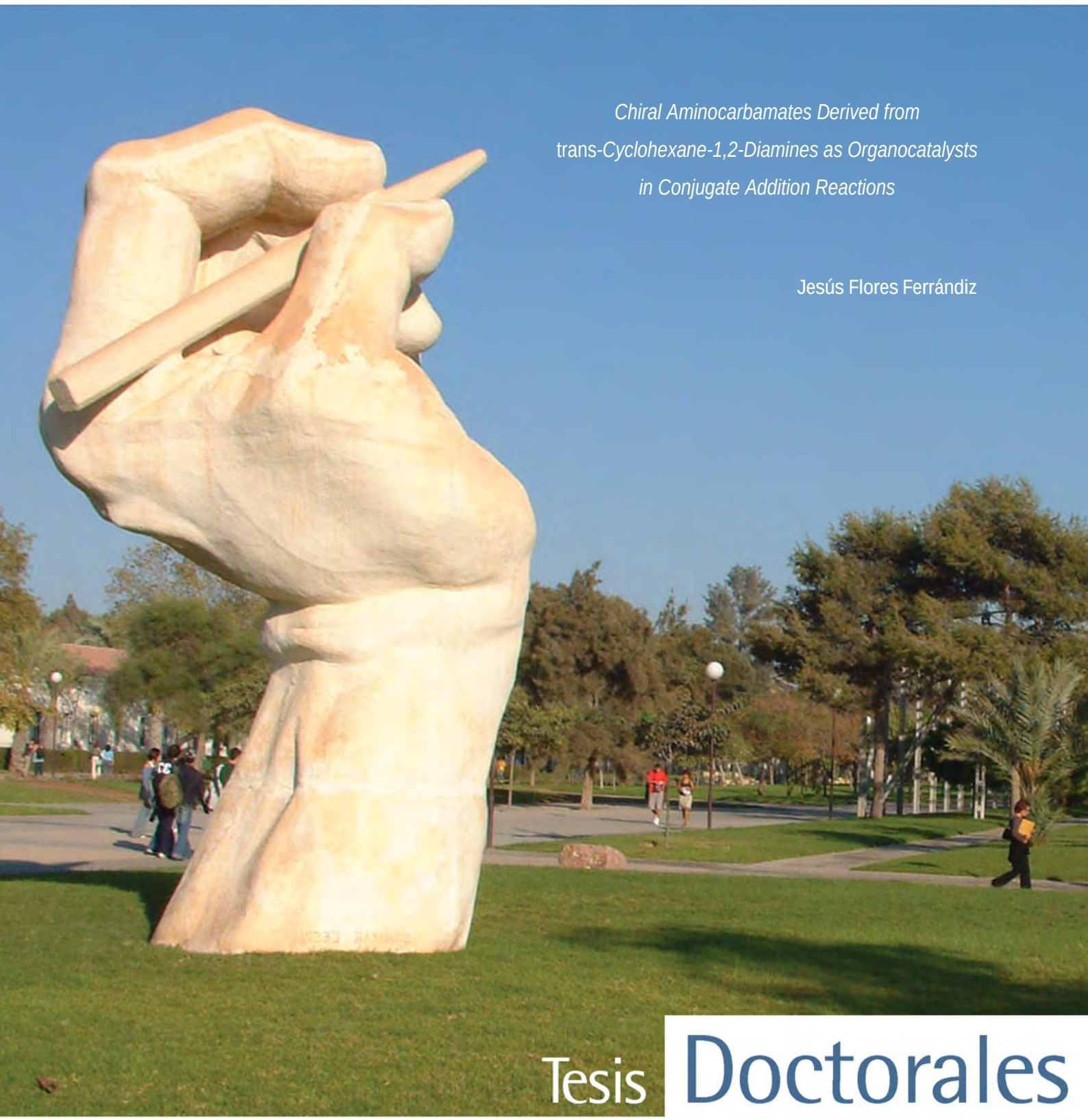
Universitat d'Alacant
Universidad de Alicante

# *Chiral Aminocarbamates Derived from* trans-*Cyclohexane-1,2-Diamines as Organocatalysts in Conjugate Addition Reactions*

Jesús Flores Ferrándiz



Tesis Doctorales

www.eltallerdigital.com

UNIVERSIDAD de ALICANTE

Universitat d'Alacant
Universidad de Alicante

**Institute of Organic Chemistry**

# *Chiral Aminocarbamates Derived from* trans-*Cyclohexane-1,2-Diamines as Organocatalysts in Conjugate Addition Reactions*

Manuscript thesis submitted for the degree of PhD at the University of Alicante by:

JESÚS FLORES FERRÁNDIZ

Alicante, September 2017

INTERNATIONAL MENTION IN THE TITLE OF DOCTOR

Scientific advisor:

Rafael Chinchilla Cruz

Professor in Organic Chemistry

Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Fase I, Universidad de Alicante.
Campus de Sant Vicent del Raspeig, Apdo. 99. E-03080 Alicante, España.
Tel. +34 965903400, ext. 2121; +34 965903549; Fax +34 965903549.
Web: http://iso.ua.es; E-mail: iso@ua.es

*Dedicated to my family and friends*



*"You do not really understand something*
*unless you can explain it to your grandmother"*
**Albert Einstein**

# TABLE OF CONTENTS

# PREFACE

The present thesis has been developed in the Department of Organic Chemistry and Institute of Organic Synthesis of the University of Alicante. Part of the results reported on this thesis have already been published or are in manuscript preparation:

“Solvent-Dependent Enantioswitching in the Michael Addition of α,α-Disubstituted Aldehydes to Maleimides Organocatalyzed by mono-*N*-Boc-Protected Cyclohexa-1,2-Diamines” Flores-Ferrándiz, J.; Chinchilla, R. *Tetrahedron: Asymmetry* **2014**, *25*, 1091-1094.

"Solvent-Induced Reversal of Enantioselectivity in the Synthesis of Succinimides by the Addition of Aldehydes to Maleimides Catalysed by Carbamate-Monoprotected 1,2-Diamines"; Flores-Ferrándiz, J.; Fiser, B.; Gómez-Bengoa, E.; Chinchilla, R. *European Journal of Organic Chemistry* **2015**, 1218-1225.

"Enantioselective Addition of Aryl Ketones and Acetone to Nitroalkenes Organocatalyzed by Carbamate-Monoprotected Cyclohexa-1,2-Diamines"; Flores-Ferrándiz, J.; Stiven, A.; Sotorríos, L.; Gómez-Bengoa, E.; Chinchilla, R. *Tetrahedron: Asymmetry* **2015**, *26*, 970-979.

"Organocatalytic Enantioselective Conjugate Addition of Aldehydes to Maleimides in Deep Eutectic Solvents"; Flores-Ferrándiz, J.; Chinchilla, R. *Tetrahedron: Asymmetry* **2017**, *28*, 302-306.

“Enantioselective Michael Addition of Ketones to Maleimides Organocatalyzed by Chiral Carbamate-Monoprotected Cyclohexa-1,2-diamines”. Manuscript in preparation.

In addition, part of the results have been presented in an international symposium:

Flash Presentation + Communication Poster: "Solvent-induced reversal of the enantioselectivity in the addition of aldehydes to maleimides organocatalyzed by carbamate-monoprotected 1,2-diamines", Flores-Ferrándiz, J.; Fiser, B.; Gómez-Bengoa, E.; Chinchilla, R.; XIV Società Chimica Italiana & Sigma-Aldrich Young Chemists Symposium, Riccione, October 2014.

This research has been generously supported by the Spanish Ministerio de Economía y Competitividad (projects CTQ2011-24151 and CTQ2015-66624-P), FEDER, the COST Action CM0905 “Organocatalysis”, and the university of Alicante (VIGROB-173 and UAUSTI14). Specially, the author acknowledges the Vicerrectorado de Investigación, Desarrollo e Innovación of the University of Alicante for a fellowship.

Theoretical calculations have been carried out by Prof. Enrique Gómez-Bengoa from the University of the Basque Country.

The thesis has been divided in two chapters:

1) Chapter I shows the results obtained in the enantioselective conjugate addition reaction of aldehydes and ketones to maleimides, obtaining enantiomerically enriched succinimide derivatives, organocatalyzed by chiral aminocarbamates from *trans*-cyclohexa-1,2-diamines.

2) Chapter II shows the results obtained in the enantioselective conjugate addition reaction of aldehydes and ketones to nitroalkenes, obtaining enantiomerically enriched γ-nitroaldehydes and γ-nitroketones, respectively, organocatalyzed by chiral aminocarbamates from *trans*-cyclohexa-1,2-diamines.

# SUMMARY

Chapter I describes the preparation of primary-amine monocarbamates from enantiopure *trans*-cyclohexane-1,2-diamines and their use as chiral organocatalysts in the enantioselective Michael addition reaction of aldehydes and ketones to maleimides, to synthesize enantiomerically enriched substituted succinimides. In the conjugate addition reaction of aldehydes to maleimides in conventional volatile organic solvents, it has been found that these organocatalysts are able to generate both enantiomers of the corresponding succinimide using only one enantiomeric form of the catalyst, just by changing the polarity of the solvent. Theoretical calculations justify the mechanism through which this inversion of enantioinduction occurred. In addition, these organocatalysts were used in the enantioselective Michael addition reaction of aldehydes to maleimides, using Deep Eutectic Solvents (DES) as recyclable and environmentally sustainable reaction medium, yielding the corresponding succinimides with excellent yields and high enantioselectivities (up to 94%). The succinimides can be extracted from the DES, which retains the chiral organocatalyst, allowing to reuse both solvent and catalyst. Moreover, the conjugate addition of ketones to maleimides using conventional solvents, allows obtaining the corresponding succinimides with excellent yields but with moderate enantioselectivities (up to 66%).

Chapter II shows the results obtained in the enantioselective Michael addition reaction of aldehydes and ketones to nitroalkenes, using the former *trans*-cyclohexane-1,2-diamine-derived aminocarbamates as chiral organocatalysts, obtaining enantioenriched γ-nitrocarbonyl compounds. In the conjugate addition of isobutyraldehyde to nitroalkenes, the corresponding γ-nitroaldehydes were obtained with enantioselectivities up to 84%. In addition, the enantioselective conjugate addition reaction of ketones to nitroalkenes allowed to obtain interesting γ-nitroketones with high enantioselectivities (up to 96%). Theoretical calculations justify the mechanism involved during this enantioselective process.

# GENERAL INTRODUCTION

## 1. Asymmetric Synthesis

The ability to control the stereochemical outcome of reactions in organic synthesis is frequently of great importance. This is because biological systems (enzymes, proteins, etc.) are chiral and therefore able to differentiate between a pair of enantiomers, each one inducing a different biochemical response. In extreme cases, one enantiomer can have a great therapeutic effect while the other can be highly toxic. The most well-known example is Thalidomide, which was commercialized between 1958 and 1963 as a racemic mixture, with the tragic consequence that one of the enantiomers was a teratogenic. The agencies tasked with the regulation of the pharmaceutical industry, for instance the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), have since then insisted on strict biological tests on the activity of each enantiomer, and current legislation allows only enantiopure compounds to be patented. Such compounds are of growing importance, not only in the pharmaceutical industry, but also in agrochemicals, perfume and as synthetic intermediates.[1]

Apart from the isolation of enantiomerically pure substances from animals and plants - the chiral pool -, and excluding the synthesis of other enantiomerically pure substances from them, there are two ways of obtaining non racemic organic compounds: resolution of racemic mixtures and asymmetric synthesis. In the first, a racemate is separated into its component enantiomers, therefore the yield of the desired product can never be more than 50%. In asymmetric synthesis, the stereochemistry of a reaction is controlled through the use of a chiral substance, added either in catalytic or stoichiometric amounts, such that the compound is transformed into an enantio- or diastereomerically enriched product.[2] A yield of up

[1] (a) Agranat, I.; Caner, H.; Caldwell, J. *Nat. Rev. Drug Discov.* **2002**, *1*, 753-768; (b) Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discov. Today* **2004**, *9*, 105-110; (c) Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, 2, 85-100; (d) Núñez, M. C.; García-Rubiño, M. E.; Conejo-García, A.; Cruz-López, O.; Kimatrai, M.; Gallo M. A.; Espinosa, A.; Campos J. M. *Curr. Med. Chem.* **2009**, *16*, 2064-2074.

[2] Gawley, R.; Aube, J.; *Principles of Asymmetric Synthesis*, 2nd Edition; Elsevier, **2012**.

to 100% is therefore suitable. Enantioselection is due to the existence of diastereomeric transition states of different energies, formed by the substrate and chiral substance. The reaction pathway will proceed via that of lower energy, resulting in the production of a higher quantity of one enantiomer.

The first method of controlling the stereochemistry of organic reactions involved the use of stoichiometric quantities of a chiral compound temporarily or permanently bonded to the reactant. However, because of the requirement for large quantities of a reactant or chiral auxiliary that in the majority of cases cannot be recovered and reused without considerable loss of efficiency, such methodologies have largely been replaced by the use of enantioselective catalysts. The use of a chiral catalyst in substoichiometric amounts has led to a revolution in the field of enantioselective synthesis, since a single molecule of a chiral catalyst is capable of generating a large number of molecules with a determined absolute configuration, and then being regenerated itself after every catalytic cycle.[3]



[3] Walsh, P. J.; Kozlowski, M. C.; *Fundamentals of Asymmetric Catalysis*; University Science Books, **2009**.

## 2. Asymmetric Organocatalysis. Generalities

Until relatively recently the catalysts used in the enantioselective synthesis of organic compounds belonged almost exclusively to two categories: transition metal complexes and enzymes. In the second half of the 20th century much progress was made in the development of transition metal catalysis,[4] culminating in the awarding of the Nobel Prize in Chemistry to Noyori, Knowles and Sharpless for their work in this area.

However, organocatalysis has recently become established as a third method in the production of enantiomerically pure organic compounds, between the two extremes of organometallic and enzymatic catalysis (Figure I).[5] The term was first used by MacMillan in 2000 building on the idea of "Organic Catalysis", introduced by Langenbeck in 1932,[6] as: "the acceleration of a chemical transformation through addition of a substoichiometric amount of an organic compound which does not contain a metal atom".[7] These molecules are known as organocatalysts and are composed principally of carbon, hydrogen and heteroatoms such as nitrogen, oxygen, sulphur or phosphorus, and are able to catalyze the reaction through the activation of the substrates, reactants or both, without the involvement of a metal atom.



[4] (a) Noyori, R.; *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**; (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; *Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, **1999**.
[5] (a) Berkessel, A.; Gröger, H.; *Asymmetric Organocatalysis*; Wiley-VCH, Weinheim, **2005**; (b) Dalko, P. I.; *Enantioselective organocatalysis*; Wiley-VCH, Weinheim, **2007**; (c) Christmann, M.; Bräse, S.; *Asymmetric Synthesis*; Wiley-VCH, Weinheim, **2012**; (d) Dalko, P. I.; *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Wiley-VCH, Weinheim, **2013**; (e) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774-793; (f) Atodiresei, I.; Vila, C.; Rueping, M. *ACS Catal.* **2015**, *5*, 1972-1985.
[6] Langenbeck, W. *Angew. Chem. Int. Ed.* **1932**, *45*, 97-98.
[7] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

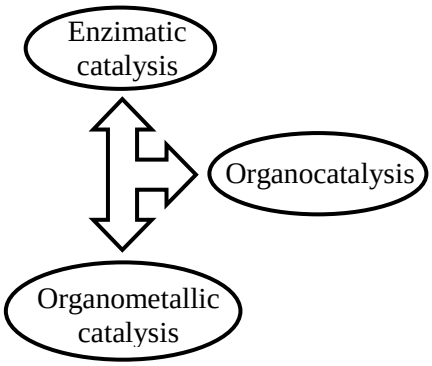
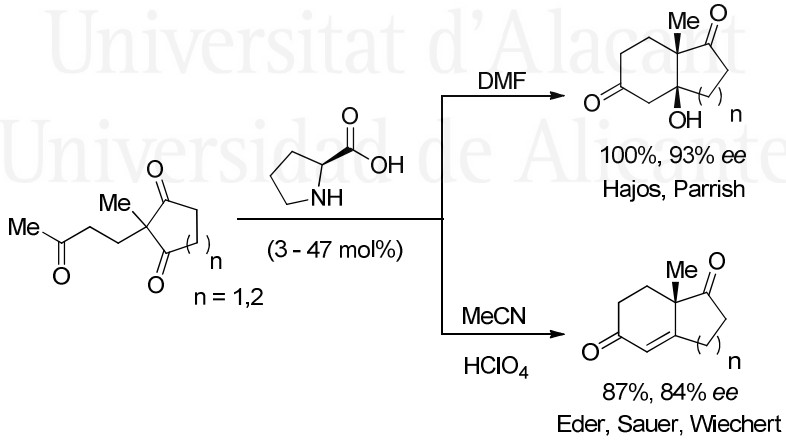



**Figure I**. Methodologies for enantioselective synthesis.

Although the recognition and widespread adoption of organocatalysis in synthetic chemistry is a relatively recent phenomenon, its roots date back to the first half of the 20th century, when low molecular weight organic compounds were used to understand the mechanisms responsible for the catalytic properties and selectivity of enzymes. Before the end of the century however, only a small number of examples of enantioselective syntheses using organocatalysts were published, an example being the famous Hajos-Parrish-Eder-Sauer-Wiechert reaction organocatalyzed by L-proline in 1971 (Scheme I),[8] which was an important advance for the synthesis of natural and biological active products, mainly steroids.[9]




**Scheme I**. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

[8] (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.
[9] Sauvée, C.; Schäfer, A.; Sundén, H.; Ma, J.-N.; Gustavsson, A.-L.; Bursteinb, E. S.; Olsson, R. *Med. Chem. Commun.* **2013**, *4*, 1439-1442.

Organocatalysis offers several advantages over traditional techniques. It avoids the use of transition metals, which is evidently beneficial from an environmental perspective, since these are frequently toxic and difficult to eliminate. In addition, organocatalysts also tend to be more stable than metal complexes, the reaction being normally carried out in air, and with wet solvents.

Moreover, the catalysts tend to be relatively cheap and easily accessible, since nature provides a multitude of enantiopure compounds such as α-amino acids, α-hydroxy acids, peptides and carbohydrates, from which organocatalysts can be obtained. Finally, the recovery of the catalyst can be easier, since many organocatalysts are suitable to be anchored to a solid support and reused more efficiently than metal organometallic or bioorganic compounds, which is a considerable advantage in an industrial context.[10]

Over the last fifteen years, great advances have been made in asymmetric organocatalysis, and it is now a widely studied area with a great diversity of applications, both academically and industrially. One of the main factors of this rapid evolution has been the aid of computational calculations,[11] which have allowed to advance enormously in the knowledge of the mechanisms of reaction.



During this time, new techniques and strategies have been developed, and syntheses once considered specific to a particular substrate have been revolutionized by a new generation of catalysts that equal or even exceed other procedures in terms of synthetic utility, applicability and stereoselectivity. Thus, this new catalytic tool

[10] (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666-1688; (b) Rostamnia, S.; Doustkhah, E. *RSC Adv*. **2014**, *4*, 28238-28248; (c) Xia, A.-B.; Zhang, C.; Zhang, Y.-P.; Guo, Y.-J.; Xiao-Long Zhang, X.-L.; Lia, Z.-B.; Xu, D.-Q. *Org. Biomol. Chem*. **2015**, *13*, 9593-9599.

[11] (a) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev*. **2011**, *111*, 5042-5137. (b) Maruoka, K.; Pápai, I.; *Computational and Theoretical Studies*; Thieme: Stuttgart, **2012**, 601-671.

has been applied satisfactorily to multicomponent and "one-pot" processes,[12] as well as in the total synthesis of natural and bioactive products.[13]

Most crucial to the success of asymmetric organocatalysis in the past decade has been the invention or identification of generic modes of catalyst activation, induction and reactivity. It was in 2008 when MacMillan described, from a mechanistic point of view, a general classification of the generic modes of activation based on the type of interaction between the organocatalyst and the substrates in the transition state responsible for the activation, distinguishing between those processes that involve the formation of covalent adducts within the catalytic cycle (covalent catalysis, Figure II) and those based on weak non-covalent interactions, such as hydrogen bonding or the formation of intimate ion pairs (non-covalent catalysis, Figure II).[14]

Most of these organocatalytic transformations are developed via covalent catalysis. To this group belong the reactions mediated by amine catalysts, including the processes involving the enamine cycle (HOMO activation of the nucleophile),[15] and the accelerated reactions by the formation of iminium intermediates (activation of the electrophile LUMO).[15] Catalyzed transformations through activation of the substrate SOMO,[15] amine or phosphine catalyzed acyl transfer reactions, the Morita-



[12] (a) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693-700; (b) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167-178; (c) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492-8509; (d) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969-4009; (e) Wende, R. C.; Schreiner, P. R. *Chem. Commum.* **2012**, *44*, 1821-1849; (f) Bharate, J. B.; Vishwakarma, R. A.; Bharate, S. B. *RSC Adv.* **2015,** *5***,** 42020-42053; (g) Shakibaei, G. I.; Bazgir, A. *RSC Adv.* **2016**, *6*, 22306-22311.

[13] (a) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *23*, 337-356; (b) Amara, Z.; Caron, J.; Joseph, D. *Nat. Prod. Rep.* **2013**, *30*, 1211-1225; (c) Dibello, E.; Gamenara, D.; Seoane, G. *Current Organocatalysis* **2015**, *2*, 124-149.

[14] MacMillan, D. W. C. *Nature*, **2008**, *455*, 304-308.

[15] (a) Watson, A.; MacMillan, D. W. C.; *Enantioselective organocatalysis involving iminium, enamine, SOMO, and photoredox activation*, in Catalytic Asymmetric Synthesis, 3rd Edition; Hoboken, NJ, **2010**, 39-57; (b) List, B.; *Science of Synthesis, Asymmetric Organocatalysis 1*; Thieme: Stuttgard, **2012**.

Baylis-Hillmann reaction, carbene-mediated reactions as well as asymmetric ylide reactions also correspond to this category.[15b]

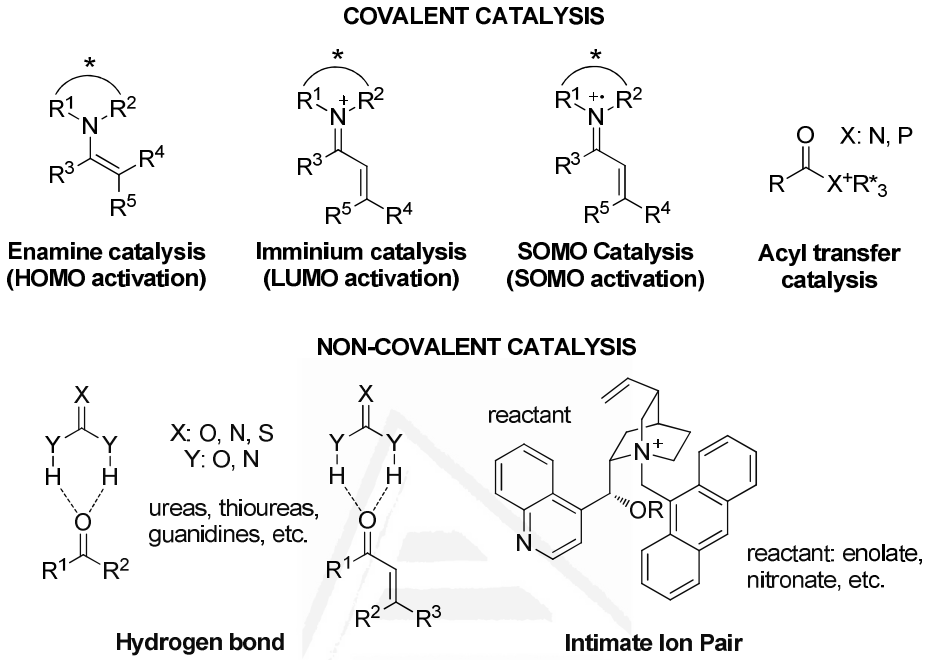



**Figure II**. Modes of activation in enantioselective organocatalysis.

On the other hand, non-covalent organocatalysis is based on the acceleration of the reaction by weak interactions between the catalyst and the substrate which stabilize the transition states. These interactions can be hydrogen bonds,[16] or the formation of ionic pairs.[17]

Sometimes a single organocatalyst promotes reactions by several modes of activation. Mechanistically they can be assigned as multifunctional catalysts.[18] A phase transfer catalysts (PTC) may work by any of the previously mentioned

[16] (a) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633-2646; (b) Pihko, P. M.; *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2009**.
[17] Legros, F.; Oudeyer, S.; Levacher, V. *Chem. Rec.* **2017**, *17*, 429-440.
[18] (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673; (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.

activation modes providing a chiral "shuttle" for reaction partners located in different phases.[19]

Among all the array of asymmetric organocatalyzed reactions, the conjugate addition reaction of carbon nucleophiles to electron-deficient alkenes is one of the most important ways of creating carbon-carbon bonds.[20] The present thesis focuses on amine catalysis, with processes involving enamine cycles in Michael addition reactions, combined to hydrogen bond interactions.



[19] a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656-5682; b) Maruoka, K.; Shirakawa, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348.

[20] (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171-196; (b) Jha, S. C.; Joshi, N. N. *ARKIVOC* **2002**, *(viii)*, 167-196; (c) Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688-1690; (d) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933-971; (e) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299-365; (f) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701-1716; (g) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42-53; (h) Heravi, M. M.; Hajiabbasi, P.; Hamidi, H. *Curr. Org. Chem.* **2014**, *18*, 489-511; (i) Nayak, S.; Chakroborty, S.; Bhakta, S.; Panda, P.; Mohapatra, S. *Res. Chem. Intermed.* **2016**, *42*, 2731-2747; (j) Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S. K.; Mohapatra, S. *RSC Adv.* **2016**, *6*, 96154-96175.

## 3. Asymmetric Organocatalysis in Alternative Reaction Media: Deep Eutectic Solvents

Nowadays, traditional volatile organic solvents (VOCs) are the common medium for carrying out organic reactions due to, among other factors, easy control over mass and heat transference, stabilization of transition states, and fast modification of reactivity: rate, selectivity, etc. When traditional solvents are regarded from an environmental point of view, they show many intrinsic drawbacks, such as accumulation in the atmosphere due to their low boiling points, flammability, high toxicity, and non-biodegradability. In addition, traditional organic solvents pose a risk to the health of those who handle them.[21]

For all these reasons, several experimental methodologies have been performed to make organocatalysis an even greener and sustainable alternative to stoichiometric approaches as well as non-catalytic conditions, by the use of benign and friendlier reaction media, all of them having a certain number of advantages, as well as disadvantages.[21]

In this line, approaches using water as preferential solvent,[22] or alternative solvents such as polyethylene glycol,[23] ionic liquids,[24] acyclic and cyclic carbonate and polycarbonate solvents,[25] and supercritical carbon dioxide,[26] have been explored for catalytic processes.



[21] Hernández, J. G.; Juaristi, E. *Chem. Commun*. **2012**, *48*, 5396-5409.
[22] (a) Raj, M.; Singh, V. K. *Chem. Commun*. **2009**, *44*, 6687-6703; (b) Mase, N.; Barbas III, C. F. *Org. Biomol. Chem*. **2010**, *8*, 4043-4050; (c) Qiao, Y.; Headley, A. D. *Green Chem*. **2013**, 15, 2690-2694.
[23] Feu, K. S.; de la Torre, A. F.; Silva, S.; de Moraes-Junior, M. A. F.; Corrêa, A. G.; Paixao, M. W. *Green Chem.* **2014**, *16*, 3169-3174.
[24] Zalewska, K.; Branco, L. C. *Mini-Rev. Org. Chem*. 2014, *11*, 141-153.
[25] North, M.; Villuendas, P.; *Org. Lett*. **2010**, *12*, 2378-2381.
[26] (a) Kuchurov, I. V.; Nigmatov, A. G.; Kryuchkova, E. V.; Kostenko, A. A.; Kucherenko, A. S.; Zlotin, S. G. *Green Chem*., **2014**, *16*, 1521-1526; b) Filatova, E. V.; Turova, O. V.; Kuchurov, I. V.; Kostenko, A. A.; Nigmatov, A. G.; Zlotin, S.G. *J. Supercrit. Fluids* **2016**, *109*, 35-42.

Recently, attention has been focused in the use of Deep Eutectic Solvents (DESs) in organic synthesis as an alternative to traditional solvents.[27] A DES is a combination of two or three components, solid Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species, which interact through hydrogen bonds, forming a eutectic mixture with a melting point lower than the individual components (Figure III).[28]

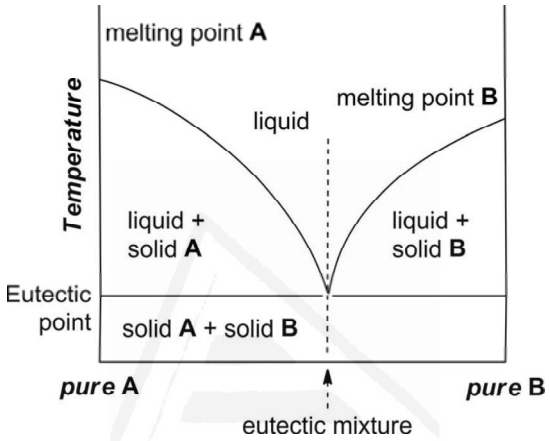



**Figure III**. Deep Eutectic Solvent phase diagram.

DESs are non-volatile, showing a low ecological footprint, attractive price and easy recyclability, and are nowadays promising "green" alternatives to conventional solvents. In addition, their high solubility in water causes organic

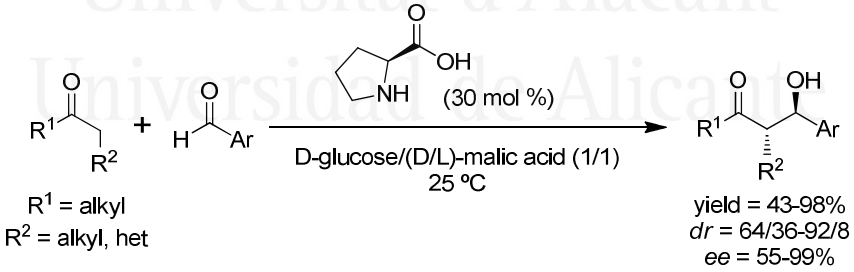
[27] (a) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. *Chem. Soc. Rev*. **2012**, *41*, 7108-7146; (b) García-Álvarez, J.; *Deep Eutectic Solvents and Their Applications as New Green and Biorenewable Reaction Media*. In *Use, Health, and Environment*, 2nd ed.; Handbook of Solvents, Vol. 2; ChemTec Publishing: Toronto, **2014**; (c) Liu, P.; Hao, J.-W.; Mo, L.-P.; Zhang, Z.-H. *RSC Adv*. **2015**, *5*, 48675-48705; (d) García-Álvarez, J.; Hevia, E.; Capriati, V. *Eur. J. Org. Chem*. **2015**, 6779-6799; (e) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Eur. J. Org. Chem.* **2016**, 612-632; (f) Khandelwal, S.; Tailor, Y. K.; Kumar, M. *J. Mol. Liq.* **2016**, *215*, 345-386; (g) Guajardo, N.; Müller, C. R.; Schrebler, R.; Carlesi, C.; Domínguez de María, P. *ChemCatChem* **2016**, *8*, 1020-1027.

[28] (a) Ruβ, C.; König, B. *Green Chem.* **2012**, *14*, 2969-2982; (b) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jerome, F. *Chem. Soc. Rev.* **2012**, *41*, 7108-7146; (c) Francisco, M.; van den Bruinhorst, A.; Kroon, M. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 3074-3085; (d) Tang, B.; Row, K. H. *Monatsh. Chem.* **2013**, *144*, 1427-1454; (e) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063-1071; (f) Smith, E. L.; Abbott, A. P.; Ryder, K. S. *Chem. Rev.* **2014**, *114*, 11060-11082.

products to precipitate or appear as an insoluble layer, avoiding extraction with organic solvents at the end of the reaction. The properties of the DES, such as conductivity, viscosity, vapour pressure and thermal stability can be fine-tuned by choosing appropriately the mixture components, large-scale preparations being thus feasible.[28]

Besides all these interesting advantages, the application of DESs in asymmetric organocatalytic synthesis is still in its infancy. Thus, the first reported example of an asymmetric organocatalyzed reaction in DESs employed in fact a tandem enzyme-proline derived combination.[29]

In 2016, three different research groups performed the intermolecular aldol reaction between ketones and non-enolizable aldehydes. Thus, Guillena and Ramón's group, performed this reaction by employing L-proline (30 mol%) as organocatalyst in natural deep eutectic solvents (NADES) at room temperature (Scheme II), obtaining the corresponding adducts in moderate to high yields (43-98%), diastereoselectivities (64/36-92/8) and enantioselectivities (55-99%).[30] In addition, the catalyst, together with the reaction media, could be recovered by simple water extraction and reused at least three times achieving similar results.




**Scheme II**. Aldol reaction organocatalyzed by L-proline in NADES.

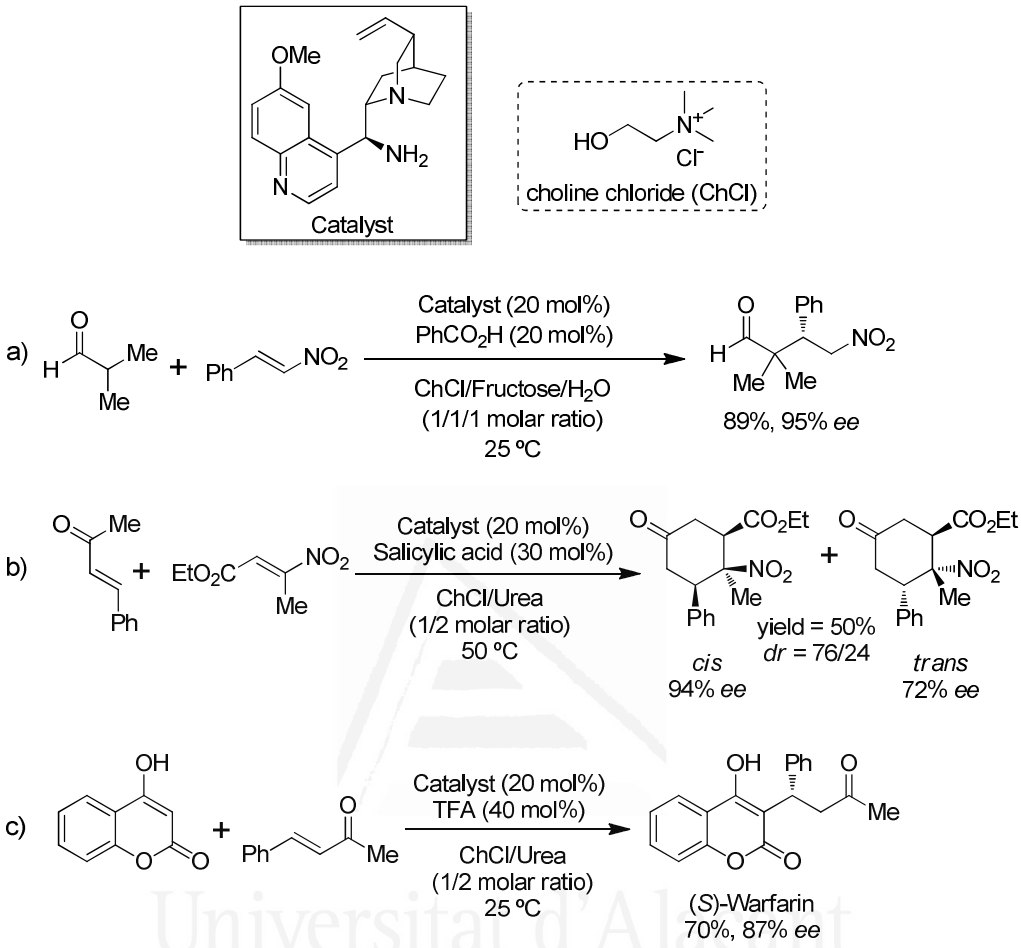
[29] (a) Müller, C. R.; Meiners, I.; Domínguez de María, P. *RSC Adv.* **2014**, *4*, 46097-46101; (b) Müller, C. R.; Rosen, A.; Domínguez de María, P. *Sustainable Chem. Processes* **2015**, *3*, 1-8.
[30] Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. *Green Chem*. **2016**, *18*, 1724-1730.

The same year, Capriati and Benaglia's group performed the intermolecular aldol reaction between cyclohexanone and 4-nitrobenzaldehyde organocatalyzed also by L-proline, employing different choline chloride (ChCl)-based DESs, under continuous flow conditions, obtaining the corresponding adduct with high yield (up to 99%), *anti*-stereoselectivity, and enantioselectivity (up to 97% *ee*). Moreover, using two different DES mixtures, the diastereoselectivity of the process could be tuned, thereby leading to the formation, under different experimental conditions, to both the *syn*- and the *anti*-isomer with very high enantioselectivity.[31]

On the other hand, Concellón and del Amo's group was able to organocatalyze this enantioselective aldol reaction by using L-isoleucine as organocatalyst, with 10 equivalents of water, in a choline chloride and ethylene glycol-based DES, obtaining the corresponding adducts in moderate to high yields (63-82%) and enantioselectivities (66-98%).[32] The products can be extracted from the reaction media with ethyl acetate, allowing the recyclability of the DES and the organocatalyst up to five times.

Capriati and Benaglia's group also performed different conjugate addition reactions involving 9-amino-9-deoxy-*epi*-quinine as organocatalyst and acid additives, in different ChCl-based DESs.[33] Examples are the conjugate addition of isobutyraldehyde to (*E*)-β-nitrostyrene, obtaining the corresponding adduct in 89% yield and 95% *ee* (Scheme III, a), the addition of (*E*)-nitroacrylates to α,β-unsaturated ketones obtaining highly functionalized cyclohexanones (Scheme III, b), and also the addition of 4-hydroxycoumarin to benzalacetone, leading to the anticoagulant drug (*S*)-Warfarin in 70% yield and in 87% *ee* (Scheme III, c).

[31] Brenna, D.; Massolo, E.; Puglisi, A.; Rossi, S.; Celentano, G.; Benaglia, M.; Capriati, V. *Beilstein J. Org. Chem*. **2016**, *12*, 2620-2626.
[32] Fanjul-Mosteirín, N.; Concellón, C.; del Amo, V. *Org. Lett*. **2016**, *18*, 4266-4269.
[33] Massolo, E.; Palmieri, S.; Benaglia, M.; Capriati, V.; Perna, F. M. *Green Chem*. **2016**, *18*, 792-797.




**Scheme III**. Different organocatalyzed asymmetric Michael addition reactions carried out in DES.

Due to the interest on green chemistry, much more research on asymmetric organocatalysis employing these environmentally friendly solvents is desirable. The present thesis shows examples of the application of DES in asymmetric Michael addition reactions.

# CHAPTER I:

## CHIRAL AMINOCARBAMATES AS ORGANOCATALYSTS IN THE MICHAEL ADDITION REACTION OF ALDEHYDES AND KETONES TO MALEIMIDES

# 1. ANTECEDENTS

Chiral succinimides are structural units found in natural products and some drug candidates (Figure I).[1] From the study of Komura and co-workers in 1987 on the production of Andrimid (**Ia**) as a new highly specific antibiotic, 1,3-substituted and 3,4-disubstituted succinimides have emerged as a new class of natural products with an important biological activity.[2]

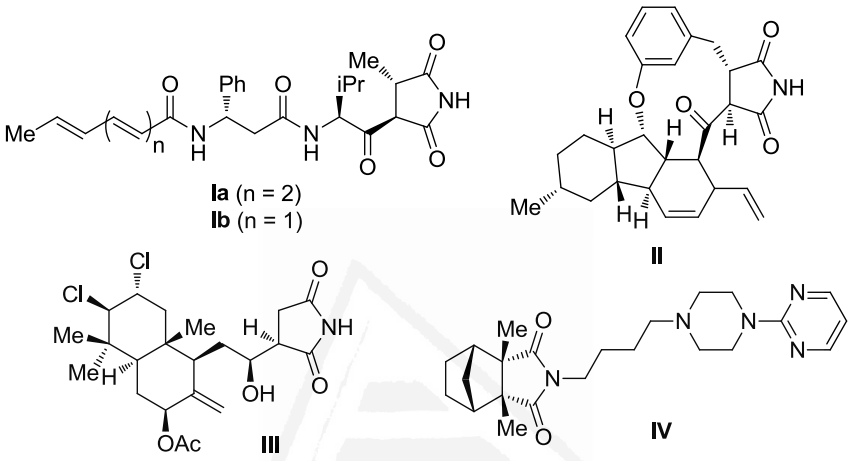



**Figure I.** Natural products bearing succinimide moieties.

For example, the chiral succinimides Andrimid (**Ia**) and Moiramide B (**Ib**) exhibit potent *in vitro* antibacterial activity against *Staphylococcus aureus*, a methicillin-resistant agent, and against a wide range of other human pathogen-resistant to antibiotics.[2a] In addition, hirsutellones A-E (such as Hirsutellone A, **II**),



[1] Curtin, M. L.; Garland, R. B.; Heyman, H. R.; Frey, R. R.; Michaelides, M. R.; Li, J.; Pease, L. J.; Glaser, K. B.; Marcotte, P. A.; Davidsen, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919-2923.

[2] (a) Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc.* **1987**, *109*, 4409-4411; (b) Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964-1973; (c) Freiberg, C.; Brunner, N. A.; Schiffer, G.; Lampe, T.; Pohlmann, M.; Habich, D.; Ziegelbauer, K. *J. Biol. Chem.* **2004**, *279*, 26066-26073; (d) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577-5583; (e) Uddin, J.; Ueda, K.; Siwu, E. R. O.; Kita, M.; Uemura, D. *Bioorg. Med. Chem.* **2006**, *14*, 6954-6961; (f) Robert, F.; Gao, H. Q.; Donia, M.; Merrick, W. C.; Hamann, M. T.; Pettetier, J. *RNA* **2006**, *12*, 717-725; (g) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini-Rev. Med. Chem.* **2012**, *12*, 671-700.

show inhibitory activity against *Mycobacterium tuberculosis* H37Ra,[3] whereas the haterumaimides A-Q (such as Haterumaimide A, **III**) have interest due to their potential use as inhibitor in the synthesis of proteins and as an antitumoral agent.[4] The structure of chiral succinimide is also present in Tandospirone (**IV**), an anxiolytic and antidepressant drug.[5] In addition, succinimides can be transformed into other interesting compounds such as γ-lactams,[6] which are important in the treatment of cancer,[7] epilepsy,[8] HIV,[9] neurodegenerative diseases and depression.[10]

The production of substituted chiral succinimides can be achieved directly by enantioselective functionalization of maleimides (Figure II).[11] Maleimides are an important group of substrates, which have been used successfully in asymmetric organocatalytic transformations. Thus, they are excellent Michael acceptors in stereoselective organocatalysis and transition metal catalysis (Figure II, a), as well as

[3] Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577-5583.

[4] (a) Uddin, M. J.; Kokubo, S.; Suenaga, K.; Ueda, K.; Uemura, D. *Heterocycles*, **2001**, *54*, 1039-1047; (b) Uddin, M. J.; Kokubo, S.; Ueda, K.; Suenaga, K.; Uemura, D. *J. Nat. Prod*. **2001**, *64*, 1169-1173; (c) Uddin, M. J.; Kokubo, S.; Ueda, K.; Suenaga, K.; Uemura, D. *Chem. Lett*. **2002**, 1028-1029.

[5] (a) Barradell, L. B.; Fitton, A. *CNS Drugs* **1996**, *5*, 147-153; (b) Nishitsuji, K.; To, H; Murakami, Y.; Kodama, K.; Kobayashi, D.; Yamada, T.; Kubo, C.; Mine, K. *Clin. Drug Investig.* **2004**, *24*, 121-126.

[6] (a) Nöth, J.; Frankowski, K. J.; Neuenswander, B.; Aubé, J.; Reiser, O. *J. Comb. Chem.* **2008**, *10*, 456-459; (b) Fensier, E.; Hill, D.; Reiser, O.; Aubé, J. *Beilstein J. Org. Chem.* **2012**, *8*, 1804-1813.

[7] Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.-H.; Neuteboom, S. T. C.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407-419.

[8] (a) Reddy, P. A.; Hsiang, B. C. H.; Lafiti, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1996**, *39*, 1898-1906; (b) Das Sarma, K.; Zhang, J.; Huang, Y.; Davidson, J. G. *Eur. J. Org. Chem.* **2006**, 3730-3737.

[9] (a) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159-1162; (b) Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689-5692.

[10] (a) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097-13105; (b) Tang, K.; Zhang, J.-T. *Neurol. Res.* **2002**, *24*, 473-478.

[11] Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem. Asian J.* **2013**, *8*, 328-346.

dienophiles/dipolarophiles in asymmetric cycloaddition (Figure II, b and c). In addition, maleimides are also used in asymmetric cascade reactions, which include the initial addition of a nucleophile to a double bond, the resulting species being added to an electrophile to generate two or more stereogenic centers (Figure II, d).

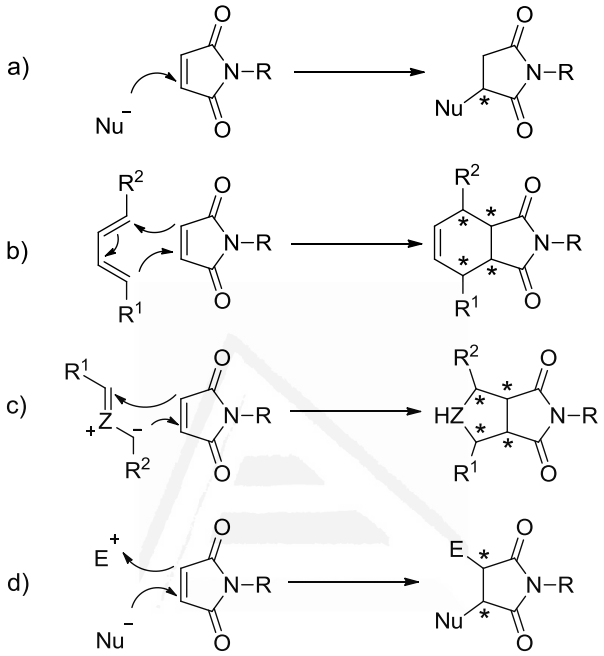



**Figure II.** Synthesis of succinimides from asymmetric reactions of maleimides.



The enantioselective Michael addition reaction of nucleophilic carbons to maleimides is probably the most direct method for preparing enantioenriched chiral succinimides using an organocatalytic strategy (Figure II, a). This addition has often been achieved by pro-nucleophilic species possessing α-acid hydrogens, using as organocatalysts bifunctional chiral compounds bearing a group able to form hydrogen bonds, and a tertiary amine.[11] The, enantioinduction is achieved after coordination of both the maleimide with the acidic hydrogens of the bifunctional organocatalyst and the enolate formed by deprotonation of the pro-nucleophile with the tertiary amine (Figure III).

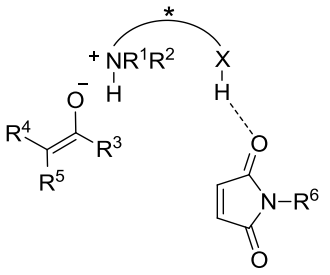


**Figure III.** Coordination model involving enolate formation in a bifuntional organocatalyst.

However, when aldehydes and ketones are used as pro-nucleophiles, an α-deprotonation by just an organic base is not feasible. In this case, an enamine-forming strategy using chiral bifunctional organocatalysts bearing primary or secondary amines are employed.[12] Thus, the creation of a transient enamine with the catalyst is the way to activate the carbonyl compound, turning it into a nucleophile (Figure IV).

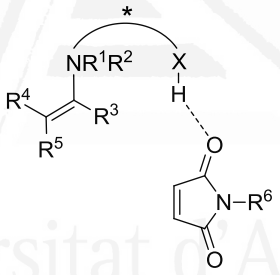


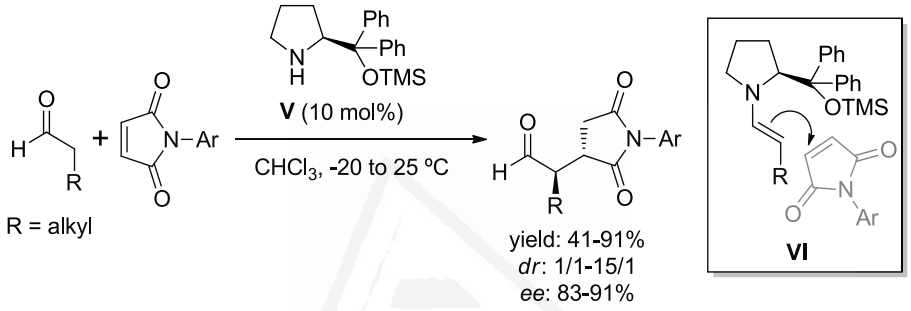
**Figure IV.** Coordination model involving enamine formation in a bifunctional organocatalyst.



The first organocatalytic enantioselective conjugate addition of aldehydes to *N*-substituted maleimides via enamine activation was reported by Cordova and co-workers in 2007.[13] Thus, α,α-phenylprolinol silyl ether (**V**) was used as the organocatalyst in the enantioselective Michael addition reaction of various aliphatic aldehydes to *N*-arylmaleimides, to give the corresponding α-substituted chiral succinimide derivatives in yields between 41-91%, diastereomeric ratios between

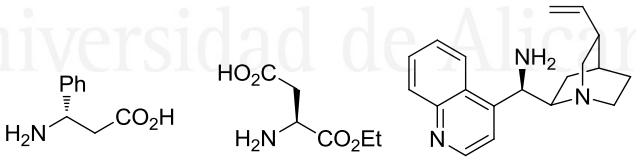
[12] (a) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051-7071; (b) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491-2513.
[13] Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Córdova, A. *Chem. Commun.* **2007**, 734-735.

1/1-15/1 and enantioselectivities between 83-99%. However, the "difficult" α,α-disubstituted aldehydes resulted in much lower enantioselectivities (51% *ee* using isobutyraldehyde). The proposed approach (**VI**) reflects steric impediments on the part of the phenyl and trimethylsilyl groups of the catalyst toward the approximation of enamine by the *Si* face. Consequently, the *Re* side is more accessible for the electrophile approach (Scheme I). This pioneering organocatalyst cannot be considered as bifunctional, no coordination of the maleimide being produced.




**Scheme I.** Asymmetric Michael addition reaction of aldehydes to maleimides organocatalyzed by **V**.

Organocatalysts based on the use of the primary-amine of amino acids, such as **VII** and **VIII,** combined with the presence of basic additives,[14] or the *Cinchona*-alkaloid-derived primary amine **IX** in combination with triphenylphosphine,[15] have proved to be effective in this enantioselective reaction involving aldehydes.



**VII**
yield: 76-99%
*dr*: 54/46-90/10
*ee*: 94-99%

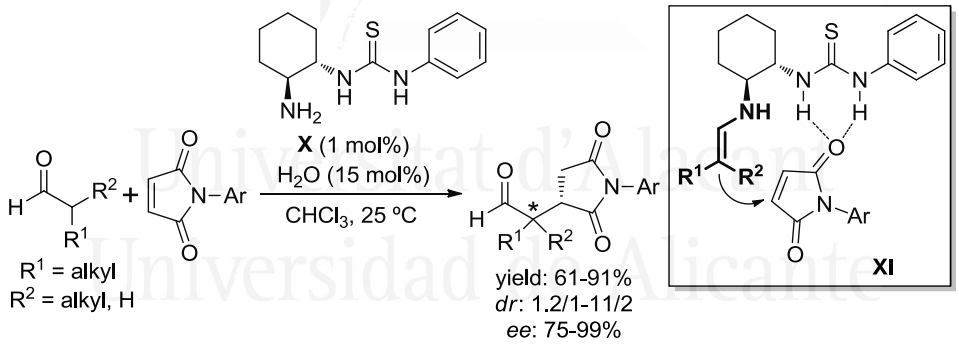
**VIII**
yield: 54-98%
*dr*: 50/50-89/11
*ee*: 23-99%

**IX**
yield: 74-99%
*dr*: 99/1
*ee*: 98-99%

[14] Kokotos, C. G. *Org. Lett.* **2013**, *15*, 2406-2409.
[15] Yang, W.; Jiang, K.-Z.; Lu, X.; Yang, H.-M.; Li, L.; Lu, Y.; Xu, L.-W. *Chem. Asian J.* **2013**, *8*, 1182-1190.

Bifunctional organocatalysts destined to perform enantioselective Michael addition reaction are frequently obtained from enantiopure 1,2-diamines, bearing a primary amine intact and an additional hydrogen bond-forming functionality. Particularly, organocatalysts derived from enantiopure *trans*-cyclohexane-1,2-diamine, a very important chiral starting material,[16] have been employed successfully in these transformations.

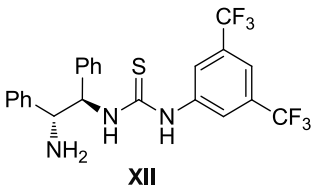
Thus, in 2010, Wang and co-workers developed a highly efficient conjugated addition reaction of α,α-disubstituted aldehydes to maleimides, organocatalized by primary amine-thiourea **X**.[17] This organocatalyst, in a very small amount and in the presence of water, gave the corresponding α,α-disubstituted succinimides with good yields (61-91%) and enantioselectivities (75-99%). In the proposed approximation **XI**, the maleimide is coordinated by double hydrogen bonding with the thiourea, favoring the approximation of enamine by the *Si* face (Scheme II).



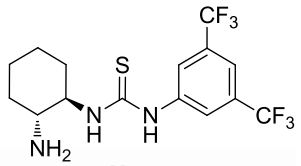

**Scheme II.** Asymmetric Michael addition reaction of α,α-disubstituted aldehydes to maleimides organocatalyzed by **X**.

[16] (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997,** *97*, 3161-3195; (b) Kouklovsky, C.; Langlois, Y.; Aguilar, E.; Fernández-García, J. M.; Sikervar, V.; *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd; **2014**.
[17] Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979-7982.

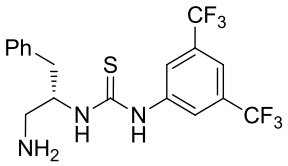
Since then, different chiral bifunctional primary amine-thiourea organocatalysts derived from enantiopure 1,2-diamines have been applied to the enantioselective Michael addition of these α,α-disubstituted aldehydes to maleimides, leading to enantioenriched succinimides in excellent results.[18] Some examples are the primary amine-thioureas **XII**,[18a] **XIII**,[18b] and **XIV**,[18d] the beyerane-containing thiourea **XV**,[18e] and the diterpene-derived bifunctional thiourea **XVI**.[18i]



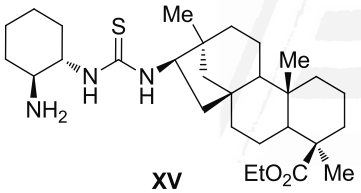
**XII**
yield: 85-99%
*dr*: 1/1-9/1
*ee*: 91-99%



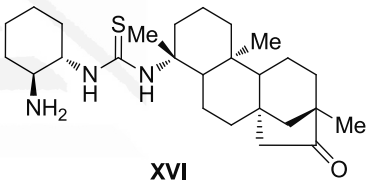
**XIII**
yield: 55-98%
*dr*: 1.1/1-3/1
*ee*: 93-99%



**XIV**
yield: 81-98%
*dr*: 56/44
*ee*: 42-99%



**XV**
yield: 66-97%
*dr*: 1.7/1-2.4/1
*ee*: 90-99%

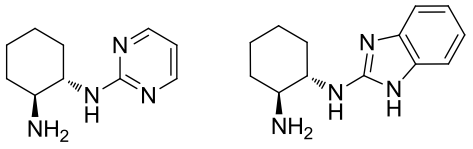


**XVI**
yield: 62-96%
*dr*: 2.2/1-2.7/1
*ee*: 60-99%



[18] (a) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767-4774; (b) Bai, J.-F.; Peng, L.; Wang, L.-l.; Wang, L. X.; Xu, X.-Y. *Tetrahedron* **2010**, *66*, 8928-8932; (c) Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979-7982; (d) Miura, T.; Masuda, A.; Ina, M.; Nakashima, K.; Nishida, S.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1605-1609. (e) Ma, Z.-W.; Liu, Y.-X.; Li, P.-l.; Ren, H.; Zhu, Y.; Tao, J.-C. *Tetrahedron: Asymmetry* **2011**, *22*, 1740-1748. (f) Ma, Z.-W.; Liu, Y.-X.; Zhang, W.-J.; Tao, Y.; Zhu, Y.; Tao, J.-C.; Tang, M.-S. *Eur. J. Org. Chem.* **2011**, 6747-6754 ; (g) Durmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2013**, *24*, 1443-1448; (h) Orlandi, S.; Pozzi, G.; Ghisetti, M.; Benaglia, M. *New J. Chem.* **2013**, *37*, 4140-4147; (i) Song, Z.-T.; Zhang, T.; Du, H.-L.; Ma, Z.-W.; Zhang, C.-H.; Tao, J.-C. *Chirality* **2014**, *26*, 121-127.

Other primary-amine organocatalysts derived from chiral *trans*-cyclohexane-1,2-diamines bearing other functionalities, have also been used to carry on the enantioselective Michael addition reaction of aldehydes to maleimides, as the case of 2-aminopyrimidine **XVII**[19] and 2-aminobenzoimidazole **XVIII** derivatives.[20]



**XVII**
yield: 70-92%
*dr*: 2/1-6/1
*ee*: 60-93%

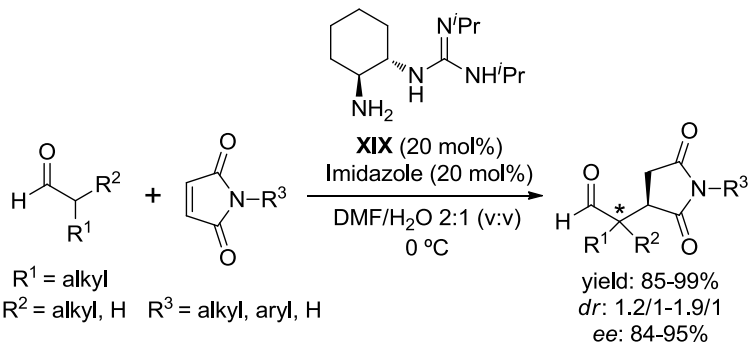


**XVIII**
yield: 47-99%
*dr*: 2/1
*ee*: 58-89%

In our research group, the enantioselective addition of aldehydes to maleimides has also been carried out using as organocatalysts the simple (1*S*,2*S*)-cyclohexane-1,2-diamines,[21] and also its aminoguanidine derivative **XIX**,[22] obtaining excellent yields and enantioselectivities (up to 95%) of the final adducts, working in a DMF/$H_2O$ mixture (2/1, v/v ratio) as solvent and using imidazole as basic additive (Scheme III).

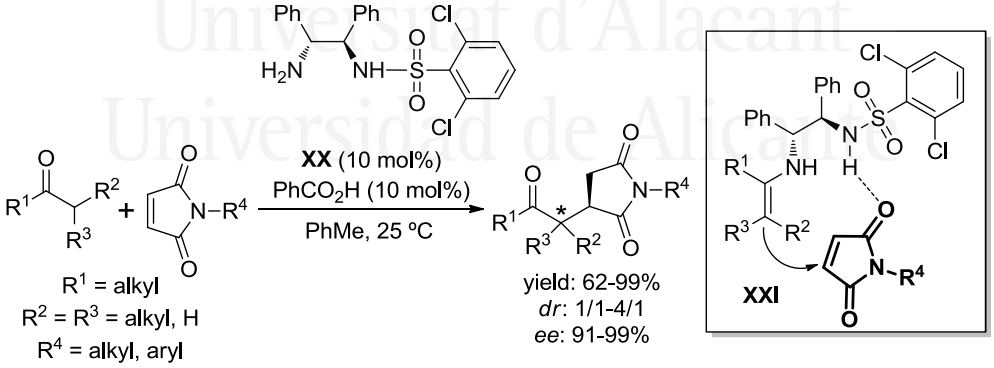


[19] Vizcaino-Milla, P.; Sansano, J. M.; Nájera, C.; Fiser, B.; Gómez-Bengoa, E. *Synthesis* **2015**, *47*, 2199-2206.
[20] Fernandes, T. A.; Vizcaíno-Milla, P.; Ravasco, J. M. J. M.; Ortega-Martínez, A.; Sansano, J. M.; Nájera, C.; Costa, P. R. R.; Fiser, B.; Gómez-Bengoa, E. *Tetrahedron: Asymmetry* **2016**, *27*, 118-122.
[21] Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Tetrahedron: Asymmetry* **2013**, *24*, 1531-1535.
[22] (a) Avila, A.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1625-1627; (b) Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5085-5092.




**Scheme III.** Asymmetric Michael addition reaction of aldehydes to maleimides organocatalyzed by **XIX**.

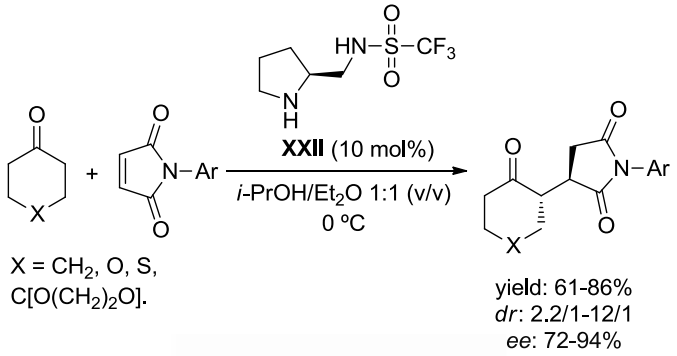
The use of ketones as pro-nucleophiles in the enantioselective organocatalyzed Michael addition to maleimides, has been much less explored. It was not until 2010 when Liang and Ye succeeded in performing the first addition of ketones to maleimides, organocatalyzed by the chiral sulphonamide **XX** in the presence of benzoic acid as additive. They obtained yields ranging from 62-99%, diastereomeric ratios between 1/1-4/1 and enantioselectivities between 91-99%. In the proposed approach **XXI**, the maleimide is coordinated by hydrogen bond to the NH of the sulphonamide, allowing the enamine to approach by the *Re* face (Scheme IV).[23]




**Scheme IV.** Asymmetric Michael addition reaction of ketones to maleimides organocatalyzed by **XX**.

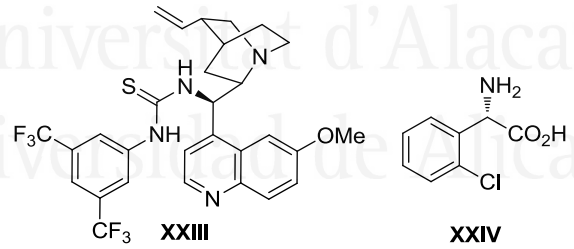
[23] Yu, F.; Jin, Z.; Sun, X.; Jin, Z.; Wen, S.; Liang, X.; Ye, J. *Chem. Commun*. **2010**, *46*, 4589-4591.

In addition, Wang and collaborators achieved in 2011 the addition of cyclic ketones to *N*-arylmaleimides, using chiral pyrrolidinyl sulfonamide **XXII** as organocatalyst, achieving good yields and enantioselectivities (Scheme V).[24]




**Scheme V.** Asymmetric Michael addition reaction of ketones to maleimides organocatalyzed by **XXII**.

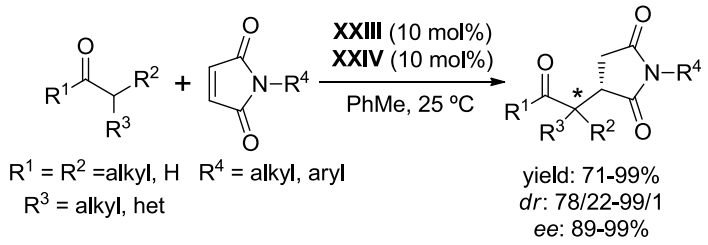
In the year 2013 the group of Zhao, using a combination of the quinidine thiourea-derivative **XXIII** and L-2-chlorophenylglycine (**XXIV**), achieved the asymmetric addition of aldehydes and ketones to maleimides, with good yields (71-99%) and high diastereo- (78/22-99/1) and enantioselectivities (89-99%) in toluene as solvent (Scheme VI).[25]




**XXIII** **XXIV**

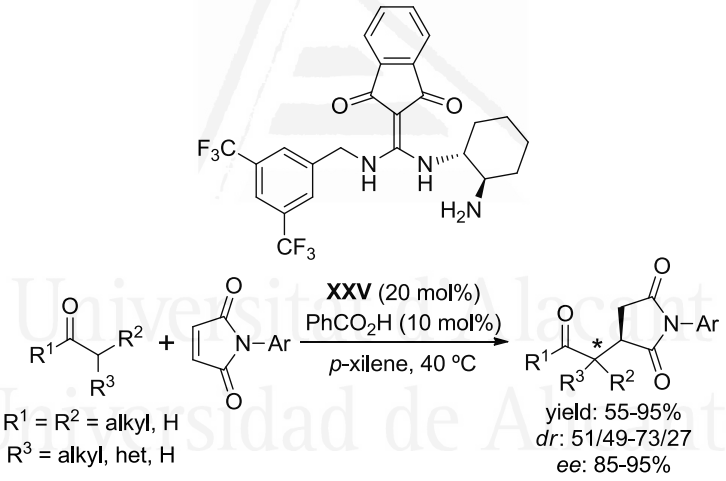


[24] Wang, J.; Zhang, M.-M.; Zhang, S.; Xu, Z.-A.; Li, H.; Yu, X.-H.; Wang, W. *Synlett* **2011**, 473-476.
[25] Muramulla, S.; Ma, J.-A.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2013**, *355*, 1260-1264.




**Scheme VI.** Asymmetric Michael addition reaction of ketones to maleimides organocatalyzed by **XXIII** and **XXIV**.

The most recent organocatalyst able to carry out the Michael addition of aldehydes and ketones to maleimides was prepared by Miura and co-workers in 2015. Thus, the organocatalyst **XXV** allowed to obtain the addition products in good yields and enantioselectivities, but with moderate diastereoselectivities (Scheme VII).[26]




**Scheme VII.** Asymmetric Michael addition reaction of ketones to maleimides organocatalyzed by **XXV**.

[26] (a) Nakashima, K.; Kawada, M.; Hirashima, S.-I.; Koseki, Y.; Miura, T. *Synlett* **2015**, *26*, 1248-1252. (b) Nakashima, K.; Kawada, M.; Hirashima, S.-I.; Kosugi, A.; Kato, M.; Yoshida, A.; Koseki, Y.; Miura, T. *Tetrahedron: Asymmetry* **2016**, *27*, 888-895.

The following work in this thesis deals to the use of bifunctional organocatalysts derived from enantiopure *trans*-cyclohexa-1,2-diamines, bearing a primary amine and a carbamate moiety, in the Michael addition reaction of aldehydes and ketones to maleimides.

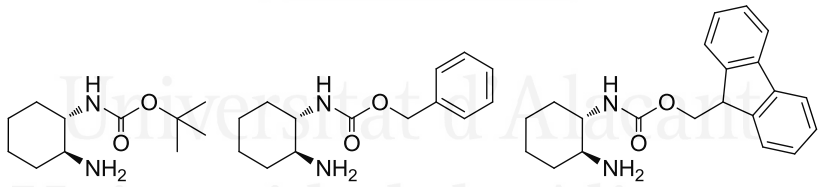
# 2. OBJECTIVES

Taking into account the present interest in the asymmetric synthesis of substituted succinimides described in the antecedents, and the lack of studies about the use of primary-amine carbamates as organocatalysts, we considered the following objectives:

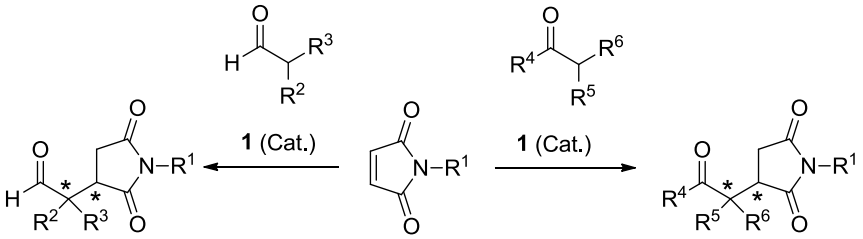
1) The synthesis of primary-amine containing monocarbamates **1**, derived from enantiopure *trans*-ciclohexane-1,2-diamines and the common carbamate amino-protecting groups: Boc, Cbz and Fmoc.

2) Use of these compounds as organocatalysts in the enantioselective Michael addition reaction of aldehydes and ketones to maleimides, in order to synthesize the corresponding enantiomerically enriched succinimides.

3) Explore the behaviour of these organocatalysts in the former reaction, but using non traditional conditions, such as the use of environmentally friendly Deep Eutectic Solvents.



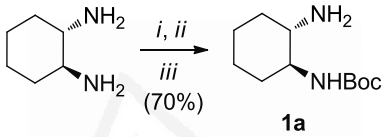
**1a** **1b** **1c**



# 3. RESULTS AND DISCUSSION

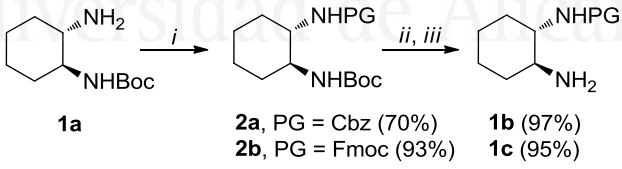
## 3.1. Synthesis of the Aminocarbamate Organocatalysts

The chiral primary-amine monocarbamates **1** employed in this study as organocatalysts were synthesized from (1*S*,2*S*)-ciclohexane-1,2-diamine as chiral source. Thus, aminocarbamate **1a**, bearing the protecting *tert*-butoxycarbonyl (Boc) group, was obtained in 70% yield according to the procedure described in the literature, consisting of the reaction of (1*S*,2*S*)-cyclohexa-1,2-diamine with 1 equivalent of hydrogen chloride, followed by subsequent treatment with di-*tert*-butyl carbonate.[27]




**Scheme 1**. (i) HCl (2M in $Et_2O$), 25 ºC; (ii) $(Boc)_2O$, MeOH, 25 ºC; (iii) NaOH (2M), 25 ºC.

Chiral aminocarbamates **1b** y **1c**, bearing the frequently used benzyloxycarbonyl (Cbz) and fluorenylmethoxycarbonyl (Fmoc) protecting groups, were prepared by reaction of the *N*-Boc-monoprotected diamine **1a** with the corresponding chloroformates, giving diprotected compounds **2a** and **2b** in 70 and 93% yield, respectively. Subsequent Boc-deprotection with trifluoroacetic acid (TFA) yielded the corresponding monoprotected compounds (Scheme 2).




**Scheme 2**. (i) CbzCl (**2b**) or FmocCl (**2c**), $NaHCO_3$ (aq), dioxane, 25 ºC; (ii) TFA, $CH_2Cl_2$, 25 ºC; (iii) $NH_4OH$, $CH_2Cl_2$, 25 ºC.

[27] Lee, D. W.; Ha, H.-J.; Lee, M. W. K. *Synth. Commun.* **2007**, *37*, 737-742.

