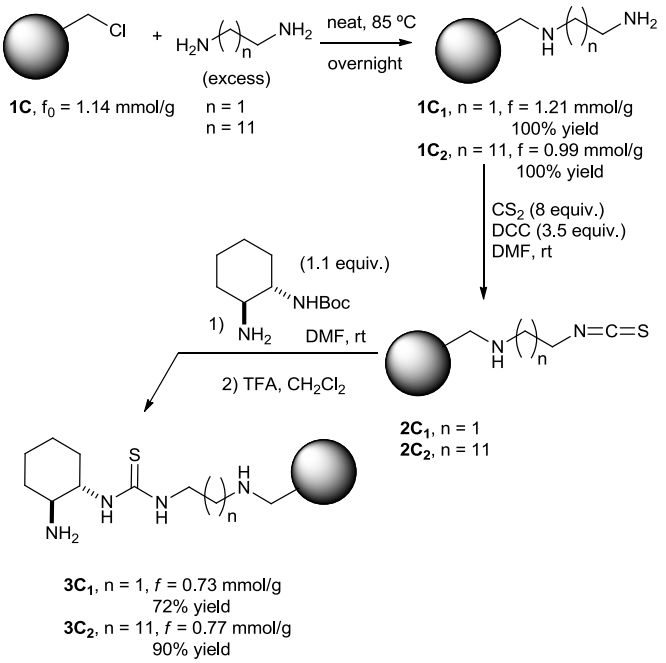
We based our design in the transformation of commercial polystyre-based resins into isothiocyanate-functionalized materials which were further reacted with diaminocyaclohexane. Initially, a linker-free design was chosen (Scheme 2). Aminomethylene polystyrene resins of two different functionalization levels (resins **1A** and **1B**) were treated with carbon disulfide and DCC to generate the corresponding isothiocyanates.[2] The formation of the isothiocyanate was tracked by FTIR and the Kaiser's test. Nitrogen and sulfur elemental analysis showed a high level of formation of the isothiocyanate. Upon reaction completion, the isothiocyanate resins **2A-B** were reacted with mono-Boc-protected diaminocyclohexane and submitted to deprotection with TFA in dichloromethane. The formation of the desired immobilized organocatalyst **3A** and **3B$_1$** was assessed by FTIR and elemental analysis (See ESI). The obtained functionalizations show the excellent reactivity of such isothiocyanate-containing resins (Scheme 2).

As a more straightforward option, resin **2B** was reacted with (*1S, 2S*)-diaminocyclohexane to afford **3B$_2$**. For the success of this approach, it was essential that the isothiocyanate groups behave as site-isolated ones. However, the lower functionalization of **3B$_2$** compared to **3B$_1$** indicated the formation of substantial amounts of bis(thiourea), as calculated by elemental analysis (Scheme 2). For this reason this method was not further considered.



Scheme 2. Synthesis of resins **3A, 3B$_1$** and **3B$_2$**.

We were also interested in studying the effect of a linker that would separate the PAT scaffold from the polymeric backbone. To this effect, two more immobilized catalysts were prepared. Merrifield resin **1C** was reacted with excess ethylenediamine and 1,12-diaminododecane. In this way, two spacers of different length were introduced to the resin. Next, the two resins were subjected to the previous thiocyanation-thiourea formation-deprotection sequence in high overall yield (Scheme 3).



Scheme 3. Synthesis of resins with linkers **3C$_1$** and **3C$_2$**.

The final materials **3C$_1$** and **3C$_2$** containing the immobilized PAT both showed a very similar level of functionalization, which indicated that both synthetic sequences worked similarly regardless of the linker used (Scheme 3).

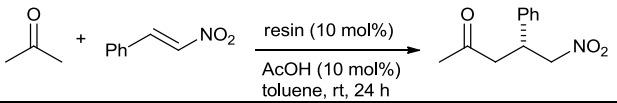
Application of PS-PAT in the Michael addition

Then, it was time to test the catalytic activity and stereoselectivity of all five resins **3**. The asymmetric Michael addition of acetone to nitrostyrene was chosen as the benchmark because it is a well-known example of reaction catalyzed by PAT.[2, 3] The results of this screening are shown in Table 1. High conversion (77-88%) was achieved for resins **3A**, **3B$_1$** and **3B$_2$** (Entries 1-3), whereas poorer results were recorded for resins with linker **3C$_1$** and **3C$_2$** (31-57% conversion, Entries 4-5). In terms of enantioselectivity, these two last resins were also clearly inferior (54-60% ee vs. 68-79% ee). It can be then concluded that the introduction of a linear linker between the PAT scaffold and the polymer backbone is deleterious for this particular reaction, no matter the length of the linker. This could de due to the presence, close to the resin backbone, of the additional secondary amino group introduced with the linker. The best performing resins (**3A-3B**) present in their structures well differentiated polar (the active moieties) and non-polar (the polymer backbone) regions in close vicinity, and this has previously shown to be a very desirable characteristic for high catalytic performance.[24]

Hence, best results were obtained with resin **3B$_1$**, affording 77% conversion and 79% ee (Entry 2, Table 1). Resin **3B$_2$** yielded higher adduct conversion (88%) but at the expense of somewhat lower ee (69% ee). Other solvents apart from the standard toluene (DMF, DMF-water and CH_2Cl_2) were tested as well, but always with diminished reactivity and enantioselectivity (See ESI).

In view of these results, catalyst separation and recycling was attempted in the presence of a small amount of water in order to minimize PAT deactivation by nitrostyrene.[25, 26] Other additives such as PEG and DiMePEG were tested as well to facilitate the diffusion of water into the polymeric matrix (Table 2).[27] First of all, it was clear that serious catalyst deactivation was taking place, since a sharp decrease in catalytic activity was observed upon recycling for both resins

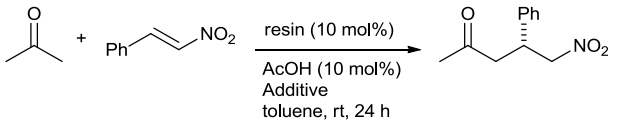
Table 1. Asymmetric Michael addition of acetone to nitrostyrene catalyzed by resins **3**.



Entry	Resin	Conv. [%][a]	ee [%][b]
1	**3A**	78	68
2	**3B$_1$**	77	79
3	**3B$_2$**	88	69
4	**3C$_1$**	31	60
5	**3C$_2$**	57	54

[a]Determined by ^{1}H NMR. [b]Determined by HPLC on a chiral stationary phase.

Table 2. Recycling studies for resins 3A and 3B2 in the asymmetric Michael addition of acetone to nitrostyrene.



	Resin	Water	Additive	Conv.[%][a]	ee [%][b]
1	**3B$_2$**	no	no	88	69
2	**3B$_2$**[c]	no	no	15	64
3	**3A**	no	no	78	68
4	**3A**[c]	no	no	25	66
5	**3A**	7 equiv.	no	93	66
6	**3A**[c]	7 equiv.	no	48	66
7	**3A**	7 equiv.	DiMePEG[d]	91	67
8	**3A**	7 equiv.	PEG[d]	87	67
9	**3A**[c]	7 equiv.	PEG[d]	48	66
10	**3A**	17 equiv.	PEG[e]	90	67
11	**3A**[c]	17 equiv.	PEG[e]	57	66

[a]Determined by ^{1}H NMR. [b]Determined by HPLC on a chiral stationary phase. [c]Upon recycling of resin from the previous entry. [d]10 mol%. [e]20 mol%.

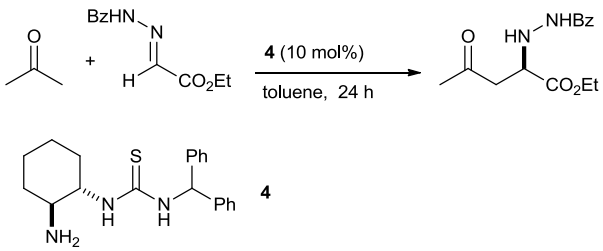
3A and **3B$_2$** (Entries 1-4, Table 2). The addition of 7 equiv. of water improved the results, and 93% conversion was achieved in the first cycle (Entry 5, compare to 78% conversion in entry 3). Catalyst activity also decreased in the second cycle, but this time the fall was less pronounced. It was thus possible to achieve 48% conversion in the same reaction time under these conditions (Entry 6, Table 2).

Then 10 mol% DiMePEG was tested as additive, besides water, but no improvement was observed (Entry 7, Table 2). The same observation was made for 10 mol% PEG (Entries 9 and 10). However, when 20 mol% PEG was tested, a slight but significant improvement was recorded upon recycling, and 57% conversion was obtained in the second run (Entries 10 and 11, Table 2). It must be noted that this result is clearly insufficient for practical purposes, but it shows how the use of certain additives can impart some stabilization and improve the catalytic system. It is also worth highlighting that the enantioselectivity of the reaction did not change regardless of the conditions used.

Application of PAS-PAT in the Mannich reaction

Looking for alternative processes where the advantages of the new catalytic resins could be more clearly appreciated, we moved to the Mannich reaction, a process efficiently catalyzed by PAT catalysts.[28] The chosen substrates involved acetone again and the *N*-benzoyl-hydrazone of ethyl glyoxylate as activated electrophile. We first used a homogeneous PAT organocatalyst, **4**, which has not been evaluated in this reaction before, to optimize the reaction conditions and the effect of the geometry of the reacting hydrazone.[28] After chromatographic separation, both *E* and *Z* hydrazones, besides the as-synthesized *E/Z*-mixture, were tested in the asymmetric Mannich reaction with acetone (Table 3).

Table 3. Optimization of the Mannich reaction of acetone and the hydrazone of ethyl glyoxylate.



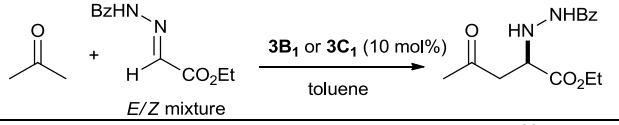
Entry	T [ºC]	Hydrazone	Yield [%][a]	ee [%][b]
1	25	*E*	43	98
2	25	*Z*	71	99
3	25	Mixture *E/Z*	65	99
4	40	*E*	62	98
5	40	Mixture *E/Z*	63	96

[a]Isolated yield after purification by flash chromatography. [b]Determined by HPLC on a chiral stationary phase.

The *Z* hydrazone substrate showed higher reactivity that the *E*-isomer, as it could be expected from its more hindered structure (Entries 1 and 2, Table 3). The Mannich product was isolated in 71% yield starting from the Z-isomer (the minor isomer), but since using the as-synthesized mixture did not lead to an important yield drop (65% yield, Entry 3) it seemed reasonable from a practical point of view to use the mixture of isomers directly. At 40 ºC (Entries 4 and 5) there was no practical difference between using the major *E*-isomer or the mixture of isomers. In all cases, excellent ee's were recorded (96-98% ee) and again the mixture of *E/Z* isomers was considered as the most practical option.

We then proceeded to transfer these results to the Mannich reaction catalyzed by polymer-supported PAT (Table 4). Resins **3A**, **3B$_1$**, **3C$_1$** and **3C$_2$** were tested. It was clear that the Mannich reaction proceeded slower in the presence of a catalytic resin than when a homogeneous catalyst was used.

Table 4. Mannich reaction of acetone with the hydrazone of ethyl glyoxylate catalysed by resins **3B$_1$** or **3C$_1$**.



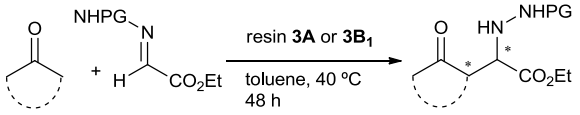
	Catalyst	T [ºC]	Reaction time [h]	Yield [%][a]	ee [%][b]
1	**3A**	40	48	75	98
2	**3B$_1$**	25	24	25	n.d.
3	**3B$_1$**	25	48	55	98
4	**3B$_1$**	40	24	40	n.d.
5	**3B$_1$**	40	48	75	97
6	**3B$_1$**	40	72	72	n.d.
7	**3C$_1$**	40	24	15	n.d.
8	**3C$_1$**	40	48	25	56
9	**3C$_2$**	40	24	22	n.d.
10	**3C$_2$**	40	48	30	40

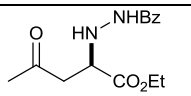
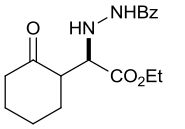
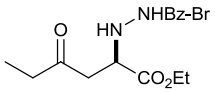
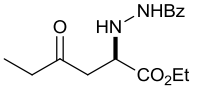
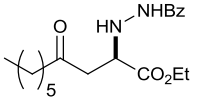
[a]Isolated yield after purification by flash chromatography. [b]Determined by HPLC on a chiral stationary phase. n.d. not determined

Resin **3B$_1$**, a polymer of high functionalization with the catalytic unit directly bound to the matrix, afforded moderate conversion after 48 hours at 25 ºC. Nevertheless, the enantioselectivity was excellent, and the product was isolated in 98% ee (Entries 2 and 3, Table 4). Performing the reaction at 40 ºC increased the yield after 48 hours up to 75%, still keeping a very high enantioselectivity (97% ee). No further improvement was observed by letting the reaction to proceed up to 72 hours (Entries 4-6, Table 4). The analogous resin of low functionalization, 3A, behaved very similar (75% yield and 98% ee, Entry 1, Table 4) and therefore it seems that the degree of functionalization is not an important parameter.

Using resin **3C$_1$**, which incorporates a CH_2CH_2 linker, poor conversion and ee was achieved even after 48 hours at 40 ºC (25% yield and 56% ee, Entries 7 and 8, Table 4). Similar results were obtained with **3C$_2$**, which contains a $(CH_2)_{12}$ linker (Entries 9 and 10). This trend, similar to that observed in the PS-PAT catalyzed Michael reaction, clearly indicate that the use of 1,ω-diamine linkers is detrimental, and that the catalytic scaffold must be close to a bulky non polar group, i. e., the polymer backbone in **3A**-**3B** or the benzhydryl group in **4**. Only in this way high reactivity, and consequently high yield and *ee*, can be achieved for the catalysts based on the (2-aminocyclohexyl)thiourea moiety.

Table 5. Substrate scope for the Mannich reaction catalysed by resins **3A** and **3B$_1$**.



	Product	Yield [%][a]	ee [%][b]	d.r.[c] (*anti*/*syn*)
1		75[g] 75[f]	97[g] 98[f]	-
2		63[f]	80 (anti)[f] 75 (syn)[f]	53/47[f]
3		40[d][f]	94[f]	-
4		34[e][f]	98[f]	-
5		58[f]	94[f]	-

[a]Isolated yield after purification by flash chromatography. [b]Determined by HPLC on a chiral stationary phase. [c]Determined by ^{1}H NMR. [d]Linear/branched 2/1. [e]Linear/branched 1.2/1. [f]With resin **3A**. [g]With resin **3B$_1$**.

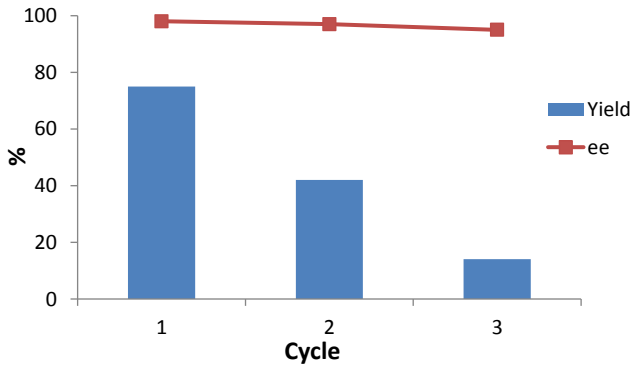


Fig. 1. Recycling of resin **3A** in the Mannich reaction of acetone and the benzoylhydrazone of ethyl glyoxylate

After these investigations, we tested the substrate scope in the Mannich reaction for the catalytically active resins **3A** and **3B$_1$**, which in practice were indistinguishable. Several ketones were reacted with the hydrazone of ethyl glyoxylate. Optimized conditions involve running the reaction at 40 ºC for 48 hours (Table 5).

