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Entwicklung von Cyclopentadienyl-Liganden zur asymmetrischen C–H Aktivierung und Synthese von Naturstoff-inspirierten Substanzbibliotheken

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Stay hungry, stay foolish.

——— *quoted by Steve Jobs*

Dedicated to my parents and a girl during my PhD study

Declaration/Erklärung

Die vorliegende Arbeit wurde in der Zeit von August 2012 bis Mai 2016 am Max-Plank-Institut für Molekulare Physiologie Dortmund unter der Anleitung von Prof. Dr. Dr. h.c. Herbert Waldmann durchgeführt.

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbstständing und nur mit den angegebenen Hilfsmitteln angefertigt habe.

The work described in this Dissertation was performed from August 2012 to May 2016 at the Max Plank Institute of Molecular Physiology Dortmund under the guidance of Prof. Dr. Dr. h.c. Herbert Waldmann.

I hereby declare that I performed the work independently and did not use any other but the indicated aids.

Dortmund 2016

Zhi-Jun Jia

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Abstract

In biology-oriented synthesis (BIOS), the areas in chemical space represented by bioactive natural products (NPs) serve as the starting points for the synthesis of compound collections, which can be defined by privileged scaffolds and diverse substitutions. To explore chemical space inspired by but beyond NPs, the rapid synthesis of compound collections based on privileged scaffolds is crucial. Given the prevalence of stereocenters in NPs, the development of corresponding enantioselective methodologies is highly valuable.

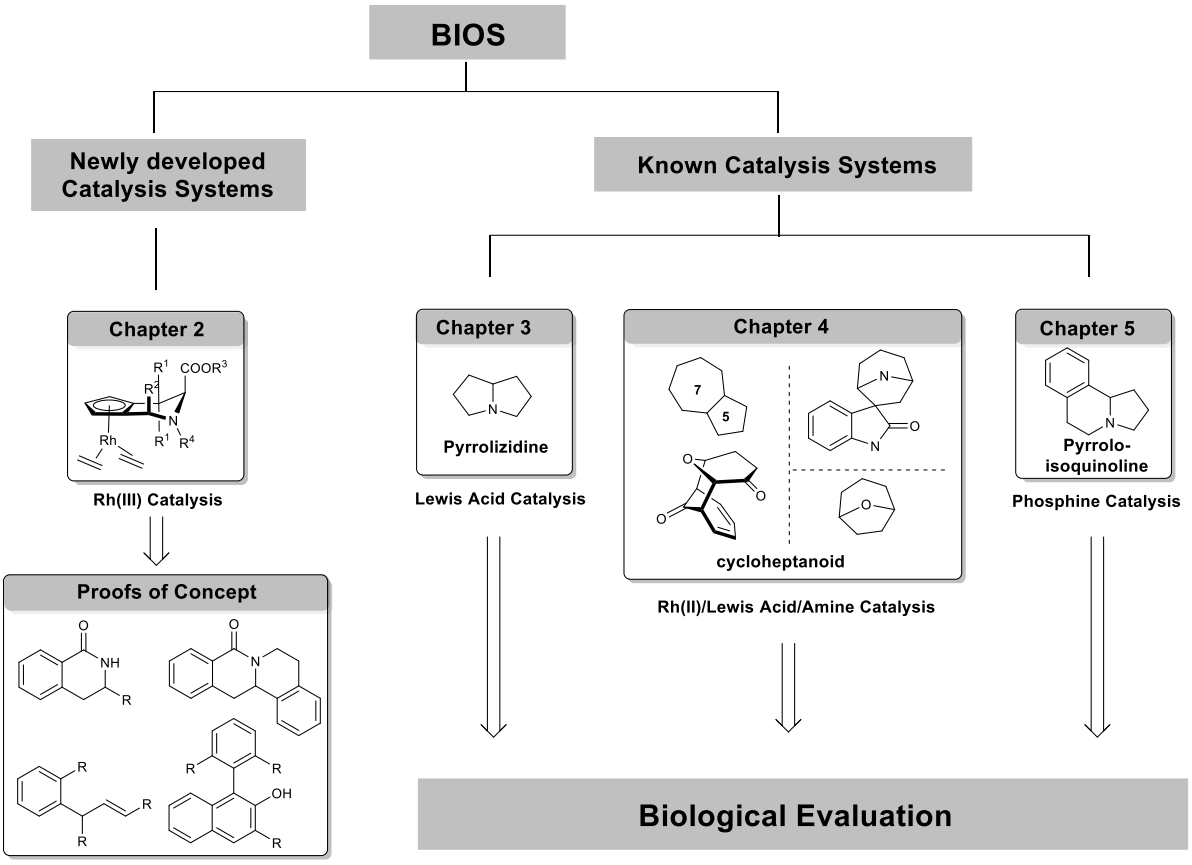


Figure 1. Overview of projects described in this thesis.

To accomplish this goal, Chapter 2 in this thesis demonstrates the development of new chiral cyclopentadienyl ligands and catalysts for enantioselective C−H activation to evolve chemistry tools for the synthesis of privileged scaffolds enriched in NPs (Fig. 1). Enantioselective activation of C–H bonds is among the most important and efficient transformations in organic synthesis, but remains considerably undeveloped due to the inert nature of C−H bonds and the lack of efficient catalysis systems. Although metal catalysis facilitated by chiral cyclopentadienyl (Cp) ligands has emerged as a highly efficient and attractive approach, the

limitations of present Cp ligands on either applicability or structural variability significantly hampered their comprehensive application. To exploit such an approach to serve for BIOS, the second chapter describes the development of a highly tunable library of chiral cyclopentadienyl (Cp) ligands and its Rh(I) complexes as precursors of Rh(III) catalysts. As proofs of concept, three different C−H activation transformations have been realized in highly enantioselective manner, including one unprecedented transformation affording axially chiral compounds.

Besides evolving chemistry tools for enantioselective C–H activation, the other major aspect of this thesis depicts the flexible application of current well-established catalysis systems for the synthesis of compound collections based on privileged scaffolds enriched in NPs (Fig. 1). The catalysis systems involved in this thesis consist of chiral Lewis acids catalysis and Rh(II) catalysis, as well as nucleophilic catalysis by using chiral amine and phosphine catalysts. Facilitated by chiral Lewis acid catalysis, Chapter 3 describes the synthesis of pyrrolizidines in highly enantioselective fashion by using 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylides as a key step. In Chapter 4, to establish efficient methods to access seven-membered carbocycles (cycloheptanoids) in an enantioselective manner, three catalysis systems are exploited involving Rh(II) catalysis, Rh(II)/Lewis aicid catalysis and amine catalysis. In this part, either chiral dirhodium(II) catalysts or chiral Lewis acids are employed to steer the enantioselective 1,3-DC of highly reactive carbonyl ylides or azomethine ylide generated from diazoketones. As alternatives for the synthesis of enantioriched cycloheptanoids, (5+2) cycloadditions of pyryliums and a stepwise strategy by using amine catalysis are also depicted. Furthermore, Chapter 5 describes the synthesis of highly functionalized pyrroloisoquinolines by means of phosphine-catalyzed dearomatizing (3+2) annulations of isoquinolinium methylides. Notably, most of the compounds shown in these three chapters were subjected to different cell-based assays, among which activities in the low micromolar range were discovered such as inhibition of Hedgehog signaling pathway.

