Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

Scienze Chimiche

Ciclo XXXI

Settore Concorsuale: 03/C1

Settore Scientifico Disciplinare: CHIM/06

BREAKING REACTIVITY BORDERS: ENGINEERING STEREOSELECTIVE REACTIONS WITH ORGANOCATALYTIC TOOLS

Presentata da: Vasco Corti

Coordinatore Dottorato

Prof. Aldo Roda

Supervisore

Prof. Luca Bernardi

Co-Supervisore

Prof.ssa Mariafrancesca Fochi

Esame finale anno 2019

Table of contents

1 Introduction

1.1 Activation modes in asymmetric organocatalysis

The discovery of new catalytic reactions is of fundamental importance to solve challenging problems in organic chemistry. The advent of asymmetric catalysis let to the development of an enormous number of methodologies to access chiral products in enantioenriched form.[1] Historically, organic reactions promoted by catalytic amounts of metal complexes with chiral ligands represented milestones of this field, resulting in 2001 in the Nobel Prize to K. Barry Sharpless for the Ti-tartrate catalytic asymmetric epoxidation of allylic alcohols[2] and to Ryoji Noyori for the BINAP-Ru catalytic asymmetric hydrogenation of ketones.[3] In early 2000, the organic chemistry community has witnessed an incredible blossoming of literature reports dealing with the development of catalytic enantioselective reactions promoted by chiral small organic molecules. It is wide accepted, by now, that organocatalysis is one of the main branches of enantioselective synthesis along with the other two previously accepted enzymatic catalysis and transition metal catalysis. The success of organocatalysis as reliable platform for reaction engineering is undoubtedly addressed to the discovery and development of new generic modes of activation. A generic modes of action can be defined as the formation of a reactive intermediate that can undergoes many different types of transformation in consistently high enantioselectivity. This is the result of the interaction of a chiral catalyst with a basic functional group, to give rise to such reactive intermediate in a highly organized and predictable manner. As a consequence, generic activation modes, which have been properly elucidated and established, can be used as tool to design new enantioselective syntheses in a relatively straightforward way.[4] Organocatalytic activation modes, which have been rationalized by mimicking the interactions between catalyst and substrate that take place in nature, can be categorized in covalent-based and non-covalent-based activation.[5] Organocatalysts belonging to the first class are able to form reactive transient intermediates relying on strong, directional interactions have afforded a reliable synthetic tool for the development of a wide variety of chemical reactions. In contrast, catalysis by non-covalent interactions, such as hydrogen-bond donor catalysis, has provided

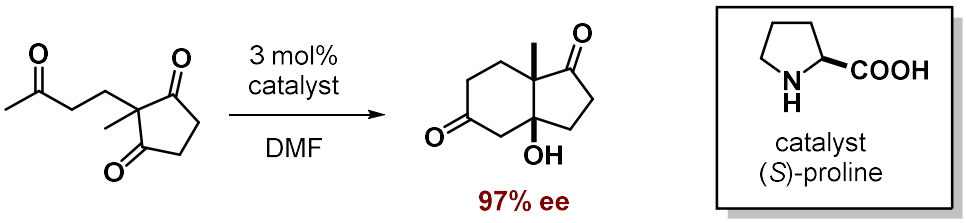
[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**.
[2] T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[3] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori *J. Am. Chem. Soc.* **1995**, *117*, 2675.
[4] D. W. C. MacMillan, *Nature*, **2008**, *455*, 304.
[5] *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis* (Eds.: A. Berkessel, H. Gröger) Wiley VCH, Weinheim, **2005**.

clear utility in enantioselective synthesis.[6] Although the interactions involved are weaker, less directional and less distance-dependent than their covalent counterpart, multiple hydrogen-bond donor moieties may cooperate in concert to accommodate the reaction partners in a highly organized transition state, thus enforcing high levels of enantioselectivity. Finally, another important non-covalent activation mode it is that one which involves the interaction of an ionic species with a chiral neutral, anionic, or cationic organocatalysts. This area is referred as ion pairing catalysis.[7]

In the following sections, the modes of action that have been main focuses during the course of these PhD studies will be highlighted.

1.1.1 Aminocatalysis: Enamine and Iminium Ion Activation

The proline-catalyzed intramolecular aldol reaction reported by Hajos and Parrish[8] in the early 1970s is one of the first report of asymmetric functionalization of carbonyl compounds (ketones and aldehydes) promoted by a chiral secondary amine (Scheme 1).

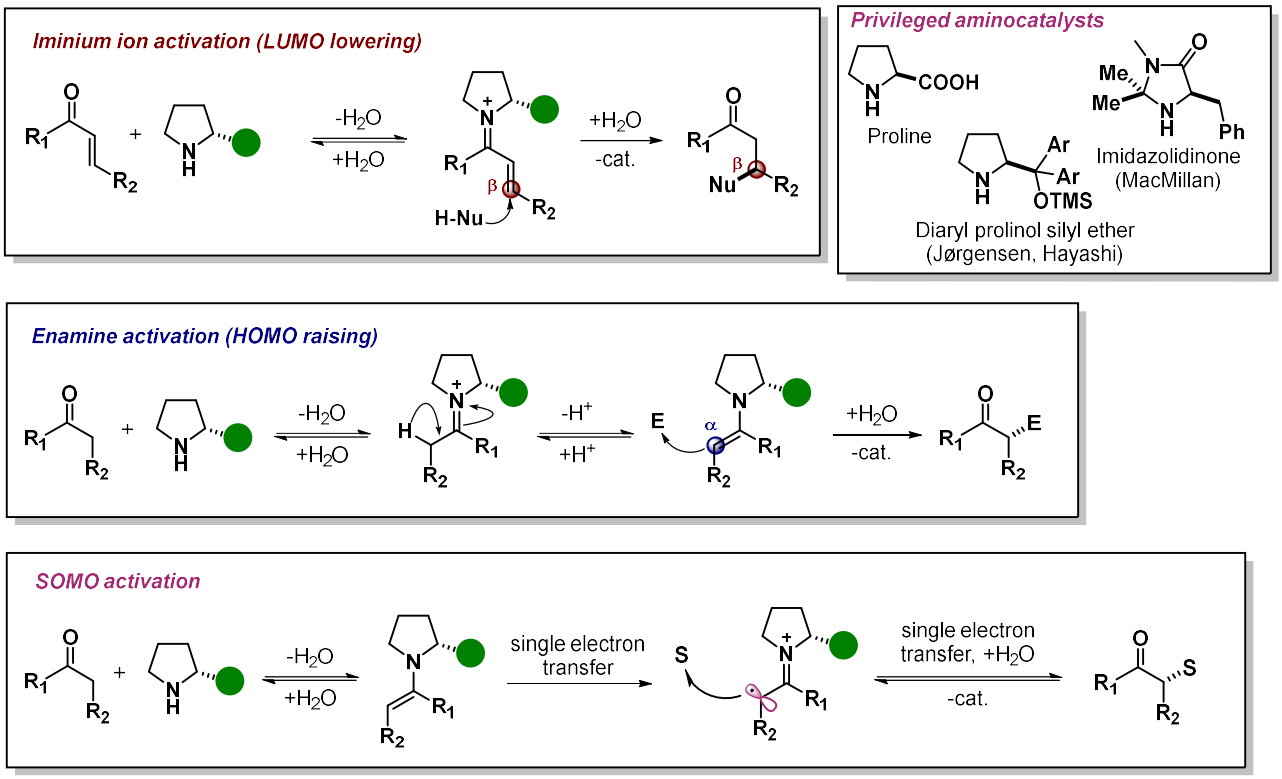


Scheme 1. Proline-catalyzed enantioselective intramolecular Aldol reaction

However, it was only in 2000 with two seminal publications that the field of asymmetric aminocatalysis was established: the proline-catalyzed intermolecular aldol reaction, reported by List, Lerner and Barbas III,[9] and the imidazolidinone asymmetric organocatalyzed Diels-Alder reaction, developed by MacMillan.[10] Based on these two reports, from then on, the field of aminocatalysis has flourished, as it quickly established itself as an independent field within asymmetric organocatalysis.[11] These two reports did not only offer alternative ways for the asymmetric version of two fundamental transformation, but they also constituted the basis for two novel organocatalytic generic activation modes of

[6] M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
[7] a) K. Barak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; b) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518.
[8] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.
[9] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[10] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[11] a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2015**, *54*, 13860.

carbonyl compounds. They are both based on covalent intermediates transiently generated upon condensation of chiral cyclic secondary amines with aldehydes or ketones (Scheme 2).



Scheme 2. LUMO lowering, HOMO raising and SOMO activation modes. Nu-H = nucleophile; E = electrophile; S = somophile

The condensation provides a positively charged iminium ion which lowers the Lowest Unoccupied Molecular Orbital (LUMO) of the intermediate. For *α*,*β*-unsaturated carbonyl compounds this effect greatly enhances the electrophilic character of the carbon at the *β*-position favouring attack of nucleophiles in reaction such as conjugated additions or pericyclic reactions.[12] Overall, the present activation mode enables the asymmetric functionalization at the *β*-position, driven by the chiral information of the chiral amine. On the other hand, in the case of isolated *π*-system, the LUMO-lowering effect increases the acidity of the *α*-protons inducing fast tautomerization to the enamine reactive intermediate. Such enamine is more nucleophilic than the corresponding enol resulting more susceptible towards electrophilic attack. This activation mode is referred as Highest Occupied Molecular Orbital (HOMO) raising and it enables the stereoselective functionalization of the a-position of carbonyl compounds. Later, the group of MacMillan introduced the concept of Single Occupied Molecular Orbital (SOMO) activation, which derives from the transiently generated

[12] G. Lelais, D. W. C. MacMillan *Aldrichim. Acta*, **2006**, *39*, 79.

enamine after single electron oxidation process. The resulting open-shell intermediate can provide a pathway to access unconventional reactivity to obtain enantioenriched products and further underlying the value of aminocatalysis in the realm of catalytic stereoselective transformations.

1.1.2 Hydrogen-Bond Donor Catalysis

Bio-mimicking the activation mode of enzymes, whose reactions are efficiently catalysed by means of multiple, spatially organized, H-bond interactions accompanied to secondary stabilization effects, a new branch of asymmetric organocatalysis has blossomed providing an enormous library of privileged scaffolds for catalyst design.

Hydrogen-bond (H-bond) catalysis is defined as LUMO-lowering activation of an electrophile by the simultaneous sharing of a hydrogen atom between the substrate (H-bond acceptor) and the catalyst (H-bond donor).

Some of the prominent structural frameworks that have proved to be successful for catalyst design and therefore enantioneduction are reported below (Figure 1).

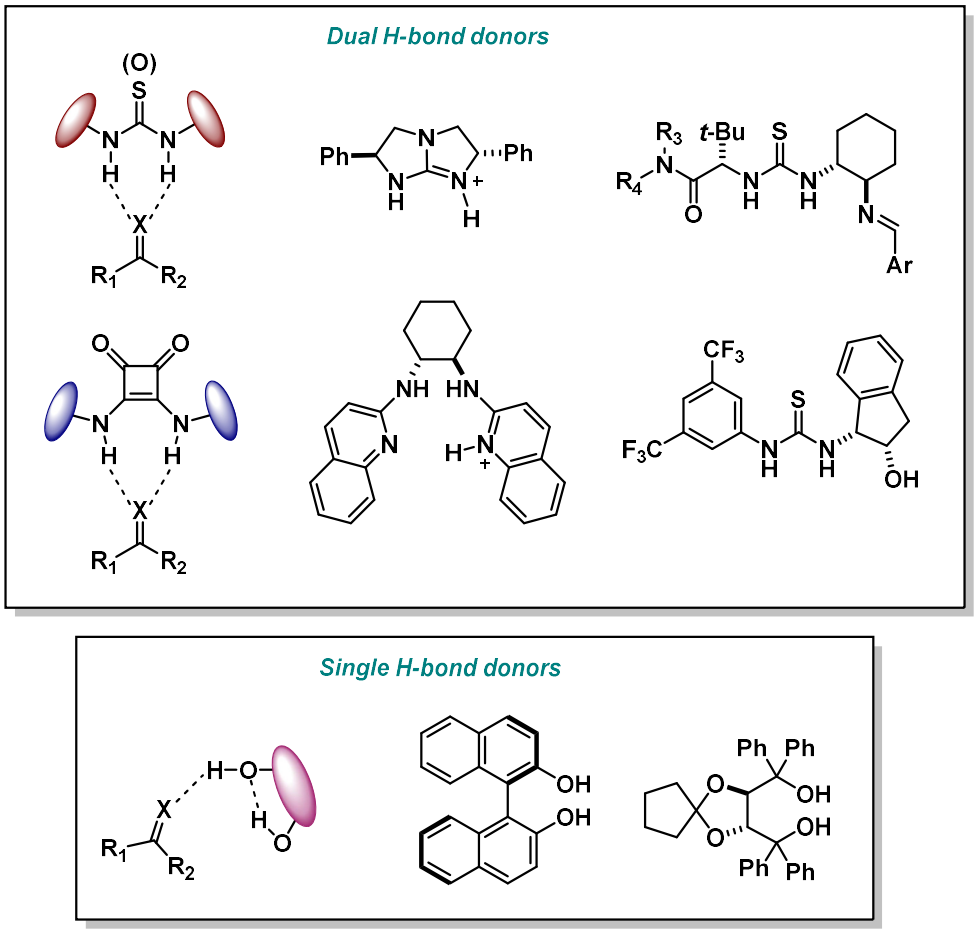


Figure 1. Representative hydrogen-bond donor catalysts

Amongst the dual H-bond donor catalysts, (thio)ureas, squaramides, as well as guanidinium ions and other structural backbones have shown to be competent species to rely on. Indeed, they have proved to deliver several applications in many different asymmetric transformation.[6, 13] Structures such as TADDOL or BINOL derivatives have been identified as highly powerful classes of catalysts among the single H-bond donors. Although their functional groups classify them as diols, an intramolecular H-bond provides structural rigidity and directionality for the activation of the desired substrates.

Despite of the obvious structural differences, this class of organocatalysts share a common fundamental motif: a single or dual H-bond donor moiety flanked by sites for secondary interactions, such as aromatic *π*-*π* stacking.

When the H-bond donor moiety is flanked to a strong Lewis base site, for example, we enter a different branch of enantioselective organocatalysis (Figure 2).[14]

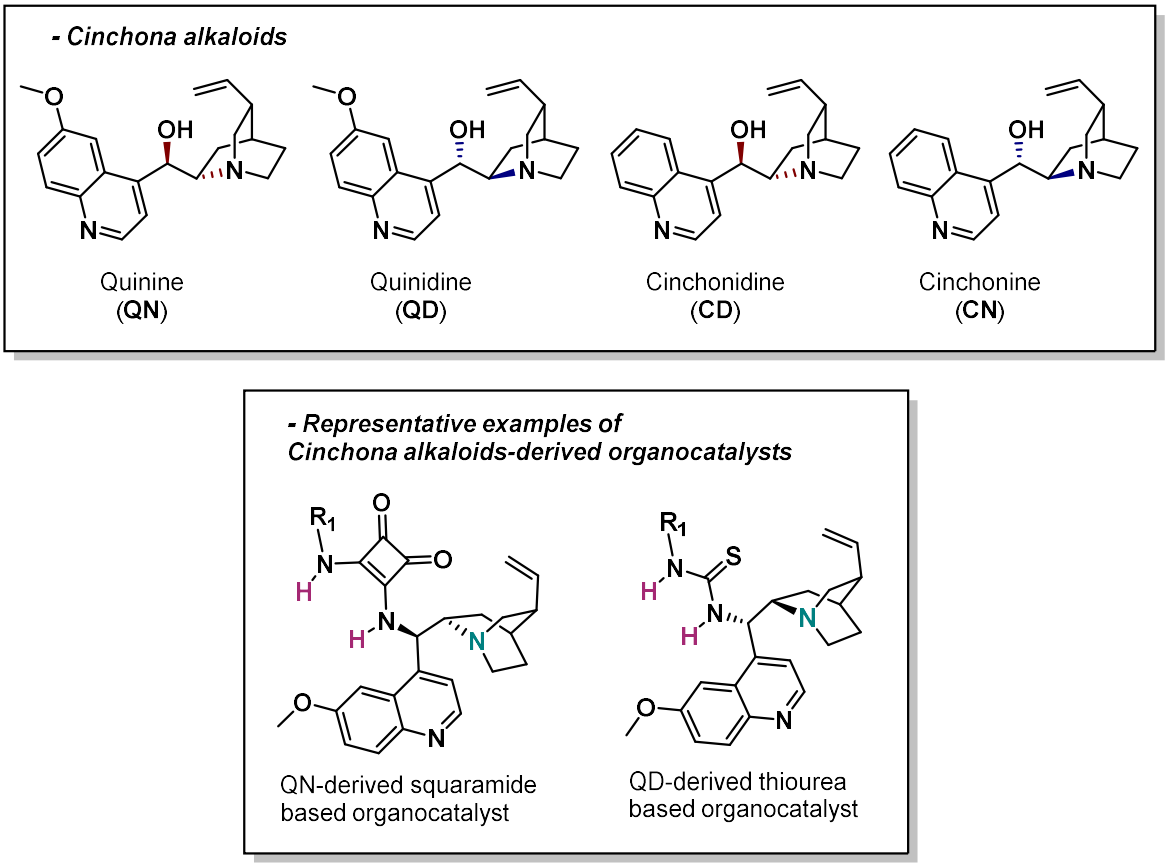


Figure 2. QN, QD, CD, CN Cinchona alkaloids and some representative bifunctional organocatalysts

[13] A. G: Doyle, E: N. Jacobsen *Chem. Rev.* **2007**, *107*, 5713.

[14] a) *Comprehensive Enantioselective Organo-catalysis: Catalysts, Reactions and Applications* S. Ingemann, H. Hiemstra, (Ed.:P.I.Dalko), Wiley-VCH, Weinheim, **2013**, Vol. 2, pp 119-160; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632; c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253; d) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890.

Due to their peculiar architecture that features multiple active sites on the same molecule, the mode of action of this class of organocatalysts, typically, relies on a tertiary amine moiety which can deprotonate pro-nucleophilic substrates; in the meanwhile, the H-bond donor functionalities can engage weak interactions with the other reaction partner to create a well-organized chiral environment in the transition state, thus achieving enantioselectivity. Among these organocatalysts, it is worth mentioning *Cinchona* alkaloids, as well as trans-1,2-diaminocyclohexane derivative, as privileged frameworks to design a wide variety of catalysts.

1.1.3 Chiral Phosphoric Acids

In 2004, Akiyama and Terada reported the use of optically pure BINOL-derived chiral phosphoric acids to promote enantioselective Mannich-type reactions to imines.[15] These organocatalysts feature a Brønsted acidic site and a Lewis basic one. Besides, the BINOL backbone can be appropriately functionalized with bulky substituents, namely stereocontrolling groups, at the 3,3'-positions in order to create a sort of chiral pocket that can arrange preferentially one relative approach between the reacting partner rather than the other to induce stereocontrol over bond formation (Figure 3).[16]

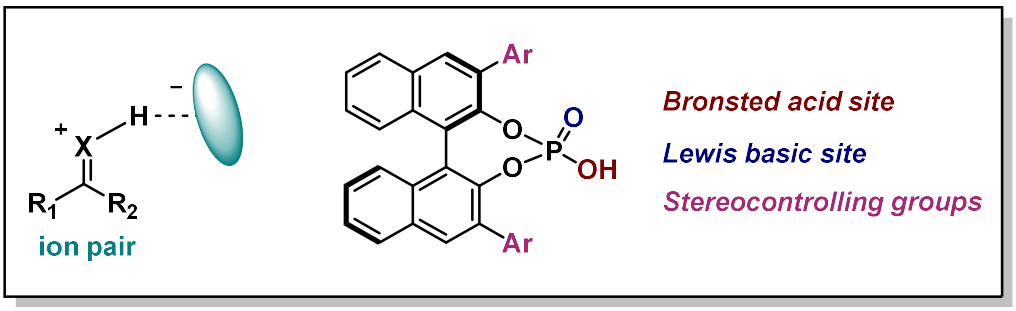


Figure 3. Asymmetric chiral phosphoric acid catalysis

Although much evidence has been provided for the H-bond interactions being crucial for achieving enantioselectivity, the strong acidity of phosphoric acids (pK_a ~ 2-4 in dimethyl

[15] a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, **2004**, *126*, 5356; b) J. Itoh, K. Yokota, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
[16] a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) M. Terada, *Synthesis*, **2010**, *12*, 1929; c) A. Kuenkel, I. Atodiresei, M. Rueping, *Chem. Soc. Rev.* **2011**, *40*, 4539; d) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

sulfoxide)[17] means that ion-pairing of fully protonated electrophile and the phosphate counterion cannot be excluded.[18]

[17] P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudörfl, A. Berkessel, A. C: O'Donoghue, *Chem. Eur. J.* **2011**, *17*, 8524.
[18] M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518

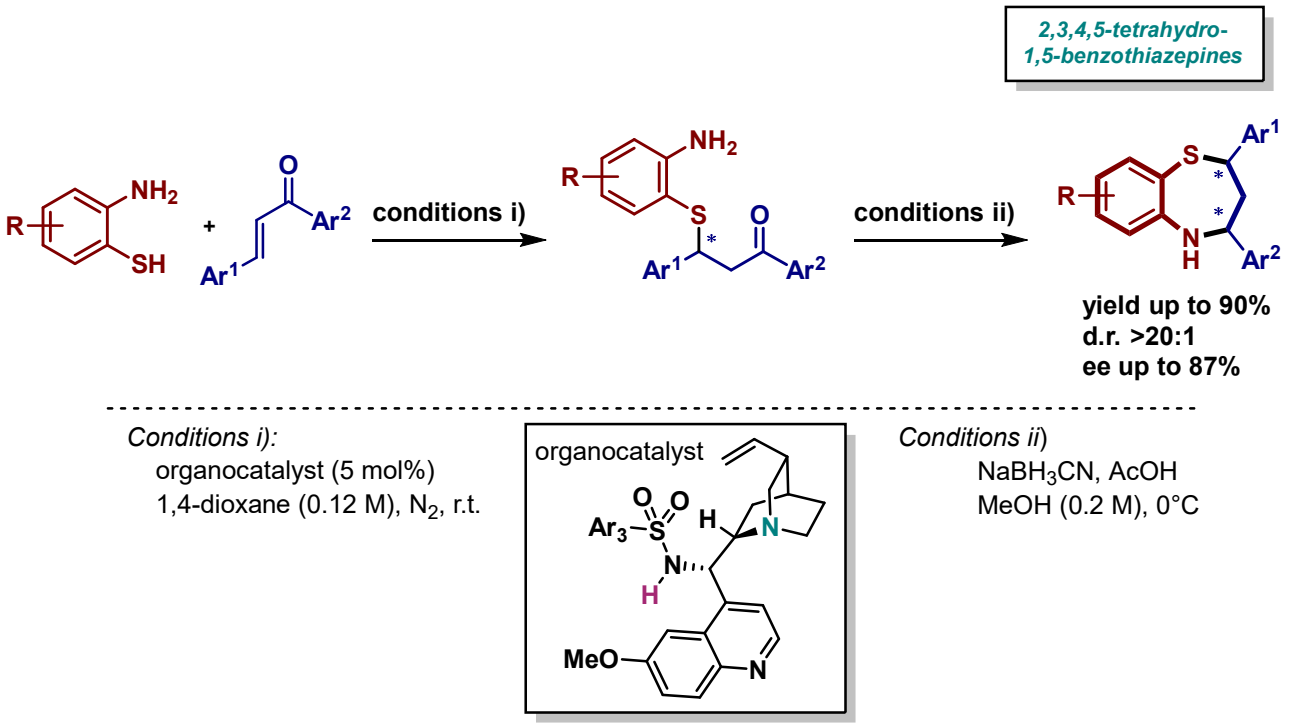
1.2 Summary of the thesis research

The following chapters describe the intrinsic versatility of organocatalysis: the potential of generic activation modes has been exploited to address difficult challenges, developing novel enantioselective catalytic methodologies. Organocatalysis has proved its tolerance in tackling demanding tasks such as the development of stereodivergent synthesis as well as exploiting new classes of reaction partners, thanks to its synergistic combination with the activation provided by transition metal catalysts.

The work described in Chapter 2 deals with the development of stereodivergent catalytic methodologies. Stereodivergency is currently a highly pursued approach in stereoselective synthesis, boosting the potential of a synthetic methodology guaranteeing its application to the preparation of the full set of stereoisomeric products.

Chapter **2.1** discusses the first example of organocatalytic asymmetric methodology to afford enantioenriched 2,3,4,5-tetrahydro-1,5-benzothiazepines.[19] Although the present literature provides many reports to obtain chiral 1,5-benzothiazepin-4-ones, a straightforward catalytic asymmetric protocol to access 2,3,4,5-tetrahydro-1,5-benzothiazepines was missing. To fill this gap, we took advantage of the bifunctional nature of 2-aminothiophenol as nucleophile for the organocatalytic Michael addition to *trans*-chalcone followed by intramolecular reductive amination of the Michael adduct without the purification of the intermediate (Scheme 3).

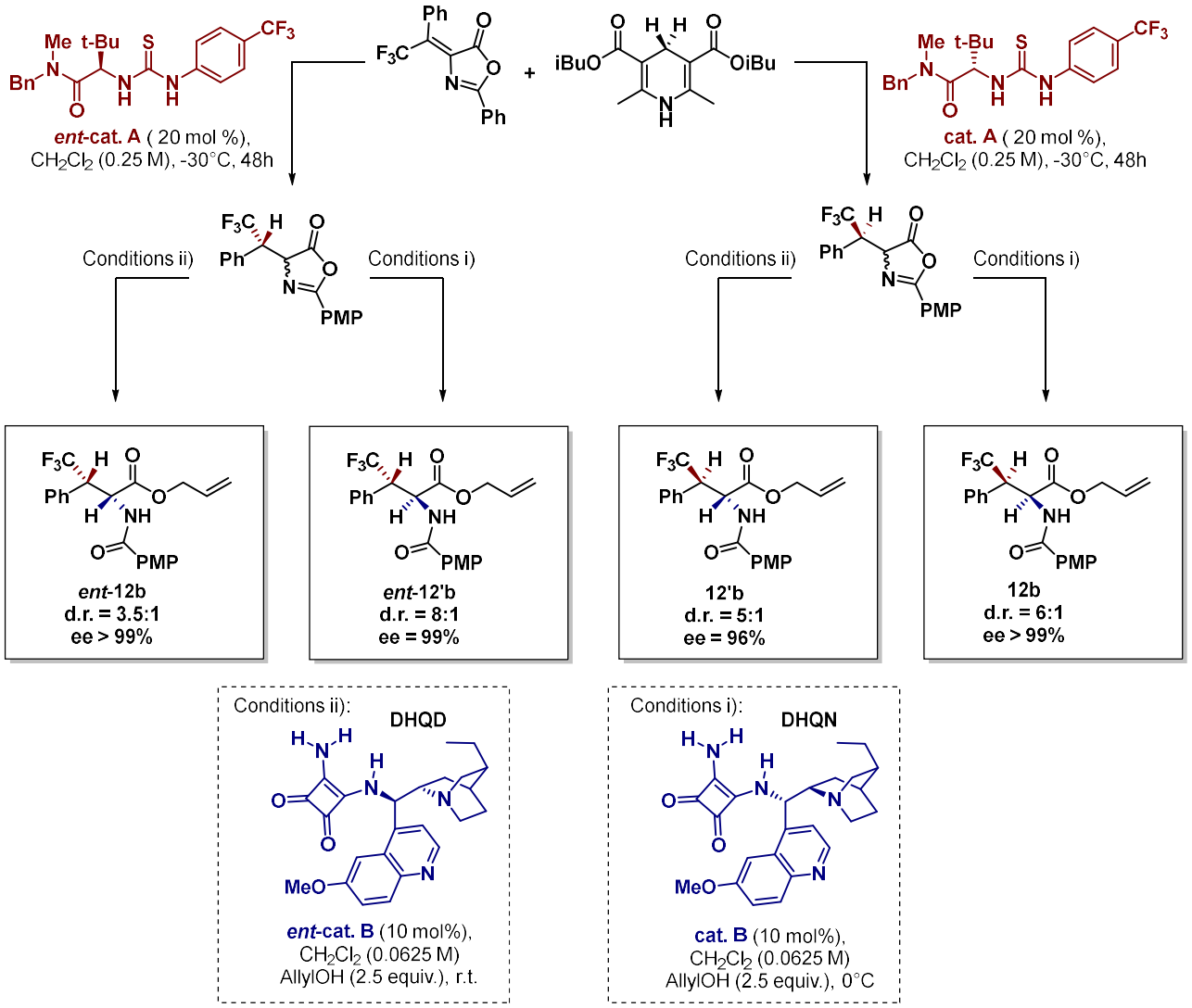
▪ [19] V. Corti, P. C. Gonzalez, J. Febvay, L. Caruana, A. Mazzanti, M. Fochi, L. Bernardi, *Eur. J. Org. Chem.* **2017**, 49.



Scheme 3.Organocatalytic asymmetric two-step procedure for the synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepines

2-Aminothiophenol is a peculiar nucleophile and, for this reason, we could not rely on the reported methodologies for the enantioselective organocatalytic Michael additions of thiophenols to *α*,*β*-unsaturated ketons, indeed we had to optimize the reaction conditions for the desired synthetic step. Initially, this methodology was intended as a potential example of stereodivergent synthesis relying on sequential catalysis. However, the strong substrate bias during the reductive amination reaction provided selectively the more stable *trans*-diastereoisomer of the cyclic product. Nevertheless, we decided to develop the first example of the organocatalytic asymmetric synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepines which are valuable bioactive target molecules.

Chapter **2.2** describes, instead, the stereodivergent synthesis of *β*,*β*-disubstituted-*α*-amino acid derivatives. The development of practical methods for the synthesis of enantiomerically pure natural and non-natural *α*-amino acids is a challenge of considerable importance, due to their numerous applications in the synthesis of chiral drugs, peptides, chiral ligands, chiral catalysts and many other valuable target molecules. This class of products can be obtained straightforwardly by the organocatalytic enantioselective transfer hydrogenation of the double bond of the arylidene azlactone derivatives, followed by the diastereoselective organocatalytic dynamic kinetic resolution of the oxazolone ring (Scheme 4).



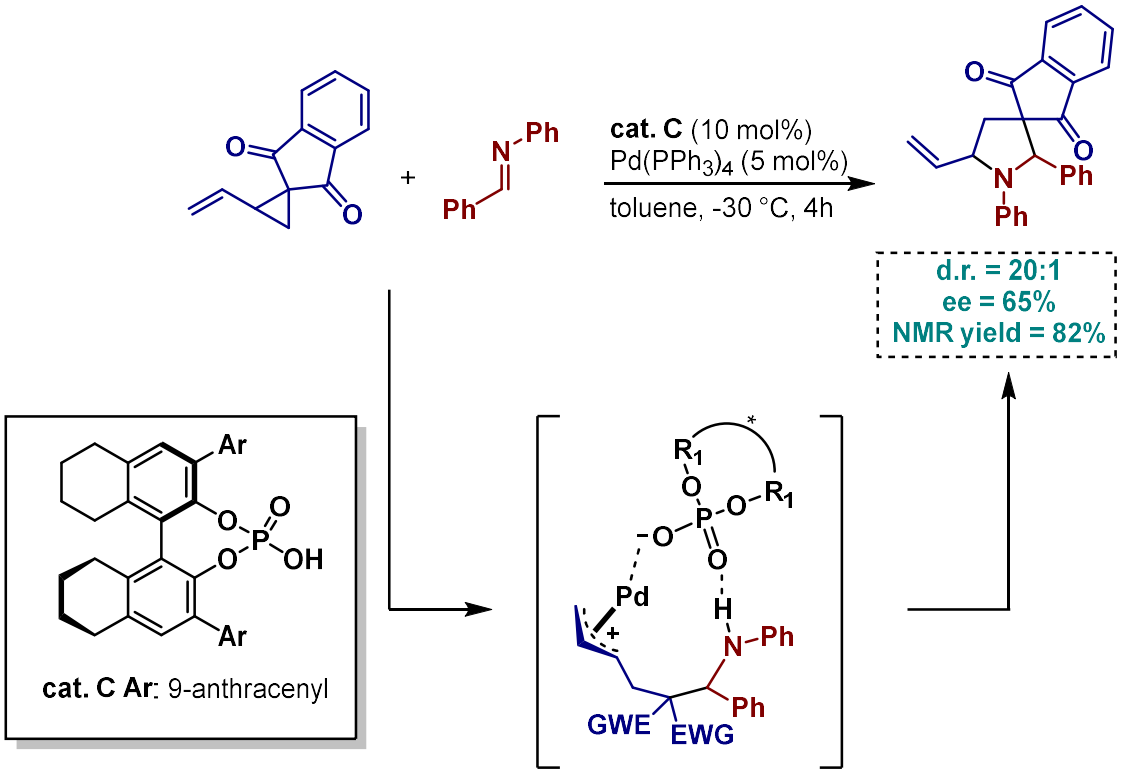
Scheme 4. Sequential catalytic approach to the stereodivergent synthesis of β,β-disubstituted-α-amino acid derivatives

This methodology relies on a sequential catalytic approach that involves the use of two different organocatalysts to promote the two different reactions. Depending on which enantiomer of each catalyst is selected for the corresponding transformation, it is possible to choose the final absolute and relative configuration of the desired product in a predictable manner. It is worth to note that a new catalyst had to be developed for the dynamic kinetic resolution process, to overcome the strong substrate bias of this step.

Chapter 3 deals with the combination of enantioselective organocatalytic concepts with substrate activation modes typical of metal catalysis. Such multicatalytic approach enables the disclosure of new reaction manifolds, not possible using the single catalytic species.

Chapter **3.1** deals with a synergistic catalysis strategy for the cycloaddition of vinylcyclopropanes and *N*-aryl imines. During the past decade, synergistic catalysis has been growing as alternative strategy for reaction development. This approach involves the concomitant activation of both reaction partners mediated by two different catalysts resulting

in a net lowering of the reaction activation energy. Besides, synergistic catalysis merges different fields and activation modes, unlocking new types of reactivity otherwise unattainable. In the studied transformation, the palladium (0) species activates the vinylcyclopropane with a ring-opening reaction, which is facilitated by the release of ring strain, forming the stabilized formal 1,3-dipole; meanwhile, the chiral phosphoric acid organocatalyst interacts with the imine to increase its electrophilic character. An efficient asymmetric version of this reaction has not been developed yet and the present approach shows the feasibility of the transformation with promising preliminary results (Scheme 5).

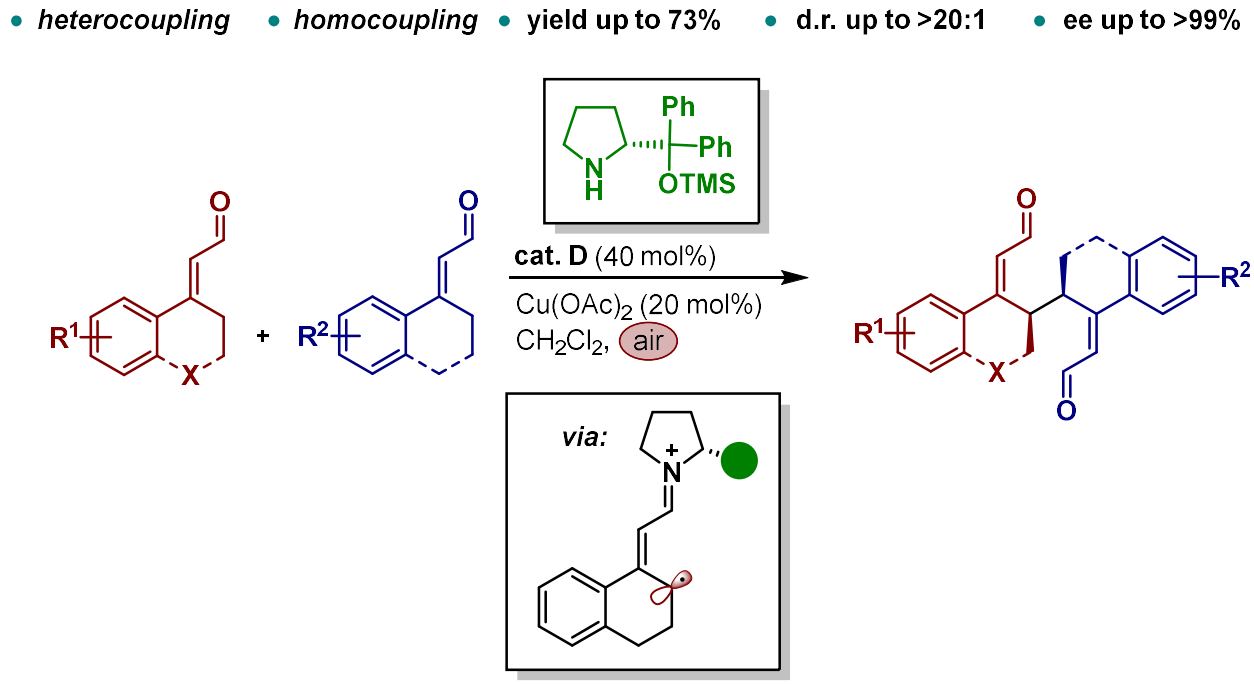


Scheme 5. Dual catalytic asymmetric cycloaddition of vinylcyclopropanes and N-aryl imines

Finally, expanding upon the identified possibility of including SOMO catalysis in the repertoire of the generic activation modes that can be exploited in aminocatalysis, we explored the opportunity of using open-shell intermediates in catalytic asymmetric transformations. The involvement of short-lived radical species in asymmetric catalysis has remained relatively unexplored until recently, owing to the inherent challenge of efficiently controlling the stereoselectivity of product formation from high-energy intermediates. However, in the group of Professor Karl Anker Jørgensen at Århus University (Denmark), we reported the first example of catalytic asymmetric oxidative *γ*-homocoupling of *α,β*-unsaturated aldehydes with air as the terminal oxidant.[20] The key of success was the use of

[20] L. Næsborg, V. Corti, L. A. Leth, P. H. Poulsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 1606.

a transition metal with the appropriate redox properties to generate a radical intermediate through single electron transfer oxidation process and being able to be re-oxidized by atmospheric oxygen. The combination of diaryl prolinol silyl ether aminocatalyst and Cu(II) performed delightfully under the optimized reaction conditions to provide the desired products with good yield and excellent stereoselectivity (Scheme 6).

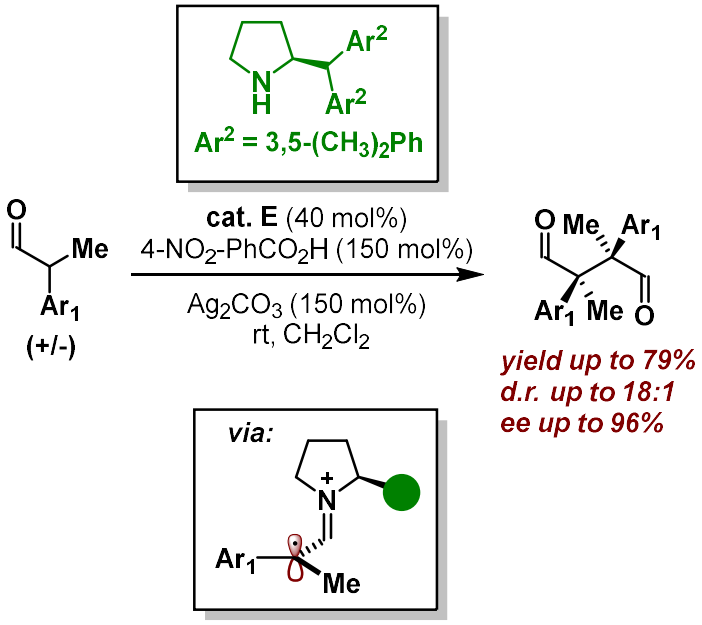


Scheme 6. Catalytic asymmetric γ-homo- and heterocoupling of α,β-unsaturated aldehydes with air as terminal oxidant

The same methodology enabled also the challenging catalytic asymmetric *γ*-heterocoupling of *α*,*β*-unsaturated aldehydes.

Besides, the same reaction concept was successfully applied to the catalytic asymmetric *α*-homocoupling of branched aldehydes.[21] In this example we had to optimize a new catalytic system as Ag(I) was found to be a more suitable oxidant for the activation of *α*-branched aldehydes as well as aminocatalyst **D** did not provide satisfactory activation. Nevertheless, the new set of optimized reaction conditions delivered the *α*-homocoupling products bearing two vicinal quaternary stereocenters in satisfactory results (Scheme 7).

[21] L. Næsborg, L. A. Leth, G. J. Reyes-Rodriguez, T. A. Palazzo, V. Corti, K. A. Jørgensen, *Chem. Eur. J.* **2018**, *24*, 14844.



Scheme 7. Catalytic asymmetric α-homocoupling of branched aldehydes

2 Stereodivergent Synthesis

Different stereoisomers of a drug may display different therapeutic effects because of the intrinsic chiral nature of human body, that is, more accurately, the chiral environment provided by biological receptors and enzymes. One of the most popular example is probably the (*R*)-enantiomer of thalidomide which has good sedative properties, while its mirror image, the (*S*)-enantiomer, is severely teratogenic (Figure 1, a). Stereoisomers of a drug can also target different receptors being optimal in the treatment of different diseases (Figure 1, b).

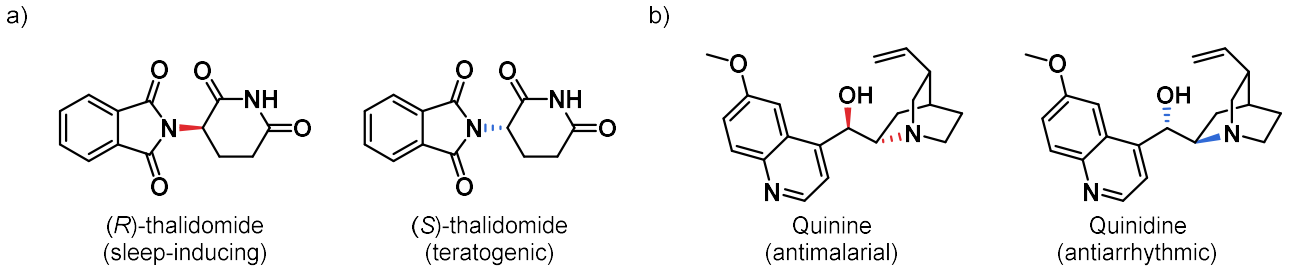


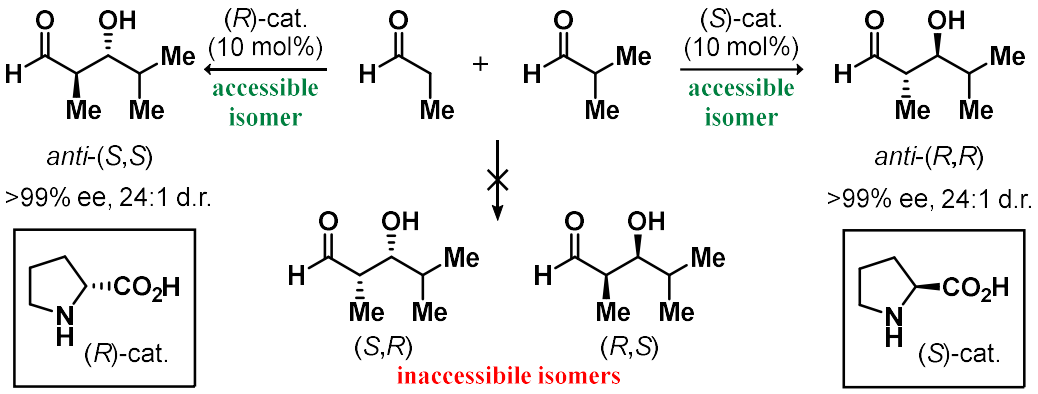
Figure 1. Diverse properties of different stereoisomers of the same molecule

This fact let synthetic chemists to conceptualize stereodivergent synthesis, which can be defined as the synthetic process that allows to access any given stereoisomers of the same product bearing multiple stereocenters from the same set of starting material.

Conventional asymmetric catalytic approaches[1] to the obtainment of a product with two stereocenters can be very effective in delivering one enantiomeric form of a selected diastereoisomer, but they often fail in the synthesis of the complementary diastereoisomer, as the catalyst dictates the configurational outcome over both chiral centres at the same time. A representative example of this scenario is reported the direct cross-aldol reaction of aldehydes developed by MacMillan.[2]

[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999.**

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

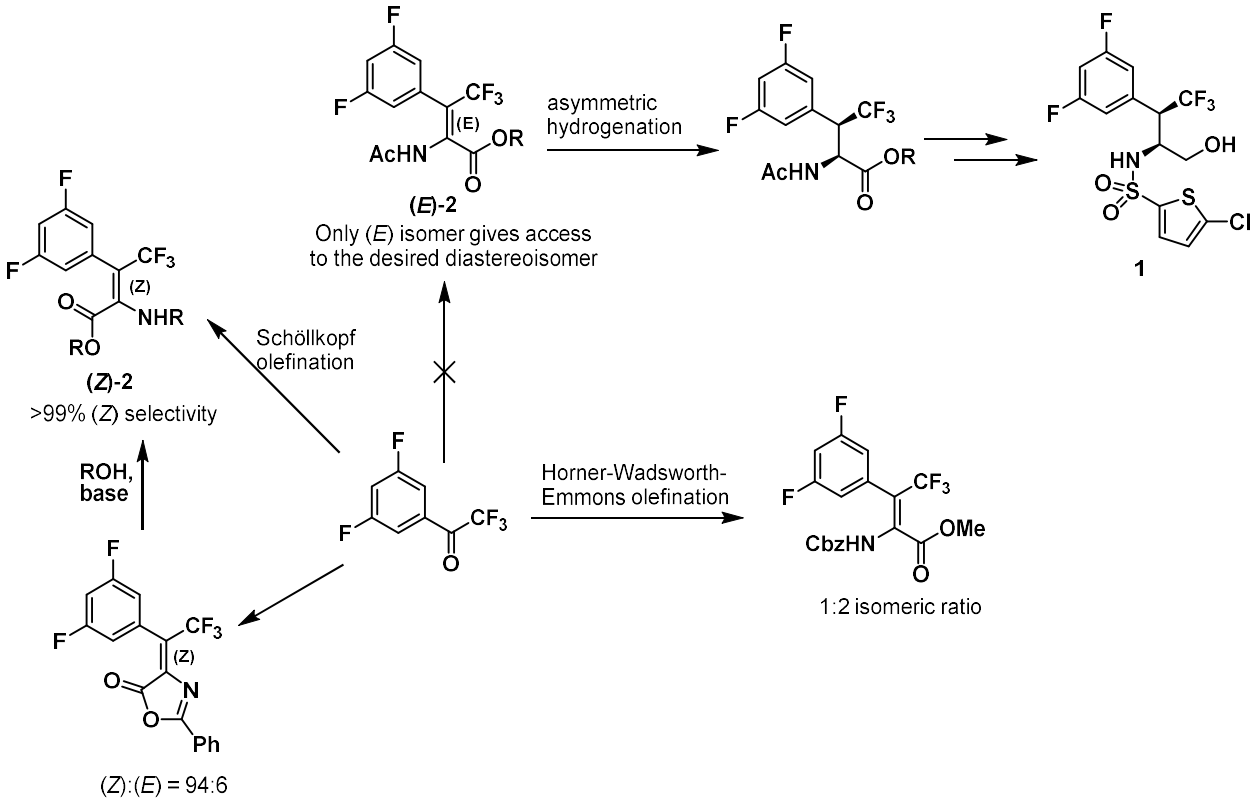


Scheme 1. Proline-catalyzed direct cross-aldol reaction of aldehydes

As shown in Scheme 1, this proline-catalysed methodology delivers the two enantiomeric forms of the *anti*-isomer with exquisite selectivity; on the other hand, with this catalytic system, the *syn*-isomer is not accessible unveiling the intrinsic limitation of this approach.

