NEW CONCEPTS AND APPLICATIONS IN CHIRAL BRØNSTED ACID AND BASE CATALYSIS

by

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ABSTRACT OF THE DISSERTATION

New Concepts and Applications in Chiral Brønsted Acid and Base Catalysis

By CHANG MIN

Dissertation Director:

Daniel Seidel

Chiral Brønsted acidic small molecules have found widespread applications as organocatalysts from the beginning of this century. Weaker Brønsted acids such as diols and (thio)ureas, typically classified as hydrogen bonding catalysts, and stronger phosphoric acids have proven to be highly effective in a wide range of asymmetric transformations. Given that the pK_a of a chiral carboxylic acid is expected to lie between that of most hydrogen bond donor and chiral phosphoric acid catalysts, it provides new potential to activate a different set of substrates requiring appropriate catalyst acidity. More importantly, by taking advantage of the judicious design of the catalyst structure, the acidity can be largely increased by the stabilization of the corresponding counterion via all kinds of interactions.

This dissertation outlines the development of a new type of conjugate-base-stabilized carboxylic acid to solve the problems that have not been addressed by previously existing catalytic systems. In addition, the development of innovative synthetic applications of known chiral phosphoric acids is also detailed. Specific projects include the inter-, intramolecular Povarov reactions of secondary amines, kinetic resolution of indolines, the synthesis of polycyclic amines via an oxidative Povarov approach, the biomimetic enantioselective synthesis of isoindolinones and a dual-catalysis approach to the kinetic resolution of 1,2-diaryl-1,2-diaminoethanes.

ACKNOWLEDGEMENTS

Parts of chapter 2 were adapted from the articles “Conjugate-Base-Stabilized Brønsted Acids as Asymmetric Catalysts: Enantioselective Povarov Reactions with Secondary Aromatic Amines” (*Angew. Chem. Int. Ed.* **2013**, *52*, 14084), “Catalytic Enantioselective Intramolecular Aza-Diels–Alder Reactions” (*Angew. Chem. Int. Ed.* **2015**, *54*, 6608) and “Stereochemically Rich Polycyclic Amines from the Kinetic Resolution of Indolines through Intramolecular Povarov Reactions” (*Chem. - Eur. J.* **2016**, *22*, 10817). Parts of chapter 3 were adapted from the article “Dual C−H Functionalization of *N*-Aryl Amines: Synthesis of Polycyclic Amines via an Oxidative Povarov Approach” (*Org. Lett.* **2014**, *16*, 2756). Parts of chapter 5 were adapted from the article “A dual-catalysis approach to the kinetic resolution of 1,2-diaryl-1,2-diaminoethanes” (*Chem. Commun.* **2012**, *48*, 10853).

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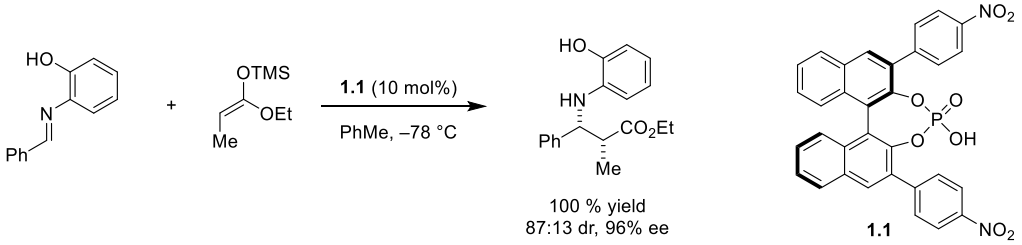
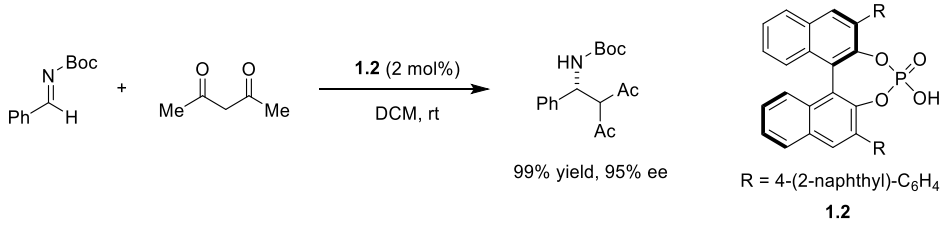
Chapter I Introduction to Chiral Brønsted Acid Catalysis

1.1 Introduction to Chiral Phosphoric Acid Catalysts

Acids have been the prevailing catalysts in innumerable chemical transformations in biological and industrial processes. Since the beginning of this century, organic chemists have witnessed the flourish of small Brønsted acidic molecules in various enantioselective C−C and C−X bond formation reactions. Hydrogen bonding catalysts[1-3] such as (thio)urea,[4-8] squaramide,[9-12] BINOL[13,14] and TADDOL[15-17] derivatives, regarded as weaker Brønsted acids in a general sense, have become one of the most popular categories of organocatalysts.[18-21] Furthermore, this concept has been extended to anion binding catalysis[22-28], and a lot of innovative applications have been established. Since the first introduction of chiral phosphoric acids as chiral Brønsted acid catalysts for asymmetric Mannich reactions by Akiyama[29] and Terada[30] independently in 2004 (Scheme 1.1 and 1.2), asymmetric Brønsted acid catalysis[31-37] has attracted considerable attention as a powerful tool in the realm of asymmetric synthesis.

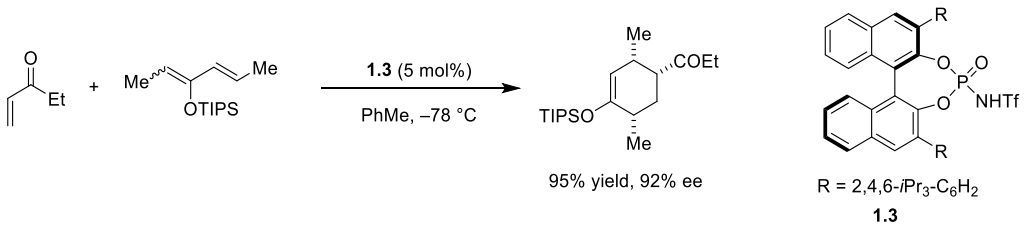


Scheme 1.1. Akiyama's work on asymmetric Mukaiyama–Mannich reaction.



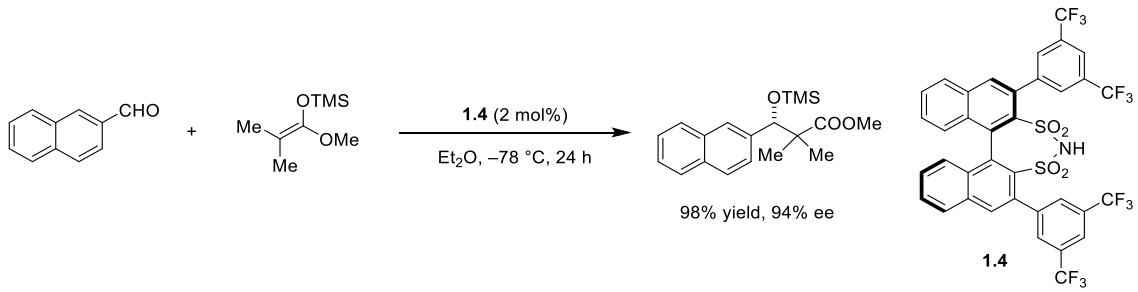
Scheme 1.2. Terada's work asymmetric Mukaiyama–Mannich reaction.

During the last decade, versatile structures of BINOL-derived phosphoric acids have been developed and enabled an number of asymmetric transformations. In a continuing trend, derivatives with higher acidities, including the corresponding nitrogen[38-41], thiol[42], and carbon acids[43], have been synthesized for the purpose of activating less basic substrates. In 2006, Yamamoto[38] introduced the chiral *N*-triflyl phosphoramide **1.3** as an efficient catalyst in the asymmetric Diels-Alder reaction. With increased acidity and reactivity, it is able to activate less basic carbonyl groups (Scheme 1.3).



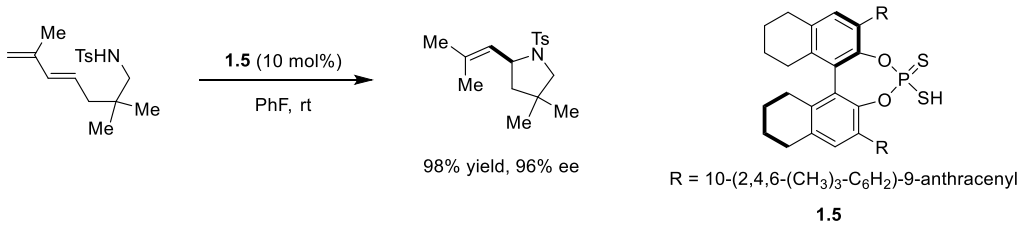
Scheme 1.3. Asymmetric Diels-Alder reaction catalyzed by *N*-triflyl phosphoramide.

The List group[40] created a new chiral cyclic disulfonimide **1.4** to promote enantioselective Mukaiyama aldol reactions. In comparison, classic chiral phosphoric acid, *N*-triflyl phosphoramide, disulfonic acid catalysts gave almost no product (< 2% yield), exhibiting the superiority of the disulfonimide moiety (Scheme 1.4).



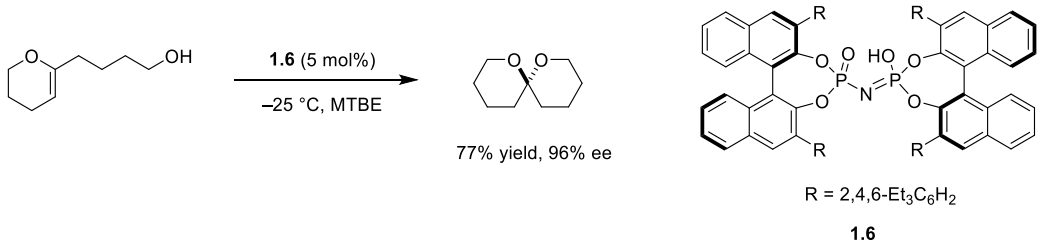
Scheme 1.4. Disulfonimide catalyzed enantioselective Mukaiyama aldol reactions

The Toste group[42] have identified dithiophosphoric acid **1.5** to catalyze the asymmetric hydroamination of dienes. The authors proposed that the highly acidic and nucleophilic chiral acid added to the diene and then underwent enantioselective S_N2' displacement (Scheme 1.5).



Scheme 1.5. Dithiophosphoric acid catalyzed asymmetric hydroamination of dienes

Recently, List *et al*. synthesized a C_2-symmetric imidodiphosphoric acid[44] motif which created a rigid and highly restricted environment, enabling a catalytic enantioselective spiroacetalization reaction (Scheme 1.6).



Scheme 1.6 Imidodiphosphoric acid catalyzed enantioselective spiroacetalization.

Nowadays, chiral phosphoric acids and their derivatives are dominant in the field of chiral Brønsted acid catalysis. Nevertheless, there are still numerous acid-mediated reactions in the literatures yet to be developed in an asymmetric fashion. With the wise choice of chiral Brønsted catalysts and substrates, those classic transformations mediated by achiral acids[45], no matter as catalysts, promoters or solvents, have the high potential to render useful enantioselectivities. In this scenario, the expansion of novel efficient catalytic systems is still highly in demand.

1.2 Asymmetric Brønsted Acid Catalysis with Chiral Carboxylic Acids

Carboxylic acids, arguably the most common acids in organic chemistry, are present in a myriad of organic compounds. Moreover, chiral carboxylic acids also widely exist in nature in the forms of amino acid, tartaric acid, malic acid, cholic acid, biotin and so forth. Nevertheless, in comparison to the thriving development of phosphoric acids, the utilization of carboxylic acids to provide critical

chiral scaffolds is largely underdeveloped. One major reason is the relatively weaker acidity of carboxylic acids which thus limits the scope of substrates able to be activated (Figure 1.1).

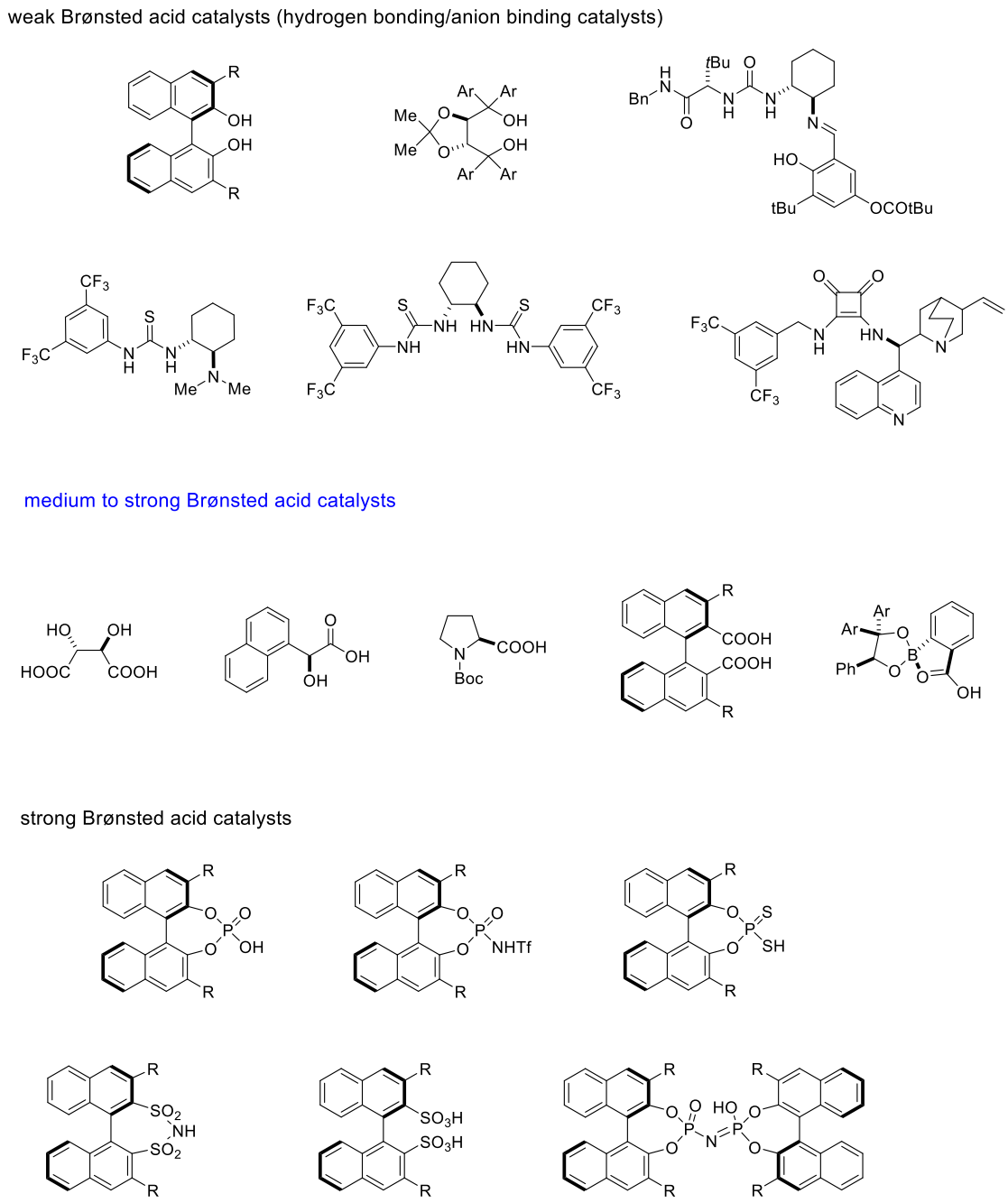


Figure 1.1. Overview of chiral Brønsted acid catalysts with different acidities.

However, choosing an acid catalyst with appropriate acidity can be decisive for the particular type of substrates. Therefore, chiral carboxylic acids were initially introduced to bridge the gap between the

weakly acidic hydrogen bond donors and the stronger phosphoric acids. Besides, nature can easily realise incredibly daunting acid-base chemistry in the absence of super acidic functionality[46]. To tune the pK_a of a specific site in the enzyme, nature has found diverse ingenious ways to create precise microenvironments. When an environment is generated in favor of stabilizing the conjugate base of the acid, the acidity can be significantly enhanced. In enzymatic reactions it is common for acidity strength changes in four to five orders of magnitude by taking advantage of electrostatic interaction, hydrogen bonding, desolvation, metal coordination, etc[47]. Taking the lessons from nature, organic chemists would be capable of creating reactive catalysts with an intelligent combination of components that stabilize the conjugate base in the absence of highly acidic moieties.

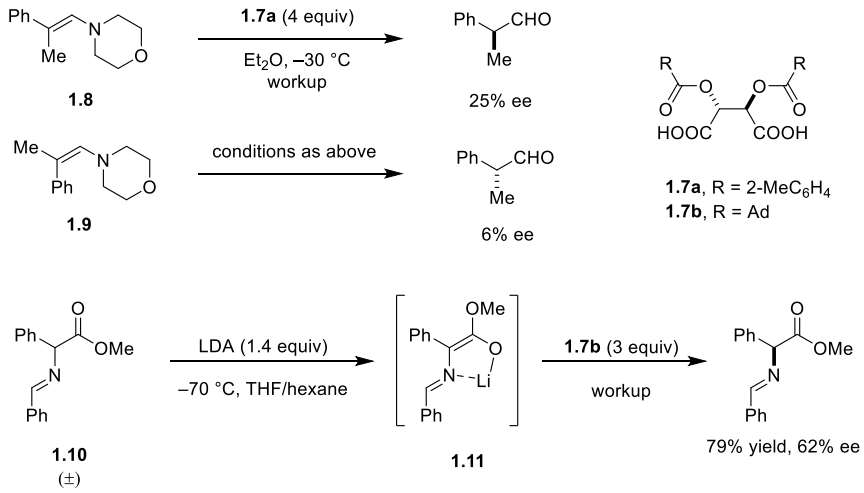
1.2.1 Tartaric Acid and Derivatives

Tartaric acid is one of the most abundant naturally occurring chiral acids. Since both enantiomers of tartaric acid are inexpensive and readily available, tartaric acid and its derivatives have been widely applied as resolving agents[48], auxiliaries and metal ligands[49]. However, even though tartaric acid is one of the strongest chiral acids (pK_{a1} = 2.90) present in the chiral pool, the examples of tartaric acid and its derivatives used directly as chiral Brønsted acid catalysts are quite limited.

1.2.1.1 Historical Use of Tartaric Acid and Derivatives as Chiral Proton Sources

Tartaric acid derivatives were first used as chiral proton sources in the enantioselective protonation of preformed enamines in the late 1970s by Duhamel and Plaquevent[50]. It was found that not only the acyl groups of the *O*,*O*-diacyltartaric acids but also the enamine geometry had critical roles in the absolute configuration and enantioselectivity of the protonation products (Scheme 1.7). When *E*-enamine **1.8** was exposed to four equivalents of **1.7a**, the (*S*)-2-phenylpropanal was obtained in 25% ee. However, under otherwise identical conditions, the *Z*-enamine **1.9** gave (*R*)-2-phenylpropanal in 6% ee. The results had excluded the possibility of an equilibrium between two resulting diastereomeric iminium ions (thermodynamic control), and the enantioselectivity difference was confirmed to be under kinetic control. Soon after, the same group applied the *O*,*O*-diacyltartaric acid **1.7b** to the deracemization of α-substituted carbonyl compounds by the enantioselective protonation of in-situ

generated lithium enolates[51]. The racemic Schiff base methyl ester **1.10** was converted to the corresponding lithium enolate **1.11** by deprotonation with lithium diisopropylamide (LDA), which was followed by the enantioselective protonation with three equivalents of **1.7b** to give optically active Schiff base ester in 79% yield and 62% ee. The intramolecular coordination between the Li and imine could lock the lithium enolate to *E*-configuration and benefit the enantioselectivity. Further hydrolysis of the Schiff base ester product would provide the corresponding α-amino acid. Even though superstoichiometric amounts of *O*,*O*-diacyltartaric acids were required in the process, the acids could be easily recycled after acidification without losing any enantiomeric purity.



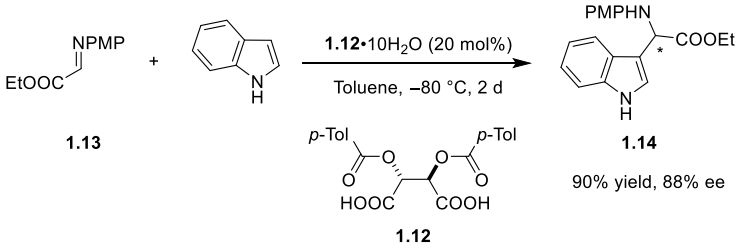
Scheme 1.7. Enantioselective protonation with diacyltartaric acids.

To better understand the relationship between the structures of *O*,*O*-diacyltartaric acids and the enantioselectivity of the protonation products, a thorough study of the effect of the acyl groups has been carried out. Unsurprisingly, the size and the distance of the bulky substituents from the carboxyl groups significantly affect the enantioselectivities[52]. It was proposed that the two bulky R substituents of *O*,*O*-diacyltartaric acids could force the two carboxyl groups to be *syn* to each other, one is serving as a proton donor and the other one as a hydrogen bond acceptor. The *syn* conformation appeared to be one main reason for ensuring high enantioselectivities, since locking the two carboxyl groups of tartaric acid *anti* to each issued in a dramatic loss in enantioselectivities. Even though the early work of enantioselective protonation is limited to the usage of superstoichiometric amount of chiral

reagents[53-57], the systematic study and consideration of the structure-enantioselectivity relationship is very enlightening for the understanding and future design of chiral Brønsted acid catalysts.

1.2.1.2 Tartaric Acid and Derivatives as Chiral Brønsted Acid Catalysts

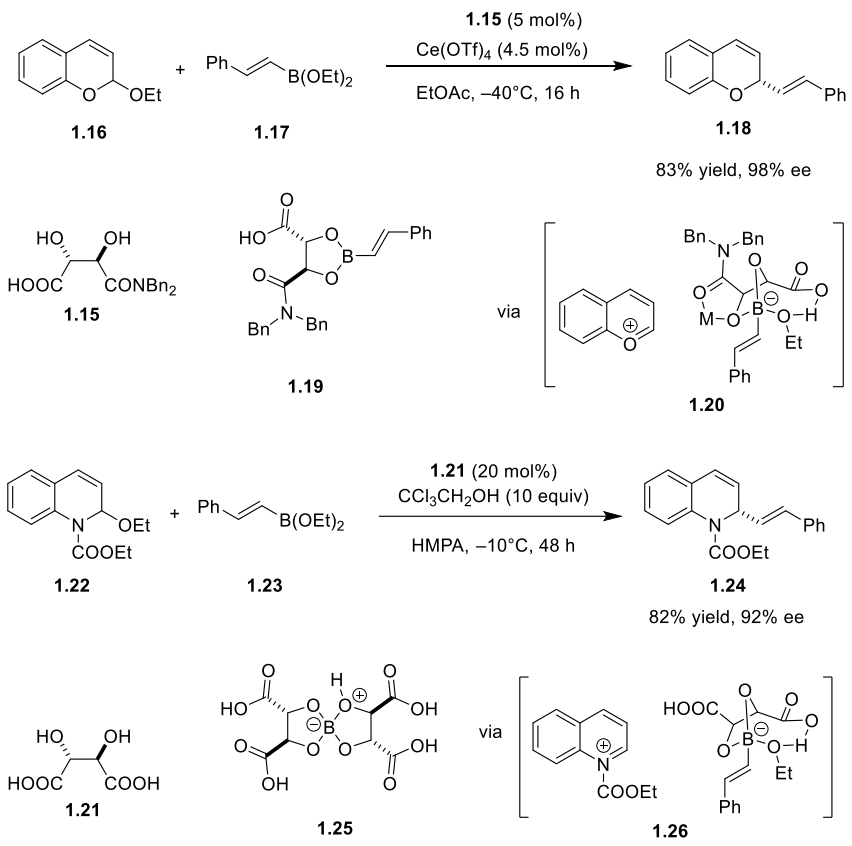
Although tartaric acid and its derivatives have been known as chiral proton sources for around 40 years in the asymmetric synthesis, their utilization as Brønsted acid catalysts began only six years ago. In 2010, Terada *et al*.[58] reported the first example of tartaric acid derivatives employed as chiral acid catalysts in an enantioselective aza-Friedel–Crafts reaction of indole with α-imino ester **1.13** (Scheme 1.8). It is interesting that the inclusion of water in the tartaric acid catalyst is essential for achieving good enantioselectivities. In comparison, rigorous exclusion of water in the presence of 4Å molecular sieves resulted in a racemic product. Furthermore, the amount of water complexed to **1.12** significantly influenced the enantioselectivity: Raising the water amount from 0.3 equivalent to 1 equivalent dramatically improved the ee, and further increasing the water content to 10 equivalents led to a relatively smaller boost. In a control experiment, the analogous aza-Friedel–Crafts reaction of *N*-methylindole afforded a racemic product, which implied that the indole N–H was crucial in the enantio-determining step, possibly as a hydrogen-bond donor to deliver secondary interactions. Even though the limited substrate scope and moderate ee were presented in this work, it proved that simple tartaric acid derivatives had the promise to be chiral Brønsted acid catalysts.



Scheme 1.8. Diacyltartaric acids enantioselective aza-Friedel–Crafts reaction.

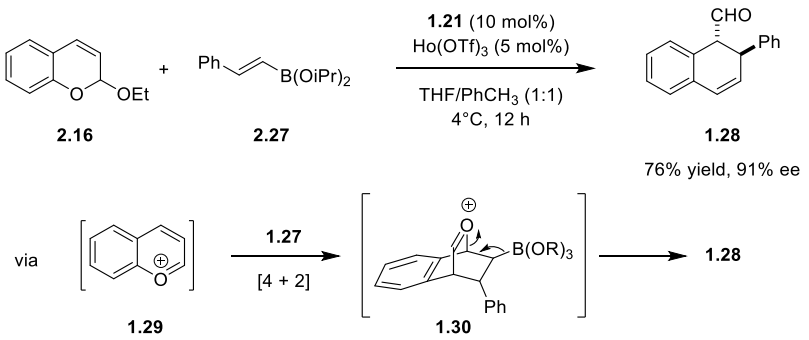
Shortly after Terada's work, Schaus and co-workers reported the mono-carboxylic acid **1.15** catalyzed enantioselective addition of vinyl or electron-rich aryl boronates to chromene acetals which gave rise to chiral chromene products[59] (Scheme 1.9). A dual catalytic system consisting of a chiral carboxylic

acid and an achiral Lewis acid was found optimal. Only moderate yield and ee were obtained without adding any Lewis acid, and the Lewis acid catalyst alone caused substantial decomposition of the chromene without any product formation. These observations suggested that the primary mode of the enantioselective catalysis was Brønsted acid catalysis which promoted the formation of the pyrylium ions **1.20**. The mechanistic studies showed that mixing the boronate and diol quickly brought about the dioxaborolane **1.19** as the isolable reactive intermediate, which could react with chromene acetals under otherwise identical conditions to give the same results as the standard procedure. Supported by the mass spectrometry and in situ FT-IR studies, the Lewis acid $Ce(OTf)_4$ was proposed to bind to the amide carbonyl group of the dioxaborolane to enhances the acidity of the boronate, and thus facilitate the formation of the chiral ion pair. Then the styryl group was delivered to the pyrylium **1.20** enantioselectively. Subsequently, the same group applied the similar catalytic system in a parallel enantioselective boronate addition to *N*-acyl quinolinium[60]. The unmodified tartaric acid **1.21** was identified to be ideal in this transformation. In contrast to the beneficial role of Lewis acidic additives in the previous work, the enantioselectivity was increased without adding any Lewis acid cocatalyst. Instead, protic additives such as CCl_3CH_2OH were employed to facilitate the catalyst turnover and then improved the yield. The authors suggested a similar catalytic cycle wherein the *N*-acyl quinolinium ion **1.26** was the key intermediate, and the catalytically viable dimeric tartaric acid adduct **1.15** was proposed to be the resting state of the catalyst.



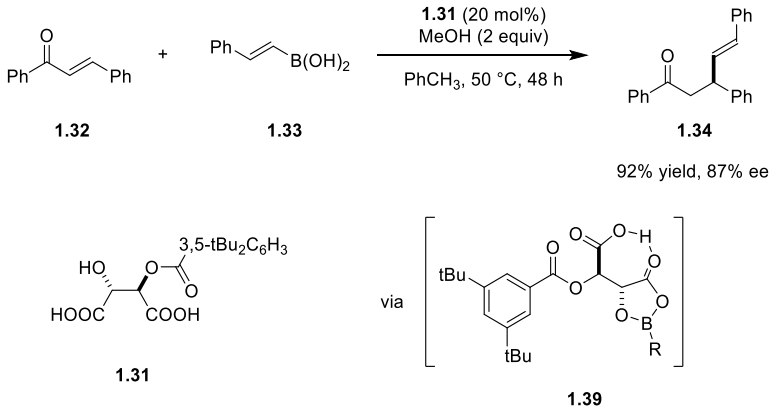
Scheme 1.9 Asymmetric addition of boronates to chromene acetal and quinoline-derived *N*,*O*-acetal.

Schaus' group then reported the tartaric acid catalyzed enantioselective [4 + 2] cycloaddition of isochromene acetals with vinylboronates which yielded dihydronaphthalene and dihydrobenzofluorene products[61] (Scheme 1.10). Similarly, the oxocarbenium **1.29** was generated under the acidic conditions and reacted with the boronate **1.27** to give the [4 + 2] cycloaddition intermediate **1.30**; further rearrangement would result in the final product **1.28**. Like their previous findings with the 1,2-addition of boronates to chromene acetals, the tartaric acid–Lewis acid combination proved to be pivotal, and there was no reaction without any rare-earth lanthanide triflates. Interestingly, even though the substrates and the catalytic system were similar to the previous work, the 1,2-addition product was never observed in this case.



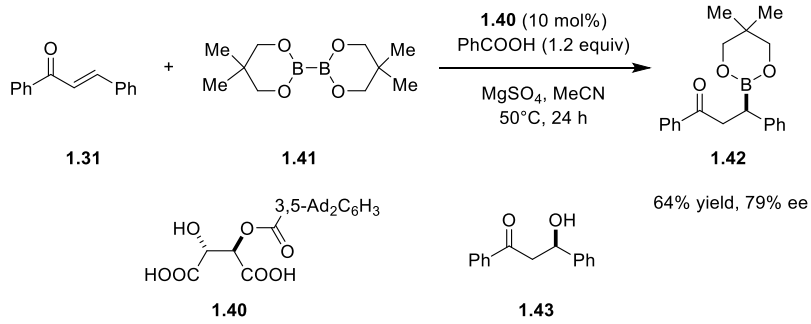
Scheme 1.10. Enantioselective [4 + 2] cycloaddition of isochromene acetals and vinylboronates.

Similarly, Sugiura *et al.* have reported the *O*-monoacyltartaric acids catalyzed enantioselective conjugate addition of boronic acids to enones[62] (Scheme 1.11). The electronic and steric effects of the mono *O*-protecting groups played a significant role in both the reactivity and enantioselectivity. The strong electron-donating methoxy group on the benzyl phenyl ring deactivated the catalyst and bulkier alkyl substituents on the 3,5-positions improved both the yield and enantioselectivity. Moreover, the protection of either of the two carboxyl groups dramatically reduced the reactivity, whereas the addition of methanol suppressed the background reaction and improved the catalytic efficiency. Concerning the reaction mechanism[63], the authors suggested that the catalyst **1.31** and boronic acid **1.33** firstly form the intermediate **1.39**. The Lewis acidity of the boron was increased due to the electron-withdrawing acyloxy group in **1.39**, which then activated the enone **1.33** via coordination to its carbonyl oxygen. The remaining free carboxyl group served as a hydrogen bond donor to stabilize the transition state by forming a strong intramolecular hydrogen bond with the acyloxy carbonyl group. This system is comparable to Yamamoto's chiral acyloxyborane (CAB) catalyst[64-69] and can be categorised into his definition of "Brønsted acid assisted Lewis acid catalysts" (BLA)[36]. Subsequently, they extended the same catalytic system to the conjugate addition to dienone.[70]



Scheme 1.11. Enantioselective conjugate addition of boronic acids to enones.

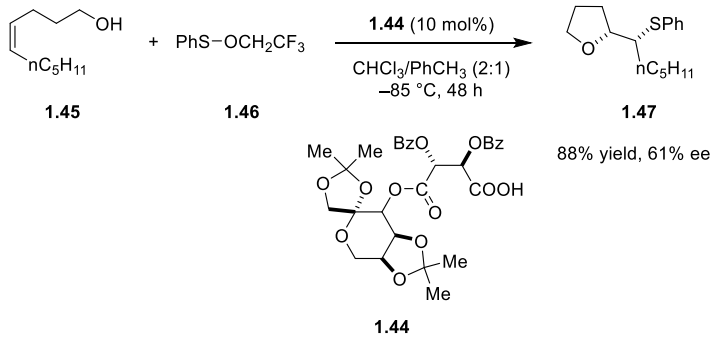
Sugiura group has also applied an even bulkier *O*-monoacyltartaric acid **1.40** to the enantioselective conjugate addition of the diboron to enones[73] (Scheme 1.12). The methanol - proven to be an effective additive previously - completely shut down the reaction here. However, the addition of benzoic acid improved the yield by facilitating the ligand exchange process. The adduct **1.42** can be facilely transformed into β-hydroxyl ketone **1.43** by treating with sodium perborate without losing any enantiomeric purity. Unlike their previous studies, no significant ligands change between the boron species **1.41** and the catalyst **1.40** was observed in this system, so the precise mechanism remained unclear at this point.



Scheme 1.12. Enantioselective conjugate addition of diboron to enones

Shi's group[74] have reported enantioselective oxysulfenylation of olefins to give enantioenriched tetrahydrofurans catalyzed by a dibenzoyl-tartaric acid monoester. The tartaric acid derivative **1.44** outcompeted several frequently used chiral phosphoric acids and

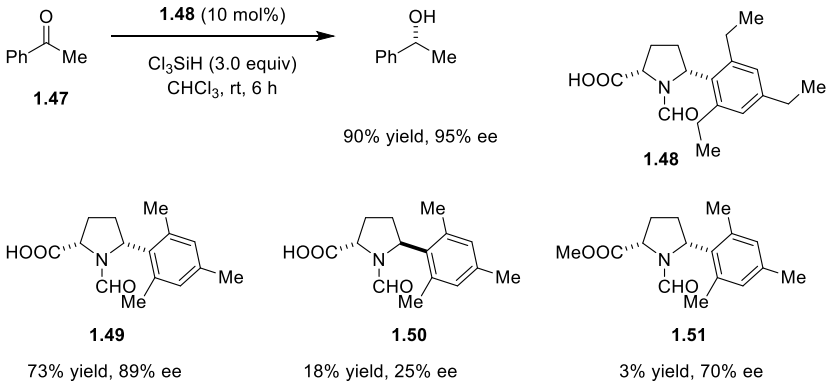
N-triflyl phosphoramide in this transformation (Scheme 1.13). In the searching for the optimal electrophilic sulfur reagent, trifluoroethyl benzenesulfenate **1.46** showed much higher reactivity than the typical *N*-(phenylthio)succinimide. Additionally, *cis*-alkenols were required under these conditions and complex mixtures were obtained for *trans*-alkenols. As for the mechanism, the chiral carboxylate was presumably serving as the counteranion to enantioselectively control the nucleophilic opening of the episulfonium ion intermediate.



Scheme 1.13. Enantioselective oxysulfenylation of olefins

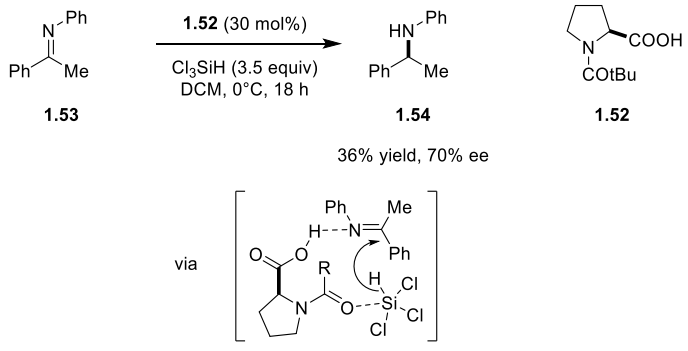
1.2.2 *N*-protected Amino Acids

In 2006, Matsumura group[75] reported the highly enantioselective reduction of arylalkyl ketones with trichlorosilane catalyzed by the bifunctional *N*-formyl-α'-aryl-*L*-proline **1.48** (Scheme 1.14). The Lewis basic formamide site was served to activate the trichlorosilane[76], and the free carboxylic acid was supposed to form a hydrogen bond with the ketone substrate. It was found that both the α-carboxylic acid moiety and a bulky α'-aryl group were essential to achieve high reactivity and enantioselectivity. Besides, these two substituents were required to be *cis* to each other and the *trans* diastereomer **1.50** gave dramatically reduced yield and ee. Furthermore, in the control experiment, the corresponding methyl ester **1.51** almost shut down the reaction completely, which illustrated the indispensable hydrogen bonding between the carboxyl group and the ketone.



Scheme 1.14. Enantioselective reduction of ketones by trichlorosilane.

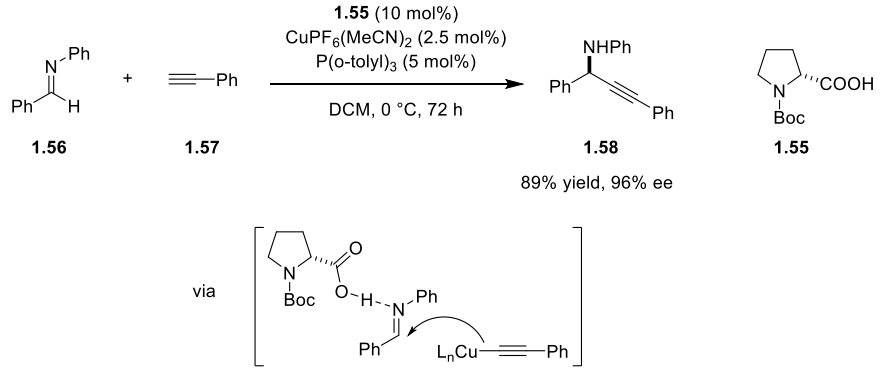
Similarly, Benaglia group[77] have reported the enantioselective reduction of ketimines by trichlorosilane catalyzed by the simple *N*-acyl *L*-proline **1.52** (Scheme 1.15). Even though low yields and moderate ee's were given in this case, the imine activation by the carboxyl group was found to be vital for the stereochemical efficiency. As a control experiment, the corresponding methyl ester gave rise to much lower yield and enantiopurity of the benzylic amine product. DFT studies indicated that the proton transfer and hydride transfer were concerted but asynchronous. It showed the hydride transfer was still in its early stage while the protonation is nearly complete, suggesting an asymmetric counteranion-directed catalytic pathway for the enantiocontrol.



Scheme 1.15. Enantioselective reduction of ketimines by trichlorosilane

In 2009, Arndtsen *et al*.[78] utilized the *N*-Boc proline **1.55** as a cocatalyst in combination with Cu(I) catalyst to realize the enantioselective synthesis of propargylamines via the coupling of alkynes and

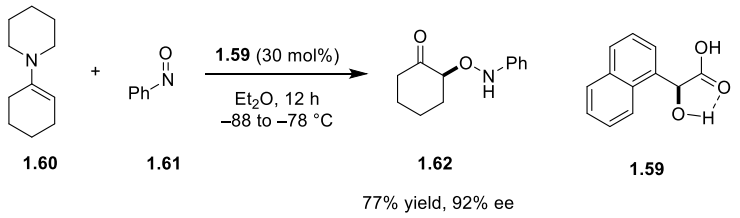
imines (Scheme 2.16). The hydrogen bonding between the carboxyl group and the imine was crucial and poor yield was obtained without any acid. One key advantage of this system is its easy tenability since the chiral sources are inexpensive amino acids, so there is no need to rely on relatively valuable chiral phosphine ligands. Furthermore, modulating the achiral phosphine ligands can also change the bulk of the copper catalyst and therefore influence the enantioselectivity. The convenient modularity allows challenging substrates such as aliphatic imines, aliphatic alkynes or *N*-alkyl imines to be tolerated by simply tuning the achiral phosphine ligands.



Scheme 1.16. Cu(I)/amino acid catalysed enantioselective imine alkynation

1.2.3 α-Hydroxy Carboxylic Acids

In 2005, Yamamoto[79] reported the regio- and enantioselective nitroso aldol reactions between achiral enamines and nitrosobenzene (Scheme 1.17). This work represents the first example of carboxylic acids as chiral Brønsted acid catalysts. When the chiral carboxylic acid **1.59** was employed as the catalyst, the highly enantioenriched *O*-nitroso aldol product **1.62** was given exclusively in ether. But when the reaction was catalyzed by TADDOL in toluene, the predominant products are the *N*-nitroso aldol adducts. The authors noted that the possible intramolecular hydrogen bond between the hydroxyl group and carboxylic oxygen might contribute to the more rigid structure and increased the acidity of the catalyst, which could be classified in their proposed "Brønsted acid assisted Brønsted acid" (BBA) system[36].



Scheme 1.17. Regio- and enantioselective nitroso-aldol reactions

1.2.4 Axially Chiral Dicarboxylic Acids

Hashimoto, Maruoka and co-workers have been developing a series of axially chiral dicarboxylic acids possessing a binaphthyl backbone[80] (Figure 1.2). Similar to chiral phosphoric acids, the 3,3'-substituents are essential for the reactivity and selectivity, thus frequently modified with sterically hindered aromatic substituents with varied electronic properties. However, Maruoka' catalysts have their unique features, for example, the intramolecular hydrogen bonding between two carboxyl groups are responsible for the increased acidity and more rigid catalyst structure. And the dihedral angle is larger than that of the BINOL-derived chiral phosphoric acids, which provides a different chiral pocket. Maruoka's dicarboxylic acids have become the most widely used chiral carboxylic acid catalysts and have been effectively exploited in a wide range of enantioselective transformations.

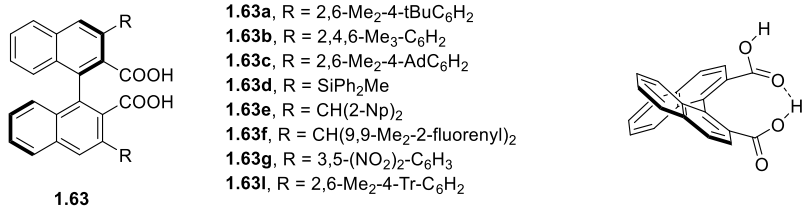
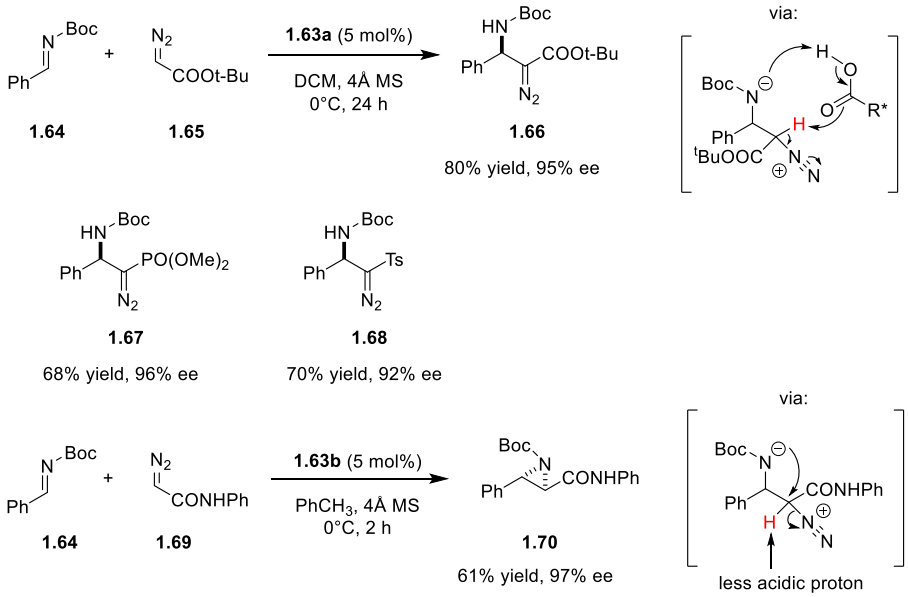


Figure 1.2. Maruoka's axially chiral dicarboxylic acids

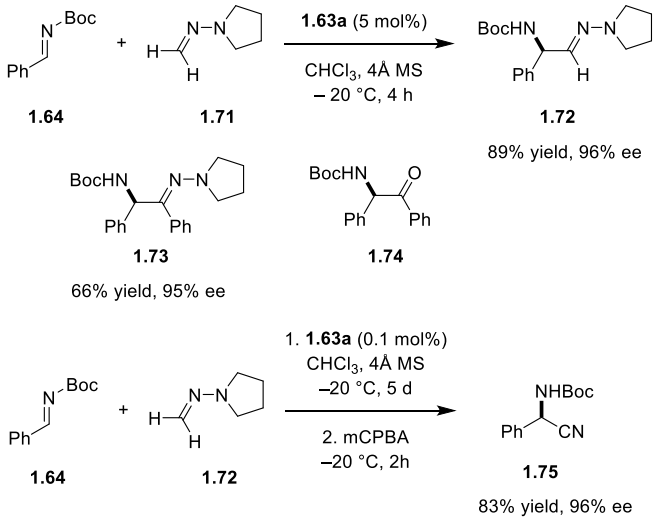
The first example of axially chiral dicarboxylic acids catalyzed enantioselective reactions was demonstrated in the asymmetric Mannich reaction of aromatic *N*-Boc imines with α-diazo acetate[81] (Scheme 1.18). Complementary to a previous example of chiral phosphoric acids catalyzed diazo Mannich reactions reported by Terada group[82], which required the utilization of *p*-dimethylaminobenzoyl aldimines to achieve high selectivity, the weaker dicarboxylic acid **1.63a**

allowed the use of more conventional *N*-Boc imine **1.64**. Furthermore, the identical reaction conditions could be extended to the addition of diazomethylphosphonate and (diazomethyl)sulfone[83] that gave enantiomerically enriched β-aminophosphonate **1.67** and β-amino sulfone **1.68** respectively. It was suggested by the authors that the deprotonation of α-proton from the potential intermediate by the catalyst's basic oxygen might facilitate the direct alkylation. Nevertheless, when the diazoacetamides were employed where the α-proton of the diazo carbonyl group is less acidic, the reactivity was switched to favor the asymmetric aziridination[84]. Prior to this work, chiral Lewis acid[85-87] and achiral Brønsted acid[88] catalyzed analogous aza-Darzens reactions were well documented to selectively give *cis* aziridine products. However, the axially chiral dicarboxylic acid **1.63b** catalyzed version is highly *trans*-selective. Theexplanation from the authors is that the unique selectivity results from the *anti*-position of the carboxamide and aryl group to avoid steric repulsion. Moreover, the favored intramolecular hydrogen bonding between the carbonyl group of Boc and amide N–H might also contribute to the *trans* selectivity. After this work, different *trans*[89,90] or *cis*[91] selective asymmetric aza-Darzens reaction catalyzed by chiral phosphoric acids or *N*-triflyl phosphoramides have also been realized.



Scheme 1.18. Enantioselective Mannich reaction and aza-Darzens reaction of *N*-Boc imine with α-diazo compounds

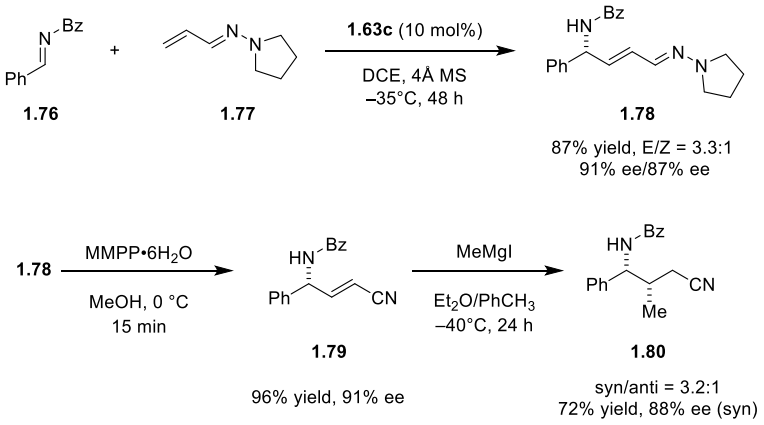
Subsequently, the same group employed **1.63a** in the imino aza−eneamine reactions of *N*-Boc imines with *N*,*N*-dialkyl hydrazones serving as acyl anion equivalents[92] (Scheme 1.19). The precedent reactions catalyzed by BINOL derivatives[93] or phosphoric acids[94] were limited to the use of formaldehyde derived *N*,*N*-dialkylhydrazone and suffered from moderate enantioselectivities. In contrast, the carboxylic acid catalyst **1.63a** was not only suitable for the addition of unsubstituted *N*,*N*-dialkylhydrazone **1.71** but also tolerated the less nucleophilic aromatic aldehyde *N*,*N*-dialkylhydrazones. Additionally, the resulting α-amino hydrazone product **1.73** could be readily transformed into α-amino ketone **1.74** without loss of any ee. In the follow-up work, the authors developed a one-pot synthesis of α-amino nitriles by simply treating the reaction solution with *m*-chloroperbenzoic acid (mCPBA) after the completion of the imino aza-enamine reaction[95]. The catalyst loading can be as low as 0.1 mol % and retain the high yield and ee, albeit with prolonged reaction time. This one-pot imino aza-enamine reaction/oxidation sequence is able to provide a practical alternative to the Strecker reaction,accessing enantiopure amino acids without handling hazardous cyanide sources.



Scheme 1.19. Enantioselective imino aza−eneamine reaction

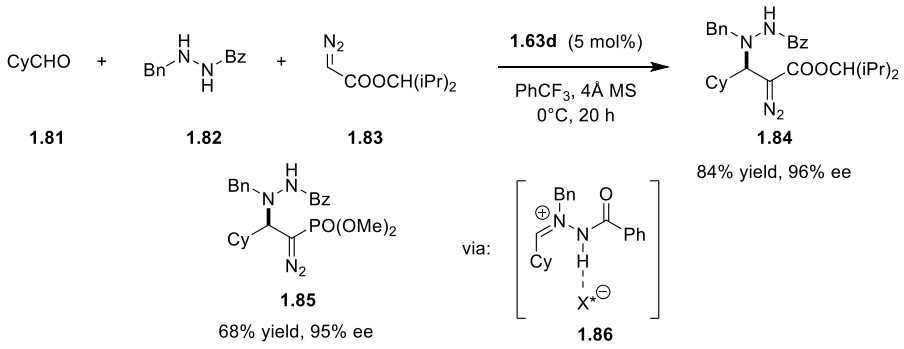
Later on, Maruoka *et al.* extended the similar catalytic system to the formal alkenylation of imines[96] using vinylogous azaenamines as the umpolung species, which allowed for the quick

access to chiral allylic amines (Scheme 1.20). The previously optimal reaction conditions only provided the desired alkenynation product in less than 20% yield as a mixture of *E*/*Z* isomers. However, replacing the *N*-Boc imine with *N*-benzoyl imine **1.76** significantly improved the reactivity and enantioselectivity. Besides, the reaction was perfectly regioselective and no C1 addition of the vinylogous azaenamine **1.77** was observed. With regard to the synthetic application, the azaenamine adduct **1.78** can be readily transformed into the α,β-unsaturated γ-amino nitrile **1.79** by treating with magnesium monoperoxyphthalate (MMPP) in nearly quantitative yield without deterioration of any ee. Additionally, the resulting material can be further functionalized via the conjugate addition of Grignard reagent to introduce one more stereogenic center with moderate diastereoselectivity.



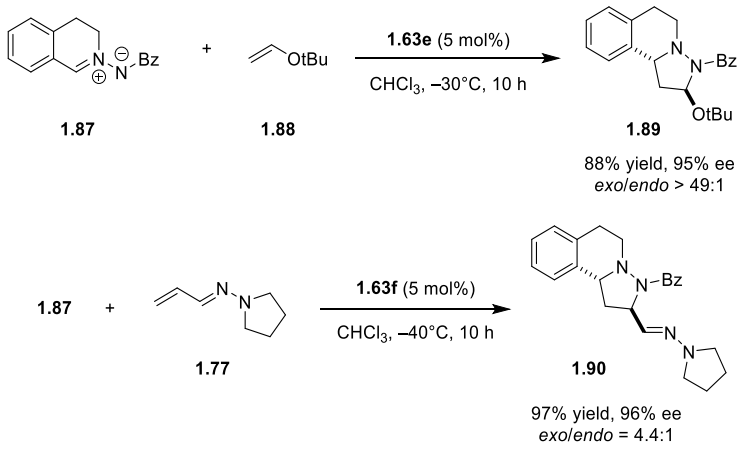
Scheme 1.20. Enantioselective vinylogous aza-enamine reaction

Azomethine imines were also viable electrophiles in Maruoka's carboxylic acid system. In the presence of **1.63d**, transient **1.86** can be produced in situ by condensation of the aldehyde **1.81** with *N*'-benzylbenzoylhydrazide **1.82**[97] (Scheme 1.21). Then this new type of prochiral electrophile could be trapped via 1,2-addition of alkyl diazoacetates or (diazomethyl)phosphonates, providing a broad range of chiral α-diazo-β-hydrazino esters and phosphonates as the analogues of β-amino acids.



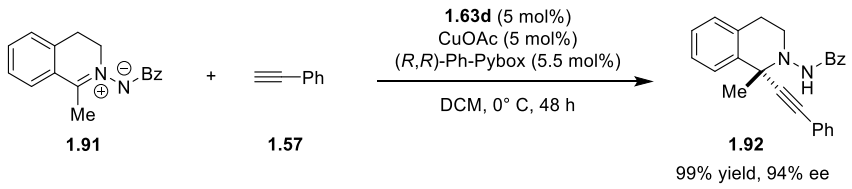
Scheme 1.21. Enantioselective addition alkyl diazoacetate to in situ generated azomethine imines.

Following their previous work of titanium/binolate catalyzed normal-electron-demand (NED) [3 + 2] cycloaddition of *C,N*-cyclic azomethine imines with electron-deficient alkenes[98], Maruoka *et al.* found that the carboxylic acid catalyst **1.63e** could be employed to activate the LUMO of 1,3-dipoles, facilitating the inverse-electron-demand (IED) 1,3-dipolar cycloaddition of the same azomethine imine **1.87** with electron-rich olefins[99] (Scheme 1.22). The *exo* addition product **1.89** was obtained exclusively in excellent yield and ee. Also, the enal-derived vinylogous aza-enamine **1.77** couldserved as the electron-rich dipolarophile, providing a different regioisomer **1.90** from the one obtained by the titanium/binolate-catalyzed NED [3+2] cycloaddition.



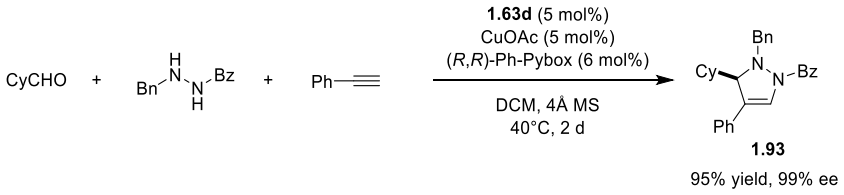
Scheme 1.22. Asymmetric inverse-electron-demand [3 + 2] cycloaddition

In contrast to the asymmetric [3 + 2] cycloaddition of *N,N*'-cyclic azomethine imines with alkynes reported by Fu[100], the *C,N*-cyclic azomethine imine **1.87** showed the unique reactivity favoring alkynylation to give a variety of C1-substituted chiral tetrahydroisoquinolines[101] (Scheme 1.23). The Cu(I)/Pybox system was found to be suitable for the alkynylation of C1-unsubstitued azomethine imines, but only moderate ee was obtained for C1-substituted azomethine imine substrates which provided a chiral tetrasubstituted carbon center. The authors then found the ee could be improved by adding the dicarboxylic acid **1.63d** as a co-catalyst to activate the azomethine imine **1.91** towards the addition of chiral Cu-acetylide. This is the first example of highly enantioselective catalytic alkynylation of the C=N double bond to furnish a chiral tetrasubstituted carbon center.



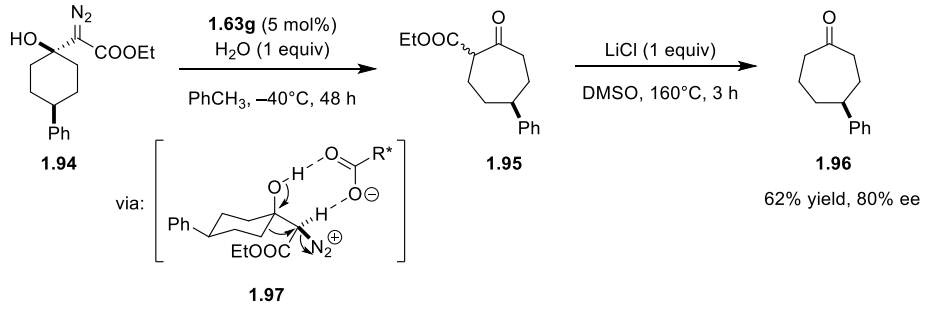
Scheme 1.23. Asymmetric alkynylation of C1-substituted *C,N*-cyclic azomethine imines.

Shortly afterwards, the CuOAc/Pybox/axially chiral dicarboxylic acid system was been fruitfully applied to the enantioselective 1,3-dipolar cycloaddition of aldehydes, hydrazides and alkynes[102] (Scheme 1.24). In this case, the addition of chiral dicarboxylic acid co-catalyst **1.63d** not only improved the enantioselectivity but also suppressed the formation of undesired alkynylation compared with the Cu(I)/Pybox alone. Under the optimized conditions, the in situ generated acyclic azomethine imines went through [3 + 2] cycloaddition almost exclusively with copper acetylides to give a variety of 3,4-disubstituted pyrazolines. The reaction has a wide substrate scope, both aromatic and aliphatic aldehydes are well tolerated.



Scheme 1.24. Enantioselective three-component 1,3-Dipolar cycloaddition

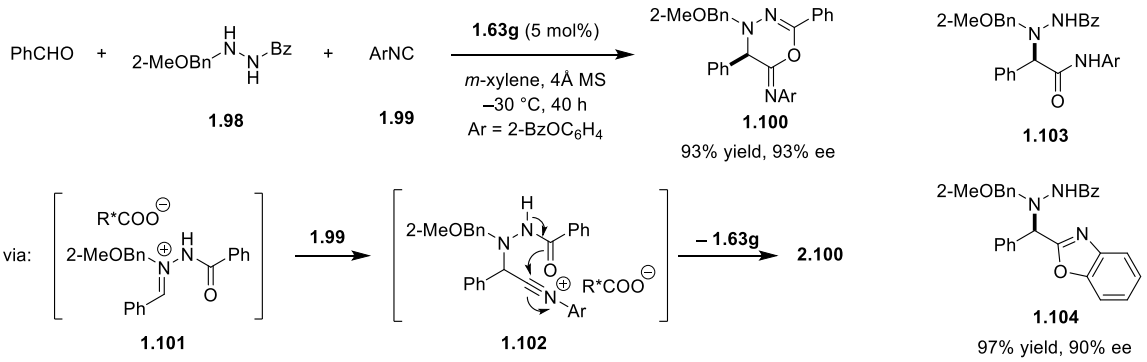
Maruoka *et al.* have developed the chiral aluminum Lewis acid catalyzed desymmetrization of 4-substituted cyclohexanone via enantioselective ring expansion with diazoacetates to give chiral cycloheptanones[103] (Scheme 1.25). They proved that the same intermediate **1.97** could be accessed by the protonation of β-diazo alcohols, and an asymmetric semipinacol rearrangement was achieved when a chiral Brønsted acid catalyst was deployed[104]. The original rearrangement product **1.95** was transformed into the cycloheptanone **1.96** via Krapcho decarboxylation for the ease of purification and determination of enantioselectivity, since the α-stereogenic centre of **1.95** was prone to epimerization. Even though only moderate yields and ee's were obtained, this method provided an organocatalytic alternative for access to chiral γ-substituted cycloheptanones.



Scheme 1.25. Desymmetrization of 4-substiteted cyclohexanone via asymmetric semipinacol rearrangement

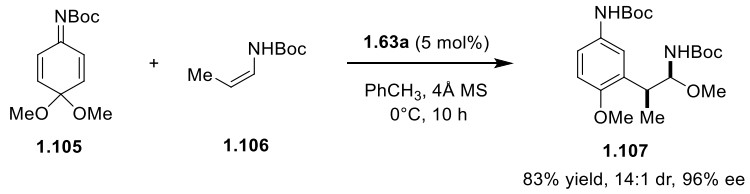
The catalytic asymmetric Ugi reaction has been a longstanding challenge for Brønsted acid catalysis, especially for chiral carboxylic acids. The major challenge is that the conjugate base of the acid catalyst can attack the highly electrophilic nitrilium intermediate and get incorporated into the product, which leads to the abortion of the catalysis. One solution to this problem is to install an additional nucleophilic site on the substrates which can be trapped intramolecularly by the nitrilium

and thus avoid the catalyst deactivation[105,106]. Maruoka et al.[107] have effectively realized this strategy with their dicarboxylic acid catalyst **1.63g** (Scheme 1.26). After the addition of isocyanide **1.99** to the in situ generated azomethine imine **1.101**, the benzoyl oxygen attacked the nitrilium intermediate and gave chiral heterocyclic product **1.100** (Scheme 1.26). **1.100** could be readily hydrolysed and afforded α-hydrazine amide **1.97** under acidic conditions without deterioration of the enantioselectivity. The authors have also developed a one-pot procedure where the Ugi reaction was followed by the cleavage of the benzoyl moiety under moderately basic conditions. The unique benzoxazole product **1.104** could be generated in this sequence in excellent yield and ee.



