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TITOLO TESI

Organocatalytic Desymmetrization Reactions: Catalyst-Controlled Enantio-, Atropo- and Diastereotopic Group Selection for the Synthesis of Central and Axial Stereogenic Elements

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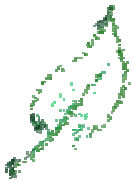

"Why do you write?

I write because I have an innate need to write.

I write because I can't do normal work as other people do. I write because I want to read books like the ones I write.

I write because I am angry at everyone.

I write because I love sitting in a room all day writing. I write because I can partake of real life only by changing it.

I write because I want others, the whole world, to know what sort of life we lived, and continue to live.

I write because I love the smell of paper, pen, and ink. I write because I believe in literature, in the art of the novel, more than I believe in anything else. I write because it is a habit, a passion. I write because I am afraid of being forgotten. I write because I like the glory and interest that writing brings. I write to be alone. Perhaps I write because I hope to understand why I am so very, very angry at everyone. I write because I like to be read.

I write because once I have begun a novel, an essay, a page I want to finish it.

I write because everyone expects me to write. I write because I have a childish belief in the immortality of libraries, and in the way my books sit on the shelf. I write because it is exciting to turn all life's beauties and riches into words. I write not to tell a story but to compose a story. I write because I wish to escape from the foreboding that there is a place I must go but—as in a dream—can't quite get to. I write because I have never managed to be happy. I write to be happy"

Orhan Pamuk, Nobel Prize for Literature Lecture

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This PhD Thesis is dedicated to the memory
of my Grandfather.

A special thought is for my Mother.
For her unconditional Love.

I feel deeply grateful for the support, during these years, of my whole Family,
All my Friends,
and my Girlfriend.

"Symmetry is for God, not for us."

— Louis de Bernières, Corelli's Mandolin

ABBREVIATIONS

Ac	Acetyl
ACDC	Asymmetric counterion-directed catalysis
AcO	Acetate
AcOH	Acetic acid
Ar	Aryl
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-Butyloxycarbonyl
CA	Cinchonine
Calc	Calculated, calculation
CBz	Carboxybenzoil
CDA	Cinchonidine
DA	Diels-Alder
DCM	Dichloromethane
DHCA	Dihydrocinchonine
DHCDA	Dihydrocinchonidine
DHQA	Dihydroquinine
DHDQA	Dihydroquinidine
DIAD	Diisopropyl azodicarboxylate
DKR	Dinamic kinetic resolution
DMAP	*N,N*-Dimethylamino pyridine
DMPU	*N,N*-Dimethylpropylene urea
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric eccess

ent	Enantiomer
er	Enantiomeric ratio
Et	Ethyl
EtOH	Ethanol
EWG	Electron-withdrawing group
Exp	experiment, experimental
gCOSY	Gradient correlation spectroscopy
GS	Ground state
h	hour
HFIP	Hexafluoroisopropanol
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
KR	Kinetic resolution
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
M	Molar (concentration)
m	meta
MBH	Morita-Bailys-Hillman
Me	Methyl
MeOH	Methanol
Moc	Methyloxycarbonyl
MS	Molecular sieves
MTBE	Methyl, *tert*-butyl ether
NBS	*N*-bromo succinimide
NHC	*N*-heterocyclic carbene

NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NPA	*N*-phosphoramide
Nu	Nucleophile
o	ortho
p	para
PA	Phosphoric acid
Ph	Phenyl
PTC	Phase-transfer catalysis, Phase-transfer catalyst
QA	Quinine
QDA	Quinidine
RDS	Rate determining step
r.t.	Room temperature
SET	Single electron transfer
SPA	Spirophosphoric acid
SQ	Squaramide
TEA	Triethylamine
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl, tetramethylsilane
TS	Transition state
TU	Thiourea

Chapter I

Introduction

1.1 General Introduction

Organic chemistry is the chemistry of compounds predominantly containing carbon atoms. Despite tremendous advances in organic synthesis in the last century, one of the greatest challenges in organic chemistry still consists of inventing new reactions to construct – or modify – carbon molecular architecture. Organic synthesis has evolved at an ever-increasing pace to a state where it has now become commonly believed that any molecule can be made by chemists, given enough time and resources.[1]

Synthetic transformations have innovated in the recent years in a way not even thinkable only a few decades ago: C-H activation of unactivated carbon, homologation reaction, photoredox activation of strong bond, the whole family of coupling reactions and so on, are just a few example of reactivity that seemed impossible not so long ago. The search for new, reliable and groundbreaking reactivity skyrocketed also thanks to the fact that molecular complexity of synthetic drug candidates in industry has continued to rise over the years, demanding more desirable attributes, always more difficult to reach.[2] The most important of these attributes is undoubtedly *chirality*. Until recently, the majority of single-isomer drugs available were those derived from natural sources (e.g. morphine, epinephrine, hyoscine) and racemates predominated, there is now a clear trend in the pharmaceutical industry towards the development of chiral API *via* enantioselective transformations or separations.

[1] Stiles, D. *Chemistry World*, **2007**, *4*, November issue.
[2] Walker, S.D. *et al.*, *J. Org. Chem.*, **2019**, *84*, 4583.

1.2 Chirality

1.2.1 History

Chirality is the property of an object not to be superimposable to its mirror image.

The word chirality is derived from the Greek χειρ (kheir), "hand," which is a common non-superimposable object. The property of being chiral is not confined to the realm of chemistry, but we can find examples of chiral objects: from the spin of a particle, where the handedness of the object is determined by the direction in which the particle spins, to geometrical shapes like *prime knots*, through DNA helicity, up to *symmetry breaking* of weak nuclear force that becomes chiral in the massless limits and affects only left-handed particles (and right-handed anti-particles) and so on. As it seems, chirality is not merely a property of molecules as a chemist could think, but a property *of the reality itself*.

Molecular chirality was discovered by Louis Pasteur, a French chemist and biologist, when he separated by hand for the first time, in 1848, the two isomers of sodium ammonium tartrate (NH_4/NaT). When Pasteur began his experiments, the structural theory of organic molecules was still many years away from being formulated and thus the molecular structure of tartaric acid was unknown. However, natural tartaric acid was recognized at the time as optically active and dextrorotatory in solution. Pasteur found that the crystals of ammonium/sodium tartrate mixed salt displayed small surfaces called hemihedral facets, which appeared as modifications to some of the edges of the crystals. These facets degraded the symmetry of the basic crystal form and he recognized that the resulting external crystal morphology was chiral. Here, the odds played against him. Indeed, only a minority of racemates crystallize such that mirror image crystals each made up of only one enantiomer are formed (known today as

conglomerate crystallization). Fortunately for Pasteur, tartaric acid salts do crystallize in this fashion. He understood that (+)-TA and (–)-TA were non-superimposable-mirror-image molecular forms of each other, and this was the discovery of molecular chirality. [3]

1.2.2 Properties of Chirality

Almost all chiral molecules important in living organisms are found in just one form: sugars are preferentially right-handed, amino acids left-handed and DNA coils into right-handed helices. This feature is called *homochirality* and is thought to be a prerequisite for the formation of the replicating molecules that led to all life. But the big question of how did our single-handed world developed from a primordial chemical soup that was both left- and right-handed?[4] Often described as 'breaking the mirror', the problem may seem trivial at first glance, but chemists still do not understand how it happened.

Chirality is based on molecular symmetry elements. In particular, Chiral molecules are always *dissymmetric* (lacking improper rotation axis S_n), but not always *asymmetric* (lacking all symmetry elements except the trivial identity).

1.2.3 *Central Chirality*

Chiral molecules having central chirality contain stereogenic centres, sp^3-hybridized atom (e.g. carbon, sulfur, phosphorous) with four different substituents as shown in the example in **Figure 1**. Two molecules having the same structure except for the absolute configuration on the chiral centre are called *enantiomers*, this is the most widespread type of chirality and consequently also the easiest to visualize and understand.

[3] Gal J., *Nat. Chem.,* **2017**, *9*, 604.

[4] Blackmond, D.G. *Angew. Chem. Int. Ed.* **2009**, *48*, 2648.

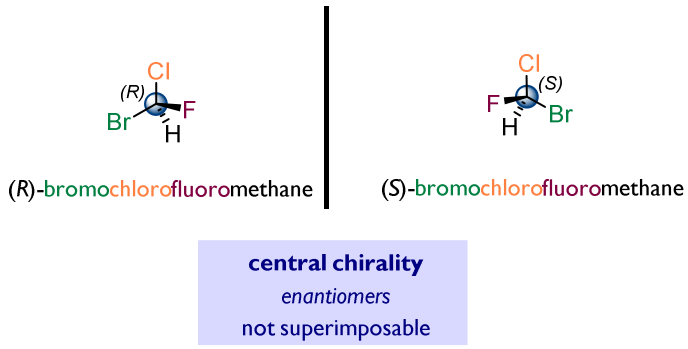

Figure 1. *example of two enantiomers*

Carbon is the most common stereogenic atom encountered in Nature thanks to its property of being tetravalent and abundant on Earth. One of the most important features of chiral molecules is the possibility of having more than one stereocenters in the same structure. The number of possible stereoisomers can be calculated elevating 2 to the power of the number of stereocenters present in the molecule, such as in the example of Cortisone shown in **Figure 2**. When two molecules have two or more stereocenters that held different configurations in the corresponding stereocenters, but not all, they are called *diastereoisomer*.

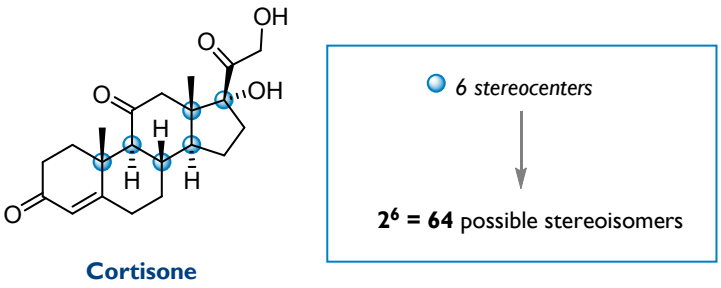

Figure 2. *Naturally occurring Cortisone and number of possible isomers*

Unlike enantiomers, the physical and chemical properties of diastereomers can in principle be different and consequently, their chemical characterization is easier and their biological activities are often different. This is the basis for derivatization of enantiomers to form diastereomers in chiral separation and also for the explanation of enantiomer activities with their chiral receptors in the body. Diastereomers, enantiomers and geometric isomers form a family called

stereoisomers that are molecules having the same chemical formulas but differing only with respect to the spatial arrangement.

1.2.4 *Axial Chirality*

A special case of stereoisomerism occurs when rotation about a single bond is sufficiently restricted due to steric hindrance or other factors such that the different conformers are separable, is called *atropisomerism* (**Figure 3**). If the stereogenic axis is the only element of chirality present in the molecule, the two atropoisomers are mirror image, and thus *enantiomers*.

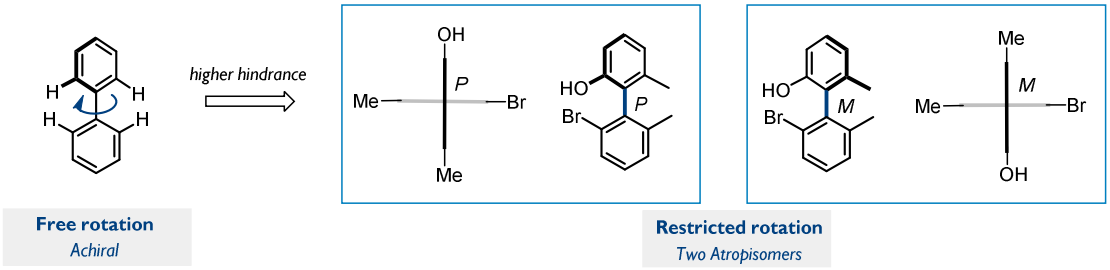

Figure 3. *example of an achiral molecule (left) and two atropisomer due to hindred rotation around C-C bond*

Generally, a stereogenic axis arise whenever a molecule has two *dissymmetric* orthogonal planes and therefore atropisomers (from gr. a- α, non- and -tropos, τροποσ, -turn) is a restricted case of the family of axially chiral compounds. Unlike molecules that feature central chirality (point chirality), they lack stereogenic centers and yet exist as enantiomers; While the atropisomers are usually defined by the chirality rule, *R* (or R_a) and *S* (or S_a) nomenclature using Cahn−Ingold−Prelog rules, it is also often represented in terms of helicity rules, *P* (positive helix) and *M* (negative helix) nomenclature (**Figure 4**).[5]

[5] E. Kumarasamy, R. Raghunathan, M.P. Sibi and J. Sivaguru, *Chem. Rev.* **2015**, *115*, 11239.

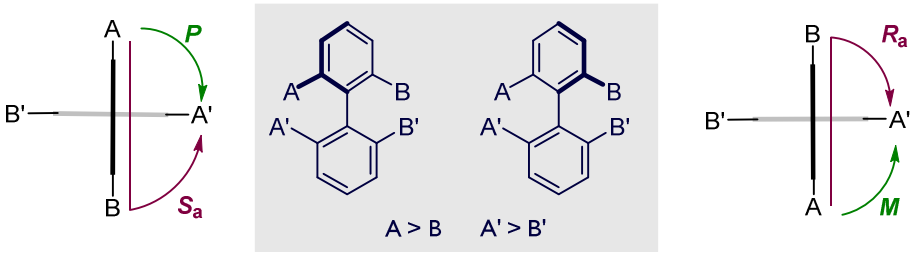

Figure 4. *Nomenclature of stereogenic axes*

The phenomenon of restricted bond rotation was first identified by Christie and Kenner in 1922 while investigating biaryl 6,6'-dinitro-2,2'-diphenic acid.[6] Ōki proposed that for being considered a "stable" atropisomers a compound should exhibit a half-life of at least 1000 s (16.7 min) at any temperature considered.[7] This is an arbitrary definition but is more efficient compared to others because it takes the temperature into account as it should be for a chemical equilibrium. These were the first kind of atropisomers ever reported[8] and are by far the most common and studied ones. However, there are many classes of known axially chiral compounds[9] such as amides,[10] anilides and ureas,[11] imides,[12] diaryl ethers, thioethers and sulfones,[13] aryl imines and styrenes,[14] *N*-aryl carbazoles and pyrroles and allenes.[15] Progress in this area saw a steep increase after the advent of biaryl based atropisomeric catalysts and discovery of many natural products with atropisomeric skeleton(s). The use of atropisomeric compounds as ligands in metal mediated catalysis has revolutionized the fields of organometallic chemistry and asymmetric synthesis (**Figure 5**).

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[6] Christie, G. H.; Kenner, J., *J. Chem. Soc., Trans.* **1922**, *121*, 614.
[7] Oki, M. *Top. Stereochem.* **1983**, *14*, 1.
[8] G. H. Christie, J. Kenner *J. Chem. Soc. Trans.*, **1922**, 614.
[9] E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru *Chem. Rev.*, **2015**, 11239.
[10] J. P. Clayden, L. W. Lai *Angew. Chem. Int. Ed.*, **1999**, 2556.
[11] T. Adler, J. Bonjoch, J. Clayden, M. Font-Bardfa, M. Pickworth, X. Solans, D. Sole, L. Vallverdu *Org. Biomol. Chem.*, **2005**, 3173.
[12] D. P. Curran, H. Qi, S. J. Geib, N. C. DeMello *J. Am. Chem. Soc.*, **1994**, 3131.
[13] J. Clayden, J. Senior, M. Helliwell *Angew. Chem. Int. Ed.*, **2009**, 6270.
[14] A. G. Pinkus, J. I. Riggs, S. M. Broughton *J. Am. Chem. Soc.*, **1968**, 5043.
[15] D. R. Taylor *Chem. Rev.*, **1967**, 317.

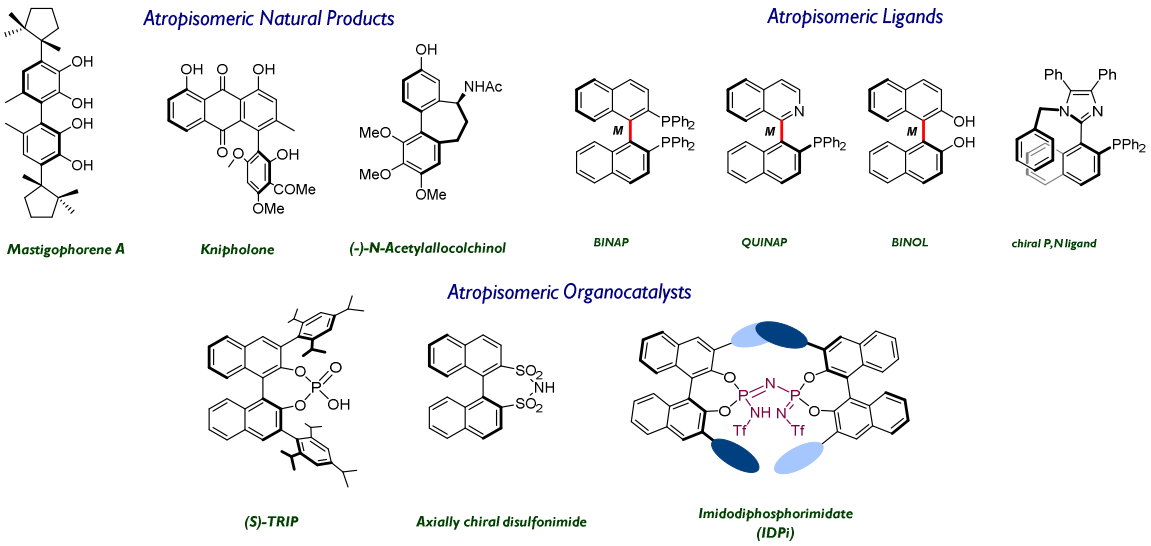


***Figure 5**. Examples of Atropisomers*

Owing to the high demand and importance of these chiral biaryl scaffolds, numerous synthetic procedures, reviews, and concepts have been published in the literature.[16ac]

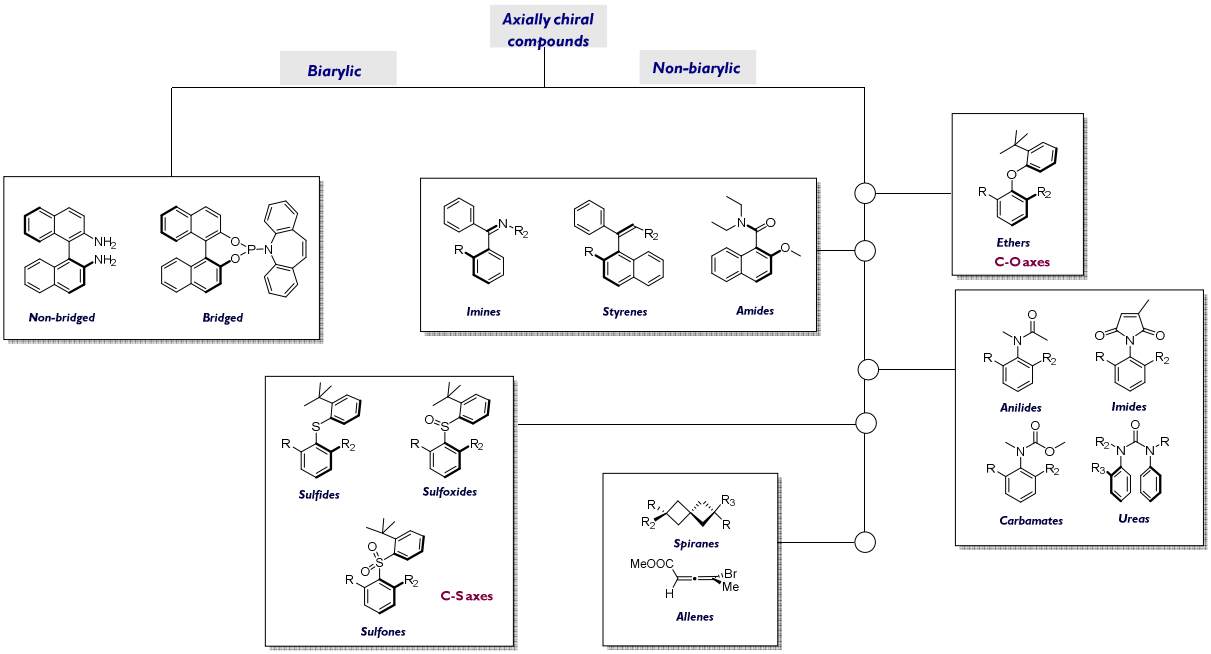


***Figure 6**. Different classes of axially chiral molecules*

[16] (a) Bringmann, G.; Menche, D., *Acc. Chem. Res.* **2001**, *34*, 615. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (c) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F., *Chem. Soc. Rev.* **2015**, *44*, 3418.

Although they are less abundant compared to centrally chiral compounds, atropisomers can still be found in many naturally[9] and synthetically[10] occurring molecules and nowadays play a central role as ligands or catalysts in asymmetric synthesis (**Figure 6**).

1.2.5 *Helical Chirality*

It is a property of screw-shaped objects, the most famous example being the macromolecule of DNA which has the shape of a right-handed double helix (**Figure 7**).

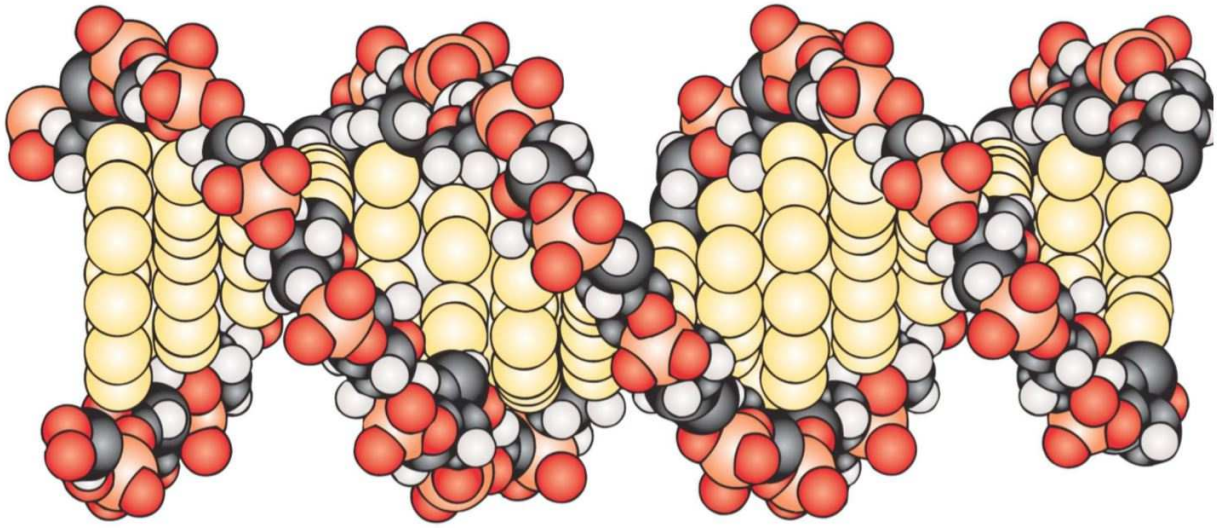


Figure 7. *DNA structure*

Simpler molecules also show this kind of chirality and the smallest structure that shows stable helical chirality is called hexahelicene (**Figure 8**).

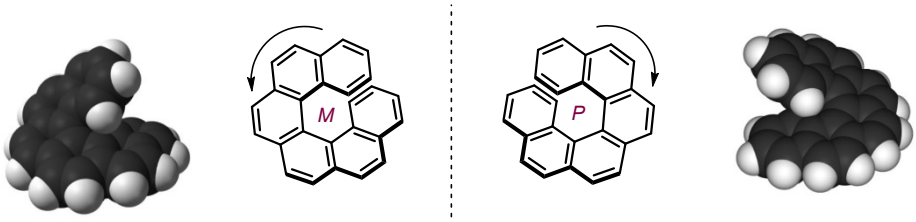
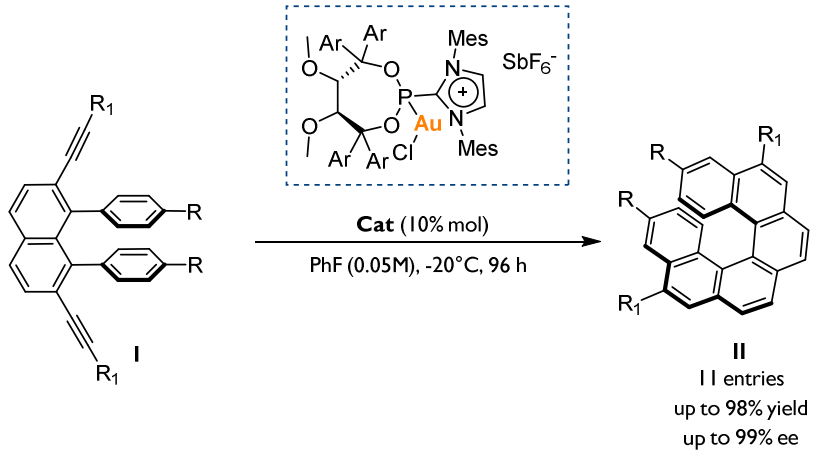


Figure 8. *enantiomers of hexahelicene*

The descriptors for helicity are ***P*** and ***M*** also in this case, with ***P*** labelling a clockwise rotation and ***M*** a counterclockwise one. There are very few examples of real enantioselective synthesis of helicenes,[17] but an effective one was recently reported by Alcarazo (**Scheme 1**).[18]



Scheme 1. *Enantioselective synthesis of hexahelicene*

They first built an achiral reagent and then employed the cationic gold phosphinite to activate the alkyne functionalities for the intramolecular hydroarylation reaction. This way they obtained substituted hexahelicene in good yield and selectivity.

1.2.6 *Chirality in Biological Systems*

Beyond the formal definition, the concept of chirality has huge implications for living organisms. Having the same physico-chemical properties, enantiomers behave the same in any achiral environment, but, as said, the essential biomolecules are chiral and occur naturally, most of the times, in only one enantiomeric form. Thus, two enantiomers of the same molecule do not always behave the same in a biological environment, and may have significantly different activity.

Rose oxide, among the first compounds isolated from rose oil in the early '60s, is a colorless to pale yellow liquid with a distinct rose scent. This compound presents

[17] For exhaustive reviews on helically chiral compounds see: a) Y. Shen, C. *Chen Chem Rev.,* **2011**, 1463; b) M. Gingras *Chem. Soc. Rev*., **2013**, 968; c) M. Gingras, G. Félix, R. Peresutti *Chem. Soc. Rev*., **2013**, 1007; d) M. Gingras *Chem. Soc. Rev*., **2013**, 1051

[18] E. González-Fernández, L. D. M. Nicholls, L. D. Schaaf, C. Farès, C. W. Lehmann, M. Alcarazo, *J. Am. Chem. Soc.,* **2017**, *139*, 1428

four distinct isomers, of which the (–)-*cis* isomer is the most desirable for fragrance and flavor use. When produced as a single compound, (–)-*cis*-rose oxide is a floral green note, with a strong, diffusive rose scent. The odor threshold is 0.5 ppb. Its enantiomer, (+)-cis-rose oxide is herbal, green floral, earthy and heavy. Its odor threshold is 50 ppb. The trans isomers are less rose-like. Diastereomer (+)-*trans*-rose oxide has an herbal green, fruity, citrus scent with an odor threshold of 80 ppb, while (–)-*trans*-rose oxide displays, herbal minty notes, with an odor threshold of 160 ppb.[19] The fact that different enantiomers of the same molecule produce different smells, is a direct proof of the presence of homochiral molecules in the human olfactory receptors.

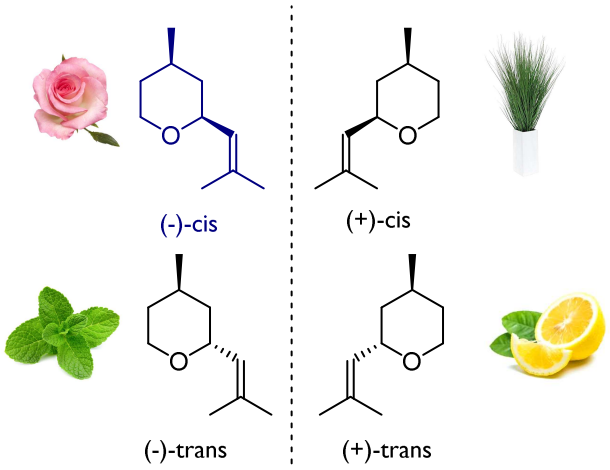


Figure 9. *Different rose oxide isomers*

Another chiral type of molecule important in biological systems are drugs and drug-like compounds. The body with its numerous homochiral compounds being amazingly chiral selector, often interact with stereoisomers of the same drug differently and metabolize each enantiomer by a separate pathway to generate different pharmacological activity. Thus, one isomer may produce the desired therapeutic activities, while the other may be inactive or, in worst cases, produce undesired or toxic effects. The activity ratio between the two different stereoisomers of a molecule is called *eudysmic ratio*. The *eutomer* is the chiral enantiomer having the

[19] M. Song, Y. Xia and E. Tomasino, *Molecules,* **2015**, *20*, 7359.

desired pharmacological activity, e.g., as an active ingredient in a drug. The *distomer,* on the other hand, is the enantiomer of the eutomer which may have undesired bioactivity or may be bio-inert. This is the case of Naproxen, one of the most known nonsteroidal anti-inflammatory drugs used for the treatment of pain, inflammatory disease and fever. In this case, only the (*S*)-enantiomer is responsible for the beneficial effects, whereas the (*R*)-enantiomer is not effective and its liver poisonous (**Figure 10**, top). Besides the very well-known case of Thalidomide, another example is Ethambutol. While the (*S*,*S*) enantiomer is effective against tuberculosis, the (*R*,*R*) form causes blindness.

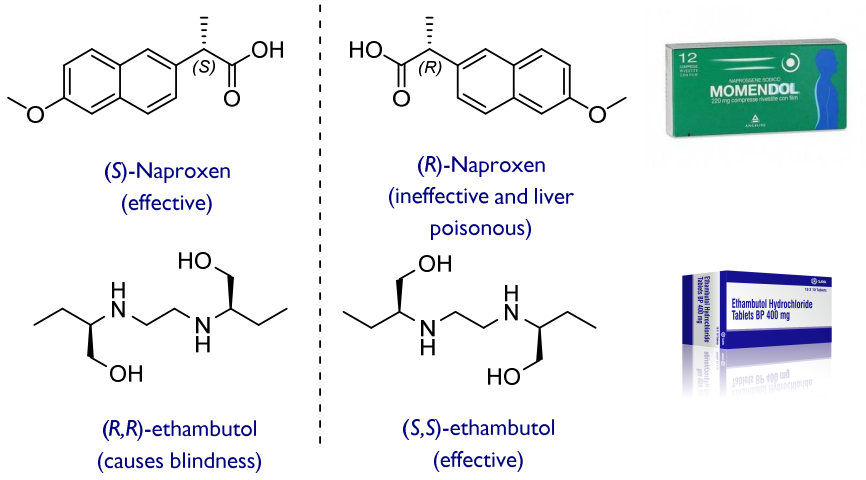


Figure 10. *Example of drugs in which enantiomers have different activity in biolgical systems*

1.3 Asymmetric Synthesis

The synthesis of enantiomerically pure chiral compounds via cost-effective methods has become an important goal in the chemical industry. Indeed, obtaining chiral molecules as single enantiomers circumvents the need to resolve a racemic mixture by costly processes (e.g., diastereomeric salts, chiral HPLC separation, biochemical resolution, or kinetic transformations). Another advantage is that, at the end of the reaction, only trace amounts of the catalytic reagent have to be removed. This is an improvement in synthesis over the traditional alternative where a chiral auxiliary had to be attached to the starting

material and needed to be excised after the diastereoselective reaction.[20] In principle, in asymmetric catalysis, a chiral catalyst reacts with a prochiral site on the substrate to generate one stereoisomer of a product preferentially. A chiral catalyst will cause diastereomeric transition states (TS) of different energies depending on the nature of the interaction. This phenomenon influences the product outcome, and favors the product arising from the lowest energy pathway. The three main strategies for achieving enantioselective synthesis, called the "three pillars" of catalysis, are *metal catalysis*, *biocatalysis* and *organocatalysis*.

1.3.1 *Asymmetric Organocatalysis*

Until 1996, enzymes and transition-metals had been considered the only classes of efficient asymmetric catalysts.[21] Biocatalysis lies in the use of enzymes as natural catalysts to perform organic transformations.[22] The main advantages of this type of catalysis include very high enantioinduction and substrate specificity. Conversely, in metal-based catalysis, the catalysts are rendered chiral by means of chiral ligands. The thus generated metal-complex catalysts are very effective even at low concentrations[23] and are therefore well suited to industrial scale synthesis.[24] For these reasons, enormous progresses have been made within the field of metal-based asymmetric catalysis, culminated in the award of Nobel Prize to Sharpless, Noyori and Knowles in 2001.

Organocatalysis relies on the use of small chiral organic molecules to catalyze organic transformations.[25] Organocatalysis roots ground into biomimetic

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[20] Mulzer, J. In Comprehensive Asymmetric Catalysis; Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag, Berlin, Heidelberg **1999**, Vol. I, Chapter 3.
[21] D. Seebach, *Angew. Chem. Int. Ed.* **1990**, *29*, 1320.
[22] A. Schmid, J. S. Dordik, B. Hauer, A. Kiener, M. Wubbolts, B. Witholt, *Nature* **2001**, *409*, 258.
[23] M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.* **2006**, *45*, 4732.
[24] H. U. Blaser, H. J. Federsel, *Asymmetric Catalysis on Industrial Scale*. Wiley VHC, Weinheim, **2011**.
[25] Selected reviews on asymmetric organocatalysis: (a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; (b) B. List, *Asymmetric Organocatalysis*. Wiley VHC, Weinheim, **2005**; (c) B. List, *Chem. Rev.* **2007**, *107*, 5413; (d) H. Pellissier, *Tetrahedron* **2007**, *63*, 926; (e) M. F. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8. (f) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; (g) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.

approach, in order to mimic the catalytic activity and selectivity of enzymes. In 2000, David W. C. MacMillan first conceptualized the term organocatalysis as the use of organic molecules with low molecular weight as catalysts in organic reactions.[26] However, before that time, the use of an organic molecule in a catalytic amount was already been reported. In 1912, Bredig and Fiske described the addition of HCN to aldehyde in the presence of cinchona alkaloids with low ee's.[27] In 1970s a milestone in the area of what would become "asymmetric organocatalysis" was posed independently by two industrial research groups from Hoffman-La Roche and Schering. They published the first, highly enantioselective, catalytic aldol reaction using the simple amino acid proline as catalyst.[28] Despite this, only few reports on the use of small organic molecules as asymmetric catalysts were published between 1968 and 1997. It seemed that these chemical studies were no interconnected to each other and there were no efforts trying to conceptualize a general organocatalytic strategy, thus the organic chemists' community overlooked organocatalysis for almost thirty years.

In 1996, reports from Shi,[29] Denmark,[30] Yang,[31] Jacobsen[32] and Corey[33] demonstrated that small organic molecules could be effectively used as powerful tools to promote organic transformations. Then, in 2000, the works from Barbas, List[34] and MacMillan, led to recognize a general mode of action of organocatalysts. This opened the way for a broad and smart applicability of organocatalysis, as it was demonstrated that a stereoselective synthesis could be planned *a priori* employing organocatalysts.

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[26] K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan*, J. Am. Chem. Soc.*, **2000**, *122*, 4243.
[27] G. Bredig and W. S. Fiske*, Biochem. Z.*, **1912**, 7.
[28] (a)Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **1974**, *39*, 161. (b) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **1971**, *10*, 496.
[29] Y. Tu, Z. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806.
[30] S. E. Denmark, Z. Wu, C. Crudden, H. Matshuhashi, *J. Org. Chem.* **1997**, *62*, 8288.
[31] D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, J.-H. Zheng, K. Cheung *J. Am. Chem. Soc.* **1996**, *118*, 491-492.
[32] M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901
[33] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157.
[34] (a) B. List, R. A. Lerner, C. F. III Barbas, *J. Am. Chem. Soc.* **2000**, *120*, 1629; (b) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336.

Organocatalysis, by now, has definitively matured to a recognized methodology, equal to organometallic and enzymatic catalysis and it is viewed as the third pillar of asymmetric synthesis. This is due to undoubted advantages such as the stability of the catalytic system (inert atmosphere or dry/degassed solvents are often not required), its non-toxicity and the possibility of using mild reaction conditions.

1.3.2 *Organocatalytic Activation Mode*

The decisive success of organocatalysis, suddenly exploded during the past decade, arise from the identification of generic modes of activation, induction and reactivity. Generic mode of activation means that reactive species interacts with the chiral catalyst in a highly organized and predictable manner.

Based on the nature of the interaction between the catalyst and the substrate, the activation modes can be classified in **covalent-based** and **non-covalent based**. As regards to the non-covalent based catalysis, hydrogen-bond donor and Brønsted acid catalysis are based on interactions between the catalyst and the substrate, mimicking the working principles of enzymes (**Figure 11**, right).[35] Within the category of covalent-based activation, a prominent position is occupied by aminocatalysis that has emerged as reliable strategy, especially to generate stereocenters at α- and β-position of carbonyl compounds (**Figure 11**, left).[36]

[35] (a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999. (b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; (c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; (d) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187.

[36] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.

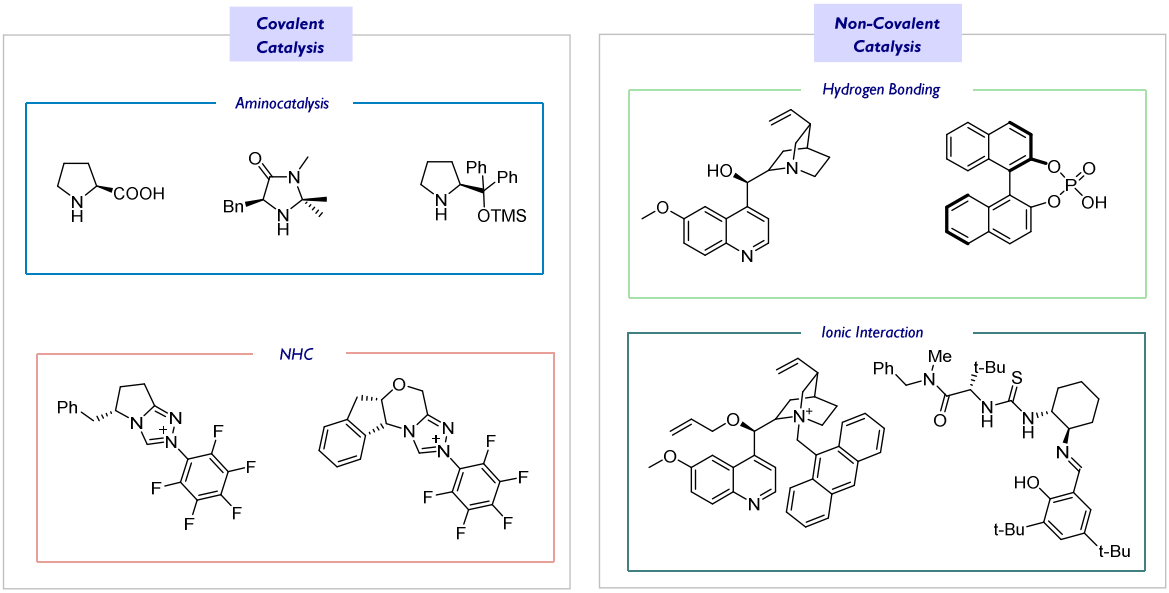


Figure 11. *Modes of activation in organocatalysis*

The understanding of the activation approaches brought to the development of catalytic strategies in which different modes of activation can be easily combined as in the case of domino/cascade reactions.[37] Furthermore, different organocatalysts can be combined with other catalytic system such as metal-based[38] or photoredox catalysts,[39] reaching a high level of sophistication.

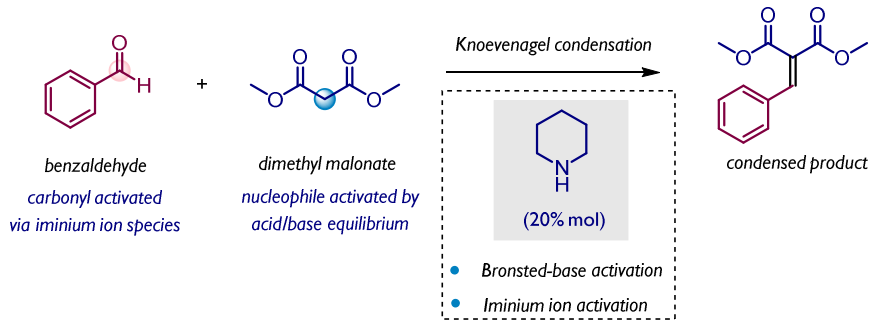
In the following paragraphs, the modes of activation typical of the catalysts encountered in next chapters will be described.

1.3.3 *Aminocatalysis*

Aminocatalysis was a huge breakthrough in the field of catalysis, offering an alternative, efficient and reliable methodology for the stereoselective C-C bond forming reaction. Asymmetric aminocatalysis offers alternatives to the activation of substrates, and can deliver unique, orthogonal, or complementary selectivities compared to metal-catalyzed processes. In addition, as any other organocatalytic

[37] (a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; (b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390.
[38] Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337.
[39] D. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77.

activation modes, it offers some interesting advantages: The metal-free organic catalysts are generally non-toxic, readily available, and stable and the reaction conditions are usually non-sensitive to air or wet solvents.[40] After the pioneeristic works of List, Barbas and MacMillan huge amounts of work has been conducted on this file and now using a small chiral amine as a catalyst is an established and efficient strategy, but its origins are dated back to 1896 when the German chemist Emil Knoevenagel reported the first achiral aminocatalytic aldol condensation reaction that takes after his name.[41]



Scheme 2. *First example of Knoevenagel condensation*

Knoevenagel first understood the potentiality of a catalytic small molecule such as an amine to promote the formation of the condensation product through the activation of a carbonyl compound, to the point that List himself admitted there is a direct connection between Knoevenagel's and his own seminal work.[42]

The importance of the works conducted by List, Lerner, Barbas and MacMillan are important not only for the reaction itself, but because they show the possible orthogonal activation mode that an amine catalyst can achieve.

[40] P. Melchiorre, M. Marigo, A. Carlone, and G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.
[41] E. Knoevenagel, *Ber. Dtsch. Chem. Ges.*, **1896**, 172.
[42] B. List, *Angew. Chem. Int. Ed.* **2010**, *1730*.

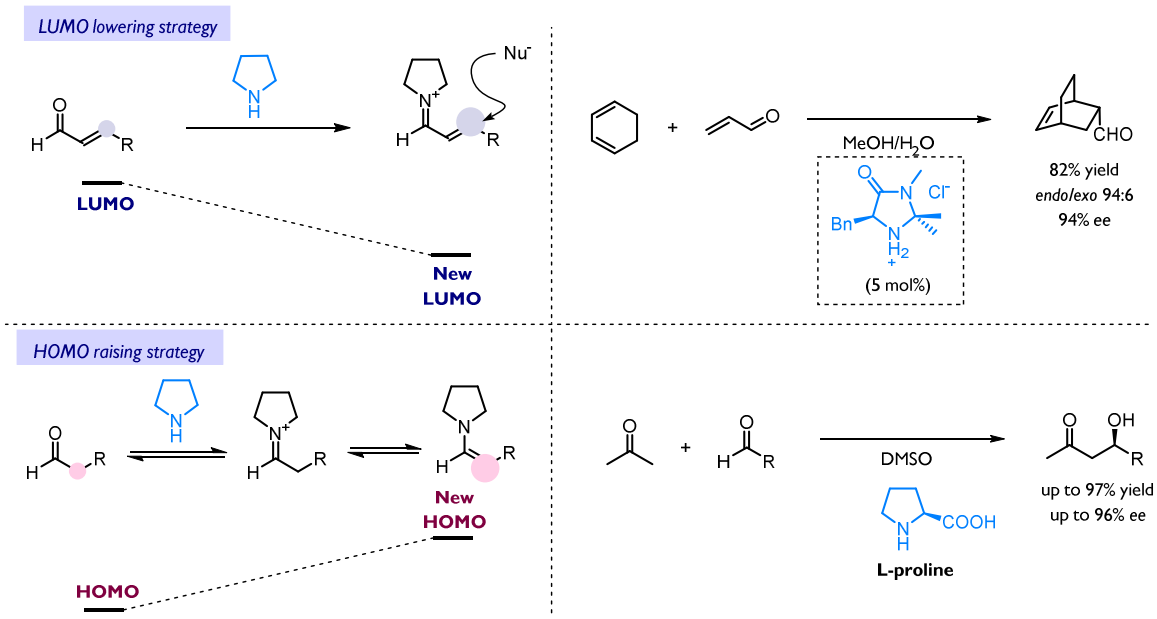


Figure 12. *Aminocatalytic activation strategies*

The reversible condensation of a chiral secondary amine with carbonyl compounds forms a positively charged intermediate, in which the energy of the lowest unoccupied molecular orbital (**LUMO**) of the system is effectively lowered, compared to the starting carbonyl. For conjugated π-systems, the electronic perturbation induced by the formation of the iminium ion allows a nucleophilic attack, such as Michael additions and pericyclic reactions (***LUMO lowering***). Another characteristic of the lowering of the LUMO activation is that the iminium ion formed increases the acidity of the α-proton. This induces a fast deprotonation, which leads tothe generation of the enamine, a nucleophilic species that can easily undergoes nucleophilic addition (***HOMO activation***). The potential of asymmetric aminocatalysis for the highly enantioselective functionalization of a broad range of carbonyl compounds was quickly recognized and stimulated a massive growth of interest and competition. Propagation of the HOMO-raising activation mode has led do the development of dienamine- and trienamine- based reactions, enabling γ- and ε-functionalizations.[43] Diarylprolinol silyl ethers (**Figure 13**), independently

[43] (a) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; (b) Z.-J. Jia, B. Gschwend, Q.-Z. Li, X. Yin. J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *135*, 5053.

developed by Jørgensen[44] and Hayashi[45] in 2005, are proline-derived catalysts which have proven to be very effective, promoting many kinds of functionalization of aldehydes, either proceeding *via* iminium ions or *via* enamines. The bulky diaryl silyl ether group is the key for the high enantioselectivities generally displayed by this catalyst. In fact, this sterically demanding moiety forces the enamine in the conformation shown (*s-trans* and π-*trans*), and shields one of its two faces very efficiently, thus determining the approach of the electrophile from the opposite face (**Figure 13a**). This mode for the enantioinduction is valid for the iminium ion activation as well. Here, the bulky fragment is extended enough to shield effectively the more distant β-position, allowing the nucleophilic attack only from the less hindered face (**Figure 13b**).

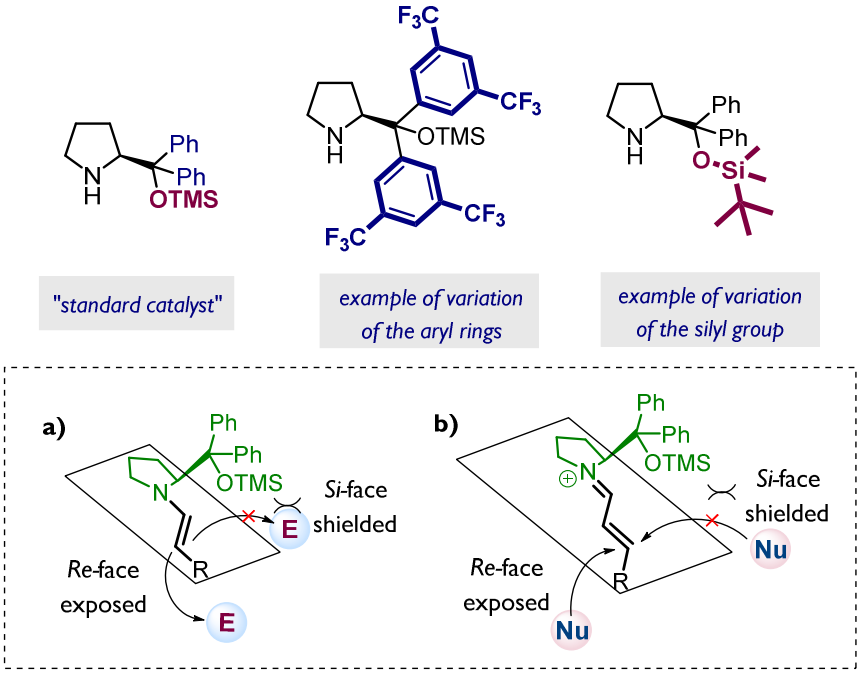


Figure 13. *Examples of Jørgensen-Hayashi catalysts and models accounting for the enantioinduction of diphenyl silyl prolinol ethers through enamine activation (a) and iminium ion activation (b).*

Besides relying on a conceptually different activation mode, these catalysts display some advantages, if compared to simple proline or unprotected prolinol.

[44] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
[45] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

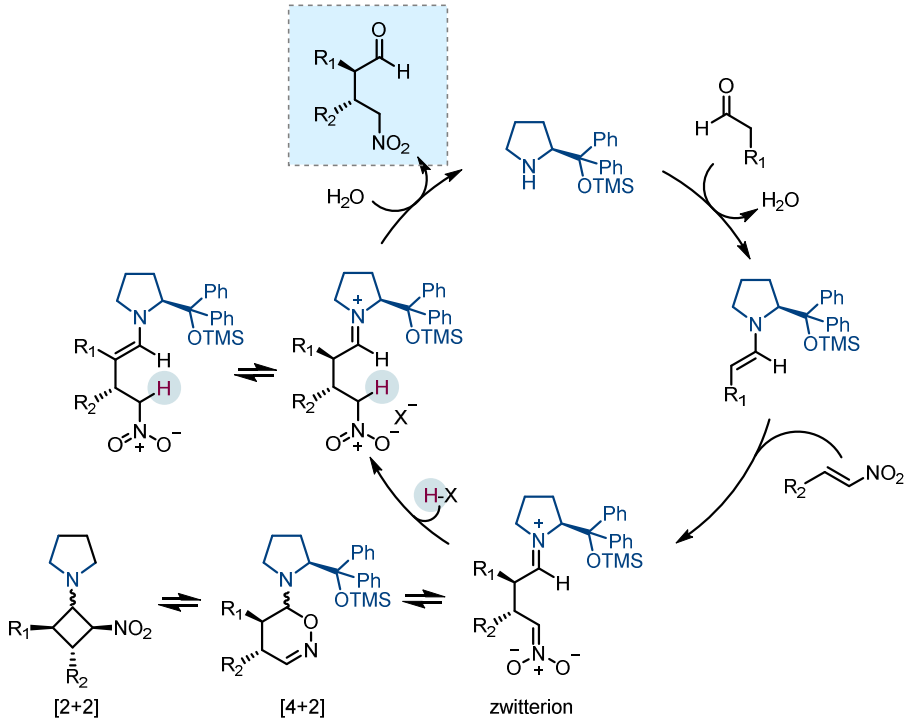
Indeed, if the first presents solubility issues, requiring most of the times very polar solvents such as DMF or *N*-methylpyrrolidone, protection avoids intramolecular parasitic reactions leading to stable unreactive off-cycle intermediates, responsible for the low activity of the latter.

In both models, the efficiency of *O*-protected diaryl prolinols is related to the size of the substituents on the catalyst. Consequently, a proper modification of the aryl structure, as well as the silyl protecting group, permits a fine tuning of the catalytic stereoinduction.

Recently, Michael addition reaction between enamine-activated aldehydes and nitroalkenes, originally reported by Hayashi,[46] has become a focus of attention. In fact, this reaction has been intensively studied from a mechanistic point of view by several groups.[47] Initial investigations led to conclude that the reaction follows the mechanism outlined in **Scheme 3**, where a cyclobutane, deriving from a formal [2+2] cycloaddition, and an oxazine *N*-oxide, deriving from a formal hetero-[4+2], are formed as "off-cycle" species (observed by NMR analysis), isomers of the productive intermediate, which is a non-cyclic zwitterion. The rate-determining step was then found to be the protonation of the zwitterionic intermediate. Therefore, addition of an acidic co-catalyst is important to achieve high reactivity and rapid turnover. These studies, conducted by Seebach and Hayashi, as well as by Blackmond and Pihko, shed light on the mechanism. Although some controversy regarding the reaction route and the role for the observed intermediates still remains, these researches gave a detailed insight into a synthetically important reaction. These studies demonstrate that the mechanisms of these reactions might be much more complex than it is often supposed to be.

[46] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

[47] (a) J. Burés, A. Armstrong, D. G. Blackmond, *Acc. Chem. Res.* **2016**, *49*, 214; (b) G. Sahoo, H. Rahaman, Á. Madarász; I. Pápai, M. Melarto, A. Valkonen, P. M. Pihko, *Angew. Chem. Int. Ed.* **2012**, *51*, 13144; (c) K. Patora-Komisarka, M. Benhound, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719; (d) T. Földes, Á. Madrasáz, Á. Révész, Z. Dobi, S. Varga, A. Hamza, P. R. Nagi, P. M. Pihko, I. Pápai, *J. Am. Chem. Soc.* **2017**, *139*, 17052; (f) D. Seebach, X. Sun, C. Sparr, M.-O. Ebert, W. B. Schweizer, A. K. Beck, *Helv. Chem. Acta* **2012**, *95*, 1064; (g) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2012**, *134*, 6741, corrigendum: *J. Am. Chem. Soc.* **2012**, *134*, 14264.



Scheme 3. *Mechanism for the enantioselective addition of nitroalkenes to enamines with some experimentally observed intermediates.*

1.3.4 *Noncovalent Catalysis*

In general, **noncovalent organocatalysts** can be classified into *hydrogen-bonding catalysts* and *Brønsted acid catalysts*, although these catalysts may rely on other additional noncovalent interactions at the same time. The general concept is the same applied until now: a chiral enantiopure species act as a catalyst so that it can promote both the reaction, but also induces chirality in the products.

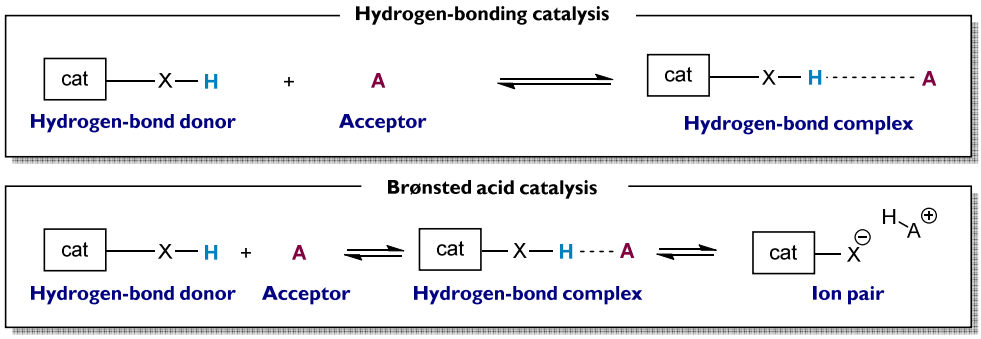


Figure 14. *Different activation mode between common organocatalytic noncovalent catalysis*

The hydrogen-bonding catalysts activation mode relies on a hydrogen bond donor, coordinating toward an electronegative hydrogen bond acceptor (**Figure**

14, top), forming a *hydrogen bond complex*. The hydrogen bonds are flexible with regard to bond length and angle. The typical bond length of a hydrogen bond is 1.5 to 2.2 Å. The hydrogen bonds are stronger than a *van der Waals* interaction, but weaker than covalent or ionic bonds. In general, the combination of a neutral electrophile (acceptor) and a weak acid catalyst (donor) leads to hydrogen-bonding catalysis. In the case of the hydrogen bond-catalyzed reactions, a direct proton transfer from the catalyst to the electrophile will not occur, so we can not see the formation of a formal ion pair.

1.3.5 *Hydrogen-Bond Donor Catalysis*

Hydrogen bond plays a dominant role in biocatalysis and it is frequently exploited by enzymes in order to promote several biochemical processes. The main function is the activation of electrophilic species towards the attack of a nucleophile. This is rendered possible since the H-bond is able to remove electronic density from the acceptor molecule. Thus, H-bond catalysis relies on the stabilization of the transition state of the reaction, induced by dipolar interactions that happen within a confined chiral space.

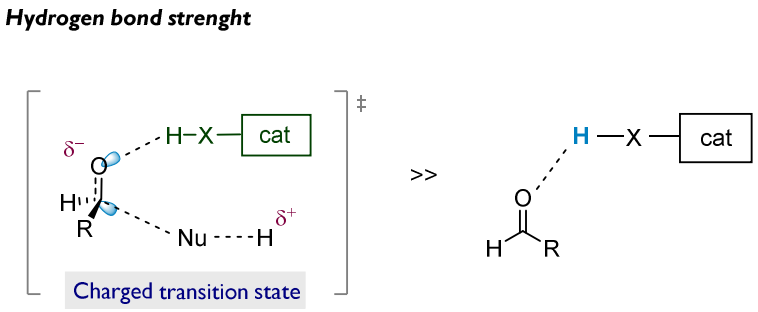
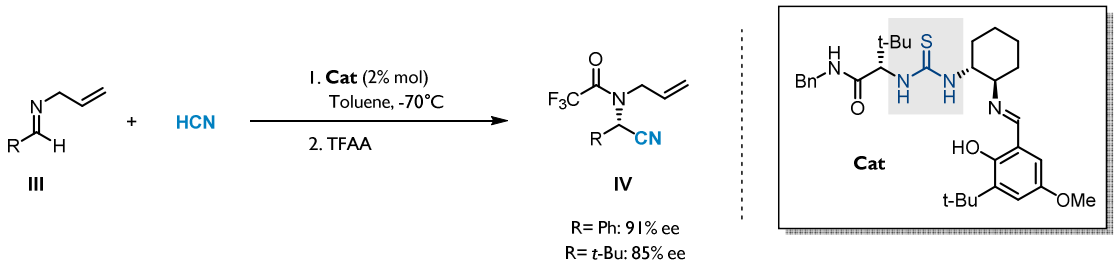


Figure 15. *charged TS stabilize the complex allowing the nucleophilic attack on the carbonyl*

The first examples of the employment of H-bond donors organocatalyst can be found in two already cited reports by Jacobsen and Corey. The authors reported that asymmetric Strecker reactions could be efficiently promoted by hydrogen-bonding catalysts, through the activation of electrophilic imines.



Scheme 4. *Chiral thiourea's catalyzed Strecker reaction*

Years later Jacobsen showed that these H-bonding based catalysts could be used for other reactions,[48] launching *de facto* the generic use of enantioselective H-bonding catalysis. The acidic portion of the catalyst can also be combined by another moiety constituted by a Brønsted basic portion (a tertiary amine), connected through a chiral framework, that can act now as a dual-activating species. Importantly, the acidic moieties are considered to be as "neutral" hydrogen bond donors, that means they do not quench the basic amine by quantitative protonation. One of the most famous catalysts of this family are derived from *Cinchona* alkaloids or from *trans*-1,2-cyclohexanediamine.

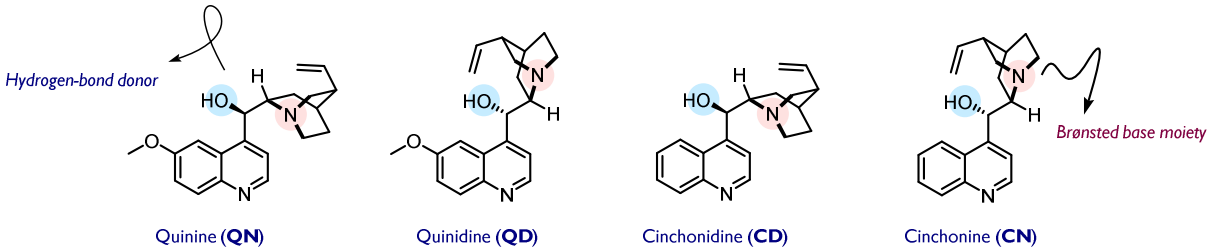


Figure 16. *Cinchona-alkaloids derivatives used as a bifunctional chiral catalysts*

The tertiary amine moiety is responsible for the basic/nucleophilic activation, whereas the alcoholic group acts as the hydrogen bond donor. The hydroxyl group can be easily turned into an ester, ether or, by means of a Mitsunobu reaction, into an amine moiety (with inversion of configuration).

This, in turn, is a versatile handle for the linkage to other H-bond donors, such as squaramides, ureas or thioureas. The modification of the substituents on their *N*-

[48] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.

atoms allows the proper modulation of steric hindrance and electronic proprieties (**Figure 17**).

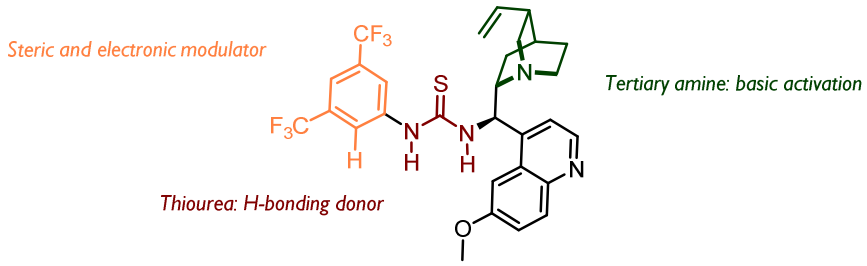


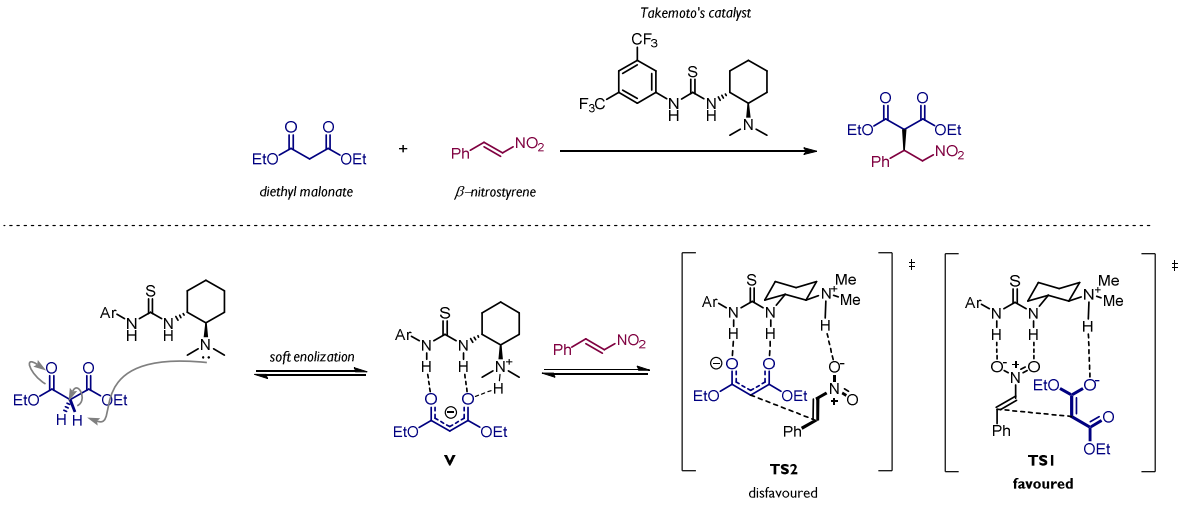
Figure 17. *Thiourea-based bifunctional catalyst derived from 9-deoxy-9-amino-*epi *Cinchona alkaloids.*

The thiourea is often functionalized with a *3,5-bis(trifluoromethyl)-phenyl* group, due to its rigidity, the electron withdrawing moiety reduces the pK_a of N–H proton and capacity to enhancing the acidity of the *ortho-* proton, to ensure more tight transition states, and thus, a better catalytic activity.[49] The Michael addition of 1,3-dicarbonyl compounds on nitroolefin mediated by H-bonding based catalysts was first developed by Takemoto in 2003.[50]

In the first step, the nucleophile is generated by deprotonation of the pronucleophile species, in a soft-enolization process. This anionic species is stabilized, and by so doing strongly anchored to the catalyst chiral scaffold, by multiple H-bonds between the protonated tertiary amine and the acidic N-H moieties of the thiourea. The electrophile is then coordinated to the thiourea protons, generating an ordered tertiary complex. Both the reaction partners are activated and brought together in a chiral environment and can easily form a new C-C bond. The thus formed nitronate is then quenched by protonation through a proton transfer from the tertiary amine moiety (now an ammonium cation), delivering the final product and releasing the free catalyst, ready to deprotonate another molecule of pronucleophile again (**Scheme 5**). The mechanism of this reaction was investigated through density functional theory (DFT) calculations by

[49] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919.
[50] Y. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

Pápai's group.[51] Between two transition states **TS1** and **TS2**, the reaction would proceed predominantly via transition state **TS1** due to the lower activation barrier.



Scheme 5*. Reaction model for the catalytic asymmetric addition of malonate to nitroalkene.*

To prove the broadness of the activation, Takemoto's group synthesized a functionalized chiral bifunctional thiourea for an enantioselective Petasis-type reaction using organoboronic acids. In the presence of catalyst and PhOCOCl, they were able to activate quinoline with vinyl boronic acid to afford the corresponding adduct in 96% ee. In this reaction, electrophilic quinoline is activated as a reactive *N*-phenoxycarbonyl quinolinium salt.

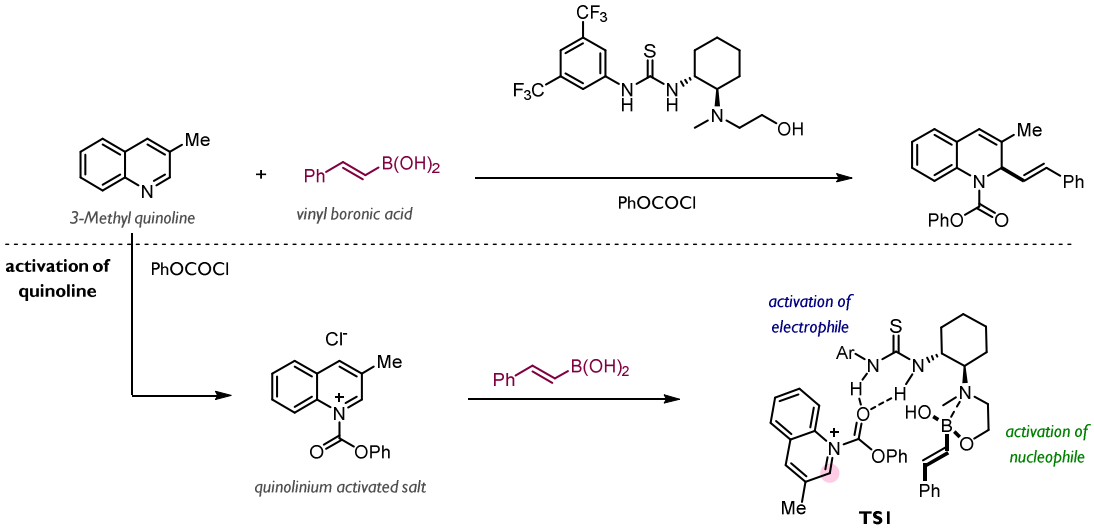


Figure 18. *Asymmetric Petasis-type reaction*

[51] Hamza A, Schubert G, Soós T, Pápai I, *J. Am. Chem. Soc.* **2006**, *128*, 13151.

Moreover, the chiral chelating aminoalcohol group of catalyst activates the vinyl boronic acid by coordinating with the boron atom and directs the stereochemical outcome of the reaction.[52]

1.3.5 *Brønsted Acid Catalysis*

Brønsted acid catalysts, as H-bond donor catalysts, are able to enhance the reactivity of electrophilic species by decreasing their electron-density. The unique versality of Brønsted acid catalysis relies on the extremely small and labile character of the catalytic active species such as the acidic hydrogen atom. As a result, an impressive diversity of complex scaffolds was recently obtained thanks to these concepts. One of the most important features of Brønsted acid catalysts is the pKa of the acidic proton: *soft acid* usually activate substrate by means of hydrogen bonds, and *hard acid*, for which direct protonation usually occurs and the chiral information is transferred through an ion-pair formation. This distinction is not an inner property of the acid, but more properly depends on the substrate-catalyst complex. One of the most known catalyst are BINOL-derived phosphoric acids introduced by Akiyama[53] and Terada[54] in 2004. Due to their axial chirality, they form a chiral cavity in which the reactions take place. Initially acting as a Brønsted acid, the catalyst protonates one molecule of substrate, the electrophilicity of which is heightened. In fact, the proton transfer goes together with the increasing Lewis basic character of the catalytic species. These emerging basicities, in turn, involved in the activation of protic nucleophiles. Such bifunctionality results in highly organized transition states and high levels of sterecontrol (**Figure 19**).

[52] Yamaoka Y, Miyabe H, Takemoto Y., *J. Am. Chem. Soc.*, **2007**, *129*, 6686.
[53] T. Akiyama, J. Itoh, F. Yokota, K. Fuchibe, *Angew.Chem.Int. Ed.* **2004**, *43*, 1566.
[54] D. Uraguchi, M. Terada, *J. Am. Chem.Soc.* **2004**, *126*, 5365.

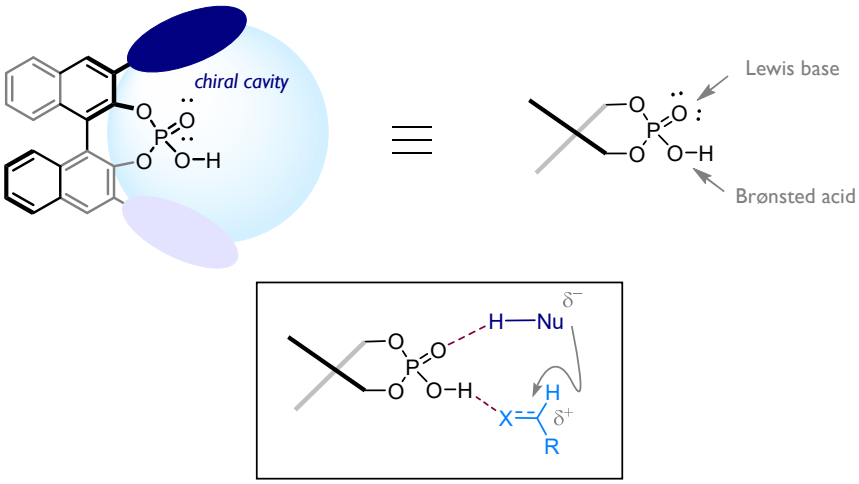
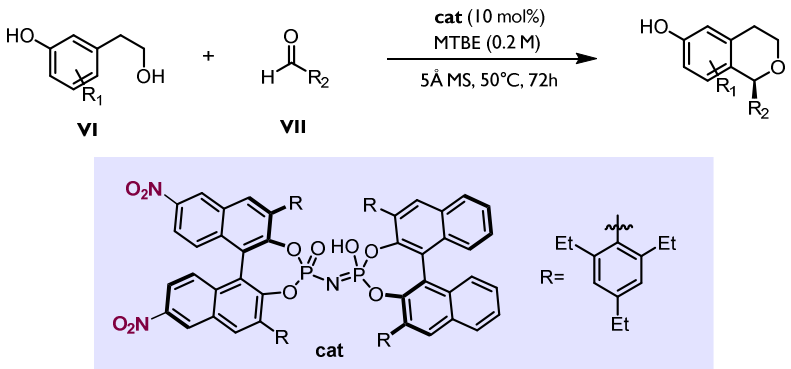
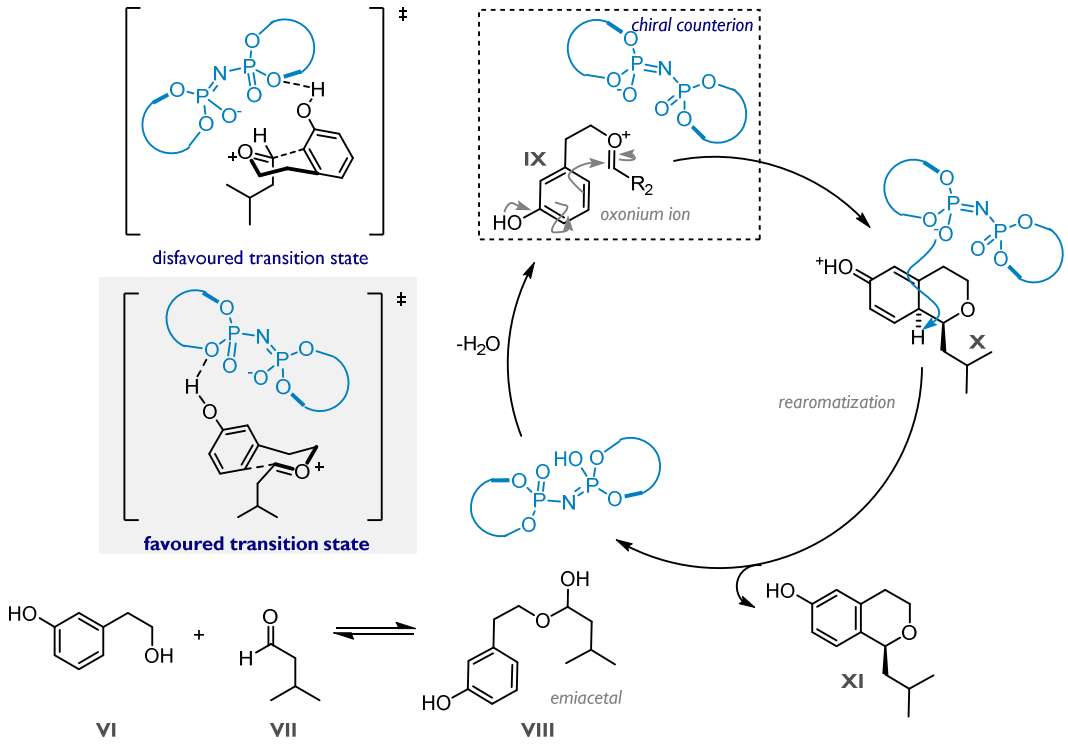


Figure 19. *Phosphoric acid activation mode*

When a catalyst is a stronger acid, the proton transfer to acceptor occurs to give an ion pair via the hydrogen bond complex. In contrast to hydrogen-bonding catalysts, the combination of basic electrophile (acceptor) and stronger acid catalyst (donor) leads to Brønsted acid catalyzed reactions. Therefore, the nucleophilic addition to basic imine is often assumed to proceed via the formation of ion pair. These catalysts might be simply distinguished in the point of view of proton transfer from catalysts. However, it is frequently difficult to make a clear distinction between hydrogen-bonding catalysts and Brønsted acid catalysts, because there is the equilibrium between a hydrogen bond complex and an ion pair.[55] One recent example of Brønsted acid catalysis reported by List[56] shows a new and unusual phosphoric acid dimer promoting an oxa-Pictet-Spengler reaction (**Scheme 6**).



[55] J. Merad, C. Lalli, G. Bernadat, J. Maury and G. Masson, *Chem. Eur. J.* **2018**, *24*, 3925.
[56] B. List, N. Tsuji, *Synfacts* **2016**;*12*, 1092.



Scheme 6. *Asymmetric oxa-Pictet-Spengler reaction*

1.4 Peptide-catalysis

Selective reactions are ubiquitous in the natural world. Due to their intricate molecular structure, in such processes, enzymes exhibit extraordinary degrees of stereoselectivity and can also display remarkable substrate specificity, allowing for very high levels of chemo and regioselectivity. The spatial arrangement of enzymes plays a significant role in selective substrate binding by creating clefts or pockets in which compounds may only fit in a certain orientation. Toward the middle range of catalyst's molecular weight, peptides composed of 2-50 amino acids have gained interest as effective catalysts for a number of enantioselective methods. Peptide catalysts possessing only a few amino acid residues could adopt a secondary structure, that can mimic the chiral pocket of a protein-based catalyst, suitable for the chirality transfer. Moreover, active as a miniaturized protein-based catalyst, the modular nature of peptides allows for *fine-tuning* of both reactivity and

selectivity. Large structural and functional diversity can be easily accessible by linking amino acids with different functional groups in their side chains with each other. For example, a diversity of 20^5 = 3.2 x 10^6 different pentapeptides is generated by combining 20 different amino acids randomly in any possible combination.

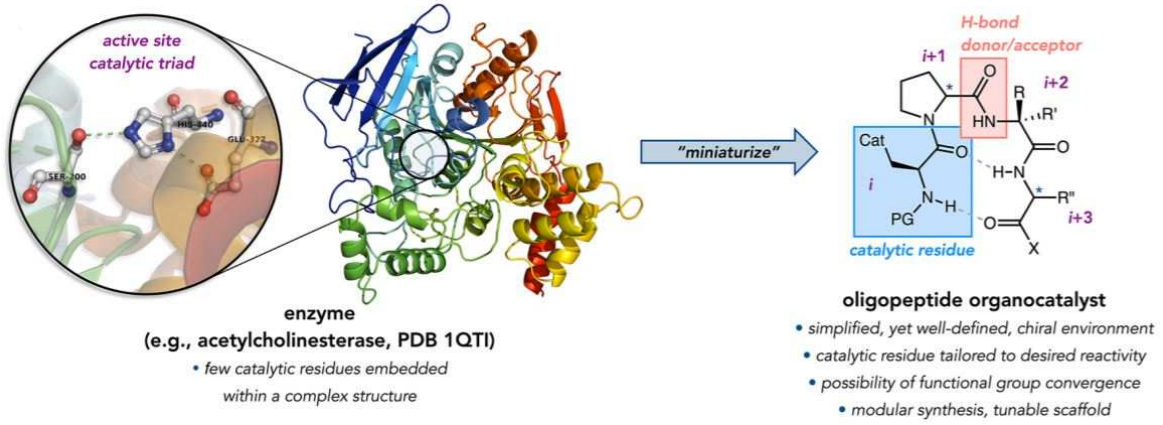
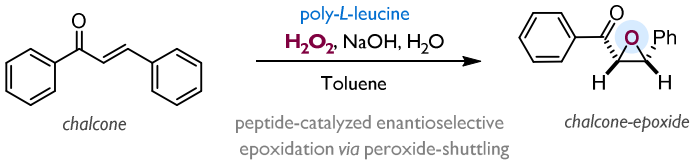
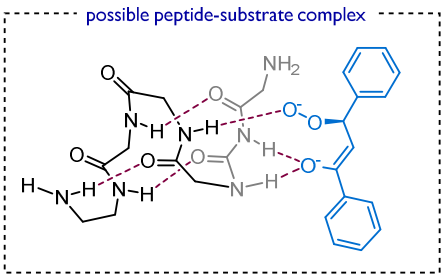


Figure 20. *Miniaturization of the active site of an enzyme*

Together, these factors produce an attractive catalyst library for asymmetric synthesis, that continued to attract the attention of chemist in the last decades. As early as the 1970s, Inoue demonstrated that poly(amino acids) are effective catalysts for the conjugate addition of thiols to enones. A few years later, Julià´ and Colonna reported the use of such olygomers in the enantioselective epoxidation of chalcones and related enones.





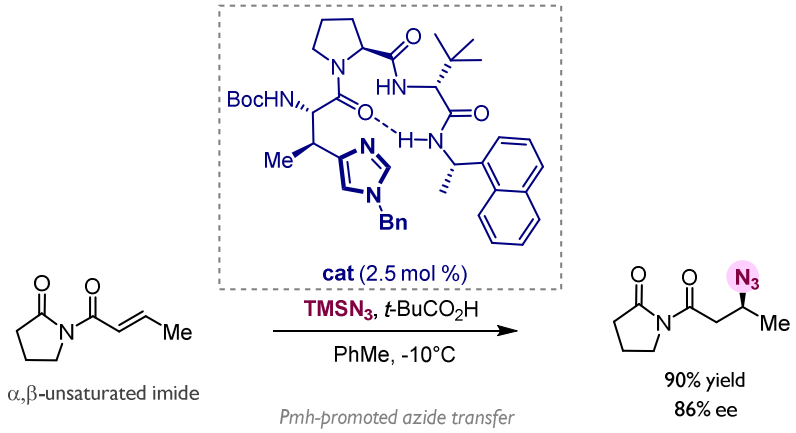
Scheme 7. *Julià-Colonna epoxidation*

In **Scheme 7** is also shown a possible aggregation model for the TS in which H-bonding with the unprotected amidic residues stabilizes the peroxide enolate intermediate and orients the structure for ring closing with hydroxide displacement.

These studies prompted the researchers to investigate other type of peptide structures, showing that oligomers are far from the only effective peptide catalysts for asymmetric synthesis; smaller peptide catalysts have also played a prominent role in enantioselective catalysis.

Recent work by several groups in the arena of group transfer reactions, enantioselective aldol reactions, formal acyl anion chemistry, enantioselective protonation of enolates, Michael additions, and the Morita-Baylis-Hillman reaction have firmly established small peptides as versatile, enantioselective catalysts.[57]

Approximately three decades after Inoue's first reports of the poly(amino acid)-catalyzed conjugate addition, it has been found that peptides are effective catalysts for direct enantioselective conjugate addition reactions. These studies conducted by Miller and coworkers have reported the enantioselective addition of $TMSN_3$ to unsaturated imides. The products of this method are easily converted to α-amino acids and triazoles with conservation of enantiomeric purity. As shown in **Scheme 8**, treatment of enone with an excess of acid and $TMSN_3$ in the presence of a tertiary amine results in smooth azidation.



Scheme 8. *Peptide-Catalyzed Enantioselective Conjugate Addition of Azide*

[57] E. A. C. Davie, S. M. Mennen, Y. Xu, and S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759−5812.

After that a variety of amine catalysts were found to be effective, it was discovered that resin-bound peptide catalyst, containing a Pmh residue, is a highly competent catalyst for the process, providing the azide in excellent yield and good to excellent enantiomeric excess.

Following these studies, the same group envisioned that enantioselective S_EAr might be of broad synthetic utility. The growing interest in atropisomeric biaryls in pharmaceuticals and natural products,[58] as well as in chiral ligands and organocatalysts,[59] prompted them to investigate a novel peptide-catalyzed atroposelective brominations. With a rational choice of the perfect substrate suited for both the nucleophilic addition and the ability of rapidly racemizes *in situ*, preferential bromination of one enantiomer by a peptide-based catalyst could establish a Curtin−Hammett scenario. This type of Dynamic Kinetic Resolution (DKR) would require a low substrate racemization barrier for the substrate, to have a rapid interconversion relative to bromination, and that the product is configurationally stable (**Figure 21**).

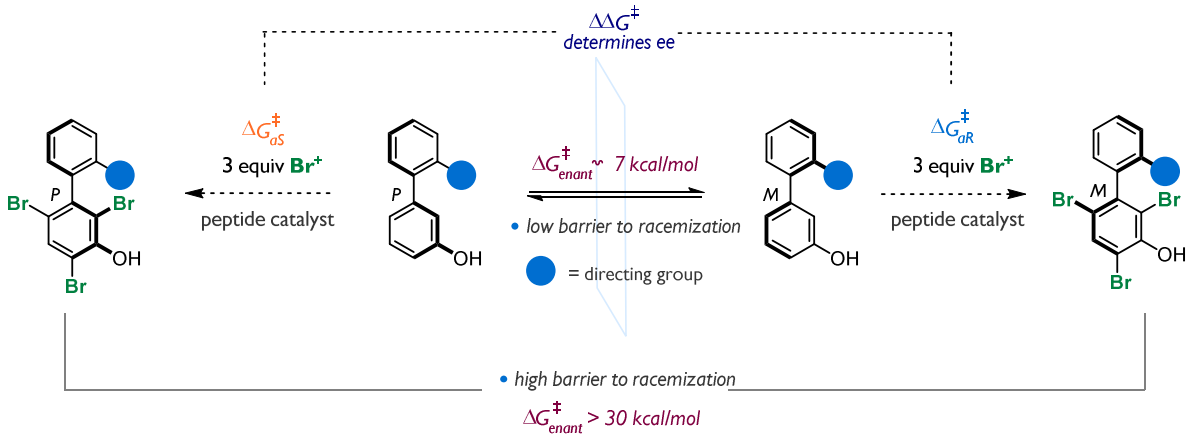


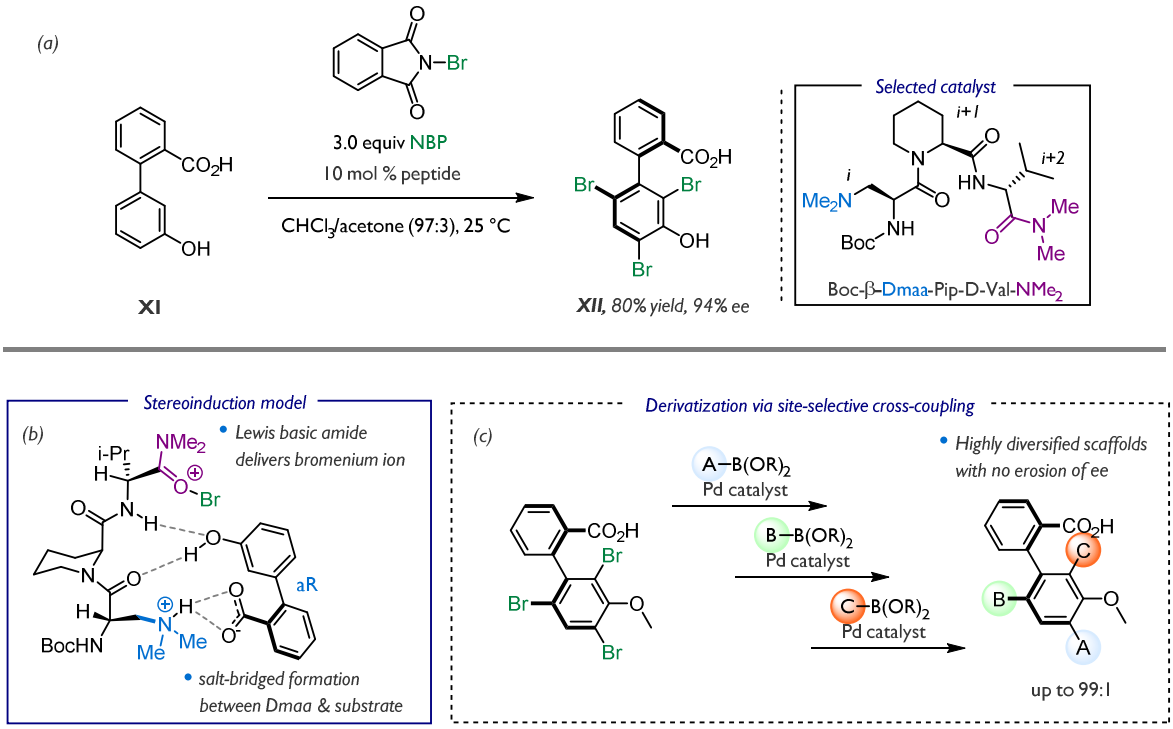
Figure 21. *Biaryl DKR via atroposelective bromination*

Compared from the previous reported example, in which Pmh was employed as active residue, this time, due to a parallel unwanted bromination of the imidazolic

[58] (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401. (b) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427.

[59] Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3070.

core, Dmaa residue was found to be perfect to promote the atroposelective reaction in high yield and excellent enantioselectivity (**Scheme 9a**).[60]



Scheme 9. *(a) Peptide-catalyzed, atroposelective biaryl bromination. (b) Proposed model for stereoinduction. (c) derivation via Palladium catalyzed cross-coupling reaction*

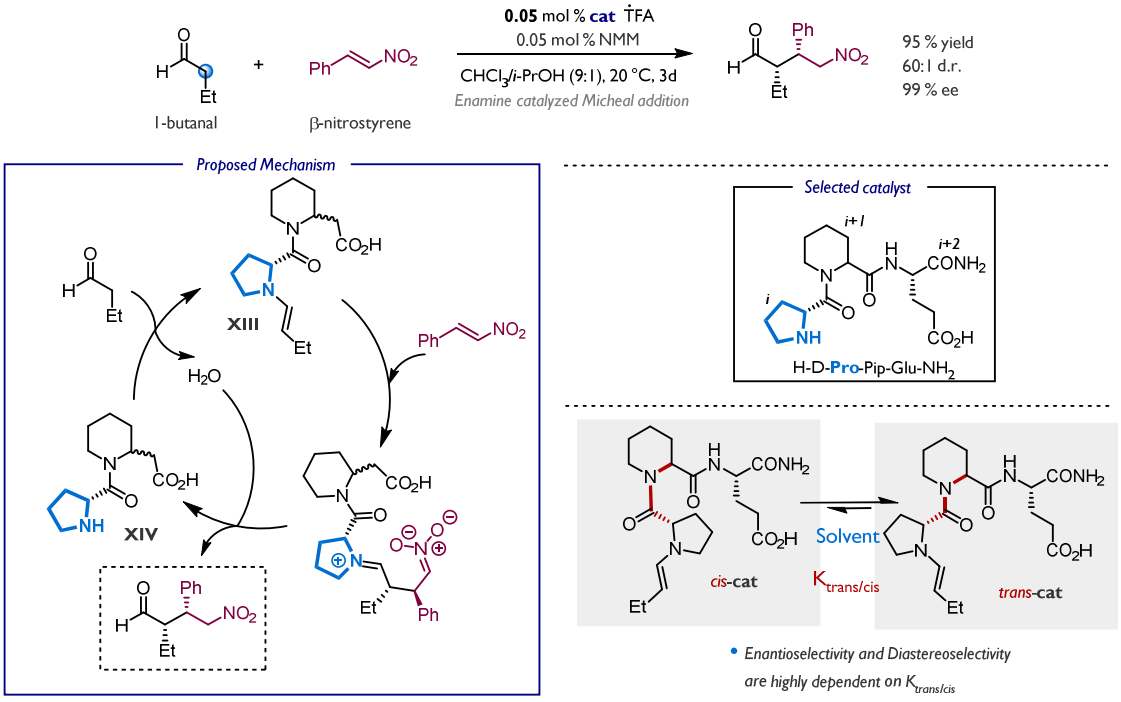
One of the advantages of selective electrophilic aromatic bromination is the possibility for further derivatization via cross-coupling. Since the tribrominated product contains three sterically and electronically distinct bromides, the same group developed an "A−B−C coupling" method that enables the synthesis of pentaphenyls and other derivatives via sequential, Pd-catalyzed cross-coupling of methyl esters (**Scheme 9c**).[61]

As we could see, due to a large number of non-rigid rotatable bonds, the main challenge for these processes relies on the ability to find the perfect catalyst with the adapt conformation to achieve the tightest transition state possible. One example on the pivotal importance in the catalyst conformation was accomplished

[60] Gustafson, J. L.; Lim, D.; Miller, S. J. *Science*, **2010**, *328*, 1251.
[61] Gustafson, J. L.; Lim, D.; Barrett, K. T.; Miller, S. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5125.

by Wennemers group in which the *trans*/*cis* ratio of the tertiary amide bond was found to have a significant effect on the stereochemical outcome of reactions catalyzed by H-Pro-Pro-Xaa-NH_2-type peptides.[62] They discovered that controlling over the *trans*/*cis* amide bond ratio provides a tool to optimize the catalytic performance of peptidic catalysts. After replacing middle Pro residue within the tripeptides with analogues of varying ring sizes (azetidine carboxylic acid, *Aze*, and piperidine carboxylic acid, *Pip*) to produce different *trans*/*cis* ratios in different solvents.

The studies revealed a direct correlation between the *trans*/*cis* amide bond ratio and the enantio- and diastereoselectivity of structurally related peptidic catalysts. They finally identified of H-D-Pro-Pip-Glu-NH_2 as a highly reactive and stereoselective amine-based catalyst that allows C−C bond formations to be performed in the presence of 0.05 mol %, which is the lowest catalyst loading yet achieved for organocatalyzed reactions that rely on an enamine-based mechanism.



Scheme 10. *Peptide-catalyzed Michael addition of aldehyde on nitrostyrene*

[62] T. Schnitzer, H. Wennemers *J. Am. Chem. Soc.* **2017**, *139*, 15356.

One of the most venerable reactions in asymmetric synthesis, especially regarding peptide-catalytic systems are *asymmetric oxidation reactions*. Many highlights of this history are potent metal-catalyzed methods,[63] ketone catalysts,[64] and also the already mentioned Julià-Colonna reaction of chalcones catalyzed by oligoamides such as poly(Ala).[65] Prof. S. J. Miller group started to develop a catalytic cycle for oxidation in which the side-chain of a peptide-embedded aspartic acid shuttles between the carboxylic acid and the corresponding peracid formed *in situ*, the system,[66] which has proven particularly effective for electrophilic oxidation, is well suited to a variety of substrate and reaction types (**Figure 22**).

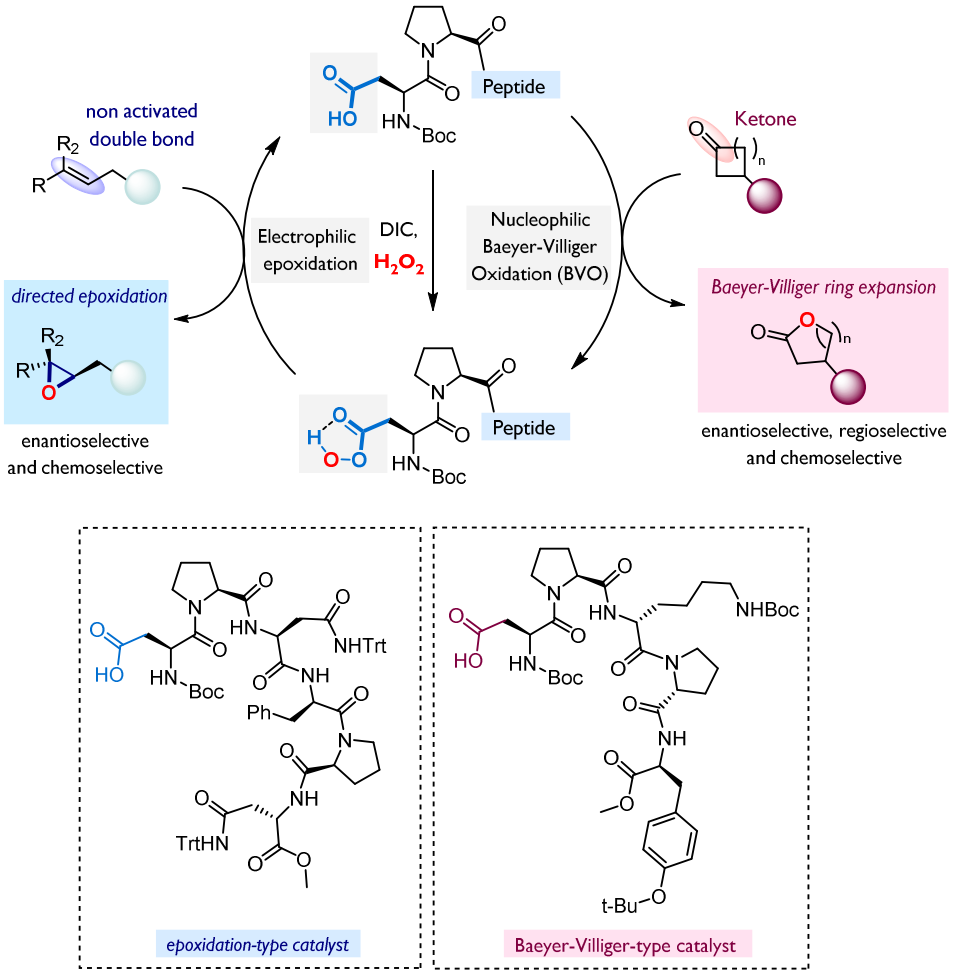


Figure 22. *Aspartic-embedded residue activation mode in epoxidation and BV reaction*

[63] Jacobsen, E. N.; Wu, M. H. In Comprehensive Asymmetric Catalysis II; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**, 649.
[64] (a) Denmark, S. E.; Wu, Z. C. *Synlett*, **1999**, 847. (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.
[65] (a) Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006**, *84*, 74. (b) Berkessel, A.; Koch, B.; Toniolo, C.; Rainaldi, M.; Broxterman, Q. B.; Kaptein, B. *Biopolymers* **2006**, *84*, 90.
[66] Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710.

The selectivity of the reaction is controlled by the peptide sequence, which may be tuned for the regio- and enantioselective oxidation of various substrates. Notably, this approach may also be applied to cases where the reversal of a substrate's intrinsic reactivity is desired. With their extensive works, they thus established that aspartyl peptides can catalyze either epoxidation reactions (as electrophilic oxidants) or BV oxidations (as nucleophilic oxidants), with accompanying diastereo-, regio, and chemoselectivity, when presented with a different site intramolecular choice.

The molecular context in which the aspartyl residue is placed the peptide sequence defines the catalyst secondary structure and provides the capacity to control orthogonal functional group.

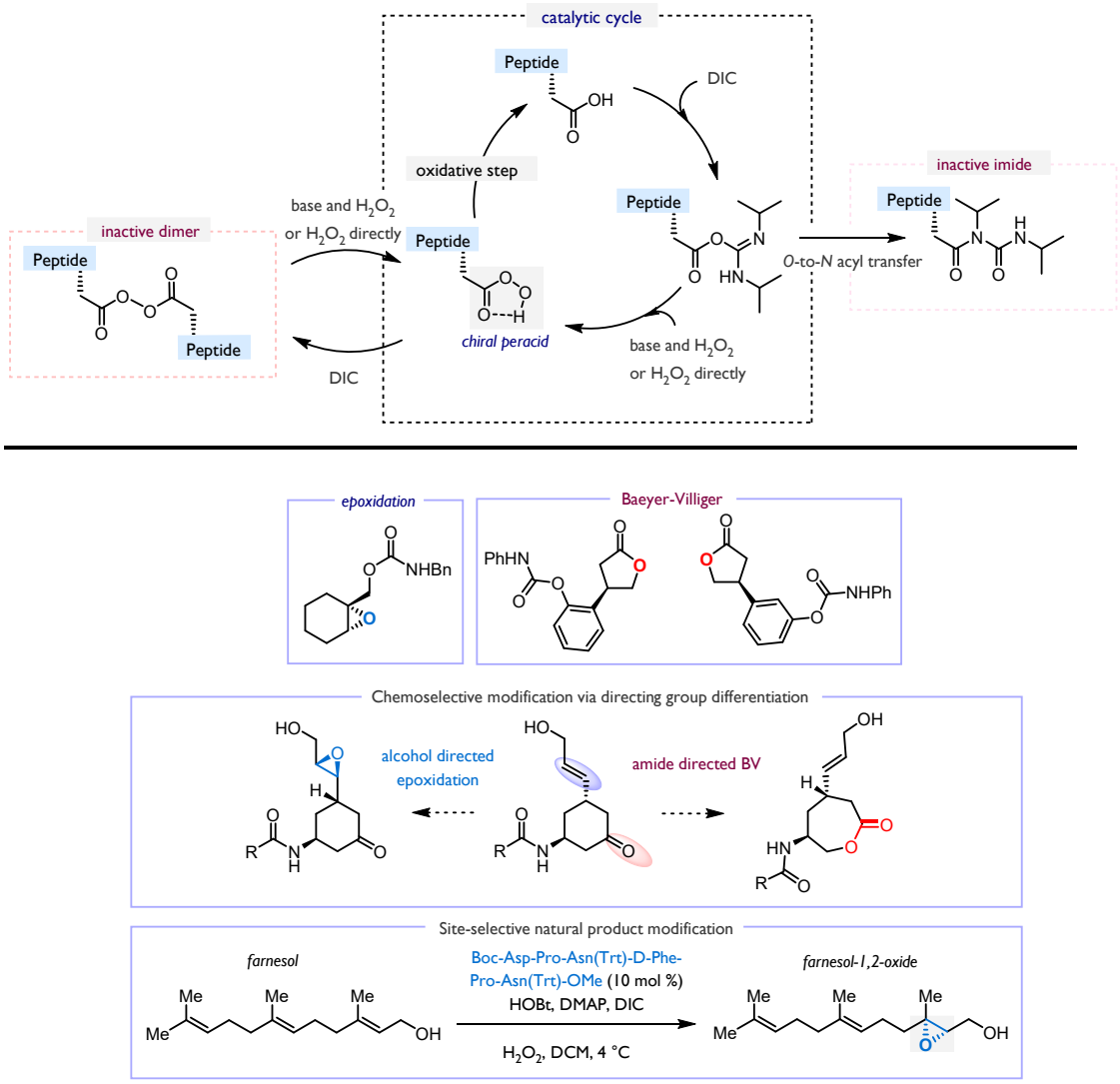


***Figure 23**. Proposed mechanism for catalyst activation (top), and selected examples of peptide catalyzed oxidation (bottom)*

The ability to dial in functional group selectivity, while controlling attendant stereoselectivity issues, is a dimension that can be used to create new possibilities for orchestrating the assembly of complex molecules, and for complex scaffold diversification. To prove that epoxidation reaction was employed in the site-selective modification of natural product such as *farnesol,* a sesquiterpene with different alkenes (**Figure 23**).

Perhaps more fundamentally, the peptide-regulated selectivity for specific functional groups within a multifunctional substrate signals control over the mechanistic behavior of common catalytic machinery, which at present seems to be known primarily only in the context of enzymes.

1.5 Desymmetrization

Enantioselective desymmetrization is a powerful tool for the generation of complex molecules from relatively simple achiral or *meso* building blocks. With the appropriate choice of reagents and catalysts, multiple stereogenic elements can be set in one reaction with high enantioselectivity, making such strategies especially attractive in complex natural product synthesis. This is the reason why researcher's interest increased in recent years focusing into developing new enantioselective desymmetrisation reactions.[67]

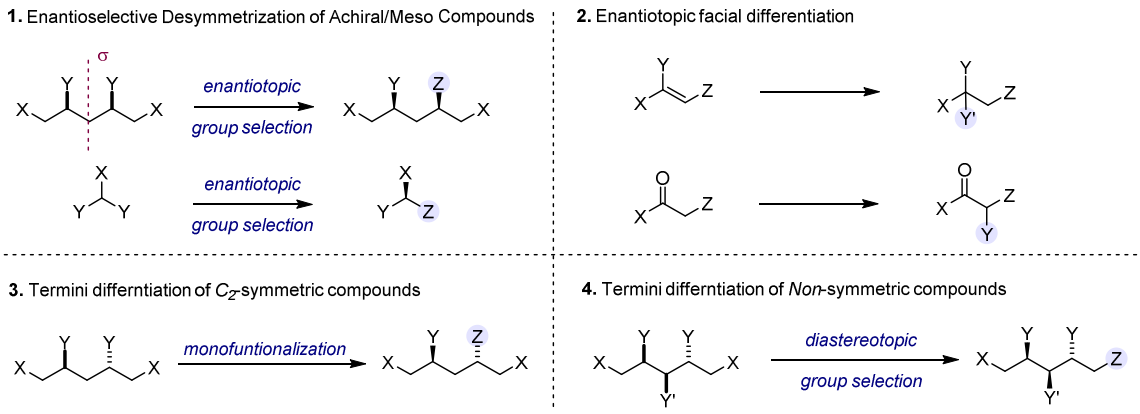
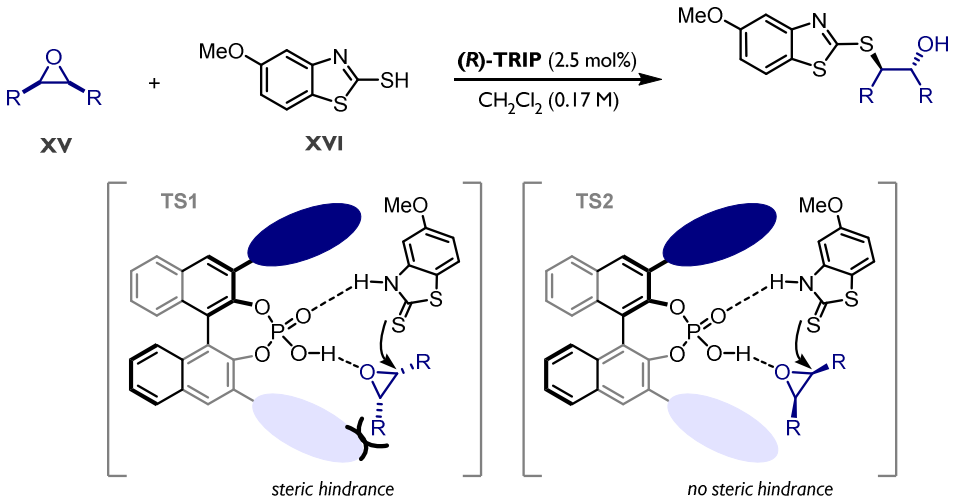


Figure 24. *Illustration of the definition of enantioselective desymmetrization*

[67] A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson and D. J. Dixon, *Chem. Soc. Rev.*, **2016**, *45*, 5474.

In particular, the advent of organocatalysis has opened up many exciting new opportunities, providing fundamentally different reactivity modes to more traditional metal-catalysed desymmetrizations.[68] One of most commonly employed substrate in desymmetrization strategies has been epoxides, *via* nucleophilic ring-opening transformations. Sun *et al.* have demonstrated this

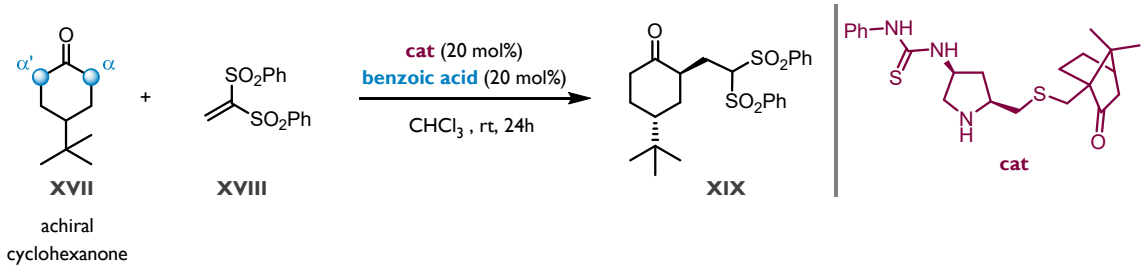


Scheme 11. *Chiral phosphoric acid-catalyzed epoxide ring opening desymmetrization*

approach, by employing enantioselective ring-opening reactions on meso-epoxides with heterocyclic thiol nucleophiles, achieving moderate to high yields with good enantiomeric excess (**Scheme 11**).[69]

Chen and co-workers reported the use of a novel camphor-derived pyrrolidine catalyst for the enantioselective Michael addition of 1,1-bis(phenylsulfonyl)ethylene to 4-substituted cyclohexanones (**Scheme 11**). Incorporating a thiourea moiety and synthesized in six steps from functionalized L-proline and camphor derivatives, in the presence of catalytic benzoic acid the bifunctional organocatalyst facilitated the formation of trans-2,4-disubstituted cyclohexanones. Unfortunately, despite the good ees, yields were dependent on the substitution pattern and poor drs were achieved.[70]

[68] D. W. MacMillan, *Nature* **2008**, *455*, 304.
[69] Z. Wang, W. K. Law and J. Sun, *Org. Lett.* **2013**, *15*, 5964.
[70] Y. M. Chen, P.-H. Lee, J. Lin and K. *Chen, Eur. J. Org. Chem.* **2013**, 2699.



Scheme 12. *Enantioselective α-alkylation of 4-substituted cyclohexanones via Michael addition to vinyl sulfone*

Because chiral compounds constitute, in general, the most expensive reagents in a synthetic sequence, and the inner difficulty of the preparation of perfectly stereodefined molecules, enantioenriched compounds are among the most expensive part in a synthetic route. Moreover, from an eco-compatible point of view, the use of chiral reagents bearing a chiral moiety that is not embedded in the final target molecule results in expensive waste. While in the case of enantioselective catalysis, researchers can circumvent these drawbacks thanks to the use a small amount of chiral catalyst, in case of multisteps synthesis, such as medicinal chemistry synthesis and total synthesis, this become great disadvantages.Hence, coupled with enantioselective catalysis, the desymmetrization of *meso* compounds appear then as a clever strategy. Indeed, complex chiral building blocks with several stereogenic elements can be prepared in a single enantioselective step using this strategy.[71] An example was accomplished in the preparation of Diospongin A, belonging to the diarylheptanoid natural products family. Despite the numerous reported syntheses of this natural product,[72] its hidden symmetry remained unexploited.

