



UNIVERSITÀ DI PARMA

UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA IN

“Scienze del Farmaco, delle Biomolecole e dei Prodotti per la Salute”

CICLO XXXV

**New Trends in Organocatalysed and Photochemical
Vinylogous Transformations.
Access to Novel Bioactive Heterocyclic Chemotypes**

Coordinatore:

Prof. Marco Mor

Tutore:

Prof. Fanca Zanardi

Co-tutore:

Prof. Claudio Curti

Dottorando:

Enrico Marcantonio

Anni accademici 2019/2020 – 2021/2022

*“Nothing has such power to broaden
the mind as the ability to investigate
systematically and truly all that comes
under thy observation in life”*

*“Nihil enim perinde animum magnitudine
extollit, ac via et vere posse singula,
quæ in hac vita nobis occurrunt”*

*- Marcus Aurelius (121 – 180 AD)
Meditations, Book III, 11.*

Preface

The work here presented summarizes the results obtained during my Ph.D. studies, which were focused on the application of organocatalysis as a powerful means to unlock the vinylogous reactivity of different poly-dentate substrate donors, thereby allowing new chemical transformations. More than eighty years ago, Reynold Clayton Fuson, an American chemist, first enunciated the principle of vinylogy realizing that, in a system of conjugate double bonds, the electronic properties of a leading functional group can be propagated along the C(sp²)-chain toward remote positions. This concept has been extensively exploited throughout the past decades as an opportunity to fuel new chemical transformations toward increasing molecular complexity. In this scenario, my efforts have been devoted to shed new light onto this established chemistry, by applying vinylogous chemistry, merged with organocatalysis, within new challenging frontiers.

The first part of the Introduction is intended to introduce the reader for well-understanding the experimental work that I performed during my Ph.D., furnishing basic concepts of organocatalysis, photocatalysis, and vinylogous reactivity. The last part of the Introduction deepens two hot-topics of the vinylogous chemical realm on which I worked and that, from a personal perspective, represent charming fields that deserve to be further broadened in the future. Subsequently, Chapter II and Chapter III describe the development of two new protocols where the principle of vinylogy elegantly allows for the stereoselective generation of two new chiral and heterocyclic uracil- and imidazole-based chemotypes featuring *in-cycle* stereocenters. The chemistry involves a previously reported uracil-pronucleophile and an inedited imidazole-based pro-diene substrate to be employed in stereoselective and organocatalysed [4+2] cycloadditions with suitable dienophiles, to give rise to new classes of chiral tetrahydroquinazolindiones and dihydrobenzimidazoles, respectively. Importantly, several uracil-based congeners also revealed promising antiviral activity. Finally, the project described in Chapter IV discloses about the exploitation of the principle of vinylogy within the radical chemistry by using chiral dienamines as radical traps. In particular, a rare example of a photochemical-driven process is described, where the dual synergistic action of organocatalysis and dithiocarbamate catalysis allows for the stereoselective γ -functionalization of α -branched enals.

All the research activity described in this thesis is the result of a shared teamwork with many other talented and enthusiastic scientists, and that without their help, support and teaching would have never been realized. Foremost I would like to express my gratitude to my supervisor *Prof. Franca Zanardi* for allowing me to be part of her research group and for taking care of me during my Ph.D. studies. A special thank goes to *Prof. Claudio Curti*, my co-supervisor, for his mentorship as a precious source of scientific inspiration. I would also like to thank *Prof. Andrea Sartori* who helped me several times with suggestions about chemistry and more. It is important for me to also thank the other members of the group *Prof. Lucia Battistini*, *Margherita Restori*, and *Dr. Kelly Bugatti*. Thanks to *Debora Guazzetti* for being such a good coworker during her M. Sc. internship and the initial period of her Ph.D. The work presented in this thesis is also due to the motivation of several undergraduate students *Elisa*, *Nicola*, *Giulia*, *Roberto*, and *Luigi* who have worked by my side. I'm grateful to *Prof. Paolo Melchiorre* for giving me the opportunity to work in his laboratories for six months in the exciting environment of the ICIQ in Tarragona (Spain), and for introducing me to the beautiful world of the photocatalysis. I would like to thank all the members of the Melchiorre Group for having made me feel part of the group since the beginning both inside and outside the lab. A special thank goes to *Dr. Matteo Balletti* who has introduced me in that new "habitat" and with whom I had the opportunity to share the third project here discussed. Finally, the most important thanks go to my family, my parents and my brother, for always supporting me.

List of publications

Some of the results described in this Ph.D. thesis have been published, or are currently under revision:

- ~ Marcantonio, E.; Curti, C.; Battistini, L.; Sartori, A.; Cardinale, L.; Pelosi, G.; Zanardi, F. Direct, Asymmetric Synthesis of Carbocycle-Fused Uracils via [4+2] Cycloadditions: a Noncovalent Organocatalysis Approach. *Adv. Synth. Catal.* **2021**, 363, 2625-2633.
- ~ Balletti, M.; Marcantonio, E.; Melchiorre, P. Development of a new photochemical organocatalytic enantioselective radical γ -functionalization of α -branched enals. *Chem. Commun.* **2022**, 58, 6072-6075.
- ~ Curti, C.; Marcantonio, E.; Sartori, A.; Battistini, L.; Zanardi, F. Accessing Chiral Dihydro- and Tetrahydroquinazoline-2,4-diones via [4+2]-Cycloadditions: from Pioneering Studies to Asymmetric Organocatalyzed Synthesis. *Targets Heterocycl. Syst.* **2022**, 26, 509-532.
- ~ Marcantonio, E.; Zanardi, F.; Curti, C.; Lombardo, M. Application of the Energetic Span Model to Noncovalent Organocatalysis: Mechanistic Insights into the Stepwise (4+2) Cycloaddition toward Chiral Fused Uracil Derivatives. *Submitted for publication*.

Table of contents

Chapter I - Introduction

1.1 Asymmetric organocatalysis and its activation modes	1
1.1.1 Aminocatalysis.....	2
1.1.2 Hydrogen-bond donor catalysis and bifunctional organocatalysis	4
1.2 Photoredox catalysis and photochemistry of enamines	7
1.3 Excitation of dithiocarbamate organocatalytic intermediates	11
1.4 The principle of vinylogy applied to π -extended donor systems	14
1.4.1 The vinylogous HOMO-raising malononitrile activation strategy	15
1.5 Toward new frontiers in the vinylogous domain	19
1.5.1 Accessing novel 3D heterocyclic chemotypes by means of vinylogous organocatalytic [4+2] cycloadditions.....	19
1.5.2 Regio- and enantioselective γ -alkylation of organocatalytic vinylogous dienamine intermediates: from polar to light-mediated radical domain.....	28
1.6 General objectives and summary	35
1.6.1 Organocatalytic stereoselective [4+2] cycloadditions toward chiral uracil-based carbocycles revealing antiviral bioactivity	35
1.6.2 Accessing enantiopure 6,7-dihydrobenzimidazoles via organocatalytic [4+2] cycloaddition reactions	36
1.6.3 Photochemical organocatalytic enantioselective radical γ -functionalization of α -branched enals.....	37

Chapter II - Organocatalytic stereoselective [4+2] cycloadditions toward chiral uracil-based carbocycles revealing antiviral bioactivity

2.1 Background	39
2.2 Target of the project.....	44
2.3 Results and discussion	45
2.3.1 Proof of concept and reaction optimization	45
2.3.2 Scope of the reaction, enhancement of enantioenrichment by recrystallization and synthetic elaborations.....	51
2.3.3 DFT-supported mechanistic insights	55
2.3.4 Anti-SARS-CoV-2 inhibitory profile of chiral fused-uracils	61
2.4 Conclusion	65
2.5 Experimental Section	66
2.5.1 General information	66
2.5.2 Catalysts and substrates synthesis.....	68
2.5.3 Experimental procedures and characterizations of products.....	73
2.5.4 Scaled-up model reaction.....	86
2.5.5 Enhancement of enantioenrichment by recrystallization	87

2.5.6 Synthetic elaboration of cycloadducts of type 11	89
2.5.7 Determination of the absolute configuration of the products	92

Chapter III - Accessing enantiopure 6,7-dihydrobenzimidazoles via organocatalytic [4+2] cycloaddition reactions

3.1 Background	97
3.2 Target of the project	102
3.3 Results and discussion	103
3.3.1 Proof of concept, reaction optimization and control experiments	103
3.3.2 Scope of the reaction and synthetic elaborations	107
3.3.3 Proposed catalytic cycle	111
3.4 Conclusion	112
3.5 Experimental section	113
3.5.1 General information	113
3.5.2 Catalysts and substrates synthesis	114
3.5.3 Experimental procedures and characterization of products	118
3.5.4 Scaled-up model reaction	133
3.5.5 Synthetic elaborations of product 13aa	133
3.5.6 Telescoped/one-pot reactions	136
3.5.7 Determination of the regiochemistry for compounds 13aa and 18	138
3.5.8 Determination of the absolute configuration of the products	141

Chapter IV - Photochemical enantioselective radical γ -functionalization of enals by means of dienamine organocatalysis

4.1 Background	143
4.2 Target of the project	148
4.3 Results and discussion	149
4.3.1 Proof of concept and reaction optimization	149
4.3.2 Scope of the reaction and synthetic elaborations	152
4.3.3 Mechanism proposal and stereochemical considerations	155
4.4 Conclusion	157
4.5 Experimental section	158
4.5.1 General information	158
4.5.2 Experimental set-up	158
4.5.3 Catalysts and substrates synthesis	160
4.5.4 Experimental procedures and characterizations of products	167
4.5.5 Scaled-up model reaction	181
4.5.6 Synthetic elaborations of product 7aa	182
4.5.7 Chromatograms of compounds 13 for the determination of the absolute configuration of products	186

4.5.8 Quantum Yield Measurement	187
---------------------------------------	-----

Chapter V - General Conclusions

General Conclusion – Acknowledgments - Author profile	191
---	-----

Chapter I

Introduction

The work developed in this research thesis merges the principle of vinylogy with the tools offered by asymmetric organocatalysis. Such a combination has led to the stereoselective generation of two novel and chiral, potentially bioactive heterocyclic chemotypes and, moreover, it allowed the disclosure of a remote and enantioselective photochemical radical functionalization of enals. This Chapter serves as a guide for the reader to touch the main topics exploited during my Ph.D. studies, starting from some basic concepts of organocatalysis, passing through their application to photochemical radical pathways, and landing on the realm of vinylogous activation strategies and transformations.

1.1 Asymmetric organocatalysis and its activation modes

The development of new catalytic and asymmetric transformations is of fundamental relevance to face unsolved challenges in organic chemistry. A relevant application of asymmetric catalysis deals with the exploitation of small chiral organic molecules as catalysts. This well-established approach takes the name of *asymmetric organocatalysis*.¹ Although organocatalysis had been exploited for a long time, its synthetic potential was recognized by the chemistry community since the year 2000, starting from two seminal works published by MacMillan and List, Lerner and Barbas III. Nowadays, it is widely accepted that organocatalysis represents one of the most important branches of stereoselective catalytic synthesis along with the previous, already well established, enzymatic and transition metal catalyses. This concept has recently culminated with the Nobel Prize in 2021 to MacMillan and List for their development of organocatalysis as a precise new tool for molecular construction.²

Although several benefits of organocatalysis can be found if compared to other catalytic approaches, the success of this field is undoubtedly directed to the possibility of designing and engineering new enantioselective transformations in a reasonably straightforward way, through the application of *generic modes of activation*.³ Most of the commonly used chiral organocatalysts can indeed interact with basic functional groups to give rise to reactive intermediates in an organized and predictable fashion, useful for promoting many different transformations with high enantioselectivity. Organocatalytic activation modalities can be classified into covalent and non-covalent activation modes.⁴ Reactive intermediates derived from covalent catalytic activations rely on strong and directional interactions, given by the generation of new effective covalent bonds. Covalent activation modes, therefore, represent reliable tools for the development of highly enantioselective transformations. On the other hand, non-covalent catalytic approaches, such as hydrogen-bond

¹ a) Qin, Y.; Zhu, L.; Luo, S. "Organocatalysis in Inert C-H Bond Functionalization" *Chem. Rev.* **2017**, *117*, 9433; b) Albrecht, L.; Albrecht, A.; Dell'Amico, L. (Eds.) "Asymmetric Organocatalysis: New Strategies, Catalysts, and Opportunities" Wiley VHC, Weinheim, **2022**.

² { HYPERLINK "<https://www.nobelprize.org/prizes/chemistry/2021/summary/>" }, access Nov. 18th, 2022.

³ a) Ríos Torres, R. (Ed.) "Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes" Wiley, Hoboken, New Jersey, **2013**; b) MacMillan, D. W. C. "The advent and development of organocatalysis" *Nature*, **2008**, *455*, 304.

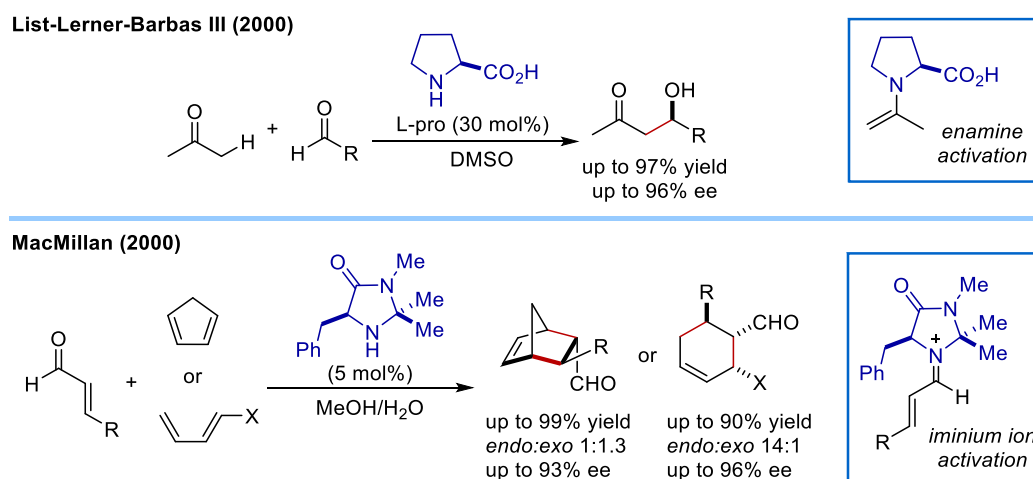
⁴ Berkessel, A.; Gröger, H. (Eds.) "Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis" Wiley VCH, Weinheim, **2005**.

catalysis, involve weaker and less directional interactions. Nevertheless, a robust net of hydrogen-bonds can orchestrate the accommodation of the reacting partners in a well-organized transition state, thus assuring stereoselectivity to the process.

The following sections aim to present the basic organocatalytic tools exploited during my Ph.D. research.

1.1.1 Aminocatalysis

The catalytic generation of enamines and iminium ions, as transient covalent intermediates, through the condensation of chiral amines with carbonyl compounds, is defined *aminocatalysis*. Although the potential of enamines and iminium ions was already established,⁵ the renaissance of aminocatalysis dates back to 2000. In that year List, Lerner and Barbas III and MacMillan independently reported two breakthrough examples of aminocatalytic enantioselective functionalization of carbonyl compounds, exploiting an enamine-mediated aldol reaction⁶ and an iminium ion-mediated Diels-Alder cycloaddition⁷, respectively (Scheme 1). Since then, the research community developed a myriad of aminocatalysed new transformations, starting to consider the covalent activation of carbonyl compounds as a reliable tool for the generation of new carbon-carbon bonds and stereocenters at their α - and β -positions.⁸



Scheme 1 Pioneering examples of modern aminocatalysis

In enamine catalysis, the chiral aminocatalyst condenses with carbonyl compounds affording iminium ions with highly acidic α -protons. The subsequent α -deprotonation generates enamines, which result in increased HOMO-orbital energies compared to the starting substrates and, thus, higher nucleophilicity. Such species can now enantioselectively react with different electrophiles affording α -functionalized carbonyl compounds upon regeneration of the aminocatalyst. In iminium ion

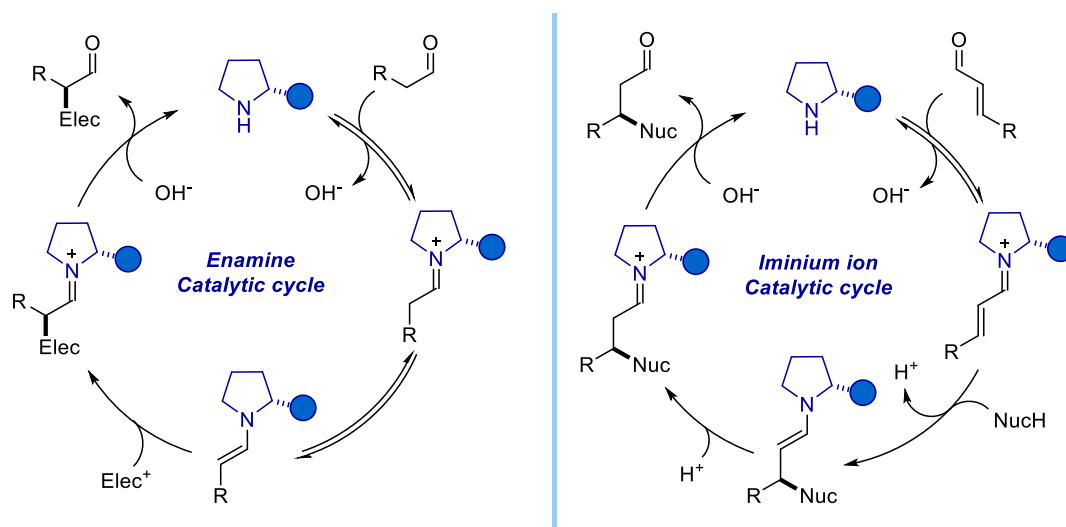
⁵ For seminal application of asymmetric aminocatalysis see: a) Hajos, Z. G.; Parrish, D. R. "Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry" *J. Org. Chem.* **1974**, 39, 1615. b) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkowicz, J.; Terrell, R. "The Enamine Alkylation and Acylation of Carbonyl Compounds" *J. Am. Chem. Soc.* **1963**, 85, 207. c) Baum, J. S.; Viehe, H. G. "Synthesis and Cycloaddition Reactions of Acetylenic Iminium Compounds" *J. Org. Chem.* **1976**, 41, 183.

⁶ List, B.; Lerner, R. A.; Barbas III, C. F. "Proline-Catalyzed Direct Asymmetric Aldol Reactions" *J. Am. Chem. Soc.* **2000**, 122, 2395.

⁷ Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. "New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction" *J. Am. Chem. Soc.* **2000**, 122, 4243.

⁸ a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. "Asymmetric Enamine Catalysis" *Chem. Rev.* **2007**, 107, 5471; b) Erkkilä, A.; Majander, I.; Pihko, P. M. "Iminium Catalysis" *Chem. Rev.* **2007**, 107, 5416.

catalysis, the condensation of the catalyst with α,β -unsaturated carbonyl compounds affords iminium ions featuring a reduced LUMO energy and improved electrophilicity if compared to the starting aldehydes or ketones. Such intermediates allow enantioselective β -functionalizations of carbonyl compounds with suitable nucleophilic species (Scheme 2).



Scheme 2 Enamine and iminium ion catalytic cycles. Elec⁺ = electrophile; NucH = nucleophile

The high enantioselectivity observed in aminocatalytic transformations is attributable to the well-defined geometry of the covalently bound catalyst-substrate intermediates.⁹ In the case of nucleophilic enamine intermediates, the catalyst scaffold generates a stereo-electronic bias leading the attack of the electrophile mainly toward one of the prochiral faces of the enamine intermediate. Such discrimination is usually induced by either hydrogen-bonding or steric interactions. On the other side, the approach of the nucleophile to iminium ion intermediates is usually guided by steric effects (Figure 1). Within sterically-driven aminocatalytic processes, the most general and reliable aminocatalysts are undoubtedly the Jørgensen/Hayashi-type diaryl prolinol silyl ethers¹⁰ and the MacMillan-type imidazolidinones.^{7,11} The reliability of these catalysts in promoting enantioselective aminocatalytic transformations relies on the well-established feature of the intermediates generated upon condensation with such organocatalysts. The α -substituent of the chiral amine provides the steric bias responsible for the reliable enantioselectivity, as a consequence of the predictable facial discrimination of the transient intermediate in aminocatalytic transformations.¹²

⁹ Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. "Asymmetric Aminocatalysis – Gold Rush in Organic Chemistry" *Angew. Chem. Int. Ed.* **2008**, 47, 6138.

¹⁰ a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. "Enantioselective Organocatalyzed α Sulfonylation of Aldehydes" *Angew. Chem. Int. Ed.* **2005**, 44, 794; b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. "Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes" *Angew. Chem. Int. Ed.* **2005**, 44, 4212; c) Jensen, K.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. "The Diarylprolinol Silyl Ether System: A General Organocatalyst" *Acc. Chem. Res.* **2012**, 45, 248.

¹¹ Lelais, G.; MacMillan, D. W. "Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation" *Aldrichim. Acta* **2006**, 39, 79.

¹² a) Seebach, D.; Grošelj, U.; Badine, M.; Schweizer, W. B.; Beck, A. K. "Isolation and X-Ray Structure of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones" *Helv. Chim. Acta* **2008**, 91, 1999; b) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. "Distinct Conformational Preferences of Prolinol and Prolinol Ether Enamines in Solution Revealed by NMR" *Chem. Sci.* **2011**, 2, 1793; c) Peelen, T. J.; Chi, Y.; Gellman, S. H. "Enantioselective Organocatalytic Michael Additions of Aldehydes to Enones with Imidazolidinones: Cocatalyst Effects and Evidence for an Enamine Intermediate" *J. Am. Chem. Soc.* **2005**, 127, 11598.

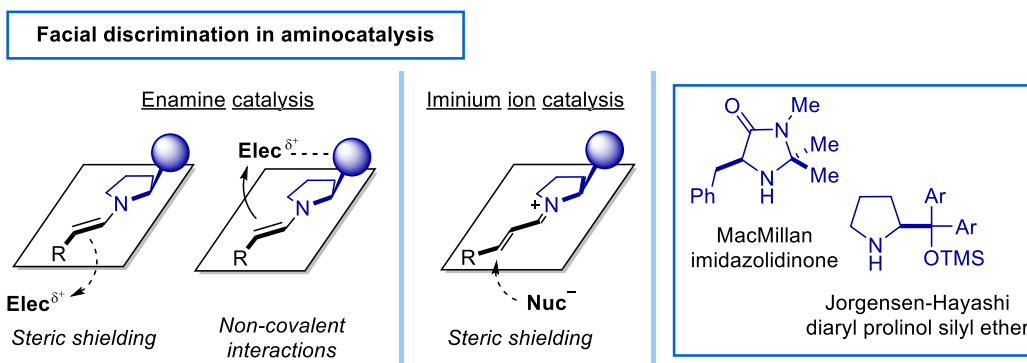
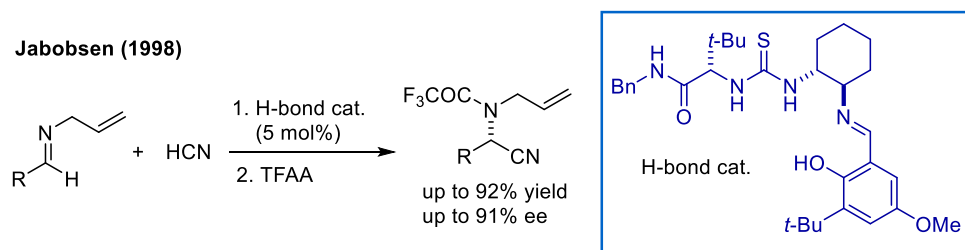


Figure 1 General facial discrimination in enamine- and iminium ion-activations by secondary amine organocatalysts and structures of MacMillan imidazolidinone and Jørgensen-Hayashi diaryl prolinol silyl ether

1.1.2 Hydrogen-bond donor catalysis and bifunctional organocatalysis

One important subfield of asymmetric organocatalysis is the *hydrogen-bond (H-bond) donor catalysis* where a LUMO-lowering activation of the electrophile takes place through the simultaneous sharing of a hydrogen atom between the substrate (H-bond acceptor) and the catalyst (H-bond donor). The flourishing of this field may be attributable to the urea-catalysed enantioselective Strecker reaction discovered by Jacobsen in 1998 (Scheme 3).¹³ The synthetic community realized that catalysis involving multiple, spatially organized, H-bond interactions provided a wide array of privileged scaffolds for catalyst design.¹⁴



Scheme 3 Thiourea-catalysed asymmetric Strecker reaction developed by Jacobsen

Within the H-bond donor catalysis, the Brønsted acidity of the organocatalyst plays a crucial role. *General acid catalysis* and *specific acid catalysis* represent two limit situations.¹⁵ The former relies on weak acidic conditions which allow the transfer of the proton to take place during the slow step of the reaction. In contrast, in the case of specific acid catalysis, the proton is fully transferred before the rate-determining step. These two limit situations are related to two different issues. Weak acidic catalysts produce a lower activation of the ground state, whereas reactions promoted by specific acid catalysis proceed through the formation of ion-pair intermediates, rendering the control of the geometry of the complex not fully granted. Nevertheless, in the last two decades, many H-donor organocatalysts belonging to both classes proved to be successful in triggering high enantioselective transformations, thus demonstrating their versatility and utility. Some of the archetypal H-bonding

¹³ Sigman, M. S.; Jacobsen, E. N. "Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries" *J. Am. Chem. Soc.* **1998**, *120*, 4901.

¹⁴ Doyle, A. G.; Jacobsen, E. N. "Small-Molecule H-Bond Donors in Asymmetric Catalysis" *Chem. Rev.* **2007**, *107*, 5713.

¹⁵ Muller, P. "Glossary of terms used in physical organic chemistry (IUPAC Recommendations 1994) *Pure and Applied Chemistry*, **1994**, *66*, 5, 1077.

organocatalysts, organized according to their Brønsted acidity, and their typical activation modes for developing asymmetric transformations are reported in Figure 2.^{13,16-22}

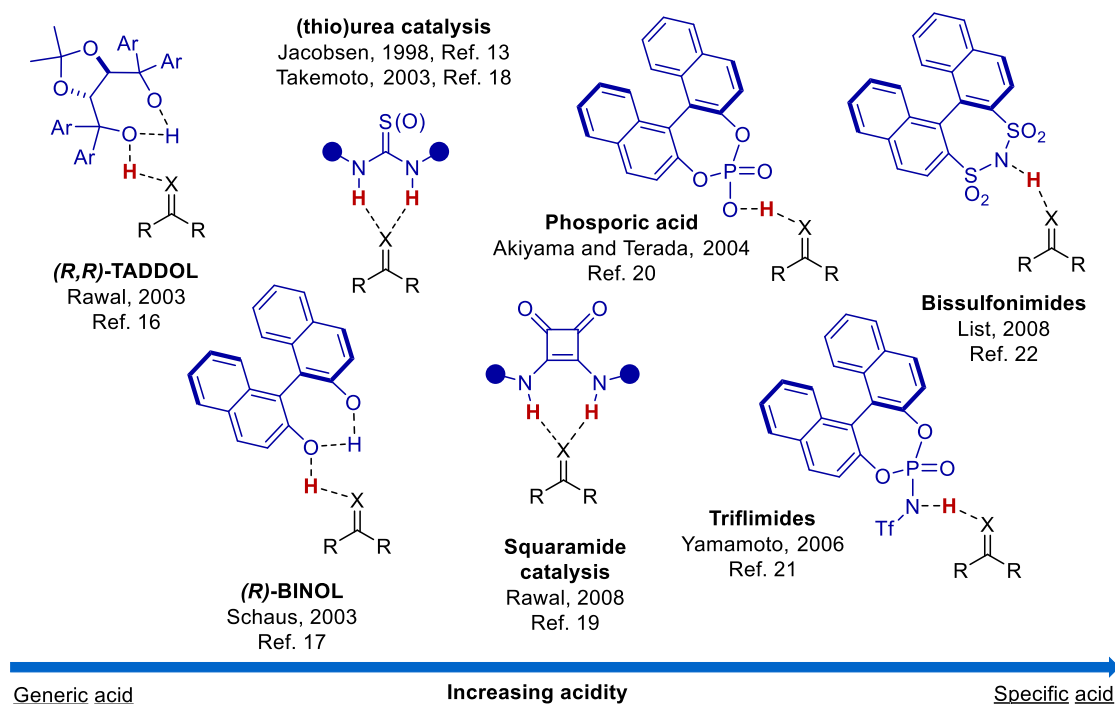


Figure 2 General activation modes and Brønsted acidic character of representative H-bonding organocatalysts

When a Lewis base functional group is incorporated into the H-bond donor catalyst, a *bifunctional organocatalyst* is realized.²³ The first example dates to 2003, when Takemoto successfully designed a bifunctional amine-thiourea catalyst able to activate both nucleophilic and electrophilic components within the development of a Michael addition of malonates to nitroolefins.¹⁸ The activation mode of this class of organocatalysts relies on the deprotonation of the pronucleophiles by a tertiary amine, while the H-bond donor moiety can engage weak interactions with electrophiles to create a well-defined chiral environment in the transition state, essential for achieving enantioselectivity (Scheme 4).

¹⁶ Huang, Y.; Unni, A. K.; Thadani A. N.; Rawal V. H. "Single enantiomers from a chiral-alcohol catalyst" *Nature*, **2003**, 424, 146.

¹⁷ McDougal, T. N.; Schaus, S. E. "Asymmetric Morita–Baylis–Hillman Reactions Catalyzed by Chiral Brønsted Acids" *J. Am. Chem. Soc.* **2003**, 125, 40, 12094.

¹⁸ Okino, T.; Hoashi, T.; Takemoto, Y. "Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts" *J. Am. Chem. Soc.* **2003**, 125, 42, 12672.

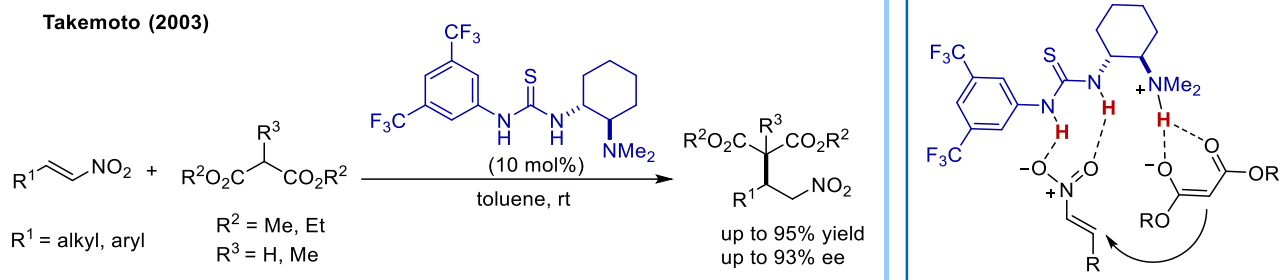
¹⁹ Malerich, J. P.; Hagihara, K.; Rawal V. K. "Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts" *J. Am. Chem. Soc.* **2008**, 130, 44, 14416.

²⁰ a) Uruguchi, D.; Terada, M. "Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation" *J. Am. Chem. Soc.*, **2004**, 126, 5356; b) Itoh, J.; Yokota, K.; Fuchibe, K.; Akiyama, T. "Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid" *Angew. Chem. Int. Ed.* **2004**, 43, 1566.

²¹ Boxer, M. B.; Yamamoto, H. "Triflimide (HNTf₂)-catalyzed aldehyde cross-aldol reaction using "super silyl" enol ethers" *Nature Protocols* **2006**, 1, 2434.

²² Cheng, X.; Vellalath, S.; Goddard, R.; List B. "Direct Catalytic Asymmetric Synthesis of Cyclic Aminals from Aldehydes" *J. Am. Chem. Soc.* **2008**, 130, 47, 15786.

²³ a) Palomo, C.; Oiarbide, M.; López, R. "Asymmetric organocatalysis by chiral Brønsted bases: implications and applications" *Chem. Soc. Rev.* **2009**, 38, 632; b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, 17, 6890; c) Siau, W.; Wang, J. "Asymmetric organocatalytic reactions by bifunctional amine-thioureas" *Catal. Sci. Technol.*, **2011**, 1, 1298; d) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. "Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions" *Adv. Synth. Catal.* **2015**, 357, 253.



Scheme 4 Bifunctional thiourea/amine-catalysed asymmetric Michael addition of malonates to nitroolefins developed by Takemoto

Others important examples of bifunctional organocatalysts contain thiourea or squaramide and *Cinchona* alkaloid frameworks. Their widespread use is due to the versatility of the tertiary amine base present in the alkaloid quinuclidine ring.²⁴

In all the three projects discussed in this thesis, the stereoselectivity observed for the reported transformations was invariably given by the chiral organocatalysts employed. In Chapter II, the exploitation of a bifunctional H-bonding organocatalytic approach is presented, while covalent aminocatalysis is responsible for imparting enantioselectivity in both Chapter III and Chapter IV, through iminium ion and enamine activation modalities, respectively.

²⁴ a) Marcelli, T.; Hiemstra, H. "Cinchona Alkaloids in Asymmetric Organocatalysis" *Synthesis* **2010**, 8, 1229; b) Connon, S. J. "Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts" *Chem. Commun.*, **2008**, 2499.

1.2 Photoredox catalysis and photochemistry of enamines

Catalysed enantioselective radical reactions have been characterized by tremendous growth during the last decade.²⁵ This is mainly due to the incessant advance of novel light-mediated strategies for the generation of radicals under mild reaction conditions.²⁶ The most prevalent approach is *photoredox catalysis*²⁷ in which a transition metal complex²⁸ or an organic dye²⁹ (*photocatalyst*, PC) absorbs a photon with suitable energy to reach its excited state (PC*). This event promotes an electronic transition from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) (Figure 3, a), thus enforcing a new electronic configuration of the molecules and changing their photophysical properties. Although the excess of energy possessed by the PC* could be dissipated in different ways, the most exploited mode for the generation of radicals is the *photoinduced-electron transfer* (PET). In the excited state, removing or adding one electron from the half-filled electronic configuration becomes indeed more favourable. This is the reason why the excitation of the photocatalyst improves its redox properties, making it both a better oxidant and reductant than in its ground state (Figure 3, b).³⁰

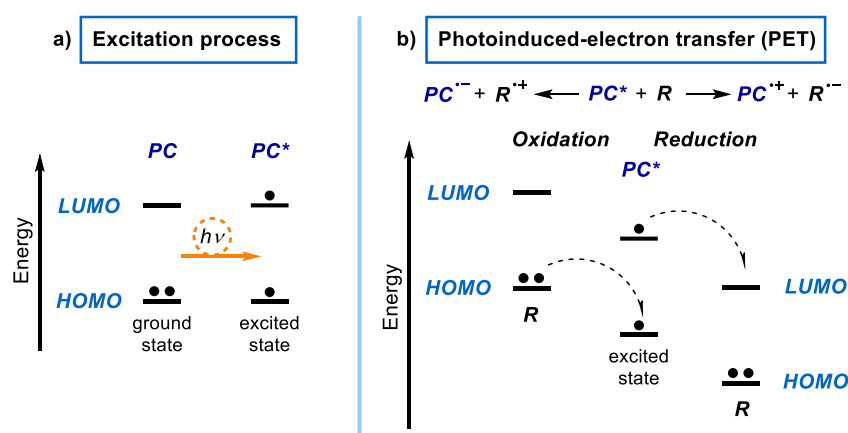


Figure 3 a) electronic configuration of a photocatalyst (PC) in its ground and excited state; b) PET from/to the excited state PC* to/from a reagent **R** is favourable

This feature may be exploited to generate radical species through *single electron transfer* (SET) events that can involve oxidative quenching cycles or reductive quenching cycles depending on the redox properties of the reaction partners (Scheme 5). Both redox events trigger the mild generation of radicals or radical ions under visible light. These unstable species will trigger the target reaction,

²⁵ Studer, A.; Curran, D. P. "Catalysis of Radical Reactions: A Radical Chemistry Perspective" *Angew. Chem. Int. Ed.* **2016**, 55, 58.

²⁶ Buzzetti, L.; Crienza, G. E. M.; Melchiorre, P. "Mechanistic Studies in Photocatalysis" *Angew. Chem. Int. Ed.* **2019**, 58, 3730.

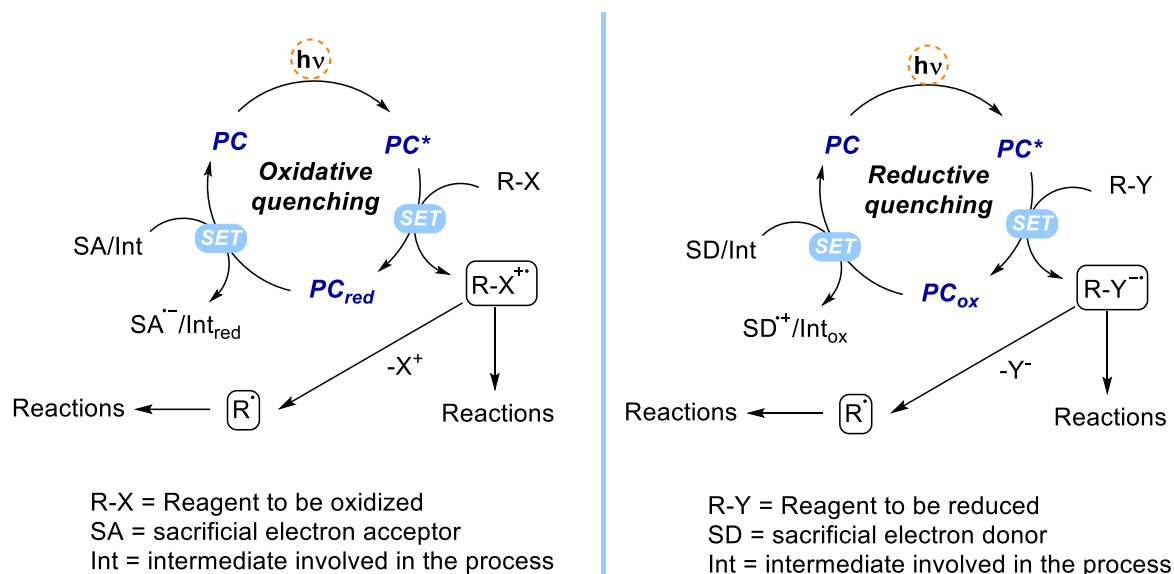
²⁷ a) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. "Photoredox Catalysis in Organic Chemistry" *J. Org. Chem.* **2016**, 81, 6898; b) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. "Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development" *ACS Catal.* **2017**, 7, 2563.

²⁸ a) Prier, C. K.; Rankic, A. D.; MacMillan, D. W. C. "Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis" *Chem. Rev.* **2013**, 113, 5322; b) Larsen, C. B.; Wegner, O. S. "Photoredox Catalysis with Metal Complexes Made from Earth-Abundant Elements" *Chem. Eur. J.* **2017**, 24, 2039.

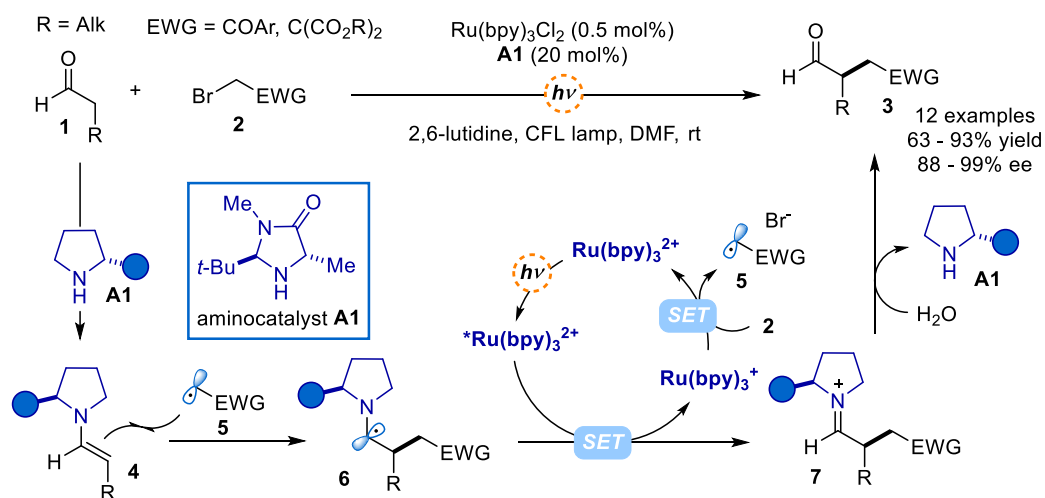
²⁹ Nicewicz, D. A.; Nguyen, T. M. "Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis" *ACS Catal.* **2014**, 4, 355.

³⁰ a) Balzani, V.; Ceroni, P.; Juris, A. (Eds.) "Photochemistry and Photophysics: Concepts, Research, Applications. Photochemistry and Photophysics. Concepts, Research, Applications" Wiley-VCH, Weinheim, **2014**; b) Balzani, V.; Giacomini, G.; Ceroni, P. "Light: A Very Peculiar Reactant and Product" *Angew. Chem. Int. Ed.* **2015**, 54, 11320.

while sacrificial agents or intermediates typically close the catalytic cycle through another SET event, regenerating the photocatalyst.³¹



The pioneering work of modern photoredox catalysis was developed by MacMillan in 2008, who employed the photoexcitation of a Ru(II) complex catalyst to promote an organocatalysed and enantioselective radical α -alkylation of aldehydes with electron-poor alkyl halides (Scheme 6).³²



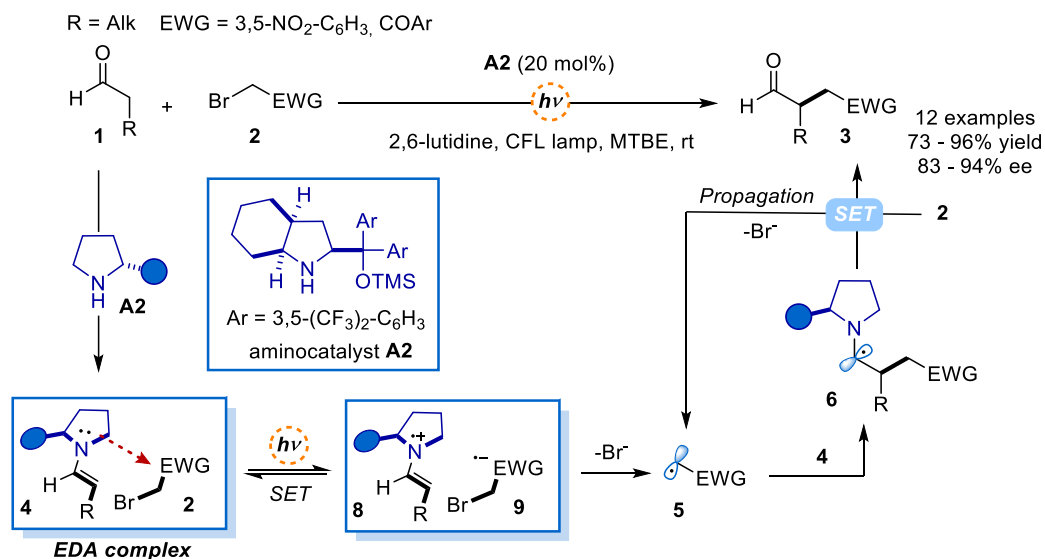
In detail, electron-poor radicals **5** can be afforded through SET between the excited Ru-based photocatalyst and alkyl bromides **2**. These intermediates can be then enantioselectively trapped by the organocatalytic enamine **4**, which is derived from the condensation between the aldehyde **1** and the aminocatalyst **A1**. The ensuing α -amino radical **6**, upon SET oxidation by the photo-excited Ru(II)

³¹ Ravelli, D.; Protti, S.; Fagnoni M. "Carbon–Carbon Bond Forming Reactions via Photogenerated Intermediates" *Chem. Rev.* **2016**, *116*, 9850.

³² Nicewicz, D. A., MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: the Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**, *322*, 77.

complex, generates the iminium ion **7** which is then hydrolysed to regenerate the aminocatalyst **A1** while delivering the enantioenriched final aldehyde **3**.

The crucial importance of this breakthrough discovery by MacMillan and co-workers resides on several reasons. Indeed, for the first time, an example of catalytic generation of radicals under mild conditions was rationalized and shared with the entire organic synthesis community, later becoming an inspiration for the next generation of chemists willing to explore the potential of the photoredox catalysis as a general tool for achieving previously unimaginable disconnections.³³ On the other side, this work demonstrated the possibility of merging radical chemistry with more classic organocatalysis activation modes, achieving high enantioselectivity as well. However, the generation of radicals is not restricted to the use of an external photocatalyst. It was demonstrated, indeed, that the excitation of organocatalytic intermediates (i.e. enamines and iminium ions) could serve directly as radical-generating platforms.³⁴ Two fundamental examples regarding the photochemistry of enamine intermediates, useful for the well-understanding of the third project that I will describe within this thesis, come from the group of Melchiorre. In 2013, this group found that when an electron-deficient benzylic bromide **2** was mixed with a chiral enamine of type **4**, the colourless mixture of the reaction turned to bright yellow.³⁵ This observation was rationalized by the generation of an *electron donor-acceptor (EDA) complex*,³⁶ which is generated upon orbitals sharing between a donor species (the enamine) and an acceptor species (the halide), thus featuring new molecular orbitals and, as consequence, new photochemical properties (Scheme 7).



Scheme 7 Photochemical activity of EDA complex for the enantioselective α -alkylation of aldehydes. The recycle of the organocatalyst **A2** is omitted for clarity.

³³ a) Pitre, S. P.; Overman, L. E. "Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis" *Chem. Rev.* **2022**, 122, 1717. b) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. "Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis?" *Angew. Chem. Int. Ed.* **2018**, 57, 10034.

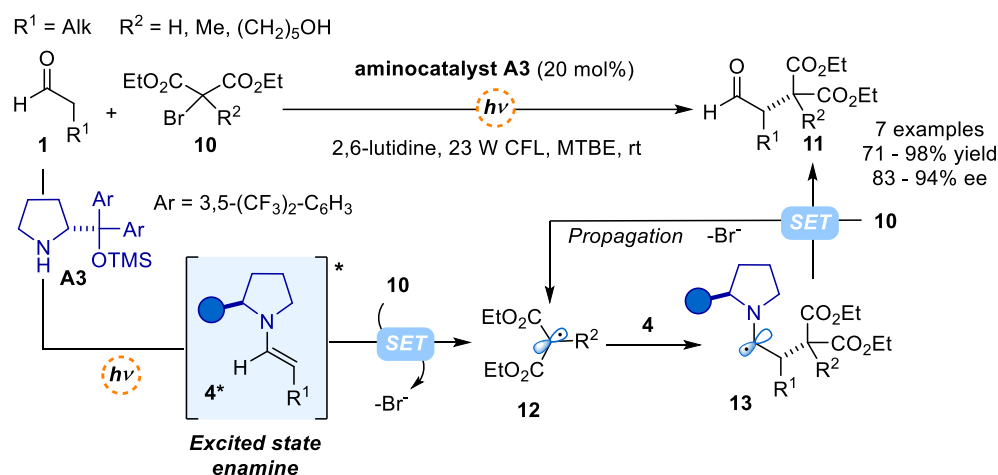
³⁴ Silvi, M.; Melchiorre, P. "Enhancing the potential of enantioselective organocatalysis with light" *Nature* **2018**, 554, 41.

³⁵ Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. "Photochemical Activity of a Key Donor–Acceptor Complex Can Drive Stereoselective Catalytic α -alkylation of Aldehydes." *Nature Chem.* **2013**, 5, 750.

³⁶ a) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P., Synthetic Methods Driven by the Photoactivity of Electron Donor–Acceptor Complexes. *J. Am. Chem. Soc.* **2020**, 142, 5461; b) Lima, C. G. S.; Lima, T. M.; Duarte, M.; Jurberg, I. D.; Paixao, M. W. "Organic Synthesis Enabled by Light-Irradiation of EDA Complexes: Theoretical Background and Synthetic Applications" *ACS Catal.* **2016**, 6, 1389.

The most relevant peculiarity related to this complex is a different transfer band at a longer wavelength of absorption, which makes the selective excitation of such complexes possible using visible light. The subsequent SET event leads to the generation of the radical anion **9**, which then evolves into the radical **5**. Another molecule of the organocatalytic enamine **4** can stereoselectively trap such radical, to finally evolve to the final product **3** in good efficiency and with high level of enantiocontrol.

Organocatalytic intermediates, besides offering the possibility to be exploited as chiral radical traps, could also be directly involved in the radical generation, providing a strategy to develop enantioselective radical transformations without any external photocatalyst. However, the formation of an EDA complex is strictly dependent on the properties of the two reacting partners. Indeed, the employment of radical precursors different from **2** did not allow the required association. Nevertheless, the same group in 2015 discovered that enamines **4** can be directly excited using 390 nm light (Scheme 8).³⁷ In its excited state, enamine is a strong reductant (estimated $E_p^{\text{red}}(\mathbf{4}^{\cdot-}/\mathbf{4}^*) \sim -2.50$ V versus Ag/AgCl, NaCl_{sat.}) and could therefore promote the generation of radical **12** upon reductive cleavage of bromomalonates **10**, which instead are not suitable compounds to generate EDA complexes. The chiral environment given by the prolinol-based organocatalyst **A3** allows for the generation of the new C-C bond of products **11** with high levels of enantioselectivities (Scheme 8).



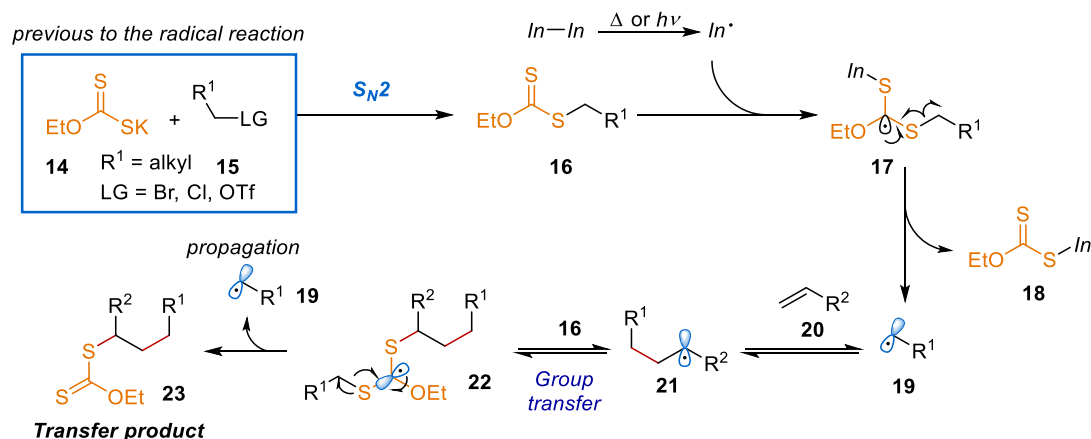
Scheme 8 Direct photoexcitation of enamines enables the enantioselective alkylation of aldehydes. The recycle of the organocatalyst **A2** is omitted for clarity.

Overall, both the EDA complex excitation and the direct excitation of organocatalytic enamines represent two powerful manifolds for the mild generation of radicals using light, offering an intriguing and sound opportunity to allow chemical connections otherwise unattained in the context of traditional polar chemistry.

³⁷ a) Silvi, M.; Arceo, A.; Jurberg, I. D.; Cassani, C.; Melchiorre, P. "Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines" *J. Am. Chem. Soc.* **2015**, *137*, 6120; b) Filippini, G.; Silvi, M.; Melchiorre, P. "Enantioselective Formal α -Methylation and α -Benzylation of Aldehydes by Means of Photo-organocatalysis" *Angew. Chem. Int. Ed.* **2017**, *56*, 4447.

1.3 Excitation of dithiocarbamate organocatalytic intermediates

Photoredox transformations unlocked the possibility to apply typical radical-generating strategies under catalytic conditions. This is also the case of *xanthate* or *dithiocarbonyl (DTC) chemistry*, which represents one of the cleverest examples of how light excitation broadened the strategies available for generations of radicals to be employed in catalytic transformations. Xanthates were exploited as radical precursors firstly by Zard, even though in stoichiometric amounts (Scheme 9).³⁸



Scheme 9 Degenerative xanthate transfer processes: typical mechanism involved

Dithiocarbonyl compounds of type **16** can be easily prepared through a nucleophilic substitution reaction (S_N2) from the corresponding sulphur-based salt **14** and simple alkyl halides or their derivatives **15**. The labile C-S bond can be homolytically cleaved by an initiator (In-In), previously activated by heat or light, to deliver a radical **19**. This species can then be intercepted by a generic olefin **20**. The following group transfer step between the ensuing new carbon-centered radical **21** and the first key intermediate **16** unveils an α-oxo radical **22** which, upon radical collapse, feeds the radical chain regenerating a new radical **19** and delivers the final transfer product **23**.

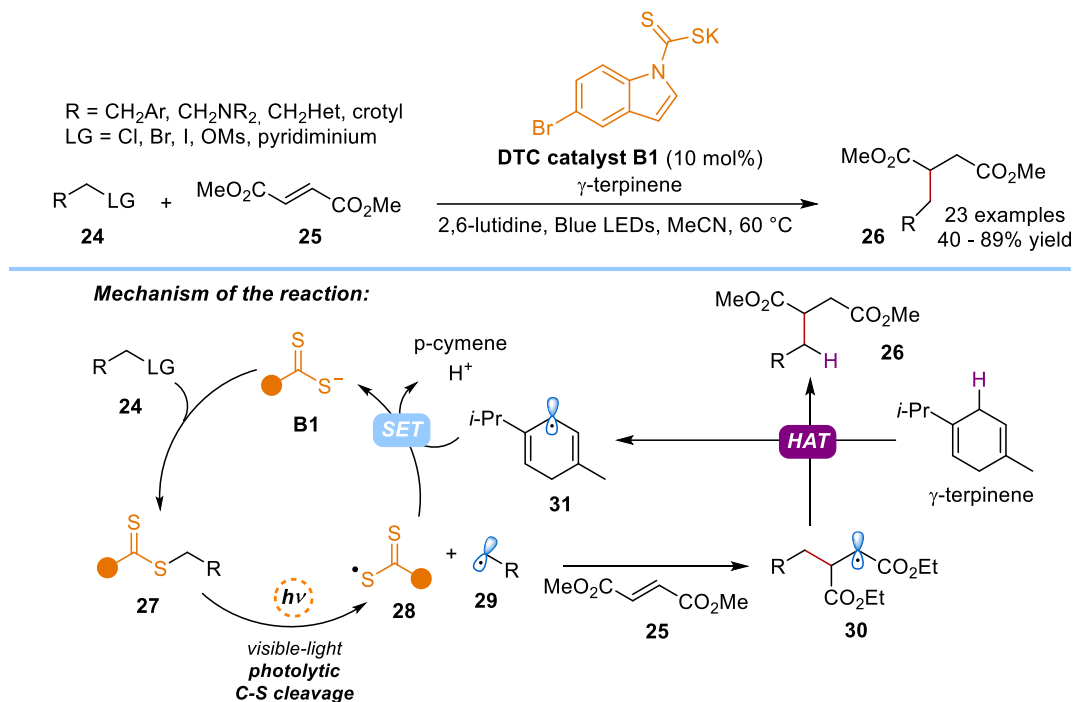
Although during the 20th century the chemistry of DTC compounds had been involved in many different radical processes, including polymerization,³⁹ they were always used in stoichiometric amounts, making necessary not only the pre-generation of the xanthate frameworks but also their further post-functionalization or removal from the final transfer product. In 2019, Melchiorre unveiled the possibility of successfully translating such stoichiometric radical-generating manoeuvre into a catalytic strategy.⁴⁰ The success of this approach relies on the *de novo* designed structure of the indole-based dithiocarbamate organocatalytic platform **B1** to be used in S_N2 substitutions with a wide array of alkyl electrophiles **24**, thus allowing the *in situ* generation of catalytic photo-active intermediates **27** (Scheme 10). The key feature of this strategy relies on the possibility to exploit visible light to generate radicals from such intermediates. Indeed, 5-bromoindole DTC catalyst **B1** showed a bathochromic shift in absorption if compared to the classic aliphatic DTCs. The excitation of the intermediates triggers the homolysis of the weak C-S bond, delivering the xanthyl radical **28** and the target radical **29**. This latter species can then be trapped within a Giese-type reaction by a

³⁸ Zard, S. Z. "On the Trail of Xanthates: Some New Chemistry from an Old Functional Group" *Angew. Chem. Int. Ed.* **1997**, 36, 672.

³⁹ Poly, J.; Cabannes-Boue, B.; Hebing, L.; Mangin, R.; Sauvage, A.; Xiao, P.; Morlet-Savary, F.; Lalevee, J. "Polymers synthesized by RAFT as versatile macrophotoinitiators" *Polym Chem* **2015**, 6, 66.

⁴⁰ Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. "Photochemical generation of radicals from alkyl electrophiles using a nucleophilic organic catalyst" *Nat. Chem.* **2019**, 11, 129.

suitable radical trap, namely dimethylfumarate **25**, delivering a carbon-centered radical of type **30**. This latter species further abstracts a hydrogen atom through a *hydrogen atom transfer* (HAT) from γ -terpinene (sacrificial reductant) to provide the desired product **26**. The incipient cyclohexadienyl radical **31** is instead of crucial importance in regenerating the DTC catalyst **B1** since the turnover event consists of a SET between **28** (E^0 (**B1**/**28**) = +0.44 V vs Ag/AgCl in CH₃CN) and **31** (E_p^{red} = +0.05 V vs Ag/AgCl in CH₃CN) to finally close the catalytic cycle.



Scheme 10 DTC organic catalytic platform as source of radicals under visible-light irradiation

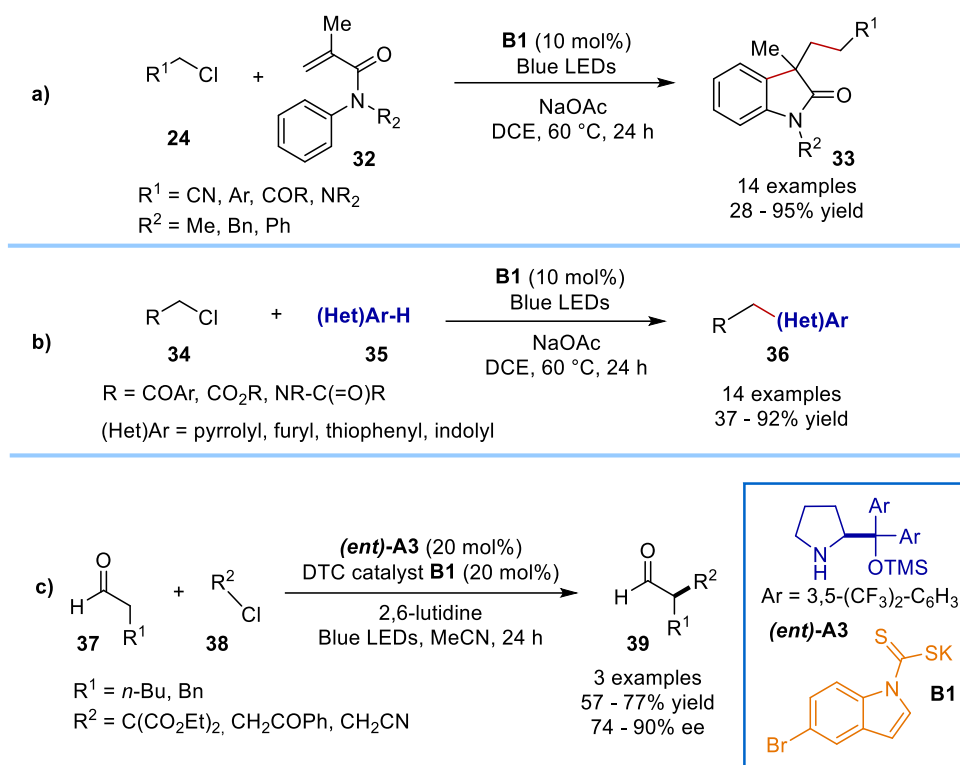
Notably, the same organocatalytic platform was also exploited to promote tandem radical addition/cyclization reactions of *N*-arylacrylamides **32** affording a total of 14 different 3,3-disubstituted oxindoles **33** (Scheme 11, a), as well as radical direct functionalizations of electron-rich (hetero)aromatics **35**, including differently substituted pyrroles, furans, thiophenes and indoles (Scheme 11, b). Finally, within the same work, the usefulness of the radical-generating catalyst was also given by merging DTC catalysis with enamine organocatalysis for the enantioselective α -alkylation of aliphatic aldehydes **37** (Scheme 11, c). Overall, this new catalytic platform has been efficiently exploited so far in Giese-type additions, acylation reactions,⁴¹ alkylations of silyl enol ethers,⁴² borylation processes⁴³ and three-component reactions.⁴⁴ However, its ability in generating radicals under mild reaction conditions could be further exploited in the future for new radical-based transformations. In this thesis, I will describe how the DTC organocatalytic platform can be combined with dienamine organocatalysis for the development of an asymmetric γ -alkylation of enals.

⁴¹ de Pedro Beato, E.; Mazzarella, D.; Balletti, M.; Melchiorre, P. "Photochemical Generation of Acyl and Carbamoyl Radicals Using a Nucleophilic Organic Catalyst: Applications and Mechanism Thereof" *Chem. Sci.* **2020**, *11*, 6312.

⁴² Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Oseka, M.; Melchiorre, P. "A Photochemical Organocatalytic Strategy for the α -Alkylation of Ketones by Using Radicals" *Angew. Chem. Int. Ed.* **2020**, *59*, 9485.

⁴³ Mazzarella, D.; Magagnano, G.; Schweitzer-Chaput, B.; Melchiorre, P. "Photochemical Organocatalytic Borylation of Alkyl Chlorides, Bromides, and Sulfonates" *ACS Catal.* **2019**, *9*, 5876.

⁴⁴ Cuadros, S.; Horwitz, M. A.; Schweitzer-Chaput, B.; Melchiorre, P. "A visible-light mediated three component radical process using dithiocarbamate anion catalysis" *Chem. Sci.* **2019**, *10*, 5484.



Scheme 11 a) Tandem radical addition/cyclization of *N*-arylacrylamides affording 3,3-disubstituted oxindoles. b) Radical functionalization of electron-rich (hetero)arenes. c) Application of DTC catalysis to enantioselective radical catalysis

1.4 The principle of vinylogy applied to π -extended donor systems

In 1935, Fuson first introduced the elegant concept of *vinylogy* stating that, in a molecule containing a system of conjugated double bonds, the influence of a functional group may be propagated along the chain, making itself apparent at a distal position.⁴⁵ The application of the principle of vinylogy to chemical transformations is a powerful synthetic tool in the toolset of organic chemists mainly since it can be considered a privileged means of communication between distant sites of a molecule to be functionalized (Figure 4).

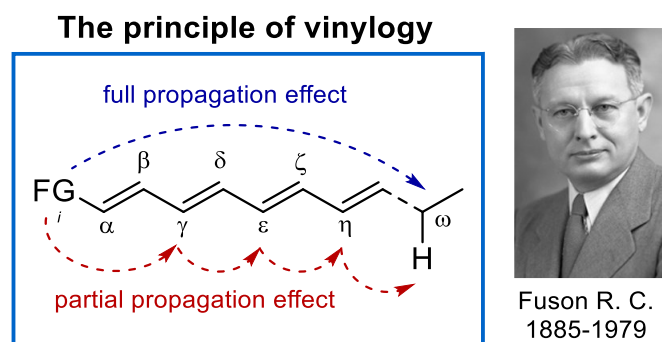
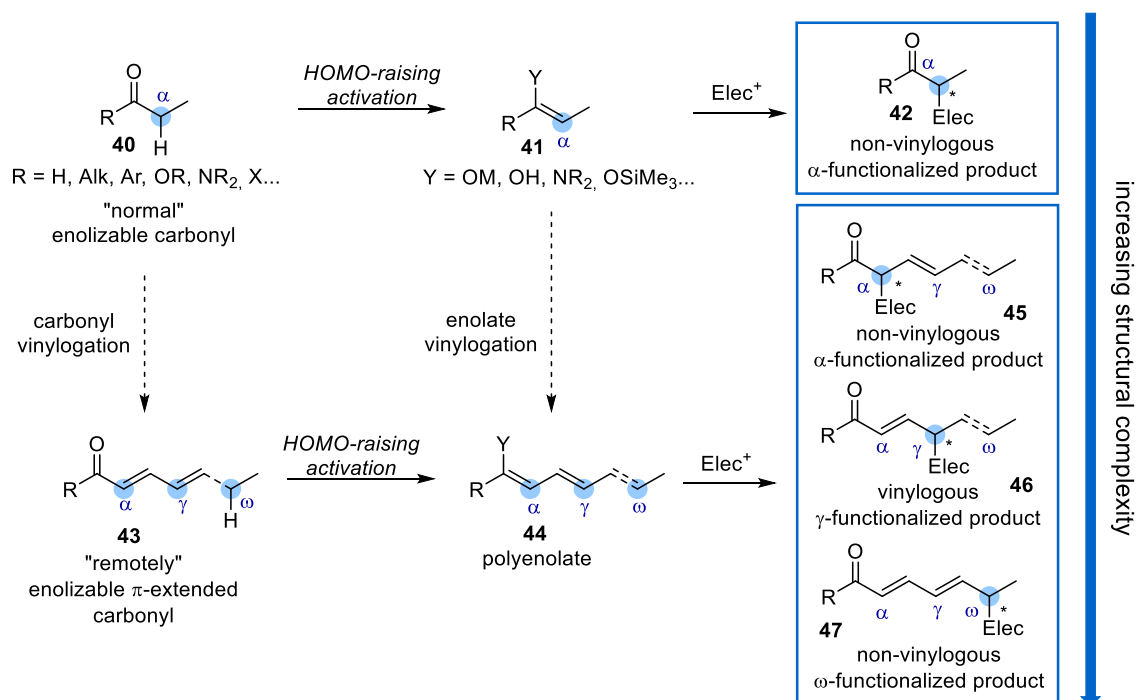


Figure 4 The principle of vinylogy

As all the projects developed during my Ph.D. research concern the distal reactivity of enolizable, π -extended donor systems,⁴⁶ their application to the principle of vinylogy is here highlighted.



The pronucleophilic acidic character of the α -site of enolizable carbonyl compounds **40** is propagated to the vinylogous and hypervinylogous γ , ϵ , ..., ω positions, making possible the generation of the

⁴⁵ Fuson, R. C. "The Principle of Vinylogy" *Chem. Rev.* **1935**, *16*, 1.

⁴⁶ Curti, C.; Battistini, L.; Sartori, A.; Zanardi F. "New Developments of the Principle of Vinylogy as Applied to π -Extended Enolate-Type Donor Systems" *Chem. Rev.* **2020**, *120*, 2448.

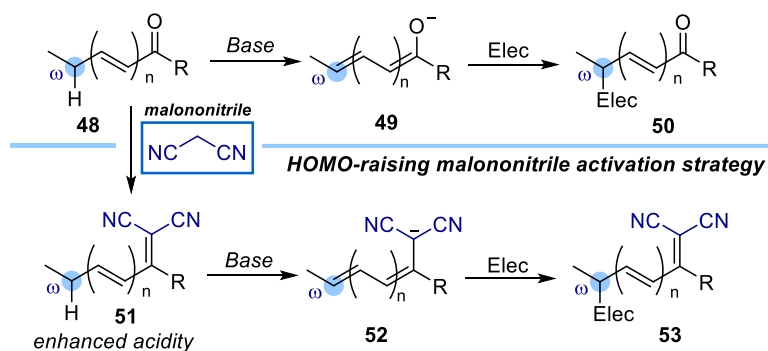
corresponding polyenolate donor intermediates **44**. Such intermediates may be then involved in enolate-based processes with different electrophiles affording a variety of products **45-47** with increased structural complexity compared to their non-vinylogous counterparts **42** (Scheme 12).

The main challenge to be handled within the development of new vinylogous transformations consists in the simultaneous control of the chemo-, regio- and stereochemistry of the reactions. For this reason, finding suitable stoichiometric or catalytic *activation strategies* that can chemoselectively activate the desired substrate, while inducing maximal level of regio- and stereocontrol, is a current topic of crucial importance.

The possibility to successfully unveil the vinylogous reactivity of the pronucleophiles employed during my research work has been crucially dependent on the careful choice of strategic HOMO-raising activation strategies, namely (i) bifunctional organocatalysis to generate dienolate donor systems⁴⁷ (Chapter II), (ii) aminocatalysis as means to afford dienamines⁴⁸ as vinylogous donors (Chapter IV) and, (iii) the stoichiometric vinylogous alkylidene malononitrile activation (Chapter III). Since the organocatalytic activation modes have already been discussed in Chapter 1.1, in the following section the stoichiometric vinylogous alkylidene malononitrile activation strategy will be introduced.

1.4.1 The vinylogous HOMO-raising malononitrile activation strategy

Finding suitable activation strategies for vinylogous pronucleophiles is one of the main challenges to be addressed within the development of remote functionalization pathways. Vinylogous processes indeed feature issues related to the chemo-, regio-, and stereocontrol of the multisite reactivity of vinylogous substrates. One of the most reliable activation strategies to circumvent such selectivity drawbacks is the vinylogous *HOMO-raising malononitrile activation strategy* (Scheme 13).⁴⁹



Scheme 13 The remote C(sp^3)-H functionalization of π -extended dicyanovinylidenes. Elec = electrophile

This approach deals with the transformation of the starting pronucleophiles **48** into the corresponding dicyanovinylidenes **51**, which hence will show higher ω -proton acidity than the starting carbonyl precursors, making the activation of such remote site easier. The double nitrile-group framework is indeed a strong electron-withdrawing-group, making in most cases mild Brønsted-base catalysis a suitable mean for the *in situ* deprotonation. The incipient anionic enolate-type donor **52** results more

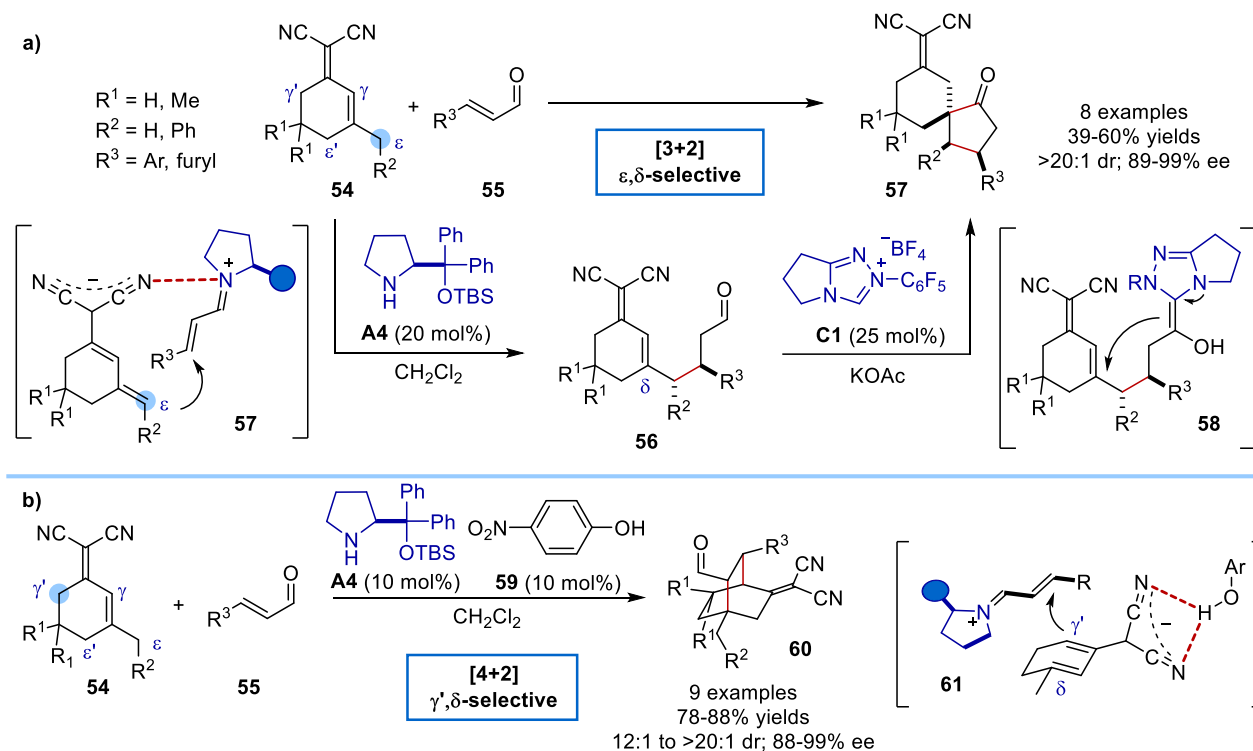
⁴⁷ Oiarbide, M.; Palomo C. “Extended Enolates: Versatile Intermediates for Asymmetric C-H Functionalization via Noncovalent Catalysis” *Chem.Eur.J.* **2021**, 27, 10226.

⁴⁸ Marcos, V.; Alemán J. “Old tricks, new dogs: organocatalytic dienamine activation of α,β -unsaturated aldehydes” *Chem. Soc. Rev.* **2016**, 45, 6812.

⁴⁹ Curti, C.; Sartori, A.; Battistini, L.; Zanardi F. “Exploring the Remote Reactivity of π -Extended Carbonyl Compounds: The Vinylogous Alkylidene Malononitrile Activation Strategy” *Synlett* **2018**, 29, 266.

stabilized as compared to the polyenolate parent **49** and thus it can act as a nucleophilic component in presence of suitable electrophiles.

Although γ -enolizable- α,α' -dicyanoalkenes have long been exploited as vinylogous pronucleophiles in catalytic and asymmetric transformations,⁵⁰ the first use of their bisvinylogous counterparts (also known as α,α' -dicyanopolyenes or extended alkylidene malononitriles) is quite recent. In 2014, our group first introduced and applied the vinylogous *HOMO-raising malononitrile activation strategy* to otherwise recalcitrant π -extended carbonyl precursors.⁵¹ In this work, the cyclohexenyl-alkylidene malononitriles **54** offered multiple pronucleophilic carbons to be activated under base conditions (e.g. ϵ,ϵ' , and γ' -positions).



Scheme 14 First example of the application of vinylogous HOMO-raising malononitrile activation strategy: a) one-pot sequential stereoselective [3 + 2] spiroannulation pathway; b) stereoselective formal [4 + 2] cycloaddition pathway

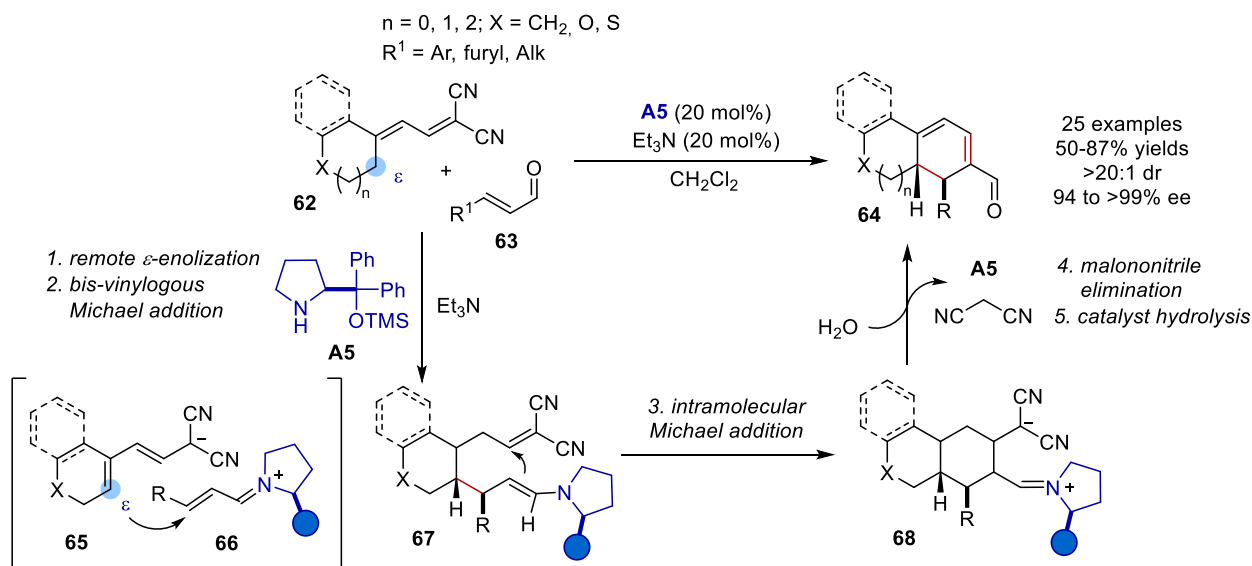
However, the reaction with enals **55**, in the presence of the aminocatalyst **A4**, afforded just the isolable ϵ -selective Michael addition products **56**. The sequential addition of the NHC pre-catalyst **C1** and a base to the reaction mixture, then engaged a telescoped one-pot 1,6-Stetter reaction, providing the spirocyclic products **57** in excellent diastereoselectivities and high enantiocontrol (Scheme 14, a). On the other hand, the addition of *p*-nitrophenol **59** as a co-catalyst in presence of the two starting reacting partners promoted a regiodivergent pathway involving a γ',δ -selective [4+2] cyclization reaction for the efficient generation of bicyclic products **60**, even in this case with excellent enantioselectivities (Scheme 14, b). The role of the co-catalyst in promoting the regiodivergence of the two pathways was rationalized by control experiments. Most probably, in the absence of *p*-nitrophenol, a Coulombic interaction between the polyenolate and the iminium ion (**57**)

⁵⁰ a) Cui, H.-L.; Chen, Y.-C. “ α,α -Dicyanoalkenes: versatile vinylogous nucleophiles for organic synthesis” *Chem. Commun.* **2009**, 4479; b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. “The Vinylogous Aldol and Related Addition Reactions: Ten Years of Progress” *Chem. Rev.* **2011**, *111*, 3076.

⁵¹ Dell’Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. “Exploring the Vinylogous Reactivity of Cyclohexenylidene Malononitriles: Switchable Regioselectivity in the Organocatalytic Asymmetric Addition to Enals Giving Highly Enantioenriched Carbabicyclic Structures” *J. Am. Chem. Soc.* **2014**, *136*, 11107.

is operative, leading to the Michael addition path. On the other side, if present, the phenol shares a hydrogen atom with the delocalized charge of the negatively charged dinitrile framework (**61**), thus promoting the Diels-Alder reaction.

Another remarkable example of this chemistry was reported, again by our group, in 2015.⁵² In this case, the authors developed a formal [4+2] cycloaddition transformation between allylidene malononitriles of type **62** as vinylogous donors and aliphatic and aromatic enals **63** in the presence of aminocatalyst **A5** (Scheme 15).



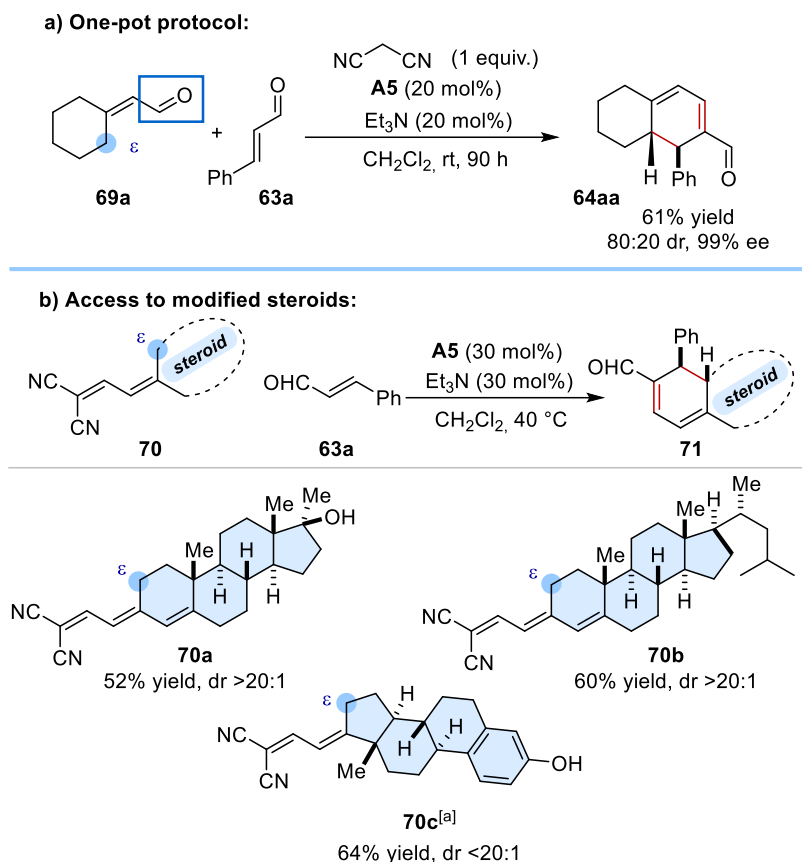
Scheme 15 Organocatalytic, enantioselective eliminative [4+2] cycloaddition of allylidene malononitriles with enals

In this case, the vinylogous malononitrile activation strategy was required to propagate the nucleophilic character of the otherwise recalcitrant pronucleophiles at the remote ϵ -position, making them suitable substrates for the transformation. The desired carbocyclic-fused products **64** were achieved in good yields, with complete diastereoselectivity and excellent enantioselectivities. The proposed mechanism deals with a stepwise formal [4+2] cycloaddition process involving a bis-vinylogous Michael addition and an intramolecular Michael organocascade as key steps. In particular, the first bis-vinylogous Michael addition of the activated donor **65** to the iminium ion **66** gives rise to the incipient enamine intermediate **67**, which then engages the intramolecular Michael addition to furnish the desired polycyclic final products **64** upon malononitrile elimination and organocatalyst hydrolysis.

Interestingly, the authors demonstrated the possibility to obtain the same product through a one-pot procedure starting from the aldehydic precursor **69**. Indeed, initial treatment of the carbonyl substrate with a stoichiometric amount of malononitrile promotes the formation of the corresponding allylidene malononitrile; subsequent one-pot addition of the other reactants still provides the cycloadduct **64a**, even though in a lower 60% yield and at the expense of diastereoselectivity (4:1 dr) (Scheme 16, a). Notably, the authors also applied the methodology to unlock the access to modified biologically relevant steroids, starting from their respective dicyano-based substrates, namely α -

⁵² Brindani, N.; Rassu, G.; Dell'Amico, L.; Zambrano, V.; Pinna, L.; Curti, C.; Sartori, A.; Battistini, L.; Casiraghi, G.; Pelosi, G.; Zanardi, F. "Organocatalytic, Asymmetric Eliminative [4 + 2] Cycloaddition of Allylidene Malononitriles with Enals: Rapid Entry to Cyclohexadiene- Embedding Linear and Angular Polycycles" *Angew. Chem., Int. Ed.* **2015**, *54*, 7386.

methyltestosterone **70a**, keto-4-cholestenone **70b** and estrone **70c** (Scheme 16, b), with comparable results both in terms of efficiency and stereoselectivities.



Scheme 16 a) One-pot malononitrile-driven [4+2] annulations. b) The protocol of the vinylogous [4+2] cycloaddition as applied to steroid-based allylidene malononitriles, [a] reaction conditions: 1) as above; 2) HF•py

Finally, the same group applied in 2016 the vinylogous malononitrile activation strategy to generate indolylmethylene malononitriles as transient diene components to be exploited in asymmetric [4+2] cycloadditions to access enantiopure dihydrocarbazoles.⁵³ In the following section, this case study will be described in more details.

⁵³ Rassu, G.; Curti, C.; Zambrano, V.; Pinna, L.; Brindani, N.; Pelosi, G.; Zanardi, F.” Exploiting the Distal Reactivity of Indolyl Methylene malononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles” *Chem. Eur. J.* **2016**, *22*, 12637.

1.5 Toward new frontiers in the vinylogous domain

During the last two decades, the main progresses that emerged in the field of vinylogous domain mostly involved the launch of novel conjugated donor species and the application of catalytic activation modes to promote stereoselective processes.⁴⁶ However, the incessant progress of the synthetic community in developing new methodologies, is also reflected nowadays on the vinylogous realm. This section aims to give a personal perspective, with comprehensive examples, on two subfields of vinylogous chemistry that represent, amongst the others, new frontiers within the vinylogous domain.

1.5.1 Accessing novel 3D heterocyclic chemotypes by means of vinylogous organocatalytic [4+2] cycloadditions

The discovery of novel and original heterocyclic frameworks is a continuous urgency in medicinal chemistry.⁵⁴ Such scaffolds are historically considered privileged motifs within the pharmaceutical field mainly thanks to two key features: (i) their ability to show various modulable substituents around a heterocyclic aromatic and/or nonaromatic core scaffold, allowing the possibility to access structural wealth, useful in the exploration of new chemical space for drug discovery (DD) purposes and, (ii) the fact that an endless number of bioactive naturally occurring molecules, including many types of human metabolites, show a heterocyclic scaffold. In this context, recent studies have shown that factors such as number of heteroatoms, fraction of C(sp³), ring systems, scaffold rigidity, and 3D shape would improve the success of a lead compound within a DD process.⁵⁵ However, these parameters have not been significantly taken into account over the past decades, producing a stagnation of the already unveiled chemical space in DD campaigns.⁵⁶

Although the methods for the preparation of “standard” fused heteroaromatic carbocycles (indoles, carbazoles, benzimidazoles, benzofurans, dibenzofurans, quinazolindiones, etc.) and their heteroatomic derivatives have already been well-established within the achiral and flat domain, equally efficient methodologies for accessing their enantioenriched 3D structural variants featuring *in-cycle* stereogenic centers (i.e. novel chemotypes) is a growing field that would require to be further investigated. In this context, the electronic properties of suitable vinylogous heteroaromatic pronucleophiles finely match the necessity of designing new enantioselective transformations to turn the most widespread heterocyclic motifs into a three-dimensional format. *Ortho*-alkyl substituted heteroaromatic aldehydes of type **72** can indeed be considered vinylogous enolizable sites to afford highly reactive *ortho*-quinodimethane (oQDM)⁵⁷ intermediates **73** through dearomative processes. Such transient polydentate donors then can be involved in remote functionalizations with suitable electrophiles. Their possible action as competent diene components to trigger [4+2] cycloaddition

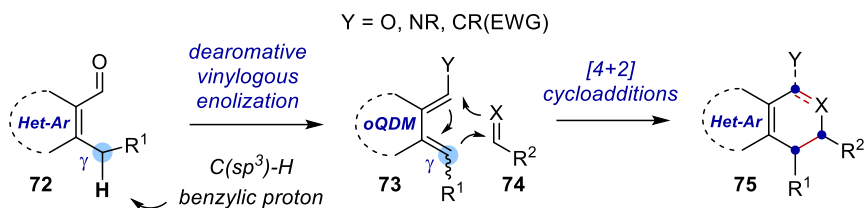
⁵⁴ a) Li J. J. (Ed.) “Heterocyclic Chemistry in Drug Discovery” Wiley, Hoboken, New Jersey, **2013**; b) Singh P. K., Silakari, O. (Eds.) “Multitargeting Heterocycles: Improved and Rational Chemical Probes for Multifactorial Diseases” Elsevier Ltd., **2018**; c) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jonesb, L. H.; Fadeyi O. F. “Modern advances in heterocyclic chemistry in drug discovery” *Org. Biomol. Chem.* **2016**, *14*, 6611.

⁵⁵ a) Nicolaou, K.C. “Advancing the Drug Discovery and Development Process” *Angew. Chem. Int. Ed.* **2014**, *53*, 9128; b) Taylor, R. D.; MacCoss, M.; Lawson A. D. G. “Rings in Drugs” *J. Med. Chem.* **2014**, *57*, 5845; c) Lovering, F.; Bikker, J.; Humblet, C. “Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success” *J. Med. Chem.* **2009**, *52*, 6752; d) Abou-Gharbia, M.; Childers, W. E. “Discovery of Innovative Therapeutics: Today’s Realities and Tomorrow’s Vision. 2. Pharma’s Challenges and Their Commitment to Innovation” *J. Med. Chem.* **2014**, *57*, 5525.

⁵⁶ Brown, D. G.; Boström, J. “Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?” *J. Med. Chem.* **2016**, *59*, 4443.