## 3.2. Enantioselective Michael Addition of Aldehydes to Maleimides in Conventional Solvents

### *3.2.1. Optimization Studies*

The search for the most appropriate reaction conditions (Table 1) began with the model Michael addition reaction of isobutyraldehyde (**3a**, 2 equiv) to *N*-phenylmaleimide (**4a**) organocatalyzed by **1a** (20 mol%) in toluene as solvent at room temperature, affording succinimide (*S*)-**5aa** almost quantitatively in 67% *ee* (Table 1, entry 1). The (*S*)-absolute configuration of the final adduct **5aa** was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature (see Experimental).

We then explored the effect of differente solvents. Thus, when hexane was used, the enantioselectivity for (*S*)-**5aa** increased up to 73%, whereas the use of ethyl ether as solvent afforded a lower *ee* (Table 1, entries 2 and 3). In addition, when $CH_2Cl_2$ and $CHCl_3$ were employed as solvents, 63% and 75% *ee*'s for (*S*)-**5aa**, respectively, were observed (Table 1, entries 4 and 5).

Unexpectedly, when DMF was used as solvent the enantioselectivity of the process reversed totally, obtaining the opposite succinimide (*R*)-**5aa** in 62% *ee* in high yield, although in a much lower reaction rate (Table 1, entry 6). This change in the enantioselectivity of a reaction promoted by the solvent is very uncommon. When dealing to enantioselective organocatalysis, as in any asymmetric catalysis, opposite enantiomeric products are typically obtained by using opposite enantiomeric organocatalysts. The possibility of obtaining both enantiomers using a single catalyst just by changing the solvent results very promising, as sometimes the use of both enantiomers of the organocatalyst is difficult or very expensive. Examples of changing the enantioselectivity of organocatalyzed reactions simply by changing the reaction solvent are scarce, and limited to the use in particular cases of

some chiral unsupported[28] and supported[29] MacMillan's imidazolidinones or α,α-diphenyl-2-pyrrolidinemethanol[30] organocatalysts, as well as conformationally flexible peptidic[31] and guanidine/bisthiourea species.[32] Therefore, the unusual enantioswitching shown in the present process is interesting, deserving a deeper study.

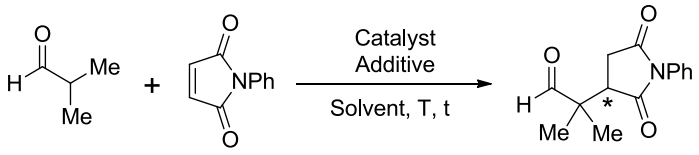
The use of solvents such as 1,4-dioxane or acetone afforded also (*R*)-**5aa** but in lower *ee's* (Table 1, entries 7 and 8). When water was employed as solvent, the reaction rate of the reaction increased considerably, affording (*R*)-**5aa** almost quantitatively, although in only 32% *ee* (Table 1, entry 9). Therefore, combining the highest *ee* and reaction rate, the use of mixtures of DMF/$H_2O$ as reaction solvent was explored. Thus, different DMF/$H_2O$ v/v ratios were assayed (Table 1, entries 10-12), obtaining the best results with the mixture DMF/$H_2O$ (2/1, v/v ratio), which afforded (*R*)-**5aa** in 90% yield and 84% *ee* (Table 1, entry 11).

Once the most appropriate solvents for achieving the highest reversal in the enantioselectivity were established [$CHCl_3$ for (*S*)-**5aa** and DMF/$H_2O$ (2/1, v/v ratio) for (*R*)-**5aa**], the effect of the catalyst loading was studied. Thus, both solvents were used with 10 and 5 mol% organocatalyst loadings (Table 1, entries 13-16), observing the higher enantioselections for the (*S*) and (*R*) stereoisomers when a loading of 10 mol% of **1a** was used [86% *ee* for (*S*)-**5aa** and 84% *ee* for (*R*)-**5aa**] (Table 1, entries 13 and 14). Lowering the reaction temperature down to 0 ºC showed a diminished enantioselectivity for **5aa** (Table 1, entries 17 and 18).



[28] Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. U. S. A.* **2004**, *101*, 5482-5487.
[29] Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Campisciano, V.; Noto, R. *Catal. Commun.* **2011**, *16*, 75-80.
[30] Sunden, H.; Rios, R.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 7865-7869.
[31] Messerer, M.; Wennemers, H. *Synlett* **2011**, 499-502.
[32] Sohtome, Y.; Yamaguchi, T.; Tanaka, S.; Nagasawa, K. *Org. Biomol. Chem.* **2013**, *11*, 2780-2786.

**Table 1**. Screening and optimization of the reaction conditions, and solvent-dependent reversal of the enantioinduction, in the enantioselective Michael addition reaction of isobutyraldehyde to *N*-phenylmaleimide.




**3a** **4a** **5aa**

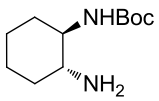
| Entry | Catalyst (mol%) | Additive (mol%)[a] | Solvent | T (ºC) | t (h) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** (20) | - | PhMe | 25 | 20 | 98 | 67 (*S*) |
| 2 | **1a** (20) | - | Hexane | 25 | 14 | 85 | 73 (*S*) |
| 3 | **1a** (20) | - | $Et_2O$ | 25 | 14 | 95 | 32 (*S*) |
| 4 | **1a** (20) | - | $CH_2Cl_2$ | 25 | 20 | 95 | 63 (*S*) |
| 5 | **1a** (20) | - | $CHCl_3$ | 25 | 20 | 99 | 75 (*S*) |
| 6 | **1a** (20) | - | DMF | 25 | 44 | 94 | 62 (*R*) |
| 7 | **1a** (20) | - | Dioxane | 25 | 50 | 85 | 58 (*R*) |
| 8 | **1a** (20) | - | Acetone | 25 | 44 | 92 | 57 (*R*) |
| 9 | **1a** (20) | - | $H_2O$ | 25 | 2 | 97 | 32 (*R*) |
| 10 | **1a** (20) | - | DMF/$H_2O$[d] | 25 | 17 | 94 | 70 (*R*) |
| 11 | **1a** (20) | - | DMF/$H_2O$[e] | 25 | 20 | 90 | 84 (*R*) |
| 12 | **1a** (20) | - | DMF/$H_2O$[f] | 25 | 24 | 88 | 80 (*R*) |
| 13 | **1a** (10) | - | $CHCl_3$ | 25 | 20 | 97 | 86 (*S*) |
| 14 | **1a** (10) | - | DMF/$H_2O$[e] | 25 | 20 | 95 | 84 (*R*) |
| 15 | **1a** (5) | - | $CHCl_3$ | 25 | 40 | 95 | 76 (*S*) |
| 16 | **1a** (5) | - | DMF/$H_2O$[e] | 25 | 40 | 93 | 82 (*R*) |
| 17 | **1a** (10) | - | $CHCl_3$ | 0 | 48 | 94 | 70 (*S*) |
| 18 | **1a** (10) | - | DMF/$H_2O$[e] | 0 | 48 | 91 | 82 (*R*) |
| 19 | **1a** (10) | HDA (10) | $CHCl_3$ | 25 | 22 | 98 | 78 (*S*) |
| 20 | **1a** (10) | HDA (10) | DMF/$H_2O$[e] | 25 | 20 | 86 | 80 (*R*) |
| 21 | **1a** (10) | $PhCO_2H$ (10) | $CHCl_3$ | 25 | 22 | 93 | 78 (*S*) |
| 22 | **1a** (10) | $PhCO_2H$ (10) | DMF/$H_2O$[e] | 25 | 22 | 84 | 80 (*R*) |
| 23 | **1a** (10) | Imidazole (10) | $CHCl_3$ | 25 | 22 | 97 | 78 (*S*) |
| 24 | **1a** (10) | Imidazole (10) | DMF/$H_2O$[e] | 25 | 22 | 90 | 77 (*R*) |
| 25 | **1b** (10) | - | $CHCl_3$ | 25 | 24 | 98 | 81 (*S*) |
| 26 | **1b** (10) | - | DMF/$H_2O$[e] | 25 | 24 | 94 | 78 (*R*) |
| 27 | **1c** (10) | - | $CHCl_3$ | 25 | 48 | 97 | 86 (*S*) |
| 28 | **1c** (10) | - | DMF/$H_2O$[e] | 25 | 48 | 96 | 78 (*R*) |
| 29 | *ent*-**1a** (10) | - | $CHCl_3$ | 25 | 20 | 97 | 84 (*R*) |
| 30 | *ent*-**1a** (10) | - | DMF/$H_2O$[e] | 25 | 20 | 94 | 83 (*S*) |

[a] HDA: Hexanedioic acid. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [d] 1/1 (v/v). [e] 2/1 (v/v). [f] 4/1 (v/v).

The influence of the presence of additives working with both solvents was then explored, using an optimized 10 mol% loading of organocatalyst **1a** and $CHCl_3$ or DMF/$H_2O$ (2/1, v/v ratio) as enantioswitching solvents. Thus, hexanedioic (HDA) or benzoic acids were used as additives but no increasing in the enantioselection for any enantiomer was observed (Table 1, entries 19-22). In addition, imidazole was also used as basic additive but also lower enantioselectivities for both enantiomers of **5aa** were observed (Table 1, entries 23 and 24).

The possibility of achieving this solvent-dependent reversal of the enantioselectivity using chiral *trans*-cyclohexa-1,2-diamines monoprotected with other carbamates as organocatalysts was then explored. Thus, when **1b** was used as organocatalyst, enantioselectivity values of 81% for (*S*)-**5aa** and 78% for (*R*)-**5aa** were obtained (Table 1, entries 25 and 26). In addition, the use of **1c** as organocatalyst afforded a similar enantioselectivity for (*S*)-**5aa** than when using **1a** but in a much longer reaction time, whereas a lower enantioselection for (*R*)-**5aa** was observed (Table 1, entries 27 and 28).

Attempting to achieve opposite enantioselections to those obtained using organocatalyst **1a**, its enantiomer *ent*-**1a** was obtained following an identical procedure but starting from (1*R*,2*R*)-cyclohexa-1,2-diamine. Using this organocatalyst under the most convenient reaction conditions [10 mol% organocatalyst loading, $CHCl_3$ or DMF/$H_2O$ (2/1, v/v ratio) as solvents, 25 ºC], the expected opposite enantioselections were observed [(*R*)-**5aa** using $CHCl_3$ as solvent and (*S*)-**5aa** using DMF/$H_2O$ (2/1, v/v ratio)] (Table 1, entries 29 and 30).




*ent*-**1a**

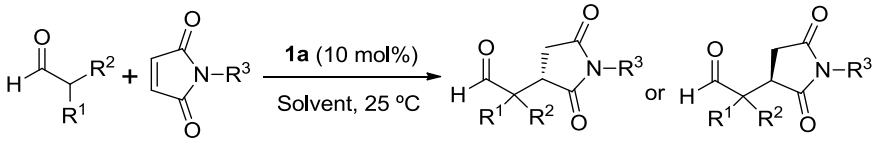
In order to rule out that the change in the enantioselectivity could be a consequence of a former evolution of the initially formed product, the succinimide (*R*)-**5aa** obtained in 84% *ee* (Table 2, entry 2) was stirred in the presence of organocatalyst **1a** (10 mol%), in $CHCl_3$ as solvent at room temperature. After 20 h, the initial succinimide (*R*)-**5aa** was recovered unaltered. In addition, the model reaction of aldehyde **3a** and maleimide **4a**, in the presence of the organocatalyst **1a** (10 mol%) in DMF/$H_2O$ (2/1, v/v ratio), was carried out during 4, 8, and 12 h, the enantioselectivity for (*R*)-**5aa** being kept in 84%.

### *3.2.2. Scope of the Reaction*

Once the most effective organocatalyst and reaction conditions [**1a** (10 mol%), $CHCl_3$ for (*S*)-enantiomer and DMF/$H_2O$ (2/1, v/v ratio) for (*R*)-enantiomer, 25 ºC] were established, the extension of this organocatalytic solvent-dependent methodology to other aldehydes and maleimides was explored (Table 2). As in the case of the model reaction, the absolute configuration of the known resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

Thus, when $CHCl_3$ was used as solvent, isobutyraldehyde (**3a**) reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro atom at the 3- and 4-position (**4b** and 4**c**) or a bromo atom at the 4-position (**4d**), and the succinimides (*S*)-**5ab**, (*S*)-**5ac** and (*S*)-**5ad** were obtained in 38, 60 and 70% *ee*, respectively (Table 2, entries 3, 5 and 7). However, when DMF/$H_2O$ (2/1, v/v ratio) was the reaction solvent, adducts (*R*)-**5ab**, (*R*)-**5ac** and (*R*)-**5ad** were isolated in 76, 74 and 70% *ee* (Table 2, entries 4, 6 and 8). In addition, when an acetyl or a methoxy group was present onto the phenyl ring of the maleimide, as in the case of **4e** and **4f**, the enantioselectivities for the corresponding enantiomeric succinimides (*S*)-**5ae**/(*R*)-**5ae** and (*S*)-**5af**/(*R*)-**5af** were 76/74% and 40/80%, respectively, depending on the use of $CHCl_3$ or DMF/$H_2O$ (2/1, v/v ratio) as solvents (Table 2, entries 9-12).

**Table 2**. Solvent-dependent reversal of the enantioinduction in the Michael addition of aldehydes to maleimides organocatalyzed by **1a**.




**3** **4** (*S*)-**5** (*R*)-**5**

| Entry | Aldehyde | | Maleimide | | Solvent | t (h) | Succinimide | | |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$, $R^2$ | No. | $R^3$ | No. | | | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Me, Me | **3a** | Ph | **4a** | $CHCl_3$ | 20 | (*S*)-**5aa** | 97 | 86 |
| 2 | | | | | DMF/$H_2O$[c] | 20 | (*R*)-**5aa** | 95 | 84 |
| 3 | Me, Me | **3a** | 3-$ClC_6H_4$ | **4b** | $CHCl_3$ | 30 | (*S*)-**5ab** | 99 | 38 |
| 4 | | | | | DMF/$H_2O$[c] | 30 | (*R*)-**5ab** | 96 | 76 |
| 5 | Me, Me | **3a** | 4-$ClC_6H_4$ | **4c** | $CHCl_3$ | 30 | (*S*)-**5ac** | 99 | 60 |
| 6 | | | | | DMF/$H_2O$[c] | 30 | (*R*)-**5ac** | 97 | 74 |
| 7 | Me, Me | **3a** | 4-$BrC_6H_4$ | **4d** | $CHCl_3$ | 30 | (*S*)-**5ad** | 99 | 70 |
| 8 | | | | | DMF/$H_2O$[c] | 30 | (*R*)-**5ad** | 98 | 70 |
| 9 | Me, Me | **3a** | 4-$AcC_6H_4$ | **4e** | $CHCl_3$ | 32 | (*S*)-**5ae** | 90 | 76 |
| 10 | | | | | DMF/$H_2O$[c] | 32 | (*R*)-**5ae** | 92 | 74 |
| 11 | Me, Me | **3a** | 2-$MeOC_6H_4$ | **4f** | $CHCl_3$ | 26 | (*S*)-**5af** | 92 | 40 |
| 12 | | | | | DMF/$H_2O$[c] | 26 | (*R*)-**5af** | 15 | 80 |
| 13 | Me, Me | **3a** | Bn | **4g** | $CHCl_3$ | 22 | (*S*)-**5ag** | 93 | 30 |
| 14 | | | | | DMF/$H_2O$[c] | 22 | (*R*)-**5ag** | 90 | 72 |
| 15 | Me, Me | **3a** | Me | **4h** | $CHCl_3$ | 21 | (*S*)-**5ah** | 94 | 53 |
| 16 | | | | | DMF/$H_2O$[c] | 21 | (*R*)-**5ah** | 91 | 68 |
| 17 | Me, Me | **3a** | H | **4i** | $CHCl_3$ | 17 | (*S*)-**5ai** | 94 | 50 |
| 18 | | | | | DMF/$H_2O$[c] | 17 | (*R*)-**5ai** | 88 | 70 |
| 19 | Et, Et | **3b** | Ph | **4a** | $CHCl_3$ | 48 | (*S*)-**5ba** | 70 | 55 |
| 20 | | | | | DMF/$H_2O$[c] | 48 | (*R*)-**5ba** | 93 | 68 |
| 21 | -$(CH_2)_4$- | **3c** | Ph | **4a** | $CHCl_3$ | 30 | (*S*)-**5ca** | 99 | 49 |
| 22 | | | | | DMF/$H_2O$[c] | 30 | (*R*)-**5ca** | 96 | 61 |
| 23 | -$(CH_2)_5$- | **3d** | Ph | **4a** | $CHCl_3$ | 48 | (*S*)-**5da** | 96 | 14 |
| 24 | | | | | DMF/$H_2O$[c] | 48 | (*R*)-**5da** | 96 | 35 |
| 25 | Me, H | **3e** | Ph | **4a** | $CHCl_3$ | 23 | (*S*,*S*)/(*R*,*S*)-**5ea** | 95[d] | 36/28 |
| 26 | | | | | DMF/$H_2O$[c] | 23 | (*R*,*R*)/(*S*,*R*)-**5ea** | 96[e] | 76/73 |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] 2/1 (v/v). [d] Mixture of diastereomers 1.4/1 determined by $^1$H NMR (300 MHz) on the reaction crude. [e] Mixture of diastereomers 1.2/1 determined by $^1$H NMR (300 MHz) on the reaction crude.

Non-*N*-arylated maleimides were also used for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide (**4g**) afforded the enantiomeric succinimides (*S*)-**5ag** and (*R*)-**5ag** in high yields and in 30 and 72% *ee*, depending on the solvent used (Table 2, entries 13 and 14). Similarly, *N*-methylmaleimide (**4h**) gave the (*S*)- and (*R*)-enantiomer of adduct **5ah** when $CHCl_3$ and DMF/$H_2O$ (2/1, v/v ratio) were the reaction solvents (53 and 68% *ee*, respectively) (Table 2, entries 15 and 16). In addition, the simple maleimide (**4i**) was also used as Michael acceptor, affording (*S*)-**5ai** (50% *ee*) using $CHCl_3$ as solvent, and (*R*)-**5ai** (70% *ee*) when the solvent was DMF/$H_2O$ (2/1, v/v ratio) (Table 2, entries 17 and 18).

Other α,α-disubstituted aldehydes were employed for this enantioswitched organocatalyzed Michael addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal (**3b**) afforded succinimides (*S*)-**5ba** (55% *ee*) and (*R*)-**5ba** (68% *ee*) using $CHCl_3$ and DMF/$H_2O$ (2/1, v/v ratio) as solvents, respectively (Table 2, entries 19 and 20). In addition, cyclopentane- (**3c**) and cyclohexanecarbaldehyde (**3d**) gave almost quantitative amounts of succinimides (*S*)-**5ca** and (*S*)-**5da** in 49 and 14% *ee*, respectively, when $CHCl_3$ was the reaction solvent, whereas (*R*)-**5ca** and (*R*)-**5da** in 61 and 35% *ee*, respectively, were isolated using DMF/$H_2O$ (2/1, v/v ratio) as solvent (Table 2, entries 21-24). Moreover, the use of an α-monosubstituted aldehyde such as propanal (**3e**) in the two solvents, allowed obtaining the Michael adducts (*R*,*S*)/(*S*,*S*)-**5ea** and (*S*,*R*)/(*R*,*R*)-**5ea**, respectively, as mixtures of diastereomers, with enantioselections up to 36 and 76%, respectively, for the major isomer [Table 2, entries 25 and 26, see footnotes d) and e)].

### *3.2.3. Theoretical Calculations*

In order to get further insight into the origin of this solvent-dependent enantioselectivity reversal, theoretical calculations of the reaction of the *N*-phenylmaleimide (**4a**) and isobutyraldehyde (**3a**) in the presence of the primary-amine catalyst **1a** were carried out. Different computational conditions were envisioned, in the gas phase, in implicit solvents (water and chloroform), and also in the presence of a discrete number of explicit water molecules, in an attempt to reproduce the experimental conditions as closely as possible, since the results are highly dependent on the reaction medium (see Experimental). Preliminary studies showed that, as expected, the initial formation of an enamine between catalyst and aldehyde is followed by the nucleophilic attack on the maleimide, according to Seebach's synclinal model (*endo* attack, Figure 1).[33] A key feature of this model is that the reacting face of the enamine diastereoselectively attacks only one of the faces of the maleimide. Thus, the lower face of the enamine (from our point of view in Figure 1) is reacting with the *Re* face of the maleimide, and the upper face of the enamine must react with *Si* face of the maleimide. It means that each face of the enamine produces only one of the final enantiomeric products. This fact is crucial to understand the following discussion, which can be based solely on the reacting face of the enamine. Meanwhile, the *exo* approaches, like the one involving the lower face of the enamine and the *Si* face of the maleimide (Figure 1), are much higher in energy, and can be safely discarded.

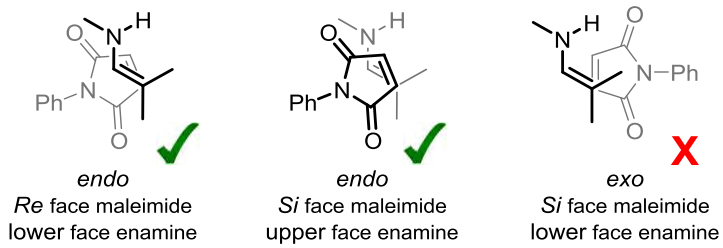



**Figure 1.** Faces of enamine and maleimide reacting through Seebach´s synclinal model.

[33] (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413-1423; (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162-172.

The initial optimizations of the enamine structures showed that in the most stable conformations (**A** and **B**, Figure 2), the NHBoc and the enamine groups are in equatorial positions of the cyclohexane ring. In both cases, the NH moiety of the NHBoc carbamate is pointing *down* from our view. The two conformations differ in the orientations that the NH enamine group can present, pointing *up* (conformation **A**) or *down* (conformation **B**, Figure 2) from the plane of the cyclohexane ring (Figure 2). According to this picture, the fragment NH-C-C-NH shows the two NH groups in *anti* (**A**) or *syn* (**B**) relative orientations. The optimization of these structures showed that they are very similar in energy, and both must be taken into account for the transition structure search. In fact, structure **B** is slightly more stable than **A** in $CHCl_3$ (1.0 kcal/mol difference), whilst they afford the same energy in water, meaning that **A** is slightly better solvated by water than by chloroform. Although with caution, we took these data as a first indication of the solvent dependence of the conformational distribution of the initial structures. We thought that this effect could be more dramatic during the transition states of the reaction, which are supposed to be quite polar, due to the significant charge transfer that takes place from the enamine to the maleimide.

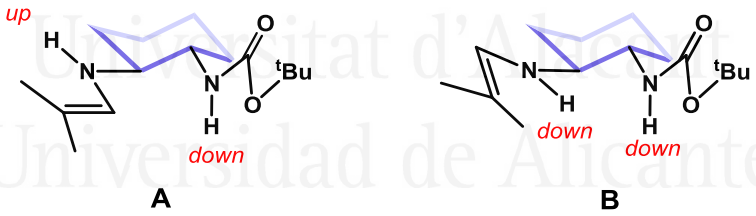



**Figure 2.** Most stable conformations of the reacting enamine.

This hypothesis in light of the computed transition state activation energies was confirmed. In conformation **A**, the maleimide could hypothetically approach the two faces of the enamine, as shown in Figure 3. If the attack takes place from the left side of the enamine, the reaction occurs through **TS-A$_R$** (*Si* face of maleimide, *R* product), whereas the approach of the maleimide from the right side of the enamine (hypothetical **TS-A$_S$**) is strongly disfavored due to steric repulsion with the large Boc group, which is blocking that face. We could not actually find any transition

state for that approach without severely distorting the structure. Noteworthy, **TS-A$_R$** shows a very polar structure, with a high negative charge developing in the maleimide/oxygen atom. Consequently, the polarity of the reaction medium must have a great influence on the activation barrier of the process. Thus, it was not surprising to find that the lowest free energy for **TS-A$_R$** corresponds to the structure computed in a water model ($\Delta G^{\ddagger}$ = 14.8 kcal/mol),[34] whilst chloroform and gas phase models present higher values ($\Delta G^{\ddagger}$ = 18.7 kcal/mol and 20.7 kcal/mol respectively). Interestingly, **TS-A$_R$** leads to the formation of the *R* enantiomer, which is experimentally obtained in the polar aqueous media.

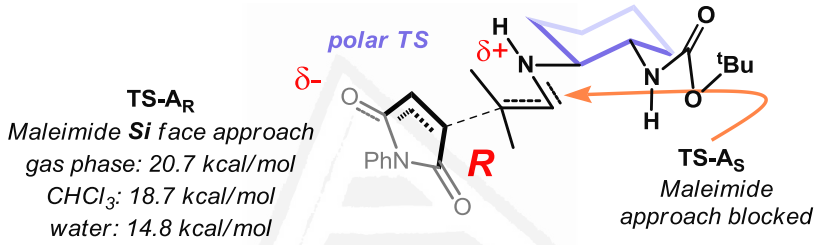



**Figure 3.** Computed activation energies for the transition state **TS-A$_R$** (corresponding to conformation **A** in Fig. 2) in the gas phase, chloroform and water models.

On the other hand, two transition states were located for conformation **B**, following the two possible approaching trajectories (**TS-B$_S$** and **TS-B$_R$**, Figure 4). In **TS-B$_S$**, the *Re* face of the maleimide is attacked by the lower face (from our view) of the enamine, whereas in **TS-B$_R$**, the *Si* face of the maleimide approaches the upper face of the enamine. Noteworthy, in **TS-B$_S$**, the maleimide/oxygen and the NHBoc group are close enough to form an intermolecular hydrogen bond, which stabilizes the developing negative charge in the maleimide/oxygen atom, producing a structure that is much less polar than **TS-A$_R$**, and therefore, less sensitive to the surrounding solvent molecules. This effect can be observed in the computed energies for **TS-B$_S$**,

[34] Energies in water shown in Figures 3 and 4 were obtained using a water model system, in the presence of one explicit molecule of water. When an implicit water model was used, the computed energies showed a similar trend, **TS-A$_R$**: 15.8 kcal/mol, **TS-B$_S$**: 16.9 kcal/mol, **TS-B$_R$**: 16.9 kcal/mol.

which do not show significant differences between the different solvent models or even in the gas phase (**TS-B$_S$**-*water* 17.7,[34] **TS-B$_S$**-*chloroform* 16.0, **TS-B$_S$**-*gas phase* 15.8 kcal/mol, Figure 4).

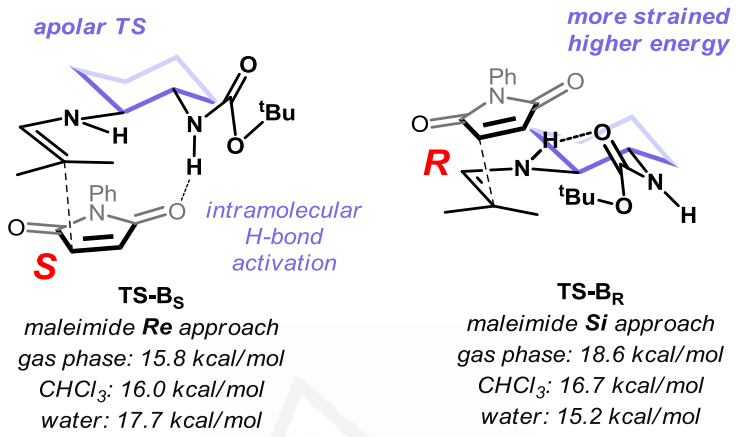



**Figure 4.** Representations and energies of the transition states **TS-B$_S$** and **TS-B$_R$**, corresponding to conformation **B** in Fig. 2.

Meanwhile, if the maleimide approaches the upper face of the enamine in conformation **B**, this leads to transition state **TS-B$_R$** (Figure 4). In a similar way as **TS-A$_R$**, the new transition structure is quite polar, and the maleimide/oxygen is better stabilized in the presence of surrounding solvent molecules. Thus, its lowest energy was measured in water (15.2 kcal/mol),[34] although this value is higher than the one corresponding to **TS-A$_R$** (14.8 kcal/mol, Figure 3). This increase in the energy is probably due to the higher internal strain that the structure presents as the result of a weak hydrogen bond formed between the enamine NH and the carbamate oxygen atom, which does not participate in the activation of the maleimide.

In summary, the most significant computational data are that the lowest calculated activation energy in water corresponds to **TS-A$_R$** (14.8 kcal/mol), a polar structure lacking intramolecular hydrogen bonds, where the surrounding water molecules are responsible for intermolecular hydrogen-bonding activation of the maleimide (Figure 5). **TS-A$_R$** produces the *R* enantiomer of the product, in agreement with the experimental results in the polar aqueous DMF medium (Table 1). Also, the lowest calculated activation energy in chloroform is **TS-B$_S$** (16.0

kcal/mol), a transition structure containing an intramolecular hydrogen bond between the maleimide and the NHBoc group (Figure 5). This transition state leads to the formation of the *S* enantiomer, which is once again, in agreement with the experimental data in chloroform (Table 1). Furthermore, these results agree with chemical common sense, that intramolecular hydrogen bonds are more significant in apolar solvents, whereas intermolecular hydrogen bonds with surrounding water molecules are present in aqueous systems.

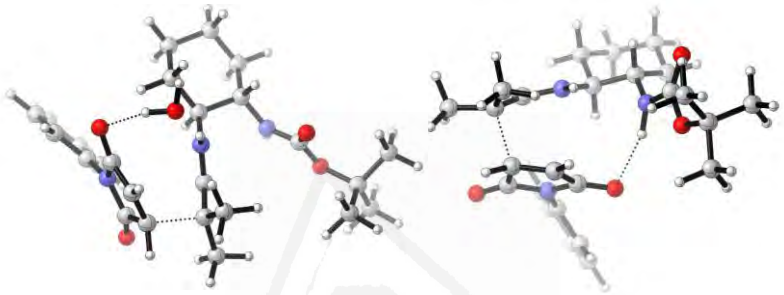



**Figure 5.** 3-D representations and energies of the transition states **TS-A$_R$**-*water* and **TS-B$_S$**-*chloroform*.

## 3.3. Enantioselective Michael Addition of Aldehydes to Maleimides in Deep Eutectic Solvents

As it was mentioned previously (General Introduction), DESs are non-volatile solvents, that shown a low ecological footprint, attractive price and easy recyclability. For these reasons, we decided to perform the former enantioselective Michael addition reaction of aldehydes to maleimides in these solvents, studying the recyclability of the catalyst and the reaction media.

### *3.3.1. Optimization Studies*

The Deep Eutectic Solvents (DES) used in this study were obtained by heating a mixture of the indicated two components with the specified molar ratio under an argon atmosphere (see Experimental).

The search for the most appropriate reaction conditions using DESs (Table 3) began with the model Michael addition reaction of isobutyraldehyde (**3a**, 2 equiv) to *N*-phenylmaleimide (**4a**), organocatalyzed by **1a** (10 mol%), in the DES formed by choline chloride and urea (ChCl/urea, 1/2 molar ratio, see Experimental) at room temperature. This reaction gave rise to a 90% yield of succinimide (*R*)-**5aa** after 24 h but in only a 36% *ee* (Table 3, entry 1). When the urea component of the DES was changed by glycerol (ChCl/Gly, 1/2 molar ratio), a higher *ee* for (*R*)-**5aa** was obtained (52%, Table 3, entry 2), which resulted even higher using ethylene glycol (ChCl/ethylene glycol, 1/2 molar ratio) (64% Table 3, entry 3), or resorcinol (ChCl/resorcinol, 1/1 molar ratio) (67%, Table 3, entry 4).

When the employed DES was the combination of tetra-*n*-butylammonium bromide (TBAB) and Gly (TBAB/Gly, 1/3 molar ratio), (*R*)-**5aa** was obtained in 85% yield and 66% *ee* (Table 3, entry 5). However, the best results were obtained using as DES the combination $Ph_3MePBr$/Gly (1/2 molar ratio), which afforded the final adduct in 96% yield and 72% *ee* (Table 3, entry 6). Thus, this last DES was used in the rest of the study.

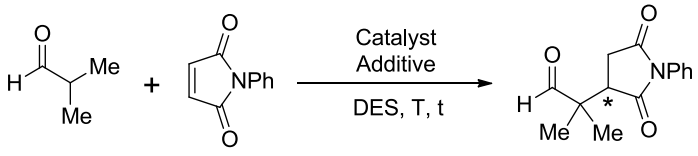
The influence of the presence of additives in both solvents was then explored. Thus, when hexanedioic acid (HDA) was added (10 mol%) to the reaction mixture, the reaction rate increased noticeably, as well as the enantioselection of the reaction, (*R*)-**5aa** being obtained in a 95% yield in only 8 h with an excellent 92% *ee* (Table 3, entry 7). The presence of other diacids, such as oxalic or phthalic acid, as additives gave much lower yields and enantioselectivities (Table 3, entries 8 and 9). When benzoic acid was added as additive, the reaction yield again was high and the enantioselection reached 86% (Table 3, entry 10). However, the addition of 3,4-dimethoxybenzoic acid allowed to achieve the best results, affording adduct (*R*)-**5aa** in a 94% *ee* and 97% isolated yield (Table 3, entry 11). This enantioselection results remarkable, as values only up to 86% were observed when using conventional solvents (see Chapter I, Table 1, entry 13). The presence of a strong electron-withdrawing group in the aromatic ring of the acid additive, as in the case of 4-nitrobenzoic acid gave a slightly lower enantioselectivity (Table 3, entry 12). The addition of bases such as imidazole or 4-*N,N*-dimethylaminopyridine (DMAP), gave good yields, but low enantioselectivities (Table 3, entries 13 and 14).

The synergistic role played by the acidic additive, when combined with the organocatalyst, in speeding up the reaction and in increasing both the yield and the *ee* results interesting. Perhaps under these conditions a chiral hydrogen bonded chelated cluster with maleimide may be playing a role in exalting its electrophilic character, thereby facilitating the nucleophilic attack by the aldehyde. It is interesting to observe that no reversal of the enantioselectivity was observed in any case.

Once the most convenient DES ($Ph_3MePBr$/Gly, 1/2 molar ratio) and additive [(3,4-$(MeO)_2C_6H_3CO_2H$, 10 mol%)] were established, the effect of the catalyst loading was studied. Increasing the loading of **1a** up to 20 mol% showed almost no influence in yield or enantioselectivity for adduct (*R*)-**5aa**, whereas diminishing it down to 5 mol% gave rise to a lower yield and *ee* in a much longer reaction time (Table 3, entries 15 and 16). In addition, lowering the reaction

temperature down to 10 ºC resulted in a very slow reaction rate and an enantioselection of only 66% (Table 3, entry 17).

**Table 3**. Screening and optimization of the reaction conditions for the enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide.




**3a** **4a** **5aa**

| Entry | Catalyst (mol%) | Additive (mol%) | DES (molar ratio)[a] | T (ºC) | t (h) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** (10) | | ChCl/urea (1/2) | 25 | 24 | 90 | 36 (*R*) |
| 2 | **1a** (10) | | ChCl/Gly (1/2) | 25 | 24 | 94 | 51 (*R*) |
| 3 | **1a** (10) | | ChCl/ethylene glycol (1/2) | 25 | 24 | 46 | 64 (*R*) |
| 4 | **1a** (10) | | ChCl/resorcinol (1/1) | 25 | 24 | 72 | 67 (*R*) |
| 5 | **1a** (10) | | TBAB/Gly (1/3) | 25 | 24 | 85 | 66 (*R*) |
| 6 | **1a** (10) | | $Ph_3MePBr$/Gly (1/2) | 25 | 24 | 96 | 72 (*R*) |
| 7 | **1a** (10) | HDA (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 92 (*R*) |
| 8 | **1a** (10) | Oxalic acid (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 28 | 72 (*R*) |
| 9 | **1a** (10) | Phthalic acid (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 58 | 72 (*R*) |
| 10 | **1a** (10) | $PhCO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 96 | 86 (*R*) |
| 11 | **1a** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 97 | 94 (*R*) |
| 12 | **1a** (10) | 4-$O_2NC_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 90 (*R*) |
| 13 | **1a** (10) | Imidazole (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 66 (*R*) |
| 14 | **1a** (10) | DMAP (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 90 | 50 (*R*) |
| 15 | **1a** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ (20) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 92 (*R*) |
| 16 | **1a** (5) | 3,4-$(MeO)_2C_6H_3CO_2H$ (5) | $Ph_3MePBr$/Gly (1/2) | 25 | 24 | 89 | 86 (*R*) |
| 17 | **1a** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 10 | 8 | 10 | 66 (*R*) |
| 18 | **1b** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 88 (*R*) |
| 19 | **1c** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 93 | 90 (*R*) |
| 20 | *ent*-**1a** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 94 (*S*) |

[a] Abbreviations: ChCl = choline chloride; DMAP = 4-*N,N*-dimethylaminopyridine; Gly = glycerol; HDA = hexanedioic acid; TBAB = tetra-*n*-butylammonium bromide. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude.

With the most appropriate catalyst loading, additive, DES and reaction temperature determined [10 mol% catalyst loading, (3,4-$(MeO)_2C_6H_3CO_2H$ (10 mol%), $Ph_3MePBr$/Gly (1/2 molar ratio), 25 ºC], other carbamates as organocatalysts were then explored. Thus, when **1b** and **1c**, were used as

organocatalyst, their performance in the model reaction was not superior to **1a**, affording adduct (*R*)-**5aa** in good yields, but with lower enantioselectivities (Table 3, entries 18 and 19).

In order to achieve opposite enantioselectivities to those obtained using organocatalyst **1a**, its enantiomer *ent*-**1a** was employed under the optimal conditions [catalyst loading (10 mol%), 3,4-$(MeO)_2C_6H_3CO_2H$ (10 mol%), $Ph_3MePBr$/Gly (1/2 molar ratio), 25 ºC]. Using this organocatalyst, the expected enantiomeric adduct (*S*)-**5aa** was obtained in identical absolute value of opposite enantioselectivity than when using **1a** (Table 3, entry 20).

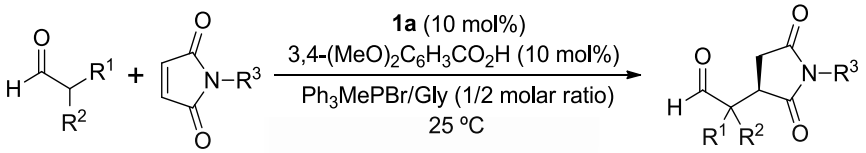
### *3.3.2. Scope of the Reaction*

Once the most effective organocatalyst and reaction conditions were established [**1a** (10 mol%), 3,4-$(MeO)_2C_6H_3CO_2H$ (10 mol%), $Ph_3MePBr$/Gly (1/2 molar ratio), 25 ºC], the extension of this methodology using DESs to other aldehydes and maleimides was explored (Table 4). As in the case of the model reaction, the absolute configuration of the known resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

Thus, when isobutyraldehyde (**3a**) reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 3- or 4-positions (**4b**, **4c** and **4d**), the corresponding succinimides (*R*)-**5ab**, (*R*)-**5ac** and (*R*)-**5ac** were obtained in very high yields in 70, 87 and 86% *ee*, respectively (Table 4, entries 2-4). In addition, when an acyl group was present onto the phenyl ring of the maleimide, as in the case of **4e**, the enantioselectivity for the corresponding succinimide (*R*)-**5ae** was 72% *ee* in a slightly lower yield (Table 4, entry 5). A similar enantioselectivity for (*R*)-**5af** was observed when an electron-releasing group, such as a methoxy, was present at the 2-position (**4f**) (Table 4, entry 6)

Non-*N*-arylated maleimides were also employed for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide (**4g**) and *N*-methylmaleimide (**4h**) gave succinimides (*R*)-**5ag** and (*R*)-**5ah** in high yields but in moderate 63 and 66% *ee*, respectively (Table 4, entries 7 and 8). In addition, the simple maleimide (**4i**) was also used as Michael acceptor, affording (*R*)-**5ai** in 90% yield and 67% *ee* (Table 4, entry 9).

**Table 4**. Enantioselective Michael addition of aldehydes to maleimides organocatalyzed by **1a** in DES.




**3** **4** (*R*)-**5**

| Entry | Aldehyde | | Maleimide | | t (h) | Succinimide | | |
|---|---|---|---|---|---|---|---|---|
| | $R^1$, $R^2$ | No. | $R^3$ | No. | | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Me, Me | **3a** | Ph | **4a** | 8 | (*R*)-**5aa** | 97 | 94 |
| 2 | Me, Me | **3a** | 3-$ClC_6H_4$ | **4b** | 8 | (*R*)-**5ab** | 95 | 70 |
| 3 | Me, Me | **3a** | 4-$ClC_6H_4$ | **4c** | 8 | (*R*)-**5ac** | 96 | 87 |
| 4 | Me, Me | **3a** | 4-$BrC_6H_4$ | **4d** | 8 | (*R*)-**5ad** | 95 | 86 |
| 5 | Me, Me | **3a** | 4-$AcC_6H_4$ | **4e** | 8 | (*R*)-**5ae** | 90 | 72 |
| 6 | Me, Me | **3a** | 2-$MeOC_6H_4$ | **4f** | 8 | (*R*)-**5af** | 93 | 70 |
| 7 | Me, Me | **3a** | Bn | **4g** | 8 | (*R*)-**5ag** | 91 | 63 |
| 8 | Me, Me | **3a** | Me | **4h** | 8 | (*R*)-**5ah** | 94 | 66 |
| 9 | Me, Me | **3a** | H | **4i** | 8 | (*R*)-**5ai** | 90 | 67 |
| 10 | Et, Et | **3b** | Ph | **4a** | 12 | (*R*)-**5ba** | 60 | 43 |
| 11 | -$(CH_2)_4$- | **3c** | Ph | **4a** | 8 | (*R*)-**5ca** | 96 | 87 |
| 12 | -$(CH_2)_5$- | **3d** | Ph | **4a** | 10 | (*R*)-**5da** | 93 | 31 |
| 13 | Me, H | **3e** | Ph | **4a** | 16 | (*R,R*)/(*S,R*)-**5ea** | 90[c] | 50/50 |
| 14 | Me, Ph | **3f** | Ph | **4a** | 20 | (*S,R*)/(*R,R*)-**5fa** | 87[d] | 85/10 |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] Mixture of diastereomers 1.4/1 determined by $^1$H NMR (300 MHz) on the reaction crude. [d] Mixture of diastereomers 4/1 determined by $^1$H NMR (300 MHz) on the reaction crude.

Other α,α-disubstituted aldehydes were employed for the organocatalyzed conjugate addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal (**3b**) afforded succinimide (*R*)-**5ba** in moderate yield and enantioselectivity (Table 4, entry 10). However, cyclopentanecarbaldehyde (**3c**) gave almost a quantitative yield of (*R*)-**5ca** in 87% *ee* (Table 4, entry 11), something very different than when using

cyclohexanecarbaldehyde (**3d**), which afforded the corresponding adduct (*R*)-**5da** with an enantioselection of only 31% (Table 4, entry 12). Moreover, the use of an α-monosubstituted aldehyde such as propanal (**3e**), allowed obtaining the adducts as a 1.4/1 mixture of diastereomers, with enantioselections of 50% for (*R*,*R*)- and (*S*,*R*)-**5ea** (Table 4, entry 13). Furthermore, when a differently α,α-disubstituted aldehyde such as 2-phenylpropanal (**3f**) was employed, the final adduct was obtained in a 4/1 diastereomeric ratio with an enantioselection of 85% for the diastereomer (*S*,*R*)-**5fa** and 10% for (*R*,*R*)-**5fa** (Table 4, entry 14).

### *3.3.3. Recycle Experiments*

The possibility of reusing the DES is the cornerstone of a synthetic methodology performed using these neoteric solvents. Therefore, the reusability of the DES, and the catalytic system, carrying out different reaction cycles of the model conjugate addition reaction between isobutyraldehyde (**3a**) and *N*-phenylmaleimide (**4a**) performed under the best reaction conditions depicted in Table 3, entry 1, was explored. Thus, once the reaction was finished, a 4/1 v/v mixture of ethyl ether/*n*-hexane was added and the resulting mixture was stirred vigorously. After the two layers settled down, the upper one, containing the final adduct (*R*)-**5aa**, was separated. Attempting to directly reuse the lower DES layer in other reaction by adding new aldehyde and maleimide resulted in low yields and just moderate enantioselectivities of the resulting adduct. This was explained after observing the presence of acid additive in the recovered organic layer (NMR).



After several attempts, it was found that refreshing the catalytic system by addition of new additive (but no new chiral organocatalyst) to the recovered DES allowed obtaining almost identical enantioselectivity and yield of (*R*)-**5aa** than when used for the first time. Following this recovery procedure, the DES (containing the organocatalyst **1a**) was suitable to be reused in other three runs without diminishing its enantioinduction (Figure 6). However, a fourth run gave rise to a lowering in the catalytic activity.

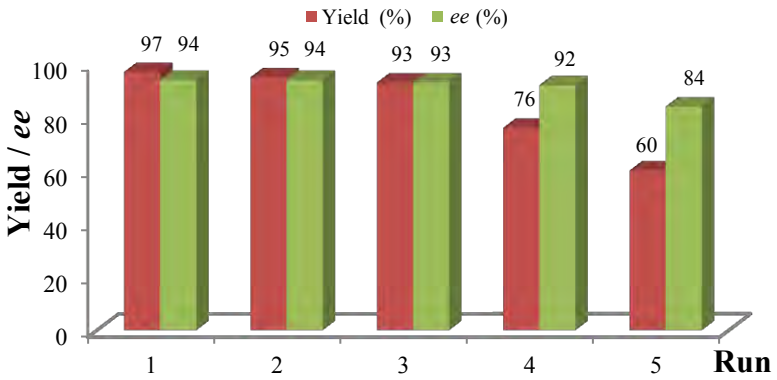



**Figure 6**. Results for the recycle experiments.

## 3.4. Enantioselective Michael Addition of Ketones to Maleimides

### *3.4.1. Optimization Studies*

As formerly, our study began with the search for the most appropriate reaction conditions (Table 5). Thus, the model Michael addition reaction of acetone (**6**, 5 equiv) to *N*-phenylmaleimide (**4a**), organocatalyzed by **1a** (20 mol%), in toluene as solvent at room temperature was carried out, affording succinimide (*S*)-**7a** almost quantitatively after 2 days reaction time, but in only 17% *ee* (Table 5, entry 1). The (*S*)-absolute configuration of the final adduct **7a** was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature (see Experimental).

Primary-amine carbamates **1b** and **1c** were also used as organocatalysts under these reaction conditions. Thus, using **1b** as organocatalysts, succinimide (*S*)-**7a** was obtained almost quantitatively, but as a racemate (Table 5, entry 2). In addition, when **1c** was employed as organocatalyst, a similar enantioselectivity was obtained than in the case of **1a**, but the yield was lowered down to 47% (Table 5, entry 3). Therefore, **1a** was chosen as organocatalyst for the rest of the study.

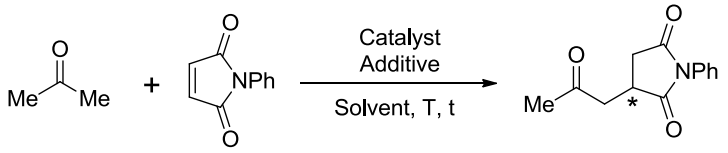
Next, the use of others solvents was explored. Thus, when using hexane or ether the enantioselectivity for (*S*)-**7a** was increased to 39 and 43% *ee*, respectively, (Table 5, entries 4 and 5). In addition, when $CH_2Cl_2$ and $CHCl_3$ were employed as solvents, the yields and enantioselectivities for (*S*)-**7a** were lowered down (Table 5, entries 6 and 7). Moreover, the use of DMF as solvent afforded (*S*)-**7a** in only 25 % yield but with a 70% *ee* (Table 5, entry 8), whereas, the use of a protic solvent such as water could not afford succinimide (*S*)-**7a** (Table 5, entry 9). Furthermore, the use of a DMF/water mixture (2/1, v/v ratio), a solvent that proved beneficial for the Michael addition reaction of aldehydes to maleimides (see Chapter I, Table 1, entry 11), gave no reaction (Table 5, entry 10). Therefore, DMF was chosen as solvent for the rest of the study.

The effect of the addition of some additives to the reaction was then explored. Thus, the addition of the basic imidazole (20 mol%), improved slightly the yield but the enantioselection was lowered down to 60% *ee* (Table 5, entry 11). The addition of HDA gave similar results in yield and enantioselectivity compared to when no additive was used (Table 5, entry 12), and the addition of benzoic acid (20 mol%) reduced the enantioselectivity of (*S*)-**7a**, but both reaction rate and chemical yield increased considerably (Table 5, entry 13). The presence of electron-withdrawing groups on the aromatic ring of the acid additive, such as 4-nitro, or electron-releasing groups, such as methoxy, did not improve the enantioselectivity for succinimide (*S*)-**7a** (Table 5, entries 14 and 15). Observing these results, benzoic acid was chosen as the most effective additive, considering the obtained high yield.



Keeping the most effective reaction conditions [**1a** (20 mol%), benzoic acid (20 mol%), DMF, 25 ºC], other parameters were changed. The organocatalyst loading was reduced to 10 mol%, but the yield diminished to 70% (Table 5, entry 16). The amount of acetone **6** could be lowered to 2 equiv, maintaining both yield and enantioselectivity (Table 5, entry 17).

**Table 5**. Screening and optimization of the reaction conditions for the enantioselective Michael addition reaction of acetone to *N*-phenylmaleimide.




**6** **4a** **7a**

| Entry | Catalyst (mol%) | Additive (mol%) | Solvent | T (ºC) | t (h) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** (20) | - | PhMe | 25 | 48 | 99 | 17 (*S*) |
| 2 | **1b** (20) | - | PhMe | 25 | 48 | 99 | 0 |
| 3 | **1c** (20) | - | PhMe | 25 | 48 | 50 | 20 (*S*) |
| 4 | **1a** (20) | - | Hexane | 25 | 48 | 94 | 39 (*S*) |
| 5 | **1a** (20) | - | $Et_2O$ | 25 | 48 | 90 | 43 (*S*) |
| 6 | **1a** (20) | - | $CH_2Cl_2$ | 25 | 48 | 30 | 26 (*S*) |
| 7 | **1a** (20) | - | $CHCl_3$ | 25 | 48 | 36 | 29 (*S*) |
| 8 | **1a** (20) | - | DMF | 25 | 48 | 25 | 70 (*S*) |
| 9 | **1a** (20) | - | $H_2O$ | 25 | 48 | n.r. | n.d. |
| 10 | **1a** (20) | - | DMF/$H_2O$[c] | 25 | 48 | n.r. | n.d. |
| 11 | **1a** (20) | Imidazole (20) | DMF | 25 | 48 | 40 | 60 (*S*) |
| 12 | **1a** (20) | HDA (20) | DMF | 25 | 48 | 30 | 70 (*S*) |
| 13 | **1a** (20) | $PhCO_2H$ (20) | DMF | 25 | 16 | 95 | 50 (*S*) |
| 14 | **1a** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ (20) | DMF | 25 | 24 | 94 | 50 (*S*) |
| 15 | **1a** (20) | 4-$O_2NC_6H_4CO_2H$ (20) | DMF | 25 | 48 | 85 | 44 (*S*) |
| 16 | **1a** (10) | $PhCO_2H$ (20) | DMF | 25 | 24 | 70 | 50 (*S*) |
| 17[d] | **1a** (20) | $PhCO_2H$ (20) | DMF | 25 | 16 | 96 | 50 (*S*) |
| 18[d] | **1a** (20) | $PhCO_2H$ (20) | DMF | 0 | 48 | 94 | 56 (*S*) |
| 19[d] | **1a** (20) | $PhCO_2H$ (20) | DMF | -5 | 72 | 94 | 64 (*S*) |
| 20[d] | **1a** (20) | $PhCO_2H$ (20) | DMF | -10 | 72 | 90 | 62 (*S*) |
| 21[d] | *ent*-**1a** (20) | $PhCO_2H$ (20) | DMF | -5 | 72 | 93 | 64 (*R*) |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] 2/1 (v/v). [d] 2 equiv of acetone were used.

Lowering the reaction temperature down to 0 ºC showed an increased enantioselectivity for succinimide (*S*)-**7a** after 48 h of reaction (Table 5, entry 18). This also happened when the reaction temperature was diminished down to -5 ºC, obtaining succinimide (*S*)-**7a** with 64% *ee*. In order to further increase the enantioselectivity, the temperature was lowered to -5 ° C, affording a value of 64% *ee* for (*S*)-**7a** with a 94% yield in 72 h (Table 5, entry 19). However, carrying out

the reaction at lower temperatures (-10 ° C), did not improve the previously obtained results (Table 5, entry 20).

Expecting to achieve an opposite enantioselection, the reaction using as organocatalyst *ent*-**1** was also performed. Using this primary amine as organocatalyst, under the most effective reaction conditions [catalyst (20 mol%), benzoic acid (20 mol%), DMF, -5 ºC], the expected adduct (*R*)-**7a** was isolated in 64% *ee* with 93% yield (Table 5, entry 21).

### *3.4.2. Scope of the Reaction*

Once the most effective organocatalyst and reaction conditions [**1a** (20 mol%), benzoic acid (20 mol%), DMF, -5 ºC] were found, the extension of this methodology to other ketones and maleimides was explored (Table 6). As in the case of the model reaction, the absolute configuration of the resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

Other acyclic ketones (pinacolone, methyl vinyl ketone and acetophenone) were employed for the organocatalyzed Michael addition reaction to *N*-phenylmaleide (**4a**), but the reaction did not take place after 3 days of reaction time. Therefore, we explore the influence of changing the substituent on the maleimide **4a**.

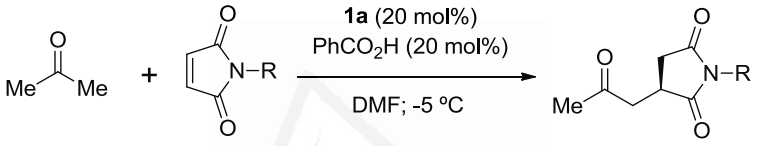


Thus, when acetone reacted with *N*-arylmaleimides bearing halogens on the aromatic ring, such as a chloro or a bromo atom at the 3- or 4-positions (**4b**, **4c** and **4d**), the corresponding succinimides (*S*)-**7b**, (*S*)-**7c** and (*S*)-**7d** were obtained in high yields in 54, 59 and 66% *ee*, respectively (Table 6, entries 2-4). In addition, when an acyl group was present onto the phenyl ring of the maleimide, as in the case of **4e**, the enantioselectivity for the corresponding succinimide (*S*)-**7e** was 58% in 90% yield (Table 6, entry 5). A 48% *ee* for (*S*)-**7f** was observed when an electron-

releasing group, such as a methoxy, was present at the 2-position (**4f**) (Table 6, entry 6).

Non-*N*-arylated maleimides were also employed for the conjugate addition with acetone. Thus, *N*-benzylmaleimide (**4g**) and *N*-methylmaleimide (**4h**) gave succinimides (*S*)-**7g** and (*S*)-**7h** in high yields but in moderate 60 and 48% *ee*, respectively (Table 6, entries 7 and 8). In addition, the simple maleimide (**4i**) was also used as Michael acceptor, but the corresponding succinimide was not obtained.

**Table 6**. Enantioselective Michael addition of acetone to maleimides organocatalyzed by **1a**.




**6** **4** **7**

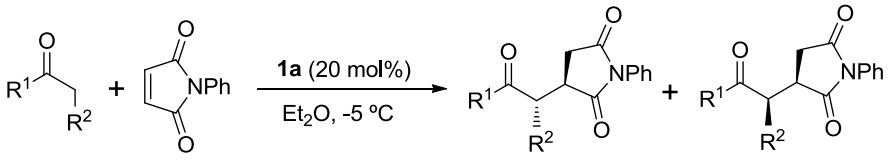
| Entry | Maleimide | | t (d) | Succinimide | | |
|---|---|---|---|---|---|---|
| | R | No. | | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Ph | **4a** | 2 | (*S*)-**7aa** | 94 | 64 |
| 2 | 3-$ClC_6H_4$ | **4b** | 2 | (*S*)-**7ab** | 92 | 54 |
| 3 | 4-$ClC_6H_4$ | **4c** | 2 | (*S*)-**7ac** | 93 | 59 |
| 4 | 4-$BrC_6H_4$ | **4d** | 3 | (*S*)-**7ad** | 88 | 66 |
| 5 | 4-$AcC_6H_4$ | **4e** | 3 | (*S*)-**7ae** | 90 | 58 |
| 6 | 2-$MeOC_6H_4$ | **4f** | 2 | (*S*)-**7af** | 89 | 48 |
| 7 | Bn | **4g** | 3 | (*S*)-**7ag** | 90 | 60 |
| 8 | Me | **4h** | 2 | (*S*)-**7ah** | 85 | 48 |
| 9 | H | **4i** | 3 | (*S*)-**7ai** | n.r. | n.d. |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude.

When this methodology was applied to the organocatalyzed Michael addition reaction of cyclic ketones **8** to *N*-phenylmaleide (**4a**), the corresponding adducts were obtained in low yield (<20%) and enantioselectivities (<20% *ee*). After several attempts, it was found that using organocatalyst **1a** (20 mol%) and diethyl ether as solvent at -5 ºC, the corresponding adducts could be obtained in good to high yields and better enantioselectivities (Table 7). In all these reactions, the diastereomeric ratio was very low, the *anti*-diastereomer being slightly predominant

than the *syn*-diastereomer. The absolute configuration of the final adducts **9** was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature (see Experimental). The major enantiomer for the *anti*-diastereomer was (3*R*,1´*S*)-**9** and (3*R*,1´*R*)-**9** for the *syn*-diastereomer.

**Table 7**. Enantioselective Michael addition of cyclic ketones to *N*-phenylmaleimides organocatalyzed by **1a**.




| Entry | Ketone | | t (d) | Succinimide | | | |
|---|---|---|---|---|---|---|---|
| | $R^1$, $R^2$ | No. | | No. | *anti*/*syn*[a] | Yield (%)[b] | *ee* (%)[c] |
| 1 | $(CH_2)_3$ | **8a** | 2 | **9aa** | 1.3/1.0 | 85 | 46/35 |
| 2 | $(CH_2)_4$ | **8b** | 2 | **9ba** | 2.3/1.0 | 91 | 40/33 |
| 3 | $(CH_2)_5$ | **8c** | 2 | **9ca** | 1.3/1.0 | 70 | 37/23 |
| 4[d] | $(CH_2)_2O(CH_2)$ | **8d** | 2 | **9da** | 1.8/1.0 | 80 | 41/26 |

[a] Mixture of diastereomers determined by $^1$H NMR (300 MHz) in the reaction crude. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [d] *anti*-**9da** maj: 3*R*,3´*R* *syn*-**9da** maj: 3*R*,3´*S*.

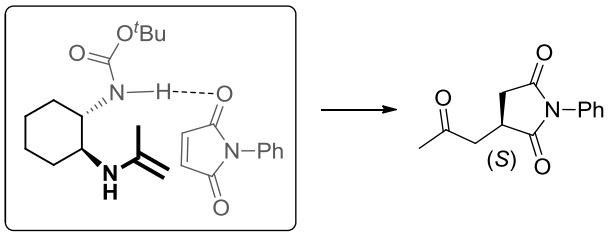
Thus, when cyclopentanone (**8a**) reacted with *N*-phenylmaleimide (**4a**), a mixture of *anti*-/*syn*-**9aa** diastereomers in a 1.3/1 ratio was obtained, with the enantioselectivity for (3*R*,1´*S*)-**9aa** being 46% and 35% for (3*R*,1´*R*)-**9aa** (Table 7, entry 1). When cyclohexanone (**8b**) reacted with **4a**, the diastereoselectivity *anti*/*syn*-**9ba** was 2.3/1, with enantioselectivities of 40 and 33% *ee* for (3*R*,1´*S*)-**9ba** and (3*R*,1´*R*)-**9ba** respectively (Table 7, entry 2). Carrying out the reaction with cycloheptanone (**8c**), an *anti*/*syn*-**9ca** diastereoselectivity 1.3/1.0 was obtained with enantioselectivities of 37 and 23% for the adducts (3*R*,1'*S*)-**9ca** and (3*R*,1'*R*)-**9ca** respectively (Table 7, entry 3). Finally, the reaction with tetrahydro-4*H*-pyran-4-one (**8d**) gave a 1.8/1.0 mixture of *anti*/*syn*-**9da** diastereomers. For *anti*-**9da** a enantioselectivity of 41% *ee* was obtained for (3*R*,3´*R*)-**9da** (the apparent change in

the absolute configuration is due to the Cahn-Ingold-Prelog rules) and for *syn*-**9da** the enantioselectivity was 26% *ee* for (3*R*,3´*S*)-**9da** (Table 7, entry 4).

The organocatalyzed Michael addition reaction of acetone (**6**) to *N*-phenylmaleide (**4a**) was also studied in DES as recyclable solvents, as in the case of the aldehydes as pro-nucleophiles (section 3.3). Thus, all the DES shown in Table 3 were employed in order to carry on the Michael addition reaction, but much lower enantioselectivities were observed compared to when conventional solvents were used. The best results for this reaction were 96% yield and only 46% *ee* for (*S*)-**7a** when the reaction was performed employing organocatalyst **1a** (20 mol%) and benzoic acid (20 mol%) as additive, in the DES formed by choline chloride and urea (ChCl/urea, 1/2 molar ratio).

### *3.4.3. Coordination Model*

The obtained enantioselectivities and the theoretical calculations carried out when using aldehydes (Section 3.2.3), allowed us to suggest a possible coordination model suitable able to justify the observed results. Thus, the acetone would react with the primary amine forming an enamine intermediate, whilst a carbonyl group of the maleimide would be coordinated to the secondary amine via a hydrogen bond. This coordination would favour the Michael addition reaction on the *Si* face of the maleimide, leading to the observed stereochemical outcome (Scheme 3).




**Scheme 3**. Hypothesized coordination of catalyst with reactants leading to the observed stereochemistry.

# 4. EXPERIMENTAL PART

## 4.1. General

### *4.1.1. Solvents and Reagents*

All solvents and reagents listed in this research were purchased with the best commercial grade and were used without purification. Aldehydes **3** were distilled before use.

### *4.1.2. Instrumentation*

Melting points were obtained with a *Reichert Thermovar* apparatus and are uncorrected. IR spectra ($cm^{-1}$) were obtained with a *Nicolet Impact 400 D-FT* spectrophotometer.

The measurement of the specific rotation values was performed at room temperature using a *Perkin-Elmer 341* polarimeter, using a sodium lamp and a 50 mm cell.

Elemental Analyses were performed at the Research Technical Services of the University of Alicante, using a *Thermo Finnigan FlashEA 1112* series equipment.



Proton ($^{1}H$ NMR) and carbon ($^{13}C$ NMR) nuclear magnetic resonance spectra were performed at the Research Technical Services of the University of Alicante, with a *Bruker AC-300* or *Bruker Avance-400*, using deuterated chloroform as solvent and tetramethylsilane (TMS) as an internal standard. The spectra of $^{1}H$ NMR were performed at 300 or 400 MHz, while the $^{13}C$ NMR became 75 or 100 MHz. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hz.

The mass spectrometric analysis was carried out using an *Agilent GC/MS-5973N* spectrometer, performing studies in the form of electron impact (EI) at 70 eV ionization source and helium as the mobile phase (2 mL/min). Samples were

introduced by injection through a gas chromatograph *Hewlett-Packard HP-6890*, equipped with a HP-5MS column 30 m length, 0.25 mm internal diameter and 0.25 μm film thickness (crosslinking 5% PHME siloxane). Ions derived from the breaks are given as *m*/*z* with relative percent intensities in brackets.

The high resolution mass spectrometry analyses (HRMS) were performed at the Research Technical Services of the University of Alicante, with an *Agilent Technologies 7200 Accurate-Mass Q-TOF GC/MS* mass spectrometer coupled to an *Agilent Technologies 7890B* gas chromatograph. The samples were introduced by split-mode injection (1:100) through the gas chromatograph, equipped with *Agilent Technologies HP-5MS UI* column, and the electronic impact (EI) at 70 eV and helium (1 mL / min) as the carrier gas in the mobile phase was used as the ionization technique.

Cooling of the reaction media was achieved using a digital *Julabo FT901* cryostat, accompanied by its temperature probe and the use of a digital thermometer *Heidolph EKT 3001*.

Thin layer chromatography (TLC) was carried out on *Schleider & Schuell* F1400/LS 254 plates coated with a 0.2 mm layer of silica gel. For detection, UV lamp of aluminum of wavelength $\lambda = 254$ nm was used.

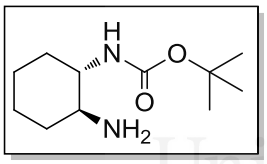
Column chromatography was performed on glass columns, using as stationary phase silica gel Merck 60, with a particle size of 0.040 to 0.063 mm. Elutions were carried on with mixtures of *n*-hexane and ethyl acetate (EtOAc) of increasing polarity.

For the determination of the enantiomeric excesses in HPLC, *Agilent-Hewlett Packard* systems consisting of a *G1311A* pump, a *G1313A* injector and a *G1316A* detector were used. The conditions (column, eluent and flow) and retention times are indicated in each case.

## 4.2. Experimental Procedures

### *4.2.1. Synthesis of Organocatalysts*

*4.2.1.1. Synthesis of* tert-*butyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate (**1a**)*:[27] A solution of 5 mL HCl (2M $Et_2O$) was added dropwise to (1*S*,2*S*)-cyclohexane-1,2-diamine (1.14 g, 10.0 mmol) in MeOH (3 mL) at 0ºC. The solution was stirred for 15 min at 25 ºC, water (1 mL) was added and the mixture was stirred for another 30 min. To this solution was added a mixture of di-*tert*-butyl dicarbonate (3.27 g, 15.0 mmol) in MeOH (4 mL) dropwise at 25 ºC for 10 min, and the resultant solution was stirred for 1h. The mixture was evaporated in vacuo (15 torr) and the solid was washed with $Et_2O$ (2 x 7 mL) to remove unreacted diamine. The solid residue was suspended with 2N NaOH (10 mL) and extracted with $CH_2Cl_2$ (3 x 7 mL). The combined organics were washed with brine (7 mL), dried ($MgSO_4$), and evaporated in vacuo (15 Torr) to obtain **1a** (1.5 g, 70%).

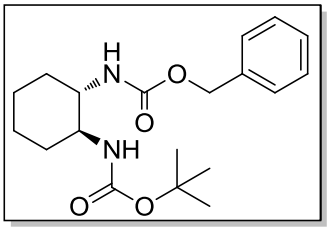



***tert*-Butyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate (1a):**[27] Off-white solid; mp = 109-111 °C ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{25}$ 24 (*c* = 1, $CHCl_3$); IR (ATR): ν = 3367, 3187, 2928, 2854, 1693, 1519, 1447, 1387, 1363, 1318, 1277, 1241, 1173, 1041, 1015 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 4.52 (s, 1H), 3.13 (dt, *J* = 10.8, 4.0 Hz, 1H), 2.33 (dt, *J* = 10.8, 4.0 Hz, 1H), 2.02-1.82 (m, 2H), 1.72-1.68 (m, 2H), 1.52 (s, 2H), 1.45 (s, 9H), 1.3-1.0 (m, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 156.1, 79.2, 57.7, 55.6, 35.2, 32.9, 28.4, 25.2, 25.1 ppm.

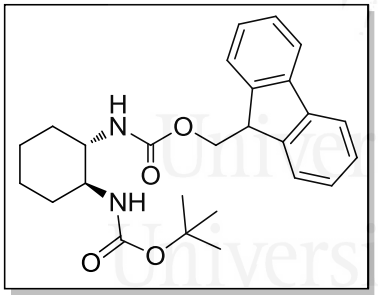
*4.2.1.2. Synthesis of dicarbamates **2a** and **2b**:*[35] To a stirred solution of **1a** (429 mg, 2.0 mmol) in 1,4-dioxane (10 mL) was added $Na_2CO_3$ aqueous (1 M, 4 mL) and a solution of benzyl chloroformate (for **2a**, 338 μL, 2.0 mmol) or 9-fluorenylmethyl chloroformate (for **2b**, 522 mg, 2.0 mmol) at 0ºC. The reaction mixture was stirred

[35] Wu, G.-P.; Ren, W.-M.; Luo, Y.; Li, B.; Zhang, W.-Z.; Lu, X.-B. *J. Am. Chem. Soc.* **2012**, *134*, 5682-5688.

for 30 min, then warmed to room temperature and stirred for additional 18 h. Water was added (8 mL) and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure (15 torr), to obtain **2a** (488 mg, 70%) or **2b** (811 mg, 93%).

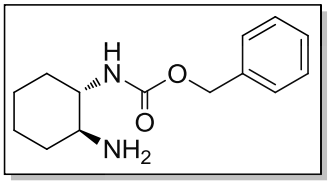


**Benzyl *tert*-butyl ((1*S*,2*S*)-cyclohexane-1,2-diyl)dicarbamate (2a):** White solid; mp = 119 °C ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{25}$ -19 (*c* = 1, $CHCl_3$); IR (ATR): ν = 3351, 2927, 2858, 1676, 1518, 1278, 1165, 1014, 700 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.36-7.29 (m, 5H), 5.32 (s, 1H), 5.07 (s, 2H), 4.71 (s, 1H), 3.32 (s, 2H), 2.09 (d, *J* = 12.7 Hz, 1H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.72 (s, 2H), 1.39(s, 9H), 1.35–1.03 (m, 4H) ppm; 156.6, 136.7, 128.6, 128.4, 127.9, 79.4, 66.4, 56.4, 54.2, 33.0, 32.7, 28.3, 24.9, 24.7 ppm; Anal. calcd. for $C_{19}H_{28}N_2O_4$: C 65.49%, H 8.10%, N 8.04%; found: C 65.86%, H 8.58%, N 7.94%.

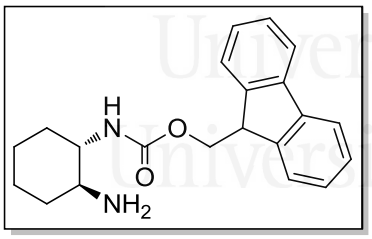


**(9*H*-Fluoren-9-yl)methyl *tert*-butyl ((1*S*,2*S*)-cyclohexane-1,2-diyl)dicarbamate (2b):** White solid; mp = 173 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{25}$ -8.5 (*c* = 1, $CHCl_3$); IR (ATR): ν = 3335, 2927, 2859, 1673, 1541, 1280, 1168, 1017, 734 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.36-7.29 (m, 5H), 5.32 (s, 1H), 5.07 (s, 2H), 4.71 (s, 1H), 3.32 (s, 2H), 2.09 (d, *J* = 12.7 Hz, 1H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.72 (s, 2H), 1.39(s, 9H), 1.35-1.03 (m, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 156.6, 136.7, 128.6, 128.4, 127.9, 79.4, 66.4, 56.4, 54.2, 33.0, 32.7, 28.3, 24.9, 24.7 ppm; Anal. calcd. for $C_{19}H_{28}N_2O_4$: C 65.49%, H 8.10%, N 8.04%; found: C 65.86%, H 8.58%, N 7.94%.