As we have shown before, the Mannich reaction of acetone proceeded smoothly and the corresponding product was isolated in high yield and excellent *ee* (Entry 1, Table 5). The reaction of cyclohexanone also furnished high product yield, although as a 1.1/1 mixture of *anti/syn* diastereomers. Enantioselectivity for both diastereomers was good, although clearly inferior to acetone (80% *ee* for *anti* and 75% *ee* for *syn*, Entry 2). 2-Butanone also furnished the Mannich adduct in good yield (60%) that was isolated as a mixture of regioisomers. The linear *vs*. branched product ratio was 2/1. High *ee* was recorded for the major linear product (94% *ee*). In this example, the *p*-bromobenzoylprotected hydrazone was used (Entry 3, Table 5). When this reaction was repeated with the benzoyl hydrazone (Entry 4) the linear Mannich product was isolated in 34% yield and 98% *ee*. Better results were obtained with 2-octanone and the benzoyl hydrazone of ethyl glyoxylate: the amount of isolated linear product increased to 58% yield, likely due to stronger steric repulsion in the pathway leading to the branched product that favour the linear regioisomer. High *ee* was also observed this time (94% ee, entry 5, Table 5).

Finally, we worked on the separation and recycling of resin **3A** applied to the benchmark Mannich reaction of acetone. Each reaction cycle was performed at 40 ºC for 48 hours. As for the Michael addition to nitrostyrene, as important loss of catalytic activity was observed after each cycle, concomitant to a slight erosion of ee, from 98 to 95% ee in the third cycle. After the third cycle, the resin activity was depleted and product could only be isolated in 14% yield (Figure 1). As in the Michael addition, we attribute this problem to catalyst deactivation although the origin of such loss of catalytic activity in the Mannich reaction is at present unknown to us.

Experimental

1. Synthesis of catalytic resin 3B$_1$:

Synthesis of isothiocyanate resin 2B.

Aminomethyl polystyrene resin **1B** (0.50 g, f_0 = 0.86 mmol g^{-1}, 0.43 mmol) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, carbon disulfide (8 equiv., 3.44 mmol, 0.21 mL) and *N,N'*-dicyclohexylcarbodiimide (3.5 equiv., 1.50 mmol, 0.31 g) were added in one portion and the mixture was stirred at room temperature overnight. The resulting resin **2B** was collected by filtration and washed with DMF, DMF:H_2O (1:1), MeOH, THF and CH_2Cl_2. Then, it was dried at 50°C in a vacuum oven overnight.

Elemental Analysis: C% 88.08; H% 7.25; N% 1.22; S% 2.64

f = (0.714/nN)%N, f = 0.87 mmol/g resin.

f_{max} = 0.83 mmol/g resin; 100% yield.

Starting from commercial resin **1A**, the same procedure was used for the synthesis of isothiocyanate resin **2A**.

Immobilization of the *trans-N*-Boc-1,2-cyclohexanediamine catalytic unit.

Isothiocyanate resin **2B** (f= 0.87 mmol g^{-1}, 0.415 mmol, 0.5 g) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, (*1S,2S*)-*trans-N*-Boc-1,2-cyclohexane diamine (1.1 equiv., 0.457 mmol, 98 mg) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by IR spectroscopy. After the dissapperance of the isothiocyanate stretching band (20-24 h), the resin was filtered and washed with DMF, MeOH, THF and CH_2Cl_2 and dried in vacuum oven at 50°C overnight.

Deprotection procedure furnishing resin 3B$_1$

Boc protected resin from the previous step was swelled in dry CH_2Cl_2 (5 mL) for 30 minutes. Then TFA (5 mL) added and the reaction mixture was stirred at room temperature. The progress of the reaction was followed by IR spectroscopy. After the dissappearence of the Boc band on IR (5-6 h), the resin was filtered and washed with abundant THF(2% Et_3N), THF:H_2O(1:1), THF, THF:MeOH (1:1), MeOH, THF and CH_2Cl_2 consecutively.

3B$_1$ Elemental Analysis: C% 83.15; H% 7.69; N% 2.96; S% 2.33

f = (0.714/nN)%N, f = 0.70 mmol/g resin.

f_{max} = 0.79 mmol/g resin; 89% yield.

Starting from isothiocyanate resin **2A**, the same procedure was employed for the synthesis of resin **3A**.

2. Procedure for the Michael addition using catalytic resin 3B$_1$.

65 mg of catalytic resin **3B$_1$** (0.1 equiv., f = 0.70 mmol g^{-1}, 0.0335 mmol) was weighed in a vial and swollen in toluene (2 mL) for 30 minutes. Nitrostyrene (1.0 equiv., 0.335 mmol, 50 mg) was added into the vial as solid. Then, AcOH (0.1 equiv., 0.0335 mmol, 2 µL of AcOH in 1 mL toluene) was added using 10 µL of a stock solution (200 µL of AcOH in 1 mL toluene) and acetone (10.0 equiv., 3.35 mmol, 0.25 mL) were added. The reaction was stirred for 24 hours at room temperature. The reaction mixture was filtered, and rinsed with 20 mL toluene. The resin was dried and used directly in the next run. ^{1}H NMR measurements of the crude reaction mixture in $CDCl_3$ gave the

conversion% values. HPLC samples were prepared in ^{i}PrOH directly from crude mixtures.

3. Procedure for the Mannich reaction using catalytic resin $3B_1$.

72 mg catalytic resin **$3B_1$** (0.1 equiv., f = 0.70 mmol g^{-1}, 0.05 mmol) was weighed in a vial and swollen in toluene (2 mL) for 30 minutes at 40 °C. Then, the corresponding *N*-benzoylhydrazone (1.0 equiv., 0.5 mmol) and the ketone (10.0 equiv., 5.0 mmol) were added in one portion and the reaction was stirred at 40 °C with a small magnetic bar at 200 rpm. After 48 h, the reaction mixture was filtered and rinsed off with 20 mL of toluene. The recovered polymer was dried and used directly in the next run. The filtrate was purified by flash chromatography on a silica gel using 1:1 EtOAc:Hexane as eluent to furnish the pure product. HPLC samples were prepared in ^{i}PrOH.

Conclusions

Primary amine thiourea (PAT) organocatalysts have been immobilized on polystyrene resins for the first time. For this purpose, we have used a click chemistry strategy (amine plus isothiocyanate reaction) which serves for the double purpose of PAT generation and binding to the support resin. When catalysts prepared in this manner were applied to the Michael addition of acetone to nitrostyrene, only modest enantioselectivities (up to 80% ee) were achieved. In any case, this study clarified the role of spacers connecting PAT and resin, helping in the definition of the optimal immobilization strategy.

Optimal PS-PAT catalysts, involving direct immobilization onto the resin, also performed better in the Mannich reaction of ketones with the hydrazone of ethyl glyoxylate. These results, along with those obtained with the use of the homogeneous analogue, **4**, indicate that the presence of a large, nonpolar fragment close to the catalytic unit is a remarkable factor in controlling catalyst activity. Good yields and very high ee's were recorded in the Mannich reaction of linear ketones with preformed glyoxylate imines, with preference for the formation of linear in front of branched adducts. Unfortunately, an important loss of catalytic activity was also observed in this case, which suggests little stability of the PAT catalysts. Further work in this respect is being carried out in our laboratories and will be reported in due course.

Acknowledgements

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ELECTRONIC SUPPLEMENTARY INFORMATION

Polymer-supported primary amine thiourea organocatalysts: application to asymmetric Michael and Mannich reactions

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1. General

All the reagents were purchased from Aldrich or TCI and used without any further purification. Commercial resins were purchased from NovaBiochem or TCI. The solvents were directly used from bottle unless otherwise is indicated. Anhydrous solvents were obtained from a Solvent Purification System. TLC chromatography was performed on silica gel 60 F_{254}aluminium sheets. Flash chromatography was performed using silica gel P60 (200-500 mesh). HPLC analyses were performed using Shimadzu with an UV-Vis detector equipment. NMR measurements were recorded with an automated Varian VNMRS 400 MHz.

2. Preparation of polymer supported PATs

2.1 Synthesis of catalytic resins 3A and $3B_1$:

Synthesis of isothiocyanate resins 2A and 2B

Aminomethyl polystyrene resin **1B** (0.50 g, f_0= 0.86 mmol g^{-1}, 0.43 mmol) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, carbon disulfide (8 equiv., 3.44 mmol, 0.21 mL) and *N,N'*-dicyclohexylcarbodiimide (3.5 equiv., 1.50 mmol, 0.31 g) were added in one portion and the mixture was stirred at room temperature. The reaction was followed by FTIR and Kaiser's test.[1] The appearence of –N=C=S strech band at 2080 cm^{-1} on IR spectrum and negative Kaiser's test indicated the completion of the reaction. The resulting resin **2B** was collected by filtration and washed with DMF, DMF:H_2O (1:1), MeOH, THF, CH_2Cl_2. Dried at 50°C in vacuum oven overnight and submitted to elemental analysis. Starting from commercial resin **1A**, the same procedure was used for the synthesis of isothiocyanate resin **2A**.

Calculation of the maximum possible substitution level of a given resin[2]:

$f_{max} = f_o/[1 + f_o(\Delta Mw)\ 10^{-3}]$

Where *fo* is the functionalization of the starting resin and ΔMw is the difference in molecular weight between the final and the initial functional fragments.

The yield (%) of the considered step can then be evaluated as $100\ f/f_{max}$.

Kaiser's test Reagents: Solution A) 500 mg ninhydrin in 10 mL ethanol **Solution B)** 80 g phenol in 20 mLethanol **Solution C)** 2 mL KCN solution (0.001 M) was diluted to 100 mL using pyridine.

A sample of the resin was placed in a vial and 2-3 drops of each reagent solution (A, B and C) were added. The vial was heated up to 100 °C for 3 minutes. The observation of the beads remain white and the solution yellow indicated the completion of the reaction (negative test). A dark blue color on the beads and solution indicates the presence of free amino groups, thus an incomplete reaction (positive test).[1]

i) **Calculation of the degree of functionalization of the commercial aminomethyl polystyrene resin 1B[2]:**

Elemental Analysis: C% 90.04; H% 7.98; N% 1.20

f= (0.714/n_N)%N, f= 0.86 mmol/g resin (0.87 mmol/g according to the supplier's analysis)

ii) **Calculation of the degree of functionalization of resins 2A and 2B [2]:**

2A: Elemental Analysis: C% 84.88; H% 7.12; N% 0.75; S% 1.55

f= (0.714/n_N)%N, f= 0.54 mmol/g resin

f_{max} **2A**= 0.56/[1 + 0.56(58-16)10^{-3}]= 0.55 mmol/g resin

On the basis of N elemental analysis, yield% **2A** = 100(0.54/0.55) = 98%

2B: Elemental Analysis: C% 88.08; H% 7.25; N% 1.22; S% 2.64

f= (0.714/n_N)%N, f= 0.87 mmol/g resin

f_{max} **2B**= 0.86/[1 + 0.86(58-16)10^{-3}]= 0.83 mmol/g resin

On the basis of N elemental analysis, yield% **2B**= 100(0.87/0.83)= 105%

Immobilization of the *trans*-*N*-Boc-1,2-cyclohexanediamine catalytic unit (Resins 3A and 3B$_1$)

Isothiocyanate resin **2B** (f= 0.87 mmol g^{-1}, 0.415 mmol, 0.5 g) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, (*1S,2S*)-*trans*-*N*-Boc-1,2-cyclohexanediamine (1.1 equiv., 0.457 mmol, 97.8 mg) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by IR spectroscopy. After the dissapperance of the isothiocyanate stretch band (t= 20-24 h), the resin was filtered and washed with DMF, MeOH, THF, CH_2Cl_2 and dried in vacuum oven at 50°C overnight.

Deprotection procedure furnishing resins 3A and 3B$_1$

Boc protected resin from the previous step was swelled in dry CH_2Cl_2 (5 mL) for 30 minutes. Then TFA (5 mL) added and the reaction mixture was stirred at room temperature. The progress of the reaction was followed by IR spectroscopy. After the dissappearence of Boc band on IR (t=5-6 h), the resin was filtered and washed with abundant amounts of THF(2% Et_3N), THF:H_2O(1:1), THF, THF:MeOH (1:1), MeOH, THF, CH_2Cl_2 consecutively. The yield of the resulting resin was calculated from the results of elemental analysis. Starting from isothiocyanate resin **2A**, the same procedure was employed for the synthesis of resin **3A**.

Resin 3A. Elemental Analysis: C% 84.70; H% 7.54; N% 2.37; S% 2.36

f = (0.714/n_N)%N, f= 0.56 mmol/g resin

f_{max} **3A** = 0.54/[1 + 0.54(172.27-16)10^{-3}]= 0.50 mmol/g resin

On the basis of N elemental analysis yield% **3A**= 100(0.56/0.50)= 112%

Resin 3B$_1$. Elemental Analysis: C% 83.15; H% 7.69; N% 2.96; S% 2.33

f = (0.714/n_N)%N, f = 0.70 mmol/g resin

f_{max} **3B$_1$** = 0.87/[1+(0.87*(114-0)*0.001] = 0.79 mmol/g resin

On the basis of N elemental analysis yield% **3B$_1$** = 100(0.70/0.79) = 89%

2.2 Synthesis of catalytic resin 3B$_2$

Starting from isothiocyanate resin **2B**, catalytic resin **3B$_2$** was synthesized using (*1S,2S*)-diaminocyclohexane instead of Boc protected analogue. Resin **2B** (f= 0.87 mmol g^{-1}, 0.415 mmol, 0.5 g) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, (*1S,2S*)-(+)-1,2-diaminocyclohexane (1.1 equiv., 0.457 mmol, 52.18 mg) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by IR spectroscopy. After the dissapperance of the isothiocyanate stretch band (t= 20-24 h), the resin was filtered and washed with DMF, MeOH, THF, CH_2Cl_2 and dried in vacuum oven at 50°C overnight.

Resin $3B_2$. [3] Elemental Analysis: C% 85.05; H% 7.80; N% 2.88; S% 2.15

For monosubstitution:
f_{max} **$3B_2$**= 0.87/[1 + 0.87(114-0)10^{-3}]= 0.79 mmol/g resin (all monosubstituted)
$\%N_{mono} = 1.4\ n_N\ f_{mono} = 1.4*3*0.79 = 3.32$

For bis substitution:
f_{max} **$3B_2$**= 0.87/[1 + 0.87(114/2)10^{-3}]= 0.83 mmol/g resin (all bis substituted)
$\%N_{bis} = 1.4 *2*0.83 = 2.32$

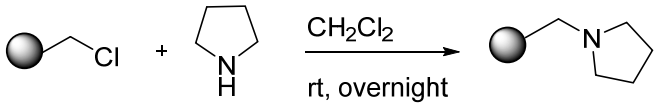
$\%N_{exp} = x\ \%N_{mono} + (1-x)\ \%N_{bis}$
Developing this equation gives: $\%N_{mono} = 1.61$, $f_{mono} = 0.38$ mmol/g
And $\%N_{bis} = 1.27$, $f_{bis} = 0.45$ mmol/g
And x = 0.56, which makes 72% of monosubstitution in the resin and a yield of monosubstitution of 0.38/0.79*100 = 48% yield.

2.3 Synthesis of linked catalytic resins $3C_1$ and $3C_2$

Synthesis of diamino resins $1C_1$ and $1C_2$

In a round bottomed flask, 0.5 g of Merrifield resin **1C** (f= 1.14 mmol g^{-1}, 0.57 mmol) was weighed. Then, excess of ethylene diamine or 1,12-diaminododecane (12 equiv.) was added and the reaction mixture was stirred vigorously at 45°C for 2 days. The resulting resin was washed with THF(2% Et_3N), THF:H_2O(1:1), THF, THF:MeOH (1:1), MeOH, THF, CH_2Cl_2 dried in the vacuum oven at 50 °C overnight and submitted to elemental analysis.

i) **Calculation of the degree of functionalization of the commercial Merrifield resin 1C:**
The commercial resin was reacted with excess pyrrolidine, and the final resin was submitted to nitrogen elemental analysis to obtain the exact functionalization.