⁵⁷ Segura, J. L.; Martin, N. “o-Quinodimethanes: Efficient Intermediates in Organic Synthesis” *Chem. Rev.* **1999**, *99*, 3199.

reactions with different classes of dienophiles **74** is of particular interest, since such reactivity may allow the generation of chiral, non-flat heterocyclic carbocycles of type **75** (Scheme 17).



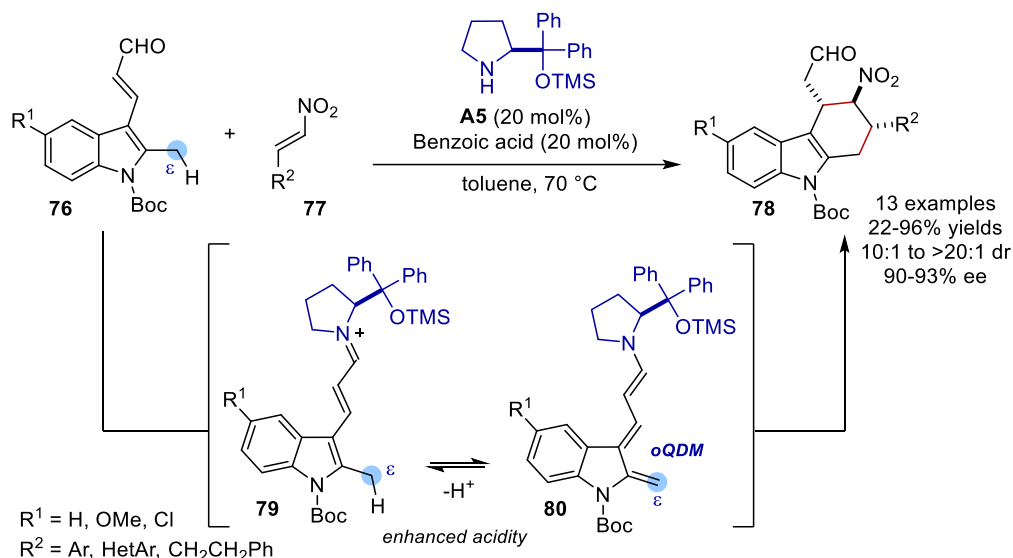
Scheme 17 General strategy for the asymmetric [4+2] cycloaddition via *o*QDM intermediates **73**

Merging the principle of vinylogy with organocatalytic activations may result in a successful strategy to control the regiochemistry and the stereoselectivity of such cyclization reactions. Indeed, while the principle of vinylogy allows the transmission of the electronic properties of the carbonyl moieties through the conjugated π -system to exquisitely control the regioselectivity, chiral organocatalysts would consign the desired products in an enantioselective format. Despite these transformations would be thermodynamically promoted by the recovery of the aromatic character of the products that are further stabilized within the new flanking 6-membered rings, their main challenge relies on the deprotonation at the C(sp³)-H benzylic site, since it entails aromaticity breaking of the starting substrate.⁵⁸ In this section, comprehensive examples of the most significant works about this highly specific and stimulating topic will be given, starting from pioneering works related to the application of clever activation strategies to increase the acidity of the protons at the aforementioned benzylic positions.

The first example of an organocatalytic reaction involving the dearomative generation of an *ortho*-quinodimethane species and subsequent re-aromatization of heteroaromatic compounds in [4+2] cycloadditions was reported by Melchiorre and co-workers in 2011.⁵⁹ In this pioneering work, the *HOMO-raising trienamine catalysis* proved to be a suitable approach to allow the dearomative ϵ -deprotonation of the iminium ion **79** generated upon condensation of *N*-protected 3-(2-methylindol-3-yl)acrylaldehydes **76** with aminocatalyst **A4** (Scheme 18). The ensuing trienamines **80** could readily participate in a Diels-Alder cycloaddition with aromatic and aliphatic nitroolefins **77**, to provide a total of 13 tetrahydrocarbazoles of type **78** in good yields and with high enantio- and diastereomeric ratio. While the enantiocontrol of the reaction was orchestrated by the steric shielding imparted by the bulky α -substituent of the prolinol-based catalyst, the electronic interactions between the electron-rich diene **80** and nitroolefins **77** governed the diastereoselectivity of the cycloaddition, making the *exo* approach favourable.

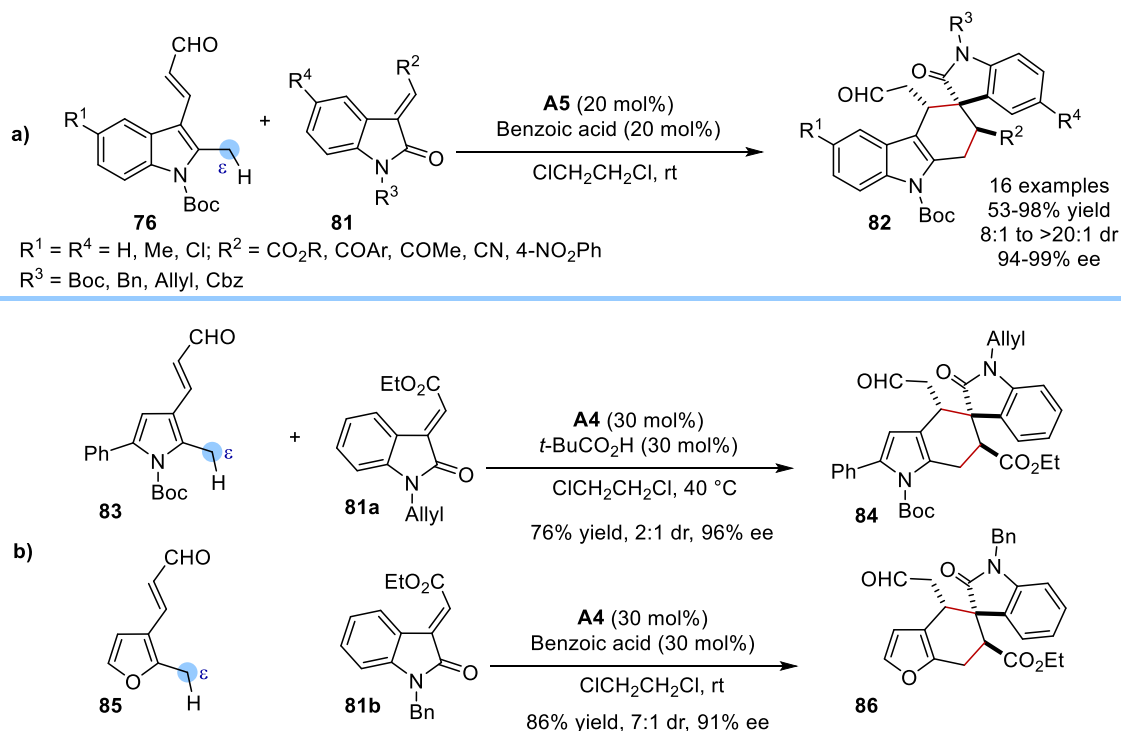
⁵⁸ Przydacz, A.; Skrzyńska, A.; Albrecht, Ł. "Breaking Aromaticity with Aminocatalysis: A Convenient Strategy for Asymmetric Synthesis" *Angew. Chem. Int. Ed.* **2019**, 58, 63.

⁵⁹ Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. "Asymmetric Catalysis of Diels-Alder Reactions with in Situ Generated Heterocyclic Ortho-Quinodimethanes" *J. Am. Chem. Soc.* **2011**, 133, 15212.



Scheme 18 Trienamine *oQDM* key intermediates for the enantioselective [4+2] cycloaddition with nitroolefins developed by Melchiorre and co-workers

The authors also demonstrated the possibility of further expanding the methodology using oxindole-based olefins **81**. Several spirocyclic tetrahydrocarbazoles **82** were obtained with comparable results both in terms of efficiency and stereoselectivity (Scheme 19, a). Notably, the trienamine activation also consigned *oQDM* intermediates of aromatic pyrrole and furan derivatives **83** and **85** to engage aminocatalytic [4+2] cycloadditions with electron-poor alkenes **81a** and **81b**. The corresponding 4,5,6,7-tetrahydroindole and 4,5,6,7-tetrahydrobenzofuran products **84** and **86** were obtained in high yields, with high enantioselectivity, and low-to-good diastereomeric ratios (Scheme 19, b).

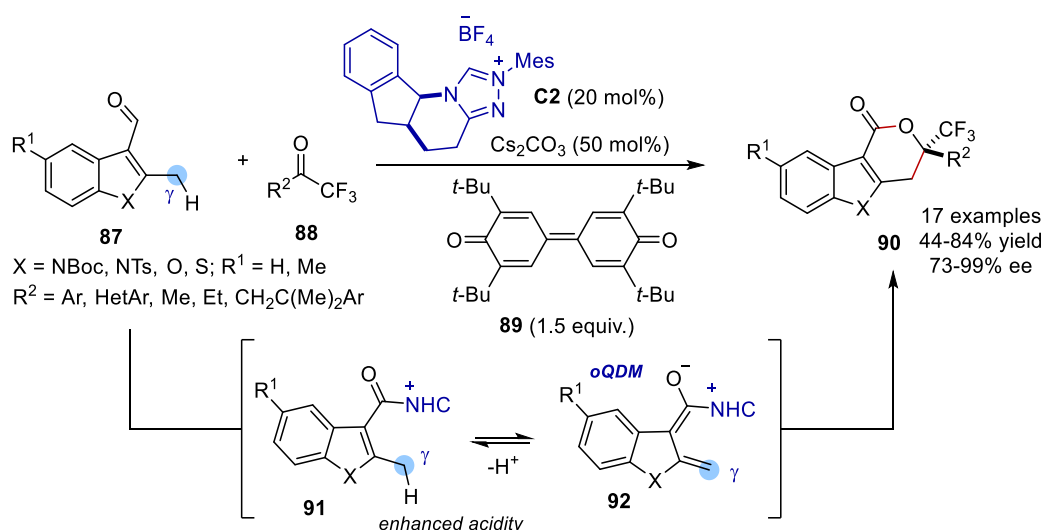


Scheme 19 a) Reactions of trienamine intermediates with electron-deficient olefins in an oxindole framework. b) Reactions of trienamine intermediates with other heteroarenes (pyrrole and furan).

This remarkable work established aminocatalysis, and especially trienamine catalysis, as an effective activation strategy to promote [4+2] cycloadditions by means of the generation of a transient ϵ -

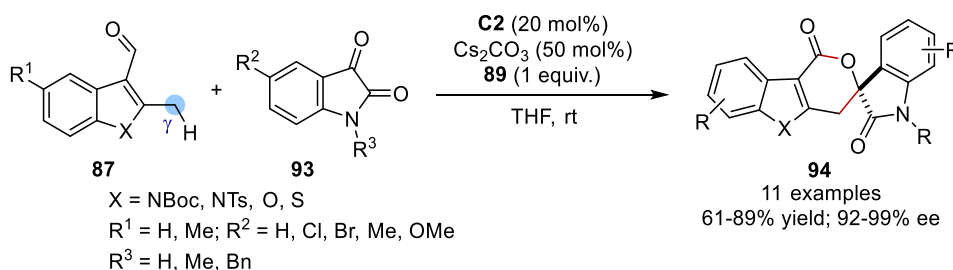
deprotonable iminium ion. However, the methodology was limited to the “extended” version of carbaldehydes, whose conjugated base would result more stabilized than the one formed from the non-extended counterpart (i.e. 2-methyl-3-carboxaldehydes of indole).

In 2013 Chi and co-workers first demonstrated how *HOMO-raising NHC catalysis* was a proper activation strategy for promoting the γ -functionalization of benzylic $C(sp^3)$ -H bonds of heteroaromatic indole, benzofuran, and benzothiophene carbaldehydes of type **87**.⁶⁰ The treatment with aromatic and aliphatic trifluoromethylketones **88** in the presence of NHC pre-catalyst **C2** under oxidative conditions given by the presence of **89**, allowed the generation of several examples of polycyclic lactone derivatives **90** in good yields and high enantioselectivities (Scheme 20). The reaction proceeds first through the generation of the Breslow intermediate (not shown) which is then oxidized to the corresponding acyl azolium **91**, whose acidity at the benzylic site is now high enough to be deprotonated. The ensuing key intermediate *o*QDM **92** finally engages the [4+2] cycloaddition to provide the desired enantioenriched products and regenerate the NHC catalyst.



Scheme 20 Acyl azolium key intermediates for the enantioselective [4+2] cycloaddition with trifluoromethylketones developed by Chi and co-workers

Slightly modified reaction conditions also allowed the generation of a panel of 11 spirocyclic products **94** derived from the reaction between the starting pronucleophiles **87** and diversely protected and substituted isatins **93** (Scheme 21).

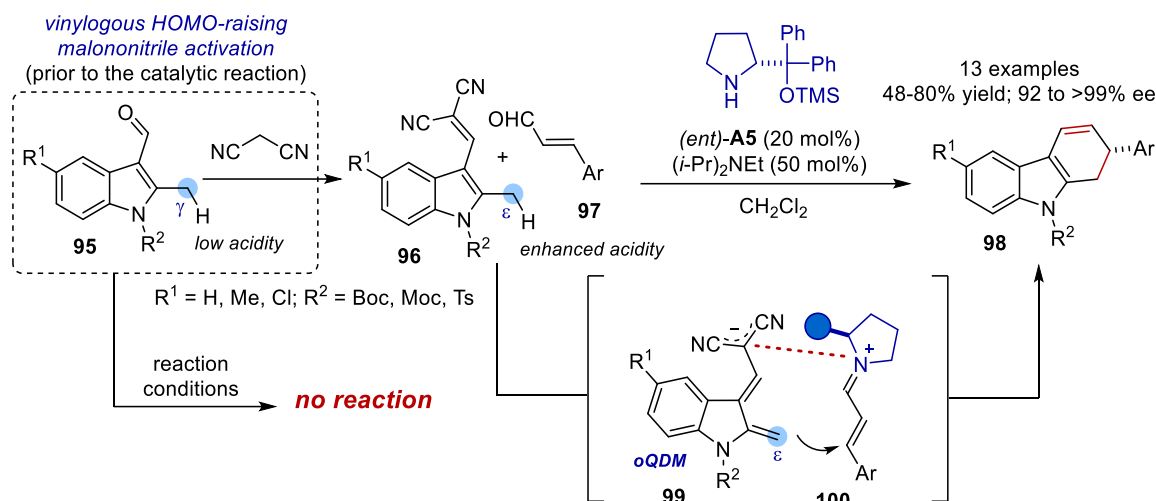


Scheme 21 Reactions of vinylogous indole-based pronucleophiles **87** intermediates with isatins **93**

Finally, in 2015 our group reported an example of eliminative formal [4+2] cycloadditions between indole-based dicyanovinylidene **96** and aromatic enals **97**.⁵³ In that work, the vinylogous HOMO-

⁶⁰ Chen, X.; Yang, S.; Song, B. A.; Chi, Y. R. “Functionalization of Benzylic $C(sp^3)$ -H Bonds of Heteroaryl Aldehydes through N Heterocyclic Carbene Organocatalysis” *Angew. Chem. Int. Ed.* **2013**, 52, 11134.

raising malononitrile activation strategy resulted successful in activating the *o*QDM diene in the presence of a tertiary amine (Scheme 22). The combination of such an activation strategy with the iminium-ion LUMO-lowering catalysis afforded enantiopure carbocyclic indole-derivatives **98** upon formal eliminative [4+2] cycloadditions in good overall yield. The key step of the transformation involves the first concomitant generation of the indole *o*QDM **99** (from distal ϵ -deprotonation of **96**) and iminium ion **100** (upon condensation of the aminocatalyst (*ent*)-**A5** with enals **97**) under the prolinol/tertiary amine catalytic system, to engage a stereoselective bis-vinylogous Michael addition. Noteworthy, the authors demonstrated, through a control experiment, that malononitrile activation allowed reactivity otherwise not allowed by simply starting from the aldehyde-precursor **95** in the same reaction conditions.



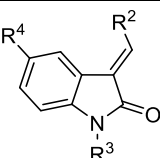
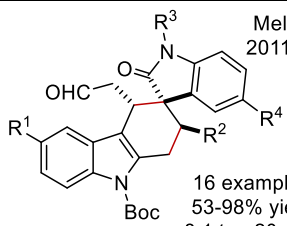
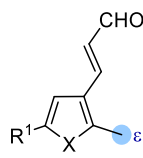
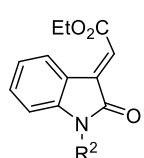
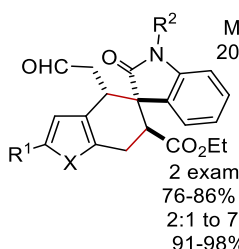
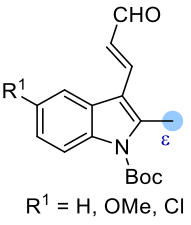
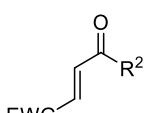
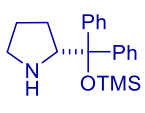
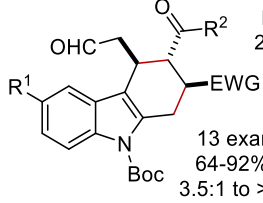
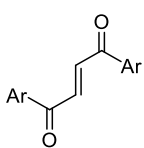
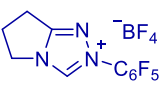
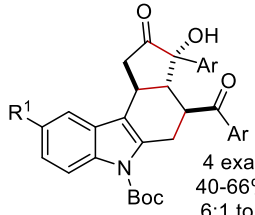
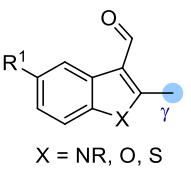
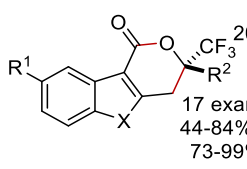
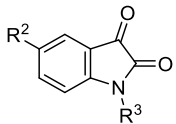
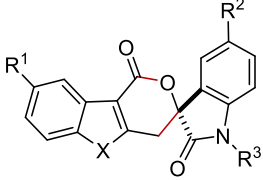
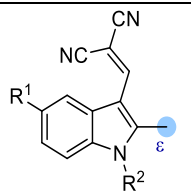
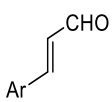
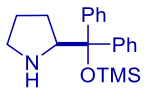
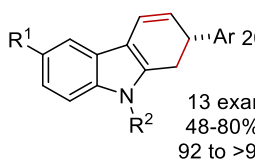
Scheme 22 HOMO-raising malononitrile activation as suitable strategy to unveil dearomative [4+2] cycloadditions to access enantiopure dihydrocarbazoles **98** developed by Zanardi and co-workers

Overall, trienamine catalysis, NHC catalysis, and malononitrile activation resulted as suitable strategies to remotely activate enolizable heterocyclic pronucleophiles, in order to promote enantioselective [4+2] cycloadditions involving *o*QDM intermediates. Although the three explicative reported examples mostly involved indole-based substrates, the chemistry here discussed has been recently applied to other heterocyclic cores, involving moreover different organocatalytic activations, such as dienamine organocatalysis and dienolate-bifunctional organocatalysis. Table 1 gives an exhaustive glance at this peculiar reactivity field, depicting all the examples developed so far, including different heterocyclic pronucleophiles (not limited to carbaldehydes), electrophiles, organocatalysts and enantioenriched polycyclic products.^{53,59-73}

Table 1. Enantioselective functionalization of benzylic C–H bonds of π -extended heteroaryl carbonyls *via* *o*QDM-mediated [4+2] cycloaddition reactions

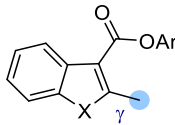
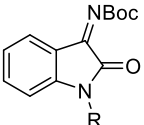
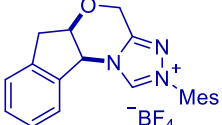
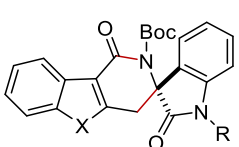
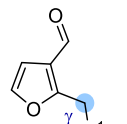
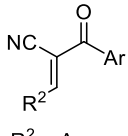
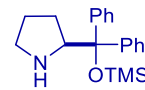
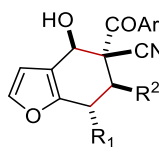
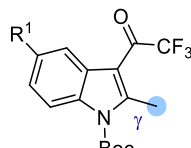
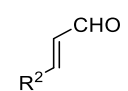
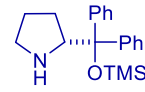
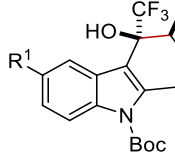
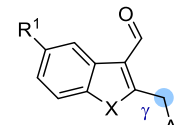
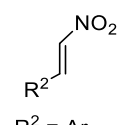
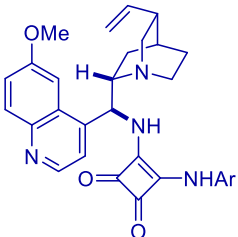
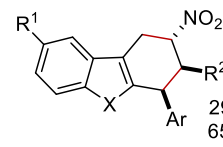
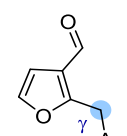
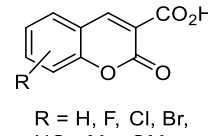
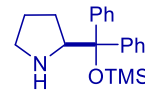
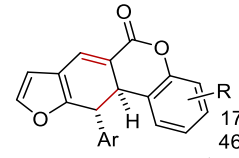
Eq. N°	pronucleophile	electrophile	catalyst/ conditions	product	Author year, ref.
1	 R ¹ = H, OMe, Cl	 R ² = Ar, HetAr, CH ₂ CH ₂ Ph	 A5 (20 mol%) BA, toluene, 70 °C	 13 examples 22-96% yields 10:1 to >20:1 dr 90-93% ee	Melchiorre, 2011, ref. 59

Table 1. Continued

Eq. N°	pronucleophile	electrophile	catalyst/ conditions	product	Author year, ref.
2	as above	 $R^2 = \text{CO}_2\text{R}, \text{COAr}, \text{COMe}, \text{CN}, 4\text{-NO}_2\text{Ph}$ $R^3 = \text{Boc}, \text{Bn}, \text{Allyl}, \text{Cbz}$ $R^4 = \text{H}, \text{Me}, \text{Cl}$	as above (cat) DCE, rt	 16 examples 53-98% yield 8:1 to >20:1 dr 94-99% ee	Melchiorre, 2011, ref. 59
3	 $X = \text{NBoc}, \text{O}$ $R^1 = \text{Ph}, \text{H}$	 $R^2 = \text{allyl}, \text{Bn}$	A5 (30 mol%) TMAA (30 mol%) or BA DCE, rt or 40 °C	 2 examples 76-86% yield 2:1 to 7:1 dr 91-98% ee	Melchiorre, 2011, ref. 59
4	 $R^1 = \text{H}, \text{OMe}, \text{Cl}$	 $R^2 = \text{Ar}, \text{HetAr}$ $\text{EWG} = \text{COAr}, \text{CO}_2\text{Et}, \text{CO}_2\text{Bn}, \text{CN}$	 <i>ent</i>-A5 (20 mol%) 2,4,6-Me₃C₆H₂CO₂H (20 mol%) toluene, 40 °C	 13 examples 64-92% yield 3.5:1 to >20:1 dr 97-99% ee	Melchiorre, 2012, ref. 61
5	as above		1. as above 2.  C3 (20 mol%) NaOAc, toluene, 50 °C	 4 examples 40-66% yield 6:1 to 8:1 dr 97-99% ee	
6	 $X = \text{NR}, \text{O}, \text{S}$	 $R^2 = \text{CF}_3$	 C2 (20 mol%) Cs₂CO₃, 89, THF, 0 °C	 17 examples 44-84% yield 73-99% ee	Chi, 2013, ref. 60
7	as above		as above	 11 examples 61-89% yield 92-99% ee	
8		$R^1 = \text{H}, \text{Me}, \text{Cl}; R^2 = \text{Boc}, \text{Moc}, \text{Ts}$ 	 A5 (20 mol%) <i>(i</i>-Pr)₂NEt CH₂Cl₂, 35 °C	 13 examples 48-80% yield 92 to >99% ee	Zanardi, Ar 2016, ref. 53

⁶¹ Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. "Multicatalytic Asymmetric Synthesis of Complex Tetracyclic Carbazoles via a Diels-Alder/Benzoin Reaction Sequence" *Org. Lett.* **2012**, *14*, 1310.

Table 1. Continued

Eq. N°	pronucleophile	electrophile	catalyst/ conditions	product	Author year, ref.
9	 X = NBoc, NTs, O, S Ar = 4-NO ₂ C ₆ H ₄	 R = Trt, Me, Bn, Ph, Allyl	 (<i>ent</i>)- C2 (20 mol%) DBU, 4 Å MS, THF, rt		Xu, 2016, ref. 62 15 examples 67-81% yield 87 to >99% ee
10	 R ¹ = Ar, Vinyl	 R ² = Ar, furyl, thiophenyl	 A5 (20 mol%) 2-OH-BA, toluene/CH ₃ CN, 4 °C		Chen, 2016, ref. 63 22 examples 68-92% yield 8:1 to >20:1 dr 72 to >99% ee
11	 R ¹ = H, OMe, Cl	 R ² = Me, Ar, furyl	 (<i>ent</i>)- A5 (2 mol%) Et ₃ N (10 mol%) CH ₃ CN, rt		Enders 2018, ref. 64 15 examples 91-99% yield 17:1 to >20:1 dr 94-99% ee
12	 X = O, S R ¹ = H, Me, Cl	 R ² = Ar, thiophenyl	 Ar = 3,5-(CF ₃) ₂ C ₆ H ₃ 1. D1 (10 mol%) CH ₂ Cl ₂ , 35 °C Et ₃ SiH, BF ₃ •Et ₂ O 2. CH ₂ Cl ₂		Xu, 2018, ref. 65 29 examples 65-95% yield >20:1 dr 91-97% ee
13	 Ar	 R = H, F, Cl, Br, NO ₂ , Me, OMe	 A5 (20 mol%) toluene, rt		Albrecht, 2019, ref. 66 17 examples 46-99% yield 15: 1 to >20:1 dr 94-98% ee

⁶² Xu, J.; Yuan, S.; Miao, M. "N-Heterocyclic Carbene Catalyzed [4 + 2] Annulation Reactions with *in Situ* Generated Heterocyclic ortho-Quinodimethanes" *Org. Lett.* **2016**, *18*, 3822.

⁶³ Duan, C.; He, Z.; Du W.; Chen, Y. "Asymmetric [4 + 2] cycloadditions with 3-furfural derivatives and α -cyano- α,β -unsaturated ketones" *Org. Chem. Front.* **2018**, *5*, 2057.

⁶⁴ Jafari, E.; Chauhan, P.; Kumar, M.; Chen, X. Y.; Li, S.; von Essen, C.; Rissanen, K.; Enders, D. "Organocatalytic Asymmetric Synthesis of Trifluoromethylated Tetrahydrocarbazoles by a Vinylogous Michael/Aldol Formal [4 + 2] Annulation" *Eur. J. Org. Chem.* **2018**, 2018, 2462.

⁶⁵ Wang, Y.; Lin, J.-B.; Xie, J.-K.; Lu, H.; Hu, X.-Q.; Xu, P.-F. "Dearomative Dienolate-Mediated Catalysis: A Remote Activation Strategy for Asymmetric Functionalization of Benzylic C–H Bonds of Heteroaryl Aldehydes" *Org. Lett.* **2018**, *20*, 5835.

⁶⁶ Bojanowski, J.; Skrzyńska, A.; Albrecht, A. "Dearomatizative and Decarboxylative Reaction Cascade in the Aminocatalytic Synthesis of 3,4-Dihydrocoumarins" *Asian J. Org. Chem.* **2019**, *8*, 844.

Table 1. Continued

Eq. N°	pronucleophile	electrophile	catalyst/ conditions	product	Author year, ref.
14	 R = Boc, Bn		 A6 (20 mol%) toluene, 70 °C	 2 examples (low anxiolytic activity found) 78-90% yield 1.6:1 to >11.5:1 dr 93-98% ee	Gomez, 2020, ref. 67
15	 R ¹ = Me, MOM, MEM	 R ² = Ar, furyl	 (<i>ent</i>)- A5 (20 mol%) CH ₂ Cl ₂ , rt	 12 examples 50-80% yield 98 to >99% ee	Zanardi, 2020, ref. 68
16	as above	 Ar = C ₆ H ₅ , 4-OMe-C ₆ H ₄	as above (cat., solvent) BA (20 mol%)	 5 examples 65-69% yield >99% ee	
17	 R ¹ = Cl, Br, I, CF ₃ , POPh ₂ , OMe, naphtyl; R ² = H, F R ³ = F, Cl, Br, I, Me, OMe, NO ₂		 (<i>ent</i>)- C2 (20 mol%) DQ, DBU DCE, -10 °C then DDQ	 57 examples 44-94% yield 72-96% ee	Ye, 2020, ref. 69
18	 R = Br, Cl	as above	as above	 13 examples 42-85% yield 78-91% ee	
19		 R = Ar, furyl	 A7 1. A7 (20 mol%) NaOAc (1 equiv.) CH ₂ Cl ₂ , rt 2. Ph ₃ P=CHCO ₂ Et (3 equiv.) CH ₂ Cl ₂ , 10 °C	 10 examples 52-86% yield 94 to >99% ee	Albrecht, 2021, ref. 70

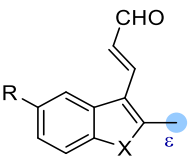
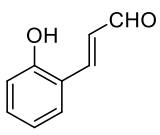
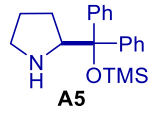
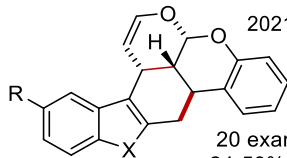
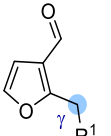
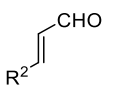
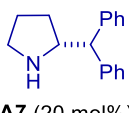
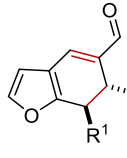
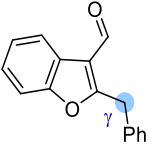
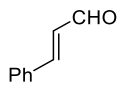
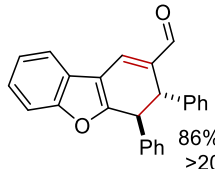
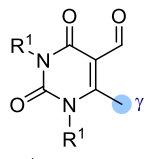
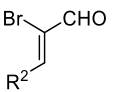
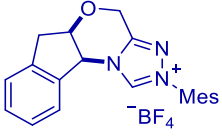
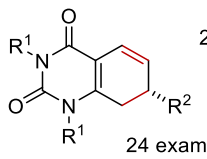
⁶⁷ Pawara, T. J.; Maqueda-Cabrera, E. E.; Alonso-Castro, A. J.; Olivares-Romero, J. L.; Cruza, D. C.; Villegas Gómez, C. "Enantioselective synthesis of tetrahydrocarbazoles via trienamine catalysis and their anxiolytic-like activity" *Bioorg. Med. Chem. Lett.* **2020**, 30, 9, 127063.

⁶⁸ Curti, C.; Rassu, G.; Lombardo, M.; Zambrano, V.; Pinna, L.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F. "Unlocking Access to Enantiopure Fused Uracils by Chemodivergent [4+2] Cross-Cycloadditions: DFT-Supported Homo-Synergistic Organocatalytic Approach" *Angew. Chem. Int. Ed.* **2020**, 59, 20055.

⁶⁹ Zhang, C.; Gao, Y.; Wang, H.; Zhou, B.; Ye, S. "Enantioselective Synthesis of Axially Chiral Benzothiophene/Benzofuran-Fused Biaryls by N-Heterocyclic Carbene Catalyzed Arene Formation" *Angew. Chem. Int. Ed.* **2021**, 60, 13918.

⁷⁰ Saktura, M.; Frankowski, S.; Joachim, B.; Albrecht, L. "Aminocatalytic Synthesis of Uracil Derivatives Bearing a Bicyclo[2.2.2]octane Scaffold via a Doubly Cycloadditive Reaction Cascade" *Synthesis* **2021**, 53, 309.

Table 1. Continued

Eq. N°	pronucleophile	electrophile	catalyst/ conditions	product	Author year, ref.
20	 X = NBoc, NMe, O, S R = H, Me, OMe, Cl		 A5 1. A5 (20 mol%) <i>m</i>-CIBA (20 mol%.) CPME, 40 °C 2. MsCl, TEA, DMAP CH₂Cl₂, rt	 20 examples 24-58% yields 97 to >99% ee	Liu, 2021, ref. 71
21	 R₁ = Ar, Vinyl	 R₂ = Ar, furyl	 A7 (20 mol%) BA (40 mol%) Et₂O, rt	 15 examples 56-95% yield 6:1 to >20:1 dr 62 to >99% ee	Albrecht, 2022, ref. 72
22	 R₁ = Ar, Vinyl	 R₂ = Ar, furyl	as above	 86% yield >20:1 dr 84% ee	
23	 R¹ = Me, Allyl, MEM, BOM	 R² = Ar, thiophenyl benzothiophenyl	 (<i>ent</i>)-C2 (10 mol%) DABCO toluene, rt	 24 examples 47-79% yield 86 to >99% ee	Du, 2022, ref. 73

In this thesis, I will show how the application of the principle of vinylogy, merged with bifunctional organocatalysis and iminium ion catalysis, allowed the generation of unprecedented, enantiopure uracil- and imidazole-based carbocycles with potential bioactivities.

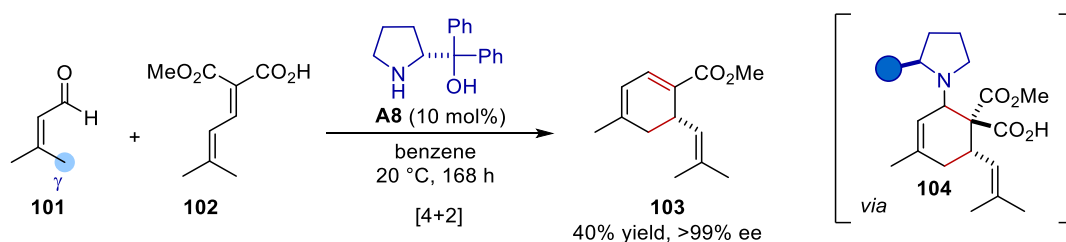
⁷¹ Ming, Y.; Lv, X.; Liu, M.; Liu, M. "Synthesis of Chiral Polycyclic Tetrahydrocarbazoles by Enantioselective Aminocatalytic Double Activation of 2-Hydroxycinnamaldehydes with Dienals" *Org. Lett.* **2021**, 23, 6515.

⁷² Topolska, A.; Frankowski, S.; Albrecht, Ł. "Differentiating Catalysis in the Dearomative [4+2]-Cycloaddition Involving Enals and Heteroaromatic Aldehydes" *Org. Lett.* **2022**, 24, 955.

⁷³ Lin, C.; Zhang, S.; Wang, J.; Chen, L.; Zhu, Y.; Du, D. "N-Heterocyclic Carbene-Catalyzed Enantioselective Synthesis of Carbocycle-Fused Uracils via Formal [4+2] Annulation/Lactone Formation/Decarboxylation Cascade" *Org. Lett.* **2022**, 24, 3631.

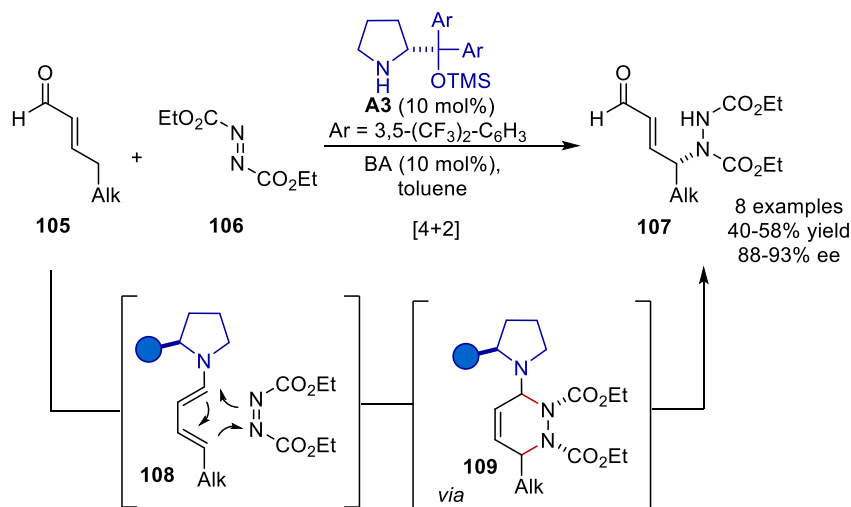
1.5.2 Regio- and enantioselective γ -alkylation of organocatalytic vinylogous dienamine intermediates: from polar to light-mediated radical domain

The seminal study of a catalytic dienamine system was reported by Serebryakov in 1998 (Scheme 23). In particular, in the presence of aminocatalyst **A8**, the γ -enolizable α,β -unsaturated aldehyde **101** and the dienophile **102** were involved in a decarboxylative [4+2] cycloaddition reaction via vinylogous enamine (dienamine) intermediate **104** for the smoothly enantioselective generation of a polysubstituted cyclohexadiene **103**.⁷⁴



Scheme 23 Seminal study of Serebryakov's catalytic dienamine system

This reactivity remained almost unexplored until 2006, when Jørgensen and co-workers disclosed the first example of enantioselective γ -amination of enals.⁷⁵ Dienamines **108**, derived upon the condensation of the aminocatalyst **A3** with linear enals **105**, act as competent dienes to react in [4+2] cycloadditions with diazo compounds **106**. Further hydrolysis of the cycloadducts **109** provides a series of enantioenriched γ -aminated adducts of type **107** in moderate to good yields (Scheme 24).



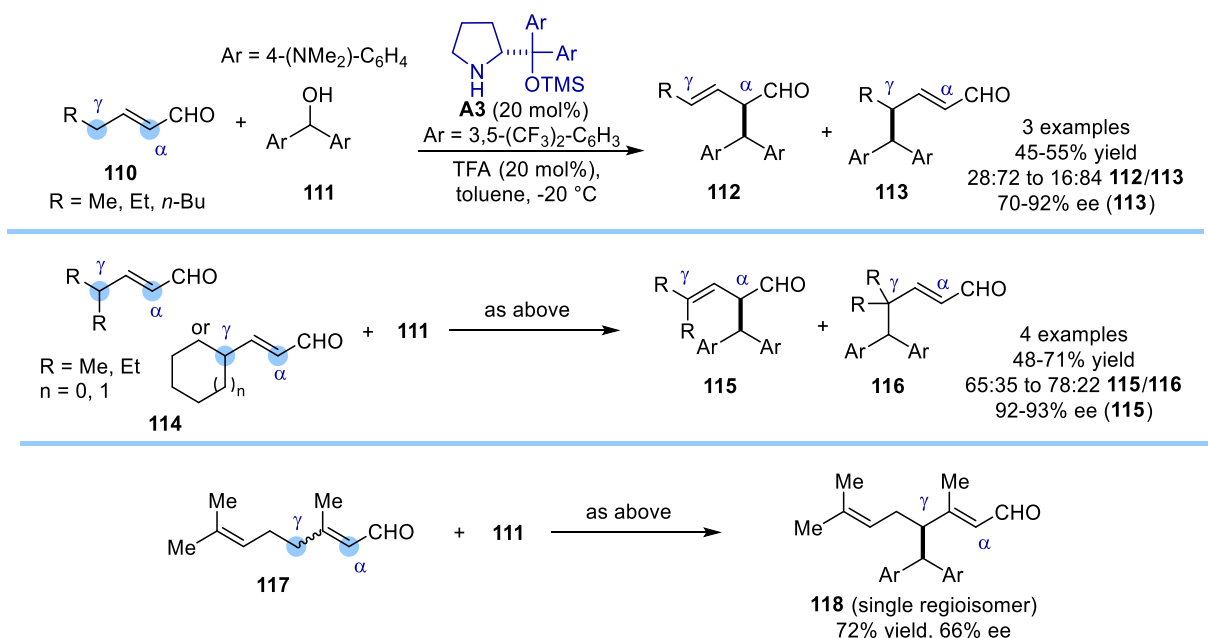
Scheme 24 Pioneering work developed by Jørgensen and co-workers involving dienamine-mediated γ -amination via [4+2] cycloaddition

The pioneering work by Jørgensen paved the way to a myriad of studies involving dienamines as organocatalytic intermediates. Moreover, it could be considered a milestone of this field since it shows an intriguing mechanistic study of the observed stereoselectivity of the process, calculating all possible equilibria that govern the conformation of dienamine's double bonds. Dienamine catalysis is nowadays considered as a straightforward strategy to promote [4+2] cycloaddition reactions with

⁷⁴ Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov M. A.; Struchkova, M. I. "The effects of the nature of catalyst and of the solvent on the stereoselectivity in amine-catalyzed asymmetric synthesis of substituted cyclohexa- 1,3-dienes from prenal and monoesters of ylidene malonic acids" *Russ. Chem. Bull.*, **1998**, 47, 82.

⁷⁵ Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. "Dienamine Catalysis: Organocatalytic Asymmetric γ -Amination of α,β -Unsaturated Aldehydes" *J. Am. Chem. Soc.*, **2006**, 128, 12973.

high stereoselectivities.⁷⁶ On the other hand, non-pericyclic and direct functionalizations of the remote γ -site in dienamine intermediates are highly challenging, due to issues related to regioselectivity and stereoselectivity of such processes. The former relies on α -regioselective competitive pathways which lead to mixtures of α/γ functionalized regioisomers, while the latter depends on the fact that the conjugated double bond system may exist as different *E/Z* geometric isomers in solution, making the stereocontrol of the new forged stereogenic centres highly challenging. In 2011, Christmann and co-workers investigated these aspects surveying a series of differently substituted enals in an organocatalytic S_N1 reaction with bis(aryl)methanols **111** as electrophiles.⁷⁷ Interestingly, it was found that the substitution patterns along the chain of the enals had a dramatic impact in governing the regio- and stereoisomeric outcome of the reactions. In particular, linear enals **110** furnished γ -alkyl product **113** (ca 20:80 α -**112**/ γ -**113**) with moderate to good enantiomeric excesses, while γ -branched enals **114** were engaged in regioselective α -alkylations, to afford preferential adducts of type **115** (ca 75:25 α -**115**/ γ -**116**) obtained with high enantioselectivities. Moreover, an example of β -branched enal **117** (i.e. citral) was also reported; in this case, the γ -functionalized product **118** was solely obtained in good yield, albeit with lower stereocontrol (Scheme 25).



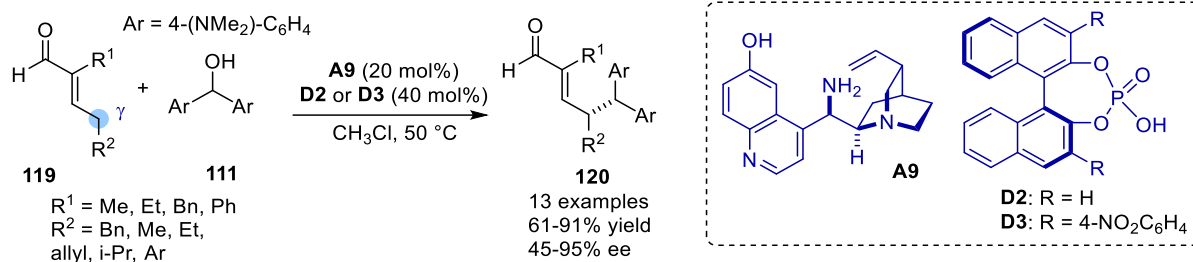
Scheme 25 Christmann's studies on the effect of substitution on organocatalytic S_N1 -type alkylations of enals

On the other hand, Melchiorre and co-workers investigated the effect of α -substitution of enals developing, in 2010, a cooperative organocatalytic direct γ -alkylation of α -branched enals **119**, again with the electrophile **111**, in presence of the aminocatalyst **A9** and the chiral organic phosphoric acid **D2** or **D3**.⁷⁸ Curiously, the reaction provided γ -alkylated products **120** exclusively, in good yields and with excellent enantioselectivities (Scheme 26).

⁷⁶ Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K.A. "Asymmetric cycloaddition reactions catalysed by diarylprolinol silyl ethers" *Chem. Soc. Rev.*, **2017**, 46, 1080.

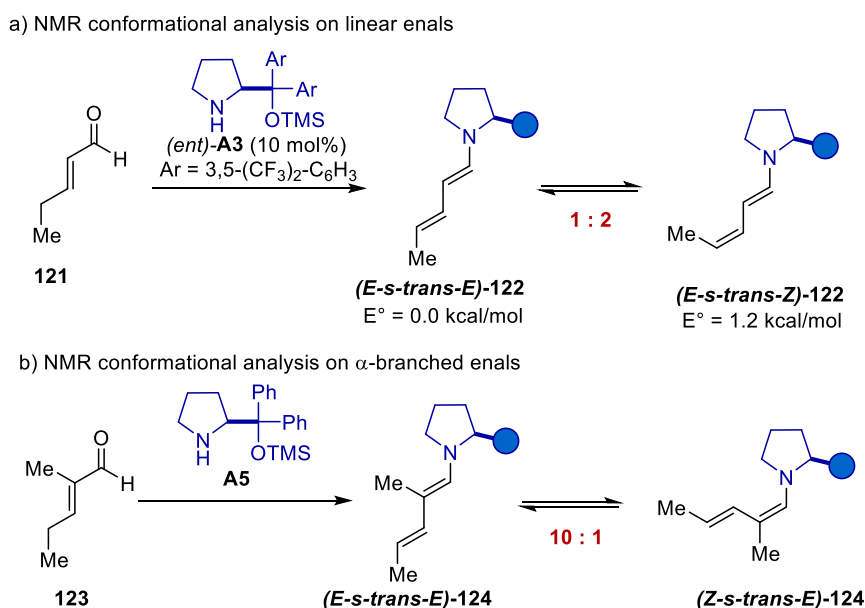
⁷⁷ Stiller, L.; Marques-Lopez, E.; Herrera, R.; Fröhlich, R.; Strohmman, C; Christmann, M. "Enantioselective α - and γ -Alkylation of α,β -Unsaturated Aldehydes Using Dienamine Activation" *Org. Lett.*, **2011**, 13, 70.

⁷⁸ Bergonzini, G.; Vera, S.; Melchiorre, P. "Cooperative Organocatalysis for the Asymmetric γ Alkylation of α -Branched Enals" *Angew. Chem., Int. Ed.*, **2010**, 49, 9685.



Scheme 26 Melchiorre's cooperative γ -selective alkylation of α -branched enals

The crucial role played by the substitution pattern on the enal, in orchestrating the regio- and enantioselectivity of these transformations, was later rationalized by the effect of such substitution on the equilibrium constants between double-bond configurations and all possible conformations of the dienamine intermediates. Some interesting aspects could be observed by analysing and comparing NMR studies performed both by the group of Jørgensen within the aforementioned work on the linear enals,⁷³ and by the Melchiorre group on dienamines deriving from the condensation of a prolinol-based aminocatalyst **A5** with 2-methylpentenal **121**.⁷⁹ Equation (a) in Scheme 27 highlights the two prominent dienamine isomers deriving from the linear enal **121** found through NMR spectroscopy. In particular, the isomer (*E-s-trans-Z*)-**122** was prevalent in solution, with a 2:1 ratio over the (*E-s-trans-E*)-**122**. DFT calculations, moreover, showed a low difference in energy between them, equal to just 1.2 kcal/mol. On the other side, in the case of α -branched enal **123**, the steric hindrance produced by the methyl hampered the presence of the (*E-s-trans-Z*)-isomer (not shown) in favour of (*E-s-trans-E*)-**124**. This latter species was found to be in equilibrium with the (*Z-s-trans-E*)-**124** counterpart with an isomeric ratio of 10:1 (Scheme 27, eq. b).



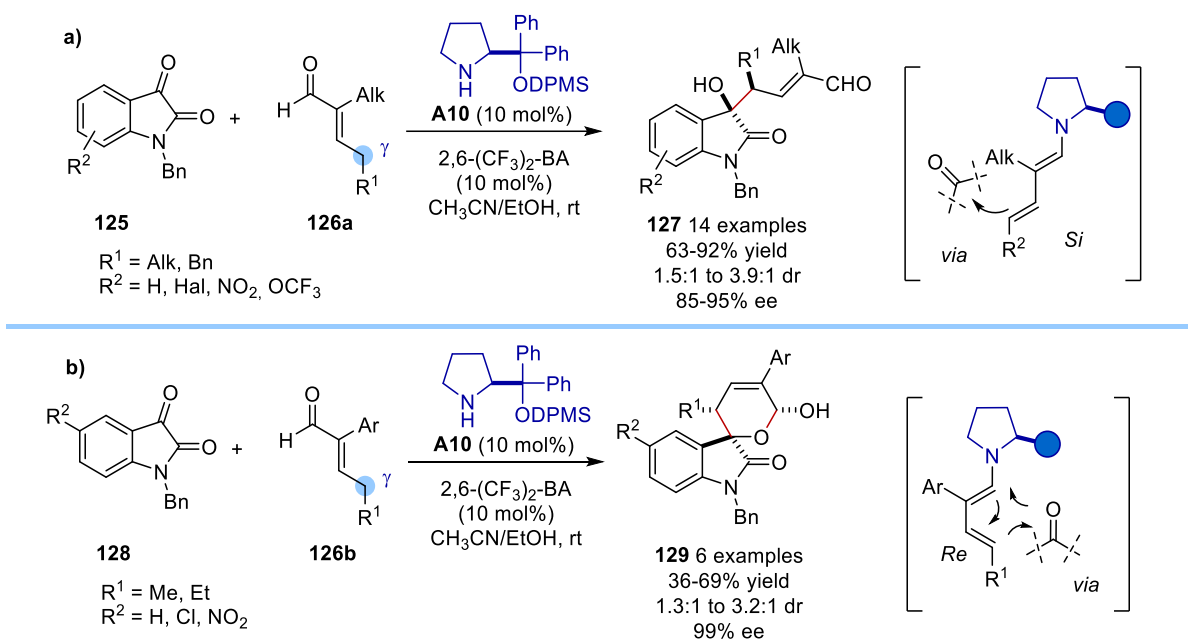
Scheme 27 Conformational equilibrium studied through NMR experiments of (a) linear and (b) α -branched enals

These results shed light not only on the importance of the α -substituent in regioselectively directing the functionalizations toward the γ -site instead of the α -position, but also in forcing the geometry of the dienamine as an important prerequisite to stereoselectively forge the distal stereocenter.

⁷⁹ Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. "Secondary amine-catalyzed asymmetric gamma-alkylation of alpha-branched enals via dienamine activation" *Helv. Chim. Acta*, **2012**, 95, 1985.

In the last decade, examples of aminocatalytic enantioselective γ -functionalization of enals have been reported, embracing important C-C forming transformations such as aldol, Michael and allylation reactions. The following paragraphs describe the relevant examples for each of these reaction classes.

In 2012, Melchiorre and co-workers reported the first example of vinylogous organocatalytic aldol reaction between alkyl-branched enals **126a** and isatins **125**, in the presence of aminocatalyst **A10**.⁸⁰ A total of 14 γ -alkylated products **127** were afforded in good yields and with high enantioselectivities. (Scheme 28, a) Interestingly, the use of α -aryl branched enals of type **126b** delivered enantiopure mixtures of isolable diastereoisomers of valuable oxindoles of type **129**. The authors rationalized these results by a hetero Diels-Alder (HAD) pathway involving (*E-s-cis-E*)-dienamines, which are coherent intermediates in justifying the pericyclic path and the observed stereochemical outcome of the reaction, even though they were not detected through NMR experiments (Scheme 28, b).

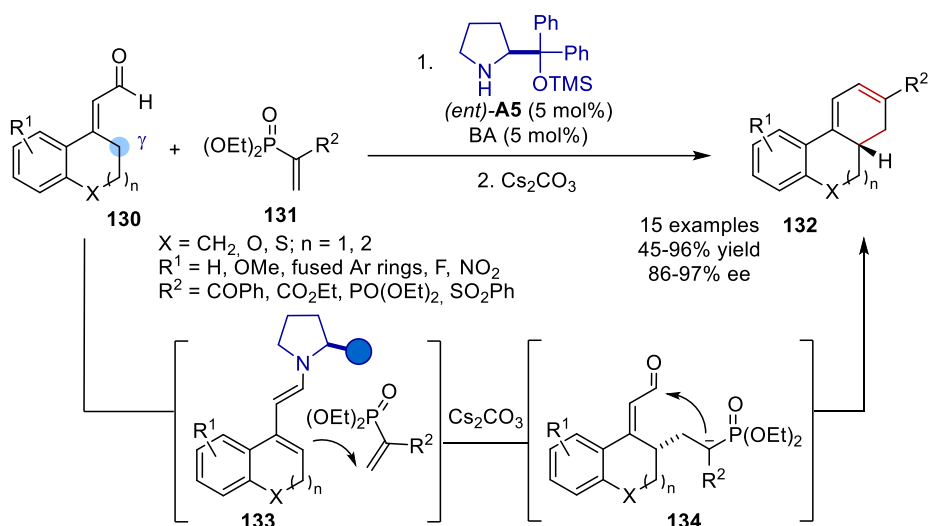


Scheme 28 First example of vinylogous aldol reaction between α -branched enals and isatins

In 2014, the Jørgensen group unveiled the possibility to use β -substituted enals as key substrates for their aminocatalytic γ -functionalization via Michael-type addition reactions.⁸¹ In details, enals **130** were involved in one-pot, two-steps cascade reactions entailing a first vinylogous Michael additions of dienamines **133** to phosphonate electrophiles **131**, followed by caesium carbonate-promoted HWE reactions to finally furnish a series of valuable products **132** in good yields and high enantioselectivities. The authors also demonstrated the possibility to exploit the same class of carbocyclic donors in formal eliminative γ,i -[4+2] cycloadditions with nitroalkenes as Michael acceptors (not shown).

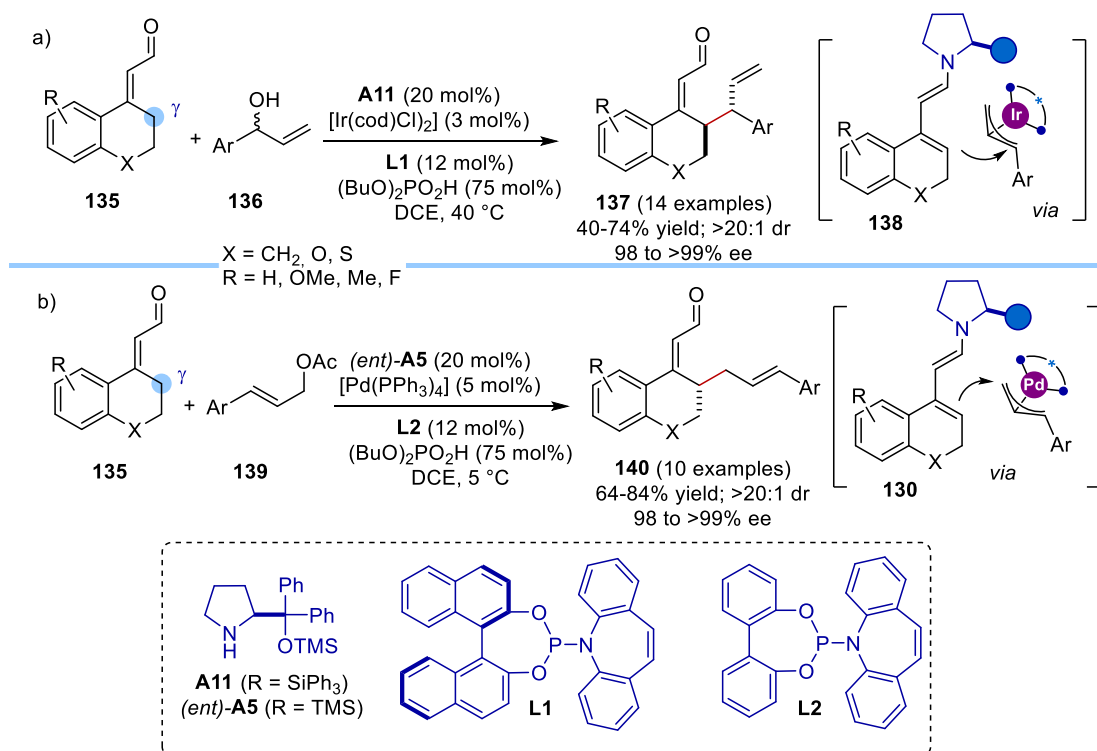
⁸⁰ Cassani, C.; Melchiorre, P. "Direct Catalytic Enantioselective Vinylogous Aldol Reaction of α -Branched Enals with Isatins" *Org. Lett.*, **2012**, *14*, 5590.

⁸¹ Donslud, B. S.; Halskov, K. S.; Leth, L. A.; Paz, B. M.; Jørgensen, K. A. "Organocatalytic asymmetric strategies to carbocyclic structures by γ -alkylation-annulation sequences" *Chem. Commun.* **2014**, *50*, 13676.



Scheme 29 Organocatalytic asymmetric γ -alkylation of β -branched enals by means of Michael addition reactions

Finally, Jørgensen and co-workers also developed synergistically catalysed asymmetric γ -allylation reactions of carbocyclic enals.⁸² The treatment of enals **135** with allyl benzyl alcohol **136** in the presence of aminocatalyst **A11** (providing the enamine **138**) and iridium-based catalyst with phosphoramidite ligand **L1** generated regio- and stereoselectively branched allylic products **137** in good yields and with excellent enantiomeric excesses (Scheme 30, a).



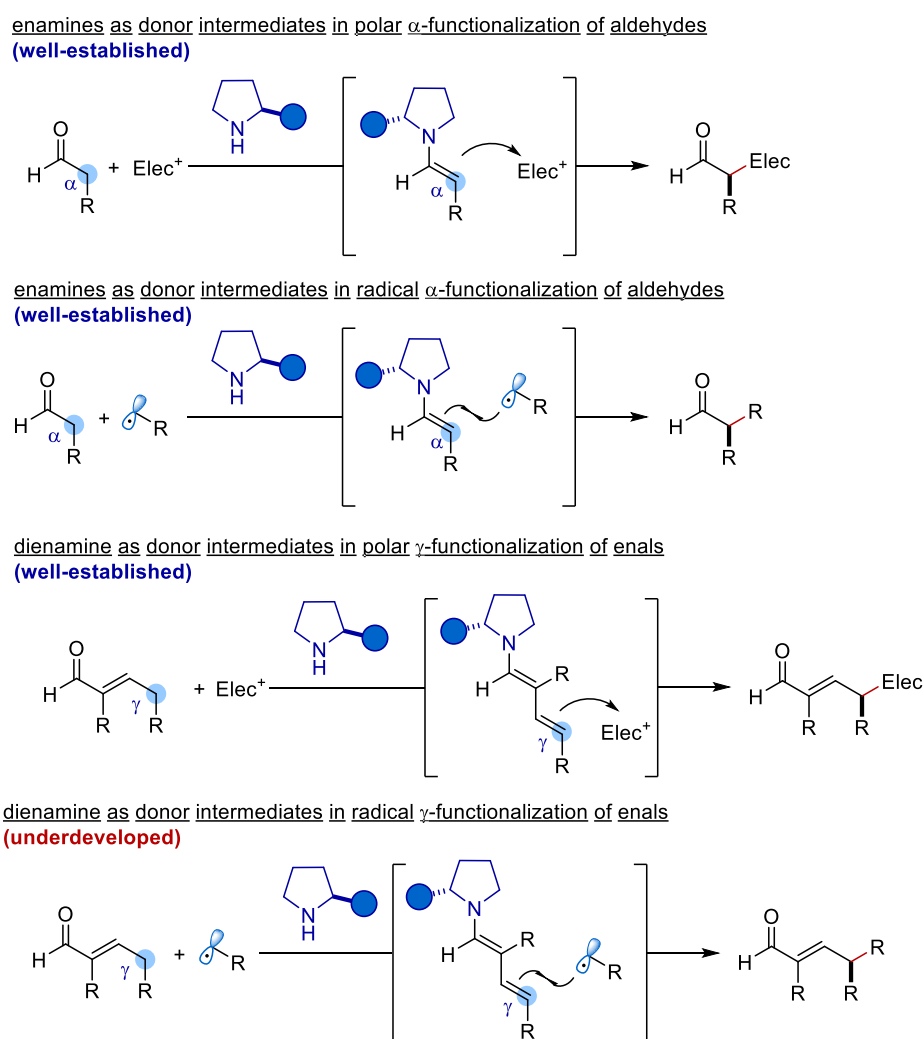
Scheme 30 Jørgensen's synergistic asymmetric γ -allylation of β -branched enals

On the other hand, the treatment of the same pronucleophiles **135** with allylic acetates of type **139** in presence of a palladium-based catalyst with achiral ligand **L2** and aminocatalyst $(ent)\text{-A5}$ afforded a series of linear allyl products **140** again in good yields and high regio- and enantioselectivities.

⁸² Næsborg, L.; Halskov, K. S.; Tur, F.; Mønsted S.; Jørgensen, K. A. Asymmetric γ -Allylation of α,β -Unsaturated Aldehydes by Combined Organocatalysis and Transition-Metal Catalysis. *Angew. Chem., Int. Ed.*, **2015**, *54*, 10193.

Interestingly, the authors demonstrated through control experiments that the linear *vs* branched selectivity was just dependant on the nature of the metal catalyst (Scheme 30, b).

Overall, during the last decades, vinylogous dienamine intermediates have emerged as important reactive platforms to target the stereocontrolled formation of stereocenters at γ -sites of suitable carbonyl precursors.⁴⁶ Concomitantly, there are no doubts about the undeniable usefulness of “not-extended” enamine catalysis as one of the most amenable catalytic activation strategies to stereoselectively functionalize the α -positions of carbonyl compounds within the polar domain.⁸³ In addition, the advent of photoredox catalysis served as a possibility to exploit enamine organocatalysis to promote radical pathways through the mediation of light, especially within the asymmetric α -functionalization of carbonyls.^{32,35,37}

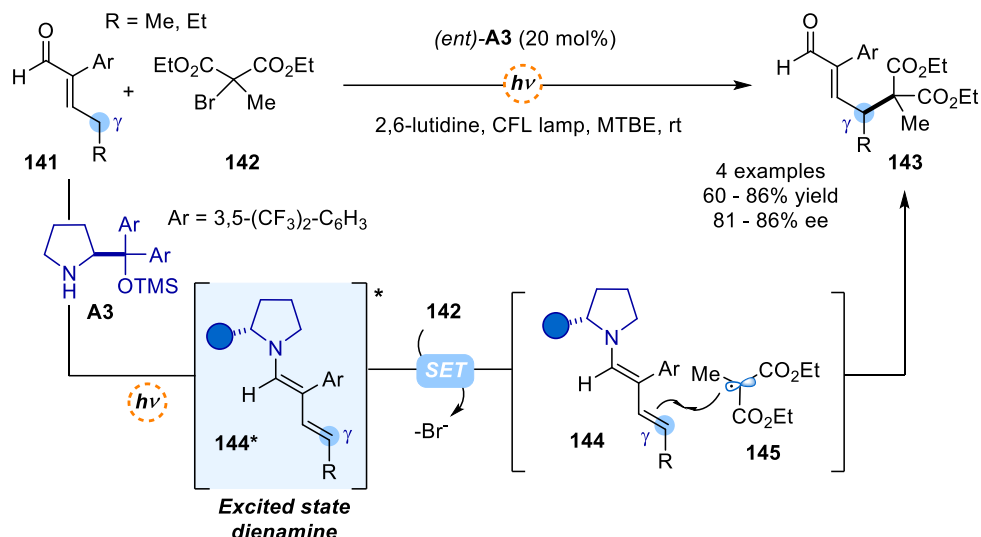


Scheme 31 Reactivity of enamine intermediates within polar and radical domains

Indeed, although several examples relying on the combination of light-mediated radical chemistry and enamine organocatalysis have been reported in the literature so far, the analogous vinylogous dienamine reactivity is still underdeveloped (Scheme 31).

⁸³ a) Mukherjee, S.; Yang, J. H.; Hoffmann, S.; List, B. “Asymmetric Enamine Catalysis” Jurberg, I. D.; Chatterjee, I.; Tannerta, R.; Melchiorre, P. When asymmetric aminocatalysis meets the vinylogy principle. *Chem. Commun.* **2013**, 49, 4869; b) List, B. “Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents” *Acc. Chem. Res.* **2004**, 37, 548.

In 2015 Melchiorre and co-workers unveiled the first and unique example of light-promoted radical reactivity in asymmetric organocatalysis exploiting the double capability of dienamines **144** in acting as radical traps while, similarly to enamines, they may generate electrophilic radicals **145** upon direct light-excitation.³⁷ Such radicals could be then trapped at the remote γ -site of the dienamine to afford final enals **143** with excellent regioselectivities and high enantioselectivities (Scheme 32; for details see Section 4.1).



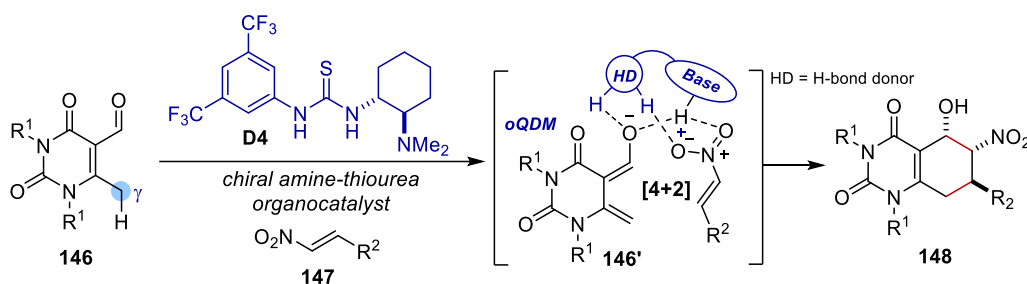
Scheme 32 Remote stereocontrol and complete γ -site selectivity within the enantioselective alkylation of enals by means of direct photoexcitation of dienamines

However, the process was restricted to the only use of tertiary bromomalonates **142** as radical precursors since the radical generation pathway was strictly dependent on the redox properties of the substrates compared to the ones of excited dienamines **144***. In this context, the application of alternative strategies for the generation of different radicals that can be trapped at remote positions of dienamine intermediates represents a new challenging synthetic field within vinylogous chemistry. In this thesis, I will show how dithiocarbamate catalysis (DTC catalysis) could be efficiently exploited as a radical generation platform to expand the regio- and enantiocontrolled radical γ -functionalization of enals.

1.6 General objectives and summary

Vinylogous reactivity is a straightforward synthetic tool to remotely functionalize molecules and increase molecular diversity. The main aim of this doctoral thesis deals with the exploration of new frontiers within the vinylogous domain, by developing new enantioselective organocatalytic transformations. The first two projects exploited the generation of transient *ortho*-quinodimethane intermediates to access novel enantiopure heterocyclic carbocycles with high appeal in terms of biological activity. The third project is based on the application of the concept of vinylogy to a light-mediated process for the discovery of new stereoselective remote functionalization of enals.

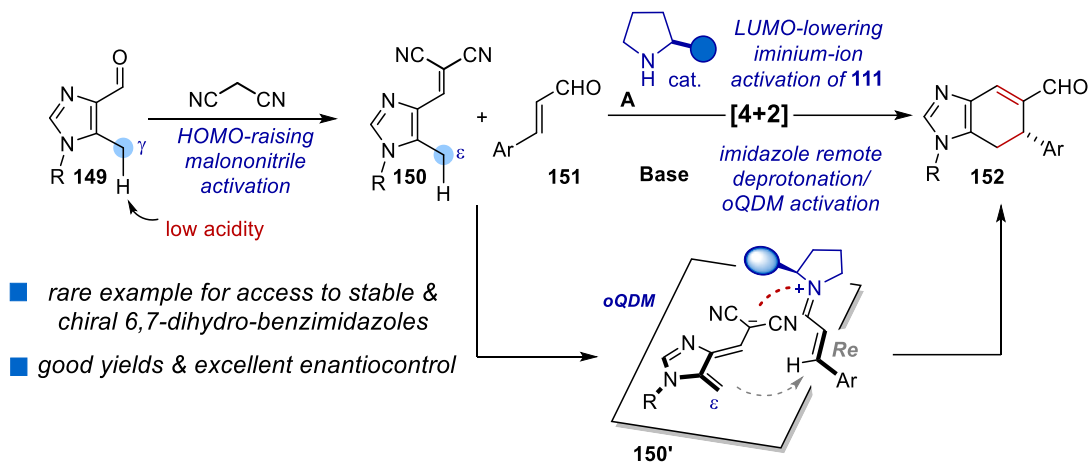
1.6.1 Organocatalytic stereoselective [4+2] cycloadditions toward chiral uracil-based carbocycles revealing antiviral bioactivity



- access to highly functionalized chiral uracil-based carbocycles
- good yields, complete diastereocontrol, high ee
- DFT calculations: unprecedented H-bond directed interactions
- antiviral bioactivity against SARS-CoV-2

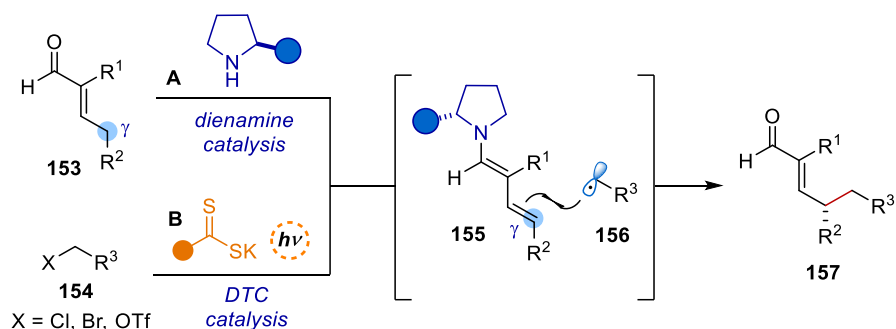
In Chapter II, an enantioselective formal [4+2] cycloaddition between vinylogous uracil-based diene precursors of type **146** and nitroolefin dienophiles **147** is described. The transformation proceeds through the challenging *in situ* generation of the dienolate *o*QDM intermediate **146'** and exploits the strategic bifunctional action of a thiourea-amine organocatalyst **D4**. A series of carbocycle-fused uracils of type **148** embedding three contiguous stereocenters were efficiently obtained with excellent diastereocontrol and good enantioselectivities. The ability to provide enantiopure products via simple one-cycle recrystallization and the possibility to further functionalize these scaffolds without losing their chiral integrity was also demonstrated. DFT calculations supported an intriguing stepwise vinylogous Michael/Henry cascade, highlighting the crucial role of the organocatalyst in triggering the dearomative formation of the *o*QDM species and orchestrating the stereochemistry of the process. Preliminary screening in cellular assays showed that some compounds of type **148** possess low-micromolar antiviral activity against SARS-CoV-2, while exhibiting low, if any, cytotoxicity.

1.6.2 Accessing enantiopure 6,7-dihydrobenzimidazoles via organocatalytic [4+2] cycloaddition reactions



In Chapter III, an unprecedented example of organocatalytic eliminative [4+2] formal cycloaddition reaction between novel imidazole-based alkylidene malononitriles **150**, functioning as γ -activatable oQDM diene precursors, and diverse enals **151**, functioning as organocatalytically activatable dienophiles, is documented. A series of *N*-protected dihydrobenzimidazoles of type **152** was efficiently obtained in one step with excellent enantioselectivities, which could be further elaborated into imidazole-containing products without losing their chiral integrity. Different challenging issues had to be faced in this endeavour, including the non-facile, remote γ -deprotonation/temporary dearomatization of the highly stable 5-methylimidazole-4-carbaldehyde precursors **149**, and cohabitation of the basic/nucleophilic imidazole ring with the amine organocatalyst. Finely merging the traceless, vinylogous HOMO-raising malononitrile activation strategy with the chiral iminium ion LUMO-lowering activation modality turned out to be a good option, efficiently consigning the unprecedented chiral heterocyclic motifs upon careful optimization of the experimental conditions.

1.6.3 Photochemical organocatalytic enantioselective radical γ -functionalization of α -branched enals



- synergistic catalysis ■ complete γ -regioselectivity ■ new disconnections
- simple alkyl halides as radical precursors (broad scope) ■ mild radical generation

In Chapter IV, the DTC catalysis was successfully merged with dienamine organocatalysis to trigger enantioselective remote γ -alkylation of α -branched enals **153** through a radical pathway, to afford a series of remotely functionalized enals of type **157**. The transformation demanded visible-light and exploited the synergistic actions of two different organocatalysts. The dithiocarbamate catalyst **B** enables the generation of radicals upon S_N2 -type activation of a great variety of commercially available primary alkyl halides **154**. Cooperatively, a prolinol-derived catalyst **A** promotes the generation of a catalytic amount of dienamines **155** from the aldehydic precursor. Such chiral dienamine traps the photogenerated radicals **156** with excellent γ -regioselectivity and good enantiocontrol. The possibilities to scale-up the process and to further synthetically manipulate the chiral catalytic products also demonstrated the usefulness of the protocol.

Chapter II

Organocatalytic stereoselective [4+2] cycloadditions toward chiral uracil-based carbocycles revealing antiviral bioactivity

2.1 Background

The naturally occurring uracil, also known as pyrimidine-2,4(1*H*,3*H*)-dione, is considered a privileged *N*-containing heterocyclic motif.¹ It plays a crucial role in establishing the RNA-based genetic code, being one of the five primary nucleobases.² Not surprisingly, uracil is a prominent pharmacophore in medicinal chemistry, adorning several structures of drugs and bioactive molecules.³ The main activities exerted by uracil-based compounds are antiviral and antitumor but recently also herbicidal, insecticidal, and bactericidal activities have emerged as non-negligible effects for this class of compound-derivatives (Figure 1, a).⁴ Moreover, the densely heteroatomic framework makes the uracil core prone to be chemically modified, especially at N1, N3, C5, and C6 sites, arising the possibility to enrich such motif with flexible aromatic/aliphatic chains and/or sugar frameworks.⁵ Moreover, it is also possible to find the uracil ring flanked with carbo- and heterocycles, which are generally flattened and C(*sp*²)-rich rings. Several examples related to the pharmacological bioactivities of the resultant fused-uracil derivatives have been reported so far, ranging from antiviral, antiallergic, antihypertensive to antitumor effects (Figure 1, b).⁶

¹ a) Mermer, A.; Keles, T.; Sirin, Y. "Recent Studies of Nitrogen Containing Heterocyclic Compounds as Novel Antiviral Agents: A Review" *Bioorg. Chem.* **2021**, *114*, 105076; b) Heravi, M. M.; Zadsirjan, V. "Prescribed Drugs Containing Nitrogen Heterocycles: An Overview" *RSC Adv.* **2020**, *10*, 44247.

² a) Arbour, C. A.; Imperiali, B. "Uridine natural products: Challenging targets and inspiration for novel small molecule inhibitors" *Bioorg. Med. Chem.* **2020**, *28*, 115661. b) Sire, J.; Quérat, G.; Esnault, C.; Priet, S. "Uracil within DNA: an actor of antiviral immunity" *Retrovirology* **2008**, *5*, 45.

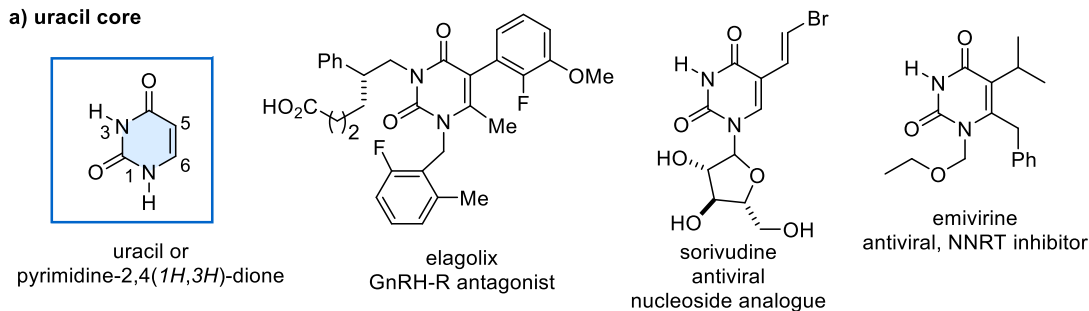
³ Ramesh, D.; Vijayakumar, B. G.; Kannan, T. "Therapeutic potential of uracil and its derivatives in countering pathogenic and physiological disorders" *Eur. J. Med. Chem.* **2020**, *207*, 112801.

⁴ a) Urits, I.; Adamian, L.; Miro, P.; Callan, J.; Patel, P. M.; Patel, M.; Berger, A. A.; Kassem, H.; Kaye, A. D.; Viswanath, O. "An Evidence-Based Review of Elagolix for the Treatment of Pain Secondary to Endometriosis" *Psychopharmacol. Bull.* **2020**, *50*, 197; b) Diasio, R. B. "Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase" *Br. J. Clin. Pharmacol.* **1998**, *46*, 1.

⁵ ZavQyalov, S. I.; Ezhova, G. I.; Kravchenko, N. E.; Kulikova, L. B.; Dorofeeva, O. V.; Rumyantseva, E. E.; Zavozin, A. G. "Natural Uracils: Synthesis and Chemical Properties" *Pharm. Chem. J.* **2003**, *37*, 337.

⁶ a) Huband, M. D.; Cohen, M. A.; Zurack, M.; Hanna, D. L.; Skerlos, L. A.; Sulavik, M. C.; Gibson, G. W.; Gage, J. W.; Ellsworth, E.; Stier, M. A.; Gracheck, S. J." In Vitro and In Vivo Activities of PD 0305970 and PD 0326448, New Bacterial Gyrase/Topoisomerase Inhibitors with Potent Antibacterial Activities versus Multidrug-Resistant Gram-Positive and Fastidious Organism Groups" *Antimicrob. Agents Chemother.* **2007**, *51*, 1191-1201; b) Parsons, A. T.; Caille, S.; Caporini, M. A.; Griffin, D. J.; Lovette, M. A.; Powazinik, W.; St-Pierre, G. "Addressing Atropisomerism in the Development of Sotorasib, a Covalent Inhibitor of KRAS G12C: Structural, Analytical, and Synthetic Considerations" *Org. Process Res. Dev.* **2022**, *55*, 20, 2892; c) Beaver, M. G.; Brown, D. B.; Campbell, K.; Fang, Y.-Q.; Ford, D. D.; Mardirossian, N.; Nagy, K. D.; Rötheli, A. R.; Sheeran, J. W.; Telmesani, R.; Parsons, A. T. "Axial chirality in the sotorasib drug substance, Part 2: Leveraging a high-temperature thermal racemization to recycle the classical resolution waste stream" *Org. Process Res. Dev.* **2022**, *26*, 9, 2636.

a) uracil core



b) fused-uracil core

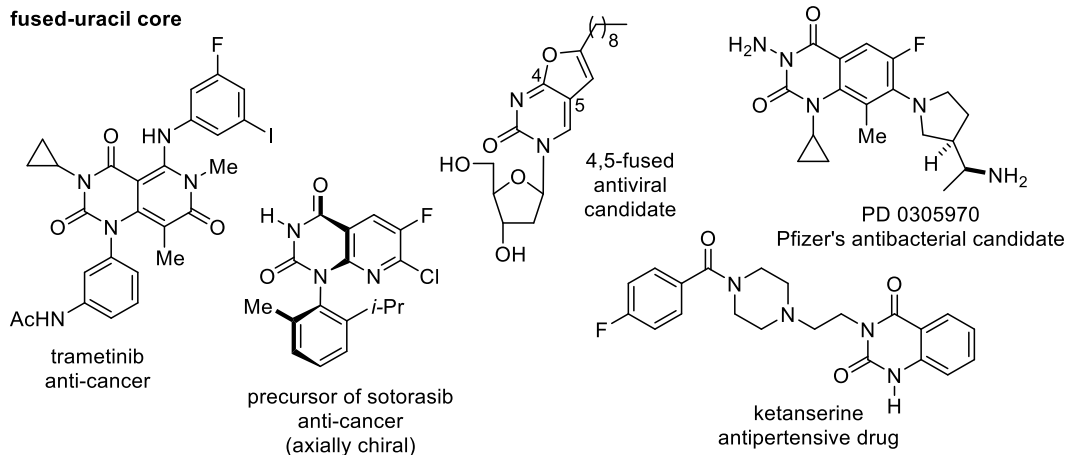
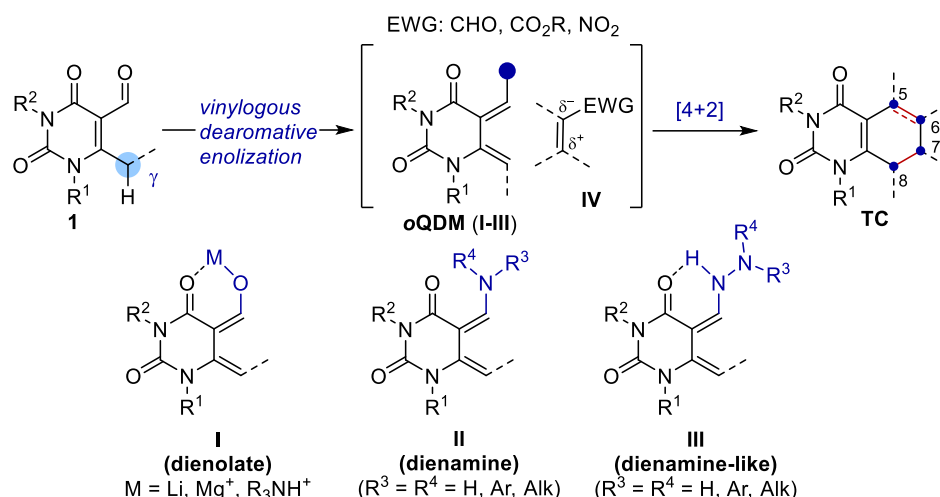


Figure 1 Examples of drug candidates containing the uracil core a), and the fused-uracil core b)

On the other hand, examples of 5,6-fused carbocyclic uracils, adorned with *in-cycle* stereogenic centres, are much rarer. Several early protocols exist where chemical access to these peculiar chiral uracil-derivatives is reported, even though in racemic formats and via non-asymmetric transformations.⁷ These early synthetic approaches invariably involve [4+2] cycloaddition reactions promoted by pre-activation of uracil pro-diene carbaldehydes of type **1**, and using stoichiometric amounts of either strong bases or primary amines (or hydrazines). Such activation methods lead to the formation of elusive and highly reactive dienolate or dienamine *o*QDM intermediates **I-III**, which then can be intercepted by electron-poor double bonds **IV** to afford the chiral, yet racemic, annulated target compounds of general formula **TC** (Scheme 1).

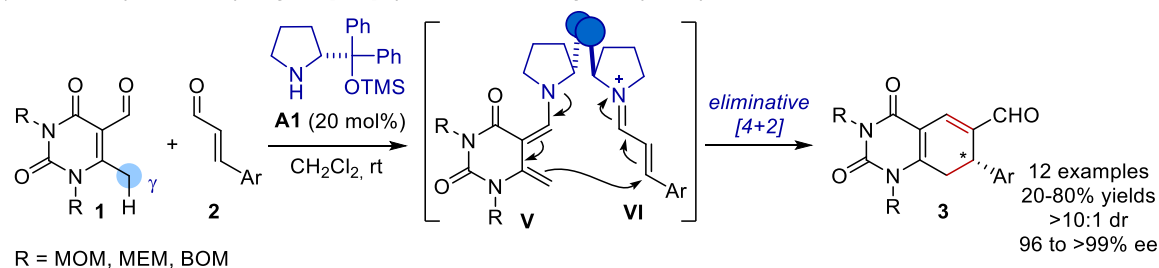
⁷ a) Senda, S.; Asao, T.; Sugiyama, I.; Hirota, K. "Cycloaddition reaction of pyrimidine-dienols with dienophiles. A new approach to quinazolines" *Tetrahedron Lett.* **1980**, 21, 531; b) Yasue, N.; Ishikawa, S.; Noguchi, M. "A Facile Generation and Stereoselective Cycloaddition Reactions of 5,6-Dihydro-5,6-bis(methylene)-2,4(1H,3H)-pyrimidinedione Intermediate" *BCSJ* **1992**, 65, 2845; c) Noguchi, M.; Sakamoto, K.; Nagata, S.; Kajigaeshi, S. A "A one-step preparation of pyrido[3,4-d]pyrimidine ring system by reaction of 5-formyl-1,3,6-trimethyl-pyrimidine-2,4(1H,3H)-dione with primary amines" *J. Heterocyclic Chem.* **1988**, 25, 205; d) Noguchi, M.; Kiriki, Y.; Ushijima, T.; Kajigaeshi, S. "The Characterization and Cycloaddition Reaction of 5,6-Dihydro-1,3-dimethyl-6-methylene-5[(substituted amino)methylene]-2,4(1H,3H)-pyrimidinediones" *BCSJ* **1990**, 63, 2938; e) Noguchi, M.; Doi, K.; Kiriki, Y.; Kajigaeshi, S. "Characterization of a Perhydro-5,6-di(methylene)-2,4-dioxypyrimidine Intermediate and its Cycloaddition Reactions Leading to Quinazoline Derivatives" *Chem. Lett.* **1989**, 18, 2115; f) Ikuno, K.; Kobayashi, T.; Harada, T.; Noguchi, M.; Kakehi, A. "Studies on fused pyrimidine derivatives. Part 14. Formation and transformation of [4 + 2] cycloadducts, cyclohepta[g]quinazoline derivatives, by the reaction of 5-(arylamino)methylene-1,3-dimethyl-6-methyleneperhydropyrimidine-2,4-diones with tropone" *J. Chem. Soc. Perkin Trans. 1* **1995**, 11, 1445.



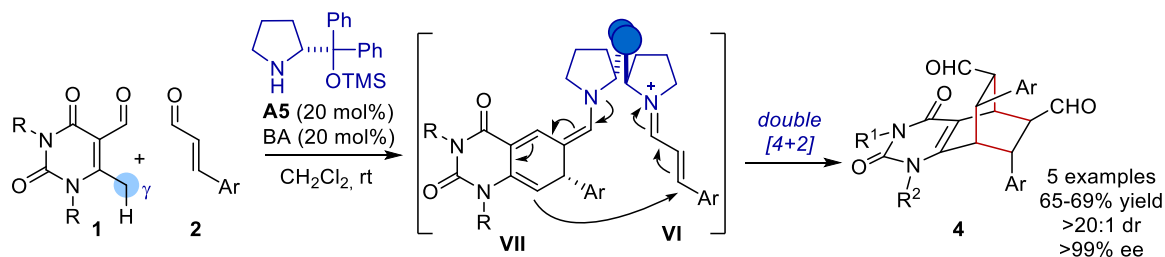
Scheme 1 oQDM-mediated [4+2] cycloaddition reactions involving uracil carbaldehydes **1**

Along this line, our group recently reported the first example of asymmetric synthesis of enantiopure uracil-fused carbocycles, by exploiting an organocatalytic chemodivergent and enantioselective [4+2] cross-cycloaddition between γ -enolizable 6-methyluracil-5-carbaldehydes **1** and cinnamaldehydes **2**.⁸ In the presence of aminocatalyst **A1**, novel bicyclic or tricyclic uracil-based carbocycles **3** and **4** were chemoselectively afforded, depending on the reaction conditions, in good yields and with excellent enantioselectivity (Scheme 2). In particular, the excess of donor **1** over the acceptor **2** favored the generation of the bicycle **3** (eq. a), while the reaction run with a ratio between substrates **1** and **2** equal to 1:3 and in presence of a catalytic amount of benzoic acid promoted the chemodivergent access to tricycles of type **4** (eq. b). Interestingly, both processes involve the generation of a catalytic amount of transient dienamine oQDM intermediates **V** as diene components in reacting with iminium ions **VI**. In the case of tricyclic compounds, a further remote enolization affords intermediate **VII**, which could behave as nucleophile for the second formal [4+2] cycloaddition with another molecule of **VI**.

a) Aminocatalytic homo-synergistic [4+2] cycloaddition leading to bicyclic systems **3**



b) Aminocatalytic homo-synergistic double [4+2] cycloaddition leading to tricyclic systems **4**

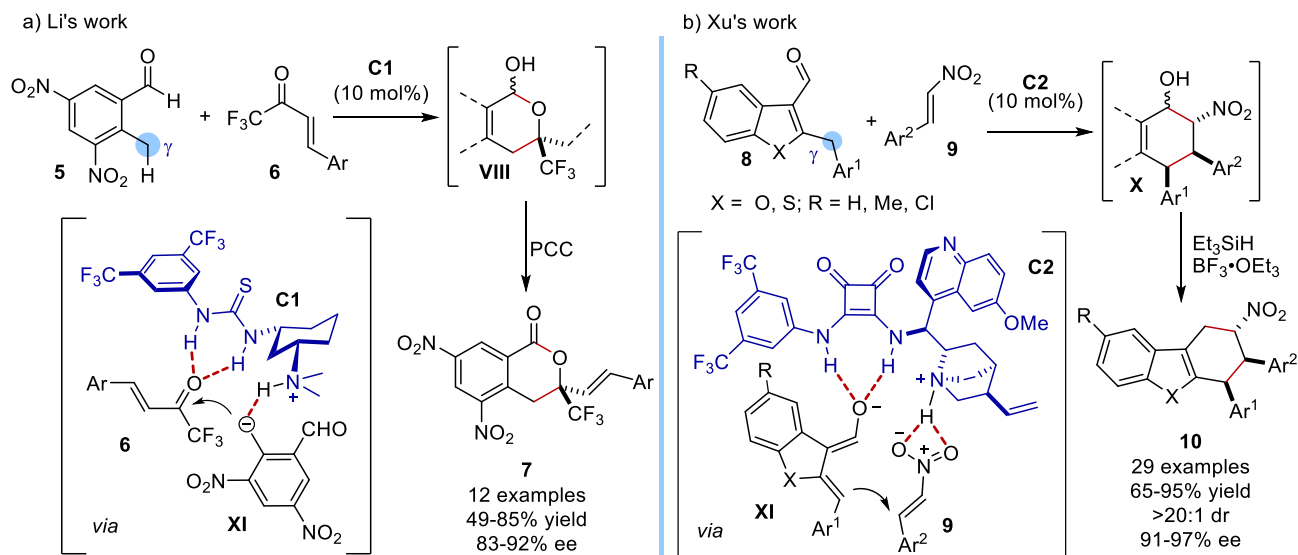


Scheme 2 Eliminative (a) and double (b) [4+2] cycloadditions developed by Zanardi and co-workers

⁸ Curti, C.; Rassu, G.; Lombardo, M.; Zambrano, V.; Pinna, L.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F. "Unlocking Access to Enantiopure Fused Uracils by Chemodivergent [4+2] Cross-Cycloadditions: DFT-Supported Homo-Synergistic Organocatalytic Approach" *Angew. Chem. Int. Ed.* **2020**, *59*, 20055.

