ASSESSING THE VERSATILITY OF ORGANOCATALYSIS AS A STRATEGY FOR ENABLING NOVEL ASYMMETRIC TRANSFORMATIONS.

Giulia Bergonzini

Dipòsit Legal: T 1661-2014

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Assessing the Versatility of Organocatalysis as a Strategy for Enabling Novel Asymmetric Transformations

Doctoral Thesis

Supervised by Prof. Paolo Melchiorre

UNIVERSITAT ROVIRA I VIRGILI

Tarragona

2013

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2013

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I STATE that the present study, entitled "Assessing the Versatility of Organocatalysis as a Strategy for Enabling Novel Asymmetric Transformations", presented by GIULIA BERGONZINI to receive the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ) and fulfills all the requirements to be awarded with the "International Doctor" mention.

Tarragona, July the 18th 2013

Doctoral Thesis Supervisor

Prof. Paolo Melchiorre

Acknowledgements

Many people have made my PhD an unforgettable experience.

I would like to start by thanking my doctoral research advisor, Prof. Paolo Melchiorre who gave me the opportunity to carry out my studies in the fascinating field of asymmetric catalysis in such a stimulating environment. *Thank you for believing in me as chemist since the first day of this adventure and for the freedom you gave me to pursue my own ideas.* Many thanks to Prof. Corey Stephenson for his warm welcome during my period in Boston, and also for his interest, generosity, and fairness throughout this experience. He made my stay in his group a pleasant and instructive experience and for this I will always be very grateful. Thanks to Prof. Corinna Schindler, for her true passion for chemistry, positivism and kindness and to Prof. Eric Jacobsen, for his scientific contribution. Thanks to all the people that are and have been part of our research group. Especially those who shared with me both the joys and the difficulties of some of the projects reported in this manuscript and a special thanks to Dr. John Murphy and Dr. Elena Arceo who donated their valuable time for proofreading this dissertation. Thanks to Gladys and Lorna for their support and help in all the administrative tasks I went through during these years. Thanks to Dr. Ana Castilla who helped Carlo and myself to build-up an entire lab when ICIQ was a new place for us. Thanks also to all the research support units at ICIQ for helping the science to happen in the institute every day, and to all the people of ICIQ, because when you meet someone and you get a smile or a kind word it makes you feel like you are at home. Special thanks to Dr. Silvia Vera, the first Post Doc who joined the group; it was fantastic working with her, who I considered to be both a great chemist and a great friend. Thanks also to her husband Alberto; who together, helped me to learn Spanish... and we had some really good times! Thanks to my AMAZING FRIEND and, for a wonderful time, colleague, Dr. Michele Retini (Michelle) whom I found to be one of the best people I've ever met. Thanks to Dr. "Calle" Wallentin for the constructive discussions and collaboration while in the lab at BU and *via* skype. Thanks to my dearest "Marlenita". We have been close to one another since the first instant we met in Boston. Thanks to Elisa Montroni and Veronica Angeli for being such good friends. Thanks also to Roberta and Claudio, for their kindness and support.

To my family, GRAZIE per l'appoggio e l'amore che mi dimostrate ogni giorno. In questi anni lontana da casa avete sempre continuato ad essere vicini a me col vostro pensiero, le vostre parole e i mille altri modi che solo voi, la mia famiglia, siete in grado di farmi sentire. Un grazie particolare ai miei genitori Danila e Giuseppe (Beppe), a mio fratello Fabio e ai miei nonni Silvana, Romano e Giulio coi quali condivido un rapporto tutto speciale.

To Carlo, thanks for helping me every day inside and outside the lab, for your support and your patience in our "24 hours a day" relationship. Living with you is true happiness.

List of Pubblications

Some of the results presented in this thesis have been published:

· "Photoredox Activation and Anion-Binding in the Dual Catalytic Enantioselective Synthesis of β-Amino Esters"
Giulia Bergonzini, Corinna S. Schindler**,** Carl-Johan Wallentin, Eric N. Jacobsen, Corey R. J. Stephenson, *Chem. Sci*., **2013**, DOI: 10.1039/C3SC52265B.

· "Dioxindole in Asymmetric Catalytic Synthesis: Direct Access to 3-Substituted 3-Hydroxy-2-Oxindoles *via* 1,4-Additions to Nitroalkenes"
Michele Retini, Giulia Bergonzini, Paolo Melchiorre, *Chem. Commun.,* **2012**, *48,* 3336-3338.

· "Dioxindole in Asymmetric Catalytic Synthesis: New Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and Application to the Preparation of Maremycin A"
Giulia Bergonzini, Paolo Melchiorre, *Angew. Chem. Int. Ed.,* **2012**, *51*, 971-974**.**
This article was highlighted in *Synfacts* by B. List and M. R. Monaco (**2012**, *8*, 0329).

· "Cooperative Organocatalysis for the Asymmetric γ-Alkylation of α-Branched Enals"
Giulia Bergonzini, Silvia Vera, Paolo Melchiorre, *Angew. Chem. Int. Ed.*, **2010**, *49*, 9685-9688.
This article was highlighted in *Synfacts* by B. List and L. Ratjen (**2011**, *1*, 0101).

Furthermore, a manuscript is in preparation describing the photochemical perfluoroalkylation of arenes *via* electron donor-acceptor complex formation presented in Chapter 5.

Just as countless paintings can be created by careful use of only a few colors,

enormous chemical diversity can be created by judicious choice of select catalysts

To my family and Carlo

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Chapter I

Introduction

Organocatalysis, now commonly viewed as the third pillar in the "trio of asymmetric catalysis" (with the other two being biocatalysis and metal catalysis), is a versatile and useful tool in contemporary asymmetric synthesis. Marked by its robust nature, it probably offers the most condition-tolerant method within the modern chemistry toolbox. The fact that organocatalysts are generally tolerant to air and moisture, as well as to many metal or organic contaminants, provides a high degree of compatibility and reliability. This makes their use particularly suitable for catalytic multistep processes such as domino/cascade as well as multicomponent reactions, because distinct modes of activation can be easily combined.[1] Furthermore, different organocatalysts can be combined together[2] or with other catalytic systems based on bio-, metal,[3] and photoredox catalysts[4] to access previously unattainable transformations.

1.1   Activation Modes in Organocatalysis

The discovery of new catalytic reactions is of fundamental importance to solve challenging problems in chemical synthesis. In the realm of organocatalysis, this task is associated with the discovery and development of new generic modes of activation, induction and reactivity. When an activation mode has been established, it is relatively straightforward to use it as a platform for the design of a wide range of new enantioselective reactions. As evidence for this statement, the relatively small number of activation modes in organocatalysis has demonstrated its applicability to a large variety of chemical transformations leading to more than 3600 manuscripts published since 2000.[5]

A generic activation mode provides a reactive species that can participate in many types of reaction with consistently high enantioselectivity. Such reactive species arise from the interaction of a chiral catalyst with a key functional group of the substrate in a highly organized

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[1] C. Grondal, M. Jeanty, D. Enders. Organocatalytic Cascade Reactions as a New Tool in Total Synthesis. *Nat. Chem.*, **2010**, *2*, 167.

[2] R. C: Wende, P. R. Schreiner. Evolution of Asymmetric Organocatalysis: Multi- and Retrocatalysis. *Green Chem.*, **2012**, *14*, 1821.

[3] Z. Du, Z. Shao. Combining Transition Metal Catalysis and Organocatalysis – an update. *Chem. Soc. Rev.,* **2013***, 42,* 1337.

[4] D. Nicewicz, D. W. C. MacMillan. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science*, **2008**, *322*, 77.

[5] Source: ISI-Web of Science as of May 2013, using the keyword: organocatalysis.

and predictable manner.[6] Based on the nature of the interaction between the catalyst and the substrate, the generic activation modes can be categorized in covalent-based and non-covalent-based activations.[7]

Catalysts activating the substrate by forming a covalent bond are among the most widely used. Chiral amines belong to this class, participating in many reactions by activating the substrate, a carbonyl compound, by the reversible formation of an enamine, an iminium ion[8] or a SOMO intermediate[9] as the reactive species (Figure 1, on the left). Those three activation modes, which mainly rely on strong, directional interactions, have afforded a reliable synthetic platform for generating stereogenic centers at the $\alpha-$ and β-positions of unmodified carbonyl compounds. Another activation mode, similar to enamine activation, uses the ability of chiral tertiary amines to transiently generate chiral ammonium enolates (Figure 1, tertiary amine catalysis).[10] A different type of covalent-based activation is represented by N-heterocyclic carbene catalysis, which has been offering a catalytic variant to the chemistry of acyl anion equivalents.[11] Concerning catalysis by non-covalent interactions (Figure 1, on the right), hydrogen-bond donor catalysis[12] has shown a clear utility in enantioselective synthesis. Although the interactions involved are generally weaker, less directional and less distance-dependent than their covalent counterparts, multiple hydrogen-bonding interactions can operate in concert through a cooperative effect ensuring high level of transition state structural organization, and thus enantioselectivity. Another important catalytic approach, also classified as a non-covalent activation mode, involves the interaction of an ionic species with a chiral neutral, anionic or cationic organocatalyst. This field is referred to as ion-pairing catalysis.[13]

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[6] D. W. C. MacMillan. The Advent and Development of Organocatalysis. *Nature*, **2008**, *455*, 304.

[7] A. Berkessel, H. Gröger. Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis. Wiley VCH, Weinheim, **2005**.

[8] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli. Asymmetric Aminocatalysis-Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6138.

[9] T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan. Enantioselective Organocatalysis Using SOMO Activation. *Science*, **2007**, *316*, 582.

[10] M. J. Gaunt, C. C. C. Johansson. Recent Developments in the Use of Catalytic Asymmetric Ammonium Enolates in Chemical Synthesis. *Chem. Rev.,* **2007**, *107*, 5596.

[11] X. Bugaut, F. Glorius. Organocatalytic Umpolung: N-Heterocyclic Carbenes and Beyond. *Chem. Soc. Rev.*, **2012**, *41*, 3511.

[12] M. S. Taylor, E. N. Jacobsen. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem. Int. Ed.*, **2006**, *45*, 1520.

[13] K. Brak, E. N. Jacobsen. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.*, **2013**, *52*, 534.
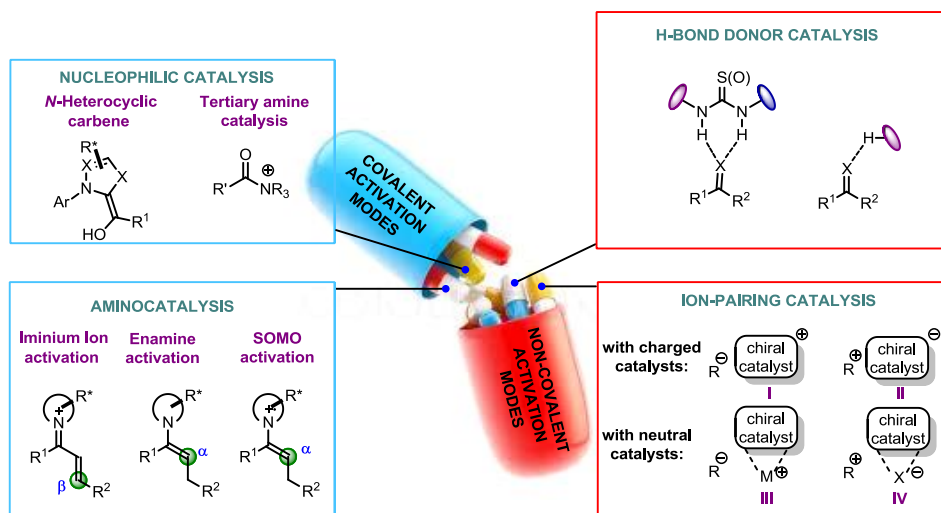
Figure 1. Generic activation modes in organocatalysis.

In the following sections, the generic modes of activation that have been key tools to address specific synthetic challenges identified within these PhD studies will be highlighted.

1.1.1 Aminocatalysis: Enamine and Iminium Ion Activation

The use of chiral amines as catalysts for the asymmetric functionalization of carbonyl compounds (aldehydes and ketones), pioneered by Hajos, Parrish, Eder, Sauer, and Wiechert in the early 1970s,[14] has witnessed a rapid development in the last years. In 2000, two seminal publications conceptualized the field of asymmetric aminocatalysis: the proline-catalyzed intermolecular Aldol reaction, published by List, Lerner and Barbas,[15] and the first asymmetric aminocatalyzed Diels-Alder reaction, developed by MacMillan.[16] Following these publications, there was an explosion in competition and high quality research on catalysis using chiral secondary amines that quickly established organocatalysis as an independent field within chemical asymmetric synthesis.[8]

Besides offering alternative asymmetric and catalytic methodologies for two fundamental carbon-carbon bond forming reactions in chemistry, these seminal studies constituted the basis for two novel organocatalytic activation modes of carbonyl compounds. Both are based on reactive covalent intermediates, transiently generated upon condensation of chiral cyclic amines

[14] a) U. Eder, G. Sauer, R. Wiechert. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 496. b) Z. G Hajos, D. R. Parrish. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.*, **1974**, *39*, 1615

[15] B. List, R. A. Lerner, C. F. Barbas III. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.*, **2000**, *122*, 2395.

[16] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels−Alder Reaction. *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

with aldehydes or ketones (Scheme 1). The condensation leads to the formation of a positively charged iminium ion intermediate. This species lowers the energy of the lowest unoccupied molecular orbital (LUMO). For conjugated π-systems, the electronic redistribution induced by iminium ion intermediates facilitates nucleophilic additions, including conjugate additions, and pericyclic reactions.[17] As a result, this activation mode, termed iminium ion activation, allows the asymmetric β-functionalization of carbonyl compounds.
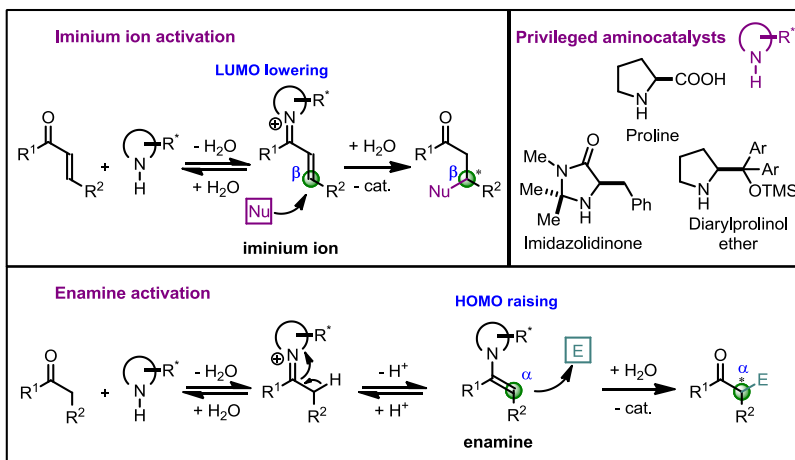
Scheme 1. Iminium ion and enamine activation modes. Nu = nucleophile; E = electrophile; cat. = aminocatalyst.

In the case of isolated π-systems, the LUMO-lowering effect increases the α-proton acidity. This induces a fast deprotonation, which leads to the generation of the enamine, a nucleophilic enolate equivalent (Scheme 1, enamine activation). These chiral enamines can stereoselectively trap a variety of electrophiles providing, after release of the catalyst, α-functionalized carbonyl compounds as products.[18]

1.1.2 Hydrogen-Bond Donor Catalysis

Hydrogen-bond (H-bond) donor catalysis is defined as LUMO-lowering activation of an electrophile by the simultaneous sharing of a hydrogen atom by the substrate (H-bond acceptor) and the catalyst (H-bond donor). A variety of chiral H-bond donors, characterized by a wide range of structural and functional frameworks, have emerged as suitable catalysts for many

[17] G. Lelais, D. W. C. MacMillan. Modern Strategies in Organic Synthesis: the Advent and Development of Iminium Ion Activation. *Aldrichim. Acta*, **2006**, *39*, 79.

[18] J. Mukherjee, J. W. Yang, S. Hoffmann, B. List. Asymmetric Enamine Catalysis. *Chem. Rev.*, **2007**, *107*, 5471.

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different enantioselective transformations. In spite of their obvious differences, the catalysts share a common fundamental design feature: a dual or single H-bond donor site flanked by sites for secondary interaction with substrates, such as aromatic, weakly basic or acidic, or strongly basic functionalities (Figure 2).[19]
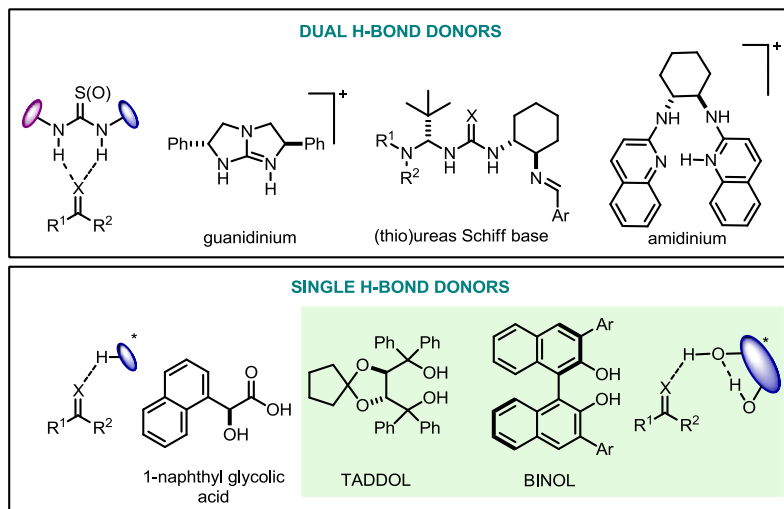
Figure 2. Representative hydrogen-bond donor catalysts.

Between the dual H-bond donor catalysts ureas, thioureas, as well as guanidinium and amidinium ions represent privileged species which have found applications in many enantioselective transformations.

Species such as TADDOL and BINOL derivatives have been identified as powerful classes of catalysts among the single H-bond donors. In this case, despite the fact that these catalysts are diols and bisphenols, transition structure organization is achieved by means of an intramolecular H-bonding interaction, which defines the orientation and enhances the polarity of the second hydroxyl group.[12]

1.1.3 Chiral Phosphoric Acid Catalysis

In 2004, Akiyama and Terada reported phosphoric acids derived from optically pure BINOL (1,1'-bi(2-naphthol)) carrying bulky 3,3'-substituents as a novel class of Brønsted acid catalysts for electrophile activation (mainly imines and carbonyl compounds).[20,21] Since these seminal papers,

[19] A. G. Doyle, E. N. Jacobsen. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.*, **2007**, *107*, 5713.
[20] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566.

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many research group expanded the application of these catalysts to various organic transformations.[22]

Although much evidence has been collected for the hydrogen-bonding interactions being crucial to the selectivity of these reactions, the strong acidity of phosphoric acid catalysts (pK_a around 2-4 in dimethyl sulfoxide)[23] means that ion-pairing between a fully protonated electrophile and the phosphate counterion cannot be excluded.[24]

On this basis, a mode of catalysis based on this latter premise of an ion-pair linked only by electrostatic interactions can be considered as a separate category of Brønsted acid catalysis (Figure 3).[13,25]

CHIRAL PHOSPHORIC ACID CATALYSIS
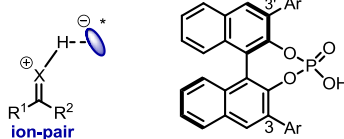
Figure 3. Asymmetric chiral phosphoric acid catalysis.

1.1.4 Anion-Binding Catalysis

The approach of anion-binding catalysis relies on the binding of a neutral hydrogen-bond donor to the reactive or unreactive counter-anion of a cationic intermediate in the stereoselective-determining step of the reaction. This recent organocatalytic activation mode takes advantage of the well-established anion-binding properties of ureas and thioureas[26] and expands the ability of chiral dual hydrogen-bond donors from solely activating neutral electrophiles to participating in reactions proceedings *via* ion-pair intermediates (Figure 4).

[21] D. Uraguchi, M. Terada. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions *via* Electrophilic Activation. *J. Am. Chem. Soc.*, **2004**, *126*, 5356.

[22] T. Akiyama. Stronger Brønsted Acids. *Chem. Rev.*, **2007**, *107*, 5744.

[23] P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudörfl, A. Berkessel, A. C. O'Donoghue. pK_a Values of Chiral Brønsted Acid Catalysis: Phosphoric Acids/Amides, Sulfonyl/Sulfuryl Imides, and Perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.*, **2011**, *17*, 8524.

[24] M. Fleischmann, D. Drettwan, E. Sugiono, M. Rueping, R. M. Gschwind. Brønsted Acid Catalysis: Hydrogen Bonding versus Ion Pairing in Imine Activation. *Angew. Chem. Int. Ed.*, **2011**, *50*, 6364.

[25] R. J. Phipps, G. L. Hamilton, F. D. Toste. The Progression of Chiral Anions from Concepts to Applications in Asymmetric Catalysis. *Nat. Chem.*, **2012**, *4*, 603.

[26] Z. Zhang, P. R. Schreiner. (Thio)urea Organocatalysis: What Can Be Learnt from Anion Recognition? *Chem. Soc. Rev.*, **2009**, *38*, 1187.

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ANION-BINDING CATALYSIS
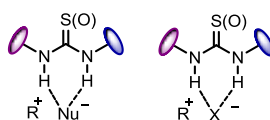
Figure 4. Ion-pair intermediates in anion-binding catalysis.

Since the first highly enantioselective nucleophilic additions to transiently generated *N*-acyl-iminium ions[27] and oxocarbenium ions catalyzed by chiral thioureas,[28] developed by the Jacobsen group, this family of molecules has been widely used (i) to assist the ionization of ion-pair precursors through anion abstraction or (ii) to control the reactivity of ion-pair intermediates through anion-binding. Representative examples are the asymmetric Strecker reaction[29] and the bicyclization of hydroxylactams.[30]

1.2   Summary of the Thesis Research

The following chapters illustrate how the intrinsic versatility of organocatalysis and the use of different activation modes have been exploited to develop new catalytic enantioselective transformations.

Chapter **2** discusses the application of dienamine activation, the vinylogous version of enamine catalysis, to nucleophilic substitution reactions (Scheme 2). The direct, γ-site selective, asymmetric S_N1 type alkylation of α-branched enals has been accomplished by a synergistic activation pathway that integrates dienamine- and chiral Brønsted acid catalysis simultaneously. The strategy enabled the chirality transfer from the catalyst to the γ-carbon reacting center, located five bonds away from the stereo-defining element within the aminocatalyst. Key to the successful implementation of this synergistic catalytic system was the compatibility of reactants, intermediates, and catalysts throughout the reaction process.

27 I. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen. Enantioselective Pictet-Spengler Type Cyclizations of Hydroxylactams: H-Bond Donor Catalysis by Anion Binding. *J. Am. Chem. Soc.*, **2007**, *129*, 13404.

28 S. E. Reisman, A. G. Doyle, E. N. Jacobsen. Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions. *J. Am. Chem. Soc.*, **2008**, *130*, 7198.

29 S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen. Scalable Catalytic Asymmetric Strecker Syntheses of Unnatural α-Amino Acids. *Nature*, **2009**, *461*, 968.

30 R. R. Knowles, S. Lin, E. N. Jacobsen. Enantioselective Thiourea-Catalyzed Cationic Polycyclizations. *J. Am. Chem. Soc.*, **2010**, *132*, 5030.
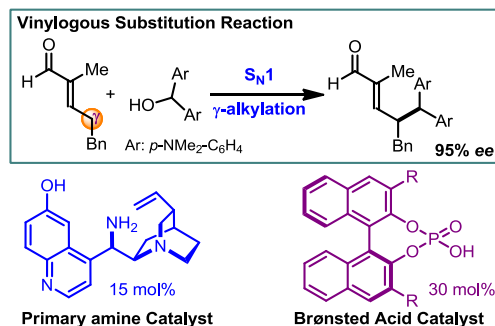
Scheme 2. Cooperative dienamine and ion-pairing catalysis for the direct asymmetric γ-alkylation of α-branched enals. Bn = benzyl.

Additionally, the vinylogous nucleophilic substitution manifold has served to realize the elusive γ-chlorination of sterically hindered enals. The study revealed the potential of chiral primary diamine catalysts for promoting the dienamine activation of α-branched enals while ensuring γ-site selective chlorination, albeit with low control of the remote stereochemistry.

Chapter **3** describes an unprecedented synthetic strategy for accessing an important target structure such as 3-substituted 3-hydroxyoxindole derivatives. The dioxindole framework with a C_3-hydroxy-bearing tetrasubstituted stereogenic center is a privileged scaffold found in many natural products. At the heart of the study was the use of dioxindole (3-hydroxy-2-oxindole), which has never been used before in organic chemistry as a competent nucleophilic partner.
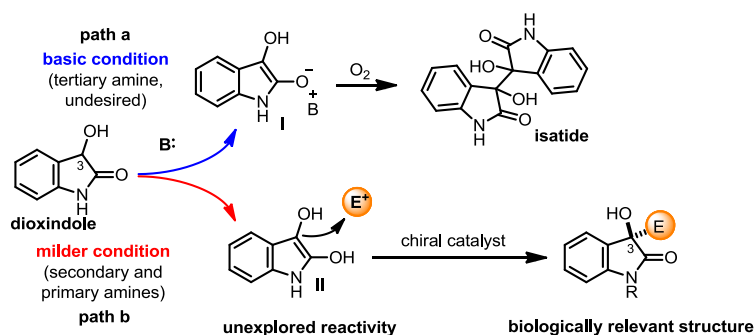
Scheme 3. Taming the dioxindole reactivity.

The main challenge associated with the use of dioxindole was a fast degradation pathway, which caused the consumption of the substrate under basic conditions (Scheme 3a).

Key factors in taming the dioxindole reactivity were the compatibility with mild primary and secondary amines and the ability of those organocatalysts to channel the intrinsic nucleophilicity of dioxindole toward a productive conjugate addition pathway (Scheme 3b). The potential

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usefulness of this reactivity in natural molecule synthesis has been provided with the straightforward preparation of maremycin A.

Chapter **4** reports the unprecedented use of anion-binding catalysis[27] to control the reactivity of a photoredox-generated ion-pair intermediate[31,32] as a new methodology for the enantioselective oxidative Mannich-type functionalization of tetrahydroisoquinolines (Scheme 4).
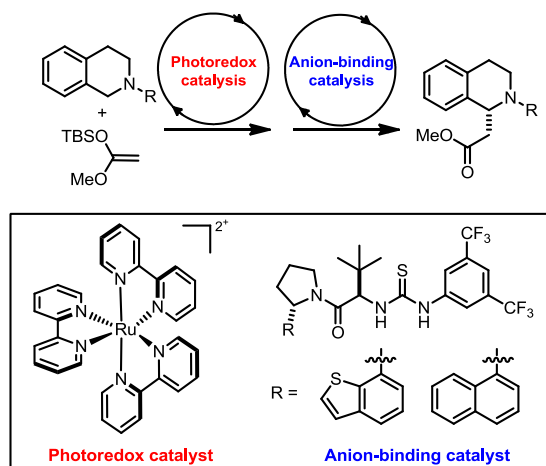
Scheme 4. Photoredox and anion-binding catalysis for the enantioselective oxidative Mannich-type functionalization of tetrahydroisoquinolines. Me = methyl; TBS = *tert*-butyldimethylsilyl.

The development of this sequential multicatalytic system was inspired by the recent application of visible light photoredox catalysis in enantioselective synthesis, as introduced by the group of Professor David W.C. MacMillan in 2008.[4] Our approach, which was developed in the research laboratories of Professor Corey R. J. Stephenson at Boston University (USA) and in collaboration with Professor Eric N. Jacobsen (Harvard University, USA), further highlights how the versatility of organocatalysis allows a combination with photoredox catalysis, thus providing powerful tools for developing novel enantioselective reactions.

Finally, expanding upon the recently identified possibility of using the photochemical activity of electron donor-acceptor (EDA) complexes to drive stereoselective catalytic transformations,[33] we have found that electron-poor benzylic substrates, such as 2-cyano-2-phenylacetate, can

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[31] A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson. Visible-Light Photoredox Catalysis: Aza-Henry Reactions *via* C−H Functionalization. *J. Am. Chem. Soc.,* **2010**, *132*, 1464.

[32] D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson. Functionally Diverse Nucleophilic Trapping of Iminium Intermediates Generated Utilizing Visible Light. *Org. Lett.*, **2012**, *14*, 94.

[33] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre. Photochemical Activity of a Key Donor-Acceptor Complex can Drive Stereoselective Catalytic α-Alkylation of Aldehydes. *Nat. Chem.*, **2013**, *5*, 750.

10 *Chapter 1*

engage in EDA complex formation with perfluorohexyl iodide. Chapter **5** details how the photochemical activity of this intermediate enables the direct perfluoro-alkylation of arenes driven by visible light. The photochemical reaction is triggered by the productive photoexcitation of an EDA complex formed between the benzylic carbanion (acting as the electron donor) and the perfluorohexyl iodide (the electron acceptor), as shown in Scheme 5.
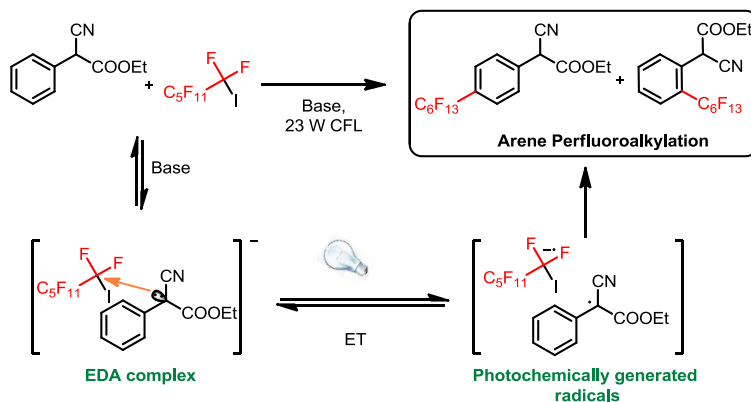
Scheme 5. The photochemical perfluoro-alkylation of arenes *via* EDA complex formation.

Preliminary experiments indicated the feasibility of accessing valuable perfluoroalkylated arenes by means of an operationally simple procedure based on a base and visible light as the only additives.

Chapter II

Cooperative Organocatalysis for the Asymmetric γ-Alkylation of α-Branched Enals

Target

Address a problem of fundamental importance in catalytic enantioselective reaction design: the remote functionalization of carbonyl compounds.
Demonstrate the potential of vinylogous nucleophilicity, induced by dienamine catalysis, within a substitution reaction pathway.
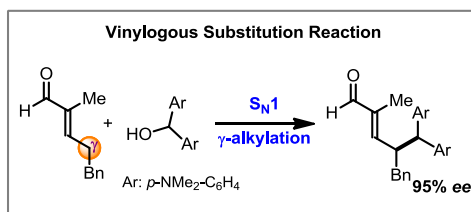
Tool

The combination of chiral Brønsted acid catalysis and dienamine activation: the transient generation of extended enamines, formed upon condensation of the chiral aminocatalyst with α,β-unsaturated aldehydes, is used to induce vinylogous nucleophilicity.[1]

Amino-Catalyst   **Brønsted Acid Catalyst**
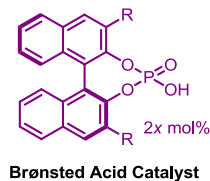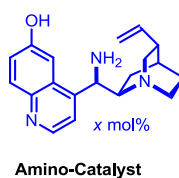
2.1 Background

The concept of dienamine catalysis was introduced in 2006 by Jørgensen and co-workers to promote the direct, enantioselective γ-amination of α,β-unsaturated aldehydes (Scheme 1).[2] This activation mode is based on the propagation of the HOMO energy-raising electronic effects, inherent to enamine activation, through the conjugated π-system of unsaturated carbonyl compounds (Figure 1).

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[1] Part of the work discussed in this chapter has been published, see: G. Bergonzini, S. Vera, P. Melchiorre. Cooperative Organocatalysis for the Asymmetric γ-Alkylation of α-Branched Enals. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9685.

[2] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen. Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.,* **2006**, *128*, 12973.

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Such an electronic transmission is particular to vinylogous reactivity, as originally defined by Fuson in 1935.[3]
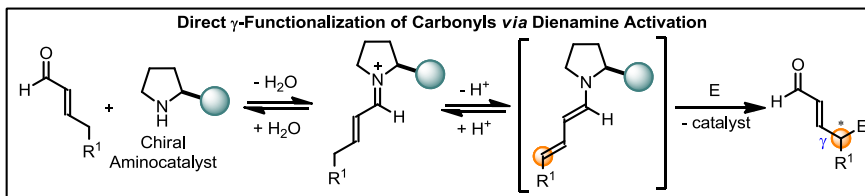
Figure 1. Dienamine activation as a remote functionalization strategy in organocatalysis. E = electrophile.

Combining asymmetric aminocatalysis with the principle of vinylogy, dienamine activation has greatly expanded the chemists' ability to functionalize carbonyl compounds at distant position, such as the γ carbon atom.[4]
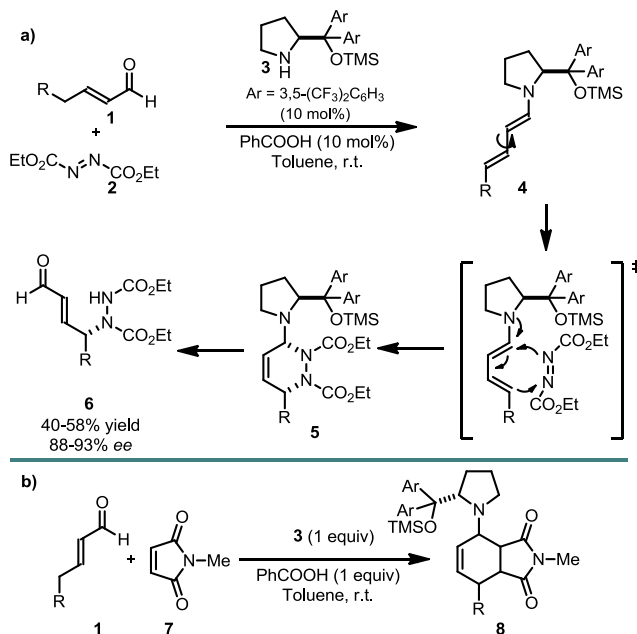
Scheme 1. The first example of dienamine catalysis: Diels-Alder reactivity.[2] PhCOOH = benzoic acid; Me = methyl; Et = ethyl; TMS = trimethylsilyl.

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[3] R. C. Fuson. The Principle of Vinylogy. *Chem. Rev.*, **1935**, *16*, 1.

[4] a) H. Jiang, Ł. Albrecht, K. A. Jørgensen. Aminocatalytic Remote Functionalization Strategies. *Chem. Sci.*, **2013**, *4*, 2287. b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre. When Asymmetric Aminocatalysis Meets the Vinylogy Principle. *Chem. Commun.*, **2013**, *49*, 4896.

Despite the promising synthetic potential of dienamine activation to provide a general platform for designing direct vinylogous reactions, the approach initially found limited applications. This was probably because the original γ-amination of unsaturated aldehydes followed a [4+2] cycloaddition path instead of a more general nucleophilic addition mechanism (Scheme 1). Evidence supporting the cycloaddition pathway was provided by theoretical studies and stereochemical information. In addition, when 2-pentenal was reacted with *N*-methylmaleimide **7** in the presence of 1 equiv of catalyst **3**,[5] the tricyclic structure **8** was readily isolated, further supporting a Diels-Alder type pathway (Scheme 1b). The all-carbon cycloadduct **8** could not eliminate the aminocatalyst **3**, thus representing a dead-end in a possible catalytic cycle.

The investigations by the Jørgensen group highlighted the promising synthetic potential of dienamine activation to provide a general synthetic methodology for designing direct vinylogous reactions. From a synthetic perspective, vinylogous processes offer efficient access to functionalized building blocks with high level of structural complexity;[6] however, challenges associated with designing such reactions are not only of stereochemical nature, but also of regioselectivity (Scheme 2).
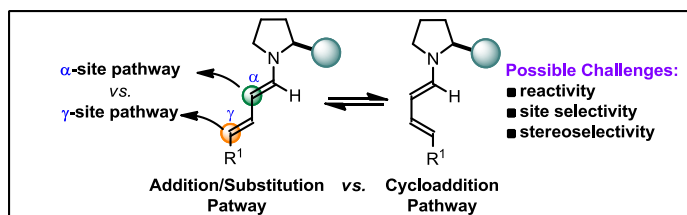
Scheme 2. Designing vinylogous processes by means of dienamine activation: challenges.

Indeed, the use of chiral secondary amines as catalysts for the formation of dienamine intermediates generally promoted an enamine pathway leading to an α-selective reaction in the presence of certain electrophiles.[7,8]

The first demonstration of the potential of dienamine activation to enforce a direct nucleophilic γ-addition pathway came with a single example reported by the Christmann group in 2008 (Scheme 3).[9]

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[5] K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen. The Diarylprolinol Silyl Ether System: a General Organocatalyst. *Acc. Chem. Res.*, **2012**, *45*, 248.

[6] G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi. The Vinylogous Aldol and Related Addition Reactions: Ten Years of Progress. *Chem. Rev.*, **2011**, *111*, 3076.

[7] N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III. A Way to Highly Enantiomerically Enriched aza-Morita–Baylis–Hillman–Type Products. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1878.

[8] E. Marquez-Lopez, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, Crossed Intramolecular Rauhut-Currier-Type Reactions *via* Dienamine Activation. *Org. Lett.*, **2009**, *11*, 4116.

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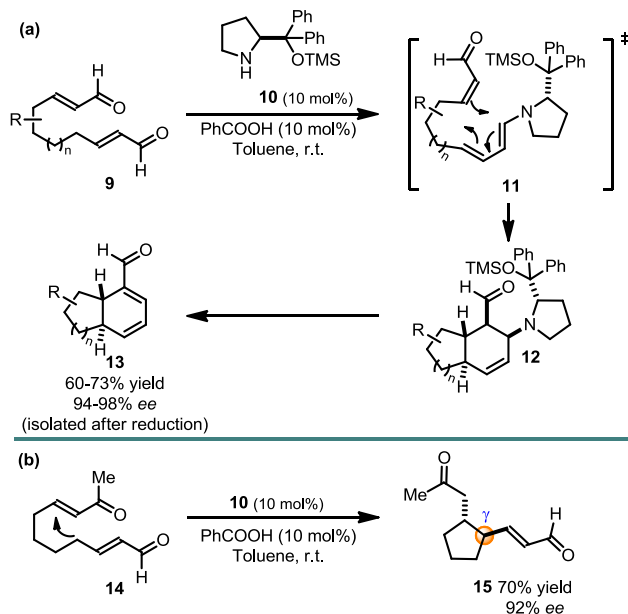
Scheme 3. (a) Intramolecular Diels-Alder reaction of dienals *via* dienamine activation. (b) The first example of direct vinylogous nucleophilic addition. Ph = phenyl.

In this study, the transient formation of the electron-rich dienamine **11**, derived from the condensation of diphenyl prolinol trimethylsilyl ether **10** with bis-aldehyde **9**,[5] initiated a rapid intramolecular Diels-Alder process (Scheme 3a). In addition, the authors reported that replacing one of the aldehydic functions in **9** with a keto moiety induced a change in the reaction manifold. Instead of the expected cyclo-addition path, a vinylogous Michael addition was observed, leading to product **15** (Scheme 3b).

Further extension of dienamine activation toward the intermolecular vinylogous nucleophilic addition was achieved by the group of Woggon.[10] An intermolecular vinylogous aldol/*oxa*-Michael domino reaction was employed as the key step for the total synthesis of α-tocopherol, one of the most significant members of the vitamin E (Scheme 4). In this approach, the direct vinylogous aldol reaction was integrated at the beginning of a cascade sequence, since it was followed by an *oxa*-Michael cyclization event. This subsequent cyclization overrode the intrinsic low reactivity of the dienamine step.

[9] R. M. de Figueiredo, R. Fröhlich, M. Christmann, Amine-Catalyzed Cyclizations of Tethered α,β-Unsaturated Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2008**, *47*, 1450.

[10] K. Liu, A. Chougnet, W.-D. Woggon. A Short Route to α-Tocopherol. *Angew. Chem. Int. Ed.*, **2008**, *47*, 5827.
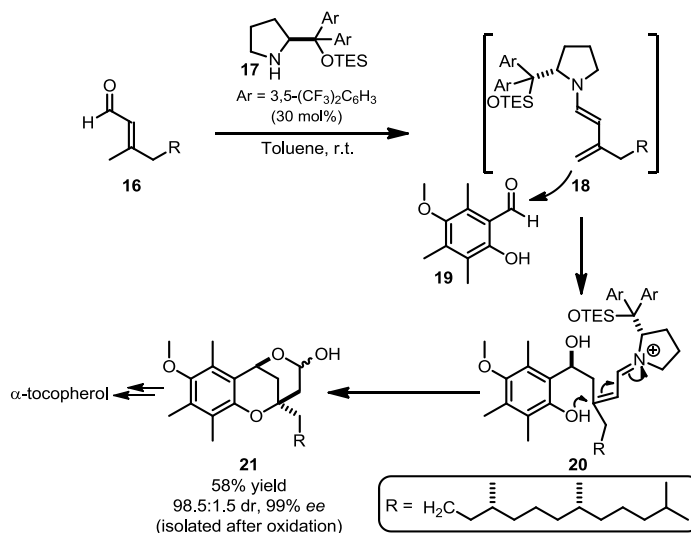
Scheme 4. Tandem vinylogous aldol/*oxa*-Michael reaction for the total synthesis of α-tocopherol. TES = triethylsilyl.

This report provided a powerful annulation strategy while also demonstrating the potential of dienamine activation to streamline the total synthesis of natural compounds. Nevertheless, despite the significant progresses achieved in the field of dienamine activation of unmodified α,β-unsaturated carbonyl substrates, a discrete example of intermolecular, asymmetric vinylogous addition remained elusive.

In 2010 the Melchiorre group reported an important advancement in the field of remote functionalization utilizing cinchona-based primary amine catalysis.[11] Specifically, they demonstrated that the multifunctional 6'-hyroxy-9-amino quinine derivative **22c** could promote the direct, vinylogous Michael addition of β-substituted cyclohexenone derivatives to nitroalkenes proceeding by dienamine activation (Scheme 5).[12] Key to developing the chemistry was the unique potential of the *cinchona*-derived amine to easily condense with a cyclic enone substrate to form the iminium ion intermediate **A**, and then to coax the selective formation of the *exo*-cyclic extended dienamine **B** over the *endo*-isomer **C** or the cross-conjugated dienamine **D**.

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[11] P. Melchiorre. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.,* **2012**, *51*, 9748.

[12] G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre. Direct Asymmetric Vinylogous Michael Addition of Cyclic Enones to Nitroalkenes *via* Dienamine Catalysis. *Proc. Natl. Acad. Sci. U.S.A.,* **2010**, *107*, 20642.

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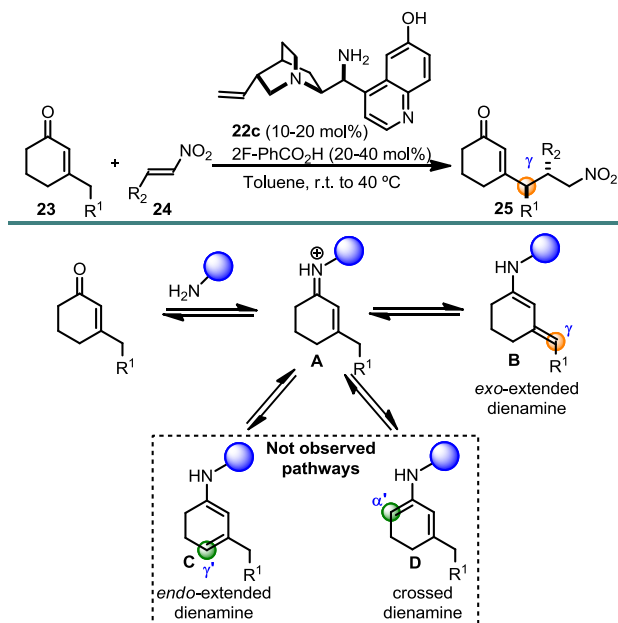
Scheme 5. Dienamine-promoted vinylogous Michael addition reaction.

The transmission of the HOMO-raising effect through the transiently generated cyclic dienamine **B** allowed for intermolecular vinylogous Michael additions to take place with high levels of selectivity. Interestingly, while primary amine catalyst **22c** led exclusively to the *exo*-cyclic extended dienamine intermediate **B**, chiral secondary amines, in the presence of the same reagent combination, induced the formation of the crossed-conjugated dienamine **D**, catalyzing a Diels-Alder-type reaction pathway.[13]

The logical extension to consolidate dienamine activation as a useful template for the γ-functionalization of unmodified carbonyls was its application to nucleophilic substitution reactions. Pursuing this target, we focused on the S_N1-type γ-alkylation of unmodified unsaturated carbonyl compounds.

The alkylation of carbonyl compounds is the archetypal nucleophilic substitution reaction. The catalytic direct asymmetric alkylation of aldehydes was possible only after the advent of asymmetric aminocatalysis. In 2004, Vignola and List presented the first example of catalytic

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[13] D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu. In Situ Enamine Activation in Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction of Cyclohexenones with Nitroolefins. *Angew. Chem. Int. Ed.*, **2009**, *48*, 3821.

asymmetric intramolecular α-alkylation of haloaldehydes under enamine activation.[14] Extension of the aminocatalytic strategy to an intermolecular version of the α-alkylation reaction was developed three years later by MacMillan and co-workers exploiting a new aminocatalytic activation mode, based on radical intermediates (SOMO activation).[15] A different approach was followed by the groups of Melchiorre[16] and Cozzi[17] in which the direct and stereoselective α-alkylation of an aldehyde was realized by using enamine activation coupled with the *in situ* generation of stabilized carbocations.

In particular, the direct nucleophilic substitution of benzhydryl alcohols developed by Cozzi represents an appealing methodology for the preparation of α-alkylated aldehydes, as water is the only by-product of the transformation (Scheme 6).[17]
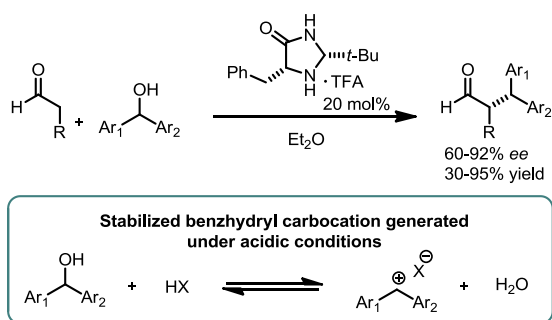
Scheme 6. Enamine-catalyzed asymmetric α-alkylation of aldehydes *via* an S$_N$1-type reaction. *t*-Bu = *tert*-butyl. Ar = aryl.

Key for the development of the chemistry was the possibility of intercepting stable carbocations, generated *in situ* under acidic conditions, with enamine intermediates. The reactivity and the formation of stable carbocations from benzhydrol substrates were extensively studied by the group of Herbert Mayr. They introduced the electrophilicity (*E*) and nucleophilicity (*N*) parameters for carbocations or related electrophiles and a plethora of nucleophiles.[18]

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[14] N. Vignola, B. List. Catalytic Asymmetric Intramolecular α-Alkylation of Aldehydes. *J. Am. Chem. Soc.*, **2004**, *126*, 450.

[15] T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan. Enantioselective Organocatalysis Using SOMO Activation. *Science*, **2007**, *316*, 582.

[16] R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre. Proline-Catalyzed Asymmetric Formal α-Alkylation of Aldehydes *via* Vinylogous Iminium Ion Intermediates Generated from Arylsulfonyl Indoles. *Angew. Chem. Int. Ed.,* **2008**, *47*, 8835.

[17] P. G. Cozzi, F. Benfatti, L. Zoli. Organocatalytic Asymmetric Alkylation of Aldehydes by S$_N$1-Type Reaction of Alcohols. *Angew. Chem. Int. Ed.*, **2009**, *48*, 1313.

[18] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A.R. Ofial, G. Remennikov, H. Schimmel. Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles. *J. Am. Chem. Soc.*, **2001**, *123*, 9500.

These values can be easily combined to quantitatively describe the rate of a variety of electrophile-nucleophile interactions and used in a rational design process for organic transformations.
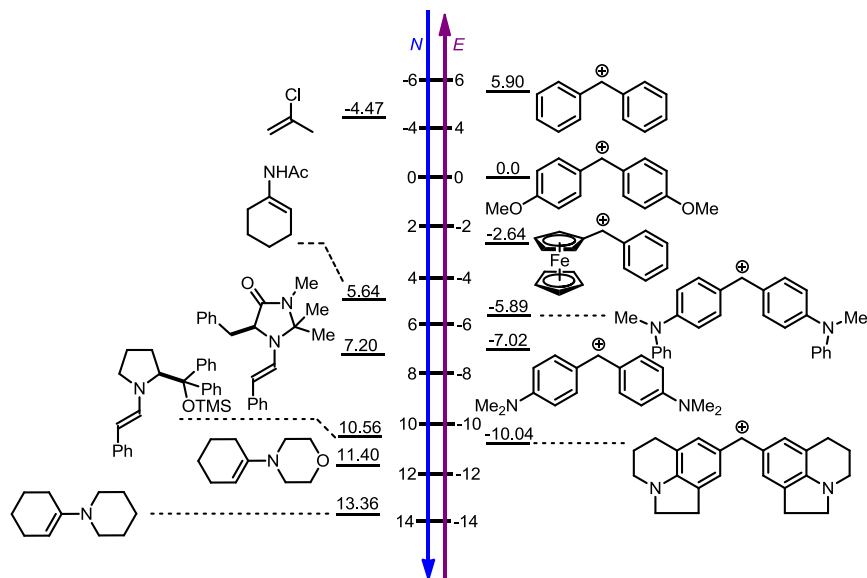
Figure 2. Selection of E and N values.[19] Ac = acetate.

Reactions of carbocations and related electrophiles with nucleophiles can be described by the following equation:

$$\log k \, (20\,°C) = s(N + E)$$

where E represents the electrophilicity of the carbocations while nucleophiles are characterized by two parameters, the nucleophilicity parameter N and the slope parameter s, the latter of which can be neglected for qualitative considerations (s ≈ 1).

The crucial question when considering a certain synthetic transformation is whether it will take place or not. This is closely related to the expected reaction rates. Considerations on the rate constant (second-order rate constant $k > 10^{-4}\,M^{-1}s^{-1}$ is required to give 50% of conversion in less than 3 h for a bi-molecular reaction which initial concentration is 1 M in both reactants) led to the conclusion that electrophiles can be expected to react with nucleophiles at room temperature when $E + N > -5$. According to Figure 2, enamines ($N ≈ 12$) and bis(4-

[19] H. Mayr, B. Kempf, A. R. Ofial. π-Nucleophilicity in Carbon-Carbon Bond-Forming Reactions. *Acc. Chem. Res.*, **2003**, *36*, 66.

dimethylamino-phenyl)methanol (E = - 7.02), which forms a stable carbocation,[20] can lead to a productive reaction. Other alcohols that form more reactive carbocations, such as benzhydrols which are placed at the top of Figure 2, showed instead no reactivity in the α-alkylation of aldehydes.

Inspired by the successful reaction of *in situ* generated carbocations with enamine intermediates[17] and hypothesizing a similar nucleophilicity of dienamine intermediates, we focused on the S_N1-type γ-alkylation of unsaturated carbonyl compounds.

2.2   Results and Discussion

As the model reaction, we chose the direct γ-alkylation of α-branched aldehyde **26** with bis(4-dimethylaminophenyl)methanol **27**, which can easily form a stabilized benzhydryl carbocation under acidic conditions (Table 1).

Recently, we had established the unique ability of 9-amino(9-deoxy)*epi* cinchona alkaloids (chiral primary amines easily derived from natural sources) to efficiently activate sterically hindered carbonyl compounds, while imparting unconventional reactivity profiles (e.g. vinylogous nucleophilicity upon condensation with cyclic enones).[12] Moreover, this catalyst class can activate the sterically hindered α-branched enals toward cascade reactions, thus combining orthogonal aminocatalytic modes.[21] The versatility of this catalyst framework prompted us to explore its application in the context of the dienamine-promoted γ-activation of α-substituted linear α,β-unsaturated aldehydes.
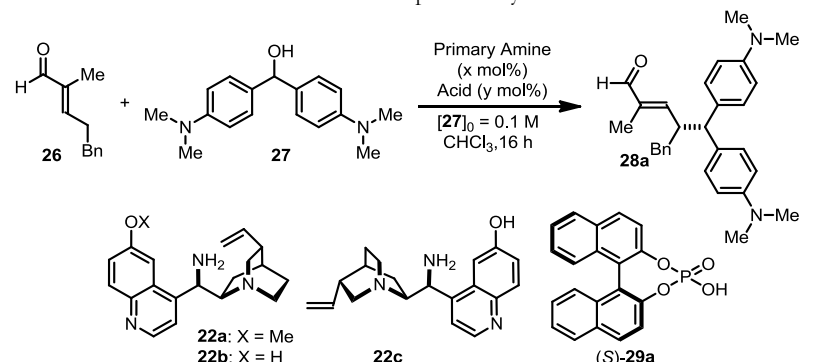
We found that 20 mol% of catalyst **22a** (directly derived from quinidine) in combination with 30 mol% of trifluoroacetic acid (TFA) as an acidic co-catalyst, led to compound **28a**, albeit with essentially no stereocontrol (Table 1, entry 1). In addition to the desired product, the formation of the dimer **30**, arising from the carbocation trapping by the alcohol **27** (Equation 1),[22] was observed. Extensive reaction optimization studies indicated that solvent, concentration and temperature were important factors influencing the reactivity. A temperature higher than 35 °C and the use of chloroform as the solvent both facilitated the complete conversion of the alcohol **27** (the limiting reagent) into the γ-alkylation product **28**. This was not by avoiding the dimer **30** formation, but more likely by speeding up the reversible regeneration of the reactive carbocation **27a** from the intermediate **30** (Equation 1).

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[20] The 4,4'-bis(dimethylamino)diphenylmethane carbocation has a half-life of 10-20 seconds, see: R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait, S. J. Steeken. Flash-Photolysis Generation and Reactivities of Triarylmethyl and Diarylmethyl Cations in Aqueous Solutions. *J. Am. Chem. Soc.*, **1989**, *111*, 3966.

[21] P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre. Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7892.

[22] The byproduct **30** has been reported also in: L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng. Asymmetric S_N1 α-Alkylation of Cyclic Ketones Catalyzed by Functionalized Chiral Ionic Liquid (FCIL) Organocatalysts. *Chem. Eur. J.*, **2010**, *16*, 2045.