*4.2.1.3. Synthesis of carbamates **1b** and **1c**:*[36] Dicarbamate **2a** (348 mg, 1.0 mmol) or **2b** (436 mg, 1.0 mmol) was dissolved in a mixture of trifluoroacetic acid and dichloromethane (4.5 mL, v/v = 1:2) and the resulting solution was stirred at room temperature for 2 h. The solvent was removed (15 torr) and the crude was dissolved in methylene chloride (2 mL). To this stirred solution was added aqueous ammonia to adjust the pH value to 9-10. The organic layer was separated and dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure (15 torr), obtaining **1b** (221 mg, 97%) or **1c** (319 mg, 95%).



**Benzyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate (1b):**[36] White solid; mp = 105 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{25}$ 24 (*c* = 1, $CHCl_3$); IR (ATR): ν = 3350, 2926, 2850, 1703, 1555, 1268, 1237, 1042, 733 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.38-7.29 (m, 5H), 5.10 (s, 2H), 4.91 (s, 1H), 3.21-3.17 (m, 1H), 2.37-2.30 (m, 1H), 2.02-1.93 (m, 2H), 1.67-1.71 (d, *J* = 8Hz, 2H), 1.41 (s, 2H), 1.40-1.03 (m, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 156.6, 136.6, 128.5, 128.1, 66.7, 58.1, 55.5, 35.3, 32.8, 25.1, 25.0 ppm.



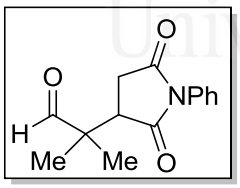
**(9*H*-Fluoren-9-yl)methyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate (1c):** White solid; mp = 160 ºC (decomp.) ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{25}$ 20 (*c* = 1, $CH_2Cl_2$); IR (ATR): ν = 3317, 2938, 2855, 1679, 1531, 1318, 1262, 1030, 735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.76 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 4.73 (m, 1H), 4.47 (m, 2H), 4.21 (t, *J* = 6.2 Hz, 1H), 3.16 (m, 1H), 2.33 (m, 1H), 1.96 (m, 2H), 1.75- 1.41 (m, 4H), 1.39-1.12 (m, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 156.6, 143.9, 141.4, 127.7, 127.0, 124.9, 120.0, 66.3, 58.0, 55.5, 47.4, 35.2, 32.8, 25.1, 25.0 ppm; Anal. calcd. for $C_{21}H_{24}N_2O_2$: C 74.97%, H 7.19%, N 8.33%; found: C 74.67%, H 6.87%, N 7.54%.

[36] Minarini, A.; Marucci, G.; Bellucci, C.; Giorgi, G.; Tumiatti, V.; Bolognesi, M. L.; Matera, R.; Rosini, M.; Melchiorre, C. *Bioorg. Med. Chem.* **2008**, *16*, 7311-7320.

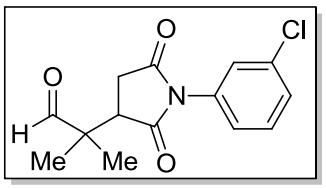
### *4.2.2. General Procedure for the Enantioselective Michael Addition Reaction of Aldehydes to Maleimides*

To a solution of **1a** (4.3 mg, 0.02 mmol) and maleimide **4** (0.2 mmol) in $CHCl_3$ (0.5 mL) or DMF/$H_2O$ mixture (2/1, v/v ratio, 0.5 mL) was added aldehyde **3** (0.4 mmol) and the mixture was stirred at 25 ºC for the time shown in Table 2 (monitored by TLC with *n*-hexane/EtOAc mixture, 7/3 v/v ratio, as eluent). The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients).

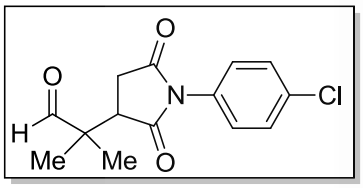
Adducts **5** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC on the reaction crude. Absolute configuration for adducts **5** was determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds it was assigned by analogy. Reference racemic samples of adducts **5** were obtained by performing the reaction using 4-methylbenzylamine (20 mol%) as organocatalyst in toluene as solvent at 25 ºC. Physical, spectroscopical and chiral HPLC data for adducts **5** are shown below:



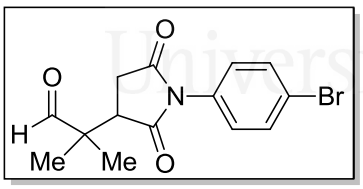

**2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methyl propanal (5aa):**[22b] White solid; mp = 105-106 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.46 (s, 1H), 7.47-7.40 (m, 2H), 7.39-7.33 (m, 1H), 7.27-7.20 (m, 2H), 3.10 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.90 (dd, *J* = 18.3, 9.5 Hz, 1H), 2.56 (dd, *J* = 18.3, 5.5 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 202.8, 176.8, 174.7, 131.6, 129.0, 128.5, 126,3, 48.3, 44.7, 31.5, 20.2, 19.1 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 25.4 min, $t_r$ (*R*) = 30.7 min.



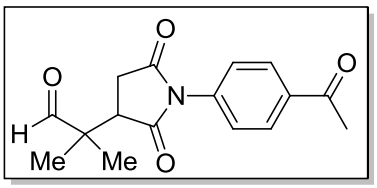
**2-(1-(3-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (5ab):**[22b] White solid; mp = 92-93 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.48 (s, 1H), 7.44-7.30 (m, 3H), 7.21-7.18 (m, 1H), 3.12 (dd, *J* = 9.6, 5.6 Hz, 1H), 2.97 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.62 (dd, *J* = 18.3, 9.6 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.8, 176.6, 174.4, 134.6, 132.8, 130.0, 128.8, 126.8, 124.7, 48.7, 44.9, 31.9, 20.4, 19.8 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 26.0 min, $t_r$ (*R*) = 30.8 min.



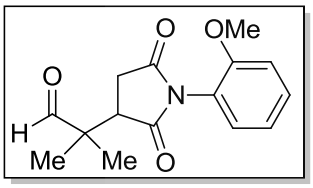
**2-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (5ac):**[22b] White solid; mp = 95-96 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.44 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 3.07 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.91 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.56 (dd, *J* = 18.3, 5.6 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.7, 176.6, 174.4, 134.2, 130.1, 129.2, 127.7, 48.5, 44.8, 31.7, 20.30, 19.5 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 30.6 min, $t_r$ (*R*) = 54.2 min.



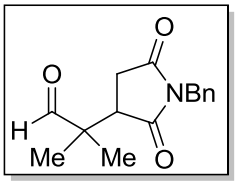
**2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (5ad):**[22b] White Solid; mp = 125-126 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.47 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 3.10 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.95 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.60 (dd, *J* = 18.3, 5.6 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.7, 176.5, 174.4, 132.2, 130.7, 128.0, 122.4, 48.6, 44.9, 31.8, 20.4, 19.7 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 30.1 min, $t_r$ (*R*) = 51.8 min.



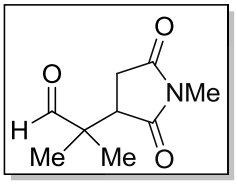
**2-(1-(4-Acetylphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (5ae):**[22b] White solid; mp = 110-112 °C; IR (ATR): ν = 2968, 1706, 1677, 1392, 1260, 1186, 1169, 864, 742 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.45 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 3.12 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.96 (dd, *J* = 18.3, 9.5 Hz, 1H), 2.63 (dd, *J* = 18.3, 5.6 Hz, 1H), 2.57 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H) ppm; $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.8, 197.2, 176.5, 174.3, 136.5, 135.8, 129.0, 126.4, 48.6, 44.9, 31.8, 26.6, 20.4, 19.6 ppm; MS (EI, 70 eV): *m/z* (%) = 272 ($M^+$-Me , 26), 259 (100); HRMS (EI): *m/z* calcd. for $C_{15}H_{14}NO_4$: 272,1001; found: 272.0922; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 38.2 min, $t_r$ (*R*) = 50.2 min.



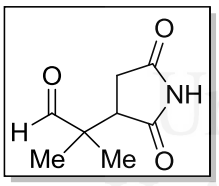
**2-(1-(2-Methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (5af):**[22b] Colorless oil; rotamers, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.59/9.51* (s, 1H), 7.41-7.37 (m, 2H), 7.14-7.08 (m, 1H), 7.05-6.99 (m, 2H), 3.78*/3.77 (s, 3H), 3.28 (dd, *J* = 9.4, 5.0 Hz, 1H)/3.21* (dd, *J* = 9.6, 5.5 Hz, 1H), 3.01*(dd, *J* = 18.7, 9.6 Hz, 1H)/2.96 (dd, *J* = 18.4, 9.4 Hz, 1H), 2.63 (dd, *J* = 18.4, 5.0 Hz, 1H)/2.58* (dd, *J* = 18.7, 5.5 Hz, 1H), 1.30*/1.28 (s, 3H), 1.26*/1.19 (s, 3H) ppm; $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.8*/202.7, 176.7*/176.5, 174.9/174.7*, 154.5*/154.4, 130.8/130.7*, 129.1*/129.0, 120.8/120.4*, 112.0, 55.7*/55.6, 48.3*/48.0, 45.1/45.0*, 31.8*/31.4, 20.1*/19.2, 19.3*/18.2 ppm; HPLC: Chiralcel AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 0.6 mL/min, $t_r$ (*S*) = 33.6 min, $t_r$ (*R*) = 36.0 min.



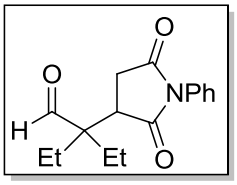

**2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-methyl propanal (5ag):**[22b] White solid; mp = 60-61 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.46 (s, 1H), 7.34-7.31 (m, 3H), 7.29-7.24 (m, 2H), 4.63-4.62 (m, 2H), 3.04 (dd, *J* = 9.3, 5.4 Hz, 1H) 2.80 (dd, *J* = 18.3, 9.3 Hz, 1H), 2.44 (dd, *J* = 18.3, 5.4 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.7, 177.3, 175.4, 135.4, 128.4, 128.3, 127.7, 47.7, 44.6, 42.1, 31.4, 19.7, 18.6 ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 11.5 min, $t_r$ (*R*) = 28.9 min.



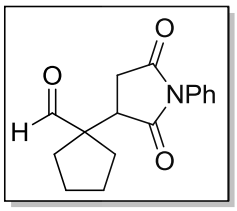

**2-(1-Methyl-2,5-dioxopyrrolidin-3-yl)-2-methyl-propanal (5ah):**[22b] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.44 (s, 1H), 3.00 (dd, *J* = 9.3, 5.4 Hz, 1H), 2.91 (s, 3H), 2.76 (dd, *J* = 18.2, 9.3 Hz, 1H), 2.39 (dd, *J* = 18.2, 5.4 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 202.8, 177.7, 175.8, 47.8, 44.8, 31.2, 24.6, 19.9, 18.8 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 14.5 min, $t_r$ (*S*) = 16.1 min.



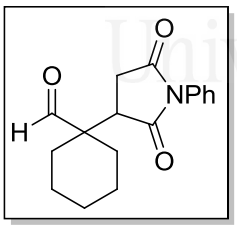

**2-(2,5-Dioxopyrrolidin-3-yl)-2-methylpropanal (5ai):**[22b] White solid; mp = 89-90 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.46 (s, 1 H), 9.26 (br s, 1H), 3.08 (dd, *J* = 9.4, 5.7 Hz, 1H), 2.82 (dd, *J* = 18.4, 9.4 Hz, 1H), 2.47 (dd, *J* = 18.4, 5.7 Hz, 1H), 1.20 (s, 3H), 1.18 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.0, 178.7, 176.7, 47.8, 46.1, 32.5, 20.0, 18.9 ppm. HPLC: Chiralpak AD-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 19.2 min, $t_r$ (*S*) = 26.1 min.



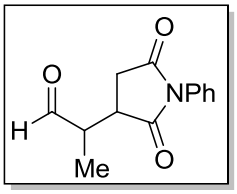
**2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-ethylbutanal (5ba):**[22b] White solid; mp = 100-102 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.61 (s, 1H), 7.50-7.42 (m, 3H), 7.40-7.36 (m, 1H), 7.29-7.25 (m, 2H), 3.24 (dd, *J* = 9.6, 5.9 Hz, 1H), 2.94 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.67 (dd, *J* = 18.4, 5.9 Hz, 1H), 2.01-1.79 (m, 3H), 1.77-1.67 (m, 1H), 1.01-0.95 (m, 6H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.0, 177.2, 174.9, 131.8, 129.0, 128.5, 126.4, 54.4, 41.8, 31.6, 24.3, 23.1, 8.0, 7.9 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 20.7 min, $t_r$ (*S*) = 22.3 min.



**1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclopentane carbaldehyde (5ca):**[22b] White solid; mp = 77-78 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.37 (s, 1H), 7.49-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.28 (m, 2H), 3.01 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.93 (dd, *J* = 17.5, 9.6 Hz, 1H), 2.55 (dd, *J* = 17.5, 4.9 Hz, 1H), 2.31-2.26 (m, 1H), 2.10-2.01 (m, 2H), 1.82-1.72 (m, 5H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 201.8, 177.6, 175.0, 132.0, 129.0, 128.5, 126.6, 60.0, 43.0, 33.0, 32.5, 32.2, 25.6 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 24.4 min, $t_r$ (*R*) = 32.2 min.



**1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclohexane carbaldehyde (5da):**[22b] White solid; mp = 132-133 ºC; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.51 (s,1H), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.23 (m, 2H), 3.20 (dd, *J* = 9.5, 5.9 Hz, 1H), 2.84 (dd, *J* = 18.2, 9.5 Hz, 1H), 2.64 (dd, *J* = 18.2, 5.9 Hz, 1H), 1.99-1.90 (m, 2H), 1.87-1.69 (m, 1H), 1.69-1.36 (m, 7H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.5, 177.0, 174.8, 131.8, 129.0, 128.5, 126.5, 52.0, 42.5, 31.4, 28.4, 27.4, 24.9, 21.2, 21.0 ppm; HPLC: Chiralcel OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 23.3 min, $t_r$ (*R*) = 29.4 min.




**2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)propanal (4ea):**[22b] Yellow oil; mixture of diastereomers (ratio: major/minor*); $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.64*/9.55 (s, 1H), 7.50-7.36 (m, 3H), 7.32-7.25 (m, 2H), 3.36-3.30*/3.24-3.15 (m, 1H), 3.31-3.00*/2.97-2.81 (m, 2H), 2.54/2.47* (dd, *J* = 14.1, 4.4 Hz, 1H), 1.31/1.27* (d, *J* = 7.8 Hz, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 201.8/201.5*, 177.7/177.6*, 175.3/175.1*, 132.0/131.7*, 129.1*/129.0, 128.7*/128.6, 126.6/126.4*, 47.0*/46.4, 40.7/39.4*, 31.6, 11.3/9.7* ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, major diastereomer: $t_r$ (*S,S*) = 18.5 min, $t_r$ (*R,R*) = 31.0 min, minor diastereomer: $t_r$ (*R,S*) = 21.0 min, $t_r$ (*S,R*) = 24.0 min.

### *4.2.3. General Procedure for the Preparation of DESs*

A mixture of the two components, with the previously specified molar ratio, was added to a round bottom flask under an argon atmosphere, and the mixture was stirred for 60 min in a temperature range between 65 and 80 ºC, obtaining the corresponding DES.[37]

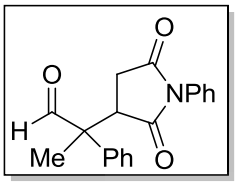
### *4.2.4. General Procedure for the Enantioselective Michael Addition Reaction of Aldehydes to Maleimides in DESs*

To a solution of **1a** (4.3 mg, 0.02 mmol), 3,4-dimethoxybenzoic acid (3.7 mg, 0.02 mmol), and maleimide (0.2 mmol) in the corresponding DES (0.5 mL) was added the aldehyde (0.4 mmol) and the reaction was vigorously stirred at 25 ºC for the time shown in Table 4 (monitored by TLC with *n*-hexane/EtOAc mixture, 7/3 v/v ratio, as eluent). The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The combined organics were washed with aq $NaHCO_3$ (2x10 mL), dried over $MgSO_4$, and the solvent was

[37] (a) Shahbaz, K.; Mjalli, F. S.; Hashim, M. A.; Al Nashef, I. M. *Energy Fuels* **2011**, *25*, 2671-2678; (b) Yusof, R.; Abdulmalek, E.; Sirat, K.; Abdul Rahman, M. B. *Molecules* **2014**, *19*, 8011-8026; (c) García, G.; Aparicio, S.; Ullah, R.; Atilhan, M. *Energy Fuels* **2015**, *29*, 2616-2644.

evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients).

Adducts **5aa**, **5ab**, **5ac**, **5ad**, **5ae**, **5af**, **5ag**, **5ah**, **5ai**, **5ba**, **5ca**, **5da** and **5ea** have formerly been described (see Experimental Part, section 4.2.2). Physical, spectroscopical and chiral HPLC data for adduct **5fa** are shown below:




**2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)propanal (5fa):**[14] Yellow oil; mixture of diastereomers (ratio: major/minor*); $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.74*/9.64 (s, 1H), 7.46-7.29 (m, 6H), 7.28-7.23 (m, 2H), 7.22-7.17*/7.09-7.04 (m, 2H), 3.81 (dd, *J* = 9.5, 4.7 Hz, 1H)/3.41* (dd, *J* = 9.5, 5.8 Hz, 1H), 2.90 (dd, *J* = 18.9, 9.5 Hz, 1H)/2.66* (dd, *J* = 18.5, 9.5 Hz, 1H), 2.53* (dd, *J* = 18.5, 5.8 Hz, 1H)/2.46 (dd, *J* = 18.9, 4.7 Hz, 4H), 1.77*/1.71 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 200.8*/198.9, 176.5*/176.4, 174.5, 137.7*/135.5, 131.8*/131.4, 129.2/129.1*, 128.9, 128.5/128.4*, 128.3/128.1*, 127.3/127.1*, 126.5*/*126.2, 56.2*/55.7, 46.3*/44.8, 32.3*/31.8, 19.3*/16.1 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, major diastereomer: $t_r$ (*R,S*) = 42.7 min, $t_r$ (*S,R*) = 52.4 min, minor diastereomer: $t_r$ (*S,S*) = 30.8 min, $t_r$ (*R,R*) = 44.2 min.

### *4.2.5. Recycle Experiments.*

To a mixture of the catalyst **1a** (4.3 mg, 0.02 mmol), 3,4-dimethoxybenzoic acid (3.7 mg, 0.02 mmol), and *N*-phenylmaleimide (34.6 mg, 0.2 mmol) in $Ph_3MePBr$/Gly (1/2 molar ratio, 0.5 mL) was added isobutyraldehyde (36.5 μL, 0.4 mmol) and the reaction was vigorously stirred for 8 h at 25 ºC. After this period, a mixture of ethyl ether/*n*-hexane (4/1, v/v, 3 mL) was added and the mixture was stirred for 2 min. The stirring was stopped to allow phase separation and the upper organic layer was removed through settling. This extractive procedure was repeated three times. The combined organic extracts were washed with aq $NaHCO_3$ (10 mL), dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients) yielding

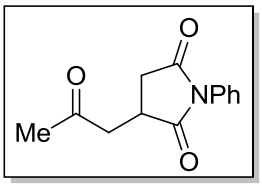
(*R*)-**5aa**. The DES layer, where catalyst **1a** remained dissolved, was evaporated in vacuo (15 Torr) at room temperature to remove volatile solvent residues, and the catalytic system was regenerated by 3,4-dimethoxybenzoic acid addition (3,7 mg, 0.02 mmol). A further run was performed with this DES, adding new isobutyraldehyde and *N*-phenylmaleimide. This reaction mixture was subjected again to the above described procedure and further reaction cycles were repeated using the same DES phase.

### *4.2.6. General Procedure for the Enantioselective Michael Addition Reaction of Acetone to Maleimides*

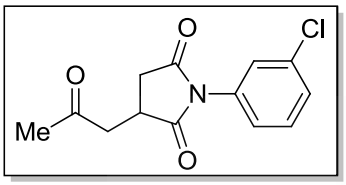
To a solution of **1a** (8.6 mg, 0.04 mmol), maleimide **4** (0.2 mmol) and benzoic acid (4.9 mg, 0.04 mmol) in DMF (0.5 mL) was added acetone **6** (30 μL, 0.4 mmol) and the mixture was stirred at -5 ºC for the time shown in Table 6 (monitored by TLC with *n*-hexane/EtOAc mixture, 7/3 v/v ratio, as eluent). The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The combined organic extracts were washed with aq $NaHCO_3$ (10 mL), dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients).



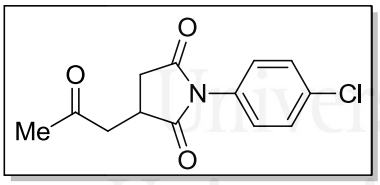
Adducts **7** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC on the reaction crude. Absolute configuration for adducts **7** was determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds it was assigned by analogy. Reference racemic samples of adducts **7** were obtained by performing the reaction using 4-methylbenzylamine (20 mol%) as organocatalyst in toluene as solvent at 25 ºC. Physical, spectroscopical and chiral HPLC data for adducts **7** are shown below:



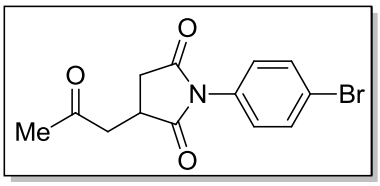
**3-(2-Oxopropyl)-1-phenylpyrrolidine-2,5-dione (7a):**[23] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.40 (m, 2H), 7.42-7.37 (m, 1H), 7.35-7.29 (m, 2H), 3.21-3.01 (m, 4H), 2.56 (dd, *J* = 17.4, 4.6 Hz, 1H), 2.21 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6, 178.5, 175.4, 132.2, 129.2, 128.6, 126.6, 43.5, 35.6, 34.6, 29.8 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 75:25, 0.7 mL/min, $t_r$ (*S*) = 34.79 min, $t_r$ (*R*) = 40.6 min.



**1-(3-Chlorophenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione (7b):**[23] White solid. Mp 110-111°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.42-7.35 (m, 3H), 7.25-7.22 (m, 1H), 3.17-3.02 (m, 4H), 2.56 (dd, *J* = 17.8, 4.8 Hz, 1H), 2.21 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6, 178.1, 174.9, 134.7, 133.2, 130.1, 128.9, 126.9, 124.8, 43.4, 35.6, 34.5, 29.7 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 85:15, 0.8 mL/min, $t_r$ (*S*) = 38.1 min, $t_r$ (*R*) = 44.3 min.

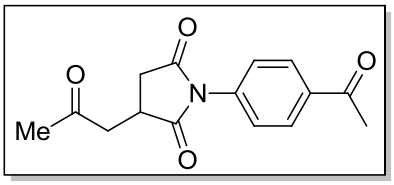


**1-(4-Chlorophenyl)-3-(2-oxopropyl) pyrrolidine-2,5-dione (7c):**[23] White solid. Mp 128-129°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.45 (d, *J* = 8.9, 2H), 7.28 (d, *J* = 8.9, 2H), 3.14-3.01 (m, 4H), 2.56 (dd, *J* = 17.4, 4.6, 1H), 2.21 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6, 178.3, 175.1, 134.4, 130.6, 129.4, 127.9, 43.4, 35.6, 34.5, 29.7 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 29.7 min, $t_r$ (*R*) = 50.6 min.

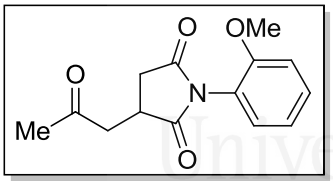


**1-(4-Bromophenyl)-3-(2-oxopropyl) pyrrolidine-2,5-dione (7d):**[23] White solid. Mp 138-139°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.60 (d, *J* = 8.8Hz, 2H), 7.22 (d, *J* = 8.8Hz, 2H), 3.17-3.00 (m, 4H), 2.54 (dd, *J* = 17.8, 4.9 Hz), 2.20 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ =

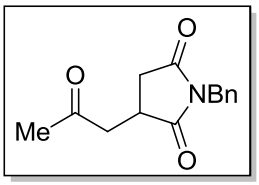
205.6, 178.2, 175.1, 132.3, 131.2, 128.2, 122.4, 43.4, 35.6, 34.5, 29.7 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 31.0 min, $t_r$ (*R*) = 46.8 min.



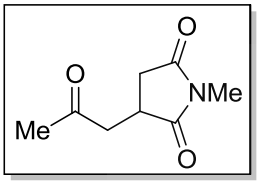

**1-(4-Acetylphenyl)-3-(2-oxopropyl) pyrrolidine-2,5-dione (7e):** Pale yellow oil; IR (ATR): ν = 2947, 1704, 1682, 1377, 1263, 1168, 834, 738 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.05 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 3.17-3.03 (m, 4H), 2.61 (s, 3H), 2.58 (dd, *J* = 17.9, 5.1, 1H), 2.21 (s, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.7, 197.1, 178.1, 174.9, 136.7, 136.3, 129.1, 126.6, 43.4, 35.6, 34.5, 29.7, 26.7 ppm; MS (EI, 70 eV): *m/z* (%) = 273 (M+, 39), 258 (100); HRMS (EI): exact mass calculated for $[M]^+$ ($C_{15}H_{15}NO_4$) requires *m/z* 273,1001, found *m/z* 273.0990; HPLC: Chiralpak AS-H, λ = 240 nm, *n*-hexane/2-propanol, 75:25, 1.0 mL/min, $t_r$ (*S*) = 45.9 min, $t_r$ (*R*) = 66.4 min.




**1-(2-Methoxyphenyl)-3-(2-oxopropyl) pyrrolidine-2,5-dione (7f):** Colorless oil; Mixture of rotamers; IR (ATR): ν = 2937, 2839, 1703, 1504, 1387, 1252, 1114, 734 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.41-7.37 (m, 1H), 7.22-7.20/7.12-7.10* (d, *J* = 7.7 Hz, 1H), 7.06-6.99 (m,2H), 3.81*/3.79 (s, 3H), 3.33-3.05 (m, 4H)/3.33-3.05*(m, 3H), 2.88-2.81* (m, 1H), 2.61-2.50 (m, 1H), 2.22*/2.19 (s, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6/205.0*, 178.4/178.3*, 175.3/175.2*, 154.7, 130.8*/130.7, 129.2/129.1*, 120.9/120.8*, 112.3*/112.10, 56.0*/55.8, 44.4*/43.5, 36.1*/35.8, 35.3*/34.8, 29.8*/29.7 ppm; MS (EI, 70 eV): *m/z* (%) = 261 (M+H, 100), 218 (77); HRMS (EI): exact mass calculated for $[M]^+$ ($C_{14}H_{15}NO_4$) requires *m/z* 261.1001, found *m/z* 261.1005; HPLC: Chiralpak AD-H, λ = 240 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 14.5 min, $t_r$ (*S*) = 18.7 min.




**1-Benzyl-3-(2-oxopropyl)pyrrolidine-2,5-dione (7g):**[23] White solid. Mp 90-91°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.39-7.36 (m, 2H), 7.33-7.25 (m, 3H), 4.66 (q, *J* = 14.2, 2H), 3.06-3.01 (m, 2H), 2.94-2.83 (m, 2H), 2.37 (dd, *J* = 18.1Hz, 5.2, 2H), 2.16 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.3, 179.0, 175.9, 135.8, 128.6, 127.8, 43.4, 42.5, 35.6, 34.6, 29.7 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 18.9 min, $t_r$ (*R*) = 25.2 min.



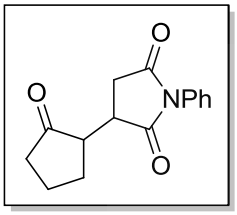

**1-Methyl-3-(2-oxopropyl)pyrrolidine-2,5-dione (7h):** colorless oil; IR (ATR): ν = 2937, 1687, 1436, 1384, 1281, 1119, 740 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 3.09-2.88 (m, 4H), 3.01 (s, 3H), 2.37 (dd, *J* = 17.8, 4.6 Hz, 1H), 2.19 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.4, 179.5, 176.4, 43.5, 35.5, 34.6, 29.8, 24.9 ppm; MS (EI, 70 eV): *m/z* (%) = 169 (M+, 35), 127 (100); HRMS (EI): exact mass calculated for $[M+H]^+$ ($C_8H_{11}NO_3$) requires *m/z* 169.0739, found *m/z* 169.0737; HPLC: Chiralpak AS-H, λ = 240 nm, *n*-hexane/2-propanol, 75:25, 1.0 mL/min, $t_r$ (*S*) = 13.6 min, $t_r$ (*R*) = 22.3 min.

### *4.2.7. General Procedure for the Enantioselective Michael Addition Reaction of Cyclic Ketones to Maleimides*



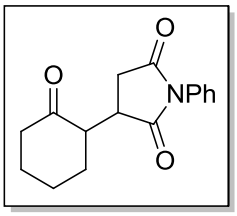
To a solution of **1a** (8.6 mg, 0.04 mmol) and *N*-phenylmaleimide (**4a**, 34.6 mg, 0.2 mmol) in $Et_2O$ (0.5 mL) was added ketone **8** (0.4 mmol) and the mixture was stirred at -5 ºC for the time shown in Table 7 (monitored by TLC with *n*-hexane/EtOAc mixture, 7/3 v/v ratio, as eluent). The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients).

Adducts **9** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC. Absolute configuration for adducts **9** was determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds it was assigned by analogy. Reference racemic samples of adducts **7** were obtained by performing the reaction using 4-methylbenzylamine (20 mol%) as organocatalyst in toluene as solvent at 25 ºC. Physical, spectroscopical and chiral HPLC data for adducts **9** are shown below:



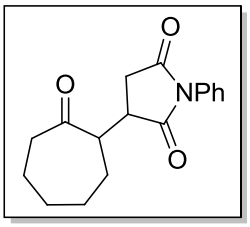

**3-(2-Oxocyclopentyl)-1-phenylpyrrolidine-2,5-dione (9aa):**[25] White solid. Mp 119-120 °C; mixture of diastereomers (ratio: 1.3/1.0, major/minor*); $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.35-7.33 (m, 1H), 7.27-7.25 (m, 1H), 3.47-3.42*/3.28-3.23 (m, 1H), 3.01-2.92 (m, 1H), 2.91-2.81(m, 1H), 2.61-2.56*/2.49-2.43 (m, 1H), 2.42-2.27 (m, 2H), 2.23-2.06/1.95-1.81* (m, 3H), 1.72-1.61 (m, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 218.1*/217.5, 178.0*/177.8, 175.2/175.1*, 132.1/131.9*, 129.2, 128.7*/128.6, 126.6/126.5*, 50.3/50.1*, 39.0/38.7*, 37.7*/37.6, 32.4/32.3*, 27.0/25.4*, 20.6/20.4* ppm; HPLC: Chiralcel IB, λ = 240 nm, *n*-hexane/2-propanol, 80:20, 0.5 mL/min, major diastereomer: $t_r$ (3*S*,1´*R*) = 34.2 min, $t_r$ (3*R*,1´*S*) = 40.5 min, minor diastereomer: $t_r$ (3*R*,1´*R*) = 27.8 min, $t_r$ (3*S*,1´*S*) = 30.3 min.



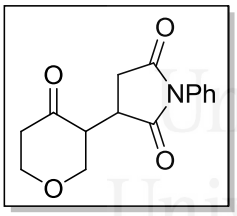



**3-(2-Oxocyclohexyl)-1-phenylpyrrolidine-2,5-dione (9ba):**[25] White solid. Mp 111-112 °C; mixture of diastereomers (ratio: 2.3/1.0, major/minor*); $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.44 (m, 2H), 7.41-7.36 (m, 1H), 7.35-7.29 (m, 2H), 3.29-3.24/3.20-3.16*(1H), 3.10-3.00*/2.88-2.82 (m, 2H), 2.65-2.51 (m, 1H), 2.50-2.30 (m, 2H), 2.20-1.96 (m, 3H), 1.81-1.55 (m, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 210.3/210.1*, 178.6*/178.4, 175.8/175.7*, 132.4/132.1*, 129.1, 128.6*/128.5, 126.8/126.6*, 52.2*/50.8, 41.9*/41.7, 41.3/40.1*, 33.4*/32.0, 31.8/30.3, 27.2*/27.0, 25.1*/24.9 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-

hexane/2-propanol, 70:30, 0.5 mL/min, major diastereomer: $t_r$ (3*R*,1´*S*) = 29.9 min, $t_r$ (3*S*,1´*R*) = 56.8 min, minor diastereomer: $t_r$ (3*S*,1´*S*) = 36.1 min, $t_r$ (3*R*,1´*R*) = 39.1 min.



**3-(2-Oxocycloheptyl)-1-phenylpyrrolidine-2,5-dione (9ca):**[23] White solid. Mp 129-130 °C; mixture of diastereomers (ratio: 1.3/1.0, major/minor*); $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.44 (m, 2H), 7.41-7.36 (m, 1H), 7.33-7.29 (m, 2H), 3.48-3.44*/3.33-3.26 (m, 1H), 3.09-2.97*/2.88-2.68 (m, 2H), 2.66-2.37 (m, 3H), 2.03-1.99 (m, 2H), 1.91-1.26 (m, 6H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 213.7/213.0*, 178.5, 175.8/175.7*, 132.3/132.1*, 129.1, 128.6*/128.5, 126.7/126.6*, 52.7*/51.7, 43.6/43.5*, 43.4/42.2*, 32.9*/31.9, 30.0*/29.9, 29.8/29.6*, 29.3/28.6*, 23.4 ppm; HPLC: Chiralpak AS-H, λ = 240 nm, *n*-hexane/2-propanol, 85:15, 0.7 mL/min, major diastereomer: $t_r$ (3*S*,1´*R*) = 40.3 min, $t_r$ (3*R*,1´*S*) = 51.6 min, minor diastereomer: $t_r$ (3*R*,1´*R*) = 36.6 min, $t_r$ (3*S*,1´*S*) = 43.4 min.



**3-(4-Oxotetrahydro-2*H*-pyran-3-yl)-1-phenylpyrrolidine-2,5-dione (9da):**[24] White solid. Mp 132-133 °C; mixture of diastereomers (ratio: 1.8/1.0, major/minor*); $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.46 (m, 2H), 7.42-7.38 (m, 1H), 7.34-7.30 (m, 2H), 4.39-4.34*/4.33-4.26 (m, 2H), 3.75-3.64*/3.56-3.46 (m, 2H), 3.12-2.54 (m, 5H), 2.43-2.37 (m, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 206.1*/205.7, 177.8*/177.3, 175.1/175.0*, 132.1, 129.1, 128.6, 126.6, 70.7*/70.6, 68.1, 52.9*/51.4, 42.5*/42.4, 37.3, 34.4*/32.1 ppm; HPLC: Chiralpak OD-H, λ = 240 nm, *n*-hexane/2-propanol, 60:40, 0.5 mL/min, major diastereomer: $t_r$ (3*R*,3´*R*) = 54.4 min, $t_r$ (3*S*,3´*S*) = 89.1 min, minor diastereomer: $t_r$ (3*S*,3´*R*) = 51.0 min, $t_r$ (3*R*,3´*S*) = 67.3 min.

### *4.2.8. Calculations*

The structures were optimized using density functional theory (DFT) with the B3LYP[38] and the 6-31G* basis set, as implemented in Gaussian 09.[39] Further reoptimization at the M06-2X/6-31G** level of theory[40] was carried out to account for the important dispersion forces in such large systems, and polarization functions for better description of hydrogen bonds involved in the reaction. Besides, solvation factors were introduced with the IEF-PCM method,[41] using chloroform or water as indicated in the text and figures. The energy values shown in Figures 3 and 4 also include single-point refinements at the M06-2X/6-311+G** level on the previously optimized structures (M06-2X/6-31G**), including polarization functions for a better description of hydrogen-bond activations. Additionally, salvation factors were introduced in the text and figures.

The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[42] were followed to verify the energy profiles connecting each transition state to the correct associated local minima.



[38] (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652; (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974-12980.

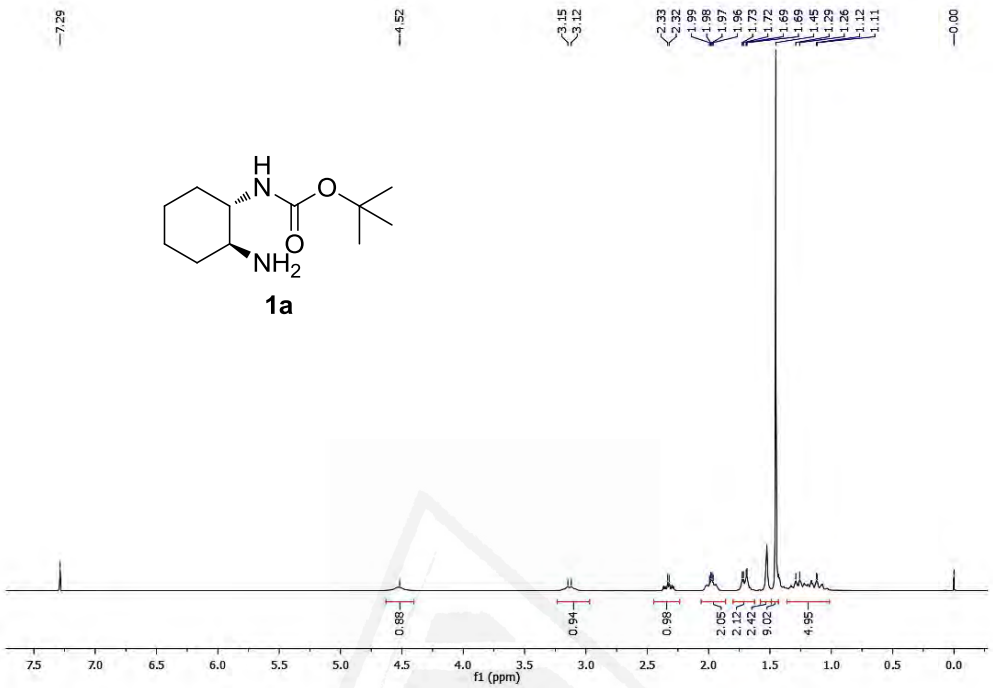
[39] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Menucci, B., Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin,. K. N.; Staroverov, V. N; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2009**.

[40] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215-241.

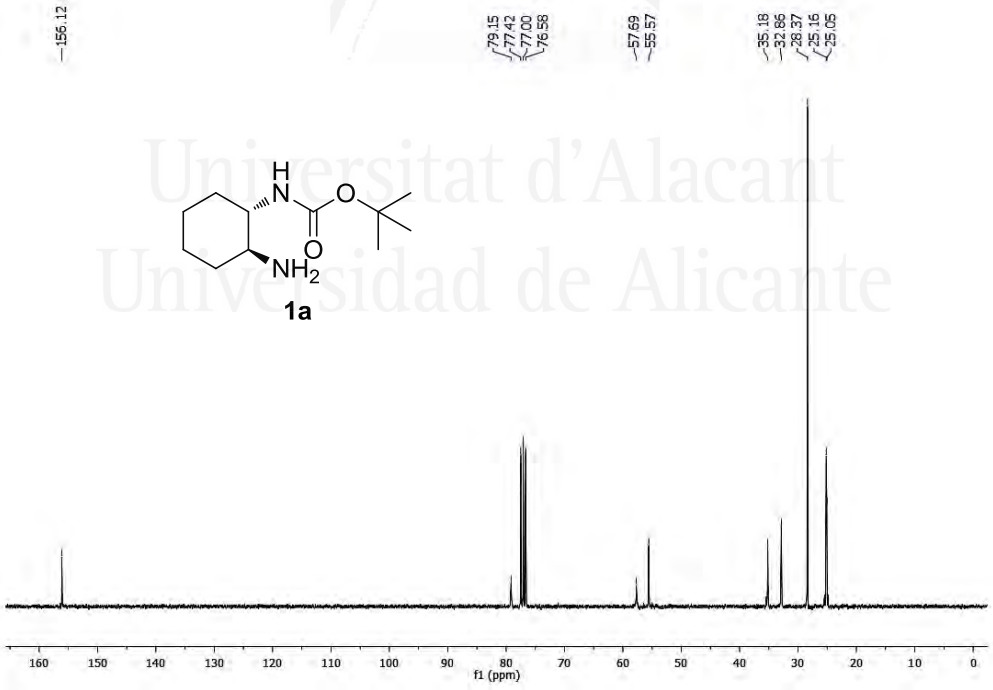
[41] (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032-3047; (b) Tomasi, J.; Mennucci, B.; Cancès, E. *THEOCHEM* **1999**, *464*, 211-226.

[42] González, C.; Schlegel, H. B. *J. Phys. Chem*. **1990**, *94*, 5523-5527.

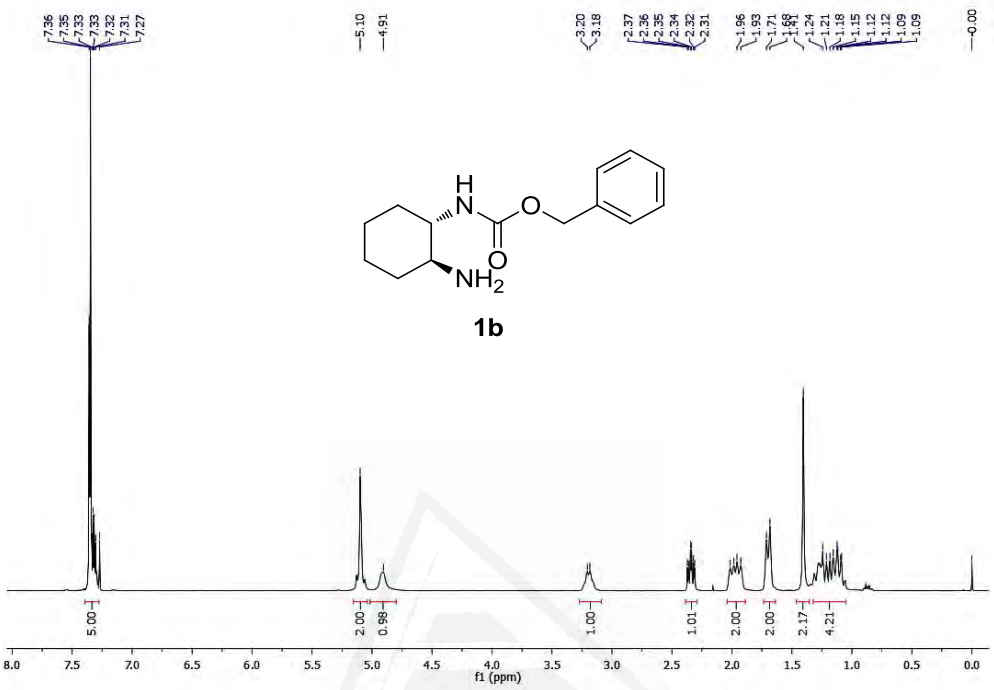
# 5. NMR SPECTRA

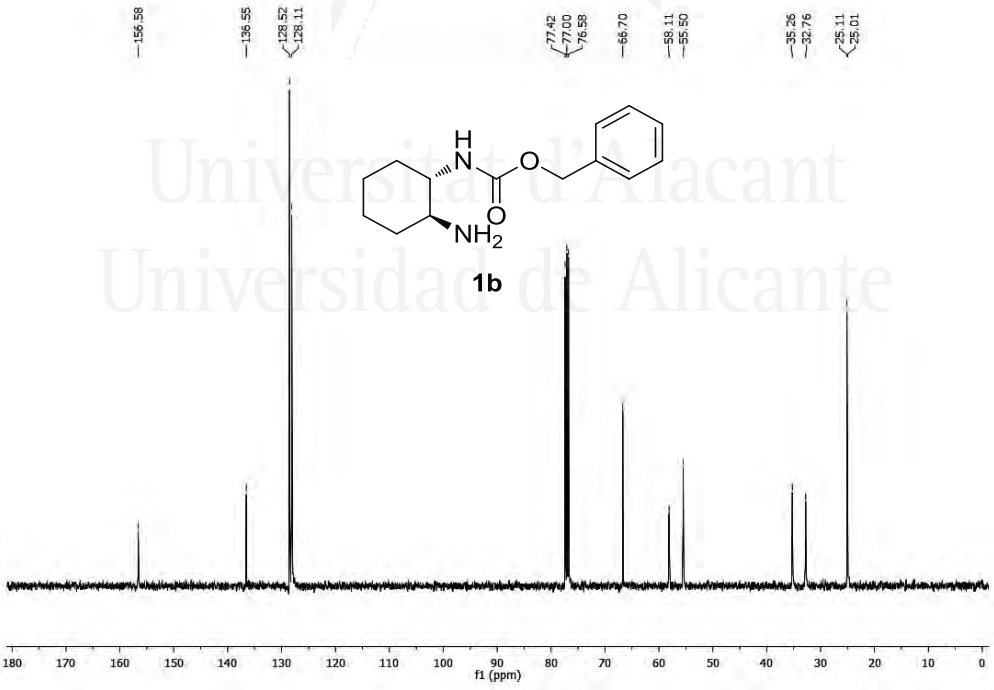


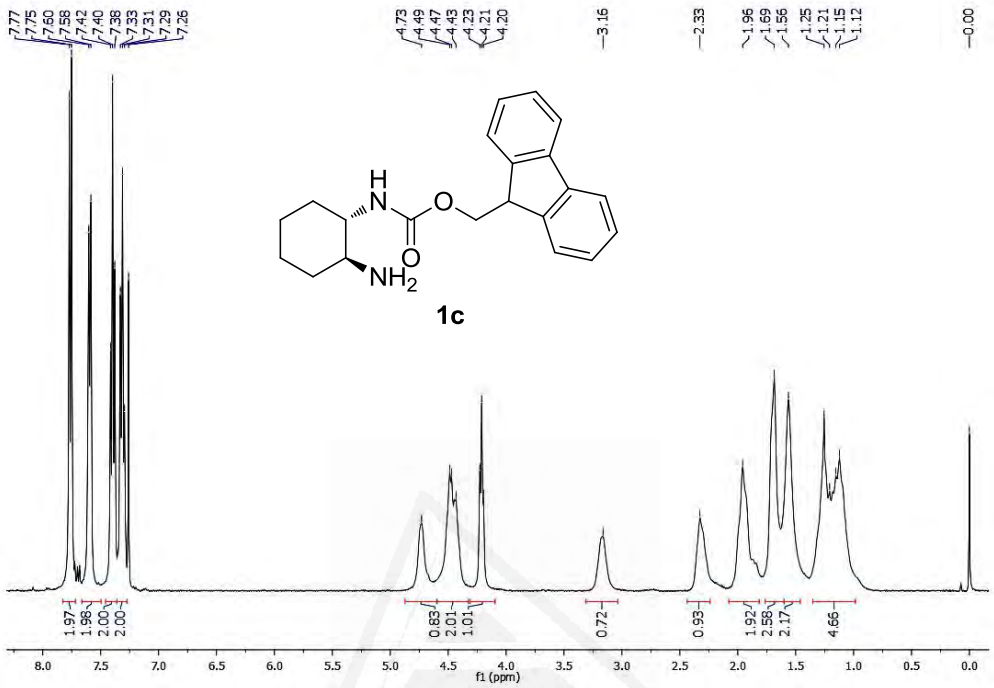

**1a**

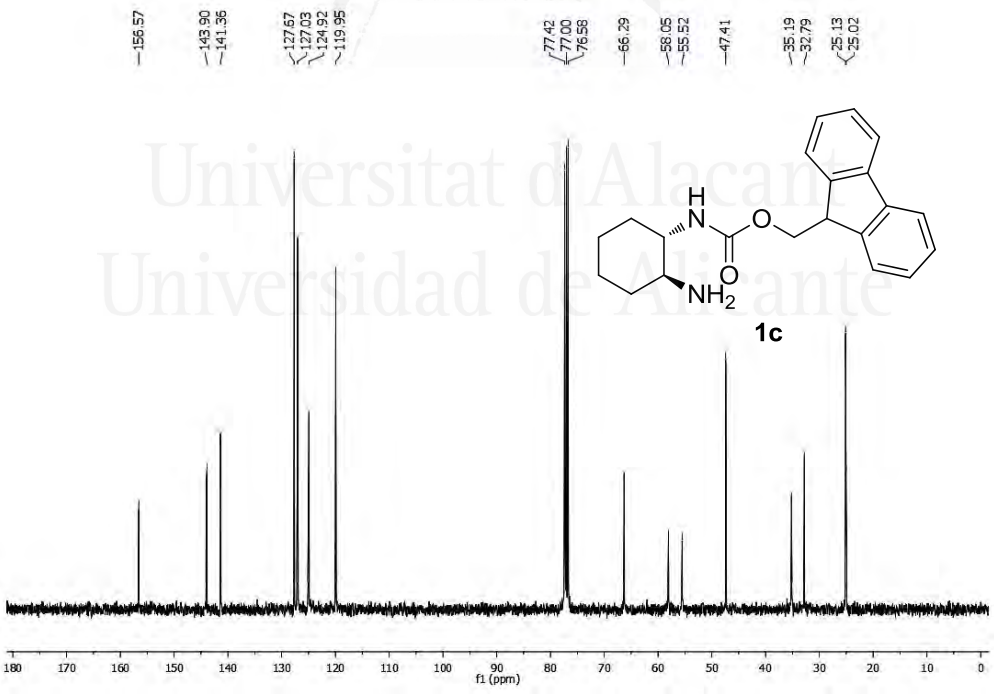


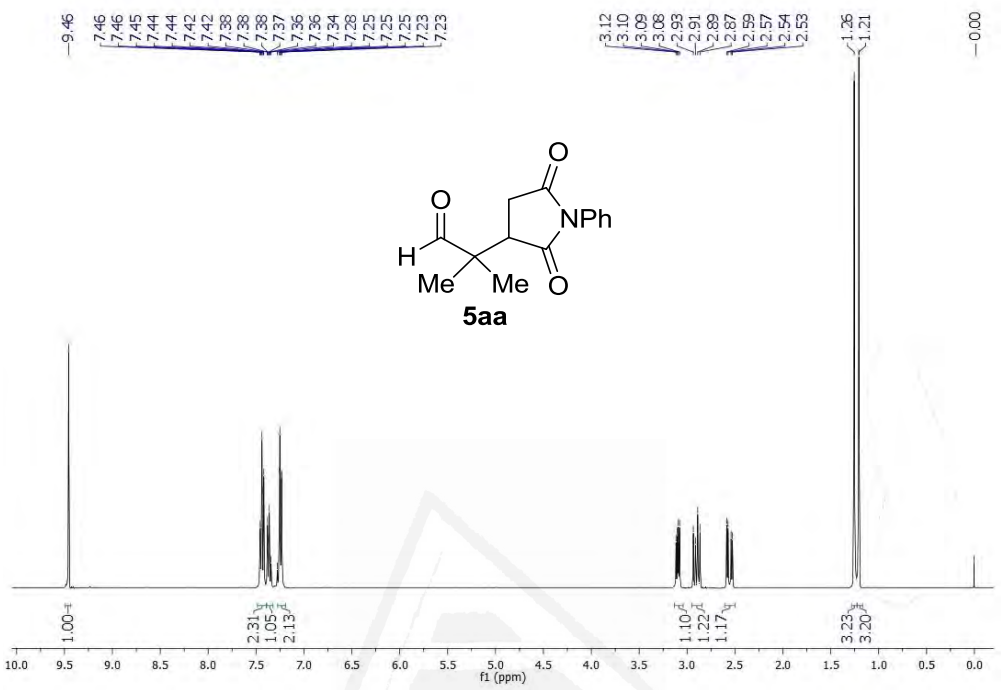

**1a**

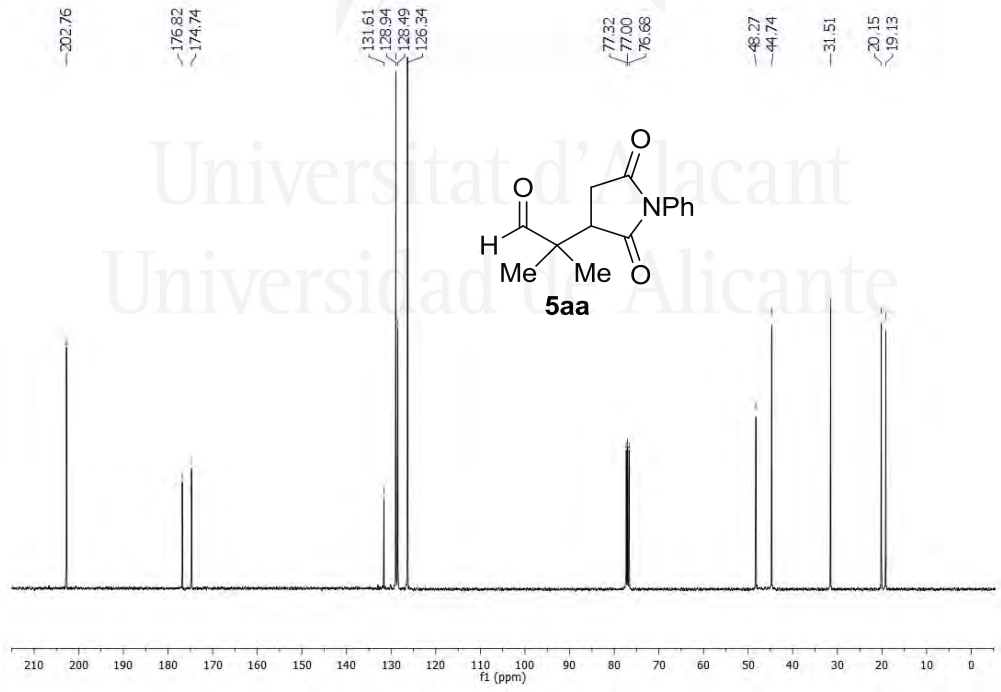


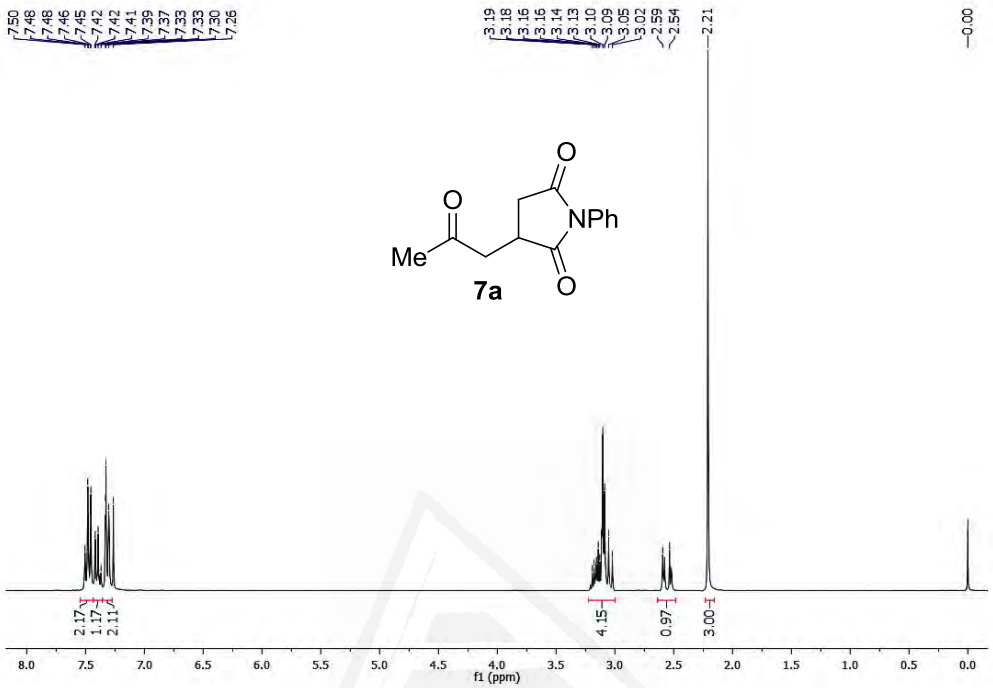



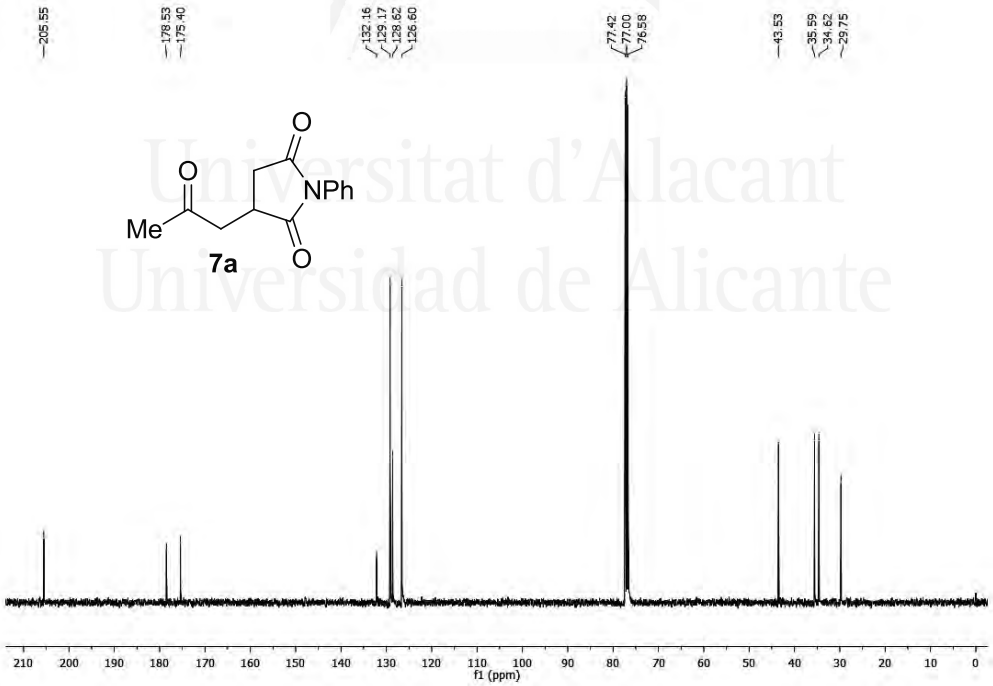






# 6. PUBLICATIONS

Tetrahedron: Asymmetry 25 (2014) 1091–1094

Contents lists available at ScienceDirect

Tetrahedron: Asymmetry

journal homepage: www.elsevier.com/locate/tetasy

# Solvent-dependent enantioswitching in the Michael addition of α,α-disubstituted aldehydes to maleimides organocatalyzed by mono-*N*-Boc-protected cyclohexa-1,2-diamines

Jesús Flores-Ferrándiz, Rafael Chinchilla *

*Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain*

ARTICLE INFO

*Article history:*
Received 6 May 2014
Accepted 19 June 2014

ABSTRACT

Enantiomerically pure mono-*N*-Boc-protected *trans*-cyclohexa-1,2-diamines are used as organocatalysts for the enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides. Using a single enantiomer of the organocatalyst, both enantiomeric forms of the resulting Michael adducts bearing a new quaternary stereocenter are obtained in high yields, by only changing the reaction solvent from chloroform (up to 86% ee) to aqueous DMF (up to 84% ee).

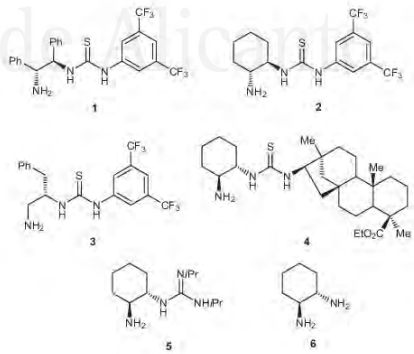


## 1. Introduction

The organocatalytic enantioselective Michael addition of carbon nucleophiles to maleimides is the most direct and easy method for preparing enantioenriched succinimide moieties,[1] which are present in natural products and some clinical drug candidates.[2] Moreover, succinimides can be transformed into γ-lactams,[3] which are privileged structural subunits for the design of pharmaceutical agents that are important in the treatment of cancer,[4] epilepsy,[5] HIV,[6] neurodegenerative disease, and depression.[7]

Carbon nucleophiles suitable for enantioselective conjugate additions to maleimides can be generated by α-deprotonation of pro-nucleophiles using chiral bifunctional organocatalysts bearing both an acidic moiety and a tertiary amine.[1] Coordination of the maleimide and the enolate generated after deprotonation to the chiral organocatalyst leads to an enantioselective process. However, when aldehydes are used as pro-nucleophiles, tertiary amines are not basic enough for the efficient generation of an enolate, and these organocatalysts cannot be employed. In this case, the enantioselective Michael addition reaction can be carried out by using amine-bearing organo catalysts that are suitable to form a transient enamine with the reacting aldehyde,[8] thus creating a chirality-inducing transition state after coordination with the maleimide. The first organocatalytic Michael addition of aliphatic aldehydes to *N*-aryl-maleimides used α,α-phenylprolinol silyl ether as the organocatalyst, although α,α-disubstituted aldehydes resulted in much lower enantioselectivities.[9]

Taking into consideration this enamine-forming approach, different bifunctional primary amine-bearing organocatalysts have been applied to enantioselective Michael additions of these 'difficult' α,α-disubstituted aldehydes to maleimides, giving high enantioselections in the corresponding succinimides.[10] Some examples include the primary amine–thioureas **1**,[10a,b] **2**[10a,b] and **3**,[10e] the beyerane-containing thiourea **4**,[10f] the primary amine–guanidine **5**,[10h,j] and even the simple *trans*-cyclohexa-1,2-diamine **6**.[10k]



* Corresponding author. Tel.: +34 965903822; fax: +34 965903549.
*E-mail address:* chinchilla@ua.es (R. Chinchilla).

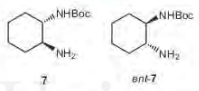
http://dx.doi.org/10.1016/j.tetasy.2014.06.014
0957-4166/

When dealing with enantioselective organocatalysis, as with any asymmetric catalysis, opposite enantiomeric products are typically obtained by using opposite enantiomeric organocatalysts. However, switching the enantioselectivity of an organocatalyst just by varying the reaction conditions, although potentially very interesting, is not an easy matter. Thus, only a few examples of switching the enantioselectivity of an organocatalyzed process by changing the counteranions of the catalyst,[11] adding bases,[12] acids,[13] or other additives,[14] or even by light irradiation,[15] have been reported. In addition, examples of changing the enantioselectivity of organocatalyzed reactions simply by changing the reaction solvent are scarce, and limited to the use in some particular cases of some chiral unsupported[16a] and supported[16b] MacMillan's imidazolidinones or α,α-diphenyl-2-pyrrolidine methanol[17] as organocatalysts, as well as conformationally flexible peptidic[18] and guanidine/bisthiourea species.[19]

Herein we report how a change in the solvent in the enantioselective addition reaction of the particularly 'difficult' α,α-disubstituted aldehydes to maleimides allows a single enantiomer of *N*-Boc-monoprotected *trans*-cyclohexa-1,2-diamines to be employed as an organocatalyst for the synthesis of both enantiomers of the final succinimides.

## 2. Results and discussion

The (1*S*,2*S*)-cyclohexa-1,2-diamine **6** was chosen as a chirality source; we performed its mono-*N*-protection with the *tert*-butoxycarbonyl (Boc) group via a procedure consisting of a reaction of **6** with 1 equiv of hydrogen chloride (2 M, $Et_2O$) and subsequent treatment with di-*tert*-butyl carbonate.[20] The chiral mono-Boc-protected diamine **7** obtained was explored as a primary amine-containing organocatalyst for the model enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide, under different reaction conditions (Table 1).



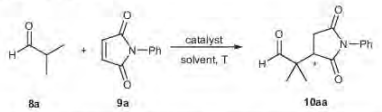

7 *ent*-7

The use of a 20 mol % loading of **7** in toluene as solvent at room temperature gave succinimide (*S*)-**10aa** in almost quantitative yield of 67% ee (Table 1, entry 1). The absolute configuration was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see Experimental).[10i] Changing the solvent to hexane gave (*S*)-**10aa** with a higher ee, whereas the use of ether as solvent lowered the enantioselectivity (Table 1, entries 2 and 3). When $CH_2Cl_2$ and $CHCl_3$ were employed as solvents, (*S*)-**10aa** was obtained with 63% and 75% ee, respectively (Table 1, entries 4 and 5).

However, when DMF was used as the solvent the enantioselectivity of the process switched completely and gave (*R*)-**10aa** with 62% ee (Table 1, entry 6). The use of water as the solvent considerably increased the reaction rate, affording also (*R*)-**10aa** almost quantitatively in 2 h although with only 32% ee (Table 1, entry 7). Therefore, we explored the possible use of mixtures of DMF/$H_2O$ as the solvent, something that has proven to be effective when primary amine–guanidines have been used as organocatalysts in this reaction.[10h,j] Thus, different DMF/$H_2O$ v/v ratios were studied (Table 1, entries 8–10), with a 2:1 v/v ratio affording (*R*)-**10aa** in 90% yield and with 84% ee (Table 1, entry 9).

Once the most appropriate solvents for achieving opposite enantioselectivities were selected [$CHCl_3$ for (*S*)-**10aa** and DMF/$H_2O$ 2:1 v/v for (*R*)-**10aa**], we explored lowering the organocatalyst loading. Thus, the amount of organocatalyst **7** was decreased to 10 and 5 mol % using both solvents (Table 1, entries 11–14); higher

**Table 1**
Screening and optimization of the reaction conditions for the enantioswitched Michael addition reaction




8a 9a 10aa

| Entry | Catalyst (mol %) | Solvent | *T* (°C) | *t* (h) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **7** (20) | PhMe | 25 | 20 | 98 | 67 (*S*) |
| 2 | **7** (20) | Hexane | 25 | 14 | 85 | 73 (*S*) |
| 3 | **7** (20) | $Et_2O$ | 25 | 14 | 95 | 32 (*S*) |
| 4 | **7** (20) | $CH_2Cl_2$ | 25 | 20 | 95 | 63 (*S*) |
| 5 | **7** (20) | $CHCl_3$ | 25 | 20 | 99 | 75 (*S*) |
| 6 | **7** (20) | DMF | 25 | 44 | 94 | 62 (*R*) |
| 7 | **7** (20) | $H_2O$ | 25 | 2 | 97 | 32 (*R*) |
| 8 | **7** (20) | DMF/$H_2O$[c] | 25 | 17 | 94 | 70 (*R*) |
| 9 | **7** (20) | DMF/$H_2O$[d] | 25 | 20 | 90 | 84 (*R*) |
| 10 | **7** (20) | DMF/$H_2O$[e] | 25 | 24 | 88 | 80 (*R*) |
| 11 | **7** (10) | $CHCl_3$ | 25 | 20 | 97 | 86 (*S*) |
| 12 | **7** (10) | DMF/$H_2O$[d] | 25 | 20 | 95 | 84 (*R*) |
| 13 | **7** (5) | $CHCl_3$ | 25 | 40 | 95 | 76 (*S*) |
| 14 | **7** (5) | DMF/$H_2O$[d] | 25 | 40 | 93 | 82 (*R*) |
| 15 | **7** (10) | $CHCl_3$ | 0 | 48 | 94 | 70 (*S*) |
| 16 | **7** (10) | DMF/$H_2O$[d] | 0 | 48 | 91 | 82 (*R*) |
| 17 | *ent*-**7** (10) | $CHCl_3$ | 25 | 20 | 97 | 84 (*R*) |
| 18 | *ent*-**7** (10) | DMF/$H_2O$[d] | 25 | 20 | 94 | 83 (*S*) |

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC.
[c] 1:1, v/v.
[d] 2:1, v/v.
[e] 4:1, v/v.

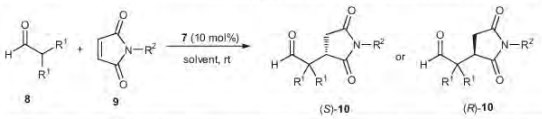
enantioselections were observed for the (*S*)- and (*R*)-stereoisomers when a loading of 10 mol % was used [86% ee for (*S*)-**10aa** and 84% ee for (*R*)-**10aa**] (Table 1, entries 11 and 12). Using this optimized 10 mol % organocatalyst loading, we lowered the reaction temperature to 0 °C, but no increase in the stereoselectivity of the reaction was observed (Table 1, entries 15 and 16).

Attempting to achieve opposite enantioselections to those obtained using organocatalyst **7**, we prepared the corresponding enantiomer *ent*-**7** following the same procedure but starting from (1*R*,2*R*)-cyclohexa-1,2-diamines. When mono-*N*-Boc-protected diamine *ent*-**7** was used as the organocatalyst under the most convenient reaction conditions [10 mol % organocatalyst loading, room temperature, $CHCl_3$ or DMF/$H_2O$ 2:1 v/v as solvent], the expected opposite enantioselections to those obtained when using **7** were observed [(*R*)-**10aa** using $CHCl_3$ as solvent and (*S*)-**10aa** using DMF/$H_2O$ 2:1 v/v] (Table 1, entries 17 and 18).

In order to determine whether the observed ee for (*R*)-**10aa** changed during the process, the model reaction of aldehyde **8a** and maleimide **9a** in the presence of organocatalyst **7** (10 mol %) was carried out in DMF/$H_2O$ 2:1 v/v with reaction times of 4, 8, and 12 h. In all cases the ee for (*R*)-**10aa** remained at 84%, the same value as to when the reaction was completed. In an attempt to rule out whether the change in the enantioselectivity was due to the former evolution of the final product, product (*R*)-**10aa** (84% ee) was combined with organocatalyst **7** (10 mol %) in $CHCl_3$ as the solvent at room temperature. After stirring for 20 h, product (*R*)-**10aa** was recovered with its enantioinduction intact.