Moreover, DFT calculations and control experiments proved a homo-synergistic catalytic approach, where two molecules of the same catalyst simultaneously activate both the nucleophilic and the electrophilic partners of the transformations.

This work furnished an important breakthrough in lighting-up the possibility to access non-racemic fused-uracil derivatives. Moreover, it represents an elegant example on how a covalent aminocatalytic activation modality can efficiently promote the formation of highly reactive *o*QDM intermediate as a diene-based synthon to be used within cycloaddition trajectories. In this context, covalent activation modalities that could be exploited to trigger the enolization of aromatic, γ -enolizable pronucleophiles have been already reasonably well-established such as (poly)enamine catalysis, NHC catalysis, and stoichiometric malononitrile activation. On the other hand, the exploitation of noncovalent activation strategies to promote analogous organocatalytic [4+2] cycloadditions have been documented so far just in two studies. In 2017, Li and co-workers developed a two-step methodology involving a [4+2] cycloaddition between dinitrotoluenaldehydes **5** as pronucleophiles and α,β -unsaturated trifluoromethyl ketones (TFMKs) **6** as dienophiles in presence of the noncovalent bifunctional organocatalyst **C1**. (Scheme 3, a).⁹ The authors proposed, as key step of the transformation, an aldol reaction between the benzylic carbanion **IX**, derived from the benzylic deprotonation of **5**, and the TFMKs **6**, where the stereoselective generation of the chiral center is governed by the organocatalyst. The subsequent hemiacetalization step (not shown) furnishes intermediate **VIII** (never isolated) which is then oxidized by one-pot addition of PCC. Overall, a total of 12 chiral 3,4-dihydrocoumarines **7** were efficiently obtained with high enantioselectivity. One year later, the Xu's group reported a beautiful work on asymmetric [4+2] cycloadditions between remotely enolizable benzothiophene(furan) carbaldehydes **8** and nitroolefins **9** under noncovalent bifunctional base-squaramide catalysis (Scheme 3, b).¹⁰



Scheme 3 [4+2] Cycloadditions developed by Liu (a) and Xu (b) by noncovalent organocatalysis

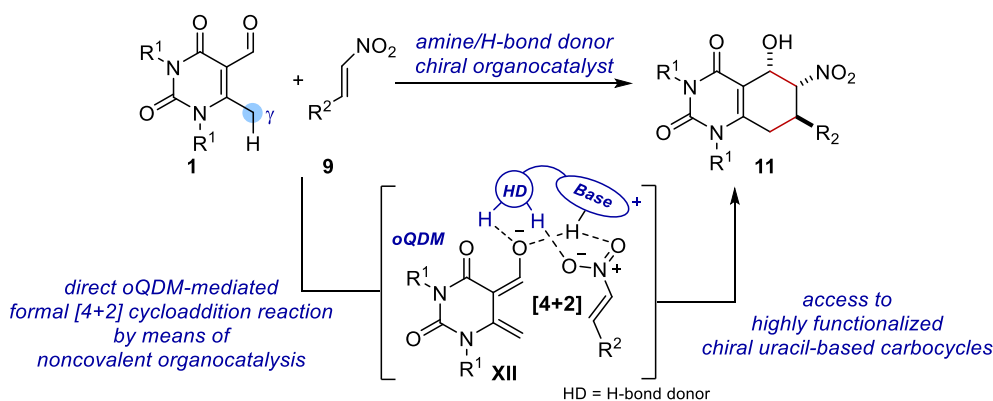
⁹ Duan, J.; Cheng, Y.; Cheng, J.; Li, R.; Li, P. Organocatalytic Asymmetric Benzylolation and Aldol-Hemiacetalization of α,β -Unsaturated Trifluoromethyl Ketones: Efficient Enantioselective Construction of 3,4-Dihydroisocoumarins” *Chem. Eur. J.* **2017**, *23*, 519.

¹⁰ Wang, Y.; Lin, J.-B.; Xie, J.-K.; Lu, H.; Hu, X.-Q.; Xu, P.-F. “Dearomative Dienolate-Mediated Catalysis: A Remote Activation Strategy for Asymmetric Functionalization of Benzylic C–H Bonds of Heteroaryl Aldehydes” *Org. Lett.* **2018**, *20*, 5835.

A series of tricyclic products of type **10** were efficiently secured as single diastereoisomers with high enantioselectivity, upon carbinol reduction of the epimeric mixtures of intermediates **X**. In this example, the authors assumed that the reaction proceeded through the base-catalysed generation of *o*QDM intermediates **XI**, which are then stereoselectively trapped by the electrophiles under the guidance of the squaramide-derived bifunctional organocatalyst **C2**.

2.2 Target of the project

Given the experience of the group in synthesizing and managing the reactivity of uracil-based vinylogous pronucleophile **1** and inspired by the precedents by Liu and Xu, the target of this project was to demonstrate the possibility to enlarge the applicability of noncovalent organocatalytic approach to the *o*QDM-mediated cycloaddition reactions (Scheme 4). In particular, the careful choice of a bifunctional amine/H-bond donor organocatalyst could allow the challenging dearomative vinylogous enolization of **1** to afford a transient uracil-based *o*QDM dienolate **XII**, which can then engage in [4+2] cycloaddition reactions with nitroolefins **9**. The bifunctional organocatalyst would act as a competent tool, enabling the activation of both reacting partners, and being responsible for the remote deprotonation of the uracil-derived pronucleophiles, while warranting stereocontrol via a putative transition state dominated by tight non-covalent interactions of both the electrophilic nitro-styrene **9** and the dienolate uracil intermediate **XII**. Such synthetic approach can open the way to a direct and highly diastereoselective entry to novel and potentially bioactive enantioenriched uracil-based carbocycles, with three contiguous stereocenters of type **11**.

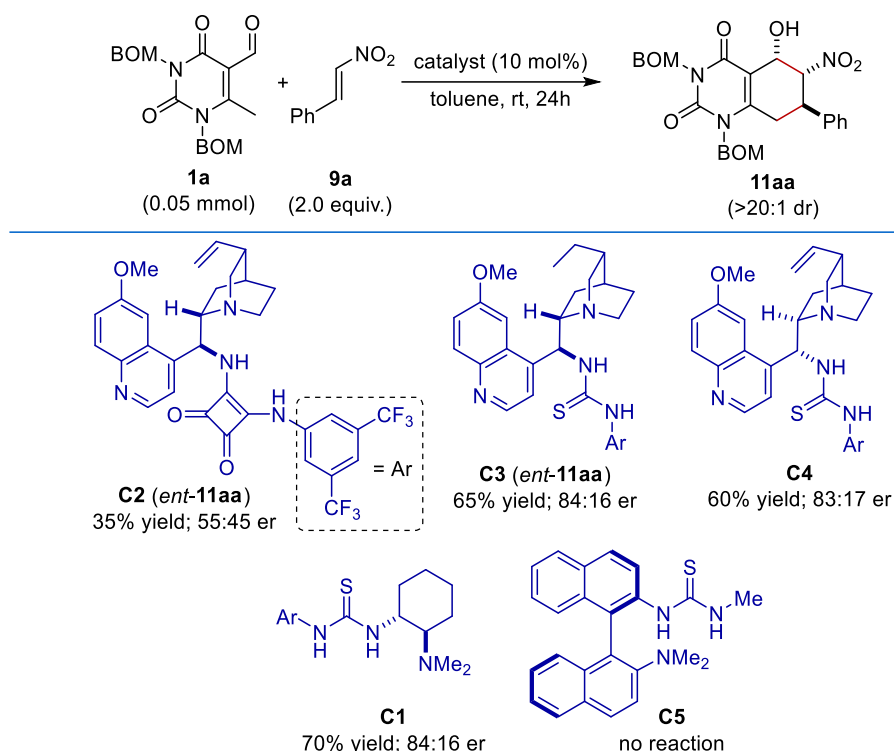


Scheme 4 Aim of this project: development of organocatalysed [4+2] cycloadditions to access highly functionalized chiral uracil-based carbocycles

2.3 Results and discussion

2.3.1 Proof of concept and reaction optimization

We set our investigation treating N^1, N^3 -dibenzyloxymethyl-substituted- (alias di-BOM) 6-methyluracil-5-carbaldehyde **1a** with *trans*- β -nitrostyrene **9a**, in toluene, in the presence of the bifunctional squaramide-based organocatalyst **C2** already used by Xu in his previous work. Pleasingly, after 24 hours at room temperature, the desired cycloadduct (*ent*)-**11aa** was obtained, though in moderate yield (35%) and as an almost racemic mixture (55:45 er). Noteworthy, the reaction furnished the desired product directly as a single diastereoisomer (>20:1 dr). Once the feasibility of the reaction was demonstrated, we started the optimisation of the reaction conditions, eager to improve both the efficiency and the enantioselectivity of the process through the screening of a series of bifunctional organocatalysts **C1-C5** (Scheme 5).



Scheme 5 Proof of concept and catalyst screening

Notably, apart from the Wang's catalyst **C5** which failed to afford the desired product, the other thiourea-amine catalysts **C1**, **C3** and **C4** furnished **11aa** in improved yields (60-70%) and, again, as a single diastereoisomer (dr >20:1). Concerning the enantioselectivity of the transformation, cinchona-thiourea catalyst **C4** provided the chiral product **11aa** in a promising 83:17 er. Consistently, dihydroquinine thiourea **C3** yielded comparable results in terms of conversion and dr, providing the enantiomer *ent*-**11aa** with a promising 16:84 er. The best yield was obtained by performing the reaction with Takemoto's catalyst **C1**, that consigned the product with a good enantiocontrol (84:16 er) and an improved efficiency (70% yield). Given these results, we were attracted by the possibility to establish the crucial role of the specific double functionality of thiourea-amine catalyst in dictating both the reactivity and the stereocontrol of the process; thus, we performed some control experiments (Table 1).

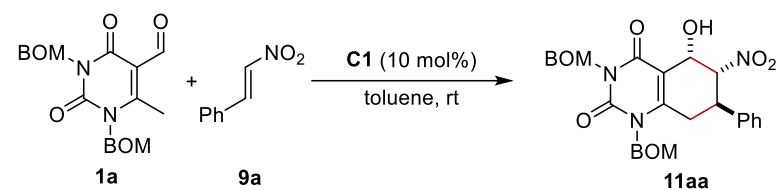
Table 1. Control experiments to investigate the role of the bifunctional catalyst

Entry ^[a]	Catalyst	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	C1	70	>20:1	84:17
2	-	no reaction	nd	nd
3	Et ₃ N	71	>20:1	50:50
4	C6	no reaction	nd	nd
5	C7	30	>20:1	52:48
6	C8	no reaction	nd	nd

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol), **9a** (2 equiv.) and the surveyed catalyst (10 mol%) in toluene (0.07 M) at rt for 24h. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral-HPLC analysis. nd = not determined

The reaction without the catalyst did not show any reactivity (entry 2) while the presence Et₃N (entry 3) promoted high diastereocontrol (dr >20:1), providing product **11aa** in a good 71% isolated yield. The achiral thiourea **C6** (entry 3) resulted completely inert, thus highlighting the need of a basic functional group to promote the γ -enolization of the aldehyde **1a**. Besides, (+)-quinidine **C7** (entry 5) furnished an almost racemic mixture of **11aa** again as a single diastereoisomer (er 52:48) and in a low 30% yield. This latter result showcased the importance of the thiourea moiety in governing the accommodation of the reactants within the transition state of the reaction. Finally, aware of the possibility to activate the aldehyde **1a** also via an aminocatalytic approach from the precedent work of our group,⁸ we decided to test the pyrrolidine-thiourea catalyst **C8** (mixed covalent/noncovalent activation), and no reactivity was observed even in this case. Overall, these results suggested the crucial importance of the co-presence of both tertiary amine and thiourea moieties within the catalyst to render the reaction feasible. We selected Takemoto's catalyst **C1** (entry 1) as the best candidate to be employed for further optimization screenings.

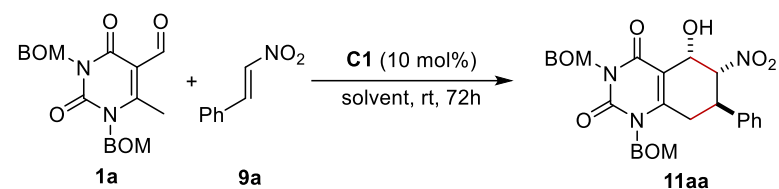
During the initial catalysts screening (Scheme 5), we observed that, after 24 hours, the reaction did not reach complete conversion. Thus, we decided to investigate the effect of the reaction time, carrying out the reaction until the complete conversion of the aldehyde **1a** (Table 2).

Table 2. Screening of reaction time and work-up methods


Entry ^[a]	Method ^[b]	Time [h]	Yield [%] ^[c]	dr ^[d]	er ^[e]
1	1	24	70	>20:1	84:16
2	1	72	77	>20:1	85:15
3	1	120	77	>20:1	84:16
4	2	72	78	>20:1	85:15

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol), **9a** (2 equiv) and catalyst **C1** (10 mol%) in toluene (0.07 M) at rt. Under the indicated reaction time, the reactions were processed according to the indicated methods. ^[b]**Method 1**: the resulting mixture was concentrated in vacuo and the residue was diluted with H₂O and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography; **Method 2**: the reaction mixture was directly subjected to flash chromatography. ^[c]Isolated yields. ^[d]Determined by ¹H NMR analysis of the crude reaction mixture. ^[e]Determined by chiral-HPLC analysis.

However, we realized that after 72 hours the reaction lingered in a sort of equilibrium that hampered any further conversion. Since no differences in terms of yield were observed by prolonging the time to 120 hours (entry 3) if compared to 72 hours (entry 2), we elected this latter as the optimal reaction time. Interestingly, the time of the reaction did not impact on the enantioselectivity of the transformation. Finally, as we could not find substantial differences in terms of efficiency and enantioselectivity using different work-up procedures (entry 2 vs 4), we decided to avoid the wasteful extraction step, directly subjecting the reaction crude mixture to chromatographic separation. We then moved to the screening of the solvent (Table 3).

Table 3. Screening of the solvent


Entry ^[a]	Solvent	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	toluene	78	>20:1	85:15
2	xylene	84	>20:1	87:13
3	CH ₂ Cl ₂	75	>20:1	76:24
4	EtOH	90	>20:1	55:45
5	THF	78	>20:1	71:29

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol, 1 equiv.), **9a** (0.1 mmol, 2 equiv.) and catalyst **C1** (10 mol%) in the solvent (0.07 M) at rt for 72h. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral-HPLC analysis.

Aprotic moderately polar solvents such as CH₂Cl₂ (entry 3) and THF (entry 5) consigned the cycloadduct in good yields but at expense of enantiomeric purity. Interestingly, ethanol (entry 4) led to generation of the product in an almost quantitative yield (90%), yet with a dramatic collapse of enantioselectivity (55:45 er). Probably, the polar and protic properties of this solvent put it in a competitive-equilibrium with the catalyst in coordinating the reactants and also transition state

through H-bond interactions, thus hampering the enantio-discrimination of the transformation. On the other hand, the reaction carried out in xylene (entry 2) provided slightly better results than toluene both in terms of yield and er. Therefore, we elected xylene as the solvent for the subsequent optimization screening involving the catalyst loading (Table 4).

Table 4. Screening of the catalyst loading

Entry ^[a]	C1 [x mol%]	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	10	84	>20:1	87:13
2	1	20	>20:1	87:13
3	20	86	>20:1	88:12

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol), **9a** (2 equiv.) and catalyst **C1** (x mol%) in xylene (0.07 M) at rt for 72h. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral-HPLC analysis.

Lowering the catalyst loading to 1 mol% (entry 2) was deleterious for the efficiency of the reaction, even though the enantioselectivity of the reaction did not suffer any decrease (20% yield, 87:13 er). Moreover, since raising the loading up to 20 mol% (entry 3) did not improve the transformation outcome, we decided to maintain 10 mol% as the best loading for the process. We then moved to the screening of the reaction temperature as a further parameter to be investigated (Table 5).

Table 5. Screening of the reaction temperature

Entry ^[a]	Temperature [°C]	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	23	84	>20:1	87:13
2	0	71	>20:1	84:16
3	-30	65	>20:1	81:19
4	60	63	>20:1	85:15

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol), **9a** (2 equiv.) and catalyst **C1** (10 mol%) in xylene (0.07 M) for 72h at the indicated temperature. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral-HPLC analysis.

Lowering the temperature to 0 °C (entry 2) and to -30 °C (entry 3) did not influence the enantioselectivity of the process, but negatively impacted on the efficiency of the reaction (from 84% at rt to 71% and 65% yield at 0°C and -30°C, respectively). When the reaction was performed at higher temperature (60 °C), cycloadduct **11aa** was provided with a similar er (85:15) as a single diastereoisomer (dr >20:1), albeit in a lower yield (63%, entry 4 vs entry 1). Thus, we decided to explore the effect of both reactants stoichiometry and concentration at room temperature (Table 6). We observed that lowering the loading of nitrostyrene **9a** in an equimolar ratio with **1a**, resulted in a better enantioselectivity of the process from 87:13 to 91:9 (entry 1 vs 2). We rationalized this result

envisaging that these new conditions could discourage the reaction between the *o*QDM dienolate and the non-activated electrophile **9a**.

Table 6. Screening of reactants stoichiometry and concentration

Entry ^[a]	1a:9a	Concentration [M]	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	1:2	0.07	84	>20:1	87:13
2	1:1	0.07	85	>20:1	91:9
3	1.5:1	0.07	77	>20:1	91:9
4 ^[e]	1:1	0.07	86	>20:1	91:9
6	1:2	0.04	49	>20:1	90:10
7 ^[f]	1:1	0.04	35	>20:1	92:8

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using 0.05 mmol of the limiting reactant **1a** or **9a** and catalyst **C1** (10 mol%) in xylene (0.07 M or 0.04 M referred to the limiting reactant) for 72 h at room temperature. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral-HPLC analysis. ^[e]The reaction was performed using **C1** (20 mol%). ^[f]The reaction was performed at 60 °C for 120 h.

Consistent results were obtained increasing the **1a:9a** ratio to 1.5:1 (entry 3) and also concomitantly increasing the **C1** loading to 20 mol% (entry 4). Entries 6 and 7 showed that higher dilution of the reaction mixture (referred to the limiting reagent) maintained similar enantiomeric ratios of the product, while penalizing the overall efficiency. Finally, we tested several additives, and the results are shown in Table 7.

Table 7. Screening of additives

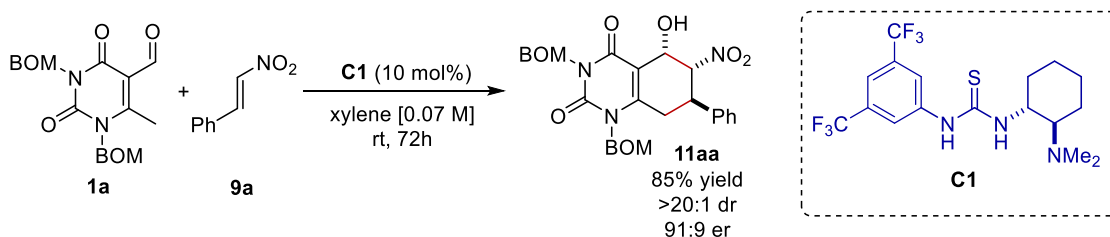
Entry ^[a]	Additive [x mol % or y% v/v]	Yield [%] ^[b]	dr ^[c]	er ^[d]
1	-	85	>20:1	91:9
2	TFE (10 mol%)	33	>20:1	90:10
3	AcOH (10 mol%)	40	>20:1	79:21
4	BA (10 mol%)	43	>20:1	91:9
5	2-Br-BA (10 mol %)	19	>20:1	68:32
6	4-Me-BA (10 mol%)	44	>20:1	73:27
7	H ₂ O (10 mol%)	63	>20:1	77:23
8	KI (50 mol%) in H ₂ O (50% v/v)	80	>20:1	89:11

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **1a** (0.05 mmol), **9a** (1 equiv), catalyst **C1** (10 mol%) and the additive (x mol%) in xylene (0.07 M) for 72 h at room temperature. ^[b]Isolated yields. ^[c]Determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by chiral HPLC analysis. ^[e]The reaction was performed at 60 °C. TFE = trifluoro ethanol; AcOH = acetic acid; BA = benzoic acid.

During the survey, a dramatic impact of the additives was observed in terms of enantioselectivity. Whereas TFE (trifluoroethanol), acetic acid and benzoic acid preserved the enantiomeric ratio of the transformation, *ortho*- and *para*- substituted benzoic acids afforded less enantioenriched cycloadducts. In any case, all acidic additives promoted a significant pauperization in terms of efficiency. The addition of 10 mol% water (entry 7) resulted in a yield decrease to 63% with concomitant drop of the enantioselectivity. Curiously, the reaction performed in a 50% (v/v) of H₂O as co-solvent, provided the desired product in higher yield (83%) but, unfortunately, with lower er. Finally, the presence of an aqueous KI solution (entry 8), gave almost comparable results with respect to the entry 1. We concluded that the addition of additives did not afford considerable improvements to the reaction.

Although through this effort-demanding parameters survey we managed to increase the efficiency of the process, we were not able to get excellent levels of enantiocontrol. A glance to all performed experiments convinced us that the main issue of this transformation might depend on the presence of a parallel reaction where the non-activated acceptors could also be attacked by the dienolate, thus resulting in partial generation of the products in a racemic format. On the other side, different competitive pathways related to different activation modalities of the organocatalyst and leading to opposite stereochemical outcome could also be operative, resulting in not-excellent enantiocontrol (*vide* Section 2.3.3).

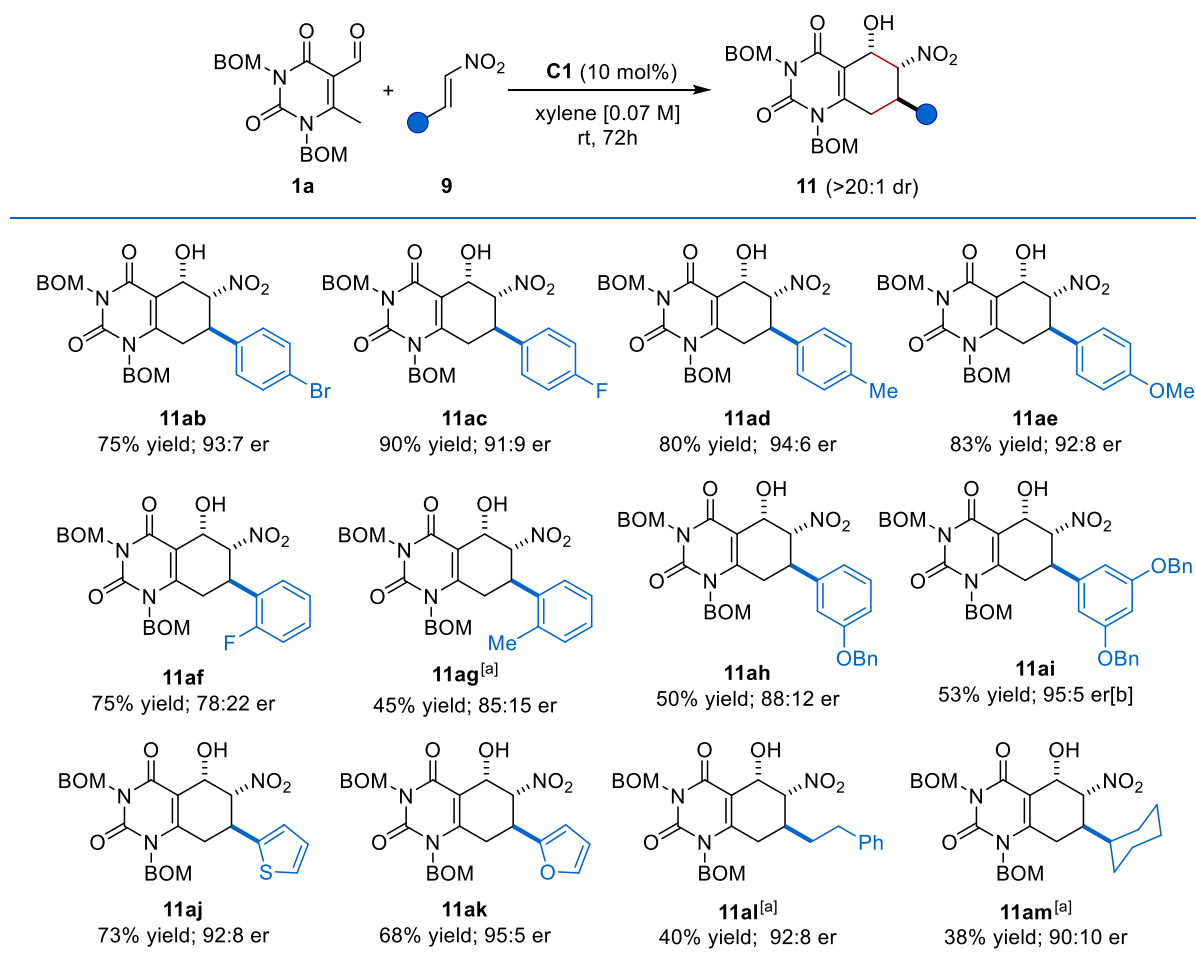
Overall, the best conditions were found by treating **1a** and **9a** (1:1 molar ratio) with 10 mol% Takemoto's catalyst **C1** in 0.07 M xylene, at room temperature for 72 hours, affording the desired cycloadduct **11aa** in 85% isolated yield, as a single diastereoisomer with 91:9 er (Scheme 6).



Scheme 6 Model [4+2] cycloaddition between **1a** and **9a** performed under the optimized reaction conditions

2.3.2 Scope of the reaction, enhancement of enantioenrichment by recrystallization and synthetic elaborations

With the optimized conditions in hand, the scope of the cycloaddition was then evaluated, starting from the variation of the electrophile (Scheme 7). The reaction between protected uracil carbaldehyde **1a** and *para*-substituted nitroolefins with different electronic nature installed on the aryl moiety **9b-9e** proved to be viable, providing the corresponding uracil-based cycloadducts **11ab-11ae** in generally good-to-high isolated yields and with good enantioselectivities (75-90% yields, 91:9-94:6 er). On the other hand, for *ortho*- and *meta*-substituted acceptors **9f-i**, inferior results in terms of efficiency and/or enantioselectivity were obtained. In the case of 2-fluoro derivative **9f**, the corresponding adduct **11af** was isolated in a 75% yield, but at the expenses of enantioselectivity (78:22 er). With bulky 3-benzyloxynitrostyrene **9h** and 3,5-dibenzyloxynitrostyrene **9i**, the reaction resulted highly enantioselective but unfortunately less efficient (50% and 53% yields; 88:12 and 95:5 er, respectively). Notably, heterocyclic nitroolefins **9j** and **9k** afforded the corresponding cycloadducts **11aj** and **11ak** in 73% and 68% yields, and 92:8 and 95:5 er. We also investigated the reactivity with notoriously inert aliphatic acceptors such as (*E*)-4-phenyl-1-nitrobutene (**9l**) and (*E*)-(2-nitrovinyl)cyclohexane (**9m**). Pleasingly, the reactions performed at 60 °C furnished the corresponding products **11al** and **11am** in 40% and 38% yields and similar enantiomeric ratios (92:8 and 90:10 er). Remarkably, during all the survey of the electrophile, all reactions proved to be completely diastereoselective, regardless of the substitution patterns of the substrates.



Scheme 7 Scope and limitations of nitroolefins **9**. ^[a]Reaction run at 60 °C

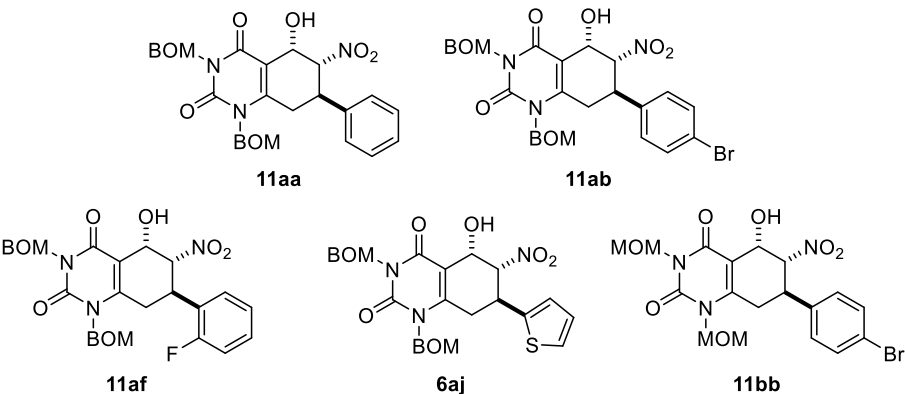
We next evaluated the variation of the uracil carbaldehydes **1** that could participate in the [4+2] cycloaddition process (Scheme 8), testing several N^1, N^3 -homoprotected uracil derivatives featuring either the methoxymethyl- (MOM, **1b**), methoxyethoxymethyl- (MEM, **1c**), or trimethylsilylethoxymethyl (SEM, **1d**) groups. In line with the dibenzyloxymethyl (di-BOM) uracil **1a**, the reactions with pronucleophiles **1b** and **1c** consigned the corresponding uracil-derived carbocycles **11ba**, **11bb**, **11be** and **11cb** in moderate-to-good yields and high enantioselectivities as single diastereoisomers (up to 88% yield and up to 94:6 er). Pleasingly, diMOM-protected uracil **1b** proved to be a viable substrate for the [4+2] cycloaddition with aliphatic nitroalkene **9m**, affording cycloadduct **11bm** in a 38% isolated yield and with 88:12 er. Finally, 1,3-diSEM product **11db** was obtained in 50% yield and 85:15 er, performing the reaction between the pronucleophile **1d** and brominated nitroolefin **9b**. The reactivity of N^1, N^3 -alkyl-substituted pronucleophiles was also evaluated with dimethyl-substituted uracil carbaldehyde **1e** that consigned the corresponding product **11ea** more efficiently than the dibenzyl compound **11fb** (52% vs 35% yields). On the other hand, cycloadduct **11fb** could be provided in higher er (88:12 vs 68:32 er). The reaction performed using N -unprotected 6-methyluracil-5-carbaldehyde **1g** resulted completely inert, highlighting the fundamental role of the nitrogen protecting group in promoting the reactivity of uracil carbaldehydes. Finally, pro-stereogenic 6-ethyl- and 6-phenylethyl uracil pronucleophiles **1h** and **1i** failed to furnish the corresponding products when combined with the acceptor **9a**, even at higher temperature.

Scheme 8 Scope and limitations of pronucleophiles **1**

The absolute configuration of all products **11** was assigned by analogy with the brominated derivative **11bb**, whose (5*S*,6*R*,7*R*) chiral arrangement was unambiguously ascertained by X-ray crystallographic analysis of a suitable crystal, in collaboration with Prof. Giorgio Pelosi from University of Parma (see Experimental part for details). Finally, we performed the model reaction between **1a** and **9a** on a 7×-scale, which proceeded smoothly, and affording product **11aa** as a single diastereoisomer (>20:1 dr) in a 78% yield (0.27 g) and with a preserved 90:10 er. This result demonstrated that this method is amenable to synthetically useful applications.

During both optimization and scope surveys, we always observed that all tested reactions ended up as heterogeneous mixtures, where the precipitate usually resulted in a near racemic mixture of the product. This peculiar feature led us to study the possible enantioenrichment of the catalytic enantioenriched cycloadducts **11** by recrystallization technique. As reported in Table 8, a small screening was performed. We started from product **11aa** obtained from the model catalytic reaction, that was provided in 91:9 er (Scheme 6). The recrystallization of such compound from a mixture of hexane and dichloromethane at reflux (method A) allowed the separation of a solid fraction and a filtrate. The evaporation of this latter allowed isolation of the almost enantiopure cycloadduct **11aa** in a good 75% yield (entry 1). Comparable results were obtained using anhydrous ethanol as solvent for the recrystallization (entry 2, method B), and for other compounds such as **11ab**, **11af**, and **11aj** (entries 3–5).

Table 8 Recrystallization procedures and production of enantiopure products **11**

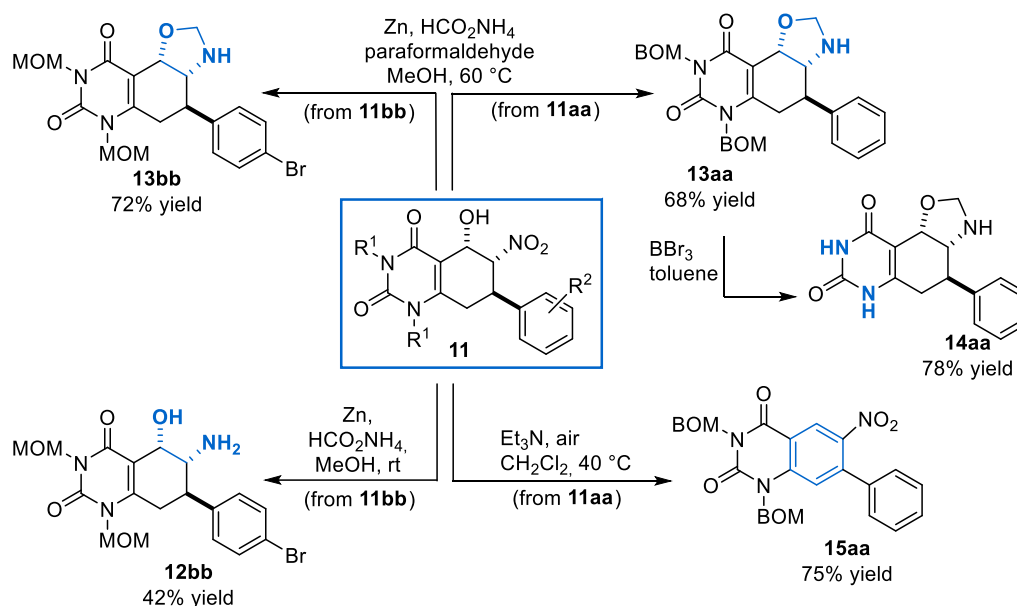
					
Entry	11	Original er ^[a]	Method ^[b]	Yield [%] ^[c]	er ^[d]
1	11aa	91:9	A	75	>99:1
2	11aa	91:9	B	78	>99:1
3	11ab	93:7	A	66	>99:1
4	11af	78:22	A	20	>99:1
5	11aj	98:2	A	78	99:1
6	11bb	91:9	B	55	>99:1 ^[e]
7	11aa	-	C	65	>99:1

^[a]Enantiomeric ratios of the indicated compounds **11** obtained as reported in Schemes 7–8. ^[b]**Method A**: dissolution of isolated, pure **11** in a mixture of hexane/CH₂Cl₂ at reflux, then slow cooling to rt. **Method B**: dissolution of isolated, pure **11** in anhydrous EtOH at reflux, then slow cooling to rt. **Method C**: dissolution of the reaction crude in EtOH at reflux, then slow cooling to rt. ^[c]Isolated yields. ^[d]Determined by chiral-HPLC analysis. ^[e]er of the precipitate fraction.

Interestingly, in the case of diMOM-protected cycloadduct **11bb**, the enantiopure fraction was the precipitate rather than the filtrate (entry 6). Overall, virtually enantiopure products could be obtained after one single cycle of recrystallization (>99:1 enantiomeric ratios). Importantly, we also demonstrated the possibility to provide enantiopure products directly from the crude reaction mixture.

As proof of this concept, the crude mixture of the reaction affording **11aa** was concentrated and subsequently dissolved in ethanol at reflux (entry 7, method C). The precipitate consisted of pure racemic **11aa**, whereas the filtrate furnished enantiopure **11aa** in a 65% isolated yield.

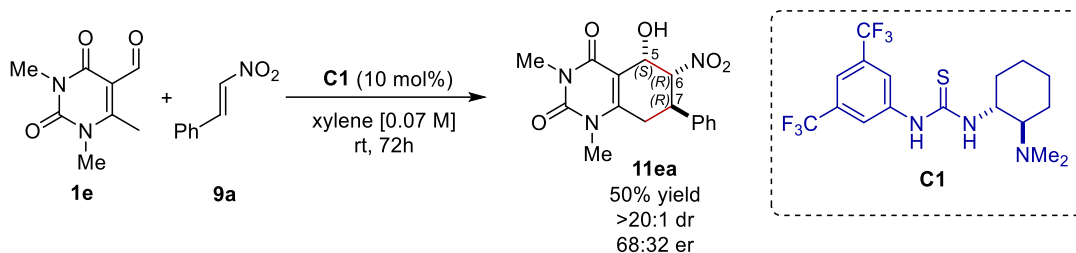
One synthetic benefit of this methodology is the possibility to obtain carbocyclic uracils **11** featuring high functional group wealth and, hence, amenable for further useful synthetic transformations. Scheme 9 shows how cycloadducts **11aa** and **11ab** could be readily manipulated into valuable derivatives. First, after several attempts (i.e. hydrogenation with Pd/C or Raney Ni, transfer hydrogenations with iron and HCl, and triethylsilane with DIPEA or Pd/C), we managed to reduce the nitro-group by treating diMOM- and diBOM-protected uracil scaffolds **11bb** and **11aa** with zinc, ammonium formate and paraformaldehyde. The corresponding chiral tricyclic *N,O*-acetals **13bb** and **13aa** were obtained in good yields (72% and 68%, respectively). Notably, reduction of **11bb** proved to be still viable also removing paraformaldehyde as trapping agent, furnishing the amino alcohol **12bb** in a moderate 42% yield. Treatment of **13aa** with BBr₃ allowed selective removal of the benzyloxymethyl groups, providing the corresponding more hydrophilic *N*¹,*N*³-deprotected derivative **14aa** in a 78% yield. Finally, although carbocycles of type **11** resulted stable to air oxidation at room temperature for months, the addition of Et₃N to **11aa** triggered a clean aromatization of the system, efficiently leading the quinazolindione **15aa** in a 75% isolated yield.



Scheme 9 Functionalization of enantioenriched carbocycle-fused uracil derivatives **11**

2.3.3 DFT-supported mechanistic insights

The full mechanism of the process was investigated through an in-depth DFT-based study,¹¹ performed by Prof. Marco Lombardo from University of Bologna. As a model reaction for our investigation, we selected the one with the most “computing-friendly” starting structures (Scheme 10). In particular, the reaction between 1,3,6-trimethyluracil-5-carbaldehyde **1e** and *trans*- β -nitrostyrene **9a** in the presence of (*R,R*)-**C1** consigned the corresponding uracil-based carbocycle (*5S,6R,7R*)-**11ea** in a 50% isolated yield and a moderate 68:32 er (Scheme 3). Although this transformation showed the lowest enantioselectivity when compared to the previous entries in Schemes 7 and 8, we envisaged it as a good reaction probe to validate our model even in a process with diverse competing kinetic pathways involved.



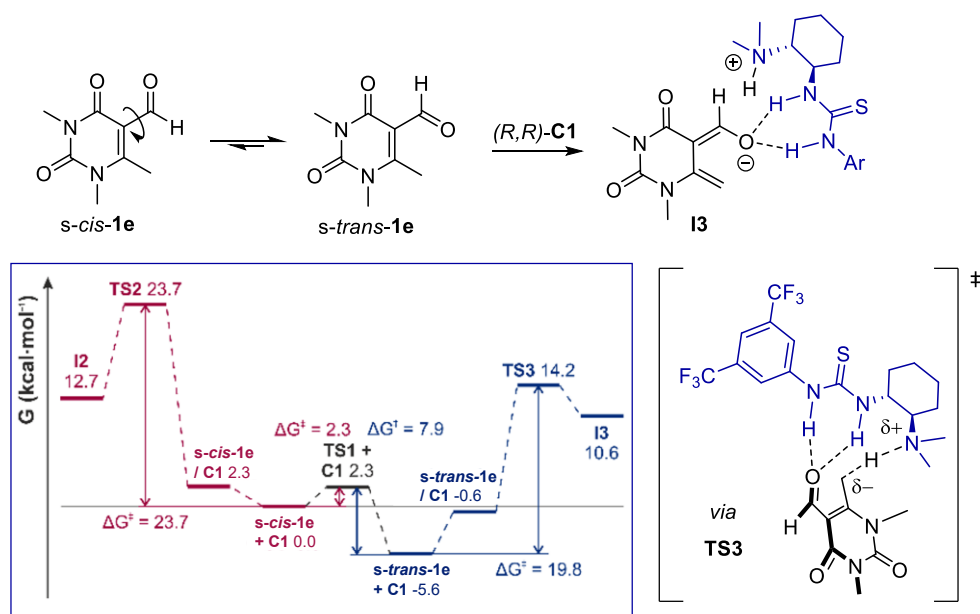
Scheme 10 Catalytic reaction between pronucleophile **1e** and *trans*- β -nitrostyrene **9a**

Based on precedent studies involving thiourea/squaramide bifunctional organocatalysts in [4+2] cycloaddition reactions, we modelled the reaction mechanism on the basis of a four-step sequence including: (i) vinylogous dearomative enolization step, (ii) vinylogous Michael addition step, (iii) intramolecular Henry-type cyclization step, and (iv) catalyst decomplexation step.

(i) Vinylogous dearomative enolization step

The deprotonation of both *s-cis* and *s-trans* pronucleophiles **1e** by the tertiary amine of (*R,R*)-**C1** was considered (Scheme 11). Although the *s-cis*-to-*s-trans* interconversion barrier resulted quite low ($\Delta G^\ddagger$ 2.3 kcal·mol⁻¹), the relative stability of the starting uracils (ΔG_{298} 10.6 kcal·mol⁻¹ for *s-trans* **1e** and 12.7 kcal·mol⁻¹ for *s-cis* **1e**) and the deprotonation energy barriers ($\Delta G^\ddagger$ 19.8 kcal·mol⁻¹ for *s-trans* **1e** and 23.7 kcal·mol⁻¹ for *s-cis* **1e**) favoured for the *s-trans* conformer, leading us to consider the preferential path involving the transient *trans*-disposed oQDM **I3**.

¹¹ a) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. “Quantum Mechanical Investigations of Organocatalysis: Mechanisms, Reactivities, and Selectivities” *Chem. Rev.* **2011**, *111*, 5042; b) Peng, Q.; Paton, R. S. “Catalytic Control in Cyclizations: From Computational Mechanistic Understanding to Selectivity Prediction” *Acc. Chem. Res.* **2016**, *49*, 1042; c) Ahn, S.; Hong, M.; Sundararajan, M.; Ess, D. H.; Baik, M.-H. “Design and Optimization of Catalysts Based on Mechanistic Insights Derived from Quantum Chemical Reaction Modeling” *Chem. Rev.* **2019**, *119*, 6509.



Scheme 11 Vinylogous dearomative enolization of **1e** and energetic profile of the deprotonation of *s-cis* **1e** (pink) vs *s-trans*-**1a** (blue) by **C1** (energies in kcal·mol⁻¹)

(ii) Vinylogous Michael addition step

For the examination of the vinylogous Michael addition step, a total of nine different activation modes were evaluated (Figure 2), ranging from modes **A** and **B** originally proposed by Takemoto¹² and Papai,¹³ mode **C** discovered by Wang,¹⁴ and the recent activation modalities **D** by Wong and **E** by Izzo,^{15,16} to four new activation modes unveiled in this work (**F-I**).

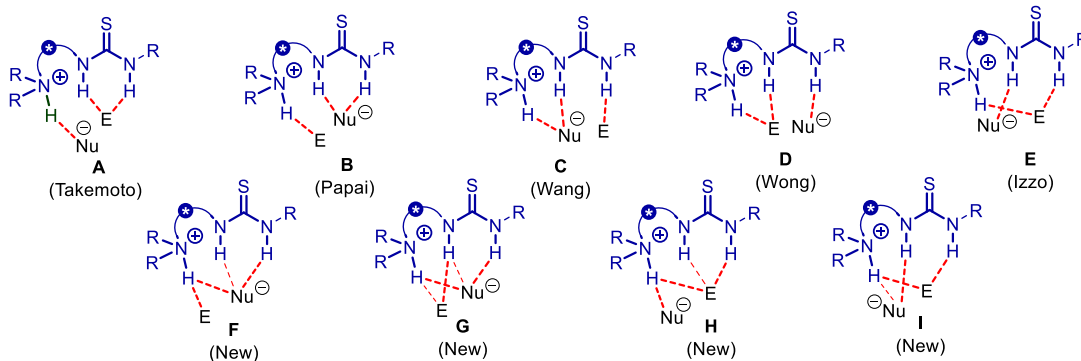


Figure 2 Dual activation modes found operative in the addition of an anionic nucleophile (Nu⁻) to a neutral electrophile (E) in the pre-reaction complexes with an amine-thiourea organocatalyst

¹² a) Okino, T.; Hoashi, Y.; Takemoto, Y. "Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts" *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) Okino, T.; Hoashi, Y.; Furukawa, t.; Xu, X.; Takemoto, Y. "Enantio- and Diastereoselective Michael Reaction of 1,3-Dicarbonyl Compounds to Nitroolefins Catalyzed by a Bifunctional Thiourea" *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

¹³ Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. "Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C–C Bond Formation" *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

¹⁴ Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. "Insights into the Dual Activation Mechanism Involving Bifunctional Cinchona Alkaloid Thiourea Organocatalysts: An NMR and DFT Study" *J. Org. Chem.* **2012**, *77*, 9813–9825.

¹⁵ Guo, J.; Wong, M. W. "Cinchona Alkaloid-Squaramide Catlyzed Sulfa-Michael Addition Reaction: Mode of Bifunctional Activation and Origin of Stereoinduction" *J. Org. Chem.* **2017**, *82*, 4362.

¹⁶ Izzo, J. A.; Myshchuk, Y.; Hirschi, J. S.; Vetticatt, M. J. "Transition State Analysis of an Enantioselective Michael Addition by a Bifunctional Thiourea Organocatalyst" *Org. Biomol. Chem.* **2019**, *17*, 3934.

Among all the calculation attempts of Michael addition between *ortho*-quinodimethane **13** and the acceptor **9a**, only four possible approaches were found to be productive in forging the new C-C bond. The energetic profile of the corresponding four pathways and sketches of pre-reactions complex and transition states are reported in Figure 3.

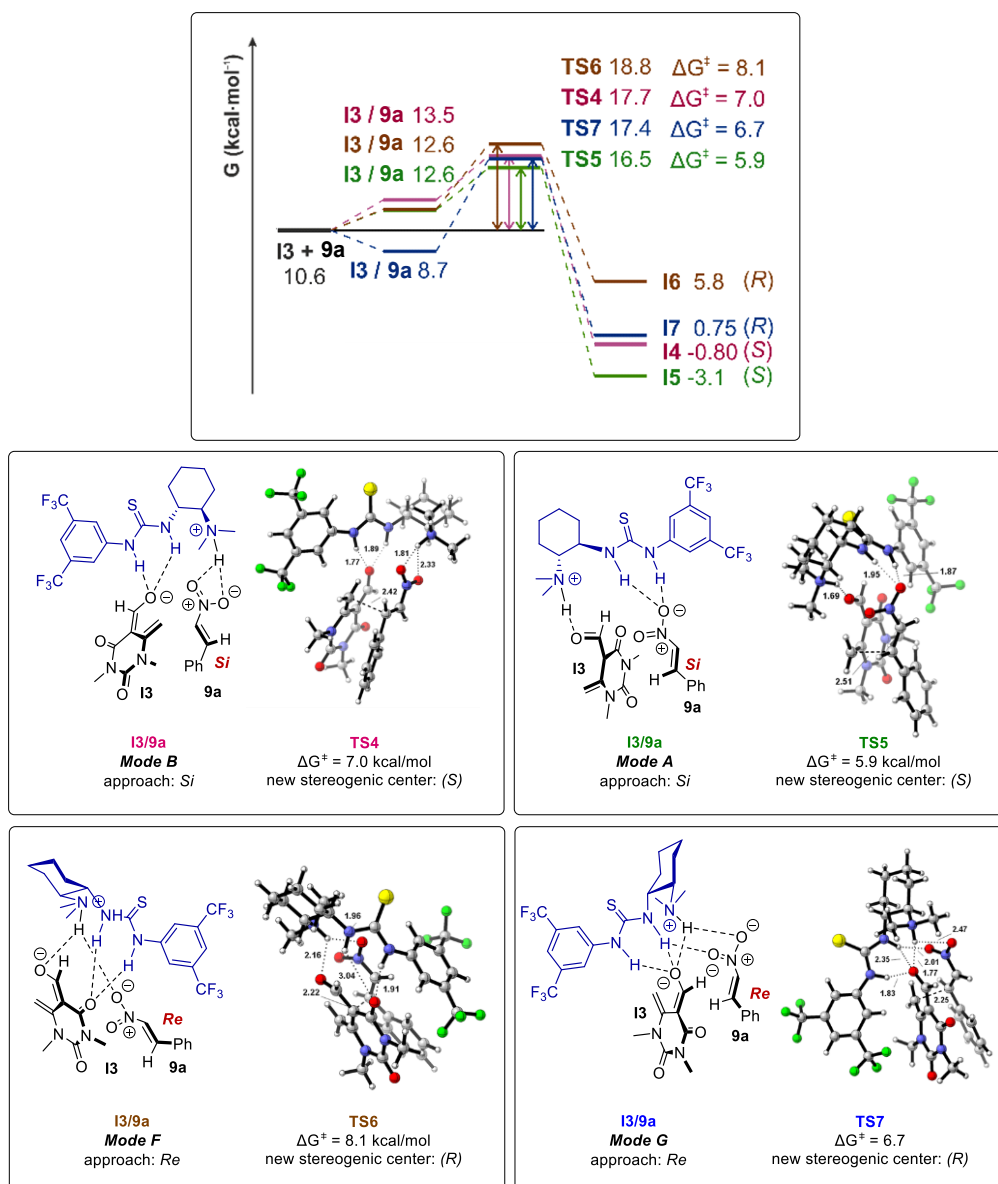


Figure 3 Overall reaction profiles (Path 1: pink, Path 2: green, Path 3: brown, Path 4: blue) for the addition of **1e** to **9a** catalyzed by **C1**, up to the Michael addition step and intermediates (**13/9a**) and transition states (TSs) for the calculated Paths 1-4 (energies in kcal·mol⁻¹, distances in Angstrom).

The most salient observation that emerged from the study of the stereo-determining vinylogous Michael addition dealt with the fact that in all cases such step is an exergonic reaction, featuring rather low activation energies (~6-8 kcal·mol⁻¹). This aspect made the stereoselectivity not completely determined by the Curtin-Hammett principle.¹⁷ On one side, the most stable pre-reaction complex (**13/9a** blue, path 4, 8.7 kcal·mol⁻¹) should indeed finalize the stereoselective generation of the new stereogenic center in the (R)-configuration exclusively. On the other hand, the most stable generated

¹⁷ Seeman, J. I. "Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin-Hammett Winstein-Holness kinetics" *Chem. Rev.* **1983**, 83, 83.

adduct (**I5** -3.1 kcal·mol⁻¹, Path 2, Figure 4) should promote the formation of the (*S*)-configuration. Overall, we think that both kinetic and thermodynamic effects are responsible in determining the stereo-induction of the step. In particular, the most plausible scenario relies on the fact that the distribution of pre-reaction complexes strongly favours one adduct ($\Delta G_{298} = 3.9$ kcal·mol⁻¹ > $\Delta G^{\ddagger}_{TS} = 0.8$ kcal·mol⁻¹), albeit the enantioselectivity is degraded within the transition states, leading to a low-selective reaction.

(iii) intramolecular Henry-type cyclization step and (iv) catalyst decomplexation step

Pleasingly, calculations of Henry cyclization step unveiled a highly diastereoselective reaction, leading to the exclusive generation of 5,6-*cis*-6,7-*trans*-configured cycloadduct, as obtained experimentally. In this case, the activation modes which resulted suitable for calculations were mode **A** for path 1, mode **F** for path 2 and two previously undisclosed activation modes for paths 3 and 4 (i.e. **H** and **I**, respectively), as shown in Figure 4.

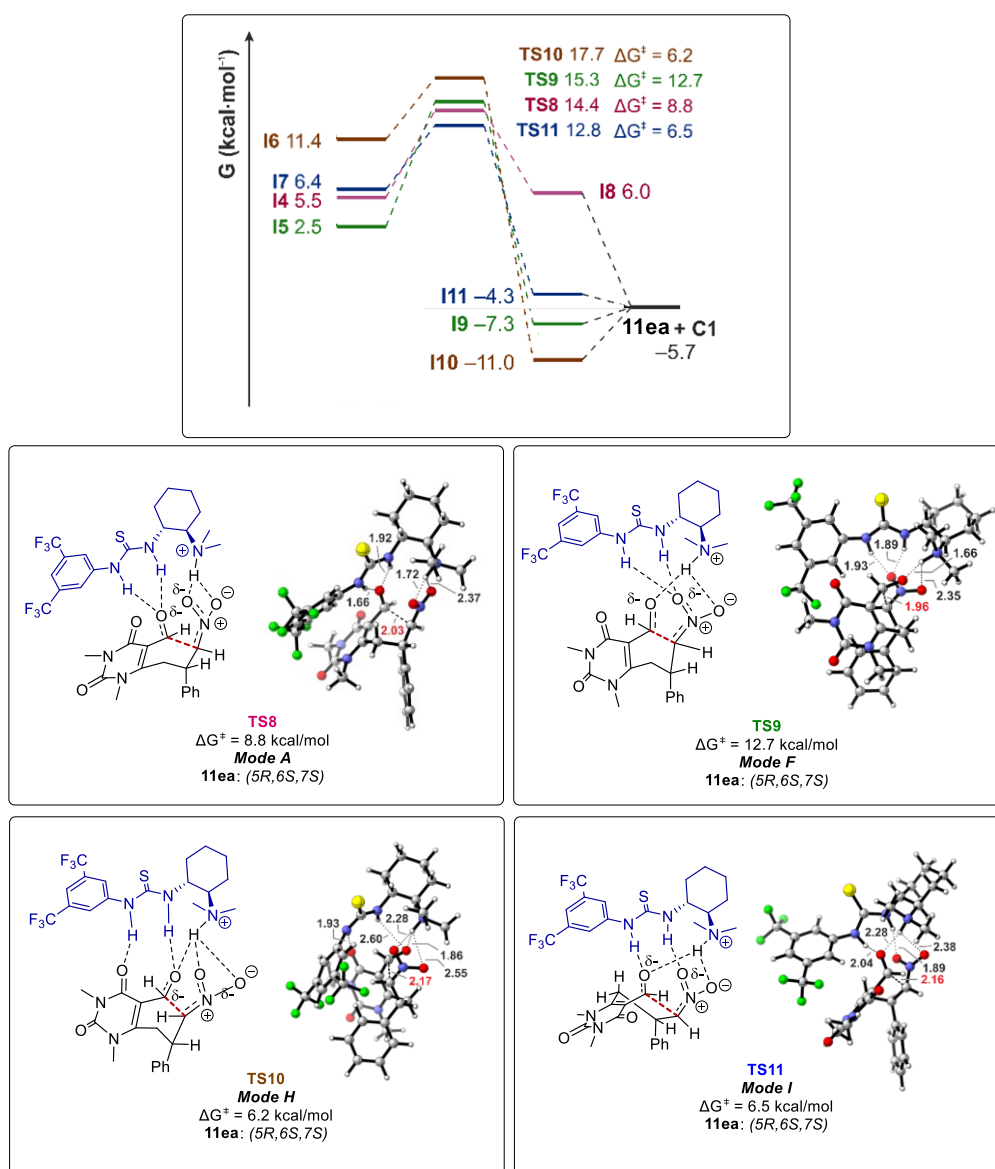


Figure 4 Overall reaction profiles (Path 1: pink, Path 2: green, Path 3: brown, Path 4: blue) for the intramolecular Henry cyclization and transition states (TSs) for the calculated Paths 1-4 (energies in kcal·mol⁻¹, distances in Angstrom).

Three out of four reactions are exergonic transformations (e.g. Paths 2-4; $\Delta G_{298} = \sim -10$ -22 kcal·mol⁻¹), while Path 1 is an almost isoergonic reaction ($\Delta G_{298} = \sim 0.5$ kcal·mol⁻¹). Interestingly, the main difference between this latter and the other pathways resides in the spontaneous proton transfer from the ammonium moiety to the final alcoholates, given by the proximity of the formyl moiety to the ammonium acidic site, as appears in **TS9**, **TS10** and **TS11**.

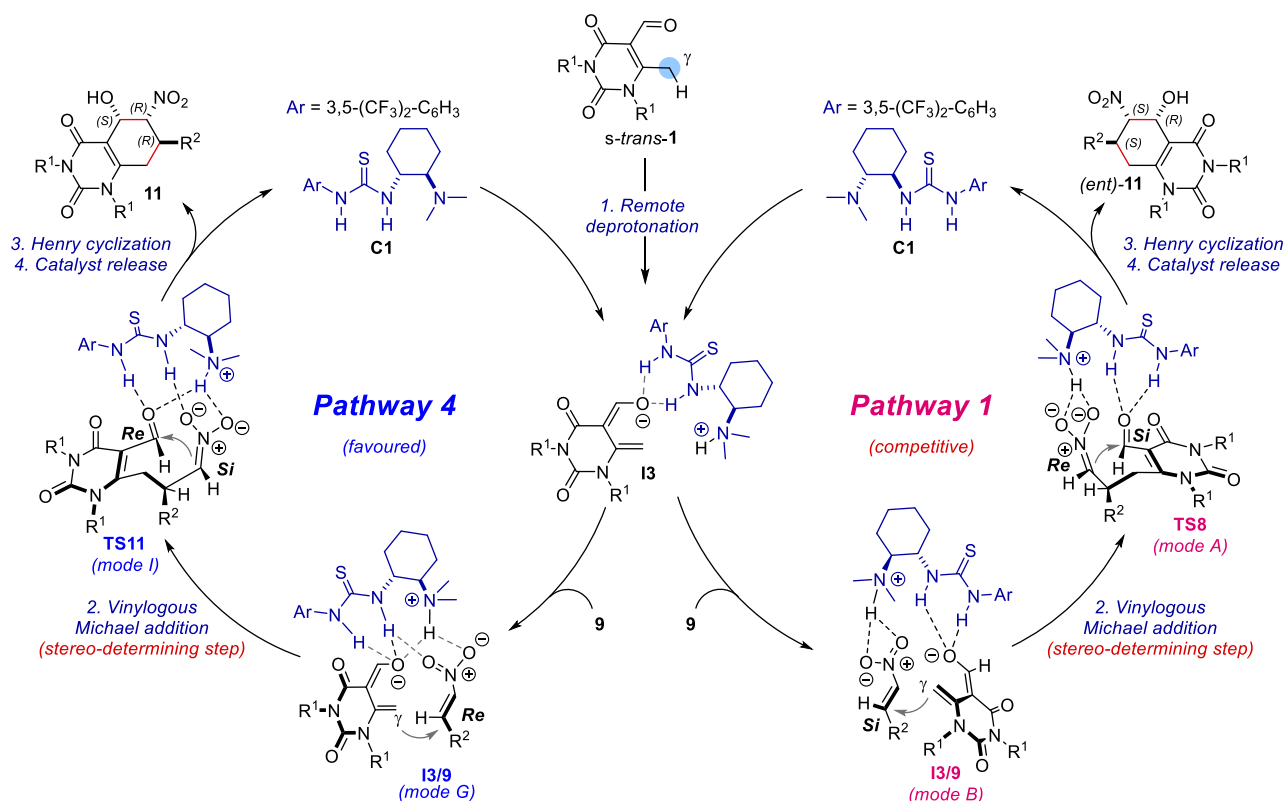
Given the challenges in unveiling which was the most efficient pathway for our process due to the absence of a clear rate-determining step, we decided to apply the *Energetic Span Model* (ESM) method.¹⁸ This approach was introduced by Kozuch and Shaik two decades ago and is considered a useful method to compare the efficiency (turnover frequency, TOF) of competing catalytic cycles, grounding on the fact that the efficiency of a catalytic reaction is not just dependent on the rate-determining step, but instead by the difference between *rate-limiting states*, i.e. the TOF-determining transition state (TDTS) and TOF-determining intermediate (TDI).¹⁹ Figure 5 shows the four complete calculated reaction profiles, starting from *s-trans*-**1e** to the product **11ea**. The first important observation here is that the overall transformation is exergonic ($\Delta G_r = -5.7$ kcal·mol⁻¹).

Figure 5 Overall reaction profiles (Path 1: pink, Path 2: green, Path 3: brown, Path 4: blue) for the addition of *s-trans* **1e** to **9a** catalyzed by **C1**, up to the final product **11ea**.

Case 1) if TDS = **I11** and TDTS = **TS7**, $\delta E = 23.0 + 4.3 - 5.7 = 21.6$ kcal/mol

¹⁸ a) Kozuch, S.; Shaik, S. “How to Conceptualize Catalytic Cycles? The Energetic Span Model” *Acc. Chem. Res.* **2011**, *44*, 101; b) Kozuch, S.; Martin, J. M. L. “Turning Over” Definitions in Catalytic Cycles” *ACS Catal.* **2012**, *2*, 2787; c) Solel, E.; Tarannam, N.; Kozuch, S. “Catalysis: Energy Is the Measure of All Things” *Chem. Commun.* **2019**, *55*, 5306.

In this example, the higher δE is the one furnished by Case 2 and thus for Path 4 the TDS will correspond to *s-trans*-**1e**, and the TDTS will be **TS7**. Overall, for all four paths, the TDTS correspond to the TS of the vinylogous Michael addition step. On the other hand, both Path 2 (green) and Path 3 (brown) have a TDI located after the TDTS and just before the decomplexation step (**I9** and **I10**). On the contrary, TDIs for both Path 1 (pink) and Path 4 (blue) correspond to the starting *s-trans*-**1e**, lying before the TDTS. Given these assumptions, the energetic span gaps result: $\delta E = 23.3$ kcal/mol for Path 1, $\delta E = 23.7$ kcal/mol for Path 2, $\delta E = 29.6$ kcal/mol for Path 3, and $\delta E = 23.0$ kcal/mol for Path 4. Finally, upon the determination of the TOF for the competing catalytic cycles, we can assume that Path 4 represents the favourite catalytic cycle (TOF = $2.8 \cdot 10^{-1} \text{ h}^{-1}$), albeit in strong competition with Path 1 (TOF = $1.9 \cdot 10^{-1} \text{ h}^{-1}$). Notably, the difference in Gibbs free energy between these two competing pathways ($\Delta\Delta G^\ddagger = 0.3 \text{ kcal}\cdot\text{mol}^{-1}$) is perfectly reflected into the 68:32 enantiomeric excess obtained experimentally, where the formation of (5*S*,6*R*,7*R*)-**11ea** via Path 4 is smoothly favored over (5*R*,6*S*,7*S*)-*ent*-**11ea** via Path 1. Based on DFT-calculations, we confirmed our hypothesis of a catalytic cycle involving a vinylogous Michael addition reaction and an intramolecular Henry cyclization, by means of the chirality transfer imparted by Takemoto's catalyst (Scheme 12).



Scheme 12 DFT-supported competitive catalytic cycles for the stepwise [4+2] cycloaddition between uracil carbaldehydes **1** and nitroalkenes **5**

Importantly, for both the key steps, two previously undisclosed activation modes were found to be productive within the favoured path 4. In both of them, the nucleophilic and electrophilic components are concomitantly activated by both the ammonium and thiourea moieties through H-bonds. In particular, within the Michael addition, catalyst **C1** establishes threefold H-bonding with the *ortho*-quinodimethane **I3**, while the nitroolefin **9** is activated by one hydrogen-bond with the thiourea and a longer hydrogen-bond with the ammonium salt (Mode G). On the other hand, within the Henry-type ring closure, the aldehyde of the uracil is two-fold bound to both the ammonium and the thiourea and, in the same way, the nitronate is channelled to both the thiourea and the ammonium salt (Mode I).

2.3.4 Anti-SARS-CoV-2 inhibitory profile of chiral fused-uracils

The recent devastating impact of the COVID-19 pandemic on public health, social life, and global economy has undoubtedly demonstrated how our society is still threatened by viruses (including respiratory viruses, such as SARS-CoV-2 and other coronaviruses) and pathogens in general, whose disastrous effects require urgent development of suitable countermeasures.²⁰

As for SARS-CoV-2, for instance, besides the development of useful vaccines in record-breaking times, mainly targeting the viral surface spike protein, diverse small-molecule (SM) antivirals have been advanced in clinical programs, mainly targeting viral enzymes involved in the coronavirus replication including the RNA-dependent RNA polymerase (RdRp), the main protease (3CLpro), and the papain-like protease (PLpro).²¹ Figure 6 shows SM drugs against SARS-CoV-2 infections clinically approved or under advanced clinical trials.²²

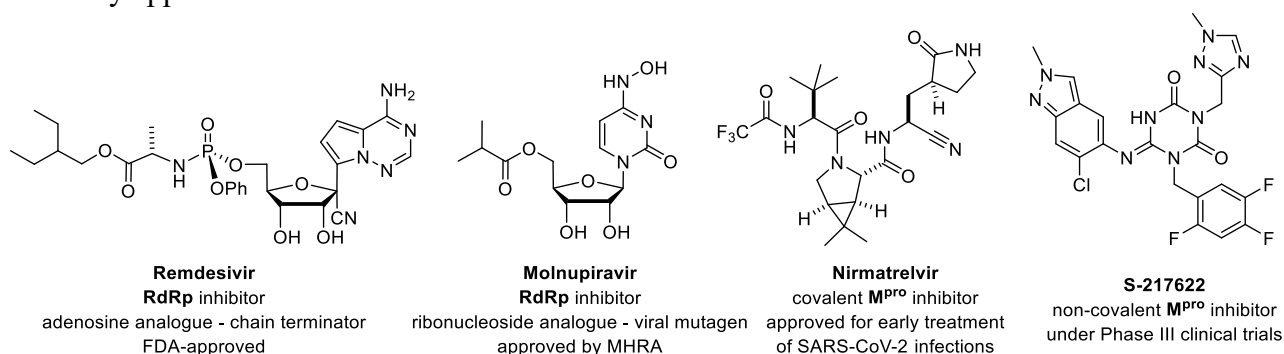


Figure 6 Chemical structures of COVID-19 antiviral drugs approved by diverse drug agencies or which are under advanced clinical trials

These viral targets display highly conserved active domains, which encourages the development of SM inhibitors with high efficacy against viral variants as well as other known or new emerging coronaviruses. Several issues, though, arise about the use of such SM inhibitors, for example concerning their actual therapeutic benefits, unsafe use in immunocompromised patients, and possible off-target effects on human enzymes and resistance development.²³ In this scenario, additional antivirals with novel structures are needed, to combat emerging variants, drug-resistant viruses and, possibly, with broad-spectrum antiviral activity. The emerging importance of factors such as scaffold rigidity and 3D shape for lead compounds to survive the DD process,²⁴ as the privileged role that the uracil core has historically played within the antiviral domain, led us to inquire whether fused-carbocyclic uracils of type **11**, **12**, **13** and **15** could exert antiviral activity, for example

²⁰ a) Nicolaou, K. C. "Advancing the Drug Discovery and Development Process" *Angew. Chem. Int. Ed.* **2014**, 53, 9128; b) Ritchie, H. Coronavirus Pandemic (COVID-19). { HYPERLINK "<https://ourworldindata.org/coronavirus>" }, access Nov. 26th, 2022.

²¹ a) Jackson, C. B.; Farzan, M.; Chen, B.; Choe, H. "Mechanisms of SARS-CoV-2 entry into cells" *Nat. Rev. Mol. Cell Biol.* **2022**, 23, 3; b) Sivaraman, H.; Yin, S.; Choong, Y. K.; Gavor, E.; Sivaraman, J. "Structural Basis of SARS-CoV-2- and SARS-CoV-Receptor Binding and Small-Molecule Blockers as Potential Therapeutics" *Annu. Rev. Pharmacol. Toxicol.* **2021**, 61, 465.

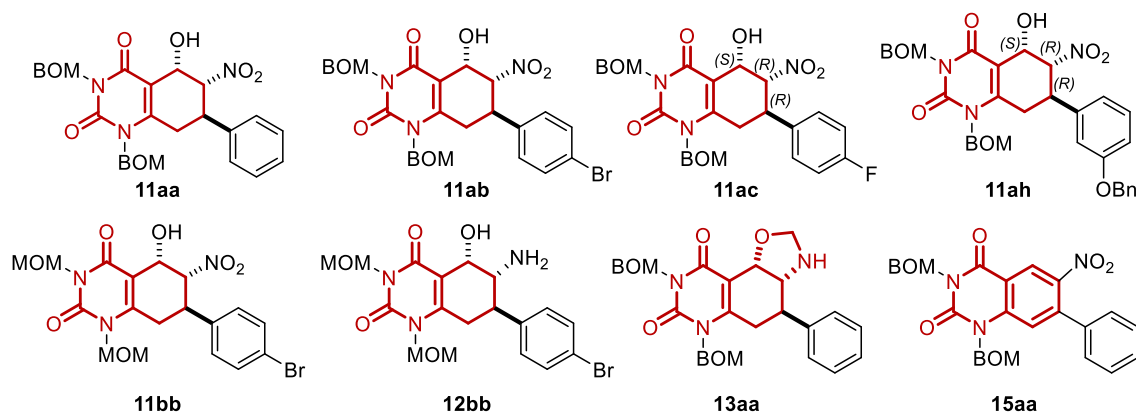
²² a) Zhao, L.; Li, S.; Zhong, W. "Mechanism of Action of Small-Molecule Agents in Ongoing Clinical Trials for SARS-CoV-2: A Review" *Front. Pharmacol.* **2022**, 13, 840639; b) J. D. A. Tyndall "S-217622, a 3CL Protease Inhibitor and Clinical Candidate for SARS-CoV-2" *J. Med. Chem.* **2022**, 65, 6496.

²³ Tan, H.; Hu, Y.; Jadhav, P.; Tan, B.; Wang, J. "Progress and Challenges in Targeting the SARS-CoV-2 Papain-like Protease" *J. Med. Chem.* **2022**, 65, 7561.

²⁴ a) Taylor, R. D.; MacCoss, M.; Lawson A. D. G. "Rings in Drugs" *J. Med. Chem.* **2014**, 57, 5845–5859; b) Lovering, F.; Bikker, J.; Humblet, C. "Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success" *J. Med. Chem.* **2009**, 52, 6752; c) Abou-Gharbia, M.; Childers, W. E. "Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation" *J. Med. Chem.* **2014**, 57, 5525.

against SARS-CoV-2. After having synthesized and purified (HPLC grade) several different compounds within the above disclosed fused uracil collection, a preliminary *in-vitro* screening against wild-type SARS-CoV-2 was performed by Prof. Kurt Vermeire from KU University of Leuven (Belgium) using U87-ACE2⁺ human glioblastoma cells,²⁵ that stably express the ACE2 receptor (a key host receptor directly involved in virus entry), and the results are shown in Table 9.

Table 9 Preliminary screening of cycloadducts of type **11**, **12**, **13** and **15** against wild-type SARS-CoV-2 in U87-ACE2⁺ cells



Entry	Compound	er ^[a]	Cells viability [%] ^[b]	CC ₅₀ [μM] ^[b]	IC ₅₀ [μM] ^[c]	
1	11aa	>99:1	96	>50	35.5	>50
2	11ab	>99:1	86	>50	>50	>50
3	11ac	99:1	101	>50	>50	>50
4	(<i>ent</i>)- 11ac	99:1	87	>50	27.3	31.4
5	11ac	racemic	95	>50	>50	>50
6	11ah	88:12	100	>50	7.41	16.6
7	(<i>ent</i>)- 11ah	92:8	95	>50	47.8	>50
8	11bb	>99:1	76	>50	32.2	33.7
9	(<i>ent</i>)- 12bb	82:18	88	>50	>50	>50
10	(<i>ent</i>)- 13aa	80:20	0	20.9	>10	>10
11	15aa	-	93	>50	>50	>50

^[a]Determined by chiral-HPLC analysis. ^[b]Determined after 4 days in the presence of 50 μM uracil-based drug using colorimetric MTS-PES assay; ^[c]Antiviral assays were performed in duplicates (two column) at four different concentrations (0.4 μM, 2 μM, 10 μM, 50 μM). IC₅₀ determined by colorimetric MTS-PES assay; results for Remdesivir, used as reference compound: IC₅₀ = 8.94 nM, 7.37 nM.

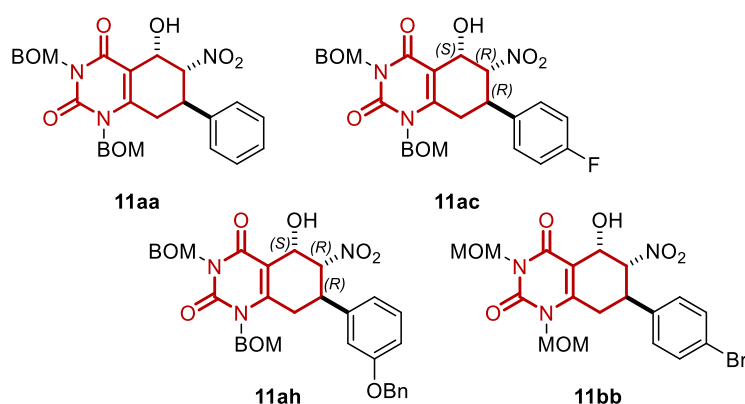
To our delight, several tested compounds showed micromolar activity (IC₅₀ = 7–48 μM) and, apart from oxazolidine **13aa**, all the other tested compounds did not show any relevant toxicity (CC₅₀ >50 μM). Regarding the activity, some interesting trends can be noticed. First, the chiral and enantiopure tetrahydroquinazolin-2,4-dione core gave superior results if compared to the achiral and flat quinazoline-2,4-dione counterpart (**11aa** vs **15aa**). Moreover, the protecting group of the uracil nitrogen played a role. Indeed, comparison between the activity of **11ab** (entry 2, IC₅₀ = >50 μM) with that of **11bb** (entry 8, IC₅₀ = 32.2 and 33.7 μM) shows that the methoxymethyl framework makes the compound more active than the benzyloxymethyl protecting group. In contrast to most of the nitro-alcohol cycloadducts of type **11**, free amino-alcohol **12bb** did not show any virus inhibition. We also investigated the effect of enantiopurity, by exploring both enantiopure and racemic versions of fluorinated compound **11ac**. Curiously, while pure (*5S,6R,7R*)-enantiomer and racemic format of

²⁵ Vanhulle, E.; Stroobants, J.; Provinciael, B.; Camps, A.; Noppen, S.; Maes, P.; Vermeire, K “SARS-CoV-2 Permissive glioblastoma cell line for high throughput antiviral screening” *Antiviral Research* **2022**, 203, 105342.

11ac completely undermined the virus inhibition potential (entries 3 and 5), enantiopure (*ent*)-**11ac** afforded intriguing results in terms of activity (entry 4, ca. 30 μ M). The effect of stereochemistry can also be appreciated by comparing entries 6 and 7. In this case, enantioenriched (*ent*)-**11ah** resulted much less active if compared with its stereoisomeric counterpart (entry 6 vs entry 7). Importantly, this latter compound resulted the most promising among all tested compounds, with a low micromolar activity (entry 6, IC_{50} = 11.0 μ M) and without any toxicity. Overall, this preliminary screening led us to define the enantioenriched *meta*-benzyloxy aryl-substituted **11ah** as the first *hit compound*.

Given these promising results, we were motivated in exploring further the antiviral potential of our uracil-based carbocycles. Thus, some congeners of type **11** were subjected to a second preliminary *in-vitro* screening, in this instance, against the Omicron strain of SARS-CoV-2 in the same cells system, and the results are shown in Table 10

Table 10 Preliminary screening of cycloadducts of type **11** against Omicron variant of SARS-CoV-2 in U87-ACE2⁺ cells



Entry	Compound	er ^[a]	IC ₅₀ [μ M] ^[b]
1	11aa	>99:1	28.4
2	11ac	99:1	46.6
3	(<i>ent</i>)- 11ac	99:1	26.9
4	11ah	88:12	19.4
5	(<i>ent</i>)- 11ah	92:8	22.4
6	11bb	>99:1	6.1

^[a]Determined by chiral-HPLC analysis. ^[b]Antiviral assays were performed at four different concentrations (0.4 μ M, 2 μ M, 10 μ M, 50 μ M). IC_{50} determined by colorimetric MTS-PES assay; results for Remdesivir: IC_{50} = >100 μ M.

Interestingly, the antiviral activities found for the Omicron variant (Table 10, IC_{50} = 6-46 μ M) resulted comparable to those determined for the wild-type virus (Table 9). As a first attempt, model compound **11aa** was tested and, pleasingly, it afforded good antiviral activity (IC_{50} = 28.4 μ M). The previous hit compound **11ah** showed virus inhibition even against this variant (entry 4, IC_{50} = 19.4 μ M). Contrary to what observed within the first antiviral screening, both enantiomers of **11ah** gave comparable results, regardless of their stereochemical disposition (entries 4 and 5). On the other side, the effect of stereochemistry can be again appreciated within the series of fluorinated compound **11ac** (entries 2 and 3). In this case, pure (5*R*,6*S*,7*S*)-*ent*-**11ac** resulted more active than its enantiomer (IC_{50} = 26.9 μ M vs IC_{50} = 46.6 μ M). Importantly, this screening allowed us to disclose a second *hit compound* in the role of the enantiopure *methoxymethyl*-protected cycloadduct **11bb** that, pleasingly, afforded low micromolar activity (entry 6, IC_{50} = 6.1 μ M). Importantly, in this experiment, the reference compound Remdesivir did not show any activity against Omicron SARS-CoV-2 virus in the employed cellular environment.

Eager to start a proper *structure-activity relationship* (SAR) study in order to increase the activity of our new chemotypes, we needed to know the actual SARS-CoV-2 biological target of compound **11ah** and **11bb**. First, a single-dose of compound **11ac** (50 μ M) in SARS-CoV-2-infected differentiated Calu-3 cells expressing high levels of ACE2 and TMPRSS2 (the two proteins on the host cells surface mainly involved in the virus entry),²⁶ no antiviral activity was observed, meaning that our hit compounds were most probably not involved in inhibiting entry-related proteins such as the virus spike. Thus, assuming a post-entry inhibition of the virus, we commissioned to an external company (BPS-Bioscience company, USA) enzyme assays of hit compound **11ah** towards three isolated wild-type SARS-CoV-2 proteins, namely PLPro, 3CLPro, and RdRp. We found that the RdRp receptor was clearly targeted by **11ah** (IC_{50} = ca. 2.1 μ M), while PLPro and 3CLPro were not, as shown in the dose-response curves reported in Figure 7.

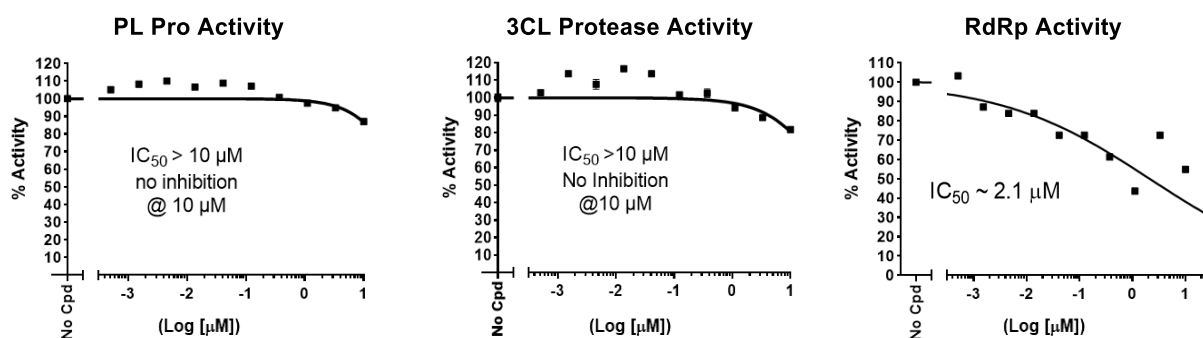


Figure 7 Dose-response curves of compound **11ah** on the enzymatic activity on isolated PL Pro, 3CL Protease and RNA-dependent RNA polymerase (SARS-CoV-2) using an *in vitro* enzymatic assay.

This result established a post-entry inhibition of the virus by compound **11ah**, which could possibly interfere with the RNA replication and transcription in the cytoplasm. Importantly, this result lays the foundations for future molecular modelling and docking investigations, to better rationalize the specific interactions between hit compound and receptor and carry out rational and reliable SAR studies towards a second-generation anti-SARS-CoV-2 uracil-carbocycle collection.

²⁶ Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S. "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor" *Cell* **2020**, *181*, 2, 271.

2.4 Conclusion

In conclusion, this project demonstrated the versatility of 6-methyl-5-carbaldehydes **1** as easily enolizable aromatic carbaldehydes to be employed in stereoselective and organocatalysed [4+2] cycloaddition reactions with nitroolefins **9** as dienophilic components, under the guidance of noncovalent bifunctional organocatalysis. A collection of 24 uracil-based carbocycles of type **11** containing three *in-cycle* stereogenic centres was efficiently obtained, as single diastereoisomers and with moderate to high enantioselectivity. The ability to provide enantiopure cycloadducts by one-cycle recrystallization techniques and the possibility to further functionalize these scaffolds were also demonstrated. DFT calculations confirmed that the transformation involves a four-step consecutive cascade featuring a key stereo-determining Michael addition involving non-aromatic *o*QDM intermediates, followed by spontaneous and highly diastereoselective intramolecular Henry reaction, both characterized by two previously undisclosed activation modes by the Takemoto's catalyst. Finally, preliminary in-cell assays aimed at establishing possible inhibitory activity against SARS-CoV-2 showed that several compounds of our collection possess low-micromolar in vitro antiviral activity with low cytotoxicity; meanwhile, assays on selected SARS-CoV-2 isolated enzymes established post-entry RdRp inhibitory activity by two hit candidates (**11ah** and **11bb**), paving the way to further synthetic challenges to refine its structure and increase its antiviral activity.

Overall, this project embraces different fields of organic chemistry, and represents a fruitful example of how the power of asymmetric organocatalysis merged with the principle of the vinylogy, resulted successful in refining the three-dimensional shape of a novel high-quality carbon-rich heterocyclic chemotype toward future medicinal chemistry applications.

2.5 Experimental Section

2.5.1 General information

Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of nitrogen or argon. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Xylene (ACS grade) refers to commercial $\geq 98.5\%$ xylenes + ethylbenzene basis ($\leq 0.05\%$ water) and was used as such without further purifications. Dichloromethane (ACS grade) was dried by distillation on CaH_2 according to standard procedures (water content $< 0.01\%$ as determined by Karl Fischer titration). Solvents for chromatography and filtration including hexane, cyclohexane, ethyl acetate, petroleum ether, DMF, acetone, anhydrous ethanol, methanol and 2-propanol were ACS or HPLC grade and used as received. NH_3 -MeOH mixture was prepared by bubbling liquid ammonia into methanol at $0\text{ }^\circ\text{C}$ for 30 min. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates with visualization under short-wavelength UV light (254 or 365 nm) and by dipping the plates with molybdate reagent (aqueous H_2SO_4 solution of ceric sulphate/ammonium molybdate) followed by heating. Flash column chromatography was performed using 40-63 μm silica gel using the indicated solvent mixtures. Analytical chiral HPLC analyses were carried out using Daicel Chiralcel OD-H (250 $\times$ 4.6 mm, 5 μm) or Lux[®] Amylose-1 (250 $\times$ 4.6 mm, 5 μm) columns as indicated. Racemic mixtures were obtained performing reactions in presence of Et_3N (10 mol%). Pure samples of *ent*-**11** were obtained via **C3**-catalyzed reactions. Optical rotation data $[\alpha]_D$ were obtained on a digital polarimeter at ambient temperature using a 100 mm cell with 1- or 5-mL capacity and are given in units of $10^{-1}\text{ deg}\cdot\text{cm}^2\cdot\text{g}^{-1}$. 1D- e 2D-NMR spectra were recorded at 400 MHz (^1H -NMR) and 100 MHz (^{13}C , ^{13}C -APT). Spectra were referenced to tetramethylsilane (0.0 ppm, ^1H ; 0.0 ppm, ^{13}C , in CDCl_3 , CD_3OD and $\text{DMSO}-d_6$). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), td (triple of doublets), m (multiplet), and bs (broad). Coupling constants, J , are reported in Hertz. ^1H and ^{13}C NMR assignments were corroborated by 1D and 2D experiments (^1H -NMR, gCOSY, gHSQC sequences). ESI-mass spectra were recorded on API 150EX apparatus and are reported in the form of (m/z). High resolution mass analysis (HR-MS) was performed on LTQ ORBITRAP XL Thermo apparatus.

Single crystal X-ray diffraction analysis of compounds **11bb**, **11cb** and **11fb** was carried out by Prof. Giorgio Pelosi from University of Parma with a Bruker D8Venture diffractometer equipped with a kappa goniometer and an Oxford cryosystem. The low temperature data collection was performed at 200K under nitrogen flux. Lorentz polarization and absorption correction were applied by the SADABS²⁷ procedure. The phase problem was solved by direct methods and the structures were refined by full-matrix least-squares on all F2 using SHELXL,²⁸ as implemented in the OLEX2 suite of programmes.^{27b} Analytical expressions of neutral atom scattering factors were taken from the International Tables for X-Ray Crystallography.²⁹ The structure drawings were obtained using ORTEPIII.³⁰

²⁷ Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.

²⁸ a) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3; b) Sheldrick, G. M. A short history of SHELX. *Acta Cryst.* **2008**, *A64*, 112.

²⁹ Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339.

³⁰ Burnett, M. N.; Johnson, C. K. ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for crystal structure illustrations. United States. doi:10.2172/369685.