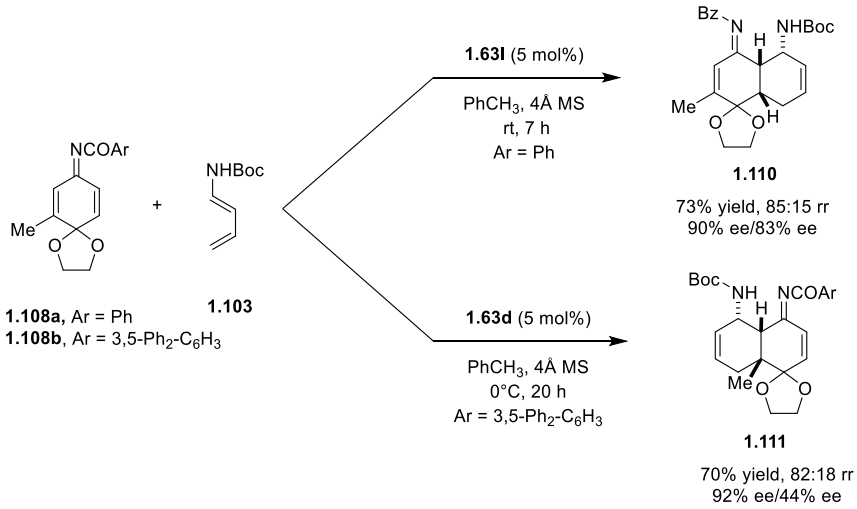
Scheme 1.26. Enantioselective Ugi-type reaction with azomethine imines.

Maruoka group then successfully utilized quinone imine ketals as electrophiles for the first time in the asymmetric Brønsted acid catalysis[108] (Scheme 1.27). After the conjugate addition of enecarbamate **1.106** to the dicarboxylic acid-activated quinone imine ketal **1.105**, one alkoxy group of the ketal would be eliminated and led to rearomatization. The freed alkoxy group then added to the resulting iminium ion from the enecarbamate intramolecularly and gave α-amino-β-aryl ether product. The quinone imine ketals functioned as substituted aromatic ring surrogates during the process and the products could be readily transformed into chiral β-aryl amines and α-aryl ethers.



Scheme 1.27. Enantioselective arylation of enecarbamates

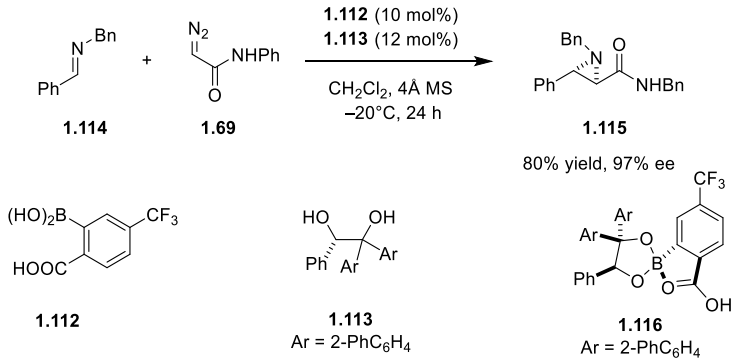
The quinone imine ketals could be also employed as dienophiles in asymmetric aza-Diels–Alder reactions to provide optically active functionalized *cis*-decalins[109] (Scheme 1.28). In the presence of dicarboxylic acid catalyst **1.63l**, *N*-benzoyl 3-methyl quinone imine ketal **1.108a** reacted with the diene carbamate **1.109** predominantly on the less hindered C=C bond and gave the *endo* addition product **1.110** exclusively. Alternatively, the cycloaddition preferentially occurred on the substituted alkene site when the bulkier catalyst **1.63d** and 3,5-diphenylbenzoyl quinone imine ketal **1.108b** were employed. The authors suggested the regioselectivity originated from the rapid interconversion of the *E/Z* isomers of the imine. With the bulkier catalyst and protecting group, the *Z* isomer was preferred in the transition site and the diene was directed to add to the more sterically crowded site.



Scheme 1.28. Enantioselective and regioselective aza-Diels–Alder reaction of quinone imine ketals

1.2.5 Boron-assisted Chiral Carboxylic Acids

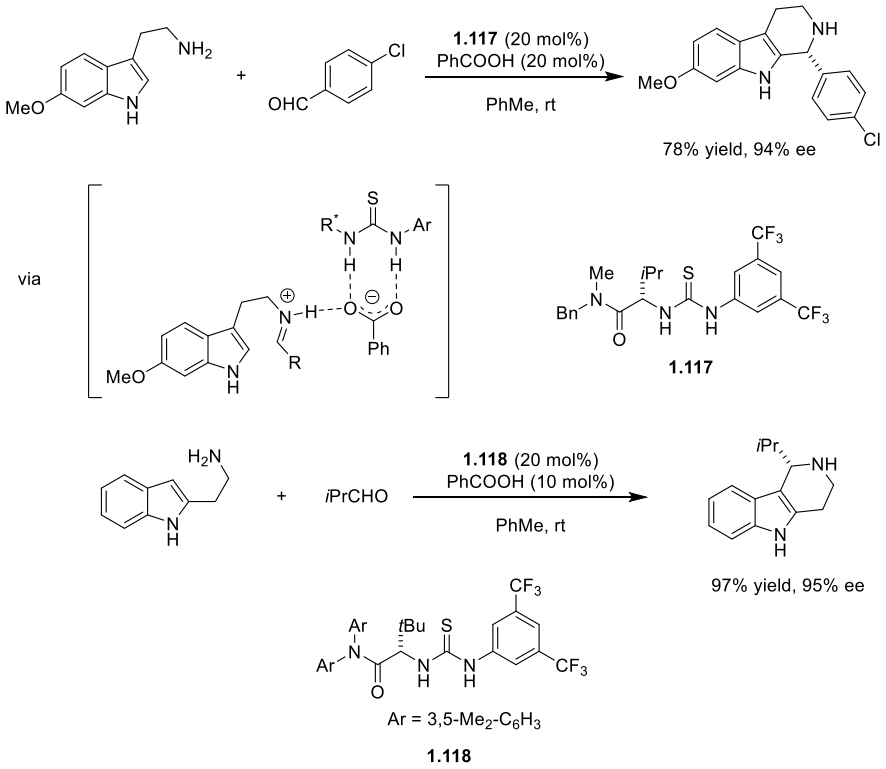
Yamamoto's concept of "Lewis acid assisted Brønsted acid Catalysts" (LBA),[36] that the acidity of Brønsted acid can be significantly increased after coordinating to a Lewis acid has been well accepted. Moreover, this combination could make the catalyst structures more organized and provide an effective chiral environment for asymmetric induction. Taking advantage of this principle, Mattson et al. designed the first achiral 2-borylbenzoic acid derivatives wherein the boronate can internally coordinate to the carboxylic acid[110]. They found the new catalyst showed superior activity over its unsubstituted or silicon-substituted benzoic acid analogues in the addition of indoles to nitroalkenes. Maruoka[111] *et al.* reported the first successful application of boron-assisted chiral carboxylic acid catalyst in the asymmetric *trans*-aziridinations of both *N*-Boc imines and less electrophilic *N*-Bn imines (Scheme 1.29). More importantly, the chiral 2-borylbenzoic acid derivative **1.116** was assembled in situ from two independent components, namely a chiral diol **1.113** that mainly controls the chiral environment and 2-boronobenzoic acid **1.112** playing a major role in the acidity. By simply combining two readily available components, diverse catalysts can be quickly accessed without resorting to tedious synthesis. Interestingly, there is an additional chiral boron center present which might also contribute to the excellent selectivity of the catalyst, given the fact that the C_2-symmetrical diols gave poor ee's.



Scheme 1.29. Chiral borylbenzoic acid catalysed asymmetric aza-Darzens reaction.

1.3 Dual Catalysis of Achiral Brønsted Acids and Chiral Anion-binding Catalysts

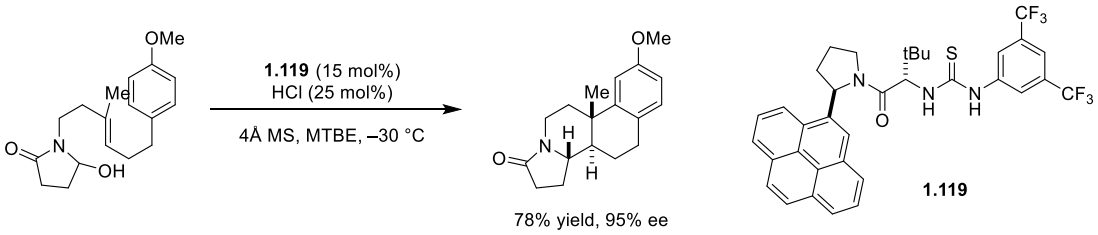
Jacobsen and co-workers have established the combination of achiral Brønsted acids and chiral (thio)urea catalysts in a variety of enantioselective transformations. In this system, the conjugate base of the Brønsted acids can be recognized by the (thio)urea catalyst so that the acidity and chiral environment can be well tuned by altering either component. The combination of weak benzoic acid and chiral thiourea catalyst successfully enabled the challenging protio-Pictet-Spengler[112] and iso-Pictet-Spengler reactions[113] (Scheme 1.30). Thethe thiourea was proposed to stabilize the key ion-pair intermediates and associate to the benzoate in the enantio-determining deprotonation step.



Scheme 1.30 Enantioselective Pictet–Spengler reaction catalyzed by chiral thiourea/benzoic acid

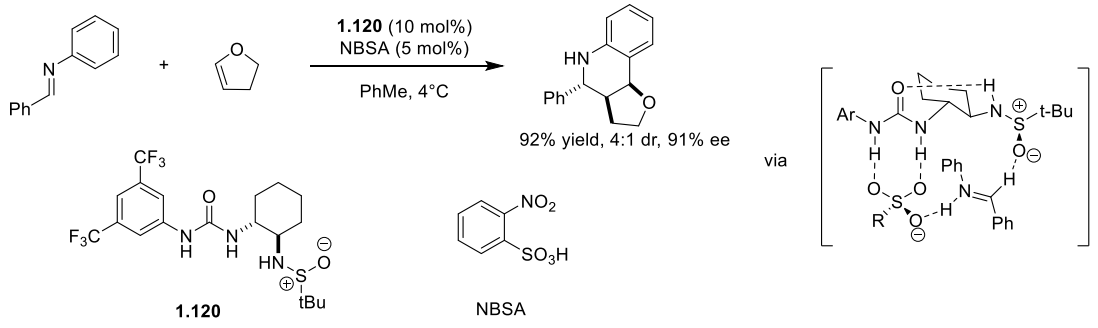
Jacobsen and co-workers recently reported the development of a new thiourea catalyst in combination with HCl for the asymmetric cationic polycyclizations[114]. Notably, the catalyst with the

more extended π-system gave better yield and ee, indicating that the secondary cation–π interaction is a principal element to stabilizing the transition state (Scheme 1.31).



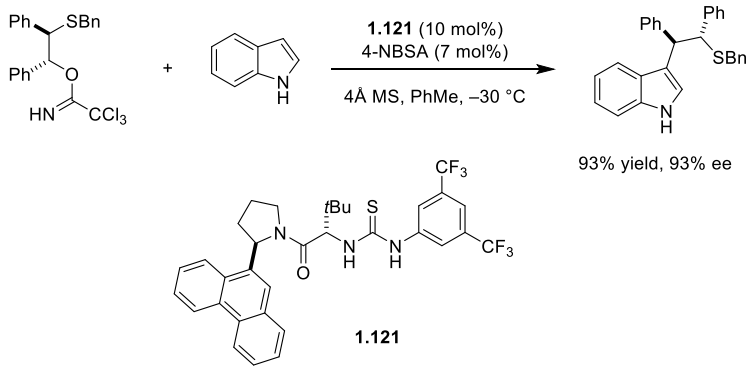
Scheme 1.31. Chiral thiourea and HCl catalyzed asymmetric polycyclizations

Jacobsen's group utilized the integration of an achiral sulfonic acid and chiral bifunctional sulfinamidourea to promote a highly enantioselective Pavarov reaction[115] (Scheme 1.32). Remarkably, the achiral acid catalyzed racemic pathway was much more rapid than the enantioselective pathway, but the high enantioselectivity was still maintained. Mechanistic studies revealed the high association equilibrium of **1.120** and the protonated imine intermediate, ensuring that the iminium ion had to go through the enantioselective pathway associated with the chiral urea.



Scheme 1.32 Chiral bifunctional sulfinamidourea catalyzed asymmetric Pavarov reaction

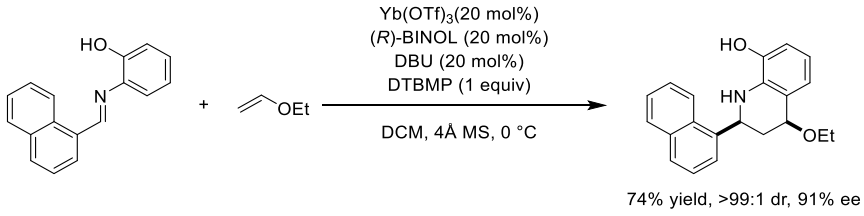
Very recently, the same group reported the arylpyrrolidino amido thioureas catalyzed enantioselective nucleophilic ring opening of episulfonium[116] (Scheme 1.33). The detailed mechanistic study showed the transition state stabilization resulted from a network of anion binding, hydrogen-bonding and cation-π interactions between the catalyst and substrates.



Scheme 1.33. Chiral thiourea catalyzed ring opening of episulfonium ions.

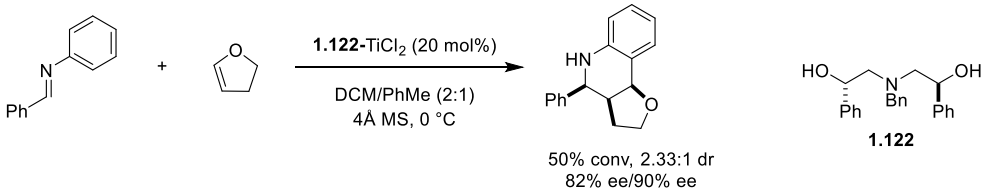
1.4 Asymmetric Povarov Reactions

Kobayashi *et al*. reported the first example of catalytic enantioselective Povarov[117-122] reaction[123], which also represented the first catalytic enantioselective aza-Diels-Alder reaction (Scheme 1.34). The chiral ytterbium Lewis acid catalyst was assembled in situ from $Yb(OTf)_3$, BINOL and DBU. DTBP (2,6-di-*t*-butyl-4-methylpyridine) was also identified as a crucial additive to interact with the phenolic hydrogen of the imine substrate.



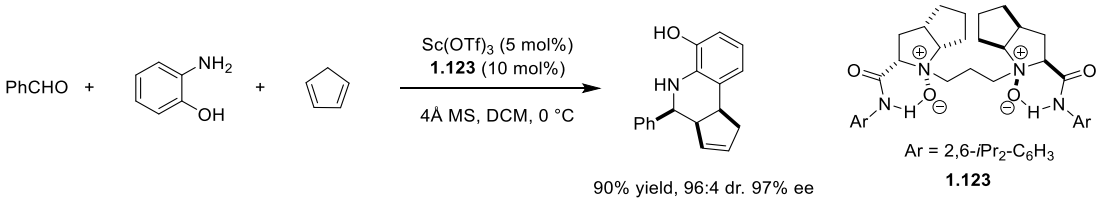
Scheme 1.34. Chiral ytterbium catalyzed asymmetric Povarov reaction.

Sundararajan group[124] reported an enantioselective Povarov reaction catalyzed by a chiral titanium complex ligated with the chiral amino diol ligand **1.122** (Scheme 1.35). The mixed solvent system and the addition of molecular sieves were crucial for achieving good enantioselectivity.



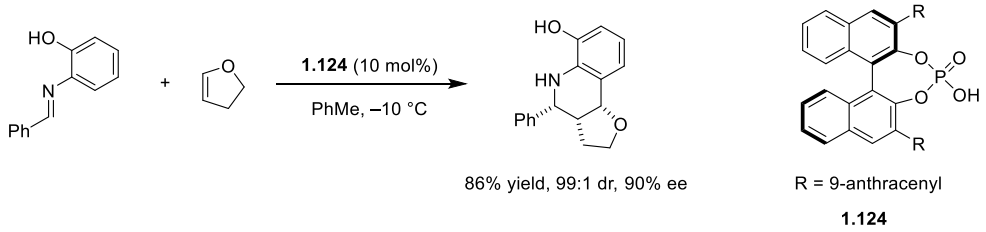
Scheme 1.35. Chiral titanium complex catalyzed asymmetric Povarov reaction.

Feng group[125] successfully applied their *N*,*N*'-dioxide-Sc(OTf)$_3$ complex to the three-component Povarov reaction with cyclopentadiene as the dienophile (Scheme 1.36). Under mild conditions, the one-pot highly enantioselective reaction gave tricyclic tetrahydroquinolines with three contiguous stereocenters. The hydroxy group on the aniline was crucial for the reaction to occur, given that the aniline or 2-methoxyaniline only afforded trace product. Later on, they also used the same catalytic system in the asymmetric Povarov reaction with α-alkyl styrenes[126].



Scheme 1.36. Chiral titanium complex catalyzed asymmetric Povarov reaction.

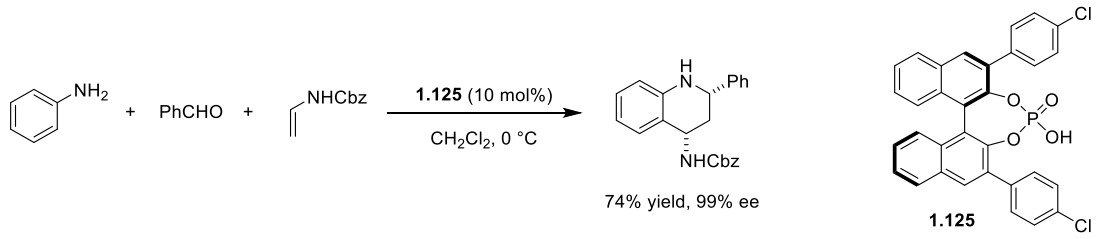
Akiyama and coworkers reported the first example of chiral phosphoric acid catalyzed inverse-electron-demand aza-Diels-Alder reaction[127] (Scheme 1.37). Various cyclic and acyclic vinyl ethers were employed as the dienophiles and gave rise to the cycloadducts in good yields and ee's. The hydroxyl group on the *N*-aryl substituent was indispensable for the high enantioselectivity, possibly due to the favorable hydrogen bonding between it and the phosphoryl oxygen.



Scheme 1.37. Chiral phosphoric acid catalyzed asymmetric Povarov reaction

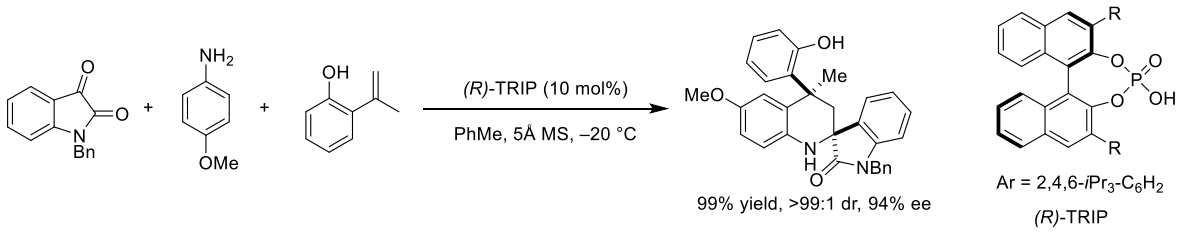
Masson and Zhu[128] reported the first example of enantioselective three-component Povarov reactions catalyzed by chiral phosphoric acids (Scheme 1.38). Comparedto Akiyama's work, an OH group on the aniline was not necessary to achieve good enantioselectivity, which provided a more general

substrate scope. The authors chose the enecarbamate as the dienophile, probably owing to its *N*–H group forming a hydrogen bond with the catalyst. They have also extended the same catalytic system to the Povarov reaction with β-substituted acyclic enecarbamates, yielding tetrahydroquinolines with three contiguous stereogenic centers in excellent diastereo- and enantioselectivities[129].



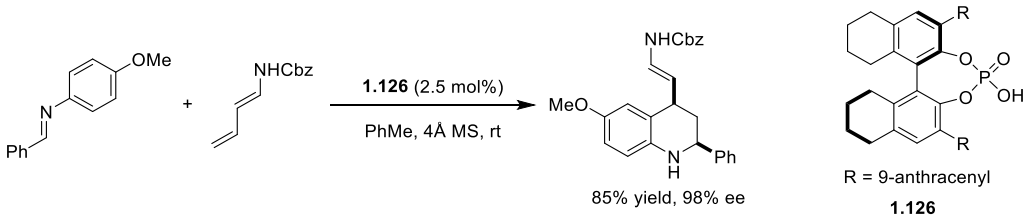
Scheme 1.38. Chiral phosphoric acid catalyzed three-component Povarov reaction

Shi and Tu reported the first Povarov reaction with ketones[130] (Scheme 1.39). The in situ produced isatin-derived 2-azadienes could cyclize with α-methyl *o*-hydroxystyrene, delivering spiro-cycle products with simultaneous construction of two quaternary stereocenters in high yields and stereoselectivities.



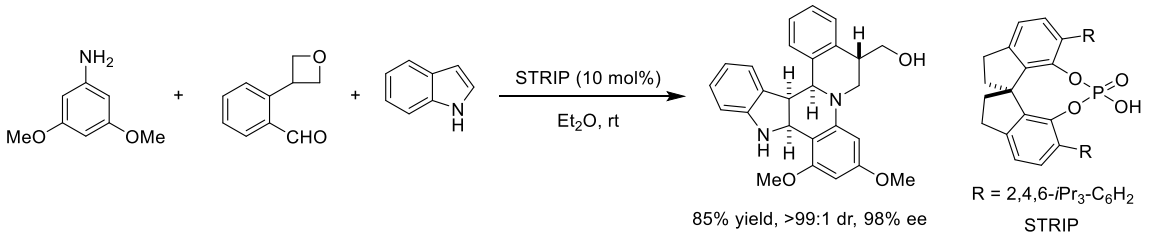
Scheme 1.39. Chiral phosphoric acid catalyzed three-component Povarov reaction with isatin.

Fochi and Caruana reported the first example of a catalytic asymmetric vinylogous Povarov reaction[131] (Scheme 1.40). Dienamines were served as the dienophiles and reacted at the terminal double bond, selectively catalyzed a chiral phosphoric acid catalyst, providing highly enantioenriched tetrahydroquinolines possessing an enecarbamate group at the 4-position.



Scheme 1.40. Chiral phosphoric acid catalyzed three-component Povarov reaction.

Indoles were firstly employed as dienophiles in the asymmetric Povarov reactions by Zhu and Sun[132] (Scheme 1.41). In the presence of a catalytic amount of SPINOL-derived phosphoric acid STRIP, the alkaloid-like polycyclic products were obtained in excellent yields and stereoselectivities. Notably, the oxetane moiety in the aldehyde as a directing group was indispensable for achieving good yields and enantioselectivities. In comparison, the simple benzaldehyde gave complex mixtures, and the desired product was only obtained in less than 20% yield.



Scheme 1.41. Chiral phosphoric acid catalyzed three-component Povarov reaction

1.5 Objectives

As introduced above, by taking advantage of the judicious design of the catalyst structure, the acidity can be largely improved by the stabilization of the corresponding counterion via all kinds of interactions. However, currently the key approach for this purpose is to install strongly electron-withdrawing groups that stabilize the conjugate base by inductive and resonance effects, which limits the catalyst structures to those with intrinsic acidity advantages such as phosphoric acids.

This dissertation aims to develop novel types of chiral Brønsted acids to solve the problems that have not been addressed by previously existing catalytic systems. Besides, we are also dedicated to the

development of innovative synthetic applications of the known chiral phosphoric acids. Chapter II will discuss the asymmetric Povarov reaction catalyzed by either our newly designed conjugate-base-stabilized Brønsted acids or chiral phosphoric acids, including three projects: inter-, intramolecular Povarov reactions of secondary amines and kinetic resolution of indolines. Chapter III will discuss the synthesis of polycyclic amines via an oxidative Povarov approach. The biomimetic enantioselective synthesis of isoindolinones catalyzed by chiral phosphoric acids will be covered in Chapter IV. The last chapter will discuss a dual-catalysis approach to the kinetic resolution of 1,2-diaryl-1,2-diaminoethanes.

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Chapter II Conjugate-Base-Stabilized Brønsted Acids as Asymmetric Catalysts

2.1 Aim and Significance

Intriguing applications of asymmetric cooperative Brønsted acid catalysis have been reported by Jacobsen and coworkers who have demonstrated that a combination of simple achiral Brønsted acids and chiral (thio)urea catalysts can enable a range of enantioselective transformations.{Xu, 2010 #3165;Klausen, 2009 #3173} The main role of the (thio)urea catalyst is to act as a chiral anion receptor of the Brønsted acid's conjugate base. Complementarily, we are aimed to introduce a new concept for asymmetric Brønsted acid catalysis that merges certain features of previous approaches while offering some unique advantages.

As illustrated in Figure 2.1, we envisioned a new type of chiral Brønsted acid in which the acidic site of the catalyst is connected via an appropriate linker to an anion receptor moiety such as a thiourea. Upon substrate protonation, the conjugate base associates with the anion recognition site, resulting in the formation of a substrate/catalyst ion pair of type I. Alternatively, the catalyst could facilitate the condensation of two different substrates to result in an ion pair of type II. While the anion may still interact with the substrate via hydrogen bonding in the type I ion pair, hydrogen bonding between the ions should be reduced markedly in the type II ion pair, resulting in strict ion-pairing. Importantly, both types of ion pairs feature a rigid anion that should facilitate an efficient transfer of chirality.

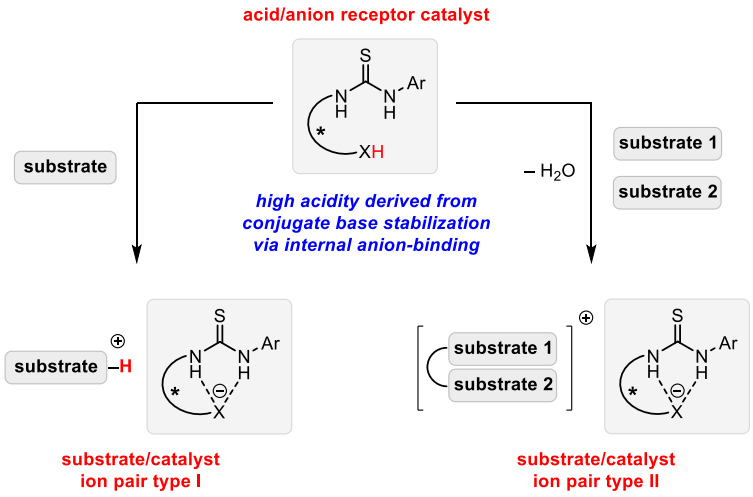


Figure 2.1. Internal anion-binding concept for asymmetric Brønsted acid/chiral anion catalysis.

While a range of acidic groups XH may be linked to an anion recognition site, we were particularly intrigued by the idea of using simple carboxylic acids. Although there are notable exceptions, in particular the prominent work of the Maruoka group, chiral carboxylic acids have not yet found widespread applications as asymmetric Brønsted acid catalysts. This is likely because carboxylic acids are ultimately limited by their relatively weak acidities, restricting the number of substrates that can be activated. The propensity of carboxylate to engage in hydrogen bonding with protonated substrate also reduces the potential level of substrate activation, as this interaction lowers the electrophilicity of the protonated species. Internal stabilization of the conjugate base (carboxylate) should circumvent both of these problems. Firstly, anion-binding to the conjugate base is expected to lower the acid's pK_a, allowing for an increase in acidity beyond what can typically be achieved for carboxylic acids. Secondly, internal anion-binding reduces the ability of the carboxylate anion to participate in additional HB interactions with the activated cationic substrate, increasing the electrophilicity of the latter. In addition, covalent attachment of the acidic site to the chiral acceptor as opposed to a dual catalysis approach addresses the potential issue of background reactivity caused by the achiral acid.

2.2 Enantioselective Povarov Reactions with Secondary Aromatic Amines.

There has been significant recent interest in the development of asymmetric Povarov reactions[1-6]. Impressive results have been achieved with chiral Lewis acids, although most studies have focused on asymmetric Brønsted acid catalysis. Particularly noteworthy in this regard are the pioneering contributions by Akiyama{Akiyama, 2006 #1029}, and Masson and Zhu{Dagousset, 2012 #8273;Dagousset, 2011 #2601;Liu, 2009 #2602}. With the exception of Jacobsen's landmark contribution{Xu, 2010 #3165} (combination of *ortho*-nitrobenzenesulfonic acid with a chiral urea catalyst), Brønsted acid catalysis of the Povarov reaction has been limited to chiral phosphoric acids. Despite these advances, catalytic enantioselective Povarov reactions with secondary aromatic amines are all but unknown. This is probably at least in part due to the requirement of these reactions to involve strict ion pairs and the difficulty associated with controlling enantioselectivity in this context. In fact, in a number of previous reports on asymmetric Povarov reactions with imines derived from primary anilines, it was proposed that hydrogen bond assisted ion pairs are a key element in controlling enantioselectivity.

2.2.1 Reaction Conditions Optimization

A number of chiral catalysts containing a carboxylic acid connected to an anion recognition site (Figure 2.2). Typically, the catalysts were readily assembled in as little as two steps, mainly taking advantage of ring opening of phthalic anhydride derivatives with primary amines bearing a (thio)urea motif. The cyclohexane diamine or BINAM derived mono-thiourea are known intermediates and can be accessed in high yields.

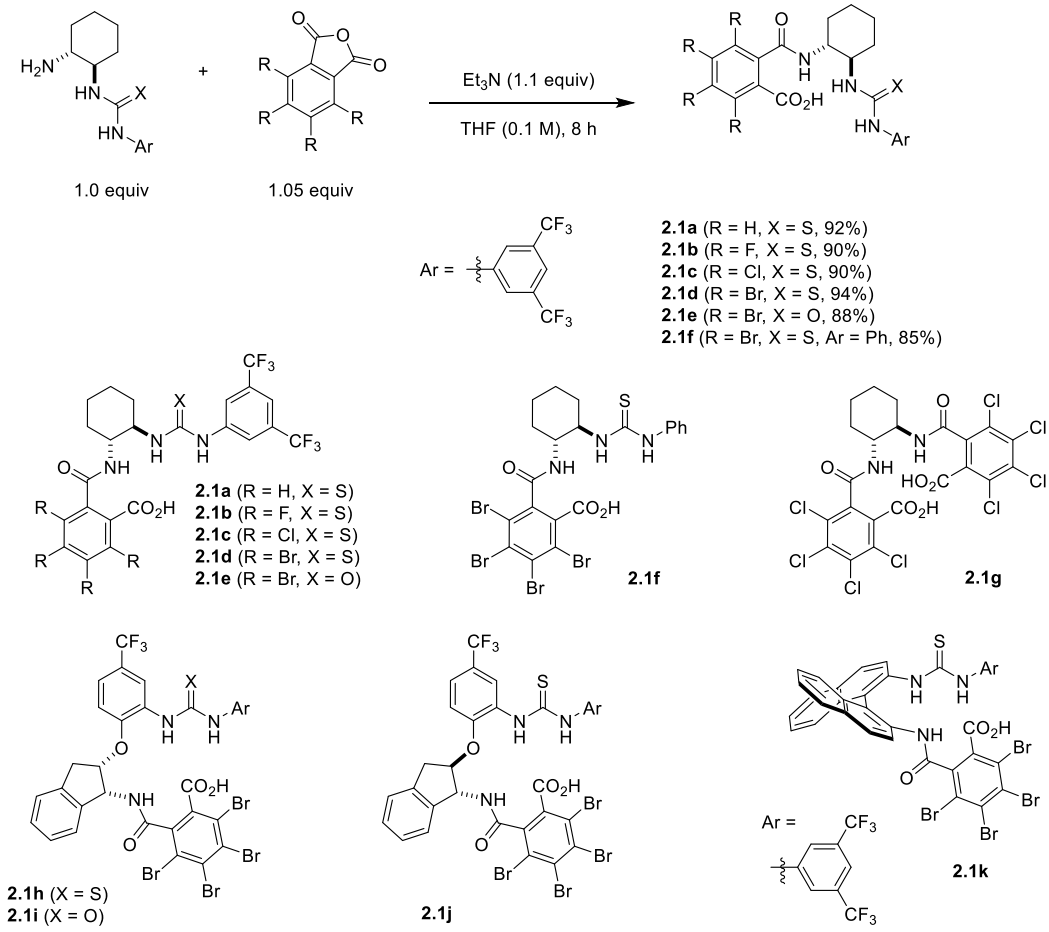


Figure 2.2. Catalysts evaluated in this study.

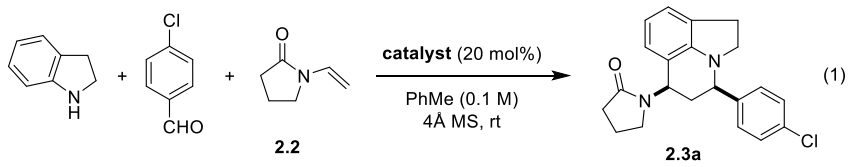
We decided to test these catalysts in a challenging Povarov reaction with indoline as the amine to give polycyclic products **2.3**, species that have previously been identified as potent tyrosine kinase inhibitors (eq 1)[7].

The three-component reaction of indoline, 4-chlorobenzaldehyde and 1-vinylpyrrolidin-2-one (**2.2**) was selected as the model reaction to evaluate the potential of the new Brønsted acid catalysts (Table 2.1). Toluene was chosen as the solvent to facilitate the formation of tight ion pairs. Catalyst **2.1a**, prepared in one step from phthalic anhydride and the corresponding 1,2-cyclohexanediamine monothiourea, was found to be capable of catalyzing this transformation. However, the reaction was sluggish and resulted in the recovery of racemic product (entry 1). A significant improvement with regard to both reactivity and selectivity was achieved with the tetrafluoro phthalic anhydride-derived

catalyst **2.127b** (entry 2). The corresponding tetrachloro catalyst **2.127c** provided another marked increase in enantioselectivity (entry 3). While the tetrabromo catalyst **2.127d** displayed an almost identical level of selectivity, a dramatic increase in reactivity was observed (entry 4). The corresponding urea catalyst **2.127e** showed reduced activity and gave rise to product with lower ee (entry 5). Replacement of the electron-withdrawing 3,5-bistrifluoromethyphenyl group for a simple phenyl-substituent (catalysts **2.127d** vs. **2.127f**) also led to a drop in reactivity and selectivity (entry 6). The presence of a thiourea moiety was found to be crucial as diacid **2.127g** failed to catalyze this transformation. *Cis*- and *trans*-aminoindanol-derived urea and thiourea acid catalysts **2.127h**–**j** were all capable of promoting the title reaction but provided product with low ee's (entries 8–10). 1,1′-Binaphthyl-2,2′-diamine-based catalyst **2.127k** also showed a promising level of reactivity albeit poor selectivity (entry 11).

Continuing with the most promising catalyst **2.127d**, various solvents were evaluated next. Perhaps not surprisingly, solvents with dielectric constants exceeding that of toluene resulted in product with reduced ee's (entries 12–16). However, a reduction in temperature and solvent molarity resulted in improved ee's. The rate of the reaction could be increased by employing two equivalents of each, 4-Cl-benzaldehyde and **2.128**. The best result was obtained in a reaction that was performed at –55 °C (entry 18). In the event, product **2.129a** was isolated in 94% yield and with 92% ee.

Table 2.1 Evaluation of Chiral Brønsted Acids in a Three-Component Povarov Reaction With Indoline.[a]



entry	catalyst	solvent	time [h]	yield (%)	ee (%)
1	**2.1a**	PhMe	96	24	0
2	**2.1b**	PhMe	96	51	28
3	**2.1c**	PhMe	96	57	58
4	**2.1d**	PhMe	72	75	59

5	**2.1e**	PhMe	96	77	36
6	**2.1f**	PhMe	96	48	28
7	**2.1g**	PhMe	48	0	-
8	**2.1h**	PhMe	60	71	11
9	**2.1i**	PhMe	72	72	3
10	**2.1j**	PhMe	96	64	0
11	**2.1k**	PhMe	72	68	23
12	**2.1d**	CH_3CN	12	77	0
13	**2.1d**	CH_2Cl_2	7	81	17
14	**2.1d**	Et_2O	30	79	34
15	**2.1d**	MTBE	15	85	31
16	**2.1d**	THF	48	74	0
17[b]	**2.1d**	PhMe	96	90	71
18[c,d,e]	**2.1d**	PhMe	110	94	92
19[d]	**2.1d**	PhMe	48	88	59
20[e]	**2.1d**	PhMe	96	74	61

[a] Reactions were performed with 0.2 mmol of indoline and 1.02 equiv of each, 4-Cl-benzaldehyde and **2.2**. Yields are isolated yields of chromatographically purified compounds. The ee's were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was conducted at 0 °C. [c] The reaction was conducted at –55 °C. [d] 2 equiv of each, 4-Cl-benzaldehyde and **2.2** were used. [e] The reaction was performed at a 0.05 M concentration.

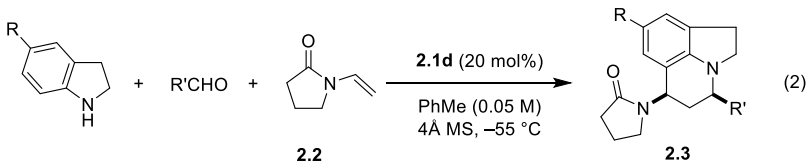
2.2.2 Substrate Scope

The scope of the transformation was evaluated employing the optimized conditions (Table 2.2). Indolines bearing different substituents at the 5-position readily underwent the three-component Povarov reaction with 4-chlorobenzaldehyde and **2.2** to produce products in good enantioselectivities (entries 1–4). Electronically diverse aromatic aldehydes with different substitution patterns provided the corresponding tetrahydroquinoline products in generally good yields and enantioselectivities (entries 5–12). Gratifyingly, aliphatic aldehydes were also viable substrates, affording products with excellent ee's (entries 13–18).

The scope of the Povarov reaction with regard to the amine was also explored (Table 2.3). High levels of enantioselectivity were observed with a number of tetrahydroquinolines (entries 1–3). Remarkably, while the dihydrobenzoxazine-derived product **2.4d** was obtained in 84% yield and near-perfect

enantioselectivity (entry 4), the corresponding sulfur analogue was isolated in only 54 percent yield and 65% ee (entry 5). Finally, tetrahydroquinoxaline-containing product **2.4f** was obtained with excellent selectivity (entry 6).

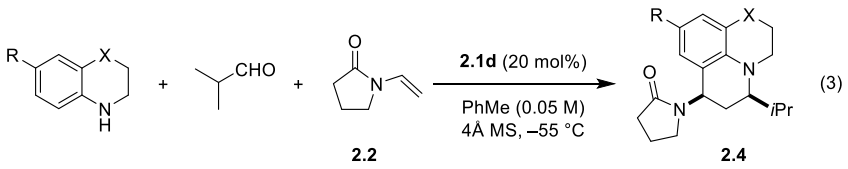
Table 2.2. Povarov Reactions With Selected Indolines and Aldehydes.[a]



entry	R	R′	time [h]	product	yield (%)	ee (%)
1	H	4-Cl-C_6H_4	110	**2.3a**	94	92
2	Cl	4-Cl-C_6H_4	120	**2.3b**	59	84
3	Br	4-Cl-C_6H_4	120	**2.3c**	76	86
4	Me	4-Cl-C_6H_4	96	**2.3d**	82	90
5	H	4-Br-C_6H_4	96	**2.3e**	86	95
6	H	4-F-C_6H_4	96	**2.3f**	76	93
7	H	4-CN-C_6H_4	96	**2.3g**	92	91
8	H	3-MeO-C_6H_4	96	**2.3h**	93	92
9	H	2-Me-C_6H_4	120	**2.3i**	80	92
10	H	2-MeO-C_6H_4	120	**2.3j**	59	93
11	H	C_6H_5	120	**2.3k**	71	79
12	H	3,4-Cl_2-C_6H_3	96	**2.3l**	88	87
13	H	*i*Pr	24	**2.3m**	96	94
14	H	*i*Bu	26	**2.3n**	53	95
15	H	*t*Bu	96	**2.3o**	65	>99
16	H	neopentyl	96	**2.3p**	91	95
17	H	cyclohexyl	96	**2.3q**	51	90
18	H	cyclopentyl	12	**2.3r**	82	88

[a] Reactions were performed with 0.2 mmol of indoline and 0.4 mmol of each, aldehyde and **2.2**. Yields are isolated yields of chromatographically purified compounds. The ee's were determined by HPLC analysis; see the Supporting Information for details.

Table 2.3. Povarov Reactions With Selected Secondary Amines.[a]



entry	R	X′	time [h]	product	yield (%)	ee (%)
1	H	CH_2	48	**2.4a**	85	91
2	Me	CH_2	72	**2.4b**	74	93
3	MeO	CH_2	72	**2.4c**	82	97
4	H	O	72	**2.4d**	84	>99
5	H	S	96	**2.4e**	54	65
6	H	NCbz	72	**2.4f**[b]	65	97

[a] Reactions were performed with 0.2 mmol of amine and 0.4 mmol of each, isobutyraldehyde and **2.2**. Yields are isolated yields of chromatographically purified compounds. The ee's were determined by HPLC analysis; see the Supporting Information for details. [b] Obtained as a 9:1 mixture of diastereomers. The ee is given for the major diastereomer.

While some of the catalysts (e.g., **2.1h**–**j**) might allow for the type of idealized bifurcated intramolecular hydrogen bonding interaction as depicted in Figure 1, this scenario appeared less likely in the case of the most selective catalyst (**2.1d**). To obtain insights into the nature of conjugate base stabilization in the anionic form of **2.1d**, we prepared the corresponding tetrabutylammonium salt. The X-ray crystal structure of this salt is depicted in Figure 3. Interestingly, the anion was found to self-aggregate, resulting in a helical chain-type superstructure. Individual catalyst units interact through bifurcated binding of the carboxylate anion to the thiourea site of the neighboring molecule. In addition, the amide *N*-H proton is engaged in an internal hydrogen bonding interaction with the thiourea sulfur atom of the same molecule, an interaction that likely increases the acidity of the thiourea site, thus contributing to better anion-binding. It remains to be established whether or not this particular type of catalyst aggregation is relevant in the catalytic cycle.

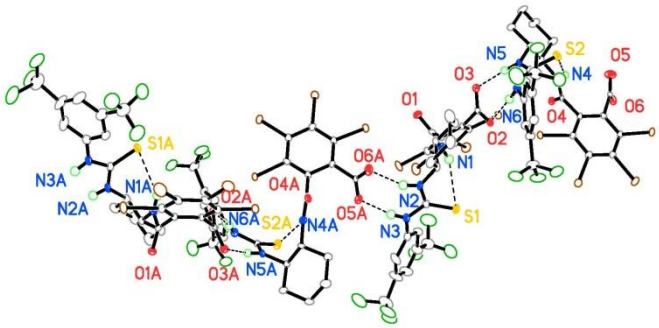
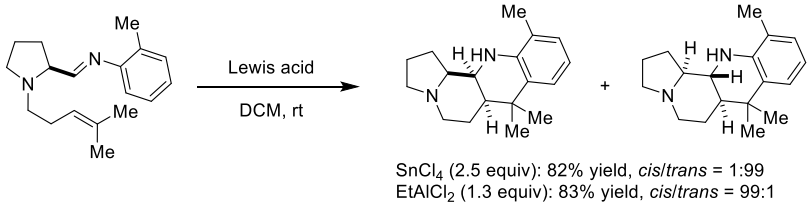


Figure 2.3. X-ray crystal structure of the tetrabutylammonium salt of catalyst **2.1d** (four repeating units). For clarity, the tetrabutylammonium cations are not shown and only selected hydrogen atoms are depicted.

In summary, we have introduced conjugate-base-stabilized Brønsted acid catalysis as a new and highly generalizable concept for asymmetric catalysis. The power of this design was demonstrated in the context of the first catalytic enantioselective Povarov reaction involving secondary aromatic amines such as indoline and tetrahydroquinoline.

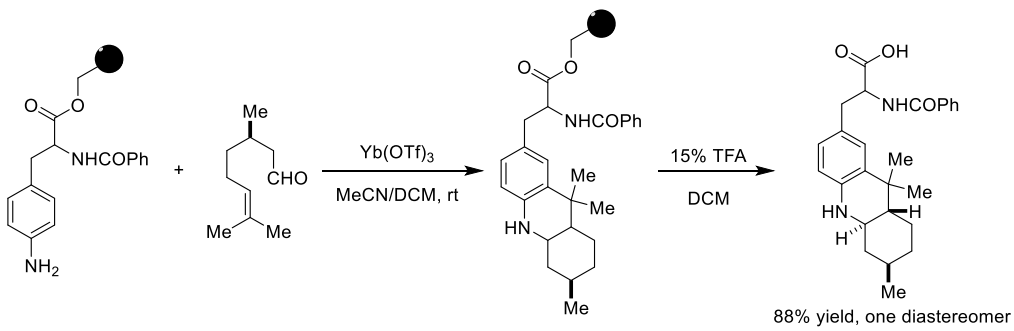
2.3 Catalytic Enantioselective Intramolecular Aza-Diels-Alder Reactions

Intramolecular Diels-Alder (IMDA) reactions are among the most powerful tools for the rapid construction of polycyclic compounds and often generate multiple stereogenic centers in a single step[8-17]. Highly diastereoselective IMDA reactions are well developed and have been applied to the asymmetric synthesis of natural products and other bioactive materials. Although far less developed than their diastereoselective variants, a number of elegant catalytic enantioselective IMDA reactions have been reported.[18-29] As a subclass of DA reactions, hetero-DA (HDA) reactions are widely used in the synthesis of biologically relevant heterocycles.[1,2,4-6] Over the past two decades, numerous reports on catalytic enantioselective intermolecular HDA reactions have appeared.[4] In stark contrast, their corresponding intramolecular variants remain rare and are largely limited to oxa-DA reactions.[30-34] To our knowledge, there has been no report on a catalytic enantioselective intramolecular aza-DA reaction, only diastereoselective examples have been disclosed[35-44]. For example, In 1994, the Laschat[36] group reported an intramolecular Povarov reaction of prolinal-derived *N*-arylimines promoted by achiral Lewis acids (Scheme 2.1). Remarkably, the diastereoselectivity was completely under reagent control. When $SnCl_4$ was employed, only the all-*trans* diastereomer was obtained. In contrast, only all-*cis* product was observed when using $EtAlCl_2$.



Scheme 2.1. Intramolecular Povarov reaction of prolinal-derived *N*-arylimine.

Kiselyov *el al*. reported the solid support synthesis of polysubstituted tetrahydroquinolines via intramolecular Povarov reactions[37] (Scheme 2.2). $Yb(OTf)_3$ could efficiently catalyze the condensation and cyclization of the immobilized 4-aminophenylalanine with (*R*)-(+)-citronellal. After cleavage of the resin with TFA, the polycyclic product was isolated as a single diastereomer.

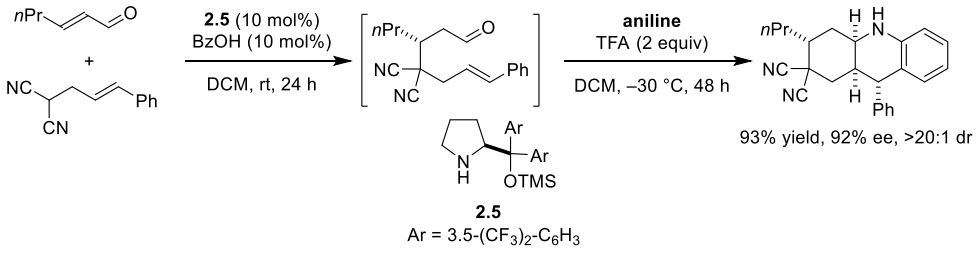


Scheme 2.2. Solid support synthesis of polysubstituted tetrahydroquinolines via intramolecular Povarov reactions.

Sabitha and co-workers[38] identified $BiCl_3$ as an effective catalyst for the cyclization between simple aniline and (*R*)-(+)-citronellal, and the *trans*-octahydroacridine product was delivered in excellent yield as a single diastereomer (Scheme 2.3).

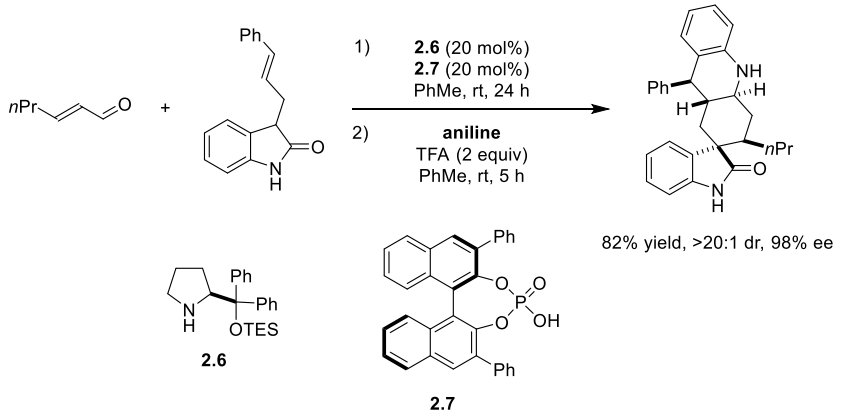
Scheme 2.3. $BiCl_3$ catalyzed stereoselective synthesis of octahydroacridines.

In 2011, Jørgensen group[45] reported the one-pot construction of octahydroacridines through a Michael addition/intramolecular Povarov reaction sequence. The strategy was initiated with the enantioselective Michael addition catalyzed by the iminium catalyst **3.1** to give the ε,ζ-unsaturated aldehyde intermediate, which was then followed by TFA-mediated diastereoselective intramolecular Povarov reaction (Scheme 2.4).



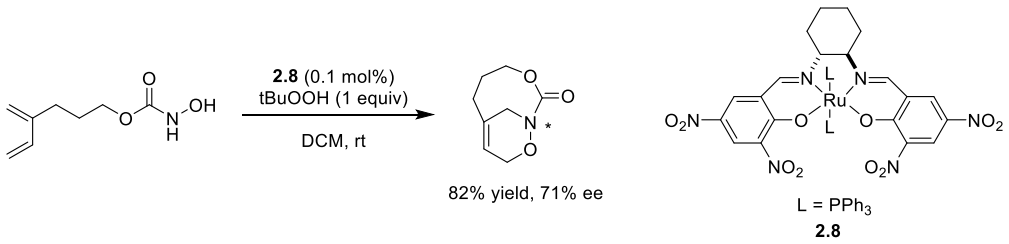
Scheme 2.4. One-pot synthesis of octahydroacridines

The Wang group[44] reported a similar one-pot asymmetric Michael/Povarov sequential reaction to synthesize spirooctahydroacridine-3,3'-oxindoles (Scheme 2.5). Starting from 3-substituted oxindoles, the chiral spirocyclohexaneoxindoles bearing five stereogenic centers were obtained in excellent yields and stereoselectivities in the presence of the iminium catalyst **2.6**. Interestingly, the addition of chiral phosphoric acid additive could further increase the reactivity and selectivity.



Scheme 2.5. One-pot synthesis of chiral spirocyclohexaneoxindoles.

In 2005, Shea and co-workers reported an enantioselective type II acyl-nitroso IMDA reaction[46] (Scheme 2.6). The Ru(II)-Salen complex **2.8** firstly served as an oxidation catalyst that promoted the oxidation of *N*-hydroxy formate ester to the corresponding nitroso formate in the presence of stoichiometric tert-butyl hydroperoxide (TBHP). Subsequently, **2.8** would be an effective asymmetric catalyst for the cyclization between the pendent diene and nitroso group, giving the bicyclic product bearing a configurationally stable bridge-headed chiral nitrogen center.

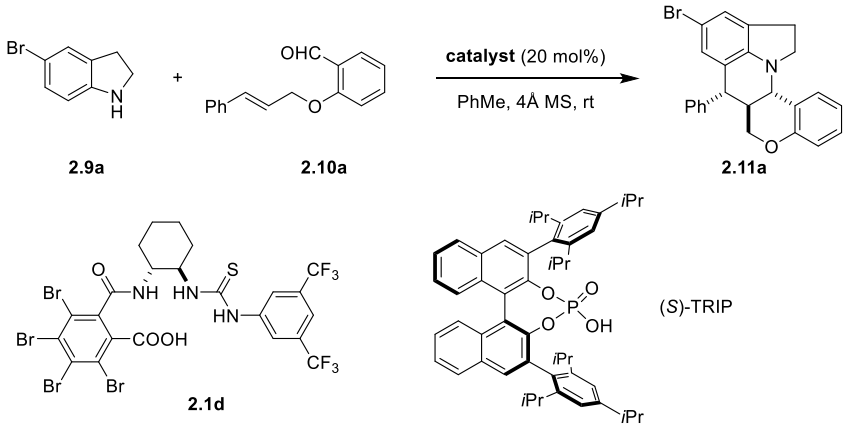


Scheme 2.6. Enantioselective type II acyl-nitroso IMDA reaction.

2.3. Optimization of Reaction Conditions

For the purpose of developing the title transformation, 6-bromoindoline (**2.9a**) and aldehyde **2.10a** were selected as model substrates. *O*-allylsalicylaldehyde derivatives closely related to **2.10a** have been used as starting materials for the synthesis of bioactive tetrahydrochromanoquinolines.[47-62] Achiral Lewis or Brønsted acids have been employed as catalysts/promoters in these intramolecular

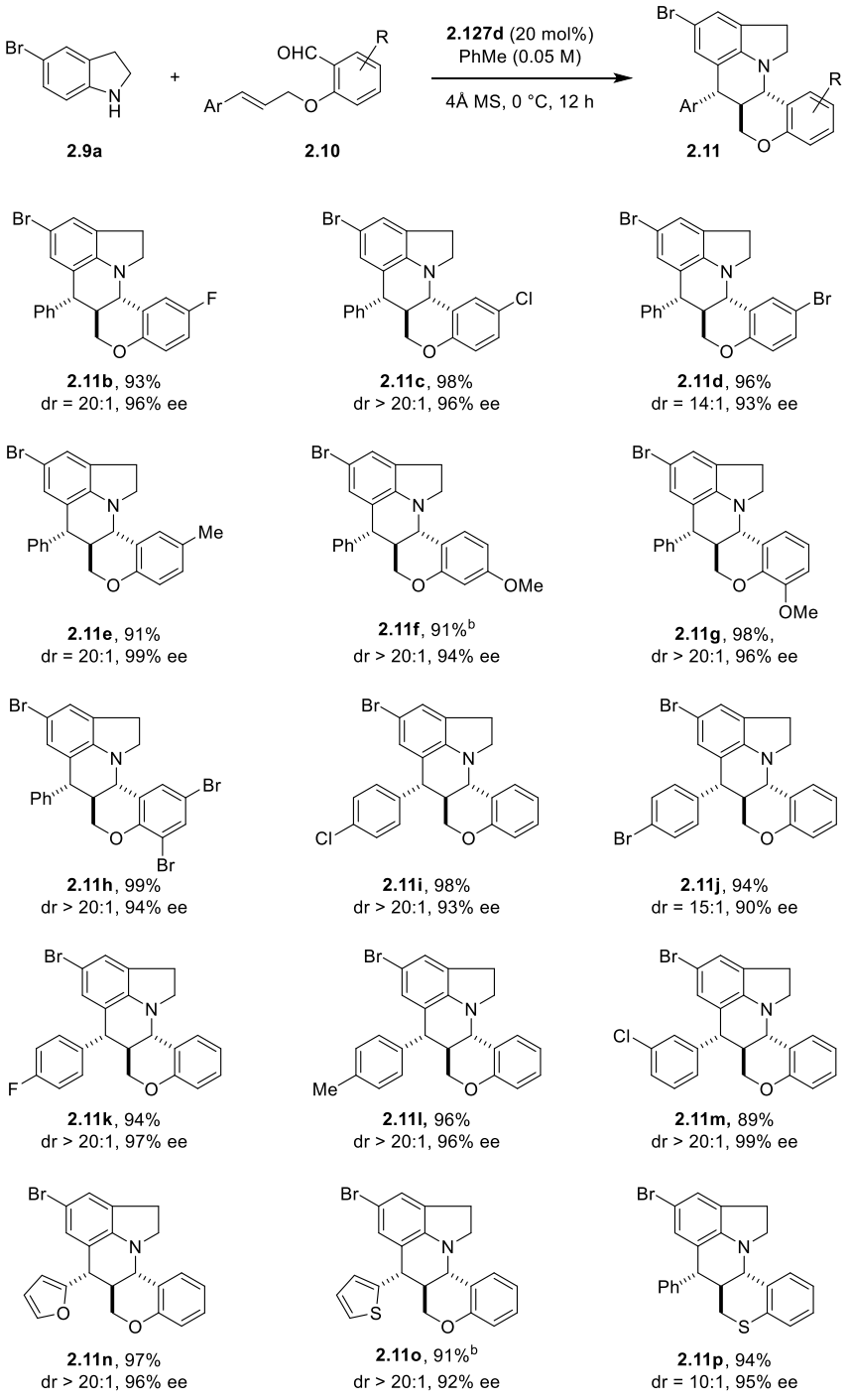
Table 2.4. Evaluation of Reaction Conditions.[a]



entry	catalyst	conc (M)	time [h]	yield (%)	dr	ee (%)
1	-	0.05	17	5	ND	-
2	**TFA**	0.05	17	14	1:1.3	-
3	**2.1d**	0.05	2	87	>20:1	97
4	(*S*)-TRIP	0.05	17	78	1:1	97/37
5	**2.1d**	0.1	2	80	>20:1	96
6	**2.1d**	0.025	17	38	11:1	91/38
7[b]	**2.1d**	0.05	12	91	>20:1	>99

[a] Reactions were performed with 0.2 mmol of **2.9a** and 1.2 equiv of **2.10a**. Yields correspond to chromatographically purified products. The dr's were determined by ^{1}H NMR of crude reaction mixtures. The ee values were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was performed at 0 °C.

Povarov reactions, typically providing products such as **2.11a** as diastereomeric mixtures. When a reaction of **2.9a** and **2.10a** was conducted in the absence of catalyst, some background reactivity was noted (Table 2.4, entry 1). Surprisingly, the relatively strong carboxylic acid TFA, which is widely used to promote intramolecular Povarov reactions, provided poor substrate conversion (entry 2).



Scheme 2.7. Scope of Aldehydes. Reactions were performed with 0.2 mmol of **2.10** and 1.2 equiv of **2.9a**. Yields correspond to chromatographically purified products. The dr's were determined by ^{1}H NMR of crude reaction mixtures. The ee values were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was run for 3 days.

Gratifyingly, **2.1d** was found to be an excellent catalyst. Following a reaction time of only two hours, **2.11a** was obtained in 87% yield and 97% ee as essentially a single diastereomer (entry 3).

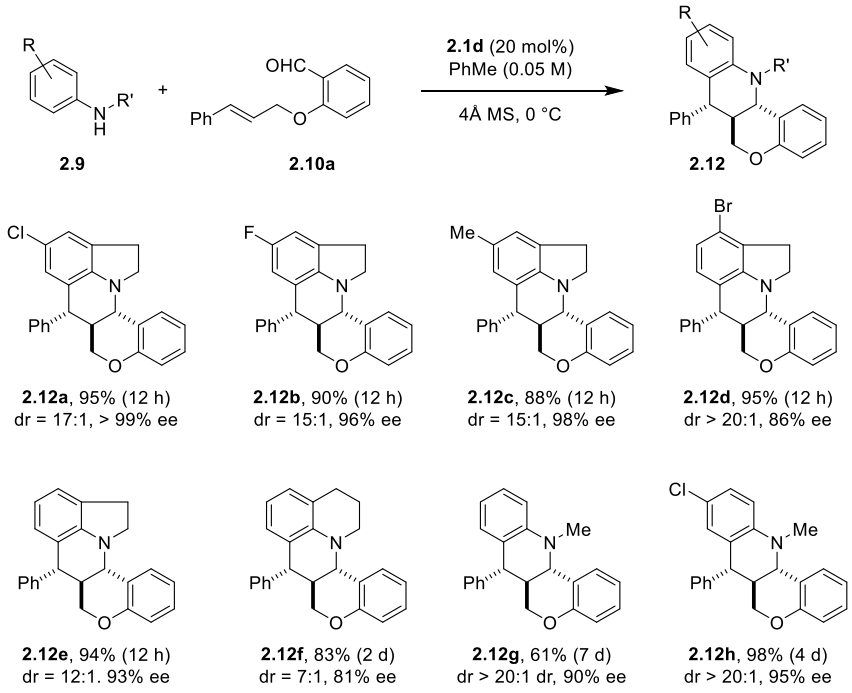
Interestingly, (*S*)-TRIP, the most widely used chiral phosphoric acid catalyst[63], while being less active, showed comparable enantioselectivity (entry 4). However, poor diastereoselectivity was observed, indicating vastly different modes of action for the two catalysts. Further evaluation of reaction conditions showed that a higher reaction molarity did not provide improvements (entry 5) while a lower substrate concentration led to a more sluggish reaction with loss of enantio- and diastereoselectivity (entry 6). A reduction of the reaction temperature to 0 °C further improved the yield of **2.11a** while raising the product ee to more than 99% (entry 7).

2.3.2 Substrate Scope

As outlined in Scheme 2.7, *O*-allylsalicylaldehyde derivatives **2.10** with different substituents on the aldehyde phenyl ring reacted smoothly with **2.9a** to produce polycyclic heterocycles **2.11** in excellent yields and with high levels of diastereo- and enantioselectivity. A marked electronic effect was observed for aldehyde **2.10f**, bearing a *p*-methoxy group. A longer reaction time (3 days) was required for this substrate, an observation that is readily rationalized by the reduced electrophilicity of the intermediate iminium ion. With regard to the dienophile component, both electron-withdrawing and electron-donating groups on the phenyl group were tolerated. Heteroarenes such as furan and thiophene rings were also readily accommodated. Finally, thiosalicylaldehyde-derived starting material **2.10p** could be successfully transformed into product **2.11p**. In this instance, the dr was slightly eroded although excellent yield and enantioselectivity was maintained.

Next, the generality of this transformation was explored with regard to the amine component (Scheme 2.8). A number of indolines performed well. Tetrahydroquinoline was found to exhibit a lower level of reactivity, while providing product **3.12f** with slightly reduced ee and dr. Gratifyingly, *N*-methyl aniline, a representative acyclic secondary amine, engaged in the formation of tetrahydrochromanoquinoline **3.12g**. While a longer reaction time was required, this product was obtained with excellent dr and ee, albeit it in moderate yield. It is worthy of note that this substrate was found to be unreactive in the corresponding intermolecular three-component reactions.[10a]

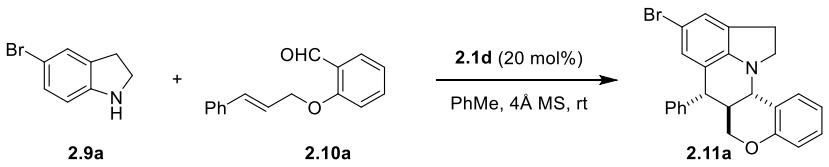
Employing a more electron-deficient acyclic substrate, namely 4-chloro-*N*-methylaniline, the corresponding product **3.12h** was obtained with excellent yield and stereoselectivity.