10 equiv.

1C Elemental Analysis: C% 89.01; H% 7.98; N% 1.60
f= (0.714/n_N)%N, f= 1.14 mmol/g resin

ii) **Calculation of the degree of functionalization of resins $1C_1$ and $1C_2$:**
Resin $1C_1$. Elemental Analysis: C% 87.62; H% 8.25; N% 3.38
f = (0.714/n_N)%N, f= 1.21 mmol/g resin
f_{max} **$1C_1$**= 1.14/[1 + 1.14(59-35.5)10^{-3}]= 1.11 mmol/g resin,
On the basis of N elemental analysis yield% = 1.21/1.11= 109%

Resin $1C_2$. Elemental Analysis: C% 87.55; H% 9.12; N% 2.76

$f = (0.714/n_N)\%N$, f= 0.99 mmol/g resin

f_{max} **$1C_2$** = 1.14/[1 + 1.14(199-35.5)10^{-3}]= 0.96 mmol/g resin,

On the basis of N elemental analysis yield% = 0.99/0.96 = 103%

Synthesis of isothiocyanate resins $2C_1$ and $2C_2$

Amino resin **$1C_1$** (f_0= 1.21 mmol g^{-1}, 0.483 mmol, 0.4 g) was swollen in DMF (4 mL) for 30 minutes at room temperature. Then, carbon disulfide (16 equiv., 7.73 mmol, 0.472 mL) and *N,N'*-dicyclohexylcarbodiimide (4.7 equiv., 2.27 mmol, 0.47 g) were added in one portion and the mixture was stirred at room temperature. The reaction was followed by FTIR and Kaiser's test. Appearence of –N=C=S strech band at 2080 cm^{-1} on IR spectrum and negative Kaiser's test indicated the completion of the reaction. Resulting resin **$2C_1$** was collected by filtration and washed with DMF, DMF:H_2O (1:1), MeOH, THF, CH_2Cl_2. Dried at 50°C in vacuum oven overnight. The resulting resin was submitted to elemental analysis. Starting from amino resin **$1C_2$**, the same procedure was used for the synthesis of **$2C_2$**.

Resin $2C_1$. Elemental Analysis: C% 80.45; H% 7.57; N% 3.53

$f = (0.714/n_N)\%N$, f = 1.26 mmol/g resin

f_{max} **$2C_1$** =1.21/[1+1.21(44-2)*0.001] = 1.15,

On the basis of N elemental analysis yield% = 1.26/1.15 = 109%

Immobilization of the *trans*-*N*-Boc-1,2-cyclohexanediamine catalytic unit

Isothiocyanate resin **$2C_1$** (f= 1.26 mmol g^{-1}, 0.63 mmol, 0.5 g) was swollen in DMF (5 mL) for 30 minutes at room temperature. Then, (1*S,*2*S*)-*trans*-*N*-Boc-1,2-cyclohexanediamine (1.1 equiv., 0.69 mmol, 147.7 mg) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by IR spectroscopy. After the dissapperance of the isothiocyanate stretch band (t= 20-24 h), the resin was filtered and washed with DMF, MeOH, THF, CH_2Cl_2 and dried in vacuum oven at 50°C overnight.

Deprotection procedure furnishing resins $3C_1$ and $3C_2$

Boc protected resin from the previous step was swelled in dry CH_2Cl_2 (5 mL) for 30 minutes. Then TFA (5 mL) added and the reaction mixture was stirred at room temperature. The progress of the reaction was followed by IR spectroscopy. After the dissappearence of Boc band on IR (t=5-6 h), the resin was filtered and washed with abundant amounts of THF(2% Et_3N), H_2O, THF, THF:MeOH (1:1), MeOH, THF, CH_2Cl_2 consecutively. The yield of the resulting resin was calculated from the results of elemental analysis. The same procedure was used for the synthesis of resin **$3C_2$** starting from isothiocyanate resin **$2C_2$**.

Resin $3C_1$. Elemental Analysis: C% 82.30; H% 7.55; N% 4.10

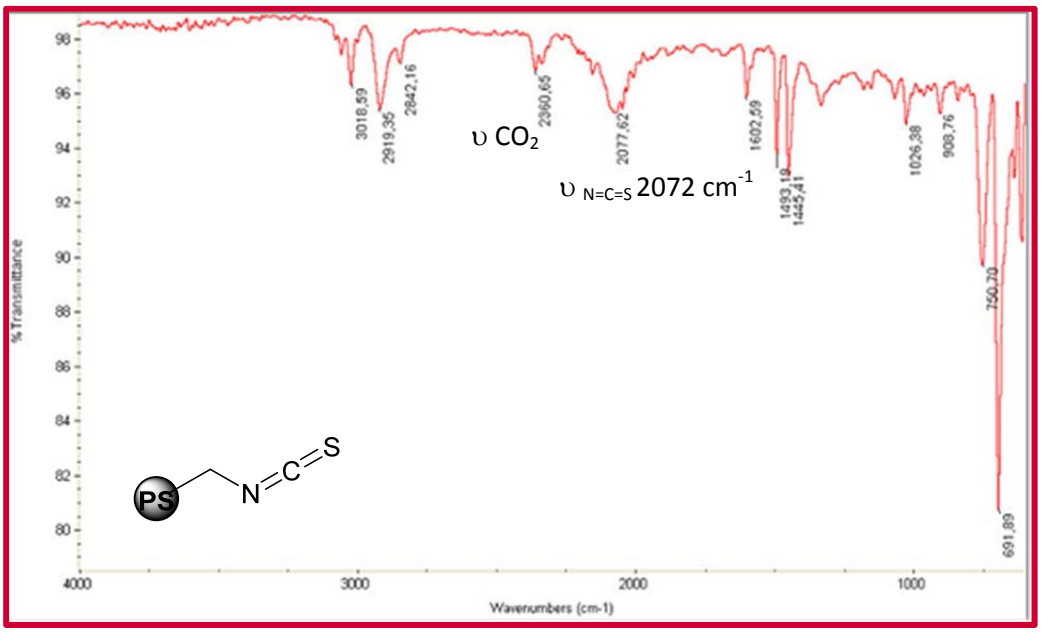
f= $(0.714/n_N)\%N$, f= 0.73 mmol/g resin

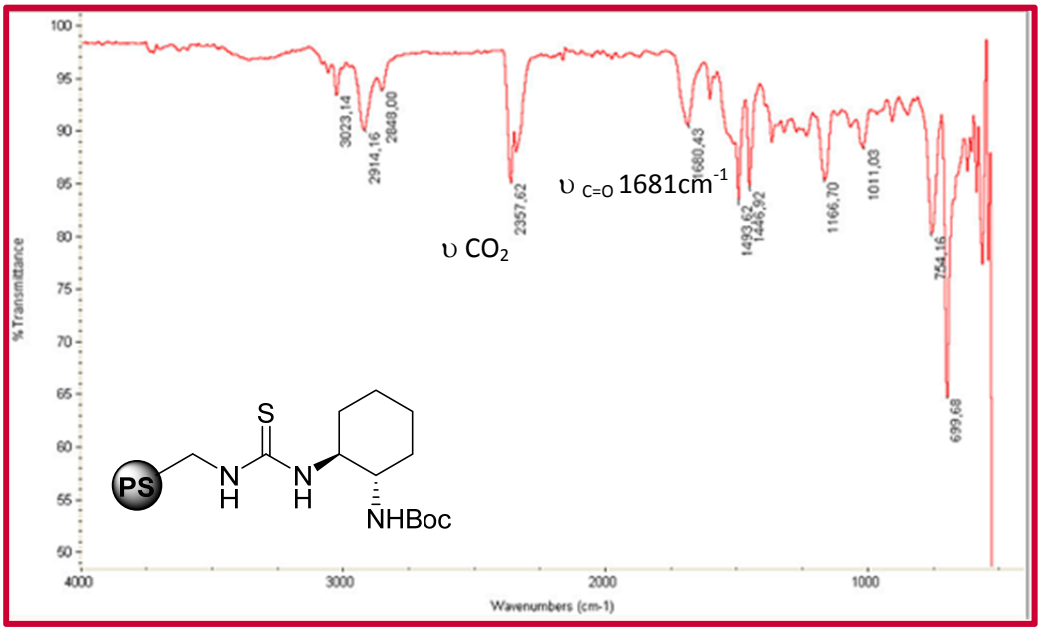
f_{max} **$3C_1$**= 1.21/[1 + 1.21(172-16)10^{-3}]= 1.02 mmol/g resin,

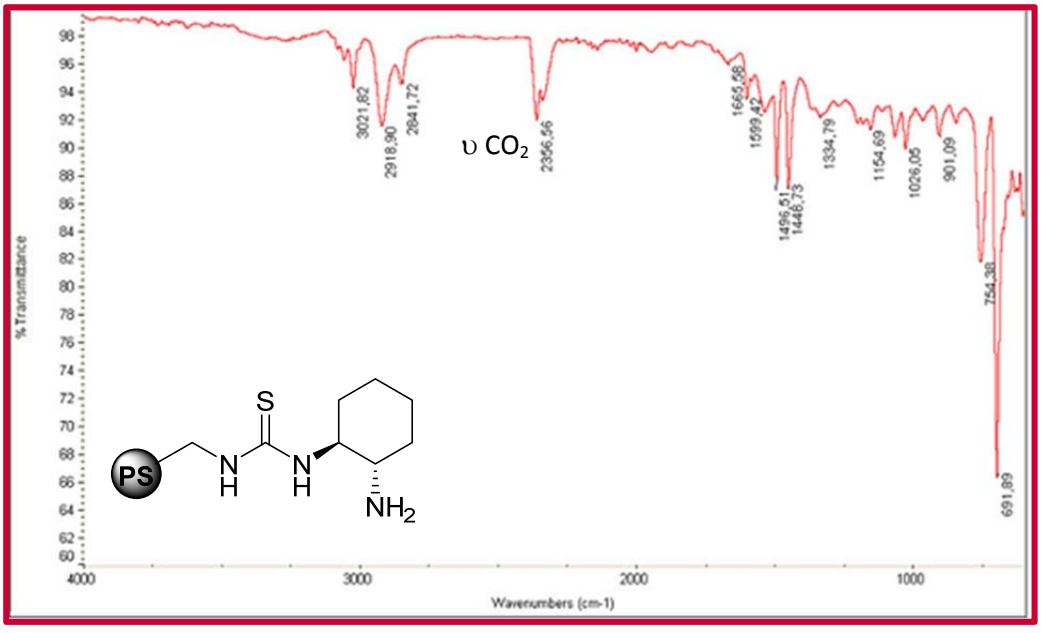
On the basis of N elemental analysis yield%= 0.73/1.02= 72%

Resin $3C_2$. Elemental Analysis: C% 79.97, H% 8.36, N% 4.31, S% 3.79
f= (0.714/n_N)%N, f= 0.77 mmol/g resin
f_{max} **$3C_2$**= 0.99/[1 + 0.99(172-16)10^{-3}]= 0.86 mmol/g resin
On the basis of N elemental analysis yield%= 0.77/0.86= 90%