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Table 1. Development of a cooperative organocatalytic system for the direct γ-alkylation of α-branched enals: preliminary results[a]

Entry	Primary amine (mol%)	Brønsted acid (mol%)	T (°C)	Conv (%)[b]	ee (%)[c]
1	**22a** (20)	TFA (30)	40	28	<5
2	**22b** (20)	TFA (30)	40	75	60
3	**22c** (20)	TFA (30)	40	59	60[e]
4	**22b** (20)	(S)-**29a** (30)	50	>95	80
5	**22b** (15)	(S)-**29a** (30)	50	>95	85
6[d]	**22b** (15)	(S)-**29a** (30)	50	>95 (82)	90
7[d]	**22b** (15)	(S)-**29a** (22.5)	50	45	85
8[d]	**22b** (10)	(S)-**29a** (20)	50	72	90

[a] Reactions carried out using 3 equiv of enal **26**. ^{1}H NMR analysis of the crude mixture indicated a highly γ-site selective alkylation pathway. Other products arising from different reaction manifolds (e.g. α-alkylation under enamine catalysis) were sporadically detected in negligible amounts. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out using 2 equiv of enal **26**. [e] The opposite enantiomer of **28a** was obtained. The absolute configuration of compound **28a** was established by chemical correlation (see experimental section for details). TFA = trifluoroacetic acid. Bn = benzyl.

The bifunctional primary amine 6'-hydroxy-9-amino-9-deoxyepiquinidine **22b** dramatically increased the enantioselectivity as well as the reaction rate of the vinylogous alkylation while maintaining complete γ-selectivity (Table 1, entry 2). The same level of enantioselectivity and similar reactivity were observed when the pseudo-enantiomer of the primary amine catalyst **22b** (6'-hydroxy-9-amino-9-deoxyepiquinine **22c**) was used (Table 1, entry 3).

Equation 1
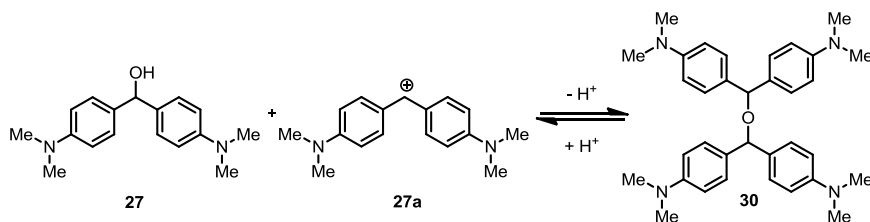
To improve the level of stereocontrol, we envisioned the possibility of integrating dienamine activation and chiral Brønsted acid catalysis. A phosphoric acid can induce the formation of a chiral contact ion-pair from alcohol **27** which may synergistically engage in a matched combination with the chiral covalent dienamine intermediate (arising from the condensation of primary amine with enal **26**).[23] Combination of **22b** with the readily available phosphoric acid (*S*)-**29a**,[24] greatly improved the enantioselectivity to a practical level (Table 1, entry 4). A loading of 15 mol% of chiral amine **22b** in a 1:2 amine/acid catalyst ratio, in combination with 2 equiv of enal **26**, was found as optimal (Table 1, entry 6).

Structural modifications of the Brønsted acid catalyst **29** revealed a strong correlation between the 3,3'-substituents and the reactivity, strictly related to the ability of inducing *in situ* carbocation formation (Table 2, entries 1-5 and Figure 3).
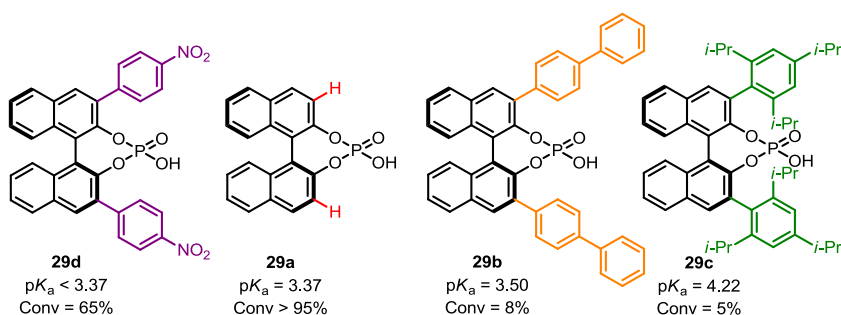
Figure 3. Correlation between 3,3'-substituents and reactivity; pK_a values in DMSO solution.[25]

The performance of different chiral phosphoric acids **29a**-**d** as co-catalysts for the γ-alkylation of α-branched enals may be associated not only to their relative pK_a values,[25] but also to their respective steric effects. The reactivity was observed to dramatically decrease for phosphoric acids with higher pK_as such as **29b** and **29c**. While among the acids able to generate the benzhydryl carbocation **27a** (acids **29a** and **29d**), higher reactivity was observed for the less sterically encumbered catalyst **29a**.

The use of **29d** as acidic co-catalyst led to an increase of the enantioselectivity up to 93% *ee* (Table 2, entry 4). Interestingly, the opposite configuration of the product could be accessed by simply selecting the appropriate configuration of the catalytic couple. Thus, combining the

[23] Q. X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong. Highly Enantioselective Alkylation Reaction of Enamides by Brønsted-Acid Catalysis. *Org. Lett.*, **2009**, *11*, 4620.

[24] Chiral phosphoric acids have found widespread applications in Brønsted acid catalysis: T. Akiyama. Stronger Brønsted Acids. *Chem. Rev.*, **2007**, *107*, 5744.

[25] P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudörfl, A. Berkessel, A. C. O'Donoghue. pK_a Values of Chiral Brønsted Acid Catalysis: Phosphoric Acids/Amides, Sulfonyl/Sulfuryl Imides, and Perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.*, **2011**, *17*, 8524.

pseudo-enantiomeric catalyst **22c**, derived from quinine, with (*R*)-**29d** afforded **28a** with opposite absolute configuration while maintaining a high level of selectivity (Table 2, entry 8). To gain insight into the specific role of each individual activation pathway, we used the mismatched catalyst combinations to promote the γ-alkylation of **26** with **27** (Table 2, entries 9 and 10). This resulted in a dramatic loss of reactivity and enantioselectivity. Moreover, the results obtained when chiral dienamine and chiral Brønsted acid catalysts were operating individually (in the presence of a racemic partner, Table 1, entry 2 and Table 2, entry 11) further supported a highly constructive and synergic cooperation in the presence of the matched-pair combination (i.e. **22b** with (*S*)-**29d** and **22c** with (*R*)-**29d**).

Table 2. Phosphoric acid structure modification[a]
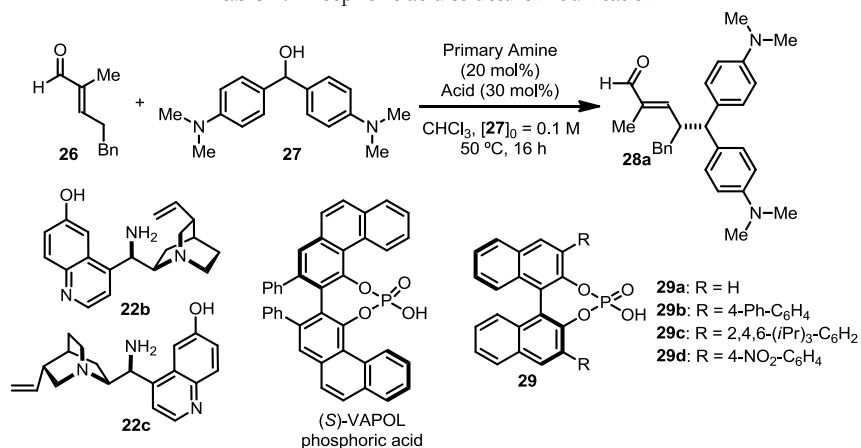
Entry	Primary amine (mol%)	Brønsted acid (mol%)	Conv (%)[b]	*ee* (%)[c]
1	**22b**(20)	**29a**(30)	>95	80
2	**22b**(20)	**29b**(30)	8	n.d.
3	**22b**(20)	**29c**(30)	5	92
4	**22b**(20)	**29d**(30)	62	93
5	**22b**(20)	(*S*)-VAPOL(30)	<5	n.d.
6[d]	**22b**(15)	**29a**(30)	>95 (82)	90
7[d]	**22b**(15)	**29d**(30)	93 (84)	95
8[d]	**22c**(15)	(*R*)-**29d**(30)	>95 (89)	90[e]
9	**22b**	(*R*)-**29d**(30)	30	21[e]
10	**22c**	**29d**(30)	24	<5
11	benzylamine	**29a**(30)	33	14

[a] Reactions carried out using 3 equiv of enal **26**. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reactions carried out using 2 equiv. of enal **26**. Numbers in parenthesis refer to yield of isolated **28a**. [e] The opposite enantiomer of **28a** was obtained. (*S*)-VAPOL phosphoric acid = (*S*)-2,2'-Diphenyl-3,3'-biphenanthryl-4,4'-diyl phosphate.

We believe that the primary amine activates the enal toward vinylogous nucleophilicity *via* dienamine formation, while the chiral phosphate anion, arising from **29**, has the dual role of

acting as counter-anion for both the protonated quinuclidine moiety, within the cinchona scaffold, and the *in situ* formed benzhydryl cation (this is consistent with the need for a 1:2 amine to acid ratio, see entries 6-8 in Table 1). Moreover, the great influence of the H-bond donor at the 6' position of the primary amine **22b** on the reactivity as well as the stereoselectivity of the γ-alkylation, prompted us to propose a mechanistic model in which both the electrophilic and nucleophilic chiral intermediates interact through a network of non-covalent interactions, as depicted in Scheme 7.
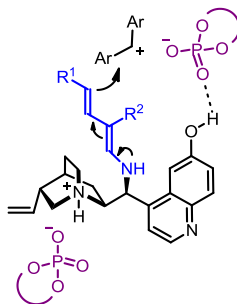
Scheme 7. Cooperative dienamine and ion-pairing catalysis for the γ-alkylation of α-branched enals.

The dual-catalyst system was then applied to the direct γ-alkylation of a variety of α-branched γ-enolizable enals. The results reported in Table 3 illustrate how different substituents at the γ-position can be accommodated without affecting either site selectivity or the enantioselectivity of the S_N1 alkylation (entries 1-6). Using the substituted phosphoric acid **29d** instead of the simple acid **29a** led to higher levels of stereocontrol (Table 3, entries 2, 3, 5). The catalytic system showed remarkable latitude in both the electronic and steric demands of the aldehydic component. Different aliphatic substituents and even a phenyl group in the α-position of the enals were well-tolerated (Table 3, entries 7-10), enabling access to a broad variety of multifunctional molecules with complete γ-selectivity and moderate to high levels of enantioselectivity. Remarkably, when R^1 was an aromatic group (Table 3, entries 11-13), the γ-alkylation protocol opened a direct access to enantioenriched benzylic carbon stereocenters.

Table 3. Asymmetric γ-alkylation of α-branched enals.[a]
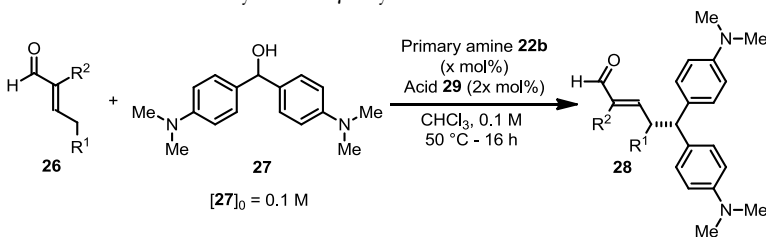
Entry	R^1	R^2	x	**29**	product	Yield (%) [b]	ee (%)[c]
1	Bn	Me	15	a	**28a**	82	90
2	Bn	Me	15	d	**28a**	84	95
3	Me	Me	15	d	**28b**	98	89
4	allyl	Me	20	a	**28c**	91	87
5	allyl	Me	15	d	**28c**	65	94
6	i-Pr	Me	20	a	**28d**	80	87
7	Et	Et	20	a	**28e**	58	82
8	Bn	Et	20	a	**28f**	82	72
9	Bn	Bn	20	a	**28g**	72	73
10	Me	Ph	20	a	**28h**	71	45
11[d]	Ph	Me	15	a	**28i**	63	90
12[d]	pCl-C_6H_4	Me	20	a	**28j**	61	82
13[d]	pMeO-C_6H_4	Me	20	a	**28k**	72	86

[a] Reaction carried out using 2 equiv of enal. [b] Yield of the isolated compounds **28**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out at 10 °C.

In addition, we explored the possibility of extending primary amine-induced vinylogous nucleophilicity to 1-cycloalkene-1-carboxaldehyde. The cooperative catalysis system previously developed afforded the γ-alkylation product **31** with high regio- and enantio-selectivity (Equation 2).
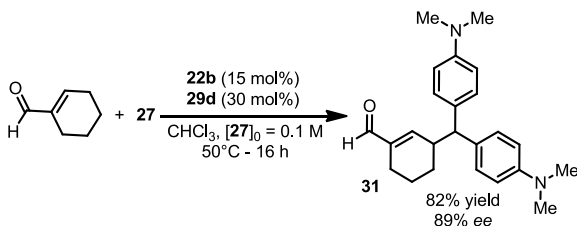
Equation 2

Finally, while trying to expand the scope of the alkylating agent, it was found that alcohols that lead to less stable carbocations are not competent substrates in the present γ-alkylation protocol, affording the products with low enantioselectivity (Equation 3).
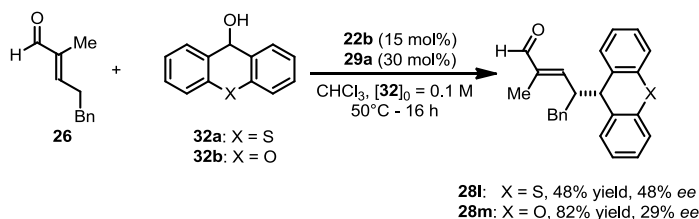
Equation 3

When applying the optimized conditions to unsubstituted linear aldehydes such as (*E*)-2-octenal, the alkylation product was formed in 82% overall yield (Equation 4). However both the site- and the enantioselectivity of the process were very poor. The (*E*)-γ-alkylated aldehyde was obtained as the major regioisomer in 52% conversion and 14% *ee* along with 30% of a 1:1 *E/Z* mixture of the α-substituted products.
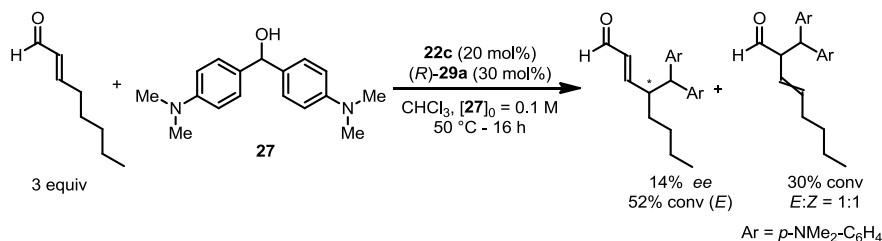
Equation 4

Concurrently to our studies, an independent investigation by Christmann *et al*. established the ability of secondary amines to promote the same S_N1-type alkylation process of unsubstituted linear enals.[26] However, the catalytic system could not completely address the challenges related to dienamine-based asymmetric processes, providing only a moderate control over the site-selectivity (α− *vs.* γ-alkylation) and high levels of enantioselectivity were achieved only for selected substrates. Substitution of the α-position in enal **26** seem thus to be an important factor in directing the alkylation reaction to the γ-carbon of the dienamine intermediate, hence ensuring a high level of regiocontrol.

2.3   Conclusions

By integrating dienamine activation and Brønsted acid catalysis we have successfully developed an efficient system for the γ-selective alkylation of α-branched enals which provided the first example of a catalytic, asymmetric vinylogous substitution reaction of unmodified carbonyl

[26] J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann. Enantioselective α- and γ-Alkylation of α,β-Unsaturated Aldehydes Using Dienamine Activation. *Org. Lett.,* **2011**, *13*, 70.

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compounds. This study confirmed the ability of chiral primary amine catalysis to effectively activate sterically hindered compound classes such as α-branched enals.

2.4 Studies on the Enantioselective γ-Chlorination of α-Branched Aldehydes *via* Dienamine Activation

Having identified an effective methodology for the enantioselective γ-alkylation reaction of α-branched enals, we envisioned the possibility to develop a different substitution reaction, namely the γ-chlorination of carbonyl compounds. Due to the metabolic properties of chlorinated compounds and their versatility in organic fragment coupling, the chlorination of carbonyl compounds has become an important objective for organic chemists. Soon after the advent of organocatalysis, and in particular of enamine catalysis as a general activation mode for the α-functionalization of carbonyl compounds, the first, direct and highly enantioselective α-chlorination of unmodified aldehydes was reported. The reaction was developed independently by the MacMillan and the Jørgensen groups in 2004 (Scheme 8).
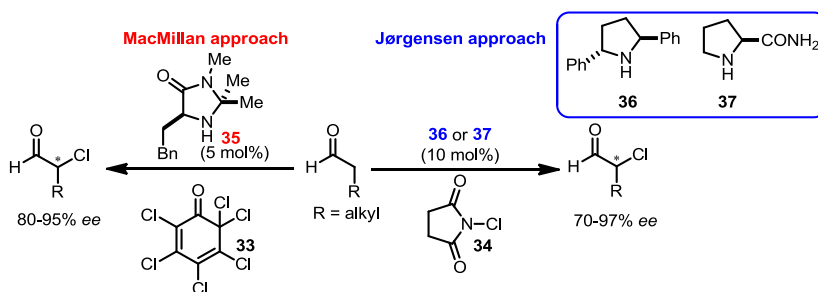
Scheme 8. Organocatalytic α-chlorination of aldehydes.

The preparation of different chiral building blocks using a variety of chemical transformations demonstrated the synthetic utility of α-chlorocarbonyls.[27,28] Interestingly, mechanistic investigation on the 2,5-diphenylpyrrolidine-catalyzed enantioselective α-chlorination of aldehydes showed that the reaction might proceed through an initial, kinetically controlled N-Cl bond formation, whereby the electrophilic chlorine atom reacts first with the nucleophilic enamine nitrogen atom, forming the *N*-chloroamonium ion intermediate (Scheme 9, Path a)

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[27] M. P. Brochu, S. P. Brown, D. W. C. MacMillan. Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes. *J. Am. Chem. Soc.*, **2004**, *126*, 4108.

[28] N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen. Direct Organocatalytic Asymmetric α-Chlorination of Aldehydes. *J. Am. Chem. Soc.*, **2004**, *126*, 4790.

rather than a direct addition to the enamine carbon atom (Scheme 9, Path b).[29]
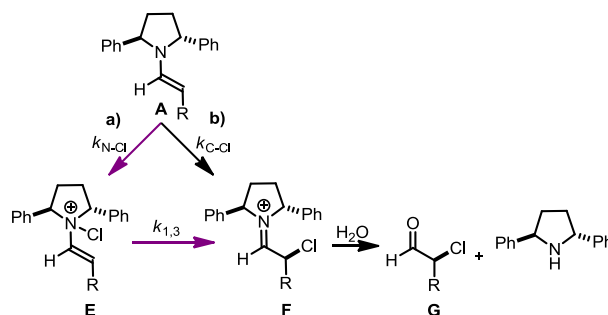
Scheme 9. Possible mechanistic pathways for the organocatalytic enantioselective α-chlorination of aldehydes.

The intermediate **E** then rapidly undergoes a 1,3-sigmatropic shift forming the termodinamically favored iminium ion **F**. The suggested *N*-attack of the electrophilic chlorine atom has also been confirmed by ESI-MS studies.[30] In view of this finding two possible pathways can thus be considered for the vinylogous γ-chlorination of aldehydes (Scheme 10).
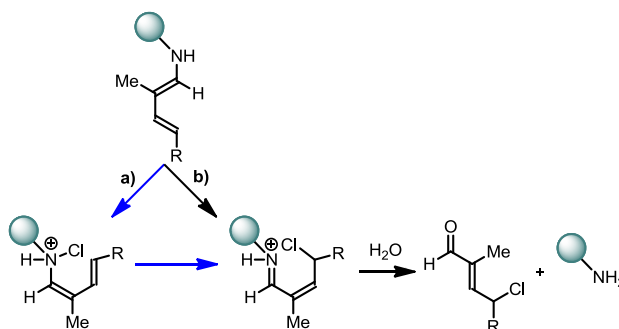
Scheme 10. Plausible mechanistic pathways for the γ-chlorination of α-branched enals.

Path b shows the direct addition of electrophilic chlorine to the dienamine carbon atom while path a illustrates the vinylogous 1,5-chlorine shift from the postulated chloronium ion.[31]

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[29] N. Halland, M. A. Lie, A. Kjærsgaard, M. Marigo, B. Schiøtt, K. A. Jørgensen. Mechanistic Investigation of the 2,5-Diphenylpyrrolidine-Catalyzed Enantioselective α-Chlorination of Aldehydes. *Chem. Eur. J.*, **2005**, *11*, 7083. For a more recent study, see: J. Burés, A. Armstrong, D. G. Blackmond. Curtin−Hammett Paradigm for Stereocontrol in Organocatalysis by Diarylprolinol Ether Catalysts. *J. Am. Chem. Soc.*, **2012**, *134*, 6741.

[30] C. A. Marquez, F. Fabbretti, J. O. Metzger. Electrospray Ionization Mass Spectrometric Study on the Direct Organocatalytic α-Halogenation of Aldehydes. *Angew. Chem. Int. Ed.*, **2007**, *46*, 6915.

[31] Not only 1,3- but also 1,5-chlorine shift have been documented. See: a) C. W. Spangler. Thermal [1, *j*] Sigmatropic Rearrangements. *Chem. Rev.*, **1976**, *76*, 187; b) R. Koch, M. W. Wong, C. Wentrup. Facile 1,3- and 1,5-Chlorine Migration. *J. Org. Chem.*, **1996**, *61*, 6809.

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A recent paper by Mayr on the electrophilicity of α-chlorinating agents showed that 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one **33** can be selected as a suitable electrophile for the organocatalytic vinylogous chlorination reaction.[32] Indeed, the *E* value associated to **33** is - 6.75, which is comparable to the *E* value of the benzhydryl alcohol perviously employed in the γ-alkylation of α-branched enals (*E* = - 7.02).

With the aim to apply the vinylogous nucleophilic substitution reactivity toward the elusive enantioselective γ-chlorination of α-branched aldehydes, we selected the commercially available 2-methyl-2-pentenal **38** and quinone **33** or *N*-chlorosuccinimide (NCS) **34** as the reaction partners.

Table 4. Direct γ-chlorination of α-branched aldehydes. Preliminary results[a]
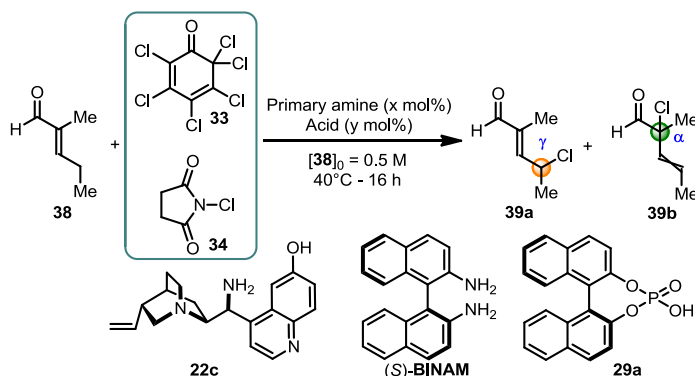
Entry	Chlorinating agent	Solvent	Primary amine (mol%)	Brønsted acid (mol%)	Conv (%)[b]	γ-Sel (%)[b]	*ee* (%)[c]
1	**33**	CHCl$_3$	**22c**(20)	**TFA**(30)	>95	65	2
2	**34**	CHCl$_3$	**22c**(20)	**TFA**(30)	>95	50	7
3	**34**	CH$_3$CN	**22c**(20)	**TFA**(30)	65	90	6
4	**34**	CH$_3$CN	**22c**(20)	(*R*)-**29a**(30)	80	93	7
5[d]	**34**	CH$_3$CN	**22c**(20)	**TFA**(30)	13	0	-
6	**34**	CH$_3$CN	(*R*,*R*)-**DPEN**(20)	**TFA**(40)	37	100	0
7	**34**	CH$_3$CN	(*S*)-**BINAM**(20)	**TFA**(40)	80	100	0
8	**34**	CH$_3$CN	(*S*)-**BINAM**(20)	**TFA**(20)	>95	80	0

[a] Reactions carried out using 1.2 equiv of chlorinating agent. [b] Determined by ^{1}H NMR analysis of an aliquot of the crude mixture. Conversion was calculated with respect to the starting aldehyde and double checked with respect to the chlorinating agent. γ-Selectivity represents the conversion of **38** to the γ-chlorinated product **39a** divided by the overall conversion of the starting enal. [c] Determined by GC analysis on chiral stationary phases. [d] Reaction carried out at 0 °C. TFA = trifluoroacetic acid. DPEN = diphenylethylenediamine.

[32] X-H. Duan, H. Mayr. Electrophilicities of α-Chlorinating Agents Used in Organocatalysis. *Org. Lett.*, **2010**, *12*, 2238.

When 20 mol% of catalyst **22c** was used in combination with 30 mol% of TFA, as an acidic co-catalyst, the γ-chlorinated aldehyde **39a** was obtained as the major regioisomer, albeit with a significant amount of α-substituted product **39b** (Table 4, entry 1). Quinone **33** and *N*-chlorosuccinimide **34** led to similar results and the readily available **34** was chosen for further optimizations. Use of acetonitrile as the solvent afforded a significant improvement in the γ-selectivity (Table 4, entry 3). The synergistic cooperation between dienamine and chiral Brønsted acid catalysis, which was crucial for developing an asymmetric enantioselective γ-alkylation reaction of α-branched enals (see section 2.2), was not effective in increasing the enantioselectivity of the γ-chlorination reaction (Table 4, entries 3-4). The use of the chiral diamine (*S*)-2,2′-bis(diphenylphosphinoamino)-1,1′-binaphthyl (BINAM) provided optimal reactivity and γ-site selectivity (Table 4, entry 7).

Intrigued by the ability of diamines to direct the reactivity toward the desired γ-site selective pathway, we decided to use chiral *(S)*-BINAM as the catalyst for the following optimization studies (Table 5).

Table 5. Co-catalyst screening[a]
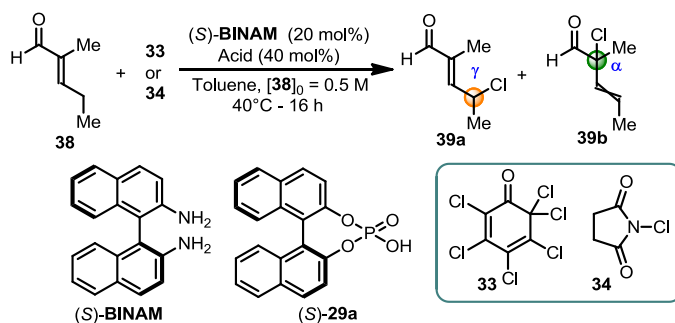
Entry	Chlorinating agent	Brønsted acid	(%) conv[b]	γ-Selectivity (%)[b]	*ee* (%)[c]
1	**33**	TFA	>95	>95	12
2	**34**	TFA	>95	80	23
3[e]	**34**	DPP	85	62	38
4[f]	**34**	(*R*)-**29a**	>95	63	43
5[f]	**34**	(*S*)-**29a**	>95	62	43
6[d]	**34**	(*S*)-**29a**	74	64	42
7[g]	**34**	(*S*)-**29a**	10	75	76

[a] Reactions carried out using 1.2 equiv of chlorinating agent. [b] Determined by ^{1}H NMR analysis of an aliquot of the crude mixture. Conversion was calculated with respect to the starting aldehyde and double checked with respect to the chlorinating agent. γ-Selectivity represents the conversion of **38** to **39a** divided by the overall conversion of the starting enal. [c] Determined by GC analysis on chiral stationary phase. [d] Reaction carried out at r.t. [e] Reaction time = 1 h. [f] Reaction time = 24 h. [g] Reaction carried out at -25 °C. DPP = diphenyl hydrogen phosphate.

The integration of the BINAM-catalytic system with a phosphoric acid as the co-catalyst improved the enantioselectivity, however not to a practical level (Table 5, entry 3). When the

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two enantiomers of the chiral co-catalyst **29a** were independently used in combination with (*S*)-BINAM, the same reactivity and stereoselectivity were observed indicating the absence of any matched-mismatched catalyst combination (Table 5, entries 4 and 5). Lowering the temperature to - 25 °C led to the desired γ-chlorinated product **39a** with good enantioselectivity, albeit in poor yields (Table 5, entry 7).Modifications of the BINAM scaffold, functionalization of the catalyst amino-moieties or employment of other chiral diamine scaffolds did not lead to any further improvement of the system (Scheme 11).
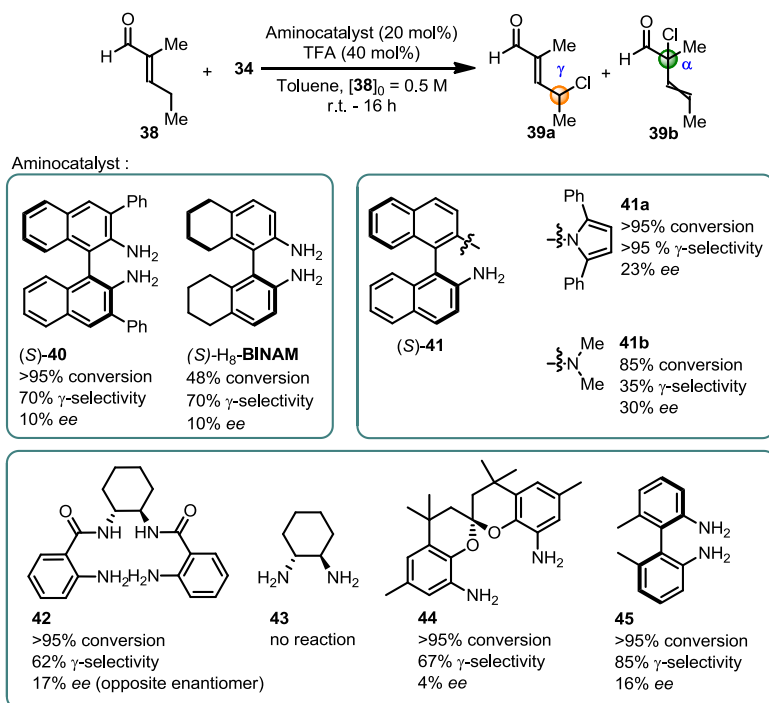
Scheme 11. γ-Chlorination reaction of α-branched enals catalyzed by different primary amines.

In conclusion, the γ-chlorination of α-branched enals under dienamine activation has been studied. Chiral primary diamines such as BINAM and its derivatives were recognized as an efficient class of catalysts promoting vinylogous nucleophilicity within substitution reaction pathway. This unprecedented chemical transformation led to the formation of the desired γ-chlorinated product with high site-selectivity albeit with only moderated enantioselectivity.

2.5 Experimental Section

2.5.1 General Informations

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hz. Carbon substitution was determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatographic purification of products was accomplished using flash chromatography (FC) on silica gel (35-70 mesh) according to the method of Still.[33] Thin layer chromatography (TLC) analysis was performed throughout this work using Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm), using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on a Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionisation (EI). Optical rotations are reported as follows: $[\alpha]_D^T$ (c in g per 100 mL, solvent). All reactions were performed in the air and using commercial solvents, without any precautions to exclude moisture unless otherwise noted. The alkylation products **28** can be stored at 0 °C for a long time without affecting the enantiomeric purity. To ensure the stability of the chlorination product **39a**, products samples were stored at temperature lower than – 20 °C.

The ^{1}H and ^{13}C NMR spectra and HPLC and GC traces are available in the literature and are not reported in the present manuscript.[1]

2.5.2 Materials

Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[34] Chiral primary amine catalysts, 9-amino(9-deoxy)epi-quinidine **22a**, and 6'-hydroxy(9-amino)9-deoxyepiquinidine **22b** and its pseudo-enantiomer 6'-hydroxy(9-amino)9-deoxyepiquinine **22c** were prepared from commercially available quinidine and quinine, respectively, following the literature procedure.[35,] The chiral phosphoric acids **29b**, and **29d**, were prepared according to the literature procedure

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[33] W. C. Still, M. Kahn, A.J. Mitra. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.,* **1978**, *43*, 2923.

[34] W. L. F. Armarengo, D. D. Perrin. *Purification of Laboratory Chemicals, 4th ed.*; Butterworth Heinemann, Oxford, **1996**.

[35] C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre. Synthesis of 9-Amino(9-deoxy)epi Cinchona Alkaloids, General Chiral Organocatalysts for the Stereoselective Functionalization of Carbonyl Compounds. *Nat. Protoc.,* **2013**, *8*, 325.

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from commercially available *(S)*-BINOL.[36,37] Catalysts **29a**, **29c**, *(S)*-BINAM, *rac*-BINAM, (*R,R*)-diphenylethylenediamine (DPEN), *(1R,2R)*-cyclohexane-1,2-diamine and catalyst **45** were purchased from Aldrich or Alfa Aesar and used as received. Catalyst **44** was kindly donated from Prof. Piet van Leeuwen group in ICIQ. Catalyst *(S)*-H$_8$-BINAM, **40** and **41b** were prepared accordingly to literature procedures starting from *(S)*-BINAM.[38,39] Catalyst **42** was synthesized from *(1R,2R)*-cyclohexane-1,2-diamine and isatoic anhydride following a literature procedure.[40] Catalyst **41a** was prepared *via* Paal-Knorr condensation (*vide infra*). Catalyst **22e** was readily prepared from (1*R*,2*R*)-cyclohexane-1,2-diamine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate as described in the literature.[41] Alcohol **27** was purchased from Acros Organics and used as received. Note that **27** is provided in 85% of purity (technical grade) and the stoichiometry of the alkylation reactions was adjusted accordingly.

2.5.3 Determination of the Enantiomeric Purity

HPLC analysis on chiral stationary phase was performed on an Agilent 1200-series instrument. Daicel Chiralpak IA or IC columns with *i*-PrOH/*n*-hexane as the eluent were used. GC analysis on chiral stationary phase (Astec CHIRALDEX G-TA column) was performed on an Agilent 7890A-series instrument. HPLC and GC traces were compared to racemic samples prepared by performing the γ-substitution of α-branched enals (i) using 40 mol% of benzylamine and 40 mol% of TFA in CHCl$_3$ at 50 °C over 16 h in the case of the γ-alkylation reaction and (ii) using 20 mol% of *rac*-BINAM and 40 mol% of TFA in acetonitrile at 40 °C over 16 h in the case of the γ-chlorination reaction.

2.5.4 Preparation of the Starting Materials

Synthesis of (S)-2'-(2,5-diphenyl-1H-pyrrol-1-yl)-[1,1'-binaphthalen]-2-amine (catalyst 41a)

In a round bottom flask equipped with Dean-Stark apparatus, 1,4-diphenylbutane-1,4-dione (48 mg, 0.2 mmol, 1 equiv) and acetic acid (1 mL, 0.017mmol, 0.085 equiv) were added sequentially to a solution of (*S*)-BINAM in toluene (1 mL). The mixture was heated at 110 °C for 14 h, then

[36] M. Yamanaka, J. Itoh, K. Fuchibe, T. Akyiama. Chiral Brønsted Acid Catalyzed Enantioselective Mannich-Type Reaction. *J. Am. Chem. Soc.*, **2007**, *129*, 6756.

[37] P. Wipf, J. K. Jung. Formal Total Synthesis of (+)-Diepoxin σ. *J. Org. Chem.*, **2000**, *65*, 6319.

[38] M. Shi, X.-G. Liu. Asymmetric Morita-Baylis-Hillman Reaction of Arylaldehydes with 2-Cyclohexen-1-one Catalyzed by Chiral Bis(Thio)urea and DABCO. *Org. Lett.*, **2008**, *10*, 1043.

[39] C.-J. Wang, M. Shi. Highly Enantioselective Allylation of Arylaldehydes Catalyzed by a Silver(I)-Chiral Binaphthylthiophosphoramide. *Eur. J. Org. Chem.*, **2003**, *15*, 2823.

[40] N. Hunter, K. Vaughan. Synthesis and Characterization of a Series of 1,x-bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes. *J. Heterocyclic Chem.*, **2006**, *43*, 731.

[41] J.-Y. Fu, X.-Y. Xu, Y.-C. Li, Q.-C. Huang, L.-X. Wang. Effective Construction of Quaternary Stereocenters by Highly Enantioselective α-Amination of Branched Aldehydes. *Org. Biomol. Chem.*, **2010**, *8*, 4524.
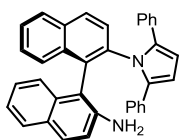
cooled to room temperature and concentrated *in vacuo*. The residue was portioned between dichloromethane and 1 M sodium hydroxide. The organic phase was separated and the aqueous phase extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by column chromatography (hexane/ethylacetate = 95:5) and the product obtained as pale yellow solid in 89% yield. HRMS *calcd*. for $(C_{36}H_{26}N_2 + H^+)$: 487.2174 found 487.2166. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.34 (d, 1H, J = 8.61 Hz), 8.18 (d, 1H, J = 8.61 Hz), 80.4 (d, 1H, J = 8.27 Hz), 7.69-7.59 (m, 2H), 7.54 (dd, 1H, J_1 = 6.85 Hz, J_2 = 1.18 Hz), 7.31-7.24 (m, 3H), 7.24-7.15 (m, 3H), 7.14-7.05 (m, 6H), 7.03 (dd, 1H, J_1 = 6.86 Hz, J_2 = 0.95 Hz), 6.72 (d, 1H, J = 8.74 Hz), 6.51 (dd, 1H, J_1 = 6.87 Hz, J_2 = 1.38 Hz), 6.18 (d, 1H, J = 3.81 Hz), 6.12 (d, 1H, J = 8.37 Hz), 6.07 (d, 1H, J = 3.81 Hz), 2.32 (bs, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 142.3, 138.2, 137.4, 136.9, 135.0, 134.2, 133.3, 133.28, 133.23, 131.3, 129.3, 128.3, 128.2, 128.1, 127.8, 127.6, 127.4, 127.3, 127.2, 127.15, 127.12, 126.0, 125.9, 125.6, 124.5, 121.5, 117.9, 112.2, 110.6, 110.3.

Preparation of α-Branched Enals[42]

R^1= Me, Et R^2= Et, Bn, Ar, *i*Pr, allyl
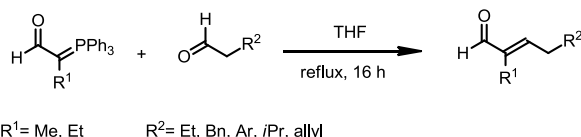
A mixture of linear aliphatic aldehyde (1 equiv) and the appropriate triphenylphosphorane (1.5 equiv) was dissolved in THF (0.5 M) and refluxed for 16 h. The solution was then allowed to reach room temperature; the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (silica gel) to yield the desired α-branched enals (yield 40-50%).

2.5.5 General Procedure for the Direct γ-Alkylation of α-Branched Enals

All the reactions were carried out in undistilled chloroform with no precautions to exclude moisture. In an ordinary vial equipped with a Teflon-coated stir bar, the chiral phosphoric acid (*S*)-**29a** or (*S*)-**29d** (0.03 mmol, 30 mol%) was added to a chloroform solution (1 mL) of the primary amine catalyst **22b** (0.015 mmol, 4.4 mg, 15 mol%). After the addition of the α-branched α-β-unsaturated aldehyde (0.2 mmol) the solution was stirred for 10 minutes at room temperature. The γ-alkylation was started by adding the alkylating agent **27** (0.1 mmol; 85% of purity, technical grade reagent). The vial was sealed, and the stirring continued at 50 °C for 16 h.

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[42] Adapted from: F. Gagosz. Unusual Gold(I)-Catalyzed Isomerization of 3-Hydroxylated 1,5-Enynes: Highly Substrate-Dependent Reaction Manifolds. *Org. Lett.*, **2005**, *7*, 4129.

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The crude reaction was directly purified by flash column chromatography (silica gel) to yield the desired product **28**.

(*R*)-4-benzyl-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (28a)
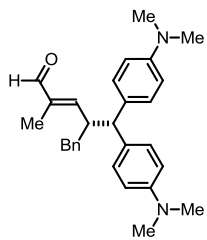
The reaction was carried out following the general procedure using the (*S*)-3,3'-bis(4-nitrophenyl)-1,1'binaphtyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ethylacetate = 85/15) in 84% yield and 95% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.08 min, τ_{minor} = 7.99 min; HRMS *calcd.* for ($C_{29}H_{34}N_2O$): 427.2749, found 427.2753; $[\alpha]_D^{25}$= -5.6 (*c* = 1.00, CHCl$_3$, 95% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.18 (s, 1H), 7.25-7.10 (m, 5H), 7.05-6.96 (m, 4H), 6.73 (d, 2H, *J* = 8.47 Hz), 6.54 (d, 2H, *J* = 8.51 Hz), 6.20 (d, 1H, J_t = 10.51 Hz), 3.78 (d, 1H, *J* = 10.34 Hz), 3.61 (dq, 1H J_q = 10.10 Hz, J_d = 3.29 Hz), 3.00 (dd, 1H, J_1 = 13.61 Hz, J_2 = 3.00 Hz), 2.92 (s, 6H), 2.84 (s, 6H), 2.40 (dd, 1H, J_1 = 13.35 Hz, J_2 = 9.97 Hz), 1.17 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$):δ 195.4, 157.4, 139.8, 139.6, 129.1, 128.6, 128.3, 128.12, 126.0, 113.1, 112.6, 54.9, 46.4, 40.7, 40.6, 39.8, 9.14.

(*S*)-4-benzyl-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (28a)

The reaction was carried out following the general procedure using 6'-hydroxy-9-amino-9-deoxyepiquinine as catalyst and the (*R*)-3,3'-bis(4-nitrophenyl)-1,1'binaphtyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ethylacetate = 85/15) in 89% yield and 90% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.99 min, τ_{minor} = 9.08 min; $[\alpha]_D^{25}$ = +5.1 (*c* = 1.00, CHCl$_3$, 90% *ee*).

The absolute configuration of compound **28a** was inferred by chemical correlation (See determination of the absolute configuration section for details).

(*R*)-5,5-bis(4-(dimethylamino)phenyl)-2,4-dimethylpent-2-enal (28b)

The reaction was carried out following the general procedure using the (*S*)-3,3'-bis(4-nitrophenyl)-1,1'binaphtyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a colourless oil by column chromatography (hexane/ ethylacetate = 85/15) in quantitative yield and 89% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 8.0 min, τ_{major} = 9.1 min; HRMS *calcd.* for ($C_{23}H_{31}N_2O$): 351.2436, found 351.2444; $[\alpha]_{26}^{D}$= -29 (*c* = 1.00, CHCl$_3$, 89% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.25 (s, 1H), 7.14 (d, 2H, J = 8.55 Hz), 7.04 (d, 2H, J = 8.70 Hz), 6.68 (d, 2H, J = 8.69 Hz), 6.58 (d, 2H, J = 8.61 Hz), 6.32 (d, 1H, J = 9.94 Hz), 3.63 (d, 1H, J = 10.47 Hz), 3.51-3.39 (m, 1H), 2.90 (s, 6H), 2.86 (s, 6H), 1.75 (s, 3H), 1.01 (d, 3H, J = 6.58 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 195.6, 160.4, 149.2, 149.0, 137.7, 132.2, 132.1, 128.6, 128.4, 112.9, 112.6, 56.3, 40.7, 40.6, 38.2, 19.0, 9.4.

(R)-4-(bis(4-(dimethylamino)phenyl)methyl)-2-methylhepta-2,6-dienal (28c)

The reaction was carried out following the general procedure using the (S)-3,3'-bis(4-nitrophenyl)-1,1'binaphtyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ ethylacetate = 85/15) in 65% yield and 94% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 5.9min, τ_{major} = 6.4 min. HRMS *calcd.* for (C$_{25}$H$_{32}$N$_2$O): 377.2593, found 377.2599; $[\alpha]_D^{26}$ = +15 (*c* = 1.00, CHCl$_3$, 94% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.25 (s, 1H), 7.15 (d, 2H, J = 8.79 Hz), 7.02 (d, 2H, J = 8.79 Hz); 6.68 (d, 2H, J = 8.78 Hz), 6.56 (d, 2H, J = 8.78 Hz); 6.24 (dd, 1H, $J1$ = 10.47 Hz, $J2$ = 0.99 Hz), 5.72-5.59 (m, 1H), 5.00-4.87 (m, 2H), 3.73 (d, 1H, J = 10.46 Hz), 3.45 (dq, 1H, J_q = 10.30 Hz, J_d = 3.61 Hz), 2.90 (s, 6H), 2.85 (s, 6H), 2.41-2.30 (m, 1H), 2.07-1.96 (m, 1H), 1.69 (d, 3H, J = 0.86 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 195.5, 158.1, 139.2, 135.4, 128.6, 128.4, 116.9, 113.0, 112.7, 54.4, 43.6, 40.7, 40.6, 37.8, 9.93.
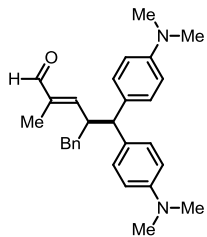
(R)-4-(bis(4-(dimethylamino)phenyl)methyl)-2,5-dimethylhex-2-enal (28d)

The reaction was carried out following the general procedure using the (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a yellow solid by column chromatography (hexane/ ethylacetate = 85/15) in 80% yield and 87% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 4.4 min, τ_{major} = 5.2 min. HRMS *calcd.* for (C$_{25}$H$_{34}$N$_2$O): 379.2749, found 379.2758; $[\alpha]_D^{25}$ = + 8.0 (*c* = 0.50, CHCl$_3$, 87% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.23 (s, 1H), 7.17 (d, 2H, J = 8.45 Hz), 7.02 (d, 2H, J = 8.83 Hz), 6.67 (d, 2H, J = 8.69 Hz), 6.53 (d, 2H, J = 8.80 Hz), 6.29 (d, 1H, J = 11.03 Hz), 3.84 (d, 1H, J = 11.23 Hz), 3.37 (dt, 1H, J_t = 11.18 Hz, J_d = 3.06 Hz), 2.89 (s, 6H), 2.83 (s, 6H), 1.96-1.84 (m, 1H), 1.70 (s, 3H), 0.88 (d, 3H, J = 6.97 Hz), 0.82 (d, 3H, J = 6.97 Hz). ^{13}C NMR (400 MHz, CDCl$_3$): δ 195.5, 156.2, 149.1, 148.9, 140.6, 128.3, 112.9, 112.7, 128.3, 126.5, 112.7, 52.68, 48.7, 40.7, 40.6, 29.8, 22.1, 15.7, 10.1.
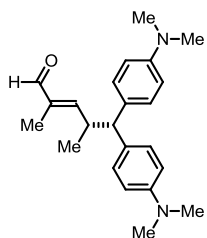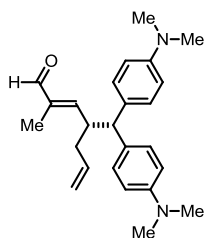
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(*R*)-4-(Bis(4-dimethylamino)phenyl)methyl)-2-ethylhex-2-enal (28e)

The reaction was carried out following the general procedure using the (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a pale yellow oil by column chromatography (hexane/diethyl ether = 9/1) in 58% yield and 82% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 15.0 min, τ_{major} = 16.7 min. HRMS *calcd.* for ($C_{25}H_{34}N_2O$): 378.2671, found 378.2679; $[\alpha]_D^{25}$ = + 18.1 (*c* = 1.00, CHCl$_3$, 82% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.82 (t, 3H, *J* = 7.04 Hz), 0.93 (t, 3H, *J* = 7.04 Hz), 2.25(q, 2H, *J* = 8.17 Hz), 2.86 (s, 6H), 2.92 (s, 6H), 3.27-3.35 (m, 1H), 3.37 (d, 1H, *J* = 9.68 Hz), 6.17 (d, 1H, *J* = 10.97 Hz), 6.57 (d, 2H, *J* = 8.8 Hz), 6.69 (d, 2H, *J* = 8.8 Hz), 7.04 (d, 2H, *J* = 8.8 Hz), 7.17 (d, 2H, *J* = 8.7 Hz), 9.25 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.3, 12.9, 18.43, 26.28, 40.4, 40.6 , 44.9, 55.1, 112.6, 112.9, 128.5, 128.9, 128.5, 128.7, 131.9, 132.2, 145.3, 149.4, 158.9, 195.7.

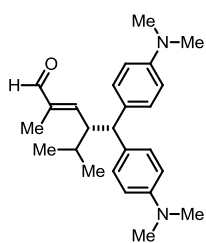### (*R*)-4-benzyl-5,5-(Bis(4-dimethylamino)phenyl)-2-ethylpent-2-enal (28f)
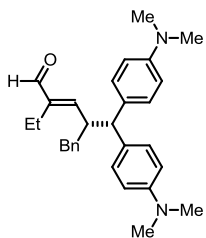
The reaction was carried out following the general procedure using the (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a pale yellow oil by column chromatography (hexane/diethyl ether = 8/2) in 82% yield and 72% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 20.3 min, τ_{minor} = 21.06 min. HRMS *calcd.* for ($C_{30}H_{36}N_2O$): 441.2906, found 441.2910; $[\alpha]_D^{25}$ = - 8.1 (*c* = 1.00, CHCl$_3$, 82% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.46 (t, 3H, *J* = 7.25 Hz), 1.69(q, 2H, *J* = 6.70 Hz), 2.42-2.49 (m, 1H), 2.86 (s, 6H), 2.95 (s, 6H), 3.01 (d, 1H, *J* = 9.68 Hz), 3.58-3.67 (m, 1H), 3.78 (d, 1H, *J* = 10.28 Hz), 6.16 (d, 1H, *J* = 10.21 Hz), 6.55 (d, 2H, *J* = 9.05 Hz), 6.75 (d, 2H, *J* = 8.5 Hz), 7.01-7.23 (m, 9H), 9.19 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.1, 18.05, 40.0, 40.1, 46.5, 55.2, 112.0, 112.5, 125.8, 128.2, 128.4, 128.8, 129.3, 131.6, 131.7, 139.4, 144.8, 149.1, 149.3, 156.1, 195.4.

(*R*)-2,4-dibenzyl-5,5-bis(4-(dimethylamino)phenyl)pent-2-enal (28g)
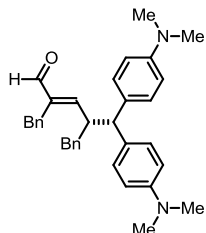
The reaction was carried out following the general procedure using (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a pale yellow oil by column chromatography (hexane/diethyl ether = 7/3) in 72% yield and 73% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.8 min, τ_{minor} =

11.5 min. HRMS *calcd.* for ($C_{35}H_{38}N_2O$): 503.3066, found 503.3062; $[\alpha]_D^{25}$ = - 21.2 (*c* = 1.00, CHCl$_3$, 73% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.44-2.50 (m, 1H), 2.68 (d, 1H, *J* = 15.2 Hz), 2.99 (s, 6H), 3.04 (s, 6H), 3.00 (dd, 1H, *J$_1$* = 3.3 Hz, *J$_2$* = 13.6 Hz), 3.11 (d, 1H, *J* = 15.3 Hz), 3.66 (m, 1H), 3.76 (d, 1H, *J* = 10.1Hz), 6.38 (d, 1H, *J* = 9.7 Hz), 6.46 (d, 2H, *J* = 9.1 Hz), 6.73 (d, 2H, *J* = 9.1 Hz), 6.85 (d, 2H, *J* = 9.1 Hz), 7.01 (d, 2H, *J* = 9.1 Hz), 7.14-7.24 (m, 9H), 9.36 (s, 1H). ^{13}C NMR (400 MHz, CDCl$_3$): δ 29.4, 29.7,40.6, 46.5, 54.9, 68.84, 112.7, 113.2, 126.5, 128.7, 129.4, 131.0, 131.8, 139.6, 142.4, 149.6, 159.2, 195.35.
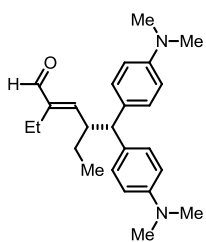
(*R*)-5,5-(Bis(4-dimethylamino)phenyl)-4-methyl-2-phenylpent-2-enal (28h)
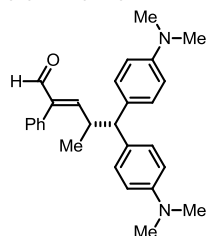
The reaction was carried out following the general procedure using (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a pale yellow oil by column chromatography (hexane/diethyl ether = 7/3) in 71% yield and 45% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ*$_{major}$* = 20.3 min, τ*$_{minor}$* = 21.06 min. HRMS *calcd.* for ($C_{28}H_{32}N_2O$): 435.2427, found 435.2436; $[\alpha]_D^{26}$ = - 81.5 (*c* = 1.00, CHCl$_3$, 82% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.07 (d, 3H, *J* = 6.69 Hz), 2.88 (s, 6H), 2.89 (s, 6H), 3.33-3.40 (m, 1H), 3.62 (d, 1H, *J* = 10.78 Hz), 6.53-6.58 (m, 4H), 6.88 (d, 2H, *J* = 8.09 Hz), 7.00 (d, 2H, *J* = 8.67 Hz), 7.06 (d, 2H, *J* = 8.6 Hz), 7.38-7.47 (m, 3H), 9.46 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.81, 38.4, 40.8, 56.5, 112.7, 112.9, 127.8, 128.2, 128.6, 129.4, 133.2, 142.9, 149,6, 161.6, 194.4.

(*R*)-5,5-bis(4-(dimethylamino)phenyl)-2-methyl-4-phenylpent-2-enal (28i)

The reaction was carried out at 10°C following the general procedure using the (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ ethylacetate = 85/15) in 63% yield and 90% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ*$_{minor}$* = 9.8 min, τ*$_{major}$* = 10.7 min; HRMS *calcd.* for ($C_{28}H_{33}N_2O$): 413.2593, found 413.2596; $[\alpha]_D^{26}$ = - 6.8 (*c* = 1.30, CHCl$_3$, 90% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.24 (s, 1H), 7.22-7.16 (m, 2H), 7.16-7.07 (m, 6H), 6.93 (d, 2H, *J* = 8.58 Hz), 6.65-6.59 (m, 3H), 6.50 (d, 2H, *J* = 8.56 Hz), 4.49 (t, 1H, *J* = 10.44 Hz), 4.25 (d, 1H, *J* = 11.03 Hz), 2.88 (s, 6H), 2.81 (s, 6H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 195.4, 157.0, 149.1, 141.8, 138.0, 128.8, 128.7, 128.5, 128.3, 126.5, 112.7, 112.6, 55.5, 50.3, 40.7, 40.6, 9.5.