[71] J. Merad, M. Candy, J. Pons, C. Bressy, *Synthesis* **2017**, *49*, 1938.

[72] Examples of total syntheses of (–)-diospongin A: (a) Chandrasekhar, S.; Shyamsunder, T.; Prakash, J. S.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47. (b) Bressy, C.; Allais, F.; Cossy, J. *Synlett* **2006**, 3455. (c) Jennings, M. P.; Sawant, K. B. *J. Org. Chem.* **2006**, *71*, 7911. (d) Yadav, J. S.; Padmavani, B.; Reddy, B. V. S.; Venugopal, C.; Rao, A. B. *Synlett* **2007**, 2045. (e) Bates, R. W.; Song, P. *Tetrahedron* **2007**, *63*, 4497. (f) Kawai, N.; Hande, S. M.; Uenishi, J. *Tetrahedron* **2007**, *63*, 9049.

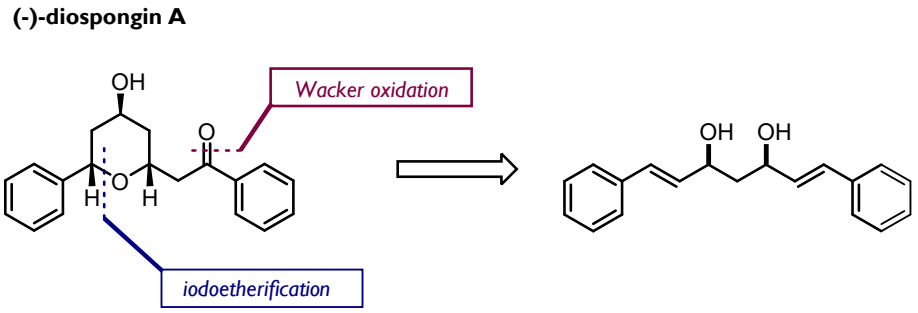
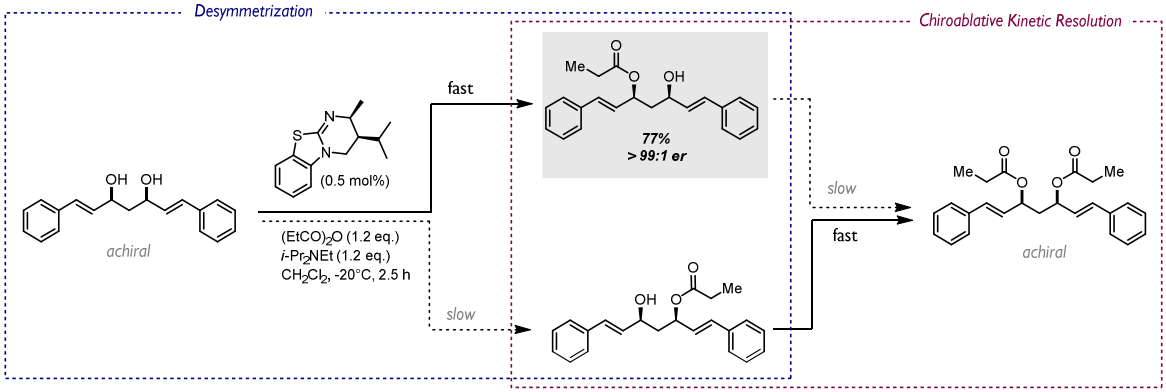


***Figure 25**. Chuzel/ Bressy's retrosynthetic analysis of (–)-diospongin A*

To achieve this goal, an associated methodology was developed to desymmetrize acyclic meso-1,3-diols, which appeared rather difficult due to the high number of possible conformations (**Figure 25**). An organocatalyzed acyl transfer was envisioned to break the symmetry of diol, easily synthesized in scalable amounts in two steps (aldol reaction and then syn-reduction of the ketone). Chiral isothioureas, acting as an enantioselective chiral acyl transfer catalyst, were found to be efficient catalyst to promote such challenging desymmetrization. The high level of enantioselectivity observed could be explained by the synergy between the desymmetrization step of diol, and the chiroablative kinetic resolution step involved in the second acylation (**Scheme 13**).



***Scheme 13.** Subtractive Horeau-type amplification during the organocatalyzed desymmetrization of meso-1,3-diol*

Chemist

Noun. [kem-is]

A person who solves a problem

You didn't know had in a way

You don't understand

See also **wizard, magician**

Chapter II

Aim of the Thesis

The aim of this Doctoral Thesis is to exploit the versatility of organocatalysis having as target the conceptualization, development and optimization of novel asymmetric organocatalytic transformations. With the perspective to expand the frontiers of this field of research in mind, the goal had been to tackle proactively challenges present in the organic chemistry scenario and solve them with innovative tools. Not only completely new reaction has been successfully accomplished, but sometimes a type of reactivity that was previously limited to stoichiometric or metal-catalyzed processes becomes accessible under a new type of catalysis, or moreover is possible, by investigating a new catalytic strategy, to impart stereoselection where only racemic protocols had been previously disclosed.

During the course of my PhD studies, various types of reactions have been devised and developed, requiring the use of different organocatalytic activation modes. Particular attention has been devoted to the study and optimization of the reaction conditions and catalyst structure, in order to maximize yield and enantiopurity of the products as well as minimizing the catalyst loading and using the mildest conditions. The substrate scope of asymmetric reactions has always been thoroughly investigated to demonstrate the broad applicability of the proposed transformations, as well as the performance of synthetic elaborations illustrating the usefulness of the developed methods.

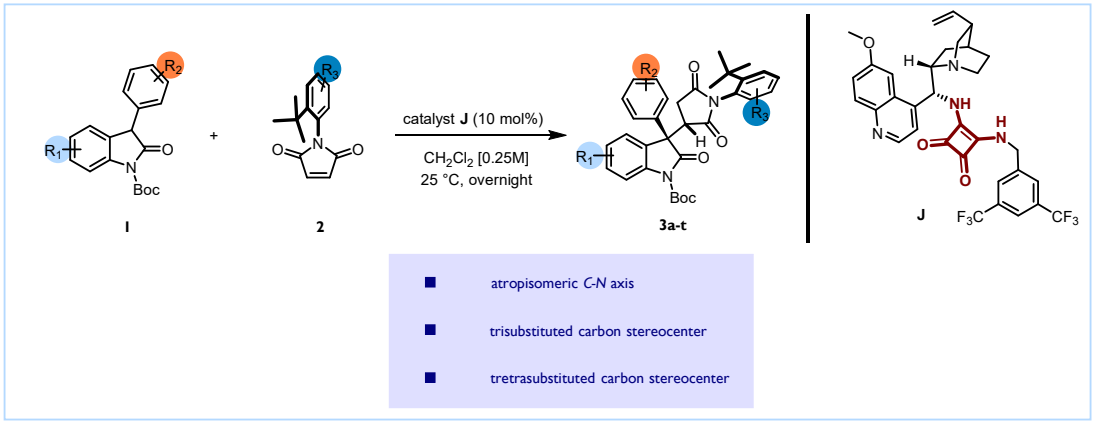
Despite being conceptually distinct work, enantioselective organocatalytic desymmetrization reaction was a *fil rouge* of my whole PhD work. Nevertheless, different catalytic strategies were employed, even if the transformations detailed in the following chapters are somehow linked together by simple and recurring modes of activation, induction and reactivity, promoted by the right catalysts.

2.1 Summary of the Research work

The following chapters describe how the intrinsic versatility of organocatalysts, combined with utilization of scaffolds previously unknown to organocatalysis, have been exploited to achieve new catalytic enantioselective processes.

In the first project (Chapter **3**) the desymmetrization of *N*-(2-*tert*-butylphenyl)maleimides was realized by means of a Michael reaction of *N*-(*tert*-butoxycarbonyl)-3-phenyloxindoles leading to the corresponding axially chiral succinimides in high yields. Michael addition on maleimides is a well-established methodology for the synthesis of chiral succinimides in an enantioselective fashion. Since the pioneering work of Curran[73], that proved for the first time the formation of atropisomeric succinimides after nucleophilic attack on the prochiral double bond of a hindered maleimides, my research group started an extensive work on the organocatalytic approach for maleimides desymmetrization. *N*-(2-*tert*-butylphenyl)maleimides have a hindered rotation of the C_{Ar}–*N* single bond. This implies the existence of a plane of symmetry in the starting material, which can be desymmetrized through nucleophilic addition at one of the two carbon atoms of the double bond, with the consequent generation of a stereogenic axis in the resulting succinimide. Because oxindole-containing molecules are extensively use in pharmaceutical industry, being a very bioactive scaffold, we envisioned the possibility of using 3-aryloxindole derived molecules as nucleophiles in the Michael addition. The resulting product would feature adjacent trisubstituted and tetrasubstituted all-carbon stereocenters and a *C*-*N* atropisomeric axis (**Scheme 14**).

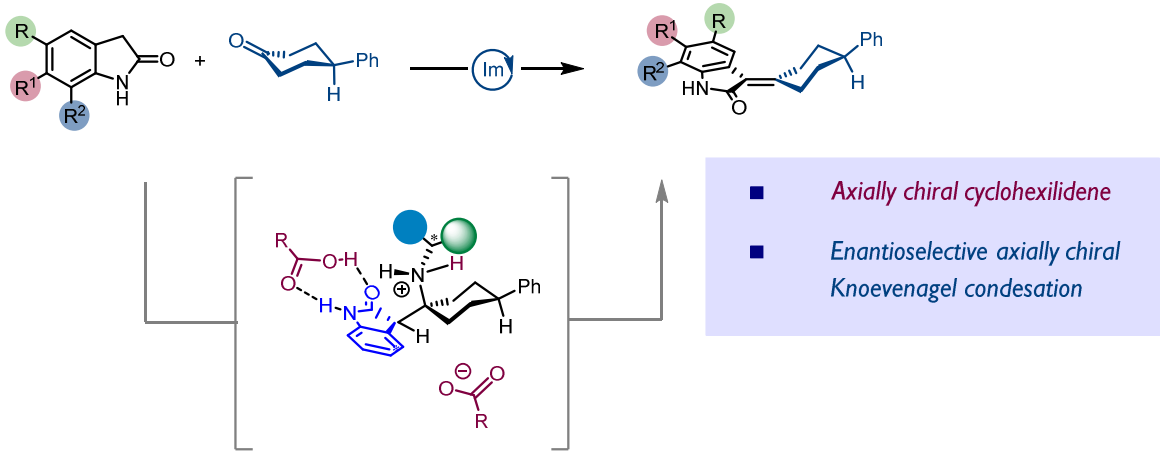
[73] Curran et al., *J. Am. Chem. Soc.,* **1994**, *116*. 3131.



Scheme 14. *Organocatalytic maleimide desymmetrization by means of Michael addition reaction*

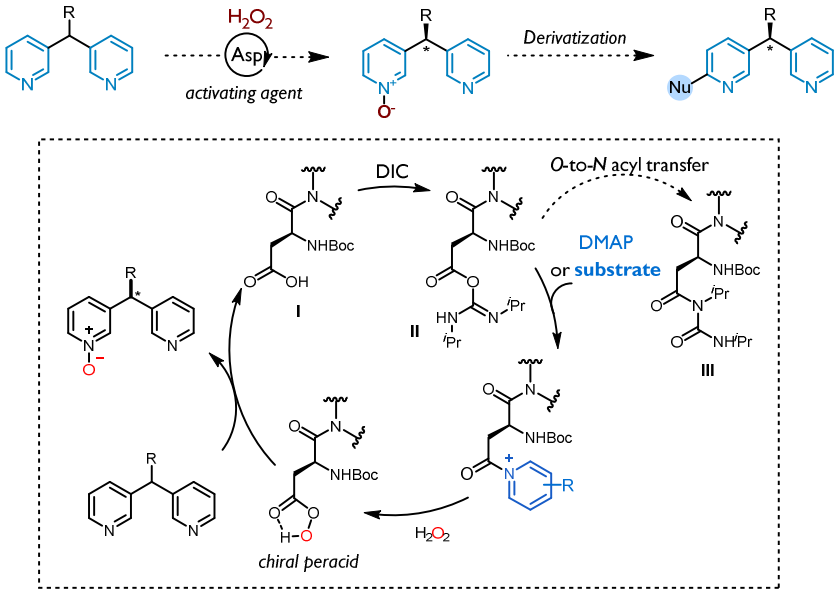
Given the chemical feature of the two starting material, the acidity of the dibenzylic hydrogen in the 3-position and the lone pairs in imidic carbonyl, we envisioned that the use of the bifunctional organocatalyst, such as thiourea- and squaramide-derivates from *cinchona* alkaloids, would be perfect to reach high level of reactivity and enantioselectivity.

My 2nd year project instead, focused on a less renowned kind of axial chirality. Indeed, usually we are prompted to imagine axial chirality only arising by the slow rotation around a single bond, namely *atropisomerism* (*vide* cap 1.2.4). Axially chiral compounds indeed can be divided in two main categories. Atropisomers, compound that are characterized by the existence of a stable stereogenic axis (biaryls, imides, anilides, amides and ethers), and compounds such as allenes and alkylidenecyclohexanes that do not fall within the definition of atropisomers, but have the symmetry broken thanks to their rigid structure. Despite the extensive work that is already been done on the enantioselective synthesis of allenes, less attention was instead encountered in the study of a catalytic way to obtain C=C cyclohexilidenes in an enantioselective fashion. Given that, we thought to employ one of the most renowned and well-established olefination reactions, such as the Knoevenagel condensation (**Scheme 15**).



Scheme 15. *Enantioselective Knoevenagel Condensation*

During my 3rd year of the PhD I spent six months working in the Prof. Scott J. Miller Laboratory at Yale University. Here I focused my attention from organocatalyst derived from natural sources, such as *cinchona* alkaloids derivatives, to catalyst derived from peptide. I will show how we developed a peptide-catalyzed enantioselective desymmetrization reaction *via* oxygen-shuttle pyridine *N*-oxidation reaction. Enantioselective syntheses of pyridines are often predicated on the use of chiral auxiliaries to the pyridine as a substituent,[13] or on an asymmetric catalytic reaction upon a pyridine containing a previously installed prochiral element.[14] Examples of chiral pyridine assembly are also known in which stereogenic centers are part of building blocks. Other examples to obtain chiral pyridines were based on the assembly through coupling of chiral reagents with the aid of asymmetric catalysis.[15] We were able, instead, to find an alternative route using non-metal catalytic molecules, in an unprecedented catalytic pyridine *N*-oxidation reaction, in which chirality is established *via* remote asymmetric desymmetrization reaction (**Scheme 16**).



Scheme 16. *Desymmetrization of diaryl-pyridyl-methanes via peptide-catalyzed N-oxidation*

Chapter III

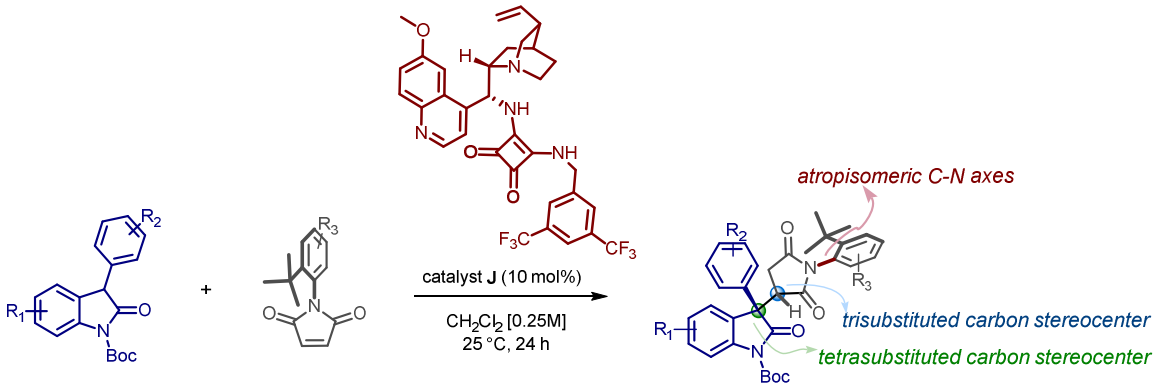
Desymmetrization of Maleimides

3.1 Targeting the Remote Control of Axial Chirality in N-(2-tert-Butylphenyl)-succinimides via Desymmetrization Strategy

All the procedures and results here described are part of- and can be found in-:

N. Di Iorio, L. Soprani, S. Crotti, E. Marotta, A. Mazzanti, P. Righi and G. Bencivenni, "Michael Addition of Oxindoles to *N*-(2-*tert*-Butylphenyl)maleimides: Efficient Desymmetrization for the Synthesis of Atropisomeric Succinimides with Quaternary and Tertiary Stereocenters", *Synthesis*, **2017**, *49*, 1519–1530. (*Invited Paper*).

Abstract:



The desymmetrization of *N*-(2-*tert*-butylphenyl)maleimides was realized by means of a Michael reaction of *N*-Boc-3-aryloxindoles leading to the corresponding axially chiral succinimides in high yields and enantiomeric excess. The use of a squaramide cinchonidine organocatalyst was fundamental to achieve the simultaneous remote control of the stereogenic axis and adjacent quaternary and tertiary stereocenters.

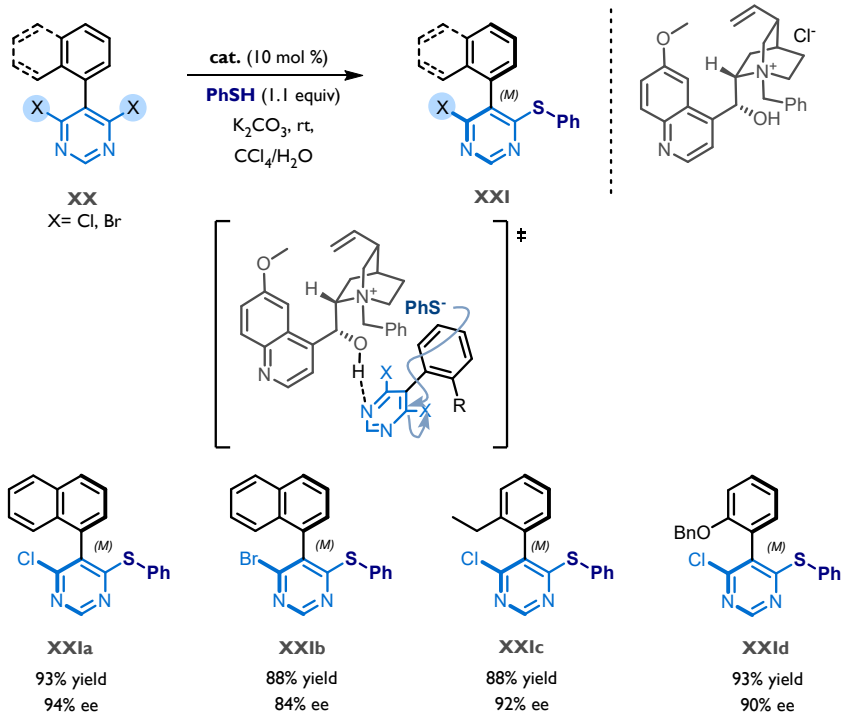
As already discussed in **Chapter 1.4** desymmetrizations reactions are now largely employed in enantioselective synthesis.[74] They initially found applications mostly for the synthesis of enantioenriched compounds bearing stereogenic centers, but they recently revealed to be efficient for the preparation of molecules containing stereogenic axes. This kind of substrates, as we said, are emerging as fundamental building blocks for the synthesis of natural and biologically active compounds, and they still continue to be primary architectures of chiral catalysts or ligands.[75]

3.2 Desymmetrization of Biaryls

One of the most important reaction for the functionalization of aromatic compounds is still *nucleophilic aromatic substitution* (NAS).[76] Useful processes have been realized following this venerable transformation. Despite NAS is a quite old transformation, the catalytic and enantioselective versions appeared only in recent years and is still one of the most used and reliable transformation in industry. In this contest the works reported by Jørgensen and Maruoka represented straightforward examples of NAS applied to the synthesis of compounds bearing a tetrasubstituted chiral center.[77] Atroposelective NAS are thus rare, but a noteworthy example was reported by Smith and his group in 2014, using PTC-generated thiophenolate as nucleophile, the substitution of a chlorine atom in biarylic pyrimidines resulted in an efficient synthesis of novel enantioenriched biaryls (**Scheme 17**). The phase-transfer catalytic system is based on a *N*-benzylquininium chloride that promotes and stabilize the formation of a

[74] I. Atodiresei, I. Schiffers, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683.
[75] G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; b) E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru, *Chem. Rev.* **2015**, *115*, 11239.
[76] E. Buncel, J. M. Dust, F. Terrier, *Chem. Rev.* **1995**, *95*, 2261.
[77] a) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670; b) S. Shirakawa, K. Koga, T. Tokuda, K. Yamamoto, K. Maruoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 6220.

Meisenheimer intermediate having both a chiral center and a chiral axis in the transition state.

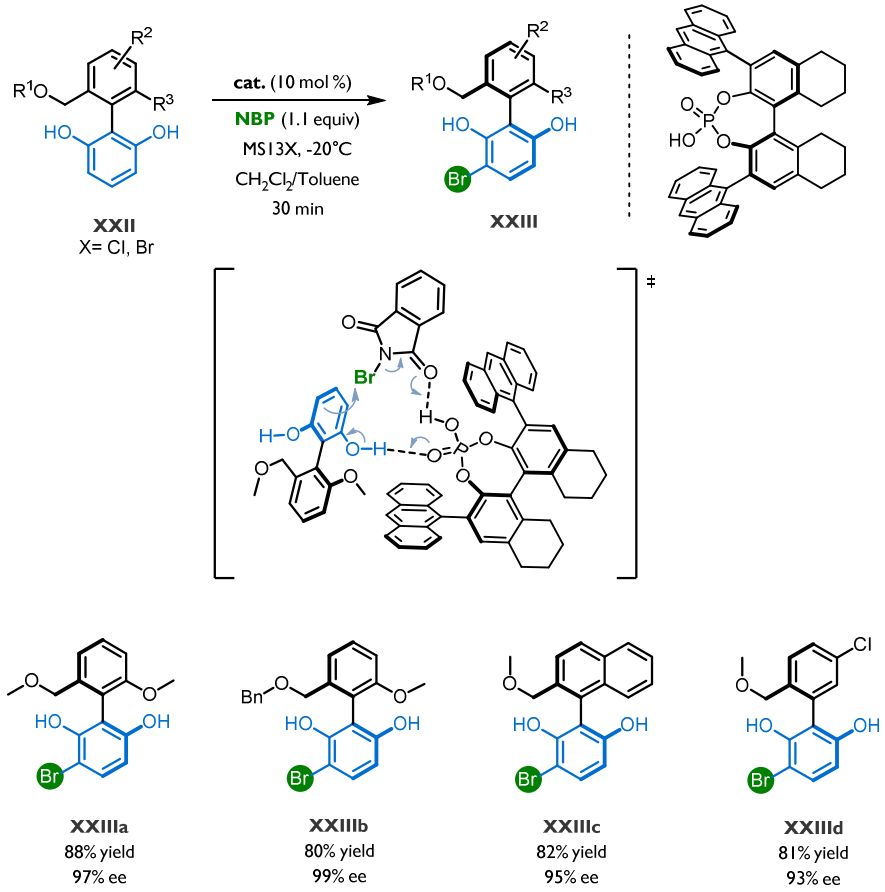


Scheme 17. *Atroposelective NAS reaction and representative examples.*

The biphasic reaction conditions were found to be fundamental for the reactivity of the catalytic system, where deprotonation of the acidic thiophenol occurred at the water/organic interface and was the captured by the quininium salt and transferred into the organic phase. Good enantioselectivities and yields were observed for a large series of substituents with different stereoelectronic properties. The halogen-containing heterobiaryls were useful for further derivatization reinforcing the generality of the whole system. An important aspect of the reaction was the possibility to increase the enantioselectivity, with the detriment of the yield of the process using an excess of thiophenol. This secondary kinetic effect is a Horeau-type chiroablative kinetic resolution which released a minor amount of the achiral doubly substituted product and an almost enantiopure axially chiral monosubstituted pyrazine.[78]

[78] R. J. Armstrong, M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822.

Another important achievement in the organocatalytic desymmetrization of biaryls was accomplished in 2013 by Akyiama, who reported the first example of the enantioselective synthesis of biaryls through a desymmetrization strategy.[79] The process was based on a chiral Brønsted acid catalyzed electrophilic bromination of achiral meta-bisphenol, specifically designed for this atroposelective transformation.



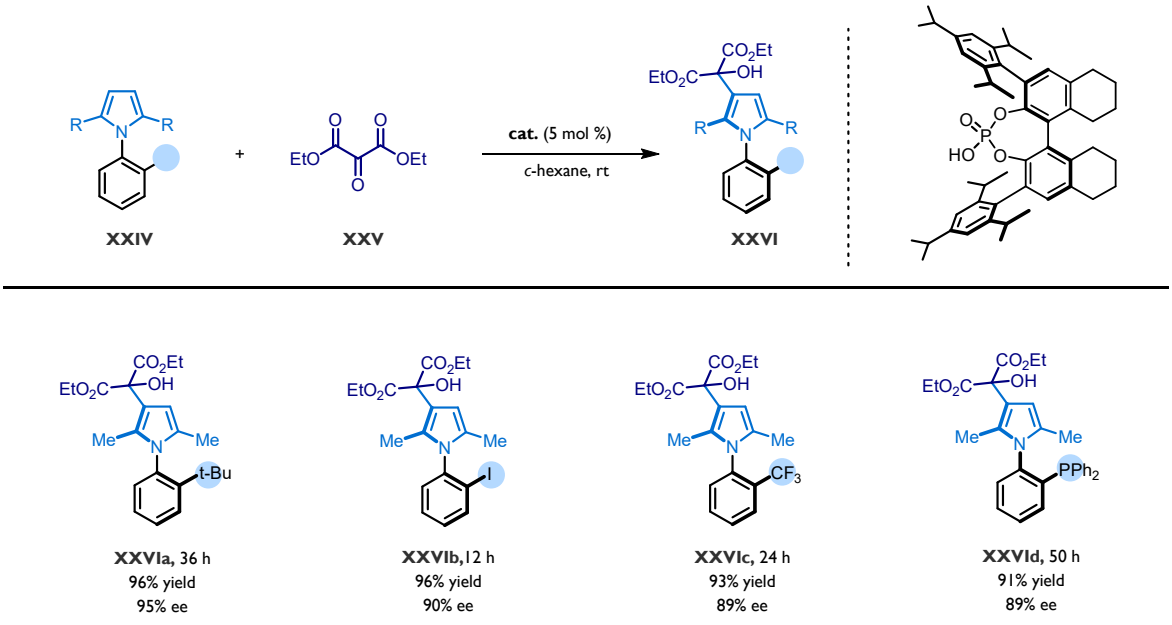
Scheme 18. *Representative examples for the atroposelective desymmetrization of biaryls via electrophilic bromination.*

The structure of the H8-chiral phosphoric acid creates a rigid and reactive chiral pocket of the catalyst. Also, this time the high level of stereoselectivity obtained is the result of a sequential mechanism made of a desymmetrization followed by a secondary kinetic resolution. This parallel reaction helps the process to reach an elevated enantioselectivity with a minimal sacrifice of the chemical yield with the

[79] K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964.

formation of the dibrominated by-product. The conformation assumed by the substrates-catalyst complex is fundamental for the observed enantioselectivity.

Organocatalytic desymmetrization for the synthesis of axially chiral heterobiaryl were not just apply to *C-C* bond biaryls, but a recent work from Bin Tan's group showed that this methodology could be successfully applied also for the formation of *C-N* axis. Due to their widespread application as *core* skeletons of a wide range of natural products and pharmaceutical agents, the synthesis of axially chiral arylpyrroles is an interesting synthetic target. Nonetheless, over the past decade, approaches to access these optically active arylpyrroles were confined to the use of chiral resolution agents or chiral column chromatography, which not only required the stoichiometric amounts of chiral reagent, but also were limited by the substrate scope. The first catalytic atroposelective Paal–Knorr reaction was established to access highly enantioenriched axially chiral arylpyrroles by the same research group recently, complicated catalytic system and narrow substrate range restricted its application. [80]



Scheme 19. *Representative examples for the atroposelective desymmetrization of arylpyrroles.*

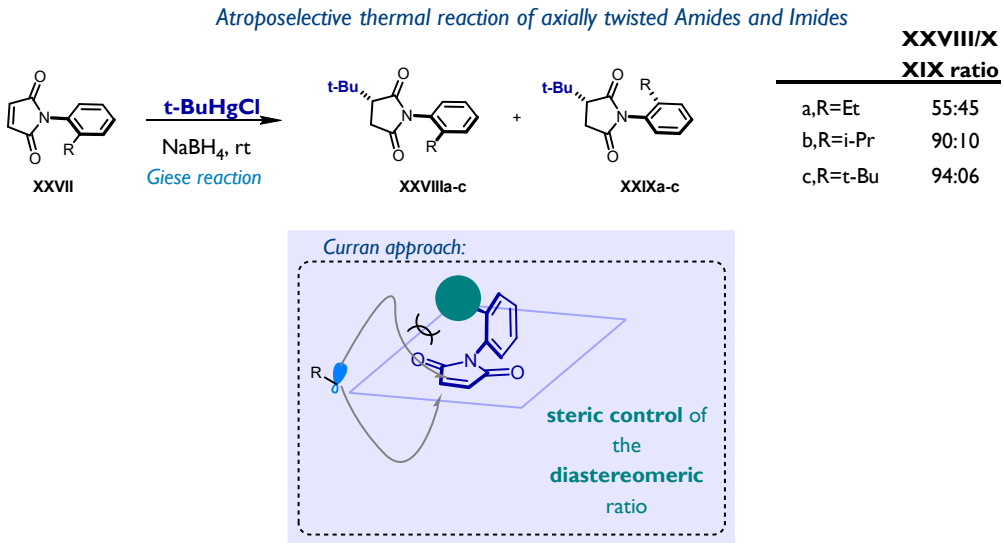
[80] Zhang, L., Zhang, J., Ma, J., Cheng, D. J. & Tan, B. *J. Am. Chem. Soc.* **2017**, *139*, 1714.

So, Tan's group developed a highly efficient and practical approach for the organocatalytic atroposelective synthesis of axially chiral arylpyrrole derivatives. Excellent yields and enantioselectivities were obtained with H8-TRIP as the chiral catalyst (**Scheme 19**).[81] Moreover, they also proved that highly enantioenriched arylpyrroles proved could be used as efficient chiral ligands in asymmetric catalysis and versatile building blocks to access other useful axially chiral molecules.

3.3 Desymmetrization of Maleimides

Maleimides represent an important class of intermediates in organic synthesis. Thanks to the double-activated double bond maleimides can undergo many types of organic transformations such as Michael additions, Diels-Alder, Morita-Bayliss-Hillmann and radical addition.[82] Maleimide can bear various substituents at the imidic nitrogen atom varying from hydrogen, alkyl chain or aromatic rings. In this particular last case, when a large substituent is placed at the *ortho-* position, the steric hindrance with the oxygen of the carbonyl groups, increases the energy-barrier required for the rotation of the N-C single bond to value close to 32.0 kcal/mol.[83] Thus a plane of symmetry which bisects the maleimide into two prochiral sides is formed. The symmetry can be broken by desymmetrization reactions and consequently a stereogenic axis is generated. This observation was realized for the first time by Curran[84] in his pioneering works on the synthesis of diastereoselective Giese reaction on prochiral maleimides (**Scheme 20**).

[81] L. Zhang, S. H. Xiang, J. Wang, J. Xiao, J. Q. Wang & B. Tan *Nat. Comm.,* **2019**, *10*, 566.
[82] P. Chauhan, J. Kaur, S. S. Chimni, *Chem. Asian J.* **2013**, *8*, 328.
[83] N. Di Iorio, P. Righi, A. Mazzanti, M. Mancinelli, A. Ciogli, G. Bencivenni, *J. Am. Chem. Soc.* **2014**, *136*, 10250.
[84] D. P. Curran, H. Qi, S. J. Geib, N. C. DeMello*, J. Am. Chem. Soc.* **1994**, *116*, 3131.



***Scheme 20**. Diastereoselective radical addition on maleimides*

This reaction, conducted without the presence of a chiral catalyst or auxiliary, was found to be highly *diastereoselective* with the *tert*-butyl group as substituent at the aromatic ring. When less sterically demanding groups were used, like methyl and isopropyl, the energy barrier for the rotation ΔG_{epi} of the N-C single bond diminished to a value not high enough to allow the existence of an atropisomeric compound. The results obtained by Curran highlighted the shielding effect of the *tert*-butyl substituent on the reaction. In fact, the addition of any kind of substituents, is preferentially directed to the side of the double bond not shielded by this large alkyl group.

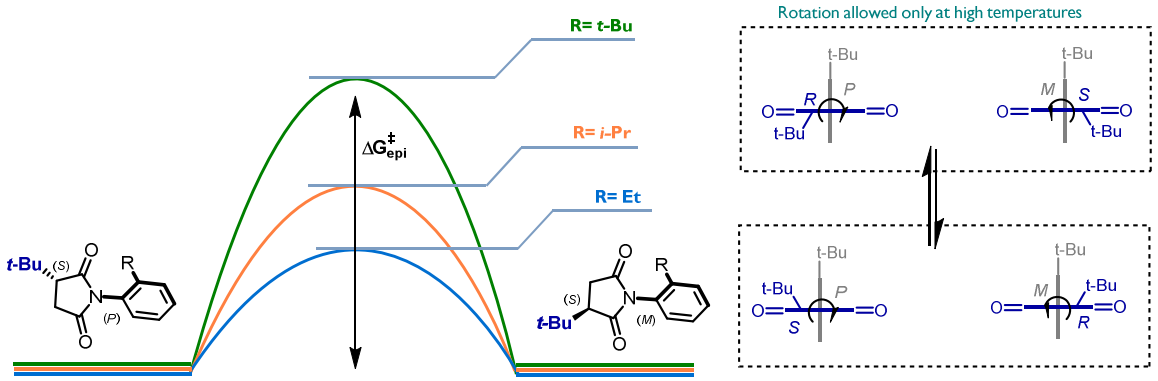
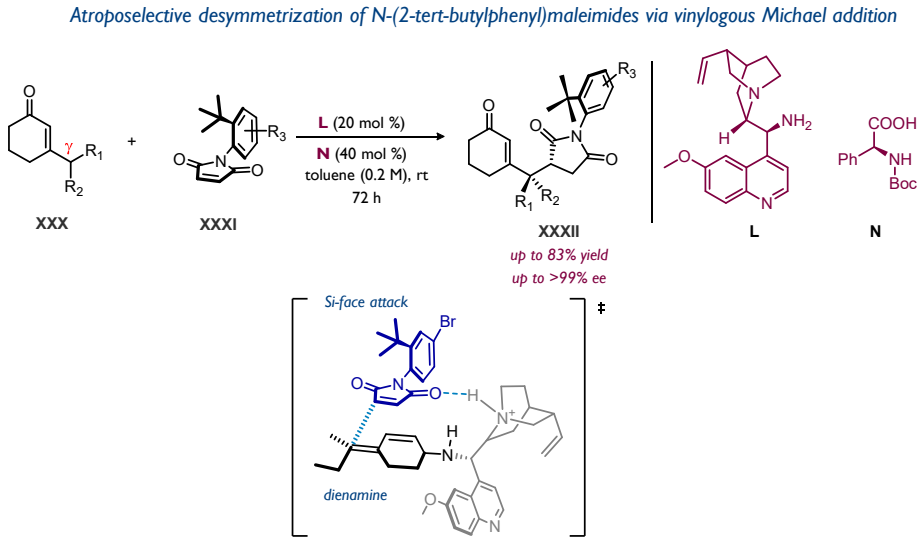


***Figure 26.** Shielding effect of different substituents*

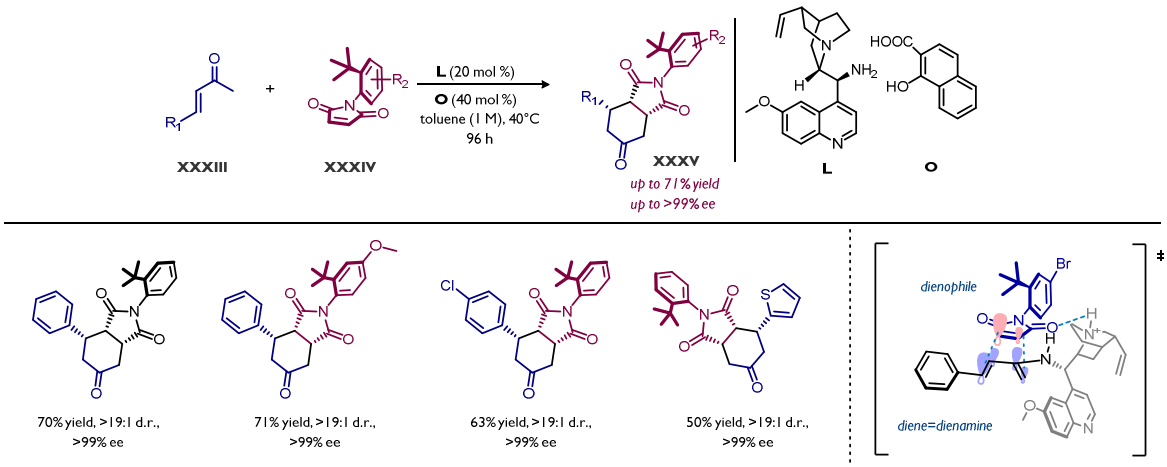
These observations inspired us to realize the first axially enantioselective desymmetrization of the *N*-(2-*tert*-butylphenyl)maleimide *core*, and we initially thought the we could use an aminocatalytic strategy. Our idea was based on the possibility that a chiral primary amine organocatalyst could generate a reactive nucleophile, *via* HOMO raising strategy (see **Chapter 1.3.3**), able to add to the electrophilic double bond of the maleimide. At the same time the primary amine should be able to recognize the two different enantiotopic sides of the maleimide symmetry plane, thus directing the addition mainly to only one of the two carbon atoms realizing an axially enantioselective desymmetrization process. Our intent was to combine a substrate-controlled diastereoselective reaction, as proved by Curran's work, and a catalyst-controlled enantioselective reaction by means of organocatalytic activation mode. The reaction of choice was found in the first example of a vinylogous Michael-type addition[85] of 3-substituted-α,β-unsaturated cyclic ketones, bearing an enolizable H in γ position, to the maleimide double bond, using the catalytic salt made of 9-amino(9-deoxy)*epi*-quinine and *N*-Boc-Phenylglycine (**Scheme 21**). The efficiency of the desymmetrization was very high as observed by the reaction with non-prochiral cyclohexenones while with prochiral nucleophiles an epimerization at the exocyclic stereocenter affected the diastereoselectivity of the process.



Scheme 21. *Desymmetrization of maleimides via vinylogous Micheal addition*

[85] I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869.

In this particular case, the two amine moieties work synergistically delivering two different kind of activations. The protonated quinuclidine group activates via H-bond the electrophile, thus favoring the addition of the vinylogous intermediate, generated after condensation of the primary amine on the carbonyl group of the α,β-unsaturated ketone. In the **Scheme 21** (bottom) is shown the proposed Transition State interaction in which we can see how the role of the catalyst is fundamental for the control of the stereochemistry of the two chiral centers and that of the chiral axis. The catalyst adapts its spatial arrangement to the conformation of the maleimide and recognizes the two *atropotopic* faces of the maleimide symmetry plane. A further demonstration of the ability of amino quinine to control the remote stereogenic axis of succinimide derivatives through a desymmetrization reaction, was given by our group during the development of the organocatalyzed formal Diels-Alder cycloaddition of dienamines, formed upon condensation of the primary amine catalyst (and the acid co-catalyst) on the unsaturated ketone. (**Scheme 22**).[86] Stereochemical evidences obtained from the X-ray structure on brominated products, showed that the cycloaddition pathway between the two species followed an *endo* approach.

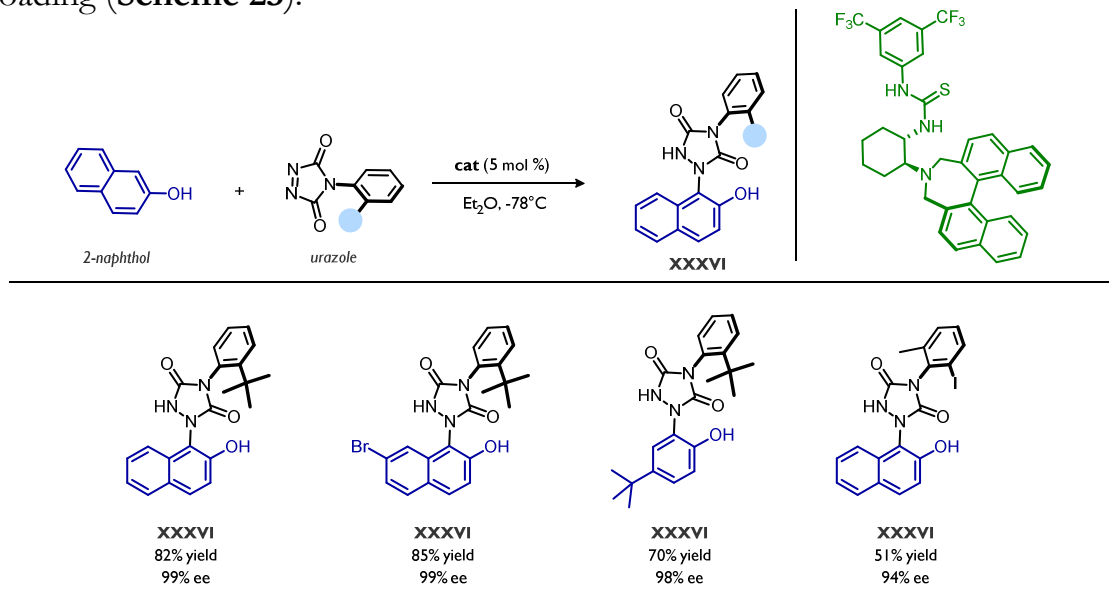


Scheme 22. *Desymmetrization of maleimides* via *aminocatalytic Diels-Alder reaction*

[86] F. Eudier, P. Righi, A. Mazzanti, A. Ciogli, G. Bencivenni, *Org. Lett.* **2015**, *17*, 1728.

The catalyst ensures the system to reach the favored transition state where the quinuclidine group of the catalyst is far away from the *tert*-butyl group (**Scheme 22**, bottom right).

A similar approach was used recently the group of Tan developed the synthesis of urazole-type molecules displaying axial chirality through a Friedel-Craft type desymmetrization reactions.[87] The synthetic strategy was based on the reaction of naphthols or indoles with 4-aryl-1,2,4-triazole-3,5-dione (ATAD) under two different catalytic activations. When β-naphthols were employed a thiourea functionalized chiral tertiary amine was used for a Brønsted base activation. Conversely, a chiral phosphoric acid, for a Brønsted acid activation was employed, when indoles were used. Both strategies were able to effectively promote the remote control over the stereogenic axis, which was realized through a selective H-bonding interaction between one of the prochiral carbonyl group of ATAD and the thiourea functional group of the catalyst. The perfect conditions were found using a chiral cyclohexyldiamine skeleton functionalized with an axially chiral binaphthyl system which was effective using only a 5 mol% of catalyst loading (**Scheme 23**).



Scheme 22. *Atroposelective addition of naphthols to azodicarboxylate catalyzed by a binfunctional organocatalyst*

[87] J.W. Zhang, J.H. Xu, D.J. Cheng, C. Shi, X.-Y. Liu, B. Tan, *Nat. Commun.* **2016**, *7*, 10677.

The scope of the reaction was expanded using bromine and iodine atoms as alternative to the *tert*-butyl substituent in the 2,6-position, generating a useful moiety for further derivatization. The reaction was also extended to phenols which were less reactive, but gave equally high enantioselectivity.

3.4 Our Project

Following these principles that worked for previously reported desymmetrizations, we wondered if a novel atroposelective Michael addition of *N*-Boc-3-aryloxindoles to *N*-(2-*tert*-butylphenyl)maleimides,[88] could be realized. Oxindole has emerged as a valuable scaffold in medicinal chemistry possessing diverse range of pharmacological activities. Products containing the oxindole scaffold, particularly important in biological activity, have become the main target of many chemical transformations. Chiral oxindoles with a quaternary stereocenter are particularly valuable substrates for pharmaceutical applications against various kinds of diseases (**Figure 27**).

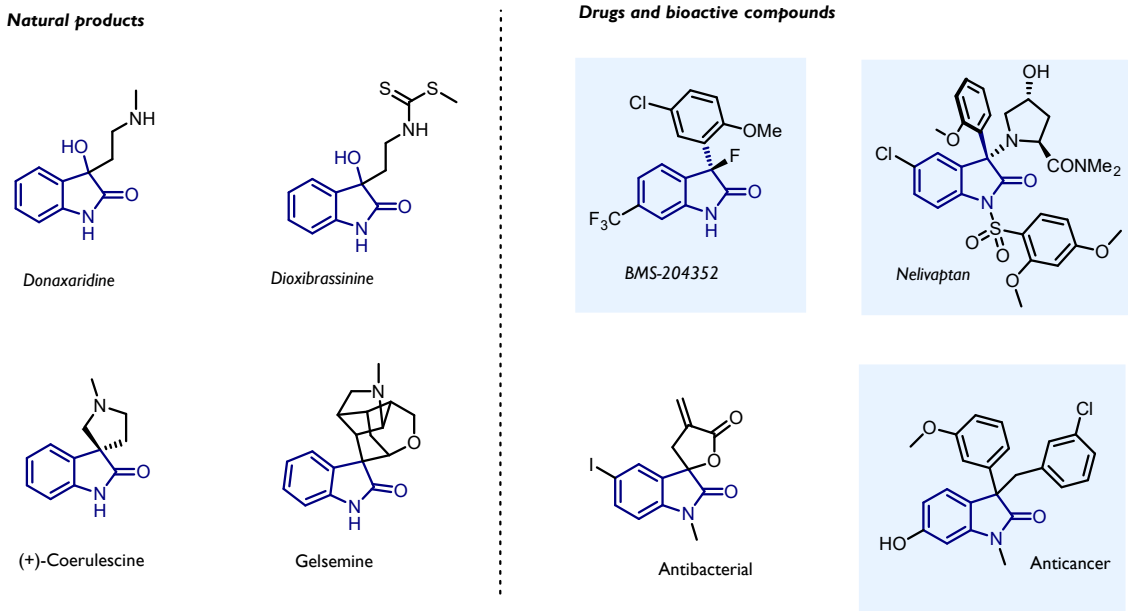


Figure 27. *Naturally occurring and bio-active examples of oxindole-containing compounds (3-aryloxindole are enlightened in blue)*

[88] For an overview on the organocatalytic reactions of maleimides, see: P. Chauhan, J. Kaur, S.S. Chimni, *Chem. Asian J.* **2013**, *8*, 328.

Although Michael additions of various kinds of oxindoles with arylmaleimides have been reported by several research groups,[89] the lack of atroposelective versions of this kind of transformation prompted us to investigate its feasibility (**Figure 28**).

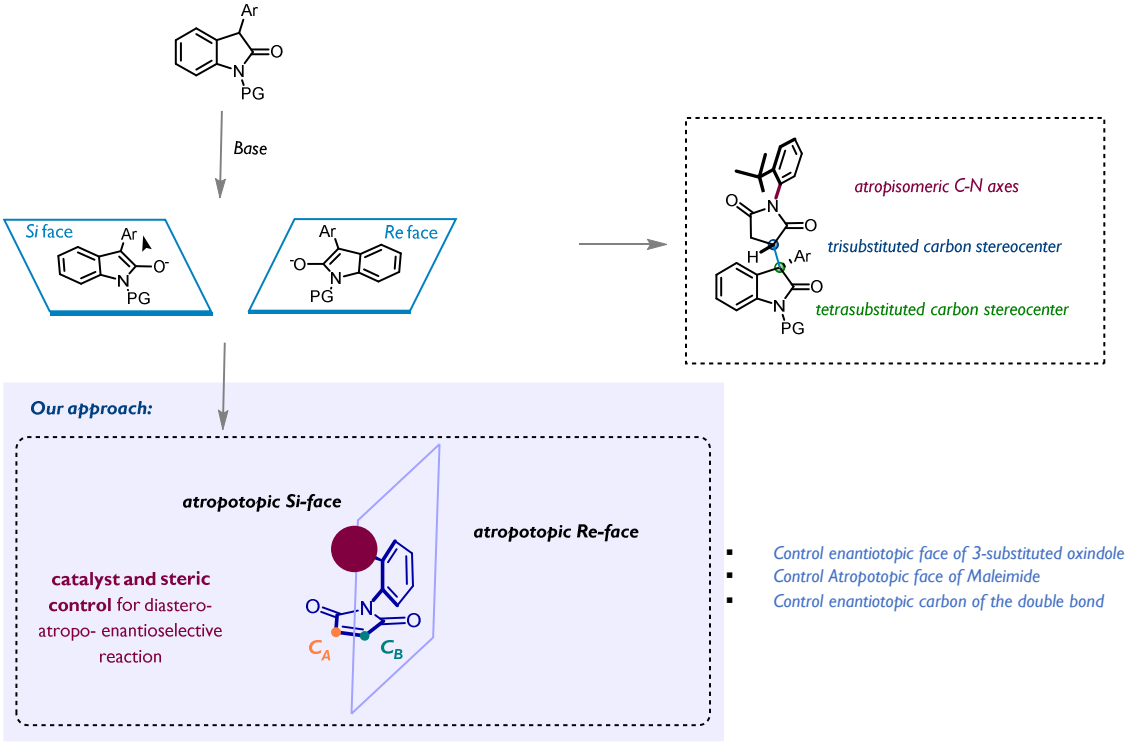


Figure 28. *Stereoselective features of the reaction*

In particular, we envisaged that the use of a bifunctional catalyst containing a basic portion, strong enough to abstract the acidic proton at C3 of the oxindole *core*, and a coordinating H-bonding functional group, to ensure a well-defined geometry in the reaction transition state, would be fundamental for the success of this transformation. The new product formed will feature a stereogenic axis and adjacent quaternary and tertiary stereocenters (**Figure 28**). We started our investigation by mixing *N*-Boc-3-phenyloxindole (**1a**) and *N*-(2-*tert*-butylphenyl)maleimide (**2a**) in the presence of the organocatalyst $(DHQ)_2PYR$ (**A**) (**Figure 25**) in dichloromethane (CH_2Cl_2) as the solvent at –78 °C for 24 hours (**Table 1**). The system was revealed to be very promising, since succinimide **3a**

[89] (a) Y. H. Liao, X. L. Liu, Z. J. Wu, L. F. Cun, X. M. Zhang, W. C. Yuan, *Org. Lett.* **2010**, *12*, 2896. (b) Li, L.; Chen, W.; Yang, W.; Pan, Y.; Liu, H.; Tan, C. H.; Jiang, Z. *Chem. Commun.* **2012**, *48*, 5124.

was obtained in 42% yield with a quite good diastereomeric ratio (5.5:1) and an enantiomeric excess of 74% (**Table 1**, entry 1). We next explored the efficiency of various *cinchona* alkaloid derivatives functionalized with a thiourea or a squaramide substituent (**Figure 29**). The results obtained with catalysts **B** and **C** highlight the important role of the thiourea functional group to perfectly arrange the reagents in the transition state. Indeed, catalyst **C** is not only able to increase the ee to 92%, but also the reactivity of the system, furnishing **3a** in a 71% isolated yield (entries 2 and 3).

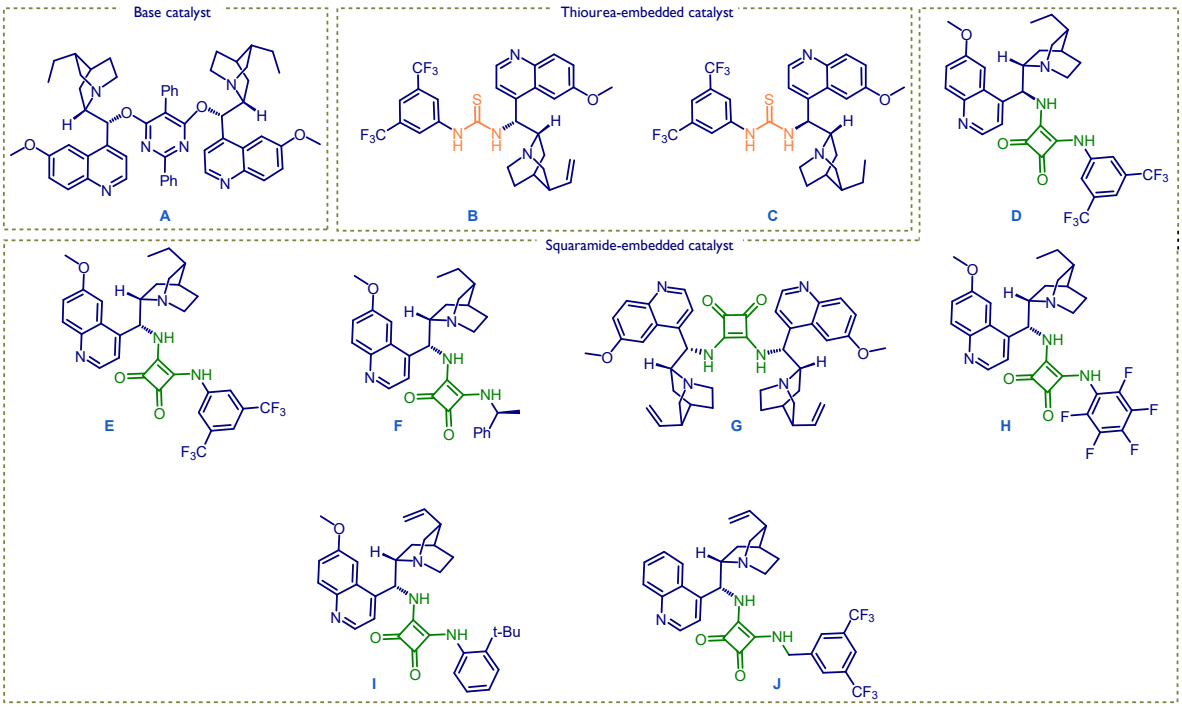
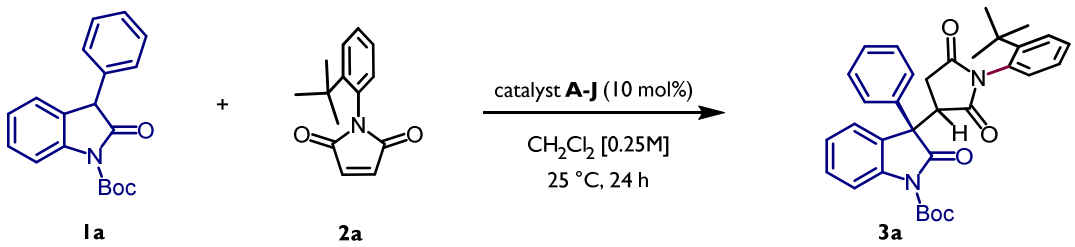


***Figure 29**. Different bifunctional catalysts*

When the squaramide-functionalized 9-*epi*-9-amino-(9-deoxy)hydroquinine **D** was tested, perfect stereocontrol was achieved, and compound **3a** was isolated as a single diastereoisomer in >99% ee, but unfortunately with a poor yield (**Table 1**, entry 4). We repeated the reaction at room temperature and were pleased to find an increase in yield and an almost unchanged diastereo- and enantioselectivity (entry 5). In general, by changing the chiral base or the squaramide we did not find improvements in the stereochemical outcome of the reaction, and also good

reactivity was maintained (entries 6–10). However, when catalyst **G** was employed, its low solubility influenced the final result negatively (entry 8). Catalyst **J** gave the best results, with succinimide **3a** isolated in 82% yield and >99% ee (entry 11).



1a **2a** **3a**

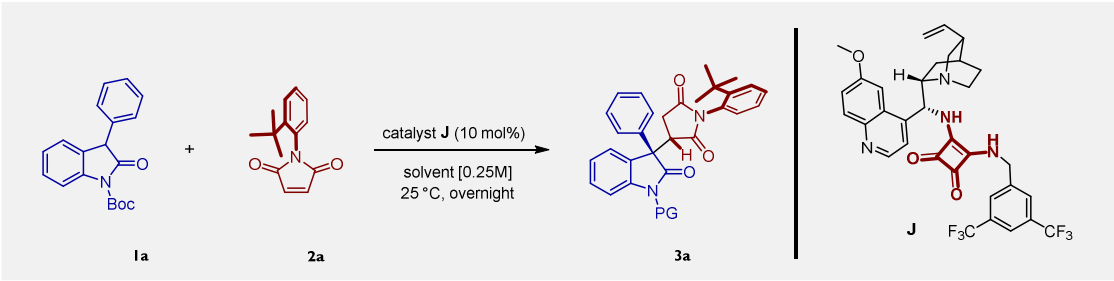
Entry	Cat.	Temp (°C)	Yield (%)	dr[c]	ee[d] (%)
1	**A**	-78	42	5.5:1	**74**
2	**B**	-78	48	1.6:1	**77**
3	**C**	-78	71	1.6:1	**92**
4	**D**	-78	22	>19:1	**>99**
5	**D**	25	81	>19:1	**98**
6	**E**	25	76	16:1	**81**
7	**F**	25	84	5.2:1	**84**
8	**G**	25	45	2.2:1	**71**
9	**H**	25	83	15.7:1	**84**
10	**I**	25	73	2.5:1	**22**
11	**J**	25	82	>19:1	**>99**

[a] Reaction conditions: **1a** (0.21 mmol), **2a** (0.2 mmol), solvent (0.8 mL).
[b] Isolated yield.
[c] Determined by 1H NMR analysis of the crude mixture.
[d] Determined by chiral HPLC analysis.

Table 1*. Optimization of the Catalyst and the Reaction Temperature*[a]

We then focused our attention on the search of the best solvent.

As it is possible to observe in **Table 2**, CH_2Cl_2 was revealed to be the best choice. Apart from chloroform, that gave similar result (entry 2), the other solvents were not able to optimally combine yield and stereocontrol as in the case of CH_2Cl_2 (compare entry 1 with entries 3–6). Also, the concentration of the reaction *media* was then evaluated, at different catalyst loadings. By decreasing the catalyst loading from 10 to 5 mol%, the yield and diastereoselectivity remained unchanged, but a small decrease of the enantioselectivity was encountered.



Entry	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	CH_2Cl_2	82	>19:1	**74**
2	$CHCl_3$	84	>19:1	**77**
3	THF	67	10:1	**92**
4	MTBE	43	10:1	**>99**
5	EtOAc	55	16:1	**98**
6	PhMe	68	12:1	**81**

[a] Reaction conditions: **1a** (0.21 mmol), **2a** (0.2 mmol), solvent (0.8 mL).
[b] Isolated yield.
[c] Determined by 1H NMR analysis of the crude mixture.
[d] Determined by chiral HPLC analysis.

Table 2. *Solvent opimization*

When the concentration was decreased to 0.1 M, the ee diminished at both 10 mol% and 5 mol% catalyst loadings. The use of 5 mol% of **J** gave only a slight increase in yield. We finally decided to use a 10 mol% catalyst loading and a concentration of 0.25 M in CH_2Cl_2.

With the optimized conditions, we then investigated the scope of phenyloxindoles **1a–g** bearing various substituents on the oxindole aromatic core (**Table 3**). In general, all the oxindoles reacted very well with **2a**, giving the corresponding atropisomeric succinimides **3a–g** in good yields and excellent stereocontrol. The electronic nature of the oxindole core in the presence of diverse electron-withdrawing and -donating groups does not alter the reactivity of the system. This is evident for halogenated oxindoles and for substrates with a methoxy or a methyl group at the 5 position.

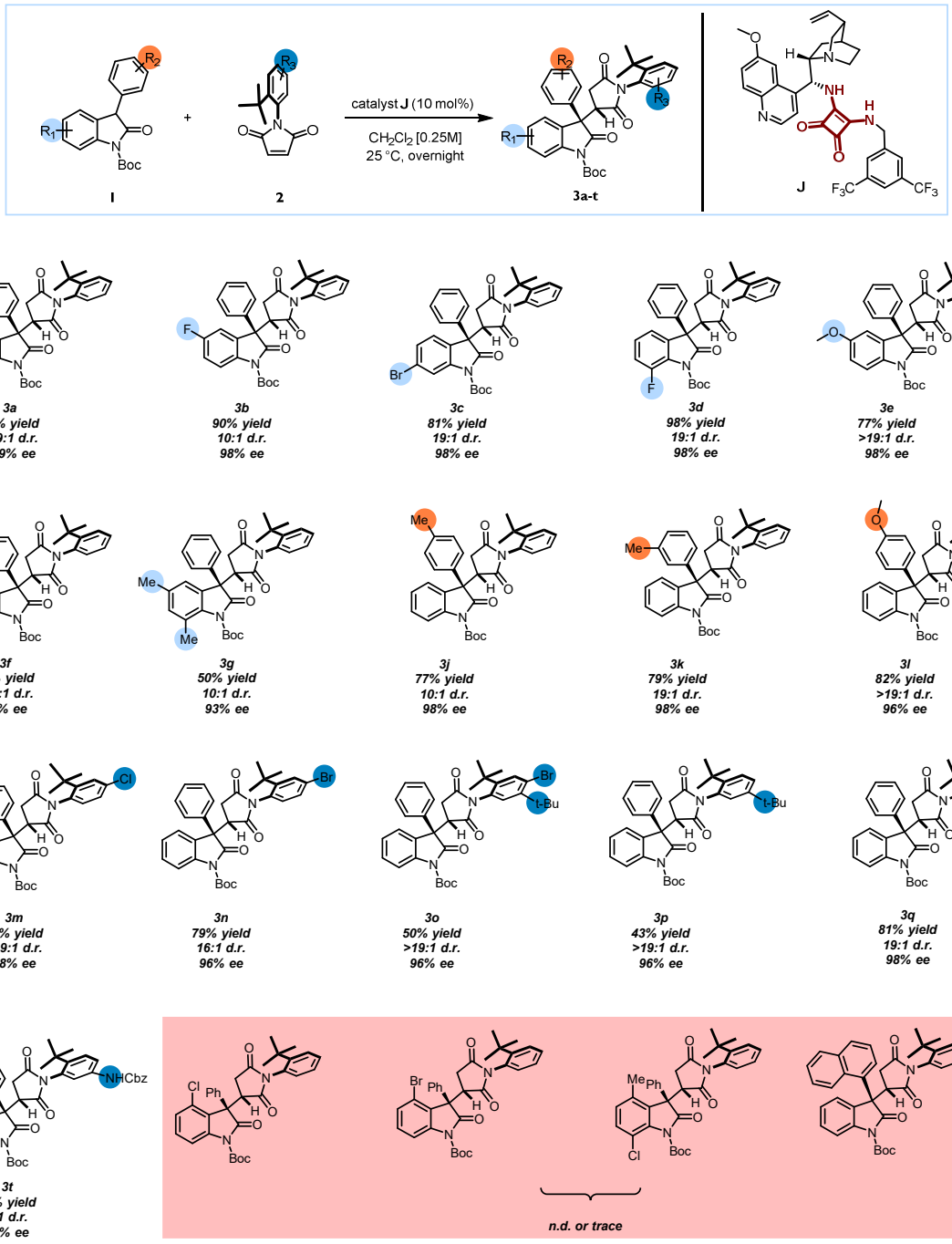


Table 3. *Scope of the reaction*

The scope of the oxindole was furthermore expanded by varying the C3 aromatic substituent. Interestingly, no loss of reactivity and stereoselectivity was observed

with para- and meta-substituents, revealing once more the efficiency of the desymmetrization. However, when two methyl substituents are present, the yield of the reaction drops to 50% (**3g**).

Finally, different maleimides were reacted with oxindole **1a**. In general, good reactivity was observed with all the substituents tested. The best results were obtained with halogenated maleimides. Maleimides with large groups have lower reactivity but good diastereo- and enantioselectivity. An opposite trend was observed with the NHCbz substituent which gave a very high yield and the lowest dr and ee (**3t**). Compound **3p** furnished a single crystal suitable for X-ray analysis. From the structure, the absolute configuration R,S,M was assigned (**Figure 30**).

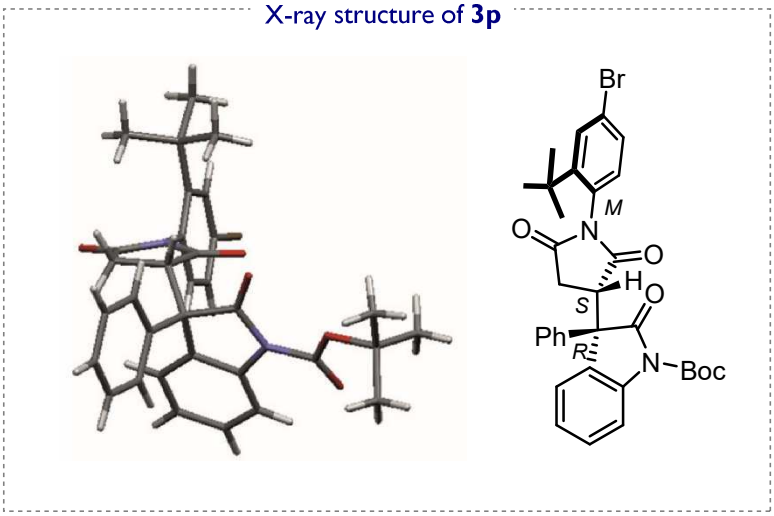


Figure 30. *X-ray structure of* ***3p***

Nevertheless, the presented desymmetrization showed some limitations. Catalyst **J** was completely unable to promote the reaction of 4-substituted oxindoles **1h–j** with maleimide **2a** (in red in **Table 3**). At the moment, we do not have convincing experimental evidence to explain the results; however, experimental data suggest the presence of a strong steric interaction between catalyst **J** and the oxindole. Indeed, when **1i** was reacted with maleimide **2a** in the presence of a catalyst without substituents, such as DABCO, **2a** was totally consumed after 24 hours, and a 4:1 mixture of racemic diastereomers of the corresponding atropisomeric succinimide **3i** was obtained. This result demonstrated that a catalyst without steric

hindrance also promotes the transformation when using a sterically demanding oxindole, thus supporting the idea of a strong steric interaction between oxindoles **1h–j** and catalyst **J** as the cause for the absence of reactivity. Indeed, further information could be obtained. The reaction with DABCO, a weaker base than the quinuclidine moiety of catalyst **J**, showed that activation of maleimide is not strictly necessary for the reaction to take place, so that the role of the squaramide is mainly to coordinate the maleimide and control the geometry of the transition state. On the basis of these results, we can propose a mechanism for the desymmetrization. The transition state is made up of a ternary complex in which catalyst **J** promotes the formation of a reactive enolate and at the same time anchors the maleimide by means of hydrogen bonds with the squaramide functionality.

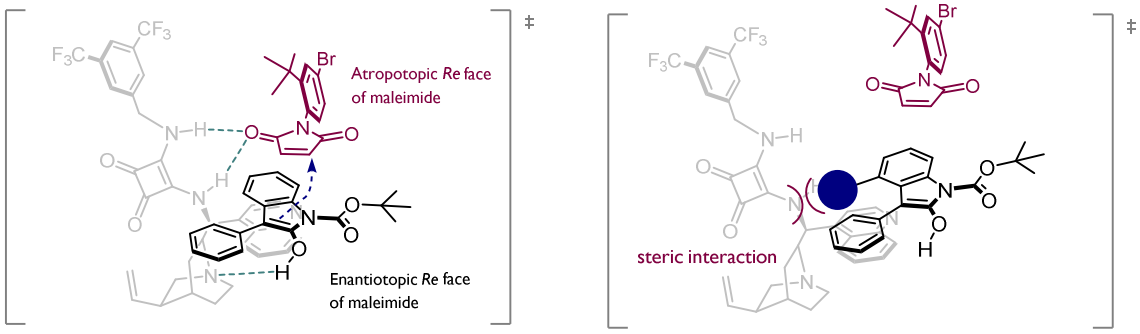


Figure 31. *Proposed TS and steric interaction of the reaction*

In this way, the *Si* face of the enolate adds to the *Re* face of the maleimide. We think that the reaction with DABCO indicates that catalyst **J** approaches the oxindole with the squaramide moiety directed outside the oxindole plane. The resulting model also explains the lack of reactivity of oxindoles **1h–j**. In fact, the presence of a bulky halogen atom or methyl group at 4-position generates a strong repulsion between the catalyst and the substrate during their reciprocal approach (**Figure 31**). In this way, the necessary conditions for the bifunctional action of J to activate the oxindole and to coordinate the maleimide simultaneously cannot be obtained.

In conclusion, during my first project, we have demonstrated the ability of a squaramide-functionalized cinchonidine derivative to promote efficiently the atroposelective desymmetrization of various *N*-(2-*tert*-butylphenyl)maleimides when using 3-phenyloxindoles as nucleophiles. The role of the catalyst appears to be fundamental for this kind of chemical transformation, as it demonstrates the unique capacity to transfer its stereochemical information for the generation of a stereogenic axis in a remote position and the construction of adjacent quaternary and tertiary stereocenters.

3.5 Experimental Section

3.5.1 General Information

All the NMR spectra were recorded on Inova 300 MHz, Gemini 400 MHz or Mercury 600 MHz Varian spectrometers for ^{1}H, 75 MHz, 100 MHz and 150 MHz for ^{13}C and 282 MHz, 376 MHz, 564 MHz for ^{19}F respectively. The chemical shifts for ^{1}H, ^{19}F, and ^{13}C are given in ppm relative to the residual signals of $CHCl_3$. Carbon multiplicities were determined by DEPT experiments. Purification of reaction products was carried out by flash chromatography on silica gel (230–400 mesh) according to the method of Still.[90] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. HRMS was carried out at the CIGS facilities of the University of Modena and Reggio Emilia on a G6520AA Accurate-Mass Q-TOF LC/MS instrument. X-ray data were acquired on a Bruker APEX-2 diffractometer. Chiral HPLC analysis was performed on an Agilent 1100 series instrument. Daicel Chiralpak AD-H or IC columns with *i*-PrOH/hexane as the eluent were used. HPLC traces for compounds **3a–g**, **k–m**, **o–t** were compared to quasi racemic samples prepared by mixing the two product antipodes obtained by performing the reactions with catalyst **J** and the pseudo-enantiomer ***ent*-J** separately. Optical rotations are reported as follows as $[\alpha]_D^{20}$ (*c* in g per 100 mL, $CHCl_3$). All reactions were carried out in air and by using undistilled solvents, without any precautions to exclude moisture, unless otherwise noted. Oxindoles **1a** and **1b**,[91] **1e–g**,[69] **1c**,[92] and **1h–k**[70] were prepared using published procedures. Maleimides **2b–g** were prepared by following literature procedures.[93] Chiral

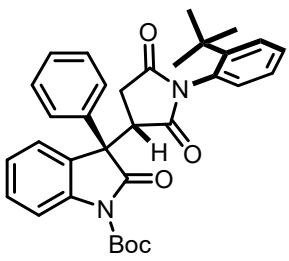
[90] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.
[91] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164.
[92] Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192.
[93] (a) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 6892. (b) Miller, C.; Hoyle, C.; Jönsson, E. PCT WO 98/54134, **1998**.

catalysts **B** and **C**,[94] **D–F**,[95] **G**,[96]and **H–J**[73] were prepared by following literature procedures.

3.2.2 Procedures

All the reactions were carried out in non-distilled solvent and stirring was provided by magnetic Teflon-coated stir bars. In an ordinary vial were placed catalyst **J** (0.02 mmol, 0.1 equiv.), the maleimide (0.2 mmol, 1.0 equiv.) and the oxindole (0.21 mmol, 1.05 equiv.) before adding the solvent (DCM, 0.8 mL; 0.25M) and after 24h under magnetic stirring, the crude mixture was flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent (50 ml). Then solvent was removed in *vacuo* and the diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude mixture. Finally, the desired compound was isolated by flash column chromatography and the enantiomeric excess was determined by means of chiral HPLC analysis.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3a).



3a

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (hexane:diethyl ether = 6:4) to give of **3a** in 82% yield 0.164 mmol, and >99% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90/10, flow rate 1 mL/min, λ = 254 nm: **3a** τ_{major} = 19.0 min.; τ_{minor} = 8.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.07 (*d*, *J* = 8.3 Hz, 1H); 7.53 (*m*, 1H); 7.45 (*dd*, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1H); 7.34 (*m*, 7H); 7.25 (*m*, 1H); 7.01 (*ddd*, $J_1 = J_2$ =

[94] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967
[95] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.
[96] Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224.

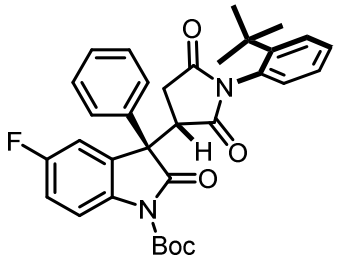
7.6 Hz, J_3 = 1.4 Hz, 1H); 5.71 (*dd*, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H); 4.44 (*dd*, J_1 = 10.3 Hz, J_2 = 4.0 Hz, 1H); 3.11 (*dd*, J_1 = 19.3 Hz, J_2 = 10.3 Hz, 1H); 2.81 (*dd*, J_1 = 19.3 Hz, J_2 = 4.0 Hz, 1H); 1.57 (*s*, 9H); 1.23 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.8, 175.7, 174.3, 148.9, 147.7, 141.5, 136.8, 134.9, 130.0, 129.9, 129.7, 129.6, 129.1, 128.5, 127.6, 127.3, 126.4, 124.4, 123.8, 116.6, 84.6, 56.9, 47.8, 35.5, 32.8, 31.6, 28.0.

$[\alpha]_D^{20}$ +193.5 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{34}N_2NaO_5$ 561.236, found 561.2359 $(M+Na)^+$. Calculated for $C_{33}H_{34}KN_2O_5$ 577.2099, found 577.2096 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-5-fluoro-2-oxo-3-phenylindoline-1-carboxylate (3b).



3b

The title compound was obtained following the general procedure to furnish the crude product as a 10:1 mixture of diastereoisomers. The crude mixture was purified by flash column chromatography (dichloromethane:hexane = 9:1) to give **3b** in 90% yield, 0.18 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, λ = 254 nm: **3b** τ_{major} = 8.3 min.; τ_{minor} = 5.8 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.08 (*dd*, J_1 = 9.2 Hz, J_2 = 4.7 Hz, 1H); 7.48 (*dd*, J_1 = 8.1 Hz, J_2 = 1.3 Hz, 1H); 7.42-7.19 (*m*, 7H); 7.09 (*m*, 2H,); 5.91 (*dd*, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H); 4.46 (*dd*, J_1 = 10.2 Hz, J_2 = 4.3 Hz, 1H); 3.13 (*dd*, J_1 = 19.5 Hz, J_2 = 10.6 Hz, 1H); 2.74 (*dd*, J_1 = 19.5 Hz, J_2 = 4.3 Hz, 1H); 1.57 (*s*, 9H); 1.24 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.8, 175.2, 174.1, 160.9, 158.5, 148.9, 147.8, 137.6, 137.5, 136.3, 129.9 (*d*, *J* = 1.5 Hz), 129.5, 129.3, 128.8 (*d*, *J* = 5.4 Hz), 128.2 (*d*,

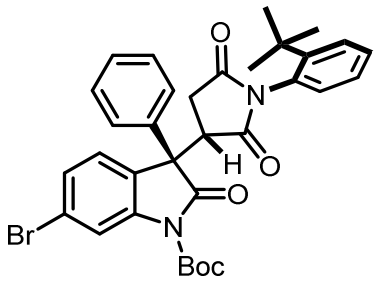
J = 7.4 Hz), 127.5, 118.0 (*d*, *J* = 8.6 Hz), 116.5 (*d*, *J* = 22.5 Hz), 111.2 (*d*, *J* = 24.3 Hz), 84.9, 57.0, 47.7, 35.6, 32.7, 31.6, 28.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm): -116.6 (1F).

$[\alpha]_D^{20}$ +123.5 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}FN_2NaO_5$ 579.2266, found 579.2263 $(M+Na)^+$. Calculated for $C_{33}H_{33}FN_2KO_5$ 595.2005, found 595.1988 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-6-bromo-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3c).



3c

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr 19:1). The crude mixture was purified by flash column chromatography (hexane:diethyl ether = 6:4) to give **3c** in 81% yield, 0.162 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90/10, flow rate 1 mL/min, λ = 254 nm: **3c** τ_{major} = 13.5 min.; τ_{minor} = 8.5 min.

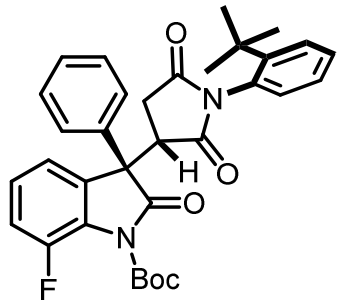
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 8.32 (*d*, *J* = 1.9 Hz, 1H); 7.48 (*m*, 2H); 7.40-7.24 (*m*, 7H); 7.22 (*d*, *J* = 8.1 Hz, 1H 2H); 7.11 (*ddd*, $J_1 = J_2$ = 7.6 Hz, J_3 = 1.4 Hz, 1H); 5.78 (*dd*, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H); 4.42 (*dd*, J_1 = 10.2 Hz, J_2 = 4.0 Hz, 1H); 3.11 (*dd*, J_1 = 19.3 Hz, J_2 = 10.2 Hz, 1H); 2.75 (*dd*, J_1 = 19.3 Hz, J_2 = 4.0 Hz, 1H); 1.57 (*s*, 9H); 1.24 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.7, 175.4, 173.8, 148.7, 147.7, 142.5, 136.2, 134.9, 131.3, 129.8, 129.5, 129.3, 128.7, 128.6, 127.5, 127.4, 125.3, 124.9, 120.1, 85.1, 56.7, 47.7, 35.5, 32.7, 31.6, 27.9.

$[\alpha]_D^{20}$ +313.1 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}BrN_2NaO_5$ 639.1465, found 639.1462 $(M+Na)^+$. Calculated for $C_{33}H_{33}BrN_2KO_5$ 655.1204, found 655.1163 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-7-fluoro-2-oxo-3-phenylindoline-1-carboxylate (3d).



3d

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr 19:1). The crude mixture was purified by flash column chromatography (hexane:diethyl ether = 1:1) to give **3d** in 98% yield, 0.196 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, λ = 254 nm: **3d** τ_{major} = 21.3 min.; τ_{minor} = 7.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.46 (*dd*, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 1H); 7.42-7.24 (*m*, 8H); 7.17 (*dd*, J_1 = 6.6 Hz, J_2 = 1.9 Hz, 1H); 7.03 (*ddd*, $J_1 = J_2$ = 7.7 Hz, J_3 = 1.3 Hz, 1H); 5.76 (*dd*, J_1 = 7.7 Hz, J_2 = 1.1 Hz, 1H); 4.43 (*dd*, J_1 = 10.2 Hz, J_2 = 4.0 Hz, 1H); 3.11 (*dd*, J_1 = 19.2 Hz, J_2 = 10.2 Hz, 1H); 2.79 (*dd*, J_1 = 19.2 Hz, J_2 = 4.0 Hz, 1H); 1.54 (*s*, 9H); 1.24 (*s*, 9H).

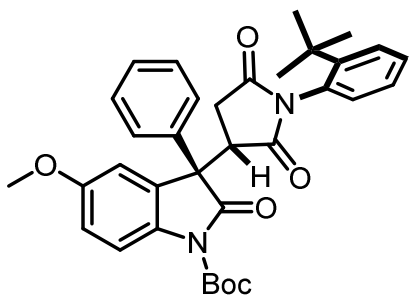
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.5, 175.4, 173.9, 150.6, 148.1, 147.7, 147.0, 136.2, 129.9 (*d*, *J* = 2.2 Hz), 129.8, 129.7, 129.6, 129.2, 128.6 (*d*, *J* = 12.5 Hz), 128.6 (*d*, *J* = 3.7 Hz), 127.4, 127.2, 125.5 (*d*, *J* = 7.0 Hz), 119.7 (*d*, *J* = 3.7 Hz), 118.4, (*d*, *J* = 20.5 Hz), 85.1, 57.5, 47.7, 35.5, 32.7, 32.6, 27.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm): -115.5 (1F).

$[\alpha]_D^{20}$ +173.0 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}FN_2NaO_5$ 579.2266, found 579.2266 $(M+Na)^+$. Calculated for $C_{33}H_{33}FN_2KO_5$ 595.2005, found 595.1996 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (3e).



3e

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 75:25) to give **3e** in 77% yield, 0.154 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3e** τ_{major} = 12.5 min.; τ_{minor} = 6.4 min.

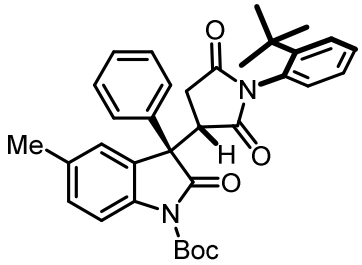
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.00 (*d*, J = 9.1 Hz, 1H); 7.46 (*dd*, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H); 7.41-7.31 (*m*, 5H); 7.27 (*m*, 1H); 7.04 (*m*, 2H); 6.88 (*d*, J = 2.6 Hz, 1H); 5.76 (*dd*, J_1 = 7.9 Hz, J_2 = 1.6 Hz, 1H); 4.44 (*dd*, J_1 = 10.1 Hz, J_2 = 3.6 Hz, 1H); 3.80 (*s*, 3H); 3.12 (*dd*, J_1 = 19.3 Hz, J_2 = 10.1 Hz, 1H); 2.79 (*dd*, J_1 = 19.3 Hz, J_2 = 3.6 Hz, 1H); 1.57 (*s*, 9H); 1.24 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.8, 175.7, 174.3, 156.8, 149.0, 147.8, 136.8, 134.7, 129.7, 129.6, 129.6, 129.1, 128.5, 128.4, 127.6, 127.3, 127.2, 117.5, 115.0, 109.7, 84.3, 57.3, 55.8, 47.7, 35.5, 32.9, 31.5, 28.0.

$[\alpha]_D^{20}$ +105.4 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{34}H_{36}N_2NaO_6$ 591.2466, found 591.2455 $(M+Na)^+$. Calculated for $C_{34}H_{36}N_2KO_6$ 607.2205, found 607.2182 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-5-methyl-2-oxo-3-phenylindoline-1-carboxylate (3f).



3f

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (dichloromethane:hexane = 90/10) to give **3f** in 82% yield, 0.164 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, λ = 254 nm: **3f** τ_{major} = 8.5 min.; τ_{minor} = 5.4 min.

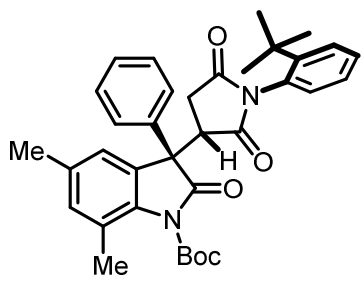
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.94 (*d*, J = 8.4 Hz, 1H); 7.46 (*dd*, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H); 7.39-7.30 (*m*, 6H); 7.26 (*ddd*, J_1 = 8.8, J_2 = 7.4 Hz, J_3 = 1.5 Hz, 1H); 7.15 (*bs*, 1H); 7.03 (*ddd*, J_1 = J_2 = 7.0 Hz, J_3 = 1.4 Hz, 1H); 5.65 (*dd*, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H); 4.42 (*dd*, J_1 = 10.1 Hz, J_2 = 3.6 Hz, 1H); 3.10 (*dd*, J_1 = 19.2 Hz, J_2 = 10.1 Hz, 1H); 2.81 (*dd*, J_1 = 19.2 Hz, J_2 = 3.6 Hz, 1H); 2.43 (*s*, 3H); 1.57 (*s*, 9H); 1.24 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.9, 175.8, 174.4, 149.0, 147.8, 139.1, 136.9, 134.2, 130.4, 129.8, 129.7, 129.6, 129.1, 128.5, 128.4, 127.7, 127.2, 126.3, 124.3, 116.4, 84.4, 57.1, 47.8, 35.5, 32.9, 31.6, 28.0, 21.1.

$[\alpha]_D^{20}$ +84.7 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{34}H_{36}N_2NaO_5$ 575.2516, found 575.2517 $(M+Na)^+$. Calculated for $C_{34}H_{36}N_2KO_5$ 591.2256, found 591.2278 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-5,7-dimethyl-2-oxo-3-phenylindoline-1-carboxylate (3g).



3g

The title compound was obtained following the general procedure to furnish the crude product as a 10:1 mixture of diastereoisomers. The crude mixture was purified by flash column chromatography (dichloromethane:hexane = 90/10) to give **3g** in 50% yield, 0.100 mmol and 93% ee.

HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3g** τ_{major} = 9.9 min.; τ_{minor} = 25.1 min.

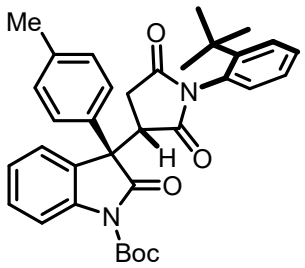
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.44 (*dd*, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H); 7.40-7.30 (*m*, 5H); 7.25 (*ddd*, J_1 = 8.9, J_2 = 7.4 Hz, J_3 = 1.5 Hz, 1H); 7.14 (*bs*, 1H,); 7.02 (*ddd*, $J_1 = J_2$ = 7.6 Hz, J_3 = 1.4 Hz, 1H); 6.98 (*bs*, 1H); 5.66 (*dd*, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H); 4.38 (*dd*, J_1 = 10.2 Hz, J_2 = 3.6 Hz, 1H); 3.08 (*dd*, J_1 = 19.4 Hz, J_2 = 10.2 Hz, 1H); 2.79 (*dd*, J_1 = 19.4 Hz, J_2 = 3.6 Hz, 1H); 2.38 (*s*, 3H); 2.23 (*s*, 3H); 1.54 (*s*, 9H); 1.23 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 176.0, 175.6, 175.4, 148.8, 147.8, 137.6, 137.2, 134.2, 133.4, 129.9, 129.8, 129.6, 129.0, 128.5, 128.3, 127.7, 127.6, 127.2, 125.1, 122.0, 84.6, 57.5, 47.6, 35.5, 32.9, 31.6, 27.7, 21.0, 20.0.

$[\alpha]_D^{20}$ +100.4 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{35}H_{38}N_2NaO_5$ 589.2673, found 589.2675 $(M+Na)^+$. Calculated for $C_{35}H_{38}N_2KO_5$ 605.2412, found 605.2397 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-(p-tolyl)indoline-1-carboxylate (3k).



3j

The title compound was obtained following the general procedure to furnish the crude product as a 10:1 mixture of diastereoisomers. The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 80/20) to give **3k** in 77% yield, 0.154 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3k** τ_{major} = 23.9 min.; τ_{minor} = 11.9 min.

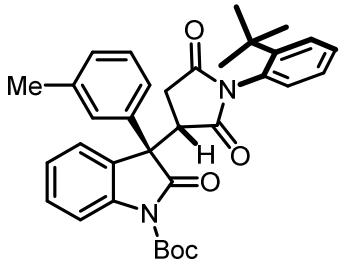
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.07 (*d*, J = 8.2 Hz, 1H); 7.51 (*m*, 1H); 7.45 (*dd*, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H); 7.37-7.30 (*m*, 2H); 7.30-7.11 (*m*, 5H); 7.01 (*ddd*, J_1 = J_2 = 7.6 Hz, J_3 = 1.4 Hz, 1H); 5.70 (*dd*, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H); 4.42 (*dd*, J_1 = 10.2 Hz, J_2 = 4.0 Hz, 1H); 3.11 (*dd*, J_1 = 19.3 Hz, J_2 = 10.2 Hz, 1H); 2.82 (*dd*, J_1 = 19.3 Hz, J_2 = 4.0 Hz, 1H); 2.33 (*s*, 3H); 1.57 (*s*, 9H); 1.23 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.9, 175.8, 174.4, 149.0, 147.7, 141.5, 138.4, 133.8, 129.9, 129.8, 129.7, 129.6, 129.6, 128.4, 127.5, 127.2, 126.5, 124.4, 123.7, 116.5, 84.5, 56.7, 47.7, 35.5, 32.8, 31.5, 28.0, 20.9.

$[\alpha]_D^{20}$ +128.8 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{34}H_{36}N_2NaO_5$ 575.2516, found 575.2511 $(M+Na)^+$. Calculated for $C_{34}H_{36}N_2KO_5$ 591.2256, found 591.225 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-(m-tolyl)indoline-1-carboxylate (3l).



3k

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr 19:1). The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 80/20) to give **3l** in 79% yield, 0.158 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3l** τ_{major} = 7.2 min.; τ_{minor} = 4.4 min.

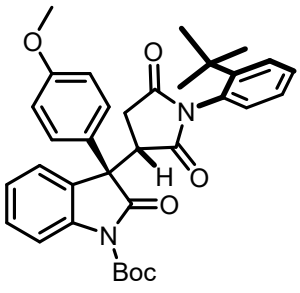
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.07 (*d*, *J* = 8.2 Hz, 1H); 7.52 (*m*, 1H); 7.45 (*dd*, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H); 7.38-7.29 (*m*, 2H); 7.29-7.20 (*m*, 2H); 7.17-7.08 (*m*, 3H); 7.01 (*ddd*, $J_1 = J_2$ = 7.6 Hz, J_3 = 1.4 Hz, 1H); 5.70 (*dd*, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H); 4.43 (*dd*, J_1 = 10.2 Hz, J_2 = 3.9 Hz, 1H); 3.12 (*dd*, J_1 = 19.2 Hz, J_2 = 10.2 Hz, 1H); 2.82 (*dd*, J_1 = 19.2 Hz, J_2 = 3.9 Hz, 1H); 2.33 (*s*, 3H); 1.58 (*s*, 9H); 1.23 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.9, 175.8, 174.3, 149.0, 147.7, 141.5, 138.9, 136.7, 129.9, 129.9, 129.6, 129.6, 129.3, 128.9, 128.5, 128.2, 127.2, 126.5, 124.7, 124.4, 123.8, 116.5, 84.5, 56.9, 47.8, 35.5, 32.8, 31.5, 28.0, 21.6.

$[\alpha]_D^{20}$ +131.1 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{34}H_{36}N_2NaO_5$ 575.2516, found 575.253 $(M+Na)^+$. Calculated for $C_{34}H_{36}N_2KO_5$ 591.2256, found 591.2282 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-3-(4-methoxyphenyl)-2-oxoindoline-1-carboxylate (3m).



3l

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 90:10) to give **3m** in 82% yield, 0.164 mmol and 96% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3m** τ_{major} = 14.6 min.; τ_{minor} = 7.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.06 (*d*, *J* = 8.3 Hz, 1H); 7.52 (*m*, 1H,); 7.45 (*d*, *J* = 8.2 Hz, 1H); 7.34 (*m*, 2H); 7.25 (*m*, 3H); 7.01 (*m*, 1H); 6.88 (*m*, 2H); 5.70 (*dd*,

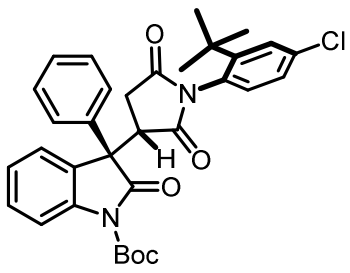
J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H); 4.39 (*dd*, J_1 = 10.3 Hz, J_2 = 3.8 Hz, 1H); 3.78 (*s*, 3H); 3.10 (*dd*, J_1 = 19.3 Hz, J_2 = 10.3 Hz, 1H); 2.83 (*dd*, J_1 = 19.3 Hz, J_2 = 3.8 Hz, 1H); 1.57 (*s*, 9H); 1.23 (*s*, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 175.9, 175.9, 174.7, 159.5, 148.9, 147.6, 141.3, 129.9, 129.8, 129.6, 129.5, 128.8, 128.5, 128.4, 127.1, 126.5, 124.3, 123.7, 116.4, 114.4, 84.5, 56.3, 55.2, 47.7, 35.4, 32.6, 31.4, 27.9.

$[\alpha]_D^{20}$ +123.6 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{34}H_{36}N_2NaO_6$ 591.2466, found 591.2467 $(M+Na)^+$. Calculated for $C_{34}H_{36}N_2KO_6$ 607.2205, found 607.2185 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)-4-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3o).



3m

The title compound was obtained following the general procedure to furnish the crude product as a single diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 75:25) to give **3o** in 90% yield, 0.180 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3o** τ_{major} = 7.9 min.; τ_{minor} = 5.3 min.

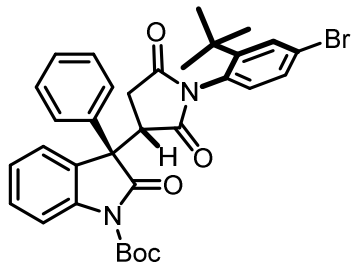
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.08 (*d*, *J* = 8.2 Hz, 1H); 7.52 (*m*, 1H,); 7.41 (*d*, *J* = 2.4 Hz, 1H); 7.34 (*m*, 7H); 7.00 (*dd*, J_1 = 8.4 Hz, J_2 = 2.4, 1H); 5.59 (*d*, *J* = 8.5 Hz, 1H); 4.44 (*dd*, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H); 3.12 (*dd*, J_1 = 19.5 Hz, J_2 = 10.2 Hz, 1H); 2.81 (*dd*, J_1 = 19.5 Hz, J_2 = 3.8 Hz, 1H); 1.58 (*s*, 9H); 1.22 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.7, 175.5, 174.2, 149.8, 148.9, 141.5, 136.6, 135.7, 131.3, 130.1, 129.1, 128.8, 128.5, 128.3, 127.6, 127.5, 126.3, 124.4, 123.8, 116.6, 84.7, 57.0, 47.8, 35.7, 32.8, 31.3, 28.0.

$[\alpha]_D^{20}$ +149.0 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}ClN_2NaO_5$ 595.197, found 595.1971 $(M+Na)^+$. Calculated for $C_{33}H_{33}ClN_2KO_5$ 611.171, found 611.1714 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(4-bromo-2-(*tert*-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3p).



3n

The title compound was obtained following the general procedure to furnish the crude product as a 16:1 mixture of diastereoisomers. The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 80:20) to give **3p** in 79% yield, 0.158 mmol and 96% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min, λ = 254 nm: **3p** τ_{major} = 10.2 min.; τ_{minor} = 6.7 min.

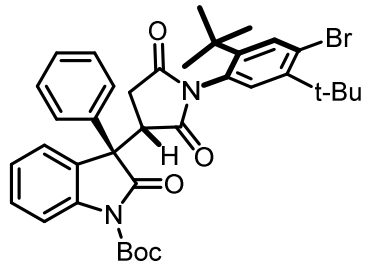
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.07 (*d*, J = 8.2 Hz, 1H); 7.57 (*d*, J = 2.2 Hz, 1H); 7.52 (*m*, 1H,); 7.40-7.30 (*m*, 7H); 7.15 (*dd*, J_1 = 8.3 Hz, J_2 = 2.2, 1H); 5.51 (*d*, J = 8.4 Hz, 1H); 4.44 (*dd*, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H); 3.11 (*dd*, J_1 = 19.3 Hz, J_2 = 10.2 Hz, 1H); 2.80 (*dd*, J_1 = 19.3 Hz, J_2 = 3.8 Hz, 1H); 1.58 (*s*, 9H); 1.22 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.6, 175.4, 174.2, 150.1, 148.9, 141.6, 136.6, 131.8, 131.5, 130.5, 130.1, 129.2, 128.8, 128.6, 127.6, 126.3, 124.4, 124.1, 123.8, 116.6, 84.7, 57.0, 47.9, 35.7, 32.8, 31.3, 28.0.

$[\alpha]_D^{20}$ +127.0 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}BrN_2NaO_5$ 639.1465, found 639.1454 $(M+Na)^+$. Calculated for $C_{33}H_{33}BrN_2KO_5$ 655.1204, found 655.1167 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(4-bromo-2,5-di-tert-butylphenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3q).



3o

The title compound was obtained following the general procedure to furnish the crude product as a single of diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (dichloromethane:hexane = 90:10) to give **3q** in 50% yield, 0.100 mmol and 96% ee.

HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3q** τ_{major} = 5.7 min.; τ_{minor} = 6.9 min.

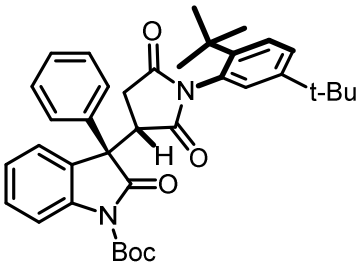
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.06 (*d*, J = 8.3 Hz, 1H); 7.63 (*s*, 1H); 7.46 (*m*, 1H,); 7.41-7.25 (*m*, 7H); 5.95 (*s*, 1H); 4.45 (*dd*, J_1 = 10.4 Hz, J_2 = 4.3 Hz, 1H); 3.10 (*dd*, J_1 = 19.6 Hz, J_2 = 10.4 Hz, 1H); 2.82 (*dd*, J_1 = 19.6 Hz, J_2 = 4.3 Hz, 1H); 1.59 (*s*, 9H); 1.30 (*s*, 9H); 1.21 (*s*, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 175.7, 175.4, 174.4, 149.0, 146.9, 146.6, 141.5, 136.9, 136.0, 130.2, 129.2, 128.6, 128.3, 127.6, 126.4, 124.6, 124.3, 123.4, 116.5, 84.7, 56.6, 47.6, 36.1, 35.1, 32.8, 31.4, 29.6, 28.1.

$[\alpha]_D^{20}$ +116.9 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{37}H_{41}BrN_2NaO_5$ 695.2091, found 695.2083 $(M+Na)^+$. Calculated for $C_{37}H_{41}BrN_2KO_5$ 711.183, found 711.1938 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2,5-di-*tert*-butylphenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3r).



3p

The title compound was obtained following the general procedure to furnish the crude product as a single of diastereoisomer (dr >19:1). The crude mixture was purified by flash column chromatography (dichloromethane:hexane = 80:20) to give **3r** in 43% yield, 0.086 mmol and >99% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min, λ = 254 nm: **3r** τ_{major} = 6.1 min.; τ_{minor} = 5.2 min.

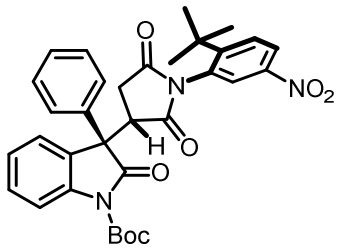
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.06 (*d*, *J* = 8.3 Hz, 1H); 7.50 (*m*, 1H); 7.44-7.30 (*m*, 8H); 7.26 (*m*, 1H); 5.81 (*d*, *J* = 2.1 Hz, 1H); 4.44 (*dd*, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H); 3.10 (*dd*, J_1 = 19.4 Hz, J_2 = 10.2 Hz, 1H); 2.81 (*dd*, J_1 = 19.4 Hz, J_2 = 3.8 Hz, 1H); 1.58 (*s*, 9H); 1.22 (*s*, 9H); 1.14 (*s*, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 175.9, 175.8, 174.4, 150.1, 149.0, 144.4, 141.6, 136.9, 130.2, 129.1, 129.0, 128.5, 128.1, 127.6, 127.0, 126.8, 126.4, 124.4, 123.8, 116.4, 84.6, 56.8, 47.7, 35.1, 34.1, 32.8, 31.6, 31.1, 28.0.

$[\alpha]_D^{20}$ +128.3 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{37}H_{42}N_2NaO_5$ 617.2986, found 617.2979 $(M+Na)^+$. Calculated for $C_{37}H_{42}N_2KO_5$ 633.2725, found 633.2727 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl-3-((*S*)-1-(2-(*tert*-butyl)-5-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3s).



3q

The title compound was obtained following the general procedure to furnish the crude product as a single of diastereoisomer (dr 19:1). The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 75:25) to give **3s** in 81% yield, 0.162 mmol and 98% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 1 mL/min, λ = 254 nm: **3s** τ_{major} = 17.6 min.; τ_{minor} = 9.7 min.

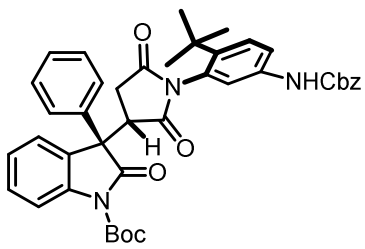
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.08 (*m*, 2H,); 7.67 (*m*, 1H,); 7.63 (*d*, J = 9.0 Hz, 1H); 7.48 (*ddd*, $J_1 = J_2$ = 7.5 Hz, J_3 = 1.1 Hz, 1H); 7.38 (*m*, 6H); 6.56 (*d*, J = 2.5 Hz, 1H); 4.47 (*dd*, J_1 = 10.0 Hz, J_2 = 3.4 Hz, 1H); 3.16 (*dd*, J_1 = 19.4 Hz, J_2 = 10.0 Hz, 1H); 2.86 (*dd*, J_1 = 19.4 Hz, J_2 = 3.4 Hz, 1H); 1.58 (*s*, 9H); 1.27 (*s*, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 175.6, 175.3, 174.3, 155.9, 148.8, 146.5, 141.4, 136.5, 131.1, 130.9, 129.8, 129.3, 128.7, 127.7, 125.8, 125.6, 124.9, 124.3, 123.6, 116.8, 84.8, 57.2, 48.1, 36.4, 32.9, 31.3, 28.0.

$[\alpha]_D^{20}$ +111.2 (*c* 1.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{33}H_{33}N_3NaO_7$ 606.2211, found 606.2202 $(M+Na)^+$. Calculated for $C_{33}H_{33}N_3KO_7$ 622.195, found 622.1919 $(M+K)^+$.

(*M*)-(*R*)-*tert*-butyl3-((*S*)-1-(5-(((benzyloxy)carbonyl)amino)-2-(tert-butyl)phenyl)-2,5-dioxopyrrolidin-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (3t).



3t

The title compound was obtained following the general procedure to furnish the crude product as a 6:1 mixture of diastereoisomers. The crude mixture was purified by flash column chromatography (hexane:ethyl acetate = 70:30) to give **3t** in 94% yield, 0.188 mmol and 86% ee.

HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80/20, flow rate 0.8 mL/min, λ = 254 nm: **3t** τ_{major} = 35.8 min.; τ_{minor} = 17.8 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.04 (*d*, J = 8.7 Hz, 1H); 7.50-7.25 (*m*, 15H,); 6.47 (*bs*, 1H); 5.73 (*bs*, 1H); 5.17 (*m*, 2H); 4.42 (*dd*, J_1 = 10.1 Hz, J_2 = 3.9 Hz, 1H); 3.07 (*dd*, J_1 = 19.4 Hz, J_2 = 10.1 Hz, 1H); 2.77 (*dd*, J_1 = 19.4 Hz, J_2 = 3.9 Hz, 1H); 1.56 (*s*, 9H); 1.20 (*s*, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 175.7, 175.4, 174.4, 148.9, 141.3, 136.7, 136.7, 136.0, 134.8, 129.8, 129.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.1, 127.6, 127.2, 126.4, 125.0, 123.6, 119.9 (*bs*), 116.5, 84.6, 66.9, 56.8, 47.8, 35.1, 32.7, 31.5, 27.9.

$[\alpha]_D^{20}$ +378.8 (*c* 2.00, $CHCl_3$).

HRMS-ESI-ORBITRAP (+): calculated for $C_{41}H_{41}N_3NaO_7$ 710.2837, found 710.2832 $(M+Na)^+$. Calculated for $C_{41}H_{41}N_3KO_7$ 726.2576, found 726.2575 $(M+K)^+$.

Acknowledgment

This work was financially supported by the University of Bologna (FARB Project "Catalytic transformation of biomass-derived materials into high added-value chemicals" and RFO-2014 funds)

Chapter IV

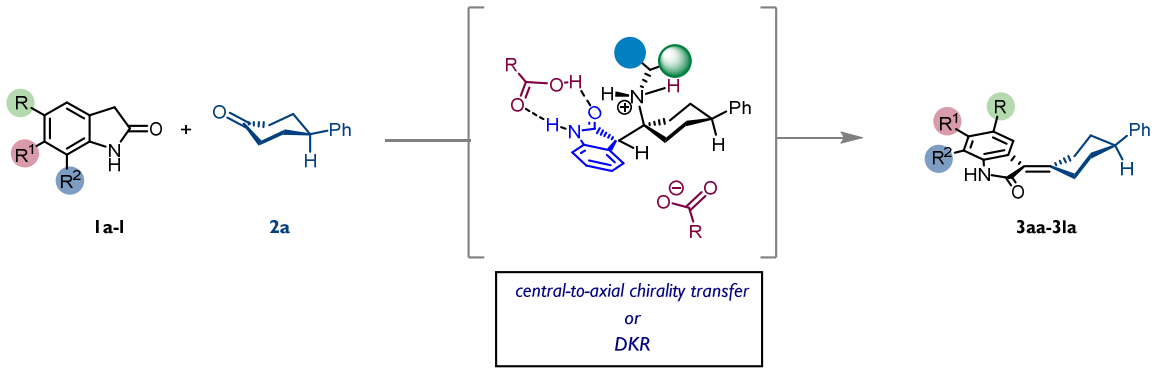
Desymmetrization of Prochiral Cyclohexanones via *Knoevenagel Condensation*

4.1 Asymmetric Synthesis of Axially Chiral Cyclohexylidene Oxindoles via Organocatalytic Knoevenagel Condensation

All the procedures and results here described are part of- and can be found in-:

S. Crotti, N. Di Iorio, C. Artusi, A. Mazzanti, P. Righi, and G. Bencivenni, "Asymmetric Synthesis of Axially Chiral Cyclohexylidene Oxindoles via Organocatalytic Knoevenagel Condensation.", *Org. Lett.*, **2019**, *21*, 3013-3017.

Abstract:



The organocatalytic axially enantioselective Knoevenagel condensation (*a*EKC) between prochiral cyclohexanones and oxindoles is presented. The reaction is promoted by a primary amine organocatalyst derived from a *cinchona* alkaloyds and an acid co-cocatalyst. In the optimal condition the reaction proceeded smoothly to furnish the condensed product, an unprecedented example of novel cyclohexylidene oxindoles displaying axial chirality. The reaction pathway has been investigated through DFT calculations studies to determine the stereo-determining step and the possible transition states.