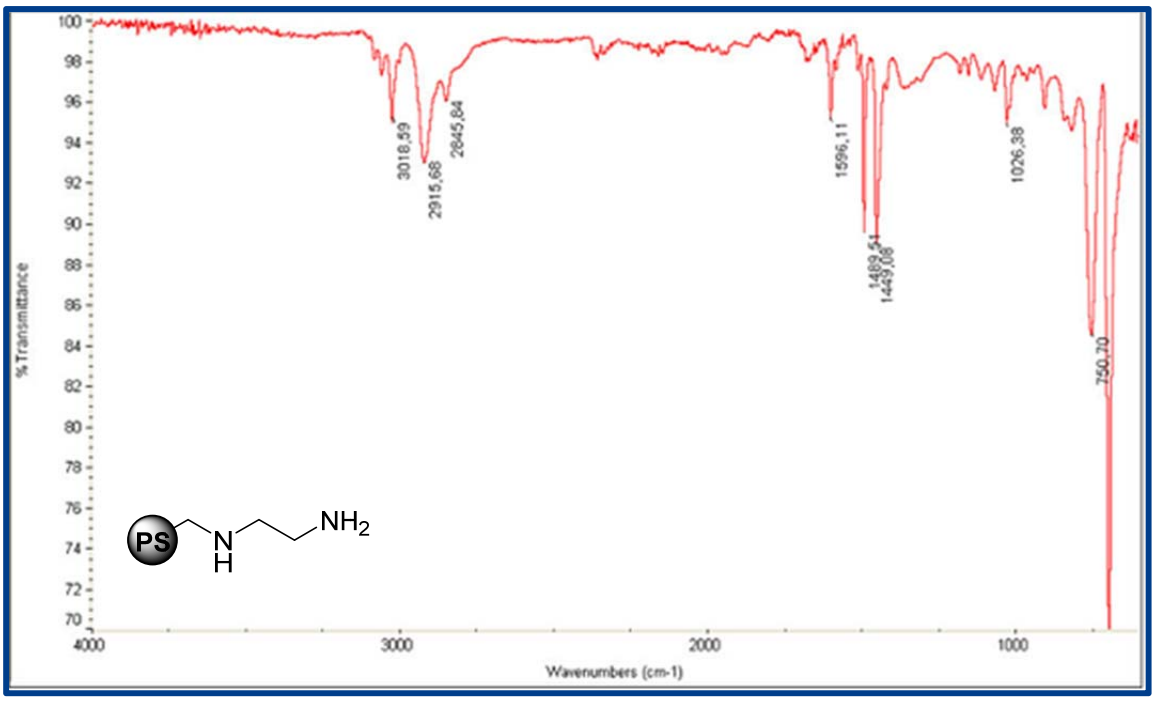
IR Spectra for catalyst **3B$_1$**

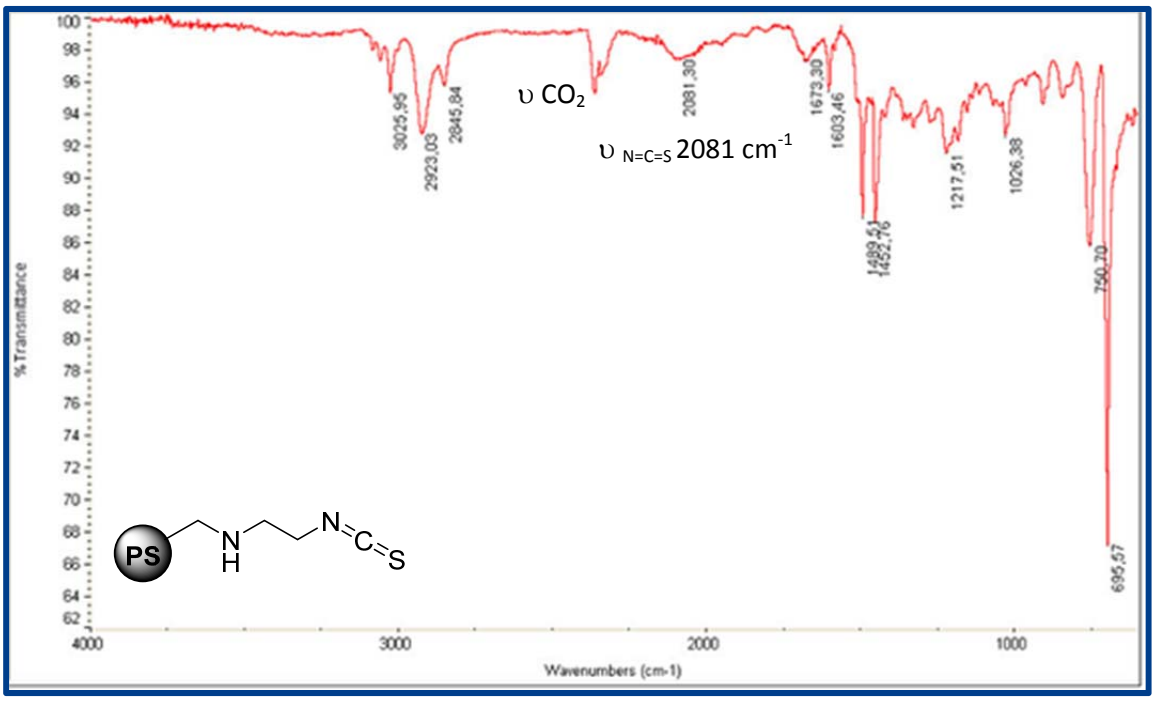


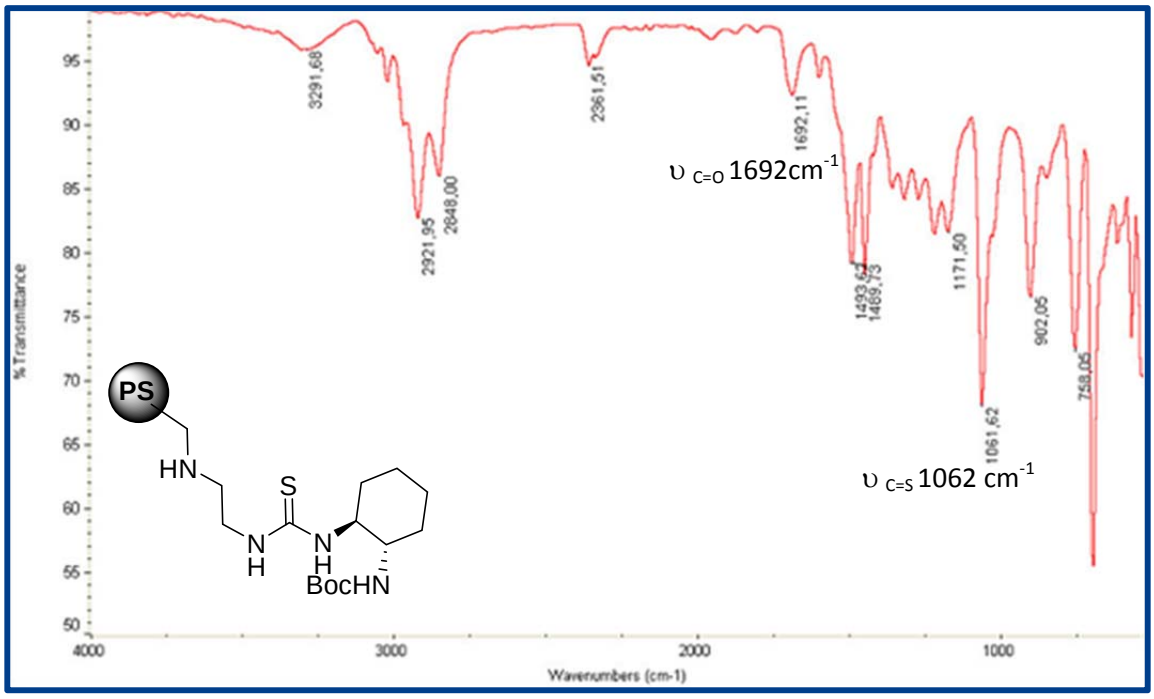


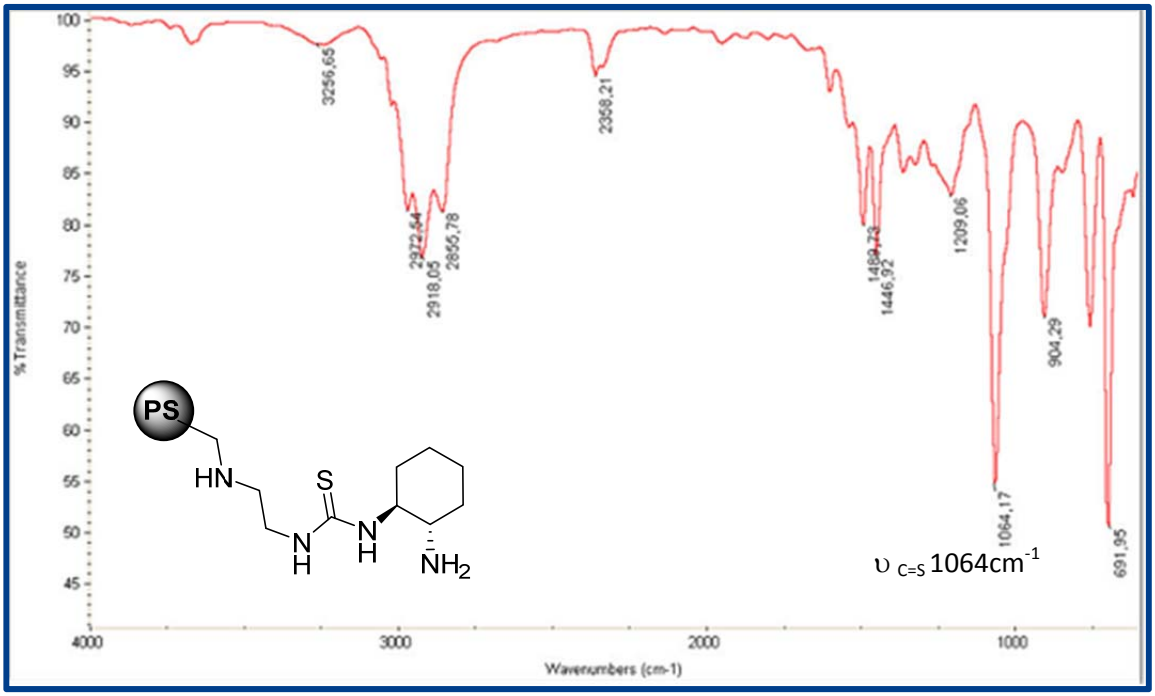


IR Spectra for catalyst **3C$_1$**






3291,68
2921,95
2848,00
2361,51
1692,11
1493,62
1469,73
1171,50
1061,62
902,05
758,05
υ C=O 1692cm-1
υ C=S 1062 cm-1
PS
HN
S
N
H
N
H
BocHN
% Transmittance
Wavenumbers (cm-1)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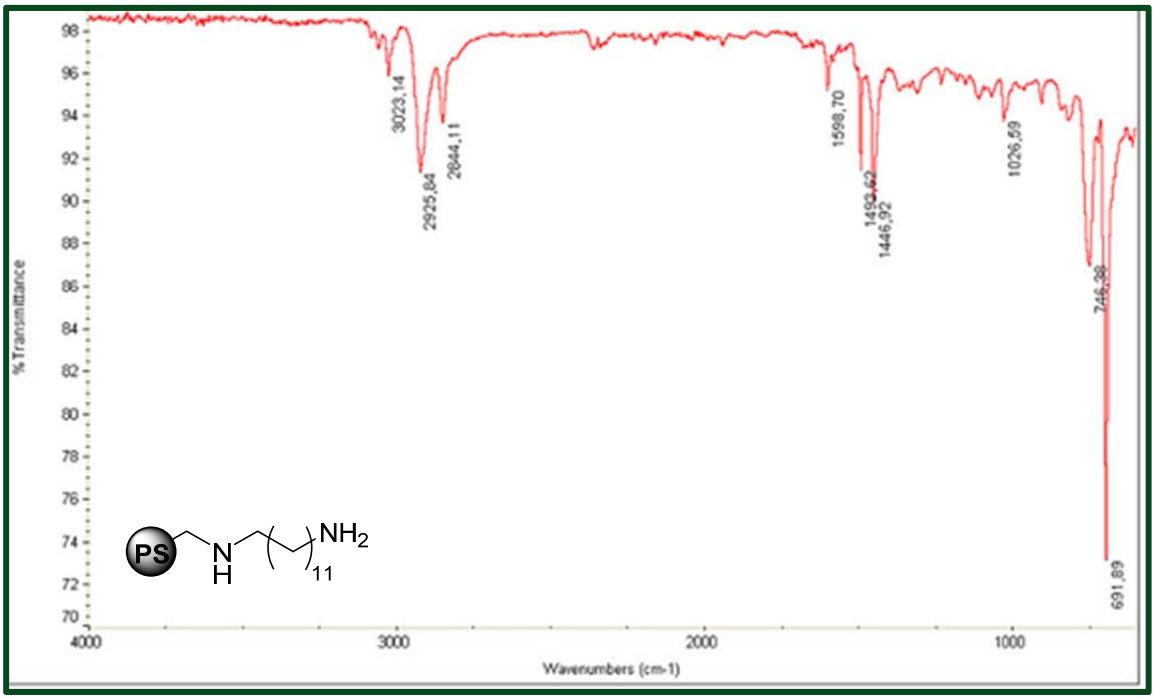
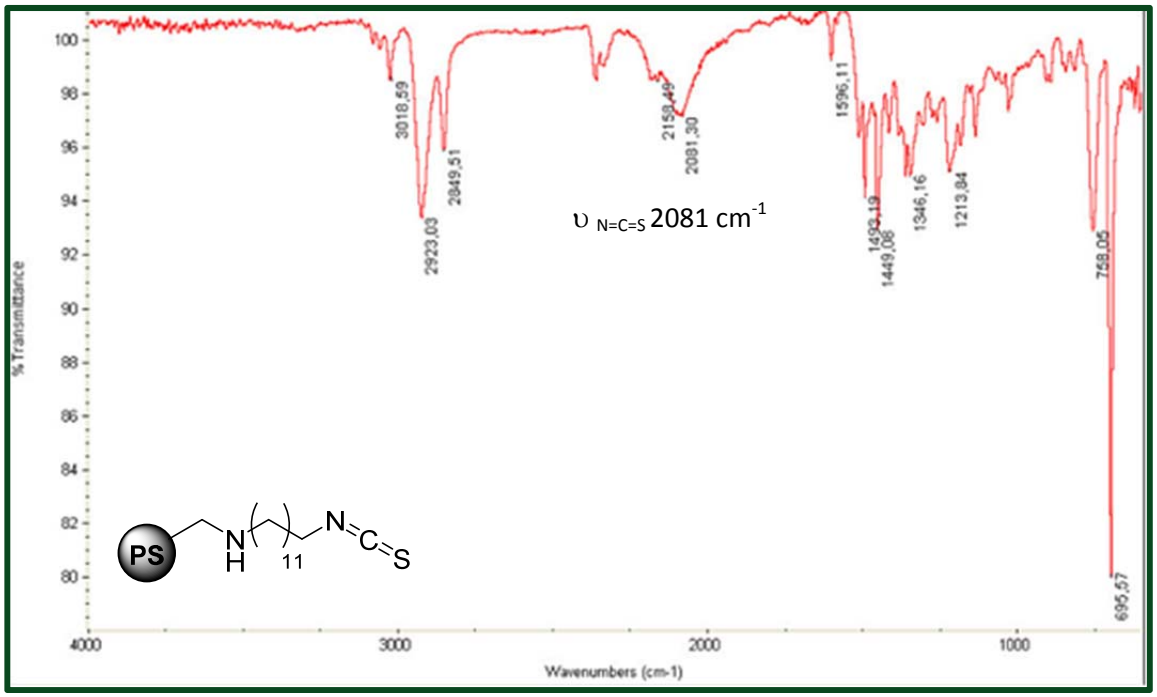
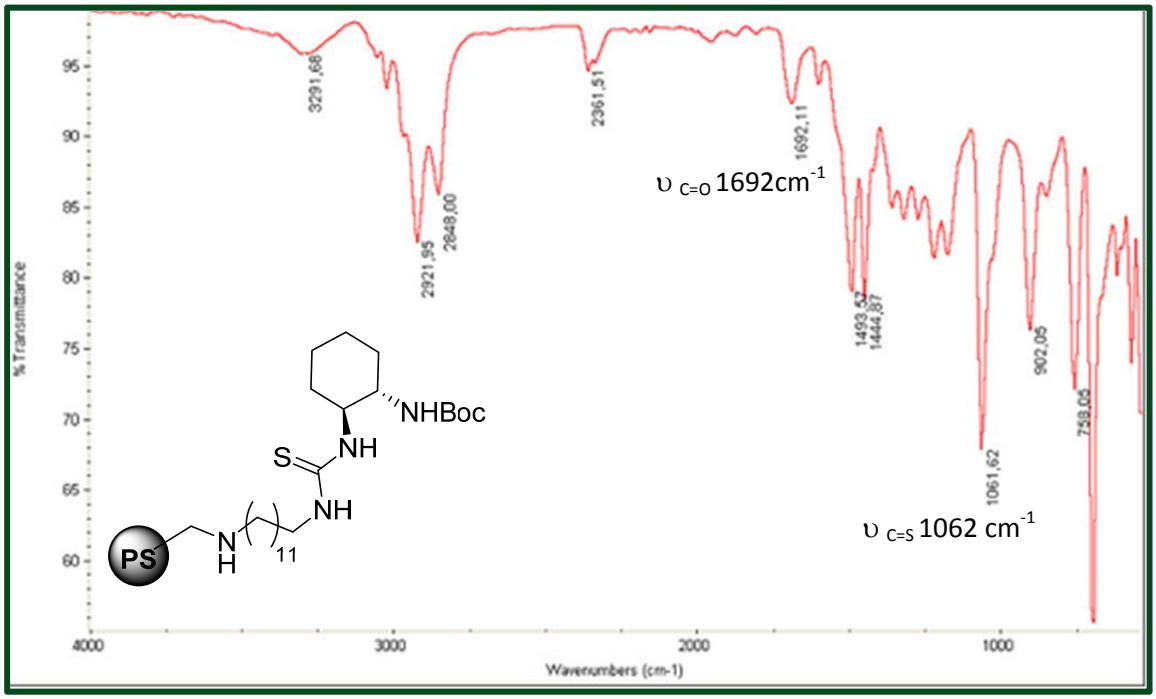
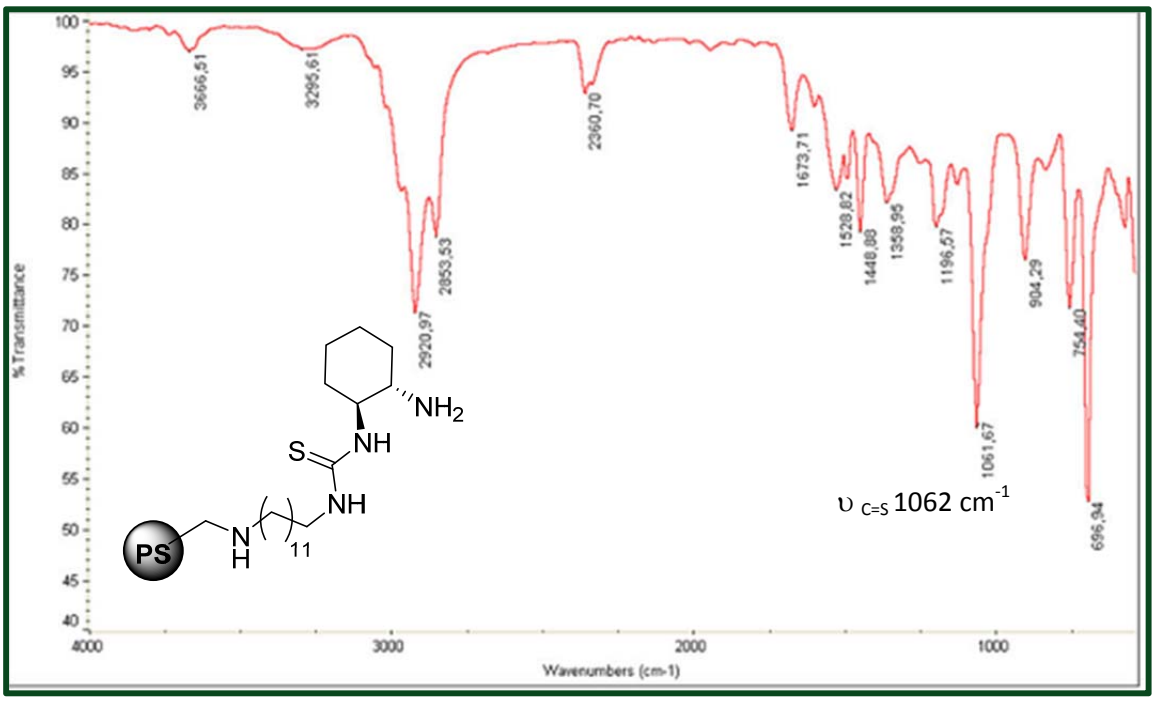
2972,64
2918,05
2855,78
2358,21
1489,73
1446,92
1209,06
904,29
1064,17
691,95
υ C=S 1064cm-1
PS
HN
S
N
H
N
H
NH2
% Transmittance
Wavenumbers (cm-1)