Zusammenfassung

In der Biologie-orientierten Synthese (BIOS) wird der durch bioaktive Verbindungen, insbesondere Naturstoffe (engl. *natural products*; NPs), repräsentierte Strukturraum als Ausgangspunkt für die Synthese von Substanzbibliotheken genutzt. Die Bibliotheken basieren auf vielfältig substituierten privilegierten Gerüsten. Mit dem Ziel den von NPs inspirierten chemischen Raum sowohl zu nutzen, als auch zu erweitern, ist die effiziente Synthese von Substanzbibliotheken ausgehend von privilegierten Gerüstmolekülen von entscheidender Bedeutung.

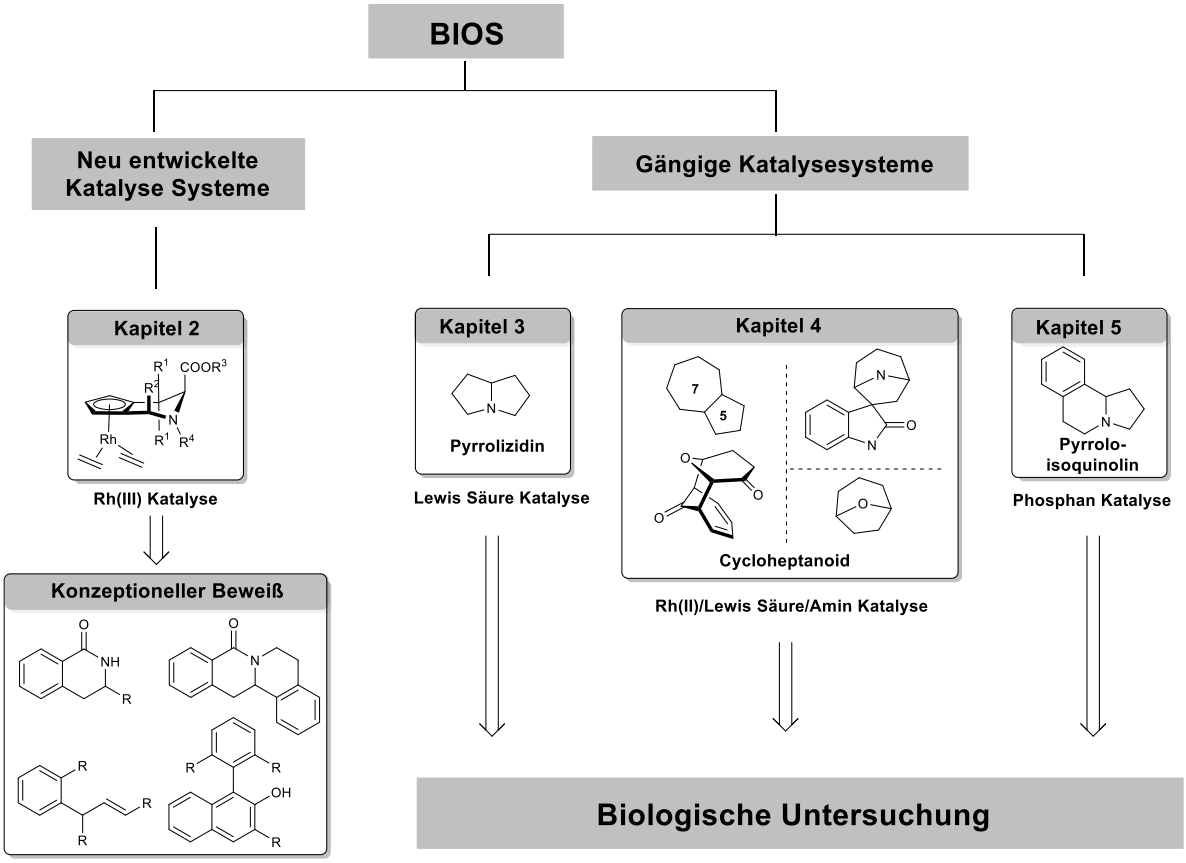


Abbildung 1. Übersicht der in dieser Arbeit beschriebenen Projekte.

Um dieses Ziel zu erreichen wurde in Kapitel 2 dieser Arbeit die Entwicklung neuer chiraler Cyclopentadienylliganden für die katalytische, enantioselektive C–H Aktivierung als Weiterentwicklung bekannter chemischer Werkzeuge für die Synthese privilegierter Grundgerüste, die mit großer Häufigkeit in NPs zu finden sind, demonstriert (Abbildung 1). Die enantioselektive Funktionalisierung von C–H Bindungen ist eine der bedeutendsten und effizientesten Transformationen in der organischen Synthese, welche jedoch bedingt durch die

inerte Natur von C–H Bindungen und die bislang noch langsame Entwicklung effizienter Katalysesysteme bisher unterentwickelt blieb. Auch wenn sich die Metalkatalyse, vermittelt durch chirale Cyclopentadienylliganden (Cp), als hoch effizienter und attraktiven Ansatz etabliert hat, sind Cp Liganden in ihrer Variabilität stark limitiert, was eine umfassende Anwendbarkeit einschränkt. Zur Etablierung dieses Ansatzes als Grundlage für BIOS beschreibt das zweite Kapitel die Entwicklung einer Bibliothek von präzise steuerbaren chiralen Cyclopentadienylliganden und deren Rh(I)-Komplexen als Vorläufer für Rh(III)-Katalysatoren. Als konzeptioneller Beweis wurden drei verschiedene C–H Funktionalisierungen mit hoher Enantioselektivität realisiert, einschließlich einer neuen Transformation, welche axial chriale Verbindungen lieferte.