With the most effective reaction conditions in hand [**7** (10 mol %), $CHCl_3$ for (*S*)-enantiomer and DMF/$H_2O$ 2:1 v/v for (*R*)-enantiomer, rt] we extended this organocatalytic solvent-dependent enantioswitching methodology to other aldehydes and maleimides (Table 2).[21] As in the case of the model reaction, the absolute configuration of the resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature.[22,23]

**Table 2**
Solvent-dependent enantioswitched Michael addition of aldehydes to maleimides organocatalyzed by mono-Boc-protected 1,2-diamine **7**




**8** **9** (*S*)-**10** (*R*)-**10**

| Entry | Aldehyde | | Maleimide | | Solvent | *t* (h) | Adduct No. | Yield[a] (%) | ee[b,c] (%) |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | No. | $R^2$ | No. | | | | | |
| 1 | Me | **8a** | Ph | **9a** | $CHCl_3$ | 20 | (*S*)-**10aa** | 97 | 86 |
| 2 | | | | | DMF/$H_2O$ 2:1 | 20 | (*R*)-**10aa** | 95 | 84 |
| 3 | Me | **8a** | 4-$ClC_6H_4$ | **9b** | $CHCl_3$ | 30 | (*S*)-**10ab** | 99 | 60 |
| 4 | | | | | DMF/$H_2O$ 2:1 | 30 | (*R*)-**10ab** | 97 | 74 |
| 5 | Me | **8a** | 4-$BrC_6H_4$ | **9c** | $CHCl_3$ | 30 | (*S*)-**10ac** | 99 | 70 |
| 6 | | | | | DMF/$H_2O$ 2:1 | 30 | (*R*)-**10ac** | 98 | 70 |
| 7 | Me | **8a** | 4-$AcC_6H_4$ | **9d** | $CHCl_3$ | 26 | (*S*)-**10ad** | 92 | 40 |
| 8 | | | | | DMF/$H_2O$ 2:1 | 26 | (*R*)-**10ad** | 15 | 80 |
| 9 | Me | **8a** | Me | **9e** | $CHCl_3$ | 21 | (*S*)-**10ae** | 94 | 53 |
| 10 | | | | | DMF/$H_2O$ 2:1 | 21 | (*R*)-**10ae** | 91 | 68 |
| 11 | Me | **8a** | H | **9f** | $CHCl_3$ | 17 | (*S*)-**10af** | 94 | 50 |
| 12 | | | | | DMF/$H_2O$ 2:1 | 17 | (*R*)-**10af** | 88 | 70 |
| 13 | Et | **8b** | Ph | **9a** | $CHCl_3$ | 48 | (*S*)-**10ba** | 70 | 55 |
| 14 | | | | | DMF/$H_2O$ 2:1 | 48 | (*R*)-**10ba** | 93 | 68 |
| 15 | $-(CH_2)_4-$ | **8c** | Ph | **9a** | $CHCl_3$ | 30 | (*S*)-**10ca** | 99 | 49 |
| 16 | | | | | DMF/$H_2O$ 2:1 | 30 | (*R*)-**10ca** | 96 | 61 |
| 17 | $-(CH_2)_5-$ | **8d** | Ph | **9a** | $CHCl_3$ | 48 | (*S*)-**10da** | 96 | 14 |
| 18 | | | | | DMF/$H_2O$ 2:1 | 48 | (*R*)-**10da** | 96 | 35 |

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities determined by chiral HPLC.[22]
[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.[22]

Thus, when $CHCl_3$ was used as the solvent, isobutyraldehyde reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 4-position of **9b** and **9c**, and the succinimides (*S*)-**10ab** and (*S*)-**10ac** were obtained in 60% and 70% ee, respectively (Table 2, entries 3 and 5). However, when DMF/$H_2O$ 2:1 v/v was the reaction solvent, adducts (*R*)-**10ab** and (*R*)-**10ac** were isolated in 74% and 70% ee (Table 2, entries 4 and 6). When an acetyl group was present on the phenyl ring of the maleimide, as in the case of **9d**, the enantioselectivities for the corresponding enantiomeric succinimides (*S*)-**10ad** and (*R*)-**10ad** were 40% and 80%, depending on the use of $CHCl_3$ or DMF/$H_2O$ 2:1 v/v as the solvent, respectively (Table 2, entries 7 and 8).

Non-*N*-arylated maleimides were also employed for the conjugate addition with isobutyraldehyde. Thus, *N*-methylmaleimide **9e** gave the (*S*)- and (*R*)-enantiomer of adduct **10ae** depending on the use of $CHCl_3$ and DMF/$H_2O$ 2:1 v/v as the reaction solvent (53% and 68% ee, respectively) (Table 2, entries 9 and 10). Maleimide (**9f**) was also used as a Michael acceptor and afforded (*S*)-**10af** (50% ee) when using $CHCl_3$ as the solvent, and (*R*)-**10af** (70% ee) when the solvent was DMF/$H_2O$ 2:1 v/v (Table 2, entries 11 and 12).

Other α,α-disubstituted aldehydes were employed for the organocatalyzed Michael addition reaction to *N*-phenylmaleimide. 2-Ethylbutanal **8b** afforded succinimides (*S*)-**10ba** (55% ee) and (*R*)-**10ba** (68% ee) using $CHCl_3$ and DMF/$H_2O$ 2:1 v/v as solvents, respectively (Table 2, entries 13 and 14). Cyclopentane-**8c** and cyclohexane carbaldehyde **8d** gave almost quantitative amounts of succinimides (*S*)-**10ca** and (*S*)-**10da** with 49% and 14% ee, respectively, when $CHCl_3$ was the reaction solvent, while (*R*)-**10ca** and (*R*)-**10da** were obtained with 61% and 35% ee, respectively when using DMF/$H_2O$ 2:1 v/v (Table 2, entries 15–18).

## 3. Conclusion

It can be concluded that the easily prepared *N*-Boc-monoprotected chiral *trans*-cyclohexa-1,2-diamines can be used as organocatalysts in the high-yielding enantioselective conjugate addition of α,α-disubstituted aldehydes to different maleimides, giving rise to an uncommon solvent-dependent enantioswitched reaction. Thus, both the (*S*)- or (*R*)-enantioenriched forms of the Michael adducts can be obtained by employing a single mirror form of the organocatalyst, by simply changing the reaction solvent from chloroform to aqueous *N*,*N*-dimethylformamide. Further studies devoted to gaining insight into the origin of this solvent-induced stereoselectivity switch, as well as extending this methodology to other organocatalysts and substrates are currently underway.

## Acknowledgments

We thank the financial support from the Spanish Ministerio de Economía y Competitividad (Project CTQ2011-24151), FEDER, the COST Action CM0905 'Organocatalysis', and the University of Alicante.

## References

1. Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem. Asian J.* **2012**, *8*, 328–346.
2. (a) Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc.* **1987**, *109*, 4409–4411; (b) Malochet-Grivois, C.; Roussakis, C.; Robillard, N.; Biard, J. F.; Riou, D.; Debitus, C.; Verbist, J. F. *Anticancer Drug Des.* **1992**, *7*, 493–502; (c) Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964–1973; (d) Freiberg, C.; Brunner, N. A.; Schiffer, G.; Lampe, T.; Pohlmann, J.; Brands, M.; Raabe, M.; Haebich, D.; Ziegelbauer, K. *J. Biol. Chem.* **2004**, *279*, 26066–26073; (e) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577–5583; (f) Uddin, J.; Ueda, K.; Siwu, E. R. O.; Kita, M.; Uemura, D. *Bioorg. Med. Chem.* **2006**, *14*, 6954–6961; (g) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini-Rev. Med. Chem.* **2012**, *12*, 671–700.
3. (a) Nöth, J.; Frankowski, K. J.; Neuenswander, B.; Aubé, J.; Reiser, O. *J. Comb. Chem.* **2008**, *10*, 456–459; (b) Fenster, E.; Hill, D.; Reiser, O.; Aube, J. *Beilstein J. Org. Chem.* **2012**, *8*, 1804–1813.
4. Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.-H.; Neuteboom, S. T. C.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407–419.

5. (a) Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1996**, *39*, 1898–1906; (b) Das Sarma, K.; Zhang, J.; Huang, Y.; Davidson, J. G. *Eur. J. Org. Chem.* **2006**, 3730–3737.
6. (a) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162; (b) Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689–5692.
7. (a) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; (b) Tang, K.; Zhang, J.-T. *Neurol. Res.* **2002**, *24*, 473–478.
8. (a) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; (b) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491–2513.
9. Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Córdova, A. *Chem. Commun.* **2007**, 734–735.
10. (a) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774; (b) Bai, J.-F.; Peng, L.; Wang, L.-L.; Wang, L.-X.; Xu, X.-Y. *Tetrahedron* **2010**, *66*, 8928–8932; (c) Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979–7982; (d) Miura, T.; Nishida, S.; Masuda, A.; Tada, N.; Itoh, A. *Tetrahedron Lett.* **2011**, *52*, 4158–4160; (e) Miura, T.; Masuda, A.; Ina, M.; Nakashima, K.; Nishida, S.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1605–1609; (f) Ma, Z.-W.; Liu, Y.-X.; Li, P.-L.; Ren, H.; Zhu, Y.; Tao, J.-C. *Tetrahedron: Asymmetry* **2011**, *22*, 1740–1748; (g) Ma, Z.-W.; Liu, Y.-X.; Zhang, W.-J.; Tao, Y.; Zhu, Y.; Tao, J.-C.; Tang, M.-S. *Eur. J. Org. Chem.* **2011**, 6747–6754; (h) Avila, A.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1625–1627; (i) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J.* **2012**, *18*, 4088–4098; (j) Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5085–5092; (k) Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Tetrahedron: Asymmetry* **2013**, *24*, 1531–1535; (l) Durmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2013**, *24*, 1443–1448; (m) Kokotos, C. G. *Org. Lett.* **2013**, *15*, 2406–2409; (n) Muramulla, S.; Ma, J.-A.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2013**, *355*, 1260–1264; (o) Orlandi, S.; Pozzi, G.; Ghisetti, M.; Benaglia, M. *New J. Chem.* **2013**, *37*, 4140–4147; (p) Yang, W.; Jiang, K.-Z.; Lu, X.; Yang, H.-M.; Li, L.; Lu, Y.; Xu, L.-W. *Chem. Asian J.* **2013**, *8*, 1182–1190.
11. Mazón, P.; Chinchilla, R.; Nájera, C.; Guillena, G.; Kreiter, R.; Klein Gebbink, R. J. M.; van Koten, G. *Tetrahedron: Asymmetry* **2002**, *13*, 2181–2185.
12. (a) Blackmond, D. G.; Moran, A.; Hughes, M.; Armstrong, A. *J. Am. Chem. Soc.* **2010**, *132*, 7598–7599; (b) Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 8899–8903.
13. Moteki, S. A.; Han, J.; Arimitsu, S.; Akakura, M.; Nakayama, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 1187–1190.
14. (a) Wu, F.-C.; Da, C.-S.; Du, Z.-X.; Guo, Q.-P.; Li, W.-P.; Yi, L.; Jia, Y.-N.; Ma, X. *J. Org. Chem.* **2009**, *74*, 4812–4818; (b) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138–6139.
15. Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429–1432.
16. (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482–5487; (b) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Campisciano, V.; Noto, R. *Catal. Commun.* **2011**, *16*, 75–80.
17. Sunden, H.; Rios, R.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 7865–7869.
18. Messerer, M.; Wennemers, H. *Synlett* **2011**, 499–502.
19. Sohtome, Y.; Yamaguchi, T.; Tanaka, S.; Nagasawa, K. *Org. Biomol. Chem.* **2013**, *11*, 2780–2786.
20. Lee, D. W.; Ha, H.-J.; Lee, W. K. *Synth. Commun.* **2007**, *37*, 737–742.
21. *Typical experimental procedure for the enantioselective Michael addition reaction:* To a solution of **7** or *ent*-**7** (0.04 mmol) and **9** (0.2 mmol) in DMF/$H_2O$ (2:1, v/v) (0.5 mL) was added aldehyde **8** (0.4 mmol) and the reaction was stirred at rt until completion (TLC). A solution of 2 M HCl (10 mL) was then added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed with water (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated (15 torr). The resulting crude was purified by flash chromatography (hexane/AcOEt) to afford adducts **10**, which gave consistent spectroscopic data with those reported in the literature.[10]
22. *Enantioselectivities were determined by HPLC using n-hexane/2-propanol mixtures as eluant and the following chiral columns:* Chiralcel OD-H for **10aa**, **10ab**, **10ac**, **10ca**, **10da**, Chiralpak AS-H for **10ad**, **10ae**, **10ba**, and Chiralpak AD-H for **10af**. Reference racemic samples of adducts **10** were obtained by performing the reaction using 4-methylbenzylamine (20 mol %) as the organocatalyst in toluene as the solvent at room temperature.
23. The absolute configurations for adducts **10** were determined according to the described order of elution of their enantiomers in chiral HPLC.[10]

FULL PAPER

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201403415

# Solvent-Induced Reversal of Enantioselectivity in the Synthesis of Succinimides by the Addition of Aldehydes to Maleimides Catalysed by Carbamate-Monoprotected 1,2-Diamines

**Jesús Flores-Ferrándiz,[a] Béla Fiser,[b] Enrique Gómez-Bengoa,[b] and Rafael Chinchilla*[a]**

**Keywords:** Asymmetric catalysis / Organocatalysis / Michael addition / Enantioselectivity / Solvent effects / Transition states

A simple change in the polarity of the solvent allows both enantiomers of substituted succinimides to be obtained in the enantioselective conjugate addition reaction of aldehydes, mainly α,α-disubstituted, to maleimides catalysed by chiral carbamate-monoprotected *trans*-cyclohexane-1,2-diamines. Using a single enantiomer of the organocatalyst, both enantiomers of the resulting Michael adducts are obtained in high yields by simply changing the reaction solvent from aqueous DMF (up to 84 % *ee*) to chloroform (up to 86 % *ee*). Theoretical calculations are used to explain this uncommon reversal of the enantioselectivity; two transition state orientations of different polarities are differently favoured in polar or nonpolar solvents.

## Introduction

In enantioselective organocatalysis, as in any asymmetric catalysis, opposite enantiomeric products are typically obtained by using opposite enantiomers of the organocatalysts. However, being able to switch the enantioselectivity of an organocatalytic reaction simply by changing the reaction conditions is an exciting matter of great potential interest. One of the main reasons for this is that having both enantiomeric forms of certain organocatalysts can be difficult or costly.

Although it is rare, there are some reported examples of enantioselective organocatalytic reactions where both enantiomers are obtained using a single enantiomer of the catalyst. These results are always unexpected and serendipitous.[1] Thus, a few examples of switching the enantioselectivity of an organocatalytic process by changing the counteranion in the catalyst,[2] by adding bases,[3] acids,[4] or other additives,[5] or even by light irradiation[6] have been reported.

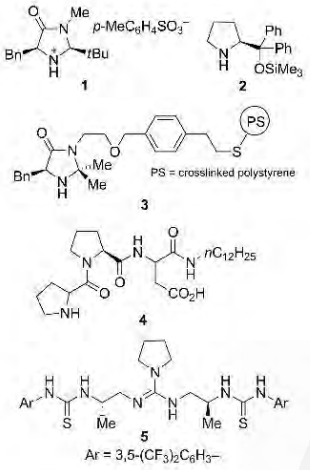
However, it would be simpler just to change the reaction solvent, and some examples of solvent-dependent enantioselectivity reversal have been reported. Thus, an inversion of enantioselectivity was discovered in the enantioselective Michael addition of dimethyl malonate to chalcone catalysed by a quininium ammonium salt when the reaction medium was changed from conventional organic solvents to ionic liquids.[7] A solvent-dependent enantioselectivity reversal was also observed when the imidazolidinone salt **1** was used as an organocatalyst in the Michael addition of an indole to acrolein for the synthesis of a pyrroloindoline.[8] Later, α,α-phenylprolinol silyl ether **2** was shown to catalyse the enantioselective α-phenylselenenylation of isovaleraldehyde, and a change in the sense of the enantioselectivity was observed when the polarity of the solvent was changed.[9] A similar solvent-influenced reversal of the enantioselectivity of this α-phenylselenenylation reaction was also reported when polystyrene-supported imidazolidinone **3** was used as a recoverable organocatalyst.[10]

An inversion of enantioselectivity induced by a change in the solvent has also been observed in the enantioselective Michael addition of cyclohexanone to chalcones using 1-ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt as an organocatalyst.[11] Furthermore, some conformationally flexible organocatalysts have been used in reactions in which the sense of enantioselectivity is solvent dependent: peptidic system **4** in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde,[12] and bisthiourea/guanidine **5** in a recent Mannich-type addition of malonates to *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) aldimines.[13] No explanation for why a particular enantiomer of the final product is obtained using one solvent and the opposite enantiomer is obtained using another has been given in any of the reported cases.

[a] Departamento de Química Orgánica,
Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO),
Universidad de Alicante,
Apdo. 99, 03080 Alicante, Spain
E-mail: chinchilla@ua.es
http://dqorg.ua.es/en/
[b] Departamento de Química Orgánica I, Universidad del País Vasco,
Apdo. 1072, 20080 San Sebastián, Spain

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403415.




1 2 3 4 5

From the huge array of enantioselective organocatalytic reactions, those leading to enantioenriched substituted succinimides have aroused interest in recent years. These compounds are present in natural products and some clinical drug candidates,[14] and can be transformed into γ-lactams,[15] which are subunits for the design of pharmaceutical agents important in the treatment of cancer,[16] epilepsy,[17] HIV,[18] neurodegenerative disease, and depression.[19]

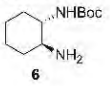
The easiest and most direct way of preparing enantioenriched succinimide moieties is by organocatalytic enantioselective Michael addition of carbon nucleophiles to maleimides.[20] These carbon nucleophiles can be generated by α-deprotonation of pro-nucleophiles using chiral bifunctional organocatalysts bearing both a basic tertiary amine and an acidic moiety able to coordinate the maleimide.[20] However, when aldehydes are used as pro-nucleophiles, tertiary amines are not basic enough to generate an enolate, and the enantioselective Michael addition reaction is carried out by using amine-contaning organocatalysts that can form a transient enamine with the reacting aldehyde.[21]

The first organocatalytic Michael addition of aliphatic aldehydes to *N*-aryl-substituted maleimides used α,α-phenylprolinol silyl ether as an organocatalyst, but the "difficult" α,α-disubstituted aldehydes resulted in much lower enantioselectivities.[22] Since then, different chiral bifunctional primary-amine-containing organocatalysts have been applied to the enantioselective Michael addition of these α,α-disubstituted aldehydes to maleimides leading to enantioenriched succinimides. Most of the catalysts were primary amine thioureas,[23] but primary amine guanidines,[24] amino acids,[25] amino acids combined with amine thioureas,[26] amines,[27] and 1,2-diamines[28] have also been used.

In this paper, we describe how a simple change of the reaction solvent can produce a reversal of the enantioselectivity of the conjugate addition of aldehydes to maleimides catalysed by chiral carbamate-monoprotected *trans*-cyclohexane-1,2-diamines.[29] In this way, a single enantiomeric form of a simple organocatalyst can be used for the preparation of both enantiomeric forms of the corresponding substituted succinimides. The origin of this uncommon solvent-dependent enantioswitching can be explained by theoretical calculations.

## Results and Discussion

We attempted to explore the behaviour of chiral mono-Boc-protected diamine **6** as a primary-amine-containing bifunctional organocatalyst for the enantioselective conjugate addition reaction of aldehydes to *N*-substituted maleimides. This Boc-containing amine **6** was obtained following a reported procedure involving the reaction of (1*S*,2*S*)-cyclohexane-1,2-diamine with 1 equiv. of hydrogen chloride, followed by treatment with di-*tert*-butyl carbonate.[30] The enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide was chosen as a model reaction to test the efficiency of **6** as an organocatalyst (Table 1).




**6**

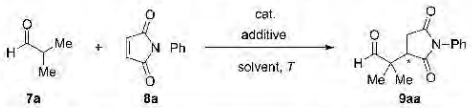
Initially, primary amine **6** (20 mol-%) was used in toluene as solvent at room temperature, and this gave succinimide (*S*)-**9aa** almost quantitatively with 67% *ee* (Table 1, entry 1). The absolute configuration for **9aa** was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see Exp. Section).[24b] When hexane was used as solvent, the enantioselectivity for (*S*)-**9aa** increased to 73% *ee*, whereas the use of ethyl ether resulted in a lower *ee* (Table 1, entries 2 and 3). When $CH_2Cl_2$ and $CHCl_3$ were used as solvents, 63 and 75% *ee* values, respectively, for (*S*)-**9aa** were observed (Table 1, entries 4 and 5).

Unexpectedly, when DMF was used as solvent, the enantioselectivity of the process reversed totally, and the oppositely configured succinimide [i.e., (*R*)-**9aa**]was obtained in high yield and with 62% *ee*, albeit with a much lower reaction rate (Table 1, entry 6). The use of solvents such as 1,4-dioxane or acetone also gave (*R*)-**9aa** with lower *ee* values (Table 1, entries 7 and 8). When water was used as the solvent, the rate of the reaction increased considerably and (*R*)-**9aa** was formed almost quantitatively, albeit with only 32% *ee* (Table 1, entry 9). Therefore, combining the highest *ee* and reaction rate, we explored the use of mixtures of DMF and $H_2O$ as reaction solvent. Thus, different DMF/$H_2O$ v/v ratios were tested (Table 1, entries 10–12). A 2:1, v/v mixture of DMF and $H_2O$ gave (*R*)-**9aa** in 90% yield with 84% *ee* (Table 1, entry 11).

Having established the most appropriate solvents for achieving a reversal in the enantioselectivity [i.e., $CHCl_3$ for

Table 1. Screening and optimization of the reaction conditions for the reversal of the enantioselectivity in the Michael addition reaction.




7a 8a 9aa

| Entry | Catalyst (mol-%) | Additive (mol-%)[a] | Solvent | T [°C] | t [h] | Yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **6** (20) | – | PhMe | 25 | 20 | 98 | 67 (*S*) |
| 2 | **6** (20) | – | hexane | 25 | 14 | 85 | 73 (*S*) |
| 3 | **6** (20) | – | $Et_2O$ | 25 | 14 | 95 | 32 (*S*) |
| 4 | **6** (20) | – | $CH_2Cl_2$ | 25 | 20 | 95 | 63 (*S*) |
| 5 | **6** (20) | – | $CHCl_3$ | 25 | 20 | 99 | 75 (*S*) |
| 6 | **6** (20) | – | DMF | 25 | 44 | 94 | 62 (*R*) |
| 7 | **6** (20) | | dioxane | 25 | 50 | 85 | 58 (*R*) |
| 8 | **6** (20) | | acetone | 25 | 44 | 92 | 57 (*R*) |
| 9 | **6** (20) | – | $H_2O$ | 25 | 2 | 97 | 32 (*R*) |
| 10 | **6** (20) | – | DMF/$H_2O$[d] | 25 | 17 | 94 | 70 (*R*) |
| 11 | **6** (20) | – | DMF/$H_2O$[e] | 25 | 20 | 90 | 84 (*R*) |
| 12 | **6** (20) | – | DMF/$H_2O$[f] | 25 | 24 | 88 | 80 (*R*) |
| 13 | **6** (10) | – | $CHCl_3$ | 25 | 20 | 97 | 86 (*S*) |
| 14 | **6** (10) | – | DMF/$H_2O$[e] | 25 | 20 | 95 | 84 (*R*) |
| 15 | **6** (5) | – | $CHCl_3$ | 25 | 40 | 95 | 76 (*S*) |
| 16 | **6** (5) | – | DMF/$H_2O$[e] | 25 | 40 | 93 | 82 (*R*) |
| 17 | **6** (10) | – | $CHCl_3$ | 0 | 48 | 94 | 70 (*S*) |
| 18 | **6** (10) | – | DMF/$H_2O$[e] | 0 | 48 | 91 | 82 (*R*) |
| 19 | **6** (10) | HDA (10) | $CHCl_3$ | 25 | 22 | 98 | 78 (*S*) |
| 20 | **6** (10) | HDA (10) | DMF/$H_2O$[e] | 25 | 20 | 86 | 80 (*R*) |
| 21 | **6** (10) | $PhCO_2H$ (10) | $CHCl_3$ | 25 | 22 | 93 | 78 (*S*) |
| 22 | **6** (10) | $PhCO_2H$ (10) | DMF/$H_2O$[e] | 25 | 22 | 84 | 80 (*R*) |
| 23 | **6** (10) | Imidazole (10) | $CHCl_3$ | 25 | 22 | 97 | 78 (*S*) |
| 24 | **6** (10) | Imidazole (10) | DMF/$H_2O$[e] | 25 | 22 | 90 | 77 (*R*) |
| 25 | *ent*-**6** (10) | – | $CHCl_3$ | 25 | 20 | 97 | 84 (*R*) |
| 26 | *ent*-**6** (10) | – | DMF/$H_2O$[e] | 25 | 20 | 94 | 83 (*S*) |
| 27 | **12** (10) | – | $CHCl_3$ | 25 | 24 | 98 | 81 (*S*) |
| 28 | **12** (10) | – | DMF/$H_2O$[e] | 25 | 24 | 94 | 78 (*R*) |
| 29 | **13** (10) | – | $CHCl_3$ | 25 | 48 | 97 | 86 (*S*) |
| 30 | **13** (10) | – | DMF/$H_2O$[e] | 25 | 48 | 96 | 78 (*R*) |

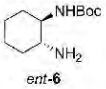
[a] HDA: hexanedioic acid. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC[24b] analysis of the crude product mixture. [d] 1:1, v/v. [e] 2:1, v/v. [f] 4:1, v/v.



(*S*)-**9aa**, and DMF/$H_2O$ (2:1, v/v) for (*R*)-**9aa**], we decided to lower the organocatalyst loading. Thus, both solvents were used with 10 and 5 mol-% organocatalyst loadings (Table 1, entries 13–16), and higher enantioselectivities for both the *S* and *R* stereoisomers were observed when a loading of 10 mol-% of **6** was used [86% *ee* for (*S*)-**9aa**, and 84% *ee* for (*R*)-**9aa**] (Table 1, entries 13 and 14). Lowering the reaction temperature to 0 °C resulted in a diminished enantioselectivity for **9aa** (Table 1, entries 17 and 18).

We then explored the influence of the presence of additives, using an optimized 10 mol-% loading of organocatalyst **6**, and $CHCl_3$ and DMF/$H_2O$ (2:1, v/v) as enantioswitching solvents. Thus, hexanedioic (HDA) or benzoic acids were used as additives (10 mol-%), but no increase in the enantioselectivity was observed for either enantiomer (Table 1, entries 19–22). Imidazole was also tested as an additive (10 mol-%), as its presence has been shown to be beneficial in this Michael addition reaction,[24b] but lower enantioselectivities for both enantiomers of **9aa** were also observed here (Table 1, entries 23 and 24).

Attempting to achieve opposite enantioselectivities to those obtained using organocatalyst **6**, we obtained its enantiomer *ent*-**6**, following an identical procedure but starting from (1*R*,2*R*)-cyclohexane-1,2-diamine. Using this mono-Boc-protected diamine *ent*-**6** as organocatalyst, under the most convenient reaction conditions [i.e., organocatalyst (10 mol-%), room temperature, $CHCl_3$ or DMF/$H_2O$ (2:1, v/v) as solvent], the expected opposite enantioselectivities were observed [i.e., (*R*)-**9aa** using $CHCl_3$ as solvent, and (*S*)-**9aa** using DMF/$H_2O$ (2:1, v/v)] (Table 1, entries 25 and 26).

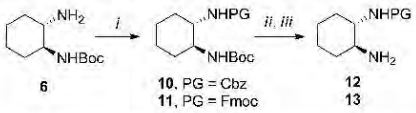



*ent*-**6**

We then explored the possibility of achieving this solvent-dependent reversal of enantioselectivity using chiral *trans*-cyclohexane-1,2-diamines monoprotected with other carbamates as organocatalysts. We chose the frequently

used benzyloxycarbonyl (Cbz) and fluorenylmethoxycarbonyl (Fmoc) protecting groups. Thus, Cbz- and Fmoc-monoprotected diamines **12** and **13**, respectively, were prepared by reaction of *N*-Boc-monoprotected diamine **6** with the corresponding chloroformates to give diprotected compounds **10** and **11**, followed by trifluoroacetic acid (TFA)-induced *N*-Boc deprotection (Scheme 1).

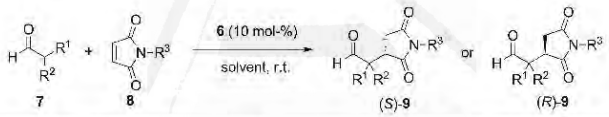



Scheme 1. (i) CbzCl (for **10**) or FmocCl (for **11**), $NaHCO_3$ (aq.), dioxane, room temp.; (ii) TFA, $CH_2Cl_2$, r.t.; (iii) $NH_4OH$, $CH_2Cl_2$, r.t.

These Cbz- and Fmoc-monoprotected chiral diamines **12** and **13**, respectively, were also tested as organocatalysts in the model Michael addition reaction, using the most convenient reaction conditions as determined above [i.e., organocatalyst (10 mol-%), room temperature, $CHCl_3$ or DMF/$H_2O$ (2:1, v/v) as solvent] (Table 1, entries 27–30). Again, a reversal in the enantioselectivity of the process was observed when changing the solvent between $CHCl_3$ (*S* enantiomer) and DMF/$H_2O$ (2:1, v/v) (*R* enantiomer). Thus, when mono-Cbz-protected diamine **12** was used as organocatalyst, *ee* values of 81% *ee* for (*S*)-**9aa** and 78% *ee* for (*R*)-**9aa** were obtained (Table 1, entries 27 and 28). When Fmoc-containing primary amine **13** was used as the organocatalyst, it gave a similar enantioselectivity for (*S*)-**9aa** to when Boc derivative **6** was used, but after a much longer reaction time, whereas the enantioselectivity for (*R*)-**9aa** was lower (Table 1, entries 29 and 30).

Once the most effective organocatalyst and reaction conditions [i.e., **6** (10 mol-%), $CHCl_3$ for the *S* enantiomer, and DMF/$H_2O$ (2:1, v/v) for the *R* enantiomer, room temp.] were established, we went on to explore the extension of this organocatalytic solvent-dependent method to other aldehydes and maleimides (Table 2). As for the model reaction, the absolute configurations of the known succinimide products were assigned according to the order of elution of their enantiomers in chiral HPLC when compared to the literature (see Experimental section).

Table 2. Solvent-dependent reversal of enantioselectivity in the Michael addition of aldehydes to maleimides catalysed by *N*-Boc-monoprotected 1,2-diamine **6**.




| Entry | Aldehyde R¹ | R² | 7 | Maleimide R³ | 8 | Solvent | *t* [h] | Succinimide | Yield [%][a] | *ee* [%][b,c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | Me | **7a** | Ph | **8a** | $CHCl_3$ | 20 | (*S*)-**9aa** | 97 | 86 |
| 2 | | | | | | DMF/$H_2O$, 2:1 | 20 | (*R*)-**9aa** | 95 | 84 |
| 3 | Me | Me | **7a** | 3-$ClC_6H_4$ | **8b** | $CHCl_3$ | 30 | (*S*)-**9ab** | 99 | 38 |
| 4 | | | | | | DMF/$H_2O$, 2:1 | 30 | (*R*)-**9ab** | 96 | 76 |
| 5 | Me | Me | **7a** | 4-$ClC_6H_4$ | **8c** | $CHCl_3$ | 30 | (*S*)-**9ac** | 99 | 60 |
| 6 | | | | | | DMF/$H_2O$, 2:1 | 30 | (*R*)-**9ac** | 97 | 74 |
| 7 | Me | Me | **7a** | 4-$BrC_6H_4$ | **8d** | $CHCl_3$ | 30 | (*S*)-**9ad** | 99 | 70 |
| 8 | | | | | | DMF/$H_2O$, 2:1 | 30 | (*R*)-**9ad** | 98 | 70 |
| 9 | Me | Me | **7a** | 4-$AcC_6H_4$ | **8e** | $CHCl_3$ | 26 | (*S*)-**9ae** | 92 | 40 |
| 10 | | | | | | DMF/$H_2O$, 2:1 | 26 | (*R*)-**9ae** | 15 | 80 |
| 11 | Me | Me | **7a** | 2-$MeOC_6H_4$ | **8f** | $CHCl_3$ | 32 | (*S*)-**9af** | 90 | 76 |
| 12 | | | | | | DMF/$H_2O$, 2:1 | 32 | (*R*)-**9af** | 92 | 74 |
| 13 | Me | Me | **7a** | Bn | **8g** | $CHCl_3$ | 22 | (*S*)-**9ag** | 93 | 30 |
| 14 | | | | | | DMF/$H_2O$, 2:1 | 22 | (*R*)-**9ag** | 90 | 72 |
| 15 | Me | Me | **7a** | Me | **8h** | $CHCl_3$ | 21 | (*S*)-**9ah** | 94 | 53 |
| 16 | | | | | | DMF/$H_2O$, 2:1 | 21 | (*R*)-**9ah** | 91 | 68 |
| 17 | Me | Me | **7a** | H | **8i** | $CHCl_3$ | 17 | (*S*)-**9ai** | 94 | 50 |
| 18 | | | | | | DMF/$H_2O$, 2:1 | 17 | (*R*)-**9ai** | 88 | 70 |
| 19 | Et | Et | **7b** | Ph | **8a** | $CHCl_3$ | 48 | (*S*)-**9ba** | 70 | 55 |
| 20 | | | | | | DMF/$H_2O$, 2:1 | 48 | (*R*)-**9ba** | 93 | 68 |
| 21 | –($CH_2$)$_4$– | | **7c** | Ph | **8a** | $CHCl_3$ | 30 | (*S*)-**9ca** | 99 | 49 |
| 22 | | | | | | DMF/$H_2O$, 2:1 | 30 | (*R*)-**9ca** | 96 | 61 |
| 23 | –($CH_2$)$_5$– | | **7d** | Ph | **8a** | $CHCl_3$ | 48 | (*S*)-**9da** | 96 | 14 |
| 24 | | | | | | DMF/$H_2O$, 2:1 | 48 | (*R*)-**9da** | 96 | 35 |
| 25 | H | Me | **7e** | Ph | **8a** | $CHCl_3$ | 23 | (*S,S*)/(*R,S*)-**9ea** | 95[d] | 36/28 |
| 26 | | | | | | DMF/$H_2O$, 2:1 | 23 | (*R,R*)/(*S,R*)-**9ea** | 96[e] | 76/73 |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities determined by chiral HPLC analysis of the crude product mixture. [c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC (see Experimental section). [d] Mixture of diastereomers 1.4:1, as determined by $^1H$ NMR (300 MHz) spectroscopic analysis of the crude product mixture. [e] Mixture of diastereomers 1.2:1, as determined by $^1H$ NMR (300 MHz) spectroscopic analysis of the crude product mixture.

Thus, when $CHCl_3$ was used as solvent, isobutyraldehyde reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro substituent at the 3- or 4-position (i.e., **8b** and **8c**, respectively), or a bromo substituent at the 4-position (i.e., **8d**), and the corresponding succinimides [i.e., (*S*)-**9ab**, (*S*)-**9ac**, and (*S*)-**9ad**] were obtained with 38, 60, and 70% *ee*, respectively (Table 2, entries 3, 5, and 7). However, when DMF/$H_2O$ (2:1, v/v) was used as the reaction solvent, adducts (*R*)-**9ab**, (*R*)-**9ac**, and (*R*)-**9ad** were isolated with 76, 74, and 70% *ee* (Table 2, entries 4, 6, and 8). In addition, when an acetyl or a methoxy group was present on the phenyl ring of the maleimide, as in the case of **8e** and **8f**, the *ee* values the corresponding enantiomeric succinimides (*S*)-**9ae**/(*R*)-**9ae** and (*S*)-**9af**/(*R*)-**9af** were 40/80% *ee* and 76/74% *ee*, respectively, depending on whether $CHCl_3$ or DMF/$H_2O$ (2:1, v/v) was used as the solvent (Table 2, entries 9–12).

Non-*N*-arylated maleimides were also used for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide (**8g**) gave enantiomeric succinimides (*S*)-**9ag** and (*R*)-**9ag** in high yields and with 30 and 72% *ee*, depending on the solvent used (Table 2, entries 13 and 14). Similarly, *N*-methylmaleimide (**8h**) gave the *S* and *R* enantiomers of adduct **9ah** when $CHCl_3$ and DMF/$H_2O$ (2:1, v/v) were used as the reaction solvent (53 and 68% *ee*, respectively; Table 2, entries 15 and 16). In addition, the simple maleimide (**8i**) was also used as a Michael acceptor, and gave (*S*)-**9ai** (50% *ee*) when $CHCl_3$ was used as solvent, and (*R*)-**9ai** (70% *ee*) when the solvent was DMF/$H_2O$ (2:1, v/v) (Table 2, entries 17 and 18).

Other α,α-disubstituted aldehydes were used for this enantioswitching organocatalytic Michael addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal (**7b**) gave succinimides (*S*)-**9ba** (55% *ee*) and (*R*)-**9ba** (68% *ee*) using $CHCl_3$ and DMF/$H_2O$ (2:1, v/v) as solvents, respectively (Table 2, entries 19 and 20). In addition, cyclopentanecarbaldehyde (**7c**) and cyclohexanecarbaldehyde (**7d**) gave almost quantitative amounts of succinimides (*S*)-**9ca** and (*S*)-**9da** with 49 and 14% *ee*, respectively, when $CHCl_3$ was the reaction solvent, whereas (*R*)-**9ca** and (*R*)-**9da** were isolated with 61 and 35% *ee*, respectively, when DMF/$H_2O$ (2:1, v/v) was used as solvent (Table 2, entries 21–24). Moreover, the use of propanal (**7e**), an α-monosubstituted aldehyde, in the two solvents allowed Michael adducts (*R*,*S*)/(*S*,*S*)-**9ea** and (*S*,*R*)/(*R*,*R*)-**9ea**, respectively, to be obtained as mixtures of diastereomers, with *ee* values of up to 36 and 76% *ee*, respectively, for the major isomer (Table 2, entries 25 and 26, see footnotes[d,e]).

In an attempt to rule out the possibility that the change in the enantioselectivity could be a consequence of a further transformation of the initially formed product, succinimide (*R*)-**9aa** obtained with 84% *ee* (Table 2, entry 2) was stirred in the presence of organocatalyst **6** (10 mol-%), in $CHCl_3$ as solvent at room temperature. After 20 h, succinimide (*R*)-**9aa** was recovered unchanged. In addition, the model reaction of aldehyde **7a** with maleimide **8a** in the presence of organocatalyst **6** (10 mol-%) in DMF/$H_2O$ (2:1, v/v) was carried out for 4, 8, and 12 h, and the *ee* for (*R*)-**9aa** remained at 84% *ee*.

To get further insight into the origin of this solvent-dependent enantioselectivity reversal, we carried out theoretical calculations on the reaction of *N*-phenylmaleimide (**8a**) and isobutyraldehyde (**7a**) in the presence of primary-amine catalyst **6**. Different computational conditions were envisioned (see Exp. Section) − in the gas phase, in implicit solvents (water and chloroform), and also in the presence of a discrete number of explicit water molecules − in an attempt to reproduce the experimental conditions as closely as possible, since the results are highly dependent on the reaction medium. Preliminary studies showed that, as expected, the initial formation of an enamine between the catalyst and the aldehyde is followed by nucleophilic attack on the maleimide, according to Seebach's synclinal model (*endo* attack, Figure 1).[31] A key feature of this model is that the reacting face of the enamine completely diastereoselectivelyattacks only one of the faces of the maleimide. Thus, the lower face of the enamine (from our point of view in Figure 1) reacts with the *Re* face of the maleimide, and the upper face of the enamine must react with the *Si* face of the maleimide. This means that each face of the enamine produces only one of the final enantiomeric products. This fact is crucial to understanding the following discussion, which can be based solely on the reacting face of the enamine. Meanwhile, the *exo* approaches, like the one involving the lower face of the enamine and the *Si* face of the maleimide (Figure 1), are much higher in energy, and can be safely disregarded.

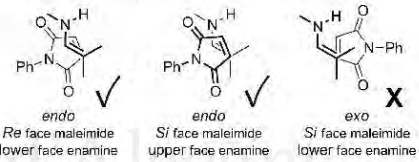



Figure 1. Faces of enamine and maleimide reacting through Seebach's synclinal model.

The initial optimizations of the enamine structures showed that in the most stable conformations (i.e., **A** and **B**, Figure 2), the NHBoc and enamine groups are in equatorial positions of the cyclohexane ring. In both cases, the NH moiety of the NHBoc carbamate is pointing *down* from our view. The two conformations differ in the orientations that the NH enamine group can present, pointing *up* (conformation **A**) or *down* (conformation **B**) from the plane of the cyclohexane ring (Figure 2). According to this picture, the fragment NH–C–C–NH shows the two NH groups in *anti* (**A**) or *syn* (**B**) relative orientations. The optimization of these structures showed that they are very similar in energy, and both must be taken into account for the transition-structure search. In fact, structure **B** is slightly more stable than **A** in $CHCl_3$ (1.0 kcal/mol difference), whereas they have the same energy in water. This means that **A** is slightly better solvated by water than by chloroform. We cautiously took these data as a first indication of the solvent dependence of the conformational distribution of the initial struc-

tures. We thought that this effect could be more dramatic during the transition states of the reaction, which are supposed to be quite polar, due to the significant charge transfer that takes place from the enamine to the maleimide.

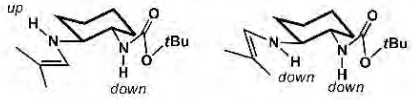



Figure 2. Most stable conformations of the reacting enamine.

We confirmed this hypothesis in the light of the computed transition state activation energies. In conformation **A**, the maleimide could hypothetically approach the two faces of the enamine, as shown in Figure 3. If the attack takes place from the left-hand side of the enamine, the reaction occurs through TS-$\mathbf{A}_R$ (*Si* face of maleimide, *R* product), whereas the approach of the maleimide from the right-hand side of the enamine (hypothetical TS-$\mathbf{A}_S$) is strongly disfavoured due to steric repulsion from the large Boc group, which is blocking that face. We could not actually find any transition state for that approach without severely distorting the structure. It is noteworthy that TS-$\mathbf{A}_R$ is a very polar structure, with a high degree of negative charge developing in the maleimide oxygen atom. Consequently, the polarity of the reaction medium must have a great influence on the activation barrier of the process. Thus, it was not surprising to find that the lowest free energy for TS-$\mathbf{A}_R$ corresponds to the structure computed in a water model ($\Delta G^{\ddagger}$ = 14.8 kcal/mol),[32] while the chloroform and gas phase models present higher values ($\Delta G^{\ddagger}$ = 18.7 and 20.7 kcal/mol, respectively). Interestingly, TS-$\mathbf{A}_R$ leads to the formation of the *R* enantiomer, which is experimentally obtained in the polar aqueous medium.

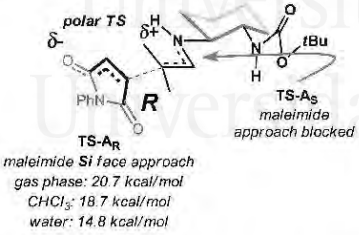



Figure 3. Computed activation energies for transition state TS-$\mathbf{A}_R$ (corresponding to conformation **A** in Figure 2) in the gas phase, chloroform, and water models. Structures and values were obtained at the M06-2X/6-311+G**//M06-2X/6-31G** level of theory.

On the other hand, two transition states were located for conformation **B**, following the two possible approaching trajectories (TS-$\mathbf{B}_S$ and TS-$\mathbf{B}_R$, Figure 4). In TS-$\mathbf{B}_S$, the *Re* face of the maleimide is attacked by the lower face (from our view) of the enamine, whereas in TS-$\mathbf{B}_R$, the *Si* face of the maleimide approaches the upper face of the enamine. In TS-$\mathbf{B}_S$, the maleimide oxygen and the HNBoc group are close enough to form an intermolecular hydrogen bond, which stabilizes the developing negative charge in the maleimide oxygen atom, producing a structure that is much less polar than TS-$\mathbf{A}_R$, and therefore, less sensitive to the surrounding solvent molecules. This effect can be observed in the computed energies for TS-$\mathbf{B}_S$, which do not show significant differences between the different solvent models, or even the gas phase (TS-$\mathbf{B}_S$ *water*: 17.7,[32] TS-$\mathbf{B}_S$ *chloroform*: 16.0, TS-$\mathbf{B}_S$ *gas phase*: 15.8 kcal/mol, Figure 4).

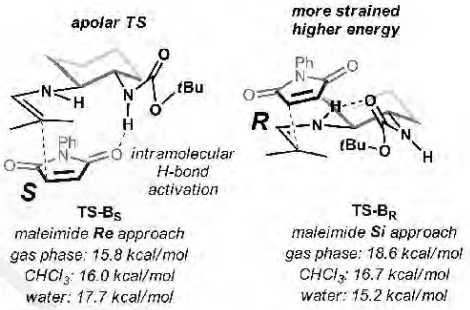



Figure 4. Representations and energies of transition states TS-$\mathbf{B}_S$ and TS-$\mathbf{B}_R$, corresponding to conformation **B** in Figure 2. Structures and values were obtained at the M06-2X/6-311+G**//M06-2X/6-31G** level of theory.

Meanwhile, if the maleimide approaches the upper face of the enamine in conformation B, this leads to transition state TS-$\mathbf{B}_R$ (Figure 4). Similarly to TS-$\mathbf{A}_R$, this transition structure is quite polar, and the maleimide oxygen is better stabilized in the presence of surrounding solvent molecules. Thus, its lowest energy was measured in water (15.2 kcal/mol),[32] although this value is higher than the one corresponding to TS-$\mathbf{A}_R$ (14.8 kcal/mol, Figure 3). This increase in the energy is probably due to the higher internal strain that the structure presents as the result of a weak hydrogen bond formed between the enamine NH and the carbamate oxygen atom, which does not participate in the activation of the maleimide.

In summary, the most significant computational data are that the lowest calculated activation energy in water corresponds to TS-$\mathbf{A}_R$ (14.8 kcal/mol), a polar structure lacking intramolecular hydrogen bonds, where the surrounding water molecules are responsible for intermolecular hydrogen-bonding activation of the maleimide (Figure 5). TS-$\mathbf{A}_R$ produces the *R* enantiomer of the product, which is consistent with the experimental results in the polar aqueous DMF medium (Table 1). Also, the lowest calculated activation energy in chloroform is TS-$\mathbf{B}_S$ (16.0 kcal/mol), a transition structure containing an intramolecular hydrogen bond between the maleimide and the NHBoc groups (Figure 5). This transition state leads to the formation of the *S* enantiomer, which is once again consistent with the experimental data in chloroform (Table 1). Furthermore, these results agree with chemical common sense, that intramolec-

ular hydrogen bonds are more significant in nonpolar solvents, whereas intermolecular hydrogen bonds with surrounding water molecules are present in aqueous systems.


Figure 5. 3D representations and energies of transition states TS-$\mathbf{A}_R$-*water* and TS-$\mathbf{B}_S$-*chloroform*.

## Conclusions

Easily prepared carbamate-monoprotected chiral *trans*-cyclohexane-1,2-diamines can be used as organocatalysts in the high-yielding enantioselective conjugate addition of aldehydes, mainly α,α-disubstituted, to different maleimides, in a solvent-dependent enantioswitchable reaction. Thus, both *S*- or *R*-enantioenriched forms of the corresponding succinimides can be obtained using a single enantiomer of the organocatalyst, just by changing the reaction solvent from chloroform to aqueous *N*,*N*-dimethylformamide. Theoretical calculations are able to show the reason for this solvent-dependent reversal of enantioselectivity. The most polar transition state (i.e., TS-$\mathbf{A}_R$) presents the lowest energy in water, and it is responsible for the major formation of the *R* enantiomer. The least polar transition state (i.e., TS-$\mathbf{B}_S$) accounts for the formation of the *S* enantiomer in chloroform, consistent with the experimental results.

## Experimental Section

**General Remarks:** The syntheses of all organocatalysts, as well as their physical and spectroscopic data, are described in the Supporting Information. The absolute configurations of adducts **9** were determined according to the described order of elution of their enantiomers in chiral HPLC. Reference racemic samples of adducts **9** were obtained by performing the reaction using 4-methylbenzylamine (20 mol-%) as organocatalyst in toluene as solvent at 25 °C.

**Typical Procedure for the Enantioselective Michael Addition Reaction:** Aldehyde **7** (0.4 mmol) was added to a solution of **6** (0.04 mmol) and **8** (0.2 mmol) in $CHCl_3$ or DMF/$H_2O$ (2:1, v/v; 0.5 mL), and the reaction was stirred at room temp. until TLC showed that it was complete. HCl (2 M aq.; 10 mL) was added, and the mixture was extracted with EtOAc (3× 10 mL). The organic phase was washed with water (2× 10 mL), dried ($MgSO_4$), filtered, and evaporated (15 Torr). The resulting residue was purified by flash chromatography (hexane/EtOAc) to give adducts **9**.

Succinimides **9** have already been described.[24b] Their $^1H$ and $^{13}C$ NMR spectroscopic data and retention times in chiral HPLC for both enantiomers can be found in the Supporting Information.

**Computational Methods:** The structures were initially optimized using density functional theory (DFT) with the B3LYP[33] and the 6-31G* basis set, as implemented in Gaussian 09.[34] Further reoptimization at the M06-2X/6-31G** level of theory[35] was carried out to account for the important dispersion forces in such large systems. The energy values shown in Figures 3 and 4 also include single-point refinements at the M06-2X/6-311+G** level on the previously optimized structures (M06-2X/6-31G**), including polarization functions for a better description of hydrogen-bond activations. Additionally, solvation factors were introduced with the IEF-PCM method,[36] using chloroform or water as indicated in the text and figures.

We also performed single-point calculations at the B3LYP/6-311+G** level of theory, and the relative values are similar to those of the M06-2X energies. Therefore, they have not been included in the manuscript, and are collected in the Supporting Information. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies.

The intrinsic reaction coordinates (IRC)[37] were followed to verify the energy profiles connecting each transition state to the correct associated local minima.

## Acknowledgments

The authors are grateful for the financial support from the Spanish Ministerio de Economía y Competitividad (MEC) (project number CTQ2011-24151), Fondos Europeos para el Desarrollo Regional (FEDER), the COST Action CM0905 "Organocatalysis", the FP7 Marie Curie Action of the European Commission via the ITN ECHONET Network (FP7-MCITN-2012-316379), the University of Alicante and the University of the Basque Country. The authors also thank SGI/IZO-SGIker (UPV/EHU) and the University of Szeged, Department of Chemical Informatics for allocation of computational resources. J. F.-F. acknowledges the Vicerrectorado de Investigación, Desarrollo e Innovación of the University of Alicante for a predoctoral fellowship.

[1] M. Bartók, *Chem. Rev.* **2010**, *110*, 1663–1705.
[2] P. Mazón, R. Chinchilla, C. Nájera, G. Guillena, R. Kreiter, R. J. M. Klein Gebbink, G. van Koten, *Tetrahedron: Asymmetry* **2002**, *13*, 2181–2185.
[3] a) S.-H. Chen, B.-C. Hong, C.-F. Su, S. Sarshar, *Tetrahedron Lett.* **2005**, *46*, 8899–8903; b) D. G. Blackmond, A. Moran, M. Hughes, A. Armstrong, *J. Am. Chem. Soc.* **2010**, *132*, 7598–7599.
[4] S. A. Moteki, J. Han, S. Arimitsu, M. Akakura, K. Nakayama, K. Maruoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 1187–1190; *Angew. Chem.* **2012**, *124*, 1213–1216.
[5] a) S. Arseniyadis, P. V. Subhash, A. Valleix, S. P. Mathew, D. G. Blackmond, A. Wagner, C. Mioskowski, *J. Am. Chem. Soc.* **2005**, *127*, 6138–6139; b) F.-C. Wu, C.-S. Da, Z.-X. Du, Q.-P. Guo, W.-P. Li, L. Yi, Y.-N. Jia, X. Ma, *J. Org. Chem.* **2009**, *74*, 4812–4818.
[6] J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429–1432.
[7] R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351–5353.
[8] J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487.
[9] H. Sunden, R. Rios, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 7865–7869.
[10] F. Giacalone, M. Gruttadauria, P. Agrigento, V. Campisciano, R. Noto, *Catal. Commun.* **2011**, *16*, 75–80.
[11] Y. Qian, S. Xiao, L. Liu, Y. Wang, *Tetrahedron: Asymmetry* **2008**, *19*, 1515–1518.

[12] M. Messerer, H. Wennemers, *Synlett* **2011**, 499–502.
[13] a) Y. Sohtome, T. Yamaguchi, S. Tanaka, K. Nagasawa, *Org. Biomol. Chem.* **2013**, *11*, 2780–2786; b) Y. Sohtome, K. Nagasawa, *Org. Biomol. Chem.* **2014**, *12*, 1681–1685.
[14] a) A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya, K. Nakanishi, K. Nishiyama, M. Sugiura, H. Kita, *J. Am. Chem. Soc.* **1987**, *109*, 4409–4411; b) C. Malochet-Grivois, C. Roussakis, N. Robillard, J. F. Biard, D. Riou, C. Debitus, J. F. Verbist, *Anti-Cancer Drug Des.* **1992**, *7*, 493–502; c) Y. Ando, E. Fuse, W. D. Figg, *Clin. Cancer Res.* **2002**, *8*, 1964–1973; d) C. Freiberg, N. A. Brunner, G. Schiffer, T. Lampe, J. Pohlmann, M. Brands, M. Raabe, D. Haebich, K. Ziegelbauer, *J. Biol. Chem.* **2004**, *279*, 26066–26073; e) M. Isaka, N. Rugseree, P. Maithip, P. Kongsaeree, S. Prabpai, Y. Thebtaranonth, *Tetrahedron* **2005**, *61*, 5577–5583; f) J. Uddin, K. Ueda, E. R. O. Siwu, M. Kita, D. Uemura, *Bioorg. Med. Chem.* **2006**, *14*, 6954–6961; g) M. N. Aboul-Enein, A. A. El-Azzouny, O. A. Saleh, Y. A. Maklad, *Mini-Rev. Med. Chem.* **2012**, *12*, 671–700.
[15] a) J. Nöth, K. J. Frankowski, B. Neuenswander, J. Aubé, O. Reiser, *J. Comb. Chem.* **2008**, *10*, 456–459; b) E. Fenster, D. Hill, O. Reiser, J. Aube, *Beilstein J. Org. Chem.* **2012**, *8*, 1804–1813.
[16] D. Chauhan, L. Catley, G. Li, K. Podar, T. Hideshima, M. Velankar, C. Mitsiades, N. Mitsiades, H. Yasui, A. Letai, H. Ovaa, C. Berkers, B. Nicholson, T.-H. Chao, S. T. C. Neuteboom, P. Richardson, M. A. Palladino, K. C. Anderson, *Cancer Cell* **2005**, *8*, 407–419.
[17] a) P. A. Reddy, B. C. H. Hsiang, T. N. Latifi, M. W. Hill, K. E. Woodward, S. M. Rothman, J. A. Ferrendelli, D. F. Covey, *J. Med. Chem.* **1996**, *39*, 1898–1906; b) K. Das Sarma, J. Zhang, Y. Huang, J. G. Davidson, *Eur. J. Org. Chem.* **2006**, 3730–3737.
[18] a) A. Spaltenstein, M. R. Almond, W. J. Bock, D. G. Cleary, E. S. Furfine, R. J. Hazen, W. M. Kazmierski, F. G. Salituro, R. D. Tung, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162; b) W. M. Kazmierski, W. Andrews, E. Furfine, A. Spaltenstein, L. Wright, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689–5692.
[19] a) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; b) K. Tang, J.-T. Zhang, *Neurol. Res.* **2002**, *24*, 473–478.
[20] P. Chauhan, J. Kaur, S. S. Chimni, *Chem. Asian J.* **2012**, *8*, 328–346.
[21] a) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; b) A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron* **2014**, *70*, 2491–2513.
[22] G.-L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayah, A. Cordova, *Chem. Commun.* **2007**, 734–735.
[23] a) F. Yu, Z. Jin, H. Huang, T. Ye, X. Liang, J. Ye, *Org. Biomol. Chem.* **2010**, *8*, 4767–4774; b) J.-F. Bai, L. Peng, L.-l. Wang, L.-X. Wang, X.-Y. Xu, *Tetrahedron* **2010**, *66*, 8928–8932; c) F. Xue, L. Liu, S. Zhang, W. Duan, W. Wang, *Chem. Eur. J.* **2010**, *16*, 7979–7982; d) T. Miura, S. Nishida, A. Masuda, N. Tada, A. Itoh, *Tetrahedron Lett.* **2011**, *52*, 4158–4160; e) T. Miura, A. Masuda, M. Ina, K. Nakashima, S. Nishida, N. Tada, A. Itoh, *Tetrahedron: Asymmetry* **2011**, *22*, 1605–1609; f) Z.-w. Ma, Y.-x. Liu, P.-l. Li, H. Ren, Y. Zhu, J.-c. Tao, *Tetrahedron: Asymmetry* **2011**, *22*, 1740–1748; g) Z.-W. Ma, Y.-X. Liu, W.-J. Zhang, Y. Tao, Y. Zhu, J.-C. Tao, M.-S. Tang, *Eur. J. Org. Chem.* **2011**, 6747–6754; h) M. Durmaz, A. Sirit, *Tetrahedron: Asymmetry* **2013**, *24*, 1443–1448; i) S. Orlandi, G. Pozzi, M. Ghisetti, M. Benaglia, *New J. Chem.* **2013**, *37*, 4140–4147.
[24] a) A. Avila, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2012**, *23*, 1625–1627; b) A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera, *Eur. J. Org. Chem.* **2013**, 5085–5092.
[25] a) T. C. Nugent, A. Sadiq, A. Bibi, T. Heine, L. L. Zeonjuk, N. Vankova, B. S. Bassil, *Chem. Eur. J.* **2012**, *18*, 4088–4098; b) C. G. Kokotos, *Org. Lett.* **2013**, *15*, 2406–2409.
[26] S. Muramulla, J.-A. Ma, J. C.-G. Zhao, *Adv. Synth. Catal.* **2013**, *355*, 1260–1264.
[27] W. Yang, K.-Z. Jiang, X. Lu, H.-M. Yang, L. Li, Y. Lu, L.-W. Xu, *Chem. Asian J.* **2013**, *8*, 1182–1190.
[28] A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera, *Tetrahedron: Asymmetry* **2013**, *24*, 1531–1535.
[29] Communication: J. Flores-Ferrándiz, R. Chinchilla, *Tetrahedron: Asymmetry* **2014**, *25*, 1091–1094.
[30] D. W. Lee, H.-J. Ha, W. K. Lee, *Synth. Commun.* **2007**, *37*, 737–742.
[31] a) D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413–1423; b) D. Seebach, A. K. Beck, J. Golinski, J. N. Hay, T. Laube, *Helv. Chim. Acta* **1985**, *68*, 162–172.
[32] The energies in water shown in Figures 3 and 4 were obtained using a water model system in the presence of one explicit molecule of water. When an implicit water model was used, the calculated energies showed a similar trend: TS-$\mathbf{A}_R$: 15.8 kcal/mol, TS-$\mathbf{B}_S$: 16.9 kcal/mol, TS-$\mathbf{B}_R$: 16.9 kcal/mol; see the Supporting Information for further details.
[33] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; c) W. Kohn, A. D. Becke, R. G. Parr, *J. Phys. Chem.* **1996**, *100*, 12974–12980.
[34] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, revision E.01, Gaussian, Inc., Wallingford CT, **2009**.
[35] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.
[36] a) E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3047; b) J. Tomasi, B. Mennucci, E. Cancès, *THEOCHEM* **1999**, *464*, 211–226.
[37] C. González, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.

Received: October 31, 2014
Published Online: January 15, 2015

Tetrahedron: Asymmetry 28 (2017) 302–306

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Organocatalytic enantioselective conjugate addition of aldehydes to maleimides in deep eutectic solvents

Jesús Flores-Ferrándiz, Rafael Chinchilla *

*Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain*

ARTICLE INFO

*Article history:*
Received 3 November 2016
Revised 16 November 2016
Accepted 12 December 2016
Available online 28 December 2016

ABSTRACT

The conjugate enantioselective addition of aldehydes, mainly α,α-disubstituted, to maleimides leading to enantioenriched succinimides, has been achieved in recyclable deep eutectic solvents at room temperature. Enantiomerically pure carbamate-monoprotected *trans*-cyclohexane-1,2-diamines are used as organocatalysts, affording high yields and up to 94% *ee* of the final succinimides. The product can be extracted from the deep eutectic solvent, which retains the chiral organocatalyst, allowing both the solvent and catalyst to be reused.



## 1. Introduction

Over the last few years, enantioselective organocatalysis has established itself as a crucial synthetic tool when the stereoselective preparation of compounds of interest is intended.[1] Thus, the use of small chiral metal-free molecules as catalysts is environmentally advantageous if the synthetic procedure is designed to be scaled-up. However, some disadvantages still hamper the consideration of enantioselective organocatalysis as a common methodology in chemical industry. Among them are the frequent use of rather large amounts of organocatalyst, something that makes its recovery and reuse an important matter, as well as the usual necessity of employing conventional hazardous volatile organic compounds as solvents to achieve the highest enantioselections.

Recently, attention has been focused in the use of deep eutectic solvents in organic synthesis as an alternative to volatile organic compounds.[2] A deep eutectic solvent is a combination of two or three components which interact through hydrogen bonds, to form a eutectic mixture with a melting point lower than the individual components.[3] Deep eutectic solvents are non-volatile, have a low ecological footprint, are inexpensive and easy to recycle, and are nowadays promising 'green' alternatives to conventional solvents.

Despite these potential advantages, the use of deep eutectic solvents in enantioselective organocatalyzed reactions remains very scarce. The first reported example of an asymmetric organocatalyzed reaction with deep eutectic solvents employed in fact a tandem enzyme-proline derived combination.[4] Only two very recent publications can be considered 'purely organocatalytic', involving 9-amino-9-deoxy-*epi*-quinine[5] and proline[6] as chiral organocatalysts.

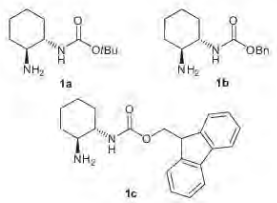
Enantioselective organocatalysis has been successfully employed for the preparation of enantioenriched succinimides,[7] which are interesting compounds in natural products and drug candidates.[8] Succinimides can be easily transformed into γ-lactams,[9] which are important in the design of pharmaceutical agents.[10]

The most direct method for preparing enantioenriched succinimides in an organocatalytic fashion is by the enantioselective conjugate addition of carbon nucleophiles to maleimides.[7] The nucleophile can be generated by deprotonation of a carbon pro-nucleophile using chiral basic amine-containing organocatalysts. However, when aldehydes are used as pro-nucleophiles, an α-deprotonation with just an organic base is not feasible. In this case, an enamine-forming strategy using chiral organocatalysts bearing a primary or secondary amine is employed.[11] Thus, many enamine-forming chiral organocatalysts have been reported for the enantioselective conjugate addition of aldehydes, to maleimides.[12]

We have previously reported the use of single enantiomers of carbamate-monoprotected *trans*-cyclohexa-1,2-diamines **1** as chiral organocatalyst in the conjugate addition of aldehydes, particularly the challenging α,α-disubstituted, to maleimides.[12q,s] As mentioned previously, a common disadvantage of this type of enantioselective organocatalytic procedure is the use of non-recoverable volatile organic compounds. Herein we report how deep eutectic solvents can be used in this enantioselective addition reaction, reusing both solvent and organocatalyst.

* Corresponding author. Tel.: +34 965903822; fax: +34 965903549.
*E-mail address:* chinchilla@ua.es (R. Chinchilla).

http://dx.doi.org/10.1016/j.tetasy.2016.12.009
0957-4166/




## 2. Results and discussion

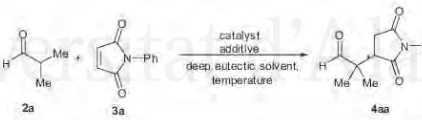
The carbamate-monoprotected *trans*-cyclohexane-1,2-diamines **1** were prepared from (1*S*,2*S*)-cyclohexane-1,2-diamine, as previously described.[12r] The derivative monoprotected with the *tert*-butoxycarbonyl (Boc) group **1a** was primarily chosen as the chiral enamine-forming organocatalyst in the model enantioselective conjugate addition reaction of isobutyraldehyde **2a** to *N*-phenylmaleimide **3a**, in different deep eutectic solvents (Table 1).

Thus, the use of a 10 mol % loading of **1a** in the deep eutectic solvent formed by choline chloride and urea (ChCl/urea, 1/2 molar ratio, see Section 4) at room temperature, gave rise after 24 h to a 90% yield of succinimide (*R*)-**4aa**, but with only 36% *ee* (Table 1, entry 1). The absolute configuration was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see Section 4).[12r] When the urea component of the deep eutectic solvent was changed to glycerol (ChCl/Gly, 1/2 molar ratio), a higher *ee* for (*R*)-**4aa** was obtained (52%, Table 1, entry 2). Higher enantiomeric excesses were obtained when using ethylene glycol (ChCl/ethylene glycol, 1/2 molar ratio) (64% Table 1, entry 3), or resorcinol (ChCl/resorcinol, 1/1 molar ratio) (67%, Table 1, entry 4).

When the employed deep eutectic solvent was the combination of tetra-*n*-butylammonium bromide (TBAB) and Gly (TBAB/Gly, 1/3 molar ratio), (*R*)-**4aa** was obtained in 85% yield and with 66% *ee* (Table 1, entry 5). However, the best results were obtained using as deep eutectic solvent the combination $Ph_3MePBr$/Gly (1/2 molar ratio), which afforded the final adduct in 96% yield and with 72% *ee* (Table 1, entry 6). Thus, this last deep eutectic solvent was used for the rest of our studies.

According to the literature, the presence of acid additives is frequently beneficial to this reaction.[12b,f,o,s] Therefore, we decided to evaluate the influence of an acid component. Thus, when hexanedioic acid (HDA) was added (10 mol %) to the reaction mixture, the reaction rate increased noticeably, as well as the enantioselection of the reaction, with (*R*)-**4aa** being obtained in 95% yield in only 8 h with an excellent 92% *ee* (Table 1, entry 7). The presence of other diacids, such as oxalic or phthalic acid, as additives gave much lower yields and enantioselectivities (Table 1, entries 8 and 9). When benzoic acid was added, the reaction yield was high and the enantioselection reached 86% (Table 1, entry 10). However, the addition of 3,4-dimethoxybenzoic acid gave the best results, affording adduct (*R*)-**4aa** with 94% *ee* and in 97% isolated yield (Table 1, entry 11). This enantioselectivity is remarkable, as values of only up to 86% were observed when using conventional volatile organic compounds as solvents.[12r] The presence of a strong electron-withdrawing group in the aromatic ring of the acid additive, as in the case of 4-nitrobenzoic acid, led to slightly lower enantioselectivity (Table 1, entry 12). The addition of bases such as imidazole or 4-*N*,*N*-dimethylaminopyridine (DMAP), which has

**Table 1**
Optimization of the reaction conditions in the model enantioselective conjugate addition in deep eutectic solvents




| Entry | Catalyst (mol %) | Additive (mol %) | Deep eutectic solvent (molar ratio)[a] | *T* (°C) | *t* (h) | Yield[b] (%) | *ee*[c,d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** (10) | | ChCl/urea (1/2) | 25 | 24 | 90 | 36 (*R*) |
| 2 | **1a** (10) | | ChCl/Gly (1/2) | 25 | 24 | 94 | 51 (*R*) |
| 3 | **1a** (10) | | ChCl/ethylene glycol (1/2) | 25 | 24 | 46 | 64 (*R*) |
| 4 | **1a** (10) | | ChCl/resorcinol (1/1) | 25 | 24 | 72 | 67 (*R*) |
| 5 | **1a** (10) | | TBAB/Gly (1/3) | 25 | 24 | 85 | 66 (*R*) |
| 6 | **1a** (10) | | $Ph_3MePBr$/Gly (1/2) | 25 | 24 | 96 | 72 (*R*) |
| 7 | **1a** (10) | HDA (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 92 (*R*) |
| 8 | **1a** (10) | Oxalic acid (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 28 | 72 (*R*) |
| 9 | **1a** (10) | Phthalic acid (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 58 | 72 (*R*) |
| 10 | **1a** (10) | $PhCO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 96 | 86 (*R*) |
| 11 | **1a** (10) | $3,4\text{-}(OMe)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 97 | 94 (*R*) |
| 12 | **1a** (10) | $4\text{-}O_2NC_6H_2CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 90 (*R*) |
| 13 | **1a** (10) | Imidazole (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 66 (*R*) |
| 14 | **1a** (10) | DMAP (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 90 | 50 (*R*) |
| 15 | **1a** (20) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (20) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 92 (*R*) |
| 16 | **1a** (5) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (5) | $Ph_3MePBr$/Gly (1/2) | 25 | 24 | 89 | 86 (*R*) |
| 17 | **1a** (10) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 10 | 8 | 10 | 66 (*R*) |
| 18 | **1b** (10) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 94 | 88 (*R*) |
| 19 | **1c** (10) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 93 | 90 (*R*) |
| 20 | *ent*-**1a** (10) | $3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10) | $Ph_3MePBr$/Gly (1/2) | 25 | 8 | 95 | 94 (*S*) |

[a] Abbreviations: ChCl = choline chloride; DMAP = 4-*N*,*N*-dimethylaminopyridine; Gly = glycerol; HDA = hexanedioic acid; TBAB = tetra-*n*-butylammonium bromide.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivity determined by chiral HPLC.
[d] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.

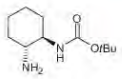
been shown to accelerate catalytic cycles when enamine-forming organocatalysts are involved,[13] gave good yields, but low enantioselectivities (Table 1, entries 13 and 14).

The synergistic role played by the acidic additive, when combined with the organocatalyst, in speeding up the reaction and in increasing both the yield and the *ee* is noteworthy. Perhaps a chiral H-bonded chelated cluster with maleimide may be playing a role in exalting its electrophilic character, thereby facilitating the nucleophilic attack by the aldehyde.

Once the most convenient deep eutectic solvent ($Ph_3MePBr$/Gly, 1/2 molar ratio) and additive [3,4-$(OMe)_2C_6H_3CO_2H$, 10 mol %) were established, we next studied the influence of the amount of organocatalyst **1a**. Increasing the loading of **1a** up to 20 mol % showed almost no influence on the yield or enantioselectivity for adduct (*R*)-**4aa**, whereas decreasing it to 5 mol % gave rise to a lower yield and *ee* in a much longer reaction time (Table 1, entries 15 and 16). Lowering the reaction temperature down to 10 °C resulted in a very slow reaction rate and an enantioselection of only 66% (Table 1, entry 17).

With the optimal catalyst loading, additive, deep eutectic solvent and reaction temperature determined, we next explored the organocatalytic behaviour of the other chiral carbamate-monoprotected *trans*-cyclohexane-1,2-diamines **1b** and **1c**, bearing a benzyloxycarbonyl (Cbz) and a fluorenylmethoxycarbonyl (Fmoc) protecting group, respectively. Their performance in the model reaction was not superior to **1a**, affording adduct (*R*)-**4aa** in good yields, but with lower enantioselectivities (Table 1, entries 18 and 19). Finally, we carried out a blank reaction in absence of organocatalyst **1** but in the presence of an additive, and observed no reaction.

In order to achieve opposite enantioselectivities to those obtained using organocatalyst **1a**, we obtained its enantiomer *ent*-**1a**, following an identical procedure but starting from (1*R*,2*R*)-cyclohexane-1,2-diamine.[12c] By using this mono-Boc-protected diamine as the organocatalyst, under the most convenient reaction conditions [*ent*-**1a** (10 mol %), 3,4-$(OMe)_2C_6H_3CO_2H$ (10 mol %), $Ph_3MePBr$/Gly (1/2 molar ratio), rt], the expected enantiomeric adduct (*S*)-**4aa** was obtained in identical absolute values of opposite enantioselectivity than when using **1a** as the organocatalyst (Table 1, entry 20).



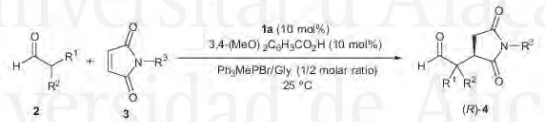

*ent*-**1a**

We subsequently explored the extension of the procedure to other aldehydes and *N*-substituted maleimides, by employing the above mentioned optimized reaction conditions (Table 2). As in the case of the model reaction, the absolute configuration of the resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature.[12c]

Thus, when isobutyraldehyde was reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 3- or 4-positions **3b**, **3c** and **3d**, the corresponding succinimides (*R*)-**4ab**, (*R*)-**4ac** and (*R*)-**4ac** were obtained in high yields and with 70, 87 and 86% *ee*, respectively (Table 2, entries 2–4). In addition, when an acyl group was present on the phenyl ring of the maleimide, as in the case of **3e**, the enantioselectivity for the corresponding succinimide (*R*)-**4ae** was 72% *ee* in a slightly lower yield (Table 2, entry 5). A similar enantioselectivity for (*R*)-**4af** was observed when an electron-releasing group, such as a methoxy, was present at the 4-position **3f** (Table 2, entry 6)

Non-*N*-arylated maleimides were also employed for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide **3g** and *N*-methylmaleimide **3h** gave succinimides (*R*)-**4ag** and (*R*)-**4ah** in high yields but with moderate 63 and 66% *ee*, respectively (Table 2, entries 7 and 8). In addition, the simple maleimide **3i** was also used as a Michael acceptor, affording (*R*)-**4ai** in 90% yield and with 67% *ee* (Table 2, entry 9).