IR Spectra for catalyst **3C$_2$**





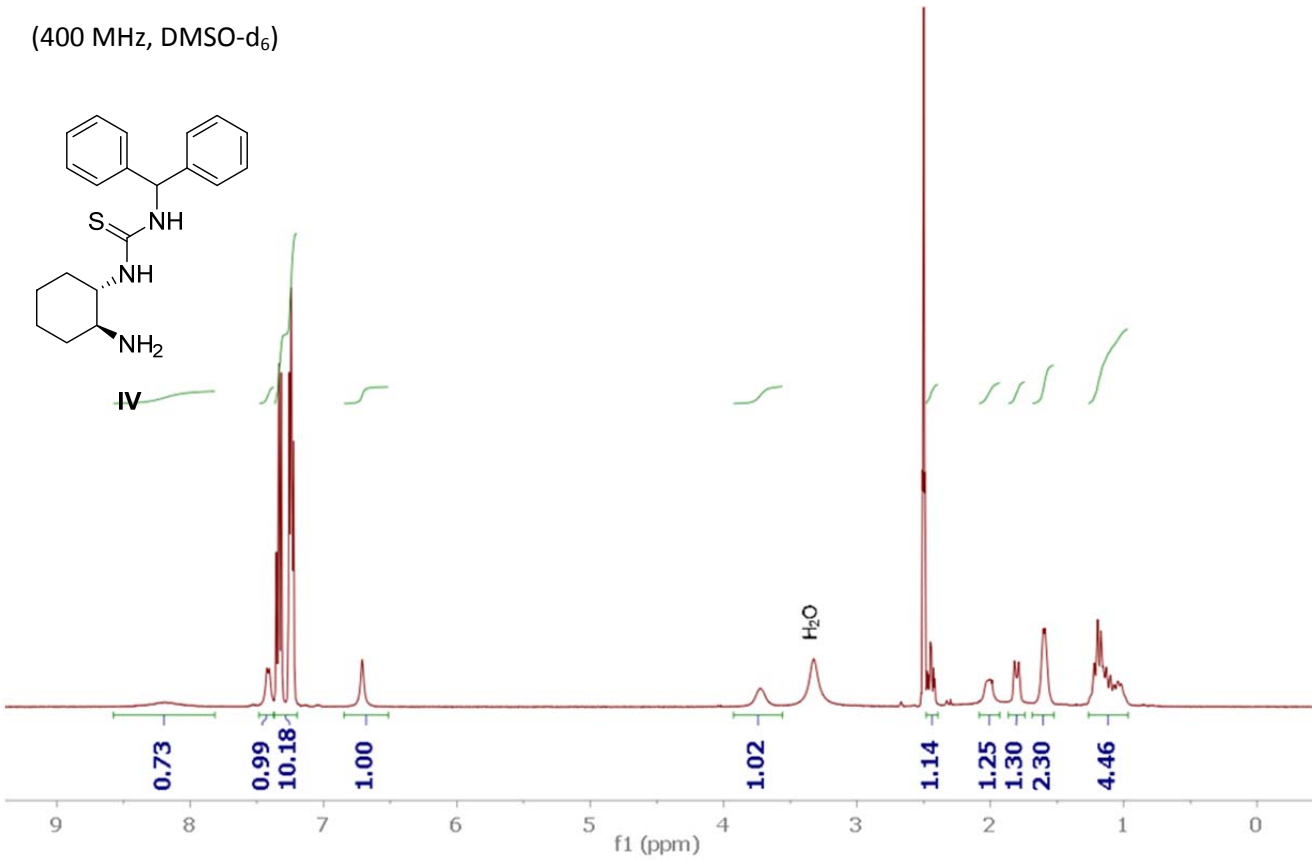

3291,68
2921,95
2848,00
2361,51
1692,11
1493,57
1444,87
1061,62
902,05
759,05
υ C=O 1692cm-1
υ C=S 1062 cm-1
NHBoc
NH
S
NH
PS
N
H
11
% Transmittance
Wavenumbers (cm-1)


3666,51
3295,61
2920,97
2853,53
2360,70
1673,71
1528,82
1448,88
1359,95
1196,57
1061,67
904,29
754,40
696,94
υ C=S 1062 cm-1
NH2
NH
S
NH
PS
N
H
11
% Transmittance
Wavenumbers (cm-1)

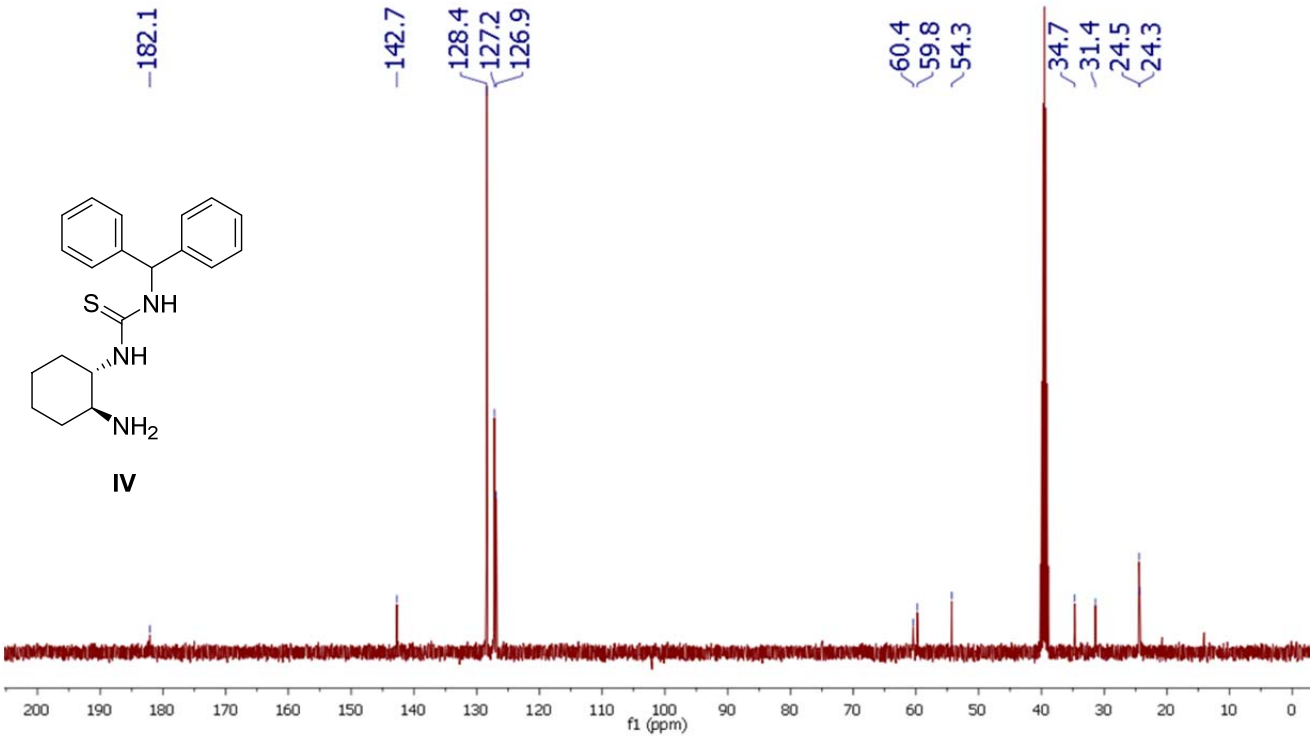
3. Synthesis and NMR spectra for the catalyst 4.

The catalyst **IV** was prepared according to the described procedure starting from the corresponding amine precursor.[4] Unprotected (1S,2S)-diaminocyclohexane was used instead of Boc protected diamine to avoid potential acid contamination during the deprotection step.

(400 MHz, DMSO-d_6)



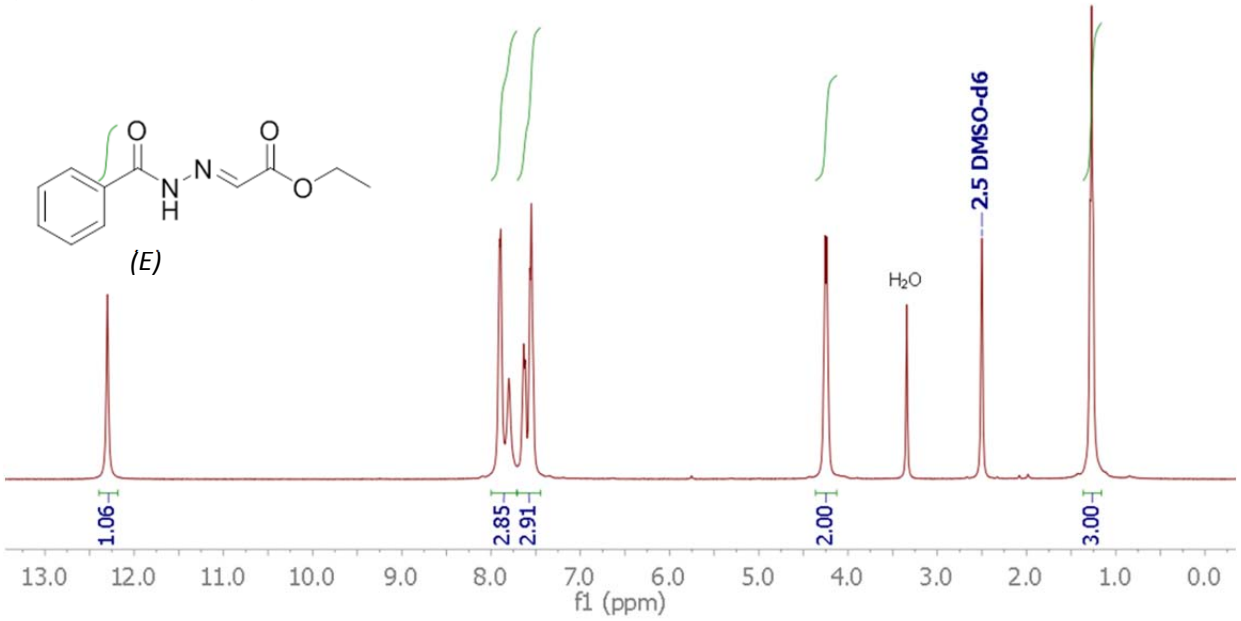
(100 MHz, DMSO-d_6)



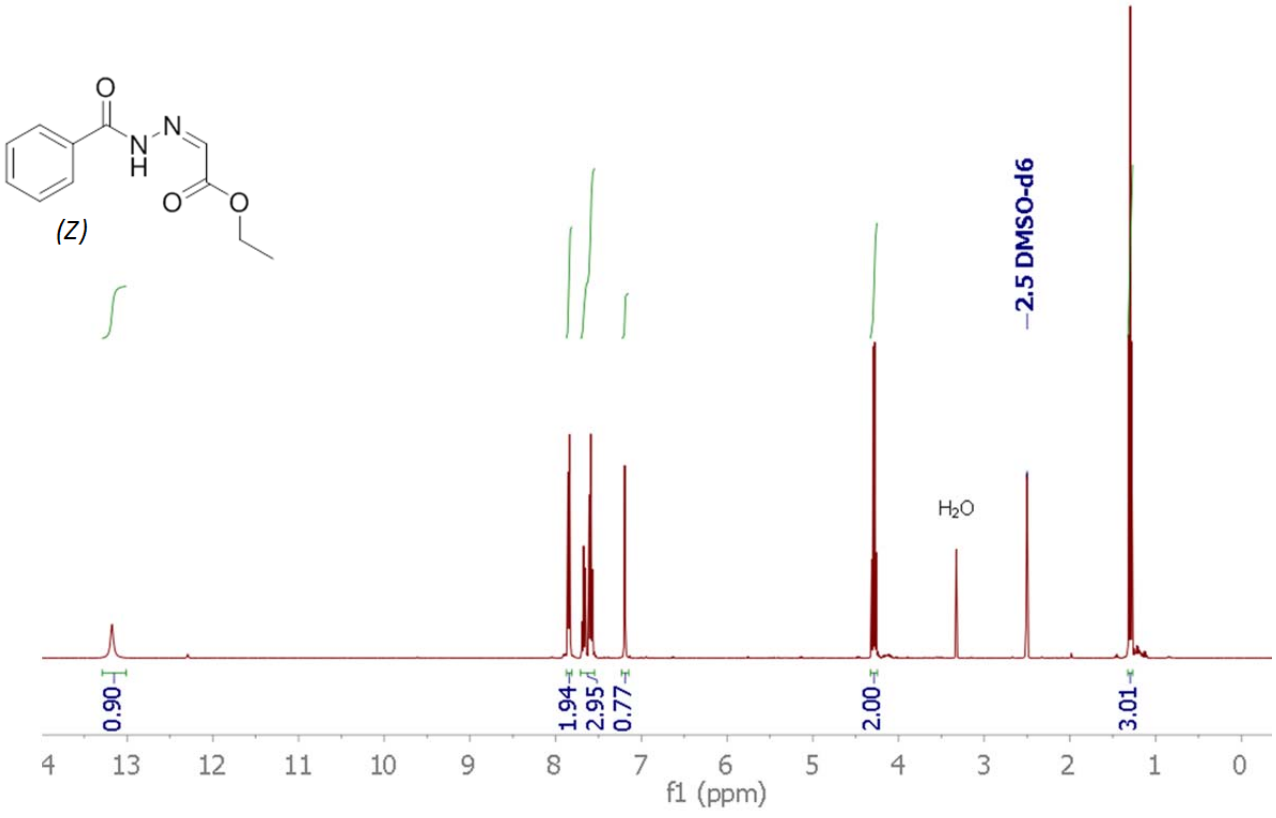
4. General procedure for the synthesis of *N*-Benzoylhydrazones and NMR spectra

36.7 mmol benzoylhydrazine (1.0 equiv., 5.0 g) was dissolved in EtOH. To this solution ethyl glyoxylate (1 equiv., 36.7 mmol, 50% in toluene) was added. The reaction mixture was stirred at 80 °C overnight and then cooled down to room temperature and the solvent was evaporated. The crude mixture was purified on silica gel column to give *E* and *Z* isomeric products. (1:1 EtOAc:Hexane) ^{1}H NMR showed 1:4 *Z:E* ratio of isomers. (R_f *Z*= 0.7, R_f *E*= 0.4)