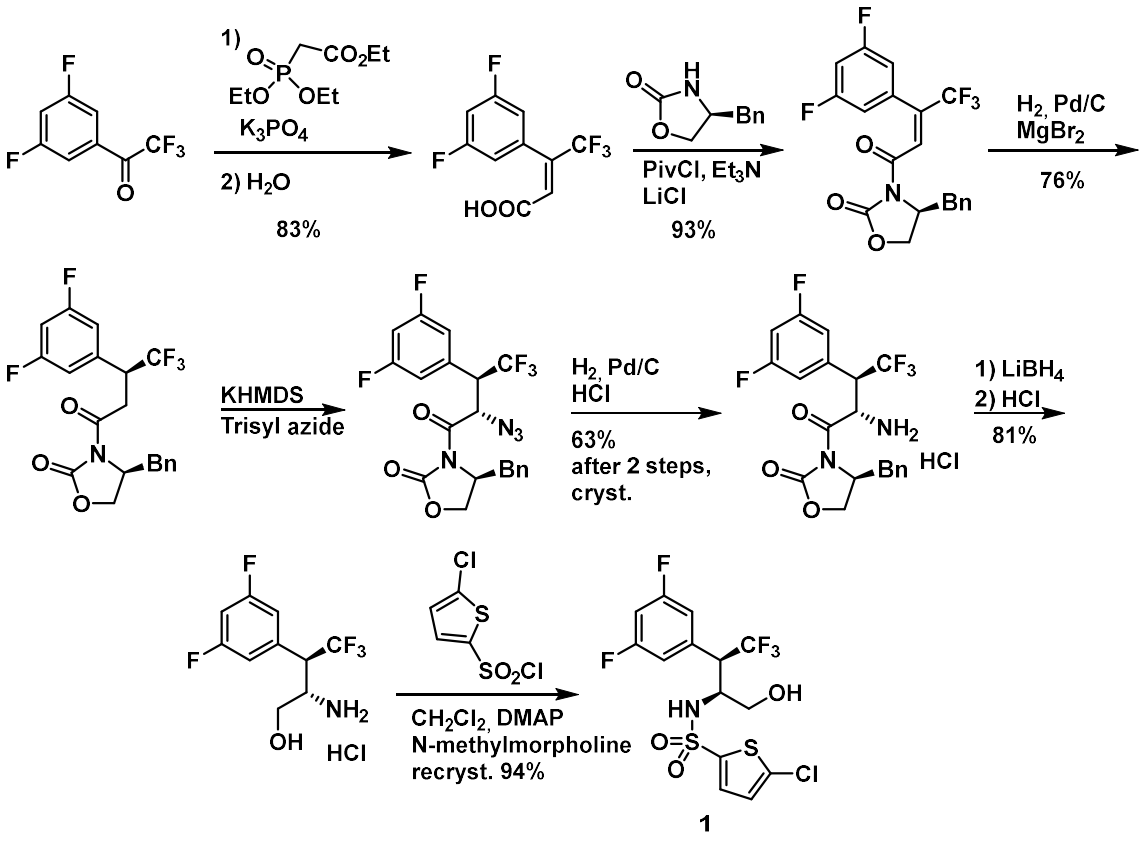
Sometimes, an appealing synthetic approach to obtain a target compound cannot be feasible because one of the planned reactions should occur with the "unnatural" selectivity or with the reversed selectivity of a well-established methodology. This was the case of a kg scale process development reported by Alimardanov *et al.*[3] in which the enantioselective production of a 3-aryl-3-trifluoromethyl-2-aminopropanol derivative **1** was tackled. The most straightforward strategy to the synthesis of derivative **1** with the desired stereoselectivity was an asymmetric hydrogenation approach of the (*E*)-isomer of the tetrasubstituted olefin **2** (Scheme 2).

[3] A. Nikitenko, T. J. Connolly, G. Feigelson, A. W. Chan, Z. Ding, M. Ghosh, X. Shi, J. Ren, E. Hansen, R. Farr, M. MacEwan, S. Tadayon, D. M. Springer, A. F. Kreft, D. M. Ho, J. R. Potoski, A. Alimardanov *Org. Process Res. Dev.* **2009**, *13*, 1161.



*Scheme 2. Proposed synthesis to target compound **1** and several attempts to obtain the desired olefine with the right configuration*

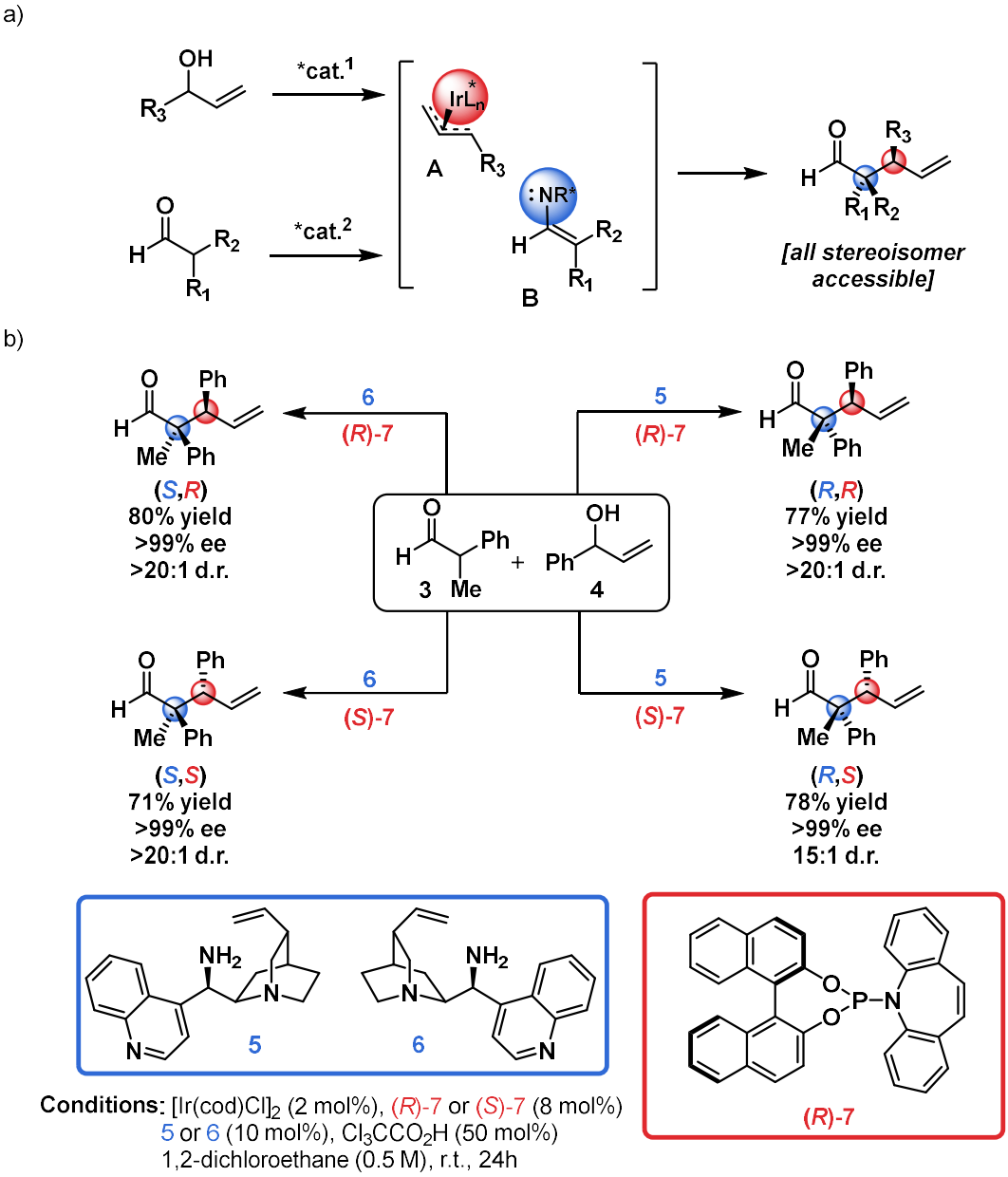
All the olefination reactions tested failed in affording the desired (*E*)-isomer forcing the authors to develop an alternative synthetic process which counts seven synthetic steps instead of the three-four synthetic steps involved in the originally designed process (Scheme 3).



*Scheme 3. Large scale Synthesis of **1***

There is a multitude of examples where stereodivergence is the result of the serendipitously modification of experimental parameters, such as the structure of the catalyst or the use of additives.[4] Ideally, a stereodivergent synthesis should employ the same set of catalysts and reaction conditions to access the various diastereoisomers of the final product.[5] In this sense, two strategies, which enable the rationalization and prediction of the stereochemical outcome, have been developed. The first approach is clearly described in the stereodivergent *α*-allylation of branched aldehydes reported by Carreira.[6] This elegant methodology (Scheme 4, a) relies on a dual catalytic system where the two reaction partners are concurrently and independently activated using two different chiral catalysts, each able to enforce configurational control over the formation of its corresponding stereocenter, providing access to the full set of stereoisomeric products.

[4] M. Bihani, J. C.-G Zhao, *Adv. Synth. Catal.* **2017**, *359*, 534.
[5] a) S. Krautwald, E. M. Carreira *J. Am. Chem. Soc.* **2017**, *139*, 5627; b) M. T. Oliveira, M. Luparia, D. Audisio, N. Maulide *Angew. Chem. Int. Ed.* **2013**, *52*, 13149.
[6] S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira *Science*, **2013**, *340*, 1065.

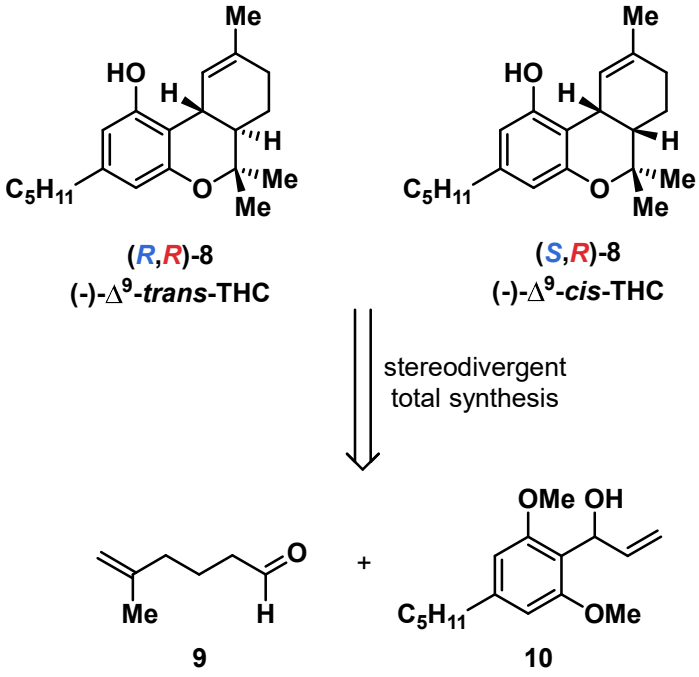


Scheme 4. a) Dual catalysis; b) Stereodivergnet dual catalytic synthesis of all stereoisomers of the product

More in detail, the electrophilic transiently generated *π*-allyliridium intermediate **A** (Scheme 4) is trapped by nucleophilic addition of enamine **B** (formed in situ from the corresponding aldehyde). The simultaneous activation of aldehyde **3** and alcohol **4** by two distinct catalysts enables the prediction of the configuration of both stereogenic centres in the product, by simple choice of the proper combination of amine catalyst (pseudoenantiomers **5**, **6**) and ligand enantiomers ((*R*)- or (*S*)-**7**).

Such stereodivergent processes find a great potential in the synthesis of optically active natural products as they provide more streamlined and conceptually simpler synthetic pathways to all the existing stereoisomer of the given compounds. Generally, the preparation of a single diastereoisomer of a natural product relies on a synthetic design

procedure that takes into account the *ad hoc* choice of starting materials (depending on their availability) and the combinations of substrate- and/or catalyst controlled reactions. As such, the synthesis of the complementary diastereoisomers results in the deviation from the initial synthetic sequence, forcing organic chemists to a time-consuming and effort-demanding design process in order to develop alterative procedures.[7] As opposed to this, the incorporation of a stereodivergent catalytic protocol in a target-oriented synthesis may dramatically simplify the synthetic process as the full set of stereoisomers can be targeted at the same time. With respect to this, the group of Carreira demonstrated the power of stereodivergent catalysis reporting the total synthesis of the four stereoisomers of Δ^9-tetrahydrocannabinol (Δ^9-THC).[8] Both *cis*-isomer (*S*,*R*)-**8** and *trans*-isomer (*R*,*R*)-**8** are found in nature (Scheme 5).



*Scheme 5. Retrosynthetic analysis of Δ⁹-THCs **8***

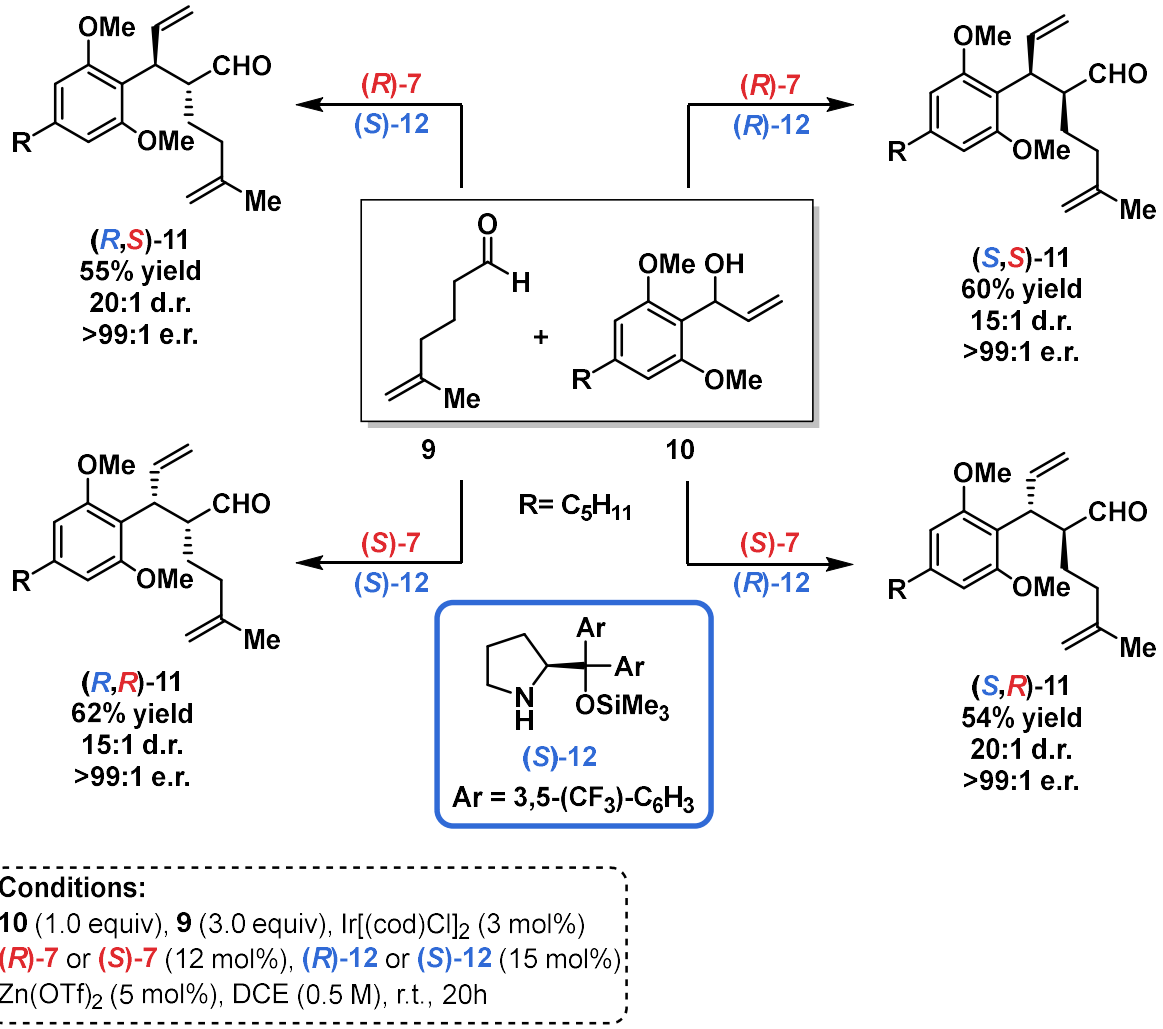
Thanks to a retrosynthetic analysis,[9] the authors managed to design, as starting point, the stereodivergent allylation reaction of linear aldehyde **9** using the allylic alcohol derivative **10**

[7] For examples of the synthesis of all four stereoisomers of mefloquine see: a) J. Ding, D. G. Hall, *Angew. Chem. Int. Ed.* **2013**, *52*, 8069; b) N. Schützen-meister, M. Müller, U. M. Reinscheid, C. Griesinger, A. Leonov, *Chem. Eur. J.* **2013**, *19*, 17584; for other selected recent examples, see: c) Y. Sridhar, P. Srihari, *Eur. J. Org. Chem.* **2013**, 578; d) M. Valli, P. Bruno, D. Sbarbada, A. Porta, G. Vidari, G. Zanoni, *J. Org. Chem.* **2013**, *78*, 5556; e) M. Morgen, S. Bretzke, P. Li, D. Menche, *Org. Lett.* **2010**, *12*, 4494.

[8] M. A. Schafroth, G. Zuccarello, S. Krautwald, D. Sarlah, E. M. Carreira *Angew. Chem. Int. Ed.* **2014**, *53*, 13898.

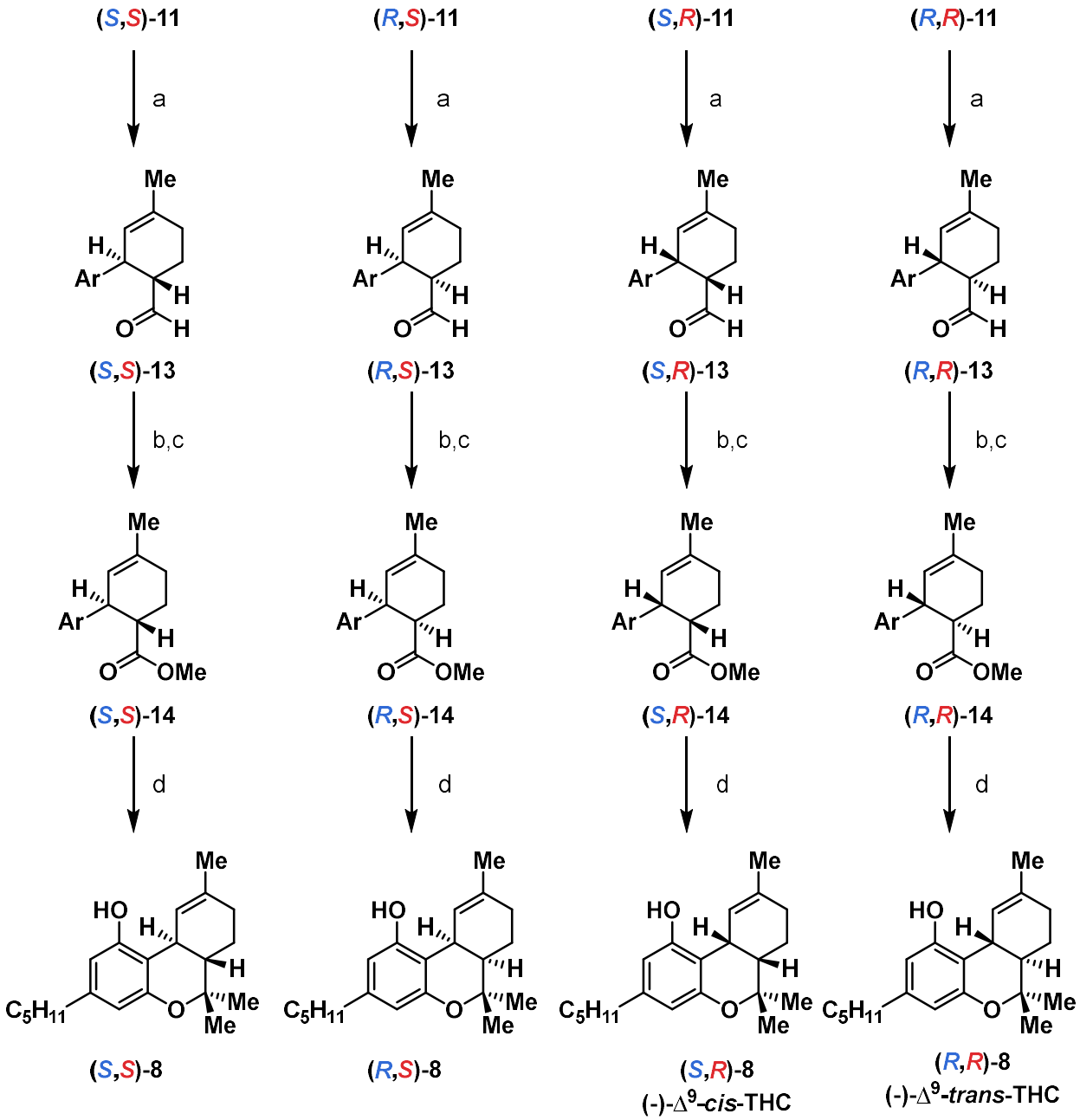
[9] a) *The Logic of Chemical Synthesis* (Eds.: E. J. Corey, X.-M. Cheng), Wiley-Interscience, New York, **1995**; b) *Organic Synthesis: The Disconnection Approach*, 2nd ed. (Eds.: S. Warren, P. Wyatt), Wiley, Weinheim, **2009**.

(Scheme 5). The dual Ir/amine-catalytic system promotes the reaction with excellent selectivities and comparable yields, thus enabling the obtainment of the four stereoisomeric precursors of Δ^9-THC (Scheme 6).



*Scheme 6. Stereodivergent dual Ir/amine-catalyzed synthesis of aldehyde intermediate **11***

This protocol combines an early dual-catalytic stereodivergent reaction with a uniform sequence of synthetic steps by which each stereoisomer is advanced to the corresponding stereoisomer of Δ^9-THC **8** (Scheme 7).

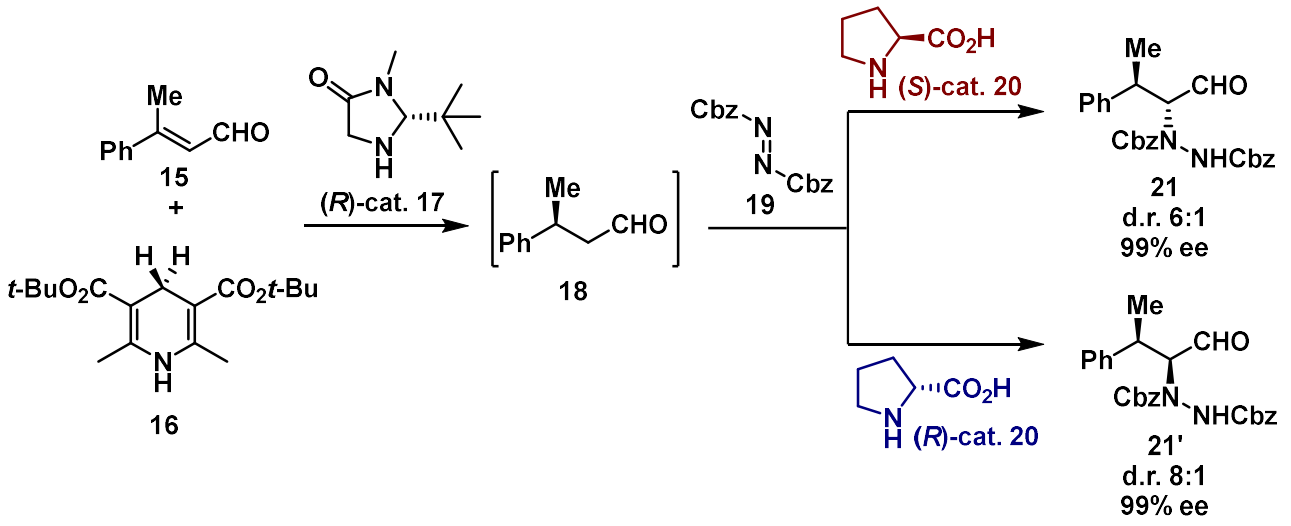


Reagents and conditions: (a) Grubbs's second-generation catalyst (3 mol%), CH_2Cl_2, rt, 92% for (*S*,*S*)-**13**, 87% for (*R*,*S*)-**13**, 90% for (*S*,*R*)-**13**, 85% for (*R*,*R*)-**13**; (b) $NaClO_2$ (2.3 equiv), NaH_2PO_4 (2.0 equiv), 2-methyl-2-butene (30 equiv), t-BuOH/H_2O, rt; (c) Me_3SiCHN_2 (1.1 equiv), C_6H_6/MeOH (1:1), 0 °C, 66% for (*S*,*S*)-**14**, 60% for (*R*,*S*)-**14**, 61% for (*S*,*R*)-**14**, 65% for (*R*,*R*)-**14**; (d) MeMgI (10 equiv), Et_2O, 0 to 160 °C, ambient pressure to 150 mmHg; then addition of $ZnBr_2$, $MgSO_4$ upon workup in CH_2Cl_2, rt, 57% for (*S*,*S*)-**8**, 41% for (*R*,*S*)-**8**, 45% for (*S*,*R*)-**8**, 65% for (*R*,*R*)-**8**.

Scheme 7. Synthesis of the four stereoisomers of Δ⁹-THC by a uniform sequence of step

The second strategy of stereodivergent synthesis, instead, is based on two different catalysts acting sequentially in the generation of the two stereocenters. Formally, this process involves a first catalytic enantioselective reaction followed by a catalyst-controlled diastereoselective reaction of a chiral substrate, which mandatorily encounters the scenario

of matched/mismatched effects (see Chapter 2.2.2 for a detailed discussion). However, this approach have proved to furnish a great tool in stereodivergent syntheses, being very effective in many examples,[10] such as the so-called cycle-specific organocascade catalysis reported by MacMillan[11] (Scheme 8).



Scheme 8. Cycle-specific organocatalysis: a representative example

In this methodology, the conjugated aldehyde **15** is doubly functionalized in a two-step catalytic sequential process: the first transformation is the enantioselective transfer hydrogenation of the carbon-carbon double bond promoted by chiral imidazolidinone **17** using the Hantzsch ester derivative **16** as hydrogen source. The following step is the diastereoselective electrophilic functionalization of aldehyde **18**, catalysed by proline **20**, using the azodicarboxylate **19** as electrophile in order to obtain the two diastereoisomers of the final product **21** with high selectivity. This set of catalytic transformations allows the authors to predict the final configuration of the product by simple selection of the proper enantiomer of each catalyst in each reaction.

Stereodivergent sequential catalytic processes have been one of the main focuses of my graduate education. In this chapter, I will present two examples dealing with this topic.

[10] As representative examples: a) S.-L. Shi, Z. L. Wong, S. L. Buchwald *Nature*, **2016**, *532*, 353; b) C. Hung, T. Saget, E. Gnanamani, B. M. Trost, *Nature Catalysis* **2018**, *1*, 523; c) R. Millet, A. M. Träff, M. L. Petrus, J.-E. Bäckvall *J. Am. Chem. Soc.* **2010**, *132*, 15182; d) K. Baer, M. Krausßer, E. Burda, W. Hummel, A. Berkessel, H. Gröger *Angew. Chem. Int. Ed.* **2009**, *48*, 9355 e) Y. Kwon, A. Chinn, B. Kim, S. J. Miller *Angew. Chem. Int. Ed.* **2018**, *57*, 6251.

[11] B. Simmons, A. M. Walji, D. W. C. MacMillan *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.

2.1 Organocatalytic Asymmetric Sulfa-Michael Addition of 2-Aminothiophenols to Chalcones: First Enantioselective Access to 2,3,4,5-Tetrahydro-1,5-benzothiazepines

2.1.1 Background

The 1,5-benzothiazepinic motif (Figure 1) is a privileged scaffold in the field of pharmaceutical science, as in multiple cases it has exhibited prominent biological activities in the central nervous system as well as other therapeutic properties, including the treatment of cardiovascular diseases.[1]

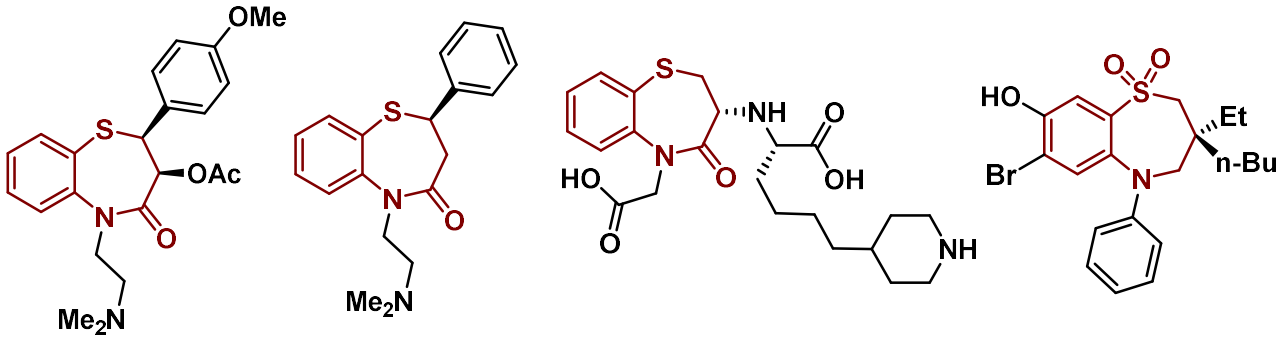
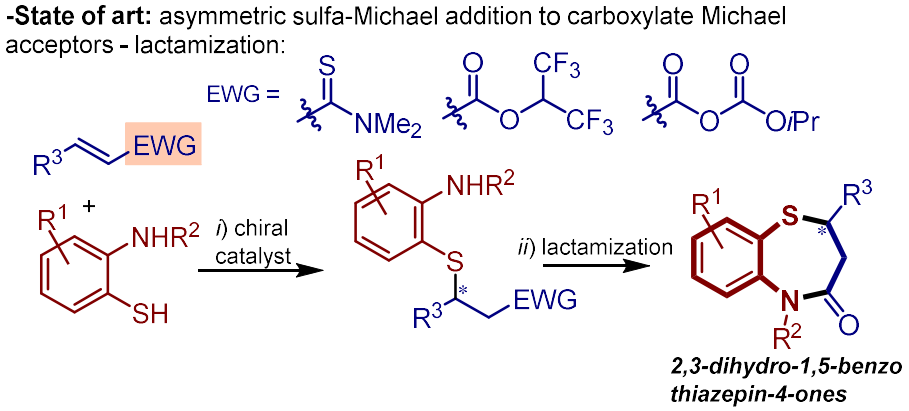


Figure 1. Chiral 1,5-benzothiazepines: privileged structures in pharmaceutical chemistry

Chiral 1,5-benzothiazepines are even more valuable since their medical activity might be enhanced by the unsymmetrical framework; this is the case of diltiazem, for example, where only the (2*S*,3*S*) stereoisomer displays the desired cardio vasodilating action. Because of their prominent role in drug development process, the synthesis of optically active 1,5-benzothiazepines have greatly motivated the scientific community to expand the array of their catalytic asymmetric routes, which are desirable technologies for the creation of efficient industrial processes. One of the most straightforward routes to obtain the 1,5-benzothiazepinic framework is the formal [4+3] catalytic asymmetric cycloaddition of carboxylate-based Michael acceptors and 2-aminothiophenols.[2] These methodologies rely

[1] For a review on 1,5-benzothiazepines as a versatile pharmocophore, see: J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C.Trivedi, J. S. Singh, K. S. Jain, A. K. Shah, *Eur. J. Med. Chem.* **2008**, *43*,2279.
[2] K. Asano, S. Matsubara *ACS Catal*. **2018**, *8*, 6273.

on an initial asymmetric sulfa-Michael reaction,[3] followed by a lactamization step to deliver the seven-membered ring products (Scheme 1).

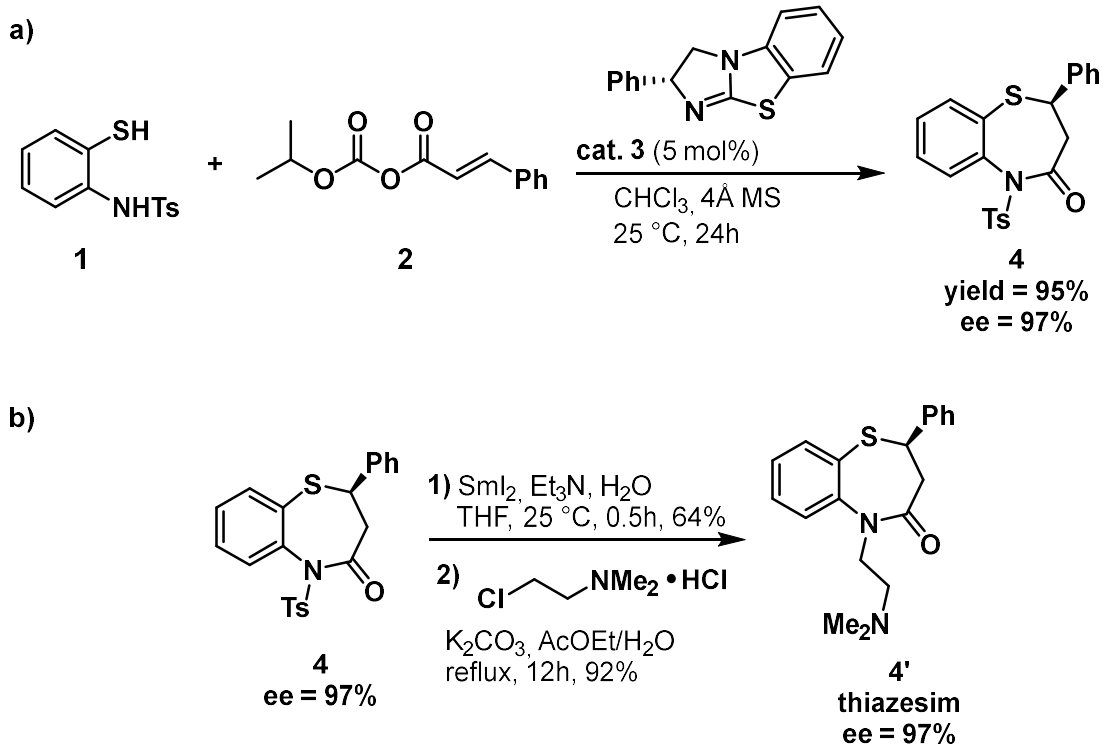


Scheme 1. Sequential asymmetric sulfa-Michael – cyclization processes to access 2,3-dihydro-1,5-benzothiazepin-4-one derivatives.

In 2015, Matsubara reported an elegant example in which the [4+3] net cycloaddition of 2-aminothiophenol **1** and *α,β*-unsaturated substrate **2** in presence of benzotetramisole catalyst **3** delivers the enantioenriched benzothiazepinic derivative **4** (Scheme 2, a).[4]

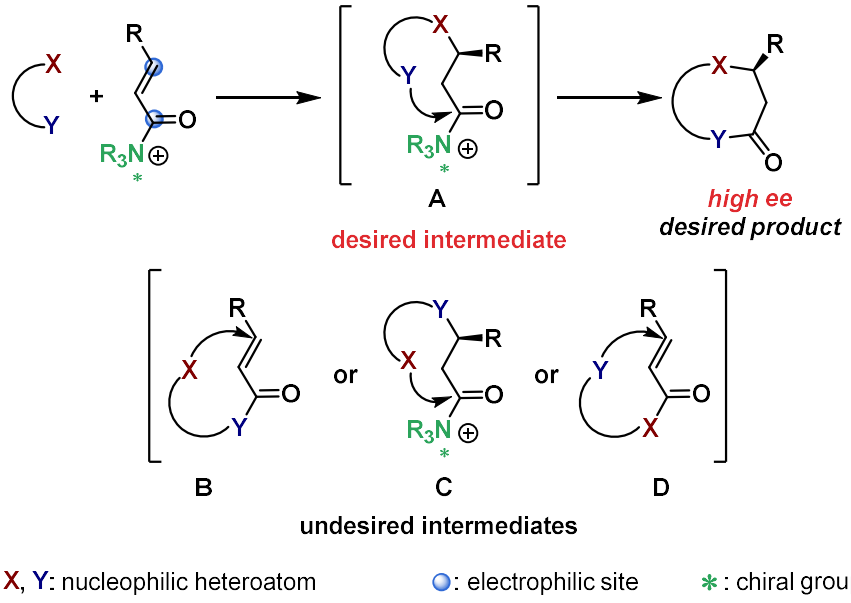
[3] For comprehensive reviews on organocatalytic sulfa-Michael reactions, see: a) D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959; b) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114* , 8807; for seminal work, see: c) R. Helder, R. Arends, W. Bolt, H. Hiemstra, H. Wynberg, *Tetrahedron Lett.* **1977**, *18*, 2181; d) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417; recent instructive computational studies: e) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 1170; f) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 9041.

[4] Y. Fukata, K. Asano, S. Matsubara *J. Am. Chem. Soc.* **2015**, *137*, 5320.



*Scheme 2. Net-cycloaddition between carboxylate derivative **2** and 2-aminothiophenol **1***

This methodology relies on the use of transiently generated *α,β*-unsaturated acylammonium species which undergoes nucleophilic attack by a reaction partner featuring two nucleophilic sites. As shown in Scheme 3, besides the desired pathway via intermediate **A**, alternative reactions derived by the formation of intermediates **B**-**D** could also take place lowering in this way the enantioselectivity or generating the undesired regioisomer.

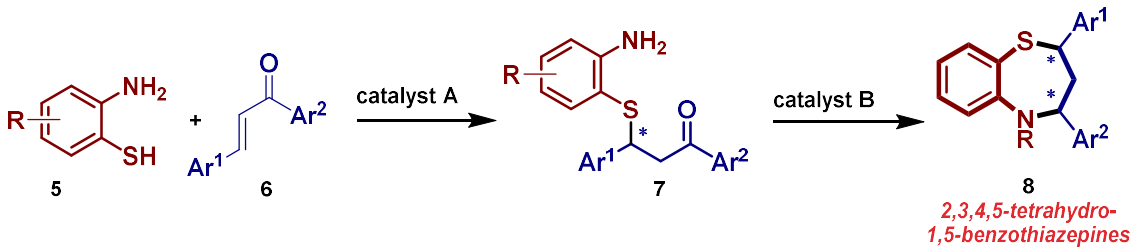


Scheme 3. Net cycloaddition between α,β-unsaturated acylammonium ion and nucleophilic counterpart bearing two heteroatoms

However, the authors noticed the high chemoselectivity of the described intermediates **A** which exclusively trapped the sulfur-centred nucleophile at the *β* position via an asymmetric sulfa-Michael addition. This methodology delivered all the 1,5-benzotiazepin-4-one products **4** in perfect regioselectivities and good-to-excellent enantioselectivities regardless of electronic or steric characteristics of substituents on the reaction partners. Besides, starting from product **4,** the authors accomplished the asymmetric synthesis of thiazesim **4'** with only two synthetic steps and retention of the enantiomeric excess (Scheme 2, b).

2.1.2 Aim of the project

As described before, chiral 1,5-benzothiazepines play a prominent role in drug development. However, the present catalytic asymmetric methodologies employ carboxylate Michael acceptors, thus only deliver the 1,5-benzotiazepin-4-one core (highlighted in Scheme 1).[2] In contrast, there are no catalytic asymmetric examples to obtain the 2,3,4,5-tetrahydro-1,5-benzothiazepinic scaffold bearing an amine moiety instead of the amide group. To fill this gap, we envisaged that a two catalytic sequential process using 2-aminothiophenols **5** as bidentated nucleophiles and *α,β*-unsaturated ketones **6** as electrophiles, would afford the reactive Michael adduct **7**, which upon intramolecular catalytic diastereoselective reductive amination, would deliver the desired 2,3,4,5-tetrahydro-1,5-benzothiazepine **8** (Scheme 4) in an enantioenriched form. In addition to this, exploiting a different chiral catalyst in each catalytic reaction we thought to be able to control the formation of the two chiral centres independently, thus resulting in the development of a stereodivergent synthesis enabling the obtainment of all possible stereoisomers. Annulation reactions of optically pure substrates delivering six-membered rings are usually strongly influenced by either the substrate bias to place the bulky substituent in the more stable equatorial position of the chair conformation or electronic effects. As such, we hypothesised that the higher conformational freedom of a seven-membered ring would render more plausible a scenario in which the catalyst would better enforce its control on the transition state over the substrate bias during the reductive amination reaction.



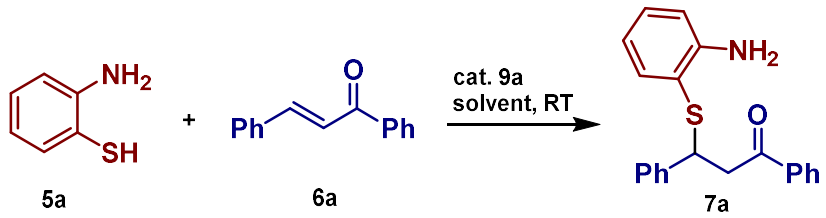
Scheme 4. Sequential catalytic enantioselective sulfa-Michael addition followed by reductive amination to afford 2,3,4,5-tetrahydro-1,5-benzothiazepines

2.1.3 Results and Discussion

We set out our investigations on the reaction between 2-aminothiophenol **5a** and *trans*-chalcone **6a** (Table 1) applying the previously reported reaction conditions for the organocatalytic enantioselective addition of simple thiophenols to this type of substrate which entailed the use of catalyst **9a** (Figure 2), toluene and at room temperature.[5]

[5] a) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137; b) J. Skarżewski, M. Zielińska-Błajet, I. Turowska-Tyrk, *Tetrahedron Asymmetry* **2001**, *12*, 1923.

*Table 1. Screening of catalysts **9** and conditions in the test reaction between 2-aminothiophenol (**5a**) and trans-chalcone (**6a**): representative results*



Entry[a]	Cat. **9** (mol %)	Solvent [M]	Conv.[b] [%]	ee[c] [%]
1	**9a** [10]	toluene [0.18]	65	32[d]
2	**9b** [10]	toluene [0.18]	62	20[d]
3	**9c** [10]	toluene [0.18]	84	18
4	**9d** [10]	toluene [0.18]	66	70
5	**9e** [10]	toluene [0.18]	50	rac
6	**9f** [10]	toluene [0.18]	64	50
7	**9g** [10]	toluene [0.18]	92	21
8	**9d** [10]	CH_2Cl_2 [0.18]	>99	40
9	**9d** [10]	CH_3CN [0.18]	80	62
10	**9d** [10]	acetone [0.18]	>99	66
11	**9d** [10]	THF [0.18]	50	74
12	**9d** [10]	1,4-dioxane [0.18]	68	80
13	**9d** [5]	1,4-dioxane [0.18]	60	82
14	**9d** [1]	1,4-dioxane [0.18]	46	46
15[e]	**9d** [5]	1,4-dioxane [0.12]	>99	86

[a] Conditions: *trans*-chalcone (**6a** 0.10 mmol), catalyst **9**, solvent, 2-aminothiophenol (**5a**, 0.15 mmol), r.t., 1-5 h. [b] Determined by 1H NMR spectroscopy after filtration through a plug of silica gel and solvent evaporation. [c] Determined by chiral stationary phase HPLC. [d] *ent*-**7a** was obtained as major enantiomer. [e] Reaction performed with degassed 1,4-dioxane, adding nucleophile **5a** as a 1,4-dioxane solution.

Unfortunately, these reaction conditions did not result suitable for nucleophile **5a** probably because of its $-NH_2$ free moiety capable of extra –H bond coordinations (Table 1, entry 1). Therefore, we started a thorough optimization of the reaction conditions. We initially screened other bifunctional organocatalysts **9b-g** (represented in Figure 2) featuring the

acidic –H bond donor moiety flanked to a basic tertiary amine functional group (Table 1, entries 2-7).[6]

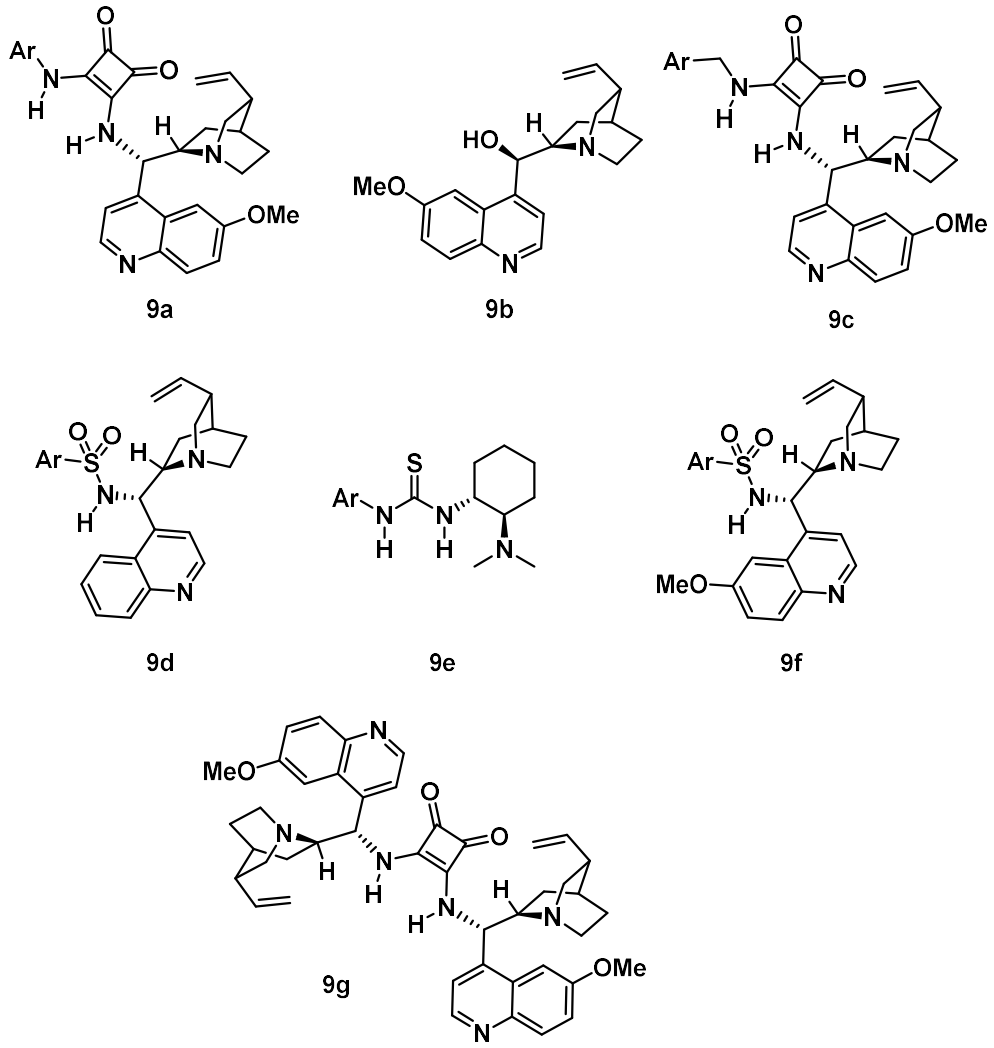


*Figure 2. Representative bifunctional catalysts **9a-g** screened in the reaction. Ar= 3,5-(F$_3$C)C$_6$H$_3$*

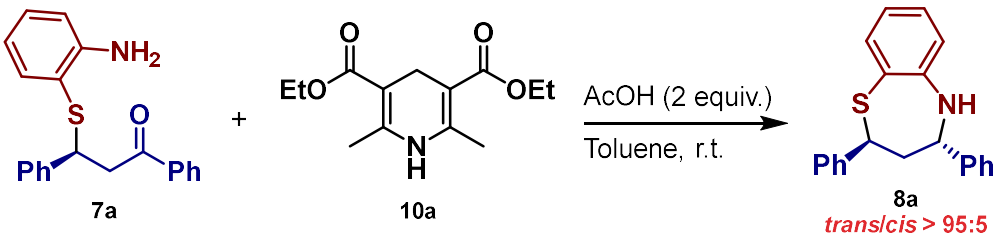
We chose catalyst **9d**, a sulphonamide derived from 9-amino(9-deoxy)epicinchonidine,[7] as it gave the best enantioselectivity (Table 1, entry 4). Then, we tested different solvents in order to evaluate their influence on the enantioselectivity and 1,4-dioxane gave the best result (Table 1, entries 8-12). We found out that lowering catalyst loading to 5 mol% slightly improved the enantioselectivity (Table 1, entry 13), whereas further lowering it to 1 mol% was detrimental (Table 1, entry 14). Despite the promising results obtained so far (Table 1,

[6] For some reviews, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; b) H. Miyabe, Y. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785; c) S. J. Connon, *Chem. Commun.* **2008**, 2499; d) S. Ingemann, H. Hiemstra, in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications, Vol. 2* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**, pp. 119–160; e) *Sustainable Catalysis Without Metals or Other Endangered Metals, Part 2*, (Ed.: M. North), RSC, Cambridge, **2016**; f) P. Chauhan, S.Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253; g) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890.