Calculations were performed by Prof. Marco Lombardo from University of Bologna using Gaussian 16, Revision C.01.³¹ Geometries were optimized using the M06-2X density functional³² and the 6-31G(d) basis set within the IEFPCM model (solvent = toluene)³³ and further confirmed to be stationary points on the potential energy surface by frequency calculations. Transition states were confirmed to join the correct minimum energy structures by IRC calculations. Single point energies were calculated using the M06-2X density functional and 6-311++g(d,p) basis set within the IEFPCM model (solvent = toluene).³² and corrected using the program GoodVibes (Truhlar's quasi-harmonic approximation).³⁴ Molecules possessing conformational mobility were first optimized using molecular mechanics (MMFF94 force field); all the conformers within a 10 kcal·mol⁻¹ window were then re-optimized using DFT and only the lowest energy conformer was used in all subsequent calculations. All molecule illustrations were made using with CYLView.³⁵ Energetic Span calculations were made using the program AUTOF (Excel version).³⁶

Biological experiments were performed by Prof. Kurt Vermeire from KU University of Leuven.

Virus: All virus-related work was conducted in the high-containment biosafety level 3 facilities of the Rega Institute from the Katholieke Universiteit (KU) Leuven (Leuven, Belgium), in accordance with institutional guidelines. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) isolates were recovered from nasopharyngeal swabs of RT-qPCR-confirmed human cases obtained from the University Hospital (Leuven, Belgium).

Wild type virus infection and antiviral assays: One day prior to the experiment, U87.ACE2⁺ cells were seeded in 96-well microtiter plates. The following day, 0.4 μM, 2 μM, 10 μM and 50 μM solution of the test compounds were prepared in virus infection media, overlaid on cells, and virus was added to each well. Cells were incubated at 37 °C under 5% CO₂ for the duration of the experiment. At endpoints (4 days p.i.), the virus-induced cytopathic effect (CPE) was microscopically evaluated. Inhibition was calculated by comparison to virus control wells with no inhibitor added. IC₅₀ values were determined by interpolation. Four days after infection, the cell viability of virus-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxy-methoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt, using the CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega). The optical density (OD) of the samples was compared to appropriate cell control replicates (cells without virus and drugs) and virus control wells (cells with virus but without drugs). The concentration that inhibited SARS-CoV-2-induced cell death by 50% (IC₅₀) was calculated from interpolation.

³¹ Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, et al. Fox, Gaussian, Inc., Wallingford CT (2016).

³² Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

³³ J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

³⁴ G. Luchini, J. V. Alegre-Requena, I. Funes-Ardoiz, R. S. Paton, *F1000Research* **2020**, *9*, 291; <https://github.com/patonlab/GoodVibes>

³⁵ C. Y. Legault, CYLView, Université de Sherbrooke: Sherbrooke, Quebec, Canada, **2009**; { HYPERLINK "<http://www.cylview.org>" }.

³⁶ a) S. Kozuch, *WIREs Comput. Mol. Sci.* **2012**, *2*, 795; b) ESM calculations were made using the free program AUTOF (Excel version). See { HYPERLINK "<https://www.bgu.ac.il/~kozuch/software.html>" }, access Dec. 17th, 2022. .

2.5.2 Catalysts and substrates synthesis

Catalysts

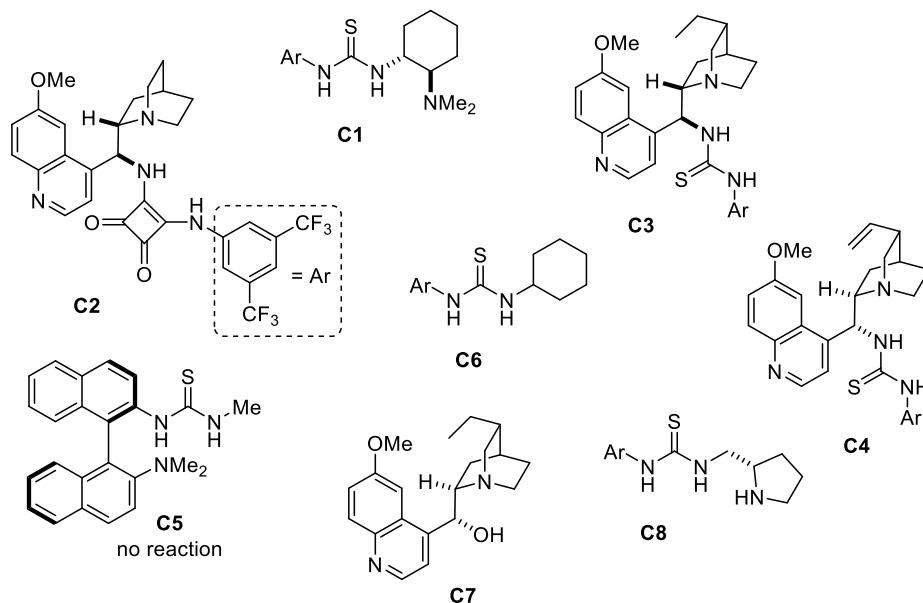


Figure 8 Catalysts used in this study

Catalysts **C1-C8** were commercially available and were used as such without further purification.

Pronucleophiles

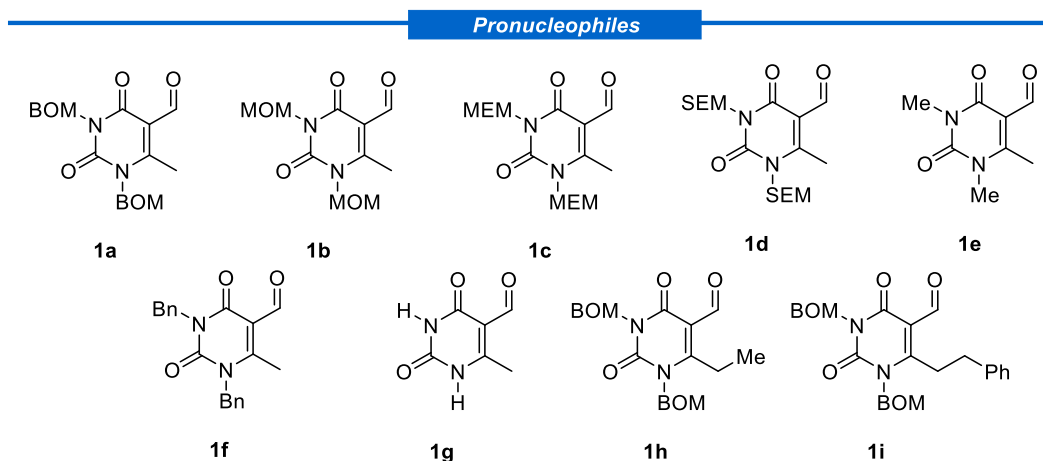
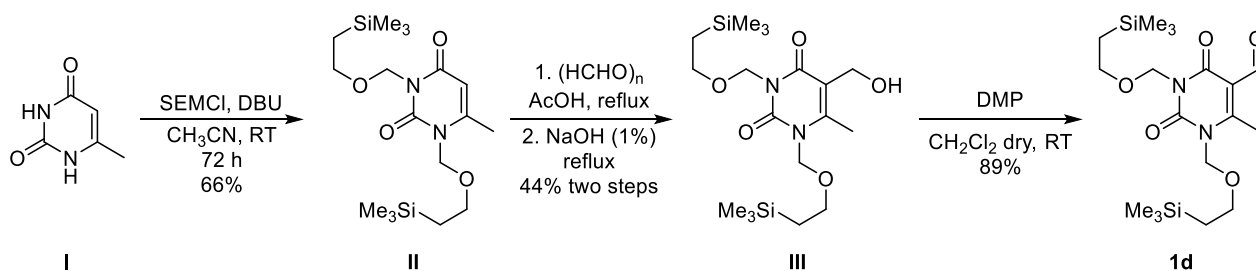


Figure 9 Pronucleophiles used in this study

Pronucleophiles **1a-1c**, **1e** and **1g** were prepared from commercial 6-methyluracil following a reported procedure.⁸ Analytical and spectroscopic data fully matched those reported in literature.

Preparation of 6-methyl-1,3-bis[(2-(trimethylsilyl)ethoxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (**1d**)



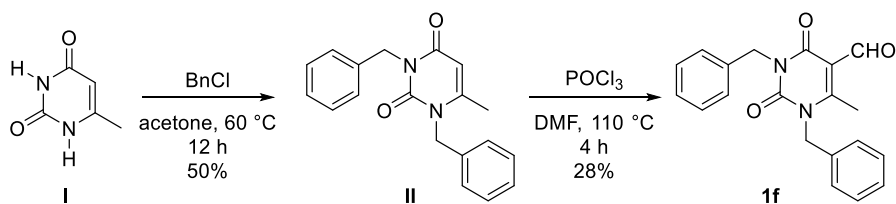
A suspension of commercial 6-methyluracil **I** (300 mg, 2.37 mmol, 1.0 equiv) in MeCN (30 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.78 mL, 5.23 mmol, 2.2 equiv) and stirred at rt for 30 min. The resulting clear solution was cooled to 0 °C and treated dropwise with (2-(chloromethoxy)ethyl)trimethylsilane (SEMCl; 1.1 mL, 5.95 mmol, 2.5 equiv). After 3 days, the reaction resulted complete; the resulting mixture was concentrated in vacuo and the residue was diluted with H₂O (40 mL) and extracted with CH₂Cl₂ (4 × 20 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (cyclohexane/AcOEt 7:3) to yield protected uracil intermediate **II** (606 mg, 66%) as a white solid. A mixture of **II** (606 mg, 1.45 mmol, 1.0 equiv) and paraformaldehyde (174 mg, 5.8 mmol, 4.0 equiv) in glacial acetic acid (5 mL) was heated to reflux for 6 h. The reaction mixture was then concentrated in vacuo, and the resulting resin was sequentially washed with portions of acetone and methanol. The resulting crude was suspended in a 1% aqueous solution of NaOH (8 mL) and then heated at reflux for 1 h. The reaction mixture was acidified to pH 5 with 10% HCl and then extracted with CH₂Cl₂ (4 × 20 mL) and EtOAc (4 × 20 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and finally concentrated in vacuo to yield a crude that was purified by silica gel flash chromatography (cyclohexane/AcOEt 6:4) to provide protected alcohol **III** (266 mg, 44% two steps) as a white solid. To a stirred solution of alcohol **III** (260 mg, 0.62 mmol, 1.0 equiv.) in CH₂Cl₂ dry (30 mL), kept under an argon atmosphere at rt, Dess Martin Periodinane (DMP, 396 mg, 0.93 mmol, 1.5 equiv) was added. After 2 h, the reaction was quenched with a saturated aqueous solution of NaHCO₃ and Na₂S₂O₃ (15 mL) and kept under stirring for 30 min. After this period, the resulting solution was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and evaporated in vacuo to yield a crude that was purified by silica gel flash chromatography (cyclohexane/AcOEt 8:2) to provide protected aldehyde **1d** (230 mg, 89%) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H, CHO), 5.47 (bs, 2H, SEM), 5.45 (s, 2H, SEM), 3.70 (m, 4H, SEM), 2.87 (s, 3H, Me), 0.96 (m, 4H, SEM), 0.02 (s, 9H, SEM), 0.01 (s, 9H, SEM).

¹³C-NMR (100 MHz, CDCl₃) δ 190.0 (Cq, CHO), 162.4 (Cq, C4), 161.6 (Cq, C6), 151.4 (Cq, C2), 108.7 (Cq, C5), 73.4 (CH₂, SEM), 73.4 (CH₂, SEM), 72.4 (CH₂, SEM), 67.9 (CH₂, SEM), 67.7 (CH₂, SEM), 18.2 (CH₂, SEM), 18.1 (CH₂, SEM), 15.2 (CH₃, Me), -1.3 (3C, CH₃, SEM), -1.4 (3C, CH₃, SEM).

ESI-MS [M+H]⁺ = 415.6; [M+Na]⁺ = 437.5

Preparation of 1,3-dibenzyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (**1f**)



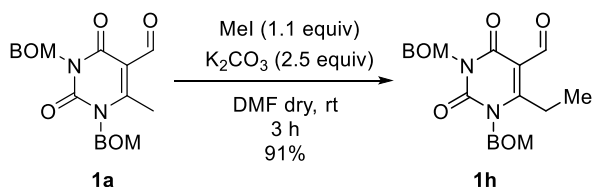
To a stirred solution of commercial 6-methyluracil **I** (1.0 g, 7.93 mmol, 1.0 equiv) in acetone (20 mL) K_2CO_3 (3.78 g, 27.8 mmol, 3.5 equiv) was added and the resulting suspension was kept under vigorous stirring at room temperature. After 30 min, benzyl chloride (3.2 mL, 27.8 mmol, 3.5 equiv) was added and the reaction mixture was heated for 3 h at $60\text{ }^{\circ}\text{C}$. The progress of reaction was monitored by TLC and, after completion of the reaction, the resulting suspension was filtered and concentrated by rotary evaporation to yield a crude that was recrystallized from ethyl acetate to get 1,3-dibenzyl-6-methyluracil **II** (1.2 g, 50 %) as a yellowish solid, that was used as such without further purifications. To a stirred solution of 1,3-dibenzyl-6-methyluracil **II** (300 mg, 1.07 mmol, 1.0 equiv) in dry DMF (2 mL) kept at $0\text{ }^{\circ}\text{C}$ under an ice bath, phosphorous oxychloride (POCl_3 , 0.10 mL, 1.61 mmol, 1.5 equiv) was added dropwise. After 5 min, the reaction mixture was heated to $120\text{ }^{\circ}\text{C}$ for 4 h. The resulting mixture was evaporated in vacuo and the obtained crude material was then stirred in ethanol (10 mL) for 30 minutes. The precipitated solid was collected by filtration to afford 60 mg of the aldehyde **1f** (28 %) as an off-white solid.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 10.32 (s, 1H, CHO), 7.53 (m, 2H, Bn), 7.28-7.38 (m, 6H, Bn), 7.16 (m, 2H, Bn), 5.26 (s, 2H, CH_2Ph), 5.24 (s, 2H, CH_2Ph), 2.71 (s, 3H, Me).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 190.1 (Cq, CHO), 162.4 (Cq, C4), 160.9 (Cq, C6), 151.3 (Cq, C2), 136.2 (Cq, Ph, Bn), 134.9 (Cq, Ph, Bn), 129.2 (2C, CH, Ph, Bn), 129.1 (2C, CH, Ph, Bn), 128.6 (2C, CH, Ph, Bn), 128.2 (CH, Ph), 127.9 (CH, Ph), 126.2 (2C, CH, Ph), 108.5 (Cq, C5), 48.0 (CH_2 , CH_2Ph), 44.8 (CH_2 , CH_2Ph), 15.9 (CH_3 , Me).

ESI-MS $[\text{M}+\text{H}]^+ = 335.4$; $[\text{M}+\text{Na}]^+ = 357.3$

Preparation of 1,3-bis((benzyloxy)methyl)-6-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (**1h**)



To a stirred solution of 6-methyluracil-carbaldehyde **1a** (60 mg, 0.15 mmol, 1.0 equiv) in DMF dry (1.5 mL), K_2CO_3 (52 mg, 0.38 mmol, 2.5 equiv) was added and the resulting suspension was kept under vigorous stirring at room temperature. After 15 min., iodomethane (10 μL , 0.16 mmol, 1.1 equiv) was added dropwise at $0\text{ }^{\circ}\text{C}$. After stirring at room temperature for 3h, the mixture was acidified to pH 6 with an aqueous 1 N HCl solution and then extracted with CH_2Cl_2 ($3 \times 20\text{ mL}$). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and finally concentrated in

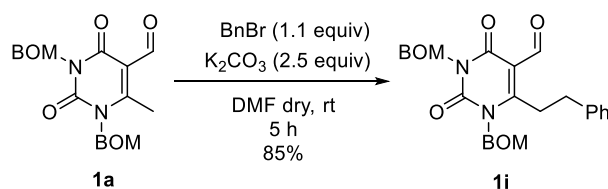
vacuo to yield a crude that was purified by silica gel flash chromatography (petroleum ether/AcOEt 3:7) to provide pro-stereogenic carbaldheyde **1h** (55.7 mg, 91%) as a white lucid oil.

¹H-NMR (400 MHz, CDCl₃) δ 10.23 (s, 1H, CHO), 7.51-7.18 (m, 10H, Ph), 5.61-5.46 (m, 4H, BOM), 4.73 (d, J = 9.6 Hz, 4H, BOM), 3.24 (q, J = 7.5 Hz, 2H, CH₂), 1.23 (t, J = 7.5 Hz, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 189.1 (CH, CHO), 166.5 (Cq), 162.6 (Cq), 151.5 (Cq), 137.7 (Cq), 136.8 (Cq), 128.6 (2C, CH, Ph), 128.4 (2C, CH, Ph), 128.3 (CH, Ph), 127.9 (CH, Ph), 127.8 (2C, CH, Ph), 127.6 (2C, CH, Ph), 107.7 (Cq), 73.1 (CH₂, BOM), 72.6 (CH₂, BOM), 72.4 (CH₂, BOM), 70.8 (CH₂, BOM), 21.6 (CH₂, Et), 13.0 (CH₃, Et).

ESI-MS [M+H]⁺ = 409.2; [M+Na]⁺ = 431.2

Preparation of 1,3-bis((benzyloxy)methyl)-2,4-dioxo-6-phenethyl-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (**1i**)



To a stirred solution of 6-methyluracil-carbaldheyde **1a** (40 mg, 0.10 mmol, 1.0 equiv) in DMF dry (3 mL), K₂CO₃ (35 mg, 0.25 mmol, 2.5 equiv) was added and the resulting suspension was kept under vigorous stirring at room temperature. After 15 min., benzyl bromide (13 μ L, 0.11 mmol, 1.1 equiv) was added dropwise at room temperature. After stirring for 5h, the mixture was acidified to pH 6 with an aqueous 1 N HCl solution and then extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and finally concentrated in vacuo to yield a crude that was purified by silica gel flash chromatography (petroleum ether/AcOEt 1:1) to provide uracil-carbaldheyde **1i** (41.2 mg, 85%) as a yellow oil.

¹H-NMR (400 MHz, CDCl₃) δ 10.30 (s, 1H, CHO), 7.62 – 7.10 (m, 15H, Ph), 5.72 – 5.39 (m, 4H, BOM), 4.90 – 4.66 (m, 4H, BOM), 3.64 – 3.34 (m, 2H, phenylethyl), 2.88 – 2.80 (m, 2H, phenylethyl).

¹³C-NMR (100 MHz, CDCl₃) δ 189.2 (CH, CHO), 164.3 (Cq), 162.5 (Cq), 151.4 (Cq), 139.6 (Cq), 137.7 (Cq), 136.7 (Cq), 128.8 (2C, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (4C, CH, Ar), 128.3 (CH, Ar), 127.9 (3C, CH, Ar), 127.7 (2C, CH, Ar), 126.9 (CH, Ar), 108.0 (Cq), 73.4 (CH₂, BOM), 72.7 (CH₂, BOM), 72.4 (CH₂, BOM), 70.9 (CH₂, BOM), 35.0 (CH₂, phenylethyl), 30.9 (CH₂, phenylethyl).

ESI-MS [M+H]⁺ = 409.2; [M+Na]⁺ = 431.2

Electrophiles

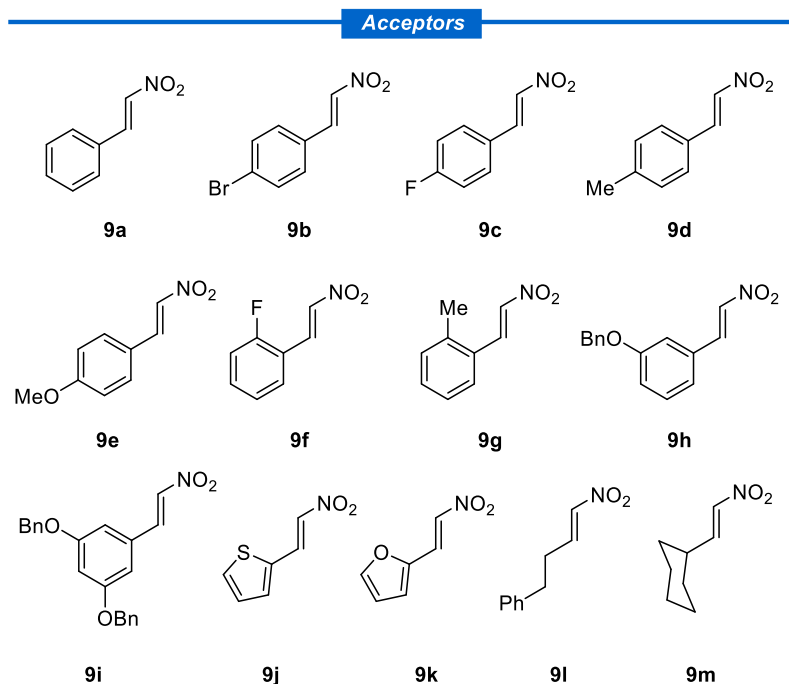


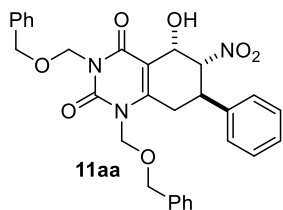
Figure 10 Nitroolefins used in this study

trans- β -Nitrostyrene **9a** was commercially available and was used as such without further purification. Nitroolefins **9b-9m** were prepared by base condensation of the corresponding aldehydes with nitromethane, following a reported procedure.³⁷ Analytical and spectroscopic data fully matched those reported in literature.

³⁷ Ferraro, A.; Bernardi, L.; Fochi, M. "Organocatalytic Enantioselective Transfer Hydrogenation of β Amino Nitroolefins" *Adv. Synth. Catal.* **2016**, 358, 1561.

2.5.3 Experimental procedures and characterizations of products

Representative procedure 1: Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11aa]



In a round-bottomed flask equipped with a magnetic stir bar and kept under nitrogen atmosphere, 1,3-bis((benzyloxy)methyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv) and *trans*- β -nitrostyrene **9a** (13.3 mg, 0.089 mmol, 1 equiv) were dissolved in xylene (1.25 mL) at 25 °C. Takemoto's catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) was then added and the resulting reaction was stirred

at 25 °C and monitored by TLC. After 72 h, the heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 41 mg of (+)-**11aa** (85% yield) as a pale-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.22-7.46 (m, 15H, Ph), 5.55 (1/2 ABq, J = 9.8 Hz, 1H, BOM), 5.50 (1/2 ABq, J = 9.8 Hz, 1H, BOM), 5.38-5.47 (m, 2H, BOM + H5), 5.31 (d, J = 11.3 Hz, 1H, BOM), 4.94 (dd, J = 12.4, 3.9 Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.65 (s, 2H, BOM), 3.99 (ddd, J = 11.7, 11.7, 5.8 Hz, 1H, H7), 3.46 (bs, 1H, OH), 3.30 (dd, J = 18.7, 6.0 Hz, 1H, H8a), 2.73 (dd, J = 18.7, 11.1 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 151.7 (Cq), 149.3 (Cq), 139.0 (Cq), 137.9 (Cq), 136.9 (Cq), 129.3 (2C, CH, Ph), 128.6 (2C, CH, Ph), 128.4 (2C, CH, Ph), 128.2 (CH, Ph), 128.0 (CH, Ph), 127.9 (2C, CH, Ph), 127.7 (3C, CH, Ph), 127.2 (2C, CH, Ph), 108.9 (Cq), 87.2 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 71.0 (CH₂, BOM), 63.1 (CH, C5), 36.8 (CH, C7), 34.0 (CH₂, C8).

$[\alpha]_D^{20}$ +27.4 (c = 1.0 g/100 mL, CHCl₃)

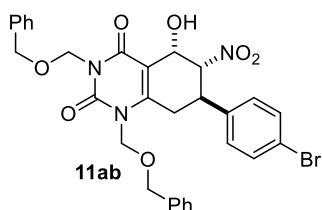
Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): 14.5 min (minor), 26.8 min (major) (91.1:8.9 er).

ESI-MS $[M+H]^+$ = 544.6; $[M+Na]^+$ = 566.5

HRMS calcd for C₃₀H₂₉N₃O₇ ($[M+H]^+$): 544.2084, found: 544.2063

Scope of the electrophile

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-(4-bromophenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ab]



Compound **11ab** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-1-bromo-4-(2-nitrovinyl)benzene **9b** (20.3 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 41.5 mg of (+)-**11ab**

(75% yield) as a pale-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.48-7.58 (m, 2H, Ar), 7.23-7.44 (m, 10H, Ph), 7.12-7.21 (m, 2H, Ar), 5.54 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.49 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.38-5.46 (m, 2H, BOM + H5), 5.31 (d, J = 10.8 Hz, 1H, BOM), 4.87 (dd, J = 12.4, 4.0 Hz, 1H, H6), 4.73 (s, 2H,

BOM), 4.59-4.70 (m, 2H, BOM), 3.96 (ddd, $J = 12.3, 11.9, 5.9$ Hz, 1H, H7), 3.40 (bs, 1H, OH), 3.26 (dd, $J = 18.7, 6.0$ Hz, 1H, H8a), 2.67 (dd, $J = 18.6, 11.2$ Hz, 1H, H8b).

^{13}C -NMR (100 MHz, CDCl_3) δ 161.8 (Cq), 151.8 (Cq), 149.0 (Cq), 138.2 (Cq), 137.9 (Cq), 136.9 (Cq), 132.5 (2C, CH, Ar), 129.0 (2C, CH, Ar), 128.7 (2C, CH, Ar), 128.4 (3C, CH, Ar), 128.0 (2C, CH, Ar), 127.8 (CH, Ar), 127.7 (2C, CH, Ar), 122.0 (Cq), 109.0 (Cq), 87.1 (CH, C6), 73.1 (CH_2 , BOM), 72.6 (CH_2 , BOM), 72.2 (CH_2 , BOM), 71.1 (CH_2 , BOM), 63.1 (CH, C5), 36.4 (CH, C7), 33.8 (CH_2 , C8).

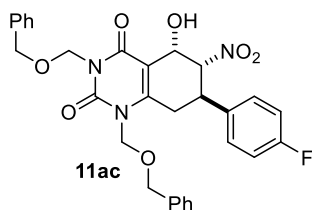
$[\alpha]_{\text{D}}^{20} +17.2$ ($c = 0.5$ g/100 mL, CHCl_3)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min^{-1} , 254 nm): 13.4 min (minor), 44.3 min (major) (93.1:6.9 er).

ESI-MS $[\text{M}+\text{H}]^+ = 623.5$; $[\text{M}+\text{Na}]^+ = 645.4$

HRMS calcd for $\text{C}_{30}\text{H}_{28}\text{BrN}_3\text{O}_7$ ($[\text{M}+\text{H}]^+$): 622.1189, found: 622.1172

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-(4-fluorophenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ac]



Compound **11ac** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-1-fluoro-4-(2-nitrovinyl)benzene **9c** (14.9 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25°C . After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) to afford

45 mg of (+)-**11ac** (90% yield) as a white amorphous solid.

^1H -NMR (400 MHz, CDCl_3) δ 7.21-7.44 (m, 12H, Ar), 7.04-7.14 (m, 2H, Ar), 5.54 (1/2 ABq, $J = 9.7$ Hz, 1H, BOM), 5.49 (1/2 ABq, $J = 9.7$ Hz, 1H, BOM), 5.37-5.46 (m, 2H, H5 + BOM), 5.32 (d, $J = 11.2$ Hz, 1H, BOM), 4.87 (dd, $J = 11.9, 4.4$ Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.59-4.70 (m, 2H, BOM), 3.98 (ddd, $J = 11.8, 11.7, 5.8$ Hz, 1H, H7), 3.39 (bs, 1H, OH), 3.27 (dd, $J = 18.6, 6.0$ Hz, 1H, H8a), 2.69 (dd, $J = 18.7, 11.2$ Hz, 1H, H8b).

^{13}C -NMR (100 MHz, CDCl_3) δ 161.3 (d, $^1J_{\text{C,F}} = 247$ Hz, Cq, Ar), 161.8 (Cq), 151.7 (Cq), 149.1 (Cq), 137.8 (Cq), 136.8 (Cq), 134.6 (d, $^4J_{\text{C,F}} = 3$ Hz, Cq, Ar), 128.9 (2C, d, $^3J_{\text{C,F}} = 8$ Hz, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.9 (2C, CH, Ar), 127.8 (CH, Ar), 127.7 (2C, CH, Ar), 116.2 (2C, d, $^2J_{\text{C,F}} = 21$ Hz, CH, Ar), 108.9 (Cq), 87.2 (CH, C6), 73.0 (CH_2 , BOM), 72.5 (CH_2 , BOM), 72.2 (CH_2 , BOM), 71.0 (CH_2 , BOM), 63.1 (CH, C5), 36.1 (CH, C7), 33.9 (CH_2 , C8).

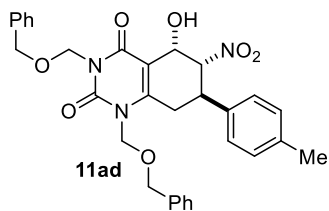
$[\alpha]_{\text{D}}^{20} +23.0$ ($c = 1$ g/100 mL, CHCl_3)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min^{-1} , 254 nm): t_{R} 12.1 min (minor), 35.8 min (major) (90.9:9.1 er).

ESI-MS $[\text{M}+\text{H}]^+ = 562.6$; $[\text{M}+\text{Na}]^+ = 584.5$

HRMS calcd for $\text{C}_{30}\text{H}_{28}\text{FN}_3\text{O}_7$ ($[\text{M}+\text{H}]^+$): 562.1989, found: 562.1960

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-(*p*-tolyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ad]



Compound **11ad** was prepared according to representative procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv.), (*E*)-1-methyl-4-(2-nitrovinyl)benzene **9d** (14.5 mg, 0.089 mmol, 1 equiv.) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 39.7 mg of (+)-**11ad** (80% yield) as a yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.25-7.44 (m, 10H, Ar), 7.14-7.24 (m, 4H, Ar), 5.54 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.49 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.36-5.46 (m, 2H, H5 + BOM), 5.31 (d, J = 11.3 Hz, 1H, BOM), 4.92 (dd, J = 12.1, 2.8 Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.65 (s, 2H, BOM), 3.95 (ddd, J = 11.6, 11.4, 5.9 Hz, 1H, H7), 3.29 (dd, J = 19.0, 6.0 Hz, 1H, H8a), 3.20 (b, 1H, OH), 2.73 (dd, J = 18.8, 11.1 Hz, 1H, H8b), 2.37 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 161.9 (Cq), 151.8 (Cq), 149.5 (Cq), 138.0 (Cq), 137.9 (Cq), 137.0 (Cq), 136.0 (Cq), 130.0 (2C, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.9 (2C, CH, Ar), 127.8 (3C, CH, Ar), 127.1 (2C, CH, Ar), 109.0 (Cq), 87.4 (CH, C6), 73.1 (CH₂, BOM), 72.5 (CH₂, BOM), 72.2 (CH₂, BOM), 71.1 (CH₂, BOM), 63.2 (CH, C5), 36.5 (CH, C7), 34.1 (CH₂, C8), 21.2 (CH₃, Me).

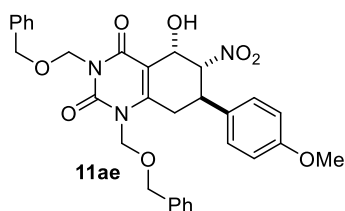
$[\alpha]_D^{20}$ + 24.7 (c = 0.3 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): t_R 12.4 min (minor), 23.6 min (major) (93.7:6.3 er).

ESI-MS $[M+H]^+$ = 558.6; $[M+Na]^+$ = 580.5

HRMS calcd for C₃₁H₃₁N₃O₇ ($[M+H]^+$): 558.2240, found: 558.2228

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-7-(4-methoxyphenyl)-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ae]



Compound **11ae** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv.), (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **9e** (15.9 mg, 0.089 mmol, 1 equiv.) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 42.4 mg of (+)-**11ae** (83% yield) as a pale-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.25-7.45 (m, 10H, Ar), 7.16-7.25 (m, 2H, Ar), 6.85-6.98 (m, 2H, Ar), 5.54 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.49 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.43 (1/2 ABq, J = 11.3 Hz, 1H, BOM), 5.38 (d, J = 2.9 Hz, 1H, H5), 5.32 (1/2 ABq, J = 11.3 Hz, 1H, BOM), 4.88 (dd, J = 12.4, 3.0 Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.65 (s, 2H, BOM), 3.94 (ddd, J = 11.6, 11.4, 5.8 Hz, 1H, H7), 3.83 (s, 3H, OMe), 3.44 (b, 1H, OH), 3.28 (dd, J = 18.7, 6.0 Hz, 1H, H8a), 2.72 (dd, J = 18.7, 11.0 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 159.2 (Cq), 151.7 (Cq), 149.4 (Cq), 137.9 (Cq), 136.9 (Cq), 130.7 (Cq), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (2C, CH, Ar), 128.2 (CH, Ar), 127.8 (2C, CH, Ar), 127.7 (3C, CH, Ar), 114.6 (2C, CH, Ar), 108.8 (Cq), 87.5 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 71.0 (CH₂, BOM), 63.1 (CH, C5), 55.4 (CH₃, OMe), 36.1 (CH, C7), 34.0 (CH₂, C8).

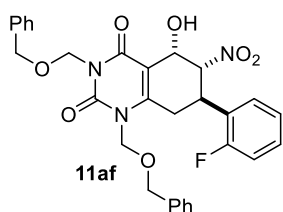
$[\alpha]_D^{20}$ +21.7 (c = 0.5 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 16.7 min (minor), 29.5 min (major) (92.1:7.9 er).

ESI-MS $[M+H]^+ = 574.6$; $[M+Na]^+ = 596.5$

HRMS calcd for C₃₁H₃₁N₃O₈ ($[M+H]^+$): 574.2189, found: 574.2173

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-(2-fluorophenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11af]



Compound **11af** was prepared according to representative procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-1-fluoro-2-(2-nitrovinyl)benzene **9f** (14.9 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 8:2) to afford 37.5 mg of (+)-**11af** (75% yield) as a pale-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) 7.24-7.46 (m, 12H, Ar), 7.07-7.20 (m, 2H, Ar), 5.39-5.58 (m, 4H, BOM + H5), 5.33 (d, $J = 11.3$ Hz, 1H, BOM) 5.12 (d, $J = 12.5$ Hz, 1H, H6), 4.60-4.80 (m, 4H, BOM), 4.16 (ddd, $J = 11.9, 11.8, 5.9$ Hz, 1H, H7), 3.28 (dd, $J = 18.3, 5.3$ Hz, 1H, H8a), 3.10 (bs, 1H, OH), 2.90 (dd, $J = 18.5, 11.3$ Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 160.7 (d, $^1J_{C,F} = 245$ Hz, Cq, Ar), 151.7 (Cq), 149.2 (Cq), 137.9 (Cq), 136.9 (Cq), 130.1 (CH, Ar), 129.8 (d, $^3J_{C,F} = 9$ Hz, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.9 (2C, CH, Ar), 127.7 (3C, CH, Ar), 125.5 (d, $^3J_{C,F} = 12$ Hz, CH, Ar), 125.0 (d, $^4J_{C,F} = 3$ Hz, Cq, Ar), 116.5 (2C, d, $^2J_{C,F} = 22$ Hz, CH, Ar), 116.4 (Cq, Ar), 108.9 (Cq), 85.8 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.2 (CH₂, BOM), 71.0 (CH₂, BOM), 63.1 (CH, C5), 33.1 (CH, C7), 31.6 (CH₂, C8).

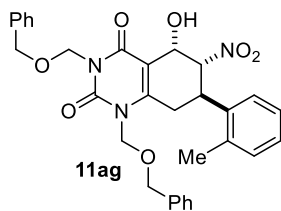
$[\alpha]_D^{20}$ +20.0 (c = 1.0 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 12.0 min (minor), 19.7 min (major) (78.1:21.9 er).

ESI-MS $[M+H]^+ = 562.6$; $[M+Na]^+ = 584.5$

HRMS calcd for C₃₀H₂₈FN₃O₇ ($[M+H]^+$): 562.1989, found: 562.1978

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-(*o*-tolyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ag]



Compound **11ag** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-1-methyl-2-(2-nitrovinyl)benzene **9g** (14.5 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 60 °C. After 120 h, the resulting mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 22.3 mg of (+)-**11ag** (45% yield)

as a yellow resin.

¹H-NMR (400 MHz, CDCl₃) δ 7.18-7.44 (m, 13H, Ar), 7.04-7.14 (m, 1H, Ar), 5.39-5.58 (m, 4H, BOM + H5), 5.27 (d, J = 11.3 Hz, 1H, BOM), 5.00 (d, J = 12.2 Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.65 (s, 2H, BOM), 4.25 (ddd, J = 11.6, 11.6, 6.1 Hz, 1H, H7), 3.17-3.32 (m, 2H, H8a + OH), 2.62 (dd, J = 18.7, 11.2 Hz, 1H, H8b), 2.53 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 151.7 (Cq), 149.3 (Cq), 137.8 (Cq), 137.4 (Cq), 136.9 (Cq, 2C), 131.3 (CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.8 (2C, CH, Ar), 127.7 (3C, CH, Ar), 127.6 (CH, Ar), 127.0 (CH, Ar), 123.9 (CH, Ar), 108.9 (Cq), 87.0 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 70.9 (CH₂, BOM), 63.2 (CH, C5), 33.1 (CH, C7), 29.7 (CH₂, C8), 19.5 (CH₃, Me).

$[\alpha]_D^{20}$ +14.7 (c = 0.8 g/100 mL, CHCl₃)

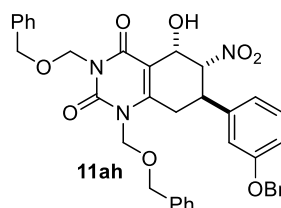
Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):

t_R 14.4 min (minor), 30.7 min (major) (85.0:15.0 er).

ESI-MS $[M+H]^+$ = 558.6; $[M+Na]^+$ = 580.5

HRMS calcd for C₃₁H₃₁N₃O₇ ($[M+H]^+$): 558.2240, found: 558.2221

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-(3-(benzyloxy)phenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ah]



Compound **11ah** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-1-(benzyloxy)-3-(2-nitrovinyl)benzene **9h** (22.7 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 8:2) to afford 28.9 mg of (+)-**11ah**

(50% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.22-7.51 (m, 15H, Ar), 6.83-6.99 (m, 3H, Ar), 5.54 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.49 (1/2 ABq, J = 9.7 Hz, 1H, BOM), 5.36-5.46 (m, 2H, BOM + H5), 5.30 (d, J = 11.3 Hz, 1H, BOM), 5.09 (s, 2H, Bn), 4.91 (dd, J = 11.8, 3.3 Hz, 1H, H6), 4.74 (s, 2H, BOM), 4.65 (s, 2H, BOM), 3.95 (ddd, J = 11.6, 11.5, 5.7 Hz, 1H, H7), 3.29 (dd, J = 18.8, 6.0 Hz, 1H, H8a), 3.12 (bs, 1H, OH), 2.72 (dd, J = 18.7, 11.1 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 159.3 (Cq), 151.7 (Cq), 149.3 (Cq), 140.7 (Cq), 137.8 (Cq), 136.9 (Cq), 136.6 (Cq), 130.4 (CH, Ar), 128.7 (2C, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C,

CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 127.9 (2C, CH, Ar), 127.7 (3C, CH, Ar), 127.6 (2C, CH, Ar), 119.5 (CH, Ar), 114.5 (CH, Ar), 113.8 (CH, Ar), 108.8 (Cq), 87.0 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 71.0 (CH₂, BOM), 70.2 (CH₂, OBn), 63.1 (CH, C5), 36.8 (CH, C7), 33.9 (CH₂, C8).

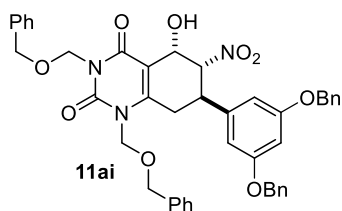
$[\alpha]_D^{20} +16.8$ (c = 1.0 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 19.8 min (minor), 32.6 min (major) (87.6:12.4 er).

ESI-MS $[M+H]^+ = 650.7$; $[M+Na]^+ = 672.6$

HRMS calcd for C₃₇H₃₅N₃O₈ ($[M+H]^+$): 650.2502, found: 650.2476

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-(3,5-bis(benzyloxy)phenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ai]



Compound **11ai** was prepared according to Representative Procedure 1 using: carbalddehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv.), (*E*)-(((5-(2-nitrovinyl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzene **9i** (32.2 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel

(petroleum ether/ ethyl acetate 8:2) to afford 35.6 mg of (+)-**11ai** (53% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.24-7.50 (m, 20H, Ar), 6.47-6.62 (m, 3H, Ar), 5.53 (1/2 ABq, $J = 9.8$ Hz, 1H, BOM), 5.48 (1/2 ABq, $J = 9.8$ Hz, 1H, BOM), 5.36-5.46 (m, 2H, BOM + H5), 5.29 (d, $J = 11.3$ Hz, 1H, BOM), 5.04 (s, 4H, Bn), 4.87 (dd, 12.5, 4.0 Hz, 1H, H6), 4.73 (s, 2H, BOM), 4.65 (s, 2H, BOM), 3.90 (ddd, $J = 11.9, 11.8, 5.8$ Hz, 1H, H7), 3.36-3.18 (m, 2H, OH + H8a), 2.70 (dd, $J = 18.7, 11.1$ Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 160.5 (2C, Cq), 151.7 (Cq), 149.2 (2C, Cq), 141.5 (Cq), 137.9 (Cq), 136.9 (Cq), 136.5 (Cq), 128.7 (4C, CH, Ar), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 128.2 (2C, CH, Ar), 127.9 (2C, CH, Ar), 127.7 (7C, CH, Ar), 108.8 (Cq), 106.6 (2C, CH, Ar), 100.9 (CH, Ar), 86.9 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 71.0 (CH₂, BOM), 70.3 (2C, CH₂, OBn), 63.2 (CH, C5), 37.0 (CH, C7), 33.9 (CH₂, C8).

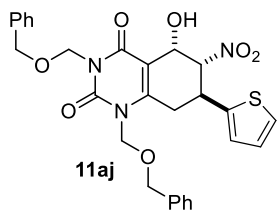
$[\alpha]_D^{20} +11.0$ (c = 1.0 g/100 mL, CHCl₃)

Chiral HPLC CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 25.6 min (minor), 29.3 min (major) (94.5:5.5 er).

ESI-MS $[M+H]^+ = 756.8$; $[M+Na]^+ = 778.7$

HRMS calcd for C₄₄H₄₁N₃O₉ ($[M+H]^+$): 756.2921, found: 756.2902

Synthesis of (5*S*,6*R*,7*S*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-(thiophen-2-yl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11aj]



Compound **11aj** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-2-(2-nitrovinyl)thiophene **9j** (13.8 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 35.7 mg of (+)-**11aj** (73% yield) as a dark yellow resin.

¹H-NMR (400 MHz, CDCl₃) δ 7.22-7.43 (m, 11H, Ar + thiophenyl), 6.96-7.07 (m, 2H, thiophenyl), 5.54 (1/2 ABq, *J* = 9.7 Hz, 1H, BOM), 5.49 (1/2 ABq, *J* = 9.7 Hz, 1H, BOM), 5.44 (d, *J* = 11.3 Hz, 1H, BOM), 5.32-5.39 (m, 2H, BOM + H5), 4.82 (dd, *J* = 11.9, 2.4 Hz, 1H, H6), 4.61-4.78 (m, 4H, BOM), 4.27-4.38 (m, 1H, H7), 3.49 (bs, 1H, OH), 3.42 (dd, *J* = 19.0, 5.6 Hz, 1H, H8a), 2.86 (dd, *J* = 18.7, 10.8 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.7 (Cq), 151.7 (Cq), 148.8 (Cq), 141.7 (Cq), 137.8 (Cq), 136.9 (Cq), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.9 (2C, CH, Ar), 127.7 (3C, CH, Ar), 127.3 (CH, Ar), 126.1 (CH, Ar), 124.8 (CH, Ar), 108.8 (Cq), 88.4 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 71.0 (CH₂, BOM), 63.0 (CH, C5), 34.5 (CH, C7), 32.6 (CH₂, C8).

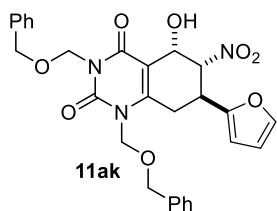
[α]_D²⁰ +26.7 (c = 0.5 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): *t*_R 15.3 min (minor), 21.6 min (major) (92.3:7.7 er).

ESI-MS [M+H]⁺ = 550.6; [M+Na]⁺ = 572.5

HRMS calcd for C₂₈H₂₇N₃O₇S ([M+H]⁺): 550.1648, found: 550.1638

Synthesis of (5*S*,6*R*,7*S*)-1,3-bis((benzyloxy)methyl)-7-(furan-2-yl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ak]



Compound **11ak** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-2-(2-nitrovinyl)furan **9k** (12.4 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 32.3 mg of (+)-**11ak**

(68% yield) as a light-yellow resin.

¹H-NMR (400 MHz, CDCl₃) δ 7.24-7.45 (m, 11H, Ph + furyl), 6.28-6.39 (m, 2H, furyl), 5.42-5.58 (m, 3H, BOM), 5.29-5.40 (m, 2H, BOM + H5), 4.91 (dd, *J* = 11.8, 4.0 Hz, 1H, H6), 4.60-4.79 (m, 4H, BOM), 4.14 (ddd, *J* = 11.2, 11.1, 6.0 Hz, 1H, H7), 3.43 (bs, 1H, OH), 3.28 (dd, *J* = 18.6, 6.1 Hz, 1H, H8a), 2.97 (dd, *J* = 18.6, 10.6 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.7 (Cq), 151.7 (Cq), 150.9 (Cq), 148.9 (Cq), 142.4 (CH, furyl), 137.8 (Cq), 136.8 (Cq), 128.6 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.3 (CH, Ar), 127.9 (2C, CH,

Ar), 127.8 (CH, Ar), 127.7 (2C, CH, Ar), 110.8 (CH, furyl), 108.7 (Cq), 108.3 (CH, furyl), 85.4 (CH, C6), 73.1 (CH₂, BOM), 72.5 (CH₂, BOM), 72.2 (CH₂, BOM), 71.0 (CH₂, BOM), 62.8 (CH, C5), 31.0 (CH, C7), 30.4 (CH₂, C8).

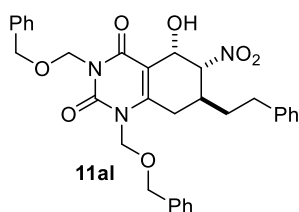
$[\alpha]_D^{20} +46.8$ (c = 0.3 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
12.2 min (minor), 18.1 min (major) (95.0:5.0 er).

ESI-MS $[M+H]^+ = 534.5$; $[M+Na]^+ = 556.4$

HRMS calcd for C₂₈H₂₇N₃O₈ ($[M+H]^+$): 534.1876, found: 534.1838

Synthesis of (5*S*,6*R*,7*S*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-phenethyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11al**]**



Compound **11al** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-(4-nitrobut-3-en-1-yl)benzene **9l** (15.8 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 60 °C. After 120 h, the resulting mixture then directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 20.3 mg of (+)-**11al** (40% yield) as a white

amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.15-7.40 (m, 15H, Ph), 5.35-5.57 (m, 4H, BOM), 5.22 (s, 1H, H5), 4.71 (s, 2H, BOM), 4.68 (s, 2H, BOM), 4.50 (dd, $J = 11.0, 3.5$ Hz, 1H, H6), 3.27 (b, 1H, OH), 3.20 (dd, $J = 18.3, 6.0$ Hz, 1H, H8a), 2.64-2.88 (m, 3H), 2.43 (dd, $J = 18.3, 9.6$ Hz, 1H, H8b), 1.98-2.12 (m, 1H), 1.73-1.62 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 151.7 (Cq), 149.3 (Cq), 140.2 (Cq), 137.8 (Cq), 136.9 (Cq), 128.7 (2C, CH, Ar), 128.6 (2C, CH, Ar), 128.3 (5C, CH, Ar), 127.8 (2C, CH, Ar), 127.7 (3C, CH, Ar), 126.5 (CH, Ar), 108.5 (Cq), 87.7 (CH, C6), 73.1 (CH₂, BOM), 72.5 (CH₂, BOM), 72.2 (CH₂, BOM), 70.9 (CH₂, BOM), 62.8 (CH, C5), 33.4 (CH₂, phenylethyl), 32.3 (CH₂, phenylethyl), 30.1 (CH, C7), 29.8 (CH₂, C8).

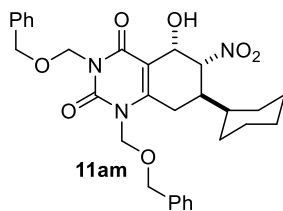
$[\alpha]_D^{20} +58.0$ (c = 1.0 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 15.8 min (minor), 35.2 min (major) (91.4:8.6 er).

ESI-MS $[M+H]^+ = 572.6$; $[M+Na]^+ = 594.5$

HRMS calcd for C₃₂H₃₃N₃O₇ ($[M+H]^+$): 572.2397, found: 572.2383

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-7-cyclohexyl-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-**11am**]



Compound (+)-**11am** was prepared according to Representative Procedure 1 using: carbaldehyde **1a** (35.0 mg, 0.089 mmol, 1 equiv), (*E*)-(2-nitrovinyl)cyclohexane **9m** (13.8 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 60 °C. After 120 h, the resulting mixture was then directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 18.6 mg of (+)-**11am** (38% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.24-7.43 (m, 10H, Ar), 5.40-5.57 (m, 4H, BOM), 5.22 (d, J = 3.8 Hz, 1H, H5), 4.60-4.78 (m, 5H, BOM + H6), 3.30 (bs, 1H, OH), 2.97 (dd, J = 18.2, 6.0 Hz, 1H, H8a), 2.70-2.82 (m, 1H, H7), 2.59 (dd, J = 18.2, 9.5 Hz, 1H, H8b), 1.49-1.89 (m, 7H, Cy), 1.12-1.39 (m, 4H, Cy).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 151.8 (Cq), 150.1 (Cq), 137.8 (Cq), 136.9 (Cq), 128.6 (2C, CH, Ar), 128.3 (3C, CH, Ar), 127.8 (2C, CH, Ar), 127.7 (3C, CH, Ar), 108.4 (Cq), 85.8 (CH, C6), 73.0 (CH₂, BOM), 72.5 (CH₂, BOM), 72.1 (CH₂, BOM), 70.9 (CH₂, BOM), 63.0 (CH, C5), 37.0 (CH, C7), 35.1 (CH, Cy), 31.0 (CH₂, C8), 26.6 (CH₂, Cy), 26.5 (CH₂, Cy), 26.2 (CH₂, Cy), 26.1 (CH₂, Cy), 25.2 (CH₂, Cy).

$[\alpha]_D^{20}$ +36.9 (c = 0.7 g/100 mL, CHCl₃)

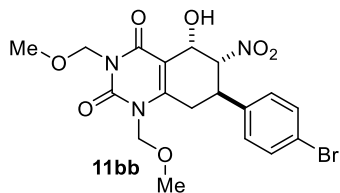
Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): t_R 12.4 min (minor), 38.5 min (major) (89.9:10.1 er).

ESI-MS $[M+H]^+$ = 550.6; $[M+Na]^+$ = 572.5

HRMS calcd for C₃₀H₃₅N₃O₇ ($[M+H]^+$): 550.2553, found: 550.2537

Scope of the pronucleophile

Synthesis of (5*S*,6*R*,7*R*)-7-(4-bromophenyl)-5-hydroxy-1,3-bis(methoxymethyl)-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-**11bb**]



Compound (+)-**11bb** was prepared according to Representative Procedure 1 using: 1,3-bis(methoxymethyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1b** (21.5 mg, 0.089 mmol, 1 equiv), (*E*)-1-bromo-4-(2-nitrovinyl)benzene **9b** (20.3 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25

°C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 4:6) to afford 36.8 mg of (+)-**11bb** (88% yield) as a white-yellow crystal. A portion of the obtained solid was recrystallized in anhydrous ethanol to afford colourless crystals that were suitable for X-ray analyses (Vide Infra).

m.p.: 200-201 °C

¹H-NMR (400 MHz, CDCl₃) δ 7.45-7.54 (m, 2H, Ar), 7.12-7.23 (m, 2H, Ar), 5.46 (bs, 1H, H5), 5.41 (1/2 ABq, J = 9.5 Hz, 1H, MOM), 5.37 (1/2 ABq, J = 9.5 Hz, 1H, MOM), 5.34 (1/2 ABq, J = 11.1 Hz, 1H, MOM), 5.18 (1/2 ABq, J = 11.1 Hz, 1H, MOM), 4.98 (dd, J = 12.5, 3.8 Hz, 1H, H6), 3.94-

4.08 (m, 2H, H7 + OH), 3.45 (s, 3H, MOM), 3.39 (s, 3H, MOM), 3.30 (dd, $J = 18.6, 5.9$ Hz, 1H, H8a), 2.70 (dd, $J = 18.6, 11.3$ Hz, 1H, H8b).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 161.9 (Cq), 151.9 (Cq), 149.3 (Cq), 138.1 (Cq), 132.4 (2C, CH, Ar), 129.0 (2C, CH, Ar), 122.0 (Cq), 109.0 (Cq), 87.1 (CH, C6), 74.8 (CH_2 , MOM), 72.7 (CH_2 , MOM), 63.1 (CH, C5), 58.2 (CH_3 , MOM), 57.5 (CH_3 , MOM), 36.4 (CH, C7), 33.9 (CH_2 , C8).

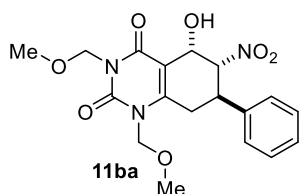
$[\alpha]_{\text{D}}^{20} +25.8$ ($c = 0.5$ g/100 mL, MeOH)

Chiral HPLC (CHIRALCEL OD-H, 70/30 Hexane/Ethanol, 1.0 mL min $^{-1}$, 254 nm):
 t_{R} 18.3 min (major), 21.2 min (minor) (91.4:8.6 er).

ESI-MS $[\text{M}+\text{H}]^+ = 471.3$; $[\text{M}+\text{Na}]^+ = 493.2$

HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{BrN}_3\text{O}_7$ ($[\text{M}+\text{H}]^+$): 470.0563, found: 470.0550

Synthesis of (5*S*,6*R*,7*R*)-5-hydroxy-1,3-bis(methoxymethyl)-6-nitro-7-phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11ba]



Compound (+)-**11ba** was prepared according to Representative Procedure 1 using: carbaldehyde **1b** (21.5 mg, 0.089 mmol, 1 equiv), *trans*- β -nitrostyrene **9a** (13.3 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 4:6) to afford 27.9 mg of (+)-**11ba** (80% yield) as a white-yellow amorphous solid.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.32-7.39 (m, 2H, Ph), 7.26-7.31 (m, 3H, Ph), 5.48 (d, $J = 3.9$ Hz, 1H, H5), 5.41 (1/2 ABq, $J = 9.5$ Hz, 1H, MOM), 5.38 (1/2 ABq, $J = 9.5$ Hz, 1H, MOM), 5.34 (1/2 ABq, $J = 11.1$ Hz, 1H, MOM), 5.16 (1/2 ABq, $J = 11.2$ Hz, 1H, MOM), 5.03 (dd, $J = 12.4, 4.0$ Hz, 1H, H6), 4.02 (ddd, $J = 11.8, 11.7, 5.9$ Hz, 1H, H7), 3.46 (s, 3H, MOM), 3.38 (s, 3H, MOM), 3.31 (dd, $J = 18.7, 5.9$ Hz, 1H, H8a), 2.73 (dd, $J = 18.7, 11.2$ Hz, 1H, H8b).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 161.9 (Cq), 151.9 (Cq), 149.5 (Cq), 138.9 (Cq), 132.4 (2C, CH, Ph), 128.9 (2C, CH, Ph), 127.6 (CH, Ph), 108.9 (Cq), 87.1 (CH, C6), 74.6 (CH_2 , MOM), 72.4 (CH_2 , MOM), 63.1 (CH, C5), 58.2 (CH_3 , MOM), 57.5 (CH_3 , MOM), 36.9 (CH, C7), 33.9 (CH_2 , C8).

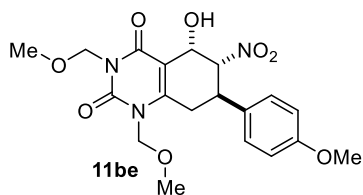
$[\alpha]_{\text{D}}^{20} +26.7$ ($c = 0.6$ g/100 mL, MeOH)

Chiral HPLC (CHIRALCEL OD-H, 80/20 Hexane/Ethanol, 1.0 mL min $^{-1}$, 254 nm):
 t_{R} 28.0 min (major), 39.7 min (minor) (83.2:16.8 er).

ESI-MS $[\text{M}+\text{H}]^+ = 392.4$; $[\text{M}+\text{Na}]^+ = 414.3$

HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_7$ ($[\text{M}+\text{H}]^+$): 392.1458, found: 392.1429

Synthesis of (5*S*,6*R*,7*R*)-5-hydroxy-1,3-bis(methoxymethyl)-7-(4-methoxyphenyl)-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione (+)-**11be**



Compound (+)-**11be** was prepared according to Representative Procedure 1 using: carbaldehyde **1b** (21.5 mg, 0.089 mmol, 1 equiv), (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **9e** (15.9 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 4:6) to afford 28.1 mg of (+)-**11be** (75% yield) as a yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.19-7.27 (m, 2H, Ar), 6.87-6.94 (m, 2H, Ar), 5.39-5.52 (m, 3H, MOM + H5), 5.38 (1/2 ABq, J = 11.0 Hz, 1H, MOM), 5.20 (1/2 ABq, J = 11.1 Hz, 1H, MOM), 4.99 (dd, J = 12.3, 4.0 Hz, 1H, H6), 3.99 (ddd, J = 11.6, 11.4, 6.0 Hz, 1H, H7), 3.81 (s, 3H, OMe), 3.47 (s, 3H, MOM), 3.41 (s, 1H, MOM), 3.24-3.37 (m, 2H, H8a + OH), 2.75 (dd, J = 18.7, 11.0 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.9 (Cq), 159.3 (Cq), 151.9 (Cq), 149.6 (Cq), 130.6 (Cq), 128.3 (2C, CH, Ar), 114.6 (2C, CH, Ar), 108.9 (Cq), 87.5 (CH, C6), 74.6 (CH₂, MOM), 72.6 (CH₂, MOM), 63.2 (CH, C5), 58.1 (CH₃), 57.5 (CH₃), 55.3 (CH₃), 36.2 (CH, C7), 34.0 (CH₂, C8).

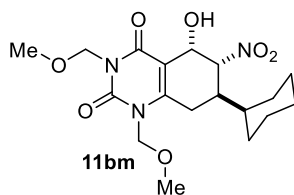
$[\alpha]_D^{20}$ +18.5 (c = 0.8 g/100 mL, MeOH)

Chiral HPLC (CHIRALCEL OD-H, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): t_R 23.3 min (major), 27.5 min (minor) (84.5:15.5 er).

ESI-MS $[M+H]^+$ = 422.4; $[M+Na]^+$ = 444.3

HRMS calcd for C₁₉H₂₃N₃O₈ ($[M+H]^+$): 422.1563, found: 422.1529

Synthesis of (5*S*,6*R*,7*R*)-7-cyclohexyl-5-hydroxy-1,3-bis(methoxymethyl)-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-**11bm**]



Compound (+)-**11bm** was prepared according to Representative Procedure 1 using: carbaldehyde **1b** (21.5 mg, 0.089 mmol, 1 equiv), (*E*)-(2-nitrovinyl)cyclohexane **9m** (13.8 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 13.5 mg of (+)-**11bm** (38% yield) as a white-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 5.26-5.50 (m, 5H, MOM + H5), 4.74 (dd, J = 11.3, 3.9 Hz, 1H, H6), 3.47 (s, 3H, MOM), 3.46 (s, 3H, MOM), 3.02 (dd, J = 18.3, 6.1 Hz, 1H, H8a), 2.77-2.90 (m, 1H, H7), 2.53-2.68 (m, 1H, H8b), 1.49-1.91 (m, 5H, Cy), 1.00-1.39 (m, 6H, Cy).

¹³C-NMR (100 MHz, CDCl₃) δ 161.9 (Cq), 152.0 (Cq), 150.4 (Cq), 108.4 (Cq), 85.9 (CH, C6), 74.7 (CH₂, MOM), 72.6 (CH₂, MOM), 63.1 (CH, C5), 58.1 (CH₃, MOM), 57.5 (CH₃, MOM), 37.1 (CH, C7), 35.1 (CH, Cy), 31.0 (CH₂, C8), 26.6 (CH₂, Cy), 26.5 (CH₂, Cy), 26.2 (CH₂, Cy), 26.1 (CH₂, Cy), 25.2 (CH₂, Cy).

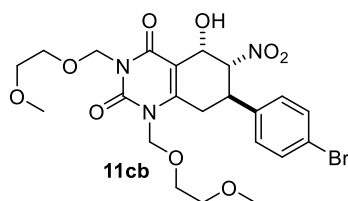
$[\alpha]_D^{20}$ +58.3 (c = 0.5 g/100 mL, MeOH)

Chiral HPLC (Amylose 1, 85/15 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
*t*_R 22.3 min (major), 28.3 min (minor) (88.4:11.6 er).

ESI-MS [M+H]⁺ = 398.4; [M+Na]⁺ = 420.3

HRMS calcd for C₁₈H₂₇N₃O₇ ([M+H]⁺): 398.1927, found: 398.1904

Synthesis of (5*S*,6*R*,7*R*)-7-(4-bromophenyl)-5-hydroxy-1,3-bis((2-methoxyethoxy)methyl)-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11cb]



Compound (+)-**11cb** was prepared according to Representative Procedure 1 using: 1,3-bis(2-methoxyethoxy)methyl-6-methyl-uracil-5-carbaldehyde **1c** (29.4 mg, 0.089 mmol, 1 equiv), (*E*)-1-bromo-4-(2-nitrovinyl)benzene **9b** (20.3 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting heterogeneous mixture was directly subjected to flash

chromatography on silica gel (petroleum ether/ ethyl acetate 3:7) to afford 37.3 mg of (+)-**11cb** (75% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.43-7.58 (m, 2H, Ar), 7.14-7.25 (m, 2H, Ar), 5.52 (1/2 ABq, *J* = 9.7 Hz, 1H, MEM), 5.48 (1/2 ABq, *J* = 9.7 Hz, 1H, MEM), 5.39-5.46 (m, 2H, H5 + MEM), 5.32 (d, *J* = 11.2 Hz, 1H, MEM), 4.97 (dd, *J* = 12.4, 4.0 Hz, 1H, H6), 3.99 (ddd, *J* = 11.6, 11.5, 5.9 Hz, 1H, H7), 3.85-3.92 (m, 1H, OH), 3.78-3.84 (m, 2H, MEM), 3.66-3.76 (m, 2H, MEM), 3.51-3.55 (m, 2H, MEM), 3.46-3.51 (m, 2H, MEM), 3.29-3.43 (m, 7H, MEM + H8a), 2.77 (dd, *J* = 18.6, 11.3 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.8 (Cq), 151.9 (Cq), 149.4 (Cq), 138.3 (Cq), 132.3 (2C, CH, Ar), 129.0 (2C, CH, Ar), 121.8 (Cq), 108.8 (Cq), 87.2 (CH, C6), 73.6 (CH₂, MEM), 71.7 (CH₂, 2C, MEM), 71.5 (CH₂, MEM), 70.0 (CH₂, MEM), 68.8 (CH₂, MEM), 63.1 (CH, H5), 59.1 (CH₃, 2C, MEM), 36.4 (CH, C7), 33.8 (CH₂, C8).

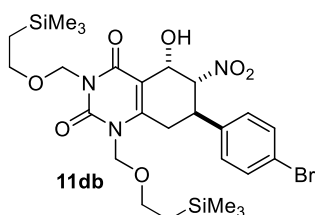
[α]_D²⁰ +27.6 (c = 0.01 g/100 mL, MeOH)

Chiral HPLC (CHIRALCEL OD-H, 80/20 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
*t*_R 33.3 min (minor), 44.5 min (major) (93.7:6.3 er).

ESI-MS [M+H]⁺ = 559.4; [M+Na]⁺ = 581.3

HRMS calcd for C₂₂H₂₈BrN₃O₉ ([M+H]⁺): 558.1087, found: 558.1069

Synthesis of (5*S*,6*R*,7*R*)-7-(4-bromophenyl)-5-hydroxy-6-nitro-1,3-bis((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11db]



Compound (+)-**11db** was prepared according to Representative Procedure 1 using: 6-methyl-2,4-dioxo-1,3-bis((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1d** (36.9 mg, 0.089 mmol, 1 equiv), (*E*)-1-bromo-4-(2-nitrovinyl)benzene **9b** (20.3 mg, 0.089 mmol, 1 equiv) and catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting mixture was directly subjected to flash

chromatography on silica gel (petroleum ether/ ethyl acetate 8:2) to afford 28.6 mg of (+)-**11db** (50% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.48-7.56 (m, 2H, Ar), 7.16-7.20 (m, 2H, Ar), 5.26-5.64 (m, 4H, H5 + SEM), 5.21 (d, J = 11.3 Hz, 1H, SEM), 4.99 (dd, J = 12.4, 4.0 Hz, 1H, H6), 4.02 (ddd, J = 11.9, 11.8, 5.9 Hz, 1H, H7), 3.60-3.77 (m, 4H, SEM), 3.54 (bs, 1H, OH), 3.36 (dd, J = 18.6, 5.9 Hz, 1H, H8a), 2.74 (dd, J = 18.6, 11.3 Hz, 1H, H8b), 0.96-1.02 (m, 2H, SEM), 0.88-0.96 (m, 2H, SEM), 0.03 (s, 9H, SEM), 0.01 (s, 9H, SEM).

¹³C-NMR (100 MHz, CDCl₃) δ 161.9 (Cq), 151.7 (Cq), 149.1 (Cq), 138.1 (Cq), 132.4 (2C, CH, Ar), 128.9 (2C, CH, Ar), 122.0 (Cq), 108.8 (Cq), 87.0 (CH, C6), 72.8 (CH₂, SEM), 70.7 (CH₂, SEM), 67.9 (CH₂, SEM), 67.7 (CH₂, SEM), 63.2 (CH, C5), 36.5 (CH, C7), 33.8 (CH₂, C8), 18.2 (CH₂, SEM), 18.0 (CH₂, SEM), -1.4 (CH₃, 6C).

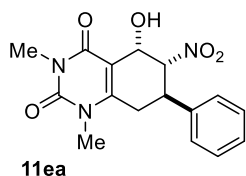
$[\alpha]_D^{20}$ +12.8 (c = 0.9 g/100 mL, MeOH)

Chiral HPLC (Amylose 1, 95/5 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 23.0 min (major), 26.8 min (minor) (85.0:15.0 er).

ESI-MS $[M+H]^+$ = 643.7; $[M+Na]^+$ = 665.6

HRMS calcd for C₂₆H₄₀BrN₃O₇Si₂ ($[M+H]^+$): 642.1666, found: 642.1643

Synthesis of (5*S*,6*R*,7*R*)-7-(4-bromophenyl)-5-hydroxy-1,3-dimethyl-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **11ea**



Compound **11ea** was prepared according to Representative Procedure 1 using: 1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1e** (16.2 mg, 0.089 mmol, 1 equiv.), (*E*)-1-bromo-4-(2-nitrovinyl)benzene **9b** (13.3 mg, 0.089 mmol, 1 equiv.) and Takemoto's catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25 °C. After 72 h, the resulting mixture was then directly

subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 14.7 mg of **11ea** (50% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.47-7.38 (m, 2H, Ph), 7.36-7.31 (m, 3H, Ph), 5.53 (d, J = 3.9 Hz, 1H, H5), 5.05 (dd, J = 12.4, 3.9 Hz, 1H, H6), 4.08 (ddd, J = 11.7, 11.7, 6.1 Hz, 1H, H7), 3.60 (bs, 1H, OH), 3.14 (dd, J = 18.4, 6.1 Hz, 1H, H8a), 2.67 (dd, J = 18.3, 11.1 Hz, 1H, H8b).

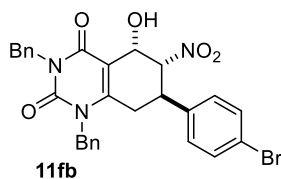
¹³C-NMR (100 MHz, CDCl₃) δ 162.1 (Cq), 151.6 (Cq), 148.5 (Cq), 139.0 (Cq), 132.5 (2C, CH, Ar), 129.4 (2C, CH, Ar), 128.2 (CH, Ph), 127.1 (2C, CH, Ph), 107.8 (Cq), 87.1 (CH, C6), 63.3 (CH, C5), 37.0 (CH, C7), 35.5 (CH₂, C8), 31.2 (CH₃, Me), 29.7 (CH₃, Me).

Chiral HPLC (CHIRALCEL OD-H, 95/5 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 24.3 min (major), 35.4 min (minor) (68.0:32.0 er).

ESI-MS $[M+H]^+$ = 332.3; $[M+Na]^+$ = 354.2

HRMS calcd for C₃₀H₂₉N₃O₇ ($[M+H]^+$): 331.1168, found: 331.1147

Synthesis of (5*S*,6*R*,7*R*)-1,3-dibenzyl-7-(4-bromophenyl)-5-hydroxy-6-nitro-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11fb]



Compound (+)-**11fb** was prepared according to representative procedure 1 using: 1,3-dibenzyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1f** (29.7 mg, 0.089 mmol, 1 equiv.), (E)-1-bromo-4-(2-nitrovinyl)benzene **9b** (20.3 mg, 0.089 mmol, 1 equiv.) and Takemoto's catalyst **C1** (3.7 mg, 0.009 mmol, 0.1 equiv.) in xylene at 25 °C. After 72 h, the resulting mixture was then directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 6:4) to afford 17.5 mg of (+)-**11fb** (35% yield) as a white amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.42-7.55 (m, 4H, Ar), 7.28-7.39 (m, 7H, Ar), 7.00-7.12 (m, 3H, Ar), 5.49 (d, J = 3.0 Hz, 1H, H5), 5.10-5.38 (m, 3H, Bn), 5.00 (d, J = 15.8 Hz, 1H, Bn), 4.88 (dd, J = 11.8, 2.9 Hz 1H, H6), 3.85-4.03 (m, 1H, H7), 3.04 (dd, J = 18.5, 5.7 Hz, 1H, H8a), 2.54 (dd, J = 18.4, 10.9 Hz, 1H, H8b).

¹³C-NMR (100 MHz, CDCl₃) δ 161.7 (Cq), 151.7 (Cq), 148.4 (Cq), 137.9 (Cq), 136.3 (Cq), 135.1 (Cq), 132.4 (2C, CH, Ar), 129.3 (2C, CH, Ar), 129.1 (2C, CH, Ar), 128.8 (2C, CH, Ar), 128.5 (2C, CH, Ar), 128.2 (CH, Ar), 127.9 (CH, Ar), 126.1 (2C, CH, Ar), 122.0 (Cq), 108.5 (Cq), 86.9 (CH, C6), 63.3 (CH, C5), 47.5 (CH₂, Bn), 45.2 (CH₂, Bn), 36.5 (CH, C7), 34.6 (CH₂, C8).

$[\alpha]_D^{20}$ +9.0 (c = 0.3 g/100 mL, AcOEt)

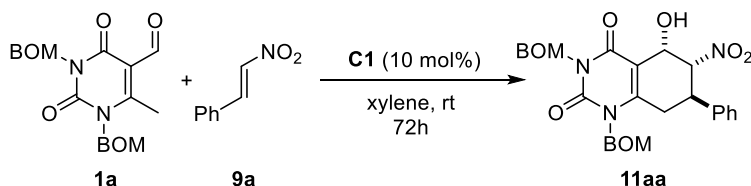
Chiral HPLC (Amylose 1, 80/20 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm): t_R 31.2 min (minor), 35.6 min (minor) (87.9:12.1 er).

ESI-MS $[M+H]^+ = 563.4$; $[M+Na]^+ = 585.3$

HRMS calcd for C₂₈H₂₄BrN₃O₅ ($[M+H]^+$): 562.0978, found: 562.0951

2.5.4 Scaled-up model reaction

Synthesis of (5*S*,6*R*,7*R*)-1,3-bis((benzyloxy)methyl)-5-hydroxy-6-nitro-7-phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-11aa]

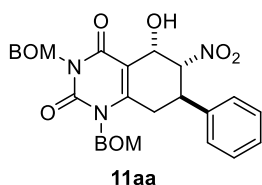


In a round-bottomed flask equipped with a magnetic stir bar and kept under nitrogen atmosphere, 1,3-bis((benzyloxy)methyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1a** (250 mg, 0.63 mmol, 1 equiv) and *trans*- β -nitrostyrene **9a** (94.0 mg, 0.63 mmol, 1 equiv) were dissolved in xylene (8.8 mL) at 25 °C. Takemoto's catalyst **C1** (14.9 mg, 0.063 mmol, 0.1 equiv) was then added and the resulting reaction was stirred at 25 °C. After 72 h, the mixture was directly subjected to flash chromatography on silica gel (petroleum ether/ ethyl acetate 7:3) to afford 267 mg of **11aa** (78% yield, 90:10 er) as a pale-yellow solid.

2.5.5 Enhancement of enantioenrichment by recrystallization

Method A (Representative Procedure 2)

Preparation of enantiopure (5*S*,6*R*,7*R*)-11aa

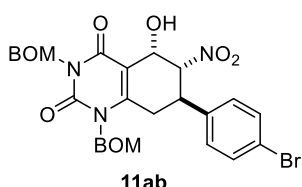


Compound (+)-**11aa** (41 mg, 0.075 mmol, er 91:9) was dissolved in 9 mL of *n*-hexane and 3.9 mL of CH₂Cl₂ under reflux until full dissolution. The resulting solution was subjected to crystallization over a period of 12 h at rt and then filtered over a Buckner funnel. The filtrate was evaporated under reduced pressure to afford 31.0 mg (0.057 mmol, 75% yield) of enantiopure (+)-**11aa** (er > 99:1) as an amorphous solid.

$[\alpha]_D^{20} +33.8$ (c = 0.8 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
*t*_R 14.9 min (minor), 28.2 min (major) (99.1:0.9 er).

Preparation of enantiopure (5*S*,6*R*,7*R*)-11ab

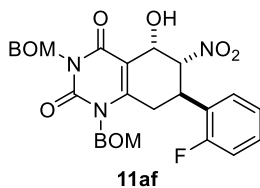


Enantiopure (+)-**11ab** was obtained according to Representative Procedure 2 by dissolving compound (+)-**11ab** (41 mg, 0.066 mmol, er 93:7) in 9.5 mL of *n*-hexane and 2.9 mL of CH₂Cl₂ under reflux. The filtrate was evaporated under reduced pressure to afford 27.1 mg (0.043 mmol, 66% yield) of enantiopure (+)-**11ab** (>99:1 er) as an amorphous solid.

$[\alpha]_D^{20} +18.0$ (c = 0.2 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
*t*_R 15.3 min (minor), 47.8 min (major) (99.7:0.3 er).

Preparation of enantiopure (5*S*,6*R*,7*R*)-11af

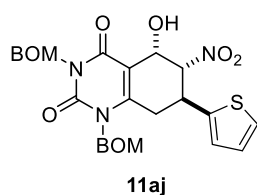


Enantiopure (+)-**11af** was obtained according to Representative Procedure 2 dissolving compound (+)-**11af** (37 mg, 0.066 mmol, er 78:22) in 7.1 mL of *n*-hexane and 1.8 mL of CH₂Cl₂ under reflux. The filtrate was evaporated under reduced pressure to afford 7.3 mg (0.013 mmol, 20% yield) of enantiopure (+)-**11af** (>99:1 er) as an amorphous solid.

$[\alpha]_D^{20} +31.2$ (c = 1.0 g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
*t*_R 13.4 min (minor), 23.3 min (major) (99.7:0.3 er).

Preparation of enantiopure (5*S*,6*R*,7*S*)-11aj



Enantiopure (+)-**11aj** was obtained according to Representative Procedure 2 by dissolving compound (+)-**11aj** (36 mg, 0.065 mmol, 92:8 er) in 9.0 mL of *n*-hexane and 3.4 mL of CH₂Cl₂ under reflux. The filtrate was evaporated under reduced pressure to afford 16.8 mg (0.049 mmol, 78% yield) of (+)-**11aj** (99:1 er) as an amorphous solid.

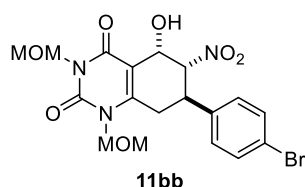
$[\alpha]_D^{20} +40.0$ ($c = 0.005$ g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):

t_R 14.9 min (minor), 21.0 min (major) (99.0:1.0 er).

Method B

Preparation of enantiopure (5*S*,6*R*,7*R*)-11bb



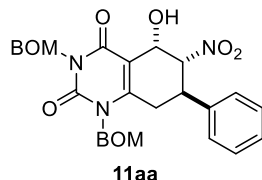
Compound (+)-**11bb** (37 mg, 0.079 mmol, 91:9 er) was dissolved in 3.1 mL of anhydrous ethanol at rt. The resulting solution was subjected to crystallization for 12 h at rt and then filtered through a Buckner funnel. The precipitate was collected to afford 20.4 mg (0.043 mmol, 55% yield) of (+)-**11bb** (97:3 er) as white crystals.

$[\alpha]_D^{20} +30.8$ ($c = 0.5$ g/100 mL, MeOH)

Chiral HPLC (Amylose 1, 70/30 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):

t_R 21.7 min (major), 31.7 min (minor) (99.2:0.8 er).

Preparation of enantiopure (5*S*,6*R*,7*R*)-11aa



Enantiopure (+)-**11aa** was obtained according to Method B by dissolving compound (+)-**11aa** (43 mg, 0.079 mmol, 91:9 er) in 2.3 mL of ethanol under reflux. The filtrate was evaporated under reduced pressure to afford 33.1 mg (0.061 mmol, 78% yield), of (+)-**11aa** (99.0:1.0 er) as an amorphous solid.

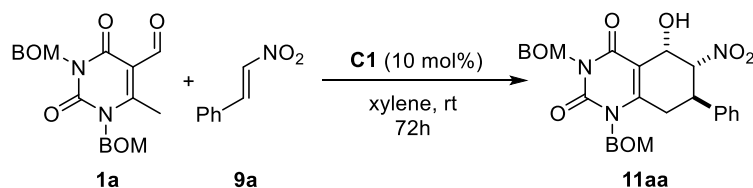
$[\alpha]_D^{20} +33.8$ ($c = 0.8$ g/100 mL, CHCl₃)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):

t_R 14.9 min (minor), 28.2 min (major) (99.1:0.9 er).

Method C

Preparation of enantiopure (5*S*,6*R*,7*R*)-11aa



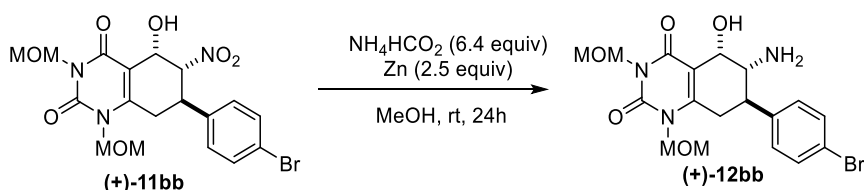
Compound **11aa** was prepared according to a slightly modified Representative Procedure 1 using: 1,3-bis((benzyloxy)methyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1a** (30 mg, 0.076 mmol, 1 equiv), *trans*- β -nitrostyrene **9a** (11.3 mg, 0.076 mmol, 1 equiv) and Takemoto's catalyst **C1** (3.1 mg, 0.008 mmol, 0.1 equiv) in xylene at 25 °C. After 72 h, the resulting mixture was evaporated under reduced pressure and the crude was dissolved in 800 μ L of ethanol under reflux. The resulting solution was slowly cooled to rt and left to crystallize for 12 h. The resulting heterogeneous mixture was then filtered over a Buckner funnel, and the filtrate was evaporated under reduced pressure to afford 27 mg (0.050 mmol, 65% yield) of enantiopure (+)-**11aa** (99.1:0.9 er) as an amorphous solid.

$[\alpha]_D^{20} +33.8$ ($c = 0.8$ g/100 mL, CHCl_3)

Chiral HPLC (CHIRALCEL OD-H, 60/40 Hexane/Ethanol, 1.0 mL min⁻¹, 254 nm):
 t_R 14.9 min (minor), 28.2 min (major) (99.1:0.9 er).

2.5.6 Synthetic elaboration of cycloadducts of type 11

Synthesis of (5*S*,6*R*,7*R*)-6-amino-7-(4-bromophenyl)-5-hydroxy-1,3-bis(methoxymethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione [(+)-12bb**]**



To a solution of nitro-derivative (+)-**11bb** (30 mg, 0.064 mmol, 91:9 er) in MeOH dry (2.5 mL) cooled to 0 °C (ice bath), ammonium formate (20.8 mg, 0.33 mmol, 6.4 equiv) and Zn (8.3 mg, 0.13 mmol, 2.5 equiv) were added. The resulting heterogeneous mixture was then allowed to reach room temperature (25 °C) and vigorously stirred for 24 h. The progress of reaction was monitored by TLC. The resulting suspension was filtered and concentrated in vacuo to afford a crude that was purified by silica gel flash chromatography (AcOEt:MeOH/NH₃ 9.5:0.5) to yield amine (+)-**12bb** (12 mg, 42% yield) as a pale-yellow resin.

¹H-NMR (400 MHz, CD₃OD) δ 7.54-7.67 (m, 2H, Ar), 7.33-7.41 (m, 2H, Ar), 5.38-5.46 (m, 3H, MOM), 5.25 (d, $J = 11.1$ Hz, 1H, MOM), 4.89-4.92 (m, 1H, H5), 3.44 (s, 3H, MOM), 3.37 (s, 3H, MOM), 3.30-3.35 (m, 2H, H6 + H7), 3.21 (dd, $J = 18.4, 5.0$ Hz, 1H, H8a), 2.97 (dd, $J = 18.4, 10.7$ Hz, 1H, H8b).

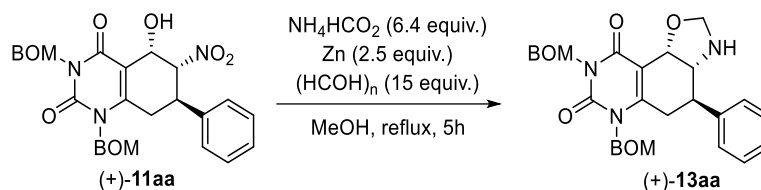
¹³C-NMR (100 MHz, CD₃OD) δ 162.1 (Cq), 152.3 (Cq), 150.7 (Cq), 139.2 (Cq), 132.0 (2C, CH, Ar), 130.2 (2C, CH, Ar), 121.2 (Cq), 109.9 (Cq), 74.3 (CH₂, MOM), 72.1 (CH₂, MOM), 62.5 (CH, C5), 56.6 (CH₃, MOM), 55.9 (CH₃, MOM), 53.4 (CH, C6), 39.9 (CH, C7), 33.3 (CH₂, C8).

$[\alpha]_D^{20} +11.7$ ($c = 0.2$ g/100 mL, MeOH)

ESI-MS $[M+H]^+ = 441.3$; $[M+Na]^+ = 463.2$

HRMS calcd for C₁₈H₂₂BrN₃O₅ ($[M+H]^+$): 440.0821, found: 440.0794

Representative procedure 3: synthesis of (3*aR*,4*R*,9*bS*)-6,8-bis((benzyloxy)methyl)-4-phenyl-3,3*a*,4,5,6,9*b*-hexahydrooxazolo[5,4-*f*]quinazoline-7,9(2*H*,8*H*)-dione [(+)-13*aa*]



To a solution of nitro-derivative (+)-11*aa* (40 mg, 0.073 mmol, 91:9 er) in MeOH dry (4.3 mL) cooled to 0 °C (ice bath), ammonium formate (30 mg, 0.47 mmol, 6.4 equiv), Zn (12 mg, 0.18 mmol, 2.5 equiv) and paraformaldehyde (33 mg, 1.10 mmol, 15 equiv) were added. The suspension was then vigorously stirred under reflux for 5 h. The resulting mixture was then filtered and concentrated under reduced pressure. The resulting solid was extracted with CH₂Cl₂ (3 × 10 mL), the combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 3.5:6.5) to provide oxazolidine (+)-13*aa* (27 mg, 68%) as a pale-yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.40-7.48 (m, 3H, Ph), 7.24-7.39 (m, 12H, Ph), 6.03 (bs, 1H, NH), 5.44-5.63 (m, 3H, BOM), 5.23-5.33 (m, 1H, BOM), 5.12-5.19 (m, 1H, H5), 4.81-4.90 (m, 2H, oxazolidine), 4.77 (s, 2H, BOM), 4.61-4.69 (m, 2H, BOM), 3.70-3.84 (m, 1H, H6), 3.07-3.19 (m, 1H, H8a), 2.66-2.76 (m, 2H, H8b + H7).

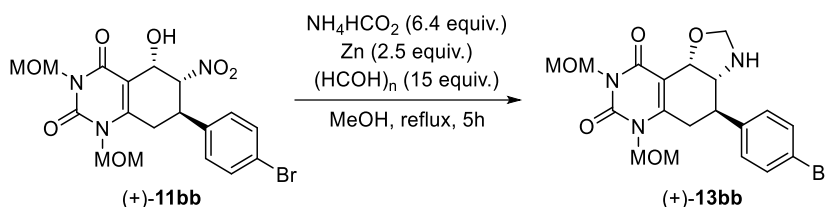
¹³C-NMR (100 MHz, CDCl₃) δ 162.2 (Cq), 152.1 (Cq), 150.5 (Cq), 138.0 (Cq), 137.0 (Cq), 129.1 (CH, Ar), 128.5 (CH, 2C, Ar), 128.3 (2C, CH, Ar), 128.2 (CH, Ar), 127.9 (2C, CH, Ar), 127.8 (3C, CH, Ar), 127.6 (2C, CH, Ar), 127.5 (2C, CH, Ar), 125.5 (Cq), 107.3 (Cq), 89.9 (CH₂, oxazolidine), 73.1 (CH₂, BOM), 72.4 (CH₂, BOM), 71.9 (CH₂, BOM), 71.1 (CH, C6), 70.8 (CH₂, BOM), 68.7 (CH, C5) 39.5 (CH, C7), 33.0 (CH₂, C8).

[α]_D²⁰ +26.3 (c = 0.7 g/100 mL, CHCl₃)

ESI-MS [M+H]⁺ = 498.5; [M+Na]⁺ = 520.4

HRMS calcd for C₂₉H₂₇N₃O₅ ([M+H]⁺): 498.2029, found: 498.2005

Synthesis of (3*aR*,4*R*,9*bS*)-4-(4-bromophenyl)-6,8-bis(methoxymethyl)-3,3*a*,4,5,6,9*b*-hexahydrooxazolo[5,4-*f*]quinazoline-7,9(2*H*,8*H*)-dione [(+)-13*bb*]



Oxazolidine **13bb** was prepared from nitro-derivative (+)-11*bb* (40 mg, 0.085 mmol, 91:9 er), following Representative Procedure 3 using ammonium formate (34.3 mg, 0.54 mmol, 6.4 equiv), Zn (13.9 mg, 0.21 mmol, 2.5 equiv) and paraformaldehyde (38.3 mg, 1.28 mmol, 15 equiv) in MeOH (5.0 mL). The resulting suspension was filtered and then extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated by rotary

evaporation. The resulting crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 2:8) to yield pure product (+)-**13bb** (27.7 mg, 72% yield) as a yellow amorphous solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.48-7.60 (m, 2H, Ar), 7.27-7.39 (m, 2H, Ar), 5.40-5.46 (m, 3H, MOM), 5.27 (d, J = 11.1 Hz, 1H, MOM), 5.11 (d, J = 5.0 Hz, 1H, H5), 4.87 (1/2 ABq, J = 8.2 Hz, 1H, oxazolidine), 4.71 (1/2 ABq, J = 8.1 Hz, 1H, oxazolidine), 3.85 (dd, J = 12.4, 5.0 Hz, 1H, H6), 3.44 (s, 3H, MOM), 3.38 (s, 3H, MOM), 3.12 (dd, J = 17.6, 4.7 Hz, 1H, H8a), 2.94 (dd, J = 17.6, 11.8 Hz, 1H, H8b), 2.78 (ddd, J = 12.1, 12.0, 4.6 Hz, 1H, H7).