Scheme 2.8. Scope of Aromatic Amines. Reactions were performed with 0.2 mmol of **2.10a** and 1.2 equiv of **2.9**. Yields correspond to chromatographically purified products. The dr's were determined by ^{1}H NMR of crude reaction mixtures. The ee values were determined by HPLC analysis; see the Supporting Information for details.

An unusual and interesting observation was made in the course of this study. While racemic samples of cycloaddition products were easily obtainable with TFA, a complicating factor was that diastereomeric mixtures of two products were typically obtained. In some cases, a third diastereomer was observed. This prompted us to evaluate racemic **2.1d** (*rac*-**2.1d**) as a catalyst in order to obtain diastereomerically enriched racemic products for HPLC analysis. Remarkably, *rac*-**2.1d** at a 20 mol % loading was nearly ineffective in accelerating the formation of *rac*-**2.11a** from **2.9a** and **2.10a**. Non-linear effects were then evaluated in an effort to develop a more detailed understanding of this phenomenon (Table 2.5). Interestingly, the ee of product **2.11a** remained at a nearly identical level down to a catalyst ee of only 10%. However, the reaction rate gradually slowed down with reduced catalyst ee, with a substantial drop in reactivity being noted for a catalyst composition of less than 50% ee. Concurrent with the reduction in reaction rate, the diastereoselectivity diminished gradually.

Table 2.5. Non-linear Effects Study.[a]



entry	**2.1d** (% ee)	Time	yield (%)	dr	ee (%)
1	100	2h	91	>20:1	97/-
2	90	7d	82	12:1	98/53
3	80	7d	80	10:1	97/46
4	70	7d	78	8:1	97/40
5	60	7d	74	8:1	97/35
6	50	7d	70	7:1	97/30
7	40	7d	48	4:1	97/8
8	30	7d	30	4:1	95/7
9	20	7d	23	1.7:1	97/9
10	10	7d	16	2:1	96/6
11	0	7d	14	1:2	-
12	No cat.	7d	7	1:1	-

[a] Reactions were performed with 0.2 mmol of **2.9a** and 1.2 equiv of **2.10a** in the presence of **2.1d** with different ee's. Yields are those of chromatographically purified compounds. dr was determined by ^{1}H NMR of crude reaction mixture. The ee values were determined by HPLC analysis. Reactions in entries 7–12 did not reach full conversion of **2.10a** after 7 days.

The exceptionally pronounced non-linear effect, combined with the correlating observation that *rac*-**2.1d** is a nearly ineffective catalyst, suggests a high degree of aggregation between (*R*,*R*)- and (*S*,*S*)-enantiomers. Importantly, aggregation of enantiomerically pure **2.1d** might also be relevant to the catalytic process. Such aggregation was previously noted in the solid-state structure of the tetrabutylammonium salt of (*R*,*R*)- **2.1d**.[10a] In fact, the observation that a reduction in reaction molarity (see Table 3.1, entry 6) leads to a reduced diastereoselectivity is consistent with the notion that a de-aggregated or less aggregated catalyst anion might facilitate the formation of the minor product diastereomer.[20] To gain some insights into the completely different activity between the

enantiopure and racemic **2.1d**, we obtain the X-ray structure of the tetrabutylammonium salt of rac-**2.1d**. It showed that the (*R*,*R*) enantiomer was bound to (*S*,*S*) enantiomer through hydrogen bonding, forming a diastereomer-like oligomer comparing with the enantiopure **2.1d** (Figure 2.4). In a space-filled view (Figure 2.5), we can see that the ent-**2.1d** has a well-defined pocket between two adjacent molecules, probably providing a vacant site to bind and activate substrates. In contrast, the crystal structure of rac-**2.1d** is packed and possibly explain the relatively low reactivity.

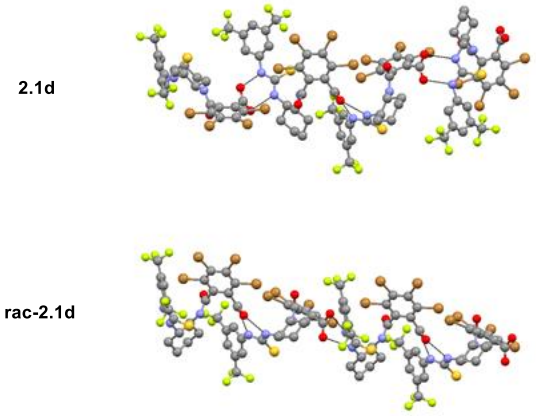


Figure 2.4. X-ray structure of the enantiopure and racemic **2.1d**

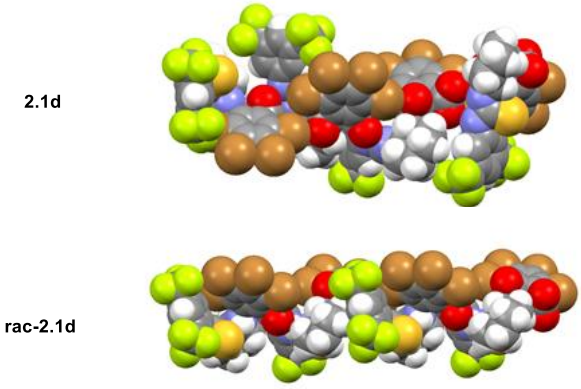
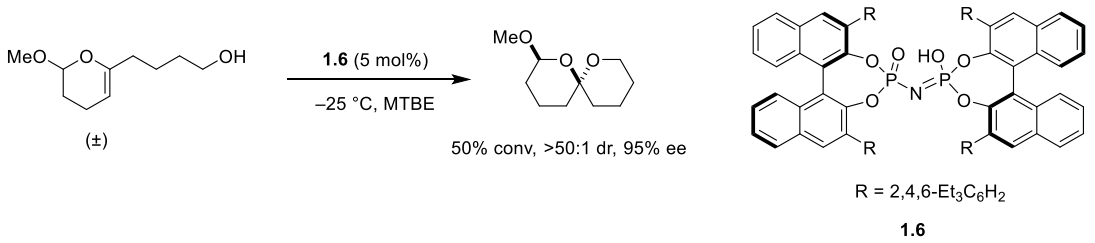


Figure 2.5. Space-filled mode X-ray structure of the enantiopure and racemic **2.1d**

In summary, we have reported a highly enantio- and diastereoselective organocatalytic intramolecular Povarov reaction as the first example of a catalytic enantioselective intramolecular aza-Diels-Alder reaction. A chiral conjugate-base-stabilized carboxylic acid catalyst was found to be uniquely effective in facilitating this transformation.

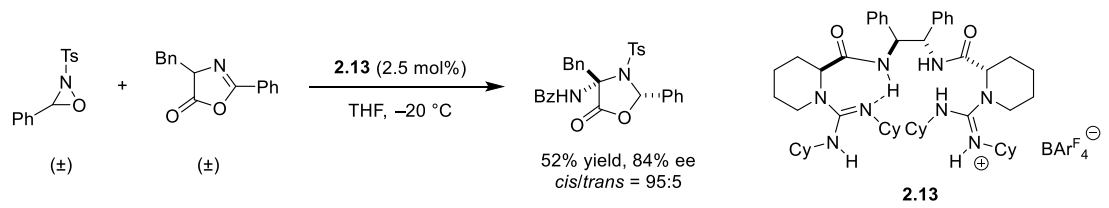
2.4 Stereochemically Rich Polycyclic Amines from the Kinetic Resolution of Indolines through Intramolecular Povarov Reactions

Catalytic kinetic resolution is a valuable approach to obtain enantioenriched compounds when the substrates are readily available in their racemic forms but difficult to synthesize directly as single enantiomers.[64-71] Typically, the focus is on transforming one substrate enantiomer into a product from which it can be liberated again in a subsequent step. Most catalytic kinetic resolutions do not generate new stereogenic centers and are optimized to maximize the ee of the recovered, unreacted starting material. An intriguing alternative involves reactions of racemic substrates with achiral reaction partners that generate products with one or more new stereogenic centers.[72-82] If properly controlled by a chiral catalyst, this enables the synthesis of products with a richer stereochemistry than achievable with achiral substrates, yet without requiring access to enantiopure starting materials.[83] For example, the List group[72] reported the application of an imidodiphosphoric acid catalyst in the kinetic resolution of racemic substituted enol ether via spiroacetalization, both the bisacetal product and recycled enolacetal starting material were obtained in excellent enantioselectivities (Scheme 2.9).



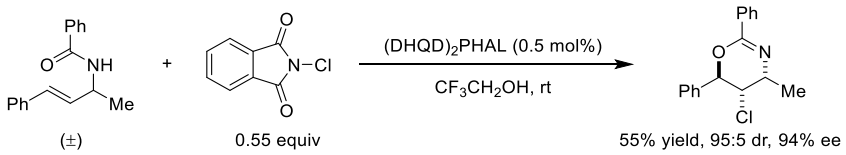
Scheme 2.9. Kinetic resolution of the racemic substituted enol ether via spiroacetalization.

The Feng group[84] reported the first example of oxyamination of azlactones with oxaziridines catalyzed by a chiral bisguanidinium salt (Scheme 2.10). The oxazolin-4-one product with one more stereogenic center was obtained in good diastereo- and enantioselectivity.



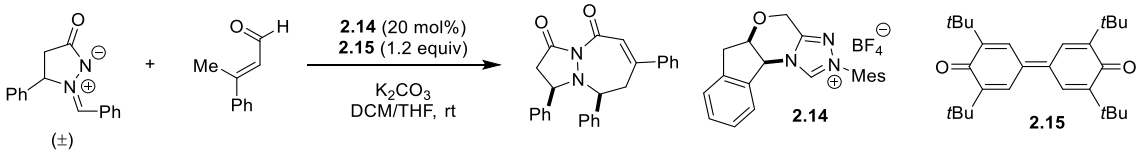
Scheme 2.10. Oxyamination of azlactones with oxaziridines.

In 2013, the Borhan group[85] showed the first example of kinetic resolution of unsaturated amides via chlorocyclization reaction (Scheme 2.11). NMR studies disclosed that the Lewis base catalyst was protonated by CF_3CH_2OH in solution, and the protonated catalyst served as a hydrogen bond donor for the key molecular recognition and enabling the resolution.



Scheme 2.11. Kinetic resolution of unsaturated amides via chlorocyclization.

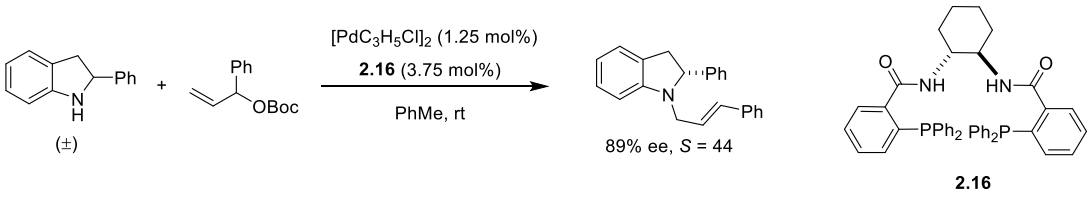
The Chi group[77] disclosed the kinetic resolution of azomethine imines via *N*-heterocyclic carbene (NHC)-catalyzed [3 + 4] cycloaddition (Scheme 2.12). Under oxidative conditions, NHC-catalyzed remote activation of enals delivered transient vinyl enolates as 1,4-dipolarophiles, which could react with 1,3-dipolar azomethine imines to generate seven-membered heterocyclic products in high enantioselectivities.



Scheme 2.12. Kinetic resolution of unsaturated amides via chlorocyclization.

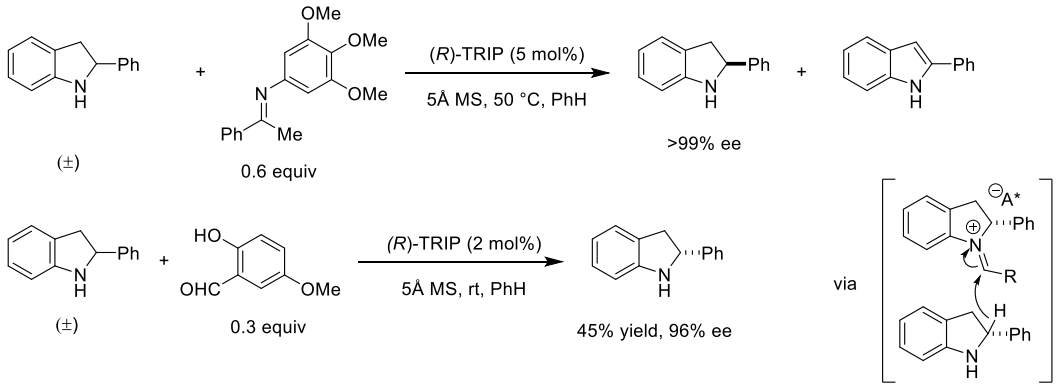
Despite the significant appeal of this general concept, no such reaction appears to be known with racemic, nucleophilic amines. With regard to small-molecule catalysis, nucleophilic amines are

among the most challenging substrates to resolve. This is particularly true when utilizing *N*-acylation as the mode of resolution, given the significant background reactivity amines exhibit for most common acylating reagents.[86-95] After Fu's first report[96] on the kinetic resolution of indolines using their planar-chiral DMAP derivatives, Hou's group[97] reported the kinetic resolution of indolines via Pd-Catalyzed asymmetric allylic amination (Scheme 2.13). In the presence of Trost's chiral ligand **2.16**, the recycled enantioenriched indolines and *N*-allylated indolines were obtained in high enantioselectivities.



Scheme 2.13. Kinetic resolution of indolines via Pd-Catalyzed asymmetric allylic amination.

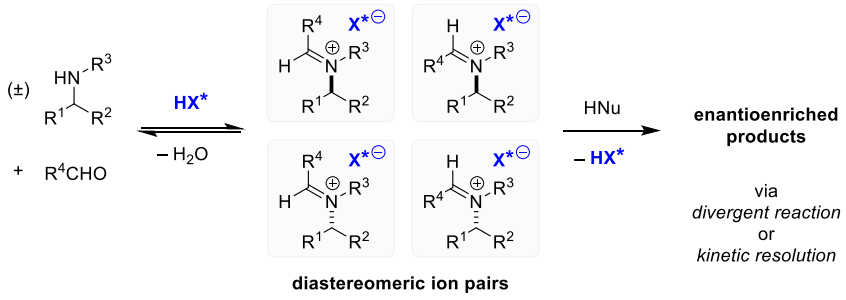
Akiyama and coworkers[98-100] recently reported interesting intermolecular redox approaches to the kinetic resolution of 2-substituted indolines in which one enantiomer of the starting material is oxidized to the corresponding indole (Scheme 2.14).



Scheme 2.14. Oxidative Kinetic resolution of indolines.

We are intrigued by the utilization of racemic indolines in intramolecular aza-Diels Alder (Povarov) reactions to generate stereochemically well-defined polycyclic products with four stereogenic centers.

We envisioned the utilization of racemic secondary amines as starting materials in reactions that involve intermediate iminium ions. In the presence of a chiral Brønsted acid catalyst, condensation of a racemic secondary amine with an achiral aldehyde could give rise to up to four diastereomeric ion pairs (Scheme 2.15). While seemingly challenging to control, the reaction of one or more of these iminium ions with a nucleophile or cycloaddition partner (HNu) could result in enantioenriched products. The successful kinetic resolution could occur in several ways. The catalyst could facilitate the selective formation of only one of the possible iminium ions, followed by a diastereoselective reaction, or the iminium ion formation could be nonselective but only one of the diastereomeric ion pairs reacts to form enantioenriched product. In the latter case, reversibility of the iminium ion formation is a prerequisite for an efficient process. Alternatively, stereodivergent reactions could occur in which both enantiomers of the amine undergo the reaction but form different non-enantiomeric product isomers. In all cases, the outcome of the reaction would be controlled by a chiral anion.



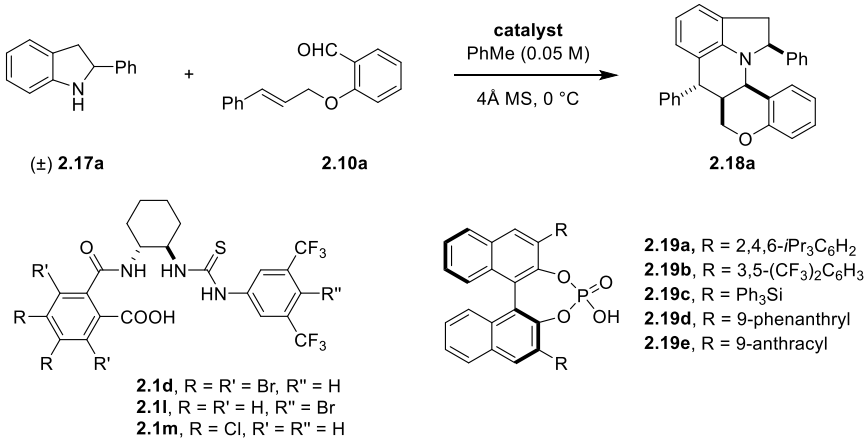
Scheme 2.15. Enantioenriched products from racemic amines via intermediate iminium ions.

2.4.1 Optimization of reaction conditions

In the context of developing a new class of chiral Brønsted acid catalysts that possess both a carboxylic acid and an anion binding site,[101-104] we recently reported the first examples of catalytic enantioselective intramolecular Povarov reactions, involving indoline and related amines as starting materials. We reasoned that the corresponding reaction with racemic 2-substituted indolines would be ideally suited to test the concept outlined in Scheme 4.7. The prevalence of the indoline nucleus as a key component of bioactive materials and the significant interest in complex

tetrahydrochromanoquinolines[47,50,56,58-60] provided further impetus for this study. In order to evaluate this process, racemic 2-phenylindoline (**2.17a**) and aldehyde **2.10a** were selected as model substrates (Table 4.1). To ensure full conversion of **2.10a** in the event of a kinetic resolution, an excess of **2.17a** (2.4 equiv) was used. No reaction was observed in the absence of a catalyst (entry 1). In contrast to the reaction with parent indoline which was only moderately accelerated by trifluoroacetic acid (TFA), here TFA proved to be an efficient catalyst, providing product **2.18a** in good yield and diastereoselectivity (entry 2). Acid-thiourea compound **2.1d**, previously identified as an efficient catalyst for both inter- and intramolecular Povarov reactions with achiral indolines, showed excellent reactivity and provided promising results (entry 3). However, attempts to increase the enantioselectivity to synthetically useful levels failed with this class of catalysts.

Table 2.6. Evaluation of reaction conditions.[a]



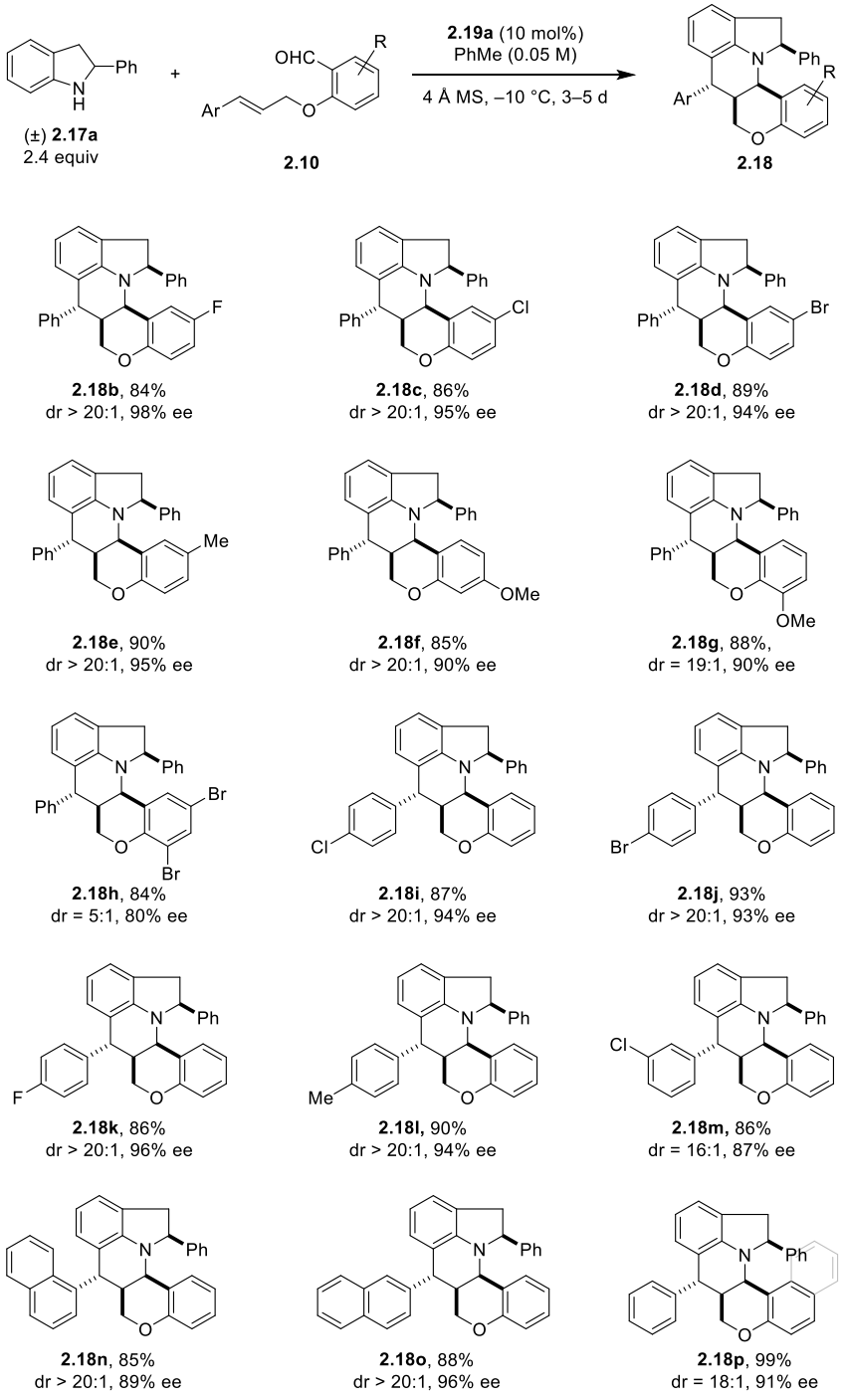
entry	catalyst (mol%)	time [h]	yield (%)	dr	ee (%)
1	-	12	0	-	-
2	TFA (20)	10	85	14:1	-
3	**2.1d** (20)	2	89	12:1	70
4	**2.1l** (20)	24	82	>20:1	0
5	**2.1m**(20)	20	85	>20:1	34
6	**2.19a** (10)	10	87	>20:1	93
7[b]	**2.19a** (10)	72	88	>20:1	95

8[c]	**2.19a** (10)	12	85	>20:1	90
9[c]	**2.19b** (10)	10	87	>20:1	0
10[c]	**2.19c** (10)	24	32	>20:1	47
11[c]	**2.19d** (10)	24	73	>20:1	59
12[c]	**2.19a** (10)	24	79	>20:1	67
13[c], [d]	**2.19a** (10)	120	47	>20:1	92
14[c], [e]	**2.19a** (10)	12	82	>20:1	91

[a] Reactions were performed with 0.2 mmol of **2.18a** and 2.4 equiv of **2.17a**. Yields correspond to chromatographically purified products. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The ee values were determined by HPLC analysis; see the experimental section for details. [b] The reaction was run at –10 °C, the unreacted 2-phenylindoline was recovered with 75% ee (conversion = 44%, s = 88) [c] 2 equiv of **2.17a** were used. [d] The reaction was run at –20 °C. [e] The reaction was performed at a 0.1 M concentration.

We then turned our attention to chiral phosphoric acids. Gratifyingly, **(*S*)-TRIP** (**2.19a**) provided excellent results, despite of being inferior to catalyst **2.1d** in our previously reported intramolecular Povarov reaction with simple indoline. After a reaction time of 10 hours, **2.18a** was obtained in 87% yield and 93% ee as essentially a single diastereomer (entry 6). Lowering the temperature to –10°C further improved the ee of **2.18a** to 95% although a longer reaction time was required (entry 7). Consistent with a kinetic resolution process, the enantioselectivity was slightly eroded upon decreasing the amount of **2.17a** to 2 equiv (entry 8). Other chiral phosphoric acids catalyzed the title reaction but gave inferior results (entry 9–12). Further modification of temperature (entry 13) or concentration (entry 14) was unfruitful. Notably, in each case examined, product formation is consistent with a kinetic resolution pathway; stereodivergent product formation was not observed.

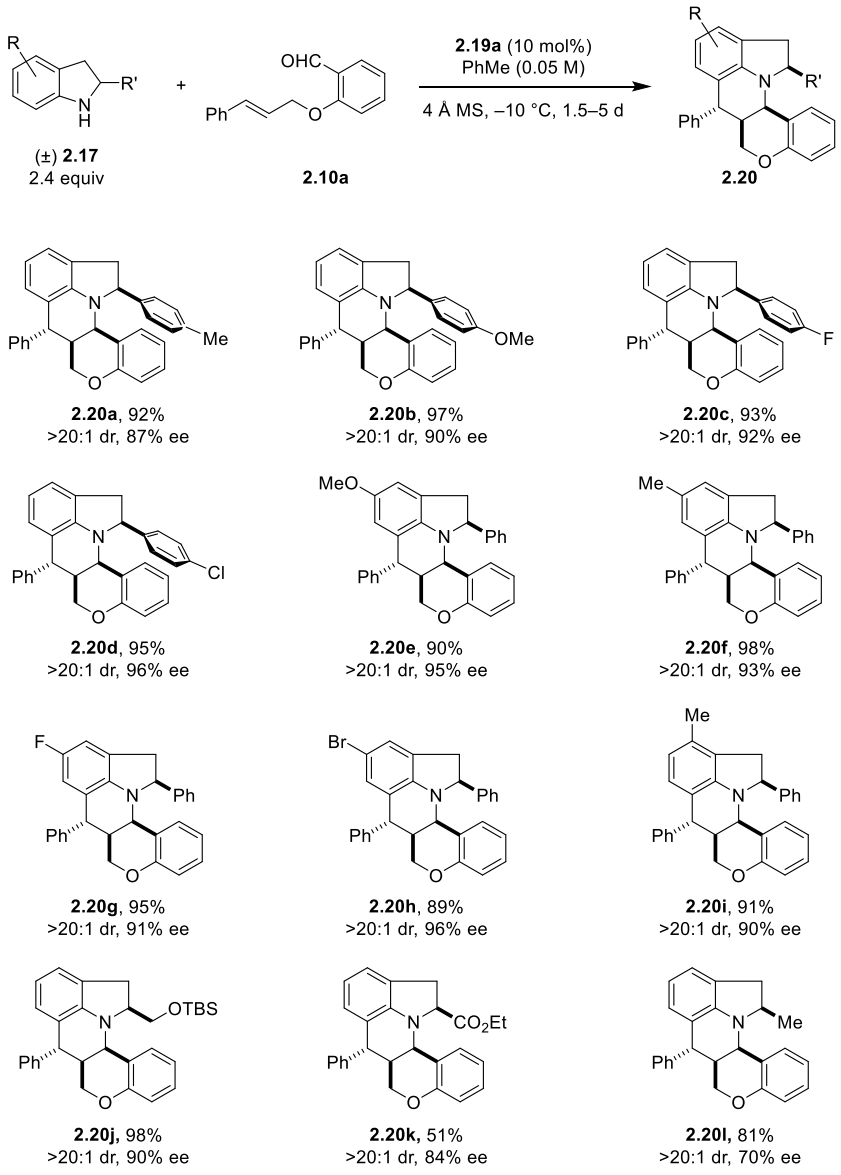
2.4.2 Substrate Scope



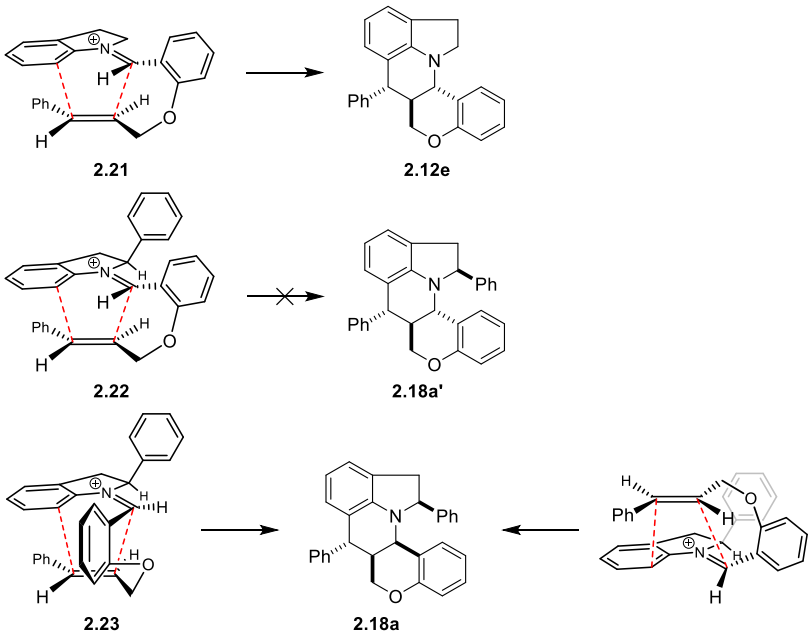
Scheme 2.16. Aldehyde scope. Reactions were performed with 0.2 mmol of **2.10** and 2.4 equiv of **2.17a**. Yields correspond to chromatographically purified products. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The ee values were determined by HPLC analysis; see the experimental section for details.

The scope of this transformation was evaluated with a range of *O*-allylsalicylaldehyde derivatives (Scheme 2.16). A range of substituents on the aldehyde phenyl ring and the styrene component were

readily tolerated in reactions with **4.7a**, producing polycyclic heterocycles in excellent yields and diastereo- and enantioselectivities. Variation of the indoline cycloaddition partner was evaluated next (Scheme 2.17). A number of 2-arylindolines with diverse substituents in different ring positions performed well. In addition, a TBS protected alcohol and an ethyl ester substituent were accommodated. A reduction in selectivity was observed in case of 2-methyl indoline.



Scheme 2.17. Indoline scope. Reactions were performed with 0.2 mmol of **2.10a** and 2.4 equiv of **2.17**. Yields correspond to chromatographically purified products. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The ee values were determined by HPLC analysis; see the experimental section for details.



Scheme 2.18. Stereochemical considerations.

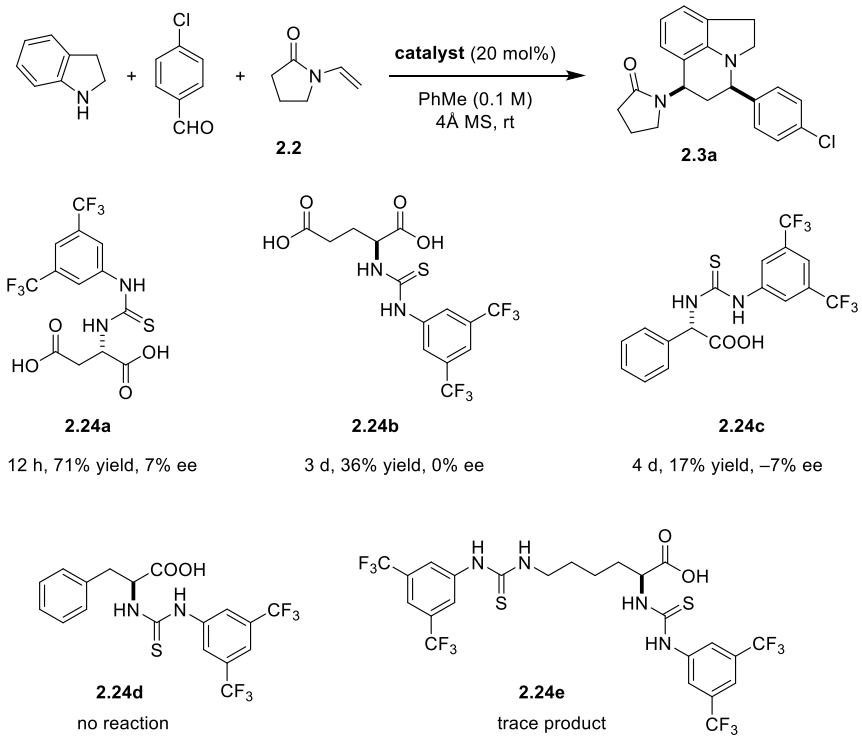
The stereochemical outcome of the reaction is worth commenting on. The major product diastereomer obtained with 2-phenylindoline (**2.17a**) is different from that previously observed with unsubstituted indoline (Scheme 2.18). The formation of **2.12e** is consistent with proposed transition structure **2.21**. However, product **2.18a′** which would be expected to form based on the corresponding transition structure **2.22** was not observed. This is likely the result of unfavorable steric interactions in **2.22**. As a consequence, a different iminium ion geometry may be preferred for 2-substituted indolines. Indeed, the formation of **2.18a** is consistent with proposed transition structure **2.23**. Alternatively, **2.18a** may be formed via exo-transition state

In summary, we have introduced a new approach for the rapid synthesis of polycyclic amines via aza-Diels Alder (Povarov) reactions, utilizing the kinetic resolution of 2-substituted indolines to enhance the stereochemical complexity of the products. The concept of exploiting the differential formation/reactivity of diastereomeric iminium ion pairs will likely be applicable to a range of other transformations.

2.5 Exploration of Other Systems

2.5.1 Amino Acid-derived Thiourea-acid

Amino acid derived thiourea-acids[105,106] have been manipulated as acid additives in enamine catalysis, however, they have never been utilized as chiral Brønsted acid catalysts, probably due to the flexibility and weak acidity of the aliphatic carboxylic acid, or because the thiourea and the acidic site are in the unfavorable position to bind to each other. Given the easy access to these catalysts (one step from readily available amino acids), we were curious to see if they could catalyze our Povarov reaction. As illustrated in Scheme 2.19, the catalysts generally gave low enantioselectivities.

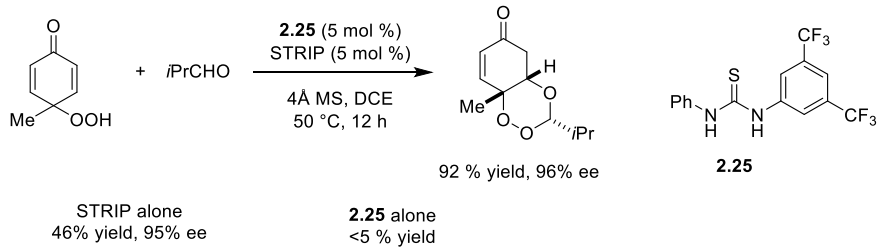


Scheme 2.19. Chiral phosphoric acid catalyzed three-component Povarov reaction.

2.5.2 Dual Catalysis of Chiral Phosphoric Acid and Achiral Anion-binding Catalyst

Rovis and coworkers[107] have shown the first example of the combination of chiral phosphoric acid and achiral thiourea catalyst in the enantioselective synthesis of 1,2,4-trioxanes via desymmetrization of *p*-peroxyquinols (Scheme 2.20). Notably, lowering the catalyst loading from 10 mol% to 5 mol%

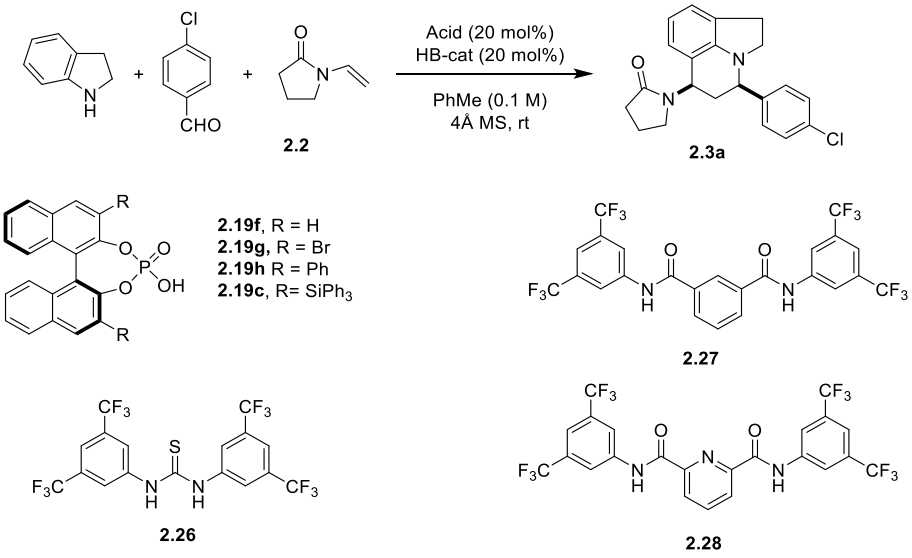
resulted in decreased yield, but the addition of an achiral thiourea as a cocatalyst could restore the reactivity. The thiourea catalyst alone did not catalyze the reaction.



Scheme 2.20. Enantioselective synthesis of 1,2,4-trioxanes via desymmetrization of p-peroxyquinols

We decided to investigate if choosing an appropriate C_2-symmetric achiral hydrogen bond donor in the presence of a simple chiral phosphoric acid would bring about a highly enantioselective reaction. Through in

Table 2.7. Combination of chiral phosphoric acid and achiral anion binding catalyst in Povarov reactions



entry	Cat.	time	yield (%)	ee (%)
1	**2.19f + 2.26**	7h	75	0
2	**2.19f + 2.27**	6h	81	-3
3	**2.19f + 2.28**	7h	78	7
4	**2.19g + 2.26**	12h	94	0
5	**2.19g**	3d	58	-20
6	**2.19h + 2.26**	28h	82	-7

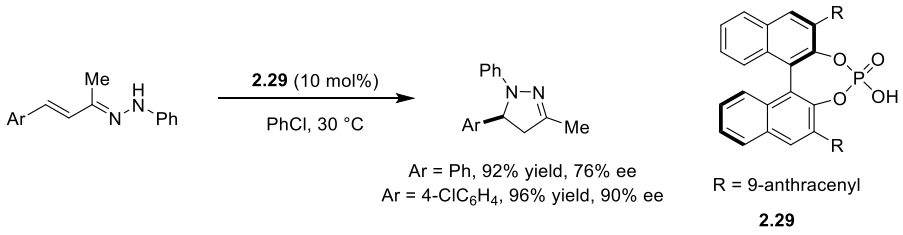
7	**2.19h**	3d	21	-11
8	**2.19c + 2.26**	3d	69	-15
9	**2.19c**	3d	trace	-
11	**1.6**	3d	0	-
12	**2.1d + 2.26**	10h	81	51

situ formation of a supramolecular catalytic species, the tedious synthesis of a bulky catalyst backbone can be avoided. As shown in Table 2.4, we tested a series of simple chiral phosphoric acids and achiral hydrogen bond catalysts. The addition of hydrogen bond donors did improve the reactivity, probably by stabilizing the phosphonate, but the enantioselectivities were not promising. Interestingly, the addition of the achiral thiourea to our thiourea-acid catalyst **2.1d** significantly enhanced its activity and shortened the reaction time (Table 2.7, entry 12), indicating a strong anion-stabilizing effect.

2.6 Application in Other Enantioselective Reactions

2.6.1 Asymmetric 6π Electrocyclization

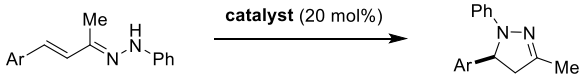
In 2009, List[108] group reported a chiral phosphoric acid catalyzed cycloisomerization of α,β-unsaturated hydrazones to pyrazolines (Scheme 2.21). This is the first example of a catalytic asymmetric 6π electrocyclization. In order to compare our new catalysts with the phosphoric acid, we chose this reaction as an example.



Scheme 2.21. Asymmetric 6π electrocyclization catalyzed by chiral phosphoric acid.

As shown in the Table 2.8, similar to our Pavarov reaction, toluene is the most suitable solvent and **2.1d** showed slightly better reactivity and enantioselectivity than its chlorine analogue **2.1c**. For the model substrate, our catalyst gave comparable ee to List's report. However the 4-Cl derivative gave inferior results (entry 6), so further optimization is still needed.

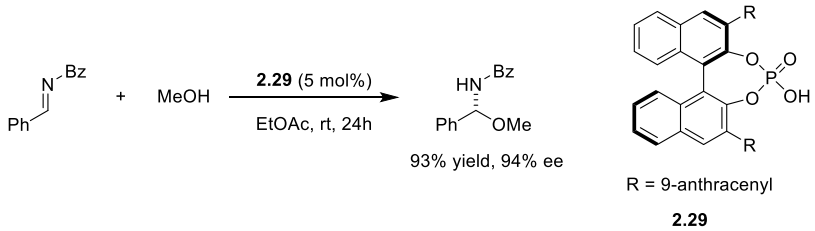
Table 2.8. Reaction condition optimization of asymmetric 6π electrocyclization.



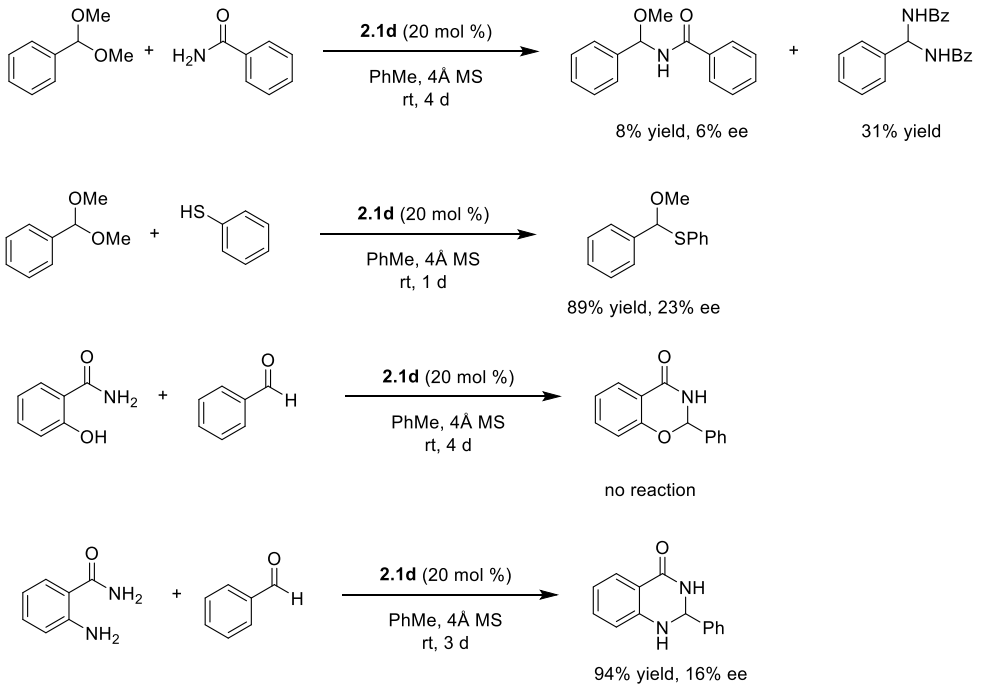
entry	Ar	cat.	temp.	solvent	time	yield (%)	ee (%)
1	Ph	**2.1c**	rt	PhMe	4d	61	73
2	Ph	**2.1c**	37 °C	PhMe	2d	81	68
3	Ph	**2.1c**	rt	PhCl	4d	57	67
4	Ph	**2.1d**	rt	PhMe	4d	68	75
5	Ph	**2.1g**	rt	PhMe	2d	No reaction	-
6	4-Cl-C_6H_4	**2.1d**	rt	PhMe	4d	70	78

2.6.2 Asymmetric Synthesis of Aminal/*N*,*O*-acetal

Antilla *et al.* reported the asymmetric synthesis of *N*,*O*-acetals via addition of alcohols to imines catalyzed by a chiral phosphoric acid[109] (Scheme 2.22). To test if our catalyst is capable of interacting with the oxacarbenium intermediate, we started from the readily available acetal as the model substrate, which was easier to handle than the moisture sensitive imines. Probably due to the instability of the *N*,*O*-acetal product, double addition of the benzamide occurred and gave the achiral aminal as the major product. In contrast, the corresponding *N*,*S*-aminal formation was highly efficient but the ee was still low (Scheme 2.23).



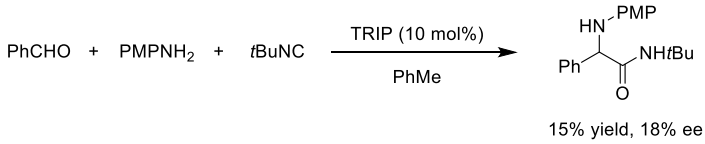
Scheme 2.22. Asymmetric addition of alcohols to imines.



Scheme 2.23. Enantioselective synthesis of *N*,*O*-acetals or aminals.

2.6.3 Asymmetric Ugi Reaction

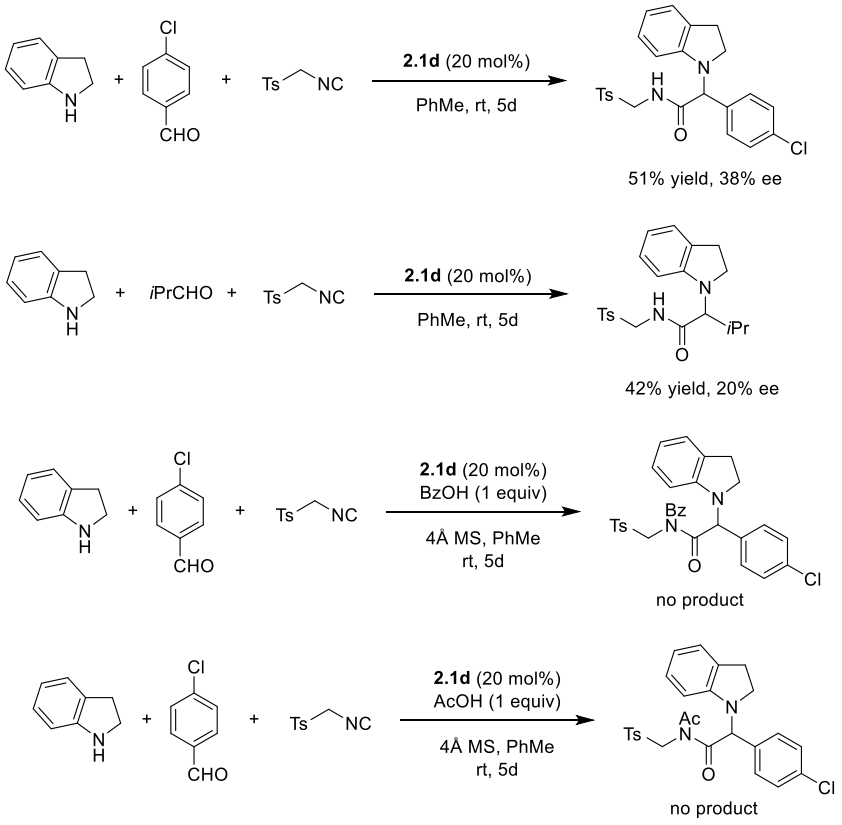
In 2009, List group reported a three-component Ugi reaction to gain access to the α-amino amide from an aldehyde, a primary amine and an isocyanide catalyzed by phenyl phosphinic acid. However, when they were trying to develop the enantioselective version with chiral phosphoric acid, only poor yields and ee's were obtained (Scheme 2.24).



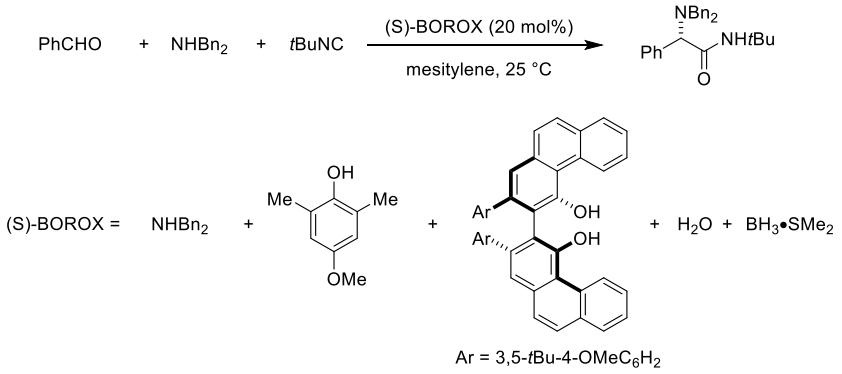
Scheme 2.24 Three-component Ugi reaction.

Given the success of our catalyst **2.1d** in the enantioselevtive addition to iminium ions, we attempted to apply it in the enantioselective Ugi reactions of secondary amines. In general, the three-component reactions gave moderate yields and ee's, the reaction rates slowed during the course of the reaction probably due to the incorporation of the catalyst into the product. The endeavor in using

the four-component Ugi reaction to synthesize dipeptides was unfruitful and no product was obtained. Meanwhile, the Wulff group published a successful three-component asymmetric catalytic Ugi reaction of secondary amines catalyzed by the chiral BOROX catalyst[110] (Scheme 2.25).



Scheme 2.24 Attempts at enantioselective Ugi reactions.



Scheme 2.25. BOROX catalyzed enantioselective three-component Ugi reactions.

Experimental Section

General Information: Toluene was freshly distilled from sodium under nitrogen prior to use. Reactions were run under a nitrogen atmosphere. Purification of reaction products was carried out by flash chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS–500 or 400 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm and $(CD_3)_2SO$ at 2.50 ppm. Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, comp = complex; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS–500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm and $(CD_3)_2SO$ at 39.5 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C.

General Procedure A

Catalysts **2.1a**–**2.1f** were prepared according to the following general procedure:

To a solution of amino(thio)urea (2.59 mmol) in THF (0.1 M, 25.9 mL) in a 50 mL round bottom flask were added the anhydride (2.72 mmol) and triethylamine (2.85 mmol). The resulting mixture was stirred for 8 h. After full conversion of the amino(thio)urea as judged by TLC analysis, the reaction mixture was concentrated and then purified by flash silica gel chromatography using ethyl acetate as the eluent. The combined fractions were reduced to a volume of 40 mL and washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Finally, the solvent was removed under reduced pressure and the resulting white solid was dried under high vacuum.

General Procedure

To a solution of **2.30** (2.3 mmol) in ethyl acetate (8.5 mL, 0.27 M), was added palladium on charcoal (10% w/w, 200 mg). The resulting suspension was placed under a hydrogen atmosphere following three cycles of a vacuum/hydrogen purge. The mixture was then stirred for 8 h at which point the starting material could no longer be detected by TLC analysis. Subsequently, 3,5-bistrifluoromethylisothiocyanate (1.2 equiv, 0.5 mL) was added and the reaction mixture stirred for an additional six hours. The reaction mixture was then concentrated under reduced pressure and the crude product purified by flash silica gel chromatography using EtOAc/Hexanes (1:1 v/v) as the eluent to give **2.31a** in 70 % yield.

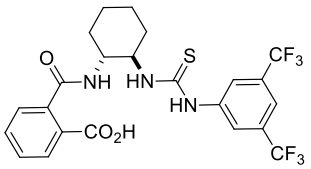
Compounds **2.31b** and **2.31c** were also prepared by following the above procedure.

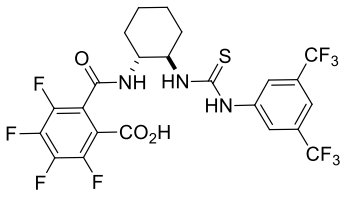
General Procedure C

To a solution of **2.31a** (1.47 mmol) in CH_2Cl_2 (2.1 mL, 0.7 M), TFA (2.1 mL) was added at 0 ºC. The resulting reaction mixture was then allowed to warm to room temperature. After stirring for 24 hours the reaction was quenched by adding saturated aqueous $NaHCO_3$ (10 mL). Dichloromethane was

removed under reduced pressure and the remaining aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a gradient of EtOAc/Hexanes (1:4) to EtOAc/Hexanes (3:2) to give **2. 32a** in 60% yield.

Compounds **2.32b** and **2.32c** were also prepared by following the above procedure.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)benzoic acid (2.1a):  Following the general procedure **A**, monothiourea compound was combined with phthalic anhydride to provide **2.1a** as a white solid in 92% yield (1.3 g); mp = 169–171 ºC; R_f = 0.46 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +42.0 (c 1.0, EtOH); IR (KBr) 3323, 2927, 1691, 1572, 1535, 1318, 1207, 1121, 698 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.90 (s, 1H), 10.18 (s, 1H), 8.34 (br s, 1H), 8.29 (s, 2H), 8.08 (br s, 1H), 7.88–7.77 (m, 1H), 7.75 (s, 1H), 7.62–7.37 (comp, 3H), 4.40–4.18 (m, 1H), 4.02–3.86 (m, 1H), 2.29–2.14 (m, 1H), 2.08–1.91 (m, 1H), 1.86–1.66 (comp, 2H), 1.56–1.23 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 181.1, 169.5, 168.8, 142.9, 139.5, 131.8, 131.6, 130.9 (q, J_{C-F} = 33.0 Hz), 130.2, 130.0, 128.6, 124.2 (q, J_{C-F} = 272.1 Hz), 123.0, 117.0, 58.3, 52.9, 32.3, 32.2, 25.3, 25.2; *m/z* (ESI-MS) 534.0 $[M + H]^+$.

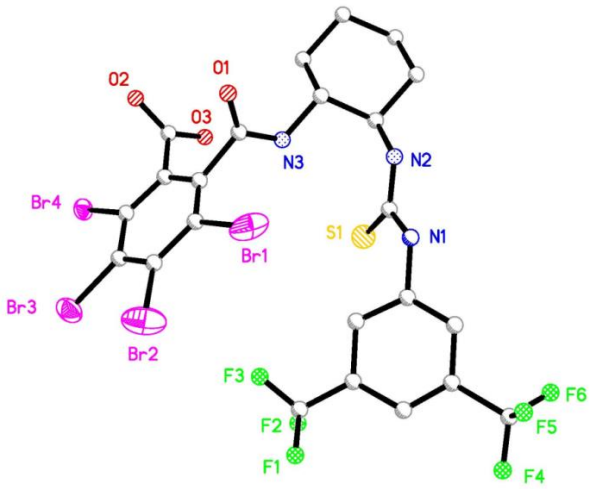
2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetraflurobenzoic acid (2.1b):  Following the general procedure **A**, monothiourea compound was combined with tetrafluorophthalic anhydride to provide **2.1b** as a white solid in 90% yield (1.5 g); mp = 134–136 ºC; R_f = 0.17 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +43.0 (c 1.0, EtOH); IR (KBr) 3331, 2944, 1728, 1633, 1541, 1475, 1384, 1278, 1181, 1108, 1066, 682 cm^{-1};

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.00 (br s, 1H), 10.02 (s, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.21 (s, 2H), 8.04 (br s, 1H), 7.70 (s, 1H), 4.47–4.14 (m, 1H), 3.97–3.82 (m, 1H), 2.29–2.03 (m, 1H), 2.01–1.85 (m, 1H), 1.79–1.58 (comp, 2H), 1.53–1.06 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.4, 162.5, 160.1, 146.1–143.8 (m), 144.6–142.4 (m), 142.0, 141.7–139.5 (m), 141.4–139.0 (m), 130.1 (q, $J_{C\text{-}F}$ = 32.7 Hz), 125.7 (q, $J_{C\text{-}F}$ = 272.6 Hz), 122.6–122.3 (m), 122.2–121.9 (m), 117.7–117.4 (m), 116.3–115.9 (m), 56.6, 52.3, 31.4, 31.0, 24.1; *m/z* (ESI-MS) 605.9 $[M + H]^+$.

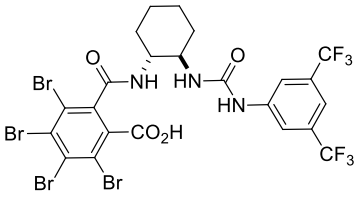
2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrachlorobenzoic acid (2.1c): Following the general procedure **A**, monothiourea compound was combined with tetrachlorophthalic anhydride to provide **2.1c** as a white solid in 90% yield (1.6 g); mp = 170–172 ºC; R_f = 0.18 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +24.5 (c 1.0, EtOH); IR (KBr) 3328, 2932, 1709, 1627, 1541, 1385, 1317, 1278, 1182, 1131, 682, 653 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.25 (br s, 1H), 10.19 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.27 (s, 2H), 7.99 (br s, 1H), 7.77 (s, 1H), 4.38–4.19 (m, 1H), 3.99–3.87 (m, 1H), 2.23–2.06 (m, 1H), 2.00–1.88 (m, 1H), 1.82–1.64 (comp, 2H), 1.48–1.20 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.9, 165.5, 163.6, 142.8, 136.6, 134.6, 133.8, 133.6, 131.0 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.2, 129.3, 124.2 (q, $J_{C\text{-}F}$ = 272.3 Hz), 123.0, 117.1, 57.8, 52.8, 32.2, 32.0, 24.9; *m/z* (ESI-MS) 669.7 (^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl) $[M + H]^+$; 671.6 (^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl) [M + H], 673.7 (^{35}Cl/^{35}Cl/^{37}Cl/^{37}Cl) $[M + H]^+$.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1d): Following the general procedure **A**, monothiourea compound was combined with tetrabromophthalic anhydride to provide **2.1d** as a white solid in 94% yield (2.2 g); mp = 174–176 ºC; R_f = 0.21 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +10.7 (c 1.0, EtOH); IR (KBr) 3325, 2927, 1735, 1654, 1629, 1551, 1528, 1383, 1277, 1182, 1128, 678, 632 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.1 (br s, 1H), 10.2 (s, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.27 (s, 2H), 7.99 (br s, 1H), 7.77 (s, 1H), 4.37–4.15 (m, 1H), 3.97–3.82 (m, 1H), 2.27–2.07 (m, 1H), 2.00–1.89 (m, 1H), 1.83–1.65 (comp, 2H), 1.51–1.22 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.9, 166.6, 165.0, 142.8, 139.0, 137.8, 130.9 (q, J_{C-F} = 31.5 Hz), 130.7, 130.5, 124.1 (q, J_{C-F} = 272.5 Hz), 123.4, 123.1, 122.4, 117.1, 57.7, 52.6, 32.0, 24.9; *m/z* (ESI-MS) 849.5 ($^{79}Br/^{79}Br/^{79}Br/^{79}Br$) $[M + H]^+$, 851.3 ($^{79}Br/^{79}Br/^{79}Br/^{81}Br$) $[M + H]^+$.

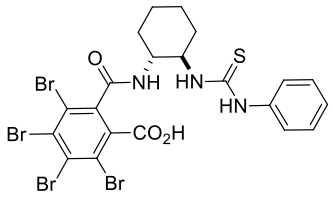
Tetrabutylammonium salt of 2.1d: Catalyst **2.1d** (20 mg, 0.024 mmol) was dissolved in 3 mL of dichloromethane. Tetrabutylammonium acetate (1 equiv, 7.1 mg) was added and the resulting solution was stirred for 12 h. Crystals suitable for X-ray crystallography were obtained through slow diffusion of hexanes into the dichloromethane solution at room temperature. The tetrabutylammonium salt of **2.1d** was characterized by X-ray crystallography (tetrabutylammonium cation not shown):



The requisite CIF has been deposited with the CCDC (deposition # 961074).

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1e): 

Following the general procedure **A**, monourea compound was combined with phthalic anhydride to provide **2.1e** as a white solid in 88% yield (1.9 g); mp > 200 ºC; R_f = 0.18 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –1.0 (c 1.0, EtOH); IR (KBr) 3247, 2940, 2861, 1743, 1647, 1560, 1386, 1278, 1176, 1128, 684, 637 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 13.98 (br s, 1H), 9.22 (s, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.04 (s, 2H), 7.51 (s, 1H), 6.29 (d, *J* = 7.9 Hz, 1H), 3.80–3.65 (m, 1H), 3.60–3.45 (m, 1H), 1.98–1.86 (m, 2H), 1.76–1.57 (comp, 2H), 1.46–1.18 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.7, 164.0, 154.4, 142.6, 138.3, 136.7, 130.6 (q, J_{C-F} = 32.5 Hz), 129.8, 129.5, 123.3 (q, J_{C-F} = 273.0 Hz), 122.4, 121.5, 117.2, 113.4, 52.1, 32.4, 31.1, 24.1, 23.9; *m/z* (ESI-MS) 833.4 ($^{79}Br/^{79}Br/^{79}Br/^{79}Br$) $[M + H]^+$, 855.3 ($^{79}Br/^{79}Br/^{79}Br/^{79}Br$) $[M + Na]^+$.

2,3,4,5-Tetrabromo-6-(((1*R*,2*R*)-2-(3-phenylthioureido)cyclohexyl)carbamoyl)benzoic acid (2.1f): 

Following the general procedure **A**, monothiourea compound was combined with tetrabromophthalic anhydride to provide **2.1f** as a white solid in 85% yield (1.7 g); mp > 200 ºC; R_f = 0.15 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +3.83 (c 1.0, EtOH); IR (KBr) 3266, 2934, 1717, 1648, 1540, 1449, 1262, 695 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.06 (br s, 1H), 9.60 (br s, 1H), 8.67 (br s, 1H), 7.82–6.90 (comp, 5H), 4.45–4.07 (m, 1H), 3.96–3.65 (m, 1H), 2.39–2.04 (m, 2H), 1.81–1.52 (comp, 2H), 1.51–0.96 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.6, 165.7, 164.0, 139.2, 138.2, 136.9, 129.8, 129.5, 128.5, 124.0, 122.9, 122.5, 121.4, 56.9, 51.7,

31.4, 31.2, 24.1; *m/z* (ESI-MS) 713.5 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) [M + H]$^+$, 715.4 (^{79}Br/^{79}Br/^{79}Br/^{81}Br) [M + H]$^+$, 717.7 (^{79}Br/^{79}Br/^{81}Br/^{81}Br) [M + H]$^+$.