[7] S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem.* **2008**, *120*, 7990; *Angew. Chem. Int. Ed.* **2008**, *47*, 7872.

entry 13), we faced a serious impediment during the optimization process: the poor reproducibility of the experimental results such as enantioselectivity and conversion. After a thorough investigation we found out that dimerization of 2-aminothiophenol **5a** to the corresponding disulphide, which occurs to various extent during the reaction, could strongly affect the conversion values. Besides, this type of Michael addition is very fast (1-5 h) and, probably, a protocol that involves the addition of neat nucleophile **5a** to the reaction mixture containing *trans*-chalcone **6a** and organocatalyst **9d** is effected by mixing effects, that is the reaction does not occur at the desired dilution but during the mixing process, compromising in this way the enantiomeric excess. In order to overcome these issues we had to fine-tune the reaction set up thus developing a fully reproducible protocol which consisted of the use of a degassed 1,4-dioxane to exclude oxygen and the addition of a solution of nucleophile **5a** to the mixture (Table 1, entry 15).

Afterwards, we moved to prove the feasibility of the diastereoselective cyclization of enantioenriched Michael adduct **7a** in order to deliver the optically active 1,5-benzothiazepine **8a**. We envisaged, relying on the reported literature,[8] that a chiral phosphoric acid mediated reductive amination using a hydride donor such as a Hantzsch ester derivative **10a** would allow us to control the generation of the second chiral centre thus obtaining, hopefully, promising results to tackle the development of a stereodivergent process.

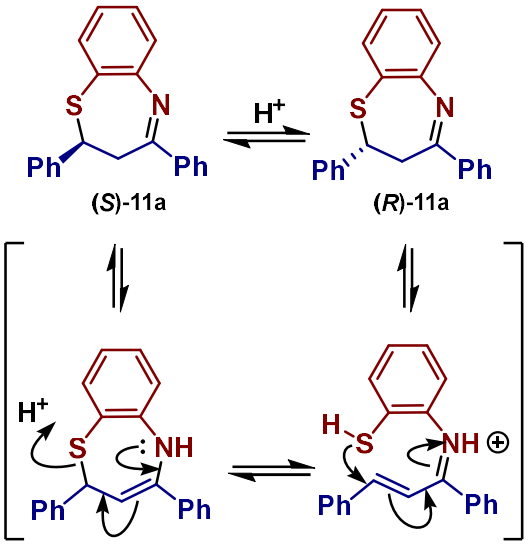


Scheme 5. Evaluation of the substrate bias in the reductive amination reaction

In order to evaluate the substrate bias in the annulation reaction, we performed the reductive amination reaction using acetic acid as promoter. Unfortunately, as shown in Scheme 5, the reaction delivered only the *trans*-diastereoisomer, that is, this transformation is fully substrate controlled rendering almost impossible to overcome its bias by using a chiral catalyst. A series of experiments using various acids and hydride donors gave very similar results. However, even if a diastereodivergent process did not appear to be feasible, the

[8] a) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84. b) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820. c) C. Zheng, S.-L. You *Chem. Soc. Rev.* **2012**, *41*, 2498. C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388.

present synthetic sequence is the first example delivering enantioenriched 2,3,4,5-tetrahydro-1,5-benzothiazepines **8**, therefore we thought that even a simpler diastereo- and enantioselective reaction giving compounds **8** would be a worth goal. We thus set out the study of the second synthetic step, the reductive amination, without using chiral catalysts. This apparently simple transformation required a complete investigation since from the very first attempts to cyclize intermediate **7a** we detected a significant drop of the enantiomeric excess established in the sulfa-Michael reaction. Indeed, racemization of imine intermediate **11a** through retro-sulfa-Michael mechanism may easily occur in presence of acids,[9] which are generally required to promote this type of reaction (Scheme 6).



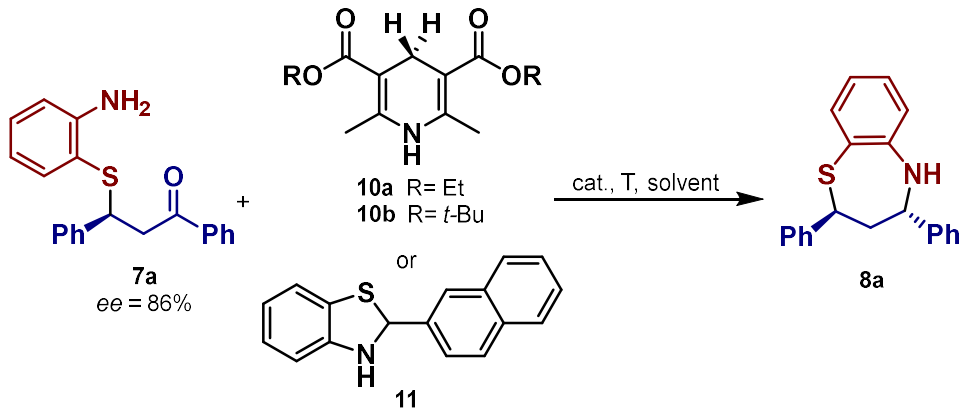
Scheme 6. Plausible racemization pathway occurring during reductive amination

In order to preserve the enantiomeric excess achieved in the sulfa-Michael addition, we carried out a complete optimization of the reaction parameters (Table 2). Initial attempts, using Hantzsch ester derivative **10a** and diphenyl phosphate as acidic promoter,[8a] were accompanied by remarkable detriment of the enantioselectivity (Table 2, entries 1,2). A better preservation of the enantiomeric excess was observed when toluene was employed as solvent, albeit with poor conversion values despite the increment of the reaction temperature (Table 2, entries 3-5), while carrying out the reaction in dichloromethane slightly improved the selectivity (Table 2, entry 6). Different hydride sources were also tested in the transformation, such as *tert*-butyl substituted Hantzsch ester derivative **10b**, which performed significantly better than **10a**, whereas the reaction did not occur in presence of naphthyl-substituted benzothiazoline derivative **11** (Table 2, 7-9). Other acid promoters did not improve the results so far obtained (Table 2, entries 10-12); although the use of *para*-

[9] For 1,5-benzodiazepine racemization through a retro-aza-Michael pathway, see: K. Horiguchi, E. Yamamoto, K. Saito, M. Yamanaka, T. Akiyama, *Chem. Eur. J.* **2016**, *22*, 8078.

toluenesulfonic acid gave a promising result in terms of selectivity, the resulting conversion value was very poor. This was ascribed to the easy air-oxidation of **10b**, as shown by ^{1}H NMR spectrum. Finally, the loss of enantioenrichment was overcome by using some rather classic reductive amination conditions, that is using $NaBH_3CN$ in presence of AcOH (Table 2, entries 13). Lowering the reaction temperature to 0° C prevented any loss of enantiomeric excess, thus establishing the optimal reaction conditions for the reductive amination step.

Table 2. Screening of reaction conditions in the reductive amination reaction: representative results



Entry	Cat. [mol%]	Reducing agent	Solvent [M]	T [°C]	Conv.[b] [%]	*ee*[c] [%, **8a**]
1	$(PhO)_2P(O)OH$ [20]	**10a**	1,4-dioxane [0.12]	r.t.	65	8
2	$(PhO)_2P(O)OH$ [5]	**10a**	1,4-dioxane [0.12]	r.t.	31	15
3	$(PhO)_2P(O)OH$ [20]	**10a**	Toluene [0.12]	r.t.	34	68
4	$(PhO)_2P(O)OH$ [20]	**10a**	Toluene [0.2]	0	20	64
5	$(PhO)_2P(O)OH$ [20]	**10a**	Toluene [0.2]	40	41	60
6	$(PhO)_2P(O)OH$ [20]	**10a**	CH_2Cl_2 [0.2]	r.t.	65	69
7	$(PhO)_2P(O)OH$ [20]	**10b**	1,4-dioxane [0.12]	r.t.	68	60
8	$(PhO)_2P(O)OH$ [20]	**11**	1,4-dioxane [0.12]	r.t.	<10	n.d.
9	$(PhO)_2P(O)OH$ [20]	**10b**	Toluene [0.2]	r.t.	61	80
10	TU[d] [20]	**10b**	Toluene [0.2]	r.t.	>10	n.d.
11	Al_2O_3 neutral	**10b**	Toluene [0.2]	r.t.	Decomp.	-
12	*p*-TSA [ca. 20%]	**10b**	Toluene [0.2]	r.t.	10	83
13	AcOH [200]	$NaBH_3CN$[e]	MeOH [0.2]	r.t.	>95	84
14	AcOH [200]	$NaBH_3CN$[e]	MeOH [0.2]	0	>95	86

[a] Conditions: Michael adduct 7**a** (0.10 mmol, 86% *ee*), solvent (x M), acidic promoter (x mol%), reducing agent (0.15 mmol). [b] Conversion in desired product **8a** determined by ^{1}H NMR after filtration on a plug of silica gel and solvent evaporation. [c] Determined by CSP-HPLC on the purified product **8a**. [d] TU = 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (Schreiner thiourea). [e] 0.40 mmol were used.

Thanks to its crystalline properties, it was possible to obtain product **8a** in nearly enantiopure form after a single crystallization from methanol. Single-crystal X-ray analysis allowed us to determine its absolute configuration, that is (1*S*,3*S*).

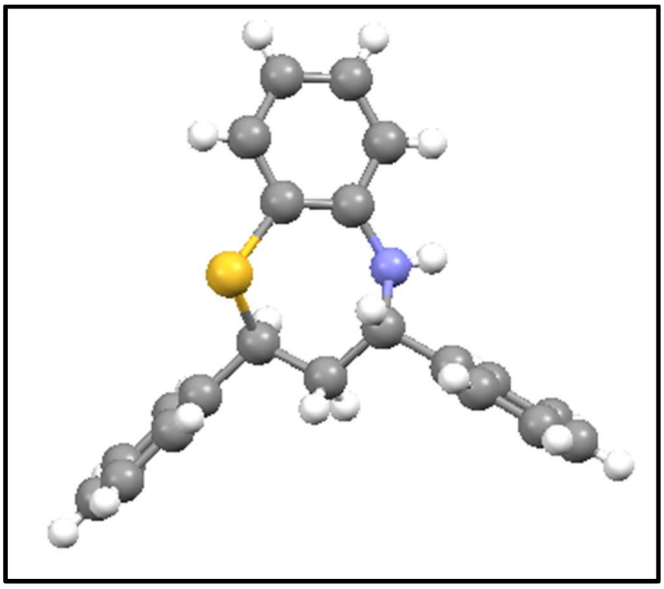
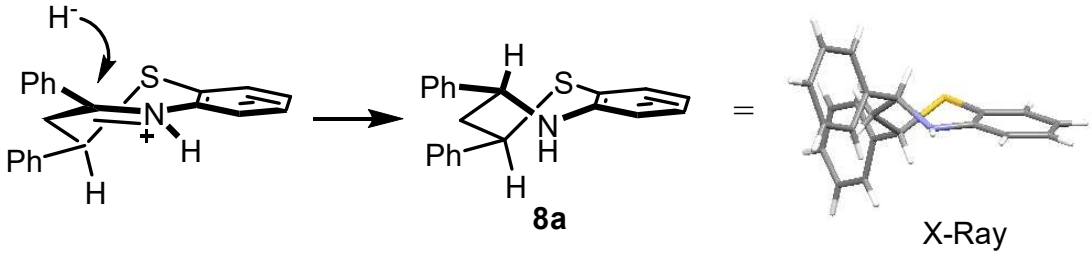


*Figure 3. X-ray structure of compound **8a***

The relative 1,3-*trans* configuration of **8a** is in line with the previous literature data reported for the synthesis of these compounds in racemic form.[10] In the most stable conformation of compound **8a**, a twist boat conformation,[11] the 1,3-*trans* conformation arranges the two bulky phenyl groups in more favourable pseudoequatorial positions, as inferred from the X-ray analysis and related literature data.[10b, 10c,12] For this reason, the full diastereoselectivity observed can be rationalized considering a transition state resembling the twist-boat conformation of product **8a** and by implicating a selective attack of the hydride to the *Re* face of the iminium ion to place the 4-phenyl ring in a pseudoequatorial position (Scheme 7).



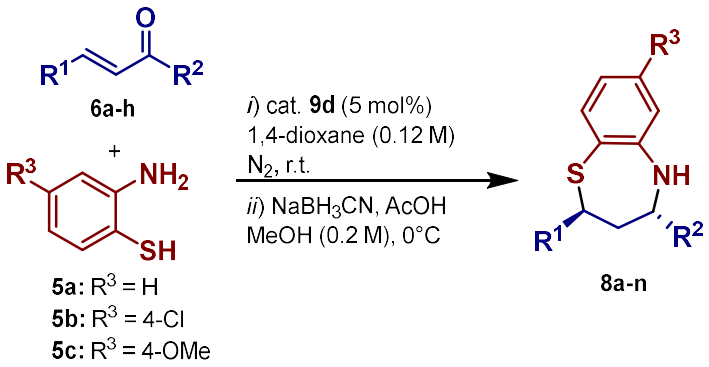
Scheme 7. Rationalization of the trans selectivity of the reduction

After the optimization of the reaction conditions of both synthetic steps, we evaluated the reaction scope (Table 3). *trans*-Chalcones **6a-c**, **6f** bearing a substituent at the *para*-position

[10] a) W. D. Stephens, L. Field, *J. Org. Chem.* **1959**, *24*, 1576; b) M. Muthukumar, K. Thanikasalam, E. M. Mohamed, J. N. Low, C. Glidewell, *Acta Cryst. C*, **2004**, *60*, o421; c) P. Laavanya, K. Panchanatheswaran, M. Muthukumar, R. Jeyaraman, J. A. Karuse Bauer, *Acta Cryst. E*, **2002**, *58*, o701. In the latter paper, the drawing shows the incorrect isomer; the X-Ray structure indicates *trans*-stereochemistry.
[11] J. B. Hendrickson, *J. Am. Chem. Soc.* **1961**, *83*, 4537.
[12] A. Entrena, J. M. Campos, M. A. Gallo, A. Espinosa, *ARKIVOC* **2005**, *vi*, 88.

of the phenyl ring at the double bond reacted smoothly and afforded corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepine **8a-c**, **8f** in moderate to good yields and with enantiselectivities around 80% (Table 3, entries 1-3, 6). A substituent at the *meta*-position on the same ring was well tolerated (Table 3, entry 4) while further increasing steric hindrance in proximity of the reactive centre, such as for substrates **6e**, **6j**, did not prove to be beneficial for the enantioselectivity (Table 3, entries 5, 10). Substitution at the ketonic phenyl group or at both phenyl rings gave comparable results (Table 3, entries 7-9). When aliphatic substituents were employed instead of the aromatic ones the reaction did not provide satisfactory results (Table 3, entries 11, 12). Eventually, an increment in the selectivity was observed when the reaction was carried out with substituted 2-aminothiophenols **5b**, **5c** (Table 3, entries 13, 14). All reactions gave 1,5-benzothiazepines **8a-n** as single diastereoisomers; their relative and absolute configurations were assigned by analogy with compound **8a**.

Table 3. Scope of the reaction



Entry[a]	**6**: R^1 , R^2	**5**	**8**, Yield[b] [%]	ee [%][c]
1	**6a**: Ph, Ph	**5a**	**8a**, 80	86 (98%)[d]
2	**6b**: 4-BrC_6H_4, Ph	**5a**	**8b**, 83	80]
3	**6c**: 4-MeC_6H_4, Ph	**5a**	**8c**, 77	82
4	**6d**: 3-MeC_6H_4, Ph	**5a**	**8d**, 85	79
5	**6e**: 2-MeC_6H_4, Ph	**5a**	**8e**, 65	55
6	**6f**: 4-MeOC_6H_4, Ph	**5a**	**8f**, 79	80
7	**6g**: Ph, 4-MeOC_6H_4	**5a**	**8g**, 82	80
8	**6h**: Ph, 4-MeC_6H_4	**5a**	**8h**, 75	80
9	**6i**: 4-MeC_6H_4, 4-ClC_6H_4	**5a**	**8i**, 71	78
10	**6j**: 1-naphthyl, Ph	**5a**	**8j**, 90	71
11	**6k**: Et, Ph	**5a**	**8k**, n. d.	rac.
12	**6l**: Ph, Me	**5a**	**8l**, 75	43
13	**6a**: Ph, Ph	**5b**	**8m**, 70	87
14	**6a**: Ph, Ph	**5c**	**8n**, 73	81

[a] Conditions: 1. *trans*-chalcones **6a-l** (0.20 mmol), 1,4-dioxane (870 µL), catalyst **9d** (5 mol%), 2-aminothiophenols **2a-c** in 1,4-dioxane (0.30 mmol in 800 µL), r.t., 5 h, filtration on silica gel, evaporation; 2. MeOH (1.0 mL), $NaBH_3CN$ (0.80 mmol), AcOH (0.40 mmol), 0 °C. [b] Yield of isolated product after chromatography on silica gel. A single *trans*-diastereoisomer was obtained in all cases. [c] Determined by CSP-HPLC on the purified products **8a-n**. [d] After a single recrystallization.

2.1.4 Conclusions

To summarize, we developed a catalytic asymmetric sulfa-Michael addition of 2-aminothiophenols **5** to *trans*-chalcones **6**, which after a highly diastereoselective reductive amination afforded the corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepines **8** in moderate to good yields and enantioselectivities. A careful optimization of both reaction steps was essential to face various challenges such as the unsuitability of previously reported protocols for asymmetric additions of simpler thiophenols to *trans*-chalcones **6**, the poor stability of the 2-aminothiophenol substrates **5**, and the stereochemical lability of the Michael adducts under the acidic conditions required in the reductive amination step. Being the catalytic asymmetric addition of 2-aminothiophenols **5** to *trans*-chalcones **6** unreported so far, the present protocol represents the first enantioselective access to 2,3,4,5-tetrahydro-1,5-benzothiazepine structures **8**.

2.1.5 Experimental Section

2.1.5.1 General Methods

^{1}H, ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR.[13] ^{13}C NMR were acquired under ^{1}H broadband decoupling. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electronspray (ES) ionization technique. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at λ = 254 nm. Melting points were measured on a Stuart Scientific melting point apparatus SMP3 and are not corrected.

2.1.5.2 Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. 1,4-Dioxane was degassed according to the pump-freeze-thaw method. Chalcones **6b-k** were prepared according to a reported literature procedure.[14] 4-Phenyl-3-buten-2-one **6l** was purchased from Sigma-Aldrich supplier and used without any

[13] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.
[14] S.-j. Chen, G.-p. Lu, C. Cai, *RSC Adv.* **2015**, *5*, 13208.

further purification. 2-Aminothiophenols **5b,c** were prepared following a modified literature procedure.[15] Catalyst **9d** was prepared according to a literature procedure, using 9-amino(9-deoxy)epicinchonidine instead of 9-amino(9-deoxy)epiquinine.[16]

*2.1.5.3 General procedure to prepare racemic products **5** as HPLC reference:*

To a test tube equipped with a magnetic stirring bar, *trans*-chalcones **6a-l** (0.1 mmol), 1,4-dioxane (0.833 mL, 0.12 M), a catalytic amount of Et_3N (1 drop) and 2-aminothiophenols **5a-c** (0.2 mmol) were added. The mixture was stirred for 2 h, then acetic acid (11.4 µL, 0.2 mmol) and $NaBH_3CN$ (25 mg, 0.4 mmol) were added portion-wise until TLC analysis (eluent *n*-hexane/EtOAc 5:1) showed complete conversion of the corresponding Michael adduct. Afterwards, the reaction was diluted with CH_2Cl_2, quenched with a saturated aqueous solution of Na_2CO_3 and then extracted three times with CH_2Cl_2. The combined organic layers were filtered through a short plug of silica gel, and the solvent removed under reduced pressure. The crude was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2 1:1) to afford the corresponding 1,5-benzothiazepines **8a-n**.

*2.1.5.4 General procedure for the organocatalytic reaction of chalcones **6a-l** with 2-aminothiophenols **5a-c** followed by reductive amination to prepare enantioenriched products **8a-n**:*

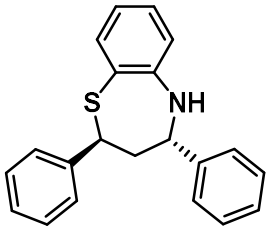
In a Schlenk tube equipped with a magnetic stirring bar, under N_2 atmosphere, *trans*-chalcones **6a-l** (0.20 mmol) and catalyst **9d** (5.6 mg, 0.010 mmol, 5.0 mol%) were dissolved in degassed 1,4-dioxane (870 µL). A solution of 2-aminothiophenols **5a-c** in degassed 1,4-dioxane (0.30 mmol in 800 µL) was then added. The reaction mixture was stirred until ^{1}H-NMR analysis showed complete conversion (less than 5 h). The mixture was then filtered through a short plug of silica gel, the Schlenk tube washed two times with CH_2Cl_2, these washings filtered through the same plug, the plug flushed with CH_2Cl_2, and all the solvents evaporated under vacuum. The thus obtained sulfa-Michael crude products **7** were re-

[15] Y. Fukata, K. Asano, S. Matsubara, *J. Am. Chem. Soc*. **2015**, *137*, 5320. The sticky solid resulting from the reaction was filtered, washed several times with Et_2O and redissolved with water which was then acidified to pH = 3 with HCl 3 M. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting 2-aminothiophenols **2b,c** were used without any further purification.
[16] S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem. Int. Ed.* **2008**, *47*, 7872.

dissolved in CH_2Cl_2, transferred to a test tube equipped with a magnetic stirring bar and the solvent evaporated by flushing the tube with N_2. 1.0 mL of MeOH was then added to the residue, and the resulting solution cooled to 0 °C with stirring. $NaBH_3CN$ (50 mg, 0.80 mmol) and acetic acid (22.8 µL, 0.40 mmol) were added portion-wise every 2 h until TLC analysis (eluent *n*-hexane/EtOAc 5:1) showed complete consumption of the corresponding sulfa-Michael adducts **7**. Afterwards, the reaction was quenched with 1.0 mL of a saturated Na_2CO_3 aqueous solution, and the mixture extracted three times with CH_2Cl_2. The organic layers were filtered through a short plug of silica gel, the plug flushed with CH_2Cl_2, and the solvents removed under vacuum. Purification by column chromatography on silica gel (*n*-hexane/CH_2Cl_2 1:1) afforded the corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepines **8a-n**. ^{1}H-NMR analysis of the products **8a-n** showed the presence of a single *trans*-diastereoisomer.

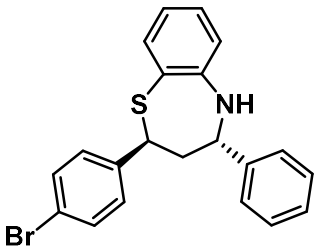
2.1.5.5 Characterisation data

(2*S*,4*S*)-2,4-Diphenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8a)



Following the general procedure, the title compound was obtained in 80% yield as a white solid (m. p. 120-122 °C). ^{1}H-NMR ($CDCl_3$ 400 MHz) δ = 7.46-7.41 (m, 2H), 7.40-7.37 (m, 6H), 7.26-7.20 (m, 2H), 7.16 (dd, J = 7.8, 1.6 Hz, 1H), 6.94 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 6.70 (dt, J = 7.5, 1.3 Hz, 1H), 6.47 (dd, J = 8.0, 1.1 Hz, 1H), 5.56 (dd, J = 11.1, 4.5 Hz, 1H), 5.17 (dd, J = 11.2, 4.8 Hz, 1H), 3.60 (br s, 1H), 2.57 (ddd, J = 13.4, 10.5, 5.0 Hz, 1H), 2.47 (ddd, J = 13.5, 11.4, 4.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$ 100 MHz) δ = 147.4, 143.2, 141.6, 131.5, 129.1, 128.82, 128.0, 127.5, 127.4, 127.0, 121.3, 119.9, 118.6, 58.8, 48.3, 45.3; ESI-MS m/z = 340 $[M + Na]^+$; $[\alpha]^{20}_D$ = -162 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 20.54 min, t_{min} = 22.15 min, *ee* = 86%).

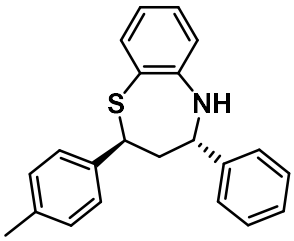
(2*S*,4*S*)-2-(4-Bromophenyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8b)



Following the general procedure, the title compound was obtained in 83% yield as a white solid (m. p. 63-65 °C). ^{1}H-NMR ($CDCl_3$ 400 MHz) δ = 7.41-7.30 (m, 7H), 7.23 (d, J = 8.6 Hz, 2H), 7.15 (dd, J = 7.8, 1.5 Hz, 1H), 6.96 (ddd, J = 7.9, 7.2, 1.6 Hz, 1H), 6.72 (dt, J = 7.6, 1.4 Hz, 1H), 6.50 (dd, J = 8.0, 1.3 Hz, 1H), 5.51 (dd, J = 10.5, 4.2 Hz, 1H), 5.09 (dd, J = 11.1, 4.8 Hz, 1H), 3.62 (br s, 1H), 2.55 (ddd, J = 13.4, 10.8, 5.1

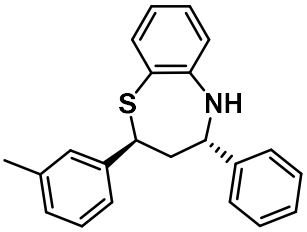
Hz, 1H), 2.42 (ddd, J = 13.4, 11.3, 4.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$ 100 MHz) δ = 147.4, 143.0, 140.6, 131.9, 131.5, 129.12, 129.10, 128.0, 127.2, 127.0, 121.2, 120.9, 120.0, 118.69, 58.7, 47.4, 45.0; ESI-MS m/z = 418-420 $[M + Na]^+$; $[\alpha]^{20}_D$ = -227 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralcel OD, *n*-hexane/*i*-PrOH 80:20, flow = 1 mL/min, λ = 254 nm, t_{maj} = 7.93 min, t_{min} = 9.72 min *ee* = 80%).

(2*S*,4*S*)-4-Phenyl-2-(*p*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8c)



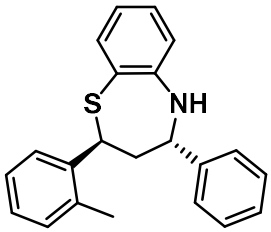
Following the general procedure, the title compound was obtained in 77% yield as a white solid (m. p. 115-117 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.46-7.21 (m, 7H), 7.16-7.10 (m, 3H), 6.94 (dt, J = 7.8, 1.5 Hz, 1H), 6.70 (dt, J = 7.6, 7.4 Hz, 1H), 6.48 (dd, J = 7.9, 1.3 Hz, 1H), 5.56 (dd, J = 10.7, 4.8 Hz, 1H), 5.14 (dd, J = 11.3, 5.1 Hz, 1H), 3.59 (br s, 1H), 2.55 (ddd, J = 13.4, 10.4, 5.1 Hz, 1H), 2.47 (ddd, J = 13.5, 11.3, 4.3 Hz, 1H), 2.31 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 147.4, 143.3, 138.5, 137.1, 131.4, 129.5, 129.0, 127.9, 127.2, 127.0, 126.9, 121.4, 119.8, 118.5, 58.8, 48.0, 45.2, 21.1; ESI-MS m/z = 354 $[M + Na]^+$; $[\alpha]^{20}_D$ = -238 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 16.26 min, t_{min} = 19.48 min, *ee* = 82%).

(2*S*,4*S*)-4-Phenyl-2-(*m*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8d)



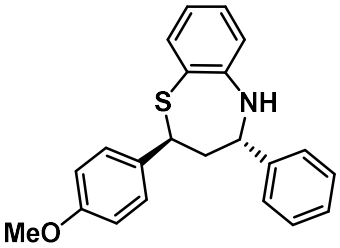
Following the general procedure, the title compound was obtained in 85% yield as a yellow solid (m. p. 49-51 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.48 (d, J = 7.3 Hz, 2H), 7.44-7.32 (m, 3H), 7.27-7.16 (m, 4H), 7.09 (d, J = 7.3 Hz, 1H), 6.98 (dt, J = 7.3, 1.6 Hz, 1H), 6.74 (dt, J = 7.5, 1.3 Hz, 1H), 6.52 (dd, J = 8.0, 1.2 Hz, 1H), 5.63 (dd, J = 10.7, 4.5 Hz, 1H), 5.15 (dd, J = 11.4, 5.2 Hz, 1H), 3.64 (bs, 1H), 2.61 (ddd, J = 13.6, 10.4, 5.2 Hz, 1H), 2.51 (ddd, J = 13.4, 11.4, 4.4 Hz, 1H), 2.36 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 147.4, 143.2, 141.4, 138.5, 131.4, 129.1, 128.7, 128.2, 128.1, 127.9, 127.0, 126.9, 124.3, 121.3, 119.8, 118.5, 58.8, 48.3, 45.3, 21.4; ESI-MS m/z = 366-368 $[M + Cl]^-$; $[\alpha]^{20}_D$ = -251 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 12.36 min, t_{min} = 13.50 min, *ee* = 79%).

(2*S*,4*S*)-4-Phenyl-2-(*o*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8e)



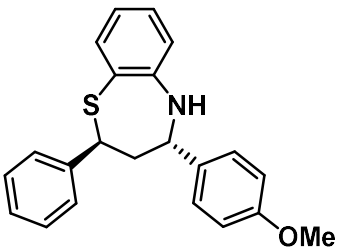
Following the general procedure, the title compound was obtained in 65% yield as a yellow solid (m. p. 101-106 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.50 (d, J = 7.7 Hz, 2H), 7.45-7.33 (m, 4H), 7.24-7.15 (m, 4H), 6.99 (dt, J = 7.3, 1.6 Hz, 1H), 6.74 (dt, J = 7.5, 1.3 Hz, 1H), 6.53 (dd, J = 8.0, 1.4 Hz, 1H), 5.68 (dd, J = 10.1, 4.6 Hz, 1H), 5.43 (dd, J = 11.2, 5.2 Hz, 1H), 3.64 (bs, 1H), 2.63-2.47 (m, 2H), 2.45 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 146.3, 142.2, 138.4, 134.6, 130.2, 129.7, 128.0, 126.9, 126.3, 126.0, 125.9, 125.49, 125.46, 120.5, 118.8, 117.6, 57.9, 43.2, 42.9, 18.6; ESI-MS m/z = 366-368 $[M + Cl]^-$; $[\alpha]^{20}_D$ = -142 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 9.01 min, t_{min} = 10.62 min, *ee* = 55%).

(2*S*,4*S*)-2-(4-Methoxyphenyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8f)



Following the general procedure, the title compound was obtained in 79% yield as a white solid (m. p. 69-71 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.46-7.25 (m, 7H), 7.14 (dd, J = 7.8, 1.6 Hz, 1H), 6.94 (ddd, J = 8.0, 7.4, 1.6 Hz, 1H), 6.84 (m, 2H), 6.70 (dt, J = 7.5, 1.3 Hz, 1H), 6.48 (dd, J = 8.1, 1.2 Hz, 1H), 5.53 (dd, J = 10.2, 4.2 Hz, 1H), 5.15 (dd, J = 11.2, 5.0 Hz, 1H), 3.76 (s, 3H), 3.59 (br s, 1H), 2.55 (ddd, J = 13.6, 10.7, 5.0 Hz, 1H), 2.47 (ddd, J = 13.3, 11.2, 4.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 158.9, 147.4, 143.3, 133.6, 131.4, 129.1, 128.5, 127.9, 127.0, 126.9, 121.4, 119.8, 118.5, 114.2, 58.8, 55.3, 47.6, 45.3; ESI-MS m/z = 370 $[M + Na]^+$; $[\alpha]^{20}_D$ = -246 (c = 0.50 $CHCl_3$). The ***ee*** was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 24.92 min, t_{min} = 30.63 min, *ee* = 80%).

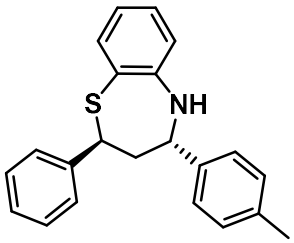
(2*S*,4*S*)-4-(4-Methoxyphenyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8g)



Following the general procedure, the title compound was obtained in 82% yield as a white solid (m. p. 121-123 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.38-7.28 (m, 6H), 7.26-7.21 (m, 1H), 7.15 (dd, J = 7.8, 1.5 Hz, 1H), 6.97-6.88 (m, 3H), 6.69 (dt, J = 7.6, 1.4 Hz, 1H), 6.47 (dd, J = 7.9, 1.2 Hz, 1H), 5.53, (dd, J = 10.6, 4.4 Hz, 1H), 5.14 (dd, J = 11.5, 5.0 Hz, 1H), 3.81 (s, 3H), 3.54 (br s, 1H), 2.56 (ddd, J = 13.7, 10.5, 5.0 Hz, 1H), 2.45 (ddd, J = 13.5, 11.6, 4.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 159.2, 147.4, 141.6, 135.3, 131.4, 128.8, 128.2, 127.4, 127.0, 121.2, 119.8, 118.5, 114.3, 58.2, 55.4, 48.3,

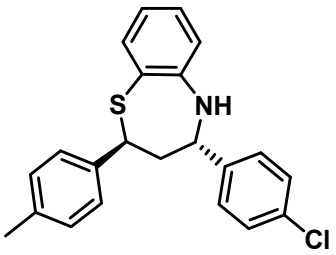
45.2; ESI-MS m/z = 370 $[M + Na]^+$; $[\alpha]^{20}_D$ = -237 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 27.32 min, t_{min} = 35.57 min, *ee* = 80%).

(2*S*,4*S*)-2-Phenyl-4-(*p*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8h)



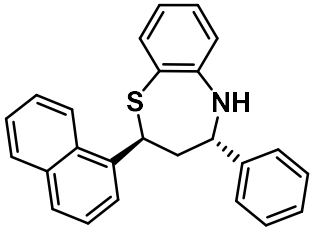
Following the general procedure, the title compound was obtained in 75% yield as a white solid (m. p. 103-106 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.37-7.12 (m, 10H), 6.93 (dt, J = 7.2, 1.5 Hz, 1H), 6.68 (dt, J = 7.3, 1.3 Hz, 1H), 6.45 (dd, J = 8.0, 1.2 Hz, 1H), 5.53 (dd, J = 10.7, 4.2 Hz, 1H), 5.15 (dd, J = 11.4, 5.0 Hz, 1H), 3.56 (br s, 1H), 2.55 (ddd, J = 13.2, 10.2, 4.6 Hz, 1H), 2.45 (ddd, J = 13.2, 11.0, 4.3 Hz, 1H), 2.34 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 147.5, 141.6, 140.3, 137.7, 131.4, 129.7, 128.8, 127.4, 127.4, 127.0, 126.9, 121.2, 119.8, 118.5, 58.5, 48.3, 45.2, 21.1; ESI-MS m/z = 354 $[M + Na]^+$; **[**$\alpha]^{20}_D$ = -279 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 18.04 min, t_{min} = 22.18 min, *ee* = 80%).

(2*S*,4*S*)-4-(4-Chlorophenyl)-2-(*p*-tolyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8i)



Following the general procedure, the title compound was obtained in 71% yield as a yellow solid (m. p. 66-68 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.35-7.12 (m, 9H), 6.96 (dt, J = 7.6, 1.6 Hz, 1H), 6.71 (dt, J = 7.6, 1.5 Hz, 1H), 6.49 (dd, J = 8.0, 1.2 Hz, 1H), 5.50 (dd, J = 10.0, 4.1 Hz, 1H), 5.12 (dd, J = 11.4, 5.1 Hz, 1H), 3.59 (br s, 1H), 2.55 (ddd, J = 13.3, 10.4, 4.8 Hz, 1H), 2.45-2.33 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 147.4, 140.09, 140.06, 137.8, 133.1, 131.4, 129.7, 128.9, 128.8, 127.2, 126.9, 120.9, 119.9, 118.6, 58.4, 47.4, 45.1, 21.1; ESI-MS m/z = 388-390 $[M + Na]^+$; $[\alpha]^{20}_D$ = -211 (c = 0.50 $CHCl_3$). The ***ee*** was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 25.90 min, t_{min} = 31.42 min, ***ee*** = 78%).

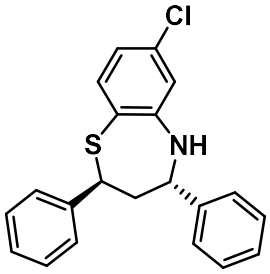
(2*S*,4*S*)-2-(Naphthalen-1-yl)-4-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8j)



Following the general procedure, the title compound was obtained in 90% yield as a white solid (m. p. 144-146 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 8.16 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.55-7.28 (m, 9H), 7.17 (dd, J = 7.7, 1.5 Hz, 1H), 6.98 (dt, J = 7.4, 1.6 Hz, 1H), 6.72 (dt, J = 7.6, 1.3 Hz, 1H), 6.53 (dd,

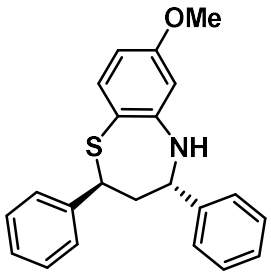
J = 8.0, 1.3 Hz, 1H), 5.97 (dd, J = 11.6, 5.0 Hz, 1H), 5.74 (dd, J = 10.3, 4.3 Hz, 1H), 3.68 (br s, 1H), 2.71 (ddd, J = 13.6, 11.6, 4.4 Hz, 1H), 2.63 (ddd, 13.4, 10.4, 4.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 147.5, 143.2, 137.3, 134.1, 131.4, 130.8, 129.1, 129.0, 128.2, 128.0, 127.12, 127.09, 126.4, 125.8, 125.5, 124.6, 123.5, 121.5, 119.9, 118.6, 58.9, 44.3; ESI-MS m/z = 390 $[M + Na]^+$; $[\alpha]^{20}_D$ = -295 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 20.85 min, t_{min} = 17.85 min, *ee* = 71%).

(2*S*,4*S*)-7-Chloro-2,4-diphenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8m)



Following the general procedure, the title compound was obtained in 70% yield as a yellow solid (m. p. 122-124 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.44-7.21 (m, 10H), 7.05 (d, J = 8.3 Hz, 1H), 6.65 (dd, J = 8.2, 2.2 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 5.58 (ddd, J = 10.6, 4.0, 1.7 Hz, 1H), 5.11 (dd, J = 11.5, 5.1 Hz, 1H), 3.62 (br s, 1H), 2.59 (ddd, J = 13.4, 10.5, 5.0 Hz, 1H), 2.47 (ddd, J = 13.5, 11.3, 4.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 148.2, 142.6, 141.1, 132.4, 132.3, 129.1, 128.8, 128.1, 127.5, 127.2, 126.9, 119.60, 119.57, 117.9, 58.5, 48.4, 44.9; ESI-MS m/z = 374-376 $[M + Na]^+$; $[\alpha]^{20}_D$ = -230 (c = 0.50 $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralcel OD, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 10.48 min, t_{min} = 12.92 min, *ee* = 87%).

(2*S*,4*S*)-7-Methoxy-2,4-diphenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine (8n)



Following the general procedure, the title compound was obtained in 73% yield as a white solid (m. p. 112-114 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.50-7.22 (m, 10H), 7.12 (d, J = 8.6 Hz, 1H), 6.35 (dd, J = 8.6, 2.8 Hz, 1H), 6.11 (d, J = 2.6 Hz, 1H), 5.58 (dd, J = 10.3, 3.9 Hz, 1H), 5.00 (dd, J = 11.0, 5.0 Hz, 1H), 3.73 (s, 3H), 3.68 (br s, 1H), 2.61 (ddd, J = 13.6, 10.4, 5.1 Hz, 1H), 2.50 (ddd, J = 13.4, 11.0, 3.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 159.3, 148.6, 143.3, 141.8, 132.8, 129.0, 128.7, 127.9, 127.31, 127.26, 127.0, 112.7, 106.0, 104.0, 58.6, 55.2, 48.4, 45.4; ESI-MS m/z = 370 $[M + Na]^+$; $[\alpha]^{20}_D$ = -170 (c = 0.50, $CHCl_3$). The *ee* was determined by chiral stationary phase HPLC (Chiralcel OD, *n*-hexane/*i*-PrOH 90:10, flow = 0.75 mL/min, λ = 254 nm, t_{maj} = 10.46 min, t_{min} = 12.88 min, *ee* = 81%).

2.2 Sequential Catalytic Approach Towards the Stereodivergent Synthesis of β,β-Disubstituted-α-Aminoacid Derivatives.

2.2.1 Background

Natural *α*-amino acids represent an inestimable source of chiral building blocks that find application in an extraordinary variety of fields; they serve as starting materials in the preparation of a wealth of enantiomerically pure pharmaceuticals, organocatalysts, ligands for transition-metal catalysts and many other types of chiral compounds.[1] Over the past years, in order to broaden the availability of these compounds, an enormous number of catalytic asymmetric routes towards the synthesis of enantiomerically enriched non-natural *α*-amino acids have been developed. In this respect, azlactones (also known as oxazolones or oxazol-5(4*H*)-ones) represent an attractive alternative as their scaffold consists of "masked" amino acids (Figure 1).[2]

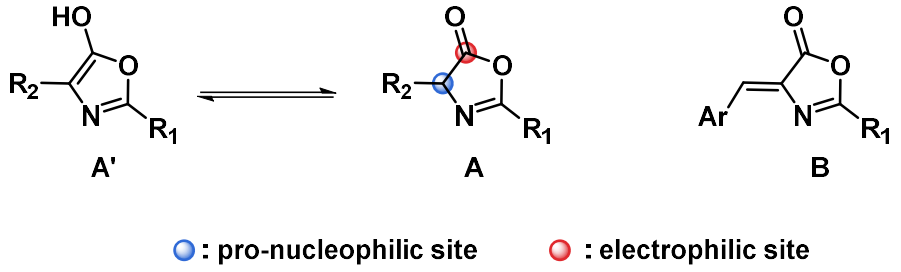


*Figure 1. Structure of azlactone **A**, its enol tautomer **A'** and arylidene azlactone **B**, also known as Erlenmeyer azlactone*

Azlactones are easily prepared either by the Erlenmeyer azlactone synthesis[3] or from readily available amino acids by N-acylation (e.g. with benzoyl chloride) followed by cyclization-dehydration in the presence of a condensation agent (e.g. acetic anhydride).[4] Structurally speaking, oxazolones or azlactones (**A**) are five-membered ring lactones containing a

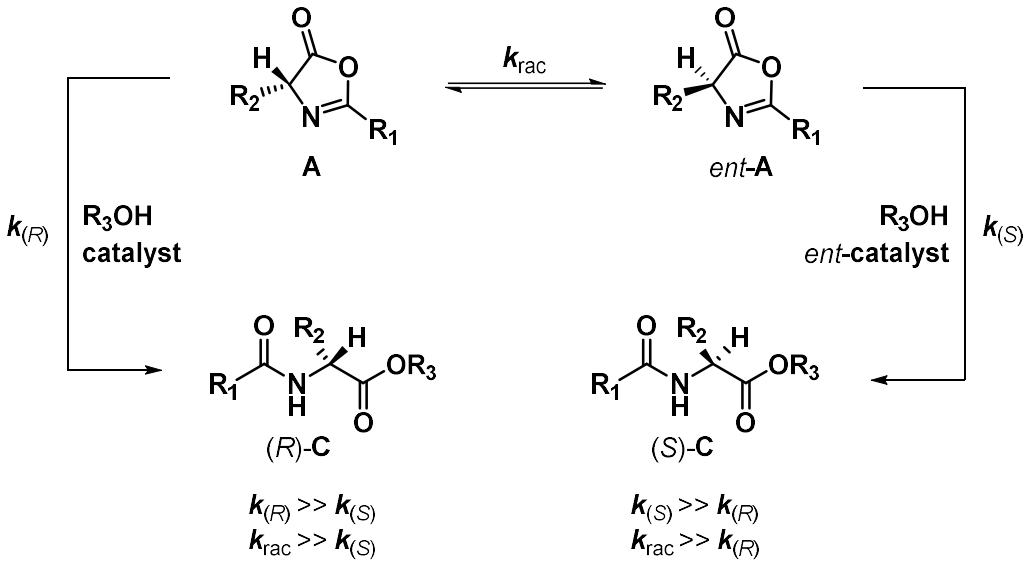
[1] a) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788. b) R. N. Patel in *Stereoselective Biocatalysis* (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, pp. 877 – 902. c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481. d) H. Gröger, K. Drauz in *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**, pp. 131 – 147.

[2] a) P. P. de Castro, A. G. Carpanez, G. W. Amarante, *Chem. Eur. J.* **2016**, *22*, 10294; b) A.-N. R. Alba, R. Rios, *Chem Asian J.* **2011**, *6*, 720.

[3] a) F. Erlenmeyer, *Annalen der Chemie*, **275**, 1. doi:10.1002/jlac.18932750102; b) J. Plöchl, *Berichte der deutschen chemischen Gesellschaft*, **1884**, *17*, 1616.

[4] H. E. Carter, *Org. React.* **1946**, *3*, 198.

nitrogen atom at the *β*-position with respect of the carbonylic moiety. Their versatility is associated with the presence of a rather acidic proton at the C_4 ($pK_a \sim 9$);[5] the decrease of the pK_a value is due to the aromatic character of the corresponding enol tautomer **A'** (Figure 1). Over the past decades, the catalytic asymmetric dynamic kinetic resolution (DKR) of racemic azlactones,[6] through alcoholysis reaction (Scheme 1), have found great attention in the field of asymmetric catalysis, since it leads to the formation of *N*-acyl *α*-aminoesters.

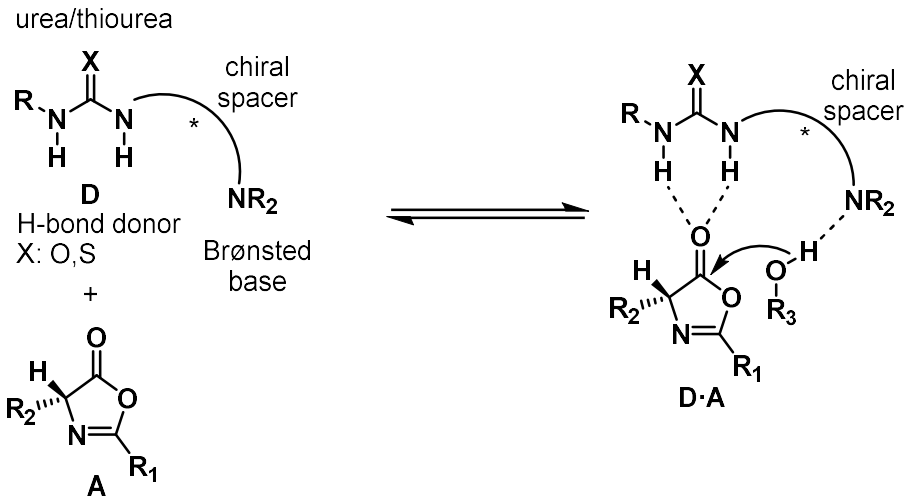


*Scheme 1. Basis of the dynamic kinetic resolution of azlactones **A***

The first efficient highly enantioselective example of organocatalytic asymmetric DKR of azlactones was reported by Berkessel *et al*[6a] in which they demonstrated, by ^1H NMR analysis, that a substrate-catalyst interaction occurs by hydrogen-bonding interactions in order to generate molecular aggregate **D·A**.