Neben der Weiterentwicklung chemischer Werkzeuge für die enantioselektive C–H Aktivierung lag das Hauptaugenmerk dieser Arbeit auf der flexiblen Anwendung von modernen, bereits etablierten Katalysesystemen zur Darstellung von Substanzbibliotheken basierend auf privilegierten Grundgerüsten (Abbildung 1). Die in dieser Arbeit eingesetzten Katalysesysteme umfassen sowohl chirale Lewis-Säure- und Rh(II)-Katalysatoren, als auch chirale Amin- und Phosphankatalysatoren. Vermittelt durch chirale Lewis-Säure-Katalyse, beschreibt Kapitel 3 die Synthese von Pyrrolizidinen durch 1,3-dipolare Cycloaddition (1,3-DC) mit hoher Enantioselektivität. Kapitel 4 beschreibt die Etablierung einer effizienten Methode, welche den Zugang zu siebengliedrigen Carbocyclen (Cycloheptanoide) in enantioselektiver Weise eröffnet. Anwendung finden drei Katalysesysteme basierend auf Rh(II)-, Rh(II)/Lewis-Säure- und Amin-Katalyse. In diesem Teil wurden entweder chirale Dirhodium(II)-Katalysatoren oder chirale Lewis-Säuren, zur Steuerung der enantioselektiven 1,3-DC von hochreaktiven Carbonylyliden oder Azomethinyliden erzeugt aus Diazoketonen eingesetzt. Als Alternative zur Synthese von enantiomerenangereicherten Cycloheptanoiden, wurden die (5+2) Cycloaddition von Pyrylium und eine sequentielle Strategie, durch den Einsatz von Amin-Katalysatoren untersucht. Zusätzlich beschreibt Kapitel 5 die Synthese von hochfunktionalisierten Pyrroloisochinolinen durch phosphinkatalysierte dearomatisierende (3+2) Annulierung von Isochinolinmethyliden. Die Mehrheit der Verbindungen, welche in den Kapiteln 3-5 angeführt sind, wurde mit verschiedenen zellbasierten Assays untersucht. Biologische Aktivität wurde im niedrigen mikromolekularen Bereich identifiziert, wobei die Inhibition des Hedgehog Signalweges beobachtet wurde.

Chapter 1. General Introduction

1.1 Introduction

As reliable and rich starting points, bioactive natural products (NPs) have been inspiring drug discovery in the history of medicinal chemistry, and also empowering the exploration of complex biological networks by using bioactive small molecules in chemical biology research.[1-3] Through interactions with multiple proteins in both biosynthesis and displaying bioactivities, NPs represent diverse areas in chemical space explored and selected in evolution by nature.[4-7] Due to limited material and time, NPs selected by evolution might only represent a fraction of chemical space binding to corresponding proteins, therefore the extension of chemical space represented by NPs by organic synthesis is indispensable. However, it is estimated that the number of drug-like small molecules exceeds 10^{60}.[8] Hence, it is unfeasible to explore all these possibilities by organic synthesis. Taken together, it is necessary to develop a practical navigation to efficiently identify biologically relevant areas from the nearly infinite chemical space defined by small molecules.

The chemical space of NPs can be defined by conserved NP scaffolds together with diverse substituents for complementary differentiation.[5] In this regard, the common scaffolds of NPs featured with conservatism can be recognized as ‘privileged’, with which NPs exhibit diverse bioactivity tuned with the decoration of substituents. Accordingly, the privileged scaffolds of NPs in the Dictionary of Natural Product (DNP) were classified hierarchically, resulting in the Structural Classification of Natural Products (SCONP) (Fig. 2).[5] In analogue to small molecules, the binding sites of proteins can be correspondingly characterized by highly conserved fold types and variable side chains. In this scenario, Protein Structure Similarity Clustering (PSSC) was proposed based on the structural similarity of protein binding sites.[5] The basic reasoning of PSSC relies on the hypothesis that the protein with the conserved scaffold or subfold of its binding site should be bound by specific compounds sharing common scaffolds. Based on these two complementary approaches, biology-oriented synthesis (BIOS) was termed and provides a guideline for the design and synthesis of focused compound collections.

In light of BIOS, two criteria are supposed to be critical for the synthesis of specific compound collections, including the rapid access of privileged scaffolds with biological relevance and the adequate variability for substitutions. In addition, compared with those compounds obtained by combinatorial chemistry based on the major consideration of chemical accessibility, NPs distinguish themselves by not only the increased molecular complexity but also the prevalence

of stereocenters. Hence, to meet all these requirements, the development of efficient methodologies to access complex privileged scaffolds with sufficient substitution patterns, especially in an enantioselective manner, would be invaluable and highly desirable.

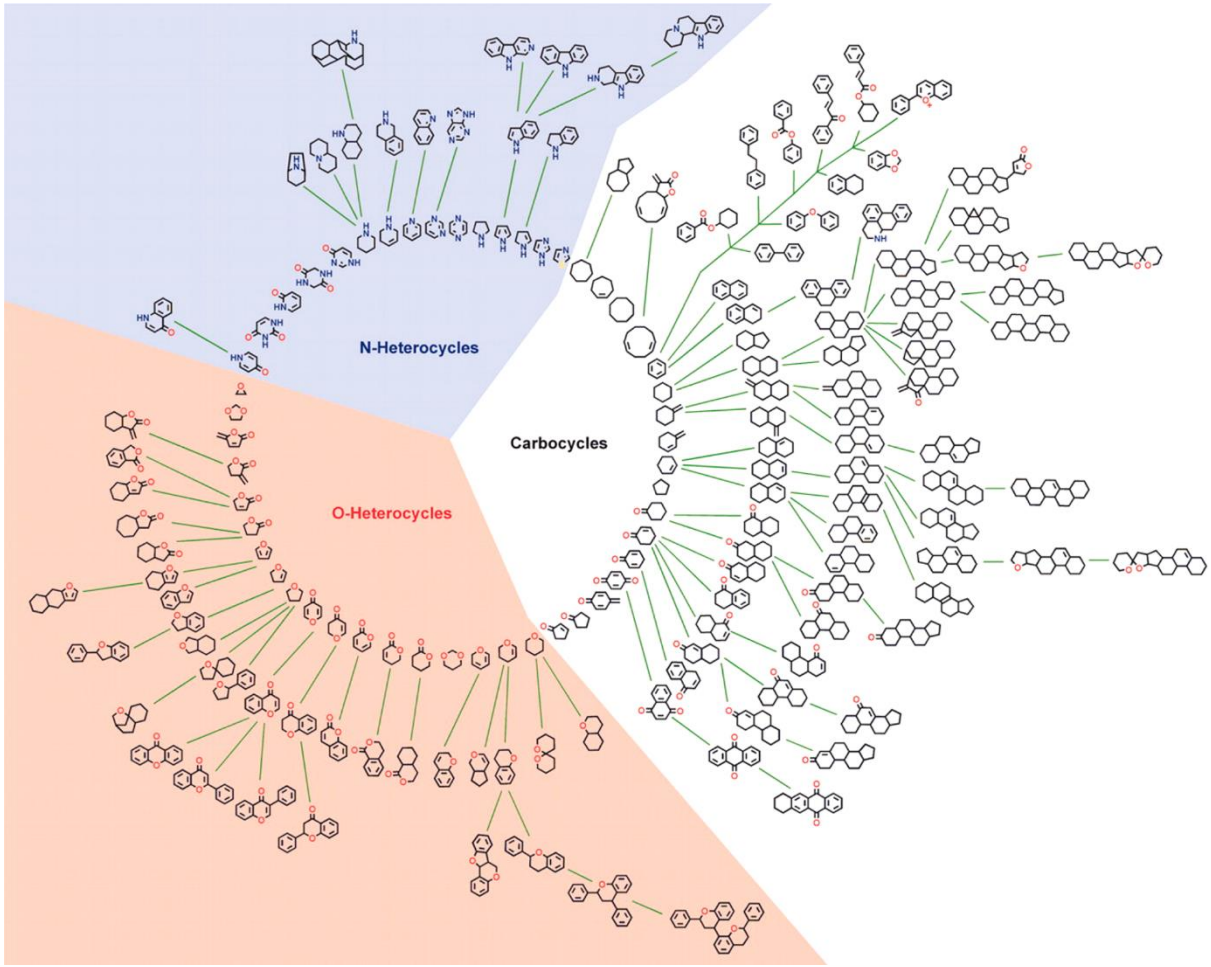


Figure 2. Graphic representation of the Structural Classification of Natural Product (SCONP). Reprinted from ref[9], copyright (2005) National Academy of Sciences.