4.2 Alkylidencycloalkanes

During the last years, asymmetric organocatalysis revealed to be an elective platform to perform the synthesis of atropisomers,[97] an important class of chiral molecules bearing a stereogenic axis that originates from the restricted rotation along a single bond (see **Chapter 1.2.3**).[98] This *unconventional* element of chirality, is the structural feature of many natural and bioactive compounds as well as catalysts or ligands for asymmetric synthesis.[99]

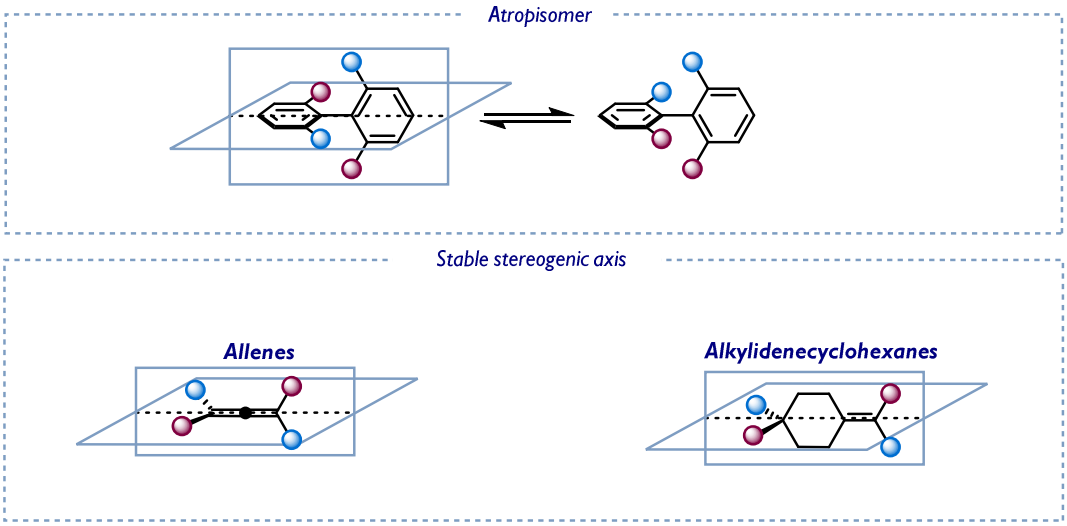


Figure 32. *Example of axially chiral compounds*

[97] a) P. Renzi, *Org. Biomol. Chem.*, **2017**, *15*, 4506. b) Y.-B. Wang, B. Tan *Acc. Chem. Res.* **2018**, *51*, 534. c) G. Bencivenni *Synlett*, **2015**, *26*, 1915. d) S. Shirakawa, S. Liu, S. Kaneko, *Chem.-Asian J.* **2016**, *11*, 330. For representative examples see: d) A. Link, C. Sparr *Angew. Chem. Int. Ed.,* **2014**, *53,* 5458. e) L. Zhang, J. Zhang, J. Ma, D.-J. Cheng, B. Tan *J. Am. Chem. Soc.* **2017**, *139*, 1714. f) O. Quinonero, M. Jean, N. Vanthuyne, C. Roussel, D. Bonne, T. Constantieux, C. Bressy, X. Bugaut, J. Rodriguez *Angew. Chem. Int. Ed.* **2016**, *55*, 1401. g) Y. Liu, Y.-L. S. Tse, F. Y. Kwong, Y.-Y. Yeung *ACS Catal.* **2017**, *7*, 4435. h) J. D. Jolliffe, R. J. Armstrong, M. D. Smith *Nat. Chem.* **2017**, *9*, 558. i) N. Di Iorio, P. Righi, A. Mazzanti, M. Mancinelli, A. Ciogli, G. Bencivenni *J. Am. Chem. Soc.* **2014**, *136*,10250. j) Y. Tan, S. Jia, F. Hu, Y. Liu, L. Peng, D. Li, H. Yan *J. Am. Chem. Soc.* **2018**, *140*, 16893. k) J.-W. Zhang, J.-H. Xu, D.-J. Cheng, C. Shi, X.-Y. Liu, B. Tan, *Nat. Commun.* **2016**, *7*, 10677. k) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez *J. Am. Chem. Soc.* **2017**, *139*, 2140. l) S.-L. Li, C. Yang, Q. Wu, H.-L. Zheng, X. Li, J.-P. Cheng *J. Am. Chem. Soc.* **2018**, *140*, 12836. m) Y. Tan, S. Jia, F. Hu, Y. Liu, L. Peng, D. Li, H. Yan *J. Am. Chem. Soc.* **2018**, *140*, 49, 16893.

[98] a) Ōki, M., *Recent Advances in Atropisomerism. In Topics in Stereochemistry*; *Vol. 14* (Eds: E. L. Eliel, S. H. Wilen, N. L. Allinger), John Wiley and Sons: New York, **2007**, pp 1−81. b) K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry, M. Yamanaka, *Synlett* **2002**, 1561.

[99] a) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning *Chem. Rev.* **2011**, *111*, 563. b) E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru *Chem. Rev.* **2015**, *115*, 11239. c) Y. Chen, S. Yekta, A. K. Yudin *Chem. Rev.* **2003**, *103*, 3155. d) P. Kočovský, Š. Vyskočil, M. Smrčina *Chem. Rev.* **2003**, *103*, 3213. e) B. Zilate, A. Castrogiovanni, C. Sparr *ACS Catal.* **2018**, *8*, 2981. f) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert *Chem. Soc. Rev.,* **2015**, *44*, 3418.

Less attention was probably payed to another important class of axially chiral compounds such as allenes and alkylidenecycloalkanes[100] (**Figure 32**).

This type of axial chirality arises, as we already discussed, not from a slow rotation caused by stereo or electronic effect, but rather on their inner rigid structure. Because of their diffusion in nature, the chemistry of chiral allenes has been largely studied in the past, and various enantioselective syntheses utilizing different catalytic strategies are known.[101] Alkylidenecycloalkanes, despite a few applications as precursors of chiral liquid crystals and in circular dichroism studies, encountered less attention, and their catalytic enantioselective syntheses are rare.[102] Previous approaches have been focused on two main strategies:

1. the construction of the double bond by means of Horner−Wadsworth−Emmons (HWE) or Peterson olefination using a stoichiometric amount of chiral reagent or ligands

2. reduction of prochiral alkylidene cyclohexanone derivatives.

The first asymmetric synthesis of alkylidenecycloalkanes was accomplished by Hanessian in 1984 by means of Wittig-type olefination.

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[100] a) E. L. Eliel, S. H. Wilen in *Stereochemistry of Organic Compounds*, John Wiley-Interscience: New-York, **1994**. b) B. Testa, *Principles of Organic Stereochemistry. In Studies in Organic Chemistry*; *Vol.* 6 (Ed: P. G. Gassman), Dekker: New-York, **1979**.

[101] a) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. b) R. K. Neff, D. E. Frantz *ACS Catal.* **2014**, *4*, 519. c) T. Hashimoto, K. Sakata, F. Tamakuni, M. J. Dutton, K. Maruoka *Nat. Chem.*, **2013**, *5*, 240. d) J. Yu, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 4050. e) M. Oku, S. Arai, K. Katayama, T. Shioiri, *Synlett* **2000**, 493. f) H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, 131, 7212. g) T. Inokuma, M. Furukawa, Y. Suzuki, T. Kimachi, Y. Kobayashi, Y. Takemoto, *ChemCatChem* **2012**, *4*, 983. h) T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470. i) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664.

[102] a) R. Eelkema, B. L. Feringa, *Org. Biomol. Chem.* **2006**, *4*, 3729. b) G. Solladié, G. Zimmermann *Angew. Chem. Int. Ed.* **1984**, *23*, 348. c) J. H. Brewster, J. E. Privett, *J. Am. Chem. Soc.* **1966**, *88*, 1419. d) M. Duraisamy, H. M. Walborsky, *J. Am. Chem. Soc.* **1983**, *105*, 3252. e) Y. Zhang, G. B. Schuster *J. Org. Chem.* **1995**, *60*, 7192. f) R. F: Bradford, G. B. Schuster, *J. Org. Chem.* **2003**, *68*, 1075.

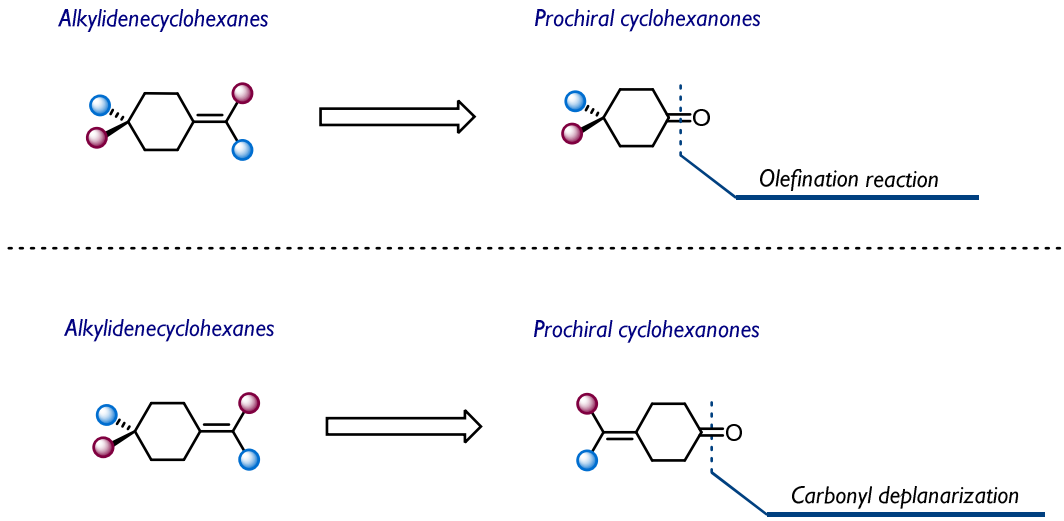


Figure 33. *Approach for the synthesis of alkylidenecyclohexanes*

One of the many problems that are omnipresent in Wittig-type olefinations is controlling the stereochemistry of unsymmetrical olefins. Using what they say to be a topologically unique stoichiometric enantiomeric chiral bicyclic phosphonamide derived from cyclohexanediamine reagents, they have demonstrated a remarkable stereodifferentiating reactivity toward alkyl cyclohexanones.

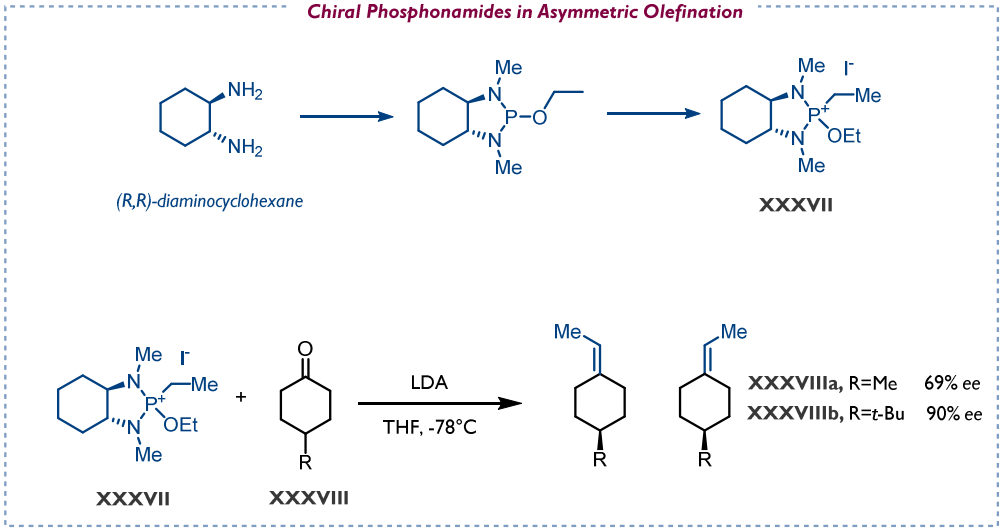
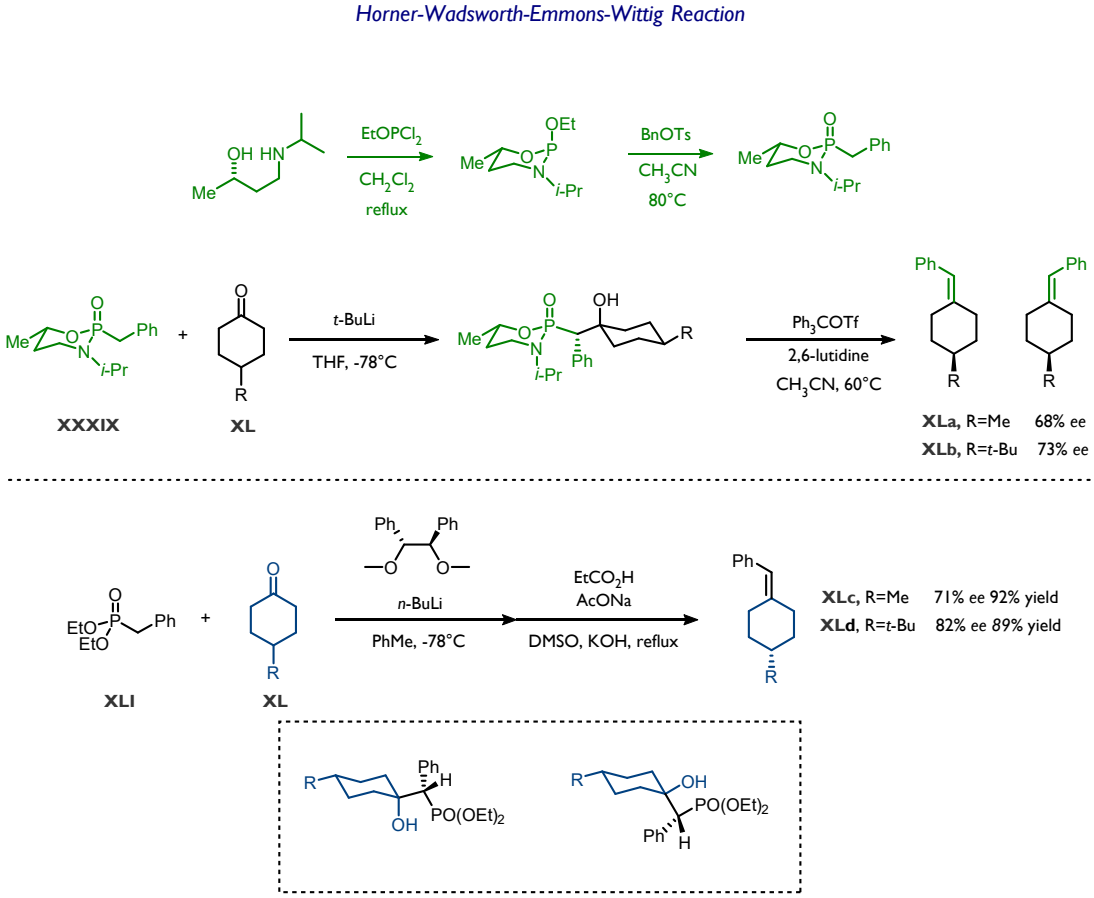


Figure 34. *Hanessian synthesis of chiral alkylidencyclohexanes*

Despite the harsh reaction condition, they were able to obtained the desired product in good yield and enantiomeric excess. A similar strategy was adopted by Denmark and Tomioka, but this time with a stabilized phosphonate in a Horner−Wadsworth−Emmons (HWE) type reaction. In the first approach a stoichiometric chiral phosphonamidate was activated with a strong base and after the chiral transfer the stereoinformation was transferred to the alkylidene product. Tomioka instead for the first time presented an achiral lithium phosphonate, controlled by an external chiral ligand, that undergoes the addition to a ketone, and the resulting chiral alcohol undergoes stereoselective olefination.

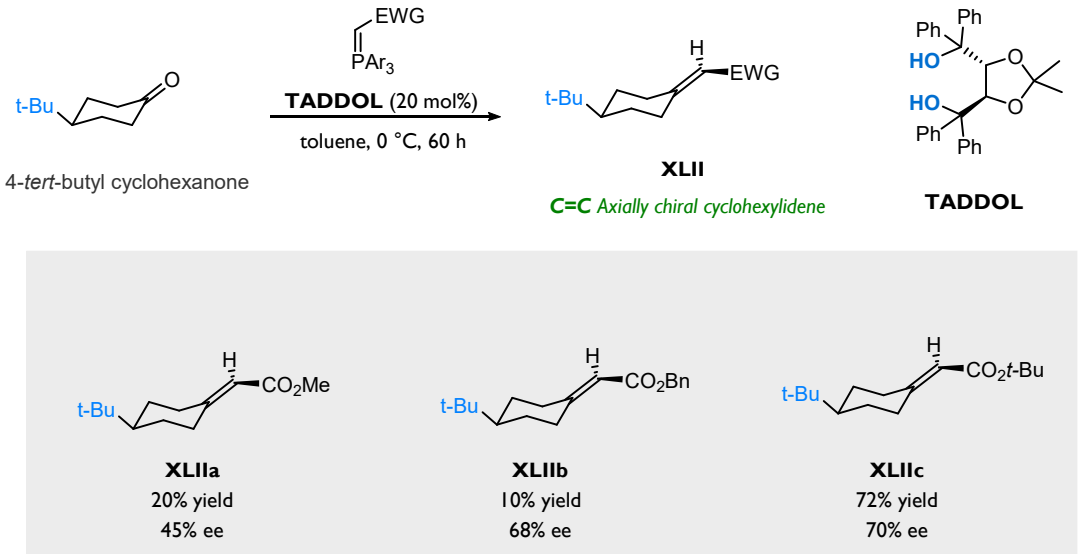


Scheme 23. *HWE-type synthesis of alkylidenecyclohexanes*

An important contribution has been recently proposed by Bernardi, [103] who realized the first catalytic synthesis of axially chiral trisubstituted alkylidenes

[103] L. Gramigna, S. Duce, G. Filippini, M. Fochi, M. Comes Franchini, L. Bernardi *Synlett*, **2011**, *18*, 2745.

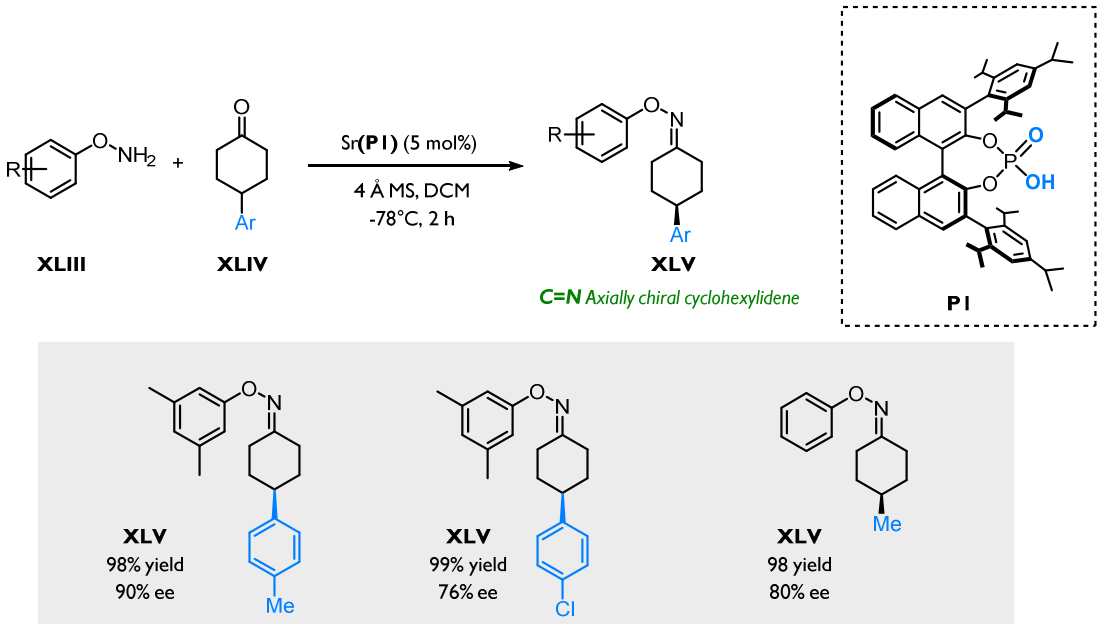
through organocatalyzed Wittig reaction. In this work they set their focus on the Wittig reaction with stabilized phosphorus ylides, which is known to proceed irreversibly through an asynchronous [2+2]-cycloaddition pathway. To achieve enantioenrichment in the resulting alkenes, they envisioned the use of chiral H-bond donors as catalysts, to coordinate the cyclohexanone carbonyl which bears a partial negative charge during the cycloaddition. *Stereospecificity* in the elimination of phosphine oxide in fact ensure full central-to-axial chirality transfer. Unfortunately, despite the novelty of this approach, the reaction was limited to the use of 4-*tert*-butyl-cyclohexanone to achieve enantioenrichment. Moreover, usually low to moderate yields and moderate to good enantiomeric excesses were obtained (**Scheme 25**).



Scheme 24. *TADDOL catalyzed organocatalytic Wittig reaction*

In 2017 Antilla, developed an efficient catalytic asymmetric reaction for the desymmetrization of 4-phenyl cyclohexanones to novel axially chiral cyclohexylidene oxime ethers. The reaction was promoted *via* LUMO-lowering activation of the prochiral cyclohexanone by means of a Brønsted acid catalyst.

Interestingly, for the first time a catalytic approach was employed for the synthesis of C=N axially chiral alkylidene-type molecules (**Scheme 26**).[104]

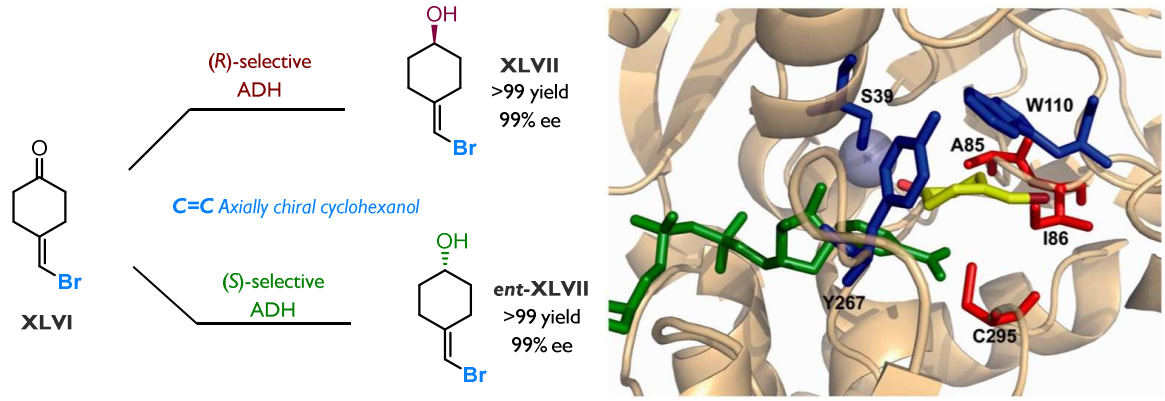


Scheme 25. *Synthesis of axially chiral oxime ethers.*

To further show the utility of the methodology, they also have demonstrated the DKR process of α-branched cyclohexanones for the synthesis of useful products. To the best of my knowledge, the only example of the orthogonal approach for the synthesis of axially chiral cyclohexilidene was accomplished by Reetz and co-workers in a biocatalytic ketone reduction catalyzed by alcohol dehydrogenase catalyst (**ADH**). The paper points out the challenge of this transformation; They indeed also envisioned the possibility of using a catalytic enantioselective reduction using chiral transition-metal catalysts. Unfortunately, every catalytic system tried, even one of the most efficient chiral Ru-based catalysts ((TsDPEN)(*p*-cymene)$RuCl_2$) in ketone reduction, only formation of alcohol as a racemate was observed. Thanks to this observation they had to switch to a catalyst with a strict and confined geometry (**Scheme 27**, right). With this approach they

[104] S. K. Nimmagadda, S. C. Mallojjala, L. Woztas, S. E. Wheeler, J. C. Antilla *Angew. Chem. Int. Ed.* **2017**, *56*, 2454.

were able to achieve perfect yield and perfect enantioselectivity in both the two enantiomers, which means that a wide variety of structurally different axially chiral compounds was readily accessible in *R*- or *S*-form.[105]



Scheme 26. *Reetz's biocatalytic syntheis of cyclohexanol via ketone reduction*

4.3 Enantioselective Knoevenagel condensation

The Knoevenagel condensation (KC) represents one of the earliest and most important organocatalytic olefination processes; however, enantioselective versions are rare. The first example has been recently reported by List, who used the KC for the dynamic kinetic resolution of racemic α-branched aldehydes.[106] Exploiting the iminium ion-enamine equilibrium that cause the loss of stereochemical information on the preexisting chiral center and further catalyst-controlled diastereoselective nucleophilic addition, after a stereodefined elimination of the catalyst they were able to obtain the condensed product in high yield and enantiomeric excess (**Figure 35**, left). Surprisingly, to date, the use of this venerable transformation for the synthesis of axially chiral olefins remains totally unexplored. Our idea was to design a new variant of the Knoevenagel reaction that could assemble prochiral 4-substituted cyclohexanones and 2-

[105] R. Agudo, G. D. Roiban, M. T. Reetz *J. Am. Chem. Soc.* **2013**, *135*, 1665.
[106] A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List *Angew. Chem. Int. Ed.*, **2011**, *50*, 1707.

oxindoles to realize the enantioselective generation of a new stereogenic axis in an alkylidene framework (**Figure 35**, right).

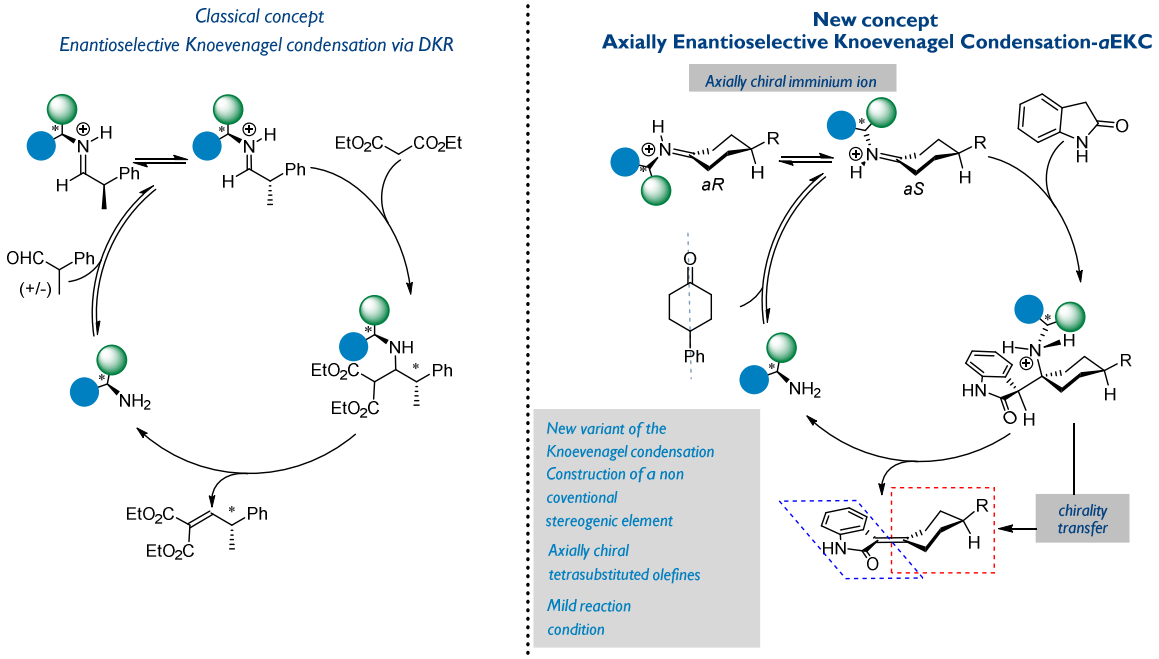


***Figure 35**. List DKR of alpha-branched aldehydes and our approach for the synthesis of alkylidenoxyndoles*

We envisioned that a chiral amine could form a pair of diastereomeric iminium ions, already bearing a stereogenic axis, followed by the nucleophilic addition-elimination sequence. The 3-alkyloxindole intermediate formed can undergo a *point-to-axial chirality transfer* path[107] that make all the stereogenic elements to collapse into the newly formed axially chiral tetrasubstituted 3-alkylideneoxindoles. The axially enantioselective Knoevenagel condensation (*a*EKC) represents a valid alternative in the field of enantioselective olefinations offering a milder, cheaper, and easier-to-handle strategy than the previously reported methodologies which required the use of chiral reagents, stoichiometric amounts of ligands, and strong bases. Indeed, in light of the role that many axially

[107] Y. Nichi, K. Wakasugi, K. Koga, Y. Tana *J. Am. Chem. Soc.* **2004**, *124*, 5358.

chiral compounds cover as drugs and biologically active compounds,[108] the synthesis of novel axially chiral molecules is highly desirable.

It could be interesting to show the possible stereoselective feature of this reaction. The first implication that one can see is the attack of the two possible prochiral faces by the oxindole, *Si* and *Re*. The two prochiral faces can undergo nucleophilic addition on the already *axially chiral epimeric iminium ion*. Being two diastereoisomers, they are conceptually different in energy, but it is interesting that what usually is a *cis-trans* conformational difference between the two electrophilic species now is an element of chirality, particularly axial chirality. Moving on in the attack, there are the two possible faces of the iminium ion, that we can call *re* and *si*, on purpose without the capital letter, because the newly formed center pseudo-asymmetric. Finally, the outcomes of the final collapse of all the stereoelements into an axially chiral alkylideneoxindole is shown. Keep in mind that this outcome arises only from the assumption that an antiperiplanar E_2 elimination occurs. All these implications are shown in **Figure 36**.

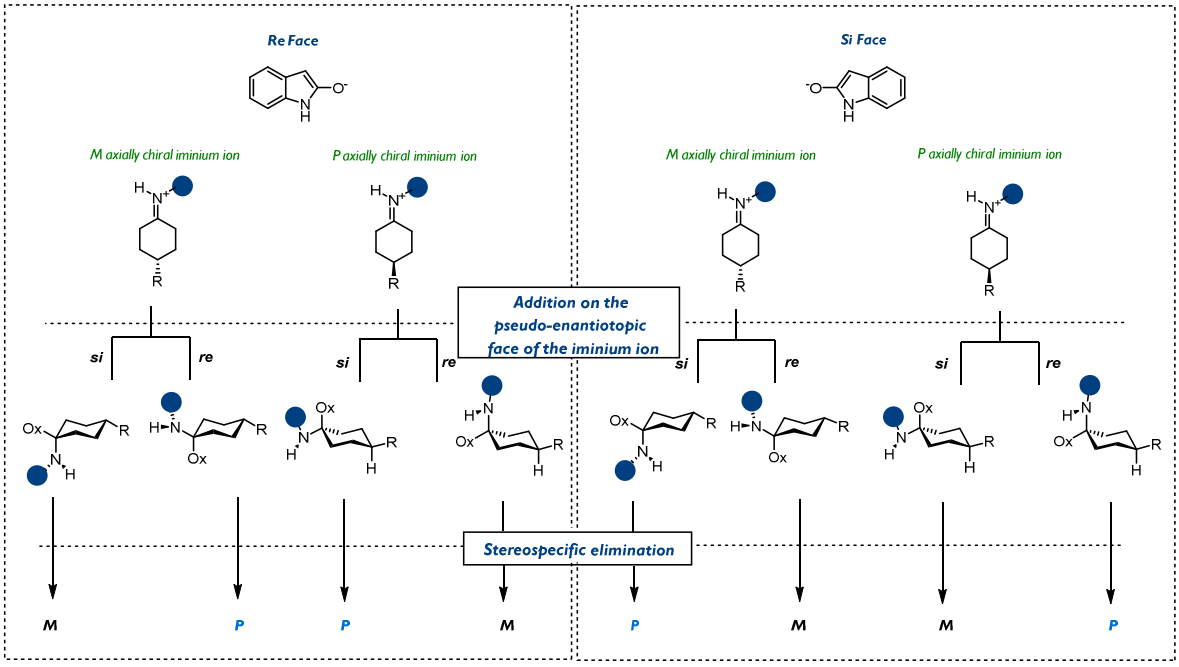
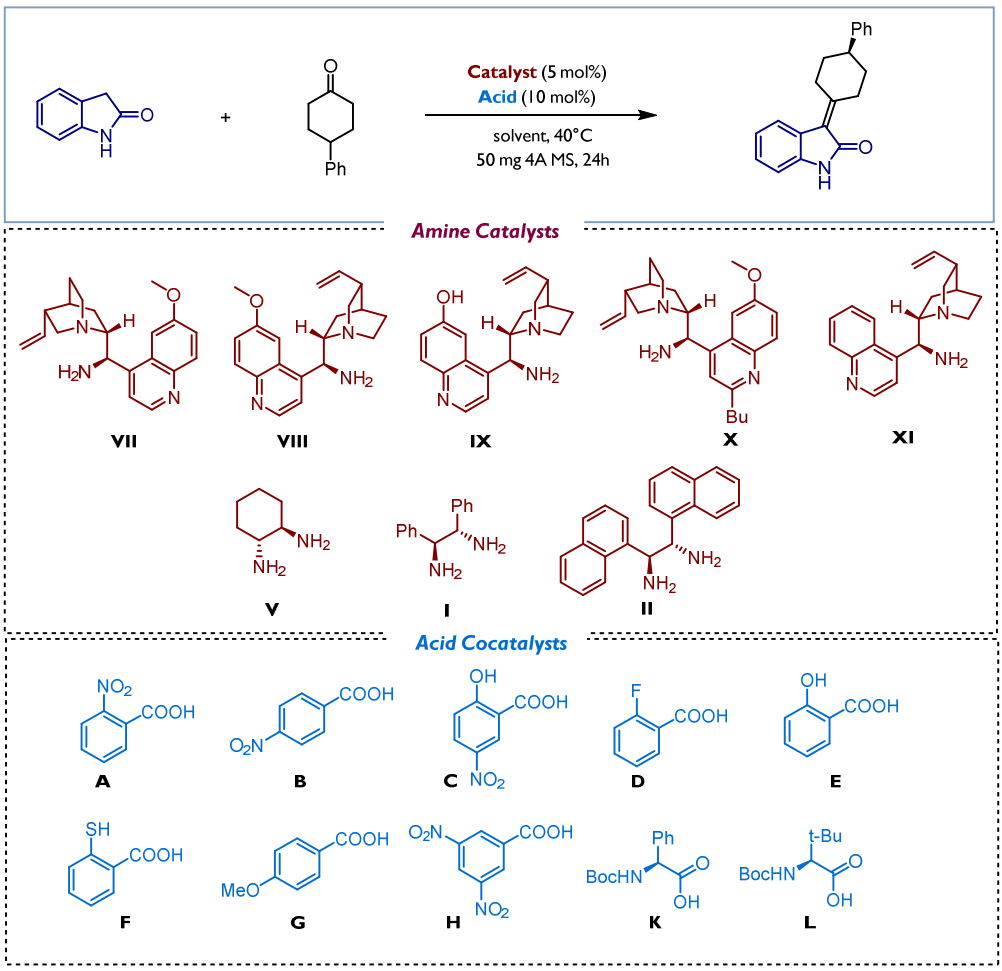


Figure 36. *Possible outcome after the collapse of all the stereoelements into an axially chiral cyclohexylidene.*

[108] (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398. (b) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J., *J. Med. Chem.* **2011**, *54*, 7005.

We started our investigation by screening various chiral amines as catalysts (**Table 4**). Cinchona alkaloid primary amines, due to their ease of condensation on the carbonyl group of cyclohexanone,[109] catalyzed the *a*EKC in high yield and enantiomeric ratio. A 5 mol % of 9-*epi*-NH_2-QDA (**VII**), in combination with 10 mol % of 3,5-dinitrobenzoic acid (**H**), gave **3aa** in 55% yield and 14:86 er (entry 1). With this catalytic combination, we studied different solvents and found an increment of the yield using toluene (entry 2-6). Although the reaction was not completely homogeneous, a concentration of 0.4 M was chosen to ensure optimal reactivity and enantiocontrol (entry 7). Higher values were detrimental because of the scarce solubility of oxindole (entries 8 and 9). The screening of acidic additives (entries 10−21) revealed that benzoic acid derivatives provided better results than chiral acids (entries 18−20). At the end of this detailed screening, 3,5-dinitrobenzoic acid **H** remained the best acidic cocatalyst.



[109] (a) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748. (b) Jadhav, M. S.; Righi, P.; Marcantoni, E.; Bencivenni, G. *J. Org. Chem.* **2012**, *77*, 2667. (c) Lifchits, O.; Demoulin, N.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9680.

Entry	Catalyst	Acid	Solvent (M)	Yield[b] (%)	ee[c] (%)
1	**VII**	**H**	MeOH (0.1)	55	14:86
2	**VIII**	**H**	MeOH (0.1)	52	85:15
3	**IX**	**H**	MeOH (0.1)	0	n.d.
4	**X**	**H**	MeOH (0.1)	49	14:86
5	**XI**	**H**	MeOH (0.1)	45	83:17
6	**VII**	**H**	Toluene (0.1)	63	14:86
7	**VII**	**H**	Toluene (0.4)	90	13:87
8	**VII**	**H**	Toluene (0.7)	62	14:86
9	**VII**	**H**	Toluene (1.0)	64	13:87
10	**VII**	**A**	Toluene (0.4)	70	14:86
11	**VII**	**B**	Toluene (0.4)	45	12:88
12	**VII**	**C**	Toluene (0.4)	62	20:88
13	**VII**	**D**	Toluene (0.4)	n.d.	19:81
14	**VII**	**E**	Toluene (0.4)	60	14:86
15	**VII**	**F**	Toluene (0.4)	n.d.	19:81
16	**VII**	**G**	Toluene (0.4)	43	15:85
17	**VII**	**I**	Toluene (0.4)	n.d.	22:78
18	**VII**	**J**	Toluene (0.4)	0	n.d.
19	**VII**	**K**	Toluene (0.4)	12	20:80
20	**VII**	**L**	Toluene (0.4)	28	19:81

[a]Reactions were performed on a 0.1 mmol scale using a 1:1 ratio between **1a** and **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. d When the reaction was performed without MS, compound 3aa was obtained in 8% yield and 59:41 e.r. after 24 hours.

Table 4. *Optimization of the reaction condition of the Knoevenagel Condensation*

With the optimized conditions, the scope and limitation of the *a*EKC reaction were studied (**Table 5**). The reaction could be performed using oxindoles with different substituents (**3aa− la**). In general, a good control of the stereochemical outcome was obtained. Various substituents with different electronic properties gave high yields of the corresponding alkylideneoxindole (**3ba−da, 3fa−ga, 3ja, 3la**); however, poor yields could be observed when highly insoluble oxindoles were used (**3ea, 3ha−ia, 3ka**). The presence of a strong electron-withdrawing nitro group was detrimental for both yield and stereocontrol (**3ka**).

The scope of several prochiral cyclohexanones **2b−j** was then explored. Good yields and er were obtained for new cyclohexylidene oxindoles **3ab−aj** with aromatic and aliphatic substituents. In the case of aliphatic cyclohexanones, the size of the substituent was a discriminant factor (not exclusively) for the enantiomeric ratio of the product. The larger the group, the higher the enantioselectivity.

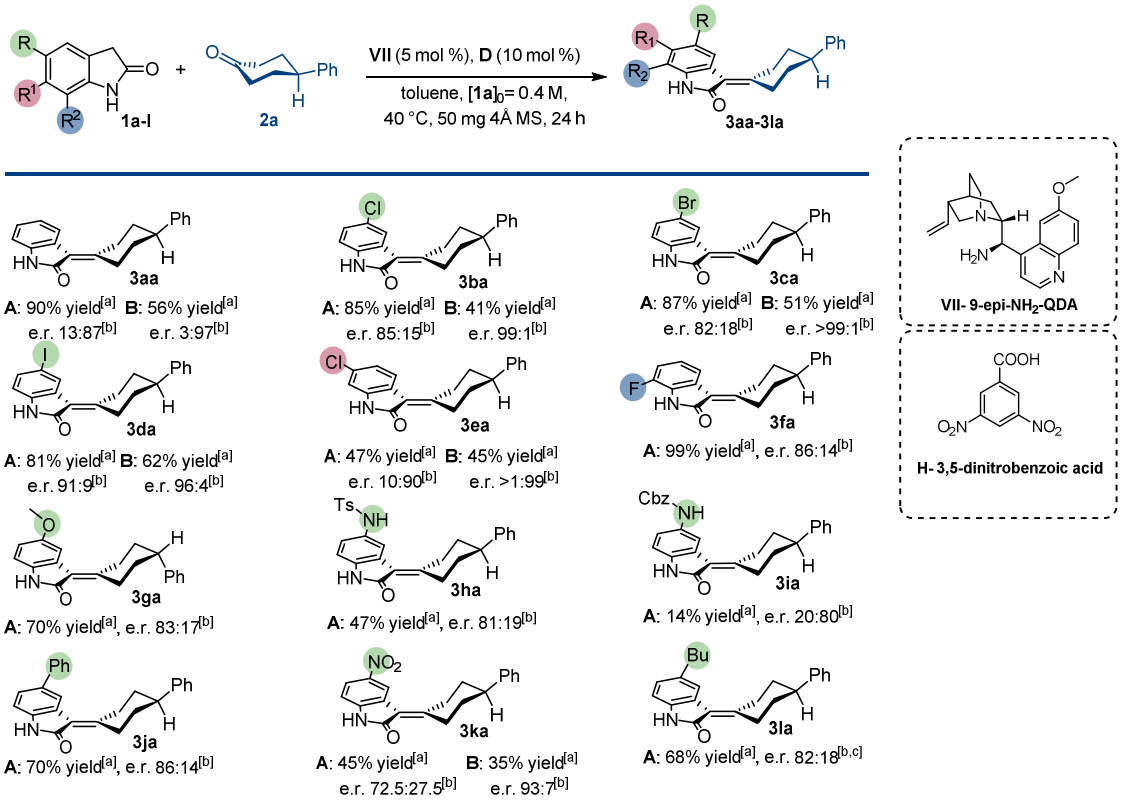


Table 5. *Scope on the oxindole*

This could be possibly due to the conformational equilibrium of 4-substituted cyclohexanones where the presence of a large group ensures that only one side of the iminium group is effectively accessible by the nucleophile. This is the specific case for ketones **2g** and **2h**. With ketones **2f** and **2i**, the conformational equilibrium is not completely shifted toward the equatorial conformer, and a poor enantiocontrol is observed because both sides of the iminium ion are accessible. The reaction can be extended to cyclobutanones but with poor yield and er (**3aj**), while 4-phenylcyclooctanone is not reactive at all.

A possible derivatization of the 3-alkylideneoxindole was identified in the epoxidation of the double bond. Enantiopure **3aa** was treated with *m*-CPBA, and the resulting epoxide can be isolated in 86% yield as a 5:1 mixture of diastereoisomers **5aa** and **5aa'** and both with a 98.5:1.5 er (**Scheme 26**, top).

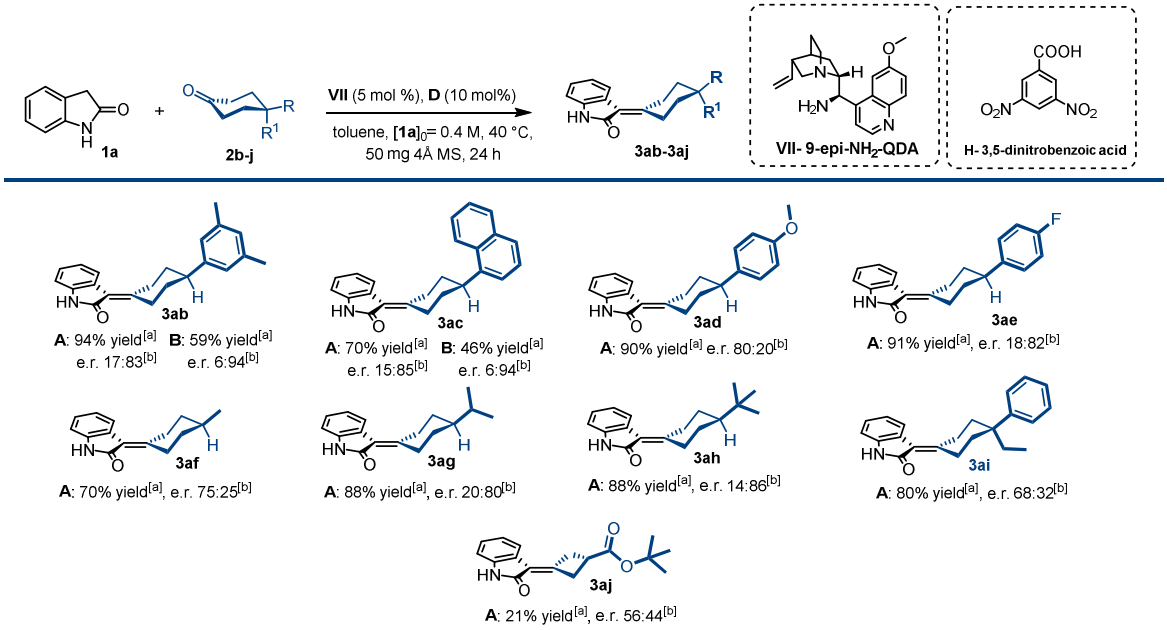
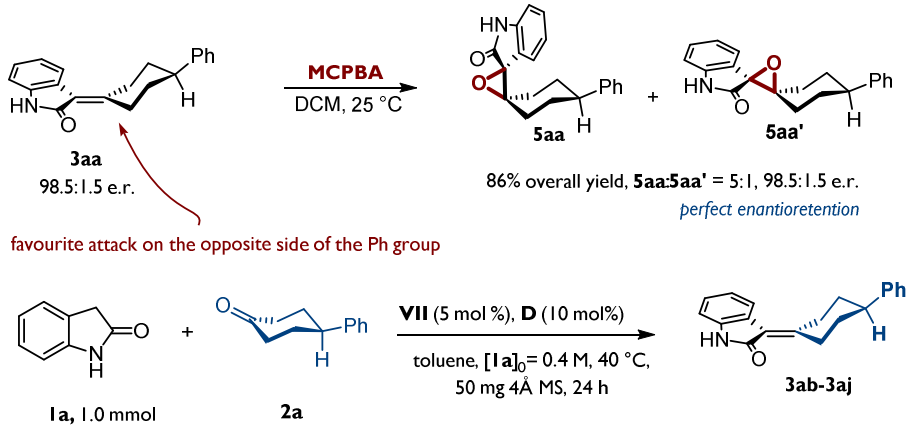


Table 6. *Scope on the cyclohexanones*

Furthermore, the reproducibility of the *a*EKC was tested in a 1 mmol scale reaction. As shown in **Scheme 26**, bottom, compound **3aa** was obtained in 85% of isolated yield and 84:16 er.



Scheme 27. *Derivatization and 1.0 mmol scale reaction*

In order to investigate the reaction mechanism that explains the stereochemical outcome of the reaction, a detailed DFT computational study was performed.

All of the quantum-chemical computations were performed using the Gaussian 16 package.[110] Preliminary computational studies on the iminium ions and the transition states for the addition of oxindole to the iminium ion were performed using at the B3LYP/6-31G(d) level of theory. The B3LYP/6-31G(d) method has been widely used to model organocatalytic reactions.[111] Recently, issues associated to the B3LYP in accounting for dispersion have been pointed out. However, Goodman compared various density functionals and found that for transition-structure geometry optimizations, B3LYP is slightly less accurate than newer, dispersion-inclusive functionals, which are more computationally demanding.[112]

After the preliminary studies, the computational studies examining the main points of the reaction paths leading to major (a*S*)- and minor (a*R*)-product were studied at 313 K using the metahybrid DFT functional M06-2X2[113,114] together with the universal continuum solvation model (SMD). The thermal corrections evaluated on the optimized geometries at 313 K from the unscaled vibrational frequencies[115] with the M06-2X/6-31G(d)/SMD(toluene) level of theory were then added to the M06-2X/6-311++G(2d,p)/SMD(toluene) electronic energies to obtain the corrected free energies.[116]

The free energy corrections were calculated using Truhlar's quasi-harmonic approximation[117] as implemented in the GoodVibes program.[118]

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110 Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

111 (a) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042−5137. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569.

112 Simón, L.; Goodman, J. M. *Org. Biomol. Chem.* **2011**, *9*, 689−700.

113 Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

114 All M06-2X computations were performed using Gaussian 09 default parameters ("G09Defaults" keyword)

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116 A. Moran, A. Hamilton, C. Bo, P. Melchiorre *J. Am. Chem. Soc.* **2013**, *135*, 9091-9098

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118 GoodVibes v. 2.02; DOI: 10.5281/zenodo.595246.

Iminium ions

The reaction of the 9-*epi*-9-amminoquinidine (9-*epi*-NH_2-QDA) catalyst with 4-phenylcyclohexanone, in the presence of 3,5-dinitrobenzoic acid, affords the two diastereoisomeric iminium ions (R_a)- and (S_a)-**A**.

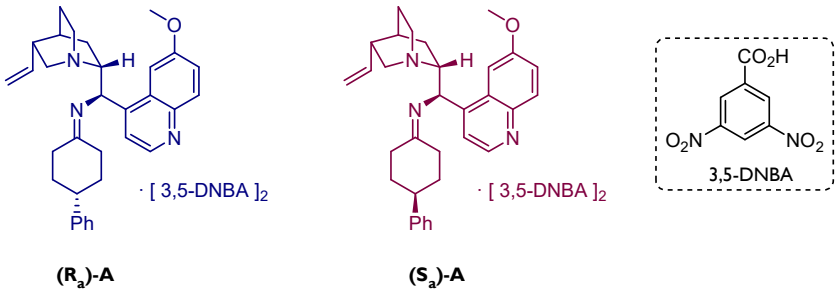


Figure 37. *Two diastereomeric iminium ion aS and aR*

Previous extensive conformational analysis on cinchona alkaloids and their iminium derivatives[119] showed that the cinchona alkaloids prefer to adopt the *anti-open* conformation which was the only one considered in the following calculations.

A relaxed potential energy surface (PES) scan at the semiempirical PM6 level was performed on both iminium ions (R_a)- and (S_a)-**A** by the systematic variation of the C9-N bond dihedral angle. All the structures within 5 kcal/mol from the one with the lowest energy were reoptimized at the B3LYP/6-31G(d) level.

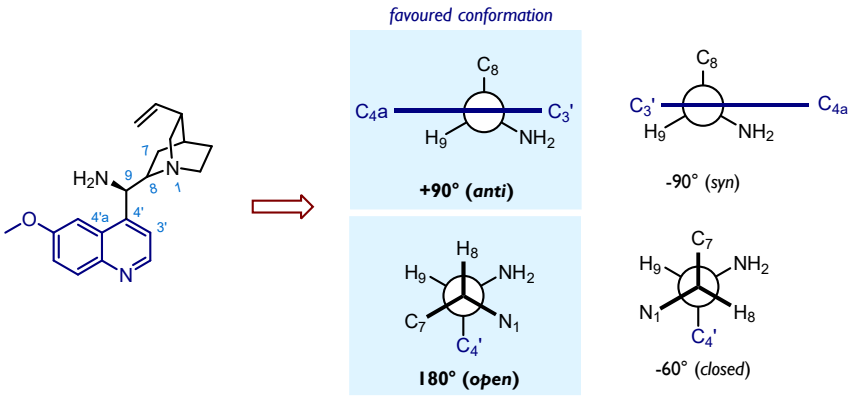
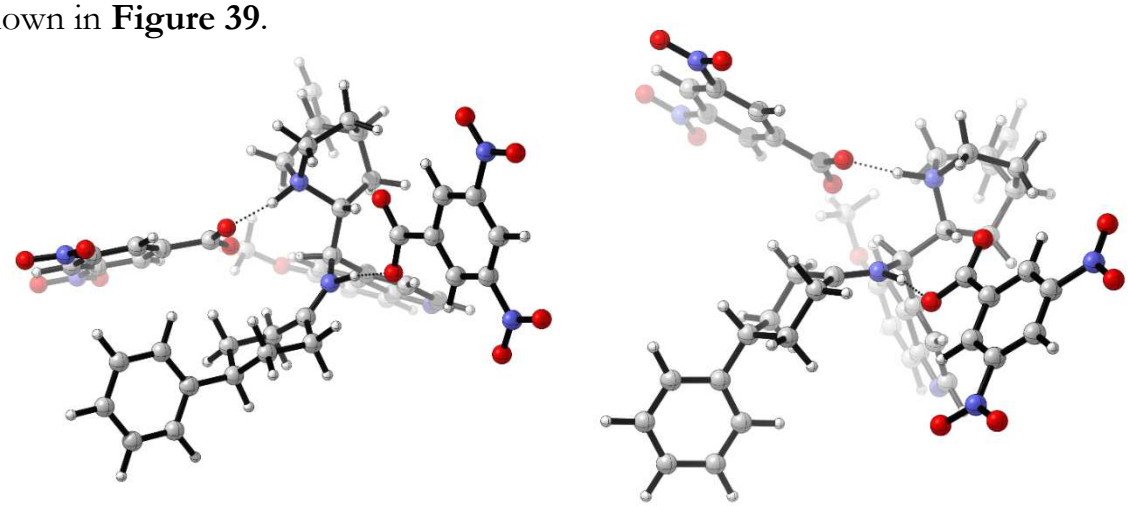


Figure 38. *Newman projection of favoured anti-open conformation*

[119] Y. Lam , K. N. Houk *J. Am. Chem. Soc.* **2015** *137*, 2116-2127

A total of six conformations were located for the iminum ion (*aR*)-**A** and five for (*aS*)-**A** which accounted for a cumulative distribution of ca. 80 : 20 in favor of (*aR*)-**A**. The lowest energy conformation located for both (*aR*)-**A** and (*aS*)-**A** are shown in **Figure 39**.



(a*R*)-**A**: qh-G: 0.0 (a*S*)-**A**: qh-G: 0.8

Figure 39. *Equilibrium geometries for (aR)-iminium ion (left) and (aS)-iminium ion (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. relative free energy; qh-G, relative Truhlar quasi-harmonic corrected free energy [kcal/mol].*

Transition states for the nucleophilic addition of oxindole to the iminium ion

We then focused our attention to the search transition states for the nucleophilic addition step of the oxindole to the lowest energy conformation of the iminium ions (*aR*)- and (*aS*)-**A**. Sixteen starting points were selected for this search, which are the result of the variation of four structural motifs:

(*i*) axial configuration (*aR*) or (*aS*) of the starting iminium ion with the phenyl group in an equatotial disposition;
(*ii*) same as (*i*) but with the phenyl in an axial disposition;
(*iii*) heterotopic *Re* or *Si* face of the starting oxindole;
(*iv*) heterotopic *re* or *si* face[120] of the iminium ion. This search resulted in the location of eight transition state structures (**TS-1a** – **TS-1h**). Selected data for these eight transition state geometries are reported in **Table 7.**

[120] E. L. Eliel, S. H. Wilen in *Stereochemistry of Organic Compounds*, Wiley 1994, p. 484

Entry	E[a] [kcal/mol]	qh-G(T)[b] [kcal/mol]	Imaginary freq. [cm^{-1}]
TS-1°	0.0	0.0	-53.8
TS-1b	1.1	2.0	-152.4
TS-1c	4.0	4.1	-79.2
TS-1d	5.0	6.3	-162.6
TS-1e	5.0	6.3	-181.5
TS-1f	7.2	7.4	-94.9
TS-1g	11.1	11.4	-95.9
TS-1h	11.6	11.3	-123.9

Table 7*. a) Relative electronic energy at the B3LYP/6-311+G(2d,p)-PCM(toluene) level of theory. b) relative free energy calculated from Gaussian results at the B3LYP/6-31G(d) level of theory using Truhlar's quasi-harmonic approximation as implemented*[117] *in the GoodVibes program*[118]

The two lower energy transition state structures **TS-1a** and **TS-1b** are shown in **Figure 36**, **TS-1a** is the attack from the *Re* face of the oxindole to the *re* face of the iminium ion (*aS*)-**A** while **TS-1b** is the attack of the *Si* face of the oxindole to the *re* face of the same iminium ion (*aS*)-**A**. All the located transition states showed that the oxindole unit binds via hydrogen bonding of its amidic moiety to a carboxylic acid unit. A feature that is kept throughout the entire reaction path.

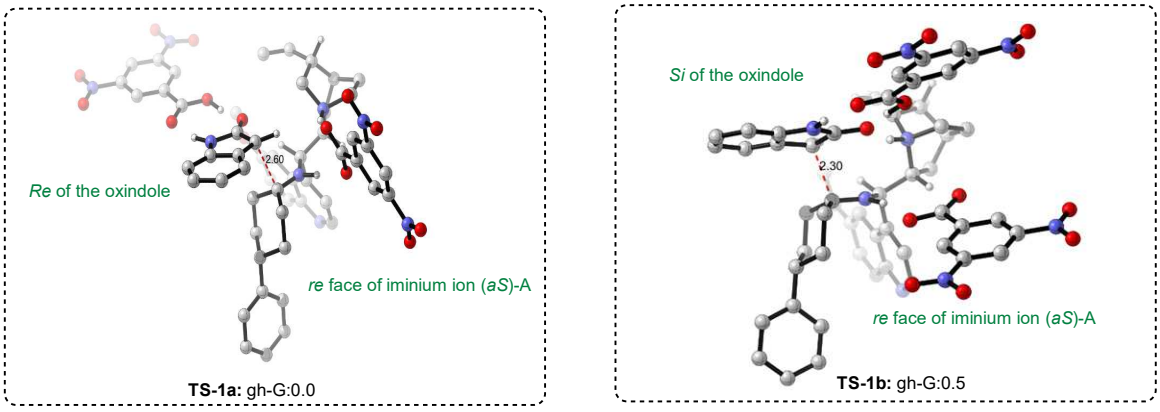
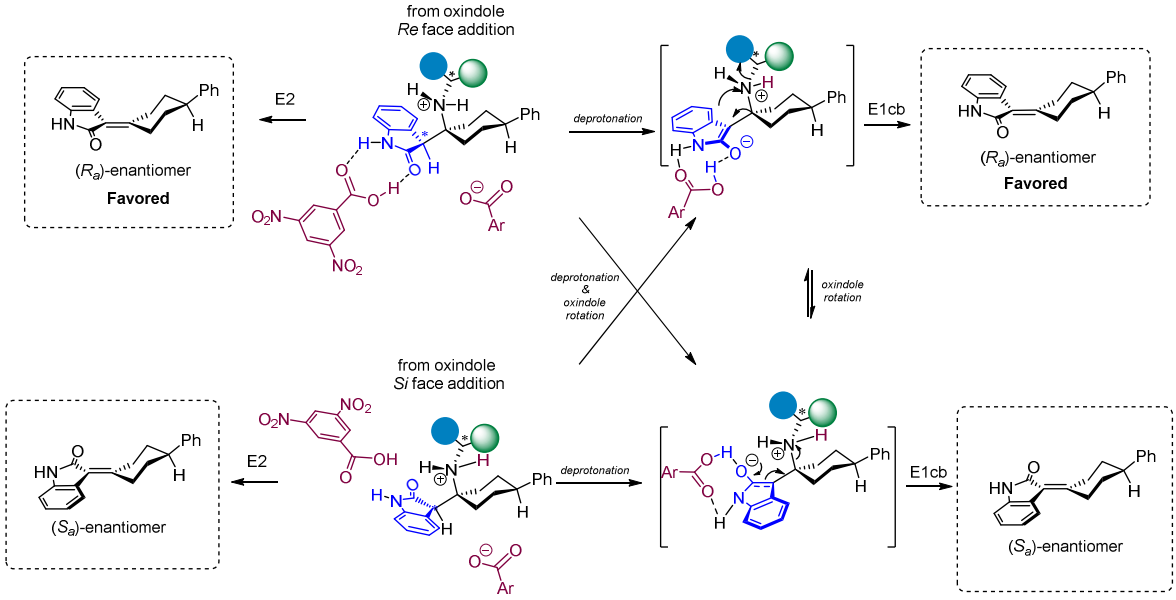


Figure 40. *Transition state geometries leading to (aR)-product (left) and to the (aS)-product (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. qh-G, relative Truhlar quasi-harmonic corrected free energy [kcal/mol].*

Transition states for the final E1cb elimination.

For the final elimination step, in which the atropisomeric double bond is formed and the product is released from the catalyst, we investigated both the E2 and the E1cb hypothesis. Both mechanisms require the preliminary protonation of the amine nitrogen to create a good leaving group.

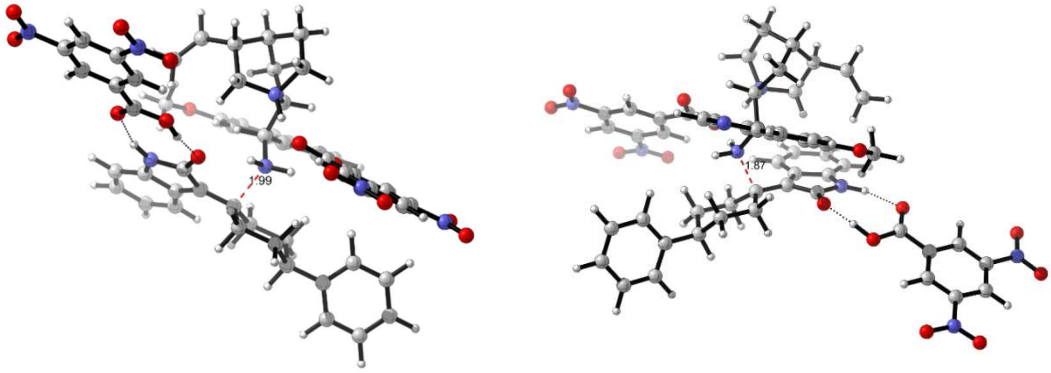


Scheme 28. *Alternative pathways for the final elimination to the products: E2 (left) and E1cb (right)*

The E2 mechanism is stereospecific since the oxindole proton on C3 must take an *anti* disposition relative to the ammonium leaving group. So, in this case, the stereo-determining step would be the initial nucleophilic attack of the oxindole to the iminium ion, which sets the chirality on oxindole C3 and, through the stereospecific E2 elimination, also the configuration of the final product.

For the E1cb to occur the only requirement is that the π system of the enolate must be vertically aligned with the σ-bond that is broken. Prior to the E1cb elimination a relative rotation of the oxindole moiety might occur and therefore both of the enolate rotamers might be formed from the same addition intermediate. E1cb elimination on each enolate rotamer leads to a different enantiomer of the product. Then under these conditions the E1cb step becomes the stereo-determining step.

If, as might well be the case, the barrier to this rotation is lower in energy compared to that of the following E1cb steps. Then the system composed of the equilibrating two rotamers and the two products is under Curtin-Hammett conditions and the ratio of the products is determined only by difference of the transition state energies of the two E1cb steps, a difference which is determined solely by the chiral catalyst. The geometries for the two E1cb transition states were located and were found to favor the transition state leaving to (a*R*)-product by 4.6 kcal/mol (**Figure 41**).



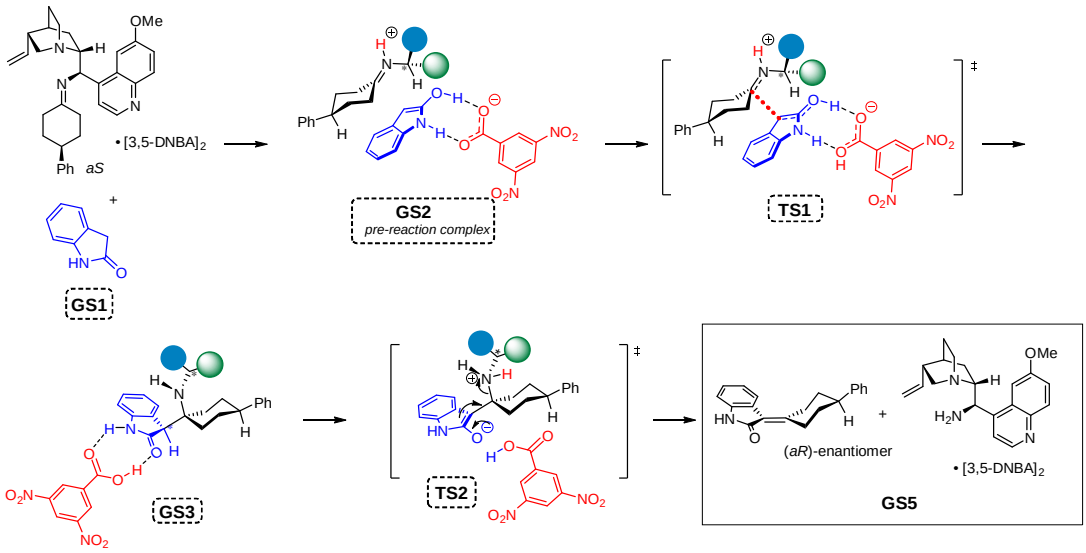
TS-2a: qh-G_{313}: 0.0

Im.Freq.: -240.53 cm^{-1}

TS-2b: qh-G: 2.0

Im.Freq.: -225.27 cm^{-1}

Figure 41. *Transition state geometries leading to the major (aR)-product (left) and to the minor (aS)-product (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. qh-G, relative Truhlar quasi-harmonic corrected free energy [kcal/mol].*



Scheme 29. *Main steps in the proposed reaction path for the asymmetric enantioselective Knoevenagel condensation (aEKC).*

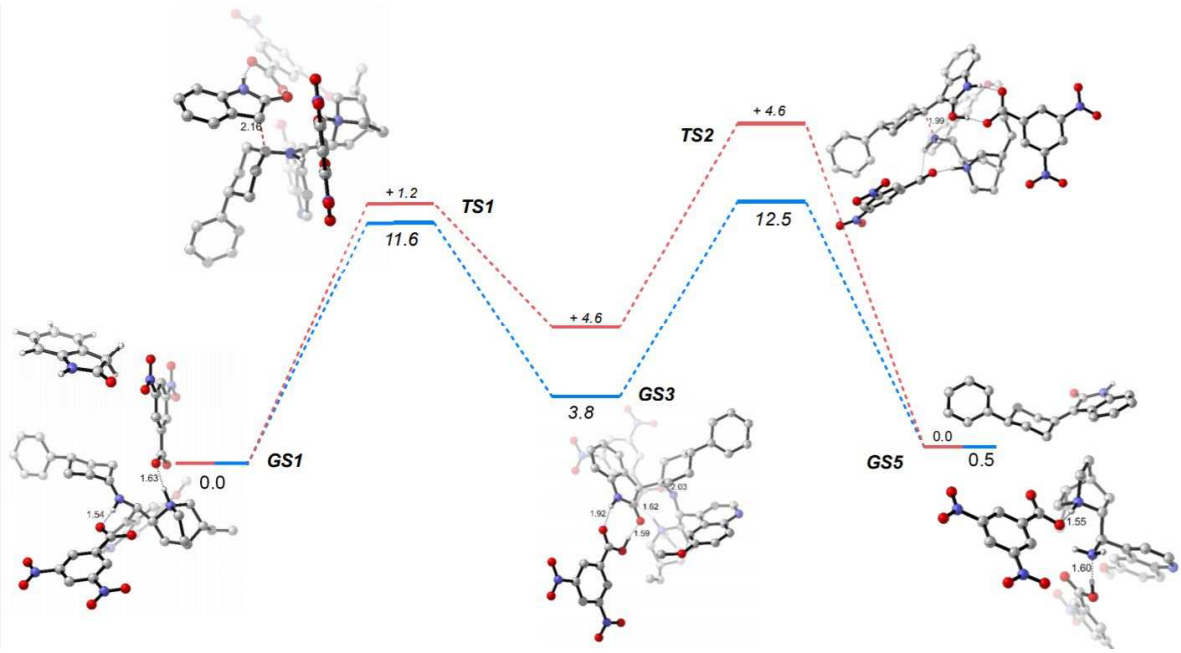


Figure 42. Corrected free energies (G) at the B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. *All values are in kcal/mol. Blue: reaction path to the major (a*R*)-product; red: reaction path to the minor (a*S*)-product. Values for the red path are expressed relative to the corresponding values of the blue path. 3D representations refer to structures of the reaction pathway to the major (a*R*)-product.*

In conclusion we report the axially enantioselective Knoevenagel condensation. The process is highly efficient, with a large scope for both ketone and oxindole, and furnished a rare example of synthesis of axially chiral 3-alkylideneoxindoles which can be readily functionalized through standard organic procedure. This reaction represents an important application of aminocatalysis for the synthesis of axially chiral oxindoles with possible biological applications. The theoretical study gave an important elucidation on the reaction mechanism, which proceeded through an E1cb elimination.

4.4 Experimental Section

All the NMR spectra were recorded on Inova 300 MHz, Gemini 400 MHz or Mercury 600 MHz Varian spectrometers for ^{1}H, 75 MHz, 100 MHz and 150 MHz for ^{13}C and 282 MHz, 376 MHz, 564 MHz for ^{19}F respectively. The chemical shifts (δ) for ^{1}H, ^{19}F and ^{13}C are given in ppm relative to internal standard TMS (0.0 ppm) or residual signals of $CHCl_3$ (7.26 ppm) or DMSO (2.48 ppm). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High Resolution Mass spectra were obtained from the CIGS facilities of the University of Modena and Reggio Emilia on a G6520AA Accurate-Mass Q-TOF LC/MS instrument. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. HPLC traces for all compounds were compared to *quasi* racemic samples prepared by mixing the two product antipodes obtained performing the reactions with catalyst **VII** and the *pseudo*-enantiomer **VIII** separately. Since the crude reaction mixture was in all cases enough clean to allow the direct hplc analysis, the spectra reported in the dedicate section are relative to the crude mixture for both work up procedures **A** and **B**. Optical rotations have not been determined due to a partial instability of the products if stored for long period and exposed to light even for few hours. All reactions were carried out without any precaution to exclude moisture and oxygen. Chiral catalyst **I** and **V** are commercially available. Catalyst **II**,[121] **III**,[1] **IV**,[1] **VI**,[122] **VII**,[123] **VIII**,[3] **IX**,[3] **X**,[124] **XI**[3] were prepared following literature procedures.

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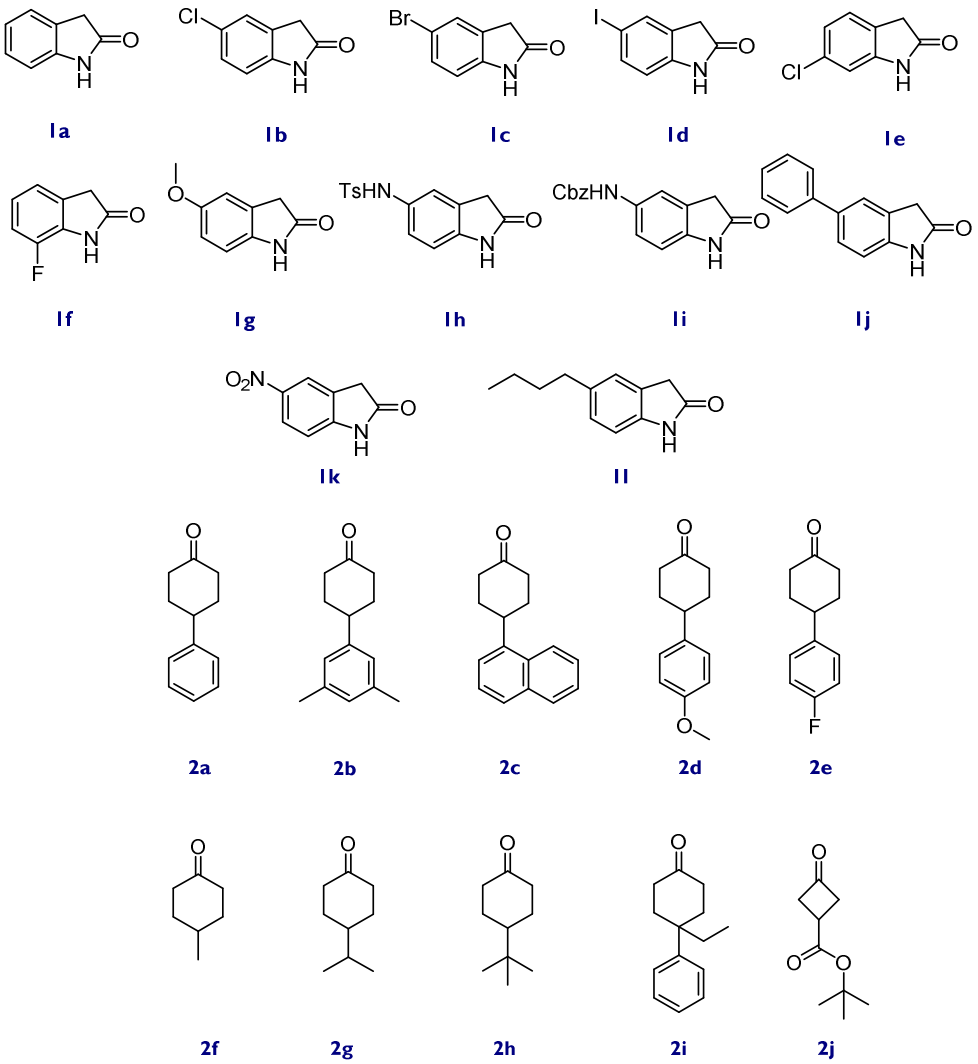
Oxindoles **1a**, **1b**, **1c**, **1e**, **1f** and **1i** were commercially available. Oxindole **1d**,[125] **1h**,[126] **1i**,[127] **1j**[128] were prepared following the literature procedure and their NMR spectra were consistent with those previously reported. Cyclohexanones **2a**, **2f**, **2g**, **2h** and **2j** were commercially available. Ketones **2b**, **2c**, **2d**, **2e** and **2i** have been prepared following the literature procedures[129] and their NMR spectra were consistent with those previously reported.

Oxindoles and Ketones use for the *a*EKC



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[127] T. P. Cho, H. G. Davis; L. Xiaoyuan US2002/52369, **2002**, A1.
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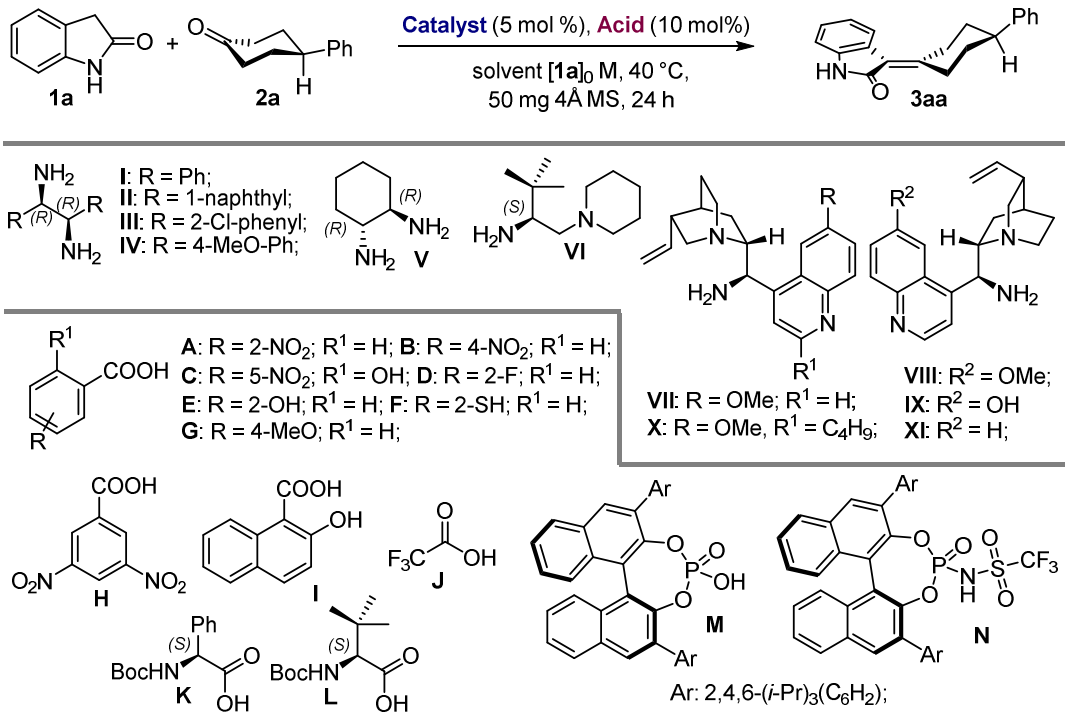
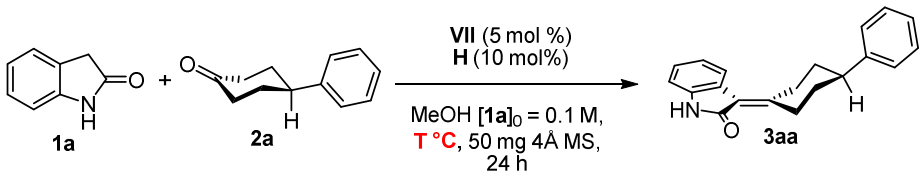
Screening of the reaction conditions



Scheme S 1. *Screening of organocatalyst*[a]

Entry	Catalyst	Acid	Solvent	Yield(%)[b]	E.r.[c]
1	**I**	**H**	MeOH	12	34:66
2	**II**	**H**	Toluene	17	18:82
3	**III**	**H**	Toluene	46	25:75
4	**IV**	**H**	Toluene	13	19.5:80.5
5	**V**	**H**	Toluene	28	37:63
6[d]	**VI**	**H**	MeOH	----	-----
7	**VII**	**H**	MeOH	55	14:86
8	**VIII**	**H**	MeOH	52	85:15
9[d]	**IX**	**H**	MeOH	----	-----
10	**X**	**H**	MeOH	49	14:86
11	**XI**	**H**	MeOH	45	87:13
12[e]	**VII**	**H**	MeOH	8	41:59

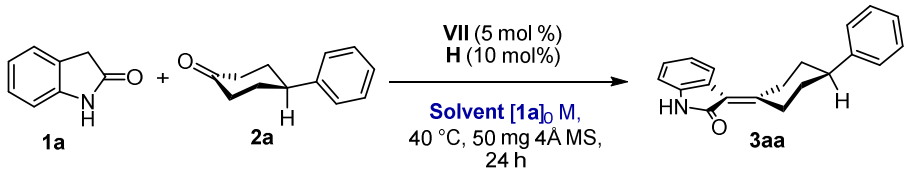
[a]Reactions were performed using 0.2 mmol of **1a** and 0.2 mmol of **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase [d]No product was obtained. [e]Reaction without Molecular Sieves.



Entry	Temperature (°C)	Yield (%)[b]	E.r.[c]
1	**25**	24	15:85
2	**40**	55	14:86

[a]Reactions were performed using 0.2 mmol of **1a** and 0.2 mmol of **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase

Table S 1. *Screening of Temperature.*

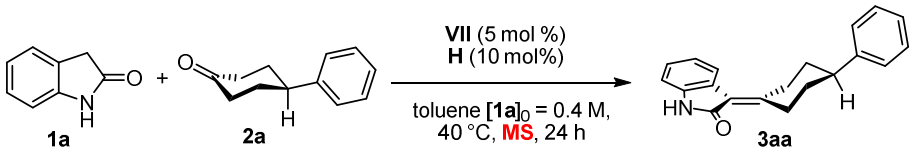


Entry	Solvent	$[1a]_0$ M	Yield (%)[b]	E.r.[c]
1	**MeOH**	**0.1**	55	14:86
2	**Toluene**	**0.1**	63	14:86
3	***i*-PrOH**	**0.1**	18	15:85
4	**Tetrahydrofuran**	**0.1**	49	26:74
5	**Chlorobenzene**	**0.1**	50	19:81
6	**Dichloromethane**	**0.1**	22	22:78
7	**Dimethylsulfoxide**	**0.1**	18	20:80

8	**Toluene**	**0.4**	90	13:87
9	**Toluene**	**0.7**	62	14:86
10	**Toluene**	**1.0**	64	13:87

[a]Reactions were performed using 0.2 mmol of **1a** and 0.2 mmol of **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase.

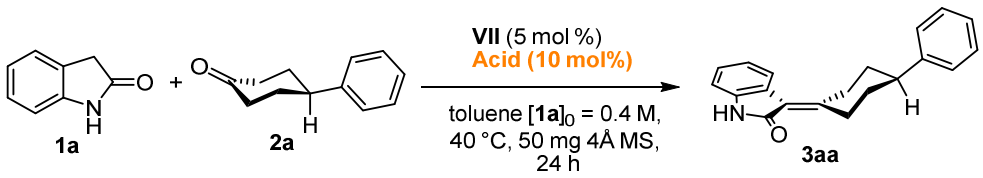
Table S 2. Screening of Solvents



Entry	Molecular Sieves (mg)	Yield (%)[b]	Ee (%)[c]
1	**4 Å (50)**	90	13:87
2[d]	**4 Å (50)**	90	14:86
3	**5 Å (50)**	n.d.	15:85
4	**3 Å (50)**	n.d.	14:86

[a]Reactions were performed using 0.2 mmol of **1a** and 0.2 mmol of **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]Powdered MS were used.

Table S 3. *Screening of molecular sieves*



Entry	Acid	Yield (%)[b]	E.r.[c]
1	**A**	70	13.5:86.5
2	**B**	45	12:88
3	**C**	62	20:80
4	**D**	n.d.	19:81

5	**E**	60	14:86
6	**F**	n.d.	19:81
7	**G**	43	15:85
8	**H**	90	13:87
9	**I**	n.d.	22:78
10 [d]	**J**	-----	----
11	**K**	12	20:80
12	**L**	28	19:81
13	**M**	<10	20:80
14	**N**	<10	20:80

[a]Reactions were performed using 0.2 mmol of **1a** and 0.2 mmol of **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase [d]No product was obtained.

Table S 4. *Screening of Acid*

Determination of the absolute configuration

Despite several efforts, crystals suitable for X-ray diffraction (XRD) analysis could not be obtained. Therefore, absolute configuration was assigned by comparison of the experimental electronic circular dichroism (ECD) with that calculated by time-dependent density functional theory (TD-DFT). Quantum-mechanical (QM) calculations of chiroptical properties has become easily accessible and a widespread tool for assigning absolute configurations of several classes of molecules.[130]

Conformational searching

The (a*R*) configuration of the product was arbitrarily chosen and a molecular mechanics (MM) conformational search was run using the Merck molecular force-

[130] For reviews and examples, see: (a) G. Pescitelli, T. Bruhn *Chirality* **2016**, *28*, 466; (b) C. Adamo, D. Jacquemin *Chem. Soc. Rev.,* **2013**, *42*, 845; (c) A. E. Nugroho, H. Morita *J Nat Med* **2013**; *68*, 1.

field (MMFF) as implemented in the SCAN application of the TINKER molecular modeling package.[131] The search was run starting from both structures with the phenyl group in the axial and in the equatorial disposition of the cyclohexylidene ring. The search yielded three different conformations within a range of 10 kcal/mol from the lowest one. These three structures were then quickly optimized using DFT at the B3LYP/3-21G level of theory eliminating duplicates. This first round of optimization yielded only two conformations corresponding to different geometries, one with the phenyl group in the equatorial disposition and the other with the phenyl group in the axial disposition.

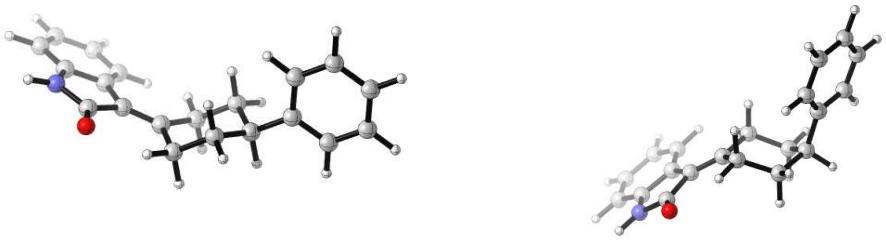
These two conformations were further optimized both at the B3LYP/6-311+G(2d,p) and at M06-2X/6-311+G(2d,p) level of theory, without noting any significant difference between the structures computed with the B3LYP and the M06-2X functionals. Therefore, the B3LYP geometries were used in the following steps.

Finally, the gas-phase geometries were reoptimized at the same B3LYP/6-311+G(2d,p) level, this time including the solvent effect (polarizable continuum model, PCM) both in *n*-hexane and in 2-propanol. Again, no significant difference was noted between the geometry obtained for *n*-hexane and that obtained for 2-propanol and therefore the geometry optimized at the PCM(*n*-hexane)/B3LYP/6-311+G(2d,p) was used for the following steps. All geometries obtained were verified to be minima by running a frequency calculation at the same level of theory that showed the absence of any imaginary frequency. The two final conformations (Fig. 1) were found to be separated by 3.42 kcal/mol.[132] Thus the minor axial conformer contributes less than 0.5% to the Boltzmann distribution

[131] TINKER 8: A Modular Software Package for Molecular Design and Simulation. Joshua A. Rackers, Marie L. Laury, Chao Lu, Zhi Wang, Louis Lagardère, Jean-Philip Piquemal, Pengyu Ren, Jay W. Ponder, **2018**.

[132] This is Gaussian "Electronic Energy (EE)". Similar values were obtained considering: zero-point energy correction (3.63 kcal/mol); thermal correction to energy (3.53 kcal/mol); thermal correction to enthalpy (3.52 kcal/mol) or thermal correction to free energy (3.89 kcal/mol)

and the following TD-DFT computations were run only for the major equatorial conformer. [133]



equatorial (E = 0.00 kcal/mol) axial (E = 3.42 kcal/mol)

Figure S 1. *Geometries of the equatorial and axial conformations of the (a*R*)-enantiomer calculated with the B3LYP/6-311+G(2d,p) model chemistry.*

Torsional twist at the C=C double bond

The computed minimum (Fig. 1) has a slight torsional twist at the C=C double bond: the dihedral angle θ (C1-C2-C3-C4) is equal to +7.4° (Fig. 2). This forces the carbonyl oxygen in a *syn* disposition with respect to the phenyl group. Particular care was devoted to find if also the *anti* conformation is populated. In fact, this conformation is diastereomeric to the *syn* (Fig. 2) and might contribute differently to the ECD spectrum. Indeed, preliminary calculations showed that the geometry of the compound X where the θ angle was arbitrarily fixed at -7.4° (*anti* conformation) has very different chiroptical properties with respect to those computed for the *syn* conformer. For example, they show very different computed optical rotations.

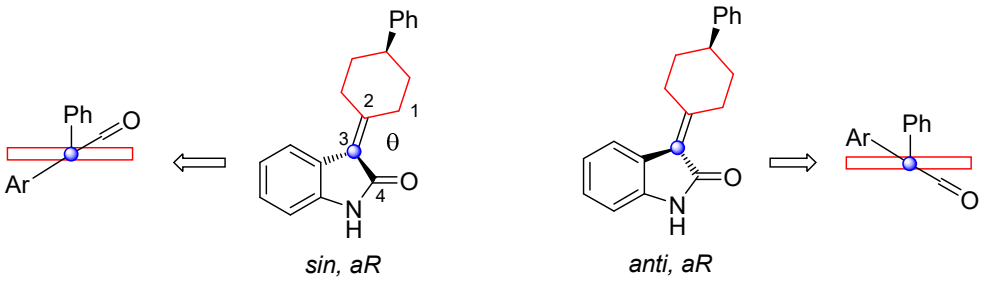


Figure S 2. *Possible diastereomeric conformations of* ***3aa*** *arising from a torsional twist of the C=C double bond; sin and anti refer to the disposition of the oxygen atom with respect of that of the phenyl group.*

[133] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)

Then, starting from the computed minimum (Fig. S1), a relaxed potential energy surface (PES) scan was performed by varying the dihedral angle θ of the C=C double bond from 21° (*syn*) to -18° (*anti*) with a 3° step. The energy profile that was obtained is showed in **Figure S3**.

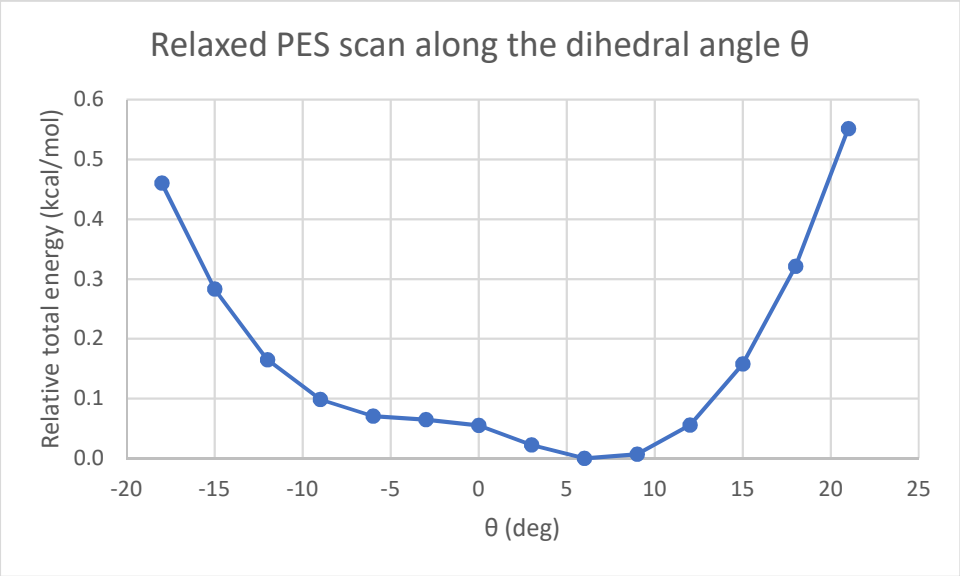


Figure S 3. *Result of the relaxed PES scan along the dihedral angle θ.*

The profile in figure S3, does not allow to safely rule out that a very shallow energy well might exist at a θ value around -6° and hence that a very low barrier *anti* conformation might be populated. This conformation would be about 0.8 kcal/mol above the computed minimum with a Boltzmann distribution of about 20% at 298 K. In the attempt to find if this *anti* conformation exists, the geometry with θ value of -12° from the previous PES scan was used as the starting geometry for a careful minimum search. Any constrain was removed and DFT calculations at the B3LYP/6-311+G(2d,p) with a very tight convergence criteria were performed. The calculation was repeated several times also using maximum step sizes of ½ and 1/3 of the default one. No *anti* conformation was found from these calculations as they always yielded the already known *sin* conformation which therefore was the only one considered in the following ECD simulations.

Absolute configuration.

Absolute configuration was assigned by comparison of experimental electronic circular dichroism (ECD) spectrum to that calculated by TD-DFT methods. The experimental ECD spectrum of a solution of compound **3aa** in a 60:40 mixture of HPLC-grade hexane/2-propanol (about $1 \cdot 10^{-4}$ M) was acquired with a cell path of 0.2 cm in the 190-400 nm region by the sum of 16 scans at 50 nm/min scan rate (Fig. S4). The spectrum shows a broad positive band at 258 nm and two negative bands between 218 and 204 nm.

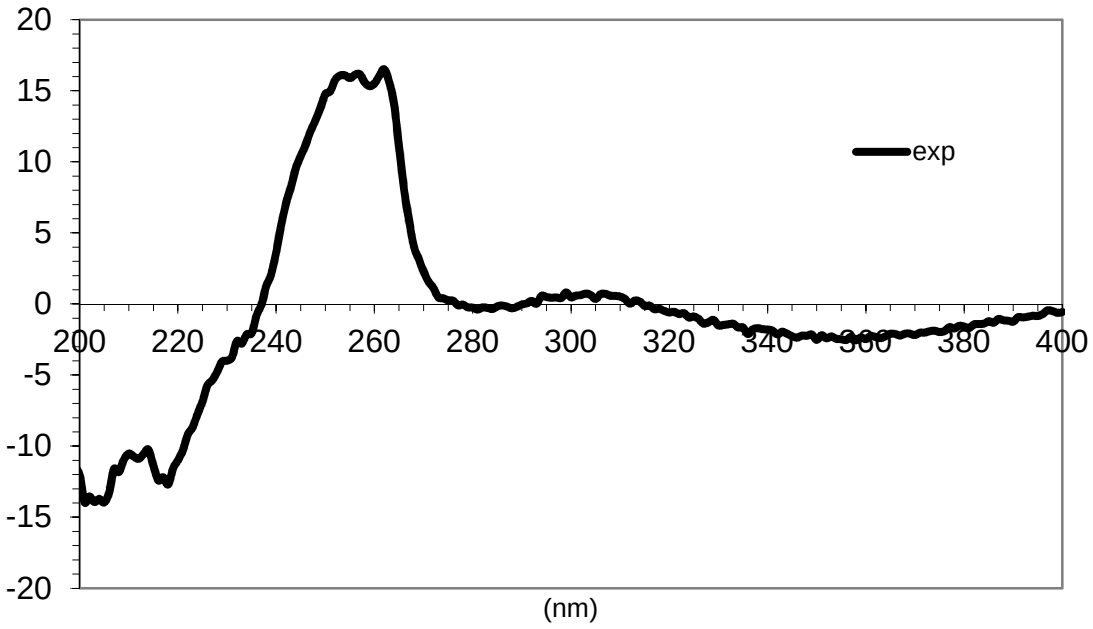


Figure S 4. *Experimental ECD spectrum of compound* ***3aa****.*

The TD-DFT simulations of the ECD spectrum of compound **3aa** were performed using the geometry of the single equatorial conformation which was found to be essentially the unique conformation populated at room temperature. For data redundancy, calculations were performed with the hybrid functionals BH&HLYP[134] and M06-2X,[135] with ωB97XD that includes empirical

[134] In Gaussian 09 the BH&HLYP functional has the form: $0.5*E_X^{HF} + 0.5*E_X^{LSDA} + 0.5*\Delta E_X^{Becke88} + E_C^{LYP}$

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

dispersion,[136] and with CAM-B3LYP[137] that includes long range correction (Fig. S5). The calculations employed the 6-311++G(2d,p) basis set, that usually yields good performances at a reasonable computational cost.[138]

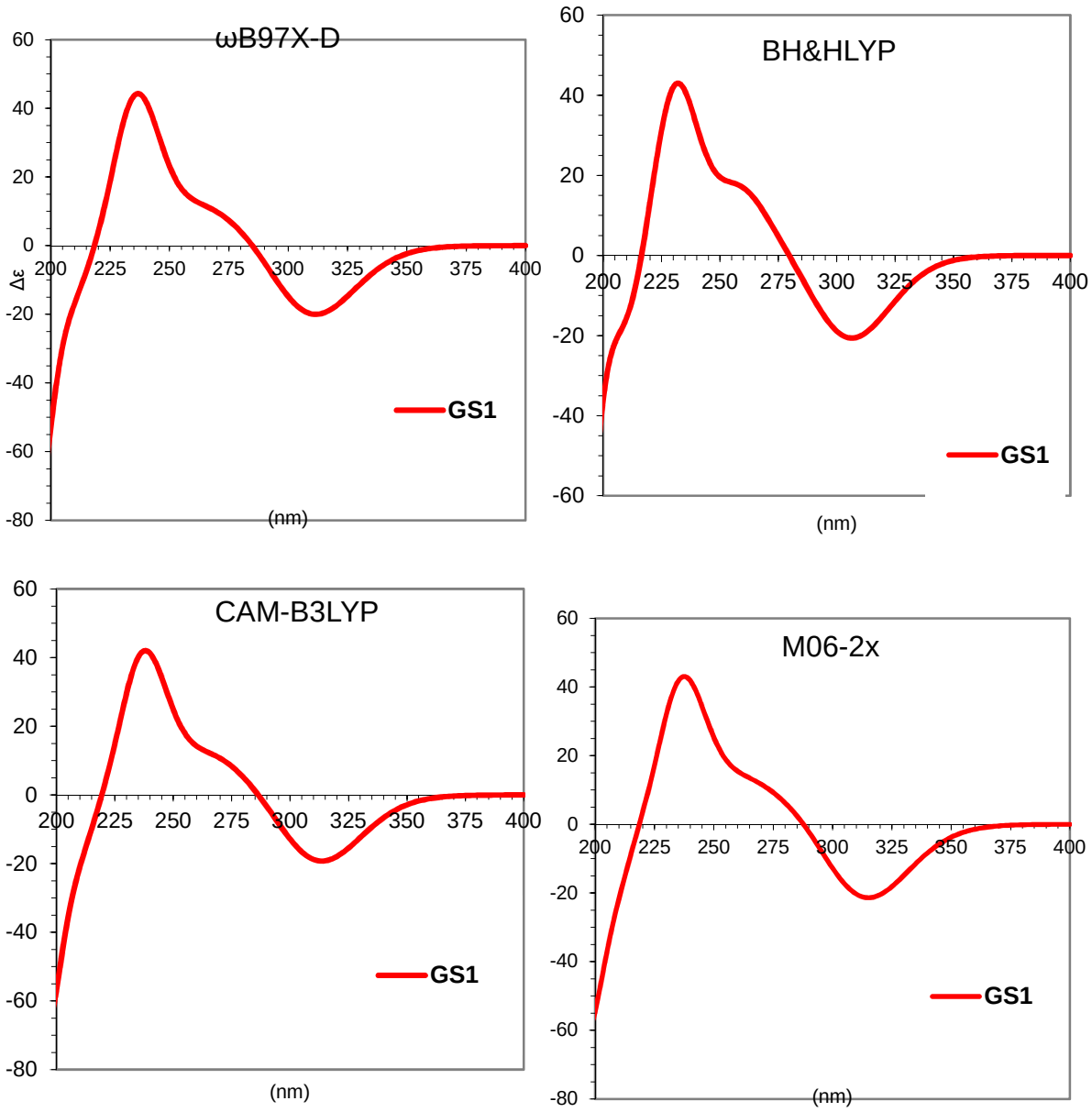


Figure S 5. *TD-DFT simulated spectra calculated for of* ***3aa*** *assuming the a*R *absolute configuration and using CAM-B3LYP, BH&HLYP, M06-2X, ωB97XD and the 6-311++G(2d,p) basis set. For each conformation, the first 50 excited states were calculated, and the spectrum was obtained using a 0.25 eV line half-width at half height.*

[136] J-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, **2008**, *10*, 6615-6620.
[137] T. Yanai, D. Tewand, and N. Handy, *Chem. Phys. Lett.* **2004**, *393*, 51-57.
[138] a) M. Meazza, M. E. Light, A. Mazzanti and R. Rios. *Chem. Sci.* **2016**, *7*, 984; b) P. Gunasekaran, S. Perumal, J. Carlos Menéndez, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2014**, *79*, 11039–11050. c) L. Caruana, M. Fochi, M. Comes Franchini, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2014**, *50*, 445-447. d) M. Ambrogi, A. Ciogli, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2013**, *78*, 3709-3719. e) L. Caruana, M. Fochi, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2013**, *49*, 880-882.

The rotational strengths were calculated in both length and velocity representation, obtaining similar results (RMS difference < 5%) that ruled out large basis set incompleteness errors (BSSE).[139] The four different functionals provide similar results (Figure S6).

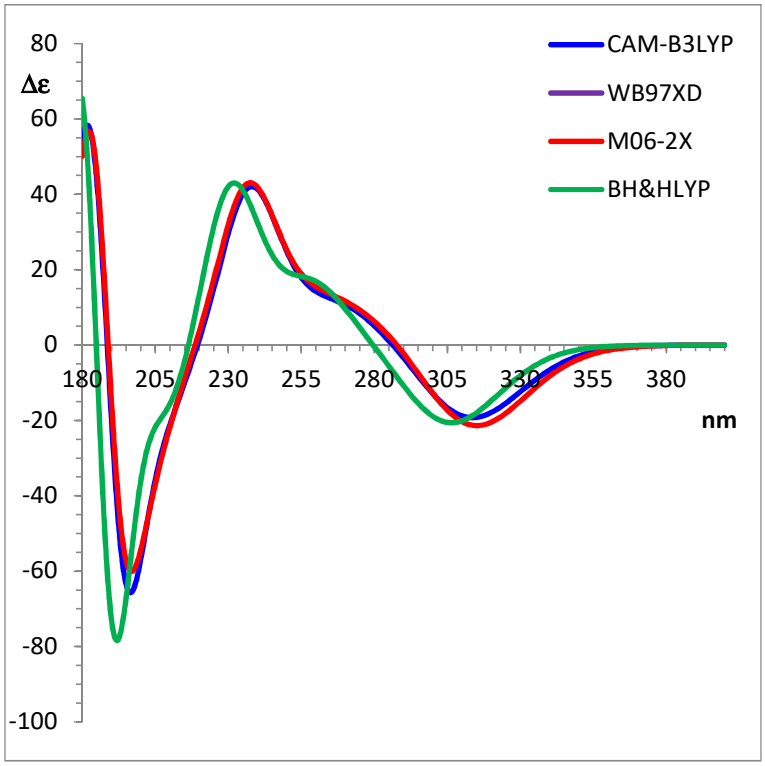


Figure S 6*. TD-DFT simulated ECD spectra calculated for the same conformation of* ***3aa*** *assuming the aR absolute configuration, and using CAM-B3LYP, BH&HLYP, M06-2X, ωB97XD and the 6-311++G(2d,p) basis set. For each conformation, the first 50 excited states were calculated, and the spectrum was obtained using a 0.25 eV line half-width at half height.*

The simulated spectra were vertically scaled to get the best match with the intensity of the experimental spectrum. Red-shifts were applied by comparison of the experimental with the simulated UV spectrum, (scaling factors: 0.40, 0.40, 0.40, 0.40; red shift: 16, 18, 16, 20 nm for CAM-B3LYP, ωB97XD, M06-2X and BH&HLYP, respectively). In all the cases the simulated spectra for the a*R* absolute configuration match very well the experimental spectrum (Figure S7).

[139]P. J. Stephens, D.M. McCann, F. J. Devlin, J.R. Cheeseman and M. J. Frisch, *J. Am. Chem. Soc.* **2004**, *126*, 7514-7521.

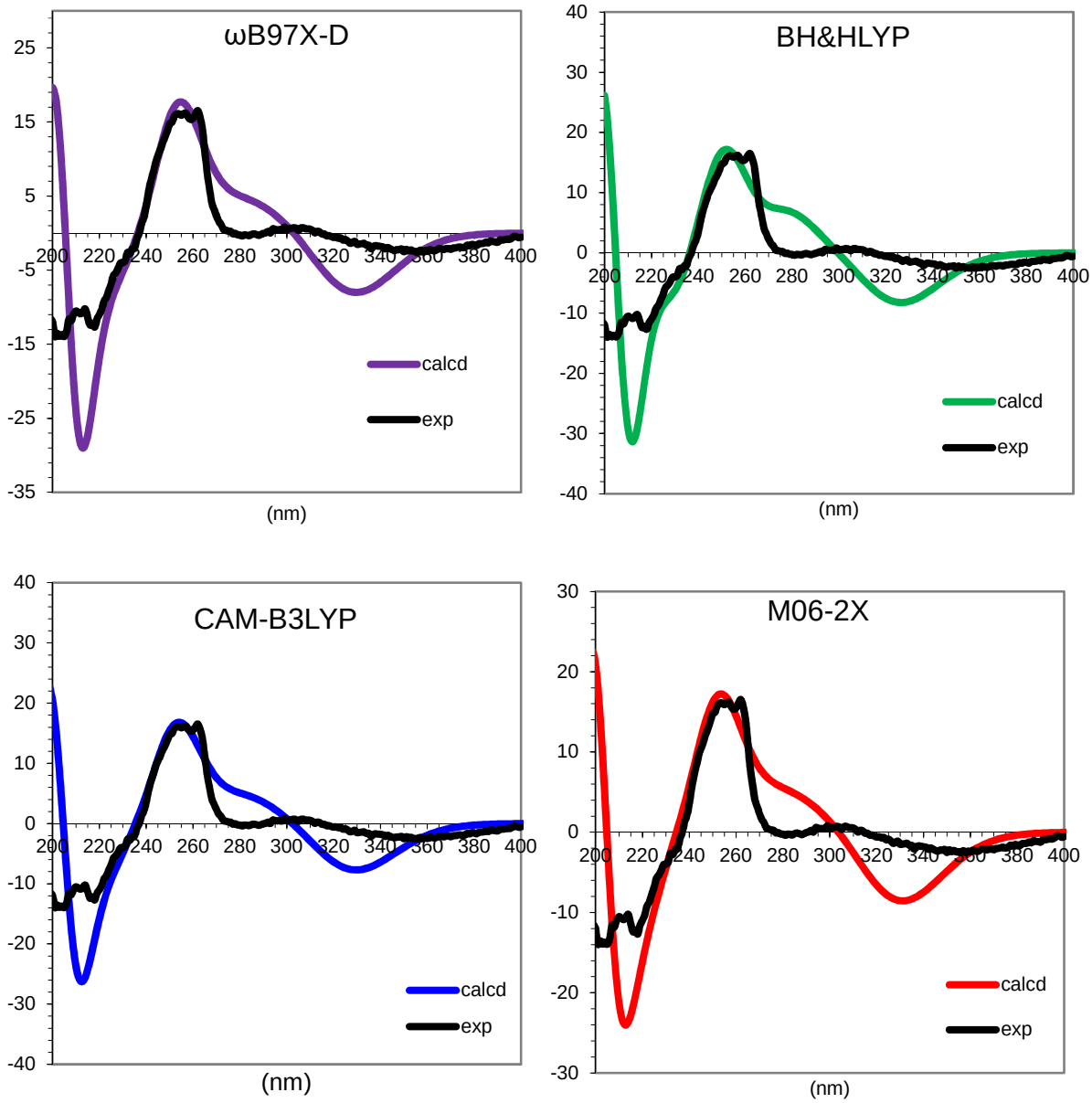
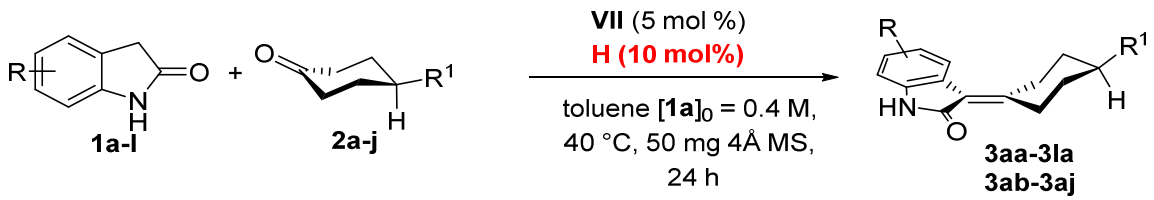


Figure S 7. *Simulations of the experimental ECD spectrum of* ***3aa****. For each quadrant, the black line corresponds to the experimental spectrum. The colored lines correspond to the simulations obtained using the populations derived from PCM-B3LYP/6-311++G(2d,p) optimization. Simulated spectra were scaled and red-shifted for the best fit to the experimental spectrum.*

General procedure for the catalytic Knoevenagel condensation of oxindoles and 4-substituted cyclohexanones



- **PLUG (Procedure A)**

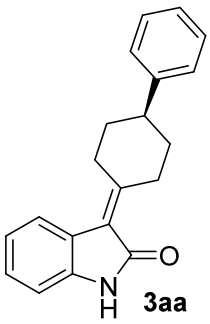
The reactions were carried out on a 0.2 mmol scale in shaded, 1.5mL vials equipped with a magnetic stirrer. The catalyst, the acid, the oxindole, the ketone and the molecular sieves were placed in the vial before addition of toluene (500 μL) and the reaction was allowed to stir at 40° C in a sand bath away from light. After 24 hours the solution was diluted in 15 ml of DCM/EtOAc 1/1 and flushed through a plug of silica (~30 mL of DCM/EtOAc 1/1) to remove the catalyst using aluminium foils on the glassware to shield the light from the crude which, was immediately injected in the HPLC to check the enantiomeric ratio. Finally, the product was purified with flash column chromatography using the proper mixture of hexane and ethylacetate as eluent.

- **FILTRATION (Procedure B)**

The reactions were carried out on a 0.2 mmol scale in shaded, 1.5mL vials equipped with a magnetic stirrer. The catalyst, the acid, the oxindole, the ketone and the molecular sieves were placed in the vial before addition of toluene (500 μL) and the reaction was allowed to stir at 40° C in a sand bath away from light. After 24 hours the solution was diluted with DCM (1 mL) and filtered through a

13 mm Syringe Filter w/0.45 μm PTFE membrane with DCM (1 mL). The resulting solution was then plugged according to Procedure A.