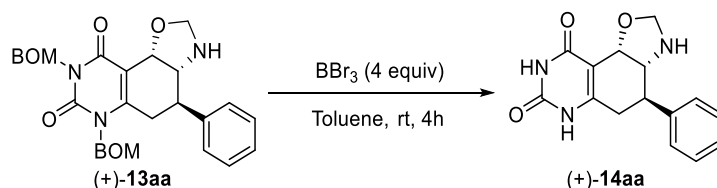
¹³C-NMR (100 MHz, CD₃OD) δ 162.8 (Cq), 152.3 (Cq), 151.9 (Cq), 140.7 (Cq), 131.2 (CH, 2C, Ar), 129.6 (2C, CH, Ar), 120.3 (Cq), 106.8 (Cq), 89.1 (CH₂, oxazolidine), 74.5 (CH₂, MOM), 72.1 (CH₂, MOM), 71.3 (CH, C6), 68.6 (CH, C5), 56.6 (CH₃, MOM), 55.8 (CH₃, MOM), 38.8 (CH, C7), 32.0 (CH₂, C8).

$[\alpha]_D^{20}$ +8.9 (c = 0.6 g/100 mL, CHCl₃)

ESI-MS $[M+H]^+$ = 453.3; $[M+Na]^+$ = 475.2

HRMS calcd for C₁₉H₂₂BrN₃O₅ ($[M+H]^+$): 452.0821, found: 452.0793

Synthesis of (3a*R*,4*R*,9b*S*)-4-phenyl-3,3a,4,5,6,9b-hexahydrooxazolo[5,4-*f*]quinazoline-7,9(2*H*,8*H*)-dione [(+)-**14aa**]



To a stirred suspension of oxazolidine (+)-**13aa** (40 mg, 0.076 mmol) in toluene (1 mL), under nitrogen atmosphere at rt, BBr₃ was added dropwise (52 μ L, 0.30 mmol, 4 equiv). The progress of reaction was monitored by TLC and after 5 hours, 4 mL of a saturated aqueous solution of NaHCO₃ were added and the mixture was stirred for 1 additional hour. The aqueous phase was then isolated by a separating funnel and evaporated under reduced pressure. The resulting solid was dissolved in EtOH (15 mL) under reflux. The obtained solution was crystallized for 12 h at rt. The precipitate was filtered, and the filtrate was evaporated in vacuo. This latter was subjected to flash chromatography on silica gel (EtOAc:MeOH 9.5:0.5) to finally yield 17 mg of **14aa** (78% yield) as a pale-yellow amorphous solid.

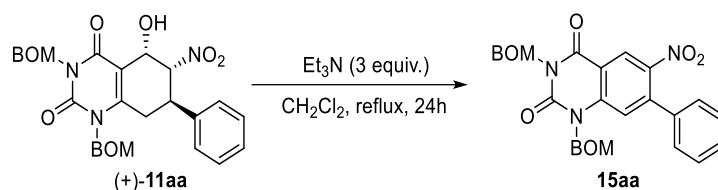
¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.08 (bs, 1H, NH), 10.97 (bs, 1H, NH), 8.81 (s, 1H, NH), 7.36-7.43 (m, 1H, Ph), 7.29-7.36 (m, 3H, Ph), 7.19-7.27 (m, 1H, Ph), 4.80 (d, J = 4.8 Hz, 1H, H5), 4.75 (1/2 ABq, J = 7.9 Hz, 1H, oxazolidine), 4.46 (1/2 ABq, J = 7.9 Hz, 1H, oxazolidine), 3.74 (dd, J = 11.8, 4.8 Hz, 1H, H6), 2.61-2.82 (m, 2H, H8a + H7), 2.41-2.48 (m, 1H, H8b).

¹³C-NMR (100 MHz, DMSO-*d*₆) δ 164.5 (Cq), 151.8 (Cq), 151.4 (Cq), 142.8 (Cq), 128.8 (2C, CH, Ar), 128.4 (2C, CH, Ar), 127.1 (CH, Ar), 104.6 (Cq), 89.5 (CH₂, oxazolidine), 71.9 (CH, C5), 67.9 (CH, C6), 38.9 (CH, C7), 33.6 (CH₂, C8).

ESI-MS $[M+H]^+$ = 286.3; $[M+Na]^+$ = 308.2

HRMS calcd for C₁₅H₁₅N₃O₃ ($[M+H]^+$): 286.1192, found: 286.1169

Synthesis of 1,3-bis((benzyloxy)methyl)-6-nitro-7-phenylquinazoline-2,4(1*H*,3*H*)-dione (**15aa**)



To a suspension of nitro-derivative (+)-**11aa** (30 mg, 0.055 mmol) in CH₂Cl₂ (2 mL), 23 μL of Et₃N (0.165 mmol, 3 equiv) were added and the resulting mixture was allowed to stir under reflux. After 24 h, the crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 8:2) to yield pure **15aa** (20.4 mg, 75% yield) as a yellow amorphous solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H, H5), 7.10-7.68 (m, 16H, Ph + H8), 5.69 (s, 2H, BOM), 5.64 (s, 2H, BOM), 4.76 (s, 2H, BOM), 4.69 (s, 2H, BOM).

¹³C-NMR (100 MHz, CDCl₃) δ 160.1 (Cq), 150.91 (Cq), 144.7 (Cq), 143.5 (Cq), 141.6 (Cq), 137.6 (Cq), 136.7 (Cq), 136.4 (Cq), 129.2 (CH, Ar), 129.0 (2C, CH, Ar), 128.5 (2C, CH, Ar), 128.4 (2C, CH, Ar), 128.2 (CH, Ar), 127.8 (3C, CH, Ar), 127.7 (4C, CH, Ar), 125.9 (CH, Ar), 118.7 (CH, Ar), 114.6 (Cq), 73.8 (CH₂, BOM), 72.5 (CH₂, BOM), 71.8 (CH₂, BOM), 71.3 (CH₂, BOM).

ESI-MS [M+H]⁺ = 496.5; [M+Na]⁺ = 518.4

HRMS calcd for C₂₈H₂₁N₃O₆ ([M+H]⁺): 496.1509, found: 496.1499

2.5.7 Determination of the absolute configuration of the products

Determination of the Absolute Configuration of Bicyclic Products 11

The absolute configuration of compound (+)-**11bb** was certified as 5*S*,6*R*,7*R* by single crystal X-ray analysis of a suitable crystal. Hence, by analogy, the 5*S*,6*R*,7*R* -configuration of all other products **11** was established.

CRYSTAL DATA FOR (+)-11bb: C₁₈H₂₀BrN₃O₇, orthorhombic, *P*2₁2₁2₁, *a*=10.351(3)Å, *b*=9.547(3)Å, *c*= 19.492(6)Å, *V*=1926.2(10)Å³; *Z*=4; *d*_{calc}=1.622 mg/cm³, *F*(000)= 960, CuKα radiation (λ = 1.54184), μ=3.339, Tot. refl.= 26955, *hkl* range= -12<*h*<12, -11<*k*<11, -18<*l*<24; Theta range 4.54-73.27, unique reflections= 3563, number of parameters = 265, GooF= 1.253, *R*=0.048, *wR*₂=0.142 Flack *x* = 0.045(5) determined using 1400 quotients [(*I*⁺)-(*I*⁻)]/[(*I*⁺)+(*I*⁻)].³⁸

CCDC 2049345-2049348 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via { HYPERLINK "www.ccdc.cam.ac.uk/data_request/cif" }.

³⁸ Parsons, S.; Flack, H.D.; Wagner, T. "Use of intensity quotients and differences in absolute structure refinement" *Acta Cryst.* **2013**, B69, 249.

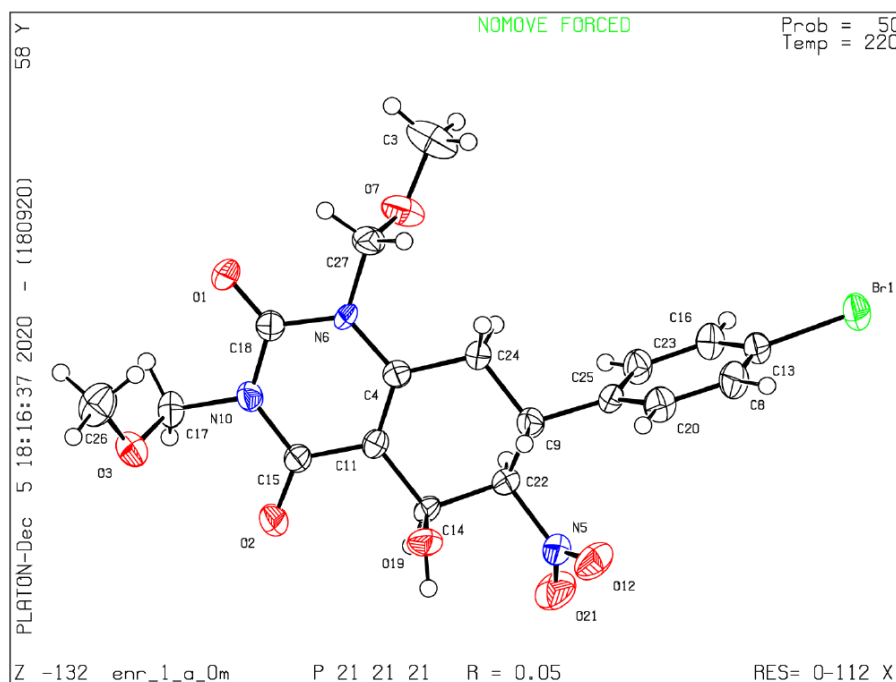


Figure 8 ORTEP representation of (+)-**11bb**

Determination of the Relative Configuration of Products **11**

The relative configuration of compounds **6** was also confirmed by single crystal X-ray analysis of racemic 4-Br-MOM derivative **11bb**, 4-Br-MEM derivative **11cb** and 4-Br-benzyl derivative **11fb**. Hence, by analogy, the *cis* relationship between H5 and H6 and the *trans* relationship between H5 and H7 of all other products were established.

CRYSTAL DATA for (±)-11bb**:** C₁₈H₂₀BrN₃O₇, monoclinic, *P*2₁/*c*, *a*=9.8288(8)Å, *b*=10.0205(8)Å, *c*=20.7385(16)Å, β=102.919(3)°, *V*=1990.8(3)Å³; *Z*=4; *d*_{calc}=1.569 mg/cm³, *F*(000)=960, CuKα radiation (λ = 1.54184), μ=3.230, Tot. refl.=23286, *hkl* range= -12<*h*<12, -12<*k*<12, -25<*l*<25; Theta range 4.38-74.89, unique reflections=3986, number of parameters = 281, GooF=1.009, *R*=0.070, *wR*₂=0.225.

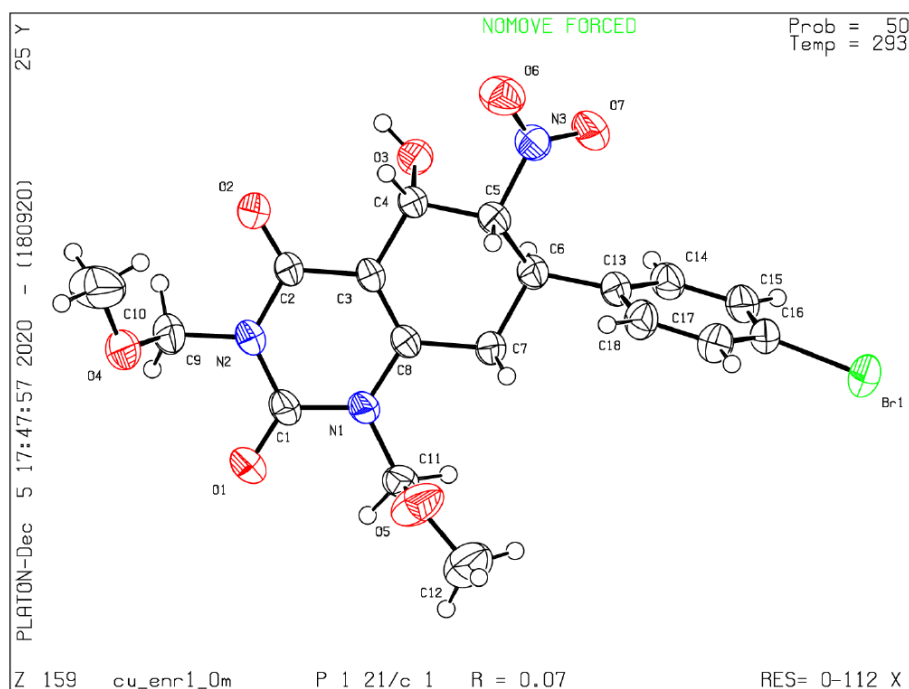


Figure 9 ORTEP representation of (±)-11bb

CRYSTAL DATA for (±)-11cb: $C_{22}H_{28}BrN_3O_9$, monoclinic, $P2_1/c$, $a=14.726(2)\text{\AA}$, $b=11.361(1)\text{\AA}$, $c=16.004(2)\text{\AA}$, $\beta=116.551(5)^\circ$, $V=2395.1(5)\text{\AA}^3$, $Z=4$; $d_{\text{calc}}=1.546\text{ mg/cm}^3$, $F(000)=1148$, MoK α radiation ($\lambda=0.71069$), $\mu=1.774$, Tot. refl.= 48260, hkl range= $-17<h<18$, $-13<k<13$, $-19<l<19$; Theta range 2.29-25.78, unique reflections= 4567, number of parameters = 330, GooF= 1.071, $R=0.049$, $wR2=0.133$.

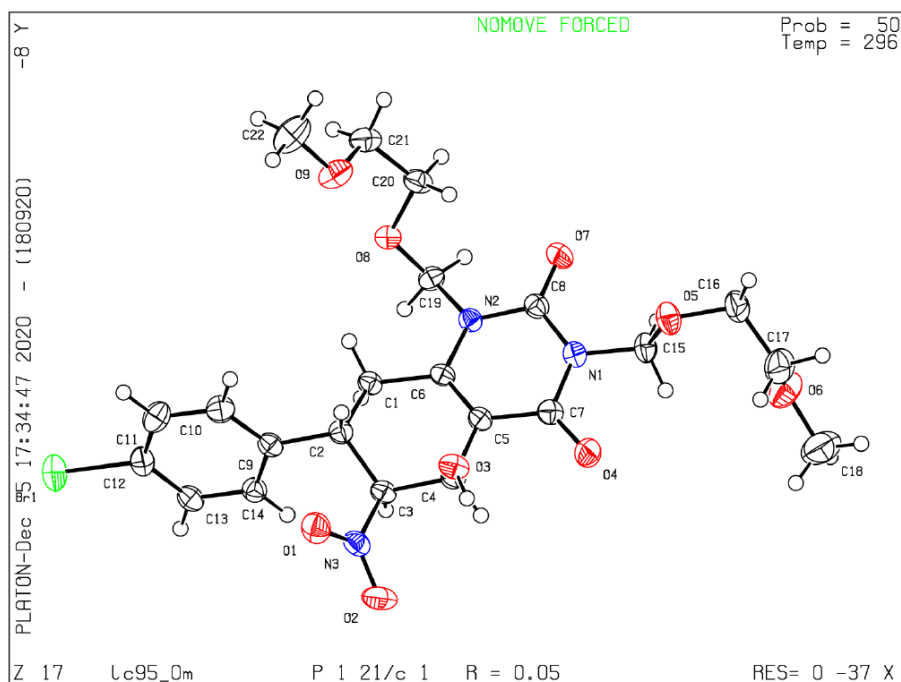


Figure 10 ORTEP representation of (±)-11cb

CRYSTAL DATA for (±)-11fb: C₂₈H₂₄BrN₃O₅, monoclinic, *P*2₁/*n*, *a*=14.0349(5)Å, *b*=8.9625(3)Å, *c*=20.6047(8)Å, β=102.633(1)°, *V*=2529.1(2) Å³; *Z*=4; *d*_{calc}=1.477 mg/cm³, *F*(000)=1152, CuKα radiation (λ = 1.54184), μ=2.589, Tot. refl.=71101, *hkl* range= -17<*h*<17, -11<*k*<10, -25<*l*<25; Theta range 4.28-74.71, unique reflections=5165, number of parameters = 374, GooF=1.051, *R*=0.043, *wR*₂=0.120.

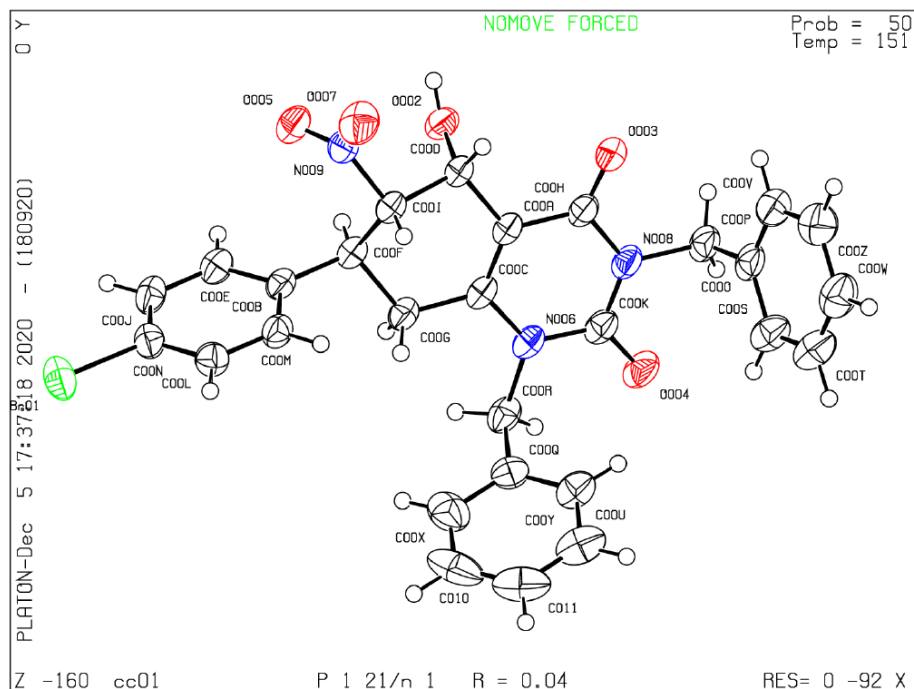


Figure 11 ORTEP representation of (±)-11fb

Chapter III

Accessing enantiopure 6,7-dihydrobenzimidazoles via organocatalytic [4+2] cycloaddition reactions

3.1 Background

The nitrogen-containing, aromatic *imidazole heterocycle* plays a pivotal role among different areas of knowledge including chemical, biological and material sciences.¹ In biological systems it is mostly found in the form of the amino acid histidine, standing out within an endless number of active sites, useful in catalysing crucial life-driving processes, such as the cleavage of thermodynamically stable C-O and C-P bonds in DNA and RNA filaments.² More in details, the amphoteric nature of the imidazole ring, as well as its peculiar electronic properties, account for its unique and modulable trimodal catalytic behaviour as either acid and base, or nucleophile, depending on the specific necessity, as schematically shown in Figure 1.³

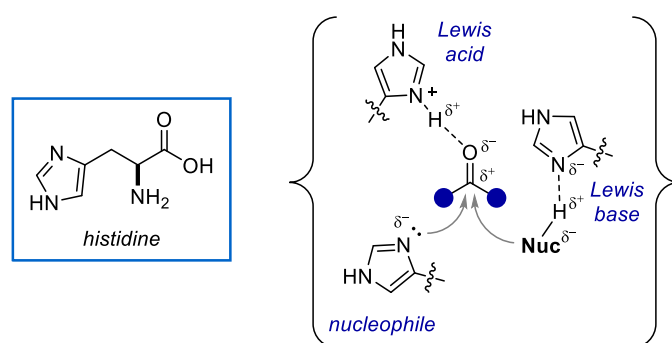


Figure 1 Chemical structure of histidine and its peculiar acidic, basic and nucleophilic catalysis promoted by the imidazole subunit

Versatile chemical features of the imidazole core not only favour its direct molecular recognition by several receptor targets,⁴ but they also could serve as tools to “guide” other linked-bioactive groups, by directing them, and allowing the desired pharmacophoric drug-receptor interaction.⁵ These two features are useful in rationalising the tremendous impact that the imidazole motif and its fused aromatic carbocyclic counterpart (i.e. benzo[*d*]imidazole) possess amongst medicinally relevant nitrogen heterocycles. In fact, a myriad of imidazole-containing drugs is used in the clinic as

¹ a) Zheng, X.; Ma, Z.; Zhang, D. “Synthesis of Imidazole-Based Medicinal Molecules Utilizing the van Leusen Imidazole Synthesis” *Pharmaceuticals* **2020**, *13*, 37; 1; b) Asif, M. “A Mini Review: Biological Significances of Nitrogen Hetero Atom Containing Heterocyclic Compounds” *Int. J. Bioorg. Chem.* **2017**, *2*, 146; c) Anderson, E. B.; Long, T. E “Imidazole- and imidazolium-containing polymers for biology and material science applications” *Polymer* **2010**, *51*, 2447.

² Silva, V.B.; Orth, E.S. “Imidazole and Catalysis: A Perfect Match” *Quim. Nova.* **2021**, *44*, 318.

³ Richaud, A.; Barba-Behrens, N.; Méndez, F. “Chemical Reactivity of the Imidazole: A Semblance of Pyridine and Pyrrole?” *Org. Lett.* **2011**, *13*, 972.

⁴ Verma, A.; Joshi, S.; Singh, D. “Imidazole: Having Versatile Biological Activities” *J. Chem.* **2013**, *1*, 1.

⁵ Petit, S.; Fruit, C.; Bischoff, L. “New Family of Peptidomimetics Based on the Imidazole Motif” *Org. Lett.* **2010**, *12*, 4928.

anticancer, antifungal, antibacterial, anti-inflammatory, antineuropathic, antihistaminic and antiviral active ingredients, as illustrated by examples in Figure 2.⁶

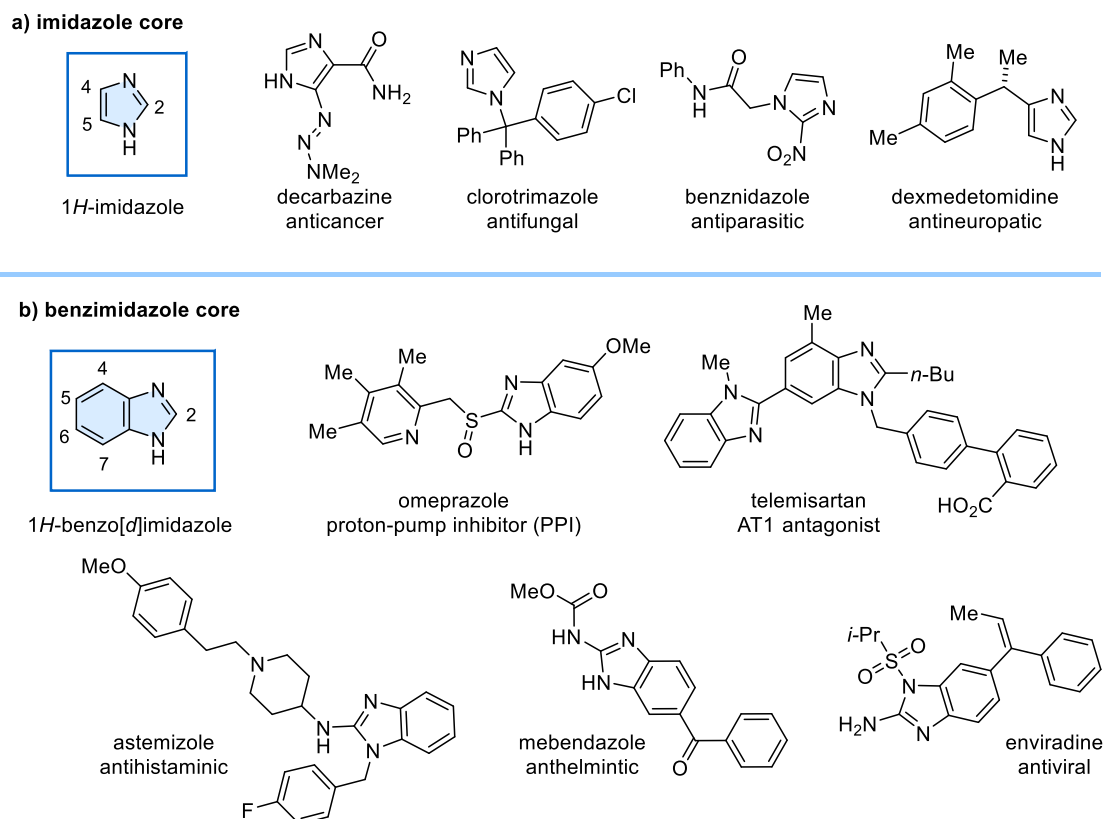


Figure 2 Examples of drug candidates containing the imidazole core a) or the benzimidazole core b)

At the same time, chemical modification of the imidazole-core under mild catalytic reaction conditions is challenging to pursue, given possible side-reactions directly involving the imidazole-substrate and the other reactive partners. Indeed, synthetic access to imidazole-based compounds or their carbocyclic-fused counterparts mostly involves the *de novo* construction of such heterocyclic ring.⁷

As repeatedly mentioned along this thesis, the discovery of synthetic methods allowing the prompt assembly of novel chiral heterocyclic core motifs featuring an increased three-dimensional shape not only has represented an important engine of chemical innovation, but it has also positively impacted and shaped the research in drug discovery programs.⁸ In particular, the chemistry of *in situ*-generated

⁶ For comprehensive reviews on imidazole-based medicinal chemistry, see: a) Zhang, L.; Peng, X.; Damu, G. L. V.; Geng, R.; Zhou, C. "Comprehensive review in current developments of imidazole-based medicinal chemistry" *Med. Res. Rev.* **2014**, *34*, 2, 340; b) Alghamdi, S.; Suliman, R.; Almutairi, K.; Kahtani, K.; Aljatli, D. "Imidazole as a Promising Medicinal Scaffold: Current Status and Future Direction" *Drug. Des. Devel. Ther.* **2021**, *15*, 3289. For comprehensive reviews on benzimidazole-based medicinal chemistry, see: a) Keri, R.; Hiremathad, A.; Budagumpi, S.; Nagaraja, B. M. "Comprehensive Review in Current Developments of Benzimidazole-Based Medicinal Chemistry" *Chem. Biol. Drug. Des.* **2015**, *86*, 1, 19; b) Gaba, M.; Mohan, C. "Development of drug based on imidazole and benzimidazole bioactive heterocycles: Recent advances and future directions" *Med. Chem. Res.* **2016**, *25*, 173.

⁷ a) Shabalin, D. A.; Camp, J. E. "Recent advances in the synthesis of imidazoles" *Org. Biomol. Chem.* **2020**, *18*, 3950; b) Tolomeu, H. V.; Fraga, C. A. M. "Imidazole: Synthesis, Functionalization and Physicochemical Properties of a Privileged Structure in Medicinal Chemistry" *Molecules* **2023**, *28*, 838.

⁸ Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A.W.; Wilson, D.M.; Wood, A. "Organic synthesis provides opportunities to transform drug discovery" *Nat.Chem.* **2018**, *10*, 383.

highly reactive *ortho*-quinodimethanes (*o*QDMs) has gained remarkable consideration.⁹ As described in Chapter 1.5.1, the launch of stereoselective transformations involving these valuable intermediates under organocatalytic conditions is of particular interest but, at the same time, they are difficult to achieve due to the temporary loss of the aromatic character of the starting pronucleophile.¹⁰ Nevertheless, during the last decade, several remarkable protocols have been reported, which exploited *five-membered aromatic heterocyclic* derivatives as suitable and organocatalyst-activatable vinylogous precursors of *o*QDM donors, and furnished novel and enantioenriched heterocyclic compounds.¹¹

Citing examples already briefly given in the introduction of this thesis and specifically focusing here on five-membered aromatic heterocyclic precursors, we recall Melchiorre's work in 2011, who developed highly stereoselective Diels-Alder reactions between ε -enolizable 3-indolyl-, 3-furyl-, and 3-pyrrolyl-acroleins **1** with activated double bonds through the generation of *o*QDM trienamine intermediates **I** (Scheme 1, a).¹² An aminocatalytic approach was also exploited later by the group of Chen, who disclosed the generation of intriguing dienamine *o*QDMs **II** from 2-alkyl-substituted 3-furfurals **2**, which were stereoselectively attacked at their benzylic remote site by 2-nitroallylic acetates, affording acyclic furan-based products (Scheme 1, b).¹³ On the other hand, Chi and co-workers exploited oxidative *N*-heterocyclic carbene (NHC) catalysis to activate 2-methylindole-3-carboxaldehydes **3**, as well as benzofuran and benzothiophene analogues, into the corresponding NHC-tethered *o*QDMs **III**, which then acted as diene components in [4+2] cycloadditions with trifluoromethylketones (Scheme 1, c).¹⁴ Finally, Xu and co-workers recently exploited non-covalent bifunctional Brønsted base organocatalysis to give rise to transient dienolate *o*QDM intermediates **IV** from inert heteroaryl aldehydes such as 2-benzyl-benzothiophene- or benzofuran-3-carbaldehydes **4**,

⁹ a) Matsuya, Y.; Ohsawa, N.; Nemoto, H. "Accelerated Electrocyclic Ring-Opening of Benzocyclobutenes under the Influence of a β -Silicon Atom" *J. Am. Chem. Soc.* **2006**, *128*, 412; b) Kuwano, R.; Shige, T. "Palladium-Catalyzed Formal [4+2] Cycloaddition of *o*-Xylylenes with Olefins" *J. Am. Chem. Soc.* **2007**, *129*, 3802; c) Ueno, S.; Ohtsubo, M.; Kuwano, R. "[4+2] Cycloaddition of *o*-Xylylenes with Imines Using Palladium Catalyst" *J. Am. Chem. Soc.* **2009**, *131*, 12904; d) Yoshida, H.; Mukae, M.; Ohshita, J. "Facile access to boryltetralins and borylnaphthalenes via a cycloaddition using *o*-quinodimethanes" *Chem. Commun.* **2010**, *46*, 5253; e) Zhu, S. F.; Liang, R. X.; Jiang, H. F.; Wu, W. Q. "An Efficient Route to Polysubstituted Tetrahydronaphthols: Silver-Catalyzed [4+2] Cyclization of 2-Alkylbenzaldehydes and Alkenes" *Angew. Chem. Int. Ed.* **2012**, *51*, 10861.

¹⁰ Przydacz, A.; Skrzyńska, A.; Albrecht, Ł. "Breaking Aromaticity with Aminocatalysis: A Convenient Strategy for Asymmetric Synthesis" *Angew. Chem. Int. Ed.*, **2019**, *58*, 63.

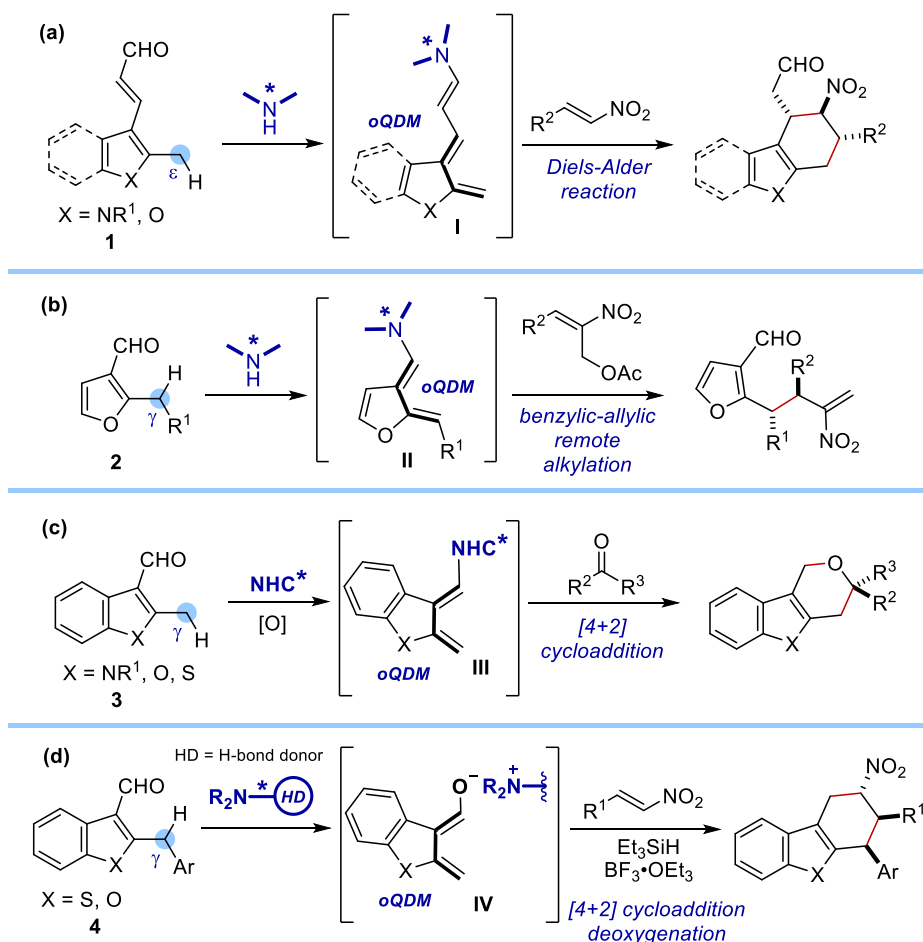
¹¹ Curti, C.; Battistini, L.; Sartori, A.; Zanardi, F. "New Developments of the Principle of Vinylogy as Applied to π -Extended Enolate-Type Donor Systems" *Chem. Rev.* **2020**, *120*, 2448.

¹² Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. "Asymmetric Catalysis of Diels-Alder Reactions with *in Situ* Generated Heterocyclic *Ortho*-Quinodimethanes" *J. Am. Chem. Soc.* **2011**, *133*, 15212. For other examples of aminocatalytic activation of "extended" five-membered heterocycles, see: a) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. "Multicatalytic Asymmetric Synthesis of Complex Tetrahydrocarbazoles via a Diels-Alder/Benzoin Reaction Sequence" *Org. Lett.* **2012**, *14*, 1310; b) Ming, Y.; Lv, X.; Liu, M.; Liu, M. "Synthesis of Chiral Polycyclic Tetrahydrocarbazoles by Enantioselective Aminocatalytic Double Activation of 2-Hydroxycinnamaldehydes with Dienals" *Org. Lett.* **2021**, *23*, 6515.

¹³ He, X.; Zhao, H.; Duan, C.; Han, X.; Du, W.; Chen, Y. "Asymmetric Benzylic Allylic Alkylation Reaction of 3-Furfural Derivatives by Dearomatizative Dienamine Activation" *Chem. Eur. J.* **2018**, *24*, 6277. For other examples of aminocatalytic activation of furan-based pronucleophile, see: a) Duan, C.; He, Z.; Du, W.; Chen, Y. "Asymmetric [4 + 2] cycloadditions with 3-furfural derivatives and α -cyano- α,β -unsaturated ketones" *Org. Chem. Front.* **2018**, *5*, 2057; b) Bojanowski, J.; Skrzyńska, A.; Albrecht, A. "Dearomatizative and Decarboxylative Reaction Cascade in the Aminocatalytic Synthesis of 3,4-Dihydrocoumarins" *Asian J. Org. Chem.* **2019**, *8*, 844; c) Topolska, A.; Frankowski, S.; Albrecht, Ł. "Differentiating Catalysis in the Dearomatizative [4+2]-Cycloaddition Involving Enals and Heteroaromatic Aldehydes" *Org. Lett.* **2022**, *24*, 955.

¹⁴ Chen, X.; Yang, S.; Song, B. A.; Chi, Y. R. "Functionalization of Benzylic C(sp³)-H Bonds of Heteroaryl Aldehydes through *N*-Heterocyclic Carbene Organocatalysis" *Angew. Chem. Int. Ed.* **2013**, *52*, 11134. For another example of NHC activation of five-membered heterocycles, see: Xu, J.; Yuan, S.; Miao, M. "*N*-Heterocyclic Carbene Catalyzed [4 + 2] Annulation Reactions with *in Situ* Generated Heterocyclic *ortho*-Quinodimethanes" *Org. Lett.* **2016**, *18*, 3822.

to be engaged in one-pot/two-step [4+2]-cycloaddition/deoxygenation reactions with nitroolefins (Scheme 1, d).¹⁵



Scheme 1 Generation of various organocatalyst-tethered five-membered heterocyclic oQDMs and subsequent asymmetric reactions

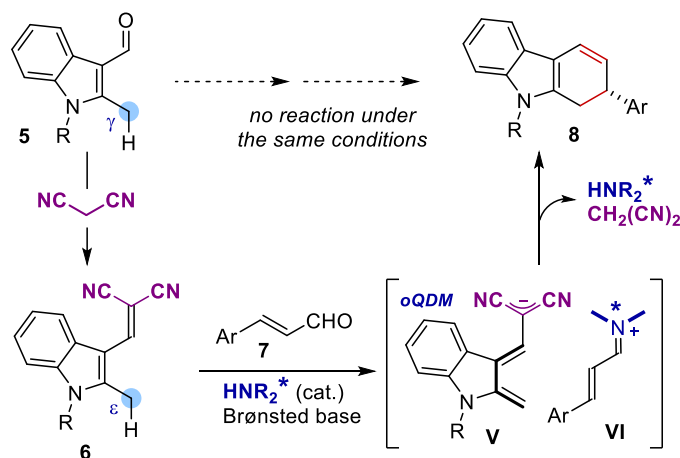
Organocatalytic strategies involving five-membered heterocyclic oQDMs also concern transformations where the organocatalyst engages LUMO-lowering activations of the electrophile exclusively, whereas the activation of the starting heteroaryl pronucleophiles is given by the presence of a sub-stoichiometric amount of a Brønsted base. This is the case of a work, previously reported by our group, dealing with the development of a formal, eliminative [4+2] cycloaddition reaction between indolyl methylenemalononitriles **6** and cinnamaldehydes **7**.¹⁶ In particular, the *HOMO-raising malononitrile activation strategy*¹⁷ (see also Chapter 1.4.1) was exploited as an *escamotage*, according to which the otherwise inert carbaldehyde precursors **5** were chemoselectively and temporarily activated into methylenemalononitriles **6** via reaction with stoichiometric amounts of malononitrile. Upon treatment of **6** with **7** and the amine organocatalyst, the annulation reaction of

¹⁵ Wang, Y.; Lin, J.-B.; Xie, J.-K.; Lu, H.; Hu, X.-Q.; Xu, P.-F. "Dearomative Dienolate-Mediated Catalysis: A Remote Activation Strategy for Asymmetric Functionalization of Benzylic C–H Bonds of Heteroaryl Aldehydes" *Org. Lett.* **2018**, *20*, 5835.

¹⁶ Rassu, G.; Curti, C.; Zambrano, V.; Pinna, L.; Brindani, N.; Pelosi, G.; Zanardi, F. "Exploiting the Distal Reactivity of Indolyl Methylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles" *Chem. Eur. J.* **2016**, *22*, 12637.

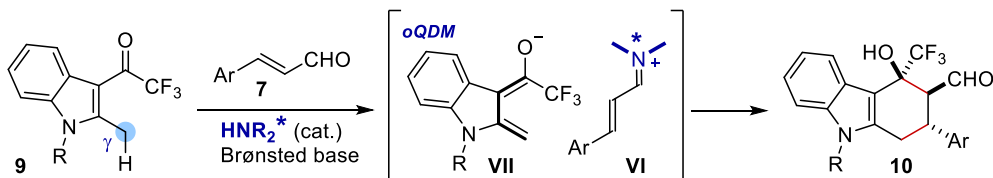
¹⁷ Curti, C.; Sartori, A.; Battistini, L.; Zanardi, F. "Exploring the Remote Reactivity of π -Extended Carbonyl Compounds: The Vinylogous Alkylidene Malononitrile Activation Strategy" *Synlett* **2018**, *29*, 266.

the corresponding of *o*QDM donors **V** with iminium ions **VI** (derived from the starting aromatic enals **7**) was triggered, ultimately giving access to enantiopure dihydrocarbazoles **8** (Scheme 2).



Scheme 2 Previously reported vinylogous HOMO-raising activation strategy developed by Zanardi and co-workers as applied to γ -enolizable indole-3-carbaldehydes **5** for the asymmetric construction of chiral dihydrocarbazoles **8**

Along this line, two years later, Enders and co-workers exploited the strong electron-withdrawing character of the trifluoromethyl group to promote the remote enolization of 3-(trifluoroacetyl)-2-methyl-indoles of type **9** under tertiary amine catalysis (Scheme 3).¹⁸ The incipient *o*QDM dienolate **VII** can enantioselectively trap catalytic chiral dienophiles **VI**, generated upon condensation of aminocatalyst on the starting α,β -unsaturated aldehyde **7**, to furnish a series of trifluoromethyl tetrahydrocarbazoles **10**.



Scheme 3 Previous work by Enders et al. for the generation of chiral trifluoromethyl tetrahydrocarbazoles **10**

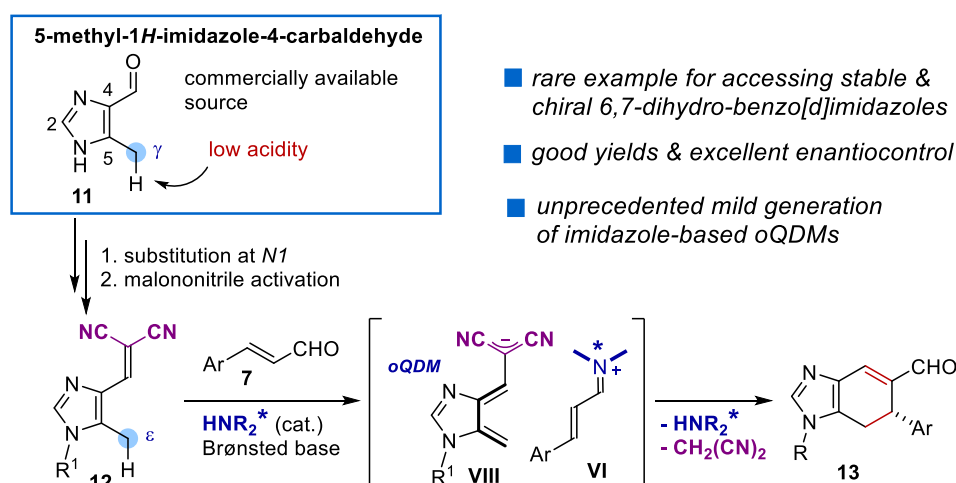
Despite the aforementioned previous examples embrace the reactivity of a broad array of five-membered heterocyclic-based substrates as *o*QDM precursors, organocatalytic dearomative *o*QDM-mediated processes have never been applied to the *imidazole* core so far, probably due to its previously mentioned intrinsic peculiar chemical properties, that may hamper both the temporarily disruption of imidazole quite pronounced aromatic character,¹⁹ and its cohabitation with the commonly used organocatalysts (often featuring weak base or acidic moieties).

¹⁸ Jafari, E.; Chauhan, P.; Kumar, M.; Chen, X. Y.; Li, S.; von Essen, C.; Rissanen, K.; Enders, D. "Organocatalytic Asymmetric Synthesis of Trifluoromethylated Tetrahydrocarbazoles by a Vinylogous Michael/Aldol Formal [4 + 2] Annulation" *Eur. J. Org. Chem.* **2018**, 2018, 2462.

¹⁹ Alonso, M.; Herradón, B. "Neural Networks as a Tool To Classify Compounds According to Aromaticity Criteria" *Chem. Eur. J.* **2007**, 13, 3913.

3.2 Target of the project

Capitalizing on results reported in this state of the art, the challenging goal of this work was to realize a sound methodology that could provide access to unprecedented chiral and stable imidazole-fused carbocycles starting from commercially available imidazole-based materials via dearomative generation of transient imidazole-based *o*QDM intermediates.²⁰ We focused on novel imidazole-based alkylidene malononitriles **12**, whose hypervinylogation of the methyl at C5 with the dicyano moiety would make the benzylic C(*sp*³)-H deprotonation feasible under mild base conditions. This event would furnish *o*QDM dienes **VIII**, which then undergo eliminative [4+2] formal cycloaddition reactions with iminium ion dienophiles **VI** (generated *in situ* by condensation of the enal with the organocatalyst), to finally consign a series of enantiopure *N*-protected 6,7-dihydrobenzo[*d*]imidazoles of type **13** (Scheme 4). To the best of our knowledge, access to this heterocyclic skeleton via the proposed disconnection approach is still unprecedented²¹ and, moreover, just one single precedent from the Jørgensen group related to the dearomative aminocatalytic activation of an imidazole-based substrate has been reported so far.²² Salient features of this transformation are: (i) the perspective of accessing the 6,7-dihydrobenzo[*d*]imidazole scaffold in a straightforward way, and (ii) the exploitation of the traceless-vinylogous HOMO-raising malononitrile activation strategy on otherwise inert and commercially available 5-methyl-1*H*-imidazole-4-carbaldehyde precursor **11** to give rise to unique imidazole-based *o*QDM intermediates through mild remote deprotonation/temporary dearomatization of the highly aromatic imidazole core.



Scheme 4 Aim of the work: exploiting the remote reactivity of imidazolyl methylenemalononitriles **12** to trigger their organocatalysed [4+2] cycloaddition with enals and unlock access to chiral 6,7-dihydro-benzo[*d*]imidazoles **13**

²⁰ A sole example of imidazole-based *o*QDM has been reported, leading to mixtures of aromatic and/or racemic fused-imidazoles under harsh reaction conditions: a) Neochoritis, C.; Livadiotou, D.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. "The first application of an imidazole *o*-quinodimethane in Diels–Alder reactions leading to the synthesis of benzimidazoles" *Tetrahedron Lett.* **2007**, 48, 2275; b) Neochoritis, C.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. "A Versatile One-Pot Synthesis of Fused Polycyclic Imidazole-naphthoquinone Derivatives through Imidazole-4,5-quinodimethane Generation Followed by Diels–Alder Cycloaddition" *Synlett* **2007**, 16, 2596.

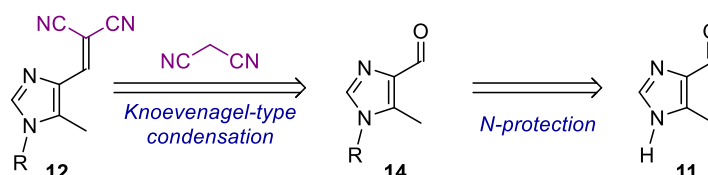
²¹ The access to a couple of racemic 6,7-dihydrobenzo[*d*]imidazoles from vinylimidazoles has been reported: a) Ray, A.; Mukherjee, S.; Das, J.; Bhandari, M. K.; Du, H.; Yousufuddin, M.; Lovely, C. J. "Preparation and Diels–Alder reactions of 1'-heterosubstituted vinylimidazoles" *Tetrahedron Lett.* **2015**, 56, 3518; b) Bhandari, M. R.; Herath, A. K.; Rasapalli, S.; Yousufuddin, M.; Lovely, C. J. "Total Synthesis of the Nagelamides – Synthetic Studies toward the Reported Structure of Nagelamide D and Nagelamide E Framework" *J. Org. Chem.* **2020**, 85, 20, 12971.

²² Bertuzzi, G.; Thøgersen, M. K.; Giardinetti, M.; Vidal-Albalat, A.; Simon, A.; Houk, K. N.; Jørgensen, K. A. "Catalytic Enantioselective Hetero-[6+4] and -[6+2] Cycloadditions for the Construction of Condensed Polycyclic Pyrroles, Imidazoles, and Pyrazoles" *J. Am. Chem. Soc.* **2019**, 141, 7, 3288.

3.3 Results and discussion

3.3.1 Proof of concept, reaction optimization and control experiments

At the outset of our study, we prepared a series of imidazole-based malononitrile substrates **12** following the retrosynthetic sequence shown in Scheme 5, that involves a *N*-protection step on commercially available substrate **11** and the subsequent Knoevenagel-type reaction between imidazole carbaldehyde precursors **14** and malononitrile (see Experimental section for details).



Scheme 5 Retrosynthetic sequence followed to prepare substrates of type **12**

To test the feasibility of the project, an initial exploration was performed using *N*-tosyl-protected imidazole-based malononitrile **12a** and cinnamaldehyde **7a** as model reaction partners. The reaction was carried out in the presence of 20 mol% Hayashi-Jørgensen prolinol catalyst **A1** and DIPEA (0.5 equiv.) in dichloromethane (0.06 M concentration) at room temperature for 72 hours, using excess **7a** (3 equiv.). Pleasingly, the reaction provided access to the desired cycloadduct **13aa** as a single enantiomer (ee >99%), albeit in a moderate 40% yield (Table 1, entry 1).

Table 1 Screening of solvents

Entry ^[a]	Solvent	Yield [%] ^[b]	ee [%] ^[c]
1	CH ₂ Cl ₂	40	>99
2 ^[d]	CH ₂ Cl ₂	32	99
3	DCE	15	nd
4	Toluene	-	-
5	Et ₂ O	-	-
6	MeOH	-	-
7	MeCN	23	nd
8 ^[e]	DMF	38	>99
9 ^[e]	DMSO	23	>99
10	CH ₂ Cl ₂ /DMF 1:1	55	>99
11	CH ₂ Cl ₂ /DMSO 1:1	35	>99
12	CH ₂ Cl ₂ /DMF 2:1	63	>99
13	CH ₂ Cl ₂ /DMSO 2:1	43	nd

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **12a** (0.064 mmol, 1 equiv.), **7a** (3 equiv.), catalyst **A1** (20 mol%) and DIPEA (0.5 equiv.) in the indicated solvent (0.06 M) at rt for 72 h. ^[b]Isolated yields. ^[c]Determined by chiral-HPLC analysis. ^[d]Reaction run in CH₂Cl₂ [0.3 M]. ^[e]Reaction run for 48 h. nd = not determined.

As the efficiency of the reaction did not improve by increasing the concentration of the system (entry 2), we realized that the low kinetic profile of the process relied on the poor solubility of the pronucleophile **12a** in dichloromethane. Thus, we decided starting the optimization of the reaction through screening of the solvent component (Table 1). In most of the tested solvents such as DCE, toluene, Et₂O, methanol, and acetonitrile, the imidazole substrate resulted almost insoluble, furnishing very low yields, if any, of **13aa** (entries 3-7). On the other hand, DMF and DMSO allowed full conversion of **12a** (monitored by TLC analysis) after shorter reaction time (48 hours), with both reactions evolving as homogeneous mixtures; however, again, product **13aa** was obtained with low efficiency (entries 8 and 9). Employing equimolar mixtures of DMF with CH₂Cl₂ gave superior results, maintaining complete enantioselectivity (entry 10). The best performance (63% yield) was achieved by performing the reaction in a 2:1 CH₂Cl₂/DMF solvent mixture, as shown in entry 12. We then moved to the screening of the base, and the results are shown in Table 2.

Table 2 Screening of the base

Entry ^[a]	Base [x equiv.]	Yield [%] ^[b]	ee [%] ^[c]
1	DIPEA (0.5 equiv.)	63	>99
2	Et ₃ N (0.5 equiv.)	70	>99
3	DABCO (0.5 equiv.)	41	nd
4	DBU (0.5 equiv.)	-	-
5	NaOAc (0.5 equiv.)	45	-
6	Cs ₂ CO ₃ (0.5 equiv.)	-	-
7	<i>t</i> -BuOK (0.5 equiv.)	30	nd
8	Et ₃ N (0.2 equiv.)	54	>99
9	Et ₃ N (1.0 equiv.)	43	>99

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **12a** (0.064 mmol, 1 equiv.), **7a** (3 equiv.), catalyst **A1** (20 mol%) and the indicated base in CH₂Cl₂/DMF 2:1 (0.06 M) at rt for 72 h. ^[b]Isolated yields. ^[c] Determined by chiral-HPLC analysis. nd = not determined.

Amongst all tested tertiary amine and inorganic bases, the use of Et₃N provided the cycloadduct **13aa** in a superior yield (70%) and excellent enantioselectivity (entry 2). On the contrary, DBU and caesium carbonate did not furnish any traces of the product (entries 4 and 6). The loading of the base was also evaluated, by performing the reaction with 0.2 equiv. (entry 8) or 1.0 equiv. (entry 9) triethylamine. Both conditions gave inferior results if compared to entry 2 and, thus, we decided to maintain 0.5 equiv. as the best loading of the base component. Notably, the base proved essential to the success of the reaction, as reported in the control experiments (see Scheme 6).

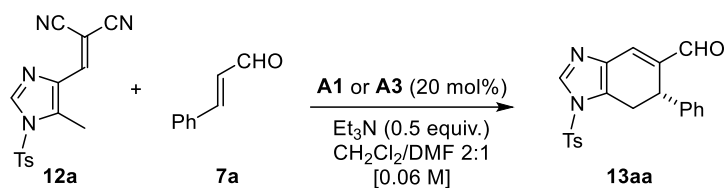
To further optimized the process, a survey of aminocatalysts **A** was performed (Table 3).

Table 3 Survey of organocatalysts

Entry ^[a]	Aminocatalyst	Yield [%] ^[b]	ee [%] ^[c]
1	A1	70	>99
2 ^[d]	A1	30	nd
3	A2	15	nd
4	A3	72	>99
5	A4	32	nd
6	A5	-	-

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **12a** (0.064 mmol, 1 equiv.), **7a** (3 equiv.), the indicated catalyst **A** (20 mol%) and Et₃N (0.5 equiv.) in CH₂Cl₂/DMF 2:1 (0.06 M) at rt for 72 h. ^[b]Isolated yields. ^[c]Determined by chiral-HPLC analysis. ^[d]Reaction performed using 10 mol% **A1**. nd = not determined.

Entry 2 shows that the efficiency of the process significantly dropped of about 40% when the catalyst loading was reduced to 10 mol%. While *tert*-butyldimethylsilyl-protected prolinol **A3** gave competitive results both in terms of efficiency and enantioselectivity if compared to **A1** (entry 4 vs entry 1), reactions using trifluoromethyl-substituted prolinol **A2** (entry 3) or hindered pyrrolidine **A4** (entry 5) resulted still viable but much less efficient. Moreover, no traces of product were detected using MacMillan-type imidazolidinone **A5** (entry 6). Finally, we performed a last round of optimization evaluating the impact of the reactant stoichiometry, temperature, and reaction time (Table 4). The reaction performed with an equimolar ratio of the pronucleophile **12a** and the electrophile **7a** in presence of either **A1** or **A3** consigned the product in slightly lower yields and comparable enantioselectivity, curiously reaching full conversion in just 24 hours (entries 3 and 4). To our delight, we found that excess **12a** in presence of aminocatalyst **A1** allowed the generation of cycloadduct **13aa** in an improved yield (entry 5, 83%, ee >99%). On the other hand, the reaction carried out under the same reaction conditions, but promoted by catalyst **A3**, resulted in the full conversion of **7a** after a prolonged reaction time (48 hours), but it proved less efficient than the one promoted by catalyst **A1** (entry 6). Increasing the temperature to 35 °C resulted detrimental for the process catalysed by trimethylsilyl-protected prolinol **A1** (entry 7), probably due to partial degradation of the aminocatalyst. Finally, entry 8 shows that the reaction performed at 60 °C in the presence of the more stable aminocatalyst **A3**, provided the generation of the desired cycloadduct in 24 hours, with a high 78% yield and as single enantiomer.

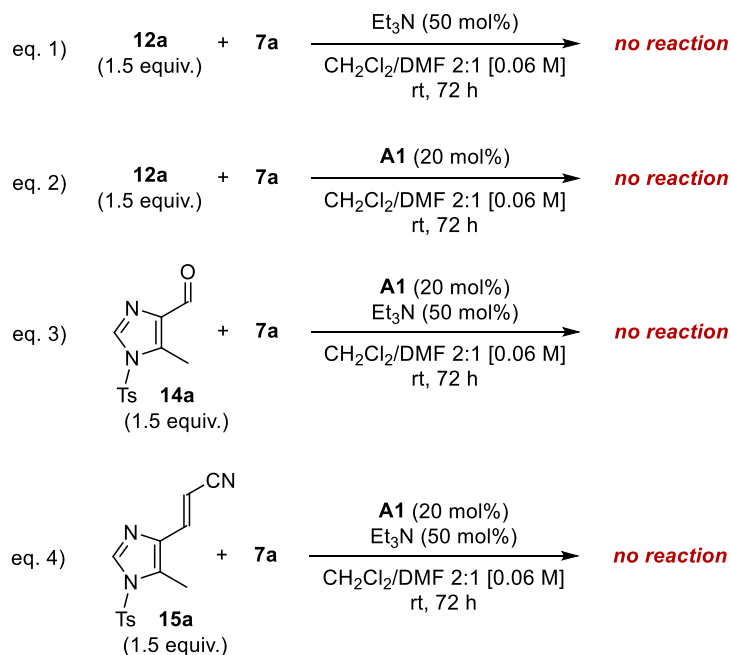
Table 4 Screening of stoichiometry, temperature and reaction time

Entry ^[a]	12a/7a	Aminocatalyst	T [°C]	Reaction time [h]	Yield [%] ^[b]	ee [%] ^[c]
1	1:3	A1	25 °C	72	70	>99
2	1:3	A3	25 °C	72	72	>99
3	1:1	A1	25 °C	24	60	>99
4	1:1	A3	25 °C	24	58	>99
5	1.5:1	A1	25 °C	24	83	>99
6	1.5:1	A3	25 °C	48	65	>99
7	1.5:1	A1	35 °C	24	61	>99
8	1.5:1	A3	60 °C	24	78	>99

^[a]Unless otherwise noted, all reactions were performed under inert atmosphere using **12a** and **7a** as substrates (0.067 mmol of the limiting reactant), catalyst **A1** (20 mol%) and Et₃N (0.5 equiv.) in CH₂Cl₂/DMF 2:1 (0.06 M).

^[b]Isolated yields. ^[c]Determined by chiral-HPLC analysis.

Overall, optimal reaction conditions were found by performing the reaction between **7a** (1 equiv.) and **12a** (1.5 equiv.), in the presence of 20 mol% aminocatalyst **A1** and Et₃N (0.5 equiv.) at 0.06 M in 2:1 CH₂Cl₂/DMF solvent mixture, at room temperature (25 °C), for 24 h, thus providing the desired imidazole-based carbocycle **13aa** in a very good 83% isolated yield and excellent enantioselectivity (ee >99%). Finally, control experiments ascertained the necessity of the concomitant presence of both aminocatalyst and base promoters for the transformation to take place (Scheme 6, eqs. 1 and 2).

**Scheme 6** Control experiments

Moreover, the reaction performed under the optimized reaction conditions, but starting from imidazole-based carbaldehyde **14a**, did not furnish any product, thus suggesting the fundamental role

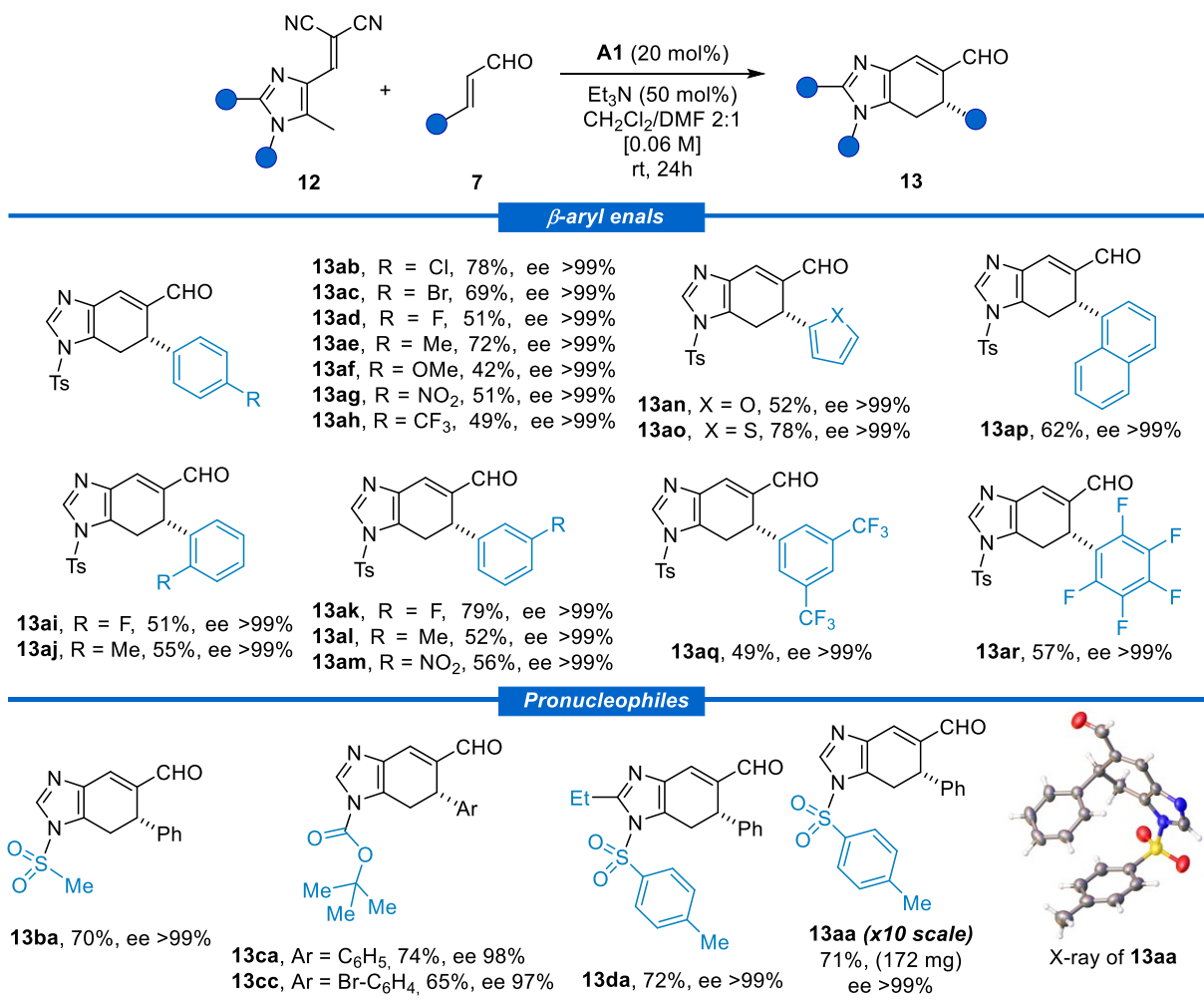
exerted by the malononitrile unit in activating the pronucleophile (Scheme 6, eq. 3). This issue was also confirmed by treating acrylonitrile **15a** – bearing one cyano moiety instead of two - with **7a** under the optimal reaction conditions (Scheme 6, eq. 4); the system resulted completely inert, emphasizing the role of the bis-nitrile handle in activating the imidazole substrate.

3.3.2 Scope of the reaction and synthetic elaborations

With the optimal conditions in hand, we then investigated the generality of the [4+2] cycloaddition reaction object of this work. Scheme 7 shows that various aromatic enals bearing electron-withdrawing (**7b-d**, **7g**, **7h**) or electron-donating (**7e**, **7f**) substituents at the *para*-position of the aryl ring were suitable substrates for the reaction, providing access to the corresponding cycloadducts **13ab-ah** in moderate-to-high isolated yields and with excellent enantioselectivities (in all cases, ee >99%). With *ortho*-substituted cinnamaldehydes, a certain drop in the overall efficiency was observed: for both 2-fluoro and 2-methyl derivatives **7i** and **7j**, completely enantioselective transformations were attained, but at the expense of efficiency (**13ai**, 51% yield, **13aj**, 55% yield). Slightly better results were obtained using *meta*-substituted acceptors (**13ak-13ai-13am**), as demonstrated by fluorinated product **13ak**, that was furnished in a good 79% isolated yield. Notably, the reaction proved to be viable even using heterocyclic acceptors such as 2-furyl- and 2-thiophenyl acroleins **7n** and **7o**, as the corresponding heteroaromatic products **13an** and **13ao** were isolated in 52% and 78% yields, respectively, as single enantiomers (ee >99%). Moreover, the highly hindered 1-naphthyl moiety was efficiently installed at C6 of the 6,7-dihydrobenzo[*d*]imidazole scaffold as shown for compound **13ap** (62% yield, ee >99%). Finally, the process developed in this study offered the possibility to employ polysubstituted β -aryl enals, as demonstrated by highly fluorinated cycloadducts **13aq** and **13ar**, which were obtained in moderate yields and excellent enantioselectivities.

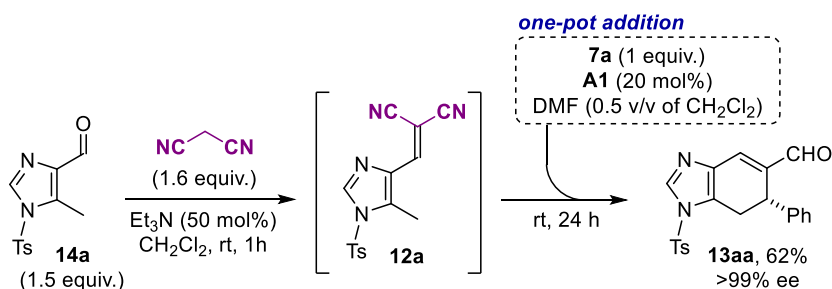
We next evaluated diversely *N*^{*l*}-substituted imidazole pronucleophiles that could participate to the formal cycloaddition. As for the model tosyl-protecting group, the reaction between *N*-methylsulphonyl **12b** and cinnamaldehyde **7a** allowed the generation of product **13ba** in a good yield (70%) and excellent enantioselectivity (ee >99%). Similar results were obtained using *N*^{*l*}-Boc protected imidazole **12c**, generating products **13ca** and **13cc** with slightly lower enantiomeric excesses (98% ee and 97% ee, respectively). Finally, variation at the C2 of the imidazole core proved to be tolerated. In particular, the reaction involving 2-ethyl-*N*^{*l*}-tosyl-imidazole **12d** furnished the corresponding cycloadduct **13da** in good isolated yield (72%) and with complete enantiocontrol (ee >99%).

We also performed the reaction between **12a** and **7a** on a 10× scale as compared to the standard one. Pleasingly, the reaction proceeded smoothly to afford product **13aa** in a slightly lower 71% yield (0.17 g) and, again, excellent enantioselectivity (ee >99%). Of note, the absolute configuration of the products was derived by correlation to the sulphur-containing cycloadduct **13aa** and the bromine-containing compound (*ent*)-**13cc**, whose crystalline structures allowed them to be subjected to useful single crystal X-ray crystallographic analyses, which assigned a C6(*S*) absolute configuration for compound **13aa** and C6(*R*) for compound (*ent*)-**13cc**.



Scheme 7 Scope of the cycloaddition

Importantly, we sought to investigate whether 6,7-dihydrobenzo[*d*]imidazoles of type **13** could be also obtained by starting from the corresponding carbaldehydes of type **14** through an *in situ* generation of the corresponding alkylidene-malononitriles **12**. As a proof of this assumption, we demonstrated that enantiopure cycloadduct **13aa** could be generated in a quite good 62% yield by starting from imidazole-based carbaldehyde **14a** and through a telescoped/one-pot procedure. In particular, the first treatment of **14a** with malononitrile and a sub-stoichiometric amount of triethylamine in dichloromethane generated alkylidene-malononitrile intermediate **12a** almost quantitatively (checked by NMR analysis). After 1 hour, the subsequent one-pot addition of cinnamaldehyde **7a**, aminocatalyst **A1** and the required amount of DMF, efficiently triggered the desired and highly enantioselective [4+2] cycloaddition reaction, as shown in Scheme 8.



Scheme 8 Telescoped/one-pot procedure of the model reaction

Although the methodology developed in this work resulted quite robust and general, some limitations were found, especially regarding the substitution pattern at the *N*-atom of the imidazole ring (Figure 3). Indeed, electron-rich protecting groups, such as benzyl- **12e** or benzyloxymethyl- (BOM-) **12f**, completely defused the reactivity of the system. These results underline the importance of having a strong electron-poor group bound to the nitrogen atom. The electronic properties of the protecting group may play a crucial role in activating the low-acidic methyl at the C5 site during the first deprotonation step. Consistently, fused-carbocyclic imidazole **12h** did not furnish any product, while just traces of the cycloadduct were detected by NMR using benzoyl-protected pronucleophile **12g**. Regarding the electrophile, aliphatic enal **7s** resulted completely inert, even at high temperature, when treated with pronucleophile **12a** under the optimal reaction conditions.

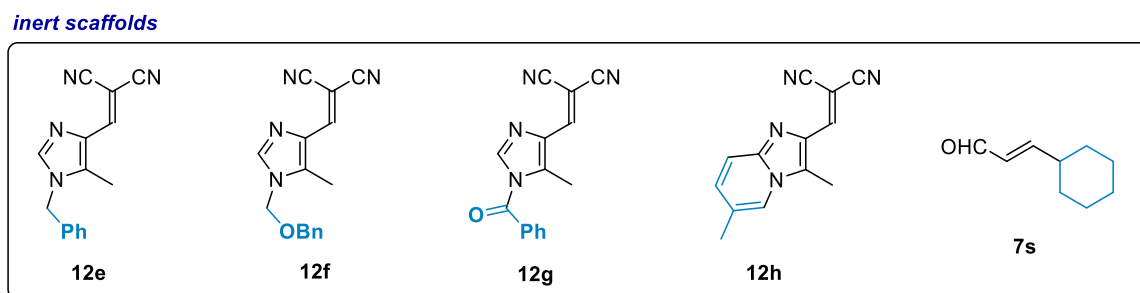
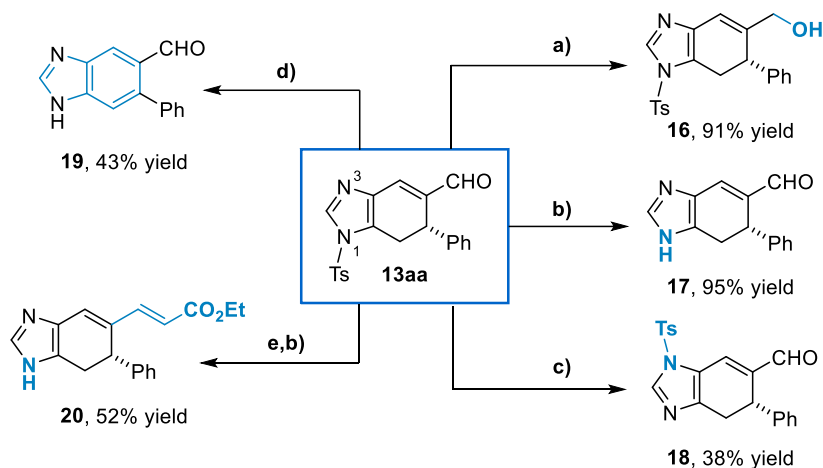


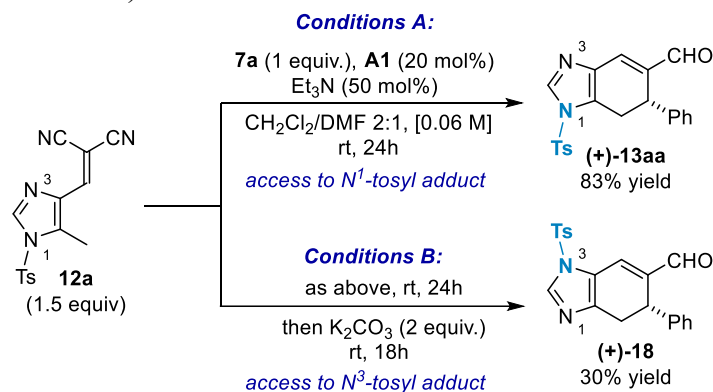
Figure 3 Unreactive substrates for the [4+2] cycloaddition developed in this study

Moreover, we envisioned the products of type **13** as amenable platforms to be further synthetically elaborated (Scheme 9). First, we reduced the aldehyde moiety with NaBH₄ to afford the corresponding primary alcohol **16** in a high 91% yield (*path a*). The possibility to successfully remove the tosyl-group within **13aa** was also pursued upon treatment with simple imidazole as a scavenger agent in combination with K₂CO₃ (*path b*). The corresponding free-imidazole **17** was obtained in almost quantitative yield, along with the isolation of pure *N*-tosyl imidazole as a by-product. Importantly, we discovered that treatment of **13aa** with just K₂CO₃ as the base, promoted unprecedented intermolecular 1,3-shift of the tosyl-group to furnish regioisomer **18**, even though in moderate yield (*path c*, 38% yield), and accompanied by the unreacted starting material. The regiochemistry of **18** was determined by NMR, through NOESY experiment (see Experimental section for further details). Curiously, treatment of **13aa** under the basic reaction conditions of *path c* but increasing the temperature to 60 °C and prolonging the reaction time to 24 h, gave rise to complete aromatization, furnishing the 5,6-disubstituted benzimidazole derivative **19** (43% yield, *path d*). Entries related to *path c* and *path d* represent initial attempts of post-functionalizations of products of type **13** that still deserve experimental-work to be improved. Optimisation processes and mechanism investigations of such reactions are now ongoing in our laboratories. Finally, a two-step Horner-Emmons olefination/imidazole deprotection consigned the highly conjugated and extended ester **20** in an overall 52% yield (*path e*).



Scheme 9 Synthetic elaborations performed on catalytic product **13aa**. Conditions: (a) NaBH₄ (2 equiv.), MeOH, 0 °C, 1 h; (b) imidazole (1.5 equiv.), K₂CO₃ (2 equiv.), DMF, rt, 2 h; (c) K₂CO₃ (2 equiv.), DMF, rt, 2 h; (d) K₂CO₃ (2 equiv.), DMF, 60 °C, 24 h; (e) ethyl 2-(diethoxyphosphoryl)acetate (1.5 equiv.), NaH (1.7 equiv.), CH₂Cl₂, rt, 48 h.

Importantly, the reaction discovered treating **13aa** under *conditions c* in Scheme 9 led us to accomplish a straightforward divergent approach to regioselectively access either *N*¹- or *N*³-tosylated isomers **13aa** and **18**, by starting in both cases from the standard *N*¹-protected imidazole pronucleophile **12a** (Scheme 10).

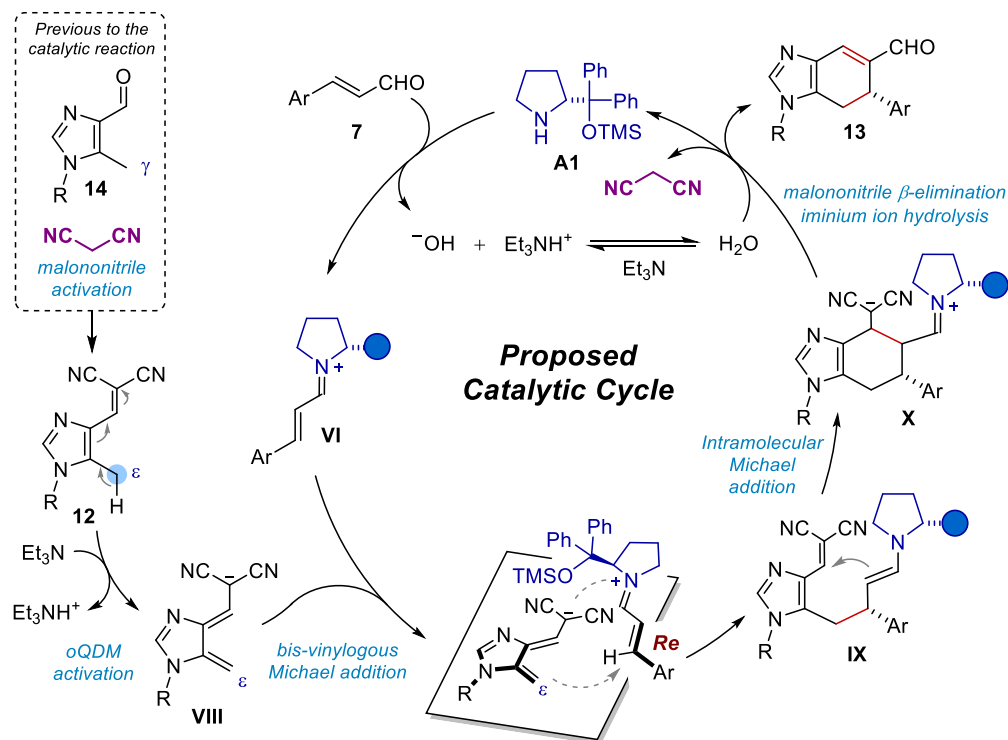


Scheme 10 Regiodivergent synthesis of 6,7-dihydrobenzo[*d*]imidazoles **13aa** and **18** starting from imidazole-based pronucleophile **12a**. Numbering of nitrogen atoms in products **13aa** and **18** are assigned based on the common precursor **12a** for clarity and do not correspond to the actual IUPAC numbering.

Indeed, while the model reaction between pronucleophile **12a** and cinnamaldehyde **7a** furnished chiral *N*¹-substituted cycloadduct **13aa** in a high 83% yield (*conditions A*), treatment of **12a** under the same conditions for 24 h, followed by the telescoped addition of K₂CO₃, provided access to the chiral *N*³-tosyl isomer **18** after further 18 h, albeit with an inferior 30% overall yield and accompanied by unreacted starting material and traces of its *C*⁶,*C*⁷-unsaturated analogous (*conditions B*).

3.3.3 Proposed catalytic cycle

Based on previous studies unveiling the stepwise nature of analogous cycloaddition reactions,^{23,9} we propose the mechanism illustrated in Scheme 11, involving bis-vinylogous Michael-type addition and intramolecular Michael annulation as key steps.



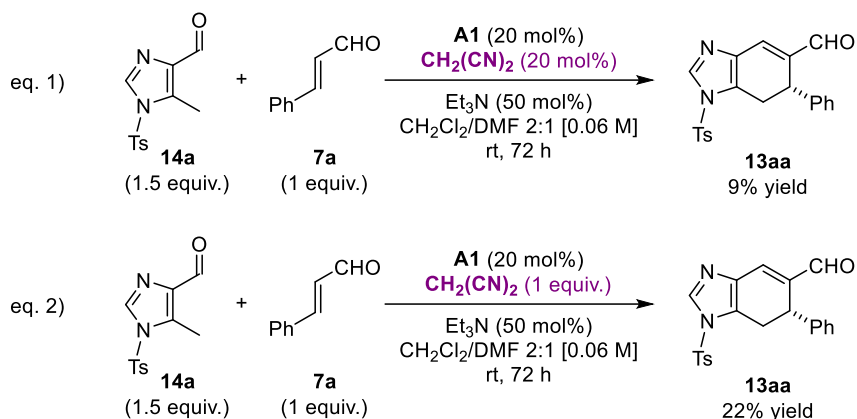
Scheme 11 Proposed catalytic cycle

More in details, the initial formation of imidazole oQDMs **VIII** and iminium ions **VI** from the corresponding alkylidene-malononitriles **12** and enals **7** is allowed by the cooperative action of prolinol **A1** catalyst and sub-stoichiometric Et₃N promoter. The hindered α-substituent of the pyrrolidine ring within catalyst **A1** elegantly orchestrates the stereochemistry in forging the stereocenter at C6 during the bis-vinylogous Michael addition between **VIII** and **VI** (*Re* face attack). The ensuing enamine-alkylidenemalononitrile intermediates **IX** readily undergo the subsequent intramolecular Michael addition to generate unstable tetrahydrobenzimidazoles **X** that, upon malononitrile β-elimination and iminium ion hydrolysis, regenerate aminocatalyst **A1**, finally consigning the desired cycloadducts **13**.

Given the eliminative nature of the cycloaddition, one molecule of malononitrile is released in the catalytic cycle. Based on this assumption, we investigated the possibility to carry out the reaction via dual synergistic organocatalysis, with concomitant HOMO-raising activation of imidazole carbaldehydes **14** by catalytic malononitrile and LUMO-lowering activation of enals **7** by **A1** catalyst. Unfortunately, just traces of product **13aa** were isolated from the reaction between carbaldehyde **14a** and cinnamaldehyde **7a** in presence of a catalytic amounts of malononitrile and **A1** (Scheme 12, eq.

²³ a) Curti, C.; Rassu, G.; Lombardo, M.; Zambrano, V.; Pinna, L.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F. "Unlocking Access to Enantiopure Fused Uracils by Chemodivergent [4+2] Cross-Cycloadditions: DFT-Supported Homo-Synergistic Organocatalytic Approach" *Angew. Chem. Int. Ed.* **2020**, 59, 20055; b) McLeod, D.; Izzo, J. A.; Jørgensen, D. K. B.; Lauridsen, R. F.; Jørgensen, K. A. "Development and Investigation of an Organocatalytic Enantioselective [10 + 2] Cycloaddition" *ACS Catal.* **2020**, 10, 10784.

1). Slightly better results, but still insufficient, were achieved exploring a possible three-component reaction in the presence of stoichiometric amounts of malononitrile (Scheme 12, eq. 2).



Scheme 12 Attempts of catalytic (eq. 1) and *in situ* stoichiometric (eq. 2) malononitrile activation

These attempts suggest that the required initial Knoevenagel-type step transforming aldehyde **14a** into **13a** could not take place under the reaction conditions, but at the same time, they suggest possible future investigations related to the translation of the malononitrile activation strategy into a catalytic manifold.

3.4 Conclusion

In summary, in this work a highly enantioselective organocatalytic eliminative [4+2] formal cycloaddition reaction between 2-imidazolyl methylenemalononitriles and enals was developed. The methodology exploited the HOMO-raising malononitrile activation strategy to unlock the generation of under-represented imidazole-based *o*QDM intermediates under mild reaction conditions. This study represents the first entry to chiral enantiopure 6,7-dihydrobenzo[*d*]imidazoles, which also proved suitable platforms for further synthetic elaborations. A regiodivergent strategy to selectively generate either *N*¹- or *N*³-tosyl imidazole-based model products was put into practice. The usefulness of the protocol was finally enriched by performing the model reaction in a scaled-up format as well as through a telescoped/one-pot procedure.

3.5 Experimental section

3.5.1 General information

Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of nitrogen or argon. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Dichloromethane (ACS grade) was dried by distillation on CaH₂ according to standard procedures (water content <0.01% as determined by Karl Fischer titration). Solvents for chromatography and filtration including hexane, ethyl acetate, petroleum ether, DMF, anhydrous ethanol and 2-propanol were ACS or HPLC grade and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates with visualization under short-wavelength UV light (254 or 365 nm) and by dipping the plates with molybdate reagent (aqueous H₂SO₄ solution of ceric sulphate/ammonium molybdate), and DNP and K₂MnO₄ aqueous solutions followed by heating. Flash column chromatography was performed using 40-63 μ m silica gel using the indicated solvent mixtures. Analytical chiral HPLC analyses were carried out using Daicel Chiralcel OD-H (250 $\times$ 4.6 mm, 5 μ m), Lux[®] Amylose-1 (250 $\times$ 4.6 mm, 5 μ m) and Welk-O1 (250 $\times$ 4.6 mm, 5 μ m) columns as indicated. Racemic mixtures were artificially obtained mixing products obtained separately from aminocatalysts **A1** and (*ent*)-**A1**. Optical rotation data $[\alpha]_D$ were obtained on a digital polarimeter at ambient temperature using a 100 mm cell with 1- or 5-mL capacity and are given in units of 10⁻¹ deg·cm²·g⁻¹. 1D- and 2D-NMR spectra were recorded at 400 MHz (¹H-NMR) and 100 MHz (¹³C, ¹³C-APT). Spectra were referenced to tetramethylsilane (0.0 ppm, ¹H; 0.0 ppm, ¹³C, in CDCl₃). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), dd (double doublet), td (triple of doublets), m (multiplet), and bs (broad singlet). Coupling constants, *J*, are reported in Hertz. ¹H and ¹³C-NMR assignments were corroborated by 1D and 2D experiments (¹H-NMR, gCOSY, gHSQC sequences). ESI-mass spectra were recorded on API 150EX apparatus and are reported in the form of (*m/z*). High resolution mass analysis (HR-MS) was performed on LTQ ORBITRAP XL Thermo apparatus. Single crystal X-ray diffraction analysis of compounds **13aa** and (*ent*)-**13cc** was carried out by Prof. Giorgio Pelosi at the University of Parma (Department of Chemistry, Life Sciences and Environmental Sustainability) with a Bruker D8Venture diffractometer equipped with a kappa goniometer and an Oxford cryosystem. The low temperature data collection was performed at 200K under nitrogen flux. Lorentz polarization and absorption correction were applied by the SADABS²⁴ procedure. The phase problem was solved by direct methods and the structures were refined by full-matrix least-squares on all F² using SHELXL,²⁵ as implemented in the OLEX2 suite of programmes.^{27b} Analytical expressions of neutral atom scattering factors were taken from the International Tables for X-Ray Crystallography.²⁶ The structure drawings were obtained using ORTEPIII.²⁷

²⁴ Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.

²⁵ a) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, C71, 3; b) Sheldrick, G. M. A short history of SHELX. *Acta Cryst.* **2008**, A64, 112.

²⁶ Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, 42, 339.

²⁷ Burnett, M. N.; Johnson, C. K. ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for crystal structure illustrations. United States. doi:10.2172/369685.

3.5.2 Catalysts and substrates synthesis

Catalysts

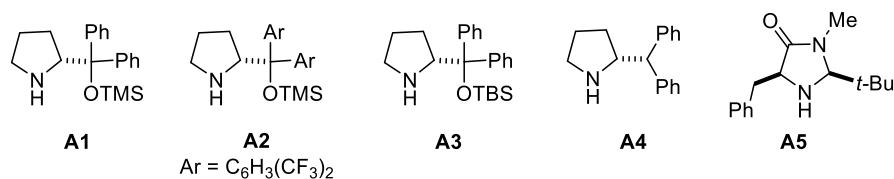


Figure 4 Catalysts used in this transformation

Catalysts **A1-A5** were commercially available and were used as such without further purifications.

Electrophiles

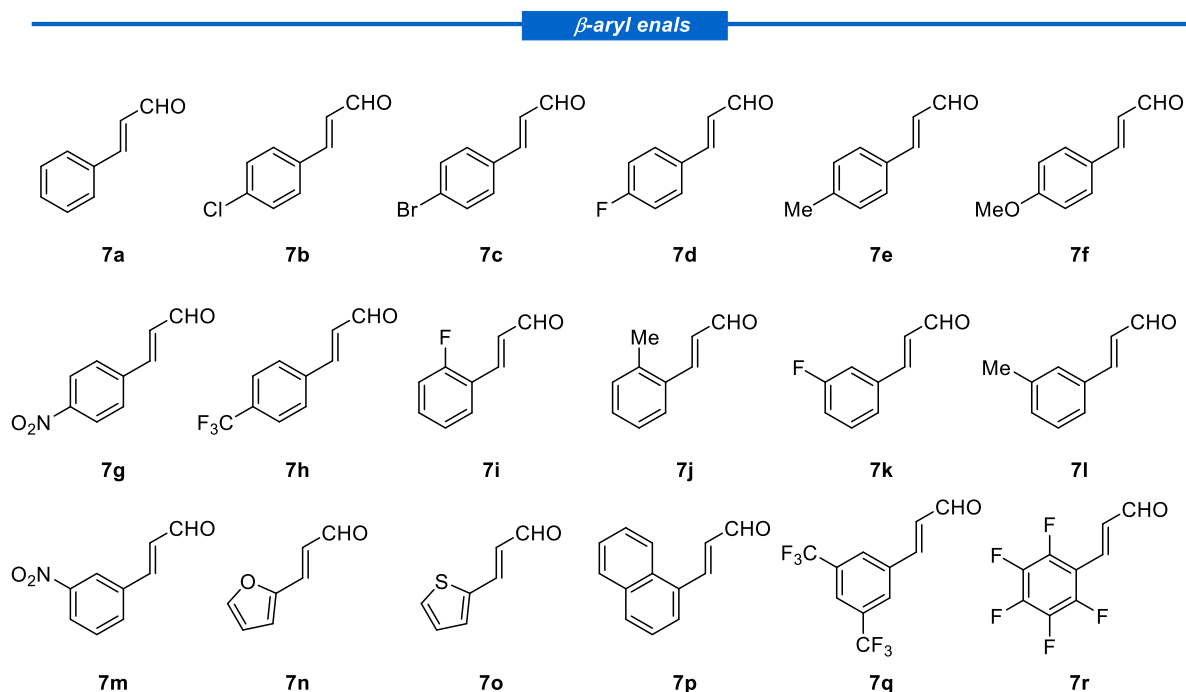


Figure 5 Cinnamaldehydes used in this study

Cinnamaldehyde **7a** was commercially available and used without further purification. Enals **7b-7r** were prepared from the respective commercial benzaldehydes following a reported procedure.²⁸

²⁸ Kim, E.; Koh, M.; Lim, B. J.; Park, S. B., *J. Am. Chem. Soc.* **2011**, *133*, 17, 6642.