1.2 **Objectives**

Over the last decade, a wide range of privileged scaffolds enriched in NPs has been constructed rapidly through C−H activation enabled by cyclopentadienyl (Cp) metal complexes, especially by Rh(III) analogues.[10-12] Surprisingly, it was not until 2012 that the use of corresponding chiral Cp ligands emerged as a general approach to steer such asymmetric transformations.[13,14] However, the present chiral Cp ligands suffer from either limited applicability or constricted structural variability.[15] To evolve such chemistry tool to serve for BIOS, the discovery of novel Cp ligands would be highly valuable and desirable. Inspired by the pioneering work by Dr. Marco Potowski, it was envisioned that (6+3) cycloadducts featured with easy accessibility and

flexible structural variability could be explored as suitable chiral Cp ligands.[16,17] In this regard, Chapter 2 in this thesis will depict the endeavor to design and synthesize a new type of chiral Cp ligands and Rh(I) complexes, as well as their applications into the construction of versatile NPs scaffolds.

To build *N*-heterocycles, 1,3-dipolar cycloaddition reactions (1,3-DC) of azomethine ylides are among one of the most efficient methods. In continuation to the effort in our lab to construct compound libraries by harnessing the power of 1,3-DC, further extension of previously established compound libraries based on pyrrolizidines is one of the goals in this thesis.[18] This work will be presented in chapter 3.

According to BIOS, the privileged scaffolds in bioactive NPs can be regarded as the starting point for the synthesis of compound collections to identify promising hits.[5] Owing to the continuous interest in Englerin A in our group, the construction of seven-membered carbocycles embodied in Englerin A is another target in this thesis.[19] Chapter 4 will demonstrate versatile approaches in detail to this end.

As another potential method to build *N*-heterocycles, the phosphine-catalyzed annulation reactions of azomethine ylides and allenes have not been investigated.[20,21] Based on this consideration, chapter 5 will show the synthesis of nitrogen-contained pyrroloisoquinolines through phosphine-catalyzed annulation reactions of isoquinolinium methylides and allenes.

Chapter 2. Development of Tunable Cyclopentadienyl Ligands for General Enantioselective C−H Activation

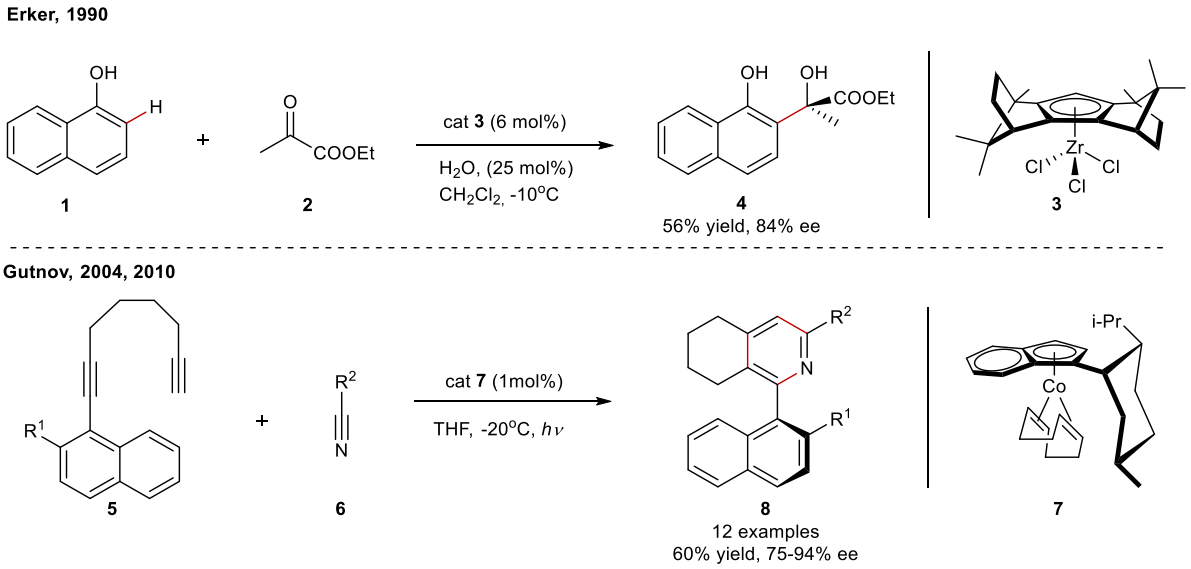
2.1 Introduction

2.1.1 Chiral Cyclopentadienyl Ligands in Asymmetric Catalysis

Catalytic asymmetric synthesis is one of the most active fields in organic chemistry which significantly benefits from the development of novel chiral ligands for metal complex catalysis. As common design principles of 'privileged' ligands, high chemical robustness, adjustability, scaffold rigidity, as well as enriched ligand pool facilitated by ease of synthesis have been generally recognized by the chemistry community.[22] In spite of numerous chiral ligands developed in the past decades, only a few ligands such as bisoxazoline ligands and SALEN ligands can be regarded as 'privileged', with systematic variation on their scaffolds and a wide spectrum of applications in various mechanistically different reactions.[22,23] In sharp contrast to these privileged ligands, chiral cyclopentadienyl (Cp) ligands with noncoordinating substituents were only applied very recently in asymmetric catalysis.[24-26] However, the achiral Cp ligands, especially its pentamethylcyclopentadienyl analog (Cp*), have emerged as a dominant class of anionic ancillary ligands with broad application in versatile transition metals catalysis.[27] In addition, for some reactions catalyzed by Co(I)[28], Rh(I)[29], Rh(III)[10-12], Ir(III)[30], and Ru(II)[31], chirality can only be induced by Cp ligands since all coordinating sites of such metal complexes besides Cp ligands are required during catalytic process, which highlights the necessity of development of chiral Cp ligands further.