UNIVERSITAT ROVIRA I VIRGILI
ASSESSING THE VERSATILITY OF ORGANOCATALYSIS AS A STRATEGY FOR ENABLING NOVEL ASYMMETRIC TRANSFORMATI
Giulia Bergonzini
Dipòsit Legal: T 1661-2014

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(R)-4-(4-chlorophenyl)-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (28j)
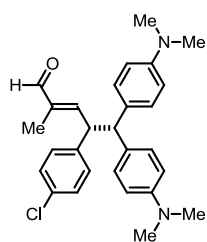
The reaction was carried out at 10 °C following the general procedure using the (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ diethyl ether = 90/10) in 61% yield and 82% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 9/1 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 9.8 min, τ_{major} = 10.7 min. HRMS *calcd.* for ($C_{28}H_{31}ClN_2O$): 447.2224, found 447.2203; $[\alpha]_D^{25}$ = - 6.8 (*c* = 1.00, CHCl₃, 82% *ee*).

^{1}H NMR (400 MHz, CDCl₃): δ 9.27 (s, 1H), 7.19 (d, 2H, *J* = 8.82 Hz), 7.10 (t, 3H, *J* = 8.8 Hz), 6.94 (d, 2H, *J* = 8.58 Hz), 6.64-6.57 (m, 3H), 6.53 (d, 2H, *J* = 8.56 Hz), 4.51 (t, 1H, *J* = 10.32 Hz), 4.21 (d, 1H, *J* = 11.30 Hz), 2.91 (s, 6H), 2.84 (s, 6H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, CDCl₃): δ 195.2, 156.2, 149.2, 140.1, 138.4, 132.2, 129.6, 128.8, 128.7, 112.7, 55.6, 49.7, 40.6, 9.5.

(R)-4-(4-methoxyphenyl)-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (28k)
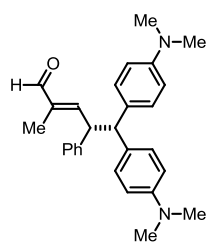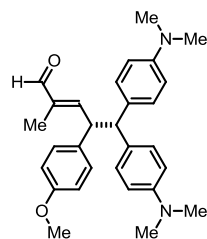
The reaction was carried out at 10 °C following the general procedure using the (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ diethyl ether = 90/10) in 72% yield and 86% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 8/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 21.9 min, τ_{major} = 25.8 min. HRMS *calcd.* for ($C_{29}H_{34}N_2O_2$): 465.2505, found 465.2518; $[\alpha]_D^{26}$ = - 9.8 (*c* = 1.00, CHCl₃, 86% *ee*).

^{1}H NMR (400 MHz, CDCl₃): δ 9.25 (s, 1H), 7.11 (d, 2H, *J* = 8.78 Hz), 7.08 (d, 2H, *J* = 8.55 Hz), 6.94 (d, 2H, *J* = 8.38 Hz); 6.71 (d, 2H, *J* = 8.81 Hz), 6.61 (d, 2H, *J* = 8.81 Hz), 6.53 (d, 2H, *J* = 8.56 Hz), 4.51 (t, 1H, *J* = 10.32 Hz), 4.27 (d, 1H, *J* = 10.57 Hz), 3.75 (s, 3H), 2.91 (s, 6H), 2.84 (s, 6H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, CDCl₃): δ 195.2, 158.2, 157.4, 149.2, 149.7, 137.7, 133.8, 131.3, 129.6, 128.8, 113.7, 55.6, 49.7, 40.7, 9.4.

3-(bis(4-(dimethylamino)phenyl)methyl)cyclohex-1-enecarbaldehyde (31)
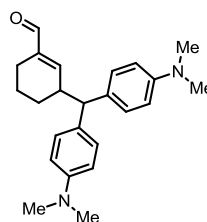
The reaction was carried out following the general procedure using the (*S*)-3,3'-bis(4-nitrophenyl)-1,1'binaphtyl-2,2'-diyl hydrogenphosphate as acid to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/ethylacetate = 85/15) in 82% yield and 89% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.7 min, τ_{minor} = 10.0 min. HRMS *calcd.* for ($C_{24}H_{30}N_2O$): 385.2280, found 385.2274; $[\alpha]_D^{26}$ = - 8.1 (*c* = 1.00, CHCl₃, 89% *ee*).

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.26 (s, 1H), 7.16 (d, 2H, J = 8.67 Hz), 7.12 (d, 2H, J = 8.80 Hz), 6.71-6.64 (m, 4H), 6.62 (bs, 1H), 3.54 (d, 1H, J_t = 11. 14 Hz), 3.18-3.08 (m, 1H), 2.90 (s, 6H), 2.89 (s, 6H), 2.34-2.31 (m, 1H), 2.13-2.00 (m, 1H), 1.89-1.67 (m, 2H), 1.58-1.42 (m, 1H), 1.24-1.19 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 194.9, 154.6, 149.2, 149.1, 141.6, 131.9, 131.4, 128.6, 128.3, 113.0, 112.9, 54.9, 41.1, 40.7, 40.7, 28.1, 21.7, 20.7.

4-chloro-2-methylpentanal (39a)
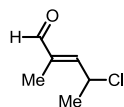
The reaction was carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, the chiral phosphoric acid (*S*)-**29a** (0.04 mmol, 40 mol%) was added to a solution of (*S*)-BINAM (0.02 mmol, 20 mol%) in 0.2 mL of toluene. After the addition of the α-branched α-β-unsaturated aldehyde **38** (0.1 mmol) the solution was stirred for 10 minutes at room temperature. The γ-chlorination was started by adding the chlorinating agent **34** (0.12 mmol, 1.2 equiv). The vial was sealed, and the stirring continued at 40 °C for 16h. The crude reaction was directly purified by flash column chromatography (hexane/ethylacetate = 98/2) to yield the desired product as pale yellow oil in 58% yield and 42% *ee*. The *ee* was determined by GC analysis on Astec CHIRALDEX G-TA column: 50 °C to 70 °C (ramp 5 °C per minute), isotherm at 70 °C for 15 min, 70 °C to 90 °C (ramp 5 °C per minute), then isotherm at 90 °C for 10 minutes; flow rate = 1.00 ml/min, τ_{major} = 33.1 min, τ_{minor} = 32.8 min.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.46 (s, 1H), 6.43 (dq, 1H, J_d = 9.64 Hz, J_q = 1.42 Hz), 4.94 (dq, 1H, J_d = 9.58 Hz, J_q = 6.60 Hz), 1.81 (d, 3H, J = 1.42 Hz), 1.68 (d, 3H, J = 6.60 Hz).

2.5.6 Determination of the Absolute Configuration for the γ-Alkylation Reaction

The absolute configuration of compound **28a** was inferred by chemical correlation (Scheme 12). Following the procedure described by Benfatti *et al.,*[17] compound **A** was synthesized in 82% *ee* and (*R*) absolute configuration. After homologation and reduction of the carbonyl the alcohol (*S*)-**C** was obtained. By comparison of the HPLC traces and $[\alpha]_D^{25}$ values of the alcohols **D** (directly obtained from the reduction with sodium borohydride of the product **28a**) and (*S*)-**C**, it was possible to assign the absolute configuration of the stereocenter generated in the organocatalytic reaction. All other absolute configurations were assigned by analogy based on a uniform reaction mechanism.
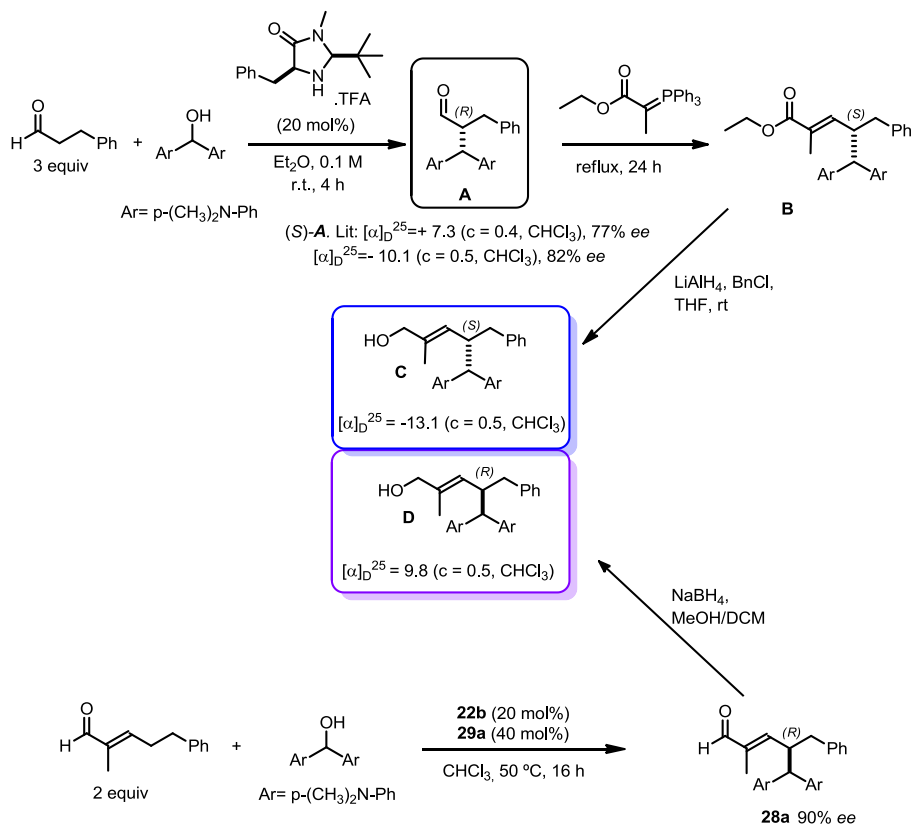
Scheme 12. Determination of the Absolute configuration of product **28a**.

Preparation of ester B
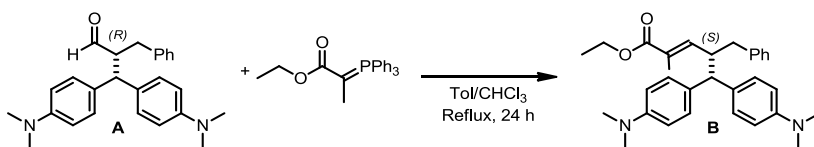
A solution of **A**[17] (0.17mmol, 67mg) and (carbethoxyethylidene)triphenyl-phosphorane (2 equiv, 0.34 mmol) in toluene/CHCl$_3$ (1 mL/0.2 mL) was refluxed for 24h. After cooling to room temperature, the resulting mixture was concentrated under reduced pressure to give a crude product that was purified by flash column chromatography (hexane/diethyl ether = 9/1) giving the pure ester **B** as a white solid in 80% yield (63 mg, 0.13 mmol).

Preparation of alcohol C

Method A[43]:
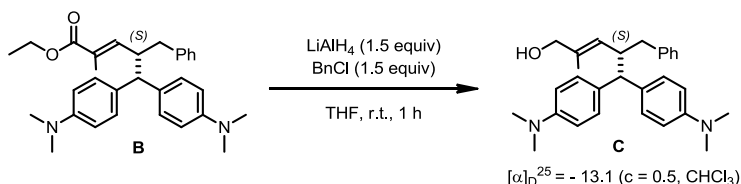
A solution of BnCl (1.5 equiv) was added in dry THF (1 mL/mmol) was added dropwise at room temperature to a stirred suspension of LiAlH$_4$ (1.5 equiv) in dry THF (4 mL/mmol). After stirring for 15 min, a solution of α,β-unsaturated ester **B** in dry THF was added dropwise to the suspension. The reaction mixture was stirred at room temperature for 2 hours. Then the reaction was quenched with water, filtered and the filtrate was dried with MgSO$_4$. The solvent was concentrated under reduced pressure and the crude product **C** was isolated by column chromatography (hexane/diethyl ether = 8/2) in 86% yield.

Method B
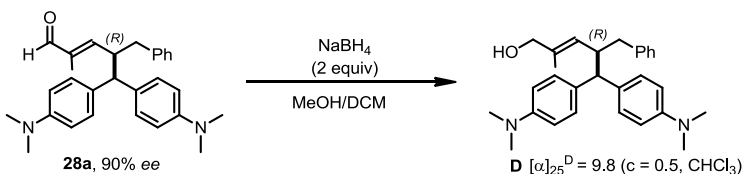
A suspension of NaBH$_4$ (0.08 mmol, 3 mg, 4 equiv) in MeOH was added dropwise to a solution of aldehyde **28a** (0.02 mmol, 8.56 mg, 90% *ee*) in MeOH/DCM (1/1) at 0 °C. The reaction was stirred at the same temperature for 30 min, quenched with H$_2$O (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was concentrated under reduced pressure and the crude product was isolated by column chromatography (hexane/diethyl ether = 8/2) in 92% yield (7.8 mg, 0.018mmol).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25-7.03 (m, 9H), 6.75 (d, 2H, *J* = 9.56), 6.60 (d, 2H, *J* = 8.78 Hz), 5.13 (d, 1H, *J* = 10.02 Hz), 3.73 (m, 1H), 3.67(d, 1H, *J* = 10.63 Hz), 3.30 (m, 1H), 2.9 (s, 6H), 2.8 (s, 6H), 2.3 (m, 2H).

[43] Wang, X.; Li, X.; Xue, J.; Zhao, Y.; Zhang, Y. A Novel and Efficient Procedure for the Preparation of Allylic Alcohols from α,β-Unsaturated Carboxylic Esters Using LiAlH$_4$/BnCl. *Tetrahedron Lett.,* **2009**, *50*, 413.

2.5.7 GC Traces for the γ-Chlorination of 2-Methyl-2-Pentenal
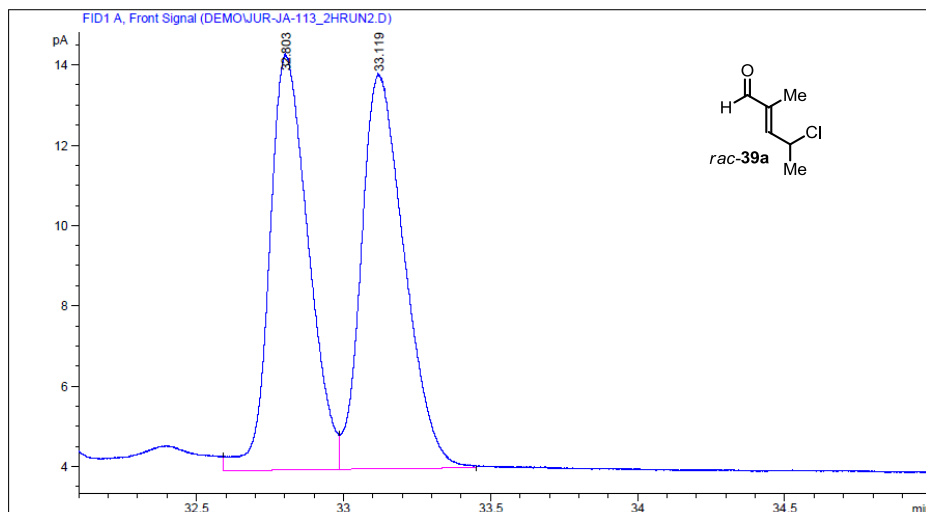
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.803	VV	0.1391	94.66942	10.31587	48.6722
2	33.119	VB	0.1459	99.83453	9.81098	51.3278
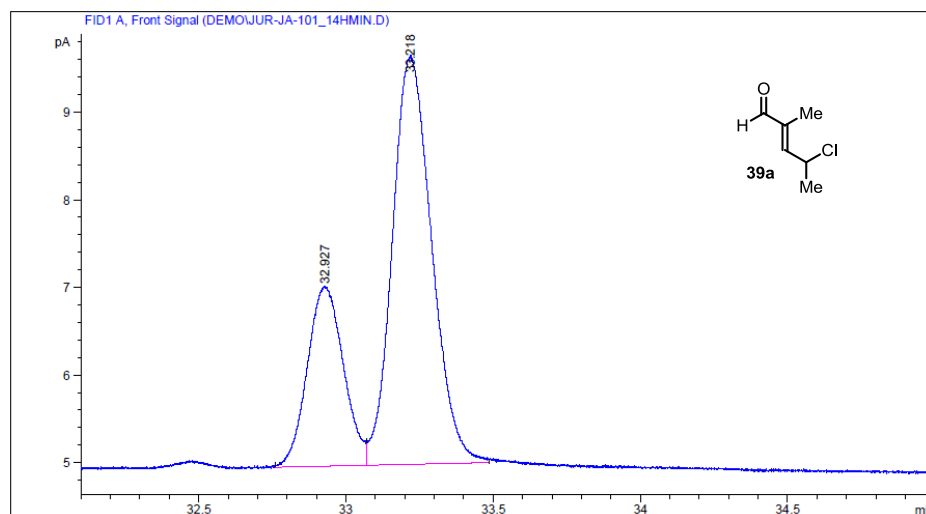
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.927	BV	0.1102	17.48130	2.04285	28.7885
2	33.218	VB	0.1232	43.24199	4.63686	71.2115

Chapter III

Dioxindole in Asymmetric Catalytic Synthesys: New Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles

Target

Identify a direct and novel catalytic asymmetric route to access enantioenriched 3-substituted 3-hydroxyoxindoles which are regarded as important scaffolds found in biologically active compounds.

Tool

The inherent nucleophilicity of dioxindole (3-hydroxy-2-oxindole) and its application in asymmetric catalytic processes.[1]
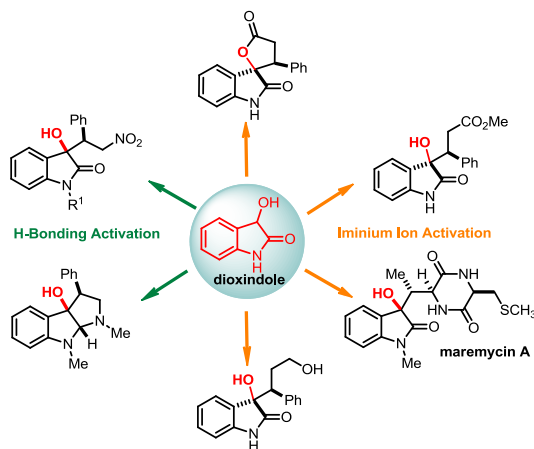
3.1   Background

The dioxindole framework featuring a hydroxyl-bearing tetrasubstituted carbon stereocenter at the 3-position is recognized as a privileged heterocyclic motif. It represents the core of a large family of bioactive natural products and a series of pharmaceutically active compounds (Figure 1).[2] It has been shown that a well stereochemical arrangement of this structure greatly influences the biological activity. Therefore, development of synthetic routes to a C_3-stereogenic

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[1] The work discussed in this chapter has been published. See: a) G. Bergonzini, P. Melchiorre. Dioxindole in Asymmetric Synthesis: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A. *Angew. Chem. Int. Ed.*, **2012**, *51*, 971. b) M. Retini, G. Bergonzini, P. Melchiorre. Dioxindole in Asymmetric Synthesis: Direct Access to 3-Substituted 3-Hydroxy-2-Oxindoles *via* 1,4-Additions to Nitroalkenes. *Chem. Commun.*, **2012**, *48*, 3336.

[2] S. Peddibhotla. 3-Substituted-3-Hydroxy-2-Oxindole, an Emerging New Scaffold for Drug Discovery with Potential Anti-Cancer and other Biological Activities. *Curr. Bioact. Compd.*, **2009**, *5*, 20.

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center, retaining the hydroxyl moiety, is of paramount importance. This has provided the impetus for developing highly stereoselective routes to this particular target structure.
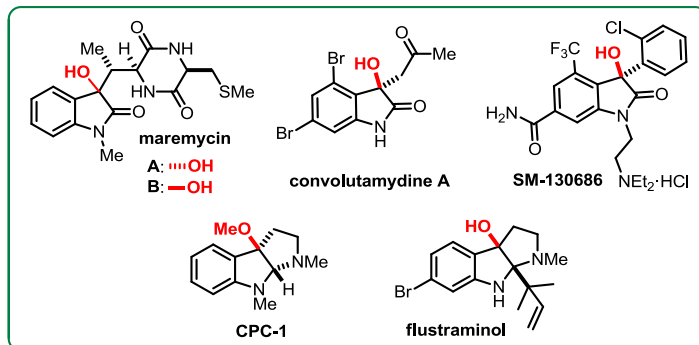
Figure 1. Naturally occurring and biologically active 3-hydroxyoxindoles derivatives.
Me = methyl. Et = ethyl.

In the last few years, different catalytic asymmetric methodologies have been reported, including metal-based and organocatalytic methods.[3] These strategies mainly rely on: (i) nucleophilic additions to isatins, (ii) intramolecular arylation reactions and (iii) the direct hydroxylation of 3-substituted oxindoles by means of the deprotonative activation of racemic 3-alkyl- or aryl-substituted oxindoles (Scheme 1).[4]
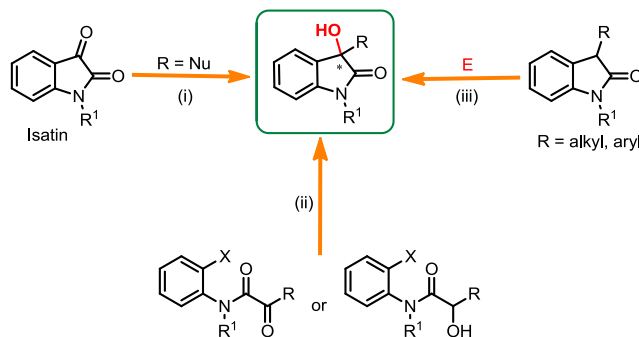
Scheme 1. Synthetic strategies for the catalytic asymmetric synthesis of 3-hydroxyoxindoles. Nu = nucleophile, E = oxygen-centered electrophile.

In particular, using the deprotonative activation and the subsequent asymmetric addition to oxygen-centered electrophiles, catalytic asymmetric hydroxylation of 3-aryl and 3-alkyl-

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[3] F. Zhou, Y.-L. Liu, J. Zhou. Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position. *Adv. Synth. Catal.*, **2010**, *352*, 1381.

[4] A. Kumar, S. S. Chimni. Catalytic Asymmetric Synthesis of 3-Hydroxyoxindole: a Potentially Bioactive Molecule. *RSC Advances*, **2012**, *2*, 9748.

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oxindoles has been developed using oxaziridines,[5] molecular oxygen,[6] and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)[7] as oxidants (Figure 2a). Moreover, asymmetric O-selective aminooxylation and benzoyloxylation of 3-substituted oxindoles have been reported providing a method for the construction of a C-O bond and the creation of a tetrasubstituted stereogenic center at the C_3 position of oxindoles.[8,9]
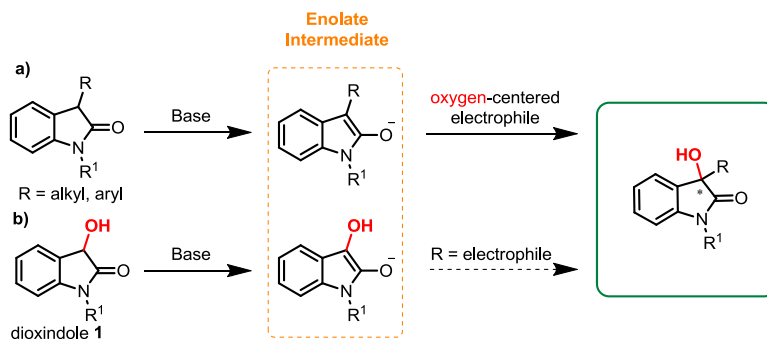
Figure 2. Deprotonative activation of 3-substituted oxindole and dioxindole derivatives for the synthesis of 3-substituted-3-hydroxyoxindoles.

We reasoned that dioxindole (3-hydroxy-2-oxindole) **1** could be used as a competent nucleophile under deprotonative activation conditions (Figure 2b). The nucleophilic addition of **1** (which has already installed the valuable hydroxyl moiety at the C_3-oxindole position) to an electrophile, would avoid the needing of using oxygen-centered electrophiles. This approach would greatly broaden the range of electrophiles amenable to an asymmetric transformation, providing an unexplored and versatile strategy for stereoselectively accessing chiral frameworks of high synthetic value. Given this synthetic potential, it was surprising that dioxindole had never been used as a competent nucleophile in conjugate addition pathways. The only precedent was published in 1956, where it was reported that the tetrahydropyranyl ether of dioxindole **1** was

[5] T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa. Lewis Acid-Catalyzed Enantioselective Hydroxylation Reactions of Oxindoles and α-Keto Esters Using DBFOX Ligand. *J. Am. Chem. Soc.,* **2006**, *128*, 16488.

[6] D. Sano, K. Nagata, T. Itoh. Catalytic Asymmetric Hydroxylation of Oxindoles by Molecular Oxygen Using a Phase-Transfer Catalyst. *Org. Lett.,* **2008**, *10*, 1593.

[7] K. Shen, X. Liu, G. Wang, L. Lin, X. Feng. Facile and Efficient Enantioselective Hydroxyamination Reaction: Synthesis of 3-Hydroxyamino-2-Oxindoles Using Nitrosoarenes. *Angew. Chem. Int. Ed.,* **2011**, *50*, 4684.

[8] T. Bui, N. R. Candeias, C. F. Barbas III. Dimeric Quinidine-Catalyzed Enantioselective Aminooxygenation of Oxindoles: an Organocatalytic Approach to 3-Hydroxyoxindole Derivatives. *J. Am. Chem. Soc.*, **2010**, *132*, 5574.

[9] Z. Zhang, W. Zheng, J. C. Antilla. Highly Enantioselective Catalytic Benzoyloxylation of 3-Aryloxindoles Using Chiral VAPOL Calcium Phosphate. *Angew. Chem. Int. Ed.,* **2011**, *50*, 1135.

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successfully reacted with ethyl acrylate in the presence of alkali alcoholates (Scheme 2).[10] Nevertheless, when the authors tried to directly use dioxindole **1** in the Michael addition under strongly basic conditions, they obtained "deeply colored mixtures and… intractable tars".[11]
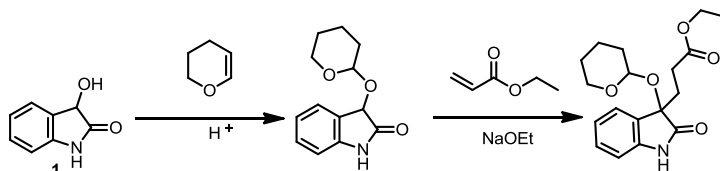
Scheme 2. Michael addition of the tetrahydropyranyl ether of dioxindole with ethyl acrylate.

Despite the lack of literature reports, we believed that dioxindole could participate as a nucleophile in conjugate addition reactions as readily as, or more readily than, 3-alkyloxindoles. Motivated by our interest in devising new and versatile strategies for stereoselectively accessing 3-substituted-3-hydroxyoxindoles we thus investigated the feasibility of an organocatalytic stereocontrolled conjugate addition of dioxindole to Michael acceptors under basic conditions.

3.2   Understanding the Dioxindole Reactivity

In order to evaluate our reasoning, we examined the reactivity of compound **1** under different conditions. Dioxindole was easily derived from commercially available isatin by simple reduction as described in Section 3.6.7. Extensive studies, with selected results summarized in Table 1, eventually allowed us to tame the strong nucleophilic character of dioxindole **1**.

We first examined the feasibility of a deprotonative activation of dioxindole. Exposure of a solution of **1** to an aerobic atmosphere and in the presence of a base (i.e. a tertiary amine such as 1,4-diazabicyclo[2.2.2]octane (DABCO), quinine, or Takemoto catalyst **C**; see entries 1, 2, 5 in Table 1) led to the fast and almost quantitative formation of isatide, the pinacol dimeric form of **1**, which was isolated as an insoluble white solid.

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[10] P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, S. Hamashige. Studies in the Indole Series. XVI. Oxindole-3-alanine and Dioxindole-3-alanine. *J. Am. Chem. Soc.*, **1956**, *78*, 3503.

[11] P. L. Julian, H. C. Printy, E. E. Dailey. Studies in the Indole Series. XV. Dioxindole-3-propionic Acid. *J. Am. Chem. Soc.*, **1956**, *78*, 3501.

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Table 1. Understanding the dioxindole reactivity[a]
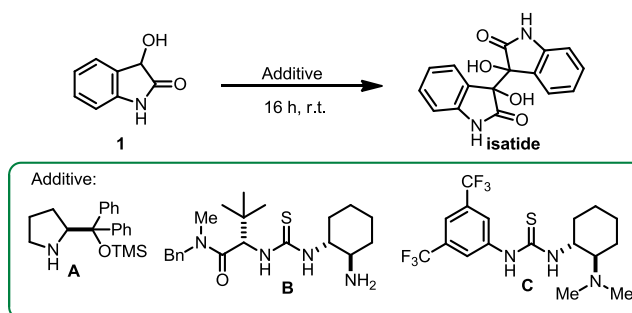
Entry	additive (mol%)	Yield (%)[b] Isatide[c]
1	DABCO (5)	39
2	Quinine (5)	37
3	**A** (5)	11
4[d]	**B** (20)	15
5[d]	**C** (20)	32

[a] Studies carried out using 0.1 mmol of **1** in 0.1 mL of acetone. [b] Determined by ^{1}H NMR analysis of the crude mixture after evaporation of the solvent and dilution in 0.6 mL of deuterated dimethyl sulfoxide (DMSO-d6) in which also the isatide is quantitatively detectable (completely soluble). [c] The maximum yield for isatide is 50%, because two oxindole units are merged. [d] Reaction carried out using 0.4 mL of dichloromethane as solvent. Ph = phenyl; Me = methyl; Bn = benzyl; TMS = trimethylsilyl.

The oxidative dimerization of dioxindole under strong basic conditions (Scheme 3a) which leads to isatide formation, has been already reported.[12,13,14,15] The first step involves the deprotonation of **1** followed by oxidation of the enolate **I** to a radical **II** by molecular oxygen. Subsequent collapse of the radical intermediate **II** by a radical-radical coupling mechanism affords the observed isatide. The dioxindole radical **II** as an intermediate has been proposed by Koch *et al.*[14] They reported that **II** is a merostabilized carbon free radical in that the radical is highly stabilized due to the conjugative stabilizing effect of the electron-withdrawing carbamido group and the electron-donating hydroxyl substituent, a phenomenon named the captodative

[12] G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer, R. Blankespoor. Semidiones. X. Semidione Radical Anions Derived from Indan-2,3-dione, Coumaran-2,3-dione, Thianaphthalenequinone, Isatin, and N-Hydroxyisatin. Nitroxide Radicals Derived from Isatin, Dioxindole, Oxindole, and Other Indole Derivatives. *J. Am. Chem. Soc.*, **1970**, *92*, 2762.

[13] E. Ziegler, T. Kappe, R. Salvador. Synthesen von Heterocyclen, 44. Mit: Eine Synthese des Isatins. *Monatsh. Chem.,* **1963**, *94*, 453.

[14] R. W. Bennett, D. L. Wharry, T. H. Koch. Formation Kinetics of an Amino Carboxy Type Merostabilized Free Radical. *J. Am. Chem. Soc.*, **1980**, *102*, 2345.

[15] O. J. Sonderegger, T. Bürgi, L. K. Limbach, A. Baiker. Enantioselective Reduction of Isatin Derivatives over Cinchonidine Modified Pt/Alumina. *J. Mol. Cat. A*, **2004**, *217*, 93.

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effect.[16] By stabilizing the radical, the captodative effect favors homolytic reactions such as dimerization or coupling, wich in this case lead to the formation of isatide. The easy generation of merostabilized radicals by the oxidation of the corresponding captodative carbanions is due to the destabilization effect of the electron-donating group on the negatively charged intermediate. This is the reason why the oxidation of captodative carbanions to merostabilized radicals can be simply achieved in the presence of oxygen.[17]
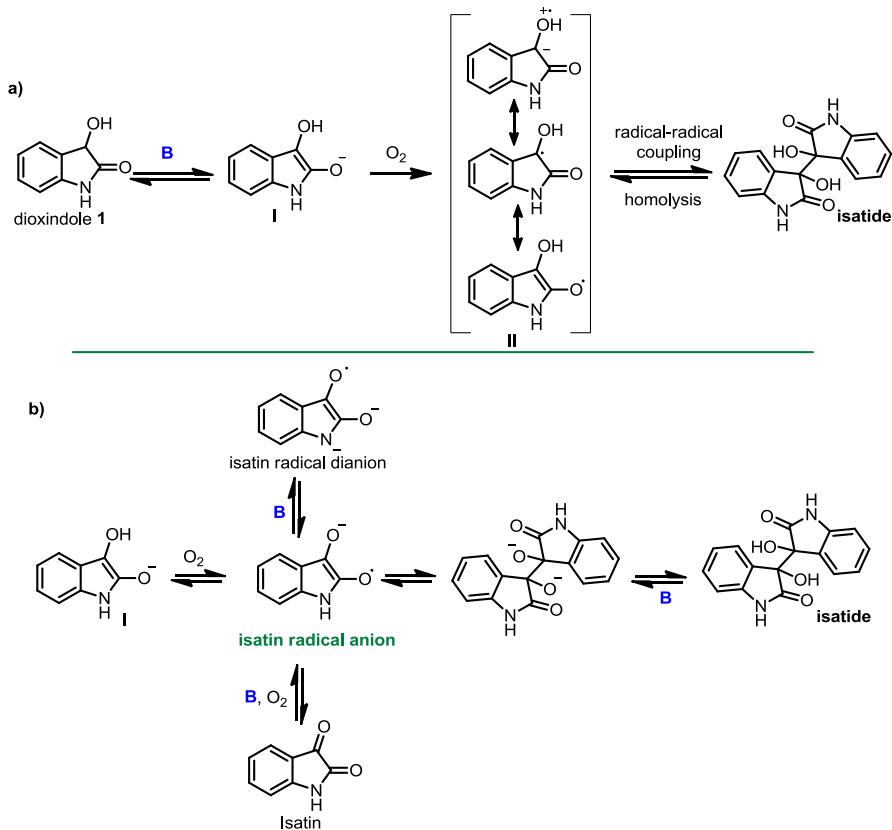
Scheme 3. The dioxindole oxidative coupling pathway leading to isatide. B = base.

A different oxidative pathway has instead been proposed by Russell *et al.* (Scheme 3b).[12] The authors reported that in highly basic conditions (dimethyl sulfoxide solutions of potassium *tert*-butoxide) dioxindole reacts with traces of oxygen to yield the corresponding isatin radical anion (or dianion depending on the basicity of the media) as intermediate in the dimerization process.

[16] H. G. Viehe, Z. Janousek, R. Merenyi, L. Stella. The Captodative Effect. *Acc. Chem. Res.*, **1985**, *18*, 148.
[17] G. A. Russell, G. Kaupp. Oxidation of Carbanions. IV. Oxidation of Indoxyl to Indigo in Basic Solution. *J. Am. Chem. Soc.*, **1969**, *91*, 3851.

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The radical isatin anion and dianion were also produced starting from isatin or isatide by treatment with dimethyl sulfoxide (DMSO) containing potassium *tert*-butoxide as the base. Once isatide is formed, it has already been shown that it can undergo a disproportionation reaction leading to dioxindole **1** and isatin (Scheme 4).[15]
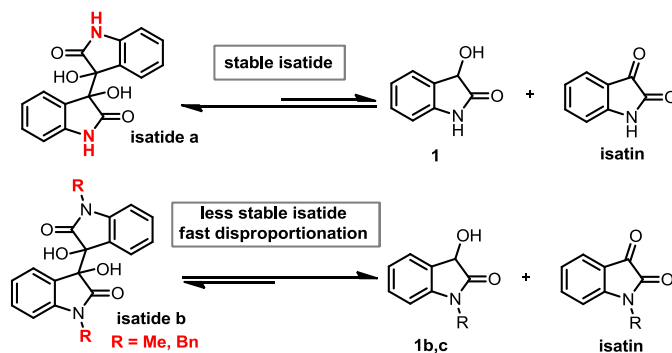
Scheme 4. The disproportionation of isatide.

We detected that isatides derived from the free amide or *N*-protected dioxindoles (**a** and **b** in Scheme 4) show different stability under basic conditions. While isatide **a** is a persistent and stable species under basic conditions (most likely due to its low solubility), isatide **b** easily disproportionates to the corresponding *N*-protected isatin and dioxindole.

Having identified the difficulties linked to the use of dioxindole as potential nucleophile under strongly basic conditions, we reasoned that the use of a milder, less basic organocatalyst could minimize the amount of the transiently generated enolate intermediate **I** and the subsequent oxidative coupling, while channeling the nucleophilicity of the dioxindole toward a more productive reaction pathway (Scheme 5).
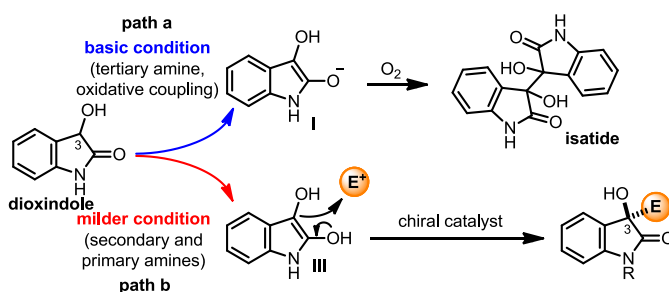
Scheme 5. Taming the dioxindole reactivity: in the presence of a tertiary amine and trace of oxygen, an oxidative enolate coupling leads to the formation of the dimeric isatide (path a). Milder reaction conditions (i.e. the use of a secondary amine) preserve the intrinsic high nucleophilic power of dioxindole (path b).

We found that dioxindole can coexist with the chiral secondary and primary amines **A** and **B** (Table 1, entries 3 and 4), a necessary condition for preserving the intrinsically nucleophilic

character of dioxindole. This observation provided the foundations for designing two unprecedented, direct, catalytic asymmetric routes to enantioenriched 3-substituted 3-hydroxyoxindoles using dioxindole as the nucleophile. In the following sections, the enantioselective organocatalytic Michael addition of dioxindole to α,β-unsaturated aldehydes, under iminium ion activation, and to nitroalkenes, by means of hydrogen-bond donor catalysis, will be described.

The straightforward accessibility to hexahydropyrrolo[2,3-*b*]indole derivatives and the preparation of the natural molecule maremycin A demonstrate the usefulness of the dioxindole reactivity.

3.3 Stereoselective Conjugate Addition of Dioxindole to α,β-Unsaturated Aldehydes and Stereocontrolled Synthesis of Maremycin A

The conjugate addition of nucleophiles to α,β-unsaturated aldehydes promoted by chiral secondary amine catalysts is a well-established organocatalytic methodology for the stereoselective β-functionalization of carbonyl compounds (See Chapter I).[18] Given the established ability of the diphenyl silyl prolinol catalyst **A** to infer high level of stereocontrol in this kind of transformations,[19] **A** was used to promote the reaction between dioxindole **1** and cinnamaldehyde **2**. Extensive screening of the standard reaction parameters were performed, with selected results summarized in Table 2. The reaction between **1** and cinnamaldehyde was followed by a fast hemiacetalization, which led to a mixture of the two anomers of the hemiacetal intermediate. Direct *in situ* oxidation of the crude mixture with pyridinium chlorochromate (PCC) gave the corresponding spiro oxindole γ-butyrolactones **3a** and **4a** with high optical purity (Table 2, entry 1). The synthesized spiro oxindole γ-butyrolactones are valuable compounds whose structural motif is common to many biologically active natural products.[20] Rather unexpectedly, we observed that a large excess over the catalyst of *ortho*-fluorobenzoic acid (2-FBA) as an additive induced an acceleration of the Michael addition, while completely minimizing the amount of isatide formed through the oxidative pathway (Table 2, entry 2). 50 mol% of the acidic additive with respect to amine **A** allowed us to reduce the amine catalyst loading to 1 mol%, while maintaining high enantioselectivity and reactivity (the reaction reaches completion over 16 h, Table2, entry 3).

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[18] D. Almaşi, D. A. Alonso, C. Nájera. Organocatalytic Asymmetric Conjugate Additions. *Tetrahedron: Asymmetry*, **2007**, *18*, 299.

[19] K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen. The Diarylprolinol Silyl Ether System: a General Organocatalyst. *Acc. Chem. Res.*, **2012**, *45*, 248.

[20] G. Büchi, P. R. DeShong, S. Katsumura, Y. Sugimura. Total Synthesis of Tryptoquivaline G. *J. Am. Chem. Soc.*, **1979**, *101*, 5084.

Table 2. Selected optimization studies[a]

| Entry | A (mol%) | additive (mol%) | Yield (%)[b] | | ee (%)[d] |
			Isatide[c]	3a+4a	3a+4a
1	5	-	6	24	96/97
2	5	2-FBA (5)	< 5	85	97/97
3	1	2-FBA (50)	-	99	97/97
4	0.5	2-FBA (50)	-	81	97/97
5[e]	1	2-FBA (1)	12	< 5	n.d.

[a] Reactions performed on a 0.05 mmol scale with $[2]_0 = 0.6$ M in acetone. All the reactions afforded a poor diastereomeric distribution (ranging from 1.4:1 to 1:1). [b] Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 2,5-dimethylfuran as the internal standard. [c] The maximum yield for isatide is 50%, since two oxindole units are merged. [d] Determined by HPLC analysis on chiral stationary phases [e] $[2]_0 = 0.06$ M in acetone. 2-FBA = *ortho*-fluorobenzoic acid; PCC = pyridinium chlorochromate; DCM = dichloromethane.

Experimental observations suggest that this reaction acceleration could be related to an increased solubility of **1** in acidic media. Indeed, under the reaction conditions (initial concentration of aldehyde $[2]_0 = 0.6$ M in acetone) dioxindole is only partially soluble, a condition that prevents reagent degradation. A control experiment performed in DMSO, which completely dissolves **1**, indicated that a fast oxidative coupling occurred, leading to the formation of isatide as the main product (no hemiacetal was observed, Scheme 6).
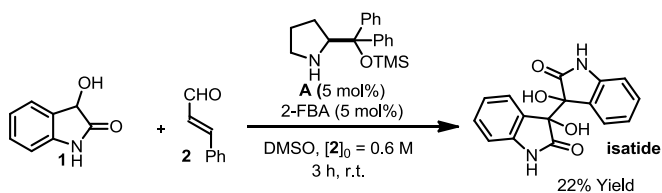
Scheme 6. Understanding the dioxindole reactivity: oxidative coupling in DMSO.

When acetone is used as the solvent, the addition of an acid could probably induce the formation of the more soluble enediol intermediate **III** (Table 3), assuring a constant yet low amount of nucleophile in the organic solvent. The formation of the enediol **III** has already been considered in the work of Baiker *et al.*, which reported that both tertiary amines and acids reduce the optical purity of enantioenriched dioxindole **1** by promoting keto-enol tautomerization.[15] Entries 2 and 3 (Table 3) support this interpretation: when the reaction was carried out in high dilution ($[2]_0 = 0.01$ M in acetone) which completely solubilized the dioxindole **1**, the reactivity was no longer sensitive to the amine **A**/*ortho*-fluorobenzoic acid ratio.

Table 3. Acid effect[a]
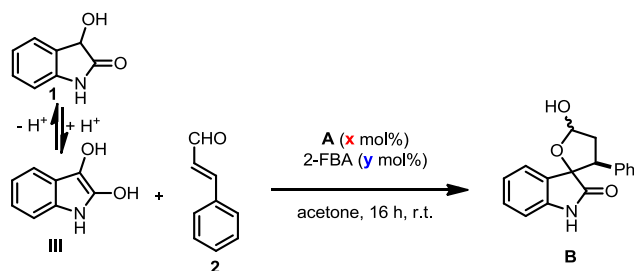
Entry	$[2]_0$	x (mol%)	y (mol%)	Yield (%)[b] 3a+4a
1	0.6	1	50	99
2	0.01	2	2	23
3	0.01	2	50	24

[a] Reactions performed on a 0.05 mmol scale using 1.2 equiv of cinnamaldehyde **2** with $[2]_0$ = 0.6 M. A stock solution of the catalyst was prepared diluting 6.5 mg (0.02 mmol) in 2 mL of acetone ($[A]$ = 0.01 M) and directly used in the catalytic reactions.[b] Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 2,5-dimethylfuran as the internal standard.

Structure-reactivity studies on the nucleophile revealed that the reactivity is strongly influenced by the substitution pattern of dioxindole **1** (Scheme 7).
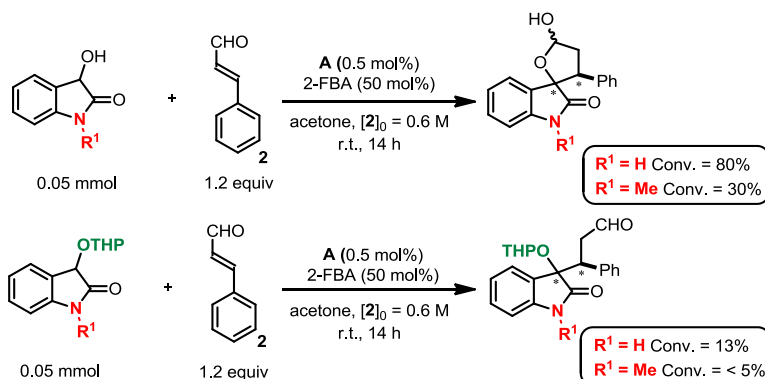
Scheme 7. Nucleophile structure-reactivity studies.

By protecting the hydroxyl group and/or the amido moiety, the solubility of the corresponding dioxindole was substantially increased and the acceleration induced by an excess of acidic additive was not observed. These experiments confirmed that the partial solubility of dioxindole **1** under the reaction conditions may prevent the reagent degradation. We selected the conditions reported in Table 2, entry 3 (**A**: 1 mol%; 2-FBA: 50 mol%) to evaluate the scope of the reaction. It was found that a wide range of β-substituted enals were well-tolerated, including differently substituted aryl groups as well as heteroaryl, alkenyl and alkyl moieties in the β-

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position (Table 4). The spiro oxindole γ-butyrolactones **3** and **4** were isolated in good to high chemical yield with high to excellent enantiomeric excess. As a limitation of the system, an ester moiety led to a moderate level of enantioselectivity (Table 4, entry 11).

Table 4 Organocatalyzed Michael addition of dioxindole to different enals[a]

Entry	R^1	product	Yield (%)[b] 3/4	*ee* (%)[c] 3/4
1	Ph	a	98 (43/55)	97/97
2	4-MeO-C_6H_4	b	63 (24/39)	97/98
3	4-NO_2-C_6H_4	c	89 (47/42)	88/92
4	2-NO_2-C_6H_4	d	92 (43/49)	94/98
5	4-Cl-C_6H_4	e	93 (39/54)	97/98
6	2-furanyl	f	65 (30/35)	96/97
7	3-thiophenyl	g	91 (38/53)	99/99
8	(indolyl-Me, Boc)	h	74 (39/35)	96/97
9	CH=CHCH$_3$	i	79 (29/50)	89/97
10[d]	pentyl	j	63	98/86
11	CO_2Et	k	72	66/70

[a] Reactions performed on a 0.2 mmol scale using 1.2 equiv of enals with $[2]_0$ = 0.6 M in acetone. All the reactions afforded a poor diastereomeric distribution (ranging from 1.5:1 to 1:1). [b] The total yield of the spiro γ-butyrolactones (obtained by PCC oxidation of the crude) is reported; the values between brackets refer to the yield of the isolated diastereomerically pure compounds **3** and **4**. [c] Determined by HPLC analysis on chiral stationary phases on the isolated **3** and **4**. [d] 5 mol% of both the catalyst **A** and of 2-FBA was used. Boc = *tert*-butoxycarbonyl.

Although the conjugate addition proceeds with poor control over the relative stereochemistry,[21] the possibility of easily isolating, by simple chromatography, the two diasteroisomers for almost all the adducts **3** and **4** testifies to the synthetic utility of the process. The absolute and relative configuration of the stereogenic centers of compound **3e** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis.[22]

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[21] The modest stereocontrol observed when catalyst **A** promotes the conjugate addition of prochiral carbon nucleophiles to α,β-unsaturated aldehydes is not surprising. For an example see: D. A. Alonso, S. Kitagaki, N. Utsumi, C.F. Barbas III. Towards Organocatalytic Polyketide Synthases with Diverse Electrophile Scope: Trifluoroethyl Thioesters as Nucleophiles in Organocatalytic Michael Reactions and Beyond. *Angew. Chem. Int. Ed.*, **2008**, *47*, 4588.

[22] CCDC 848635 contains the supplementary crystallographic data for compound **3e**.
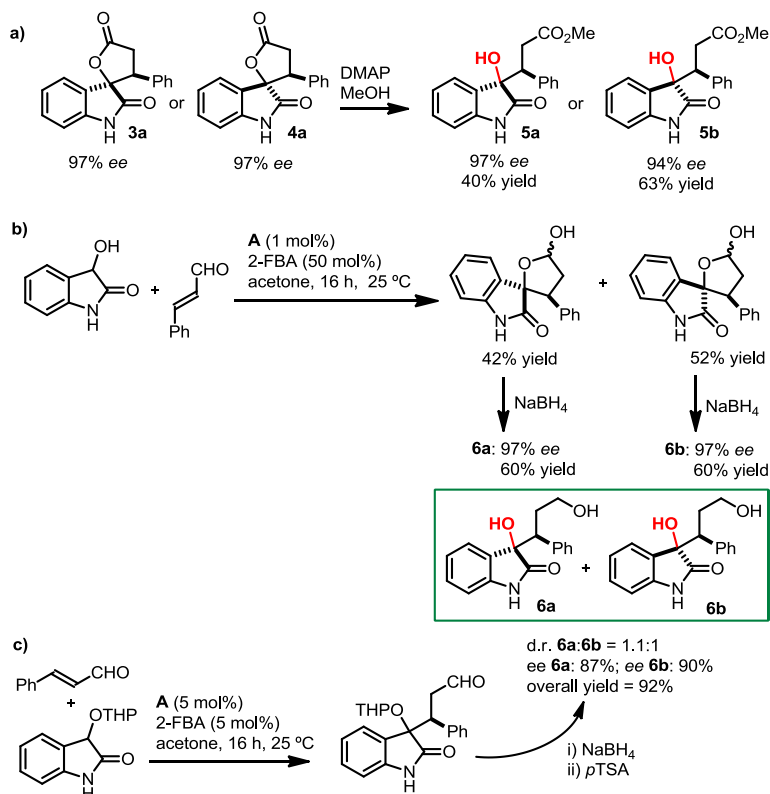
Further explorations of the conjugate addition reaction were carried out to expand the scope of the nucleophilic component. As summarized in Table 5, dioxindole derivatives bearing different substituents at the C_5 and C_7 positions (entries 1-4) performed well under the reaction conditions. The presence of a substituent on the nitrogen atom slightly lowered the reactivity of the catalytic system, while preserving the high enantioselectivity (entries 5-6). Finally, we demonstrated that a 3-hydroxy benzofuranone derivative is also a competent substrate in the present reaction conditions (entry 7).

Table 5 Organocatalyzed Michael addition of dioxindole derivatives to cinnamaldehyde[a]

Entry	R^1	R^2	X	product	yield (%)[b] 3/4	ee (%)[c] 3/4
1	Me	H	N-H	l	89 (32/57)	97/97
2	CF_3O	H	N-H	m	92 (44/48)	97/93
3	Br	H	N-H	n	64 (24/40)	96/96
4	H	Br	N-H	o	93	95/95
5[d]	H	H	N-Me	p	67 (39/28)	90/94
6[d]	H	H	N-Bn	q	92	95/95
7[d]	t-butyl	t-butyl	O	r	72 (30/42)	96/97

[a] Reactions carried on a 0.2 mmol scale using 1.2 equiv of cinnamaldehyde with $[2]_0 = 0.6$ M in acetone. [b] The total yield of the spiro γ-butyrolactones (obtained by PCC oxidation of the crude reaction mixture) is reported; the values between brackets refer to the yield of the isolated diastereomerically pure compounds **3** and **4**. [c] Determined by HPLC analysis on chiral stationary phases on the isolated **3** and **4**. [d] 5 mol% of the catalyst **A** and of 2-FBA was used.

The spiro oxindole γ-butyrolactones **3** and **4** are valuable complex compounds. The central goal of our studies, however, was to devise a novel and versatile strategy for stereoselectively accessing 3-substituted 3-hydroxyoxindole derivatives. The results reported in Scheme 8a-b demonstrate how standard product manipulations easily led to the target compounds **5** and **6**. A complementary approach to 3-hydroxyoxindoles **6a-b** can be envisaged when using an O-protected dioxindole derivative (THP = tetrahydropyranyl) as the nucleophile of the Michael addition, followed by a simple reduction/deprotection sequence (Scheme 8c).

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Scheme 8. Products derivatization.
DMAP = 4-Dimethylaminopyridine; *p*TSA = *para*-toluensulfonic acid.

The application of a new synthetic strategy for streamlining the preparation of complex natural molecules is generally considered an important validation of its synthetic potential and usefulness.[23] By exploiting the dioxindole reactivity, we envisioned a straightforward access to maremycin A, a diketopiperazine alkaloid recently isolated from the culture broth of marine Streptomyces species B 9173. [24]

[23] J. T. Mohr, M. R. Krout, B. M. Stoltz. Natural Products as Inspiration for the Development of Asymmetric Catalysis. *Nature*, **2008**, *455*, 323.
[24] W. Balk-Bindseil, E. Helmke, H. Weyland, H. Laatsch. Maremycin A and B, New Diketopiperazines from a Marine Streptomyces sp. *Liebigs Ann.*, **1995**, 1291.

56   Chapter 2
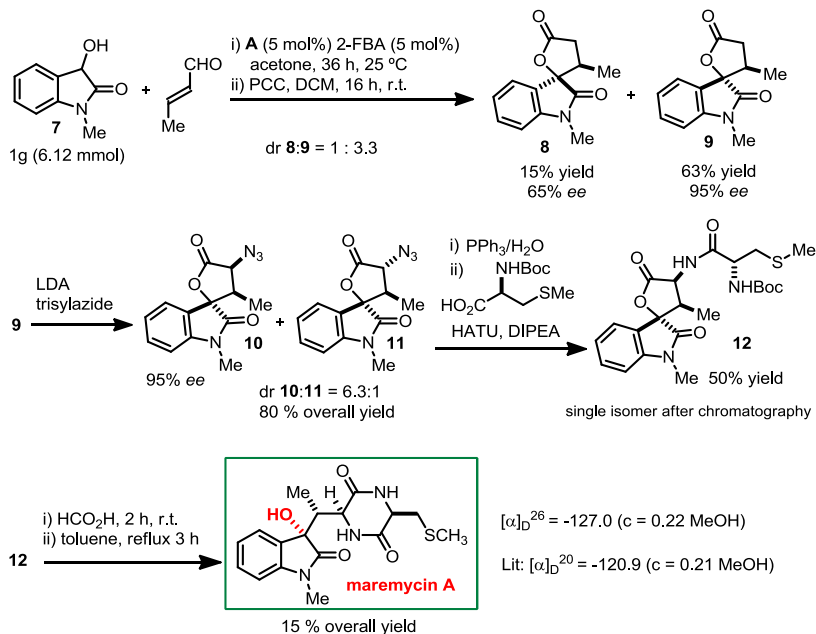
Scheme 9. Stereocontrolled synthesis of maremycin A.
LDA = lithium diisopropylamide; HATU = (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-
tetramethyluronium hexafluorophosphate); DIPEA = N,N-diisopropylethylamine.