Pronucleophiles

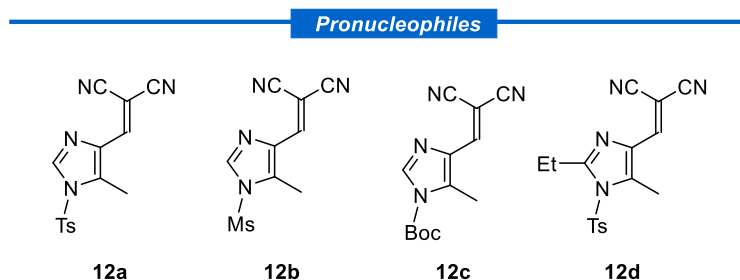
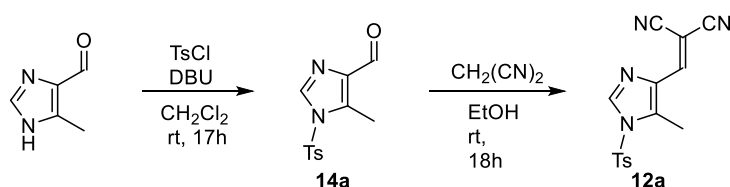


Figure 6 Pronucleophiles used in this study

Pronucleophiles **12a-d** were prepared through a two-step procedure involving *N*-protection/Knoevenagel-type reaction sequence.

Synthesis of 2-[(5-methyl-1-tosyl-1*H*-imidazol-4-yl)methylene]malononitrile **12a**



To a stirred solution of commercial 5-methyl-1*H*-imidazole-4-carbaldehyde (1 g, 9.08 mmol, 1.0 equiv.) in dichloromethane (4.57 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 3.38 mL, 22.7 mmol, 2.5 equiv.) was added at 0 °C. After 15 min., *p*-toluenesulfonyl chloride (TsCl, 3.46 g, 18.16 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at 25 °C. After 17 hours, the mixture was acidified to pH 5 with an aqueous 1N HCl solution and then extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 60:40) to yield imidazole **14a** (2.1 g, 87%) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.96 (s, 1H, CHO), 8.16 (s, 1H, H₂), 7.83 (m, 2H, Ar), 7.41 (m, 2H, Ar), 2.63 (s, 3H, Me), 2.46 (s, 3H, Me).

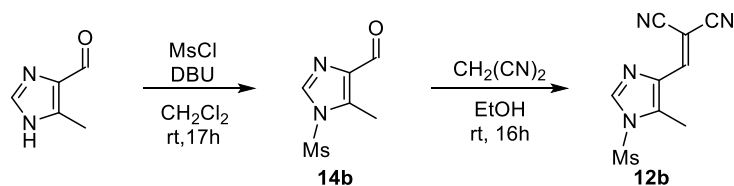
¹³C-NMR (100 MHz, CDCl₃) δ 187.6 (CH, CHO), 147.2 (Cq), 138.5 (Cq), 137.2 (CH, C2), 134.5 (Cq), 133.9 (Cq), 130.7 (2C, CH, Ar), 127.9 (2C, CH, Ar), 21.8 (CH₃, Ts), 10.0 (CH₃, Me).

To a stirred suspension of compound **14a** (520 mg, 1.97 mmol, 1.0 equiv.) in absolute ethanol (10 mL), malononitrile (195 mg, 2.95 mmol, 1.5 equiv.) was added. After 18 hours, the precipitate was filtered, washed with ethanol and dried to afford compound **12a** (500 mg, 81%) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H, H₂), 7.85 – 7.83 (m, 2H, Ar), 7.46 – 7.44 (m, 2H, Ar), 7.43 (s, 1H, alkylidene), 2.5 (s, 3H, Me), 2.46 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 147.6 (Cq), 146.0 (CH, alkylidene), 138.8 (CH, C2), 135.9 (Cq), 134.8 (Cq), 133.5 (Cq), 130.9 (2C, CH, Ar), 130.7 (Cq), 127.9 (2C, CH, Ar), 114.3 (Cq), 112.4 (Cq), 21.9 (CH₃, Ts), 10.0 (CH₃, Ts).

Synthesis of 2-[(5-methyl-1-mesyl-1*H*-imidazol-4-yl)methylene]malononitrile **12b**



To a stirred solution of commercial 5-methyl-1*H*-imidazole-4-carbaldehyde (1 g, 9.08 mmol, 1.0 equiv.) in dichloromethane (10 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 3.38 mL, 22.7 mmol, 2.5 equiv.) was added at 0 °C. After 15 min., mesyl chloride (MsCl, 1.77 mL, 22.7 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at 25 °C and monitored by TLC. After 17 hours, the reaction was quenched with 1N aq HCl and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 40:60) to afford **14b** as a yellow solid (0.92 g, 54%).

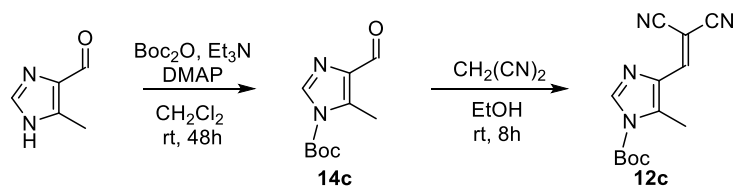
¹H-NMR (400 MHz, CDCl₃) δ 10.04 (s, 1H, CHO), 8.02 (s, 1H, H₂), 3.38 (s, 3H, Me), 2.82 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 187.7 (CH, CHO), 138.7 (C_q), 137.1 (CH, C₂), 134.2 (C_q), 43.7 (CH₃, Ms), 10.1 (CH₃, Me).

To a stirred suspension of compound **14b** (300 mg, 1.59 mmol, 1.0 equiv.) in absolute ethanol (7.7 mL), malononitrile (157 mg, 2.38 mmol, 1.5 equiv.) was added at room temperature. After 16 hours, the precipitate was filtered, washed with ethanol and dried to afford compound **12b** (203 mg, 54%) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.1 (s, 1H, H₂), 7.55 (s, 1H, alkylidene), 3.36 (s, 3H, Me), 2.64 (s, 3H, Me).

Synthesis of *tert*-butyl 4-(2,2-dicyanovinyl)-5-methyl-1*H*-imidazole-1-carboxylate **12c**



To a stirred solution of commercial 5-methyl-1*H*-imidazole-4-carbaldehyde (1 g, 9.08 mmol, 1.0 equiv.) in dichloromethane (68 mL), di-*tert*-butyl dicarbonate (Boc₂O; 3.96 g, 18.16 mmol, 2.0 equiv.) and triethylamine (Et₃N; 1.27 mL, 9.08 mmol, 1.0 equiv.) were added sequentially. After 10 min., 4-(dimethylamino)pyridine (DMAP; 331 mg, 2.71 mmol, 0.3 equiv.) was added and the reaction mixture was stirred at 25 °C. After 48 hours, the reaction resulted complete and the mixture was concentrated in vacuo. The residue was diluted with H₂O and extracted with CH₂Cl₂ (3×). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 65:35) to yield imidazole **14c** (1.6 g, 84%) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.93 (s, 1H, CHO), 7.99 (s, 1H, H2), 2.71 (s, 3H, Me), 1.59 (s, 9H, *tert*-butyl).

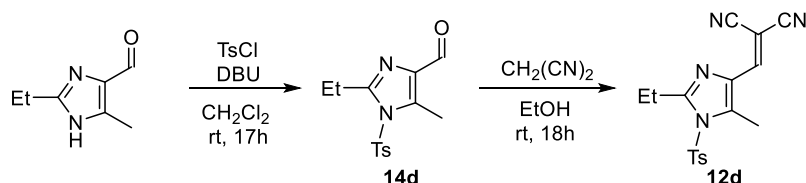
¹³C-NMR (100 MHz, CDCl₃) δ 187.4 (CH, CHO), 147.2 (Cq), 139.8 (Cq), 138.4 (CH, C2), 136.3 (Cq), 87.1 (Cq), 27.9 (CH₃, 3C, Boc), 11.4 (CH₃, Me).

To a suspension of compound **14c** (500 mg, 2.38 mmol, 1.0 equiv) in absolute ethanol (3.9 mL), malononitrile (236 mg, 3.57 mmol, 1.5 equiv) was added. After 8 hours, the precipitate was filtered, washed with ethanol and dried under reduced pressure to afford compound **12c** (183.8 mg, 75%) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H, H2), 7.56 (s, 1H, H6), 2.61 (s, 3H, Me), 1.67 (s, 9H, Boc).

¹³C-NMR (100 MHz, CDCl₃) δ 146.5 (CH, alkylidene), 139.3 (CH, C2), 137.9 (Cq), 134.6 (Cq), 114.8 (Cq), 112.7 (Cq), 87.7 (2Cq), 80.2 (Cq), 27.9 (CH₃, Boc), 11.5 (CH₃, Me).

Synthesis of 2-[(2-ethyl-5-methyl-1-tosyl-1*H*-imidazol-4-yl)methylene]malononitrile **12d**



To a stirred solution of commercial 2-ethyl-5-methyl-1*H*-imidazole-4-carbaldehyde (300 mg, 2.17 mmol, 1.0 equiv.) in dichloromethane (1.5 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.81 mL, 5.42 mmol, 2.5 equiv.) was added at 0 °C. After 15 min., *p*-toluenesulfonyl chloride (TsCl, 827 mg, 4.34 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at 25 °C and monitored by TLC. After 17 hours, the mixture was acidified to pH 5 with an aqueous 1 N HCl solution and then extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 60:40) to afford imidazole **14d** (355 mg, 56%) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.95 (s, 1H, CHO), 7.75 (d, *J* = 8.5 Hz, 2H, Ar), 7.40 (d, *J* = 8.2 Hz, 2H, Ar), 3.06 (q, *J* = 7.4 Hz, 2H, CH₂, Et), 2.72 (s, 3H, CH₃, Ts), 2.48 (s, 3H, CH₃, Me), 1.40 (t, *J* = 7.4 Hz, 3H, CH₃, Et).

¹³C-NMR (100 MHz, CDCl₃) δ 187.1 (CH, CHO), 152.3 (Cq), 146.6 (Cq), 136.8 (Cq), 135.9 (Cq), 135.2 (Cq), 130.5 (2C, CH, Ar), 127.2 (2C, CH, Ar), 23.4 (CH₃, Ts), 21.8 (CH₂, Et), 12.0 (CH₃, Me or Et), 11.4 (CH₃, Me or Et).

To a suspension of compound **14d** (250 mg, 0.85 mmol, 1.0 equiv.) in absolute ethanol (4.5 mL) stirred under nitrogen atmosphere at room temperature, malononitrile (84 mg, 1.27 mmol, 1.5 equiv.) was added. After 18 hours, the precipitate was filtered, washed with ethanol and dried to afford compound **12d** (205 mg, 71%) as a pink solid.

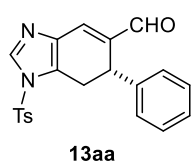
¹H-NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 8.5 Hz, 2H, Ar), 7.46 (s, 1H, alkylidene), 7.42 (d, J = 8.0 Hz, 2H, Ar), 3.05 (q, J = 7.3 Hz, 2H, Et), 2.54 (s, 3H, Ts), 2.50 (s, 2H, Ts), 1.42 (t, J = 7.3 Hz, 3H, Et).

¹³C-NMR (100 MHz, CDCl₃) δ 153.6 (Cq), 147.0 (Cq), 146.0 (CH, alkylidene), 137.8 (Cq), 134.8 (Cq), 132.3 (Cq), 130.7 (2C, CH, Ar), 127.2 (2C, CH, Ar), 114.8 (Cq), 112.4 (Cq), 80.5 (Cq), 23.5 (CH₃, Ts), 21.8 (CH₂, Et), 11.7 (CH₃, Me or Et), 11.1 (CH₃, Me or Et).

3.5.3 Experimental procedures and characterization of products

Scope of the electrophile

General procedure A: Synthesis of (*S*)-6-phenyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13aa]



In a 4mL vial equipped with a magnetic bar and kept under nitrogen atmosphere, aminocatalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.) was dissolved in dichloromethane (730 μ L) at 25 °C. Compound *trans*- β -cinnamaldehyde **7a** (8.06 μ L, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.), DMF (370 μ L) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.)

were sequentially added. The resulting suspension was stirred at 25 °C and, after 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford 20.1 mg of **13aa** (83% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H, CHO), 8.07 (s, 1H, H₂), 7.57 (d, J = 8.4 Hz, 2H, Ar), 7.43 (s, 1H, H₄), 7.21 – 7.12 (m, 3H, 2Ar + 1Ph), 7.13 – 7.05 (m, 2H, Ph), 7.04 – 6.97 (m, 2H, Ph), 4.40 – 4.33 (m, 1H, H₆), 3.42 – 3.34 (m, 2H, H_{7a} + H_{7b}), 2.41 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.3 (CH, CHO), 146.5 (Cq), 141.2 (Cq), 139.1 (CH, C₄), 138.4 (Cq), 138.2 (CH, C₂), 138.0 (Cq), 134.3 (Cq), 130.4 (2C, CH, Ar), 129.9 (Cq), 128.6 (2C, CH, Ar), 127.2 (2C, CH, Ar), 126.9 (CH, Ar), 126.6 (2C, CH, Ar), 35.7 (CH, C₆), 28.8 (CH₂, C₇), 21.7 (CH₃, Ts).

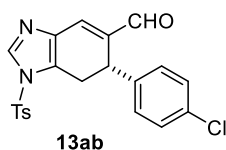
$[\alpha]_D^{20}$ +36.0 (c = 0.1 g/100 mL, CHCl₃).

Chiral HPLC for (*ent*)-**13aa** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *R*_t 16.8 min (major), 32.3 min (minor) (99.9:0.1 er).

ESI-MS 379.11 [M+H]⁺, 401.09 [M+Na]⁺.

HRMS calcd for C₂₁H₁₈N₂O₃S ([M+H]⁺): 379.1116, found: 379.1111

Synthesis of (*S*)-6-(4-chlorophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13ab]



Compound **13ab** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-chloro-cinnamaldehyde **7b** (10.66 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ab** (20.6 mg, 78% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H, CHO), 8.08 (s, 1H, H₂), 7.55 – 7.53 (m, 2H, Ar), 7.46 (s, 1H, H₄), 7.20 – 7.18 (m, 2H, Ar), 7.06 – 7.04 (m, 2H, Ph), 6.92 – 6.90 (m, 2H, Ph), 4.34 – 4.31 (d, J = 8.2 Hz, 1H, H₆), 3.39 (dd, J = 18.0, 8.2 Hz, 1H, H_{7a}), 3.29 (dd, J = 17.9, 1.2 Hz, 1H, H_{7b}), 2.45 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.1 (CH, CHO), 146.9 (C_q), 139.4 (CH, C₄), 138.4 (C_q), 138.1 (C_q), 138.0 (2C, C_q + CH, C₂), 134.2 (C_q), 132.8 (C_q), 130.4 (2C, CH, Ar), 129.5 (C_q), 128.7 (2C, CH, Ar), 128.0 (2C, CH, Ar), 127.1 (2C, CH, Ar), 35.2 (CH, C₆), 29.0 (CH₂, C₇), 21.8 (CH₃, Ts).

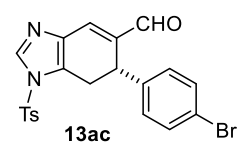
$[\alpha]_D^{20}$ +27.6 (c = 0.7 g/100 mL, CHCl₃).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 16.3 min (minor), 47.0 min (major) (99.8:0.2 er).

ESI-MS 413.07 [M+H]⁺, 435.05 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇ClN₂O₃S ([M+H]⁺): 413.0727, found: 413.0729

Synthesis of (*S*)-6-(4-bromophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13ac]



Compound **4ac** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-bromo-cinnamaldehyde **7c** (13.51 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ac** (20.1 mg, 69% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H, CHO), 8.07 (s, 1H, H₂), 7.55 – 7.52 (m, 2H, Ar), 7.47 (s, 1H, H₄), 7.22 – 7.20 (m, 2H, Ar), 7.19 – 7.18 (m, 2H, Ph), 6.88 – 6.85 (m, 2H, Ph), 4.31 (dd, J = 8.9, 1.7 Hz, 1H, H₆), 3.39 (dd, J = 18.0, 8.9 Hz, 1H, H_{7a}), 3.30 (dd, J = 18.0, 1.7 Hz, 1H, H_{7b}), 2.46 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.1 (CH, CHO), 146.9 (Cq), 139.9 (Cq), 139.4 (CH, C4), 138.4 (CH, C2), 138.0 (Cq), 137.9 (Cq), 134.2 (Cq), 131.7 (2C, CH, Ar), 130.9 (Cq), 130.4 (2C, CH, Ar), 128.4 (2C, CH, Ar), 127.0 (2C, CH, Ar), 120.9 (Cq), 35.2 (CH, C6), 29.0 (CH₂, C7), 21.8 (CH₃, Ts).

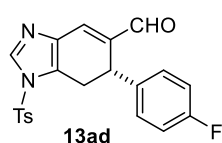
$[\alpha]_D^{20}$ +36.0 (c = 0.1 g/100 mL, CHCl₃).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 16.3 min (minor), 43.9 min (major) (99.8:0.2 er).

ESI-MS 457.02 [M+H]⁺, 480.00 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇BrN₂O₃S ([M+H]⁺): 457.0222, found: 457.0218

Synthesis of (*S*)-6-(4-fluorophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-**13ad**]



Compound **13ad** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-fluoro-cinnamaldehyde **7d** (9.6 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 48 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **4ad** (12.9 mg, 51% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H, CHO), 8.09 (s, 1H, H2), 7.58 – 7.56 (m, 2H, Ar), 7.45 (s, 1H, H4), 7.20 – 7.18 (m, 2H, Ar), 6.96 – 6.93 (m, 2H, Ph), 6.78 – 6.74 (m, 2H, Ph), 4.33 (dd, J = 8.8, 1.7 Hz, 1H, H6), 3.38 (dd, J = 18.0, 8.8 Hz, 1H, H7a), 3.29 (dd, J = 18.0, 1.7 Hz, 1H, H7b), 2.42 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.2 (CH, CHO), 161.8 (d, $^1J_{C,F}$ = 245.2 Hz, Cq, Ar), 146.8 (Cq), 139.2 (CH, C4), 138.3 (CH, C2), 138.0 (Cq), 136.7 (Cq), 134.2 (Cq), 130.4 (2C, CH, Ar), 129.6 (Cq), 128.2 (2C, d, $^3J_{C,F}$ = 8.0 Hz, CH, Ar), 127.1 (2C, CH, Ar), 115.3 (2C, d, $^2J_{C,F}$ = 21.4 Hz, CH, Ar), 35.0 (CH, C6), 29.7 (CH₂, C7), 21.6 (CH₃, Ts).

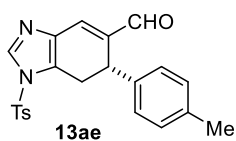
$[\alpha]_D^{20}$ +29.3 (c = 0.1 g/100 mL, CHCl₃).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 15.3 min (minor), 32.2 min (minor) (99.6:0.4 er).

ESI-MS 397.10 [M+H]⁺, 419.08 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇FN₂O₃S ([M+H]⁺): 397.1022, found: 397.1023

Synthesis of (*S*)-6-(*p*-tolyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13ae]



Compound **13ae** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-methyl-cinnamaldehyde **7e** (9.36 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13a3** (18.1 mg, 72% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H, CHO), 8.06 (s, 1H, H₂), 7.62 – 7.55 (m, 2H, Ar), 7.40 (s, 1H, H₄), 7.21 – 7.15 (m, 2H, Ar), 6.92 – 6.87 (m, 4H, Ph), 4.33 (dd, J = 8.3, 2.6 Hz, 1H, H₆), 3.40 (dd, J = 18.0, 2.6 Hz, 1H, H_{7a}), 3.34 (dd, J = 18.0, 8.3 Hz, 1H, H_{7b}), 2.42 (s, 3H, Me), 2.29 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.4 (CH, CHO), 146.5 (Cq), 139.0 (CH, C₄), 138.6 (Cq), 138.2 (2Cq), 138.0 (CH, C₂), 136.5 (Cq), 134.4 (Cq), 130.4 (2C, CH, Ar), 130.0 (Cq), 129.3 (2C, CH, Ar), 127.2 (2C, CH, Ar), 126.5 (2C, CH, Ar), 35.3 (CH, C₆), 28.8 (CH₂, C₇), 21.7 (CH₃, Me), 21.0 (CH₃, Ts).

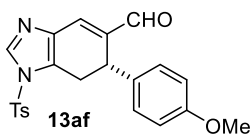
$[\alpha]_D^{20}$ +121.0 (c = 0.2 g/100 mL, CHCl₃).

Chiral HPLC for (*ent*)-**13ae** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *R*_t 17.1 min (major), 43.0 min (minor) (99.9:0.1 er).

ESI-MS 393.13 [M+H]⁺, 415.11 [M+Na]⁺.

HRMS calcd for C₂₂H₂₀N₂O₃S ([M+H]⁺): 393.1273, found: 393.1272

Synthesis of (*S*)-6-(4-methoxyphenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13af]



Compound **13af** was prepared according to General Procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-methoxy-cinnamaldehyde **7f** (10.38 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13af** (11.1 mg, 42% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H, CHO), 8.06 (s, 1H, H₂), 7.64 – 7.54 (m, 2H, Ar), 7.39 (s, 1H, H₄), 7.22 – 7.14 (m, 2H, Ar), 6.96 – 6.87 (m, 2H, Ph), 6.67 – 6.58 (m, 2H, Ph), 4.37 – 4.19 (m, 1H, H₆), 3.78 (s, 3H, OMe), 3.37 – 3.31 (m, 2H, H_{7a} + H_{7b}), 2.43 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.4 (CH, CHO), 158.6 (Cq), 146.6 (Cq), 138.9 (CH, C4), 138.7 (Cq), 138.2 (Cq), 138.0 (2C, Cq + CH, C2), 134.3 (Cq), 133.2 (Cq), 129.9 (2C, CH, Ar), 127.7 (2C, CH, Ar), 127.2 (2C, CH, Ar), 113.9 (2C, CH, Ar), 55.2 (CH₃, OMe), 34.9 (CH, C6), 29.0 (CH₂, C7), 21.7 (CH₃, Ts).

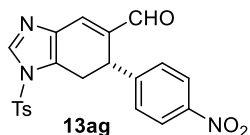
$[\alpha]_D^{20}$ +26.0 (c = 0.05 g/100 mL, CHCl₃).

Chiral HPLC for (*ent*)-**13af** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *Rt* 23.4 min (major), 75.3 min (minor) (99.9:0.1 er).

ESI-MS 409.12 [M+H]⁺, 431.10 [M+Na]⁺.

HRMS calcd for C₂₂H₂₀N₂O₄S ([M+H]⁺): 408.1144, found: 408.1147

Synthesis of (*S*)-6-(4-nitrophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[d]imidazole-5-carbaldehyde [(+)-**13ag**]



Compound **13ag** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-nitro-cinnamaldehyde **7g** (11.34 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L) at 25 °C. After 48 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ag** (13.9 mg, 51% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H, CHO), 8.13 (s, 1H, H2), 7.96 – 7.93 (m, 2H, Ph), 7.63 – 7.60 (m, 2H, Ar), 7.51 (s, 1H, H4), 7.22 – 7.20 (m, 2H, Ar), 7.17 – 7.15 (m, 2H, Ph), 4.46 – 4.43 (m, 1H, H6), 3.44 (dd, J = 18.1, 9.3 Hz, 1H, H7a), 3.32 (dd, J = 18.1, 1.5 Hz, 1H, H7b), 2.39 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 190.9 (CH, CHO), 148.6 (Cq), 147.2 (Cq), 139.8 (CH, C4), 138.6 (Cq), 137.9 (2C, Cq + CH, C2), 137.1 (Cq), 134.15 (Cq), 130.5 (2C, CH, Ar), 129.2 (Cq), 127.6 (2C, CH, Ar), 127.2 (2C, CH, Ar), 123.8 (2C, CH, Ar), 35.6 (CH, C6), 28.4 (CH₂, C7), 21.6 (CH₃, Ts).

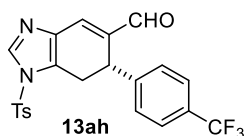
$[\alpha]_D^{20}$ +191.0 (c = 0.07 g/100 mL, CHCl₃).

Chiral HPLC for (*ent*)-**13ag** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *Rt* 25.8 min (major), 49.5 min (minor) (99.9:0.1 er).

ESI-MS 424.10 [M+H]⁺, 446.08 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇N₃O₅S ([M+H]⁺): 423.0889, found: 423.0893

Synthesis of (*S*)-1-tosyl-6-(4-(trifluoromethyl)phenyl)-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13ah]



Compound **13ah** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-4-trifluoromethylcinnamaldehyde **7h** (12.81 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L) at 25 °C. After 48 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ag** (14.4 mg, 49 % yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H, CHO), 8.09 (s, 1H, H2), 7.62 – 7.50 (m, 2H, Ar), 7.50 (s, 1H, H4), 7.36 (d, *J* = 8.2 Hz, 2H, Ar), 7.17 (d, *J* = 8.1 Hz, 2H, Ar), 7.12 (d, *J* = 8.1 Hz, 2H, Ar), 4.43 (dd, *J* = 9.0, 1.9 Hz, 1H, H6), 3.45 (dd, *J* = 18.1, 9.1 Hz, 1H, H7a), 3.35 (dd, *J* = 18.1, 1.9 Hz, 1H, H7b), 2.39 (s, 3H, Ts).

¹³C-NMR (101 MHz, CDCl₃) δ 191.0 (CH, CHO), 147.6 (Cq), 146.9 (Cq), 146.0 (Cq), 139.6 (CH, C4), 138.4 (CH, C2), 138.0 (Cq), 132.1 (q, ²*J*_{C,F} = 21.4 Hz, Cq), 130.4 (2C, CH, Ar), 129.4 (Cq), 127.9 (Cq), 127.1 (4C, CH, Ar), 125.5 (d, ³*J*_{C,F} = 4 Hz, 2C, CH, Ar), 124.1 (q, ¹*J*_{C,F} = 271 Hz, Cq, CF₃), 35.5 (CH, C6), 28.8 (CH₂, C7), 21.5 (CH₃, Ts).

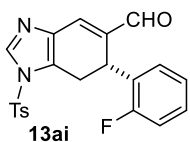
$[\alpha]_D^{20}$ +42.5 (*c* = 0.004 g/100 mL, MeOH).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *R*_t 13.7 min (minor), 26.2 min (major) (99.7:0.3 er).

ESI-MS 447.10 [M+H]⁺, 469.08 [M+Na]⁺.

HRMS calcd for C₂₂H₁₇F₃N₂O₃S ([M+H]⁺): 447.0990, found: 447.0994

Synthesis of (*R*)-6-(2-fluorophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(–)-13ai]



Compound **13ai** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-2-fluoro-cinnamaldehyde **7i** (9.6 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L) at 25 °C. After 48 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ai** (12.9 mg, 51% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H, CHO), 8.04 (s, 1H, H2), 7.59 – 7.52 (m, 3H, 2H Ar + H4), 7.20 – 7.11 (m, 3H, Ar), 7.06 – 6.96 (m, 1H, Ar), 6.82 – 6.66 (m, 2H, Ar), 4.72 (dd, *J* = 8.3, 3.0 Hz, 1H, H6), 3.41 – 3.20 (m, 2H, H7a + H7b), 2.39 (s, 3H, Ts).

^{13}C -NMR (100 MHz, CDCl_3) δ 190.8 (CH, CHO), 161.3 (d, $^1J_{\text{C,F}} = 247$ Hz, Cq, Ar), 146.5 (Cq), 140.4 (CH, C4), 138.3 (CH, C2), 137.7 (Cq), 136.8 (Cq), 134.2 (Cq), 130.4 (2C, CH, Ar), 129.9 (Cq), 128.4 (d, $^2J_{\text{C,F}} = 7$ Hz, Cq, Ar), 127.6 (d, $^3J_{\text{C,F}} = 3$ Hz, CH, Ar), 127.1 (2C, CH, Ar), 126.9 (CH, Ar), 123.8 (d, $^3J_{\text{C,F}} = 3$ Hz, CH, Ar), 115.8 (d, $^2J_{\text{C,F}} = 22$ Hz, CH, Ar), 29.7 (CH, C6), 27.9 (CH_2 , C7), 21.7 (CH_3 , Ts).

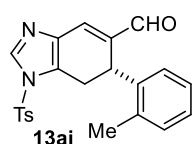
$[\alpha]_{\text{D}}^{20}$ -14.0 ($c = 0.1$ g/100 mL, CHCl_3).

Chiral HPLC for (*ent*)-**13ai** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min^{-1} , 220 nm): R_t 17.8 min (major), 24.8 min (minor) (99.9:0.1 er).

ESI-MS 397.10 $[\text{M}+\text{H}]^+$, 419.08 $[\text{M}+\text{Na}]^+$.

HRMS calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$): 397.1022, found: 397.1019

Synthesis of (*R*)-6-(*o*-tolyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(*-*)-**13aj**]



Compound **13aj** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-2-methyl-cinnamaldehyde **7j** (9.36 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et_3N ; 4.46 μL , 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μL) and DMF (370 μL). After 24 hours, the resulting mixture

was quenched with saturated aqueous solution of NaHCO_3 and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/ AcOEt 70:30) to afford **13aj** (13.8 mg, 55% yield) as a yellow solid.

^1H -NMR (400 MHz, CDCl_3) δ 9.55 (s, 1H, CHO), 8.04 (s, 1H, H2), 7.53 (s, 1H, H4), 7.45 (d, $J = 8.4$ Hz, 2H, Ar), 7.16 (d, $J = 7.5$ Hz, 1H, Ar), 7.12 – 7.02 (m, 3H, Ar), 6.76 (t, $J = 7.4$ Hz, 1H, Ar), 6.67 (d, $J = 7.1$ Hz, 1H, Ar), 4.58 – 4.53 (m, 1H, H6), 3.38 (dd, $J = 15.5, 7.7$ Hz, 1H, H7a), 3.13 (dd, $J = 15.5, 1.4$ Hz, 1H, H7b), 2.52 (s, 3H, Me), 2.37 (s, 3H, Me Ts).

^{13}C -NMR (100 MHz, CDCl_3) δ 191.2 (CH, CHO), 146.3 (Cq), 139.5 (CH, C4), 139.1 (Cq), 138.4 (Cq), 138.3 (CH, C2), 138.0 (Cq), 134.7 (Cq), 134.2 (Cq), 131.0 (CH, Ar), 130.3 (2C, CH, Ar), 129.6 (Cq), 126.8 (2C, CH, Ar), 126.7 (CH, Ar), 125.9 (CH, Ar), 125.4 (CH, Ar), 29.7 (CH, C6), 28.0 (CH_2 , C7), 21.7 (CH_3 , Ts), 19.7 (CH_3 , Me).

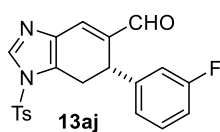
$[\alpha]_{\text{D}}^{20}$ -16.0 ($c = 0.05$ g/100 mL, CHCl_3).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min^{-1} , 220 nm): R_t 13.8 min (minor), 21.2 min (major) (99.6:0.4 er).

ESI-MS 393.13 $[\text{M}+\text{H}]^+$, 415.11 $[\text{M}+\text{Na}]^+$.

HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$): 393.1273, found: 393.1277

Synthesis of (S)-6-(3-fluorophenyl)-1-tosyl-6,7-dihydro-1H-benzo[d]imidazole-5-carbaldehyde [(+)-13ak]



Compound **13ak** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-3-fluoro-cinnamaldehyde **7k** (9.6 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ak** (20.0 mg, 79% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H, CHO), 8.10 (s, 1H, H2), 7.64 – 7.56 (m, 2H, Ar), 7.46 (s, 1H, H4), 7.23 – 7.18 (m, 2H, Ar), 7.08 (td, J = 8.0, 7.9, 6.0 Hz, 1H, Ar), 6.88 – 6.79 (m, 2H, Ar), 6.64 – 6.56 (m, 1H, Ar), 4.35 (dd, J = 8.7, 2.3 Hz, 1H, H6), 3.39 (dd, J = 18.2, 8.6 Hz, 1H, H7a), 3.32 (dd, J = 18.0, 2.3 Hz, 1H, H7b), 2.41 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.1 (CH, CHO), 162.7 (d, $^1J_{C,F}$ = 246 Hz, Cq, Ar), 146.8 (Cq), 143.7 (d, $^3J_{C,F}$ = 7 Hz, Cq, Ar), 139.4 (CH, C2), 138.4 (CH, C4), 137.9 (Cq), 137.8 (Cq), 134.1 (Cq), 130.5 (2C, CH, Ar), 130.1 (d, $^3J_{C,F}$ = 8 Hz, CH, Ar), 129.6 (Cq), 127.1 (2C, CH, Ar), 122.5 (d, $^4J_{C,F}$ = 3 Hz, CH, Ar), 113.9 (d, $^2J_{C,F}$ = 21 Hz, CH, Ar), 113.4 (d, $^2J_{C,F}$ = 22 Hz, CH, Ar), 35.4 (CH, C6), 28.7 (CH₂, C7), 21.7 (CH₃, Ts).

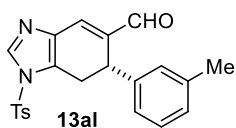
$[\alpha]_D^{20}$ +54.5 (c = 0.004 g/100 mL, MeOH).

Chiral HPLC for (*ent*)-**13aj** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *Rt* 17.0 min (major), 37.1 min (minor) (99.6:0.4 er).

ESI-MS 397.10 [M+H]⁺, 419.08 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇FN₂O₃S ([M+H]⁺): 397.1022, found: 397.1026

Synthesis of (S)-6-(*m*-tolyl)-1-tosyl-6,7-dihydro-1H-benzo[d]imidazole-5-carbaldehyde [(+)-13al]



Compound **13al** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-3-methyl-cinnamaldehyde **7l** (9.36 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13aj** (13.1 mg, 52% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H, CHO), 8.06 (s, 1H, H₂), 7.57 (d, J = 8.5 Hz, 2H, Ar), 7.43 (s, 1H, H₄), 7.17 (d, J = 8.2 Hz, 2H, Ar), 7.04 – 6.93 (m, 2H, Ar), 6.86 – 6.76 (m, 2H, Ar), 4.36 – 4.31 (m, 1H, H₆), 3.40 – 3.36 (m, 2H, H_{7a} + H_{7b}), 2.41 (s, 3H, Ts), 2.19 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 191.4 (CH, CHO), 146.4 (Cq), 141.1 (Cq), 139.1 (CH, C₄), 138.5 (Cq), 138.2 (CH, C₂), 138.1 (Cq), 138.0 (Cq), 134.3 (Cq), 130.4 (2C, CH, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 127.3 (CH, Ar), 127.1 (2C, CH, Ar), 127.0 (Cq), 123.6 (CH, Ar), 35.7 (CH, C₆), 29.7 (CH₂, C₇), 21.7 (CH₃, Ts), 21.4 (CH₃, Me).

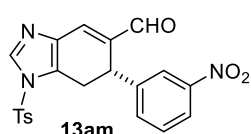
$[\alpha]_D^{20}$ +25.6 (c = 0.004 g/100 mL, MeOH).

Chiral HPLC for (*ent*)-**13al** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 16.7 min (major), 47.5 min (minor) (99.9:0.1 er).

ESI-MS 393.13 [M+H]⁺, 415.11 [M+Na]⁺.

HRMS calcd for C₂₂H₂₀N₂O₃S ([M+H]⁺): 393.1273, found: 393.1271

Synthesis of (*S*)-6-(3-nitrophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-**13am**]



Compound **13am** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-3-nitrocinnamaldehyde **7m** (11.34 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13am** (15.3 mg, 56% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.59 (s, 1H, CHO), 8.13 (s, 1H, H₂), 8.02 – 7.97 (m, 1H, Ar), 7.82 – 7.79 (m, 1H, Ar), 7.64 – 7.59 (m, 2H, Ar), 7.55 (s, 1H, H₄), 7.39 – 7.32 (m, 2H, Ar), 7.20 – 7.14 (m, 2H, Ar), 4.45 (d, J = 8.2 Hz, 1H, H₆), 3.45 (dd, J = 18.1, 8.2 Hz, 1H, H_{7a}), 3.31 (dd, J = 18.1, 1.4 Hz, 1H, H_{7b}), 2.39 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 190.9 (CH, CHO), 147.0 (Cq), 143.2 (Cq), 139.9 (CH, C₄), 138.7 (CH, C₂), 138.0 (Cq), 137.1 (Cq), 135.6 (Cq), 134.1 (Cq), 133.1 (CH, Ar), 130.4 (2C, CH, Ar), 129.6 (CH, Ar), 129.1 (Cq), 127.2 (2C, CH, Ar), 122.1 (CH, Ar), 121.5 (CH, Ar), 35.4 (CH, C₆), 29.7 (CH₂, C₇), 21.7 (CH₃, Ts).

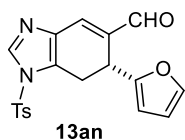
$[\alpha]_D^{20}$ +92.1 (c = 0.24 g/100 mL, CHCl₃).

Chiral HPLC for (*ent*)-**13am** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 27.6 min (major), 48.4 min (minor) (99.8:0.2 er).

ESI-MS 424.10 [M+H]⁺, 446.08 [M+Na]⁺.

HRMS calcd for C₂₁H₁₇N₃O₅S ([M+H]⁺): 423.0889, found: 423.0894

Synthesis of (*R*)-6-(furan-2-yl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde (-)-[13an]



Compound **13an** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), enal **7n** (7.82 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13an** (12.3 mg, 52% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H, CHO), 8.05 (s, 1H, H₂), 7.75 (d, *J* = 8.5 Hz, 2H, Ar), 7.40 (s, 1H, H₄), 7.34 (d, *J* = 8.0 Hz, 2H, Ar), 7.12 (dd, *J* = 1.9, 0.8 Hz, 1H, furyl), 6.10 (dd, *J* = 3.2, 1.9 Hz, 1H, furyl), 5.76 – 5.73 (m, 1H, furyl), 4.49 (dd, *J* = 8.4, 1.3 Hz, 1H, H₆), 3.66 (dd, *J* = 17.8, 1.4 Hz, 1H, H_{7a}), 3.14 (dd, *J* = 17.9, 8.5 Hz, 1H, H_{7b}), 2.46 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 190.8 (CH, CHO), 153.3 (Cq), 146.6 (Cq), 141.6 (CH, furyl), 139.7 (CH, C₄), 138.1 (CH, C₂), 137.4 (Cq), 135.8 (Cq), 134.4 (Cq), 130.5 (2C, CH, Ar), 127.4 (2C, CH, Ar), 110.0 (CH, furyl), 105.7 (CH, furyl), 29.8 (CH, C₆), 25.4 (CH₂, C₇), 21.8 (CH₃, Ts).

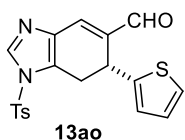
$[\alpha]_D^{20}$ -95.1 (*c* = 0.004 g/ 100 mL, MeOH).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *R_t* 16.2 min (minor), 24.5 min (major) (99.9:0.1 er).

ESI-MS 369.09 [M+H]⁺, 391.07 [M+Na]⁺.

HRMS calcd for C₁₉H₁₆N₂O₄S ([M+H]⁺): 369.0909, found: 369.0907

Synthesis of (*R*)-6-(thiophen-2-yl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13ao]



Compound **13ao** was prepared according to general procedure A using: catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), enal **7o** (8.84 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ao** (19.2 mg, 78% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H, CHO), 8.10 (s, 1H, H₂), 7.73 (d, *J* = 8.5 Hz, 2H, Ar), 7.35 (s, 1H, H₄), 7.31 – 7.29 (m, 2H, Ar), 6.91 (dd, *J* = 5.1, 1.3 Hz, 1H, thiophenyl), 6.71 (dd, *J* = 5.1,

3.5 Hz, 1H, tiophenyl), 6.65 – 6.62 (m, 1H, tiophenyl), 4.67 (d, J = 8.5 Hz, 1H, H6), 3.54 (dd, J = 17.9, 1.4 Hz, 1H, H7a), 3.30 (dd, J = 17.8, 8.5 Hz, 1H, H7b), 2.45 (s, 3H, Ts).

^{13}C -NMR (100 MHz, CDCl_3) δ 190.9 (CH, CHO), 146.7 (Cq), 143.8 (Cq), 138.5 (CH, C4), 138.3 (CH, C2), 137.7 (Cq), 134.4 (Cq), 130.5 (3C, CH, Ar + Cq), 130.0 (Cq), 127.5 (2C, CH, Ar), 126.2 (CH, tiophenyl), 124.4 (CH, tiophenyl), 123.2 (CH, tiophenyl), 31.2 (CH, C6), 28.9 (CH_2 , C7), 21.8 (CH_3 , Ts).

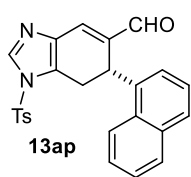
$[\alpha]_{\text{D}}^{20}$ +36.7 (c = 0.004 g/100 mL, MeOH).

Chiral HPLC for (*ent*)-**13ao** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min $^{-1}$, 220 nm): R_t 21.2 min (major), 33.7 min (minor) (99.6:0.4 er).

ESI-MS 385.07 $[\text{M}+\text{H}]^+$, 407.05 $[\text{M}+\text{Na}]^+$.

HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$ ($[\text{M}+\text{H}]^+$): 385.0681, found: 385.0685

Synthesis of (*S*)-6-(naphthalen-1-yl)-1-tosyl-6,7-dihydro-1*H*-benzo[d]imidazole-5-carbaldehyde [(*-*)-**13ap**]



Compound **13ap** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-1-naphthalencinnamaldehyde **7p** (11.66 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et_3N ; 4.46 μL , 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μL) and DMF (370 μL). After 24 hours, the resulting mixture

was quenched with saturated aqueous NaHCO_3 solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ap** (17.1 mg, 62% yield) as a yellow solid.

^1H -NMR (400 MHz, CDCl_3) δ 9.66 (s, 1H, CHO), 8.22 – 8.15 (m, 1H, Ar), 8.04 (s, 1H, H2), 7.92 – 7.86 (m, 1H, Ar), 7.72 – 7.63 (m, 2H, Ar), 7.62 – 7.54 (m, 2H Ar + H4), 7.19 – 7.14 (m, 2H, Ar), 7.05 – 6.97 (m, 1H, Ar), 6.87 – 6.82 (m, 1H, Ar), 6.67 – 6.60 (m, 2H, Ar), 5.19 (d, J = 9.3 Hz, 1H, H6), 3.52 (dd, J = 17.8, 9.3 Hz, 1H, H7a), 3.35 (dd, J = 17.8, 1.2 Hz, 1H, H7b), 2.24 (s, 3H, Me).

^{13}C -NMR (100 MHz, CDCl_3) δ 191.1 (CH, CHO), 146.0 (Cq), 140.6 (CH, C4), 138.2 (Cq), 138.1 (CH, C2), 137.7 (Cq), 134.6 (Cq), 133.8 (Cq), 133.6 (Cq), 130.2 (Cq), 130.1 (Cq), 129.8 (2C, CH, Ar), 129.2 (CH, Ar), 127.4 (CH, Ar), 126.6 (2C, CH, Ar), 126.5 (CH, Ar), 125.6 (CH, Ar), 125.0 (CH, Ar), 123.2 (CH, Ar), 123.0 (CH, Ar), 31.3 (CH, C6), 28.2 (CH_2 , C7), 21.6 (CH_3 , Ts).

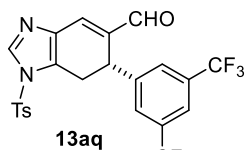
$[\alpha]_{\text{D}}^{20}$ -312.1 (c = 0.2 g/100 mL, CHCl_3).

Chiral HPLC for (*ent*)-**13ap** (WELK-O1, 60/40 Hexane/Ethanol, 0.8 mL min $^{-1}$, 220 nm): R_t 19.6 min (major), 94.0 min (minor) (100:0. er).

ESI-MS 429.13 $[\text{M}+\text{H}]^+$, 451.11 $[\text{M}+\text{Na}]^+$.

HRMS calcd for $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$): 429.1273, found: 429.1269

Synthesis of (*S*)-6-(3,5-bis(trifluoromethyl)phenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(*-*)-13aq]



Compound **13aq** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*-3,5-bis(trifluoromethyl)cinnamaldehyde **7q** (17.16 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF

(370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13aq** (16.1 mg, 49% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.59 (s, 1H, CHO), 8.14 (s, 1H, H₂), 7.65 (s, 1H, H₄), 7.60 – 7.54 (m, 2H, Ar), 7.45 – 7.40 (m, 2H, Ar), 7.18 – 7.11 (m, 2H, Ar), 4.47 (d, J = 9.1 Hz, 1H, H₆), 3.49 (dd, J = 18.2, 9.1 Hz, 1H, H₇), 3.23 (dd, J = 18.2, 0.9 Hz, 1H, H₇), 2.36 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 190.8 (CH, CHO), 146.9 (Cq), 143.6 (Cq), 140.2 (CH, C₄), 138.8 (CH, C₂), 138.0 (Cq), 136.5 (Cq), 134.0 (Cq), 131.9 (q, $^2J_{C,F}$ = 33 Hz, 2C, Cq), 130.4 (2C, CH, Ar), 128.7 (Cq), 127.0 (2C, CH, Ar), 126.9 (q, $^3J_{C,F}$ = 4.0 Hz, 2C, CH), 123.0 (q, $^1J_{C,F}$ = 273 Hz, 2C, CF₃), 121.0 (d, $^3J_{C,F}$ = 4 Hz, CH, Ar), 35.5 (CH, C₆), 28.9 (CH₂, C₇), 21.5 (CH₃, Ts).

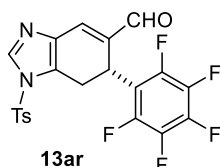
$[\alpha]_D^{20}$ -94.5 (c = 0.004 g/100 mL, MeOH).

Chiral HPLC for (*ent*)-**13aq** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *R_t* 9.3 min (major), 15.8 min (minor) (99.7:0.3 er).

ESI-MS 515.09 [M+H]⁺, 537.07 [M+Na]⁺.

HRMS calcd for C₂₃H₁₆F₆N₂O₃S ([M+H]⁺): 515.0864, found: 515.0856

Synthesis of (*R*)-6-(perfluorophenyl)-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(*-*)-13ar]



Compound **13ar** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), enal **7r** (14.21 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF

(370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ar** (17.1 mg, 57% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H, CHO), 8.12 (s, 1H, H₂), 7.76 (d, J = 8.5 Hz, 2H, Ar), 7.41 (d, J = 1.7 Hz, 1H, H₄), 7.39 – 7.35 (m, 2H, Ar), 4.69 (dd, J = 11.2, 7.3 Hz, 1H, H₆), 3.50 (dd, J = 18.4, 11.6 Hz, 1H, H_{7a}), 3.08 (dd, J = 18.4, 6.9 Hz, 1H, H_{7b}), 2.47 (s, 3H, Ts).

¹³C-NMR (400 MHz, CDCl₃) δ 190.8 (CH, CHO), 147.2 (CH, C4), 140.6 (2Cq), 138.3 (CH, C2), 135.6 (2C, d, ¹J_{C,F} = 300 Hz, Cq), 134.2 (Cq), 132.4 (Cq), 130.6 (2C, CH, Ar), 130.1 (Cq), 128.6 (2C, d, ²J_{C,F} = 70 Hz, Cq), 128.1 (d, ²J_{C,F} = 7 Hz, Cq), 128.0 (2C, d, ¹J_{C,F} = 60 Hz, Cq), 127.4 (2C, CH, Ar), 29.7 (CH, C6), 26.8 (CH₂, C7), 21.7 (CH₃, Ts).

[α]_D²⁰ -128.0 (*c* = 0.2 g/100 mL, CHCl₃).

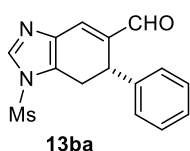
Chiral HPLC for (*ent*)-**13ar** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *Rt* 12.8 min (major), 15.6 min (minor) (99.7:0.3 er).

ESI-MS 469.07 [M+H]⁺, 491.05 [M+Na]⁺.

HRMS calcd for C₂₁H₁₃F₅N₂O₃S ([M+H]⁺): 469.0645, found: 469.0644

Scope of the nucleophile

Synthesis of (*S*)-1-(methanesulfonyl)-6-phenyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-**13ba**]



Compound **13ba** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*- β -cinnamaldehyde **7a** (8.06 μ L, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12b** (24.41 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 30:70) to afford **13ba** (9.7 mg, 70% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H, CHO), 7.98 (s, 1H, H2), 7.54 (s, 1H, H4), 7.25 – 7.15 (m, 5H, Ph), 4.46 (dd, *J* = 9.2, 1.4 Hz, 1H, H6), 3.51 (dd, *J* = 18.1, 9.3 Hz, 1H, H7), 3.38 (dd, *J* = 18.0, 1.7 Hz, 1H, H7), 3.02 (s, 3H, Me).

¹³C-NMR (100 MHz, CDCl₃) δ 191.4 (CH, CHO), 141.2 (Cq), 139.0 (CH, C4), 138.7 (Cq), 138.2 (Cq), 138.0 (CH, C2), 129.7 (Cq), 128.9 (2C, CH, Ar), 127.4 (CH, Ar), 126.6 (2C, CH, Ar), 35.9 (CH₃, Ms), 29.7 (CH, C6), 29.1 (CH₂, C7).

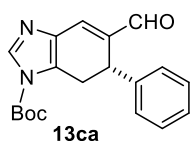
[α]_D²⁰ +170.0 (*c* = 0.07 g/100 mL, CHCl₃).

Chiral HPLC (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): *Rt* 20.5 min (minor), 33.0 min (major) (99.9:0.1 er).

ESI-MS 303.08 [M+H]⁺, 325.06 [M+Na]⁺.

HRMS calcd for C₁₅H₁₄N₂O₃S ([M+H]⁺): 303.0803, found: 303.0808

Synthesis of *tert*-butyl (S)-5-formyl-6-phenyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-1-carboxylate [(+)-13ca]



Compound **13ca** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*- β -cinnamaldehyde **7a** (8.06 μ L, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12c** (24.8 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13ca** (15.4 mg, 74% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H, CHO), 8.06 (s, 1H, H₂), 7.49 (s, 1H, H₄), 7.25 – 7.18 (m, 5H, Ph), 4.42 (dd, J = 9.7, 1.8 Hz, 1H, H₆), 3.59 (dd, J = 18.7, 1.8 Hz, 1H, H₇), 3.48 (dd, J = 18.7, 9.7 Hz, 1H, H₇), 1.61 (s, 9H, Boc).

¹³C-NMR (100 MHz, CDCl₃) δ 191.5 (CH, CHO), 146.9 (Cq), 146.5 (Cq), 142.6 (Cq), 139.9 (CH, C₄), 138.8 (CH, C₂), 137.6 (Cq), 128.7 (Cq), 127.0 (2C, CH, Ar), 126.9 (3C, 2 CH Ar + CH Ar), 86.7 (Cq), 35.8 (CH, C₆), 29.7 (CH₂, C₇), 27.9 (3C, CH₃, Boc).

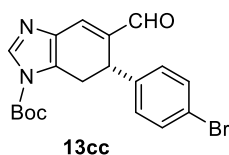
$[\alpha]_D^{20}$ +379.6 (c = 0.27 g/100 mL, CHCl₃).

Chiral HPLC (AMYLOSE-1, 90/10 Hexane/Ethanol, 0.7 mL min⁻¹, 220 nm): R_t 19.0 min (minor), 21.3 min (major) (99.0:1.0. er).

ESI-MS 325.16 [M+H]⁺, 347.14 [M+Na]⁺.

HRMS calcd for C₁₉H₂₀N₂O₃ ([M+H]⁺): 325.1552, found: 325.1548

Synthesis of *tert*-butyl (S)-6-(4-bromophenyl)-5-formyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-1-carboxylate [(+)-13cc]



Compound **13cc** was prepared according to general procedure A using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), enal **7c** (13.51 mg, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12c** (24.8 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13cc** (16.7 mg, 65% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.59 (s, 1H, CHO), 8.07 (s, 1H, H₂), 7.51 (s, 1H, H₄), 7.36 (d, J = 8.5 Hz, 2H, Ar), 7.10 (d, J = 8.5 Hz, 2H, Ar), 4.36 (dd, J = 9.0, 2.6 Hz, 1H, H₆), 3.53 (dd, J = 18.7, 2.7 Hz, 1H, H_{7a}), 3.46 (dd, J = 18.8, 9.1 Hz, 1H, H_{7b}), 1.62 (s, 9H, Boc).

¹³C-NMR (100 MHz, CDCl₃) δ 191.3 (CH, CHO), 146.9 (Cq), 141.6 (Cq), 140.0 (CH, C4), 138.9 (CH, C2), 137.2 (Cq), 137.1 (Cq), 131.8 (2C, CH, Ar), 130.9 (Cq), 128.7 (2C, CH, Ar), 120.9 (Cq), 86.8 (Cq), 35.3 (CH, C6), 29.6 (CH₂, C7), 27.9 (3C, CH₃, Boc).

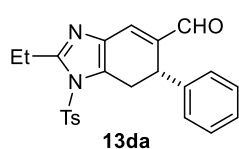
$[\alpha]_D^{20}$ +202.9 ($c = 0.004$ g/100 mL, MeOH).

Chiral HPLC (AMYLOSE-1, 90/10 Hexane/Ethanol, 0.7 mL min⁻¹, 220 nm): R_t 25.8 min (minor), 28.7 min (major) (98.5:1.5. er).

ESI-MS 403.07 [M+H]⁺, 425.05 [M+Na]⁺.

HRMS calcd for C₁₉H₁₉BrN₂O₃ ([M+H]⁺): 403.0657, found: 403.0656

Synthesis of (*S*)-2-ethyl-6-phenyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(*-*)-**13da**]



Compound **13da** was prepared according to general procedure using catalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*- β -cinnamaldehyde **7a** (8.06 μ L, 0.064 mmol, 1.0 equiv.), alkylidene malononitrile **12d** (32.68 mg, 0.096 mmol, 1.5 equiv.) and triethylamine (Et₃N; 4.46 μ L, 0.032 mmol, 0.5 equiv.) in dichloromethane (730 μ L) and DMF (370 μ L). After 24 hours, the resulting mixture was quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 30:70) to afford **13da** (18.7 mg, 72% yield) as a yellow solid.

¹H-NMR (400 MHz, CDCl₃) δ 9.59 (s, 1H, CHO), 7.47 (s, 1H, H2), 7.33 (d, $J = 8.5$ Hz, 2H, H4), 7.24 – 7.17 (m, 3H, Ar), 7.17 – 7.08 (m, 4H, Ar), 4.41 (dd, $J = 9.2, 1.6$ Hz, 1H, H6), 3.62 (dd, $J = 18.3, 1.6$ Hz, 1H, H7a), 3.48 (dd, $J = 18.3, 9.1$ Hz, 1H, H7b), 3.18 – 3.04 (m, 1H, Et), 2.86 – 2.74 (m, 1H, Et), 2.39 (s, 3H, Ts), 1.36 (t, $J = 7.4$ Hz, 3H, Et).

¹³C-NMR (100 MHz, CDCl₃) δ 191.3 (CH, CHO), 153.2 (Cq), 146.0 (Cq), 141.2 (Cq), 139.6 (CH, C4), 137.8 (Cq), 135.4 (Cq), 134.8 (Cq), 131.4 (Cq), 130.3 (2C, CH, Ar), 128.7 (2C, CH, Ar), 127.0 (CH, Ar), 126.9 (2C, CH, Ar), 126.7 (2C, CH, Ar), 35.9 (CH, C6), 31.0 (CH₂, C7), 22.9 (CH₂, Et), 21.7 (CH₃, Ts), 11.7 (CH₃, Et).

$[\alpha]_D^{20}$ -62.0 ($c = 0.60$ g/100 mL, CHCl₃).

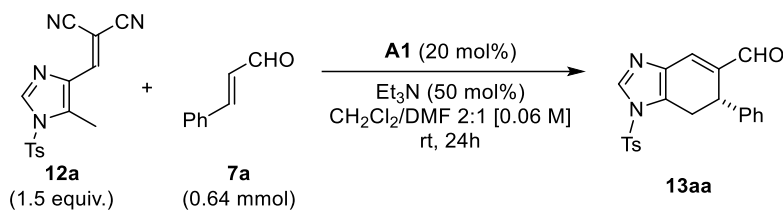
Chiral HPLC for (*ent*)-**13da** (WELK-O1, 75/25 Hexane/Ethanol, 1.0 mL min⁻¹, 220 nm): R_t 11.9 min (major), 26.6 min (minor) (99.7:0.3 er).

ESI-MS 407.15 [M+H]⁺, 429.13 [M+Na]⁺.

HRMS calcd for C₂₃H₂₂N₂O₃S ([M+H]⁺): 407.1429, found: 407.1425

3.5.4 Scaled-up model reaction

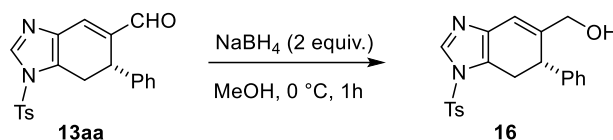
Synthesis of (*S*)-6-phenyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13aa]



In a 50mL round-bottom flask charged with a stirring bar the aminocatalyst **A1** (0.13 mmol, 42 mg, 0.2 eq.), CH₂Cl₂ (7.3 mL), *trans*- β -cinnamaldehyde **7a** (81 μ L, 0.64 mmol, 1.0 equiv.), alkylidene malononitrile **12a** (300 mg, 0.96 mmol, 1.5 equiv.), DMF (3.7 mL) and triethylamine (Et₃N; 45 μ L, 0.32 mmol, 0.5 equiv.) were sequentially added. The resulting heterogeneous mixture was stirred at 25 °C for 24 hours and, then, quenched with saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13aa** (0.17 g, 71% yield) as a yellow solid. The enantiomeric excess of the product was determined to be >99% by HPLC analysis on a WELK-O1 column (eluent: Hexane/Ethanol = 75:25; flow rate 1 mL/min, λ = 220 nm. *R*_t 16.8 min (major), 32.3 min (minor) (99.9:0.1 er).

3.5.5 Synthetic elaborations of product 13aa

Synthesis of (*S*)-(6-phenyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methanol [(+)-16]



In a 25mL round bottom flask charged with a magnetic stirring bar the substrate **13aa** (20.1 mg, 0.053 mmol) was dissolved in MeOH (2.3 mL). The solution was placed in an ice bath and cooled to 0 °C before the addition of NaBH₄ (4.02 mg, 0.106 mmol). The reaction was stirred at 0 °C for 1 hour and then removed from the ice bath. The reaction mixture was quenched with an aqueous solution HCl 10% v/v (pH = 5). The organic phase was extracted two times with EtOAc and dried over anhydrous Na₂SO₄. After filtration, the solution was concentrated under vacuum and the crude was purified by silica gel flash chromatography (petroleum EtOAc/MeOH 98:2) to afford the title compound **16** in 91% yield (18.1 mg) as a white solid.

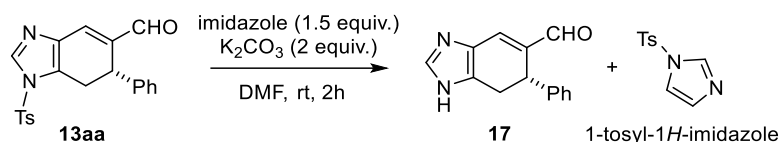
¹H-NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H, H₂), 7.48 (d, *J* = 8.4 Hz, 2H, Ar), 7.22 – 7.16 (m, 1H, Ar), 7.15 – 7.08 (m, 4H, Ar), 7.07 – 7.03 (m, 2H, Ar), 6.68 (s, 1H, H₄), 4.05 (bs, 2H, CH₂), 3.80 (dd, *J* = 9.3, 3.1 Hz, 1H, H₆), 3.38 (dd, *J* = 17.0, 9.5 Hz, 1H, H_{7a}), 3.19 (dd, *J* = 17.3, 3.1 Hz, 1H, H_{7b}), 2.38 (s, 3H, Ts).

¹³C-NMR (100 MHz, CDCl₃) δ 145.8 (Cq), 141.4 (Cq), 139.7 (CH, C₄), 139.1 (Cq), 136.7 (CH, C₂), 134.8 (Cq), 130.2 (2C, CH, Ar), 128.7 (2C, CH, Ar), 127.2 (2C, CH, Ar), 126.9 (2C, CH, Ar), 126.8 (CH, Ar), 122.5 (Cq), 117.8 (Cq), 64.7 (CH₂), 41.1 (CH, C₆), 29.7 (CH₂, C₇), 21.7 (CH₃, Ts).

$[\alpha]_D^{20} +563.6$ ($c = 0.004$ g/100 mL, MeOH).

ESI-MS 381.14 $[M+H]^+$, 403.12 $[M+Na]^+$.

Synthesis of (*S*)-6-phenyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-17]



In a 10 mL round bottom flask charged with a magnetic stirring bar the substrate **13aa** (20 mg, 0.053 mmol) was dissolved in DMF (2.5 mL). Potassium carbonate (14.6 mg, 0.106 mmol) and imidazole (5.4 mg, 0.080 mmol) were sequentially added. The reaction was stirred at room temperature for 2 h. The organic phase was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/EtOAc 60:40 to 100% EtOAc) to afford product **17** (11.3 mg, 95% yield) along with 1-tosyl-1*H*-imidazole (10.7 mg) as a by-product.

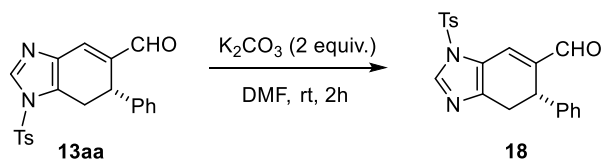
^1H -NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H, CHO), 7.62 (s, 1H, H4), 7.49 (bs, 1H, H2), 7.19 (s, 5H, Ph), 4.38 (d, $J = 9.6$ Hz, 1H, H6), 3.38 (dd, $J = 17.2, 9.6$ Hz, 1H, H7a), 3.06 (d, $J = 17.2$ Hz, 1H, H7b).

^{13}C -NMR 191.5, 142.4, 139.7 (2C), 136.7, 130.5, 128.6, 128.4, 127.1, 126.9, 36.2, 29.7.

$[\alpha]_D^{20} +312.0$ ($c = 0.1$ g/100 mL, $CHCl_3$).

ESI-MS 225.10 $[M+H]^+$, 247.08 $[M+Na]^+$.

Synthesis of (*S*)-5-phenyl-1-tosyl-4,5-dihydro-1*H*-benzo[*d*]imidazole-6-carbaldehyde [(+)-18]



In a 10 mL round bottom flask charged with a magnetic stirring bar the substrate **13aa** (20 mg, 0.053 mmol) was dissolved in degassed DMF (1 mL). Potassium carbonate (14.6 mg, 0.106 mmol) was added, and the reaction was stirred at room temperature for 2 h. The organic phase was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/EtOAc 70:30) to afford product **18** (7.6 mg, 38% yield).

^1H -NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H, CHO), 8.10 (s, 1H, H2), 7.83 (d, $J = 8.4$ Hz, 2H, Ar), 7.67 (s, 1H, H7), 7.41 (d, $J = 8.1$ Hz, 2H, Ar), 7.18 – 7.10 (m, 1H, Ar), 7.10 – 7.01 (m, 2H, Ar), 6.94

– 6.89 (m, 2H, Ar), 4.34 (d, $J = 9.6$ Hz, 1H, H5), 3.30 (dd, $J = 17.8, 9.7$ Hz, 1H, H4a), 3.08 (dd, $J = 17.8, 1.6$ Hz, 1H, H4b), 2.51 (s, 3H, Ts).

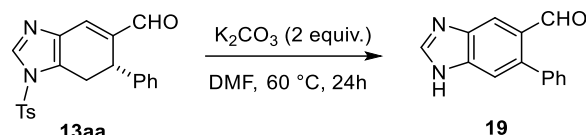
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 190.8 (CH, CHO), 146.8 (Cq), 145.8 (Cq), 139.9 (CH; C2), 139.2 (Cq), 134.7 (Cq), 131.8 (Cq), 130.7 (CH, C7), 128.5 (2C, CH, Ar), 128.2 (Cq), 127.5 (Cq), 127.2 (2C, CH, Ar), 127.0 (CH, Ar), 126.7 (2C, CH, Ar), 35.8 (CH, C5), 30.6 (CH_2 , C4), 21.8 (CH_3 , Ts).

$[\alpha]_{\text{D}}^{20} +48.0$ ($c = 0.05$ g/100 mL, CHCl_3).

Chiral HPLC for (*ent*)-**18** (WELK-O1, 75/25 Hexane/Ethanol, 1 mL min $^{-1}$, 220 nm): R_t 34.0 min (major), 19.6 min (minor) (99.6:0.4 er).

ESI-MS 379.11 $[\text{M}+\text{H}]^+$, 401.09 $[\text{M}+\text{Na}]^+$.

Synthesis of 6-phenyl-1*H*-benzo[*d*]imidazole-5-carbaldehyde [**19**]



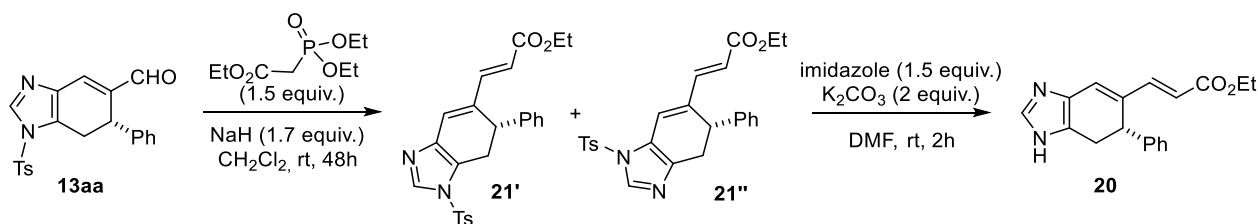
In a 10 mL round bottom flask charged with a magnetic stirring bar the substrate **13aa** (20 mg, 0.053 mmol) was dissolved in degassed DMF (1 mL). Potassium carbonate (14.6 mg, 0.106 mmol) was added, and the reaction was stirred at 60 °C for 24 h. The organic phase was extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (100% EtOAc) to afford product **18** (5.1 mg, 43% yield).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 10.02 (s, 1H, CHO), 8.40 (s, 1H, H2), 8.30 (s, 1H, H4), 7.72 (s, 1H, H7), 7.53 – 7.41 (m, 6H, Ar + NH).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 192.6, 144.1, 141.5, 138.4, 130.5, 130.4, 129.8, (2C) 128.4, 127.9.

ESI-MS 223.09 $[\text{M}+\text{H}]^+$, 245.07 $[\text{M}+\text{Na}]^+$.

Synthesis of ethyl (*S,E*)-3-(6-phenyl-6,7-dihydro-1*H*-benzo[*d*]imidazol-5-yl)acrylate [(+)-**20**]



In a 3 mL round bottom flask NaH (0.058 mmol, 1.1 equiv.) was dissolved in DCM (1.5 mL). Phosphonoacetate (1.5 equiv.) was then added to the solution which was stirred for 30 minutes. The substrate **13aa** (20 mg, 0.053 mmol) was then added and the reaction was stirred for 48 h. After total

consumption of the starting material (checked by TLC), the reaction was quenched with a saturated aqueous solution of NaHCO₃ and the organic phase was extracted three times with EtOAc, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/EtOAc 50:50) to afford a 1:1 mixture of regioisomers **21'** and **21''** (14.3 mg, 60% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 6.5 Hz, 2H_{region1 or 2}), 7.83 (d, J = 8.4 Hz, 1H_{region 2 or 1}), 7.47 – 7.37 (m, 3H_{region1} + 3H_{region2}), 7.28 (s, 1H_{region1 or 2}), 7.25 (s, 1H_{region2 or 1}), 7.20 – 7.10 (m, 2H_{region1} + 2H_{region2}), 7.08 – 7.01 (m, 5H_{region1 or 2} + 1H_{region2 or 1}), 6.86 – 6.83 (m, 2H_{region2 or 1}) 5.79 (d, J = 15.7 Hz, 2H_{region1 or 2}), 5.73 (d, J = 15.9 Hz, 1H_{region2 or 1}), 4.24 – 4.10 (m, 2H_{region1} + 2H_{region2}), 4.06 (d, J = 8.8 Hz, 1H_{region1}), 4.03 (d, J = 9.1 Hz, 1H_{region2}), 3.43 (dd, J = 17.5, 8.8 Hz, 1H_{region1}), 3.37 – 3.24 (m, 1H_{region1} + 1H_{region2}), 2.94 (d, J = 17.3 Hz, 1H_{region2}), 2.51 (s, 3H_{region1 or 2}), 2.37 (s, 3H_{region2 or 1}), 1.33 – 1.21 (m, 3H_{region1} + 3H_{region2}).

In a 5 mL round bottom flask charged with a magnetic stirring bar the mixture of regioisomers **21'** and **21''** (14.3 mg, 0.032 mmol) was dissolved in DMF (2 mL). Potassium carbonate (2 equiv.) and imidazole (1.5 equiv.) were sequentially added. The reaction was stirred at room temperature for 2 h. The organic phase was extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (100% EtOAc) to afford product **20** (8.1 mg, 86% yield)

¹H-NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H, H2), 7.44 (d, J = 15.7 Hz, 1H, acryl), 7.26 – 7.16 (m, 6H, Ar + NH), 7.04 (s, 1H, H4), 5.72 (d, J = 15.6 Hz, 1H, acryl), 4.22 – 4.11 (m, 2H, Et), 4.09 (d, J = 9.4 Hz, 1H, H6), 3.49 – 3.36 (m, 2H, Et), 1.27 (t, J = 7.1 Hz, 3H, Et).

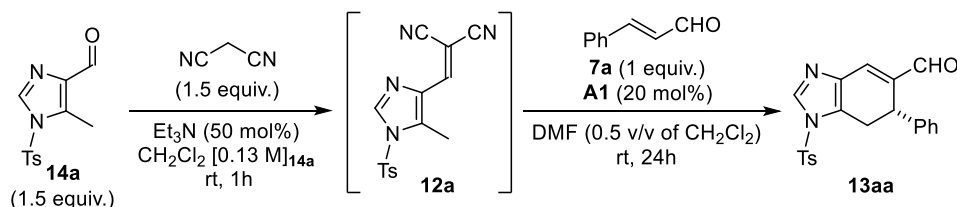
¹³C-NMR (100 MHz, CDCl₃) δ 167.5, 145.5, 142.0, 135.3, 132.7, 128.7, 128.5 (2C), 127.0, 127.0, 116.0, 60.3, 40.4, 30.7, 29.7, 14.3.

$[\alpha]_D^{20}$ +240.3 (c = 0.004 g/100 mL, MeOH).

ESI-MS 295.15 [M+H]⁺, 317.13 [M+Na]⁺.

3.5.6 Telescoped/one-pot reactions

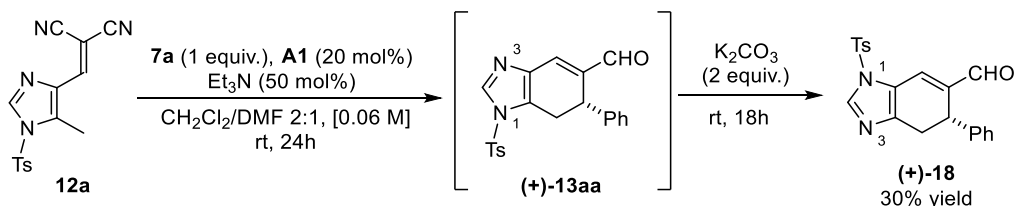
Synthesis of (*S*)-6-phenyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde [(+)-13aa]



In a 4mL vial equipped with a magnetic bar and kept under nitrogen atmosphere, imidazole-carbaldehyde **14a** (25.4 mg, 0.096 mmol, 1.5 equiv.) was dissolved in dichloromethane (730 μ L). Malononitrile (6.3 mg, 0.096 mmol) and triethylamine (4.46 μ L, 0.032 mmol, 0.5 equiv.) were added. After 1h, aminocatalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.), *trans*- β -cinnamaldehyde **7a** (8.06 μ L, 0.064 mmol, 1.0 equiv.) and DMF (370 μ L) were sequentially added. The resulting suspension was stirred at 25 °C and, after 24 hours, the resulting mixture was quenched with saturated aqueous

solution of NaHCO₃ and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **13aa** (15.0 mg, 62% yield) as a yellow solid. The enantiomeric excess of the product was determined to be >99% by HPLC analysis on a WELK-O1 column (eluent: Hexane/Ethanol = 75:25; flow rate 1 mL/min, λ = 220 nm. R_t 16.8 min (major), 32.3 min (minor) (99.9:0.1 er).

Synthesis of (S)-5-phenyl-1-tosyl-4,5-dihydro-1H-benzo[d]imidazole-6-carbaldehyde [(+)-18]



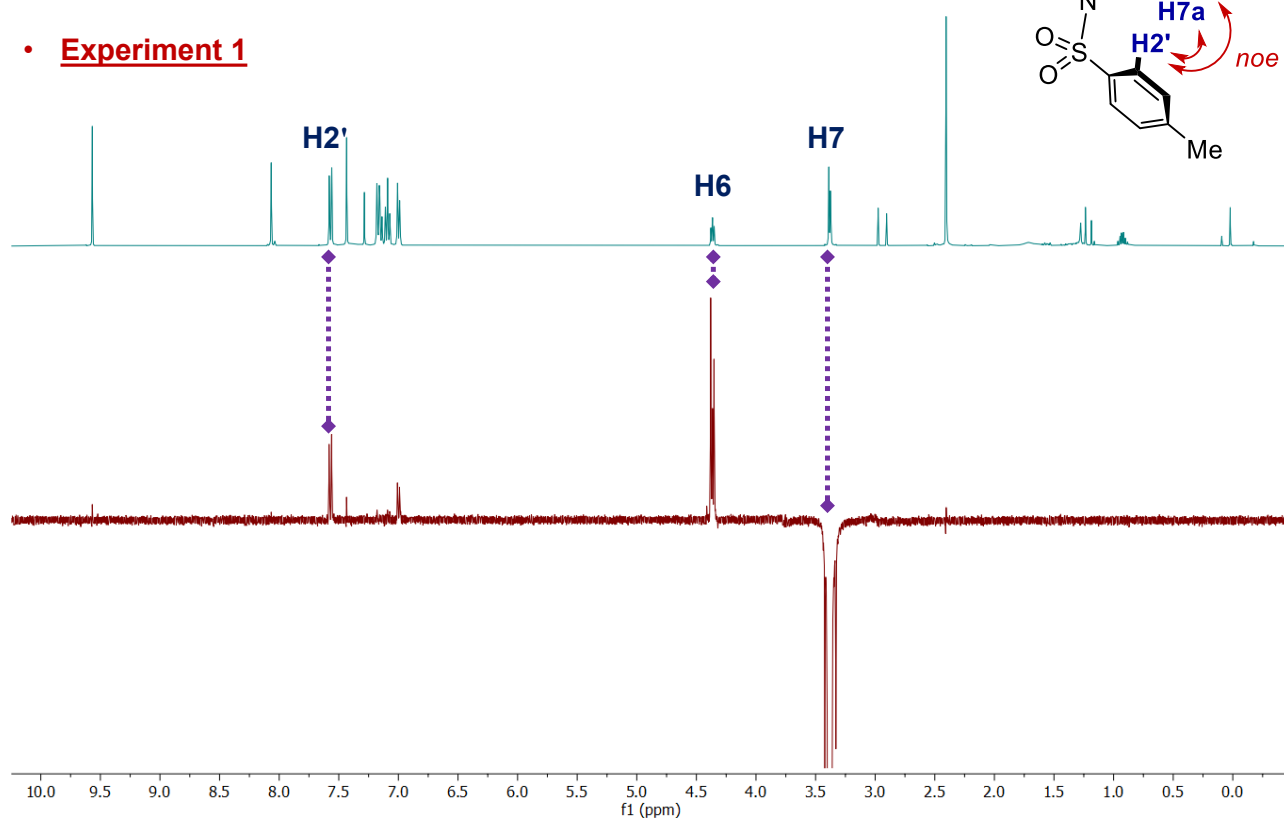
In a 4mL vial equipped with a magnetic bar and kept under nitrogen atmosphere, aminocatalyst **A1** (4.2 mg, 0.013 mmol, 0.2 equiv.) was dissolved in dichloromethane (730 μL) at 25 °C. Enal *trans*-β-cinnamaldehyde **7a** (8.06 μL, 0.064 mmol, 1.0 equiv.), alkyldiene malononitrile **12a** (30 mg, 0.096 mmol, 1.5 equiv.), DMF (370 μL) and triethylamine (Et₃N; 4.46 μL, 0.032 mmol, 0.5 equiv.) were sequentially added. The resulting suspension was stirred at 25 °C and, after 24 hours, 2 equiv. of K₂CO₃ were added. After further 18 hours, the reaction was quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The crude was purified by silica gel flash chromatography (petroleum ether/AcOEt 70:30) to afford **18** (9.2 mg, 38% yield) as a yellow solid. The enantiomeric excess of the product was determined to be >99% by HPLC analysis on a WELK-O1 column (eluent: Hexane/Ethanol = 75:25; flow rate 1 mL/min, λ = 220 nm. R_t 34.0 min (major), 19.6 min (minor) (99.6:0.4 er).

3.5.7 Determination of the regiochemistry for compounds **13aa** and **18**

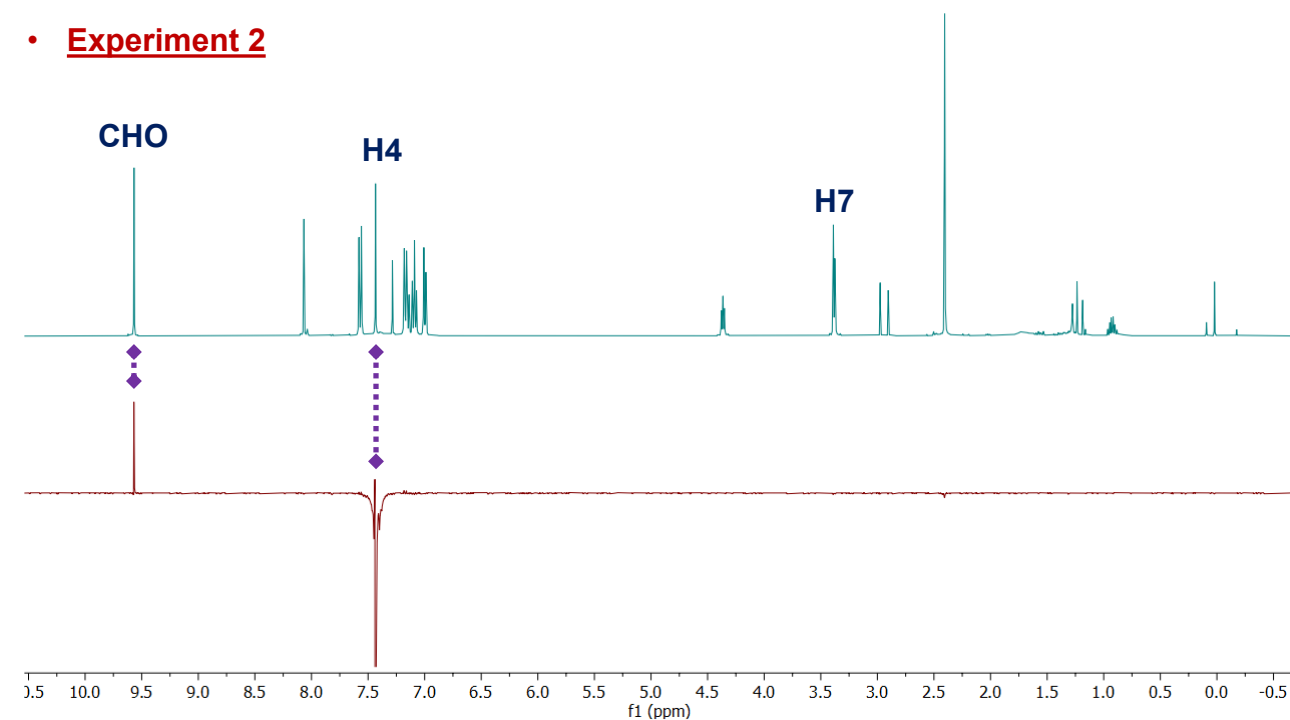
The regiochemistry of the two isomers **13aa** and **18** has been assigned through 1D-¹H NMR-selective NOESY experiments in CDCl₃ at 400 MHz. In particular, the presence of a correlation between both H7 protons and H2' (experiment 1) and the absence of correlation between H4 and H2' (experiment 2) ascertained that the tosyl group is bound to the N1 within **13aa**. On the other hand, the presence of correlation between H7 and H2' (experiment 3) and the absence of correlation between H2' and both H4a and H4b protons (experiments 4 and 5) ascertained that the tosyl group is bound to N1 (former N3) within compound **18**.

Analysis of compound **13aa**

- Experiment 1

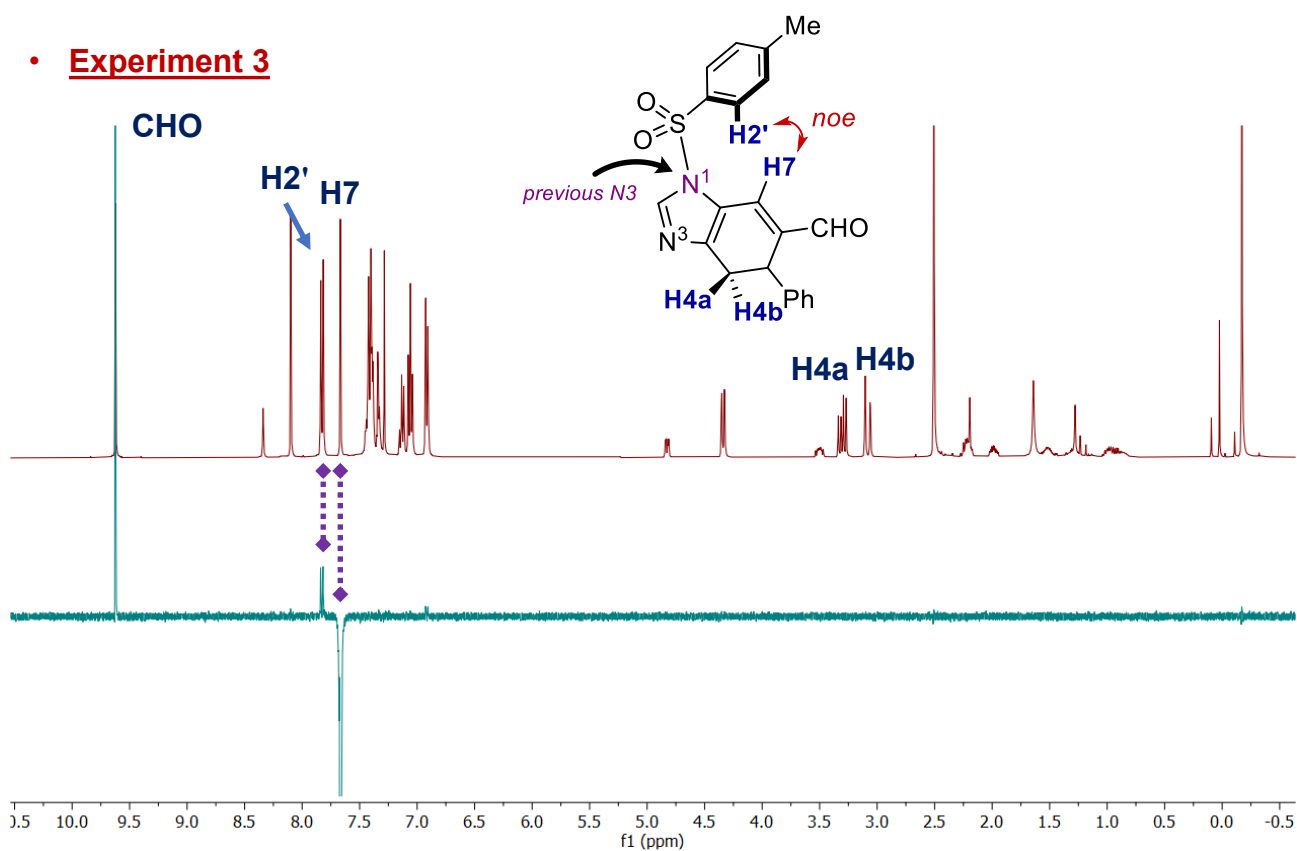


- **Experiment 2**

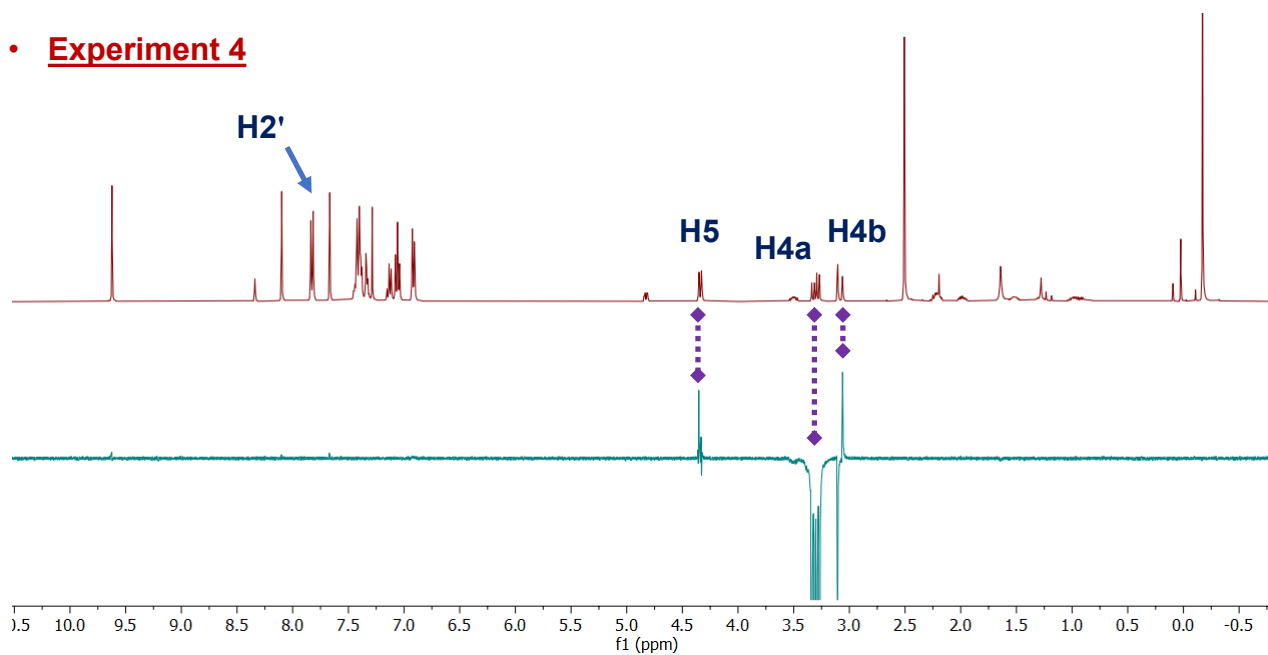


Analysis of compound 18

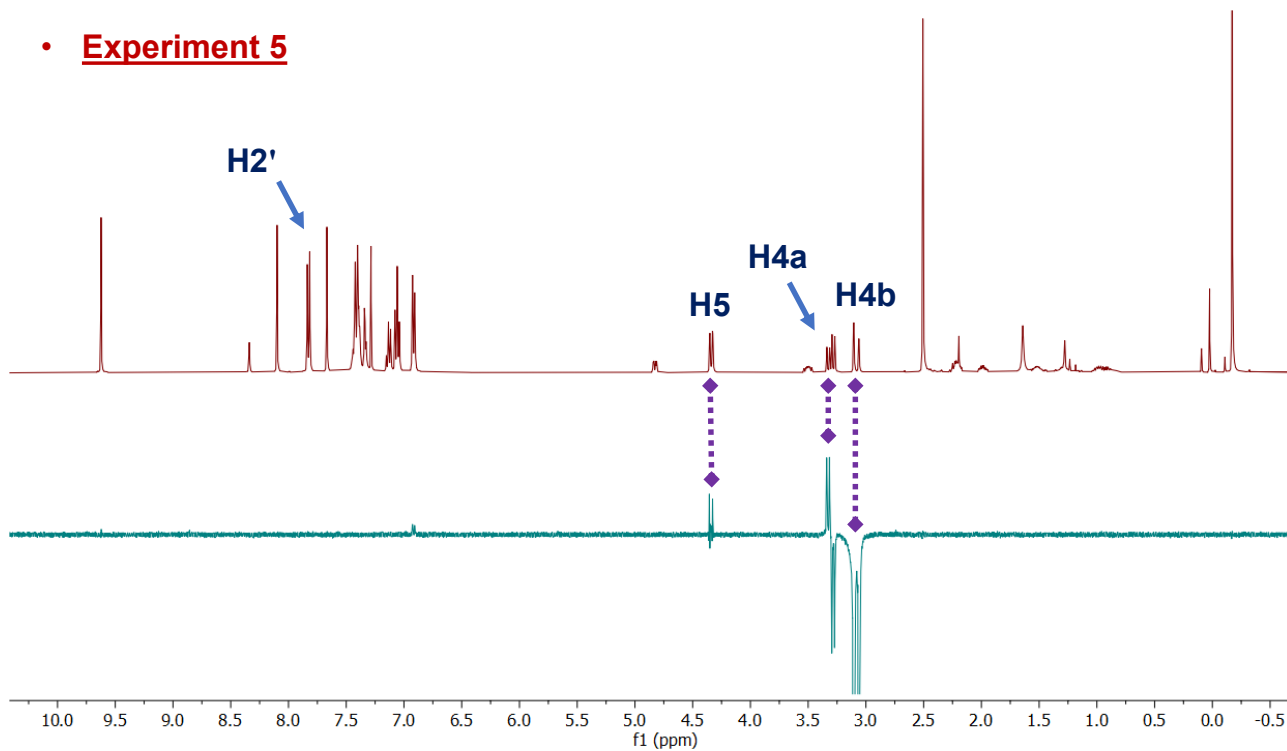
- **Experiment 3**



- **Experiment 4**



- **Experiment 5**



3.5.8 Determination of the absolute configuration of the products

Determination of the Absolute Configuration of Bicyclic Products 13

The absolute configuration of compounds (+)-**13aa** (obtained from aminocatalyst **A1**) and (-)-*ent*-**13cc** (obtained from aminocatalyst (*ent*)-**A1**) was certified as 6*S* and 6*R*, respectively, by single crystal X-ray analyses of suitable crystals. Hence, by analogy, the 6*S*-configuration of all other products **13** was established.