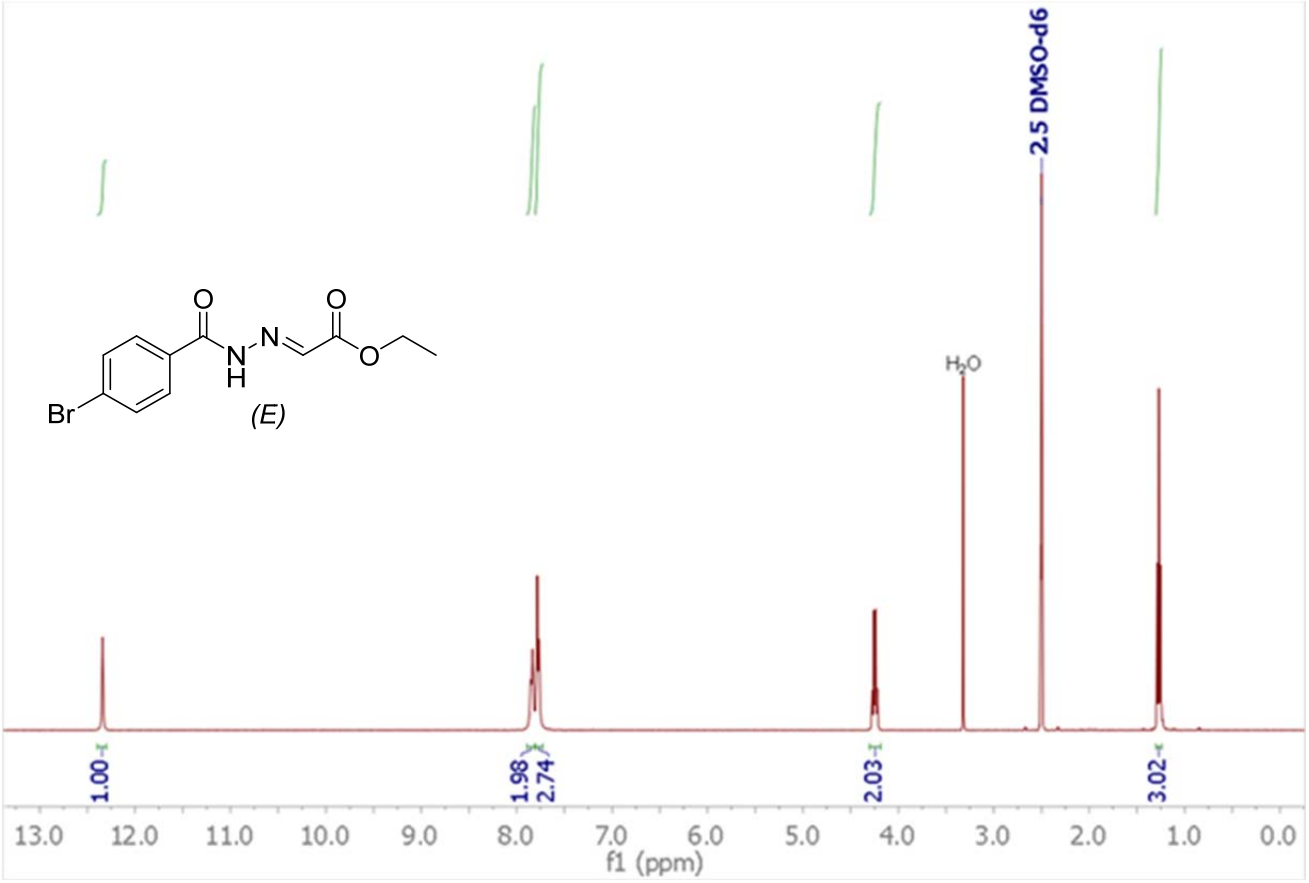
(400 MHz, DMSO-d_6)



(400 MHz, DMSO-d_6)



(400 MHz, DMSO-d_6)



5. Typical procedure for the Michael addition reaction using catalytic resin $3B_2$

65 mg catalytic resin **$3B_2$** (0.1 equiv., *f*= 0.51 mmol g^{-1}, 0.0335 mmol) was weighed in a vial and swollen in toluene (2 mL) for 30 minutes. Nitrostyrene (1.0 equiv., 0.335 mmol, 50 mg) was added into the vial as solid. Then, AcOH (0.1 equiv., 0.0335 mmol, 2 µL of AcOH in 1 mL toluene) was added using 10 µL of a stock solution (200 µL of AcOH in 1 mL toluene) and acetone (10.0 equiv., 3.35 mmol, 0.25 mL) were added. The reaction was stirred for 24 hours at room temperature. The reaction mixture was filtered, and rinsed with 20 mL toluene. The resin was dried and used directly in the next run. ^{1}H NMR measurements of the crude reaction mixture in $CDCl_3$ gave the conversion% values. HPLC samples were prepared in *i*PrOH directly from crude mixtures.

Solvent screening using resin $3B_2$

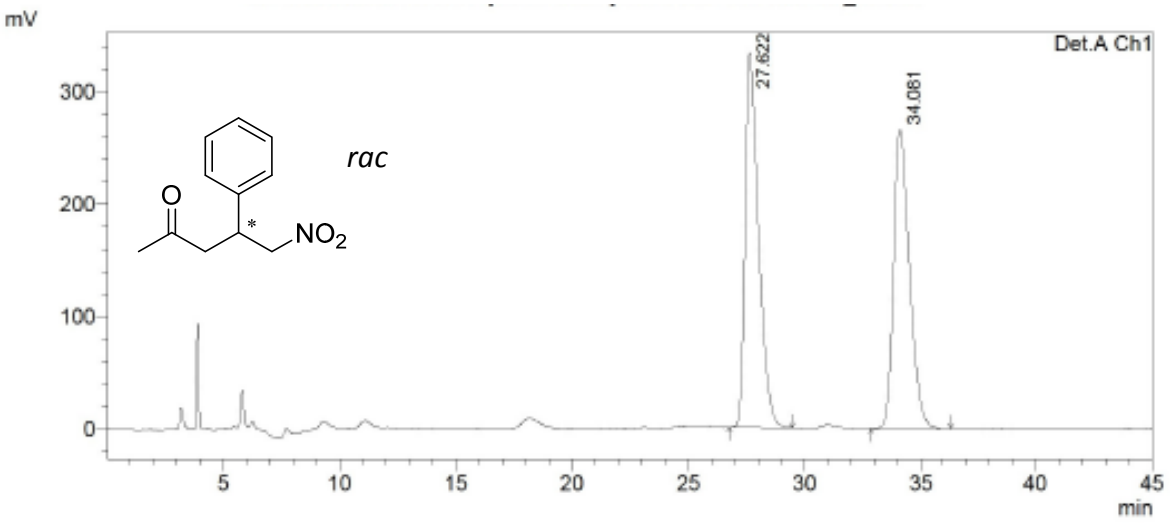
entry	solvent	time (h)	conv % [a]	ee%[b]
1	toluene	24	88	69
2	DMF	65	10	55
3	H_2O: DMF (1:1)	65	7	n.d.
4	DCM	24	78	65

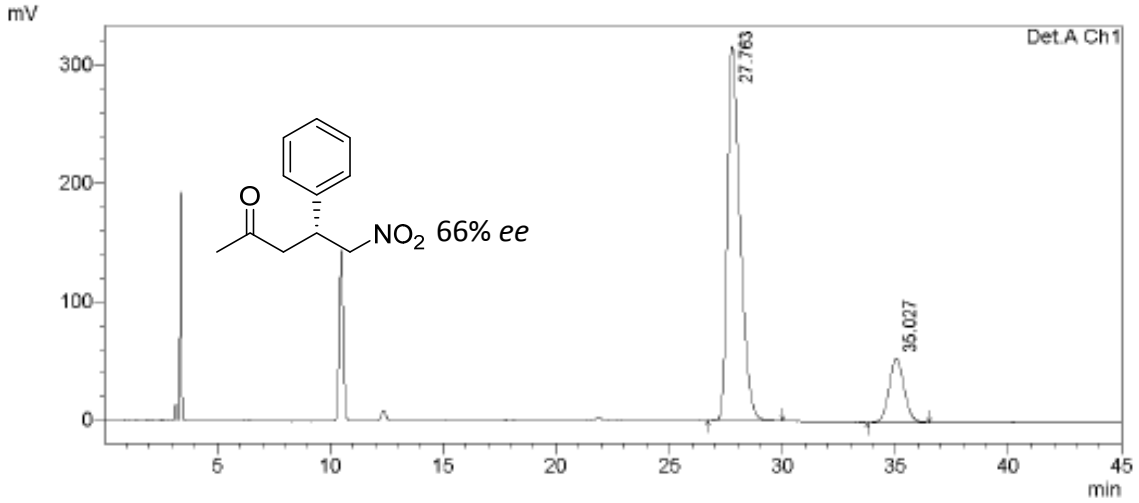
[a] Conversions are based on ^{1}H NMR measurements. **[b]** Determined by chiral HPLC analysis.

6. HPLC chromatogram and NMR spectrum for the chiral Michael addition product

DL-Proline was used for the synthesis of racemic Michael addition product.

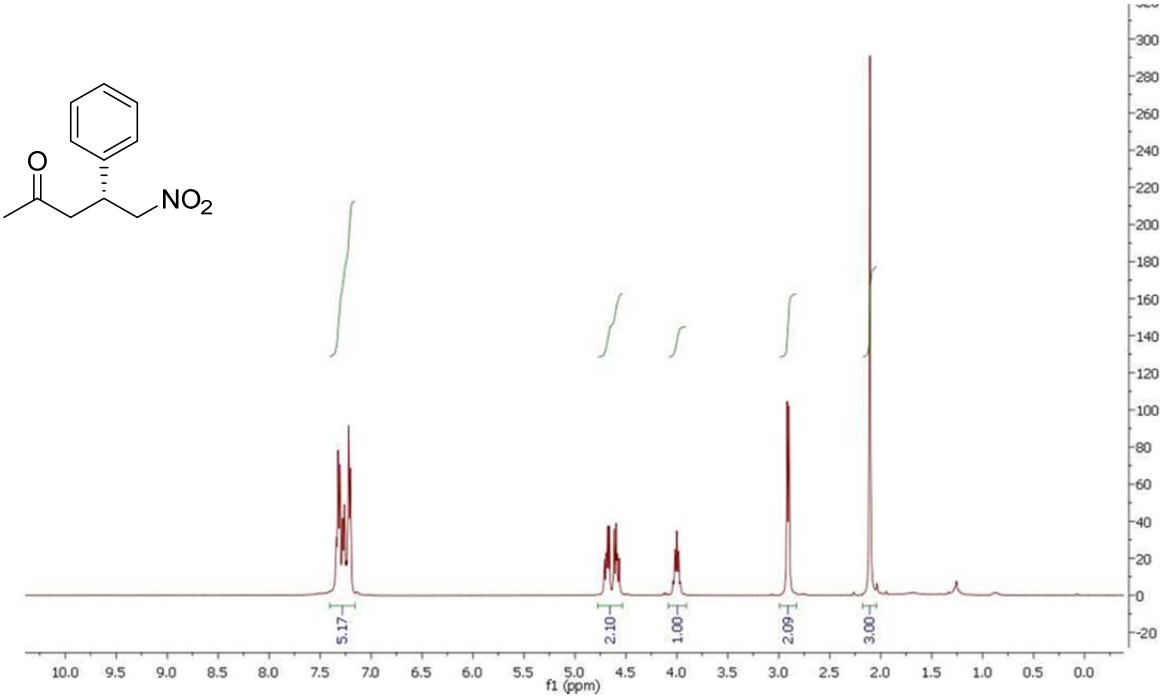
Conditions for HPLC: Phenomenex Lux 5u-Amylose-2 column, Hexane: *i*PrOH, 90:10, 1 mL/min, 209 nm.





Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.763	12322124	315178	83.306	85.432
2	35.027	2469365	53743	16.694	14.568
Total		14791489	368921	100.000	100.000

(400 MHz, $CDCl_3$)



7. Typical procedure for Mannich type reactions

Using catalytic resin $3B_1$

72 mg catalytic resin **$3B_1$** (0.1 equiv., *f*= 0.70 mmol g^{-1}, 0.05 mmol) was weighed in a vial and swollen in toluene (2 mL) for 30 minutes at 40 °C. Then, the corresponding *N*-benzoylhydrazone (1.0 equiv., 0.5 mmol) and the ketone (10.0 equiv., 5.0 mmol) were added in one portion and the reaction was stirred at 40 °C with a small magnetic bar at 200 rpm. After 48 h, the reaction mixture was filtered and rinsed of with 20 mL of toluene. The recovered polymer was dried and used directly in the next run. The filtrate was purified on a silica gel column using 1:1 EtOAc:Hexane as eluent to furnish the pure product. HPLC sample was prepared in *i*PrOH.

Using homogeneous catalyst 4

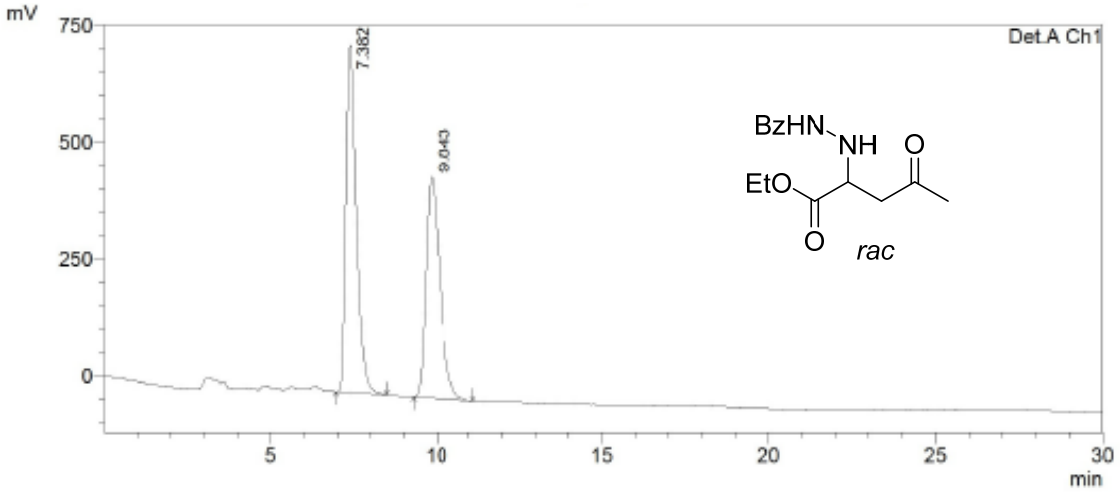
8.5 mg catalyst **4** (0.1 equiv., 0.025 mmol) was weighed in a vial and dissolved in toluene (1 mL). Then, corresponding *N*-benzoylhydrazone (1.0 equiv., 0.25 mmol) and the ketone (10.0 equiv., 2.5 mmol) were added in one portion and the reaction was stirred at room temperature for 24 h. The crude reaction mixture was purified on a silica gel column using EtOAc:Hexane (1:1) as eluent to furnish the pure product. HPLC sample was prepared in *i*PrOH.