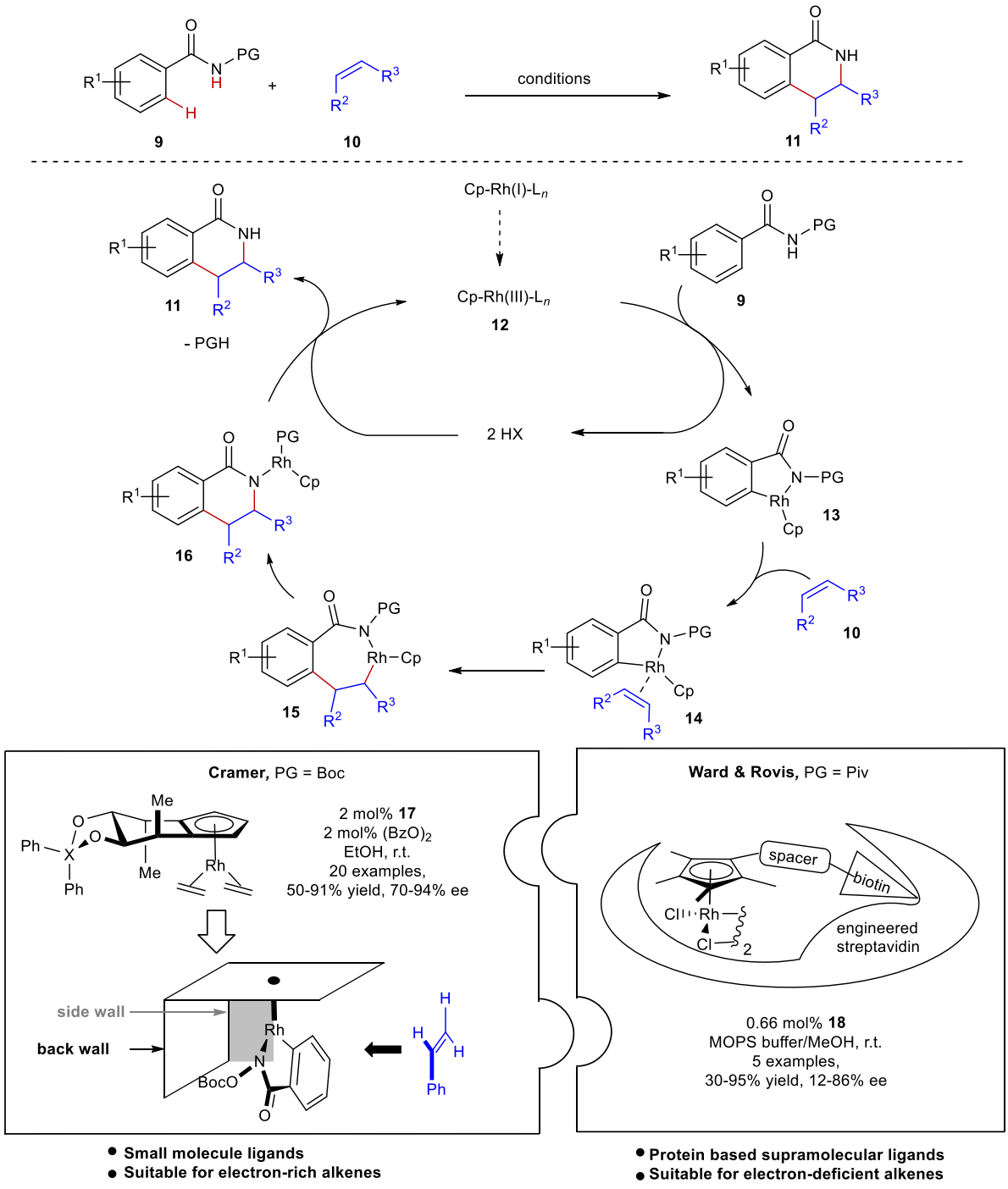
Since the discovery of ferrocene in 1951,[32] it is rather straightforward that enantioselectivity of Cp-metal complexes catalyzed transformations can be introduced by means of chiral moieties in Cp ligands. In fact, there was a period when chemists showed strong interest in development of such ligands around 1980's, but only a limited number of chiral Cp derivatives were synthesized and rarely applied in asymmetric metal catalysis.[24,33] Furthermore, only poor enantioselectivity was obtained for most of those few applications based on chiral Cp ligands. There are only two reports in which chiral Cp ligands delivered considerable enantiocontrol before 2012 (Scheme 1). In 1990, Erker reported successful enantiocontrol of Friedel-Crafts hydroxyalkylation of 1-naphthol **1** by using a chiral Cp-Zr complex **3**, affording product **4** with up to 84% ee.[25] In this case, the chiral Cp-Zr complex **3** is supposed to activate ethyl pyruvate **2** as a Lewis acid to deliver chirality in catalytic process. Later on, the first organometallic reaction using chiral Cp-Co complex was described by Gutnov and Heller in 2004[26] and further extended in 2010[34], providing axially chiral compounds **8** *via* a [2+2+2] reaction of 1,7-octadiynes **5** and nitriles **6**. This strategy could also be applied to the synthesis of phosphorus-

bearing axially chiral compounds by using propargylic phosphine oxides and acetylene. Although these two early successful reports show great potential for the application of chiral Cp ligands in asymmetric catalysis, these ligands are severely limited by the variability of ligand scaffolds, which restricts systematic catalyst optimization for broad application in other transformation.



Scheme 1. Early examples of enantioselective catalysis based on chiral Cp ligands.

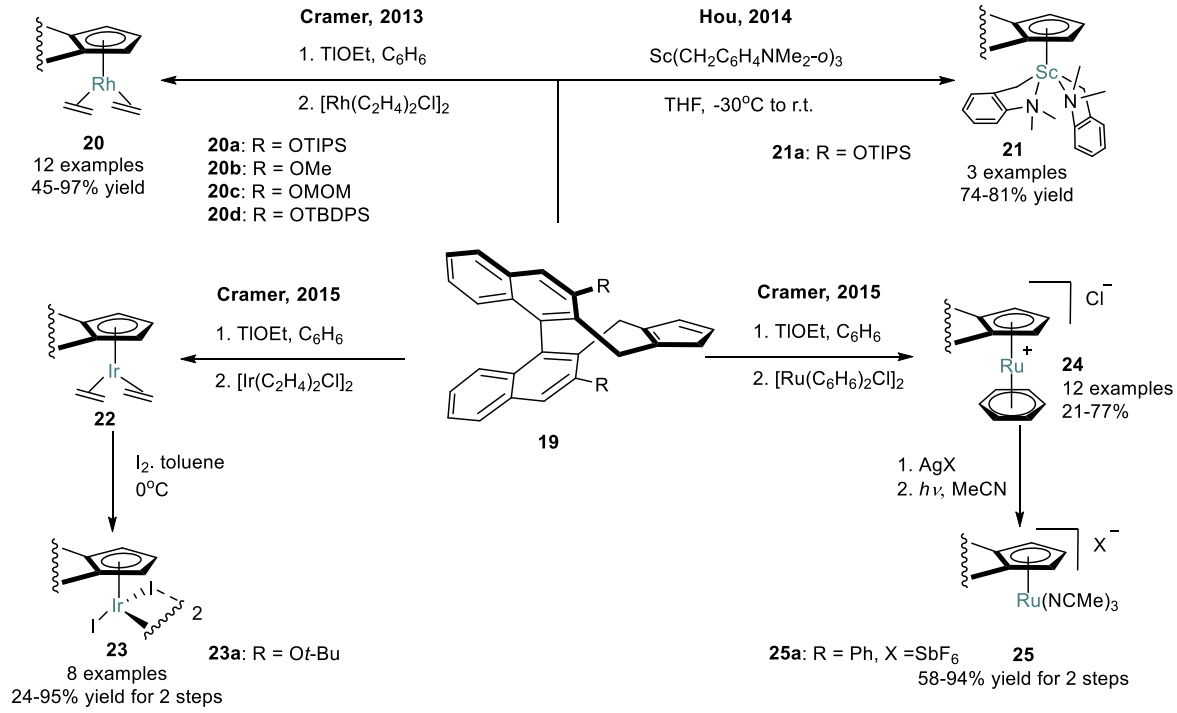
In the last decade, the rapid development of Cp*Rh(III) catalyzed C−H functionalizations evoked the tremendous interest in chiral Cp ligands in the chemistry community.[10-12] One of those transformations facilitated by Cp*Rh(III) is the synthesis of dihydroisoquinolones from hydroxamates and alkenes under mild conditions, discovered by Fagnou[35] and Glorius[36] in 2011 (Scheme 2). According to the proposed mechanism, the active catalyst CpRh(III) **12** coordinates to the substrate **9** by N−H bond insertion. The following C−H bond cleavage step gives intermediate **13** through a carboxylate assisted concerted-metalation-deprotonation (CMD) process. Afterwards the coordination of alkene to Rh(III) provides intermediate **14**, which is subjected to a subsequent migratory insertion to yield rhodacycle **15**. After reductive elimination to generate **16**, the desired product **11** is delivered upon protonation process.