[5] a) M. Goodman, L. Levine, *J. Am. Chem. Soc.* **1964**, *86*, 2918; b) J. De Jersey, B. Zerner, *Biochemistry* **1969**, *8*, 1967; c) M. Slebioda, M. A. St-Amand, F. M. F. Chen, N. L. Benoiton, *Can. J. Chem.* **1988**, *66*, 2540.

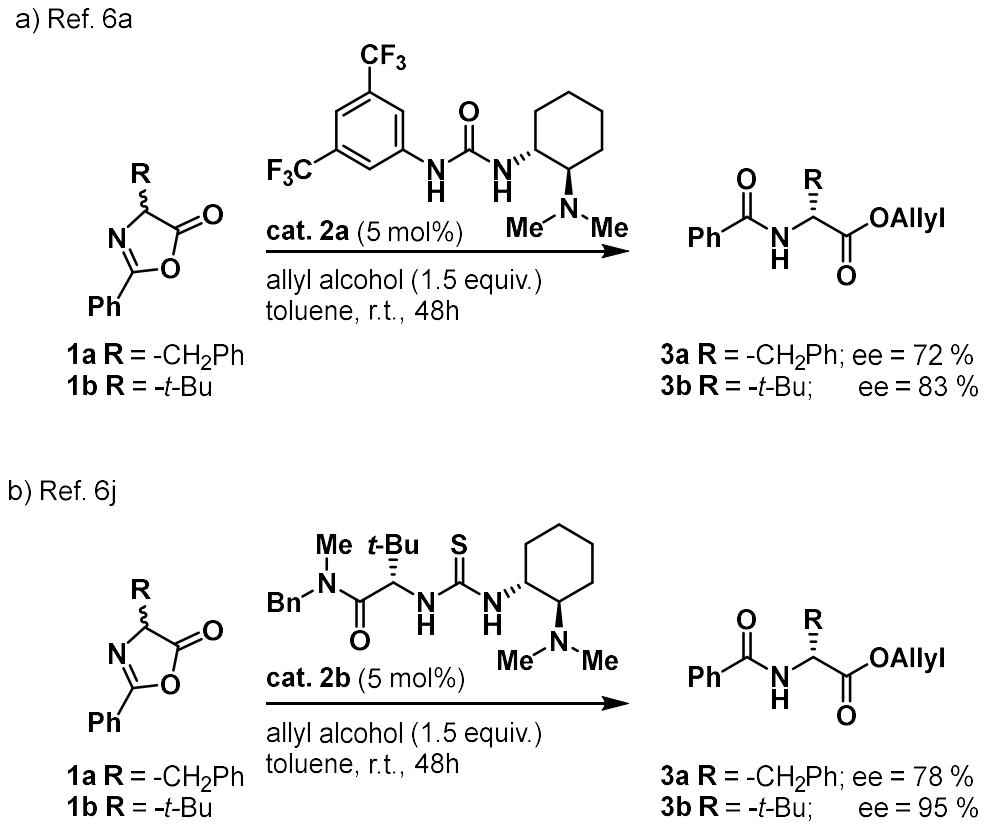
[6] For a nonenzymatic DKR of azlactones see: J. Liang, J. C. Ruble, G. C Fu, *J. Org. Chem.* **1998**, *63*, 3154. For alcohols as nucleophiles see: a) F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, A. Berkessel, *Angew. Chem. Int. Ed.* **2005**, *44*, 807; b) D. A. Chaplin, M. E. Fox, S. H. B. Kroll, *Chem. Commun.* **2014**, *50*, 5858; c) A. J. Metrano, S. J. Miller, *J. Org. Chem.* **2014**, *79*, 1542; d) X. Yang, G. Lu, V. B. Birman, *Org. Lett.* **2010**, *12*, 892; e) G. Lu, V. B. Birman, *Org. Lett.* **2011**, *13*, 356; f) S. Tallon, F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* **2015**, *54*, 813; *Angew. Chem.* **2015**, *127*, 827; For thiols as nucleophiles see: g) Z. Rodriguez-Docampo, C. Quigley, S. Tallon, S. J. Connon, *J. Org. Chem.* **2012**, *77*, 2407; h) C. Palacio, S. J. Connon, *Eur. J. Org. Chem.* **2013**, 5398; i) Z.-C. Geng, N. Li, J. Chen, X.-F. Huang, B. Wu, G.-G Liu, X.-W. Wang, *Chem Commun.* **2012**, *48*, 4713; j) S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, A. Berkessel, *Chem. Commun.* **2005**, 1898. For amines as nucleophiles see: k) Y.-C. Zhang, Q. Yang, X. Yang, Q.-N. Zhu, F. Shi, *Asian J. Org. Chem.* **2016**, *5*, 914; For oximes as nucleophiles see: l) K. Yu, X. Liu, X. Lin, L. Lin, X. Feng, *Chem. Commun.* **2015**, *51*, 14897.



*Scheme 2. Interactions in the azlactone-catalyst aggregate **D·A** and mechanism of alcoholysis*

The supramolecular complex **D·A** the carbonyl group is activated towards racemization (by enolization) by the H-bond moiety of the catalyst, while the nucleophilicity of the alcohol is enhanced by an interaction with the tertiary amine of the catalyst.[7] In this reaction model of the ring opening reaction, one of the two diastereomeric supramolecular aggregates **D·A**, resulting from the interaction of the catalyst **D** with **A** or its enantiomeric form *ent*-**A**, is expected to react faster to deliver the enantioenriched product.

[7] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am Chem. Soc.* **2003**, *125*, 12672.

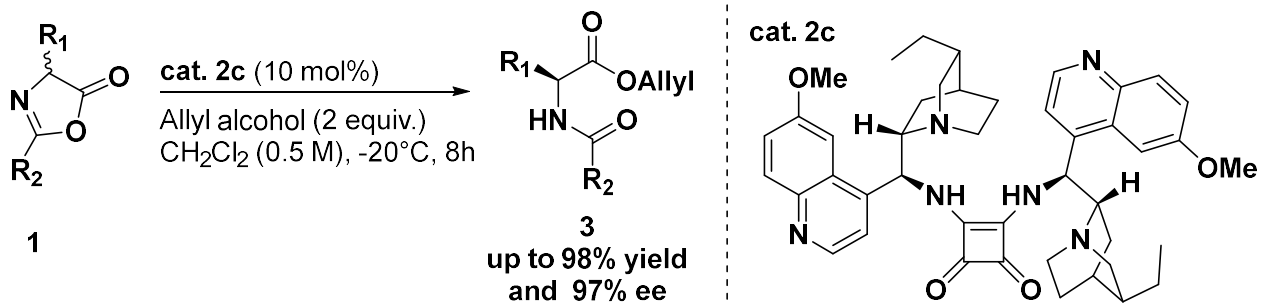


*Scheme 3. Organocatalytic asymmetric DKR of azlactones **1a,b** promoted by urea-derived catalysts **2a,b**: representative results*

The present methodology relies on the Takemoto-type urea bifunctional organocatalyst **2a**[7] to promote the nucleophilic attack of allylic alcohol to azlactones **1a**,**b**, thus delivering the *N*-acyl protected *α*-aminoester products **3a,b** in an enantioenriched form. Some initial results are shown in Scheme 3. The same group reported a second-generation thiourea catalyst **2b** in which they replaced the aryl group with the amine derived by NH-Boc protected L-*tert*-leucine amino acid.[6j] In this example, the selectivity of the reaction is enhanced, especially when bulky R group on the azlactone are employed.

Later, in 2009, Song and co-workers[8] developed the catalytic DKR of azlactones with alcohols mediated by the squaramide-based dimeric dihydroquinine alkaloid **2c** [6f, 9] (Scheme 4).

[8] J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang, C. E. Song, *Chem. Commun.* **2009**, 7224.
[9] a) P. Renzi, C. Kronig, A. Carlone, S. Eröksüz, A. Berkessel, M. Bella, *Chem. Eur. J.* **2014**, *20*, 11768; b) E. H. Nam, S. E. Park, J. S. Oh, S. Some, D. Y. Kim, H. Y. Bae C. E. Song, *Bull. Korean Chem. Soc.* **2011**, *32*, 3127; c) W. Yang and D.-M. Du, *Chem. Commun.* **2011**, *47*, 12706; g) N. Molleti, V. K. Singh, *Org. Biomol. Chem.* **2015**, *13*, 5243.



*Scheme 4. Catalytic DKR of the racemic valine-derived azlactone **1** with allyl alcohol*

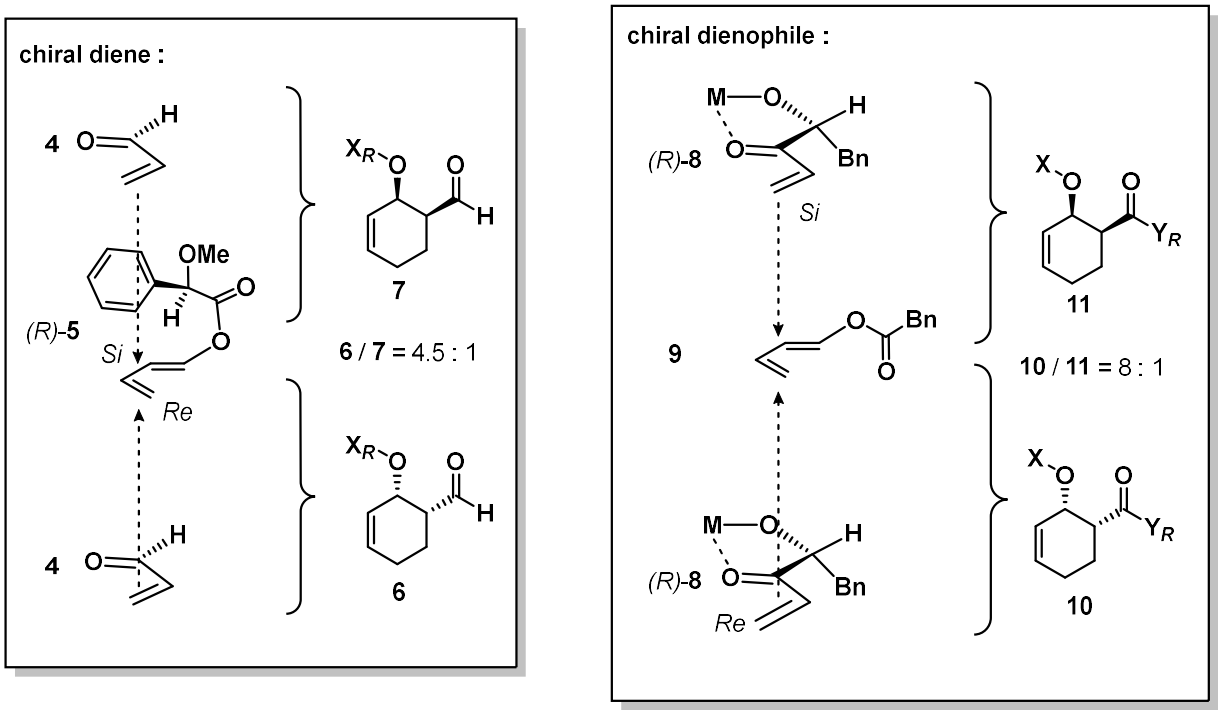
Although urea/thiourea based bifunctional organocatalysts are prone to form supramolecular self-associated aggregates, which increasing the concentration or lowering the temperature can negatively affect both their activity and stereoselectivity,[10] the authors demonstrated that the steric bulk of catalyst **2c** is able to prevent this self-assembling phenomena delivering products **3** in excellent yield and enantioselectivity even at relatively high concentration.

2.2.2. Interactions of Two Chiral Reactants, Concept of Matched and Mismatched Pairs and Evaluation of the Selectivity

The interaction of two chiral reactants can be approximately evaluated considering a set of reaction models in which the facial diastereoselectivity is assessed for each single reactant.[11] For example, the pericyclic Diels-Alder reaction of Trost's chiral diene (*R*)-**5**[12] with achiral acrolein **4** mediated by $BF_3{\cdot}OEt_2$ leads to the formation of a 4.5 : 1 mixture of diastereoisomers **6** and **7** respectively (Scheme 5, left). This selectivity can be rationalized by taking into account the conformation adopted by (*R*)-**5** in the proposed transition state. The bulky phenyl group of the diene covers one face of the *π*-system, that is, the *Si* face is more shielded because of steric clash. Similarly, butadienyl phenyl acetate **9**, an achiral diene, is predicted to approach the *Re* face of the chiral dienophile (*R*)-**8**, which arranges in a chelated five-membered ring conformation in presence of $BF_3{\cdot}OEt_2$ (Scheme 5, right). In this case, the two faces of the double bond of (*R*)-**8** are differentiated by the (small) hydrogen

[10] a) H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin, C. E. Song, *Chem. Commun.* **2008**, 1208; b) G. Tárkányi, P. Király, S. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.* **2008**, *14*, 6078.
[11] W. Choy, J. S. Petersen, L. R. Sita, S. Masamune, *Angew. Chem. Int. Ed.* **1985**, *24*, 1.
[12] D. O'Krongly, J. L. Belletire, B. M. Trost, *J. Am. Chem. Soc.* **1980**, *102*, 7595.

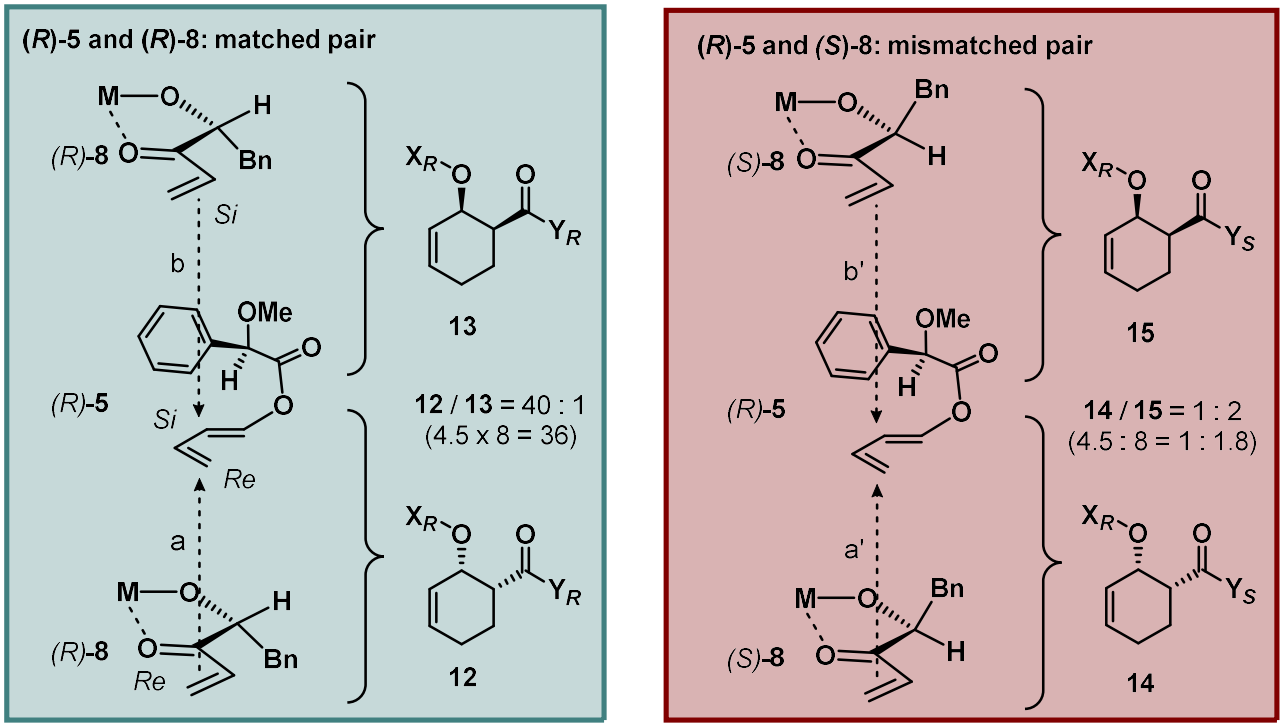
and the (large) benzyl groups of the chiral centre. The facial diastereoselectivity of (*R*)-**8** is indeed 8 : 1 in favour of the formation of **10** over **11**.



*Scheme 5. Facial diastereoselectivity induced by (R)-**5** and (R)-**8** in a Diels-Alder reaction*

Now that facial diastereoselectivities have been evaluated for both reactants, one can evaluate the interaction of the two together (Scheme 6). Compare the interactions of the *Re* face of (*R*)-**8** and the *Re* face of (*R*)-**5** (arrow a) with that between the *Si* face of (*R*)-**8** and the *Si* face of (*R*)-**8** (arrow b) which should lead to products **12** and **13** respectively (Scheme 6, blue box). Both the benzyl substituent of (*R*)-**8** and the phenyl group of (*R*)-**5** face each other: the resulting steric clash in the corresponding transition state disfavours the formation of product **13**. Indeed, the reactants are acting in concert to form product **12**, resulting in a **12** / **13** ratio of 40 : 1, which is higher than the selectivity of either reactant. It is possible to refer to this combination of reactant configurations as ***matched pair***. In contrast, the reaction between (*R*)-**5** and(*S*)-**8** delivers a stereochemical outcome considerably different (note that the chirality of dienophile **8** is now reversed). Now, in both face interactions (a' and b', Scheme 6, red box) either the phenyl group of (*S*)-**8** or the benzyl group of (*R*)-**5** produce unfruitful steric repulsion between the two reacting *π*-systems. Therefore, the facial diastereoselectivities of (*R*)-**5** and (*S*)-**8** are counteracting each other to the formation of products **14** and **15**. For this reason (*R*)-**5** and(*S*)-**8** can be called as ***mismatched pair*** delivering products **14** and **15** in a 1 : 2 ratio, which is smaller than either of the two selectivities. The rationalization of this type of scenario will be extremely helpful to the understanding of ***matched*** and ***mismatched pairs*** encountered in the project that will be

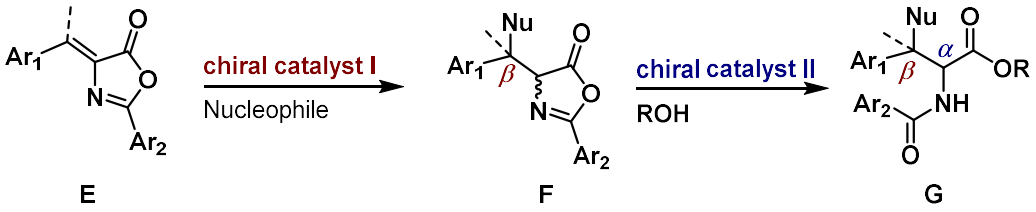
presented hereafter. As a rule of thumb, the selectivity in the matched case is the multiplication of the two separate selectivities, while in the mismatched case the resulting selectivity is the division (Scheme 6).



Scheme 6.Interaction of the two chiral reactants in the Diels-Alder reaction

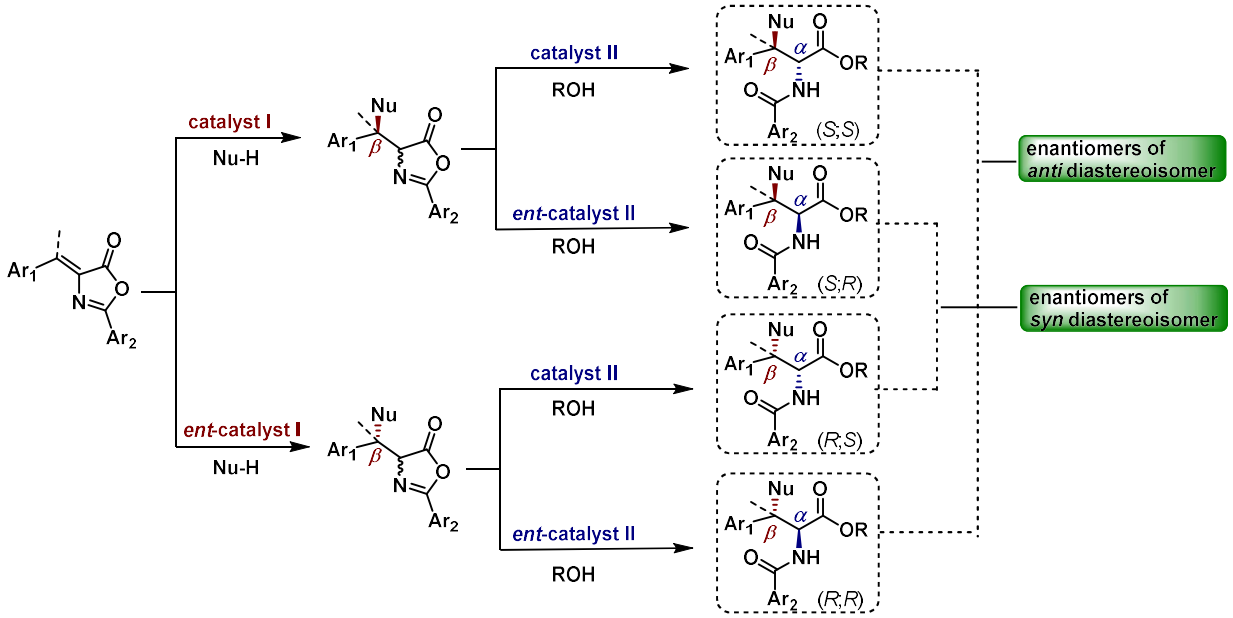
2.2.3 Aim of the Project

As described before in paragraph 2, there is a high demand of streamlined stereodivergent processes that give access to all possible stereoisomers of a desired chiral product bearing multiple stereocenters. With respect to this, we envisaged that exploiting the double nature of an Erlenmeyer azlactone derivative **E** (in a two-step catalytic sequence, it would be possible the development of a stereodivergent synthesis. More in detail, a first organocatalytic asymmetric Michael addition promoted by **chiral catalyst I** would deliver the C_4-substituted azlactone **F** with the defined configuration at the *β*-position that upon ring-opening reaction, through an organocatalytic asymmetric DKR mediated by **chiral catalyst II** (different from **chiral catalyst I**), would afford *N*-protected *α*-aminoester **G** setting in this way the configuration of the *α*-chiral centre (Scheme 7).



*Scheme 7. Sequential catalytic process to access all possible stereoisomers of product **G***

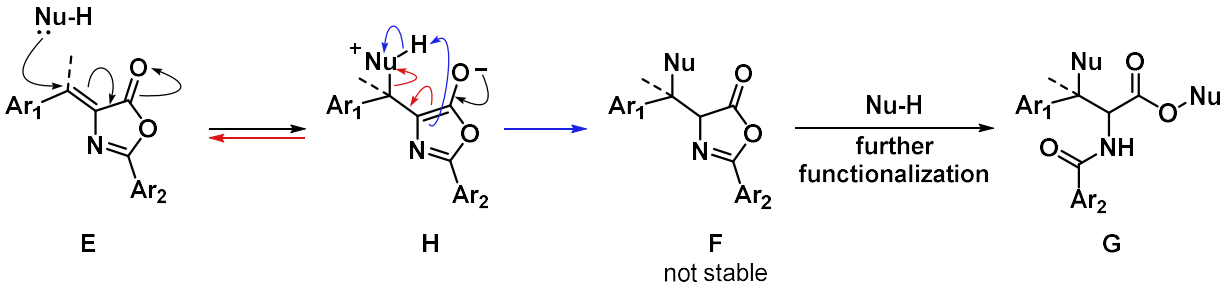
In this scenario, each catalyst is able to control the stereoselective bond-forming event of only one stereogenic centre, as such the selection of the proper enantiomer of the corresponding catalyst enables the achievement of the desired configuration in the final product (Scheme 8).



Scheme 8.Planned stereodivergent synthesis using a sequential catalytic approach

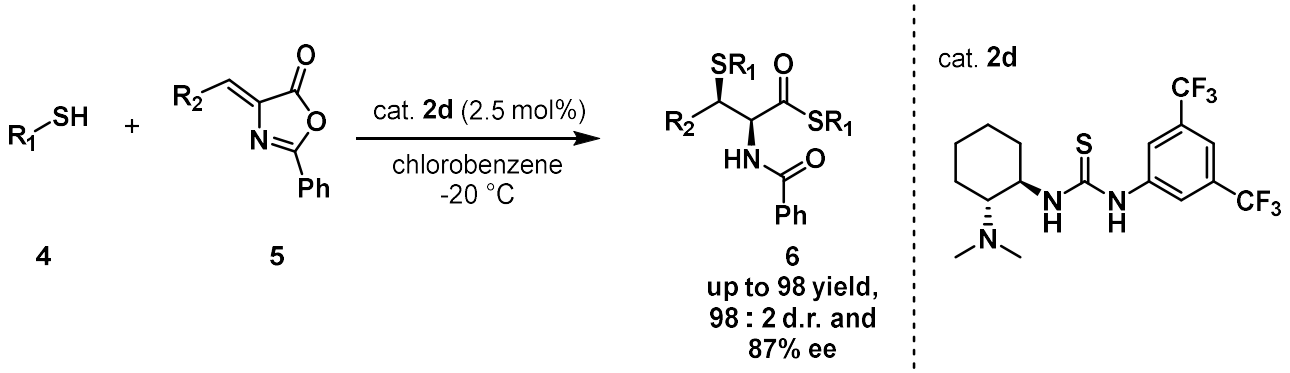
Curiously, it is very difficult to stop at the Michael adduct after a single addition of nucleophile to Erlenmeyer-type azlactones; in fact, there are no examples of asymmetric catalytic Michael addition to arylidene azlactones, whereas a multitude of asymmetric catalytic methodologies have been developed in which the oxazolone, functionalized at C_4 atom, acts as nucleophile.[13] This is probably because of the aromatic-like nature of the resulting enolate upon the addition. Enolate **H** probably prefers to give back the nucleophile through a retro-Michael reaction (Scheme 9, red pathway), rather than accepting a proton at the C_4 position to afford Michael adduct **J** (Scheme 9, blue pathway).

[13] For some selected organocatalytic examples see: a) G. Li, W. Sun, J. Li, F. Jia, L. Hong, R. Wang, *Chem. Commun.* **2015**, *51*, 11280; b) D. Uraguchi, K. Yoshioka, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370; c) E. P. Ývila, R. M. S. Justo, V. P. Gonçalves, A. A. Pereira, R. Diniz, G. W. Amarante, *J. Org. Chem.* **2015**, *80*, 590.



*Scheme 9. Reversible Michael addition of Erlenmeyer azlactones **E***

On the other hand, arylidene azlactones have been extensively used in catalytic asymmetric annulation reactions to afford chiral functionalised cyclic products in an enantioenriched form.[14] Generally, the reaction of monofunctional nucleophiles, such as thiols, to this peculiar *α,β*-unsaturated system results in double addition thus delivering, once again, the open-product.[6l] In 2012, Wang and co-workers reported the organocatalytic asymmetric thio-Michael/ring opening process, in which arylidene azlactones **5** are reacted with an excess of thiophenols in presence of Takemoto's catalyst **2d**, in order to deliver the products in excellent yield and good selectivity. This synthetic sequence is not able to stop at the Micheal adduct as upon the first nucleophilic addition the intermediate undergoes the ring-opening reaction to afford product **6** (Scheme 10).



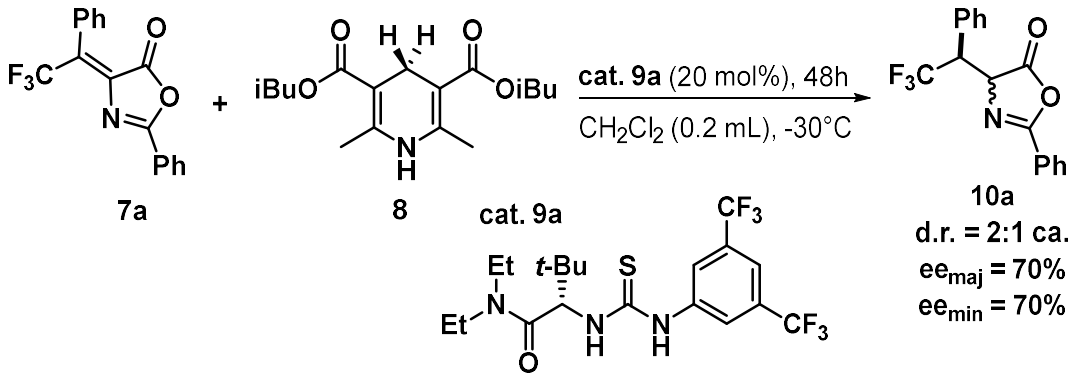
Scheme 10. Organocatalytic asymmetric thio-Michael/ring opening reaction

2.2.4 Results and Discussion

After a long effort-demanding and intensive investigation of suitable azlactones, nucleophiles, chiral catalysts, reaction temperatures, solvent and dilution, we found that the organocatalytic enantioselective hydrogen transfer gave promising results as first step of the

[14] For some selected examples see: a) B. M. Trost, P. J. Morris, *Angew. Chem. Int. Ed.* **2011**, *50*, 6167; b) M. Q. Zhou, J. Zuo, B. D. Cui, J. Q. Zhao, Y. You, M. Bai, Y. Z. Chen, X. M. Zhang, W. C. Yuan, *Tetrahedron* **2014**, *70*, 5787; c) P. J. Morris, S. J. Sprague, B. M. Trost, *J. Am. Chem. Soc.* **2012**, *134*, 17823; d) S. Izumi, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2016**, *18*, 696; e) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943; f) H. Jiang, B. Gschwend, L. Albrecht, S. G. Hansen, K. A. Jørgensen *Chem. Eur. J.* **2011**, *17*, 9032.

sequential catalytic synthesis. More in detail, carrying the reaction with Erlenmeyer azlactone **7a**, derived from the 2,2,2-trifluoroacetophenone, in presence of Hantzsch ester derivative **8**[15] catalysed by the Jacobsen-type thiourea[16] **9a**, in CH_2Cl_2 as solvent at -30 °C to inhibit background reaction, delivered the hydrogenated corresponding product **10a** in a 2:1 diastereomeric ratio and ee values (determined after alcoholysis) of 70% for both diastereisomers (Scheme 11).

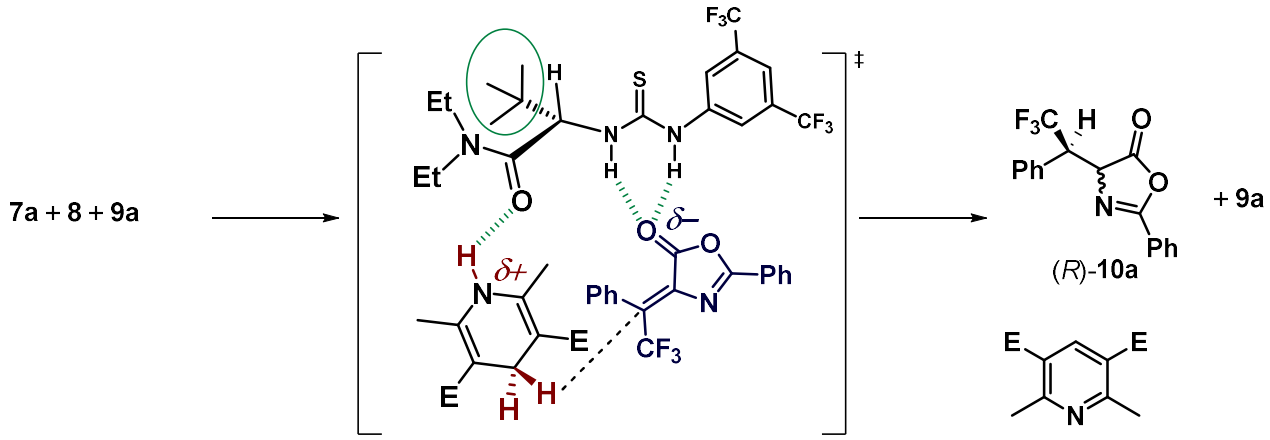


*Scheme 11. Preliminary results of the organocatalytic enantioselective hydrogen transfer of arylidene azlactone **7a** and Hantzsch ester **8***

Based on previously determined conformations and mode of action of amido-thiourea catalysts related to **9a**[16a, b] it might be possible to propose a reaction model in which the bulky *tert*-butyl group on the catalyst locks its conformation and thus defines its geometry (Scheme 12). In this model, it is tentatively proposed a double coordination of the catalyst resulting from the stabilization of the dipolar transition state leading to (*R*)-adduct **10**. More in detail, the thiourea moiety binds the negative charge at the oxygen of the carbonyl group; meanwhile the amide oxygen coordinates the –NH group of the Hantzsch ester positively charged during the hydride-transfer step.

[15] a) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*,13862; b) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976; c) E. Martinelli, A. C. Vicini, M. Mancinelli, A. Mazzanti, P. Zani, L. Bernardi, M. Fochi, *Chem. Commun.* **2015**, *51*, 658; d) E. Massolo, M. Benaglia, M. Orlandi, S. Rossi, G. Celentano, *Chem. Eur. J.* **2015**, *21*, 3589; e) J. F. Schneider, F. C. Falk, R. Frçhlich, J. Paradies, *Eur. J. Org. Chem.* **2010**, 2265; f) J. F. Schneider, M. B. Lauber, V. Muhr, D. Kratzer, J. Paradies, *Org. Biomol. Chem.* **2011**, 9, 4323; g) J. C. Anderson, P. J. Koovits, *Chem .Sci.* **2013**, *4*, 2897; h) L.-A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong, E. Meggers, *J. Am. Chem. Soc.* **2013**, 135, 10598.

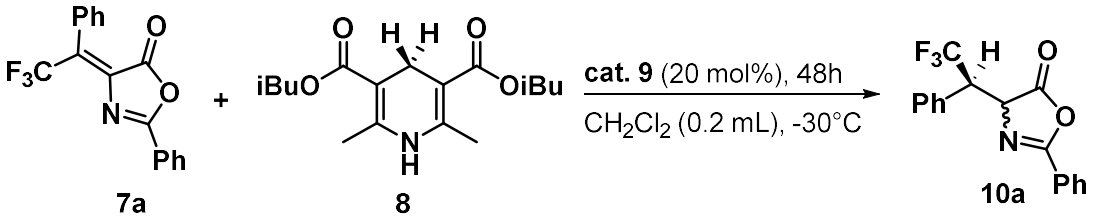
[16] a) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358; b) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature*, **2009**, *461*, 968; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; e) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci.* U. S. A., **2010**, *107*, 20678.

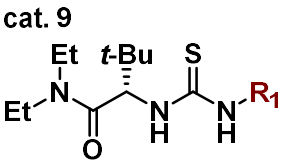


*Scheme 12. Proposed transition state leading to (R)-**10a***

Variations to the reaction conditions reported in Scheme 11, which did not prove fruitful, include the use of other solvents (toluene, ethers, etc.), urea and squaramide catalysts, other hydride donors (benzothiazolines), and other Hantzsch esters with different ester groups compared to **10a**. Furthermore, temperatures higher than -30 °C gave the product with lower enantioselectivity, while lowering the temperature depressed the catalytic process. Similarly, screening additives (molecular sieves, $MgSO_4$, etc) did not lead to any results improvement. Accordingly, we set out an in-depth optimization of the catalyst structure, taking advantage of its modular synthesis, in order to increase the enantiomeric excess of product **10a** (Table 1). Absolute and relative configuration of product **10a** have not been determined yet, the (*R*) configuration at the *β*-carbon (derived from the tentative model) will be depicted hereinafter as I believe it will help the visualization and the conceptualization of the overall perspective of this project, even though it might not be the correct one.

*Table 1. Screening of the R_1-substituent of catalyst **9***





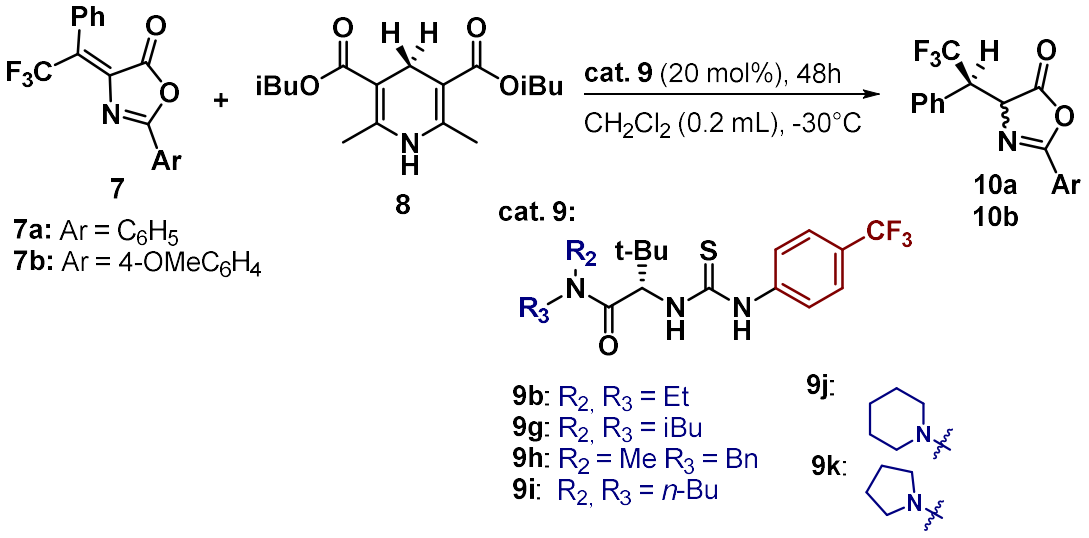
9a: R_1 = 3,5-$(CF_3)_2C_6H_3$
9b: R_1 = 4-$CF_3C_6H_4$
9c: R_1 = 3,5-$(CF_3)_2C_6H_3CH_2$-
9d: R_1 = CF_3CH_2-
9e: R_1 = 4-FC_6H_4
9f: R_1 = 4-$NO_2C_6H_4$

Entry[a]	**9** (20 mol%)	Conv.[b] [%]	ee_{maj} [%][c]	ee_{min} [%][c]
1	**9a**	>95	70	70
2	**9b**	>95	78	75
3	**9c**	>95	55	50
4	**9d**	>95	60	50
5	**9e**	>95	64	60
6	**9f**	>95	72	71

[a] Conditions: azlactone **7a** (0.05 mmol), CH_2Cl_2 (200 µL), catalyst **9** (20 mol%), Hantzsch ester **8** (0.75 mmol), -30 °C, 48h. [b] Determined on the crude mixture by ^{19}F NMR analysis. [c] Determined by CSP-HPLC on the purified product after treatment of **10a** with AllylOH (2 equiv.) and Et_3N (0.02 equiv.).

The first screening was carried out by varying the thiourea substituent on the “right” portion of the catalyst. All the catalysts tested performed similarly in terms of conversion, however swapping from catalyst **9a** to catalyst **9b** bearing the -CF_3 EWG-group at the *para* position of the aromatic ring, increased the enantioselectivity of **10a** (Table 1, entry 2). The reaction did not provide satisfactory results when aliphatic group (cat. **9c**, **d**) were employed (Table 1, entries 3,4). Finally, the nature of the EWG-group (cat. **9e**, **f**) was found to have an influence on the selectivity of the reaction (Table 1, entries 5,6).

*Table 2. Screening of the R_2, R_3-substituents of catalyst **9***

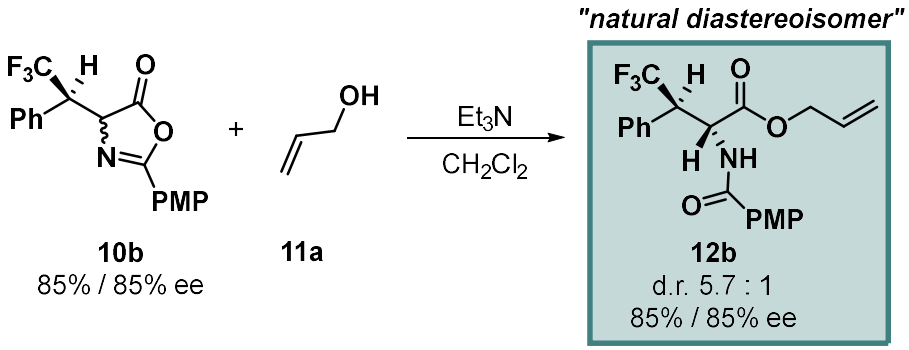


Entry[a]	7	9 (20 mol%)	Conv.[b] [%]	ee_{maj} [%][c]	ee_{min} [%][c]
1	**7a**	**9b**	>95	78	75
2	**7b**	**9b**	>95	83	84
3	**7b**	**9g**	>95	70	70
4	**7b**	**9h**	>95	85	85
5	**7b**	**9i**	>95	78	78
6	**7b**	**9j**	>95	75	76
7	**7b**	**9k**	>95	78	80

[a] Conditions: azlactone **7a** (0.05 mmol), CH_2Cl_2 (200 µL), catalyst **9** (20 mol%), Hantzsch ester **8** (0.75 mmol), -30 °C, 48h. [b] Determined on the crude mixture by ^{19}F NMR analysis. [c] Determined by CSP-HPLC on the purified product after treatment of **10a** with AllylOH (2 equiv.) and Et_3N (0.02 equiv.).

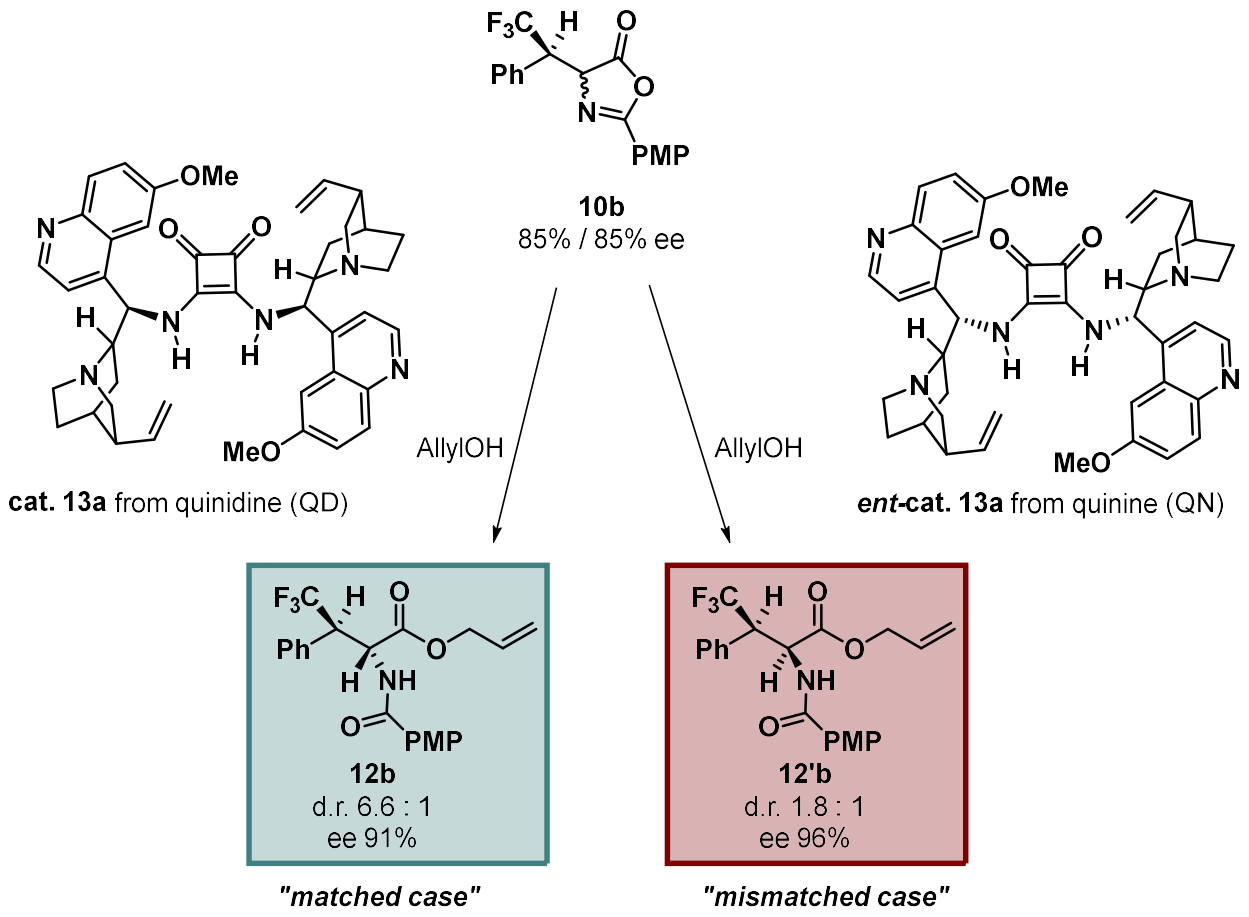
Preliminary studies on the azlactone structure revealed that, amongst the substituent tested, a *para*-methoxy substituent on the aryl group of the five-membered ring (substrate **7b**) improves the enantioselectivity of the reaction compared to other aryl groups (Table 2, entry 2). For this reason, we chose to continue our study on the optimization of the catalyst structure with substrate **7b**. Neither linear nor branched C_4 aliphatic chains on the amide moiety, as well as six- or five-membered ring, increased the enantioselectivity of the reaction (Table 2, entries 3,5-7). Finally, catalyst **9h** performed slightly better than catalyst **9b**, affording the product with 85 % ee value (Table 2, entry 4). This result set the best reaction conditions for the organocatalytic asymmetric reduction of substrate **7b**. Afterwards, we moved to the study of the second synthetic step: the organocatalytic asymmetric DKR of azlactone derivative **10b**. It is worth considering that performing this reaction in presence of

an achiral promoter such as Et_3N in presence of allylic alcohol, the corresponding opened product is delivered in 5.7:1 diastereomeric ratio (Scheme 13). This result shows a considerable substrate bias in this transformation- that is the reaction is partially substrate-controlled.



Scheme 13. Evaluation of substrate bias in the alcoholysis reaction

We initially applied the best conditions reported in the literature for this transformation.[8] When squaramide-based dimeric (QD) quinidine-derived organocatalyst **13a** was employed, product **12b** was delivered with 6.6 : 1 diastereomeric ratio and 91% ee (matched case). On the other hand, carrying out the reaction with squaramide-based dimeric (QN) quinine-derived organocatalyst ***ent*-13a**, diastereisomeric product **12'b** was obtained with opposite diastereoselectivity (d.r. 1.8 : 1) and 96% ee (Scheme 14).



*Scheme 14. Feasibility of the diastereodivergent DKR of **15b***

It is very useful trying to rationalize the results obtained in Scheme 14:

1. The feasibility of the diastereodivergent process has been demonstrated, as the two pseudoenantiomeric forms of catalyst **13a** afforded opposite diastereiosomeric products **12b**.
2. It must be noted that, according to the Horeau's principle,[17] enantioenrichment of the major diastereoisomer of product **12b** occurred during the ring-opening reaction.
3. Selectivity of a reaction that involves two chiral reactants is not obvious.

With respect to this, an approximation of this problem may be rationalized as it follows.

[17] a) A. Horeau, *Tetrahedron*, **1969**, *10*, 3121. b) A. M. Harned, *Tetrahedron* **2018**, *74*, 3797.