**Table 2**
Enantioselective conjugate addition of aldehydes to maleimides organocatalyzed by **1a** in a deep eutectic solvent




**2** **3** (*R*)-**4**

| Entry | Aldehyde | | | Maleimide | | *t* (h) | Adduct No. | Yield[a] (%) | *ee*[b,c] (%) |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | No. | $R^3$ | No. | | | | |
| 1 | Me | Me | **2a** | Ph | **3a** | 8 | (*R*)-**4aa** | 97 | 94 |
| 2 | Me | Me | **2a** | 3-$ClC_6H_4$ | **3b** | 8 | (*R*)-**4ab** | 95 | 70 |
| 3 | Me | Me | **2a** | 4-$ClC_6H_4$ | **3c** | 8 | (*R*)-**4ac** | 96 | 87 |
| 4 | Me | Me | **2a** | 4-$BrC_6H_4$ | **3d** | 8 | (*R*)-**4ad** | 95 | 86 |
| 5 | Me | Me | **2a** | 4-$AcC_6H_4$ | **3e** | 8 | (*R*)-**4ae** | 90 | 72 |
| 6 | Me | Me | **2a** | 2-$MeOC_6H_4$ | **3f** | 8 | (*R*)-**4af** | 93 | 70 |
| 7 | Me | Me | **2a** | Bn | **3g** | 8 | (*R*)-**4ag** | 91 | 63 |
| 8 | Me | Me | **2a** | Me | **3h** | 8 | (*R*)-**4ah** | 94 | 66 |
| 9 | Me | Me | **2a** | H | **3i** | 8 | (*R*)-**4ai** | 90 | 67 |
| 10 | Et | Et | **2b** | Ph | **3a** | 12 | (*R*)-**4ba** | 60 | 43 |
| 11 | $-(CH_2)_4-$ | | **2c** | Ph | **3a** | 8 | (*R*)-**4ca** | 96 | 87 |
| 12 | $-(CH_2)_5-$ | | **2d** | Ph | **3a** | 10 | (*R*)-**4da** | 93 | 31 |
| 13 | Me | Ph | **2e** | Ph | **3a** | 20 | (*S,R*)/(*R,R*)-**4ea** | 87[d] | 85/10 |
| 14 | H | Me | **2f** | Ph | **3a** | 16 | (*R,R*)/(*S,R*)-**4fa** | 90[e] | 50/50 |

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities determined by chiral HPLC.
[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.
[d] Mixture of diastereomers 4/1 determined by $^1H$ NMR (300 MHz) in the reaction crude.
[e] Mixture of diastereomers 1.4/1 determined by $^1H$ NMR (300 MHz) in the reaction crude.

Other α,α-disubstituted aldehydes were employed for the organocatalyzed conjugate addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal **3b** afforded succinimide (*R*)-**4ba** with moderate yield and enantioselectivity (Table 2, entry 10). However, cyclopentanecarbaldehyde **2c** gave almost a quantitative yield of (*R*)-**4ca** with 87% *ee* (Table 2, entry 11), something very different than when using cyclohexanecarbaldehyde **2d**, which afforded the corresponding adduct (*R*)-**4da** with an enantioselection of only 31% (Table 2, entry 12). Moreover, when a different α,α-disubstituted aldehyde such as 2-phenylpropanal **2e** was employed, the final adduct was obtained in a 4/1 diastereomeric ratio with an enantioselection of 85% for the diastereomer (*S,R*)-**4ea** and 10% for (*R,R*)-**4ea** (Table 2, entry 13). Furthermore, the use of an α-monosubstituted aldehyde such as propanal **2f**, allowed us to obtain the adducts as a 1.4/1 mixture of diastereomers, with enantioselections of 50% for (*R,R*)- and (*S,R*)-**4fa** (Table 2, entry 14).

The possibility of reusing the deep eutectic solvent is the cornerstone of a synthetic methodology performed using these neoteric solvents. Therefore, we explored the reusability of the deep eutectic solvent, and the catalytic system, by carrying out different reaction cycles of the model conjugate addition reaction performed under the best reaction conditions depicted in Table 2, entry 1. Thus, once the reaction was finished, a 4/1 v/v mixture of ethyl ether/*n*-hexane was added and the resulting mixture was stirred vigorously. After the two layers settled down, the upper layer, containing the final adduct, was separated. Attempting to directly reuse the lower deep eutectic solvent layer in other reaction by adding new aldehyde and maleimide resulted in low yields and moderate enantioselectivities of the resulting adduct (*R*)-**4aa**. This was explained after observing the presence of acid additive in the recovered organic layer (NMR). After several attempts, it was found that refreshing the catalytic system by the addition of new additive (but no new chiral organocatalyst) to the recovered deep eutectic solvent allowed us to obtain (*R*)-**4aa** with almost identical enantioselectivity and yield than when used for the first time. Following this recovery procedure, the deep eutectic solvent containing the organocatalyst **1a** could be reused four times without diminishing its enantioinduction (Table 3). However, a fifth reaction cycle led to a decrease in the catalytic activity.

**Table 3**
Recycle experiments. Yields and *ee*'s of (*R*)-**4aa** after consecutive reaction cycles[a]

| Reaction cycle | Yield[b] (%) | *ee*[c] (%) |
|---|---|---|
| 1 | 97 | 94 |
| 2 | 95 | 94 |
| 3 | 93 | 93 |
| 4 | 76 | 92 |
| 5 | 60 | 84 |

[a] **1a** (10 mol %), 3,4-$(MeO)_2C_6H_3CO_2H$ (10 mol %), $Ph_3MePBr$/Gly (1/2 molar ratio), 25 °C, 8 h.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivitity determined by chiral HPLC.

## 3. Conclusions

It can be concluded that deep eutectic solvents can be used as reusable solvents in enantioselective conjugate additions of aldehydes, mainly α,α-disubstituted, to *N*-substituted maleimides, to afford enantioenriched substituted succinimides. Carbamate-monoprotected *trans*-cyclohexa-1,2-diamines have been employed as enantiomerically pure organocatalysts, with the mono-Boc-substituted derivative affording the best results. The reaction can be carried out in the presence of a carboxylic acid as an additive at room temperature. Once the reaction is completed, the final adduct can be separated by extraction, and the deep eutectic solvent retaining the organocatalyst, can be reused up to four times after the addition of fresh additive, while keeping its enantiodifferentiation activity. These results demonstrate than the use of deep eutectic solvents in enantioselective organocatalytic reactions can result in efficient and green strategies, and afford even better enantioselections than when conventional volatile organic compounds are used.

## 4. Experimental

### 4.1. General

All reagents were commercially available and used without further purification. Organocatalysts **1** were obtained as described.[12c] All known adducts **4** were characterized by spectroscopic methods.[12f] Enantioselectivities and absolute configurations were determined on the reaction crude by HPLC analyses[12f] on an Agilent 1100 series equipped with chiral columns (Chiralcel OD-H: **4aa**, **4ab**, **4ac**, **4ad**, **4ca**, **4da**, **4ea**;[12f] Chiralcel AD-H: **4af**; Chiralpak AS-H: **4ae**, **4ah**, **4ba**; Chiralpak AD-H: **4ag**, **4ai**, **4fa**), using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualised under UV light. For chromatography we employed Merck silica gel 60 (0.063–0.2 mm).

### 4.2. General procedure for the preparation of deep eutectic solvents

A mixture of the two components, with the previously specified molar ratio, was added to a round bottom flask and the mixture was stirred for 60 min in a temperature range between 65 and 80 °C, obtaining the corresponding deep eutectic solvent.[14]

### 4.3. Enantioselective conjugate addition reaction. General procedure

To a mixture of catalyst **1** (0.02 mmol), additive (0.02 mmol), and maleimide (0.2 mmol) in the corresponding deep eutectic solvent (0.5 mL) was added the aldehyde (0.4 mmol) and the reaction was vigorously stirred during the necessary reaction time (TLC, Table 2) at rt. Next 2 M HCl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined organics were washed with aq $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$) and evaporated (15 torr), and the resulting crude was purified by flash chromatography (hexane/EtOAc gradients) affording adduct **4**.

### 4.4. Recycling experiments

To a mixture of catalyst **1a** (4.3 mg, 0.02 mmol), 3,4-dimethoxybenzoic acid (3,7 mg, 0.02 mmol), and *N*-phenylmaleimide (34.6 mg, 0.2 mmol) in $Ph_3MePBr$/Gly (1/2 molar ratio, 0.5 mL) was added isobutyraldehyde (36.5 μL, 0.4 mmol) and the reaction was vigorously stirred for 8 h at rt. After this period, a mixture of ethyl ether/*n*-hexane (4/1, v/v, 3 mL) was added and the mixture was stirred for 2 min. The stirring was stopped to allow for phase separation and the upper organic layer was removed through settling. This extractive procedure was repeated three times. The combined organic extracts were washed ($NaHCO_3$ aq, 10 mL), dried ($MgSO_4$), evaporated (15 torr) and purified by flash chromatography on silica gel (hexane/EtOAc gradients) to yield (*R*)-**4aa**. The deep eutectic solvent layer, where catalyst **1a** remained dissolved, was evaporated in vacuo to remove volatile solvent residues

(15 torr) and the catalytic system was regenerated by 3,4-dimethoxybenzoic acid addition (3,7 mg, 0.02 mmol). A further run was performed with this deep eutectic solvent, adding new isobutyraldehyde and *N*-phenylmaleimide. This reaction mixture was subjected again to the above described procedure and further reaction cycles were repeated using the same deep eutectic solvent phase.

## Acknowledgments

We thank the financial support from the Spanish Ministerio de Economía y Competitividad (project CTQ2015-66624-P) and the University of Alicante (VIGROB-173 and UAUSTI14). J. F.-F. particularly acknowledges the Vicerrectorado de Investigación y Transferencia de Conocimiento of the University of Alicante for a fellowship.

## References

1. *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013.
2. (a) Liu, P.; Hao, J.-W.; Mo, L.-P.; Zhang, Z.-H. *RSC Adv.* **2015**, *5*, 48675–48704; (b) García-Álvarez, J.; Hevia, E.; Capriati, V. *Eur. J. Org. Chem.* **2015**, 6779–6799; (c) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Eur. J. Org. Chem.* **2016**, 612–632; (d) Khandelwal, S.; Tailor, Y. K.; Kumar, M. *J. Mol. Liq.* **2016**, *215*, 345–386; (e) Guajardo, N.; Müller, C. R.; Schrebler, R.; Carlesi, C.; Domínguez de María, P. *ChemCatChem* **2016**, *8*, 1020–1027.
3. (a) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jerome, F. *Chem. Soc. Rev.* **2012**, *41*, 7108–7146; (b) Francisco, M.; van den Bruinhorst, A.; Kroon, M. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3074–3085; (c) Tang, B.; Row, K. H. *Monatsh. Chem.* **2013**, *144*, 1427–1454; (d) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. *ACS Sustain. Chem. Eng.* **2014**, *2*, 1063–1071; (e) Smith, E. L.; Abbott, A. P.; Ryder, K. S. *Chem. Rev.* **2014**, *114*, 11060–11082.
4. (a) Müller, C. R.; Meiners, I.; Domínguez de María, P. *RSC Adv.* **2014**, *4*, 46097–46101; (b) Müller, C. R.; Rosen, A.; Domínguez de María, P. *Sustain. Chem. Processes* **2015**, *3*, 1–8.
5. Massolo, E.; Palmieri, S.; Benaglia, M.; Capriati, V.; Perna, F. M. *Green Chem.* **2016**, *18*, 792–797.
6. Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. *Green Chem.* **2016**, *18*, 1724–1730.
7. Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem. Asian J.* **2012**, *8*, 328–346.
8. (a) Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964–1973; (b) Freiberg, C.; Brunner, N. A.; Schiffer, G.; Lampe, T.; Pohlmann, J.; Brands, M.; Raabe, M.; Haebich, D.; Ziegelbauer, K. *J. Biol. Chem.* **2004**, *279*, 26066–26073; (c) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577–5583; (d) Uddin, J.; Ueda, K.; Siwu, E. R. O.; Kita, M.; Uemura, D. *Bioorg. Med. Chem.* **2006**, *14*, 6954–6961; (e) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini-Rev. Med. Chem.* **2012**, *12*, 671–700.
9. (a) Nöth, J.; Frankowski, K. J.; Neuenswander, B.; Aubé, J.; Reiser, O. *J. Comb. Chem.* **2008**, *10*, 456–459; (b) Fenster, E.; Hill, D.; Reiser, O.; Aube, J. *Beilstein J. Org. Chem.* **2012**, *8*, 1804–1813.
10. (a) Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1996**, *39*, 1898–1906; (b) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162; (c) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; (d) Tang, K.; Zhang, J.-T. *Neurol. Res.* **2002**, *24*, 473–478; (e) Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689–5692; (f) Das Sarma, K.; Zhang, J.; Huang, Y.; Davidson, J. G. *Eur. J. Org. Chem.* **2006**, 3730–3737; (g) Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.-H.; Neuteboom, S. T. C.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407–419.
11. (a) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; (b) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491–2513.
12. (a) Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Cordova, A. *Chem. Commun.* **2007**, 734–735; (b) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774; (c) Bai, J.-F.; Peng, L.; Wang, L.-L.; Wang, L.-X.; Xu, X.-Y. *Tetrahedron* **2010**, *66*, 8928–8932; (d) Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979–7982; (e) Miura, T.; Masuda, A.; Ina, M.; Nakashima, K.; Nishida, S.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1605–1609; (f) Ma, Z.-W.; Liu, Y.-X.; Li, P.-L.; Ren, H.; Zhu, Y.; Tao, J.-C. *Tetrahedron: Asymmetry* **2011**, *22*, 1740–1748; (g) Ma, Z.-W.; Liu, Y.-X.; Zhang, W.-J.; Tao, Y.; Zhu, Y.; Tao, J.-C.; Tang, M.-S. *Eur. J. Org. Chem.* **2011**, 6747–6754; (h) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J.* **2012**, *18*, 4088–4098; (i) Avila, A.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1625–1627; (j) Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5085–5092; (k) Orlandi, S.; Pozzi, G.; Ghisetti, M.; Benaglia, M. *New J. Chem.* **2013**, *37*, 4140–4147; (l) Kokotos, C. G. *Org. Lett.* **2013**, *15*, 2406–2409; (m) Muramulla, S.; Ma, J.-A.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2013**, *355*, 1260–1264; (n) Yang, W.; Jiang, K.-Z.; Lu, X.; Yang, H.-M.; Li, L.; Lu, Y.; Xu, L.-W. *Chem. Asian J.* **2013**, *8*, 1182–1190; (o) Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Tetrahedron: Asymmetry* **2013**, *24*, 1531–1535; (p) Durmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2013**, *24*, 1443–1448; (q) Flores-Ferrándiz, J.; Chinchilla, R. *Tetrahedron: Asymmetry* **2014**, *25*, 1091–1094; (r) Flores-Ferrándiz, J.; Fiser, B.; Gómez-Bengoa, E.; Chinchilla, R. *Eur. J. Org. Chem.* **2015**, 1218–1225; (s) Vizcaíno-Milla, P.; Sansano, J. M.; Nájera, C.; Fiser, B.; Gómez-Bengoa, E. *Synthesis* **2015**, *47*, 2199–2206; (t) Fernandes, T. D. A.; Vizcaíno-Milla, P.; Ravasco, J. M. J. M.; Ortega-Martinez, A.; Sansano, J. M.; Nájera, C.; Costa, P. R. R.; Fiser, B.; Gómez-Bengoa, E. *Tetrahedron: Asymmetry* **2016**, *27*, 118–122.
13. Zhang, X.-J.; Liu, S.-P.; Li, X.-M.; Yang, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833–835.
14. (a) Shahbaz, K.; Mjalli, F. S.; Hashim, M. A.; Al Nashef, I. M. *Energy Fuels* **2011**, *25*, 2671–2678; (b) Yusof, R.; Abdulmalek, E.; Sirat, K.; Abdul Rahman, M. B. *Molecules* **2014**, *19*, 8011–8026; (c) García, G.; Aparicio, S.; Ullah, R.; Atilhan, M. *Energy Fuels* **2015**, *29*, 2616–2644.

# CHAPTER II:

## CHIRAL AMINOCARBAMATES AS ORGANOCATALYSTS IN THE MICHAEL ADDITION REACTION OF ALDEHYDES AND KETONES TO β-NITROALKENES

# 1. ANTECEDENTS

The enantioselective preparation of γ-nitrocarbonyl derivatives has gained great importance in recent years as key precursors of many important compounds. This is derived from the fact that the nitro group can be easily transformed into a wide variety of valuable compounds (Figure I),[1] such as amines.[2] Indeed this ability to act as a mask for later transformation has led to the nitro group being described as a "synthetic chameleon".[3]

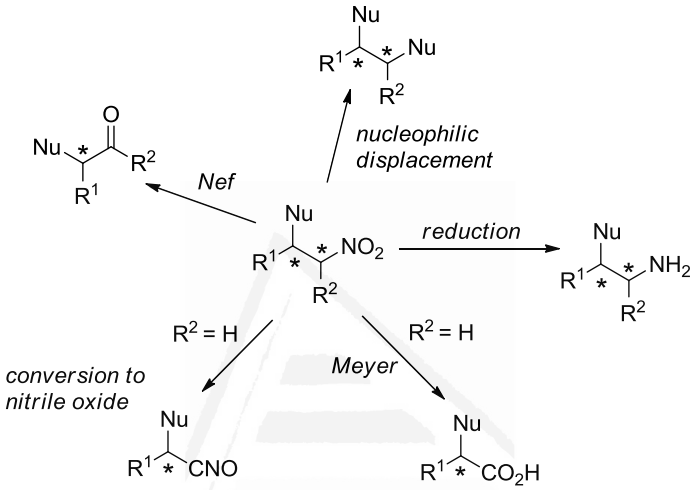



**Figure I.** Synthetic utility of the nitro group.

The enantioselective addition of aldehydes and ketones to β-nitrostyrenes is particularly interesting, as the corresponding γ-nitroaldehydes or γ-nitroketones can be used as intermediates in the preparation of alkaloids,[4] aminoacids,[5] antitumorals,[6] antibiotics,[7] peptidomimetics,[8] marine metabolites[9] and β-arylated γ-aminobutyric

[1] Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894.
[2] Goksu, H.; Sert, H.; Kilbas, B.; Sen, F. *Curr. Org. Chem.* **2017**, *21*, 794-820.
[3] Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592-1604.
[4] (a) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833-1836; (b) Zou, W.; Vembaiyan, K.; Bhasin, M.; Williams, D. T. *Carbohydr. Res.* **2009**, *344*, 2144-2150; (c) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556-559.
[5] (a) Ma, H.; Liu, K.; Zhang, F.-G.; Zhu, C.-L.; Nie, J.; Ma, J.-A. *J. Org. Chem.* **2010**, *75*, 1402-1409; (b) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036-4037.
[6] Szanto, G.; Hegedus, L.; Mattyasowszky, L.; Simon, A.; Simon, A.; Bitter, L.; Toth, G.; Toke, L.; Kadas, L. *Tetrahedron* **2009**, *65*, 8412-8417.
[7] Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901-7904.
[8] Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 5195-5198.

acids, which are pharmacologically important GABA analogues,[10] and exhibit a range of pharmacological activities including antidepressant, anticonvulsant, anxiolytic and others.[11]

Commercial examples are Baclofen and Phenibut, their synthesis from enantioenriched γ-nitroketones, being shown in Figure II.[12] Baclofen (sold as a racemate) is used in the treatment of spasticity.[13] In addition, recent studies shown that (*R*)-Baclofen, is more efficient than its enantiomer, for autism treatment (STX209 or Arbaclofen).[14] Phenibut is a tranquilizer and nootropic drug,[15] in which the *R*-enantiomer is 100 times more potent than the *S*-enantiomer.[16]

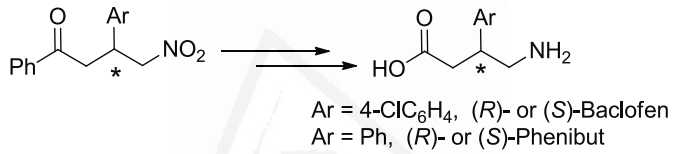



**Figure II.** Synthesis of Baclofen and Phenibut starting from γ-nitroketones.

Nowadays, the enantioselective Michael addition reaction of enolizable carbonyl compounds, in particular aldehydes and ketones, to nitroalkenes promoted by a chiral organocatalyst is one of the most common and convenient procedures for



[9] Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776-779.
[10] Kerr, D. I. B.; Ong, J. *Med. Res. Rev.* **1992**, *12*, 593-636.
[11] (a) Gajcy, K.; Lochynski, S.; Librowski, T. *Curr. Med. Chem.* **2010,** *17*, 2338-2347; (b) Andresen, H.; Aydin, B. E.; Mueller, A.; Iwersen-Bergmann, S. *Drug Test Anal.* **2011,** *3*, 560-568; (c) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini Rev. Med. Chem.* **2012,** *12*, 671-700.
[12] Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2012**, *354*, 740-746.
[13] (a) Olpe, H. R.; Demieville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133-136; (b) Berthelot, P.; Vaccher, C.; Flouquet, N.; Debaert, M.; Luyckx, M.; Brunet, C. *J. Med. Chem.* **1991**, *34*, 2557-2560; (c) Kerr, D. I. B.; Ong, J.; Doolette, D. J.; Abbenante, J.; Prager, R. H. *Eur. J. Pharmacol.* **1993**, *236*, 239-245.
[14] Hopkins, C. R. *ACS Chem. Neurosci*. **2011**, *2*, 381-381.
[15] Lapin, I. *CNS Drug Rev.* **2001**, *7*, 471-481.
[16] Dambrova, M.; Zvejniece, L.; Liepinsh, E.; Cirule, H.; Zharkova, O.; Veinberg, G.; Kalvinsh, I. *Eur. J. Pharmacol*. **2008**, *583*, 128-134.

achieving the synthesis of γ-nitrocarbonyl compounds in an enantiomerically enriched form.[17]

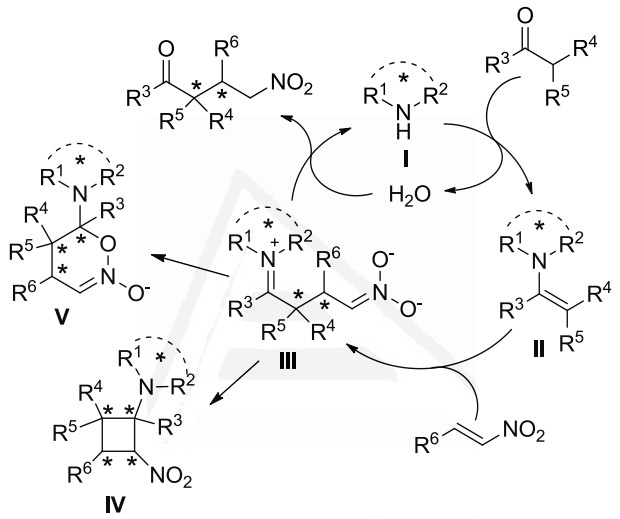
Concerning the mechanism of this process, the nowadays accepted catalytic cycle for this reaction involves enamines as nucleophiles (Scheme I).[17j] The presence of additives as co-catalysts, mainly carboxylic acids, is frequently necessary to achieve good optical and chemical yields. Thus, the chiral amine organocatalyst **I** would react with the carbonyl compound forming an enamine **II** (for primary amines, $R^1$=H, initially an imine in tautomeric equilibrium with the enamine) which would add stereoselectively to the nitroolefin, leading to the nitronate adduct **III**. This intermediate is then hydrolyzed driving to the final γ-nitrocarbonyl compound and the initial amine organocatalyst. It is interesting to remark that formation of cyclobutane **IV** and 1,2-oxazine *N*-oxide **V** derivatives has been observed in this process,[18] these compounds being resting states of the organocatalyst. Its formation would "remove" the amine catalyst from the cycle, which would explain the mentioned frequent necessity of adding acid co-catalysts for achieving good results. The presence of an acid not only would promote a faster imine-enamine equilibrium, but also would protonate the nitronate **III**, blocking the formation of the **IV** and **V** byproducts. This could also be achieved internally if the amine catalyst bears an acidic functionality. In addition, there are evidences that, at least in some cases, support the re-formation of an enamine from intermediates **III**,



[17] (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894; (b) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123-3135; (c) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299-365; (d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701-1716; (e) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1-13; (f) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561-2601; (g) Somanathan, R.; Chávez, D.; Servín, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; de Parodi, C. A.; González, J. *Current Organic Chemistry* **2012**, *16*, 2440-2461; (h) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051-7071; (i) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627-2648; (j) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gómez, C.; Guillena, G.; Pastor, I. P.; Ramón, D. J. *Molecules* **2017**, *22*, 895-955.

[18] Sahoo, G.; Rahaman, H.; Madarasz, Á.; Pápai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13144-13148.

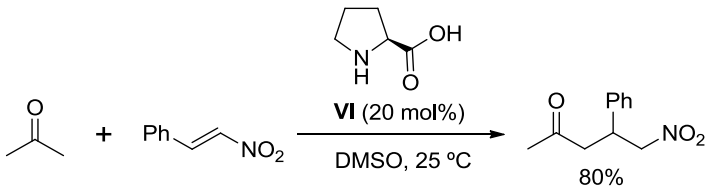
**IV**, **V**, with stereoselectivity now being controlled by the diastereoselectivity of enamine protonation.[19] Moreover, the presence of organic bases has sometimes also shown a positive effect as co-catalyst, as they can accelerate the reaction after favoring the creation of the enamine intermediate. Moreover, if suitable hydrogen-forming groups are also present in the chiral amine catalyst, the nitro group of the nitroalkene will be coordinated. Therefore, the enamine and the electrophile will be close enough to get a high enantioinduction.



**Scheme I.** Catalytic cycle of the conjugate addition of aldehydes and ketones to nitroalkenes promoted by primary or secondary chiral amines.

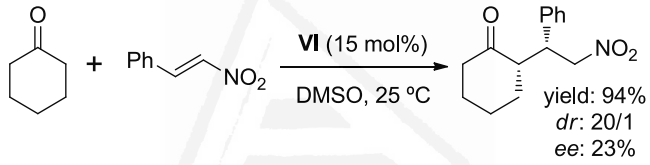
In 2001, two independent groups reported the first Michael addition reaction of ketones to nitroalkenes, leading to γ-nitroketones, employing as organocatalyst the naturally occurring amino acid L-proline (**VI**, 20 mol%). The Barbas's group carried on the addition of acetone to *trans*-β-nitrostyrene, obtaining the corresponding γ-nitroketone in good yield (80%) but as a racemate (Scheme II).[20]

[19] Duschmalé, J.; Wiest, J.; Wiesner, M.; Wennemers, H. *Chem. Sci.* **2013**, *4*, 1312-1318.
[20] Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc*. **2001**, *123*, 5260-5262.



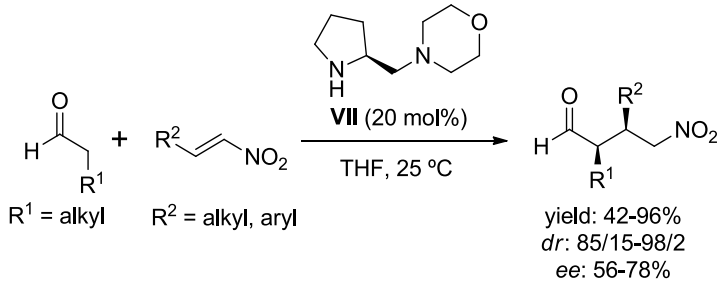

**Scheme II.** Michael addition reaction of acetone to *trans*-β-nitrostyrene organocatalyzed by **VI**.

The List's group, using the same organocatalyst **VI** (15 mol%), under identical conditions to those reported by Barbas, performed the addition of cyclohexanone to *trans*-β-nitrostyrene, obtaining the corresponding adduct with a 20/1 *syn*/*anti* diastereoselectivity, in 94% yield. However, only a 23% of enantiomeric excess was achieved (Scheme III).[21]




**Scheme III.** Asymmetric Michael addition reaction of cyclohexanone to *trans*-β-nitrostyrene organocatalyzed by **VI**.

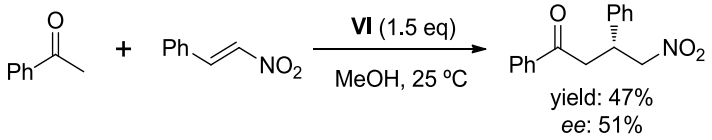
Barbas was also the first author to describe the Michael addition reaction of aldehydes to nitroolefins using as organocatalyst the proline derivative (*S*)-2-(morpholinomethyl)-pyrrolidine (**VII**) in THF as solvent (Scheme IV),[22] obtaining the corresponding γ-nitroaldehydes in moderate to good yields (42-96), with good to high diastereoselectivities (85/15-98/2) and moderate enantioselectivities (56-78%).




**Scheme IV.** Asymmetric Michael addition reaction of aldehydes to nitroolefins organocatalyzed by **VII**.

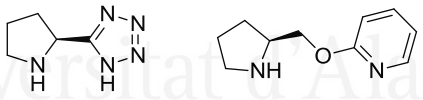
[21] List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423-2425.
[22] Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737-3740.

In 2002, Enders described the effect of the solvent in the Michael addition reaction of acetone to *trans*-β-nitrostyrene, improving slightly the enantioselectivity of the reaction organocatalyzed by **VI** (up to 12% *ee*) when methanol was used as solvent.[23] At the same time, Enders also described the first direct organocatalytic asymmetric conjugate addition reaction of acetophenone to *trans*-β-nitrostyrene, obtaining the desired γ-nitroketone in 47% yield and 51% *ee* (Scheme V).[23]




**Scheme V.** Asymmetric Michael addition reaction of acetophenone to *trans*-β-nitrostyrene organocatalyzed by **VI**.

Several catalysts, derived from proline (**VI**), were then synthesized in order to increase the enantioselection of the reaction between aldehydes and ketones to nitroolefins, such as tetrazole **VIII**,[24] and the pyrrolidine–pyridine-based **IX**,[25] obtaining the corresponding γ-nitrocompounds with moderate to high yields and enantioselectivities.




**VIII**
yield: 47-96%
*dr*: 6/1-19/1
*ee*: 33-73%

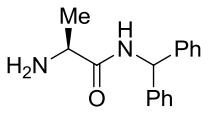
**IX**
yield: 53-99%
*dr*: 94/6-99/1
*ee*: 57-99%



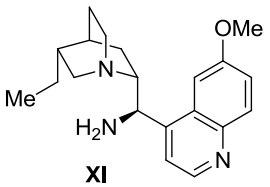
Other primary amine-containing amino acid derivatives have been employed as organocatalysts for the Michael addition reaction of ketones to nitroolefins, for example, the alanine derivative **X**. This catalyst could afford the reaction between cyclic and acyclic ketones to different nitroalkenes obtaining the corresponding γ-nitroketones in good yields (45-92%), with low to excellent diastereoselectivities

[23] Enders, D.; Seki, A. *Synlett* **2002**, 26-28.
[24] Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96.
[25] Xu, D.-Z.; Shi, S.; Wang, Y. *Eur. J. Org. Chem.* **2009**, 4848-4853.

and up to 98% *ee*.[26] In addition, the chiral primary-amine derived from a *Cinchona* alkaloid **XI** has been reported as an effective organocatalyst for the Michael addition reaction of ketones and aldehydes to nitroalkenes, obtaining the corresponding adducts with good yields (56-97%), moderate to good diastereoselectivities (2/1-20/1) and enantiomeric excesses up to 99% *ee*.[27]




**X**
yield: 45-92%
*dr*: 1/2-38/1
*ee*: 23-99%

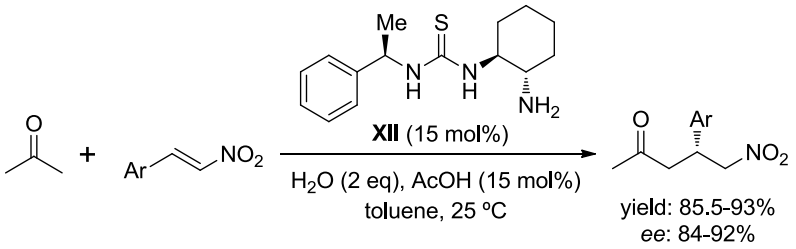



**XI**
yield: 56-97%
*dr*: 2/1-20/1
*ee*: 65-99%

Nowadays, most of the reported procedures in the enantioselective Michael addition reaction of enolizable aldehydes, acetone and arylated ketones to nitroalkenes, involve the use of bifunctional organocatalysts bearing a primary amine and a hydrogen bond-forming functionality, derived from enantiopure *trans*-cyclohexane-1,2-diamine, a commonly employed chiral auxiliary (see Chapter I, Antecedents).

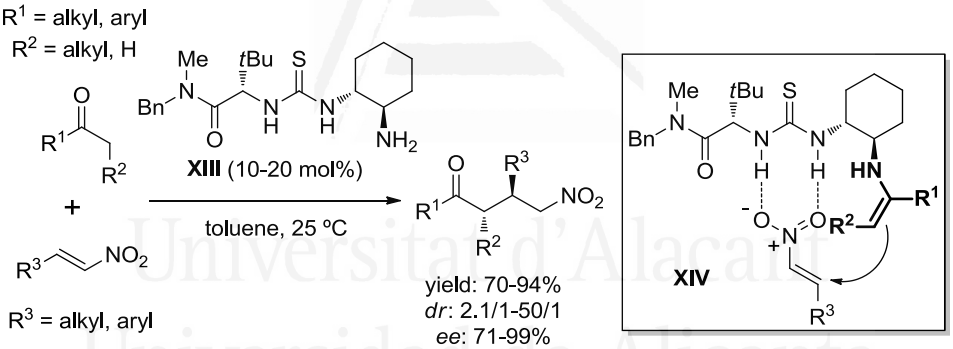
One of the most versatile organocatalyst to perform the Michael addition reaction of carbonyl compounds to nitroalkenes are thiourea-based compounds containing a primary amine to form the transient enamine.[28] Thus, the thiourea-based organocatalyst **XII** was reported by Tsogoeva as effective promoting the addition of acetone to different aromatic nitroalkenes giving the γ-nitroketones in good to high yields (86-93%) and enantioselectivities (84-92% *ee*), with toluene as solvent and acetic acid as co-catalyst (Scheme VI).[29]

[26] Xu, Y.; Cordova, A. *Chem. Commun.* **2006**, 460-462.
[27] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599-602.
[28] Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem*. **2013**, *11*, 7051-7071.
[29] Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451-1453.




**Scheme VI.** Asymmetric Michael addition reaction of acetone to nitroalkenes organocatalyzed by **XII**.

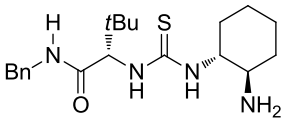
The same year, Jacobsen and Huang reported also the use of primary amine-thiourea organocatalyst **XIII** for the addition of ketones to nitroolefins, obtaining the corresponding γ-nitroketones in good to high yields (70-94%) and enantioselectivities (71-99% *ee*) and excellent diastereoselectivities (up to 50/1). The observed *anti* diastereoselectivity suggests formation of a *Z*-enamine intermediate in the approximation model **XIV** (Scheme VII).[30]




**Scheme VII.** Asymmetric Michael addition reaction of ketones to nitroolefins organocatalyzed by **XIII**.

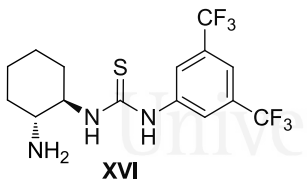
Removal of the methyl substituent from the amide group in catalyst **XIII**, was also performed by Jacobsen, affording organocatalyst **XV**, which allowed obtaining high yields (78-94%) and excellent enantioselectivities (94-99% *ee*) in the Michael addition of α,α-disubstituted aldehydes to nitroolefins.[31]

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

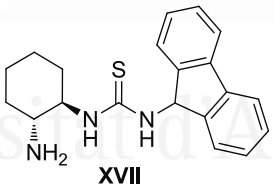


**XV**
yield: 78-94%
*dr*: 3.1/1-50/1
*ee*: 94-99%

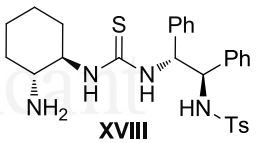
Considering the efficacy of the thiourea group as a hydrogen bonding donor, many other organocatalysts derived from chiral 1,2-diamines, have been synthesized and successfully used in the reaction Michael enantioselective addition of aldehydes and ketones to nitroalkenes, obtaining the corresponding adducts with enantioselectivities up to 99%. Some examples are amine-thiourea **XVI** (for aldehydes),[32] **XVII**,[33] **XVIII**[34] and the saccharide-derived **XIX** (for ketones),[35] and the rosin-derived **XX** (for aldehydes and ketones).[36] Also, the *Cinchona*-derivative **XXI**, has been reported as an efficient organocatalyst for the addition of aldehydes to nitroalkenes obtaining excellent yields (79-98%) and enantioselectivities (90-99% *ee*).[37]



**XVI**
yield: 57-83%
*dr*: 92/8-98/2
*ee*: 97-99%



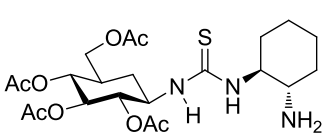
**XVII**
yield: 16-86%
*ee*: 61-90%



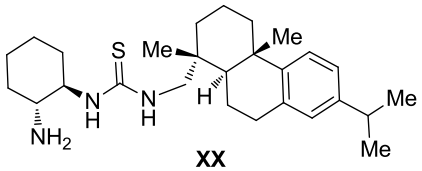
**XVIII**
yield: 71-96%
*ee*: 84-99%



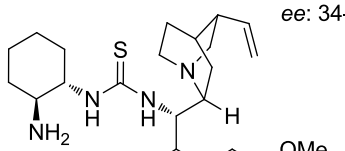
[32] Uehara, H.; Barbas, C. F., III *Angew. Chem. Int. Ed.* **2009,** *48*, 9848-9852.
[33] Yu, L.; Li, P. *Tetrahedron Lett.* **2014**, *55*, 3697-3700.
[34] Sun, Z.-W.; Peng, F.-Z.; Li, Z.-Q.; Zou, L.-W.; Zhang, S.-X.; Li, X.; Shao, Z.-H. *J. Org. Chem.* **2012**, *77*, 4103-4110.
[35] Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923-925.
[36] (a) Jiang, X.; Zhang, Y.; Chan, A.S.C.; Wang, R. *Org. Lett*. **2009**, *11*, 153-156; (b) Guo, X.-T.; Sha, F.; Wu, X.-Y. *Res. Chem. Intermed.* **2016,** *42*, 6373-6380.
[37] Chen, J.-R.; Zou, Y.-Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W.-J. *Tetrahedron* **2010,** *66*, 5367-5372.



**XIX**
yield: 42-99%
*ee*: 94-98%

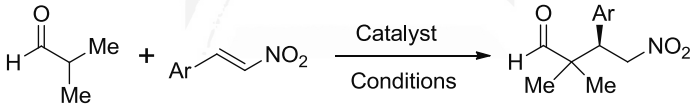


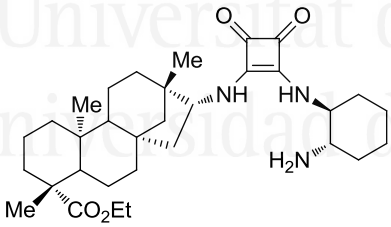
**XX**
yield: 64-99%
*dr*: 66/34-83/17
*ee*: 34-99%



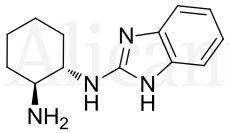
**XXI**
yield: 80-96%
*ee*: 90-97%

Other organocatalysts derived from chiral cyclohexa-1,2-diamines bearing different functional groups, such as the primary-amine squaramide **XXII**,[38] and also the primary-amine-containing benzimidazole **XXIII**,[39] have been recently reported for the Michael addition of isobutyraldehyde to nitroalkenes (Scheme VIII).



**XXII** (15 mol%)
$CHCl_3$, 25 ºC
yield: 70-98%
*ee*: 90-99%

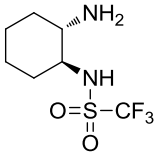


**XXIII** (20 mol%)
$CH_2Cl_2$, 25 ºC
yield: 52-99%
*ee*: 74-92%

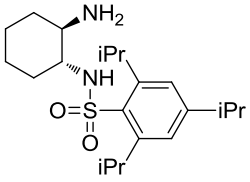
**Scheme VIII.** Asymmetric Michael addition reaction of ketones to nitroalkenes organocatalyzed by **XXII** and **XXIII**.

[38] Ma, Z.-W.; Liu, X.-F.; Sun, B.; Huang, X.-H.; Tao, J.-C. *Synthesis* **2017,** *49*, 1307-1314.
[39] Fernandes, T. A.; Vizcaíno-Milla, P.; Ravasco, J. M. J. M.; Ortega-Martínez, A.; Sansano, J. M.; Nájera, C.; Costa, P. R. R.; Fiser, B.; Gómez-Bengoa, E. *Tetrahedron: Asymmetry* **2016**, *27*, 118-122.

The primary amine-sulfonamides **XXIV**,[40] and **XXV**,[41] have also been able to carry on the Michael reaction of aryl ketones to nitroalkenes with high enantioselectivities (57-96%) and moderate to good yields (32-94%).

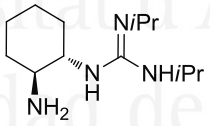


**XXIV**
yield: 33-94%
*dr*: 1/1-3/1
*ee*: 57-96%



**XXV**
yield: 32-72%
*ee*: 81-98%

Our group reported the use of the primary amine-guanidine **XXVI** as an efficient organocatalyst for the conjugate addition reaction of isobutyraldehyde to different nitroketones, affording the corresponding enantioenriched γ-nitroaldehydes in good yields (73-95%) and enantioselectivities (65-80%), working in a DMF/$H_2O$ mixture (1/4, v/v ratio) as solvent and using imidazole as basic additive. However, this organocatalyst cannot be considered as bifunctional, as it has been determined by theoretical calculations that, probably due to the presence of water, the guanidine function is not coordinated to the nitro group in the transition state.[42]



**XVI**
yield: 73-95%
*ee*: 65-80%

The following work deals to the synthesis of bifunctional organocatalysts derived from enantiopure *trans*-cyclohexa-1,2-diamines, bearing a primary amine and a carbamate moiety, and its use as organocatalyst in the Michael addition reaction of aldehydes and ketones to nitroalkenes.

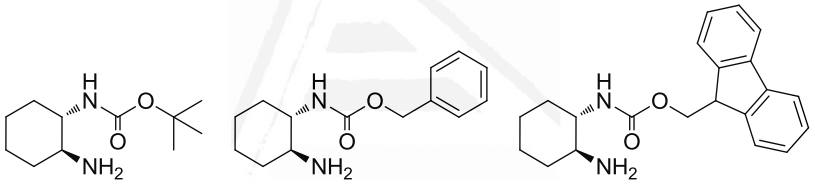
[40] Xue, F.; Zhang, S.; Duan, W.; Wang, W. *Adv. Synth. Catal.* **2008**, *350*, 2194-2198.
[41] Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305-1308.
[42] Avila, A.; Chinchilla, R.; Fiser, B.; Gómez-Bengoa, E.; Nájera, C. *Tetrahedron: Asymmetry* **2014**, *25*, 462-467.

# 2. OBJECTIVES

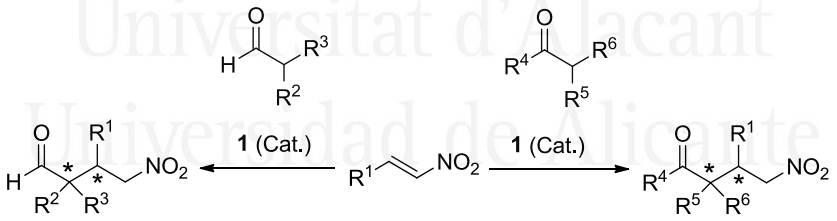
Due to the interest in the enantioselective synthesis of γ-nitrocarbonyl compounds described in the antecedents, and the lack of studies about the use of primary-amine carbamates as organocatalysts, we considered the following objectives:

1) Use of the primary-amine containing monocarbamates **1**, in the enantioselective Michael addition reaction of aldehydes and ketones to β-nitroalkenes, in order to synthesize the corresponding enantioenriched γ-nitroaldehyde and γ-nitroketone derivatives.

2) Explore the behaviour of these organocatalysts in the former reaction, using non traditional conditions, such as the use of the more environmentally friendly Deep Eutectic Solvents.



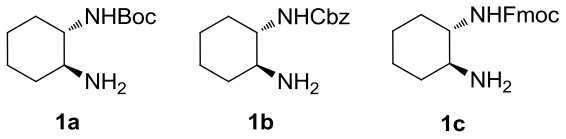
**1a** **1b** **1c**



# 3. RESULTS AND DISCUSSION

## 3.1. Synthesis of the Aminocarbamate Organocatalysts

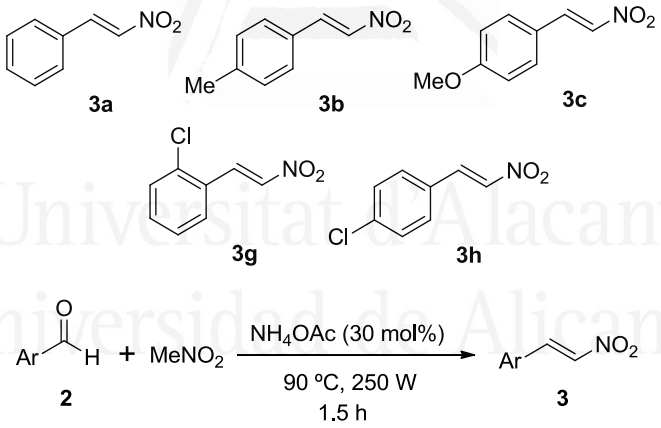
The aminocarbamates **1** used as organocatalysts in this study were synthesized as detailed in Chapter I.




**1a** **1b** **1c**

## 3.2. Synthesis of β-Nitroalkenes

The nitroalkenes employed as electrophiles were purchased (**3a**, **3b**, **3c**, **3g** and **3h**) or were prepared by reaction of the corresponding aldehyde **2** with nitromethane under microwave conditions (90 ºC, 250 W), using ammonium acetate as catalyst (Scheme 1).[43]

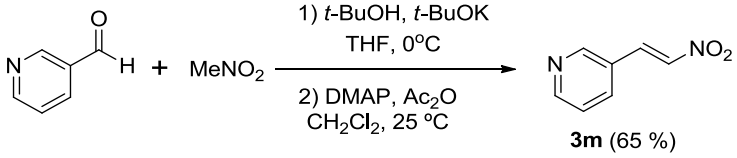



**3d**: Ar = 3,4-$(OCH_2O)C_6H_3$ (85%)
**3e**: Ar = 3,4,5-$(MeO)_3C_6H_2$ (78%)
**3f**: Ar = 4-$FC_6H_4$ (83%)
**3i**: Ar = 4-$BrC_6H_4$ (80%)
**3j**: Ar = 4-$CF_3C_6H_4$ (90%)
**3k**: Ar = 4-$O_2NC_6H_4$ (79%)
**3l**: Ar = 2-Naphtyl (90%)
**3n**: Ar = 2-Furyl (76%)

**Scheme 1**. Microwave-assisted synthesis of β-nitroalkenes

[43] Rodríguez, J. M.; Pujol, M. D. *Tetrahedron Lett.* **2011**, *52*, 2629-2632.

The pyridinyl-containing nitroalkene **3m**, was prepared in 65% yield by reaction of nicotinaldehyde and nitromethane with *tert*-butyl alcohol and *t*-BuOK at 0 ºC in THF, followed by reaction with DMAP and $Ac_2O$ in $CH_2Cl_2$ (Scheme 2).[44]




**Scheme 2**. Synthesis of nitroalkene **3m**

## 3.3. Enantioselective Michael Addition of Aldehydes to β-Nitroalkenes

### *3.3.1. Optimization Studies*

The search for the most appropriate reaction conditions (Table 1) began with the model Michael addition reaction of isobutyraldehyde (**4**) (2 equiv) to *trans*-β-nitrostyrene (**3a**), organocatalyzed by **1a** (20 mol%), in toluene as solvent at room temperature. The reaction afforded the corresponding adduct (*S*)-**5a** in less than 5% yield and with a 70% *ee* after 2 d reaction time (Table 1, entry 1). The (*S*)-absolute configuration of the final adduct **5a** was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature (see Experimental).

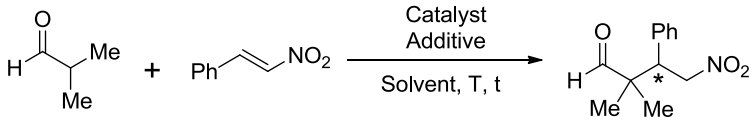
The use of others solvents was also explored. Thus, when hexane was used, the enantioselectivity for (*S*)-**5a** decreased to 57%, whereas the use of ethyl ether afforded a higher 78% *ee*, very low yields being obtained for both solvents (Table 1, entries 2 and 3). In addition, when $CH_2Cl_2$ and $CHCl_3$ were employed as solvents, an 84% *ee* for (*S*)-**5a** was observed, but only in 7 and 10% yield, respectively (Table 1, entries 4 and 5).

[44] Kuster, G. J. T.; Steeghs, R. H. J.; Scheeren, H. W. *Eur. J. Org. Chem*. **2001**, 553-560.

A similar switching in the enantioselectivity of the process with the solvent than the observed in Chapter I was found. Thus, when a polar solvent such as DMF was used, a 15% *ee* was obtained for the opposite γ-nitroaldehyde (*R*)-**5a** (Table 1, entry 6). In contrast, when a protic solvent, such as water, was employed, no inversion of the enantioselectivity was detected (Table, 1 entry 7). We also explore the use of mixtures of DMF/$H_2O$ as reaction solvents, obtaining in all cases the enantiomer (*R*)-**5a** but with low enantioselectivities, although in good yields (Table 1, entries 8-10). The DMF/$H_2O$ mixture (2/1, v/v ratio) afforded (*R*)-**5a** in 81% yield and 25% *ee* (Table 1, entry 9).

As observed, the use of $CHCl_3$ and the DMF/$H_2O$ mixture (2/1, v/v ratio) as solvents afforded the best enantioselectivities for the corresponding adducts (*S*)-**5a** and (*R*)-**5a**, respectively. The influence of the presence of additives in both solvents was then explored. Thus, the use of acid and basic additives in the DMF/$H_2O$ mixture (2/1, v/v ratio) did not improve the previous 25% *ee* of (*R*)-**5a** obtained when no additive was employed (Table 1, entries 11-16). Therefore, we decided to continue the study with $CHCl_3$ as the solvent, as the reversal in the enantioselectivity was not able to reach decent values for the opposite enantiomer. Thus, when hexanedioic (HDA) or benzoic acid were used as additives the yields were very low and no positive effect on the enantioselectivity for (*S*)-**5a** was observed (Table 1, entries 17-18). In contrast, basic additives such as imidazole, 4-(dimethylamino)pyridine (DMAP), 1,1,3,3-tetramethylguanidine (TMG) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were able to increase the yield of (*S*)-**5a** but with no change on the enantioselectivity (Table 1, entries 19-22). The best results concerning yield and enantioselectivity were obtained with the use of DABCO as basic additive, obtaining (*S*)-**5a** in 67% yield and 84% *ee* (Table 1, entry 22).

**Table 1**. Screening and optimization of the reaction conditions for the enantioselective Michael addition of isobutyraldehyde to *trans*-β-nitrostyrene.




**4** **3a** **5a**

| Entry | Catalyst (mol%) | Additive (mol%)[a] | Solvent | T (ºC) | t (d) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** (20) | - | PhMe | 25 | 2 | <5[d] | 70 (*S*) |
| 2 | **1a** (20) | - | Hexane | 25 | 2 | <5[d] | 57 (*S*) |
| 3 | **1a** (20) | - | $Et_2O$ | 25 | 2 | 9 | 78 (*S*) |
| 4 | **1a** (20) | - | $CHCl_3$ | 25 | 2 | 10 | 84 (*S*) |
| 5 | **1a** (20) | - | $CH_2Cl_2$ | 25 | 2 | 7 | 84 (*S*) |
| 6 | **1a** (20) | - | DMF | 25 | 2 | 21 | 11 (*R*) |
| 7 | **1a** (20) | - | $H_2O$ | 25 | 2 | 9 | 52 (*S*) |
| 8 | **1a** (20) | - | DMF/$H_2O$[e] | 25 | 1 | 80 | 11 (*R*) |
| 9 | **1a** (20) | - | DMF/$H_2O$[f] | 25 | 1 | 81 | 25 (*R*) |
| 10 | **1a** (20) | - | DMF/$H_2O$[g] | 25 | 1 | 78 | 23 (*R*) |
| 11 | **1a** (20) | HDA (20) | DMF/$H_2O$[f] | 25 | 1 | 67 | 20 (*R*) |
| 12 | **1a** (20) | $PhCO_2H$ (20) | DMF/$H_2O$[f] | 25 | 1 | 70 | 23 (*R*) |
| 13 | **1a** (20) | Imidazole (20) | DMF/$H_2O$[f] | 25 | 1 | 86 | 20 (*R*) |
| 14 | **1a** (20) | DMAP (20) | DMF/$H_2O$[f] | 25 | 1 | 80 | 17 (*R*) |
| 15 | **1a** (20) | TMG (20) | DMF/$H_2O$[f] | 25 | 1 | 45 | 15 (*R*) |
| 16 | **1a** (20) | DABCO (20) | DMF/$H_2O$[f] | 25 | 1 | 85 | 12 (*R*) |
| 17 | **1a** (20) | HDA (20) | $CHCl_3$ | 25 | 2 | <5[d] | 83 (*S*) |
| 18 | **1a** (20) | $PhCO_2H$ (20) | $CHCl_3$ | 25 | 2 | <5[d] | 60 (*S*) |
| 19 | **1a** (20) | Imidazole (20) | $CHCl_3$ | 25 | 2 | 30 | 84 (*S*) |
| 20 | **1a** (20) | DMAP (20) | $CHCl_3$ | 25 | 2 | 50 | 83 (*S*) |
| 21 | **1a** (20) | TMG (20) | $CHCl_3$ | 25 | 2 | 35 | 84 (*S*) |
| 22 | **1a** (20) | DABCO (20) | $CHCl_3$ | 25 | 2 | 67 | 84 (*S*) |
| 23 | **1a** (30) | DABCO (30) | $CHCl_3$ | 25 | 1 | 86 | 84 (*S*) |
| 24 | **1a** (20) | DABCO (30) | $CHCl_3$ | 25 | 2 | 86 | 84 (*S*) |
| 25 | **1a** (10) | DABCO (30) | $CHCl_3$ | 25 | 2 | 63 | 83 (*S*) |
| 26 | **1a** (20) | DABCO (30) | $CHCl_3$ | 0 | 3 | 70 | 84 (*S*) |
| 27 | **1b** (20) | DABCO (30) | $CHCl_3$ | 25 | 2 | 81 | 82 (*S*) |
| 28 | **1c** (20) | DABCO (30) | $CHCl_3$ | 25 | 2 | 78 | 80 (*S*) |
| 29 | *ent*-**1a** (20) | DABCO (30) | $CHCl_3$ | 25 | 2 | 85 | 84 (*R*) |

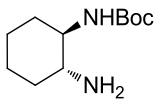
[a] HDA: hexanedioic acid; DMAP: 4-(dimethylamino)pyridine; TMG: 1,1,3,3-Tetramethylguanidine; DABCO: 1,4-diazabicyclo[2.2.2]octane. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [d] Estimated on the reaction crude by $^1$H NMR . [e] 1:1 (v/v). [f] 2:1 (v/v). [g] 4:1 (v/v).

The effect of the catalyst and additive loadings was also studied (Table 1, entries 23-25). Thus, when 30 mol% of catalyst and 30 mol% of the basic additive were used, an 84% *ee* for (*S*)-**5a** was obtained in 86% yield (Table 1, entry 23). Identical results were obtained by using 20 mol% of catalyst and 30 mol% of the basic additive (Table 1, entry 24), but when the organocatalyst loading was reduced to 10 mol%, maintaining 30 mol% of the basic additive, yield diminished down to 63% (Table 1, entry 25).

With the optimal conditions found [**1a** (20 mol%), DABCO (30 mol%), $CHCl_3$], the reaction temperature was lowered down to 0 ºC, but the enantioselectivity for (*S*)-**5a** was not improved, the yield decreasing to 70% after 3 days reaction time (Table 1, entry 26).

The use of organocatalysts **1b** and **1c** under the previous optimal conditions [catalyst (20 mol%), DABCO (30 mol%), $CHCl_3$, 25 ºC] was explored. When **1b** was used as catalyst, 82% *ee* and 81% yield was obtained for (*S*)-**5a** (Table 1, entry 27). In addition, when **1c** was employed, the enantioselectivity resulted lowered down to 80% *ee* with 78% yield (Table 1, entry 28). Therefore, **1a** was chosen as the most efficient organocatalyst for the rest of the study.

Expecting to achieve an opposite enantioselection, the reaction using *ent*-**1a** (prepared as shown in Chapter I) as the organocatalyst was also performed. Using the most effective reaction conditions [catalyst (20 mol%), DABCO (30 mol%), $CHCl_3$, 25 ºC], the expected adduct (*R*)-**5a** was isolated in 84% *ee* and 85% yield (Table 1, entry 29).




*ent*-**1a**

### *3.3.2. Scope of the Reaction*

Once the most effective organocatalyst and reaction conditions were established [**1a** (20 mol%), DABCO (30 mol%), $CHCl_3$, 25 ºC], the extension of this methodology to other aldehydes and nitroolefins was explored (Table 2). As in the case of the model reaction, the absolute configuration of the known resulting γ-nitroaldehydes was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

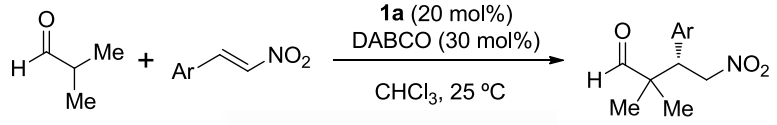
Different aldehydes (2-ethylbutyraldehyde, cyclopentanecarboxaldehyde, cyclohexanecarboxaldehyde and propionaldehyde) were employed for the organocatalyzed Michael addition reaction to *trans*-β-nitrostyrene (**3a**), but very low yields (<5%) were obtained after 3 days of reaction. Moreover, when diphenylacetaldehyde and 2-phenylpropionaldehyde were used for the Michael addition reaction, the corresponding adducts were obtained as racemates. Therefore, we explore the influence of changing the substituent on the nitroolefin **3a**.

When nitroalkenes **3b** and **3c**, bearing electron-releasing groups, such as methyl or methoxy, on the aromatic ring, were used, the corresponding Michael adducts (*S*)-**9b** and (*S*)-**9c** were isolated in good yields and with enantioselectivities of 82% and 81%, respectively (Table 2, entries 2 and 3). In addition, when other electron-releasing systems were present, as in the case of a dioxolane moiety (**3d**) or 3,4,5-trimethoxy groups (**3e**), the enantioselectivities for the obtained adducts (*S*)-**5d** and (*S*)-**5e** were 80 and 78%, respectively (Table 2, entries 4 and 5).

The presence of halogen groups on the aromatic ring of the nitroalkene such as fluoro (**3f**), chloro (**3g**) and (**3h**), and bromo (**3i**), gave the corresponding adducts (*S*)-**5f**, (*R*)-**5g**, (*S*)-**5h** and (*S*)-**5i** in 76, 70, 73 and 75% *ee* (Table 2, entries 6-9). With stronger electron-withdrawing groups in the aromatic ring of the nitroalkene, like 4-trifluoromethyl (**3j**) or 4-nitro (**3k**), the corresponding adducts (*S*)-**5j** and (*S*)-**5k** were isolated in 69 and 67% *ee* respectively (Table 2, entries 10 and 11).

When the nitroalkene **3l**, bearing a 2-naphthyl group, was employed as a Michael acceptor, the corresponding adduct (*S*)-**5l** was obtained in 80% *ee* (Table 2, entry 12). In addition, the influence of the presence of heteroarylated rings in the nitroalkene was also explored with the use of the 3-pyridyl- and 2-furyl-containing nitroalkenes **3m** and **3n** as Michael acceptors, which gave rise to adducts (*S*)-**5m** and (*S*)-**5n** in 66% and 78% *ee*, respectively (Table 2, entries 13 and 14).

**Table 2**. Enantioselective Michael addition of isobutyraldehyde to nitroalkenes organocatalyzed by **1a**.




**4** **3** **5**

| Entry | β-Nitroolefin | | t (d) | γ-Nitroaldehyde | | |
|---|---|---|---|---|---|---|
| | Ar | No. | | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Ph | **3a** | 2 | (*S*)-**5a** | 86 | 84 |
| 2 | 4-$MeC_6H_4$ | **3b** | 2 | (*S*)-**5b** | 78 | 82 |
| 3 | 4-$MeOC_6H_4$ | **3c** | 2 | (*S*)-**5c** | 76 | 81 |
| 4 | 3,4-$(OCH_2O)C_6H_3$ | **3d** | 3 | (*S*)-**5d** | 70 | 80 |
| 5 | 3,4,5-$MeOC_6H_2$ | **3e** | 3 | (*S*)-**5e** | 72 | 78 |
| 6 | 4-$FC_6H_4$ | **3f** | 2 | (*S*)-**5f** | 81 | 76 |
| 7 | 2-$ClC_6H_4$ | **3g** | 3 | (*R*)-**5g**[c] | 75 | 70 |
| 8 | 4-$ClC_6H_4$ | **3h** | 2 | (*S*)-**5h** | 80 | 73 |
| 9 | 4-$BrC_6H_4$ | **3i** | 2 | (*S*)-**5i** | 80 | 75 |
| 10 | 4-$F_3CC_6H_4$ | **3j** | 2 | (*S*)-**5j** | 78 | 69 |
| 11 | 4-$O_2NC_6H_4$ | **3k** | 2 | (*S*)-**5k** | 83 | 67 |
| 12 | 2-Naphthyl | **3l** | 2 | (*S*)-**5l** | 82 | 80 |
| 13 | 3-Pyridyl | **3m** | 3 | (*S*)-**5m** | 70 | 66 |
| 14 | 2-Furyl | **3n** | 2 | (*S*)-**5n** | 78 | 78 |

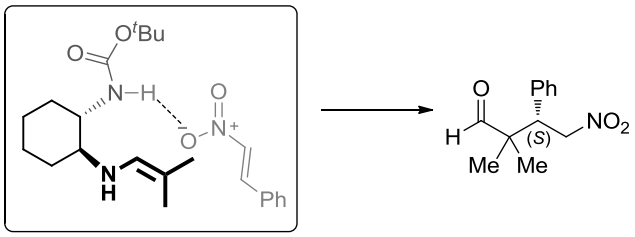
[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] No change in the enantioselectivity sense, just an effect of the CIP rules.

When nitroolefins bearing alkyl, instead of aromatic, substituents were used as electrophiles in the Michael addition reaction with isobutyraldehyde (**4**), such as (*E*)-(2-nitrovinyl)cyclohexane or (*E*)-(4-nitrobut-3-en-1-yl)benzene, the corresponding adducts were not obtained after 3 days of reaction time.

Organocatalyst **1a** was also employed in the Michael addition reaction of isobutyraldehyde (**4**) to *trans*-β-nitrostyrene (**3a**) in DES as a reaction media. Thus, all the DESs shown in Chapter I (Table 3) were employed in order to perform the model Michael addition reaction. However, very low enantioselectivities were obtained (<20%). The highest 20% *ee* for (*S*)-**5a**, in 43% yield, was achieved when the reaction was performed employing 20 mol% catalyst loading and DMAP (20 mol%) as additive, in the DES formed by choline chloride and urea (ChCl/urea, 1/2 molar ratio) at room temperature.

### *3.3.3. Coordination Model*

The obtained enantioselectivities allowed us to suggest a possible coordination model to justify the observed results. Thus, the isobutyraldehyde would react with the primary amine to form an enamine intermediate, whilst the nitro group would be coordinated to the secondary amine via a hydrogen bond. This coordination structure would favour the Michael addition reaction on one face of the *trans*-β-nitrostyrene, leading to the observed stereochemistry (Scheme 3). The presence of polar solvents would avoid the coordination of the nitro group. In this case, the carbamate moiety would sole act as a blocking group which would force the approaching of the nitroalkene to the opposite side of the enamine, leading preferentially to the other enantiomer. However, in this case the blocking effect seems to be not so effective as shown in Chapter I, so the enantioselectivity of the opposite enantiomer results much lower.




**Scheme 3**. Hypothesized coordination of catalyst with reactants leading to the observed stereochemistry

## 3.4. Enantioselective Michael Addition of Ketones to β-Nitroalkenes

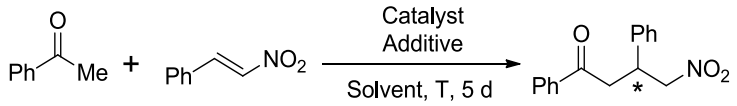
### *3.4.1. Optimization Studies*

Firstly, the search for the most appropriate organocatalyst and reaction conditions (Table 1) began using the model conjugate addition reaction of acetophenone (**4a**) (2 equiv) to *trans*-β-nitrostyrene (**3a**), organocatalyzed by **1a** (20 mol%) in toluene as a solvent at room temperature. This model reaction results particularly interesting, as the use of aromatic ketones in this reaction leads to important drug precursors (Antecedents, Figure II). Under these conditions, the corresponding adduct (*R*)-**7aa** was obtained in 62% isolated yield and with a 88% *ee* after 5 d reaction time (Table 3, entry 1). The (*R*) absolute configuration of the final adduct was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature (see Experimental). This adduct (*R*)-**7aa** is a precursor of the (*R*)-isomer of the drug Baclofen (Arbaclofen or STX209).

Using **1b** as organocatalysts under these reaction conditions did not change the enantioselectivity of the process, although the isolated yield of the final adduct diminished (Table 3, entry 2). In addition, when **1c** was employed as organocatalyst, the enantioselectivity was lowered down to 68% (Table 3, entry 3). Therefore, **1a** was chosen as organocatalyst for the rest of the study.

The use of others solvents was also explored. Thus, hexane or ether diminished both yield and enantioselectivity for (*R*)-**7aa** (Table 3, entries 4 and 5), whereas when dichloromethane and chloroform were attempted, the last one raised slightly both yield and enantioselectivity (Table 3, entries 6 and 7). In addition, a polar solvent such as DMF afforded only a 50% *ee* of (*R*)-**7aa**, and a protic one such as water proved not beneficial (Table 3, entries 8 and 9). Moreover, the use of a DMF/water mixture (2/1, v/v ratio), gave a poor enantioselection (Table 3, entry 10).

**Table 3**. Screening and optimization of the reaction conditions for the enantioselective Michael addition of acetophenone to *trans*-β-nitrostyrene.




**6a** **3a** **7aa**

| Entry | Catalyst (mol-%) | Additive (mol-%) | Solvent | T (ºC) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** (20) | - | PhMe | 25 | 62 | 88 (*R*) |
| 2 | **1b** (20) | - | PhMe | 25 | 55 | 88 (*R*) |
| 3 | **1c** (20) | - | PhMe | 25 | 60 | 68 (*R*) |
| 4 | **1a** (20) | - | Hexane | 25 | 58 | 86 (*R*) |
| 5 | **1a** (20) | - | $Et_2O$ | 25 | 50 | 82 (*R*) |
| 6 | **1a** (20) | - | $CH_2Cl_2$ | 25 | 63 | 87 (*R*) |
| 7 | **1a** (20) | - | $CHCl_3$ | 25 | 65 | 89 (*R*) |
| 8 | **1a** (20) | - | DMF | 25 | 60 | 50 (*R*) |
| 9 | **1a** (20) | - | $H_2O$ | 25 | 53 | 60 (*R*) |
| 10 | **1a** (20) | - | DMF/$H_2O$[c] | 25 | 60 | 42 (*R*) |
| 11 | **1a** (20) | Imidazole (20) | $CHCl_3$ | 25 | 60 | 80 (*R*) |
| 12 | **1a** (20) | $PhCO_2H$ (20) | $CHCl_3$ | 25 | 65 | 90 (*R*) |
| 13 | **1a** (20) | 4-$ClC_6H_4CO_2H$ (20) | $CHCl_3$ | 25 | 78 | 85 (*R*) |
| 14 | **1a** (20) | 4-$O_2NC_6H_4CO_2H$ (20) | $CHCl_3$ | 25 | 70 | 83 (*R*) |
| 15 | **1a** (20) | 4-$MeC_6H_4CO_2H$ (20) | $CHCl_3$ | 25 | 67 | 87 (*R*) |
| 16 | **1a** (20) | 2,4,6-$(Me)_3C_6H_2CO_2H$ (20) | $CHCl_3$ | 25 | 80 | 82 (*R*) |
| 17 | **1a** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ (20) | $CHCl_3$ | 25 | 73 | 93 (*R*) |
| 18 | **1a** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ (10) | $CHCl_3$ | 25 | 60 | 88 (*R*) |
| 19 | **1a** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ (20) | $CHCl_3$ | 10 | 65 | 90 (*R*) |
| 20 | *ent*-**1a** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ (20) | $CHCl_3$ | 25 | 71 | 93 (*S*) |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] 2/1 (v/v).

Then, the effect of the addition of some additives to the reaction, employing chloroform as the most effective reaction solvent, was explored. Thus, the addition of the basic imidazole (20 mol%), was detrimental for the enantioselectivity compared to when no additive was used (Table 3, entry 11). Therefore, we switched to the use of aromatic carboxylic acids as additives (20 mol%). The addition of benzoic acid (20 mol%) resulted in a slight improvement of yield and enantioselectivity compared to when no additive was used (Table 3, entry 12). This

positive result prompted us to explore if a modulation of the pKa of the additive by changing the substituent on the aromatic ring could be beneficial.

The presence of electron-withdrawing groups on the aromatic ring of the acid additive, such as 4-chloro or 4-nitro, increased the yield of adduct (*R*)-**7aa**, although reduced the enantioselectivity of the process (Table 3, entries 13 and 14). Therefore, the presence of additives bearing electron-releasing groups, such as methyl or methoxy was explored (Table 3, entries 15-17). Among them, the best results were achieved when 3,4-dimethoxybenzoic acid was used as additive, giving rise to γ-nitroketone (*R*)-**7aa** in a 93% *ee* with a 73% isolated yield (Table 3, entry 17).