2-(((1*R*,2*R*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1k): Tetrabromophthalic anhydride (0.95 mmol) was added to a solution of aminothiourea (0.9 mmol) in THF (9.0 mL, 0.1 M) (Scheme **S2**). The resulting mixture was stirred for 24 h. After full conversion, the reaction mixture was concentrated and purified by flash silica gel chromatography with ethyl acetate as the eluent. The combined fractions were reduced to a volume of 40 mL and washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure and drying under high vacuum, **2.1k** was obtained as an off-white solid in 40% yield (0.55 g); mp > 200 ºC; R_f = 0.31 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ – 3.0 (c 0.5, EtOH); IR (KBr) 3424, 1648, 1507, 1381, 1278, 1179, 1135, 700, 681 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.3 (br s, 1H), 10.16–9.95 (comp, 2H), 9.31 (br s, 1H), 8.24–8.11 (comp, 2H), 8.09–7.98 (comp, 2H), 7.92 (br s, 2H), 7.84 (d, *J* = 8.8, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 8.7, 1H), 7.59–7.39 (comp, 3H), 7.37–7.25 (m, 1H), 7.24–7.11 (m, 1H), 6.95 (d, *J* = 8.6, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.9, 165.9, 163.7, 144.4, 141.6, 141.4, 137.6, 136.7, 136.1, 135.5, 135.2, 133.9, 133.4, 133.3, 132.7, 132.6, 132.4, 132.3(7), 132.0, 130.7, 130.0(4), 130.0, 129.7(3) (q, $J_{C\text{-}F}$ = 33.0 Hz), 129.7 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.1–128.6 (m), 128.5–127.4 (m), 127.1–125.5 (m), 125.5–125.1 (m), 124.4–123.3 (m), 123.3 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.1–122.7 (m), 121.8, 121.6, 121.4, 117.2–116.8 (m), 109.8; *m/z* (ESI-MS) 1019.4 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) [M + H]$^+$, 1023.2 (^{79}Br/^{79}Br/^{81}Br/^{81}Br) [M + H]$^+$.

***tert*-Butyl((1*R*,2*S*)-2-(2-nitro-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.30):** Following the reported procedure[8] (4 mmol scale), compound **2.30** was obtained as yellow solid in 75% yield (1.3 g); mp = 126–128 ºC; R_f = 0.35 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +17.0 (c 1.0, EtOH); IR (KBr) 1693, 1545, 1517, 1335, 1289, 1161, 1128, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 6.9 Hz, 1H), 7.34–7.27 (comp, 3H), 7.22 (d, *J* = 6.9 Hz, 1H), 5.60–5.47 (comp, 2H), 5.39–5.31 (m, 1H), 3.35 (dd, *J* = 17.0, 4.7 Hz, 1H), 3.21 (app d, *J* = 17.0 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 153.8, 140.5, 139.6, 138.2, 131.2 (q, J_{C-F} = 3.4 Hz), 128.6, 127.8, 125.1, 124.3, 123.9 (q, J_{C-F} = 3.7 Hz), 123.3 (q, J_{C-F} = 34.5 Hz), 123.0 (q, J_{C-F} = 272.3 Hz), 115.8, 81.6, 80.1, 58.3, 36.9, 28.4; *m/z* (ESI-MS) 460.9 $[M + Na]^+$.

4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.31a): Following the general procedure **B**, compound **2.31a** was obtained as a white solid in 70% yield (1.1 g); mp = 186–188 ºC; R_f = 0.25 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +56.4 (c 1.0, EtOH); IR (KBr) 2983, 1686, 1618, 1544, 1383, 1334, 1278, 1130, 1052, 700, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.38–9.22 (comp, 2H), 8.18 (s, 2H), 7.65 (s, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.35–7.28 (comp, 2H), 7.27 (s, 1H), 7.20 (d, *J* = 7.1 Hz, 1H), 5.40–5.27 (m, 1H), 5.08 (d, *J* = 7.6 Hz, 1H), 4.85–4.69 (m, 1H), 3.47–3.26 (comp, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 157.1, 151.4, 140.4, 139.3, 138.3, 132.0 (q, J_{C-F} = 33.4 Hz), 131.6.–131.3 (m), 129.9.–129.6 (m), 128.1, 125.6, 125.4.–125.2 (m), 124.0 (q, J_{C-F} = 272.2 Hz), 123.4 (q, J_{C-F} = 272.2 Hz), 123.3 (app d, *J* = 3.2 Hz), 123.3, 122.2.–121.9 (m), 120.0, 119.9–119.6 (m), 118.7–118.2 (m), 83.4, 81.4, 58.0, 37.0, 28.5; *m/z* (ESI-MS) 701.9 $[M + Na]^+$.

***tert*-Butyl ((1*R*,2*S*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.31b):** Following the general procedure **B** (3,5-bistriflouromethylisocyanate (1.2 equiv, 0.5 mL) was used), compound **2.31b** was obtained as a white solid in 85% yield (1.3 g); mp = 108–110ºC; R_f = 0.40 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +76.7 (c 0.5, EtOH); IR (KBr) 2985, 1671, 1615, 1551, 1475, 1387, 1279, 1245, 1131, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.92 (s, 1H), 8.46 (s, 1H), 8.31 (s, 1H), 8.04 (s, 2H), 7.66 (s, 1H), 7.55–7.22 (comp, 6H), 7.21–7.08 (m, 1H), 5.43–5.21 (comp, 2H), 3.51–3.43 (m, 1H), 3.27–3.15 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 155.9, 152.1, 149.1, , 141.3, 140.8, 139.7, 130.9 (q, J_{C-F} = 32.7 Hz), 128.9, 128.3, 127.2, 125.1, 124.5 (q, J_{C-F} = 271.7 Hz), 123.2 (q, J_{C-F} = 272.9 Hz), 124.1, 121.4 (q, J_{C-F} = 32.6 Hz), 119.7 (app d, J = 4.1 Hz), 117.9–117..6 (m), 115.2–114.9, 114.8(8)–114.6, 112.9, 79.9, 78.2, 57.8, 37.2, 27.7; *m/z* (ESI-MS) 685.7 $[M + Na]^+$.

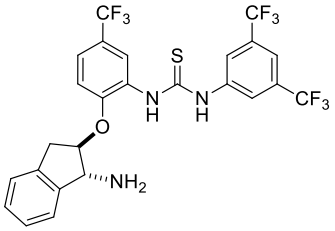
***tert*-Butyl((1*R*,2*R*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.31c):** Starting from *N*-Boc-(*R,R*)-*trans*-aminoindanol[8] and following the general procedure **B**, compound **2.31c** was obtained as an off white solid in 87% yield (1.4 g); mp = 85–87ºC; R_f = 0.25 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ -80.9 (c 0.5, EtOH); IR (KBr) 2983, 1618, 1474, 1444, 1383, 1334, 1278, 1130, 1052, 733, 681 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.47 (s, 1H), 9.68 (s, 1H), 8.26 (s, 2H), 8.20 (s, 1H), 7.76 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.24–7.15 (comp, 4H), 5.25–5.13 (comp, 2H), 3.54 (dd, J = 16.3 Hz, 7.1 Hz, 1H), 2.95 (dd, J = 16.2 Hz, 5.2 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.7, 155.6, 153.6, 141.4, 141.1, 138.9, 130.1 (q, J_{C-F} = 33.0 Hz), 128.4, 128.1, 127.1, 124.6, 124.0, 124.2

(q, $J_{C\text{-}F}$ = 271.2 Hz), 123.5, 123.3, 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.0, 120.9 (q, $J_{C\text{-}F}$ = 32.4 Hz), 117.0, 114.5, 84.4, 78.2, 60.9, 36.3, 28.1; *m/z* (ESI-MS) 701.8 $[M + Na]^+$.

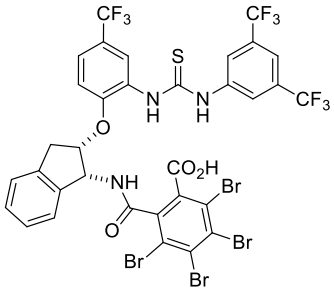
***tert*-Butyl ((1*R*,2*S*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.32a):** Following the general procedure **C**, compound **2.32a** was obtained as a white solid in 60% yield (0.512 g); mp = 86–88 ºC; R_f = 0.14 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +84.0 (c 0.5, EtOH); IR (KBr) 3284, 3049, 2965, 1617, 1545, 1473, 1443, 1382, 1334, 1174, 701, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s 1H), 7.76 (s, 2H), 7.53 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.28–7.08 (comp, 4H), 7.02 (d, *J* = 8.6 Hz, 1H), 4.97–4.82 (m, 1H), 4.44 (d, *J* = 5.4 Hz, 1H), 3.17 (dd, *J* = 16.6, 5.5 Hz, 1H), 3.08 (dd, *J* = 16.7, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 151.9, 142.9, 139.9, 138.4, 131.8 (q, $J_{C\text{-}F}$ = 33.3 Hz), 129.0, 128.6, 127.7, 125.3, 124.9, 124.3 (q, $J_{C\text{-}F}$ = 33.3 Hz), 123.8 (q, $J_{C\text{-}F}$ = 271.6 Hz), 123.7–123.1 (m), 122.9 (q, $J_{C\text{-}F}$ = 272.6 Hz), 122.3–122.1 (m), 118.8–118.1 (m), 115.6–115.2 (m), 113.2, 82.4, 58.0, 36.5; *m/z* (ESI-MS) 850.1 $[M + H]^+$.

1-(2-(((1*R*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl)oxy)-5-(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (2.32b): Following the general procedure **C**, compound **2.32b** was obtained as a light brown solid in 72% yield (0.596 g); mp = 170–172 ºC; R_f = 0.15 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +39.3 (c 1.0, EtOH); IR (KBr) 3319, 3104, 1667, 1560, 1477, 1447, 1388, 1339, 1281, 1131, 702, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.93 (s, 1H), 8.46 (s, 1H), 8.11 (s, 2H), 7.68 (s 1H), 7.64–7.57 (m, 1H), 7.542–7.40 (comp, 3H), 7.39–7.30 (comp, 3H), 5.48–5.39 (m, 1H), 5.03 (d, *J* = 5.6 Hz, 1H), 3.20 (dd, *J* = 16.9, 5.8 Hz, 1H), 3.31 (s, 2H), 3.20 (dd, *J* = 16.8, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 152.4, 148.5, 141.6, 139.9, 137.8, 130.8 (q, $J_{C\text{-}F}$ = 33.1 Hz), 129.2 (app d, *J* = 9.9 Hz), 127.3, 125.2, 124.9, 124.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.1 (q, $J_{C\text{-}F}$ = 272.2 Hz), 121.8 (q, $J_{C\text{-}F}$ = 32.2 Hz), 119.9–119.6

(m), 118.3–117.8 (m), 116.6–116.2 (m), 115.6, 114.8–114.4 (m), 113.2, 78.2, 55.8, 36.1; *m/z* (ESI-MS) 563.9 $[M + H]^+$.

***tert*-Butyl((1*R*,2*R*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (2.32c):** 

Following the general procedure **C**, compound **2.32c** was obtained as an off white solid in 70% yield (0.597 g); mp = 54–56 ºC; R_f = 0.17 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –65.4 (c 0.5, EtOH); IR (KBr) 3265, 3057, 2916, 1616, 1593, 1548, 1443, 1382, 1334, 1278, 1173, 1129, 701, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.25 (s, 1H), 8.19 (s, 2H), 7.70 (s, 1H), 7.57–7.46 (comp, 2H), 7.45–7.35 (comp, 2H), 7.31–7.15 (comp, 4H), 4.97–4.88 (m, 1H), 4.49 (d, J = 4.4 Hz, 1H), 3.59 (dd, J = 16.5, 7.0 Hz 1H), 2.90 (dd, J = 16.4, 5.2 Hz, 1H), 1.25 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 178.3, 152.9, 143.6, 142.9, 138.9, 130.5 (q, J_{C-F} = 32.6 Hz), 129.9 (q, J_{C-F} = 32.7 Hz), 129.4, 127.9, 126.9, 124.6, 124.4 (q, J_{C-F} = 271.3 Hz), 124.3, 123.3 (q, J_{C-F} = 272.6 Hz), 123.2–123.9 (m), 123.6–123.3 (m), 122.1–121.7 (m), 120.6 (q, J_{C-F} = 32.4 Hz), 116.2–115.8 (m), 114.3, 86.9, 61.9, 36.3 ; *m/z* (ESI-MS) 579.7 $[M + H]^+$.

2-(((1*R*,2*S*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1h): 

Following the general procedure **A**, monothiourea compound **2.32a** was combined with tetrabromophthalic anhydride to provide **2.1h** as a white solid in 85% yield (0.759 g); mp = 156–159 ºC; R_f = 0.57 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +65.8 (c 0.5, EtOH); IR (KBr) 3357, 1655, 1618, 1546, 1439, 1382, 1332, 1277, 1177, 1130, 681 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.32 (br s, 1H), 10.53 (br s, 1H), 9.45 (br s, 1H), 9.10–8.83 (m,

1H), 8.56 (s, 1H), 8.18 (s, 2H), 7.77 (s, 1H), 7.66–6.97 (comp, 6H), 6.03–5.77 (m, 1H), 5.48–5.26 (m, 1H), 3.43 (app d, J = 15.1 Hz, 1H), 3.17 (app d, J = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.1, 166.4, 164.6, 151.8, 141.3, 140.4, 139.5, 137.5, 137.1, 130.2 (q, $J_{C\text{-}F}$ = 33.2 Hz), 129.8, 128.7, 128.2, 127.1, 126.4, 125.3, 124.9, 124.6, 124.2 (q, $J_{C\text{-}F}$ = 271.1 Hz), 123.4, 123.2 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.7, 122.2, 121.3, 120.8 (q, $J_{C\text{-}F}$ = 32.1 Hz), 117.2–116.7 (m), 114.5–114.0 (m), 79.7, 55.7, 36.9, *m/z* (ESI-MS) 1043.8 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$; 1044.5 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$.

2-(((1*R*,2*S*)-2-(2-(3-Argioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1i): Following the general procedure **A**, monothiourea compound **2.32b** was combined with tetrabromophthalic anhydride to provide compound **2.1i** as a white solid in 90% yield (0.791 g); mp = 105–107 ºC; R_f = 0.56 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +37.0 (c 0.5, EtOH); IR (KBr) 3338, 2938, 1712, 1652, 1549, 1444, 1386, 1338, 1179, 1133, 702, 682 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.41 (br s, 1H), 9.54 (br s, 1H), 9.03 (app d, J = 7.4 Hz, 1H), 8.45 (s, 1H), 8.23–7.98 (comp, 2H), 7.75 (s, 1H), 7.63 (s, 1H), 7.61–7.54 (comp, 2H), 7.49–6.71 (comp, 5H), 6.05–5.80 (m, 1H), 5.36–5.11 (m, 1H),), 3.56 (app d, J = 17.3 Hz, 1H), 3.27 (app d, J = 17.3 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 166.3, 164.4, 151.9, 148.5, 141.2, 140.2, 139.9, 137.3, 131.1 (q, $J_{C\text{-}F}$ = 31.5 Hz), 131.0 (q, $J_{C\text{-}F}$ = 32.6 Hz), 129.8, 129.4, 128.5, 125.1, 124.5, 124.6 (q, $J_{C\text{-}F}$ = 271.2 Hz), 123.3 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.6, 121.8, 121.5, 121.3, 121.0, 119.4, 116.7, 114.9, 114.6, 112.6, 80.4, 55.8, 37.3; *m/z* (ESI-MS) 1026.1 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$; 1028.2 (^{79}Br/^{79}Br/^{79}Br/^{81}Br) $[M]^+$.

2-(((1*R*,2*R*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (2.1j): Following the general procedure **A**, monothiourea compound **2.32c** was combined with tetrabromophthalic anhydride to provide compound **2.1j** as an off white solid in 90% yield (0.804 g); mp = >200 ºC R_f = 0.45 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –92.5 (c 0.5, EtOH,); IR (KBr) 3417, 1652, 1548, 1382, 1332, 1278, 1174, 1131, 739, 681, 640 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.63 (br s, 1H), 9.92 (br s, 1H), 9.26 (d, *J* = 7.7 Hz, 1H), 8.25 (s, 2H), 8.11 (s, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.48 ((d, *J* = 8.1 Hz, 1H), 7.34 (app d, *J* = 6.4 Hz, 1H), 7.30–7.12 (comp, 3H, 5.64–5.51 (m, 1H), 5.14–5.0 (m, 1H), 3.62 (dd, *J* = 16.3 Hz, , *J* = 5.4 Hz, 1H), 3.02 (app d, *J* = 16.10 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.7, 166.4, 164.4, 153.7, 141.4, 139.9, 139.6, 137.6, 130.0 (q, J_{C-F} = 32.9 Hz), 129.6, 128.4, 128.1, 127.1, 125.3, 125.0, 124.7, 123.2 (q, J_{C-F} = 272.6 Hz), 124.0–123.8 (m), 123.8–123.6 (m), 123.5–123.1 (m), 122.8, 121.3, 121.0, 120.7, 120.5, 117.3–116.8 (m), 114.2, 83.4, 59.6, 36.8; *m/z* (ESI-MS) 1043.3 ($^{79}Br/^{79}Br/^{79}Br/^{79}Br$) $[M + H]^+$; 1046.3 ($^{79}Br/^{79}Br/^{81}Br/^{81}Br$) $[M]^+$.

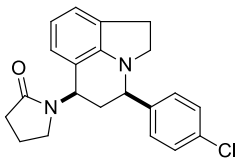
6,6'-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(azanediyl))bis(carbonyl))bis(2,3,4,5-tetrachlorobenzoic acid) (2.1g): Tetrachlorophthalic anhydride (1.05 mmol) and triethylamine (1.05 mmol) were added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (0.5 mmol) in THF (5.0 mL, 0.1 M) (Scheme **S4**) The resulting mixture was stirred for 12 h. The solvent was removed and the residue was re-dissolved in ethyl acetate (100 mL). This solution was washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure and drying under high vacuum, **2.1g** was obtained as a white solid in 67% yield (230 mg); mp = 198–200 ºC; R_f = 0.13 (MeOH/EtOAc 20:80 v/v); $[\alpha]_D^{20}$ –35.8 (c 0.2, EtOH,); IR (KBr) 3285, 2934, 1701,

1635, 1523, 1343, 1322, 1298, 1266, 649 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.2 (br s, 2H), 8.69–8.46 (comp, 2H), 3.98–3.77 (comp, 2H), 1.97–1.82 (comp, 2H), 1.73–1.54 (comp, 2H), 1.52–1.22 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.2, 163.1, 135.7, 135.4, 132.9, 132.8, 129.7, 128.6, 50.9, 28.5, 22.4, 22.3; *m/z* (ESI-MS) 686.5 ($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M + H]^+$, 688.6 ($^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl$) $[M + H]^+$.

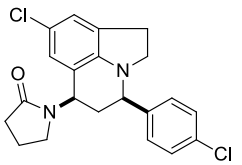
II Preparation and characterization data of products:

General procedure **D**: A flame dried vial was charged with aldehyde (0.4 mmol, 2 equiv), **2.1d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (4 mL) was added and the resulting mixture was cooled to –55 °C over 15 min. The aromatic amine was then added (0.2 mmol, 1 equiv). After five minutes, 1-vinylpyrrolidin-2-one (**2.2**) (43 μL, 0.4 mmol, 2 equiv) was added and the reaction mixture was stirred at –55 °C. When indoline could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography.

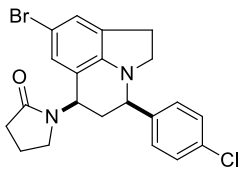
General procedure **E**: A flame dried vial was charged with aldehyde (0.4 mmol, 2 equiv), **2.1d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (3 mL) was added and the resulting mixture was cooled to –55 °C over 15 min. A solution of the aromatic amine (0.2 mmol, 1 equiv) in 1 mL of toluene was then added. After five minutes, 1-vinylpyrrolidin-2-one (**2.2**) (43 μL, 0.4 mmol, 2 equiv) was added and the reaction mixture was stirred at –55 °C. When the amine could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography.

1-((4*R*,6*R*)-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3a):  Following the general procedure **D**, compound **2.3a** was obtained as a white solid in 94% yield (66.2 mg); mp = 167–168 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +73.6 (c 0.4, $CHCl_3$, 92% *ee*); IR (KBr) 2952, 2912, 1686, 1478, 1455, 1270, 1013, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (comp, 4H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.81–6.66 (comp, 2H), 5.68 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.99 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.35–3.22 (comp, 3H), 3.02–2.90 (m, 1H), 2.88–2.80 (m, 1H), 2.78–2.68 (m, 1H), 2.57–2.38 (comp, 2H), 2.22–2.09 (comp, 2H), 2.07–1.96 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 150.8, 140.1, 133.2, 129.8, 128.8, 128.2, 124.2, 123.6, 119.4, 117.2, 62.3, 53.3, 47.6, 42.3, 36.6, 31.3, 28.7, 18.1; *m/z* (ESI–MS) 353.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.2 min (major) and t_R = 14.8 min (minor).

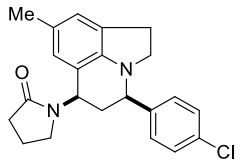
The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-8-chloro-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3b):  Following the general procedure **E**, compound **2.3b** was obtained as a light brown solid in 59% yield (45.6 mg); mp =178–179 °C; R_f= 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +37.9 (c 0.3, $CHCl_3$, 84% *ee*); IR (KBr) 2961, 2929, 2835, 1683, 1480, 1466, 1286, 1202, 859, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (comp, 4H), 6.98 (s, 1H), 6.72 (s, 1H), 5.63 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.97 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.37–3.22 (comp, 3H), 3.03–2.88 (m, 1H), 2.86–2.70 (comp, 2H), 2.58–2.38 (comp, 2H), 2.22–1.99 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 149.4, 139.6, 133.6, 131.8, 129.0, 128.3, 124.5, 124.1, 123.9, 118.6, 62.4, 53.5, 47.4, 42.3, 36.4, 31.2, 28.6, 18.1; *m/z* (ESI–MS) 387.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 13.0 min (major) and t_R = 25.2 min (minor).

The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-8-bromo-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3c):  Following the general procedure **E**, compound **2.3c** was obtained as a light brown solid in 76% yield (65.7 mg); mp = 184–185 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2950, 2831, 1686, 1488, 1457, 1271, 1209, 822, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (comp, 4H), 7.10 (s, 1H), 6.84 (s, 1H), 5.62 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.96 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.33–3.21 (comp, 3H), 3.00–2.88 (m, 1H), 2.87–2.78 (m, 1H), 2.78–2.68 (m, 1H), 2.58–2.36 (comp, 2H), 2.17–2.00 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 150.1, 139.6, 133.4, 132.1, 128.9, 128.2, 126.8, 126.7, 118.8, 111.2, 62.1, 53.3, 47.4, 42.3, 36.4, 31.2, 28.5, 18.1; *m/z* (ESI–MS) 433.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.4 min (major) and t_R = 16.4 min (minor).

The absolute configuration was assigned by analogy.

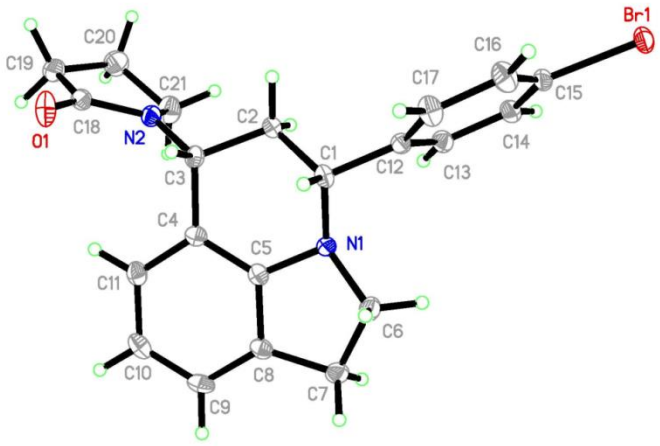
1-((4*R*,6*R*)-4-(4-chlorophenyl)-8-methyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3d):  Following the general procedure **E**, compound **2.3d** was obtained as a white solid in 82% yield (60 mg); mp = 110–111 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +24.5 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2947, 2915, 2886, 2820, 1686, 1487, 1426, 1268, 1014, 841, 525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.26 (comp, 4H), 6.86 (s, 1H), 6.57 (s, 1H), 5.65 (dd, *J* = 10.9, 6.9 Hz, 1H), 3.91 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.37–3.22 (comp, 3H), 3.02–2.87 (m, 1H), 2.86–2.75 (m, 1H), 2.73–2.60 (m, 1H), 2.58–2.39 (comp, 2H), 2.25 (s, 3H), 2.20–1.96 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 148.8, 140.3, 133.2, 130.2, 129.0, 128.8, 128.3, 124.6, 124.3, 117.0, 62.8, 53.8, 47.6, 42.3, 36.8, 31.4, 28.8, 21.0, 18.1; *m/z* (ESI–MS) 368.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-

H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 15.9 min (major) and t_R = 33.3 min (minor).

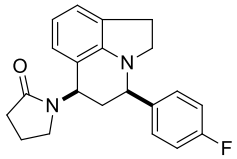
The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(4-bromophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3e): Following the general procedure **D**, compound **2.3e** was obtained as a white solid in 86% yield (68.1 mg); mp = 201–202 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +17.3 (c 0.4, $CHCl_3$, 95% *ee*); IR (KBr) 2950, 2841, 1683, 1481, 1457, 1269, 1023, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.79–6.69 (comp, 2H), 5.67 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.98 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.37–3.22 (comp, 3H), 3.05–2.91 (m, 1H), 2.89–2.79 (m, 1H), 2.78–2.67 (m, 1H), 2.58–2.37 (comp, 2H), 2.22–2.08 (comp, 2H), 2.07–1.95 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 150.8, 140.7, 131.9, 129.9, 128.7, 124.3, 123.7, 121.4, 119.6, 117.3, 62.4, 53.4, 47.6, 42.3, 36.6, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 399.8 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 12.7 min (major) and t_R = 28.8 min (minor).

The absolute configuration of **2.3e** was assigned by X-ray crystallography:

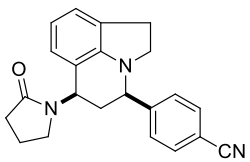


Compound **2.3e** was crystallized from hexanes/dichloromethane through slow diffusion at room temperature. The requisite CIF has been deposited with the CCDC (deposition # 960973).

1-((4*R*,6*R*)-4-(4-fluorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3f): 

Following the general procedure **D**, compound **2.3f** was obtained as a white solid in 76% yield; mp = 181–182 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ + 55.6 (c 0.4, $CHCl_3$, 93% *ee*); IR (KBr) 2959, 2840, 1682, 1482, 1269, 1152, 842, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.34 (comp, 2H), 7.13–7.00 (comp, 3H), 6.82–6.66 (comp, 2H), 5.69 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.99 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.37–3.22 (comp, 3H), 3.02–2.90 (m, 1H), 2.88–2.79 (m, 1H), 2.77–2.67 (m, 1H), 2.56–2.38 (comp, 2H), 2.26–2.09 (comp, 2H), 2.08–1.96 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 163.4, 161.5, 151.3, 137.7 (d, J_{C-F} = 3.2 Hz), 130.2, 128.7 (d, J_{C-F} = 8.1 Hz), 124.5, 123.9, 119.7, 117.5, 115.8 (d, J_{C-F} = 21.4 Hz), 62.5, 53.7, 48.0, 42.7, 37.1, 31.6, 29.1, 18.5; *m/z* (ESI–MS) 338.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.0 min (major) and t_R = 25.9 min (minor).

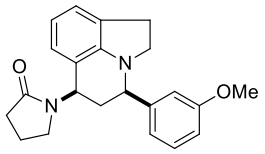
The absolute configuration was assigned by analogy.

4-((4*R*,6*R*)-6-(2-oxopyrrolidin-1-yl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-4-yl)benzonitrile (2.3g): 

Following the general procedure **D**, compound **2.3g** was obtained as a white solid in 92% yield; mp = 124–126 °C; R_f = 0.20 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +8.7 (c 0.4, $CHCl_3$, 91% *ee*); IR (KBr) 2953, 2839, 2227, 1678, 1458, 1286, 1146, 1058, 730, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.12–7.01 (m, 1H), 6.82–6.73 (comp, 2H), 5.69 (dd, *J* = 10.2, 7.6 Hz, 1H), 4.08 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.33–3.22 (comp, 3H), 3.06–2.95 (m, 1H), 2.92–2.82 (m, 1H), 2.79–2.67 (m, 1H), 2.55–2.41 (comp, 2H), 2.21–2.11 (comp, 2H), 2.07–1.97 (comp, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 150.3, 146.9, 132.7, 130.0, 127.9, 124.4, 123.9, 120.2, 118.6, 117.5, 111.7, 62.9, 53.6, 47.6, 42.4, 36.4, 31.4, 28.9, 18.2; *m/z* (ESI–MS) 344.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 12.9 min (major) and t_R = 31.0 min (minor).

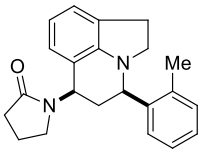
The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(3-methoxyphenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3h): 

Following the general procedure **D**, compound **2.3h** was obtained as a white solid in 93% yield (64.7 mg); mp = 165–167 °C; R_f= 0.21 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +32.3 (c 0.4, $CHCl_3$, 92% *ee*); IR (KBr) 2950, 2841, 1675, 1597, 1460, 1420, 1282, 1036, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (app t, *J* = 8.2 Hz, 1H), 7.13–6.96 (comp, 3H), 6.88–6.81 (m, 1H), 6.80–6.67 (comp, 2H), 5.68 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.99 (dd, *J* = 10.7, 2.5 Hz, 1H), 3.82 (s, 3H), 3.37 (app t, *J* = 8.4 Hz, 1H), 3.34–3.22 (comp, 2H), 3.03–2.92 (m, 1H), 2.89–2.81 (m, 1H), 2.80–2.71 (m, 1H), 2.60–2.39 (comp, 2H), 2.27–2.11 (comp, 2H), 2.10–1.95 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.8, 160.0, 143.2, 129.9, 129.6, 124.1, 123.5, 119.2, 119.1(7), 117.1, 113.0, 112.2, 62.8, 55.1, 53.3, 47.7, 42.3, 36.6, 31.3, 28.7, 18.1; *m/z* (ESI–MS) 349.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.6 min (major) and t_R = 15.6min (minor).

The absolute configuration was determined by analogy.

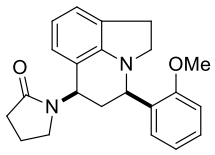
1-((4*R*,6*R*)-4-(o-tolyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3i): Following the general procedure **D**, compound **2.3i** was obtained as a white solid in 80% yield (53.1 mg); mp = 89–91 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +19.2 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 2947, 2926, 2846, 1686, 1457, 1285, 1191, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.34–7.12 (comp, 3H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.83–6.65 (comp, 2H), 5.70 (app t, J = 8.9 Hz, 1H), 4.36–4.22 (m, 1H), 3.46–3.33 (m, 1H), 3.27 (app t, *J* = 6.9 Hz, 2H), 3.06–2.92 (m, 1H), 2.90–2.79 (m, 1H), 2.76–2.64 (m, 1H), 2.57–2.41 (m, 2H), 2.36 (s, 3H), 2.18–2.07 (comp, 2H), 2.05–1.93 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.4, 139.3, 135.1, 130.6, 130.0, 127.1, 126.4, 124.3, 123.5, 123.4(8), 119.2, 117.3, 58.2, 53.5, 47.7, 42.4, 35.5, 31.4, 28.8, 19.2, 18.2; *m/z* (ESI–MS) 333.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.2 min (major) and t_R = 12.8 min (minor).

The absolute configuration was assigned by analogy.

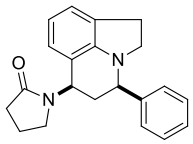
1-((4*R*,6*R*)-4-(2-methoxyphenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3j): Following the general procedure **D**, compound **2.3j** was obtained as a white solid in 59% yield (41.1 mg); mp = 83–84 °C; R_f = 0.21 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2952, 2837, 1683, 1457, 1243, 1026, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29–7.22 (m, 1H), 7.05–6.98 (comp, 2H), 6.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.79–6.66 (comp, 2H), 5.70 (dd, *J* = 11.5, 6.4 Hz, 1H), 4.57 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.82 (s, 3H), 3.44 (app t, *J* = 8.2 Hz, 1H), 3.27 (app t, *J* = 7.0 Hz, 2H), 3.05–2.93 (m, 1H), 2.89–2.80 (m, 1H), 2.78–2.67 (m, 1H), 2.58–2.37 (comp, 2H), 2.25–2.16 (m, 1H), 2.12–1.95 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 156.7, 151.4, 137.9, 130.1, 129.4, 128.2, 127.2, 124.3, 123.4, 120.7, 119.3, 110.5, 55.3, 55.1, 53.4, 47.7, 42.4, 35.0, 31.5, 28.8, 18.2; *m/z* (ESI–MS) 349.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-



H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.7 min (major) and t_R = 12.1 min (minor).

The absolute configuration was assigned by analogy.

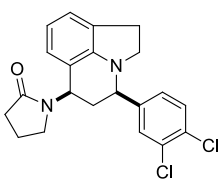
1-((4*R*,6*R*)-4-phenyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3k): Following the general procedure **D**, compound **2.3k** was obtained as a white solid in 71% yield (45.1 mg); mp = 171–172 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +6.4 (c 0.5, $CHCl_3$, 79% *ee*); IR (KBr) 2949, 2914, 1689, 1478, 1450, 1272, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.40 (comp, 2H), 7.37 (app t, *J* = 7.5 Hz, 2H), 7.34–7.27 (m, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.83–6.66 (comp, 2H), 5.69 (dd, *J* = 11.3, 6.5 Hz, 1H), 4.02 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.42–3.21 (comp, 3H), 3.04–2.92 (m, 1H), 2.90–2.81 (m, 1H), 2.79–2.71 (m, 1H), 2.56–2.39 (comp, 2H), 2.27–2.11 (comp, 2H), 2.08–1.94 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 141.6, 129.9, 128.7, 127.7, 126.9, 124.3, 123.6, 119.3, 117.3, 63.0, 53.4, 47.8, 42.4, 36.8, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 319.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.3 min (major) and t_R = 16.8 min (minor).

The absolute configuration was assigned by analogy.

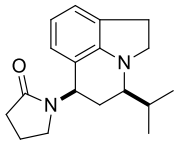
1-((4*R*,6*R*)-4-(3,4-dichlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (2.3l): Following the general procedure **D**, compound **2.3l** was obtained as a white solid in 88% yield (68.1 mg); mp = 151–152 °C; R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 87% *ee*); IR (KBr) 2948, 2829, 1685, 1480, 1268, 1012, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.06–7.00



(m, 1H), 6.79–6.70 (comp, 2H), 5.66 (app t, 1H, *J* = 8.0 Hz), 3.96 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.34–3.23 (comp, 3H), 3.05–2.92 (m, 1H), 2.90–2.80 (m, 1H), 2.79–2.68 (m, 1H), 2.59–2.37 (comp, 2H), 2.20–2.09 (comp, 2H), 2.04–1.98 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 150.5, 142.0, 132.9, 131.6, 130.8, 129.9, 128.9, 126.4, 124.3, 123.8, 119.9, 117.3, 62.1, 53.5, 47.6, 42.4, 36.6, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 387.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.4 min (major) and t_R = 13.2 min (minor).

The absolute configuration was assigned by analogy.

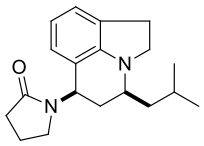
1-((4*R*,6*R*)-4-isopropyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3m): Following the general procedure **D**, compound **2.3m** was obtained as a white solid in 96% yield (54.5 mg); mp = 159–160 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ 24.5 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2956, 2842, 1683, 1460, 1420, 1287, 1269, 1206, 776, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 6.9 Hz, 1H), 6.71–6.56 (comp, 2H), 5.53 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.56 (app t, *J* = 7.5 Hz, 1H), 3.33–3.17 (comp, 2H), 3.02–2.76 (comp, 4H), 2.57–2.45 (comp, 2H), 2.14–1.96 (comp, 3H), 1.95–1.77 (comp, 2H), 0.96 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.6, 129.5, 124.2, 123.3, 118.8, 117.4, 62.3, 52.2, 47.9, 42.4, 31.5, 28.8, 28.7, 25.7, 19.1, 18.2, 14.8; *m/z* (ESI–MS) 285.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.0 min (minor).

The absolute configuration was assigned by analogy.

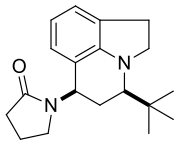
1-((4*S*,6*R*)-4-isobutyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3n): Following the general procedure **D**, compound **2.3n** was obtained as a colorless oil in 53% yield (31.6 mg); R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (neat) 2944, 2840, 1678, 1454, 1277, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.9 Hz, 1H), 6.79–6.56 (comp, 2H), 5.54 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.74–3.60 (m, 1H), 3.32–3.15 (comp, 2H), 3.09–2.74 (comp, 4H), 2.57–2.39 (comp, 2H), 2.17 (ddd, *J* = 12.8, 6.5, 1.9 Hz, 1H), 2.08–1.94 (comp, 2H), 1.87–1.67 (comp, 2H), 1.63–1.51 (m, 1H), 1.47–1.32 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 151.3, 129.7, 124.3, 123.3, 119.1, 117.6, 56.2, 52.8, 47.3, 43.0, 42.4, 32.5, 31.5, 28.8, 24.5, 24.2, 22.0, 18.2; *m/z* (ESI–MS) 299.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 7.7 min (major) and t_R = 9.8 min (minor).

The absolute configuration was assigned by analogy.

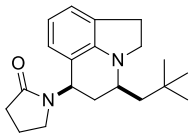
1-((4*R*,6*R*)-4-(tert-butyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3o): Following the general procedure **D**, compound **2.3o** was obtained as a colorless oil in 65% yield; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +5.0 (c 0.8, $CHCl_3$, 99% *ee*); IR (neat) 2948, 2848, 1674, 1450, 1270, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 6.7 Hz, 1H), 6.78–6.54 (comp, 2H), 5.52 (dd, *J* = 11.8, 6.0 Hz, 1H), 3.87–3.67 (m, 1H), 3.32–3.18 (comp, 2H), 3.13–3.03 (m, 1H), 3.02–2.76 (comp, 3H), 2.58–2.45 (comp, 2H), 2.14–1.85 (comp, 4H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.7, 128.9, 123.8, 123.2, 118.8, 117.5, 66.3, 55.8, 48.0, 42.3, 34.0, 31.5, 29.3, 29.1, 28.3, 18.2; *m/z* (ESI–MS) 299.7 $[M+ H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 32.3 min (major).

The absolute configuration was assigned by analogy.

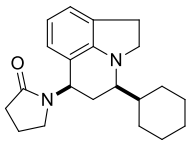
1-((4*S*,6*R*)-4-neopentyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3p): Following the general procedure **D**, compound **2.3p** was obtained as a colorless oil in 91% yield (56.9 mg); R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +7.4 (c 0.5, $CHCl_3$, 95% *ee*); IR (neat) 2950, 2850, 1680, 1456, 1274, 1206, 855, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.7 Hz, 1H), 6.82–6.55 (comp, 2H), 5.55 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.71 (app t, *J* = 7.6 Hz, 1H), 3.30–3.22 (m, 1H), 3.21–3.14 (m, 1H), 3.03–2.78 (comp, 4H), 2.54–2.43 (comp, 2H), 2.18 (ddd, *J* = 13.0, 6.4, 2.1 Hz, 1H), 2.03–1.90 (comp, 3H), 1.77 (d, *J* = 14.0 Hz, 1H), 1.35 (dd, *J* = 14.5, 7.9 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.6, 130.3, 124.3, 123.4, 119.3, 117.9, 55.5, 53.2, 47.3, 46.9, 42.3, 35.8, 31.5, 30.3, 29.9, 28.7, 28.6; *m/z* (ESI–MS) 314.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.9 min (major) and t_R = 11.9 min (minor).

The absolute configuration was assigned by analogy.

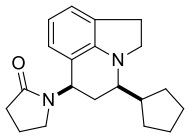
1-((4*R*,6*R*)-4-cyclohexyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3q): Following the general procedure **D**, compound **2.3q** was obtained as a white solid in 51% yield (33.1 mg); mp = 156–158 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +23.5 (c 0.2, $CHCl_3$, 90% ee); IR (KBr) 2926, 2848, 1686, 1458, 1267, 1207, 776, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.8 Hz, 1H), 6.76–6.53 (comp, 2H), 5.52 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.56 (app t, *J* = 7.0 Hz, 1H), 3.34–3.09 (comp, 2H), 3.01–2.77 (comp, 4H), 2.61–2.34 (comp, 2H), 2.05–1.86 (comp, 5H), 1.84–1.77 (comp, 2H), 1.75–1.65 (comp, 2H), 1.52 (d, *J* = 11.9 Hz, 1H), 1.31–1.14 (comp, 4H), 1.09–0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.8, 129.5, 124.2, 123.3, 118.7, 117.3, 62.2, 52.3, 48.0, 42.4, 39.8, 31.5, 29.9, 28.8, 27.3, 26.9, 26.8(8), 26.6, 25.8, 18.2; *m/z* (ESI–MS) 326.0 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.5 min (major) and t_R = 11.3 min (minor).

The absolute configuration was assigned by analogy.

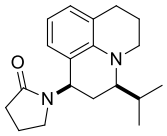
1-((4*R*,6*R*)-4-cyclopentyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(2.3r): Following the general procedure **D**, compound **2.3r** was obtained as a white solid in 82% yield (50.8 mg); mp = 124–125 °C; R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ -4.4 (c 0.5, $CHCl_3$, 88% *ee*); IR (KBr) 2954, 2861, 1683, 1456, 1428, 1287, 1206, 1055, 842, 779, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 6.8 Hz, 1H), 6.70–6.48 (comp, 2H), 5.47 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.71–3.46 (m, 1H), 3.30–3.06 (comp, 2H), 3.00–2.76 (comp, 4H), 2.55–2.33 (comp, 2H), 2.28–2.09 (m, 1H), 2.00–1.88 (comp, 3H), 1.86–1.76 (m, 1H), 1.75–1.60 (comp, 2H), 1.59–1.43 (comp, 4H), 1.42–1.25 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.5, 129.4, 124.1, 123.2, 118.8, 117.4, 60.2, 52.9, 47.8, 47.7, 42.3, 42.2, 41.7, 31.5, 28.9, 27.9, 26.4, 25.7, 18.1; *m/z* (ESI–MS) 311.9 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.8 min (major) and t_R = 12.3 min (minor).

The absolute configuration was assigned by analogy.

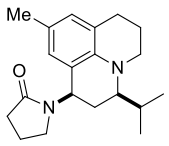
1-((1*R*,3*R*)-3-isopropyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one



(2.4a): Following the general procedure **D**, compound **2.4a** was obtained as a white solid in 85% yield (50.6 mg); mp = 164–165 °C; R_f= 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +75.2 (c 0.5, $CHCl_3$, 91% *ee*); IR (KBr) 2954, 2840, 1685, 1464, 1280, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–6.80 (m, 1H), 6.64–6.49 (comp, 2H), 5.43 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.42–3.31 (m, 1H), 3.31–3.23 (comp, 2H), 3.23–3.16 (m, 1H), 2.85–2.68 (comp, 2H), 2.65–2.55 (comp, 1H), 2.55–2.43 (comp, 2H), 2.43–2.28 (m, 1H), 2.14–1.95 (comp, 3H), 1.94–1.72 (comp, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 144.5, 127.7, 124.4, 123.2, 120.1, 116.0, 61.4, 48.2, 45.0, 42.3, 31.4, 27.7, 27.2, 25.4, 22.8,

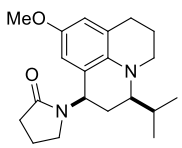
19.5, 18.2, 14.3; *m/z* (ESI–MS) 299.7 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.3 min (major) and t_R = 14.5 min (minor).

The absolute configuration was assigned by analogy.

1-((1*R*,3*R*)-3-isopropyl-9-methyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one (2.4b): 

Following the general procedure **E**, compound **2.4b** was obtained as a white solid in 74% yield (46.3 mg); mp = 114–116°C; R_f = 0.28 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +38.4 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2947, 2839, 1671, 1458, 1420, 1286, 1269, 1086, 1010, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.40 (s, 1H), 5.42 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.38–3.30 (m, 1H), 3.29–3.20 (comp, 2H), 3.12 (app dt, *J* = 11.1, 3.5 Hz, 1H), 2.76–2.64 (comp, 2H), 2.61–2.45 (comp, 3H), 2.37–2.29 (m, 1H), 2.15 (s, 3H), 2.08–1.95 (comp, 3H), 1.86–1.76 (comp, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 142.5, 128.7, 125.4, 124.5, 123.8, 120.3, 61.4, 48.3, 45.0, 42.4, 31.5, 27.6, 27.3, 25.5, 23.0, 20.4, 19.6, 18.3, 14.3; *m/z* (ESI–MS) 314.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.7 min (major) and t_R = 7.9 min (minor).

The absolute configuration was assigned by analogy.

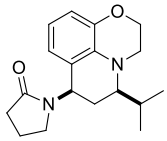
1-((1*R*,3*R*)-3-isopropyl-9-methoxy-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one (2.4c): 

Following the general procedure **E**, compound **2.4c** was obtained as a white solid in 82% yield (53.8 mg); mp = 124–126 °C; R_f = 0.22 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +68.3 (c 0.7, $CHCl_3$, 97% *ee*); IR (KBr) 2962, 2928, 2835, 1683, 1485, 1285, 1193, 1082, 887, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 2.8 Hz, 1H), 6.21 (d, *J* = 2.8 Hz, 1H), 5.48–5.38 (m, 1H), 3.67 (s, 3H), 3.38–3.18 (comp, 3H), 3.11–3.00 (m, 1H), 2.80–2.68 (m, 1H), 2.67–2.54 (comp, 2H), 2.53–2.45 (comp, 2H), 2.36–2.26 (m, 1H), 2.10–1.91 (comp, 4H), 1.89–1.72 (comp, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 151.0, 139.3, 125.9, 121.7, 113.6, 109.5, 61.5, 55.6, 48.4, 44.8, 42.4, 31.4, 27.8, 27.2, 25.3, 23.0, 19.6, 18.2, 14.3; *m/z* (ESI–MS) 329.9[M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 30.4 min (major) and t_R = 34.9 min (minor).

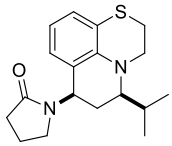
The absolute configuration was assigned by analogy.

1-((5*R*,7*R*)-5-isopropyl-3,5,6,7-tetrahydro-2H-[1,4]oxazino[2,3,4-ij]quinolin-7-yl)pyrrolidin-2-one (2.4d): Following the general procedure **D**, compound **2.4d** was obtained as a light red solid in 84% yield; mp = 183–184 °C; R_f = 0.28 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ -15.4 (c 0.5, $CHCl_3$, >99% *ee*); IR (KBr) 2945, 2865, 1724, 1636, 1541, 1475, 1384, 1181, 1108, 974, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68–6.62 (m, 1H), 6.62–6.56 (m, 1H), 6.45–6.38 (m, 1H), 5.48 (dd, *J* = 12.1, 6.1 Hz, 1H), 4.36–4.26 (comp, 2H), 3.34 (app dt, *J* = 11.6, 2.4 Hz, 1H), 3.30–3.22 (m, 1H), 3.21–3.14 (m, 1H), 3.05 (ddd, *J* = 11.2, 3.3, 2.4 Hz, 1H), 2.91–2.79 (m, 1H), 2.55–2.45 (comp, 2H), 2.36–2.23 (m, 1H), 2.09–1.96 (comp, 2H), 1.94–1.74 (comp, 2H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 144.4, 134.4, 121.8, 118.6, 118.5, 115.1, 65.6, 60.5, 48.1, 42.3, 42.0, 31.4, 26.7, 24.5, 19.3, 18.1, 14.2; *m/z* (ESI–MS) 301.2 [M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.3 min (major).



The absolute configuration was assigned by analogy.

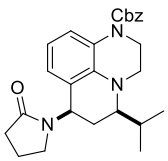
1-((5*R*,7*R*)-5-isopropyl-3,5,6,7-tetrahydro-2H-[1,4]thiazino[2,3,4-ij]quinolin-7-yl)pyrrolidin-2-one (2.4e): Following the general procedure **D**, compound **2.4e** was obtained as a light brown oil in 54% yield; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +35.7 (c 0.5, $CHCl_3$, 54% *ee*); IR (neat) 2955, 2845, 1694, 1472, 1364, 774 cm^{-}



[1]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02–6.96 (m, 1H), 6.59 (app t, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.37 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.76–3.66 (m, 1H), 3.36–3.18 (comp, 4H), 3.01–2.93 (comp, 2H), 2.58–2.46 (comp, 2H), 2.33–2.23 (m, 1H), 2.14–2.03 (comp, 2H), 1.94–1.81 (comp, 2H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 143.6, 126.9, 123.1, 121.3, 121.2, 117.8, 62.3, 48.0, 46.7, 42.5, 31.3, 29.4, 28.1, 26.0, 19.5, 18.3, 14.7; *m/z* (ESI–MS) 317.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 254 nm, t_R = 8.3 min (major), t_R = 10.3 min (minor).

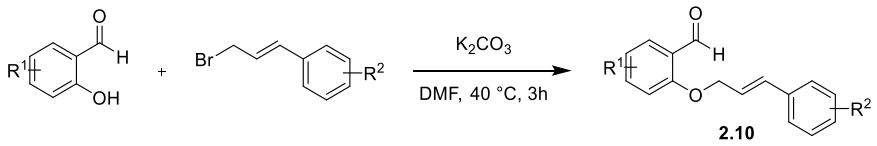
The absolute configuration was assigned by analogy.

(5*R*,7*R*)-benzyl-5-isopropyl-7-(2-oxopyrrolidin-1-yl)-2,3,6,7-tetrahydropyrido[1,2,3-de]quinoxaline-1(5H)-carboxylate (2.4f): Following the general procedure **E**, compound **2.4f** was obtained as a light brown oil in 65% yield (9:1 dr); R_f= 0.25 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ -3.2 (c 0.5, $CHCl_3$, 97% *ee*); IR (neat) 2961, 2933, 1689, 1386, 1278, 1132, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.46–7.28 (comp, 6H), 6.62 (app t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 6.7 Hz, 1H), 5.42 (dd, *J* = 12.1, 4.6 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 3.6 –3.41 (comp, 3H), 3.29–3.16 (comp, 3H), 2.96–2.86 (m, 1H), 2.49–2.46 (comp, 2H), 2.32–2.22 (m, 1H), 2.09 –2.03 (comp, 2H), 1.90–1.78 (comp, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 154.0, 136.3, 128.5, 128.0, 127.9, 121.2, 121.1, 116.5, 67.5, 61.4, 47.9, 45.7, 42.4, 31.4, 27.5, 25.2, 19.4, 18.2, 14.5; *m/z* (ESI–MS) 434.9 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 22.7 min (major), t_R = 34.7 min (minor).



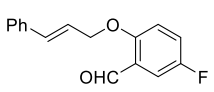
The absolute configuration was assigned by analogy.

Preparation and characterization data of starting materials of intramolecular Povarov reactions:



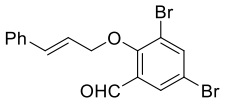
The synthesis of compounds **2.10** was adopted from a known procedure: To a solution of cinnamyl bromide (2.0 g, 10.1 mmol, 1.01 equiv) in DMF (15 mL) was added salicylaldehyde (1.05 mL, 10 mmol, 1 equiv) and K_2CO_3 (2.1 g, 15 mmol, 1.5 equiv) at rt. The resulting mixture was stirred at 40 °C for 3 hours and then cooled to rt and diluted with EtOAc (40 mL). This mixture was washed with 10% aqueous KOH (2 x 10 mL), H_2O (2 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

2-(cinnamyloxy)-5-fluorobenzaldehyde (2.10b): Following the general procedure, compound **2.10b**



was obtained as a white solid in 92% yield (2.36 g); mp = 77–78 °C; R_f = 0.28 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3337, 3066, 2940, 2868, 1679, 1485, 1378, 1255, 1149, 965, 815, 727, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.51 (d, J = 3.0, 1H), 7.53 (dd, J = 8.2, 3.2 Hz, 1H), 7.48–7.40 (comp, 2H), 7.40–7.32 (comp, 2H), 7.32–7.21 (comp, 2H), 7.01 (dd, J = 9.1, 3.9 Hz, 1H), 6.76 (d, J = 16.0 Hz, 1H), 6.41 (dt, J = 15.9, 5.7 Hz, 1H), 4.80 (dd, J = 5.7, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6 (d, $J_{C–F}$ = 2.5 Hz), 157.9, 157.2 (d, $J_{C–F}$ = 2.5 Hz), 156.0, 135.9, 133.8, 127.6 (d, $J_{C–F}$ = 261.3 Hz), 128.2, 125.9 (d, $J_{C–F}$ = 6.3 Hz), 123.1, 122.4 (d, $J_{C–F}$ = 23.8 Hz), 114.7 (d, $J_{C–F}$ = 6.3 Hz), 114.0 (d, $J_{C–F}$ = 23.8 Hz), 69.8; *m/z* (ESI-MS) 279.2 [M + Na]$^+$.

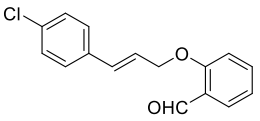
3,5-dibromo-2-(cinnamyloxy)benzaldehyde (2.10h): Following the general procedure, compound



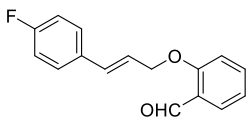
2.10h was obtained as a white solid in 88% yield (3.48 g); mp = 93–95 °C;

R_f = 0.30 (Hexanes/EtOAc 98:2 v/v); IR (KBr) 3065, 2940, 1694, 1574, 1443, 1361, 1215, 1147, 935, 869, 741, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.31 (s, 1H), 7.96 (d, *J* = 2.5 Hz, 1H), 7.91 (d, *J* = 2.5 Hz, 1H), 7.44–7.37 (comp, 2H), 7.34 (comp, 2H), 7.31–7.27 (m, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.78 (dd, *J* = 6.6, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0, 157.8, 141.4, 135.9, 135.9, 132.2, 130.6, 128.8, 128.6, 126.9, 122.4, 119.7, 118.3, 76.9; *m/z* (ESI-MS) 418.8 $[M + Na]^+$.

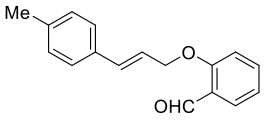
(*E*)-2-((3-(4-chlorophenyl)allyl)oxy)benzaldehyde (2.10i): Following the general procedure, compound **2.10i** was obtained as a white solid in 87% yield (2.37 g); mp = 81–83 °C; R_f = 0.21 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3029, 2892, 2849, 1686, 1600, 1482, 1406, 1384, 1246, 1159, 984, 756, 652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.56 (s, 1H), 7.86 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57–7.51 (m, 1H), 7.40–7.27 (comp, 4H), 7.11–6.96 (comp, 2H), 6.72 (d, *J* = 16.1 Hz, 1H), 6.40 (dt, *J* = 16.0, 5.5 Hz, 1H), 4.81 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 160.8, 135.8, 134.6, 133.8, 132.1, 128.8, 128.5, 127.8, 125.1, 124.1, 121.0, 112.8, 68.9; *m/z* (ESI-MS) 295.3 $[M + Na]^+$.



(*E*)-2-((3-(4-fluorophenyl)allyl)oxy)benzaldehyde (2.10k): Following the general procedure, compound **2.10k** was obtained as a white solid in 85% yield (2.18 g); mp = 57–59 °C; R_f = 0.20 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3059, 2890, 2851, 1686, 1597, 1483, 1384, 1229, 981, 846, 756 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) 10.56 (s, 1H), 7.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.63–7.49 (m, 1H), 7.48–7.30 (comp, 2H), 7.15–6.95 (comp, 4H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.9, 5.7 Hz, 1H), 4.80 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 162.5 (d, $J_{C–F}$ = 246.3 Hz), 160.9, 135.8, 132.3, 132.2 (d, $J_{C–F}$ = 2.5 Hz), 128.5, 128.1 (d, $J_{C–F}$ = 7.5 Hz), 125.1, 123.1 (d, $J_{C–F}$ = 2.5 Hz), 120.9, 115.5 (d, $J_{C–F}$ = 21.3 Hz), 112.8, 68.9; *m/z* (ESI-MS) 279.2 $[M + Na]^+$.

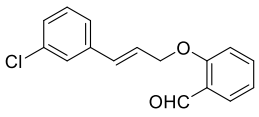


(*E*)-2-((3-(*p*-tolyl)allyl)oxy)benzaldehyde (2.10l): Following the general procedure, compound

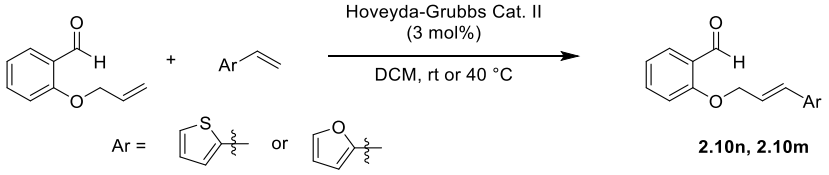


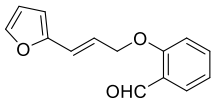
2.10l was obtained as a white solid in 84% yield (2.11 g); mp = 91–93 °C; R_f = 0.32 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3335, 3014, 2867, 1686, 1596, 1482, 1375, 1235, 1104, 977, 840, 770, 652, 489 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) 10.60 (s, 1H), 7.88 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.54 (app t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.07–7.00 (comp, 2H), 6.74 (d, *J* = 15.8 Hz, 1H), 6.38 (dt, *J* = 16.0, 5.8 Hz, 1H), 4.78 (d, *J* = 5.7 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 160.9, 137.9, 135.7, 133.4, 133.2, 129.2, 128.2, 126.4, 125.0, 122.2, 120.7, 112.8, 69.1, 21.1; *m/z* (ESI-MS) 275.1 $[M + Na]^+$.

(*E*)-2-((3-(3-chlorophenyl)allyl)oxy)benzaldehyde (2.10m): Following the general procedure, compound



2.10m was obtained as a white solid in 74% yield (2.02 g); mp = 68–70 °C; R_f = 0.23 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3338, 3065, 2930, 2868, 1683, 1596, 1458, 1378, 1244, 1011, 974, 849, 760, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.57 (s, 1H), 7.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.62–7.48 (m, 1H), 7.40 (s, 1H), 7.34–7.18 (comp, 3H), 7.13–6.95 (comp, 2H), 6.70 (d, *J* = 16.1 Hz, 1H), 6.43 (dt, *J* = 16.0, 5.5 Hz, 1H), 4.81 (dd, *J* = 5.4, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 160.7, 137.9, 135.8, 134.6, 131.8, 129.8, 128.5, 128.0, 126.4, 125.1, 125.0, 124.8, 121.0, 112.8, 68.7; *m/z* (ESI-MS) 295.0 $[M + Na]^+$.





(*E*)-2-((3-(furan-2-yl)allyl)oxy)benzaldehyde (2.10n): To a solution of 2-vinylfuran (1.13 g, 12 mmol, 6 equiv) in CH_2Cl_2 (10.0 mL) in a 25 mL round bottom flask were added 2-allyloxybenzaldehyde (324 mg, 2 mmol, 1 equiv) and Hoveyda-Grubbs second-generation catalyst (50 mg, 0.08 mmol, 4 mol%). The resulting mixture was stirred at rt for 17 h and then at 40 ºC for 22 h. The reaction mixture was concentrated under reduced pressure and purified by flash silica gel chromatography using EtOAc/Hexanes (97:3 v/v) as the eluent to afford **3.5n** in 18% yield (83.2 mg) as a colorless oil; R_f = 0.23 (Hexanes/EtOAc 97:3 v/v); IR (neat) 2935, 2829, 1652, 1600, 1453, 1366, 1242, 1159, 960, 757 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) 10.56 (s, 1H), 7.85 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.67–7.46 (m, 1H), 7.40–7.35 (m, 1H), 7.15–6.88 (comp, 2H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.45–6.24 (comp, 3H), 4.80 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 160.9, 151.8, 142.4, 135.9, 128.5, 125.1, 121.8, 121.4, 120.9, 112.9, 111.4, 109.0, 68.6; *m/z* (ESI-MS) 251.0 $[M + Na]^+$.

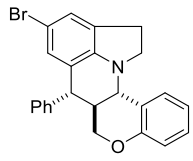
(*E*)-2-((3-(thiophen-2-yl)allyl)oxy)benzaldehyde (2.10o): To a solution of 2-vinylthiophene (1.10 g, 10 mmol, 5 equiv) in CH_2Cl_2 (10 mL) in a 25 mL round bottom flask were added 2-allyloxybenzaldehyde (324 mg, 2 mmol, 1 equiv) and Hoveyda-Grubbs second-generation catalyst (38 mg, 0.06 mmol, 3 mol%). The resulting mixture was stirred at 40 ºC for 66 h. The reaction mixture was concentrated under reduced pressure and purified by flash silica gel chromatography using EtOAc/Hexanes (97:3 v/v) as the eluent to afford **3.5o** in 49% yield (239.2 mg) as a white solid; mp = 76–78 °C; R_f = 0.36 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3110, 2929, 2873, 1682, 1596, 1452, 1307, 1231, 997, 965, 849, 764, 712 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) 10.57 (s, 1H), 7.86 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.60–7.50 (m, 1H), 7.21 (d, *J* = 5.0 Hz, 1H), 7.08–7.00 (comp, 3H), 7.00–6.96 (m, 1H), 6.89 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 5.7 Hz, 1H), 4.79 (dd, *J* = 5.7, 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 160.9, 141.1, 135.9, 128.5, 127.5, 126.6, 126.5, 125.1, 125.0, 122.8, 121.0, 112.9, 68.7; *m/z* (ESI-MS) 267.0 $[M + Na]^+$.

Preparation and characterization data of products:

General procedure **F**: A flame dried vial was charged with aldehyde (0.2 mmol, 1 equiv), **2.127d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (4 mL) was added and the resulting mixture was cooled to 0 °C over 10 min. The aromatic amine was then added (0.24 mmol, 1.2 equiv) and the reaction mixture was stirred at 0 °C. When aldehyde could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography.

General procedure **G**: A flame dried vial was charged with aldehyde (0.2 mmol, 1 equiv), **2.127d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (3 mL) was added and the resulting mixture was cooled to 0 °C over 10 min. A solution of the aromatic amine in toluene (1 mL) was then added (0.24 mmol, 1.2 equiv) and the reaction mixture was stirred at 0 °C. When aldehyde could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography.