(*aR*)-3-(4-phenylcyclohexylidene)indolin-2-one (3aa)



3aa

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

Procedure A: 90% yield (52.2 mg) and e.r. 13:87

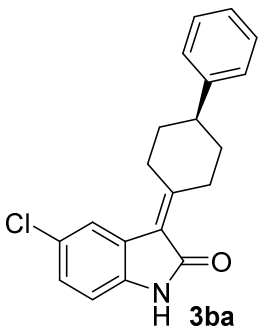
Procedure B: 56% yield (32.4 mg) and e.r. 3:97.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 18.0 min, τ_{Minor} = 14.1 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}NNaO]^+$ 312.1359, found 312.1357 $[M+Na]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 7.27 – 7.21 (m, 2H), 7.18 – 7.13 (m, 3H), 6.93 (td, *J* = 7.7, 1.0 Hz, 1H), 6.82 – 6.77 (m, 1H), 4.81 – 4.56 (m, 1H), 3.51 (d, *J* = 14.3 Hz, 1H), 2.87 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.46 (td, *J* = 13.6, 4.8 Hz, 1H), 2.29 – 2.08 (m, 3H), 1.84 – 1.62 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 162.6, 145.8, 139.4, 128.5, 127.8, 126.8, 126.3, 124.1, 123.8, 121.7, 120.6, 109.5, 43.6, 35.0, 34.7, 32.7, 29.6.

(*aR*)-5-chloro-3-(4-phenylcyclohexylidene)indolin-2-one (3ba)



3ba

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

Procedure A: 85% yield (54.9 mg) and e.r. 85:15

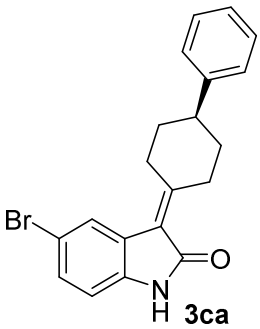
Procedure B: 41% yield (26.5 mg) and e.r. 99:1.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 8.2 min, τ_{Minor} = 11.0 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}ClNO]^+$ 324.1150, found 324.1149 $[M+H]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.27 (m, 4H), 7.22 – 7.15 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.66 (m, 1H), 2.93 (m, 1H), 2.56 (m, 1H), 2.21 – 2.00 (m, 3H), 1.67 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 162.2, 145.9, 141.9, 131.9, 128.4, 126.7, 12.1, 125.0, 122.2, 120.6, 119.6, 109.1, 42.6, 34.6, 34.3, 32.1, 28.6.

(*aR*)-5-bromo-3-(4-phenylcyclohexylidene)indolin-2-one (3ca)



3ca

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

Procedure A: 87% yield (64.0 mg) and e.r. 82:18

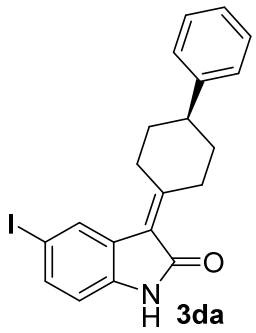
Procedure B: 51% yield (37.5 mg) and e.r. >99:1

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 8.3 min, τ_{Minor} = 11.1 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}BrNO]^+$ 368.0645, found 368.0644 $[M+H]^+$.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 7.35 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.21 – 7.16 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.74 – 4.50 (m, 1H), 3.37 (s, 1H), 2.94 (tt, *J* = 11.9, 3.6 Hz, 1H), 2.67 – 2.52 (m, 1H), 2.25 (td, *J* = 13.5, 4.8 Hz, 1H), 2.14 (d, *J* = 12.7 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.75 (qd, *J* = 12.8, 4.0 Hz, 1H), 1.62 (qd, *J* = 12.7, 3.9 Hz, 1H).

^{13}C NMR (150 MHz, DMSO-d_6) δ 168.9, 163.9, 146.3, 140.1, 130.7, 128.8, 127.2, 126.5, 126.3, 125.8, 120.2, 113.2, 111.4, 42.9, 35.0, 34.6, 32.5, 29.1.

(*aR*)-5-iodo-3-(4-phenylcyclohexylidene)indolin-2-one (3da)



3da

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

Procedure A: 81% yield (67.2 mg) and e.r. 91:9

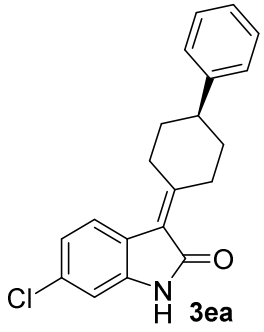
Procedure B: 62% yield (51.4 mg) and e.r. 96:4

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 8.2 min, τ_{Minor} = 11.1 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{18}INNaO]^+$ 438.0325, found 348.0326 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.88 (d, J = 1.6 Hz, 1H), 7.51 (dd, J = 8.1, 1.5 Hz, 1H), 7.33 – 7.18 (m, 5H), 6.68 (d, J = 8.1 Hz, 1H), 4.66 (d, J = 14.3 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.04 – 2.85 (m, 1H), 2.61 – 2.52 (m, 1H), 2.28 – 2.01 (m, 3H), 1.80 – 1.58 (m, 2H)

^{13}C NMR 13C NMR (151 MHz, DMSO-d_6) δ 167.6, 162.6, 145.1, 138.9, 129.5, 127.6, 125.9, 125.3, 125.1, 124.6, 118.9, 111.9, 110.2, 41.7, 33.8, 33.4, 31.3, 27.8.

(*aR*)-6-chloro-3-(4-phenylcyclohexylidene)indolin-2-one (3ea)



3ea

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

Procedure A: 47% yield (30.6 mg) and e.r. 10:90

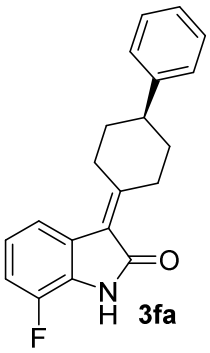
Procedure B: 45% yield (29.1 mg) and e.r. 1:99

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 23.2 min, τ_{Minor} = 19.7 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}ClNO]^+$ 324.1150, found 324.1149 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.23 (m, 4H), 7.22 – 7.14 (m, 1H), 6.97 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 4.65 (d, *J* = 14.2 Hz, 1H), 3.43 (overlapped with DMSO water, 1H), 3.04 – 2.82 (m, 1H), 2.57 (overlapped with DMSO, 1H), 2.28 – 2.00 (m, 3H), 1.81 – 1.54 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 162.2, 145.9, 141.9, 131.9, 128.4, 126.7, 12.1, 125.0, 122.2, 120.6, 119.6, 109.1, 42.6, 34.6, 34.3, 32.1, 28.6.

(*aR*)-7-fluoro-3-(4-phenylcyclohexylidene)indolin-2-one (3fa)



3fa

The reaction was carried out following the general. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 95:5).

Procedure A: 99% yield (61 mg) and e.r 86:14.

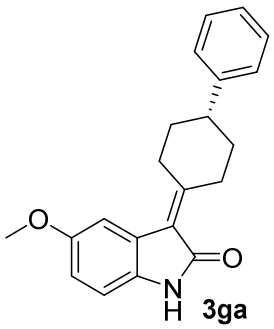
The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70:30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 11.9 min, τ_{Minor} = 16.0 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}FNO]^+$ 308.1445, found 308.1444 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.22 (m, 4H), 7.21 – 7.15 (m, 1H), 7.09 (ddd, *J* = 10.1, 8.4, 0.8 Hz, 1H), 6.94 (ddd, *J* = 8.4, 7.8, 5.3 Hz, 1H), 4.74 – 4.63 (m, 1H), 3.47 (d, *J* = 14.4 Hz, 1H), 2.95 (tt, *J* = 11.9, 3.6 Hz, 1H), 2.55 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.24 (td, *J* = 13.4, 4.7 Hz, 1H), 2.18 – 2.00 (m, 2H), 1.68 (dqd, *J* = 41.2, 12.8, 3.8 Hz, 2H).

^{19}F NMR (376 MHz, DMSO-d_6) -134.03 (dd, *J* = 10.2, 5.2 Hz).

^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 163.6, 148.0, 146.3, 145.6, 128.8, 128.1, 128.0, 127.2, 126.7, 126.7, 126.5, 122.0, 122.0, 120.6, 120.6, 120.3, 120.3, 115.0, 114.9, 43.0, 35.1, 34.8, 32.5, 29.0.

(*aS*)-5-methoxy-3-(4-phenylcyclohexylidene)indolin-2-one (3ga)



3ga

The reaction was carried out following the general procedure with pseudoenantiomeric catalyst **VIII**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

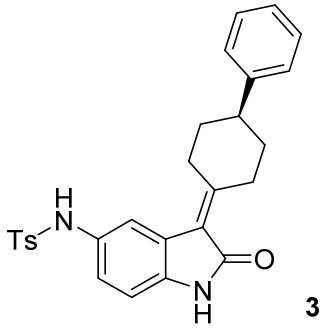
Procedure A: 70% yield (52.2 mg) and e.r. 17:83.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 17.8 min, τ_{Minor} = 15.0 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{21}NNaO_2]^+$ 342.1465, found 342.1464 $[M+Na]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.33 – 7.20 (m, 6H), 6.81 – 6.69 (m, 2H), 4.78 (d, *J* = 14.2 Hz, 1H), 3.80 (s, 3H), 3.54 (d, *J* = 14.2 Hz, 1H), 2.94 (m, 1H), 2.51 (m, 1H), 2.39 – 2.11 (m, 3H), 1.82 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17031, 162.8, 155.0, 145.8, 133.4, 133.4, 128.5, 126.8, 126.3, 125.11, 121.0, 111.9 (double), 109.4, 56.,0 43.5, 34.9, 34.7, 32.6, 29.6.

(*aR*)-4-methyl-N-(2-oxo-3-(4-phenylcyclohexylidene)indolin-5-yl)benzenesulfonamide (3ha)



3ha

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (DCM:EtOAc = 70:30).

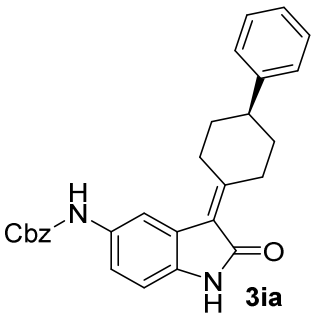
Procedure A: 47% yield (43.5 mg) and e.r. 81:19.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 30.0 min, τ_{Minor} = 37.5 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{27}H_{26}N_2NaO_3S]^+$ 481.1556, found 481.1555 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 9.73 (s, 1H), 7.59 – 7.52 (m, 2H), 7.35 – 7.12 (m, 8H), 6.87 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 4.62 (d, *J* = 13.9 Hz, 1H), 3.10 (d, *J* = 14.0 Hz, 1H), 3.01 – 2.80 (m, 1H), 2.41 (td, *J* = 13.7, 12.8, 3.9 Hz, 1H), 2.26 (s, 3H), 2.23 – 1.98 (m, 3H), 1.69 – 1.46 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 168.8, 161.5, 145.8, 142.9, 137.9, 136.5, 130.6, 129.5, 128.4, 126.9, 126.7, 126.1, 123.5, 122.7, 120.3, 118.7, 109.3, 42.6, 34.7, 34.3, 31.7, 28.5, 20.9.

Benzyl-(*aR*)-(2-oxo-3-(4-phenylcyclohexylidene)indolin-5-yl)carbamate (3ia)



3ia

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (DCM:EtOAc = 70:30).

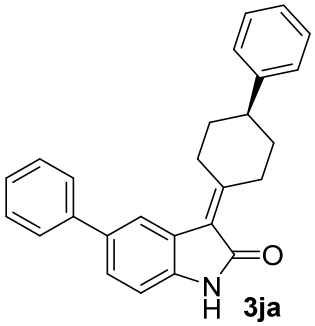
Procedure A: 14% yield (12.3 mg) and e.r. 20:80.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 22.4 min, τ_{Minor} = 17.7 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{28}H_{26}N_2NaO_3]^+$ 461.1836, found 461.1635 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.54 (s, 1H), 7.86 (s, 1H), 7.50 – 7.04 (m, 12H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.71 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 12.1 Hz, 1H), 2.95 (t, *J* = 11.9 Hz, 1H), 2.37 – 1.95 (m, 4H), 1.83 – 1.54 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 161.2, 154.0, 146.4, 137.2, 128.8, 128.8, 128.4, 127.2, 123.9, 121.2, 109.4, 66.0, 43.1, 35.2, 34.7, 32.1, 29.0.

(*aR*)-5-phenyl-3-(4-phenylcyclohexylidene)indolin-2-one (3ja)



The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

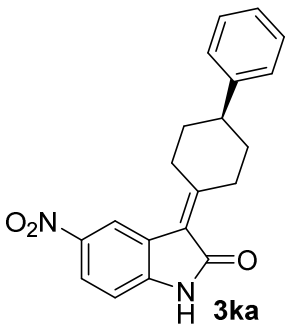
Procedure A: 70% yield (51.1 mg) and e.r. 86:14.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70:30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 8.2 min, τ_{Minor} = 11.3 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{24}NO]^+$ 366.1852, found 366.1851 $[M+H]^+$.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.51 – 7.37 (m, 3H), 7.37 – 7.24 (m, 5H), 7.18 (m, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 4.71 (m, 1H), 3.62 – 3.50 (m, 1H), 2.95 (m, 1H), 2.59 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 2.11 – 2.01 (m, 1H), 1.78 (m, 1H), 1.63 (m, 1H).

^{13}C NMR (150 MHz, DMSO-d_6) δ 169.0, 161.6, 146.0, 140.9, 140.2, 133.4, 128.9, 128.4, 126.7 (double), 126.6, 126.5, 126.1, 124.0, 122.2, 120.5, 109.6, 42.6, 34.7, 34.2, 32.1, 28.6.

(*aR*)-5-nitro-3-(4-phenylcyclohexylidene)indolin-2-one (3ka)



The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

Procedure A: 45% yield (30.1 mg) and e.r. 72.5:27.5.

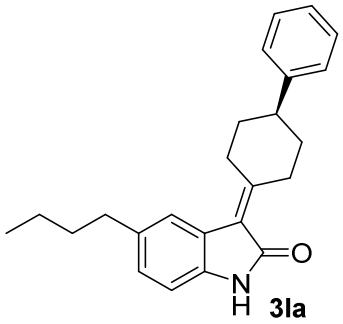
Procedure B: 35% yield (51.1 mg) and e.r. 93:7.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 50:50, flow rate 0.6 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 9.2 min, τ_{Minor} = 12.2 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{18}N_2NaO_3]^+$ 357.1210, found 357.1208 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.40 (d, *J* = 2.2 Hz, 1H), 8.16 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.33 – 7.24 (m, 4H), 7.19 (ddd, *J* = 6.9, 5.7, 2.5 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 3.51 – 3.39 (d, *J* = 14.6 Hz, 1H), 3.05 – 2.88 (m, 1H), 2.68 (m, 1H), 2.43 – 2.01 (m, 3H), 1.73 (m, 2H)

^{13}C NMR (75 MHz, DMSO-d_6) δ 168.9, 165.9, 146.4, 145.8, 141.5, 128.4, 126.8, 126.1, 124.8, 123.5, 119.0, 118.7, 109.2, 42.28, 34.4, 34.0, 32.2, 28.9.

(*aR*)-5-butyl-3-(4-phenylcyclohexylidene)indolin-2-one (3la)



3la

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20).

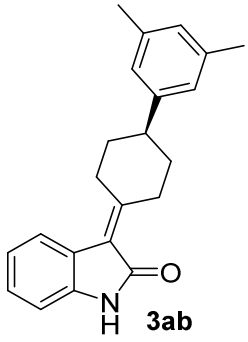
Procedure A: 68% yield (36.9 mg) and e.r. 82:18.

The ee was determined by HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 90:10, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 16.5 min, τ_{Minor} = 18.2 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{27}NNaO]^+$ 368.1985, found 368.1985 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.52 – 7.41 (m, 1H), 7.31 – 7.16 (m, 5H), 6.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.72 (d, *J* = 13.9 Hz, 1H), 3.49 (d, *J* = 14.4 Hz, 1H), 2.92 (td, *J* = 12.0, 6.0 Hz, 1H), 2.51 (p, *J* = 1.9 Hz, 3H), 2.25 – 2.00 (m, 3H), 1.80 – 1.48 (m, 4H), 1.30 (q, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 169.52, 160.67, 146.47, 138.98, 135.26, 128.82, 128.04, 127.20, 126.51, 124.21, 123.87, 121.21, 109.38, 43.16, 35.33, 35.23, 34.73, 34.29, 32.36, 28.91, 22.21, 14.26.

(*aR*)-3-(4-(3,5-dimethylphenyl)cyclohexylidene)indolin-2-one (3ab)



3ab

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

Procedure A: 94% yield (59.6 mg) and e.r. 83:17.

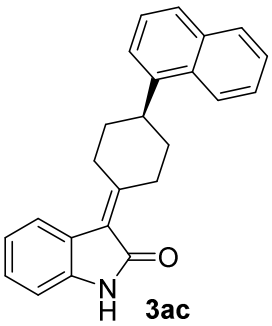
Procedure B: 59% yield (37.4 mg) and e.r. 94:6

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 50/50, flow rate 0.6 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 9.6 min, τ_{Minor} = 12.9 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{22}H_{23}NNaO]^+$ 318.1852, found 318.1853 $[M+H]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.67 – 7.61 (m, 1H), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H), 6.99 (td, *J* = 7.7, 1.1 Hz, 1H), 6.88 (d, *J* = 1.1 Hz, 1H), 6.85 (s, 3H), 4.82 – 4.71 (m, 1H), 3.56 (d, *J* = 14.2 Hz, 1H), 2.87 (ddd, *J* = 12.0, 8.2, 3.7 Hz, 1H), 2.50 (td, *J* = 13.7, 4.8 Hz, 1H), 2.29 (d, *J* = 0.7 Hz, 6H), 2.26 – 2.11 (m, 3H), 1.90 – 1.68 (m, 2H).

^{13}C NMR ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.9, 145.8, 139.4, 137.9, 127.9, 127.7, 124.7, 124.1, 123.8, 121.7, 120.6, 109.5, 43.5, 35.1, 34.8, 32.9, 29.8, 21.3.

(*aR*)-3-(4-(naphthalen-1-yl)cyclohexylidene)indolin-2-one (3ac)



The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

Procedure A: 70% yield (47.5 mg) and e.r. 15:85

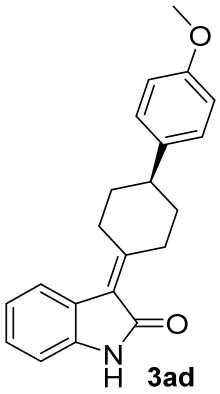
Procedure B: 46% yield (31.2 mg) and e.r. 6:94

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 28.5 min, τ_{Minor} = 20.1 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{21}NNaO]^+$ 362.1515, found 362.1512 $[M+Na]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.23 – 8.15 (m, 1H), 7.90 – 7.85 (m, 1H), 7.76 – 7.62 (m, 3H), 7.60 – 7.34 (m, 5H), 7.19 (td, *J* = 7.7, 1.1 Hz, 1H), 7.01 (td, *J* = 7.7, 1.1 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.92 – 4.79 (m, 1H), 3.77 (tt, *J* = 11.8, 3.5 Hz, 1H), 3.64 (dd, *J* = 15.3, 4.0 Hz, 1H), 2.68 (td, *J* = 13.7, 4.7 Hz, 1H), 2.54 – 2.29 (m, 3H), 2.03 – 1.83 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.3, 141.7, 139.5, 134.0, 131.3, 129.1, 127.8, 126.8, 125.9, 125.7, 125.4, 124.1, 123.9, 123.0, 122.3, 121.7, 120.9, 109.5, 38.3, 34.4, 34.2, 33.0, 29.9.

(*aR*)-3-(4-(4-methoxyphenyl)cyclohexylidene)indolin-2-one (3ad)



The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

Procedure A: 90% yield (57.5 mg) and e.r. 80:20

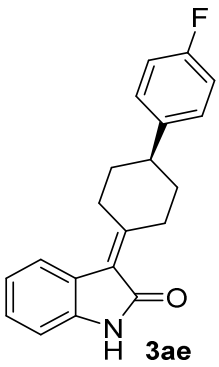
Procedure B: 48% yield (30.7 mg) and e.r. 57:43

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 23.3 min, τ_{Minor} = 36.9 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{21}NNaO_2]^+$ 342.1465, found 342.1464 $[M+Na]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.67 – 7.62 (m, 1H), 7.23 – 7.11 (m, 3H), 7.00 (td, *J* = 7.7, 1.1 Hz, 1H), 6.89 – 6.82 (m, 3H), 4.82 – 4.70 (m, 1H), 3.79 (s, 3H), 3.61 – 3.50 (m, 1H), 2.90 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.51 (td, *J* = 13.7, 4.8 Hz, 1H), 2.23 (dddd, *J* = 21.6, 14.3, 12.2, 5.9 Hz, 3H), 1.87 – 1.69 (m, 2H).

^{13}C NMR (75 MHz,$CDCl_3$) δ 169.7, 162.6, 158.0, 139.3, 138.0, 127.7, 127.6, 124.1, 123.8, 121.7, 120.5, 113.9, 109.4, 55.3, 42.7, 35.2, 35.0, 32.8, 31.6, 29.7, 22.6, 14.1.

(*aR*)-3-(4-(4-fluorophenyl)cyclohexylidene)indolin-2-one (3ae)



3ae

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

Procedure A: 91% yield (55.9 mg) and e.r. 18:82

Procedure B: 62% yield (37.5 mg) and e.r. 5:95

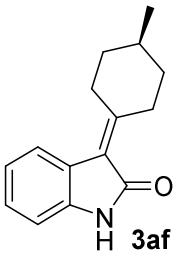
The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70:30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 31.4 min, τ_{Minor} = 22.3 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{18}FNNaO]^+$ 330.1265, found 330.1263 $[M+Na]^+$.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.41 (s, 1H), 7.63 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.24 – 7.11 (m, 3H), 7.05 – 6.94 (m, 3H), 6.92 – 6.83 (m, 1H), 4.88 – 4.70 (m, 1H), 3.64 – 3.51 (m, 1H), 2.93 (m, 1H), 2.51 (m, 1H), 2.34 – 2.11 (m, 2H), 1.88 – 1.62 (m, 3H).

^{19}F NMR (286 MHz, $CDCl_3$) δ -117.1.

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 163.0, 162.0, 159.8, 141.5, 141.4, 139.5, 128.2, 128.0, 127.8, 124.0, 123.8, 121.7, 120.8, 115.3, 115.0, 109.6, 42.8, 35.1, 34.9, 32.6, 29.6.

(*aR*)-3-(4-methylcyclohexylidene)indolin-2-one (3af)



3af

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

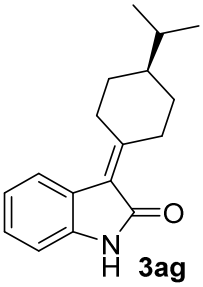
Procedure A: 91% yield (41.3 mg) and e.r. 75:25

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 14.4 min, τ_{Minor} = 18.3 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{15}H_{18}NO]^+$ 228.1383, found 228.1381 $[M+H]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.65 – 7.58 (m, 1H), 7.17 (td, *J* = 7.7, 1.1 Hz, 1H), 6.98 (td, *J* = 7.7, 1.2 Hz, 1H), 6.91 – 6.82 (m, 1H), 4.49 (dt, *J* = 14.2, 2.0 Hz, 1H), 3.46 – 3.33 (m, 1H), 2.47 – 2.18 (m, 2H), 2.00 (ddtd, *J* = 18.4, 10.9, 4.0, 2.3 Hz, 2H), 1.28 (dtdd, *J* = 23.6, 12.7, 10.9, 4.0 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.20, 164.21, 139.41, 127.55, 124.19, 123.73, 121.55, 120.27, 109.48, 36.00, 35.63, 32.36, 31.72, 29.28, 21.57.

(*aR*)-3-(4-isopropylcyclohexylidene)indolin-2-one (3ag)



3ag

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

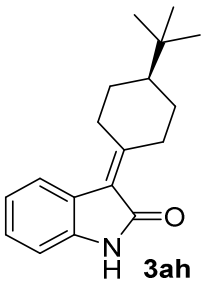
Procedure A: 88% yield (39.6 mg) and e.r. 20:80

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 30.4 min, τ_{Minor} = 26.5 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{17}H_{22}NO]^+$ 256.1696, found 256.1696 $[M+H]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.16 (td, *J* = 7.7, 1.1 Hz, 1H), 6.98 (td, *J* = 7.7, 1.2 Hz, 1H), 6.86 (ddd, *J* = 7.7, 1.2, 0.5 Hz, 1H), 4.57 – 4.41 (m, 1H), 3.47 – 3.38 (m, 1H), 2.30 (dddd, *J* = 41.2, 14.1, 12.1, 4.9 Hz, 2H), 2.09 – 1.94 (m, 2H), 1.63 – 1.18 (m, 4H), 0.90 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.13, 164.67, 164.59, 139.39, 127.51, 124.23, 121.54, 120.07, 109.44, 42.99, 32.60, 32.31, 30.74, 30.39, 29.38, 19.90.

(*aR*)-3-(4-(*tert*-butyl)cyclohexylidene)indolin-2-one (3ah)



3ah

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

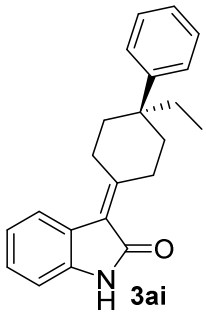
Procedure A: 88% yield (47.4 mg) and e.r. 14:86

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70/30, flow rate 0.8 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 19.5 min, τ_{Minor} = 14.5 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{18}H_{24}NO]^+$ 270.1852, found 270.1853 $[M+Na]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.60 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.17 (td, *J* = 7.7, 1.1 Hz, 1H), 6.98 (td, *J* = 7.7, 1.1 Hz, 1H), 6.90 – 6.83 (m, 1H), 4.49 (dd, *J* = 14.5, 2.0 Hz, 1H), 3.44 (dd, *J* = 14.4, 2.3 Hz, 1H), 2.44 – 2.19 (m, 2H), 2.13 – 1.97 (m, 2H), 1.46 – 1.24 (m, 3H), 0.89 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.16, 164.53, 139.40, 127.50, 124.23, 123.70, 121.53, 120.02, 109.45, 46.93, 32.92, 32.62, 29.55, 28.30, 27.96, 27.46.

(*aR*)-3-(4-ethyl-4-phenylcyclohexylidene)indolin-2-one (3ai)



3ai

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 70:30).

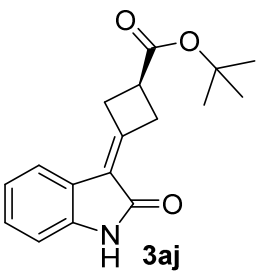
Procedure A: 80% yield (50.8 mg) and e.r. 68:32

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 50:50, flow rate 0.6 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 49.9 min, τ_{Minor} = 62.2 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{22}H_{23}NNaO]^+$ 340.1672, found 340.1671 $[M+Na]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.33 (m, 4H), 7.27–7.06 (m, 2H), 6.91 (td, *J* = 7.7, 1.2 Hz, 1H), 6.82 – 6.76 (m, 1H), 3.88 (dt, *J* = 15.5, 5.1 Hz, 1H), 3.08 (dt, *J* = 15.4, 5.0 Hz, 1H), 2.50 (p, *J* = 1.8 Hz, 4H), 2.43 – 2.22 (m, 1H), 1.76 (dddd, *J* = 28.0, 14.2, 10.4, 4.0 Hz, 2H), 1.59 (q, *J* = 7.3 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 169.25, 161.79, 145.46, 140.91, 128.74, 128.12, 127.13, 126.08, 124.10, 123.77, 121.34, 120.81, 109.57, 35.85, 35.77, 35.51, 28.86, 25.38, 8.62.

(*aR*)-*tert*-butyl 3-(2-oxoindolin-3-ylidene)cyclobutane-1-carboxylate (3aj)



The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 60:40).

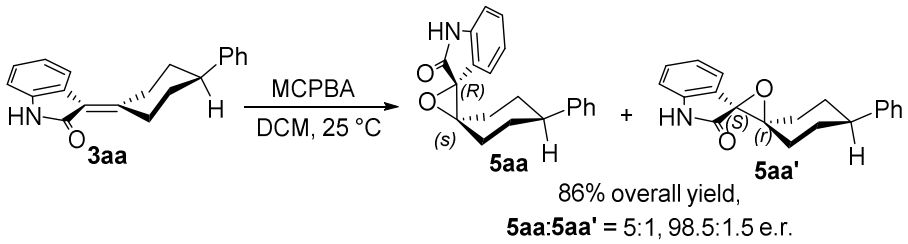
Procedure A: 21% yield (14.3 mg) and e.r. 56:44

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 50:50, flow rate 0.6 mL/min, 25 °C, λ = 254 nm: τ_{Major} = 9.1 min, τ_{Minor} = 17.6 min. HRMS-ESI-ORBITRAP (+): calculated for $[C_{17}H_{19}NNaO_3]^+$ 308.1257, found 308.1256 $[M+Na]^+$.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.18 (dd, J_1 = J_2 = 7.6 Hz, 2H), 7.05 – 6.96 (m, 1H), 6.85 (ddd, J = 7.4, 0.9 Hz, 1H), 3.76 – 3.64 (m, 1H), 3.60 – 3.47 (m, 2H), 3.47 – 3.36 (m, 2H), 1.49 (s, J = 0.5 Hz, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 168.4, 156.4, 139.7, 128.1, 123.2, 122.1, 121.9, 121.4, 109.6, 81.0, 37.6, 36.8, 35.9, 28.1.

(1*s*,3'*R*)-4-phenyldispiro[cyclohexane-1,2'-oxirane-3',3''-indolin]-2''-one (5aa) and (1*r*,3'*S*)-4-phenyldispiro[cyclohexane-1,2'-oxirane-3',3''-indolin]-2''-one (5aa')



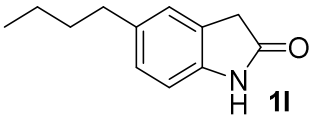
In an ordinary vial containing product **3aa** (0.1 mmol, 1 equiv, 28.9 mg) and *m*-CPBA (0.11 mmol, 1.1 equiv, 24.7 mg of commercially available 77% *m*-CPBA) was added DCM (5.8 mL, 0.017 M) and the solution was left in an ice bath under magnetic stirring. After 2 hours, the crude was diluted with more DCM and quenched with a $NaHCO_3$ aqueous solution. After 2 extractions and removal of

water with anhydrous $MgSO_4$, flash column chromatography (hexane:EtOAc 70:30) afforded 27 mg of title compound (70% isolated yield) as a 5:1 mixture of diastereoisomers. HPLC analysis on a Daicel Chiralpak AD-H column (hexane/*i*-PrOH 40/60, flow rate 0.3 mL/min, 25° C, λ = 254 nm) showed a 98.5:1.5 e.r. on both diastereoisomers. HRMS-ESI-ORBITRAP (+): calculated for $[C_{20}H_{19}NNaO_2]^+$ 328.1308, found 328.1308 $[M+Na]^+$.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.78 (bs, 1H), 7.37 – 7.18 (m, 7H), 7.04 (ddd, *J* = 7.6, 1.0 Hz, 1H), 6.97 (d, *J* = 8.0, 1H), 2.89 (m, 1H), 2.71 (m, 1H), 2.24 – 1.67 (m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4 (double), 146.1, 145.4, 142.1, 142.0, 129.7 (double), 128.5, 1283, 126.8, 126.6, 126.3, 126.2, 124.9, 124.5, 123.4, 123.3, 122.3, 122.1, 110.7, 110.6, 71.8, 70.5, 65.6, 64.7, 43.7, 43.0, 33.2, 32.9, 32.1, 31.9, 30.4, 30.2, 29.7, 27.5.

5-butyloxindole (1l)



1l

The reaction was carried out following the literature procedure.[140]

5-butylisatin (15 mmol, 1 equiv) was placed in a 100 mL round flask and suspended in MeOH (37.5 mL, 0.4 M) before adding hydrazine (30.15 mmol, 2.6 ml of 55% solution in water, 2 equiv). The solution was left refluxing (2 to 3 hours) under magnetic stirring until the formation of a precipitate is observed, then cooled to room temperature. The precipitate was filtered on a gooch funnel, washed with water, cold MeOH and cold Et_2O to afford the pure hydrazone that was added to a freshly prepared solution of EtONa in EtOH (3.7 equiv of metallic

[140] (a) S. Crotti, G. Belletti, N. Di Iorio, E. Marotta, A. Mazzanti, P. Righi, G. Bencivenni *RSC Adv.*, **2018**, *8*, 33451. (b) S. Crotti, N. Di Iorio, A. Mazzanti, P. Righi, G. Bencivenni *J. Org. Chem.* **2018**, *83*, 12440.

Na dissolved in EtOH so that the hydrazone is 0.4M). This new solution was once again heated to reflux until the reagent disappeared (TLC monitoring), then it was cooled and quenched with 10% HCl. The crude was now extracted with DCM, made anhydrous over $MgSO_4$ and purified by either flash column chromatography or crystallization to obtain the pure oxindole. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 75:25) and the title compound was obtained in 63% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 7.13 – 6.94 (m, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.51 (s, 2H), 2.75 – 2.42 (m, 2H), 1.69 – 1.45 (m, 2H), 1.45 – 1.20 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 140.3, 137.0, 127.6, 125.3, 124.6, 109.5, 36.4, 35.3, 34.0, 22.2, 13.9.

Computational details

All of the quantum-chemical computations were performed using the Gaussian 16 package.[141] Preliminary computational studies on the iminium ions and the transition states for the addition of oxindole to the iminium ion were performed using at the B3LYP/6-31G(d) level of theory. The B3LYP/6-31G(d) method has been widely used to model organocatalytic reactions.[142] Recently, issues associated to the B3LYP in accounting for dispersion have been pointed out. However, Goodman compared various density functionals and found that for transition-structure geometry optimizations, B3LYP is slightly less accurate than newer, dispersion-inclusive functionals, which are more computationally demanding.[143]

After the preliminary studies, the computational studies examining the main points of the reaction paths leading to major (a*S*)- and minor (a*R*)-product were studied at 313 K using the metahybrid DFT functional M06-2X2[144,145] together with the universal continuum solvation model (SMD). The thermal corrections evaluated on the optimized geometries at 313 K from the unscaled vibrational frequencies[146] with the M06-2X/6-31G(d)/SMD(toluene) level of theory were then added to the M06-2X/6-311++G(2d,p)/SMD(toluene) electronic energies to obtain the corrected free energies.[147]

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141 Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

142 (a) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042−5137. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-.Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569.

143 Simón, L.; Goodman, J. M. *Org. Biomol. Chem.* **2011**, *9*, 689−700.

144 Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

145 All M06-2X computations were performed using Gaussian 09 default parameters ("G09Defaults" keyword)

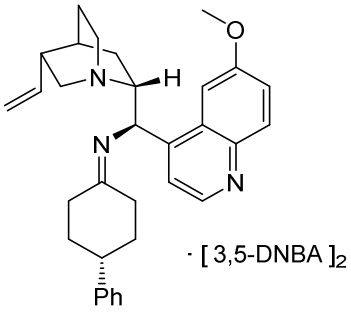
146 I. M. Alecu, J. Zheng, Y. Zhao, and D. G. Truhlar *J. Chem. Theory Comput.* **2010**, *6,* 2872-2887.

147 Y. Lam , K. N. Houk J. Am. Chem. Soc. 2015 137, 2116-2127 29 A. Moran, A. Hamilton, C. Bo, P. Melchiorre J. Am. Chem. Soc. 2013 135, 9091-9098

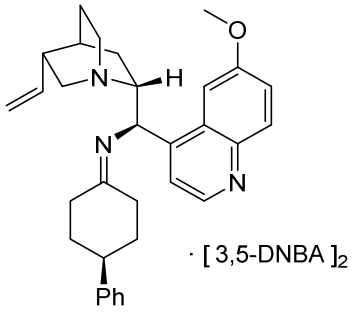
The free energy corrections were calculated using Truhlar's quasi-harmonic approximation[148] as implemented in the GoodVibes program.[149]

Iminium Ion

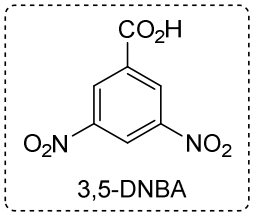
The reaction of the 9-*epi*-9-amminoquinidine (9-*epi*-NH_2-QDA) catalyst with 4-phenylcyclohexanone, in the presence of 3,5-dinitrobenzoic acid, affords the two diastereoisomeric iminium ions (*aR*)- and (*aS*)-**A**.



(*aR*)-**A**



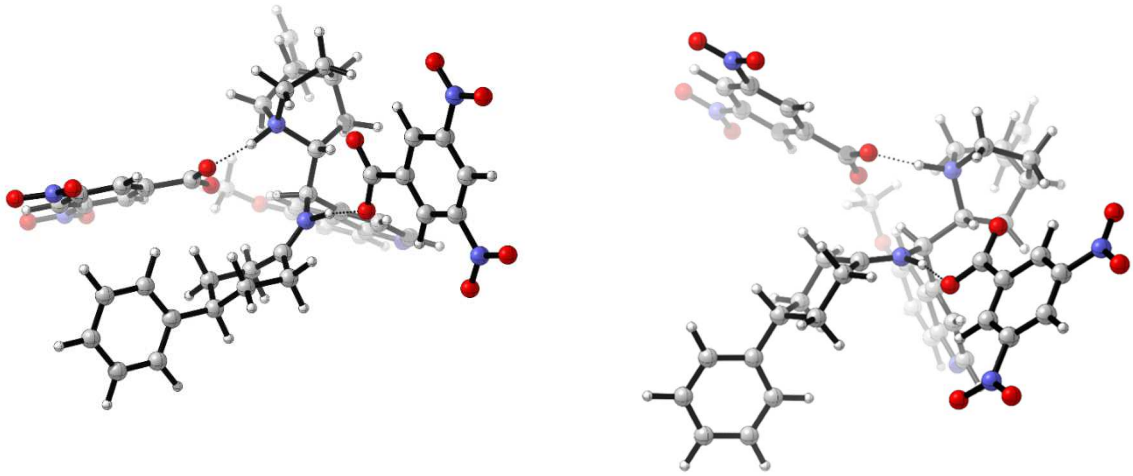
(*aS*)-**A**



Previous extensive conformational analysis on cinchona alkaloids and their iminium derivatives showed that the cinchona alkaloids prefer to adopt the *anti-open* conformation which was the only one considered in the following calculations. A relaxed potential energy surface (PES) scan at the semiempirical PM6 level was performed on both iminium ions (*aR*)- and (*aS*)-**A** by the systematic variation of the C9-N bond dihedral angle. All the structures within 5 kcal/mol from the one with the lowest energy were reoptimized at the B3LYP/6-31G(d) level. A total of six conformations were located for the iminium ion (*aR*)-**A** and five for (*aS*)-**A** which accounted for a cumulative distribution of ca. 80 : 20 in favor of (*aR*)-**A**. The lowest energy conformation located for both (*aR*)-**A** and (*aS*)-**A** are shown in Fig. S7

[148] (a) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556−14562. (b) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813−2818.

[149] GoodVibes v. 2.02; DOI: 10.5281/zenodo.595246.



(a*R*)-**A**: G°: 0.0 (a*S*)-**A**: G°: 0.8

Figure S 8. *Equilibrium geometries for (aR)-iminium ion (left) and (aS)-iminium ion (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. The reported energies (in Kcal/mol) are the Free energies, corrected using the quasi-harmonic approach y [kcal/mol].*

Transition states for the nucleophilic addition of oxindole to the iminium ion[150]

We then focused our attention to the search transition states for the nucleophilic addition step of the oxindole to the lowest energy conformation of the iminium ions (*aR*)- and (*aS*)-**A**. Sixteen starting points were selected for this search, which are the result of the variation of four structural motifs: (i) axial configuration (*aR*) or (*aS*) of the starting iminium ion with the phenyl group in an equatorial disposition; (ii) same as (i) but with the phenyl in an axial disposition; (iii) heterotopic *Re* or *Si* face of the starting oxindole; (iv) heterotopic *re* or *si* face[151] of the iminium ion. This search resulted in the location of eight transition state structures (**TS-1a** – **TS-1h**). Selected data for these eight transition state geometries are reported in Table S6.

[150] All 3D representations were obtained using CYLview visualization software: CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)

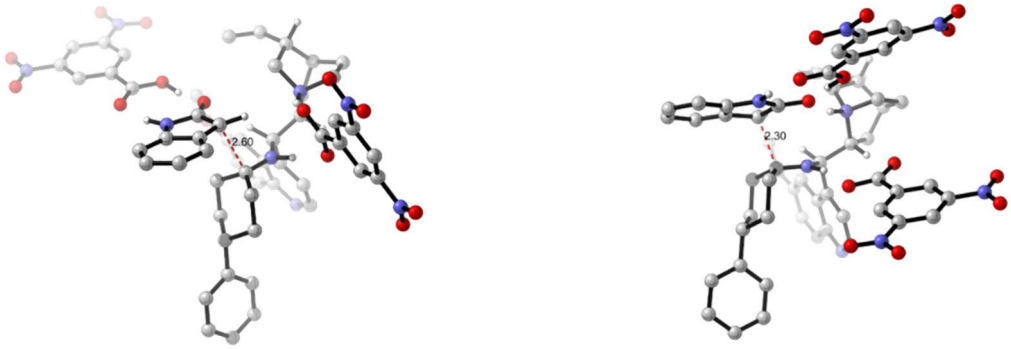
[151] E. L. Eliel, S. H. Wilen in *Stereochemistry of Organic Compounds*, Wiley 1994, p. 484

Table S 5

Entry	E[a] [kcal/mol]	qh-G(T)[b] [kcal/mol]	Imaginary freq. [cm^{-1}]
TS-1a	0.0	0.0	-53.8
TS-1b	1.1	2.0	-152.4
TS-1c	4.0	4.1	-79.2
TS-1d	5.0	6.3	-162.6
TS-1e	5.0	6.3	-181.5
TS-1f	7.2	7.4	-94.9
TS-1g	11.1	11.4	-95.9
TS-1h	11.6	11.3	-123.9

a) Relative electronic energy at the B3LYP/6-311+G(2d,p)-PCM(toluene) level of theory. b) relative free energy calculated from Gaussian results at the B3LYP/6-31G(d) level of theory using Truhlar's quasi-harmonic approximation as implemented[117] in the GoodVibes program

The two lower energy transition state structures **TS-1a** and **TS-1b** are shown in Fig. S8. **TS-1a** is the attack from the *Re* face of the oxindole to the *re* face of the iminium ion (*aS*)-**A** while **TS-1b** is the attack of the *Si* face of the oxindole to the *re* face of the same iminium ion (*aS*)-**A**. All the located transition states showed that the oxindole unit binds via hydrogen bonding of its amidic moiety to a carboxylic acid unit. A feature that is kept throughout the entire reaction path.

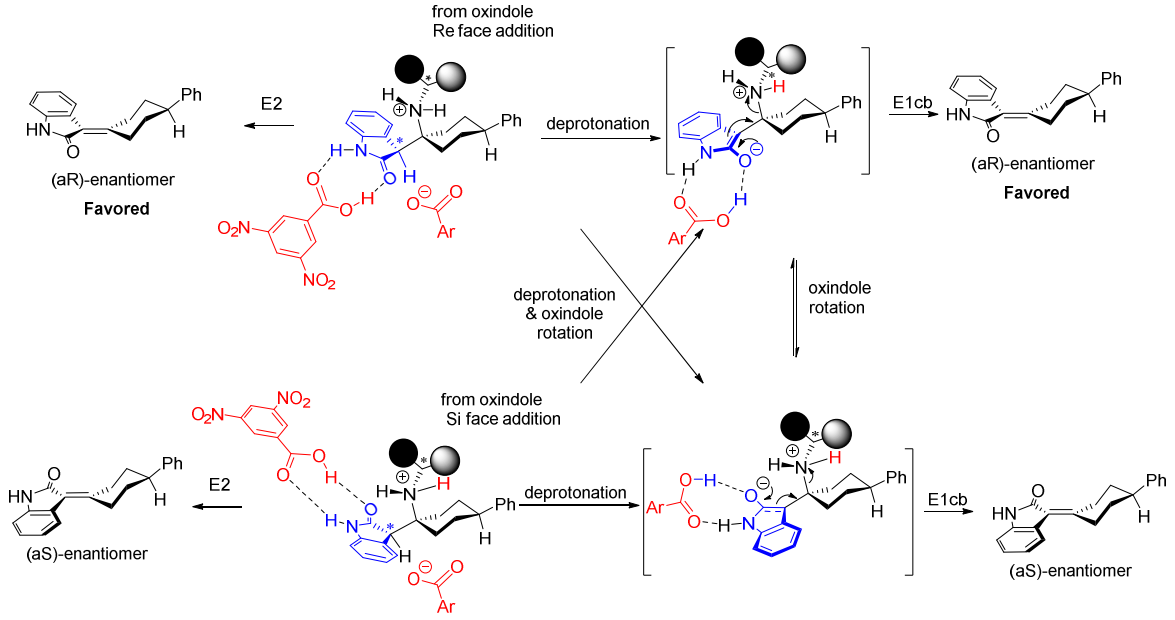


TS-1a: qh-G: 0.0 **TS-1b**: qh-G: 0.5

Figure S 9. *Transition state geometries leading to (aR)-product (left) and to the (aS)-product (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. qh-G, relative Truhlar quasi-harmonic corrected free energy [kcal/mol].*

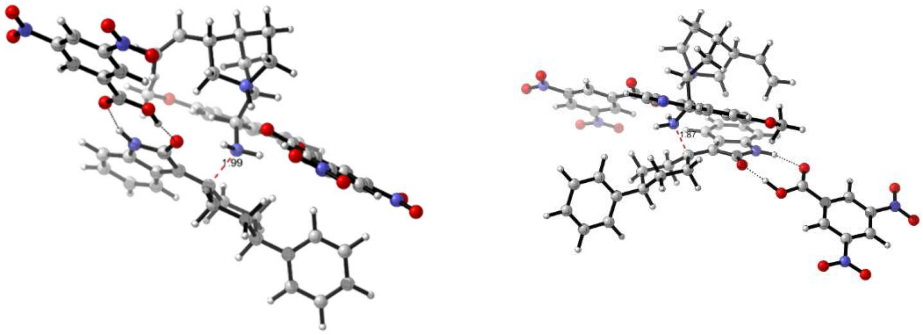
Transition states for the final E1cb elimination

For the final elimination step, in which the atropisomeric double bond is formed and the product is released from the catalyst, we investigated both the E2 and the E1cb hypothesis. Both mechanisms require the preliminary protonation of the amine nitrogen to create a good leaving group.



Scheme S 2. *Alternative pathways for the final elimination to the products: E2 (left) and E1cb (right).*

For the E1cb to occur the only requirement is that the π system of the enolate must be vertically aligned with the σ-bond that is broken. Prior to the E1cb elimination a relative rotation of the oxindole moiety might occur and therefore both of the enolate rotamers might be formed from the same addition intermediate. E1cb elimination on each enolate rotamer leads to a different enantiomer of the product. Then under these conditions the E1cb step becomes the stereo-determining step. If, as might well be the case, the barrier to this rotation is lower in energy compared to that of the following E1cb steps. Then the system composed of the equilibrating two rotamers and the the two products is under Curtin-Hammett conditions and the ratio of the products is determined only by difference of the transition state energies of the two E1cb steps, a difference which is determined solely by the chiral catalyst.

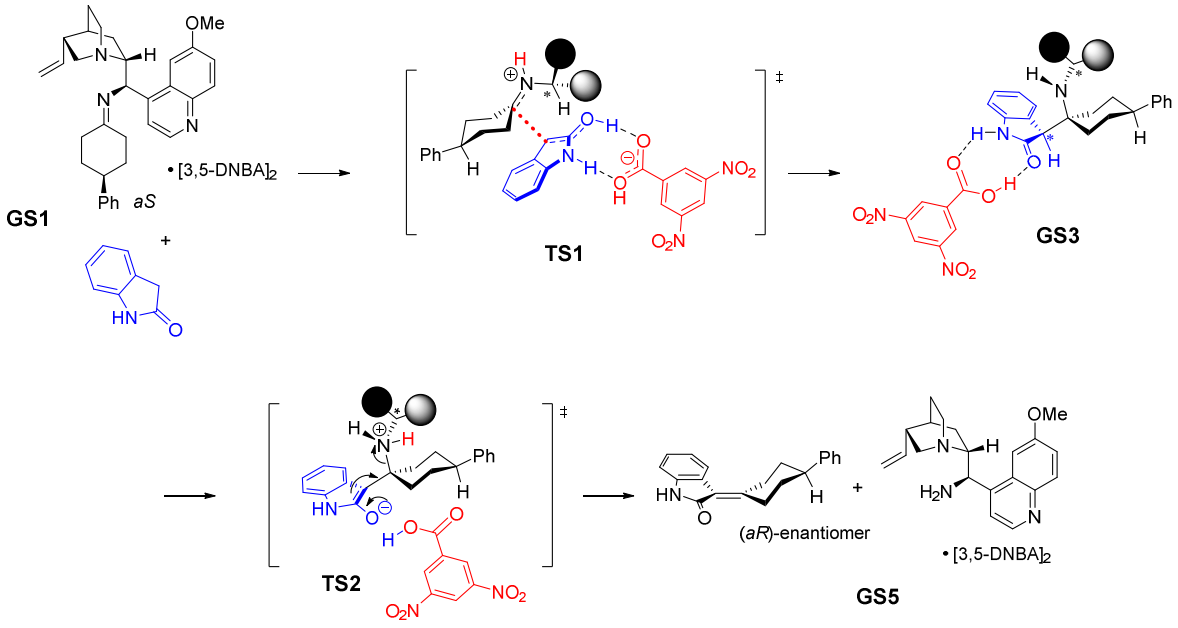


TS-2a: qh-G: 0.0 **TS-2b**: qh-G: 2.0

Figure S 10. *Transition state geometries leading to the major (aR)-product (left) and to the minor (aS)-product (right). The geometries were obtained at B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. qh-G, relative Truhlar quasi-harmonic corrected free energy [kcal/mol].*

The transition state for the E2 elimination to the favored (a*R*)-product could also be located and was found to be ca. 15 kcal/mol higher than the corresponding E1cb step.

The geometries for the two E1cb transition states were located and were found to favor the transition state leading to (a*R*)-product by 2.0 kcal/mol which gives a calculated product ratio of about 95:5, in good agreement with the experimental value of 86:14 (**Figure S10**)



Scheme S 3. *Main steps in the proposed reaction path for the asymmetric enantioselective Knoevenagel condensation (aEKC).*

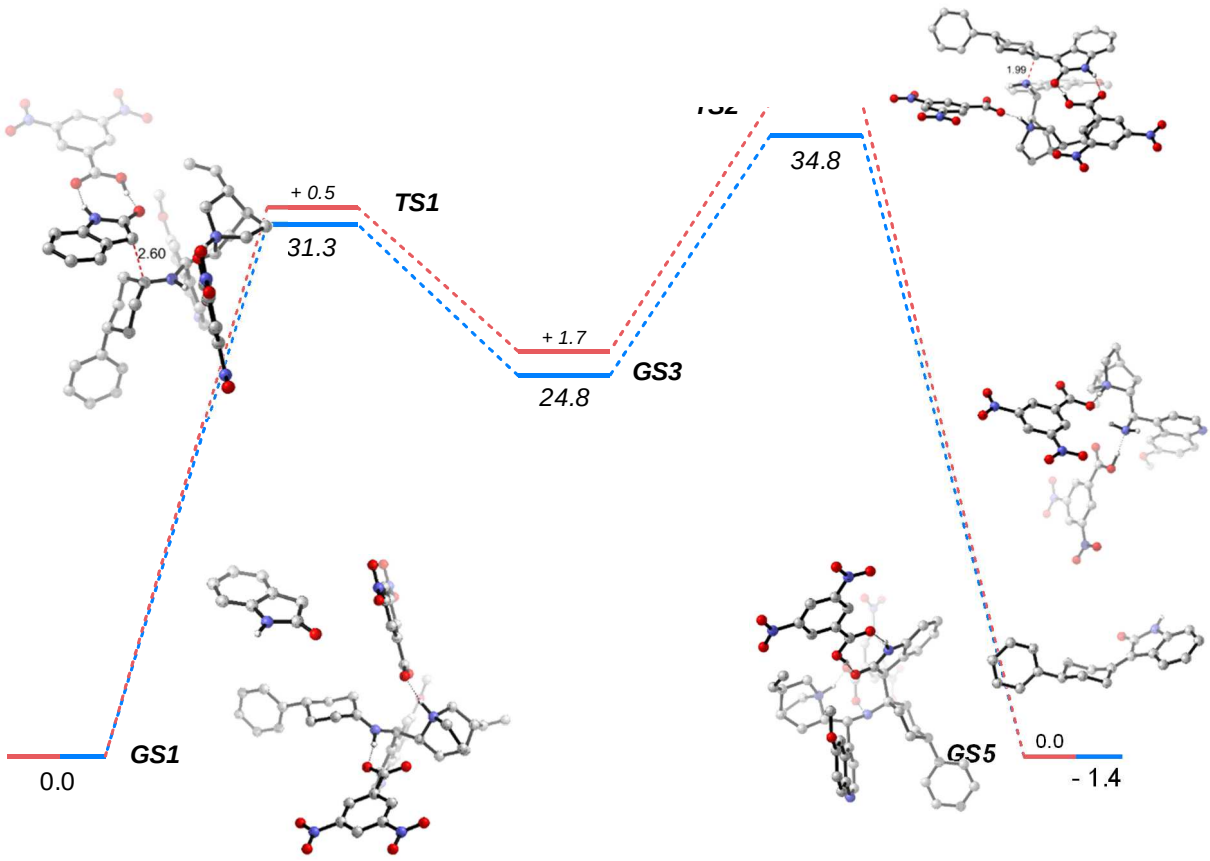


Figure S 11. Corrected free energies (G) at the B3LYP/6-311+G(2d,p)-PCM(toluene)//B3LYP/6-31G(d) level of theory. *All values are in kcal/mol. Blue: reaction path to the major (aR)-product; red: reaction path to the minor (aS)-product. Values for the red path are expressed relative to the corresponding values of the blue path. 3D representations refer to structures of the reaction pathway to the major (aR)-product*

Chapter V

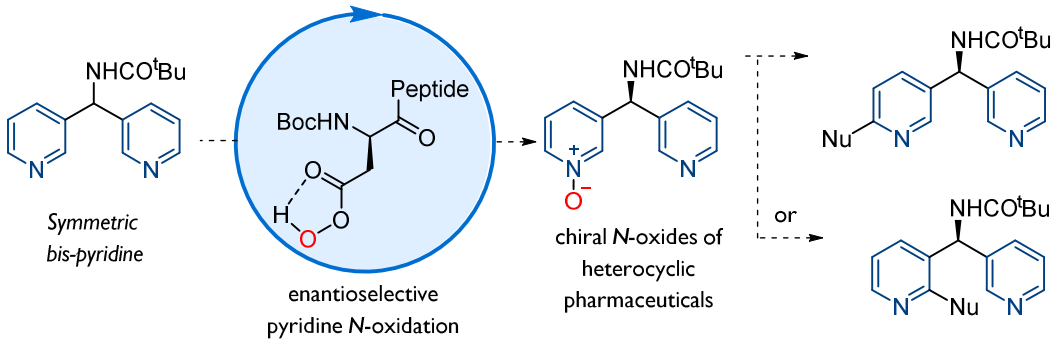
Desymmetrization of Bis-Heteroaryls via *Enantioselective Pyridine* N*-oxidation*

5.1 Catalytic Enantioselective Pyridine N-Oxidation via peptide-catalyzed-peroxide shuttle transfer

All the procedures and results described herein are part of- and can be found in-:

S.-Y. Hsieh, Y. Tang, S. Crotti, E. A. Stone and S. J. Miller*, "Catalytic enantioselective Pyridine N-Oxidation.", *J. Am. Chem. Soc.* **2019**, *141*, 46, *18624*.

Abstract:



The catalytic, enantioselective *N*-oxidation of substituted pyridines is described. The approach is predicated on a biomolecule-inspired catalytic cycle wherein high levels of asymmetric induction are provided by aspartic acid-containing peptides as the aspartyl side chain shuttles between free acid and peracid forms. Desymmetrizations of bis(pyridine) substrates bearing a remote pro-stereogenic center are demonstrated, presenting a new entry into chiral pyridine frameworks in a heterocycle-rich molecular environment. Representative functionalizations of the enantioenriched pyridine *N*-oxides further document the utility of this approach. Demonstration of the asymmetric *N*-oxidation in two venerable drug-like scaffolds, Loratadine[152] and Varenicline[153], show the likely generality of the

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[152] J. Menardo, F. Horak, M. R. Danzig, W. Czarlewski *Clin. Therap.*, **1997**, *19*, 1278.

[153] R. Niaura, C. Jones, P. Kirkpatrick *Nat. Rev. Drug Disc.* **2006**, *5*, 537.

method for highly variable and distinct chiral environments, while also revealing that the approach is applicable to both pyridines and 1,4-pyrazines.

5.2 Synthesis of enantioenriched pyridines

Pyridine derivatives are a class of azacycles having diverse applications in agrochemicals, pharmaceutical and material science. Many substituted pyridines continue to emerge with high frequency in disclosures of biologically active compound, as they can be found in numerous natural products, active pharmaceuticals, and functional materials.[154] Accordingly, methods for synthesizing differentially substituted analogs are highly coveted.[2] Strategies for constructing pyridine-containing molecules in optically enriched form are generally indirect, given the planarity of the heteroaromatic pyridine *N*-nucleus. Nonetheless, methodologies for achieving "*asymmetric*", or enantioselective, syntheses of pyridine-containing molecules are essential, given the extant and growing number of heterocyclic chiral molecules now found in drugs and drug candidates (**Figure 43**).

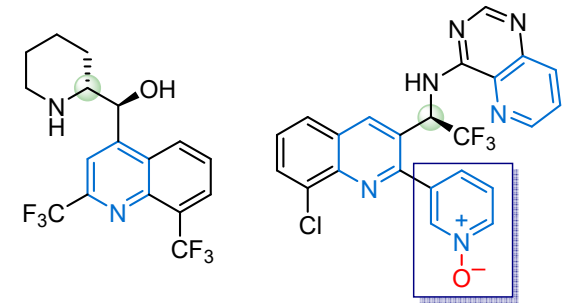

***Figure 43**. Example of bioactive pyridine derivatives.*

There is an increasing drive in the pharmaceutical industry for higher degrees of three dimensionality in lead compounds, which necessitates asymmetric introduction of chiral elements.[155]

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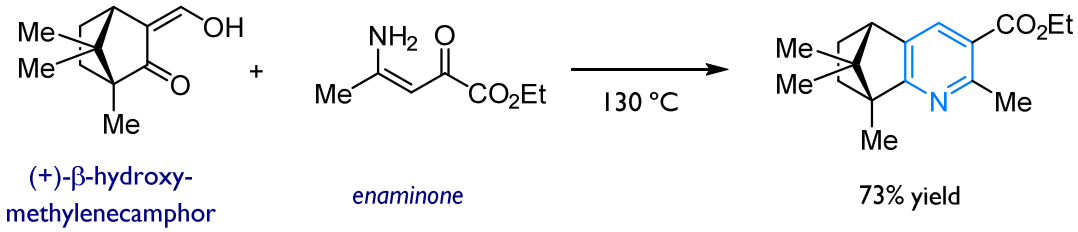
[154] (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014,** *57*, 5845–5859. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

[155] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

Pyridines are important moiety for a wide range of biological activities. Naturally occurring, they play a fundamental role in many important compounds such as the vitamins niacin and pyridoxine, the ubiquitous redox system NADP/NADPH and several alkaloids including nicotine. Consequently, the pyridine ring is utilized in many pharmaceutical active ingredients and possibly even more commonly found in agrochemical products. This can be rationalized by the fact that simple pyridines readily undergo metabolism *via* oxidation or methylation pathways forming the corresponding pyridinium ions.[156] Although many of these metabolites are potentially highly toxic to humans they are conveniently and rapidly excreted from the body through kidney metabolism. With a good understanding of the pharmacokinetics and distribution profile pyridines can therefore be tolerated in the context of pharmaceuticals. Increasing their functionalization could be a useful tool for electronically tuning them against direct oxidation, and thus, be more resilient to metabolic changes.

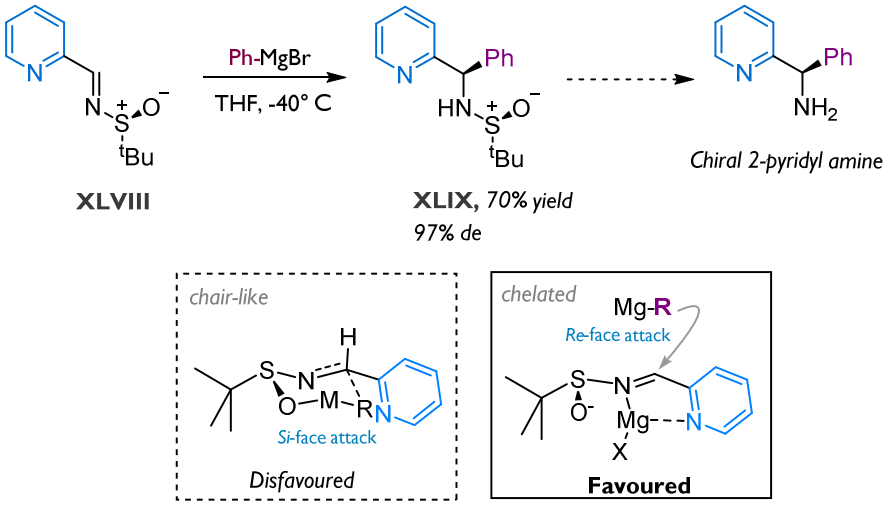
Enantioselective syntheses of pyridines are often predicated using two main strategies. The first is the use enantiopure building blocks. Using this strategy in 2004 was reported the reaction of (+)-β-hydroxymethylene-camphor with enaminone. The researchers were able to obtain the corresponding camphor-based chiral pyridine derivatives in good yields with complete regioselectivity (**Scheme 31**).[157]



Scheme 30. *Assembly with chiral building blocks*

[156] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319
[157] C. Tanyeli *et al.*, *Teth. Lett.,* **2004**, *45,* 6641.

The second approach is based on the use of chiral auxiliaries. These are appended to the pyridine as an easily-installable substituent and then removed following the stereoselective addition through facial diastereoselective recognition. In 2004, it was developed a viable synthetic route to access chiral 2-pyridyl amines in high yields and diastereoselectivities through Grignard addition on picolinic aldheyde-derived Ellman-type imine.[158] The reaction gave the corresponding chiral 2-pyridil amine in good yield and with good to moderate diastereomeric ratio. The observed final chiral induction is opposite to that predicted via a chair-like-controlled transition state and provides an example of the reversal of selectivity in the addition of nucleophiles to chiral imines bearing an α-coordinating group.



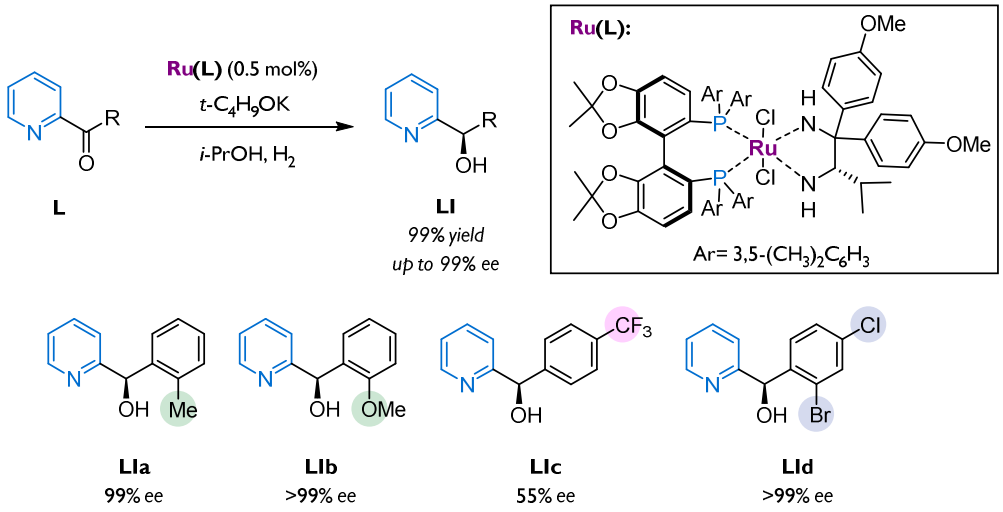
***Scheme 31**. Synthesis of 2-pyridyl amine via Grignard addition on Ellmann-type imine*

Asymmetric catalytic approaches are scarce. Using asymmetric catalysts, chiral pyridines can be accessed by performing an asymmetric catalytic reaction on a pyridine with a prochiral element.

This last approach was proved in Zhang and Rotovelomanana-Vidal's work in which they achieved the enantioselective reduction of various substituted aryl-pyridyl ketones.[159] The hydrogenation was conducted in the presence of the

[158] G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, X.-W. Sun, *Acc. Chem. Res.* **2008**, *417*, 831.
[159] X. Tao, W. Li, X. Ma, X. Li, W. Fan, X. Xie, T. Ayad, V. Ratovelomanana-Vidal, Z. Zhang *J. Org. Chem.* **2012**, *771*, 612.

bifunctional Ru-XylSunPhos-Daipen complex that was able to promote the reaction in excellent yields and with enantiomeric excesses up to >99%. Upon introduction of a readily removable ortho-bromo atom to the phenyl ring, an important chiral intermediate for some histamine H1 antagonists was obtained by hydrogenation with 97.3% ee (**Scheme 33**).

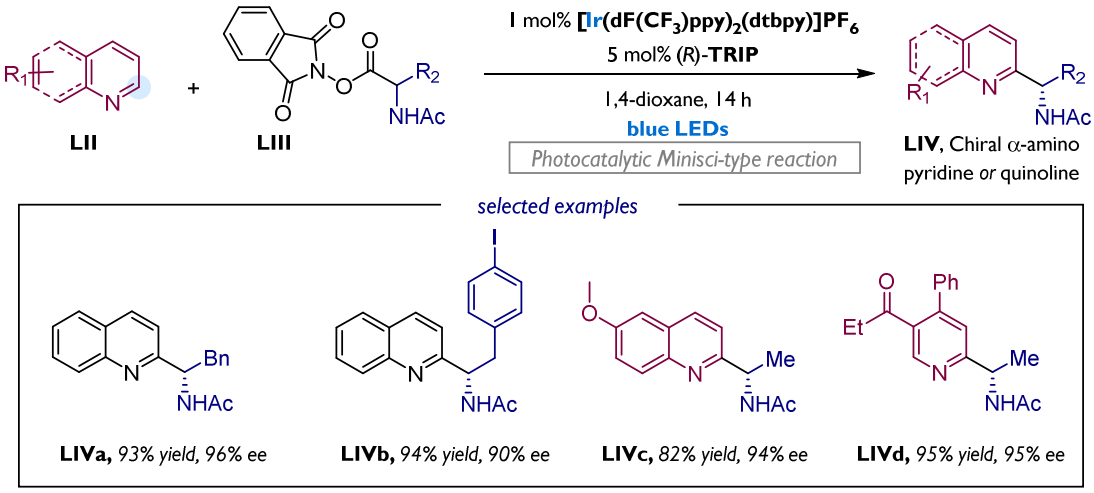


Scheme 32. *Enantioselective reduction of variuous prochiral pyridyl ketones.*

An important example of direct asymmetric coupling in a dual catalytic system, is the recently reported Minisci-type addition on pyridine and quinolone of *in situ* generated nucleophilic radicals. Phipps and co-workers disclosed the direct addition of α-amino alkyl radicals formed after single-electron oxidation, by virtue of a combination of asymmetric Brønsted acid catalysis and photoredox catalysis.[160] This catalytic approach does not require prefunctionalization of the heterocycle and allows excellent control of both enantioselectivity and regioselectivity. The products generated possess structural features highly desirable in pharmaceutical compounds: a basic heteroarene, a protected primary amine, and a defined stereocenter, all in close proximity. In addition, this work constitutes a rare case of noncovalent organocatalysis being applied to control enantioselectivity in a single-electron process. The activation of the quinolone

[160] R. S. J. Proctor, H. J. Davis, R.J. Phipps, *Science*, **2018**, *360*, 419.

substrate proceeds through the first protonation of the nuclephilic nitrogen from the chiral phosphoric acid. The conjugate chiral anion of the corresponding acid remains associated with the pyridinium cation through electrostatic and hydrogen-bonding interactions. Consequentely the heteroarene's lowest unoccupied molecular orbital (LUMO) is considerably lowered upon protonation, and, thereby providing substrate activation in a chiral environment.



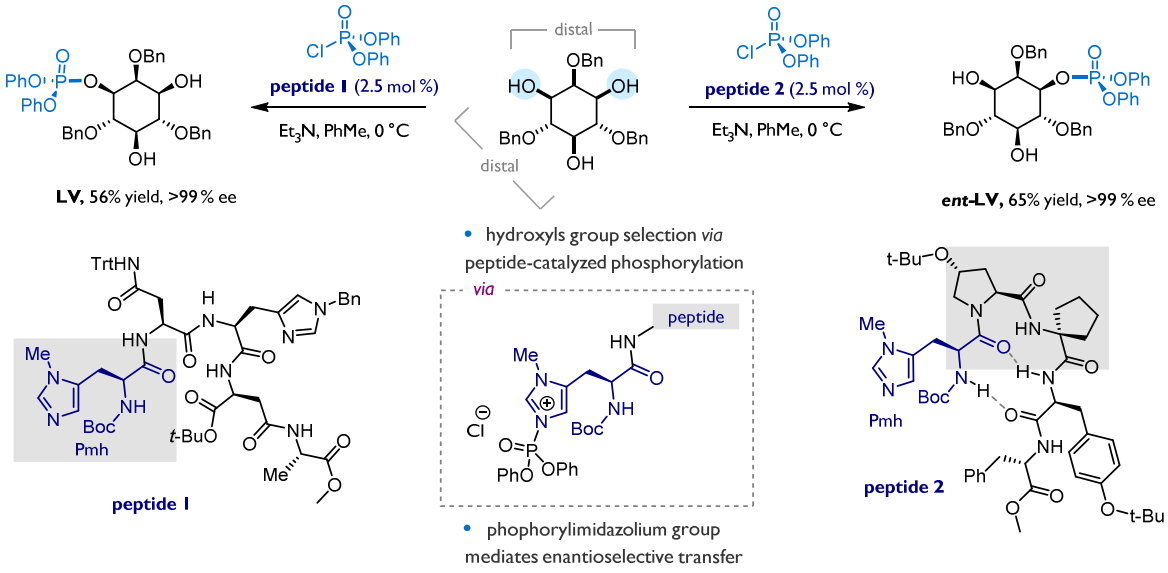
***Scheme 33**. Photocatalytic Minisci-type reaction.*

5.3 Peptide-catalyzed desymmetrization reaction

Inspired by the possibility of developing small-molecule enzyme mimics with broad synthetic applicability, several groups have sought to design short-sequence peptides that capture essential features of enzymatic active sites within greatly simplified molecular frameworks.[161] One of the first peptide-catalyzed desymmetrization reported was inspired by kinases, which are known to be able to selectively phosphorylate substrates bearing multiple active sites *in vivo*. Histidine-dependent kinases, containing an imidazolic basic portion, capable of promoting acyl transfer reactions, through a reactive phosphorylimidazolium

[161] (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610. (b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759− 5812. (c) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036−12041. (d) Akagawa, K.; Kudo, K. *Acc. Chem. Res.* **2017**, *50*, 2429−2439.

intermediate. Enantioselective phosphorylation of symmetric *myo*-inositol derivatives affords a biomimetic transformation of this type and would streamline access to phosphorylated *myo*-inositol natural products.[162]



Scheme 34. *Enantiodivergent phosphorylation of a myo-inositol derivative.*

The strength of peptide-catalyzed reaction is here enlightened. Changing the structural residues can turn out in a completely different conformation both in the ground state than in the Transition State of the transformation, delivering enantio- diastereo-, chemo- and site-selective reactions.

The inositol desymmetrization demonstrated that peptide-based catalysts can differentiate enantiotopic sites in close proximity, *via* enantiotopic group selection. Remote asymmetric induction has been for a long time a long-standing challenge in the organic catalysis *scenario*, often viewed as the purview of enzymes, given their macromolecular dimensions.

The platform to prove this concept was the remote desymmetrization of *bis*-(phenol), wherein the enantiotopic hydroxyl groups are separated from the prochiral center by 5.7 Å and from one another by a nearly a nanometer (9.79 Å).

[162] (a) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781−1785. (b) Sculimbrene, B. R.; Miller, *J. Am. Chem. Soc.* **2001**, 123, 10125−10126.

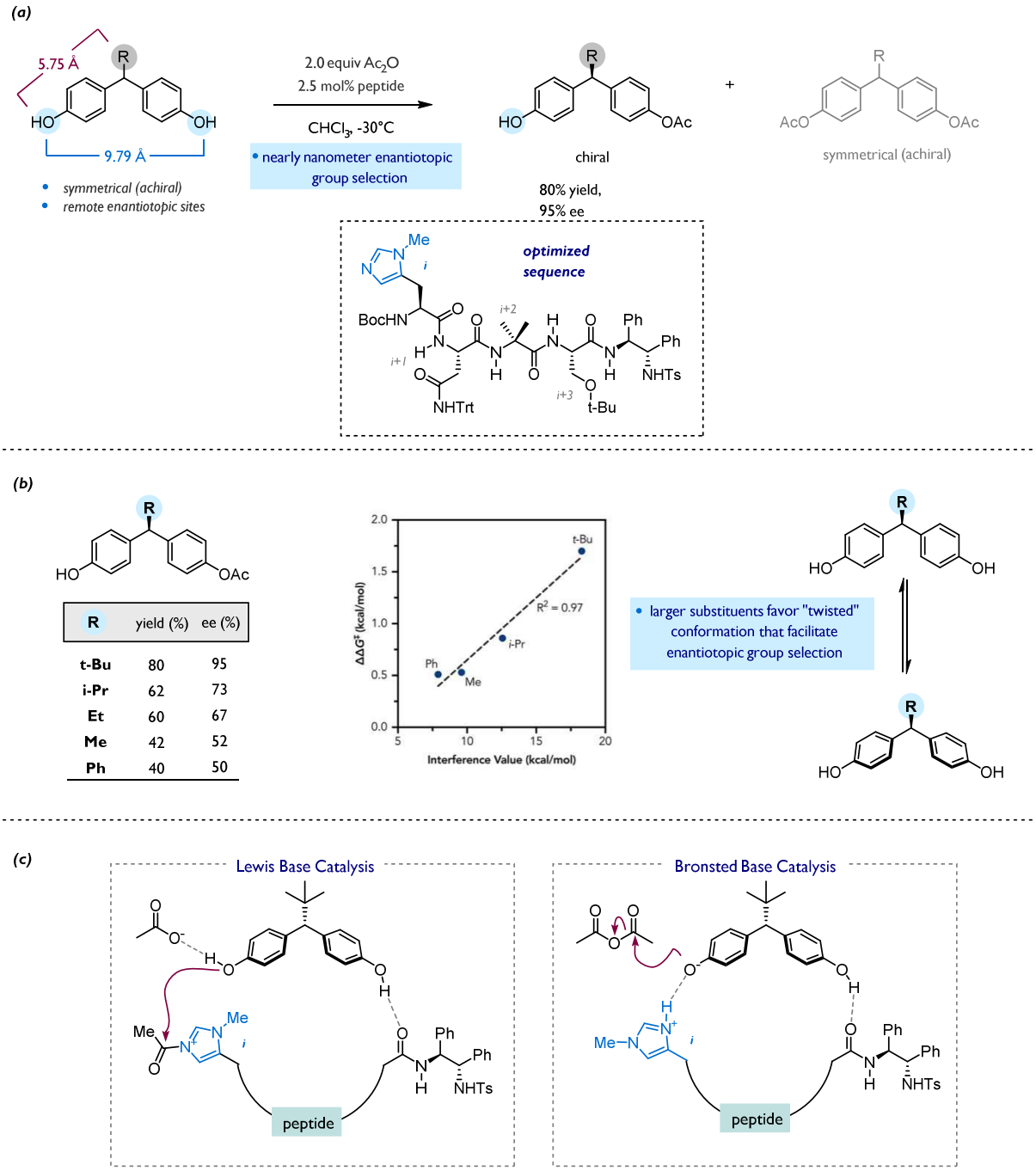
The catalyst library, over 450 peptides, was designed around two structural elements:

(a) To be sufficiently long to interact with both phenols of the starting diarylphenols in the hypothesis of an operating bifuntional mechanism, so hexapeptides seemed the perfect catalytic platform.

(b) To mirror the structural domains of the substrate the terminal residues were selected among those with aromatic side chains, while the central ones were chosen aliphatic.

After an extensive screening tetrapeptide were actually found to be long enough to have the perfect interactions in the substrate-catalyst complex to provided mono(acetate) in 80% isolated yield and 95% ee (**Scheme 36a**). As often observed in desymmetrization reaction *via* group selection, 20% of *bis*(acetate) was also formed, but extensive studies showed how secondary kinetic effects only minimally contributed to the observed ee (k_{rel} = 1.4).

NMR studies showed that the degeneracy in the aryl resonances of is lost upon catalyst−substrate association, suggesting that the optimal catalyst is the one that breaks the bis(phenol) symmetry via noncovalent interactions. While investigating the scope of this reaction, it was found that yield and enantioselectivity diminished steadily with decreasing steric demand of the prochiral substituent (**Scheme 36b**). LFERs correlating the enantioselectivity with various steric parameters, was has been investigated, including Sternhell interference energies. Steep negative slopes suggested sensitivity to the size of the substituent. One interpretation is that the steric profile of the substituent influences the propeller-like twisting of the *bis*(phenol), facilitanting the tightness of the interaction with the catalyst.



Scheme 35. *(a) Peptide-catalyzed remote desymmetrization of a bis(phenol). (b) Methine substituent effects. Mechanistic questions in the bis(phenol) desymmetrization.*

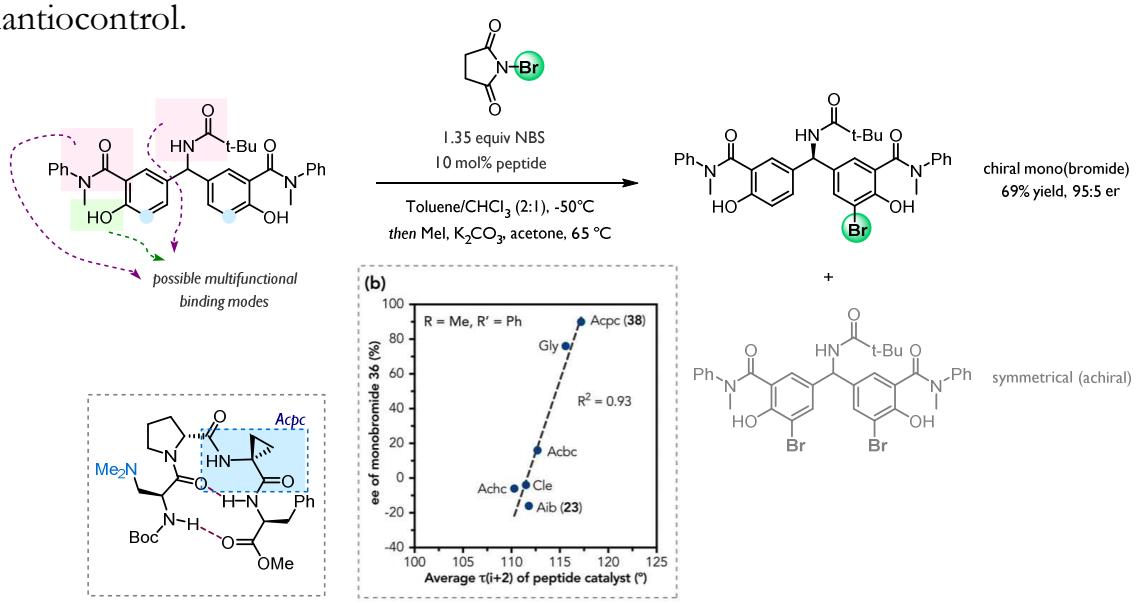
The mechanism of the catalytic Pmh residue of peptide could follow two limiting paths:

(1) Lewis base activation of acetic anhydride

(2) Brønsted base activation of the bis(phenol) (**Scheme 34c**).

While acylation of aliphatic alcohols, such as the *myo*-inositols previously described, more likely proceeds *via* Lewis base catalysis through phosphorylation of the histidine as shown in **Scheme 34**, both possibilities are accessible in this scenario, due to the increased acidity of phenols. The precise activation mode remains undetermined yet.

Finally, a further contribution in this field is the enantioselective desymmetrization *via* electrophilic aromatic halogenation. After an extensive work on atroposelective versions, in a complementary way, desymmetrizing bromination was investigated utilizing a Dmaa-containing peptide to remotely differentiate enantiotopic phenols. The concept is to utilize Brønsted base activation of a phenol, to render it more phenolate-like and thus accelerating the kinetic. Enantio-discrimination could either occur analogously to the mechanism proposed for the previously mentioned bis(phenol) case or by taking advantage of a different intermolecular H-bond between the catalyst and the prochiral amido group. To avoid polybromination, which could erode yields with complicated product mixtures, the *ortho*-position was blocked with an electronically deactivating carbonyl amido group, which might also slow the bromination kinetic to allow a better enantiocontrol.



Scheme 36. *Peptide-catalyzed, desymmetrizing bromination of diarylmethylamido-bis(phenol)s. (b) Correlation between crystallographic τ(i + 2) and enantioselectivity.*

Acpc-containing peptide was found to effectively differentiate the enantiotopic arenes of pivalamides, providing monobromides with good yield and enantiomeric excess. Again, higher selectivities were observed for wider τ(i + 2) values. This possibly suggests that peptide interacts with the substrate as prehelical type I' β-turns.

In this wide scenario, we thought to investigate a new substrate suitable for a desymmetrization for an unprecedented catalytic pyridine *N*-oxidation reaction, in which chirality is established *via* remote asymmetric desymmetrization. The transformation could be employed as a useful tool in pharmaceutical and medicinal chemistry to access high valuable compounds. The strategy thought is to use the active catalytic species, formed after the activation of aspartic acid-embedded peptide in the chiral aspartic peracid that can be attacked by a nucleophilic pyridine.

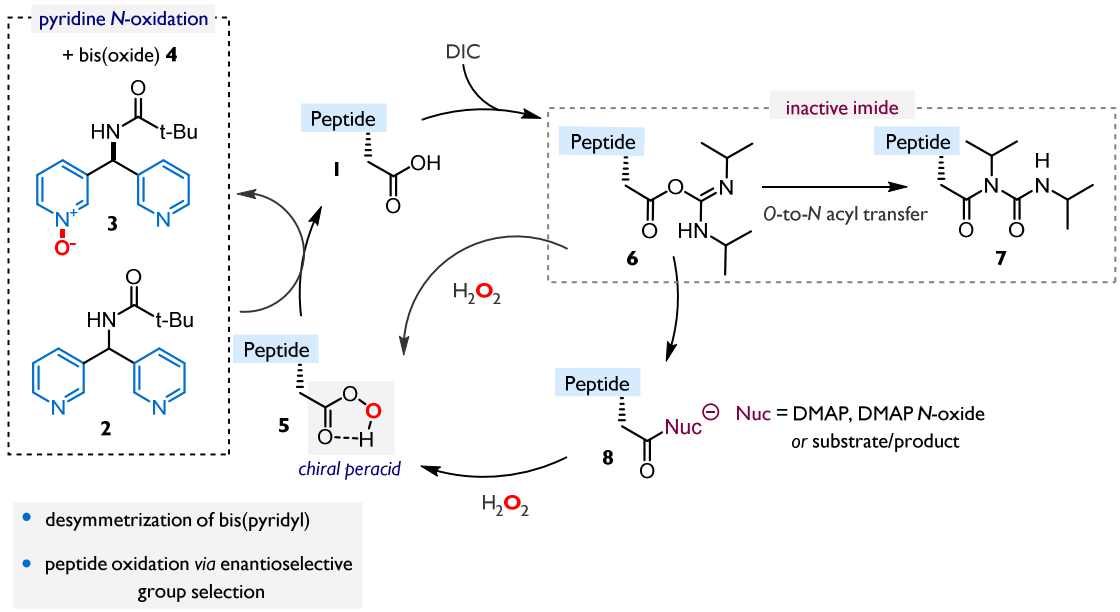


Figure 44. *Mechanistic consideration for enantioselective pyridine N-oxidation*

Our approach required the identification of an appropriate catalytic cycle for pyridine *N*-oxidation, and the design of a substrate-type that would allow us to investigate the enantioselectivity outcomes. We then wondered if the recently explored family of biologically inspired oxidation catalysts might suffice. I have

shown, in **Chapter 1.4**, that aspartic acid-containing catalysts exhibit significant prowess as enantioselective epoxidation[163] or asymmetric Baeyer–Villiger (BV)[164] catalysts that also exert control over migratory aptitude in BV reactions. Furthermore, the peptide sequence can control functional group selectivity, selecting olefins (epoxidation) or ketones (BV), even if both are present within the same molecule, overcoming the specter of cross-reactivity.[165] Moreover, because these catalysts exhibit high chemoselectivity in the presence of electron-rich heterocycles,[166] we thought they might have the mechanistic generality to serve as selective pyridine *N*-oxidation catalysts, as projected in **Figure 44**.

Overoxidation to form bis(*N*-oxide) product **4** is also possible, as overreaction is a general issue associated with desymmetrization methodologies, wherein double functionalization can occur. Nevertheless, in analogy to epoxidation and BV oxidation, we relied on carbodiimide activation of **1** to chaperone the Asp-containing catalysts to the Asp-based peracid **5**. The desired pyridine *N*-oxidation then completes the catalytic cycle and regenerates **1**.

One interesting difference between the pyridine *N*-oxidation and the prior epoxidation and BV catalytic systems is that in this new application, both the substrate **2** and product **3** can serve as transient co-catalysts for the reaction, preventing deleterious rearrangement of the intermediate *O*-acyl urea **6** to the catalytically inactive *N*-acyl urea **7**, possibly through the formation of intermediates like **8**. In our earlier studies, we had deliberately assigned this function to the additive DMAP or DMAP *N*-oxide. Notably, we observed no

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[163] (a) Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710–8711. (b) Lichtor, P. A.; Miller, S. J. *Nat. Chem.* **2012**, *4*, 990–995.

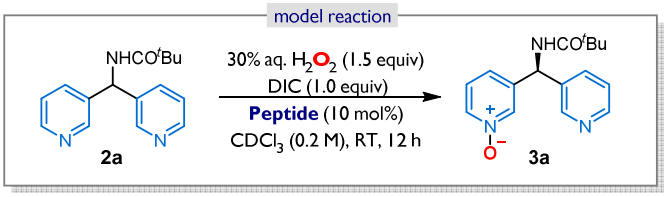
[164] Romney, D. K.; Colvin, S. M.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136,* 14019–14022.

[165] Alford, J. S.; Abascal, N. C.; Shugrue, C. R.; Colvin, S. M.; Romney, D. K.; Miller, S. J. *ACS Cent. Sci.* **2016**, *2*, 733–739.

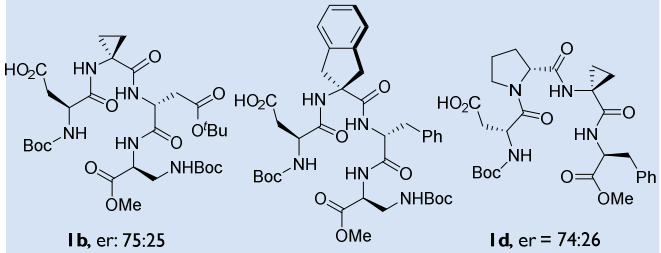
[166] Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 9104–9111. (b) Mercado-Marin, E. V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R. *Nature* **2014**, *509*, 318–324.

particular advantage or disadvantage to the incorporation of extra DMAP on the selectivity in the current studies.

At our first attempt, we were pleased to see that with 10 mol% of Boc-Asp-OMe (**1a**) as the catalyst, 63% yield of **2a** could be achieved, albeit in racemic form (**Table 8**, entry 1).



(a) Initial Screening of *On-bead* or Designed Catalysts



1b, er: 75:25 (on-bead screening: er: 69.5:30.5)

1c, er: 72:28 (on-bead screening: er: 70:30)

1d, er = 74:26

(b) Tabulated Data for Catalyst and Reaction Optimization

Entry	Peptide	er, **3a**
1[a]	Boc-Asp-OMe, **1a**	50:50
2	Boc-D-Asp-D-Pro-Acpc-Phe-OMe, **1d**	74:26
3	Boc-Asp-D-Pro-Acpc-Phe-OMe, **1e**	52:48
4	Boc-Asp-Pro-Acpc-Phe-OMe, **1f**	36:64
5	Boc-D-Asp-Pro-Acpc-Phe-OMe, **1g**	48:52
6[b]	Boc-D-Asp-D-Pro-Acpc-Phe-OMe, **1d** (PhMe)	72.5:27.5
7[b]	Boc-D-Asp-D-Pro-Acpc-Phe-OMe, **1d** (polar solvents)[c]	< 62:38
8	Boc-D-Asp-D-Pro-Acbc-Phe-OMe, **1h**	56:44
9	Boc-D-Asp-D-Pro-Cle-Phe-OMe, **1i**	54:46
10	^{t}BuNHCO-D-Asp-D-Pro-Acpc-Phe-OMe, **1j**	79.5:20.5
11	Boc-Gly-D-Asp-D-Pro-Acpc-Phe-OMe, **1k**	78: 22
12	Boc-Phe-D-Asp-D-Pro-Acpc-Phe-OMe, **1l**	76.5:23.5
13	Boc-D-Phe-D-Asp-D-Pro-Acpc-Phe-OMe, **1m**	83.5:16.5
14	Boc-D-Phg-D-Asp-D-Pro-Acpc-Phe-OMe, **1n**	84:16
15[d]	Boc-D-Phg-D-Asp-D-Pro-Acpc-Phe-OMe, **1n**	86:14
16	Boc-Pro-D-Asp-D-Pro-Acpc-Phe-OMe, **1o**	74:26
17	Boc-D-Pro-D-Asp-D-Pro-Acpc-Phe-OMe, **1p**	71:29

Table 8. *Screening of peptide catalysts from one-bead-one-compound (OBOC) library and proline-type β-turn peptides.* [a] *The mono-N-oxide* ***2a*** *was produced in 63% yield.* [b] *Instead of $CDCl_3$, the solvent listed in parentheses was used in this reaction.* [c] *Polar solvents included: EtOAc, Et_2O, and THF.* [d] *The reaction was performed at 4 °C. Enantiomeric ratios were measured according to the eluent order. Optimization of reaction conditions for pyridine N-oxidation with peptide* ***1n*** *performed on 0.05 mmol scale.*

After proving the feasibility of the reaction, we focused our attention on the enantioselectivity. Given the unprecedented strategy in literature for pyridine *N*-oxidation, the explicit design of chiral catalysts was difficult to think *a priori*. Thus, we decided that a useful system to decide an adapt starting point could be a combinatorial approach in the discovery of a "hit" catalyst to a class of β-turn-biased catalysts we have previously employed for many asymmetric reactions.[167] For the combinatorial approach, we applied the one-bead-one-compound (OBOC) library concept.[168] Application of this approach (*better described in the experimental section of this Chapter*) to the desymmetrization of **2a** led to the identification of a number of "hit" catalysts, including **1b** and **1c** (**Table 8a**). These catalysts delivered **3a** with appreciable enantioselectivity under the conditions of the assay (resin-bound **1b**, 69.5:30.5 enantiomeric ratio (er); resin-bound **1c**, 70:30 er).

To prove the catalytic activity the synthesis and evaluation under homogeneous conditions were studied. The catalytic reactions gave validating results (**1b**, 75:25 er; **1c**, 72:28 er). In parallel, our chirality assessment of β-turn-biased catalysts included a survey for all the possible diastereomers of canonical Boc-Asp-Pro-type tetramers (**Table 8**, entries 2–5). The survey of the stereochemical disposition of each residue in the β-turn-biased sequence (entries 2–5) revealed that Boc-D-Asp-D-Pro-Acpc-Phe-OMe (**1d**) was indeed optimal, delivering the 74:26 er, while other diastereomers gave lower selectivity.

Nevertheless, we suspect that any of the three scaffolds depicted in **Table 8a** could in principle be optimized for the selective oxidation of **2a** to **3a**.

We decided to pursue catalysts related structures **1d,** investigating different parameters to improve the binding ability, exploring simple variations of side

[167] (a) Metrano, A. J.; Miller, S. J. *Acc. Chem. Res.* **2019**, *52*, 199–215. (b) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 492–516.

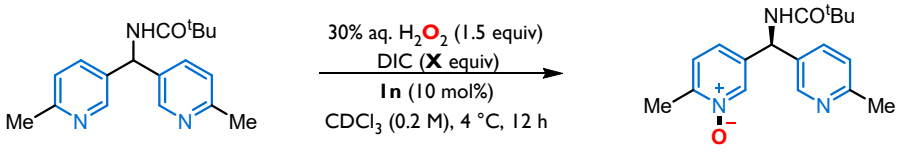
[168] (a) Lam, K. S.; Lebl, M.; Krchnák, V. *Chem. Rev.* **1997**, *97*, 411–448. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610. (c) Revell, J. D.; Wennemers, H. *Curr. Opin. Chem. Biol.* **2007**, *11*, 269–278.

chains and stereochemical configurations at each position of the catalyst. Several illustrative and heuristic substitutions are shown in **Table 8b**. As already mentioned, the monomeric protected Asp-derived catalyst **1a** delivered the product in racemic form, indicating that some higher-order structure would be necessary for enantioselectivity (**Table 8b**, entry 1). Deuterated chloroform also emerged as the preferred solvent with catalyst **1d** in a preliminary survey (entries 6–7).[169]

Variation of the *i*+2 residue generally led to catalysts with lower selectivity (entries 8–9); yet, variation of substituents to the *N*-terminal side of the peptide sequence led to promising improvements. For instance, an *N*-terminal *tert*-butylurea substituent (**1j**, entry 10) resulted in improved selectivity of nearly 80:20 er.

The elongation of the peptide chain in a pentapeptide proved equally favorable for the er (entries 11–17). Of these catalysts, peptide **1n** with a Boc-d-phenylglycine (Boc-d-Phg, entry 15) *N*-terminal residue delivered **3a** with an 86:14 er. Accordingly, we elected to examine this catalyst further with a variety of reaction conditions and for studies of substrate scope.

A drastic change in the enantioselectivity was observed when the nature of the 6- and 6'-positions of **2** was investigated. When a methyl group was installed at the 6- and 6'-positions (**2b**), a profound increase in the er was observed and **3b** was produced with 92:8 er, and in 71% isolated yield (**Table 9**).



2b **3b** + bis(*N*-oxide) **4b**

Entry	DIC equiv	Yield **3b** [%]	er, **3b**	Yield **4b** [%]
1	1.0	71%	92:8	12%
2	1.2	73%	93.5:6.5	18%
3	1.4	68%	96:4	30%
4	1.6	55%	98.5:1.5	45%

Table 9. *Optimization of reaction conditions for pyridine N-oxidation with peptide* ***1n*** *performed on 0.05 mmol scale.*

[169] $CDCl_3$ was initially utilized due to the possibility of monitoring the reaction. Non-deuterated chloroform was also checked, and it was found to perform equally well. Nevertheless, for consistency, we choose to employ deuterated chloroform for further investigations.

Moreover, we discovered that there was a degree of secondary kinetic resolution in the overoxidation of **3b** (to give **4b**) that led to further er enhancement (entries 2–4). Indeed, **3b** was generated with >98:2 er when 1.6 equiv of DIC was employed, albeit with a small sacrifice in yield (55% yield). With this level of enantioselectivity, we turned our attention to the scope and limitations for this new asymmetric process.

Our explorations led to the identification of several excellent substrates, even if some of them did not work as well. Rerunning the reaction under the optimal condition (1.5 equiv oxidant, 0.2 M in substrate, 4 °C), **3a** was isolated in 75% yield with 87:13 er (Table 10). The 6,6'-methyl substituted pyridine *N*-oxide **3b** was isolated in 76% yield with 97:3 er. Bulkier substituents gave even better enantioselectivities and *iso*-Propyl-bearing product **3c** was obtained in excellent selectivity (71% yield, 99:1 er), as well as *tert*-butyl substituted compound **3d** (70% yield, 98.5:1.5 er), despite the requirement of 48 h reaction time due to lower reactivity, due to the shielding effect on the nucleophilic nitrogen. Similarly, the cyclohexyl-bearing substrate **2e** was converted to **3e** with 99:1 er (69% isolated yield).

Aryl-substituted pyridines were also well-tolerated by catalyst **1n**, as illustrated by the isolations of **3f** (78% yield, 98:2 er), **3g** (78% yield, 99:1 er), **3h** (74 % yield, 98:2 er) and **3i** (79% yield, 96:4 er). Some other more exotic substituents were also promising, as bis(quinoline) **3j** was isolated in 79% yield with 97:3 er under these conditions.

Highly electron-rich substituents, as in the case of 6,6'-Bismethoxy-substituted **2k,** were instead less tolerated, although **3k** was still isolated with 88:12 er and in 67% yield. Altering the position of the pyridyl substituent to 5,5'-dimethylation resulted in partially selectivity, as **3l** was isolated with 87:13 er and 65% yield. The absolute configuration of *N*-oxide **3l** was determined by single crystal X-ray diffraction, which enabled the assignment of the remaining substrates by analogy.

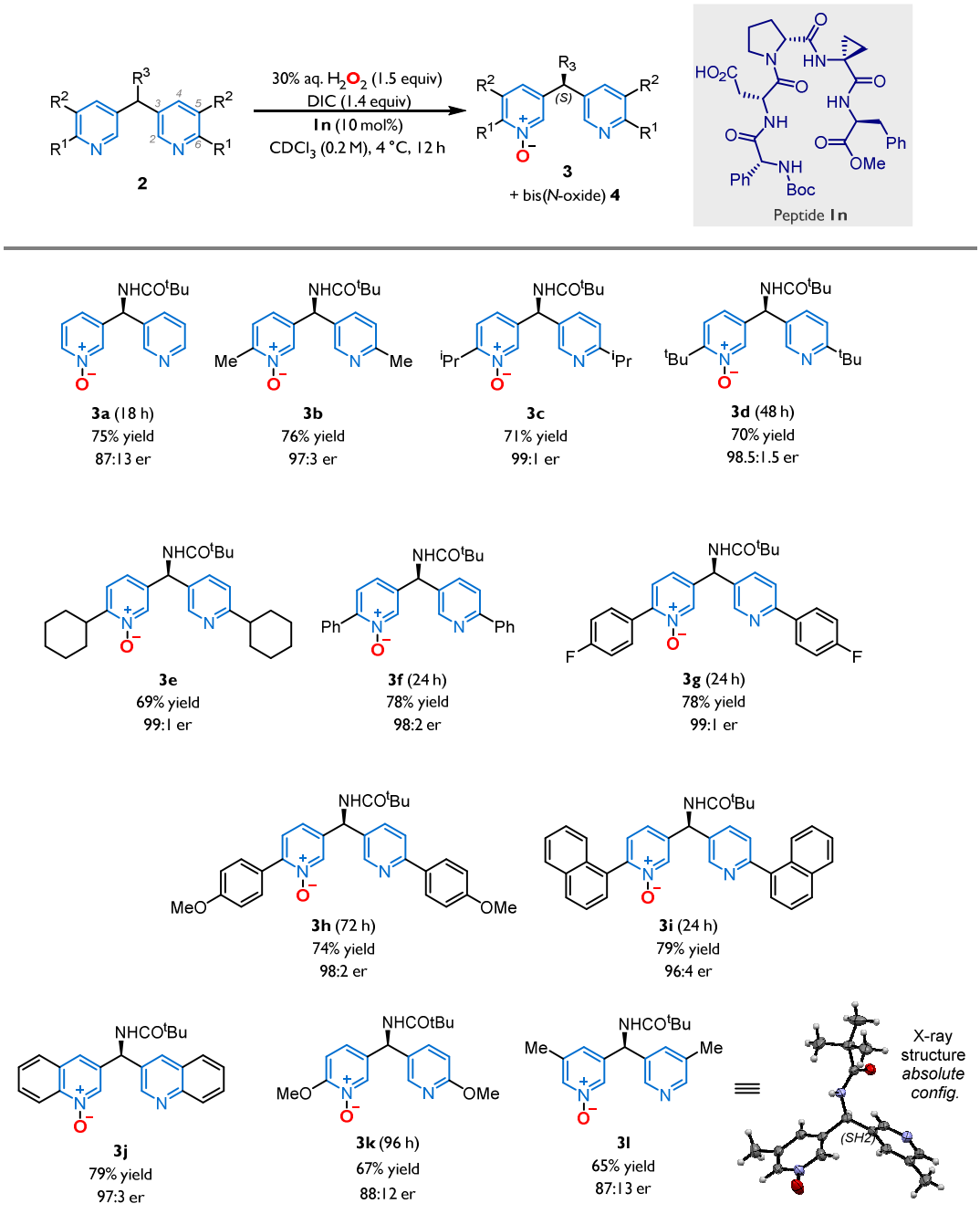


Table 10. *Substrate scope of the desymmetrization of bis(pyridine)s.*

On the other hand, **Table 11** depicts several substrates that failed to react as well with peptide **1n**, including substitution at the 2-position of the pyridine (**3m**) or when the pyridyl moieties are bridged at the 4-positions (**3n**). These two cases afforded products that were nearly racemic with catalyst **1n**. In addition, compounds related to **3** generally exhibited higher selectivity when the bridging

amide group was a secondary pivaloyl amide. When the free *N*-H group was replaced with N-Me (**3o**), selectivity was greatly diminished (54:46 er), suggesting that the secondary amide may play a mechanistic role as a hydrogen bond donor. When the pivaloyl group was converted to benzoyl (**3p**) or acetyl (**3q**), in absence of methylation, selectivity was partially restored (84:16 er and 72:28 er, respectively). It is certainly possible that re-optimization with another catalyst from our library might address these classes in a more selective manner.

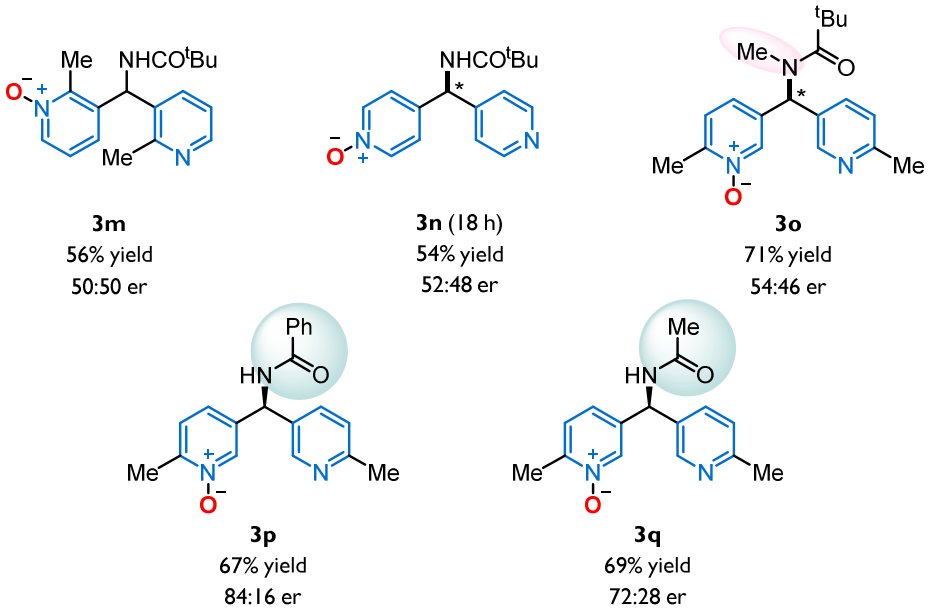


Table 11. *Substrates reacted with low to no selectivity.*

Given the stereochemical outcomes of the reaction, we tried to offer some speculation in analogy to previous studies. The substrate-catalyst complex is shown in **Figure 45**. The activated aspartic peracid catalytic intermediate is proposed to interact with the substrate in a manner that favors the formation of the (*S*)-enantiomer, consistently with the crystal structure obtained. This model is predicated on well-precedented conformational analyses for Pro-Acpc peptides.[170] In this speculative transition state, the peptide adopts a type II' β-turn conformation in the reactive complex.

[170] Hurtley, A. E.; Stone, E. A.; Metrano, A. J.; Miller, S. J. *J. Org. Chem.* **2017**, *82*, 11326–11336.

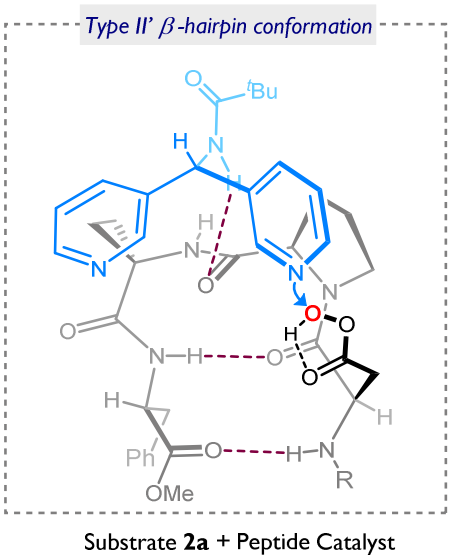
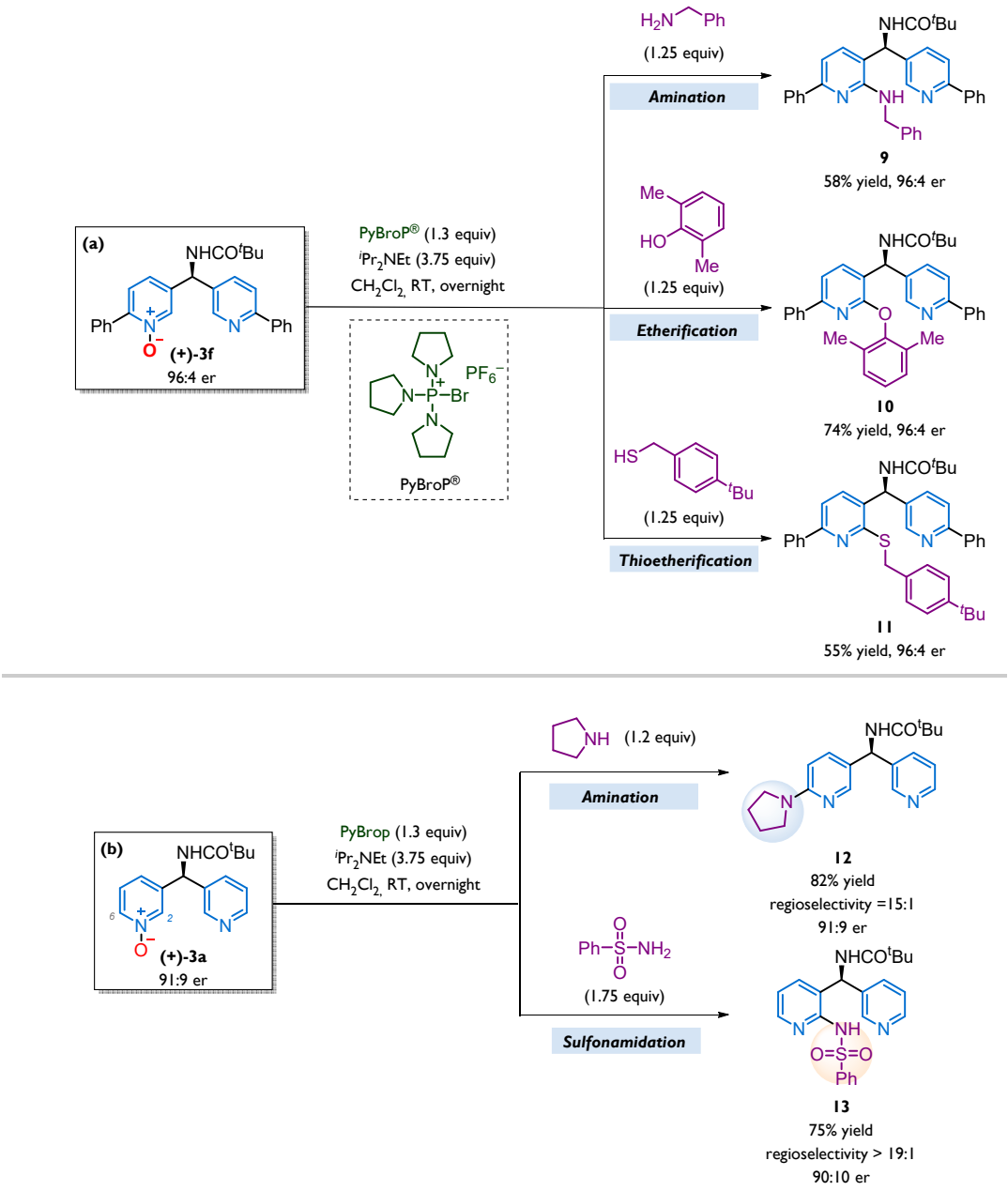


***Figure 45**. A speculative and heuristic model for the enantiomeric outcome.*

To prove the versality of this new methodology, derivatization of the product to afford highly valuable substituted chiral pyridine scaffolds was investigated. The optically enriched pyridine *N*-oxides provide a platform for the synthesis of chiral pyridine-containing scaffolds. For example, Ph-substituted pyridine *N*-oxide **3f** was permuted to aminopyridine **9**, aryloxypyridine **10**, and thioether variant **11** under established PyBroP®-based substitution conditions (**Scheme 38a**).[171] Parenthetically, the desymmetrized unsubstituted pyridine *N*-oxide **3a** may also be regioselectively diversified. For example, starting from recrystallized material of **3a** (91:9 er), amination delivered **12** in a 15:1 ratio of 2/6 positional regioisomers with complete stereoretention, while sulfonamidation (**13**) occurred in a >19:1 ratio of 6/2 positional regioisomers (**Scheme 38b**). This strategy appeared to be interesting, because the catalytic pyridine *N*-oxidation doesn't only desymmetrize the achiral starting material with the formation of a new stereocenter, but it simultaneously installs a new reactive functionality. The final desymmetrized substituted pyridine could thus be considered as the product of a formal enantioselective two step C-H desymmetrization.