Keeping the most effective reaction conditions [**1a** (20 mol%), 3,4-dimethoxybenzoic acid (20 mol%), $CHCl_3$, 25 ºC], other parameter changes were explored. The organocatalyst loading was reduced to 10 mol%, but both enantioselectivity and yield diminished (Table 3, entry 18). This also happened when the reaction temperature was lowered down to 10 ºC (Table 3, entry 19).

Expecting to achieve an opposite enantioselection, the reaction using as organocatalyst *ent*-**1** was also performed. Using this primary amine as organocatalyst under the most effective reaction conditions [catalyst (20 mol%), 3,4-dimethoxybenzoic acid (20 mol%), $CHCl_3$, 25 ºC], the expected adduct (*S*)-**7aa** was isolated in 93% *ee* (Table 3, entry 20).

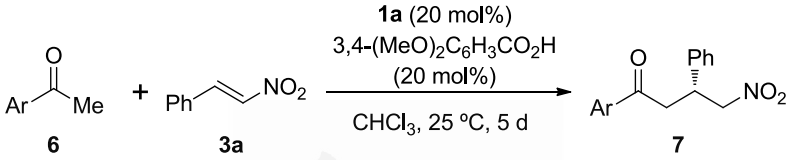


### *3.4.2. Scope of the Reaction*

Once the most effective organocatalyst and reaction conditions [**1a** (20 mol%), 3,4-dimethoxybenzoic acid (20 mol%), $CHCl_3$, 25 ºC] were found, the extension of this methodology to other ketones and nitroolefins was explored (Table 4). As in the case of the model reaction, the absolute configuration of the known resulting γ-nitroaldehydes was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

First, the reaction of arylated ketones **6**, differently substituted on the aromatic ring, to *trans*-β-nitrostyrene (**3a**) was performed (Table 4). Thus, when an electron-releasing group such as a methyl was present at the 3- and 4-position of the aromatic ring (**6b** and **6c**), the resulting adducts (*R*)-**7ba** and (*R*)-**7ca** were obtained in 86 and 91% *ee*, respectively (Table 4, entries 2 and 3), whereas the presence of a 4-methoxy substituent (**6d**) yielded (*R*)-**7da** also in 91% *ee* (Table 4, entry 4).

**Table 4**. Enantioselective Michael addition of aryl ketones to *trans*-β-nitrostyrene organocatalyzed by **1a**.




**6** **3a** **7**

| Entry | Ketone | | γ-Nitroketones | | |
|---|---|---|---|---|---|
| | Ar | No. | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Ph | **6a** | (*R*)-**7aa** | 73 | 93 |
| 2 | 3-$MeC_6H_4$ | **6b** | (*R*)-**7ba** | 70 | 86 |
| 3 | 4-$MeC_6H_4$ | **6c** | (*R*)-**7ca** | 70 | 91 |
| 4 | 4-$MeOC_6H_4$ | **6d** | (*R*)-**7da** | 63 | 91 |
| 5 | 4-$FC_6H_4$ | **6e** | (*R*)-**7ea** | 68 | 88 |
| 6 | 3-$ClC_6H_4$ | **6f** | (*R*)-**7fa** | 68 | 85 |
| 7 | 4-$ClC_6H_4$ | **6g** | (*R*)-**7ga** | 70 | 86 |
| 8 | 4-$BrC_6H_4$ | **6h** | (*R*)-**7ha** | 70 | 88 |
| 9 | 4-$IC_6H_4$ | **6i** | (*R*)-**7ia** | 67 | 88 |
| 10 | 3-$F_3CC_6H_4$ | **6j** | (*R*)-**7ja** | 71 | 82 |
| 11 | 4-$F_3CC_6H_4$ | **6k** | (*R*)-**7ka** | 68 | 83 |
| 12 | 4-$O_2NC_6H_4$ | **6l** | (*R*)-**7la** | 58 | 75 |
| 13 | 2-Naphthyl | **6m** | (*R*)-**7ma** | 71 | 89 |
| 14 | 2-Pyridyl | **6n** | (*R*)-**7na** | 85 | 68 |

[a] Isolated yield after flash chromatography; [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude.

The presence of halogens in the aromatic ring, as in the case of ketones **6e-i**, gave rise to the corresponding adducts (*R*)-**7ea-ia**, their enantioselectivities being in the range 85-88% (Table 4, entries 5-9). In addition, the presence of other electron-withdrawing substituents, such as the trifluoromethyl (**6j**, **6k**) and nitro (**6l**) groups,

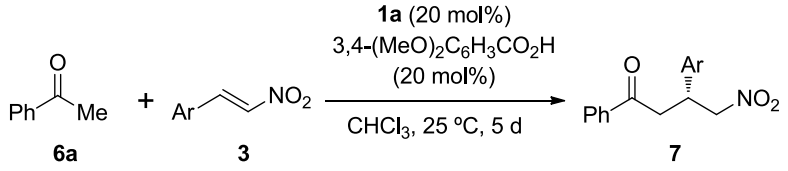
resulted in lower enantioselections for the corresponding adducts (*R*)-**7ja**, (*R*)-**7ka** and (*R*)-**7la** (Table 4, entries 10-12).

Moreover, the use of a polyaromatic ketone such as 1-(naphthalen-2-yl)ethan-1-one (**6m**) afforded the γ-nitroketone (*R*)-**7ma** in 89% *ee* (Table 4, entry 13), whereas the use of a heteroaromatic ketone such as 1-(pyridin-2-yl)ethan-1-one (**6n**) yielded the corresponding adduct (*R*)-**7na** in a much lower 68% *ee* (Table 4, entry 14).

Then, the influence of changing the substituent on the nitroalkene **3**, in the Michael addition reaction with acetophenone (**6a**) was explored (Table 5). Thus, when a 4-methyl was present on the aromatic ring (**3b**), the resulting (*R*)-**7ab** was isolated in 90% *ee*, a similar value to when a 4-methoxy group (**3c**) was present [(*R*)-**7ac**, 89% *ee*] (Table 5, entries 1 and 2). In addition, when other electron-releasing systems were present, as in the case of the dioxolane moiety (**3d**) and 3,4,5-trimethoxy groups (**3e**), the enantioselectivities for the obtained adducts (*R*)-**7ad** and (*R*)-**7ae** were 90 and 89%, respectively (Table 5, entries 3 and 4).

When halogen groups were present on the aromatic ring of **3** (**3f-i**), the corresponding γ-nitroketones (*R*)-**7af-ai** were isolated with enantioselectivities ranging from 86 to 93% (Table 5, entries 5-8). Adduct (*R*)-**7ah** results particularly interesting, as is an intermediate in the preparation of the commercial drug Phenibut (Antecedents, Figure II). In addition, the presence of other electron-withdrawing substituents such as the 4-trifluoromethyl (**3j**) and 4-nitro (**3k**) afforded adducts (*R*)-**7aj** and (*R*)-**7ak** in 87 and 88% *ee*, respectively (Table 5, entries 9 and 10). Moreover, the presence of a system such as the 2-naphthyl (**3l**) allowed to prepare (*R*)-**7al** in 90% *ee* (Table 5, entry 11), and the use of heteroaromatic systems such as a 3-pyridyl (**3m**) and 2-furyl (**3n**) yielded γ-nitroketones (*R*)-**7am** and (*S*)-**7an**, with enantioselections of 86 and 96%, respectively (Table 5, entries 12 and 13).

**Table 5**. Enantioselective Michael addition of acetophenone to nitroalkenes organocatalyzed by **1a**.




**6a** **3** **7**

| Entry | β-Nitroalkene | | γ-Nitroketones | | |
|---|---|---|---|---|---|
| | Ar | No. | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | 4-$MeC_6H_4$ | **3b** | (*R*)-**7ab** | 70 | 90 |
| 2 | 4-$MeOC_6H_4$ | **3c** | (*R*)-**7ac** | 72 | 89 |
| 3 | 3,4-$(OCH_2O)C_6H_3$ | **3d** | (*R*)-**7ad** | 60 | 90 |
| 4 | 3,4,5-$(MeO)_3C_6H_2$ | **3e** | (*R*)-**7ae** | 56 | 89 |
| 5 | 4-$FC_6H_4$ | **3f** | (*R*)-**7af** | 75 | 87 |
| 6 | 2-$ClC_6H_4$ | **3g** | (*R*)-**7ag** | 77 | 93 |
| 7 | 4-$ClC_6H_4$ | **3h** | (*R*)-**7ah** | 73 | 90 |
| 8 | 4-$BrC_6H_4$ | **3i** | (*R*)-**7ai** | 70 | 86 |
| 9 | 4-$F_3CC_6H_4$ | **3j** | (*R*)-**7aj** | 68 | 87 |
| 10 | 4-$O_2NC_6H_4$ | **3k** | (*R*)-**7ak** | 75 | 88 |
| 11 | 2-Naphthyl | **3l** | (*R*)-**7al** | 69 | 90 |
| 12 | 3-Pyridyl | **3m** | (*R*)-**7am** | 70 | 86 |
| 13 | 2-Furyl | **3n** | (*S*)-**7an**[c] | 74 | 96 |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] No change in the enantioselectivity sense, just an effect of the CIP rules.

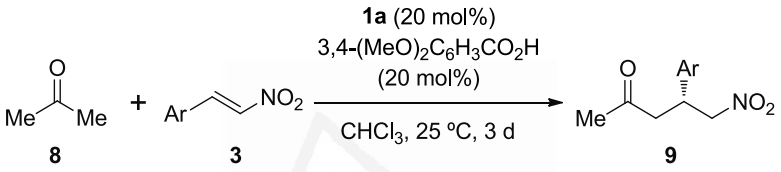


When nitroalkenes bearing alkyl, instead of aromatic, substituents were used as electrophiles in the Michael addition reaction with acetophenone (**6a**), such as (*E*)-(2-nitrovinyl)cyclohexane or (*E*)-(4-nitrobut-3-en-1-yl)benzene, the corresponding adducts were not obtained after 5 days of reaction time.

Simultaneously, the use of organocatalyst **1a**, under the former reaction conditions, in the conjugate addition of the simple acetone (5 equiv), to these nitroalkenes was performed (Table 6). Thus, when acetone (**8**) reacted with *trans*-β-nitrostyrene (**3a**), the corresponding γ-nitroketone (*R*)-**9a** was isolated in a 92% yield and in 70% *ee* (Table 6, entry 1). When a 4-methyl or a 4-methoxy group was present in the nitroalkene, the corresponding adducts (*R*)-**9b** and (*R*)-**9c** were obtained in 67 and 70% *ee*, respectively (Table 6, entries 2 and 3).

The presence of halogen groups such as a 4-fluoro and 4-chloro gave rise to higher enantioselections of the isolated adducts (*R*)-**9f** and (*R*)-**9h**, respectively (Table 6, entries 4 and 5). However, the reaction with a 4-trifluoromethylated nitroalkene (**3j**) produced a lower enantioselectivity for the γ-nitroketone (*R*)-**9j** (Table 6, entry 6), as well as when using the 2-naphthyl-nitroalkene **3j** (Table 6, entry 7). Finally, a higher enantioselection for adduct (*S*)-**9n** (84%) was observed when using a 2-furyl as substituent in the nitroalkene (**3n**) (Table 6, entry 8).

**Table 6**. Enantioselective Michael addition of acetone to nitroalkenes organocatalyzed by **1a**.

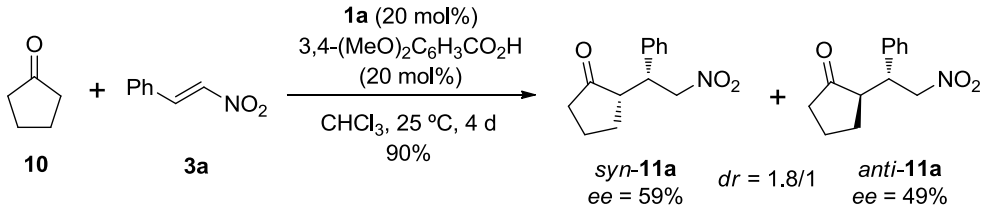



**8** **3** **9**

| Entry | β-Nitroolefin | | γ-Nitroketones | | |
|---|---|---|---|---|---|
| | Ar | No. | No. | Yield (%)[a] | *ee* (%)[b] |
| 1 | Ph | **3a** | (*R*)-**9a** | 92 | 70 |
| 2 | 4-$MeC_6H_4$ | **3b** | (*R*)-**9b** | 85 | 67 |
| 3 | 4-$MeOC_6H_4$ | **3c** | (*R*)-**9c** | 85 | 70 |
| 4 | 4-$FC_6H_4$ | **3f** | (*R*)-**9f** | 79 | 74 |
| 5 | 4-$ClC_6H_4$ | **3h** | (*R*)-**9h** | 87 | 78 |
| 6 | 4-$F_3CC_6H_4$ | **3j** | (*R*)-**9j** | 70 | 69 |
| 7 | 2-Naphthyl | **3l** | (*R*)-**9l** | 71 | 62 |
| 8 | 2-Furyl | **3n** | (*S*)-**9n**[c] | 78 | 84 |

[a] Isolated yield after flash chromatography. [b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. [c] No change in the enantioselectivity sense, just an effect of the CIP rules.

Finally, other cyclic ketones, such as cyclopentanone, cyclohexanone and cycloheptanone, were tested under the optimal conditions [**1a** (20 mol%), 3,4-dimethoxybenzoic acid (20 mol%), $CHCl_3$, 25 ºC]. Interestingly, only the cyclopentanone (**10**) afforded the corresponding γ-nitroketone as a mixture of diastereomers in a 1.8/1 *syn*/*anti*-**11a** ratio and enantioselectivities of 59 and 49% respectively (Scheme 4).




**Scheme 4**. Enantioselective Michael addition of cyclopentanone to *trans*-β-nitrostyrene organocatalyzed by **1a**.

Organocatalyst **1a** was also employed in the Michael addition reaction of acetophenone (**6a**) to *trans*-β-nitrostyrene (**3a**) in Deep Eutectic Solvents as a reaction media. Thus, all the DESs shown in Chapter I (Table 3) were employed in order to perform the Michael addition reaction. However, lower enantioselectivities were obtained compared to when conventional solvents were used. A 60% *ee* for (*R*)-**7aa**, in 53% yield, was achieved when the reaction was performed employing 20 mol% catalyst loading and $PhCO_2H$ (20 mol%) as additive, in the DES formed by choline chloride and glycerol (ChCl/gly, 1/2 molar ratio) at room temperature.

### *3.4.3. Theoretical Calculations*

In order to justify the origin and sense of the observed enantioselectivity, theoretical calculations on the reactions of acetophenone (**6a**) and acetone (**8**) with *trans*-β-nitrostyrene (**3a**), catalyzed by **1a** catalyst, were carried out. Different computational methods (see Experimental), and conditions, like the gas phase system and a water solvent model, as extreme situations of apolar and very polar environments were used. The choice of solvent was seen to have a significant impact on the enantioselectivity (Table 3), and we were intrigued by the high *ee*´s that were obtained in chloroform and other apolar solvents, while the use of water or DMF has been shown to be detrimental for the observed selectivity.

Following the literature evidence, it was assumed that the reaction took place through the Seebach´s synclinal model,[45] where the nitroalkene is approaching the enamine through an *endo*-type transition state (Figure 1, left). In that model, the attack from the lower face of the enamine (from our point of view) stereo-specifically determines the formation of the *R* enantiomer through reaction with the *Re* face of *trans*-β-nitrostyrene. Consequently, the approach from the upper face of the enamine (not shown) would deliver the *S* enantiomer. The *exo* variant of the reaction would lead to opposite results, but according to Seebach´s model and initial calculations, this alternative is not operative and can be safely discarded.

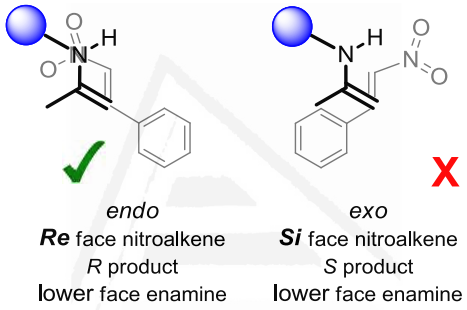



**Figure 1**. Seebach´s synclinal model (left) for the reaction of the enamine model and nitrostyrene.

As shown in Chapter I, in the related reaction [enamine + maleimide], also catalyzed by **1a**, it was found that the polarity of the solvent had an effect on the conformation of the catalyst, and more significantly, on the differential stabilization of the diastereomeric transition states. Thus, in the simplest alternative, the electrophile can be activated by an intramolecular hydrogen bond with the NHBoc hydrogen of the catalyst (**TSA$_{Me}$-R** and **TSA$_{Ph}$-R**, Figure 2). Due to the relative disposition of the NH groups of the enamine and the NHBoc moieties, the electrophile shows a clear preference for the approach through the lower face of the enamine, leading to the formation of the *R* enantiomer. This effect is independent of the source of the enamine, either coming from acetone or acetophenone.

[45] (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413-1423; (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162-172.

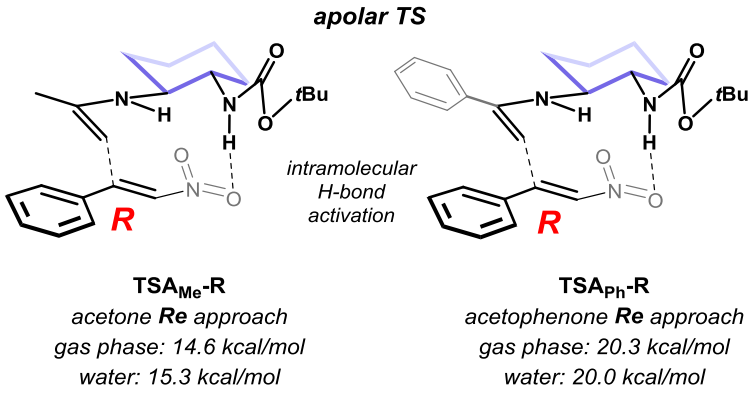



**Figure 2**. Calculated Gibbs Free activation energies for the **TSA-**type transition states in the gas phase and water models.

The presence of the internal hydrogen bond makes this transition state very apolar, and thus, quite insensitive to the polarity of the solvent. When calculated in the gas phase (as the extreme case for an apolar environment), the Gibbs Free activation energy was as low as 14.6 kcal/mol for acetone derived enamine (**TSA$_{Me}$-R**), and 20.3 kcal/mol for the acetophenone (**TSA$_{Ph}$-R**). As expected, the energies in water are similar to the gas phase, increasing slightly to 15.3 kcal/mol for acetone, and staying ca. 20.0 kcal/mol for acetophenone.

A second main approach was found, wherein the nucleophile attacks from the upper face of the enamine (Figure 3), in the distal position from the NHBoc group, and thus, without the possibility of forming any intramolecular hydrogen bond. In **TSB$_{Me}$-S** and **TSB$_{Ph}$-S**, the attack takes place from the left side (from our point of view in Figure 3) of the enamine, thorough the *Si* face of the nitroalkene (*S* enantiomer), whereas the approach of the nitroalkene from the right side of the enamine (hypothetical TSC) is strongly disfavoured due to steric repulsion with the large Boc group, which is blocking that face. It was no possible actually to find any transition state for that approach without severely distorting the structure. The transition structures in Figure 3 are very polar, showing a clear separation of the developing positive and negative charges on the enamine and the nitroalkene, respectively. This type of situations are very sensitive to the environment; highly

favoured in polar solvents, and specially in protic solvents (water) which are able to solvate and activate the electrophile by the formation of intermolecular hydrogen bonds. Consequently, the calculated energies in water (16.9 and 19.3 kcal/mol) are lower than in the gas phase (17.8 and 21.7 kcal/mol).

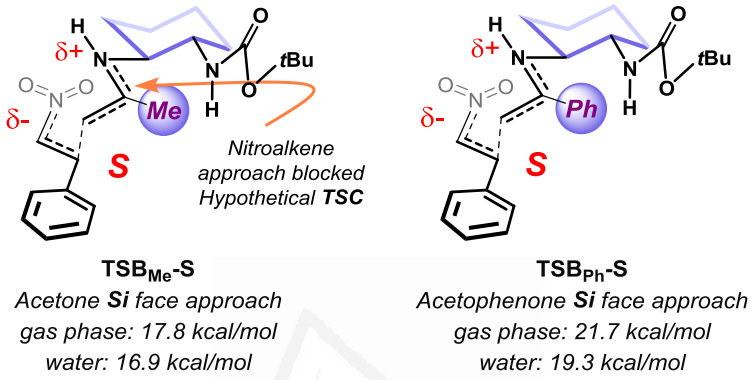



**Figure 3**. Calculated Gibbs Free activation energies for the **TSB**-type transition states in the gas phase and water models.

These computational data are able to explain the experimental findings. If the reaction is performed in an apolar system, the lowest-in-energy transition states are **TSA$_{Me}$-R** and **TSA$_{Ph}$-R**, bearing the internal hydrogen bond activation, which explains the highly enantioselective formation of the *R* enantiomer. As the polarity of the solvent increases, the polar transition states (TSB-type, Figure 3) gain relative significance, inducing a deleterious effect on the enantioselectivity (Table 3, entries 8, 9 and 10). Furthermore, these results also agree with the common chemical sense, by which intramolecular hydrogen bonds are stronger in apolar solvents, while intermolecular hydrogen bonds with surrounding water molecules are present in aqueous systems. Finally, 3D representations of the operative transition states for acetophenone in the gas phase and in the water model are shown in Figure 4.

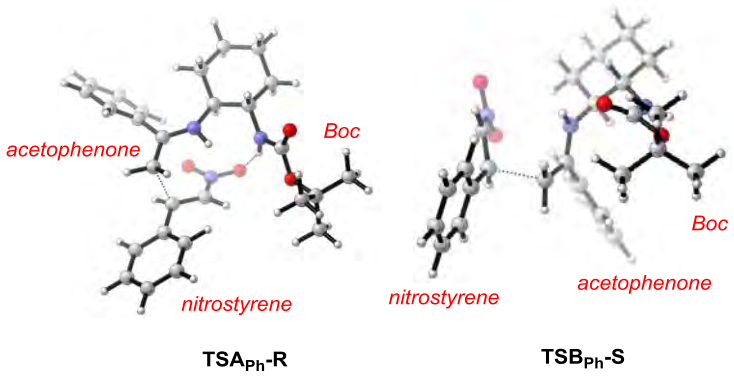



**Figure 4.** 3-D representation of the transition states for the reaction of acetophenone and nitrostyrene

# 4. EXPERIMENTAL PART

## 4.1. General

### *4.1.1. Solvents and Reagents*

All solvents and reagents listed in this research were purchased with the best commercial grade and were used without purification. Aldehydes **4** were distilled before use.

### *4.1.2. Instrumentation*

Melting points were obtained with a *Reichert Thermovar* apparatus and are uncorrected. IR spectra ($cm^{-1}$) were obtained with a *Nicolet Impact 400 D-FT* spectrophotometer.

Proton ($^{1}H$ NMR) and carbon ($^{13}C$ NMR) nuclear magnetic resonance spectra were performed at the Research Technical Services of the University of Alicante, with a *Bruker AC-300* or *Bruker Avance-400*, using deuterated chloroform as solvent and tetramethylsilane (TMS) as an internal standard. The spectra of $^{1}H$ NMR were performed at 300 or 400 MHz, while the $^{13}C$ NMR became 75 or 100 MHz. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hz.



The mass spectrometric analysis was carried out using an *Agilent GC/MS-5973N* spectrometer, performing studies in the form of electron impact (EI) at 70 eV ionization source and helium as the mobile phase (2 mL/min). Samples were introduced by injection through a gas chromatograph *Hewlett-Packard HP-6890*, equipped with a HP-5MS column 30 m length, 0.25 mm internal diameter and 0.25 μm film thickness (crosslinking 5% PHME siloxane). Ions derived from the breaks are given as *m*/*z* with relative percent intensities in brackets.

The high resolution mass spectrometry analyses (HRMS) were performed at the Research Technical Services of the University of Alicante, with an *Agilent Technologies 7200 Accurate-Mass Q-TOF GC/MS* mass spectrometer coupled to an

*Agilent Technologies 7890B* gas chromatograph. The γ-nitroaldehyde samples were introduced by split-mode injection (1:100) through the gas chromatograph, equipped with *Agilent Technologies HP-5MS UI* column, and the electronic impact (EI) at 70 eV and helium (1 mL / min) as the carrier gas in the mobile phase was used as the ionization technique. The γ-nitroketone samples were introduced using the DIP probe, chemical ionization (CI) employing methane being used as the ionization technique.

Cooling of the reaction media was achieved using a digital *Julabo FT901* cryostat, accompanied by its temperature probe and the use of a digital thermometer *Heidolph EKT 3001*.

Thin layer chromatography (TLC) was carried out on *Schleider & Schuell* F1400/LS 254 plates coated with a 0.2 mm layer of silica gel. For detection, UV lamp of aluminum of wavelength λ = 254 nm was used.

Column chromatography was performed on glass columns, using as stationary phase silica gel Merck 60, with a particle size of 0.040 to 0.063 mm. Elutions were carried on with mixtures of *n*-hexane and ethyl acetate (EtOAc) of increasing polarity.

For the determination of the enantiomeric excesses in HPLC, *Agilent-Hewlett Packard* systems consisting of a *G1311A* pump, a *G1313A* injector and a *G1316A* detector were used. The conditions (column, eluent and flow) and retention times are indicated in each case.

## 4.2. Experimental Procedures

### *4.2.1. Synthesis of β-Nitroalkenes 3d,e,f,i,j,k,l,n*[43]

The aldehyde (1 mmol) was added to a microwave reaction tube, along with $NH_4OAc$ (23.1 mg, 0.3 mmol). Nitromethane was added (2 ml) and the tube was placed in the microwave reactor. The microwave apparatus was set to a power of 250 W and a temperature of 90 ºC, and the reaction left to run for 1.5 h. Upon completion, the solvent was removed under reduced pressure (15 Torr). The solid product was then washed with a MeOH/$H_2O$ (1:1) mix (2 mL), before being dried. The crude products were purified by column chromatography (*n*-hexane/EtOAc), affording the corresponding β-nitroalkenes: **3d** (164 mg, 85%), **3e** (169 mg, 78%), **3f** (139 mg, 83%), **3i** (182 mg, 80%), **3j** (195 mg, 89%), **3k** (153 mg, 80%), **3l** (179 mg, 89%) y **3n** (106 mg, 76%).

### *4.2.2. Synthesis of β-Nitroalkene 3m*[44]

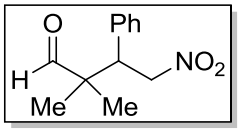
A mixture of nicotinaldehyde (1.00 g, 0.01 mol), $CH_3NO_2$ (0.9 mL, 0.016 mol), *t*-BuOH (10 mL), and THF (10 mL) was stirred at 0 ºC and *t*-BuOK (62 mg, 0.06 eq) was added. After 2 h the conversion of the aldehyde was complete (monitored by TLC with EtOAc as eluent) and the mixture was diluted with $H_2O$ (5 mL) and extracted with $Et_2O$ (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine. The aqueous layer was back extracted with $Et_2O$ (10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure (15 Torr), to afford the β-nitro alcohol. The β-nitro alcohol (1.00 g, 6 mmol), DMAP (36 mg, 0.4 mmol) and $Ac_2O$ (0.668 g, 6 mmol) were then dissolved in $CH_2Cl_2$ (30 mL) and stirred for 2 h, after which time the solution was neutralized with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with brine and the aqueous layer was back extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and

concentrated under reduced pressure (15 Torr), to afford β-nitroalkene **3m** (586 mg, 65%).

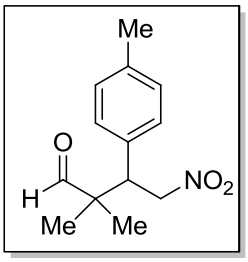
### *4.2.3. General Procedure for the Enantioselective Michael Addition Reaction of Isobutyraldehyde to Nitroalkenes*

To a solution of **1a** (8.6 mg, 0.04 mmol), the nitroalkene **3** (0.2 mmol) and DABCO (6.7 mg, 0.06 mmol) in $CHCl_3$ (0.5 mL) was added isobutyraldehyde (36.5 μL, 0.4 mmol) and the mixture was stirred at 25 ºC for the time shown in Table 2 (monitored by TLC with *n*-hexane/EtOAc mixture, 8/2 v/v ratio, as eluent). The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give a crude product, which was purified by flash chromatography (*n*-hexane/AcOEt gradients).

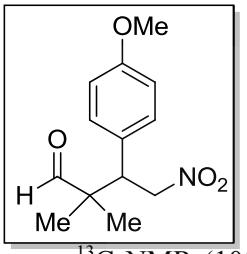
Adducts **5** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC on the reaction crude. Absolute configuration for adducts **5** was determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds it was assigned by analogy. Reference racemic samples of adducts **5** were obtained by performing the reaction using 4-methylbenzylamine (20 mol%) as organocatalyst in toluene as solvent at 25 ºC. Physical, spectroscopical and chiral HPLC data for adducts **5** are shown below:



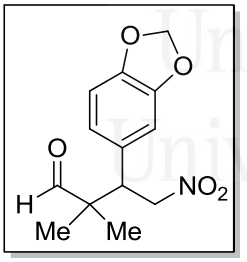

**2,2-Dimethyl-4-nitro-3-phenylbutanal (5a):**[42] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.52 (s, 1H), 7.35-7.28 (m, 3H), 7.22-7.17 (m, 2H), 4.85 (dd, *J* = 13.1, 11.3 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.79 (dd, *J* = 11.3, 4.2 Hz, 1H), 1.12 (s, 3H), 0.99 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.2, 135.3, 129.0, 128.6, 128.0, 76.2, 48.3, 48.1, 21.5, 18.7 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 13.4 min, $t_r$ (*S*) = 19.1 min.



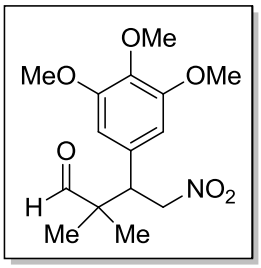

**2,2-Dimethyl-4-nitro-3-(*p*-tolyl)butanal (5b):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.52 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.83 (dd, *J* = 12.9, 11.4 Hz, 1H), 4.67 (dd, *J* = 12.9, 4.2 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.32 (s, 3H), 1.12 (s, 3H), 1.00 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.4, 137.8, 132.1, 129.3, 128.9, 76.3, 48.2, 48.1, 21.5, 21.0, 18.8 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 10.7 min, $t_r$ (*S*) = 15.1 min.



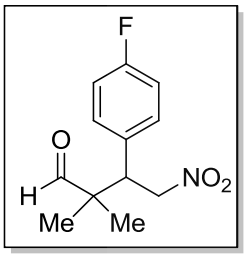

**3-(4-Methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (5c):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.51 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.81 (dd, *J* = 12.8, 11.4 Hz, 1H), 4.66 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.78 (s, 3H), 3.73 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.11 (s, 3H), 0.99 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.4, 159.2, 130.0, 127.0, 114.0, 76.4, 55.1, 48.3, 47.7, 21.4, 18.7 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 14.6 min, $t_r$ (*S*) = 20.6 min.



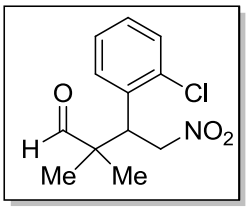

**3-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-4-nitrobutanal (5d):** Colorless oil; IR (ATR): ν = 2972, 2904, 2817, 1722, 1552, 1491, 1444, 1376, 1241, 1038, 931, 816 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.51 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.96 (s, 2H), 4.78 (dd, *J* = 13.0, 11.4 Hz, 1H), 4.65 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.70 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.13 (s, 3H), 1.02 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.2, 147.9, 147.4, 128.8, 122.6, 109.1, 108.3, 101.2, 76.5, 48.3, 21.6, 19.0 ppm; MS (EI, 70 eV): *m/z* (%) = 265 ($M^+$, 10), 148 (100); HRMS (EI): *m/z* calcd. for $C_{13}H_{15}NO_5$ $[M]^+$: 265.0952, found: 265.0947; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 19.9 min, $t_r$ (*S*) = 27.0 min.



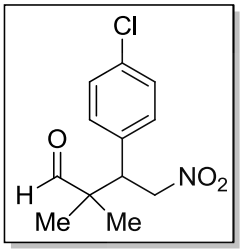

**2,2-Dimethyl-4-nitro-3-(3,4,5-trimethoxyphenyl)butanal (5e):** Colorless oil; IR (ATR): ν = 2972, 2939, 2835, 1722, 1589, 1552, 1460, 1242, 1124, 1005, 729 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.52 (s, 1H), 6.38 (s, 2H), 4.85 (dd, *J* = 13.1, 11.3 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.70 (dd, *J* = 11.3, 4.2 Hz, 1H), 1.16 (s, 3H), 1.06 (s, 3H) ppm; $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.3, 153.1, 137.7, 131.0, 106.2, 76.3, 60.7, 56.1, 48.9, 48.2, 21.7, 19.3 ppm; MS (EI, 70 eV): *m/z* (%) = 311 ($M^+$, 16), 194 (100), 179 (35); HRMS (EI): *m/z* calcd. for $C_{15}H_{21}NO_6$ $[M]^+$: 311.1369, found: 311.1367; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 20.2 min, $t_r$ (*S*) = 23.4 min.



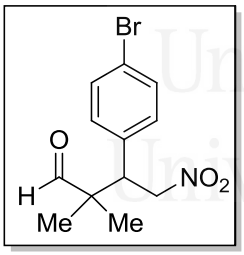

**3-(4-Fluorophenyl)-2,2-dimethyl-4-nitrobutanal (5f):**[42] Colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.51 (s, 1H), 7.21-7.17 (m, 2H), 7.05-7.01 (m, 2H), 4.82 (dd, *J* = 13.1, 11.4 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.78 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H) ppm; $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.0, 162.4 (d, *J* = 247.4 Hz), 131.2 (d, *J* = 3.1 Hz), 130.6 (d, *J* = 8.2 Hz), 115.7 (d, *J* = 21.5 Hz), 76.3, 48.2, 47.7, 21.6, 18.8 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 11.8 min, $t_r$ (*S*) = 19.7 min.




**3-(2-Chlorophenyl)-2,2-dimethyl-4-nitrobutanal (5g):**[46] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.55 (s, 1H), 7.44-7.40 (m, 1H), 7.31-7.21 (m, 3H), 4.89-4.80 (m, 1H), 4.73 (dd, *J* = 13.3, 4.1 Hz, 1H), 4.63 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.17 (s, 3H), 1.08 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.8, 135.8, 133.7, 130.4, 129.1, 128.2, 127.1, 76.2, 49.0, 42.4, 20.9, 18.6 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 11.1 min, $t_r$ (*R*) = 27.9 min.

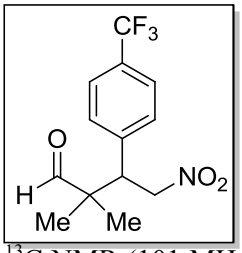



**3-(4-Chlorophenyl)-2,2-dimethyl-4-nitrobutanal (5h):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.50 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 4.83 (dd, *J* = 13.1, 11.4 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.77 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.8, 134.1, 133.9, 130.4, 128.9, 76.1, 48.1, 47.8, 21.7, 18.8 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 13.6 min, $t_r$ (*S*) = 21.3 min.

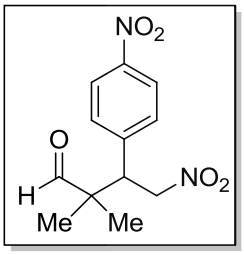



**3-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal (5i):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.50 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 4.82 (dd, *J* = 13.2, 11.4 Hz, 1H), 4.69 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.76 (dd, *J* = 11.4, 4.1 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.8, 134.5, 131.9, 130.7, 122.2, 76.0, 48.1, 47.9, 21.7, 18.9 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 15.2 min, $t_r$ (*S*) = 21.9 min.

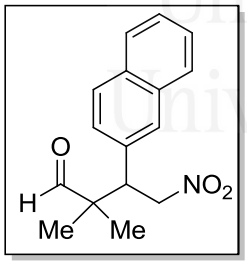
[46] Bai, J.-F.; Xu, X.-Y.; Huang, Q.-C.; Peng, L.; Wanga, L.-W. *Tetrahedron Lett.* **2010**, *51*, 2803-2805.




**2,2-Dimethyl-4-nitro-3-(4-(trifluoromethyl)phenyl)butanal (5j):**[47] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.50 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 3H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.89 (dd, *J* = 13.3, 11.4 Hz, 1H), 4.74 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.88 (dd, *J* = 11.4, 4.1 Hz, 1H), 1.14 (s, 3H), 1.02 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.5, 139.8, 130.4 (q, *J* = 32.7 Hz), 125.7 (q, *J* = 3.6 Hz), 123.8 (q, *J* = 272.2 Hz), 75.9, 48.1, 21.8, 18.9 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 12.4 min, $t_r$ (*S*) = 20.7 min.



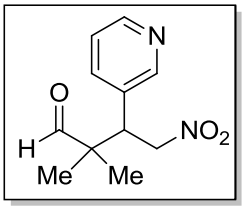

**2,2-Dimethyl-4-nitro-3-(4-nitrophenyl)butanal (5k):**[42] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.49 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 4.93 (dd, *J* = 13.5, 11.5 Hz, 1H), 4.78 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.94 (dd, *J* = 11.5, 4.0 Hz, 1H), 1.17 (s, 3H), 1.05 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.1, 147.6, 143.3, 130.1, 123.8, 75.7, 48.2, 48.1, 21.8, 19.0 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*R*) = 18.3 min, $t_r$ (*S*) = 27.7 min.



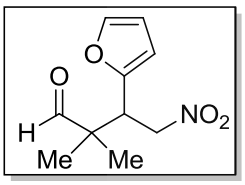

**2,2-Dimethyl-3-(naphthalen-2-yl)-4-nitrobutanal (5l):**[42] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.57 (s, 1H), 7.84-7.82 (m, 3H), 7.68 (d, *J* = 1.3 Hz, 1H), 7.54-7.46 (m, 2H), 7.34 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.00 (dd, *J* = 13.1, 11.3 Hz, 1H), 4.79 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.97 (dd, *J* = 11.3, 4.1 Hz, 1H), 1.19 (s, 3H), 1.05 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.2, 133.0, 132.9, 132.8, 128.4, 128.3, 127.8, 127.6, 126.5, 126.5, 126.3, 76.3, 48.6, 48.4, 21.7, 19.0 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*R*) = 19.0 min, $t_r$ (*S*) = 35.6 min.



[47] Porta, R.; Coccia, F.; Annunziata, R.; Puglisi, A. *ChemCatChem* **2015**, *7*, 1490-1499.




**2,2-Dimethyl-4-nitro-3-(pyridin-3-yl)butanal (5m):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.50 (s, 1H), 8.56 (d, *J* = 3.9 Hz, 1H), 8.51 (s, 1H), 7.63-7.57 (m, 1H), 7.30 (dd, *J* = 8.3, 5.2 Hz, 1H), 4.89 (dd, *J* = 13.3, 11.4 Hz, 1H), 4.75 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.83 (dd, *J* = 11.4, 4.1 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.3, 150.4, 149.4, 136.2, 131.5, 123.5, 75.7, 48.2, 46.0, 21.8, 18.8 ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 13.1 min, $t_r$ (*R*) = 15.0 min.



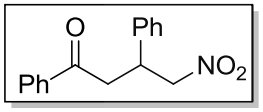

**3-(Furan-2-yl)-2,2-dimethyl-4-nitrobutanal (5n):**[42] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 9.52 (s, 1H), 7.37 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (dd, *J* = 3.3, 0.6 Hz, 1H), 4.76 (dd, *J* = 12.9, 11.1 Hz, 1H), 4.59 (dd, *J* = 12.9, 3.9 Hz, 1H), 3.93 (dd, *J* = 11.1, 3.9 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 203.4, 149.7, 142.7, 110.4, 109.6, 74.8, 48.1, 42.2, 21.1, 19.0 ppm; HPLC: Chiralpak OD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*R*) = 9.6 min, $t_r$ (*S*) = 14.7 min.

### *4.2.4. General Procedure for the Enantioselective Michael Addition Reaction of Ketones to Nitroalkenes*

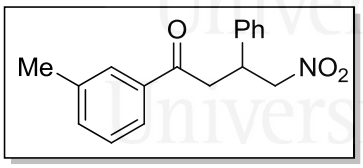


To a solution of **1a** (8.6 mg, 0.04 mmol), the nitroalkene (0.2 mmol) and 3,4-dimethoxybenzoic acid (7.3 mg, 0.04 mmol) in $CHCl_3$ (0.5 mL) was added the ketone (0.4 mmol for **6a-n**; 74 μL, 1 mmol for **8**; 36.5 μL, 0.4 mmol for **10**) and the mixture was stirred at 25 ºC for the time shown in Tables 4-6 (monitored by TLC with *n*-hexane/EtOAc mixture, 7/3 v/v ratio, as eluent). The reaction was quenched with HCl 2M (10 mL) and the mixture was extracted with AcOEt (3 x 10 mL). The combined organic extracts were washed with aq $NaHCO_3$ (10 mL), dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to get the crude product, which was purified by silica gel chromatography (*n*-hexane/AcOEt gradients).

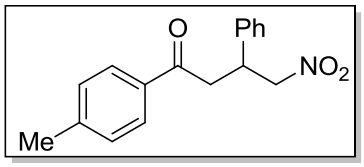
Adducts **7**, **9** and **11** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC on the reaction crude. Absolute configuration for adducts **7**, **9** and **11** was determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds it was assigned by analogy. Reference racemic samples of adducts **7**, **9** and **11** were obtained by performing the reaction using an equimolecular mixture of **1** and *ent*-**1** (20 mol%) as organocatalyst in toluene as solvent at 25 ºC. Physical, spectroscopical and chiral HPLC data for adducts **7** are shown below:



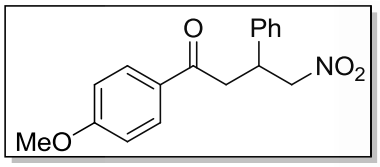

**4-Nitro-1,3-diphenylbutan-2-one (7aa):**[36] White solid, mp 88-89 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.92 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 8.2, 6.9 Hz, 2H), 4.84 (dd, *J* = 12.5, 6.7 Hz, 1H), 4.70 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.29-4.17 (m, 1H), 3.50 (dd, *J* = 16.3, 5.0 Hz, 1H), 3.42 (dd, *J* = 16.3, 6.0 Hz, 1H) ppm; 13C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.8, 139.1, 136.4, 133.6, 129.1, 128.7, 128.0, 127.9, 127.4, 79.6, 41.5, 39.3 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 8.7 min, $t_r$ (*R*) = 10.3 min.



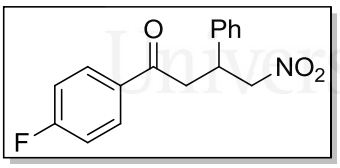

**4-Nitro-3-phenyl-1-(*m*-tolyl)butan-1-one (7ba):**[36] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.72-7.70 (m, 2H), 7.40-7.25(m, 7 H), 4.81-4.86(dd, *J* = 6.8 Hz, 12.8 Hz, 1H), 4.83 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.68 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.27-4.17 (m, 1H), 3.47 (dd, *J* = 17.9, 6.5 Hz, 1H), 3.40 (dd, *J* = 17.9, 7.7 Hz, 1H), 2.39 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 197.0, 139.1, 138.5, 136.3, 134.3, 129.0, 128.5, 128.5, 127.8, 127.4, 125.2, 79.5, 41.5, 39.2, 21.3 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 7.2 min, $t_r$ (*R*) = 8.9 min.




**4-Nitro-3-phenyl-1-(*p*-tolyl)butan-1-one (7ca):**[48] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.86-7.78 (m, 2H), 7.35-7.23 (m, 7H), 4.83 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.67 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.26-4.15 (m, 1H), 3.45 (dd, *J* = 17.6, 6.4 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.40 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.4, 144.4, 139.2, 133.8, 129.3, 129.0, 128.1, 127.8, 127.4, 79.5, 41.3, 39.3, 21.6 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 8.9 min, $t_r$ (*R*) = 10.5 min.



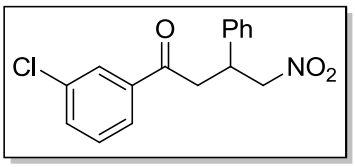

**1-(4-Methoxyphenyl)-4-nitro-3-phenylbutan-1-one (7da):**[36] White solid, mp 90-91 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.94 (d, *J* = 9.0 Hz, 4H), 7.38-7.23 (m, 5H), 6.93 (d, *J* = 8.9 Hz, 4H), 4.84 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.68 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.27-4.15 (m, 1H), 3.87 (s, 3H), 3.43 (dd, *J* = 17.5, 6.4 Hz, 1H), 3.35 (dd, *J* = 17.5, 7.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.3, 163.8, 139.3, 130.3, 129.4, 129.00, 127.8, 127.4, 113.8, 79.6, 55.5, 41.1, 39.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 18.9 min, $t_r$ (*R*) = 23.1 min.



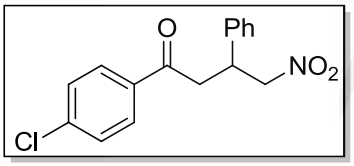

**1-(4-Fluorophenyl)-4-nitro-3-phenylbutan-1-one (7ea):**[49] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.98-7.93 (m, 2H), 7.37-3.32 (m, 2H), 7.31-7.24 (m, 3H), 7.16-7.10 (m, 2H), 4.83 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.69 (dd, *J* = 12.4, 7.7 Hz, 1H), 4.27-4.17 (m, 1H), 3.47 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.40 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.2, 165.6 (d, *J* = 254.6 Hz), 138.9, 132.7 (d, *J* = 2.8 Hz), 130.8 (d, *J* = 9.3 Hz), 129.0, 127.8, 127.3, 115.5 (d, *J* = 21.8 Hz), 79.4, 41.3, 39.2 ppm; HPLC: Chiralpak AS-H,

[48] 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.
[49] Evans, D.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583-11592.

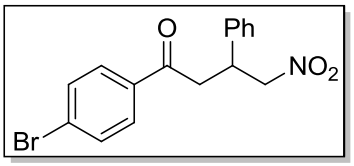
λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 9.4 min, $t_r$ (*R*) = 11.3 min.



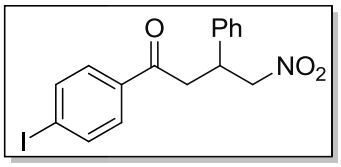

**1-(3-Chlorophenyl)-4-nitro-3-phenylbutan-1-one (7fa):**[48] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.87 (t, *J* = 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.9, 2.1, 1.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.35-7.31 (m, 2H), 7.30-7.25 (m, 3H), 4.80 (dd, J = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.25-4.17 (m, 1H), 3.46 (dd, *J* = 17.8, 6.6 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.5, 138.8, 137.8, 135.0, 133.4, 130.0, 129.1, 128.1, 127.9, 127.4, 126.0, 79.4, 41.6, 39.1 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 8.5 min, $t_r$ (*R*) = 10.6 min.



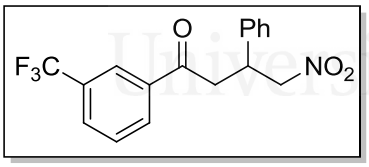

**1-(4-Chlorophenyl)-4-nitro-3-phenylbutan-1-one (7ga):**[36] White solid, mp 67-68 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.84 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.35-7.31 (m, 2H), 7.30-7.24 (m, 3H), 4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.24-4.17 (m, 1H), 3.44 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.39 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.6, 140.00, 138.9, 134.6, 129.4, 129.1, 129.0, 127.9, 127.4, 79.4, 41.4, 39.2 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 10.5 min, $t_r$ (*R*) = 12.6 min.




**1-(4-Bromophenyl)-4-nitro-3-phenylbutan-1-one (7ha):**[48] White solid, mp 86-87 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.76 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.36-7.29 (m, 2H), 7.28-7.24 (m, 3H), 4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.24-4.17 (m, 1H), 3.44 (dd, *J* = 17.7, 6.5 Hz, 1H), 3.38 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.8, 138.8, 135.0, 132.0, 129.5, 129.1, 128.8, 127.9, 127.4, 79.4, 41.4, 39.2 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 11.8 min, $t_r$ (*R*) = 14.5 min.

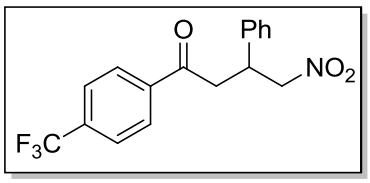



**1-(4-Iodophenyl)-4-nitro-3-phenylbutan-1-one (7ia):**[41] White solid, mp 98-99 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.81 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.40-7.17 (m, 5H), 4.80 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.67 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.25-4.15 (m, 1H), 3.45 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.38 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.1, 138.8, 138.0, 135.5, 129.3, 129.1, 127.9, 127.4, 101.6, 79.4, 41.3, 39.2 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 14.4 min, $t_r$ (*R*) = 17.9 min.

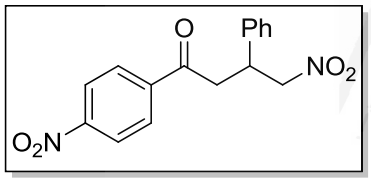



**4-Nitro-3-phenyl-1-(3-(trifluoromethyl) phenyl) butan-1-one (7ja):** Colorless oil; IR (ATR): ν = 3066, 2922, 1690, 1550, 1409, 1321, 1167, 1126, 1065 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.10 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.39-7.21 (m, 5H), 4.83 (dd, *J* = 12.5, 7.0 Hz, 1H), 4.71 (dd, *J* = 12.5, 7.6 Hz, 1H), 4.28-4.21 (m, 1H), 3.52 (dd, *J* = 17.8, 6.6 Hz, 1H), 3.46 (dd, *J* = 17.8, 7.1 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.5, 138.7, 136.8, 131.4 (q, *J* = 33.3 Hz), 131.12, 129.9 (q, *J* = 3.4 Hz), 129.5, 129.2, 128.0, 127.4, 124.8 (q, *J* = 3.9Hz), 123.5 (q, *J* = 273.7Hz), 79.4, 41.6, 39.2 ppm; MS (EI, 70 eV): *m/z* (%) = 287 (100), 275 (46), 185 (54), 173 (28), 145 (41), 130 (17), 103 (21), 77 (15); HRMS (CI-$CH_4$): *m/z* calcd. for

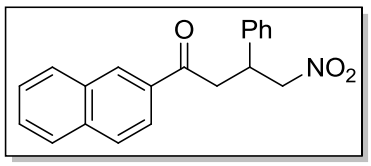
$C_{17}H_{15}F_3NO_3$ $[M+H]^+$: 338,0999, found: 338.1005; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 7.8 min, $t_r$ (*R*) = 9.7 min.




**4-Nitro-3-phenyl-1-(4-(trifluoromethyl) phenyl)-butan-1-one (7ka):**[34] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.00 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.37-7.17 (m, 5H), 4.81 (dd, *J* = 12.5, 7.0 Hz, 1H), 4.69 (dd, *J* = 12.5, 7.6 Hz, 1H), 4.27-4.18 (m, 1H), 3.51 (dd, *J* = 17.9, 6.7 Hz, 1H), 3.45 (dd, *J* = 17.9, 7.1 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.9, 139.0, 138.7, 134.7 (q, *J* = 32.7 Hz), 129.1, 128.3, 128.0, 127.4, 125.7 (q, *J* = 3.6 Hz), 123.4 (q, *J* = 272.9 Hz), 79.4, 41.8, 39.2 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 7.1 min, $t_r$ (*R*) = 8.4 min.

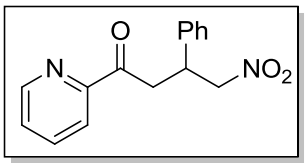



**4-Nitro-1-(4-nitrophenyl)-3-phenylbutan-1-one (7la):**[34] Pale yellow solid, mp 91-92 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.28 (d, *J* = 8.9 Hz, 1H), 8.05 (d, *J* = 8.9 Hz, 1H), 7.37-7.31 (m, 2H), 7.31-7.24 (m, 3H), 4.81 (dd, *J* = 12.5, 7.1 Hz, 1H), 4.71 (dd, *J* = 12.5, 7.5 Hz, 1H), 4.26-4.19 (m, 1H), 3.55 (dd, *J* = 17.8, 6.7 Hz, 1H), 3.50 (dd, *J* = 17.8, 7.0 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.4, 140.6, 138.5, 129.1, 129.0, 128.0, 127.3, 123.9, 79.3, 42.0, 39.1 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 32.8 min, $t_r$ (*R*) = 36.7 min.

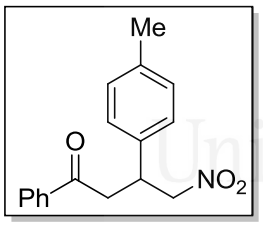



**1-(Naphthalen-2-yl)-4-nitro-3-phenylbutan-1-one (7ma):**[41] White solid, mp 78-79 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.41 (s, 1H), 7.96 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 8.1, 4.1 Hz, 2H), 7.62-7.52 (m, 2H), 7.38- 7.29 (m, 4H), 7.28-7.25 (m, 1H), 4.87 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.72 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.32-4.24 (m, 1H), 3.60 (dd, *J* = 18.3, 7.1 Hz, 1H), 3.54 (dd, *J* = 18.3, 8.2 Hz, 1H) ppm; $^{13}$C NMR (101

MHz, $CDCl_3$): $\delta_C$ = 196.7, 139.1, 135.7, 133.6, 132.4, 129.8, 129.5, 129.0, 128.7, 128.6, 127.8, 127.6, 127.4, 126.9, 123.5, 79.6, 41.5, 39.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 10.6 min, $t_r$ (*R*) = 11.9 min.



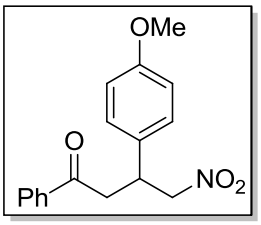

**4-Nitro-3-phenyl-1-(pyridin-2-yl)butan-1-one (7na):**[50] White solid, mp 59-61 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.65 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.98 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.7, 4.8, 0.9 Hz, 1H), 7.34-7.28 (m, 4H), 7.27-7.19 (m, 1H), 4.79 (dd, *J* = 12.4, 6.7 Hz, 1H), 4.68 (dd, *J* = 12.4, 8.3 Hz, 1H), 4.28-4.21 (m, 1H), 3.83 (dd, *J* = 18.2, 7.0 Hz, 1H), 3.62 (dd, *J* = 18.2, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 198.5, 152.6, 148.9, 139.2, 136.9, 128.9, 127.6, 127.5, 121.8, 79.8, 40.7, 39.2 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 8.5 min, $t_r$ (*R*) = 9.4 min.



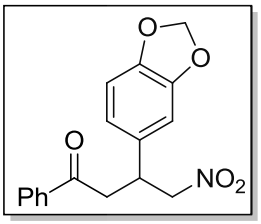

**4-Nitro-1-phenyl-3-(p-tolyl)butan-1-one (7ab):**[36] White solid, mp 72-73 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94-7.88 (m, 2H), 7.60-7.52 (m, 1H), 7.48-7.41 (m, 2H), 7.19-7.09 (m, 4H), 4.80 (dd, *J* = 12.4, 6.6 Hz, 1H), 4.65 (dd, *J* = 12.4, 8.0 Hz, 1H), 4.22-4.14 (m, 1H), 3.45 (dd, *J* = 17.6, 6.4 Hz, 1H), 3.39 (dd, *J* = 17.6, 7.4 Hz, 1H), 2.30 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.9, 137.5, 136.3, 136.0, 133.5, 129.7, 128.7, 128.0, 127.2, 79.7, 41.5, 38.9, 21.0 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 7.9 min, $t_r$ (*R*) = 10.1 min.



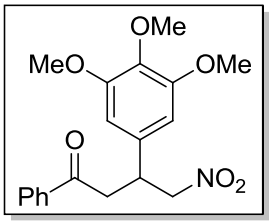
[50] Blay, G.; Incerti, C.; Muñoz, M.C.; Pedro, J.R. *Eur. J. Org. Chem.* **2013**, 1696-1705.




**3-(4-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one (7ac):** [36] White solid, mp 69-70 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.96-7.85 (m, 2H), 7.63-7.52 (m, 1H), 7.47-7.41 (m, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.79 (dd, *J* = 12.3, 6.6 Hz, 1H), 4.64 (dd, *J* = 12.3, 8.0 Hz, 1H), 4.21-4.14 (m, 1H), 3.77 (s, 1H), 3.45 (dd, *J* = 17.6, 6.5 Hz, 1H), 3.39 (dd, *J* = 17.6, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.9, 159.0, 136.4, 133.5, 130.9, 128.7, 128.5, 128.0, 114.4, 79.8, 55.2, 41.6, 38.6 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 14.6 min, $t_r$ (*R*) = 17.6 min.



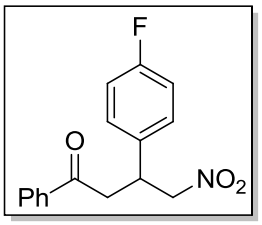

**3-(Benzo[*d*][1,3]dioxol-5-yl)-4-nitro-1-phenylbutan-1-one (7ad):**[49] White solid, mp 82-83 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94-7.91 (m, 2H), 7.61-7.54 (m, 1H), 7.50-7.43 (m, 2H), 6.76 (d, *J* = 1.1 Hz, 1H), 6.74 (d, *J* = 1.3 Hz, 2H), 5.93 (s, 2H), 4.78 (dd, *J* = 12.4, 6.5 Hz, 1H), 4.62 (dd, *J* = 12.4, 8.1 Hz, 1H), 4.18-4.11 (m, 1H), 3.44 (dd, *J* = 17.6, 6.5 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.4 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.8, 148.1, 147.1, 136.3, 133.6, 132.7, 128.7, 128.0, 120.7, 108.7, 107.7, 101.2, 79.7, 41.6, 39.1 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 20.0 min, $t_r$ (*R*) = 25.9 min.



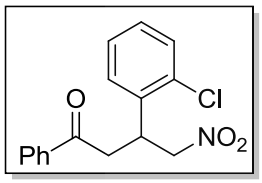

**4-Nitro-1-phenyl-3-(3,4,5-trimethoxyphenyl)butan-1-one (7ae):**[51] White solid, mp 142-143 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.95-7.90 (m, 2H), 7.63-7.54 (m, 1H), 7.50-7.42 (m, 2H), 4.83 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.69 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.23-4.12 (m, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.47 (dd, *J* = 17.6, 6.3 Hz, 1H), 3.38 (dd, *J* = 17.6, 7.5 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.9, 153.5, 137.6, 136.4, 134.7, 133.6, 128.7, 128.0,

[51] Wang, L.; Xu, X.; Huang, J.; Peng, L.; Huang, Q.; Wang, L. *Lett. Org. Chem.* **2010**, *5*, 367-372.

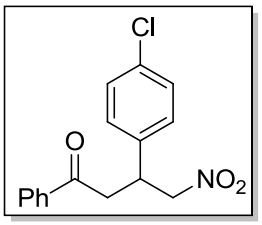
104.6, 79.4, 60.7, 56.2, 41.6, 39.6 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 14.9 min, $t_r$ (*R*) = 17.1 min.



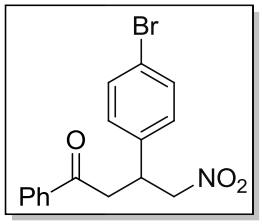

**3-(4-Fluorophenyl)-4-nitro-1-phenylbutan-1-one (7af):**[12] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.95-7.87 (m, 2H), 7.62-7.54 (m, 1H), 7.49-7.42 (m, 2H), 7.30-7.23 (m, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 4.82 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.66 (dd, *J* = 12.5, 8.2 Hz, 1H), 4.26-4.19 (m, 1H), 3.46 (dd, *J* = 17.7, 6.7 Hz, 1H), 3.41 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.6, 162.1 (d, *J* = 246.6 Hz), 136.2, 134.8 (d, *J* = 3.2 Hz), 133.6, 129.1 (d, *J* = 8.1 Hz), 128.7, 128.0, 115.9 (d, *J* = 21.5 Hz), 79.5, 41.5, 38.6 ppm; HPLC: Chiralpak AS-H , λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 9.6 min, $t_r$ (*R*) = 11.1 min.



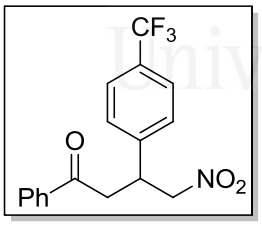

**3-(2-Chlorophenyl)-4-nitro-1-phenylbutan-1-one (7ag):**[36] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.62-7.54 (m, 1H), 7.49-7.43 (m, 2H), 7.43-7.39 (m, 1H), 7.31-7.27 (m, 1H), 7.27-7.18 (m, 2H), 4.89 (dd, *J* = 12.8, 6.9 Hz, 1H), 4.85 (dd, *J* = 12.8, 6.7, 1H), 4.72-66 (m, 1H), 3.58 (dd, *J* = 17.9, 7.4 Hz, 1H), 3.52 (dd, *J* = 17.9, 6.4 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.7, 136.2, 133.7, 133.6, 130.4, 129.0, 128.7, 128.4, 128.0, 127.3, 77.5, 39.8, 36.1 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 8.3 min, $t_r$ (*R*) = 9.4 min.



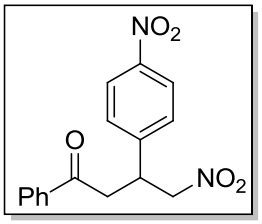

**3-(4-Chlorophenyl)-4-nitro-1-phenylbutan-1-one (7ah):**[36] White solid, mp 48-49 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.91 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.62-7.55 (m, 1H), 7.50-7.44 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.27-7.21 (m, 2H), 4.81 (dd, *J* = 12.6, 6.5 Hz, 1H), 4.66 (dd, *J* = 12.6, 8.2 Hz, 1H), 4.25-4.18 (m, 1H), 3.46 (dd, *J* = 17.8, 6.7 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.4, 137.6, 136.2, 133.7, 129.2, 128.8, 128.7, 128.0, 79.3, 41.3, 38.6 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 9.4 min, $t_r$ (*R*) = 11.7 min.



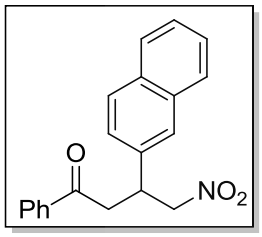

**3-(4-Bromophenyl)-4-nitro-1-phenylbutan-1-one (7ai):**[48] White solid, mp 66-67 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.90 (d, *J* = 8.4 Hz, 2H), 7.61-7.55 (m, 1H), 7.49-7.41 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.81 (dd, *J* = 12.6, 6.4 Hz, 1H), 4.65 (dd, *J* = 12.6, 8.2 Hz, 1H), 4.23-4.16 (m, 1H), 3.45 (dd, *J* = 17.8, 6.7 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.4, 138.1, 136.1, 133.7, 132.1, 129.2, 128.7, 127.9, 121.7, 79.2, 41.2, 38.7 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 9.8 min, $t_r$ (*R*) = 12.7 min.



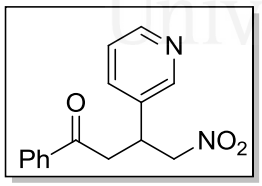

**4-Nitro-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one (7aj):**[34] Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.93-7.89 (m, 2H), 7.61-7.58 (m, 3H), 7.49-7.42 (m, 4H), 4.86 (dd, *J* = 12.7, 6.4 Hz, 1H), 4.71 (dd, *J* = 12.7, 8.2 Hz, 1H), 3.51 (dd, *J* = 17.9, 6.7 Hz, 1H), 3.44 (dd, *J* = 17.9, 7.2 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.3, 143.2, 136.1, 133.8, 130.15 (q, *J* = 32.8 Hz), 128.8, 128.0, 126.34, 126.0 (q, *J* = 3.8 Hz), 123.85 (q, *J* = 272.1 Hz), 79.0, 41.2, 39.0 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 6.7 min, $t_r$ (*R*) = 8.0 min.




**4-Nitro-3-(4-nitrophenyl)-1-phenylbutan-1-one (7ak):**[12] White solid, mp 102-103 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.25-8.18 (m, 2H), 7.94-7.88 (m, 2H), 7.63-7.56 (m, 1H), 7.53-7.40 (m, 4H), 4.89 (dd, *J* = 12.9, 6.2 Hz, 1H), 4.75 (dd, *J* = 12.9, 8.3 Hz, 1H), 4.43-4.35 (m, 1H), 3.54 (dd, *J* = 18.0, 6.8 Hz, 1H), 3.47 (dd, *J* = 18.0, 7.0 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.9, 147.4, 146.6, 135.9, 133.9, 128.8, 128.6, 128.0, 124.2, 78.8, 41.0, 38.9 ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 22.2 min, $t_r$ (*R*) = 36.5 min.

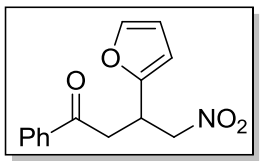



**3-(Naphthalen-2-yl)-4-nitro-1-phenylbutan-1-one (7al):**[36] White solid, mp 89-90 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.91 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.85-7.74 (m, 3H), 7.72 (d, *J* = 1.3 Hz, 1H), 7.58-7.51 (m, 1H), 7.51-7.35 (m, 5H), 4.89 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.76 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.43-4.35 (m, 1H), 3.56 (dd, *J* = 17.7, 6.4 Hz, 1H), 3.49 (dd, *J* = 17.7, 7.5 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.7, 136.5, 136.3, 133.5, 133.3, 132.8, 128.9, 128.7, 128.0, 127.8, 127.6, 126.5, 126.4, 126.2, 125.1, 79.5, 41.5, 39.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 10.3 min, $t_r$ (*R*) = 13.1 min.

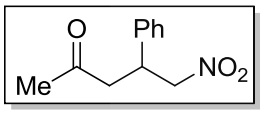



**4-Nitro-1-phenyl-3-(pyridin-3-yl)butan-1-one (7am):** Colorless oil; IR (ATR): ν = 3035, 2929, 2857, 1684, 1549, 1428, 1267, 1177, 1024 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.62 (d, *J* = 2.2 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.96-7.88 (m, 2H), 7.66 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.50-7.44 (m, 2H), 7.31-7.28 (m, 1H), 4.88 (dd, *J* = 12.8, 6.4 Hz, 1H), 4.73 (dd, *J* = 12.8, 8.1 Hz, 1H), 4.27 (dd, *J* = 14.6, 6.8 Hz, 1H), 3.50 (d, *J* = 6.9 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.1, 149.2, 149.0, 136.1, 135.3, 134.9, 133.8, 128.8, 128.0, 123.8, 78.9, 41.0, 36.9 ppm; MS (EI, 70 eV): *m/z* (%) = 207 (69), 131 (11), 117 (34), 105 (100), 77 (51), 51 (17); HRMS (CI-$CH_4$): *m/z* calcd. for $C_{15}H_{15}N_2O_3$ $[M+H]^+$:

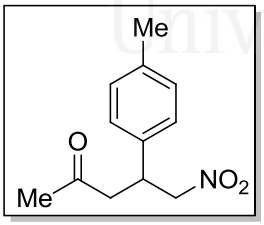
271,1077, found: 271.1070; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*R*) = 22.0 min, $t_r$ (*S*) = 38.2 min.




**3-(Furan-2-yl)-4-nitro-1-phenylbutan-1-one (7an):**[36] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.01-7.91 (m, 2H), 7.63-7.56 (m, 1H), 7.52-7.44 (m, 2H), 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 4.81 (dd, *J* = 12.6, 6.1 Hz, 1H), 4.75 (dd, *J* = 12.6, 7.3 Hz, 1H), 4.37-4.30 (m, 1H), 3.53 (dd, *J* = 17.9, 6.1 Hz, 1H), 3.43 (dd, *J* = 17.9, 7.5 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.5, 151.9, 142.3, 136.2, 133.6, 128.7, 128.0, 110.5, 107.1, 77.2, 38.9, 33.1 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*R*) = 8.7 min, $t_r$ (*S*) = 9.7 min.

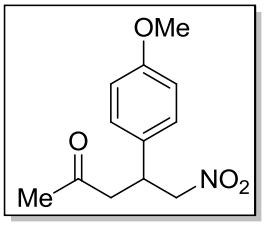



**5-Nitro-4-phenylpentan-2-one (9a):**[52] White solid, mp 113-114 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.34-7.19 (5H, m), 4.68 (dd, *J* = 12.3, 6.9 Hz, 1H), 4.58 (dd, *J* = 12.3, 7.9 Hz, 1H), 4.06-3.96 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.09 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.4, 138.8, 129.0, 127.8, 127.3, 79.4, 46.0, 39.0, 30.3 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 75:25, 1.0 mL/min, $t_r$ (*S*) = 9.5 min, $t_r$ (*R*) = 11.4 min.

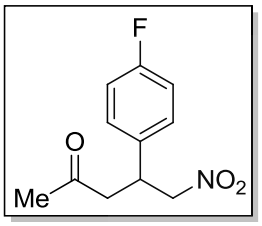



**5-Nitro-4-(p-tolyl)pentan-2-one (9b):**[52] White solid, mp 66-68 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.16-7.06 (m, 4H), 4.67 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.57 (dd, *J* = 12.2, 7.7 Hz, 1H), 4.01-3.92 (m, 1H), 2.89 (d, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.11 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.5, 137.6, 135.7, 129.7, 127.2, 79.6, 46.2, 38.7, 30.4, 21.0 ppm; HPLC: Chiralpak AS-H , λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (*S*) = 9.4 min, $t_r$ (*R*) = 12.4 min.

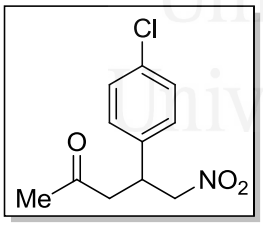
[52] Lu, A.; Liu, T.; Wu, R.; Wang, Y.; Zhou, Z.; Wu, G.; Fang, J.; Tang, C. *Eur. J. Org. Chem.* **2010**, 5777–5781.




**4-(4-Methoxyphenyl)-5-nitropentan-2-one (9c):**[52] White solid, mp 93-94 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.13 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7Hz, 2H) 4.66 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.55 (dd, J = 12.2, 7.8 Hz, 1H), 4.00-3.91 (m, 1H), 2.88 (d, *J* =7.1 Hz, 2H), 3.78 (s, 3H), 2.11 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6, 159.1, 130.6, 128.4, 114.4, 79.7, 55.3, 46.3, 38.4, 30.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 15.9 min, $t_r$ (*R*) = 29.1 min.

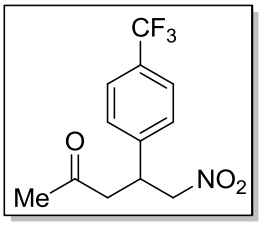



**4-(4-Fluorophenyl)-5-nitropentan-2-one (9f):**[53] White solid, mp 81-82 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.22-7.18 (m, 2H), 7.04-6.99 (m, 2H), 4.68 (dd, *J* = 12.4, 6.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.05-3.95 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.12 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.1, 162.2 (d, *J* = 246.7 Hz), 134.6 (d, *J* = 3.4 Hz), 129.0 (d, *J* = 8.2 Hz), 115.97 (d, *J* = 21.6 Hz), 79.4, 46.1, 38.3, 30.3 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 9.2 min, $t_r$ (*R*) = 11.8 min.