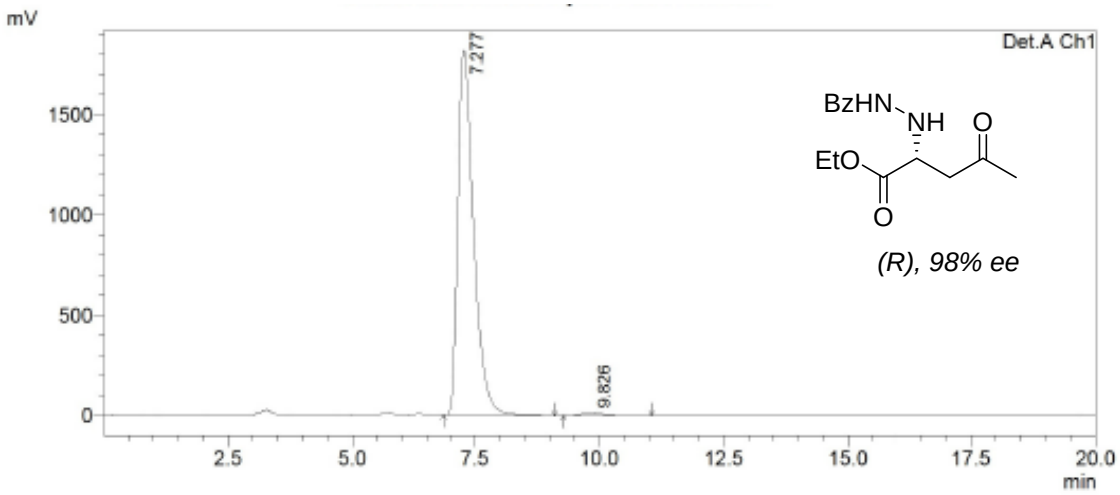
8. HPLC chromatograms and NMR spectra for the chiral Mannich products

HPLC Analysis

Racemic form of catalyst **4** was used for the synthesis of all racemic mixtures. All HPLC data was compared to and matched with those reported in the literature.[5]

Conditions: OD column, 30:70 *i*PrOH:hexane, flow= 1mL/min, λ= 209 nm

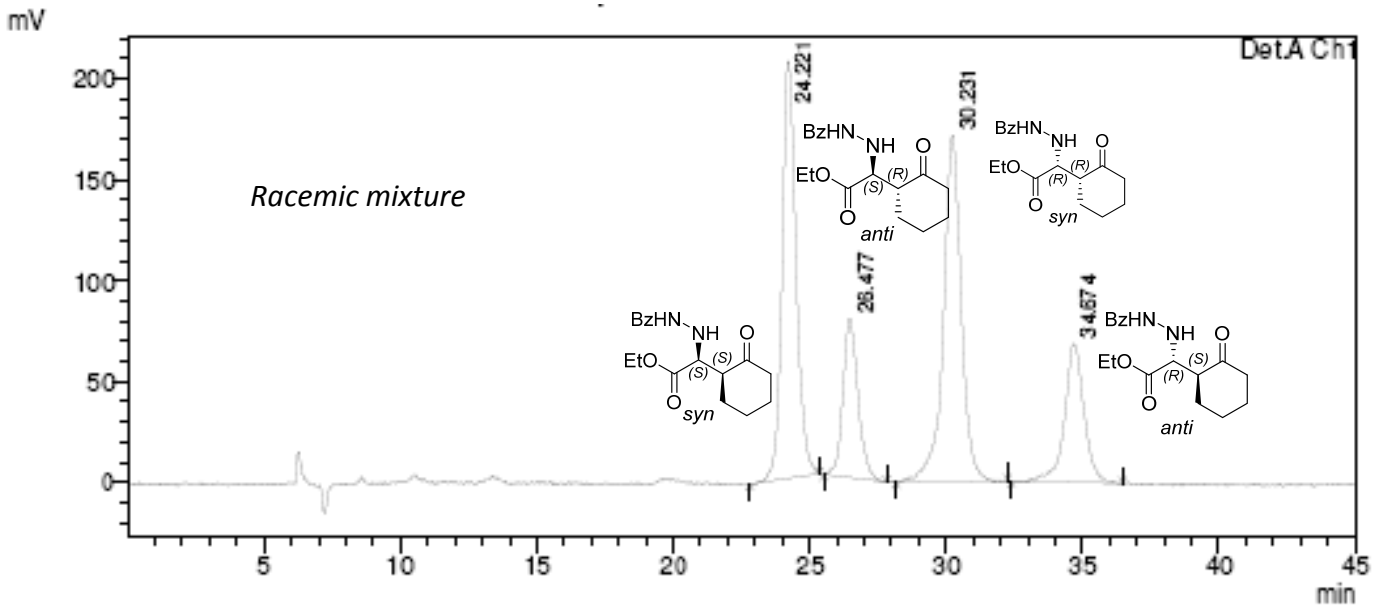


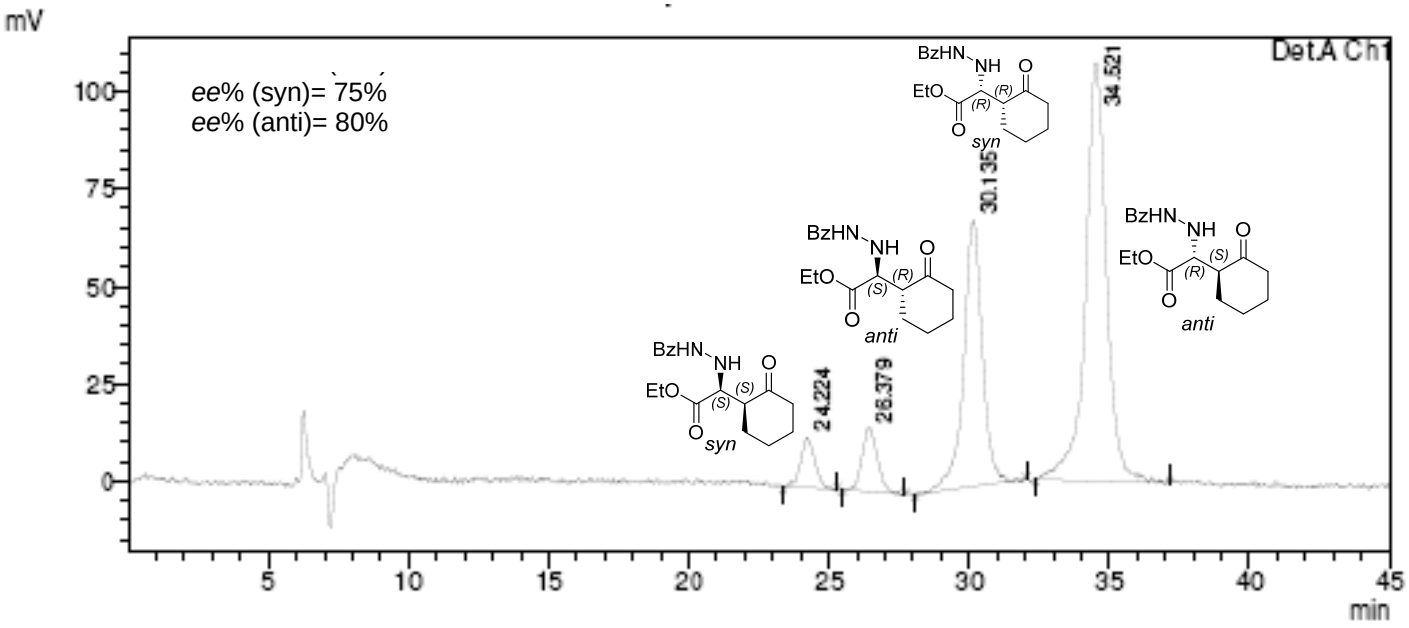


Detector A Ch1 209nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.277	40098182	1815355	98.996	99.222
2	9.826	406661	14234	1.004	0.778
Total		40504843	1829589	100.000	100.000

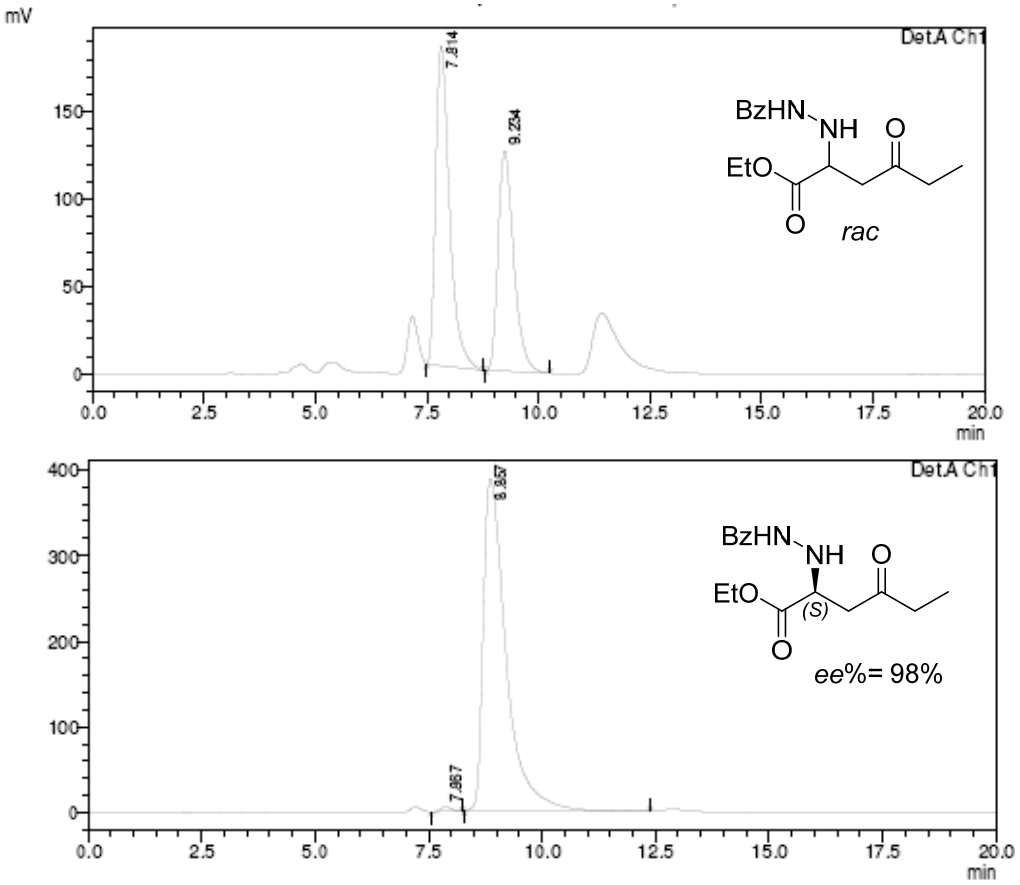
Conditions: IA column, 12:8:80 DCM:*i*PrOH:hexane, flow= 0.5 mL/min, λ= 209 nm



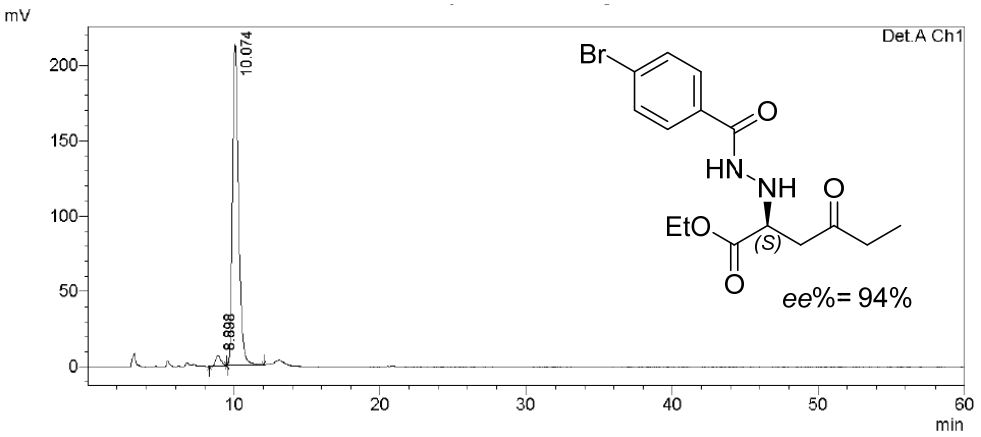


Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.224	440520	13035	4.487	6.371
2	26.379	618489	16247	6.300	7.941
3	30.135	3140032	68106	31.985	33.286
4	34.521	5618260	107222	57.228	52.403
Tota		9817301	204610	100.000	100.000

Conditions: OD column, 20:80 *i*PrOH:hexane, flow= 1 mL/min, λ= 209 nm



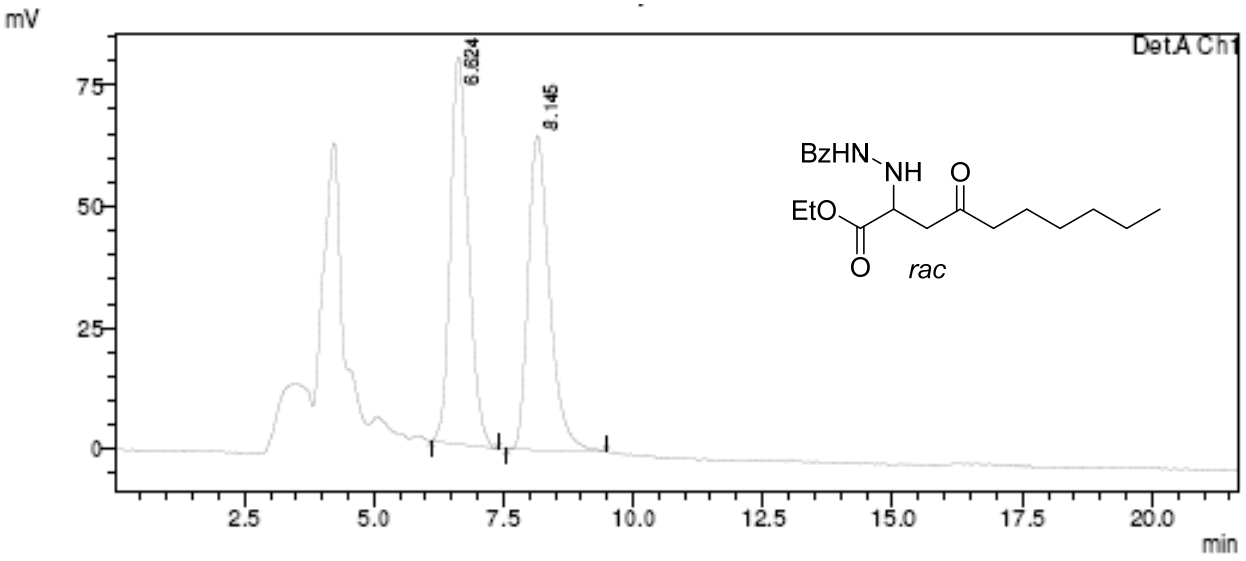
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.867	87861	5316	0.639	1.352
2	8.857	13656603	387959	99.361	98.648
Total		13744463	393275	100.000	100.000

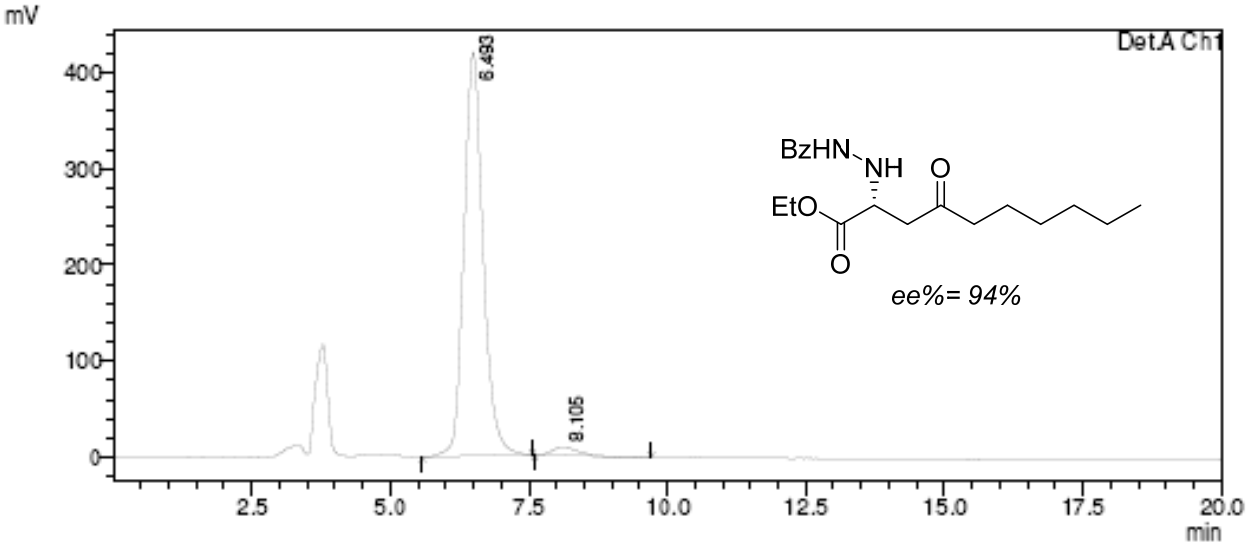


Detector A Ch1 209nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.898	175724	6948	2.762	3.166
2	10.074	6186998	212485	97.238	96.834
Total		6362722	219433	100.000	100.000