Scheme 2. Two complementary chiral Cp ligands for enantioselective synthesis of dihydroisoquinolones.

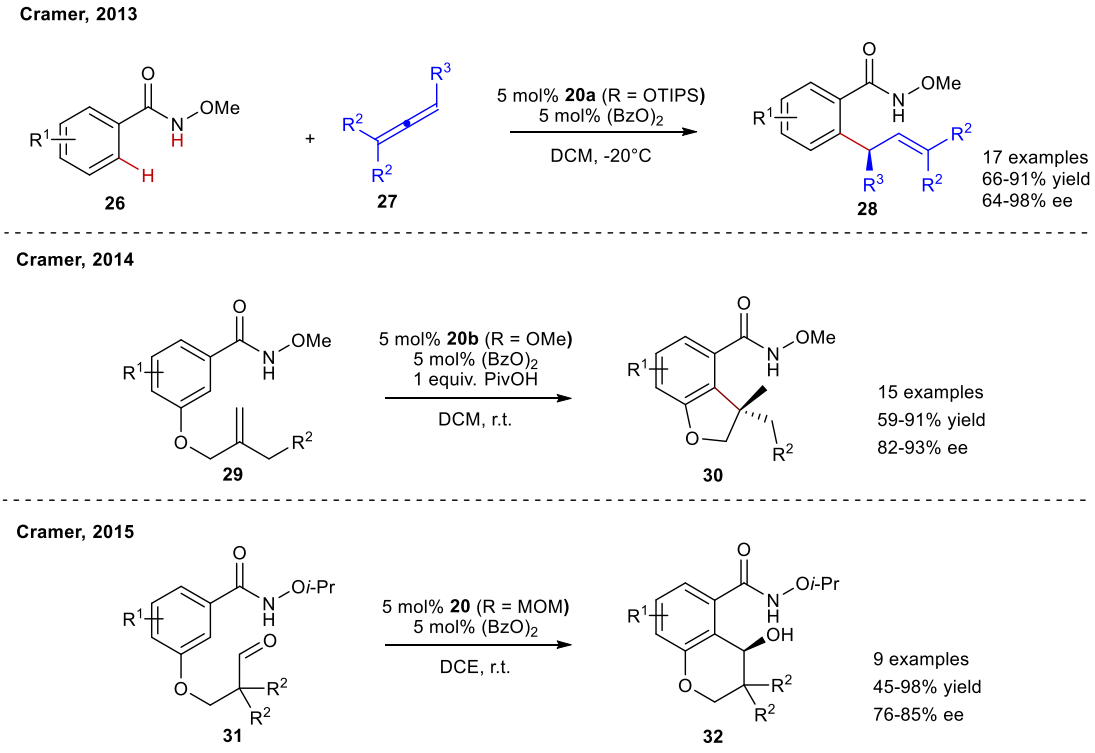
Using this transformation as a model reaction, two complementary strategies to design chiral Cp ligands leading to efficient chirality induction were developed by Ward and Rovis as well as Cramer in 2012 (Scheme 2).[13,14] The corresponding Rh(I) complexes were synthesized due to their air-stability and easy handleability, and could be transformed to reactive Rh(III) catalysts under the treatment of an oxidant. In the work by Cramer,[13] a series of cyclohexyl-substituted chiral Cp ligands was designed and synthesized in 5-7 steps, affording the desired

dihydroisoquinolones with excellent yield and enantioselectivity. In this catalyst system, hydroxamates with different substitutions on diverse positions and specific types of electron-rich alkenes were well tolerated. According to the hypothesis of back/side wall proposed by the authors, the methyl group in catalyst **17** acts as side wall which determines the orientation of hydroxamate in intermediate **13**. Meanwhile, two phenyl groups far away from the Rh as back shields force alkene to approach in opposite direction near Cp moiety. Subsequently, larger substitution on alkene, such as the phenyl group in styrene, tends to point away from Cp moiety due to unfavorable steric interaction. Such diastereoselective coordination of alkene forms intermediate **14**. In this scenario, the chirality at metal is already able to define the stereochemistry in the final product **11** *via* a enantiodetermining migratory insertion process. Complementary to small molecule Cp ligands aforementioned, Ward and Rovis employed their protein-based Cp ligands **18** to induce enantioselectivity to the same transformation by chiral environment defined by specific streptavidin.[14] Relatively fewer examples were demonstrated with 30-95% yield and 12-86% ee. Interestingly, the substrate scope of alkenes in this catalyst system is restricted to electron-deficient acrylates, which is complementary to Cramer's work. The authors attributed this behavior to more electron-rich and bulky nature of Cp* implanted in protein-based ligands.



Scheme 3. Chiral binaphthyl Cp complexes with Rh(I), Sc(III), Ir(III), and Ru(II).