CRYSTAL DATA for (+)-13aa: C₂₁H₁₈N₃O₃S₁, monoclinic, *P*2₁, *a*=9.551(3)Å, *b*=20.152(7)Å, *c*= 9.745(3)Å, β= 99.049(10)°, *V*= 1852.4(10) Å³; *Z*=4; *d*_{calc}=1.357 mg/cm³, *F*(000)= 792, CuKα radiation (λ = 1.54178), μ=1.755, Tot. refl.= 76252, *hkl* range= -11<*h*<11, -25<*k*<25, -12<*l*<12; Theta range 4.59-77.20, unique reflections= 7431, number of parameters = 489, GooF= 1.043, *R*=0.032, *wR*₂=0.081, Flack parameter = 0.055(2)

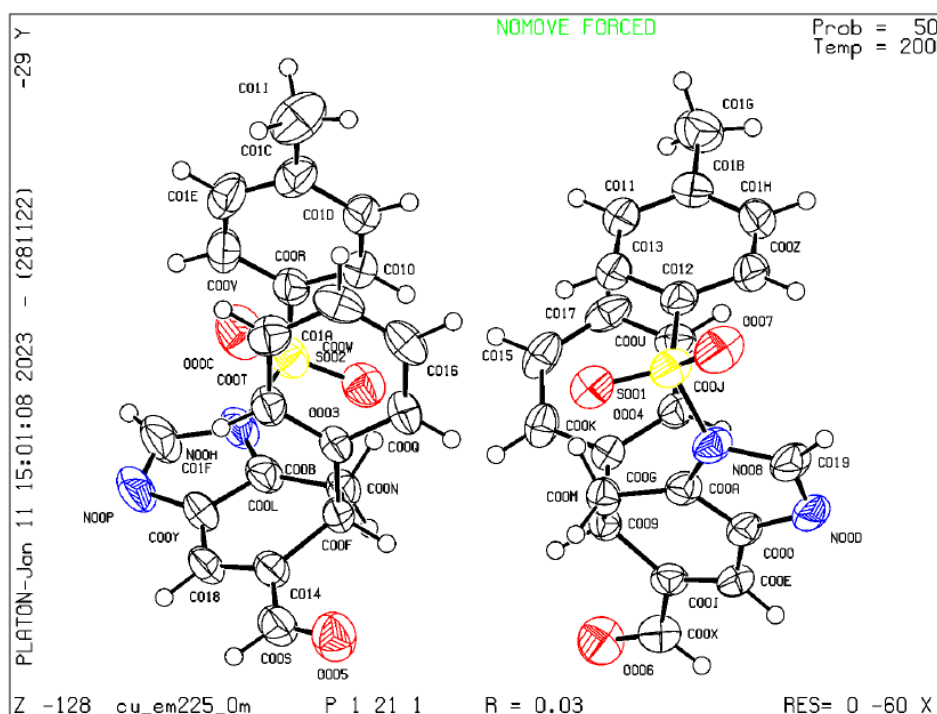


Figure 6 ORTEP representation of (+)-**13aa**

CRYSTAL DATA for (-)-13cc: C₁₉H₁₉Br₁N₂O₃, triclinic, *P*1, *a*= 5.8284(8)Å, *b*= 12.316(2)Å, *c*= 14.256(2)Å, α = 111.518(4)°, β= 95.808(6)°, γ = 101.189(4)° *V*=917.1(2) Å³; *Z*=2; *d*_{calc}=1.460 mg/cm³, *F*(000)= 412, MoKα radiation (λ = 0.71073), μ=2.261, Tot. refl.= 52131, *hkl* range= -7<*h*<7, -15<*k*<15, -17<*l*<17; Theta range 2.84-25.90, unique reflections= 6877, number of parameters = 457, GooF= 1.054, *R*=0.020, *wR*₂=0.049, Flack parameter = 0.065(2)

Chapter IV

Photochemical enantioselective radical γ -functionalization of enals by means of dienamine organocatalysis

The project discussed in this Chapter was conducted under the supervision of Prof. Paolo Melchiorre at Institut Català d'Investigació Química (ICIQ) in Tarragona (Spain), and in collaboration with Matteo Balletti, who performed the discovery of the reaction, its optimization, evaluation of part of the reaction scope and the synthetic elaborations of products. I was involved in part of the optimization of the reaction, and evaluation of part of the scope.

4.1 Background

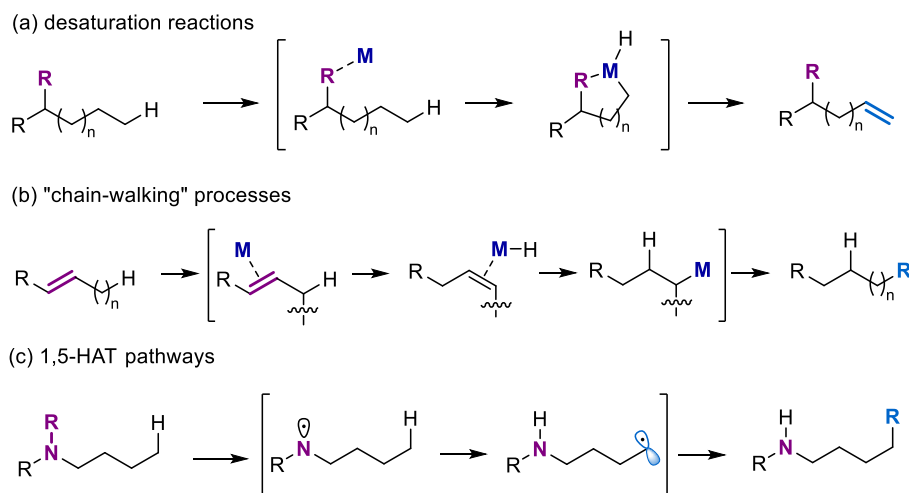
The activation of a C-H bond that is not adjacent to a leading functional group corresponds to the concept of remote functionalization.¹ The importance of this approach deals with the possibility to functionalize generally inactive positions, avoiding the direct manipulation of a specific functional group. For example, the use of transition metals can be exploited to promote desaturation reactions in a site remote with respect to a chelating moiety (Scheme 1, a).² Metal complexes resulted also suitable in cross-coupling transformations to make inert and remote C-H bonds reactive in acyclic and aliphatic simple frameworks through “chain-walking” reactions (Scheme 1, b).³ Finally, the renaissance of radical chemistry favoured the discovery of remote radical functionalization of aliphatic chains, using *N*-centered radicals as promoters of remote C-H activations through 1,5-HAT manifolds (Scheme 1, c).⁴ Remote functionalization processes have had an enormous effect in increasing the molecular complexity, being an actual tool for chemists to be used in retrosynthetic plans. Nevertheless, this approach is difficult to apply within asymmetric catalytic transformations, especially for saturated acyclic systems, whose intrinsic flexibility could hamper the ability of the catalyst to transmit stereocontrol at remote positions.

¹ a) Sommer, H.; Julia-Hernandez, F.; Martin, R.; Marek, I. “Walking metals for remote functionalization” *ACS Cent. Sci.*, **2018**, *4*, 153; b) Vasseur, A.; Bruffaerts, J.; Marek, I. “Remote functionalization through alkene isomerization” *Nat. Chem.*, **2016**, *8*, 209; c) Franzoni B.; Mazet, C. “Recent trends in Pd-catalyzed remote functionalization of carbonyl compounds” *Org. Biomol. Chem.* **2014**, *12*, 233.

² Shwartz, H. “Remote functionalization of C-H and C-C bonds by “naked” transition-metal ions (Cosi Fan Tutte)” *Acc. Chem. Res.* **1989**, *22*, 282.

³ Janssen-Müller, D.; Sahoo, B.; Sun, S.; Martin, R. “Tackling Remote *sp*³ C–H Functionalization via Ni-Catalyzed chain-walking Reactions” *Isr. J. Chem.* **2020**, *60*, 195.

⁴ Sarkar, S.; Shing Cheung, K. P.; Gevorgian, V. “C–H functionalization reactions enabled by hydrogen atom transfer to carbon-centered radicals” *Chem. Sci.* **2020**, *11*, 12974.



Scheme 1 Examples of general strategies for remote functionalizations

In this scenario, the principle of vinylogy as applied to conjugated π -system donors, merged with proper catalytic activation strategies, represents an effective method to accomplish this overwhelming issue.⁵ For instance, dienamine organocatalysis, which involves the activation of enals with a chiral amine catalyst, proved to be a suitable approach to unveil asymmetric and γ -selective functionalization of carbonyl substrates, while forging remote stereocenters.⁶ In particular, the vinylogous nucleophilic character of catalytic dienamine intermediates has been widely exploited for enantioselective cycloaddition reactions,⁷ aldol,⁸ Michael,⁹ S_N1 alkylation,¹⁰ and Tsuji-Trost allylation¹¹ processes (Scheme 2).

⁵ a) Fuson, R. C. "The Principle of Vinylogy" *Chem. Rev.* **1935**, *16*, 1; b) Curti, C.; Battistini, L.; Sartori, A.; Zanardi F. "New Developments of the Principle of Vinylogy as Applied to π -Extended Enolate-Type Donor Systems" *Chem. Rev.* **2020**, *120*, 2448;

⁶ Marcos, V.; Alemán J. "Old tricks, new dogs: organocatalytic dienamine activation of α,β -unsaturated aldehydes" *Chem. Soc. Rev.* **2016**, *45*, 6812.

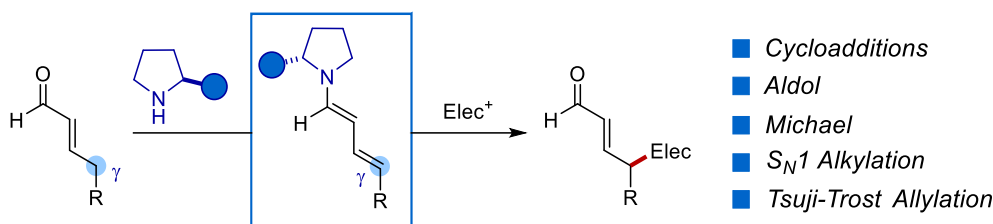
⁷ For a review see: a) Klier, L.; Tur, F.; Poulsen P. H.; Jørgensen, K. A. "Asymmetric cycloaddition reactions catalysed by diarylprolinol silyl ethers" *Chem. Soc. Rev.* **2017**, *46*, 1080, and references therein. For selected examples, see: b) Albrecht, L.; Dickmeiss, G.; Acosta, F. C.; Rodriguez-Esrich, C.; Davis, R. L.; Jørgensen, K. A. "Asymmetric Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis" *J. Am. Chem. Soc.* **2012**, *134*(5), 2543; c) Martín-Santos, C.; Jarava-Barrera, C.; del Pozo, S.; Parra, A.; Díaz-Tendero, S.; Mas-Ballester, S.; Cabrera, S.; Alemann, J. "Highly Enantioselective Construction of Tricyclic Derivatives by the Desymmetrization of Cyclohexadienones" *Angew. Chem. Int. Ed.* **2014**, *53*, 8184.

⁸ a) Liu, K.; Chougnat, A.; Woggon, W. D. "A Short Route to α -Tocopherol" *Angew. Chem. Int. Ed.* **2008**, *47*, 5827; b) Cassani, C.; Melchiorre, P. "Direct Catalytic Enantioselective Vinylogous Aldol Reaction of α -Branched Enals with Isatins" *Org. Lett.*, **2012**, *14*, 5590.

⁹ a) Donslud, B. S.; Halskov, K. S.; Leth, L. A.; Paz, B. M.; Jørgensen, K. A. "Organocatalytic asymmetric strategies to carbocyclic structures by γ -alkylation-annulation sequences" *Chem. Comm.* **2014**, *50*, 13676; b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. "Cooperative dienamine/hydrogen-bonding catalysis: enantioselective formal [2+2] cycloaddition of enals with nitroalkenes" *Angew. Chem., Int. Ed.* **2012**, *51*, 4104.

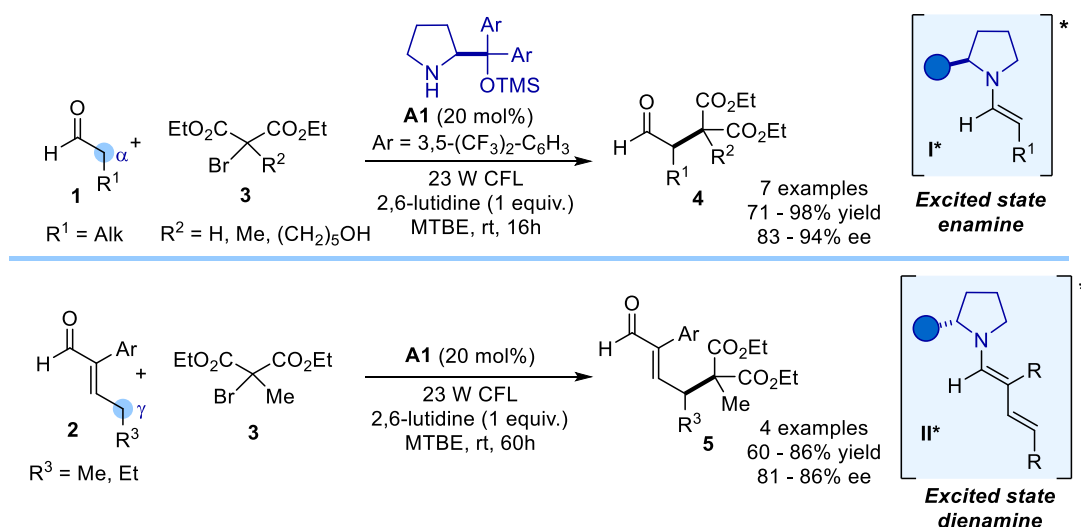
¹⁰ a) Stiller, L.; Marques-Lopez, E.; Herrera, R.; Frohlich, R.; Strohmman, C; Christmann, M. "Enantioselective α - and γ -Alkylation of α,β -Unsaturated Aldehydes Using Dienamine Activation" *Org. Lett.*, **2011**, *13*, 70; b) Bergonzini, G.; Vera, S.; Melchiorre, P. "Cooperative Organocatalysis for the Asymmetric γ Alkylation of α -Branched Enals" *Angew. Chem., Int. Ed.*, **2010**, *49*, 9685.

¹¹ Næsborg, L.; Halskov, K. S.; Tur, F.; Mønsted S.; Jørgensen, K. A. Asymmetric γ -Allylation of α,β - Unsaturated Aldehydes by Combined Organocatalysis and Transition-Metal Catalysis. *Angew. Chem., Int. Ed.*, **2015**, *54*, 10193.



Scheme 2 Dienamine-based catalysis in the polar domain

All the aforementioned examples involve traditional two-electron ionic pathways. On the other hand, the use of dienamine catalysis within the photochemical radical domain is still immature. This lack is quite surprising, since the peculiar capability of enamine parents to behave as radical trap for the radical α -functionalization of carbonyl compounds has already been established in several reports.¹² One sole example of radical enantioselective γ -functionalization by means of catalytic dienamine intermediates was reported by Melchiorre and co-workers in 2015 within the development of enantioselective and organocatalytic alkylation reactions of aldehydes and enals driven by the direct photoexcitation of enamines (Scheme 3; see also introduction of this thesis, Scheme 8).¹³ In particular, the authors unveiled, for the first time, the properties of excited enamines **I** and dienamines **II**, deriving from the condensation of catalyst **A1** on aldehydes **1** or enals **2**, to act as strong reductants for the generation of malonyl radicals upon single electron transfer (SET) with radical precursors of type **3**. A series of α - and γ -functionalized carbonyl products **4** and **5** were achieved in good yields and enantioselectivities.

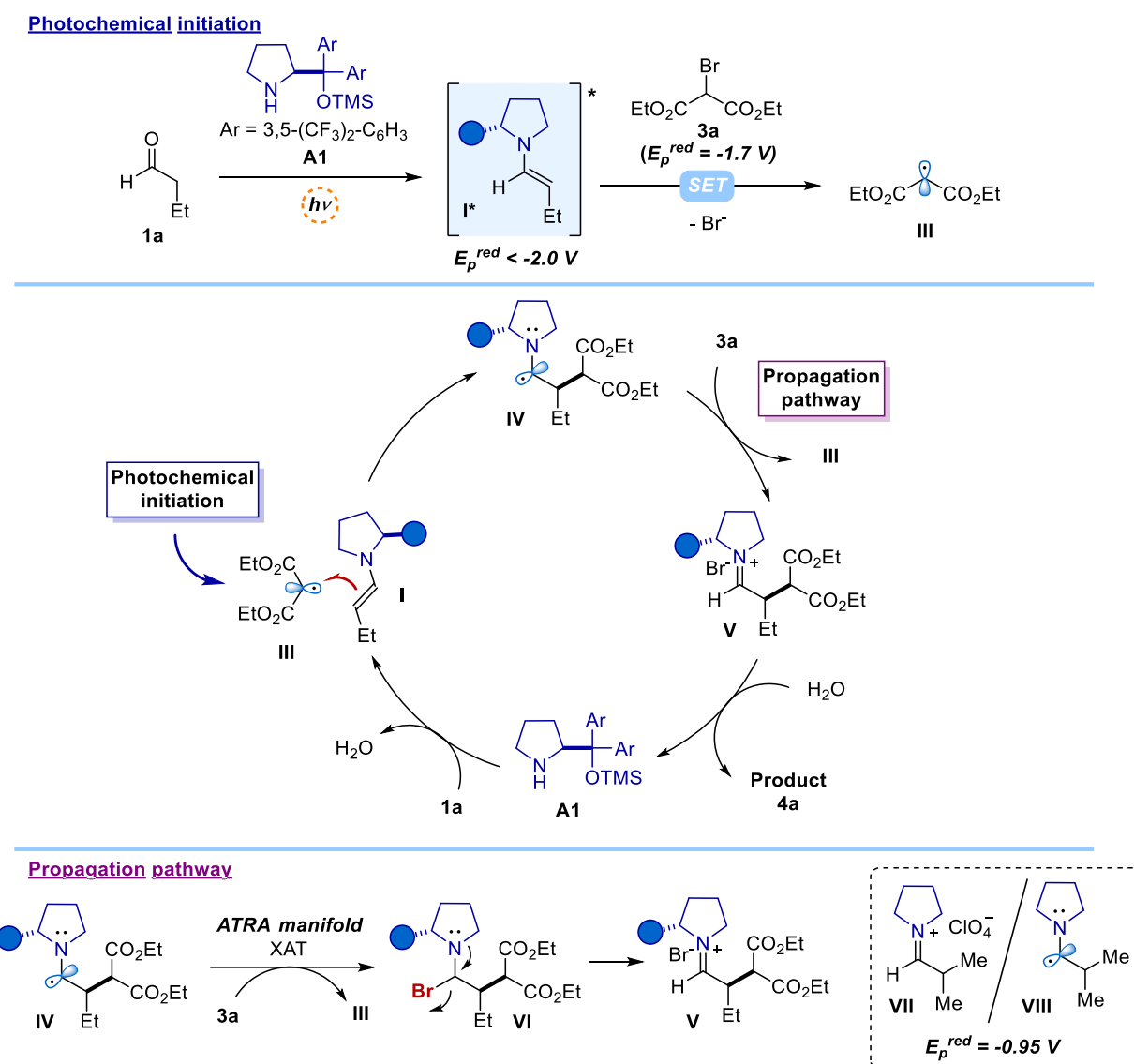


Scheme 3 Enantioselective organocatalytic alkylation of aldehydes and enals driven by the direct photoexcitation of enamines developed by Melchiorre and co-workers

¹² a) Nicewicz, D. A.; MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: the Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**, 322, 77; b) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. "Photochemical Activity of a Key Donor–Acceptor Complex Can Drive Stereoselective Catalytic α -alkylation of Aldehydes." *Nature Chem.* **2013**, 5, 750; c) Silvi, M.; Melchiorre, P. "Enhancing the potential of enantioselective organocatalysis with light" *Nature* **2018**, 554, 41.

¹³ Silvi, M.; Arceo, A.; Jurberg, I. D.; Cassani, C.; Melchiorre, P. "Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines" *J. Am. Chem. Soc.* **2015**, 137, 6120.

The subsequent year, the same group published a detailed experimental study on the model reaction between aldehyde **1a** and diethyl bromomalonate **3a** to determine the mechanism of the process (Scheme 4).¹⁴



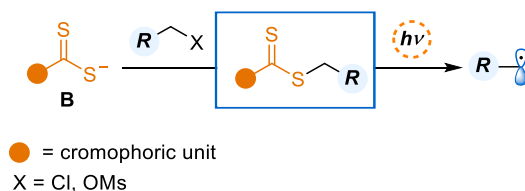
Scheme 4 Full mechanism of the alkylation of enamines by means of direct excitation radical generation strategy

The most salient observations were: (i) the radical generation was actually given by direct photoexcitation of enamines through SET (estimated $E_p^{\text{red}}(\text{I}^+/\text{I}^*) < -2.0 \text{ V}$ versus Ag/AgCl, NaCl_{sat.} vs $E_p^{\text{red}}(\text{3a}/\text{3a}^\cdot) = -1.7 \text{ V}$ versus Ag/AgCl, NaCl_{sat.}) over possible EDA-complex radical generation strategies (no bathochromic shift was observed by mixing enamine and radical precursor via UV-Vis absorption analysis), and (ii) the process involved a radical chain propagation instead of a radical-radical coupling between **III** and **IV** (measured quantum yield Φ equal to 20). Importantly, the nature of the radical propagation pathway was found to involve an atom transfer radical addition (ATRA) manifold, specifically an halogen atom transfer (XAT), over a SET process between **III** and **V** since the reduction potential of **VII**, that should mimic **V**, did not match the one of the radical precursor

¹⁴ Bahamonde, A.; Melchiorre, P. "Mechanism of the Stereoselective α -Alkylation of Aldehydes Driven by the Photochemical Activity of Enamines" *J. Am. Chem. Soc.* **2016**, *138*, 8019.

III ($E_p^{\text{red}}(\text{VII/VIII}) = -0.9 \text{ V}$ versus Ag/AgCl, NaCl_{sat.} vs $E_p^{\text{red}}(\text{3a/3a}^{\cdot-}) = -1.7 \text{ V}$ versus Ag/AgCl, NaCl_{sat.}).

However, in the case of dienamines, this methodology was limited to the use of tertiary bromomalonates **3** as radical precursors, just due to the strict dependence of the radical generation mechanism to the redox properties of the substrates. In this scenario, the exploitation of a catalytic radical generation strategy that does not rely on the redox properties of the substrates could enlarge the applicability of the aforementioned protocol for other remote radical functionalizations by means of organocatalytic dienamine intermediates. As mentioned in the introduction (Chapter 1.3), in 2019, Melchiorre and co-workers launched a general catalytic strategy for generating radical species which exploited the ability of a nucleophilic dithiocarbonyl anion (DTC) organocatalyst **B** to undergo S_N2-based activation of substrates (including alkyl chlorides and mesylates), which would be inert to classical radical-generating approaches.¹⁵ The resulting catalytic intermediates can instead promote homolytic cleavage of the weak C–S bond to furnish the target radical upon blue light irradiation (Scheme 5). Recently, this method has been successfully applied to Giese-type reactions, acylation reactions,¹⁶ alkylations of silyl enol ethers,¹⁷ borylation processes¹⁸ and three-component reactions.¹⁹



Scheme 5 The principle of DTC catalysis as general radical generation strategy

¹⁵ Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. "Photochemical generation of radicals from alkyl electrophiles using a nucleophilic organic catalyst" *Nat. Chem.* **2019**, *11*, 129.

¹⁶ de Pedro Beato, E.; Mazzarella, D.; Balletti, M.; Melchiorre, P. "Photochemical Generation of Acyl and Carbamoyl Radicals Using a Nucleophilic Organic Catalyst: Applications and Mechanism Thereof" *Chem. Sci.* **2020**, *11*, 6312.

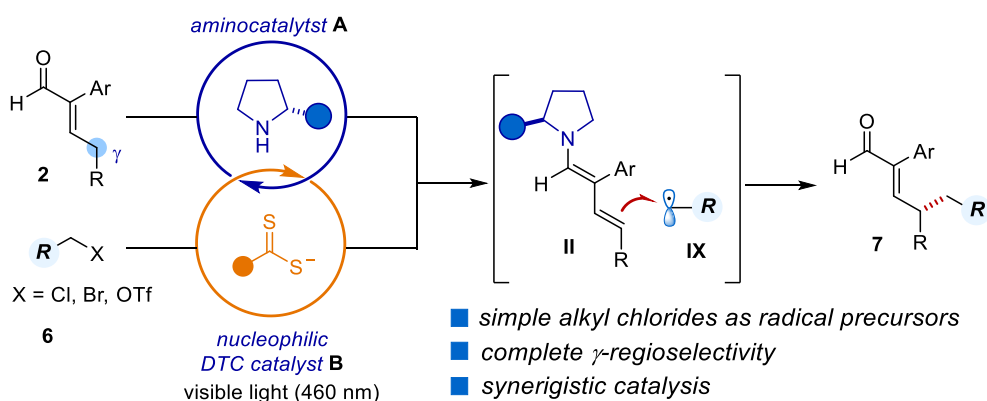
¹⁷ Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Oseka, M.; Melchiorre, P. "A Photochemical Organocatalytic Strategy for the α -Alkylation of Ketones by Using Radicals" *Angew. Chem. Int. Ed.* **2020**, *59*, 9485.

¹⁸ Mazzarella, D.; Magagnano, G.; Schweitzer-Chaput, B.; Melchiorre, P. "Photochemical Organocatalytic Borylation of Alkyl Chlorides, Bromides, and Sulfonates" *ACS Catal.* **2019**, *9*, 5876.

¹⁹ Cuadros, S.; Horwitz, M. A.; Schweitzer-Chaput, B.; Melchiorre, P. "A visible-light mediated three component radical process using dithiocarbamate anion catalysis" *Chem. Sci.* **2019**, *10*, 5484.

4.2 Target of the project

The aim of this project was devoted to complement the previous study regarding the possibility to employ organocatalytic dienamines as radical traps, specifically by increasing its synthetic applicability. We envisioned that the synergistic action of dienamine catalysis with DTC catalysis as general and reliable generating radical activations could be successful for promoting enantioselective radical γ -alkylations of α -branched enals **2** to achieve a wide array of diverse remotely functionalized and enantioenriched α,β -unsaturated aldehydes of type **7**. More in details, the nucleophilic DTC catalyst **B** would furnish target radicals **IX** upon S_N2 reactions with simple alkyl chlorides **6** and blue light irradiation, while the aminocatalyst **A** would condense on the starting α -branched enals **2**, thus affording dienamines **II**. The nucleophilic vinylogous character of this latter would, finally, promote the radical trapping step, consigning a series of enantioenriched γ -alkyl enals **7** (Scheme 6).



Scheme 6 Aim of this project: development of a synergistically organocatalysed enantioselective radical alkylation of α -branched enals

4.3 Results and discussion

4.3.1 Proof of concept and reaction optimization

The feasibility of the reaction was demonstrated by running the reaction between 2-phenylpentenal **2a** and chloroacetonitrile **6a** in the presence of 20 mol% Jørgensen-Hayashi aminocatalyst **A1**, 20 mol% 5-bromoindole DTC catalyst **B1**, 2,6-lutidine as a base, and toluene as solvent. Pleasingly, after 24 hours under blue LED irradiation ($\lambda_{\text{max}} = 465$ nm), the desired γ -functionalized product **7aa** was obtained in 40% yield and 77:23 er (entry 1, Table 1). Of note, no traces of α -alkylated product were detected. Control experiments (entries 2-4) showed that the simultaneous presence of catalysts **A1** and **B1**, as well as light were fundamental to activate both substrates and achieve the desired product, confirming the synergistic action of the two catalysts. With these observations in mind, we started the screening of several parameters, to optimize both efficiency and stereoselection of the transformation.

Table 1 Proof of concept and control experiments

2a (3 equiv.) + **6a** (0.2 mmol) $\xrightarrow[\text{2,6-lutidine (1.2 equiv.)}]{\text{A1 (20 mol\%), B1 (20 mol\%)}}$ **7aa**
blue LEDs, toluene [0.3 M]
25 °C, 24h

catalysts

A1
Ar = 3,5-C₆H₃(CF₃)₂

B1

Entry ^[a]	Deviations	NMRy [%] ^[b]	er ^[c]
1	-	40	77:23
2	No aminocatalyst A1	nr	-
3	No DTC catalyst B1	nr	-
4	No light	nr	-

^[a]The reactions were performed under argon atmosphere using **2a** (0.6 mmol), **6a** (0.2 mmol), catalysts **A1** and **B1** (20 mol% each) and 2,6-lutidine (1.2 equiv.) in toluene [0.03 M] under blue LEDs irradiation at rt for 24h. ^[b]Determined by ¹H-NMR analysis on the crude of the reaction using trichloroethylene as internal standard. ^[c]Determined by UPC² analysis. nr = no reaction

The role of the solvent was first evaluated, and the results are shown in Table 2. While the enantioselectivity of the process resulted largely independent from the nature of the reaction medium, ethereal solvents, such as THF and CPME, afforded the best results in terms of efficiency (70% yields, entries 4 and 5). On the other hand, polar solvents, such as MeCN and DMF, were not suitable for the reaction to take place (entries 2 and 3), while halogenated solvents, such as DCM and TFT, gave slightly inferior results (entries 6 and 7). Interestingly, the presence of a catalytic amounts of benzoic acid, that generally accelerates the aminocatalyst condensation step,²⁰ in this case was deleterious (entry 8). Given these results, we elected THF as the best solvent to be employed in further screenings.

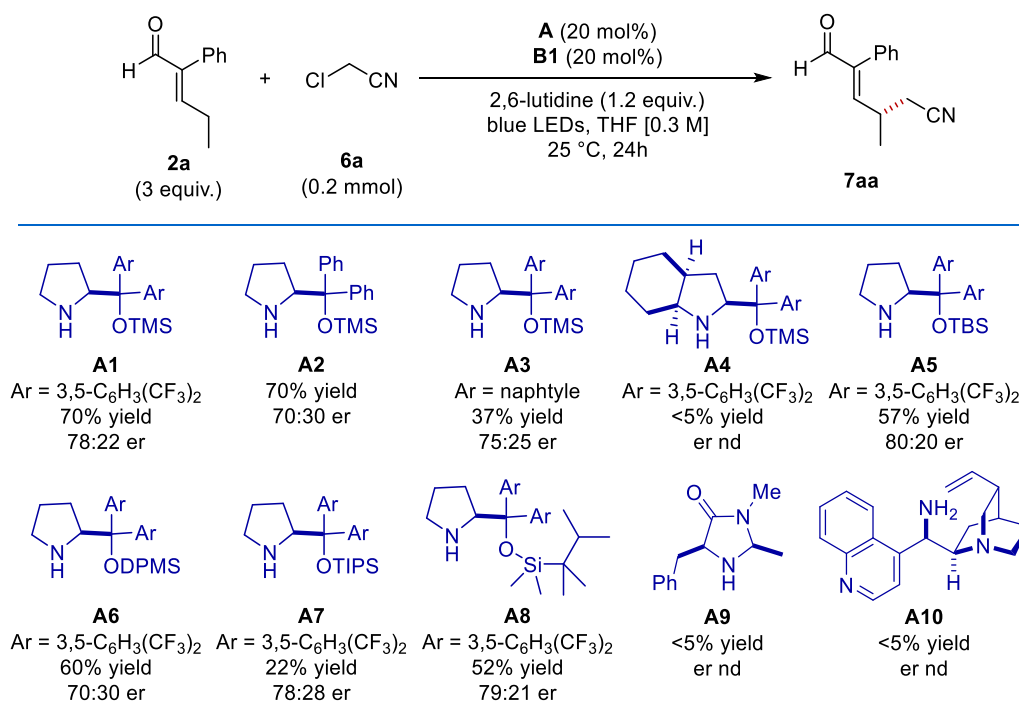
²⁰ Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. "Additive effects on Asymmetric Catalysis" *Chem. Rev.* **2016**, *116*, 4006.

Table 2 Screening of the solvent

Entry ^[a]	Solvent	NMRy [%] ^[b]	er ^[c]
1	Tol	40	77:23
2	MeCN	18	79:21
3	DMF	<5	nd
4	THF	70	77:23
5	CPME	69	77:23
6	CHCl ₃	66	78:22
7	TFT	42	78:22
8 ^[d]	Tol	13	77:23

^[a]The reactions were performed under argon atmosphere using **2a** (0.6 mmol), **6a** (0.2 mmol), catalysts **A1** and **B1** (20 mol% each) and 2,6-lutidine (1.2 equiv.) in the indicated solvent [0.3 M] under blue LEDs irradiation at rt for 24 h. ^[b]Determined by ¹H-NMR analysis on the crude of the reaction using trichloroethylene as internal standard. ^[c]Determined by UPC² analysis. ^[d]Reaction performed in the presence of 0.3 equiv. benzoic acid. CPME = cyclopentyl methyl ether; TFT = trifluorotoluene. nd = not determined

Eager to improve the stereoselectivity of the transformation, we performed the screening of prolinol-derived aminocatalysts **A** (Scheme 7). Using the less sterically demanding diphenylprolinol silyl ether **A2**, product **7aa** was obtained with the same efficiency but at the expense of enantiomeric ratio (er 70:30). Coherently, the bulkier naphthyl moiety in catalyst **A3** resulted in improved er (75:22), even though in a lower 37% yield. Bicyclic aminocatalyst **A4** did not show any reactivity, probably due to the increased difficulty for this bulky catalyst in condensing with the starting α -branched enal **2a**. Also, MacMillan-type catalyst **A9** and primary amine **A10** also did not afford any product.



Scheme 7 Survey of aminocatalysts **A**; yields refer to NMR yields

Once we realized that the trifluoromethyl-substituted prolinol scaffold was crucial in obtaining a promising result in terms of stereoselection and efficiency, we explored the effect of the silylether protecting group. Among aminocatalysts **A1**, **A5-A8**, the best result in terms of enantioselectivity was achieved by using *tert*-butyldimethylsilyl protected prolinol **A5**, which provided the desired product in a good 80:20 er, despite a lowered yield (57%). Anyway, we selected this latter as the best candidate to be employed in the further screening to further improve the reaction efficiency. We performed a third round of optimization, testing the impact of parameters such as nature of DTC catalyst, temperature, catalytic loadings and reaction concentration (Table 3).

Table 3 Screening of others reaction parameters

$\text{2a (3 equiv.)} + \text{6a (0.2 mmol)} \xrightarrow[\text{2,6-lutidine (1.2 equiv.), blue LEDs, THF [0.3 M], 25 °C, 24h}]{\text{A5 (20 mol\%), B1 (20 mol\%)}} \text{7aa}$

A5
Ar = C₆H₃(CF₃)₂

B1

B2

B3

Entry ^[a]	Deviations	NMRy [%] ^[b]	er ^[c]
1	-	57	80:20
2	20 mol% of B2	<5	nd
3	20 mol% of B3	<5	nd
4	10 mol% of A5	22	80:20
5	40 mol% of A5	59	80:20
6	30 mol% of B1	67	80:20
7	T = 10 °C	<5	nd
8	T = 60 °C	58	50:50
9	60 h rxn	62	68:32
10	THF [0.7 M]	75(70)	80:20

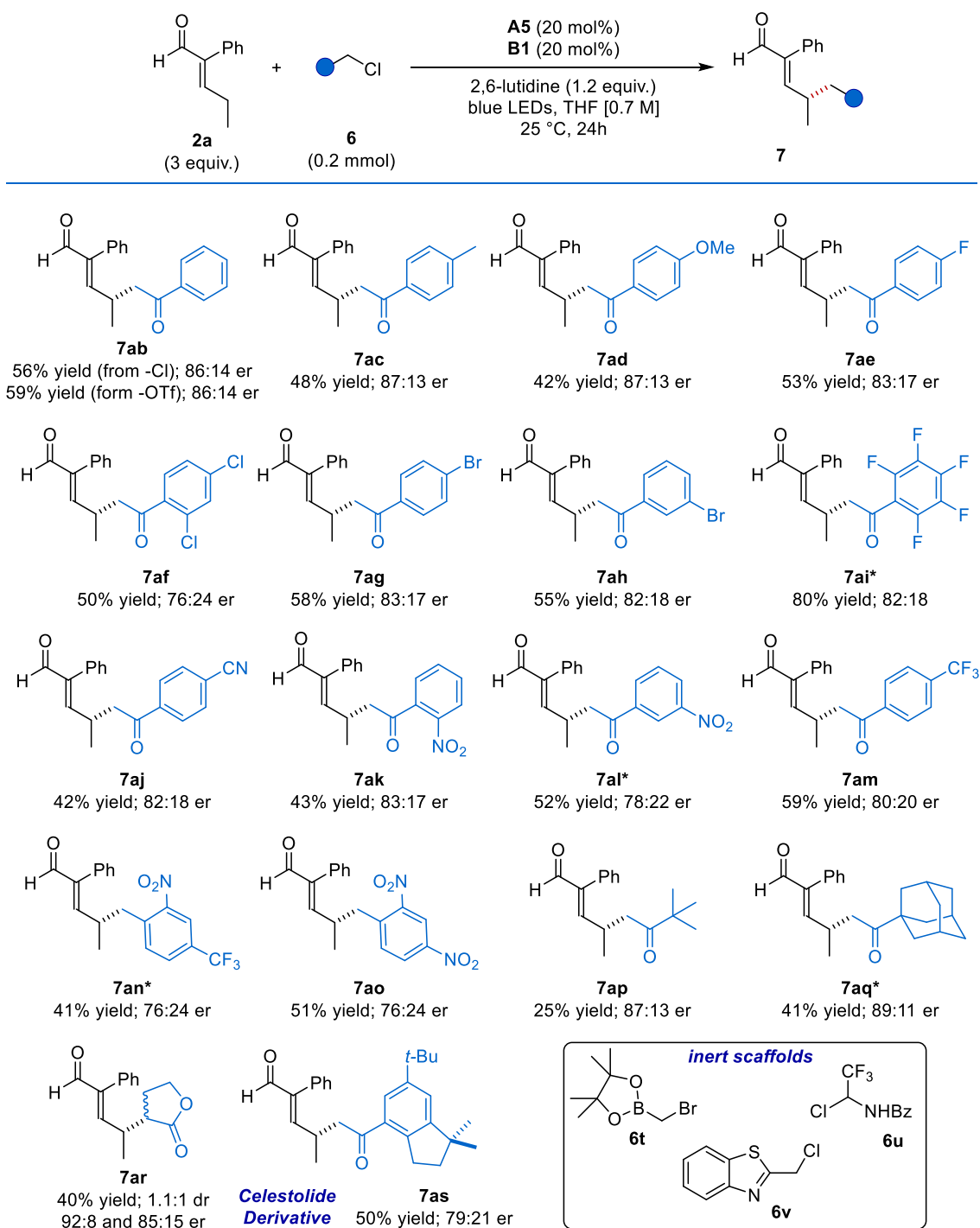
^[a]The reactions were performed under argon atmosphere using **2a** (0.6 mmol), **6a** (0.2 mmol), catalysts **A** and **B** (20 mol% each) and 2,6-lutidine (1.2 equiv.) in THF [0.3 M] under blue LEDs irradiation at rt for 24 h. ^[b]Determined by ¹H-NMR analysis on the crude of the reaction using trichloroethylene as internal standard. ^[c]Determined by UPC² analysis. nd = not determined

First, a screening of the DTC catalyst was performed but, unfortunately, neither commercially available ethyl xanthate **B2**, nor pyrazole-based **B3** were able to provide the desired product (entries 2 and 3), probably due to the low absorption of the corresponding intermediates in the blue light region. Regarding the aminocatalytic loading, despite the use of 10 mol% **A5** resulted in low conversion (entry 4), even increasing its amount to 40 mol% gave inferior results if compared to the starting 20 mol% (entry 5 vs entry 1). An increased 67% NMR yield was obtained by increasing the catalytic loading of DTC **B1** to 30 mol% (entry 6). Thus, we moved to the evaluation of the effect of the temperature. When the reaction was carried out cooling the temperature to 10 °C (entry 7), just traces of desired product **7aa** were obtained, while the reactivity was restored when the temperature was increased at 60 °C, despite the product was afforded as a racemic mixture (entry 8). Moreover, in entry 9 we decided to lengthen the reaction time and we observed that, after 60 h, the product was obtained in a low 68:32 er, probably due to a racemization process driven by either the basic conditions of the mixture or the condensation of the aminocatalyst on product **7aa**. Finally, entry 10

demonstrates that concentration played a crucial role in controlling the efficiency of the process. Indeed, optimized reaction conditions were finally found by running the reaction in a 0.7 M mixture for 24 h, providing the desired product **7aa** in a good 70% isolated yield and good enantioselectivity (80:20 er).

4.3.2 Scope of the reaction and synthetic elaborations

We first performed an exploratory survey of alkyl chloride radical precursors **6** with various structural and electronic properties in reactions with enal **2a** (Scheme 8).

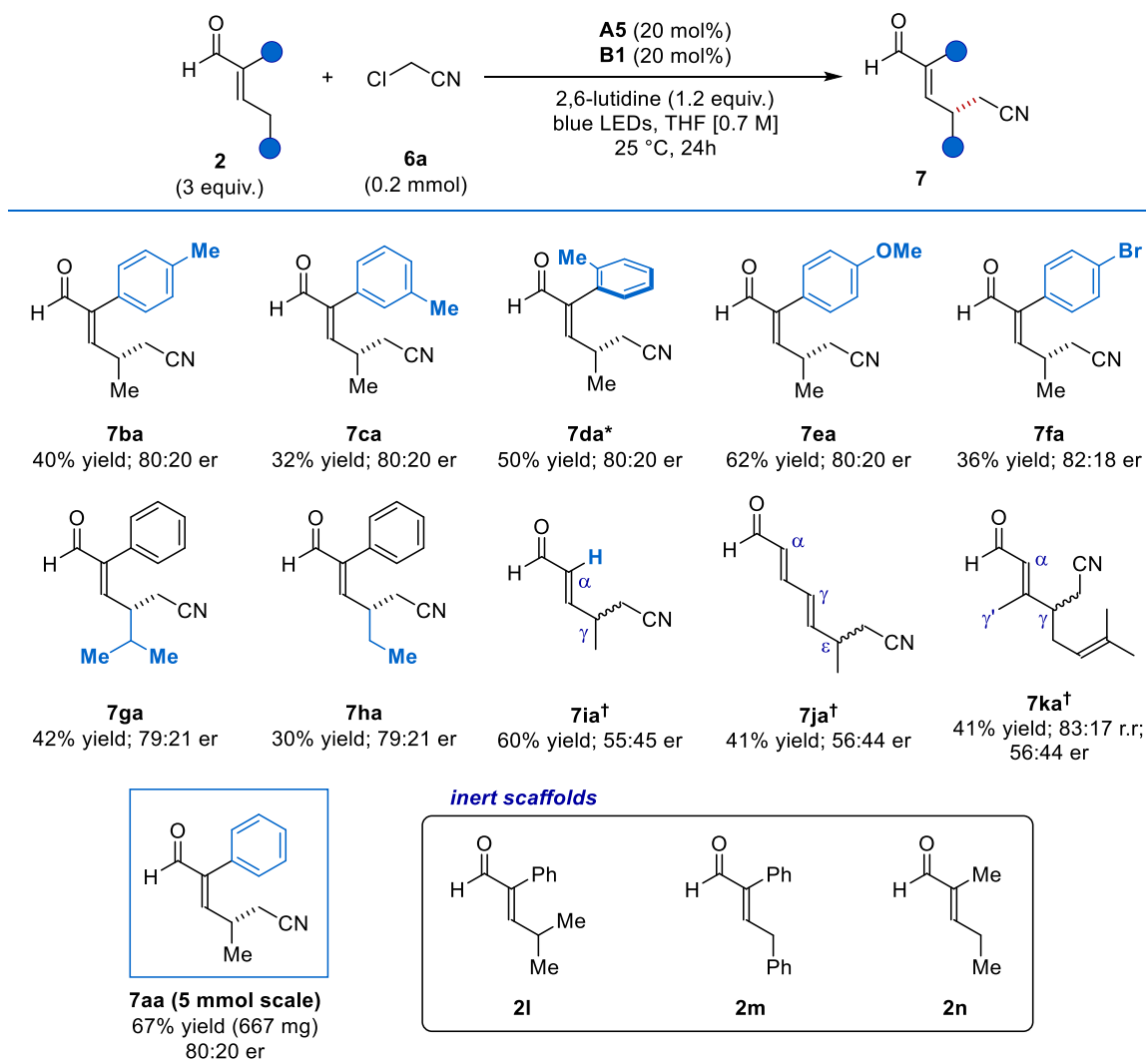


Scheme 8 Survey of radical precursors **6** that can react with enal **1a**. *Using the corresponding bromide as radical precursor. Yields refer to isolated yields

Pleasingly, we found that the methodology could be successfully applied to a wide array of primary alkyl chlorides. In particular, a broad range of variously substituted phenacyl chlorides **6b-6m** were well-tolerated in generating the corresponding products **7ab-7am** with moderate to good yields (42-80% yields), and with generally improved enantiomeric ratios with respect to the one obtained for the model reaction (76:24-87:13 er). Interestingly, we demonstrated that even phenacyl triflates could be operative in the transformation, due to the S_N2 pathway through which the catalyst **B1** operates. As proof of this concept, we demonstrated the possibility to provide product **7ab** in a 59% isolated yield and 83:17 er starting from the corresponding triflate-radical precursor. Both electron-withdrawing (products **7aj**, **7ak**) and electron-rich (products **7ac**, **7ad**) substituents on the aromatic ring of the phenacyl scaffold proved to be viable for the transformation. Regarding the steric component, the reaction was almost unaffected by bromine or chlorine substituents in *ortho*-, *meta*-, and *para*-sites of the aryl moiety (products **7af-7ah**). We also demonstrated that rings containing fluorinated atoms could also be installed at the γ -site of the corresponding enals (**7ae**, **7al**, **7am**). Importantly, aliphatic α -halogen ketones (**6ap**, **6aq**) and secondary α -bromo ester (**6ar**) resulted suitable radical precursors, providing the corresponding products (**7ap-7ar**) with high enantioselectivity, albeit in moderate yields. Deactivated benzyl halides **6an** and **6ao** managed to furnish the corresponding radical precursors, that were then trapped by dienamine **2a** at the remote γ position to generate products **7an** and **7ao**, respectively. Finally, the usefulness of the protocol was demonstrated installing the biorelevant *celestolide* scaffold within product **7as**. Unfortunately, boronated, aminated and heterocyclic radical precursors **6t**, **6u** and **6v** resulted unreactive substrates.

We next switched to the radical trap component, taking into consideration different α -branched enals **2** which could participate in the transformation with chloroacetonitrile **6a**, as described in Scheme 9. Electron-neutral (**7ba-7da**), electron-rich (**7ea**) and electron-poor substituents in various positions of the α -aryl ring were well tolerated, despite they resulted in somewhat reduced reactivity (32-62% yields). Similarly, differently β -aliphatic substituted enals (**2g**, **2h**) proved suitable in furnishing the corresponding products **7ga** and **7ha** in comparable enantioselectivity. More hindered β -isopropyl and β -benzyl enals **2l** and **2m** did not show any reactivity.

The crucial importance of the aromatic α -substituent both in terms of efficiency and stereocontrol was also demonstrated. An aliphatic group, such as using 2-methylpentenal **2n**, completely inhibited the reaction, while the lack of substituents (e.g. in pentenal **2i**) resulted in a still complete γ -regioselectivity, furnishing product **7ia** exclusively, though with almost no stereocontrol. This latter result is somehow surprisingly, since it is in contrast to traditional polar dienamine-based reactivity of non-branched enals, that generally provides mixtures of α - and γ -functionalized products.^{10a} To further investigate this issue, we carried out the reaction with hepta-2,4-dienal **2j**, that in principle may react at both the α - and γ -positions upon trienamine generation. Pleasingly, only the ε -functionalized product **7ja** was obtained, albeit in a racemic format. The lack of enantioinduction for the generation of **7ia** and **7ja** underlined the importance of the α -substituent, that likely plays a role in enforcing a preferred conformation of the vinylogous enamine intermediates (*vide infra*). In addition, β -disubstituted citral **2k** still reacted with complete γ -regioselectivity, triggering the preferential generation of the more substituted regioisomer **7ka**. To showcase the practicality of the transformation, we finally performed the model reaction between **2a** and **6a** on a 5 mmol scale; pleasingly, these conditions did not impact the outcome of the process, and 0.7 g product **7aa** were obtained with comparable efficiency and enantioselectivity (67% yield, 80:20 er, complete γ -site selectivity).



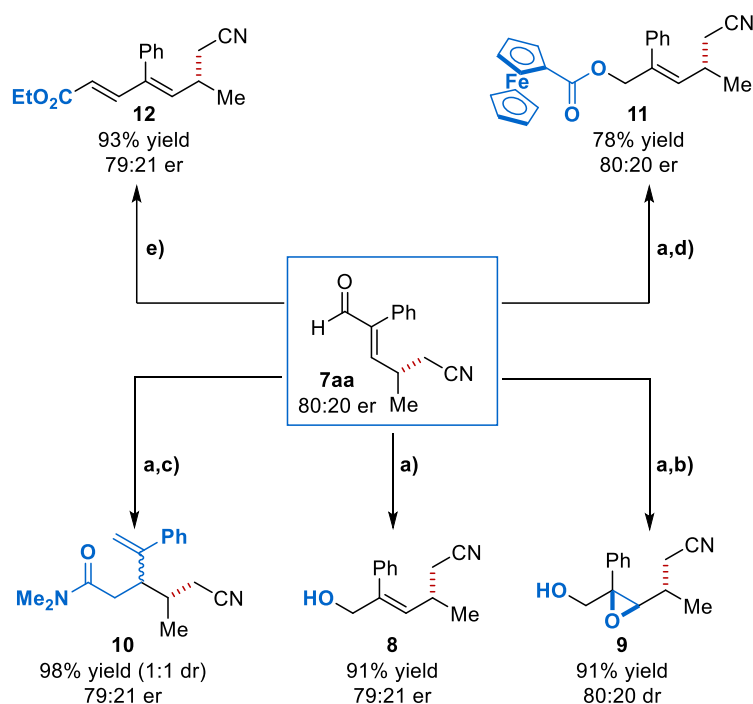
Scheme 9 Survey of enals **1** that can react with α -chloroacetonitrile **6a**. *Product isolated as 1:1 atropisomeric ratio.

†Using catalyst **A9**. Yields refer to isolated yields

Overall, this new methodology allows for the direct installation of a stereocenter at the remote- γ position of the starting enals, leaving the α,β -unsaturated system amenable for further synthetic elaborations. As described in Scheme 10, several transformations were performed on the enantioenriched product **7aa** (80:20 er). Treatment of **7aa** with sodium borohydride gave the corresponding allylic alcohol **8** in a 91% isolated yield (*path a*). This latter compound proved to be a suitable substrate for a stereospecific Sharpless epoxidation²¹ (*path b*), affording epoxide **9** with three contiguous stereocenters in 90% yield and with 4:1 dr. Moreover, a 1:1 diastereoisomeric mixture of the chiral dimethylamide **10** was produced in almost quantitative yield through the [3,3]-sigmatropic Claisen rearrangement (*path c*, 79:21 er for each diastereoisomer).²² Esterification with ferrocenyl carboxylic acid efficiently afforded the corresponding ester **11** with no loss of enantiomeric purity (*path d*, 78% yield, 80:20 er). Finally, coupling of **7aa** with (carbethoxymethyl)triphenylphosphonium bromide smoothly produced the ε -functionalized unsaturated ester **12** through a Wittig-type olefination (*path e*).

²¹ Katsuki, T.; Sharpless, K. B. "The first practical method for asymmetric epoxidation" *J. Am. Chem. Soc.* **1980**, *102*, 5974.

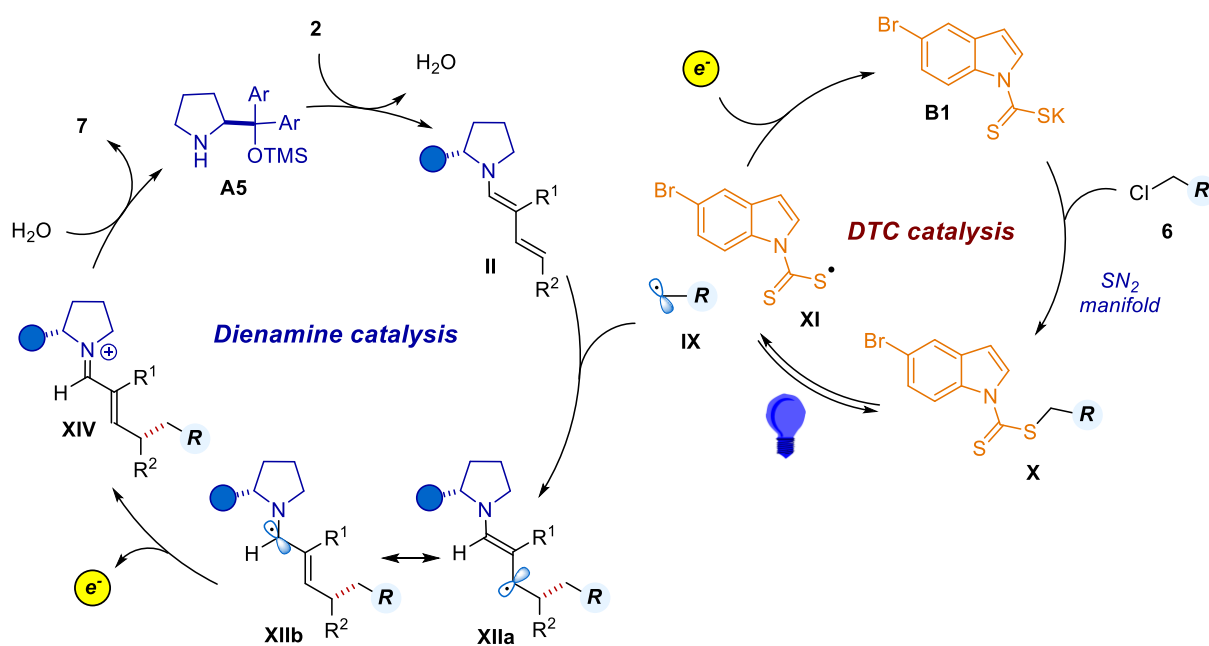
²² Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. "CLAISEN'sche Umlagerungen bei Allyl- und Benzylalkoholen mit Hilfe von Acetalen des *N,N*-Dimethylacetamids. Vorläufige Mitteilung" *Helv. Chem. Acta*, **1964**, *47*, 2425.



Scheme 10 Synthetic elaborations of product **7aa**. Conditions: (a) NaBH₄, MeOH, 1h, 0 °C; (b) (-)-diethyl-D-tartrate (23 mol%), Ti(OiPr)₄ (20 mol%), *t*-BuOOH, DCM, 20 °C; (c) *N,N*-dimethylacetamide dimethyl acetal, xylene, 110 °C; (d) ferrocenyl carboxylic acid, oxalyl chloride, DMF; (e) (carbethoxymethyl)triphenylphosphonium bromide, DCE

4.3.3 Mechanism proposal and stereochemical considerations

Based on previous reports on dienamine organocatalysis and DTC catalysis, we envisage the catalytic cycle detailed in Scheme 11, where aminocatalyst **A5** and DTC catalyst **B1** work in concert to promote the generation of the final product **7**.



Scheme 11 Proposed catalytic cycle

More in details, the photoactive intermediate **X** is generated through a S_N2 reaction between alkyl chloride **6** and the DTC catalyst **B1**. Blue light excitation of **X** triggers the homolytic cleavage step,

furnishing the kinetically stable thiyl-radical **XI** and the primary carbon-centered radical **IX**. This latter is then enantioselectively trapped by dienamine **II**, generated upon condensation of enal **2** with aminocatalyst **A5**, exclusively at the remote γ -carbon. Regarding the DTC-catalyst turnover event, we suppose a single electron oxidation of the ensuing radical **XIIa**, that is in resonance with the α -amino radical **XIIb** ($E_p^{\text{red}}(\text{XIIb/XIV}) = -0.92$ to -1.12 V versus SCE),²³ by the thiyl radical **XI** (the parent ethyl xanthogenate anion, where the indole-based moiety is substituted by -OEt, has reduction potential $E_p^{\text{red}}(\text{B/XI}) = +0.04$ V versus SCE).²⁴ Final hydrolysis of iminium ion **XIV** accounts for the generation of the final γ -alkyl product **7**, regenerating the chiral catalyst **A5**. As we could not exclude DTC turnover event involving ATRA manifold, we measured the quantum yield (Φ , see Experimental Section for details), that resulted as low as 0.0014. This result confirmed a close catalytic cycle, were a radical chain propagation, if present, is not the dominant path.

Following the standard rules of facial discrimination operated by Jørgensen-type catalyst, the steric clash provoked by the α -substituent of the (*S*)-prolinol catalyst would suggest that the (*Re*) approach of the dienamine (*Z-s-trans-E*)-**IIa** is not consistent with the experimentally determined stereochemistry (Figure 1, a). Despite an extensive investigation is still needed, it is plausible to envisage that either of the two geometric isomers (*Z-s-cis-E*)-**IIb**^{8b} or (*E-s-trans-E*)-**IIc** (Figure 1) are operative radical traps. The plausible coexistence of diverse possible dienamine isomers, as well as the difficulty of the catalyst in perfectly discriminating one of the prochiral faces of the dienamine at remote positions would be responsible for the sub-optimal enantioselectivity of the process; at the same time, this observation paves the way to further studies about this challenging and fascinating field.

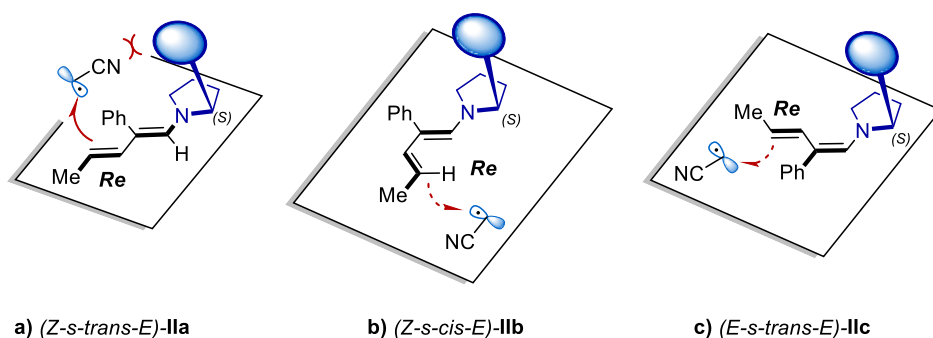


Figure 1 Stereochemical considerations on prochiral dienamine approach within the enantio-determining step of the process

²³ a) Wayner, D. D. M.; Dannenberg, J. J.; Griller, D. "Oxidation potentials of α -aminoalkyl radicals: bond dissociation energies for related radical cations" *Chem. Phys. Lett.* **1986**, 131, 189; b) Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. "Enantioselective α -Alkylation of Aldehydes by Photoredox Organocatalysis: Rapid Access to Pharmacophore Fragments from β -Cyanoaldehydes" *Angew. Chem. Int. Ed.* **2015**, 54, 9668.

²⁴ Dag, O.; Yaman, S. O.; Onal, A. M.; Isci, H. "Spectroelectrochemistry of potassium ethylxanthate, bis(ethylxanthato)nickel(II) and tetraethylammonium tris(ethylxanthato)nickelate(II)" *J. Chem. Soc. Dalton Trans.* **2001**, 2819.

4.4 Conclusion

In this project, the possibility to develop a synergistic organocatalytic reaction for the photochemical regio- and enantioselective remote alkylation of enals was put into practice. Aminocatalysis was exploited to afford dienamines, while DTC catalysis was elected as radical generating platform. A wide array of diversely γ -functionalized enals were provided in complete remote site selectivity and overall acceptable enantiocontrol. This protocol represents a rare example of enantioselective γ -functionalization process, where vinylogous dienamines smoothly act as radical traps at distant positions. Finally, the usefulness of this protocol was highlighted by scaled-up reaction and various synthetic elaborations on the products.

4.5 Experimental section

4.5.1 General information

All reactions were set up under an argon atmosphere in oven-dried glassware. Synthesis grade solvents were used as purchased. Anhydrous solvents were taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using forced-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were employed, using UV light as the visualizing agent and an acidic mixture of vanillin or basic aqueous potassium permanganate (KMnO₄) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. The NMR spectra and UPC² traces of enantioenriched product can be found in the supporting information published on-line. The NMR spectra were recorded at 400 MHz and 500 MHz for ¹H and 100 or 125 MHz for ¹³C. The chemical shift (δ) for ¹H and ¹³C are given in ppm relative to residual signals of the solvents (CHCl₃ @ 7.26 ppm ¹H-NMR and 77.16 ppm ¹³C-NMR, and tetramethylsilane @ 0 ppm). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; q, quartet; m, multiplet; bs, broad signal; app, apparent. UPC² analysis on chiral stationary phase was performed on a Waters Acquity instrument using ID3, IG, IA3, IC, IB and OJ chiral columns. The exact conditions for the analyses are specified within the characterization section. High resolution mass spectra (HRMS) were obtained from the ICIQ HRMS unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization. (ESI). Yields refer to isolated materials of >95% purity as determined by ¹H-NMR.

4.5.2 Experimental set-up

The 3D printed photoreactor consisted of a 9 cm diameter crystallizing dish with a 3D printed support of 6 positions, and a hole of 22 mm in the middle to allow ventilation. A commercial 1-meter LED strip was wrapped around the crystallizing dish. In order to control the temperature, a fan was used to cool down the reactor. Reaction temperature was measured, through a vial containing a thermometer, and it stayed between 35-40 °C (Figure 2). Each of the positions could be used to fit a standard 16 mm diameter vial with a Teflon screw cap.

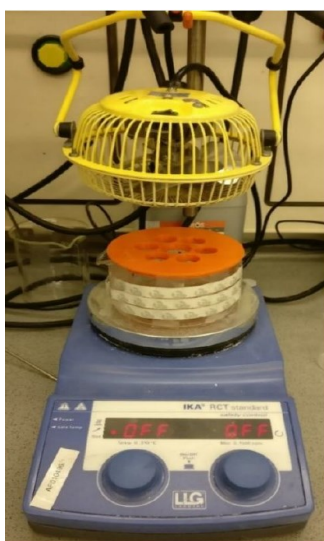


Figure 2 Photoreactor used in this study

Experiments at 465 nm were conducted using a 1m strip, 14.4W “LEDXON MODULAR 9009083 LED, SINGLE 5050” purchased from Farnell, catalogue number 9009083. The emission spectrum of these LEDs was recorded (Figure 3). The emission maximum was determined as 465 nm with a spectral width of 30 nm (450-480 nm) at half peak intensity and a total spectral width of 120 nm (420-540 nm).

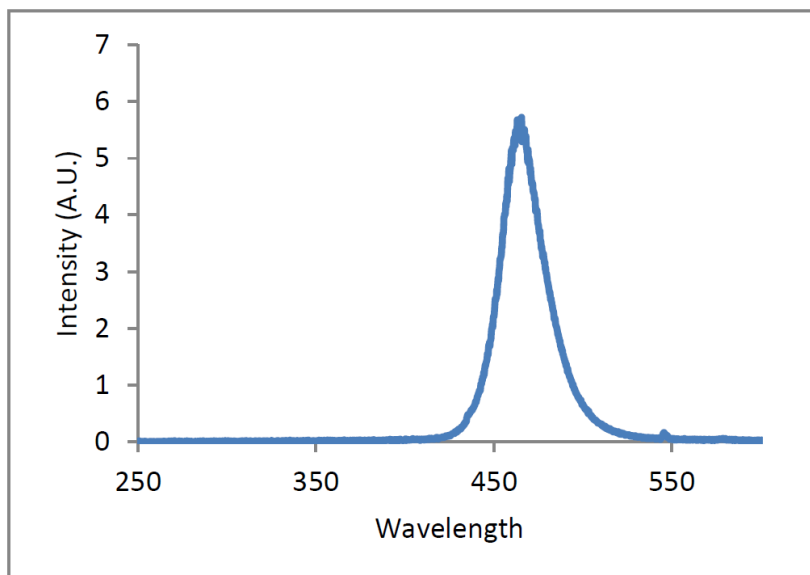


Figure 3 Emission spectrum of the 465 nm LED strip used in this study

4.5.3 Catalysts and substrates synthesis

Catalysts

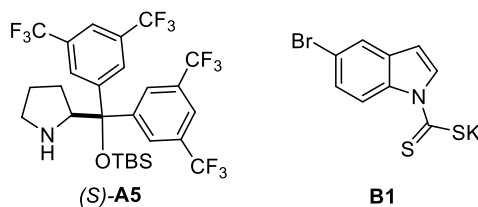
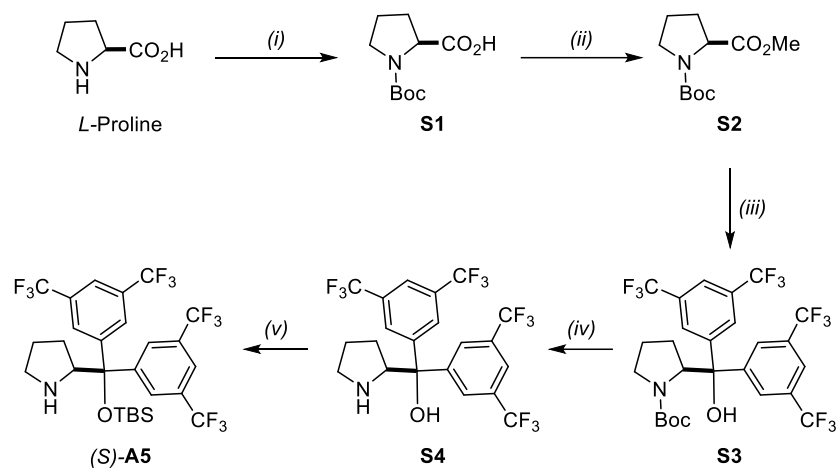


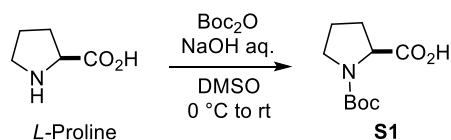
Figure 4 Catalysts used in this transformation

Dithiocarbamate catalyst **B1** was prepared from 5-bromoindole by a one-step synthesis previously reported by the Melchiorre group.¹⁵ Aminocatalyst **A5** was synthesized starting from L-proline by a 5-step synthesis described below. All the product matched the spectroscopic characterization reported in literature.



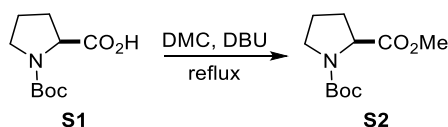
Scheme 12 Synthetic approach exploited for the preparation of aminocatalyst **A5**

Synthesis of (tert-butoxycarbonyl)-L-proline **S1**



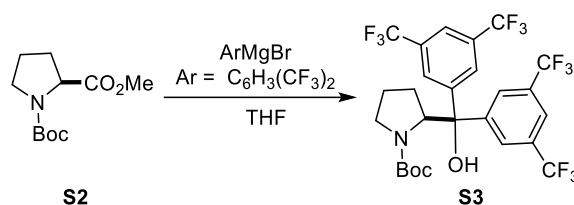
To a solution of (*S*)-proline (8.0 g, 69 mmol) in aq. NaOH (1M, 130 mL) and dioxane (33 mL) at 0 °C was added Boc₂O (18 g, 82 mmol) portionwise over 20 min. The resulting mixture was stirred at 0 °C for 30 min, then allowed to warm to 23 °C and stirred overnight. The organic solvent was removed under reduced pressure. The remaining aqueous solution was acidified to pH ~2 with aq. KHSO₄ (1 M). The aqueous solution was extracted with CHCl₃ (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, and concentrated by rotary evaporation to afford the target carbamate **S1** (14.2 g, 95% yield) as a white solid, which was sufficiently pure to be taken on to the next step.

Synthesis of 1-(*tert*-butyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate **S2**



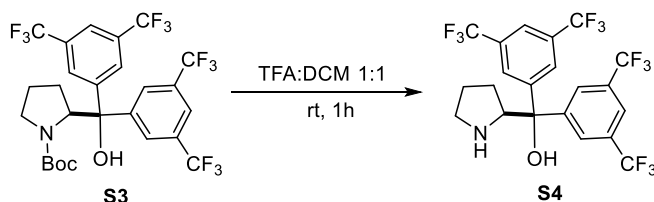
DBU (9.9 g, 9.8 mL equiv) was added to a solution of *N*-Boc Proline **S1** (14 g, 65 mmol) in dimethyl carbonate (DMC, 250 mL 0.25M), and the resulting mixture was heated to reflux. Upon completion, the reaction mixture was cooled to room temperature and diluted with either EtOAc and H₂O. The aqueous layer was removed, and the organic layer was washed with H₂O, twice with 2 M HCl or 10% aqueous citric acid, twice with saturated aqueous NaHCO₃, and twice with H₂O. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum to afford the target ester **S2** (14.6 g, 98% yield) as a pale-yellow oil which was sufficiently pure to be taken on to the next step.

Synthesis of (*S*)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol **S3**



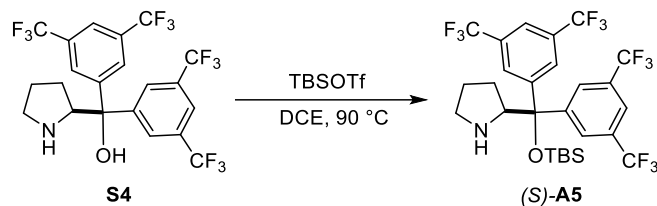
In a two-necked round bottom flask equipped with septum and condenser containing a stirring bar were added the Mg turnings (1.59 g, 65.4 mmol). The air was removed through vacuum air flaming for 30 minutes. To the Mg was added anhydrous THF (30 mL) and the reaction was stirred for 2 minutes after which a crystal of I₂ was added (the solution turns brownish). At this stage the aryl bromide (11.98 mL, 65.4 mmol) was added portion wise to the suspension of Mg. During the addition the solution turns gradually to grey (note: exothermic reaction). Once the addition of the aryl bromide was complete, the solution was refluxed for 1 hour at 65°C. After the indicated time the solution was cooled to 0°C and the Proline ester **S2** (as 1M solution in dry THF, 5 g, 21.8 mmol) was added via syringe. The reaction was stirred overnight and then slowly quenched with H₂O. The reaction crude was then filtered on cotton before being extracted 2 times with AcOEt (or DCM). The collected organic phases were then collected and anhydriified over MgSO₄, filtered and concentrated under vacuum to obtain a dark brown oil which contains the product. The oil was then purified by Flash Chromatography o silica gel (100%hexane to 95:5 hexane:AcOEt) to afford the Prolinol **S3** (10.1 g, 73% yield) as an orange and dense oil.

Synthesis of *tert*-butyl (*S*)-2-(bis(3,5bis(trifluoromethyl)phenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate **S4**



Prolinol **S4** (9.4 g, 15.95 mmol) was dissolved in a 1:1 mixture of DCM:TFA and stirred for 1 hour at room temperature. The solution was then basified to pH 7 using a solution of NaHCO₃. The organic phase was then extracted with DCM 3 times. After anhydriification with NaSO₄ and removal of the solvent the free amine **S5** (7.3 g, 92% yield) was obtained as an orange oil.

Synthesis of (S)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((tert-butyl)dimethylsilyl)oxy)methylpyrrolidine **A5**

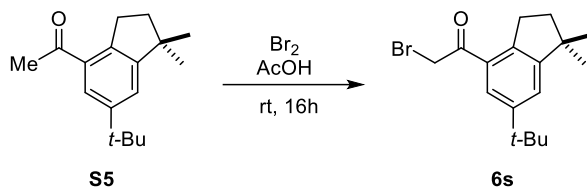


In a two-necked round bottom flask equipped with condenser and a magnetic stirring bar was made a 0.4M solution of substrate **S4** (5.00 g, 9.5 mmol) in DCE. Triethylamine (5.97 mL, 42.8 mmol) and TBSOTf (4.38 mL, 19.04 mmol) were added sequentially while stirring. The reaction was then stirred under reflux overnight. After cooling the reaction mixture was quenched with brine. The organic phase was extracted with Et₂O 3 times and after anhydrication over MgSO₄ the crude was purified by Flash Chromatography on silica gel (2% Et₂O in Pentane) to afford the catalyst **A5** (3.2 g, 50% yield) as a pale-yellow oil which solidifies at low temperature.

Radical precursors

Most of the radical precursors **6** used in this study were commercial and were purchased in the highest purity available from Sigma-Aldrich, Fluka, Alfa Aesar, Fluorochem, and used as received, without further purifications. Phenacyl chlorides that are not commercially available were synthesized using known literature procedures²⁵ and their characterization matched with the literature reported data.

Synthesis of 2-bromo-1-(6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan- 1-one **6s**



Ketone **S5** (1.95 g, 8.0 mmol) was dissolved in glacial AcOH (0.2M) and treated dropwise with Br₂ (0.411 mL, 17.7 mmol) in AcOH (1.3 M) at r.t. The mixture was stirred at r.t. for 16 h and then the solvent was removed by rotary evaporation. The crude mixture was evaporated under reduced pressure, and purified by column chromatography (eluent: pentane/Et₂O 8:2) to afford 1.50 g of the desired product **6s** (4.64 mmol, 58% yield) as a colourless oil.

¹H-NMR (300 MHz, CDCl₃) δ 7.71 (s, 1H), 7.38 (s, 1H), 4.48 (s, 1H), 3.18 (td, J = 7.3, 1.2 Hz, 2H), 1.95 (td, J = 7.3, 1.3 Hz, 2H), 1.36 (s, 9H), 1.27 (s, 6H).

¹³C-NMR (101 MHz, CDCl₃) δ 192.88, 154.99, 150.24, 142.52, 130.41, 124.89, 124.40, 43.65, 41.47, 34.91, 33.13, 31.60, 30.93, 28.88.

²⁵ a) Zhu, Y.; Cai, Q.; Gao, Q.; Jia, F.; Liu, M.; Gao, M.; Wu, A. *Tetrahedron*, **2013**, 69, 6392; b) Lee, J. C.; Bae, Y. H.; Chang, S.-K. *Bull. Korean. Chem. Soc.* **2003**, 24, 407.

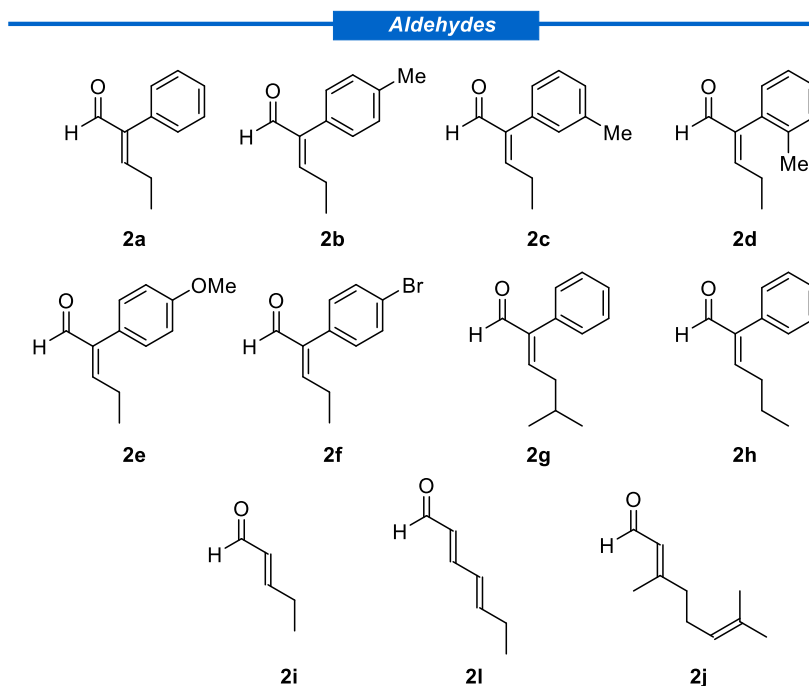
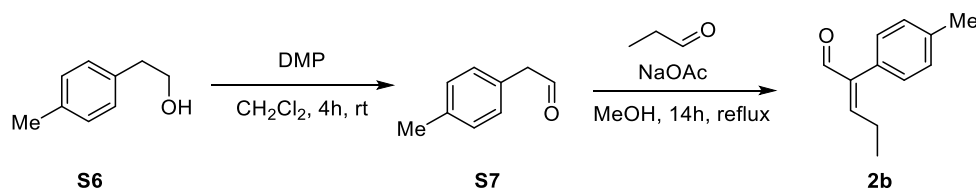


Figure 5 Enals used in this study

2-Phenyl-2-Pentenal **2a**, 2-Pentenal **2i**, 2,4-Heptadienal **2l**, 5-Methyl-2-phenyl-2-hexenal **2g** and Citral **2j** were commercially available and were used without further purifications. Aldehydes **2b**, **2c**, **2d**, **2e**, **2f** and **2h** and were synthesized through a two-step procedure using known and slightly modified protocols.²⁶

Synthesis of (*E*)-2-(*p*-tolyl)pent-2-enal (**2a**):



To a stirred solution of alcohol **S6** (1.36 g, 10.0 mmol) in CH_2Cl_2 dry (60 mL), 6.4 g of Dess-Martin Periodinane (15 mmol) were added under argon. After 3h the reaction was quenched with saturated aqueous solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). After 30 min, the resulting mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 10:1) to give 631 mg of the corresponding aldehyde **S7** (4.7 mmol, 47% yield) as a colorless oil. Analytical and spectroscopic data fully matched those reported in literature.

To a stirred solution of **S7** (631 mg, 4.7 mmol) in MeOH (9.5 mL), 1.01 mL of propionaldehyde (14.1 mmol) and 385 mg of NaOAc (4.7 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting material was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL),

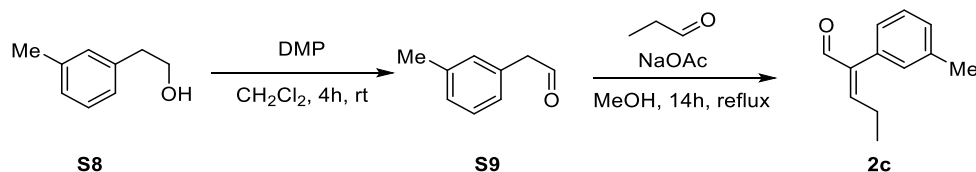
²⁶ a) Kolonko, K. J.; Reich, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 9668; b) Schreiber, W. L.; Pittet, A. O., Vock, M.H. *J. Agric. Food Chem.* **1974**, *22*, 269.

dried over MgSO_4 , filtered, evaporated under reduced pressure. The excess of propionaldehyde was removed by column chromatography (eluent: hexane/EtOAc 99:1) and then the residue (mixture of desired product and self-condensed by-product) purified by Kugelrohr distillation (2.1×10^{-1} bar, 90°C) to afford 296 mg the corresponding enal **2a** (1.7 mmol, 36% yield) as a colorless oil.

^1H -NMR (500 MHz, CDCl_3) δ 9.63 (s, 1H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.09 (d, $J = 8.1$ Hz, 2H), 6.71 (t, $J = 7.5$ Hz, 1H), 2.49 – 2.33 (m, 5H), 1.14 (t, $J = 7.5$ Hz, 3H).

^{13}C -NMR (126 MHz, CDCl_3) δ 194.1, 157.7, 143.3, 137.7, 129.6, 129.3 (2C), 129.0 V, 23.3, 21.3, 13.3.

Synthesis of (*E*)-2-(*m*-tolyl)pent-2-enal (**2c**)



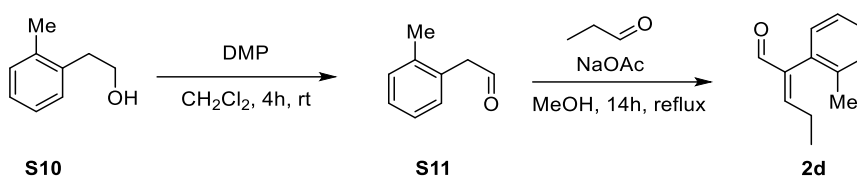
To a stirred solution of alcohol **S8** (1.36 g, 10.0 mmol) in CH_2Cl_2 dry (60 mL), 6.4 g of Dess-Martin Periodinane (15 mmol) were added under argon. After 3h the reaction was quenched with saturated aqueous solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). After 30 min, the resulting mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 10:1) to give 872 mg of the corresponding aldehyde **S9** (6.5 mmol, 65% yield) as a colorless oil. Analytical and spectroscopic data fully matched those reported in literature.

To a stirred solution of **S9** (872 mg, 6.5 mmol) in MeOH (13 mL), 1.39 mL of propionaldehyde (19.5 mmol) and 540 mg of NaOAc (6.5 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting material was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure. The excess of propionaldehyde was removed by column chromatography (eluent: hexane/EtOAc 99:1) and then the residue (mixture of desired product and self-condensed by-product) purified by Kugelrohr distillation (2.1×10^{-1} bar, 90°C) to afford 362 mg the corresponding enal **2c** (2.1 mmol, 32% yield) as a colorless oil.

^1H -NMR (500 MHz, CDCl_3) δ 9.63 (s, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.21 – 7.15 (m, 1H), 7.03 – 6.94 (m, 2H), 6.71 (t, $J = 7.5$ Hz, 1H), 2.47 – 2.33 (m, 5H), 1.13 (t, $J = 7.5$ Hz, 3H).

^{13}C -NMR (126 MHz, CDCl_3) δ 193.9, 157.7, 143.6, 137.8, 132.5, 130.0, 128.7, 128.1, 126.4, 23.2, 21.5, 13.3.

Synthesis of (*E*)-2-(*o*-tolyl)pent-2-enal (**2d**)



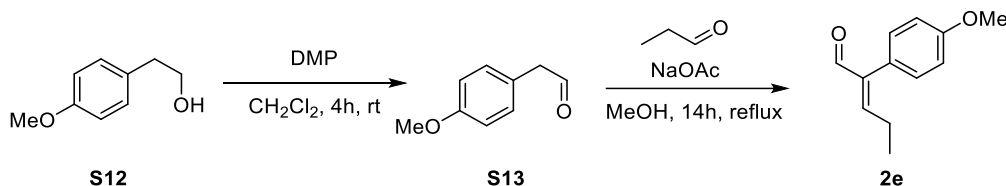
To a stirred solution of alcohol **S10** (1.36 g, 10.0 mmol) in CH_2Cl_2 dry (60 mL), 6.4 g of Dess-Martin Periodinane (15 mmol) were added under argon. After 3h the reaction was quenched with saturated aqueous solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). After 30 min, the resulting mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 10:1) to give 791 mg of the corresponding aldehyde **S11** (5.9 mmol, 59% yield) as a colorless oil. Analytical and spectroscopic data fully matched those reported in literature.

To a stirred solution of **S11** (591 mg, 5.9 mmol) in MeOH (12 mL), 1.26 mL of propionaldehyde (17.7 mmol) and 484 mg of NaOAc (5.9 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting material was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: pentane/ Et_2O 9:1) to afford 452 mg the corresponding enal **2d** (2.6 mmol, 44% yield) as a light-yellow oil.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 9.64 (d, $J = 0.6$ Hz, 1H), 7.27 – 7.25 (m, 1H), 7.25 – 7.16 (m, 2H), 6.96 (d, $J = 7.1$ Hz, 1H), 6.84 (t, $J = 7.5$ Hz, 1H), 2.24 – 2.14 (m, 2H), 2.12 (s, 3H), 1.09 (t, $J = 7.5$ Hz, 3H).

$^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 194.10, 157.65, 143.33, 137.71, 129.30, 128.96, 23.25, 21.28, 13.31.

Synthesis of (*E*)-2-(4-methoxyphenyl)pent-2-enal (**2e**)



To a stirred solution of alcohol **S12** (1.5 g, 10.0 mmol) in CH_2Cl_2 dry (60 mL), 6.4 g of Dess-Martin Periodinane (15 mmol) were added under argon. After 3h the reaction was quenched with saturated aqueous solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). After 30 min, the resulting mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 4:1) to give 795 mg of the corresponding aldehyde **S13** (5.3 mmol, 53% yield) as a colorless oil. Analytical and spectroscopic data fully matched those reported in literature.

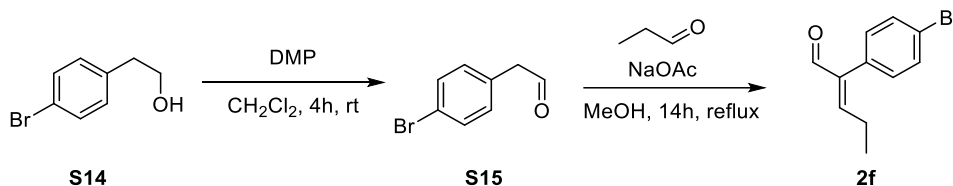
To a stirred solution of **S13** (795 mg, 5.3 mmol) in MeOH (10 mL), 1.13 mL of propionaldehyde (15.9 mmol) and 434 mg of NaOAc (5.3 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting

material was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 9:1) to afford 413 mg the corresponding enal **2e** (2.2 mmol, 41% yield) as a light-yellow oil.