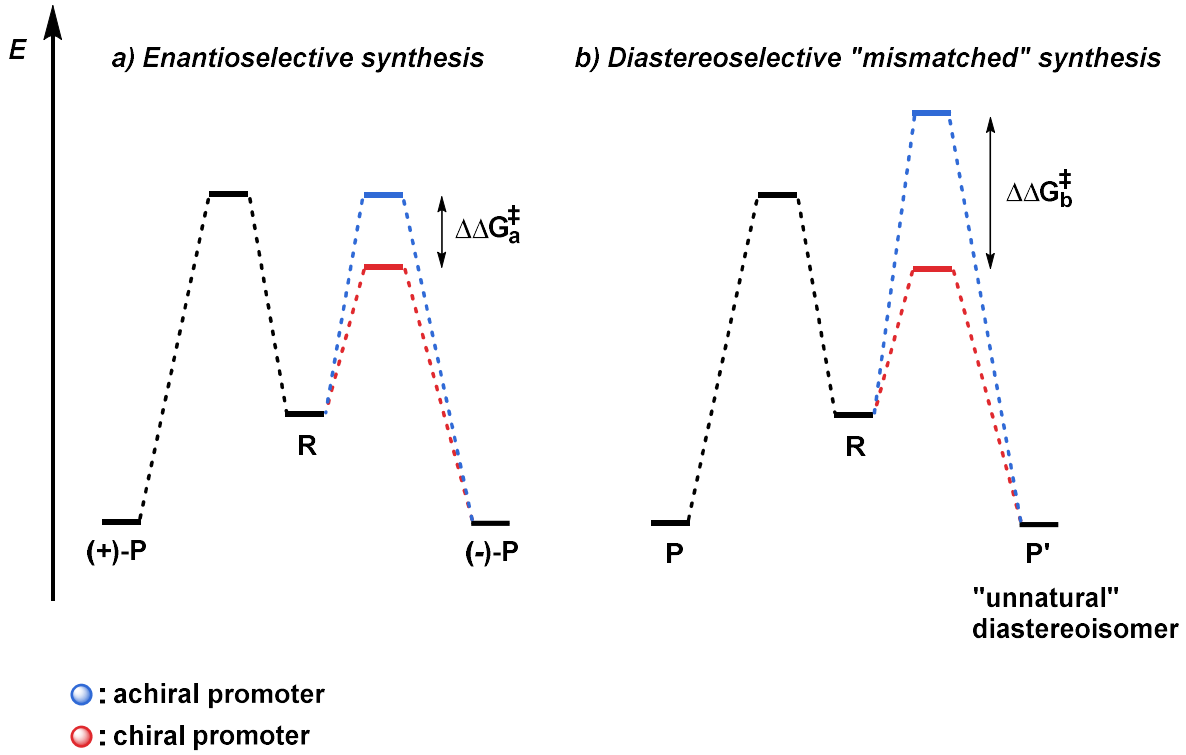
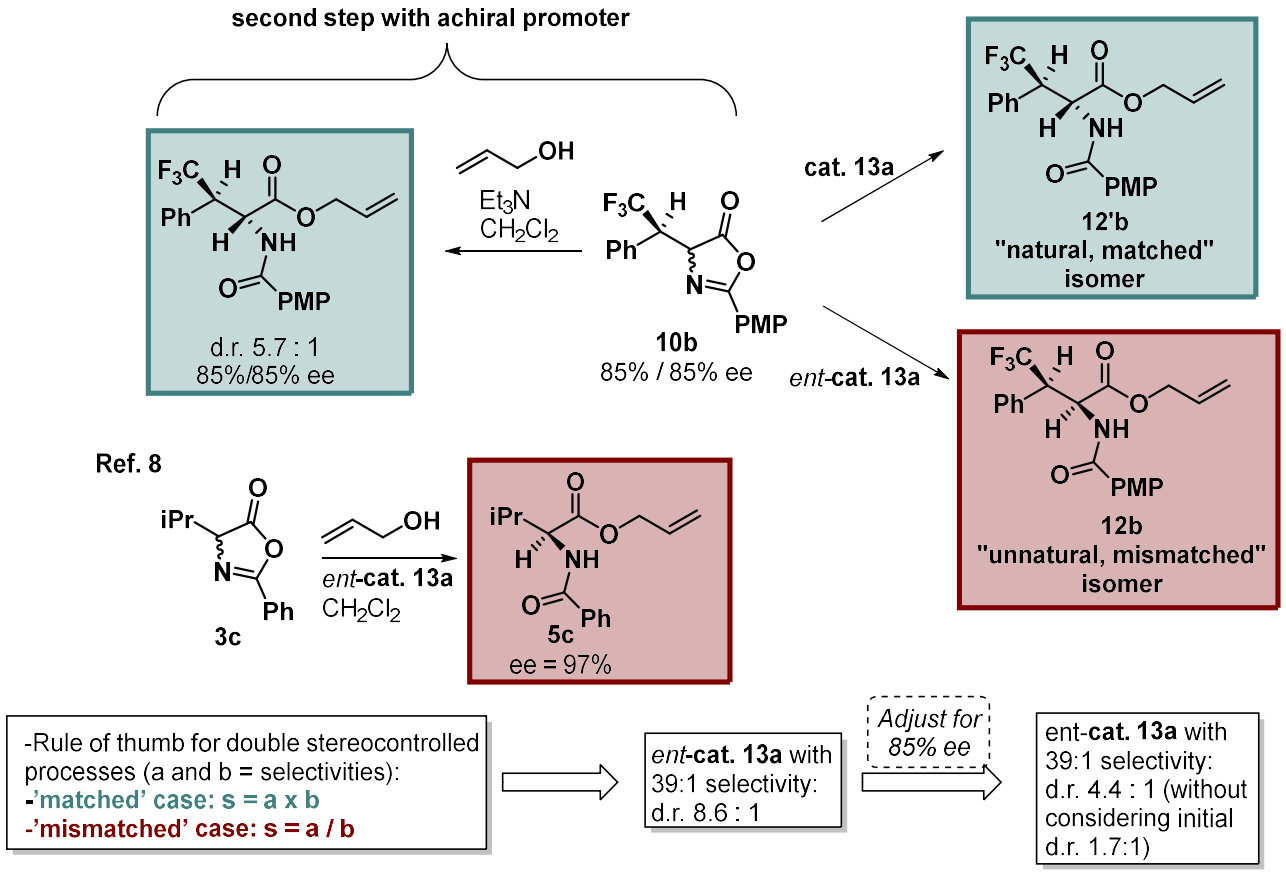


Figure 2. Diastereodivergent vs enantioselective synthesis under kinetic control, a simplified picture

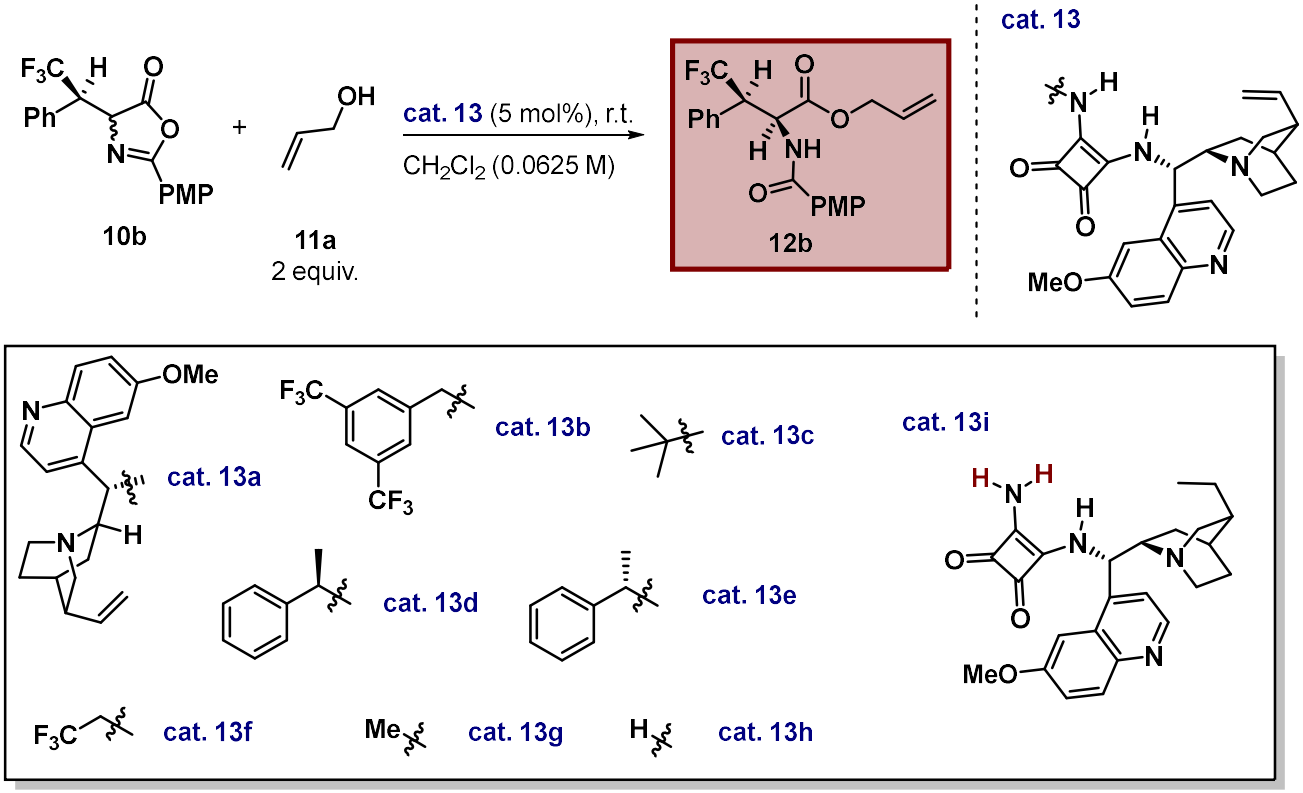
In a catalytic enantioselective reaction (Figure 2, a), in which the two transition states leading to opposite enantiomers have the same energy, the substrate-chiral catalyst interactions result in the stabilization of one of the two diastereomeric transition states favouring the preferential formation of one enantiomeric form of the desired product over the other. On the other hand, in a catalytic diastereoselective reaction of a chiral substrate (Figure 2, b), the two transition states leading to complementary diastereoisomers do not have the same energy. Therefore, the chiral substrate-chiral catalyst interactions must provide a greater stabilization, in the case of the formation of the "unnatural" isomer, to reach satisfactory levels of selectivity, because of the natural bias of the reaction to give the "natural" isomer ($\Delta\Delta G_b^{\ddagger} > \Delta\Delta G_a^{\ddagger}$). Accordingly, in our case, even the use of a very highly selective catalyst for the asymmetric DKR azlactones, such as catalyst *ent*-**cat. 13a** (Scheme 15, ee = 97%, ca. 39:1)[8] results in poor values of diastereoselectivity of product **12'b** (mismatched case). In fact, as a rule of thumb, the diastereoselectivity of a double stereoselective process in the mismatched case is obtained dividing the selectivity enforced by the catalyst by the one enforced by the substrate.[11] On top of that, it must be taken into account that, in our specific case, the chiral substrate is not enantiomerically pure (ee = 85%), thus leading to a further adjustment that lowers the diastereoselectivity even more. It is easier now to understand the intrinsic difficulty in tackling the synthesis of different diastereoisomers of the same product.



*Scheme 15. Approximation of the selectivity in the mismatched case of DKR of azlactone **10b***

In order to maximize as much as possible the diastereoselectivity of the reaction in the mismatched case, we set out the optimization of catalyst structure **13**. Preliminary studies set CH_2Cl_2 (0.0625 M), 2 equivalents of allylic alcohol **11a** and 5 mol% loading of squaramide-based organocatalysts as starting conditions (Table 3). A large number of experiments using other catalyst classes and reactions (e.g. thiolysis) did not give better results.

*Table 3. Screening of catalyst **13** for the asymmetric DKR of azlactone derivative **10b***



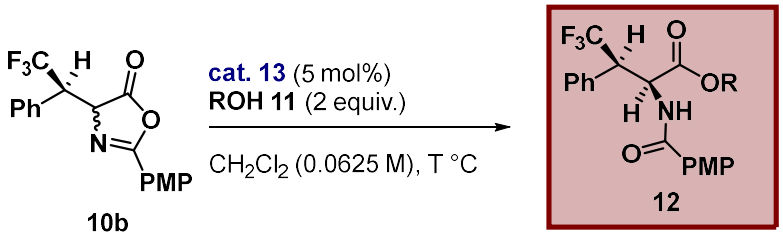
Entry[a]	**13** (5 mol%)	t (h)	Conv. [%][b]	d.r. [%][b]
1	**13a**	42	>95	1.8 : 1
2	**13b**	42	>95	2.8 : 1
3	**13c**	42	>95	1.9 : 1
4	**13d**	42	>95	2.4 : 1
5	**13e**	42	>95	1.5 : 1
6	**13f**	42	68	2.9 : 1
7	**13g**	42	80	3.1 : 1
8	**13h**	42	50	4.6 : 1
9	**13i**	24	>95	4.9 : 1

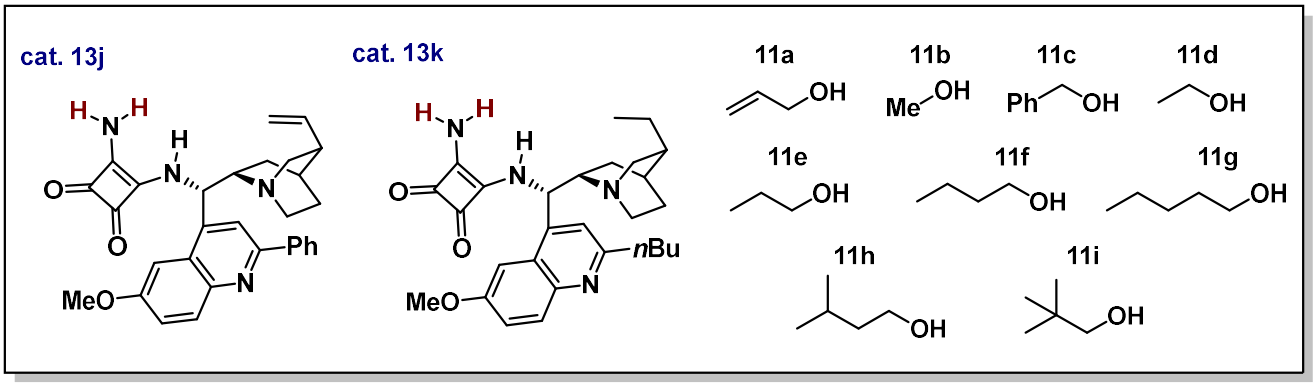
[a] Conditions: azlactone **10b** (0.05 mmol), alcohol **11a** (2 equiv.), CH_2Cl_2 (800 µL), catalyst **13** (5 mol%), r.t.
[b] Determined on the crude mixture by ^{19}F NMR analysis.

As shown in Table 3 it seems there is a direct dependence between the steric bulk of the squaramide portion of the catalyst and the diastereoselectivity (Table 3, entries 1-8): the lower the steric hindrance the higher the d.r. value. Catalyst **13h** bearing a free $–NH_2$ moiety afforded product **12b** in 4.6 d.r., albeit with moderate conversion due to its poor solubility in CH_2Cl_2 (Table 3, entry 8). In order to address this problem we synthesised its dihydroquinine

(DHQN)-derived analogue **13i**, which is normally more soluble in organic solvents. Pleasingly, performing the reaction in presence of catalyst **13i**, product **12b** was obtained in 4.9 : 1 d.r. and more than 95% conversion within 24h (Table 3, entry 9). A final screening of reaction temperature, catalyst loading, reaction temperature and catalyst structure let us to set the optimized reaction conditions for the diastereoselective dynamic kinetic resolution of azlactone **10b** (Table 4).

*Table 4. Screening of catalyst **13**, alcohol **11** and reaction temperature for the the asymmetric DKR of azlactone derivative **10b***



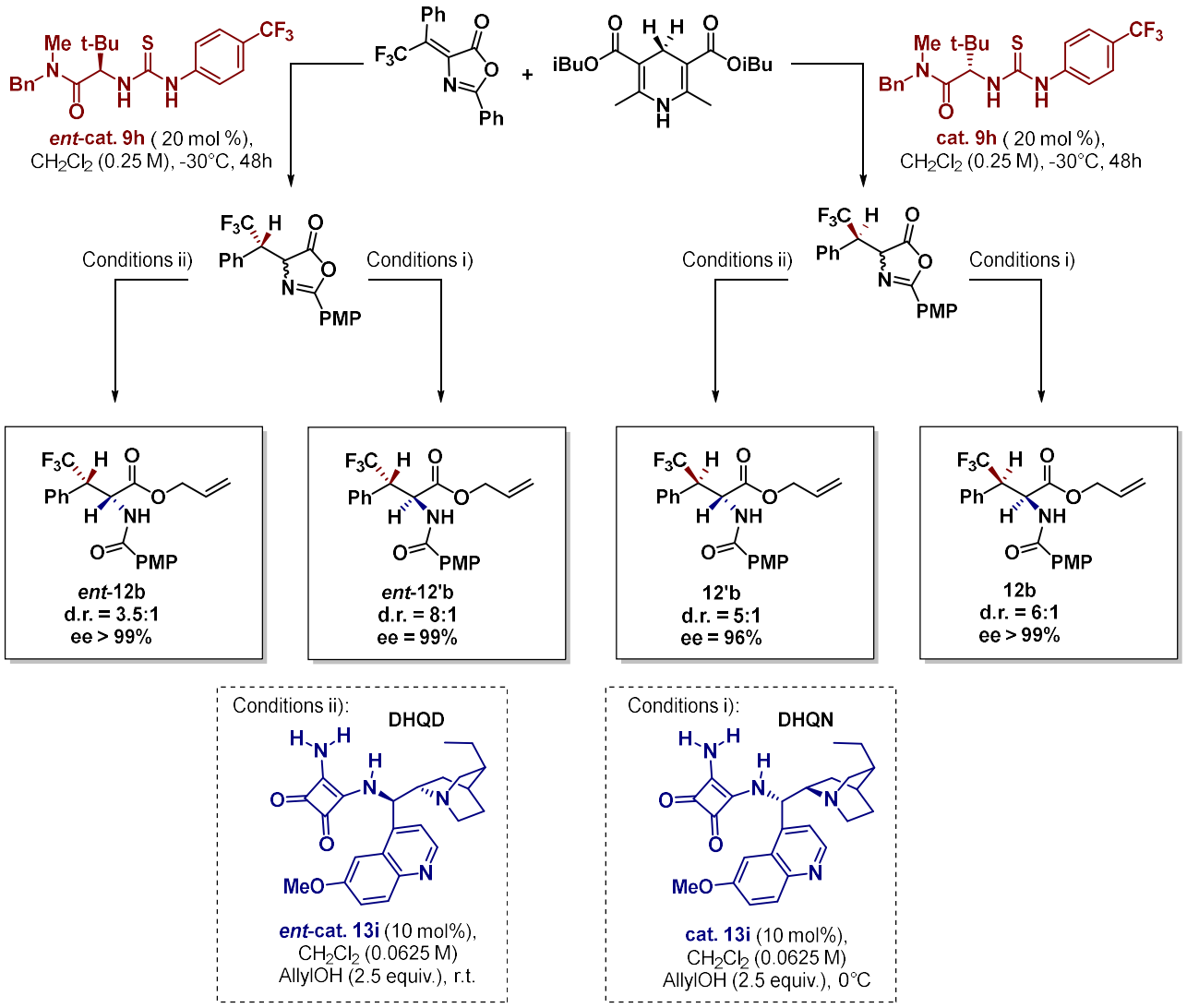


Entry[a]	**13** (mol%)	**ROH 11** (2 equiv.)	T [°C]	Conv. [%][b]	d.r. [%][b]
1	**13i**	**11a**	r.t.	>95	4.9 : 1
2	**13j**	**11a**	r.t.	10	3.8 : 1
3	**13k**	**11a**	r.t.	>95	4.0 : 1
4	**13i**	**11b**	r.t.	n.d[c].	4.4 : 1
5	**13i**	**11c**	r.t.	>95	3.4 : 1
6	**13i**	**11a**	0	>95	5.9 :1
7	**13i**	**11b**	0	n.d.[c]	5.0 : 1
8	**13i**	**11c**	0	>95	4.1 : 1
9	**13i**	**11d**	0	72	5.3 : 1
10	**13i**	**11e**	0	68	6.0 : 1
11	**13i**	**11f**	0	73	6.0 : 1
12	**13i**	**11g**	0	64	5.0 : 1
13	**13i**	**11h**	0	38	4.0 : 1
14	**13i**	**11i**	0	10	6.0 :1

[a] Conditions: azlactone **10b** (0.05 mmol), alcohol **11** (2 equiv.), CH_2Cl_2 (800 µL), catalyst **13** (5 mol%), 24h. [b] Determined on the crude mixture by ^{19}F NMR analysis. [c] The crude mixture showed the presence of side products.

We initially studied the influence catalysts **13j** and **13k** substituted at the 2-position of the quinoline core: the additional phenyl substituent of catalyst **13j** was found to be detrimental especially for the conversion value of the reaction, while the *n*-butyl substituent on catalyst **13k** provided product **12b** in full conversion but lower d.r. (Table 4, entries 2,3). Finally, we carried out a screening of alcohols **11** to evaluate their influence in the diastereoselective reaction. Comparing the results obtained with alcohols **11a-c** at r.t. (Table 4, entries 1, 4, 5) and 0 °C (Table 4, entries 6-8) it is possible to confirm that better d.r. values can be achieved when the reaction is carried out a 0 °C. As shown in Table 4, aliphatic alcohols with longer aliphatic chain delivered corresponding products **12** with similar diastereoselectivity, albeit with generally lower conversion values (Table 4, 9-12). Isoamyl alcohol **11h** afforded the corresponding *α*-amino ester **12** in poor conversion and diastereoselectivity (Table 4, entry13). Although the good d.r. value obtained with neopentyl alcohol **11i**, this reaction provided only 10% of conversion (Table 4, entry14). It is worth mentioning that during the study of this transformation we noted did not collect completely reproducible results in terms of reaction conversion. This could be probably due to some catalyst deactivation events that can take place because of the small scale that we used to perform the experiments. Accordingly, we decide to set as optimized conditions the use of catalyst **13i**, increasing catalyst loading to 10 mol% to have a more robust system, 2 equivalents of allylic alcohol **11a**, CH_2Cl_2 (0.0625 M) at 0 °C.

Established the optimal reaction conditions for both synthetic steps, we decided to perform four different set of experiments using al the possible combination of organocatalysts **9h** and **13i** in order to prove the feasibility of the stereodivergent process and to collect preliminary results for all the relative matched and mismatched cases (Scheme 16).



*Scheme 16. Preliminary results for the stereodivergent synthesis of α-amino acid derivatives **12** using a sequential catalytic approach*

Overall, the stereodivergent process seems to be feasible. We were able to synthesize all the stereoisomeric forms of product **12b** with excellent values of enantiomeric excess and, taking into account substrate bias in the DKR reaction, good diastereoselectivities. Entries involving the participation of DHQD-derived organocatalyst *ent*-cat. **13i** suffered from lower catalytic activity (compared to cat. **13i**). This effect can probably be ascribed to its *quasi*-enantiomeric structure that does not exactly replicate the same transition state during the DKR of substrate **10b**.

2.2.5 Conclusions

In conclusion, we studied the possibility to develop a stereodivergent two-step process based on sequential organocatalysis. The overall process relies, as first transformation, on the asymmetric organocatalytic hydrogen transfer of azlactone **7b** catalysed by a Jacobsen-

type thiourea derivative **9h,** using Hantzsch ester **8** as hydride donor. The second reaction, instead, is the organocatalytic asymmetric DKR of azlactone derivative **10b** catalysed by squaramide-based Cinchona alkaloids derivatives, such as **13i**, in presence of allyl alcohol **11a**. We thoroughly investigated and optimized both synthetic steps devoting particular attention to the maximization of the stereoselectivity and yield of the reaction. Although reasonably high enantiomeric excess is provided in the asymmetric hydrogenation of substrate **7b**, it fixes a limit to the possible maximum value of diastereoselectivity of the DKR. Nevertheless, in light of the observed substrate bias for this transformation, satisfying values of diastereoselectivity of the mismatched case were achieved when reaction was carried out in presence of the new developed organocatalyst **13i**. Furthermore, promising preliminary results were obtained in the synthesis of all possible stereoisomers starting from the same set of starting materials. A one pot protocol proved to be feasible too, as long as the amount of Hantzsch ester **8** was lowered to 1.1 equivalents, since this species was found to interfere with the catalyst used in the DKR step. As future perspectives, we will try to increase the stereoselectivites of both steps, to study in detail the scope of this new reaction, as well as its application to target structures.

2.2.6 Experimental Section

2.2.6.1 General Methods

^{1}H, ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR.[18] ^{13}C NMR were acquired under ^{1}H broadband decoupling. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electronspray (ES) ionization technique. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at λ = 254 nm.

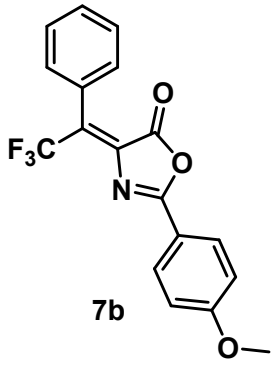
[18] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.

2.2.6.2 Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Catalysts **9** were prepared according to a reported literature procedure.[19] Catalysts **13** were prepared according to a reported literature procedure.[20]

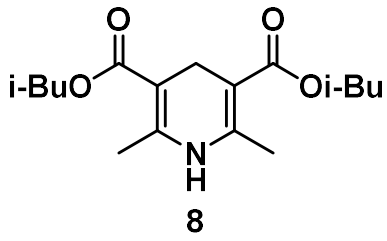
2.2.6.3 General procedure for the synthesis of arylidene azlactone derivatives ***7a*** and ***7b***

Azlactones **7a,b** were prepared according to a reported literature procedure.[21]



To a round bottom flask equipped with magnetic stirring bar, *N*-(4-methoxybenzoyl) glycine (or hyppuric acid) (5 mmol), acetic anhydride (7.5 mL) and K_2CO_3 (2.5 mmol) were added at room temperature. After 30 minutes, 2,2,2-trifluoroacetophenone (5 mmol) was added and the resulting suspension stirred for 18 h. Subsequently, 40 mL of water were added to the yellow suspension and stirred for 18 h. The resulting precipitate is then filtered and washed with cold water. The solid is then purified by column chromatography silica gel using (CH_2Cl_2 as eluent). The collected fractions containing the Z-E mixture were finally recrystallized from *n*-hexane affording pure Z isomer (as confirmed by X-Ray analysis on a single crystal) of the desired product **7b** in 50% yield. **^{1}H NMR (300 MHz, $CDCl_3$):** 8.22 – 8.06 (m, 2H), 7.64 – 7.41 (m, 3H), 7.41 – 7.30 (m, 2H), 7.09 – 6.93 (m, 2H), 3.92 (s, 3H). **^{19}F NMR (282 MHz**, **$CDCl_3$):** δ -59.38 (s).

2.2.6.4 Synthesis of Hantzsch ester derivative ***8***

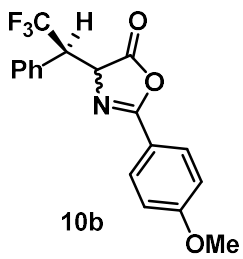


In an oven-dried round bottom flask equipped with magnetic stirring bar are added isobutyl acetoacetate (60 mmol), paraformaldehyde (30 mmol), water (30 mL) and ammonium acetate (30 mmol). The reaction is vigorously stirred at 70 °C under inert atmosphere and after 1 hour it is cooled to r.t., the precipitate is filtered, washed with water and cold methanol. Eventually, the filtrate is recrystallized from methanol to afford the desired dihydropyridine 8 in 45% yield. **^{1}H NMR**

[19] E. Massolo, M. Orlandi, S. Rossi, G. Celentano, M. Benaglia, *Chem. Eur. J.* **2015**, *21*, 3589.
[20] J. P. Malerich, K. Hagihara, V. H. Rawal *J. Am. Chem. Soc.* **2008**, *130*, 14416.
[21] A. Nikitenko, T. J. Connolly, G. Feigelson, A. W. Chan, Z. Ding, M. Ghosh, X. Shi, J. Ren, E. Hansen, R. Farr, M. MacEwan, S. Tadayon, D. M. Springer, A. F. Kreft, D. M. Ho, J. R. Potoski, A. Alimardanov *Org. Process Res. Dev.* **2009**, *13*, 1161.

(300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 3.88 (d, *J* = 6.4 Hz, 4H), 3.31 (s, 2H), 2.19 (s, 6H), 1.96 (dq, *J* = 13.3, 6.6 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 12H).

*2.2.6.5 General procedure for catalytic asymmetric reduction of azlactone **7b***



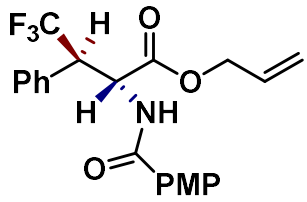
10b

In a reaction tube equipped with magnetic stirring bar, azlactone **7b** (0.5 mmol) and catalyst **9h** (20 mol %) are dissolved in CH_2Cl_2 (2 mL). The mixture is cooled to -30° C and after five minutes Hantzsch ester derivative **8** (0.75 mmol) is added. The reaction is stirred for 48 h at -30° C until full consumption of the starting material checked by ^{19}F NMR on the crude mixture. Then, the crude mixture is directly loaded onto column chromatography on silica gel e quickly filtered eluting with CH_2Cl_2. The desired product **10b** is isolated as yellowish sticky oil in 90% yield. Major diastereoisomer **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.94 – 7.83 (m, 2H), 7.37 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 6.97 – 6.87 (m, 2H), 5.02 (d, *J* = 2.9 Hz, 1H), 4.06 (ddd, *J* = 20.4, 9.5, 2.7 Hz, 1H), 3.87 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -67.02 (d, *J* = 9.8 Hz). Minor diastereoisomers: **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.05 – 7.97 (m, 2H), 7.74 – 7.67 (m, 2H), 7.47 – 7.38 (m, 3H), 7.04 – 6.97 (m, 2H), 4.75 (d, *J* = 2.7 Hz, 1H), 4.06 (ddd, *J* = 20.4, 9.5, 2.7 Hz, 1H), 3.89 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -65.88 (d, *J* = 9.1 Hz).

*2.2.6.6 General procedure for dynamic kinetic resolution of azlactone **7b** to deliver a-amino esters **12b***

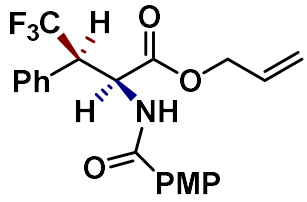
In a reaction tube equipped with magnetic stirring bar, intermediate **7b** (0,05 mmol), catalyst **13i** are dissolved in CH_2Cl_2 (0.8 mL), allyl alcohol **11a** (0.1 mmol) is added and the reaction is stirred at the appropriate temperature until full consumption of the starting material (checked by TLC). Then, the crude mixture is filtered through a short plug on silica gel and eluted with Et_2O. The desired product is purified by column chromatography on silica gel (CH_2Cl_2) to afford the title compound in 95% yield **12b.**

2.2.6.7 Characterization data



12'b

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.31 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.23 (d, *J* = 9.0 Hz, 1H), 5.90 (ddt, *J* = 17.1, 10.4, 6.2 Hz, 1H), 5.42 – 5.23 (m, 2H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.14 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.84 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -66.27 (d, *J* = 9.5 Hz). HPLC: (Chiralpak AD-H, *n*-hexane/*i*-PrOH 80:20, 0,75 mL/min, λ = 254 nm, $t_{r\,maj}$ = 11 min; $t_{r\,min}$ = 21 min; ee = 96%.



12b

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.35 (s, 5H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 9.0 Hz, 1H), 5.72 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.46 (dd, *J* = 9.0, 6.8 Hz, 1H), 5.27 – 5.16 (m, 2H), 4.61 – 4.44 (m, 2H), 4.05 (qd, *J* = 9.5, 6.8 Hz, 1H), 3.86 (s, 3H), **^{19}F NMR (282 MHz, $CDCl_3$)** δ -64.05 (d, *J* = 9.5 Hz). HPLC: (Chiralpak AD-H, *n*-hexane/*i*-PrOH 80:20, 0,75 mL/min, λ = 254 nm) *syn*-isomer: $t_{r\,min}$ = 14 min; $t_{r\,maj}$ = 24 min; ee>99%.

3 Dual catalysis

Catalysis is probably one of the most powerful approaches to reaction engineering and development. Within the realm of chemical synthesis, the concept of traditional mono-catalysis relies on the employment of a single catalyst which is able to interact and activate one substrate, thereby lowering the energetic barrier to bond formation with a second, non-activated, reactant. This concept has been extensively exploited to develop and access a wide variety of new chemical reactions and activation modes. As opposed to this, multi-catalysis strategies have recently begun to emerge as great synthetic tool to access a new set of difficult chemical transformations otherwise unattainable. Within the field of dual catalysis there are many different areas and a classification based on the modes of action of the two catalysts is desirable.

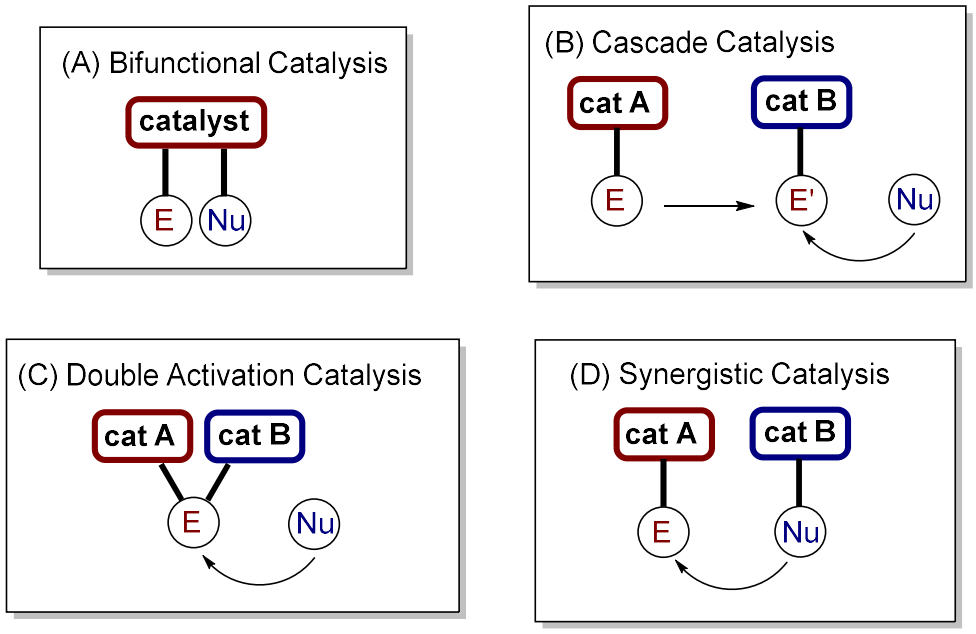


Figure 1. Classification of catalytic systems involving two catalysts

When both electrophile and nucleophile are activated by two different functional groups on the same catalyst, dual catalysis has been defined as *bifunctional catalysis* (Figure 1, A).[1] If both catalysts activate the same reacting partner, but in a sequential fashion (*i.e.* the substrate delivers an intermediate which is further activated by the second catalyst), it is

[1] For reviews on bifunctional catalysis, see: a) M. Kanai, S. Matsunaga, N. Kumagai, M. Shibasaki, *Acc. Chem. Res.* **2009**, *42*, 1117; b) R. Breslow, *J. Mol. Catal.* **1994**, *91,* 161; c) N. Yoshikawa, M. Shibasaki, *Chem. Rev.* **2002**, *102*, 2187; d) Y. Wang, L. Deng in *Catalytic Asymmetric Synthesis*, 3rd Ed, ed. I. Ojima, *John Wiley & Sons*, New Jersey, **2010**, p 59; e) M. Kanai, M. Shibasaki in *New Frontiers in Asymmetric Catalysis*, ed. K. Mikami and M. Lautens, *John Wiley & Sons*, New Jersey, **2007**, p 383.

classified as *cascade catalysis* (Figure 1, B).[2] It is possible to define *double activation catalysis* if both catalysts work in concert to activate the same substrate (Figure 1, C).[3] Finally, when electrophile and nucleophile are activated simultaneously by two different catalysts, instead, it is classified as *synergistic catalysis* (Figure 1, D).[4]

A very efficient approach to dual catalysis is combining organocatalysis with transition-metal catalysis.[5] Separately, this two fields of catalysis have largely contributed to unlock new pathways in the landscape of reaction development. However, their respective mode of action are diverse in nature resulting in a complementary array of chemical transformations and substrate manipulations. As such, it is easy to visualize their potential in enabling reactions that would be otherwise unattainable by the use of either catalysts. Intrinsic challenges such as self-quenching events upon mixing of the two catalytic species (e.g. strong Lewis bases with strong Lewis acids) as well as solvent compatibility of both catalysts can be generally overcome by accurate selection of appropriate catalytic systems. On the other hand, the concept of dual catalysis unlocks different scenarios as the possibility for enantioselectivity enhancement if both organocatalyst and transition metal catalyst (by means of chiral ligands) work in concert to deliver the same enantiomeric form of the product (matched pair). Finally, it enables the choice of multiple sites for chiral enforcement, which may give rise to the development of stereodivergent syntheses. One of the best examples illustrating the full potential of this form of multi-catalysis approach is undoubtedly the stereodivergent allylation of branched aldehydes reported by Carreira and coworkers.[6] In this very elegant example, the alcohol is activated by an iridium complex to form the cationic *π*-allyl-Ir-complex **A**, while the *α*-branched aldehyde is condensed with a chiral primary amine catalyst to generate the reactive intermediate **B**. The two reactive species generated

[2] For examples of cascade catalysis, see: a) S. Belot, K. A. Vogt, C. Besnard, N. Krause and A. Alexakis, *Angew. Chem. Int. Ed.* **2009**, *48*, 8923; b) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; c) K. Sorimachi, M. Terada, *J. Am. Chem. Soc* **2008**, *130*, 14452; d) Q. Cai, Z.-A. Zhao, S.-L. You, *Angew. Chem. Int. Ed.* **2009**, *48*, 7428; e) B. Simmons, A. M. Walji, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *48*, 4349; f) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628.

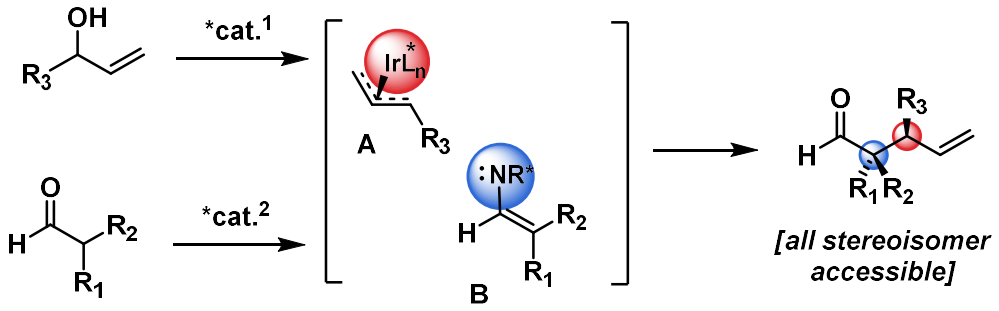
[3] For examples of double activation catalysis, see: (a) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science*, **2010**, *327*, 986; b) M. Rubina, M. Conley, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 5818; c) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336; d) Y. Shi, S. M. Peterson, W. W. Haberaecker III, S. A. Blum, *J. Am. Chem. Soc.* **2008**, *130*, 2168; e) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222.

[4] For examples of synergistic catalysis, see: a) A. E. Allen, D: W. C. MacMillan, *Chem. Sci*. **2012**, *3*, 633; b) S. Afewerki, A. Córdova, *Chem. Rev.* **2016**, *116*, 13512; d) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365.

[5] a) Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337; b) Z.-P. Yang, W. Zhang, S.-L. You *J. Org. Chem.* **2014**, *79*, 7785; c) R. M. Koenigs, I. Atodiresei, M. Rueping, *Chem. Eur. J.* **2010**, *16*, 9350.

[6] S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira *Science*, **2013**, *340*, 1065

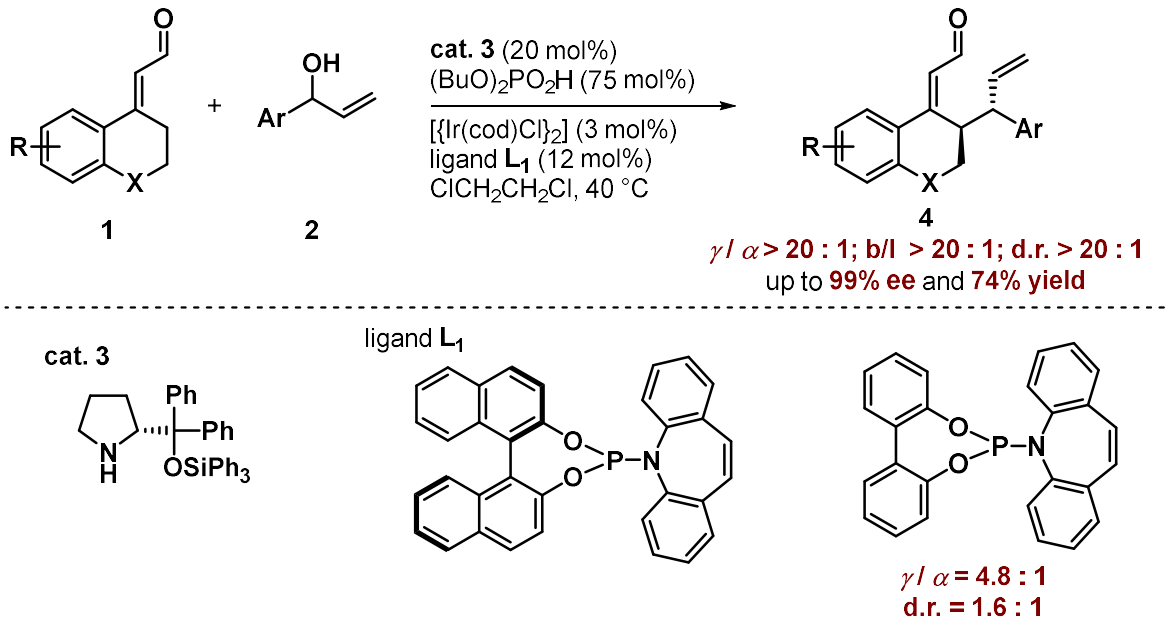
in situ can be coupled to deliver all possible stereoisomer of the desired *α*-allylated aldehyde by selection of the proper enantiomer of the two catalysts (Scheme 1).



Scheme 1. Synergistic approach to the α-allylation of branched aldehydes

For an exhaustive description of this methodology, please see Chapter 2.

Similarly, Jørgensen *et. al.* extended this reaction concept to the *γ*-allylation of *α*-tetralone derived aldehydes **1**, using the prolinol-derived organocatalyst **3**, allyl alcohols **2** as allylating agent in presence of [{Ir(cod)Cl}$_2$] and chiral phosphoramidite-based ligand **L$_1$** to deliver the branched *γ*-allylated product **4** with very high levels of selectivity (Scheme 2).[7]

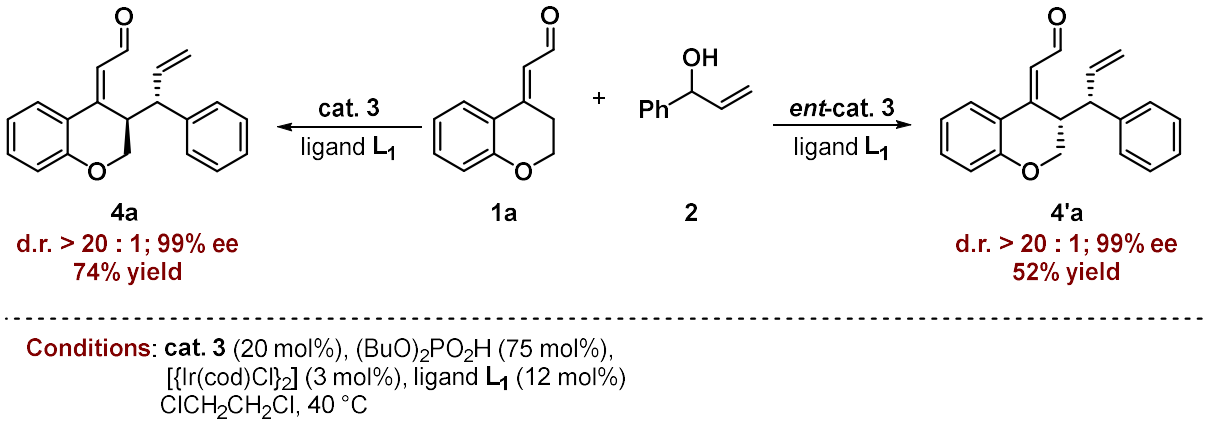


*Scheme 2. Asymmetric γ-allylation of α,β-unsaturated aldehydes to branched allylated products **4***

While aminocatalyst **3** was able to discriminate the two faces of the dienamine very efficiently, it was crucial for the regio- as well as the diastereoselectivity to carry out the reaction in presence of chiral ligand **L$_1$**, since the corresponding achiral version afforded product **4** with poor results (Scheme 2). The synergistic catalytic approach allowed the authors to accomplish formal stereodivergent *γ*-allylation of α,β-unsaturated aldehydes **1**

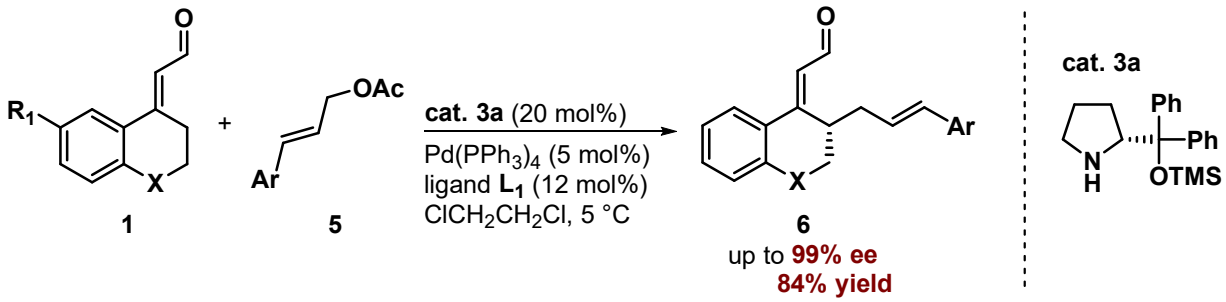
[7] L. D. Næsborg, K. S. Halskov, F. Tur, S. M. N. Mønsted, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 10193.

that was formally demonstrated carrying out the reaction with the enantiomeric form of catalyst *ent*-**3** (Scheme 3).