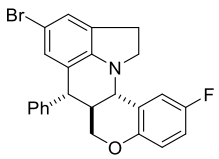
(6a*S*,7*R*,13a*S*)-9-bromo-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11a): Following the general procedure **G**, compound **2.11a** was obtained as a white solid in 91% yield (76.1 mg, >20:1 dr); mp = 194–195 °C; R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +196.1 (c 0.5, $CHCl_3$, >99% *ee*); IR (KBr) 2982, 2817, 1490, 1454, 1220, 758, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.56 (app dt, *J* = 7.8, 1.3 Hz, 1H), 7.39–7.34 (comp, 2H), 7.33–7.29 (m, 1H), 7.24–7.18 (comp, 3H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.00–6.92 (m, 1H), 6.87 (app dd, *J* = 8.2, 1.3 Hz, 1H), 6.61(s, 1H), 4.24–4.11 (comp, 2H), 3.97 (app dd, *J* = 10.9, 3.6 Hz, 1H), 3.82 (d, *J* = 11.9 Hz, 1H), 3.75 (app t, *J* = 11.2 Hz, 1H), 3.47 (app dt, *J* = 12.8, 8.2 Hz, 1H), 3.11–2.93 (comp, 2H), 2.89–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 149.7, 141.7, 131.7, 129.4, 128.9, 128.8(8), 128.8(5), 127.4, 125.7, 125.3, 121.8, 120.4, 118.0, 111.6,



67.1, 58.9, 56.3, 45.9, 44.7, 29.1; *m/z* (ESI–MS) 418.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 23.4 min (major).

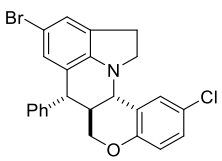
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-2-fluoro-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11b): Following the general procedure **G**, compound **2.11b** was obtained as a white solid in 93% yield (81.2 mg, 20:1 dr); mp = 172–174 °C; R_f = 0.42 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +136.6 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2828, 1492, 1453, 825, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.39–7.26 (comp, 4H), 7.23–7.17 (comp, 2H), 7.12 (s, 1H), 6.94–6.89 (m, 1H), 6.83–6.79 (m, 1H), 6.60 (s, 1H), 4.19–4.10 (comp, 2H), 3.95 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.80 (d, *J* = 11.9 Hz, 1H), 3.73 (app t, *J* = 11.2 Hz, 1H), 3.47–3.39 (m, 1H), 3.11–2.96 (comp, 2H), 2.85–2.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (d, $J_{C–F}$ = 236.9 Hz), 152.0 (d, $J_{C–F}$ = 2.5 Hz), 149.4, 141.5, 131.7, 129.4, 129.0, 128.9, 127.5, 125.8, 125.4, 122.8 (d, $J_{C–F}$ = 7.2 Hz), 118.9 (d, $J_{C–F}$ = 8.4 Hz), 115.8 (d, $J_{C–F}$ = 22.9 Hz), 114.9 (d, $J_{C–F}$ = 23.6 Hz), 112.0, 67.3, 59.0, 56.2, 45.8, 44.5, 29.1; *m/z* (ESI–MS) 436.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.2 min and t_R = 8.2 min (major).



The absolute configuration was assigned by analogy.

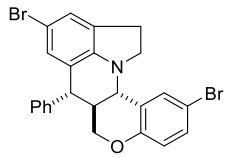
(6a*S*,7*R*,13a*S*)-9-bromo-2-chloro-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11c): Following the general procedure **G**, compound **2.11c** was obtained as a white solid in 98% yield (88.7 mg, >20:1 dr); mp = 210–212 °C; R_f = 0.49 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +226.1 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2820, 1486, 1451, 1299, 825, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.46 (d, *J* = 2.5 Hz, 1H), 7.31–7.21 (comp, 3H), 7.15–7.02 (comp, 4H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.52



(s, 1H), 4.09–3.99 (comp, 2H), 3.88 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.72 (d, *J* = 11.9 Hz, 1H), 3.65 (app t, *J* = 11.2 Hz, 1H), 3.35 (app dt, *J* = 12.8, 8.2 Hz, 1H), 3.03–2.88 (comp, 2H), 2.76–2.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 149.4, 141.5, 131.7, 129.4, 129.0, 128.9, 128.5, 127.5, 125.9, 125.2, 123.4, 119.3, 112.0, 67.3, 58.8, 56.3, 45.8, 44.4, 29.1; *m/z* (ESI–MS) 452.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.1 min and t_R = 16.8 min (major).

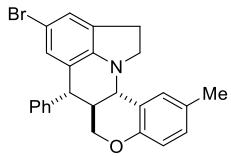
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-2,9-dibromo-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11d): Following the general procedure **G**, compound **2.11d** was obtained as a white solid in 96% yield (95.4mg, 14:1 dr); mp = 213–214 °C; R_f = 0.49 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +222.5 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2813, 1482, 1451, 1298, 823, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.68 (d, *J* = 2.4 Hz, 1H), 7.40–7.27 (comp, 4H), 7.22–7.16 (comp, 2H), 7.12 (s, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 6.60 (s, 1H), 4.18–4.07 (comp, 2H), 3.97 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.80 (d, *J* = 11.9 Hz, 1H), 3.73 (app t, *J* = 11.2 Hz, 1H), 3.42 (app dt, *J* = 12.7, 8.2 Hz, 1H), 3.12–2.95 (comp, 2H), 2.83–2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 149.5, 141.5, 131.7, 131.6, 131.4, 129.4, 129.0, 128.9, 127.5, 125.8, 125.1, 124.0, 119.7, 112.5, 111.9, 67.3, 58.7, 56.2, 45.7, 44.4, 29.1; *m/z* (ESI–MS) 496.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.9 min and t_R = 16.3 min (major).



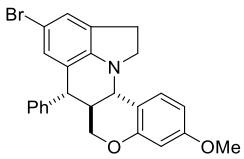
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-2-methyl-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11e): Following the general procedure **G**, compound **2.11e** was obtained as a white solid in 91% yield (78.6 mg, 20:1 dr); mp = 191–192 °C; R_f = 0.46 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +177.2 (c 0.5, $CHCl_3$, 99% *ee*); IR (KBr) 2836, 1496, 1224, 1180, 1038, 826, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40–7.27 (comp, 4H), 7.22–7.17 (comp, 2H), 7.12 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.61 (s, 1H), 4.20–4.08 (comp, 2H), 3.93 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.71 (app t, *J* = 11.1 Hz, 1H), 3.46 (app dt, *J* = 12.8, 8.3 Hz, 1H), 3.10–2.94 (comp, 2H), 2.87–2.75 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.8, 141.8, 131.7, 129.5(4), 129.4(9), 129.3(8), 129.1, 128.9, 127.4, 125.7, 125.4, 121.5, 117.7, 111.5, 67.1, 58.9, 56.3, 45.9, 44.9, 29.1, 20.9; *m/z* (ESI–MS) 432.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.4 min and t_R = 16.0 min (major).



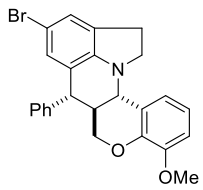
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-3-methoxy-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11f): Following the general procedure **G**, compound **2.11f** was obtained as a white solid in 91% yield (81.5 mg, >20:1 dr); mp = 207–209 °C; R_f = 0.26 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +151.7 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2977, 2816, 1620, 1505, 1452, 1288, 1167, 851, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.45 (d, *J* = 8.8 Hz, 1H), 7.39–7.29 (comp, 3H), 7.23–7.16 (comp, 2H), 7.11 (s, 1H), 6.60 (s, 1H), 6.55 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.40 (d, *J* = 2.8 Hz, 1H), 4.14–4.07 (comp, 2H), 3.94 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H), 3.72 (app t, *J* = 11.2 Hz, 1H), 3.43 (app dt, *J* = 12.8, 8.3 Hz, 1H), 3.07–2.93 (comp, 2H), 2.84–2.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.1, 149.8, 141.8, 131.6, 129.7, 129.4, 128.9, 127.4, 125.7, 125.3, 114.1, 111.5, 107.6, 102.1, 67.1, 58.6, 56.2, 55.3, 45.8, 44.8, 29.1; *m/z* (ESI–MS) 448.3 $[M + H]^+$;



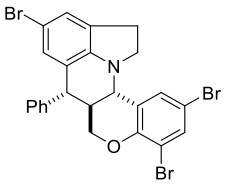
HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 18.4 min and t_R = 21.8 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-4-methoxy-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11g): 

Following the general procedure **G**, compound **2.11g** was obtained as a white solid in 98% yield (87.9 mg, >20:1 dr); mp = 205–207 °C; R_f = 0.14 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +218.3 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2818, 1482, 1454, 1216, 1073, 754, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36–7.32 (comp, 2H), 7.31–7.27 (m, 1H), 7.21–7.16 (comp, 3H), 7.11 (s, 1H), 6.91 (app t, *J* = 8.1 Hz, 1H), 6.83 (app d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 4.19 (d, *J* = 9.7 Hz, 1H), 4.15 (app t, *J* = 8.0 Hz, 1H), 4.09 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.84 (s, 3H), 3.83–3.74 (comp, 2H), 3.44 (app dt, *J* = 12.6, 8.2 Hz, 1H), 3.07–2.93 (comp, 2H), 2.89–2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 149.2, 145.7, 141.5, 131.7, 129.4, 128.9, 128.2, 127.4, 125.7, 125.3, 122.5, 120.6, 119.9, 111.6, 110.6, 67.4, 58.9, 56.3, 55.9, 45.7, 44.6, 29.1; *m/z* (ESI–MS) 448.3 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.2 min and t_R = 9.5 min (major).

The absolute configuration was assigned by analogy.

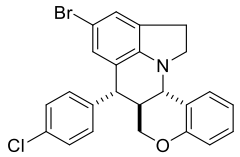
(6a*S*,7*R*,13a*S*)-2,4,9-tribromo-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11h): 

Following the general procedure **G**, compound **2.11h** was obtained as a white solid in 99% yield (114 mg, 17:1 dr); mp = 117–118 °C; R_f = 0.47 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +176.9 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2949, 2819, 1470, 1453, 1240, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.64 (d, *J* = 2.2 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.39–7.28 (comp, 3H), 7.20–7.15 (comp, 2H), 7.13 (s, 1H), 6.61 (s, 1H), 4.20–4.04 (comp, 3H), 3.86–3.76 (comp, 2H), 3.39 (app dt, *J* = 12.7, 8.1 Hz, 1H),

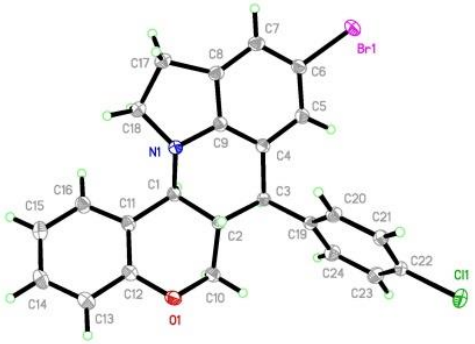
3.13–2.94 (comp, 2H), 2.83–2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 141.1, 134.7, 131.6, 130.6, 129.4, 129.0, 128.9, 127.7, 126.0, 125.3, 125.0, 112.8, 112.3, 112.2, 68.2, 58.7, 56.3, 45.7, 44.4, 29.1; *m/z* (ESI–MS) 574.0 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.4 min and t_R = 14.5 min (major).

The absolute configuration was assigned by analogy.

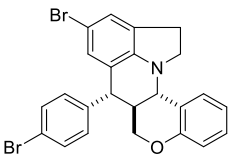
(6a*S*,7*R*,13a*S*)-9-bromo-7-(4-chlorophenyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11i): Following the general procedure **G**, compound **2.11i** was obtained as a white solid in 98% yield (88.8 mg, >20:1 dr); mp = 228–230 °C; R_f = 0.36 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +179.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2975, 2825, 1488, 1453, 1220, 834, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (app dt, *J* = 7.9, 1.2 Hz, 1H), 7.38–7.31 (comp, 2H), 7.24–7.18 (m, 1H), 7.17–7.10 (comp, 3H), 6.99–6.93 (m, 1H), 6.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.57 (s, 1H), 4.20–4.10 (comp, 2H), 3.94 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.81 (d, *J* = 11.9 Hz, 1H), 3.74 (app t, *J* = 11.2 Hz, 1H), 3.46 (app dt, *J* = 12.7, 8.2 Hz 1H), 3.09–2.93 (comp, 2H), 2.82–2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 149.7, 140.4, 133.2, 131.8, 130.2, 129.2, 129.1, 129.0, 128.9, 125.9, 124.6, 121.6, 120.4, 118.0, 111.6, 66.9, 58.8, 56.2, 45.3, 44.8, 29.1; *m/z* (ESI–MS) 452.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.8 min and t_R = 19.2 min (major).



The enantioenriched product **2.11i** was crystallized from hexanes/dichloromethane through slow diffusion at room temperature and the absolute configuration was assigned by X-ray crystallography

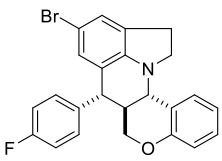


(6a*S*,7*R*,13a*S*)-9-bromo-7-(4-bromophenyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11j):



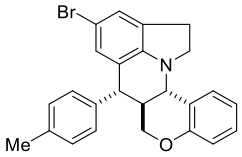
Following the general procedure **G**, compound **2.11j** was obtained as a white solid in 94% yield (93.5 mg, 15:1 dr); mp = 230–232 °C; R_f = 0.36 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +133.2 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2974, 2823, 1487, 1453, 1220, 1012, 830, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.54 (app d, *J* = 7.9 Hz, 1H), 7.53–7.46 (comp, 2H), 7.24–7.19 (m, 1H), 7.13 (s, 1H), 7.12–7.06 (comp, 2H), 6.96 (app td, *J* = 7.6, 1.4 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.57 (s, 1H), 4.24–4.11 (comp, 2H), 3.94 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.74 (app t, *J* = 11.2 Hz, 1H), 3.47 (app dt, *J* = 12.5, 8.3 Hz, 1H), 3.11–2.94 (comp, 2H), 2.86–2.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 149.7, 140.9, 132.1, 131.8, 130.6, 129.2, 129.0, 128.8, 125.9, 124.5, 121.6, 121.3, 120.4, 118.0, 111.6, 66.8, 58.8, 56.2, 45.3, 44.7, 29.1; *m/z* (ESI–MS) 496.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.1 min and t_R = 20.0 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-7-(4-fluorophenyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11k): 

Following the general procedure **G**, compound **2.11k** was obtained as a white solid in 94% yield (82.1 mg, >20:1 dr); mp = 232–233 °C; R_f = 0.37 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +184.9 (c 0.5, $CHCl_3$, 97% *ee*); IR (KBr) 2821, 1490, 1454, 1217, 841, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.56 (app d, *J* = 8.0 Hz, 1H), 7.25–7.15 (comp, 3H), 7.12 (s, 1H), 7.10–7.02 (comp, 2H), 6.96 (app t, *J* = 7.6 Hz, 1H), 6.88 (app d, *J* = 8.1 Hz, 1H), 6.58 (s, 1H), 4.21–4.10 (comp, 2H), 3.95 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.82 (d, *J* = 11.9 Hz, 1H), 3.74 (app t, *J* = 11.1 Hz, 1H), 3.47 (app dt, *J* = 12.5, 8.2 Hz, 1H), 3.10–2.93 (comp, 2H), 2.86–2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (d, $J_{C–F}$ = 245.0 Hz), 155.9, 149.7, 137.4 (d, $J_{C–F}$ = 3.3 Hz), 131.8, 130.3 (d, $J_{C–F}$ = 7.9 Hz), 129.3, 129.0, 128.9, 125.9, 125.0, 121.7, 120.4, 118.0, 115.9 (d, $J_{C–F}$ = 21.3 Hz), 111.7, 66.9, 58.9, 56.3, 45.1, 44.9, 29.1; *m/z* (ESI–MS) 436.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.1 min and t_R = 15.6 min (major).

The absolute configuration was assigned by analogy.

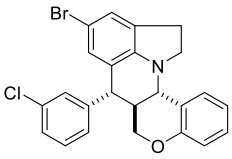
(6a*S*,7*R*,13a*S*)-9-bromo-7-(*p*-tolyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11l): 

Following the general procedure **G**, compound **2.11l** was obtained as a white solid in 96% yield (83.0 mg, >20:1 dr); mp = 212–214 °C; R_f = 0.39 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +167.0 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2819, 1489, 1453, 1225, 1178, 827, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.57 (app d, *J* = 7.9 Hz, 1H), 7.24–7.13 (comp, 3H), 7.14–7.05 (comp, 3H), 6.95 (app td, *J* = 7.5, 1.4 Hz, 1H), 6.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.62 (s, 1H), 4.19–4.11 (comp, 2H), 3.98 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.81–3.70 (comp, 2H), 3.46 (app dt, *J* = 12.7, 8.2 Hz, 1H), 3.10–2.93 (comp, 2H), 2.85–2.76 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 149.7, 138.6, 137.0, 131.6, 129.6, 129.4, 128.9, 128.8, 125.7, 125.6, 121.9, 120.3, 118.0, 111.6, 67.2, 59.0, 56.3,

45.5, 44.7, 29.1, 21.1; *m/z* (ESI–MS) 432.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.6 min and t_R = 19.7 min (major).

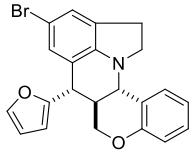
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-7-(3-chlorophenyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11m): Following the general procedure **G**, compound **2.11m** was obtained as a white solid in 89% yield (80.5 mg, >20:1 dr); mp = 200–202 °C; R_f = 0.31 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +165.9 (c 0.5, $CHCl_3$, 99% *ee*); IR (KBr) 2833, 1489, 1452, 1228, 1178, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.56 (app d, *J* = 7.9 Hz, 1H), 7.34–7.28 (comp, 2H), 7.25–7.16 (comp, 2H), 7.17–7.05 (comp, 2H), 7.00–6.93 (m, 1H), 6.88 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.58 (s, 1H), 4.21–4.09 (comp, 2H), 3.95 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.81 (d, *J* = 11.9 Hz, 1H), 3.75 (app t, *J* = 11.2 Hz, 1H), 3.46 (app dt, *J* = 12.8, 8.3 Hz, 1H), 3.09–2.93 (comp, 2H), 2.85–2.74 (m, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ 155.8, 149.8, 144.0, 134.8, 131.8, 130.2, 129.2, 128.9(4), 128.8(6), 127.8, 127.1, 126.0, 124.3, 121.7, 120.5, 118.0, 111.6, 66.9, 58.7, 56.2, 45.6, 44.8, 29.1; *m/z* (ESI–MS) 452.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.8 min and t_R = 17.3 min (major).



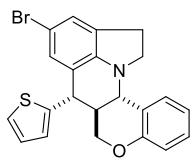
The absolute configuration was assigned by analogy.

(6a*S*,7*S*,13a*S*)-9-bromo-7-(furan-2-yl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11n): Following the general procedure **G**, compound **2.11n** was obtained as a white solid in 97% yield (79.2 mg, >20:1 dr); mp = 158–160 °C; R_f = 0.37 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +167.0 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2956, 2823, 1489, 1453, 1230, 1178, 1008, 754, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.55 (app d, *J* = 7.9 Hz, 1H), 7.42–7.36 (m, 1H), 7.25–7.19 (m, 1H), 7.13 (s, 1H), 6.96



(app td, *J* = 7.6, 1.3 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.82 (s, 1H), 6.39 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 4.22–4.05 (comp, 3H), 4.01 (d, *J* = 12.1 Hz, 1H), 3.78 (app t, *J* = 11.2 Hz, 1H), 3.52–3.38 (m, 1H), 3.12–2.86 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 153.4, 149.4, 142.3, 132.0, 129.0, 128.9, 128.5, 126.1, 122.0, 121.6, 120.4, 118.0, 111.7, 110.3, 108.3, 67.2, 58.7, 56.2, 42.2, 38.9, 29.1; *m/z* (ESI–MS) 408.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.1 min and t_R = 14.5 min (major).

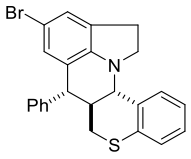
The absolute configuration was assigned by analogy.

(6a*S*,7*S*,13a*S*)-9-bromo-7-(thiophen-2-yl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.11o): 

Following the general procedure **G**, compound **2.11o** was obtained as a white solid in 91% yield (77.3 mg, >20:1 dr); mp = 174–175 °C; R_f = 0.32 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +166.7 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 2815, 1489, 1454, 1235, 1178, 763, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (app d, *J* = 7.9 Hz, 1H), 7.29–7.25 (m, 1H), 7.22 (app t, *J* = 7.7 Hz, 1H), 7.12 (s, 1H), 7.04–6.98 (comp, 2H), 6.96 (app t, *J* = 7.6 Hz, 1H), 6.90 (app d, *J* = 8.3 Hz, 1H), 6.80 (s, 1H), 4.26–4.05 (comp, 4H), 3.76 (app t, *J* = 11.1 Hz, 1H), 3.46 (app dt, *J* = 12.9, 8.2 Hz, 1H), 3.08–2.93 (comp, 2H), 2.92–2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 149.0, 144.5, 131.8, 129.1, 129.0, 128.9, 126.9, 126.7, 126.1, 125.0, 124.6, 121.5, 120.4, 118.1, 111.8, 67.2, 59.0, 56.2, 45.5, 40.8, 29.1; *m/z* (ESI–MS) 424.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.5 min and t_R = 20.5 min (major).

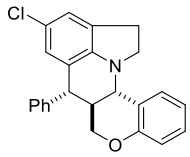
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-bromo-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-pyrrolo[3,2,1-*ij*]thiochromeno[4,3-*b*]quinoline (2.11p): Following the general procedure **G**, compound **2.11p** was obtained as a white solid in 94% yield (81.7 mg, 10:1 dr); mp = 93–95 °C; R_f = 0.47 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –154.8 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 2833, 2360, 1482, 1454, 754, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.69 (app d, *J* = 7.6 Hz, 1H), 7.40 (app d, *J* = 7.4 Hz, 1H), 7.37–7.27 (comp, 4H), 7.24–7.19 (comp, 3H), 7.13 (s, 1H), 6.54 (s, 1H), 4.13 (app t, *J* = 8.3 Hz, 1H), 4.00–3.92 (comp, 2H), 3.26–3.17 (m, 1H), 3.06–2.99 (m, 1H), 2.95–2.89 (m, 1H), 2.71–2.59 (comp, 2H), 2.52–2.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 141.8, 139.7, 136.0, 131.5, 129.7, 129.3, 128.9(1), 128.9(0), 128.6, 127.3, 126.7, 126.2, 125.8, 125.4, 111.5, 62.2, 55.8, 49.4, 46.5, 33.0, 28.8; *m/z* (ESI–MS) 434.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99.5/0.5, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 18.5 min and t_R = 31.1 min (major).



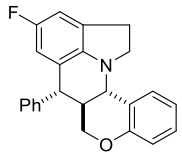
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-9-chloro-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.12a): Following the general procedure **F**, compound **2.12a** was obtained as a white solid in 95% yield (71.1 mg, 17:1 dr); mp = 193–194 °C; R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +179.3 (c 0.5, $CHCl_3$, >99% *ee*); IR (KBr) 2984, 2815, 1490, 1455, 1222, 759, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.58 (app dt, *J* = 7.8, 1.3 Hz, 1H), 7.39–7.34 (comp, 2H), 7.34–7.29 (m, 1H), 7.25–7.16 (comp, 3H), 7.02–6.92 (comp, 2H), 6.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.48 (s, 1H), 4.23–4.12 (comp, 2H), 3.98 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.81 (d, *J* = 11.9 Hz, 1H), 3.76 (app t, *J* = 11.2 Hz, 1H), 3.47 (app dt, *J* = 12.8, 8.2 Hz, 1H), 3.11–2.94 (comp, 2H), 2.91–2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 149.1, 141.7, 131.3, 128.9, 128.8, 127.4, 126.5, 124.8, 124.6, 123.0, 121.8, 120.4, 118.0, 67.1, 59.1, 56.4, 45.9, 44.7, 29.2; *m/z* (ESI–MS) 374.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 23.2 min (major).



The absolute configuration was assigned by analogy.

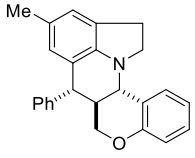
(6a*S*,7*R*,13a*S*)-9-fluoro-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.12b): Following the general procedure **F**, compound **2.12b** was



obtained as a white solid in 90% yield (64.3 mg, 15:1 dr); mp = 184–185 °C; R_f = 0.38 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +108.2 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2820, 1490, 1478, 1466, 1225, 759, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.60 (app dt, *J* = 7.9, 1.2 Hz, 1H), 7.41–7.27 (comp, 3H), 7.27–7.15 (comp, 3H), 7.02–6.93 (m, 1H), 6.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.76 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.22 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.26–4.08 (comp, 2H), 4.00 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 1H), 3.77 (app t, *J* = 11.2 Hz, 1H), 3.44 (app dt, *J* = 12.9, 8.1 Hz, 1H), 3.11–2.92 (comp, 2H), 2.92–2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 156.0, 141.9, 131.0, 128.9(2), 128.9(0), 128.8(4), 128.8(2), 127.4, 122.1, 120.3, 118.0, 112.7 ($J_{C–F}$ = 23.8 Hz), 110.4 ($J_{C–F}$ = 23.8 Hz), 67.1, 59.3, 56.8, 46.1, 44.8, 29.4; *m/z* (ESI–MS) 358.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 230 nm, tR = 12.1 min and tR = 21.2 min (major).

The absolute configuration was assigned by analogy.

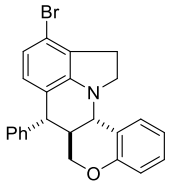
(6a*S*,7*R*,13a*S*)-9-methyl-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.12c): Following the general procedure **F**, compound **2.12c** was



obtained as a white solid in 88% yield (62.1 mg, 15:1 dr); mp = 120–122 °C (decomposition); R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +82.0 (c 0.5, $CHCl_3$, 98% *ee*); IR (KBr) 2982, 2853, 1489, 1451, 1229, 757, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.62 (app dt, *J* = 7.9, 1.2 Hz, 1H), 7.42–7.16 (comp, 6H), 7.00–6.94 (m, 1H), 6.93–6.83 (comp, 2H), 6.34 (s, 1H), 4.24–4.09 (comp, 2H), 4.00 (dd, *J* = 10.9, 3.6 Hz 1H), 3.84 (d, *J* = 11.9 Hz, 1H), 3.78 (app t, *J* = 11.1 Hz, 1H), 3.41 (app dt, *J* = 12.8, 8.0 Hz, 1H), 3.11–2.81 (comp, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 148.5, 142.8, 129.7, 129.0, 128.9(8),

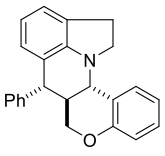
128.6(9), 128.6(8), 127.0, 123.5, 122.5, 120.3, 117.9, 67.3, 59.4, 56.8, 46.0, 45.2, 29.4, 20.9; *m/z* (ESI–MS) 354.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.2 min and t_R = 14.4 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,13a*S*)-10-bromo-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.12d): 

Following the general procedure **F**, compound **2.12d** was obtained as a white solid in 95% yield (79.3 mg, >20:1 dr); mp = 140–142 °C; R_f = 0.45 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +118.3 (c 0.5, $CHCl_3$, 86% *ee*); IR (KBr) 2853, 1489, 1451, 1227, 756, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.58 (app dt, *J* = 7.8, 1.3 Hz, 1H), 7.41–7.27 (comp, 3H), 7.25–7.17 (comp, 3H), 7.02–6.92 (m, 1H), 6.88 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 8.2 Hz, 1H), 4.24 (d, *J* = 9.7 Hz, 1H), 4.18 (app t, *J* = 8.2 Hz, 1H), 3.98 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.84–3.73 (comp, 2H), 3.54 (app dt, *J* = 12.7, 8.3 Hz, 1H), 3.13–2.96 (comp, 2H), 2.88–2.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 151.5, 142.1, 129.6, 128.9(3), 128.8(9), 128.8(5), 128.8(2), 127.3, 122.5(1), 122.4(7), 121.7, 120.4, 118.0, 117.2, 67.1, 58.8, 55.3, 45.7, 44.6, 30.4; *m/z* (ESI–MS) 418.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 12.8 and 23.2 min (major).

The absolute configuration was assigned by analogy.

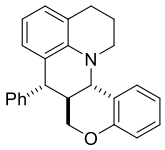
(6a*S*,7*R*,13a*S*)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (2.12e): 

Following the general procedure **F**, compound **2.12e** was obtained as a white solid in 94% yield (63.8 mg, 12:1 dr); mp = 145–147 °C; R_f = 0.38 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ +114.6 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2971, 2821, 1489, 1451, 1227, 758, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.64 (app d, *J* = 7.9

Hz, 1H), 7.40–7.34 (comp, 2H), 7.33–7.28 (m, 1H), 7.27–7.18 (comp, 3H), 7.05 (app d, *J* = 7.1 Hz, 1H), 6.98 (app t, *J* = 7.6 Hz, 1H), 6.90 (app d, *J* = 8.2 Hz, 1H), 6.67 (app t, *J* = 7.4 Hz, 1H), 6.53 (app d, *J* = 7.8 Hz, 1H), 4.27–4.15 (comp, 2H), 4.02 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.89 (d, *J* = 11.9 Hz, 1H), 3.80 (app t, *J* = 11.2 Hz, 1H), 3.48 (app dt, *J* = 12.7, 8.2 Hz, 1H), 3.13–2.97 (comp, 2H), 2.95–2.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 142.7, 130.5, 129.4, 129.0, 128.7(4), 128.7(0), 127.1, 126.9, 123.7, 122.6, 122.3, 120.3, 119.9, 117.9, 67.3, 59.1, 56.4, 46.1, 45.0, 29.4; *m/z* (ESI–MS) 340.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.2 min and t_R = 17.4 min (major).

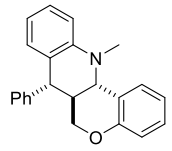
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,14a*S*)-7-phenyl-6a,12,13,14a-tetrahydro-6*H*,7*H*,11*H*-chromeno[4,3-*b*]pyrido[3,2,1-*ij*]quinoline (2.12f): Following the general procedure **F**, compound **2.12f** was obtained as a white solid in 83% yield (58.7 mg, 7:1 mixture of diastereomers); mp = 124–125 °C; R_f = 0.43 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ + 84.0 (c 0.5, $CHCl_3$, 81% *ee*); IR (KBr) 2936, 1487, 1452, 1227, 758, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) 7.47 (app d, *J* = 7.7 Hz, 1H), 7.37–7.27 (comp, 3H), 7.22–7.11 (comp, 3H), 7.01 (app td, *J* = 7.5, 1.2 Hz, 1H), 6.97 (app d, *J* = 7.2 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.65 (app t, *J* = 7.5 Hz, 1H), 6.52 (app d, *J* = 7.7 Hz, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.02 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.90–3.77 (comp, 2H), 3.22–3.11 (m, 1H), 3.00–2.93 (m, 1H), 2.85–2.73 (comp, 2H), 2.53–2.43 (m, 1H), 2.22–2.12 (m, 1H), 2.01–1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 156.0, 142.6, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 127.8, 127.5, 127.0, 125.6, 120.6, 119.7, 117.2, 69.5, 57.9, 48.0, 45.7, 39.1, 26.5, 24.1; *m/z* (ESI–MS) 354.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.6 min and t_R = 10.8 min (major).



The absolute configuration was assigned by analogy.

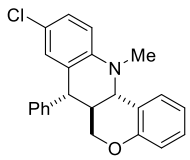
(6a*S*,7*R*,12a*S*)-12-methyl-7-phenyl-6a,7,12,12a-tetrahydro-6*H*-chromeno[4,3-*b*]quinoline (2.12g):



Following the general procedure **F**, compound **2.12g** was obtained as a white solid in 61% yield (40.0 mg, >20:1 dr); mp = 160–162 °C; R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +261.9 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2897, 1483, 1453, 1234, 749, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.61 (app d, *J* = 7.4 Hz, 1H), 7.37–7.31 (comp, 2H), 7.30–7.26 (m, 1H), 7.23–7.10 (comp, 5H), 7.02 (app t, *J* = 7.5 Hz, 1H), 6.88–6.81 (comp, 2H), 6.80–6.74 (m, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.13 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.82 (app t, *J* = 11.0 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 1H), 2.76 (s, 3H), 2.57–2.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 143.6, 131.2, 130.6, 129.0, 128.9, 128.7, 128.3, 127.0, 126.9, 123.7, 122.0, 120.9, 117.1, 104.7, 68.3, 58.3, 48.4, 40.0, 34.1; *m/z* (ESI–MS) 328.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.3 min and t_R = 13.4 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12a*S*)-9-chloro-12-methyl-7-phenyl-6a,7,12,12a-tetrahydro-6*H*-chromeno[4,3-*b*]quinoline (2.12h):

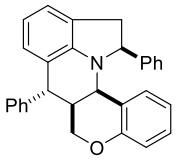


Following the general procedure **F**, compound **2.12h** was obtained as a white solid in 98% yield (70.9 mg, >20:1 dr); mp = 148–149 °C; R_f = 0.45 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ +272.3 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 2888, 1479, 1230, 1037, 761, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.63–7.53 (m, 1H), 7.39–7.27 (comp, 3H), 7.21–7.16 (m, 1H), 7.15–7.08 (comp, 4H), 7.02 (app td, *J* = 7.5, 1.3 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.71–6.75 (m, 1H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.10 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.80 (app t, *J* = 11.0 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H), 2.73 (s, 3H), 2.53–2.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 142.6, 132.9, 130.0, 128.9(3), 128.8(5), 128.7(7), 128.5, 127.3, 125.1, 121.0, 117.2, 68.1, 58.3, 48.3, 40.0, 33.9; *m/z* (ESI–MS) 362.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.0 min and t_R = 10.0 min (major).

The absolute configuration was assigned by analogy.

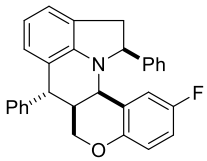
Preparation and characterization data of kinetic resolution of indoline products:

General procedure: A flame dried vial was charged with aldehyde (0.2 mmol, 1 equiv), **2.17a** (15 mg, 0.02 mmol, 0.1 equiv), and powdered 4 Å M.S. (100 mg). Freshly distilled toluene (3 mL) was added and the resulting mixture was cooled to –10 °C over 10 min. The indoline in 1 mL toluene was then added (0.48 mmol, 2.4 equiv) and the reaction mixture was stirred at –10 °C. After the aldehyde was consumed (as judged by TLC), triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to room temperature. The crude mixture was purified directly by flash chromatography.

(6a*S*,7*R*,12*S*,13a*R*)-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18a**): 

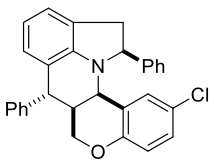
Following the general procedure, compound **2.18a** was obtained as a white foam in 88% yield (73 mg); mp = 87–88 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –271.9 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 3025, 1601, 1490, 1465, 1227, 751, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.34–7.28 (comp, 2H), 7.22 (app t, *J* = 7.3 Hz, 1H), 7.16–7.07 (comp, 4H), 7.05–6.91 (comp, 4H), 6.85–6.71 (comp, 3H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.24 (app t, *J* = 7.4 Hz, 1H), 4.84 (app t, *J* = 10.0 Hz, 1H), 4.64 (dd, *J* = 12.4, 10.1 Hz, 1H), 4.36 (dd, *J* = 10.2, 4.4 Hz, 1H), 4.00–3.93 (comp, 2H), 3.48 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.93 (dd, *J* = 16.1, 10.9 Hz, 1H), 2.52–2.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 148.1, 147.0, 143.8, 131.3, 129.2, 128.4, 128.3, 128.2, 127.7, 127.0, 126.4, 126.2, 126.1, 122.3, 120.4, 119.7, 119.1, 118.7, 115.5, 70.6, 67.0, 52.2, 42.4, 42.0, 41.4; *m/z* (ESI–MS) 416.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.4 min (major) and t_R = 10.3 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-2-fluoro-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18b**): 

Following the general procedure, compound **2.18b** was obtained as a white foam in 84% yield (73 mg); mp = 115–116 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –342.5 (c 0.5, $CHCl_3$, 98% *ee*); IR (KBr) 2952, 2838, 1494, 1266, 756, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33–7.26 (comp, 2H), 7.23–7.18 (m, 1H), 7.17–7.12 (comp, 2H), 7.11–7.06 (comp, 2H), 7.06–6.94 (comp, 4H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.74 (app t, *J* = 7.5 Hz, 1H), 6.49–6.39 (comp, 2H), 6.32 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.79 (dd, *J* = 11.0, 8.9 Hz, 1H), 4.57 (dd, *J* = 12.1, 10.3 Hz, 1H), 4.32 (ddd, *J* = 10.3, 4.5, 1.1 Hz, 1H), 3.96–3.87 (comp, 2H), 3.45 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.95 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.45–2.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (d, $J_{C–F}$ = 237.3 Hz), 149.8, 147.8, 146.6, 143.5, 128.5, 128.3, 128.1, 127.8, 127.0, 126.5, 126.5, 126.3, 122.4, 121.3, 119.9, 119.1, 117.3 (d, $J_{C–F}$ = 23.2 Hz), 116.5 (d, $J_{C–F}$ = 7.8 Hz), 115.7 (d, $J_{C–F}$ = 23.2 Hz), 70.9, 67.0, 52.1, 42.3, 41.6, 41.3; *m/z* (ESI–MS) 434.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.4 min (major) and t_R = 10.6 min.

The absolute configuration was assigned by analogy.

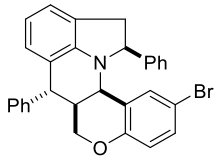
(6a*S*,7*R*,12*S*,13a*R*)-2-chloro-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18c**): 

Following the general procedure, compound **2.18c** was obtained as a white foam in 86% yield (77 mg); mp = 156–157 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –374.8 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 2951, 1601, 1485, 1263, 1229, 754, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32–7.27 (comp, 2H), 7.23–7.18 (m, 1H), 7.17–7.12 (comp, 2H), 7.10–7.03 (comp, 4H), 7.02 (d, *J* = 7.1 Hz, 1H), 7.00–6.95 (m, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.75 (app t, *J* = 7.8 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.42 (d, *J* = 8.7 Hz, 1H), 4.79 (dd, *J* = 11.0, 8.9 Hz, 1H),

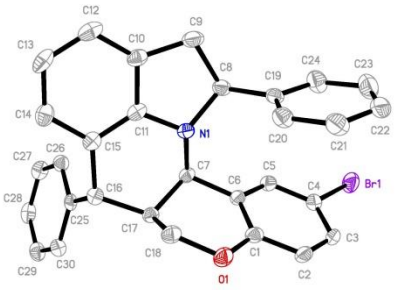
4.58 (dd, *J* = 12.2, 10.4 Hz, 1H), 4.33 (dd, *J* = 10.4, 4.5 Hz, 1H), 3.97–3.86 (comp, 2H), 3.45 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.95 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.45–2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 147.7, 146.6, 143.5, 131.1, 128.9, 128.5, 128.3, 128.1, 127.9, 127.0, 126.6, 126.5, 126.3, 123.3, 122.4, 121.7, 119.9, 119.0, 117.0, 70.9, 67.1, 51.9, 42.3, 41.6, 41.3; *m/z* (ESI–MS) 450.7 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.2 min (major) and t_R = 9.9 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-2-bromo-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18d**): Following the general procedure, compound **2.18d** was obtained as a white foam in 89% yield (88 mg); mp = 167–168 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –348.7 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 3028, 2830, 1601, 1488, 1463, 1228, 753, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.33–7.26 (comp, 2H), 7.24–7.18 (m, 1H), 7.17–7.12 (comp, 2H), 7.11–7.05 (comp, 4H), 7.04–6.95 (comp, 2H), 6.85–6.78 (comp, 2H), 6.75 (app t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.37 (d, *J* = 8.8 Hz, 1H), 4.79 (dd, *J* = 11.0, 8.9 Hz, 1H), 4.58 (dd, *J* = 11.7, 10.5 Hz, 1H), 4.33 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.97–3.87 (comp, 2H), 3.45 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.95 (dd, *J* = 16.1, 11.0 Hz 1H), 2.44–2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 147.7, 146.6, 143.4, 134.1, 131.8, 128.5, 128.3, 128.1, 127.9, 127.0, 126.6, 126.3, 122.4, 122.3, 120.0, 119.0, 117.4, 110.7, 71.0, 67.1, 51.9, 42.3, 41.6, 41.3; *m/z* (ESI–MS) 494.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.1 min (major) and t_R = 9.3 min.



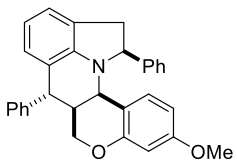
The enantioenriched product was crystallized from dichloromethane through slow evaporation at room temperature and the absolute configuration was assigned by X-ray crystallography



The requisite CIF has been deposited with the CCDC (deposition # 1455869).

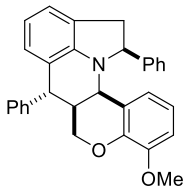
(6a*S*,7*R*,12*S*,13a*R*)-2-methyl-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18e**): Following the general procedure, compound **2.18e** was obtained as a white foam in 90% yield (77 mg); mp = 155–157 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –359.6 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 3024, 2833, 1601, 1485, 1466, 1225, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.29–7.27 (comp, 2H), 7.21–7.15 (m, 1H), 7.14–7.05 (comp, 4H), 7.03–6.95 (comp, 3H), 6.94–6.89 (m, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.73 (app t, *J* = 7.5 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 4.80 (dd, *J* = 11.1, 8.9 Hz, 1H), 4.59 (dd, *J* = 12.2, 10.2 Hz, 1H), 4.31 (ddd, *J* = 10.3, 4.4, 1.1 Hz, 1H), 3.95–3.85 (comp, 2H), 3.43 (dd, *J* = 16.0, 8.9 Hz, 1H), 2.91 (dd, *J* = 16.0, 11.3 Hz, 1H), 2.47–2.41 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 148.1, 147.0, 143.9, 132.1, 129.6, 128.4, 128.3, 128.1, 127.6, 127.5, 127.0, 126.4, 126.3, 126.1, 122.2, 119.8, 119.6, 119.2, 115.3, 71.1, 67.0, 52.2, 42.5, 42.0, 41.4, 19.9; *m/z* (ESI–MS) 430.3 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.0 min (major) and t_R = 10.1 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-3-methoxy-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18f**): 

Following the general procedure, compound **2.18f** was obtained as a white foam in 85% yield (76 mg); mp = 196–198 °C; R_f = 0.23 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –275.6 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 3026, 2830, 1489, 1465, 1224, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33–7.28 (comp, 2H), 7.23–7.19 (m, 1H), 7.15–7.06 (comp, 4H), 7.05–6.93 (comp, 4H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.73 (app t, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 6.08 (d, *J* = 2.5 Hz, 1H), 5.80 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.80 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.60 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.33 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.98–3.88 (comp, 2H), 3.58 (s, 3H), 3.46 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.92 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.48–2.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 154.5, 148.1, 147.0, 143.9, 131.9, 128.4, 128.3, 128.1, 127.7, 127.0, 126.4, 126.3, 126.0, 122.3, 119.5, 119.0, 113.2, 105.3, 100.7, 70.6, 67.0, 55.2, 51.6, 42.5, 42.1, 41.3; *m/z* (ESI–MS) 446.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.3 min (major) and t_R = 11.5 min.

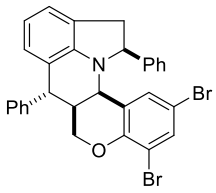
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-4-methoxy-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18g**): 

Following the general procedure, compound **2.18g** was obtained as a white solid in 88% yield (78 mg); mp = 227–228 °C; R_f = 0.10 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –362.1 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 3025, 2834, 1490, 1462, 1225, 753, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31–7.27 (comp, 2H), 7.23–7.15 (m, 1H), 7.12–7.06 (comp, 4H), 7.03–6.94 (comp, 3H), 6.94–6.88 (m, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.73 (app t, *J* = 7.4 Hz, 1H), 6.40 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.29 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.20 (app t, *J* = 7.8 Hz, 1H), 4.81 (dd, *J* = 10.7, 9.1 Hz, 1H), 4.69 (dd, *J* = 12.5, 10.2 Hz, 1H), 4.49 (dd, *J* = 10.2, 4.5 Hz, 1H). 4.00–3.91 (comp, 2H), 3.73 (s, 3H), 3.46 (dd, *J* = 16.1, 9.2 Hz, 1H), 2.89 (dd, *J* = 16.1, 10.7 Hz, 1H), 2.52–2.43 (m, 1H); ^{13}C NMR

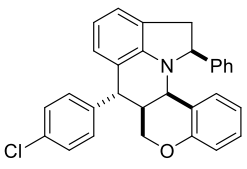
(125 MHz, $CDCl_3$) δ 148.1, 147.4, 147.0, 144.0, 143.2, 128.4, 128.3, 128.2, 127.5, 127.0, 126.4, 126.2, 126.0, 123.4, 122.3, 121.1, 119.7, 118.9, 118.4, 111.3, 70.2, 67.4, 55.9, 51.8, 42.4, 41.9, 41.4; *m/z* (ESI–MS) 446.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.2 mL/min, UV = 280 nm, t_R = 23.3 min (major) and t_R = 25.1 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-2,4-dibromo-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18h**): 

Following the general procedure, compound **2.18h** was obtained as a white foam in 84% yield (96 mg); mp = 123–124 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –160.9 (c 0.5, $CHCl_3$, 80% *ee*); IR (KBr) 3028, 2834, 1600, 1490, 1465, 1228, 754, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32–7.24 (comp, 3H), 7.23–7.19 (m, 1H), 7.16–6.94 (comp, 8H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.78–6.73 (m, 1H), 6.70–6.66 (m, 1H), 4.75 (dd, *J* = 11.4, 8.8 Hz, 1H), 4.67 (dd, *J* = 13.0, 10.4 Hz, 1H), 4.53–4.46 (m, 1H), 3.99–3.84 (comp, 2H), 3.50–3.41 (m, 1H), 2.98–2.88 (m, 1H), 2.46–2.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 147.4, 146.4, 143.2, 134.6, 133.2, 129.2, 128.6, 128.3, 128.2, 127.8, 127.0, 126.8, 126.7, 126.4, 126.2, 123.3, 122.6, 120.2, 118.7, 70.8, 68.0, 51.8, 42.0, 41.5, 41.2; *m/z* (ESI–MS) 574.7 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.9 min (major) and t_R = 14.5 min.

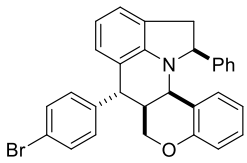
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-(4-chlorophenyl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18i**): 

Following the general procedure, compound **2.18i** was obtained as a white foam in 87% yield (78 mg); mp = 124–125 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –324.1 (c 0.5,

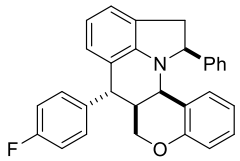
$CHCl_3$, 94% *ee*); IR (KBr) 3025, 2832, 1600, 1490, 1464, 1226, 752, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.26–7.24 (comp, 2H), 7.12–6.88 (comp, 8H), 6.82–6.70 (comp, 3H), 6.62 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 1H), 6.23 (app tt, *J* = 7.4, 1.0 Hz, 1H), 4.81 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.59 (dd, *J* = 12.1, 10.3 Hz, 1H), 4.32 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.95–3.87 (comp, 2H), 3.45 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.90 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.44–2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 148.0, 145.4, 143.7, 132.3, 131.3, 129.7, 129.3, 128.6, 128.0, 127.7, 127.2, 126.3, 126.2, 122.5, 120.3, 119.8, 118.8, 118.6, 115.6, 70.6, 66.9, 52.1, 41.9, 41.3; *m/z* (ESI–MS) 450.7 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 21.4 min and t_R = 25.9 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-(4-bromophenyl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18j**): 

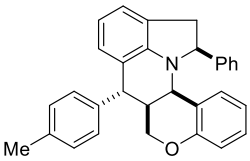
Following the general procedure, compound **2.18j** was obtained as a white foam in 93% yield (92 mg); mp = 130–131 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –341.1 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 3026, 2833, 1602, 1489, 1464, 1226, 751, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.44–7.37 (comp, 2H), 7.10–7.05 (comp, 2H), 7.03–6.89 (comp, 6H), 6.81–6.69 (comp, 3H), 6.64–6.59 (m, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 6.23 (app tt, *J* = 7.5, 1.0 Hz, 1H), 4.81 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.59 (dd, *J* = 12.4, 10.2 Hz, 1H), 4.32 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.93–3.87 (comp, 2H), 3.45 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.91 (dd, *J* = 16.2, 11.0 Hz, 1H), 2.43–2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 148.0, 145.9, 143.6, 131.5, 131.3, 130.1, 129.3, 128.0, 127.7, 127.2, 126.3, 126.2, 122.5, 120.4, 120.2, 119.8, 118.9, 118.5, 115.6, 70.6, 66.9, 52.1, 41.9, 41.8, 41.3; *m/z* (ESI–MS) 494.2 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 21.6 min and t_R = 26.2 min (major).

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-(4-fluorophenyl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18k**): 

Following the general procedure, compound **2.18k** was obtained as a white foam in 86% yield (75 mg); mp = 104–105 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –269.1 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 3028, 2835, 1492, 1464, 1228, 754, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.12–7.03 (comp, 4H), 7.03–6.90 (comp, 6H), 6.82–6.70 (comp, 3H), 6.63 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.50 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.23 (app td, *J* = 7.4, 1.2 Hz, 1H), 4.81 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.60 (dd, *J* = 12.2, 10.2 Hz, 1H), 4.32 (ddd, *J* = 10.4, 4.5, 1.2 Hz, 1H), 3.98–3.88 (comp, 2H), 3.45 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.91 (dd, *J* = 16.2, 10.9 Hz, 1H), 2.44–2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (d, J_{C-F} = 244.0 Hz), 153.7, 148.0, 143.7, 142.7 (d, J_{C-F} = 2.5 Hz), 131.3, 129.7 (d, J_{C-F} = 7.5 Hz), 129.3, 128.0, 127.7, 127.2, 126.3, 126.2, 122.4, 120.3, 119.7, 119.0, 118.8, 115.6, 115.2 (d, J_{C-F} = 21.3 Hz), 70.6, 66.9, 52.0, 42.0, 41.7, 41.3; *m/z* (ESI–MS) 434.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.9 min (major) and t_R = 6.8 min.

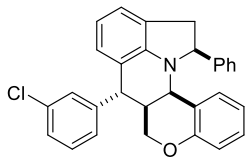
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-12-phenyl-7-(p-tolyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18l**): 

Following the general procedure, compound **2.18l** was obtained as a white foam in 90% yield (77 mg); mp = 142–143 °C; R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –380.2 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 3024, 2830, 1603, 1489, 1468, 1220, 753, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.15–7.04 (comp, 4H), 7.06–6.88 (comp, 6H), 6.85–6.67 (comp, 3H), 6.61 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.49 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.21 (app td, *J* = 7.4, 1.1 Hz, 1H), 4.81 (dd, *J* = 10.9, 9.0 Hz, 1H), 4.61 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.33 (ddd, *J* = 10.2, 4.5, 1.1 Hz, 1H), 3.97–3.89 (comp, 2H), 3.45 (dd,

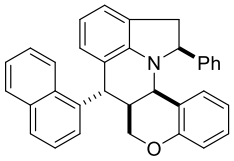
J = 16.1, 9.0 Hz, 1H), 2.90 (dd, *J* = 16.4, 11.0 Hz, 1H), 2.46–2.40 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 148.1, 144.1, 143.9, 136.0, 131.4, 129.2, 129.1, 128.2, 128.1, 127.6, 127.0, 126.3, 126.1, 122.2, 120.5, 119.6, 119.4, 118.7, 115.5, 70.6, 67.0, 52.2, 42.0, 41.4, 20.9; *m/z* (ESI–MS) 430.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 11.2 min (major) and t_R = 12.1 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-(3-chlorophenyl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18m**): 

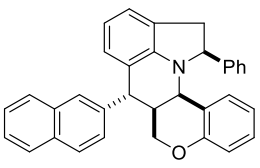
Following the general procedure, compound **2.18m** was obtained as a white foam in 86% yield (78 mg); mp = 94–95 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –283.4 (c 0.5, $CHCl_3$, 87% *ee*); IR (KBr) 3023, 2830, 1489, 1460, 1220, 750, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.25–7.16 (comp, 2H), 7.12–7.06 (comp, 3H), 7.04–6.89 (comp, 5H), 6.81–6.71 (comp, 3H), 6.65 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.50 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.27–6.21 (m, 1H), 4.83 (dd, *J* = 10.8, 9.1 Hz, 1H), 4.60 (dd, *J* = 12.2, 10.3 Hz, 1H), 4.32 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.94–3.88 (comp, 2H), 3.46 (dd, *J* = 16.1, 9.1 Hz, 1H), 2.91 (dd, *J* = 16.1, 10.8 Hz, 1H), 2.48–2.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 148.9, 148.1, 143.7, 134.4, 131.3, 129.7, 129.3, 128.4, 128.0, 127.7, 127.3, 126.7, 126.6, 126.3, 126.2, 122.6, 120.2, 119.8, 118.8, 118.2, 115.6, 70.5, 66.8, 52.1, 42.2, 41.8, 41.3; *m/z* (ESI–MS) 450.8 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.6 min (major) and t_R = 8.8 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-(naphthalen-1-yl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18n**): 

Following the general procedure, compound **2.18n** was obtained as a white solid in 85% yield (79 mg); mp = 252–253 °C; R_f = (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –129.6 (c 0.5, $CHCl_3$, 89% *ee*); IR (KBr) 3027, 2947, 1491, 1464, 1226, 752, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.18 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.59 (app t, *J* = 7.7 Hz, 1H), 7.50 (app t, *J* = 7.7 Hz, 1H), 7.35 (app t, *J* = 7.8 Hz, 1H), 7.12–7.02 (comp, 3H), 6.99–6.88 (comp, 3H), 6.87–6.81 (comp, 2H), 6.77 (app t, *J* = 7.6 Hz, 1H), 6.72 (app t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 6.14 (app t, *J* = 7.9 Hz, 1H), 4.88–4.74 (comp, 3H), 4.64–4.56 (m, 1H), 3.89–3.84 (m, 1H), 3.48 (dd, *J* = 16.0, 9.0 Hz, 1H), 2.93 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.59–2.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 148.7, 143.9, 142.8, 133.9, 131.3, 130.9, 129.2(0), 129.2(4), 128.5, 127.6, 127.1, 127.0(7), 127.0(4), 126.6, 126.2, 126.0, 125.7, 125.2, 122.4, 120.4, 119.8, 118.7, 115.5, 70.5, 66.9, 52.2, 41.7, 40.5, 37.7; *m/z* (ESI–MS) 466.4 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.8 min and t_R = 11.7 min (major).

The absolute configuration was assigned by analogy.

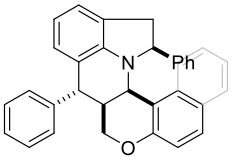
(6a*S*,7*R*,12*S*,13a*R*)-7-(naphthalen-2-yl)-12-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18o**): 

2.18o was obtained as a white foam in 88% yield (82 mg); mp = 170–172 °C; R_f = 0.32 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –343.6 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 3026, 2830, 1600, 1490, 1464, 1226, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.86–7.73 (comp, 3H), 7.49–7.41 (comp, 3H), 7.35–7.31 (m, 1H), 7.16–6.91 (comp, 6H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.81–6.71 (comp, 2H), 6.61 (app dt, *J* = 7.6, 1.2 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.22 (app tt, *J* = 7.4, 1.1 Hz, 1H), 4.89–4.83 (m, 1H), 4.71–4.64 (m, 1H), 4.40 (dd, *J* = 10.4, 4.5 Hz, 1H), 4.12–3.97 (comp, 2H), 3.50 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.95 (dd, *J* =

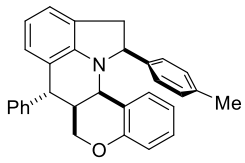
16.4, 10.8 Hz, 1H), 2.60–2.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 148.2, 144.3, 143.8, 133.3, 132.2, 131.3, 129.2, 128.3, 127.8, 127.7, 127.6, 127.2, 127.0, 126.7, 126.3, 126.2, 126.1, 125.7, 122.4, 120.4, 119.7, 119.1, 118.8, 115.5, 70.6, 67.1, 52.3, 42.5, 41.9, 41.4; *m/z* (ESI–MS) 466.4 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.9 min (major) and t_R = 9.2 min.

The absolute configuration was assigned by analogy.

(8a*S*,9*R*,14*S*,15a*R*)-9,14-diphenyl-8a,13,14,15a-tetrahydro-8*H*,9*H*-benzo[5,6]chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.18p**): Following the general procedure, compound **2.18p** was obtained as a white foam in 99% yield (92 mg); mp = 175–176 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –312.0 (c 0.5, $CHCl_3$, 91% *ee*); IR (KBr) 3025, 1600, 1463, 1262, 1227, 1091, 748, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.08 (d, *J* = 8.5 Hz, 1H), 7.55–7.47 (comp, 2H), 7.42–7.36 (comp, 2H), 7.33–7.25 (comp, 5H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.83 (app t, *J* = 7.4 Hz, 1H), 6.80–6.74 (comp, 2H), 6.73–6.68 (comp, 2H), 6.68–6.64 (comp, 2H), 4.98 (app t, *J* = 9.8 Hz, 1H), 4.95–4.92 (m, 1H), 4.77 (dd, *J* = 13.0, 10.1 Hz, 1H), 4.50 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.14–4.06 (m, 1H), 3.49 (dd, *J* = 16.2, 9.3 Hz, 1H), 2.93 (dd, *J* = 16.3, 10.3 Hz, 1H), 2.64–2.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 147.9, 147.1, 143.3, 132.7, 129.7, 128.4, 128.3(7), 128.3(5), 128.3(1), 126.9, 126.6, 126.4, 125.9, 125.7, 125.2, 122.4, 122.3, 120.9, 119.2, 118.0, 112.1, 68.8, 66.4, 44.6, 42.5, 41.6, 41.2; *m/z* (ESI–MS) 466.3 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.8 min (major) and t_R = 14.4 min.

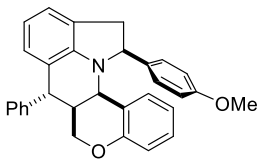


The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-7-phenyl-12-(p-tolyl)-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20a**): 

Following the general procedure, compound **2.20a** was obtained as a white foam in 92% yield (79 mg); mp = 161–162 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –304.8 (c 0.5, $CHCl_3$, 87% *ee*); IR (KBr) 3028, 2830, 1604, 1490, 1466, 1226, 751, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32–7.27 (comp, 2H), 7.23–7.18 (m, 1H), 7.13–7.08 (comp, 2H), 7.02–6.96 (comp, 3H), 6.84–6.75 (comp, 4H), 6.72 (app t, *J* = 7.4 Hz, 1H), 6.62 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 6.23 (app tt, *J* = 7.4, 1.0 Hz, 1H), 4.79 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.59 (dd, *J* = 12.1, 10.2 Hz, 1H), 4.33 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.98–3.92 (comp, 2H), 3.43 (dd, *J* = 16.0, 8.9 Hz, 1H), 2.92 (dd, J = 16.0, 10.9 Hz, 1H), 2.47–2.41 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 148.1, 146.8, 140.6, 135.6, 131.4, 128.9, 128.4, 128.3(9), 128.3(2), 128.1, 127.1, 126.4, 126.3, 122.3, 120.6, 119.5, 119.1, 118.7, 115.5, 70.5, 67.0, 52.1, 42.4, 41.8, 41.3, 20.9; *m/z* (ESI–MS) 430.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.4 min (major) and t_R = 4.9 min.

The absolute configuration was assigned by analogy.

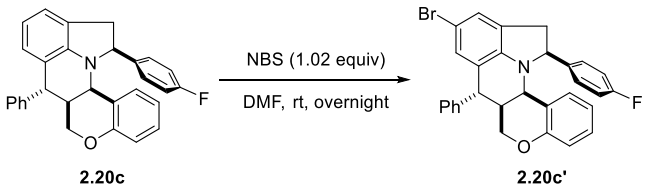
(6a*S*,7*R*,12*S*,13a*R*)-12-(4-methoxyphenyl)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20b**): 

Following the general procedure, compound **2.20b** was obtained as a white foam in 97% yield (86 mg); mp = 177–178 °C; R_f = 0.20 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –327.9 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 3026, 2837, 1604, 1492, 1460, 1226, 752, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35–7.29 (comp, 2H), 7.25–7.20 (m, 1H), 7.16–7.11 (comp, 2H), 7.08–7.00 (comp, 3H), 6.87–6.80 (comp, 2H), 6.75 (app t, *J* = 7.3 Hz, 1H), 6.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.59–6.53 (comp, 3H), 6.30 (app td, *J* = 7.4, 1.2 Hz, 1H), 4.81 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.61 (dd, *J* = 12.0, 10.3 Hz, 1H), 4.35 (ddd, *J* = 10.4, 4.5, 1.1 Hz, 1H), 4.00–3.95 (comp, 2H), 3.71 (s, 3H), 3.44 (dd, *J* = 16.0, 8.9 Hz, 1H), 2.94 (dd, *J* = 16.0, 10.9 Hz, 1H), 2.50–2.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 158.0, 153.7, 148.1, 146.8, 135.9, 131.4, 129.1, 128.5, 128.4, 128.1, 127.5, 127.1, 126.5, 122.3, 120.7, 119.6, 119.2, 118.8, 115.6, 113.3, 70.3, 67.0, 55.3, 52.2, 42.4, 41.8, 41.4; *m/z* (ESI–MS) 446.3 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.1 mL/min, UV = 280 nm, t_R = 59.1 min (major) and t_R = 62.1 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-12-(4-fluorophenyl)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20c**): Following the general procedure, compound **2.20c** was obtained as a white foam in 93% yield (81 mg); mp = 183–184 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –317.6 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3030, 2847, 1604, 1508, 1490, 1463, 1220, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.34–7.27 (comp, 2H), 7.25–7.19 (m, 1H), 7.14–7.09 (comp, 2H), 7.09–7.01 (comp, 3H), 6.88–6.81 (comp, 2H), 6.77 (app t, *J* = 7.4 Hz, 1H), 6.70–6.64 (comp, 2H), 6.61 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.28 (app td, *J* = 7.4, 1.2 Hz, 1H), 4.83 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.62 (dd, *J* = 12.5, 10.2 Hz, 1H), 4.36 (ddd, *J* = 10.3, 4.6, 1.2 Hz, 1H), 3.99–3.93 (comp, 2H), 3.46 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.88 (dd, *J* = 16.1, 10.8 Hz, 1H), 2.52–2.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1 (d, $J_{C–F}$ = 243.9 Hz), 153.7, 147.9, 146.9, 139.6 (d, $J_{C–F}$ = 3.1 Hz), 131.3, 129.4, 128.4, 128.3, 128.2(6), 127.6 (d, $J_{C–F}$ = 7.9 Hz), 126.8, 126.4, 122.3, 120.3, 119.8, 119.1, 118.8, 115.7, 114.4 (d, $J_{C–F}$ = 21.5 Hz), 69.8, 67.0, 52.1, 42.4, 42.0, 41.4; *m/z* (ESI–MS) 434.5 $[M + H]^+$.