Scheme 9 illustrates our synthetic plan,[25] which began with a gram scale addition reaction of *N*-methyl dioxindole **7** to crotonaldehyde. After PCC oxidation, the major diastereoisomer of the spiro oxindole γ-butyrolactones **9** was isolated by chromatography in good yield and with 95% *ee*. Formation of the corresponding lithium enolate and treatment with trisylazide gave the azide **10**,[26] which has the desired three-dimensional arrangement, as the major isomer (6.3:1 dr). The Staudinger reduction was followed by amidation with *N*-Boc-*S*-methyl-*L*-cysteine. This afforded, after purification, compound **12** as a single stereoisomer. Maremycin A was finally accessed after removal of the Boc protective group and formation of the diketopiperazine ring[27] in 15% overall yield starting from dioxindole **7**.

[25] For a precedent synthetic route to maremicyn A see: T. Ueda, M. Inada, I. Okamoto, N. Morita, O. Tamura. Synthesis of Maremycins A and D₁ *via* Cycloaddition of a Nitrone with (*E*)-3-Ethylidene-1-methylindolin-2-one. *Org. Lett.*, **2008**, *10*, 2043.

[26] A. Giannis, P. Heretsch, V. Sarli, A. Stößel. Synthesis of Cyclopamine Using a Biomimetic and Diastereoselective Approach. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7911.

[27] P. K. Subramanian, D. M. Kalvin, K. Ramalingam, R.W. Woodard. Synthesis of (1*S*,2*R*)- and (1*S*,2*S*)-1-Amino[2-²H]Cyclopropane-l-Carboxylic Acids: The Total ¹H NMR Assignment of Cyclo [ACC-α-Methyl-Phe]. *J. Org. Chem.*, **1989**, *54*, 70.

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3.4 Direct Access to 3-Substituted 3-Hydroxy-2-Oxindoles *via* 1,4-Additions to Nitroalkenes

A recent hot topic in asymmetric catalytic synthesis is the enantioselective addition of racemic 3-substituted oxindoles to a wide variety of electrophiles.[7] In particular, the asymmetric 1,4-addition to nitroalkenes has become a benchmark for measuring progress within the enantioselective addition of racemic 3-substituted oxindole frameworks.[3] The pioneering, independent contributions by the groups of Barbas III[28] and Shibasaki[29] on the use of *N*-Boc protected 3-alkyloxindoles have been followed by the studies of Maruoka and colleagues,[30] who exploited the high reactivity of *N*-Boc protected 3-aryloxindoles to design a base-free phase transfer reaction with nitroolefins in a water rich solvent. Recently, Zhou and co-workers expanded the scope of this reaction to include free amide 3-aryl and 3-alkyloxindoles.[31]

We further contributed to the progress of the catalytic asymmetric 1,4-addition of 3-substituted oxindoles to nitroalkenes, demonstrating that dioxindole **1** is a competent nucleophile of this transformation. The chemistry provides access to valuable 3-substituted 3-hydroxyoxindole derivatives. Key factors in the development of the methodology were the ability to channel the highly nucleophilicity of **1** toward a productive reaction pathway and the use of a chiral primary amine thiourea as an effective hydrogen-bond donor catalyst.

Initial studies on the organocatalytic stereoselective 1,4-addition of **1** to *trans-β*-nitrostyrene **13** were performed under general base activation. Selected results are reported in Table 6. When using quinine or Takemoto catalyst **C**, only a minor amount of the conjugate addition product **14** was formed (with a moderate preference for the *anti* diastereoisomer), while the dioxindole **1** was consumed through a fast and almost quantitative formation of isatide (Table 6, entries 1-2). These experimental results further confirmed the incompatibility of dioxindole in the presence of tertiary amines, because of the competing oxidative dimerization pathway (Scheme 3). The bifunctional primary amine thiourea **B** was identified as a promising catalyst.[32] This is because it induced the formation of the adduct **14** with good stereoselectivity (Table 6, entry 3) while

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[28] T. Bui, S. Syed, C. F. Barbas III. Thiourea-Catalyzed Highly Enantio- and Diastereoselective Additions of Oxindoles to Nitroolefins: Application to the Formal Synthesis of (+)-Physostigmine. *J. Am. Chem. Soc.*, **2009**, *131*, 8758.

[29] Y. Kato, M. Yurutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki. A Homodinuclear Mn(III)$_2$-Schiff Base Complex for Catalytic Asymmetric 1,4-Additions of Oxindoles to Nitroalkenes. *J. Am. Chem. Soc.*, **2009**, *131*, 9168.

[30] R. He, S. Shirakawa, K. Maruoka. Enantioselective Base-Free Phase-Transfer Reaction in Water-Rich Solvent. *J. Am. Chem. Soc.*, **2009**, *131*, 16620.

[31] M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao, J. Zhou. Cinchona Alkaloid-Based Phosphoramide Catalyzed Highly Enantioselective Michael Addition of Unprotected 3-Substituted Oxindoles to Nitroolefins. *Chem. Sci.*, **2011**, *2*, 2035.

[32] H. Huang, E. N. Jacobsen. Highly Enantioselective Direct Conjugate Addition of Ketones to Nitroalkenes Promoted by a Chiral Primary Amine−Thiourea Catalyst. *J. Am. Chem. Soc.*, **2006**, *128*, 7170.

preserving the integrity of dioxindole. Interestingly, catalyst **B** switched the diastereoselectivity of the process, leading to the preferential formation of the *syn*-**14** isomer.

Table 6 Selected optimization studies[a]
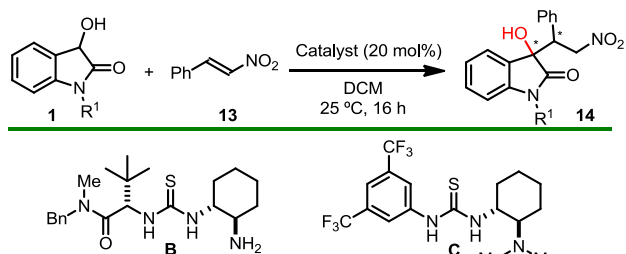
Entry	Catalyst	R[1]	13 (equiv)	Yield (%)[b] Isatide[c]	14	dr[b] *anti/syn*	ee (%)[d] *anti/syn*
1	quinine	H (**1**)	1.2	25	21	5:1	35/<5
2	**C**	H (**1**)	1.2	27	22	3:1	12/nd
3	**B**	H (**1**)	1.2	15	54	1:2.1	11/57
4	**B**	Me(**1b**)	1.2	13[d]	44	1:2.1	35/80
5	**B**	Bn (**1c**)	1.2	8[d]	69	1:2.1	50/87
6	**B**	Bn (**1c**)	1[e]	<5[d]	>95	1:2.5	43/89
7[f]	**B**	Bn (**1c**)	1[e]	<5[d]	35	1:2	30/75
8[g]	**B**	Bn (**1c**)	1[e]	<5[d]	95	1:4	57/94

[a] Reactions performed on a 0.05 mmol scale using 1.2 equiv of **13** with $[1]_0$ = 0.25 M in dichloromethane (DCM). [b] Both dr and yield were determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethyl benzene as the internal standard. *Ee* values determined by HPLC analysis. [c] The maximum yield for isatide is 50%, since two oxindole units are merged. [d] With dioxindoles **1b-c**, the isatides generated *via* the oxidative coupling likely undergo a disproportionation leading to dioxindole and isatin (see Scheme 4, Chapter 3.2). The reported values refer to the amount of the corresponding isatins detected. [e] Performed with 1.5 equiv of **1c**. [f] Performed at -20 °C. [g] $[13]_0$ = 0.05 M in DCM.

This bifunctional catalyst **B** was selected for further optimization studies. Protecting the nitrogen of dioxindole with a methyl or a benzyl group markedly increased the enantioselectivity of the transformation (Table 6, entries 4-5). Improved results were obtained using a slight excess of dioxindole (1.5 equiv, Table 6, entry 6). Further studies on the **B**-catalyzed 1,4-addition of dioxindole **1c** to nitrostyrene **13** revealed an unusual correlation between reaction temperature and stereoselectivity (reduced *ee* observed at lower temperature, Table 6, entry 7). This was rationalized on the basis of a self-aggregation of the catalyst, not uncommon for bifunctional thiourea-based catalysts,[33] which may determine the formation of dimer or higher aggregates characterized by different catalytic and/or stereoselective profiles. Figure 3 and Table 7 report

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[33] H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Baea, C. E. Song. DOSY NMR for Monitoring Self Aggregation of Bifunctional Organocatalysts: Increasing Enantioselectivity with Decreasing Catalyst Concentration. *Org. Biomol. Chem.*, **2010**, *8*, 3918.

the NMR dilution experiments and DOSY (diffusion ordered spectroscopy) carried out to gain insights into the self-association of the catalyst **B**.
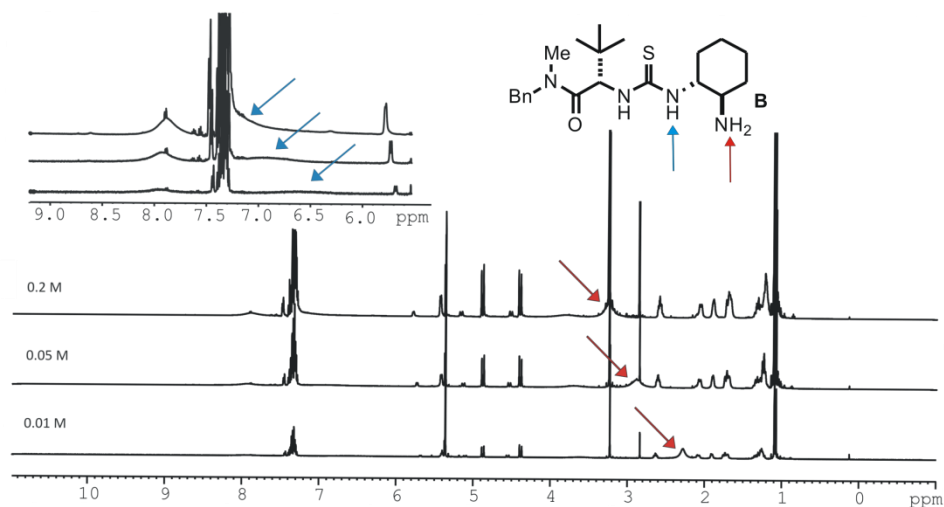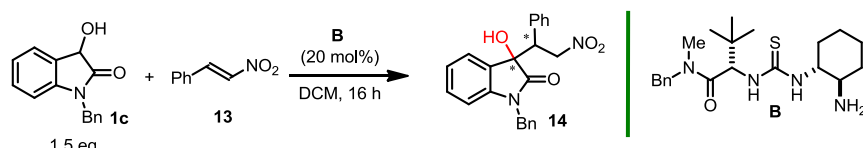

Figure 3. ¹H NMR Spectroscopic data for self-association of catalyst B.

NMR dilution experiments of **B** (Figure 3) performed in dichloromethane-*d2* showed marked concentration dependencies for the chemical shift of –C(=S)N(H) proton and –NH$_2$ protons. The chemical shift of the primary amine protons was shifted downfield from 2.2 to 3.2 ppm upon increasing its concentration from 0.01 M to 0.2 M (red arrows in figure 3) and the chemical shift of the –C(=S)N(H) proton was shifted downfield from 6.5 to 7.2 ppm (blue arrows in figure 3). This concentration dependency is consistent with the hydrogen-bonding self-association of **B**.

Results of the DOSY experiments are shown in Table 7. These results indicate that the translational diffusion coefficient (D) of the thiourea **B** significantly decreases when the concentration increases. As the translational diffusion coefficient can be influenced by intermolecular interactions, the relationship between the diffusion coefficient D and the concentration is a strong indication of the formation of dimers or higher order catalyst aggregates. The *ee* values obtained at different concentrations are fairly consistent with the diffusion coefficients (D) of the catalyst, indicating that the degree of catalyst self-association plays a crucial role in determining the enantioselectivity. The results suggest that the catalyst's monomeric form, favoured under more dilute reaction conditions, is the most selective species.

Table 7 DOSY (diffusion ordered spectroscopy) spectroscopic NMR experiments

13 Conc. (M)	B Conc. (M)	dr[a] anti/syn	ee (%)[b] anti/syn	$D\ (10^{-10}\,m^2s^{-1})$[c]
1	0.2	1:1.6	23/63	3.23
0.25	0.05	1:2.5	43/89	9.74
0.05	0.01	1:4	57/94	12.02

[a] Determined by ^{1}H NMR of the crude mixture. [b] Determined by chiral HPLC analysis on a chiral stationary phase. [c] Diffusion coefficient D obtained by DOSY experiments on samples of catalyst solutions in CD_2Cl_2. The experiments were carried on a Bruker Avance spectrometer, 500 MHz, equipped with a 5-mm broadband observe (BBO) z axis gradient probes capable of generating 55 G/cm field strengths.

Building upon these observations, we used a $[13]_0$ = 0.05 M in dichloromethane (DCM), which resulted in a higher level of both diastereo- and enantio-selectivity (4:1 dr, 94% *ee*, Table 6, entry 8). These conditions were selected to examine the scope of the Michael addition by evaluating differently substituted nitroalkenes (Table 8, entries 1-8). A variety of β-nitrostyrene derivatives were well-tolerated, regardless of their electronic properties. The corresponding adducts **14** were obtained in good to high yield and *syn* diastereoselectivity with high control over the absolute stereochemistry (*ee* up to 96%).

As a limitation of the system, aliphatic nitroalkenes did not react under the described conditions. A series of dioxindole derivatives bearing different substituents at the C_5 and C_7 positions proved to be competent nucleophiles of the conjugate addition to nitrostyrene (Table 8, entries 9-12). The presence of a different substituent at the dioxindole nitrogen atom (*i.e.* a methyl group, Table 8, entry 13) was well-tolerated, while the absence of a substituent affected the efficiency of the catalytic system (Table 8, entry 14). Importantly, the major *syn* diastereoisomer could be isolated by flash chromatography allowing access to synthetically useful quantities of enantioenriched **14**. Crystals from bromide **14k** were suitable for anomalous dispersion X-ray analysis, which established the absolute configuration of the Michael adduct.[34]

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[34] CCDC 85939 contains the supplementary crystallographic data for compound **14k**.

Table 8 Scope of the addition of dioxindole derivatives to nitroalkenes[a]

Entry	R^1	R^2	R^3	R^4	14	dr	Yield (%)[b]	ee (%)[c]
1	Bn	H	H	Ph	a	4:1	91 (69)	94
2	Bn	H	H	4-MeO-C$_6$H$_4$	b	4:1	98 (75)	93
3	Bn	H	H	4-Me-C$_6$H$_4$	c	4:1	96 (74)	94
4	Bn	H	H	4-CF$_3$-C$_6$H$_4$	d	3.2:1	78 (56)	90
5	Bn	H	H	4-Cl-C$_6$H$_4$	e	3.2:1	80 (60)	84
6	Bn	H	H	2-Br-C$_6$H$_4$	f	4:1	60	85
7	Bn	H	H	Furan-2-yl	g	3.6:1	94 (60)	96
8	Bn	H	H	Thiophen-3-yl	h	2.7:1	89 (62)	95
9	Bn	Me	H	Ph	i	3.3:1	78 (58)	95
10	Bn	Me	Me	Ph	j	2.8:1	78 (59)	87
11	Bn	Br	H	Ph	k	2.8:1	76 (61)	88
12	Bn	H	Br	Ph	l	2:1	75 (46)	73
13	Me	H	H	Ph	m	3:1	73 (48)	90
14	H	H	H	Ph	n	2:1	50	66

[a] Reactions performed on a 0.2 mmol scale using 20 mol% of catalyst **B** 1.5 equiv of dioxindoles and [**13**]$_0$ = 0.05 M in DCM at rt over 16 h. [b] The total yield of the isolated products is given; the values between brackets refer to the yield of the isolated diastereomerically pure compounds *syn*-**14**, which can easily be separated by chromatography on silica gel. [c] *ee* values refer to the major *syn* diastereoisomer **14**.

The preparation of compound **15**, which bears the hexahydropyrrolo[2,3-*b*]indole unit found in many natural molecules,[35] through standard manipulations of compound **14m**, testifies to the potential synthetic usefulness of this previously unexplored reactivity (Scheme 10).

90% *ee*

75% overall yield
87% *ee*
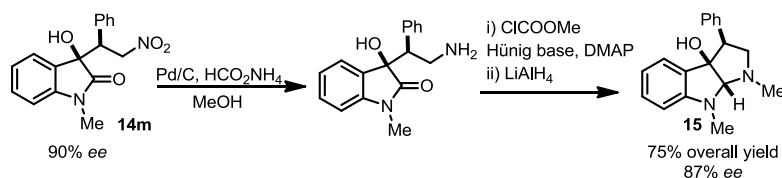
Scheme 10. Preparation of hexahydropyrrolo[2,3-*b*]indole derivative **15**.

We then focused on extensive structure/stereoselectivity correlation studies in order to understand the importance of the structural and stereochemical elements of the organocatalyst **B** in dictating the selectivity of the reaction. Our motivation was that primary amine thiourea derivatives of type **B** were originally conceived (and then successfully used) by Jacobsen and

35 P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Alvarez. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-*b*]Indole. *Chem. Eur. J.*, **2011**, *17*, 1388.

colleagues to synergistically combine hydrogen-bond donor catalysis with the covalent activation of aldehydes and ketones, through the intermediacy of covalently bounded catalyst-enamine species.[32] Since the substrates involved in the present chemistry do not provide the chemical handle necessary for covalent activation, we wished to identify the structural elements that make the primary amine thiourea **B** effective in the realm of hydrogen-bond donor catalysis (non-covalent activation mode). To this end we investigated the addition of dioxindole **1c** to **13** in DCM using modified thiourea derivatives. The results are reported in Scheme 11.
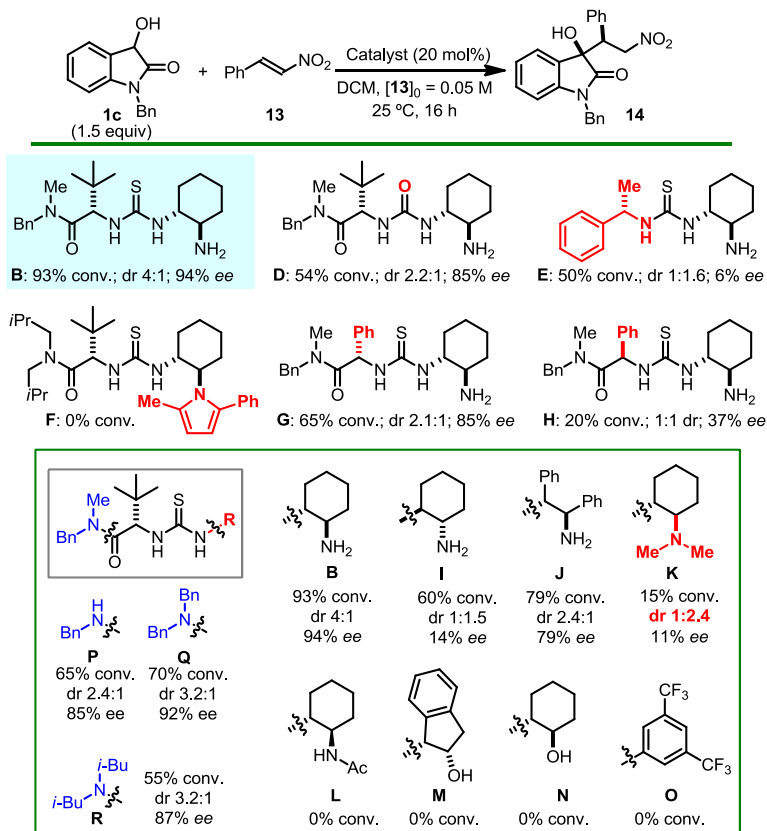
Scheme 11. Catalyst structure/reactivity and stereoselectivity correlation studies.

The urea catalyst **D** was slightly less reactive and stereoselective than its thiourea analogue **B**. The amido-moiety and the primary amine were soon recognized as essential elements for catalysis, since their absence dramatically affected the outcome of the reaction (catalysts **E**-**F**). It appeared that only a well-defined relative spatial arrangement of the catalytic moieties, as dictated by the absolute configurations of three stereocentres, brought about an effective catalysis. The stereochemistry and the nature of the substituent within the amino acid component were both important for achieving high stereoselectivity, with (*S*)-*tert*-leucine

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providing optimal results (compare catalysts **B**, **G, H** and **B**, **P**, **Q**, **R**). In addition, a specific stereochemistry of the diaminocyclohexane backbone was required (**B** against **I**). Surprisingly, replacing the primary amine in **B** with the corresponding *N*,*N*-dimethyl tertiary amine (**K**) caused an inversion of the diastereoselectivity together with a complete loss of enantiocontrol. This suggests an uncommon mechanistic scenario where the primary amino moiety is not operating as a Brønsted base, but serving as a suitable chemical handle for hydrogen-bonding activation. The requirement of a primary amine for catalytic activity can be clearly observed by the results obtained with catalysts **L**, **M** and **N**, which bear functional groups with slightly different hydrogen-bonding abilities with respect to **B**.

All these results suggest a cooperative mechanism of catalysis of the thiourea, the amido-group, and the primary amino moiety, which synergistically channel the process toward a highly stereoselective pathway by concomitant activation of both the electrophilic and nucleophilic partners. On the basis of the absolute configuration of product **14k**, a plausible mechanism was proposed to reconcile the catalyst structure/reactivity and stereoselectivity correlation studies (Figure 4).
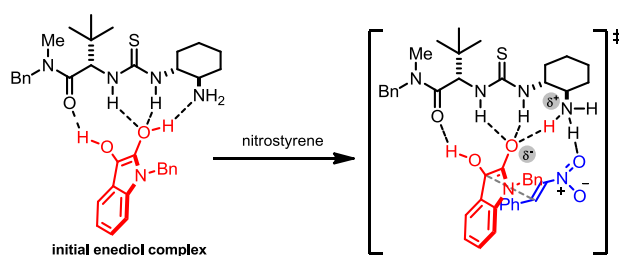

Figure 4. Proposed enol-based mechanism using primary amine-thiourea catalyst **B**.

It is plausible that the primary amine-thiourea catalyst **B** stabilizes the enol form of the dioxindole through hydrogen bonding instead of promoting the formation of an enolate intermediate. During the C-C bond-forming event, the nascent negative charge is stabilized by the thiourea unit, while the build-up of the positive charge on the ammonium ion directs the approach of the nitrostryrene. This is consistent with the striking difference in the reaction outcome observed when using catalyst **K**, and with the fact that catalyst **B** greatly minimizes the oxidative coupling pattern (which is driven by oxidation of the enolate intermediate **I** depicted in Scheme 3). In addition, the potential of primary amine-thiourea catalyst to operate trough enol-based chemistry has already been demonstrated.[36] The proposed cooperative catalysis system is additionally supported by the completely suppressed reactivity observed using *O*-protected

[36] D. A. Yalalov, S. B. Tsogoeva, T. E. Shubina, I. M. Martynova, T. Clark. Evidence for an Enol Mechanism in a High Enantioselective Mannich-Type Reaction Catalyzed by Primary Amine-Thiourea. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6624.

dioxindole **1b**-OTHP and the lost of stereocontrol observed when dioxindole **1**-OTHP was used (Scheme 12a).
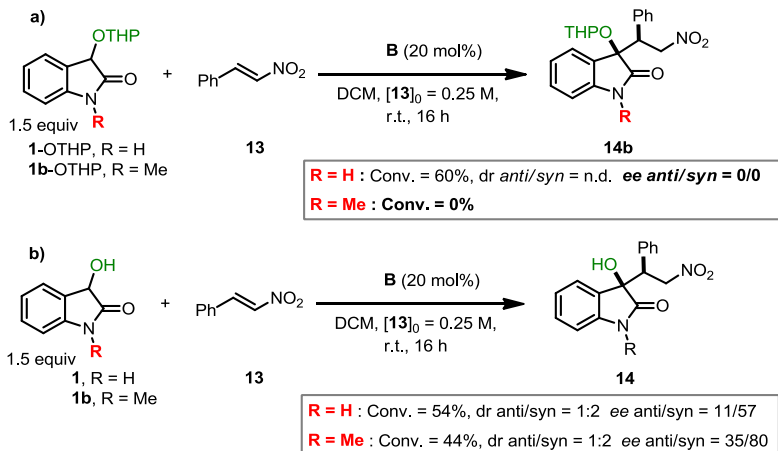
Scheme 12. Protection of the hydroxyl group dramatically affects the outcome of the reaction as the nucleophile loses an essential element for selectively binding to the catalyst.

These results indicate that the hydroxyl moiety of dioxindole is an essential element engaged in the key interaction with catalyst **B** to create a well structured transition state. The improved stereoselectivity obtained by using *N*-protected dioxindole **1b** respect to the N-H derivative **1** (Scheme 12b), can be explained considering the proposed transition state. The N-H on the dioxindole scaffold is a H-bond donor that can compete with the hydroxy group for the coordination to the catalyst amido-group, thus affecting the structure of the transition state.

3.5   Conclusions

Two new organocatalytic routes for the stereoselective synthesis of important target structures such as 3-substituted 3-hydroxyoxindole derivatives have been described. At the heart of the study was the use of dioxindole, which has never been used before as a competent partner in nucleophilic addition reactions. [37] Key factors in taming the dioxindole reactivity were the compatibility with mild primary and secondary amine organocatalysts and the ability of these catalysts to channel the intrinsic nucleophilicity of dioxindole toward a productive conjugate addition mechanism. The straightforward preparation of the diketopiperazide alkaloid

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[37] Soon after the publication of this work, dioxindole has been utilized as substrate under dinuclear zinc-ProPhenol complex catalysis, see: B. M. Trost, K. Hirano. Dinuclear Zinc Catalyzed Asymmetric Spirannulation Reaction: an Umpolung Strategy for Formation of α-Alkylated-α- Hydroxyoxindoles. *Org. Lett.*, **2012**, *14*, 2446.

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maremycin A and the hexahydropyrrolo[2,3-*b*]indole derivative **15** demonstrated the potential synthetic usefulness of this previously unexplored reactivity in natural product synthesis.

3.6   Experimental Section

3.6.1   General Informations

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents (CHCl$_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. When necessary, ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal.

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI). X-ray data were obtained from the ICIQ X-Ray Unit using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector. Optical rotations are reported as follows: $[\alpha]_D^T$ (c in g per 100 mL, solvent). The ^{1}H and ^{13}C NMR spectra and HPLC and GC traces are available in the literature and are not reported in the present manuscript.[1]

3.6.2   General Procedures

All the reactions were set up under air and using freshly distilled solvents, without any precautions to exclude moisture, unless otherwise noted. Chromatographic purification of products was accomplished using flash chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF$_{254}$, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante (KMnO$_4$), and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

3.6.3   Determination of Diastereomeric Ratios

Conjugate addition of dioxindole to α,β-unsaturated aldehydes: the diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture on the spiro oxindole γ-butyrolactones products **3** and **4**, after the PCC oxidation step.

1,4-Addition of dioxindole to nitroalkenes: the diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture on the Michael addition products **14**.

3.6.4   Determination of Enantiomeric Purity

HPLC analysis on chiral stationary phase was performed on an Agilent 1200-series instrumentation. Daicel Chiralpak AD-H, IA, IB or IC columns and Daicel Chiralcel OD-H with *i*-PrOH/hexane as the eluent were used.

Conjugate addition of dioxindole to α,β-unsaturated aldehydes: HPLC traces were compared to racemic samples prepared by mixture of two enantiomeric final products obtained using (*S*)-**A** and (*R*)-**A** catalysts.

1,4-Addition of dioxindole to nitroalkenes: HPLC traces were compared to racemic samples prepared by purification of the compounds obtained using DABCO (1,4-diazabicyclo[2.2.2]octane) as the catalyst of the reaction. Note that DABCO induces a marked preference for the *anti* diastereoisomer, while catalyst **B** affords preferentially the *syn* product.

3.6.5   Determination of Yield and Conversion in the Optimization Studies

The conversion of the starting materials and the yield of product in the optimization studies related to the conjugate addition of dioxindole to α,β-unsaturated aldehydes depicted in Table 2 were determined by ^{1}H NMR spectroscopy adding an internal standard to the crude reaction mixture: 2,5-dimethylfuran: δ 2.26 ppm (s, 6H), 5.84 (s, 2H). Since in all instances the conversion of enal was equal to the yield of product, in some cases the yield was determined by integration of the signals of the unreacted cinnamaldehyde in the ^{1}H NMR spectra (cinnamaldehyde ^{1}H NMR signal: δ 9.71 ppm (d) and dioxindole NMR signal: δ 4.93 ppm (d)).

The conversion of the starting materials and the yield of product in the optimization studies related to the 1,4-addition of dioxindole to nitroalkenes depicted in Table 6 were determined by ^{1}H NMR spectroscopy adding an internal standard in the crude reaction: hexamethylbenzene: δ 2.22 ppm (s, 18H). Since in all instances the conversion of nitrostyrene was equal to the yield of product, in some cases the yield was determined by integration of the signals of the unreacted nitrostyrene in the ^{1}H NMR spectra (nitrostyrene ^{1}H NMR signal: δ 8.01 ppm (d); 1-benzyl-3-hydroxyindolin-2-one **1c** ^{1}H NMR signal: δ 5.16 ppm (s)).

3.6.6   Materials

Commercial grade reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification; where necessary, they were purified as recommended.[38] Chiral secondary amines are commercially available (Aldrich or Alfa Aeser);

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[38] W. L. F. Armarengo, D. D. Perrin. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, **1996**.

catalys **A** was purified by flash column chromatography prior to use and stored at 4°C under argon to avoid undesired desilylation that would affect the catalytic potential of the amine.

Catalyst **B** (*S*)-2-[[(1*R*,2*R*)-2-Aminocyclohexyl] thioureido]-*N*-benzyl-*N*-3,3-trimethylbutanamide is commercially available (Aldrich); all the other thiourea and urea catalysts were synthesized according to literature procedures.[39,40]

Dioxindole **1** has been synthesized starting from commercial available isatin following the procedure described within Chapter 3.6.7. The 3-hydroxy-3H-benzofuran-2-one derivative (entry 7, Table 5) has been synthesized starting from commercial available 2,4-di-*tert*-butylphenol and glyoxylic acid following the procedure reported in the literature.[41] The ((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one and 1-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one (*O*-THP protected dioxindoles) has been synthesized starting from the corresponding dioxindoles following the procedure reported in the literature.[11]

Most of the unsaturated aldehydes were purchased from Aldrich or Alfa Aeser and used as received. Enal bearing the 3-thiophenyl group in the β-position (entry 7, Table 4) has been synthesized following procedures reported in the literature.[42] The enal bearing the *tert*-butyl 2-methyl-1H-indole-1-carboxylate group in the β-position (entry 8, Table 4) has been synthesized following procedures reported in the literature.[43]

trans-β-Nitrostyrene **13** was purchased from Aldrich and used as received. All the other nitrostyrene substrates were synthesized according to literature procedures.[43]

3.6.7   Preparation of the Starting Materials

Synthesis of 3-hydroxy-5-methylindolin-2-one, 5-bromo-3-hydroxyindolin-2-one, 3-hydroxy-5-(trifluoromethoxy)indolin-2-one and 7-bromo-3-hydroxyindolin-2-one
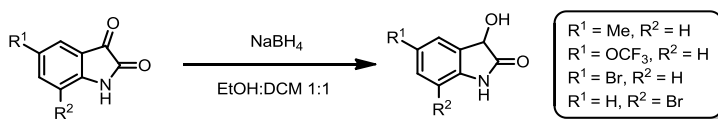
Procedure: commercially available isatins (2 mmol) were added in small portions to a stirred suspension of sodium borohydride (3 mmol, 113 mg, 1.5 equiv) in 12 mL of a 1:1 dichloromethane/ethanol mixture at 0 °C. The mixture was vigorously stirred at this

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[39] A. G. Wenzel, E. N. Jacobsen. Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids. *J. Am. Chem. Soc.,* **2002**, *124*, 12964.

[40] P. Vachal, E. N. Jacobsen. Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids. *Org. Lett.*, **2000**, *2*, 867.
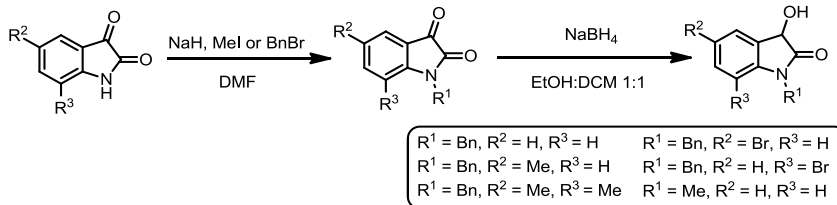
[41] P. Nesvadba, L. Bugnon, P. Dubs, S. Evans. A Versatile New Synthesis of 3-Aryl-3H-benzofuran-2-Ones. *Synlett*, **1999**, *S1*, 863.

[42] I. Sagud, F. Faraguna, Z. Marini, M. Sindler-Kulyk. Photochemical Approach to Naphthoxazoles and Fused Heterobenzoxazoles from 5-(Phenyl/Heteroarylethenyl)Oxazoles. *J. Org. Chem.*, **2011**, *76*, 2904.

[43] Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre. Asymmetric Catalysis of Diels–Alder Reactions with *In Situ* Generated Heterocyclic *ortho*-Quinodimethanes. *J. Am. Chem. Soc.*, **2011**, *133*, 15212.

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temperature until the suspension became colorless (about 5 min). Then water (0.2 mL) was added and the reaction mixture was stirred until bubbling stop. The mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel using a 1:1 mixture of hexane/diethyl ether, or crystallized by ethyl acetate/hexane to separate the 3-hydroxy-2-oxoindole derivatives from the pigments formed during the extraction and evaporation procedures.

Synthesis of dioxindole 1b and 1c derivatives

R^1 = Bn, R^2 = H, R^3 = H	R^1 = Bn, R^2 = Br, R^3 = H
R^1 = Bn, R^2 = Me, R^3 = H	R^1 = Bn, R^2 = H, R^3 = Br
R^1 = Bn, R^2 = Me, R^3 = Me	R^1 = Me, R^2 = H, R^3 = H

Procedure: a solution of commercially available isatins (5 mmol) in 15 mL of dry DMF was slowly added to a suspension of sodium hydride (6.5 mmol, 1.3 equiv, 60% w/w in mineral oil) in 15 mL of dry DMF at 0 °C. The suspension was stirred for 2 h at 0 °C. Then, 1.5 equiv of the alkylating agent (methyl iodide or benzil bromide) was added. The mixture was stirred for 2 h at room temperature and water was added until precipitation of the *N*-protected isatin. Crystallization from hexane/ethyl acetate afforded the pure products in about 70% yield. The pure *N*-protected isatins (2 mmol) were added in small portions to a stirred suspension of sodium borohydride (3 mmol, 113 mg, 1.5 equiv) in 12 mL of a 1:1 dichloromethane/ethanol mixture at 0 °C. The mixture was vigorously stirred at this temperature until the suspension became colorless (about 5 min). Then water (0.2 mL) was added and the reaction mixture was stirred until bubbling stopped. The mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel using a 1:1 mixture of hexane/diethyl ether, or crystallized by ethyl acetate/hexane to separate the *N*-protected-3-hydroxy-2-oxoindole derivatives from the pigments formed during the extraction and evaporation procedures.

Synthesis of 1-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one
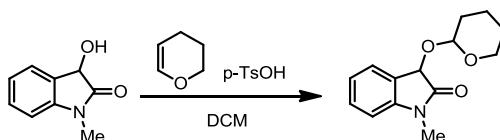

1-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one was obtained adding *p*-toluenesulfonic acid monohydrate (0.01 equiv) to a mixture of 3-hydroxy-1-methylindolin-2-one and dihydropyran (5 equiv) in dry dichloromethane (0.2 M) at 0 °C. The reaction mixture was stirred

for 1.5 h at room temperature and then partitioned between diethyl ether and a brine/saturated sodium bicarbonate/water 1:1:2 solution. The organic phase was washed twice with saturated brine, dried (MgSO$_4$), and evaporated in vacuo. Purification by chromatography on silica (hexane:ethyl acetate 80:20) gave the product as yellow oil in 85% yield.
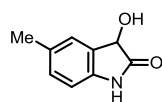
3.6.8 NMR data of the Starting Materials

3-hydroxyindolin-2-one
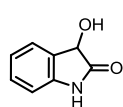
^{1}H NMR (400 MHz, DMSO-d_6): δ 4.82 (d, 1H, *J* = 7.50 Hz), 6.15 (d, 1H, *J* = 7.50 Hz), 6.15 (d, 1H, *J* = 7.54 Hz), 6.78 (d, 1H, *J* = 7.65 Hz), 6.96 (t, 1H, *J* = 7.62 Hz), 7.20 (t, 1H, *J* = 7.68 Hz), 7.28 (d, 1H, *J* = 7.28 Hz), 10.22 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 69.6, 109.9, 121.9, 125.2, 129.4, 129.8, 142.6, 178.4 ppm.

3-hydroxy-5-methylindolin-2-one

^{1}H NMR (400 MHz, MeOD): δ 2.30 (s, 3H), 4.85 (br s, 1H), 6.74 (d, 1H, *J* = 8.05 Hz), 7.03-7.07 (m, 1H), 7.17-7.19 (m, 1H). ^{13}C NMR (100 MHz, MeOD): δ 21.1, 71.2, 110.9, 126.7, 130.1, 130.7, 133.3, 140.7, 180.6 ppm.
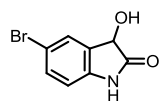
3-hydroxy-5-(trifluoromethoxy)indolin-2-one
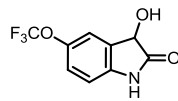
^{1}H NMR (400 MHz, DMSO-d_6): δ 4.90 (d, 1H, *J* = 7.51 Hz), 6.31 (d, 1H, *J* = 7.51 Hz), 6.86 (d, 1H, *J* = 8.56 Hz), 7.19-7.23 (m, 1H), 7.24-7.27 (m, 1H), 10.41 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.7, 110.8, 118.9, 122.6, 131.6, 141.9, 143.6, 143.6, 178.3 ppm.
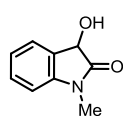
5-bromo-3-hydroxyindolin-2-one

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.87 (d, 1H, *J* = 7.57 Hz), 6.26 (d, 1H, *J* = 7.57 Hz), 6.76 (d, 1H, *J* = 7.84 Hz), 7.36-7.41 (m, 2H), 10.36 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.1, 111.5, 113.1, 127.5, 131.5, 131.9, 141.5, 177.4 ppm.
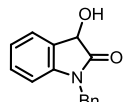
3-hydroxy-1-methylindolin-2-one

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.17 (s, 3H), 4.66 (br s, 1H), 5.10 (s, 1H), 6.81 (d, 1H, *J* = 7.92 Hz), 7.10 (dt, 1H, *J$_1$* = 7.52 Hz, *J$_2$* = 0.92 Hz), 7.32 (t, 1H, *J* = 7.64 Hz), 7.46 (d, 1H, *J* = 7.46 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 26.4, 70.0, 108.6, 123.4, 125.3, 126.9, 130.0, 144.0, 176.9 ppm.
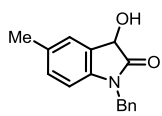
1-benzyl-3-hydroxyindolin-2-one

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.04 (br s, 1H), 4.88 (complex system, 2H), 5.17-5.21 (m, 1H), 6.72 (d, 1H, *J* = 7.93 Hz), 7.07 (dt, 1H, *J$_t$* = 7.54, *J$_d$* = 0.89 Hz), 7.18-7.34 (m, 6H), 7.47 (d, 1H, 7.45 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.0, 70.0, 109.6, 123.4, 125.3, 127.1, 127.4, 127.9, 128.9, 129.8, 135.4, 143.1, 177.3 ppm.
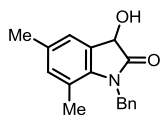
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### 1-benzyl-3-hydroxy-5-methylindolin-2-one

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.30 (s, 3H), 3.99 (br s, 1H), 4.85 (complex system, 2H), 5.16 (s, 1H), 6.59 (d, 1H, J = 7.95 Hz), 6.98-7.03 (m, 1H), 7.22-7.34 (m, 6H,) ppm.^{13}C NMR (100 MHz, CDCl$_3$): δ 20.9, 43.8, 69.9, 109.2, 126.05, 126.9, 127.3, 127.71, 128.8, 129.9, 132.9, 135.4, 140.5, 177.0 ppm.

1-benzyl-3-hydroxy-5,7-dimethylindolin-2-one

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.21 (s, 3H), 2.29 (s, 3H) 3.81(d, 1H, J = 4.97 Hz), 5.13-5.18 (m, 3H), 6.82 (s, 1H), 7.14-7.21 (m, 3H), 7.23-7.36 (m, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 18.4, 20.6, 45.0, 69.4, 120.0, 123.9, 125.6, 127.3, 127.7, 128.9, 133.0, 134.0, 137.0, 138.5, 177.9 ppm.

1-benzyl-5-bromo-3-hydroxyindolin-2-one
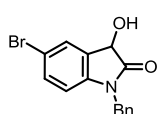
^{1}H NMR (400 MHz, CDCl$_3$): δ 3.59 (d, 1H, J = 4.60 Hz), 4.89 (complex system, 2H), δ 5.18 (d, 1H, J = 4.08 Hz), 6.60 (d, J = 8.41 Hz), 7.25-7.39 (m, 6H), 7.59-7.61 (m. 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 43.9, 69.5, 111.0, 116.0, 127.2, 127.9, 128.5, 128.6, 128.9, 132.6, 134.8, 142.0, 176.3 ppm.

5,7-di-tert-butyl-3-hydroxybenzofuran-2(3H)-one
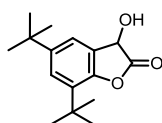
^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (s, 9H), 1.39 (s, 9H), 3.25 (br d, 1H, J = 5.49Hz), 5.31 (br d, 1H, J = 5.49Hz), 7.33-7.37 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 29.7, 31.7, 34.5, 35.0, 68.1, 120.0, 125.0, 125.1, 134.0, 147.9, 149.7, 176.1 ppm.

3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one
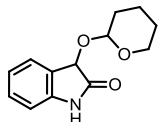
^{1}H NMR (400 MHz, CDCl$_3$): δ 1.40-1.93(m, 6H), 3.55-3.66 (m, 1H), 4.01-4.09 (m, 0.75H), 4.20-4.28 (m, 0.25H), 5.13 (s, 0.75H), 5.17 (s, 0.25H), 5.18-5.20 (m, 0.25H), 5.31-5.36 (m, 0.75H), 6.81-6.90 (m, 1H), 6.97-7.06 (m, 1H), 7.18-7.26 (m, 1H), 7.33 (d, 0.25H, J = 7.34 Hz), 7.38 (d, 0.75H, J = 7.34 Hz), 9.02 (br s, 0.75H), 9.21 (br s, 0.25H). ^{13}C NMR (100 MHz, CDCl$_3$): δ =18.6, 19.0, 25.3, 25.4, 30.3, 30.4, 62.0, 62.6, 72.2, 72.8, 97.4, 98.0, 110.4, 110.6, 122.6, 122.8, 125.5, 126.0, 126.1, 126.9, 129.8, 129.9, 141.7, 141.8, 176.9, 178.1 ppm.

1-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one
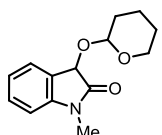
1H NMR (400 MHz, CDCl3): δ 1.49-1.95 (m, 6H), 3.14 (s, 2.25H), 3.17 (s, 0.75H), 3.58-3.67 (m, 1H), 4.02-4.09 (m, 0.75H), 4.25-4.32 (m, 0.25H), 5.11 (s, 0.75H), 5.15 (s, 0.25H), 5.19-5.22 (m, 0.25H), 5.38-5.42 (m, 0.75H), 6.76-6.81 (m, 1H), 7.01-7.09 (m, 1H), 7.28-7.33 (m, 1H), 7.35 (d, 0.25H, J = 7.29 Hz), 7.41 (d, 0.75H, J = 7.29 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 18.4, 19.1, 25.4, 25.5, 26.1, 26.3, 30.3, 30.4,

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Dioxindole in Asymmetric Catalytic Synthesis   71

61.7, 62.6, 71.5, 72.2, 97.2, 98.1, 108.4, 108.5, 122.8, 122.9, 125.2, 125.7, 125.8, 126.5, 129.8, 129.9, 144.4, 144.5, 174.1, 175.4 ppm.

3.6.9   General Procedure for the Michael Addition of Dioxindole to Enals
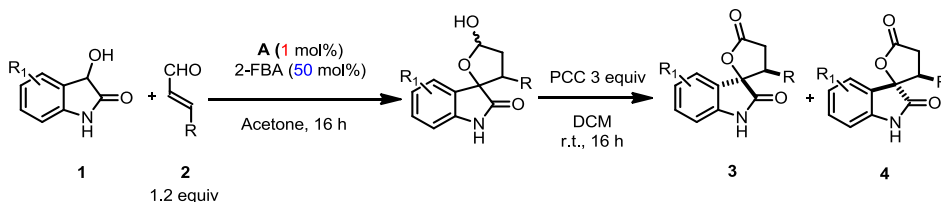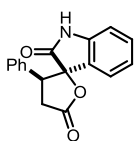

All the reactions were carried out in acetone (ACS grade reagent) without any precaution for excluding air and moisture. A vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **A** (15.5 μL of a freshly prepared 0.13 M solution of the catalyst in acetone, 0.002 mmol, 1 mol%) and 0.4 mL of acetone. Then, *ortho*-fluorobenzoic acid (0.1 mmol, 14.0 mg, 50 mol%) was added in one portion and the resulting solution was stirred at room temperature for 10 minutes. The reaction was started by the sequential addition of the α,β-unsaturated aldehyde **2** (0.24 mmol, 1.2 equiv) and the dioxindole **1** (0.2 mmol). The vial was sealed and stirring continued over 16 hours at 25 °C. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (10 mL). Solvent was removed in vacuo and the crude of the reaction dissolved in 1 mL of dichloromethane. Then pyridinium chlorochromate (PCC, 0.6 mmol, 129.3 mg, 3 equiv) was added in one portion and the resulting yellow suspension was stirred at room temperature for 16 hours. The resulting mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (10 mL). Solvent was removed in vacuo and the diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis of the crude mixture. Adducts **3** and **4** were isolated by flash column chromatography on silica gel or preparative TLC.

When the reaction did not reach full conversion after 16 h reaction time, the products were isolated in their hemiacetal form and subsequently oxidized. Indeed, the direct oxidation of the crude hemiacetals, following the general procedure, would afford an inseparable mixture of the spiro lactones **3** and **4** and the isatin (oxidation of the unreacted dioxindole). Adducts **3** and **4** were then isolated as single diastereoisomers by flash column chromatography or preparative TLC.

(2*R*,3*S*)-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3a) and (2*S*,3*S*)-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4a)

The reaction was carried out following the general procedure to furnish the crude products as a 1.1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 2.91 ppm (dd), δ_{minor} 3.10 ppm (dd). The two compounds **3a** and **4a** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/dietyl ether = 95/5).

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(**3a** – Table 4, entry 1). The title compound was isolated as a single diastereoisomer (R_f = 0.24 dichloromethane/diethyl ether 9/1) in 43% yield (white solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 29.6 min, τ_{minor} = 34.0 min. $[\alpha]_D^{26}$ = -46.3 (c = 0.79, CHCl3, 97% *ee*). HRMS *calcd.* for ($C_{17}H_{13}NO_3$+Na): 302.0793, found 302.0802.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.91 (dd, 1H, J_1 = 16.69 Hz, J_2 = 8.10 Hz), 3.79 (dd, 1H, J_1 = 16.85 Hz, J_2 = 13.64 Hz), 4.09 (dd, 1H, J_1 = 13.57 Hz, J_2 = 8.03 Hz), 6.71 (d, 1H, J = 7.98 Hz), 6.96 (d, 2H, J = 7.35 Hz), 7.14-7.24 (m, 5H), 7.33 (dt, 1H, J_t = 7.85 Hz, J_d = 1.17 Hz), 7.53 (d, 1H, J = 7.23 Hz) ppm.
^{13}C NMR (100 MHz, CDCl$_3$): δ 32.1, 50.9, 86.3, 110.4, 123.5, 124.6, 125.0, 127.6, 128.3, 128.6, 131.3, 191.9, 141.2, 174.0, 174.7 ppm.
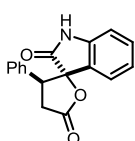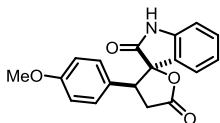
(**4a** – Table 4, entry 1). The title compound was isolated as a single diastereoisomer (R_f = 0.21 dichloromethane/diethyl ether = 9/1) in 55% yield (pale yellow solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 23.7 min, τ_{minor} = 33.0 min. $[\alpha]_D^{27}$ = -18.5 (*c* = 0.37, CHCl$_3$, 97% *ee*). HRMS *calcd.* for ($C_{17}H_{13}NO_3$+Na): 302.0793, found 302.0800.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.10 (dd, 1H, J_1 = 17.61Hz, J_2 = 4.63 Hz), 3.70 (dd, 1H, J_1 = 17.65 Hz, J_2 = 8.77 Hz), 4.03 (dd, 1H, J_1 = 8.63 Hz, J_2 = 4.72 Hz), 6.30 (d, 1H, J = 7.67 Hz), 6.73 (dt, 1H, J_t = 7.71 Hz, J_d = 0.78 Hz), 6.80 (d, 1H, J = 7.84 Hz), 7.03-7.07 (m, 2H), 7.19 (dt, 1H, J_t = 7.74 Hz, J_d = 1.34 Hz), 7.27-7.29 (m, 3H), 7.41(brs, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 34.0, 47.9, 86.2, 110.4, 122.7, 123.5, 124.0, 125.8, 126.4, 127.9, 128.2, 128.7, 130.8, 136.7, 140.6, 176.0, 176.1 ppm.

(2*R*,3*S*)-3-(4-methoxyphenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3b) and (2*S*,3*S*)-3-(4-methoxyphenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4b)

The reaction was carried out following the general procedure to furnish the crude product as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 3.05 ppm (dd), δ_{minor} 2.88 ppm (dd). The mixture of the diastereoisomers **3b** and **4b** was isolated by flash column chromatography (dichloromethane/diethyl ether = 95/5) in 89% overall yield. To obtain the single diastereoisomers a preparative TLC (dichloromethane/tetrahydrofuran = 90/10) was used.

(**3b** – Table 4, entry 2). The title compound was isolated as a single diastereoisomer (R_f = 0.25 dichloromethane/tetrahydrofuran = 90/10) in 24% yield (white solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 70:30

hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 23.4 min, τ_{minor} = 27.7 min. $[\alpha]_D^{26}$= - 74.5 (c = 0.75, CHCl$_3$, 97% ee). HRMS $calcd.$ for (C$_{18}$H$_{15}$NO$_4$+Na): 332.0914, found 332.0899.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.88 (dd, 1H, J_1 = 16.90 Hz, J_2 = 7.95 Hz), 3.69-3.76 (m, 4H), 4.03 (dd, 1H, J_1 = 13.83 Hz, J_2 = 7.90 Hz), 6.68-6.72 (m, 3H), 6.88 (d, 2H, J = 8.61 Hz), 7.10 (br s, 1H), 7.18 (dt, 1H, J_t = 7.71 Hz, J_d = 1.14 Hz), 7.32 (dt, 1H, J_t = 7.70 Hz, J_d = 1.13 Hz), 7.51 (d, 1H, J = 7.74 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.3, 50.4, 55.1, 86.3, 110.3, 113.9, 123.5, 123.7, 124.6, 125.1, 128.7, 131.2, 141.2, 159.4, 174.0, 174.8 ppm.
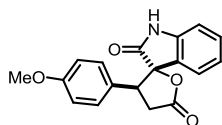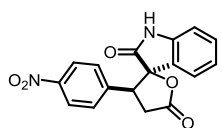
(**4b** – Table 4, entry 2). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.21 dichloromethane/tetrahydrofuran = 90/10) in 39% yield (white solid). The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.2 min, τ_{minor} = 25.3 min. $[\alpha]_D^{27}$= - 76.1 (c = 0.62, CHCl$_3$, 98% ee). HRMS $calcd.$ for (C$_{18}$H$_{15}$NO$_4$+Na): 332.0914, found 332.0899.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.05 (dd, 1H, J_1 = 17.50Hz, J_2 = 4.78 Hz), 3.68 (dd, 1H, J_1 = 17.48 Hz, J_2 = 8.67 Hz), 3.80 (s, 3H), 3.99 (dd, 1H, J_1 = 8.82, J_2 = 4.77 Hz), 6.36 (d, 1H, J = 7.41 Hz), 6.75-6.83 (m, 4H), 6.96 (d, 2H, J = 8.46 Hz), 7.20 (dt, 1H, J_t = 7.72 Hz, J_d = 1.08 Hz), 7.71(brs, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 34.2, 47.3, 55.2, 86.3, 110.2, 114.0, 122.7, 123.7, 126.6, 128.7, 129.0, 130.7, 140.5, 159.3, 175.8, 176.0 ppm.

(2*R*,3*S*)-3-(4-nitrophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3c) and (2*S*,3*S*)-3-(4-nitrophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4c)
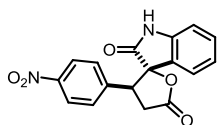
The reaction was carried out following the general procedure to furnish the crude products as a 1.1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 3.12 ppm (dd), δ_{minor} 2.98 ppm (dd). The two compounds **3c** and **4c** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/dietyl ether = 95/5).