Scheme 3. Proof of concept of the stereodivergent γ-allylation of α,β-unsaturated aldehydes

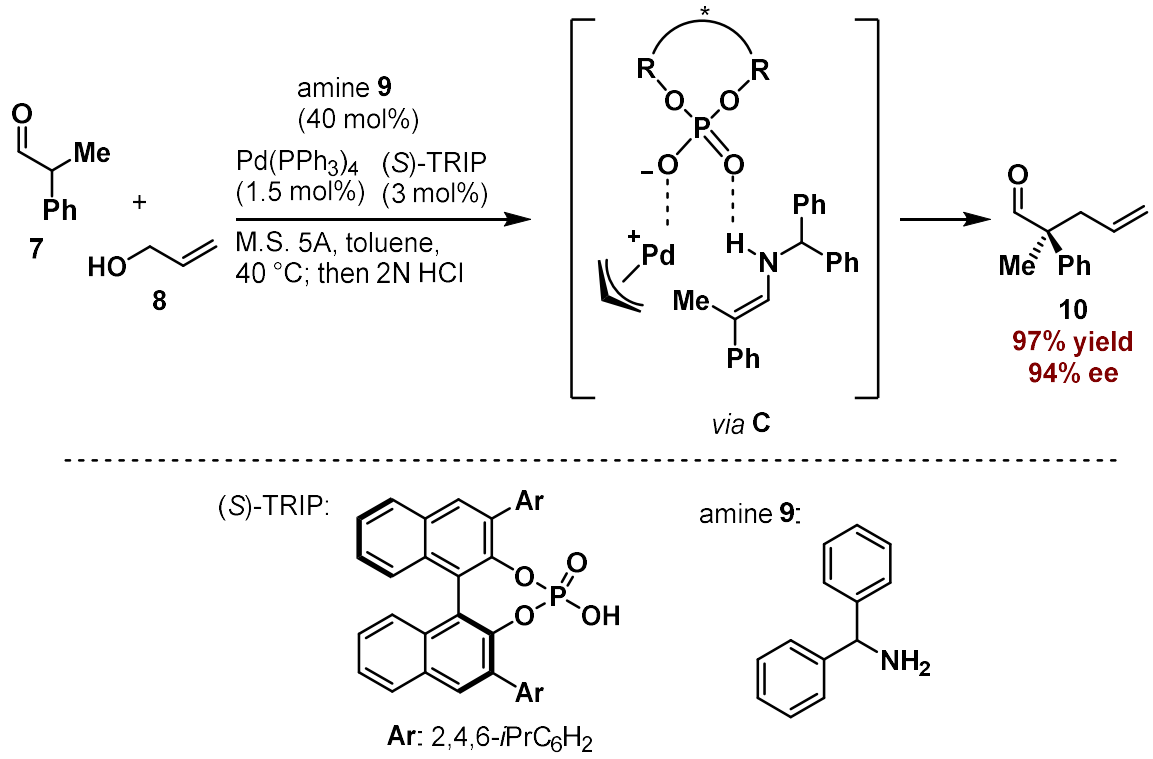
In addition to this, the same reaction concept was expanded to linear allylated product **6** by replacing the iridium metal catalyst with $Pd(PPh_3)_4$ using similar reaction conditions to the previous ones (Scheme 4). This method provides access to all six stereo- and regio-isomers of the *γ*-allylated product (4 stereoisomers of the branched product and 2 stereoisomers of the linear product) in a divergent fashion by simple selection of the appropriate combination of catalysts set.



*Scheme 4. Asymmetric γ-allylation of α,β-unsaturated aldehydes to linear allylated products **6***

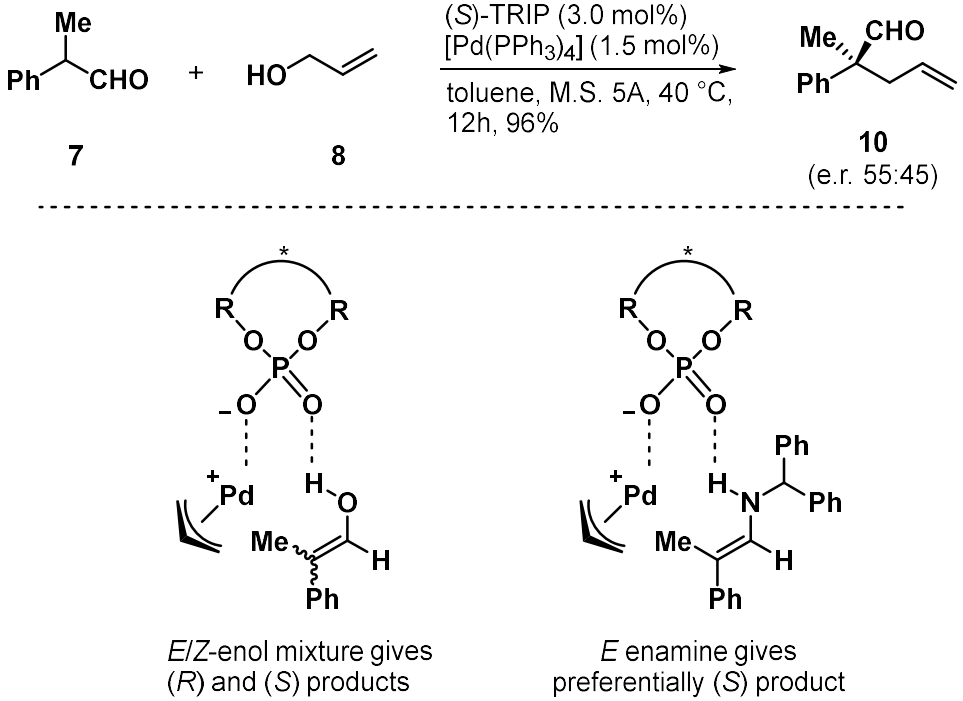
A different approach to tackle the problem of direct enantioselective *α*-allylation of aldehydes has been developed by the group of List in 2007 (Scheme 5)[8] taking advantage of the so called Asymmetric Counterion-Directed Catalysis (ACDC).[9] *It refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral enantiomerically pure anion provided by the catalyst*.

[8] G. Jiang, B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 9471. S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336.
[9] M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518.



Scheme 5. Asymmetric α-allylation of branched aldehydes with allylic alcohol

Aldehyde **7** reacts with benzhydrylamine **9** to generate the active enamine intermediate that is able to intercept the cationic *π*-allyl-Pd-complex generated in situ upon oxidative addition of the Pd(0) catalyst to allylic alcohol **8**, thus delivering product **10**. The whole process is mediated by chiral phosphoric acid (*S*)-TRIP: it facilitates the oxidative addition of Pd rendering the alcohol moiety a better leaving group and it accelerates enamine formation as well as hydrolysis of the corresponding iminium ion. Finally, it covers the essential role of chiral catalyst inducing the desired enantioselectivity to the product through the proposed supramolecular adduct **C** in which both the *π*-allyl-Pd-complex and enamine are coordinated to the organocatalyst (Scheme 5). The authors demonstrated that the configurational stability displayed by the enamine instead of the corresponding enolate is critical to achieve high values of enantioselectivity (Scheme 6).

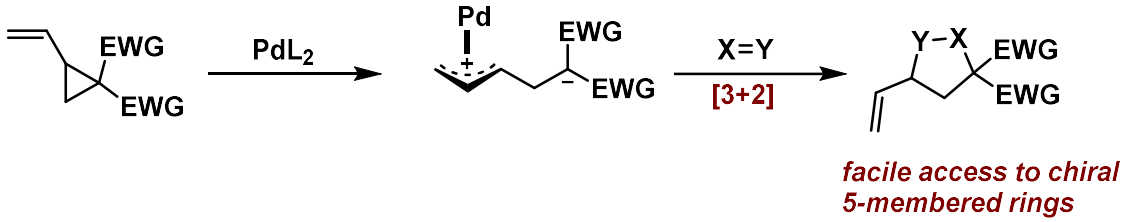


Scheme 6. Control experiment in the dual catalytic asymmetric direct α-allylation of branched aldehydes

3.1 Asymmetric dual catalytic [3+2] cycloaddition of vinyl cyclopropanes with imines en route to chiral functionalised pyrrolidines.

3.1.1 Background

Activated Vinyl CycloPropanes (VCPs) are a class of valuable synthetic synthons of formal 1,3-dipoles and indeed they find a wide range of applications because of their synthetic versatility (Scheme 1).



Scheme 1. Vinylcyclopropanes as formal 1,3-dipoles

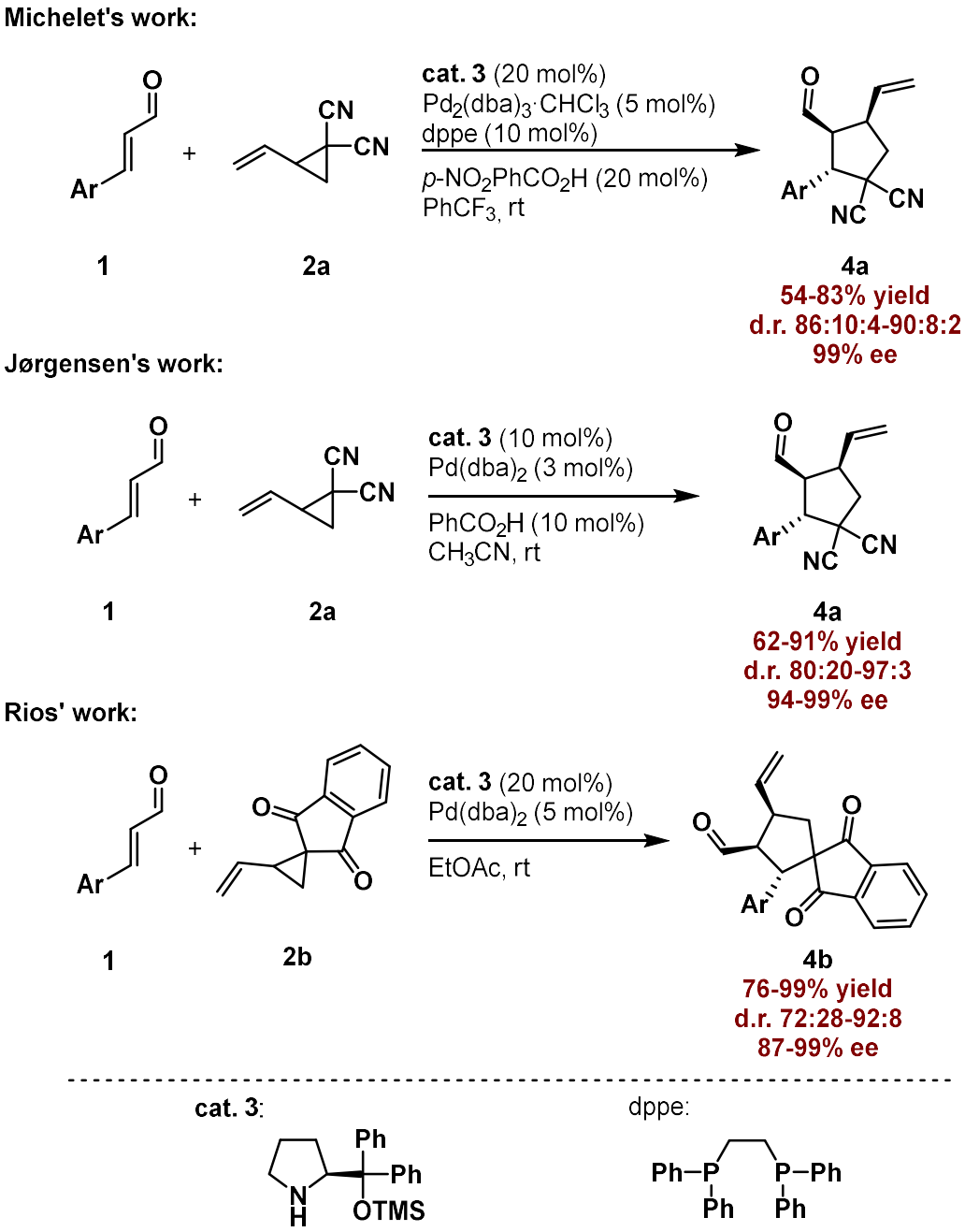
Thanks to the presence of two electron withdrawing groups and to the strain of the cyclopropane ring, they can be easily activated in situ by palladium[1] or other transition metal catalysts[2] to generate highly reactive intermediates which have been largely exploited in cycloaddition reactions. Over the last decade, VCPs have attracted a lot of attention in the field of catalytic transformations.[1,2] However, only recently few examples of [3+2] catalytic asymmetric cycloaddition combining transition-metal catalysis and organocatalysis in a synergistic fashion have been reported.[3] The group of Jørgensen, Michelet and Rios independently reported the catalytic asymmetric formal [3+2] cycloaddition between VCPs and enals (Scheme 2).

---

[1] For racemic versions, see: a) I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1985**, *26*, 3825; b) A. T. Parsons, M. J. Campbell, J. S. Johnson, *Org. Lett.* **2008**, *10*, 2541; c) A. F. G. Goldberg, B. M. Stoltz, *Org. Lett.* **2011**, *13*, 4474. For asymmetric versions, see: d) P. J. Morris, B. M. Trost, *Angew. Chem. Int. Ed.* **2011**, *50*, 6167; e) P. J. Morris, S. J. Sprague, B. M. Trost, *J. Am. Chem. Soc.* **2012**, *134*, 17823; f) L.-Y. Mei, Y. Wei, M. Shi, Q. Xu, *Organometallics* **2012**, *31*, 7591; g) L.-Y. Mei, Y. Wei, M. Shi, Q. Xu, *Organometallics* **2013**, *32*, 3544; h) F. Wei, C.-L. Ren, D. Wang, L. Liu, *Chem. Eur. J.* **2015**, *21*, 2335; i) Z.-S. Liu, W.-K. Li, T.-R. Kang, L. He, Q.-Z. Liu, *Org. Lett.* **2015**, *17*, 150; j) W.-K. Li, Z.-S. Liu, L. He, T.-R. Kang, Q.-Z. Liu, *Asian J. Org. Chem.* **2015**, *4*, 28; k) M.-S. Xie, Y. Wang, J.-P. Li, C. Du, Y.-Y. Zhang, E.-J. Hao, Y.-M. Zhang, G.-R. Qu, H.-M. Guo, *Chem. Commun.* **2015**, *51*, 12451. For a review on VCPs reactivity, see: a) M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479.

[2] a) B. D. Sherry, A. Fürstner, *Chem. Commun.* **2009**, 7116; b) J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 18618; c) A. P. Dieskau, M. S. Holzwarth, B. Plietker, *J. Am. Chem. Soc.* **2012**, *134*, 5048; d) D. Pursley, B. Plietker, *Synlett* **2014**, *25*, 2316; e) R. Tombe, T. Kurahashi, S. Matsubara, *Org. Lett.* **2013**, *15*, 1791;

[3] a) K. H. Halskov, L. D. Næsborg, F. Tur, K. A. Jørgensen, *Org. Lett.* **2016**, *18*, 2220; c) M. Meazza, R. Rios, *Chem. Eur. J.* **2016**, *22*, 9923; c) M. Laugeois, S. Ponra, V. Ratovelomanana-Vidal, V. Michelet, M. R. Vitale, *Chem. Commun.* **2016**, *52*, 5332.



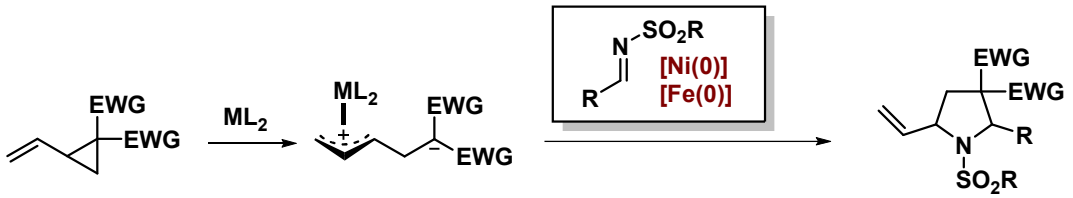
Scheme 2. [3+2] dual catalytic asymmetric cycloaddition of enals and VCPs

VCP derivatives **2** are activated by palladium catalyst to afford the zwitterionic stabilized intermediate which undergoes [3+2] cycloaddition with the organocatalytically generated iminium ion, to deliver the enantioenriched five-membered rings bearing three chiral centres. The scope of the methodology is evaluated with respect of both enals and VCP derivatives achieving in all cases very satisfying values of diastereo- and enantioselectivity as well as excellent yields.

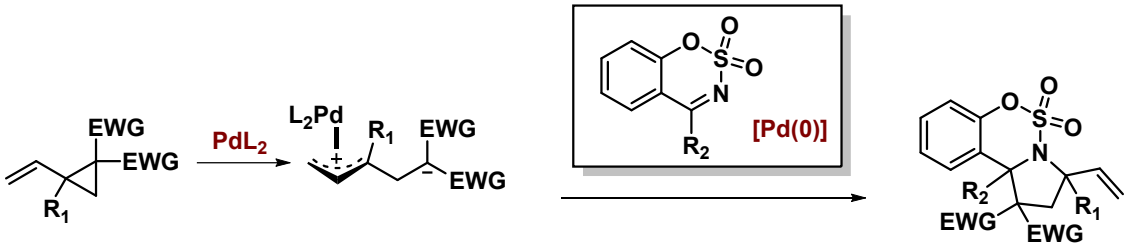
3.1.2 Aim of the project

The substrate scope of dual catalytic cycloaddition of VCPs is so far limited to enals that can be very efficiently activated by chiral secondary amines by LUMO lowering strategy. [3+2] Cycloadditions of VCPs and imines affording polyfunctionalized pyrrolidines are known in literature, but, because of their low electrophilic character, the reaction is restricted to activated imines, such as *N*-sulfonyl ones, in presence of stronger Lewis acids (Nickel[2e] or Iron[2c,d]). Only recently it has been demonstrated that also Pd is able to promote this reaction (Scheme 3).[4] In these methodologies, the transformation seems to be limited to *N*-sulfonyl imines and there are no efficient enantioselective reports except for some preliminary results obtained by the group of Matsubara[2e] relying on the use of phosphine-based chiral ligands (ee < 60%), and by the group of Campagne[4c] in which the phosphoramidite-based ligand delivers high enantioselctivities only in some limited examples (ee ~ 90%).

- previous work by Matsubara and Plietker:



- previous work by Guo, Vitale and Campagne:

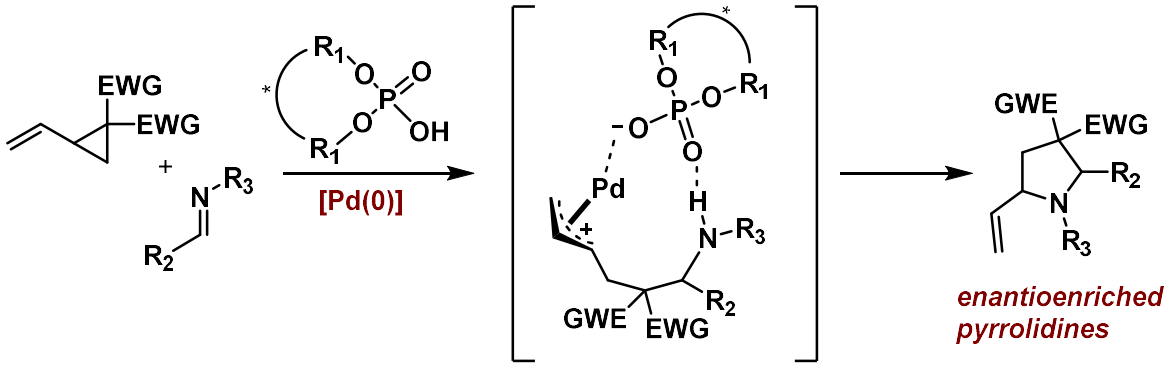


Scheme 3. Previous reports on the [3+2] catalytic cycloaddition of vinylcyclopropanes and imines

Chiral phosphoric acids have proved to represent a prominent tool in asymmetric catalytic nucleophilic addition to imines.[5] To broaden the scope to other dipolarophiles and to fill the gap of an asymmetric [3+2] cycloadditions VCPs to imines, we questioned whether it would be possible to exploit chiral phosphoric acids to enhance the electrophilicity of imines, and at the same time to induce enantiocontrol in the reaction. A bond-forming event, in which

[4] a) Q. Wang, C. Wang, W. Shi, Y. Xiao, H. Guo, *Org. Biomol. Chem.* **2018**, *16*, 4881; b) J. Ling, M. Laugeois, V. Ratovelomanana-Vidal, M. R. Vitale, *Synlett* **2018**, *29*, 2288; c) K. Spielmann, E. Tosi, A. Lebrun, G. Niel, A. van der Lee, R. M. de Figueiredo, J. M. Campagne, *Tetrahedron*, **2018**, *74*, 6497.
[5] a)T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) M. Terada, *Chem. Commun*, 2008, 4097; c) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

the Brønsted acid is coordinated to both the 1,3-dipole and dipolarophile in order to enforce stereochemical control, is proposed as key step for the methodology (Scheme 4).



Scheme 4. Synergistic catalytic asymmetric [3+2] cycloaddition merging chiral phosphoric organocatalyst and palladium catalysis

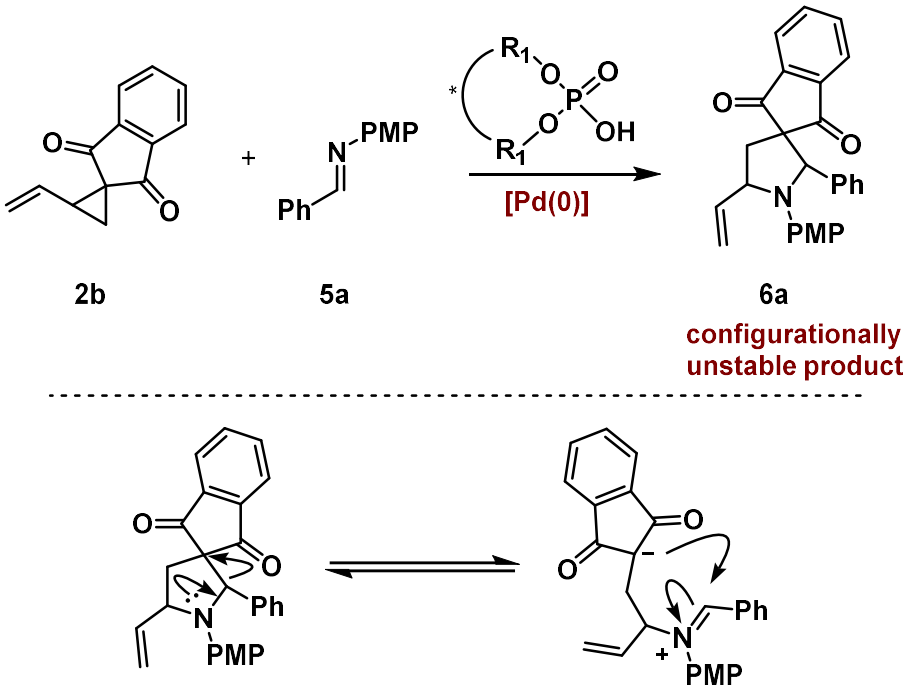
3.1.3 Results and Discussion

Initially, a range of VCPs substituted with different electron withdrawing groups was tested with various benzaldehyde derived imines, using a combination of $Pd(PPh_3)_4$ and diphenylphosphoric acid as catalyst. This preliminary investigation allowed to reach the following conclusions:

-VCPs substituted with ester groups are not reactive: presumably, ester groups do not stabilize sufficiently the negative charge of the dipole, hindering its formation and the possibility to carry out the reaction under mild conditions. In contrast, VCPs carrying cyano or keto groups could afford the pyrrolidine products.

-Activated (i.e. N-sulfonyl) imines did not require acid activation for the reaction to occur, thus preventing the possibility to achieve stereocontrol in the reaction by a chiral (phosphoric) acid. N-aryl imines required instead acid activation, thus making them promising candidates for the planned approach.

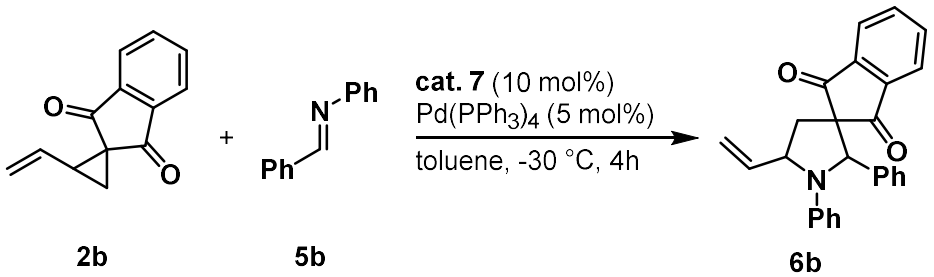
After a long series of experiments, some promising reactivity data, yet preliminary, were observed when *p*-methoxyphenyl imine **5a** was treated with achiral diphenylphosphate phosphoric acid, VCP **2b** and $Pd(PPh_3)_4$ at -30 °C in toluene. However, we found that product **6a** was not configurationally stable leading to diastereoisomeric erosion in the reaction mixture as well as during chromatographic purification. Indeed, an acid promoted retro-Mannich reaction took place opening the product thus isomerizing one chiral centre. Subsequent catalyst-uncontrolled Mannich addition to the iminium ion let in fact to product epimerization (Scheme 5).



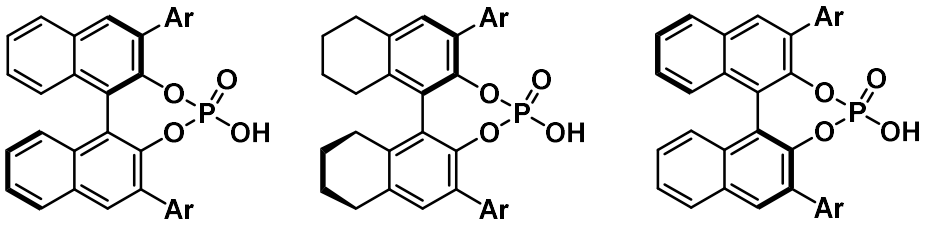
*Scheme 5. Proposed pathway for the racemization of pyrrolidine product **6a***

Thankfully, simple changes in substrate structure, using a less electron rich N-phenyl imine **5b**, were effective enough to obtain a more stable product which let us to carry out the screening process of the reaction conditions. We started our study of the [3+2] cycloaddition of *N*-phenyl imine **5b** and 1,3-indandione-derived VCP **2b** in presence of chiral phosphoric acids **7** (Table 1) and $Pd(PPh_3)_4$. In first place, we carried out the screening of various chiral organocatalyst to find out which one would deliver the highest enantiomeric excess and diastereoisomeric ratio.

*Table 1. Screening of chiral phosphoric acids for the asymmetric [3+2] cycloaddition of imine **5b** and VCP **2b***



cat. 7 :



7a Ar: 2,4,6-*i*PrC$_6$H$_2$
7b Ar: 4-PhC$_6$H$_4$
7c Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$

7d Ar: 9-anthracenyl

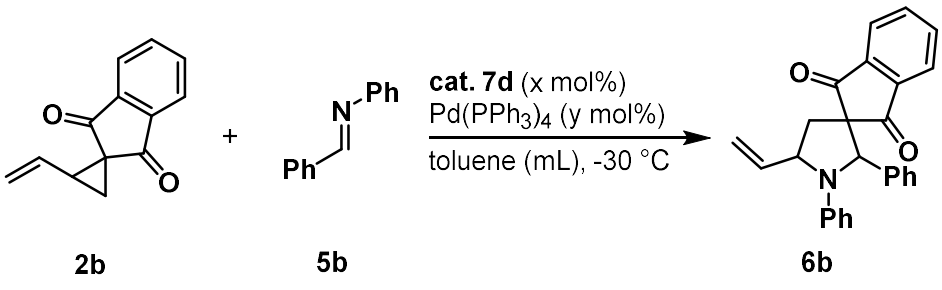
7e Ar: -SiPh$_3$
7f Ar: 4-NO$_2$C$_6$H$_4$

Entry[a]	**cat. 7** (10 mol%)	Conv. [%][b]	NMR Yield [%][b]	d.r.[b]	ee$_{maj}$ [%][c]	ee$_{min}$ [%][c]
1	**7a**	>95	95	1.8:1	rac	-16
2	**7b**	>95	88	1.5:1	6	-10
3	**7c**	>95	93	0.8:1	rac	Rac
4	**7d**	>95	81	3.2:1	42	11
5	**7e**	>95	87	1.8:1	-10	rac
6	**7f**	>95	86	0.5:1	-14	5

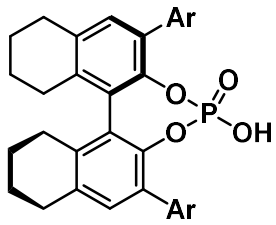
[a] Conditions: imine **5b** (0.055 mmol), VCP **2b** (0.05 mmol), toluene (0.2 mL), organocatalyst **7** (10 mol%), Pd(PPh$_3$)$_4$ (5 mol%), -30 °C, 4h. [b] Determined on the crude mixture by ^{1}H NMR analysis. Determined by chiral stationary phase HPLC analysis.

As it is shown in Table 1, although catalysts **7a-c** (Table 1, entries 1-3), **7e,f** (Table 1, entries 5,6) afforded the desired product with very poor selectivity, catalyst **7d** (Table 1, entry 4) was found to deliver product **6b** with 42% ee of the major diastereoisomer and 3.2 : 1 diastereoisomeric ratio. Afterwards, we moved to set the best Pd/organocatalyst ratio and the best dilution to perform the transformation (Table 2).

*Table 2. Screening of Pd/organocatalyst ratio and dilution for the [3+2] cycloaddition of imine **5b** and VCP **2b***



2b **5b** **6b**



7d Ar: 9-anthracenyl

Entry[a]	**cat. 7d** (mol%)	$Pd(PPh_3)_4$ (mol%)	toluene (mL)	T [°C]	Conv. [%][b]	d.r.[b]	ee_{maj} [%][c]	ee_{min} [%][c]
1	10	5	0.2	-30	>95	3.2:1	42	11
2	15	5	0.2	-30	>95	2.0:1	52	-11
3	20	5	0.2	-30	>95	1.8:1	52	-23
4	5	5	0.2	-30	>95	5.3:1	58	15
5	5	10	0.2	-30	>95	7.0:1	60	35
6	5	10	0.4	-30	>95	14:1	62	rac
7	5	10	0.6	-30	>95	>20:1	65	-11
8	5	10	0.8	-30	>95	>20:1	60	-14
9	5	10	0.1	-30	>95	1:1.9	61	rac

[a] Conditions: imine **5b** (0.055 mmol), VCP **2b** (0.05 mmol), toluene (mL), organocatalyst **7** (mol%), $Pd(PPh_3)_4$ (mol%), -30 °C. [b] Determined on the crude mixture by ^1H NMR analysis. Determined by chiral stationary phase HPLC analysis.

Increasing the molar amount of organocatalyst **7d** slightly improved the enantioselectivity of the reaction (Table 2, entries 1-3), while using equimolar amounts of the two catalysts improved both the ee and d.r. values (Table 2, entry 4). A 1:2 molar ration between organocatalyst and $Pd(PPh_3)_4$ slightly raised the diastereoselectivity (Table 2, entry 5). Performing the reaction in a more diluted system dramatically improved the d.r. up to more than 20:1 also reaching the best enantioselectivity observed so far (Table 2, entry 7). This is probably due to the lower acidic organocatalyst concentration that does not promote

product epimerization. Indeed, when the reaction was run in a more concentrated system the d.r. dropped (Table 2, entry 9). Typically, drying agents such as molecular sieves are used in combination with chiral phosphoric acid since their catalytic activity may be influenced by water traces that are present in the solvent.[6] We therefore evaluated the effects of a water-free system but, unfortunately, neither molecular sieves of different pore sizes (3, 4, 5 Å), nor anhydrous magnesium or sodium sulphate proved to be beneficial for the selectivity of the reaction. Finally, a screening of solvents was carried out in order to evaluate their influence on the reaction. As expected, polar solvents such as CH_3CN or EtOAc delivered product **6b** in a racemic form, probably because of catalyst coordination, while performing the reaction in other solvents did not improve the enantioselectivity nor the diastereoselectivity. Toluene was found to be the best solvent for this transformation.

3.1.4 Conclusions and Perspectives

In this chapter some preliminary results about the asymmetric dual catalytic [3+2] cycloaddition of vinyl cyclopropanes and *N*-phenyl imines have been presented. A different approach from the previously reported enabled us to develop this reaction with non-activated imines (e.g. *N*-aryl imines). The polyfunctionalized pyrrolidine product was obtained in modest enantioselectivity (about 65%), good diastereoselectivity and yields (e.g. >20.1 d.r., ~80% yield). Great efforts will be dedicated to the improvement of the enantiomeric excess. As future perspective, the influence of phosphine-based ligands on the palladium catalyst will be investigated. More in detail, it will be tested bidentate ligands or monodentate ligands of different sizes, as well as chiral ligands (including phosphorimidites-based ligands) paying particular attention to the matched and mismatched effects that will be encountered in presence of the chiral organocatalyst.

3.1.5 Experimental Section

3.1.5.1 General Methods

^1H, ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H and ^{13}C NMR.[7] ^{13}C NMR were acquired under ^1H broadband decoupling. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electronspray (ES) ionization technique. Optical rotations were

[6]

[7] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.

measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at λ = 254 nm. Melting points were measured on a Stuart Scientific melting point apparatus SMP3 and are not corrected.

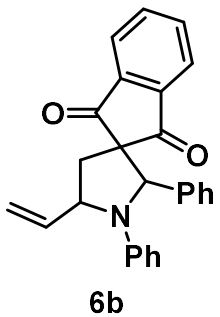
3.1.5.2 Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Vinylcyclopropane **2b** was prepared according to a reported literature procedure.[8] Imines 5a,b were prepared according to a reported literature procedure.[9]

*3.1.5.3 General procedure for the catalytic asymmetric [3+2] cycloaddition of vinylcyclopropane **2b** and imine **5b***

To a solution of VCP **2b** (0.5 mmol) in toluene (0.6 mL) in a reaction tube equipped with magnetic stirring bar, are added catalyst **7d** (0.0025 mmol) and imine **5b** (0.055 mmol). The reaction is cooled to -30 °C, after 5 minutes $Pd(PPh_3)_4$ is added to the reaction mixture and stirred until full consumption of the starting material as shown by TLC analysis. Then, the crude mixture is filtered through a small plug on silica gel and eluted with Et_2O. The reaction crude is purified by column chromatography on silica gel (*n*-hexane/EtOAc 4 : 1) to afford the title compound **6b**.

3.1.5.4 Characterization data



6b

Major diastereoisomer: **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.94 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.73 (td, *J* = 7.4, 1.3 Hz, 1H), 7.66 (td, *J* = 7.4, 1.2 Hz, 1H), 7.58 (ddd, *J* = 7.5, 1.3, 0.8 Hz, 1H), 7.02 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.97 – 6.87 (m, 5H), 6.62 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.56 – 6.49 (m, 2H), 5.80 (ddd, *J* = 17.1, 9.8, 8.7 Hz, 1H), 5.42 – 5.33 (m, 2H), 5.29 – 5.17 (m, 2H), 2.54 (dd, *J* = 13.0, 7.1 Hz, 1H), 2.36 (dd, *J* = 13.0, 7.8 Hz, 1H). HPLC: (Chiralpak OD-H, *n*-hexane/*i*-PrOH 95:5, 0,75 mL/min, λ = 254 nm, t_{r1} = 10.4 min; t_{r2} = 11.2 min. Minor diastereoisomer: **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.03 – 7.96 (m, 1H), 7.86 – 7.70 (m, 3H), 7.24 – 7.07 (m, 6H), 6.78 – 6.65 (m, 4H), 6.41 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1H), 5.48 (d, *J* = 17.3 Hz, 1H), 5.34 (d, *J* = 10.2 Hz, 1H), 4.95 (s, 1H), 4.82 (q,

[8] A. P. Dieskau, M. S. Holzwarth, B. Plietker, *J. Am. Chem. Soc.* **2012**, 134, 5048−5051
[9] G. Men, J. M. Lehn, *J. Am. Chem. Soc.* **2017**, *139*, 2474.

J = 7.5 Hz, 1H), 2.55 (dd, *J* = 13.1, 7.8 Hz, 1H), 2.44 (dd, *J* = 13.2, 7.3 Hz, 1H). (Chiralpak OD-H, *n*-hexane/*i*-PrOH 95:5, 0,75 mL/min, λ = 254 nm, t_{r1} = 12.6 min, t_{r2} = 15.7 min.

3.2 Catalytic Asymmetric Oxidative γ-Coupling of α,β-unsaturated Aldehydes with Air as the Terminal Oxidant

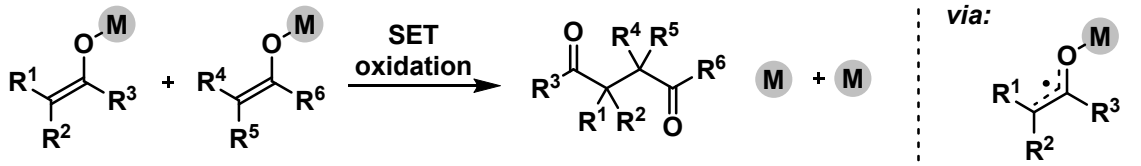
3.2.1 Background

In the realm of asymmetric synthesis, asymmetric catalytic transformations represent prominent tools in the generation of chiral enantioenriched molecules.[1] Readily available chiral amines have shown to be very effective in the activation of carbonyl compounds and consequent stereoinduction in the reaction with both electrophiles and nucleophiles.[2] They have been exploited not only in the field of polar reactivity, in which, for example, a nucleophile reacts with an electrophile, but also in the field of open-shell intermediates.[3] Recently, catalytic reactions involving radical intermediates have flourished, as synthetic chemists are increasingly more prone to include radical transformations in a synthetic route.[4] Accordingly, the potential of open-shell intermediates in reaction development has been recognised; therefore new methods of generating and controlling radical reactions in an enantioselective manner are of great interest. However, the involvement of short-living radical intermediates in asymmetric catalysis has remained unexplored until recently because of the intrinsic challenges of efficiently controlling the stereoselective bond formation from highly energetic species. Although open-shell intermediates can be generated by various methods in a relatively simple manner, control of radical formation and conversion of the highly reactive species into the desired product in a selective way is difficult and enantioselective methodologies are scarce. Nevertheless, the use of radicals gives rise to novel and unprecedented reaction concepts, such as the oxidative coupling of two nucleophiles, which would not be feasible by means of polar reactivity.[5] The use of single-

[1] a) R. Noyori, *Asymmetric Catalysis in Organic Chemistry*, Wiley, Hoboken, **1994**; b) I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley, New York, **2000**.
[2] See, for example: a) P.I. Dalko, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Wiley-VCH, Weinheim, **2013**; b) B. List, *Asymmetric Organocatalysis*, Springer, Heidelberg, **2009**; c) D.W.C. MacMillan, *Nature* **2008**, *455*, 304; d) B.S. Donslund, T.K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, 54, 13860; *Angew. Chem.* **2015**, *127*, 14066.
[3] D. A. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582.
[4] a) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin, Y. Jia, *Org. Lett.* **2010**, *12*, 4066; b) H.-Q. Do, H. Tran-Vu, O. Daugulis, *Organometallics* **2012**, *31*, 7816; c) A. Studer, D. A. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58; *Angew. Chem.* **2016**, *128*, 58; d) S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2016**, *55*, 5290; *Angew. Chem.* **2016**, *128*, 5376; e) J. Xuan, A. Studer, *Chem. Soc. Rev.* **2017**, *46*, 4329; f) W. Zhang, A. Li, *Nat. Chem.* **2017**, *9*,198; g) K. Zhao, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 3754; *Angew. Chem.* **2017**, *129*, 3808; h) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692.
[5] a) K. Wu, Z. Huang, X. Qi, Y. Li, G. Zhang, C. Liu, H. Yi, L. Meng, E. E. Bunel, J. T. Miller, C. W. Pao, J. F. Lee, Y. Lan, A Lei, *Sci. Adv.* **2015**, *1*, e1500656; b) T. Amaya, Y. Maegawa, T. Masuda, Y. Osafune, T. Hirao, *J. Am. Chem. Soc.* **2015**, *137*, 10072; c) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780.

electron-transfer reagents (SET) has been widely applied to donate or accept one single electron in order to form the desired radical species.[4] SET reagents in stoichiometric amounts have been successfully engaged in the oxidative coupling of preformed enol ethers and enolates affording versatile 1,4-dicarbonyl building blocks (Scheme 1).[6, 5b]

Open-shell strategy: Stoichiometric SET oxidant and stoichiometric activation of substrates



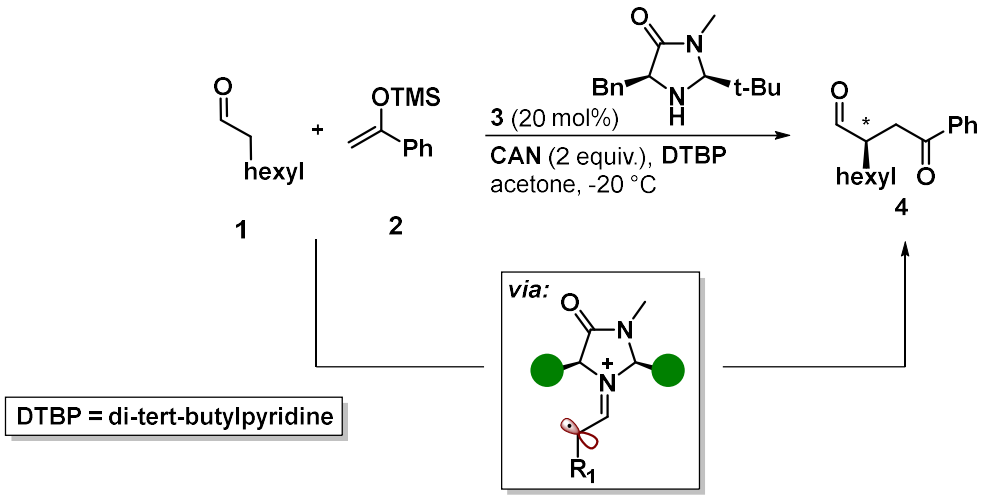
• Coupling of nucleophiles • Preformed enolates • Stoichiometric oxidant • No enantioselectivity

Scheme 1. Oxidative α-coupling of preformed enolates with a stoichiometric amount of oxidant

This type of transformation is very difficult to perform only exploiting polar reactivity as both reaction partners are nucleophilic in nature. Besides, it is an oxidative process in which either stoichiometric amount of SET reagent or stoichiometric amount of sacrificial oxidant to regenerate the SET reagent are needed. Finally, overstoichiometric amounts of base have to be used to ensure complete deprotonation of the carbonyl starting material thus obtaining the reactive enol ether. The group of MacMillan extended this concept to the organocatalytic enantioselective *α*-enolation of aldehydes with enolsilanes relying on single occupied molecular orbital (SOMO) activation mode (Scheme 2).[7]

[6] a) M. P. De Martino, P. S. Baran, *Angew. Chem. Int. Ed.* **2006**, *45*, 7083; *Angew. Chem.* **2006**, *118*, 7241; b) M. P. De Martino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546; see also: c) A. N. White, T. Rovis, *J. Am. Chem. Soc.* **2015**, *137*, 10112.
[7] H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*,7004.

Organocatalysis-SOMO strategy: Stoichiometric amounts SET and catalytic activation of substrates



• Coupling of nucleophiles • Preformed enolate • Organocatalysis • Stoichiometric oxidant • Enantioselective

Scheme 2. Oxidative a-coupling of aldehydes with preformed enolates by organocatalysis with excess of CAN as the oxidant

For example, *n*-octanal **1** reacts with chiral imidazolidinone catalyst **3** to generate the organocatalitically active enamine which undergoes SET oxidation in presence of a suitable oxidant such as ceric ammonium nitrate (CAN). Then, the putative 3*π*-electron SOMO-activated radical cation is trapped at the *α*-position by the concomitant presence of enolsilane **2** to deliver the carbon-centered -OTMS species, which upon second SET oxidation event forms the corresponding oxocarbenium ion that easily undergoes hydrolysis of the silyl group in order to render the final product (Scheme 2).

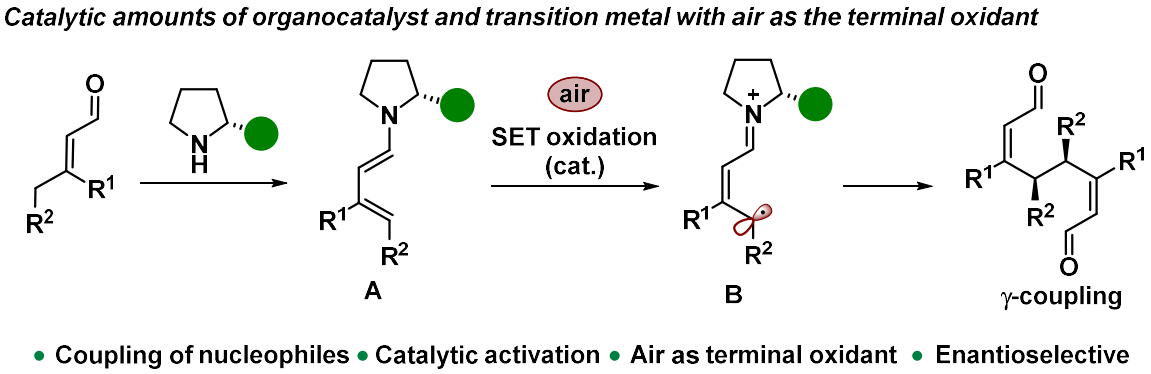
It is worth mentioning that also photoredox catalytic strategies have been broadly applied to develop catalytic asymmetric transformation and, more in detail, to generate SOMO-activated enamines that can participate to carbon-carbon bond-forming reactions.[8]

3.2.2 Aim of the Project

The oxidative coupling of preformed enolates is a very important chemical transformation as it delivers 1,4-dicarbonyl compounds which are valuable synthetic synthons of organic chemistry. In contrast, the catalytic enantioselective oxidative coupling of enolate equivalents (e.g. enamines) using atmospheric oxygen as terminal oxidant to regenerate a

[8] a) For a perspective, see: Mària Mečiarovà, P. Tisovskỳ, R. Šebesta, *New J. Chem.* **2016**, *40*, 4855; for examples, see: b) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218; c) D. Wang, L. Zhang, S. Luo, *Org. Lett.* **2017**, *19*, 4924; d) G. Filippini, M. Silvi, P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 4447; *Angew. Chem.* **2017**, *129*, 4518; e) M. Silvi, C. Verrier, Y. P. Rey, L.Buzzetti, P. Melchiorre, *Nat. Chem.* **2017**, *9*, 868; f) A. G. Capacci, J. T. Malinowski, N. J. McAlpine, J. Kuhne, D. W. C. MacMillan, *Nat. Chem.* **2017**, *9*,1073; g) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872.

substoichiometric amount of SET reagent has never been reported. In order to address this challenging transformation and to develop an alternative approach to give access to the class of dicarbonyl compounds, we decied to study the merger of organocatalysis for carbonyl activation and a transition metal catalyst, featuring the appropriate redox properties. Ultimately, we set our focus on the oxidation of dienamine **A** to generate the organocatalitically activated open-shell intermediate **B** and being re-oxidized by atmospheric oxygen as sacrificial oxidant. This strategy might disclose a novel method to include SET reagents in a substoichimetric fashion and, at the same time, to induce stereochemical control over bond formation relying on intermediates such as **B** (Scheme 3).



Scheme 3. Asymmetric oxidative γ-coupling of α,β-unsaturated aldehydes by merging organocatalysis and a catalytic amount of a transition metal that is readily re-oxidized by air

The catalytic asymmetric *γ*-coupling of *α*,*β*-unsaturated aldehydes displays various intrinsic challenges: for example, a main issue might be the regioselectivity of the radical species can react at both the *α*- or *γ*-position (Figure 1).[9] A further challenge is diastereoselectivity since only one diastereoisomer is chiral while the other one is the *meso* form. Finally, organocatalyst has to enforce high levels of enantioselectivity over remote functionalization (Figure 1).

[9] a) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120; for reviews on dienamines in asymmetric catalysis, see: b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869; c) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865; d) V. Marcos, J. Aleman, *Chem. Soc. Rev.* **2016**, *45*, 6812.