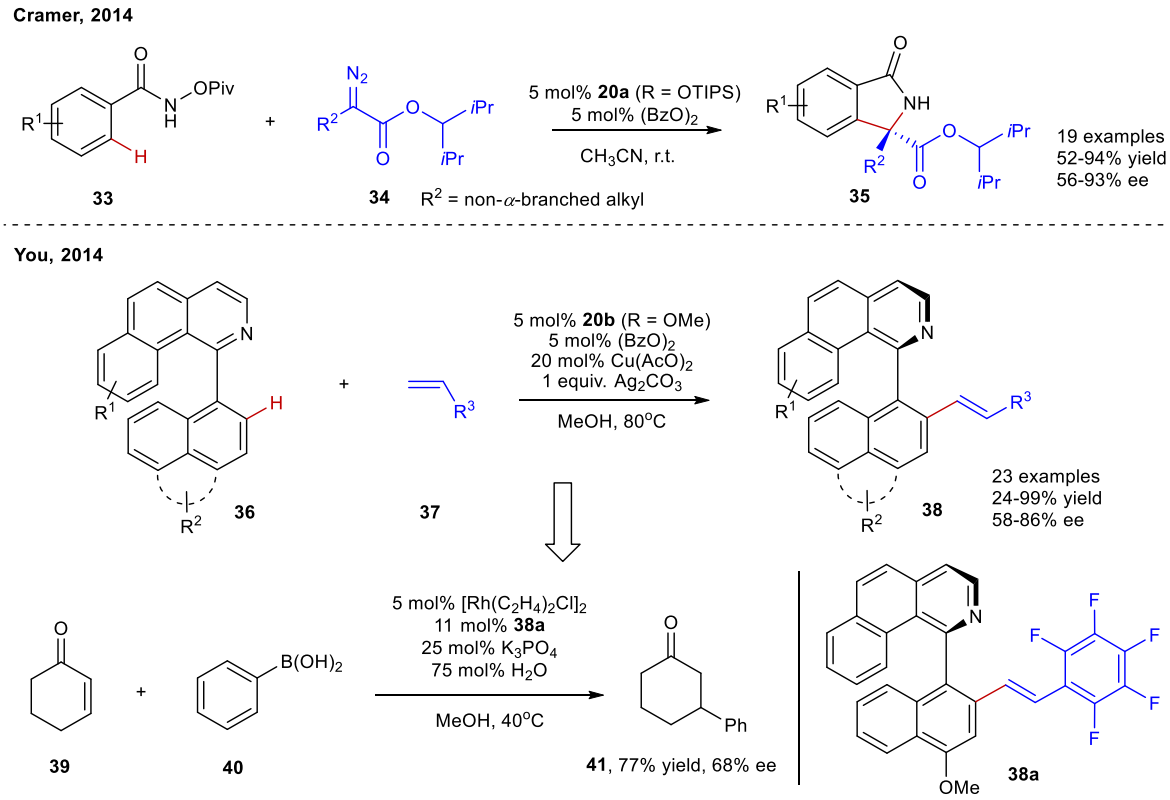
However, the abovementioned two ligands could not be applied in more transformations, presumably due to limited generality of these catalyst systems and the multi-step preparation of ligands. In 2013, Cramer developed a second generation of Cp ligands **19** based on chiral BINOL scaffold (Scheme 3).[37] The outcome of excellent enantiocontrol by such ligands was rationalized by the authors with the same back/side wall hypothesis. In such scenario, the binaphthyl moiety characterizes the back wall in analogy to the bi-phenyl group in **17**, while R as only variable group in **19** plays the role of side wall as counterpart of methyl group in **17**. In spite of the relatively lengthier synthesis route (4-14 steps) and only one position for late stage modification, this binaphthyl family showed great generality for diverse metals and reactions with distinct mechanism, as well as enhanced reactivity and enantioselectivity.[15,38] Since the discovery of such ligands, not only rhodium(I) complexes but also complexes with scandium(III)[39], iridium(III)[40], and ruthenium(II)[41] were successfully synthesized and applied in corresponding asymmetric catalyses.



Scheme 4. Application of binaphthyl Cp ligands in rhodium(III) catalyzed enantioselective reaction of benzamides.

The ligand **19** was initially proposed in 2013 by an enantioselective C−H allylations of *N*-methoxybenzamides **26** using Rh(I) complex **20a** as catalyst,[37] whose non-asymmetric version was firstly discovered by Ma[42] and Glorius (Scheme 4).[43] Notably, catalysts **20** based

on binaphthyl resulted in significantly enhanced enantiocontrol compared to catalyst **17** which was optimal in the dihydroisoquinolone synthesis. Both steric and electronic variations of benzamides **26** as well as versatile allenes **27** were compatible in the reactions, affording the desired products **28** with up to 91% yield and 98% ee. Inspired by the pioneering work, remarkable progress has been achieved in this field, especially in the discovery of more transformations by employing binaphthyl CpRh(I) complexes. In 2014, Cramer et al. extended their substrate types to disubstituted alkenes based on similar mechanism.[44] An asymmetric hydroarylation of tethered olefins on benzamides **29** was demonstrated, providing diverse dihydrobenzofurans **30** with up to 90% yield and 92% ee by utilizing **20b** as catalyst (Scheme 4). In this case, one quaternary center can be formed through a 5-exo-trig cyclization process. Later on, aldehydes **31** also proved to be suitable for this transformation, producing hydroxychromanes **32** in up to 98% yield and up to 85% ee (Scheme 4).[45] In addition, in both cases the binaphthyl Cp ligands proved again to be superior to cyclohexyl-substituted Cp ligands in terms of either reactivity or enantioselectivity.