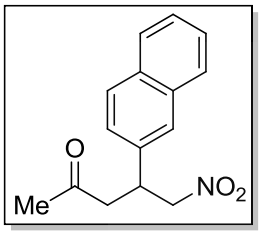



**4-(4-Chlorophenyl)-5-nitropentan-2-one (9h):**[52] White solid, mp 90-92 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.31 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 4.68 (dd, *J* = 12.4, 6.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.04-3.96 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.13 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.0, 137.3, 133.8, 129.2, 128.8, 79.2, 45.9, 38.4, 30.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 11.2 min, $t_r$ (*R*) = 15.5 min.

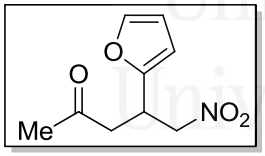
[53] Peng, L.; Xu, X.-Y.; Wang, L.-L.; Huang, J.; Bai, J.-F.; Huang, Q.-C.; Wang, L.-X. *Eur. J. Org. Chem.* **2010**, 1849-1853.




**5-Nitro-4-(4-(trifluoromethyl)phenyl)pentan-2-one (9j):**[54] Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.60 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.73 (dd, *J* = 12.6, 6.5 Hz, 1H), 4.62 (dd, *J* = 12.6, 8.0 Hz, 1H), 4.14-4.03 (m, 1H), 2.94 (dd, *J* = 6.9, 0.9 Hz, 2H), 2.14 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.7, 142.9, 130.2 (q, *J* = 32.8 Hz), 127.9, 126.0, 123.8 (d, *J* = 272.2 Hz), 78.8, 45.8, 38.6, 30.3ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 6.5 min, $t_r$ (*R*) = 7.8 min.



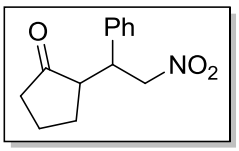

**4-(Naphthalen-2-yl)-5-nitropentan-2-one (9l):**[54] White solid, mp 101-103 °C; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.86-7.78 (m, 3H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.53-7.45 (m, 2H), 7.34 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.78 (dd, *J* = 12.4, 6.9 Hz, 1H), 4.70 (dd, *J* = 12.4, 7.7 Hz, 1H), 4.25-4.14 (m, 1H), 3.00 (d, *J* = 7.0 Hz, 2H), 2.13 (s, 3H); $^{13}$C NMR: (75 MHz, $CDCl_3$): $\delta_C$ = 205.3, 136.1, 133.3, 132.8, 128.9, 127.8, 127.6, 126.5, 126.2, 125.0, 79.3, 46.1, 39.1, 30.4 ppm; HPLC: Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (*S*) = 10.4 min, $t_r$ (*R*) = 14.4 min.




**4-(Furan-2-yl)-5-nitropentan-2-one (9n):**[52] Colorless oil; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.35-7.33 (m, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 4.68 (dd, *J* = 6.6, 1.6 Hz, 2H), 4.15-406 (m, 1H), 2.94 (dd, *J* = 8.3, 7.0 Hz, 2H), 2.18 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.0, 151.6, 142.3, 110.5, 107.1, 77.2, 43.5, 32.9, 30.2 ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, $t_r$ (*S*) = 26.4 min, $t_r$ (*R*) = 29.3 min.



[54] Akagawa, K.; Suzuki, R.; Kudo, K. *Asian J. Org. Chem.* **2014**, *3*, 514-522.




**2-(2-Nitro-1-phenylethyl)cyclopentanone (11a):**[52] Colorless oil; mixture of diastereomers (ratio: 1.8/1 *syn*/*anti**); $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.31-7.21 (m, 3H), 7.20-7.10 (m, 2H), 5.33 (dd, *J* = 12.9, 5.5 Hz, 1H), 5.01 (m, 1H), 4.71 (dd, *J* = 12.9, 9.6 Hz, 1 H), 3.87-3.80 (m, 1H)*/3.74-3.65 (m, 1H), 2.56-2.24 (m, 2H), 2.19-2.03 (m, 1H), 1.94-1.55 (m, 3H), 1.54-1.40 (m, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 219.0*/218.5, 137.7/137.4*, 128.9*/128.85, 128.4, 127.9/127.8*, 78.2/77.1*, 51.4*/50.4, 44.1/44.0*, 39.2*/38.6, 28.3/27.0*, 20.5*/20.2 ppm; HPLC: Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, *anti* diastereomer: $t_r$ (*R,R*) = 9.3 min, $t_r$ (*S,S*) = 10.5 min, *syn* diastereomer: $t_r$ (*R,S*) = 11.4 min, $t_r$ (*S,R*) = 15.1 min.

### *4.2.5. Calculations*

The structures were optimized by using density functional theory (DFT) with the B3LYP[55] and the 6-31G* basis set as implemented in Gaussian 09.[56] The structures were re-optimized at M06-2X/6-311+G** level of theory[57] on the previously optimized structures,[58] including polarization functions for better

[55] (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652; (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974-12980.

[56] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Menucci, B., Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin,. K. N.; Staroverov, V. N; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2009**.

[57] Zhao, Y.; Truhlar, D. G.; *Theor. Chem. Acc.* **2008**, *120*, 215-241.

[58] The use of the M06-2X/6-311+G** (or closely related method) level of theory has been justified in previous H-bond organocatalyzed reactions. See for example: (a) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014,** *20*, 5631-5639; (b) Simón, L.; Goodman, J. M. *Org. Biomol. Chem.* **2011**, *9*, 689-700.

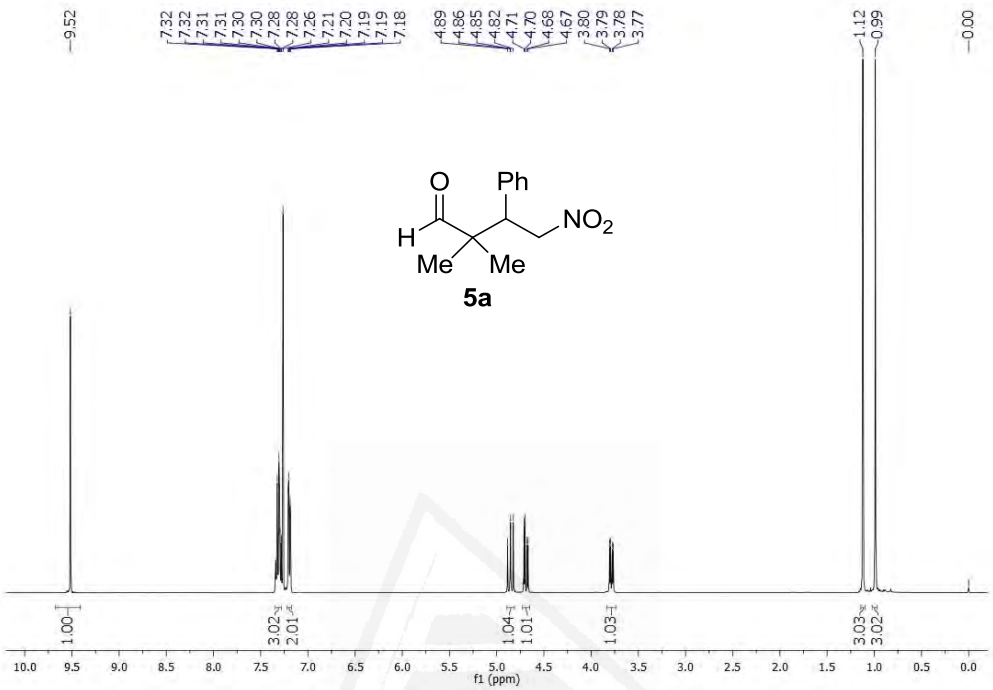
description of hydrogen bond activations and to better account for the dispersion forces of such large systems. Besides, solvation factors were introduced with the IEF-PCM method,[59] using water as indicated in the text and figures.

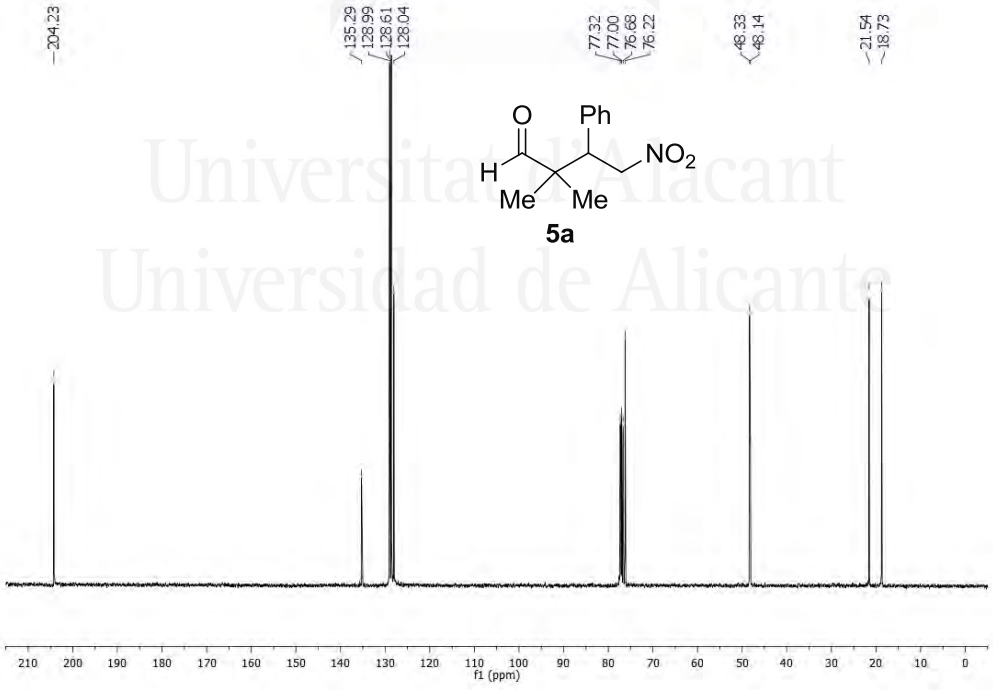
We also performed single-point calculations at B3LYP-D3/6-311+G** level of theory, including Grimme´s dispersion with the original D3 damping function, and the relative values were similar to those of the M06-2X energies.[60] The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[61] were followed to verify the energy profiles connecting each TS to the correct associated local minima. 3D structures were drawn using the CyL view software.[62]

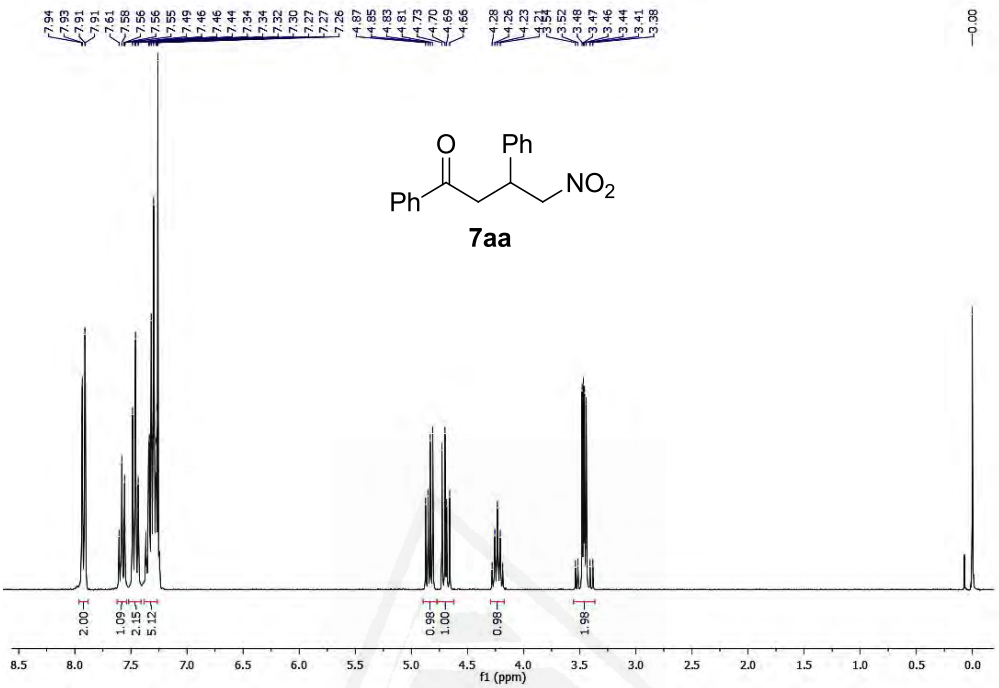


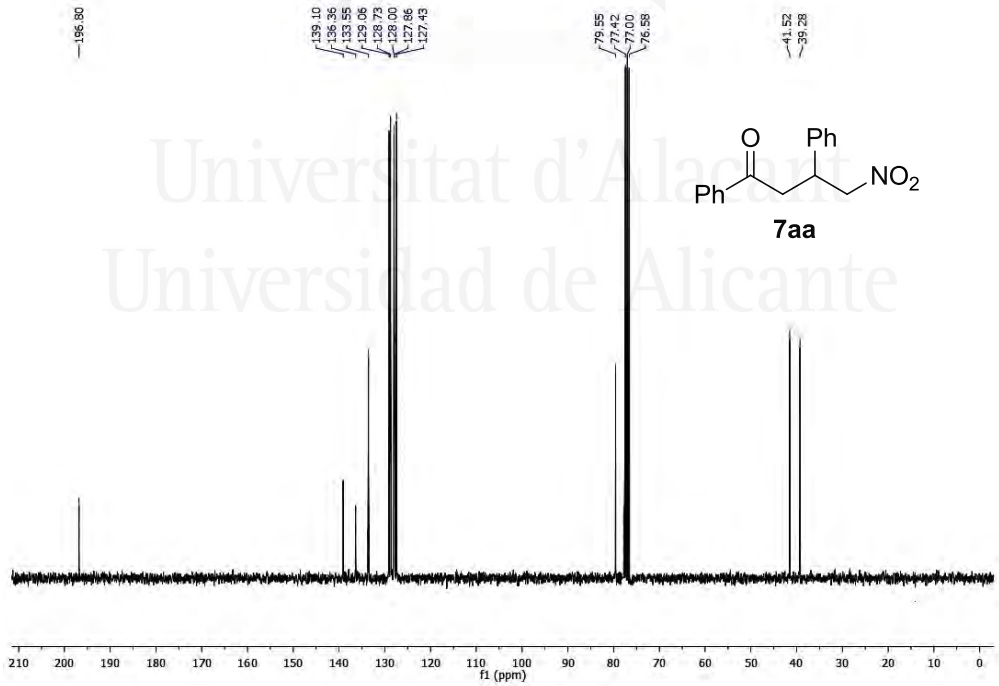
[59] (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032-3047. (b) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct. (Theochem)* **1999**, *464*, 211-226.
[60] Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104/1-154104/19.
[61] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523-5527.
[62] Legault, C. Y.; *CYLview*, v. 1.0b, Université de Sherbrooke, **2009**.

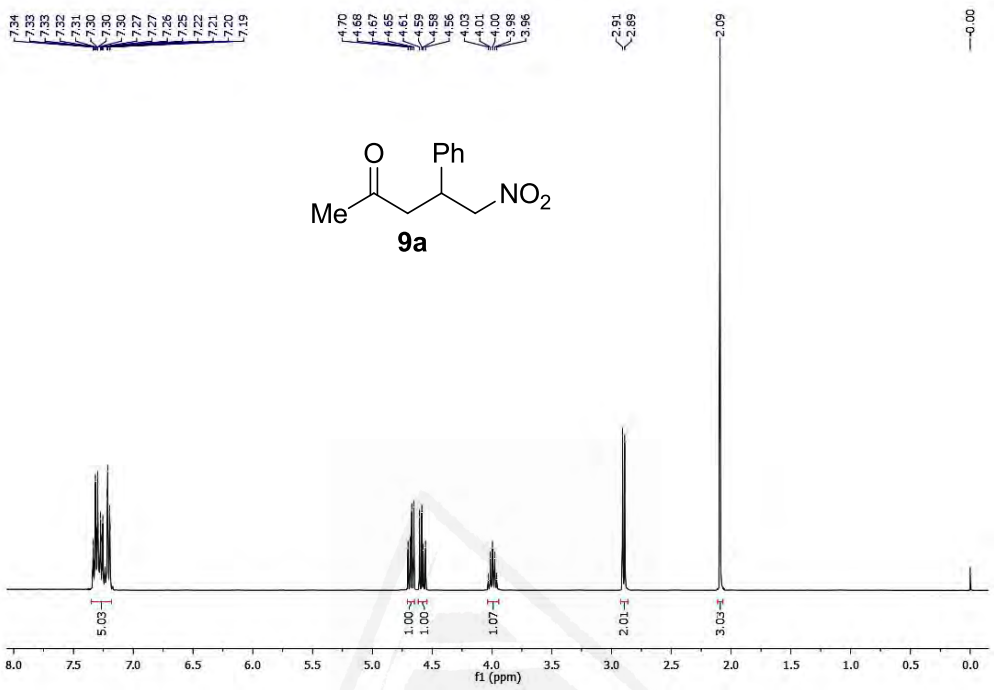
# 5. NMR SPECTRA

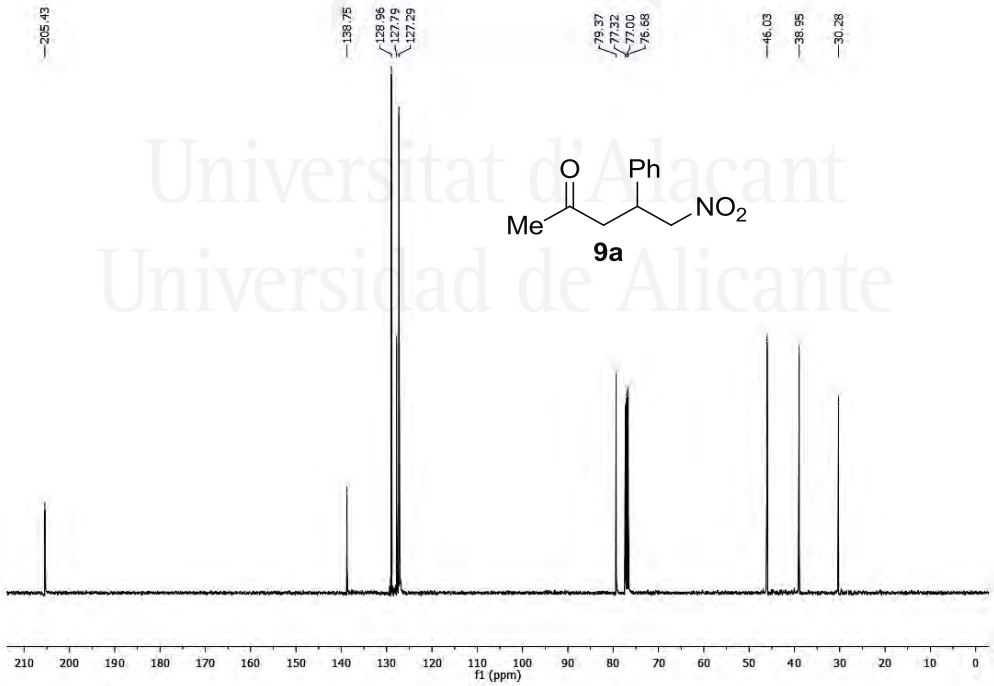






# 6. PUBLICATIONS

Tetrahedron: Asymmetry 26 (2015) 970–979

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Enantioselective addition of aryl ketones and acetone to nitroalkenes organocatalyzed by carbamate-monoprotected cyclohexa-1,2-diamines

Jesús Flores-Ferrándiz [a], Alexander Stiven [a], Lia Sotorríos [b], Enrique Gómez-Bengoa [b,*], Rafael Chinchilla [a,*]

[a] Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
[b] Departamento de Química Orgánica I, Universidad del País Vasco, Apdo. 1072, 20080 San Sebastián, Spain

ARTICLE INFO

*Article history:*
Received 7 July 2015
Accepted 17 July 2015
Available online 31 July 2015

ABSTRACT

Enantiomerically pure carbamate-monoprotected *trans*-cyclohexane-1,2-diamines are used as chiral organocatalysts for the addition of aryl ketones and acetone to nitroalkenes to give enantioenriched β-substituted γ-nitroketones. The reaction was performed in the presence of 3,4-dimethoxybenzoic acid as an additive, in chloroform as the solvent at room temperature, achieving enantioselectivities up to 96%. Theoretical calculations are used to justify the observed sense of the stereoinduction.



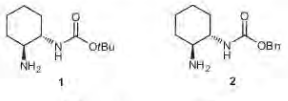
## 1. Introduction

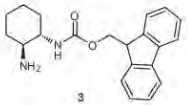
The enantioselective preparation of γ-nitrocarbonyl compounds is an interesting synthetic topic, since they are precursors of important compounds such as alkaloids,[1] aminoacids,[2] antitumorals,[3] antibiotics,[4] peptidomimetics[5] and marine metabolites[6], among others.[7] The direct conjugate addition of carbonyl compounds to conjugated nitroalkenes by means of metal-free organic catalysts represents a convenient access to this type of compounds. Therefore, over the past few years, much progress has been made in the development of organocatalytic-based methodologies for accomplishing this task.[8]

Nonetheless, the direct organocatalytic asymmetric conjugate addition of aromatic ketones to nitroalkenes is still considered a 'difficult' process and is much less explored. The enantioselective addition of aromatic ketones to β-nitrostyrenes is particularly interesting, as the corresponding γ-nitroketones can be used as intermediates in the preparation of β-arylated γ-aminobutyric acids, which are pharmacologically important $GABA_B$ agonists.[9] Commercial examples include baclofen,[10] used in the treatment of spasticity, and phenibut,[11] a tranquilizer and nootropic drug.

Although the enantioselective addition of particular aryl ketones, such as acetophenone, to β-nitrostyrene has been described using proline[12] or proline-derived organocatalysts,[13] most of the reported procedures using arylated ketones and nitroalkenes involve the use of chiral primary amine-containing NH-functionalized species, such as amides,[14] sulfonamides[15] and thioureas,[16] the last achieving the best results. Using these primary amine-containing bifunctional organocatalysts, the enantioselectivity is induced by the addition of a transient enamine to the nitroolefin, which is hydrogen bond-coordinated by the NH group of the additional functionality.

We have recently reported the use of primary amines from chiral *trans*-cyclohexane-1,2-diamines **1–3**, monosubstituted with the common Boc, Cbz and Fmoc protecting groups, respectively, as organocatalysts in the enantioselective Michael addition reactions of aldehydes to maleimides.[17] Herein we report the use of these simple primary amine-containing species as chiral organocatalysts in the conjugate addition reactions of arylated ketones, or even acetone, to nitroalkenes, leading to enantioenriched β-substituted γ-nitroketones. Theoretical calculations have been used to explain the observed sense of enantioselectivity.




* Corresponding authors. Tel.: +34 96 5903728; fax: +34 96 5903549.
*E-mail addresses:* enrique.gomez@ehu.es (E. Gómez-Bengoa), chinchilla@ua.es (R. Chinchilla).

http://dx.doi.org/10.1016/j.tetasy.2015.07.011
0957-4166/

## 2. Results and discussion

Carbamate-monoprotected primary amines **1**–**3** were employed as organocatalysts and were prepared by monoprotection of (1*S*,2*S*)-cyclohexane-1,2-diamine with the common *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and fluorenylmethoxycarbonyl (Fmoc) groups as previously reported.[17b] The search for the most appropriate organocatalyst and reaction conditions (Table 1) began using the model conjugate addition reaction of acetophenone **4a** (2 equiv) to (*E*)-β-nitrostyrene **5a**, organocatalyzed by **1** (20 mol %) in toluene as the solvent at room temperature, which afforded the corresponding adduct (*R*)-**6aa** in 62% isolated yield and with 88% ee after 5 d reaction time (Table 1, entry 1). The (*R*)-absolute configuration of the final adduct was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature.[16c] This adduct (*R*)-**6aa** is a precursor of the drug baclofen.[16h]

When the Cbz-monoprotected diamine **2** was used as the organocatalyst under these reaction conditions, the enantioselectivity of the process remained unchanged, although the isolated yield of the final adduct decreased (Table 1, entry 2). In addition, when the Fmoc-monoprotected primary amine **3** was employed, the enantioselectivity decreased to 68% (Table 1, entry 3). Therefore, we chose the Boc-containing primary amine **1** as the organocatalyst for the rest of the study.

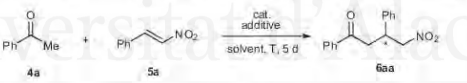
The use of others solvents was also explored. Thus, dichloromethane and chloroform were tested, with the latter slightly increasing both the yield and enantioselectivity (Table 1, entries 4 and 5), whereas the use of hexane or ether diminished both values (Table 1, entries 6 and 7). In addition, a polar solvent such as DMF afforded only 50% ee of (*R*)-**6aa**, while a protic one such as water proved not beneficial (Table 1, entries 8 and 9). Moreover, the use of a combination of DMF/water (2:1, v/v), a solvent mixture that has proven effective in enantioselective conjugate additions of aldehydes to maleimides organocatalyzed by **1**,[17] gave poor enantioselection (Table 1, entry 10).

We next explored the effect of the addition of some additives to the reaction, employing chloroform as the reaction solvent. Thus, the addition of the basic imidazole (20 mol %), which has previously been shown to be beneficial in some conjugate addition reactions,[18] was detrimental for the enantioselectivity in this case, compared to when no additive was used (Table 1, compare entries 5 and 11). Therefore, we switched to the use of carboxylic acids as additives (20 mol %), since it is known that they can facilitate the interconversion of different intermediates of the catalytic enamine cycle.[8g,19] Thus, the addition of benzoic acid (20 mol %) resulted in a slight improvement in the yield and enantioselectivity compared to when no additive was used (Table 1, compare entries 5 and 12). This positive result prompted us to explore if a modulation of the pKa of the additive by changing the substituent in the aromatic ring could be beneficial.

The presence of electron-withdrawing groups in the aromatic ring of the acid additive, such as chloro or nitro, increased the yield of adduct (*R*)-**6aa**, although it reduced the enantioselectivity of the process (Table 1, entries 13 and 14). Therefore, the presence of additives bearing electron-releasing groups, such as a methyl or methoxy group, was explored (Table 1, entries 15–17). Among them, the best results were achieved when 3,4-dimethoxybenzoic acid was used as the additive (Table 1, entry 17), giving rise to γ-nitroketone (*R*)-**6aa** with 93% ee (Table 1, entry 17). Although not spectacular, the presence of this acid additive was slightly positive for the enantioselectivity, but also improved the chemical yield.

Keeping the most effective reaction conditions [**1** (20 mol %), 3,4-dimethoxybenzoic acid (20 mol %), $CHCl_3$, 25 °C], other parameter changes were explored. Thus, the stoichiometry of the reaction was modified and 5 equiv of acetophenone were used; no significant changes were observed in either the yield or stereoselectivity (Table 1, entry 18). In addition, the organocatalyst loading was reduced to 10 mol %, but the former values diminished (Table 1,

**Table 1**
Screening and optimization of the reaction conditions for the enantioselective addition reaction of acetophenone to (*E*)-β-nitrostyrene

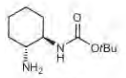



| Entry | Catalyst (mol %) | Additive[a] (mol %) | Solvent | *T* (°C) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** (20) | — | PhMe | 25 | 62 | 88 (*R*) |
| 2 | **2** (20) | — | PhMe | 25 | 55 | 88 (*R*) |
| 3 | **3** (20) | — | PhMe | 25 | 60 | 68 (*R*) |
| 4 | **1** (20) | — | $CH_2Cl_2$ | 25 | 63 | 87 (*R*) |
| 5 | **1** (20) | — | $CHCl_3$ | 25 | 65 | 89 (*R*) |
| 6 | **1** (20) | — | Hexane | 25 | 58 | 86 (*R*) |
| 7 | **1** (20) | — | $Et_2O$ | 25 | 50 | 82 (*R*) |
| 8 | **1** (20) | — | DMF | 25 | 60 | 50 (*R*) |
| 9 | **1** (20) | — | $H_2O$ | 25 | 53 | 60 (*R*) |
| 10 | **1** (20) | — | DMF/$H_2O$[c] | 25 | 60 | 42 (*R*) |
| 11 | **1** (20) | Imidazole (20) | $CHCl_3$ | 25 | 60 | 80 (*R*) |
| 12 | **1** (20) | $PhCO_2H$ | $CHCl_3$ | 25 | 65 | 90 (*R*) |
| 13 | **1** (20) | 4-$ClC_6H_4CO_2H$ | $CHCl_3$ | 25 | 78 | 85 (*R*) |
| 14 | **1** (20) | 4-$O_2NC_6H_4CO_2H$ | $CHCl_3$ | 25 | 70 | 83 (*R*) |
| 15 | **1** (20) | 4-$MeC_6H_4CO_2H$ | $CHCl_3$ | 25 | 67 | 87 (*R*) |
| 16 | **1** (20) | 2,4,6-$(Me)_3C_6H_2CO_2H$ | $CHCl_3$ | 25 | 80 | 82 (*R*) |
| 17 | **1** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ | $CHCl_3$ | 25 | 73 | 93 (*R*) |
| 18[d] | **1** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ | $CHCl_3$ | 25 | 70 | 92 (*R*) |
| 19 | **1** (10) | 3,4-$(MeO)_2C_6H_3CO_2H$ | $CHCl_3$ | 25 | 60 | 88 (*R*) |
| 20 | **1** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ | $CHCl_3$ | 10 | 65 | 90 (*R*) |
| 21 | *ent*-**1** (20) | 3,4-$(MeO)_2C_6H_3CO_2H$ | $CHCl_3$ | 25 | 71 | 93 (*S*) |

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC (Ref. 16c).
[c] 2/1, v/v.
[d] 5 equiv of **4a** were used.

entry 19). This also happened when the reaction temperature was lowered to 10 °C (Table 1, entry 20).

In an attempt to achieve opposite enantioselection, we also performed the reaction using organocatalyst *ent*-**1**, which was prepared similarly but using (1*R*,2*R*)-cyclohexane-1,2-diamine as the chirality source.[17b] Using this primary amine as organocatalyst (20 mol %) under the most effective reaction conditions [3,4-dimethoxybenzoic acid (20 mol %), $CHCl_3$, 25 °C], the expected adduct (*S*)-**6a** was isolated in 93% ee (Table 1, entry 21).

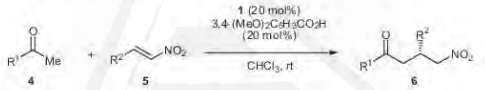


*ent*-**1**

Next we explored the scope of this organocatalyzed conjugate addition reaction by modifying the ketone and the nitroalkene under the most favourable reaction conditions [**1** (20 mol %), 3,4-dimethoxybenzoic acid (20 mol %), $CHCl_3$, 25 °C], the obtained results are summarized in Table 2.

First, we performed the reaction of arylated ketones **4**, differently substituted on the aromatic ring, to (*E*)-β-nitrostyrene **5a**. Thus, when an electron-releasing group such as a methyl was present at the 3- or 4-position of the aromatic ring **4b** and **4c**, the resulting adducts (*R*)-**6ba** and (*R*)-**6ca** were obtained with 86% and 91% ee, respectively (Table 2, entries 2 and 3), whereas the presence of a 4-methoxy substituent **4d** yielded (*R*)-**6da** with 91% ee (Table 2, entry 4). The presence of halogens in the aromatic ring, as in the case of ketones **4e–i**, gave the corresponding adducts (*R*)-**6ea–ia**, with 85–88% enantioselectivities (Table 2, entries 5–9). In addition, the presence of other electron-withdrawing substituents, such as the trifluoromethyl **4j**, **4k** and nitro **4l** groups, resulted in lower enantioselections for the corresponding adducts (*R*)-**6ja**, (*R*)-**6ka** and (*R*)-**6la** (Table 2, entries 10–12). Moreover, the use of a polyaromatic ketone, such as 1-(naphthalen-2-yl)ethan-1-one **4m** afforded the γ-nitroketone (*R*)-**6ma** with 89% ee (Table 2, entry 13), whereas the use of a heteroaromatic ketone,

**Table 2**
Enantioselective addition of ketones to nitroalkenes organocatalyzed by **1**




4 5 6

| Entry | Ketone[a] | | Nitroalkene | | *t* (d) | Adduct No. | Yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|---|---|---|---|
| | $R^1$ | No. | $R^2$ | No. | | | | |
| 1 | Ph | **4a** | Ph | **5a** | 5 | (*R*)-**6aa** | 73 | 93 |
| 2 | 3-$MeC_6H_4$ | **4b** | Ph | **5a** | 5 | (*R*)-**6ba** | 70 | 86 |
| 3 | 4-$MeC_6H_4$ | **4c** | Ph | **5a** | 5 | (*R*)-**6ca** | 70 | 91 |
| 4 | 4-$MeOC_6H_4$ | **4d** | Ph | **5a** | 5 | (*R*)-**6da** | 63 | 91 |
| 5 | 4-$FC_6H_4$ | **4e** | Ph | **5a** | 5 | (*R*)-**6ea** | 68 | 88 |
| 6 | 3-$ClC_6H_4$ | **4f** | Ph | **5a** | 5 | (*R*)-**6fa** | 68 | 85 |
| 7 | 4-$ClC_6H_4$ | **4g** | Ph | **5a** | 5 | (*R*)-**6ga** | 70 | 86 |
| 8 | 4-$BrC_6H_4$ | **4h** | Ph | **5a** | 5 | (*R*)-**6ha** | 70 | 88 |
| 9 | 4-$IC_6H_4$ | **4i** | Ph | **5a** | 5 | (*R*)-**6ia** | 67 | 88 |
| 10 | 3-$F_3CC_6H_4$ | **4j** | Ph | **5a** | 5 | (*R*)-**6ja** | 71 | 82 |
| 11 | 4-$F_3CC_6H_4$ | **4k** | Ph | **5a** | 5 | (*R*)-**6ka** | 68 | 83 |
| 12 | 4-$O_2NC_6H_4$ | **4l** | Ph | **5a** | 5 | (*R*)-**6la** | 58 | 75 |
| 13 | 2-Naphthyl | **4m** | Ph | **5a** | 5 | (*R*)-**6ma** | 71 | 89 |
| 14 | 2-Pyridinyl | **4n** | Ph | **5a** | 5 | (*R*)-**6na** | 85 | 68 |
| 15 | Ph | **4a** | 4-$MeC_6H_4$ | **5b** | 5 | (*R*)-**6ab** | 70 | 90 |
| 16 | Ph | **4a** | 4-$MeOC_6H_4$ | **5c** | 5 | (*R*)-**6ac** | 72 | 89 |
| 17 | Ph | **4a** | 3,4-$(OCH_2O)C_6H_3$ | **5d** | 5 | (*R*)-**6ad** | 60 | 90 |
| 18 | Ph | **4a** | 3,4,5-$(MeO)_3C_6H_2$ | **5e** | 5 | (*R*)-**6ae** | 56 | 89 |
| 19 | Ph | **4a** | 4-$FC_6H_4$ | **5f** | 5 | (*R*)-**6af** | 75 | 87 |
| 20 | Ph | **4a** | 2-$ClC_6H_4$ | **5g** | 5 | (*R*)-**6ag** | 77 | 93 |
| 21 | Ph | **4a** | 4-$ClC_6H_4$ | **5h** | 5 | (*R*)-**6ah** | 73 | 90 |
| 22 | Ph | **4a** | 4-$BrC_6H_4$ | **5i** | 5 | (*R*)-**6ai** | 70 | 86 |
| 23 | Ph | **4a** | 4-$F_3CC_6H_4$ | **5j** | 5 | (*R*)-**6aj** | 68 | 87 |
| 24 | Ph | **4a** | 4-$O_2NC_6H_4$ | **5k** | 5 | (*R*)-**6ak** | 75 | 88 |
| 25 | Ph | **4a** | 2-Naphthyl | **5l** | 5 | (*R*)-**6al** | 69 | 90 |
| 26 | Ph | **4a** | 3-Pyridinyl | **5m** | 5 | (*R*)-**6am** | 70 | 86 |
| 27 | Ph | **4a** | 2-Furanyl | **5n** | 5 | (*S*)-**6an** | 74 | 96 |
| 28 | Me | **4o** | Ph | **5a** | 3 | (*R*)-**6oa** | 92 | 70 |
| 29 | Me | **4o** | 4-$MeC_6H_4$ | **5b** | 3 | (*R*)-**6ob** | 85 | 67 |
| 30 | Me | **4o** | 4-$MeOC_6H_4$ | **5c** | 3 | (*R*)-**6oc** | 85 | 70 |
| 31 | Me | **4o** | 4-$FC_6H_4$ | **5f** | 3 | (*R*)-**6of** | 79 | 74 |
| 32 | Me | **4o** | 4-$ClC_6H_4$ | **5h** | 3 | (*R*)-**6oh** | 87 | 78 |
| 33 | Me | **4o** | 4-$F_3CC_6H_4$ | **5j** | 3 | (*R*)-**6oj** | 70 | 69 |
| 34 | Me | **4o** | 2-Naphthyl | **5l** | 3 | (*R*)-**6ol** | 71 | 62 |
| 35 | Me | **4o** | 2-Furanyl | **5n** | 3 | (*S*)-**6on** | 78 | 84 |

[a] 2 equiv of **4a–n** were used; 5 equiv of **4o** were used.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivities determined by chiral HPLC.
[d] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC (see Section 4).

such as 1-(pyridin-2-yl)ethan-1-one **4n** yielded the corresponding adduct (*R*)-**6na** with a much lower 68% ee (Table 2, entry 14).

We next explored the influence of changing the substituent on the nitroalkene **5**. Thus, when a 4-methyl was present on the aromatic ring **5b**, the resulting (*R*)-**6ab** was isolated with 90% ee, a similar value to when a 4-methoxy group **5c** was present [(*R*)-**6ac**, 89% ee] (Table 2, entries 15 and 16). In addition, when other electron-releasing systems were present, as in the case of the dioxole moiety **5d** and 3,4,5-trimethoxy groups **5e**, the enantioselectivities for the obtained adducts (*R*)-**6ad** and (*R*)-**6ae** were 90% and 89%, respectively (Table 2, entries 17 and 18).

When halogen groups were present on the aromatic ring of **5** (**5f-i**), the corresponding γ-nitroketones (*R*)-**6af–ai** were isolated with enantioselectivities ranging from 86% to 93% (Table 2, entries 19–22). Adduct (*R*)-**6ah** is particularly interesting, since it is an intermediate in the preparation of the commercial drug phenibut.[16b] In addition, the presence of other electron-withdrawing substituents such as the 4-trifluoromethyl **5j** and 4-nitro **5k** afforded adducts (*R*)-**6aj** and (*R*)-**6ak** with 87% and 88% ee, respectively (Table 2, entries 23 and 24). Moreover, the presence of a system such as 2-naphthyl **5l** allowed us to prepare (*R*)-**6al** with 90% ee (Table 2, entry 25), while the use of heteroaromatic systems such as a 3-pyridyl **5m** and 2-furanyl **5n** yielded γ-nitroketones (*R*)-**6am** and (*S*)-**6an** (no change in the enantioselectivity sense, just an effect of the CIP rules), with enantioselectivities of 86% and 96%, respectively (Table 2, entries 26 and 27).

Finally, we explored the use of organocatalyst **1**, under the former reaction conditions, in the conjugate addition of the simple acetone (5 equiv), to these nitroalkenes (Table 2). Thus, when acetone **4o** was reacted with (*E*)-β-nitrostyrene **5a**, the corresponding γ-nitroketone (*R*)-**6oa** was isolated in a 92% yield and in 70% ee (Table 2, entry 28). When a 4-methyl or a 4-methoxy group was present in the nitroalkene, the corresponding adducts (*R*)-**6ob** and (*R*)-**6oc** were obtained with 67 and 70% ee, respectively (Table 2, entries 29 and 30), whereas the presence of a halogen group such as a 4-fluoro and 4-chloro gave rise to higher enantioselections of the isolated adducts (*R*)-**6of** and (*R*)-**6oh**, respectively (Table 2, entries 31 and 32). However, the reaction with a 4-trifluoromethylated nitroalkene **5j** produced a lower enantioselectivity for the γ-nitroketone (*R*)-**6oj** (Table 2, entry 33), as well as when using the 2-naphthyl-nitroalkene **5j** (Table 2, entry 34). Finally, a higher enantioselectivity for adduct (*S*)-**6on** (84%) was observed when using 2-furanyl as the substituent in nitroalkene **5n** (Table 2, entry 35).

In order to justify the origin and sense of the observed enantioselectivity, we carried out theoretical calculations on the reactions of acetophenone **4a** and acetone **4o** with nitrostyrene **5a**, catalyzed by the NHBoc derivative **1**. We made use of different computational methods (M06-2X and B3LYP-D3, see the Section 4.3), and conditions, such as a gas phase system and a water solvent model, as extreme situations of apolar and very polar environments. The choice of solvent was seen to have a significant impact on the enantioselectivity (Table 1), and we were intrigued by the high ee's that were obtained in chloroform and other apolar solvents, while the use of water or DMF was seen to be detrimental for the observed selectivity.

Following the literature evidence, and our own previous calculations, we assumed that the reaction took place through Seebach's synclinal model,[20] where the nitroalkene approached the enamine through an *endo*-type transition state (Fig. 1, left). In that model, the attack from the lower face of the enamine (from our point of view) stereo-specifically determines the formation of the (*R*)-product through reaction with the Re face of nitrostyrene. Consequently, the approach from the upper face of the enamine (not shown) gave the (*S*)-product. The *exo* variant of the reaction would lead to opposite results, but according to Seebach's model and our initial calculations, this alternative is not operative and can be safely discarded.

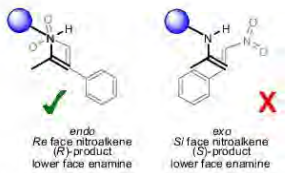



**Figure 1.** Seebach's synclinal model (left) for the reaction of the enamine model and nitrostyrene.

We have previously studied a related reaction (enamine and maleimide), which was also catalyzed by **1**,[17b] determining that the polarity of the solvent had an effect on the conformation of the catalyst, and more significantly, on the differential stabilization of the diastereomeric transition states. Thus, in the simplest alternative, the electrophile can be activated by an intramolecular H-bond with the NHBoc hydrogen of the catalyst (**TSA$_{Me}$-R** and **TSA$_{Ph}$-R**, Fig. 2). Due to the relative disposition of the NH groups of the enamine and the NHBoc moieties, the electrophile showed a clear preference for the approach through the lower face of the enamine, leading to the formation of the (*R*)-products. This effect is independent of the source of the enamine, either coming from acetone or acetophenone.

The presence of the internal hydrogen bond makes this transition state very apolar, and thus quite insensitive to the polarity of the solvent. When computed in the gas phase (as the extreme case for an apolar environment), the Gibbs Free activation energy was as low as 14.6 kcal/mol for the acetone derived enamine **TSA$_{Me}$-R**, and 20.3 kcal/mol for the acetophenone **TSA$_{Ph}$-R**. As expected, the energies in water were similar to the gas phase, increasing slightly to 15.3 kcal/mol for acetone, and staying ca. 20.0 kcal/mol for acetophenone.

A second main approach was found, wherein the nucleophile attacks from the upper face of the enamine (Fig. 3), in the distal position from the NHBoc group, and thus, without the possibility of forming any intramolecular H-bond. In TSB$_{Me}$-S and TSB$_{Ph}$-S, the attack takes place from the left side (from our point of view in Fig. 3) of the enamine, thorough the Si face of the nitroalkene [(*S*)-product], whereas the approach of the nitroalkene from the right side of the enamine (hypothetical TSC) is strongly disfavoured due to steric repulsion with the large Boc group, which blocks that face. We could not actually find any transition state for this approach without severely distorting the structure. The transition structures in Figure 3 are very polar, showing a clear separation of the developing positive and negative charges on the enamine and the nitroalkene, respectively. This type of situation is very sensitive to the environment; highly favoured in polar solvents, and especially in protic solvents (water) which are able to solvate and activate the electrophile by the formation of intermolecular H-bonds. Consequently, the computed energies in water (16.9 and 19.3 kcal/mol) are lower than in the gas phase (17.8 and 21.7 kcal/mol).

These computational data are thus able to explain the experimental findings. If the reaction is performed in an apolar system, the lowest-in-energy transition states are **TSA$_{Me}$-R** and **TSA$_{Ph}$-R**, bearing the internal H-bond activation, which explains the highly enantioselective formation of the (*R*)-product. As the polarity of

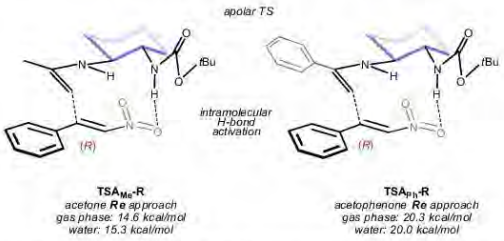



**Figure 2.** Computed Gibbs Free activation energies for the TSA-type transition states in the gas phase and water models.

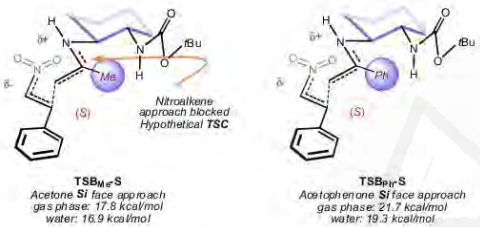



**Figure 3.** Computed Gibbs Free activation energies for the TSB-type transition states in the gas phase and water models.

the solvent increases, the polar transition states (TSB-type, Fig. 3) gain relative significance, inducing a deleterious effect on the enantioselectivity (Table 1, entries 8, 9 and 10). Furthermore, these results also agree with the common chemical sense, by which intramolecular H-bonds are stronger in apolar solvents, while intermolecular H-bonds with surrounding water molecules are present in aqueous systems. Finally, 3D representations[20] of the operative transition states for acetophenone in the gas phase and in the water model are shown in Figure 4.

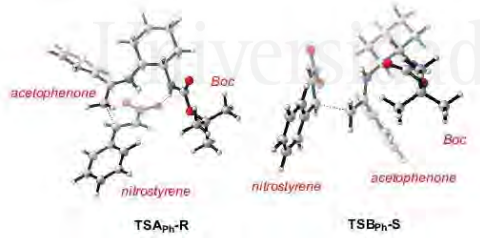



**Figure 4.** 3-D representation of the transition states for the reaction of acetophenone and nitrostyrene

## 3. Conclusions

In conclusion that primary amine-containing carbamates, prepared easily by monoprotection of enantiomerically pure *trans*-cyclohexane-1,2-diamines with the common Boc, Cbz and Fmoc groups, can act as organocatalysts in the enantioselective addition of aryl ketones to nitroalkenes, leading to enantiomerically enriched β-substituted γ-nitroketones. Good yields and enantioselectivities can be achieved in the presence of 3,4-dimethoxybenzoic acid as the additive. Furthermore, acetone can also be used as pro-nucleophile, but affording lower enantioselections. Theoretical calculations suggest that the presence of an intramolecular H-bond activation of the nitrostyrene with the NHBoc moiety of the catalyst is responsible for the preferential formation of the (*R*)-product in apolar solvents such as chloroform. The partial rupture of the H-bond in polar solvents, such as water or DMF, induces the formation of a more polar transition state [(*S*)-enantiomer], thus explaining the deleterious effect of the solvent polarity on the enantioselectivity of the reaction.

## 4. Experimental

### 4.1. General

All reagents and solvents were of the best grade available and used without further purification. IR data were collected with a Nicolet Impact 400D-FT spectrometer. The $^{1}$H and $^{13}$C NMR spectroscopic data were recorded at 25 °C with a Bruker AC-300 at 300 and 75 MHz, respectively, or a Bruker AC-400 at 400 and 101 MHz, respectively, with TMS as the internal standard. MS spectra were registered with an Agilent MS 5973 (GC). HRMS analyses were performed with an Agilent 7200 Accurate-Mass Q-TOF instrument (DIP probe), using chemical ionization (methane). Nitroalkenes **5** were purchased or prepared according to a reported procedure,[21] except for **5m**, which was obtained following another methodology.[22] Absolute configurations for adducts **6** were determined according to the described order of elution of their enantiomers in chiral HPLC, whereas in the case of new compounds, it was assigned by analogy. In the case of compounds **6aa** and **6on**, the employed HPLC chiral columns were the same than those reported in the literature (Chiralpak AS-H and AD-H, respectively). It has been assured for the rest of the adducts that the employed Chiralpak AS-H column maintains the same elution order of the enantiomers than when using a Chiralpak AD-H column, but giving cleaner determinations in the reaction crude. Reference racemic samples of adducts **6** were obtained by performing the reaction using an equimolecular mixture of **1** and *ent*-**1** (20 mol %) as organocatalyst in toluene as solvent at 25 °C.

### 4.2. General procedure for the enantioselective conjugate addition reaction

To a solution of **1** (8.6 mg, 0.04 mmol), the nitroalkene (0.2 mmol) and 3,4-dimethoxybenzoic acid (7.3 mg, 0.04 mmol) in $CHCl_3$ (0.5 mL) was added the ketone (0.4 mmol for **4a**–**n**, 74 μL, 1 mmol for **4o**) and the mixture was stirred at 25 °C for the

time shown in Table 2. The reaction was quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 × 10 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated (15 Torr) to give the crude product, which was purified by silica gel chromatography (*n*-hexane/AcOEt gradients).

Adducts **6** were identified by comparison of their spectroscopic data with those of the literature. Their enantiomeric excesses were determined by chiral HPLC.

#### 4.2.1. (*R*)-4-Nitro-1,3-diphenylbutan-2-one 6aa[16c]

White solid, mp 88–89 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.92 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 8.2, 6.9 Hz, 2H), 4.84 (dd, *J* = 12.5, 6.7 Hz, 1H), 4.70 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.29–4.17 (m, 1H), 3.50 (dd, *J* = 16.3, 5.0 Hz, 1H), 3.42 (dd, *J* = 16.3, 6.0 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.8, 139.1, 136.4, 133.6, 129.1, 128.7, 128.0, 127.9, 127.4, 79.6, 41.5, 39.3 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.7 min, $t_r$ (major) = 10.3 min.

#### 4.2.2. (*R*)-4-Nitro-3-phenyl-1-(m-tolyl)butan-1-one 6ba[16c]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.72–7.70 (m, 2H), 7.40–7.25 (m, 7 H), 4.81–4.86 (dd, *J* = 6.8 Hz, 12.8 Hz, 1H), 4.83 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.68 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.27–4.17 (m, 1H), 3.47 (dd, *J* = 17.9, 6.5 Hz, 1H), 3.40 (dd, *J* = 17.9, 7.7 Hz, 1H), 2.39 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 197.0, 139.1, 138.5, 136.3, 134.3, 129.0, 128.5, 128.5, 127.8, 127.4, 125.2, 79.5, 41.5, 39.2, 21.3 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 7.2 min, $t_r$ (major) = 8.9 min.

#### 4.2.3. (*R*)-4-Nitro-3-phenyl-1-(p-tolyl)butan-1-one 6ca[16c]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.86–7.78 (m, 2H), 7.35–7.23 (m, 7H), 4.83 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.67 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.26–4.15 (m, 1H), 3.45 (dd, *J* = 17.6, 6.4 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.40 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.4, 144.4, 139.2, 133.8, 129.3, 129.0, 128.1, 127.8, 127.4, 79.5, 41.3, 39.3, 21.6 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.9 min, $t_r$ (major) = 10.5 min.

#### 4.2.4. (*R*)-1-(4-Methoxyphenyl)-4-nitro-3-phenylbutan-1-one 6da[16c]

White solid, mp 90–91 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.94 (d, *J* = 9.0 Hz, 4H), 7.38–7.23 (m, 5H), 6.93 (d, *J* = 8.9 Hz, 4H), 4.84 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.68 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.27–4.15 (m, 1H), 3.87 (s, 3H), 3.43 (dd, *J* = 17.5, 6.4 Hz, 1H), 3.35 (dd, *J* = 17.5, 7.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.3, 163.8, 139.3, 130.3, 129.4, 129.00, 127.8, 127.4, 113.8, 79.6, 55.5, 41.1, 39.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 18.9 min, $t_r$ (major) = 23.1 min.

#### 4.2.5. (*R*)-1-(4-Fluorophenyl)-4-nitro-3-phenylbutan-1-one 6ea[23]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.98–7.93 (m, 2H), 7.37–3.32 (m, 2H), 7.31–7.24 (m, 3H), 7.16–7.10 (m, 2H), 4.83 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.69 (dd, *J* = 12.4, 7.7 Hz, 1H), 4.27–4.17 (m, 1H), 3.47 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.40 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.2, 165.6 (d, *J* = 254.6 Hz), 138.9, 132.7 (d, *J* = 2.8 Hz), 130.8 (d, *J* = 9.3 Hz), 129.0, 127.8, 127.3, 115.5 (d, *J* = 21.8 Hz), 79.4, 41.3, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 9.4 min, $t_r$ (major) = 11.3 min.

#### 4.2.6. (*R*)-1-(3-Chlorophenyl)-4-nitro-3-phenylbutan-1-one 6fa[16e]

Colourless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.87 (t, *J* = 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.9, 2.1, 1.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.35–7.31 (m, 2H), 7.30–7.25 (m, 3H), 4.80 (dd, J = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.25–4.17 (m, 1H), 3.46 (dd, *J* = 17.8, 6.6 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.5, 138.8, 137.8, 135.0, 133.4, 130.0, 129.1, 128.1, 127.9, 127.4, 126.0, 79.4, 41.6, 39.1 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.5 min, $t_r$ (major) = 10.6 min.

#### 4.2.7. (*R*)-1-(4-Chlorophenyl)-4-nitro-3-phenylbutan-1-one 6ga[16c]

White solid, mp 67–68 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.84 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.35–7.31 (m, 2H), 7.30–7.24 (m, 3H), 4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.24–4.17 (m, 1H), 3.44 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.39 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.6, 140.00, 138.9, 134.6, 129.4, 129.1, 129.0, 127.9, 127.4, 79.4, 41.4, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 10.5 min, $t_r$ (major) = 12.6 min.

#### 4.2.8. (*R*)-1-(4-Bromophenyl)-4-nitro-3-phenylbutan-1-one 6ha[16e]

White solid, mp 86–87 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.76 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.36–7.29 (m, 2H), 7.28–7.24 (m, 3H), 4.81 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.24–4.17 (m, 1H), 3.44 (dd, *J* = 17.7, 6.5 Hz, 1H), 3.38 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.8, 138.8, 135.0, 132.0, 129.5, 129.1, 128.8, 127.9, 127.4, 79.4, 41.4, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 11.8 min, $t_r$ (major) = 14.5 min.

#### 4.2.9. (*R*)-1-(4-Iodophenyl)-4-nitro-3-phenylbutan-1-one 6ia[15b]

White solid, mp 98–99 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.81 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.40–7.17 (m, 5H), 4.80 (dd, *J* = 12.5, 6.8 Hz, 1H), 4.67 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.25–4.15 (m, 1H), 3.45 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.38 (dd, *J* = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.1, 138.8, 138.0, 135.5, 129.3, 129.1, 127.9, 127.4, 101.6, 79.4, 41.3, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 14.4 min, $t_r$ (major) = 17.9 min.

#### 4.2.10. (*R*)-4-Nitro-3-phenyl-1-(3-(trifluoromethyl)phenyl)-butan-1-one 6ja

Colourless oil; IR (ATR): $\nu$ = 3066, 2922, 1690, 1550, 1409, 1321, 1167, 1126, 1065 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.10 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.39–7.21 (m, 5H), 4.83 (dd, *J* = 12.5, 7.0 Hz, 1H), 4.71 (dd, *J* = 12.5, 7.6 Hz, 1H), 4.28–4.21 (m, 1H), 3.52 (dd, *J* = 17.8, 6.6 Hz, 1H), 3.46 (dd, *J* = 17.8, 7.1 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.5, 138.7, 136.8, 131.4 (q, *J* = 33.3 Hz), 131.12, 129.9 (q, *J* = 3.4 Hz), 129.5, 129.2, 128.0, 127.4, 124.8 (q, *J* = 3.9 Hz), 123.5 (q, *J* = 273.7 Hz), 79.4, 41.6, 39.2 ppm; MS (EI, 70 ev): *m/z* (%) = 287 (100), 275 (46), 185 (54), 173 (28), 145 (41), 130 (17), 103 (21), 77 (15); HRMS (CI-$CH_4$): *m/z* calcd for $C_{17}H_{15}F_3NO_3$ $[M+H]^+$: 338.0999, found: 338.1005; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (minor) = 7.8 min, $t_r$ (major) = 9.7 min.

**4.2.11. (*R*)-4-Nitro-3-phenyl-1-(4-(trifluoromethyl)phenyl)-butan-1-one 6ka**[16g]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.00 (d, $J$ = 8.2 Hz, 2H), 7.71 (d, $J$ = 8.2 Hz, 2H), 7.37–7.17 (m, 5H), 4.81 (dd, $J$ = 12.5, 7.0 Hz, 1H), 4.69 (dd, $J$ = 12.5, 7.6 Hz, 1H), 4.27–4.18 (m, 1H), 3.51 (dd, $J$ = 17.9, 6.7 Hz, 1H), 3.45 (dd, $J$ = 17.9, 7.1 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.9, 139.0, 138.7, 134.7 (q, $J$ = 32.7 Hz), 129.1, 128.3, 128.0, 127.4, 125.7 (q, $J$ = 3.6 Hz), 123.4 (q, $J$ = 272.9 Hz), 79.4, 41.8, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 7.1 min, $t_r$ (major) = 8.4 min.

**4.2.12. (*R*)-4-Nitro-1-(4-nitrophenyl)-3-phenylbutan-1-one 6la**[16g]

Pale yellow solid, mp 91–92 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.28 (d, $J$ = 8.9 Hz, 1H), 8.05 (d, $J$ = 8.9 Hz, 1H), 7.37–7.31 (m, 2H), 7.31–7.24 (m, 3H), 4.81 (dd, $J$ = 12.5, 7.1 Hz, 1H), 4.71 (dd, $J$ = 12.5, 7.5 Hz, 1H), 4.26–4.19 (m, 1H), 3.55 (dd, $J$ = 17.8, 6.7 Hz, 1H), 3.50 (dd, $J$ = 17.8, 7.0 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 195.4, 140.6, 138.5, 129.1, 129.0, 128.0, 127.3, 123.9, 79.3, 42.0, 39.1 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 32.8 min, $t_r$ (major) = 36.7 min.

**4.2.13. (*R*)-1-(Naphthalen-2-yl)-4-nitro-3-phenylbutan-1-one 6ma**[15b]

White solid, mp 78–79 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.41 (s, 1H), 7.96 (dd, $J$ = 8.7, 1.6 Hz, 1H), 7.93 (d, $J$ = 8.1 Hz, 1H), 7.86 (dd, $J$ = 8.1, 4.1 Hz, 2H), 7.62–7.52 (m, 2H), 7.38–7.29 (m, 4H), 7.28–7.25 (m, 1H), 4.87 (dd, $J$ = 12.5, 6.6 Hz, 1H), 4.72 (dd, $J$ = 12.5, 8.0 Hz, 1H), 4.32–4.24 (m, 1H), 3.60 (dd, $J$ = 18.3, 7.1 Hz, 1H), 3.54 (dd, $J$ = 18.3, 8.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.7, 139.1, 135.7, 133.6, 132.4, 129.8, 129.5, 129.0, 128.7, 128.6, 127.8, 127.6, 127.4, 126.9, 123.5, 79.6, 41.5, 39.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 10.6 min, $t_r$ (major) = 11.9 min.

**4.2.14. (*R*)-4-Nitro-3-phenyl-1-(pyridin-2-yl)butan-1-one 6na**[24]

White solid, mp 59–61 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.65 (ddd, $J$ = 4.8, 1.7, 0.9 Hz, 1H), 7.98 (dt, $J$ = 7.7, 0.9 Hz, 1H), 7.80 (td, $J$ = 7.7, 1.7 Hz, 1H), 7.46 (ddd, $J$ = 7.7, 4.8, 0.9 Hz, 1H), 7.34–7.28 (m, 4H), 7.27–7.19 (m, 1H), 4.79 (dd, $J$ = 12.4, 6.7 Hz, 1H), 4.68 (dd, $J$ = 12.4, 8.3 Hz, 1H), 4.28–4.21 (m, 1H), 3.83 (dd, $J$ = 18.2, 7.0 Hz, 1H), 3.62 (dd, $J$ = 18.2, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 198.5, 152.6, 148.9, 139.2, 136.9, 128.9, 127.6, 127.5, 121.8, 79.8, 40.7, 39.2 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.5 min, $t_r$ (major) = 9.4 min.

**4.2.15. (*R*)-4-Nitro-1-phenyl-3-(p-tolyl)butan-1-one 6ab**[16c]

White solid, mp 72–73 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94–7.88 (m, 2H), 7.60–7.52 (m, 1H), 7.48–7.41 (m, 2H), 7.19–7.09 (m, 4H), 4.80 (dd, $J$ = 12.4, 6.6 Hz, 1H), 4.65 (dd, $J$ = 12.4, 8.0 Hz, 1H), 4.22–4.14 (m, 1H), 3.45 (dd, $J$ = 17.6, 6.4 Hz, 1H), 3.39 (dd, $J$ = 17.6, 7.4 Hz, 1H), 2.30 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.9, 137.5, 136.3, 136.0, 133.5, 129.7, 128.7, 128.0, 127.2, 79.7, 41.5, 38.9, 21.0 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 7.9 min, $t_r$ (major) = 10.1 min.

**4.2.16. (*R*)-3-(4-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one 6ac**[16c]

White solid, mp 69–70 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.96–7.85 (m, 2H), 7.63–7.52 (m, 1H), 7.47–7.41 (m, 2H), 7.20 (d, $J$ = 8.7 Hz, 2H), 6.85 (d, $J$ = 8.7 Hz, 2H), 4.79 (dd, $J$ = 12.3, 6.6 Hz, 1H), 4.64 (dd, $J$ = 12.3, 8.0 Hz, 1H), 4.21–4.14 (m, 1H), 3.77 (s, 1H), 3.45 (dd, $J$ = 17.6, 6.5 Hz, 1H), 3.39 (dd, $J$ = 17.6, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.9, 159.0, 136.4, 133.5, 130.9, 128.7, 128.5, 128.0, 114.4, 79.8, 55.2, 41.6, 38.6 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 14.6 min, $t_r$ (major) = 17.6 min.

**4.2.17. (*R*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-4-nitro-1-phenylbutan-1-one 6ad**[23]

White solid, mp 82–83 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94–7.91 (m, 2H), 7.61–7.54 (m, 1H), 7.50–7.43 (m, 2H), 6.76 (d, $J$ = 1.1 Hz, 1H), 6.74 (d, $J$ = 1.3 Hz, 2H), 5.93 (s, 2H), 4.78 (dd, $J$ = 12.4, 6.5 Hz, 1H), 4.62 (dd, $J$ = 12.4, 8.1 Hz, 1H), 4.18–4.11 (m, 1H), 3.44 (dd, $J$ = 17.6, 6.5 Hz, 1H), 3.37 (dd, $J$ = 17.6, 7.4 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.8, 148.1, 147.1, 136.3, 133.6, 132.7, 128.7, 128.0, 120.7, 108.7, 107.7, 101.2, 79.7, 41.6, 39.1 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 20.0 min, $t_r$ (major) = 25.9 min.

**4.2.18. (*R*)-4-Nitro-1-phenyl-3-(3,4,5-trimethoxyphenyl)butan-1-one 6ae**[16f]

White solid, mp 142–143 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.95–7.90 (m, 2H), 7.63–7.54 (m, 1H), 7.50–7.42 (m, 2H), 4.83 (dd, $J$ = 12.5, 6.6 Hz, 1H), 4.69 (dd, $J$ = 12.5, 8.0 Hz, 1H), 4.23–4.12 (m, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.47 (dd, $J$ = 17.6, 6.3 Hz, 1H), 3.38 (dd, $J$ = 17.6, 7.5 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.9, 153.5, 137.6, 136.4, 134.7, 133.6, 128.7, 128.0, 104.6, 79.4, 60.7, 56.2, 41.6, 39.6 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (minor) = 14.9 min, $t_r$ (major) = 17.1 min.

**4.2.19. (*R*)-3-(4-Fluorophenyl)-4-nitro-1-phenylbutan-1-one 6af**[16b]

Colourless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.95–7.87 (m, 2H), 7.62–7.54 (m, 1H), 7.49–7.42 (m, 2H), 7.30–7.23 (m, 2H), 7.02 (t, $J$ = 8.7 Hz, 2H), 4.82 (dd, $J$ = 12.5, 6.5 Hz, 1H), 4.66 (dd, $J$ = 12.5, 8.2 Hz, 1H), 4.26–4.19 (m, 1H), 3.46 (dd, $J$ = 17.7, 6.7 Hz, 1H), 3.41 (dd, $J$ = 17.7, 7.3 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.6, 162.1 (d, $J$ = 246.6 Hz), 136.2, 134.8 (d, $J$ = 3.2 Hz), 133.6, 129.1 (d, $J$ = 8.1 Hz), 128.7, 128.0, 115.9 (d, $J$ = 21.5 Hz), 79.5, 41.5, 38.6 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 9.6 min, $t_r$ (major) = 11.1 min.

**4.2.20. (*R*)-3-(2-Chlorophenyl)-4-nitro-1-phenylbutan-1-one 6ag**[16c]

Colourless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94 (dd, $J$ = 8.4, 1.3 Hz, 2H), 7.62–7.54 (m, 1H), 7.49–7.43 (m, 2H), 7.43–7.39 (m, 1H), 7.31–7.27 (m, 1H), 7.27–7.18 (m, 2H), 4.89 (dd, $J$ = 12.8, 6.9 Hz, 1H), 4.85 (dd, $J$ = 12.8, 6.7, 1H), 4.72–66 (m, 1H), 3.58 (dd, $J$ = 17.9, 7.4 Hz, 1H), 3.52 (dd, $J$ = 17.9, 6.4 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.7, 136.2, 133.7, 133.6, 130.4, 129.0, 128.7, 128.4, 128.0, 127.3, 77.5, 39.8, 36.1 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.3 min, $t_r$ (major) = 9.4 min.

**4.2.21. (*R*)-3-(4-Chlorophenyl)-4-nitro-1-phenylbutan-1-one 6ah**[16c]

White solid, mp 48–49 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.91 (dd, $J$ = 8.4, 1.3 Hz, 2H), 7.62–7.55 (m, 1H), 7.50–7.44 (m, 2H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.27–7.21 (m, 2H), 4.81 (dd, $J$ = 12.6, 6.5 Hz, 1H), 4.66 (dd, $J$ = 12.6, 8.2 Hz, 1H), 4.25–4.18 (m, 1H), 3.46 (dd, $J$ = 17.8, 6.7 Hz, 1H), 3.40 (dd, $J$ = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.4, 137.6, 136.2, 133.7, 129.2, 128.8, 128.7, 128.0, 79.3, 41.3, 38.6 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm,

*n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 9.4 min, $t_r$ (major) = 11.7 min.

#### 4.2.22. (*R*)-3-(4-Bromophenyl)-4-nitro-1-phenylbutan-1-one 6ai[16e]

White solid, mp 66–67 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.90 (d, *J* = 8.4 Hz, 2H), 7.61–7.55 (m, 1H), 7.49–7.41 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.81 (dd, *J* = 12.6, 6.4 Hz, 1H), 4.65 (dd, *J* = 12.6, 8.2 Hz, 1H), 4.23–4.16 (m, 1H), 3.45 (dd, *J* = 17.8, 6.7 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.2 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.4, 138.1, 136.1, 133.7, 132.1, 129.2, 128.7, 127.9, 121.7, 79.2, 41.2, 38.7 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 9.8 min, $t_r$ (major) = 12.7 min.

#### 4.2.23. (*R*)-4-Nitro-1-phenyl-3-(4-(trifluoromethyl)phenyl)-butan-1-one 6aj[16g]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.93–7.89 (m, 2H), 7.61–7.58 (m, 3H), 7.49–7.42 (m, 4H), 4.86 (dd, *J* = 12.7, 6.4 Hz, 1H), 4.71 (dd, *J* = 12.7, 8.2 Hz, 1H), 3.51 (dd, *J* = 17.9, 6.7 Hz, 1H), 3.44 (dd, *J* = 17.9, 7.2 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.3, 143.2, 136.1, 133.8, 130.15 (q, *J* = 32.8 Hz), 128.8, 128.0, 126.34, 126.0 (q, *J* = 3.8 Hz), 123.85 (q, *J* = 272.1 Hz), 79.0, 41.2, 39.0 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 6.7 min, $t_r$ (major) = 8.0 min.

#### 4.2.24. (*R*)-4-Nitro-3-(4-nitrophenyl)-1-phenylbutan-1-one 6ak[16h]

White solid, mp 102–103 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.25–8.18 (m, 2H), 7.94–7.88 (m, 2H), 7.63–7.56 (m, 1H), 7.53–7.40 (m, 4H), 4.89 (dd, *J* = 12.9, 6.2 Hz, 1H), 4.75 (dd, *J* = 12.9, 8.3 Hz, 1H), 4.43–4.35 (m, 1H), 3.54 (dd, *J* = 18.0, 6.8 Hz, 1H), 3.47 (dd, *J* = 18.0, 7.0 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 195.9, 147.4, 146.6, 135.9, 133.9, 128.8, 128.6, 128.0, 124.2, 78.8, 41.0, 38.9 ppm; HPLC: Chiralpak AD-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (minor) = 22.2 min, $t_r$ (major) = 36.5 min.

#### 4.2.25. (*R*)-3-(Naphthalen-2-yl)-4-nitro-1-phenylbutan-1-one 6al[16c]

White solid, mp 89–90 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.91 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.85–7.74 (m, 3H), 7.72 (d, *J* = 1.3 Hz, 1H), 7.58–7.51 (m, 1H), 7.51–7.35 (m, 5H), 4.89 (dd, *J* = 12.5, 6.6 Hz, 1H), 4.76 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.43–4.35 (m, 1H), 3.56 (dd, *J* = 17.7, 6.4 Hz, 1H), 3.49 (dd, *J* = 17.7, 7.5 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.7, 136.5, 136.3, 133.5, 133.3, 132.8, 128.9, 128.7, 128.0, 127.8, 127.6, 126.5, 126.4, 126.2, 125.1, 79.5, 41.5, 39.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 10.3 min, $t_r$ (major) = 13.1 min.

#### 4.2.26. (*R*)-4-Nitro-1-phenyl-3-(pyridin-3-yl)butan-1-one 6am

Colourless oil; IR (ATR): ν = 3035, 2929, 2857, 1684, 1549, 1428, 1267, 1177, 1024 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 8.62 (d, *J* = 2.2 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.96–7.88 (m, 2H), 7.66 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.50–7.44 (m, 2H), 7.31–7.28 (m, 1H), 4.88 (dd, *J* = 12.8, 6.4 Hz, 1H), 4.73 (dd, *J* = 12.8, 8.1 Hz, 1H), 4.27 (dd, *J* = 14.6, 6.8 Hz, 1H), 3.50 (d, *J* = 6.9 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 196.1, 149.2, 149.0, 136.1, 135.3, 134.9, 133.8, 128.8, 128.0, 123.8, 78.9, 41.0, 36.9 ppm; MS (EI, 70 ev): *m/z* (%) = 207 (69), 131 (11), 117 (34), 105 (100), 77 (51), 51 (17); HRMS (CI-$CH_4$): *m/z* calcd for $C_{15}H_{15}N_2O_3$ $[M+H]^+$: 271.1077, found: 271.1070; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (major) = 22.0 min, $t_r$ (minor) = 38.2 min.