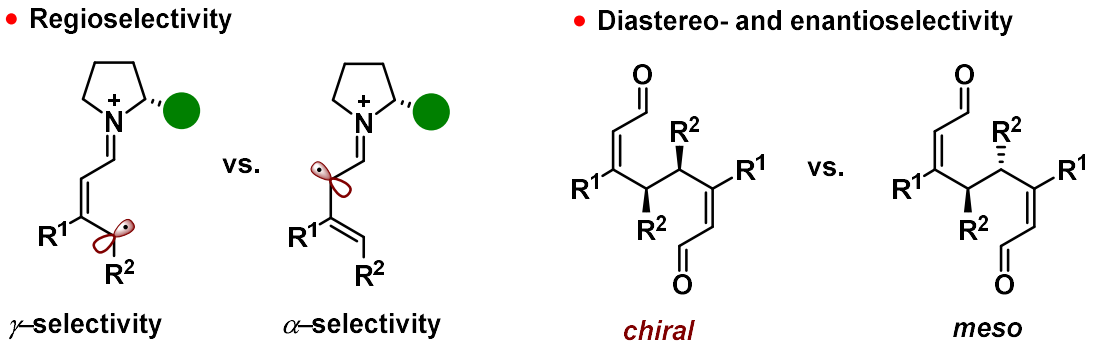


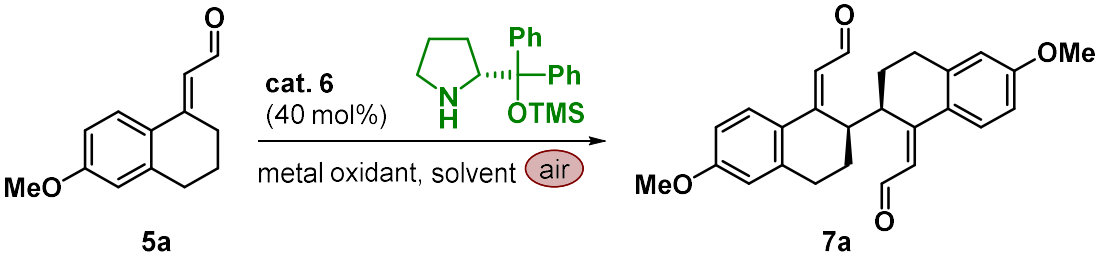
Figure 1. Main challenges in the catalytic asymmetric γ-coupling of α,β-unsaturated aldehydes

3.2.3 Results and Discussion

As proof of concept, we initially carried out the enantioselective homocoupling reaction using stoichiometric amount of Fe(III) and Cu(II) in presence of *α*,*β*-unsaturated aldehyde **5a** and organocatalyst **6**.[10] Delightfully, $Cu(OAc)_2$ was able to afford the desired product with full consumption of the starting material; on the other hand, $FeCl_3$ provided no reaction (Table 1, entries 1,2).

[10] a) H.-B. Yang, N. Selander, *Chem. Eur. J.* **2017**, *23*, 1779; b) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.* **2017**, 139, 2484; c) X.-H. Ho, W.-J. Jung, P.K. Shyam, H.-Y. Jang, *Chem. Sci. Technol.* **2014**, *4*,1914; d) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*,9016.

Table 1. Screening of the reaction conditions for the γ-coupling of cyclic α,β-unsaturated aldehydes with an enantioselective oxidative catalytic system.

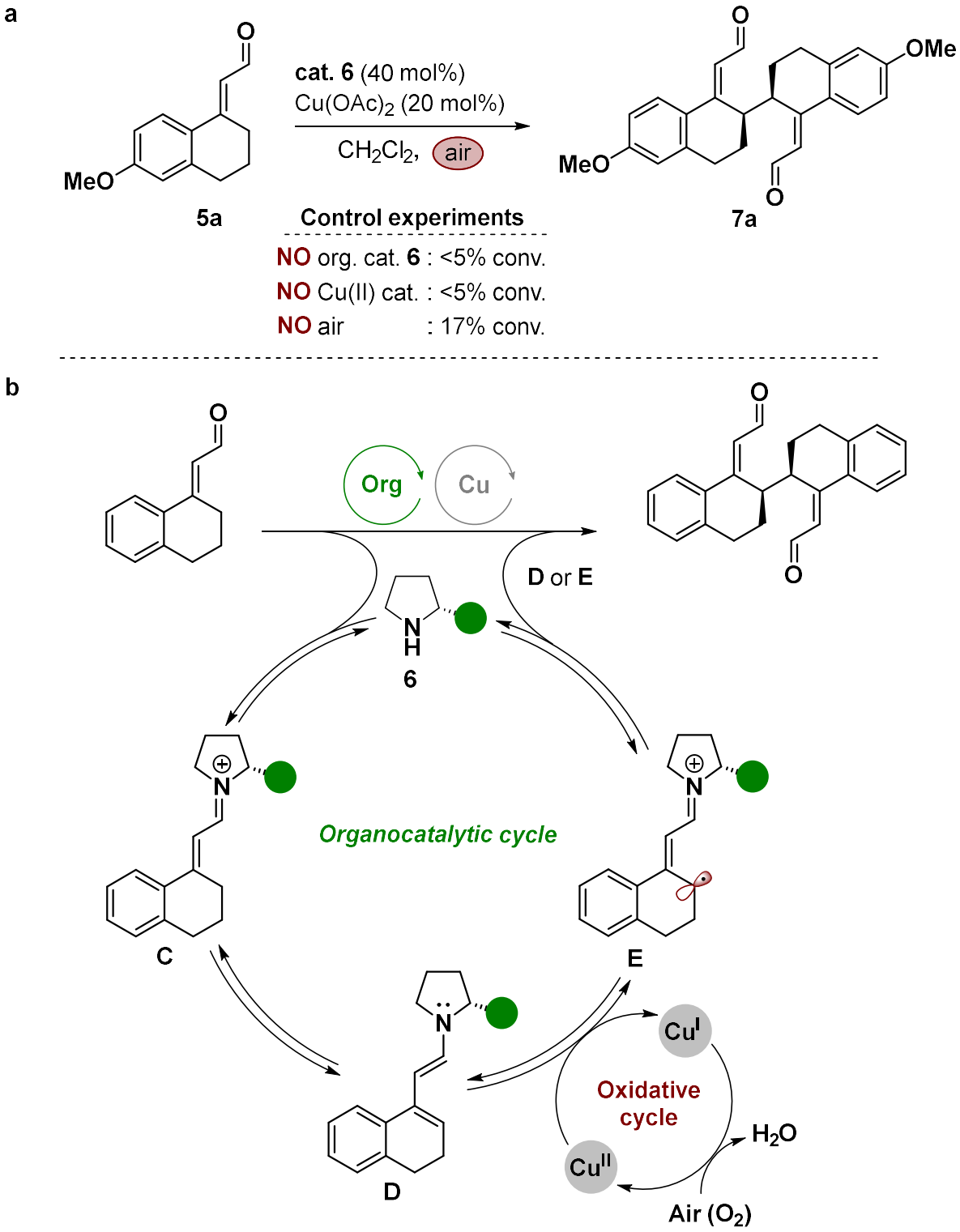


Entry[a]	Solvent (mL)	Oxidant [mol%]	Conv. [%]	d.r.	ee [%]
1[b-d]	DCE	$FeCl_3$ (300)	-	-	-
2[b]	DCE	$Cu(OAc)_2$ (300)	>95	-	-
3[b]	DCE	$Cu(OAc)_2$ (2)	>95 (51)	18:1	>99
4[b]	PhMe	$Cu(OAc)_2$ (2)	0	-	-
5[b]	$PhCF_3$	$Cu(OAc)_2$ (2)	>95 (30)	22:1	>99
6[b]	$CHCl_3$	$Cu(OAc)_2$ (2)	>95 (35)	6:1	>99
7[b]	CH_2Cl_2	$Cu(OAc)_2$ (2)	>95 (53)	15:1	>99
8[e]	CH_2Cl_2	$Cu(OAc)_2$ (20)	>95 (65)	17:1	>99
9[c,f]	CH_2Cl_2	$Cu(OAc)_2$ (20)	>95	-	-

[a] Reactions were carried out on a 0.1 mmol scale with 2.0 equivalents of **5a** and 40 mol% of the aminocatalyst **6** (it should be noted that this corresponds to 20 mol% per equivalent of the *α,β*-unsaturated aldehyde) in 0.6 mL of solvent. In brackets is the yield of the isolated product. [b] The reaction was performed on a 0.05 mmol scale. [c] The reaction was performed with 0.2 mL of solvent. [d] A messy reaction was observed by ^1H NMR spectroscopy of the crude mixture; however, the desired product was present. [e] Full conversion was observed after 8h. [f] The reaction was performed under an O_2 atmosphere. TMS = trimethylsilyl

Encouraged by these results, we questioned whether it was feasible to include $Cu(OAc)_2$ in a catalytic fashion and, with great pleasure, we found out that it was possible to lower its loading down to 2 mol% in an open-air system to obtain the desired product **7a** in 51% yield and excellent selectivity (Table 1, entry 3). A solvent screening revealed that halogenated solvents were crucial for reactivity and performing the reaction in CH_2Cl_2 resulted in a little increment of yield (Table 1, entries 4-7). The optimal amount of $Cu(OAc)_2$ was found to be 20 mol% as it afforded product **7a** in 65% yield (Table 1, entry 8). Finally, we performed an experiment in which pure oxygen rather than air was used: the reaction delivered a complex mixture of products amongst which product **7a** was also detected (Table 1, entry 9). In order to gain insight into the enantioselective *γ*-coupling of *α,β*-unsaturated system, we carried out

several control experiments: no conversion was obtained when the reaction was performed in absence of organocatalyst **5** or in absence of Cu^{II} source (Scheme 4).



Scheme 4. Mechanistic proposal of the enantioselective oxidative γ-coupling of α,β-unsaturated aldehydes based on simple investigations and observations.

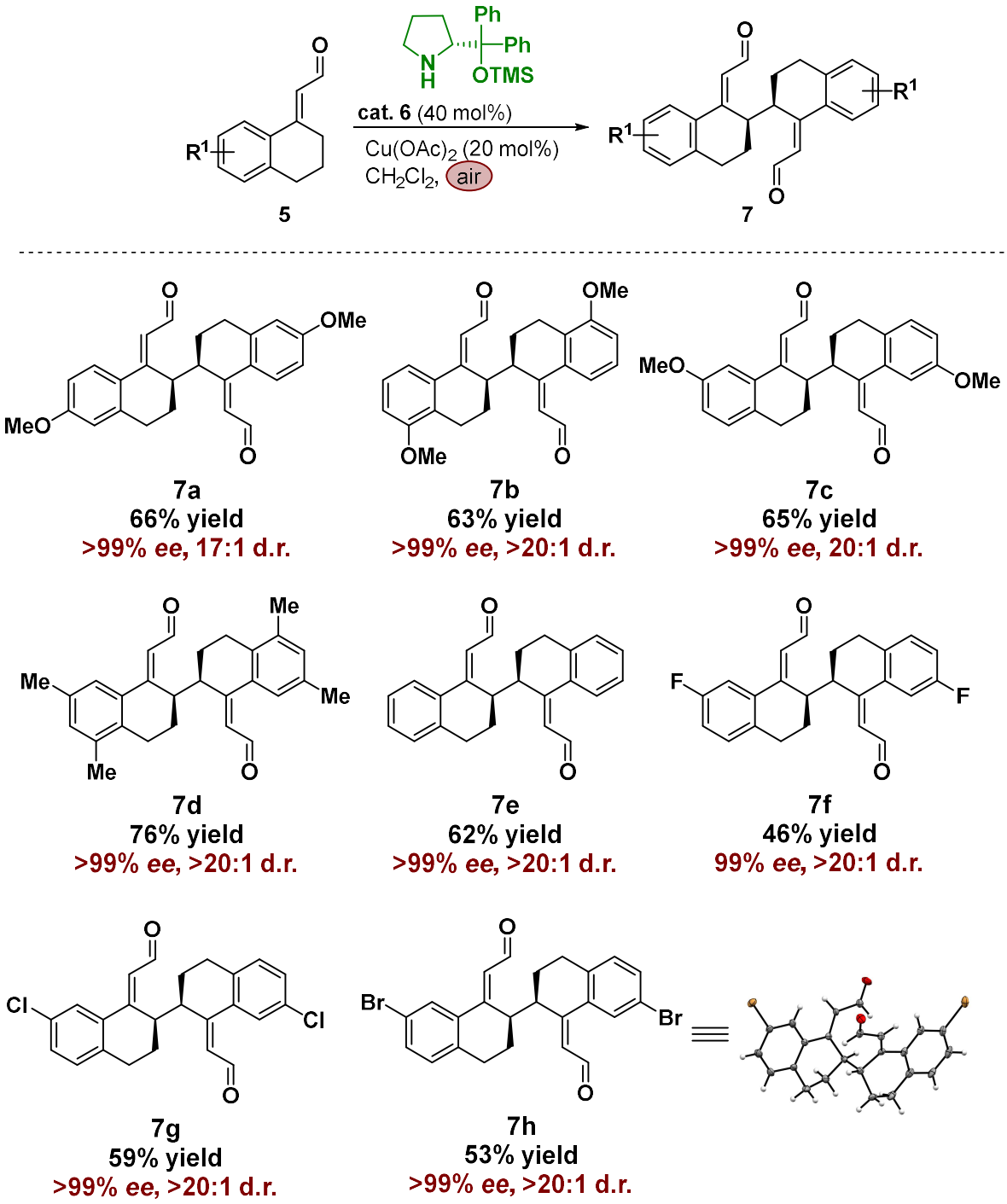
Interestingly, when the reaction was carried out under inert atmosphere we observed only 17% conversion suggesting the necessity of an oxidative cycle combined to the one of Cu^{II}/Cu^{I} to sustain the whole process. Based on these observations, we proposed the

catalytic cycle depicted in Scheme 4. In first place, aminocatalyst reacts with the *α*,*β*-unsaturated aldehyde to form the iminium ion intermediate **C** that, upon tautomerization to the corresponding enamine **D**, undergoes SET-oxidation process. This reaction is triggered by the presence in the reaction mixture of Cu^{II} to generate the highly reactive radical cation **E**[11] which can now encounter two different pathways: it can either deliver the desired product in a radical-radical termination process followed by the hydrolysis of the resulting iminium ion, or it can add to the more electron-rich dienamine intermediate **D**, which after a second SET event promoted by Cu^{II} can afford the coupling product, followed by hydrolysis of the iminium ion to enable organocatalyst turnover. Finally, the Cu^{I} species, resulting from the oxidation events, is re-oxidized by air to Cu^{II}.

Established the optimal reaction conditions, we evaluated the reaction scope of the enantioselective *γ*-coupling of *α*,*β*-unsaturated aldehydes (Table 2).

[11] J. J. Devery, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers, *Angew. Chem. Int. Ed.* **2010**, *49*, 6106; *Angew. Chem.* **2010**, *122*, 624.

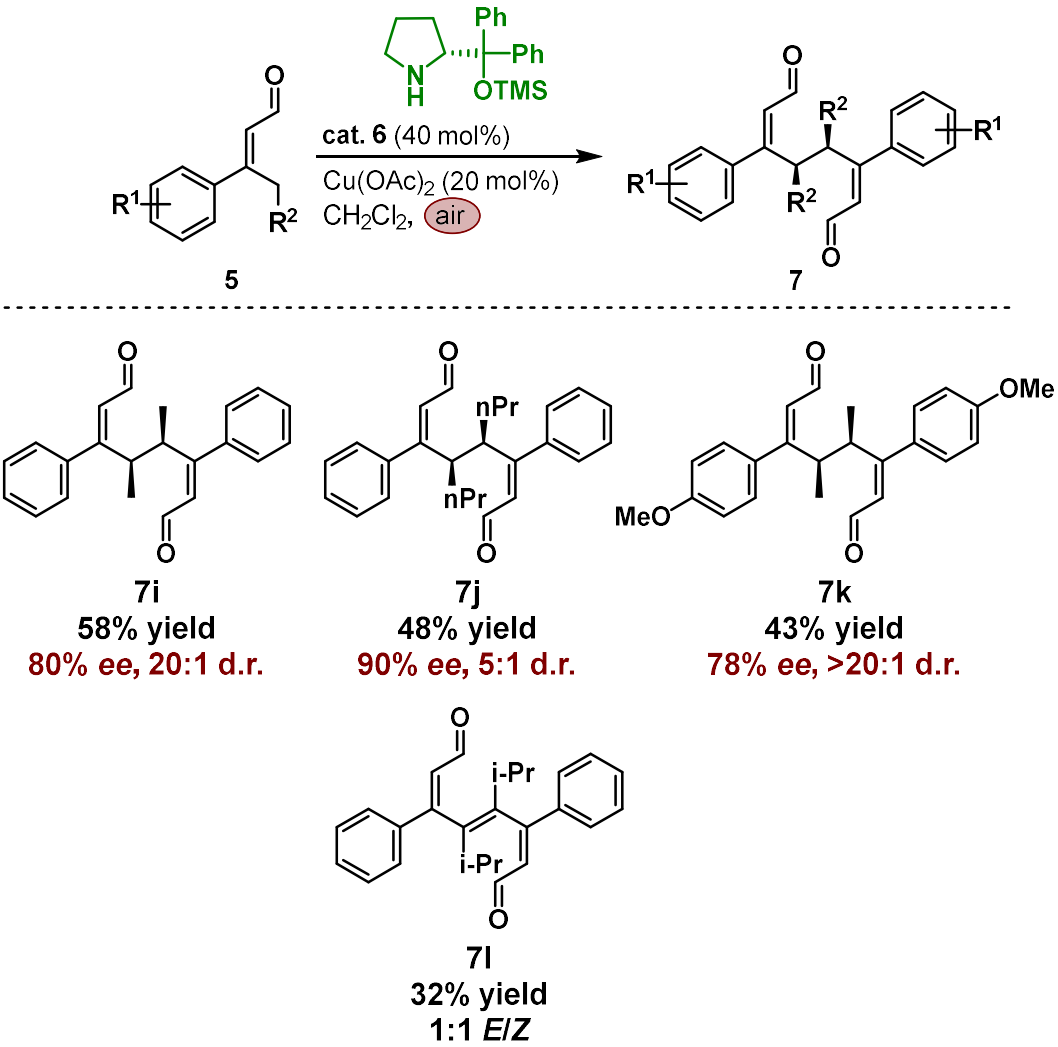
*Table 2. Substrate scope for the enantioselective oxidative γ-coupling of cyclic α,β-unsaturated aldehydes **5** using organocatalyst **6** and $Cu(OAc)_2$ as promoters in the presence of air as the terminal oxidant.*



As shown in Table 2, cyclic *α*,*β*-unsaturated aldehydes functionalized with an electron-rich substituent at three different positions of the phenyl ring delivered the corresponding *γ*–coupling products **7a-c** in 63-66% yields and excellent stereoselectivities (> 99% ee). The dimethyl substituted substrate **5d** underwent smooth coupling to afford product **7d** in slightly higher yield (76%) and same enantioselectivity. Unsubstituted *γ*–coupling product **7e** was also obtained with similar results (62% yield and 99% ee). Pleasingly, we found out that halogen containing substrates tolerated the oxidative transformation smoothly affording the

desired products **7f-h** in excellent selectivity and satisfactory yields (46-53%). In order to expand this methodology to different substrates we decided to use acyclic *α,β*-unsaturated aldehyde such as **5i**. To our delight, this substrate underwent a regioselective reaction to afford *γ*–coupling product **7i** in comparable yield and good stereoselectivity (Table 3).

*Table 3. Substrate scope for the enantioselective oxidative γ-coupling of acyclic α,β-unsaturated aldehydes **5** using organocatalyst **6** and $Cu(OAc)_2$ as promoters in the presence of air as the terminal oxidant.*

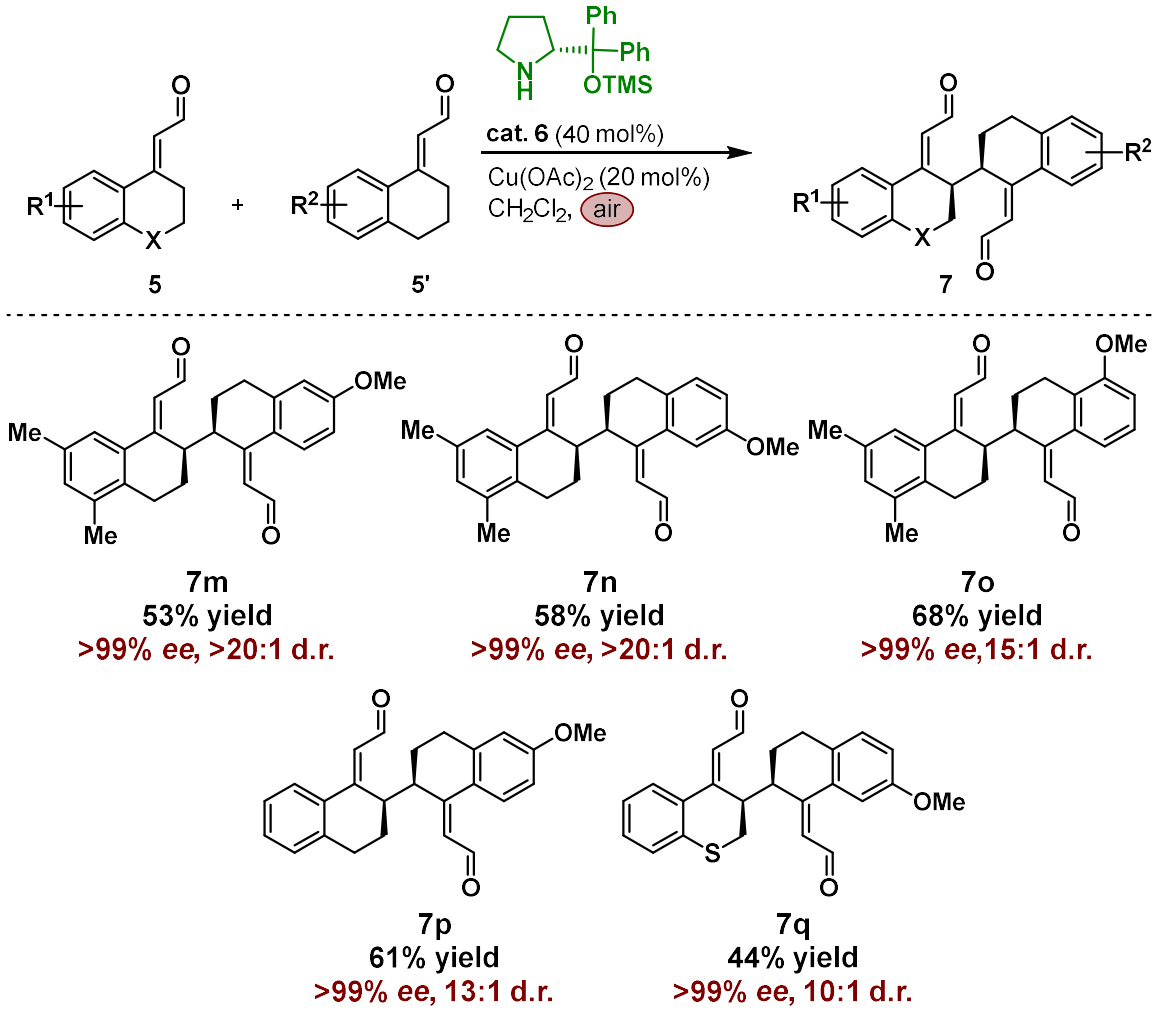


Variations were tolerated at both the alkyl substituent and substitution pattern on the aromatic moiety achieving moderate yields, excellent d.r. in some cases and up to 90% ee, as demonstrated by the synthesis of products **7i-k** (Table 3). Interestingly, when an *i*Pr group was used as alkyl substituent, the overoxidized product **7l** was isolated; this compound is probably derived from a second activation-oxidation event to form the more stable and fully conjugated side product (Table 3).

Afterwards, we turned our attention to tackle another challenge and to attempt the development of the enantioselective catalytic *γ*–heterocoupling of cyclic *α,β*-unsaturated aldehydes. Selectivity-wise, this transformation is difficult to perform as we have to bias the

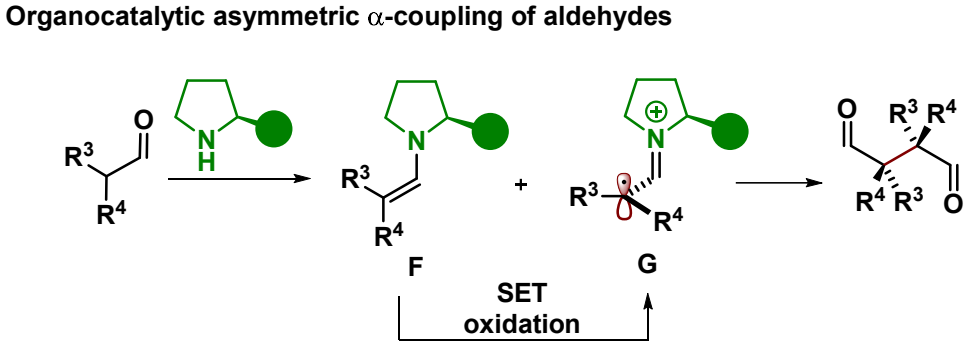
system towards the hetero-*γ*-coupling reaction in order to circumvent the formation of the homo-*γ*-coupling product, which would highly affect the yield of the desired crossed product. This transformation was initially demonstrated carrying out the reaction using an excess (3 equiv.) of the disubstituted *α*,*β*-unsaturated aldehyde **5d** with different aldehydes bearing a methoxy substituent at various position of the phenyl ring **5a-c** (Table 4).

*Table 4. Substrate scope for the enantioselective oxidative hetero-γ-coupling of acyclic α,β-unsaturated aldehydes **5** using organocatalyst **6** and $Cu(OAc)_2$ as promoters in the presence of air as the terminal oxidant.*



Gratefully, a ^{1}H NMR analysis on the crude mixture revealed the presence of the desired product along with, obviously, the homocoupling product **7d** as it is the substrate used in excess. As shown in Table 4, products **7m-o** were obtained with satisfactory yields (53-68%) and excellent enantioselectivity (>99% ee). To our delight, unsubstituted *α*,*β*-unsaturated aldehyde **5e** as well as the more challenging substrate bearing a sulfur atom, which is well known to generate sulfur-centered radicals relatively easy, delivered the corresponding hetero-*γ*-coupling products **7p** and **7q** in moderate yields, good d.r. and excellent enantioselectivity (Table 4).

In an effort to further expand the concept of the catalytic enantioselective oxidative homocoupling, we decided to set out the study of the asymmetric homocoupling of simple aldehydes. As such, we turned our attention to linear aldehydes that would afford 1,4-dicarbonyl compounds that are highly valuable motives, however synthetic stereoselective methodologies to access this scaffold are underdeveloped. This can be due to a variety of reasons including steric repulsion and selective control in the activation of only one coupling partner. Nevertheless, 1,4-dicarbonyl pattern is commonly found in natural products,[12] drug scaffold[13] and are key synthons in many named reactions in organic chemistry.[14] In order to address the enantioselective synthesis of the 1,4-dialdehyde backbone, we envisaged that the oxidative system applied to *α*,*β*-unsaturated aldehydes would be also effective for simple aldehydes (Scheme 5).



Scheme 5. Direct organocatalytic α-coupling of aldehydes mediating the possible construction of vicinal quaternary stereogenic centers.

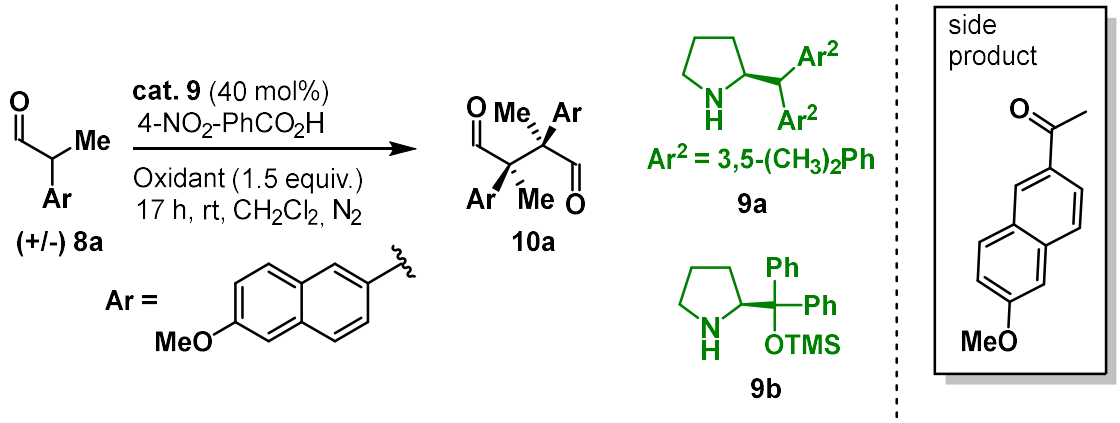
Similarly, an appropriate aldehyde should generate the organoncatalitically activated enamine species **F** that can be further activated through SET oxidation process to provide the reactive radical cation **G**. Eventually, the 1,4-dialdehyde is obtained either by radical-radical recombination of **G** or addition of radical cation **G** to enamine **F** and second SET oxidation (*vide infra*).

We thus studied the reaction of linear primary 2-phenylacetaldehyde in presence of aminocatalyst **6** and $Cu(OAc)_2$ (20 mol%); however, we isolated from the crude mixture a compound containing a carbon-carbon double bond linking the two aldehydes. This type of

[12] a) H. Seto, T. Sato, S. Urano, J. Uzawa, H. Yonehara, *Tetrahedron Lett.* **1976**, 4367; b) S. Omura, A. Hirano, Y. Iwai, R. Masuma, *J. Antibiot.* **1979**, *32*, 786; c) A. Furusaki, T. Matsumoto, H. Ogura, H. Takayanagi, A. Hirano, S. Omura, *J. Chem. Soc.*, *Chem. Commun.* **1980**, 698; d) T. Kosuge, K. Tsuji, K. Hirai, K. Yamaguchi, T. Okamoto, Y. Iitaka, *Tetrahedron Lett.* **1981**, *22*, 3417.
[13] a) M. Whittaker, C. D. Floyd, P. Brown, A. J. H. Gearing, *Chem. Rev.* **1999**, *99*, 2735; b) T. Fujisawa, K. Igeta, S. Odake, Y. Morita, J. Yasuda, T. Morikawa, *Bioorg. Med. Chem.* **2002**, *10*, 2569.
[14] a) C. Paal, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756; b) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863.

product was also observed in the methodology described previously (Table 3), as well as it has been similarly reported in the literature for ketones.[15]

*Table 5. Screening results for the oxidative homo-coupling of α-branched aldehyde **8a***



Entry[a]	4-Nitrobenzoic acid	Oxidant	Conv. [%]	d.r.	ee [%]
1[b,c]	0	$Cu(OAc)_2$/air	4	1:1	-
2[c]	0	Ag_2CO_3	90	1:1	46
3[d]	0	Ag_2CO_3	89	1:1	0
4	0	Ag_2CO_3	96	2:1	60
5	0	$AgNO_3$[e]	27	2:1	>99
6	0	$FeCl_3$[e]	0	-	-
7[f]	150	Ag_2CO_3	>95 (78)	12:1	92
8[g]	150	Ag_2CO_3	0	-	-
9	150	-	0	-	-

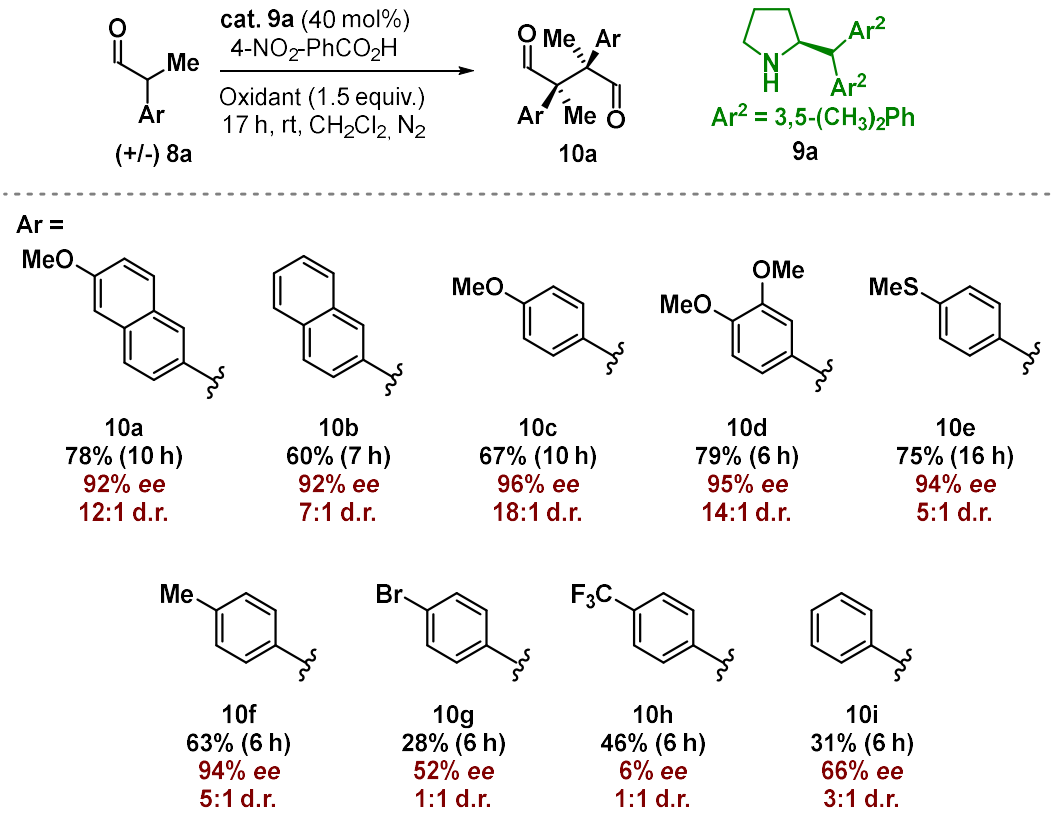
[a] Reactions were carried out on a 0.05 mmol scale with 2.0 equiv. of **8a** and 40 mol% of the aminocatalyst **9** (it should be noted that this corresponds to 20 mol% per equiv. of aldehyde) in 0.4 mL of solvent. Isolated yield is given in brackets. Conversions and diastereomeric ratios are measured by ^{1}H NMR analysis on the crude mixture. [b] 20 mol% $Cu(OAc)_2$ was employed in an open-air system. [c] The catalyst **9b** was employed. [d] L-Proline was employed as catalyst. [e] 3 equiv. of metal salt used. [f] Reactions were carried out on a 0.1 mmol scale. [g] Control experiment performed in the absence of organocatalyst.

Encouraged by the observed reactivity, which served as proof of concept, we postulated that the involvement of *α*-branched aldehydes would prevent the formation of the double bond and, more importantly, would afford the corresponding coupling product bearing two vicinal quaternary stereocenters that are very difficult to obtain in an enantioenriched form.[16]

[15] S. Manna, A. P. Antonchick, *Angew. Int. Chem. Ed.* **2016**, *55*, 5290; *Angew. Chem.* **2016**, *128*, 5376.
[16] a) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature*, **2016**, *532*, 218; b) L. Ye, Q.-S. Gu, Y. Tian, X. Meng, G.-C. Chen, X.-Y. Liu, *Nat. Commun.* **2018**, *9*,227.

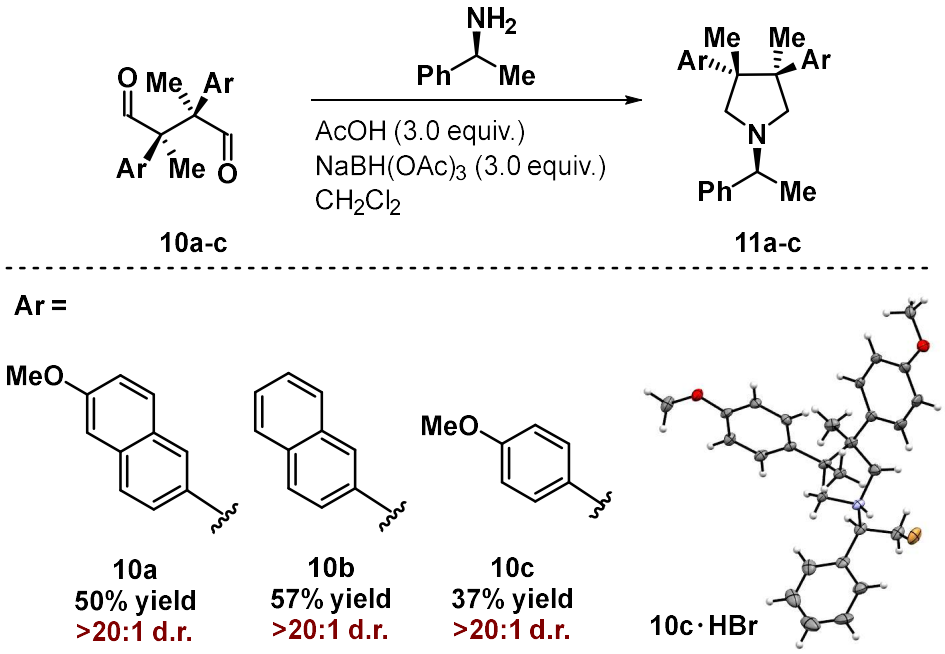
Preliminary results showed that subjecting 2-(6-methoxynaphthalen-2-yl)propanal **8a** to the air/Cu^{II} oxidative system provided the corresponding acetophenone derivative side product. In order to avoid this side reaction, we started the optimization of the reaction conditions to develop a more suitable oxidative system for *α*-branched aldehydes (Table 5, entry 1). Switching from $Cu(OAc)_2$ to stoichiometric Ag_2CO_3 dramatically increased reaction conversion, albeit providing product **10a** in moderate enantioselectivity and poor d.r. (Table 5, entry 2). A short catalyst screening pointed out organocatalyst **2a** as best candidate to perform this reaction since it provided product **10a** with 60% ee. Although $AgNO_3$ afforded the desired product excellent enantioselectivity, the corresponding conversion value was unsatisfying as well as the d.r. value (Table 5, entry 5); on the other hand, when $FeCl_3$ was employed in the reaction, it did not provide any conversion (Table 5, entry 6). Thankfully, the combination of *p*-NO_2-benzoic acid as additive and Ag_2CO_3 as SET reagent afforded the desired product in good d.r., good yield and excellent enantioselectivity (Table 5, entry 7). Finally, no product formation was detected in the control experiment with no aminocatalyst as well as the control experiment with no Ag_2CO_3, demonstrating their crucial role for this transformation (Table 5, entries 8,9). In order to explore the generality of the present reaction, various *α*-branched were tested under the optimized reaction conditions.

*Table 6. Organocatalytic enantioselective oxidative homo-coupling of α-branched aldehydes **8***

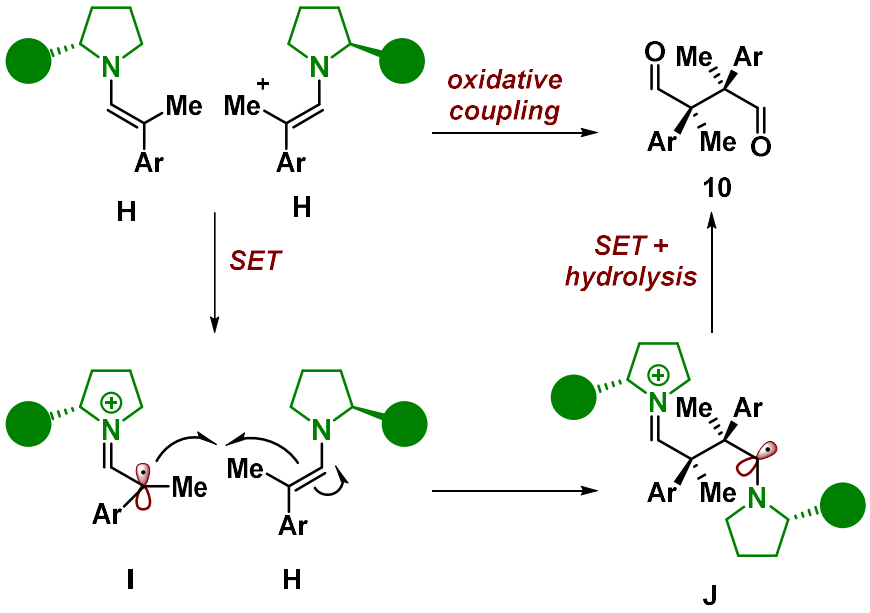


2-Naphthyl-derived *α*-branched aldehydes **8a**,**b** underwent catalytic enantioselective homocoupling to provide corresponding 1,4-dialdehydes in good, yield, good d.r. and excellent enantioselectivity (Table 6). Methoxy substituted aldehydes **8c,d** reacted smoothly under the optimized reaction conditions to afford the corresponding *α*-coupling products **10c**,**d** with 96% ee and 95% ee respectively, very good d.r. and good yields. Pleasantly, also substrate **8e**, bearing a sulphide substituent, resulted suitable for this oxidative system providing product **10e** with remarkable results (Table 6). Furthermore, the reaction of *p*-tolil-substituted aldehyde **8f** delivered **10f** in 63% yield, 5:1 d.r. and 94% ee. In contrast, the results reported in entries **10g-i** point out the limitations of this methodology as aldehydes lacking the beneficial stabilizing effects of electron-donating substituents on the aromatic moiety perform worse in the reaction delivering generally the corresponding products in lower yields and stereoselectivities. To further demonstrate the synthetic potential of this methodology, 1,4-dialdehydes **10a-c** were converted into 3,4-tetrasostituted pyrrolidines **11a-c** by means of reductive amination reaction with chiral (*S*)-1-phenylethan-1-amine (Table 7).

*Table 7. Reductive amination of homo-coupling products **10a-c** for the formation of chiral pyrrolidines **11a-c***



With only one simple transformation it was possible to obtain valuable chiral pyrrolidines that are known to represent core structures for the synthesis of chiral ligands and catalysts.[17] Besides, pyrroles and pyrrolidines represent prominent structures in bioactive molecules.[18] On the basis of experimental evidences,[19] the following reaction pathway is proposed (Scheme 6).



Scheme 6. Proposed reaction mechanism for the oxidative homo-coupling of α-branched aldehydes.

This mechanistic proposal relies on the assumption that enamine **H**, generated by the condensation of aldehyde **8** and aminocatalyst **9a**, undergoes SET oxidation in presence of Ag_2CO_3. Then, the highly reactive intermediate **I** is able to add to another equivalent of enamine **H** to provide the *α*-aminyl radical species, which upon second SET oxidation-hydrolysis sequence delivers the desired 1,4-dicarbonyl compound. This mechanistic hypothesis was confirmed by several mechanistic studies such as density functional (DFT) calculations to determine ionization potential (IP) of the relevant species,[3,20] competition experiments combined to Hammett-type plots, and a Newcomb radical clock that could distinguish between radical and cationic pathway.[21]

[17] a) S. Cicchi, G. Ghini, L. Lascialfari, A. Brandi, F. Betti, D. Berti, S. Ferrati, P. Baglioni, *Chem. Commun.* **2007**, 1424; b) B. S. Donslund, A. Monleón, J. Larsen, L. Ibsen, K. A. Jørgensen, *Chem. Commun.* **2015**, *51*, 13666; c) M. Shi, Y. Satoh, T. Makihara, Y. Masaki, *Tetrahedron: Asymmetry* **1995**, *6*, 2109.
[18] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
[19] L. Næsborg, L. A. Leth, G. J. Reyes-Rodríguez, T. A. Palazzo, V. Corti K. A. Jørgensen, *Chem. Eur. J.* **2018**, *24*, 14844.
[20] K. Müller, F. Previdoli, H. Desilvestrio, *Helv. Chim. Acta* **1981**, *64*, 2497.
[21] M.-H. Le Tadic-Biadatti, M. Newcomb, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1467

3.2.4 Conclusions

A novel catalytic system for the enantioselective coupling of aldehydes has been developed. With respect to the regioselective *γ*-coupling of *α*-tetralone derived aldehydes, the simple catalytic system relies on substoichiometric amount of $Cu(OAc)_2$, which can be re-oxidized by air as terminal oxidant, in combination with substoichiometric amount of aminocatalyst. The methodology provided homocoupling and heterocoupling product with full ragioselectivity for the *γ*-position in satisfactory yields and excellent diastereo- and enantioselectivities. Control experiments highlighted the necessity of both oragnocatalyst and Cu^{II} species to be present simultaneously. Besides, it has been demonstrated that air plays a central role for the catalytic cycle to be sustained. In order to broaden the scope of the novel catalytic system, we explored the enantioselective coupling of *α*-branched aldehydes. Unfortunately, $Cu(OAc)_2$ was not suitable for *α*-branched aldehydes, however a combination of *p*-NO_2-benzoic acid organocatalyst **9a** and Ag_2CO_3 afforded the desired 1,4-dialdehydes with good yields, good d.r. and excellent enantioselectivity. The present reaction concept enabled the access to unconventional reactivity giving rise to new avenues in organocatalytic asymmetric reaction development and serving as a key to unlock an array of new methodologies in organic synthesis.

3.2.5 Experimental section

3.2.5.1 General Methods

The NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^1H NMR and 77.16 for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; td, triple doublet; dd, double doublet; ddd, double double doublet; ddt, double double triplet; tdd, triple double doublet; m, multiplet. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Bruker Maxis Impact mass spectrometer using electrospray ionization (ESI+). Analytical thin layer chromatography (TLC) was performed using precoated aluminum-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation. Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter and $[\alpha]_D$ values are given in deg·cm·g-1 dm-1 ; concentration c is listed in g·(100 mL)-1 . The enantiomeric excess (ee) of the products were determined by Ultra Performance Convergence Chromatography (UPC^2) using Daicel

Chiralpak IA, IB, IC and ID columns as chiral stationary phases. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (SiO_2 60, 230-400 mesh, Fluka) or Iatrobeads 6RS-8060 (SES GmbH – Analysesysteme) was used. Racemic samples of compounds **7a-q** were prepared following the general procedure 3.2.5.3 using a 1:1 mixture of products prepared with (*S*)-**6** and (*R*)-**6** respectively

3.2.5.2 Materials for the enantioselective oxidative coupling of a,β-unsaturated aldehydes mediated by $Cu(OAc)_2$ using air as a terminal oxidant

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. *α*,*β*-Unsaturated aldehydes **5a-q** were synthesised from their corresponding ketones, which were commercially available, via a Horner-Wadsworth-Emmons and DIBAL-H reduction sequence according to the procedures previously reported.[22] Analytical data were in accordance with reported values.[22]

3.2.5.3 General procedure for the enantioselective oxidative coupling of a,β-unsaturated aldehydes mediated by $Cu(OAc)_2$ using air as a terminal oxidant

A 4 mL glass vial equipped with a magnetic stirring bar was charged with aminocatalyst **6** (0.04 mmol, 0.40 equiv.), *α*,*β* -unsaturated aldehyde **5** (0.20 mmol, 2.0 equiv.), and CH_2Cl_2 (0.6 mL). To the resulting mixture was added $Cu(OAc)_2$ (0.020 mmol, 0.20 equiv.). The vial was closed with a septum pinched with a needle, the resulting mixture was stirred until full consumption of the starting material aldehyde (see Figure 2). The crude product was loaded directly onto the column. FC on Iatrobeads yielded product **7**.

[22] a) H. Jiang, K. S. Halskov, T. K. Johansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 3842; b) K. S. Halskov, B. S. Donslund, S. Barfüsser, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2014**, *53*, 4137; c) B. S. Donslund, K. S. Halskov, L. A. Leth, B. M. Paz, K. A. Jørgensen, *Chem. Commun.* **2014**, *50*, 13676.