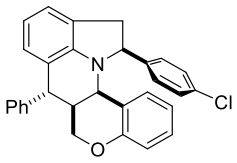


2.20c **2.20c'**

Due to the poor separation of **2.20c** on chiral HPLC columns, it was transformed to **2.20c**'to determine the ee: **2.20c** (43 mg, 0.1 mmol) was dissolved in 1 ml of DMF and then NBS (18 mg, 1.02 equiv) was added as a solid. The reaction mixture was stirred overnight and the crude product purified directly by flash chromatography to give **6c'** as a white solid in 89% yield (45 mg); mp = 183–184 °C; R_f = 0.34 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3027, 2837, 1604, 1491, 1466, 1224, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35–7.27 (comp, 2H), 7.25–7.20 (m, 1H), 7.12–7.05 (comp, 3H), 7.04–6.96 (comp, 2H), 6.96–6.92 (m, 1H), 6.86–6.80 (m, 1H), 6.70–6.62 (comp, 2H), 6.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.51 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.27 (app td, *J* = 7.4, 1.1 Hz, 1H), 4.82 (dd, *J* = 10.6, 9.1 Hz, 1H), 4.50 (dd, *J* = 12.4, 10.3 Hz, 1H), 4.33 (ddd, *J* = 10.4, 4.6, 1.2 Hz, 1H), 3.95–3.86 (comp, 2H), 3.43 (dd, *J* = 16.4, 9.1 Hz, 1H), 2.85 (dd, *J* = 16.3, 10.8 Hz, 1H), 2.48–2.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2 (d, J_{C-F} = 244.5 Hz), 153.6, 146.9, 146.1, 139.1 (d, J_{C-F} = 3.0 Hz), 131.2, 130.6, 129.5, 128.9, 128.6, 128.2, 127.6 (d, J_{C-F} = 8.1 Hz), 126.7, 125.6, 120.6, 119.8, 118.9, 115.8, 114.5 (d, J_{C-F} = 21.6 Hz), 111.4, 69.6, 66.7, 51.8, 42.3, 41.7, 40.9; *m/z* (ESI–MS) 514.7 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.2 min and t_R = 5.7 min (major).

The absolute configuration was assigned by analogy.

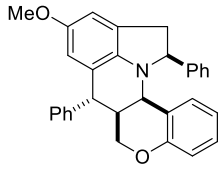
(6a*S*,7*R*,12*S*,13a*R*)-12-(4-chlorophenyl)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20d**): Following the general procedure, compound **2.20d** was obtained as a white foam in 95% yield (85 mg); mp = 175–176 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –331.1 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 3020, 2852, 1601, 1489, 1464, 1228, 749, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36–7.30 (comp, 2H), 7.26–7.21 (m, 1H), 7.19–7.10 (comp, 2H), 7.08–7.03 (comp, 3H), 7.00–6.95 (comp, 2H), 6.92–6.84 (comp, 2H), 6.82–6.77 (m, 1H), 6.63 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.31 (app td, *J* = 7.4, 2.4 Hz, 1H), 4.84 (dd, *J* = 10.2, 9.1, Hz, 1H), 4.64 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.39 (ddd, *J* = 10.3, 4.6, 1.4 Hz, 1H), 4.04–3.94 (comp, 2H), 3.49 (dd, *J* = 16.1,



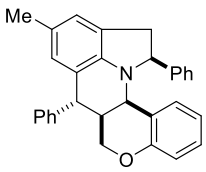
9.1 Hz, 1H), 2.89 (dd, *J* = 16.1, 10.9 Hz, 1H), 2.57–2.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 147.8, 146.9, 142.5, 131.5, 131.2, 129.4, 128.4, 128.2(8), 128.2(7), 127.7, 127.5, 126.7, 126.4, 122.3, 120.2, 119.9, 119.1, 118.8, 115.7, 69.7, 66.9, 52.0, 42.4, 41.9, 41.3; *m/z* (ESI–MS) 450.7 [M + H]$^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.9 min (major) and t_R = 7.8 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-9-methoxy-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20e**): Following the general procedure, compound **2.20e** was obtained as a white foam in 90% yield (80 mg); mp = 130–131 °C; R_f = 0.20 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –299.0 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 3026, 2832, 1491, 1479, 1225, 750, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.31–7.26 (comp, 2H), 7.22–7.17 (m, 1H), 7.14–7.05 (comp, 4H), 7.00–6.88 (comp, 3H), 6.78–6.73 (m, 1H), 6.67–6.64 (m, 1H), 6.57 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.52–6.48 (m, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 6.20–6.15 (m, 1H), 4.74 (dd, *J* = 11.2, 8.7 Hz, 1H), 4.66 (dd, *J* = 12.4, 10.1 Hz, 1H), 4.33 (ddd, *J* = 10.2, 4.5, 1.1 Hz, 1H), 3.91–3.83 (comp, 2H), 3.67 (s, 3H), 3.38 (dd, *J* = 16.2, 8.9 Hz, 1H), 2.86 (dd, *J* = 16.2, 11.2, 1.2 Hz, 1H), 2.47–2.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 153.7, 146.8, 143.7, 142.4, 131.3, 129.1, 128.4, 128.3, 127.6, 126.5, 126.3, 126.1, 120.6, 119.4, 118.6, 117.3, 115.5, 112.1, 110.4, 71.2, 67.1, 56.0, 52.9, 42.8, 42.3, 41.6; *m/z* (ESI–MS) 446.3 [M + H]$^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.4 min (major) and t_R = 11.7 min.

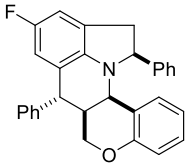


The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-9-methyl-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20f**): 

Following the general procedure, compound **2.20f** was obtained as a white foam in 98% yield (84 mg); mp = 142–143 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –358.0 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 3026, 2835, 1491, 1474, 1224, 1116, 750, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36–7.29 (comp, 2H), 7.25–7.20 (m, 1H), 7.17–7.09 (comp, 4H), 7.02–6.92 (comp, 3H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.79 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 6.65 (d, *J* = 1.7 Hz, 1H), 6.63 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.55–6.52 (m, 1H), 6.23 (app td, *J* = 7.4, 1.2 Hz, 1H), 4.80 (dd, *J* = 11.0, 8.9 Hz, 1H), 4.68 (dd, *J* = 12.4, 10.2 Hz, 1H), 4.36 (ddd, *J* = 10.3, 4.5, 1.2 Hz, 1H), 3.95–3.91 (comp, 2H), 3.43 (dd, *J* = 15.9, 8.9 Hz, 1H), 2.90 (dd, *J* = 16.0, 11.0 Hz, 1H), 2.50–2.43 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 147.1, 146.0, 143.9, 131.4, 129.1, 128.4, 128.3, 128.2, 127.6, 127.2, 126.4, 126.2, 126.0, 123.3, 120.5, 118.9, 118.6, 115.5, 70.9, 67.1, 52.5, 42.5, 42.2, 41.5, 21.0; *m/z* (ESI–MS) 450.7 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 5.5 min (major) and t_R = 11.7 min.

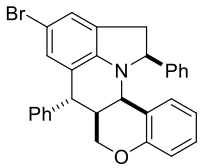
The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-9-fluoro-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20g**): 

Following the general procedure, compound **2.20g** was obtained as a white foam in 95% yield (82 mg); mp = 93–94 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –290.2 (c 0.5, $CHCl_3$, 91% *ee*); IR (KBr) 3024, 1611, 1491, 1465, 1226, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35–7.29 (comp, 2H), 7.26–7.22 (m, 1H), 7.16–7.09 (comp, 4H), 7.04–6.93 (comp, 3H), 6.83– 6.74 (comp, 2H), 6.63 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.56–6.50 (comp, 2H), 6.24 (app td, *J* = 7.4, 1.2 Hz, 1H), 4.83 (dd, *J* = 11.1, 8.9 Hz, 1H), 4.63 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.35 (ddd, *J* = 10.3, 4.5, 1.2 Hz, 1H), 3.95–3.88 (comp, 2H), 3.43 (dd, *J* = 16.3, 9.0 Hz, 1H), 2.91 (dd, *J* = 16.3, 11.1 Hz, 1H), 2.50–2.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6 (d, J_{C-F} = 236.5 Hz), 153.7, 146.2, 144.2, 143.3, 131.3, 129.3, 128.5, 128.4(7)

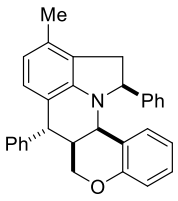
(d, $J_{C–F}$ = 8.3 Hz), 128.2, 127.7, 126.6, 126.3, 126.2, 120.2, 119.7 (d, $J_{C–F}$ = 7.7 Hz), 118.7, 115.6, 113.7 (d, $J_{C–F}$ = 23.1 Hz), 110.4 (d, $J_{C–F}$ = 24.6 Hz), 71.0, 66.8, 52.5, 42.6, 41.8, 41.1; *m/z* (ESI–MS) 434.4 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.4 min (major) and t_R = 5.5 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-9-bromo-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20h**): 

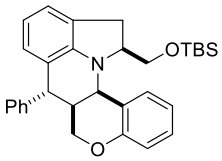
Following the general procedure, compound **2.20h** was obtained as a white foam in 89% yield (88 mg); mp = 165–167 °C; R_f = 0.33 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –346.2 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 3024, 2834, 1489, 1466, 1230, 756, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31–7.27 (comp, 2H), 7.22–7.18 (m, 1H), 7.11–7.07 (comp, 3H), 7.02–6.89 (comp, 4H), 6.82–6.71 (comp, 3H), 6.62 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.51–6.47 (m, 1H), 6.22 (app td, *J* = 7.4, 1.1 Hz, 1H), 4.82 (dd, *J* = 10.9, 9.0 Hz, 1H), 4.62 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.34 (ddd, *J* = 10.2, 4.5, 1.1 Hz, 1H), 3.97–3.92 (comp, 2H), 3.45 (dd, *J* = 16.1, 9.0 Hz, 1H), 2.90 (dd, *J* = 16.1, 10.9 Hz, 1H), 2.48–2.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 148.1, 147.0, 143.8, 131.3, 129.2, 128.4, 128.3, 128.1, 127.7, 127.0, 126.4, 126.2, 126.1, 122.3, 120.4, 119.7, 119.1, 118.7, 115.5, 70.6, 67.0, 52.2, 42.4, 41.9, 41.4; *m/z* (ESI–MS) 494.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.8 min (major) and t_R = 6.8 min.

The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*S*,13a*R*)-10-methyl-7,12-diphenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20i**): 

Following the general procedure, compound **2.20i** was obtained as a white foam in 91% yield (78 mg); mp = 96–97 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –293.7 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 3026, 2835, 1601, 1491, 1469, 1228, 754, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.30–7.27 (comp, 2H), 7.22–7.16 (m, 1H), 7.15–7.04 (comp, 4H), 7.01–6.89 (comp, 3H), 6.81–6.69 (comp, 2H), 6.63 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.52–6.45 (m, 1H), 6.22 (app td, *J* = 7.3, 1.0 Hz, 1H), 4.82 (dd, *J* = 10.6, 9.2 Hz, 1H), 4.63 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.33 (ddd, *J* = 10.3, 4.5, 1.1 Hz, 1H), 3.95–3.90 (comp, 2H), 3.44 (dd, *J* = 16.1, 9.2 Hz, 1H), 2.78 (dd, *J* = 16.1, 10.6 Hz, 1H), 2.48–2.41 (m, 1H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 147.7, 147.2, 144.1, 131.9, 131.4, 129.2, 128.4, 128.3, 127.6, 126.3, 126.2, 126.0, 125.4, 121.1, 120.5, 118.7, 116.5, 115.5, 110.0, 70.3, 67.1, 52.2, 42.3, 41.9, 40.4, 18.3; *m/z* (ESI–MS) 430.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.5 min (major) and t_R = 6.4 min.

The absolute configuration was assigned by analogy.

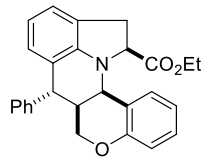
(6a*S*,7*R*,12*S*,13a*R*)-12-(((tert-butyldimethylsilyl)oxy)methyl)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20j**): 

Following the general procedure, compound **2.20j** was obtained as a white foam in 98% yield (95 mg); mp = 61–63 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –158.3 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2927, 2854, 1602, 1490, 1464, 1230, 753, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.34–7.29 (comp, 2H), 7.29–7.26 (m, 1H), 7.26–7.21 (comp, 2H), 7.17–7.11 (comp, 2H), 7.04–6.99 (m, 1H), 6.91–6.83 (comp, 2H), 6.69–6.61 (comp, 2H), 4.34 (app t, *J* = 10.4 Hz, 1H), 4.26 (ddd, *J* = 10.5, 4.1, 1.0 Hz, 1H), 4.13 (d, *J* = 2.8 Hz, 1H), 4.02–3.95 (m, 1H), 3.86 (d, *J* = 3.1 Hz, 1H), 3.30 (dd, *J* = 16.3, 9.3 Hz, 1H), 3.23 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.12 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.06 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.43–2.37 (m, 1H), 0.84 (s, 9H), –0.06 (s, 6H); ^{13}C NMR (125

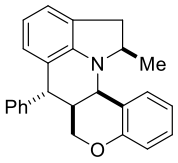
MHz, $CDCl_3$) δ 154.4, 148.0, 146.0, 130.3, 129.6, 128.6, 128.4, 127.5, 127.3, 126.5, 122.5, 122.4, 119.8, 119.2, 118.5, 116.6, 66.8, 65.8, 65.7, 51.9, 42.0, 40.9, 33.9, 25.8, 18.2, –5.4; *m/z* (ESI–MS) 484.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.0 min (major) and t_R = 4.7 min.

The absolute configuration was assigned by analogy.

Ethyl (6a*S*,7*R*,12*S*,13a*R*)-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline-12-carboxylate (**2.20k**): Following the general procedure, compound **2.20k** was obtained as a white foam in 51% yield (42 mg); mp = 154–155 °C; R_f = 0.17 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –380.1 (c 0.5, $CHCl_3$, 84% *ee*); IR (KBr) 2983, 2851, 1732, 1492, 1286, 1227, 764, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31–7.26 (comp, 2H), 7.23–7.13 (comp, 2H), 7.12–7.05 (comp, 2H), 7.05–6.95 (comp, 2H), 6.84–6.72 (comp, 3H), 6.67 (app t, *J* = 7.4 Hz, 1H), 4.55 (dd, *J* = 12.3, 10.3 Hz, 1H), 4.43 (app t, *J* = 9.9 Hz, 1H), 4.32–4.26 (m, 1H), 4.00–3.87 (comp, 2H), 3.74–3.65 (m, 1H), 3.54–3.41 (comp, 2H), 3.06 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.53–2.46 (m, 1H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 154.8, 146.7, 146.4, 130.7, 130.0, 128.5, 128.3, 128.2, 126.5, 125.4, 122.7, 120.3, 119.2, 119.1(7), 117.9, 116.3, 66.9, 65.5, 60.8, 50.7, 42.4, 41.4, 34.7, 13.7; *m/z* (ESI–MS) 412.4 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.2 mL/min, UV = 280 nm, t_R = 30.8 min (major) and t_R = 32.8 min.



The absolute configuration was assigned by analogy.

(6a*S*,7*R*,12*R*,13a*R*)-12-methyl-7-phenyl-6a,11,12,13a-tetrahydro-6*H*,7*H*-chromeno[4,3-*b*]pyrrolo[3,2,1-*ij*]quinoline (**2.20l**): 

Following the general procedure, compound **2.20l** was obtained as a white foam in 81% yield (57 mg); mp = 157–158 °C; R_f = 0.35 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^{D}_{20}$ –235.5 (c 0.5, $CHCl_3$, 70% *ee*); IR (KBr) 3027, 2880, 1601, 1468, 1220, 753, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33–7.16 (comp, 5H), 7.15–7.09 (comp, 2H), 6.99–6.94 (m, 1H), 6.87–6.80 (comp, 2H), 6.64–6.56 (comp, 2H), 4.38–4.21 (comp, 2H), 4.07 (d, *J* = 3.1 Hz, 1H), 3.97–3.87 (m, 1H), 3.84 (d, *J* = 4.2 Hz, 1H), 3.24 (dd, *J* = 15.7, 8.6 Hz, 1H), 2.71 (dd, *J* = 16.0, 10.2, Hz, 1H), 2.39–2.29 (m, 1H), 1.01 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 148.3, 145.5, 130.4, 129.4, 128.7, 128.4, 127.3(4), 127.2(7), 126.5, 122.8, 122.1, 119.7, 119.6, 118.4, 116.4, 66.8, 61.5, 52.3, 41.9, 40.4, 38.5, 21.8; *m/z* (ESI–MS) 354.2 $[M + H]^+$; Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.7 min (major) and t_R = 12.5 min.

The absolute configuration was assigned by analogy.

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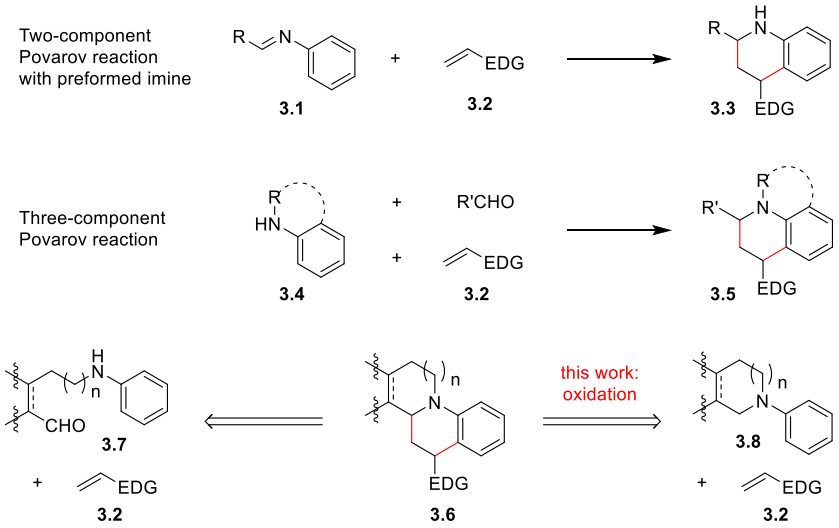
Chapter III Dual C–H Functionalization of *N*-Aryl Amines: Synthesis of Polycyclic Amines via an Oxidative Povarov Approach

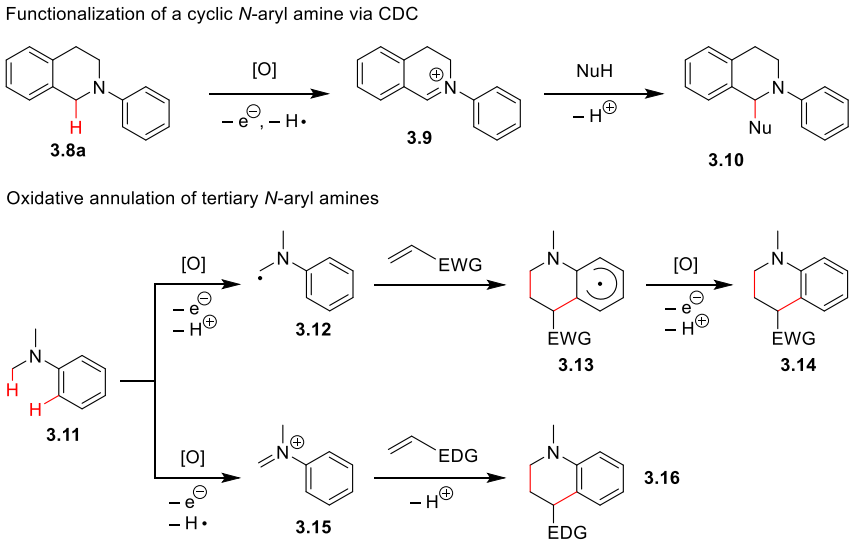
3.1 Introduction

Povarov reaction[1] typically takes advantage of an *N*-aryl imine or iminium ion.[2-7] This transformation generally requires a Lewis or Brønsted acid catalyst or promoter and provides an efficient route to tetrahydroquinolines (Scheme 3.1).[8-17] Povarov reactions are commonly performed as two-component transformations in which a preformed imine **3.1** engages an electron-rich dienophile **3.2** to form tetrahydroquinoline product **3.3**. Three-component variants are also popular and involve the condensation of an amine **3.4** with an aldehyde (or a ketone) and a dienophile **3.2**.[2-7] While the two-component method is limited to imines derived from primary amines, the three-component approach is also applicable to secondary *N*-aryl amines, including cyclic amines.[18-24] The latter enables the formation of polycyclic products **3.5** in



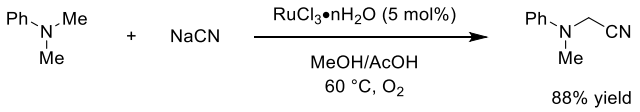
Scheme 3.1. Variants of the Povarov reaction.

which two rings are fused to the same aryl group. In contrast, the classic Povarov reaction is not readily applicable to the synthesis of polycyclic amines of type **3.6**. A typical two-component Povarov approach to these compounds would require an aminoaldehyde **3.7**, species that are not readily accessible. Other approaches to polycyclic frameworks related to **3.6** typically require *ortho*-functionalized *N*-aryl amines and/or additional steps. These methods include intramolecular redox transformations,[25-29] oxidative couplings,[30-34] C–N bond formation via Pd-catalysis[35] or benzyne intermediates,[36, 37] and Bischler-Napieralski reactions followed by reduction.[38] As part of our continuing efforts to develop practical methods for the C–H functionalization of amines,[39-60] herein we report an alternate Povarov approach to polycyclic tetrahydroquinolines **3.6** that utilizes the in situ oxidation of readily available *N*-aryl imines **3.8**.



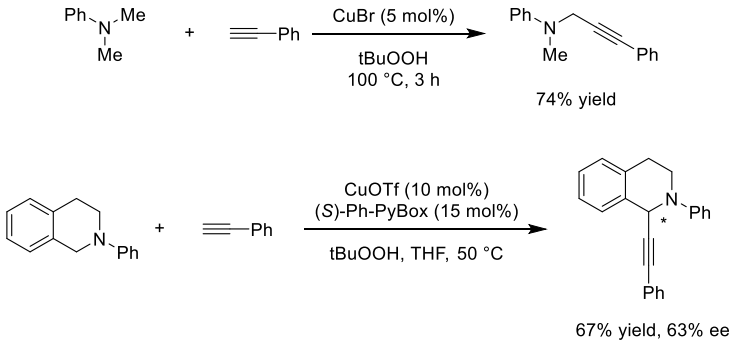
Scheme 3.2. Examples of oxidative amine C–H functionalizations.

The oxidative C–H functionalization of amines has a venerable history and was greatly popularized by the pioneering studies of the Murahashi[61-64] and Li[65-69] groups, who advanced the applicability of catalytic approaches. For example, in 2003, Murahashi[61] *el al*. reported the first example of ruthenium catalyzed oxidative cyanation of tertiary amines with sodium cyanide under aerobic conditions, delivering the α-aminonitrile products in excellent yields (Scheme 3.3).



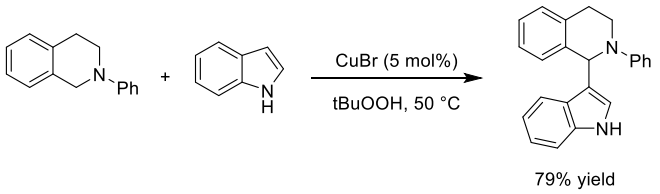
Scheme 3.3. Aerobic Ru-catalyzed oxidative cyanation of tertiary amines

Accordingly, the Li group[65] described a CuBr-catalyzed alkynylation tertiary amines using TBHP as the stoichiometric oxidant (Scheme 3.4). This reaction represented the C–C coupling between the sp^3 C–H bond and sp C–H bond. They have also shown that in the presence of CuOTf and chiral PyBOX ligand, the chiral alkynylation product could be obtained in moderate enantioselectivity[70].



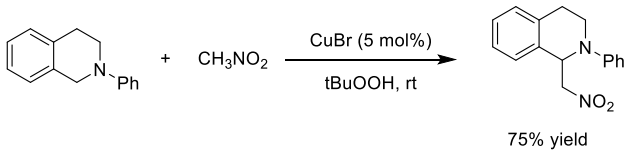
Scheme 3.4. Cu-catalyzed alkynylation tertiary amines.

Later on, they applied the same oxidative system to the addition of indole to tetrahydroisoquinolines, as an example of C–C bond formation between sp^3 C–H and sp^2 C–H bonds[67] (Scheme 3.5).



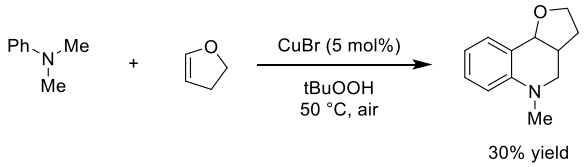
Scheme 3.5. Cu-catalyzed direct indolation of tetrahydroisoquinolines.

As an example of C–C coupling between the two sp^3 C–H bonds, Li's group showed the CuBr-catalyzed aza-Henry reaction between *N*-aryl tertiary amines and nitroalkanes[68] (Scheme 3.6).



Scheme 3.6. CuBr-catalyzed aza-Henry reaction between N-aryl tertiary amines and nitroalkanes.

Oxidative reactions in which a C–H bond is replaced with a functional group are now widely referred to as cross-dehydrogenative coupling reactions (CDC reactions).[69-88] A typical CDC reaction involves the oxidation of a tertiary amine such as **3.8a** to an iminium ion (e.g., **3.9**), followed by capture of **3.9** with a nucleophilic species (NuH) to form product **3.10** (Scheme 3.2).[89-112] The vast majority of these transformations employ *N*-aryl tetrahydroisoquinolines and lead to the mono-functionalization of the benzylic α-position of these substrates. Few transformations of *N*-aryl amines have been reported that, in addition to α-functionalization, simultaneously result in the functionalization of an *ortho* aryl C–H bond. An example of such a process is the oxidation of **3.11** to radical **3.12** which subsequently engages an electron-deficient olefin to give product **3.14** via the oxidation of radical intermediate **3.13**.[113-115] With regard to the proposed oxidative Povarov reaction, to our knowledge such a process has only been realized with *N*,*N*-dimethylanilines (e.g., **3.11**),[116-119] giving relatively simple *N*-alkyl tetrahydroquinoline derivatives **3.16** (via iminium ion **3.15**), products that are also accessible via classic Povarov reactions that utilize *N*-methyl aniline as the substrate.[120-125] For example, in 2009, Zhang group[119] reported the CuBr-catalyzed oxidative Povarov reaction of *N*,*N*-dimethylaniline and 2,3-dihydrofuran to produce tricyclic tetrahydroquinolines (Scheme 3.7).

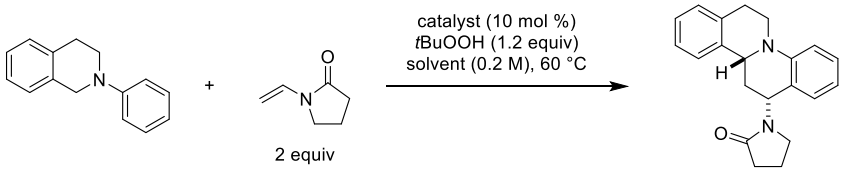


Scheme 3.7. CuBr-catalyzed oxidative Povarov reaction of *N*,*N*-dimethylanilines and 2,3-dihydrofuran.

3.2 Optimization of Reaction Conditions

The title reaction was first evaluated using *N*-phenyl 1,2,3,4-tetrahydroisoquinoline (**3.8a**) and 1-vinylpyrrolidin-2-one (**2.2**) as model substrates (Table 3.1). A preliminary survey of various methods for amine oxidation led to the identification of *tert*-butyl hydroperoxide (TBHP) as the most promising terminal oxidant, other oxidative systems such as aerobic conditions and stoichiometric DDQ gave inferior yields (Table 3.2). Out of a number of copper salts that were tested as catalysts in reactions performed in acetonitrile solution, copper(I) bromide provided the best results (entry 2). With regard to product yield, 1,2-dichloroethane was found to be superior to acetonitrile and other solvents such as tetrahydrofuran, dioxane, methanol, chloroform and toluene. A reaction performed under neat conditions resulted in a dramatically reduced yield of **3.18a** (entry 13). Decreasing the amount of **2.2** from two to 1.1 equivalents had no adverse effects on the reaction outcome (entry 14). Under these optimized conditions, **3.18a** was obtained in 62% isolated yield and with a dr of 6:1 in favor of the endo-product.

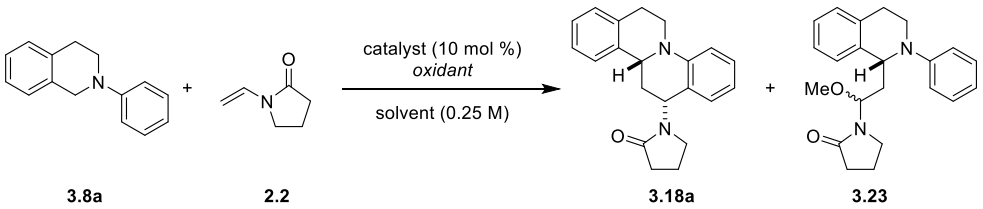
Table 3.1. Reaction development.[a]



entry[a]	catalyst	solvent	time [h]	dr[b]	yield[c] (%)
1	CuCl	CH_3CN	24	10:1	60
2	CuBr	CH_3CN	24	8.7:1	65
3	$CuBr_2$	CH_3CN	24	10:1	50
4	$CuCl_2$	CH_3CN	10	12:1	27
5	CuI	CH_3CN	24	7:1	49
6	$Cu(OTf)_2$	CH_3CN	24	1:1	26
7	CuBr	THF	24	5:1	49
8	CuBr	$C_2H_4Cl_2$	24	5.8:1	81
9	CuBr	dioxane	24	5.2:1	59
10	CuBr	MeOH	32	4.6:1	49
11	CuBr	$CHCl_3$	32	3:1	60
12	CuBr	PhMe	32	2.7:1	20
13	CuBr	-	24	ND	13
14[d]	CuBr	$C_2H_4Cl_2$	24	6:1	80 (62[e])

[a] Reactions were performed with 0.2 mmol of **3.8a**, 0.4 mmol of **2.2**, 0.02 mmol of catalyst, and 0.24 mmol of *t*BuOOH (5.5 M in decane) in 1 mL of solvent. [b] The dr was determined by ^{1}H NMR of the crude reaction mixture. [c] Yield was determined by ^{1}H NMR with an internal standard. [d] 1.1 equiv of **3.17a** was used. [e] Isolated yield..

Table 5.2 Evaluation of additional oxidants.[a]



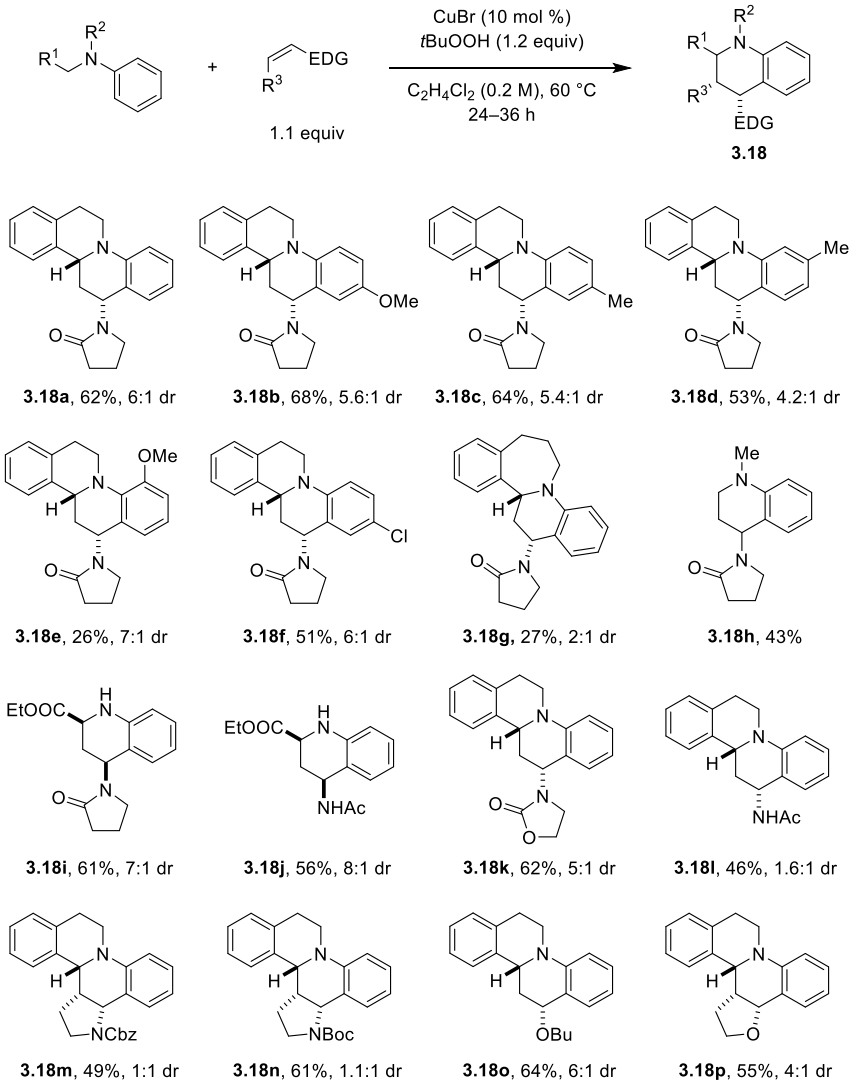
entry[a]	Catalyst	oxidant	solvent	time (h)	temp (°C)	yield[b] (%)	dr[c]
1	$CuCl_2$•$2H_2O$	O_2	MeOH	24	rt	55(18[d])	>20:1
2	$CuCl_2$•$2H_2O$	O_2	MeOH	24	52	56(34[d])	4.5:1
3	$CuCl_2$•$2H_2O$	O_2	EtOAc	24	rt	42	5:1
4	$CuCl_2$•$2H_2O$	O_2	THF	24	rt	42	8:1
5	$CuCl_2$•$2H_2O$	O_2	THF	24	rt	27	>20:1
6	$CuCl_2$•$2H_2O$	O_2	CH_2Cl_2	24	rt	26	11:1
7	$CuCl_2$•$2H_2O$	O_2	CH_3CN	24	rt	26	>20:1
8	$CuCl_2$•$2H_2O$	O_2	THF	60	52	50	>20:1
9	None	DDQ[e]	THF	24	rt	38	10:1

[a]Reactions were performed with 0.2 mmol of **3.8a**, 0.4 mmol of **2.2**, 0.02 mmol of $CuCl_2$•$2H_2O$ in 0.8 mL of solvent under an oxygen atmosphere (balloon). [b]Yield was determined by ^{1}H NMR, using1,3,5-trimethoxybenzene as an internal standard. [c]dr was determined by ^{1}H NMR of crude reaction mixtures. [d]Yield of byproduct **3.23**. [e]1.1 equiv DDQ was used, reaction was performed under nitrogen.

3.3 Substrate Scope

The scope of the oxidative Povarov reaction was evaluated on a set of amine/dienophile combinations (Scheme 3.8). A range of tetrahydroisoquinolines with different substituents on the *N*-aryl ring readily underwent cycloaddition with 1-vinylpyrrolidin-2-one (**2.2**) to produce the corresponding products **3.18** in moderate to good yields. However, *ortho*-substituents on the *N*-aryl ring proved problematic, presumably due to developing $A_{1,3}$-type strain in the transition state of this reaction. As a

consequence, product **3.18e** was isolated in only in 26% yield. Although low-yielding, *N*-phenyl tetrahydroazepine also engaged in a reaction with **3.17a** to form polycyclic product **3.18g**. To our knowledge, this represents the first example of a tetrahydroazepine derivative undergoing a CDC-type reaction.

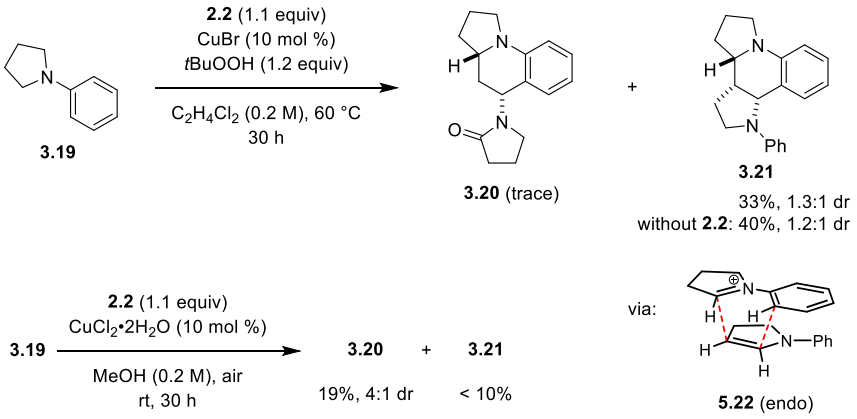


Scheme 3.8. Scope of the reaction. Reactions were performed with 0.5 mmol of the amine**,** 0.55 mmol of the dienophile**,** 0.05 mmol of CuBr, and 0.6 mmol of *t*BuOOH (5.5 M in decane) in 2.5 mL of $C_2H_4Cl_2$. All yields are combined isolated yields of both diastereomers.

In order to explore the generality of the method, two acyclic aniline derivatives were tested. *N*,*N*-dimethylaniline, upon reacting with **3.17a**, provided the expected product **3.18h** in 43% yield. An *N*-phenylglycine ester was also found to be a suitable substrate, giving cyclic amino acid derivative **3.18i**,

in 61% yield. This illustrates the potential utility of this method in the direct C–H functionalization of peptide derivatives.[126-128] Finally, the scope of the oxidative Povarov reaction was explored with regard to the dienophile. Various acyclic and cyclic enol ethers and enamides readily underwent the title reaction to provide polycyclic products in moderate to good yields. The diastereoselectivity for some of these reactions was rather poor.

An attempt to extend the scope of the oxidative Povarov reaction to *N*-phenyl pyrrolidine (**3.19**) as the amine initially only led to the formation of trace amounts of the expected product **3.20** (Scheme 3.9). Instead, oxidation of **3.19** in the presence of **3.17a** resulted in the formation of **3.21** as a 1.3:1 mixture of diastereomers in 33% yield. The yield of **3.21** increased to 40% when the reaction was conducted in the absence of **2.2**. This substrate dimerization (i.e. via **3.22**) is easily rationalized as the iminium ion resulting from the oxidation of **3.19** is expected to exist in equilibrium with its corresponding enamine.[22] As was observed previously with cyclic enecarbamates, the diastereoselectivity of this process was found to be low.



Scheme 3.9. Oxidative functionalization of *N*-phenyl pyrolidine.

In order to obtain the desired product **3.20**, a number of other conditions were evaluated. Gratifyingly, **3.20** was obtained, albeit in only 19% yield, in a reaction that was conducted in methanol, using copper(II) chloride dihydrate as the catalyst and air as the terminal oxidant. In this instance, dimerization product **3.21** was obtained in less than 10% yield. This change in product distribution

may be rationalized on the basis that the intermediate iminium ion can be captured by methanol to form the corresponding *N*,*O*-acetal which in turn could act as a reservoir for the iminium ion, thus reducing the concentration of the *N*-phenyl pyrrolidine enamine.

3.4 Summary

In summary, we have reported oxidative Povarov reactions of various *N*-aryl amines as a method to rapidly access polycyclic amines. These reactions feature the dual functionalization of both a $C(sp^3)$–H and a $C(sp^2)$–H bond and are likely to be amenable to enantioselective catalysis.

Experimental Section

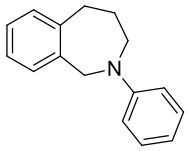
Evaluation of additional oxidants

Procedure: Under an atmosphere of oxygen, $CuCl_2 \cdot 2H_2O$ (3.4 mg, 0.02 mmol, 0.1 equiv), **3.8a** (42 mg, 0.2 mmol, 1.0 equiv), **2.2** (43 μL, 0.4 mmol, 2 equiv) were dissolved in anhydrous MeOH (0.8 mL). The resulting mixture was stirred at rt. Upon consumption of **3.8a** as judged by TLC analysis, the reaction mixture was diluted and filtered through a short plug of silica gel. The solvent was removed in vacuo and the residue was dissolved in $CDCl_3$ for ^1H NMR analysis (1,3,5-trimethoxybenzene was added as an internal standard).

Synthesis of the substrates

N-aryl tetrahydroisoquinolines[136], 2,3,4,5-tetrahydro-1H-benzo[c]azepine[137] and 3-vinyloxazolidin-2-one[138] were synthesized according to reported procedures.

2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (3.8g):



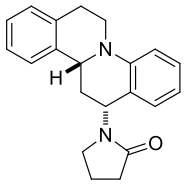
The synthesis of **3.8g** was adopted from a known procedure for the synthesis of *N*-aryl tetrahydroisoquinolines[136]. A 100 mL flask was charged with bis(dibenzylideneacetone)palladium(0) (44.9 mg, 0.078 mmol), (±)BINAP (97 mg, 0.156 mmol), and toluene (5.27 mL). The resulting solution was degassed and backfilled with nitrogen followed by heating to 110 °C for 15 min. Then the solution was allowed to cool to rt after which sodium *tert*-butoxide (375 mg, 3.90 mmol), 2,3,4,5-tetrahydro-1H-benzo[c]azepine (287 mg, 1.95 mmol), and bromobenzene (0.204 mL, 1.95 mmol) were added. The solution was heated at reflux for 18 h and monitored by TLC. After completion of the reaction the mixture was cooled to rt, filtered through a short plug of Celite and washed with toluene. The solvent was removed under vacuum. The residue was purified by flash chromatography using EtOAc/hexanes (5:95 v/v) to give the title product in 75% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (app d, J = 7.0 Hz, 1H), 7.24–7.06

(comp, 5H), 6.82 (app d, *J* = 8.3 Hz, 2H), 6.63 (app t, *J* = 7.2 Hz, 1H), 4.61 (s, 2H), 3.80 (app t, *J* = 5.4 Hz, 2H), 3.05–2.96 (comp, 2H), 1.97–1.86 (comp, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 147.6, 141.6, 138.6, 129.8, 129.5, 129.2, 127.2, 125.8, 116.1, 112.6, 55.0, 52.2, 35.8, 25.8; m/z (ESI–MS) 224.3 $[M + H]^+$.

Preparation and characterization data of products:

General procedure: Under nitrogen, an oven dried vial was charged with CuBr (7.2 mg, 0.05 mmol, 0.1 equiv), *N*-phenyl tetrahydroisoquinoline (**3.8a**) (104.5 mg, 0.5 mmol, 1.0 equiv) and anhydrous $C_2H_4Cl_2$ (2.5 mL). 1-vinylpyrrolidin-2-one (**2.2**) (59 μL, 0.55 mmol, 1.1equiv) was added and the resulting mixture was stirred for 5 min. *t*BuOOH(5.5 M in decane) was then added (109 μL, 0.6 mmol, 1.2 equiv). After five minutes, the reaction mixture was slowly heated to 60°C and kept at this temperature for 24–36 hours. After completion of the reaction, the reaction mixture was allowed to cool to rt, diluted with ethyl acetate and filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography.

13-*cis*-1-(7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one (3.18a):

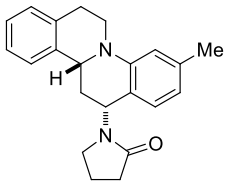


Following the general procedure, compound **3.18a** was obtained as a white solid in 62% yield (6:1 mixture of two diastereomers); Characterization data of the major diastereomer: mp = 152–153 ºC (decomposed); R_f= 0.30 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2917, 2894, 1682, 1601, 1487, 1456, 1419, 1308, 1283, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.25–7.11 (comp, 5H), 6.93 (app d, *J* = 7.6 Hz, 1H), 6.87 (app d, *J* = 8.3 Hz, 1H), 6.74 (app t, *J* = 7.4 Hz, 1H), 5.77 (dd, *J* = 11.7, 6.5 Hz, 1H), 4.57 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.99–3.88 (m, 1H), 3.21–3.04 (comp, 4H), 2.94–2.86 (m, 1H), 2.59–2.44 (comp, 3H), 2.16–2.06 (m, 1H), 2.03–1.92 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 147.5, 137.2, 134.8, 128.5, 128.4, 127.2, 126.4, 126.3, 125.8, 121.4, 117.9, 113.0, 55.9, 48.6, 43.4, 42.4, 34.0, 31.4, 29.7, 18.2; *m/z* (ESI–MS) 319.0 $[M + H]^+$.

13-*cis*-1-(2-methoxy-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one (3.18b): Following the general procedure, compound **3.18b** was obtained as a brownish solid and in 68% yield (5.6:1 mixture of two diastereomers); Characterization data of the major diastereomer: mp = 136–138 ºC (decomposed); R_f= 0.19 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2934, 2888, 1684, 1493, 1425, 1288, 1050, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25–7.11 (comp, 4H), 6.87 (app d, *J* = 9.0 Hz, 1H), 6.78 (dd, *J* = 9.0, 3.1 Hz 1H), 6.55 (app d, 3.1 Hz, 1H), 5.74 (dd, *J* = 11.6, 6.9 Hz, 1H), 4.43 (dd, *J* = 11.1, 2.6 Hz 1H), 3.78–3.75 (m, 1H), 3.74 (s, 3H), 3.21–3.15 (m, 1H), 3.13–3.01 (comp, 3H), 2.98–2.91 (m, 1H), 2.55–2.41 (comp, 3H), 2.14–2.05 (m, 1H), 2.02–1.92 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 152.8, 142.4, 137.1, 134.5, 128.6, 126.4, 126.2, 126.1, 123.7, 116.1, 114.1, 112.8, 56.3, 55.8, 48.9, 44.5, 42.4, 33.2, 31.4, 29.9, 18.2; *m/z* (ESI–MS) 349.1 $[M + H]^+$.

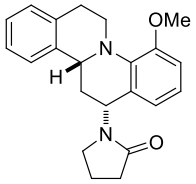
13-*cis*-1-(2-methyl-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one (3.18c): Following the general procedure, compound **3.18c** was obtained as a brownish solid in 64% yield (5.4:1 mixture of two diastereomers); Characterization data of the major diastereomer: mp = 118–120 ºC (decomposed); R_f= 0.29 (Hexanes/EtOAc 60:40 v/v); IR (KBr): 2933, 2890, 1680, 1486, 1422, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25–7.13 (comp, 4H), 7.02–6.94 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.77–6.74 (m, 1H), 5.74 (dd, *J* = 11.6, 6.7 Hz, 1H), 4.48 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.90–3.82 (m, 1H), 3.20–3.14 (m, 1H), 3.13–3.01 (comp, 3H), 2.94–2.86 (m, 1H), 2.58–2.43 (comp, 3H), 2.23 (s, 3H), 2.14–2.06 (m, 1H), 2.01–1.91 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 145.6, 137.2, 134.6, 128.9, 128.5, 127.7, 127.5, 126.3, 126.2, 125.9, 121.7, 113.7, 56.1, 48.6, 43.7, 42.4, 33.8, 31.4, 29.8, 20.4, 18.2; *m/z* (ESI–MS) 333.1 $[M + H]^+$.

13-*cis*-1-(3-methyl-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one (3.18d): Following the general procedure, compound **3.18d** was obtained as a reddish oil in 53% yield (4.2:1 mixture of two diastereomers);

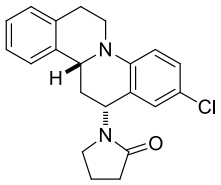


Characterization data of the major diastereomer： R_f= 0.28 (Hexanes/EtOAc 60:40 v/v); IR (neat): 2895, 1689, 1492, 1432, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25–7.22 (m, 1H), 7.20–7.10 (comp, 4H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 5.57 (app t, *J* = 7.7 Hz, 1H), 4.37 (dd, 11.0, 2.5 Hz, 1H), 4.01–3.95 (m, 1H), 3.14–3.00 (comp, 2H), 2.84–2.80 (m, 1H), 2.77–2.71 (m, 1H), 2.70–2.64 (m, 1H), 2.61–2.55 (m, 1H), 2.36–2.25 (comp, 3H), 2.12 (s, 3H), 1.78–1.69 (m, 1H), 1.63–1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 149.1, 138.4, 137.3, 134.4, 128.6, 128.3, 126.2, 126.1(6), 125.9, 120.8, 120.4, 111.2, 55.9, 46.3, 43.7, 43.0, 35.3, 31.1, 29.0, 19.3, 17.8; *m/z* (ESI–MS) 333.1 $[M + H]^+$.

13-*cis*-1-(4-methoxy-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one (3.18e): Following the general procedure, compound **3.18e** was obtained as a solid in 26% yield (7:1 mixture of two diastereomers); Characterization data of the major diastereomer： R_f= 0.20 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2932, 2880, 1683, 1052, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.22–7.08 (comp, 4H), 6.98 (app t, *J* = 7.9 Hz, 1H), 6.78 (app d, *J* = 8.0 Hz 1H), 6.70 (app d, *J* = 8.0Hz, 1H), 5.72 (dd, *J* = 11.7, 7.1 Hz, 1H), 4.43 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.88 (s, 3H), 3.65 (ddd, *J* = 11.9, 5.7, 1.9 Hz, 1H), 3.34–3.25 (m, 1H), 3.23–3.16 (m, 1H), 3.10–3.01 (m, 1H), 2.96 (app td, *J* = 11.9, 3.2 Hz, 1H), 2.80–2.71 (m, 1H), 2.58–2.41 (m, 2H), 2.29–2.18(m, 1H), 2.09–2.01 (m, 1H), 2.02–1.92 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 152.9, 138.9, 137.4, 134.3, 128.7, 128.0, 127.2, 126.3, 125.8, 123.0, 119.1, 109.8, 55.8, 55.6, 49.3, 44.6, 42.3, 31.3, 30.1, 28.1, 18.1; *m/z* (ESI–MS) 349.4 $[M + H]^+$.

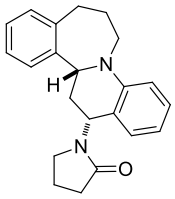


13-*cis*-1-(2-chloro-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)pyrrolidin-2-one



(3.18f): Following the general procedure, compound **3.18f** was obtained as a brownish solid in 51% yield (6:1 mixture of two diastereomers); Characterization data of the major diastereomer： R_f= 0.27 (Hexanes/EtOAc 60:40 v/v); mp = 84–86 ºC (decomposed); IR(KBr): 2925, 1683, 1488, 1418, 1286, 753, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25–7.12 (comp, 4H), 7.08 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.88–6.83 (m, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 5.70 (dd, *J* = 11.8, 6.3 Hz, 1H), 4.54 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.88–3.77 (m, 1H), 3.24–2.99 (comp, 4H), 2.93–2.84 (m, 1H), 2.59–2.41 (comp, 3H), 2.15–1.95 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 146.0, 136.8, 134.5, 128.5, 128.2, 126.5, 126.5, 126.3, 125.6, 123.0, 122.6, 114.2, 55.7, 48.3, 43.5, 42.3, 33.6, 31.2, 29.5, 18.1; *m/z* (ESI–MS) 354.1 $[M + H]^+$.

14-*cis*-1-(6,7,8,12b,13,14-hexahydrobenzo[3,4]azepino[1,2-a]quinolin-14-yl)pyrrolidin-2-one



(3.18g): Following the general procedure, compound **3.18g** was obtained as a brown solid in 27% yield (2:1 mixture of two diastereomers); Characterization data of the 2:1 mixture of two diastereomers： mp = 67–70 ºC (decomposed); R_f= 0.30 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2933, 1686, 1601, 1489,1362, 1284, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25–7.04 (comp, 15 H), 7.02 (app d, *J* = 7.4 Hz, 1H), 6.80 (app d, *J* = 7.4, 2H), 6.71 (app d, *J* = 8.4 Hz, 1H), 6.66 (app d, *J* = 8.3 Hz, 2H), 6.63–6.57 (comp, 3H), 5.65 (dd, *J* = 12.4, 4.7 Hz, 2H), 5.21 (app t, *J* = 4.2 Hz, 1H), 4.96 (dd, *J* = 12.1, 3.3 Hz, 2H), 4.70 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.71 (dd, *J* = 15.3, 6.5 Hz, 1H), 3.58 (dd, *J* = 15.4, 6.9 Hz, 2H), 3.42–3.23 (comp, 6H), 3.22–3.07 (comp, 5H), 3.04–2.96 (m, 1H), 2.59–2.45 (comp, 8H), 2.37–2.15 (comp, 7H), 2.10–1.90 (comp, 9H), 1.69–1.56 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 174.8, 144.7, 144.6, 140.8, 140.7, 137.8, 137.2, 137.1, 130.4, 130.3, 130.1, 129.6, 128.5, 127.5, 127.3, 127.2, 126.9, 126.7, 125.4, 119.0, 117.9, 115.4, 115.1, 110.3, 109.8, 63.9, 61.1, 48.2, 48.1(6), 46.5, 45.1, 44.2, 42.3, 35.4, 34.9, 31.6, 31.4, 30.4, 29.9, 24.9, 24.8, 18.4, 18.3; *m/z* (ESI–MS) 333.0 $[M + H]^+$.

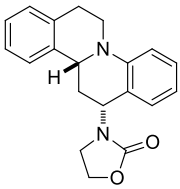
1-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (3.18h): Following the general procedure, compound **3.18h** was obtained as a white solid in 43% yield; mp = 76–78 ºC (decomposed); R_f= 0.30 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2928, 2874, 1686, 1501, 1422, 1331, 1284, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15–7.10 (m, 1H), 6.86 (app dt, *J* = 7.5, 1.3Hz, 1H), 6.68–6.58 (comp, 2H), 5.41 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.36–3.30 (m, 1H), 3.26–3.17 (comp, 2H), 3.14–3.08 (m, 1H), 2.87 (s, 3H), 2.52–2.42 (comp, 2H), 2.18–2.10 (m, 1H), 2.08–1.91 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 147.3, 128.5, 127.5, 119.8, 116.8, 111.8, 49.5, 47.8, 43.4, 39.3, 31.4, 26.6, 18.2; *m/z* (ESI–MS) 231.2 $[M + H]^+$.

4-*cis*-ethyl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylate (3.18i): Following the general procedure, compound **3.18i** was obtained as a white solid in 61% yield (7:1 mixture of two diastereomers); Characterization data of the major diastereomer: R_f= 0.31 (Hexanes/EtOAc 50:50 v/v); IR(KBr): 3265, 2968, 1717, 1630, 1469, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.06–7.01 (m, 1H), 6.81 (app dt, *J* = 7.6, 1.4Hz, 1H), 6.68 (app td, *J* = 7.5, 1.2 Hz, 1H), 6.61 (dd, *J* = 8.0, 1.1Hz, 1H), 5.59 (dd, *J* = 11.7, 5.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.18 (dd, *J* = 11.7, 2.8 Hz, 1H), 3.21–3.09 (comp, 2H), 2.54–2.44 (comp, 2H), 2.41–2.37 (m, 1H), 2.05–1.98 (comp, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 171.8, 143.9, 128.3, 126.6, 118.4, 118.2, 115.1, 61.6, 53.3, 47.8, 42.3, 31.3, 28.6, 18.2, 14.1; *m/z* (ESI–MS) 289.3 $[M + H]^+$.

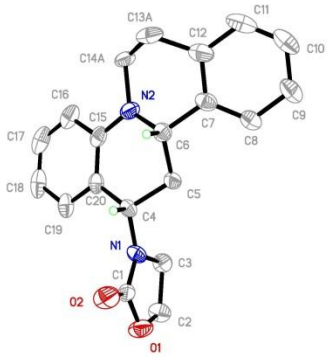
4-*cis*-ethyl-4-acetamido-1,2,3,4-tetrahydroquinoline-2-carboxylate (3.18j): Following the general procedure, compound **3.18j** was obtained as a white solid in 56% yield (8:1 mixture of two diastereomers); Characterization data of the major diastereomer: mp = 181–182 ºC; R_f= 0.28 (Hexanes/EtOAc 80:20 v/v); IR(KBr): 3398, 3272, 2977, 1727, 1640,

1548, 1487, 1220, 1032, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14–7.04 (comp, 2H), 6.72 (app td, *J* = 7.5, 1.2 Hz, 1H), 6.64 (app d, *J* =7.5 Hz, 1H), 5.75 (d, *J* = 7.9 Hz, 1H), 5.25–5.18 (m, 1H), 4.24–4.11 (comp, 3H), 2.54–2.47 (m, 1H), 2.18 (dt, *J* = 13.2, 7.5 Hz, 1H), 1.99 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 169.6, 143.1, 128.8, 128.1, 120.2, 118.2, 115.0, 61.4, 52.0, 45.3, 30.8, 23.3, 14.1; *m/z* (ESI–MS) 262.9 $[M + H]^+$.

13-*cis*-3-(7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)oxazolidin-2-one (3.18k):

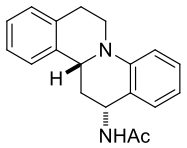


Following the general procedure, compound **3.18k** was obtained as a white solid in 62% yield (5:1 mixture of two diastereomers); Characterization data of the major diastereomer： mp = 159–161 ºC (decomposed); R_f= 0.30 (Hexanes/EtOAc 60:40 v/v); IR(KBr): 2891, 1749, 1600, 1488, 1431, 1260, 1045, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.29–7.15 (comp, 5H), 7.08 (app dt, *J* = 7.7, 1.4 Hz, 1H), 6.89 (app d, *J* = 8.3 Hz, 1H), 6.78 (app t, *J* = 7.4, 1H), 5.52 (dd, *J* = 11.4, 6.5 Hz, 1H), 4.57 (dd, *J* = 11.5, 2.0 Hz, 1H), 4.34–4.24 (comp, 2H), 3.98–3.90 (m, 1H), 3.33–3.24 (comp, 2H), 3.13–3.04 (comp, 2H), 2.95–2.84 (m, 1H), 2.60 (ddd, *J* = 12.6, 6.6, 2.6 Hz, 1H), 2.20–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 147.3, 136.9, 134.7, 128.8, 128.6, 127.3, 126.5, 126.3, 125.7, 120.5, 118.0, 113.1, 62.1, 55.7, 50.7, 43.3, 39.8, 33.9, 29.5; *m/z* (ESI–MS) 321.2 $[M + H]^+$. The stereochemistry of **3.18k** was assigned by X-ray crystallography:



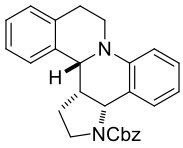
Compound **3.18k** was crystallized from hexanes/dichloromethane through slow diffusion at room temperature.

13-*cis*-*N*-(7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinolin-13-yl)acetamide (3.18l):



Following the general procedure, the mixture of both diastereomers of **3.18l** was obtained as a reddish solid in 46% yield (1.6:1 mixture of two diastereomers); Characterization data of the 1.6:1 mixture of two diastereomers： mp = 128–130 ºC (decomposed); R_f= 0.30 (Hexanes/EtOAc 80:20 v/v); IR(KBr): 3271, 2801, 1637, 1550, 1489, 1371, 1284, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomor): δ 7.30–7.11 (comp, 6H), 6.87 (app t, *J* = 8.7 Hz, 1H), 6.76–6.70 (m, 1H), 5.65 (d, *J* = 8.8 Hz, 1H), 5.47–5.40 (m, 1H), 4.61–4.54 (m, 1H), 4.02–3.92 (m, 1H), 3.25–3.14 (m, 1H), 3.12–3.03 (m, 1H), 2.85 (app tt, *J* = 15.9, 3.9 Hz, 1H), 2.75 (ddd, *J* = 13.0, 6.0, 3.3 Hz, 1H), 1.97 (s, 3H); ^1H NMR (500 MHz, $CDCl_3$) (minor diastereomor): δ 7.30–7.11 (comp, 6H), 6.87 (app t, *J* = 8.7 Hz, 1H), 6.76–6.70 (m, 1H), 5.97 (d, *J* = 7.1 Hz, 1H), 5.11 (dt, *J* = 7.3, 3.8 Hz, 1H), 4.40–4.33 (m, 1H), 4.02–3.92 (m, 1H), 3.25–3.14 (m, 1H), 3.12–3.03 (m, 1H), 2.85 (app tt, *J* = 15.9, 3.9 Hz, 1H),2.64 (app dt, *J* = 13.7, 3.2 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (1.6:1 mixture of two diastereomers) δ 169.7, 168.8, 146.2, 146.0, 137.5, 137.4, 135.1, 134.9, 130.2, 129.2, 128.7, 128.6, 128.4, 127.6, 126.4(2), 126.4(0), 126.2, 125.8, 125.5, 123.9, 122.0, 117.6, 117.3, 112.8, 112.6, 55.4, 52.0, 46.4, 46.1, 44.1, 43.7, 36.4, 35.4, 29.1, 28.9, 23.5, 23.4, 23.1; *m/z* (ESI–MS) 293.2 $[M + H]^+$.

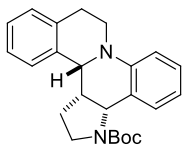
11c-*cis*-14a-*cis*-benzyl-6,7,11c,12,13,14a-hexahydroisoquinolino[2,1-a]pyrrolo[3,2-c]quinoline-14(11bH)-carboxylate (3.18m):



Following the general procedure, compound **3.18m** was obtained as a yellow solid in 49% yield (1:1 mixture of two diastereomers); Characterization data of the 1:1 mixture of two diastereomers： R_f= 0.20 (Hexanes/EtOAc 90:10 v/v); IR(KBr): 2952, 2892, 1698, 1489, 1455, 1411, 1109, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.51–7.27 (comp, 14H), 7.24–7.13 (comp, 6H), 7.10 (app d, *J* = 7.5 Hz, 1H), 7.05 (app d, *J* = 7.5 Hz, 1H), 6.92 (app d, *J* = 8.0 Hz, 2H), 6.77 (app t, *J* = 7.6 Hz, 2H), 5.31–5.19 (comp, 3H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 7.6 Hz, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 4.34 (d, *J* =

4.3 Hz, 1H), 4.19–4.10 (comp, 2H), 4.06–3.95 (comp, 2H), 3.73–3.66 (m, 1H), 3.64–3.58 (m, 1H), 3.57–3.49 (comp, 2H), 3.33–3.10 (comp, 6H), 2.78–2.63 (comp, 2H), 2.34–2.27 (m, 1H), 2.25–2.18 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 155.6, 145.4, 143.8, 138.4, 138.0, 137.0, 136.7, 134.9, 134.5, 129.2, 129.1, 129.0, 128.4, 128.4, 128.2, 128.0, 127.9(5), 127.9(0), 127.8(7), 127.7, 127.4, 126.6, 126.5(5), 126.4(9), 126.4(4), 126.3, 125.8, 124.9, 124.7, 119.2, 118.9, 113.1, 113.0, 67.0, 66.8, 60.4, 59.1, 55.0, 54.3, 46.0, 45.6, 45.4, 45.3, 45.0, 41.7, 34.6, 29.0, 28.6, 27.3; *m/z* (ESI–MS) 411.1 $[M + H]^+$.