#### 4.2.27. (*S*)-3-(Furan-2-yl)-4-nitro-1-phenylbutan-1-one 6an[16c]

Colourless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.01–7.91 (m, 2H), 7.63–7.56 (m, 1H), 7.52–7.44 (m, 2H), 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 4.81 (dd, *J* = 12.6, 6.1 Hz, 1H), 4.75 (dd, *J* = 12.6, 7.3 Hz, 1H), 4.37–4.30 (m, 1H), 3.53 (dd, *J* = 17.9, 6.1 Hz, 1H), 3.43 (dd, *J* = 17.9, 7.5 Hz, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 196.5, 151.9, 142.3, 136.2, 133.6, 128.7, 128.0, 110.5, 107.1, 77.2, 38.9, 33.1 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 8.7 min, $t_r$ (major) = 9.7 min.

#### 4.2.28. (*R*)-5-Nitro-4-phenylpentan-2-one 6oa[25]

White solid, mp 113–114 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.34–7.19 (5H, m), 4.68 (dd, *J* = 12.3, 6.9 Hz, 1H), 4.58 (dd, *J* = 12.3, 7.9 Hz, 1H), 4.06–3.96 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.09 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.4, 138.8, 129.0, 127.8, 127.3, 79.4, 46.0, 39.0, 30.3 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 75:25, 1.0 mL/min, $t_r$ (minor) = 9.5 min, $t_r$ (major) = 11.4 min.

#### 4.2.29. (*R*)-5-Nitro-4-(*p*-tolyl)pentan-2-one 6ob[25]

White solid, mp 66–68 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.16–7.06 (m, 4H), 4.67 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.57 (dd, *J* = 12.2, 7.7 Hz, 1H), 4.01–3.92 (m, 1H), 2.89 (d, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.11 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.5, 137.6, 135.7, 129.7, 127.2, 79.6, 46.2, 38.7, 30.4, 21.0 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min, $t_r$ (minor) = 9.4 min, $t_r$ (major) = 12.4 min.

#### 4.2.30. (*R*)-4-(4-Methoxyphenyl)-5-nitropentan-2-one 6oc[25]

White solid, mp 93–94 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.13 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H) 4.66 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.55 (dd, J = 12.2, 7.8 Hz, 1H), 4.00–3.91 (m, 1H), 2.88 (d, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.11 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.6, 159.1, 130.6, 128.4, 114.4, 79.7, 55.3, 46.3, 38.4, 30.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 15.9 min, $t_r$ (major) = 29.1 min.

#### 4.2.31. (*R*)-4-(4-Fluorophenyl)-5-nitropentan-2-one 6of[26]

White solid, mp 81–82 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.22–7.18 (m, 2H), 7.04–6.99 (m, 2H), 4.68 (dd, *J* = 12.4, 6.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.05–3.95 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.12 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.1, 162.2 (d, *J* = 246.7 Hz), 134.6 (d, *J* = 3.4 Hz), 129.0 (d, *J* = 8.2 Hz), 115.97 (d, *J* = 21.6 Hz), 79.4, 46.1, 38.3, 30.3 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 9.2 min, $t_r$ (major) = 11.8 min.

#### 4.2.32. (*R*)-4-(4-Chlorophenyl)-5-nitropentan-2-one 6oh[25]

White solid, mp 90–92 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.31 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 4.68 (dd, *J* = 12.4, 6.6 Hz, 1H), 4.57 (dd, *J* = 12.4, 7.9 Hz, 1H), 4.04–3.96 (m, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.13 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.0, 137.3, 133.8, 129.2, 128.8, 79.2, 45.9, 38.4, 30.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 11.2 min, $t_r$ (major) = 15.5 min.

#### 4.2.33. (*R*)-5-Nitro-4-(4-(trifluoromethyl)phenyl)pentan-2-one 6oj[27]

Colourless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.60 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.73 (dd, *J* = 12.6, 6.5 Hz, 1H), 4.62 (dd, *J* = 12.6, 8.0 Hz, 1H), 4.14–4.03 (m, 1H), 2.94 (dd, *J* = 6.9, 0.9 Hz, 2H), 2.14 (s, 3H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta_C$ = 204.7, 142.9, 130.2 (q, *J* = 32.8 Hz), 127.9, 126.0, 123.8 (d, *J* = 272.2 Hz), 78.8, 45.8, 38.6, 30.3 ppm; HPLC: Chiralpak AS-H,

$\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 6.5 min, $t_r$ (major) = 7.8 min.

#### 4.2.34. (*R*)-4-(Naphthalen-2-yl)-5-nitropentan-2-one 6ol[27]

White solid, mp 101–103 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.86–7.78 (m, 3H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.53–7.45 (m, 2H), 7.34 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.78 (dd, *J* = 12.4, 6.9 Hz, 1H), 4.70 (dd, *J* = 12.4, 7.7 Hz, 1H), 4.25–4.14 (m, 1H), 3.00 (d, *J* = 7.0 Hz, 2H), 2.13 (s, 3H); $^{13}$C NMR: (75 MHz, $CDCl_3$): $\delta_C$ = 205.3, 136.1, 133.3, 132.8, 128.9, 127.8, 127.6, 126.5, 126.2, 125.0, 79.3, 46.1, 39.1, 30.4 ppm; HPLC: Chiralpak AS-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 70:30, 1.0 mL/min, $t_r$ (minor) = 10.4 min, $t_r$ (major) = 14.4 min.

#### 4.2.35. (*S*)-4-(Furan-2-yl)-5-nitropentan-2-one 6on[25]

Colourless oil; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ = 7.35–7.33 (m, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 4.68 (dd, *J* = 6.6, 1.6 Hz, 2H), 4.15–406 (m, 1H), 2.94 (dd, *J* = 8.3, 7.0 Hz, 2H), 2.18 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta_C$ = 205.0, 151.6, 142.3, 110.5, 107.1, 77.2, 43.5, 32.9, 30.2 ppm; HPLC: Chiralpak AD-H, $\lambda$ = 210 nm, *n*-hexane/2-propanol, 90:10, 1.0 mL/min, $t_r$ (major) = 26.4 min, $t_r$ (minor) = 29.3 min.

### 4.3. Calculations

The structures were optimized using density functional theory (DFT) with the B3LYP[28] and the 6-31G* basis set as implemented in Gaussian 09.[29] The structures were re-optimized at M06-2X/6-311+G** level of theory[30] on the previously optimized structures,[31] including polarization functions for better description of hydrogen bond activations and to better account for the dispersion forces of such large systems. Besides, solvation factors were introduced with the IEF-PCM method,[32] using water as indicated in the text and figures.

We also performed single-point calculations at B3LYP-D3/6-311+G** level of theory, including Grimme's dispersion with the original D3 damping function, and the relative values were similar to those of the M06-2X energies.[33] The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[34] were followed to verify the energy profiles connecting each TS to the correct associated local minima. 3D structures were drawn using the CyL view software.[35]

### Acknowledgments

We thank the financial support from the Spanish Ministerio de Economía y Competitividad (project CTQ2011-24151), FEDER, the COST Action CM0905 'Organocatalysis', the FP7 Marie Curie Action of the European Commission via the ITN ECHONET Network (FP7-MCITN-2012-316379), and the universities of Alicante and the Basque Country. We also thank SGI/IZO-SGIker (UPV/EHU) for allocation of computational resources. J.F.-F. acknowledges the Vicerrectorado de Investigación, Desarrollo e Innovación of the University of Alicante for a fellowship. A.S. thanks the University of Edinburgh for an ERASMUS fellowship.

### References

1. (a) Zou, W.; Vembaiyan, K.; Bhasin, M.; Williams, D. T. *Carbohydr. Res.* **2009**, *344*, 2144–2150; (b) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556–559.
2. (a) Ma, H.; Liu, K.; Zhang, F.-G.; Zhu, C.-L.; Nie, J.; Ma, J.-A. *J. Org. Chem.* **2010**, *75*, 1402–1409; (b) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037.
3. Szanto, G.; Hegedus, L.; Mattyasovszky, L.; Simon, A.; Simon, A.; Bitter, I.; Toth, G.; Toke, L.; Kadas, I. *Tetrahedron* **2009**, *65*, 8412–8417.
4. Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901–7904.
5. Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195–5198.
6. Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776–779.
7. (a) Elsner, P.; Jiang, H.; Nielsen, J. B.; Pasi, F.; Jorgensen, K. A. *Chem. Commun.* **2008**, 5827–5829; (b) Karthikeyan, T.; Sankararaman, S. *Tetrahedron: Asymmetry* **2008**, *19*, 2741–2745; (c) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357–9367; (d) Krayer, M.; Ptaszek, M.; Kim, H.-J.; Meneely, K. R.; Fan, D.; Secor, K.; Lindsey, J. S. *J. Org. Chem.* **2010**, *75*, 1016–1039.
8. (a) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135; (b) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716; (d) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1–13; (e) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601; (f) Somanathan, R.; Chavez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya, d. P. C.; Gonzalez, J. *Curr. Org. Chem.* **2012**, *16*, 2440–2461; (g) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; (h) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627–2648.
9. Kerr, D. I. B.; Ong, J. *Med. Res. Rev.* **1992**, *12*, 593–636.
10. (a) Olpe, H. R.; Demieville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133–136; (b) Berthelot, P.; Vaccher, C.; Flouquet, N.; Debaert, M.; Luyckx, M.; Brunet, C. *J. Med. Chem.* **1991**, *34*, 2557–2560; (c) Kerr, D. I. B.; Ong, J.; Doolette, D. J.; Abbenante, J.; Prager, R. H. *Eur. J. Pharmacol.* **1993**, *236*, 239–245.
11. Lapin, I. *CNS Drug Rev.* **2001**, *7*, 471–481.
12. Enders, D.; Seki, A. *Synlett* **2002**, 26–28.
13. (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Synthesis* **2004**, 1509–1521; (b) Xu, D.-Z.; Shi, S.; Wang, Y. *Eur. J. Org. Chem.* **2009**, 4848–4853; (c) Barbayianni, E.; Bouzi, P.; Constantinou-Kokotou, V.; Ragoussis, V.; Kokotos, G. *Heterocycles* **2009**, *78*, 1243–1252; (d) Chandrasekhar, S.; Kumar, T. P.; Haribabu, K.; Reddy, C. R.; Kumar, C. R. *Tetrahedron: Asymmetry* **2011**, *22*, 697–702.
14. Liu, J.; Yang, Z.; Liu, X.; Wang, Z.; Liu, Y.; Bai, S.; Lin, L.; Feng, X. *Org. Biomol. Chem.* **2009**, *7*, 4120–4127.
15. (a) Xue, F.; Zhang, S.; Duan, W.; Wang, W. *Adv. Synth. Catal.* **2008**, *350*, 2194–2198; (b) Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305–1308.
16. (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; (b) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923–925; (c) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153–156; (d) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355–1362; (e) 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; (f) Wang, L.; Xu, X.; Huang, J.; Peng, L.; Huang, Q.; Wang, L. *Lett. Org. Chem.* **2010**, *7*, 367–372; (g) Sun, Z.-W.; Peng, F.-Z.; Li, Z.-Q.; Zou, L.-W.; Zhang, S.-X.; Li, X.; Shao, Z.-H. *J. Org. Chem.* **2012**, *77*, 4103–4110; (h) Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2012**, *354*, 740–746; (i) Orlandi, S.; Pozzi, G.; Ghisetti, M.; Benaglia, M. *New J. Chem.* **2013**, *37*, 4140–4147; (j) Yu, L.; Li, P. *Tetrahedron Lett.* **2014**, *55*, 3697–3700.
17. (a) Flores-Ferrándiz, J.; Chinchilla, R. *Tetrahedron: Asymmetry* **2014**, *25*, 1091–1094; (b) Flores-Ferrándiz, J.; Fiser, B.; Gómez-Bengoa, E.; Chinchilla, R. *Eur. J. Org. Chem.* **2015**, 1218–1225.
18. Avila, A.; Chinchilla, R.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5085–5092.
19. Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609.
20. (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413–1423; (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162–172.
21. Rodríguez, J. M.; Pujol, M. D. *Tetrahedron Lett.* **2011**, *52*, 2629–2632.
22. Kuster, G. J. T.; Steeghs, R. H. J.; Scheeren, H. W. *Eur. J. Org. Chem.* **2001**, 553–560.
23. Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592.
24. Blay, G.; Incerti, C.; Muñoz, M. C.; Pedro, J. R. *Eur. J. Org. Chem.* **2013**, 1696–1705.
25. Lu, A.; Liu, T.; Wu, R.; Wang, Y.; Zhou, Z.; Wu, G.; Fang, J.; Tang, C. *Eur. J. Org. Chem.* **2010**, 5777–5781.
26. Peng, L.; Xu, X.-Y.; Wang, L.-L.; Huang, J.; Bai, J.-F.; Huang, Q.-C.; Wang, L.-X. *Eur. J. Org. Chem.* **2010**, 1849–1853.
27. Akagawa, K.; Suzuki, R.; Kudo, K. *Asian J. Org. Chem.* **2014**, *3*, 514–522.
28. (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974–12980.
29. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Menucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T., ; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrewski, V. G.; Voth,

G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian: Wallingford, CT, 2009.
30. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
31. The use of the M06-2X/6-311+G** (or closely related method) level of theory has been justified in previous H-bond organocatalyzed reactions. See for example: (a) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639; (b) Simón, L.; Goodman, J. M. *Org. Biomol. Chem.* **2011**, *9*, 689–700.
32. (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3047; (b) Tomasi, J.; Mennucci, B.; Cancès, E. J. *Mol. Struct. (Theochem.)* **1999**, *464*, 211–226.
33. Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104/1–154104/19.
34. Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
35. Legault, C. Y. *CYLview, v. 1.0b*; Université de Sherbrooke, 2009. http://www.cylview.org.

# CONCLUSIONS

1. Easily prepared primary amine-containing carbamate-monoprotected chiral *trans*-cyclohexa-1,2-diamines **1** are effective organocatalysts in the enantioselective conjugate addition of aldehydes, mainly α,α-disubstituted, to *N*-substituted maleimides, affording substituted succinimides. This process shows an unusual switching of the enantioselectivity promoted by the solvent. Thus, both (*S*)- or (*R*)-enantioenriched forms of the corresponding final succinimides are obtained employing a single mirror form of the organocatalyst, just by changing the reaction solvent from chloroform to aqueous *N*,*N*-dimethylformamide. Theoretical calculations justify this solvent dependent reversal of enantioselectivity, revealing different transition states in polar and apolar solvents.

2. These monocarbamate organocatalysts can perform the enantioselective conjugate addition of aldehydes to maleimides in Deep Eutectic Solvents (DESs) as reusable and more environmentally friendly medium, the use of an acid additive being necessary. Once the reaction is complete, the final adduct can be separated by extraction, and the DES, which retains the organocatalyst, can be reused keeping its enantiodifferentiation activity (up to 94% *ee*). These results demonstrate that the use of DESs in enantioselective organocatalytic reactions can result in efficient and green strategies, sometimes affording even better enantioselections than when conventional solvents are used.

3. The enantioselective conjugate addition of acetone and cyclic ketones to maleimides can be carried out using these organocatalysts, yielding enantioenriched substituted succinimides with moderate enantioselectivities when conventional solvents are used (up to 66% *ee*). The use of DESs as reaction medium affords lower enantioselectivities (up to 46% *ee*).

4. These organocatalysts promote the enantioselective conjugate addition of isobutyraldehyde to nitroalkenes in the presence of a basic additive, leading to enantiomerically enriched β-substituted γ-nitroaldehydes. A certain inversion of the enantioinduction of the reaction takes place due to the polarity of the solvent, as in the case of using maleimides as electrophiles, but only good enantioselectivities are obtained when using chloroform as solvent (up to 84% *ee*). However, the efficiency of the organocatalysts is poor when DESs are the reaction media, resulting in very low enantioselectivities (up to 20% *ee*).

5. The enantioselective addition of aryl ketones to nitroalkenes organocatalyzed by these monocarbamate organocatalysts and acid additives is very efficient, and leads to enantiomerically enriched β-substituted γ-nitroketones (up to 96% *ee*). Acetone is also a suitable pro-nucleophile, although producing lower enantioselections (up to 84% *ee*). Theoretical calculations indicate that the presence of an intramolecular hydrogen bond activation of the nitrostyrene with the NH of the carbamate moiety of the catalyst is responsible for the preferential enantioselection in apolar solvents. The partial rupture of the hydrogen bond in polar solvents, explains the deleterious effect of the solvent polarity on the enantioselectivity of the reaction. In this case, the use of DESs as solvents is less efficient and the enantioselection of the final adducts decreases to only moderate values (up to 60% *ee*).

# ACKNOWLEDGEMENTS

The success of this thesis depends largely on the encouragement and guidelines of many others. I would like to express my gratitude to the people who have been fundamental in the successful completion of this thesis.

First and foremost, I would like to express my sincere gratitude to my supervisor, Dr. Rafael Chinchilla for giving me the opportunity to work in his group, allowing me to grow up as a scientist. Thank you for your patient, for all your advices and for all the good moments we have lived together during the last years.

I would also like to express my gratitude to Dr. Gabriela Guillena, who initiated me in the organic chemistry research world, for her patience and support. I would also like to thank Drs. Diego Alonso, Alejandro Baeza, Pedro Bonete and Minerva Plaza for their great help and friendship.

A special mention to Dr. Beatriz Maciá, who kindly welcomed and helped me during my stay at the Metropolitan Manchester University, thank you for your hospitality, amability and guideness.

I thank my labmates for the stimulating discussions, and for all the fun we had during this time, especially to Edgar Maciá, José Ramón Martínez, Irina Sempere, Diego Felipe and Verónica Selva. I would like to thank also the secretaries of the Department and the Institute, Arturo Bernabeu, Sergio Sepulveda, Eugenia Hernaiz and Juan Carlos Sabuco and the laboratory technicians Rosa Ortiz, Joanvi Ivars and María Ángeles Chorro for their excellent assistance.

A very special gratitude goes out to all my friends who have supported me along the way. One of them, Antonio Carlos Sánchez, for the design of the cover of this thesis.

Last but not least, I wish to take this opportunity to express a sense of gratitude and love to my beloved parents Jesús and Rosi, my grandparents Miguel and Práxedes, and my brother Juan Carlos, for their support and motivation throughout this thesis and all my life in general.

# RESUMEN EN CASTELLANO

## INTRODUCCIÓN GENERAL

### 1. Síntesis asimétrica

La síntesis asimétrica abarca el conjunto de operaciones químicas enfocadas a la obtención estereoselectiva de compuestos quirales. Particularmente, la importancia de disponer de metodologías que conduzcan a la preparación enantioselectiva de compuestos reside en el hecho de que la actividad biológica y las propiedades terapéuticas de muchos fármacos están asociadas a un único enantiómero. Esto es debido a que los sistemas biológicos (enzimas, proteínas, etc.) son entidades quirales capaces de reconocer diferencialmente cada uno de los miembros de una pareja de enantiómeros y, en consecuencia, cada uno puede inducir una respuesta bioquímica diferente, hasta el punto de que un enantiómero puede actuar como un fármaco de gran valor terapéutico, mientras que el otro puede ser altamente tóxico. El ejemplo más conocido se encuentra en el caso de la talidomida, que fue comercializada entre los años 1958 y 1963 como mezcla racémica, con la trágica consecuencia de que uno de los enantiómeros era teratogénico. Las agencias de evaluación de medicamentos europea (European Medicines Agency, EMA) y americana (Food and Drug Administration, FDA) exigen desde entonces pruebas biológicas estrictas de la actividad de cada enantiómero, y la legislación actual solo permite patentar compuestos enantioméricamente puros.



Prescindiendo del aislamiento de compuestos enantioméricamente puros de plantas o animales -chiral pool-, y excluyendo asimismo su transformación en otros compuestos también enantioméricamente puros, los métodos para acceder a compuestos orgánicos no racémicos, ya sea a partir de precursores aquirales o quirales racémicos, se pueden clasificar en dos grandes categorías: las resoluciones de mezclas racémicas y las síntesis asimétricas. En las primeras, se parte de un racemato que se separa en sus componentes enantioméricos (es decir, la estereogenia se ha generado previamente), por lo que el rendimiento químico máximo alcanzable es del 50%, salvo en los casos en que la molécula es configuracionalmente lábil,

como ocurre en las resoluciones totales espontáneas y en las resoluciones cinéticas dinámicas. En las síntesis asimétricas, se controla el curso estereoquímico de una reacción mediante el empleo de una sustancia quiral (ya sea en cantidad catalítica o estequiométrica), de manera que un compuesto proquiral es transformado en un compuesto quiral enantioméricamente enriquecido, pudiéndose alcanzar un rendimiento químico del 100%. La enantioselección es consecuencia de la existencia de estados de transición diastereoméricos (y, por tanto, de diferente energía) en los que intervienen los sustratos y la sustancia quiral, y del camino preferencial a través de uno de ellos (el de menor energía), para dar mayoritariamente un enantiómero del producto final.

Los primeros métodos de control de la estereoquímica en las transformaciones orgánicas implicaban el uso de cantidades estequiométricas de un compuesto quiral que permanecía unido temporal o permanentemente al sustrato objeto de la transformación. Sin embargo, estas metodologías presentan el inconveniente de que requieren cantidades estequiométricas de un reactivo o auxiliar quiral que, en la mayoría de los casos, no se puede recuperar íntegramente y reutilizar sin pérdida de eficacia, por lo que actualmente han quedado desbancadas por la catálisis asimétrica. Esta última estrategia, que utiliza un catalizador quiral en cantidad subestequiométrica, ha supuesto una auténtica revolución en el campo de la síntesis asimétrica, ya que una única molécula de catalizador quiral es capaz de generar un elevado número de moléculas con una determinada configuración absoluta, regenerándose tras cada ciclo catalítico. Por todo lo anteriormente expuesto, las catálisis enantioselectivas constituyen las operaciones de mayor relieve dentro del ámbito de la síntesis asimétrica.

## 2. Organocatálisis enantioselectiva

Hasta finales del siglo XX las principales metodologías en la síntesis asimétrica catalítica se basaban en la utilización de procesos enzimáticos o bien catálisis con complejos de metales de transición quirales. Entre estos dos extremos surgió una tercera metodología consistente en la utilización de moléculas orgánicas quirales como catalizadores, y que se conoce como organocatálisis.

La organocatálisis enantioselectiva es una de las metodologías más novedosas y versátiles para la preparación de compuestos orgánicos enantioméricamente enriquecidos. Fue definida en el año 2000 por MacMillan, a partir del concepto de "Organic Catalysis" introducido por Langenbeck en 1932, como: "la utilización de moléculas orgánicas de bajo peso molecular como catalizadores en reacciones orgánicas". A estas moléculas se las conoce como organocatalizadores y están compuestas fundamentalmente por carbono e hidrógeno, así como por nitrógeno, oxígeno, azufre o fósforo. Estas moléculas al ser añadidas en cantidades subestequiométricas, aceleran reacciones orgánicas mediante la activación de los sustratos, de los reactivos o de ambos, sin la intervención directa de ningún átomo metálico en el estado de transición responsable de la activación (Figura 1).



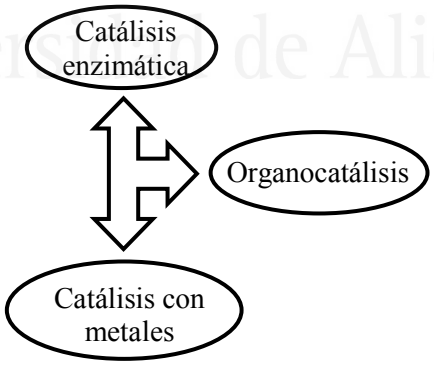



**Figura 1**. Metodologías para la síntesis enantioselectiva.

A pesar del reciente reconocimiento e introducción de la organocatálisis en la catálisis asimétrica, sus raíces históricas datan de la primera mitad del siglo XX, cuando se utilizaban compuestos orgánicos de bajo peso molecular para imitar los mecanismos responsables de la actividad catalítica y selectividad de las enzimas. Sin embargo, hasta finales del siglo pasado se publicaron solo un número reducido de transformaciones enantioselectivas empleando organocatalizadores (principalmente alcaloides de Cinchona y aminoácidos) con fines preparativos, como en el caso de la síntesis de la cetona de Wieland-Miescher, catalizada por L-prolina, en la reacción de Hajos-Parrish-Eder-Sauer-Wiechert.

Sin embargo, es durante los últimos quince años cuando la organocatálisis enantioselectiva ha evolucionado a un ritmo extraordinario, hasta convertirse en una próspera área con una amplia diversidad de aplicaciones, consolidándose como una tercera metodología dentro del ámbito de la síntesis asimétrica, de central importancia tanto en el entorno académico como en el industrial. Uno de los factores principales de esta rápida evolución ha sido la ayuda de cálculos computacionales, que han permitido avanzar enormemente en el conocimiento de los mecanismos de reacción.

Los organocatalizadores utilizados en organocatálisis enantioselectiva generalmente no son caros, suelen ser robustos, y pueden ser tomados directamente de la naturaleza, como es el caso de α-aminoácidos, α-hidroxiácidos, péptidos y glúcidos. Además, suelen ser más estables que los complejos metálicos o los biocatalizadores por lo que no es necesario mantener condiciones inertes dado que las reacciones se pueden realizar bajo una atmósfera aeróbica y con disolventes húmedos. Por último, la recuperación del organocatalizador suele ser más simple que en el caso de catalizadores basados en complejos metálicos o en biocatalizadores, pudiéndose anclar a un soporte sólido y reutilizar de una manera más eficaz que los análogos organometálicos o bioorgánicos, lo que supone una gran ventaja para su utilización en aplicaciones industriales.

Fue en el año 2008 cuando MacMillan describió, desde un punto de vista mecanístico, una clasificación general de los modos genéricos de activación en base al tipo de interacción entre el organocatalizador y el/los sustratos en el estado de transición responsable de la activación, distinguiendo entre aquellos procesos que implican la formación de aductos covalentes dentro del ciclo catalítico (catálisis covalente, Figura 2) y aquéllos basados en interacciones débiles no covalentes, tales como el enlace de hidrógeno o la formación de pares iónicos íntimos (catálisis no covalente, Figura 2).

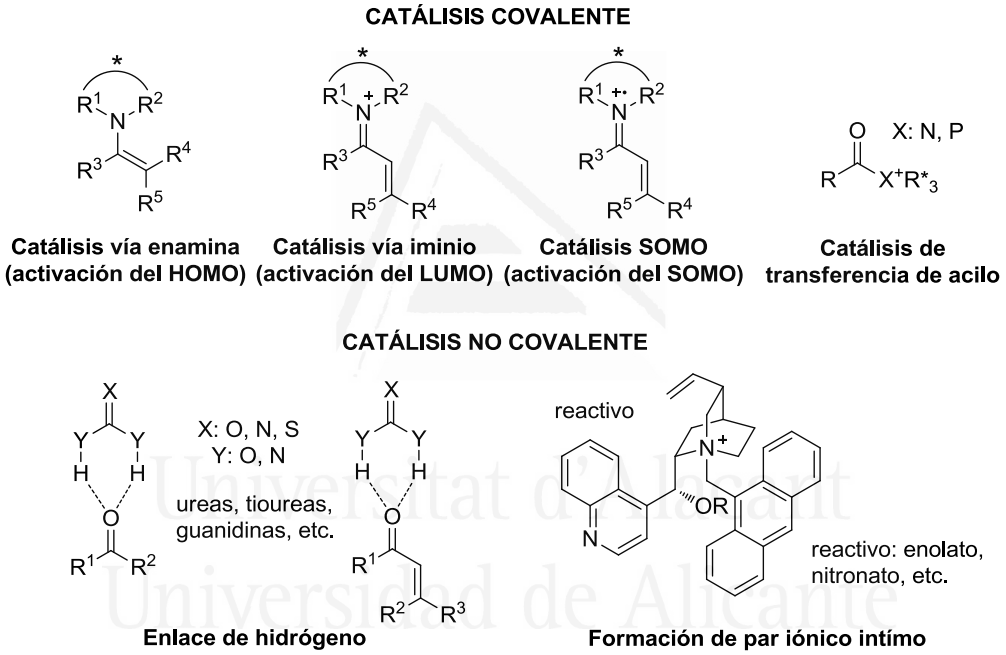



**Figura 2.** Ejemplos de modos de activación en procesos organocatalizados.

La mayor parte de las transformaciones organocatalizadas se desarrollan vía catálisis covalente. A este grupo pertenecen las reacciones mediadas por catalizadores amínicos, incluyendo los procesos que implican el llamado ciclo de la enamina (activación del HOMO del nucleófilo), y las reacciones aceleradas mediante la formación de intermedios iminio (activación del LUMO del electrófilo). Las transformaciones catalizadas a través de la activación del SOMO del sustrato, reacciones de transferencia del grupo acilo catalizadas por aminas o fosfanos, la

reacción de Morita-Baylis-Hillmann, reacciones mediadas por carbenos, así como reacciones de iluro asimétricas, también corresponden a esta categoría.

Por otra parte, la organocatálisis no covalente se basa en la aceleración de la reacción mediante interacciones débiles entre el catalizador y el sustrato, siendo estas interacciones del tipo ácido-base: formación de pares iónicos y de enlaces de hidrógeno.

## 3. Organocatálisis enantioselectiva en medios alternativos: Disolventes Eutécticos Profundos

Los disolventes empleados tradicionalmente en síntesis orgánica son compuestos orgánicos volátiles (VOCs). Los VOCs han demostrado ser una de las principales fuentes de contaminación medioambientales, y a su vez, representan un riesgo para la salud de quienes los manejan. Es por este principal motivo que en los últimos años se haya incrementado el uso de los disolventes eutécticos profundos (DESs) en síntesis orgánica como medio de reacción ecológico y reutilizable.

Los DESs son líquidos a temperatura ambiente y se forman a partir de una mezcla eutéctica: una composición única de dos o más componentes sólidos que sufren un cambio de fase a una temperatura determinada. Este punto de fusión tan bajo en los DESs se debe principalmente a la formación de una extensa red tridimensional mediante enlace de hidrógeno a partir de los componentes de la mezcla.

Los DESs presentan un alto potencial para sustituir a los VOCs tradicionales ya que poseen varias ventajas frente a ellos, tales como: su nula presión de vapor, su origen renovable, su inexistente o muy baja toxicidad, la elevada economía atómica en su formación y su alta solubilidad en agua hace que los productos orgánicos precipiten o aparezcan como una capa insoluble, evitando la extracción con disolventes orgánicos en el final de la reacción.

A pesar de las ventajas que presenta el uso de DES en síntesis orgánica, sólo un reducido número de artículos que estudian reacciones organocatalizadas enantioselectivas han sido publicadas hasta la fecha.

Dadas las ventajas que presentan los DESs con respecto a los VOCs tradicionales, se decidió estudiar el efecto que presentan estos nuevos disolventes en diferentes reacciones de adición Michael.

## CAPÍTULO I. AMINOCARBAMATOS QUIRALES COMO ORGANOCATALIZADORES EN LA REACCIÓN MICHAEL DE ALDEHÍDOS Y CETONAS A MALEIMIDAS

### 1. Antecedentes

Las succinimidas quirales son unidades estructurales encontradas en productos naturales y algunos candidatos para fármacos (Figura 3). Desde el estudio de Komura y colaboradores en 1987, sobre la obtención de la Andrimida como nuevo antibiótico altamente específico, las succinimidas 1,3-sustituidas y 3,4-disustituidas han emergido como una nueva clase de productos naturales con una importante actividad biológica.

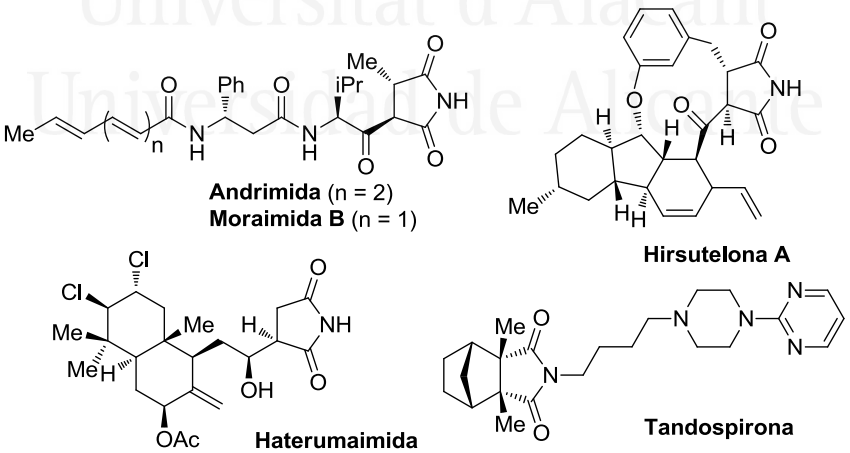



**Figura 3.** Productos naturales con unidades de succinimidas en su estructura.

Así, las succinimidas quirales Andrimida y Moiramida B exhiben una actividad antibacterial *in vitro* potente contra el *Staphylococcus aureus*, un agente resistente a la meticilina, y contra un gran rango de otros agentes patógenos humanos resistentes a los antibióticos. Por otra parte, la Hirsutelona A muestra actividad inhibidora contra la *Mycobacterium tuberculosis H37Ra*, mientras que la Haterumaimida A tiene interés debido a su uso potencial como inhibidor en la síntesis de proteínas y como fármaco antitumoral. La estructura de succinimida quiral está también presente en la Tandospirona, un fármaco ansiolítico y antidepresivo. Además, las succinimidas pueden ser transformadas en otros compuestos interesantes, tales como las γ-lactamas, las cuales son importantes en el tratamiento de la epilepsia, VIH, enfermedades neurodegenerativas y depresión.

La obtención de succinimidas quirales sustituidas puede lograrse de forma directa mediante la funcionalización de maleimidas. Las maleimidas son un importante grupo de sustratos y han sido usadas con éxito en transformaciones asimétricas.

La reacción de adición Michael enantioselectiva de carbonos nucleofílicos a maleimidas es probablemente el método más directo para preparar succinimidas quirales enantioenriquecidas empleando una estrategia organocatalítica. Dicha adición se ha conseguido frecuentemente partiendo de especies pro-nucleofílicas que poseen hidrógenos ácidos en α usando compuestos quirales bifuncionales como organocatalizadores, que poseen un grupo con hidrógenos capaces de formar enlaces de hidrógeno, y una amina terciaria. Así, la enantioinducción es lograda tras la formación del estado de transición, el cual engloba la coordinación de la maleimida con los hidrógenos ácidos del organocatalizador, y el enolato formado tras desprotonación del pro-nucleófilo con la amina terciaria.

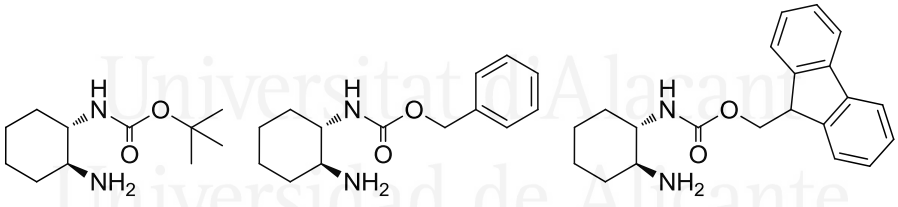
Sin embargo, los aldehídos y cetonas son especies pro-nucleofílicas que presentan una difícil α-desprotonación para la formación del enolato, por lo que, necesitan un mecanismo de activación diferente. Es por ello que se han sintetizado

nuevos organocatalizadores en los cuales el esqueleto de la molécula presenta una amina primaria o secundaria, en vez de terciaria, como agente de activación del pro-nucleófilo en el estado de transición durante el proceso estereoselectivo. Así, la creación de una enamina transitoria con el catalizador es la forma de activar el compuesto carbonílico, convirtiéndolo en nucleófilo.

De entre los organocatalizadores que han sido utilizados para la adición Michael enantioselectiva de aldehídos y cetonas a maleimidas, destacan los organocatalizadores bifuncionales derivados de *trans*-ciclohexano-1,2-diaminas enantiopuras, que son auxiliares quirales comúnmente empleados, y que poseen funcionalidades tales como un grupo amino primario y la posibilidad de formar enlaces de hidrógeno con el carbonilo de la maleimida.

**2. Objetivos**

**1.** Sintetizar organocatalizadores a partir de *trans*-ciclohexano-1,2-diaminas enantiopuras **1**, que poseen una amina primaria y los grupos carbamato protectores Boc, Cbz y Fmoc.

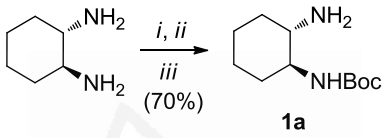



**2.** Estudiar el uso de estos derivados quirales **1** como organocatalizadores en reacciones de adición Michael enantioselectivas de aldehídos y cetonas a maleimidas, con el fin de sintetizar las correspondientes succinimidas enantioméricamente enriquecidas. Estudiar dicha actividad catalítica en disolventes orgánicos convencionales (VOCs) y en disolventes eutécticos profundos (DESs), disolventes medioambientalmente más favorables.

## 3. Discusión de resultados

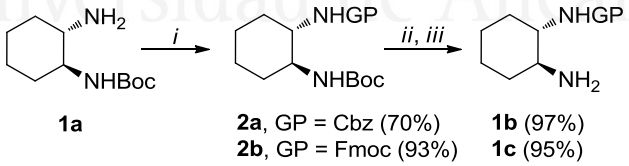
### 3.1. Síntesis de los organocatalizadores

Los aminocarbamatos quirales **1a**, **1b**, y **1c**, que han sido empleados como organocatalizadores en este estudio, fueron preparados a partir de (1*S*,2*S*)-ciclohexano-1,2-diamina. El aminocarbamato quiral **1a**, con el grupo *terc*-butoxicarbonilo, se obtuvo por mono-Boc protección de uno de los grupos amino, tal y como se muestra en el Esquema 1:




**Esquema 1**. (i) HCl (2M en $Et_2O$), 25 ºC; (ii) $(Boc)_2O$, MeOH, 25 ºC; (iii) NaOH (2M), 25 ºC.

Los aminocarbamatos **1b** y **1c**, con los grupos protectores benciloxicarbonilo (Cbz) y 9-fluorenilmetoxicarbonilo (Fmoc) respectivamente, se obtuvieron por reacción de los cloroformiatos correspondientes con **1a**, obteniendo los intermedios diprotegidos **2a** y **2b**. El posterior tratamiento con ácido trifluoroacético (TFA) para la desprotección del grupo protector Boc dio lugar a los aminocarbamatos correspondientes (Esquema 2).

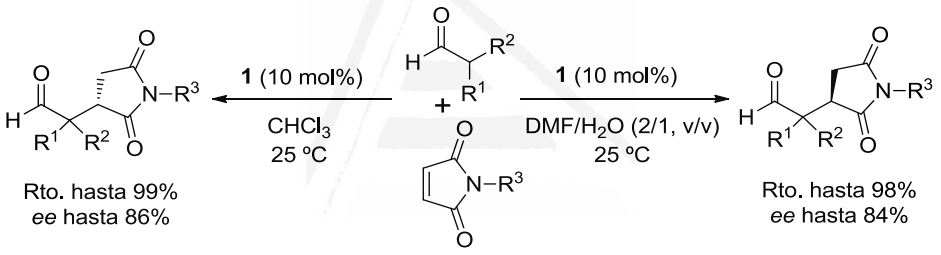



**Esquema 2**. (i) CbzCl (**2b**) o FmocCl (**2c**), $NaHCO_3$ (ac), dioxano, 25 ºC; (ii) TFA, $CH_2Cl_2$, 25 ºC; (iii) $NH_4OH$, $CH_2Cl_2$, 25 ºC.

Estos organocatalizadores derivados de (1*S*,2*S*)-ciclohexano-1,2-diamina se han utilizado en reacciones de adición Michael enantioselectiva de aldehídos y cetonas a maleimidas, para sintetizar succinimidas enantioméricamente enriquecidas.

### 3.2. Adición Michael enantioselectiva de aldehídos a maleimidas

En la reacción de adición conjugada de isobutiraldehído a *N*-fenilmaleimida en disolventes convencionales, se ha descubierto que estos organocatalizadores permiten obtener ambos enantiómeros de la correspondiente succinimida utilizando solo una forma enantiomérica del catalizador, simplemente variando la polaridad del disolvente. Así, empleando una sola forma enantiomérica del organocatalizador quiral, y variando el disolvente de la reacción, es posible obtener ambos enantiómeros de las succinimidas correspondientes. Esta metodología sintética puede ampliarse a diferentes aldehídos y maleimidas, obteniéndose excesos enantioméricos de hasta el 86% en medios apolares, y del 84% en medios polares (Esquema 3).




**Esquema 3**. Adición Michael enantioselectiva de aldehídos a maleimidas en disolventes convencionales.

Se han realizado cálculos teóricos para justificar el mecanismo a través del cual se producía esta inversión de la enantioinducción con el disolvente. Así, se han propuesto dos posibles estados de transición, uno para disolventes apolares en donde la maleimida se coordina con el organocatalizador mediante enlaces de hidrógeno (Figura 4, a), y otro para disolventes polares en los cuales la formación de enlaces de hidrógeno con el organocatalizador está impedido por la presencia de moléculas de agua que solvatan los reactivos (Figura 4, b).

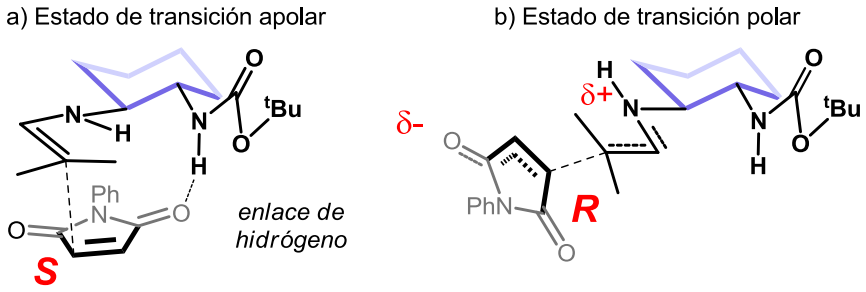
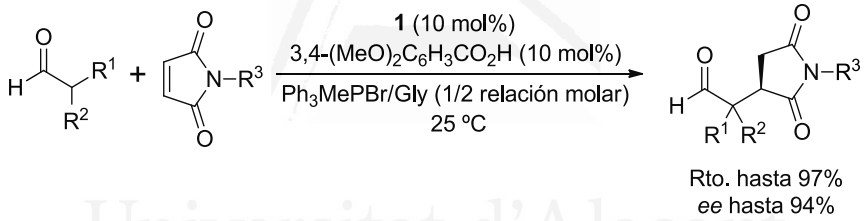



**Figura 4.** Estados de transición propuestos para justificar la inversión de la enantioinducción.

Además, estos organocatalizadores pueden ser utilizados en la reacción de adición Michael enantioselectiva de aldehídos a maleimidas, utilizando DESs como medio de reacción reciclable y medioambientalmente sostenible, obteniendo las succinimidas con excelentes rendimientos y altas enantioselectividades, hasta el 94%, al utilizar un DES compuesto por bromuro de trifenilmetil fosfonio y glicerol, en una relación molar 1/2, junto con un aditivo ácido a 25 ºC (Esquema 4).




**Esquema 4**. Adición Michael enantioselectiva de aldehídos a maleimidas en DESs

Las succinimidas pueden ser extraídas del DES, en el que el organocatalizador quiral se mantiene retenido, permitiendo la reutilización tanto del disolvente como del catalizador. Así, tras la adición de nuevos reactivos y de aditivo ácido, la reacción se pudo llevar a cabo hasta un cuarto ciclo de reacción sin aparente pérdida de enantioselectividad (Figura 5).

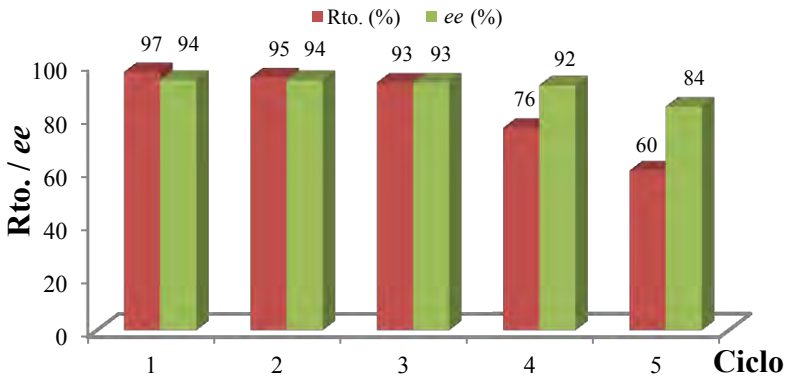
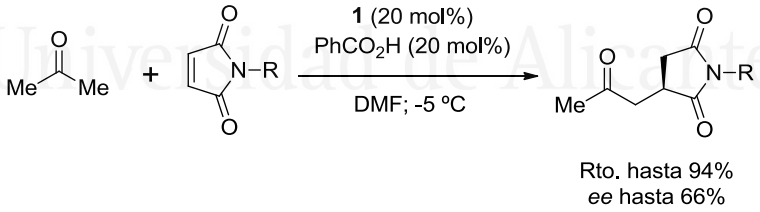



**Figura 5**. Resultados para experimentos de reciclado.

### 3.3. Adición Michael enantioselectiva de cetonas a maleimidas

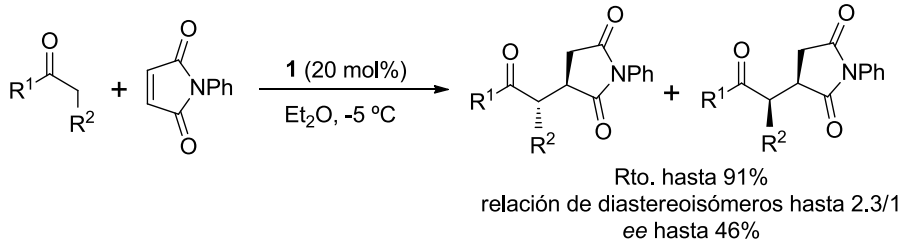
Los organocatalizadores derivados de (1*S*,2*S*)-ciclohexano-1,2-diamina **1** han sido eficaces también en la reacción de adición conjugada de acetona a maleimidas en disolventes convencionales permitendo obtener las correspondientes succinimidas con excelentes rendimientos y moderadas enantioselectividades, hasta el 66%, al llevar a cabo la reacción utilizando DMF como disolvente, ácido benzóico como aditivo y a una temperatura de reacción de -5 ºC (Esquema 6). Al tratar de llevar a cabo la reacción de adición con otras cetonas acíclicas, no se pudo obtener los correspondientes productos de adición.




**Esquema 5**. Adición Michael enantioselectiva de acetona a maleimidas.

Al tratar de expandir la metodología encontrada para la adición Michael de acetona a otras cetonas cíclicas, no se obtuvieron las succinimidas con buenos resultados, por lo que fue necesario estudiar nuevas condiciones para llevar a cabo la reacción de adición, cambiando el uso de DMF como disolvente por dietil éter, manteniendo la temperatura de reacción a -5 ºC (Esquema 6). Con estas nuevas

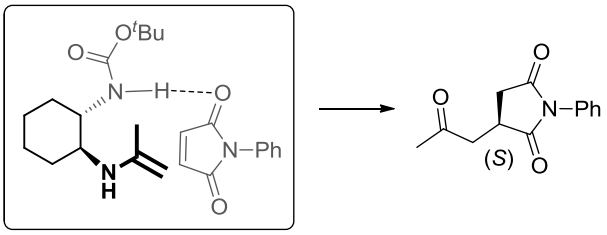
condiciones, se pudieron aislar los productos de adición con excelentes rendimientos, con una relación de diastereoisómeros de hasta 2.3/1, y con enantioselectividades de hasta el 46%.




**Esquema 6**. Adición Michael enantioselectiva de cetonas cíclicas a maleimidas.

La reacción de adición de Michael entre acetona y *N*-fenilmaleimida se estudió también con el uso DESs como disolventes medioambientalmente más favorables. Sin embargo, las enantioselectividades obtenidas, hasta un 46%, fueron inferiores a las obtenidas al llevar a cabo la reacción en disolventes convencionales. Los mejores resultados se obtuvieron con un DES compuesto por cloruro de colina y urea, en una relación molar 1/2, en presencia de un aditivo ácido a una temperatura de 25 ºC.

Las enantioselectividades obtenidas y los cálculos teóricos realizados al utilizar aldehídos permitieron sugerir un posible modelo de coordinación adecuado capaz de justificar los resultados observados. De este modo, la acetona reaccionaría con la amina primaria del organocatalizador, formando una intermedio enamina, mientras que un grupo carbonilo de la maleimida estaría coordinado a la amina del grupo carbamato a través de un enlace de hidrógeno. Esta coordinación favorecería la reacción de adición de Michael por la cara *Si* de la maleimida, dando lugar al resultado estereoquímico observado (Esquema 7).




**Esquema 7**. Modelo de coordinación propuesto.

## CAPÍTULO II. AMINOCARBAMATOS QUIRALES COMO ORGANOCATALIZADORES EN LA REACCIÓN MICHAEL DE ALDEHÍDOS Y CETONAS A NITROOLEFINAS

### 1. Antecedentes

La preparación enantioselectiva de compuestos γ-nitrocarbonílicos ha obtenido una gran importancia en los últimos años por ser considerados como precursores clave para muchos compuestos de alto valor añadido. Esto se debe al hecho de que el grupo nitro puede ser transformado fácilmente en un gran variedad de compuestos relevantes (Figura 6), como las aminas. De hecho, esta habilidad del grupo nitro para permanecer "enmascarado" y posteriormente ser transformado le ha llevado a ser conocido como un "camaleón sintético".



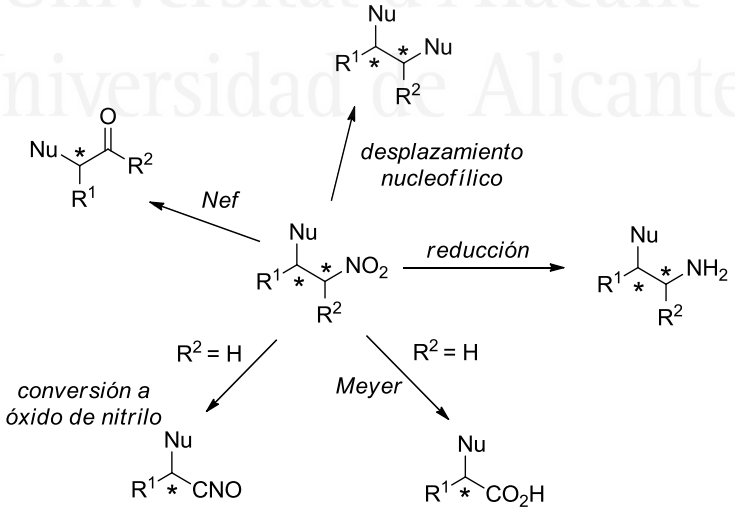



**Figura 6.** Utilidad sintética del grupo nitro.

Particularmente, los γ-nitroaldehídos y γ-nitrocetonas pueden ser usados como intermediarios en la preparación de alcaloides, aminoácidos, antitumorales, antibióticos, peptidomiméticos, metabolitos marinos y ácidos β-arilados así como importantes análogos del ácido γ-aminobutárico (GABA) que exhiben un gran rango de actividades farmacológicas, desempeñando papeles como antidepresivos, anticonvulsionantes y ansiolíticos, entre otros. Baclofen y Fenibut representarían dos ejemplos comercializados de derivados de GABA sintetizados a partir de γ-nitrocetonas enantioenriquecidas (Figura 7). Baclofen (vendido como racemato) se usa en el tratamiento de la espasticidad. Además, estudios recientes han demostrado que el (*R*)-Baclofen es más eficaz que su enantiómero para el tratamiento del autismo (STX209 o Arbaclofen). Fenibut es un fármaco nootrópico usado como tranquilizante, en el que el enantiómero *R* resulta ser 100 veces más potente que el *S*.

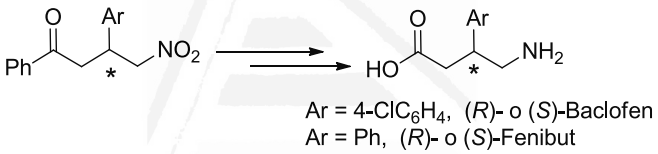
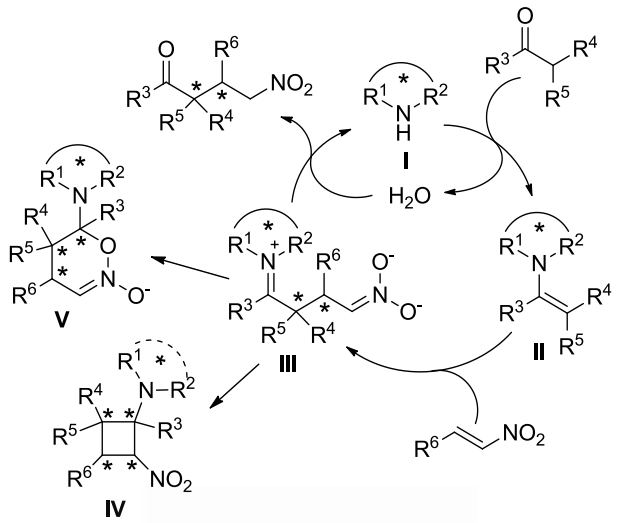



**Figura 7.** Síntesis de Baclofen y Fenibut a partir de γ-nitrocetonas.

Hoy en día, la reacción de adición Michael enantioselectiva de compuestos carbonílicos enolizables, en particular aldehídos y cetonas, a nitroalquenos, promovida por un organocatalizador quiral, es uno de los procedimientos más comunes y convenientes para conseguir la síntesis de compuestos γ-nitrocarbonílicos de manera enantioenriquecida.

Con respecto al mecanismo de este proceso, el ciclo catalítico aceptado a día de hoy involucra la presencia de enaminas como nucleófilos (Esquema 8). La presencia de aditivos que actúen como co-catalizadores, principalmente ácidos carboxílicos, es necesaria frecuentemente para conseguir buenos rendimientos ópticos y químicos. Así, la amina quiral que actúa como organocatalizador **I** reaccionaría con el compuesto carbonílico formando la enamina **II** (para aminas primarias, $R^1$=H, inicialmente una imina en equilibrio tautomérico con una

enamina), que otorgaría estereoselectividad a la nitroolefina, lo cual llevaría al nitronato **III** como aducto. Este aducto es entonces hidrolizado conduciendo al compuesto γ-nitrocarbonílico final y al organocatalizador inicial, la amina. Resulta interesante destacar que se ha observado la formación del ciclobutano **IV** y el *N*-óxido de 1,2-oxazina **V** a lo largo de este proceso, siendo estos compuestos productos secundarios del organocatalizador. Su formación "retiraría" la amina catalítica del ciclo, lo que podría explicar la frecuente necesidad de añadir co-catalizadores ácidos para la obtención de buenos resultados. La presencia de un ácido no solo favorecería un equilibrio imina-enamina más rápido, sino que además protonaría el nitronato **III**, bloqueando la formación de los subproductos **IV** y **V**. Esta situación podría ser, a su vez, alcanzada internamente si la amina catalítica poseyera alguna funcionalidad ácida. De hecho, existen evidencias de que, al menos en algunos casos, esto facilitaría la re-formación de la enamina a partir de los intermediarios **III**, **IV** y **V**, con la estereoselectividad siendo en este caso controlada por la diastereoselectividad de la protonación de la enamina. Además, la presencia de bases orgánicas ha presentado en ocasiones buenos efectos como co-catalizadores, ya que pueden acelerar la reacción al favorecer la formación del intermediario de la enamina. Asimismo, si la amina catalítica presenta, además, grupos con capacidad de formar enlaces de hidrógeno (organocatalizadores bifuncionalizados), el grupo nitro del nitroalqueno quedará coordinado durante la reacción. Así, la enamina y el electrófilo se encontrarán lo suficientemente próximos el uno del otro como para proporcionar un alto valor en cuanto a la enantioinducción del producto esperado.



**Esquema 8.** Ciclo catalítico de la adición conjugada de aldehídos y cetonas a nitroalquenos promovido por aminas quirales primarias o secundarias.

Existe un número muy elevado de organocatalizadores bifuncionales que han sido utilizados para la adición Michael enantioselectiva de aldehídos y cetonas a nitroolefinas. Entre ellos destacan los derivados de *trans*-ciclohexano-1,2-diaminas enantiopuras, que son auxiliares quirales comúnmente empleados, y que poseen funcionalidades tales como un grupo amino primario y la posibilidad de formar enlaces de hidrógeno con el grupo nitro.

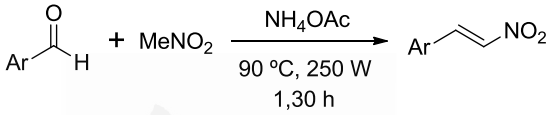
## 2. Objetivos

**1.** Estudiar la utilización de los aminocarbamatos quirales **1** como organocatalizadores en reacciones de adición Michael enantioselectivas de aldehídos y cetonas a nitroolefinas, con el fin de sintetizar compuestos γ-nitroaldehídos y γ-nitrocetonas enantioméricamente enriquecidos. Estudiar dicha actividad catalítica en disolventes orgánicos convencionales y en líquidos eutécticos profundos (DES).

## 3. Discusión de resultados

### 3.1. Preparación de los β-nitroalquenos

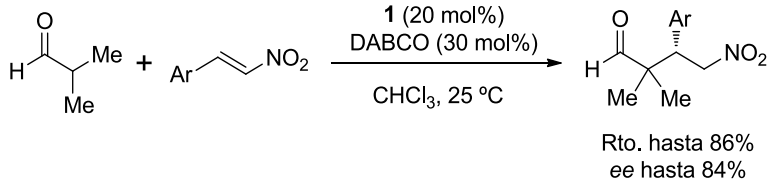
Los β-nitroalquenos aromáticos empleados en el presente estudio como aceptores Michael se obtuvieron comercialmente o se sintetizaron siguiendo un procedimiento previamente descrito, consistente en la reacción entre el correspondiente aldehído con nitrometano, en presencia de acetato de amonio y a 90 ºC, bajo la influencia de microondas (Esquema 8).




**Esquema 8.** Síntesis de β-nitroalquenos por microondas

### 3.2. Adición Michael enantioselectiva de aldehídos a nitroolefinas

Los organocatalizadores derivados de (1*S*,2*S*)-ciclohexano-1,2-diamina se utilizaron para llevar a cabo la adición de isoburiraldehído a *trans*-β-nitroestireno, observando al igual que en el Capítulo I, una ligera inversión en la enantioselectividad dependiente de la polaridad del medio de reacción. No obstante, para esta reacción de adición, la inversión en la enantioselectividad no fue capaz de alcanzar valores decentes en medios polares, obteniéndose los mejores valores de exceso enantiomérico para medios apolares. De este modo, utilizando disolventes como cloroformo y un aditivo básico como el DABCO (1,4-diazabiciclo[2.2.2]octano) a una temperatura de reacción de 25 ºC, se obtuvieron los correspondientes γ-nitroaldehídos con buenas enantioselectividades, hasta el 84% (Esquema 9).

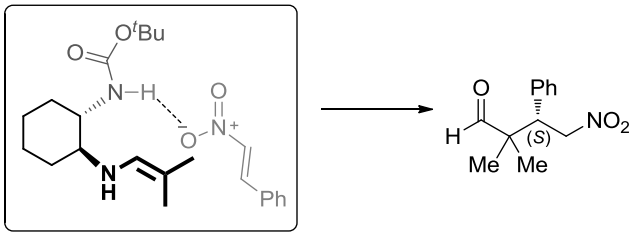



**Esquema 9**. Adición Michael enantioselectiva de isobutrialdehído a nitroolefinas.

La reacción de adición de Michael entre acetofenona y *trans*-β-nitroestireno también se estudió con el uso DESs como disolventes reciclables. Sin embargo, las enantioselectividades obtenidas, hasta un 20%, fueron inferiores en comparación a las obtenidas al llevar a cabo la reacción en disolventes convencionales. Los mejores resultados se obtuvieron al utilizar el DES formado por cloruro de colina y urea, en una relación molar 1/2, en presencia de un aditivo básico y llevando a cabo la reacción a 25 ºC.

Las enantioselectividades obtenidas permitieron sugerir un posible modelo de coordinación para justificar los resultados observados. Así, el isobutiraldehído reaccionaría con la amina primaria para formar un enamina intermedio, mientras que el grupo nitro estaría coordinado a la amina secundaria a través de un enlace de hidrógeno. Esta estructura de coordinación favorecería la reacción de adición de Michael en una cara del *trans*-β-nitroestireno, dando lugar a la estereoquímica observada (Esquema 10). La presencia de disolventes polares evitaría la coordinación del grupo nitro. En este caso, el resto carbamato solo actuaría como un grupo que impediría estéricamente el acercamiento del nitroalqueno al lado opuesto de la enamina, conduciendo preferentemente al otro enantiómero. Sin embargo, en este caso el efecto de bloqueo parece no ser tan eficaz como se muestra en el capítulo I, por lo que la enantioselectividad del enantiómero opuesto resulta mucho más baja.

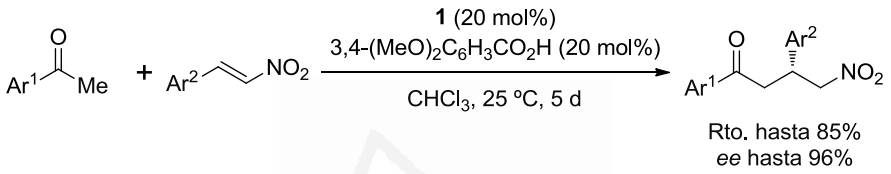





**Esquema 10**. Modelo de coordinación propuesto.

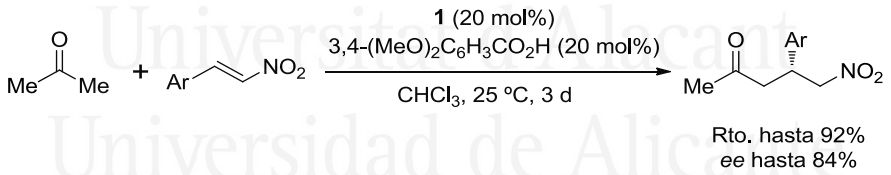
### 3.3. Adición Michael enantioselectiva de cetonas a nitroolefinas

La reacción de adición conjugada enantioselectiva de cetonas aromáticas a nitroolefinas, utilizando los organocatalizadores derivados de (1*S*,2*S*)-ciclohexano-1,2-diamina **1** permitió obtener interesantes γ-nitrocetonas con una muy alta enantioselectividad, hasta el 96%, al llevar a cabo la reacción utilizando cloroformo como disolvente y un aditivo ácido, a una temperatura de reacción de 25 ºC (Esquema 11).



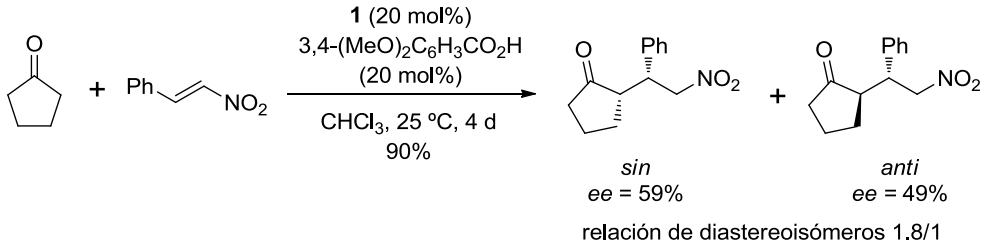

**Esquema 11**. Adición Michael enantioselectiva de cetonas aromáticas a nitroolefinas.

También pudo llevarse a cabo la adición Michael enantioselectiva de acetona a diferentes nitroolefinas, siendo las correspondientes enantioselectivas obtenidas inferiores a cuando se utilizaron cetonas aromáticas, hasta un 84% (Esquema 12).




**Esquema 12**. Adición Michael enantioselectiva de acetona a nitroolefinas.

Al llevar a cabo el estudio en la adición conjugada de cetonas cíclicas, únicamente la ciclopentanona fue capaz de reaccionar con el *trans*-β-nitroestireno para dar la correspondiente γ-nitrocetona como una mezcla de diastereoisómeros 1.8/1 *sin*/*anti* (Esquema 13).




**Esquema 13**. Adición Michael enantioselectiva de ciclopentanona a *trans*-β-nitroestireno.

La reacción de adición de Michael entre acetofenona y *trans*-β-nitroestireno también se estudió con el uso DES como nuevos disolventes medioambientalmente más favorables y reciclables. Sin embargo, las enantioselectividades obtenidas, hasta un 60%, fueron inferiores a las obtenidas al llevar a cabo la reacción en disolventes convencionales. Este valor de 60% *ee* se obtuvo al llevar a cabo la reacción utilizando el DES formado por cloruro de colina y glicerol, en una relación 1/2, utilizando un aditivo ácido y llevando a cabo la reacción a 25 ºC.

Se realizaron cálculos teóricos para tratar de justificar el mecanismo a través del cual se produce este proceso enantioselectivo. Se encontró que, si la reacción se realiza en un sistema apolar, los estados de transición de menor energía, llevan asociada la activación por enlace de hidrógeno con el organocatalizador quiral, lo que explica la formación altamente enantioselectiva del enantiómero *R* (Figura 8). A medida que aumenta la polaridad del disolvente, los estados de transición polar (Figura 9) ganan relevancia, induciendo un efecto perjudicial sobre la enantioselectividad dado que la presencia de moléculas de agua impiden la formación de los enlaces de hidrógeno con el organocatalizador. Además, estos resultados también coinciden con el sentido químico común, por el cual los enlaces de hidrógeno intramoleculares son más fuertes en disolventes apolares, mientras que los enlaces de hidrógeno intermoleculares con moléculas de agua circundantes están presentes en sistemas acuosos.

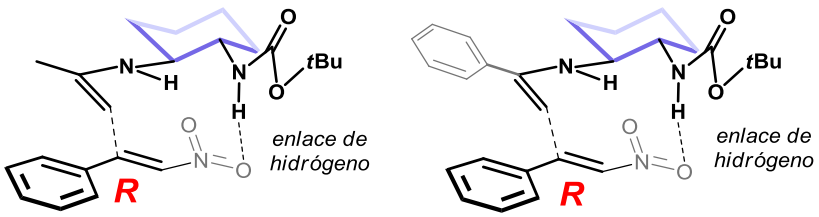



**Figura 8**. Estados de transición propuestos en disolventes apolares.

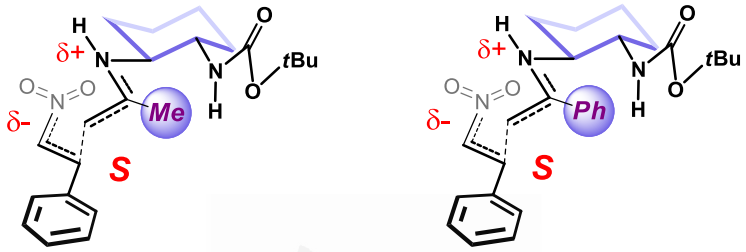



**Figura 9** Estados de transición propuestos en disolventes polares.

## CONCLUSIONES

**1.** Los aminocarbamatos derivados de *trans*-ciclohexano-1,2-diaminas enantioméricamente puras monoprotegidos con los grupos Boc, Cbz y Fmoc, han sido utilizados como organocatalizadores en la adición Michael enantioselectiva de aldehídos, principalmente α,α-disustituidos, a maleimidas *N*-sustituidas. Este proceso muestra un cambio inusual de la enantioselectividad promovida por el disolvente. De este modo, se obtienen ambas formas (*S*)- o (*R*)-enantioenriquecidas de las succinimidas finales correspondientes empleando una única forma enantiomérica del organocatalizador, simplemente cambiando el disolvente de reacción de cloroformo a *N*,*N*-dimetilformamida acuosa. Los cálculos teóricos justifican esta inversión de la enantioselectividad, dependiente del disolvente, revelando diferentes estados de transición en disolventes polares y apolares.

**2.** Estos organocatalizadores pueden realizar la adición conjugada enantioselectiva de aldehídos a maleimidas, en disolventes Eutécticos Profundos (DESs) como medio reutilizable y más respetuoso con el medio ambiente, siendo necesario el uso de un aditivo ácido. Una vez completada la reacción, el aducto final

puede separarse por extracción, y el DES, que retiene el organocatalizador, puede reutilizarse manteniendo su actividad de enantiodiferenciación (hasta 94% *ee*). Estos resultados demuestran que el uso de DESs en reacciones organocatalíticas enantioselectivas puede resultar en estrategias eficientes y verdes, que a veces ofrecen enantioselectividades aún mejores que cuando se usan disolventes convencionales.

**3.** La adición conjugada enantioselectiva de acetona y cetonas cíclicas a maleimidas puede llevarse a cabo usando estos organocatalizadores, produciendo succinimidas sustituidas enantioenriquecidas con moderadas enantioselectividades cuando se usan disolventes convencionales (hasta 66% *ee*). El uso de los DESs como medio de reacción proporciona enantioselectividades inferiores (hasta 46% *ee*).

**4.** Estos organocatalizadores permiten también realizar la adición conjugada enantioselectiva de isobutiraldehído a nitroalquenos en presencia de un aditivo básico, que conduce a γ-nitroaldehídos β-sustituidos enantioméricamente enriquecidos. Se produce una cierta inversión de la enantioinducción de la reacción debido a la polaridad del disolvente, como en el caso de la utilización de maleimidas como electrófilos, pero sólo se obtienen buenas enantioselectividades cuando se usa cloroformo como disolvente (hasta 84% *ee*). Sin embargo, la eficiencia de los organocatalizadores es pobre cuando los DESs son los medios de reacción, lo que da lugar a enantioselectividades muy bajas (hasta 20% *ee*).

**5.** La adición enantioselectiva de aril cetonas a nitroalquenos organocatalizada por los organocatalizadores derivados de *trans*-ciclohexano-1,2-diaminas, junto con un aditivo ácido, conduce a γ-nitrocetonas β-sustituidas enantioméricamente enriquecidas (hasta 96% *ee*). La acetona también es un pro-nucleófilo adecuado, aunque produce enantioselectividades inferiores (hasta 84% *ee*). Los cálculos teóricos indican que, la presencia de una activación por enlace de hidrógeno intramolecular del nitroestireno con el NH del carbamato del catalizador,

es responsable de la enantioselección preferencial en disolventes apolares. La ruptura parcial del enlace de hidrógeno en disolventes polares, explica el efecto deletéreo de la polaridad del disolvente sobre la enantioselectividad de la reacción. En este caso, el uso de los DESs como disolventes es menos eficiente y la enantioselección de los aductos finales disminuye a valores sólo moderados (hasta 60% *ee*).