(**3c** – Table 4, entry 3). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.24 dichloromethane/dietyl ether = 90/10) in 47% yield (white solid). The enantiomeric excess was determined to be 88% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 25.0 min, τ_{minor} = 22.7 min. $[\alpha]_D^{27}$= - 57.4 (c = 1.55, MeOH, 88% ee). HRMS $calcd.$ for (C$_{17}$H$_{12}$N$_2$O$_5$): 323.0668, found 323.0661.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.98 (dd, 1H, J_1 = 16.75 Hz, J_2 = 8.07 Hz), 3.77 (dd, 1H, J_1 = 16.72 Hz, J_2 = 13.77 Hz), 4.18 (dd, 1H, J_1 = 13.62 Hz, J_2 = 8.10 Hz), 6.76 (d, 1H, J = 8.10), 7.13 (d, 2H, J = 8.74 Hz), 7.22 (dt, 1H, J_t = 7.74 Hz, J_d = 0.78 Hz), 7.36 (dt, 1H, J_t = 7.67 Hz, J_d = 1.15 Hz), 7.49 (br s, 1H), 7.55 (d, 1H, J = 7.63 Hz), 8.02 (d, 2H, J = 9.00 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.0, 50.4, 85.9, 110.8, 123.7, 123.9, 124.1, 124.6, 128.6, 128.7, 131.8, 139.5, 141.1, 147.9, 173.6, 173.7 ppm.

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(**4c** – Table 4, entry 3). The title compound was isolated as a single diastereoisomer (R_f = 0.21 dichloromethane/diethyl ether = 90/10) in 42% yield (white solid). The enantiomeric excess was determined to be 92% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 23.3 min, τ_{minor} = 33.9 min. $[\alpha]_D^{27}$= - 53.3 (*c* = 0.39, MeOH, 92% *ee*). HRMS *calcd.* for ($C_{17}H_{12}N_2O_5$): 323.0668, found 323.0661.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.12 (dd, 1H, J_1 = 17.62Hz, J_2 = 5.67 Hz), 3.67 (dd, 1H, J_1 = 17.62 Hz, J_2 = 8.75 Hz), 4.16 (dd, 1H, J_1 = 8.65, J_2 = 5.52 Hz), 6.40 (d, 1H, J = 7.65 Hz), 6.78 (dt, 1H, J_t = 7.67 Hz, J_d = 1.10 Hz), 6.81 (d, 1H, J = 7.87 Hz), 7.18-7.24 (m, 3H), 7.53 (br s, 1H), 8.12 (d, 1H, J = 8.72 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.6, 47.7, 85.3, 110.7, 122.9, 123.1, 123.9, 125.9, 128.8, 131.3, 140.4, 143.6, 147.6, 174.4, 174.8 ppm.

(2*R*,3*S*)-3-(2-nitrophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3d) and (2*S*,3*S*)-3-(2-nitrophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4d)

The reaction was carried out following the general procedure to furnish the crude products as a 1.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 3.08 ppm (dd), δ_{minor} 2.98 ppm (dd). The two compounds **3d** and **4d** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/diethyl ether = 95/5).
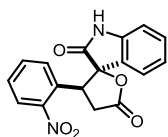
(**3d** – Table 4, entry 4). The title compound was isolated as a single diastereoisomer (R_f = 0.23 dichloromethane/diethyl ether = 90/10) in 43% yield (white solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak AD-H column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 20.4 min, τ_{minor} = 13.8 min. $[\alpha]_D^{27}$= - 116.5 (*c* = 0.83, CHCl$_3$, 94% *ee*). HRMS *calcd.* for ($C_{17}H_{12}N_2O_5$+Na): 347.0644, found 347.0643.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.98 (dd, 1H, J_1 = 18.21 Hz, J_2 = 0.94 Hz), 3.92 (dd, 1H, J_1 = 17.99 Hz, J_2 = 9.43 Hz), 4.84 (d, 1H, J = 9.27 Hz), 5.83 (d, 1H, J = 7.66), 6.58 (dt, 1H, J_t = 7.61 Hz, J_d = 0.91 Hz), 6.84 (d, 1H, J = 7.80), 7.17 (dt, 1H, J_t = 7.86 Hz, J_d = 1.24 Hz), 7.51-7.59 (m, 2H), 7.79 (dt, 1H, J_t = 7.60 Hz, J_d = 1.21 Hz), 7.87 (dd, 1H, J_1 = 8.13 Hz, J_2 = 1.20 Hz), 7.94 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 34.2, 41.8, 85.4, 110.5, 122.4, 123.2, 124.9, 125.5, 128.1, 129.3, 131.0, 133.6, 133.9, 141.6, 148.7, 175.5, 175.7 ppm.
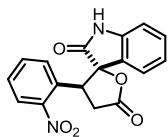
(**4d** – Table 4, entry 4). The title compound was isolated as a single diastereoisomer (R_f = 0.18 dichloromethane/diethyl ether = 90/10) in 49% yield (pale yellow solid). The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak AD-H column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.0 min, τ_{minor} = 9.4 min. $[\alpha]_D^{26}$= + 211.8 (*c* = 1.35, CHCl$_3$, 98% *ee*). HRMS *calcd.* for ($C_{17}H_{12}N_2O_5$+Na): 347.0644, found 347.0647.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.08 (dd, 1H, J_1 = 17.08 Hz, J_2 = 8.20 Hz), 3.73 (dd, 1H, J_1 = 17.00 Hz, J_2 = 12.87 Hz), 5.11 (dd, 1H, J_1 = 12.84, J_2 = 8.22 Hz), 6.67 (d, 1H, J = 7.97 Hz), 7.13-7.20 (m, 2H),

7.32 (dt, 1H, J_t = 7.92 Hz, J_d = 1.35 Hz), 7.34-7.44 (m, 2H), 7.54 (dd, 1H, J_1 = 8.15 Hz, J_2 = 1.27 Hz), 7.58 (dt, 1H, J_t = 7.65 Hz, J_d = 1.39 Hz) 7.78 (dd, 1H, J_1 = 7.93 Hz, J_2 = 1.07 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.9, 43.1, 86.1, 110.4, 123.1, 124.2, 124.8, 125.5, 126.1, 129.1, 129.2, 131.7, 132.7, 140.6, 150.6, 173.6, 173.9 ppm.

(2*R*,3*S*)-3-(4-chlorophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3e) and (2*S*,3*S*)-3-(4-chlorophenyl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4e)

The reaction was carried out following the general procedure to furnish the crude products as a 1.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 3.05 ppm (dd), δ_{minor} 2.90 ppm (dd). The two compounds **3e** and **4e** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/diethyl ether = 95/5).
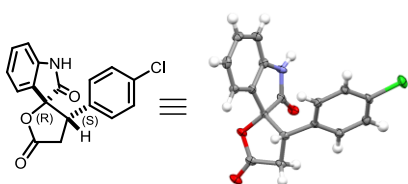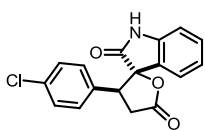

(**3e** – Table 4, entry 5). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.25 dichloromethane/diethyl ether = 90/10) in 39% yield (white solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 17.6 min, τ_{minor} = 20.5 min. $[\alpha]_D^{27}$= - 96.1 (*c* = 1.17, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{17}$H$_{12}$ClNO$_3$+Na): 336.0403, found 336.0402.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.90 (dd, 1H, J_1 = 16.96 Hz, J_2 = 8.14 Hz), 3.70 (dd, 1H, J_1 = 16.92 Hz, J_2 = 13.70 Hz), 4.05 (dd, 1H, J_1 = 13.70 Hz, J_2 = 8.02 Hz), 6.74 (d, 1H, J = 7.65), 6.88 (d, 2H, J = 8.47 Hz), 7.13-7.22 (m, 3H), 7.34 (dt, 1H, J_t = 7.67 Hz, J_d = 1.22 Hz), 7.51 (d, 1H, J = 7.56 Hz), 7.66 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.1, 50.3, 86.2, 110.7, 123.7, 124.5, 124.6, 128.8, 129.0, 130.5, 131.5, 134.3, 141.3, 174.2, 174.4 ppm.

The relative and absolute configuration for **3e** was unambiguously inferred by anomalous dispersion X-ray crystallographic analysis. Crystals of compound **3e** were obtained by slow evaporation of DCM at room temperature. CCDC 848635.
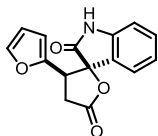

(**4e** – Table 4, entry 5). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.21 dichloromethane/diethyl ether = 90/10) in 54% yield (white solid). The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 15.0 min, τ_{minor} = 19.4 min. $[\alpha]_D^{27}$= - 56.3 (*c* = 1.08, CHCl$_3$, 98% *ee*). HRMS *calcd.* for (C$_{17}$H$_{12}$ClNO$_3$+Na): 336.0403, found 336.0410.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.05 (dd, 1H, J_1 = 17.64 Hz, J_2 = 5.11 Hz), 3.65 (dd, 1H, J_1 = 17.64 Hz, J_2 = 8.69 Hz), 4.01 (dd, 1H, J_1 = 8.57, J_2 = 5.07 Hz), 6.37 (d, 1H, J = 7.53 Hz), 6.78 (dt, 1H, J_t = 7.67 Hz, J_d = 0.95 Hz), 6.82 (d, 1H, J = 7.82 Hz), 6.96 (d, 2H, J = 8.49 Hz) 7.17-7.25 (m, 3H), 8.30 (br s, 1H), ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.9, 47.3, 86.0, 110.7, 122.9, 123.3, 126.2, 128.9, 129.2, 131.0, 134.1, 135.0, 140.6, 175.5, 175.9 ppm.

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(2*R*,3*S*)-3-(furan-2-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3f) and (2*S*,3*S*)-3-(furan-2-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4f)

The reaction was carried out following the general procedure to furnish the crude product as a 1.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 4.04 ppm (dd), δ_{minor} 4.14 ppm (dd). The mixture of the diastereoisomers **3f** and **4f** was isolated by flash column chromatography (dichloromethane/diethyl ether = 95/5) in 78% overall yield. To obtain the two compounds as single diastereoisomers a preparative TLC (dichloromethane/diethyl ether = 90/10) was carried out.

(**3f** – Table 4, entry 6). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.28 dichloromethane/diethyl ether = 90/10) in 30% yield (white solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.4 min, τ_{minor} = 20.8 min. [α]$_D^{27}$ = - 37.8 (*c* = 0.3, CHCl$_3$, 96% *ee*). HRMS *calcd.* for (C$_{15}$H$_{11}$NO$_4$+Na): 292.0586, found 292.0599.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.98 (dd, 1H, J_1 = 17.03 Hz, J_2 = 8.29 Hz), 3.67 (dd, 1H, J_1 = 16.92 Hz, J_2 = 13.16 Hz), 4.14 (dd, 1H, J_1 = 13.50 Hz, J_2 = 8.31 Hz), 6.06 (d, 1H, J = 3.21), 6.23 (dd, 1H, J_1 = 3.30 Hz, J_2 = 1.85 Hz), 6.81 (d, 1H, J = 7.87), 7.16(dt, 1H, J_t = 7.69 Hz, J_d = 0.76 Hz), 7.20 (dd, 1H, J_1 = 1.84 Hz, J_2 = 0.76 Hz), 7.35 (dt, 1H, J_t = 7.69 Hz, J_d = 1.08 Hz), 7.43-7.48 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.1, 44.6, 84.5, 108.0, 110.4, 110.5, 123.6, 124.7, 125.0, 131.3, 141.3, 142.7, 147.4, 173.8, 173.9 ppm.
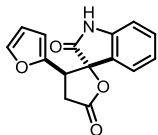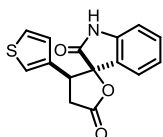

(**4f** – Table 4, entry 6). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.25 dichloromethane/diethyl ether = 90/10) in 35% yield (white solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 12.1 min, τ_{minor} = 15.8 min. [α]$_D^{26}$ = - 60.2 (*c* = 1.38, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{15}$H$_{11}$NO$_4$+Na): 292.0586, found 292.0595.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.01 (dd, 1H, J_1 = 17.38 Hz, J_2 = 4.08 Hz), 3.61 (dd, 1H, J_1 = 17.42 Hz, J_2 = 9.10 Hz), 4.04 (dd, 1H, J_1 = 9.39, J_2 = 4.18 Hz), 6.08 (d, 1H, J = 3.27 Hz), 6.27 (dd, 1H, J_1 = 3.27 Hz, J_2 = 1.84 Hz), 6.45 (d, 1H, J = 7.68 Hz), 6.81-6.88 (m, 2H), 7.21-7.26 (m, 1H), 7.30 (dd, 1H, J_1 = 1.79 Hz, J_2 = 0.60 Hz), 7.26 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.7, 41.6, 85.4, 108.5, 110.4, 110.5, 123.1, 123.6, 125.9, 131.1, 140.7, 142.4, 150.6, 175.0, 175.5 ppm.

**(2*R*,3*S*)-3-(thiophen-3-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3g) and (2*S*,3*S*)-3-(thiophen-3-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4g)**

The reaction was carried out following the general procedure to furnish the crude products as a 1.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 4.09 ppm (dd), δ_{minor} 4.14 ppm (dd). The two compounds **3g** and **4g** were isolated as single diastereoisomers by flash column chromatography (hexane/ethyl acetate = 65/35).

(**3g** – Table 4, entry 7). The title compound was isolated as a single diastereoisomer (R_f = 0.23 hexane/ethyl acetate = 50/50) in 38% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IB column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min,

λ = 215, 254 nm: τ_{major} = 36.6 min, τ_{minor} = 40.7 min. $[\alpha]_D^{27}$ = - 79.9 (*c* = 0.2, CHCl$_3$, 99% *ee*). HRMS *calcd.* for (C$_{15}$H$_{11}$NO$_3$S+Na): 308.0357, found 308.0352.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.98 (dd, 1H, J_1 = 16.88 Hz, J_2 = 8.10 Hz), 3.70 (dd, 1H, J_1 = 16.94 Hz, J_2 = 13.62 Hz), 4.14 (dd, 1H, J_1 = 13.94 Hz, J_2 = 8.33 Hz), 6.57 (dd, 1H, J_1 = 5.18 Hz, J_2 = 1.52 Hz), 6.76 (d, 1H, J = 8.06 Hz), 6.91-6.94 (m, 1H), 6.99 (br s, 1H), 7.15-7.21 (m, 2H), 7.35(dt, 1H, J_t = 7.69 Hz, J_d = 1.47 Hz), 7.50 (d, 1H, J = 6.99 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.1, 46.7, 85.5, 110.3, 123.1, 123.6, 124.6, 125.1, 126.3, 126.4, 131.4, 133.3, 141.3, 173.8, 174.4 ppm.
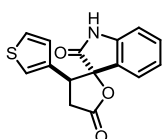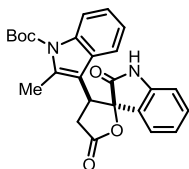
(**4g** – Table 4, entry 7). The title compound was isolated as a single diastereoisomer (R_f = 0.19 hexane/ethyl acetate = 50/50) 53% yield (pale yellow solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IB column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 40.8 min, τ_{minor} = 43.7 min. $[\alpha]_D^{27}$ = - 92.2 (*c* =

0.1, CHCl$_3$, 99% *ee*). HRMS *calcd.* for (C$_{15}$H$_{11}$NO$_3$S+Na): 308.0357, found 308.0352.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.01 (dd, 1H, J_1 = 17.63 Hz, J_2 = 4.76 Hz), 3.67 (dd, 1H, J_1 = 17.60 Hz, J_2 = 8.89 Hz), 4.09 (dd, 1H, J_1 = 8.46 Hz, J_2 = 4.48 Hz), 6.37 (d, 1H, J = 7.16 Hz), 6.76 (dd, 1H, J_1 = 4.93 Hz, J_2 = 1.28 Hz), 6.77-6.82 (m, 2H), 6.94-6.97 (m, 1H), 7.21(dt, 1H, J_t = 7.62 Hz, J_d = 1.09 Hz), 7.23-7.25 (m, 1H), 7.35 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 34.7, 43.6, 85.7, 110.1, 122.8, 122.9, 123.7, 126.3, 126.6, 126.9, 130.9, 137.8, 140.5, 175.2, 175.5 ppm.

tert-butyl 3-((2*R*,3*S*)-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indolin]-3-yl)-2-methyl-1H-indole-1-carboxylate (3h) and tert-butyl 3-((2*S*,3*S*)-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indolin]-3-yl)-2-methyl-1H-indole-1-carboxylate (4h)

The reaction was carried out following the general procedure to furnish the crude product as a 1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ 1.61 ppm (s), δ 1.63 ppm (s). The mixture of the diastereoisomers in their hemiacetal form was isolated by flash column chromatography (dichloromethane/dietyl ether = 95/5) in 82% overall yield. The isolated hemiacetal compounds were oxidized and the corresponding spirolactones **3h** and **4h** were obtained as single diastereoisomers by flash column chromatography (dichloromethane/dietyl ether = 95/5).

(**3h** – Table 4, entry 8). The title compound was isolated as a single diastereoisomer (R_f = 0.22 dichloromethane/diethyl ether 9/1) in 39% yield (pale yellow solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.6 min, τ_{minor} =

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10.8 min. $[\alpha]_D^{27}$= - 128.5 (c = 1.4, CHCl$_3$, 96% ee). HRMS $calcd.$ for (C$_{25}$H$_{24}$N$_2$O$_5$+Na): 455.1583, found 455.1578.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.61 (s, 9H), 2.05 (s, 3H), 2.88 (dd, 1H, J_1 = 16.85 Hz, J_2 = 8.13 Hz), 4.21 (dd, 1H, J_1 = 16.54 Hz, J_2 = 13.66 Hz), 4.30 (dd, 1H, J_1 = 13.59 Hz, J_2 = 8.11 Hz), 6.67 (d, 1H, J = 7.76 Hz), 7.10-7.21 (m, 4H), 7.28 (dt, 1H, J_t = 7.68 Hz, J_d = 1.31 Hz), 7.53 (d, 1H, J = 7.58 Hz), 7.75 (d, 1H, J = 8.06 Hz), 8.02 (d, 1H, J = 8.13 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8, 28.1, 31.4, 44.5, 84.3, 85.7, 108.0, 110.5, 114.9, 120.3, 122.4, 123.1, 123.5, 124.8, 125.2, 127.4, 131.1, 135.7, 137.2, 141.3, 150.1, 174.9, 175.3 ppm.
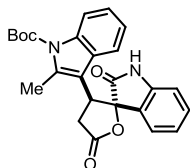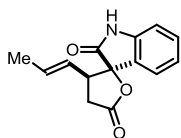
(**4h** – Table 4, entry 8). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.19 dichloromethane/diethyl ether 9/1) in 35% yield (pale yellow solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ$_{major}$ = 13.2 min, τ$_{minor}$ = 17.7 min. $[\alpha]_D^{26}$= - 63.4 (c = 1.4, CHCl$_3$, 97% ee). HRMS $calcd.$ for (C$_{25}$H$_{24}$N$_2$O$_5$+Na): 455.1583, found 455.1594.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.63 (s, 9H), 2.07 (s, 3H), 3.22 (dd, 1H, J_1 = 18.16 Hz, J_2 = 2.06 Hz), 3.76 (dd, 1H, J_1 = 18.23 Hz, J_2 = 10.07 Hz), 4.27 (dd, 1H, J_1 = 10.22 Hz, J_2 = 1.89 Hz), 6.22 (d, 1H, J = 7.71 Hz), 6.62 (dt, 1H, J_t = 7.70 Hz, J_d = 1.03 Hz), 6.83 (d, 1H, J = 7.77 Hz), 7.16 (dt, 1H, J_t = 7.60 Hz, J_d = 1.23 Hz), 7.26-7.33 (m, 2H), 7.51-7.57 (m, 1H), 7.96 (br s, 1H), 8.11-8.17 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.4, 28.2, 33.4, 39.7, 84.3, 86.4, 110.2, 114.8, 115.7, 118.6, 122.9, 123.3, 123.4, 123.8, 126.6, 127.7, 130.8, 135.6, 136.3, 140.7, 150.2, 176.9, 177.1 ppm.

(2R,3S)-3-(prop-1-en-1-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3i) and (2S,3S)-3-(prop-1-en-1-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4i)

The reaction was carried out following the general procedure to furnish the crude product as a 1.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{maj}5.07-5.19 ppm (m), δ_{min} 5.24-5.35 ppm (m). The mixture of the diastereoisomers in their hemiacetal form was isolated by flash column chromatography (hexane/ethyl acetate = 60/40) in 84% overall yield. The isolated hemiacetal compounds were oxidized and the corresponding spirolactones **3i** and **4i** were obtained as single diastereoisomers by flash column chromatography (dichloromethane/dietyl ether = 95/5).

(**3i** – Table 4, entry 9). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.23 dichloromethane/diethyl ether 9/1) in 29% yield (white solid). The enantiomeric excess was determined to be 89% by HPLC analysis on a Daicel Chiralpak IA column: 95:5 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ$_{major}$ = 38.5 min, τ$_{minor}$ = 34.8 min. $[\alpha]_D^{27}$= - 21.6 (c = 0.62, CHCl$_3$, 89% ee). HRMS $calcd.$ for (C$_{14}$H$_{13}$NO$_3$+Na): 266.0793, found 266.0799.

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^{1}H NMR (400 MHz, CDCl$_3$): δ 1.56 (dd, 3H, J_1 = 6.55 Hz, J_2 = 1.27 Hz), 2.74 (dd, 1H, J_1 = 16.97 Hz, J_2 = 8.17 Hz), 3.19 (dd, 1H, J_1 = 17.02 Hz, J_2 = 12.64 Hz), 3.39 (dt, 1H, J_d = 12.71 Hz, J_t = 8.01 Hz), 5.24-5.35 (m, 1H), 5.44 (dq, 1H, J_d = 15.28 Hz, J_q = 6.41 Hz), 6.86 (d, 1H, J = 7.79 Hz), 7.12 (dt, 1H, J_t = 7.72 Hz, J_d = 1.00 Hz), 7.29-7.39 (m, 2H), 7.65 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 17.8, 33.6, 49.0, 85.5, 110.3, 123.5, 123.6, 124.6, 125.2, 131.0, 131.9, 141.3, 174.6, 175.1 ppm.
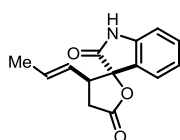

(**4i** – Table 4, entry 9). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.19 dichloromethane/diethyl ether 9/1) in 50% yield (pale yellow solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IA column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 41.7 min, τ_{minor} = 47.3 min. [α]$_D^{26}$= - 44.2 (*c* = 1.15, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{14}$H$_{13}$NO$_3$+Na): 266.0793, found 266.0802.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.55 (dd, 3H, J_1 = 6.43 Hz, J_2 = 1.38 Hz), 2.74 (dd, 1H, J_1 = 17.39 Hz, J_2 = 8.61 Hz), 3.14 (dd, 1H, J_1 = 17.57 Hz, J_2 = 8.61 Hz), 3.49 (q, 1H, J_q = 8.42 Hz), 5.07-5.19 (m, 1H), 5.54 (dq, 1H, J_d = 15.26 Hz, J_q = 6.45 Hz), 6.90 (d, 1H, J = 7.74 Hz), 7.06 (dt, 1H, J_t = 7.63 Hz, J_d = 0.85 Hz), 7.21 (d, 1H, J = 7.58 Hz), 7.31 (dt, 1H, J_t = 7.76 Hz, J_d = 1.19 Hz), 8.28 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 17.7, 34.0, 46.0, 85.5, 110.8, 123.0, 124.6, 125.6, 125.9, 130.7, 130.9, 140.7, 175.0, 175.4 ppm.

3-pentyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (j)

The reaction was carried out following the general procedure using 5 mol% of catalyst A and 5 mol% of *ortho*-fluorobenzoic acid, to furnish the crude product as a 2.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{maj} 6.95 ppm (d), δ_{min}6.90-6.93 ppm (m). The mixture of the diastereoisomers **3j** and **4j** was isolated by flash column chromatography (hexane/ethyl acetate = 65/35) in 63% overall yield as a pale yellow solid.
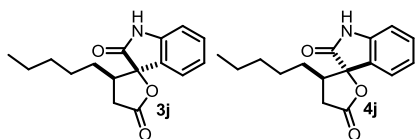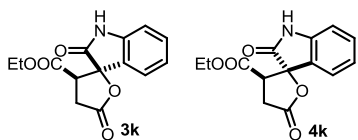

(**3j/4j** – Table 4, entry 10). The enantiomeric excess was determined to be 98% for the compound **3j** by HPLC analysis on a Daicel Chiralpak IA column: 97:3 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 57.5 min, τ_{minor} = 61.6 min. The enantiomeric excess was determined to be 86% for the compound **4j** by HPLC analysis on a Daicel Chiralpak IA column: 97:3 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 67.9 min, τ_{minor} = 48.2 min. [α]$_D^{25}$= - 64.0 (*c* = 0.93, CHCl). HRMS *calcd.* for (C$_{16}$H$_{19}$NO$_3$+Na): 296.1263, found 296.1277.

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.73-0.82 (m, 3H$_{maj}$, 3H$_{min}$), 1.03-1.34 (m, 8H$_{maj}$, 8H$_{min}$), 2.59 (dd, 1H$_{maj}$, J_1 = 17.28 Hz, J_2 = 9.93 Hz), 2.72-2.83 (m, 2H$_{min}$), 2.87-2.97 (m, 1H$_{maj}$, 1H$_{min}$), 3.05 (dd, 1H$_{maj}$, J_1 = 17.28 Hz, J_2 = 8.42 Hz), 6.90-6.93 (m, 1H$_{min}$), 6.95 (d, 1H$_{maj}$, J = 7.87 Hz), 7.05-7.13 (m, 1H$_{maj}$, 1H$_{min}$), 7.23 (1H$_{maj}$, J = 7.15 Hz), 7.30-7.36 (m, 1H$_{maj}$, 2H$_{min}$), 8.65 (br s, 1H$_{maj}$), 8.69 (br s, 1H$_{min}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8, 22.2, 22.3, 27.1, 27.7, 28.4, 30.3, 31.41, 31.44,

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33.7, 34.1, 42.4, 45.6, 86.0, 110.7, 111.2, 123.1, 123.5, 124.5, 124.7, 125.6, 125.7, 131.0, 131.2, 141.0, 141.6, 175.2, 175.7, 176.1 ppm.

3-(prop-1-en-1-yl)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (k)

The reaction was carried out following the general procedure to furnish the crude product as a 1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ 0.82 ppm (t), δ 1.12 ppm (t). The mixture of the diastereoisomers in their hemiacetal form was isolated by flash column chromatography (hexane/ethyl acetate = 40/60) in 79% overall yield. The isolated hemiacetal compounds were oxidized and the corresponding 1:1 mixture of spirolactones **3k** and **4k** was isolated by flash column chromatography (dichloromethane/dietyl ether = 90/10) in 72% overall yield as a pale yellow solid.
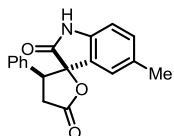

(**3k/4k** – Table 4, entry 11). The enantiomeric excess of compound **3k** was determined to be 66% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 24.1 min, τ_{minor} = 20.1 min. The enantiomeric excess of compound **4k** was determined to be 70% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.7 min, τ_{minor} = 12.4 min. $[\alpha]_D^{25}$= - 31.8 (*c* = 0.71, CHCl$_3$, mixture of diastereoisomers). HRMS *calcd.* for (C$_{14}$H$_{13}$NO$_5$+Na): 298.0686, found 298.0691.

^{1}H NMR (400 MHz, CDCl$_3$, mixture of diastereoisomers): δ 0.82 (t, 3H, J_t = 6.98 Hz), 1.12 (t, 3H, J_t = 7.10 Hz), 3.01 (dd, 1H, J_1 = 17.72 Hz, J_2 = 9.65 Hz), 3.08 (dd, 1H, J_1 = 18.02 Hz, J_2 = 9.48 Hz), 3.33 (dd, 1H, J_1 = 18.02 Hz, J_2 = 8.67 Hz), 3.54 (dd, 1H, J_1 = 17.72 Hz, J_2 = 12.10 Hz), 3.77-3.93 (m, 4H), 3.99-4.18 (m, 2H), 6.89-6.95 (m, 2H), 7.04 (dt, 1H, J_t = 7.59 Hz, J_d = 0.86 Hz), 7.09-7.15 (m, 1H), 7.19 (d, 1H, J = 7.65 Hz), 7.30-7.39 (m, 3H), 8.16-8.67 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.4, 13.6, 30.3, 30.9, 47.0, 48.3, 61.7, 62.0, 82.5, 82.6, 110.8, 110.9, 123.4, 123.5, 124.1, 124.5, 124.9, 125.3, 131.64, 131.66, 141.2, 142.0, 167.9, 168.4, 173.4, 173.6, 174.6, 174.8 ppm.

(2R,3S)-5'-methyl-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3l) and (2S,3S)-5'-methyl-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4l)

The reaction was carried out following the general procedure to furnish the crude products as a 1.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 2.00 ppm (s), δ_{minor} 2.39 ppm (s). The two compounds **3l** and **4l** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/diethyl ether = 98/2).

(**3l** – Table 5, entry 1). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.24 dichloromethane/diethyl ether 95/5) in 32% yield (colorless oil). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate

1.00 mL/min, λ = 215, 254 nm: τ_{major} = 30.8 min, τ_{minor} = 40.0 min. $[\alpha]_D^{27}$ = - 90.6 (c = 0.94, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{18}$H$_{15}$NO$_3$+Na): 316.0950, found 316.0936.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.39 (s, 3H), 2.89 (dd, 1H, J_1 = 16.83 Hz, J_2 = 7.88 Hz), 3.77 (dd, 1H, J_1 = 16.75 Hz, J_2 = 13.68 Hz), 4.07 (dd, 1H, J_1 = 13.83 Hz, J_2 = 8.10 Hz), 6.60 (d, 1H, J = 8.01 Hz), 6.92-6.99 (m, 2H), 7.08-7.25 (m, 5H), 7.34 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 21.1, 32.1, 50.7, 86.5, 110.2, 125.0, 125.2, 127.6, 128.3, 128.6, 131.6, 132.1, 133.2, 138.9, 174.3, 174.8 ppm.
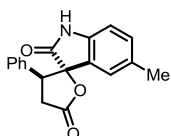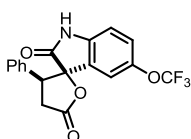

(**4l** – Table 5, entry 1). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.21 dichloromethane/diethyl ether 95/5) in 57% yield (pale yellow oil). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 27.2 min, τ_{minor} = 34.4 min. $[\alpha]_D^{27}$ = - 37.8 (c = 1.1, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{18}$H$_{15}$NO$_3$+Na): 316.0950, found 316.0944.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.00 (s, 3H), 3.08 (dd, 1H, J_1 = 17.54 Hz, J_2 = 4.39 Hz), 3.67 (dd, 1H, J_1 = 17.49 Hz, J_2 = 8.86 Hz), 3.99 (dd, 1H, J_1 = 8.93 Hz, J_2 = 4.61 Hz), 6.00 (br s, 1H), 6.68 (d, 1H, J = 7.97 Hz), 6.95 (d, 1H, J = 7.78 Hz), 6.98-7.05 (m, 2H), 7.25-7.28 (m, 3H), 7.95 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 20.7, 33.9, 47.8, 86.4, 110.0, 123.5, 127.2, 128.0, 128.1, 128.6, 131.0, 132.2, 136.8, 138.1, 176.1, 176.3 ppm.

(2*R*,3*S*)-3-phenyl-5'-(trifluoromethoxy)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3m) and (2*S*,3*S*)-3-phenyl-5'-(trifluoromethoxy)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4m)

The reaction was carried out following the general procedure to furnish the crude products as a 1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ 2.92 ppm (dd), δ 3.08 ppm (dd). The two compounds **3m** and **4m** were isolated as single diastereoisomers by flash column chromatography (hexane/dietyl ether = 50/50).


(**3m** – Table 5, entry 2). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.22 hexane/diethyl ether 50/50) in 44% yield (white solid). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak AD-H column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 30.6 min, τ_{minor} = 33.6 min. $[\alpha]_D^{27}$ = - 73.0 (c = 1.31, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{18}$H$_{12}$NO$_4$F$_3$+Na): 386.0616, found 386.0613.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.92 (dd, 1H, J_1 = 17.27 Hz, J_2 = 8.08 Hz), 3.73 (dd, 1H, J_1 = 17.19 Hz, J_2 = 13.87 Hz), 4.06 (dd, 1H, J_1 = 13.93 Hz, J_2 = 8.11 Hz), 6.75 (d, 1H, J = 8.40 Hz), 6.91-6.97 (m, 2H), 7.15-7.27 (m, 4H), 7.43 (d, 1H, J = 8.40 Hz), 7.87 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 31.9, 51.1, 86.1, 111.3, 118.5, 119.4, 121.5, 124.5, 126.5, 127.6, 128.6, 128.8, 131.4, 139.9, 145.2, 174.2 ppm.

(**4m** – Table 5, entry 2). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.19 hexane/diethyl ether 50/50) in 48% yield (white solid). The enantiomeric excess was determined to be 93% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00
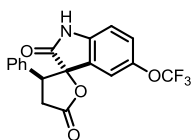
mL/min, λ = 215, 254 nm: τ_{major} = 9.7 min, τminor = 11.9 min. $[\alpha]_D^{27}$= -31.9 (c = 1.05, CHCl$_3$, 93% *ee*). HRMS *calcd.* for (C$_{18}$H$_{12}$NO$_4$F$_3$+Na): 386.0616, found 386.0598.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.08 (dd, 1H, J_1 = 17.98 Hz, J_2 = 4.03 Hz), 3.72 (dd, 1H, J_1 = 17.98 Hz, J_2 = 8.80 Hz), 4.00 (dd, 1H, J_1 = 8.81 Hz, J_2 = 3.68 Hz), 6.07 (br s, 1H), 6.85 (d, 1H, J = 8.53 Hz), 6.97-7.09 (m, 3H), 7.26-7.32 (m, 3H), 8.69 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.9, 47.8, 85.9, 111.1, 120.4, 124.2, 124.9, 127.7, 128.7, 128.9, 136.3, 139.3, 144.42, 144.4, 175.7, 176.5 ppm.

(2*R*,3*S*)-5'-bromo-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3n) and (2*S*,3*S*)-5'-bromo-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4n)

The reaction was carried out following the general procedure to furnish the crude products as a 1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ 2.91 ppm (dd), δ 3.08 ppm (dd). The two compounds **3n** and **4n** were isolated as single diastereoisomers by flash column chromatography (dichloromethane/dietyl ether = 98/2).
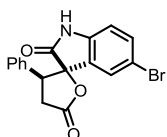
(**3n** – Table 5, entry 3). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.18 dichloromethane/diethyl ether 95/5) in 24% yield (white solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 11.1 min, τ_{minor} = 12.7 min. $[\alpha]_D^{27}$= -148.6 (c = 1.44, CHCl$_3$, 96% *ee*). HRMS *calcd.* for (C$_{17}$H$_{12}$NO$_3$Br+Na): 379.9898, found 379.9890.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.91 (dd, 1H, J_1 = 17.17 Hz, J_2 = 8.15 Hz), 3.74 (dd, 1H, J_1 = 17.14 Hz, J_2 = 13.82 Hz), 4.06 (dd, 1H, J_1 = 13.95 Hz, J_2 = 8.06 Hz), 6.62 (d, 1H, J = 8.46 Hz), 6.95-7.00 (m, 2H), 7.16-7.27 (m, 3H), 7.46 (dd, 1H, J_1 = 8.42 Hz, J_2 = 2.21 Hz), 7.55 (br s, 1H), 7.66 (d, 1H, J = 1.86 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 31.9, 51.0, 85.9, 111.9, 116.0, 127.1, 127.6, 127.8, 128.5, 128.7, 131.5, 134.2, 140.2, 173.6, 174.1ppm.
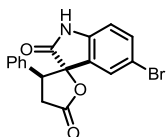
(**4n** – Table 5, entry 3). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.15 dichloromethane/diethyl ether 95/5) in 40% yield (pale yellow solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.2 min, τ_{minor} = 12.2 min. $[\alpha]_D^{27}$= + 35.9 (c = 0.96, CHCl$_3$, 96% *ee*). HRMS *calcd.* for (C$_{17}$H$_{12}$NO$_3$Br+Na): 379.9898, found 379.9881.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.08 (dd, 1H, J_1 = 18.02 Hz, J_2 = 4.46 Hz), 3.68 (dd, 1H, J_1 = 18.00 Hz, J_2 = 8.69 Hz), 3.99 (dd, 1H, J_1 = 8.76 Hz, J_2 = 4.32 Hz), 6.24 (d, 1H, J = 2.14 Hz), 6.71 (d, 1H, J = 8.44 Hz), 6.98-7.04 (m, 2H), 7.27-7.36 (m, 3H), 8.37 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.7, 47.8, 86.0, 111.8, 115.3, 125.4, 127.8, 128.6, 128.9, 129.7, 133.6, 136.4, 139.6, 175.7, 175.9 ppm.

7'-bromo-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (o)

The reaction was carried out following the general procedure to furnish the crude product as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{maj} 3.04 ppm (dd), δ_{min} 2.93ppm (dd). The mixture of the diastereoisomers **3o** and **4o** was isolated by flash column chromatography (hexane/ethyl acetate = 90/10 then 80/20) in 93% overall yield as a yellow solid.
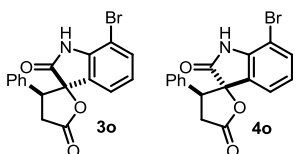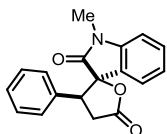

(**3o/4o** – Table 5, entry 4). The enantiomeric excess of compound **3o** was determined to be 95% by HPLC analysis on a Daicel Chiralpak AD-H column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 35.7 min, τ_{minor} = 31.5 min. The enantiomeric excess of compound **4o** was determined to be 95% by HPLC analysis on a Daicel Chiralpak AD-H column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 39.0 min, τ_{minor} = 56.4 min. $[\alpha]_D^{25}$= - 36.5 (*c* = 1.13, CHCl$_3$). HRMS *calcd.* for (C$_{17}$H$_{12}$NO$_3$Br+Na): 379.9898, found 379.9880.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.93 (dd, 1H$_{min}$, J_1 = 16.72 Hz, J_2 = 7.83 Hz), 3.04 (dd, 1H$_{maj}$, J_1 = 17.89 Hz, J_2 = 3.82 Hz), 3.70 (dd, 1H$_{maj}$, J_1 = 17.79 Hz, J_2 = 8.89 Hz), 3.78 (dd, 1H$_{min}$, J_1 = 16.98 Hz, J_2 = 13.84 Hz), 3.98 (dd, 1H$_{maj}$, J_1 = 8.63 Hz, J_2 = 3.77 Hz), 4.07 (dd, 1H$_{min}$, J_1 = 13.75 Hz, J_2 = 7.82 Hz), 6.13 (d, 1H$_{maj}$, J = 7.73 Hz), 6.59 (dd, 1H$_{maj}$, J_1 = 8.18 Hz, J_2 = 7.61 Hz), 6.94-7.13 (m, 7H), 7.18-7.26 (m, 3H), 7.26-7.31 (m, 6H), 7.44-7.55 (m, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 31.9, 33.9, 47.9, 51.0, 86.3, 86.8, 87.1, 123.4, 123.8, 124.7, 124.9, 125.3, 126.4, 127.5, 127.9, 128.4, 128.6, 128.81, 128.84, 131.5, 133.6, 133.9, 136.7, 140.0, 174.2, 174.5, 175.5 ppm.

(2*R*,3*S*)-1'-methyl-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (3p) and (2*S*,3*S*)-1'-methyl-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (4p)

The reaction was carried out following the general procedure using 5 mol% of catalyst **A** and 5 mol% of *ortho*-fluorobenzoic acid, to furnish the crude product as a 1.4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{maj} 2.81 ppm (s), δ_{min} 3.21 ppm (s). The mixture of the diastereoisomers in their hemiacetal form was isolated by flash column chromatography (hexane/ethyl acetate = 70/30) in 70% overall yield. The isolated hemiacetal compounds were oxidized and the corresponding spirolactones **3p** and **4p** were obtained as single diastereoisomers by flash column chromatography (hexane/ethyl acetate = 90/10).

(**3p** – Table 5, entry 5). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.23 hexane/ethyl acetate 80/20) in 39% yield (pale yellow solid). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak IC column: 60:40 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 24.7 min, τ_{minor} = 43.6 min. $[\alpha]_D^{27}$= - 52.8 (*c* = 1.26, CHCl$_3$, 90% *ee*). HRMS *calcd.* for (C$_{18}$H$_{15}$NO$_3$+Na): 316.0950, found 316.0965.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.81 (s, 3H), 2.91 (dd, 1H, J_1 = 16.88 Hz, J_2 = 7.96 Hz), 3.82 (dd, 1H, J_1 = 16.93 Hz, J_2 = 13.67 Hz), 4.07 (dd, 1H, J_1 = 13.67 Hz, J_2 = 7.97 Hz), 6.66 (d, 1H, J = 7.86 Hz), 6.87-6.95 (m, 2H), 7.11-7.24 (m, 4H), 7.38 (dt, 1H, J_t = 7.83 Hz, J_d = 1.16 Hz), 7.53 (dd, 1H, J_1 = 7.62 Hz, J_2 = 0.88 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 25.8, 32.1, 50.86.4, 108.5, 123.4, 124.1, 124.7, 127.5, 128.2, 128.4, 131.2, 132.0, 144.3, 172.5, 174.8 ppm.
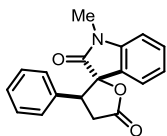

(**4p** – Table 5, entry 5). The title compound was isolated as a single diastereoisomer (R$_f$ = 0.18 hexane/ethyl acetate 80/20) in 28% yield (pale yellow solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 60:40 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 31.3 min, τ_{minor} = 38.4 min. [α]$_D^{28}$= - 45.1 (c = 1.05, CHCl$_3$, 94% ee). HRMS $calcd.$ for (C$_{18}$H$_{15}$NO$_3$+Na): 316.0950, found 316.0952.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.07 (dd, 1H, J_1 = 17.60 Hz, J_2 = 4.64 Hz), 3.21 (s, 3H), 3.71 (dd, 1H, J_1 = 17.58 Hz, J_2 = 8.83 Hz), 3.96 (dd, 1H, J_1 = 8.79 Hz, J_2 = 4.74 Hz), 6.26 (d, 1H, J = 7.38 Hz), 6.68-6.78 (m, 1H), 6.95-7.05 (m, 2H), 7.19-7.26 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 26.4, 34.1, 47.8, 85.9, 108.4, 122.7, 123.2, 126.0, 127.8, 128.1, 128.6, 130.7, 136.9, 143.7, 174.2, 176.0 ppm.

1'-benzyl-3-phenyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (q)

The reaction was carried out following the general procedure using 5 mol% of catalyst **A** and 5 mol% of $ortho$-fluorobenzoic acid, to furnish the crude product as a 1.1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{maj} 2.95 ppm (dd), δ_{min} 3.15 ppm (dd). The mixture of the diastereoisomers **3q** and **4q** was isolated by flash column chromatography (hexane/ethyl acetate = 90/10) in 92% overall yield as a yellow solid.
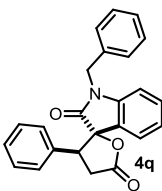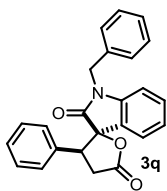
(**3q/4q** – Table 5, entry 6). The enantiomeric excess of compound 3q was determined to be 95% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 70.8 min, τ_{minor} = 119.6 min. The enantiomeric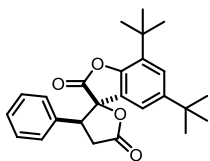 excess of compound **4q** was determined to be 95% by HPLC analysis on a Daicel Chiralpak IC column: 85:15 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 75.9 min, τ_{minor} = 89.6 min. [α]$_D^{28}$= - 109.4 (c = 1.22, CHCl). HRMS $calcd.$ for (C$_{24}$H$_{19}$NO$_3$+Na): 392.1263, found 392.1269.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.95 (dd, 1H$_{maj}$, J_1 = 16.69 Hz, J_2 = 8.13 Hz), 3.15 (dd, 1H$_{min}$, J_1 = 17.55 Hz, J_2 = 5.99 Hz), 3.65 (dd, 1H$_{min}$, J_1 = 17.55 Hz, J_2 = 8.64 Hz), 3.91 (dd, 1H$_{maj}$, J_1 = 16.69 Hz, J_2 = 13.66 Hz), 4.05-4.25 (m, 3H), 4.81 (d, 1H$_{min}$, J = 15.56 Hz), 4.94-5.02 (m, 2H), 6.39-6.47 (m, 4H), 6.62 (d, 1H$_{min}$, J = 8.00 Hz), 6.72 (dt, 1H$_{min}$, J_t = 7.68 Hz, J_d = 0.94 Hz), 6.96-7.03 (m, 4H), 7.05-7.25 (m, 14H), 7.27-7.36 (m, 4H), 4.56 (d, 1H$_{maj}$, J = 7.54 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 32.2, 34.0, 43.6, 44.0, 48.2, 50.8, 86.0, 86.3, 109.6, 109.9, 122.7, 123.4, 123.5, 124.2,

(2'R,3'S)-5,7-di-tert-butyl-3'-phenyl-2H,3'H-spiro[benzofuran-3,2'-furan]-2,5'(4'H)-dione (3r) and (2'S,3'S)-5,7-di-tert-butyl-3'-phenyl-2H,3'H-spiro[benzofuran-3,2'-furan]-2,5'(4'H)-dione (4r)

The reaction was carried out following the general procedure using 5 mol% of catalyst **A** and 5 mol% of *ortho*-fluorobenzoic acid, to furnish the crude products as a 1.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ 0.99 ppm (s), δ 1.18 ppm (s). The two compounds **3r** and **4r** were isolated as single diastereoisomers by flash column chromatography (hexane/diethyl ether = 90/10).

(**3r** – Table 5, entry 7). The title compound was isolated as a single diastereoisomer (R_f = 0.25 hexane/diethyl ether 80/20) in 30% yield (white solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 6.8 min, τ_{minor} = 9.8 min.

$[\alpha]_D^{28}$= - 32.1 (*c* = 0.79, CHCl$_3$, 96% *ee*). HRMS *calcd.* for (C$_{25}$H$_{28}$O$_4$+Na): 415.1885, found 415.1902.

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.99 (s, 9H), 1.35 (s, 9H), 3.07 (dd, 1H, J_1 = 17.59 Hz, J_2 = 2.64 Hz), 3.75 (dd, 1H, J_1 = 17.59 Hz, J_2 = 8.76 Hz), 3.95 (dd, 1H, J_1 = 8.76 Hz, J_2 = 2.64 Hz), 5.97 (d, 1H, J = 2.15 Hz), 6.97-7.00 (m, 2H), 7.22 (d, 1H, J = 2.09 Hz), 7.27-7.32 (m, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 29.5, 31.1, 34.0, 34.3, 34.5, 48.6, 84.3, 121.0, 125.8, 128.0, 128.6, 128.9, 133.4, 136.4, 147.0, 149.3, 174.3, 175.4 ppm.
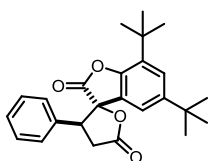
(**4r** – Table 5, entry 7). The title compound was isolated as a single diastereoisomer (R_f = 0.21 hexane/diethyl ether 80/20) in 57% yield (colorless oil). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.0 min, τ_{minor} = 7.4 min.

$[\alpha]_D^{28}$= - 63.7 (*c* = 1.26, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{25}$H$_{28}$O$_4$+Na): 415.1885, found 415.1900.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.18 (s, 9H), 1.38 (s, 9H), 2.96 (dd, 1H, J_1 = 17.04 Hz, J_2 = 7.93 Hz), 3.72 (dd, 1H, J_1 = 17.04 Hz, J_2 = 13.87 Hz), 4.08 (dd, 1H, J_1 = 13.87 Hz, J_2 = 7.93 Hz), 6.77-6.83 (m, 2H), 7.14-7.25 (m, 3H), 7.40 (dd, 2H, J_1 = 11.34 Hz, J_2 = 2.08 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 29.2, 31.2, 31.5, 34.2, 35.0, 51.5, 85.8, 118.4, 122.8, 126.1, 127.2, 128.72, 128.79, 131.1, 134.1, 148.7, 149.6, 172.2, 173.9 ppm.

3.6.10 Products Derivatization

(S)-methyl 3-((R)-3-hydroxy-2-oxoindolin-3-yl)-3-phenylpropanoate (5a) and (S)-methyl 3-((S)-3-hydroxy-2-oxoindolin-3-yl)-3-phenylpropanoate (5b)
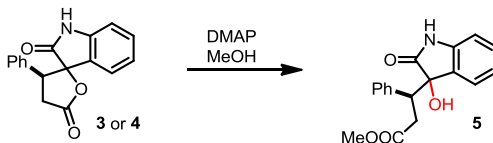
1.1 equivalents of DMAP (4-(Dimethylamino)pyridine) were added (13.4 mg, 0.11 mmol) to a stirred solution of compound **3** or **4** (27.9 mg, 0.1 mmol) in methanol. The solution was stirred at room temperature overnight. The methanol was removed *in vacuo* and the product **5** was isolated by flash column chromatography (hexane/ethyl acetate = gradient from 3/2 to 1/1).
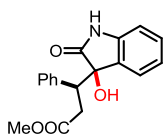
(**5a** – Scheme 8). The title compound was obtained starting from the compound 3a and it was isolated as white solid in 40% yield. The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.0 min, τ_{minor} = 12.6 min. $[\alpha]_D^{28}$ = + 2.5 (*c* = 0.30, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{18}$H$_{17}$NO$_4$+Na): 334.1055, found 334.1059.
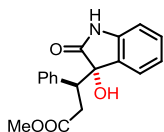
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.92 (dd, 1H, J_1 = 16.33 Hz, J_2 = 8.35 Hz), 3.40–3.50 (m, 2H), 3.58 (s, 3H), 3.86 (dd, 1H, J_1 = 8.59 Hz, J_2 = 6.04 Hz), 6.59 (d, 1H, J = 7.81 Hz), 6.91-7.05 (m, 3H), 7.06-7.18 (m, 4H), 7.26-7.32 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 33.2, 49.2, 51.9, 77.9, 99.9, 109.7, 122.8, 124.6, 127.2, 127.8, 129.0, 129.7, 129.9, 136.6, 139.8, 173.6, 178.0 ppm.

(**5b** – Scheme 8). The title compound was obtained starting from the compound 4a and it was isolated as white solid in 63% yield. The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.6 min, τ_{minor} = 11.4 min. $[\alpha]_D^{28}$ = - 2.9 (*c* = 0.905, CHCl$_3$, 94% *ee*). HRMS *calcd.* for (C$_{18}$H$_{17}$NO$_4$+Na): 334.1055, found 334.1059.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.89 (dd, 1H, J_1 = 15.89 Hz, J_2 = 9.73 Hz), 3.42 (dd, 1H, J_1 = 15.74 Hz, J_2 = 5.23 Hz), 3.56 (s, 3H), 3.66 (br s, 1H), 3.75 (dd, 1H, J_1 = 9.74 Hz, J_2 = 5.26 Hz), 6.64 (d, 1H, J = 7.73 Hz), 6.77-6.86 (m, 1H), 7.01-7.15 (m, 1H), 7.22-7.26 (m, 1H), 7.34 (d, 1H, J = 7.38 Hz), 7.62 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 34.2, 49.4, 51.8, 78.9, 110.1, 122.7, 125.4, 127.4, 127.8, 128.3, 128.95, 128.97, 136.6, 140.6, 172.9, 179.2 ppm.

UNIVERSITAT ROVIRA I VIRGILI
ASSESSING THE VERSATILITY OF ORGANOCATALYSIS AS A STRATEGY FOR ENABLING NOVEL ASYMMETRIC TRANSFORMATI
Giulia Bergonzini
Dipòsit Legal: T 1661-2014

Dioxindole in Asymmetric Catalytic Synthesis   **87**

Synthesis of (*R*)-3-hydroxy-3-((*S*)-3-hydroxy-1-phenylpropyl)indolin-2-one (6a) and (*S*)-3-hydroxy-3-((*S*)-3-hydroxy-1-phenylpropyl)indolin-2-one (6b) starting from dioxindole 1
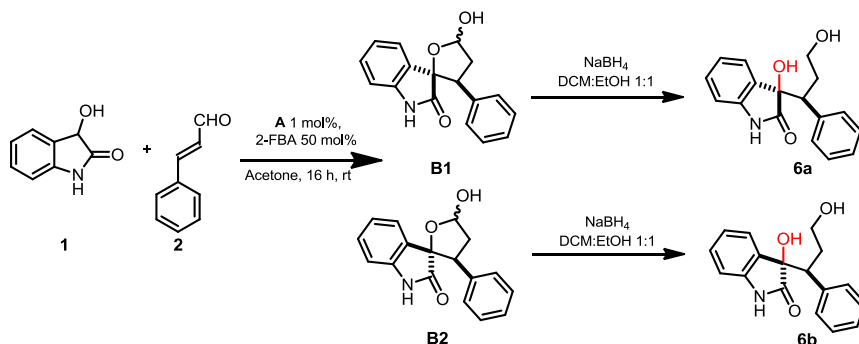
The reaction was carried out following the general procedure to furnish the hemiacetals **B1** and **B2**, obtained as single diastereoisomers by flash column chromatography (hexane/ethyl acetate = 60/40; $R_{f\,B1}$ = 0.25 hexane/ethyl acetate = 60/40, $R_{f\,B2}$ = 0.21 hexane/ethyl acetate = 50/50).

The corresponding hemiacetal **B** (28.1 mg, 0.1 mmol) was added in small portions to a stirred suspension of NaBH$_4$ (0.15 mmol, 5.7 mg, 1.5 equiv) in 1 mL of a 1:1 dichloromethane /ethanol mixture at 0 °C. The mixture was vigorously stirred at this temperature for 30 min (TLC monitoring). Then water (50 μL) was added and the reaction was stirred until bubbling stop. The mixture was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent evaporated under reduced pressure. The residue was dissolved and purified by flash chromatography using a mixture of hexane/ethyl acetate (gradient from 1:1 to pure ethyl acetate) to give the pure product **6**.
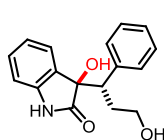
(**6a** – Scheme 8). The title compound was obtained starting from the compound **B1** and it was isolated as a white solid in 60% yield (from **1**). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.8 min, τ_{minor} = 16.5 min. $[\alpha]_D^{28}$ = + 34.7 (*c* = 0.95, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{17}$H$_{17}$NO$_3$+Na): 306.1106, found 306.1095.