[171] (a) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254–5257. (b) Londregan, A. T.; Jennings, S.; Wei, L., *Org. Lett.* **2011**, *13*, 1840–1843.

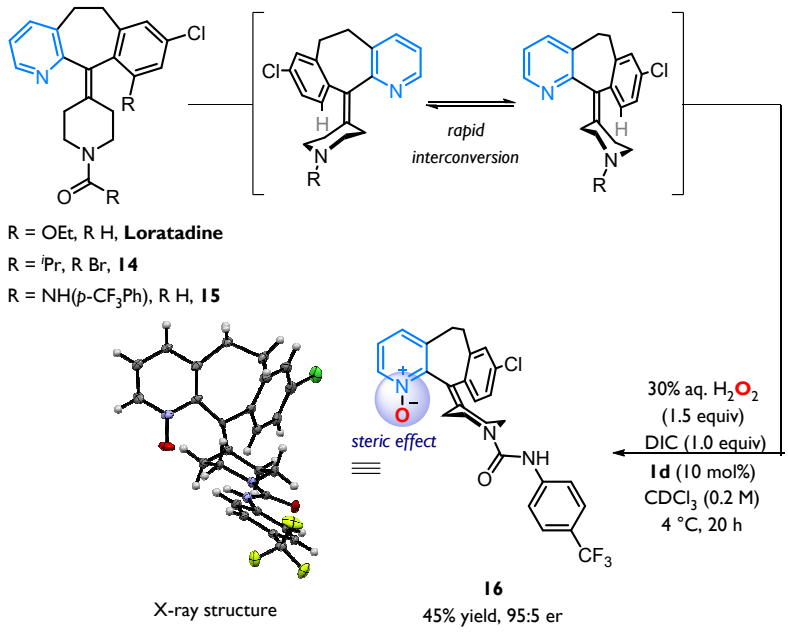


Scheme 37. *(a) Derivatization of enantioenriched* ***3f*** *via amination, etherification, and thioetherification. (b) Derivatization of enantioenriched* ***3a*** *through regioselective amination, arylation, and sulfonamidation.*

After addressing the scope of the reaction and demonstrating the its applicability to various substrates, the generality of the process has been investigated, to see if the strategy could be transferred with genuinely different classes of substrates.

We concluded then with two exotic and demanding applications in unambiguously drug-like scaffolds. Loratadine,[172] the active ingredient in the allergy medicine Claritin®, exhibits unusual stereochemical properties.

For example, while Loratadine itself doesn't have enough shielding effect from the substituents and doesn't exhibit stable enantiomers due to the rapid conformational interconversion, compounds like **14**, in which a more steric demanding moiety is installed, can be isolated with optically purity due to high barriers to racemization of the helically chiral enantiomers (**Scheme 39**).[173] Thus, we wondered whether or not catalytic, enantioselective pyridine *N*-oxidation of Loratadine derivative **15** could be subjected to dynamic kinetic resolution. Notably, catalyst **1d** afforded **16** in 45% yield with 95:5 er (Fig. 4C). Pyridine *N*-oxidation is preferred, although we also observed 28% conversion to the corresponding epoxide under these conditions, as assayed by LC/MS. This result highlights the applicability of this chemistry beyond desymmetrization.

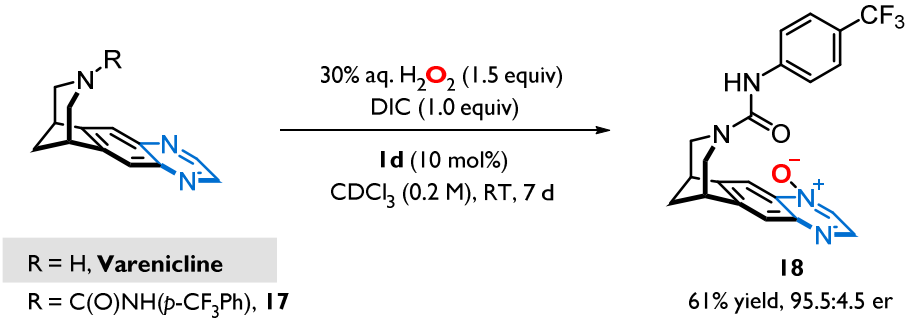


Scheme 38. *Dynamic kinetic resolution of Loratadine derivative* ***15***

[172] Clissold, S. P.; Sorkin, E. M.; Goa, K. L. *Drugs* **1989**, *37,* 42–57. (b) Piwinski, J. J.; Wong, J. K.; Chan, T. M.; Green, M. J.; Ganguly, A. K. *J. Org. Chem.* **1990,** *55*, 3341–3350.

[173] Morgan, B.; Zaks, A.; Dodds, D. R.; Liu, J.; Jain, R.; Megati, S.; Njoroge, F. G.; Girijavallabhan, V. M. *J. Org. Chem.* **2000**, *65,* 5451–5459

Moreover, we demonstrated another important, useful and dramatically different from our starting material could be efficiently desymmetrized using this peptide-catalyzed strategy. We choose a scaffold related to Varenicline[174] containing a pyrazine heterocycle that under the catalytic condition, afforded pyrazine N-oxide **18** with catalyst **1d** in 61% yield and with 95.5:4.5 er (**Scheme 40**). This last result suggests that the present approach may have generality with respect to other, enantio- and site-selective heteroarene *N*-oxidations.



***Scheme 39**. Desymmetrization of Varenicline derivative **17**.*

In conclusion, this work described a new enantioselective useful tool for the synthesis of enantioenriched pyridine. The reaction, employing aspartic acid-derived peracid catalysis afforded the desired product in good yield and enantioselectivity. This chemistry not only extends the general utility of this catalytic cycle beyond epoxidation and Baeyer-Villiger oxidations, but also provides strategic access to optically enriched heterocycles in a class of substrates fertile for studies of bioactivity. The compounds obtained were also directly derivatized with a different variety of possibly interesting substituents. We also efficiently demonstrated the enantioselective derivatization of drug-like scaffolds for a range of different heterocycle. We anticipate that this approach will be of

[174] (a) Rouden, J.; Lasne, M.-C.; Blanchet, J.; Baudoux, J. "(–)-Cytisine and Derivatives: Synthesis, Reactivity, and Applications" *Chem. Rev.* **2014**, *114*, 712–778. (b) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D.; O'Neill, B. T. *J. Med. Chem.* **2005**, *48*, 3474–3477.

interest and use in fundamental and applied studies in both process-oriented and discovery-oriented synthetic chemistry settings.

5.4 Experimental section

Author Contributions

All authors contributed to the conceptualization of the project, the planning of experiments, and interpretation of results. The work was not conducted linearly or independently by each member of the team, and thus inserting only the experiment run by the author of this Thesis would have been difficult for the reader. S.J.M. directed the research. S.Y.H. conceptualized the reaction and performed the initial *on-beads* screening. S.Y.H, S.C. and Y.T. synthesized the peptide sequence. S.Y.H, Y.T. and S.C. were involved in the synthesis of starting materials. S.Y.H, Y.T. and S.C. performed the catalytic reaction. E.A.S. conducted the reaction on drug-like molecules. S.C. performed the derivatization reactions. conducted the experiments. S.Y.H and S.J.M wrote the manuscript with input from all authors.

Materials and Methods

General Information. Room temperature (rt) is considered 20–23 °C. All reactions were carried out without exclusion of air or moisture, unless otherwise stated. All commercially available reagents and solvents were obtained from common suppliers and used as received without further purification, unless otherwise indicated. Acetonitrile (MeCN), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (PhMe) were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et_3N) and *N,N*-diisopropyl ethylamine ($^iPr_2NEt$) were distilled over CaH_2 under a nitrogen atmosphere prior to use. Deionized water was used for reactions, extraction solutions, and reversed phase chromatography. HPLC grade solvents were used for all other chromatography.

Analytical Methods.

• **TLC and Column Chromatography:** Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp and/or stained with potassium permanganate ($KMnO_4$) or ninhydrin. Retention factor (R_f) values are reported. Normal phase flash column chromatography was conducted using either silica gel 60 Å (32–63 microns) or an automated Biotage® Isolera™ One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 mm silica) cartridge. Reverse phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 mm silica) or SNAP Ultra C18 (HP Sphere, 25 mm silica) cartridge. Whichever column chromatography was applied, the desired fractions (confirmed by TLC or UPLC-MS) were collected and concentrated *in vacuo* to afford the product.

• **NMR:** Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-*d* ($CDCl_3$), dimethylsulfoxide-d_6 (DMSO-d_6), acetone-d_6, methanol-d_4 (CD_3OD), and acetonitrile-d_3 (CD_3CN) were purchased from Cambridge Isotopes and used as received. DMSO-d_6/CD_3OD ampules were used immediately upon opening. NMR spectra were processed with MestReNova software (v. 10.0.2) using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. ^{1}H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Proton chemical shifts (δ) are reported in ppm and referenced to residual solvent peaks for $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm), acetone-d_6 (δ 2.05 ppm), and CD_3OD (δ 3.31 ppm).[1] Proton data are reported as chemical shift, multiplicity (noted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept),

multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc.) coupling constants [Hz], and integration. ^{13}C NMR spectra were obtained on Agilent 400 (100) MHz, 500 (126) MHz, or 600 (150) MHz spectrometers with full proton decoupling. Carbon chemical shifts (δ) are reported in ppm and referenced to residual solvent peaks for $CDCl_3$ (δ 77.16 ppm), DMSO-d_6 (δ 39.52 ppm), acetone-d_6 (δ 29.84 ppm), and CD_3OD (δ 49.00 ppm) with multiplicity and coupling constants [Hz] indicated when present. ^{19}F NMR spectra were obtained on Agilent 400 (376) MHz or 500 (471) MHz spectrometers without proton *decoupling*. Fluorine chemical shifts (δ) are referenced to $CFCl_3$ (δ 0.00 ppm) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, multiplicity, coupling constant [Hz], and integration.

• **Infrared Spectroscopy:** Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select ν_{max} are reported in cm^{-1}.

• **Mass Spectrometry:** Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 mm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI.

• **Optical Rotation:** Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 20 °C and reported as follows: $[\alpha]_{\lambda}^{\text{temp}}$, concentration (*c* in g/100 mL), and solvent.

• **Analytical HPLC:** Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (254 nm) and columns (chiral supports, 5 μm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.

Abbreviations

2-Abz	2-aminobenzoic acid
Ac	acetyl
Acbc	1-aminocyclobutane carboxylic acid
Achc	1-aminocyclohexane carboxylic acid
Acpc	1-aminocyclopropane carboxylic acid
Ahx	6-aminohexanoic acid
Aib	2-aminoisobutyric acid
Aic	2-aminoindane carboxylic acid
aq	aqueous
Aze	(2*S*)-azetidine-2-carboxylic acid
Bn	benzyl
Bz	benzoyl
Boc	*tert*-butoxycarbonyl

^{t}Bu	*tert*-butyl
Cbz	carbobenzyloxy
Chg	cyclohexylglycine
Cle	cycloleucine (1-aminocyclopentane carboxylic acid)
Cl-HOBt	6-chloro-1-hydroxybenzotriazole dihydrate
Cy	cyclohexyl
Dap	2,3-diaminoproprionic acid
DIC	*N,N'*-diisopropylcarbodiimide
de	diastereomeric excess
dr	diastereomeric ratio
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC•HCl hydrochloride	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
Fm	9-fluorenylmethyl
Fmoc	fluorenylmethyloxycarbonyl

FT	Fourier transform
HATU	*O*-(7-aza-1-benzotriazolyl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HCTU	*O*-(6-chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hyp	(2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid
IR	infrared
LCMS	liquid chromatography mass spectrometry
Me	methyl
1-Nal	(2*S*)-2-amino-3-(1-naphthyl)propanoic acid
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
Ph	phenyl
Phg	2-amino-2-phenylacetic acid
Pip	2-piperidinecarboxylic acid
Piv	pivaloyl
^{i}Pr	isopropyl

RP	reversed phase
rt or RT	room temperature
sat	saturated
Tf	trifluoromethanesulfonate or triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl silane
TLC	thin-layer chromatography
TOF	time-of-flight
Trt	triphenylmethyl or trityl
Ts	tosyl
UPLC-MS	ultra-performance liquid chromatography mass spectrometry

Supplementary Text

1. Preparation of OBOC library and procedures for on-bead screening

1.1. Synthesis of on-bead library: The one-bead-one-compound (OBOC) library was prepared *via* solid-phase peptide synthesis (SPPS) followed by previous procedures from the Miller group. Peptide synthesis was performed on Polystyrene A RAM resin (Rapp Polymere, 0.57 mmol/gram, 500–560 m), using the Fmoc protecting group strategy, except the *N*-terminal aspartic acid was coupled with the Boc-Asp(OFm)-OH amino acid monomer. The synthesis of the library began with a certain amount of bead resin, which corresponded to approximately 3 beads per sequence. For each coupling, the resin was divided evenly based on the number of amino acids desired at that position, then recombined for the deprotection (split and pool strategy). When the bead resin was unevenly divided and some of the amino acids were applied more to that position than others, a biased OBOC library can be established (**Table S6**).

Every coupling and deprotection was performed twice to ensure reaction completion. To swell the beads, the resin was suspended in CH_2Cl_2 for 30 minutes prior to the first coupling. A "wash cycle" consisted of suspending the resin in DMF or CH_2Cl_2, then leaving the resin suspended for 30 seconds before filtering. A complete wash cycle contained a wash with DMF and a wash with CH_2Cl_2.

Table S 6. *Design of OBOC library and screening results.*

A. **First generation of biased OBOC library**

Boc–Asp–Xxx———Xxx———Xxx——Ahx–Ahx–●

1	Pro	Acpc	D-Phe	each × 2
	2-Abz	D-Ala	Ala	each × 1
	Aic	Asn(Trt)	Asn(Trt)	
	Asn(Trt)	D-Asp(O^{t}Bu)	Gly	
	Dap(Boc)	Dap(Boc)	Leu	
	D-Hyp(^{t}Bu)	Gly	Lys(Ac)	
	D-Phe	D-Hyp(^{t}Bu)	D-Ser(Bn)	
	Pip	Pro	Thr(^{t}Bu)	
	D-Thr(Bn)	D-Thr(Bn)	D-Val	

results with on-bead catalyst *vs.* solution-phased catalyst

- **reference catalyst (from *ent*-1d):**
  Boc–Asp—Pro———Acpc———D-Phe—Ahx–Ahx–● –18% ee
- **hit catalyst:**
  Boc–Asp—Aic—D-Asp(O^{t}Bu)—Leu—Ahx–Ahx–● 26% ee
  Boc–Asp—D-Phe–D-Asp(O^{t}Bu)-Lys(Ac)–Ahx–Ahx–● 29% ee
- **sequence validation:**
  Boc-D-Asp–D-Pro———Acpc———Phe—OMe **(1d)** 48% ee
  Boc–Asp—Aic—D-Asp(O^{t}Bu)—Leu—OMe 43% ee
  Boc–Asp—D-Phe–D-Asp(O^{t}Bu)-Lys(Ac)–OMe 38% ee

B. **Second generation of biased OBOC library**

Boc–Asp–Xxx———Xxx———Xxx——Ahx–Ahx–●

2	Aic	D-Asp(O^{t}Bu)	Leu	each × 2
	D-Phe		Lys(Ac)	each × 1
	Pro	Aic	Asn(Trt)	
	Achc	Aze	Asp(O^{t}Bu)	
	Acpc	D-Phe	Dap(Boc)	
	1-Nal	D-Pro	1-Nal	
	D-Ser(Bn)	D-Ser(Bn)	D-Phe	
		1-Nal	Ser(Bn)	
		D-Asn(Trt)		
		D-Phg		

results with on-bead catalyst *vs.* solution-phased catalyst

Boc–Asp–Acpc–D-Asp(O^{t}Bu)–Dap(Boc)–Ahx–Ahx–● 39% ee
Boc–Asp—Aic———D-Phe———Dap(Boc)–Ahx–Ahx–● 40% ee

- **sequence validation:**
  Boc–Asp–Acpc–D-Asp(O^{t}Bu)–Dap(Boc)–OMe **(1b)** 50% ee
  Boc–Asp—Aic———D-Phe———Dap(Boc)–OMe **(1c)** 44% ee

• **First generation of biased OBOC library:** From the initial screening, a designed peptide (Boc-D-Asp-D-Pro-Acpc-Phe-OMe, **1d**) provided modest enantioselectivity (~50% ee) for the *N*-oxidation of substrate **2a**. The amino acids from the *i*+1 to *i*+3 positions of this sequence were used for the design of an OBOC biased library. This OBOC library (first generation) contained 729 theoretical sequences, prepared from 200.0 mg of resin (0.114 mmol of total peptide). Residues "Pro", "Acpc", and "D-Phe" were applied twice more than others on each position (Fig. S1A, left table).

• **Second generation of biased OBOC library:** Based on the results from the first OBOC library, this second generation biased library containing 504 theoretical sequences, prepared from 200.0 mg of resin (0.114 mmol of total

peptide). Residues "Aic", "D-Phe", "D-Asp(O*t*Bu)", "Leu", and "Lys(Ac)" were applied twice more than others on each position (**Figure S6**, left table).

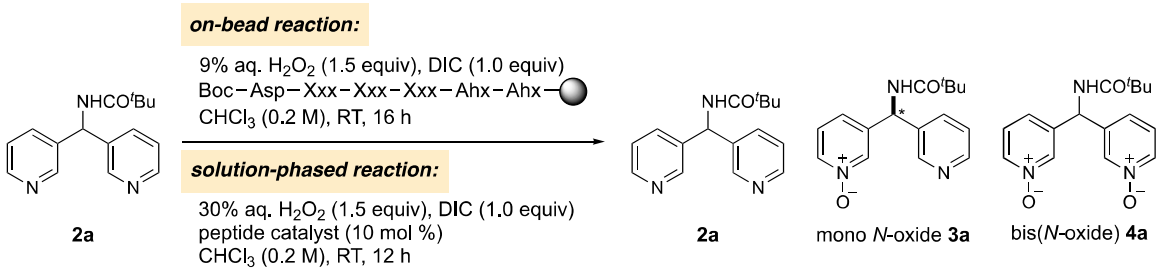
• **Coupling of amino acid:** Each amino acid (5 equiv), HCTU (5 equiv), and Cl-HOBt (5 equiv) were suspended in *N*-methylpyrrolidinone (0.02 M). *N*-methylmorpholine (10 equiv) was added, and the mixture was agitated to homogeneity and aged at room temperature. After 5 min, the mixture was added to the reaction vessel containing the bead resin, which was then gently agitated at room temperature. After 1 h, the resin was filtered, then subjected to 5 complete wash cycles. *Each coupling was conducted twice prior to the next deprotection.*

• **Deprotection of Fmoc group:** The bead resin was suspended in piperidine/DMF (20% v/v, 0.02 M) and gently agitated at room temperature. After 20 min, the resin was filtered and subjected to 5 complete wash cycles. *Each deprotection was conducted twice prior to the next coupling.*

• **Deprotection of Fm group:** This deprotection was followed the same protocol as the Fmoc deprotection, except that the deprotection cycle was conducted 10 min each for 4 times. After filtering, the bead resin was subjected to 5 complete wash cycles and 3 wash cycles with methanol and dried *in vacuo*.

1.2. Pyridine *N*-oxidations with on-bead catalysts or resynthesized catalyst for validation

Table S 7.



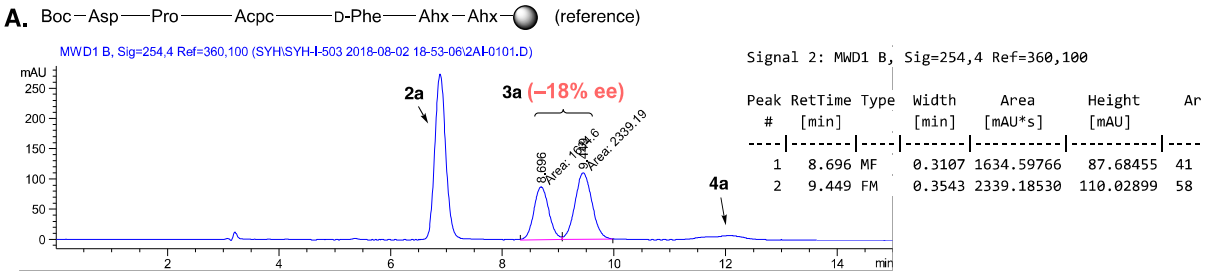
• **On-bead reaction:** Great care was taken to manually deliver each bead (catalyst loading ~0.08 μmol/bead, 0.1 equiv) into a 200 μL glass insert in an HPLC vial, to ensure that each bead was intact and rested on the bottom of the vial insert. H_2O_2 (9% w/w in H_2O, 0.4 μL, 1.20 μmol, 1.5 equiv) was added onto the bottom of the insert, followed by the addition of a solution of substrate **2a** (0.2 mg, 0.8 μmol, 1.0 equiv) and DIC (0.1 μL, 0.8 μmol, 1.0 equiv) in $CHCl_3$ (HPLC grade, 4.0 μL, 0.2 M). The reaction was agitated on an orbital shaker at room temperature for 16 h. Once complete, the solution was diluted with $CHCl_3$ (HPLC grade, 150 μL), then transferred to a 1.0 mL syringe containing a short pad of Na_2SO_3 (~0.4 mL volume) and filtered through a PTFE filter. The filtrate was directly subjected to HPLC analysis.

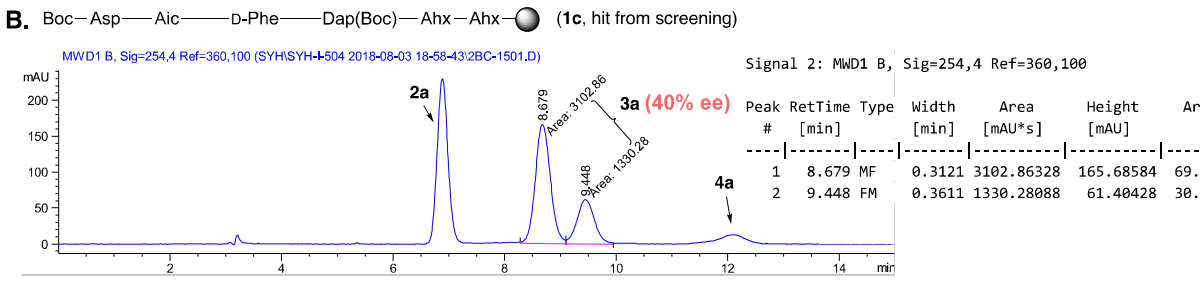
• **Solution-phased reaction** (*to validate the result of the peptide catalyst from screening*)**:** In a HPLC vial, to a solution of substrate **2a** (13.5 mg, 50.0 μmol, 1.0 equiv) and resynthesized peptide catalyst (5.0 μmol, 10 mol %) in $CHCl_3$ (HPLC grade, 250 μL, 0.2 M), H_2O_2 (30% w/w in H_2O, 7.7 μL, 75.0 μmol, 1.5 equiv) and then DIC (7.7 μL, 50.0 μmol, 1.0 equiv) were added. The reaction was stirred at RT vigorously for 12 h before the addition of Na_2SO_3 (~20.0 mg). The mixture was

filtered through a PTFE filter (0.45 μm) rinsed with $CHCl_3$ (HPLC grade, 4 mL), and the filtrate was directly subjected to HPLC analysis.

• **Data analysis:** Substrate **2a**, mono *N*-oxide (both enantiomers) **3a**, and bis(*N*-oxide) **4a** can be separated on Chiralpak® IG column within 15 min (**Table S8**). This is sufficient to screen a great number of reactions in a reasonable time frame. From the known catalyst (Boc-D-Asp-D-Pro-Acpc-Phe-OMe, **1d**), its enantiomeric form ***ent*-1d** was applied to prepare an on-bead catalyst with Ahx-Ahx as a general *C*-terminal linker. This on-bead catalyst was used for the enantioselective *N*-oxidation of substrate **2a**, offering the mono *N*-oxide product **3a** with –18% ee, which can be taken as a *reference*. By screening with OBOC library, any resulting mono *N*-oxide with enantioenrichment greater than 18% ee, or less than –18% ee, indicates such on-bead catalyst utilized is potentially more selective than the *reference*. Even so, this "better" on-bead catalyst (*hit* catalyst) still requires the determination of its sequence and validation of its selectivity in the solution phase.

Table S 8. *Analytical HPLC traces of the reaction mixtrure using (**A**) the reference catalyst and (**B**) a select hit catalyst from the screening of OBOC library.*[a]



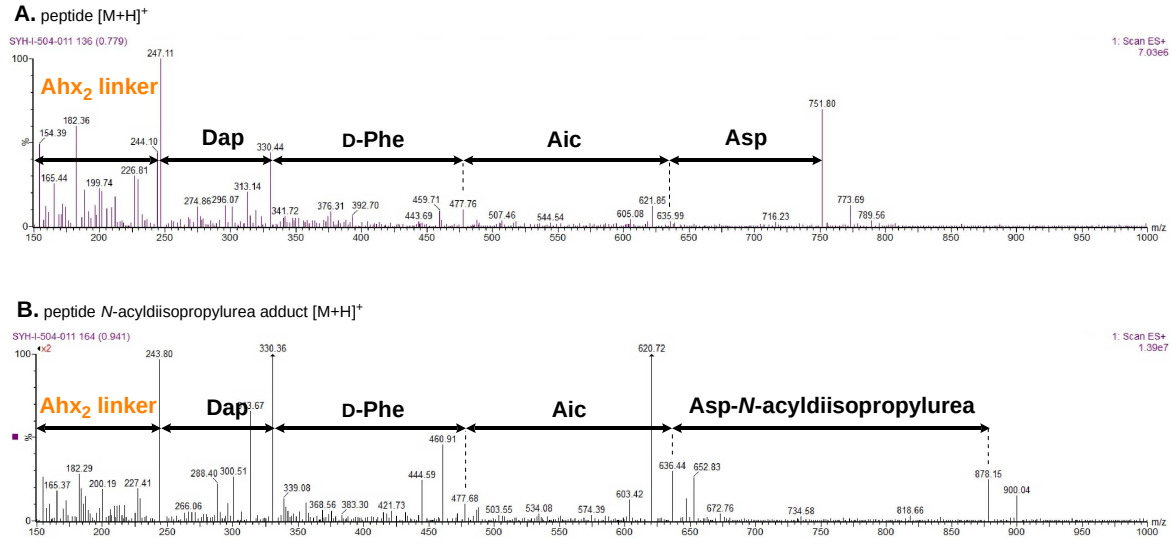


[a]HPLC method: column: Chiralpak® IG; eluent: isocratic 100% EtOH; flow rate: 1.0 mL/min; temperature: 40 °C; monitor detection: 254 nm; retention time: t_R = 6.9 min (substate **2a**), 8.7 min (mono *N*-oxide (*S*)-**3a**), 9.4 min (mono *N*-oxide (*R*)-**3a**), and 12.1 min (bis(*N*-oxide) **4a**).

• **Peptide cleavage:** In the reaction vials, the beads corresponding to *hit* catalysts were washed twice with H_2O, twice with methanol, and dried *in vacuo* for >30 min. The beads were suspended in a mixture of TFA/H_2O/TIPS (v/v/v = 95:2.5:2.5). After 30 min, the cleavage mixtures were carefully transferred to clean, separate vials, and concentrated with a stream of N_2.

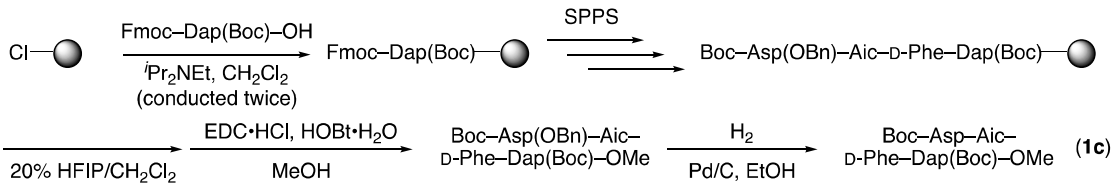
• **Determination of on-bead peptide sequence:** The residue from the peptide cleavage process was dissolved in MeCN (~250 µL) and analyzed by UPLC/MS (cone voltage adjusted to 60–75 V for better fragmentation). In most cases, the chromatograms displayed two prominent ion peaks, corresponding to the $[M+H]^+$ of the protonated peptide (**Table S9a**), as well as the *N*-acyldiisopropylurea adduct that is formed from activation of the aspartate side-chain with DIC, followed by *O*-to-*N* acyl transfer (**Table S9b**).

Table S 9. *Analysis of MS fragments of* hit *catalyst (**1c**) for identifying the peptide sequence.*



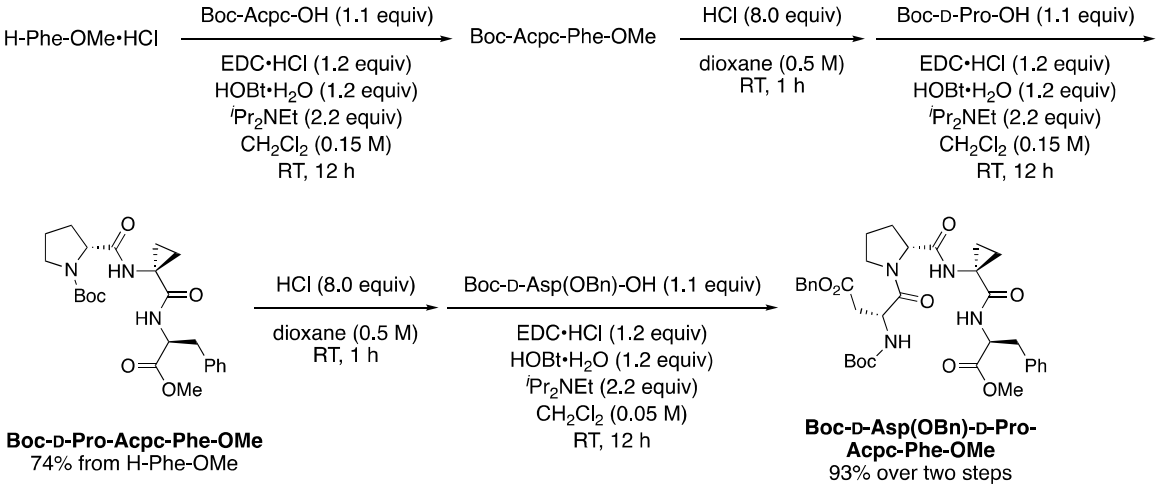
For validation, sequences of interest were resynthesized on 2-chlorotrityl polystyrene resins (**Figure S12**) and subjected to the solution-phased reaction condition described above. Reproduction of the enantiomeric excess from the initial screen was taken as validation of the peptide sequence. However, it was also found that the enhancement of selectivity from the on-bead catalysts (–18% ee *vs.* 40% ee) didn't guarantee the similar effect from the solution-phased catalysts (48% ee *vs.* 44% ee) since a different peptide sequence (Pro *vs.* non-Pro) may lead to distinct interaction between immobilized phase and solution phase. Moreover, with the success from extension and modification on the *i*–1 position of **1d**, a further optimized OBOC library was not performed.

Figure S 12*. Resynthesis of hit peptide sequence, Boc-Asp-Aic-D-Phe-Dap(Boc)-OMe (**1c**).*



Solution phase peptide synthesis of catalysts 1d and 1n

Synthesis of Boc-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe



(a) H-Phe-OMe-HCl (647.0 mg, 3.0 mmol, 1.0 equiv), Boc-Acpc-OH (664.0 mg, 3.3 mmol, 1.1 equiv), EDC•HCl (690.1 mg, 3.6 mmol, 1.2 equiv), and HOBt•H_2O (551.3 mg, 3.6 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20.0 mL, 0.15 M), followed by addition of *i*-Pr_2NEt (1149.7 μL, 6.6 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 12 h, and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc, washed with citric acid (0.5 M *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue (Boc-Acpc-Phe-OMe) was then used directly in the next step without further purification.

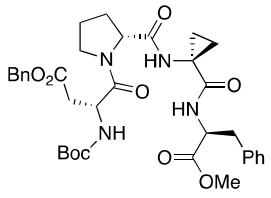
(b) To the peptide residue (Boc-Acpc-Phe-OMe), HCl (4 N in dioxane, 6.0 mL, 24.0 mmol, 8.0 equiv) was added. The reaction was stirred at room temperature for 1 h followed by evaporation *in vacuo* to dryness. The deprotected peptide was used directly without further purification.

(c) The peptide residue (H-Acpc-Phe-OMe•HCl), Boc-D-Pro-OH (710.3 mg, 3.3 mmol, 1.1 equiv), EDC•HCl (690.1 mg, 3.6 mmol, 1.2 equiv), and HOBt•H_2O (551.3 mg, 3.6 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20.0 mL, 0.15 M), followed by addition of *i*-Pr_2NEt (1149.7 μL, 6.6 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 12 h, and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc, washed with citric acid (0.5 M *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 30%–100% MeOH/H_2O over 12 CV) to afford the desired product (Boc-D-Pro-Acpc-Phe-OMe, 1022.6 mg, 74%) as colorless oil.

(d) To the peptide residue (Boc-D-Pro-Acpc-Phe-OMe, 459.5 mg, 1.0 mmol, 1.0 equiv), HCl (4 N in dioxane, 2.0 mL, 24.0 mmol, 8.0 equiv) was added. The reaction was stirred at room temperature for 1 h followed by evaporation *in vacuo* to dryness. The deprotected peptide was used directly without further purification.

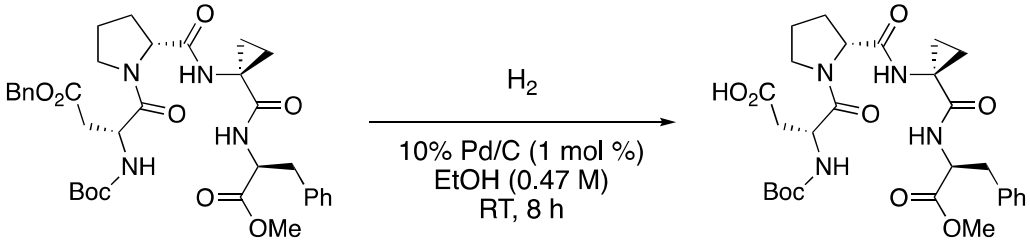
(e) The peptide residue (H-D-Pro-Acpc-Phe-OMe•HCl), Boc-D-Asp(OBn)-OH (355.7 mg, 1.1 mmol, 1.1 equiv), EDC•HCl (230.0 mg, 1.2 mmol, 1.2 equiv), and HOBt•H_2O (183.8 mg, 1.2 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20.0 mL, 0.05 M), followed by addition of *i*Pr_2NEt (383.2 μL, 2.2 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 12 h, and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc, washed with citric acid (0.5 M *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18

25 g; gradient 30%–80% MeOH/H_2O over 12 CV) to afford the desired product (Boc-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe, 617.4 mg, 93%) as colorless oil.



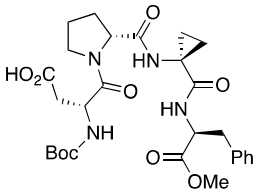
TLC: R_f (10% MeOH/EtOAc) = 0.85; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.54–7.50 (m, 2 H), 7.34–7.16 (m, 10 H), 5.13 (d, *J* = 9.5 Hz, 1 H), 5.06 (dd, *J* = 25.0, 11.5 Hz, 2 H), 4.82 (td, *J* = 10.3, 3.7 Hz, 1 H), 4.67 (q, *J* = 7.4 Hz, 1 H), 4.43 (dd, *J* = 8.6, 4.9 Hz, 1 H), 3.91–3.85 (m, 1 H), 3.82–3.76 (m, 1 H), 3.47 (s, 3 H), 3.29 (dd, *J* = 16.8, 10.8 Hz, 1 H), 3.09 (d, *J* = 7.2 Hz, 2 H), 2.79 (dd, *J* = 16.8, 3.7 Hz, 1 H), 2.32–2.23 (m, 1 H), 2.06–1.91 (m, 3 H), 1.63 (ddd, *J* = 10.1, 7.6, 4.6 Hz, 1 H), 1.42 (s, 9 H), 1.33–1.28 (m, 1 H), 1.03 (ddd, *J* = 10.0, 7.7, 4.7 Hz, 1 H), 0.90 (ddd, *J* = 10.0, 7.6, 4.0 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 172.83, 172.75, 171.9, 171.6, 171.5, 155.0, 136.9, 135.1, 129.5, 128.73, 128.68, 128.59, 128.47, 126.9, 80.8, 67.5, 61.9, 54.7, 51.9, 48.3, 48.1, 38.2, 37.6, 34.2, 29.6, 28.4, 24.9, 17.0, 16.7; **IR** (neat, ν/cm^{-1}) = 1712, 1636, 1499, 1443, 1202, 1164, 731, 700; **HRMS** (ESI, *m*/*z*): calcd for $C_{35}H_{45}N_4O_9$ = 665.3187; found = 665.3165.

2.2. Synthesis of catalyst 1d (Boc-D-Asp-D-Pro-Acpc-Phe-OMe)



Boc-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe

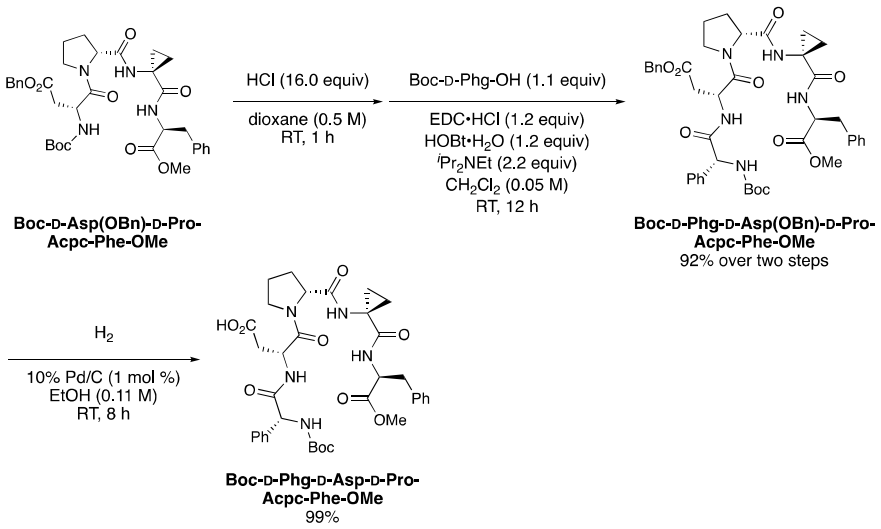
Boc-D-Asp-D-Pro-Acpc-Phe-OMe, 1d
98%



Peptide Boc-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe (617.4 mg, 0.93 mmol, 1.00 equiv) was dissolved in EtOH (2 mL, 0.47 M), followed by the addition of 10% Pd/C (moistened with water, 9.9 mg, 9.3 μmol, 0.01 equiv). The reaction flask was backfilled with H_2 three times, and the reaction was stirred at room temperature for 8 h. The reaction was filtered through a pad of celite and Millipore Millex LCR Hydrophilic PTFE filter (pore size: 0.45 μm, filter diameter: 33 mm, non-sterile) with washing by CH_2Cl_2/EtOH. The filtrate was evaporated *in vacuo* to afford the desired product (523.7 mg, 98%) as a white foamy solid.

TLC: R_f (10% MeOH/EtOAc) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.43 (d, *J* = 6.7 Hz, 1 H), 7.33 (s, 1 H), 7.29–7.18 (m, 5 H), 5.26 (d, *J* = 9.4 Hz, 1 H), 4.82 (td, *J* = 9.4, 4.2 Hz, 1 H), 4.54 (q, *J* = 7.1 Hz, 1 H), 4.39 (dd, *J* = 8.5, 5.0 Hz, 1 H), 4.01 (br, 1 H), 3.87–3.68 (m, 3 H), 3.58 (s, 3 H), 3.16–3.02 (m, 3 H), 2.75 (dd, *J* = 16.2, 4.3 Hz, 1 H), 2.28–2.20 (m, 1 H), 2.01–1.82 (m, 3 H), 1.57–1.50 (m, 1 H), 1.42–1.38 (m, 1 H), 1.41 (s, 9 H), 1.01 (ddd, *J* = 9.9, 7.6, 4.6 Hz, 1 H), 0.92–0.86 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 174.0, 173.8, 172.6, 172.2, 171.5, 155.1, 136.3, 129.4, 128.6, 127.1, 80.7, 61.9, 55.3, 52.6, 48.5, 47.9, 37.6, 37.2, 34.2, 29.7, 28.4, 24.9, 17.3, 17.2; **IR** (neat, ν/cm^{-1}) = 1709, 1633, 1512, 1440, 1203, 1160, 701; **HRMS** (ESI, *m*/*z*): calcd for $C_{29}H_{39}N_4O_9$ = 575.2717; found = 575.2741.

2.3. Synthesis of catalyst 1n (Boc-D-Phg-D-Asp-D-Pro-Acpc-Phe-OMe)

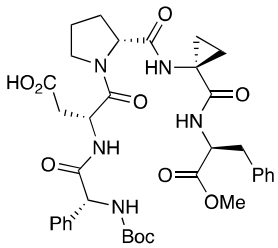


(a) To the peptide residue (Boc-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe, 166.2 mg, 0.25 mmol, 1.0 equiv), HCl (4 N in dioxane, 1.0 mL, 4.0 mmol, 16.0 equiv) was added. The reaction was stirred at room temperature for 1 h followed by evaporation *in vacuo* to dryness. The deprotected peptide was used directly without further purification.

(b) The peptide residue (H-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe), Boc-D-Phg-OH (70.3 mg, 0.28 mmol, 1.1 equiv), EDC•HCl (57.5 mg, 0.3 mmol, 1.2 equiv), and HOBt•H_2O (45.9 mg, 0.28 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20.0 mL, 0.05 M), followed by addition of $^iPr_2NEt$ (66.3 μL, 0.38 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 12 h, and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc, washed with citric acid (0.5 M *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 30%–70% MeCN/H_2O over 12 CV) to afford the desired product

(Boc-D-Phg-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe, 184.5 mg, 92%) as colorless oil.

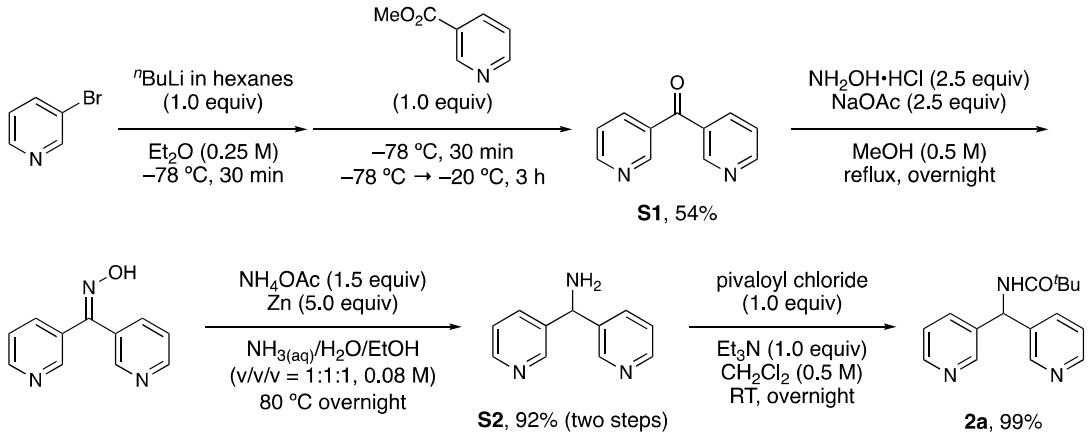
(c) Peptide Boc-D-Phg-D-Asp(OBn)-D-Pro-Acpc-Phe-OMe (184.5 mg, 0.22 mmol, 1.00 equiv) was dissolved in EtOH (2 mL, 0.47 M), followed by the addition of 10% Pd/C (moistened with water, 2.1 mg, 2.2 μmol, 0.01 equiv). The reaction flask was backfilled with H_2 three times, and the reaction was stirred at room temperature for 8 h. The reaction was filtered through a pad of celite and Millipore Millex LCR Hydrophilic PTFE filter (pore size: 0.45 μm, filter diameter: 33 mm, non-sterile) with washing by CH_2Cl_2/EtOH. The filtrate was evaporated *in vacuo* to afford the desired product (154.0 mg, 99%) as a white foamy solid.



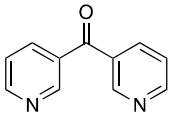
TLC: R_f (10% MeOH/EtOAc) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.40 (d, *J* = 6.9 Hz, 1 H), 7.32–7.19 (m, 9 H), 7.18–7.10 (m, 3 H), 5.57 (s, 1 H), 5.15 (s, 1 H), 5.04 (td, *J* = 8.4, 4.3 Hz, 1 H), 4.55 (q, *J* = 7.0 Hz, 1 H), 4.25 (dd, *J* = 8.4, 5.5 Hz, 1 H), 4.11 (br, 1 H), 3.63 (q, *J* = 4.2 Hz, 2 H), 3.56 (s, 3 H), 3.15–2.94 (m, 3 H), 2.73 (dd, *J* = 15.9, 4.2 Hz, 1 H), 2.24–2.11 (m, 1 H), 1.94–1.78 (m, 3 H), 1.52 (ddd, *J* = 10.1, 7.7, 4.7 Hz, 1 H), 1.42–1.37 (m, 1 H), 1.36 (s, 9 H), 1.00 (ddd, *J* = 10.0, 7.6, 4.7 Hz, 1 H), 0.86 (ddd, *J* = 10.1, 7.7, 4.3 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 174.1, 173.5, 172.5, 171.9, 170.4, 170.2, 155.2, 137.4, 136.2, 129.4, 129.2, 128.7, 128.6, 127.2, 127.1, 80.6, 62.0, 59.1, 55.3, 52.6, 47.9, 47.8, 37.7, 36.5, 34.2, 29.6, 28.4, 24.9, 17.3, 17.2; **IR** (neat, ν/cm^{-1}) = 1633, 1497, 1442, 1203, 1162, 744, 699; **HRMS** (ESI, *m*/*z*): calcd for $C_{36}H_{46}N_5O_{10}$ = 708.3245; found = 708.3261.

3. Synthesis of bis(pyridine) substrates

Synthesis of substrate **2a**



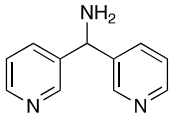
Di(pyridin-3-yl)methanone (S1)



To a dry solution of *n*-BuLi (2.5 M in hexanes; 10.00 mL, 25.0 mmol, 1.0 equiv) in Et_2O (60 mL) at –78 °C under Ar, 3-bromopyridine (2.41 mL, 25.0 mmol, 1.0 equiv) was added dropwise. After the reaction was kept stirred for 30 min at the same temperature, a solution of methyl nicotinate (3.43 g, 25.0 mmol, 1.0 equiv) in dry Et_2O (30 mL) was added slowly. The reaction was kept at –78 °C for another 30 min, and was warmed slowly to –20 °C over 3 h before quenched by 2 N $HCl_{(aq)}$. The mixture was then warmed to room temperature, basified with *sat* $NaHCO_{3\,(aq)}$, and evaporated *in vacuo* to remove the volatile. The residue was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 0%–5% MeOH/CH_2Cl_2) to afford the desired product, which can be further triturated with Et_2O/pentane to obtain a white solid (2.46 g, 54%).

TLC: R_f (5% MeOH/CH_2Cl_2) = 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.98 (d, *J* = 2.1 Hz, 2 H), 8.82 (dd, *J* = 4.8, 1.9 Hz, 2 H), 8.11 (dt, *J* = 7.8, 1.9 Hz, 2 H), 7.46 (dt, *J* = 8.6, 3.3 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.3, 153.6, 150.9, 137.2, 132.4, 123.7; **IR** (neat, ν/cm^{-1}) = 1583, 1418, 1331, 1296, 1195, 1116, 1020, 943, 926, 844, 814, 728, 709, 697, 670, 621, 568, 422, 411; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_9N_2O$ = 185.0714; found = 185.0701.

Di(pyridin-3-yl)methanamine (S2)



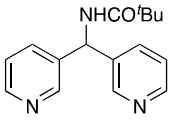
Di(pyridin-3-yl)methanone **S1** (1.84 g, 10.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.66 g, 25.0 mmol, 2.5 equiv), and sodium acetate (anhydrous, 2.05 g, 25.0 mmol, 2.5 equiv) were suspended in MeOH (20 mL, 0.5 M), and the mixture was heated to reflux and stirred overnight. The reaction was cooled to room temperature and MeOH was removed mostly *in vacuo*. After the addition of H_2O, white precipitate (oxime product) was formed, filtered, dried, and collected for the next step without further purification.

The oxime product and ammonium acetate (1.16 g, 15.0 mmol, 1.5 equiv) were suspended in the mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 120 mL, 0.08 M) and the mixture was stirred and heated to 80 °C. At this temperature, Zn (3.27 g, 50.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue

can be further triturated with Et_2O/pentane to obtain the desired amine (1.71 g, 92% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.30; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.65 (d, *J* = 2.3 Hz, 2 H), 8.49 (dd, *J* = 4.8, 1.7 Hz, 2 H), 7.69 (dt, *J* = 7.9, 2.0 Hz, 2 H), 7.24 (dd, *J* = 7.8, 4.7 Hz, 2 H), 5.30 (s, 1 H), 1.79 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 149.0, 148.8, 139.9, 134.5, 123.7, 55.7; **IR** (neat, ν/cm^{-1}) = 3338, 1620, 1588, 1576, 1475, 1418, 1326, 1307, 1024, 912, 832, 794, 779, 708, 668, 641, 624, 568, 443, 414; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_{12}N_3$ = 186.1031; found = 186.1036.

N-(Di(pyridin-3-yl)methyl)pivalamide (2a)

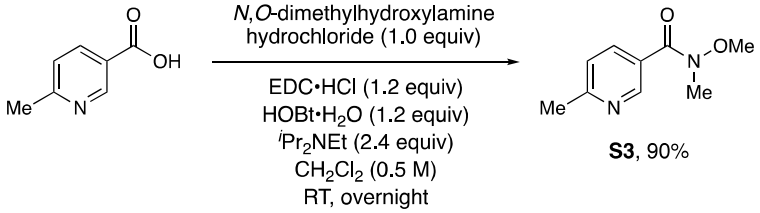


Di(pyridin-3-yl)methanamine **S2** (926.2 mg, 5.0 mmol, 1.0 equiv) and Et_3N (836.9 μL, 6.0 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (10 mL, 0.5 M), followed by slow addition of pivaloyl chloride (615.8 μL, 5.0 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (1.34 g, 99%) as a white solid.

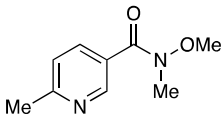
TLC: R_f (EtOAc) = 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.33–8.30 (m, 4 H), 7.35 (dt, *J* = 8.0, 2.1 Hz, 2 H), 7.10 (dt, *J* = 8.0, 4.6 Hz, 2 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 6.15 (d, *J* = 7.8 Hz, 1 H), 1.07 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 148.8, 148.7, 136.1, 134.9, 123.4, 52.6, 38.6, 27.3; **IR** (neat, ν/cm^{-1}) = 3307, 2982, 1636, 1587, 1578, 1516, 1476, 1426, 1365, 1296, 1198, 1022, 853,

815, 801, 787, 772, 723, 707, 649, 622, 600, 569, 493, 469, 427; **HRMS** (ESI, *m/z*): calcd for $C_{16}H_{20}N_3O$ = 270.1606; found = 270.1602.

Synthesis of substrate **2b**



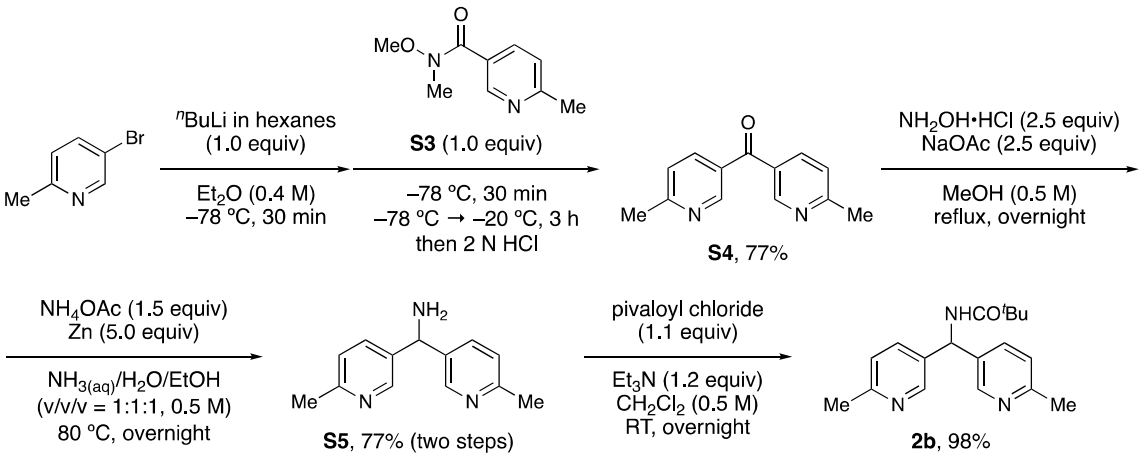
N-Methoxy-*N*,6-dimethylnicotinamide (S3)



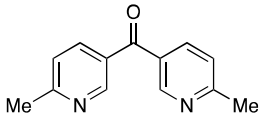
6-Methylnicotinic acid (5.49 g, 40.0 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (3.90 g, 40.0 mmol, 1.0 equiv), EDC•HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 9.20 g, 48.0 mmol, 1.2 equiv), and HOBt•H_2O (1-hydroxybenzotriazole monohydrate, 7.35 g, 48.0 mmol, 1.2 equiv) were mixed in CH_2Cl_2 (80 mL, 0.5 M), followed by the addition of $^{i}Pr_2NEt$ (16.72 mL, 96.0 mmol, 2.4 equiv). The reaction was stirred at room temperature overnight, and evaporated *in vacuo*. The residue was dissolved in EtOAc, and the organic phase was washed with citric acid (10% *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 120 g; gradient 0%–10% EtOAc/hexanes over 2 CV, 10%–60% EtOAc/hexanes over 12 CV, and 60%–100% EtOAc/hexanes over 5 CV) to afford the desired product (6.49 g, 90%) as colorless oil.

TLC: R_f (EtOAc) = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.77 (dd, *J* = 2.3, 0.9 Hz, 1 H), 7.85 (dd, *J* = 8.1, 2.3 Hz, 1 H), 7.12 (d, *J* = 8.1 Hz, 1 H), 3.47 (s, 3 H), 3.28 (s, 3 H), 2.51 (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 167.5,

160.7, 148.8, 136.5, 126.8, 122.4, 61.1, 29.6, 24.4; **IR** (neat, ν/cm^{-1}) = 1633, 1596, 1418, 1381, 1215, 1028, 973, 889, 843, 744, 561, 468; **HRMS** (ESI, *m*/*z*): calcd for $C_9H_{13}N_2O_2$ = 181.0977; found = 181.0968.



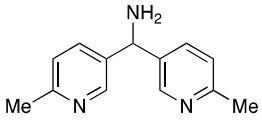
Bis(6-methylpyridin-3-yl)methanone (S4)



To a solution of ^{n}BuLi (2.5 M in hexanes; 15.7 mL, 39.3 mmol, 1.0 equiv) in dry Et$_2$O (100 mL) at –78 °C under N_2, 5-bromo-2-methylpyridine (6.58 g, 39.3 mmol, 1.0 equiv) was added dropwise. After the reaction was kept stirred for 30 min at the same temperature, *N*-methoxy-*N*,6-dimethylnicotinamide **S3** (7.08 g, 39.3 mmol, 1.0 equiv) was added slowly. The reaction was then kept stirring at –78 °C for another 30 min, and was allowed to warm to –20 °C over 3 h before quenched with 2 N $HCl_{(aq)}$. The mixture was warmed to room temperature, basified with *sat* $NaHCO_{3\ (aq)}$, and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 100% EtOAc over 2 CV and 0%–20% MeOH/EtOAc over 15 CV) to afford the desired product (6.38 g, 77%) as a white solid.

TLC: R_f (50% MeOH/EtOAc) = 0.80; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.83 (d, *J* = 2.3 Hz, 2H), 7.97 (dd, *J* = 8.1, 2.3 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 2.61 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.1, 163.3, 150.6, 137.5, 130.0, 123.2, 24.9; **IR** (neat, ν/cm^{-1}) = 1647, 1588, 1374, 1304, 1287, 1226, 1130, 1021, 937, 920, 857, 843, 798, 751, 731, 708, 591, 556, 480, 467, 416, 401; **HRMS** (ESI, *m/z*): calcd for $C_{13}H_{13}N_2O$ = 213.1028; found = 213.1020.

Bis(6-methylpyridin-3-yl)methanamine (S5)



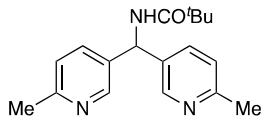
Bis(6-methylpyridin-3-yl)methanone **S4** (6.38 g, 30.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (4.99 g, 75.0 mmol, 2.5 equiv), and sodium acetate (anhydrous, 6.15 g, 75.0 mmol, 2.5 equiv) were suspended in MeOH (60 mL, 0.5 M), and the mixture was heated to reflux and stirred overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. The residue was extracted with CH_2Cl_2 and water, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The oxime product was obtained and subjected to reduction without further purification.

The oxime product and ammonium acetate (3.47 g, 45.0 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 60 mL, 0.5 M) and stirred with heating to 80 °C. At this temperature, Zn powder (9.81 g, 150.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 1.0 M $NaOH_{(aq)}$. The organic

extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 2 CV and 20%–100% MeOH/EtOAc over 15 CV) to afford the desired product (4.93 g, 77%, over two steps) as colorless oil.

TLC: R_f (50% MeOH/EtOAc) = 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.45 (d, *J* = 2.5 Hz, 2 H), 7.49 (dd, *J* = 8.0, 2.5 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 5.17 (s, 1 H), 2.45 (s, 6 H), 1.85 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 157.5, 147.8, 137.1, 134.7, 123.2, 55.1, 24.0; **IR** (neat, ν/cm^{-1}) = 3274, 1595, 1568, 1487, 1445, 1377, 1298, 1133, 1028, 924, 832, 782, 755, 735, 644, 608, 570, 484; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{16}N_3$ = 214.1344; found = 214.1349.

N-(Bis(6-methylpyridin-3-yl)methyl)pivalamide (2b)

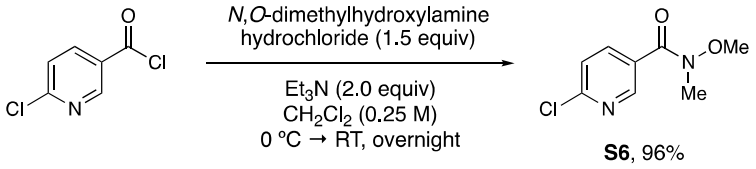


Bis(6-methylpyridin-3-yl)methanamine **S5** (2.13 g, 10.0 mmol, 1.0 equiv) and Et_3N (1.68 mL, 12.0 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20 mL, 0.5 M), followed by slow addition of pivaloyl chloride (2.40 mL, 11.0 mmol, 1.1 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/hexanes to obtain the desired product (2.91 g, 98%) as a white solid.

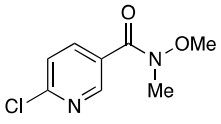
TLC: R_f (10% MeOH/EtOAc) = 0.65; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.36 (t, *J* = 2.4 Hz, 2 H), 7.33 (dt, *J* = 8.0, 2.6 Hz, 2 H), 7.08 (dd, *J* = 8.1, 2.4 Hz, 2 H), 6.21 (d, *J* = 7.5 Hz, 1 H), 6.17 (dd, *J* = 7.5, 2.2 Hz, 1 H), 2.50 (s, 6 H), 1.19

(s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 158.1, 148.1, 135.4, 133.3, 123.3, 52.6, 38.8, 27.6, 24.2; **IR** (neat, ν/cm^{-1}) = 3324, 1631, 1601, 1525, 1491, 1319, 1303, 1204, 1032, 840, 790, 754, 737, 723, 673, 644, 613, 576, 481, 409; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{24}N_3O$ = 298.1919; found = 298.1898.

Synthesis of substrate **S7**

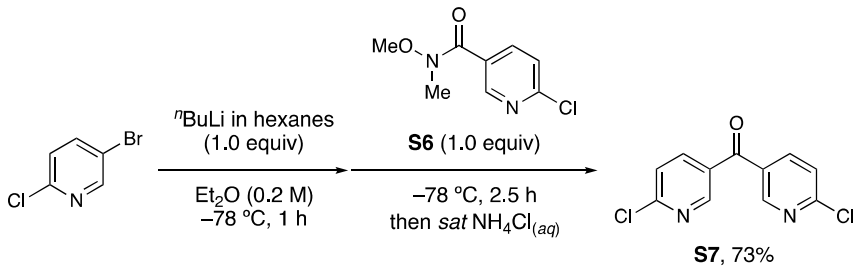


6-Chloro-*N*-methoxy-*N*-methylnicotinamide (S6)

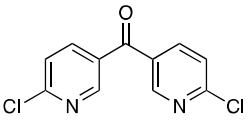


To an ice-cooled solution of 6-chloronicotinoyl chloride (7.04 g, 40.0 mmol, 1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (5.85 g, 60.0 mmol, 1.5 equiv) in CH_2Cl_2 (160 mL, 0.25 M), Et_3N (11.16 mL, 80.0 mmol, 2.0 equiv) was added slowly. The reaction was allowed to warm to room temperature and stir overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 30%–70% EtOAc/hexanes) to afford the desired product (7.70 g, 96%) as colorless oil.

TLC: R_f (70% EtOAc/hexanes) = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.74 (dd, *J* = 2.4, 0.7 Hz, 1 H), 8.00 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.36 (dd, *J* = 8.3, 0.8 Hz, 1 H), 3.54 (s, 3 H), 3.36 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 166.2, 153.4, 149.8, 139.2, 128.6, 123.9, 61.5, 33.2; **IR** (neat, ν/cm^{-1}) = 1638, 1584, 1559, 1454, 1416, 1384, 1359, 1218, 1170, 1138, 1103, 1021, 974, 888, 840, 765, 752, 711, 564, 504, 472, 442, 410; **HRMS** (ESI, *m*/*z*): calcd for $C_8H_{10}{}^{35}ClN_2O_2$ = 201.0431; found = 201.0435.



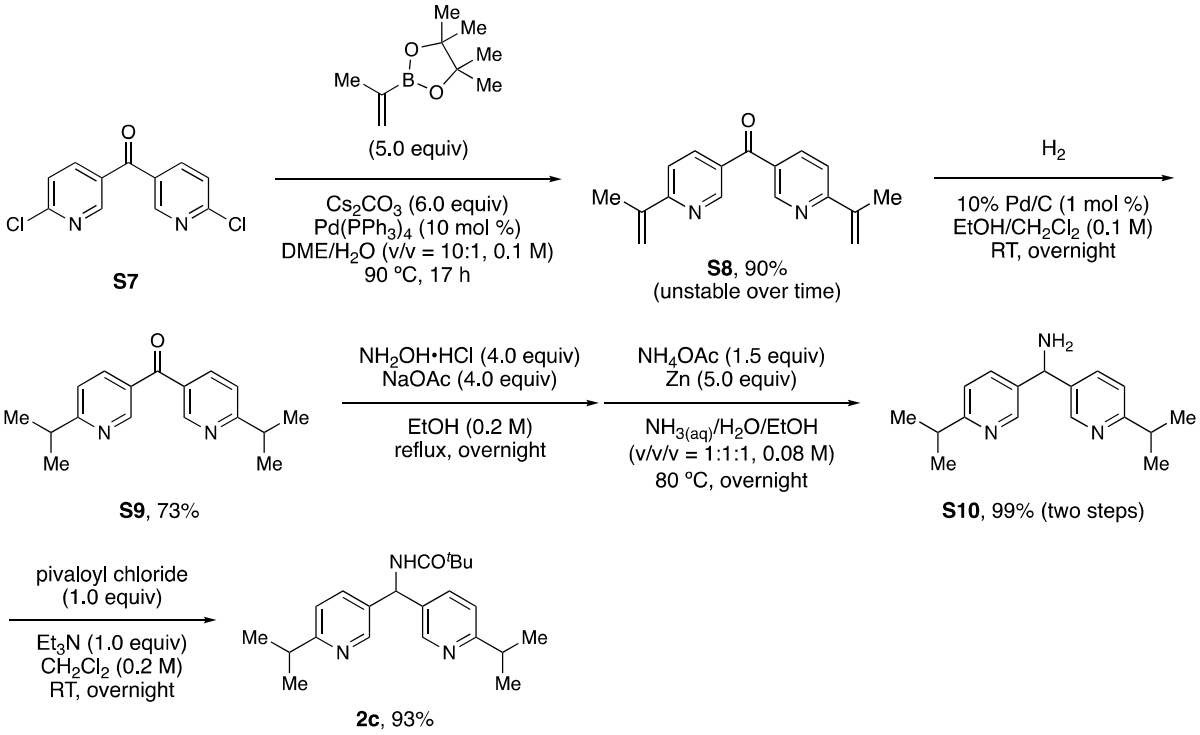
Bis(6-chloropyridin-3-yl)methanone (S7)



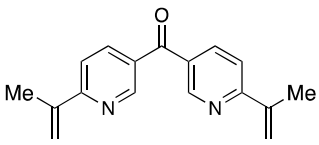
To a dry solution of ^{n}BuLi (2.5 M in hexanes; 12.00 mL, 30.0 mmol, 1.0 equiv) in Et$_2$O (70 mL) at –78 °C under Ar, a solution of 5-bromo-2-chloropyridine (5.77 g, 30.0 mmol, 1.0 equiv) in Et$_2$O (38 mL) was added dropwise. After the reaction was stirred for 1 h at the same temperature, a solution of 6-chloro-*N*-methoxy-*N*-methylnicotinamide **S6** (6.02 g, 30.0 mmol, 1.0 equiv) in dry Et$_2$O (30 mL) was added slowly. The reaction was kept stirring at –78 °C for another 2.5 h before quenched with *sat* NH$_4$Cl$_{(aq)}$. The mixture was then warmed to room temperature, and evaporated *in vacuo* to remove the volatiles, forming a white precipitate. After triturated with H$_2$O/pentane/Et$_2$O, the solid was filtered, dried, and collected for the next step without further purification. The desired product was obtained (5.54 g, 73%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.76 (dd, J = 2.4, 0.8 Hz, 2 H), 8.09 (dd, J = 8.3, 2.4 Hz, 2 H), 7.52 (dd, J = 8.3, 0.8 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 190.8, 156.1, 151.0, 139.6, 131.0, 124.9; **IR** (neat, ν/cm^{-1}) = 1649, 1570, 1547, 1458, 1358, 1299, 1275, 1248, 1144, 1097, 1016, 993, 976, 929, 856, 843, 787, 763, 738, 703, 638, 597, 511, 477, 467; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_6{}^{35}Cl_2N_2O_2$ = 252.9935; found = 252.9935.

Synthesis of substrate **2c**



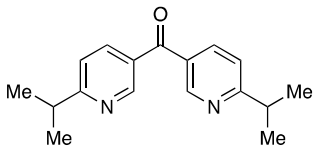
Bis(6-(prop-1-en-2-yl)pyridin-3-yl)methanone (S8)



Bis(6-chloropyridin-3-yl)methanone **S7** (1.01 g, 4.0 mmol, 1.0 equiv), isopropenylboronic acid pinacol ester (3.76 mL, 20.0 mmol, 5.0 equiv), cesium carbonate (7.82 g, 24.0 mmol. 6.0 equiv), and $Pd(PPh_3)_4$ (0.46 g, 0.4 mmol, 0.1 equiv) were mixed in degassed DME/H_2O (v/v = 10:1, 40 mL, 0.1 M) under Ar. The reaction was stirred and heated at 90 °C for 17 h, and then allowed to cool to room temperature, followed by addition of *sat* $NaHCO_{3\,(aq)}$. After evaporation *in vacuo*, the residue was extracted with CH_2Cl_2, and organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 5%–20% EtOAc/hexanes) to afford

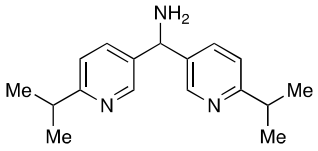
the desired product (937.7 mg, 90%) as a white solid. **TLC**: R_f (20% EtOAc/hexanes) = 0.47. The product was not stable over time, thus further characterization was not performed.

Bis(6-isopropylpyridin-3-yl)methanone (S9)



Bis(6-(prop-1-en-2-yl)pyridin-3-yl)methanone **S8** (793.0 mg, 3.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2/EtOH (v/v =1:1, 30 mL, 0.1 M), followed by the addition of 10% Pd/C (moistened with water, 31.9 mg, 0.3 mmol, 0.1 equiv). The reaction flask was backfilled with H_2 three times, and the reaction was stirred at room temperature overnight. After all the alkene was fully hydrogenated (confirmed by UPLC/MS), the reaction was filtered through a pad of celite and Millipore Millex LCR Hydrophilic PTFE filter (pore size: 0.45 μm, filter diameter: 33 mm, non-sterile) with washing by CH_2Cl_2/EtOH. The filtrate was evaporated *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 (gradient 5%–20% EtOAc/hexanes) to afford the desired product (584.7 mg, 73%) as colorless oil. **TLC**: R_f (20% EtOAc/hexanes) = 0.20; **HRMS** (ESI, *m*/*z*): calcd for $C_{17}H_{21}N_2O$ = 269.1654; found = 269.1664. Further characterization was not collected.

Bis(6-isopropylpyridin-3-yl)methanamine (S10)



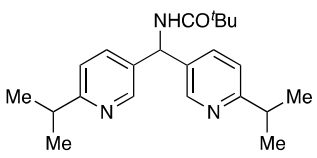
Bis(6-isopropylpyridin-3-yl)methanone **S9** (536.7 mg, 2.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (531.9 mg, 8.0 mmol, 4.0 equiv), and sodium acetate (anhydrous, 656.2 mg, 8.0 mmol, 4.0 equiv) were suspended in EtOH (10 mL, 0.2 M), and the

mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and EtOH was removed mostly *in vacuo*. After the addition of H_2O, white precipitate (oxime product) formed, which was filtered, dried, and collected for the next step without further purification.

The oxime product and ammonium acetate (231.2 mg, 3.0 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 25 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (653.8 mg, 10.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The desired amine was obtained (536.1 mg, 99% over two steps) as a colorless oil without further purification.

TLC: R_f (10% MeOH/EtOAc) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.55 (d, *J* = 2.4 Hz, 2 H), 7.63 (dd, *J* = 8.1, 2.4 Hz, 2 H), 7.14 (dd, *J* = 8.1, 0.8 Hz, 2 H), 5.25 (s, 1 H), 3.04 (hept, *J* = 6.9 Hz, 1 H), 1.85 (br, 2 H), 1.28 (d, *J* = 6.9 Hz, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 166.5, 147.7, 137.3, 134.9, 120.6, 55.2, 36.0, 22.57, 22.56; **IR** (neat, ν/cm^{-1}) = 2962, 2927, 1597, 1567, 1486, 1396, 836; **HRMS** (ESI, *m*/*z*): calcd for $C_{17}H_{24}N_3$ = 270.1970; found = 270.1982

N-(Bis(6-isopropylpyridin-3-yl)methyl)pivalamide (2c)

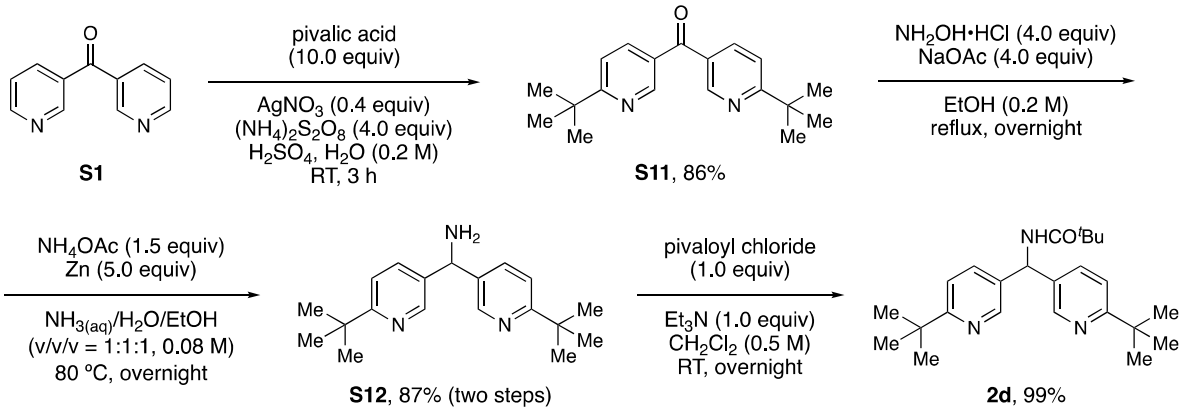


Bis(6-isopropylpyridin-3-yl)methanamine **S10** (484.9 mg, 1.8 mmol, 1.0 equiv) and Et_3N (301.3 μL, 2.2 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (9.0 mL, 0.2 M), followed

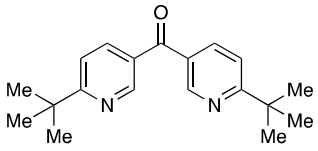
by slow addition of pivaloyl chloride (221.7 μL, 1.2 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (592.5 mg, 93%) as a white solid.

TLC: R_f (30% EtOAc/hexanes) = 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.40 (d, *J* = 2.4 Hz, 2 H), 7.39 (dd, *J* = 8.1, 2.4 Hz, 2 H), 7.13 (dd, *J* = 8.1, 0.8 Hz, 2 H), 6.19 (d, *J* = 7.5 Hz, 2 H), 6.14 (d, *J* = 7.5 Hz, 1 H), 3.03 (hept, *J* = 6.9 Hz, 1 H), 1.27 (d, *J* = 6.9 Hz, 12 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 167.0, 148.0, 135.6, 133.6, 120.8, 52.8, 38.9, 36.1, 27.6, 22.6; **IR** (neat, ν/cm^{-1}) = 3329, 2962, 2930, 2869, 1632, 1601, 1569, 1512, 1488, 1388, 1362, 1325, 1291, 1201, 1063, 1028, 955, 870, 855, 840, 830, 641, 603, 575, 549, 407; **HRMS** (ESI, *m*/*z*): calcd for $C_{22}H_{32}N_3O$ = 354.2545; found = 354.2555.

Synthesis of substrate **2d**



Bis(6-(*tert*-butyl)pyridin-3-yl)methanone (S11)

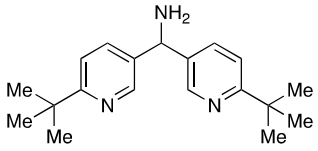


Di(pyridin-3-yl)methanone **S1** (1.11 g, 6.0 mmol. 1.0 equiv), pivalic acid (6.13 g, 60.0 mmol, 10.0 equiv), and silver nitrate (0.41 g, 2.4 mmol, 0.4 equiv) were mixed in 10% $H_2SO_{4\ (aq)}$ (15 mL). To the stirring mixture, a solution of ammonium persulfate (5.48 g, 24.0 mmol, 4.0 equiv) in H_2O (15 mL) was slowly added. The reaction was stirred at room temperature for 3 h, basified with ammonia water solution to pH 9–10, and extracted using CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then dissolved in EtOAc and passed through a pad of SiO_2. The filtrate was evaporated *in vacuo* to afford the desired product (1.52 g, 86%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.95–8.94 (m, 2 H), 8.06 (dd, *J* = 8.3, 2.4 Hz, 2 H), 7.48 (dd, *J* = 8.3, 0.9 Hz, 2 H), 1.40 (s, 18 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.4, 174.0, 150.2, 137.5, 130.0, 119.0, 38.2, 30.1; **IR** (neat, ν/cm^{-1}) = 2958, 2865, 1651, 1590, 1551, 1479,

1464, 1382, 1362, 1282, 1204, 1130, 1031, 1020, 948, 924, 854, 794, 736, 716, 573, 540, 436; **HRMS** (ESI, *m/z*): calcd for $C_{19}H_{25}N_2O$ = 297.1967; found = 297.1966.

Bis(6-(*tert*-butyl)pyridin-3-yl)methanamine (S12)

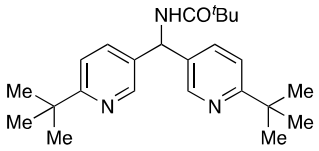


Bis(6-(*tert*-butyl)pyridin-3-yl)methanone **S11** (1.19 g, 4.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.06 g, 16.0 mmol, 4.0 equiv), and sodium acetate (anhydrous, 1.31 g, 16.0 mmol, 4.0 equiv) were suspended in EtOH (20 mL, 0.2 M), and the mixture was heated to reflux and stirred overnight. The reaction was cooled to room temperature and EtOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) formed, which was filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (0.46 g, 6.0 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 50 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (1.31 g, 20.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired amine (1.04 g, 87% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.54 (d, *J* = 2.4 Hz, 2 H), 7.62 (dd, *J* = 8.3, 2.4 Hz, 2 H), 7.28 (dd, *J* = 8.3, 0.8 Hz, 2 H), 5.23 (s, 1 H), 1.73 (br, 2 H), 1.32 (s, 18 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 168.5, 147.5, 136.9, 134.7, 119.1, 55.2, 37.3, 30.3; **IR** (neat, ν/cm^{-1}) = 2962, 2902, 2863, 1594, 1563, 1484, 1460, 1393, 1359, 1313, 1285, 1201, 1148, 1129, 1121, 1059, 1021, 911, 875, 852, 822, 801, 780, 704, 637, 595, 581, 563, 497; **HRMS** (ESI, *m*/*z*): calcd for $C_{19}H_{28}N_3$ = 298.2283; found = 298.2298.

N-(Bis(6-(*tert*-butyl)pyridin-3-yl)methyl)pivalamide (2d)

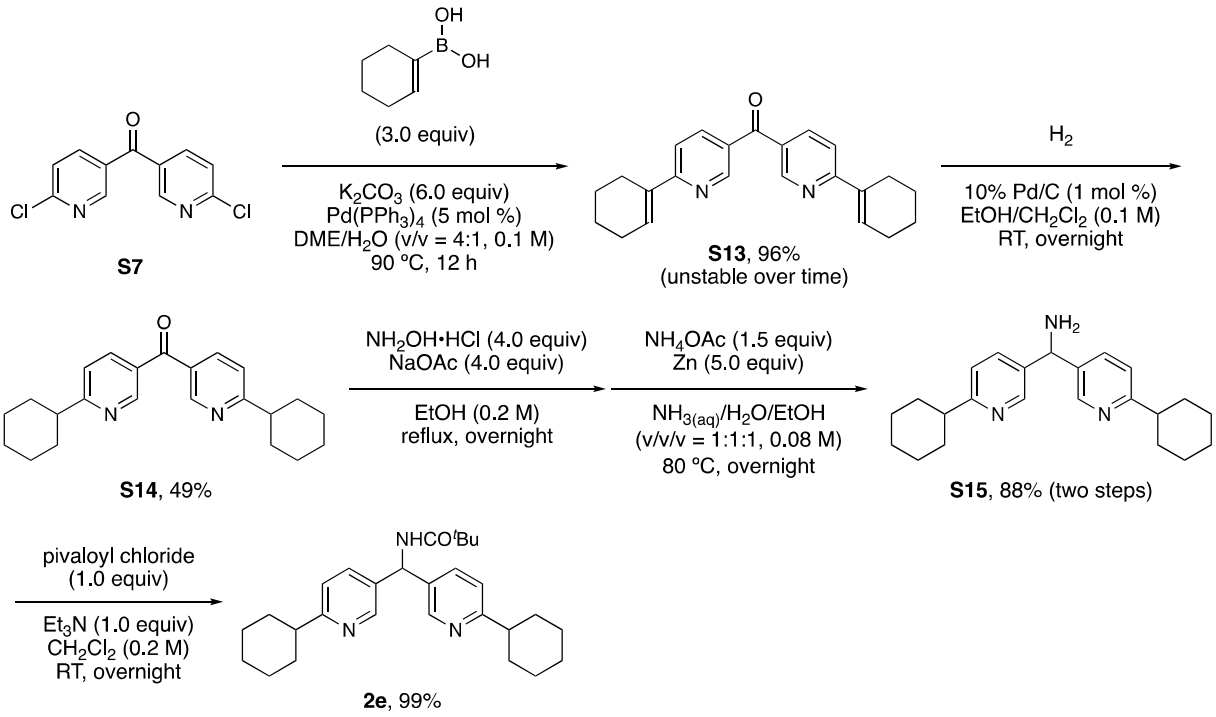


Bis(6-(*tert*-butyl)pyridin-3-yl)methanamine **S12** (594.9 mg, 2.0 mmol, 1.0 equiv) and Et_3N (334.7 μL, 2.4 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (9 mL, 0.2 M), followed by slow addition of pivaloyl chloride (246.3 μL, 2.0 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (752.6 mg, 99%) as a white solid.

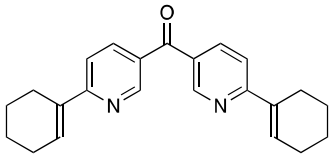
TLC: R_f (30% EtOAc/hexanes) = 0.30; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.42 (d, *J* = 2.4 Hz, 2 H), 7.41 (dd, *J* = 8.2, 2.5 Hz, 2 H), 7.30 (dd, *J* = 8.3, 0.8 Hz, 2 H), 6.21 (d, *J* = 7.4 Hz, 1 H), 6.15 (d, *J* = 7.5 Hz, 1 H), 1.33 (s, 18 H), 1.22 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 169.0, 147.5, 135.4, 133.2, 119.3, 52.8, 38.9, 37.4, 30.3, 27.7; **IR** (neat, ν/cm^{-1}) = 3318, 2960, 2903, 2868, 1638, 1600, 1559, 1521, 1486, 1394, 1364, 1329, 1297, 1284, 1202, 1127, 1028,

874, 860, 836, 790, 716, 706, 638, 607, 582, 558, 544, 432; **HRMS** (ESI, *m*/*z*): calcd for $C_{24}H_{36}N_3O$ = 382.2858; found = 382.2855.

Synthesis of substrate **2e**



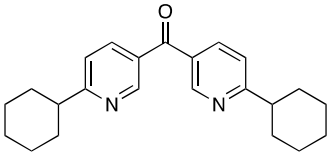
Bis(6-(cyclohex-1-en-1-yl)pyridin-3-yl)methanone (S13)



Bis(6-chloropyridin-3-yl)methanone **S7** (1.01 g, 4.0 mmol, 1.0 equiv), cyclohex-1-en-1-ylboronic acid (1.51 g, 12.0 mmol, 3.0 equiv), potassium carbonate (3.32 g, 24.0 mmol. 6.0 equiv), and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol, 0.05 equiv) were mixed in degassed DME/H_2O (v/v = 4:1, 40 mL, 0.1 M) under Ar. The reaction was stirred and heated at 90 °C for 12 h, and then allowed to cool to room temperature, followed by addition of *sat* $NaHCO_{3\,(aq)}$. After evaporation *in vacuo*, the residue was extracted with CH_2Cl_2, and the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 5%–15% EtOAc/hexanes) to afford the desired product (1.32 g, 96%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.27. The product was not stable over time, thus further characterization was not performed.

Bis(6-cyclohexylpyridin-3-yl)methanone (S14)

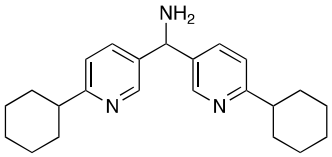


Bis(6-(cyclohex-1-en-1-yl)pyridin-3-yl)methanone **S13** (1.03 g, 3.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2/EtOH (v/v =1:1, 30 mL, 0.1 M), followed by the addition of 10% Pd/C (moistened with water, 31.9 mg, 0.3 mmol, 0.1 equiv). The reaction flask was backfilled with H_2 three times, and the reaction was stirred at room temperature overnight. After all of the alkene was fully hydrogenated (confirmed by UPLC/MS), the reaction was filtered through a pad of celite and Millipore Millex LCR Hydrophilic PTFE filter (pore size: 0.45 μm, filter diameter: 33 mm, non-sterile) with washing by CH_2Cl_2/EtOH. The filtrate was evaporated *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 (gradient 5%–15% EtOAc/hexanes) to afford the desired product (514.0 mg, 49%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.90 (d, *J* = 2.3 Hz, 2 H), 8.02 (dd, *J* = 8.2, 2.3 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 2.78 (tt, *J* = 12.0, 3.3 Hz, 2 H), 1.96 (apparent d, *J* = 11.4 Hz, 4 H), 1.86 (apparent d, *J* = 13.1 Hz, 4 H), 1.74 (apparent d, *J* = 12.3 Hz, 2 H), 1.54 (apparent q, *J* = 12.6 Hz, 4 H), 1.41 (apparent qt, *J* = 13.0, 3.2 Hz, 4 H), 1.27 (apparent qt, *J* = 15.7, 3.0 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.3, 171.1, 150.6, 137.7, 130.4, 121.0, 46.9, 32.8, 26.5, 26.1; **IR** (neat, ν/cm^{-1}) = 2917, 2848, 1640, 1585, 1555, 1446, 1389, 1296, 1282, 1147, 1003, 956, 927, 893, 850, 841, 829, 791, 760,

721, 666, 632, 532, 522, 506; **HRMS** (ESI, *m/z*): calcd for $C_{23}H_{29}N_2O$ = 349.2280; found = 349.2286.

Bis(6-cyclohexylpyridin-3-yl)methanamine (S15)



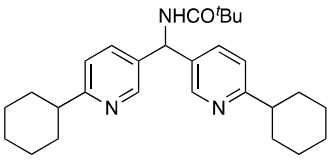
Bis(6-cyclohexylpyridin-3-yl)methanone **S14** (348.5 mg, 1.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (266.0 mg, 4.0 mmol, 4.0 equiv), and sodium acetate (anhydrous, 328.1 mg, 4.0 mmol, 4.0 equiv) were suspended in EtOH (5 mL, 0.2 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and EtOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) formed, which was filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (115.6 mg, 3.0 mmol, 1.5 equiv) were suspended in the mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 12.5 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (326.9 mg, 5.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remaining liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further

triturated with Et_2O/pentane to obtain the desired amine (307.9 mg, 88% over two steps) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.37; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.52 (d, *J* = 2.4 Hz, 2 H), 7.59 (dd, *J* = 8.1, 2.4 Hz, 2 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 5.21 (s, 1 H), 2.65 (tt, *J* = 11.9, 3.4 Hz, 2 H), 1.90 (dd, *J* = 13.2, 2.1 Hz, 4 H), 1.82 (dt, *J* = 13.0, 3.3 Hz, 4 H), 1.73–1.68 (m, 2 H), 1.73 (br, 2 H), 1.47 (qd, *J* = 12.4, 2.9 Hz, 4 H), 1.37 (qt, *J* = 12.8, 3.2 Hz, 4 H), 1.24 (qt, *J* = 12.6, 3.5 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 165.8, 147.9, 137.4, 134.9, 121.0, 55.3, 46.3, 33.04, 33.02, 26.7, 26.2; **IR** (neat, ν/cm^{-1}) = 3368, 3270, 2917, 2847, 1594, 1564, 1482, 1447, 1396, 1335, 1309, 1173, 1138, 1054, 1021, 1003, 894, 871, 850, 835, 818, 801, 773, 754, 672, 652, 642, 619, 587, 537, 515, 439; **HRMS** (ESI, *m*/*z*): calcd for $C_{23}H_{32}N_3$ = 349.2596; found = 349.2596.

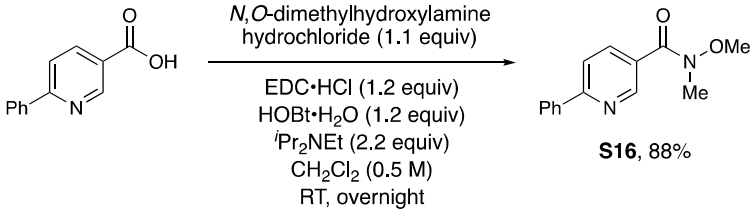
N-(Bis(6-cyclohexylpyridin-3-yl)methyl)pivalamide (2e)



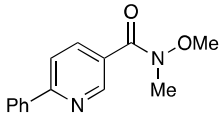
Bis(6-cyclohexylpyridin-3-yl)methanamine **S15** (209.7 mg, 0.6 mmol, 1.0 equiv) and Et_3N (100.4 μL, 0.6 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (9.0 mL, 0.2 M), followed by slow addition of pivaloyl chloride (73.9 μL, 0.7 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (258.0 mg, 99%) as a white solid.

TLC: R_f (30% EtOAc/hexanes) = 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.39 (d, *J* = 2.4 Hz, 2 H), 7.37 (dd, *J* = 8.1, 2.4 Hz, 2 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 6.18 (d, *J* = 7.4 Hz, 1 H), 6.13 (d, *J* = 7.4 Hz, 1 H), 2.66 (tt, *J* = 11.9, 3.4 Hz, 2 H), 1.90 (apparent d, *J* = 10.6 Hz, 4 H), 1.83 (dt, *J* = 13.0, 3.3 Hz, 4 H), 1.72 (apparent d, *J* = 12.8 Hz, 2 H), 1.48 (qd, *J* = 12.4, 3.0 Hz, 4 H), 1.38 (qt, *J* = 12.8, 3.1 Hz, 4 H), 1.29–1.22 (m, 2 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 166.2, 148.0, 135.5, 133.6, 121.2, 52.8, 46.3, 38.9, 33.0, 27.6, 26.6, 26.1; **IR** (neat, ν/cm^{-1}) = 3334, 2921, 2851, 1635, 1598, 1567, 1512, 1483, 1461, 1446, 1408, 1399, 1366, 1323, 1225, 1198, 1074, 1028, 1002, 954, 864, 849, 827, 778, 744, 654, 645, 602, 578, 549, 528, 419, 410; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{40}N_3O$ = 434.3171; found = 434.3194.

Synthesis of substrate **2f**



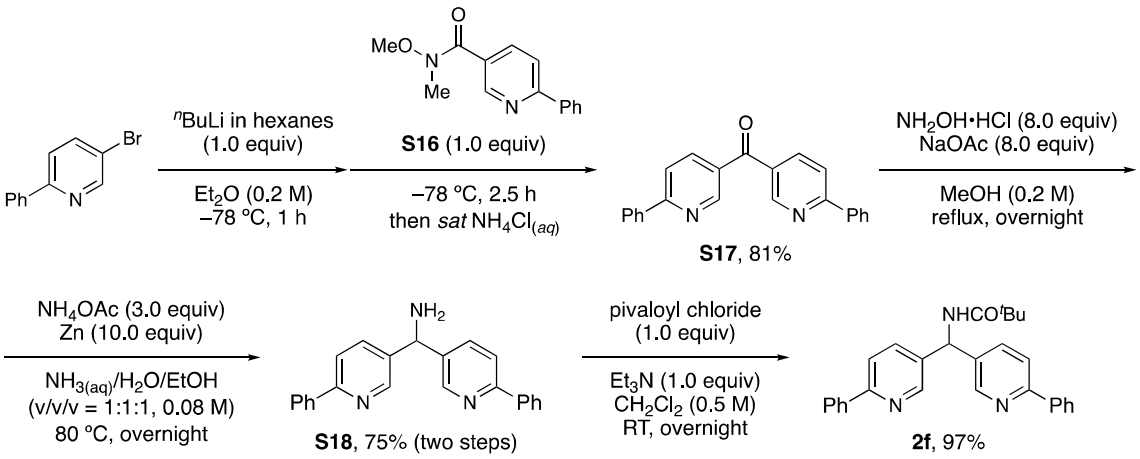
N-Methoxy-*N*-methyl-6-phenylnicotinamide (S16)



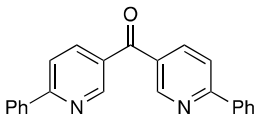
6-Phenylnicotinic acid (1.00 g, 5.0 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (0.54 g, 5.5 mmol, 1.1 equiv), EDC•HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 1.15 g, 6.0 mmol, 1.2 equiv), and HOBt•H_2O (1-hydroxybenzotriazole monohydrate, 0.92 g, 6.0 mmol, 1.2 equiv) were mixed in CH_2Cl_2 (10 mL, 0.5 M), followed by the addition of $^{i}Pr_2NEt$ (1.92 mL, 11.0 mmol, 2.2 equiv). The reaction was stirred at room temperature overnight and evaporated *in vacuo*. The residue was dissolved in EtOAc, and the organic phase was washed with *sat* $NaHCO_{3\,(aq)}$ and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 60 g; gradient 30%–60% MeCN/H_2O over 10 CV, 60%–100% MeCN/H_2O over 2 CV, and 100% MeCN over 2 CV) to afford the desired product (1.06 g, 88%) as colorless oil.

TLC: R_f (30% EtOAc/hexanes) = 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 9.04 (d, *J* = 2.5 Hz, 1 H), 8.10 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.03 (d, *J* = 7.0 Hz, 2 H), 7.77 (dd, *J* = 8.2, 2.6 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.45–7.41 (m, 1 H), 3.58 (s, 3 H), 3.39 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 167.5, 159.0, 149.5,

138.5, 137.3, 129.7, 128.9, 128.0, 127.2, 119.6, 61.4, 33.3; **IR** (neat, ν/cm^{-1}) = 1634, 1589, 1555, 1461, 1445, 1416, 1381, 1295, 1272, 1237, 1217, 1181, 1072, 1020, 974, 889, 849, 793, 772, 743, 692, 644, 574, 531, 406; **HRMS** (ESI, *m*/*z*): calcd for $C_{14}H_{15}N_2O_2$ = 243.1134; found = 243.1136.



Bis(6-phenylpyridin-3-yl)methanone (S17)

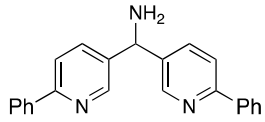


To a solution of 5-bromo-2-phenylpyridine (1.03 g, 4.4 mmol, 1.0 equiv) in dry Et_2O (15 mL) at –78 °C under Ar, ^{n}BuLi (2.5 M in hexanes; 1.75 mL, 4.4 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred for 1 h at the same temperature, a solution of *N*-methoxy-*N*-methyl-6-phenylnicotinamide **S16** (1.06 g, 4.4 mmol, 1.0 equiv) in dry Et_2O (5 mL) was added slowly. The reaction was then kept stirring at –78 °C for another 2.5 h before quenched with *sat* $NH_4Cl_{(aq)}$. The mixture was warmed to room temperature, and evaporated *in vacuo* to remove the volatiles, forming a white precipitate. After triturated with H_2O/pentane/Et_2O, the solid was filtered, dried,

and collected for use in the next step without further purification. The desired product was obtained (1.20 g, 81%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 9.14 (d, *J* = 2.2 Hz, 2 H), 8.25 (dd, *J* = 8.3, 2.2 Hz, 2 H), 8.11 (d, *J* = 7.3 Hz, 4 H), 7.92 (d, *J* = 8.3 Hz, 2 H), 7.55–7.48 (m, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 192.9, 161.0, 151.2, 138.21, 138.19, 130.9, 130.3, 129.1, 127.6, 120.2; **IR** (neat, ν/cm^{-1}) = 1634, 1585, 1552, 1466, 1445, 1367, 1300, 1288, 1269, 1144, 1073, 1017, 956, 928, 853, 843, 783, 738, 713, 685, 586, 544, 431, 414; **HRMS** (ESI, *m*/*z*): calcd for $C_{23}H_{17}N_2O$ = 337.1341; found = 337.1359.

Bis(6-phenylpyridin-3-yl)methanamine (S18)



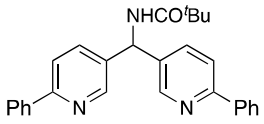
Bis(6-phenylpyridin-3-yl)methanone **S17** (1.20 g, 3.6 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.90 g, 28.6 mmol, 8.0 equiv), and sodium acetate (anhydrous, 2.34 g, 28.6 mmol, 8.0 equiv) were suspended in MeOH (7.2 mL, 0.5 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) was formed, filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (0.83 g, 10.7 mmol, 3.0 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 45 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (2.33 g, 35.7 mmol, 10.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the

mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired amine (903.7 mg, 75% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.76 (d, *J* = 2.2 Hz, 2 H), 7.98–7.96 (m, 4 H), 7.79 (dd, *J* = 8.3, 2.3 Hz, 2 H), 7.70 (dd, *J* = 8.3, 0.9 Hz, 2 H), 7.48–7.44 (m, 4 H), 7.42–7.39 (m, 2 H), 5.37 (s, 1 H), 1.84 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 156.8, 148.6, 139.1, 138.4, 135.3, 129.1, 128.9, 127.0, 120.6, 55.3; **IR** (neat, ν/cm^{-1}) = 3369, 3274, 3065, 1592, 1559, 1471, 1446, 1390, 1314, 1294, 1185, 1157, 1133, 1072, 1060, 1021, 940, 920, 889, 860, 833, 809, 783, 746, 738, 727, 699, 686, 654, 644, 634, 611, 588, 549, 518, 498, 461; **HRMS** (ESI, *m*/*z*): calcd for $C_{23}H_{20}N_3$ = 338.1657; found = 338.1680.

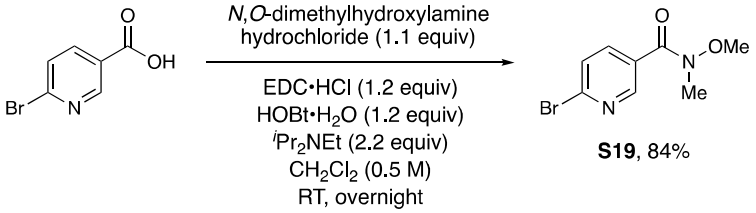
N-(Bis(6-phenylpyridin-3-yl)methyl)pivalamide (2f)



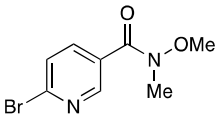
Bis(6-phenylpyridin-3-yl)methanamine **S18** (809.8 mg, 2.4 mmol, 1.0 equiv) and Et_3N (401.7 μL, 2.9 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (12 mL, 0.2 M), followed by slow addition of pivaloyl chloride (295.6 μL, 2.4 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (977.8 mg, 97%) as a white solid.

TLC: R_f (30% EtOAc/hexanes) = 0.23; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.64 (d, *J* = 2.3 Hz, 2 H), 7.99–7.97 (m, 4 H), 7.71 (d, *J* = 8.2 Hz, 2 H), 7.58 (dd, *J* = 8.2, 2.3 Hz, 2 H), 7.49–7.46 (m, 4 H), 7.44–7.40 (m, 2 H), 6.36 (d, *J* = 7.5 Hz, 1 H), 6.31 (d, *J* = 7.5 Hz, 1 H), 1.27 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.9, 157.2, 148.7, 138.8, 136.0, 134.6, 129.3, 128.9, 127.0, 120.6, 52.8, 39.0, 27.7; **IR** (neat, ν/cm^{-1}) = 1645, 1596, 1561, 1510, 1475, 1447, 1400, 1376, 1318, 1293, 1223, 1191, 1147, 1074, 1018, 921, 854, 840, 783, 738, 689, 638, 588, 542, 487; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{28}N_3O$ = 422.2232; found = 422.2246.

Synthesis of intermediates **S19–S21**



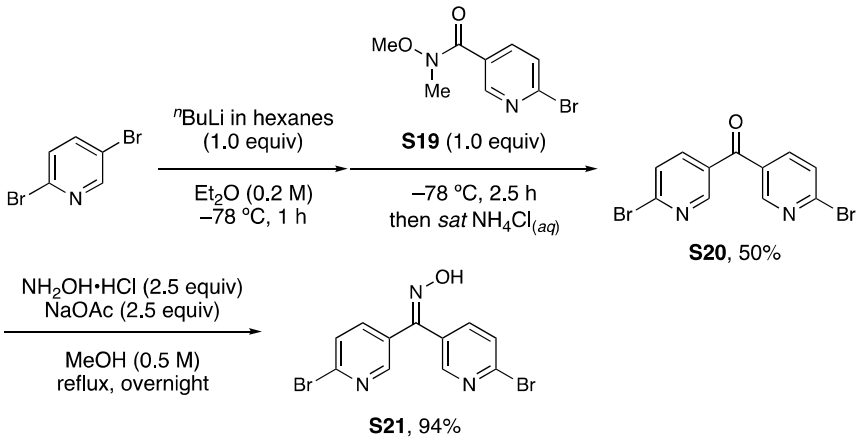
6-Bromo-*N*-methoxy-*N*-methylnicotinamide (S19)



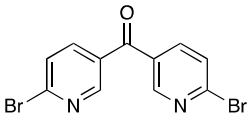
6-Bromonicotinic acid (8.08 g, 40.0 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (4.29 g, 44.0 mmol, 1.1 equiv), EDC•HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 9.20 g, 48.0 mmol, 1.2 equiv), and HOBt•H_2O (1-hydroxybenzotriazole monohydrate, 7.35 g, 48.0 mmol, 1.2 equiv) were mixed in CH_2Cl_2 (80 mL, 0.5 M), followed by the addition of ^{i}Pr$_2$NEt (15.33 mL, 88.0 mmol, 2.2 equiv). The reaction was stirred at room temperature overnight and evaporated *in vacuo*. The residue was dissolved in EtOAc, and the organic phase was washed with *sat* $NaHCO_{3\,(aq)}$ and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (gradient 10%–40% EtOAc/hexanes) to afford the desired product (8.25 g, 84%) as colorless oil.

TLC: R_f (50% EtOAc/hexanes) = 0.47; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.68 (d, J = 2.4 Hz, 1 H), 7.86 (dd, J = 8.3, 2.4 Hz, 1 H), 7.51 (d, J = 8.3 Hz, 1 H), 3.51 (s, 3 H), 3.33 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 166.2, 150.0, 144.2, 138.7, 128.9, 127.6, 61.4, 33.1; **IR** (neat, ν/cm^{-1}) = 1637, 1575, 1554, 1447, 1415, 1383, 1356, 1283, 1217, 1169, 1085, 1019, 973, 886, 838, 746, 709, 655, 625,

562, 460, 406; **HRMS** (ESI, *m*/*z*): calcd for $C_8H_{10}{}^{79}BrN_2O_2$ = 244.9926; found = 244.9934.



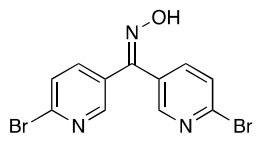
Bis(6-bromopyridin-3-yl)methanone (S20)



To a dry solution of *n*BuLi (2.5 M in hexanes; 8.00 mL, 20.0 mmol, 1.0 equiv) in Et_2O (52 mL) at –78 °C under Ar, a solution of 5-bromo-2-chloropyridine (4.74 g, 20.0 mmol, 1.0 equiv) in Et_2O (30 mL) was added dropwise. After the reaction was stirred for 1 h at the same temperature, a solution of 6-bromo-*N*-methoxy-*N*-methylnicotinamide **S19** (4.90 g, 30.0 mmol, 1.0 equiv) in dry Et_2O (10 mL) was added slowly. The reaction was kept stirring at –78 °C for another 2.5 h before quenched with *sat* $NH_4Cl_{(aq)}$. The mixture was then warmed to room temperature and evaporated *in vacuo* to remove the volatiles, forming a white precipitate. After triturated with H_2O/pentane/Et_2O, the solid was filtered, dried, and collected for the next step without further purification. The desired product was obtained (3.42 g, 50%) as a yellowish solid.

TLC: R_f (10% EtOAc/hexanes) = 0.23; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.72 (dd, *J* = 2.5, 0.8 Hz, 2 H), 7.97 (dd, *J* = 8.2, 2.5 Hz, 2 H), 7.69 (dd, *J* = 8.2, 0.8 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 191.2, 151.2, 147.4, 139.1, 131.3, 128.7; **IR** (neat, ν/cm^{-1}) = 1658, 1567, 1545, 1458, 1361, 1305, 1276, 1241, 1082, 1016, 947, 926, 852, 839, 771, 760, 735, 719, 698, 633, 584, 492, 480, 438, 429, 404; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_7{}^{79}Br_2N_2O$ = 340.8925; found = 340.8933.