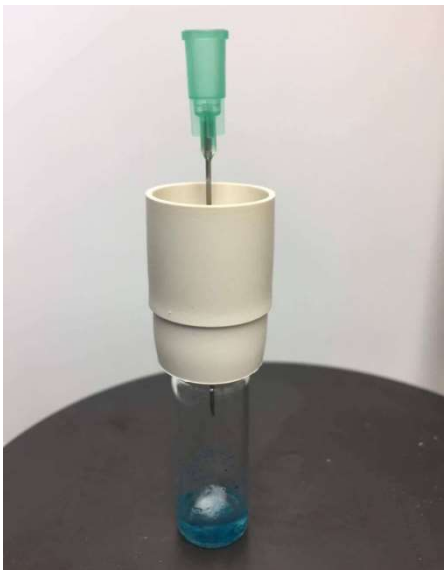
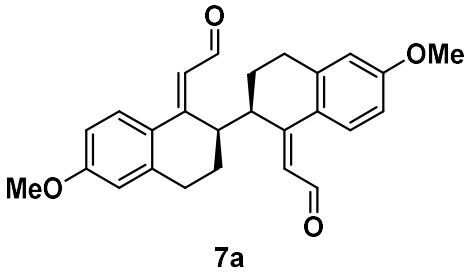


Figure 2. Simple reaction set up for the oxidative coupling mediated by $Cu(OAc)_2$ using air as a terminal oxidant

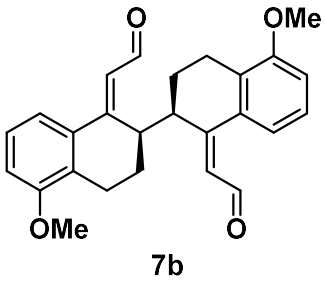
3.2.5.4 Characterisation data

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5a** (40.4 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 8h. Isolated as a yellow solid by FC on iatrobeads using EtOAc/CH_2Cl_2 1:10 as eluent (26.6 mg, 66% yield 17:1 d.r., >99%e.e). $[\alpha]_D^{22}$ = 508.2 (*c* 0.9, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.7 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 2H), 6.22 (d, *J* = 8.2 Hz, 2H), 3.83 (s, 6H), 3.66 (s, 2H), 3.11 (ddd, *J* = 18.4, 12.8 5.8 Hz, 2H), 2.94 (dd, *J* = 17.9, 6.3 Hz, 2H), 2.35 (dd, J = 14.1, 5.7 Hz, 2H), 2.12 (td, J = 13.4, 6.3 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.0 (2C), 161.8 (2C), 158.7 (2C), 139.6 (2C), 128.6 (2C), 125.1 (2C), 123.9 (2C), 114.2 (2C), 113.8 (2C), 55.5 (2C), 33.6 (2C), 24.8 (2C), 24.5 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{26}O_4$ $[M+Na]^+$: 425.1723; found: 425.1722. **UPC^2**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 7.74 min; t_{minor} = 9.08 min.



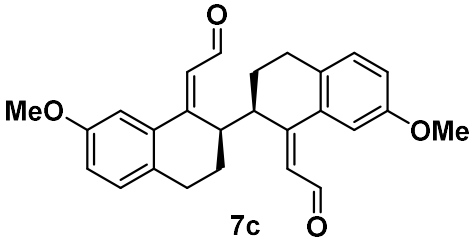
7a

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(5-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5b** (40.4 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 5h. Isolated as an off-white solid by FC on iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent (25.4 mg, 63% yield, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 688.8 (*c* 0.7, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.76 (d, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.26 (d, *J* = 8.1 Hz, 2H), 3.87 (s, 6H), 3.67 (s, 2H), 2.97 (dd, *J* = 18.8, 6.7 Hz, 2H), 2.84 (ddd, *J* = 18.8, 12.3, 6.2 Hz, 2H), 2.43 (dd, J = 14.3, 6.2 Hz, 2H), 2.09 – 1.94 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.2 (2C), 159.4 (2C), 157.2 (2C), 133.6 (2C), 127.8 (2C), 126.6 (2C), 125.4 (2C), 118.8 (2C), 111.8 (2C), 55.6 (2C), 33.2 (2C), 23.9 (2C), 19.1 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{26}O_4$ $[M+Na]^+$: 425.1723; found: 425.1724 **UPC²**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 9.25 min; t_{minor} = 10.86 min.



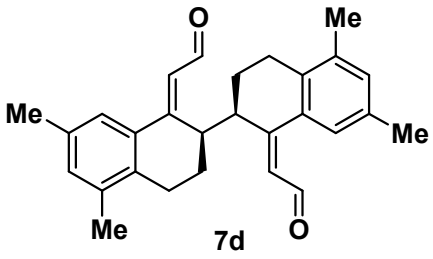
7b

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(7-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5c** (40.4 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 6h. Isolated as a yellow solid by FC on iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent (26.6 mg, 65% yield, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 524.6 (*c* 0.9, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.90 (d, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 8.5 Hz, 2H), 6.96 (dd, *J* = 8.5, 2.6 Hz, 2H), 6.88 (d, *J* = 2.6 Hz, 2H), 6.25 (d, *J* = 8.1 Hz, 2H), 3.78 (s, 6H), 3.69 (s, 2H), 3.07 (ddd, *J* = 18.2, 12.6, 5.9 Hz, 2H), 2.93 (dd, *J* = 17.5, 6.2, 2H), 2.37 (dd, *J* = 14.9, 5.1 Hz, 2H), 2.11 (td, J = 13.3, 6.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.1 (2C), 159.1 (2C), 158.6 (2C), 133.3 (2C), 130.7 (2C), 129.9 (2C), 125.3 (2C), 119.2 (2C), 109.8 (2C), 55.6 (2C), 33.7 (2C), 24.8 (2C), 23.7 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{26}O_4$ $[M+H]^+$: 403.1904; found: 403.1909 **UPC²**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 8.67 min; t_{minor} = 12.92 min.



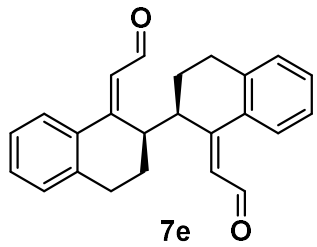
7c

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5d** (40.0 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 5.5h. Isolated as an off-white solid by FC on iatrobeads using EtOAc/CH_2Cl_2 1:100 as eluent (30.3 mg, 76% yield, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 541.7 (*c* 0.7, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.66 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 3.4 Hz, 4H), 6.20 (d, *J* = 8.1 Hz, 2H), 3.62 (s, 2H), 2.83 (dd, *J* = 9.7, 3.7 Hz, 4H), 2.47-2.42 (m, 2H), 2.29 (s, 6H), 2.25 (s, 6H), 2.13-2.00 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.2 (2C), 160.2 (2C), 136.9 (2C), 136.6 (2C), 133.8 (2C), 132.9 (2C), 132.6 (2C), 125.3 (2C), 124.8 (2C), 33.2 (2C), 24.5 (2C), 22.2 (2C), 21.1 (2C), 19.5 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{28}H_{30}O_2$ $[M+H]^+$: 399.2319; found: 399.2324. **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 6.15 min; t_{minor} = 7.38 min.

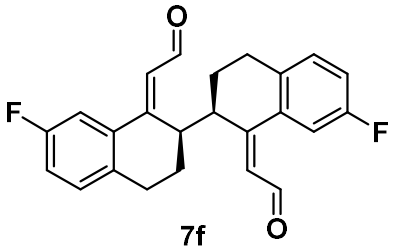


7d

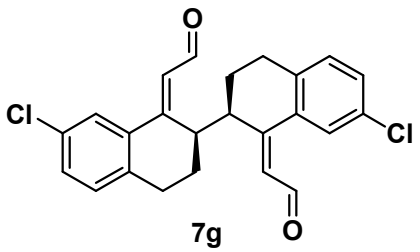
Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **7e** (34.4 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 5h. Isolated as a yellow solid by FC on iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent (21.2 mg, 62% yield, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 656.3 (*c* 0.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.84 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 2H), 7.28-7.22 (m, 4H), 6.28 (d, *J* = 8.1 Hz, 2H), 3.72 (s, 2H), 3.16 (ddd, *J* = 18.4, 12.6, 6.0 Hz, 2H), 3.02 (dd, *J* = 18.0, 6.4 Hz, 2H), 2.40 (dd, *J* = 14.2, 5.9 Hz, 2H), 2.14 (td, *J* = 13.4, 6.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 189.9 (2C), 158.8 (2C), 137.6 (2C), 132.6 (2C), 131.1 (2C), 129.7 (2C), 127.5 (2C), 126.9 (2C), 125.3 (2C), 33.5 (2C), 24.5 (2C), 24.4 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{22}O_2$ $[M+H]^+$: 343.1693; found: 343.1698. **UPC^2**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 7.73 min; t_{minor} = 9.09 min.



Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(7-fluoro-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **7f** (40.4 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 3h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:100 to 1:50 as eluent (17.4 mg, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = +279.3 (*c* 0.9, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.98 (d, *J* = 7.8 Hz, 2H), 7.21 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.16-7.06 (m, 4H), 6.24 (d, *J* = 7.8 Hz, 2H), 3.73 (s, 2H), 3.17-3.04 (m, 2H), 2.98 (dd, *J* = 17.6, 6.3 Hz, 2H), 2.39 (dd, *J* = 14.1, 5.3 Hz, 2H), 2.13 (td, *J* = 12.7, 6.3 Hz, 2H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -113.77 (q, *J* = 7.7 Hz, 2F). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 189.4 (2C), 161.7 (d, *J* = 246.8 Hz, 2C), 157.0 (d, *J* = 2.2 Hz, 2C), 134.2 (d, *J* = 7.0 Hz, 2C), 133.2 (d, *J* = 3.0 Hz, 2C), 131.4 (d, *J* = 7.8 Hz, 2C), 125.90 (2C), 118.6 (d, *J* = 21.8 Hz, 2C), 112.8 (d, *J* = 22.3 Hz, 2C), 33.2 (2C), 24.6 (2C), 23.9 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{20}F_2O_2$ $[M+H]^+$: 379.1504; found: 379.1498. **UPC^2**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 6.53 min; t_{minor} = 10.77 min.

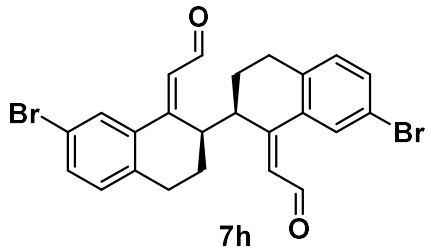


Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(7-chloro-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **7g** (41.3 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 6h. Isolated as an off-white solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:100 as eluent (24.3 mg, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 457.0 (*c* 0.33, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.95 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 2.2 Hz, 2H), 7.34 (dd, *J* = 8.3, 2.1 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.25 (d, *J* = 7.7 Hz, 2H), 3.70 (s, 2H), 3.10 (m, 2H), 2.98 (dd, *J* = 18.1, 6.5, Hz, 2H), 2.37 (dd, *J* = 14.3, 5.8 Hz, 2H), 2.12 (td, J = 13.6, 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 189.2 (2C), 156.6 (2C), 135.8 (2C), 134.2 (2C), 133.3 (2C), 131.11 (2C), 131.07 (2C), 126.4 (2C), 125.9 (2C), 33.2 (2C), 24.4 (2C), 24.0 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{20}Cl_2O_2$ $[M+Na]^+$: 433.0733; found: 433.0734 **UPC²**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 8.93 min; t_{minor} = 10.57 min.



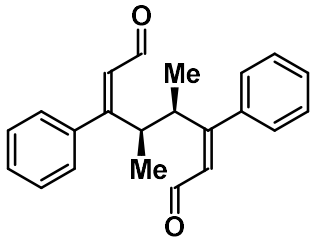
7g

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(7-bromo-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **7h** (50.2 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 6h. Isolated as an off-white solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:100 as eluent. (26.5 mg, >20:1 d.r., >99% e.e.). $[\alpha]_D^{22}$ = 293.9 (*c* 0.3, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.94 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 2.0 Hz, 2H), 7.49 (dd, *J* = 8.2, 2.0 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.24 (d, *J* = 7.7 Hz, 2H), 3.70 (s, 2H), 3.07 (ddd, 18.3, 12.4, 5.9 Hz, 2H), 2.98 (dd, *J* = 17.8, 6.3, Hz, 2H), 2.37 (dd, *J* = 14.4, 5.7 Hz, 2H), 2.12 (td, J = 13.2, 6.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 189.1 (2C), 156.5 (2C), 136.3 (2C), 134.6 (2C), 134.0 (2C), 131.3 (2C), 129.4 (2C), 126.0 (2C), 121.2 (2C), 33.2 (2C), 24.3 (2C), 24.1 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{20}Br_2O_2$ $[M+H]^+$: 500.9882; found: 500.9879 **UPC²**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 5.55 min; t_{minor} = 5.80 min.



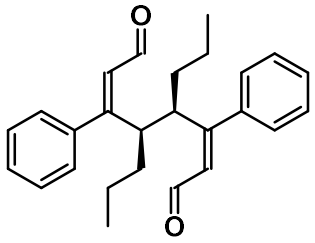
7h

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 3-phenylpent-2-enal **5i** (32.0 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 6.5h. Isolated as an orange oil by FC on iatrobeads using EtOAc / CH_2Cl_2 1:20 as eluent (18.5 mg, 58% yield, 20:1 d.r., 81% e.e.). $[\alpha]_D^{22}$ = 21.7 (*c* 0.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.39 (d, *J* = 7.8 Hz, 2H), 7.54-7.41 (m, 2H), 7.38-7.34 (m, 4H), 7.00-6.98 (m, 4H), 6.04 (d, *J* = 7.9 Hz, 2H), 2.73-2.67 (m, 2H), 1.04 (d, 6.5 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 193.9 (2C), 168.6 (2C), 137.0 (2C), 129.5 (2C), 128.9 (4C), 128.6 (4C), 128.5 (2C), 43.1 (2C), 11.5 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{22}O_2$ $[M+H]^+$: 319.1693; found: 319.1699 **UPC²**: IC, CO_2/MeOH gradient, 3.0 mL·min^{-1}; t_{major} = 4.19 min; t_{minor} = 4.33 min.



7i

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 3-phenylhept-2-enal **5j** (34.8 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). Additional 0.2 mL of CH_2Cl_2 were added to the reaction mixture after 6h. The starting material was fully consumed after 21h. Isolated as an orange solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:50 as eluent (18.0 mg, 48% yield, 5:1 d.r., 90% e.e.). $[\alpha]_D^{22}$ = 2.0 (*c* 0.6, CH_2Cl_2).



7j

Diagnostic signals for the major isomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 7.16, 4H), 6.02 (d, *J* = 7.8 Hz, 2H), 2.51 (d, *J* = 10.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (2C), 166.4 (2C), 137.6 (2C), 129.0 (2C), 128.9 (2C), 128.8 (4C), 128.4 (4C), 49.4 (2C), 27.8 (2C), 20.6 (2C), 14.2 (2C).

Diagnostic signals for the minor isomer:

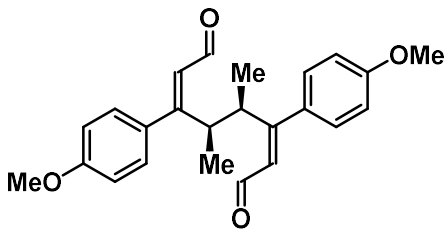
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9, 4H), 6.07 (d, *J* = 7.8 Hz, 2H), 2.67-2.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4 (2C), 166.5 (2C), 138.0 (2C), 130.2 (2C), 129.2 (4C), 129.1 (4C), 128.4 (2C), 52.0 (2C), 34.3 (2C), 20.8 (2C), 14.1 (2C).

Overlap of the observed signals:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 4H), 1.69-1.04 (m, 8H), 0.90-0.84 (m, 6H).

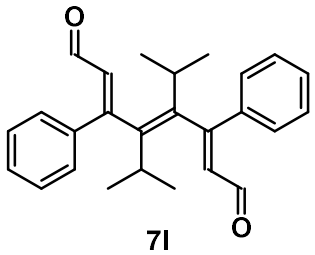
HRMS (ESI+) *m*/*z* calcd. for $C_{26}H_{30}O_2$ [M+Na]$^+$: 397.2138; found: 397.2148 **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.15 min; t_{minor} = 3.10 min; t_{meso}= 3.31.

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 3-(4-methoxyphenyl)but-2-enal **5k** (35.2 mg, 0.20 mmol, 2.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). Additional 0.2 mL of CH_2Cl_2 were added to the reaction mixture after 15h. The starting material was fully consumed after 19h. Isolated as an orange solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:20 as eluent (16.3 mg, 43% yield,>20:1 d.r., 78% e.e.). $[\alpha]_D^{22}$ = 37.0 (*c* 0.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.41 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 4H), 6.90 (d, *J* = 8.7 Hz, 4H), 6.01 (d, *J* = 7.8 Hz, 2H), 3.87 (s, 6H), 2.74-2.65 (m, 2H), 0.90 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 194.1 (2C), 168.5 (2C), 160.7 (2C), 130.5 (4C), 129.1 (2C), 128.1 (2C), 114.0 (4C), 55.6 (2C), 43.2 (2C), 11.4 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{26}O_4$ [M+H]$^+$: 379.1904; found: 379.1904 **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 4.26 min; t_{minor} = 4.68 min.



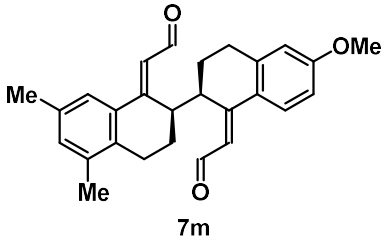
7k

Synthesised according to general procedure 3.2.5.3, using (+/-)-aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 5-methyl-3-phenylhex-2-enal **5l** (37.6 mg, 0.20 mmol, 2.0 equiv.), $ClCH_2CH_2Cl$ (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 3d. Isolated as a yellow oil by FC on iatrobeads using CH_2Cl_2 as eluent (12.1 mg, 32% yield, 1:1 E:Z). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (d, *J* = 2.8 Hz, 2H), 9.64 (d, *J* = 3.0 Hz, 2H), 7.50-7.42 (m, 12H), 7.39 (dd, *J* = 8.0; 1.7 Hz, 4H), 7.30 (dd, *J* =7.4, 2.2 Hz 4H), 6.57 (d, *J* = 7.7 Hz 2H), 6.41 (d, *J* = 7.6 Hz, 2H), 3.09 (hept, *J* = 6.9 Hz, 2H), 2.82 (hept, *J* = 7.0 Hz, 2H), 1.15 (d, *J* = 6.9 Hz, 12H), 1.12 (d, *J* = 6.9 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 209.4 (2C), 206.8, (2C), 193.8 (2C), 190.6 (2C), 161.2 (2C), 156.6 (2C), 133.9 (2C), 132.4 (2C), 131.22 (2C), 131.20 (2C),130.0 (4C), 129.9 (2C), 129.5 (4C), 128.7 (4C), 127.5 (2C), 127.2 (4C), 40.9 (2C), 37.5 (2C), 18.5, (4C), 18.0 (4C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{28}O_2$ [M+H]$^+$: 373.2162; found: 373.2164.



7l

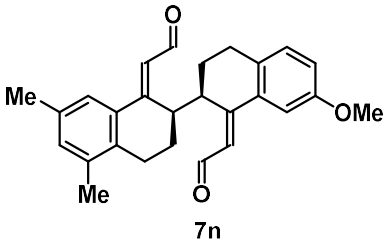
Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5a** (20.2 mg, 0.10 mmol, 1.0 equiv.), 2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5d** (60.1 mg, 0.30 mmol, 3.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.).



7m

The starting material was fully consumed after 16h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:30 to 1:10 as eluent. (21.2 mg, >20:1 dr, >99% e.e.). $[\alpha]_D^{22}$ = +250.7 (*c* 1.0, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.90 (d, *J* = 8.1 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.12-7.08 (m, 2H), 6.81 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.73-6.70 (m, 1H), 6.27 (d, *J* = 8.2 Hz, 1H), 6.16 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.71-3.58 (m, 2H), 3.19-3.08 (m, 1H), 2.96 (dd, *J* = 18.1, 5.9 Hz, 1H), 2.86-2.80 (m, 2H), 2.48-2.41 (m, 1H), 2.40-2.32 (m, 1H), 2.30 (s, 3H), 2.28-2.23 (m, 4H), 2.16-2.06 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.2, 190.0, 161.8, 160.2, 158.8, 139.5, 137.0, 136.7, 133.9, 133.0, 132.5, 128.6, 125.4, 125.3, 125.1, 123.7, 114.2, 113.7, 55.5, 33.5, 33.4, 24.8, 24.6, 24.5, 22.2, 21.1, 19.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{28}O_3$ $[M+H]^+$: 401.2111; found: 401.2115. **UPC^2**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 8.36 min; t_{minor} = 8.83 min.

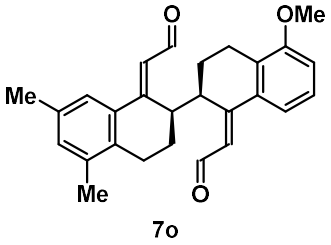
Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(7-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5c** (20.2 mg, 0.10 mmol, 1.0 equiv.), 2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5d** (60.1 mg, 0.30 mmol, 3.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.).



7n

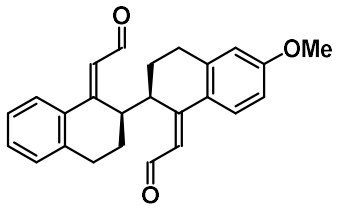
The starting material was fully consumed after 16h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:20 as eluent (23.2 mg, >20:1 dr, >99% e.e.). $[\alpha]_D^{22}$ = 470.6 (*c* 0.8, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.87 (d, *J* = 8.1 Hz, 1H), 8.70 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.09 (s, 2H), 6.96 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.25 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 8.2 Hz, 1H), 3.78 (s, 3H), 3.66 (tdd, *J* = 14.4, 11.1, 3.2, 2H), 3.08 (ddd, *J* = 18.2, 12.5, 6.0 Hz, 2H), 2.93 (dd, *J* = 17.6, 6.5 Hz, 1H), 2.85-2.81 (m, 2H), 2.47-2.34 (m, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 2.14-2.04 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.2, 190.1, 160.1, 159.2, 158.6, 137.0, 136.7, 133.8, 133.4, 133.0, 132.5, 130.7, 129.8, 125.3, 125.2, 124.9, 119.1, 109.9, 55.6, 33.5, 33.3, 24.8, 24.6, 23.7, 22.2, 21.1, 19.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{28}O_3$ $[M+Na]^+$: 423.1931; found: 423.1934. **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 8.20 min; t_{minor} = 9.53 min.

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(5-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5b** (20.2 mg, 0.10 mmol, 1.0 equiv.), 2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5d** (60.1 mg, 0.30 mmol, 3.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 16h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:20 as eluent. (27.2 mg, 15:1 dr, >99% e.e.). $[\alpha]_D^{22}$ = +383.5 (*c* 0.8, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.74 (d, *J* = 8.2 Hz, 1H), 8.69 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7. 08 (d, *J* = 5.2, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.1, 1H), 6.26-6.22 (m, 2H), 3.88 (s, 3H), 3.70-3.61 (m, 2H), 2.98 (dd, *J* = 18.8, 6.8 Hz, 1H), 2.90-2.80 (m, 3H), 2.48-2.41 (m, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 2.11-1.99 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.22, 190.20, 160.4, 159.2, 157.2, 137.0, 136.7, 133.8, 133.7, 133.0, 132.6, 127.8, 126.5, 125.35, 125.33, 124.9, 118.8, 111.7, 55.6, 33.21, 33.18, 24.5, 24.0, 22.2, 21.1, 19.5, 19.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{28}O_3$ $[M+Na]^+$: 423.1931; found: 423.1934. **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 7.47 min; t_{minor} = 7.77 min.



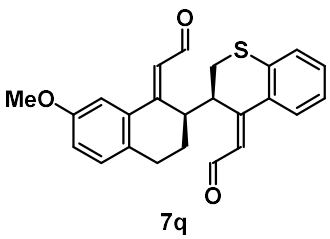
7o

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5e** (17.2 mg, 0.10 mmol, 1.0 equiv.), 2-(6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5a** (60.7 mg, 0.30 mmol, 3.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 16h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:30 as eluent. (22.7 mg, 13:1 dr, >99% e.e.) $[\alpha]_D^{22}$ = 449.6 (*c* 0.7, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.93 (d, *J* = 8.1 Hz, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 7.46-7.35 (m, 3H), 7.28-7.21 (m, 2H), 6.81 (dd, *J* = 8.8; 2.7 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 8.1 Hz, 1H), 6.20 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.73-3.64 (m, 2H), 3.14 (ddt, *J* = 18.5; 12.3; 5.9 Hz, 2H), 2.98 (td, *J* = 17.4; 6.5 Hz, 2H), 2.41-2.34 (m, 2H), 2.18-2.06 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 190.1, 189.8, 161.8, 158.8, 158.6, 139.5, 137.7, 132.6, 131.1, 129.7, 128.6, 127.5, 126.9, 125.4, 125.2, 123.8, 114.2, 113.8, 55.5, 33.63, 33.56, 24.8, 24.6, 24.5, 24.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{25}H_{24}O_3$ $[M+H]^+$: 373.1798; found: 373.1803. **UPC^2**: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 5.38 min; t_{minor} = 11.36 min.



7p

Synthesised according to general procedure 3.2.5.3, using aminocatalyst **6** (13 mg, 0.04 mmol, 0.40 equiv.), 2-(thiochroman-4-ylidene)acetaldehyde **5i** (19.0 mg, 0.10 mmol, 1.0 equiv.), 2-(7-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)acetaldehyde **5d** (60.7 mg, 0.30 mmol, 3.0 equiv.), CH_2Cl_2 (0.6 mL), $Cu(OAc)_2$ (3.6 mg, 0.020 mmol, 0.20 equiv.). The starting material was fully consumed after 14h. Isolated as a yellow solid by FC on iatrobeads using EtOAc / CH_2Cl_2 1:20 as eluent. (17.2 mg, 10:1 dr, >99% e.e.). $[\alpha]_D^{22}$ = +77.2 (*c* 0.6, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (d, *J* = 7.8 Hz, 1H), 8.79 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7. 30 (d, *J* = 7.4, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.16-7.09 (m, 2H), 6.97 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 8.0, 5.3 Hz, 2H),4.11 (dt, *J* = 10.8, 3.3 Hz, 1H), 3.93 (dt, *J* = 10.8, 3.3 Hz, 1H), 3.85-3.79 (m, 1H), 3.77 (s, 3H), 3.55 (dd, *J* = 13.6, 3.0 Hz, 1H), 3.24 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.08-2.98 (m, 1H), 2.43 ((dt, *J* = 16.3, 3.9 Hz, 1H), 2.25-2.10 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 189.7, 189.3, 158.74, 158.66, 154.8, 135.2, 133.9, 131.3, 130.8, 129.5, 129.4, 129.2, 127.0, 126.2, 125.7, 125.6, 119.0, 110.0, 55.7, 33.0, 31.1, 28.6, 24.6, 23.6. **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{22}O_3S$ $[M+Na]^+$: 413.1182; found: 413.1180. **UPC^2**: IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 9.24 min; t_{minor} = 8.48 min.



7q

3.2.5.5 Materials for the enantioselective oxidative coupling of α-branched aldehydes mediated by Ag_2CO_3

Synthesis of *α*-branched aldehydes **8a-h** was performed using literature procedures[23] and analytical data were found to be in accordance of the previously reported values. Racemic samples of compounds **10a-i** were prepared following the general procedure 3.2.5.6 using pyrrolidine or 1-(2-aminoethyl)piperidine as a catalyst.

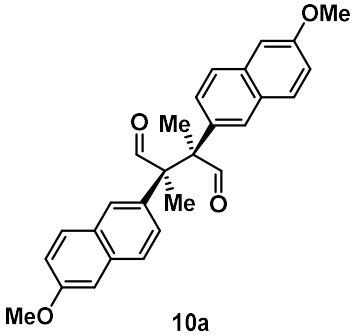
3.2.5.6 General procedure for the enantioselective oxidative coupling of α-branched aldehydes mediated by Ag_2CO_3

A flame dried 4 mL glass vial equipped with a magnetic stirring bar was charged with aminocatalyst **9** (0.04 mmol, 0.40 equiv.), *α*-branched aldehyde **8** (0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (0.150 mmol, 1.50 equiv.), and dry CH_2Cl_2 (0.4 mL). To the resulting mixture Ag_2CO_3 (0.150 mmol, 1.50 equiv.) was added. The vial was flushed with nitrogen

[23] a) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; b) X. Mo, D. G. Hall, *J. Am. Chem. Soc.* **2016**, *138*, 10762.

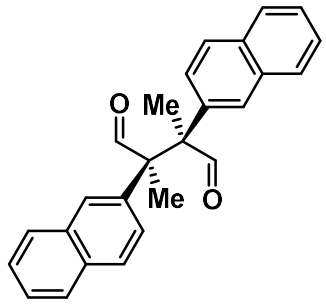
atmosphere, and the reaction mixture was stirred until full consumption of the starting material aldehyde. The crude product was loaded directly onto the column. FC on Iatrobeads yielded product **11**.

3.2.5.7 Characterisation data



10a

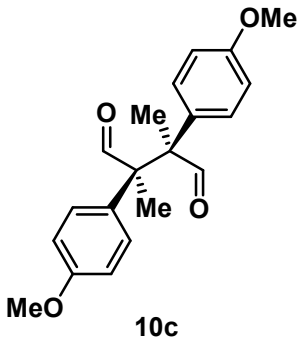
Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(7-methoxynaphthalen-2-yl)propanal **8a** (42.9 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 10 h. Isolated as a white solid by FC on Iatrobeads using CH_2Cl_2 as eluent (34.0 mg, 78% yield, 12:1 d.r., 92% ee). $[\alpha]_D^{22}$ = 289.4 (c 0.4, CH_2Cl_2).**^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.86 (s, 2H), 7.61 (dd, J = 8.8, 3.6 Hz, 4H), 7.29 (d, J =2.0 Hz, 2H), 7.15 (dd, J = 8.9, 2.5 Hz, 2H), 7.12 (d, J = 2.5 Hz, 2H), 6.89 (dd, J = 8.7, 2.0 Hz, 2H), 3.94 (s, 6H), 1.66 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 201.8 (2C), 158.3 (2C), 133.8 (2C), 131.9 (2C), 129.9 (2C), 129.0 (2C), 128.2 (2C), 127.6 (2C), 126.4 (2C), 119.4 (2C), 105.3 (2C), 58.8 (2C), 55.5 (2C), 19.1 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{28}H_{26}O_4$ $[M+H]^+$: 427.1904; found: 427.1907. UPC^2: ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 4.99; t_{minor} = 5.10 min.



10b

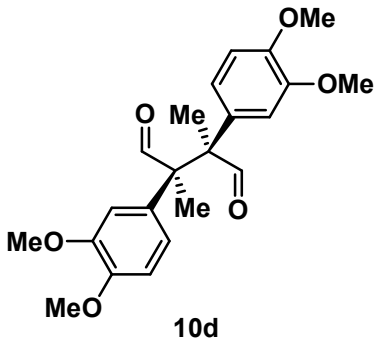
Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(naphthalen-2-yl)propanal **8b** (26.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 7.5 h. Isolated as a white solid by FC on Iatrobeads using CH_2Cl_2 as eluent (23.8 mg, 60% yield, 7:1 d.r., 92% ee). An unknown impurity co-eluted with the desired product, 5% remains in the isolated product and has been subtracted from the yield assuming a molecular weight equal to that of the product. $[\alpha]_D^{22}$ = 203.0 (c 0.6, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.89 (s, 2H), 7.84 (dd, J = 7.6, 1.6 Hz, 2H), 7.72 (d, J = 8.7 Hz, 4H), 7.51 (m, 4H), 7.40 (d, J = 1.9 Hz, 2H), 6.93 (dd, J = 8.7, 2.0 Hz, 2H), 1.69 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.6 (2C), 134.3 (2C), 132.7 (2C), 132.6 (2C), 129.3 (2C), 128.4 (2C), 127.6 (2C), 127.5 (2C), 127.0 (2C), 126.7 (2C), 126.5 (2C), 58.9 (2C), 19.1 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{26}H_{22}O_2$ $[M+H]^+$

: 367.1693; found: 367.1697 UPC^2 : IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 4.95; t_{minor} = 5.18 min.



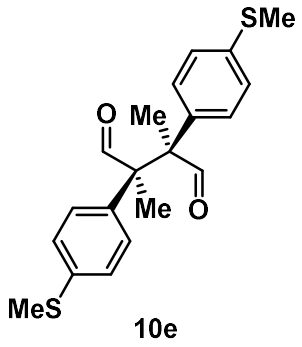
10c

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(4-methoxyphenyl)propanal **8c** (32.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 10 h. Isolated as a white solid by FC on Iatrobeads using CH_2Cl_2 as eluent. Before concentration the collected fractions were washed with $NaHCO_3$ and dried over $MgSO_4$ to yield **10c** (22.0 mg, 67% yield, 18:1 d.r., 96% ee). $[\alpha]_D^{22}$ = 130.5 (c 0.4, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.72 (s, 2H), 6.85-6.74 (m, 8H), 3.81 (s, 6H), 1.49 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.9 (2C), 159.0 (2C), 130.7 (4C), 126.7 (2C), 113.4 (4C), 58.2 (2C), 55.4 (2C), 18.9 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{22}O_4$ $[M+H]^+$: 327.1591; found: 327.1592. UPC^2 : ID, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 3.47; t_{minor} = 3.55 min.



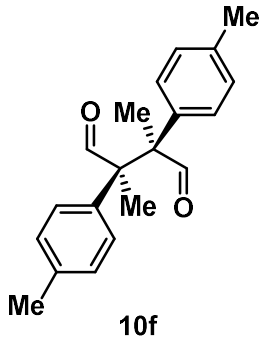
10d

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(3,4-dimethoxyphenyl)propanal **8d** (38.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 6.5 h. Isolated as a white foam by FC on Iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent. Before concentration the collected fractions were washed with $NaHCO_3$ and dried over $MgSO_4$ to yield **10d** (30.5 mg, 79% yield, 14:1 d.r., 95% ee). $[\alpha]_D^{22}$ = 114.3 (c 0.25, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.72 (s, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.47 (dd, J =8.4, 2.3 Hz, 2H), 6.30 (d, J =2.3, 2H), 3.87 (s, 6H), 3.69 (s, 6H), 1.52 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.7 (2C), 148.6 (2C), 148.2 (2C), 129.0 (2C), 122.2 (2C), 112.9 (2C), 110.2 (2C), 58.5 (2C), 56.0 (2C), 55.8 (2C), 19.0 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{22}H_{26}O_6$ $[M+K]^+$: 425.1361; found: 425.1356. UPC^2 : IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 6.29; t_{minor} = 5.94 min.



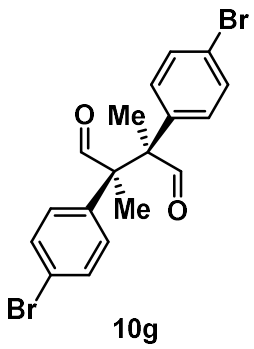
10e

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(4-(methylthio)phenyl)propanal **8e** (32.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 16 h. Isolated as a white solid by FC on Iatrobeads using CH_2Cl_2 as eluent. Before concentration the collected fractions were washed with $NaHCO_3$ and dried over $MgSO_4$ to yield **10e** (27.1 mg, 75% yield, 5:1 d.r., 94% ee). $[\alpha]_D^{22}$ = 192.0 (c 0.1, CH_2Cl_2). Diagnostic signals for the major isomer: 1H NMR (400 MHz, CDCl3): δ 9.71 (s, 2H), 7.17-7.12 (m, 4H), 6.82-6.76 (m, 4H), 2.48 (s, 6H), 1.50 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.5 (2C), 138.5 (2C), 133.1 (2C), 130.0 (4C), 125.6 (4C), 58.3 (2C), 18.7 (2C), 15.4 (2C). Diagnostic signals for the minor isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.88 (s, 2H), 7.07-7.01 (m, 4H), 6.76-6.71 (m, 4H), 2.44 (s, 6H), 1.58 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.0 (2C), 138.3 (2C), 134.2 (2C), 129.8 (4C), 125.5 (4C), 58.7(2C), 17.6 (2C), 15.6 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{22}O_2S_2$ $[M+H]^+$: 359.1139; found: 359.1138. UPC^2 : IB, CO_2/MeOH gradient, 3.0 mL·min^{-1} ; t_{major} = 3.57; t_{minor} = 3.64 min.



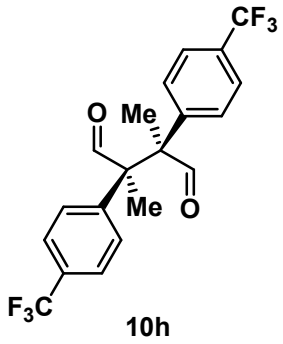
10f

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(4-methylphenyl)propanal **8f** (38.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 6.5 h. Isolated as a white foam by FC on Iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent to yield **10f** (18.5 mg, 63% yield, 5:1 d.r., 94% ee). $[\alpha]_D^{22}$ = 79.1 (c 0.6, CH_2Cl_2). Diagnostic signals for the major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.74 (s, 2H), 7.09 (d, J =7.9, 4H), 6.76 (d, J =8.2, 4H), 2.34 (s, 6H), 1.50 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.9 (2C), 137.5 (2C), 133.8 (2C), 129.5 (4C), 128.8 (4C), 58.4 (2C), 21.1 (2C), 18.8 (2C). Diagnostic signals for the minor isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 2H), 6.99 (d, J =8.0, 4H), 6.71 (d, J =8.3, 4H), 2.30 (s, 6H), 1.58 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.7 (2C), 137.3 (2C), 134.8 (2C), 129.3 (4C), 128.6 (4C), 58.6 (2C), 21.1 (2C), 17.6(2C). **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{22}O_2$ $[M+H]^+$: 295.1693; found: 295.1700. UPC^2 : IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 3.81; t_{minor} = 3.96 min.



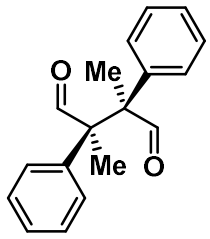
10g

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(4-bromophenyl)propanal **8g** (38.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 6.5 h. Isolated as a white foam by FC on Iatrobeads using EtOAc/CH_2Cl_2 1:20 as eluent to yield **10g** (11.9 mg, 28% yield, 1:1 d.r., 52% ee). $[\alpha]_D^{22}$ = 35.8 (c 0.5, CH_2Cl_2). Diagnostic signals for the major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (s, 2H), 7.43 (d, J =8.6, 4H), 6.74 (d, J =8.6, 4H), 1.51 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.9 (2C), 135.5 (2C), 131.4 (4C), 131.24 (4C), 122.5 (2C), 58.3 (2C), 18.7 (2C). Diagnostic signals for the minor isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.84 (s, 2H), 7.33 (d, J =8.6, 4H), 6.68 (d, J =8.7, 4H), 1.60 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.2 (2C), 136.6 (2C), 131.17 (4C), 131.16 (4C), 122.3 (2C), 58.9 (2C), 17.6 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{18}H_{16}O_2Br_2$ $[M+H]^+$: 424.9569; found: 424.9566. UPC^2 : IB, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 3.25; t_{minor} = 3.46 min.



10h

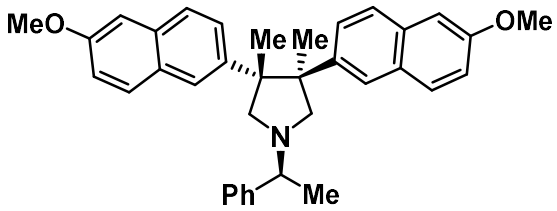
Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (11.7 mg, 0.04 mmol, 0.40 equiv.), 2-(4-(trifluoromethyl)phenyl)propanal **8h** (40.4 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 6.5 h. Isolated as a white foam by FC on Iatrobeads using CH_2Cl_2 as eluent to yield **10h** (18.3 mg, 46% yield, 1.2:1 d.r., 6% ee). Diagnostic signals for the major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.74 (s, 2H), 7.58 (d, J = 8.2, 4H), 7.02 (d, J = 8.2, 4H), 1.57 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.6 (2C), 140.5 (2C, q, J = 1.1 Hz), 129.8 (8C), 125.2 (2C, q, J = 3.7), 123.9 (2C, q, J = 272 Hz), 58.7 (2C), 18.8 (2C). **^{19}F NMR (376 MHz, $CDCl_3$):** δ –62.70. Diagnostic signals for the minor isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.87 (s, 2H), 7.44 (d, J = 8.2, 4H), 6.93 (d, J = 8.2, 4H), 1.69 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.7 (2C), 141.5 (2C, q, J = 1.1 Hz), 129.7 (8C), 124.9 (2C, q, J = 3.7), 123.8 (2C, q, J = 272 Hz) 59.3 (2C), 17.7 (2C). **^{19}F NMR (376 MHz, $CDCl_3$):** –62.77. **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{16}F_6O_2$ $[M+H]^+$: 403.1127; found: 403.1129. UPC^2 : IA, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 2.111; t_{minor} = 1.971 min.



10i

Synthesised according to general procedure 3.2.5.6, using aminocatalyst **9a** (13 mg, 0.04 mmol, 0.40 equiv.), 2-phenylpropanal **8i** (26.8 mg, 0.20 mmol, 2.0 equiv.), *p*-NO_2PhCO_2H (25.2 mg, 0.150 mmol, 1.50 equiv.), dry CH_2Cl_2 (0.4 mL), Ag_2CO_3 (41.1 mg, 0.15 mmol, 1.5 equiv.). The starting material was fully consumed after 6 h. Isolated as a white solid by FC on Iatrobeads using CH_2Cl_2 as eluent to yield **10i** (8.2 mg, 31% yield, 2.5:1 d.r., 66% ee). $[\alpha]_D^{22}$ = 45.0 (c 0.2, CH_2Cl_2). Diagnostic signals for the major isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.77 (s, 2H), 7.32-7.25 (m, 6H), 6.86 (dd, J =7.8, 1.9 Hz, 4H), 1.54 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.7 (2C), 136.9 (2C), 129.6 (4C), 128.0 (4C), 127.8 (2C), 58.7 (2C), 18.7 (2C). Diagnostic signals for the minor isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (s, 2H), 7.22-7.13 (m, 6H), 6.80 (d, J =7.1 Hz, 4H), 1.63 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.4 (2C), 138.0 (2C), 129.4 (4C), 127.9 (4C), 127.6 (2C), 59.1 (2C), 17.6 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{18}H_{18}O_2$ $[M+H]^+$: 267.1380; found: 267.1379 UPC^2 : IC, CO_2/*i*PrOH gradient, 3.0 mL·min^{-1} ; t_{major} = 3.47; t_{minor} = 3.57 min.

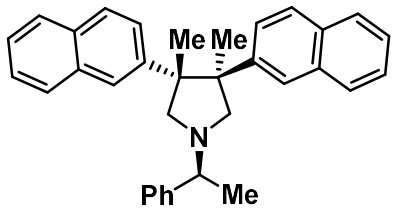
3.2.5.8 Reductive amination performed on oxidative homo-coupling adducts of α-branched aldehydes.



11a

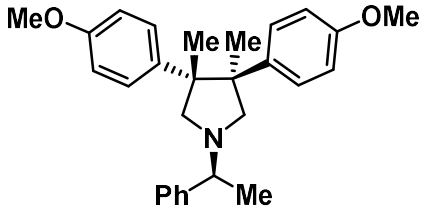
A vial equipped with a magnetic stirring bar was charged with the homocoupling adduct **10a** (42.7 mg, 0.1 mmol, 1 equiv.), 0.5 mL of CH_2Cl_2, (*S*)-(−)-α-methylbenzylamine (26 µL, 0.2 mmol, 2.0 equiv.) acetic acid (17.2 µL, 0.3 mmol, 3.0 equiv.). To the resulting mixture sodium triacetoxyborohydride (63.6 mg, 0.3 mmol, 3 equiv.) was added and the solution was stirred until full consumption of the aldehyde starting material. The reaction was quenched with a saturated solution of Na_2CO_3 (2 mL) and then extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by FC using CH_2Cl_2 as eluent, affording **11a** as a white solid in 50% yield. $[\alpha]_D^{22}$ = 91.9 (c 0.8, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64-7.55 (m, 6H), 7.49-7.41 (m, 4H), 7.30 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H),7.07-7.03 (m, 4H), 3.84 (s, 6H), 3.49 (d, J = 9.3 Hz, 2H), 3.43 (q, J = 6.5 Hz, 1H), 2.66 (d, J = 9.3 Hz, 2H), 1.42 (d, J = 6.4 Hz, 3H) 1.09 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** 157.5 (2C), 146.5, 142.0 (2C), 132.9 (2C), 129.7 (2C), 128.62 (2C), 128.58 (2C), 127.5 (2C), 127.3 (2C), 127.0, 125.9 (2C), 125.3 (2C), 118.7 (2C), 105.4 (2C), 66.5

(2C), 65.8, 55.5 (2C), 51.1 (2C), 28.8 (2C), 24.0. **HRMS** (ESI+) *m/z* calcd. for $C_{36}H_{37}NO_2$ $[M+H]^+$: 516.2897; found: 516.2905.



11b

A vial equipped with a magnetic stirring bar was charged with homo-coupling adduct **10b** (53 mg, 0.14 mmol, 1 equiv.), 0.6 mL of CH_2Cl_2, (*S*)-(−)-α-methylbenzylamine (36 µL, 0.28 mmol, 2.0 equiv.) acetic acid (24 µL, 0.42 mmol, 3.0 equiv.). To the resulting mixture sodium triacetoxyborohydride (89 mg, 0.42 mmol, 3.0 equiv.) was added and the solution was stirred until full consumption of the aldehyde starting material. The reaction was quenched with a saturated solution of Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by FC using CH_2Cl_2/pentane 9:1 as eluent, affording **11b** as a white solid in 57% yield. $[\alpha]_D^{22}$ = 62.6 (c 0.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88-7.79 (m, 6H), 7.77 (d, J = 1.9 Hz, 2H), 7.62 (dd, J = 8.6, 1.9 Hz, 2H), 7.58 (d, J = 7.1 Hz, 2H), 7.53-7.45 (m, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 3.63 (d, J = 9.3 Hz, 2H), 3.55 (q, J = 6.4 Hz, 1H), 2.80 (d, J = 9.3 Hz, 2H), 1.54 (d, J = 6.5 Hz, 3H), 1.23 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 146.5, 144.4 (2C), 133.2 (2C), 131.9 (2C), 128.6 (2C), 128.2 (2C), 127.5 (2C), 127.3 (2C), 127.1 (2C), 127.0 (3C), 125.9 (2C), 125.6 (2C), 125.4 (2C), 66.7 (2C), 65.7, 51.2 (2C), 28.8 (2C), 24.0. **HRMS** (ESI+) *m/z* calcd. for $C_{34}H_{33}N$ $[M+H]^+$: 456.2686; found: 456.2696.



11c

A vial equipped with a magnetic stirring bar was charged with the homocoupling adduct **10c** (39.2 mg, 0.12 mmol, 1 equiv.), 0.6 mL of CH_2Cl_2, (*S*)-(−)-α-methylbenzylamine (31 µL, 0.24 mmol, 2.0 equiv.) acetic acid (20.6 µL, 0.36 mmol, 3.0 equiv.). To the resulting mixture sodium triacetoxyborohydride (76.3 mg, 0.3 mmol, 3 equiv.) was added and the solution was stirred until full consumption of the aldehyde starting material. The reaction was quenched with a saturated solution of Na_2CO_3 (2 mL) and then extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by FC using CH_2Cl_2 as eluent, affording **11c** as a white solid in 37% yield. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48-7.45 (m, 2H), 7.37-7.33 (m, 2H), 7.27-7.22 S10 (m, 5H), 6.84 (d, J = 8.9 Hz, 4H), 3.82 (s, 6H), 3.43 (m, 3H), 2.63 (q, J = 9.3 Hz, 2H), 1.44 (d, J = 6.5 Hz, 3H), 1.04 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):**

157.6 (2C), 146.5, 138.6 (2C), 128.6 (4C), 128.5 (2C), 127.3 (2C), 126.9, 112.9 (4C), 66.2 (2C), 65.7, 55.3 (2C), 50.4 (2C), 28.6 (2C), 23.9. **HRMS** (ESI+) *m/z* calcd. for $C_{28}H_{33}NO_2$ $[M+H]^+$: 416.2584; found: 416.2593.

*3.2.5.9 Procedure for crystal **11c·HBr**:*

In a 4 mL screw cap vial, equipped with a stirring bar, the pyrrolidine **11c** (0.044 mmol), 2 mL of EtOAc and 1mL of HBr (48% water solution) were added. The solution was stirred for 15 min and extracted with EtOAc (2 x 2 mL). The collected organic layers were dried over $MgSO_4$, filtered and removed under reduced pressure. The resulting ammonium salt was re-dissolved in a minimum amount of MeOH/CH_2Cl_2 in order to obtain a crystal by slow evaporation of solvent.