Conditions: OD column, 30:70 *i*PrOH:hexane, flow= 1 mL/min, λ= 209 nm



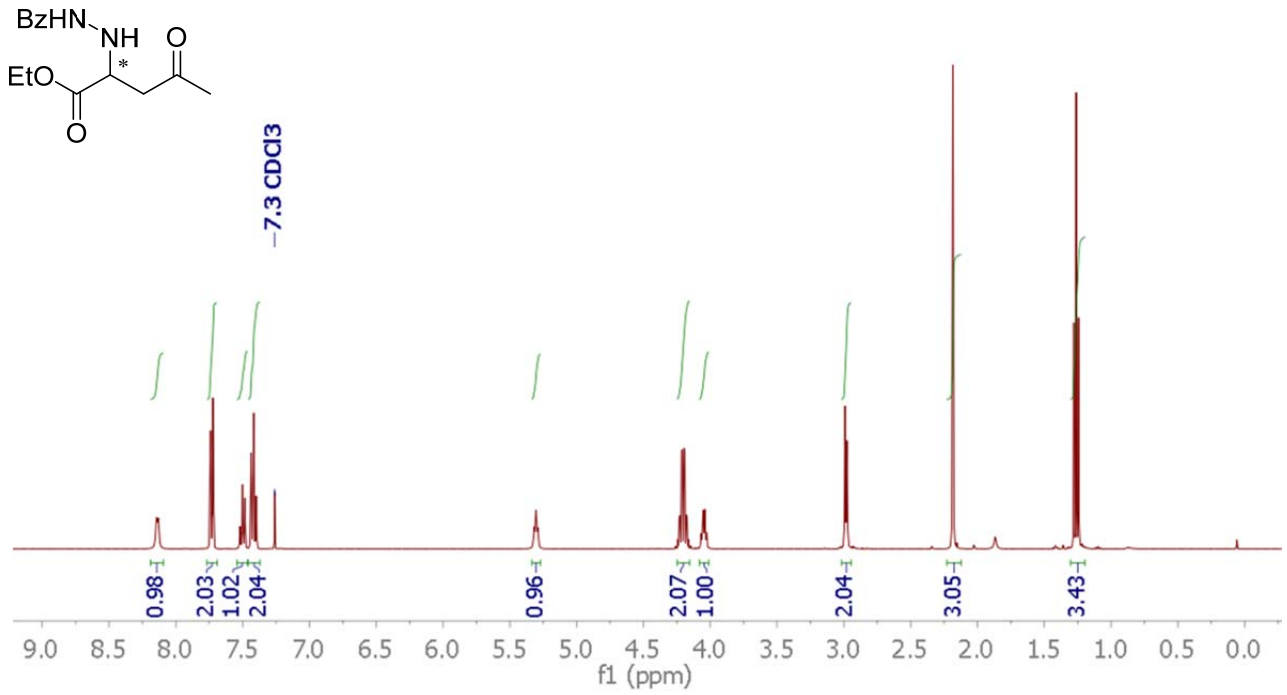


Detector A Ch1 209nm

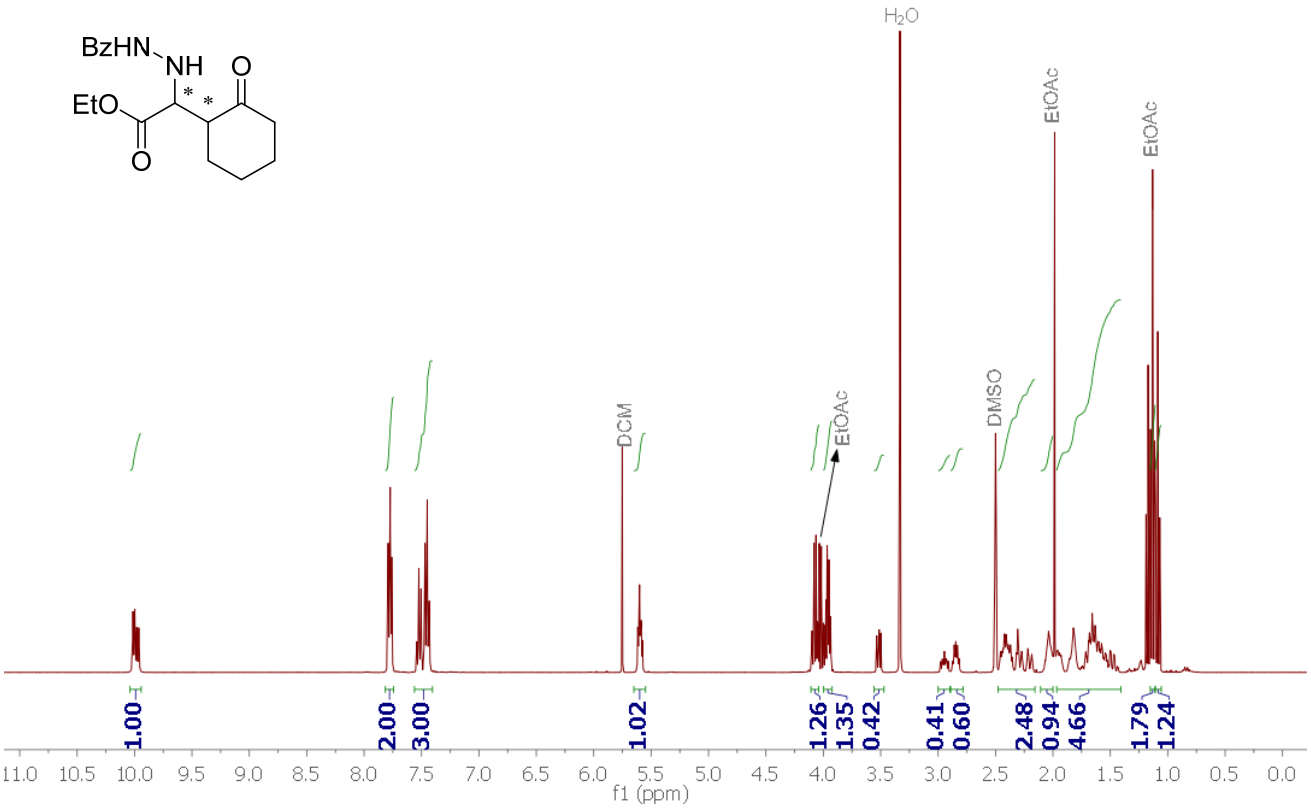
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.493	10130507	419775	97.253	97.802
2	8.105	286164	9434	2.747	2.198
Total		10416671	429209	100.000	100.000

^{1}H NMR Spectra

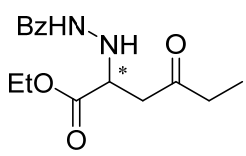
(400 MHz, $CDCl_3$)



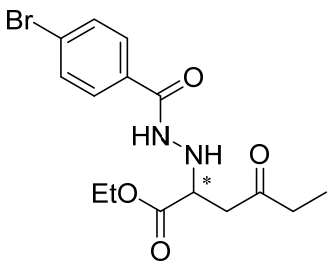
(400 MHz, DMSO-d_6)



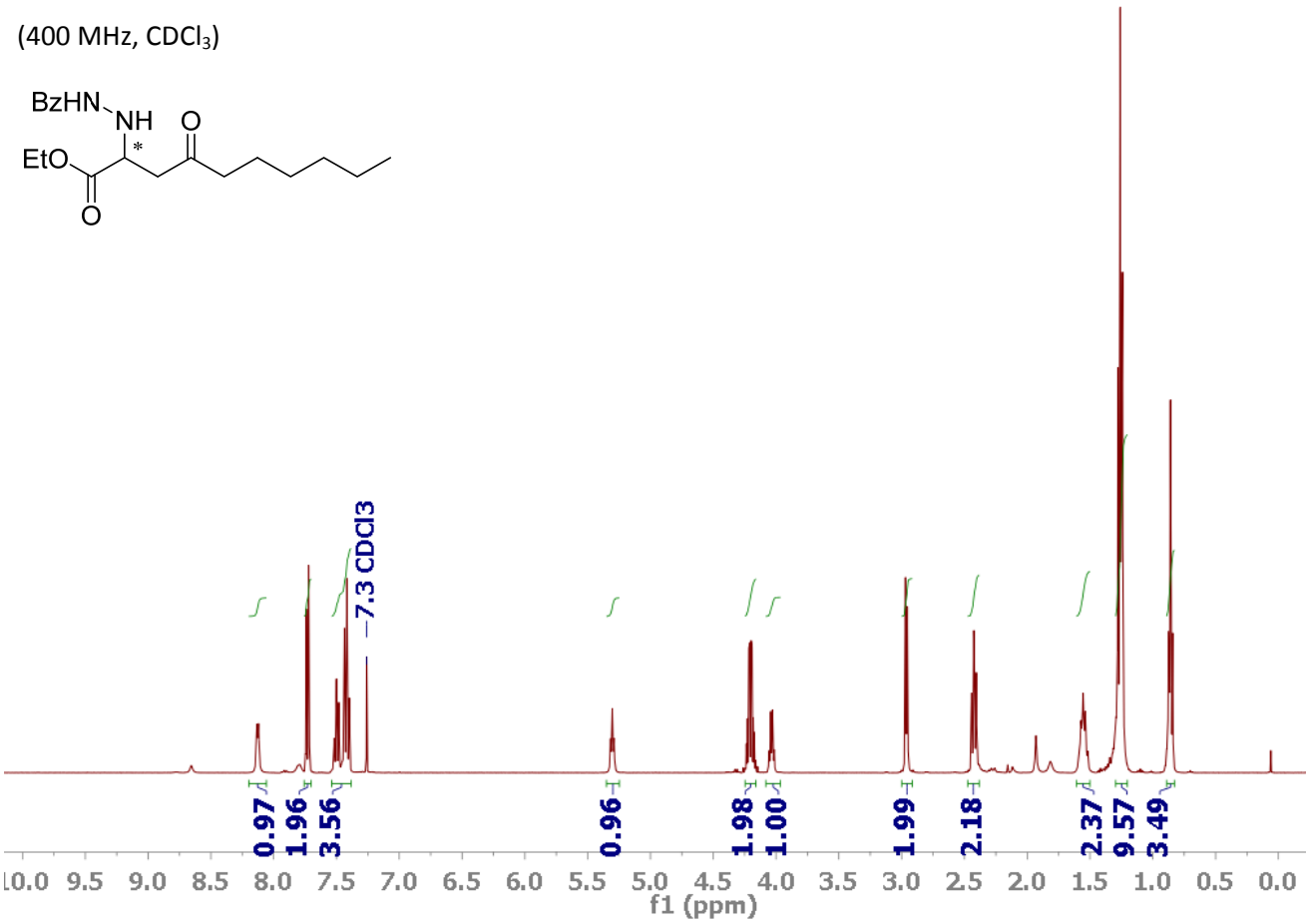
(400 MHz, DMSO-d_6)



(400 MHz, $CDCl_3$)



(400 MHz, $CDCl_3$)



9. References

[1] E. Kaiser, R. L. Colescott, C.D. Bossinger, P.I. Cook, *Anal. Biochem,.* **1970,** 34, 595-598.

[2] For a reference to the formulas, see: A. Bastero, D. Font, M. A. Pericas, *J. Org. Chem.*, **2007**, 72, 2460-2468.

[3] For a reference for the calculation of *mono* and *bis* functionalizations, see: R. Marcos, C. Jimeno and M. A. Pericas, *Adv. Synth. Catal.*, **2011**, 353, 1345-1352.

[4] For the synthetic procedure see: S. B. Tsogoeva; S. Wei, *Chem. Commun.***, 2006**, 1451-1453.

[5] D. A. Yalalov, S. B. Tsogoeva, T. E. Shubina, I. M. Martynova, T. Clark, *Angew. Chem. Int. Ed.,* **2008**, 47, 6624 –6628.

CONCLUSIONS

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PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS
Zeynep Inci Günler

CONCLUSIONS

In **Chapter 2** kinetic and structural studies by continous ^{1}H NMR for the Michael addition of acetone to *trans*-β-nitrostyrene catalyzed by PATs allowed us to identify the reaction pathways and the roles of acetic acid and water additives in the catalytic cycle. Acetic acid facilitates the hydrolysis of imine intermediates, thus, leads to catalysis and also minimizes the double-addition side product formation. Water minimizes the catalyst deactivation by nitrostyrene therefore leads to higher final yields, although it slows down the reaction **(PAPER A)**.

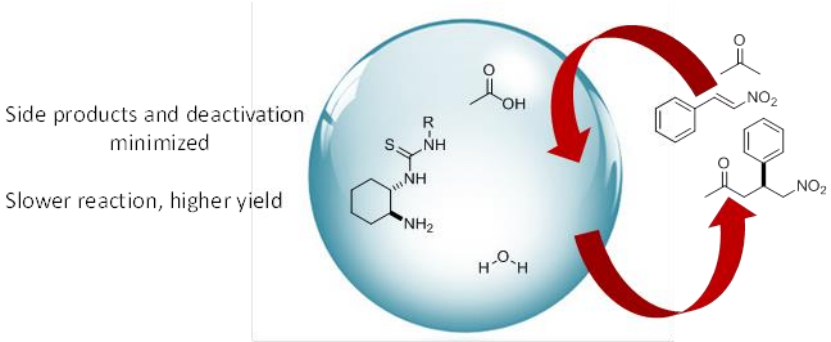

Figure 1. Graphical abstract of **PAPER A**

In the second section of this chapter, the effects of concentration in PAT catalyzed Michael addition of acetone to *trans*-β-nitrostyrenes have been investigated. Improvement in conversions and enantioselectivities was observed upon dilution for five different PAT organocatalysts. The optimal concentration for a range of nitrostyrenes was found to be 0.15 M. This enhancements must be attributed to the stabilization of the catalyst upon dilution and a decrease of catalyst deactivation by nitrostyrene. No sign of catalyst aggregation phenomena was observed **(PAPER B)**.

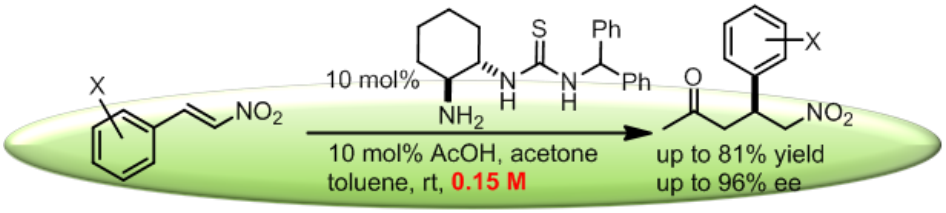

Figure 2. Graphical abstract of **PAPER B**

In **Chapter 3** the design and synthesis of immobilized primary amine-thioureas have been demonstrated for the first time. These catalysts have shown modest results in Michael addition reaction of acetone to *trans*-β-nitrostyrene. In spite of the use of water and other additives the catalysts could not be recycled efficiently, probably due to the catalyst deactivation phenomena that we have demonstrated in our previous work (see Chapter 2). These catalysts showed better results in Mannich-type addition of ketones to *N*-benzoylhydrazones. Nevertheless, an important loss of activity was also observed for this reaction. This work demonstrates the low stability of PAT catalysts, thus, further modifications on the design of supported PATs and the reaction conditions are necessary for the recycling of these catalysts **(Paper C)**.

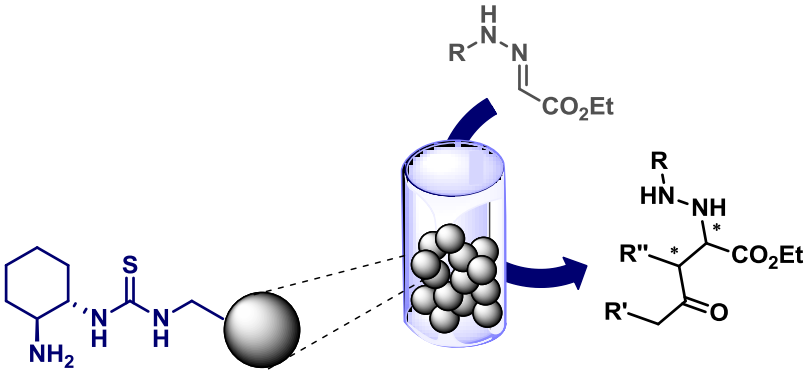

Figure 3. Graphical abstract of **PAPER C**

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