11c-*cis*-14a-*cis*-*tert*-butyl-6,7,11c,12,13,14a-hexahydroisoquinolino[2,1-a]pyrrolo[3,2-c]quinoline-14(11bH)-carboxylate (3.18n): Following the general procedure, compound **3.18n** was obtained as a yellow oil in 61% yield (1.1:1 mixture of two diastereomers); Characterization data of the 1.1:1 mixture of two diastereomers：



R_f= 0.22 (Hexanes/EtOAc 90:10 v/v); IR(neat): 2942, 2880, 1690, 1482, 1101, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.43 (app d, *J* = 7.7 Hz, 1H), 7.36–7.27 (comp, 3H), 7.25–7.07 (comp, 7H), 7.04 (app d, *J* = 7.6 Hz, 1H), 6.94–6.86 (comp, 2H), 6.84 (app t, *J* = 7.6 Hz, 1H), 6.76 (app t, *J* = 7.6 Hz, 1H), 4.96 (d, *J* = 7.5 Hz, 1H), 4.81 (d, *J* = 7.9 Hz, 1H), 4.30 (d, *J* = 4.2 Hz, 1H), 4.21–3.95 (comp, 3H), 3.65–3.56 (m, 1H), 3.50–3.40 (comp, 3H), 3.37–3.01 (comp, 6H), 2.79–2.61 (comp, 2H), 2.33–2.24 (m, 1H), 2.22–2.10 (comp, 2H), 2.06–1.94 (m, 1H), 1.56–1.44 (comp, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 155.2, 145.6, 144.0, 138.6, 138.1, 134.9, 134.5, 129.1, 129.0, 127.8, 127.2, 127.1, 126.5, 126.4, 124.9, 124.8, 119.2, 118.9, 112.9, 79.7, 79.2, 60.6, 59.3, 55.0, 53.5, 45.9, 45.2, 45.2, 44.9, 41.8, 34.6, 29.3, 28.8, 28.6, 27.5, 26.2; *m/z* (ESI–MS) 377.3 $[M + H]^+$.

13-*cis*-13-Butoxy-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinoline (3.18o): Following the general procedure, compound **3.18o** was obtained as a reddish oil in 64% yield (6:1 mixture of two diastereomers); Characterization data of the major diastereomer： R_f= 0.30 (Hexanes/EtOAc 95:5 v/v); IR(neat): 2845, 1610, 1475, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.43 (app dt, *J* = 7.6, 1.4 Hz, 1H), 7.29–7.26 (m, 1H), 7.25–7.13 (comp, 4H), 6.81–6.75 (comp, 2H), 4.82(dd, *J* =11.0, 5.5 Hz, 1H), 4.55 (dd, *J* = 11.7, 3.1 Hz, 1H), 3.88 (app dt, *J* = 11.8, 4.7 Hz, 1H), 3.74–3.69 (m, 1H), 3.61–3.55 (m, 1H), 3.20–3.14 (m, 1H), 3.12–3.05 (m, 1H), 2.88 (app dt, *J* = 15.4, 4.3 Hz, 1H), 2.81 (ddd, *J* = 12.3, 5.8, 3.2 Hz, 1H), 2.03 (app td, *J* = 11.9, 10.7 Hz, 1H), 1.70–1.62 (comp, 2H), 1.50–1.42 (comp, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 138.1, 135.2, 128.5, 128.3, 126.9, 126.3, 126.2, 125.5, 117.5, 112.3, 74.3, 68.1, 55.2, 44.0, 35.5, 32.3, 29.4, 19.5, 14.0; *m/z* (ESI–MS) 308.1 $[M + H]^+$.

11c-*cis*-14a-*cis*-7,11b,11c,12,13,14a-hexahydro-6H-furo[3,2-c]isoquinolino[2,1-a]quinoline (3.18p): Following the general procedure, compound **3.18p** was obtained as a brownish oil in 55% yield (4:1 mixture of two diastereomers); Characterization data of the major diastereomer： R_f= 0.20 (Hexanes/EtOAc 95:5 v/v); IR(neat): 2855, 1600, 1466, 1071, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.42 (app dt, *J* = 7.5, 1.1 Hz, 1H), 7.30–7.27(m, 1H), 7.25–7.19 (comp, 3H), 7.18–7.14 (m, 1H), 6.88–6.78 (comp, 2H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.06 (d, *J* = 8.5 Hz, 1H), 4.02 (td, *J* = 8.3, 5.2 Hz, 1H), 3.93–3.83 (comp, 2H), 3.27 (td, *J* = 11.2, 3.7 Hz, 1H), 3.17–3.09 (m, 1H), 2.83 (app dt, *J* = 15.5, 3.6 Hz, 1H), 2.76 (app tt, *J* = 8.2, 6.5 Hz, 1H), 2.30–2.13 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 137.4, 135.8, 129.1, 128.6, 128.4, 126.6, 126.3, 126.0, 124.5, 118.3, 113.2, 75.2, 65.7, 58.3, 45.1, 44.5, 30.4, 29.0; *m/z* (ESI–MS) 278.3 $[M + H]^+$.

5-*cis*-1-(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-5-yl)pyrrolidin-2-one (3.20): Under an oxygen atmosphere, an oven dried vial was charged with $CuCl_2 \cdot 2H_2O$ (8.5 mg, 0.05 mmol, 0.1 equiv). Anhydrous MeOH (2.5 mL), 1-phenylpyrrolidine (72 μl, 0.5 mmol, 1.0 equiv) and 1-vinylpyrrolidin-2-one (**2.2**) (59 μL, 0.55 mmol, 1.1 equiv) were added and the resulting mixture was stirred at rt. After 24 hours, the reaction mixture was concentrated and purified by flash chromatography to give compound **3.20** as a yellowish oil in 19% yield (4:1 mixture of two diastereomers); Characterization data of the major diastereomer: R_f= 0.30 (Hexanes/EtOAc 60:40 v/v); IR(neat): 2855, 1680, 1280, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.11 (app t, *J* = 8.0 Hz, 1H), 6.80 (app d, *J* = 7.6 Hz, 1H), 6.61 (app d, *J* = 8.0 Hz, 1H), 6.45 (app d, *J* = 8.0 Hz, 1H), 5.54 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.62–3.53(m, 1H), 3.31–3.18 (comp, 4H), 2.57–2.43 (comp, 2H), 2.17–1.92 (comp, 6H), 1.72–1.63 (m, 1H), 1.58–1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 144.9, 129.3, 128.4, 125.9, 115.8, 111.2, 56.7, 48.3, 42.3, 32.8, 31.4, 31.2, 29.7, 23.4, 18.2; *m/z* (ESI–MS) 257.4 $[M + H]^+$.

1-phenyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinoline (3.21): Under nitrogen, an oven dried vial was charged with CuBr (7.2 mg, 0.05mmol, 0.1equiv), anhydrous DCE (2.5 mL), 1-phenylpyrrolidine (72 ul, 0.5 mmol, 1.0 equiv) and *t*BuOOH(5.5 M in decane) (109 μl, 0.6 mmol, 1.2 equiv). The reaction mixture was slowly heated to 60°C and kept at this temperature for 36 hours. Then the reaction mixture was allowed to cool to rt, diluted with ethyl acetate and filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography to give **3.21** as a colorless oil in 40% yield (1.2:1 mixture of two diastereomers). The characterization data matched the reported literature[139].

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Chapter IV Biomimetic Enantioselective Synthesis of Isoindolinones

4.1 Introduction

4.1.1 Enantioselective Synthesis of Isoindolinones

The chiral isoindolinone (phthalimidine) moiety occurs as a fundamental structure in a wide range of natural products[1-3] and bioactive molecules[4-7] (Figure 4.1). Therefore, organic chemists have long-standing interests in the enantioselective synthesis of this scaffold[8,9].

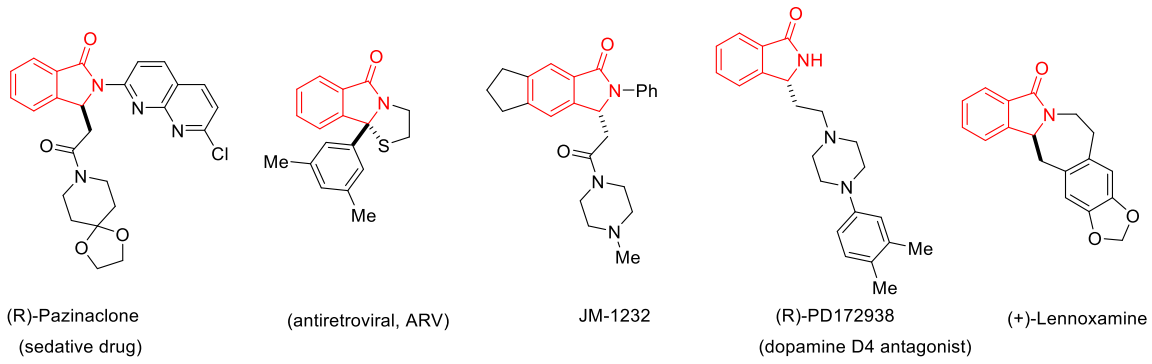
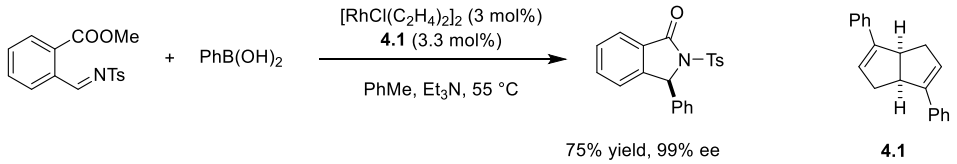


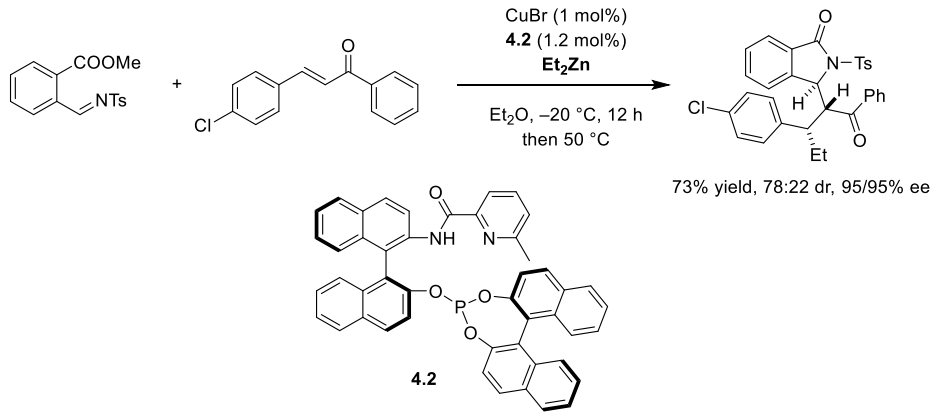
Figure 4.1. natural products and bioactive molecules bearing isoindolinone scaffolds.

In 2007, the Lin group[10] reported the first example of an enantioselective synthesis of isoindolinones via Rh-catalyzed arylation of *N*-tosylarylimines with arylboronic acids in the presence chiral diene ligand **4.1** (Scheme 4.1).



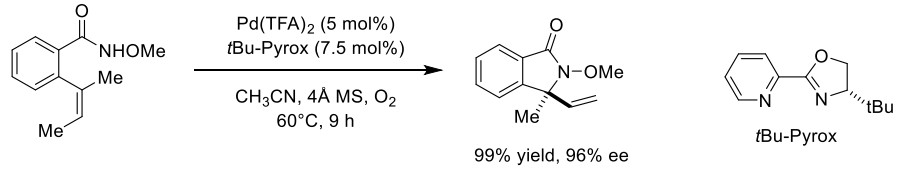
Scheme 4.1. Rh-catalyzed arylation of *N*-Tosylarylimines with arylboronic acids.

Later on, Huang and coworkers[11] revealed the construction of chiral isoindolinones with multiple stereogenic centers via a domino diastereo- and enantioselective catalytic Michael addition/Mannich reaction (Scheme 4.2). In the presence of a catalytic amount of CuBr and chiral *P*,*N*-ligand **4.2**, Et_2Zn added to the chalcones enantioselectively, then the resulting enolate intermediate could attack the imine and generate chiral isoindolinones with three contiguous stereogenic centers.



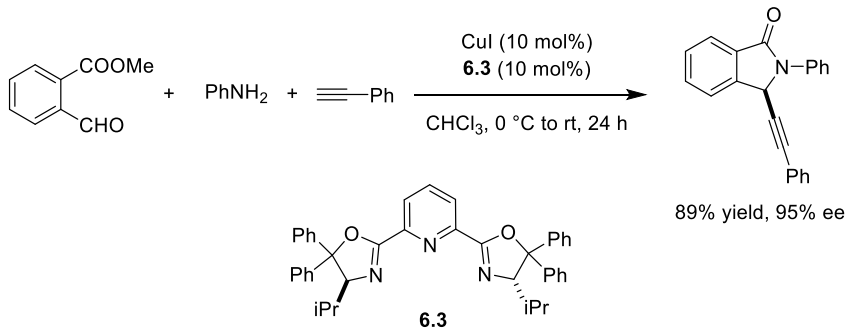
Scheme 4.2. Construction of chiral isoindolinones via domino Michael Addition/Mannich Reaction

A different strategy was utilized by Zhang and co-workers[12] who reported an asymmetric aerobic aza-Wacker-type reaction to create isoindolinones possessing quaternary carbon stereogenic centers (Scheme 4.3).



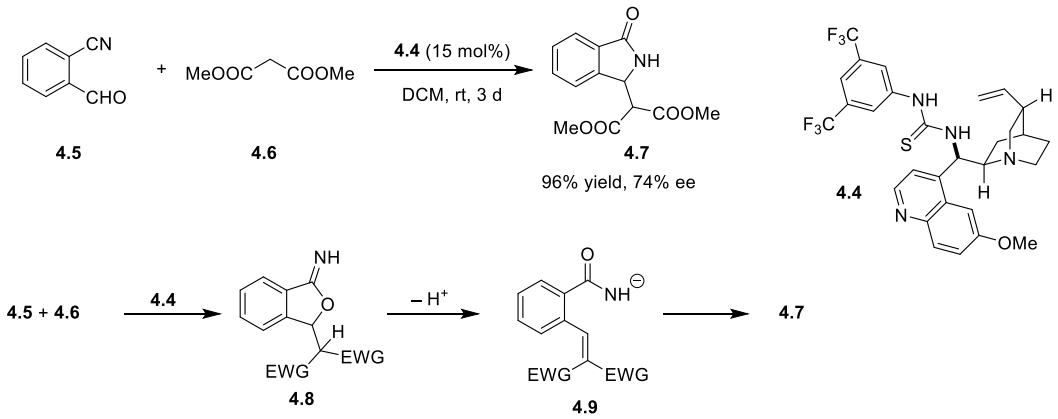
Scheme 4.3. Asymmetric aerobic intramolecular aza-Wacker-Type reaction.

Singh's group[13] reported access to chiral isoindolinones via a three-component alkynylation/lactamization sequence (Scheme 4.4). In the presence of Cu(I) catalyst and chiral Pybox ligand **4.3**, the copper alkynide could attack the in situ formed imine from methyl 2-formylbenzoate and aniline, giving 1-alkynyl the isoindolinone in excellent yield and ee.



Scheme 4.4. Synthesis of chiral isoindolinones via alkynylation/lactamization sequence.

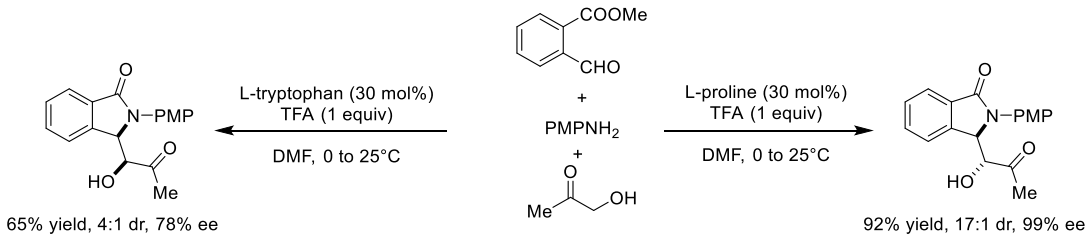
Massa *el al.* disclosed the first example[14,15] of an organocatalyzed enantioselective synthesis of chiral isoindolinones in an interesting aldol cyclization-rearrangement sequence of malonates with 2-cyanobenzaldehyde **4.5** (Scheme 4.5). The bifunctional thiourea catalyst **4.4** proved to be optimal to promote the particular transformation. With regard to the mechanism, the authors proposed that the aldol addition of **4.6** to **4.5** is followed by cyclization to generate the iminolactone **4.8**. Deprotonation results in ring-opened intermediate **4.9**, and the subsequent intramolecular conjugate addition gives rise to the final product **4.7**. Later on, the authors reported the same transformation under phase-transfer conditions.[16]



Scheme 4.5. Synthesis of chiral isoindolinones in an aldol cyclization-rearrangement sequence

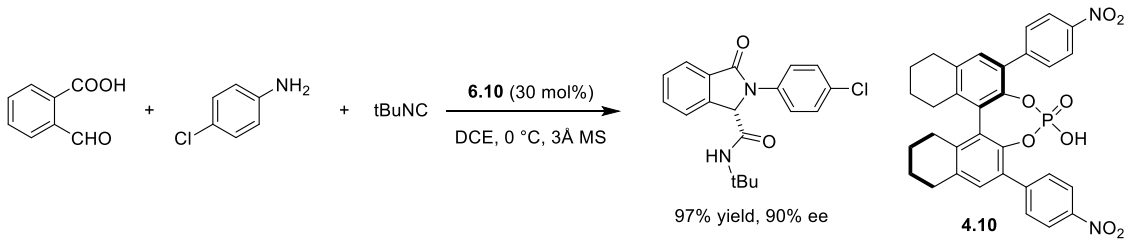
Singh's group[17] utilized enamine catalysis in the construction of isoindolinones via a tandem Mannich/lactamization reaction (Scheme 4.6). With proline as the catalyst, the *syn*-products were

obtained in excellent yields and stereoselectivities. The reactions were *anti*-selective when employing catalytic tryptophan under otherwise identical conditions.



Scheme 4.6. Synthesis of chiral isoindolinones via tandem Mannich/lactamization.

Very recently, Zhu's group[18] built isoindolinone scaffolds via the Ugi reaction of isonitriles with 3-(arylamino)isobenzofuran-1(3H)-ones catalyzed by chiral phosphoric acid **4.10** (Scheme 4.7). The same products could be also accessed via an enantioselective Ugi four center three-component reaction starting from 2-formylbenzoic acids, anilines, and isonitriles albeit with higher catalyst loading. Mechanistic studies revealed that the enantioselectivity originated from the dynamic kinetic resolution of the primary Ugi adduct prior to the Mumm rearrangement, rather than the addition of isonitriles to the imines formed in situ.

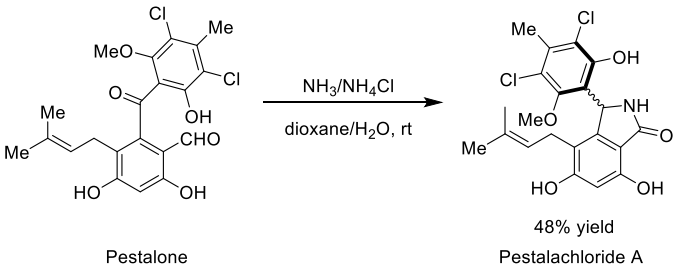


Scheme 4.7. Synthesis of chiral isoindolinones via Ugi reaction.

4.1.2 Biomimetic Synthesis of Isoindolinones

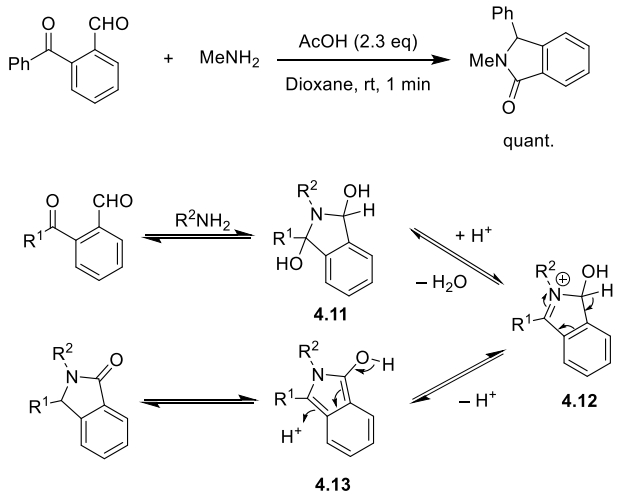
In 2001, the Fenical group[19] disclosed the first isolation and structure determination of pestalone, a natural produced by a marine deuteromycete. A pestalone derivative bearing a highly functionalized benzophenone moiety was reported to be a highly potent antibiotic against methicillin-resistant *Staphylococcus aureus* (MIC = 37 ng/mL) and vancomycin-resistant *Enterococcus faecium* (MIC=78

ng/mL). In 2008, Che[20] *et al.* isolated the new chlorinated benzophenone derivative pestalachloride A as a racemic mixture of two inseparable atropisomers. The authors proposed that its racemization was due to the presence of a stabilized carbocation intermediate, similar to the mechanism of racemization in pestacin.[21] Moreover, pestalachloride A exhibited potent antifungal activity against *F. culmorum* (IC_{50} = 0.89 μM) with a highly related structure to pestalone, pestalachloride A was considered as its lactamized or cyclized product. Due to its particularly promising antibiotic properties and limited availability from natural sources, the Schmalz group[22] conducted an efficient total synthesis of pestalone. More importantly, they found that when simply treating pestalone with NH_3 in aqueous NH_4Cl under very mild conditions, the only major product pestalachloride A was quickly formed as a mixture of two atropisomers, which might indicate that the formation of the racemic natural product was under non-enzymatic conditions (Scheme 4.8).



Scheme 4.8. Transformation of pestalone into pestalachloride A.

Inspired by their surprising findings, the Schmalz group utilized this transformation in the synthesis of various 3-substituted isoindolinones from aliphatic primary amines and 2-acylbenzaldehydes under acidic conditions[23] (Scheme 4.9). It was proposed that the primary amine could initially react with both of the carbonyls to form a cyclic bis-hemiaminal **4.11**, then the hydroxyisoindole **4.12** was produced after water elimination. Lastly, the tautomerization of **4.13** resulted in the final lactam product.



Scheme 4.9. Synthesis of isoindolinones from aliphatic primary amines and 2-acylbenzaldehydes

Recently, Bringmann, Konig and co-workers[24] reported the isolation of marilines A–C bearing isoindolinone scaffolds from the sponge-derived fungus *Stachylidium* sp. Different from the related isoindolinones known from fungal metabolism, these marilines uniquely possessed methyl groups at C8. As for the mariline A, the nitrogen is substituted with a functionalized phenyl ring. To date, similar structural patterns are only present in clitocybin A[25]. The small calculated rotation barrier around the *N*,*C*-axis suggested a free rotation could occur. Furthermore, it also showed that the *M*-atropo-diastereomer was thermodynamically more favored than the *P*-isomer (ΔE = 2.81 kcal/mol), probably owing to the larger steric repulsion between the methyl group at C8 and the alkoxyl side chain. As opposed to an analogous post-biosynthetic racemization of pestalachloride A, the authors suggested that both enantiomers of mariline A are genuine products of the biosynthetic process, given that no racemization occurred when subjecting enantiopure mariline A to harsh conditions such as KOH, HCl and elevated temperatures. With regard to the biosynthetic pathway, the authors were in agreement with Schmalz's proposal.

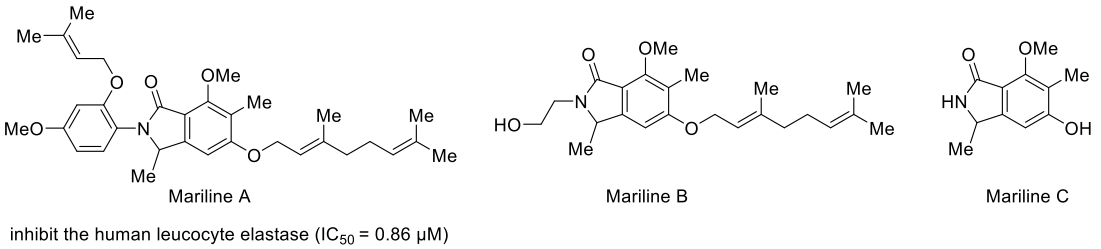
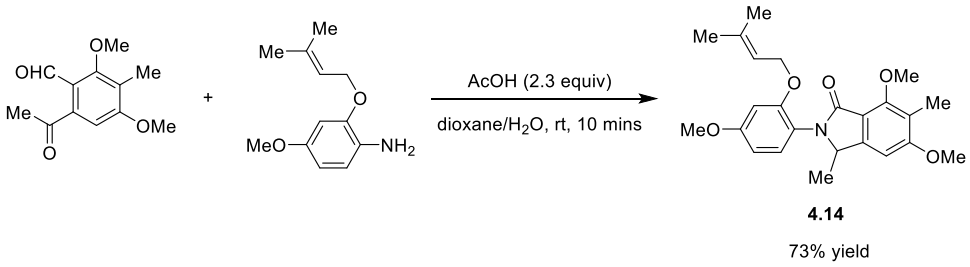


Figure 4.2. Marilines A–C.

To probe the proposed biosynthesis in vitro, the Schmalz group[26] carried out the synthesis of **4.14** as a simplified analogue of mariline A with the acylbenzaldehyde and aromatic primary amine. Notably, the electron-rich phenyl ring was required for the aromatic amine, whereas aniline itself only led to a complex mixture without appreciable amounts of the desired product, signifying the specific substrate combinations which nature seems to take advantage of in this biosynthesis.

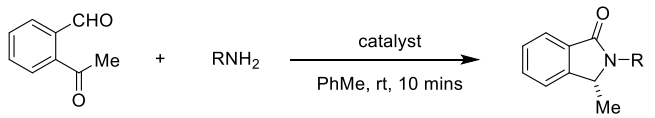


Scheme 4.10. Biomimetic synthesis of isoindolinones related to the marilines.

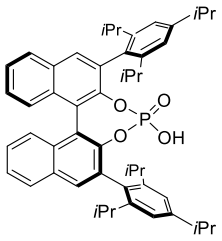
Inspired by Schmalz's seminal work, we surmised that when an appropriate chiral Brønsted acid catalyst was employed, the enantioselective synthesis of isoindolinones might be achieved by mimicking the biosynthesis of pestalachloride A and marilines. In this way, various optically active mariline analogues can be quickly assembled with simple alkyl groups at the C8 position, which were elusive to access by previously reported methodologies.

4.2 Optimization of Reaction Conditions

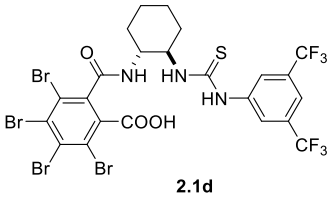
Table 4.1. Evaluation of reaction conditions[a]



4.15a **4.16** **4.17**



2.19a



2.1d

entry	R	cat	yield (%)	ee (%)
1	Cbz	**2.19a** (10 mol%)	No reaction	-
2	*t*Bu	**2.19a** (10 mol%)	No reaction	-
2	Bn	**2.19a** (10 mol%)	44	13
3	Bn	**2.1d** (20 mol%)	41	33
4	PMP	**2.19a** (10 mol%)	54	0
5	2,4-$(OMe)_2C_6H_3$	**2.19a** (10 mol%)	66	49
6	2,4-$(OMe)_2C_6H_3$	**2.1d** (20 mol%)	60	4
7	Ph	**2.19a** (10 mol%)	trace	-
8	2,6- $(OMe)_2C_6H_3$	**2.19a** (10 mol%)	67	65
9	2,6-$(OMe)_2C_6H_3$	**2.1d** (20 mol%)	55	6
10	2-$OMeC_6H_4$	**2.19a** (10 mol%)	49	10
11	3,4,5-$(OMe)_3C_6H_3$	**2.19a** (10 mol%)	70	19
12	2,6-$Me_2C_6H_3$	**2.19a** (10 mol%)	88	11
13	2-$OtBuC_6H_4$	**2.19a** (10 mol%)	71	83
14	2-$OtBuC_6H_4$	**2.1d** (20 mol%)	72	11
15[b]	2-$OtBuC_6H_4$	**2.19a** (10 mol%)	54	49
16[c]	2-$OtBuC_6H_4$	**2.19a** (10 mol%)	75	97
17[d]	2-$OtBuC_6H_4$	**2.19a** (10 mol%)	65	93
18[b]	2-$OtBuC_6H_4$	**2.19a** (1 mol%)	71	97
19[c,d]	2-$OtBuC_6H_4$	**2.19a** (1 mol%)	72	97
20[c]	2-$OtBuC_6H_4$	**2.19a** (0.1 mol%)	55	92

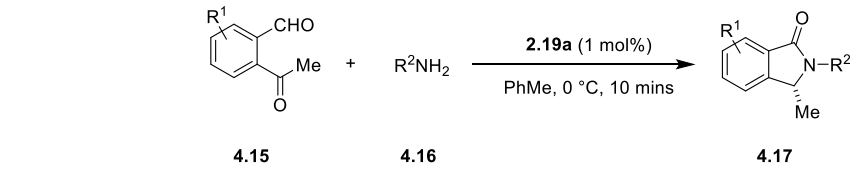
[a]Reactions were performed with 0.1 mmol scale in 1 ml toluene. Yields correspond to isolated yields, ee was determined by chiral HPLC. All the reactions were completed in 10 minutes, prolonged reaction time has no effect on the yield or ee. [b]In the presence of 4Å MS. [c]The reaction was run at 0 °C. [d]The reaction was run at –20 °C. [e]5 equiv water was added.

To evaluate this process, the ketoaldehyde **4.15a** was selected as the model substrate to test various amine components (Table 4.1). The primary amines protected by electron-withdrawing Cbz (entry 1) or bulky *t*Bu (entry 2) were inert in this transformation. Benzyl amine gave moderate yield and poor ee in the presence of either **2.19a** or **2.1d**. With regard to aromatic amines, the electron-rich ones generally exhibited higher reactivity and selectivity, which was in accordance with nature's choice of substrate combination. Similar to Schmalz's observations, the simple aniline brought about a complex

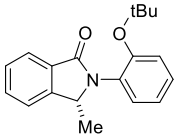
mixture with only trace amount of desired product (entry 7). Gratifyingly, we found that sterically crowded electron-rich aromatic amines afforded improved yields and ee's in the presence of **2.19a** (entry 5 and 8). Accordingly, we tested 2-OtBu aniline with bulky alkoxy substituent ortho to the amine, which gave promising enantioselectivity (entry 13). Interestingly, even though the reaction generated water as the byproduct, but the addition of molecular sieves resulted in a dramatic decrease in the yield and ee (entry 15), indicating an indispensable role of water in the process. Moreover, lowering the temperature to 0 °C brought about a significant increase in ee (entry 16), but further decreasing the temperature to –20 °C caused deterioration in reactivity and enantioselectivity (entry 17). Practically, the catalyst loading could be reduced to 1 mol% while retaining the good reactivity and selectivity (entry 18). Besides, the reaction was insensitive to moisture and the addition of water had no effect (entry 19). Surprisingly, when reducing the catalyst loading to as low as 0.1 mol%, excellent ee could still be obtained albeit with a lower yield (entry 20).

4.3 Substrate Scope

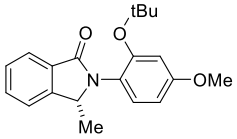
The scope of this transformation was evaluated with a range of ketoaldehydes and primary aromatic amines (Scheme 4.11). Various substituents on the amine phenyl ring with a bulky alkoxy group on the *ortho* position were readily tolerated. The *o*-phenylenediamine derivative also gave the isoindolinone **4.17d** in good yield and ee. As for the ketoaldehyde component, either electron-donating or electron-withdrawing groups on different positions on the phenyl ring were suitable substrates and generated the isoindolinone products in moderate to good yields and excellent ee's. The 3-alkyl group can be changed to ethyl and benzyl group, but larger substituents resulted in reduced yield and ee. Suprisingly, we observed diastereomeric products when we used 2-tBu anilines as the amine component. Interestingly, the product **4.17r** was obtained as a atropodiastereomeric equilibrium. During the course of the reaction, only the kinetic product was observed. But the thermodynamic product gradually appeared with prolonged reaction time.



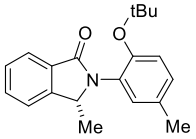
4.15 **4.16** **4.17**



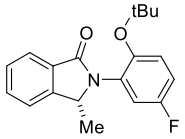
4.17a, 71% yield, 97% ee



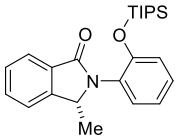
4.17b, 73% yield, 97% ee



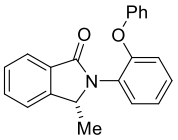
4.17c, 70% yield, 94% ee



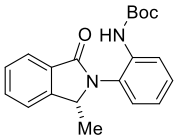
4.17d, 50% yield, 94% ee



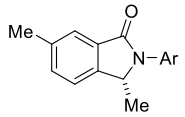
4.17e, 52% yield, 96% ee



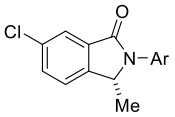
4.17f, 80% yield, 83% ee



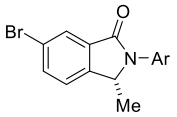
4.17g, 61% yield, 86% ee



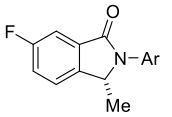
4.17h, 74% yield, 86% ee
Ar = 2-O*t*Bu-C_6H_4



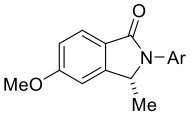
4.17i, 53% yield, 98% ee



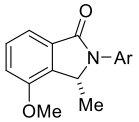
4.17j, 49% yield, 90% ee



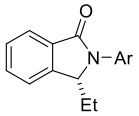
4.17k, 64% yield, 94% ee



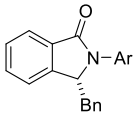
4.17l, 72% yield, 96% ee



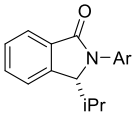
4.17m, 65% yield, 86% ee



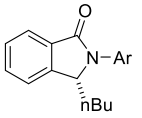
4.17n, 70% yield, 85% ee



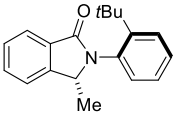
4.17o, 52% yield, 71% ee



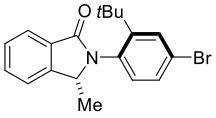
4.17p, 19% yield, 21% ee



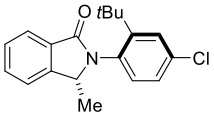
4.17q, 67% yield, 65% ee



4.17r, 75%, 7.5:1 dr, 93% ee



4.17s, 63%, 7:1 dr, 90% ee



4.17t, 63%, 7:1 dr, 90% ee

Scheme 4.11. Substrate scope. Reactions were performed with 0.2 mmol **4.15** and 0.4 mmol **4.16** in 2 ml toluene at 0 °C. Yields correspond to isolated yields, ee was determined by chiral HPLC. All the reactions were completed in 10 minitues, prolonged reaction time has no effect on the yield or ee.

Moreover, after the purification process, the thermodynamically stable diastereomer was the major product obtained. The two diastereomers are isolatable, but the pure fraction of the unstable diastereomer quickly turned into the mixture of both diastereomers. The thermodynamically stable diastereomer won't change into the unstable one at rt, but the atropodiastereomeric equilibrium can be achieved at elevated temperature. Previous reports on atroposelective synthesis of the molecules bearing a chiral carbon center have to rely on transferring the chirality pre-existing in the molecules[27-

[34]. The direct synthesis should be highly valuable given the vast co-existence of atropisomerism and chiral carbons in various natural products such as Vancomycin (Figure 4.3).

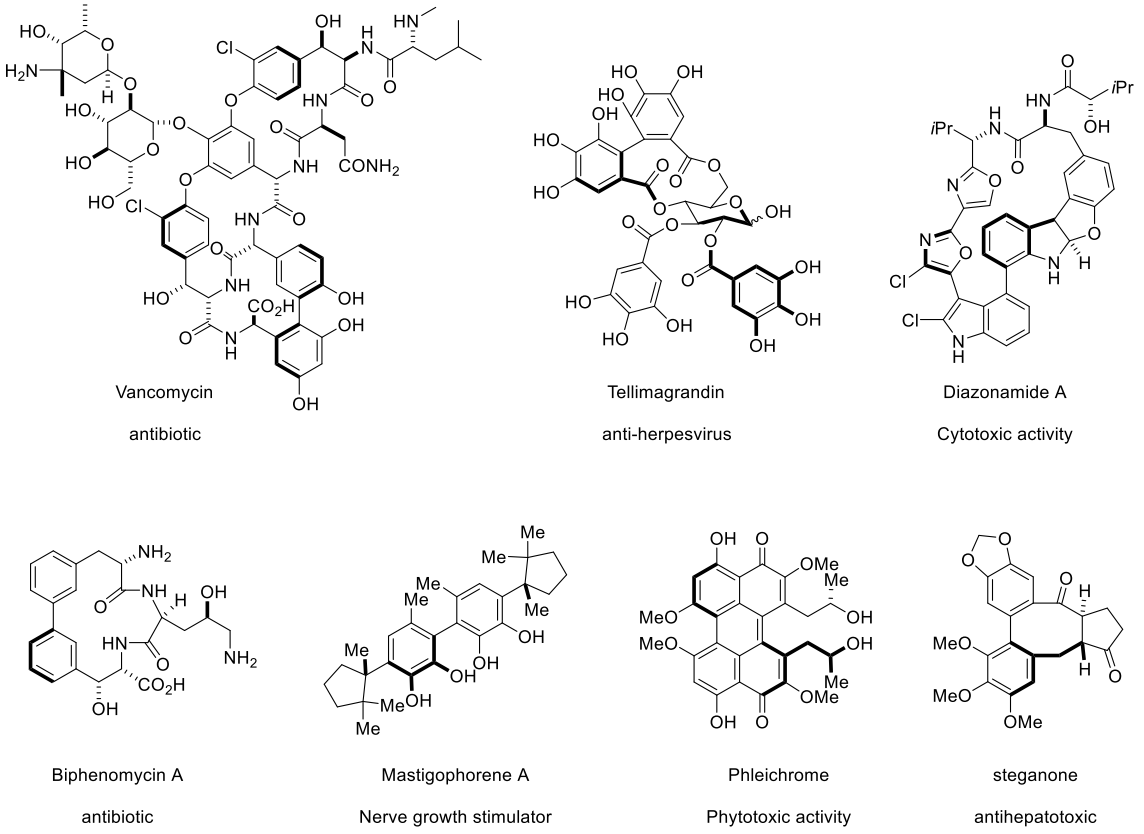


Figure 4.3. Natural products possessing both point and axial chirality.

4.4 Summary

In summary, we have successfully achieved the enantioselective synthesis of 3-alkyl isoindolinones catalyzed by chiral phosphoric acids via a biomimetic approach. The previously inaccessible optically pure 3-methyl isoindolinones corresponding to the marilines can be efficiently assembled in high efficiency. Moreover, the catalyst loading was as low as 1 mol% and the reactions were complete in only 10 minutes. Lastly, the atropisomerism can be introduced with a bulky amine opponent, which represents the first example of the simultaneous introduction of atropisomer and chiral carbon atoms directly from achiral starting materials.

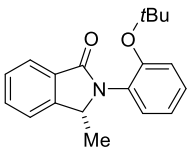
Experimental Section

Preparation and characterization data of products:

General procedure: Under N_2, a vial was charged with ketoaldehyde (0.2 mmol, 1 equiv) and (*S*)-TRIP (1.5 mg, 0.002 mmol, 0.01 equiv). Freshly distilled toluene (2 mL) was added and the resulting mixture was cooled to 0 °C over 10 min. The aromatic amine was then added (0.4 mmol, 2 equiv) and the reaction mixture was stirred at 0 °C. When aldehyde could no longer be detected by TLC analysis (typically < 10 min), the reaction mixture was directly purified by flash chromatography.

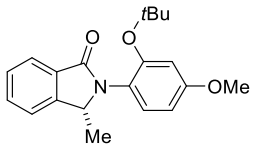
Characterization of products:

(*R*)-2-(2-(tert-butoxy)phenyl)-3-methylisoindolin-1-one (4.17a): Following the general procedure,



compound **4.17a** was obtained as a white solid in 71% yield (42 mg); mp = 130–131 °C; R_f = 0.31 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –22.7 (c 0.5, $CHCl_3$, 97% *ee*); IR (KBr) 2977, 1686, 1496, 1374, 1158, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.96–7.90 (m, 1H), 7.63–7.56 (m, 1H), 7.52–7.46 (comp, 2H), 7.42 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.29–7.24 (m, 1H), 7.19–7.13 (comp, 2H), 5.46 (q, *J* = 6.8 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 147.5, 131.8, 131.7, 130.8, 130.3, 127.9(2), 127.8(6), 124.5, 124.1, 123.8, 122.0, 80.6, 57.1, 28.9, 19.0; *m/z* (ESI–MS) 318.1 $[M + Na]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.7 min and t_R = 11.7 min (major).

(*R*)-2-(2-(tert-butoxy)-4-methoxyphenyl)-3-methylisoindolin-1-one (4.17b): Following the general

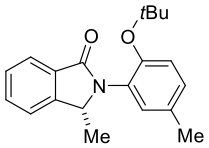


procedure, compound **4.17b** was obtained as a white solid in 73% yield (47.5 mg). mp = 144–146 °C; R_f = 0.15 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –11.2 (c 0.5, $CHCl_3$, 97% *ee*); IR (KBr) 2979, 1686, 1495, 1371, 1155, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.96–7.88 (m, 1H), 7.60–7.55 (m, 1H), 7.50–7.45 (comp, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 6.76–6.67 (comp, 2H), 5.41–5.28 (m, 1H), 3.81 (s, 3H), 1.27 (d,

J = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.1, 147.4, 131.7, 131.6, 130.5, 127.8, 124.0, 123.5, 121.9, 110.4, 108.4, 80.7, 57.1, 55.4, 28.8, 18.9; *m/z* (ESI–MS) 348.1 [M + Na]$^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.4 min and t_R = 6.3 min (major).

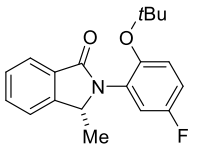
The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butoxy)-5-methylphenyl)-3-methylisoindolin-1-one (4.17c): Following the general procedure, compound **4.17c** was obtained as a white solid in 70% yield (43 mg). mp = 151–152 °C; R_f = 0.35 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ –29.2 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2963, 1686, 1490, 1382, 1159, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.63–7.57 (m, 1H), 7.52–7.45 (comp, 2H), 7.25–7.20 (m, 1H), 7.11–7.00 (comp, 2H), 5.54–5.42 (m, 1H), 2.34 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 147.5, 133.6, 131.7, 130.5(4), 130.4(6), 128.6, 127.9, 124.6, 124.1, 122.0, 80.3, 57.1, 28.8, 20.7, 19.0; *m/z* (ESI–MS) 332.1 [M + Na]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 17.8 min and t_R = 20.7 min (major).



The absolute configuration was assigned by analogy.

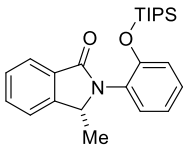
(*R*)-2-(2-(tert-butoxy)-5-fluorophenyl)-3-methylisoindolin-1-one (4.17d): Following the general procedure, compound **4.17d** was obtained as a white solid in 50% yield (31 mg). mp = 106–108 °C; R_f = 0.37 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ –32.0 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2979, 1691, 1497, 1371, 1158, 882, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (app dt, *J* = 7.5, 1.0 Hz, 1H), 7.61 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.52–7.47 (comp, 2H), 7.21 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.08 (dd, *J* = 9.0, 5.4 Hz, 1H), 6.97 (ddd, *J* = 9.0, 7.6, 3.1 Hz, 1H), 5.53 (q, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 9H); ^{13}C NMR (125



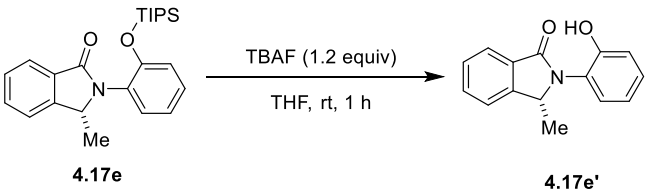
MHz, $CDCl_3$) δ 167.3, 158.4 (d, $J_{C–F}$ = 243.6 Hz), 147.4, 132.1, 131.3, 129.5, 128.1, 125.7, 124.2, 122.0, 116.9 (d, $J_{C–F}$ = 24.0 Hz), 114.4 (d, $J_{C–F}$ = 22.7 Hz), 80.9, 56.9, 28.7, 19.0; *m/z* (ESI–MS) 336.1 $[M + Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.2 min (major) and t_R = 9.3 min.

The absolute configuration was assigned by analogy.

(*R*)-3-methyl-2-(2-((triisopropylsilyl)oxy)phenyl)isoindolin-1-one (4.17e): Following the general procedure, compound **4.17e** was obtained as a colorless oil in 52% yield (41 mg). R_f = 0.37 (Hexanes/EtOAc 80:20 v/v); IR (film) 2972, 1688, 1490, 1365, 1151, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.91 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.57 (app td, *J* = 7.5, 1.1 Hz, 1H), 7.52–7.42 (comp, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.24–7.19 (m, 1H), 7.01 (app td, *J* = 7.6, 1.3 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.13 (q, *J* = 6.8 Hz 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.27–1.16 (comp, 3H), 1.04–0.92 (comp, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 152.4, 147.4, 132.0, 131.6, 130.7, 128.7, 127.9, 127.1, 124.0, 121.8, 121.2, 119.2, 57.6, 18.8, 17.8(3), 17.8(1), 12.8; *m/z* (ESI–MS) 418.0 $[M + Na]^+$; The ee was determined after deprotection due to the unseparated enantiomers on chiral HPLC.



Due to the poor separation of both enantiomers of **4.17e** on chiral HPLC columns, it was transformed to **4.17e'** to determine the ee.



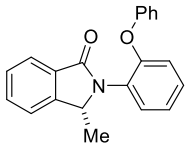
4.17e **4.17e'**

The procedure was modified from a reported literature[3]: **4.17e** (20 mg, 0.05 mmol) was dissolved in 0.5 ml THF and 60 μL TBAF solution (0.06 mmol, 1.2 equiv) in THF (1.0 M) was added. The mixture

was stirred for 15 min at room temperature. It was then quenched with water (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layer was dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography to give **4.17e'** as a white solid in 89% yield (10.7 mg); mp = 175–177 °C; R_f = 0.14 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –161.6 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 3072, 2973, 1652, 1592, 1456, 1373, 1280, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.45 (s, 1H), 7.94 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.65 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.58–7.50 (comp, 2H), 7.27–7.23 (m, 1H), 7.19–7.12 (comp, 2H), 7.04–7.00 (m, 1H), 5.35 (q, *J* = 6.8 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 151.8, 147.5, 132.5, 130.6, 128.7, 128.0, 125.6, 124.2, 123.4, 122.1, 121.2, 121.0, 58.4, 18.3; *m/z* (ESI–MS) 262.1 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H , *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.1 min (major) and t_R = 13.8 min.

The absolute configuration was assigned by analogy.

(*R*)-3-methyl-2-(2-phenoxyphenyl)isoindolin-1-one (4.17f): Following the general procedure, compound **4.17f** was obtained as a semi-solid in 80% yield (50.5 mg). R_f = 0.27 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –9.6 (c 0.5, $CHCl_3$, 83% *ee*); IR (film) 2973, 1686, 1494, 1365, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.89 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.56 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48–7.41 (comp, 2H), 7.32–7.26 (comp, 3H), 7.21 (app td, *J* = 7.6, 1.5 Hz, 1H), 7.07–7.03 (m, 1H), 7.02–6.97 (comp, 3H), 5.23 (q, *J* = 6.8 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 156.6, 153.0, 147.3, 131.8, 131.5, 130.4, 129.7, 128.7, 128.0, 127.8, 124.1, 123.9, 123.5, 121.9, 119.7, 118.7, 57.8, 18.8; *m/z* (ESI–MS) 338.2 $[M + Na]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 230 nm, t_R = 18.5 min (major).and t_R = 20.9 min.



The absolute configuration was assigned by analogy.

***tert*-butyl (*R*)-(2-(1-methyl-3-oxoisoindolin-2-yl)phenyl)carbamate (4.17g):** Following the general procedure, compound **4.17g** was obtained as a white solid in 61% yield (41 mg); mp = 119–120 °C; R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –64.1 (c 0.5, $CHCl_3$, 86% *ee*); IR (KBr) 2977, 1724, 1677, 1514, 1161, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.00–7.91 (comp, 2H), 7.65 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (app t, *J* = 7.5, Hz, 1H), 7.51 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.38–7.33 (m, 1H), 7.24–7.14 (comp, 3H), 5.12 (q, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 1.36 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 153.4, 147.4, 135.6, 132.2, 130.9, 128.5, 128.2, 126.2, 124.5, 124.3, 122.1, 80.3, 59.3, 28.2, 18.4; *m/z* (ESI–MS) 361.0 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.0 min and t_R = 7.6 min (major).

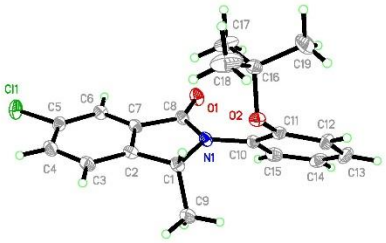
The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butoxy)phenyl)-3,6-dimethylisoindolin-1-one (4.17h): Following the general procedure, compound was obtained as a white solid in 74% yield (46 mg); mp = 118–120 °C; R_f = 0.28 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –24.0 (c 0.5, $CHCl_3$, 86% *ee*); IR (KBr) 2974, 1690, 1496, 1375, 1163, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.75–7.72 (m, 1H), 7.44–7.38 (comp, 2H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.27–7.24 (m, 1H), 7.19–7.12 (comp, 2H), 5.42 (q, *J* = 7.0 Hz, 1H), 2.46 (s, 3H), 1.27–1.21 (comp, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6, 144.8, 137.9, 132.8, 131.8, 131.0, 130.3, 127.8, 124.6, 124.3, 123.8, 121.7, 80.6, 56.9, 28.9, 21.3, 19.1; *m/z* (ESI–MS) 332.1 $[M + Na]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.9 min and t_R = 7.5 min (major).

The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butoxy)phenyl)-6-chloro-3-methylisoindolin-1-one (4.17i): Following the general procedure, compound **4.17i** was obtained as a white solid in 53% yield (35 mg). mp = 148–149 °C; R_f = 0.30 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –36.4 (c 0.5, $CHCl_3$, 98% *ee*); IR (KBr) 2975, 1687, 1497, 1381, 1158, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.90 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.44–7.37 (comp, 2H), 7.29–7.25 (m, 1H), 7.19–7.12 (comp, 2H), 5.48–5.34 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 145.6, 134.2, 133.5, 131.9, 130.4, 130.1, 128.1, 124.2, 123.8, 123.3, 80.6, 56.9, 28.9, 18.9; *m/z* (ESI–MS) 352.0 $[M + Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.2 min (major).and t_R = 9.4 min.

The crystal was crystallized from hexanes/chloroform through slow diffusion at room temperature and the absolute configuration was assigned by X-ray crystallography



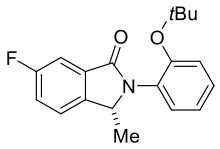
The requisite CIF has been deposited with the CCDC (deposition # 1511145).

(*R*)-6-bromo-2-(2-(tert-butoxy)phenyl)-3-methylisoindolin-1-one (4.17j): Following the general procedure, compound **4.17j** was obtained as a white solid in 49% yield (36 mg). mp = 158–160 °C; R_f = 0.31 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –25.1 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2971, 1694, 1485, 1391, 763 cm^{-1}; ^1H NMR (500

MHz, $CDCl_3$) 8.06 (d, *J* = 1.9 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.43–7.34 (comp, 2H), 7.29–7.25 (m, 1H), 7.18–7.13 (comp, 2H), 5.41 (q, *J* = 7.1 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 146.1, 134.7, 133.8, 130.3, 130.1, 128.1, 127.3, 124.3, 123.8, 123.7, 122.0, 80.7, 57.0, 28.9, 18.8; *m/z* (ESI–MS) 396.0 (^{79}Br) $[M + Na]^+$; *m/z* (ESI–MS) 398.0 (^{81}Br) $[M + Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.5 min (major).and t_R = 10.1 min.

The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butoxy)phenyl)-6-fluoro-3-methylisoindolin-1-one (4.17k): Following the general procedure, compound **4.17k** was obtained as a white solid in 64% yield. mp = 167–168 °C; R_f = 0.36 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ –28.1 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2977, 1691, 1500, 1384, 1263, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.59 (dd, *J* = 7.7, 2.5 Hz, 1H), 7.46–7.42 (m, 1H), 7.39 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.32–7.24 (comp, 2H), 7.19–7.13 (comp, 2H), 5.41 (q, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.4 (d, $J_{C–F}$ = 3.4 Hz), 162.8 (d, $J_{C–F}$ = 246.8 Hz), 142.9 (d, $J_{C–F}$ = 2.3 Hz), 133.8 (d, $J_{C–F}$ = 8.4 Hz), 130.5, 130.1, 128.1, 124.3, 123.7, 123.5 (d, $J_{C–F}$ = 8.2 Hz), 119.3 ($J_{C–F}$, *J* = 23.7 Hz), 110.7 ($J_{C–F}$ = 23.4 Hz), 80.6, 56.9, 28.9, 19.0; *m/z* (ESI–MS) 336.1 $[M + Na]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.9 min and t_R = 8.5 min (major).



The absolute configuration was assigned by analogy.

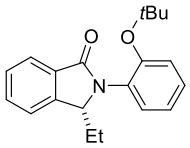
(*R*)-2-(2-(tert-butoxy)phenyl)-5-methoxy-3-methylisoindolin-1-one (4.17l): Following the general procedure, compound **4.17l** was obtained as a white solid in 72% yield (47 mg). mp = 144–146 °C; R_f = 0.15 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ – 14.1 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2966, 1682, 1496, 1375, 1163, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.84 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.27–7.22 (m, 1H), 7.18–7.11 (comp, 2H), 7.00 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 5.41 (q, *J* = 6.6 Hz, 1H), 3.90 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 163.0, 149.8, 131.1, 130.3, 127.7, 125.5, 124.6, 124.3, 123.8, 114.4, 106.9, 80.6, 56.8, 55.6, 28.8, 19.1; *m/z* (ESI–MS) 348.1 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 0.1 mL/min, UV = 280 nm, t_R = 99.4 min and t_R = 106.4 min (major).

The absolute configuration was assigned by analogy.

(*R*)-2-(2-(*tert*-butoxy)phenyl)-4-methoxy-3-methylisoindolin-1-one (4.17m): Following the general procedure, compound **4.17m** was obtained as a white solid in 65% yield (42 mg). mp = 102–103 °C; R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –22.6 (c 0.5, $CHCl_3$, 86% *ee*); IR (KBr) 2971, 1680, 1491, 1370, 1153, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.53 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.47–7.39 (comp, 2H), 7.28–7.22 (m, 1H), 7.19–7.12 (comp, 2H), 7.05 (dd, *J* = 8.1, 0.8 Hz, 1H), 5.46 (q, *J* = 6.9 Hz, 1H), 3.92 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 154.7, 135.0, 133.6, 130.3, 129.4, 127.8, 124.5, 123.7, 116.1, 113.2, 110.0, 80.5, 56.0, 55.4, 28.9, 17.4; *m/z* (ESI–MS) 348.1 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.8 min and t_R = 6.8 min (major).

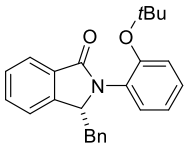
The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butoxy)phenyl)-3-ethylisoindolin-1-one (4.17n): Following the general procedure, compound **4.17n** was obtained as a white solid in 70% yield (43 mg); mp = 96–98 °C; R_f = 0.36 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –20.3 (c 0.5, $CHCl_3$, 85% *ee*); IR (KBr) 2973, 1693, 1497, 1375, 1159, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.94 (app dt, *J* = 7.5, 1.1 Hz, 1H), 7.59 (app t, *J* = 7.5 Hz, 1H), 7.52–7.45 (comp, 3H), 7.28–7.24 (m, 1H), 7.18 (app td, *J* = 7.6, 1.6 Hz, 1H), 7.14 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.64–5.55 (m, 1H), 1.92–1.82 (m, 1H), 1.70–1.62 (m, 1H), 1.22 (s, 9H), 0.52 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 145.4, 132.7, 131.7, 129.9, 127.8, 127.7, 124.1, 123.9, 122.1, 80.7, 61.3, 28.8, 24.2, 6.8; *m/z* (ESI–MS) 332.1 $[M + Na]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 280 nm, t_R = 5.6 min and t_R = 8.2 min (major).



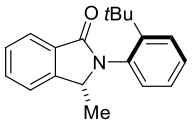
The absolute configuration was assigned by analogy.

(*R*)-3-benzyl-2-(2-(tert-butoxy)phenyl)isoindolin-1-one (4.17o): Following the general procedure, compound **4.17o** was obtained as a semi-solid in 52% yield (39 mg); R_f = 0.29 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –26.9 (c 0.5, $CHCl_3$, 71% *ee*); IR (film) 2962, 1684, 1488, 1370, 749 cm^{-1}; ^1H NMR (500 MHz, CDCl3) 7.94–7.85 (m, 1H), 7.51–7.39 (comp, 3H), 7.30–7.14 (comp, 6H), 7.04–6.95 (comp, 2H), 6.87 (dd, *J* = 6.7, 1.8 Hz, 1H), 5.90–5.75 (m, 1H), 3.21 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.53 (dd, *J* = 13.6, 9.4 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 145.4, 136.5, 132.0, 131.3, 130.8, 130.2, 129.7, 128.3, 128.0, 127.7, 126.7, 124.9, 124.1, 123.9, 123.1, 80.7, 61.7, 39.2, 28.8; (ESI–MS) 394.1 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.4 min (major) and t_R = 11.6 min.



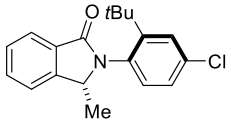
The absolute configuration was assigned by analogy.

(*R*)-2-(2-(tert-butyl)phenyl)-3-methylisoindolin-1-one (4.17r): Following the general procedure, compound **4.17r** was obtained as a white solid in 75% yield (42 mg); mp = 199–200 °C; R_f = 0.29 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –8.9 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2974, 1686, 1501, 1369, 1156, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.93 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.64–7.58 (comp, 2H), 7.53–7.45 (comp, 2H), 7.39–7.34 (m, 1H), 7.28–7.25 (m, 1H), 7.02 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.89 (q, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 149.3, 147.2, 134.0, 133.2, 131.8, 131.7, 129.1, 128.7, 128.3, 126.8, 124.2, 122.1, 59.8, 35.9, 32.0, 19.5; (ESI–MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, major diastereomer: t_R = 8.8 min (major) and t_R = 11.3 min, minor diastereomer: t_R = 6.1 min and t_R = 23.9 min (major).



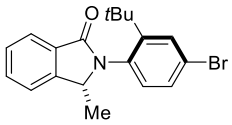
The absolute configuration was assigned by analogy.

(*R*)-2-(2-(*tert*-butyl)-4-chlorophenyl)-3-methylisoindolin-1-one (4.17s): Following the general procedure, compound **4.17s** was obtained as a white solid in 65% yield (40 mg); mp = 104–105 °C; R_f = 0.32 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –25.8 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2974, 1684, 1509, 1373, 1155, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.92 (app td, *J* = 7.6, 0.9 Hz, 1H), 7.61 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.55–7.46 (comp, 2H), 7.28–7.23 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.87 (q, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 151.5, 147.1, 134.5(6), 134.5(7), 132.8, 132.0, 131.4, 129.4, 128.4, 127.0, 124.3, 122.1, 59.6, 36.1, 31.8, 19.5; (ESI–MS) 314.0 $[M + H]^+$, (ESI–MS); HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, major diastereomer: t_R = 5.6 min (major) and t_R = 8.7 min, minor diastereomer: t_R = 4.6 min and t_R = 13.7 min (major).



The relative stereochemistry is confirmed by 2D-NMR analysis (interaction between benzylic C–H and *t*Bu group). The absolute configuration was assigned by analogy.

(*R*)-2-(4-bromo-2-(*tert*-butyl)phenyl)-3-methylisoindolin-1-one (4.17t): Following the general procedure, compound **4.17t** was obtained as a white solid in 63% yield (45 mg); mp = 104–105 °C; R_f = 0.32 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ 7.9 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2975, 1684, 1507, 1374, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.92 (app dt, *J* = 7.6, 1.0 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.61 (app dt, *J* = 7.5, 1.2 Hz 1H), 7.53–7.47 (comp, 2H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.87 (q, *J* = 6.8 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 151.8, 147.1, 134.9, 133.3, 132.4, 132.0, 131.4, 130.0, 128.4, 124.3, 123.0, 122.1, 59.6, 36.1, 31.8, 19.5; (ESI–MS) 380.1 (^{79}Br) $[M + Na]^+$, (ESI–MS) 382.1 (^{81}Br) $[M + Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, major diastereomer: t_R = 8.8 min (major) and t_R = 15.1 min.



The absolute configuration was assigned by analogy.