¹H-NMR (500 MHz, CDCl₃) δ 9.62 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.68 (t, J = 7.5 Hz, 1H), 3.85 (s, 3H), 2.42 (p, J = 7.5 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 194.2, 159.3, 157.5, 142.9, 130.6 (2C), 124.7, 113.7 (2C), 55.3, 23.2.

Synthesis of (*E*)-2-(4-bromophenyl)pent-2-enal (**2f**)



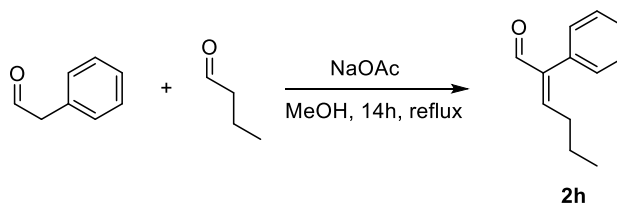
To a stirred solution of alcohol **S14** (2.0 g, 10.0 mmol) in CH₂Cl₂ dry (60 mL), 6.4 g of Dess-Martin Periodinane (15 mmol) were added under argon. After 3h the reaction was quenched with saturated aqueous solutions of NaHCO₃ and Na₂S₂O₃ (20 mL). After 30 min, the resulting mixture was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 3:1) to give 1.4 g the corresponding aldehyde **S15** (7.1 mmol, 72% yield) as a light-yellow oil. Analytical and spectroscopic data fully matched those reported in literature.

To a stirred solution of **S15** (1.4 g, 7.1 mmol) in MeOH (14 mL), 1.52 mL of propionaldehyde (21.3 mmol) and 582 mg of NaOAc (7.1 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting material was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 9:1) to afford 899 mg the corresponding enal **2f** (3.7 mmol, 53% yield) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃) 9.59 (s, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 6.73 (t, J = 7.6 Hz, 1H), 2.37 (p, J = 7.5 Hz 2H), 1.12 (t, J = 7.5 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃) δ 193.3, 158.2, 142.4, 131.5 (2C), 131.4, 131.1 (2C), 23.2, 13.2.

Synthesis of (*E*)-2-phenylhex-2-enal (**2h**)



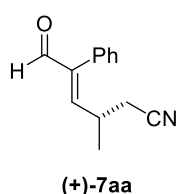
To a stirred solution of phenylacetaldehyde (1.0 g, 8.3 mmol) in MeOH (16 mL), 2.24 mL of butyraldehyde (24.9 mmol) and 680 mg of NaOAc (8.3 mmol) were sequentially added. The resulting mixture was heated to reflux for 14h. Subsequently, the solvent was evaporated under vacuum and the resulting material was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, evaporated under reduced pressure, and purified by column chromatography (eluent: hexane/EtOAc 9:1) to afford 709 mg the corresponding enal **1g** (4.1 mmol, 49% yield) as a light-yellow oil.

¹H-NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H), 7.45 – 7.34 (m, 3H), 7.20 – 7.16 (m, 2H), 6.75 (t, J = 7.5 Hz, 1H), 2.37 (q, J = 7.5 Hz, 2H), 1.56 (q, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H)

¹³C-NMR (101 MHz, CDCl₃) δ 193.8, 156.4, 144.1, 132.7, 129.4 (2C), 128.2 (2C), 127.9, 31.7, 22.1, 13.8.

4.5.4 Experimental procedures and characterizations of products

General procedure A: Synthesis of (*S,E*)-3-methyl-6-oxo-5-phenylhex-4-enenitrile [(+)-**7aa**]



In an oven dried 5 mL vial equipped with a Teflon septum screw cap and a magnetic stirring bar, (*E*)-2-phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.) and aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.) were dissolved in 250 μ L of degassed THF. After 5 minutes 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L) and dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) were added. The reaction mixture was degassed through

Ar sparging for 20 seconds before closing the cap. The vial was then sealed with parafilm and placed in the 3D printed support photoreactor (Figure 2) and irradiated under stirring. After 20 hours, the solvent was evaporated under reduced pressure and the residue purified by column chromatography (eluent: hexane/EtOAc 8:2) to afford 27.9 mg of the corresponding product (0.14 mmol, 70%, 80:20 *er*) as a pale-orange oil. The enantiomeric excess of the product was determined to be 80:20 by UPC² analysis on a Daicel Chiralpak IA- 3 column (eluent: CO₂/IPA = 90:10; flow rate 1 mL/min, λ = 300 nm. τ Major = 3.54 min, τ Minor = 3.66 min.

¹H-NMR (500 MHz, CDCl₃) δ 9.67 (s, 1H), 7.49 – 7.37 (m, 3H), 7.20 – 7.11 (m, 2H), 6.54 (d, J = 10.3 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.44 (d, J = 6.3 Hz, 2H), 1.28 (d, J = 6.7 Hz, 3H). 157

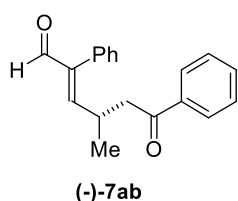
¹³C-NMR (126 MHz, CDCl₃) δ 193.0, 153.9, 144.7, 131.9, 129.0 (2C), 128.6 (2C), 128.5, 117.3, 30.7, 24.1, 19.7.

$[\alpha]_D^{20}$ +86.2 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₈H₂₅NO₄Na]⁺ [M+Na]⁺: 222.0895; found: 222.0889.

Scope of Radical Precursors

Synthesis of (*S,E*)-4-methyl-6-oxo-2,6-diphenylhex-2-enal [(*-*)-7ab]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-phenylethan-1-one **6b** (30.9 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ab** (31.2 mg, 56%

yield) as a yellow oil. The enantiomeric excess of the product was determined to be 84:16 by UPC² analysis on a Daicel Chiralpak IG column (eluent: CO₂/IPA = 90:10; flow rate 1 mL/min, λ = 320 nm. τ Major = 3.17 min, τ Minor = 3.98 min.

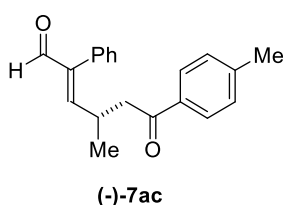
¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.93 – 7.81 (m, 2H), 7.57 (ddt, J = 7.9, 6.9, 1.3 Hz, 1H), 7.48 – 7.34 (m, 5H), 7.21 – 7.15 (m, 2H), 3.39 – 3.37 (m, 1H), 3.10 – 3.07 (m, 2H), 1.19 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 197.9, 193.8, 159.2, 143.2, 136.6, 133.3, 132.6, 129.2 (2C), 128.7 (2C), 128.4 (2C), 128.1 (2C), 128.0, 45.0, 30.4, 20.1.

$[\alpha]_D^{20}$ -76.4 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₈O₂Na]⁺ [M+Na]⁺: 301.1204; found: 301.1199.

Synthesis of (*S,E*)-4-methyl-6-oxo-2-phenyl-6-(*p*-tolyl)hex-2-enal [(*-*)-7ac]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-(*p*-tolyl)ethan-1-one **6c** (42.6 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to

afford product **7ac** (28.1 mg, 48% yield) as a pale yellow. The enantiomeric excess of the product was determined to be 85:15 by UPC² analysis on a Daicel 158 Chiralpak IG column (eluent: CO₂/IPA = 90:10; flow rate 1 mL/min, λ = 320 nm. τ Major = 3.80 min, τ Minor = 4.12 min.

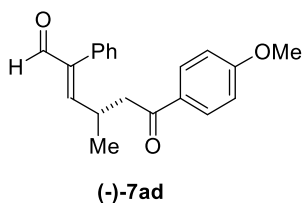
¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.45 – 7.32 (m, 3H), 7.25 – 7.21 (m, 2H), 7.20 – 7.15 (m, 2H), 6.61 (d, J = 10.2 Hz, 1H), 3.38 – 3.27 (m, 1H), 3.06 (dd, J = 6.8, 1.5 Hz, 2H), 2.42 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 197.5, 193.8, 159.4, 144.1, 143.1, 134.2, 132.6, 129.4 (2C), 129.2 (2C), 128.4 (2C), 128.2 (2C), 128.0, 44.9, 30.5, 21.7, 20.0.

$[\alpha]_D^{20}$ -15.6 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₂₀H₂₀O₂Na]⁺ [M+Na]⁺: 315.1361; found: 315.1356.

Synthesis of (*S,E*)-6-(4-methoxyphenyl)-4-methyl-6-oxo-2-phenylhex-2-enal [(-)-7ad]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-(4-methoxy)ethan-1-one **6d** (45.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified

by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7ad** (32.0 mg, 53% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 83:17 by UPC² analysis on a Daicel Chiralpak IG column (eluent: CO₂/IPA=20:80; flow rate 1 mL/min, λ = 320 nm. τ_{Major} = 4.15 min, τ_{Minor} = 4.39 min.

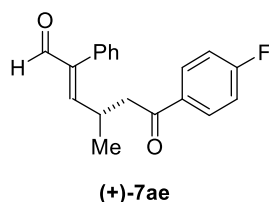
¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.84 (d, J = 8.9 Hz, 2H), 7.43 – 7.32 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 10.1 Hz, 1H), 3.88 (s, 3H), 3.39 – 3.23 (m, 1H), 3.03 (d, J = 6.8 Hz, 2H), 1.17 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 196.4, 193.8, 163.6, 159.4, 143.1, 132.6, 130.4 (2C), 129.7, 129.2 (2C), 128.4 (2C), 128.0, 113.8 (2C), 55.5, 44.7, 30.6, 20.1.

$[\alpha]_{\text{D}}^{20}$ -51.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₂₀H₂₀O₃Na]⁺ [M+Na]⁺: 331.1310; found: 331.1305.

Synthesis of (*S,E*)-6-(4-fluorophenyl)-4-methyl-6-oxo-2-phenylhex-2-enal [(+)-7ae]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-(4-fluorophenyl)ethan-1-one **6e** (43.4 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash

column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ae** (31.4 mg, 53% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 83:17 by UPC² analysis on a Daicel Chiralpak IG column (eluent: CO₂/IPA = 90:10; flow rate 1 mL/min, λ = 320 nm. τ_{Major} = 3.30 min, τ_{Minor} = 3.54 min.

¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.87 (dd, J = 8.9, 5.4 Hz, 2H), 7.48 – 7.32 (m, 3H), 7.22 – 7.14 (m, 2H), 7.14 – 7.04 (m, 2H), 6.60 (d, J = 10.2 Hz, 1H), 3.39 – 3.24 (m, 1H), 3.04 (d, J = 6.8 Hz, 2H), 1.19 (d, J = 6.7 Hz, 3H).

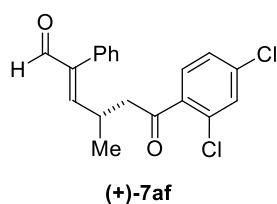
¹⁹F-NMR (471 MHz, CDCl₃) δ -104.87.

¹³C-NMR (126 MHz, CDCl₃) δ 196.2, 193.7, 165.8 (d, $^1J_{\text{C,F}}$ = 255 Hz), 158.9, 143.2, 133.0 (d, $^4J_{\text{C,F}}$ = 3 Hz), 132.6, 130.7 (d, $^3J_{\text{C,F}}$ = 9 Hz, 2C), 129.2 (2C), 128.4 (2C), 128.1, 115.8 (d, $^2J_{\text{C,F}}$ = 22 Hz, 2C), 44.9, 30.4, 20.0.

$[\alpha]_{\text{D}}^{20}$ +63.4 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇FO₂Na]⁺ [M+Na]⁺: 319.1110; found: 319.1105.

Synthesis of (*S,E*)-6-(2,4-dichlorophenyl)-4-methyl-6-oxo-2-phenylhex-2-enal [(+)-7af]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro- 1-(2,4-dichlorophenyl)ethan-1-one **6f** (53.6 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 75:25) to afford product **7af** (34.7 mg, 50% yield) as a yellowish oil. The enantiomeric excess of the product was determined to be 76:24 by UPC² analysis on a Daicel Chiralpak IG column (eluent: 85:15 CO₂/MeOH; flow rate 1.00 mL/min, λ = 240 nm. τ_{Major} = 3.47 min, τ_{Minor} = 3.79 min.

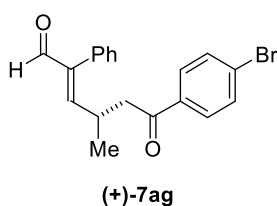
¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.44 – 7.35 (m, 4H), 7.33 – 7.28 (m, 1H), 7.18 – 7.14 (m, 2H), 6.56 (d, J = 10.2 Hz, 1H), 3.35 – 3.23 (m, 1H), 3.07 (dd, J = 6.8, 1.7 Hz, 2H), 1.19 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 199.6, 193.6, 158.2, 143.2, 137.7, 137.0, 132.4, 132.1, 130.5, 130.2, 129.1 (2C), 128.4 (2C), 128.1, 127.5, 49.1, 30.4, 20.1.

$[\alpha]_{\text{D}}^{20}$ +87.0 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₆Cl₂O₂Na]⁺ [M+Na]⁺: 369.0425; found: 369.0420.

Synthesis of (*S,E*)-6-(4-bromophenyl)-4-methyl-6-oxo-2-phenylhex-2-enal [(+)-7ag]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro- 1-(4-bromophenyl)ethan-1-one **6g** (55.6 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7ag** (42 mg, 58% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IE column (eluent: CO₂/IPA = 85:15; flow rate 1 mL/min, λ = 320 nm. τ_{Major} = 3.54 min, τ_{Minor} = 3.66 min.

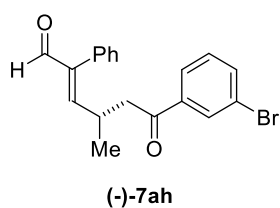
¹H-NMR (500 MHz, CDCl₃) δ 9.62 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 7.43 – 7.35 (m, 3H), 7.19 – 7.14 (m, 2H), 6.59 (d, J = 10.2 Hz, 1H), 3.32 (dq, J = 10.2, 6.8 Hz, 1H), 3.04 (d, J = 6.8 Hz, 2H), 1.19 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 196.8, 193.6, 158.6, 143.3, 135.2, 132.5, 131.9, 129.5, 129.1, 128.50, 128.4, 128.1, 44.9, 30.4, 20.0.

$[\alpha]_{\text{D}}^{20}$ +19.2 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇BrO₂Na]⁺ [M+Na]⁺: 379.0310; found: 379.0291.

Synthesis of (*S,E*)-6-(3-bromophenyl)-4-methyl-6-oxo-2-phenylhex-2-enal [(-)-7ah]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-bromo-1-(3-bromophenyl)ethan-1-one **6h** (55.6 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ah** (39.3 mg, 52% yield) as a yellowish oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IG column (eluent: 80:20 CO₂/MeCN; flow rate 1.00 mL/min, λ = 250 nm. τ Major = 3.95 min, τ Minor = 4.18 min.

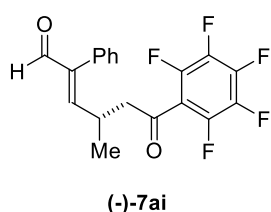
¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 8.01 (t, J = 1.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.45 – 7.34 (m, 3H), 7.32 (t, J = 7.9 Hz, 1H), 7.20 – 7.15 (m, 2H), 6.59 (d, J = 10.2 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.06 (d, J = 6.7 Hz, 2H), 1.19 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 196.4, 193.6, 158.6, 143.3, 138.3, 136.1, 132.5, 131.1, 130.3, 129.2 (2C), 128.4 (2C), 128.1, 126.5, 123.1, 45.0, 30.3, 20.1.

$[\alpha]_D^{20}$ -30.7 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇BrO₂Na]⁺ [M+Na]⁺: 379.0310; found: 379.0304.

Synthesis of (*S,E*)-4-methyl-6-oxo-6-(perfluorophenyl)-2-phenylhex-2-enal [(-)-7ai]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-bromo-1-(perfluorophenyl)ethan-1-one **6i** (57.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: 85:15) to afford product **7ai** (60.8 mg, 80% yield) as a yellowish oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IA-3 column (eluent: 91:9 CO₂/MeCN; flow rate 1.00 mL/min, λ = 255 nm. τ Minor = 2.18 min, τ Major = 2.32 min.

¹H-NMR (500 MHz, CDCl₃) δ 9.61 (s, 1H), 7.45 – 7.33 (m, 3H), 7.19 – 7.13 (m, 2H), 6.53 (d, J = 10.2, 1H), 3.34 – 3.22 (m, 1H), 2.98 (dt, J = 7.0, 1.4, 1.4, 2H), 1.22 (d, J = 6.7, 3H).

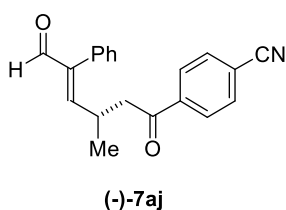
¹⁹F-NMR (471 MHz, CDCl₃) δ -140.63 – -141.10 (m), -148.61 (t, J = 20.7 Hz), -159.26 – -159.84 (m).

¹³C-NMR (126 MHz, CDCl₃) δ 193.4, 191.8, 157.0, 144.2 (d, ¹ $J_{C,F}$ = 255 Hz), 143.4, 142.8 (d, ¹ $J_{C,F}$ = 260 Hz), 137.5 (d, ¹ $J_{C,F}$ = 255 Hz), 132.2, 129.0 (2C), 128.4 (2C), 128.2, 114.3 (t, ² $J_{C,F}$ = 18 Hz), 51.2 (t, ⁴ $J_{C,F}$ = 2 Hz), 30.1, 20.0.

$[\alpha]_D^{20}$ -57.3 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₃F₅O₂Na]⁺ [M+Na]⁺: 391.0733; found: 391.0728.

Synthesis of (*S,E*)-4-(3-methyl-6-oxo-5-phenylhex-4-enoyl)benzonitrile [(-)-7aj]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 4-(2-chloroacetyl)benzonitrile **6j** (44.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7aj** (26.0 mg, 42% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IE column (eluent: 85:15 CO₂/MeCN; flow rate 1.00 mL/min, λ = 220 nm. τ Major = 3.54 min, τ Minor = 3.66 min.

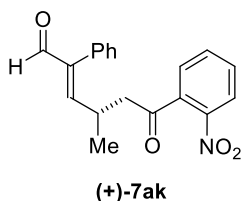
¹H-NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 7.94 – 7.83 (m, 2H), 7.77 – 7.63 (m, 2H), 7.43 – 7.31 (m, 3H), 7.19 – 7.10 (m, 2H), 6.56 (d, J = 10.1 Hz, 1H), 3.30 (dq, J = 10.1, 6.7 Hz, 1H), 3.12 – 3.01 (m, 2H), 1.19 (d, J = 6.7 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃) δ 196.34, 193.44, 158.00, 143.35, 139.26, 132.50, 132.44, 129.09, 128.40, 128.12, 117.76, 116.51, 45.21, 30.17, 19.98.

$[\alpha]_D^{20}$ -46.2 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₂₀H₁₇NO₂Na]⁺ [M+Na]⁺: 326.1157; found: 326.1151.

Synthesis of (*S,E*)-4-methyl-6-(2-nitrophenyl)-6-oxo-2-phenylhex-2-enal [(+)-7ak]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-(2-nitrophenyl)ethan-1-one **6k** (48.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ak** (27.8 mg, 43% yield) as a brownish oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 90:10 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ Major = 4.17 min, τ Minor = 4.31 min.

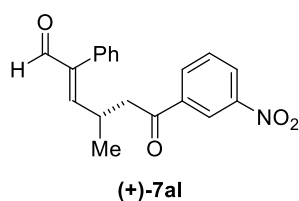
¹H-NMR (500 MHz, CDCl₃) δ 9.65 (s, 1H), 8.15 (dd, J = 8.1, 1.2 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.65 – 7.59 (m, 1H), 7.47 – 7.42 (m, 2H), 7.41 – 7.38 (m, 1H), 7.26 – 7.23 (m, 3H), 6.64 (d, J = 10.2 Hz, 1H), 3.40 – 3.29 (m, 1H), 2.99 – 2.85 (m, 2H), 1.23 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 199.8, 193.8, 158.4, 143.3, 137.6, 134.4, 132.6, 130.6, 129.3, 129.2 (2C), 128.4 (2C), 128.1, 127.4, 124.5, 49.0, 29.8, 19.9.

$[\alpha]_D^{20}$ +15.3 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇NO₄Na]⁺ [M+Na]⁺: 346.1055; found: 346.1050.

Synthesis of (*S,E*)-4-methyl-6-(3-nitrophenyl)-6-oxo-2-phenylhex-2-enal [(+)-7al]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-bromo-1-(3-nitrophenyl)ethan-1-one **6l** (48.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified

by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7al** (33.6 mg, 52% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 78:22 by UPC² analysis on a Daicel Chiralpak IG column (eluent: 85:15 CO₂/MeCN; flow rate 1.00 mL/min, λ = 220 nm. τ Major = 4.00 min, τ Minor = 4.12 min.

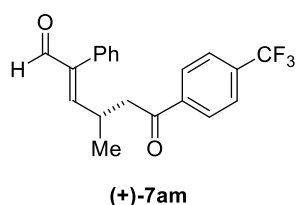
¹H-NMR (500 MHz, CDCl₃) δ 9.63 (s, 1H), 8.68 (t, J = 1.9 Hz, 1H), 8.42 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 8.18 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.19 – 7.15 (m, 2H), 6.60 (d, J = 10.2 Hz, 1H), 3.43 – 3.30 (m, 1H), 3.15 (d, J = 6.7 Hz, 2H), 1.24 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 195.5, 193.5, 158.0, 143.4, 137.7, 133.5, 132.4, 130.0, 129.7, 129.1 (2C), 128.4 (2C), 128.2, 127.6, 122.9, 45.2, 30.2, 20.1.

$[\alpha]_D^{20}$ +21.0 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇NO₄Na]⁺ [M+Na]⁺: 346.1055; found: 346.1050.

Synthesis of (*S,E*)-4-methyl-6-oxo-2-phenyl-6-(4-(trifluoromethyl)phenyl)hex-2-enal [(+)-7am]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-chloro-1-(4-(trifluoromethyl)phenyl)ethan-1-one **6m** (44.2 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified

by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7am** (27.8 mg, 59% yield) as a brownish oil. The enantiomeric excess of the product was determined to be 81:19 by UPC² analysis on a Daicel Chiralpak OJ column (eluent: 90:10 CO₂/EtOH; flow rate 1.00 mL/min, λ = 250 nm. τ Major = 2.29 min, τ Minor = 2.83 min.

¹H-NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 7.94 – 7.88 (m, 2H), 7.74 – 7.65 (m, 2H), 7.40 – 7.31 (m, 3H), 7.11 – 7.17 (m, 2H), 6.57 (d, J = 10.1 Hz, 1H), 3.25 – 3.38 (m, 1H), 3.08 (d, J = 6.8 Hz, 2H), 1.19 (d, J = 6.7 Hz, 3H).

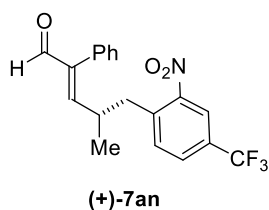
¹⁹F-NMR (376 MHz, CDCl₃) δ -63.27

¹³C-NMR (126 MHz, CDCl₃) δ 196.8, 193.5, 158.2, 143.4, 139.1, 134.6 (q, J = 32.7 Hz), 132.5, 129.1, 128.4, 128.4, 128.1, 125.8 (q, J = 3.8 Hz), 123.5 (q, J = 272.8 Hz), 45.3, 30.3, 20.0.

$[\alpha]_D^{20}$ +58.7 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₇NO₄Na]⁺ [M+Na]⁺: 346.1055; found: 346.1050.

Synthesis of (*S,E*)-4-methyl-5-(2-nitro-4-(trifluoromethyl)phenyl)-2-phenylpent-2-enal [(+)-7an]



Synthesized according to the general procedure A using phenylpent-2-enal **1a** (0.6 mmol, 96 mg, 3 equiv.), 1-(bromomethyl)-2-nitro-4-(trifluoromethyl)benzene **6n** (56.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent:

hexane/EtOAc 8:2) to afford product **7an** (29.1 mg, 41% yield) as a pale orange oil. The enantiomeric excess of the product was determined after reduction to the corresponding alcohol by adding 2 eq. of NaBH₄ to a 1:1=MeOH:DCM solution of the product (cooled at 0°C through ice bath). The enantiomeric ratio of the corresponding alcohol was measured to be 76:24 by UPC² analysis on a Daicel Chiralpak IA-3 column (eluent: 90:10 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ Major = 2.87 min, τ Minor = 3.12 min.

¹H-NMR (500 MHz, CDCl₃) δ 9.58 (s, 1H), 8.11 – 8.08 (m, 1H), 7.70 – 7.63 (m, 1H), 7.34 – 7.21 (m, 4H), 6.67 (dd, J = 8.0, 1.6 Hz, 2H), 6.50 (d, J = 10.4 Hz, 1H), 3.19 (dd, J = 12.8, 4.6 Hz, 1H), 3.14 – 3.06 (m, 1H), 3.02 (dd, J = 12.8, 9.3 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H).

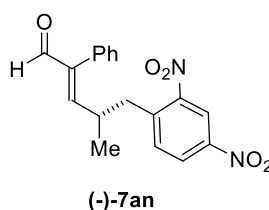
¹⁹F-NMR (471 MHz, CDCl₃) δ -62.89.

¹³C-NMR (126 MHz, CDCl₃) δ 193.2, 157.2, 144.2, 138.3, 133.4, 131.9, 130.4 (q, $^4J_{C,F}$ = 34 Hz), 129.1 (q, $^3J_{C,F}$ = 4 Hz), 128.8 (d, $^2J_{C,F}$ = 80 Hz), 128.7 (2C), 128.2 (2C), 128.1, 122.7 (q, $^1J_{C,F}$ = 273 Hz), 122.2 (d, $^3J_{C,F}$ = 4 Hz), 39.4, 35.2, 20.4.

$[\alpha]_D^{20}$ +69.8 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₉H₁₆F₃NO₃Na]⁺ [M+Na]⁺: 386.0979; found: 386.0974.

Synthesis of (*S,E*)-5-(2,4-dinitrophenyl)-4-methyl-2-phenylpent-2-enal [(-)-7ao]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 1-(chloromethyl)-2,4-dinitrobenzene **6o** (52.2 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford

product **7ao** (34.7 mg, 51% yield) as an orange oil. The enantiomeric excess of the product was determined to be 76:24 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 90:10 CO₂/IPA; flow rate 1.00 mL/min, λ = 255 nm. τ Major = 5.36 min, τ Minor = 5.38 min.

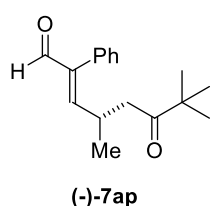
¹H-NMR (500 MHz, CDCl₃) δ 9.58 (s, 1H), 8.67 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 8.5, 2.4 Hz, 1H), 7.38 – 7.22 (m, 5H), 6.77 – 6.71 (m, 2H), 6.50 (d, J = 10.2 Hz, 1H), 3.22 (1/2 ABq, J = 12.7, 4.7 Hz, 1H), 3.18 – 3.10 (m, 1H), 3.07 (1/2 ABq, J = 12.7, 9.0 Hz, 1H), 1.29 (d, J = 6.4 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 193.0, 156.6, 149.2, 146.6, 144.2, 141.2, 133.7, 131.9, 128.7 (2C), 128.3 (2C), 128.2, 126.6, 120.3, 39.4, 35.1, 20.5.

$[\alpha]_D^{20}$ -91.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₈H₁₆N₂O₅Na]⁺ [M+Na]⁺: 363.0957; found: 363.0961.

Synthesis of (*S,E*)-4,7,7-trimethyl-6-oxo-2-phenyloct-2-enal [(-)-7ap]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 1-chloro-3,3-dimethylbutan-2-one **6p** (35.8 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to afford product **7ap** (13.0 mg, 25% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 87:13 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 93:7 CO₂/MeCN; flow rate 1.00 mL/min, λ = 250 nm. τ Minor = 2.73 min, τ Major = 2.85 min.

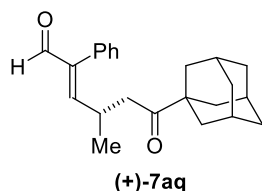
¹H-NMR (500 MHz, CDCl₃) δ 9.60 (s, 1H), 7.46 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.23 – 7.19 (m, 2H), 6.53 (d, J = 10.2 Hz, 1H), 3.25 – 3.12 (m, 1H), 2.61 (ABq, J = 17.3, 6.5 Hz, 2H), 1.12 (s, 9H), 1.07 (d, J = 6.6 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 213.3, 193.9, 159.7, 142.9, 132.6, 129.2 (2C), 128.4 (2C), 128.0, 42.8, 31.6, 29.7, 26.2, 19.9.

$[\alpha]_D^{20}$ -11.2 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₇H₂₂O₂Na]⁺ [M+Na]⁺: 281.1518; found: 281.1512.

Synthesis of (*S,E*)-6-((3*R*,5*R*,7*R*)-adamantan-1-yl)-4-methyl-6-oxo-2-phenylhex-2-enal [(+)-7aq]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 1-((3*R*,5*R*,7*R*)-adamantan-1-yl)-2-bromoethan-1-one **6q** (51.4 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to

afford product **7aq** (17 mg, 41% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 89:11 by UPC² analysis on a Daicel Chiralpak OJ column (eluent: 90:10 CO₂/MeCN; flow rate 1.00 mL/min, λ = 220 nm. τ Minor = 2.43 min, τ Major = 2.90 min.

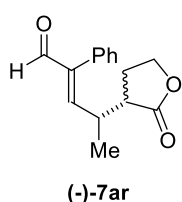
¹H-NMR (500 MHz, CDCl₃) δ 9.59 (s, 1H), 7.45 – 7.40 (m, 2H), 7.38 – 7.33 (m, 1H), 7.24 – 7.19 (m, 2H), 6.52 (d, J = 10.2 Hz, 1H), 3.23 – 3.11 (m, 1H), 2.57 (ABq, J = 17.2, 6.5 Hz, 2H), 2.09 – 2.01 (m, 2H), 1.79 – 1.74 (m, 8H), 1.71 – 1.65 (m, 3H), 1.58 (s, 2H), 1.06 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 213.1, 193.9, 160.0, 142.8, 132.7, 129.2 (2C), 128.3 (2C), 128.0, 42.4, 38.1, 36.5, 29.6, 27.9, 20.0.

$[\alpha]_D^{20}$ +23.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₂₃H₂₈O₂Na]⁺ [M+Na]⁺: 359.1987; found: 359.1982.

Synthesis of (*E*)-4-(2-oxotetrahydrofuran-3-yl)-2-phenylpent-2-enal [(*-*)-7ar]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 3-bromodihydrofuran-2(3*H*)-one **6r** (33.0 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.).

The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ar** as a mixture 1.2:1 of the two diastereoisomers (20.0 mg, 41% yield) as a colorless oil. The enantiomeric excess of the diastereoisomeric products was determined to be 91:9 for diastereoisomer 1 and 86:14 for diastereoisomer 2 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 87:13 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ Major_{dias1} = 4.91 min, τ Minor_{dias1} = 5.04 min; τ Minor_{dias2} = 5.39 min, τ Major_{dias2} = 5.83 min.

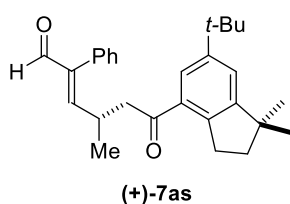
¹H-NMR (500 MHz, CDCl₃) δ 9.66 (s, 1H_{dias1} + 1H_{dias2}), 7.46 – 7.35 (m, 3H_{dias1} + 3H_{dias2}), 7.18 – 7.13 (m, 2H_{dias1} + 2H_{dias2}), 6.75 (d, J = 10.6 Hz, 1H_{dias1}), 6.64 (d, J = 10.5 Hz, 1H_{dias2}), 4.33 (td, J = 8.9, 8.8, 2.8 Hz, 1H_{dias1}), 4.28 – 4.22 (m, 1H_{dias2}), 4.22 – 4.16 (m, 1H_{dias1} + 1H_{dias2}), 3.10 – 2.97 (m, 1H_{dias1} + 1H_{dias2}), 2.70 – 2.58 (m, 1H_{dias1} + 1H_{dias2}), 2.38 – 2.27 (m, 1H_{dias1} + 1H_{dias2}), 2.11 – 1.95 (m, 1H_{dias1} + 1H_{dias2}), 1.29 (d, J = 6.7 Hz, 1H_{dias1}), 1.21 (d, J = 6.9 Hz, 1H_{dias2}).

¹³C-NMR (126 MHz, CDCl₃) [signals of both diastereoisomers] δ 193.5, 193.4, 176.9, 176.8, 155.8, 155.2, 144.3, 144.0, 132.4, 132.3, 129.1 (4C), 128.6 (4C), 128.3, 128.2, 66.3 (2C), 43.9, 43.4, 34.0, 33.9, 26.5, 26.0, 17.6, 17.0.

$[\alpha]_D^{20}$ -8.2 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₅H₁₆O₃Na]⁺ [M+Na]⁺: 267.0997; found: 267.0992.

Synthesis of (*S,E*)-6-(6-(*tert*-butyl)-1,1-dimethyl-2,3-dihydro-1*H*-inden-4-yl)-4-methyl-6-oxo-2-phenylhex-2-enal [(*+*)-7as]



Synthesized according to the general procedure A using phenylpent-2-enal **2a** (0.6 mmol, 96 mg, 3 equiv.), 2-bromo-1-(6-(*tert*-butyl)-1,1-dimethyl-2,3-dihydro-1*H*-inden-4-yl)ethan-1-one **6s** (64.6 mg, 0.2 mmol), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to afford product **7as** (40.0 mg, 50% yield) as a pale-yellow oil.

The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IA-3 column (eluent: 92:8 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ Major = 3.82 min, τ Minor = 3.73 min.

¹H-NMR (500 MHz, CDCl₃) δ 9.59 (s, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.14 – 7.07 (m, 2H), 6.61 (d, J = 10.3 Hz, 1H), 3.31 (dq, J = 10.3, 6.7 Hz, 1H), 3.11 (m, 2H), 3.05 (m, 2H), 1.91 (t, J = 7.2 Hz, 2H), 1.32 (s, 9H), 1.25 (d, J = 3.3 Hz, 6H), 1.17 (d, J = 6.7 Hz, 3H).

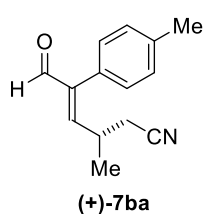
¹³C-NMR (126 MHz, CDCl₃) δ 199.9, 193.8, 159.4, 154.6, 149.9, 142.8, 141.2, 133.2, 132.5, 129.1, 128.3, 127.9, 123.8, 123.4, 46.6, 43.4, 41.4, 34.7, 31.5, 30.8, 30.6, 28.7, 28.7, 20.2.

$[\alpha]_D^{20}$ +51.4 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for $[C_{28}H_{34}O_2Na]^+$ $[M+Na]^+$: 425.2456; found: 425.2451.

Scope of enals

Synthesis of (*S,E*)-3-methyl-6-oxo-5-(*p*-tolyl)hex-4-enenitrile [(+)-7ba]



Synthesized according to the general procedure A using (*E*)-2-(*p*-tolyl)pent-2-enal **2b** (0.6 mmol, 104 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to afford product **7ba** (17.1 mg, 40% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 80:20 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 90:10 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ_{Minor} = 4.02 min, τ_{Major} = 4.18 min.

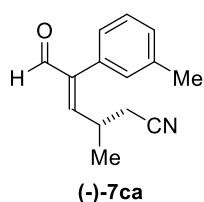
¹H-NMR (500 MHz, CDCl₃) δ 9.66 (s, 1H), 7.25 (d, J = 7.7 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.51 (d, J = 10.3 Hz, 1H), 3.14 – 3.01 (m, 1H), 2.44 (d, J = 6.3 Hz, 2H), 2.40 (s, 3H), 1.28 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 193.3, 153.8, 144.6, 138.4, 129.4 (2C), 128.9 (3C), 117.4, 30.6, 24.1, 21.3, 19.7.

$[\alpha]_D^{20}$ +45.0 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for $[C_{14}H_{15}NONa]^+$ $[M+Na]^+$: 236.1051; found: 236.1046.

Synthesis of (*R,E*)-3-methyl-6-oxo-5-(*m*-tolyl)hex-4-enenitrile [(–)-7ca]



Synthesized according to the general procedure A using (*E*)-2-(*m*-tolyl)pent-2-enal **2c** (0.6 mmol, 104 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to afford product **7ca** (13.6 mg, 40% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 80:20 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 90:10 CO₂/MeCN; flow rate 1.00 mL/min, λ = 225 nm. τ_{Minor} = 3.08 min, τ_{Major} = 3.20 min.

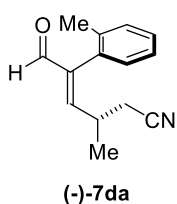
¹H-NMR (500 MHz, CDCl₃) δ 9.66 (s, 1H), 7.37 – 7.31 (m, 1H), 7.24 – 7.20 (m, 1H), 6.98 – 6.92 (m, 2H), 6.52 (d, J = 10.3 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.45 (d, J = 6.3 Hz, 2H), 2.42 – 2.36 (m, 3H), 1.29 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 193.1, 153.8, 144.9, 138.4, 131.9, 129.6, 129.3, 128.5, 126.7, 126.0, 117.4, 30.6, 24.1, 19.7.

$[\alpha]_D^{20}$ -19.7 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for $[C_{14}H_{15}NONa]^+$ $[M+Na]^+$: 236.1051; found: 236.1041.

Synthesis of (*R,E*)-3-methyl-6-oxo-5-(*o*-tolyl)hex-4-enenitrile [(-)-7da]



Synthesized according to the general procedure A using (*E*)-2-(*o*-tolyl)pent-2-enal **2d** (0.6 mmol, 104 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1) to afford product **7da** as a mixture 1:1 of the two rotamers (21.3 mg, 50% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 80:20 for both rotamers by UPC² analysis on a Daicel Chiralpak IC column (eluent: 90:10 CO₂/MeCN; flow rate 1.00 mL/min, λ = 225 nm. $\tau_{\text{Minor rot1}}$ = 3.21 min, $\tau_{\text{Major rot1}}$ = 3.38 min; $\tau_{\text{Minor rot2}}$ = 3.71 min, $\tau_{\text{Major rot2}}$ = 3.89 min).

¹H-NMR (500 MHz, CDCl₃, 25 °C) δ 9.70 – 9.66 (m, 1H_{rot1} + 1H_{rot2}), 7.35 – 7.17 (m, 3H_{rot1} + 3H_{rot2}), 7.02 (d, J = 7.4 Hz, 1H_{rot1}), 6.94 (d, J = 7.5 Hz, 1H_{rot2}), 6.69 – 6.63 (m, 1H_{rot1} + 1H_{rot2}), 2.85 – 2.74 (m, 1H_{rot1} + 1H_{rot2}), 2.45 (d, J = 6.3 Hz, 2H_{rot1}), 2.39 (d, J = 6.3 Hz, 2H_{rot2}), 2.16 (s, 3H_{rot1}), 2.12 (s, 3H_{rot2}), 1.28 (d, J = 6.8 Hz, 3H_{rot1}), 1.20 (d, J = 6.7 Hz, 3H_{rot2}).

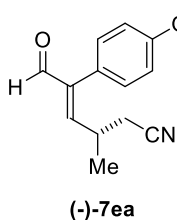
¹H-NMR (500 MHz, CDCl₃, 60 °C) δ 9.67 (s, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.18 (m, 1H), 7.03 – 6.93 (m, 1H), 6.63 (d, J = 9.9 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.44 – 2.36 (m, 2H), 2.15 (s, 3H), 1.29 – 1.19 (m, 3H).

¹³C-NMR (101 MHz, CDCl₃) [signals of both rotamers] δ 192.7, 192.6, 154.3, 154.2, 145.5 (2C), 136.4, 136.1, 132.0 (2C), 130.5, 130.3, 129.2, 129.0, 128.8 (2C) 126.1, 126.0, 117.4 (2C), 31.0, 30.9, 24.1, 23.7, 19.9, 19.8, 19.7, 19.6.

$[\alpha]_D^{20}$ -44.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₄H₁₅NOH]⁺ [M+H]⁺: 214.1231; found: 214.1224.

Synthesis of (*R,E*)-5-(4-methoxyphenyl)-3-methyl-6-oxohex-4-enenitrile [(-)-7ea]



Synthesized according to the general procedure A using (*E*)-2-(4-methoxyphenyl)pent-2-enal **2e** (0.6 mmol, 114 mg, 3 equiv.), α -chloroacetonitrile **2a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7ea** (28.4 mg, 62% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 80:20 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 85:15 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ_{Minor} = 4.30 min, τ_{Major} = 4.47 min).

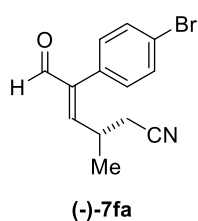
¹H-NMR (500 MHz, CDCl₃) δ 9.66 (s, 1H), 7.10 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.49 (d, J = 10.3 Hz, 1H), 3.85 (s, 3H), 3.15 – 3.05 (m, 1H), 2.45 (d, J = 6.3 Hz, 2H), 1.29 (d, J = 6.8 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 193.4, 159.7, 153.8, 144.2, 130.3 (2C), 123.9, 117.4, 114.2 (2C), 55.3, 30.7, 24.1, 19.7.

$[\alpha]_D^{20}$ -96.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₄H₁₅NO₂Na]⁺ [M+Na]⁺: 252.1000; found: 252.0995.

Synthesis of (*S,E*)-5-(4-bromophenyl)-3-methyl-6-oxohex-4-enenitrile [(*-*)-7fa]



Synthesized according to the general procedure A using (*E*)-2-(4-bromophenyl)pent-2-enal **2f** (0.6 mmol, 143 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7fa** (20.0 mg, 36% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 82:18 by UPC² analysis on a Daicel Chiralpak IC column (eluent: 80:20 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ Minor = 4.09 min, τ Major = 4.29 min).

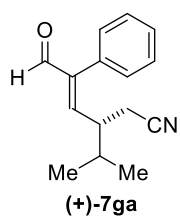
¹H-NMR (500 MHz, CDCl₃) δ 9.66 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.56 (d, J = 10.4 Hz, 1H), 3.13 – 2.93 (m, 1H), 2.46 (d, J = 6.0 Hz, 2H), 1.28 (d, J = 6.7 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 192.5, 154.4, 143.8, 131.9 (2C), 130.8 (2C), 130.7, 123.0, 117.2, 30.8, 24.1, 19.7.

$[\alpha]_D^{20}$ -33.9 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₃H₁₂BrNONa]⁺ [M+Na]⁺: 299.9999; found: 299.9987.

Synthesis of (*S,E*)-3-isopropyl-6-oxo-5-phenylhex-4-enenitrile [(*+*)-7ga]



Synthesized according to the general procedure A using (*E*)-5-methyl-2-phenylhex-2-enal **2g** (0.6 mmol, 113 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ga** (19.1 mg, 42% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IB column (eluent: 90:10 CO₂/MeCN; flow rate 1 mL/min, λ = 320 nm. τ Minor = 2.61 min, τ Major = 2.73 min).

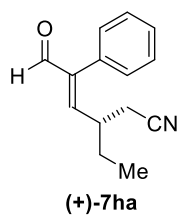
¹H-NMR (500 MHz, CDCl₃) δ 9.71 (s, 1H), 7.55 – 7.31 (m, 3H), 7.20 – 7.13 (m, 2H), 6.59 (d, J = 10.8 Hz, 1H), 2.75 – 2.62 (m, 1H), 2.52 – 2.49 (m, 2H), 1.96 – 1.83 (m, 1H), 0.95 (t, J = 7.0 Hz, 6H).

¹³C-NMR (126 MHz, CDCl₃) δ 192.9, 152.3, 146.8, 132.1, 129.2 (2C), 128.6 (2C), 128.4, 117.6, 41.7, 31.4, 20.7, 20.1, 19.6.

$[\alpha]_D^{20}$ +35.3 (c = 1 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₅H₁₇NONa]⁺ [M+Na]⁺: 250.1208; found: 250.1202.

Synthesis of (*S,E*)-3-ethyl-6-oxo-5-phenylhex-4-enenitrile [(+)-7ha]



Synthesized according to the general procedure A using (*E*)-2-phenylhex-2-enal **2h** (0.6 mmol, 104 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A5** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ha** (12.8 mg, 30% yield) as a colorless oil. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IB column (eluent: 90:10 CO₂/MeCN; flow rate 1.00 mL/min, λ = 250 nm. τ_{Minor} = 2.50 min, τ_{Major} = 2.59 min).

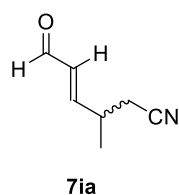
¹H-NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 7.48 – 7.38 (m, 3H), 7.20 – 7.13 (m, 2H), 6.51 (d, J = 10.6 Hz, 1H), 2.89 – 2.77 (m, 1H), 2.47 (d, J = 6.2 Hz, 2H), 1.75 – 1.59 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 192.9, 153.2, 146.2, 132.0, 129.1, 128.6, 128.4, 117.4, 37.0, 27.1, 22.3, 11.4.

$[\alpha]_{\text{D}}^{20}$ +12.1 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₄H₁₅NOH]⁺ [M+H]⁺: 214.1226; found: 214.1226.

Synthesis of (*rac*)-(*E*)-6-methyl-3-(4-oxobut-2-en-2-yl)hept-5-enenitrile [7ia]



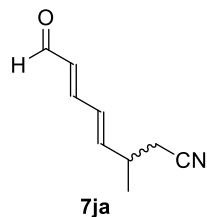
Synthesized according to the general procedure A using *trans*-2-Pentenal **2i** (0.6 mmol, 50.5 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A9** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 7:3) to afford product **7ia** (14.5 mg, 59% yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 9.56 (d, J = 7.6 Hz, 1H), 6.76 (dd, J = 15.8, 6.9 Hz, 1H), 6.18 (ddd, J = 15.8, 7.6, 1.3 Hz, 1H), 2.89 (m, 1H), 2.51 (dd, J = 6.5, 1.4 Hz, 2H), 1.31 (d, J = 6.8 Hz, 3H).

¹³C-NMR (126 MHz, CDCl₃) δ 193.2, 156.8, 132.7, 117.3, 33.4, 23.6, 18.6.

HRMS (ESI) m/z calculated for [C₇H₁₀NO]⁺ [M+H]⁺: 124.0762; found: 124.0757.

Synthesis of (*rac*)-(4*E*,6*E*)-3-methyl-8-oxoocta-4,6-dienenitrile [7ja]



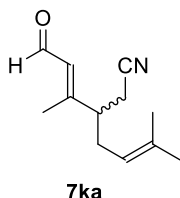
Synthesized according to the general procedure A using 2,4-Heptadienal **2j** (0.6 mmol, 66 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μ L), aminocatalyst **A9** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μ L, 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 85:15) to afford product **7ja** (13 mg, 43% yield) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 9.57 (d, J = 7.9 Hz, 1H), 7.13 – 7.02 (m, 1H), 6.47 – 6.34 (m, 1H), 6.17 (dt, J = 15.2, 7.5 Hz, 2H), 2.77 (m, 1H), 2.45 (d, J = 6.5 Hz, 2H), 1.27 (d, J = 6.8 Hz, 3H).

^{13}C -NMR (126 MHz, CDCl_3) δ 193.5, 150.8, 145.6, 132.0, 129.0, 117.7, 33.9, 24.3, 19.2.

HRMS (ESI) m/z calculated for $[\text{C}_9\text{H}_{10}\text{NO}]^+ [\text{M}]^+$: 148.0762; found: 148.0757.

Synthesis of (*rac*)-(*E*)-6-methyl-3-(4-oxobut-2-en-2-yl)hept-5-enenitrile [7ka]



Synthesized according to the general procedure A using *Citral* **2k** (0.6 mmol, 91 mg, 3 equiv.), α -chloroacetonitrile **6a** (0.2 mmol, 12.6 μL), aminocatalyst **A9** (0.04 mmol, 25.6 mg, 0.2 equiv.), dithiocarbamate catalyst **B1** (0.04 mmol, 12.4 mg, 0.2 equiv.) and 2,6-lutidine (0.24 mmol, 25.5 μL , 1.2 equiv.). The crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford product **7ka** (21 mg, 55% yield) as a yellowish oil.

^1H -NMR (500 MHz, CDCl_3) δ 10.04 (d, $J = 7.5$ Hz, 1H), 5.92 (d, $J = 7.5$ Hz, 1H), 5.00 – 4.94 (m, 1H), 2.62 – 2.41 (m, 3H), 2.29 (t, $J = 6.9$ Hz, 2H), 2.19 (d, $J = 1.2$ Hz, 3H), 1.70 (s, 3H), 1.62 (s, 3H).

^{13}C -NMR (126 MHz, CDCl_3) δ 190.8, 160.8, 136.1, 128.6, 119.2, 117.9, 45.9, 31.1, 25.9, 20.8, 18.11, 15.6.

HRMS (ESI) m/z calculated for $[\text{C}_{15}\text{H}_{17}\text{NONa}]^+ [\text{M}+\text{Na}]^+$: 146.0581; found: 146.0585.

4.5.5 Scaled-up model reaction

Experimental set-up

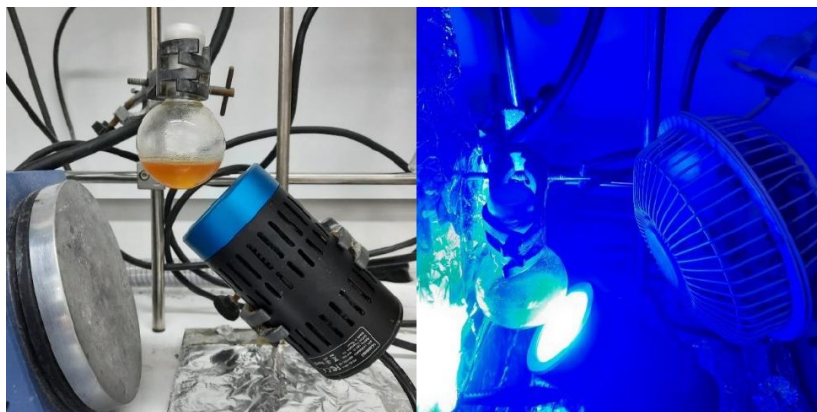
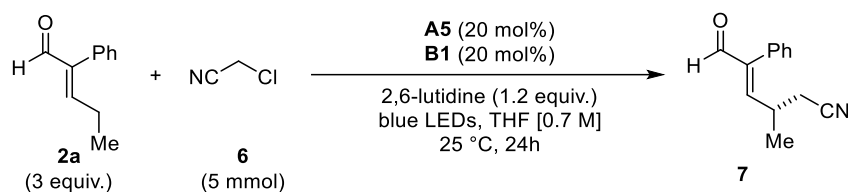


Figure 6 Set-up employed for the scaled-up reaction

The experimental setup for the scaled-up reaction consisted of 50ml round bottom flask placed on a stirring plate. The light source was provided by a 456nm Kessil Lamp placed under the reactor; to avoid over-heating the reactor was cooled using a cooling fan placed on the side of the reactor as illustrated in Figure 6.

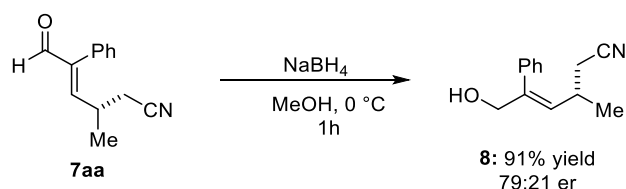
Synthesis of (*S,E*)-3-methyl-6-oxo-5-phenylhex-4-enenitrile [(+)-7aa]



In a 50ml round-bottom flask charged with a stirring bar were added sequentially the aminocatalyst **A5** (1 mmol, 640 mg, 0.2 eq.), THF (3.5 mL) and phenylpent-2-enal **2a** (15 mmol, 2.40 mL, 3 eq.). The reaction was stirred for 5 minutes before the addition of 2,6- lutidine (6 mmol, 395 μ L, 1.2 eq.) and α -chloroacetonitrile **6a** (5 mmol, 317 μ L, 1 eq.). Finally, dithiocarbamate **B1** (1 mmol, 310 mg, 0.2 eq.) was added and the reactor was closed with a rubber septum. The solution was degassed through argon bubbling for 5 minutes while stirring and then the reactor capped with a septum and sealed with parafilm. A 456 nm Kessil Lamp was placed approximately 3 cm from the reactor and switched on at 100% intensity. The solution was irradiated under vigorous stirring overnight. After 24 hours the lamp was turned off and the solvent was removed through rotary evaporation. The product was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 8:2) to afford the product **7aa** as a pale-orange oil in a 67% yield (average yield on 2 different runs). The enantiomeric excess of the product was determined to be 80:20 by UPC² analysis on a Daicel Chiralpak IA- 3 column (eluent: CO₂/IPA = 90:10; flow rate 1 mL/min, λ = 300 nm. τ_{Major} = 3.54 min, τ_{Minor} = 3.66 min.

4.5.6 Synthetic elaborations of product 7aa

Synthesis of (*S,E*)-6-hydroxy-3-methyl-5-phenylhex-4-enenitrile [(−)-8]



In a 10 mL round bottom flask charged with a magnetic stirring bar the substrate **7aa** (60.0 mg, 0.3 mmol) was dissolved in MeOH (0.5M). The solution was placed in an ice bath and cooled to 0°C before the addition of NaBH₄ (34.0 mg, 0.9 mmol). The reaction was stirred at 0°C for 1 hour and then removed from the ice bath. Distilled water (2ml) was then slowly added to the solution while stirring. The organic phase was extracted two times with EtOAc and dried over anhydrous Magnesium Sulphate. After filtration, the solution was concentrated under vacuum to afford the title compound **5a** in 91% yield as pale-yellow oil. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IA- 3 column (eluent: 80:20 CO₂/IPA; flow rate 1.00 mL/min, λ = 220 nm. τ_{Major} = 3.54 min, τ_{Mjnor} = 3.66 min.

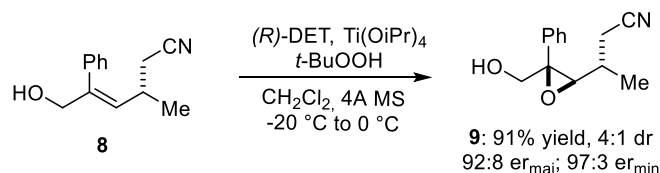
¹H-NMR (500 MHz, CDCl₃) δ 7.39 (m, 2H), 7.33 (m, 1H), 7.19 (m, 2H), 5.58 (d, J = 10.1 Hz, 1H), 4.31 (d, J = 1.4 Hz, 2H), 2.65 (m, 1H), 2.27 (d, J = 6.6 Hz, 2H), 1.13 (d, J = 6.7 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃) δ 142.8, 137.9, 129.2, 128.9, 128.5, 127.9, 118.6, 67.6, 30.2, 25.2, 20.8.

$[\alpha]_D^{20}$ -17.2 ($c = 0.5$ g/100 mL, CHCl_3)

HRMS (ESI) m/z calculated for $[\text{C}_{14}\text{H}_{16}\text{NO}]^+ [\text{M}+\text{H}]^+$: 202,1232; found: 202,1226.

Synthesis of (*S*)-3-((2*R*,3*R*)-3-(hydroxymethyl)-3-phenyloxiran-2-yl)butanenitrile [(+)-**9**]



Diethyl L-(+)-tartrate (7.9 μL , 0.046 mmol) and titanium tetraisopropoxide (12 μL , 0.04 mmol) were added sequentially to a mixture of powdered activated 4 Å molecular sieves and dichloromethane (200 mL) at $0\text{ }^\circ\text{C}$ with stirring. The reaction mixture was cooled to $-20\text{ }^\circ\text{C}$, tert-butyl hydroperoxide (6 M in hexane, 87 μL , 0.520 mmol) was added dropwise over 0.2 h, and the resulting mixture was stirred at $-20\text{ }^\circ\text{C}$ for 1 h. A 1.1M solution of **8** (40.25 mg, 0.200 mmol) in dry DCM was then added dropwise over 0.2 h. After stirring for 15 h at $-20\text{ }^\circ\text{C}$, the reaction mixture was poured into 7ml of a freshly prepared ferrous sulfate solution (66 g of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and 22 g of citric acid in 200 mL of H_2O) at $-20\text{ }^\circ\text{C}$ and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O . The combined organic layer was dried, filtered, and concentrated in vacuo. To the residue in Et_2O (300 mL) was added 30% NaOH (3 mL), and the resultant mixture was stirred at $0\text{ }^\circ\text{C}$ for 1 h. The two phases were separated, and the aqueous phase was extracted twice with Et_2O . The combined organic phases were washed with brine, dried, filtered, and then concentrated in vacuo. The product was purified by Flash Chromatography on silica gel (7:3 Hex:EtOAc) to afford the title compound **9** as a colorless oil in 79% yield (8:2 mixture of both diastereoisomers). The enantiomeric excess of the two diastereoisomers of the product was determined to be 97:3 and 92:8 by UPC2 analysis on a Daicel Chiralpak IE column (eluent: 80:20 CO_2/IPA ; flow rate 1.00 mL/min, $\lambda = 250$ nm $\tau_{\text{Major}}^{\text{dias1}} = 4.13$ min, $\tau_{\text{Minor}}^{\text{dias1}} = 4.06$ min; $\tau_{\text{Minor}}^{\text{dias2}} = 4.32$ min, $\tau_{\text{Major}}^{\text{dias2}} = 4.40$ min).

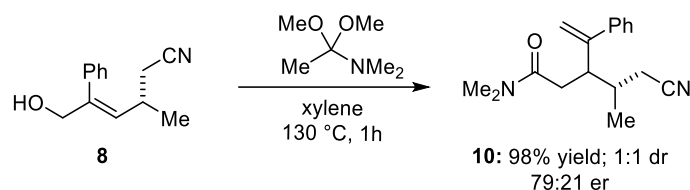
^1H -NMR (500 MHz, CDCl_3) δ 7.40 – 7.32 (m, 10H $_{\text{diast1}} + \text{diast2}$), 4.00 (d, $J = 1.7$ Hz, 1H $_{\text{diast1}}$), 3.97 (d, $J = 1.3$ Hz, 1H $_{\text{diast2}}$), 3.26 (m, 4H $_{\text{diast1}} + \text{diast2}$) 1.43 – 1.24 (m, 2H $_{\text{diast1}} + \text{diast2}$) 1.21 (d, $J = 6.7$ Hz, 3H $_{\text{diast1}}$), 1.00 (d, $J = 6.9$ Hz, 3H $_{\text{diast2}}$).

^{13}C -NMR (126 MHz, CDCl_3) [signals of both diastereoisomers] δ 134.8, 134.6, 128.9, 128.6, 128.6, 128.3, 126.7, 126.6, 117.9, 117.5, 67.6, 66.9, 66.6, 64.1, 63.6, 63.1, 29.9, 29.0, 22.1, 20.8, 17.0, 15.0.

$[\alpha]_D^{20}$ +40.9 ($c = 0.5$ g/100 mL, CHCl_3)

HRMS (ESI) m/z calculated for $[\text{C}_{20}\text{H}_{23}\text{N}_2]^+ [\text{M}+\text{H}]^+$: 291.1861; found: 291.1856

Synthesis of 3-((*S*)-1-cyanopropan-2-yl)-*N,N*-dimethyl-4-phenylpent-4-enamide



In an oven dried Schlenk tube charged with a magnetic stirring bar, the alcohol **8** (2 eq.) was dissolved in Xylene (0.3M). *N,N*-dimethylacetamide dimethyl acetal (3 eq.) was subsequently added and the solution was then stirred for 1 hour at 130 °C. After the indicated time the starting material was totally consumed (checked by TLC) and the reaction was removed from the oil bath. After the reaction cooled down the solution was concentrated through rotary evaporation and the product was purified by Flash Chromatography on silica gel (1:1 Hex:EtOAc) to afford the title compound **10** as a brownish oil in quantitative yield as a 1:1 mixture of diastereoisomers. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IE column (eluent: 90:10 CO₂/EtOH; flow rate 1.00 mL/min, λ = 250 nm. $\tau_{\text{Major diast1}}$ = 6.85 min, $\tau_{\text{Minor diast1}}$ = 7.12 min; $\tau_{\text{Minor diast2}}$ = 7.84 min, $\tau_{\text{Major diast2}}$ = 8.35 min.

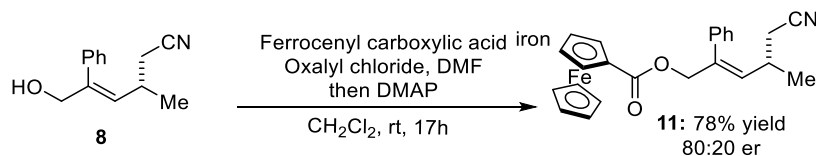
¹H-NMR (500 MHz, CDCl₃) δ 7.48 (m, 4H *diast1* + *diast2*), 7.34 (m, 6H *diast1* + *diast2*), 5.38 (s, 1H *diast1*), 5.34 (s, 1H *diast2*), 5.06 (s, 1H *diast1*), 4.99 (s, 1H *diast2*), 3.47 (m, 1H *diast2*), 3.37 (m, 1H *diast1*), 3.07 (s, 3H *diast2*), 3.03 (s, 3H *diast1*), 2.97 (s, 3H *diast2*), 2.94 (s, 3H *diast1*), 2.80-2.65 (m, 2H *diast1* + *diast2*), 2.60-2.00 (m, 8H *diast1* + *diast2*), 1.13 (d, J = 6.7 Hz, 3H *diast2*), 1.09 (d, J = 6.8 Hz, 3H *diast1*).

¹³C-NMR (126 MHz, CDCl₃) [signals of both diastereoisomers] δ 171.1, 171.0, 150.9, 150.2, 142.8, 142.4, 128.6, 128.5, 127.8, 126.9, 126.9, 119.3, 119.2, 113.7, 113.6, 44.5, 44.1, 37.4, 37.4, 35.7, 34.4, 34.3, 33.9, 33.4, 23.0, 22.0, 17.2, 17.0.

$[\alpha]_D^{20}$ -88.3 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₇H₂₃N₂O]⁺ [M+H]⁺: 271.1810; found: 271.1805

Synthesis of (*S,E*)-5-cyano-4-methyl-2-phenylpent-2-en-1-yl ferrocenylonate [(-)-**11**]



To a suspension of ferrocenecarboxylic acid (104 mg, 0.450 mmol) in DCM (1 mL) were added oxalyl chloride (0.036 mL, 0.420 mmol) and three drops of dry DMF at 0 °C. After the gas evolution ceased and the reaction mixture turned into a clear solution, it was stirred for 0.5 h at rt. Next, a solution of **8** (65 mg, 0.32 mmol) and DMAP (106 mg, 0.870 mmol) in DCM (1 mL) was added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched by adding a small amount of silica gel and concentrating to dryness. The crude product was purified by flash chromatography on silica gel (70:30 Hexane:EtOAc) to afford the title product **5d** as an orange oil in 78% yield. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on

a Daicel Chiralpak IB column (eluent: 85:15 CO₂/MeCN; flow rate 1.00 mL/min, λ = 250 nm. τ_{Minor} = 3.47 min, τ_{Major} = 3.67 min.

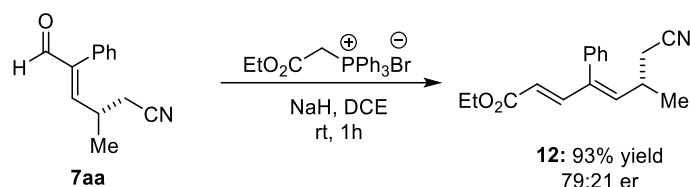
¹H-NMR (500 MHz, CDCl₃) δ 7.42 (m, 2H), 7.34 (m, 1H), 7.28 (m, 2H), 5.69 (d, J = 10.2 Hz, 1H), 4.89 (qd, J = 13.0, 1.1 Hz, 2H), 4.74 (bs, 2H), 4.28 (bs, 2H), 2.72 (m, 1H), 2.31 (d, J = 6.5 Hz, 2H), 1.16 (d, J = 6.7 Hz, 3H)

¹³C-NMR (101 MHz, CDCl₃) δ 171.4, 138.6, 137.6, 132.3, 128.8, 128.4, 128.0, 118.3, 71.6, 70.4, 69.9, 68.1, 30.2, 25.0, 20.6

$[\alpha]_{\text{D}}^{20}$ -54.7 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₂₄H₂₃NNaO₂Fe]⁺ [M+Na]⁺: 436.0975; found: 436.0970

Synthesis of ethyl (*S*,*2E*,*4Z*)-7-cyano-6-methyl-4-phenylhepta-2,4-dienoate [(+)-12]



In an oven dried Shlenk tube the Wittig reagent (2 eq.) was dissolved in DCE (0.1M respect to the substrate). Sodium Hydride (2.2 eq.) was subsequently added to the solution which was then stirred for 10 minutes. The substrate **7aa** was added and the reaction was stirred 1h. After total consumption of the starting material (checked by TLC) the reaction was quenched with water and the organic phase was extracted twice with EtOAc, dried over anhydrous MgSO₄ and concentrated by rotary evaporation. The product was purified by Flash Chromatography on silica gel (85:15 Hex:EtOAc) to afford the title compound **12** as a brownish oil in 93% yield. The enantiomeric excess of the product was determined to be 79:21 by UPC² analysis on a Daicel Chiralpak IG column (eluent: 90:10 CO₂/IPA; flow rate 1.00 mL/min, λ = 250 nm. τ_{Minor} = 5.31 min, τ_{Major} = 4.02 min.

¹H-NMR (500 MHz, CDCl₃) δ 7.47 (d, J = 15.6 Hz 1H), 7.41 (m, 2H), 7.36 (m, 1H), 7.11 (m, 2H), 5.92 (d, J = 10.2 Hz, 2H), 5.40 (d, J = 15.6 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.59 (m, 1H), 2.29 (d, J = 6.5 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H).

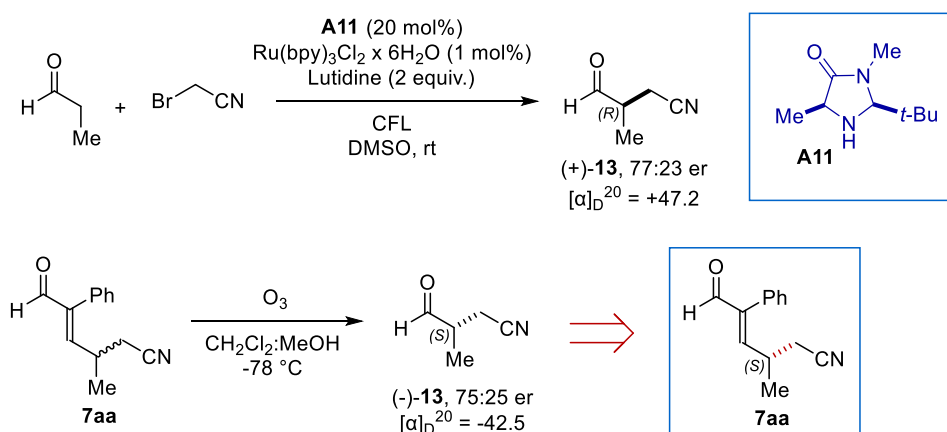
¹³C-NMR (101 MHz, CDCl₃) δ 167.0, 147.5, 141.8, 141.4, 135.8, 128.9, 128.9, 128.0, 121.5, 118.0, 60.5, 31.0, 24.6, 20.2, 14.4.

$[\alpha]_{\text{D}}^{20}$ +65.9 (c = 0.5 g/100 mL, CHCl₃)

HRMS (ESI) m/z calculated for [C₁₇H₁₉NO₂Na]⁺ [M+Na]⁺: 292.1313; found: 292.1883

4.5.7 Chromatograms of compounds **13** for the determination of the absolute configuration of products

The absolute configuration of products **7** was determined by correlation with compound **13**. In particular, the model product **7aa** was subjected to ozonolysis reaction to provide the corresponding α -branched aldehyde (-)-**13**, that possesses negative optical rotation equal to $[\alpha]_D^{20} = -42.5$ ($c = 1$ g/100 mL, CHCl_3). The same compound was obtained by subjecting propanal and α -bromo acetonitrile under MacMillan's conditions used for the α -cyanomethylation of aldehydes, in the presence of aminocatalyst **A11**.^{23b} In this previous work, compound **13** was not actually reported by MacMillan and co-workers; instead, the analogous product derived by octanal was reported, resulting in the (*R*)-configured enantiomer. An original sample of **13** was prepared under MacMillan's conditions and using the same catalyst **A11**, and the product in our hands gave an optical rotation of $[\alpha]_D^{20} = +47.2$ ($c = 1$ g/100 mL, CHCl_3), demonstrating, by correlation, that the stereocenter at the γ -carbon of the major enantiomer **7aa** is (*S*)-configured (Scheme 12). This result suggests that the radical-trapping enantio-determining step of our transformation should proceed through the attack by the (*Re*) prochiral face of the dienamine to the radical.



Scheme 13 Determination of the absolute configuration of products **7** by chemical correlation

In Figure 7 are reported the chromatograms related to aldehyde **13** obtained under MacMillan's reaction conditions^{23b} and upon ozonolysis reaction on model product **7aa**.

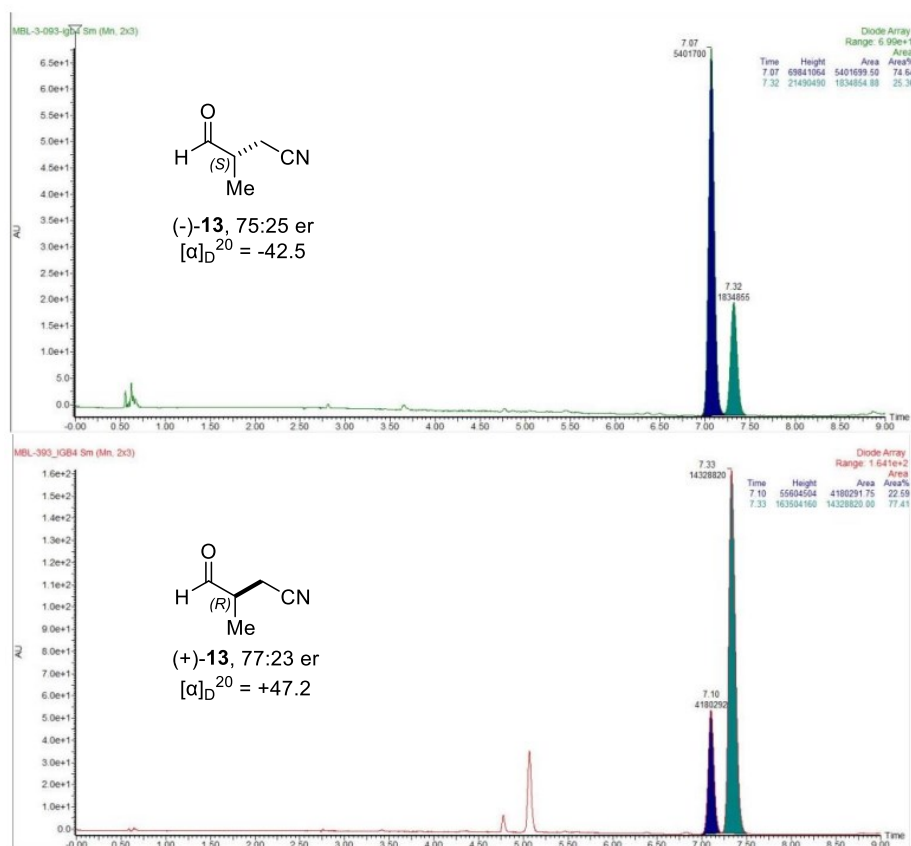


Figure 7 Upper chromatogram: **13** prepared through ozonolysis of **7aa**, prepared according to the presented γ -alkylation protocol of enals. Lower chromatogram: **13** synthesized according to the MacMillan protocol

4.5.8 Quantum Yield Measurement

A ferrioxalate actinometer solution was prepared by following the Hammond variation of the Hatchard and Parker procedure outlined in the Handbook of Photochemistry.²⁷ The ferrioxalate actinometer solution measures the decomposition of ferric ions to ferrous ions, which are complexed by 1,10-phenanthroline and monitored by UV/Vis absorbance at 510 nm. The moles of iron-phenanthroline complex formed are related to moles of photons absorbed.

The following solutions were prepared and stored in a dark laboratory (red light):

1. Potassium ferrioxalate solution: 294.8 mg of potassium ferrioxalate (commercially available from Alfa Aesar) and 139 μ L of sulfuric acid (96%) were added to a 50 mL volumetric flask, and filled to the mark with water (HPLC grade).
2. Phenanthroline solution: 0.2% by weight of 1,10-phenanthroline in water (100 mg in 50 mL volumetric flask).
3. Buffer solution: 2.47 g of NaOAc and 0.5 mL of sulfuric acid (96%) were added to a 50 mL volumetric flask, and filled to the mark with water (HPLC grade).

²⁷ Murov, S. L. Ed. Handbook of Photochemistry, Marcel Dekker, New York, 1973.

The actinometry measurements were done as follows:

1. 1 mL of the actinometer solution was added to a vial. The vial was placed in the reactor.
2. The solution was irradiated at 460 nm (irradiance 238 mW/cm²). This procedure was repeated 4 times, quenching the solutions after different time intervals: 1 sec, 2 sec, 4 sec, and 6 sec. Then a model reaction was set following the general procedure (See paragraph 4.5.5), placed in the irradiation set up and it has been irradiated for 25 minutes. This procedure has been performed other two times with different irradiation times (30 min and 35 min).
3. After irradiation, the actinometer solutions were removed and placed in a 10 mL volumetric flask containing 0.5 mL of 1,10-phenanthroline solution and 2 mL of buffer solution. These flasks were filled to the mark with water (HPLC grade).
4. The UV-Vis spectra of the complexed actinometer samples were recorded for each time interval. The absorbance of the complexed actinometer solution was monitored at 510 nm (Figure 8).

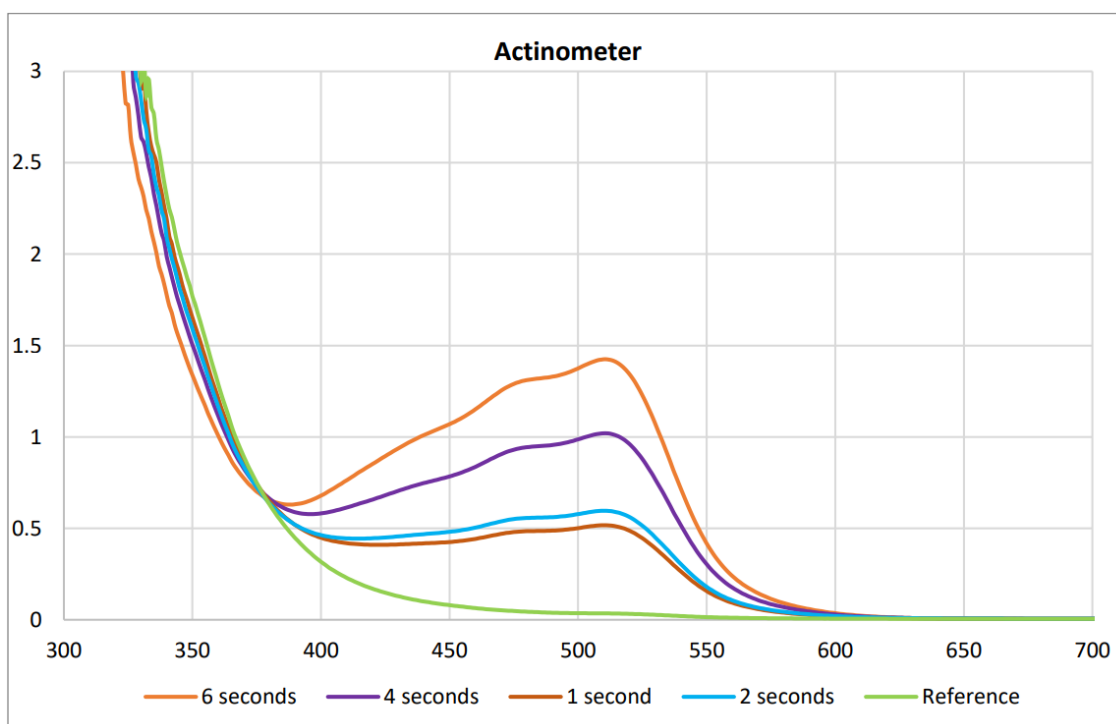


Figure 8 Actinometry

The moles of Fe²⁺ formed for each sample is determined using Beers' Law (Eq. 1):

$$\text{Mols of Fe(II)} = V1 \times V3 \times \Delta A(510 \text{ nm}) / 103 \times V2 \times l \times \epsilon(510 \text{ nm}) \quad (\text{Eq. 1})$$

where V1 is the irradiated volume (1 mL), V2 is the aliquot of the irradiated solution taken for the determination of the ferrous ions (1 mL), V3 is the final volume after complexation with phenanthroline (10 mL), l is the optical path-length of the irradiation cell (1 cm), $\Delta A(510 \text{ nm})$ is the optical difference in absorbance between the irradiated solution and the one stored in the dark, $\epsilon(510 \text{ nm})$ is the extinction coefficient the complex Fe(phen)₃²⁺ at 510 nm (11100 L mol⁻¹cm⁻¹). The moles of Fe²⁺ formed (x) are plotted as a function of time (t). The slope of this line was correlated to the moles of incident photons by unit of time (q_{n,p}⁰) by the use of the following Equation 2:

$$\Phi(\lambda) = (dx/dt) q_{n,p}^0 [1 - 10^{-A(\lambda)}] \text{ (Eq. 2)}$$

where dx/dt is the rate of change of a measurable quantity (spectral or any other property), the quantum yield (Φ) for Fe^{2+} at 458 nm is 1.1,²⁸ $[1 - 10^{-A(\lambda)}]$ is the ratio of absorbed photons by the solution, and $A(\lambda)$ is the absorbance of the actinometer at the wavelength used to carry out the experiments (460 nm). The absorbance at 460 nm $A(460)$ was measured using a Shimadzu 2401PC UV-Vis spectrophotometer in a 10 mm path quartz cuvette, obtaining an absorbance of 0.14. The photon flux $q_{n,p}^0$ was determined to be 1.12×10^{-6} .

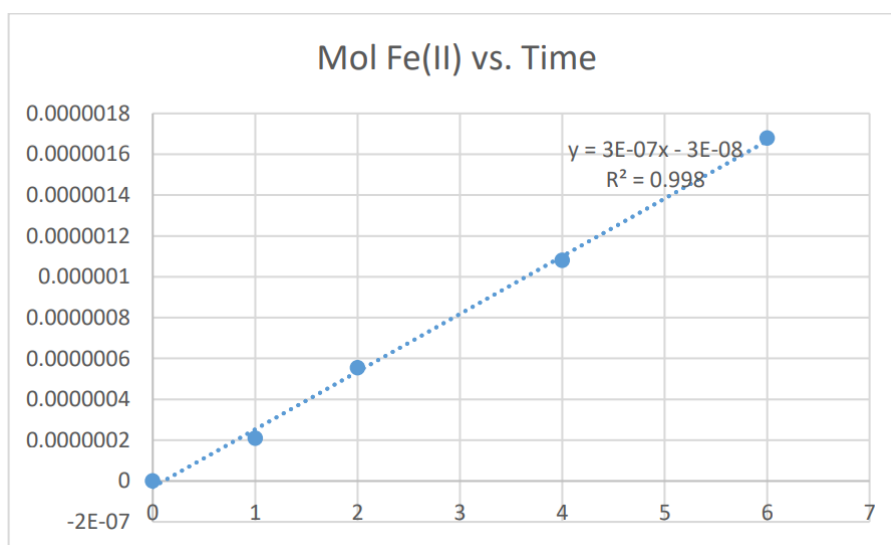


Figure 9 Plot of mols of Fe^{2+} formed vs irradiation time. Slope of the line correlates to the moles of incident photons by unit of time.

The moles of product **7aa** formed for the model reaction were determined by GC measurement (FID detector) using 1,3,5-trimethoxybenzene as internal standard. The moles of product per unit of time are related to the number of photons absorbed. The photons absorbed are correlated to the number of incident photons by the use of Equation 2. According to this, if we plot the moles of product (x) versus the moles of incident photons ($q_{n,p}^0 dt$), the slope is equal to: $\Phi(1 - 10^{-A(460 \text{ nm})})$, where Φ is the quantum yield to be determined and $A(460 \text{ nm})$ is the absorption of the reaction under study. $A(460 \text{ nm})$ was measured using a Shimadzu 2401PC UV-Vis spectrophotometer in 10 mm path quartz. An absorbance of 1.12 was determined for the model reaction mixture.

²⁸ Holubov, C. A.; Langford, C. H. *Inorg. Chim. Acta.* **1981**, 53, 59.

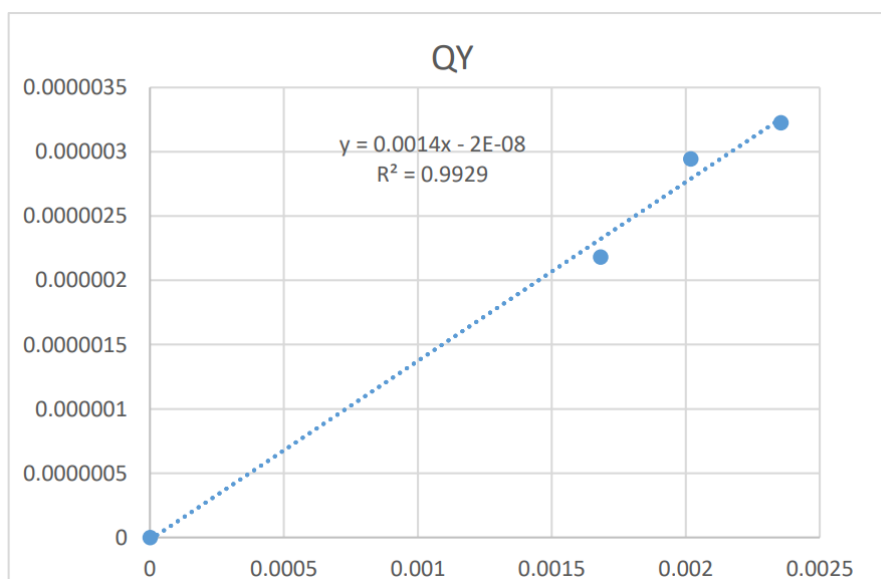


Figure 10 Plot of mols of incident photons vs mols of product formed. Slope of the line correlates to quantum yield of the photochemical transformation

The quantum yield (Φ)_{cat.} of the photochemical transformation was measured to be **0.0014**, which hints to a closed catalytic cycle being operational.

Chapter V

General Conclusions

During my Doctoral studies, the peculiar electronic properties of diverse vinylogous donor substrates have allowed the development of three unprecedented, organocatalysed and stereoselective transformations, ranging from [4+2] processes leading to novel, high-appealing and potentially bioactive heterocyclic chemotypes, to the remote functionalization of dienamines within a photochemical radical process.

Chapter II described how the use of a non-covalent organocatalytic strategy could effectively promote dearomative vinylogous enolization of heterocyclic uracil-based pronucleophiles. The chemistry relied on the diene-like character of transient *o*QDM intermediates, useful in triggering stereoselective [4+2] cycloaddition reactions with nitroolefins as dienophiles. Several novel chiral 5,6,7,8-tetrahydroquinazoline-2,4(*1H,3H*)-diones with three stereocenters were efficiently prepared, and easily enantioenriched to the maximum level of enantiopurity through simple recrystallisation procedures. The project was enriched by two fruitful academic collaborations. Prof. Marco Lombardo (University of Bologna, Italy) performed an extensive DFT calculation study, that shed light on the (non-granted) mechanism of the transformation, unveiling inedited catalyst-intermediate interaction modes; Prof. Kurt Vermeire (KU Leuven, Belgium) performed preliminary antiviral screening against wild-type and omicron SARS-CoV-2 strains of a small library of the synthesized uracils, that resulted in quite promising low-micromolar activity for different tested compounds.

In Chapter III, the launch of a novel imidazole-based vinylogous pronucleophile was described. This compound type resulted a suitable precursor for the *in situ* generation of unprecedented and valuable imidazole-based *o*QDM intermediates to be exploited within eliminative and organocatalysed [4+2] formal cycloaddition reactions, representing one of the rare examples involving the organocatalytic dearomative activation of imidazole-based substrates. The protocol constitutes a rare and straightforward entry to access chiral 6,7-dihydrobenzo[*d*]imidazole scaffold. Control experiments ascertained how the careful choice of the vinylogous malononitrile activation strategy was the key for unlocking the reactivity of the system, while the exploitation of aminocatalysis efficiently guaranteed full enantiocontrol. Unprecedented synthetic manipulations of the imidazole-based products were performed, unveiling intriguing *N*¹,*N*³-tosyl shift and imidazole/base-mediated tosyl-removal reactions.

Chapter IV described the work performed during my visiting period in the laboratories of Prof. Paolo Melchiorre at ICIQ in Tarragona, Spain. In this project we developed a rare protocol for a new, remote and enantioselective functionalization of enals. While the use of DTC-catalysis accounted for the photo-generation of radicals under mild reaction conditions, the cooperative action of the aminocatalyst resulted fundamental to promote the *in situ* formation of a catalytic amount of dienamines. The nucleophilic vinylogous character of these latter species allowed the stereo-determining radical-trap step to take place with complete regioselectivity, being invariably operative at the most remote site, and moreover with moderate to good enantioselectivity.

Overall, vinylogous and organocatalysed reactions have been shown to be useful tools in refining the three-dimensional shape of carbon-rich heterocyclic compounds and to be applied within the

chemical radical domain, representing an intriguing and useful opportunity for scientists to increase the molecular diversity even in contemporary organic synthesis.

Acknowledgments

My Ph.D. fellowship was funded by Università degli Studi di Parma (fondi di Ateneo). I wish to thank Prof. Marco Lombardo (Alma Mater Studiorum - Università di Bologna, Italy) for performing DFT calculations, Prof. Kurt Vermeire (Katholieke Universiteit Leuven, Belgium) for performing antiviral assays, and Prof. Giorgio Pelosi (Università degli Studi di Parma, Italy) for performing X-ray diffractometry analyses. I am indebted to Centro Interdipartimentale Misure “G. Casnati” (Università degli Studi di Parma, Italy) for instrumental facilities. Thanks to Prof. Luca Bernardi (Alma Mater Studiorum - Università di Bologna, Italy) and Prof. Alessandra Lattanzi (Università degli Studi di Salerno, Italy) for their careful revision work.

Author profile

Originally from Bologna (Italy), Enrico studied Industrial Chemistry at the Alma Mater Studiorum – University of Bologna (Italy) carrying out both the B. Sc. and M. Sc. internships in organic synthesis under the supervision of Prof. Luca Bernardi. There, he worked on the development of a new chemical methodology, by employing a synergistic catalytic approach based on the combination of organic phosphoric acids and palladium catalysts to engage N-aryl imines and vinylcyclopropanes in diastereoselective [3+2] cycloaddition reactions. After completing his Master’s thesis in 2019, Enrico joined the University of Parma (Italy) as a Ph.D. student in the group of Prof. Franca Zanardi. His main efforts have been devoted to the design and implementation of organocatalytic activation strategies of novel vinylogous heteroatom-containing cyclic pronucleophiles for the creation of a series of highly enantioenriched new heterocycles containing in-cycle stereocenters. In 2021 he spent six months as a visiting Ph.D. student at ICIQ (Spain) under the supervision of Prof. Paolo Melchiorre, where he contributed to the development of a photochemical and enantioselective radical γ -functionalization of enals.