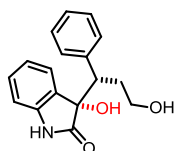^{1}H NMR (400 MHz, CDCl$_3$): δ 1.91-2.02 (m, 1H), 2.32-2.44 (m, 1H), 2.77 (br s, 1H), 3.39-3.52 (m, 2H), 3.61-3.69 (m, 1H), 4.93 (br s, 1H), 6.61 (d, 1H, *J* = 7.75 Hz), 6.94 (t, 1H, *J* = 7.70 Hz), 7.04-7.19 (m, 7H), 8.19 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 31.3, 50.7, 61.0, 78.4, 110.0, 122.5, 125.0, 127.0, 127.8, 129.3, 129.4, 130.1, 137.6, 140.2, 180.1ppm.

(**6b** – Scheme 8). The title compound was obtained starting from the compound **B2** and it was isolated as a white solid in 60% yield (from **1**). The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 17.6 min, τ_{minor} = 15.1 min. $[\alpha]_D^{28}$ = + 17.0 (*c* = 0.62, CHCl$_3$, 97% *ee*). HRMS *calcd.* for (C$_{17}$H$_{17}$NO$_3$+Na): 306.1106, found 306.1097.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.02-2.14 (m, 1H), 2.48-2.86 (m, 2H), 3.35-3.50 (m, 2H), 3.59-3.73 (m, 1H), 4.67 (br s, 1H), 6.60 (d, 1H, J = 7.77 Hz), 6.75-6.81 (m, 2H), 7.00-7.13 (m, 4H), 7.71 (t, 1H, J = 7.67 Hz), 7.43 (d, 1H, J = 7.46 Hz), 7.69 (br s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 31.7, 50.3, 60.7, 79.3, 110.0, 122.7, 125.5, 127.2, 127.9, 128.9, 129.1, 129.7, 137.5, 140.8, 180.0 ppm.

Synthesis of (*R*)-3-hydroxy-3-((*S*)-3-hydroxy-1-phenylpropyl)indolin-2-one (6a) and (*S*)-3-hydroxy-3-((*S*)-3-hydroxy-1-phenylpropyl)indolin-2-one (6b) starting from 3-((tetrahydro-2H-pyran-2-yl)oxy)indolin-2-one
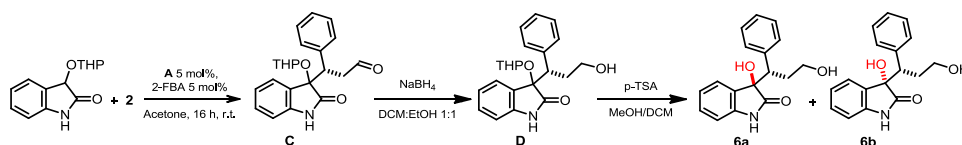
The reaction was carried out following the general procedure, using 5 mol% of the catalyst **A** and 5 mol% of *ortho*-fluorobenzoic acid. The corresponding aldehyde **C** was isolated by flash column chromatography (hexane/ethyl acetate = 70/30) as a complex mixture of diastereoisomers (THP introduces a third stereogenic center). The aldehyde was added in small portions to a stirred suspension of NaBH$_4$ (1.5 equiv) in 1 mL of a 1:1 dichloromethane/ethanol mixture at 0 °C. The mixture was vigorously stirred at this temperature for 30 min (TLC monitoring). Then water (50 μL) was added and the reaction was stirred until bubbling stop. The mixture was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent evaporated. The obtained alcohol **D** was used without further purification.

p-Toluensulfonic acid (10 mol% respect to **D**) was added to a mixture of the alcohol **D** dissolved in methanol and dichlorometane 1/1 (5 mL/mmol). After stirring at room temperature overnight, the reaction was quenched with saturated aqueous NaHCO$_3$. The layers were separated, the aqueous phase washed twice with dichloromethane, then the combined organic extracts were dried over MgSO$_4$ and concentrated *in vacuo.* Purification of the obtained residue by flash chromatography (hexane/ethyl acetate 50/50) afforded the products **6a** and **6b** as a 1.1:1 inseparable mixture of diastereoisomers in 92% overall yield; d.r. determined by integration of ^{1}H NMR signal: δ 1.91-2.02 ppm (m), δ 2.02-2.14 ppm (m).

The enantiomeric excess of compound **6a** was determined to be 87% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.8 min, τ_{minor} = 16.5 min. The enantiomeric excess of compound 6b was determined to be 90% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 17.6 min, τ_{minor} = 15.1 min.

3.6.11 Synthesis of Maremycin A

(2*S*,3*R*)-1',3-dimethyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (9)

A 25mL round bottom flask equipped with a Teflon-coated stir bar and a plastic cap was charged with (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **A** (99.7 mg, 0.306 mmol, 5

mol%) and 12.2 mL of acetone. Then, *ortho*-fluorobenzoic acid (0.306 mmol, 42.8 mg, 5 mol%) was added in one portion and the resulting solution was stirred at room temperature for 10 minutes. The reaction was started by the sequential addition of the crotonaldehyde **2** (603.5 μL, 7.34 mmol, 1.2 equiv) and the 3-hydroxy-1-methylindolin-2-one **7** (1 g, 6.12 mmol). The reaction was stirred over 16 h. The crude mixture was then flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (50 mL). Solvent was removed in vacuo and the crude of the reaction dissolved in 15 mL of dichloromethane. Then pyridinium chlorochromate (PCC, 3.9 g, 18 mmol, 3 equiv) was added in one portion and the resulting yellow suspension was stirred at room temperature for 16 h. The resulting mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (50 mL). Solvent was removed in vacuo and the crude product analyzed by ^{1}H NMR spectroscopy (3.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 2.49 ppm (dd), δ_{minor} 2.72 ppm (dd).

The title compound **9** was isolated as a single diastereoisomer (pale yellow solid) by flash column chromatography (dichloromethane/dietyl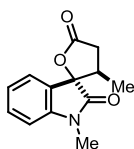 ether = 99/1 then dichloromethane/dietyl ether = 95/5) in 63% overall yield. The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak AD-H column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 49.7 min, τ_{minor} = 68.3 min. $[\alpha]_D^{26}$ = - 24 (*c* = 0.35, CHCl$_3$, 95% *ee*). HRMS *calcd.* for (C$_{13}$H$_{13}$NO$_3$+Na): 254.0786, found 254.0793.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.01 (d, 3H, *J* = 7.16 Hz), 2.49 (dd, 1H, J_1 = 17.37 Hz, J_2 = 7.02 Hz), 2.90-3.01 (m, 1H), 3.21 (s, 3H), 3.25 (dd, 1H, J_1 = 17.37 Hz, J_2 = 8.53 Hz), 6.88 (d, 1H, *J* = 7.93 Hz), 7.11 (dt, 1H, J_t = 7.63 Hz, J_d = 0.94 Hz), 7.29 (d, 1H, *J* = 7.39 Hz), 7.40 (dt, 1H, J_t = 7.88 Hz, J_d = 1.22 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 16.1, 26.5, 35.9, 37.0, 85.7, 109.0, 123.0, 124.0, 125.6, 130.9, 144.0, 174.1, 175.4 ppm.

(2*S*,3*R*,4*S*)-4-azido-1',3-dimethyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (10) and (2*S*,3*R*,4*R*)-4-azido-1',3-dimethyl-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (11)

A slighly modified literature procedure[11] has been used to achieve products **10** and **11**. LDA (2 M solution in THF; 2.34 mL, 4.68 mmol) was added dropwise at -78 °C to a stirred solution of the lactone **9** in THF (18 mL). The temperature was risen to -30 °C over 1 h and then lowered again to -78°C. Trisyl azide (10% solution in toluene, 30.8 mL, 8.58 mmol) was added in one portion and stirring was continued for 1.5 h at -78 °C. The reaction mixture was quenched with glacial acetic acid (0.7 mL), warmed to room temperature and stirred overnight. After dilution with ethyl acetate (60 mL) and saturated aqueous NH$_4$Cl (30 mL) the phase were separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), and dried over MgSO$_4$ and the solvent rotatory evaporated.

The inseparable 6.3:1 mixture of the diastereoisomers **10** and **11** (d.r. determined by integration of ^{1}H NMR signal: δ_{maj} 5.13 ppm (d), δ_{min} 4.36ppm (d) was isolated by flash column
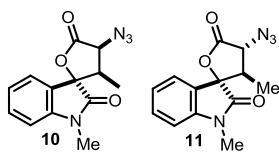
chromatography (hexane/ethyl acetate = 80/20) in 80% overall yield (colorless foam). The enantiomeric excess was determined to be 95% for the major diastereoisomer **10** by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 23.6 min, τ_{minor} = 29.1 min.

$[\alpha]_D^{25}$= - 90.5 (c = 0.95, CHCl$_3$, 6.3:1 mixture of diastereoisomers **10** and **11**, ee_{10} = 95%). HRMS *calcd.* for (C$_{13}$H$_{12}$N$_4$O$_3$+Na): 295.0807, found 295.0818.

^{1}H NMR (400 MHz, CDCl$_3$, 6.3:1 mixture of diastereoisomers **10** and **11**): δ 0.90 (d, 3H$_{min}$, J = 6.78 Hz), 1.05 (d, 3H$_{maj}$, J = 7.29 Hz), 2.82-2.95 (m, 1H$_{min}$), 3.00 (qn, 1H$_{maj}$, J = 7.43 Hz), 3.19 (s, 3H$_{maj}$), 3.23 (s, 3H$_{min}$), 4.35 (d, 1H$_{min}$, J = 12.21 Hz), 5.13 (d, 1H$_{maj}$, J = 7.74 Hz), 6.88 (d, 1H$_{maj}$, J = 7.76 Hz), 6.92 (d, 1H$_{min}$, J = 8.09 Hz), 7.10-7.19 (m, 1H$_{maj}$, 1H$_{min}$), 7.38-7.45 (m, 2H$_{maj}$, 2H$_{min}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 6.3:1 mixture of diastereoisomers 10 and 11): δ 10.8$_{maj}$, 12.4$_{min}$, 26.5$_{maj}$, 26.8$_{min}$, 40.5$_{maj}$, 43.2$_{min}$, 60.1$_{maj}$, 62.3$_{min}$, 83.3$_{min}$, 84.7$_{maj}$, 109.1$_{maj}$, 109.5$_{min}$, 122.6$_{maj}$, 123.2$_{min}$, 123.3$_{maj}$, 123.4$_{min}$, 124.7$_{min}$, 127.1$_{maj}$, 131.4$_{maj}$, 131.5$_{min}$, 144.0$_{min}$, 144.2$_{maj}$, 171.3$_{min}$, 171.5$_{min}$, 172.4$_{maj}$, 173.7$_{maj}$ ppm.

tert-butyl((*R*)-1-(((2*S*,3*R*,4*S*)-1',3-dimethyl-2',5-dioxo-4,5-dihydro-3H-spiro[furan-2,3'-indolin]-4-yl)amino)-3-(methylthio)-1-oxopropan-2-yl)carbamate (12)

Triphenylphosphine (1.0 g, 4.05 mmol, 1.3 equiv) was added to a solution of azides **10** and **11** (849 mg, 3.12 mmol) in 18 mL of tetrahydrofuran, and this solution was stirred at room temperature until no more nitrogen was released (~ 15 min). After addition of water (3.5 mL), the mixture was heated at 60 °C for 4 h and then left at 30 °C overnight. The solution was then cooled, diluted with water (60 mL), extracted with ethyl acetate (5 x 50 mL), and dried over MgSO$_4$. The solvent was removed *in vacuo*, and the residue was purified by chromatography on silica gel (dichloromethane/diethyl ether = 85/15, NH$_4$OH$_{(aq)}$ = 0.5% v/v) to give the amino lactone of compound **10** as *a single* diastereoisomer together with a small amount of phosphine oxide (byproduct of the Staudinger reduction).
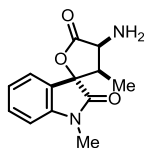
The isolated compound **10** was used in the next synthetic step without further purification. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (d, 3H, J = 7.27 Hz), 2.85 (qn, 1H, J = 7.38 Hz), 3.18 (s, 3H), 4.85 (d, 1H, J = 7.88 Hz,), 6.86 (d, 1H, J = 7.99 Hz), 7.10 (t, 1H, J_t = 7.75 Hz), 7.36-7.42 (m, 2H) ppm.

2-(1*H*-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.1 g, 3.0 mmol) was added to a stirred solution of the amino lactone prepared above (825 mg, 2.7 mmol), *N*-Boc-*S*-methyl-L-cysteine (642 mg, 1.1 mmol), and diisopropylethylamine (574 µL, 1.16 mmol) in DMF (25 mL) at 0 °C, then the mixture was stirred at room temperature for 30 min. After concentration, the residue was diluted with dichloromethane, washed with 10% aqueous HCl, a saturated aqueous solution of NaHCO$_3$ and brine, dried (MgSO$_4$), and concentrated. The residue was then diluted in ethyl acetate and washed with brine (3 x 10 mL) in order to eliminate the residual dimethylformamide.
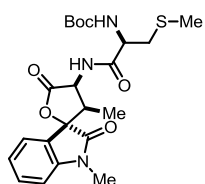
The pure compound **12** was isolated as single diastereoisomer by flash column chromatography (dichloromethane/methanol = 100/1) in 50% overall yield from **10** as white foam. $[\alpha]_D^{26}$= - 14.8 (*c* = 0.82, CHCl$_3$, single stereoisomer); HRMS *calcd.* for (C$_{22}$H$_{29}$N$_3$O$_6$S+Na): 486.1675, found 486.1678.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.01 (d, 3H, *J* = 7.46 Hz), 1.43 (s, 9H), 2.15 (s, 3H), 2.83-2.98 (m, 2H), 3.11-3.22 (m, 4H), 4.25-4.41 (m, 1H), 5.44 (d, 1H, *J* = 7.40 Hz), 5.76 (dd, 1H, *J$_1$* = 7.67 Hz, *J$_2$* =5.86 Hz), 6.85 (d, 1H, *J* = 7.76 Hz), 7.07 (t, 1H, *J* = 7.64 Hz), 7.10-7.19 (m, 1H), 7.26-7.33 (m, 1H), 7.38 (t, *J* = 7.65 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.4, 16.0, 26.4, 28.2, 36.1, 40.8, 52.5, 53.5, 80.5, 84.2, 109.0, 122.8, 122.9, 126.9, 131.3, 144.4, 155.4, 171.2, 174.41, 174.45 ppm.

Maremycin A

A slightly modified literature procedure[27] was used to finally access maremycin A. The *N*-Boc protected compound **12** (225 mg, 0.48 mmol) was dissolved in formic acid (98%, 2 mL), and the solution was stirred for 2.5 h at room temperature (monitored by TLC dichloromethane/methanol 10/1). The excess of acid was removed under reduced pressure, and the residue was taken up in toluene (8 mL) and stirred vigorously under reflux for 3 h. The resulting mixture was then cooled to 0 °C and filtered, and the residue was crystallized from methanol to yield 105.7 mg (60%) of pure maremycin A as a white solid.
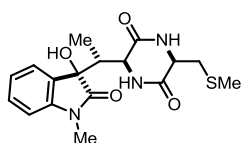
$[\alpha]_D^{26}$= - 127 (*c* = 0.22, MeOH) [lit.[24] $[\alpha]_D^{20}$= - 120.9 (*c* = 0.21, MeOH)], HRMS *calcd.* for (C$_{17}$H$_{21}$N$_3$O$_4$S+Na): 386.1150, found 386.1157.

^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 1.11 (d, 3H*, J* = 7.20 Hz), 2.01-2.07 (m, 1H), 2.09 (s, 3H), 2.80 (dd, 1H*, J$_1$* = 13.89 Hz, *J$_2$* = 3.75 Hz), 2.98 (dd, 1H*, J$_1$* = 13.89 Hz, *J$_2$* = 3.84 Hz), 3.09 (s, 3H), 4.23-4.30 (m, 1H), 4.89 (br s, 1H), 7.00 (d, 1H, *J* = 7.74 Hz), 7.04 (t, 1H, *J* = 7.53 Hz), 7.32 (t, 1H, *J* = 7.54 Hz), 7.37 (d, 1H, *J* = 7.27 Hz), 7.59 (br s, 1H), 7.92 (br s, 1H), 8.64 (br s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ 8.3, 16.4, 25.9, 36.4, 43.0, 53.5, 54.3, 76.3, 108.5, 121.8, 125.0, 129.1, 130.6, 143.0, 165.6, 168.0, 178.0 ppm. These spectra were identical with those reported in the literature.[24]

3.6.12 General Procedure for the Michael Addition of Dioxindole to Nitrostyrenes
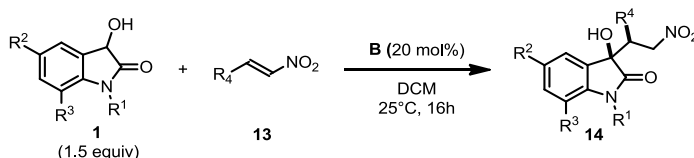
All the reactions were carried out in dichloromethane (CHROMASOLV for HPLC anhydrous) without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary round bottom flask equipped with a Teflon-coated stir bar and a plastic cap was

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charged with the *trans*-β-nitrostyrene **13** (0.2 mmol) and the dioxindole derivative **1** (0.3 mmol, 1.5 equiv). Then, (*S*)-2-[[(1*R*,2*R*)-2-aminocyclohexyl] thioureido]-*N*-benzyl-*N*-3,3-trimethylbutanamide **B** (0.04 mmol, 20 mol%) was added in one portion and the reaction was started by the addition of dichloromethane (4 mL). The round bottom flask was closed and stirring continued over 16 hours at 25 °C. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (10 mL). Solvent was removed in vacuo and the diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis of the crude mixture. The product **3** was isolated by flash column chromatography on silica gel.

(*R*)-1-benzyl-3-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14a, Table 8, entry 1)
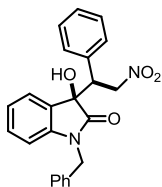
The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.46 ppm (d), δ_{minor} 6.41 ppm (d). R$_{f\,maj}$ = 0.24, R$_{f\,min}$ = 0.28 (dichloromethane/diethyl ether 98/2). The title compound 3a was isolated as a single diastereoisomer by flash column chromatography

(dichloromethane/diethyl ether = 98/2; R$_f$ = 0.24) in 69% yield (yellow solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ$_{major}$ = 7.6 min, τ$_{minor}$ = 14.0 min. [α]$_D^{26}$= -51.4 (c = 0.56, CHCl$_3$, 94% *ee*). HRMS *calcd.* for (C$_{23}$H$_{20}$N$_2$O$_4$+Na): 411.1321, found 411.1321.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.19 (bs, 1H), 4.24 (dd, 1H, J_1 = 10.65 Hz, J_2 = 4.58 Hz), 4.32 (d, 1H, J = 15.91), 4.90 (d, 1H, J = 15.91 Hz), 5.03 (dd, 1H, J_1 = 13.01 Hz, J_2 = 10.65 Hz), 5.54 (dd, 1H, J_1 = 13.01 Hz, J_2 = 4.58 Hz), 6.46 (d, 1H, J = 7.85 Hz), 6.55 (d, 2H, J = 7.10 Hz), 6.86 (d, 2H, J = 7.20 Hz). 7.08-7.35 (m, 9H) ppm.^{13}C NMR (100 MHz, CDCl$_3$): δ 44.3, 51.8, 75.9, 78.3, 110.5, 111.3, 123.5, 125.0, 126.9, 127.8, 12.8, 129.0, 129.4, 130.9, 133.6, 134.7, 138.6, 143.4, 176.8 ppm.

(*R*)-1-benzyl-3-hydroxy-3-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)indolin-2-one (14b, Table 8, entry 2)
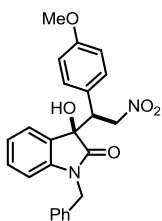

The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 3.73 ppm (s), δ_{minor} 3.71 ppm (s). R$_{f\,maj}$ = 0.26, R$_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R$_f$ = 0.26) in 75% yield

(pale yellow solid). The enantiomeric excess was determined to be 93% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ$_{major}$ = 13.5 min, τ$_{minor}$ = 30.1 min. [α]$_D^{26}$= - 87.6 (c = 0.80, CHCl$_3$, 93% *ee*). HRMS *calcd.* for (C$_{24}$H$_{22}$N$_2$O$_5$+Na): 441.1426, found 441.1432.

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.65 (bs, 1H), 3.73 (s, 3H), 4.23-4.31(m, 2H), 4.92-5.06 (m, 2H), 5.53 (dd, 1H, J_1 = 12.86 Hz, J_2 = 4.43 Hz), 6.48 (d, 1H, J = 7.76 Hz), 6.55 (d, 2H, J = 7.40 Hz), 6.63 (d, 2H,

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J = 8.50 Hz), 6.77 (d, 2H, J = 8.50 Hz), 7.09-7.19 (m, 4H), 7.23 (dt, 1H, J_t = 7.86 Hz, J_d = 1.13 Hz), 7.33-7.37 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 44.3, 51.2, 55.4, 76.2, 78.4, 110.5, 114.3, 123.5, 124.9, 125.3, 126.9, 127.8, 128.9, 129.4, 130.4, 130.9, 134.7, 143.5, 160.0, 176.9 ppm.

(*R*)-1-benzyl-3-hydroxy-3-((*S*)-2-nitro-1-(p-tolyl)ethyl)indolin-2-one (14c, Table 8, entry 3)
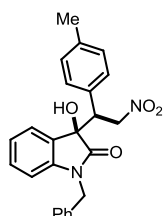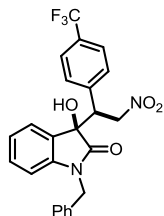
The reaction was carried out following the general procedure to furnish the crude products as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 2.29 ppm (s), δ_{minor} 2.20 ppm (s). R$_{f\,maj}$ = 0.25, R$_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R$_f$ = 0.25) in 74% yield (yellow solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.9 min, τ_{minor} = 24.7 min. $[\alpha]_D^{26}$ = - 67.2 (c = 0.97, CHCl$_3$, 94% *ee*). HRMS *calcd.* for (C$_{24}$H$_{22}$N$_2$O$_4$+Na): 425.1477, found 425.1489.

^{1}H NMR (500 MHz, CDCl$_3$): δ 2.29 (s, 3H), 3.44 (bs, 1H), 4.22-4.31 (m, 2H), 4.95 (d, 1H, J = 15.77 Hz), 5.01 (dd, 1H, J_1 = 12.92 Hz, J_2 = 10.65 Hz), 5.52 (dd, 1H, J_1 = 12.92 Hz, J_2 = 4.45 Hz), 6.47 (d, 1H, J = 7.76 Hz), 6.57 (d, 2H, J = 7.38 Hz), 6.73 (d, 2H, J = 7.97 Hz), 6.92 (d, 2H, J = 7.97 Hz), 7.08-7.24 (m, 5H), 7.32-7.36 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 21.5, 44.3, 51.5, 53.8, 76.1, 78.3, 110.5, 123.5, 125.0, 127.0, 127.8, 128.9, 129.2, 129.6, 130.4, 130.9, 134.8, 138.5, 143.5, 176.8 ppm.

(*R*)-1-benzyl-3-hydroxy-3-((*S*)-2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)indolin-2-one (14d, Table 8, entry 4)
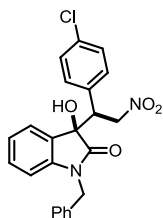
The reaction was carried out following the general procedure to furnish the crude products as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.54 ppm (d), δ_{minor} 6.50 ppm (d). R$_{f\,maj}$ = 0.26, R$_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R$_f$ = 0.26) in 56% yield (yellow solid). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak AD-H column: 85:15 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.3 min, τ_{minor} = 23.6 min. $[\alpha]_D^{25}$ = - 27.5 (c = 0.88, CHCl$_3$, 90% *ee*). HRMS *calcd.* for (C$_{24}$H$_{19}$F$_3$N$_2$O$_4$+Na): 479.1195, found 479.1186.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.91 (bs, 1H), 4.32 (d, 1H, J = 15.8 Hz), 4.38 (dd, 1H, J_1 = 11.13 Hz, J_2 = 3.82 Hz), 4.87 (d, 1H, J = 15.8 Hz), 5.06 (dd, 1H, J_1 = 13.33 Hz, J_2 = 4.03 Hz), 5.61 (dd, 1H, J_1 = 13.33 Hz, J_2 = 4.03 Hz), 6.54 (d, 1H, J = 7.72 Hz), 6.65 (d, 2H, J = 7.24 Hz), 7.00 (d, 2H, J = 8.12 Hz), 7.11-7.21 (m, 4H), 7.23-7.34 (m, 2H), 7.37 (d, 2H, J = 8.13 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$):

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δ 44.5, 51.5, 75.6, 77.9, 110.7, 123.8, 125.0, 125.8, 126.8, 126.9, 128.1, 129.1, 129.8, 130.9, 131.3, 134.55, 137.8, 143.3, 176.7 ppm.

(*R*)-1-benzyl-3-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-3-hydroxyindolin-2-one (14e, Table 8, entry 5)

The reaction was carried out following the general procedure to furnish the crude products as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.52 ppm (d), δ_{minor} 6.48 ppm (d). $R_{f\,maj}$ = 0.27, $R_{f\,min}$ = 0.31 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R_f = 0.27) in 60% yield (yellow solid).

The enantiomeric excess was determined to be 84% by HPLC analysis on a Daicel Chiralpak AD-H column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 30.8 min, τ_{minor} = 43.8 min. $[\alpha]_D^{26}$= - 58.7 (c = 1.14, CHCl$_3$, 84% *ee*). HRMS *calcd.* for (C$_{23}$H$_{19}$ClN$_2$O$_4$+Na): 445.0931, found 445.0927.

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.90 (bs, 1H), 4.25-4.32 (m, 2H), 4.92-5.03 (m, 2H), 5.56 (dd, 1H, J_1 = 13.11 Hz, J_2 = 4.08 Hz), 6.52 (d, 1H, J = 7.73 Hz), 6.54-6.59 (m, 2H), 6.78 (d, 2H, J = 8.46 Hz), 7.05-7.10 (m, 2H), 7.14 (dt, 1H, J_t = 7.73 Hz, J_d = 1.01 Hz), 7.18-7.27 (m, 4H), 7.35 (d, 1H, J = 7.91 Hz) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 44.4, 51.2, 75.8, 78.1, 110.6, 123.7, 124.9, 126.9, 126.95, 128.0, 129.0, 129.2, 130.7, 131.1, 132.1, 134.5, 134.9, 143.4, 176.7 ppm.

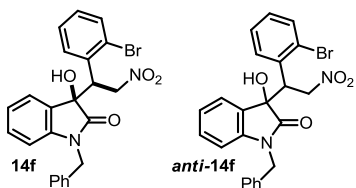### (*R*)-1-benzyl-3-((*S*)-1-(2-bromophenyl)-2-nitroethyl)-3-hydroxyindolin-2-one (14f, Table 8, entry 6)

The reaction was carried out following the general procedure to furnish the crude product as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{maj} 6.43 ppm (d), δ_{min} 6.55 ppm (d).

(**14f** – Table 8, entry 6). The title compound was isolated as a 5.2:1 diastereomeric mixture by flash column chromatography (dichloromethane/diethyl ether = 98/2; R_f = 0.30) in 60% overall yield as a pale yellow solid.The enantiomeric excess was determined to be 85% for the compound **14f** by HPLC analysis on a Daicel Chiralpak IA column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.4 min, τ_{minor} = 20.5 min. The enantiomeric excess was determined to be 22% for the compound anti-3f by HPLC analysis on a Daicel Chiralpak IA column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.5 min, τ_{minor} = 17.1 min. $[\alpha]_D^{25}$= + 18.7 (c = 0.81, CHCl$_3$, 5.2:1 mixture of diastereoisomers **14f** and ***anti*-14f**; ee_{14f} = 85%, $ee_{anti-14f}$ = 22%). HRMS *calcd.* for (C$_{23}$H$_{19}$Br$_2$NO$_4$+Na): 489.0426, found 489.0446.

^{1}H NMR (400 MHz, CDCl$_3$, 5.2:1 mixture of diastereoisomers **14f** and ***anti*-14f**): δ 4.61 (d, 1H$_{maj}$, J_1 = 16.05 Hz), 4.68-4.76 (m, 1H$_{maj}$, 1H$_{min}$), 4.82-4.91 (m, 1H$_{min}$), 5.03-5.15 (m, 2H$_{maj}$, 1H$_{min}$), 5.16-5.25 (m, 1H$_{min}$), 5.44-5.52 (m, 1H$_{min}$), 5.73 (dd, 1H$_{maj}$, J_1 = 13.84 Hz, J_2 = 4.18 Hz), 6.39-6.47 (m, 1H$_{maj}$), 6.54-6.58 (m, 1H$_{min}$), 6.67 (d, 1H$_{maj}$, J_1 = 7.90 Hz), 6.89 (dt, 1H$_{maj}$, J_t = 7.60 Hz, Jd = 0.82 Hz), 6.95-6.99 (m, 1H$_{min}$), 7.08-7.12 (m, 2H$_{maj}$), 7.14-7.39 (m, 7H$_{maj}$, 10H$_{min}$), 7.50 (dd, 1H$_{maj}$, J_1 = 8.00 Hz, J_2 = 1.40 Hz), 7.70-7.74 (m, 1H$_{min}$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, 5.2:1 mixture of diastereoisomers **14f** and **anti-14f**) δ 43.9, 47.6, 53.4, 74.8, 76.9, 109.8, 123.1, 124.9, 126.9, 127.5, 127.8, 128.9, 129.8, 130.5, 133.3, 134.1, 134.8, 142.4, 176.6 ppm.

(*R*)-1-benzyl-3-((*S*)-1-(furan-2-yl)-2-nitroethyl)-3-hydroxyindolin-2-one (14g, Table 8, entry 7)
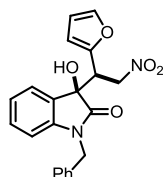
The reaction was carried out following the general procedure to furnish the crude products as a 3.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.34 ppm (dd), $\delt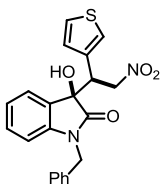a_{minor}$ 4.46 ppm (dd). R$_{f\ maj}$ = 0.25, R$_{f\ min}$ = 0.29 (dichloromethane/diethyl ether = 98/2). The title compound was isolated by flash column chromatography as an 11:1 mixture of diastereoisomers (dichloromethane/diethyl ether 98/2, R$_f$ = 0.25) in 60% yield (white solid). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IB column: 80:20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ$_{major}$ = 10.1 min, τ$_{minor}$ = 13.2 min. [α]$_D^{25}$= - 22.4 (c = 0.50, CHCl$_3$, 96% *ee*). HRMS *calcd.* for (C$_{21}$H$_{18}$N$_2$O$_5$+Na): 401.1113, found 401.1107.

^{1}H NMR (500 MHz, CDCl$_3$, major diastereoisomer): δ 3.24 (bs, 1H), 4.34 (dd, 1H, J_1 = 10.61 Hz, J_2 = 4.25 Hz), 4.60 (d, 1H, J = 15.74 Hz), 4.92 (d, 1H, J = 15.74 Hz), 5.05 (dd, 1H, J_1 = 13.33 Hz, J_2 = 10.59 Hz), 5.48 (dd, 1H, J_1 = 13.31 Hz, J_2 = 4.05 Hz), 6.04 (d, 1H, J = 3.31 Hz), 6.19 (dd, 1H, J_1 = 3.31 Hz, J_2 = 1.83 Hz), 6.63 (d, 1H, J = 8.06 Hz), 7.02-7.11 (m, 4H), 7.15 (dd, 1H, J_1 = 1.83 Hz, J_2 = 0.75 Hz), 7.20-7.29 (m, 4H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, major diastereoisomer): δ 44.4, 45.3, 73.9, 77.2, 110.2, 110.3, 110.8, 123.6, 124.8, 127.5, 127.7, 128.1, 129.1, 130.7, 135.0, 142.9, 143.1, 147.9, 176.6 ppm.

(*R*)-1-benzyl-3-hydroxy-3-((*S*)-2-nitro-1-(thiophen-3-yl)ethyl)indolin-2-one (14h, Table 8, entry 8)

The reaction was carried out following the general procedure to furnish the crude products as a 2.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.48 ppm (d), δ_{minor} 6.43 ppm (d). R$_{f\ maj}$ = 0.27, R$_{f\ min}$ = 0.31 (dichloromethane/diethyl ether = 98/2). The title compound was isolated as a single diastereoisomer by flash column chromatography (dichloromethane/diethyl ether 98/2, R$_f$ = 0.27) in 62% yield (yellow solid).

The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak IA column: 75:25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 215, 254 nm: τ$_{major}$ = 16.5 min, τ$_{minor}$ =

20.0 min. $[\alpha]_D^{26}$= - 49.8 (c = 0.85, CHCl$_3$, 95% *ee*). HRMS *calcd.* for (C$_{21}$H$_{18}$N$_2$O$_4$S+Na): 417.0885, found 417.0865.

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.78 (bs, 1H), 4.39 (d, 1H, *J* = 15.95 Hz), 4.48 (dd, 1H, *J$_1$* = 10.58 Hz, *J$_2$* = 4.40 Hz), 4.86-4.99 (m, 2H), 5.52 (dd, 1H, *J$_1$* = 12.88 Hz, *J$_2$* = 4.40 Hz), 6.48 (dd, 1H, *J$_1$* = 4.98 Hz, *J$_2$* = 1.19 Hz), 6.53 (d, 1H, *J* = 7.90 Hz), 6.70-6.76 (m, 2H), 6.87 (dd, 1H, *J$_1$* = 2.93 Hz, *J$_2$* = 1.19 Hz), 7.06-7.14 (m, 2H), 7.18-7.25 (m, 4H), 7.30-7.33 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 44.3, 47.3, 76.3, 77.9, 110.5, 123.6, 124.9, 125.4, 126.3, 127.0, 127.4, 127.5, 127.9, 129.1, 130.9, 134.2, 134.8, 143.4, 176.9 ppm.

(*R*)-1-benzyl-3-hydroxy-5-methyl-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14i, Table 8, entry 9)
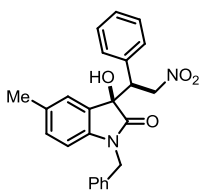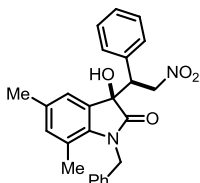

The reaction was carried out following the general procedure to furnish the crude products as a 3.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.34 ppm (d), δ_{minor} 6.29 ppm (d). R$_{f\,maj}$ = 0.26, R$_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 98/2). The title compound was isolated by flash column chromatography as a single diastereoisomer (R$_f$ = 0.26 dichloromethane/diethyl ether 98/2) in 58% yield (yellow solid). The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ$_{major}$ = 9.9 min, τ$_{minor}$ = 24.7 min. $[\alpha]_D^{25}$= - 93.3 (c = 0.47, CHCl$_3$, 95% *ee*). HRMS *calcd.* for (C$_{24}$H$_{22}$N$_2$O$_4$+Na): 425.1477, found 425.1476.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.35 (s, 3H), 3.40 (bs, 1H), 4.22-4.33 (m, 2H), 4.86 (d, 1H, *J* = 15.87 Hz), 5.05 (dd, 1H, *J$_1$* = 12.98 Hz, *J$_2$* = 10.81 Hz), 5.54 (dd, 1H, *J$_1$* = 12.98 Hz, *J$_2$* = 4.30 Hz), 6.34 (d, 1H, *J* = 7.96 Hz), 6.53 (d, 1H, *J* = 7.29 Hz), 6.87 (d, 2H, *J* = 7.29 Hz), 7.01 (d, 1H, *J* = 8.13 Hz), 7.08-7.19 (m, 6H), 7.22-7.28 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 21.5, 44.3, 51.9, 76.0, 78.4, 110.3, 125.7, 126.8, 127.2, 127.7, 128.8, 128.9, 129.0, 129.4, 131.2, 133.3, 133.6, 134.8, 141.0, 176.7 ppm.

(*R*)-1-benzyl-3-hydroxy-5,7-dimethyl-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14j, Table 8, entry 10)

The reaction was carried out following the general procedure to furnish the crude products as a 2.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 2.33 ppm (s), δ_{minor} 2.27 ppm (d). R$_{f\,maj}$ = 0.24, R$_{f\,min}$ = 0.29 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as a 9:1 mixture of diastereoisomers (R$_f$ = 0.24 dichloromethane/diethyl ether 99/1) in 59% yield (yellow solid). The enantiomeric excess was determined to be 87% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ$_{major}$ = 7.6

min, τ_{minor} = 19.5 min. $[\alpha]_D^{25}$= - 53.0 (c = 0.76, CHCl$_3$, 87% *ee*). HRMS *calcd.* for (C$_{25}$H$_{24}$N$_2$O$_4$+Na): 439.1634, found 439.1631.

^{1}H NMR (400 MHz, CDCl$_3$, major diasteroisomer): δ 1.97 (s, 3H), 2.33 (s, 3H), 3.46 (bs, 1H), 4.25 (dd, 1H, J_1 = 10.95 Hz, J_2 = 4.23 Hz), 4.65 (d, 1H, J = 17.2 Hz), 4.97 (d, 1H, J = 17.2 Hz), 5.05 (dd, 1H, J_1 = 12.88 Hz, J_2 = 10.80 Hz), 5.53, (dd, 1H, J_1 = 13.06 Hz, J_2 = 4.23 Hz), 6.42 (d, 2H, J = 7.10 Hz), 6.82-6.90 (m, 3H), 7.01 (s, 1H), 7.07-7.2 (m, 5H), 7.26-7.34 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, major diasteroisomer): δ 18.7, 21.2, 45.5, 52.1, 76.1, 77.5, 120.9, 123.6, 125.4, 127.3, 128.1, 128.8, 128.9, 129.1, 129.5, 133.3, 133.8, 135.3, 136.9, 139.1, 177.7 ppm.

(*R*)-1-benzyl-5-bromo-3-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14k, Table 8, entry 11)
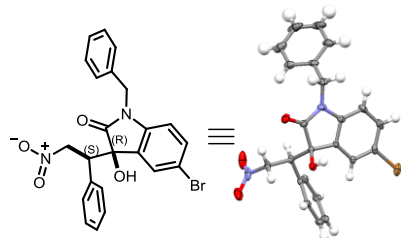

The reaction was carried out following the general procedure to furnish the crude products as a 2.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 6.32 ppm (d), δ_{minor} 6.23 ppm (d). R$_{f\ maj}$ = 0.29, R$_{f\ min}$ = 0.24 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as a single diastereoisomer (dichloromethane/diethyl ether 99/1, R$_f$ = 0.24) in 61% yield (colorless solid). The enantiomeric excess was determined to be 88% by HPLC analysis on a Daicel Chiralpak IC column: 70:30 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 6.0 min, τ_{minor} = 10.8 min. $[\alpha]_D^{26}$= - 64.9 (c = 0.99, CHCl$_3$, 88% *ee*). HRMS *calcd.* for (C$_{23}$H$_{19}$BrN$_2$O$_4$+Na): 489.0426, found 489.0439.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.79 (s, 1H), 4.23-4.35 (m, 2H), 4.85 (d, 1H, J = 16.05 Hz), 5.04 (dd, 1H, J_1 = 13.15 Hz, J_2 = 10.77 Hz), 5.53 (dd, 1H, J_1 = 13.16 Hz, J_2 = 4.43 Hz), 6.33 (d, 1H, J = 8.55 Hz), 6.51-6.57 (m, 2H), 6.89-6.94 (m, 2H), 7.09-7.21 (m, 5H), 7.26-7.37 (m, 2H), 7.37-7.41 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 44.0, 51.3, 75.3, 78.0, 111.6, 116.0, 126.5, 127.6, 127.9, 128.73, 128.78, 128.8, 129.0, 129.1, 132.9, 133.3, 133.8, 141.9, 176.2 ppm.

The relative and absolute configuration for **14k** was unambiguously inferred by anomalous dispersion X-ray crystallographic analysis. Crystals of compound **14k** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature (starting from a diastereomerically pure compound, with 88% *ee*). CCDC 85939.

(*R*)-1-benzyl-7-bromo-3-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14l, Table 8, entry 12)

The reaction was carried out following the general procedure to furnish the crude products as a 2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.22 ppm (dd), δ_{minor} 4.33 ppm (dd). R$_{f\ maj}$ = 0.26, R$_{f\ min}$ = 0.30 (dichloromethane/diethyl ether = 99/1). The title compound was isolated by flash column chromatography as an 11/1 diastereomeric

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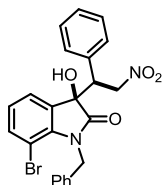
mixture (dichloromethane/diethyl ether 99/1, R_f = 0.26) in 46% yield (yellow solid). The enantiomeric excess was determined to be 73% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 7.6 min, τ_{minor} = 19.5 min. $[\alpha]_D^{24}$= + 6.1 (c = 1.22, CHCl$_3$, 73% *ee*). HRMS *calcd.* for (C$_{23}$H$_{19}$BrN$_2$O$_4$+Na): 489.0426, found 489.0430.

^{1}H NMR (400 MHz, CDCl$_3$, major diastereoisomer): δ 3.30 (bs, 1H), 4.23 (dd, 1H, J_1 = 10.55 Hz, J_2 = 4.41 Hz), 4.97-5.14 (m, 3H), 5.51 (dd, 1H, J_1 = 13.13 Hz, J_2 = 4.41 Hz), 6.58-6.65 (m, 2H), 6.85-6.91 (m, 2H), 6.98-7.75 (m, 1H), 7.15-7.26 (m, 5H), 7.29-7.37 (m, 2H), 7.45 (dd, 1H, J_1 = 8.21 Hz, J_2 = 1.19 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, major distereoisomer): δ 45.2, 51.9, 75.6, 77.4, 103.6, 124.3, 124.7, 126.1, 127.3, 128.9, 129.1, 129.3, 130.6, 133.2, 136.7, 136.9, 141.0, 144.5, 177.7 ppm.

(*R*)-3-hydroxy-1-methyl-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14m, Table 8, entry 13)
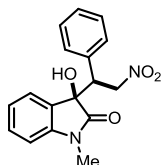

The reaction was carried out following the general procedure to furnish the crude products as a 3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.08 ppm (dd), δ_{minor} 4.25 ppm (dd). $R_{f\,maj}$ = 0.26, $R_{f\,min}$ = 0.30 (dichloromethane/diethyl ether = 95/5). The title compound was isolated by flash column chromatography as a 9:1 diastereoisomers mixture (dichloromethane/diethyl ether 95/5, R_f = 0.26) in 48% yield (yellow solid). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 12.0 min. $[\alpha]_D^{24}$= - 18.7 (c = 1.23, CHCl$_3$, 87% *ee*). HRMS *calcd.* for (C$_{17}$H$_{16}$N$_2$O$_4$+Na): 335.1008, found 335.1016.

^{1}H NMR (400 MHz, CDCl$_3$, major diastereoisomer): δ 2.81 (s, 3H), 3.67 (bs, 1H), 4.08 (dd, 1H, J_1 = 10.86 Hz, J_2 = 4.58 Hz), 5.02 (dd, 1H, J_1 = 10.68 Hz, J_2 = 13.27 Hz), 5.52 (dd, 1H, J_1 = 13.27 Hz, J_2 = 4.43 Hz), 6.62 (d, 1H, J = 7.89 Hz), 6.82-6.87 (m, 2H), 7.06-7.13 (m, 4H), 7.14-7.20 (m, 1H), 7.29-7.36 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, major diastereoisomer): δ 26.2, 51.6, 75.3, 78.5, 108.9, 123.4, 125.0, 127.4, 128.4, 128.7, 129.0, 130.8, 133.6, 143.7, 176.8 ppm.

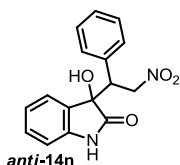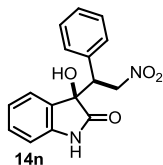### (*R*)-3-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)indolin-2-one (14n, Table 8, entry 14)

The reaction was carried out following the general procedure to furnish the crude products as a 2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signals: δ_{major} 4.02 ppm (dd), δ_{minor} 4.25 ppm (dd).


(**14n** – Table 8, entry 14). The mixture of the diastereoisomers **14n** and *anti*-**14n** was isolated by flash column chromatography (dichloromethane/diethyl ether = 80/20; R_f = 0.28) in 50% overall yield as a pale yellow

solid. The enantiomeric excess was determined to be 66% for the compound **14n** by HPLC analysis on a Daicel Chiralpak IA column: 48.5:48.5:3 hexane/dichloromethane/*i*-PrOH, flow rate 1 mL/min, λ = 215, 254 nm: τ_{major} = 34.7 min, τ_{minor} = 36.8 min. The enantiomeric excess was determined to be 0% for the compound anti-3n by HPLC analysis on a Daicel Chiralpak IA column: 48.5:48.5:3 hexane/dichloromethane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 38.9 min, τ_{minor} = 23.3 min. $[\alpha]_D^{25}$ = - 0.7 (*c* = 1.46, CHCl$_3$, 2:1 mixture of diastereoisomers **14n** and **anti-14n**; ee_{14n} = 66%, $ee_{anti-14n}$ = 0%). HRMS *calcd.* for (C$_{16}$H$_{14}$N$_2$O$_4$+Na): 321.0851, found 321.0836.
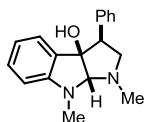
^{1}H NMR (400 MHz, CDCl$_3$, 2:1 mixture of diastereoisomers **14n** and **anti-14n**): δ 3.17-3.49 (m, 1H$_{maj}$, 1H$_{min}$), 4.02 (dd, 1H$_{maj}$, J_1 = 10.51 Hz, J_2 = 4.42 Hz), 4.25 (dd, 1H$_{min}$, J_1 = 9.91 Hz, J_2 = 4.92 Hz), 4.99 (dd, 1H$_{maj}$, J_1 = 13.27 Hz, J_2 = 10.63 Hz), 5.16-5.26 (m, 1H$_{min}$), 5.39-5.50 (m, 1H$_{maj}$, 1H$_{min}$), 6.57 (d, 1H$_{min}$, J = 7.59 Hz), 6.71 (d, 1H$_{maj}$, J = 7.89 Hz), 6.85-6.90 (m, 2H$_{maj}$), 6.90-7.01 (m, 2H $_{min}$), 7.02-7.23 (m, 4H$_{maj}$, 3H$_{min}$), 7.24-7.31 (m, 1H$_{maj}$, 1H$_{min}$), 7.37-7.61 (m, 2H$_{maj}$, 1H$_{min}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$ 2:1 mixture of diastereoisomers **14n** and **anti-14n**): δ 51.1, 51.4, 74.5, 75.4, 78.1, 78.4, 110.7, 110.8, 111.0, 111.1, 123.5, 123.7, 124.6, 125.5, 127.9, 128.4, 128.5, 128.6, 128.8, 129.0, 129.3, 130.6, 130.9, 133.3, 135.5, 140.1, 140.7, 178.7, 178.9 ppm.

3.6.13 Synthesis of (3*S*,3a*R*,8a*R*)-1,8-dimethyl-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-3a-ol (15)
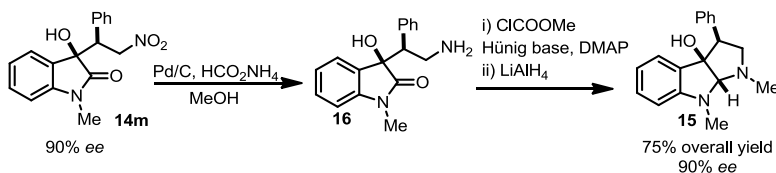
To a stirred solution of compound **14m** (27.1 mg, 0.087 mmol, 90% *ee*, single diastereoisomer) in CH$_3$OH (1 mL) Pd/C 10%, 50%wet (6 mg) and HCOONH$_4$ (38.2 mg, 0.6 mmol) were sequentially added. The reaction mixture was refluxed 1 h and then filtered on a celite pad. The pad was washed several times with CH$_3$OH and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with sat. Na$_2$CO$_3$, and the aqueous phase extracted twice with EtOAc. The combined organic phases were dried over Na$_2$SO$_4$, filtered and evaporated, affording the aminoalcohol intermediate **16** as a yellow oil. The crude material obtained in this step was dissolved in dry methylene chloride (1 mL) under an argon atmosphere. To the resultant solution, Hünig's base (68 µL, 0.39 mmol, 4.5 equiv), chloromethyl formate (27 µL, 0.34 mmol, 4 equiv) and DMAP (4.2 mg, 0.035 mmol, 40 mol%) were sequentially added at 0 °C. After the addition, the reaction was allowed to warm to room temperature and stirred over 4 h. Next, the reaction was first diluted with methylene chloride and then quenched with a saturated aqueous sodium bicarbonate solution. The aqueous layer

was separated and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The material obtained was dissolved in 3 mL of dry THF and LiAlH$_4$ (27 mg, 0.69 mmol, 8 equiv) was added at 0 °C. The resulting mixture was heated to reflux for 2 h and then cooled to 0 °C. Ethyl acetate (20 mL) and saturated aqueous NaHCO$_3$ (10 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (3x). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. Preparative TLC (EtOAc/MeOH, 92/8) afforded 18.3 mg (75%) of the desired product **15**. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.94(bs, 1H),2.76 (s, 3H), 2.99 (s, 3H), 3.22-3.27 (m, 2H), 3.47 (dd, 1H, J_1 = 8.67 Hz, J_2 = 7.64 Hz), 4.24 (s, 1H), 6.53 (d, 1H, J = 8.02 Hz), 6.69 (dt, 1H, J_1 = 7.53 Hz, J_2 = 0.83 Hz), 6.87 (dd, 1H, J_1 = 7.48 Hz, J_2 = 0.88 Hz), 7.20 (dt, 1H, J_1 = 7.65 Hz, J_2 = 1.44 Hz), 7.31-7.42 (m, 5H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 35.2, 41.4, 54.2, 59.3, 87.7, 100.0, 107.8, 117.7, 122.6, 127.5, 128.4, 129.7, 129.8, 131.3, 136.2, 151.2 ppm. The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak IC column: 80:20 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.46 min, τ_{minor} = 5.02 min. [α]$_D^{25}$= - 17.4 (c = 0.25 CHCl$_3$, ee = 87%).

Chapter IV

Photoredox Activation and Anion-Binding in the Dual Catalytic Enantioselective Synthesis of β-Amino Esters

Target

Development of a catalytic asymmetric process based on oxidative photocatalytic reactivity and non-covalent mode of organocatalytic activation.

Tool

Enantioselective C-H functionalization of tetrahydroisoquinoline derivatives through the merger of photoredox and anion-binding catalysis.[1]
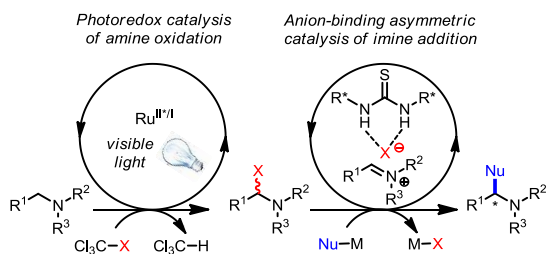
4.1   Background

Nearly a century ago, Ciamician commented that "light" is an abundant and renewable energy source for performing green chemical reactions.[2] Since then, photochemistry and photocatalysis have attracted considerable attention in organic synthesis.[3,4] However, the lack of visible light absorption by many organic molecules has limited the application of photochemical synthesis. One approach toward the activation of organic molecules that received much attention recently is visible light photoredox catalysis. In a general sense this approach relies on the ability of metal complexes and organic dyes, upon photoexcitation with visible light, to engage in single-electron-transfer (SET) process with organic substrates. The most commonly employed visible

[1] G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson. Photoredox Activation and Anion-Binding in the Dual Catalytic Enantioselective Synthesis of β-Amino Esters. *Chem. Sci.,* **2013**, DOI: 10.1039/C3SC52265B.

[2] G. Ciamician. The Photochemistry of the Future. *Science*, **1912**, *36*, 385.

[3] N. Hoffmann. Photochemical Reactions as Key Steps in Organic Synthesis. *Chem. Rev.*, **2008**, *108*, 1052.

[4] M. Fagnoni, D. Dondi, D. Ravelli. A. Albini. Photocatalysis for the Formation of the C-C Bond. *Chem. Rev.*, **2007**, *107*, 2725.

light photocatalysts are polypyridyl complexes of ruthenium and iridium, typified by the complex tris(2,2'-bipyridine) ruthenium(II) $Ru(bpy)_3^{2+}$.[5] Irradiation of $Ru(bpy)_3^{2+}$ with visible light populates the excited state $Ru(bpy)_3^{2+*}$ via metal to ligand charge transfer (MLCT). This photoexcited species has the remarkable property of being both more oxidizing and more reducing than the ground state species (Scheme 1).
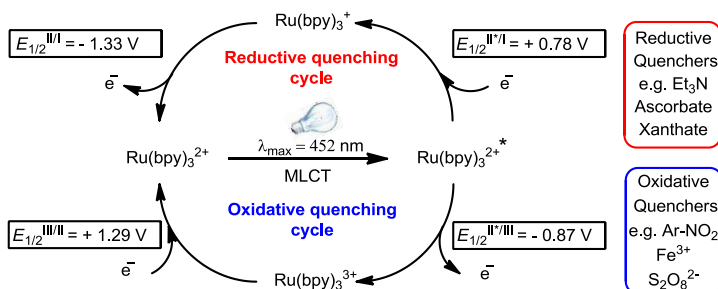
Scheme 1. Oxidative and Reductive quenching of $Ru(bpy)_3^{2+}$.

Several oxidative and reductive quenchers of the excited state are known (Scheme 1). Oxidative quenching of $Ru(bpy)_3^{2+*}$ provides $Ru(bpy)_3^{3+}$, a strong oxidant ($E_{1/2}^{III/II}$ = + 1.29 V vs. SCE in CH_3CN), while reductive quenching provides $Ru(bpy)^{3+}$, a strong reducing agent ($E_{1/2}^{II/I}$ = - 1.33 V vs. SCE in CH_3CN). Hence, depending upon the conditions employed and the proper selection of the quencher, $Ru(bpy)_3^{2+}$ can be utilized as a single electron oxidant or reductant.

The ability of this species to function as a visible light photocatalyst has been recognized and extensively investigated for applications in inorganic and material chemistry.[6] Very recently, reports from the Yoon group, the MacMillan group and the Stephenson group detailed the use of $Ru(bpy)_3^{2+}$ as a visible light photoredox catalyst to perform [2+2] enone cycloaddition,[7] α-alkylation of aldehydes[8] and reductive dehalogenation of activated alkyl halides,[9] respectively (Scheme 2). The combined efforts of these three research groups prompted a diversity of studies into the utility of photoredox catalysis as a conceptually novel approach to synthetic organic reaction development. Irradiation of photoactive catalysts with visible light can be exploited for the practical generation of synthetically useful high-energy organic intermediates such as free

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[5] C. K. Prier, D. A. Rankic, D. W. C. MacMillan. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.*, **2013**, *113*, 5322.