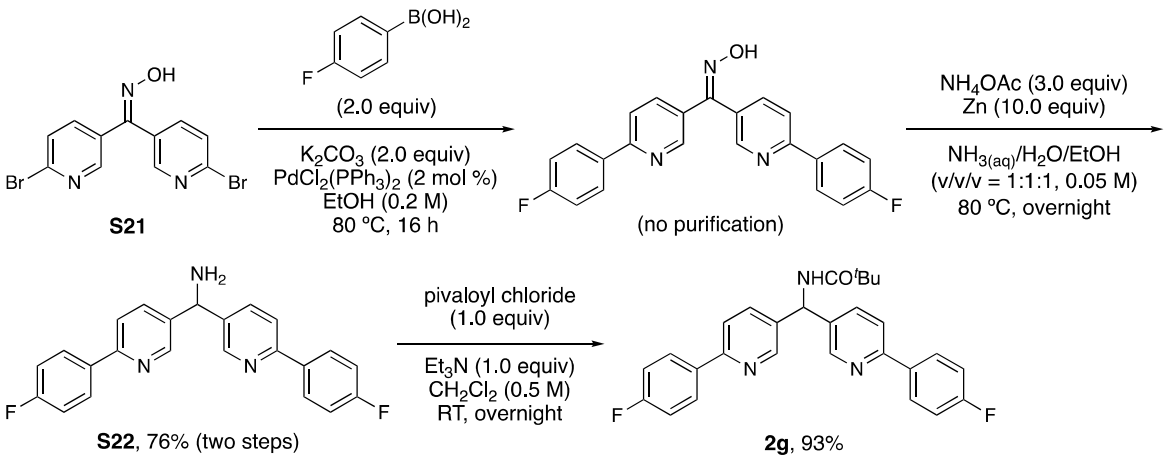
Bis(6-bromopyridin-3-yl)methanone oxime (S21)



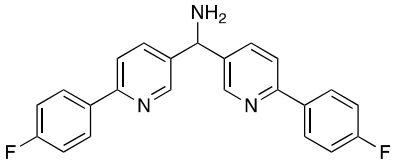
Bis(6-bromopyridin-3-yl)methanone **S20** (2.05 g, 6.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.16 g, 15.0 mmol, 2.5 equiv), and sodium acetate (anhydrous, 0.98 g, 15.0 mmol, 2.5 equiv) were suspended in MeOH (12 mL, 0.5 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. After the addition of H_2O, a precipitate was formed, filtered, dried, and collected. The desired product was obtained (2.01 g, 94%) as a yellowish solid and can be used without further purification.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.43; **^{1}H NMR** (500 MHz, acetone-d_6) δ [ppm] = 11.37 (br, 1 H), 8.48 (dd, *J* = 2.4, 0.8 Hz, 1 H), 8.45 (dd, *J* = 2.5, 0.8 Hz, 1 H), 7.83 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.80 (dd, *J* = 8.4, 2.7 Hz, 1 H), 7.77 (dd, *J* = 8.3, 0.8 Hz, 1 H), 7.63 (dd, *J* = 8.3, 0.8 Hz, 1 H); **^{13}C NMR** (126 MHz, acetone-d_6) δ [ppm] = 151.4, 150.7, 149.5, 143.2, 143.0, 140.7, 138.2, 132.5, 128.9, 128.8, 128.4; **IR** (neat, ν/cm^{-1}) = 3178, 1572, 1548, 1452, 1351, 1309, 1287, 1086, 1024, 996, 937, 922, 833, 774, 741, 735, 634, 622, 605, 516, 483, 446, 413; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_8{}^{79}Br_2N_3O$ = 355.9034; found = 355.9044.

Synthesis of substrate **2g**



Bis(6-(4-fluorophenyl)pyridin-3-yl)methanamine (S22)



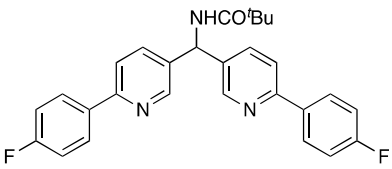
Bis(6-bromopyridin-3-yl)methanone oxime **S21** (428.4 mg, 1.2 mmol, 1.0 equiv), (4-fluorophenyl)boronic acid (335.8 mg, 2.4 mmol, 2.0 equiv), potassium carbonate (331.7 mg, 2.4 mmol. 2.0 equiv), and $PdCl_2(PPh_3)_2$ (16.9 mg, 2.4 μmol, 2 mol %) were mixed in degassed EtOH (6 mL, 0.2 M) under Ar. The reaction was stirred and heated at 80 °C for 16 h, and then allowed to cool to room temperature, followed by addition of *sat* $NaHCO_{3\,(aq)}$. H_2O/pentane was added, and the precipitate was filtered, dried, and collected to afford the bisaryl substituted oxime product. Due to low solubility, it was used directly without further purification.

The bisaryl substituted oxime product and ammonium acetate (277.5 mg, 3.6 mmol, 3.0 equiv) were then suspended in the mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 24 mL, 0.05 M) and stirred with heating to 80 °C.

At this temperature, Zn (784.6 mg, 12.0 mmol, 10.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite, with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired amine (341.1 mg, 76% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.73 (d, *J* = 2.3 Hz, 2 H), 7.98–7.92 (m, 4 H), 7.79 (dd, *J* = 8.2, 2.3 Hz, 2 H), 7.64 (dd, *J* = 8.2, 0.8 Hz, 2 H), 7.16–7.11 (m, 4 H), 5.38 (s, 1 H), 1.84 (br, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 164.9, 162.4, 155.8, 148.6, 138.4, 135.4, 135.2 (d, *J* = 3.2 Hz), 128.7 (d, *J* = 8.3 Hz), 120.3, 115.8 (d, *J* = 21.7 Hz), 55.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ [ppm] = –112.94 (tt, *J* = 8.2, 5.4 Hz); **IR** (neat, ν/cm^{-1}) = 3371, 1597, 1510, 1471, 1416, 1388, 1222, 1159, 1097, 1012, 888, 837, 824, 793, 774, 762, 692, 642, 586, 568, 530, 501, 468, 458; **HRMS** (ESI, *m*/*z*): calcd for $C_{23}H_{18}F_2N_3$ = 374.1469; found = 374.1486.

N-(Bis(6-(4-fluorophenyl)pyridin-3-yl)methyl)pivalamide (2g)

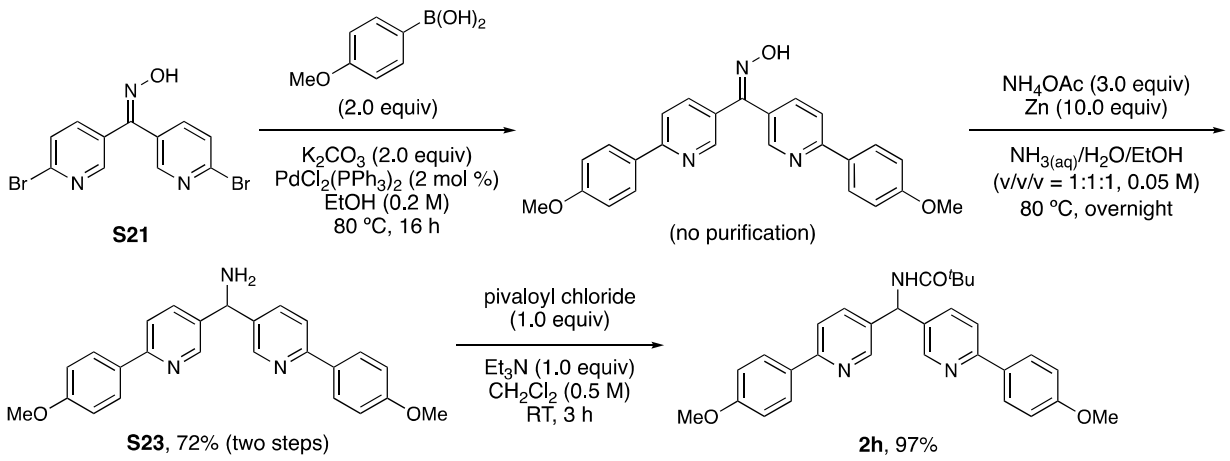


Bis(6-(4-fluorophenyl)pyridin-3-yl)methanamine **S22** (298.7 mg, 0.8 mmol, 1.0 equiv) and Et_3N (133.9 μL, 1.0 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (4 mL, 0.2 M), followed by slow addition of pivaloyl chloride (98.5 μL, 0.8 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the

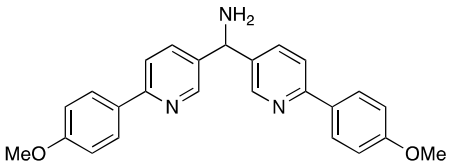
organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (340.7 mg, 93%) as a white solid.

TLC: R_f (30% EtOAc/hexanes) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.60 (d, *J* = 2.3 Hz, 2 H), 7.97–7.93 (m, 4 H), 7.66 (dd, *J* = 8.2, 1.0 Hz, 2 H), 7.57 (dd, *J* = 8.2, 2.3 Hz, 2 H), 7.17–7.11 (m, 4 H), 6.34 (d, *J* = 7.5 Hz, 1 H), 6.30 (d, *J* = 7.5 Hz, 1 H), 1.26 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 177.9, 165.0, 162.5, 156.1, 148.7, 136.0, 134.9 (d, *J* = 3.2 Hz), 134.5, 128.8 (d, *J* = 8.4 Hz), 120.2, 115.9 (d, *J* = 21.6 Hz), 52.8, 39.0, 27.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ [ppm] = –112.50 (tt, *J* = 8.8, 5.4 Hz); **IR** (neat, ν/cm^{-1}) = 3369, 1650, 1512, 1477, 1236, 1224, 1159, 829, 819, 769, 762, 712, 645, 605, 567, 542, 498, 407; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{26}F_2N_3O$ = 458.2044; found = 458.2069.

Synthesis of substrate **2h**



Bis(6-(4-methoxyphenyl)pyridin-3-yl)methanamine (S23)



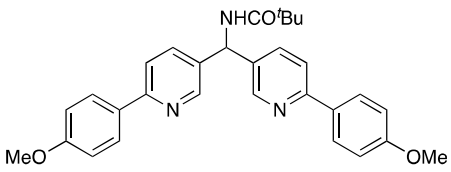
Bis(6-bromopyridin-3-yl)methanone oxime **S21** (214.2 mg, 0.6 mmol, 1.0 equiv), (4-methoxyphenyl)boronic acid (182.4 mg, 1.2 mmol, 2.0 equiv), potassium carbonate (165.8 mg, 1.2 mmol. 2.0 equiv), and $PdCl_2(PPh_3)_2$ (8.4 mg, 2.4 μmol, 2 mol %) were mixed in degassed EtOH (3 mL, 0.2 M) under Ar. The reaction was stirred and heated at 80 °C for 16 h, and then allowed to cool to room temperature, followed by addition of *sat* $NaHCO_{3\,(aq)}$. H_2O/pentane was added, and the precipitate was filtered, dried, and collected to afford the bisaryl substituted oxime product. Due to low solubility, it was used directly without further purification.

The bisaryl substituted oxime product and ammonium acetate (138.7 mg, 1.8 mmol, 3.0 equiv) were then suspended in the mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 12 mL, 0.05 M) and stirred with heating to 80 °C.

At this temperature, Zn (392.3 mg, 6.0 mmol, 10.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite, with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 *N* $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired amine (172.3 mg, 72% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.70 (d, *J* = 2.4 Hz, 2 H), 7.93–7.91 (m, 4 H), 7.74 (dd, *J* = 8.3, 2.4 Hz, 2 H), 7.63 (dd, *J* = 8.3, 0.9 Hz, 2 H), 6.99–6.96 (m, 4 H), 5.34 (s, 1 H), 3.85 (s, 6 H), 1.86 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 160.6, 156.5, 148.4, 137.8, 135.3, 131.7, 128.2, 119.8, 114.2, 55.5, 55.3; **IR** (neat, ν/cm^{-1}) = 3371, 2840, 1605, 1594, 1514, 1473, 1456, 1444, 1391, 1306, 1275, 1244, 1172, 1045, 1020, 833, 816, 788, 772, 763, 690, 641, 577, 538, 468; **HRMS** (ESI, *m*/*z*): calcd for $C_{25}H_{24}N_3O_2$ = 398.1869; found = 398.1886.

N-(bis(6-(4-methoxyphenyl)pyridin-3-yl)methyl)pivalamide (2h)

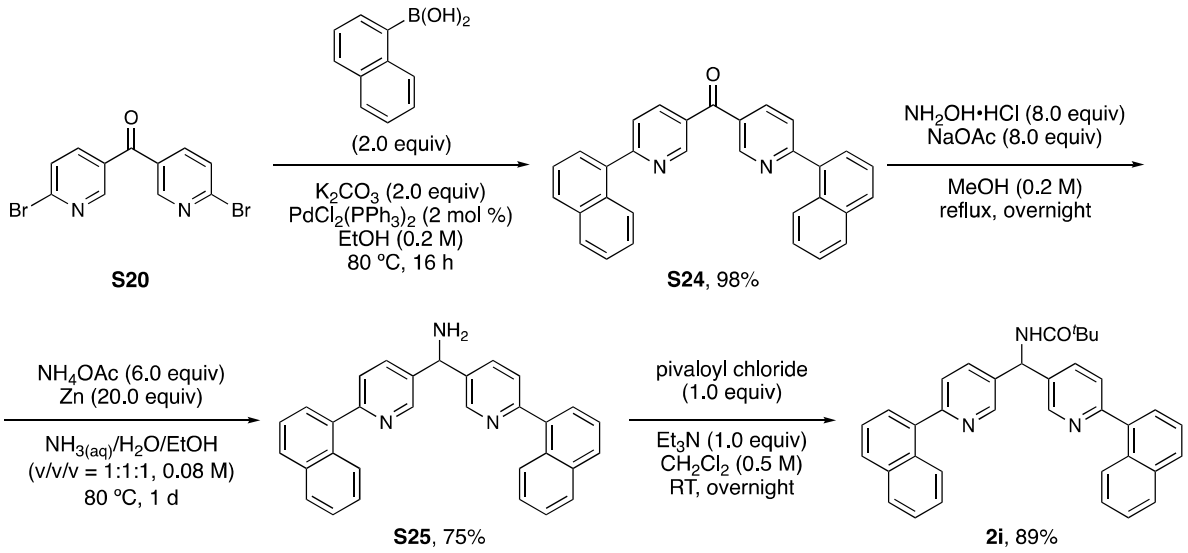


Bis(6-(4-methoxyphenyl)pyridin-3-yl)methanamine **S23** (159.0 mg, 0.4 mmol, 1.0 equiv) and Et_3N (67.0 μL, 0.5 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (2 mL, 0.2 M), followed by slow addition of pivaloyl chloride (47.3 μL, 0.4 mmol, 1.0 equiv). The reaction was stirred at room temperature for 3 h, followed by the addition of *sat* $NaHCO_{3\ (aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in*

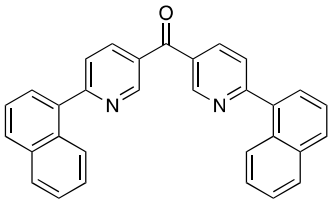
vacuo. The residue can be further triturated with Et_2O/pentane to obtain the desired product (186.8 mg, 97%) as a white solid.

TLC: R_f (50% EtOAc/hexanes) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.57 (d, *J* = 2.3 Hz, 2 H), 7.92 (d, *J* = 8.6 Hz, 4 H), 7.62 (d, *J* = 8.3 Hz, 2 H), 7.51 (dd, *J* = 8.3, 2.3 Hz, 2 H), 6.98 (d, *J* = 8.6 Hz, 4 H), 6.33 (d, *J* = 7.5 Hz, 1 H), 6.30 (d, *J* = 7.5 Hz, 1 H), 3.84 (s, 6 H), 1.25 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.8, 160.7, 156.7, 148.5, 135.9, 133.9, 131.3, 128.2, 119.7, 114.3, 55.4, 52.7, 38.9, 27.6; **IR** (neat, ν/cm^{-1}) = 3368, 2966, 1644, 1608, 1597, 1584, 1510, 1477, 1274, 1253, 1177, 1026, 821, 783, 765, 702, 607, 543, 514, 487; **HRMS** (ESI, *m*/*z*): calcd for $C_{30}H_{32}N_3O_3$ = 482.2444; found = 482.2460.

Synthesis of substrate **2i**



Bis(6-(naphthalen-1-yl)pyridin-3-yl)methanone (S24)

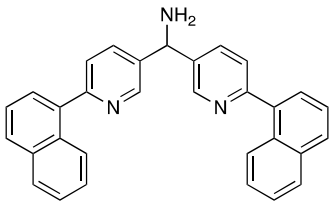


Bis(6-bromopyridin-3-yl)methanone **S20** (1.37 g, 4.0 mmol, 1.0 equiv), naphthalen-1-ylboronic acid (1.38 g, 8.0 mmol, 2.0 equiv), potassium carbonate (1.11 g, 4.0 mmol. 2.0 equiv), and $PdCl_2(PPh_3)_2$ (56.2 mg, 8.0 μmol, 2 mol %) were mixed in degassed EtOH (20 mL, 0.2 M) under Ar. The reaction was stirred and heated at 80 °C for 16 h, and then allowed to cool to room temperature, followed by addition of *sat* $NaHCO_{3\,(aq)}$. H_2O/pentane was added, and the precipitate was filtered, dried, and collected to afford the bis-coupled product (1.71 g, 98%) as a white solid. Due to low solubility, the ketone was used directly without further purification.

TLC: R_f (20% EtOAc/hexanes) = 0.30; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 9.31 (d, *J* = 2.2 Hz, 2 H), 8.37 (dd, *J* = 8.2, 2.2 Hz, 2 H), 8.21–8.18 (m, 2 H), 7.99

(d, J = 8.2 Hz, 2 H), 7.96–7.94 (m, 2 H), 7.83 (d, J = 8.1 Hz, 2 H), 7.72 (dd, J = 7.1, 1.3 Hz, 2 H), 7.61 (dd, J = 8.2, 7.1 Hz, 2 H), 7.56–7.53 (m, 4 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.0, 163.4, 150.9, 137.8, 137.3, 134.1, 130.9, 130.8, 130.0, 128.7, 128.2, 127.1, 126.3, 125.41, 125.35, 125.0; **IR** (neat, ν/cm^{-1}) = 1645, 1586, 1507, 1475, 1296, 1277, 1251, 1120, 1021, 923, 852, 780, 769, 730, 704, 568, 555, 430; **HRMS** (ESI, *m/z*): calcd for $C_{31}H_{21}N_2O$ = 437.1654; found = 437.1660.

Bis(6-phenylpyridin-3-yl)methanamine (S25)



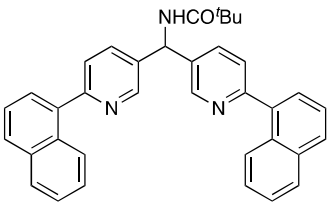
Bis(6-(naphthalen-1-yl)pyridin-3-yl)methanone **S24** (0.87 g, 2.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.06 g, 16.0 mmol, 8.0 equiv), and sodium acetate (anhydrous, 1.31 g, 16.0 mmol, 8.0 equiv) were suspended in EtOH (7.2 mL, 0.5 M), and the mixture was heated to reflux and stirred overnight. The reaction was then cooled to room temperature and EtOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) was formed, filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (0.46 g, 6.0 mmol, 3.0 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 25 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (1.31 g, 35.7 mmol, 10.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred for 12 h at the same temperature. Another portion of ammonium acetate (0.46 g, 6.0 mmol, 3.0 equiv) and Zn (1.31 g, 35.7 mmol, 10.0 equiv, **CAUTION:** slow addition) were added, and the reaction was stirred at 80 °C for another 12 h. After cooling to room temperature, the mixture was filtered through a pad of celite

with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (gradient EtOAc to 0%–10% MeOH/CH_2Cl_2) to afford the desired product (659.1 mg, 75% over two steps) as a white solid.

TLC: R_f (5% MeOH/CH_2Cl_2) = 0.33; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.91 (d, *J* = 2.2 Hz, 2 H), 8.13–8.11 (m, 2 H), 7.95–7.91 (m, 6 H), 7.63–7.60 (m, 4 H), 7.58–7.55 (m, 2 H), 7.53–7.47 (m, 4 H), 5.48 (s, 1 H), 1.98 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 158.6, 148.5, 138.3, 138.2, 135.0, 134.0, 131.2, 129.1, 128.5, 127.6, 126.6, 126.0, 125.6, 125.4, 125.2, 55.5; **IR** (neat, ν/cm^{-1}) = 3044, 1729, 1591, 1556, 1508, 1479, 1388, 1250, 1022, 970, 846, 801, 777, 691, 589, 568, 432; **HRMS** (ESI, *m/z*): calcd for $C_{31}H_{24}N_3$ = 438.1970; found = 438.2005.

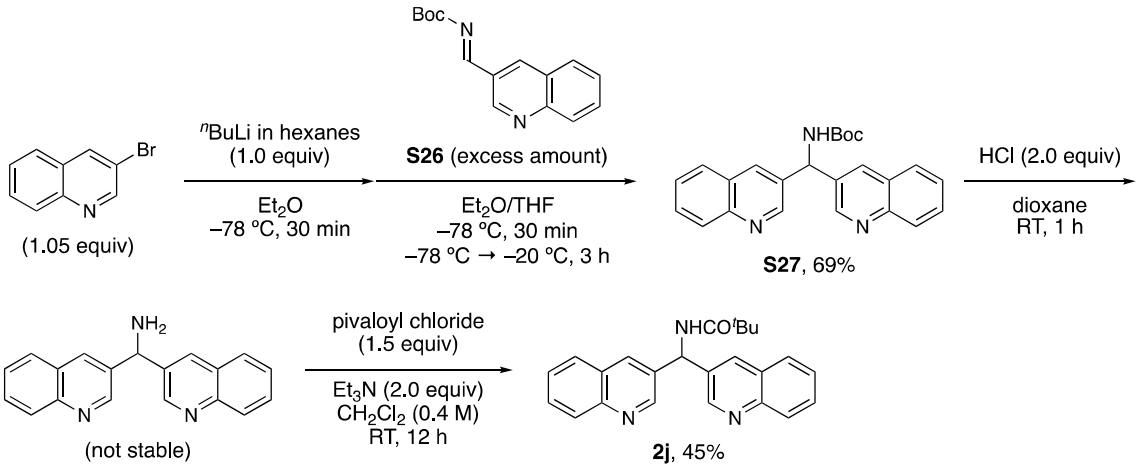
N-(bis(6-(naphthalen-1-yl)pyridin-3-yl)methyl)pivalamide (2i)



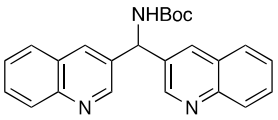
Bis(6-phenylpyridin-3-yl)methanamine **S25** (700.1 mg, 1.6 mmol, 1.0 equiv) and Et_3N (267.8 μL, 1.8 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (8 mL, 0.2 M), followed by slow addition of pivaloyl chloride (197.0 μL, 1.6 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (740.7 mg, 89%) as a white solid.

TLC: R_f (30% EtOAc/hexanes) = 0.17; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.80 (d, *J* = 2.3 Hz, 2 H), 8.14– 8.11 (m, 2 H), 7.96–7.91 (m, 4 H), 7.73 (dd, *J* = 8.1, 2.3 Hz, 2 H), 7.64–7.62 (m, 4 H), 7.57 (dd, *J* = 8.2, 7.1 Hz, 2 H), 7.54–7.48 (m, 4 H), 6.52 (d, *J* = 7.4 Hz, 1 H), 6.43 (d, *J* = 7.4 Hz, 1 H), 1.33 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 178.0, 159.0, 148.6, 137.8, 135.6, 134.5, 134.0, 131.1, 129.3, 128.5, 127.7, 126.7, 126.1, 125.6, 125.4, 125.2, 53.0, 39.1, 27.7; **IR** (neat, ν/cm^{-1}) = 3299, 2970, 1634, 1596, 1556, 1509, 1481, 1387, 1207, 1026, 972, 857, 801, 776, 738, 699, 645, 620, 569, 501, 441; **HRMS** (ESI, *m/z*): calcd for $C_{36}H_{32}N_3O$ = 522.2545; found = 522.2559.

Synthesis of substrate **2j**



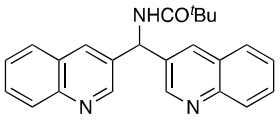
tert-Butyl (di(quinolin-3-yl)methyl)carbamate (S27)



To a 250 mL round bottom flask equipped with a stir bar, the 3-bromoquinoline (1.71 mL, 12.6 mmol, 1.05 equiv), was slowly added into a solution of ^{n}BuLi (2.5 *M* in hexanes; 4.8 mL, 12.0 mmol, 1.0 equiv) in dry Et_2O (100 mL) at –78 °C under N_2. The reaction mixture was stirred for 30 min followed by slow addition of a solution of *tert*-butyl (*E*)-(quinolin-3-ylmethylene)carbamate **S26** (excess amount, prepared on 20.0 mmol scale by literature procedure[3] and used directly) in dry THF (20 mL). The reaction was stirred at –78 °C for another 30 min, and then warmed slowly to –20 °C over 3 h before quenched with water (50 mL). The reaction mixture was then extracted with CH_2Cl_2, the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25g; gradient 0%–20% EtOAc/hexanes over 2 CV, 20–100% EtOAc/hexanes over 20 CV) to afford the desired product (3.20 g, 69%) as a white solid.

TLC: R_f (EtOAc) = 0.65; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.87 (d, *J* = 2.3 Hz, 2 H), 8.08 (dd, *J* = 8.5, 1.2 Hz, 2 H), 7.95 (apparent s, 2 H), 7.72–7.66 (m, 4 H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 2 H), 6.37 (br, 1 H), 5.82 (d, *J* = 7.9 Hz, 1 H), 1.44 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 155.1, 150.3, 147.6, 134.1, 133.7, 129.9, 129.3, 127.9, 127.7, 127.3, 80.8, 54.9, 28.4; **IR** (neat, ν/cm^{-1}) = 1705, 1501, 1160, 916, 795, 750, 734; **HRMS** (ESI, *m/z*): calcd for $C_{24}H_{24}N_3O_2$ = 386.1869; found = 386.1846.

N-(di(quinolin-3-yl)methyl)pivalamide (2j)

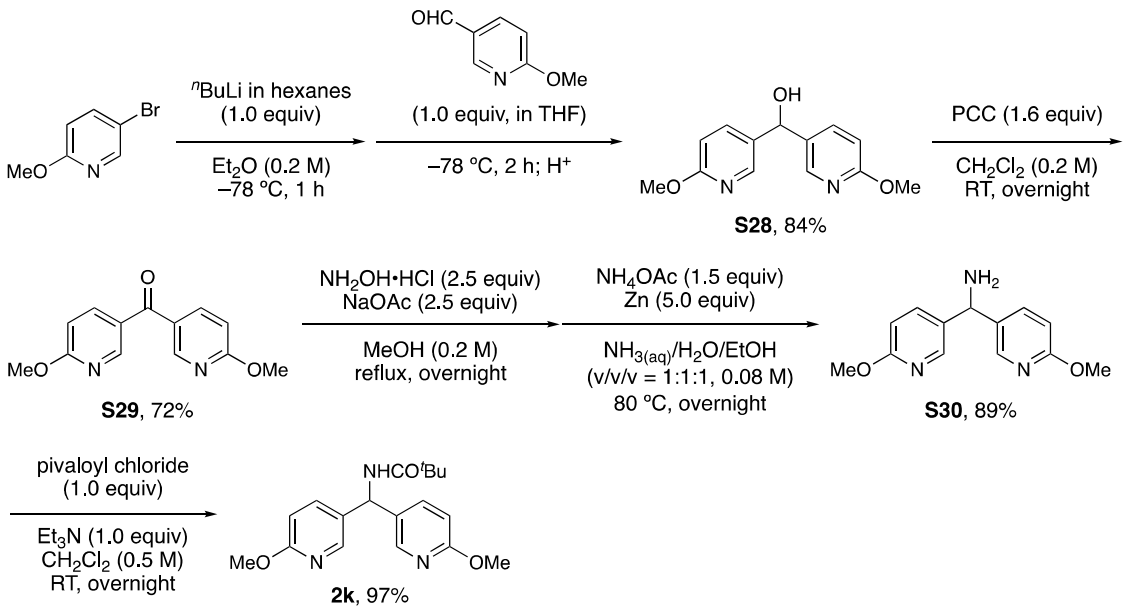


To a 100 mL round bottom flask equipped with a stir bar, *tert*-butyl (di(quinolin-3-yl)methyl)carbamate **S27** (3.20 g, 8.3 mmol, 1.0 equiv) and then HCl (16.6 mL, 66.4 mmol, 4 M in dioxane, 2.0 equiv) were added. The resulting mixture was allowed to stir for 1 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20.0 mL) and cooled in an ice bath. While stirring, Et_3N (2.33 mL, 16.8 mmol, 2.0 equiv) was added, followed by slow addition of pivaloyl chloride (1.51 mL, 12.5 mmol, 1.5 equiv). The reaction was allowed to stir at room temperature for 12 h, then quenched by 2 M $NaOH_{(aq)}$, and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The desired product can be further recrystallized with hexanes/EtOAc and obtained as a white solid (1.38 g, 45%).

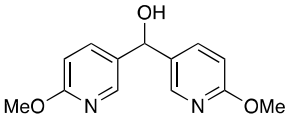
TLC: R_f (EtOAc) = 0.60; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.92 (d, *J* = 2.3 Hz, 2 H), 8.13 (d, *J* = 8.8 Hz, 2 H), 7.93 (d, *J* = 2.3 Hz, 2 H), 7.74 (td, *J* = 7.4, 1.5 Hz, 4 H), 7.57 (td, *J* = 7.4, 6.9, 1.5 Hz, 2 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* =

7.6 Hz, 1 H), 1.29 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.9, 150.2, 147.9, 134.4, 133.3, 130.1, 129.5, 128.0, 127.7, 127.5, 53.4, 39.1, 27.7; **IR** (neat, ν/cm^{-1}) = 1632, 1495, 1192, 785, 751, 614, 474, 401; **HRMS** (ESI, *m*/*z*): calcd for $C_{24}H_{24}N_3O$ = 370.1919; found = 370.1935.

Synthesis of substrate **2k**



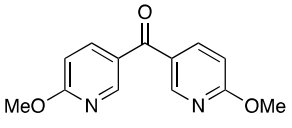
Bis(6-methoxypyridin-3-yl)methanol (S28)



To a dry solution of ^{n}BuLi (2.5 M in hexanes; 10.00 mL, 25.0 mmol, 1.0 equiv) in Et_2O (110 mL) at –78 °C under Ar, 5-bromo-2-methoxypyridine (3.01 mL, 25.0 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred for 1 h at the same temperature, a solution of 6-methoxynicotinaldehyde (3.43 g, 25.0 mmol, 1.0 equiv) in dry THF (5 mL) was added slowly. The reaction was kept stirring at –78 °C for another 2 h before quenched with 2 N $HCl_{(aq)}$. The mixture was then warmed to room temperature, basified with *sat* $NaHCO_{3\,(aq)}$, and evaporated *in vacuo* to remove the volatiles. The residue was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 0%–5% MeOH/CH_2Cl_2) to afford the desired product (5.17 g, 84%) as colorless oil.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.40; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.08 (d, *J* = 2.4 Hz, 2 H), 7.50 (dd, *J* = 8.6, 2.4 Hz, 2 H), 6.68 (dd, *J* = 8.6, 0.8 Hz, 2 H), 5.74 (s, 1 H), 3.89 (s, 6 H), 3.33 (br, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 163.9, 145.0, 137.4, 131.9, 111.1, 71.4, 53.7; **IR** (neat, ν/cm^{-1}) = 3341, 2947, 1605, 1572, 1488, 1461, 1378, 1314, 1280, 1192, 1123, 1019, 927, 828, 785, 759, 652, 630, 600, 519, 466, 411; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{15}N_2O_3$ = 247.1083; found = 247.1099.

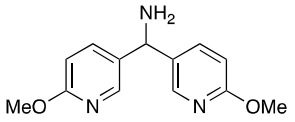
Bis(6-methoxypyridin-3-yl)methanone (S29)



To a solution of bis(6-methoxypyridin-3-yl)methanol **S28** (4.93 g, 20.0 mmol. 1.0 equiv) in CH_2Cl_2 (100 mL, 0.2 M), PCC (pyridinium chlorochromate, 6.90 g, 32.0 mmol, 1.6 equiv) was added portionwise. The reaction was stirred at room temperature overnight, followed by addition of celite (~10 g). The mixture was stirred for another hour, filtered through a pad of SiO_2 with eluent of CH_2Cl_2 and EtOAc/hexanes (0%–10%). The filtrate was evaporated *in vacuo* to afford the desired ketone product (3.53 g, 72%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.61 (s, 2 H), 8.06 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 4.02 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 191.7, 166.6, 150.4, 139.9, 127.1, 111.3, 54.2; **IR** (neat, ν/cm^{-1}) = 3052, 2954, 1645, 1599, 1494, 1378, 1364, 1309, 1287, 1267, 1124, 1020, 1010, 924, 856, 843, 781, 641, 629; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{13}N_2O_3$ = 245.0926; found = 245.0943.

Bis(6-methoxypyridin-3-yl)methanamine (S30)



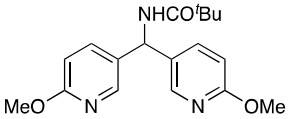
Bis(6-methoxypyridin-3-yl)methanone **S29** (735.7 mg, 3.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (498.7 mg, 7.5 mmol, 2.5 equiv), and sodium acetate (anhydrous, 615.2 mg, 7.5 mmol, 2.5 equiv) were suspended in MeOH (6 mL, 0.5 M), and the mixture was heated to reflux with stirring overnight. The reaction was then cooled to room temperature and MeOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) was formed, filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (346.9 mg, 4.5 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 40 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (980.7 mg, 15.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to afford the desired amine (653.9 mg, 89% over two steps) as yellowish oil.

TLC: R_f (50% MeOH/EtOAc) = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.13 (d, J = 2.4 Hz, 2 H), 7.51 (dd, J = 8.6, 2.4 Hz, 2 H), 6.64 (d, J = 8.6 Hz, 2 H), 5.12 (s, 1 H), 3.86 (s, 6 H), 1.67 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 163.5, 145.0, 137.4, 133.3, 111.0, 54.5, 53.5; **IR** (neat, ν/cm^{-1}) = 1604, 1572, 1489, 1390, 1313, 1284, 1258, 1025, 830; **HRMS** (ESI, *m*/*z*): calcd for

$C_{13}H_{13}N_2O_2^+$ (parent mass peak was found deaminated ($-NH_3$)) = 229.0972; found = 229.0975.

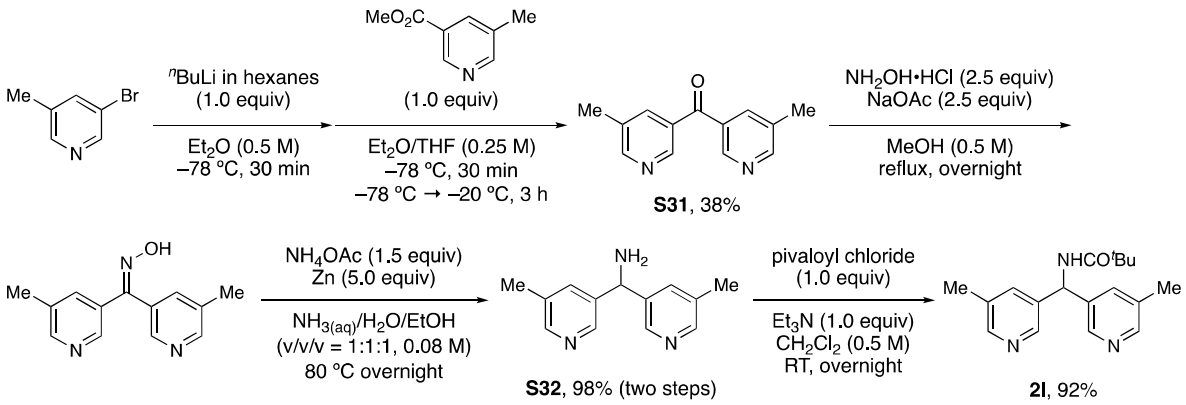
N-(Bis(6-methoxypyridin-3-yl)methyl)pivalamide (2k)



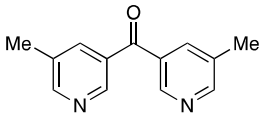
Bis(6-methoxypyridin-3-yl)methanamine **S30** (613.2 mg, 2.5 mmol, 1.0 equiv) and Et_3N (418.4 μL, 3.0 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (5 mL, 0.5 M), followed by slow addition of pivaloyl chloride (307.9 μL, 2.5 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (801.0 mg, 97%) as a white solid.

TLC: R_f (10% EtOAc/hexanes) = 0.23; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.02 (d, *J* = 2.4 Hz, 2 H), 7.36 (dd, *J* = 8.6, 2.4 Hz, 2 H), 6.70 (d, *J* = 8.6 Hz, 2 H), 6.12 (d, *J* = 7.5 Hz, 1 H), 6.05 (d, *J* = 7.5 Hz, 1 H), 3.90 (s, 6 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.6, 163.8, 145.6, 137.9, 129.4, 111.3, 53.6, 52.1, 38.9, 27.7; **IR** (neat, ν/cm^{-1}) = 3304, 2974, 1633, 1605, 1570, 1534, 1491, 1401, 1377, 1323, 1284, 1264, 1215, 1131, 1025, 830, 757, 688, 654, 613, 573; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_3$ = 330.1818; found = 330.1841.

Synthesis of substrate **2l**



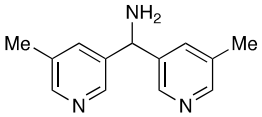
Bis(5-methylpyridin-3-yl)methanone (S31)



To a dry solution of ^{n}BuLi (2.5 M in hexanes; 10.00 mL, 25.0 mmol, 1.0 equiv) in Et_2O (80 mL) at –78 °C under Ar, 3-bromo-5-methylpyridine (2.83 mL, 25.0 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred for 30 min at the same temperature, a solution of methyl 5-methylnicotinate (3.78 g, 25.0 mmol, 1.0 equiv) in dry THF (20 mL) was added slowly. The reaction was kept at –78 °C for another 30 min, and then was warmed slowly to –20 °C over 3 h before quenched with 2 N $HCl_{(aq)}$. The mixture was then warmed to room temperature, basified with *sat* $NaHCO_{3\ (aq)}$, and evaporated *in vacuo* to remove the volatiles. The residue was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by flash column chromatography on SiO_2 (gradient 50%–100% EtOAc/hexanes) to afford the desired product, which can be further triturated with Et_2O/pentane to obtain a white solid (2.00 g, 38%).

TLC: R_f (70% EtOAc/hexanes) = 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.47 (s, 1 H), 8.34 (s, 1 H), 7.62 (s, 1 H), 2.13 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 193.0, 153.4, 147.5, 136.7, 132.9, 131.5, 17.8; **IR** (neat, ν/cm^{-1}) = 1651, 1587, 1571, 1422, 1373, 1322, 1298, 1255, 1243, 1188, 1166, 1145, 1129, 1047, 1029, 1023, 998, 963, 933, 897, 884, 787, 752, 711, 694, 653, 592, 464, 432; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{13}N_2O$ = 213.1028; found = 213.1020.

Bis(5-methylpyridin-3-yl)methanamine (S32)



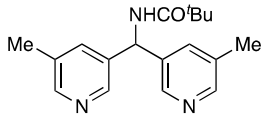
Bis(5-methylpyridin-3-yl)methanone **S31** (1.70 g, 8.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.33 g, 20.0 mmol, 2.5 equiv), and sodium acetate (anhydrous, 1.64 g, 20.0 mmol, 2.5 equiv) were suspended in MeOH (16 mL, 0.5 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. After the addition of H_2O, a white precipitate (oxime product) was formed, filtered, dried, and collected for use in the next step without further purification.

The oxime product and ammonium acetate (0.92 g, 12.0 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 120 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (2.62 g, 40.0 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 4 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further

triturated with Et_2O/pentane to obtain the desired amine (1.67 g, 98% over two steps) as a white solid.

TLC: R_f (10% MeOH/CH_2Cl_2) = 0.37; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.37 (s, 2 H), 8.24 (s, 2 H), 7.42 (s, 2 H), 5.16 (s, 1 H), 2.22 (s, 6 H), 1.75 (br, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 149.3, 145.7, 139.4, 134.8, 133.1, 55.2, 18.3; **IR** (neat, ν/cm^{-1}) = 3359, 1579, 1440, 1338, 1310, 1168, 1148, 1051, 1031, 938, 883, 742, 711, 660, 596; **HRMS** (ESI, *m/z*): calcd for $C_{13}H_{16}N_3$ = 214.1344; found = 214.1349.

N-(Bis(5-methylpyridin-3-yl)methyl)pivalamide (2l)

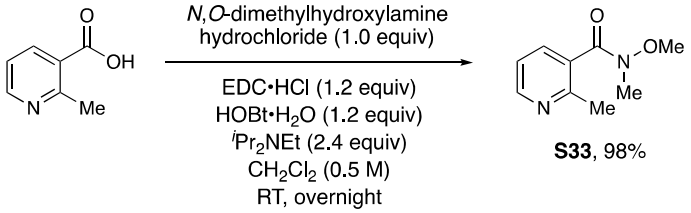


Bis(5-methylpyridin-3-yl)methanamine **S32** (1.28 g, 6.0 mmol, 1.0 equiv) and Et_3N (1.00 mL, 7.2 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (10 mL, 0.5 M), followed by slow addition of pivaloyl chloride (0.74 mL, 6.0 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of *sat* $NaHCO_{3\,(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further triturated with Et_2O/pentane to obtain the desired product (1.65 g, 92%) as a white solid.

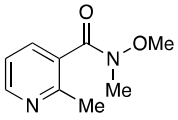
TLC: R_f (EtOAc) = 0.20; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.33 (s, 2 H), 8.28 (s, 2 H), 7.25 (s, 2 H), 6.35 (apparent br, 1 H), 6.18 (d, *J* = 7.6 Hz, 1 H), 2.28 (s, 6 H), 1.22 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.8, 149.8, 145.9, 135.8, 135.6, 133.4, 53.0, 38.9, 27.6, 18.5; **IR** (neat, ν/cm^{-1}) = 3278, 2957, 1657, 1585, 1509, 1480, 1438, 1397, 1365, 1331, 1315, 1228, 1191, 1148, 1031, 879, 752,

720, 713, 656, 636, 577, 537, 507, 450, 431; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{24}N_3O$ = 298.1919; found = 298.1898.

Synthesis of substrate **2m**



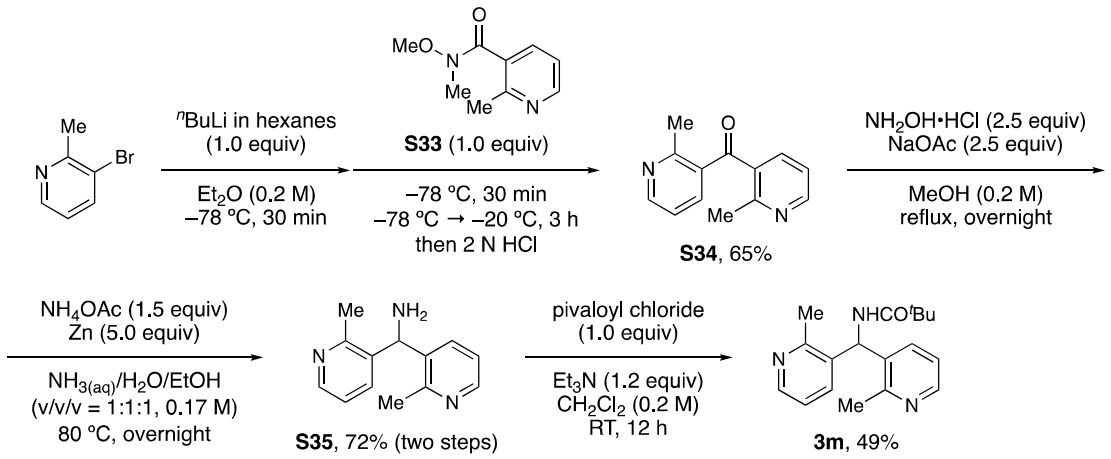
N-Methoxy-*N*,2-dimethylnicotinamide (S33)



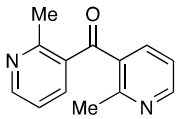
2-Methylnicotinic acid (2.74 g, 20.0 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (1.45 g, 20.0 mmol, 1.0 equiv), EDC•HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 4.60 g, 24.0 mmol, 1.2 equiv), and HOBt•H_2O (1-hydroxybenzotriazole monohydrate, 3.67 g, 24.0 mmol, 1.2 equiv) were mixed in CH_2Cl_2 (40 mL, 0.5 M), followed by the addition of $^{i}Pr_2NEt$ (8.38 mL, 48.0 mmol, 2.4 equiv). The reaction was stirred at room temperature overnight and then evaporated *in vacuo*. The residue was dissolved in EtOAc, and the organic phase was washed with citric acid (10% *aq* solution), *sat* $NaHCO_{3\,(aq)}$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 120 g; gradient 0%–30% EtOAc/hexanes over 3 CV, 30%–70% EtOAc/hexanes over 10 CV, and 70%–100% EtOAc/hexanes over 3 CV) to afford the desired product (2.53 g, 98%) as a white solid.

TLC: R_f (EtOAc) = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.44 (dd, *J* = 5.0, 1.8 Hz, 1 H), 7.50 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.07 (dd, *J* = 7.7, 5.0 Hz, 1 H), 3.35 (br s, 3 H), 3.25 (br s, 3 H), 2.46 (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ

[ppm] = ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 155.0, 149.7, 134.2, 130.5, 120.3, 61.2, 32.4, 22.5; **IR** (neat, ν/cm^{-1}) = 1640, 1572, 1438, 1382, 980, 894, 807, 743, 585, 476, 437; **HRMS** (ESI, *m*/*z*): calcd for $C_9H_{13}N_2O_2$ = 181.0977; found = 181.1968.



Bis(2-methylpyridin-3-yl)methanone (S34)

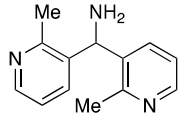


To a solution of *n*BuLi (2.5 M in hexanes; 7.2 mL, 18.0 mmol, 1.0 equiv) in dry Et_2O (100 mL) at –78 °C under N_2, 3-bromo-2-methylpyridine (3.24 g, 18.0 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred for 30 min at the same temperature, *N*-methoxy-*N*,2-dimethylnicotinamide **S33** (3.10 g, 18.0 mmol, 1.0 equiv) was added slowly. The reaction was then kept stirring at –78 °C for another 30 min, and warmed to –20 °C over 3 h before quenched with 2 N $HCl_{(aq)}$. The mixture was warmed to room temperature, basified with *sat* $NaHCO_{3\,(aq)}$, and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 100% EtOAc over 2 CV

and 0%–20% MeOH/EtOAc over 15 CV) to afford the desired product (2.76 g, 72%) as a white solid.

TLC: R_f (50% MeOH/EtOAc) = 0.80; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.64 (dd, *J* = 4.9, 1.8 Hz, 2 H), 7.59 (dd, *J* = 7.8, 1.8 Hz, 2 H), 7.20 (dd, *J* = 7.8, 4.9 Hz, 2 H), 2.64 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 198.0, 158.3, 151.6, 137.7, 133.5, 120.9, 24.2; **IR** (neat, ν/cm^{-1}) = 1666, 1580, 1566, 1431, 1284, 1251, 928, 782, 753; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{13}N_2O$ = 213.1028; found = 213.1043.

Bis(2-methylpyridin-3-yl)methanamine (S35)



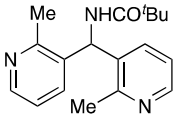
Bis(2-methylpyridin-3-yl)methanone **S34** (1.11 g, 5.2 mmol, 1.0 equiv), hydroxylamine hydrochloride (0.85 g, 13.1 mmol, 2.5 equiv), and sodium acetate (anhydrous, 1.07 g, 13.1 mmol, 2.5 equiv) were suspended in MeOH (25 mL, 0.2 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. The residue was extracted with CH_2Cl_2 and water, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The oxime product was obtained and subjected to reduction without further purification.

The oxime and ammonium acetate (0.61 g, 7.8 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 30 mL, 0.17 M) and stirred with heating to 80 °C. At this temperature, Zn (1.71 g, 26.2 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the

mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 1.0 M $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 2 CV and 20%–100% MeOH/EtOAc over 15 CV) to afford the desired product (0.80 g, 72% over two steps) as colorless oil.

TLC: R_f (50% MeOH/EtOAc) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.41 (dd, *J* = 4.9, 1.7 Hz, 2 H), 7.59 (dd, *J* = 7.7, 1.7 Hz, 2 H), 7.13 (dd, *J* = 7.7, 4.9 Hz, 2 H), 5.48 (s, 1 H), 2.51 (s, 6 H), 1.77 (br, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 156.3, 147.9, 137.2, 134.3, 121.6, 52.1, 22.2; **IR** (neat, ν/cm^{-1}) = 1574, 1436, 976, 809, 763, 738; **HRMS** (ESI, *m*/*z*): calcd for $C_{13}H_{16}N_3$ = 214.1344; found = 214.1364.

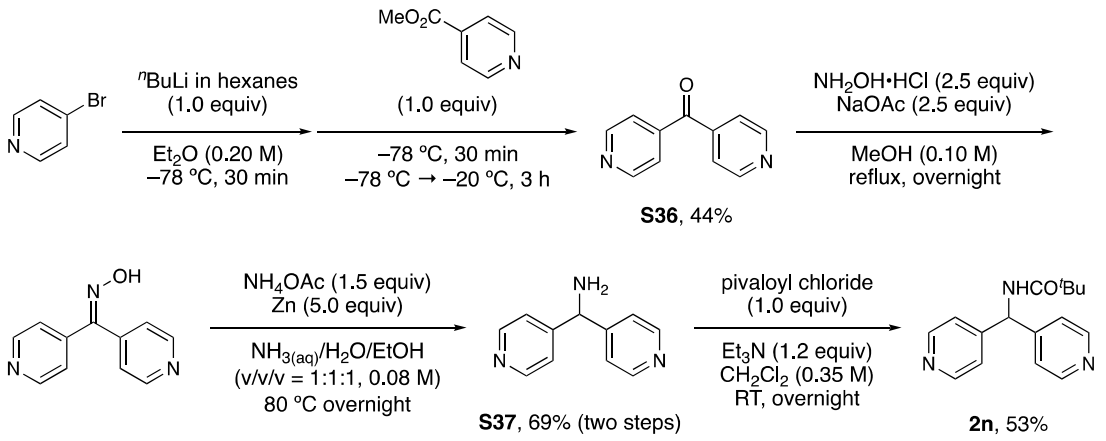
N-(Bis(2-methylpyridin-3-yl)methyl)pivalamide (2m)



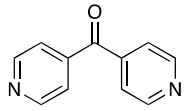
Bis(2-methylpyridin-3-yl)methanamine **S35** (789.1 mg, 3.7 mmol, 1.0 equiv) and Et_3N (615.8 μL, 4.4 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (18 mL, 0.2 M), followed by slow addition of pivaloyl chloride (455.7 μL, 3.7 mmol, 1.0 equiv). The reaction was stirred at room temperature for 12 h, followed by the addition of 2 M $NaOH_{(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue can be further recrystallized by Et_2O/hexanes to obtain the desired product (541.6 mg, 49%) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.49 (d, *J* = 4.7 Hz, 2 H), 7.29–7.27 (m, 2 H), 7.13 (dd, *J* = 7.3, 5.1 Hz, 2 H), 6.44 (d, *J* = 7.2 Hz, 2 H), 5.92 (d, *J* = 6.8 Hz, 1 H), 2.50 (s, 6 H), 1.28 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.5, 157.4, 148.6, 134.1, 133.6, 121.5, 51.0, 39.0, 27.8, 22.3; **IR** (neat, ν/cm^{-1}) = 3290, 1629, 1525, 1435, 1203, 760, 735; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O$ = 298.1919; found = 298.1932.

Synthesis of substrate **2n**



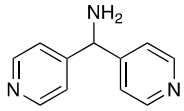
Di(pyridin-4-yl)methanone (S36)



To a dry solution of *n*BuLi (2.5 M in hexanes; 10.00 mL, 25.0 mmol, 1.0 equiv) in Et_2O (100 mL) at –78 °C under Ar, 4-bromopyridine (3.95 g, 25.0 mmol, 1.0 equiv) was added dropwise. After the reaction was stirred for 30 min at the same temperature, a solution of methyl isonicotinate (3.43 g, 25.0 mmol, 1.0 equiv) in dry Et_2O (15 mL) was added slowly. The reaction was kept at –78 °C for another 30 min, and then warmed slowly to –20 °C over 3 h before quenched with 6 M $NaOH_{(aq)}$. The mixture was then warmed to room temperature, and extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 5%–20% MeCN/H_2O over 5 CV, 20%–50% MeCN/H_2O over 5 CV, and 50%–100% MeCN/H_2O over 5 CV) to afford the desired product (2.04 g, 44%) as a white solid.

TLC: R_f (50% MeOH/EtOAc) = 0.80; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.78–8.74 (m, 4 H), 7.53–7.49 (m, 4 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 194.0, 150.7, 142.2, 122.6; **IR** (neat, ν/cm^{-1}) = 1671, 1408, 1328, 1280, 905, 832, 761, 726, 695, 638, 450, 443; **HRMS** (ESI, *m/z*): calcd for $C_{11}H_9N_2O$ = 185.0714; found = 185.0715.

Di(pyridin-4-yl)methanamine (S37)



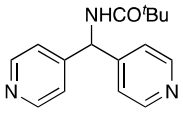
Di(pyridin-4-yl)methanone **S36** (460.2 mg, 2.5 mmol, 1.0 equiv), hydroxylamine hydrochloride (415.6 mg, 6.3 mmol, 2.5 equiv), and sodium acetate (anhydrous, 512.7 mg, 6.3 mmol, 2.5 equiv) were suspended in MeOH (25 mL, 0.1 M), and the mixture was heated to reflux with stirring overnight. The reaction was cooled to room temperature and MeOH was mostly removed *in vacuo*. The residue was extracted with CH_2Cl_2 and water, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The oxime product was obtained and subjected to reduction without further purification.

The oxime and ammonium acetate (289.1 mg, 3.8 mmol, 1.5 equiv) were suspended in a mixture of 30% $NH_{3\,(aq)}$/H_2O/EtOH (v/v/v = 1:1:1, 120 mL, 0.08 M) and stirred with heating to 80 °C. At this temperature, Zn (817.3 mg, 12.5 mmol, 5.0 equiv) was added slowly portionwise **(CAUTION!)**, and the reaction was stirred overnight at the same temperature. After cooling to room temperature, the mixture was filtered through a pad of celite with washing by EtOAc, and the filtrate was evaporated *in vacuo* to remove the volatiles. The remained liquid was extracted with CH_2Cl_2 and 1 N $NaOH_{(aq)}$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified

by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 2 CV, and 20%–100% MeOH/EtOAc over 15 CV) to afford the desired product (319.5 mg, 69% over two steps) as a colorless oil.

TLC: R_f (50% MeOH/EtOAc) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.56–8.54 (m, 4 H), 7.29–7.28 (m, 4 H), 5.14 (s, 1 H), 1.86 (br, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = δ 152.6, 150.3, 122.0, 58.3; **IR** (neat, ν/cm^{-1}) = 1591, 1428, 823, 667, 615; **HRMS** (ESI, *m*/*z*): calcd for $C_{11}H_{12}N_3$ = 186.1031; found = 186.1041.

N-(Di(pyridin-4-yl)methyl)pivalamide (2n)

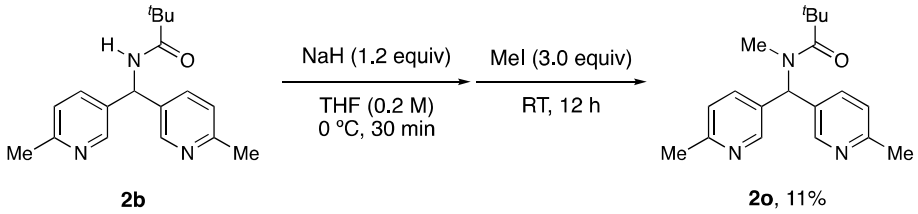


Di(pyridin-4-yl)methanamine **S37** (1.29 g, 7.0 mmol, 1.0 equiv) and Et_3N (1.18 mL, 8.4 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (20 mL, 0.35 M), followed by slow addition of pivaloyl chloride (0.86 mL, 7.0 mmol, 1.0 equiv). The reaction was stirred at room temperature overnight, followed by the addition of 2 M $NaOH_{(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was then purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 0%–5% MeCN/H_2O over 2 CV, and 5%–100% MeCN/H_2O over 20 CV) to obtain the desired product (0.99 g, 53%) as a white solid.

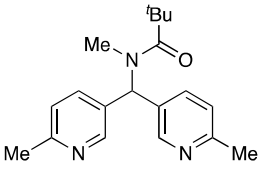
TLC: R_f (10% MeOH/EtOAc) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.59–8.57 (m, 4 H), 7.11–7.10 (m, 4 H), 6.26 (d, *J* = 7.8 Hz, 1 H), 6.18 (d, *J* = 7.8 Hz, 1 H), 1.25 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.0, 150.5,

148.8, 122.4, 55.3, 39.0, 27.6; **IR** (neat, ν/cm^{-1}) = 1657, 1599, 1419, 1203, 808, 613, 574, 481, 648; **HRMS** (ESI, *m/z*): calcd for $C_{16}H_{20}N_3O$ = 270.1606; found = 270.1630.

Substrate synthesis **2o–2q**



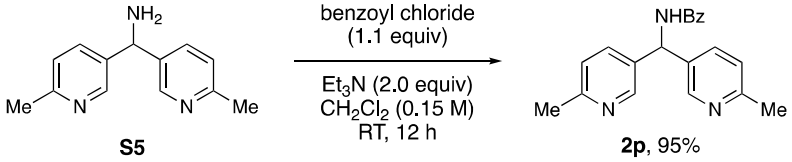
N-(Bis(6-methylpyridin-3-yl)methyl)-*N*-methylpivalamide (2o)



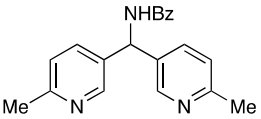
To an ice-cooled solution of *N*-(bis(6-methylpyridin-3-yl)methyl)pivalamide **2b** (639.8 mg, 3.0 mmol, 1.0 equiv) in anhydrous THF (15 mL, 0.2 M), NaH (60% dispersion in mineral oil, 144.0 mg, 3.6 mmol, 1.2 equiv) was added portionwise over 10 min **(CAUTION!)**. The reaction stirred for 30 min, followed by the addition of iodomethane (560.3 uL, 9.0 mmol, 3.0 equiv). The reaction was then allowed to warm to room temperature and stirred for 12 h before quenched with 2 M $NaOH_{(aq)}$. The mixture was extracted with CH_2Cl_2, and the organic extracts were combined, washed with brine, and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 0%–20% MeCN/H_2O over 2 CV and 20%–60% MeCN/H_2O over 15 CV) to afford the desired product (102.7 mg, 11%) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.32 (d, *J* = 2.3 Hz, 2 H), 7.34 (dd, *J* = 8.0, 2.3 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.08 (s, 1 H), 2.87 (s, 3 H), 2.55 (s, 6 H), 1.34 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.2, 157.9, 149.3, 136.8, 131.0, 123.2, 57.9, 39.5, 33.5, 28.4, 24.2; **IR**

(neat, ν/cm^{-1}) = 1625, 1360, 1262, 1222, 1082, 727; **HRMS** (ESI, *m*/*z*): calcd for $C_{19}H_{26}N_3O$ = 312.2076; found = 312.2094.



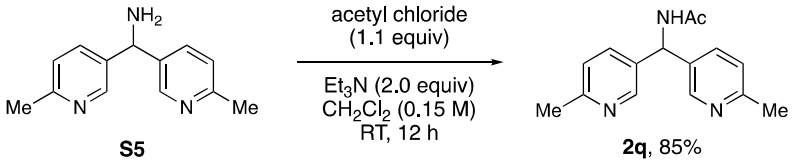
N-(Bis(6-methylpyridin-3-yl)methyl)benzamide (2p)



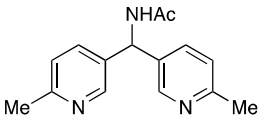
Bis(6-methylpyridin-3-yl)methanamine **S5** (639.8 mg, 3.0 mmol, 1.0 equiv) and Et_3N (829.7 μL, 6.0 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (20 mL, 0.15 M), followed by slow addition of benzoyl chloride (383.3 μL, 3.3 mmol, 1.1 equiv). The reaction was stirred at room temperature for 12 h, followed by the addition of 2 M $NaOH_{(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was further triturated using EtOAc/hexanes to obtain the desired product (866.5 mg, 95%) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.50; the ratio of rotamers were 81:19 as determined by ^{1}H NMR at room temperature; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.47–8.46 (m, 2 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.54–7.51 (m, 0.95 H), 7.47–7.40 (m, 4.05 H), 7.14–7.12 (m, 2 H), 6.79 (br s, 0.81 H), 6.71 (apparent d, *J* = 7.6 Hz, 0.19 H), 6.43 (d, *J* = 7.0 Hz, 1 H), 2.54 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 166.8, 158.4, 158.3*, 148.4, 135.5, 133.8, 133.16, 132.14*, 132.1, 128.9, 128.8*, 127.21*, 127.19, 123.4, 53.4, 24.3 (minor peaks were marked with asterisks if able to be recognized); **IR** (neat, ν/cm^{-1}) = 1634, 1523, 1487, 693, 665,

641, 587, 484, 406; **HRMS** (ESI, *m/z*): calcd for $C_{20}H_{20}N_3O$ = 318.1606; found = 318.1623.



N-(Bis(6-methylpyridin-3-yl)methyl)acetamide (2q)

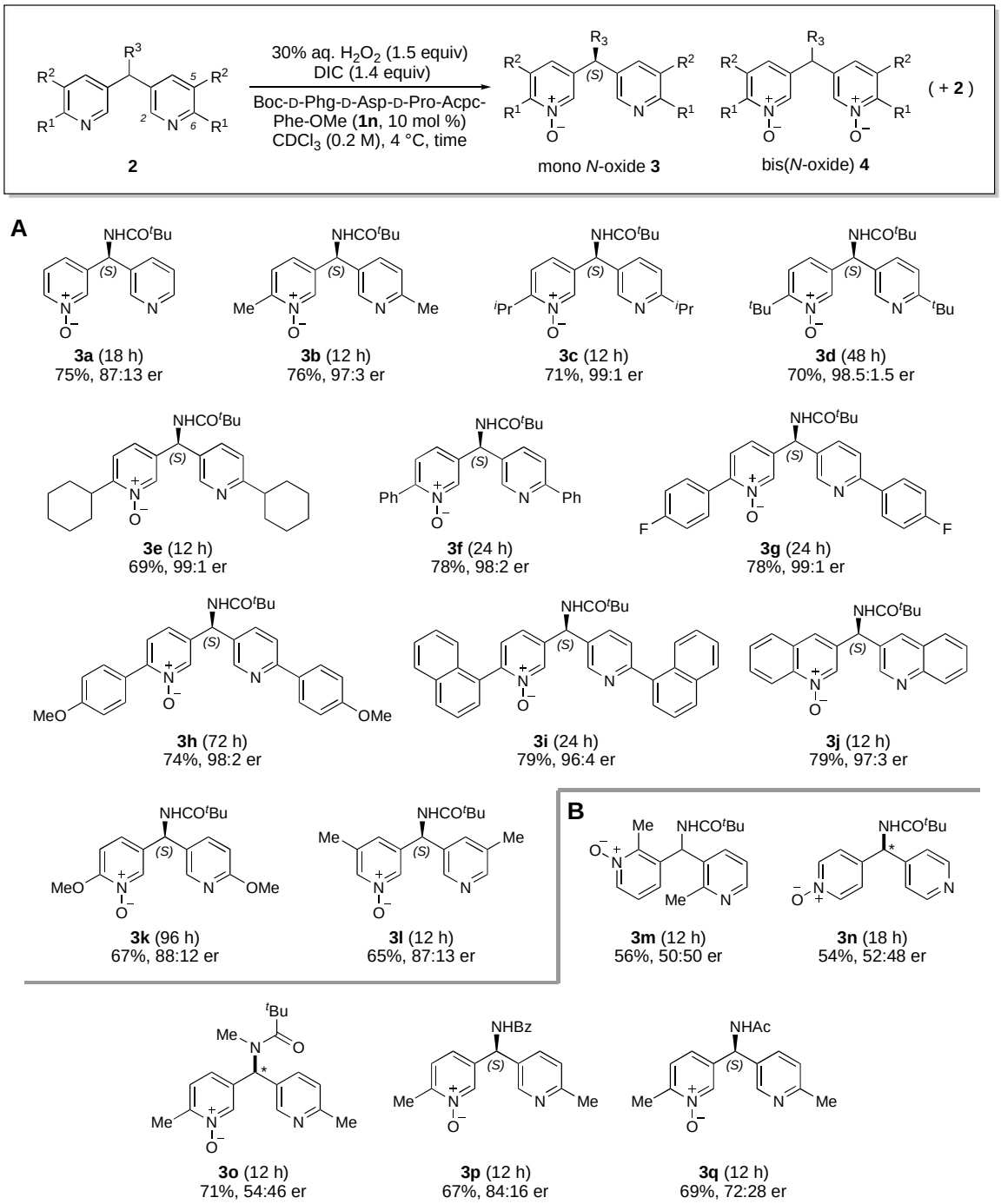


Bis(6-methylpyridin-3-yl)methanamine **S5** (639.8 mg, 3.0 mmol, 1.0 equiv) and Et_3N (829.7 μL, 6.0 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (20 mL, 0.15 M), followed by slow addition of acetyl chloride (246.7 μL, 3.3 mmol, 1.1 equiv). The reaction was stirred at room temperature for 12 h, followed by the addition of 2 M $NaOH_{(aq)}$. The mixture was extracted with CH_2Cl_2, and organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was further triturated using EtOAc/hexanes to obtain the desired product (651.0 mg, 85%) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.36 (d, *J* = 2.7 Hz, 2 H), 7.37 (dd, *J* = 8.1, 2.4 Hz, 2 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 6.56 (br s, 1 H), 6.22 (d, *J* = 7.8 Hz, 1 H), 2.51 (s, 6 H), 2.04 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 169.4, 158.1, 148.3, 135.5, 133.3, 123.3, 52.8, 24.2, 23.3; **IR** (neat, ν/cm^{-1}) = 1644, 1541, 1487, 1369, 1297, 1028, 829; **HRMS** (ESI, *m/z*): calcd for $C_{15}H_{18}N_3O$ = 256.1450; found = 256.1463.

4. General procedure and scope for enantioselective *N*-oxidation of pyridine substrates

Table S 10. *List of the scope for enantioselective N-oxidation. (A) Substrates reacted with good to excellent enantioselectivity. (B) Substrates reacted with low to no enantioselectivity.*[a]



[a]List of over-oxidation products bis(*N*-oxide) **4** were not shown in this figure.

General procedure: Substrate **2** (0.30 mmol, 1.0 equiv) and peptide **1n** (21.3 mg, 0.03 mmol, 10 mol %) were dissolved in $CDCl_3$ (1.5 mL, 0.2 M) in a 6 mL vial equipped with a stir bar, followed by addition of H_2O_2 (30% w/w in H_2O; 46.4 μL, 0.45 mmol, 1.5 equiv). The mixture was cooled to 0 °C in an ice bath. While stirring vigorously, DIC (65.0 μL, 0.42 mmol, 1.4 equiv) was added. The reaction was transported to a cold room maintained at 4 °C and allowed to stir for the reaction time before quenched by addition of Na_2SO_3. The mixture was directly purified by column chromatography (normal phase and/or reversed phase) to afford the desired mono *N*-oxide product **3** and bis(*N*-oxide) **4**.

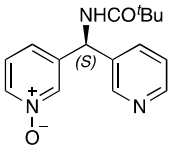
The enantiomeric ratios (ers) of mono *N*-oxides can be further determined by analytical chiral HPLC separations. Details of chromatographic conditions are indicated under each substrate.

The absolute stereochemistry of **3l** was determined by the single-crystal X-ray crystallography. Crystals of **3l** (CCDC 1950272) were obtained by recrystallization from slow diffusion of hexanes into the solution of **3l** in EtOAc, and absolute stereochemistry of the other mono *N*-oxides (**3a**–**3k**, **3p**, and **3q**) was assigned by analogy to **3l**.

The racemic mixture of mono *N*-oxides was prepared under the condition: substrate **2** (1.0 equiv), 30% aq. H_2O_2 (1.5 equiv), DIC (1.0 equiv), and Boc-Asp-OMe (**1a**, 10 mol %) in $CDCl_3$ (0.2 M) for 12 h.

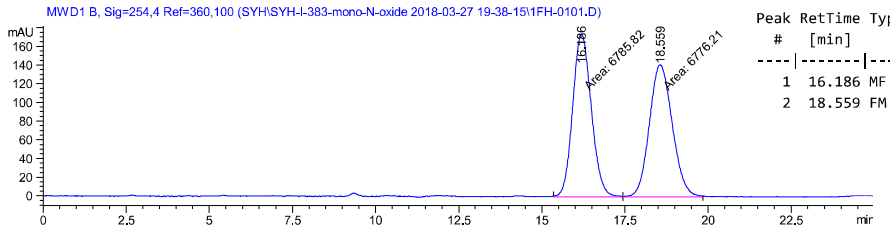
Scope for *N*-oxidation:

Oxidation of *N*-(di(pyridin-3-yl)methyl)pivalamide (2a): substrate **2a** (80.8 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 18 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–30% MeOH/EtOAc over 4 CV and 30%–40% MeOH/EtOAc over 8 CV).



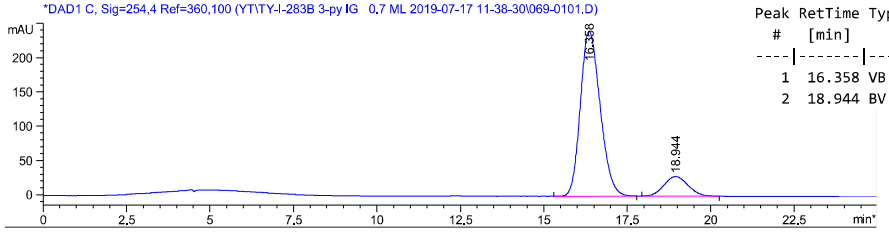
The mono *N*-oxide product **(*S*)-3-(pivalamido(pyridin-3-yl)methyl)pyridine 1-oxide** (**3a**) was obtained as a white solid (64.2 mg, 75%, er = 87:13). **TLC**: R_f (50% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.50 (d, J = 2.4 Hz, 1 H), 8.47 (dd, J = 4.7, 1.6 Hz, 1 H), 8.36 (d, J = 8.5 Hz, 1 H), 8.14–8.12 (m, 1 H), 8.12 (dt, J = 6.3, 1.3 Hz, 1 H), 7.67 (dt, J = 7.9, 1.8 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.25 (apparent d, J = 7.9 Hz, 1 H), 6.23 (d, J = 8.4 Hz, 1 H), 1.12 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.1, 148.8, 148.7, 141.2, 137.7, 137.5, 136.3, 135.1, 126.4, 124.5, 123.6, 51.3, 38.2, 27.2; **IR** (neat, ν/cm^{-1}) = 1648, 1518, 1483, 1276, 1210, 1156, 1034, 765, 713, 671; **HRMS** (ESI, m/z): calcd for $C_{16}H_{20}N_3O_2$ = 286.1556; found = 286.1565; $[\alpha]_{405}^{26}$ +34.0 (c 0.58, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 16.4 min (major) and 18.9 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

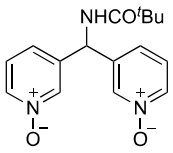


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	16.186	MF	0.6487	6785.81738	174.33839	50
2	18.559	FM	0.7986	6776.20801	141.41174	49

• enantioenriched product

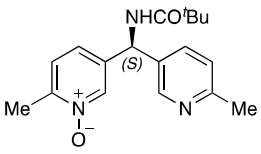


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	16.358	VB	0.6399	9892.27441	240.53583	87
2	18.944	BV	0.6983	1440.89063	28.48339	12



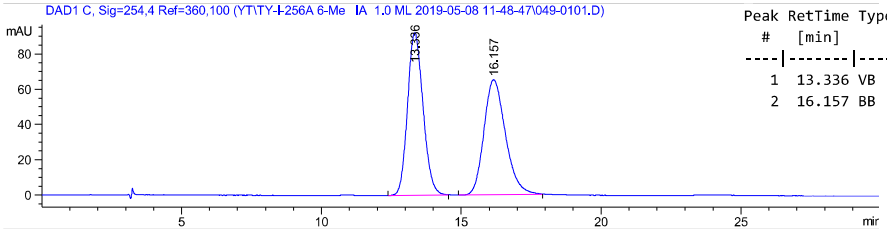
In addition, bis(*N*-oxide) product **3,3'-(pivalamidomethylene)bis(pyridine 1-oxide)** (**4a**) was obtained as a white solid (7.2 mg, 8%). **TLC**: R_f (50% MeOH/EtOAc) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.35 (d, J = 8.5 Hz, 1 H), 8.19 (t, J = 1.7 Hz, 2 H), 8.15 (dt, J = 6.5, 1.3 Hz, 2 H), 7.41 (dd, J = 8.0, 6.5 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.21 (d, J = 8.5 Hz, 1 H), 1.14 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.7, 140.7, 138.2, 138.1, 126.9, 124.8, 51.1, 38.7, 27.5; **IR** (neat, ν/cm^{-1}) = 1644, 1510, 1483, 1451, 1257, 1135; **HRMS** (ESI, *m*/*z*): calcd for $C_{16}H_{20}N_3O_3$ = 302.1505; found = 302.1483.

Oxidation of *N*-(bis(6-methylpyridin-3-yl)methyl)pivalamide (2b): substrate **2b** (89.2 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–10% MeOH/EtOAc over 3 CV and 10%–70% MeOH/EtOAc over 25 CV).



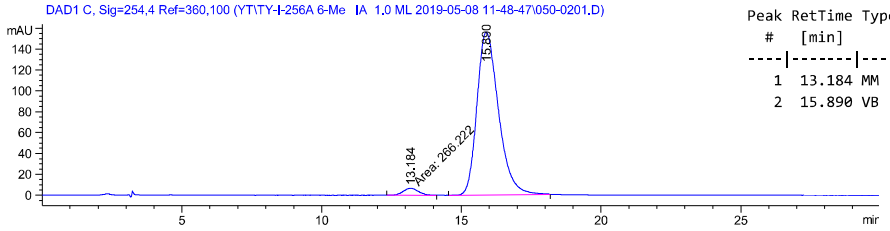
The mono *N*-oxide product **(*S*)-2-methyl-5-((6-methylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3b**) was obtained as a white solid (71.4 mg, 76%, er = 97:3). **TLC**: R_f (50% MeOH/EtOAc) = 0.60; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.33 (d, *J* = 2.1 Hz, 1 H), 8.13 (s, 1 H), 7.39 (dd, *J* = 8.0, 2.3 Hz, 1 H), 7.12 (t, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 8.1 Hz, 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 6.19 (d, *J* = 7.8 Hz, 1 H), 2.52 (s, 3 H), 2.34 (s, 3 H), 1.22 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.3, 158.5, 148.2, 147.9, 138.4, 138.2, 135.5, 132.5, 126.4, 125.5, 123.5, 51.9, 38.9, 27.5, 24.2, 17.6; **IR** (neat, ν/cm^{-1}) = 1645, 1509, 1447, 1368, 1257, 1222, 1200, 751, 730, 644, 584; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_2$ = 314.1869; found = 314.1877; $[\alpha]_{405}^{26}$ +121.6 (*c* 0.67, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 30 °C; detection: 254 nm; retention time: t_R = 13.2 min (minor) and 15.9 min (major); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

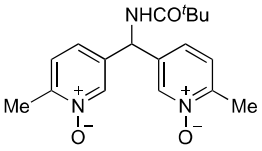


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	13.336	VB	0.6002	3556.67090	92.16872	50.
2	16.157	BB	0.8170	3493.67944	65.21613	49.

• enantioenriched product

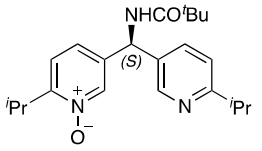


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	13.184	MM	0.6423	266.22186	6.90777	3
2	15.890	VB	0.8168	8357.97949	156.07420	96



In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-methylpyridine 1-oxide)** (**4b**) was obtained as a white solid (20.8 mg, 21%). **TLC**: R_f (50% MeOH/EtOAc) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.23 (s, 2 H), 7.26 (d, *J* = 4.6 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.05 (d, *J* = 7.8 Hz, 2 H), 6.18 (d, *J* = 7.2 Hz, 1 H), 2.46 (s, 6 H), 1.24 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.5, 148.7, 138.5, 137.3, 126.7, 125.0, 51.6, 39.1, 27.6, 17.7; **IR** (neat, ν/cm^{-1}) = 1506, 1256, 1222, 1004, 919, 725, 643, 583, 453; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_3$ = 330.1818; found = 330.1830.

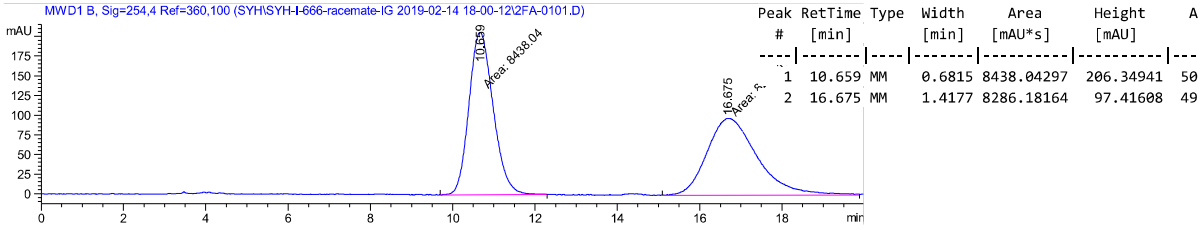
Oxidation of *N*-(bis(6-isopropylpyridin-3-yl)methyl)pivalamide (2c): substrate **2c** (106.1 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient EtOAc over 5 CV and 0%–15% MeOH/EtOAc over 20 CV).



The mono *N*-oxide product **(*S*)-2-isopropyl-5-((6-isopropylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3c**) was obtained as a white solid (78.7 mg, 71%, er = 99:1). **TLC**: R_f (10% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1 H), 8.17 (s, 1 H), 7.65 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 6.31 (s, 1 H), 3.69 (hept, *J* = 6.9 Hz, 1 H), 3.06 (hept, *J* = 6.9 Hz, 1 H), 1.28 (d, *J* = 6.9 Hz, 6 H), 1.27 (d, *J* = 6.9 Hz, 6 H), 1.21 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = ^{13}C NMR (101 MHz, CD_3OD) δ 180.7, 168.2, 158.1, 149.0, 139.9, 139.7, 138.2 (d), 134.6, 130.0, 124.6 (t), 122.3 (d), 53.0 (d), 39.8, 37.1, 28.9 (d), 27.7, 22.9, 20.5; **IR** (neat, ν/cm^{-1}) = 2965, 2162, 2024, 1650, 1517, 1488, 1397; **HRMS** (ESI,

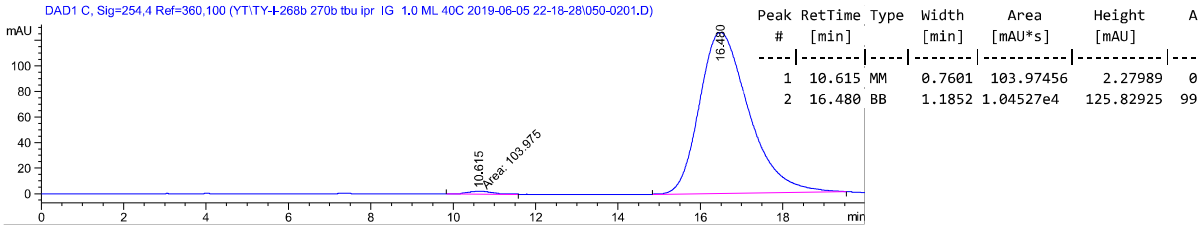
m/*z*): calcd for $C_{22}H_{32}N_3O_2$ = 370.2495; found = 370.2487; $[\alpha]_{405}^{26}$ +134.7 (*c* 0.07, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 10.6 min (minor) and 16.5 min (major); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

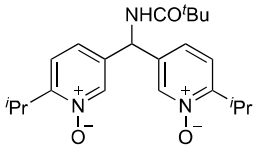


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	10.659	MM	0.6815	8438.04297	206.34941	50
2	16.675	MM	1.4177	8286.18164	97.41608	49

• enantioenriched product

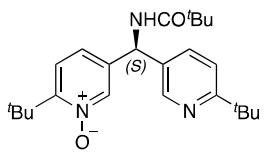


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	10.615	MM	0.7601	103.97456	2.27989	0
2	16.480	BB	1.1852	1.04527e4	125.82925	99



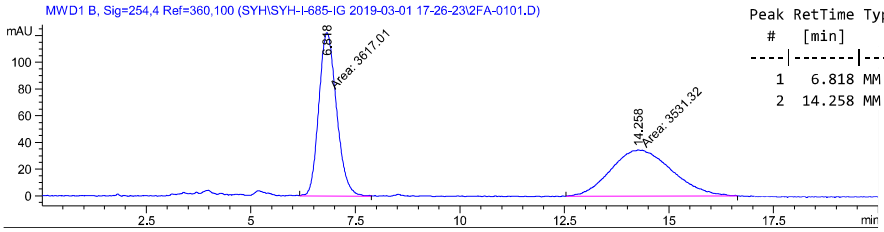
In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-isopropylpyridine 1-oxide)** (**4c**) was obtained as a white solid (32.4 mg, 28%). **TLC**: R_f (10% MeOH/EtOAc) = 0.40; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.26 (s, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 6.33 (s, 1 H), 3.72 (hept, *J* = 6.7 Hz, 2 H), 1.32 (s, 6 H), 1.30 (s, 6 H), 1.24 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.8, 158.5, 140.1, 138.4, 129.9, 124.8, 52.4, 39.8, 28.9, 27.7, 20.5; **IR** (neat, ν/cm^{-1}) = 2966, 1642, 1504, 1481, 1404, 1366, 1249, 1194, 1148, 783, 728; **HRMS** (ESI, *m*/*z*): calcd for $C_{22}H_{32}N_3O_3$ = 386.2444; found = 386.2433.

Oxidation of *N*-(bis(6-(*tert*-butyl)pyridin-3-yl)methyl)pivalamide (2d): substrate **2d** (114.5 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 48 h) according to the general procedure. The quenched reaction mixture was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 10%–40% MeOH/H_2O over 5 CV and 40%–80% MeOH/H_2O over 25 CV).



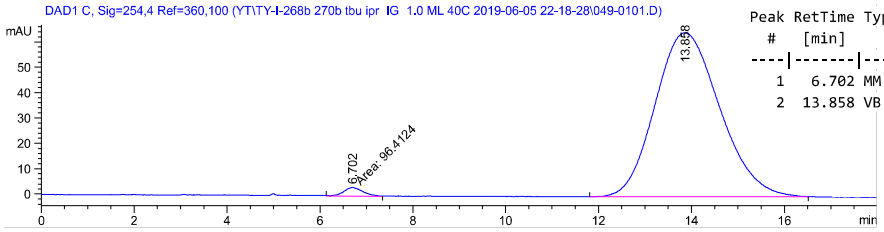
The mono *N*-oxide product **(*S*)-2-(*tert*-butyl)-5-((6-(*tert*-butyl)pyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3d**) was obtained as a white solid (83.5 mg, 70%, er = 98.5:1.5). **TLC**: R_f (10% MeOH/EtOAc) = 0.80; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.41 (d, *J* = 2.3 Hz, 1 H), 8.09 (d, *J* = 1.5 Hz, 1 H), 7.65 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 8.3 Hz, 1 H), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1 H), 6.30 (s, 1 H), 1.52 (s, 9 H), 1.36 (s, 9 H), 1.24 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.8, 170.1, 158.3, 148.8, 141.6, 140.1, 137.7, 134.0, 129.5, 125.6, 120.8, 52.8, 39.8, 38.2, 37.3, 30.5, 27.7, 27.4; **IR** (neat, ν/cm^{-1}) = 2960, 1642, 1502, 1486, 1397, 1362, 1251, 1198, 1145, 754, 715; **HRMS** (ESI, *m*/*z*): calcd for $C_{24}H_{36}N_3O_2$ = 398.2808; found = 398.2827; $[\alpha]_{405}^{26}$ +111.0 (*c* 0.49, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 6.7 min (minor) and 13.9 min (major); absolute stereochemistry was assigned by analogy to **3l**.

- racemic mixture



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	6.818	MM	0.4923	3617.01465	122.46067	50
2	14.258	MM	1.6913	3531.31860	34.79912	49

• enantioenriched product



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
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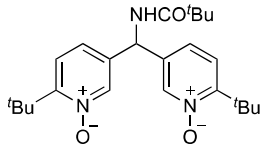
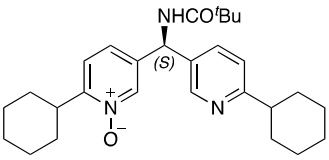
2	13.858	VB	1.1494	6246.57373	64.64206	98



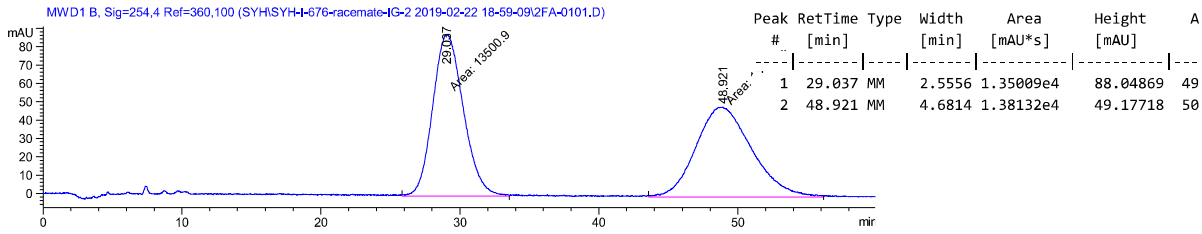
In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-(*tert*-butyl)pyridine 1-oxide)** (**4d**) was obtained as a white solid (18.6 mg, 15%). **TLC**: R_f (10% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.13 (s, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.38 (dd, *J* = 8.5, 1.6 Hz, 2 H), 6.27 (s, 1 H), 1.50 (s, 18 H), 1.22 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.8, 158.7, 141.7, 138.7, 129.3, 125.7, 52.1, 39.8, 37.3, 27.7, 27.4; **IR** (neat, ν/cm^{-1}) = 3376, 1641, 1406, 1383, 1245, 1148, 644, 585, 509, 413; **HRMS** (ESI, *m*/*z*): calcd for $C_{24}H_{36}N_3O_3$ = 414.2757; found = 414.2770.

Oxidation of *N*-(bis(6-cyclohexylpyridin-3-yl)methyl)pivalamide (2e): substrate **2e** (130.1 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–30% MeOH/EtOAc over 4 CV, and 30%–40% MeOH/EtOAc over 8 CV).

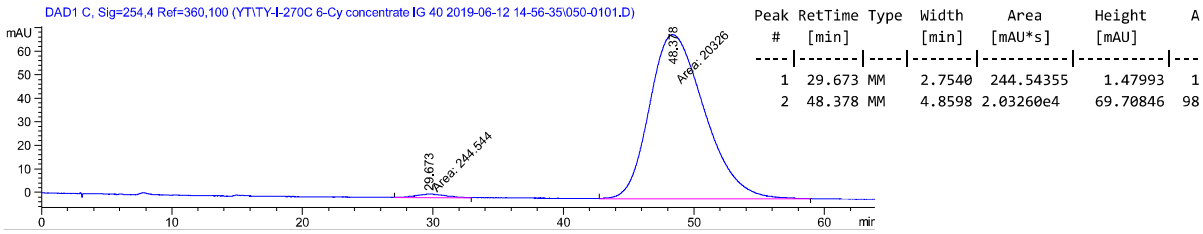


The mono *N*-oxide product **(*S*)-2-cyclohexyl-5-((6-cyclohexylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3e**) was obtained as a white solid (93.1 mg, 69%, er = 99:1). **TLC**: R_f (10% MeOH/EtOAc) = 0.80; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.37 (d, *J* = 2.3 Hz, 1 H), 8.17 (d, *J* = 1.8 Hz, 1 H), 7.66 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 6.30 (s, 1 H), 3.44 (tt, *J* = 11.6, 3.1 Hz, 1 H), 2.73 (tt, *J* = 11.9, 3.3 Hz, 1 H), 2.00 (d, *J* = 11.5 Hz, 2 H), 1.92–1.85 (m, 6 H), 1.83–1.76 (m, 2 H), 1.59–1.25 (m, 10 H), 1.23 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.8, 167.3, 157.0, 148.9, 139.8, 139.5, 138.2 (d), 134.6, 130.2, 125.1, 122.8, 53.0 (d), 47.4, 39.8, 38.6 (d), 34.0, 31.8 (d), 27.71, 27.70 (d), 27.6, 27.5, 27.1 (d); **IR** (neat, ν/cm^{-1}) = 2924, 2851, 1644, 1503, 1483, 1448, 1397, 1251, 1192, 1163; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{40}N_3O_2$ = 450.3121; found = 450.3102; $[\alpha]_{405}^{26}$ +117.9 (*c* 0.51, $CHCl_3$):; enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 29.7 min (minor) and 48.4 min (major); absolute stereochemistry was assigned by analogy to **3l**.

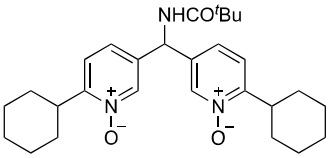
• racemic mixture



• enantioenriched product

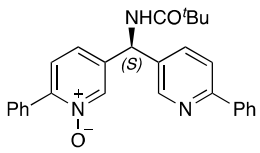


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	29.673	MM	2.7540	244.54355	1.47993	1
2	48.378	MM	4.8598	2.03260e4	69.70846	98



In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-cyclohexylpyridine 1-oxide)** (**4e**) was obtained as a white solid (36.3 mg, 26%). **TLC**: R_f (10% MeOH/EtOAc) = 0.65; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.25 (s, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.45 (dd, *J* = 8.4, 1.8 Hz, 2 H), 6.31 (s, 1 H), 3.44 (tt, *J* = 11.6, 3.2 Hz, 2 H), 2.00 (d, *J* = 12.8 Hz, 4 H), 1.89 (dt, *J* = 12.7, 3.2 Hz, 4 H), 1.83–1.78 (m, 2 H), 1.55–1.29 (m, 10 H), 1.24 (s, 9 H). (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 179.3, 155.9, 138.6, 136.8, 128.5, 123.8, 50.9, 38.4, 37.1, 30.3, 26.3, 26.0, 25.7; **IR** (neat, ν/cm^{-1}) = 2926, 2852, 1650, 1405, 1386, 1367, 1251, 1232, 1168; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{40}N_3O_3$ = 466.3070; found = 466.3093.

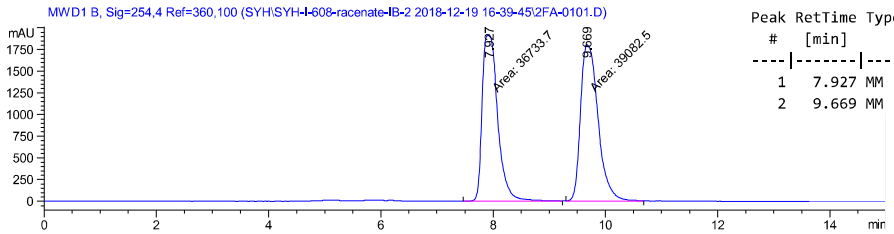
Oxidation of *N*-(bis(6-phenylpyridin-3-yl)methyl)pivalamide (2f): substrate **2f** (126.5 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 24 h) according to the general procedure. The quenched reaction mixture was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 0%–40% MeCN/H_2O over 3 CV and 40%–70% MeCN/H_2O over 20 CV).



The mono *N*-oxide product **(*S*)-2-phenyl-5-((6-phenylpyridin-3-yl)-(pivalamido)methyl)pyridine 1-oxide** (**3f**) was obtained as a white solid (102.4 mg, 78%, er = 98:2). **TLC**: R_f (EtOAc) = 0.75; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.61

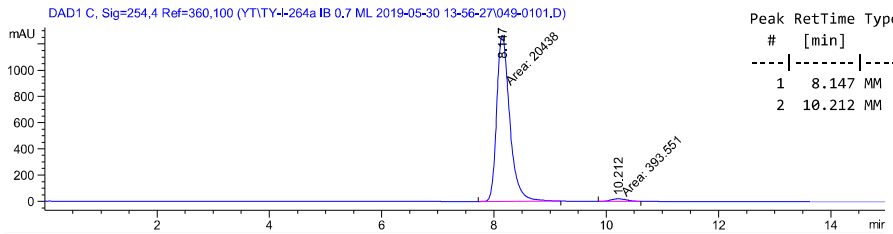
(d, J = 2.2 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 7.98–7.96 (m, 2 H), 7.87 (d, J = 8.3 Hz, 1 H), 7.82–7.78 (m, 3 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.52–7.41 (m, 7 H), 6.44 (s, 1 H), 1.27 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.8, 158.4, 149.9, 149.6, 141.1, 140.5, 139.7, 138.2, 135.4, 133.2, 131.1, 130.5, 130.4, 129.90, 129.86, 129.4, 129.1, 128.1, 122.2, 53.1 (d), 39.8, 27.8; **IR** (neat, ν/cm^{-1}) = 1642, 1514, 1478, 1379, 1257, 1047, 744, 694; **HRMS** (ESI, m/z): calcd for $C_{28}H_{28}N_3O_2$ = 438.2182; found = 438.2191; $[\alpha]_{405}^{26}$ +221.6 (c 0.42, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IB; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 8.1 min (major) and 10.2 min (minor); absolute stereochemistry was assigned by analogy to **31**.

• racemic mixture

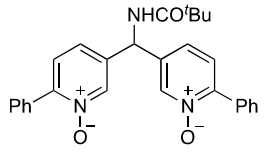


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	7.927	MM	0.3188	3.67337e4	1920.11975	48
2	9.669	MM	0.3609	3.90825e4	1805.08276	51

• enantioenriched product

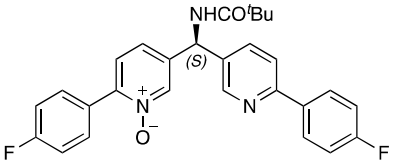


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	8.147	MM	0.2689	2.04380e4	1266.63379	98
2	10.212	MM	0.3163	393.55078	20.73675	1



In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-phenylpyridine 1-oxide)** (**4f**) was obtained as a white solid (17.7 mg, 13%). **TLC**: R_f (EtOAc) = 0.50; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.41 (s, 2 H), 7.83–7.80 (m, 4 H), 7.72–7.68 (m, 2 H), 7.60–7.56 (m, 2 H), 7.53–7.51 (m, 6 H), 6.44 (s, 1 H), 1.28 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.9, 150.1, 140.8, 139.8, 133.1, 131.2, 130.6, 129.8, 129.5, 129.3, 52.5, 39.9, 27.7; **IR** (neat, ν/cm^{-1}) = 1642, 1483, 1407, 1382, 1253, 770, 724, 695, 593, 543, 466; **HRMS** (ESI, *m/z*): calcd for $C_{28}H_{28}N_3O_3$ = 454.2131; found = 454.2137.

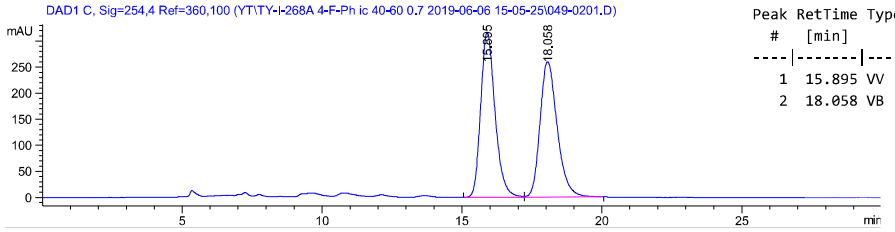
Oxidation of *N*-(bis(6-(4-fluorophenyl)pyridin-3-yl)methyl)pivalamide (2g): substrate **2g** (137.3 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 24 h) according to the general procedure. The quenched reaction mixture was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 10%–40% MeCN/H_2O over 5 CV and 40%–80% MeCN/H_2O over 25 CV).



The mono *N*-oxide product **(*S*)-2-(4-fluorophenyl)-5-((6-(4-fluorophenyl)pyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3g**) was obtained as a white solid (110.8 mg, 78%, er = 99:1). **TLC**: R_f (EtOAc) = 0.75; **^{1}H NMR** (500 MHz, DMSO-d_6) δ [ppm] = 8.62 (d, *J* = 2.3 Hz, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.31 (d, *J* = 1.9 Hz, 1 H), 8.10 (dd, *J* = 8.7, 5.7 Hz, 2 H), 7.95 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.87 (dd, *J* = 8.7, 5.8 Hz, 2 H), 7.81 (dd, *J* = 8.4, 2.3 Hz, 1 H), 7.62 (d, *J* = 8.3 Hz, 1 H), 7.36 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.28 (td, *J* = 9.0, 2.7 Hz, 4 H), 6.30 (d, *J* = 8.3 Hz, 1 H), 1.14 (s, 9 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ [ppm] = 177.2, 163.6 (d, *J* = 63.9 Hz), 161.7 (d, *J* = 64.9 Hz), 154.2, 148.7, 145.4,

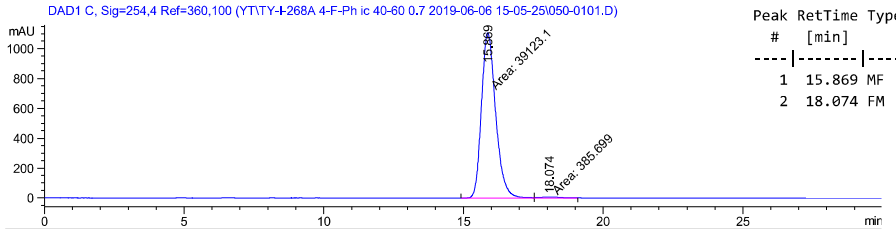
139.9, 138.8, 136.3, 135.0, 134.8 (d, J = 2.9 Hz), 131.7 (d, J = 8.5 Hz), 128.8 (d, J = 4.0 Hz), 128.7 (d, J = 8.5 Hz), 127.2, 124.8, 119.9, 115.7 (d, J = 21.5 Hz), 115.0 (d, J = 21.6 Hz), 51.0, 38.3, 27.2; **^{19}F NMR** (470 MHz, DMSO-d_6) δ [ppm] = –111.38 (apparent ddd, J = 14.3, 9.0, 5.6 Hz), –112.98 (tt, J = 8.7, 5.5 Hz); **IR** (neat, ν/cm^{-1}) = 1650, 1599, 1512, 1477, 1259, 1224, 1158, 826; **HRMS** (ESI, m/z): calcd for $C_{28}H_{26}F_2N_3O_2$ = 474.1993; found = 474.1975; $[\alpha]_{405}^{26}$ +266.2 (c 0.62, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IC; eluent: 40% EtOH/*n*hexane; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 15.9 min (major) and 18.1 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

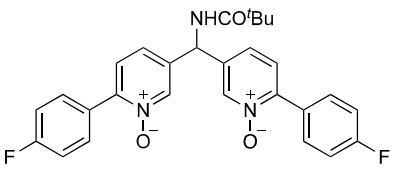


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	15.895	VV	0.5388	1.12924e4	316.09317	50
2	18.058	VB	0.6471	1.10916e4	260.33670	49

• enantioenriched product



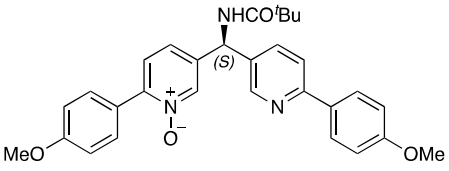
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	15.869	MF	0.5895	3.91231e4	1106.07019	99
2	18.074	FM	0.8076	385.69879	7.95948	0



In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)-bis(2-(4-fluorophenyl)pyridine 1-oxide)** (**4g**) was obtained as a white solid (32.3 mg, 22%). **TLC**: R_f (EtOAc) = 0.35; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.40 (s, 2 H), 7.88 (dd, J = 8.8, 5.4 Hz, 4 H), 7.70 (d, J = 8.3

Hz, 2 H), 7.57 (d, *J* = 8.3 Hz, 2 H), 7.26 (t, *J* = 8.7 Hz, 4 H), 6.43 (s, 1 H), 1.27 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 180.9, 164.9 (d, *J* = 249.6 Hz), 149.0, 140.8, 139.8, 133.0 (d, *J* = 8.8 Hz), 129.7, 129.3 (d, *J* = 3.5 Hz), 129.1, 116.4 (d, *J* = 22.1 Hz), 52.5, 39.9, 27.7; **^{19}F NMR** (470 MHz, DMSO-d_6) δ [ppm] = –111.38 (tt, *J* = 9.0, 5.6 Hz); **IR** (neat, ν/cm^{-1}) = 1646, 1600, 1491, 1407, 1380, 1257, 1231, 1161, 833; **HRMS** (ESI, *m*/*z*): calcd for $C_{28}H_{26}F_2N_3O_3$ = 490.1942; found = 490.1964.

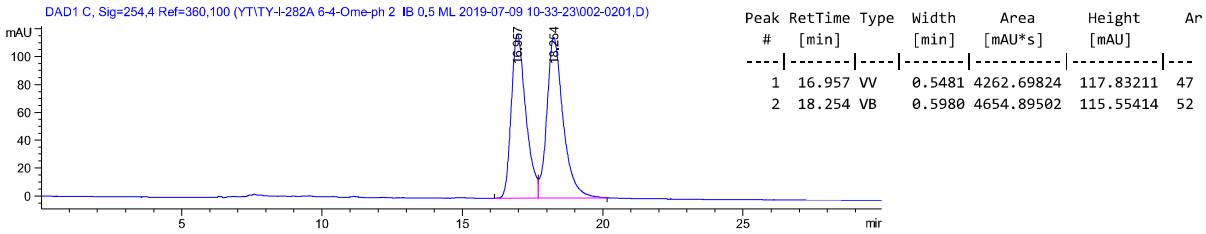
Oxidation of *N*-(bis(6-(4-methoxyphenyl)pyridin-3-yl)methyl)pivalamide (2h): substrate **2h** (144.5 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 72 h) according to the general procedure. The quenched reaction mixture was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 40% MeCN/H_2O over 8 CV and 20%–70% MeCN/H_2O over 20 CV).



The mono *N*-oxide product **(*S*)-2-(4-methoxyphenyl)-5-((6-(4-methoxyphenyl)pyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3h**) was obtained as a white solid (110.5 mg, 74%, er = 98:2). **TLC**: R_f (EtOAc) = 0.60; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.61 (d, *J* = 2.3 Hz, 1 H), 8.43 (d, *J* = 8.4 Hz, 1 H), 8.29 (d, *J* = 1.7 Hz, 1 H), 8.04 (d, *J* = 8.9 Hz, 2 H), 7.92 (d, *J* = 8.3 Hz, 1 H), 7.87–7.84 (m, 2 H), 7.79 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.35 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.06–7.01 (m, 4 H), 6.30 (d, *J* = 8.3 Hz, 1 H), 3.81 (s, 6 H), 1.18 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.2, 160.2, 159.9, 155.0, 148.6, 146.0, 139.2, 138.8, 136.1, 134.3, 130.8, 127.9, 126.7, 124.7, 124.5, 119.2, 114.2, 113.4, 55.3, 55.2, 51.0, 38.3, 27.2 (one overlapping peak in the aromatic region); **IR** (neat, ν/cm^{-1}) = 1605, 1515, 1476, 1245, 1174, 1019, 824; **HRMS**

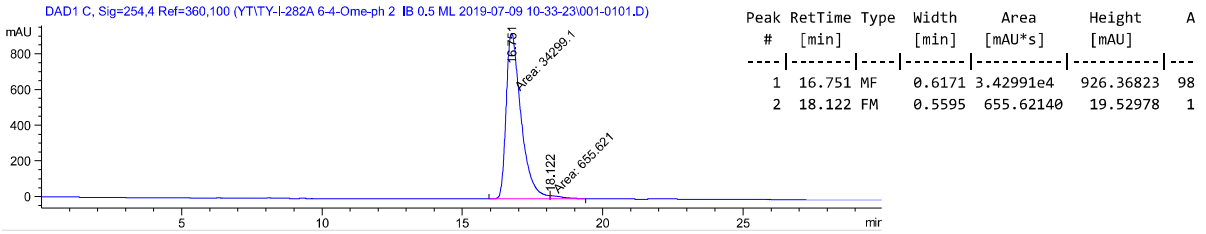
(ESI, *m*/*z*): calcd for $C_{30}H_{32}N_3O_4$ = 498.2393; found = 498.2371; $[\alpha]_{405}^{26}$ +285.6 (*c* 0.53, $CHCl_3$):; enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IB; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 16.8 min (major) and 18.1 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

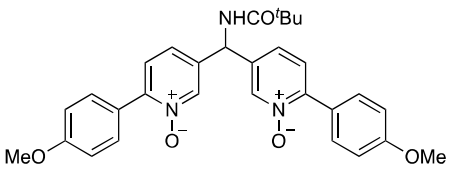


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	16.957	VV	0.5481	4262.69824	117.83211	47
2	18.254	VB	0.5980	4654.89502	115.55414	52

• enantioenriched product



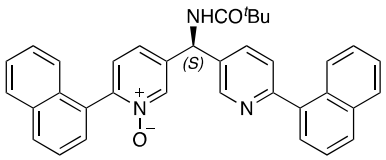
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	16.751	MF	0.6171	3.42991e4	926.36823	98
2	18.122	FM	0.5595	655.62140	19.52978	1



In addition, bis(*N*-oxide) product **5,5'-(pivalamido-methylene)bis(2-(4-methoxyphenyl)pyridine 1-oxide)** (**4h**) was obtained as a white solid (38.5 mg, 25%). **TLC**: R_f (EtOAc) = 0.45; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.42 (d, *J* = 8.4 Hz, 1 H), 8.36 (d, *J* = 1.7 Hz, 2 H), 7.88–7.84 (m, 4 H), 7.65 (d, *J* = 8.3 Hz, 2 H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 2 H), 7.05–7.01 (m, 4 H), 6.27 (d, *J* = 8.3 Hz, 1 H), 3.81 (s, 6 H), 1.18 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.3, 160.0, 146.2, 138.8, 138.3, 130.8, 126.9, 124.6, 124.4, 113.4, 55.3, 50.5, 38.3, 27.2; **IR** (neat, ν/cm^{-1}) = 1654, 1606, 1520, 1491,

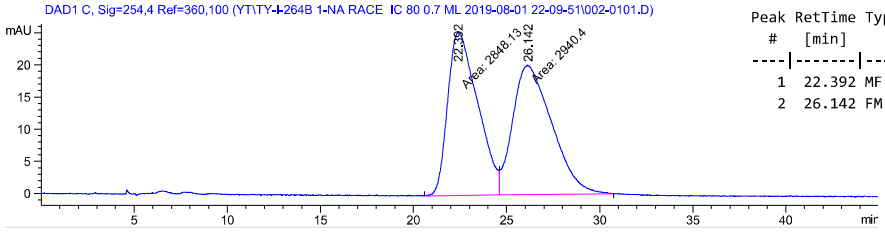
1250, 1178, 1020, 828; **HRMS** (ESI, *m*/*z*): calcd for $C_{30}H_{32}N_3O_5$ = 514.2342; found = 514.2372.

Oxidation of *N*-(bis(6-(naphthalen-1-yl)pyridin-3-yl)methyl)pivalamide (2i): substrate **2i** (156.5 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 24 h) according to the general procedure. The quenched reaction mixture was purified by reversed phase column chromatography (Biotage®, SNAP Ultra C18 25 g; gradient 0%–40% MeCN/H_2O over 3 CV and 40%–80% MeCN/H_2O over 15 CV).