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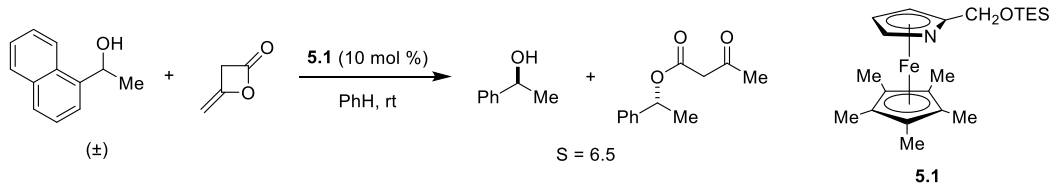
Chapter V A Dual-catalysis Approach to the Kinetic Resolution of 1,2-Diaryl-1,2-Diaminoethanes

5.1 Introduction

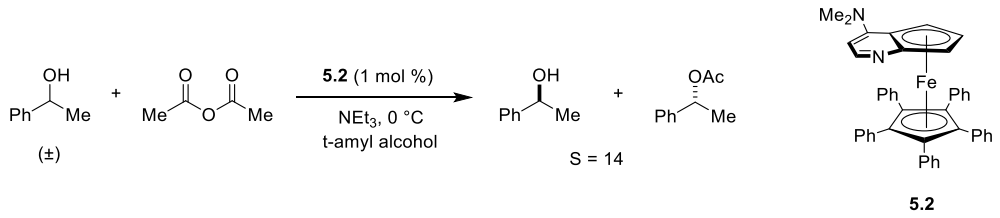
5.1.1 Nucleophilic Catalysis in Kinetic Resolution

Nucleophilic catalysis[1-7] has been shown to be an effective tool for installing asymmetry into a variety of different reactions. Chiral phosphines and chiral amines have been extensively studied, and chiral derivatives of 4-(dimethylamino) pyridine (DMAP) feature prominently among the catalysts used for kinetic resolution and desymmetrization processes. In 1996, Fu[8] *el al.* reported the very first application of planar-chiral nucleophilic catalysts assembled by π-complexation of a heterocycle to iron in asymmetric catalysis (Scheme 5.1). They have found that the azaferrocene derivative **5.1** acted as an active catalyst for the kinetic resolution of racemic secondary alcohols with diketene and the selectivity factors (s) were up to 6.5, which was the highest among the reported examples of nonenzymatic acylation of the same substrate at that time.



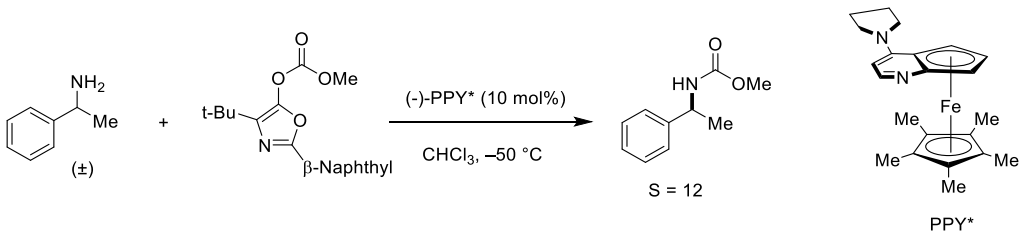
Scheme 5.1. Kinetic resolution of alcohols using planar-chiral azaferrocene catalyst

Soon after their first report, the Fu group[9] developed a second-generation planar-chiral nucleophilic catalyst **5.2**, which proved to be much more robust than any previously existing small-molecule asymmetric acylation catalyst (Scheme 5.2). In the presence of only 2 mol% **5.2**, various benzylic and allylic secondary alcohols were efficiently resolved in good to excellent selectivity with the inexpensive acetic anhydride as the acylating agent. This work represents a vital progress in the field of catalytic kinetic resolution and nucleophilic catalysis.



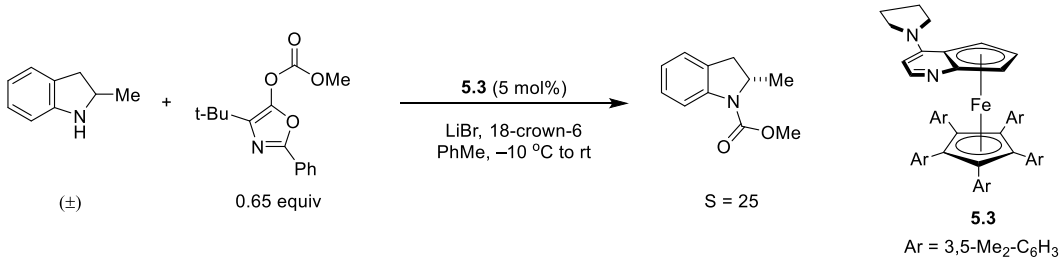
Scheme 5.2. Kinetic resolution of benzylic alcohol using planar-chiral DMAP derivative

In 2001, Fu[10] and co-workers published the first kinetic resolution of amines using a planar-chiral derivative of PPY. By using a more selective acylating agent, acylated azlactone, the background reaction was inhibited despite the high inherent nucleophilicity of amines (Scheme 5.3).



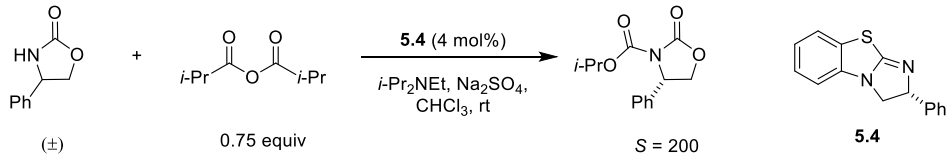
Scheme 5.3. Kinetic resolution of benzylic amine using chiral DMAP derivatives

The Fu group then applied the even bulkier PPY derivative **5.3** in the kinetic resolution of 2-substituted indolines[11] (Scheme 5.4). There was no reaction when they applied the earlier optimal conditions to this transformation, probably due to the relatively low nucleophilicity of the indoline. Later they found out the addition of halide salts was very helpful for the catalytic efficiency and selectivity, specifically, LiBr/8-crown-6 brought about the highest *s* value. This is the first example of nonenzymatic kinetic resolution of indolines.



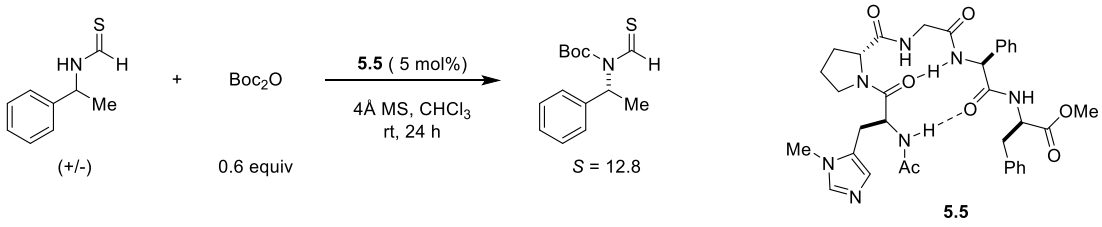
Scheme 5.4. Kinetic resolution of indolines using chiral DMAP derivatives.

Birman and co-workers developed benzotetramisole (BTM) **5.4** as a new nucleophilic catalyst (Scheme 5.5) to promote a highly selective kinetic resolution of less nucleophilic 2-oxazolidinones[12].



Scheme 5.5. Kinetic resolution of 2-oxazolidinones using benzotetramisole.

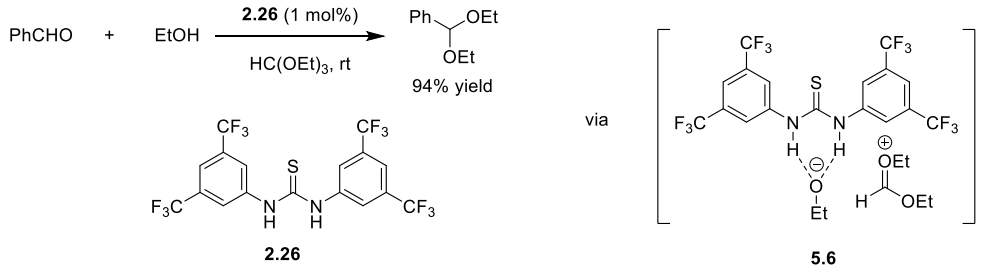
The Miller group resolved thioformamides (Scheme 5.6) with a nucleophilic peptide catalyst[13], presumably by employing the histidine residue as the nucleophilic site to attack di-tert-butyldicarbonate. Morever, the products Boc-protected thioformamides can be readily converted to chiral primary amines.



Scheme 5.6. Kinetic resolution of thioformamides with a nucleophilic peptide catalyst

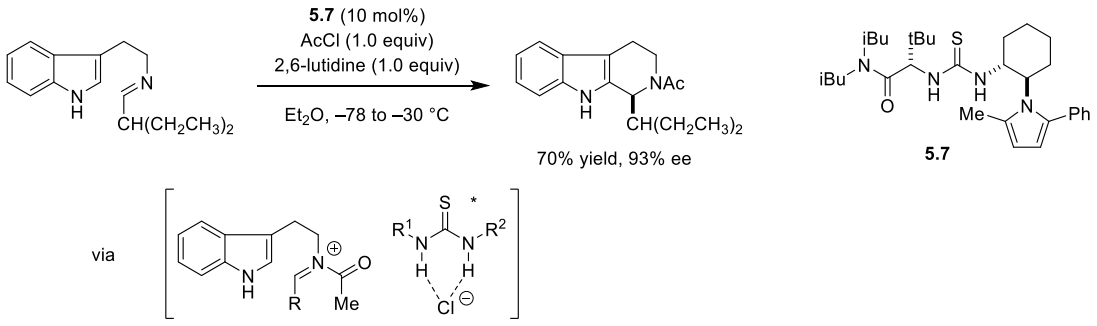
5.1.2 Anion-Binding Catalysis

In 2006, Schreiner *et al.* firstly suggested anion binding[14-20] as a novel catalytic mode[21] (Scheme 5.7). Specifically, they discovered the achiral thiourea **2.26** as a highly efficient catalyst for the acetalization of various carbonyl compounds with orthoesters. The initial hypothesis is that **2.26** can interact with the carbonyl compound via hydrogen bonding to lower its LUMO. However, when they attempted to apply the same catalyst in the thioacetalization reactions, they found that the addition of the orthoester only gave the diethyl acetal products even though the thiols are much more nucleophilic. Accordingly, they proposed an alternative mechanism that involves the thiourea-assisted heterolysis of the orthoester which generated an alkoxide rapidly attacking onto the carbonyl compounds.



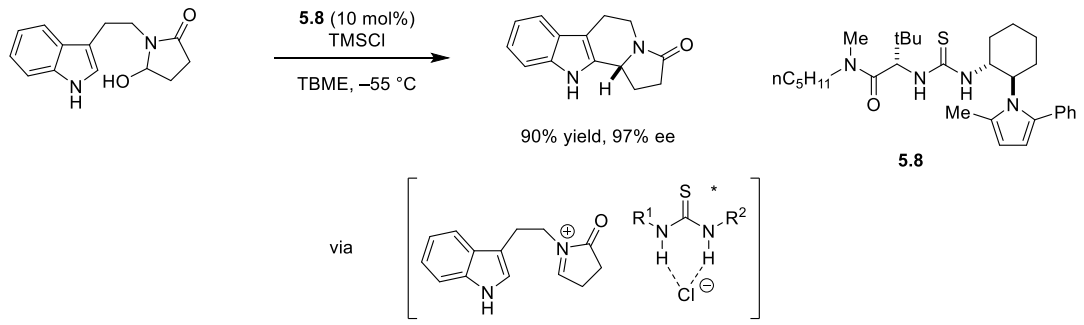
Scheme 5.7. Activation of orthoesters by anion binding.

In 2004, the Jacobsen group reported highly enantioselective, acyl Pictet–Spengler[22] reactions catalyzed by chiral thiourea **5.7** (Scheme 5.8). Although the precise mechanism remained unclear then, it was later realized to involve anion binding. Specifically, *N*-acyliminium ions were generated in situ by the acylation of imines, and the anion binding between **5.7** and the chloride of the transient acyliminium was proposed to be involved in the enantiodetermining step.



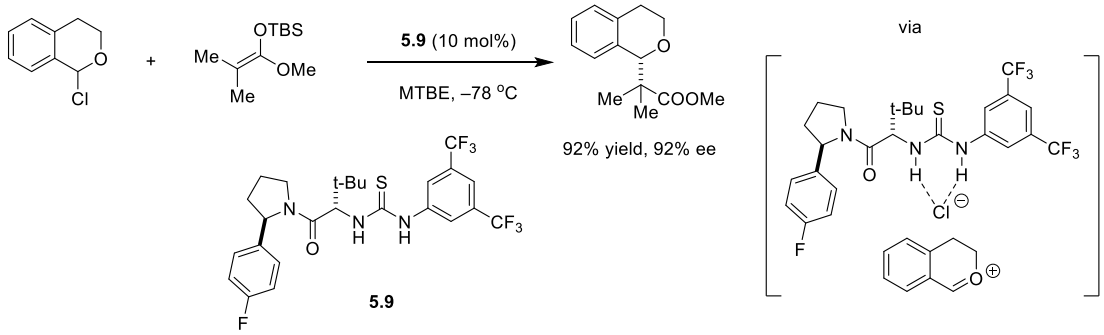
Scheme 5.8. Enantioselective, acyl Pictet–Spengler reactions

In 2007, Jacobsen[23] *et al.* applied their thiourea catalyst **5.8** in the enantioselective cyclization of tryptamine-derived hydroxylactams (Scheme 5.9). The proposed mechanism is that *N*-acyl iminium ions are generated in situ by the dehydration of hydroxylactams, and its counterion (chloride) is recognized by the chiral thiourea catalyst to provide a chiral environment for the enantio-differentiation.



Scheme 5.9. Cyclization of tryptamine-derived hydroxylactam

The same group also applied this concept to the asymmetric thiourea-catalyzed addition of silyl ketene acetals to 1-chloroisochromans[24] (Scheme 5.10). Moreover, oxocarbenium ions are involved as the electrophilic intermediates here which are generated in situ via thiourea-assisted chloride dissociation.



Scheme 5.10. Thiourea-catalyzed addition of silyl ketene acetals to 1-chloroisochromans

5.1.3 Dual catalysis of nucleophilic and anion-bonding catalysis

Our group has advanced a dual catalysis[25-31] approach in which a chiral acylating reagent is generated in situ via the interplay of a chiral anion receptor/H-bonding (HB) catalyst and DMAP or its derivatives as an achiral nucleophilic cocatalyst (Figure 5.1). In this process, a simple achiral acyl pyridinium salt I become chiral after binding of the its anion to a chiral anion binding catalyst (chiral ion pair II). This tactic offers an alternative to the use of chiral DMAP analogues and might provide potential advantages. enabling the acylative kinetic resolution of various amines and other enantioselective transformations.

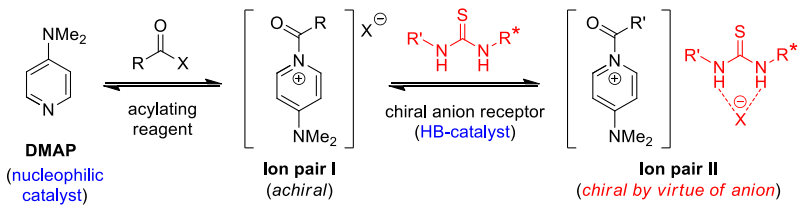
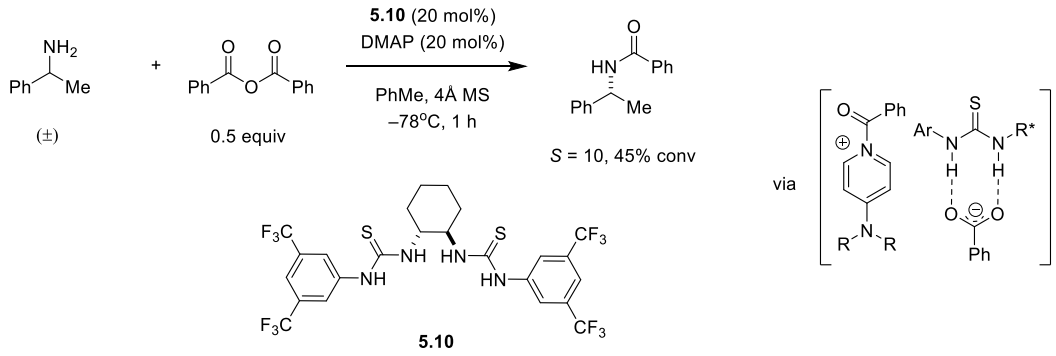


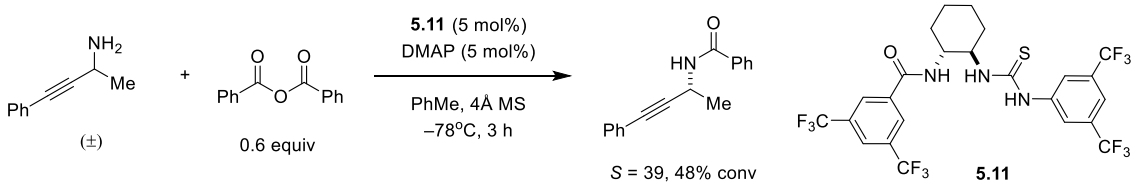
Figure 5.1. Anion-binding concept for asymmetric nucleophilic catalysis

Our group firstly demonstrated this concept in the kinetic resolution of benzylic amines[32] (Scheme 5.11). These reactions were efficiently catalyzed by readily available Nagasawa's bisthiourea catalyst[33] **5.10**. The low reaction temperature and concentration had a beneficial impact on the selectivity of the reaction, probably due to the inhibited background reaction and catalyst aggregation.



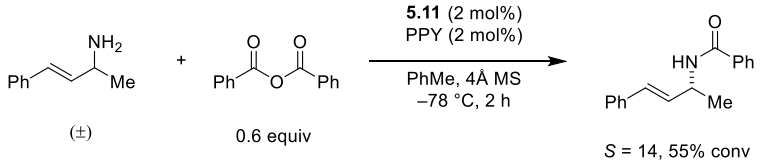
Scheme 5.11. Kinetic resolution of benzylic amines.

The strategy was then extended to the kinetic resolution of propargylic amines[34] (Scheme 5.12). After systematic modifications of the catalyst structure, our group discovered the amide-thiurea catalyst **5.11** displayed a substantial improvement in selectivity comparing with bisthiourea catalyst **5.10**. Remarkably, reducing the catalyst loading of both **5.11** and DMAP to 5 mol% loading led to the even better selectivity.



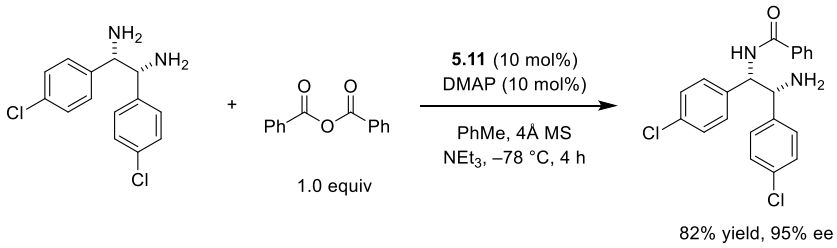
Scheme 5.12. Kinetic resolution of propargylic amines

The dual catalysis approach can be also applied to the kinetic resolution of allylic amines[35] (Scheme 5.13). Comparing with DMAP, the more nucleophilic 4-(pyrrolidino)pyridine (PPY) gave an improved selectivity factor in combination with the same anion binding catalyst **5.11**, and the catalyst loading could be as low as 2 mol % of each. This report represents the first nonenzymatic kinetic resolution of allylic amines.



Scheme 5.13. Kinetic resolution of allylic amines

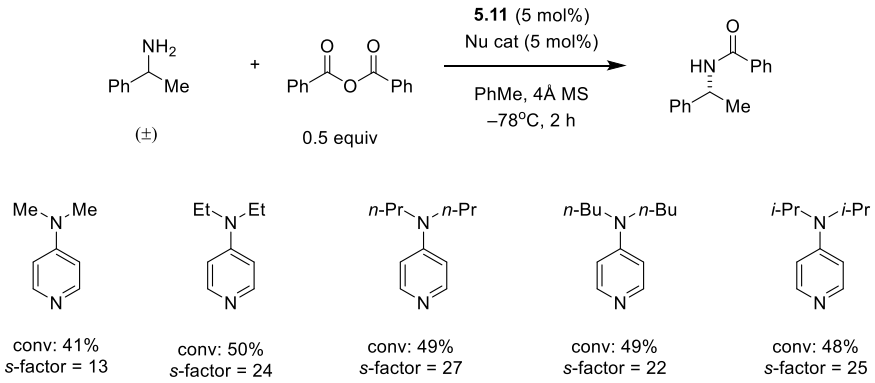
Taking the advantage of the dual catalysis system, our group developed the first desymmetrization of meso-diamines[36] via enantioselective monobenzoylation (Scheme 5.14). Under the optimized conditions, the dibenzylated products were not observed, possibly due to their poor solubility in common organic solvents.



Scheme 5.14. Catalytic enantioselective desymmetrization of meso-diamines.

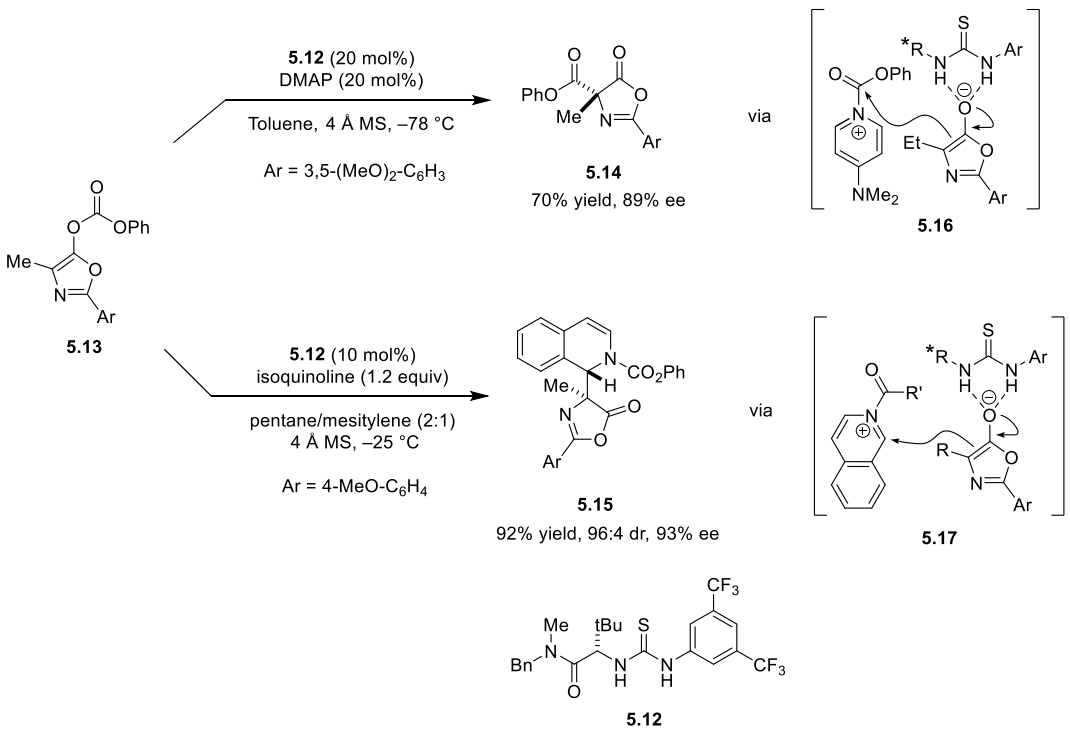
Our group has also inspected the effects of achiral nucleophilic co-catalysts on the selectivity[37] (Scheme 5.15). Under standard conditions, a notable increase in selectivity was observed when replacing DMAP with 4-(*N*,*N*-diethylamino)pyridine. Remarkably, 4-(*N*,*N*-dipropylamino)pyridine was found to be the best cocatalyst, leading to a further boost in the *s*-factor, probably as a result of

the formation of a more a more soluble ion pair that delivered an enhanced efficiency in the kinetic resolution process.



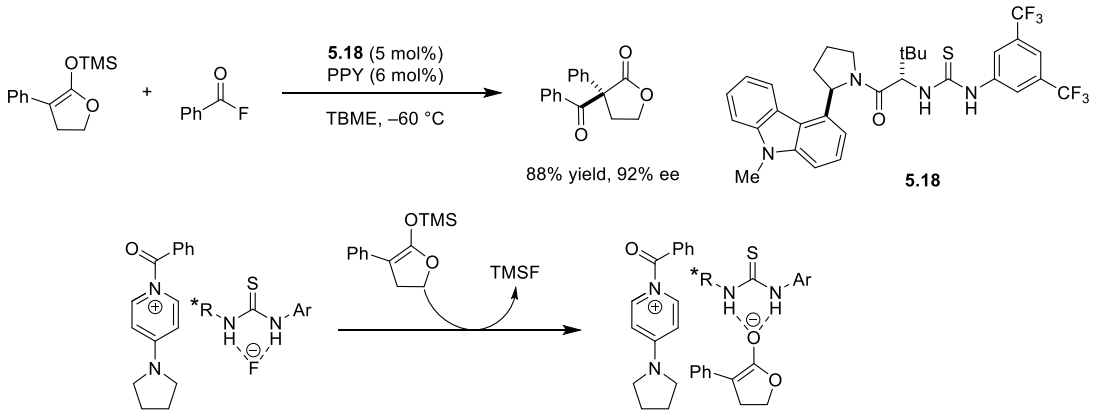
Scheme 5.15. Evaluation of various nucleophilic co-catalysts

The same concept was then successfully applied to the asymmetric Steglich reaction (Scheme 5.16)[38]. When DMAP was employed as the cocatalyst, the azlactone **5.13** was rearranged to the corresponding oxazolone **5.14** as the precursor of useful amino acid derivatives. This rearrangement went through the potential intermediate **5.16** wherein the enolate attacked the carbonyl of the acyl iminium ion. When replacing DMAP with isoquinoline as the nucleophilic catalyst, the acylisoquinolinium ion could be preferentially attacked by the enolate at the 1-position, which gave rise to **5.15** as the highly functionalized α, β-diamino acid derivative.



Scheme 5.16. Asymmetric Steglich rearrangement and addition of *O*-acylatedazlactones to isoquinolines

Jacobsen and co-workers used a similar system to attain a highly enantioselective acylation of silyl ketene acetals[39]. In their case, acid fluoride was found to be the best acylating agent, and it represented the first example of anion-binding catalyst associating with fluoride (Scheme 5.17). The lactone products containing a quaternary stereogenic center were obtained in good to excellent yields and enantioselectivities. The cation-π interaction between the carbazole moiety in **5.18** and the acylpyridinium ion was vital for the high selectivity. Activation of the silyl ketene acetal by fluoride was necessary for the reaction to occur, given that the use of benzoyl chloride completely shut down the reaction.



Scheme 5.17. Enantioselective acylation of silyl ketene acetals

5.2 Aim and significance

Chiral vicinal diamines are ubiquitous components of various natural products and drug candidates[40-42]. Moreover, they are widely used as essential building blocks for ligands or catalysts (Figure 5.2).

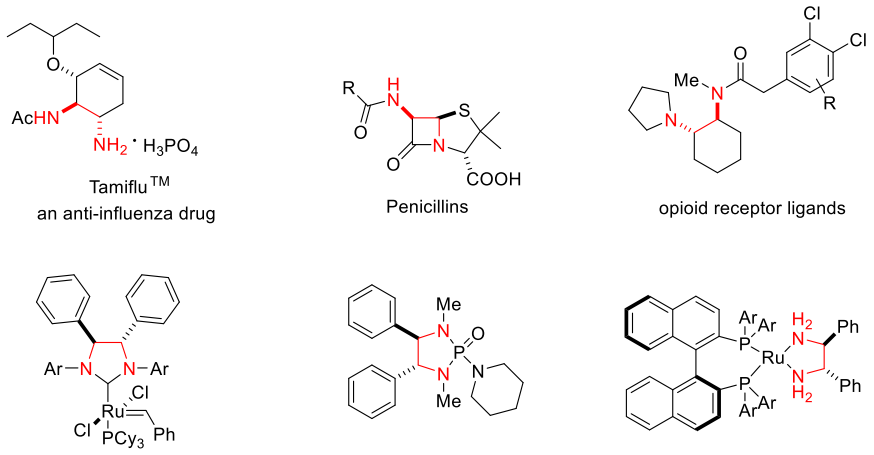
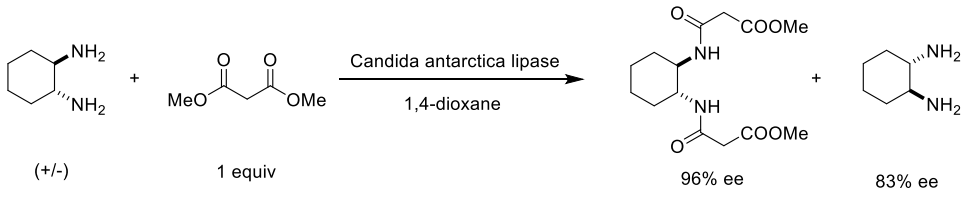


Figure 5.2. Vicinal diamines as drugs and catalysts

Consequently, the development of diastereoselective[43-45] and enantioselective[46-56] methods for the synthesis of these versatile building blocks has remained a topic of considerable interest. Despite recent advances, the most commonly used C_2-symmetrical 1,2-diamines are often prepared by means of classical resolution, requiring stoichiometric amounts of chiral resolving agents[57,58]. Highly

desirable small-molecule catalyzed kinetic resolutions of racemic 1,2-diamines have remained elusive. Even in the realm of enzymatic catalysis, kinetic resolutions of racemic diamines have been limited to relatively few examples such as trans-cyclohexane-1,2-diamine and trans-cyclopentane-1,2-diamine[59,60] (Scheme 5.18). As an added challenge for the kinetic resolution of racemic diamines, the tendency for diacylation could result in two competing kinetic resolution processes, that of the diamine and that of the mono-acylated diamine. While this scenario could potentially be advantageous, we focused on developing conditions that favor diamine mono-acylation.



Scheme 5.18. Enantioselective acylation of silyl ketene acetals

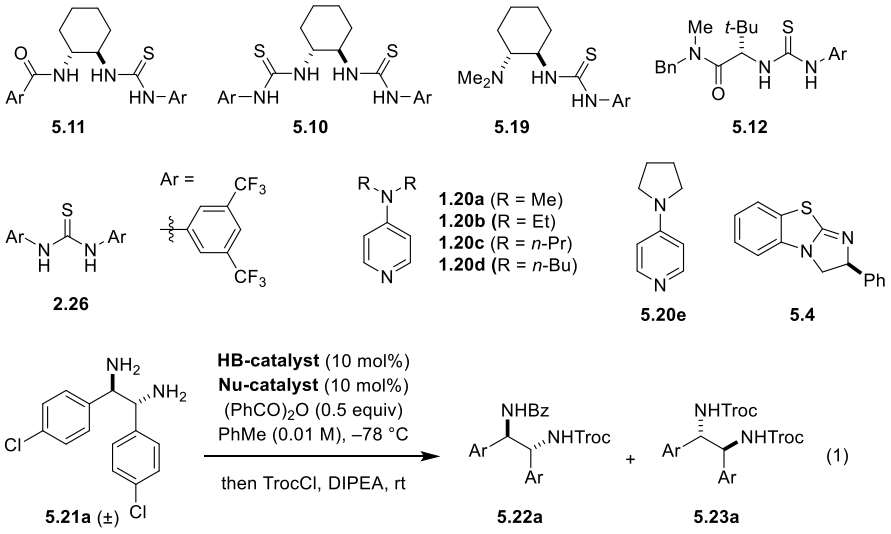
5.3 Optimization of the reaction conditions

We initiated our efforts to develop the kinetic resolution of 1,2-diamines with model substrate **5.21a**, using conditions optimized previously for the kinetic resolution of monoamines (Table 5.1). Notably, in the absence of any catalyst, 15% conversion of the substrate was observed after one hour, and a 5.6:1 ratio of mono-benzoyl diamine to di-benzoyl diamine was obtained (Table 5.1, entry 1). This level of background reactivity is substantially higher than that of the monoamines studied previously. With DMAP (**5.20a**) as the only catalyst the conversion was 32% (4:1 ratio of mono-benzoyl diamine to di-benzoyl diamine, entry 2). Catalyst **5.11** was found to catalyze the reaction in the absence of **5.21a**, but this led to essentially to no resolution (entry 3). In the presence of both **5.11** and **5.21a**, the reaction proceeded more rapidly and kinetic resolution with an s-factor of 5.5 was observed (entry 4). The addition of triethylamine as an additive led to no improvement, nor did the replacement of 4 Å molecular sieves (MS) for 3 or 5 Å MS (entries 5–7). Chiral catalysts other than **5.11**, used in combination with **5.20a**, provided inferior results (entries 8–10). Exchange of DMAP (**5.20a**) for PPY

(**5.20e**), previously shown to be advantageous in the kinetic resolution of allylic amines, led to a drop in s-factor to 4.9 (entry 11). Gratifyingly, substitution of DMAP (**5.20a**) for other closely related nucleophilic cocatalysts proved to be far more fruitful. Remarkably, 4-diethylaminopyridine (**5.20b**) led to an increase in s-factor to 13 (entry 12). Another substantial increase in selectivity was achieved with 4-di-*n*-propylaminopyridine (**5.20c**) (s-factor = 30, entry 13). Interestingly, the result for 4-di-*n*-butylaminopyridine (**5.20d**) was comparable to that obtained with **5.20b** (s-factor = 16, entry 14). These dramatic improvements in selectivity, while not currently understood, are even more pronounced than what could have been expected based on our previous findings with these modified cocatalysts.

We briefly explored the possibility of using a chiral nucleophilic catalyst. Benztetramisole (**5.4)**, previously introduced by the Birman group, was found to catalyze the reaction in the absence of ant HB-additive. Unfortunately, the reaction was rather sluggish and did not lead to any notable resolution of substrate **5.21a** (entry 16). The combination of **5.4** with the achiral Schreiner thiourea catalyst (**2.26**) resulted in a catalytically more active system, but no improvement was seen with regard to selectivity (entry 17).

Table 5.1. Evaluation of reaction conditions

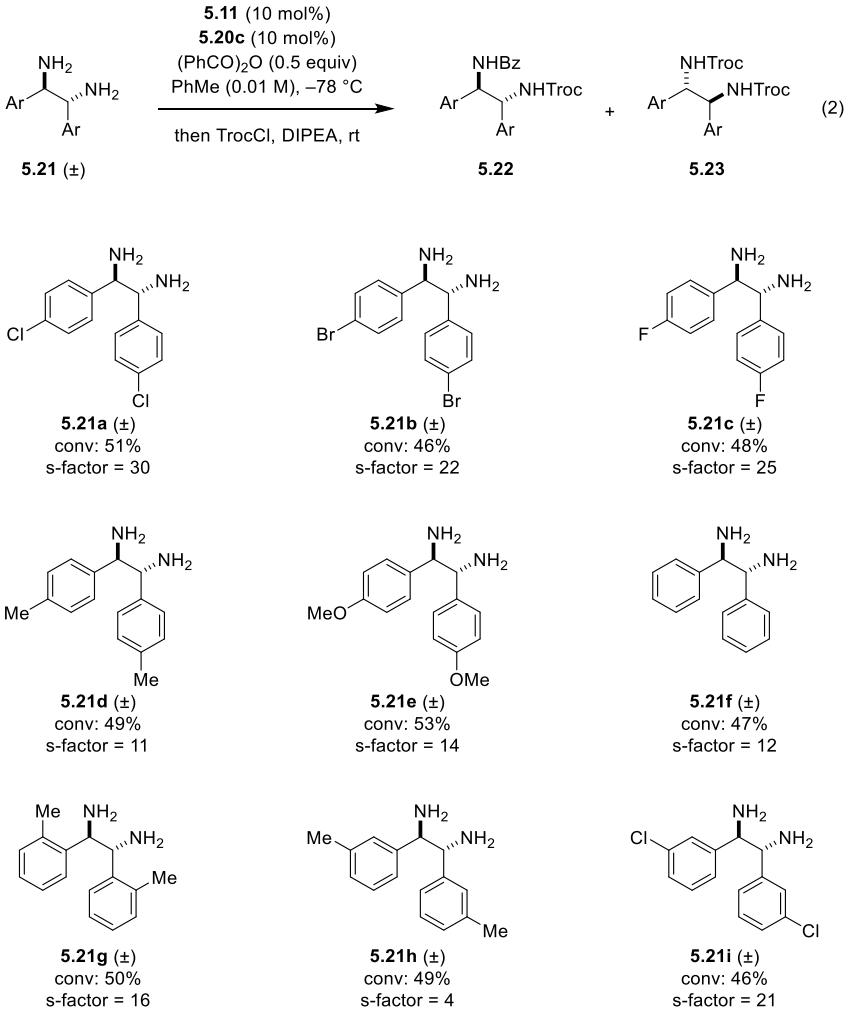


Entry	**HB** cat	**Nu** cat	Time [min]	% yield **5.22a/5.23a**	% ee **5.22a/5.23a**	con-version	S Factor
1	-	-	60	N/A[b]	N/A	15[c]	N/A
2	-	**5.20a**	60	N/A[d]	N/A	32[c]	N/A
3	**5.11**	-	30	20/66	<5/<5	ND	~1
4	**5.11**	**5.20a**	30	44/41	56/46	45	5.5
5[e]	**5.11**	**5.20a**	30	41/47	46/27	37	3.5
6[f]	**5.11**	**5.20a**	30	46/45	46/44	49	4.1
7[g]	**5.11**	**5.20a**	30	47/45	47/49	51	4.4
8	**5.10**	**5.20a**	40	46/40	50/43	46	4.5
9	**5.19**	**5.20a**	120	39/49	13/9	41	1.4
10	**5.12**	**5.20a**	120	41/44	rac	ND	1.0
11	**5.11**	**5.20e**	10	42/46	51/48	48	4.9
12	**5.11**	**5.20b**	25	45/42	75/64	46	13
13	**5.11**	**5.20c**	25	44/46	83/86	51	30
14	**5.11**	**5.20d**	25	44/45	75/78	51	16
15[h]	**5.11**	**5.20c**	50	46/42	81/74	48	21
16	-	**5.4**	180	24/64	–4/–6	ND	~1
17	**2.26**	**5.4**	180	44/46	rac	ND	1.0

[a] Reactions were performed on a 0.2 mmol scale in the presence of 4 Å MS. Yields correspond to isolated yields. Conversions and s-factors were calculated based on product ee's [b] a 5.6:1 ratio of mono- to di-amide was obtained. [c] conversion was determined by ^{1}H-NMR. [d] a 4:1 ratio of mono- to di-amide was obtained. [e] with 0.6 equiv of NEt_3 [f] with 3 Å MS instead of 4 Å MS. [g] with 5 Å MS instead of 4 Å MS. [h] with 5 mol% of each **1.11** and **1.20c**

5.4 Substrate scope

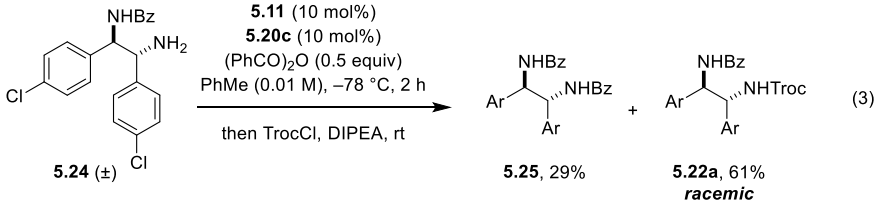
Then, we investigated the scope of the diamine resolution under the optimized conditions (Scheme 5.19). A number of racemic 1,2-diaryl-1,2-diaminoethanes bearing various substituents on the aryl groups were resolved efficiently. Generally, electron-poor diamines gave rise to higher s-factors than more electron-rich substrates, likely a consequence of an increased background reactivity of the latter. Notably, all reactions went to completion within 35 min.



Scheme 5.19. Scope of the diamine resolution.

In order to explore the possibility of a second resolution process, namely the reaction of monobenzoyl-diamine **5.24** with benzoic anhydride, racemic **5.24** was exposed to the previously established resolution conditions (eq 3). As would have been anticipated based on the results shown above, the second benzoylation was found to be substantially slower than the first one. After a reaction time of two hours, 29% conversion of **5.24** to the dibenzoyl product **5.25** had occurred as judged by ^{1}H-NMR analysis of the crude reaction mixture. Unreacted starting material **5.24** was converted to the Troc-protected product **5.22a** which was obtained in racemic fashion. Thus, no

second resolution was observed and it can be concluded that the formation of minor amounts of dibenzoyl products has no effect on the product selectivities.



5.5 Summary

In summary, we have reported the first example of a small-molecule catalyzed kinetic resolution of diamines. A number of 1,2-diaryl-1,2-diaminoethanes were efficiently resolved by monobenzoylation, using a catalytic amount of a chiral amide-thiourea anion-receptor in combination with an achiral nucleophilic cocatalyst.

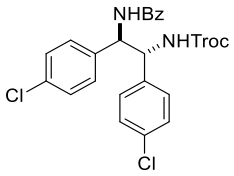
Experimental Section

General Procedure for the Resolution and Protection of Racemic Diamines:

A flame dried round bottom flask was charged with benzoic anhydride (22.6 mg, 0.1 mmol, 0.5 equiv.) and powdered 4Å MS (100 mg). Freshly distilled toluene (10 mL) and N,N-dipropylpyridine-4-amine (3.6 mg, 0.02 mmol, 0.1 equiv.) in 1 mL of toluene was added. The resulting mixture was cooled to –78 °C over 15 min and a solution of catalyst 1 (12.5 mg, 0.02 mmol, 0.1 equiv.) in 6 mL of toluene was added. After 15 min, a solution of diamine (0.2 mmol) in 3 mL of toluene was added slowly along the inner side of the flask and the reaction mixture was stirred at –78 °C. When benzoic anhydride could no longer be detected by TLC analysis, an ethanolic ammonia solution (2 M, 2 mL) was added. The reaction mixture was allowed to warm to rt, diluted with 10 mL of a 1:1 water/brine mixture and extracted with EtOAc (5 x 30 mL). After drying with anhydrous sodium sulfate, the organic layer was concentrated under reduced pressure and dissolved in 10 mL of CH_2Cl_2. The solution was cooled to 0 °C and Hünig's base and Troc-Cl were added slowly. After completion of the reaction, the resulting mixture was concentrated under reduced pressure and purified by flash chromatography.

Characterization Data of Products

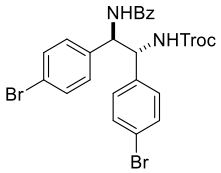
2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-chlorophenyl)ethyl)carbamate (5.22a):



Following the general procedure, compound **5.22a** was obtained as a white solid in 44% yield (49 mg); mp = 222–224 °C; R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ -29.2 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3334, 3053, 2947, 2364, 1713, 1640, 1529, 1492, 1277, 1148, 1094, 1015, 820, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.75 (d, *J* = 7.72 Hz, 2H), 7.65 – 7.32 (comp, 6H), 7.31 – 7.25 (m, 1H), 7.22 (d, *J* = 7.45 Hz, 1H), 7.06 (appt, *J* = 7.1 Hz, 3H), 6.20 (d, *J* = 8.0 Hz, 1H), 5.45 (appt, *J* = 9.2 Hz, 1H), 5.16 – 4.93 (m, 1H), 4.74 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.5, 137.2, 136.8, 133.3, 132.1, 132.0, 129.1, 129.0, 128.7, 127.1, 122.4, 122.2, 95.1, 74.6, 60.5, 59.1; m/z(ESI-MS)

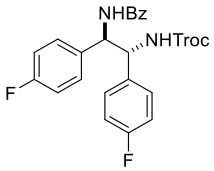
561.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (major) and t_R = 8.4 min (minor). Calculated conversion = 51; **s = 30**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-bromophenyl)ethyl)carbamate (5.22b):



Following the general procedure, compound **5.22b** was obtained as a white solid in 41% yield (53 mg); mp = 218–219 °C; R_f = 0.20 (Hexanes/EtOAc 6:1 v/v) $[\alpha]^D_{20}$ -27.8 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3334, 3055, 2950, 2362, 1715, 1642, 1531, 1492, 1280, 1148, 1097, 1015, 822, 728 cm^{-1}; ^1H NMR (500 MHz, d^6-DMSO) 8.82 (d, *J* = 9.26 Hz, 1H), 8.59 (d, *J* = 9.26 Hz, 1H), 7.91 – 7.71 (m, 2H), 7.66 – 7.52 (m, 4H), 7.50 – 7.38 (m, 4H), 7.37 – 7.11 (comp, 3H), 5.75 – 5.53 (m, 1H), 5.40 – 5.22 (m, 1H), 4.79 (d, *J* = 12.3 Hz, 1H), 4.65 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, d^6-DMSO) δ 166.9, 155.0, 140.0, 139.9, 134.9, 132.5, 132.4, 132.3, 129.7, 129.2, 128.9, 128.8, 96.9, 74.2, 59.2, 57.2; m/z (ESI-MS) 650.4 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.4 min (major) and t_R = 5.8 min (minor). Calculated conversion = 46; **s = 22**.

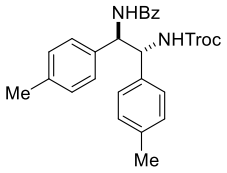
2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-fluorophenyl)ethyl)carbamate (5.22c):



Following the general procedure, compound **5.22c** was obtained as a white solid in 40% yield (42 mg); mp = 211–213 °C; R_f = 0.19 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ -31.3 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3332, 3056, 2366, 1715, 1640, 1532, 1490, 1148, 1097, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.93 – 7.68 (comp, 2H), 7.64 – 7.36 (comp, 3H), 7.25 – 7.07 (comp, 4H), 7.06 – 6.73 (comp, 4H), 6.28 (d, *J* = 8.3 Hz, 1H), 5.61 – 5.42 (m, 1H), 5.19 – 5.00 (m, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.5, 134.3, 133.8, 133.4, 131.9, 129.1, 128.6, 127.0, 115.8 (d, *J* = 21.0 Hz), 115.7 (d. *J* = 21.0 Hz), 95.1, 74.5, 60.6, 59.2; m/z (ESI-MS) 528.3 $[M+H]^+$;

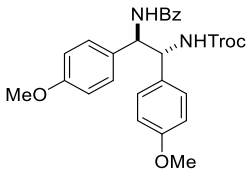
HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (major) and t_R = 8.0 min (minor). Calculated conversion = 48; **s = 25**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-di-*p*-tolylethyl)carbamate (5.22d):



Following the general procedure, compound **5.22d** was obtained as a white solid in 44% yield (45 mg); mp = 229–231 °C; $[\alpha]^D_{20}$ -21.5 (c 0.5, $CHCl_3$, 69% ee); R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); IR (KBr) 3336, 3060, 1720, 1630, 1542, 1261, 1152, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.76 (d, *J* = 7.5 Hz, 2H), 7.53 – 7.34 (comp, 3H), 7.18 – 6.92 (comp, 8H), 6.09 (d, *J* = 8.4 Hz, 1H), 5.51(app t, *J* = 9.2 Hz, 1H), 5.08 (app t, *J* = 9.4 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 2.26 (app d, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.6, 155.4, 137.8, 137.6, 135.5, 135.1, 133.8, 131.7, 129.3(5), 129.3, 128.5, 127.4, 127.3, 117.6, 95.2, 74.5, 60.8, 59.2, 21.0(8), 21.0(7); m/z (ESI-MS) 520.5 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 210 nm, t_R = 6.8 min (major) and t_R = 5.1 min (minor). Calculated conversion = 49; **s = 11**.

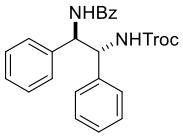
2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-methoxyphenyl)ethyl)carbamate (5.22e):



Following the general procedure, compound **5.22e** was obtained as a white solid in 45% yield (49 mg); mp = 210–213 °C; R_f = 0.10 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ -15.5 (c 0.5, $CHCl_3$, 70% ee); IR (KBr) 3330, 2950, 2831, 1718, 1637, 1515, 1250, 1176, 1028, 827, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.95 – 7.65(comp, 2H), 7.61 – 7.32 (comp, 3H), 7.25 – 7.00 (comp, 4H), 6.91 – 6.61 (comp, 4H), 6.30 – 6.11 (m, 1H), 5.61 – 5.41 (m, 1H), 5.15 – 5.00 (m, 1H), 4.71 (d, *J* = 12,0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 3.74 (app d, *J* = 6.9 Hz, 6H); m/z (ESI-MS) 552.6 $[M+H]^+$; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 159.1, 158.9, 155.3, 133.8, 131.7, 130.8, 130.3, 128.6, 128.5, 128.4, 127.0, 95.2, 74.4, 60.6, 59.0, 55.1;

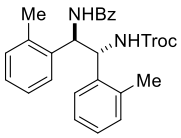
HPLC: Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 93/7, Flow rate = 1 mL/min, UV = 230 nm, t_R = 20.3 min (major) and t_R = 16.3 min (minor). Calculated conversion = 53; **s = 14**.

2,2,2-Trichloroethyl ((1*R*,2*R*)-2-benzamido-1,2-diphenylethyl)carbamate (5.22f):



Following the general procedure, compound **5.22f** was obtained as a white solid in 40% yield (39 mg); mp = 187–190 °C; R_f = 0.19 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ -24.0 (c 0.5, $CHCl_3$, 72% ee); IR (KBr) 3333. 3053, 2925, 1717, 1653, 1637, 1528, 1144, 1082, 1027, 821, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.78 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.39 (comp, 2H), 7.29 – 7.13 (comp, 10H), 6.15 (d, *J* = 8.2 Hz, 1H), 5.58 – 5.49 (m, 1H), 5.18 – 5.06 (m, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.5, 138.5, 138.0, 133.8, 131.8, 129.5, 128.73, 128.7, 128.6, 128.2, 128.0, 127.5, 127.4, 127.1, 125.2, 95.2, 74.5, 61.3, 59.8; m/z (ESI-MS) 493.2 $[M+H]^+$; Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.0 min (major) and t_R = 8.8 min (minor). Calculated conversion = 47; **s = 12**.

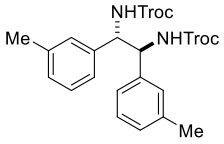
2,2,2-Trichloroethyl ((1*R*,2*R*)-2-benzamido-1,2-di-*o*-tolylethyl)carbamate (5.22g):



Following the general procedure, compound **5.22g** was obtained as a white solid in 41% yield (43 mg); mp = 220–222 °C; R_f = 0.24 (Hexanes/EtOAc 6:1 v/v) ; $[\alpha]^{D}_{20}$ -21.0 (c 0.5, $CHCl_3$, 76% ee); IR (KBr) 3328, 3061, 1713, 1636, 1541, 1257, 1152, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.79 (d, *J* = 7.7 Hz, 2H), 7.61 – 7.47 (comp, 3H), 7.46 – 7.39 (comp, 2H), 7.27 – 7.17 (comp, 2H), 7.15 – 7.07 (comp, 3H), 7.03 – 6.93 (comp, 2H), 6.02 – 5.89 (comp, 2H), 5.52 – 5.45 (m, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 155.7, 136.8, 136.2, 136.6, 136.1, 133.8, 131.8, 130.7, 130.6, 128.6, 128.1, 127.9, 127.1, 126.6, 126.5, 126.4, 126.3, 95.1, 74.5, 56.8, 55.2, 19.3,

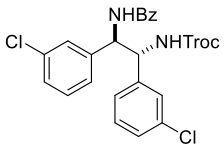
19.2(7); m/z (ESI-MS) 520.7 $[M+H]^+$; Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.8 min (major) and t_R = 7.1 min (minor). Calculated conversion = 50; **s = 16**.

Bis(2,2,2-trichloroethyl) ((1*R*,2*R*)-1,2-di-*m*-tolylethane-1,2-diyl)dicarbamate (5.22h):



Following the general procedure, compound **5.22h** was obtained as a white solid in 40% yield (41 mg); mp = 199–201 °C; IR (KBr) 3337, 3056, 2947, 1718, 1653, 1527, 1254, 711, 568 cm^{-1}; R_f = 0.24 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ -14.2 (c 0.5, $CHCl_3$, 45% ee); ^1H NMR (500 MHz, d^6-DMSO) 8.75 (d, *J* = 9.3 Hz, 1H), 8.53 (d, *J* = 9.6 Hz, 1H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.55 – 7.41 (m, 3H), 7.27 – 7.11 (m, 6H), 6.98 (d, *J* = 7.2 Hz, 2H), 5.55 (s, 1H), 5.21 (d, *J* = 5.7, 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H), 2.23 (d, *J* = 11.2 Hz, 6H); ^{13}C NMR (125 MHz, d^6-DMSO) δ 166.1, 154.2, 140.4, 140.3, 137.0 136.9, 134.4, 131.3, 128.3, 127.9, 127.7, 127.6, 127.5, 127.3, 124.2, 123.9, 96.2, 73.3, 59.2, 57.1, 21.1, 21.1(4); m/z (ESI-MS) 520.8 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.6 min (major) and t_R = 5.7 min (minor). Calculated conversion = 49; **s = 4.0**.

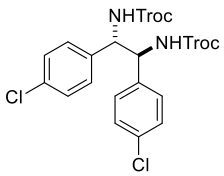
2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(3-chlorophenyl)ethyl)carbamate (**5.22i**):



Following the general procedure, compound **5.22i** was obtained as a white solid in 39% yield (43 mg); mp = 203–205 °C; R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ -27.7 (c 0.5, $CHCl_3$, 82% ee); IR (KBr) 3336, 3061, 2949, 1714, 1636, 1528, 1252, 1084, 702 cm^{-1}; ^1H NMR (400 MHz, d^6-DMSO) 8.47 (s, 1H), 7.64 (d, *J* = 7.2, 2H), 7.58 – 7.34 (comp, 10H) 7.37 – 7.26(m, 1H), 6.82 (s, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.68 (d, *J* = 6.3 Hz, 1H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 166.1, 154.1, 142.5, 142.4(8), 134.0, 132.8,

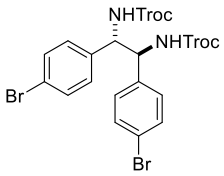
132.7(6), 131.5, 129.9, 128.3, 127.1, 127.0(9), 127.0, 126.9(0), 126.8, 125.8, 125.5, 96.0, 73.4, 58.4, 56.3; m/z (ESI-MS) 561.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.2 min (major) and t_R = 7.6 min (minor). Calculated conversion = 46; **s = 21.**

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-chlorophenyl)ethane-1,2-diyl)dicarbamate (**5.23a**):



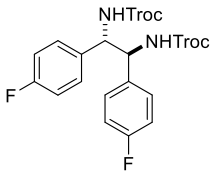
Following the general procedure, compound **5.23a** was obtained as a white solid in 46% yield (58.0 mg); mp = 205–207 °C; R_f = 0.48 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +36.7 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3330, 2952, 1710, 1537, 1278, 1144, 1093, 820, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.22 (d, *J* = 8.3 Hz, 4H), 7.03 (d, *J* = 8.3 Hz, 4H), 5.93 (s, 2H), 4.97 (dd, *J* = 5.6, 2.4 Hz, 2H), 4.82 (d, *J* = 12.2 Hz, 2H), 4.63 (d, *J* = 12.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 136.1, 134.3, 129.1 128.6, 95.2, 74.7, 60.4; m/z (ESI-MS) 633.4$[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 20.6 min (major) and t_R = 27.5 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-bromophenyl)ethane-1,2-diyl)dicarbamate (5.23b):



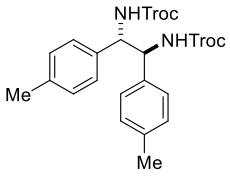
Following the general procedure, compound **5.23b** was obtained as a white solid in 42% yield (60 mg); mp = 208–210 °C; R_f = 0.45 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +19.3 (c 0.5, $CHCl_3$, 70% ee); IR(KBr) 3330, 3058, 2954, 1716, 1529, 1489, 1248, 1148, 1075, 1011, 818, 725, 568 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37 (d, *J* = 8.2 Hz, 4H), 7.05 – 6.93 (comp, 4H), 5.95 (s, 2H), 5.10 – 4.93 (m, 2H), 4.81 (d, *J* = 12.1 Hz, 2H), 4.64 (d, *J* = 12.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 136.6, 132.0, 128.9, 126.4, 122.5, 95.2, 74.7, 60.3; m/z (ESI-MS) 721.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 5.4 min (major) and t_R = 6.4 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-fluorophenyl)ethane-1,2-diyl)dicarbamate (5.23c):



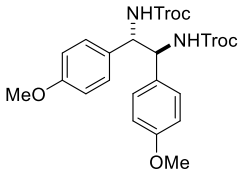
Following the general procedure, compound **5.23c** was obtained as a white solid in 45% yield (54 mg); mp = 202–203 °C; R_f = 0.41 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +29.4 (c 0.5, $CHCl_3$, 78% ee); IR(KBr) 3331, 3055, 2952, 1714, 1530, 1490, 1248, 1148, 820, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.00 (comp, 4H), 6.98 – 6.78 (comp, 4H), 6.03 (s, 2H), 5.14 – 4.94 (m, 2H), 4.82 (d, *J* = 11.9 Hz, 2H), 4.63 (d, *J* = 11.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 161.3, 155.0, 133.6, 129.0, 128.9, 115.13(d, *J* = 21.8 Hz), 95.2, 74.7, 60.5; m/z (ESI-MS) 600.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.7 min (minor).

Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-di-*p*-tolylethane-1,2-diyl)dicarbamate (5.23d):



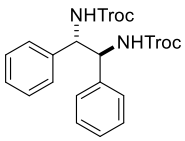
Following the general procedure, compound **5.23d** was obtained as a white solid in 44% yield (51 mg); mp = 165–168 °C; R_f = 0.44 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +17.3 (c 0.5, $CHCl_3$, 67% ee); IR (KBr) 3318, 3061, 1706, 1636, 1541, 1257, 1152, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 – 6.78 (comp, 8H), 5.93 (s, 2H), 5.13 – 4.92 (m, 2H), 4.80 (d, *J* = 11.7 Hz, 2H), 4.62 (d, *J* = 11.7 Hz, 2H), 2.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.8, 134.9, 129.3, 127.2, 95.4, 74.6, 60.5, 21.1; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.9 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-methoxyphenyl)ethane-1,2-diyl)dicarbamate (5.23e):



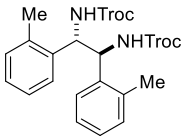
Following the general procedure, compound **5.23e** was obtained as a white solid in 44% yield (55mg); mp = 170–172 °C; R_f = 0.20 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +22.4 (c 0.5, $CHCl_3$, 80% ee); IR (KBr) 3331, 2953, 2836, 1701, 1614, 1516, 1250, 1180, 1031, 831, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.5 Hz, 4H), 6.74 (d, *J* = 8.5 Hz, 4H), 5.89 (s, 2H), 5.06 – 4.91 (m, 2H), 4.81 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 3.74 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 154.9, 130.0, 128.5, 114.0, 95.4, 74.6, 60.4, 55.2; m/z (ESI-MS) 623.8 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.5 min (major) and t_R = 9.9 min (minor).

Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)dicarbamate(5.23f):



Following the general procedure, compound **5.23f** was obtained as a white solid in 42% yield (47 mg); mp = 147–150 °C; R_f = 0.41 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +24.9 (c 0.5, $CHCl_3$, 65% ee); IR (KBr) 3329, 3061, 2955, 1705, 1541, 1254, 1148, 1082, 1027, 820, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.38 – 7.18 (comp, 6H), 7.17 – 6.98 (comp, 4H), 5.97 (s, 2H), 5.20 – 4.98 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.8, 128.7, 128.2, 127.3, 95.3, 74.7, 61.1; m/z (ESI-MS) 564.1 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.1 min (major) and t_R = 7.4 min (minor).

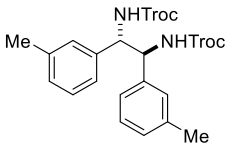
Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-di-*o*-tolylethane-1,2-diyl)dicarbamate (5.23g):



Following the general procedure, compound **5.23g** was obtained as a white solid in 44% yield (52 mg); mp = 177–178 °C; $[\alpha]^{D}_{20}$ +23.1 (c 0.5, $CHCl_3$, 75% ee); R_f = 0.47 (Hexanes/EtOAc 6:1 v/v); IR (KBr) 3320, 3055, 2950, 1707, 1650, 1527, 1255, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.44 (d, *J* = 7.7 Hz, 2H), 7.20 (app t, *J* = 7.4 Hz, 2H),

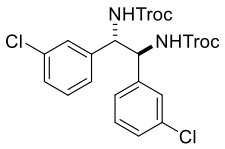
7.11 (app t, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 2H), 5.92 (s, 2H), 5.40 (dd, *J* = 5.9, 2.3 Hz, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 2.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.7, 136.2, 130.7, 128.1, 126.4, 126.3(7), 95.3, 74.7, 56.5, 19.2; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.2 min (major) and t_R = 9.0 min (minor).

Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-di-*m*-tolylethane-1,2-diyl)dicarbamate (5.23h):



Following the general procedure, compound **5.23h** was obtained as a white solid in 41% yield (48 mg); mp = 190–192 °C; R_f = 0.46 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +12.4 (c 0.5, $CHCl_3$, 44% ee) ; IR (KBr) 3318, 3055, 2950, 1707, 1650, 1527, 1255, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.15 – 6.99 (comp, 4H), 6.96 – 6.77 (comp, 4H), 5.88 (s, 2H), 5.05 – 4.94 (m, 2H), 4.82 (d, *J* = 12.2 Hz, 2H), 4.60 (d, *J* = 12.2 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 138.4, 137.7, 128.9, 128.5, 128.0, 124.5, 95.4, 74.6, 60.8, 21.3; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.0 min (major) and t_R = 16.3 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(3-chlorophenyl)ethane-1,2-diyl)dicarbamate (5.23i):



Following the general procedure, compound **5.23i** was obtained as a white solid in 43% yield (54 mg); mp = 199–202 °C; R_f = 0.48 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +25.5 (c 0.5, $CHCl_3$, 70% ee); IR (KBr) 3331, 2952, 1709, 1537, 1277, 1144, 1092, 821 cm^{-1}; ^{1}H NMR (500 MHz, d^6-DMSO) 8.30 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 2H), 7.40 – 7.24 (comp, 6H), 5.20 (app d, *J* = 8.1 Hz, 2H), 4.77 – 4.65 (comp, 4H); ^{13}C NMR (125 MHz, d^6-DMSO) δ 154.1, 142.2, 132.9, 130.1, 127.2, 126.7, 125.5, 96.0, 73.4, 58.3; m/z (ESI-MS) 633.4

$[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.8 min (major) and t_R = 8.0 min (minor).

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