[6] X. Sala, I. Romero, M. Rodriguez, L. Escriche, A. Llobet. Molecular Catalysts that Oxidize Water to Dioxygen. *Angew. Chem. Int. Ed.*, **2009**, *48*, 2842.

[7] M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.*, **2008**, *130*, 12886.

[8] D. A. Nicewicz, D. W. C. MacMillan. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science*, **2008**, *322*, 77.

[9] J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson. Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction. *J. Am. Chem. Soc.*, **2009**, *131*, 8756.

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Giulia Bergonzini
Dipòsit Legal: T 1661-2014   *Photoredox Activation and Anion-Binding in the Enantioselective Synthesis of β-Amino Esters*

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radicals and radical ions.[10] The area of photoredox catalysis has since emerged as a powerful tool for organic synthesis.[11]
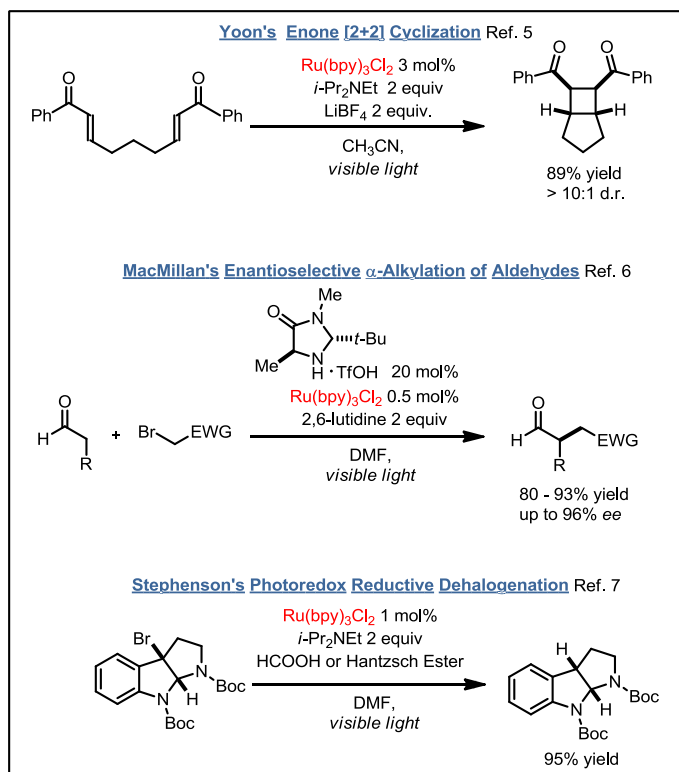
Scheme 2. Pioneering contributions of the groups of Yoon, MacMillan and Stephenson to the field of photoredox catalysis. Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; TfOH = triflic acid; Boc = *tert*-butyloxycarbonyl; DMF = dimethylformamide; EWG = electronwithdrawing group.

Successful efforts to induce enantioselective control in such photocatalyzed processes, with the goal of solving long-standing problems in asymmetric chemical synthesis, have relied thus far on covalent organocatalysis. For example, in 2008 the MacMillan group reported the merger of photoredox catalysis with enamine organocatalysis to perform the enantioselective α-alkylation of aldehydes (Scheme 3).[8]

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[10] M. A. Ischay, T. P. Yoon. Accessing the Synthetic Chemistry of Radical Ions. *Eur. J. Org. Chem.*, **2012**, *18*, 3359.

[11] J. M. R. Narayanam, Corey R. J. Stephenson. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.,* **2011***, 40,* 102.

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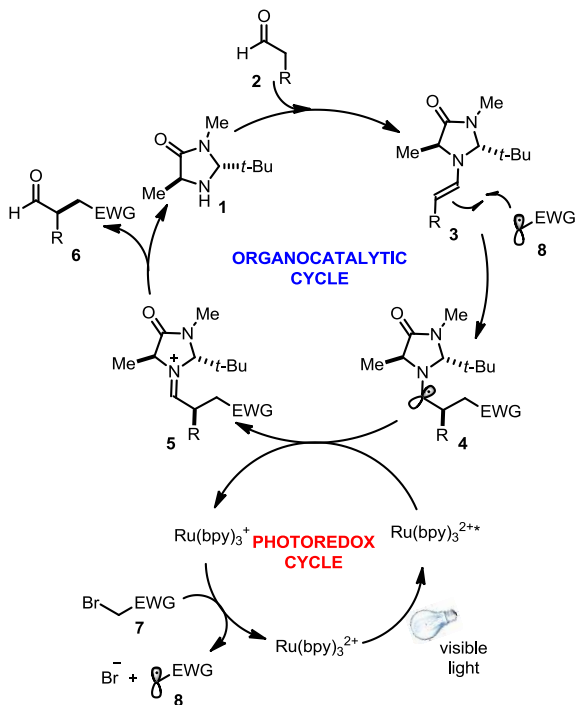
Scheme 3. Enantioselective α-alkylation of aldehydes *via* photoredox organocatalysis.
EWG = electron withdrawing group; *t*-Bu = *tert*-butyl.

Initiation of the reaction requires quenching of the photocatalyst excited state Ru(bpy)$_3^{2+}$* by a sacrificial amount of enamine **3** to provide the strongly reducing Ru(bpy)$_3^+$. This species may then transfer an electron to the alkyl bromide **7**, inducing fragmentation to afford the electron-deficient radical **8**. Meanwhile, condensation of aldehyde **2** with the imidazolidinone catalyst **1** furnishes chiral enamine **3**. Addition of the radical **8** to the *Si* face of the enamine forges the C-C bond and generates the α-aminoradical **4**. The two catalytic cycles then intersect by means of the single electron oxidation of **4** by Ru(bpy)$_3^{2+}$* to yield the iminium intermediate **5**. Hydrolysis of the iminium ion releases the α-alkylated product **6**, which is generated with high enantioselectivity (up to 96% *ee*). This general approach, which combines photoredox catalysis and enamine activation, has been extended to the α-trifluoromethylation, perfluoroalkylation and benzylation of aldehydes.[12,13]

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[12] D. A. Nagib, M. E. Scott, D. W. C. MacMillan. Enantioselective α-Trifluoromethylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.*, **2009**, *131*, 10875.

[13] H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan. Enantioselective α-Benzylation of Aldehydes *via* Photoredox Organocatalysis. *J. Am. Chem. Soc.*, **2010**, *132*, 13600.

UNIVERSITAT ROVIRA I VIRGILI
ASSESSING THE VERSATILITY OF ORGANOCATALYSIS AS A STRATEGY FOR ENABLING NOVEL ASYMMETRIC TRANSFORMATI
Giulia Bergonzini
Dipòsit Legal: T 1661-2014 *Photoredox Activation and Anion-Binding in the Enantioselective Synthesis of β-Amino Esters*

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In 2012 the Rovis group merged photoredox catalysis with *N*-heterocyclic carbene catalysis to perform the enantioselective α-acylation of amines (Scheme 4).[14]
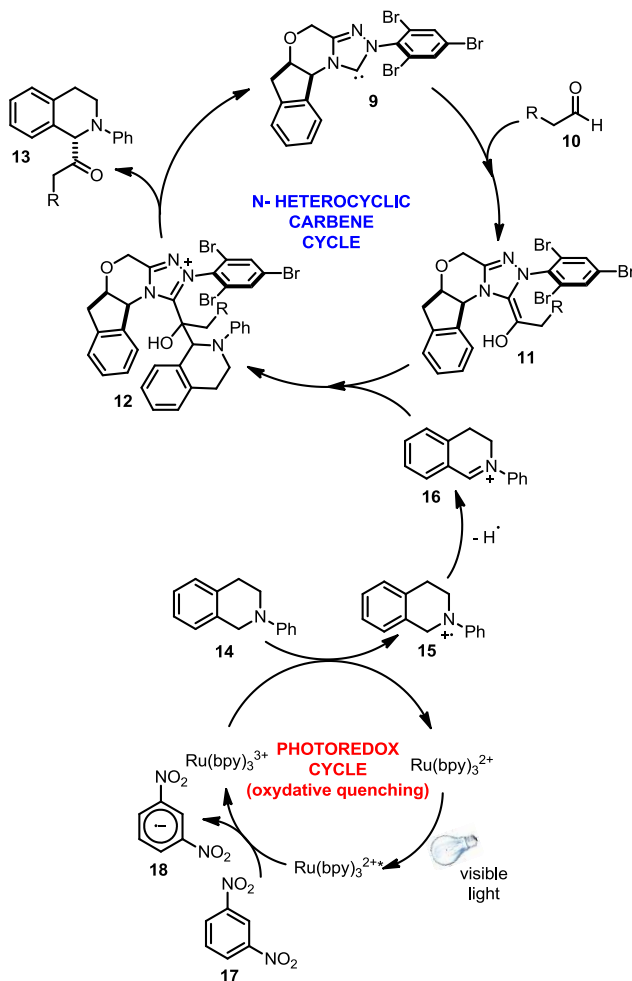
Scheme 4. Enantioselective α-acylation of amines merging photoredox catalysis and *N*-heterocyclic carbene catalysis.

In this reaction, a chiral *N*-heterocyclic carbene **9** serves to generate a chiral acyl anion equivalent **11**, which then adds to iminium ions generated *via* photoredox catalysis; in this way the tertiary amine **14** is reacted with a simple aldehyde **10** to provide the enantioenriched α-acylated amine **13**. In the photoredox cycle, oxidative quenching of Ru(bpy)$_3^{2+}$* by *meta*-

[14] D. A. DiRocco, T. Rovis. Catalytic Asymmetric α-Acylation of Tertiary Amines Mediated by a Dual Catalysis Mode: N-Heterocyclic Carbene and Photoredox Catalysis. *J. Am. Chem. Soc.*, **2012**, *134*, 8094.

dinitrobenzene **17** ($E_{1/2}$ = - 0.90 V *vs* SCE) generates Ru(bpy)$_3$$^{3+}$ and the arene radical anion **18**. Ru(bpy)$_3$$^{3+}$ can then oxidize the amine to its radical cation **15**, which after hydrogen atom abstraction yields the key iminium ion **16**. Simultaneously, the *N*-heterocyclic carbene catalyst **9** reacts with the aldehyde **10** to form the nucleophilic Breslow intermediate **11**. Attack of **11** to the iminium ion **16** forges the C-C bond, with the chiral fragment on the *N*-heterocyclic carbene catalyst backbone controlling the newly formed stereocenter. In this example, the authors exploited the formation of the reactive intermediate **16** during the oxidative quenching of Ru(bpy)$_3$$^{2+}$* under photocatalytic conditions.

The functionalization of C-H bonds adjacent to nitrogen atoms by means of photoredox catalysis was first introduced by the Stephenson group in 2010.[15]

Scheme 5. Oxidative generation of reactive iminium ion intermediate using photoredox catalysis.

In this study, the iminium ion was generated by oxidation of the amino radical cation **15** obtained by using the tertiary amine **14** as a reductive quencher for the photocatalyst. The methodology afforded the oxidative aza-Henry products between tetrahydroisoquinolines and nitroalkanes. Subsequently, Stephenson and co-workers reported an improved protocol for the generation of the iminium intermediate by reductive quenching of the photocatalyst using

[15] A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson. Visible-Light Photoredox Catalysis: Aza-Henry Reactions *via* C-H Functionalization. *J. Am. Chem. Soc.*, **2010**, *132*, 1464.

BrCCl$_3$ as stoichiometric oxidant which allowed for the successful utilization of a broad range of nucleophiles.[16] As shown in Scheme 5, Ru(bpy)$_3$$^{2+}$* is able to oxidize tertiary amines to generate the corresponding amino radical cation **15**. Accordingly, the bond dissociation energy (BDE) of the α-C-H bond is dramatically lowered (90.7 kcal/mol BDE drops to $\sim$ 17 kcal/mol using triethylamine as an example).[17] By exploiting this inherent physical characteristic of amino radical cations, the iminium ion **16** can thus be generated *via* direct H-atom abstraction or deprotonation and oxidation of the resultant α-amino radical. In this case, the Ru(I) species reduces BrCCl$_3$ to complete the photoredox cycle. The resulting CCl$_3$ radical abstracts a hydrogen atom at the α-position of the amine to generate the key intermediate **16**.

During my research period in the laboratory of Prof. Stephenson at Boston University, and in collaboration with Prof. Jacobsen at Harvard University, we were interested in the possibility of rendering this photocatalytic transformation stereoselective. Since the oxidative generation of reactive iminium ions and other tranformations initiated by visible light photocatalysis involves the reductive generation of halide anions,[18] we considered whether the use of a chiral anion-binding catalyst in combination with photocatalysis would provide opportunities for new types of enantioselective transformations.[19]

As briefly discussed in Chapter 1, asymmetric anion-binding catalysis relies on the binding of neutral hydrogen-bond donor catalysts to the unreactive or reactive counterion of cationic intermediates in the enantiodetermining transition-state. To date, successful implementations of the anion-binding approach have been documented only with catalysts bearing a (thio)urea moiety. In the realm of halide anion binding, the principle of asymmetric anion-binding has been applied successfully to transformations involving various cationic species such as *N*-acyliminium ions, oxocarbenium ions and benzhydryl cations.[20] Following this idea, we envisioned that iminium ion equivalents similar to **16** in Scheme 4 and 5, generated under mild conditions from tertiary amines by photocatalyzed oxidation, might react in a stereoselective nucleophilic addition reaction under the influence of a chiral hydrogen-bond donor catalyst (Figure 1).

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[16] D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson. Functionally Diverse Nucleophilic Trapping of Iminium Intermediates Generated Utilizing Visible Light. *Org. Lett.*, **2012**, *14*, 94.

[17] D. D. M. Wayner, J. J. Dannenberg, D. Griller. Oxidation Potentials of α-Aminoalkyl Radicals: Bond Dissociation Energies for Related Radical Cations. *Chem. Phys. Lett.*, **1986**, *131*, 189.

[18] C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson. Visible Light-Mediated Atom Transfer Radical Addition *via* Oxidative and Reductive Quenching of Photocatalysts. *J. Am. Chem. Soc.*, **2012**, *134*, 8875.

[19] Z. Zhang, P. R. Schreiner. (Thio)urea Organocatalysis—What Can Be Learnt from Anion Recognition? *Chem. Soc. Rev.*, **2009**, *38*, 1187.

[20] For a comprehensive review on ion-pairing catalysis see: K. Brak, E. N. Jacobsen. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.*, **2013**, *52*, 534.
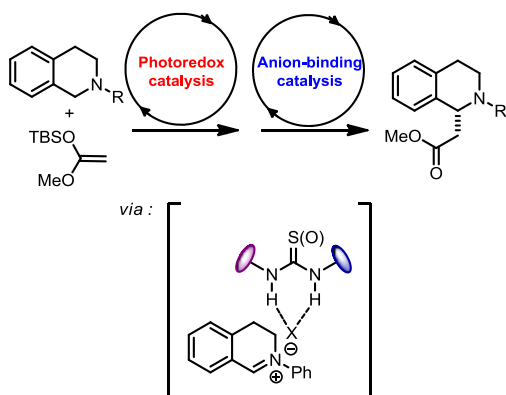
Figure 1. Merger of photoredox and anion-binding catalysis in the enantioselective addition to amines. TBS = *tert*-butyldimethylsilyl.

The merger between photoredox and anion-binding catalysis would provide a new approach for the design of asymmetric transformations.

4.2   Results and Discussion

We chose to evaluate the proposed dual catalytic reaction design in enantioselective oxidative Mannich reactions to access tetrahydroisoquinoline derived β-amino esters (Scheme 6).[21]
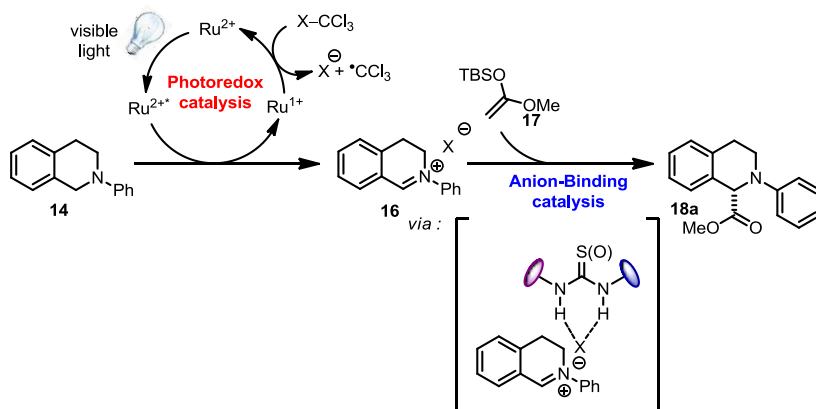
Scheme 6. Design of the dual catalytic reaction.

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[21] B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa. Recent Advances in the Catalytic Asymmetric Synthesis of β-Amino Acids. *Chem. Soc. Rev.*, **2010**, *39*, 1656.

Coupling the photocatalytic protocol for the oxidative generation of iminium ion precursors[16] to an enantioselective thiourea-catalyzed addition of enolate equivalents such as silyl ketene acetal **17**, requires identification of the appropriate photoredox and chiral thiourea catalysts, as well as reaction conditions suitable for both transformations. In relatively polar media (CH$_3$CN, CH$_2$Cl$_2$, dimethylformamide), with CCl$_4$ as the stoichiometric oxidant, the oxidative photocatalytic Mannich reaction of *N*-phenyltetrahydroisoquinoline (**14**) and silyl ketene acetal **17** afforded the desired product **18a** cleanly in the presence of chiral thiourea catalysts, but always in racemic form. In contrast, unreacted tetrahydroisoquinoline **14** could be recovered from attempted oxidations in non-polar solvents such as methyl *tert*-butyl ether (MTBE), which are optimal for attaining high enantioselectivity in anion-binding thiourea catalysis. The failure of the photoredox reaction under these conditions could be ascribed simply to the lack of solubility of the photocatalyst, even when relatively non-polar complexes such as Ru(bpy)$_3$(PF$_6$)$_2$ were employed.

The enantioselective oxidative Mannich reaction could be achieved by performing the photocatalytic oxidation in CH$_3$CN and switching the solvent to MTBE for the thiourea-catalyzed alkylation reaction (Table 1). In this way, full conversion of **14** to the corresponding iminium ion in CH$_3$CN was observed after irradiation with blue LEDs for 16 hours using 2 equiv of CCl$_4$, and tetrahydroisoquinoline **18a** was obtained in 50% *ee* upon alkylation with **17** in the presence of chiral thiourea **20a** at – 78 °C (Table 1, entry 3).
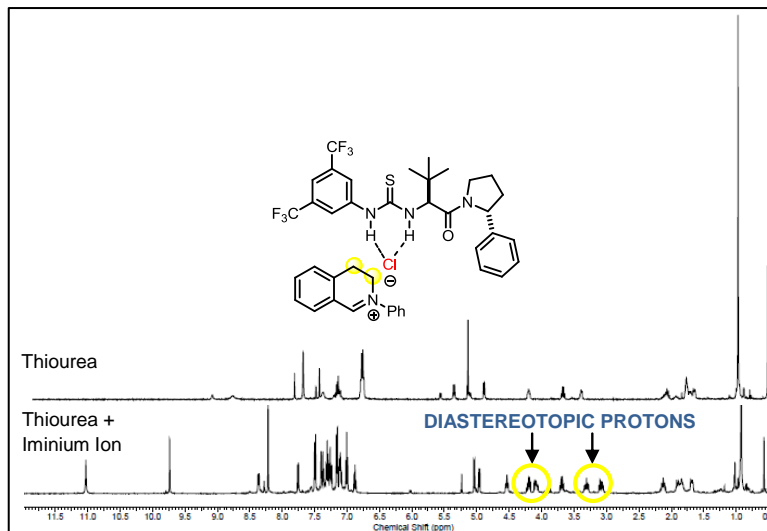

Figure 2. Ion-pairing between iminium ion **16** and thiourea **20a** showed by ^{1}H NMR experiments.

Interestingly, ^{1}H NMR experiments performed on a solution of the iminium ion **16** and the chiral thiourea **20a** in deuterated dichloromethane showed the protons on the C$_3$ and C$_4$ of **16** as

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diastereotopic (Figure 2). This observation revealed the formation of a strong thiourea-iminium ion asymmetric ion pair. Such interaction between chiral catalyst and charged nucleophile might provide the molecular organization necessary to enable discrimination between the enantiotopic faces of the charged prochiral iminium intermediate.

Table 1. Thiourea Catalyst Optimization
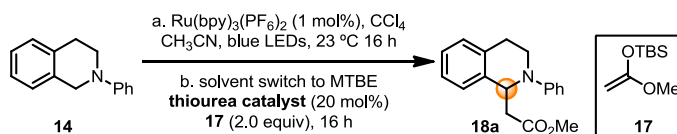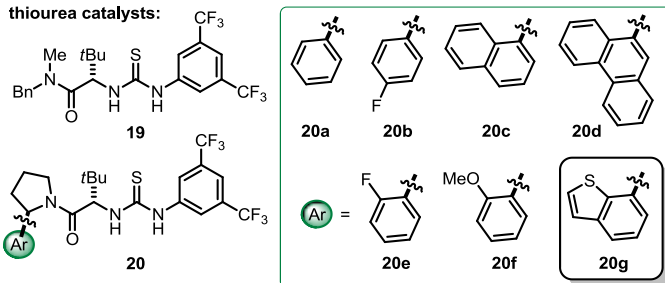
entry	thiourea catalyst	T (°C)[a]	$[\text{14a}]_0$ (M)[a]	Yield (%)[b]	ee(%)[c]
1	-	−78	0.1	0	N/A
2	**19**	−78	0.1	75	10
3	**20a**	−78	0.1	68	50
4	**20b**	−78	0.1	63	20
5	**20c**	−78	0.1	57	80
6	**20d**	−78	0.1	63	29
7	**20c**	−60	0.05	37	93
8	**20e**	−60	0.05	63	87
9	**20f**	−60	0.05	63	85
10	*ent*-**20g**	−60	0.05	69	−97

[a] Reaction temperature and concentration for the alkylation step in MTBE. [b] Yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture relative to 2,5-dimethylfuran as the internal standard. [c] Determined by HPLC on commercial chiral columns.

Enantioselective oxidative Mannich reaction of **14** and silyl ketene acetal **17** was evaluated with a variety of thiourea catalysts. Only catalysts bearing both 3,5-bis(trifluoromethyl)aniline and tertiary amide components were found to promote useful reaction rates at − 78 ˚C. Constrained arylpyrrolidine-derived thiourea catalysts of the general structure **20**, which have proven

effective in a wide range of enantioselective transformations,[22] induced significantly higher *ee*'s than catalysts bearing a less constrained tertiary amide fragment (e.g. **19**).

No obvious correlation between the expanse of the α-aryl substituent on the pyrrolidine and reaction enantioselectivity was observed (Table 1, entries 3-6). In contrast, substitution on the *ortho*-position of the arylpyrrolidine resulted in significant improvements in enantioinduction, although the electronic properties of the substituent had little impact (Table 1, entries 7-10). Further reaction optimization using catalyst **20c** revealed a significant enhancement in enantioselectivity when the reaction was conducted at – 60 °C with an initial tetrahydroisoquinoline concentration of 0.05 M (Table 1, Entries 5 and 7). After extensive evaluation of different arylpyrrolidine-derived analogs of **20**, and after studies on the connectivity of the benzo[*b*]thiophenyl moiety to the pyrrolidine ring reported in Scheme 7, thiourea **20g** was identified as an optimal catalyst for the model transformation of **16a** to **18a**.
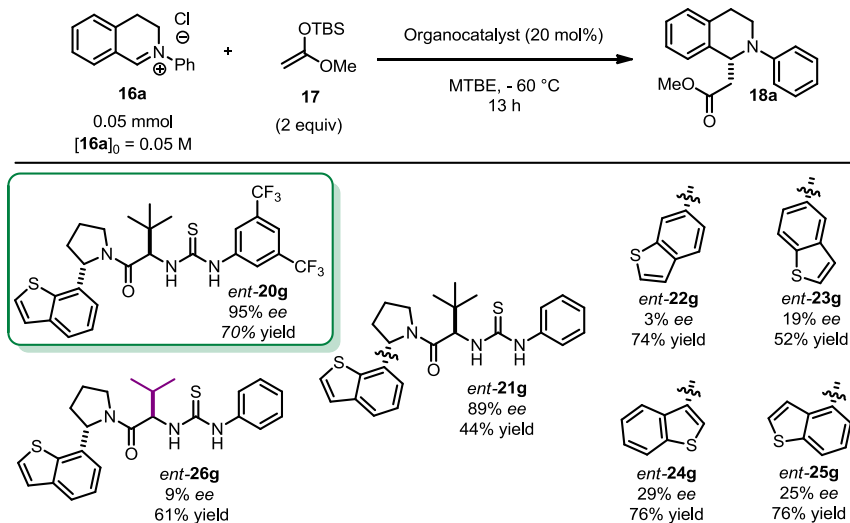
Scheme 7. Influence of the benzo[*b*]thiopenyl moiety connectivity. Yields were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture relative to 2,5-dimethylfuran as the internal standard.

During the course of the optimization studies, we observed that the identities of both the photocatalyst counterion and the halogen atom source (the oxidant) had significant effects on enantioselectivity in the thiourea-catalyzed silyl ketene acetal addition reaction (Figure 2). Consistently lower enantioselectivity was observed when using BrCCl$_3$ as the stoichiometric

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[22] S. E. Reisman, A. G. Doyle, E. N. Jacobsen. Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions. *J. Am. Chem. Soc.*, **2008**, *130*, 7198.

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oxidant compared with CCl$_4$, a result that is attributable to more favorable interactions of the chloride-bound thiourea catalyst in the enantioselectivity-determining transition structure.
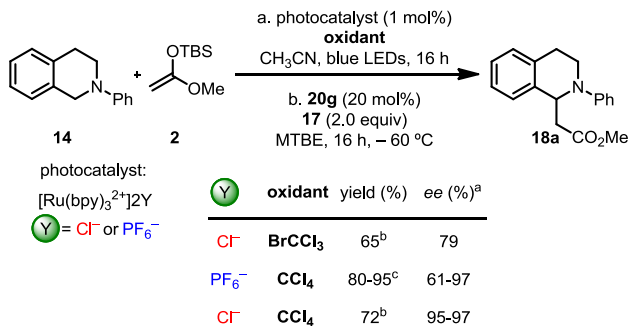

Figure 3. Counterion effect. [a] Determined by HPLC on commercial chiral columns. [b] Isolated yield after purification by chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture relative to 2,5-dimethylfuran as the internal standard.

When Ru(bpy)$_3$(PF$_6$)$_2$ was used as the photocatalyst in place of Ru(bpy)$_3$Cl$_2$ together with CCl$_4$ as the stoichiometric oxidant, highly variable enantioselectivities were obtained (e.g. 61-97% *ee* with catalyst **20g**). This unpredictable behavior associated with the use of the Ru(bpy)$_3$(PF$_6$)$_2$ photocatalyst appears to be tied to the heterogeneous nature of the alkylation reaction mixture. Although only 2 mol% of PF$_6^-$ is present in the reaction medium and the iminium ion intermediate is predominantly associated with chloride, the PF$_6^-$ may impart enhanced solubility properties to the iminium ion, and thereby enable the racemic, background reaction to a greater extent.

With optimized conditions in hand we next explored the substrate scope of the reaction (Figure 4). The time required for full conversion of the *N*-aryltetrahydroisoquinoline derivatives **16** in the oxidation reaction was highly dependent on the electronic nature of the substrate, with electron-rich derivatives being more readily oxidized. To ensure complete conversion to the iminium ion, the amine was treated under the photochemical oxidation conditions for 16 h in all cases. The position of substituents on the *N*-aryl group influenced the enantioselectivity of the oxidative alkylation addition more profoundly than did their electronic properties. Thus, *ortho*-substituted substrates generally provided higher enantiomeric excess compared to *para*-substituted analogs (**18l** *vs* **18b**; **18j** *vs* **18d**). In contrast, reaction enantioselectivities were very sensitive to the electronic nature of the substituents on the tetrahydroisoquinoline ring, with electron-rich systems generally affording lower *ee*'s and/or yields (e.g. **18e**, **18h**, **18i**).
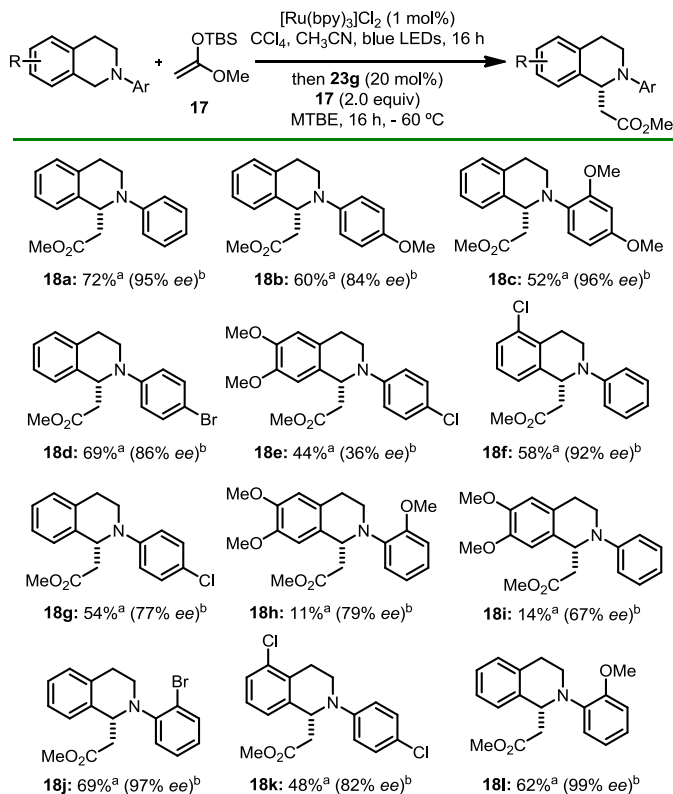
Figure 4. Substrate scope. [a] Isolated yields after chromatography on silica gel. [b] Determined by HPLC on commercial chiral columns. Absolute stereochemistry determined on **18l** after dearylation (see experimental section for details).

In order to better establish the synthetic utility of this chiral tetra-hydroisoquinoline synthetic methodology, we sought to develop a protocol for *N*-dearylation of the products to provide access to the more useful secondary amine derivatives. Electron-rich anilines have favorable redox properties that render them prone to *N*-aryl bond cleavage under oxidative conditions. Accordingly, compound **18l**, which was generated with nearly perfect enantioselectivity in the oxidative Mannich reaction, was chosen as a model substrate for dearylation studies (Scheme 8). The synthesis of **18l** was successfully scaled-up five-fold while maintaining a high level of enantioselectivity (96% *ee*) and the same reactivity.

Application of standard oxidative protocols for *para*-methoxyphenyl (PMP) or *para*-methoxybenzyl (PMB) removal utilizing cerium ammonium nitrate (CAN), bis(trifluoroacetoxy)-iodobenzene (PIFA), or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to rapid consumption of **18l** but low yields of the desired secondary amine due to product decomposition *via* over-oxidation.
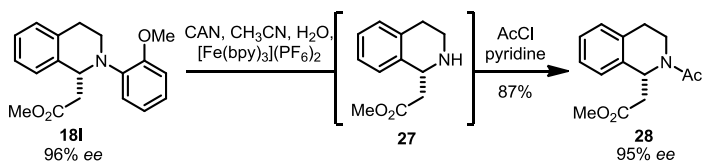
Scheme 8. Product derivatization.

We anticipated that the use of an oxidant more closely matched to the oxidation potential of the substrate would have a better chance of avoiding decomposition of the relatively sensitive secondary amine product. Evaluation of Fe(III)-based oxidants led to the identification of $[Fe(bpy)_3]^{3+}$, formed *in situ* upon treatment of $[Fe(bpy)_3](PF_6)_2$ with CAN, as a highly effective oxidant for this transformation, leading to clean conversion to the desired amine **27**. Comparison of the optical rotation of **27** with the reported value allowed the assignment of its absolute configuration. Acylation of **27** with acetyl chloride (AcCl) provided **28** (95% *ee*, 87% yield starting from **18l**) with no significant erosion of the enantiomeric purity.

4.3   Conclusions

The unprecedented merger of photoredox and asymmetric anion-binding catalysis has been successfully developed for the enantioselective oxidative C-H functionalization of tetrahydroisoquinoline derivatives. This combination of two distinct catalysis concepts led to the enantioselective synthesis of β-aminoesters which are key structural elements of many physiologically active compounds. A mild method for the selective dearylation of products bearing *N-o*-anisyl groups was also developed, thereby enabling further derivatization of the tetrahydroisoquinoline scaffold.

4.4   Experimental Section

4.4.1   General Informations

All the experimental work discussed in this chapter was carried out at Boston University. All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. For reactions run at low temperatures the caps were wrapped with Teflon® tape and parafilm to minimize the introduction of adventitious water. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Unless stated differently, all reactions were performed under inert atmosphere (Argon) and previously dried using common anhydrous techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with I_2. All compounds were purified *via* flash column chromatography using 230–400 mesh silica gel. NMR spectra were recorded on Varian Unity Plus 500 and Varian Mercury 400 spectrometers.

Chemical shifts for ^{1}H-NMR were reported as δ, parts per million (ppm), relative to the signal of CHCl$_3$ at 7.26(s) ppm. Chemical shifts for ^{13}C-NMR were reported as δ, parts per million, relative to the signal of the CDCl$_3$ 77.0 (t) ppm. Proton and carbon assignments were established using spectral data of similar compounds. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, p, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, pentet, multiplet and broad multiplet, respectively. IR spectra were recorded on an Avatar 360 FT-IR spectrometer. Mass spectra were recorded in the Mass Spectrometry Facility at the Department of Chemistry of Boston University in Boston, MA on a Waters Q-Tof API-US with ESI high-resolution mass spectrometer. The enantiomeric purity was determined by Chiral HPLC analysis performed on a Waters system using either a CHIRALPAK AD-H or a CHIRALCEL OD-H column from CHIRAL TECHNOLOGIES, INC with *i*-PrOH/hexane as the eluent. HPLC traces were compared to racemic samples prepared by performing the Oxidative Mannich Reaction in acetonitrile at room temperature, without the presence of the thiourea catalyst. Optical rotations were measured on an AUTOPOL III automatic polarimeter from RUDOLF RESEARCH ANALYTICAL. Concentration refers to removal of solvent under reduced pressure (house vacuum at *ca*. 20 mmHg). The ^{1}H and ^{13}C NMR spectra and HPLC traces are available in the literature and are not reported in the present manuscript.[1]

4.4.2 Materials

All chemicals were purchased from Sigma-Aldrich and were used as received unless otherwise stated. All solvents, excluding methyl *tert*-butyl ether (MTBE), were purchased from Fischer Scientific and further dried using Glass Contour Solvent System by SG Waters USA LLC. 1,2,3,4-Tetrahydroisoquinoline derivatives and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were prepared according to published literature procedures.[23] Catalysts have been synthesized following literature procedures.[22]

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[23] F. Y. Kwong, A. Klapars, S. L. Buchwald. Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere. *Org. Lett.*, **2012**, *4*, 581.

### 4.4.3   Experimental Procedure for Catalyst Screening
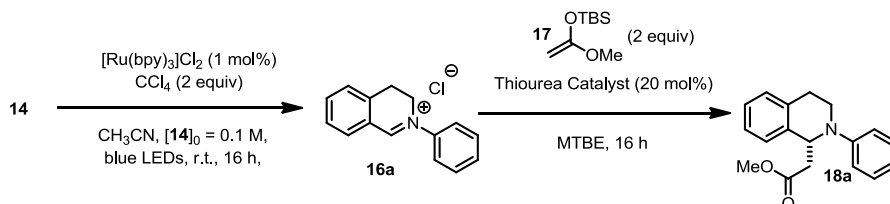
An oven-dried Schlenk flask was charged with *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **14** (0.5 mmol), [Ru(bpy)$_3$]Cl$_2$ (0.005 mmol, 0.01 equiv) and acetonitrile (5 mL). The flask was degassed (three cycles of freeze-pump-thaw) before CCl$_4$ (1 mmol, 2 equiv) was added in one portion and the resulting solution was stirred for 16 h under ambient light.

After complete generation of the iminium ion **16a**, as determined by TLC, 0.5 mL (0.05 mmol of iminium ion) of the solution was transferred to an oven-dried vial and the solvent were subsequently evaporated in vacuo. The thiourea catalyst (0.01 mmol, 0.2 equiv) and MTBE (1 mL) was added and the vial sealed with a septum equipped cap. The reaction mixture was allowed to reach the indicated temperature during a period of 30 minutes and the silyl ketene acetal 17 (0.1 mmol, 2 equiv) was added. The reaction mixture was stirred at this temperature for 16 h. The crude mixture was then quickly flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (10 ml). The solvent was removed in vacuo and the yield was determined by ^{1}H NMR spectroscopy using 2,5-dimethylfuran as an internal standard (δ 2.26 ppm (s, 6H), 5.84 (s, 2H)). The product was isolated by flash column chromatography on silica gel and the *ee* was determined by HPLC on chiral stationary phase compared to racemic samples (see section 4.4.5 for details).

4.4.4   Conditions for the Generation of Racemic Reference Compounds and Determination of Enantiomeric Purity

The transformation was performed in two steps as follows.
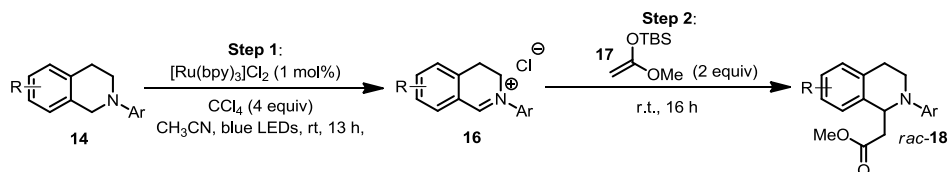
Step 1. Oxidative activation:

A mixture of tetrahydroisoquinoline (0.05 mmol), [Ru(bpy)$_3$]Cl$_2$ (0.32 mg, 1 mol%) and CH$_3$CN (0.5 mL) was degassed by three cycles of freeze-pump-thaw. CCl$_4$ (19.4 μL, 0.2 mmol, 4 equiv) was added and the mixture was stirred over-night under an inert atmosphere at room temperature while irradiated by a 30 cm, 1 W blue LED strip (λ$_{max}$ = 435 nm, at a distance of

approximately 10 cm so that the reaction mixture would not heat up during the reaction). Full conversion of the tetrahydroisoquinoline was ensured by either TLC or analyzing an aliquot of the reaction mixture with ^{1}H-NMR.

Step 2: Nucleophilic addition:

To the reaction mixture with the so formed iminium species was added the nucleophile, 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethylene (21.8 μL, 0.1 mmol, 2 equiv). The reaction mixture was stirred over-night (16 h) and was then filtered through a plug of silica using DCM (3 x 2 mL) and a mixture of DCM/Et$_2$O (1:1, 3 x 2 mL). The product was isolated by flash chromatography using a mixture of Et$_2$O in hexanes as eluent.

Racemic material of all products was used as reference for *ee* determination by HPLC on a chiral stationary phase.

4.4.5 General Procedure for the Enantioselective Oxidative Mannich Reactions to Access Tetrahydroisoquinoline Derived β-Amino Esters and Characterization Data for All New Compounds

The transformation is performed in two steps: visible light mediated photoredox activation conducted at room temperature followed by nucleophilic addition conducted at - 60 °C.
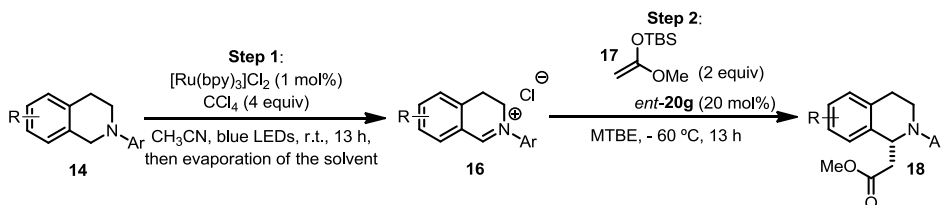
Step 1. Oxidative activation:

A mixture of tetrahydroisoquinoline (0.05 mmol), [Ru(bpy)$_3$]Cl$_2$ (0.32 mg, 1 mol%) and acetonitrile (0.5 mL) was degassed by three cycles of freeze-pump-thaw. CCl$_4$ (19.4 μL, 0.2 mmol, 4 equiv) was added and the mixture was stirred over-night under an inert atmosphere at room temperature while irradiated by a 30 cm, 1 W blue LED strip (λ_{max} = 435 nm, at a distance of approximately 10 cm so that the reaction mixture would not heat up during the reaction). Full conversion of the tetrahydroisoquinoline was ensured by either TLC or analyzing an aliquot of the reaction mixture with ^{1}H-NMR.

Step 2: Enantioselective addition:

The reaction mixture with the so formed iminium species was transferred to a glass vial equipped with a septum screw cap using additional acetonitrile (1 mL) to assure complete transfer. The solution (or suspension depending on which tetrahydroisoquinoline derivative was used) was concentrated with stirring under high vacuum at - 30 °C. The solid residue was kept under high vacuum for approximately 30 minutes at room temperature, which produced a red glassy solid. To the solid was added the thiourea catalyst *ent*-**20g** (5.9 mg, 0.01 mmol, 20 mol%)

whereupon the glass vial was sealed and then evacuated and refilled with argon three times. MTBE (1 mL) was added and the mixture was agitated with a vortex for a few seconds. The reaction mixture was then stirred at - 60 °C for 30 minutes before the addition of the nucleophile, 1-(tert-butyldimethylsilyloxy)-1-methoxyethylene (21.8 μL, 0.1 mmol, 2 equiv). The reaction mixture was stirred overnight (16 h) and was then filtered through a plug of silica gel using DCM (3 x 2 mL) and a mixture of DCM/Et$_2$O (1:1, 3 x 2 mL). The product was isolated by flash chromatography using 10% Et$_2$O in hexanes as eluent.

(*R*)-methyl 2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18a)
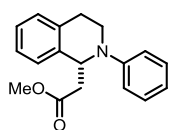
Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (10% diethyl ether in hexanes), using I$_2$ for TLC visualization, as a colorless semisolid (10.1 mg, 72% yield) in 95% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ$_{major}$ =4.6 min, τ$_{minor}$ = 6.7 min; [α]$_D^{26}$ = + 46.7 (c = 0.51, DCM); IR (thin film, cm^{-1}) 2953 (w), 2904 (w), 2841 (w), 1737 (s, C=O), 1588 (m), 1490 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24-7.21 (2H, m), 7.17-7.10 (4H, m), 6.95 (2H, d, *J* = 8.35 Hz), 6.74 (1H, t, *J* = 7.2 Hz), 5.31 (1H, t, *J* = 7.1 Hz), 3.64-3.52 (2H, m), 3.60 (3H, s), 3.04 (1H, ddd, J_1 = 16.1 Hz, J_2 = 9.0 Hz, J_3 = 5.6 Hz), 2.96 (1H, dd, J_1 = 14.9 Hz, J_2 =7.1 Hz), 2.79 (1H, dt, J_d = 16.1 Hz, J_t = 4.9 Hz), 2.66 (1H, dd, J_1 = 15.0 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.9, 148.8, 137.4, 134.6, 129.3, 128.8, 127.0, 126.7, 126.1, 118.1, 114.6, 56.3, 51.7, 41.5, 41.3, 27.0; HRMS *calcd.* for C$_{18}$H$_{20}$N$_1$O2: 282.1494; found: 282.1492.

(*R*)-methyl 2-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18b).
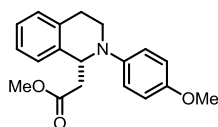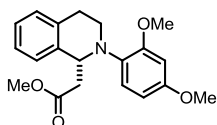
Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (15% diethyl ether in hexanes), using I$_2$ for TLC visualization, as a colorless semisolid (9.3 mg, 60% yield) in 84% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ$_{major}$ =9.0 min, τ$_{minor}$ = 14.7 min; [α]$_D^{26}$ = + 19.7 (c = 0.37, DCM); IR (thin film, cm^{-1}) 2949 (w), 2905 (w), 2833 (w), 1733 (s, C=O), 1509 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.19-7.11 (4H, m), 6.96-6.93 (2H, m), 6.84-6.81 (2H, m), 5.20 (1H, t, *J* = 7.0 Hz), 3.75 (3H, s), 3.61 (3H, s), 3.59-3.46 (2H, m), 3.04 (1H, ddd, *J* = 16.4, 10.1, 6.2 Hz), 2.92 (1H, dd, J_1 = 14.9 Hz, J_2 = 7.6 Hz), 2.74 (1H, dt, J_d = 16.4 Hz, J_t = 3.9 Hz), 2.66 (1H, dd, J_1 = 14.8 Hz, J_1 = 6.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.1, 153.1, 143.7, 137.5, 134.5, 129.0, 126.7, 126.1, 118.1, 114.6, 57.3, 55.6, 51.6, 42.2, 41.1, 26.7; HRMS *calcd.* for C$_{19}$H$_{22}$N$_1$O$_3$: 312.1600; found: 312.1586.
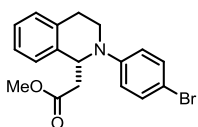
### (*R*)-methyl 2-(2-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (27c)

Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (20% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid (8.9 mg, 52% yield) in 96% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{minor} =9.9 min, τ_{major} = 16.0 min; $[\alpha]_D^{26}$ = + 31.0 (c = 0.42, DCM); IR (thin film, cm^{-1}) 2998 (w), 2948 (w), 2835 (w), 1735 (s, C=O), 1507 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.17-7.10 (4H, m), 6.81 (1H, br d, *J* = 8.6 Hz), 6.47 (1H, d, *J* = 2.9 Hz), 6.37 (1H, dd, J_1 = 8.6, 2.7 Hz), 5.18 (1H, t, *J* = 6.6 Hz), 3.83 (3H, s), 3.76 (3H, s), 3.48 (3H, s), 3.46-3.33 (2H, m), 2.99 (1H, ddd, *J* = 16.8, 10.8, 6.2 Hz), 2.83 (1H, dd, *J* = 14.9, 7.8 Hz), 2.74 (1H, d, *J* = 16.1 Hz), 2.58 (1H, dd, *J* = 15.0, 5.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.4, 156.4, 154.3, 138.4, 134.5, 133.3, 129.1, 126.8, 126.4, 125.8, 122.5, 103.6, 100.1, 56.7, 55.6, 55.5, 51.4, 43.1, 40.3, 27.8; HRMS *calcd.* for C$_{20}$H$_{24}$N$_1$O$_4$: 342.1705; found: 342.1695.

(*R*)-methyl 2-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18d)
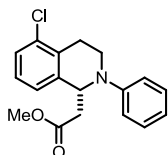

Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (10% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid (12.5 mg, 69% yield) in 86% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{minor} =8.5 min, τ_{major} = 14.0 min; $[\alpha]_D^{26}$ = + 30.6 (c = 0.5, DCM); IR (thin film, cm^{-1}) 2950 (w), 2901 (w), 2841 (w), 1734 (s, C=O), 1589 (m), 1494 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.33-7.30 (2H, m), 7.21-7.13 (4H, m), 6.86-6.83 (2H, m), 5.27 (1H, t, J_t = 7.1 Hz), 3.64 (3H, s), 3.62-3.53 (2H, m), 3.05 (1H, ddd, J_1 = 15.9 Hz, J_2 = 8.6 Hz, J_3 = 5.9 Hz), 2.96 (1H, dd, J_1 = 15.0 Hz, J_2 = 7.2 Hz), 2.82 (1H, dt, J_d = 16.2 Hz, J_t = 5.0 Hz), 2.69 (1H, dd, J_1 = 15.0 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 171.7, 147.9, 137.1, 134.4, 132.0, 128.2, 127.2, 126.7, 126.3, 116.2, 110.2, 56.3, 51.2, 41.6, 41.3, 26.8; HRMS *calcd.* for C$_{18}$H$_{19}$Br$_1$N$_1$O$_2$: 288.0388; found: 288.0221.

(*R*)-Methyl 2-(2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18e)
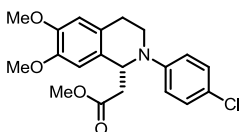
Reaction performed in accordance with the general conditions as stated above. The product was obtained in 44% yield and in 36% *ee*. The product could not be separated from the thiourea catalyst *via* flash chromatography and thus the yield is reported as ^{1}H-NMR determined yield obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =14.3 min, τ_{minor} = 19.2 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product. IR (thin film, cm^{-1}) 2956 (w), 2951 (w), 2836 (w), 1733 (s, C=O), 1595 (w), 1498 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.19-7.16 (2H, m), 6.91-6.88 (2H, m), 6.64 (2H, s), 6.61 (2H, s), 5.18 (1H, t, J_t = 7.0 Hz), 3.85 (3H, s), 3.84 (3H, s),

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3.64 (3H, s), 3.64-3.59 (1H, m), 3.54-3.49 (1H, m), 2.98 (1H, ddd, J_1 = 16.1 Hz, J_2 =9.8 Hz, J_3 = 5.6 Hz), 2.93 (1H, dd, J_1 = 14.9 Hz, J_2 =7.3 Hz), 2.72-2.66 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.0, 148.1, 147.7, 147.4, 129.0, 128.9, 126.4, 123.1, 116.2, 111.5, 109.6, 56.2, 56.0, 55.9, 51.8, 41.5, 41.2, 26.2; HRMS *calcd.* for C$_{20}$H$_{23}$ClNO$_4$: 376.1316; found: 376.1317.

(*R*)-methyl 2-(5-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (27f)

Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (10% diethyl ether in hexanes), using I$_2$ for TLC visualization, as a colorless semisolid (9.2 mg, 58% yield) in 92% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =4.7 min, τ_{minor} = 5.4 min; [α]$_D^{26}$ = + 32.2 (c = 0.41, DCM); IR (thin film, cm^{-1}) 2950 (w), 2898 (w), 2841 (w), 1738 (s, C=O), 1599 (m), 1504 (m); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.26-7.22 (3H, m), 7.12-7.06 (2H, m), 7.00-6.98 (2H, m), 6.79 (1H, dt, J_t = 7.2 Hz, J_d = 1.1 Hz), 5.34 (1H, t, J = 7.1 Hz), 3.78 (1H, dddd, J_1 = 13.6 Hz, J_2 = 6.2 Hz, J_3 = 3.3 Hz, J_4 = 1.1 Hz), 3.62 (3H, s), 3.53 (1H, ddd, J_1 = 13.6 Hz, J_2 = 10.5 Hz, J_3 =4.8 Hz), 3.03 (1H, ddd, J_1 = 17.1 Hz, J_2 =10.6 Hz, J_3 =6.1 Hz), 2.96 (1H, dd, J_1 =15.0 Hz, J_2 = 7.7 Hz), 2.84 (1H, ddd, J_1 = 17.4 Hz, J_2 = 4.9 Hz, J_3 =3.4 Hz), 2.7 (1H, dd, J_1 = 15.2 Hz, J_2 =6.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 171.7, 148.8, 139.6, 134.4, 132.7, 129.3, 127.7, 126.9, 125.2, 118.9, 115.5, 56.4, 51.8, 41.0, 40.5, 24.5; HRMS *calcd.* for C$_{18}$H$_{19}$Cl$_1$N$_1$O$_2$: 316.1104; found: 316.1107.

(*R*)-methyl 2-(2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18g)
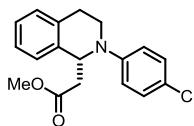
Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (10% diethyl ether in hexanes), using I$_2$ for TLC visualization, as a colorless semisolid (8.6 mg, 54% yield) in 77% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{minor} =8.0 min, τ_{major} = 13.3 min; [α]$_D^{26}$ = + 33.1 (c = 0.32, DCM); IR (thin film, cm^{-1}) 2951 (w), 2917 (w), 2850 (w), 1736 (s, C=O), 1597 (m), 1497 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.21-7.17 (4H, m), 7.16-7.13 (2H, m), 6.90-6.88 (2H, m), 5.27 (1H, t, J = 7.1 Hz), 3.63 (3H, s), 3.62-3.53 (2H, m), 3.05 (1H, ddd, J_1 = 16.1 Hz, J_2 = 9.0 Hz, J_3 = 5.9 Hz), 2.96 (1H, dd, J_1 = 14.9 Hz, J_2 = 7.3 Hz), 2.82 (1H, dt, J_t = 16.3 Hz, J_d =4.8 Hz), 2.69 (1H, dd, J_1 = 14.9 Hz, J_2 =6.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 171.8, 147.5, 137.1, 134.4, 129.1, 128.8, 127.1, 126.7, 126.3, 122.9, 115.8, 56.4, 51.8, 41.7, 41.3, 26.8; HRMS *calcd.* for C$_{18}$H$_{19}$Cl$_1$N$_1$O$_2$: 316.1104; found: 316.1093.
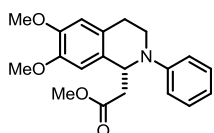
(*R*)-Methyl 2-(6,7-dimethoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18h)

Reaction performed in accordance with the general conditions as stated above. The product was obtained in 11% yield and in 79% *ee*. The product could not be separated from the thiourea catalyst *via* flash chromatography and thus is the yield reported as a ^{1}H-NMR determined yield
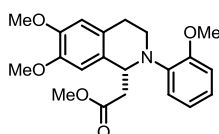
obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALCEL OD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =16.9 min, τ_{minor} = 19.9 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product**.** IR (thin film, cm^{-1}) 2950 (w), 2835 (w), 1734 (s, C=O), 1593 (w), 1514 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 6.98 (1H, ddd, J_1 = 8.1 Hz, J_2 =7.1 Hz, J_3 = 1.7 Hz), 6.90-6.83 (3H, m), 6.66 (1H, s), 6.58 (1H, s), 5.21 (1H, t, *J* = 6.9 Hz), 3.86 (3H, s), 3.85 (3H, s), 3.85 (3H, s), 3.49-3.46 (2H, m), 3.47 (3H, s), 2.92 (1H, ddd, J_1 = 16.6 Hz, J_2 = 10.5 Hz, J_3 =7.1 Hz), 2.84 (1H, dd, J_1 = 14.9 Hz, J_2 = 7.6 Hz), 2.64-2.59 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.6, 153.0, 147.8, 147.3, 139.7, 130.0, 126.3, 123.2, 121.6, 120.8, 112.0, 111.6, 109.5, 56.0, 55.8, 55.7, 51.4, 42.5, 40.5, 27.2; HRMS *calcd.* for C$_{21}$H$_{26}$NO$_5$: 372.1811; found: 372.1810.