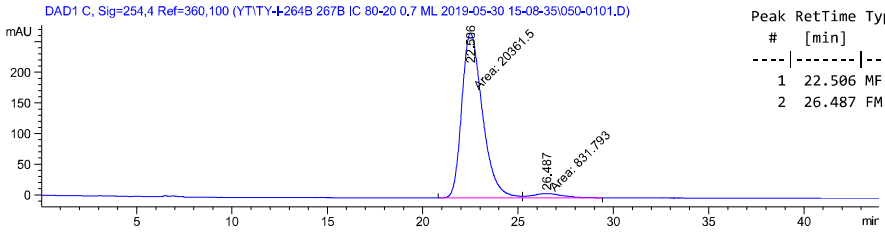
The mono *N*-oxide product **(*S*)-2-(naphthalen-1-yl)-5-((6-(naphthalen-1-yl)pyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3i**) was obtained as a white solid (127.4 mg, 79%, er = 96:4). **TLC**: R_f (EtOAc) = 0.80; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, *J* = 1.7 Hz, 1 H), 8.60 (dd, *J* = 8.4, 3.8 Hz, 1 H), 8.46 (d, *J* = 11.5 Hz, 1 H), 8.13 (d, *J* = 8.3 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 1 H), 8.07–7.99 (m, 4 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.66–7.60 (m, 4 H), 7.57–7.48 (m, 6 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 6.50 (d, *J* = 8.4 Hz, 1 H), 1.24 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.3, 157.5, 148.6, 147.0, 140.6, 138.6, 137.6, 136.1, 135.0, 133.5, 132.9, 131.4, 130.6, 130.5, 129.6, 128.9, 128.6, 128.4, 128.3, 128.0, 127.7, 126.6, 126.2, 126.1, 125.6, 125.5, 124.8, 124.5, 51.2, 38.4, 27.3 (three overlapping peaks in the aromatic region); **IR** (neat, ν/cm^{-1}) = 2183, 2037, 2030, 2020, 2009, 1979, 1645, 1510, 778; **HRMS** (ESI, *m*/*z*): calcd for $C_{36}H_{32}N_3O_2$ = 538.2495; found = 538.2495; $[\alpha]_{405}^{26}$ +145.8 (*c* 0.66, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IC; eluent: 80% EtOH/*n*hexane; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 22.5 min (major) and 26.5 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

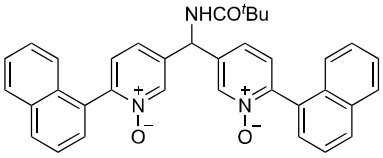


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	22.392	MF	1.8676	2848.13477	25.41751	49
2	26.142	FM	2.4381	2940.40454	20.10060	50

• enantioenriched product



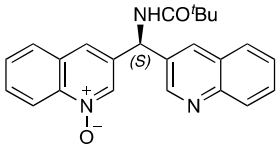
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	22.506	MF	1.2612	2.03615e4	269.07260	96
2	26.487	FM	1.9004	831.79297	7.29506	3



In addition, bis(*N*-oxide) product **5,5'-(pivalamido-methylene)bis(2-(naphthalen-1-yl)pyridine 1-oxide)** (**4i**) was obtained as a white solid (18.3 mg, 11%). **TLC**: R_f (EtOAc) = 0.60; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.53 (s, 2 H), 8.04 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 7.9 Hz, 2 H), 7.69–7.59 (m, 6 H), 7.55–7.50 (m, 4 H), 7.48–7.45 (m, 4 H), 6.56 (s, 1 H), 1.32 (s, 9 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 181.1, 150.4, 140.7, 140.6, 134.9, 132.2, 131.53, 131.49, 130.6, 129.6, 129.5, 129.1, 128.0, 127.5, 126.4, 126.3, 52.9, 40.0, 27.7; **IR** (neat, ν/cm^{-1}) = 1638, 1404, 1384, 1261, 1245, 1162, 1118, 972, 802, 775, 764, 534, 544; **HRMS** (ESI, *m*/*z*): calcd for $C_{36}H_{32}N_3O_3$ = 554.2444; found = 554.2547.

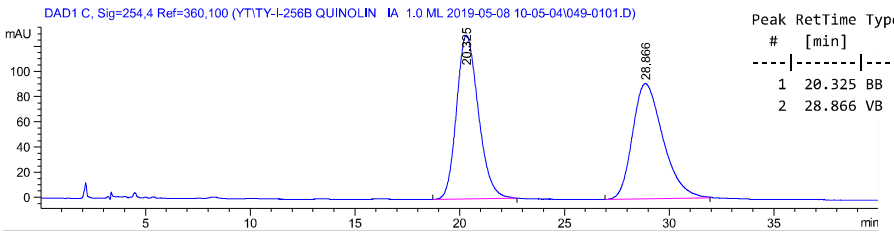
Oxidation of *N*-(di(quinolin-3-yl)methyl)pivalamide (2j): substrate **2j** (110.7 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified

by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient EtOAc over 5 CV, and 0%–40% MeOH/EtOAc over 25 CV).



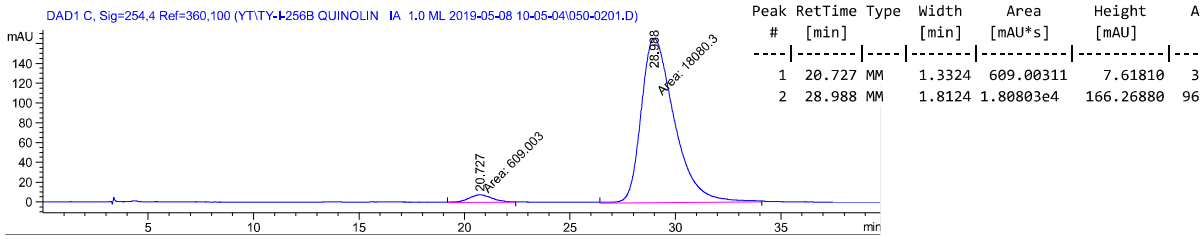
The mono *N*-oxide product **(*S*)-3-(pivalamido(quinolin-3-yl)methyl)quinoline 1-oxide** (**3j**) was obtained as a white solid (91.2 mg, 79%, er = 97:3). **TLC**: R_f (10% MeOH/EtOAc) = 0.70; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 9.01 (d, J = 1.8 Hz, 1 H), 8.62 (s, 1 H), 8.37 (d, J = 8.8 Hz, 1 H), 8.22 (s, 1 H), 8.09 (s, 1 H), 7.97 (s, 1 H), 7.71 (t, J = 7.3 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.52–7.46 (m, 2 H), 7.40–7.33 (m, 2 H), 7.22 (s, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 1.34 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 178.8, 150.3, 147.7, 139.9, 135.3, 135.2, 134.6, 132.8, 130.6, 130.0, 129.39, 129.36, 129.26, 128.1, 127.9, 127.6, 127.4, 125.5, 119.0, 52.6, 39.1, 27.7; **IR** (neat, ν/cm^{-1}) = 1490, 1480, 1406, 1368, 1331, 1272, 1216, 1139, 1088, 975, 854, 787, 750, 663, 573, 479; **HRMS** (ESI, m/z): calcd for $C_{24}H_{24}N_3O_2$ = 386.1869; found = 386.1886; $[\alpha]_{405}^{26}$ +139.9 (c 0.26, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 20.7 min (minor) and 29.0 min (major); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

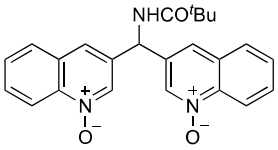


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	20.325	BB	1.0418	9394.09375	129.89325	50
2	28.866	VB	1.3298	9250.86914	91.47790	49

• enantioenriched product

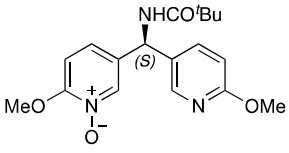


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	20.727	MM	1.3324	609.00311	7.61810	3
2	28.988	MM	1.8124	1.80803e4	166.26880	96



In addition, bis(*N*-oxide) product **3,3'-(pivalamidomethylene)bis(quinoline 1-oxide)** (**4j**) was obtained as a white solid (20.5 mg, 17%). **TLC**: R_f (10% MeOH/EtOAc) = 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.67 (s, 2 H), 8.50 (apparent d, *J* = 8.7 Hz, 3 H), 7.63 (t, *J* = 7.8 Hz, 2 H), 7.58 (d, *J* = 8.2 Hz, 2 H), 7.50–7.47 (m, 4 H), 6.51 (d, *J* = 8.3 Hz, 1 H), 1.33 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 179.1, 140.4, 135.2, 134.3, 130.8, 129.7, 129.5, 128.3, 125.3, 119.4, 52.2, 39.2, 27.7; **IR** (neat, ν/cm^{-1}) = 1656, 1581, 1504, 1369, 1217, 1140, 769, 729; **HRMS** (ESI, *m*/*z*): calcd for $C_{24}H_{24}N_3O_3$ = 402.1818; found = 402.1820.

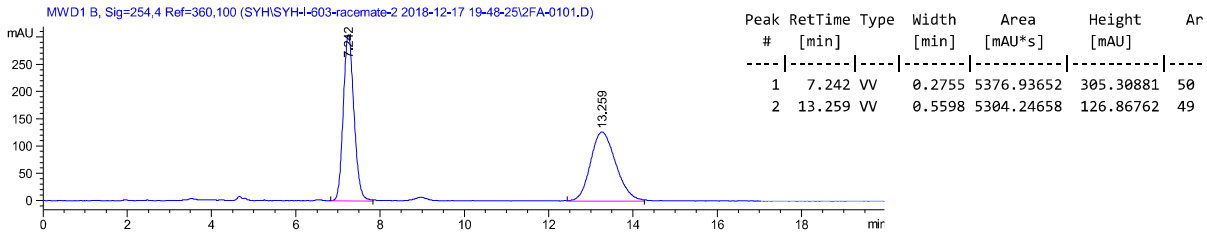
Oxidation of *N*-(bis(6-methoxypyridin-3-yl)methyl)pivalamide (2k): substrate **2k** (98.8 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 96 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient EtOAc over 5 CV, and 0%–60% MeOH/EtOAc over 20 CV).



The mono *N*-oxide product **(*S*)-2-methoxy-5-((6-methoxypyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide** (**3k**) was obtained as a white solid (69.4 mg, 67%, er = 88:12). **TLC**: R_f (50% MeOH/EtOAc) = 0.65; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.26 (d, *J* = 8.5 Hz, 1 H), 8.09 (dd, *J* = 13.5, 2.1 Hz, 2 H), 7.62 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.25 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.18 (d, *J* = 8.7 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.12 (d, *J* = 8.4 Hz, 1 H), 3.94 (s, 3 H), 3.82 (s, 3 H), 1.13 (s,

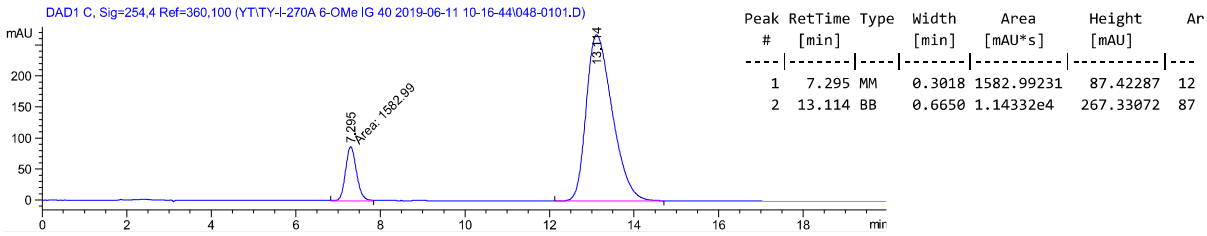
9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.0, 162.9, 157.2, 145.7, 138.5, 138.2, 132.6, 129.9, 126.0, 110.5, 108.9, 57.2, 53.3, 50.3, 38.2, 27.2; **IR** (neat, ν/cm^{-1}) = 1634, 1610, 1521, 1494, 1407, 1384, 1311, 1292, 1256, 1231, 1128, 1022; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_4$ = 346.1767; found = 346.1747; $[\alpha]_{405}^{26}$ +152.4 (*c* 0.29, $CHCl_3$):; enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 7.3 min (minor) and 13.1 min (major); absolute stereochemistry was assigned by analogy to **31**.

• racemic mixture

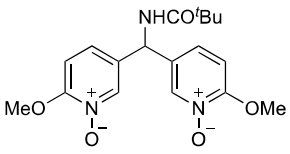


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.242	VV	0.2755	5376.93652	305.30881	50
2	13.259	VV	0.5598	5304.24658	126.86762	49

• enantioenriched product



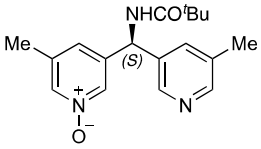
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.295	MM	0.3018	1582.99231	87.42287	12
2	13.114	BB	0.6650	1.14332e4	267.33072	87



In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(2-methoxypyridine 1-oxide)** (**4k**) was obtained as a white solid (6.5 mg, 6%). **TLC**: R_f (50% MeOH/EtOAc) = 0.45; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.24 (d, *J* = 8.6 Hz, 1 H), 8.17 (d, *J* = 2.0 Hz, 2 H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 2 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.11 (d, *J* = 8.6 Hz, 1H), 3.95 (s, 6 H), 1.14 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.0, 157.4, 138.2, 131.7, 125.8,

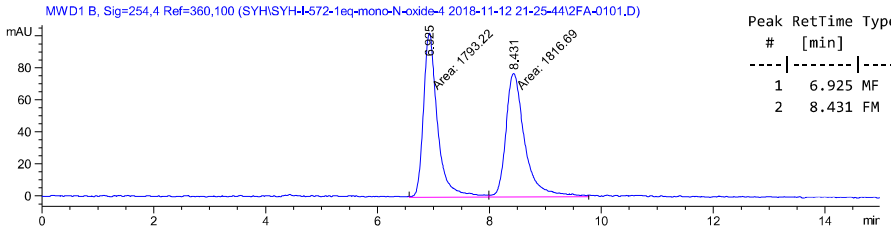
108.9, 57.2, 49.8, 38.2, 27.1; **IR** (neat, ν/cm^{-1}) = 3398, 1636, 1616, 1522, 1410, 1314, 1130, 1015; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{24}N_3O_5$ = 362.1716; found = 362.1733.

Oxidation of *N*-(bis(5-methylpyridin-3-yl)methyl)pivalamide (2l): substrate **2l** (89.3 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 2 CV, and 20%–80% MeOH/EtOAc over 25 CV).



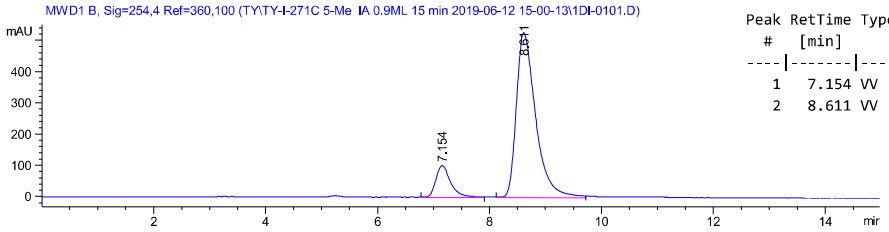
The mono *N*-oxide product **3-methyl-5-((5-methylpyridin-3-yl)(pival-amido)methyl)pyridine 1-oxide** (**3l**) was obtained as a white solid (61.1 mg, 65%, er = 87:13). **TLC**: R_f (50% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.340 (s, 1 H), 8.335 (s, 1 H), 8.30 (d, *J* = 8.5 Hz, 1 H), 8.05 (s, 1 H), 8.01 (s, 1 H), 7.51 (s, 1 H), 7.13 (s, 1 H), 6.17 (d, *J* = 8.5 Hz, 1 H), 2.28 (s, 3 H), 2.22 (s, 3 H), 1.14 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.1, 149.0, 145.9, 140.6, 137.3, 136.6, 135.9, 135.4, 135.0, 132.9, 125.6, 51.3, 38.2, 27.2, 17.9, 17.7; **IR** (neat, ν/cm^{-1}) = 1660, 1515, 1309, 1193, 1164, 859, 724, 677, 572; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{24}N_3O_2$ = 314.1869; found = 314.1879; $[\boldsymbol{\alpha}]_{\mathbf{405}}^{\mathbf{26}}$ +124.1 (*c* 0.39, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 0.9 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 7.2 min (minor) and 8.6 min (major); absolute stereochemistry was determined by the single crystal X-ray diffraction.

• racemic mixture

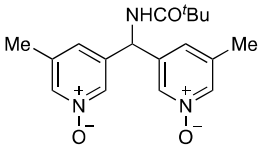


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	6.925	MF	0.2916	1793.22107	102.48090	49.
2	8.431	FM	0.3920	1816.69055	77.23248	50.

• enantioenriched product

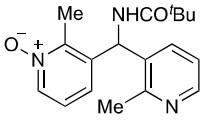


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.154	VV	0.2796	1901.58069	101.97221	13.
2	8.611	VV	0.3603	1.26792e4	527.66888	86.



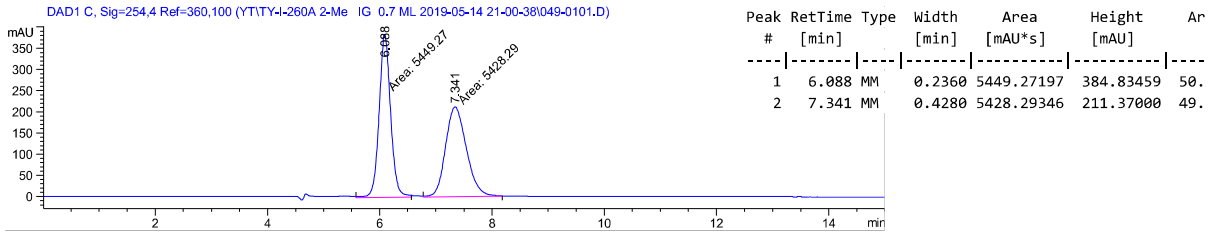
In addition, bis(*N*-oxide) product **5,5'-(pivalamidomethylene)bis(3-methylpyridine 1-oxide)** (**4l**) was obtained as a white solid (34.6 mg, 35%). **TLC**: R_f (50% MeOH/EtOAc) = 0.35; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.25 (d, J = 8.5 Hz, 1 H), 8.03 (s, 2 H), 8.01 (s, 2 H), 7.12 (s, 2 H), 6.08 (d, J = 8.5 Hz, 1 H), 2.19 (s, 6 H), 1.10 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.2, 139.6, 137.6, 136.8, 135.0, 125.6, 50.8, 38.3, 27.1, 17.7; **IR** (neat, ν/cm^{-1}) = 3398, 1648, 1602, 1480, 1408, 1385, 1306, 1165, 1015, 703; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_3$ = 330.1818; found = 330.1844.

Oxidation of *N*-(bis(2-methylpyridin-3-yl)methyl)pivalamide (2m): substrate **2m** (89.3 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–15% MeOH/EtOAc over 2 CV, and 15%–60% MeOH/EtOAc over 25 CV).



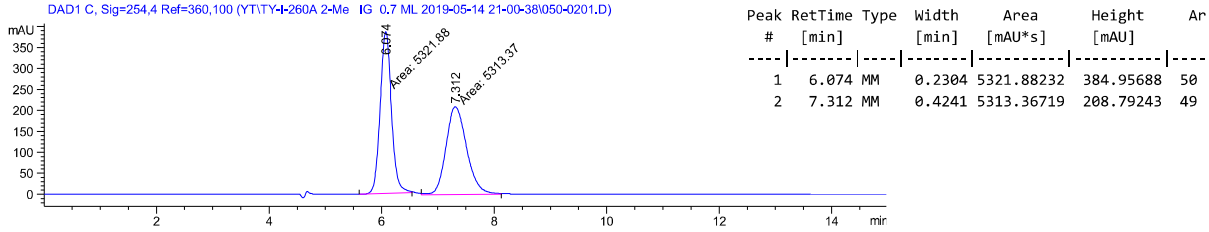
The mono *N*-oxide product **2-methyl-3-((2-methylpyridin-3-yl)(pivalamido)-methyl)pyridine 1-oxide** (**3m**) was obtained as a white solid (52.7 mg, 56%, er = 50:50). **TLC**: R_f (50% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.48 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.21 (d, *J* = 6.4 Hz, 1 H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.13–7.08 (m, 2 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 6.38 (d, *J* = 7.2 Hz, 1 H), 6.10 (d, *J* = 7.2 Hz, 1 H), 2.51 (s, 3 H), 2.36 (s, 3 H), 1.25 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 177.7, 157.4, 149.0, 148.8, 138.8, 137.8, 134.3, 132.7, 123.5, 122.6, 121.7, 51.0, 39.1, 27.7, 22.2, 13.8; **IR** (neat, ν/cm^{-1}) = 1644, 1518, 1482, 1439, 1242, 1200, 835, 736; **HRMS** (ESI, *m*/*z*): calcd for $C_{18}H_{24}N_3O_2$ = 314.1869; found = 314.1876; optical rotation was not measured due to no enatioselectivity; enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 6.1 min and 7.3 min (racemic mixture was obtained).

• racemic mixture

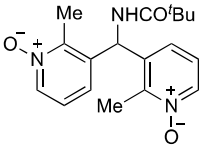


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	6.088	MM	0.2360	5449.27197	384.83459	50.
2	7.341	MM	0.4280	5428.29346	211.37000	49.

• enantioenriched product

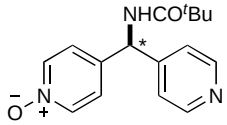


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	6.074	MM	0.2304	5321.88232	384.95688	50
2	7.312	MM	0.4241	5313.36719	208.79243	49



In addition, bis(*N*-oxide) product **3,3'-(pivalamidomethylene)bis(2-methyl-pyridine 1-oxide)** (**4m**) was obtained as a white solid (6.9 mg, 7%). **TLC**: R_f (50% MeOH/EtOAc) = 0.35; **^{1}H NMR** (500 MHz, DMSO-d_6) δ [ppm] = 8.52 (dd, J = 7.9, 2.8 Hz, 1 H), 8.28 (dd, J = 6.6, 2.9 Hz, 2 H), 7.29 (t, J = 6.7 Hz, 2 H), 6.91 (dd, J = 8.1, 2.5 Hz, 2 H), 6.23 (d, J = 6.5 Hz, 1 H), 2.24 (s, 6 H), 1.14 (s, 9 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ [ppm] = 176.9, 147.4, 138.0, 137.1, 123.7, 122.9, 50.1, 38.3, 27.1, 13.2; **IR** (neat, ν/cm^{-1}) = 3261, 1648, 1521, 1483, 1439, 1239, 1209, 833; **HRMS** (ESI, m/z): calcd for $C_{18}H_{24}N_3O_3$ = 330.1818; found = 330.1823.

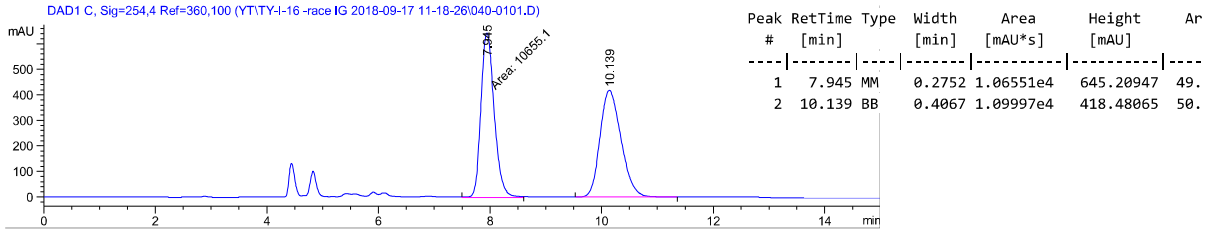
Oxidation of *N*-(di(pyridin-4-yl)methyl)pivalamide (2n): substrate **2n** (80.8 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 18 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 4 CV and 20%–45% MeOH/EtOAc over 12 CV).



The mono *N*-oxide product **4-(pivalamido(pyridin-4-yl)methyl)pyridine 1-oxide** (**3n**) was obtained as a white solid (46.2 mg, 54%, er = 52:48). **TLC**: R_f (50% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.56–8.55 (m, 2 H), 8.42 (d, J = 8.5 Hz, 1 H), 8.22–8.19 (m, 2 H), 7.30–7.28 (m, 4 H), 6.19 (d, J = 8.5 Hz, 1 H), 1.16 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.2, 149.8, 149.6, 138.6, 138.4, 125.6, 122.5, 53.3, 38.2, 27.2; **IR** (neat, ν/cm^{-1}) = 1669, 1608, 1533, 1480, 1244, 1211, 1176, 855; **HRMS** (ESI, m/z): calcd for $C_{16}H_{20}N_3O_2$ = 286.1556; found = 286.1547; enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254

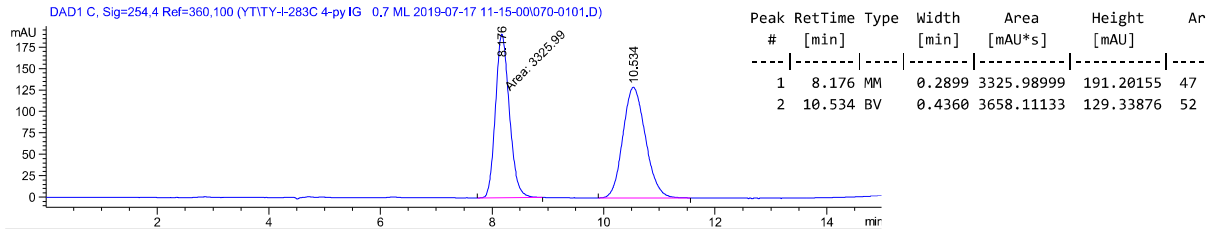
nm; retention time: t_R = 8.2 min (minor) and 10.5 min (major); absolute stereochemistry was not determined and optical rotation was not measured due to low enatioselectivity.

• racemic mixture

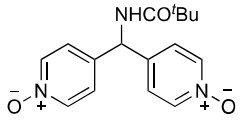


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.945	MM	0.2752	1.06551e4	645.20947	49.
2	10.139	BB	0.4067	1.09997e4	418.48065	50.

• enantioenriched product



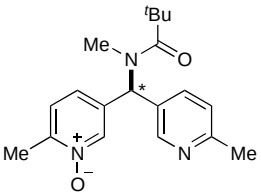
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	8.176	MM	0.2899	3325.98999	191.20155	47
2	10.534	BV	0.4360	3658.11133	129.33876	52



In addition, bis(*N*-oxide) product **4,4'-(pivalamidomethylene)bis(pyridine 1-oxide)** (**4n**) was obtained as a white solid (28.9 mg, 32%). **TLC**: R_f (50% MeOH/EtOAc) = 0.35; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.37 (d, J = 8.5 Hz, 1 H), 8.20 (apparent d, J = 7.1 Hz, 4 H), 7.29 (apparent d, J = 7.1 Hz, 4 H), 6.17 (d, J = 8.5 Hz, 1 H), 1.15 (s, 9 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 177.2, 138.6, 138.3, 125.4, 52.6, 38.2, 27.2; **IR** (neat, ν/cm^{-1}) = 1476, 1236, 1205, 1182, 1161, 849; **HRMS** (ESI, m/z): calcd for $C_{16}H_{20}N_3O_3$ = 302.1505; found = 302.1494.

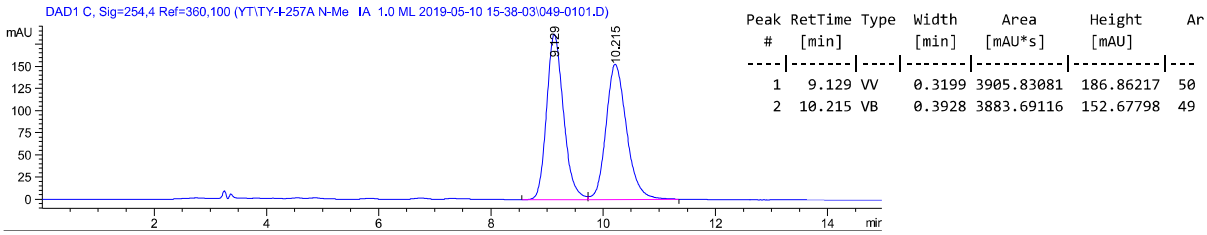
Oxidation of *N*-(bis(6-methylpyridin-3-yl)methyl)-*N*-methylpivalamide (2o): substrate **2o** (93.4 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction

mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–10% MeOH/EtOAc over 2 CV and 10%–50% MeOH/EtOAc over 20 CV).



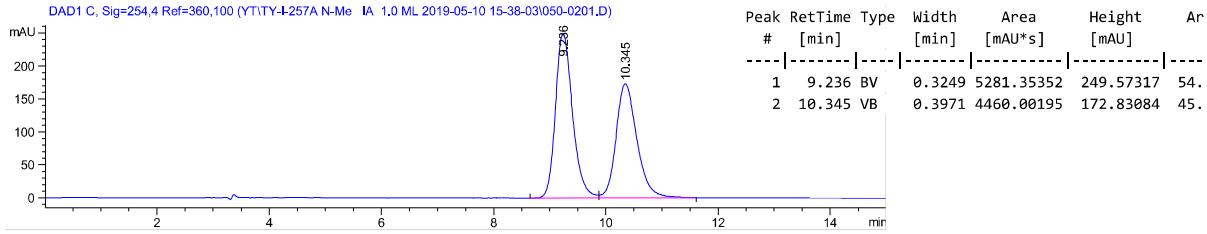
The mono *N*-oxide product **2-methyl-5-((*N*-methylpivalamido)(6-methylpyridin-3-yl)methyl)pyridine 1-oxide** (**3o**) was obtained as a white solid (69.2 mg, 71%, er = 54:46). **TLC**: R_f (50% MeOH/EtOAc) = 0.70; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.32 (d, J = 2.2 Hz, 1 H), 8.06 (s, 1 H), 7.35 (dd, J = 8.1, 2.4 Hz, 1 H), 7.24 (d, J = 8.1 Hz, 1 H), 7.16 (d, J = 8.1 Hz, 1 H), 7.01 (s, 1 H), 6.97 (d, J = 8.2 Hz, 1 H), 2.91 (s, 3 H), 2.56 (s, 3 H), 2.51 (s, 3 H), 1.34 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.3, 158.6, 149.4, 148.3, 139.1, 136.9, 135.9, 129.8, 126.4, 126.0, 123.4, 57.5, 39.6, 33.8, 28.3, 24.2, 17.7; **IR** (neat, ν/cm^{-1}) = 1625, 1479, 1401, 1360, 1262, 1222, 1082, 727; **HRMS** (ESI, *m*/*z*): calcd for $C_{19}H_{26}N_3O_2$ = 328.2025; found = 328.2036; $[\alpha]_{405}^{26}$ +3.1 (*c* 0.66, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 9.2 min (major) and 10.3 min (minor); absolute stereochemistry was not determined.

• racemic mixture

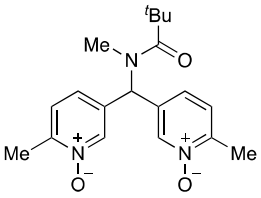


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	9.129	VV	0.3199	3905.83081	186.86217	50
2	10.215	VB	0.3928	3883.69116	152.67798	49

• enantioenriched product

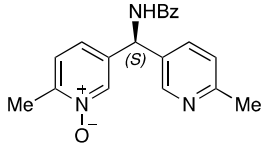


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	9.236	BV	0.3249	5281.35352	249.57317	54.
2	10.345	VB	0.3971	4460.00195	172.83084	45.



In addition, bis(*N*-oxide) product **5,5'-((*N*-methylpivalamido)-methylene)bis(2-methylpyridine 1-oxide)** (**4o**) was obtained as a white solid (28.8 mg, 28%). **TLC**: R_f (50% MeOH/EtOAc) = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.08 (s, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 1.3 Hz, 1 H), 6.95 (apparent t, *J* = 2.1 Hz, 2 H), 2.95 (s, 3 H), 2.51 (s, 6 H), 1.33 (s, 9 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 178.5, 148.9, 139.3, 134.6, 126.6, 125.9, 57.0, 39.6, 33.9, 28.3, 17.7; **IR** (neat, ν/cm^{-1}) = 1632, 1495, 1192, 785, 751, 614, 474, 401; **HRMS** (ESI, *m*/*z*): calcd for $C_{19}H_{26}N_3O_3$ = 344.1974; found = 344.1980.

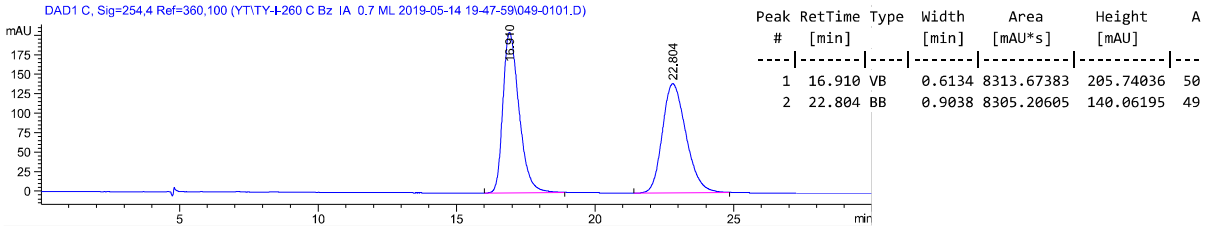
Oxidation of *N*-(bis(6-methylpyridin-3-yl)methyl)benzamide (2p): substrate **2p** (95.2 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–15% MeOH/EtOAc over 2 CV and 15%–60% MeOH/EtOAc over 20 CV).



The mono *N*-oxide product **(*S*)-5-(benzamido(6-methylpyridin-3-yl)-methyl)-2-methylpyridine 1-oxide** (**3p**) was obtained as a white solid (67.0 mg, 67%, er = 84:16). **TLC**: R_f (50% MeOH/EtOAc) = 0.80; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.45 (d, *J* = 2.2 Hz, 1 H), 8.33 (s, 1 H), 7.87 (d, *J* = 7.4 Hz, 2 H), 7.73 (dd, *J* = 8.1, 2.4 Hz, 1 H), 7.58–7.52 (m, 2 H), 7.48–7.44 (m, 3 H), 7.34 (d, *J* = 8.1 Hz, 1

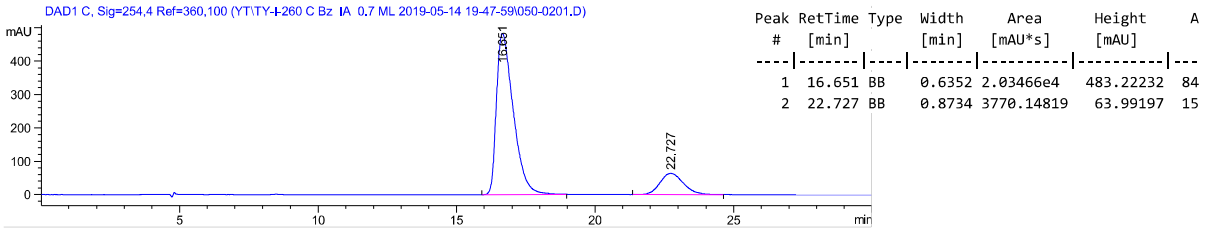
H), 6.53 (s, 1 H), 2.54 (s, 3 H), 2.50 (s, 3 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 169.8, 159.3, 149.8, 148.9, 140.1, 139.6, 138.1, 134.9, 134.4, 133.2, 129.7, 129.6, 128.7, 128.4, 125.1, 53.5, 23.5, 17.4; **IR** (neat, ν/cm^{-1}) = 1643, 1602, 1578, 1531, 1490, 1449, 1413, 1330, 1259, 1225, 711; **HRMS** (ESI, *m/z*): calcd for $C_{20}H_{20}N_3O_2$ = 314.1869; found = 334.1571; $[\alpha]_{405}^{26}$ +129.5 (*c* 0.41, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 16.7 min (major) and 22.7 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

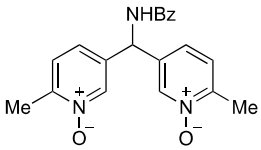


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	16.910	VB	0.6134	8313.67383	205.74036	50
2	22.804	BB	0.9038	8305.20605	140.06195	49

• enantioenriched product



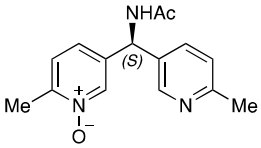
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	16.651	BB	0.6352	2.03466e4	483.22232	84
2	22.727	BB	0.8734	3770.14819	63.99197	15



In addition, bis(*N*-oxide) product **5,5'-(benzamidomethylene)bis(2-methylpyridine 1-oxide)** (**4p**) was obtained as a white solid (33.5 mg, 32%). **TLC**: R_f (50% MeOH/EtOAc) = 0.55; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 9.00 (d, *J* = 8.4 Hz, 1 H), 8.30 (s, 2 H), 7.95 (d, *J* = 8.5 Hz, 2 H), 7.48 (t, *J* = 7.4 Hz, 1 H),

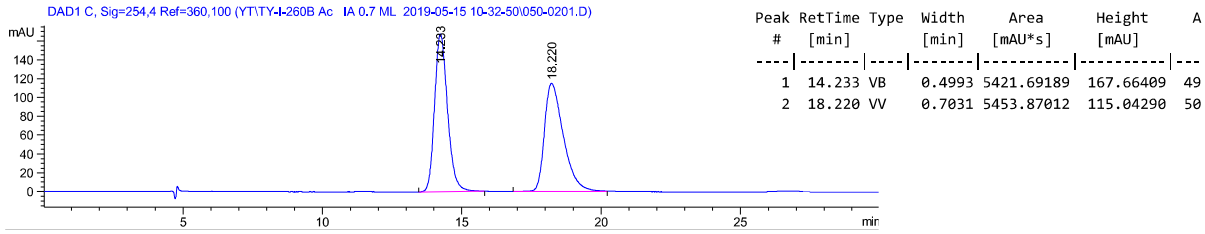
7.37 (t, J = 7.7 Hz, 2 H), 7.20–7.16 (m, 4 H), 6.47 (d, J = 8.4 Hz, 1 H), 2.38 (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 167.3, 148.5, 138.6, 137.3, 133.1, 132.2, 128.6, 127.8, 126.6, 125.9, 51.7, 17.7; **IR** (neat, ν/cm^{-1}) = 1506, 1256, 1222, 1004, 919, 725, 643, 583, 453; **HRMS** (ESI, *m/z*): calcd for $C_{20}H_{20}N_3O_3$ = 350.1505; found = 350.1505.

Oxidation of *N*-(bis(6-methylpyridin-3-yl)methyl)acetamide (2q): substrate **2q** (76.6 mg, 0.30 mmol, 1.0 equiv) was subjected to *N*-oxidation (reaction time: 12 h) according to the general procedure. The quenched reaction mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–20% MeOH/EtOAc over 2 CV and 20%–100% MeOH/EtOAc over 26 CV).



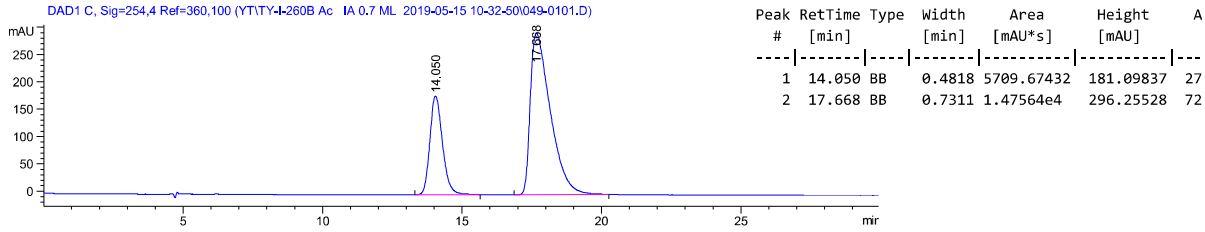
The mono *N*-oxide product **(*S*)-5-(acetamido(6-methylpyridin-3-yl)-methyl)-2-methylpyridine 1-oxide** (**3q**) was obtained as a white solid (56.1 mg, 69%, er = 72:28). **TLC**: R_f (50% MeOH/EtOAc) = 0.45; **^{1}H NMR** (400 MHz, CD_3OD) δ [ppm] = 8.38 (d, *J* = 2.1 Hz, 1 H), 8.27 (s, 1 H), 7.65 (dd, *J* = 8.1, 2.3 Hz, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 6.26 (s, 1 H), 2.53 (s, 3 H), 2.50 (s, 3 H), 2.06 (s, 3 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (101 MHz, CD_3OD) δ [ppm] = 172.6, 159.3, 149.8, 148.7, 140.2, 139.4, 137.8, 134.5, 129.4, 128.4, 125.1, 53.1, 23.5, 22.5, 17.3; **IR** (neat, ν/cm^{-1}) = 3258, 1647, 1543, 1508, 1493, 1448, 1372, 1255; **HRMS** (ESI, *m/z*): calcd for $C_{15}H_{18}N_3O_2$ = 272.1399; found = 272.1395; $[\boldsymbol{\alpha}]_{\mathbf{405}}^{\mathbf{26}}$ +183.1 (*c* 0.35, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IA; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 14.1 min (major) and 17.7 min (minor); absolute stereochemistry was assigned by analogy to **3l**.

• racemic mixture

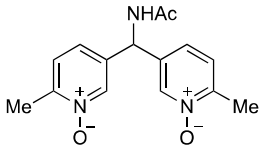


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	14.233	VB	0.4993	5421.69189	167.66409	49
2	18.220	VV	0.7031	5453.87012	115.04290	50

• enantioenriched product



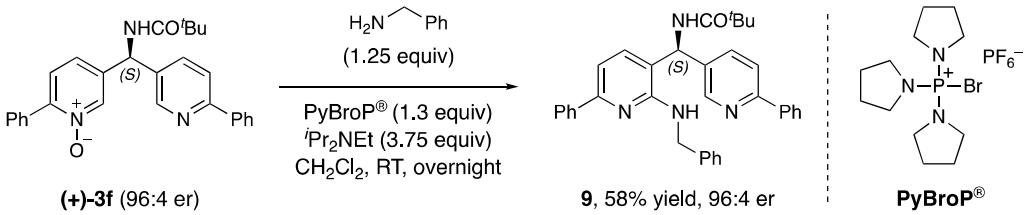
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	14.050	BB	0.4818	5709.67432	181.09837	27
2	17.668	BB	0.7311	1.47564e4	296.25528	72



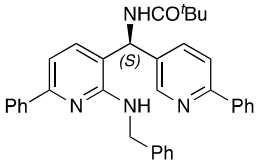
In addition, bis(*N*-oxide) product **5,5'-(acetamidomethylene)bis(2-methylpyridine 1-oxide)** (**4q**) was obtained as a white solid (24.4 mg, 30%). **TLC**: R_f (50% MeOH/EtOAc) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.54 (d, *J* = 8.6 Hz, 1 H), 8.29 (s, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 6.27 (d, *J* = 8.6 Hz, 1 H), 2.45 (s, 6 H), 2.12 (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [ppm] = 170.3, 148.5, 138.4, 137.6, 126.7, 125.8, 51.3, 23.1, 17.7; **IR** (neat, ν/cm^{-1}) = 1658, 1540, 1508, 1448, 1371, 1254, 1224, 1007; **HRMS** (ESI, *m*/*z*): calcd for $C_{15}H_{18}N_3O_3$ = 288.1348; found = 288.1351.

5. Derivatization from enantioenriched mono *N*-oxide product

(a) amination of **3f**:

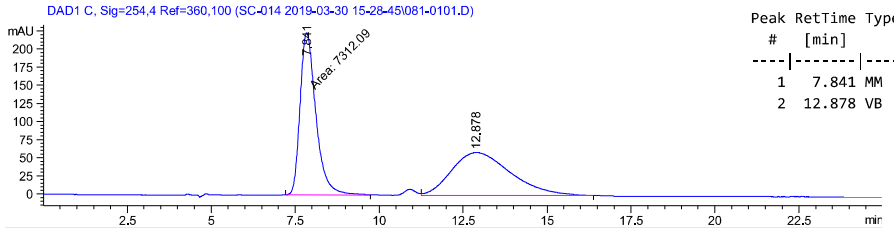


(*S*)-*N*-((2-(Benzylamino)-6-phenylpyridin-3-yl)(6-phenylpyridin-3-yl)methyl)pivalamide (9)



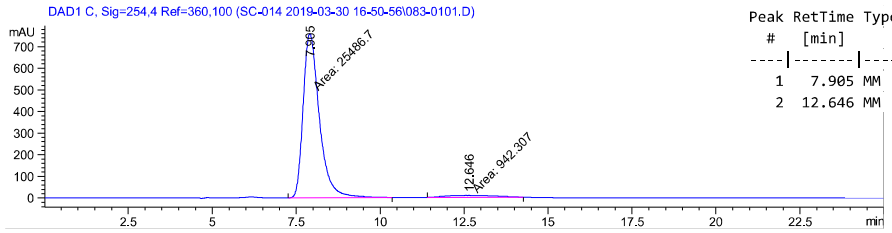
The procedure was modified from the literature (*36–37*). In a 1-dram vial equipped with a magnetic stir bar, (*S*)-2-phenyl-5-((6-phenylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide **3f** (96:4 er, 87.5 mg, 0.20 mmol, 1.00 equiv), benzylamine (27.3 μL, 0.25 mmol, 1.25 equiv) and ^{i}Pr$_2$EtN (130.6 μL, 0.75 mmol, 3.75 equiv) were dissolved in CH_2Cl_2 (0.8 mL, 0.25 M). PyBroP® (bromotripyrrolidinophosphonium hexafluorophosphate, 121.2 mg, 0.26 mmol, 1.30 equiv) was added to the solution, and the reaction was tightly capped and stirred at room temperature overnight. The crude mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 12 g; gradient 1%–6% MeOH/CH_2Cl_2 over 10 CV, 6% MeOH/CH_2Cl_2 over 2 CV, 6%–10% MeOH/CH_2Cl_2 over 3 CV, and 10% MeOH/CH_2Cl_2 over 2 CV) to afford the desired product (61.1 mg, 58%, er = 96:4) as a white solid.

• derivatization product from racemic mono *N*-oxide



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	7.841	MM	0.5458	7312.08643	223.30182	50
2	12.878	VB	1.4400	7204.80371	58.94584	49

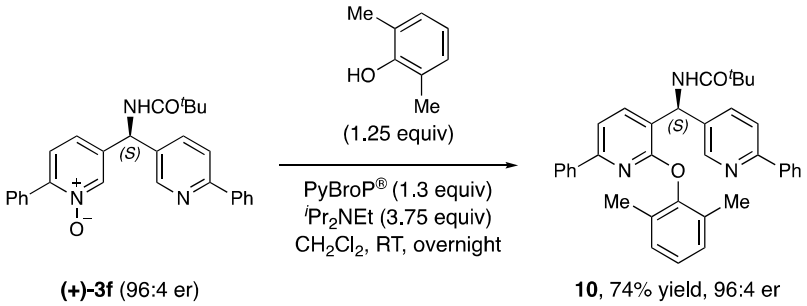
• derivatization product from enantioenriched mono *N*-oxide



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.905	MM	0.5598	2.54867e4	758.78455	96
2	12.646	MM	1.7603	942.30664	8.92181	3

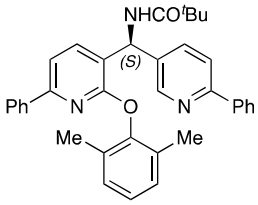
TLC: R_f (10% MeOH/DCM) = 0.85; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.65 (d, *J* = 2.3 Hz, 1 H), 8.02–7.98 (m, 4 H), 7.75 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.61 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.46–7.40 (m, 3 H), 7.38–7.36 (m, 3 H), 7.31–7.28 (m, 2 H), 7.25–7.22 (m, 1 H), 7.04 (d, *J* = 2.3 Hz, 1 H), 7.00 (d, *J* = 2.3 Hz, 1 H),6.40 (d, *J* = 8.8 Hz, 1 H), 6.19 (d, *J* = 8.7 Hz, 1 H), 5.37 (t, *J* = 5.5 Hz, 1 H), 4.93 (dd, *J* = 14.6, 5.8 Hz, 1 H), 4.72 (dd, *J* = 14.6, 5.1 Hz, 1 H), 1.19 (s, 9 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ [ppm] = 178.7, 157.1, 155.6, 155.1, 148.2, 140.3, 139.4, 138.8, 137.0, 136.0, 133.5, 129.4, 129.0, 128.9, 128.63, 128.60, 128.0, 127.1, 127.0, 126.9, 120.5, 117.9, 108.8, 49.8, 45.6, 39.1, 27.6; **IR** (neat, ν/cm^{-1}) = 1626, 1573, 1416, 1400, 1182, 870, 819, 760, 713, 647, 620, 574, 540, 456, 435; **HRMS** (ESI, *m*/*z*): calcd for $C_{35}H_{35}N_4O$ = 527.2811; found = 527.2802; $[\alpha]_{583}^{26}$ –23.4 (*c* 0.30, $CHCl_3$):; enantiomeric ratio was retained, confirmed by **HPLC**: column: Chiralpak® IC; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 7.8 min (major) and 12.8 min (minor).

(b) etherification of **3f**:



(+)-3f (96:4 er) **10**, 74% yield, 96:4 er

(*S*)-*N*-((2-(2,6-Dimethylphenoxy)-6-phenylpyridin-3-yl)(6-phenylpyridin-3-yl)methyl)pival-amide (10)

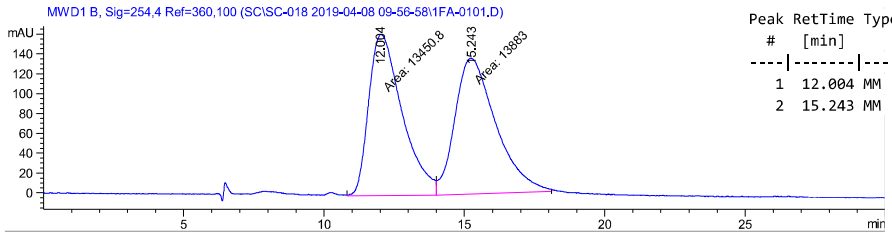


The procedure was adapted from the amination method above mentioned. In a 1-dram vial equipped with a magnetic stir bar, (*S*)-2-phenyl-5-((6-phenylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide **3f** (96:4 er, 87.5 mg, 0.20 mmol, 1.00 equiv), 2,6-dimethylphenol (30.5 mg, 0.25 mmol, 1.25 equiv) and ^{i}Pr$_2$EtN (130.6 μL, 0.75 mmol, 3.75 equiv) were dissolved in CH_2Cl_2 (0.8 mL, 0.25 M). PyBroP® (bromotripyrrolidinophosphonium hexafluorophosphate, 121.2 mg, 0.26 mmol, 1.30 equiv) was added to the solution, and the reaction was tightly capped and stirred at room temperature overnight. The crude mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 12 g; gradient 1%–6% MeOH/CH_2Cl_2 over 10 CV, 6% MeOH/CH_2Cl_2 over 2 CV, 6%–10% MeOH/CH_2Cl_2 over 1 CV, and 10% MeOH/CH_2Cl_2 over 2 CV) to afford the desired product (80.2 mg, 74%, er = 96:4) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.80; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.66 (d, *J* = 2.3 Hz, 1 H), 7.97–7.95 (m, 2 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.70–7.65

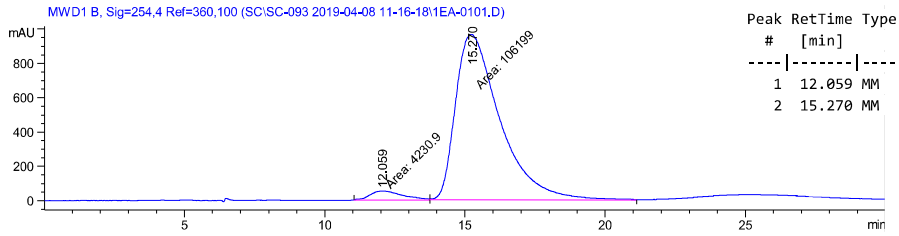
(m, 4 H), 7.51–7.45 (m, 3 H), 7.43–7.40 (m, 1 H), 7.33–7.28 (m, 3 H), 7.21–6.99 (m, 4 H), 6.60 (d, J = 8.5 Hz, 1 H), 2.04 (s, 3 H), 1.61 (s, 3 H), 1.33 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 178.0, 159.4, 156.5, 154.7, 150.1, 148.1, 139.5, 137.9, 135.3, 135.0, 129.25, 129.19, 129.0, 128.9, 128.8, 128.7, 128.4, 127.0, 126.6, 125.3, 120.4, 120.3, 114.0, 51.9, 39.2, 27.8, 17.1, 16.4 (two overlapping peaks in the aromatic region); **IR** (neat, ν/cm^{-1}) = 1642, 1498, 1474, 1440, 1389, 1268, 1244, 1174, 923, 827, 760, 741, 713, 691, 643, 571, 492; **HRMS** (ESI, m/z): calcd for $C_{36}H_{36}N_3O_2$ = 542.2808; found = 542.2803; $[\alpha]_{583}^{26}$ 51.1 (c 0.36, $CHCl_3$): +; enantiomeric ratio was retained, confirmed by **HPLC**: column: Chiralpak® IC; eluent: 100% EtOH; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 12.0 min (minor) and 15.3 min (major).

• derivatization product from racemic mono *N*-oxide



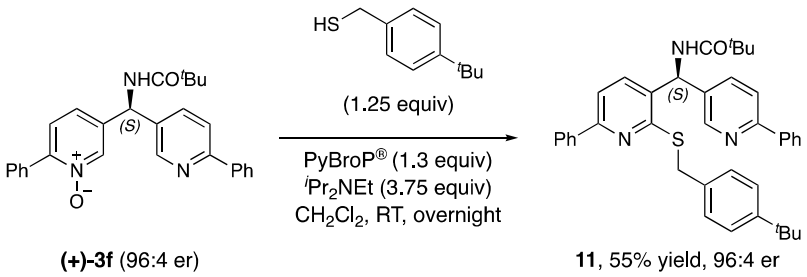
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	12.004	MM	1.3818	1.34508e4	162.23297	49
2	15.243	MM	1.6938	1.38830e4	136.60722	50

• derivatization product from enantioenriched mono *N*-oxide

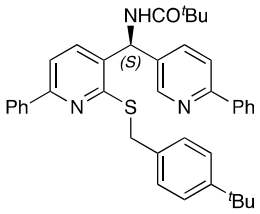


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	12.059	MM	1.3515	4230.90479	52.17625	3
2	15.270	MM	1.8384	1.06199e5	962.79346	96

(c) thioetherification of **3f**:



(*S*)-*N*-((2-((4-(*tert*-Butyl)benzyl)thio)-6-phenylpyridin-3-yl)(6-phenylpyridin-3-yl)methyl)pi-valamide (11)

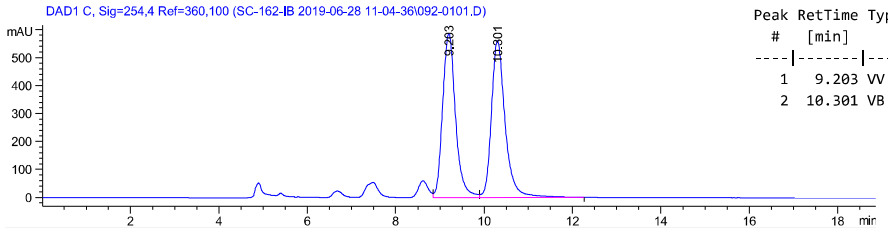


The procedure was adapted from the amination method above mentioned. In a 1-dram vial equipped with a magnetic stir bar, (*S*)-2-phenyl-5-((6-phenylpyridin-3-yl)(pivalamido)methyl)pyridine 1-oxide **3f** (96:4 er, 87.5 mg, 0.20 mmol, 1.00 equiv), (4-*tert*-butyl)benzyl mercaptan (46.7 μL, 0.25 mmol, 1.25 equiv) and ^{i}Pr$_2$EtN (130.6 μL, 0.75 mmol, 3.75 equiv) were dissolved in CH_2Cl_2 (0.8 mL, 0.25 M). PyBroP® (bromotripyrrolidinophosphonium hexafluorophosphate, 121.2 mg, 0.26 mmol, 1.30 equiv) was added to the solution, and the reaction was tightly capped and stirred at room temperature overnight. The crude mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 12 g; gradient 1%–6% MeOH/CH_2Cl_2 over 10 CV and 6% MeOH/CH_2Cl_2 over 2 CV) to afford the desired product (69.6 mg, 58%, er = 96:4) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.85; **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm] = 8.58 (s, 1 H), 8.04 (d, *J* = 8.2 Hz, 2 H), 8.00–7.97 (m, 2 H), 7.68 (d, *J* = 8.2 Hz, 1 H), 7.55–7.54 (m, 1 H), 7.50 (s, 2 H), 7.48–7.45 (m, 4 H), 7.44–7.40 (m, 2 H), 7.26–7.25 (m, 4 H), 6.62 (d, *J* = 7.6 Hz, 1 H), 6.41 (d, *J* = 7.6 Hz, 1 H), 4.69 (d, *J* = 13.4

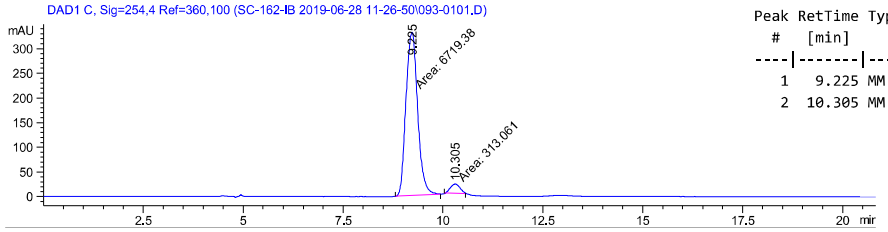
Hz, 1 H), 4.49 (d, J = 13.4 Hz, 1 H), 1.27 (s, 9 H), 1.21 (s, 9 H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm] = 178.0, 157.2, 156.5, 155.9, 150.2, 148.2, 138.5, 136.9, 136.2, 135.0, 133.9, 131.54, 131.53, 129.5, 129.4, 129.0, 128.9, 128.7, 127.1, 126.9, 125.6, 120.5, 116.1, 52.4, 39.1, 34.61, 34.56, 31.5, 27.7; **IR** (neat, ν/cm^{-1}) = 1629, 1526, 1474, 1425, 1362, 1201, 1018, 836, 741, 690, 636, 561, 407; **HRMS** (ESI, m/z): calcd for $C_{39}H_{42}N_3OS$ = 600.3049; found = 600.3059; $[\alpha]_{583}^{26}$ +33.8 (c 0.41, $CHCl_3$):; enantiomeric ratio was retained, confirmed by **HPLC**: column: Chiralpak® IB; eluent: 20% EtOH/^{n}hexane; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 9.2 min (major) and 10.3 min (minor).

• derivatization product from racemic mono *N*-oxide



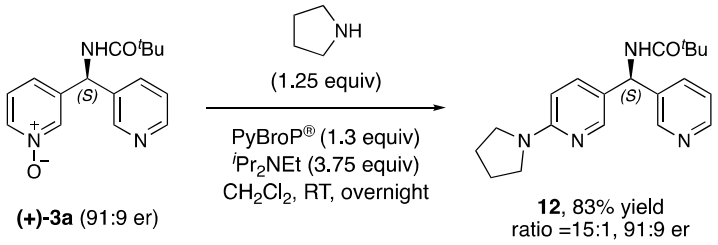
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	9.203	VV	0.3155	1.18460e4	586.87042	49
2	10.301	VB	0.3249	1.20416e4	560.03259	50

• derivatization product from enantioenriched mono *N*-oxide

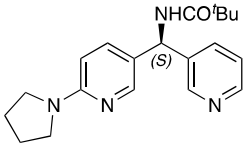


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	9.225	MM	0.3383	6719.37500	331.02069	95
2	10.305	MM	0.2772	313.06134	18.82577	4

(d) amination of **3a**:



(*S*)-*N*-(pyridin-3-yl(6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)pivalamide (12)

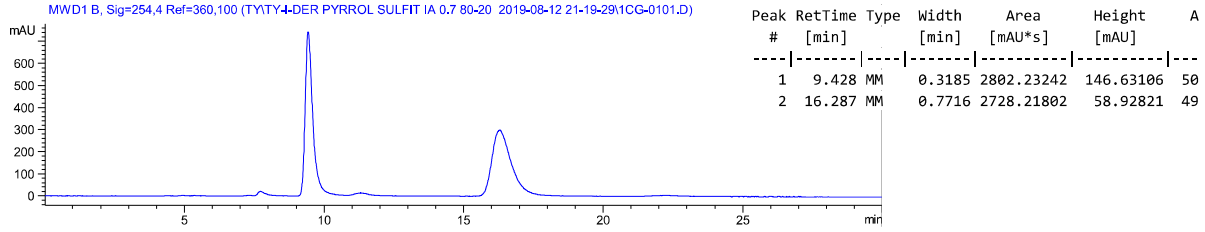


The procedure was adapted from the amination method above mentioned. In a 1-dram vial equipped with a magnetic stir bar, (*S*)-3-(pivalamido(pyridin-3-yl)methyl)pyridine 1-oxide **3a** (91:9 er, 42.8 mg, 0.15 mmol, 1.00 equiv), pyrrolidine (15.7 μL, 0.19 mmol, 1.25 equiv) and ^{i}Pr$_2$EtN (97.5 μL, 0.56 mmol, 3.75 equiv) were dissolved in CH_2Cl_2 (0.6 mL, 0.25 M). PyBroP® (93.2 mg, 0.20 mmol, 1.30 equiv) was added to the solution, and the reaction was tightly capped and stirred at room temperature overnight. The crude mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 12 g; gradient 1%–6% MeOH/CH_2Cl_2 over 10 CV, 6% MeOH/CH_2Cl_2 over 2 CV, 6%–10% MeOH/CH_2Cl_2 over 3 CV, and 10% MeOH/CH_2Cl_2 over 2 CV) to afford the desired product (41.6 mg, 82%, regioisomeric ratio = 15:1, 91:9 er) as a colorless oil.

TLC: R_f (10% MeOH/EtOAc) = 0.35; the ratio of regioisomers was 15:1 as determined by NMR; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.52–8.50 (m, 2 H), 8.00 (d, *J* = 2.5 Hz, 1 H), 7.52 (dd, *J* = 7.5, 2.3 Hz, 1 H), 7.25–7.24 (m, 1 H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.32 (d, *J* = 8.7 Hz, 1 H), 6.11 (d, *J* = 7.2 Hz, 1 H), 6.05 (d, *J* = 7.2 Hz, 1 H), 3.44–3.42 (m, 4 H), 2.02–1.98 (m, 4 H), 1.23 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 177.7, 157.0, 148.8, 148.6, 147.5, 137.2, 136.6, 134.8, 123.5, 123.0, 106.8, 53.0, 46.9, 38.9, 27.7, 25.7; **IR** (neat, ν/cm^{-1}) = 3060, 2952, 2897, 1772, 1714, 1597, 1505, 1394, 1249, 1184, 1122, 1039, 1022, 854, 719; **HRMS** (ESI, *m*/*z*): calcd for $C_{20}H_{27}N_4O$ = 339.2185; found = 339.2174; $[\alpha]_{583}^{26}$ –60.8 (*c* 0.81, $CHCl_3$):; enantiomeric ratio was retained, confirmed by **HPLC**:

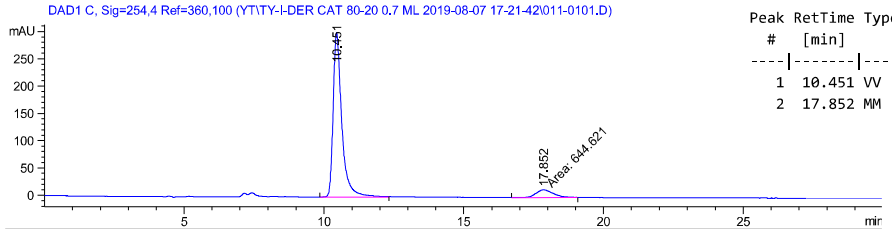
column: Chiralpak® IA; eluent: 80% EtOH/*n*hexane; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 10.5 min (major) and 17.9 min (minor).

• derivatization product from racemic mono *N*-oxide



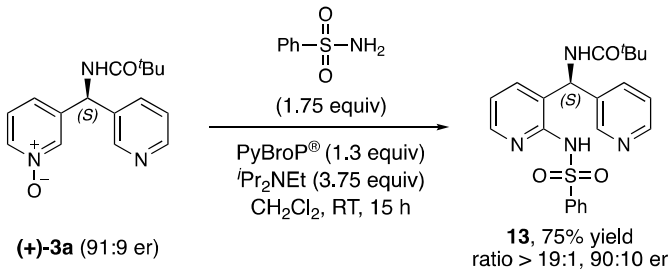
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	9.428	MM	0.3185	2802.23242	146.63106	50
2	16.287	MM	0.7716	2728.21802	58.92821	49

• derivatization product from enantioenriched mono *N*-oxide



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	10.451	VV	0.3200	6498.48242	300.88828	90
2	17.852	MM	0.7624	644.62128	14.09175	9

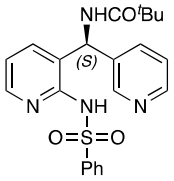
(e) sulfonamidation of **3a**:



(+)-3a (91:9 er)

13, 75% yield
ratio > 19:1, 90:10 er

(*S*)-*N*-((2-(Phenylsulfonamido)pyridin-3-yl)(pyridin-3-yl)methyl)pivalamide (13)

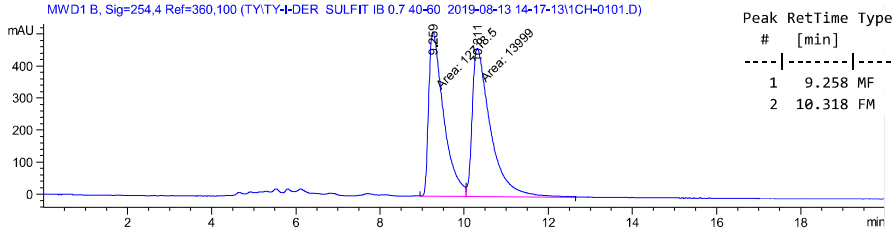


The procedure was adapted from the amination method above mentioned. In a 1-dram vial equipped with a magnetic stir bar, (*S*)-3-(pivalamido(pyridin-3-yl)methyl)pyridine 1-oxide **3a** (91:9 er, 42.8 mg, 0.15 mmol, 1.00 equiv), benzenesulfonamide (40.9 mg, 0.26 mmol, 1.75 equiv)

and $^{i}Pr_2EtN$ (97.5 µL, 0.56 mmol, 3.75 equiv) were dissolved in CH_2Cl_2 (0.6 mL, 0.25 M). PyBroP® (93.2 mg, 0.20 mmol, 1.30 equiv) was added to the solution, and the reaction was tightly capped and stirred at room temperature for 15 h. The crude mixture was purified by normal phase column chromatography (Biotage®, SNAP Ultra 12 g; gradient 1%–6% MeOH/CH_2Cl_2 over 10 CV, 6% MeOH/CH_2Cl_2 over 2 CV, 6%–10% MeOH/CH_2Cl_2 over 3 CV, and 10% MeOH/CH_2Cl_2 over 2 CV) to afford the desired product (47.7 mg, 75%, regioisomeric ratio >19:1, 90:10 er) as a colorless oil.

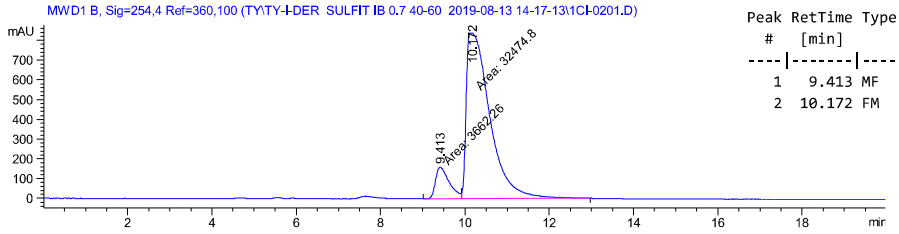
TLC: R_f (10% MeOH/EtOAc) = 0.35; the ratio of regioisomers was >19:1 as determined by NMR; **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm] = 8.37 (d, J = 4.8 Hz, 1 H), 8.33 (d, J = 2.4 Hz, 1 H), 8.21 (d, J = 9.0 Hz, 1 H), 7.77 (d, J = 7.1 Hz, 1 H), 7.63–7.51 (m, 3 H), 7.45 (t, J = 7.4 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 2 H), 7.00 (dd, J = 8.0, 4.8 Hz, 1 H), 6.68 (t, J = 6.8 Hz, 1 H), 6.24 (d, J = 9.1 Hz, 1 H), 1.19 (s, 9 H) (missing one *N*-H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm] = 178.4, 152.4, 148.4, 147.9, 142.8, 141.7, 135.8, 133.9, 133.6, 132.1, 130.5, 128.9, 125.7, 123.1, 111.5, 53.1, 39.1, 27.6; **IR** (neat, ν/cm^{-1}) = 3311, 2867, 2361, 1630, 1506, 1417, 1206, 839; **HRMS** (ESI, m/z): calcd for $C_{22}H_{25}N_4O_3S$ = 425.1647; found = 425.1623; $[\alpha]_{583}^{26}$ +74.4 (c 0.47, $CHCl_3$):; enantiomeric ratio was retained, confirmed by **HPLC**: column: Chiralpak® IB; eluent: 40% EtOH/^{n}hexane; flow rate: 0.7 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 9.4 min (minor) and 10.2 min (major).

• derivatization product from racemic mono *N*-oxide



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	9.258	MF	0.4090	4752.13721	193.66570	48.
2	10.318	FM	0.4900	5096.94336	173.37173	51.

• derivatization product from enantioenriched mono *N*-oxide

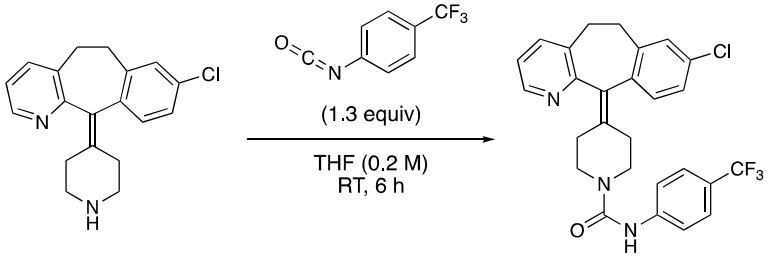


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	9.413	MF	0.3813	3662.26099	160.08775	10
2	10.172	FM	0.6448	3.24748e4	839.34460	89

Application to enantioselective *N*-oxidation of pharmaceutical derivatives

Dynamic kinetic resolution of Loratadine derivative 15

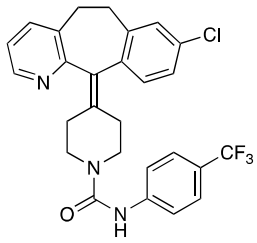
Synthesis of **15**



desloratadine

15, 93%

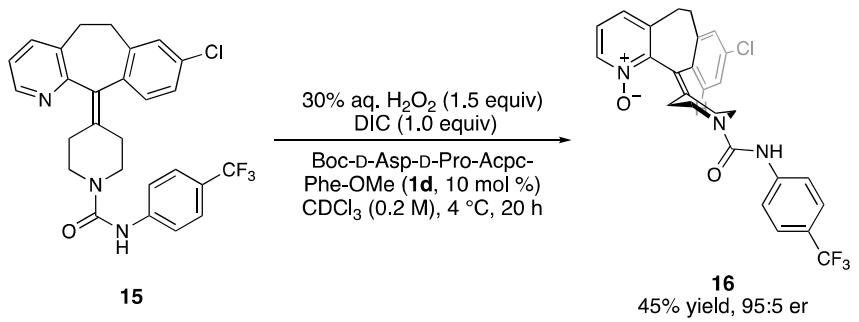
4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-*N*-(4-(trifluoro-methyl)phenyl)piperidine-1-carboxamide (15)



To a 5-dram vial equipped with a stir bar, desloratadine (0.22 g, 0.70 mmol, 1.0 equiv) was dissolved in THF (3.5 mL, 0.2 M), followed by the addition of 4-(trifluoromethyl)phenyl isocyanate (0.13 mL, 0.91 mmol, 1.3 equiv). The reaction was stirred at room temperature for 6 h, then diluted with CH_2Cl_2, and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by normal phase column chromatography (Biotage®, SNAP Ultra 50 g; gradient 0%–100% EtOAc/hexanes over 10 CV) to afford the desired product (0.32 g, 93%) as a white solid.

TLC: R_f (EtOAc) = 0.68; **^{1}H NMR** (600 MHz, $CDCl_3$) δ [ppm] = 8.43 (d, *J* = 4.7 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.51 (apparent s, 4 H), 7.22–7.17 (m, 2 H), 7.15 (s, 2 H), 6.79 (s, 1 H), 3.90–3.88 (m, 1 H), 3.81 (dt, *J* = 11.4, 4.8 Hz, 1 H), 3.42–3.35 (m, 2 H), 3.30–3.29 (m, 2 H), 2.90 (ddd, J = 15.4, 10.3, 4.4 Hz, 1 H), 2.84–2.80 (m, 1 H), 2.71 (ddd, *J* = 13.9, 8.9, 4.4 Hz, 1 H), 2.53 (ddd, *J* = 13.8, 9.1, 4.5 Hz, 1 H), 2.43–2.37 (m, 2 H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ [ppm] = 155.8, 154.4, 145.5, 142.5, 139.5, 139.2, 138.1, 137.3, 134.3, 133.5, 130.7, 129.2, 126.6, 126.2 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 32.4 Hz), 124.4 (q, *J* = 271.4 Hz), 122.9, 119.1, 45.0, 44.8, 31.64, 31.55, 30.65, 30.55 (one overlapping peak in the aromatic region); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ [ppm] = –61.92; **IR** (neat, ν/cm^{-1}) = 3325, 1653, 1600, 1532, 1413, 1317, 1252, 1156, 1106, 1063; **HRMS** (ESI, *m*/*z*): calcd for $C_{27}H_{24}ClF_3N_3O$ = 498.1560; found = 498.1548.

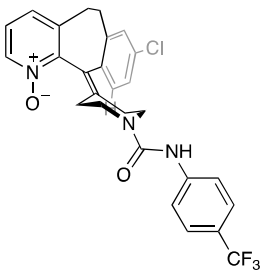
Enantioselective *N*-oxidation of **15**



15

16
45% yield, 95:5 er

(–)-8-Chloro-11-(1-((4-(trifluoromethyl)phenyl)carbamoyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine 1-oxide (16)

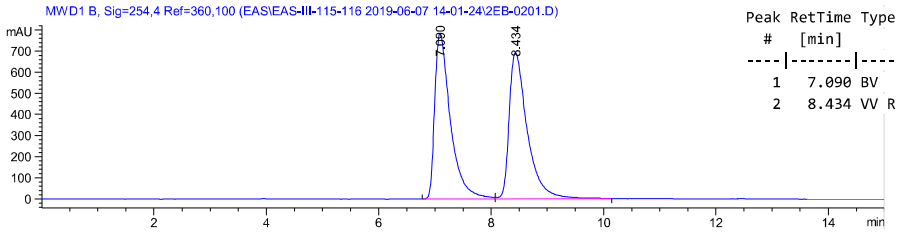


Loratadine derivative **15** (49.8 mg, 0.10 mmol, 1.0 equiv) and peptide **1d** (5.7 mg, 0.01 mmol, 10 mol %) were dissolved in $CDCl_3$ (0.5 mL, 0.2 M) in an HPLC vial equipped with a stir bar, followed by addition of H_2O_2 (30% w/w in H_2O; 15.5 µL, 0.15 mmol, 1.5 equiv). The mixture was cooled to 0 °C in

an ice bath. While stirring vigorously, DIC (15.5 μL, 0.10 mmol, 1.0 equiv) was added. The reaction was transported to a cold room maintained at 4 °C and allowed to stir for 20 h before quenched by addition of Na_2SO_3. The mixture was directly purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–10% MeOH/EtOAc over 9 CV, 10%–12% MeOH/EtOAc over 3 CV, and 12% MeOH/EtOAc over 3 CV) to afford the desired product (22.9 mg, 45%, er = 95:5) as a white solid. [Note: While pyridine *N*-oxidation is preferred, the formation of corresponding epoxide side product was found around 28%, analyzed by UPLC/MS. The epoxide side product was not fully characterized at this point.]

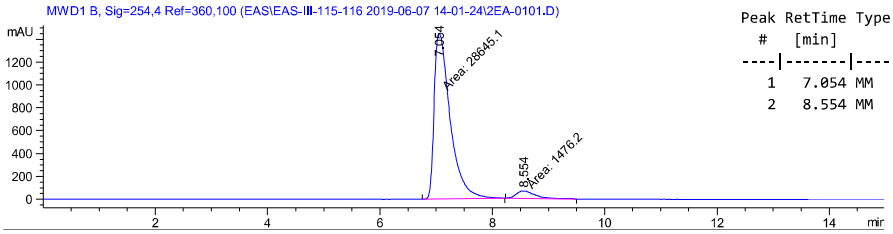
TLC: R_f (10% MeOH/EtOAc) = 0.25; **^{1}H NMR** (600 MHz, CD_3OD) δ [ppm] = 8.21 (d, *J* = 6.4 Hz, 1 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.39 (t, *J* = 7.1 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.20 (apparent s, 2 H), 3.83 (tt, *J* = 12.3, 5.3 Hz, 2 H), 3.50–3.39 (m, 4 H), 2.98–2.90 (m, 2 H), 2.60 (ddd, *J* = 13.2, 8.3, 4.2 Hz, 1 H), 2.43 (dt, *J* = 14.0, 4.7 Hz, 1 H), 2.34 (ddd, *J* = 13.2, 8.1, 4.1 Hz, 1 H), 2.04 (ddd, *J* = 14.1, 6.6, 3.9 Hz, 1 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (151 MHz, CD_3OD) δ [ppm] = 157.1, 150.8, 144.9, 142.9, 140.5, 140.4, 138.5, 134.9, 133.6, 131.3, 130.5, 127.0, 126.7 (q, *J* = 3.8 Hz), 126.2, 125.9 (q, *J* = 269.8 Hz), 125.2 (q, *J* = 32.5 Hz), 124.4, 121.0, 45.8, 45.4, 32.9, 32.8, 31.4, 31.1 (one overlapping peak in the aromatic region); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ [ppm] = –61.87; **IR** (neat, ν/cm^{-1}) = 3503, 1653, 1602, 1539, 1323, 1219, 1160, 1100, 1066, 991, 842; **HRMS** (ESI, *m*/*z*): calcd for $C_{27}H_{24}ClF_3N_3O_2$ = 514.1509; found = 514.1505; $[\boldsymbol{\alpha}]_{\mathbf{405}}^{\mathbf{26}}$ –426.1 (*c* 0.20, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IC; eluent: 30% EtOH/*n*hexane; flow rate: 1.0 mL/min: temperature: 25 °C; detection: 254 nm; retention time: t_R = 7.1 min (major) and 8.6 min (minor).

• racemic mixture



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.090	BV	0.2865	1.52061e4	783.29401	49
2	8.434	VV R	0.3306	1.54483e4	691.63916	50

• enantioenriched product



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	7.054	MM	0.3288	2.86451e4	1452.03711	95.
2	8.554	MM	0.3714	1476.20093	66.25084	4.

The absolute stereochemistry of **16** was determined by the single-crystal X-ray crystallography. Crystals of **16** (CCDC 1950546) were obtained by recrystallization from the solution of **16** in CH_2Cl_2 with addition of a few drops of distilled H_2O

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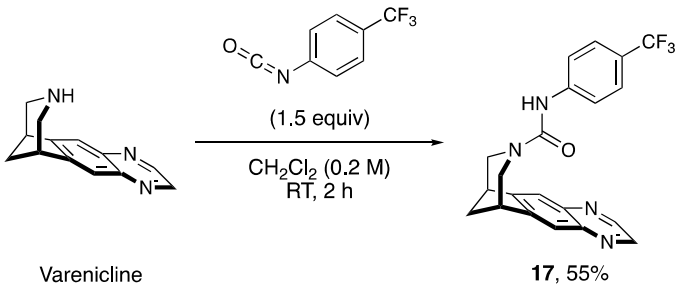
Desymmetrization of Varenicline derivative 17

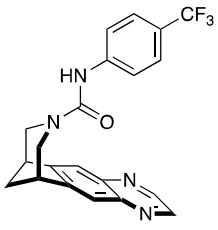
Synthesis of **17**



Varenicline

17, 55%

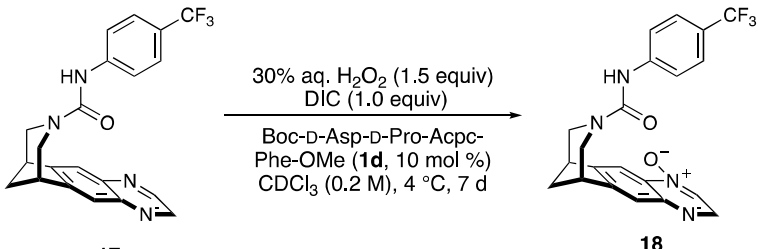
_N_-(4-(Trifluoromethyl)phenyl)-6,7,9,10-tetrahydro-8_H_-6,10-methanoazepino[4,5-_g_]quinoxaline-8-carboxamide (17)



To a 50 mL round bottom flask, Varenicline (211.2 mg, 1.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL, 0.10 M), followed by the addition of 4-(trifluoromethyl)phenyl isocyanate (0.21 mL, 1.5 mmol, 1.5 equiv). The reaction was stirred at room temperature for 2 h, during which time, a white solid gradually formed. The reaction mixture was filtered, and the solid was washed with CH_2Cl_2 and dried *in vacuo* to afford the desired product (220.5 mg, 55%) as a white solid.

TLC: R_f (10% MeOH/EtOAc) = 0.50; **^{1}H NMR** (500 MHz, CD_3OD) δ [ppm] = 8.79 (d, *J* = 1.8 Hz, 2 H), 7.94 (d, *J* = 1.8 Hz, 2 H), 7.39–7.36 (m, 2 H), 7.27–7.25 (m, 2 H), 4.17 (dd, *J* = 12.5, 3.2 Hz, 2 H), 3.57 (dt, *J* = 5.0, 2.5 Hz, 2 H), 3.47 (d, *J* = 12.0 Hz, 2 H), 2.49–2.43 (m, 1 H), 2.17 (dd, *J* = 11.1, 1.8 Hz, 1 H) (missing one *N*-H from deuterium-hydrogen exchange); **^{13}C NMR** (126 MHz, CD_3OD) δ [ppm] = 158.3, 150.7, 145.3, 144.5, 144.3, 126.5 (q, *J* = 3.8 Hz), 122.8, 121.1, 50.7, 42.0, 41.4 (two sets of quartets, coupled with CF_3, in the aromatic region were weak and not observed); **^{19}F{^{1}H} NMR** (470 MHz, CD_3OD) δ [ppm] = –63.44; **IR** (neat, ν/cm^{-1}) = 1656, 1529, 1409, 1309, 1293, 1208, 1180, 1153, 1107, 1063, 1026, 913, 839, 824, 739, 666, 556; **HRMS** (ESI, *m*/*z*): calcd for $C_{21}H_{18}F_3N_4O$ = 399.1433; found = 399.1453.

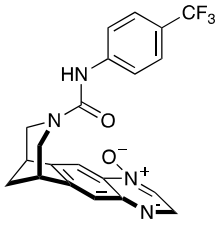
Enantioselective *N*-oxidation of **17**



17

18
61% yield, 95:5 er

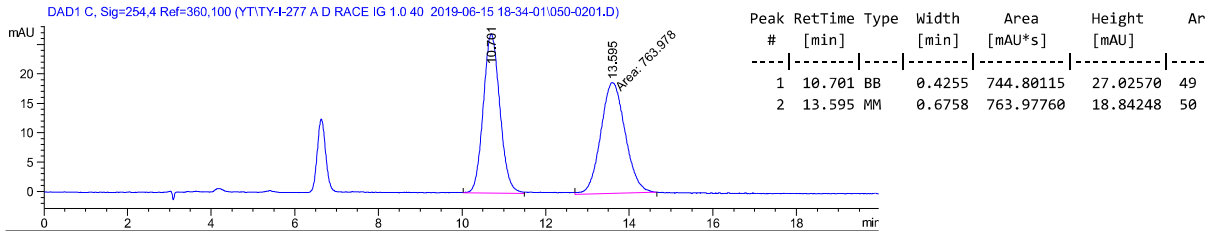
(–)-(6*S*,10*R*)-8-((4-(Trifluoromethyl)phenyl)carbamoyl)-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline 1-oxide (18)



Varenicline derivative **17** (119.5 mg, 0.30 mmol, 1.0 equiv) and peptide **1d** (17.2 mg, 0.03 mmol, 10 mol %) were dissolved in $CDCl_3$ (1.5 mL, 0.2 M) in an HPLC vial equipped with a stir bar, followed by addition of H_2O_2 (30% w/w in H_2O; 46.4 μL, 0.45 mmol, 1.5 equiv). The mixture was cooled to 0 °C in an ice bath. While stirring vigorously, DIC (65.0 μL, 0.42 mmol, 1.4 equiv) was added. The reaction was transported to a cold room maintained at 4 °C and allowed to stir for 7 d, before quenched by addition of Na_2SO_3. The mixture was directly purified by normal phase column chromatography (Biotage®, SNAP Ultra 25 g; gradient 0%–30% MeOH/EtOAc over 4 CV, and 30%–40% MeOH/EtOAc over 8 CV) to afford the desired product (75.9 mg, 61%, er = 95.5:4.5) as a white solid.

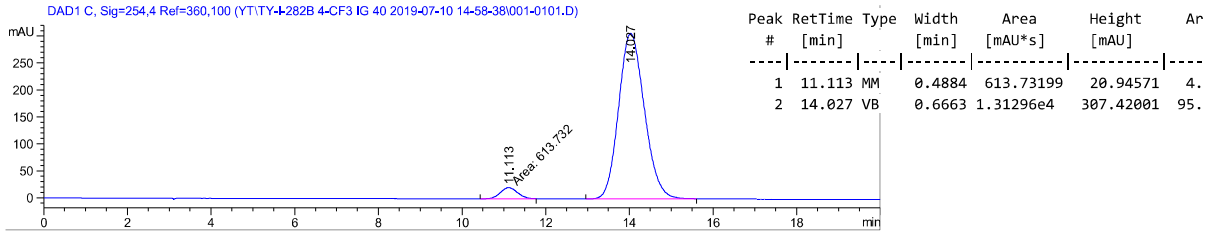
TLC: R_f (10% MeOH/EtOAc) = 0.25; **^{1}H NMR** (400 MHz, DMSO-d_6) δ [ppm] = 8.65 (d, J = 3.6 Hz, 1 H), 8.53 (d, J = 3.6 Hz, 1 H), 8.50 (s, 1 H), 8.32 (s, 1 H), 7.95 (s, 1 H), 7.43 (s, 4 H), 4.08–4.03 (m, 2 H), 3.55–3.51 (m, 2 H), 3.34 (d, J = 11.9 Hz, 2 H), 2.28 (dt, J = 10.7, 5.1 Hz, 1 H), 2.04 (d, J = 11.0 Hz, 1 H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ [ppm] = 155.5, 150.6, 149.4, 145.8, 145.7, 144.1, 136.4, 129.1, 125.4 (q, J = 3.3 Hz), 124.6 (q, J = 271.0 Hz), 122.5, 121.5 (q, J = 32.0 Hz), 118.9, 111.5, 49.0, 49.0, 40.3, 39.4, 39.2; **^{19}F{^{1}H} NMR** (470 MHz, DMSO-d_6) δ [ppm] = –60.17; **IR** (neat, ν/cm^{-1}) = 2153, 1649, 1531, 1363, 1325, 1216, 1113, 1066, 422, 410; **HRMS** (ESI, m/z): calcd for $C_{21}H_{18}F_3N_4O_2$ = 415.1382; found = 415.1399; $[\boldsymbol{\alpha}]_{\mathbf{405}}^{\mathbf{26}}$ –1067.4 (*c* 0.20, $CHCl_3$); enantiomeric ratio was determined by **HPLC**: column: Chiralpak® IG; eluent: 100% EtOH; flow rate: 1.0 mL/min: temperature: 40 °C; detection: 254 nm; retention time: t_R = 11.1 min (minor) and 14.0 min (major).

• racemic mixture



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	10.701	BB	0.4255	744.80115	27.02570	49
2	13.595	MM	0.6758	763.97760	18.84248	50

• enantioenriched product



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Ar
1	11.113	MM	0.4884	613.73199	20.94571	4.
2	14.027	VB	0.6663	1.31296e4	307.42001	95.

The absolute stereochemistry of **18** was determined by the single-crystal X-ray crystallography. Crystals of **18** (CCDC 1950273) were obtained by recrystallization from slow diffusion of hexanes into a solution of **18** dissolved in EtOAc.

X-Ray crystallographic data

General Information. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of **18**. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen

atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups).

Crystallographic details for 3l

The only exceptions for the isotropic displacement parameters of all hydrogen atoms are H1 and H4a, which were found in the difference map and freely refined. The full numbering scheme of compound **3l** can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1950272 (**3l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

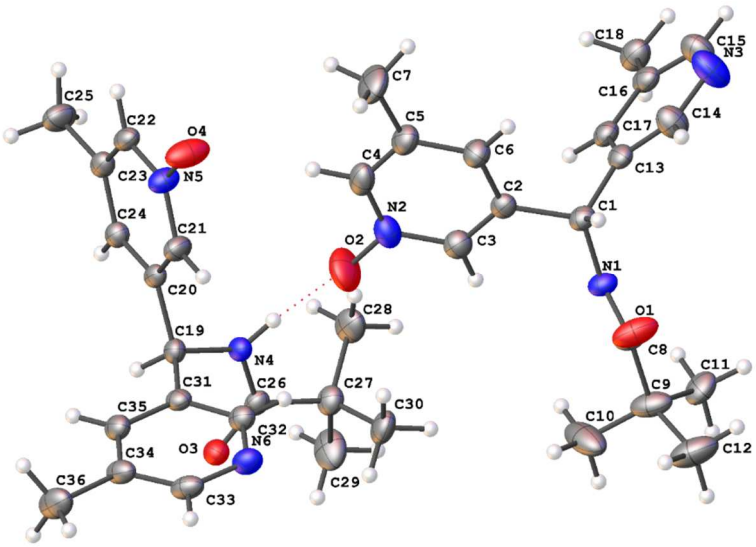


Figure S 13. *The complete numbering scheme of* ***3l*** *with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.*

Figure S13. Crystal data and structure refinement for **3l**.

Identification code **3l**

Empirical formula $C_{18}H_{23}N_3O_2$

Formula weight 313.39

Temperature 93(2) K

Wavelength 1.54184 Å

Crystal system Monoclinic

Space group $P2_1$

Unit cell dimensions a = 9.2034(2) Å α = 90°

b = 21.8162(4) Å β = 116.195(3)°

c = 9.4423(2) Å γ = 90°

Volume 1701.14(7) Å3

Z 4

Density (calculated) 1.224 Mg/m3

Absorption coefficient 0.649 mm-1

F(000) 672

Crystal size 0.200 x 0.200 x 0.200 mm3

Crystal color and habit Colorless Block

Diffractometer Rigaku Saturn 944+ CCD

Theta range for data collection 4.053 to 66.923°

Index ranges –10<=h<=10, –25<=k<=24, –11<=l<=11

Reflections collected 59724

Independent reflections 5840 [R(int) = 0.0338]

Observed reflections (I > 2sigma(I)) 5775

Completeness to theta = 66.923° 99.6 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.87977

Solution method SHELXT-2014/5 (Sheldrick, 2014)

Refinement method	SHELXL-2014/7 (Sheldrick, 2014)
Data / restraints / parameters	5840 / 1 / 434
Goodness-of-fit on F2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.1034
R indices (all data)	R1 = 0.0406, wR2 = 0.1037
Absolute structure parameter	–0.05(5)
Extinction coefficient	0.0258(13)
Largest diff. peak and hole	0.630 and –0.258 e.Å-3

Crystallographic details for 16

Compound 16 displayed four conformations due to mobility of the cycloheptane and piperidine rings. The full numbering scheme of compound **16** can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1950546 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

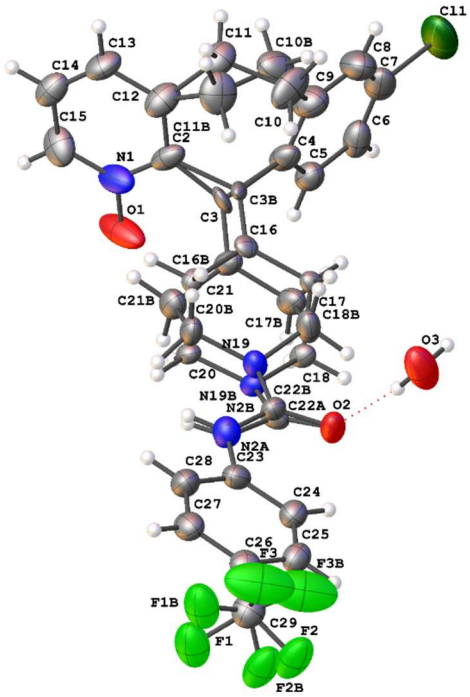


Figure S 14. *The complete numbering scheme of* ***16*** *with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.*

Table S7. Crystal data and structure refinement for **16**.

Identification code	**16**
Empirical formula	$C_{27}H_{25}ClF_3N_3O_3$
Formula weight	531.95
Temperature	93(2) K

Wavelength 1.54184 Å

Crystal system Hexagonal

Space group $P6_1$

Unit cell dimensions a = 13.6637(2) Å $\alpha = 90°$

b = 13.6637(2) Å $\beta = 90°$

c = 22.8930(4) Å $\gamma = 120°$

Volume 3701.43(13) Å3

Z 6

Density (calculated) 1.432 Mg/m3

Absorption coefficient 1.882 mm-1

F(000) 1656

Crystal size 0.200 x 0.200 x 0.100 mm3

Crystal color and habit Colorless Plate

Diffractometer Rigaku Saturn 944+ CCD

Theta range for data collection 3.735 to 66.728°

Index ranges –16<=h<=16, –15<=k<=14, –27<=l<=27

Reflections collected 138394

Independent reflections 4375 [R(int) = 0.0837]

Observed reflections (I > 2sigma(I)) 4145

Completeness to theta = 66.728° 100.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.82496

Solution method SHELXT-2014/5 (Sheldrick, 2014)

Refinement method SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters 4375 / 61 / 447

Goodness-of-fit on F2 1.056

Final R indices [I>2sigma(I)] R1 = 0.0463, wR2 = 0.1143

R indices (all data) R1 = 0.0494, wR2 = 0.1177

Absolute structure parameter 0.000(6)

Largest diff. peak and hole 0.445 and –0.517 e.Å-3

Crystallographic details for 18

The ethyl acetate is disordered over two positions. The most obvious sign of disorder was a difference map peak that corresponded to an alternate position for the carbonyl. All chemically equivalent C–C and C–O distances were restrained to be similar. The thermal parameters of the disordered groups were restrained to behave as a rigid group. Some carbons had to be split and constrained to occupy the same crystallographic space with identical thermal parameters. The site occupancies were freely refined to ~0.70/0.30 split. A similar approach was taken for the disordered aryl group. The sign of disorder for this model was an alternate peak for the N–O group. All chemically equivalent C–C, C–O, and N–O distances were restrained to be similar. The thermal parameters of the disordered groups were restrained to behave as a rigid group. The site occupancies were freely refined to ~0.80/0.20 split. The minor group thermal parameters were constrained to be identical to their chemically equivalent counter parts. All disordered hydrogen atoms were geometrically placed. The full numbering scheme of compound **18** can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1950273 (**18**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

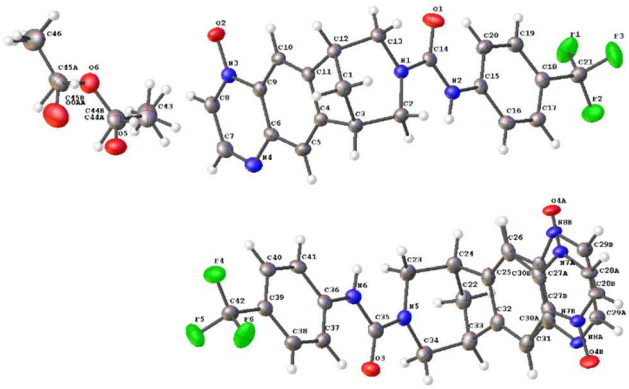


Figure S 15. *The complete numbering scheme of* ***18*** *with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.*

Figure S8. Crystal data and structure refinement for **18**.

Identification code **18**

Empirical formula $C_{23}H_{21}F_3N_4O_3$

Formula weight 458.44

Temperature 93(2) K

Wavelength 1.54184 Å

Crystal system Triclinic

Space group P1

Unit cell dimensions a = 8.4638(4) Å α = 93.398(4)°

b = 11.0323(5) Å β = 91.354(4)°

c = 11.3821(6) Å γ = 90.017(4)°

Volume 1060.64(9) Å3

Z 2

Density (calculated) 1.435 Mg/m3

Absorption coefficient 0.977 mm-1

F(000) 476

Crystal size 0.200 x 0.050 x 0.050 mm3

Crystal color and habit	Colorless Plate
Diffractometer	Rigaku Saturn 944+ CCD
Theta range for data collection	3.892 to 66.682°
Index ranges	–10<=h<=10, –13<=k<=13, –13<=l<=13
Reflections collected	38146
Independent reflections	7036 [R(int) = 0.0347]
Observed reflections (I > 2sigma(I))	6617
Completeness to theta = 66.682°	98.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.78933
Solution method	SHELXT-2014/5 (Sheldrick, 2014)
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)
Data / restraints / parameters	7036 / 27 / 630
Goodness-of-fit on F2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0815
R indices (all data)	R1 = 0.0363, wR2 = 0.0834
Absolute structure parameter	0.02(6)
Extinction coefficient	0.0076(5)
Largest diff. peak and hole	0.206 and –0.199 e.Å-3

Chapter VI

Side Projects: Vinylogous addition of alkylidene oxindole on trifluoromethyl ketones.

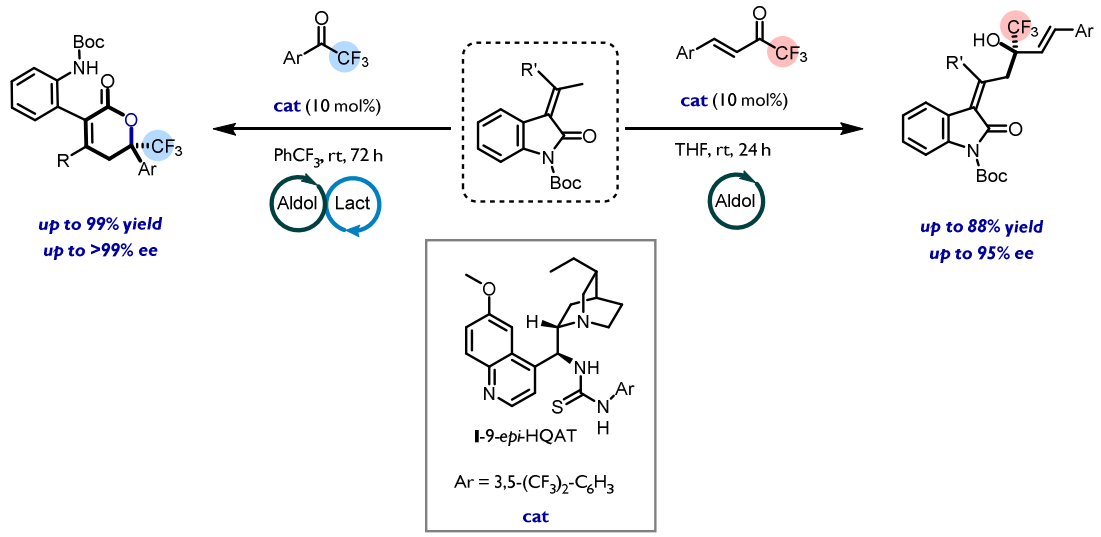
6.1 Vinylogous addition of alkylidene oxindole on trifluoromethyl ketones.

All the procedures and results here described are part of- and can be found in:

S. Crotti, N. Di Iorio, A. Mazzanti, P. Righi, and G. Bencivenni, "Enantioselective Synthesis of Trifluoromethyl α,β-Unsaturated δ-Lactones via Vinylogous Aldol-Lactonization Cascade.", *J. Org. Chem.* **2018**, *83*, 12440.

S. Crotti, G. Belletti, N. Di Iorio, E. Marotta, A. Mazzanti, P. Righi and G. Bencivenni "Asymmetric vinylogous aldol addition of alkylidene oxindoles on trifluoromethyl- α,β -unsaturated ketones" *RSC Adv.*, **2018**, *8*, 33451.

Abstract:



Vinylogous reactivity is a valuable strategy for the remote modification of a molecule. The novel vinylogous addition of alkylidene oxindole on trifluoromethyl ketone has been investigated. Aryl trifluoromethyl ketone afforded a rare aldol reaction-lactonization cascade. The reaction, catalyzed by a bifunctional tertiary amine, provides an efficient application of the vinylogous reactivity of alkylidene oxindoles for the preparation of enantioenriched trifluoromethylated α,β-unsaturated δ-lactones. Parenthetically, the addition on α,β-unsaturated

trifluoromethyl ketones has been studied. The reaction this time provides an efficient application of the vinylogous reactivity of oxindoles for the preparation of enantioenriched trifluoromethylated allylic alcohols. In both case good-to-excellent levels of yield and excellent enantioselectivity were encountered in almost any substrates.

6.1 Vinylogous Reactivity

Recently, chemists' interest for the stereocontrolled activation of a molecule has started to shift toward the generation of stereocenters in a remote position from the catalytic activation sites. The most renowned compound for which this strategy can be applied are α,β-unsaturated carbonyl compounds. Moving through the chain of a carbonyl substrate, the electronic effects inherent to enamine and iminium ion activations through the conjugated π-system of poly-unsaturated carbonyls can generate a propagation of the reactivity site. This propagation could be applied both in the HOMO-raising strategy for nucleophilic activation and for LOMO-lowering strategy to facilitate electrophilic addition (**Figure 46**). Such an electronic transmission is peculiar to vinylogous reactivity, as originally defined in 1935 by Reynold C. Fuson.[175]

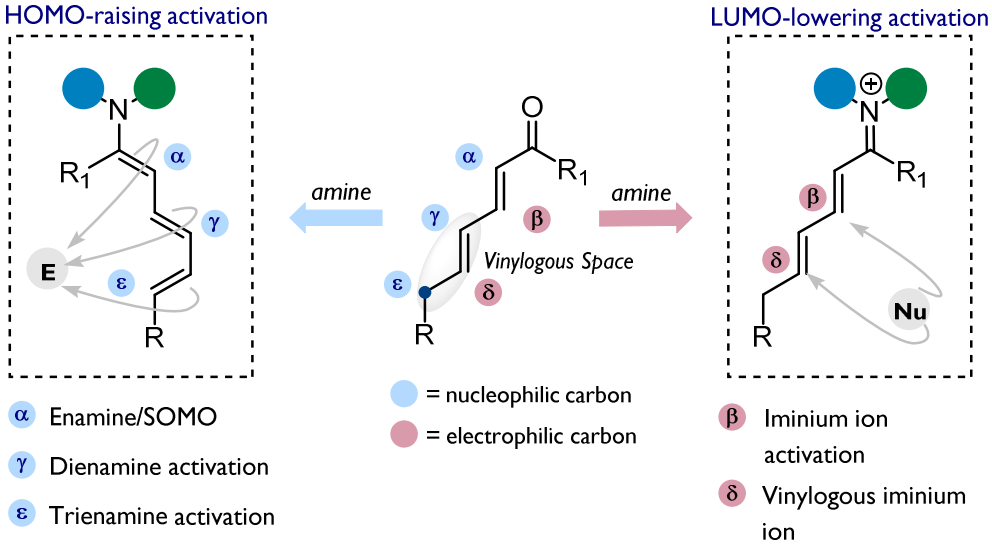
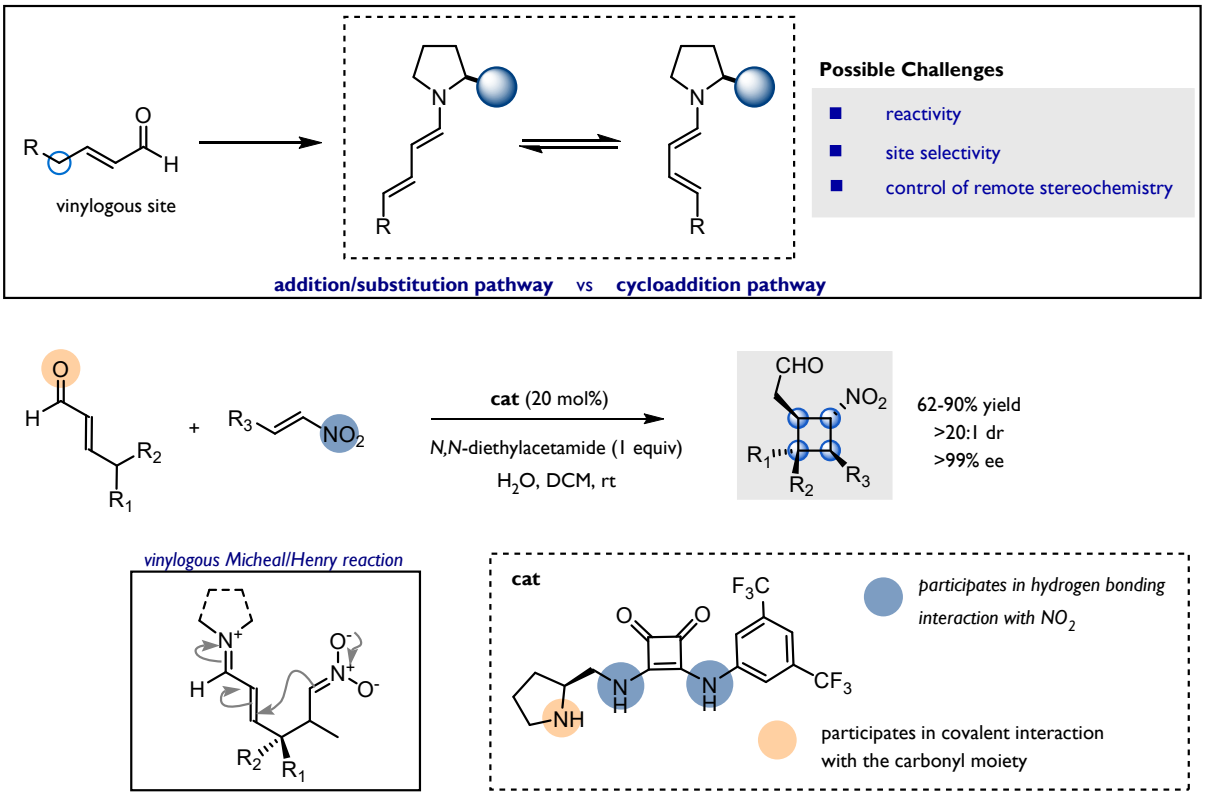


Figure 46. *Vinylogous aminocatalytic activation mode*

To show the potentiality of this activation I reported here an example of an organocascade reaction studied by Jørgensen and co-workers. In this work a new strategy is introduced, which greatly increased the synthetic power of dienamine

[175] R. C. Fuson, *Chem. Rev.*, **1935**, *16*, 1.

activation. The main idea was to design a bifunctional secondary amine-thiourea catalyst, which combines the H-bond-directing activation of the electrophilic substrate with the dienamine activation of the linear unsaturated aldehyde donor. The catalyst's simultaneous activation of the two reacting partners is able to assemble the TS in a three-dimensional molecular defined structure. This could lead to higher levels of both reactivity and stereoselectivity and, more importantly, address the issue of the site selectivity inherent to dienamine-induced vinylogous reactivity. The catalyst is a chiral secondary amine embedded with a coordinative squaramide moiety, which can act as a H-bond donor unit. The new catalyst served for the development of a formal [2+2]-cycloaddition of linear enals with nitroolefins leading to the corresponding cyclobutanes in high yields and excellent diastereo- and enantioselectivities (**Scheme 39**).[176]



Scheme 40. *Vinylogous Micheal addition/Henry reaction for the synthesis of cyclobutanes bearing four contiguous stereocenters*

[176] Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodriguez-Escrich, R. L. Davis and K. A. Jørgensen, *J. Am. Chem. Soc.*, **2012**, *134*, 2543.

The activation of a remote position in a molecule in a vinylogous fashion is not a property confined to the aminocatalytic realm. If a proton is indeed acid enough to be extracted from a base a nucleophilic vinylogous species can undergo nucleophilic addition.

Alkylidene oxindoles, for example, are suitable substrates for vinylogous processes. They have been successfully employed as nucleophiles in many reactions with different electrophilic partners. The presence of an acid proton in γ-position conjugated to an α,β-unsaturated system after deprotonation, can form a reactive dienolate, able to trap an electrophilic species (**Figure 47**, top). This strategy could be envisioned as a useful tool for a remote formation of different functionalizations.[177] The alkylidene oxindole core is a structural motif that can be found is a vast number of biologically active compounds, both pharmaceuticals and natural products (**Figure 47**, bottom).

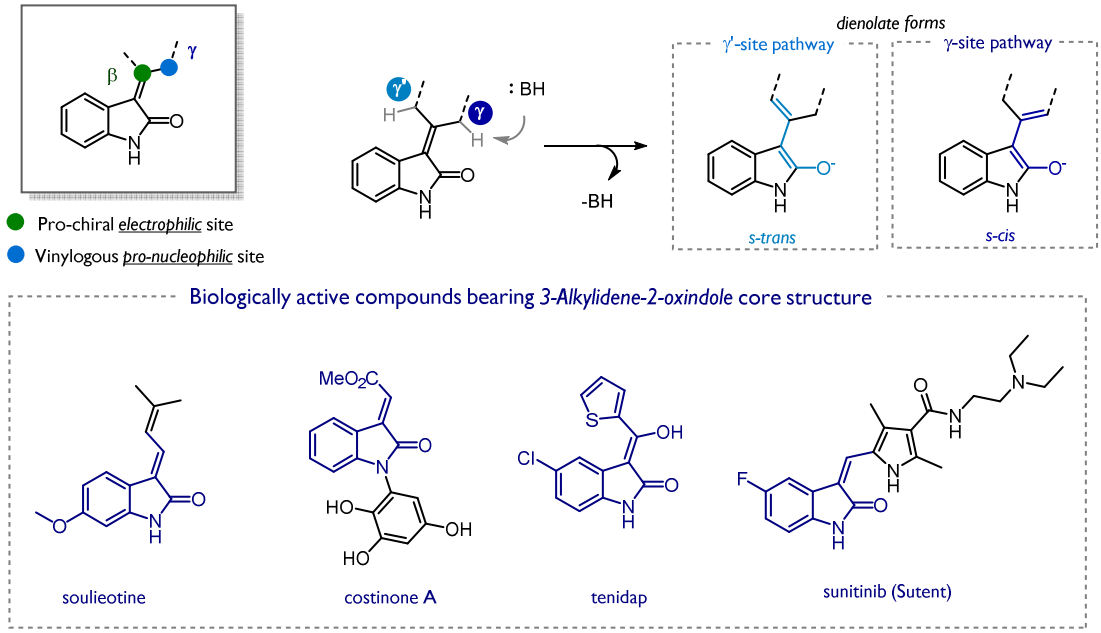
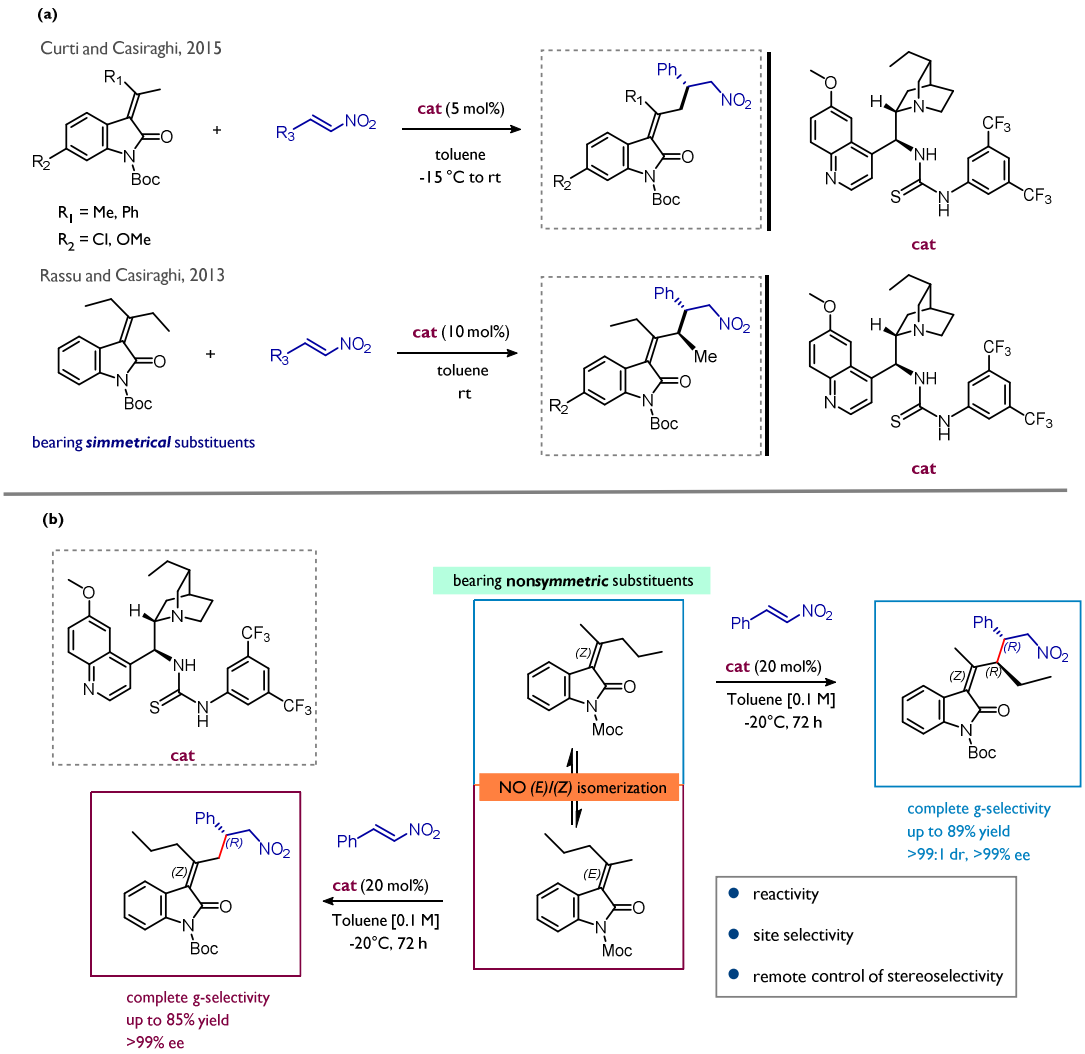


Figure 47. *(a) base-promoted formation of dienolate (b) compounds bearing alkylidene oxindole core.*

[177] (a) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6200. (b) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394. (c) Zhong, Y.; Ma, S.; Xu, Z.; Chang, M.; Wang, R. *RSC Adv.* **2014**, *4*, 49930. (d) Xiao, X.; Mei, H.; Chen, Q.; Zhao, L.; Lin, X.; Liu, X.; Feng, X. *Chem. Commun.* **2015**, *51*, 580. (e) Feng, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2017**, *82*, 1412. (g) Jadhav, A. P.; Ali, A.; Singh, R. P. *Adv. Synth. Catal.* **2017**, *359*, 1508. (f) Kumar, K.; Jaiswal, M. K.; Singh, R. P. *Adv. Synth. Catal.* **2017**, *359*, 4136.

Recently, the vinylogous reactivity has been successfully developed using organic base in a catalytic fashion. In this field, noteworthy examples are represented by the Michael addition reactions of alkylidene oxindoles with nitrostyrenes, developed by Casiraghi.[158a,178] The bifunctional catalyst, a cinchona-alkaloid derived catalyst, is able to deprotonate the vinylogous position of the oxindole and to simultaneously activate the electrophile thanks to the coordination of the thioureidic portion (**Scheme 40a**).



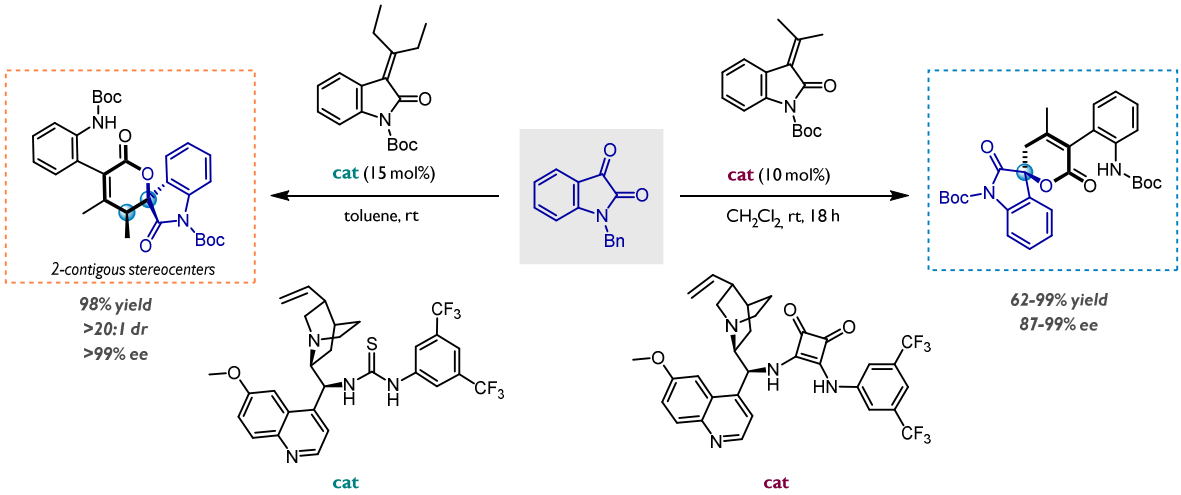
Scheme 41. *(a) addition of oxindoles bearing simmetric 3-alkylidene groups (b) Vinylogous reactivity of oxindoles bearing Nonsymmetric 3-alkylidene groups.*

[178] Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F.; Casiraghi, G. *Adv. Synth. Catal.* **2013**, *355*, 1881.

A further step to the understanding of this reactivity has been developed by our group. We developed the organocatalyzed vinylogous Michael addition of nonsymmetric alkylidene oxindoles to nitroalkenes. The complete inhibition of the interconversion between the two (E)/(Z) isomers of the starting oxindole was achieved by lowering the reaction temperature at -20 °C. The resulting products were obtained with high regio-, diastereo-, and enantiocontrol. The reaction proceeded only *via* a γ-site selective deprotonation by catalyst, which exclusively interacts via hydrogen bonding only with the nitroalkene and not with the oxindole (**Scheme 40b**).[179]

An important contribution in this field was reported by Han and co-workers in which an unexpected intramolecular lactonization, which follows the initial aldol reaction, was investigated. This organocascade approach leads, after the cleavage of the oxindole ring, to the generation of enantioenriched spirooxindole dihydropyranones in good to excellent yields with high enantioselectivities.

When a methylenic group is installed in γ-position, instead of methyl, another stereocenter contigous to the spirooxindole is set. The product was obtained with excellent yield, enantioselectivies and diasteroselectivities.



Scheme 42. *Asymmetric assembly of spirooxindoles*

[179] Di Iorio, N.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G. *J. Org. Chem.* **2015**, *80*, 7158.

The excellent yields and the high stereoselectivity obtained, showed the potentiality of these reactions as promising tools for synthetic protocols. Organofluorine compounds find many applications in agrochemical industry and in medicinal chemistry. In particular, chiral compounds containing the trifluoromethyl group (-CF_3) bonded to a stereogenic center showed potent activity against various diseases (**Figure 48**).[180]

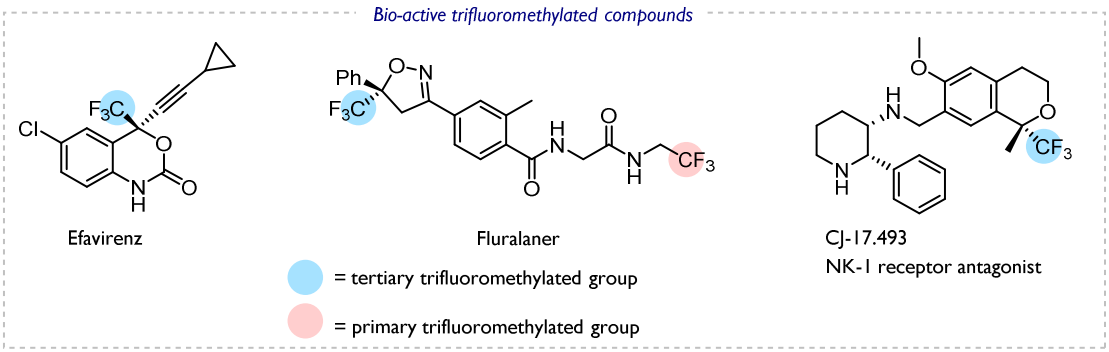


Figure 48. *Example of trifluoromethyl-containing biologically active compounds*

For these reasons the search of new fluorinated compounds is highly coveted and many research groups developed powerful fluorination and trifluoromethylation reactions.[181] Ruppert–Prakash (R–P) reagent, a trifluoromethyl-trimethylsilylane, exploits the direct nucleophilic addition of a trifluoromethyl anion on a prochiral electrophilic group. So far is considered the most common and practical method for the synthesis of trifluoromethyl compounds in an enantioselective fashion. Conversely, trifluoromethyl ketones have never been used as acceptors in vinylogous-aldol reaction.[182]

This observation prompted us to study the enantioselective vinylogous-aldol reaction of alkylidene oxindoles with diversified trifluoromethyl ketones as a powerful method for the synthesis interesting molecular architecture containing

[180] O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
[181] 7 (a) J.-A. Ma and D. J. Cahard, *Fluorine Chem.*, **2007**, *128*, 975; (b) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2009**, *131*, 10875; (c) I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, **1984**, *25*, 2195; (d) G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc.*, **1989**, *111*, 393; (e) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, **1993**, *115*, 2156;
[182] S. E. Denmark, J. R. Heemstra and G. L. Beutner, *Angew. Chem., Int. Ed.*, **2005**, *44*, 4682;

two highly biologically active molecular scaffolds, such as oxindole and enantioenriched trifluoromethylated.

We envisioned that two interesting acceptors for the vinylogous aldol reaction would have been trifluoromethyl ketones and α,β-unsaturated trifluoromethylketones. We wanted to exploit all the characteristics of the substrates and be able to control all the possible stereoselective implications.

In fact, both the two γ- and γ' -positions of the oxindole can, in principle, compete for the generation of the vinylogous nucleophile, generating a regio- and stereoselective problem. The result is that a possible mixture of either E- and Z-alkenes derived from Michael and aldol adducts can be obtained. Furthermore, while aryl trifluoromethylketones are able to react only on the carbonyl group, the use of α,β-unsaturated trifluoromethylketones sets a new chemo- and stereoselective challenge. Because of the high reactivity imparted by the CF_3-group, both the 1,2- and 1,4-addition products can indeed be formed (**Figure 49**).[183]

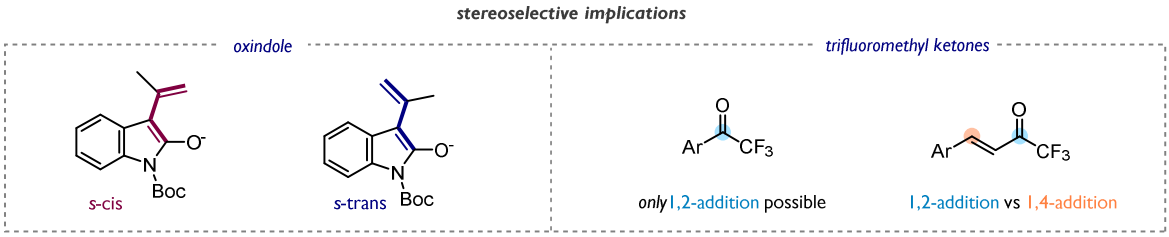


Figure 49. *Possible combination of both the nucleophile and the electrophile*

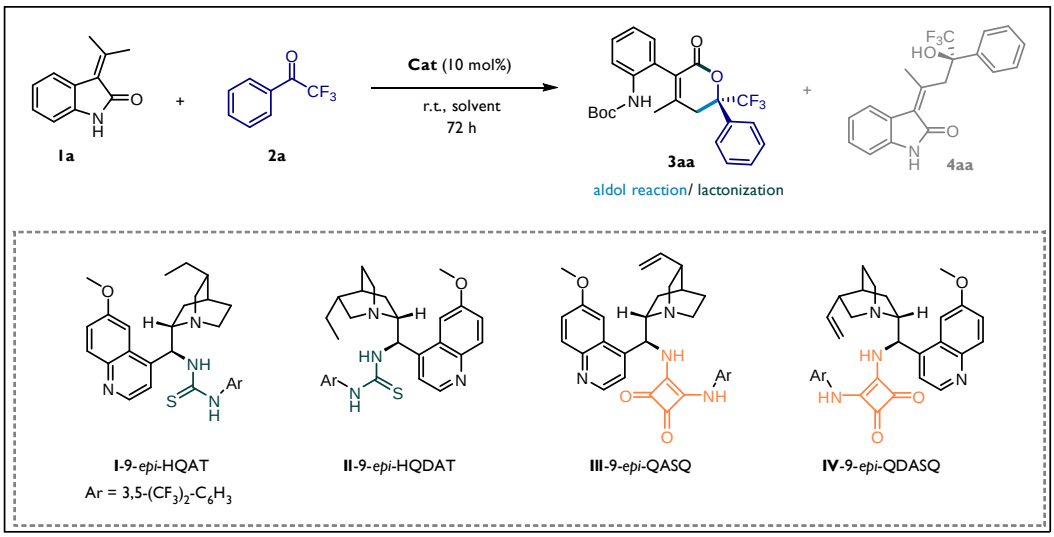
We started our investigation by exploring the reactivity of the phenyl trifluoromethylketone **1a** with alkylidene oxindole **2a**, in the presence of diverse thiourea and squaramide derivatives of Cinchona alkaloid organocatalysts (**Table**

[183] For examples of 1,2-addition: (a) G.-W. Zhang, W. Meng, H. Ma, J. Nie, W.-Q. Zhang and J.-A. Ma, *Angew. Chem., Int. Ed.*, **2011**, *50*, 3538; (b) Z.-J. Liu and J.-T. Liu, *Chem. Commun.*, **2008**, 5233. For examples of 1,4-addition: (c) L. C. Morril, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, **2013**, *4*, 4146; (d) P. Li, Z. Chai, S.-L. Zhao, Y.-Q. Yang, H.-F. Wang, C.-W. Zheng, Y.-P. Cai, G. Zhao and S.-Z. Zhu, *Chem. Commun.*, **2009**, 7369.

12). This class of catalysts has already been successfully applied to vinylogous processes[184] and demonstrated to be effective for the generation of an *s-cis* enolate after selective deprotonation at the γ-site.

Surprisingly, the reaction did not stop at the first aldol adduct, instead the reaction trifluomethylalkoxide formed is able to react in a ring opening lactonization to afford the corresponding α,β-unsaturated δ-lactone **3aa**.

In general, the catalysts were able to promote the formation of compound **3aa** in moderate to good yields and excellent enantioselectivity together with variable amounts of aldol adduct **4aa** (entries 1−4).



entry	cat	solvent	3aa/4aa[b]	yield (%) 3aa[c]	ee (%) 3aa[e]
1	I	DCM	9:1	70	>99
2	II	DCM	2:1	48	-99
3	III	DCM	4:1	56	97
4	IV	DCM	1:3	21	-91
5	I	$CHCl_3$	3:1	52	nd
6	I	Tol	6:1	62	nd
7	I	THF	1:2	20	nd
8	I	Et_2O	7:1	68	nd
9	I	MeOH	--	n.r.	--
10	I	MeCN	>19:1	96[d]	95
11	**I**	**$PhCF_3$**	**>19:1**	**96[d]**	**99**

[a]The reactions were performed on a 0.1 mmol scale using a 1:1 ratio of **1a** and **2a** and 0.5 ml of solvent. [b]Determined via ^{1}H-NMR on the crude mixture. [c]Determined via ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard. [d]Isolated yield. [e]Determined by HPLC on chiral stationary phase.

***Table 12**. catalyst and condition screeaning.*

[184] (e) Xiao, X.; Mei, H.; Chen, Q.; Zhao, L.; Lin, X.; Liu, X.; Feng, X. *Chem. Commun.* **2015**, *51*, 580. (f) Feng, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2017**, *82*, 1412.

Initially, thiourea derivatives of 9-NH_2-9-*epi*-dihydroquinine **I** gave **3aa** in a 70% yield and >99% ee (entry 1). Catalyst **II**, the pseudoenantiomer of catalyst **I**, gave **3aa** in 48% yield and 99% ee, while squaramide derivatives 9-NH_2-9-*epi*-quinine **III** and quinidine **IV** furnished the worst results (entries 2−4).

The solvents, probably due to a slight but sufficient perturbation in the TS aggregation, have a strong influence on the product selectivity, proved by the variable ratios between **3aa** and **4aa**. (entries 5−12). Only using MeCN and CF_3Ph a complete selectivity in favor of lactone **3aa** was realized. In particular in this last case, **3aa** was isolated in 96% yield and 99% ee after 72 h of reaction at 25 °C. With the optimized conditions in hand, the scope of the reaction was determined (**Table 13**). In general, catalyst **I** afforded the corresponding product **3** in high control on the stereochemistry with both electron-withdrawing and -releasing substituents at the C(5) and C(7) of the oxindole core (**3ba−ea**).

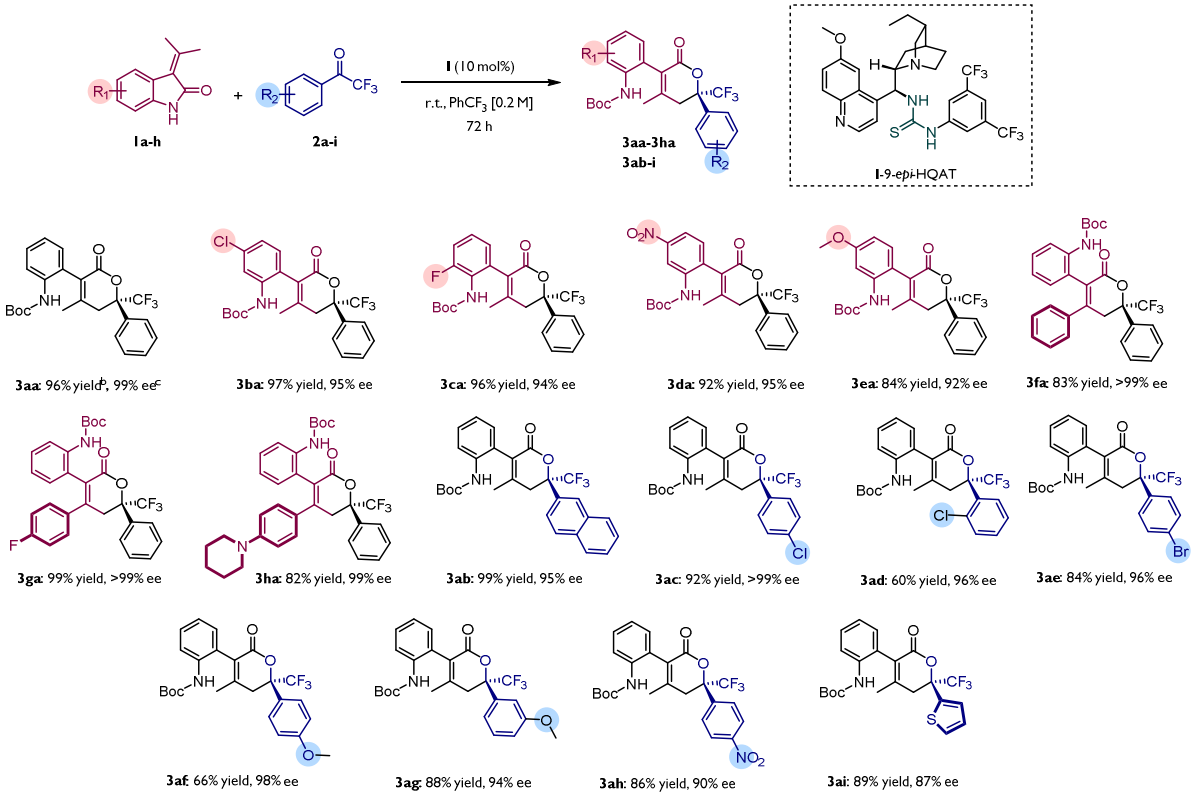
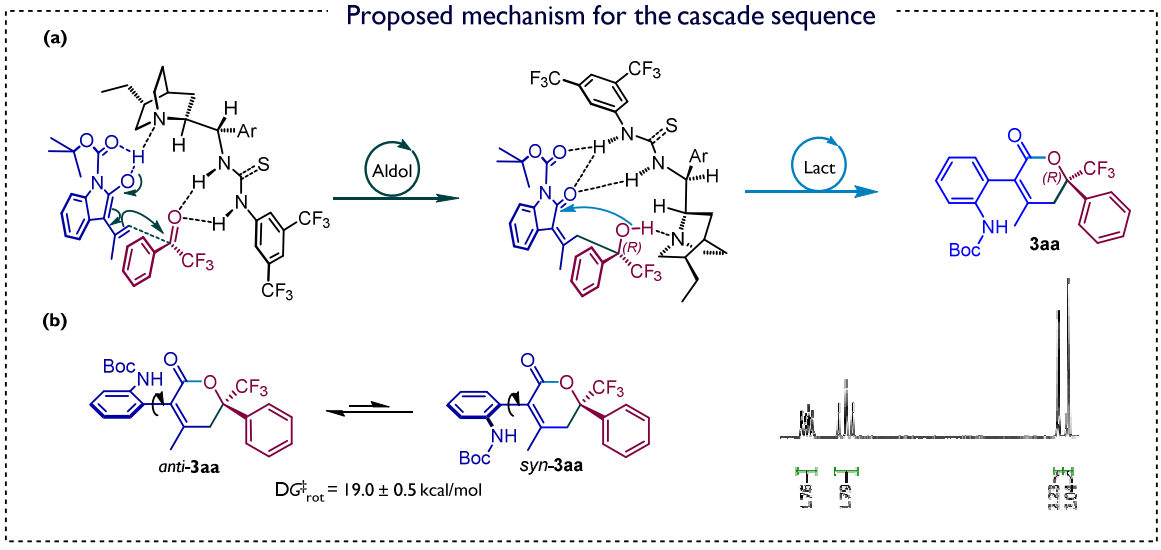


Table 13. *Scope of the vinylogous aldol reaction/lactonization cascade process*

Excellent yields and ee's were also obtained with oxindoles having different aromatic substituents at the double bond (**3fa−ha**). However, to our surprise, the reaction failed to give the desired lactones or even traces of aldol adduct when 1-*tert*-butoxycarbonyl-3-(pentan-3-ylidene)indolin- 2-one or 3- cyclohexylidene-1-(*tert*-butoxycarbonyl)indolin-2-one was employed. Various aromatic trifluoromethyl ketones **2b−i** were then prepared and used for the vinylogous aldol-cascade process in combination with oxindole **1a**. In almost all cases, the corresponding cyclic esters were the sole products obtained after 72 h in excellent yields and remarkable enantioselectivities (**3ab−ai**). Moderate yields were, however, obtained with 2-chlorotrifluoroacetophenone **2d** and 4-methoxytrifluoroacetophenone **2f**.

Interestingly, all of these trifluoromethylated lactones were isolated as mixtures of conformers due to the slow rotation of the C−C single bond between the aryl substituent and the α-carbon of the double bond. In the case of compound **3aa**, the anti/syn ratio was 58:42 in $CDCl_3$ and the energy barrier to rotation was determined to be $\Delta G_{rot}^{\ddagger} = 19.0 \pm 0.5$ kcal/mol in CD_3CN by means of 1D-EXSY experiments (**Figure 42b**)

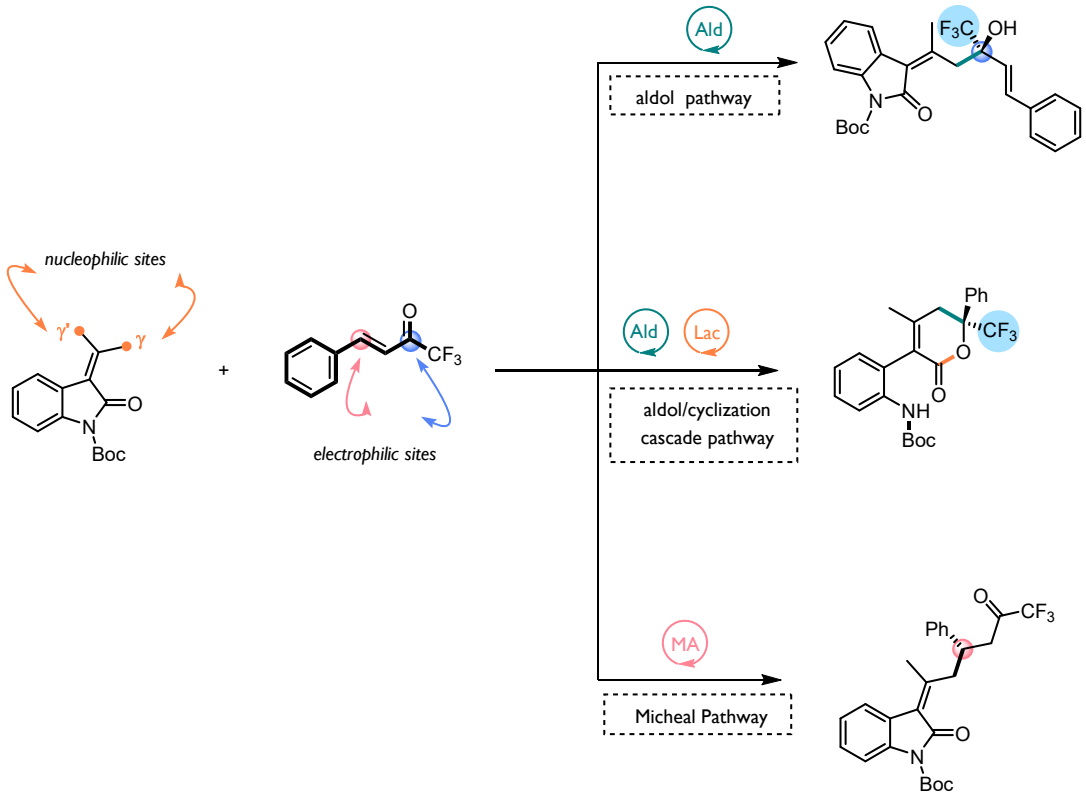


Scheme 43. *(a) proposed mechanism (b) conformational equilibrium of compound **3aa***

. The absolute configuration of compound **3aa** was determined to be R by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra. The

R absolute configuration is the result of a vinylogous addition of the oxindole to the prochiral *Si* face of the trifluoromethyl ketone (**Figure 42a**).

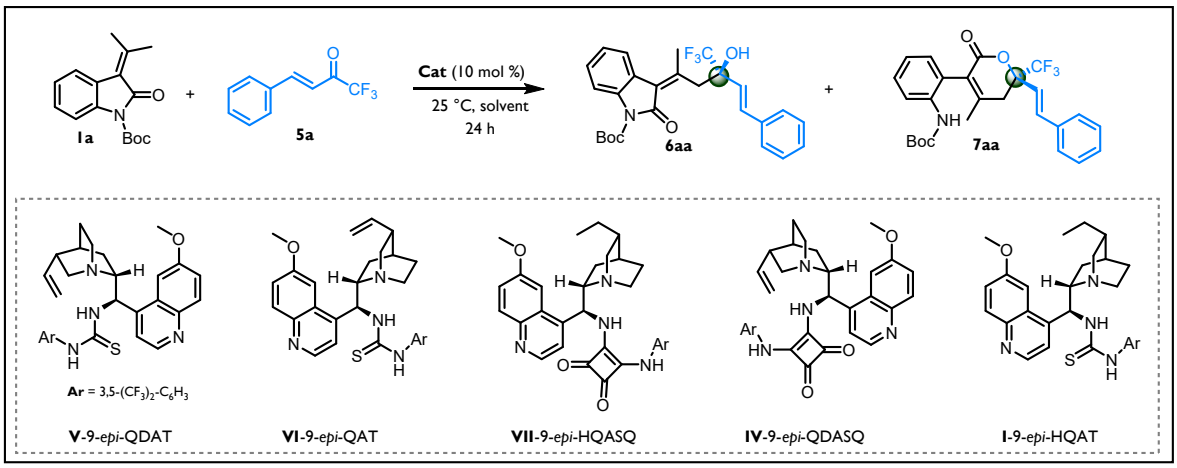
We then moved to investigate the vinylogous addition of the alkylidene oxindole on α,β-unsaturated trifluomethylketones. As already mentioned, this transformation set a new selectivity problem due to the new possible formation of Micheal addition product. The three different pathways are shown in **Scheme 43**.



Scheme 44. *Three possible pathways for the addition on a,β-unsaturated trifluoromethylketones*

So we started by mixing alkylidene oxindole **1a** with α,β-unsaturated trifluoromethylketones **5a** in the presence of diverse cinchona alkaloids organocatalysts. Using catalyst **V** surprisingly we saw the formation of a 9 : 1 mixture of the aldol adduct **6aa** together with the 5,6-dihydropyranone **7aa**. (**Table**). Interestingly the desired trifluoromethylated allylic alcohol was isolated in a 21% yield and 87% ee. From the analysis of the crude mixture during time, it was observed that **7aa** was the result of a consecutive reaction of **6aa** that starts

to be highly competitive after 24 hours. Unfortunately, compound **7aa** was highly unstable both under the reaction conditions for a prolonged reaction time and under the purification condition. We decided that a 24 hours reaction time was the perfect balance to maximize the conversion for the newly product formed product **6aa**. As it is possible to observe from **Table 14**, using catalyst **VI**, the pseudoenantiomer of **V**, the enantioselectivity of the reaction diminished sensibly (entry 2). Squaramide derivatives **VII** and **IV** (entries 3 and 4) were found not effective in this transformation, but 9-*epi*-HQAT **I** gave the best enantiocontrol, albeit with low selectivity and yield (entry 5). We tested different solvents and we observed that they highly influenced the distribution of the two products and the enantiomeric excess.



Entry	Cat	Solvent	3aa/4aa[b]	Yield [%] 3aa[c]	ee [%] 3aa[d]
1	V	DCM	9.5:1	21	87
2	VI	DCM	1.4:1	21	63
3	VII	DCM	1:1.8	12	65
4	IV	DCM	3.5:1	42	75
5	I	DCM	3.0:1	32	91
6	I	$CHCl_3$	3.3:1	18	85
7	I	DCE	1:2.2	6	66
8	I	$PhCF_3$	1:03	10	61
9	I	MeCN	1 9	3	56
10	I	To uene	1 2	15	69
11	I	MTBE	3 1	38	89
12	I	DIPE	1.6:1	16	75
13	I	dry THF	13.5:1	38	92
14[e,f]	I	dry THF	>19:1	61[g]	93

[a] The reactions were performed on a 0.2 mmol scale using a 1:1 ratio of **1a** and **2a** and 1 ml of solvent. [b] Determined via ^{1}H-NMR on the crude mixture. [c] Determined on the isolated product. [d] Determined by HPLC on chiral stationary phase. [e] 5 mol % of catalyst **V** was used. [f] 0.5 ml of solvent were used. [g] Determined via ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard.

Table 14. *Screening of the reaction conditions.*

Contrasting results were observed with other halogenated solvents such as chloroform, dichloroethane (DCE) and trifluorotoluene (entries 6–8).

In acetonitrile and toluene a low yield of **6aa** was obtained (entries 9 and 10) and ethereal solvents gave good enantiocontrol, but low selectivity (entries 11 and 12; MTBE = methyl-t-butyl ether; DIPE = diisopropyl ether). Dry THF revealed to be the best choice because its use increased the enantiomeric excess of **6aa** to 92% and gave a promising 13.5 : 1 ratio between **6aa** and **7aa** (entry 13). Using a 5 mol % of **I** and a doubly concentrated reaction, **6aa** was obtained as the sole product in 93% ee and 61% yield (entry 14).

With the optimized conditions we reacted different oxindoles **1a–e** with trifluoroketones **5a–g** (**Table 15**).

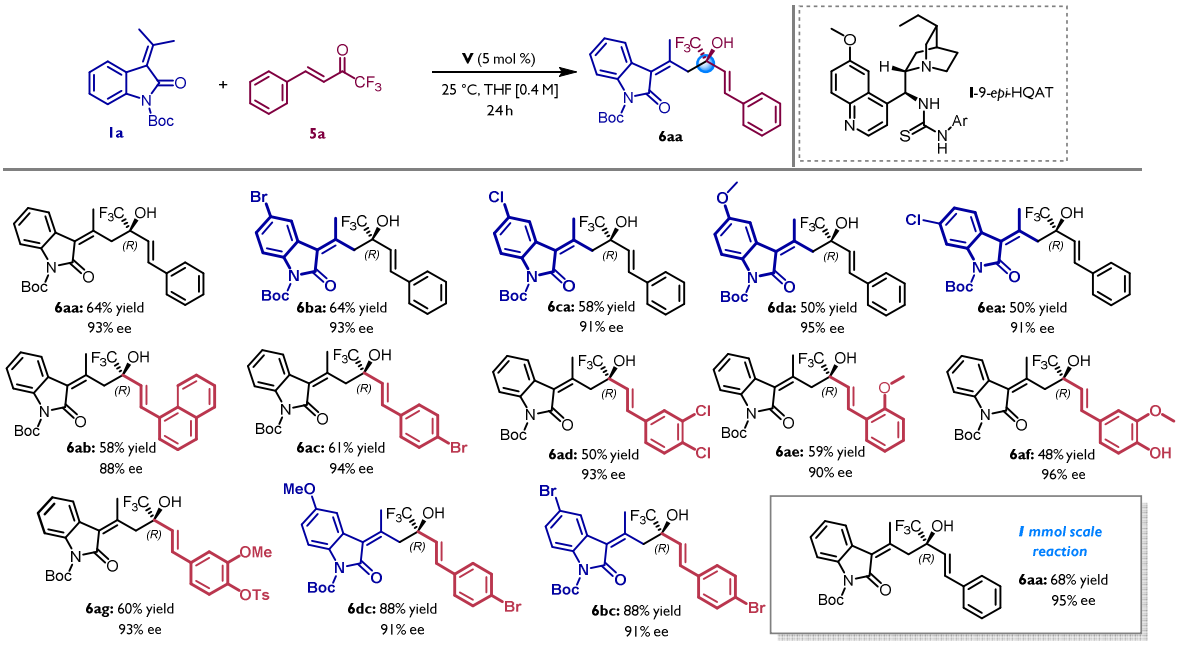
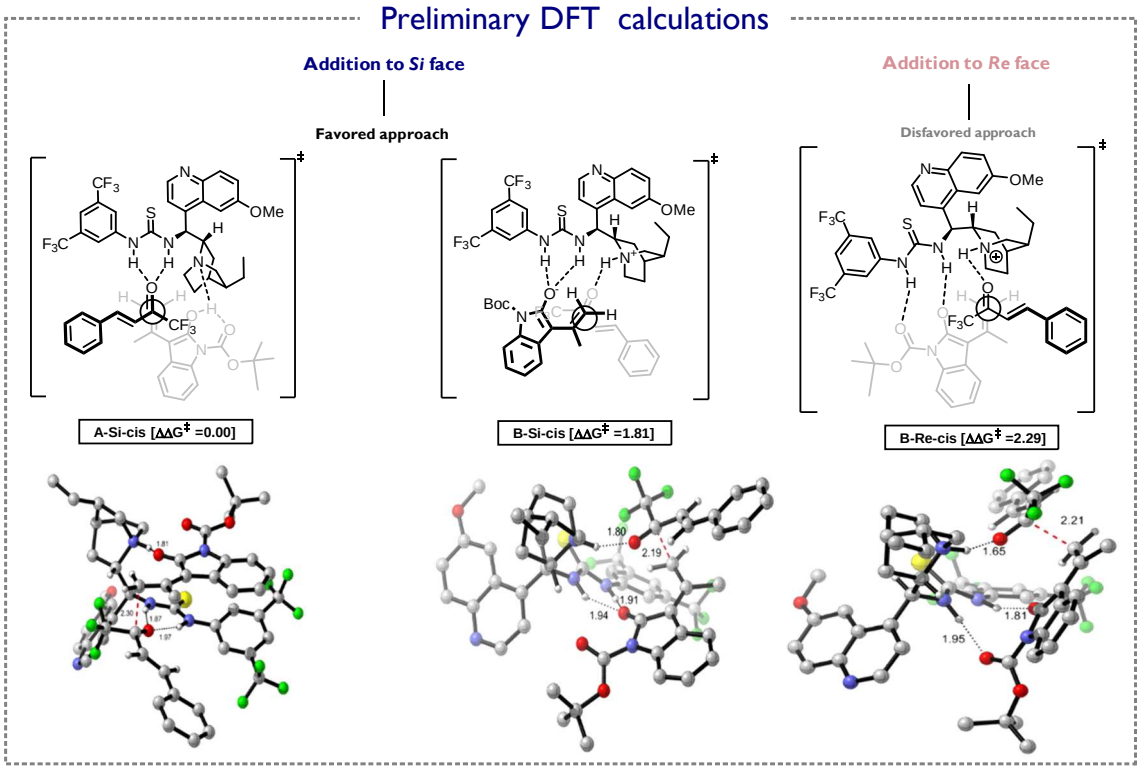


Table 15. *Scope of the vinylogous aldol reaction.*

The general trend observed is that catalyst **I** is able to give high control on the stereochemistry regardless of the electronic nature of the substituents at the C(5) and C(6) of the oxindole core. The presence of electron-withdrawing and releasing groups is in fact well tolerated (**6aa–6ea**). A good generality is observed when trifluoroketones **5b–g** were studied. In all cases the corresponding allylic alcohols

were obtained as sole products after 24 hours (**6ab–6bd**). 1,4-adducts was never found as a side product, confirming the high chemoselectivity of the aldol addition. To evaluate the utility of the process we performed a 1.0 mmol scale reaction between **1a** and **5a**. The enantioenriched allylic alcohol was obtained in a 68% yield of isolated product and 95% ee. The absolute configuration was determined to be R by means of single crystal X-ray diffraction analysis on **8aa**14 which was obtained from **6aa** after the removal of the Boc protecting group by reaction with pyrrolidine in DCM.

Seven transition states (TSs) were located using preliminary DFT calculations[185], with only three of them contributing significantly to the product enantiomer distribution. In agreement with previous studies,[186] only TSs corresponding to the mode of actions **A** or **B** of catalyst **I** have been located.



[185] For this preliminary investigation DFT calculations were performed using Gaussian 16 at the B3LYP/6-31G(d) level in the gas phase.

[186] M. N. Grayson and K. N. Houk, *J. Am. Chem. Soc.*, **2016**, *138*, 9041.

The lowest in energy (**A**-*Si*-s-*cis*) corresponds to the mode **A** addition of the oxindole to the *Si*-face of the ketone in the s-*cis* conformation and gives the (R)-enantiomer of the product. Another small fraction of the (R)-enantiomer comes from the **B**-*Si*-s-*cis* transition state, while the (S)-enantiomer arises from the **B**-*Re*-s-*cis* transition state. The results obtained account for a 96% ee in favor of the (R)-enantiomer, which is in good agreement with the observed experimental value of 93%.

In conclusion in these works we demonstrated the efficacy of a cinchona alkaloid derived thiourea to selectively catalyze the addition of alkylidene oxindoles on trifluoromethylketones. In the first study in which aryl trifluoromethylketones were employed as electrophiles, an aldol reaction/ring-opening lactonization occurred. Thanks to its bifunctional nature the catalyst was able to activate simoultaneusly the two reaction partners and selectively discriminate the two prochiral face both of the oxindole and the ketone, allowing the system to achieve high level of yield and enantioselectivity. The generality of the reaction was also investigated demonstrating its wide applicability with different electronic modification of both the reagents.

In the second work we tried to installed a new level of selectivity, utilizing α,β-unsaturated trifluomethylketones as electrophiles. We optimized the reaction conditions and proved that the same catalyst this time favor the formation of the direct 1,2-addition reaction product. This strategy is a useful tool for the synthesis of enantionenriched tertiary allylic alcohols bearing a trifluoromethyl group. Parenthetically, the scope of the reaction was investigated to prove the generality of the synthetic protocol. Generally, the enantioenriched allylic alcohol were synthesized in good yields and excellent enantioselectivities.

6.3 Experimental Section

General information

All the NMR spectra were recorded on Inova 300 MHz, Gemini 400 MHz or Mercury 600 MHz Varian spectrometers for ^{1}H, 75 MHz, 100 MHz and 150 MHz for ^{13}C and 282 MHz, 376 MHz, 564 MHz for ^{19}F respectively. The chemical shifts (δ) for ^{1}H, ^{19}F and ^{13}C are given in ppm relative to internal standard TMS (0.0 ppm) or residual signals of $CHCl_3$ (7.26 ppm). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Concerning the ^{13}C spectra of the products, we were never able to see the signal (quartet) of the fluorinated carbon regardless of the delay and the acquisition time we employed (not even a 5 days-acquisition with a 60 seconds delay at 150 MHz showed any signal). It is likely that, due to the splitting of the signal and the very high relaxation time of this particular carbon, the corresponding signal is lost in the baseline. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High Resolution Mass spectra were obtained from the Mass Facility of the Department of Chemistry and Drug Technology of the University of Rome on a Orbitrap Exactive, source: ESI (+): capillary temp: 250°C, spray voltage: 4.0 (kV), capillary voltage: 65 V, tube lens: 125 V. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. HPLC traces for all compounds were compared to racemic sample prepared using DABCO as catalyst except for compound **3ea**-**3ai**, **5ca** where a quasi racemic samples was prepared by mixing the two product antipodes obtained performing the reactions with catalyst **I** and the pseudo-enantiomer **II** separately. Optical rotations are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL,

$CHCl_3$) and the numerical values are relative to the products obtained from catalyst **I**. All reactions were carried out in air. Chiral catalyst **I**, **II**, **III**, **IV** and **V** were prepared following literature procedures.[187]

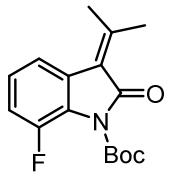
General procedure for the synthesis of N-Boc-alkylidene oxindoles

The appropriate isatin (15 mmol, 1 equiv) was placed in a 100 mL round flask and suspended in MeOH (37.5 mL, 0.4 M) before adding hydrazine (30.15 mmol, 2.6 ml of 55% solution in water, 2 equiv). The solution was left refluxing (2 to 3 hours) under magnetic stirring until the formation of a precipitate is observed, then cooled to room temperature. The precipitate was filtered on a gooch funnel, washed with water, cold MeOH and cold Et_2O to afford the pure hydrazone that was added to a freshly prepared solution of EtONa in EtOH (3.7 equiv of metallic Na dissolved in EtOH so that the hydrazone is 0.4 M). This new solution was heated to reflux until the reagent disappeared (TLC monitoring), then it was cooled and quenched with 10% HCl. The crude was now extracted with DCM, made anhydrous over $MgSO_4$ and purified by either flash column chromatography or crystallization to obtain the pure oxindole. The oxindole was then dissolved in a mixture of EtOH:Acetone 1:1 (0.5 M) before adding piperidine (4.0 equiv). After one night of reflux the temperature was allowed to go down and the crude was flushed through a plug of silica (50 mL of DCM:EtOAc 1:1 as eluent) to remove piperidine and the Knoevenagel adduct was purified by precipitation from Et_2O. The nitrogen protection was carried out dissolving the alkylidene oxindole in DCM (0.5 M) freshly filtered on basic alumina with Boc_2O (1.2 equiv) and a catalytic amount of DMAP (5% molar). The reaction was monitored via TLC and, when over, the crude was concentrated and the final product was purified by flash

[187] (a) Cassani, C.; Martín-Rapún, R.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nature Protocols* **2013**, *8*, 325. (b) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

column chromatography. NMR spectra of oxindoles **1a**, **1b**, **1d**, **1e**, **1f**, were consistent with those previously reported.[188]

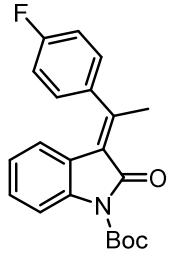
tert-Butyl 7-fluoro-2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate (1c)



1c

The title compound was synthesized following the literature procedure on a 2 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 95:5 and then 90:10) with an overall yield of 77% (91% for the Knoevenagel reaction and 85% for the protection) and a total of 450 mg of **1c** that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{16}H_{18}FNNaO_3]^+$ 314.1163, found 314.1159 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.15 – 6.97 (m, 2H), 2.62 (s, 3H), 2.40 (s, 3H), 1.61 (s, 8H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -121.52. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.4, 158.8, 149.8, 148.1, 147.3, 127.0 (d, *J* = 2.9 Hz), 124.3 (d, *J* = 7.1 Hz), 121.6 (d, *J* = 2.9 Hz), 119.1 (d, *J* = 3.7 Hz), 115.7 (d, *J* = 20.0 Hz), 84.5, 27.7, 25.8, 24.0.

tert-Butyl (E)-3-(1-(4-fluorophenyl)ethylidene)-2-oxoindoline-1-carboxylate (1g)



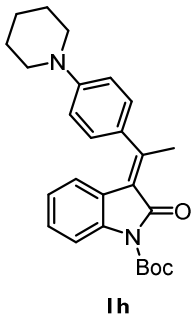
1g

The title compound was synthesized following the literature procedure on a 5 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 90:10) with an overall yield of 73% (85% for the Knoevenagel reaction and 86% for the protection) and a total of 1.29 g of 1g that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{21}H_{20}FNNaO_3]^+$

[188] (a) Rassu, G.; Zambrano, V.; Tanca, R.; Sartori, A.; Battistini, L.; Zanardi, F.; Curti, C.; Casiraghi, G. 3-Alkenyl-2-silyloxyindoles: An Enabling, Yet Understated Progeny of Vinylogous Carbon Nucleophiles. *Eur. J. Org. Chem.*, **2012**, 466. (b) Liu, Y.; Yang, Y.; Huang, Y.; Xu, X.-H.; Qing, F.-L.; Regio- and Diastereoselective Vinylogous Mannich Addition of 3-Alkenyl-2-oxindoles to α-Fluoroalkyl Aldimines. *Synlett*, **2015**, *26*, 67.

376.1319, found 376.1322 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 8.3, 1.1, 0.6 Hz, 1H), 7.31 – 7.09 (m, 5H), 6.76 (ddd, *J* = 7.7, 1.1 Hz, 1H), 6.28 – 6.19 (m, 1H), 2.76 (s, 3H), 1.68 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -121.54. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.0, 164.0, 161.5, 155.1, 149.5, 138.8 (d, *J* = 3.8 Hz), 138.3, 128.5, 128.4 (d, *J* = 8.1 Hz), 123.3, 122.9 (d, *J* = 3.6 Hz), 122.5, 116.5 (d, *J* = 21.9 Hz), 114.5, 84.1, 28.2, 23.8.

tert-Butyl (E)-2-oxo-3-(1-(4-(piperidin-1-yl)phenyl)ethylidene)indoline-1-carboxylate (1h)



1h

The title compound was synthesized following the literature procedure on a 1 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 85:15) with an overall yield of 56% (75% for the Knoevenagel reaction and 75% for the protection) and a total of 210 mg of **1h** that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{30}N_2NaO_3]^+$ 441.2149, found 441.2143 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.07 (m, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.77 (ddd, *J* = 7.7, 1.1 Hz, 1H), 6.69 – 6.58 (m, 1H), 3.32 – 3.24 (m, 4H), 2.76 (s, 3H), 1.67 (m, 15H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.3, 157.6, 152.2, 149.6, 137.8, 132.1, 128.3, 127.7, 123.6, 123.0, 122.3, 121.4, 115.6, 114.2, 83.7, 49.6, 28.1, 25.6, 24.2, 23.8.

General procedure for the synthesis of trifluoromethylketones

K_2CO_3 is added at room temperature to a DMSO (15 mL) solution of the appropriate aromatic aldehyde (5 mmol, 1.0 equiv.) and trifluoromethyl trimethylsilane (6.5 mmol, 1.3 equiv.). The reaction is completed, (check by TLC)

the mixture is poured to ice/water mixture and extracted with ethyl acetate (3 x 30 ml). The collected organic phases are washed with water (2 x 50 ml) then threated with $MgSO_4$ and filtered. The crude alcohol is purified by column chromatography using 10-15% of acetone or ethyl acetate in hexane as eluent mixture and directly added to a suspension of IBX in ethyl acetate. The resulting suspension is refluxed overnight. The crude mixture is filtered and trifluoroketone was purified by column chromatography using 5-10% of Et_2O in hexane as the eluent mixture. All trifluoromethylketones prepared were consistent with those previously reported: **2c**, **2f**, **2g**, **2h**.[189] Trifluoroketones **2a**, **2b, 2e, 2d** and **2i** were commercially available and used as is.

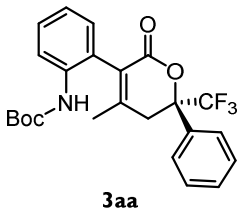
General procedure for the vinylogous aldol reaction

In an ordinary vial equipped with a teflon-coated magnetic stir bar, catalyst **I** (12 mg, 0.02 mmol, 0.1 equiv), oxindole (0.2 mmol, 1 equiv) and trifluoromethylketone (0.2 mmol, 1 equiv) were dissolved in 1 mL of $PhCF_3$. After 72 hours of stirring at 25 °C, the reaction was flushed through a short silica plug with a 1:1 mixture of DCM:EtOAc to remove the catalyst and the crude product was concentrated to perform a ^{1}H-NMR analysis to measure the yield (1,3,5-trimethoxybenzene was used as internal standard) and determine the ratio between aldol and cascade product. At this point the product was purified with flash column chromatography and the ee% was determined through HPLC on a chiral

[189] (a) Wu, W.; Qinli, T.; Taotao, C.; Zhiqiang, W. Copper-Mediated Trifluoroacetylation of Arenediazonium Salts with Ethyl Trifluoropyruvate. *Chem, Eur. J.* **2016**, *22*, 16455. (b) Schenck, H. A.; Lenkowski, P. W.; Choudhury-Mukherjee, I.; Ko, S.-H.; Stables, J. P.; Patel, M. K.; Brown, M. L. Design, Synthesis and Evaluation of Novel Hydroxyamides as Orally Available Anticonvulsants. *Bioorg. Med. Chem.* **2004**, *12*, 979. (b) Emer, E.; Twilton, J.; Tredwell, M.; Calderwood, S.; Collier, T. L.; Liegault, B.; Taillefer, M.; Gouverneur, V. Diversity-Oriented Approach to CF_3CHF-, CF_3CFBr-, CF_3CF_2-, $(CF_3)_2CH$-, and $CF_3(SCF_3)CH$-Substituted Arenes from 1-(Diazo-2,2,2-trifluoroethyl)arenes *Org. Lett.* **2014**, *16*, 6004.

stationary phase. Yield after chromatography are all cases identical to those determined via NMR analysis.

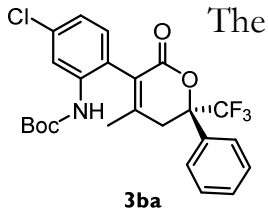
tert-Butyl (_R_)-(2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)phenyl)carbamate (3aa)



3aa

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.72/1.00 mixture of conformers in 96% yield (85.8 mg) and 99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.5 min, τ_{II} = 11.9 min. $[\alpha]_D^{25}$ –37.5 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{24}F_3NNaO_4]^+$ 470.1550, found 470.1544 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1.10 H), 7.64 – 7.40 (m, 5.14 H), 7.34 – 7.22 (m, 1.00 H), 7.17 – 7.03 (m, 0.84 H), 6.89 (td, *J* = 7.5, 1.2 Hz, 0.58 H), 6.53 (s, 0.56 H), 6.18 (dd, *J* = 7.6, 1.6 Hz, 0.57 H), 5.20 (s, 0.43 H), 3.44 (m, 1.00 H), 3.19 (m, 1.00H), 1.80 (s, 1.27 H), 1.74 (s, 1.73 H), 1.50 (s, 5.05 H), 1.43 (s, 3.70 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.32, -79.54. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.7, 160.9, 153.2, 152.8, 151.8, 151.7, 136.6, 135.9, 134.0, 133.9, 131.0, 130.1, 129.9, 129.8, 129.4, 129.3, 129.2, 128.9, 126.5, 126.3, 126.1, 125.9, 125.0, 124.1, 123.7, 123.4, 123.3, 122.2, 81.9 (q, *J* = 30.9 Hz), 81.4 (q, *J* = 30.9 Hz), 80.5, 80.4, 34.0, 33.6, 28.4, 28.3, 22.1, 22.0.

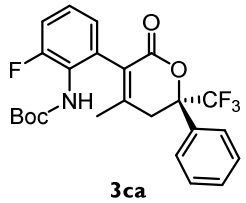
tert-Butyl (*R*)-(4-chloro-2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ba)



3ba

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.76/1.00 mixture of conformers in 97% yield (93.5 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 5.8 min, τ_{II} = 7.9 min. $[\alpha]_D^{25}$ –24.3 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1154 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1.09 H), 7.66 – 7.41 (m, 5.22 H), 7.30 – 7.20 (m, 1.20 H), 7.11 (d, *J* = 2.5 Hz, 0.40 H), 6.46 (s, 0.56 H), 6.17 (d, *J* = 2.5 Hz, 0.54 H), 5.16 (s, 0.42 H), 3.44 (m, 1.00 H), 3.20 (m, 1.00 H), 1.82 (s, 1.28 H), 1.77 (s, 1.70 H), 1.49 (s, 5.00 H), 1.42 (s, 4.00 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.31, -79.55. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 160.5, 153.0, 152.8, 152.7, 152.6, 135.5, 134.7, 133.8, 133.6, 130.7, 130.2, 130.0, 129.6, 129.4, 129.3, 129.2, 129.1, 128.5, 128.4, 126.2, 126.0, 125.3, 124.7, 124.1, 124.0, 122.2, 122.1, 82.0 (q, *J* = 30.8 Hz), 81.5 (q, *J* = 30.6 Hz), 80.9, 80.8, 34.0, 33.7, 28.3, 28.2, 22.1, 22.0.

tert-Butyl (*R*)-(2-fluoro-6-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ca)

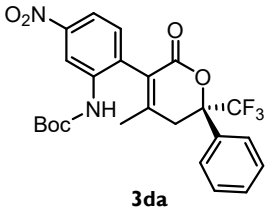


3ca

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.60/1.00 mixture of conformers in 96% yield (80.0 mg) and 94% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column:

hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 5.9 min, τ_{II} = 7.1 min. $[\alpha]_D^{25}$-198.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_4NNaO_4]^+$ 488.1455, found 488.1449 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.35 (m, 5.21 H), 7.22 (td, *J* = 8.0, 5.2 Hz, 0.43 H), 7.15 – 6.99 (m, 1.68 H), 6.99 – 6.91 (m, 0.40 H), 6.20 – 5.97 (m, 1.26 H), 4.85 (s, 0.40 H), 3.48 – 3.30 (m, 1 H), 3.17 (m, 1.00 H), 1.83 (s, 1.08 H), 1.77 (s, 1.97 H), 1.45 (s, 5.79 H), 1.37 (s, 3.58 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.41, -79.56. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 161.0, 159.4, 159.1, 157.7, 157.5, 153.5, 153.0, 151.5 (double), 134.2, 133.9, 133.4, 132.0, 130.0, 129.8, 129.2, 128.9, 127.5 (d, *J* = 27.7 Hz), 127.4 (d, *J* = 27.7 Hz), 126.3, 126.1, 125.3 (d, *J* = 3.7 Hz), 124.8 (d, *J* = 3.7 Hz), 124.6 (bs), 124.5 (bs), 124.2, 123.2 (q, *J* = 284.0 Hz), 123.1 (q, *J* = 284.0 Hz), 116.5, 116.4 (d, *J* = 11.0 Hz), 116.3 (d, *J* = 11.0 Hz), 81.9 (q, *J* = 31.0 Hz), 81.5 (q, *J* = 30.0 Hz), 80.4 (double), 34.1, 33.5, 28.1, 28.0, 22.1, 22.0.

tert-Butyl (*R*)-(2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)-4-nitrophenyl)carbamate (3da)

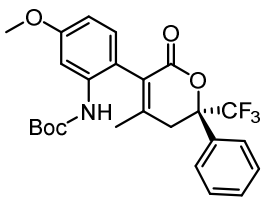


3da

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in a 0.79:1.00 mixture of conformers in 92% yield (90.7 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 7.6 min, τ_{II} = 11.9 min. $[\alpha]_D^{25}$ -98.5 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_3N_2NaO_6]^+$ 515.1400, found 515.1393 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (m, 2.36 H), 8.19 – 8.12 (m, 2H), 8.01 (d, *J* = 2.6 Hz, 1.00H), 7.66 – 7.45 (m, 12.33 H), 7.11 (d, *J* = 2.6 Hz, 1.22 H), 6.80 (bs, 1.24 H), 5.53 (bs, 0.97 H), 3.54 (dd, *J* = 7.0, 1.2 Hz, 0.98 H), 3.48 (dd, *J* = 7.1, 1.2 Hz, 1.40 H), 3.30-3.24

(m, 2.37 H), 1.86 (s, 3.29 H), 1.81 (s, 4.04 H), 1.52 (s, 11.90 H), 1.45 (s, 9.45 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.12, -79.62. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 154.4, 154.3, 152.0, 151.7, 143.1, 142.4, 142.3, 142.3, 133.6, 133.6, 130.4, 130.3, 129.5, 129.2, 127.0, 126.2, 126.1, 125.9, 125.2, 124.9, 124.4, 123.3, 123.1, 122.2, 119.8, 119.7, 82.2, 82.1 (q, *J* = 30.8 Hz), 81.6 (q, *J*=30.8 Hz) , 34.0, 31.6, 28.3, 28.2, 25.4, 22.7, 22.2, 14.1.

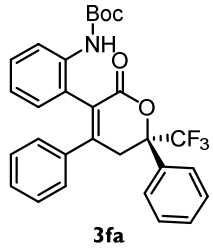
tert-Butyl (*R*)-(4-methoxy-2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ea)



3ea

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.70:1.00 mixture of conformers in 84% yield (80.3 mg) and 92% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 0.8 mL/min, 50 °C, λ = 254 nm: τ_I = 9.9 min, τ_{II} = 11.8 min. $[\alpha]_D^{25}$-113.7 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1647 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.38 (m, 10.48 H), 6.85-6.82 (dd, *J* = 8.9, 3.0 Hz, 1.78 H), 6.67 (d, *J* = 3.0 Hz, 0.71 H), 6.33 (bs, 0.98 H), 5.73 (d, *J* = 2.9 Hz, 1.00 H), 5.02 (bs, 0.60 H), 3.76 (s, 2.04 H), 3.61 (s, 3.13 H), 3.47 – 3.36 (m, 1.79 H), 3.17 (m, 1.87 H), 1.81 (d, *J* = 0.9 Hz, 2.12 H), 1.76 (d, *J* = 0.9 Hz, 3.17 H), 1.47 (s, 8.98 H), 1.41 (s, 6.11 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.38, -79.51. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.6, 160.9, 156.1, 155.8, 153.9, 153.4, 151.8, 151.7, 134.1, 133.9, 130.1, 129.8, 129.6, 129.3, 129.0, 128.9, 126.5, 126.4, 126.1, 125.1, 116.1, 115.6, 114.7, 114.0, 82.5, 82.0 (q, *J*=30.8 Hz), 81.5 (q, *J*=30.5 Hz), 80.2, 80.2, 55.5, 55.3, 34.0, 33.6, 31.6, 28.4, 28.3, 22.7, 22.1, 22.1, 14.1.

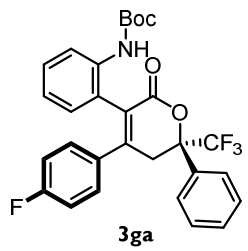
tert-Butyl (*R*)-(2-(2-oxo-4,6-diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3fa)



3fa

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.42/1.00 mixture of conformers in 83% yield (84.8 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 4.4 min, τ_{II} = 7.9 min. $[\alpha]_D^{25}$ –187.9 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{29}H_{26}F_3NNaO_4]^+$ 532.1706, found 532.1700 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.38 (m, 8.56 H), 7.25 – 7.09 (m, 5.76 H), 7.04 (dd, *J* = 7.8, 1.7 Hz, 0.63 H), 7.00 – 6.85 (m, 3.57 H), 6.78 – 6.58 (m, 1.63 H), 6.02 (dd, *J* = 7.7, 1.6 Hz, 0.77 H), 5.27 (s, 0.54 H), 3.80 (d, *J* = 8.5 Hz, 0.42 H), 3.74 (d, *J* = 8.6 Hz, 0.98 H), 3.65 (d, *J* = 6.3 Hz, 1.00H), 3.59 (d, *J* = 6.3 Hz, 0.42 H), 1.49 (s, 7.50 H), 1.39 (s, 5.66 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.01, -79.22. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.8, 161.8, 153.2, 152.5, 151.3, 151.0, 137.1, 136.9, 136.7, 135.9, 133.7 (double), 131.9, 130.5, 130.2, 129.9, 129.7 (double), 129.4, 129.1, 129.0, 128.5, 127.6, 127.5, 126.9, 126.5, 126.3, 125.4, 125.1 (double), 124.1 (bs), 123.8, 123.4, 123.1 (bs), 122.3, 121.3, 82.3 (q, *J* = 30.9 Hz), 81.9 (q, *J* = 30.5 Hz), 80.4, 80.2, 34.3, 34.0, 28.4, 28.3.

tert-Butyl (*R*)-(2-(4-(4-fluorophenyl)-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ga)

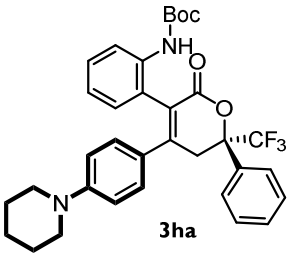


3ga

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.70:1.00

mixture of conformers in 99% yield (105 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 6.8 min, τ_{II} = 9.8 min. $[\alpha]_D^{25}$ –218.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{29}H_{25}F_4NNaO_4]^+$ 550.1612, found 550.1603 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.44 (m, 10.52 H), 7.18 (qd, *J* = 8.5, 1.7 Hz, 1.84 H), 7.07 – 6.80 (m, 8.42 H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1.88 H), 5.99 (dd, *J* = 7.7, 1.6 Hz, 0.94 H), 5.27 (bs, 0.63 H), 3.81 – 3.68 (m, 1.74 H), 3.61 (d, *J* = 7.4 Hz, 1-16 H), 3.55 (d, *J* = 7.3 Hz, 0.54 H), 1.49 (s, 9.04 H), 1.39 (s, 6.54 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.03, -79.22. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.8, 162.7, 161.7, 161.4, 153.3, 152.5, 150.0, 149.7, 137.1, 135.9, 133.7, 133.7, 132.9, 132.9, 132.7, 132.7, 131.8, 130.5, 130.2, 130.0, 129.9, 129.8, 129.8, 129.7, 129.5, 129.3, 129.1, 127.1, 126.4, 126.3, 125.6, 124.1, 123.7, 115.9, 115.6, 82.2 (q, *J* = 34.5 Hz), 81.8 (q, *J* = 30.6 Hz), 80.5, 80.4, 34.2, 34.0, 28.4, 28.3, 25.4.

tert-Butyl (*R*)-(2-(2-oxo-6-phenyl-4-(4-(piperidin-1-yl)phenyl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ha)

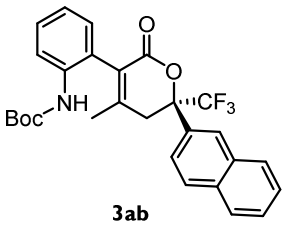


3ha

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 82:18) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 82% yield (97 mg) and 99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 11.0 min, τ_{II} = 12.0 min. $[\alpha]_D^{25}$ –281.0 (*c* 0.2, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{34}H_{35}F_3N_2NaO_4]^+$ 615.2432, found 615.2430 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.54 (m, 3.10 H), 7.53 – 7.39 (m, 3.07 H), 7.18 (dddd, *J* = 9.9, 8.6, 7.4, 1.6 Hz, 1.01 H), 7.10 (dd, *J* = 7.8, 1.6 Hz,

0.39 H), 7.02 – 6.85 (m, 2.48 H), 6.80 (s, 0.59 H), 6.71 (dd, *J* = 7.5, 1.2 Hz, 0.82 H), 6.62 (s, 1.80 H), 6.00 (dd, *J* = 7.7, 1.6 Hz, 0.62 H), 5.31 (s, 0.44 H), 3.75 – 3.56 (m, 2.00 H), 3.17 (d, *J* = 5.5 Hz, 3.94 H), 1.76 – 1.51 (m, 6.65 H), 1.47 (s, 5.31 H), 1.37 (s, 3.68 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.05, -79.32. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.4, 162.3, 153.3, 152.6, 152.2, 150.5, 150.1, 137.3, 136.0, 133.9, 131.9, 130.6, 129.9, 129.7 (double), 129.6, 129.3, 128.9, 128.8, 128.7, 126.5, 126.3, 124.7, 123.9, 123.4, 121.9, 113.9, 81.9 (q, *J* = 30.3 Hz), 81.5 (q, *J* = 30.3 Hz), 80.2, 80.0, 48.6, 33.3, 32.8, 28.4, 28.3, 25.3, 24.2.

tert-butyl (R)-(2-(4-methyl-6-(naphthalen-2-yl)-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-3-yl)phenyl)carbamate (3ab)

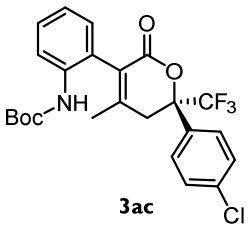


3ab

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 99% yield (98.6 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 5.5 min, τ_{II} = 6.1 min. $[\alpha]_D^{25}$ –42.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{28}H_{26}F_3NNaO_4]^+$ 520.1706, found 520.1692 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.0 Hz, 0.62 H), 8.06 – 8.05 (m, 1.05 H), 7.97 – 7.95 (m, 1.04 H), 7.94 – 7.93 (m, 0.62 H), 7.90 – 7.86 (m, 4.09 H), 7.77 (d, *J* = 8.3 Hz, 0.63H), 7.66 (dd, *J* = 8.7, 2.0 Hz, 0.1.3 H), 7.61 – 7.55 (m, 4.15 H), 7.28 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 0.63 H), 7.25 – 7.23 (m, 0.83 H), 7.16 – 7.15 (m, 0.59 H), 7.14 – 7.11 (m, 0.69 H), 6.80 (td, *J* = 7.5, 1.2 Hz, 1.0 H), 6.52 (bs, 1.02 H), 6.14 (dd, *J* = 7.6, 1.6 Hz, 1.08 H), 5.33 (bs, 0.69 H), 3.55 – 3.50 (m, 1.60 H), 3,38-3,35 (m, 0.62 H), 3.32 – 3.29 (m, 1.04 H), 1.84 (s, 1.61 H), 1.76 (s, 2.81 H), 1.50 (s, 8.18 H), 1.18 (s, 4.51 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -78.99, -79.09. ^{13}C-NMR (150 MHz,

$CDCl_3$) δ 160.7, 160.0, 152.3, 151.7, 150.7, 150.7, 135.6, 135.0, 132.5, 132.5, 131.8, 131.7, 130.3, 130.2, 129.9, 129.0, 128.3, 128.3, 128.3, 127.9, 127.7, 127.6, 126.7, 126.6, 126.5, 126.5, 126.1, 126.1, 125.6, 125.5, 125.4, 123.9, 122.7, 122.5, 121.9, 121.4, 81.2, 81.0 (q, *J* = 30.6 Hz) 80.6 (q, *J* = 30.4 Hz), 80.4, 79.5, 79.2, 33.2, 32.8, 30.6, 27.3, 27.0, 21.6, 21.1, 21.0.

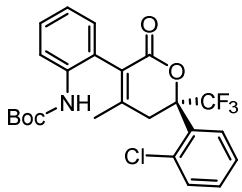
tert-Butyl (*R*)-(2-(6-(4-chlorophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ac).



3ac

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.75:1.00 mixture of conformers in 92% yield (88.7 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 7.9 min, τ_{II} = 9.5 min. $[\alpha]_D^{25}$ –87.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1156 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 1.97 H), 7.56 (d, *J* = 8.6 Hz, 1.63 H), 7.51 – 7.43 (m, 5.62 H), 7.34 – 7.28 (m, 1.96 H), 7.14 – 7.06 (m, 1.69 H), 6.97 – 6.93 (m, 1.33 H), 6.48 (bs, 1.13 H), 6.29 (dd, *J* = 7.6, 1.4 Hz, 1.24 H), 5.32 (bs, 0.79 H), 3.50 – 3.39 (m, 1.98 H), 3.21 – 3.07 (m, 2.11 H), 1.83 (s, 2.27 H), 1.76 (s, 3.00 H), 1.50 (s, 9.01 H), 1.45 (s, 6.25 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.38, -79.58. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 160.7, 153.3, 152.8, 151.7, 151.6, 136.6, 136.3, 136.2, 136.0, 132.7, 132.6, 131.0, 130.0, 129.6, 129.5, 129.4, 129.3, 127.8, 127.6, 126.5, 125.1, 124.8, 124.0, 123.9, 123.6, 122.2, 122.1, 81.5 (q, *J* = 30.8 Hz), 81.1 (q, *J* = 30.8 Hz), 80.7, 80.6, 33.9, 33.6, 28.3, 22.2, 22.2.

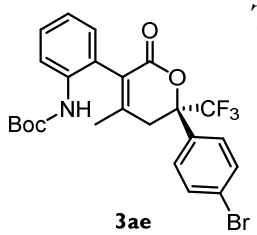
tert-Butyl (*R*)-(2-(6-(2-chlorophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ad)



3ad

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.72:1.00 mixture of conformers in 60% yield (57.8 mg) and 96% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.8 min, τ_{II} = 12.7 min. $[\alpha]_D^{25}$–45.9 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1153 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.74 (m, 3.34 H), 7.55 – 7.47 (m, 1.65 H), 7.44 – 7.27 (m, 5.07 H), 7.18 – 7.07 (m, 1.57 H), 6.92 (td, *J* = 7.5, 1.2 Hz, 1.00 H), 6.50 (bs, 0.87 H), 6.25 (dd, *J* = 7.6, 1.5 Hz, 0.97 H), 5.36 (bs, 0.60 H), 4.18 (d, *J* = 11.4 Hz, 0.79 H), 4.11 (d, *J* = 11.8 Hz, 0.96 H), 3.49 (dd, *J* = 10.2, 1.1 Hz, 0.93 H), 3.43 (dd, *J* = 10.6, 1.1 Hz, 0.79 H), 1.87 (s, 2.21 H), 1.84 (s, 3.08 H), 1.50 (s, 8.87 H), 1.47 (s, 7.10 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -77.34, -77.36. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.6, 160.9, 153.2, 153.0, 152.9, 136.7, 135.9, 133.2, 132.8, 132.2, 132.1, 131.4, 131.2, 131.2, 130.9, 130.8, 130.4, 130.0, 129.4, 129.3, 127.7, 127.5, 125.9, 124.5, 124.4, 123.8, 123.7, 123.7, 122.5, 122.5, 83.4, 82.7 (q, *J* =31.5 Hz), 82.3 (q, *J* = 31.1 Hz), 80.6, 80.5, 33.1, 32.8, 28.4, 28.3, 21.5.

tert-Butyl (*R*)-(2-(6-(4-bromophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ae)

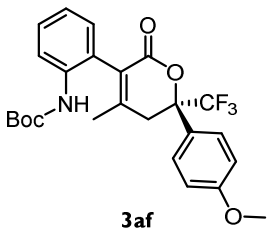


3ae

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 84% yield (88.2 mg) and 96.5% enantiomeric excess.

The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.6 min, τ_{II} = 5.9 min. $[\alpha]_D^{25}$ –54.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}BrF_3NNaO_4]^+$ 548.0655, found 548.0649 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 11.0, 8.3 Hz, 0.94 H), 7.67 – 7.54 (m, 2.07 H), 7.45 (m, 2.16 H), 7.36 – 7.26 (m, 1.07 H), 7.14 – 7.06 (m, 0.79 H), 6.94 (td, *J* = 7.5, 1.2 Hz, 0.61 H), 6.46 (s, 0.56 H), 6.29 (dd, *J* = 7.6, 1.6 Hz, 0.59 H), 5.33 (s, 0.36 H), 3.50 – 3.40 (m, 1.00 H), 3.13 (m, 1.00 H), 1.82 (s, 1.16 H), 1.75 (s, 1.78 H), 1.48 (s, 5.51 H), 1.45 (s, 3.85 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.36, -79.54. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.3, 160.6, 153.2, 152.8, 151.6, 151.5, 136.6, 135.9, 133.2, 133.1, 132.5, 132.2, 131.0, 129.9, 129.5, 129.4, 128.0, 127.8, 126.4, 125.1, 124.8, 124.6, 124.4, 123.9, 123.6, 123.4, 122.8, 122.3, 81.55 (double, q, *J* = 31.0 Hz), 80.7, 80.5, 33.8, 33.5, 28.3 (double), 22.2 (double).

tert-butyl (_R_)-(2-(6-(4-methoxyphenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)phenyl)carbamate (3af)

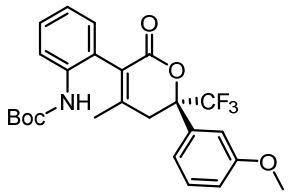


3af

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.61:1.00 mixture of conformers in 66% yield (63.0 mg) and 98% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 75:25, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 7.2 min, τ_{II} = 4.9 min. $[\alpha]_D^{25}$ –123.2 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1649 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 0.96 H), 7.48 (m, 2.16 H), 7.35 – 7.23 (m, 1.80 H), 7.17 – 7.04 (m, 0.86 H), 7.03 – 6.86 (m, 2.77 H), 6.53 (s, 0.50 H), 6.27 (dd, *J* = 7.6, 1.6 Hz,

0.55H), 5.30 (s, 0.32 H), 3.85 (s, 1.58), 3.83 (s, 1.21 H), 3.41 (m, 1.00 H), 3.15 (m, 1.00 H), 1.81 (s, 1.28 H), 1.75 (s, 1.87 H), 1.50 (s, 5.78 H), 1.43 (s, 4.11 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.70, -79.90. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.8, 161.0, 160.5, 153.3, 152.9, 151.8, 136.6, 135.9, 131.1, 130.0, 129.4, 129.2, 127.8, 127.5, 126.4, 125.5, 125.0, 124.9, 123.7, 123.4, 123.3, 121.9, 114.7, 114.2, 81.8 (q, J = 30.6 Hz), 81.3 (q, J = 30.5 Hz), 80.7 (double), 55.4, 55.2, 33.9, 33.5, 38.3, 28.2, 22.2, 22.1.

***tert*-Butyl (*R*)-(2-(6-(3-methoxyphenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ag).**

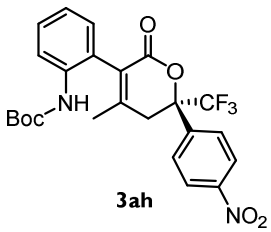


3ag

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 88% yield (84 mg) and 94% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 75:25, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 9.3 min, τ_{II} = 4.6 min. $[\alpha]_D^{25}$ –211.4 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1650 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 0.96 H), 7.48 (m, 2.16 H), 7.35 – 7.23 (m, 1.80 H), 7.17 – 7.04 (m, 0.86 H), 7.03 – 6.86 (m, 2.77 H), 6.53 (s, 0.50 H), 6.27 (dd, J = 7.6, 1.6 Hz, 0.55H), 5.30 (s, 0.32 H), 3.85 (s, 1.58), 3.83 (s, 1.21 H), 3.41 (m, 1.00 H), 3.15 (m, 1.00 H), 1.81 (s, 1.28 H), 1.75 (s, 1.87 H), 1.50 (s, 5.78 H), 1.43 (s, 4.11 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.20, -79.40. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.7, 160.9, 160.1, 159.9, 153.2, 152.8, 151.9, 151.8, 136.6, 136.0, 135.6, 135.4, 131.0, 130.3, 130.0, 129.9, 129.4, 129.2, 126.4, 125.9, 124.9, 124.1, 124.0, 123.7, 123.4, 123.2, 122.2, 122.1, 121.9, 118.5, 118.0, 115.7, 115.0, 112.7, 112.2, 81.8 (q, J = 30.8

Hz), 81.3 (q, *J* = 30.8 Hz), 80.5, 80.4, 55.4, 55.3, 34.0, 33.7, 28.3 (double), 22.1, 22.0.

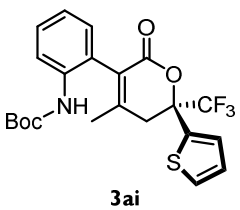
tert-Butyl (*R*)-(2-(4-methyl-6-(4-nitrophenyl)-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ah)



3ah

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.63:1.00 mixture of conformers in 86% yield (84.8 mg) and 90% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 6.6 min, τ_{II} = 10.4 min. $[\alpha]_D^{25}$ –97.2 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_3N_2NaO_6]^+$ 515.1400, found 515.1391 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.39 – 8.33 (m, 3.42 H), 7.85 (d, *J* = 8.6 Hz, 1.83 H), 7.79 (d, *J* = 8.7 Hz, 2.02 H), 7.39 – 7.29 (m, 2.56 H), 7.16 – 7.07 (m, 1.41H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1.02 H), 6.42 (bs, 0.96 H), 6.29 (dd, *J* = 7.5, 1.5 Hz, 1.00 H), 5.36 (bs, 0.77 H), 3.52 (m, 1.65 H), 3.22 (m, 1.64 H), 1.86 (s, 1.74 H), 1.81 (s, 2.77 H), 1.50 (s, 8.50 H), 1.40 (s, 5.25 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -78.80, -78.82. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 154.4, 154.3, 152.0, 151.7, 143.1, 142.4, 142.3, 142.3, 133.6, 133.6, 130.4, 130.3, 129.5, 129.2, 127.0, 126.2, 126.1, 125.9, 125.2, 124.9, 124.4, 123.3, 123.1, 122.2, 119.8, 119.7, 82.2, 82.1 (q, *J* = 30.8 Hz), 81.6 (q, *J* = 30.8 Hz) , 34.0, 31.6, 28.3, 28.2, 25.4, 22.7, 22.2, 14.1.

tert-Butyl (*S*)-(2-(4-methyl-2-oxo-6-(thiophen-2-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ai)



3ai

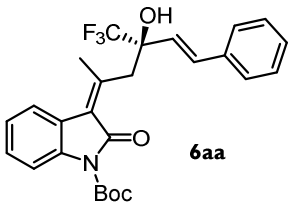
The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title

compound was obtained as a yellowish oil in a 0.99:1.00 mixture of conformers in 89% yield (87.7 mg) and 87% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.3 min, τ_{II} = 14.6 min. $[\alpha]_D^{25}$ –43.3 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{22}H_{22}F_3NNaO_4S]^+$ 476.1114, found 476.1108 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1.43 H), 7.44 (td, *J* = 5.0, 1.2 Hz, 2.16 H), 7.36 – 7.27 (m, 4.51 H), 7.13 – 7.07 (m, 4.32 H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1.22 H), 6.49 (bs, 1.18 H) 6.34 (dd, *J* = 7.6, 1.4 Hz, 1.18 H), 5.31 (bs, 0.87 H), 3.45 (m, 2.28 H), 3.09 (m, 2.32 H), 1.86 (s, 3.00 H), 1.81 (s, 3.03 H), 1.50 (s, 8.93 H), 1.48 (s, 9.56 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -80.17, -80.49. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.1, 160.2, 153.3, 152.8, 151.8, 151.6, 137.0, 136.9, 136.7, 136.0, 131.0, 130.0, 129.4, 129.3, 128.5, 128.4, 128.1, 127.7, 127.6, 127.4, 126.3, 124.9, 123.8, 123.5, 123.5, 123.4, 122.9, 121.6, 121.6, 80.8 (q, *J* = 31.8 Hz), 80.5, 80.3 (q, *J* = 31.9 Hz), 77.2, 77.0, 76.8, 35.3, 35.0, 31.6, 28.4, 28.3, 22.6, 22.1, 22.0.

General procedure for the vinylogous aldol reaction

In an 2-dram vial equipped with a teflon-coated magnetic stir bar, catalyst **I** (6 mg, 0.01 mmol, 0.05 equiv), oxindole (0.2 mmol, 1 equiv) and trifluoroketone (0.2 mmol, 1 equiv) were dissolved in 0.5 mL of anhydrous THF (freshly distilled over sodium and benzophenone) at room temperature. After 24 hours of stirring, the reaction was flushed through a short silica plug with a 1:1 mixture of DCM:EtOAc to remove the catalyst and the crude product was concentrated to perform a ^{1}H-NMR analysis to measure the yield (1,3,5-trimethoxybenzene was used as internal standard). At this point the product was purified with flash column chromatography and the ee% was determined through HPLC on a chiral stationary phase.

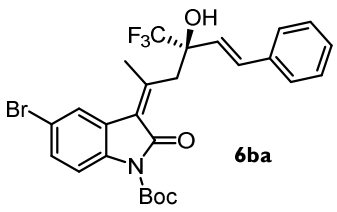
tert-Butyl (_E_)-(2-(4-methyl-2-oxo-6-styryl-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)phenyl)carbamate (6aa).



6aa

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 64% yield for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in 93% enantiomeric excess. When the reaction was performed in 1 mmol scale the crude product showed a 68% yield based on ^{1}H-NMR and 50% yield on the isolated pure product. The enantiomeric excess in this case was found to be 95%. The ee was determined by HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 5.6 min, τ_I = 6.9 min. $[\alpha]_D^{25}$ +376.5 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{26}F_3NNaO_4]^+$ 496.1712, found 496.1721 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.27 (m, 6H), 7.16 (dd, *J* = 7.7 Hz, 1.1 Hz, 1H), 6.92 (d, *J* = 15.8 Hz, 1H), 6.24 (d, *J* = 16.3 Hz, 1H), 5.39 (s, 1H), 4.35 (d, *J* = 12.6 Hz, 1H), 2.83 (d, *J* = 12.6 Hz, 1H), 2.35 (s, 3H), 1.67 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.31. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.7, 152.6, 148.8, 138.2, 135.9, 133.1, 128.8, 128.7, 128.2, 126.8, 124.2, 124.2, 123.7, 123.4, 114.7, 85.0, 78.0 (q, *J* = 28.2 Hz, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 42.0, 28.1, 27.9.

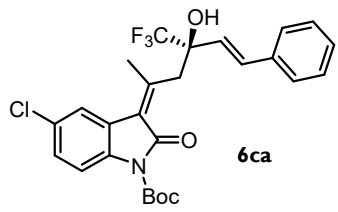
tert-Butyl (*E*)-(4-bromo-2-(4-methyl-2-oxo-6-styryl-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-3-yl)phenyl)carbamate (6ba).



6ba

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 60% yield for catalyst **V** and 47% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1) and the title compound was obtained as a yellowish oil in 92% (catalyst **V**) and 92% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: $\tau_{\mathbf{V}}$ = 5.9 min, $\tau_{\mathbf{I}}$ = 8.1 min. $[\alpha]_D^{25}$ +123.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{25}BrF_3NNaO_4]^+$ 574.0817, found 574.0833 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 1H), 7.61 (s, 1H), 7.47 – 7.24 (m, 9H), 6.91 (d, *J* = 15.8 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 5.21 (bs, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 2.87 (d, *J* = 12.5 Hz, 1H), 2.35 (s, 3H), 1.65 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.35. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8, 161.5, 154.7, 148.6, 137.1, 135.8, 133.2, 131.4, 128.7, 126.8, 125.9, 125.1, 117.3, 92.9, 85.3,77.63 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 55.3, 42.1, 28.2, 28.1.

***tert*-Butyl-(*Z*)-5-chloro-3-((*R*,*E*)-4-hydroxy-6-phenyl-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ca).**

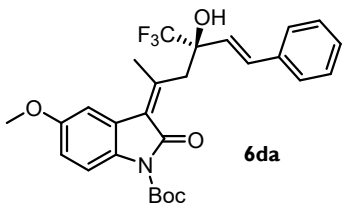


6ca

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 58% for catalyst **I** and 39% yield for catalyst **V**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1) and the title compound was obtained as a yellowish oil in 91% (catalyst **I**) and 85% (catalyst **V**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5,

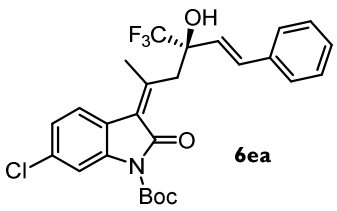
flow rate 1.0 mL/min, λ = 254 nm: τ_V = 5.9 min, τ_I = 8.3 min. $[\alpha]_D^{25}$ +216.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{25}ClF_3NNaO_4]^+$ 530.1322, found 530.1329 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 1H), 7.61 (s, 1H), 7.47 – 7.24 (m, 9H), 6.91 (d, *J* = 15.8 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 5.21 (bs, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 2.87 (d, *J* = 12.5 Hz, 1H), 2.35 (s, 3H), 1.65 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.35. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.0, 154.6, 148.6, 136.6, 135.7, 133.1, 129.7, 128.7, 128.5, 128.3, 126.8, 126.0, 124.7, 124.2, 123.4, 115.8, 85.3, 78.0 (q, *J* = 28.2 Hz), 42.1, 28.1, 28.0.

tert-Butyl (*Z*)-3-((*R*,*E*)-4-hydroxy-6-phenyl-4-(trifluoromethyl)hex-5-en-2-ylidene)-5-methoxy-2-oxoindoline-1-carboxylate (6da).



The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 50% yield for catalyst **V** and 38 % for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in 95% (catalyst **V**) and 92% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 11.5 min, τ_I = 7.4 min. $[\alpha]_D^{25}$ +280.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{27}H_{28}F_3NNaO_5]^+$ 526.1817, found 526.1803 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.28 (m, 5H), 7.06 (d, *J* = 2.6 Hz, 1H), 6.92 (d, *J* = 15.8 Hz, 1H), 6.85 (dd, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 4.34 (d, *J* = 12.5 Hz, 1H), 3.79 (s, 3H), 2.82 (d, *J* = 12.5 Hz, 1H), 2.33 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.30. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.8, 156.4, 152.9, 148.9, 135.9, 133.0, 131.9, 128.7, 128.2, 127.0, 126.8, 124.4, 123.7, 115.4, 112.8, 111.4, 84.7, 77.8 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 55.7, 42.0, 28.1, 27.8.

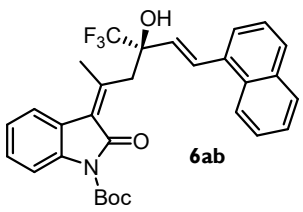
***tert*-Butyl (*Z*)-6-chloro-3-((*R*,*E*)-4-hydroxy-6-phenyl-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ea).**



6ea

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 50% yield for both catalyst **V** and **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in 91% (catalyst **V**) and 93% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: $\tau_{\mathbf{V}}$ = 9.4 min, $\tau_{\mathbf{I}}$ = 6.9 min. $[\alpha]_D^{25}$ +238.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{25}ClF_3NNaO_4]^+$ 530.1322, found 530.1329 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.43-7.38 (m, 3H), 7.35-7.27 (m, 3H), 7.13 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.90 (d, *J* = 15.8 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 5.18 (s, 1H), 4.30 (d, *J* = 12.6 Hz, 1H), 2.86 (d, *J* = 12.6 Hz, 1H), 2.32 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.34. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 153.2, 148.6, 139.0, 135.8, 134.6, 133.1, 128.7, 128.3, 126.8, 126.0, 124.8, 124.2, 123.5, 121.8, 115.4, 85.5, 77.8 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 41.9, 28.1, 27.9.

***tert*-Butyl (*Z*)-3-((*R*,*E*)-4-hydroxy-6-(naphthalen-1-yl)-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ab).**

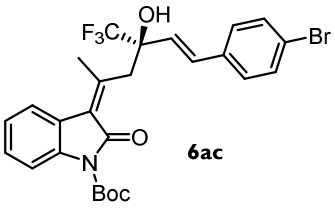


6ab

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 58% yield for catalyst **V** and 33% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 95:5) and the title compound was obtained as amorphous yellow solid in 88%

(catalyst **V**) and 88% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.7 mL/min, λ = 254 nm: τ_V = 6.5 min, τ_I = 13.2 min. $[\alpha]^{rt}_D$ +14.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{30}H_{28}F_3NNaO_4]^+$ 546.1868, found 546.1860 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.78 (m, 5H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.17 (td, J_1 = 7.7 Hz, J_2= 1.1 Hz, 1H), 6.28 (d, *J* = 15.5 Hz, 1H), 5.50 (bs, 1H), 4.41 (d, *J* = 12.7 Hz, 1H), 2.87 (d, *J* = 12.6 Hz, 1H), 2.36 (s, 3H), 1.68 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.32. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 168.7, 152.5, 148.8, 138.3, 134.1, 133.5, 131.1, 130.8, 128.8, 128.4, 127.0 – 126.9 (m), 126.9, 126.2, 125.9, 125.5, 124.3, 124.1, 123.9, 123.8, 123.3, 85.0, 42.0, 28.2, 28.1.

***tert*-Butyl (*Z*)-3-((*R*,*E*)-6-(4-bromophenyl)-4-hydroxy-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ac).**

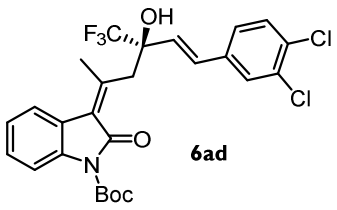


6ac

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 61% yield for catalyst **V** and 55% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1) and the title compound was obtained as a yellowish oil in 94% (catalyst **V**) and 92% (catalyst **I**) enantiomeric eccess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 7.1 min, τ_I = 9.1 min. $[\alpha]_D^{25}$ +92.0 (*c* 0.5, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{25}BrF_3NNaO_4]^+$ 574.0817, found 574.0831 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.19 – 7.12 (m, 2H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 5.42 (s, 1H), 4.32 (d, *J* = 12.6 Hz, 1H), 2.84 (d, *J* = 12.6 Hz, 1H), 2.33 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (282 MHz,

$CDCl_3$) δ -81.24. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8, 161.5,154.7, 148.6, 138.2,137.1, 135.7, 133.2, 131.4, 128.7, 126.8, 125.9, 125.1, 124.7, 117.3, 116.2, 92.9, 85.3, 77.6 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 55.3, 42.1, 28.2, 27.1.

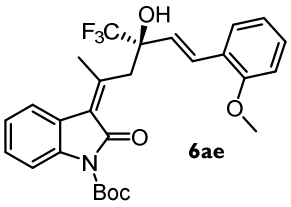
***tert*-Butyl (*Z*)-3-((*R*,*E*)-6-(3,4-dichlorophenyl)-4-hydroxy-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ad).**



6ad

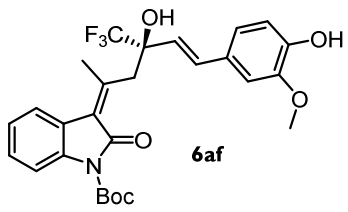
The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 50% yield for catalyst **V** and 50% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in 93% (catalyst **V**) and 87% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 5.7 min, τ_I = 5.3 min. $[\alpha]_D^{25}$ +497.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{24}Cl_2F_3NNaO_4]^+$ 564.0932, found 564.0915 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 1H), 7.53 – 7.46 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.22 – 7.13 (m, 2H), 6.84 (d, *J* = 15.7 Hz, 1H), 6.27 (d, *J* = 15.4 Hz, 1H), 5.47 (s, 1H), 4.31 (d, *J* = 12.7 Hz, 1H), 2.84 (d, *J* = 12.6 Hz, 1H), 2.32 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.13. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.7, 151.9, 148.7, 138.2, 135.9, 132.9, 132.0, 130.9, 130.6, 128.9, 128.3, 127.8, 127.0, 126.1, 125.8, 124.2, 123.2, 114.7, 85.1, 78.1 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 41.9, 28.1, 27.8.

tert-Butyl (*Z*)-3-((*R*,*E*)-4-hydroxy-6-(2-methoxyphenyl)-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ae).



The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 59% yield for catalyst **V** and 41% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1) and the title compound was obtained as a yellowish oil in 90% (catalyst **V**) and 86% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 6.5 min, τ_I = 9.1 min. $[\alpha]_D^{25}$ +72.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{27}H_{28}F_3NNaO_5]^+$ 526.1817, found 526.1832 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.51 (dd, J_1 = 8.1, J_2= 1.1 Hz, 1H), 7.41 (dd, J_1 = 7.6 Hz, J_2= 1.8 Hz, 1H), 7.31 (td, J_1 = 8.0, J_2= 1.2 Hz, 2H), 7.27 – 7.22 (m, 1H), 7.18 – 7.11 (m, 2H), 6.93 (td, J_1 = 7.5 Hz, J_2= 1.1 Hz, 1H), 6.86 (dd, J_1 = 8.3 Hz, J_2= 1.1 Hz, 1H), 5.26 (bs, 1H) 4.33 (d, J = 12.5 Hz, 1H), 3.78 (s, 3H), 2.36 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.38. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.6, 157.2, 153.1, 148.9, 138.2, 129.1, 128.6, 128.3, 127.6, 126.6, 125.0, 124.5, 124.2, 124.1, 123.5, 120.6, 114.6, 110.9, 84.7, 55.3, 42.0, 28.1, 28.1.

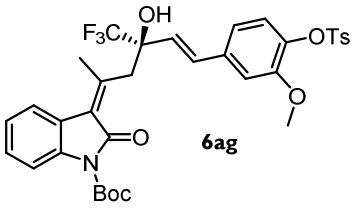
tert-Butyl (*Z*)-3-((*R*,*E*)-4-hydroxy-6-(4-hydroxy-3-methoxyphenyl)-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6af).



The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 48% yield for catalyst **V** and 45% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 4:1) and the title compound was obtained as a yellowish oil in 96% (catalyst **V**) and 92% (catalyst **I**) enantiomeric excess. The ee was determined

by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 10.4 min, τ_I = 12.2 min. $[\alpha]_D^{25}$ +60.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{27}H_{28}F_3NNaO_6]^+$ 542.1766, found 542.1760 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.11 (m, 3H), 7.01 – 6.85 (m, 3H), 6.82 (d, *J* = 15.7 Hz, 1H), 6.10 (d, *J* = 15.7 Hz, 1H), 4.31 (d, *J* = 12.5 Hz, 1H), 3.90 (s, 3H), 2.85 (d, *J* = 12.5 Hz, 1H), 2.35 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.35. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.6, 151.8, 147.8, 145.6, 144.9, 137.2, 131.7, 127.7, 127.5, 125.7, 123.2, 123.1, 122.4, 120.3, 119.2, 113.6, 113.5, 108.1, 83.9, 77.2 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 54.9, 27.1, 26.9, 24.3.

***tert*-Butyl (*Z*)-3-((*R*,*E*)-4-hydroxy-6-(3-methoxy-4-(tosyloxy)phenyl)-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6ag).**

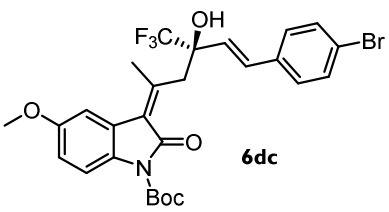


6ag

The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 67% yield for catalyst **V** and 50% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained in as a yellowish oil 92% (catalyst **V**) and 92% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 11.1 min, τ_I = 14.6 min. $[\alpha]_D^{25}$ +165.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{34}H_{34}F_3NNaO_8S]^+$ 696.1855, found 696.1878 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.17 (td, J_1= 7.7 Hz, J_2= 1.0 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, J_1 = 8.4 Hz, J_2= 1.7 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 2H), 6.21 (d, *J* = 15.7 Hz, 1H), 5.43 (s, 1H), 4.29 (d, *J* = 12.6 Hz, 1H), 3.56 (s, 3H), 2.86 (d, *J* = 12.6 Hz, 1H), 2.44 (s,

3H), 2.34 (s, 3H), 1.66 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.16. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.7, 152.2, 151.9, 148.7, 145.1, 138.2, 135.9, 133.3, 132.2, 129.4, 128.9, 128.6, 126.9, 124.9, 124.3, 124.2, 124.2, 123.3, 118.7, 114.7, 111.3, 85.1, 78.1(m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 31.6, 28.1, 27.9, 22.6, 14.1.

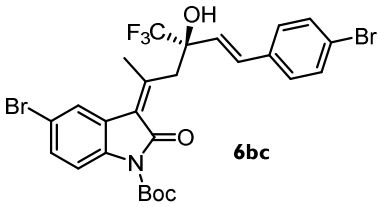
tert-Butyl (_Z_)-3-((_R_,_E_)-6-(4-bromophenyl)-4-hydroxy-4-(trifluoromethyl)hex-5-en-2-ylidene)-5-methoxy-2-oxoindoline-1-carboxylate (6dc).



6dc

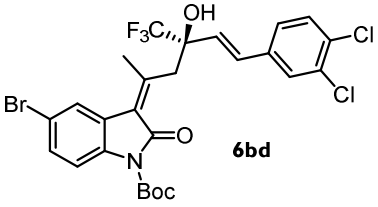
The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 60% yield for catalyst **V** and 55 % for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in 93% (catalyst **V**) and 92% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 10.6 min, τ_I = 8.8 min. $[\alpha]_D^{25}$ +292.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{27}H_{27}BrF_3NNaO_5]^+$ 604.0922, found 604.0928 $[M+Na]^+$.^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.06 (d, *J* = 2.6 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.24 (d, *J* = 15.7 Hz, 1H), 5.45 (s, 1H), 4.31 (d, *J* = 12.6 Hz, 1H), 3.79 (s, 3H), 2.83 (d, *J* = 12.6 Hz, 1H), 2.31 (s, 3H), 1.65 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.30. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.8, 156.4, 152.6, 148.8, 134.4, 133.9, 131.9, 131.9, 130.3, 129.6, 128.9, 128.0, 127.1, 124.4, 124.3, 115.4, 112.8, 111.5, 84.8, 77.8 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 55.7, 42.0, 28.1, 27.8.

tert-Butyl (*Z*)-5-bromo-3-((*S*,*E*)-6-(4-bromophenyl)-4-hydroxy-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (*ent*-6bc).



The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 57% yield for catalyst **V** and 88% for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained in as a yellowish oil 90% (catalyst **V**) and 91% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_V = 6.7 min, τ_I = 7.8 min. $[\alpha]_D^{25}$ +236.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{24}Br_2F_3NNaO_4]^+$ 651.9922 found 651.9916 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 4H), 6.86 (d, *J* = 15.8 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 5.22 (bs, 1H), 4.29 (d, *J* = 12.5 Hz, 1H), 2.88 (d, *J* = 12.5 Hz, 1H), 2.33 (s, 3H), 1.65 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.29. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9, 165.0, 158.9, 154.4, 148.6, 137.1, 134.2, 134.1, 132.0, 131.49, 130.4, 128.9, 128.0, 126.9, 126.0, 125.0, 124.1, 117.3, 116.7, 116.2, 85.4, 77.9 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 28.2, 28.1, 26.1.

tert-Butyl (*Z*)-5-bromo-3-((*R*,*E*)-6-(3,4-dichlorophenyl)-4-hydroxy-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate (6bd).



The reaction was carried out following the general procedure. ^{1}H-NMR of the crude showed a 39% yield for catalyst and 55 % for catalyst **I**. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in 83% (catalyst **V**) and 78% (catalyst **I**) enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_{V} = 7.7 min, τ_{I} = 6.3 min. $[\alpha]_{D}^{25}$ +159.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{23}BrCl_2F_3NNaO_4]^+$ 642.0037, found 642.0020 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.38 (m, 3H), 7.21 (dd, J_1 = 8.3 Hz, J_2= 2.1 Hz, 1H), 6.82 (d, *J* = 15.7 Hz, 1H), 6.27 (d, *J* = 15.3 Hz, 1H), 5.26 (s, 1H), 4.29 (d, *J* = 12.6 Hz, 1H), 2.88 (d, *J* = 12.6 Hz, 1H), 2.33 (s, 3H), 1.65 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -81.18. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8, 154.0, 148.5, 137.1, 135.8, 133.0, 132.2, 131.5, 131.1, 130.7, 128.4, 127.0, 126.1, 125.5, 124.9, 117.3, 116.2, 85.4, 77.8 (m, tetrasubstituted aliphatic carbon, partially overlapped with $CDCl_3$), 41.9, 28.1, 27.9.

Chapter VII

Conclusions and Future Outlooks

This Thesis focused on the works conducted during the time of my Doctoral Studies. During this time, we were able to tackle pro-actively a number of different interesting chemical problems using solely the tools of organic catalysis.

In the first project we investigated the ability of a bifuntional catalyst such as squaramide-functionalized *chincona-alkaloid* derivative that is efficiently able to coordinate in a concerted fashion both reagents. This simultaneous HOMO-raising and LUMO-lowering activation is able to efficiently promote the atroposelective desymmetrization of various *N*-(2-*tert*-butylphenyl)maleimides using 3-phenyloxindoles as nucleophiles.

The second projects focused on a different and less-investigated type of axial chirality, such as dynamically stable alkylidene cyclohexanes. The synthesis of this species was obtained using a primary amine/acid cocatalyst catalytic system. In order to install the rigid double bond needed for the formation of this axially chiral structure we investigated the axially enantioselective Knoevenagel condensation. This easy-to-handle process allowed us to synthesize axially chiral 3-alkylideneoxindoles with various substitution both in the electrophilic and the nucleophilic partners. This reaction represents an important application of aminocatalysis for the synthesis of axially chiral oxindoles. Theoretical studies was finally performed and gave us important elucidations on the reaction mechanism, which is postulated to proceed through an E1cb elimination.

Finally, the desymmetrization of an achiral centrally symmetric system was accomplished. This time a peptide-catalyzed approach was studied. Our work, conducted in the Miller Laboratory at *Yale University*, discovered a new tool for the synthesis of enantioenriched pyridine. Employing an aspartic acid-embedded we were able to obtain the desired product in good yield and enantioselectivity. We were pleased to find that the chemistry employed has a general utility providing strategical access to optically enriched heterocycles. The compounds obtained were also directly derivatized with a different variety of possibly interesting

substituents. The enantioselective derivatization of drug-like scaffolds for a range of different heterocycle was also studied.

In conclusion, we were able to develop innovative strategies for the synthesis of axially and centrally.stereogenic elements in a regio-, atropo-, diastereo- and enantioselective fashion. These findings add another small piece in the organocatalytic desymmetrization scenario.

In spite of the good results obtained, countless apllications are still to be found.