(*R*)-methyl 2-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18i)

Reaction performed in accordance with the general conditions as stated above. The product was obtained in 14% yield and in 67% *ee*. The product could not be separated from the thiourea catalyst *via* flash chromatography and thus is the yield reported as a ^{1}H-NMR determined yield obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALPAK AD-H, 1% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =52.4 min, τ_{minor} = 56.4 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product. IR (thin film, cm^{-1}) 2952 (w), 2849 (w), 1736 (s, C=O), 1599 (w), 1516 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.25 (2H, dd, J_1 = 9.1 Hz, J_2 = 7.1 Hz), 6.98 (2H, d, *J* = 8.1 Hz), 6.77 (1H, t, *J* = 7.2 Hz), 6.66 (1H, s), 6.61 (1H, s), 5.25 (1H, t, *J* = 7.0 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.70-3.47 (2H, m), 3.63 (3H, s), 3.03-2.94 (2H, m), 2.73-2.66 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.2, 149.0, 148.0, 147.3, 129.33, 129.25, 126.6, 118.3, 115.0, 111.5, 109.7, 56.1, 56.0, 55.9, 51.7, 41.4, 41.2, 26.4; HRMS *calcd.* for C$_{20}$H$_{24}$NO$_4$: 342.1705; found: 342.1707.

(*R*)-methyl 2-(2-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18j)
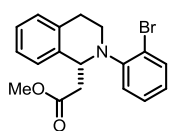
Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (10% diethyl ether in hexanes), using I$_2$ for TLC visualization, as a colorless semisolid (12.3 mg, 69% yield) in 97% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =5.2 min, τ_{minor} = 8.1 min; $[\alpha]_D^{26}$ = + 40.0 (c = 0.39, DCM); IR (thin film, cm^{-1}) 3026 (w), 2950 (w), 2837 (w), 1736 (s, C=O), 1599 (s), 1505 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.26-7.23 (2H, m), 7.19-7.12 (4H, m), 6.98-6.96 (2H, m), 6.76 (1H, t, *J* = 7.3 Hz), 5.33 (1H, t, *J* = 7.1 Hz), 3.66-3.62 (1H, m), 3.62 (3H, s), 3.59-3.54 (1H, m), 3.06 (1H, ddd, J_1 = 16.1 Hz, J_2 =8.8 Hz, J_3 =5.6 Hz), 2.98 (1H, dd, J_1 =14.9 Hz, J_2 = 7.1 Hz), 2.82 (1H, dt, *J* = 16.1, 4.9 Hz), 2.68 (1H, dd, J_1 = 14.9 Hz, J_2 = 7.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 171.9, 148.9, 137.5, 134.7, 129.3, 128.8, 127.0, 126.7, 126.2, 118.1, 114.6, 56.3, 51.7, 41.5, 41.3, 27.0; HRMS *calcd.* for C$_{18}$H$_{19}$Br$_1$N$_1$O$_2$: 360.0599; found: 360.0608.

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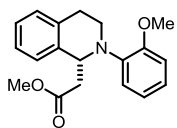**(*R*)-methyl 2-(5-chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18k)**
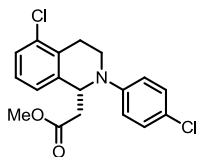
Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (7.5% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid (8.4 mg, 48% yield) in 82% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =6.9 min, τ_{minor} = 7.7 min; $[\alpha]_D^{26}$ = + 25.0 (c = 0.32, DCM); IR (thin film, cm^{-1}) 2924 (w), 2855 (w), 1736 (s, C=O), 1596 (m), 1498 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.27-7.26 (1H, m), 7.20-7.17 (2H, m), 7.12 (1H, t, *J* = 7.8 Hz), 7.07 (1H, dd, J_1 = 7.8 Hz, J_2 =0.7 Hz), 6.93-6.90 (2H, m), 5.28 (1H, t, *J* = 6.8 Hz), 3.73 (1H, dddd, J_1 = 13.6 Hz, J_2 =6.1 Hz, J_3 =3.3 Hz, J_4 =0.7 Hz), 3.64 (3H, s), 3.53 (1H, ddd, J_1 = 13.6 Hz, J_2 =10.5 Hz, J_3 =4.8 Hz), 3.01 (1H, ddd, J_1 = 17.1 Hz, J_2 =10.7 Hz, J_3 =6.0 Hz), 2.94 (1H, dd, *J* = 15.2, 7.8 Hz), 2.84 (1H, dt, J_t = 16.9 Hz, J_d =4.2 Hz), 2.7 (1H, dd, J_1 = 15.2 Hz, J_2 = 6.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 171.6, 147.5, 139.2, 134.4, 132.5, 129.1, 127.8, 127.0, 125.2, 123.7, 116.7, 56.5, 51.2, 41.0, 40.7, 24.3; HRMS *calcd.* for C$_{18}$H$_{18}$Cl$_2$N$_1$O$_2$: 350.0715; found: 350.0714.

(*R*)-methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (18l)

Reaction performed in accordance with the general conditions as stated above. The product was isolated *via* flash chromatography on silica gel (15% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid (9.7 mg, 62% yield) in 99% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =6.5 min, τ_{minor} = 10.4 min; $[\alpha]_D^{26}$ = + 41.8 (c = 0.39, DCM); IR (thin film, cm^{-1}) 2949 (w), 2832 (w), 1737 (s, C=O), 1594 (w), 1501 (s); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C) δ 7.18-7.15 (3H, m), 7.14-7.10 (1H, m), 6.98 (1H, ddd, J_1 = 9.0 Hz, J_2 = 7.1 Hz, J_3 =2.0 Hz), 6.91-6.83 (3H, m), 5.32 (1H, dd, J_1 = 7.7 Hz, J_2 =5.7 Hz), 3.86 (3H, s), 3.51-3.49 (2H, m), 3.46 (3H, s), 3.05-2.98 (1H, m), 2.86 (1H, *J* = 14.9, 7.8 Hz), 2.74 (1H, dt, J_t = 16.6 Hz, J_d =2.9 Hz), 2.61 (1H, dd, J_1 = 14.9 Hz, J_2 =5.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C) δ 172.3, 153.1, 139.7, 138.2, 134.4, 129.2, 126.8, 126.5, 125.9, 123.2, 121.65, 120.8, 112.0, 56.2, 55.6, 51.4, 42.5, 40.4, 27.8; HRMS *calcd.* for C$_{19}$H$_{22}$N$_1$O$_3$: 312.1600; found: 312.1587.

4.4.6   Scale-Up and Product Dearylation

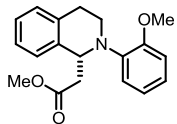**(*R*)-Methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate**

Reaction performed in accordance with the general conditions as stated above with the following exceptions; the reaction was performed on a 0.25 mmol scale and the enantioselective addition was conducted at − 40 °C for a reaction time of 48 h. The product was isolated *via* flash chromatography on

silica gel (15% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid

(48.3 mg, 62% yield) in 95% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{major} =6.5 min, τ_{minor} = 10.4 min. All spectral data was in accordance with the small scale reaction (**18l**, vide supra).

(*R*)-methyl 2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (28)
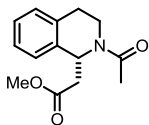
A solution of CAN (169.9 mg, 0.31 mmol, 5 eq) and H_2O (3 mL) was added to a solution of [Fe(bpy)$_3$](PF$_6$)$_2$ (252.4 mg, 0.31 mmol, 5 equiv) in CH_3CN (3 mL). The resulting blue solution was added dropwise to a solution of Methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (19.3 mg, 0.062 mmol), CH_3CN (2 mL) and water (1 mL) at room temperature. The reaction immediately turned red. The reaction was allowed to stir for 45 minutes and was then quenched with sat. Na_2CO_3 (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL) and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The so obtained solid crude was dissolved in a minimum amount of DCM (approx. 1 mL) followed by addition of Et_2O (approx. 5 mL) to precipitate the metal salts. The crude dearylated product was obtained by filtration using a cotton plugged pipette followed by evaporation of the solvent.

AcCl (7 µL, 0.093 mmol, 1.5 equiv) was added to a solution of the crude amine and pyridine (3 mL) at ambient temperature. The reaction mixture was stirred for 2 h and then quenched with H_2O (10 mL). The mixture was extracted with DCM (10 x 3 mL) and the combined organic phases was dried over Na_2SO_4 and then concentrated in vacuo. The crude was triturated with Et_2O and the suspension was allowed to rest at - 18 °C over-night. The solvent was decanted and concentrated in vacuo to give the acetylated product as a white solid in 87% yield (13 mg) and 95% *ee*. Chiral HPLC (CHIRALCEL OD-H, 15% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm) τ_{minor} =6.7 min, τ_{major} = 9.6 min; $[\alpha]_D^{26}$ = + 32.7 (c = 0.36, DCM). All spectral data was in accordance with published data.[24]

4.4.7   Determination of the Absolute Configuration
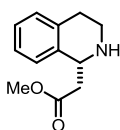
(*R*)-methyl 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate **27** was isolated from an aliquot of the crude reaction mixture in the oxidative dearylation of (*R*)-Methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (**28**) utilizing reverse phase chromatography (GILSON PLC 2020 system with a SunFire prep C18 ODB^{TM} column). Comparing with the literature $[\alpha]_D^{26}$ value for (+)-methyl (*R*)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate confirmed the absolute configuration of the

[24] H. Yamanaka, T. Shiraishi, T. Sakamoto, *Chem. Pharm. Bull.*, **1981**, *29*, 1056.

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tetrahydroisoquinoline derivative to be *R*-enantiomer.[25] $[\alpha]_D^{26}$ = + 40.7 (c = 0.1, DCM, 95% *ee*).

Literature: $[\alpha]_D^{26}$ = + 95.2 (c = 1.0, CHCl$_3$, 95% *ee*)

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[25] Y. Takeuchi, Y. Kamada, K. Nishimura, H. Nishioka, M. Nishikawa, K. Hashigaky, M. Yamato, T. Harayama. Alkoxycarbonylmethylation of (3*R*,10b*S*)-3-Phenyl-2,3,5,6-Tetrahydro-10b*H*-Oxazolo[2,3-*a*]Isoquinoline. *Chem. Pharm. Bull.*, **1994**, *42*, 796.

Chapter V

Photochemical Perfluoroalkylation of Arenes via Electron Donor-Acceptor Complex Formation
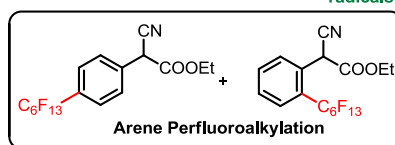
Target

Identify a new and simple methodology for the direct perfluoroalkylation of arenes.
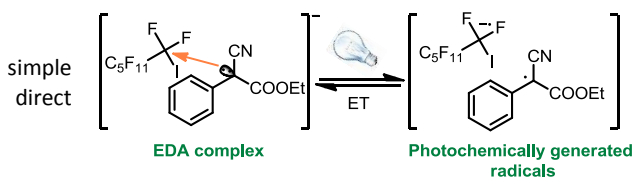
Tool

Photochemical activity of *in situ* generated electron donor-acceptor (EDA) complexes to drive the perfluoroalkylation of arenes.[1]


5.1 Background

The selective incorporation of fluorine atoms or fluoroalkyl moieties into organic compounds has become an important and rapidly developing area of research. Despite their rarity in nature, organofluorine compounds show unique physical, chemical and biological properties of interest for life and material sciences. The efficient and selective incorporation of the fluorine atom or fluorine-containing moieties into organic molecules to modulate their biological properties has currently become a routine and powerful strategy in drug design.[2] As the last research endeavor of my PhD studies, I sought to identify a new and effective strategy for the perfluoroalkylation of arenes. Initial results, detailed in this chapter, suggest the feasibility of a photochemical protocol driven by visible light.

Recently, our laboratory established a new strategy for the direct, enantioselective α-alkylation of aldehydes which constitutes the first example of photochemical asymmetric catalysis

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[1] The interaction between electron-donor and electron-acceptor in the EDA complexes, as depicted in the figures and schemes of this chapter, only aims to clarify the identity of the donor and the acceptor participating in the complex formation without any information about the molecular orbitals involved.

[2] S. Purser, P. R. Moore, S. Swallowb, V. Gouverneur. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.*, **2008**, *37*, 320.

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ASSESSING THE VERSATILITY OF ORGANOCATALYSIS AS A STRATEGY FOR ENABLING NOVEL ASYMMETRIC TRANSFORMATI
Giulia Bergonzini
Dipòsit Legal: T 1661-2014

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involving an electron donor-acceptor (EDA) complex of the reacting partners as the radiation acceptor (Scheme 1).[3]
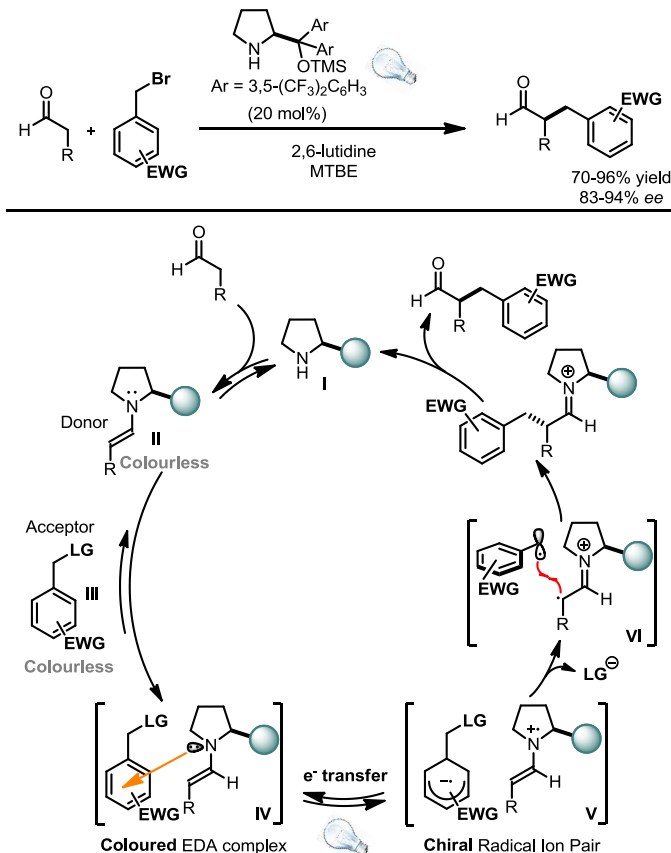
Scheme 1. First example of photochemical asymmetric catalysis *via* EDA complex formation. LG: leaving group; EWG: electron-withdrawing group. TMS = trimethylsilyl; MTBE = methyl *tert*-butyl ether.

It has been found that readily available chiral amines, with an established profile as catalysts of thermal asymmetric processes, can exert high stereocontrol in synthetically relevant intermolecular carbon-carbon bond-forming reactions driven by visible light. A mechanism (Scheme 1) involving an in-cage radical combination as the stereo-defining step was proposed. The cycle starts with the well-established condensation of chiral secondary amines of type **I** with aldehydes to form reactive nucleophilic enamine intermediates **II**. In consonance with the

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[3] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre. Photochemical Activity of a Key Donor-Acceptor Complex can Drive Stereoselective Catalytic α-Alkylation of Aldehydes. *Nat. Chem.*, **2013**, *5*, 750.

known ability of tertiary amines to form EDA complexes with molecules of high electron affinity,[4] the lone pair of the pyrrolidine ring in the enamine **II** engages in a ground-state molecular aggregation with electron accepting molecules. The low ionization potentials (IPs) of the pyrrolidine-based enamines of type **II** (e.g. 1-(but-1-enyl)pyrrolidine has an IP of 7.2 eV) qualify them as potential donors for facilitating EDA associations in the ground state.[5] EDA complexes are typically characterized by the appearance of a weak absorption band, the charge-transfer band, associated with an electron transfer (ET) from donor to acceptor.[6,7] In many cases, the energy of this transition lies within the visible frequency range raising the possibility of using visible light to activate substances that would not normally absorb in the visible spectrum.

In the alkylation of aldehydes depicted in Scheme 1, visible light irradiation of the colored EDA complex **IV** induces electron transfer (ET) to occur, leading to the chiral contact radical ion pair **V**. The presence of a suitable leaving group (LG in **V**) within the radical anion partner triggers a fragmentation event. This productively renders the positively charged intermediate pair **VI**, which brings two radicals within a geometrically restricted chiral space and in very close proximity. This environment facilitates a stereocontrolled radical combination to form a new carbon-carbon bond while forging the stereogenic center. This photochemical process results in the asymmetric intermolecular α-alkylation of aldehydes with alkyl halides, a transformation which cannot be achieved under thermal control.[8]

This precedent established that the transiently generated enamines can guide the photo-activation of the substrates by inducing the transient formation of photon-absorbing chiral electron donor-acceptor (EDA) complexes. We wondered whether this novel reactivity concept could be extended to include other electron accepting substrates, thus resulting in the design of synthetically useful photochemical asymmetric transformations of aldehydes. We selected perfluoroalkyl iodides as suitable electron-acceptor species. Our choice was motivated by a literature precedent, reporting on the possibility of generating EDA complexes between perfluoroalkyl iodides and preformed enamines.[9,10]

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[4] R. Foster. Electron Donor-Acceptor Complexes. *J. Phys. Chem.*, **1980**, *84*, 2135.

[5] K. Müller, F. Previdoli, H. Desilvestro. Enamines. II. A Theoretical and Photoelectron Spectroscopic Study of the Molecular and Electronic Structures of Aliphatic Enamines. *Helv. Chim. Acta*, **1981**, *64*, 2497.

[6] R. S. Mulliken. Molecular Compounds and their Spectra, II. *J. Am. Chem. Soc.*, **1952**, *74*, 811.

[7] S. V. Rosokha, J. K. Kochi. Fresh Look at Electron-Transfer Mechanisms *via* the Donor/Acceptor Bindings in the Critical Encounter Complex. *Acc. Chem. Res.*, **2008**, *41*, 641.

[8] P. Melchiorre. Light in Aminocatalysis: the Asymmetric Intermolecular α-Alkylation of Aldehydes. *Angew. Chem. Int. Ed.*, **2009**, *48*, 1360.

[9] D. Cantacuzène, C. Wakeselman, R. Dorme. Condensation of Perfluoroalkyl Iodides with Unsaturated Nitrogen Compounds. *J. C. S. Perkin I*, **1977**, 1365.

[10] We note that an EDA complex formation was recently postulated by the MacMillan group for the perfluoroalkylation of silylketene acetals occurring under visible light irradiation but without the need for any photocatalyst, see reference 16 in: P. V. Pham, D. A. Nagib, D. W. C. MacMillan. Photoredox Catalysis: a Mild, Operationally Simple Approach to the Synthesis of α-Trifluoromethyl Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2011**, *50*, 6119.

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5.2 Results and Discussion

With the aim to exploit the use of chiral enamines as active partners in the photo-excitation of substrates *via* EDA complex formation, we focused on the α-perfluoroalkylation of carbonyl compounds (Scheme 2).
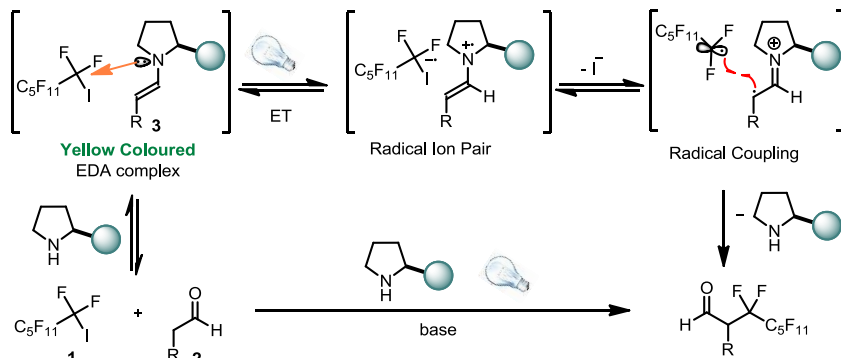

Scheme 2. α-Perfluoroalkylation of aldehydes *via* visible light irradiation of EDA complex between perfluoroalkyl iodide **1** and enamine **3**.

We postulated that the perfluoroalkylation could be achieved by the formation of an EDA complex between the amino-group of the enamine **3** (generated *in situ* by condensation of chiral secondary amine catalyst and aldehyde **2**) and the perfluorohexyl iodide **1**. Photo-induced electron transfer would lead to the formation of a radical ion pair.[11] Fragmentation of the radical anion would then produce the perfluorohexyl radical. A radical-radical coupling followed by hydrolysis of the resulting iminium ion would lead to the final α-perfluoroalkylated carbonyl compound.

Motivated by our interest in devising photocatalytic transformations proceeding through EDA complex formation as a new tool in catalytic asymmetric synthesis, we thus investigated the perfluoroalkylation reaction using butanal and perfluorohexyl iodide in the presence of the secondary amine catalysts **A** and under irradiation with a 16 W compact fluorescent light (CFL) bulb. Selected experimental data are shown in Table 1.

The use of secondary amine **A** as catalyst under mild basic conditions (Entries 1, 2) revealed that the α-perfluoroalkylation of butanal was possible. However, a fast degradation of the desired product **4** led to the *E* and *Z* isomers of **5** as the only detectable products. A viable pathway for the generation of product **5** is the HF elimination under basic conditions from the α-perfluoroalkylated aldehyde **4**.

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[11] Charge-transfer complexes between amines and R_FI have been reported. See: R. N. Haszeldine. Studies in Spectroscopy. Part V. Molecular Compound Formation with Polyhalogeno-Iodo-Compounds. *J. Chem. Soc.*, **1953**, 2622.

Table 1. Photochemical α-perfluoroalkylation of butanal *via* EDA complex[a]
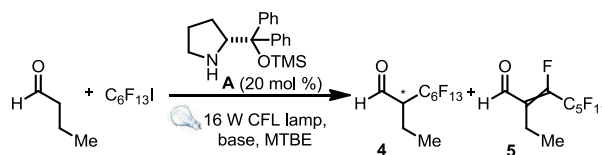
Entry	Base (equiv)	Yield (%)[b] 4/5
1	NaOAc (1.2)	0/25
2	2,6-Lutidine (1.2)	0/23
3	-	0/0
4	TREAT HF	0/0

[a] Reactions performed on a 0.1 mmol scale using 2 equiv of butanal, [butanal]$_0$ = 0.4 M. Reaction time = 16 h. [b] Yield determined by ^{1}H and ^{19}F NMR analysis of an aliquot from the crude reaction mixture through relative amounts of remaining reagents and products. Me = methyl; TREAT HF = Et$_3$N·3HF; Ph = phenyl; TMS = trimethyl silyl.

The base was found to be an essential element in the process since it quenched the deleterious HI generated as byproduct during the reaction (Entry 3). Nevertheless, it also promoted the degradation of product **4**. We thus tried to buffer the reaction media using TREAT HF (Et$_3$N·3HF), which was successfully used by the Grushin group at ICIQ to avoid a similar degradation pathway in the trifluoromethylation of α-haloketones.[12] However, the use of this additive (kindly donated by Professor Grushin) did not provide any reactivity (Entry 4).

In order to avoid the elimination pathway, we utilized α-branched aldehydes as substrate so to forge a quaternary stereogenic center. Unfortunately, instead of the quaternarization of the α-carbon, no reactivity was observed.

This prompted us to consider the possibility of using different donor substrates, other than enamines to generate EDA complexes with perfluorohexyl iodide. Our idea was to avoid the HF elimination path using electron-rich substrates with suitable substitution patterns. We hypothesized whether enolates could be used as suitable electron-donors in the reaction.[13] This idea arose by the similar reactivity between enamines and enolates, *in situ* generated in the presence of bases from activated substrates. Recent advances in the fields of chiral base catalysis and phase transfer catalysis (PTC) have established that enolizable compounds such as β-ketoesters and α-cyanoacetates can be employed in enantioselective alkylation reactions,

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[12] P. Novák, A. Lishchynskyi, V. V. Grushin. Trifluoromethylation of α‑Haloketones. *J. Am. Chem. Soc.*, **2012**, *134*, 16167.

[13] Charged nucleophiles can be suitable electron donor intermediates which participate in S$_{RN}$1 type reactions in the presence of an appropriate electron acceptor. See: R. A. Rossi, A. B. Pierini, A. B. Peñéñory. Nucleophilic Substitution Reactions by Electron Transfer. *Chem. Rev.*, **2003**, *103*, 71.

leading to the formation of all-carbon quaternary stereocenters.[14,15]

The feasibility of the photochemical perfluoroalkylation reaction *via in situ* generation of enolates under basic conditions was tested by using α-cyanoacetate **6** as the electron donor precursor in methyl *tert*-butyl ether (MTBE) and in the presence of 3 equivalents of K_2CO_3 as the base (Equation 1).[16] Surprisingly, irradiation of the bright yellow colored reaction mixture (which may be attributed to EDA complex formation between the perfluorohexyl iodide **1** and the α-cyanoacetate anion generated under the reaction conditions) did not afford the expected product **7c**. Products **7a** and **7b** were generated instead, along with the perfluorohexyl alkane H-C_6F_{13}.
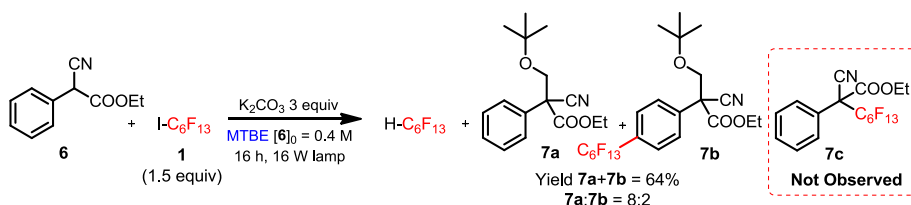
Equation 1. Yield determined by ^1H and ^{19}F NMR analysis of an aliquot from the crude reaction mixture by considering relative amounts of remaining reagents and products.

A control experiment carried out performing the reaction in the dark did not provide any reactivity, suggesting that light is necessary for the reaction to proceed. The formation of the main product **7a** can be rationalized on the basis of a hydrogen abstraction from the solvent by

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[14] Y. Wang, L. Deng. Asymmetric Acid-Base Bifunctional Catalysis with Organic Molecules. Edited by I. Ojima. *Catalytic Asymmetric Synthesis* (3rd Edition), **2010**, 59-94.

[15] S. Shirakawa, K. Maruoka. Asymmetric Phase-Transfer and Ion Pair Catalysis. Edited by I. Ojima. *Catalytic Asymmetric Synthesis* (3rd Edition), **2010**, 95-117.

[16] The reaction performed without the base did not give any product formation.

the perfluorohexyl radical **X** (see reference 17 for details). The unexpected product **7b**, perfluoroalkylated directly on the aromatic ring, was greatly intriguing to us. This reactivity might indeed open the possibility for a new methodology for the direct perfluoroalkylation of aromatic compounds under mild conditions and simply driven by visible light.[18]

In order to direct the reactivity exclusively toward the perfluoroalkylation of the aromatic ring, we used a solvent less prone to hydrogen abstraction. Switching from MTBE to acetonitrile as the reaction medium led to the *ortho*- and *para*-perfluoroalkylated products **8a** and **8b** along with a minor di-substituted product **8c** (Equation 2).
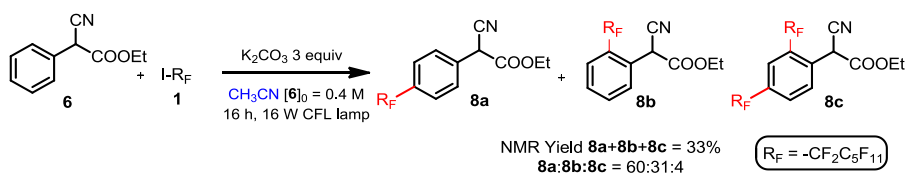
Equation 2. Yield determined by ^{1}H and ^{19}F NMR analysis of the crude reaction mixture after acidic work-up by considering relative amounts of remaining reagent **6** and products.

Scheme 3 shows a plausible mechanism for the arene perfluoroalkylation chemistry. In order to simplify the scheme, only the route leading to the major adduct **8a** (in its anionic form **XV**) was specified. Two possible mechanisms can be operating,[19] both of which would be initiated by the photoexcitation of the EDA complex generated between carbanion **VII** and the perfluorohexyl

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[17] Proposed mechanism for the formation of product **7a**:
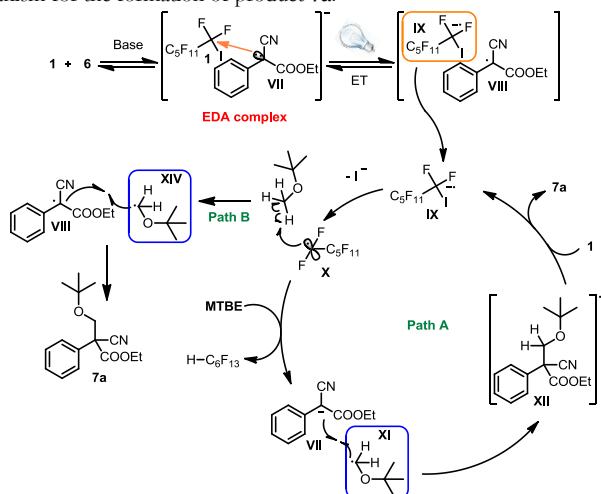
[18] A. Bravo, H.-R. Bjørsvik, F. Fontana, L. Liguori, A. Mele, F. Minisci. New Methods of Free-Radical Perfluoroalkylation of Aromatics and Alkenes. Absolute Rate Constants and Partial Rate Factors for the Homolytic Aromatic Substitution by n-Perfluorobutyl Radical. *J. Org. Chem.*, **1997**, *62*, 7128.

[19] L. M. Tolbert, D. P. Martone. Carbanion Photochemistry. 7. The S_{RN}1 *vs.* S_{ET} Photoarylation of Triphenylmethyl Anion. *J. Org. Chem.*, **1983**, *48*, 1185.

iodide. The resulting electron-transfer would then lead to the radical **VIII** and the radical anion **IX**.
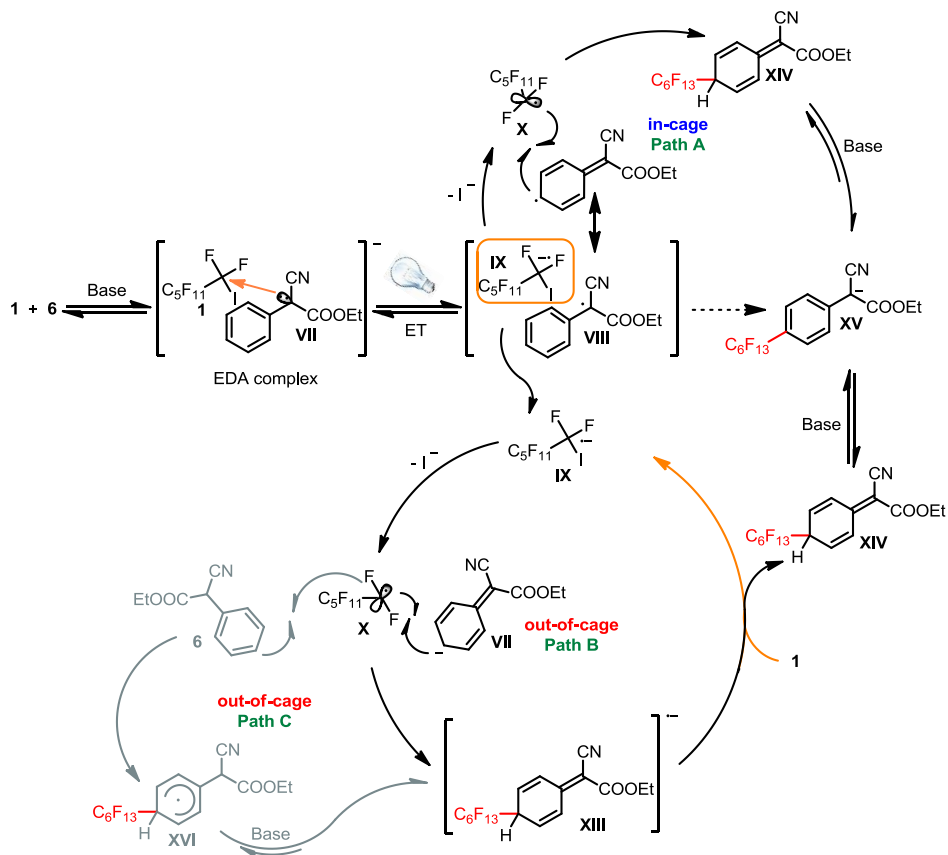
Scheme 3. Mechanistic proposal for the perfluoroalkylation of arenes *via* EDA complex formation.

As depicted in Path A, the process may proceed in the solvent cage *via* facile fragmentation of **IX** to render the carbon centered radical species **X**, which can couple with the delocalized radical **VIII** on the aromatic ring. This in-cage coupling would lead to functionalization of the *para*-position in the aromatic moiety. Once the intermediate **XIV** is formed, deprotonation by the base would directly lead to the final product **XV**.

Another feasible pathway can be conceived which follows a $S_{RN}1$ radical chain mechanism (path

B).[20] Upon the photo-induced electron transfer, the radical anion **VIII** would disassociate out of the solvent cage to render, upon fragmentation, the radical species **X**. The free radical could then add to the delocalized anion **VII** to give a radical anion **XIII** functionalized in the *para* position,[21] which could be subsequently oxidized by perfluorohexyl iodide **1**. Electron transfer to **1** would generate the intermediate **XIV** and the radical anion **IX**, thus propagating the chain. Upon deprotonation and re-aromatization of **XIV** under basic conditions, anion **XV** is generated.

An alternative $S_{RN}1$-type mechanism, can be proposed by considering the intermediate **XIII** arising from the out-of-cage coupling between the perfluorohexyl radical **X** and the aromatic system of neutral species **6**,[22,23] followed by deprotonation (path C). It has to be noted, in this regard, that under the reaction conditions substate **6** is mainly deprotonated (as shown by ^{1}H NMR analysis of an aliquot of the crude reaction mixture).

Analogous pathways can be pictured for the *ortho*-functionalization of **6**, while di-perfluoroalkylated product **8c** can be formed upon further photoexcitation of an EDA complex between anion **XV** and perfluorohexyl iodide.

We are planning to carry out further experiments to better delineate the mechanism of the transformation. First, the quantum yield of the reaction will be determined in order to differentiate between radical chain mechanism (which would be operative in the case of the $S_{RN}1$ pathways B and C) and non-chain mechanism (in-cage radical combination, pathway A).[24] Quantum yields greater than 1 are possible only for photo-induced chain reactions, in which a single photon may trigger long chain of transformations.

Second, perfluorohexyl radical **X** will be generated (following established procedures reported in the literature)[22,25] upon rigorous exclusion of light so to completely suppress the possibility of a mechanism initiated by EDA complex excitation. These conditions exclude the formation of radical **VIII** in the reaction media while mimicking the conditions for a $S_{RN}1$-type chain mechanism. The absence of any reactivity would suggest a mechanism proceeding through an

[20] This mechanism was proposed for the photostimulated α-, *ortho*-, and *para*-arylation of phenylacetic acid dianions. See: G. C. Nwokogu, J.-W. Wong, T. D. Greenwood, J. F. Wolfe. Photostimulated Reactions of Phenylacetic Acid Dianions with Aryl Halides. Influence of the Metallic Cation on the Regiochemistry of Arylation. *Org. Lett.*, **2000**, *2*, 2643.

[21] (a) J. B. Lambert, S. M. Wharry. Nuclear Magnetic Resonance Examination of Organic Dianions. *J. Am. Chem. Soc.*, **1982**, *104*, 5857. G. A. Russell. (b) The Reactions of Resonance Stabilized Anions. I. Neutralization of the α,α-Dimethylbenzyl Carbanion. *J. Am. Chem. Soc.*, **1959**, *81*, 2017.

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[23] D. A. Nagib, D. W. C. MacMillan. Trifluoromethylation of Arenes and Heteroarenes by Means of Photoredox Catalysis. *Nature*, **2011**, *480*, 224.

[24] M. Montalti, A. Credi, L. Prodi, M. T. Gandolfi. Chemical Actinometry. *Handbook of Photochemistry*. Third Edition. Taylor & Francis, Boca Raton, **2006**.

[25] W. Zhu, Z. Li. Synthesis of perfluoroalkylated sugars catalyzed by rabbit muscle aldolase (RAMA). *J. Chem. Soc. Perkin Trans. 1*, **2000**, 1105.

in-cage radical combination; in contrast, a productive reaction would support a $S_{RN}1$ radical chain mechanism.

The regioselectivity of the reaction remains an interesting question. One would expect the electrophilic perfluorohexyl radicals to react mostly at the α-position of the carbanion generated by deprotonation of ethyl 2-cyano-2-phenylacetate. The perfluoroalkylation was observed exclusively on the aromatic ring instead. This reactivity was consonant with the results obtained when performing the reaction using ethyl 2-cyanopropanoate as substrate (Scheme 4).
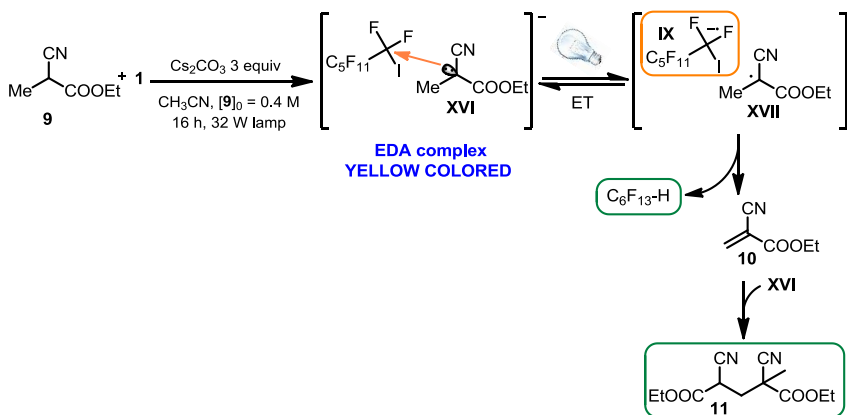
Scheme 4. Perfluoroalkylation of 2-cyanopropanoate.

The absence of the phenyl moiety in the electron donor completely prevented any perfluoroalkylation. As shown in Scheme 4, visible light irradiation of the colored EDA complex might induce electron transfer to occur, leading to radical anion **IX** and radical **XVII**. After fragmentation of radical **IX**, the resulting perfluorohexyl radical did not couple with radical **XVII** or anion **XVI**, instead it abstracted a hydrogen from **XVII** to give ethyl 2-cyanoacrylate **10**. Under basic conditions (and thus high concentration of anion **XVI**) the Michael addition product **11** was observed as the product of the reaction along with a considerable amount of polymers. Similar results were reported in the literature using methylmalonate anion.[26] This testifies to the inherent poor reactivity of α-centered radical **XVII** or anion **XVI** toward perfluorohexyl radical addition under the reaction conditions.

To gain more mechanistic insights on this unexpected reactivity further studies were performed. Representative data are reported in Table 2.

Solubility of the inorganic base in acetonitrile played an important role. The higher solubility of the base, the higher the yield of the products (entries 1-3). This can be rationalized on the basis

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[26] A. E. Feiring. Reaction of Perfluoroalkyl Iodides with Electron Donor Nucleophiles. Addition of Perfluoroalkyl Iodides to Olefins Initiated by Electron Transfer. *J. Org. Chem.*, **1985**, *50*, 3269.

of a larger amount of deprotonated **6** available for engaging in EDA complex formation with perfluorohexyl iodide **1**. The use of a soluble organic base such as 1,1,3,3-tetramethylguanidine (TMG) resulted in a good yield of product, while the use of a weaker Brønsted-base such as 2,4,6-collidine, which is unable to deprotonate cyanoester **6,** completely prevented the reactivity (entries 4-5).

Table 2. Preliminary optimization studies[a]
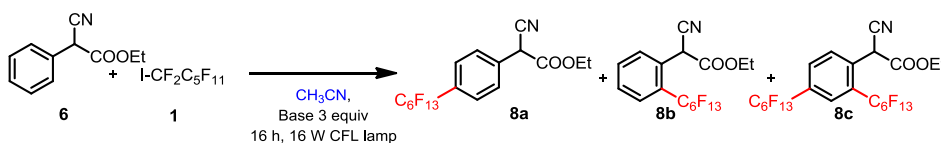
Entry	Base (equiv)	6:1	NMR Yield[b] 8a+8b+8c	Distribution[b] 8a:8b:18c
1	Na_2CO_3 (3)	1:1.5	20	57:30:8
2	K_2CO_3 (3)	1:1.5	40	60:31:4
3	Cs_2CO_3 (3)	1:1.5	75	60:33:7
4	TMG (3)	1:1.5	53	64:36:4
5	2,4,6-collidine (3)	1:1.5	0	-
6	Cs_2CO_3 (3)	1:1.1	48	64:32:3
7	Cs_2CO_3 (3)	1.5:1	43	66:32:2
8	-	1.5:1	0	-
9[c]	Cs_2CO_3 (3)	1.5:1	0	-

[a] Reactions performed on a 0.1 mmol scale using 250 μL of acetonitrile as solvent. [b] Yield determined by ^{1}H and ^{19}F NMR analysis of the crude reaction mixture after acidic work-up using 2-nitrofluorobenzene as internal standard. [c] Reaction performed in the dark. TMG = 1,1,3,3-tetramethylguanidine.

Additionally, the effect of varying the relative amount of reactants was investigated. The use of a lower amount of the perfluoroalkylating agent **1** afforded the products in low yield while reversing the stoichiometry between the two reaction partners did not provide any substantial difference (entries 6-7).

Further reaction optimization and scope evaluation is currently ongoing in our laboratories.

5.3   Mechanistic Considerations

5.3.1   Evidences for EDA Complex Formation

Our proposed mechanism (Scheme 3) involves EDA complexes as critical intermediates that play an explicit role in facilitating the observed photochemical reactivity. Accordingly, when the reaction was performed in the absence of a base, thus excluding the presence of the deprotonated nucleophile (the electron donor partner), we observed a complete lack of reactivity (Table 3, entry 8). Moreover, no reactivity was also found when the reaction was performed in the absence of light (Table 3, entry 9).

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The formation of an EDA complex was also studied by UV-Vis spectrophotometry (Figure 1). For these investigations, mixtures of the reaction partners were prepared and the absorption spectrum of each solution was recorded over the wavelength range of the visible and near UV regions of the electromagnetic spectrum (from 700 to 360 nm). The concentration was limited to 0.1 M to avoid saturation of the detector; the ratio between cyanoester **6** and perfluorohexyl iodide **1** was 1:1.5 while 1,1,3,3-tetramethylguanidine was used as the base in order to avoid a heterogeneous mixture. In the absorption spectra displayed below, a clear bathochromic shift within the visible region can be observed exclusively for the mixture of **6**, base and perfluorohexyl iodide. This new absorption band, not present in the spectra of the separate components, can be ascribed to the formation of an EDA complex between the deprotonated form of **6** and perfluorohexyl iodide as previously proposed. Analysis by NMR spectroscopy of the mixtures under study, did not show the formation of any new product; this confirmed that the new absorption band is not due to the formation of novel covalent bonds.
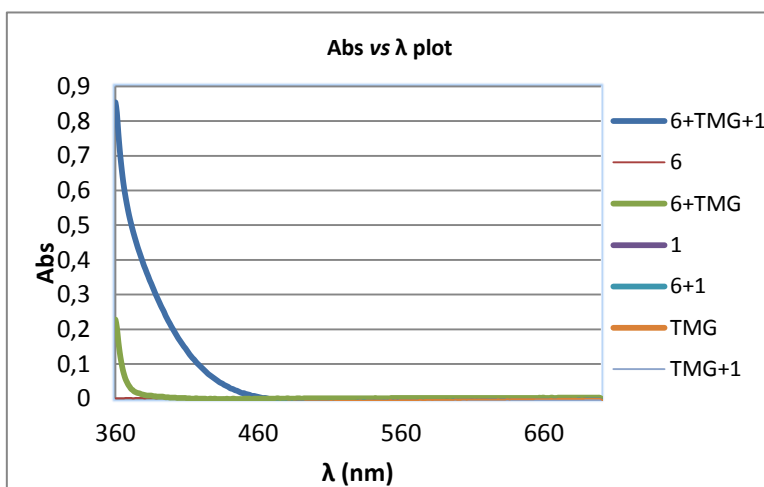

Figure 1. Plot obtained measuring solutions of reagents in acetonitrile on a Shimadzu UV-2401PC spectrophotometer equipped with a photomultiplier detector, double beam optics, and D2 and W light sources.

5.3.2 Homolytic Cleavage of the Perfluorohexyl Iodide as the Initiation Event

Commercially available compact fluorescent light (CFL) bulbs can have a residual emission in the UV region of the electromagnetic spectrum that could promote the homolytic cleavage of the perfluorohexyl iodide. To rule out the possibility of the homolytic cleavage to initiate the photochemical perfluoroalkylation reaction of arenes, the reaction was set-up in a dark and irradiated with LEDs 390 nm peak wavelength (Scheme 5).
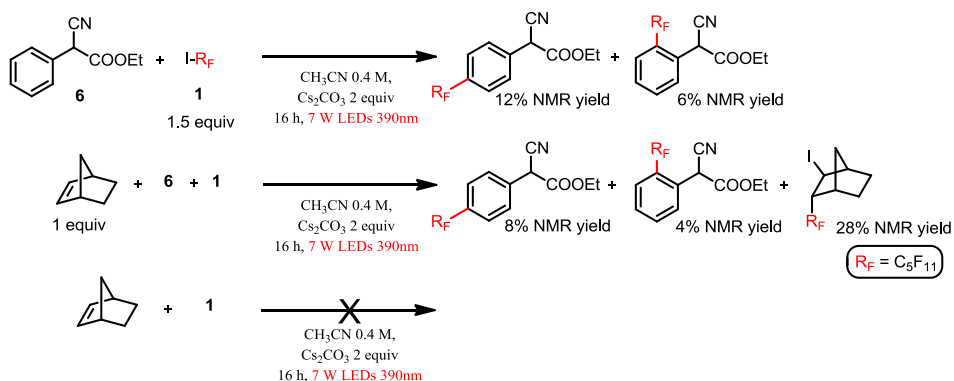
Scheme 5. Exploring the initiation step for the perfluoroalkylation of arenes.

Exclusive irradiation with low-energy light in a controlled environment (dark lab) excludes any possible contribution of higher-energy light sources. After 16 hours of irradiation, the products were generated in 18% yield (which is lower than the yield obtained under the optimized conditions due to a lower intensity light source) . Additionally, under the the the same conditions, the reaction was performed in the presence of norbornene, which is known to be an efficient substrate in the ATRA (atom transfer radical addition) reaction with perfluorohexyl iodide.[26] In this case, along with a 12% yield of the perfluoroalkylated products, 28% of the ATRA product was observed, testifying to the formation of free perfluoroalkyl radical intermediates. Finally, control experiments were performed by mixing norbornene and perfluorohexyl iodide and irradiating the reaction mixture with the same light source (390 nm). A complete absence of reactivity in these experiments support the intermediacy of an EDA complex in the reaction under study.

5.3.3   Light Induction Requirement

Experiments with successive intervals of irradiation and dark periods were performed to see if we could discriminate between $S_{RN}1$ (a radical chain process) and radical coupling mechanisms (a non-chain process).

Three identical reactions of cyanoester **6** with **1**, and in the presence of cesium carbonate were performed. The first reaction was stopped after 45 minutes of irradiation, and after acidic work-up the NMR yield of the three reaction products was determined by means of ^{1}H and ^{19}F NMR analysis (Figure 2, blue). The second reaction was, after 45 minutes of irradiation, left in the dark for a period of 250 minutes (Figure 2, red). After that time, ^{1}H and ^{19}F NMR analysis of the reaction mixture showed that the reaction did not progress any further in the absence of light. The third control reaction was irradiated for a total of 315 minutes giving higher conversion in the products (Figure 2, green). These results demonstrate that light is a necessary component of the reaction. Although they do not definitively rule out a radical chain mechanism, the results show that any chain propagation process must be short-lived.
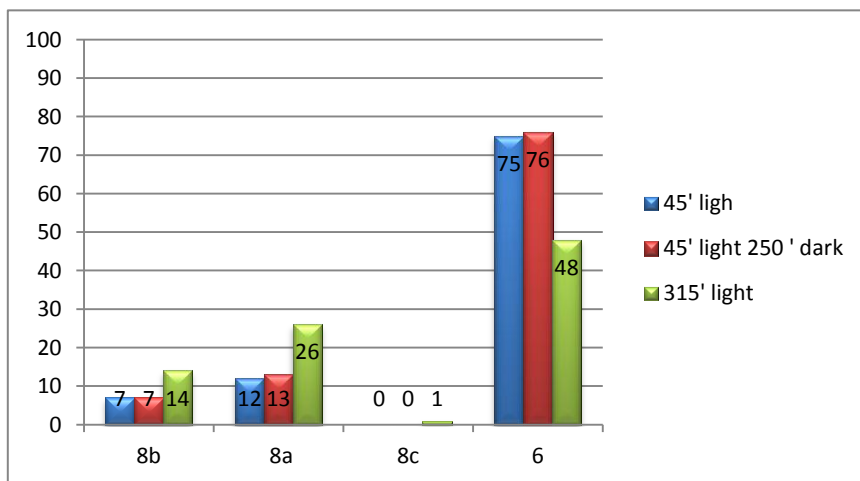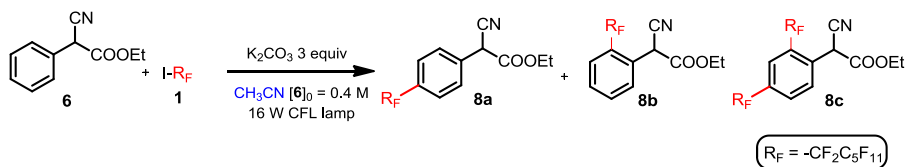
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Figure 2. Light ON-OFF experiment.

Additional studies aimed to further understand the reaction mechanism and explore potential applications of this photoinduced reaction are currently ongoing.

5.4   Conclusions

We have found that ethyl 2-cyano-2-phenylacetate **6** can direct photochemically promoted perfluoroalkylation toward aromatic substitution. The reaction is induced by the productive photo-excitation of an EDA complex between the benzylic carbanion as the electron donor and the perfluorohexyl iodide as the electron acceptor. The chemistry leads to valuable perfluoroalkylated arenes through an operationally simple procedure, requiring only a base and light as additives. Further investigation on the generality of the method and the mechanism are currently ongoing in our laboratories.

5.5   Experimental Section

5.5.1   General Informations

The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at 400 MHz or 500 MHz for ^{1}H and ^{19}F or at 100 MHz and 125 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents (CHCl$_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR).

Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. When necessary, ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Data for ^{19}F NMR are reported in terms of chemical shift and multiplicity. High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI). UV-Vis measurements were carried out on a Shimadzu UV-2401PC spectrophotometer equipped with a photomultiplier detector, double beam optics, and D2 and W light sources.

5.5.2   General Procedures

All reactions were performed under an argon atmosphere using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased and the reaction mixtures were deoxygenated by three cycles of freeze-pump-thaw. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF$_{254}$, 0.25 mm) were employed, using UV light as the visualizing agent and an acidic mixture of *para*-anisaldehyde or basic aqueous potassium permangante (KMnO$_4$) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

5.5.3   Materials

Commercial grade reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification.

5.5.4   General Procedure for the Light-Driven Perfluoroalkylation of Arenes

A 10 mL Schlenk tube was charged with ethyl 2-cyano-2-phenylacetate **6** (0.1 mmol), acetonitrile (0.4 M referring to **6**), the base (2 equiv), the perfluoroalkylating agent **1** (1.5 equiv). The reaction mixture was degassed *via* freeze pump thaw (x3), and the vessel refilled with argon. After the reaction mixture was thoroughly degassed, the tube was sealed and positioned approximately 5 cm away from the light source. A household full spectrum 23-W compact fluorescent light (CFL) bulb was used for irradiating the reaction mixture. After stirring for the indicated time, the crude mixture was diluted with dichloromethane (2 mL) and washed with 1 M aqueous HCl (2 x 5 mL), and dried over MgSO$_4$. Solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography to afford the title compounds **8a** and **8b** in the stated yield.

Ethyl 2-cyano-2-(4-(perfluorohexyl)phenyl)acetate 8a and ethyl 2-cyano-2-(2-(perfluorohexyl)phenyl)acetate 8b

The reaction was carried out following the general procedure to furnish the crude product as a 2:1 mixture of regioisomers. The two regioisomers were isolated by flash column chromatography (hexane/diethyl ether = 90/10)
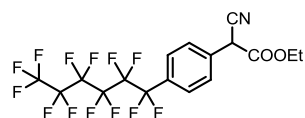
8a was isolated as a single regioisomer (R_f = 0.5 hexane/diethyl ether 1/1) in 47% yield (yellow oil). HRMS *calcd.* for ($C_{17}H_{10}F_{13}NO_2$+Na): 530.0396, found 530.0409.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.31 (t, 3H, J = 7.13 Hz), 4.29 (q, 2H, J = 7.13 Hz), 4.83 (s, 1H), 7.63-7.71 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.7, 40.1, 63.6, 110.2, 110.7, 111.2, 115.4, 115.5, 116.7 126.6, 129.3, 129.5, 130.0, 131.2, 133.1, 164.3ppm. ^{19}F NMR (376 MHz, CDCl$_3$) δ - 126.2 (m, 2F), - 122.9 (m, 2F), - 121.8 (m, 2F), -121.5 (m, 2F), - 111.1 (t, 2F, J = 14.24 Hz), - 80.9 (t, 3F, J = 10.30 Hz) ppm
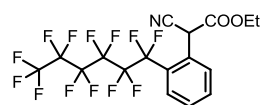
8b was isolated as a single regioisomer (R_f = 0.2 hexane/diethyl ether 1/1) in 26% yield (yellow oil). HRMS *calcd.* for ($C_{17}H_{10}F_{13}NO_2$+Na): 530.0396, found 530.0392.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.31 (t, 3H, J = 7.01 Hz), 4.24-4.36 (m, 2H), 5.13 (s, 1H), 7.57-7.63 (m, 1H,), 7.66-7.75 (m, 2H), 7.81 (d, 1H, J = 7.80 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8, 43.4, 63.7, 110.2, 110.7, 111.1, 114.80, 114.89, 115.5, 127.9, 128.2, 128.3, 128.5, 128.6, 133.9, 164.1 ppm. ^{19}F NMR (376 MHz, CDCl$_3$) δ - 126.1 (m, 2F), - 122.7 (m, 2F), - 121.5 (m, 2F), -120.8 (m, 2F), - 104.6 (t, 2F, J = 15.45 Hz), - 80.8 (t, 3F, J = 10.30 Hz) ppm