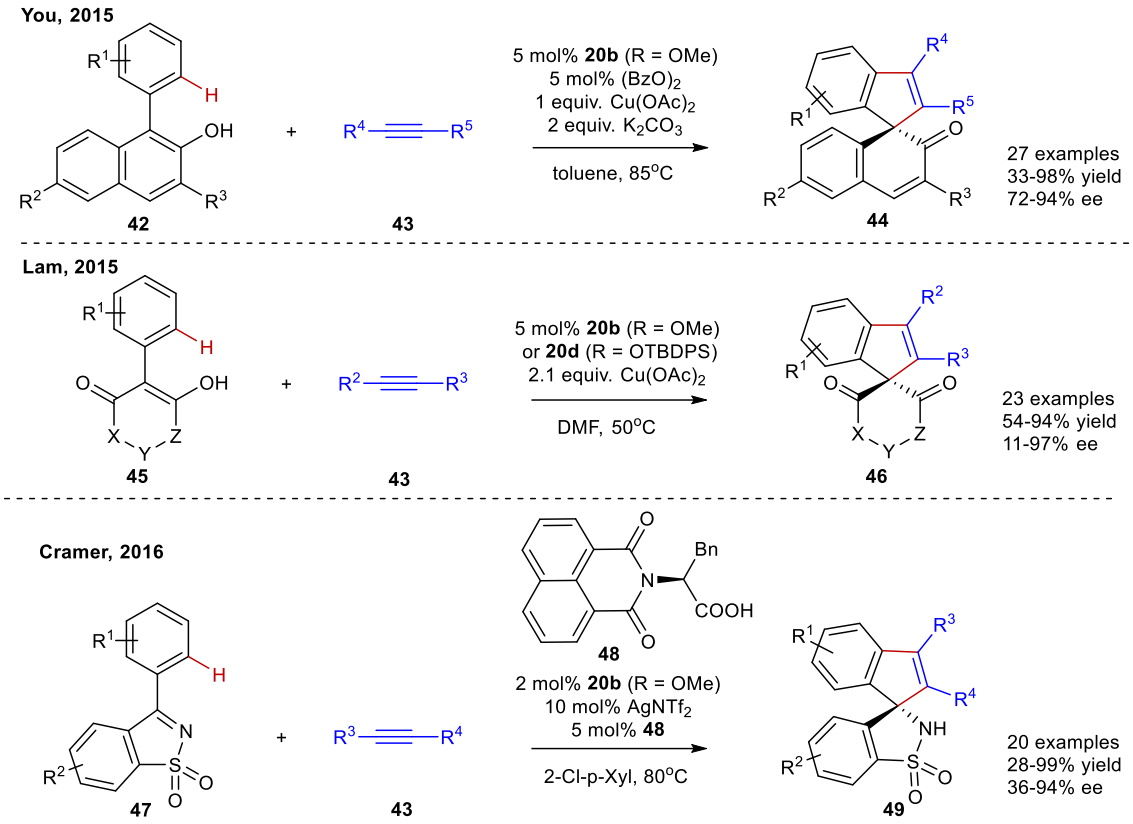


Scheme 5. Enantioselective synthesis of isoindolones axially chiral biaryl compounds.

In the last few years, ligand **19** has also proved compatible with a few other transformations with different mechanism. In 2014, Cramer reported an enantioselective synthesis of

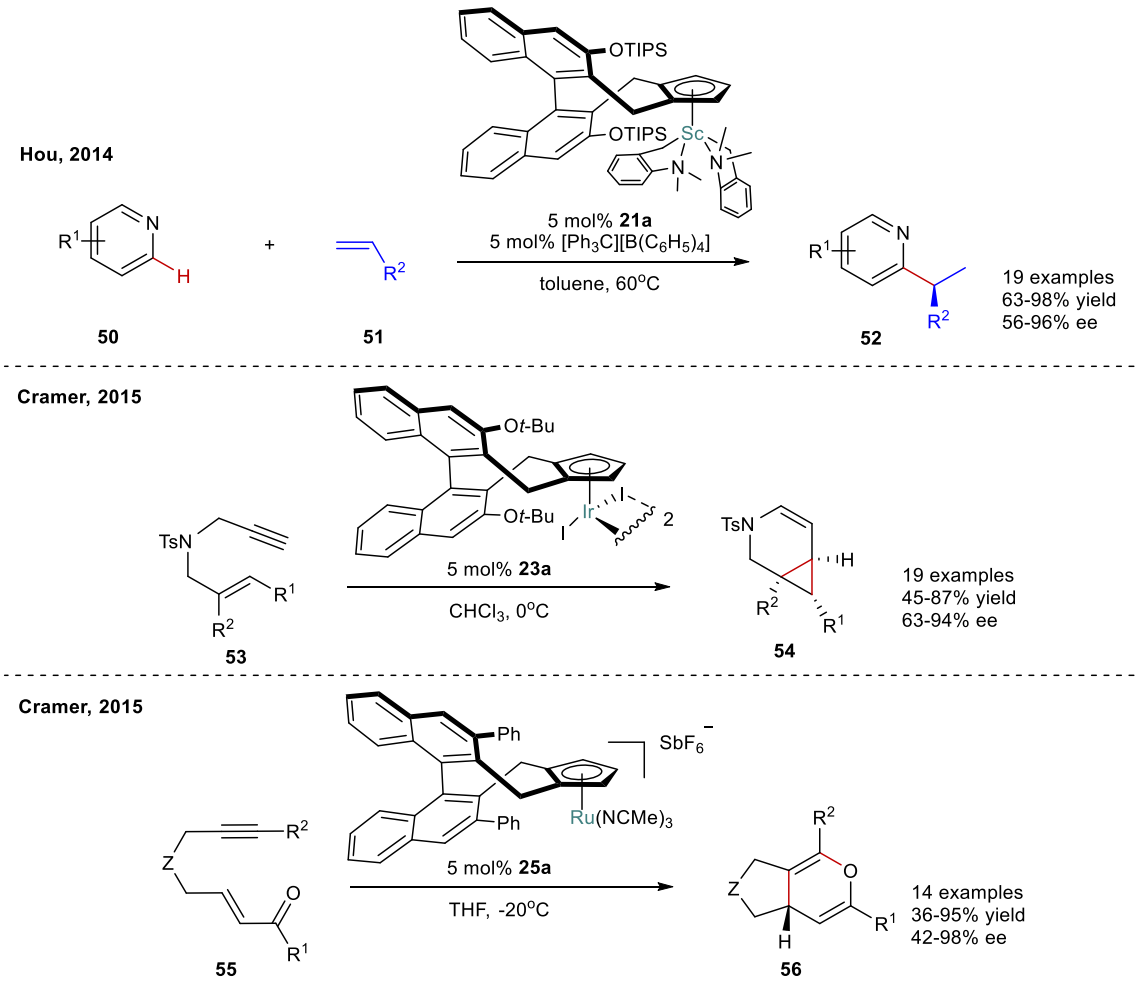
isoindolones **35** *via* carbene insertion, inspired by the methodology developed by Rovis (Scheme 5).[46] By enhancing the steric discrimination between R^2 and ester group, diazo compounds **34** with a bulky 2,4-dimethyl-3-pentyl ester and alkyl groups as R^2 were able to deliver the final product **35** in up to 94% yield and with up to 93% ee. With regard to the substrate scope, high enantioselectivity and acceptable reactivity could be realized with hydroxamates **33** with diverse substitutions and bulky diazoesters **34** without α-substitutions. In the same year, an interesting approach to access axially chiral biaryl compounds was demonstrated by You (Scheme 5).[47] Regarding to the design principle, the interconversion of biaryl substrates **36** at low temperature can be hampered by alkenylation at *ortho*-position through a rhodium-catalyzed asymmetric dehydrogenative Heck reaction assisted by pyridine moiety as a directing group, resulting in stable axially chiral compounds **38**. After screening of catalysts, **20b** was proved to be optimal, delivering up to 86% ee and 96% yield. For the substrate scope, although this reaction proceeded well with various alkenes **37**, reactivity and enantioselectivity were especially sensitive to variation on biaryl substrates **36**. Hence, the substrate scope of bialy substrates was significantly limited. Impressively, this work also demonstrated such axially chiral biaryl compounds such as **38a** were capable to be applied as ligands for a rhodium(I) catalyzed conjugate addition of phenylboronic acid **40** to cyclohexanone **39**.

In 2015, the same group developed an enantioselective intermolecular (3+2) annulation reactions of 1-aryl-2-naphthols **42** and disubstituted alkynes **43** by the dearomatization strategy (Scheme 6).[48] The spirocyclic *β*-naphthalenones **44** bearing a quaternary chiral center were able to be obtained through this reaction with up to 98% yield and up to 94% ee. Independently, Lam reported the asymmetric synthesis of spiroindenes **46** based on a similar mechanism (Scheme 6).[49] The desired products were obtained by the reaction of enols **45** and internal alkynes **43** with up to 94% yield and up to 97% ee. Later on, another method to access chiral spirocyclic compounds based on sultam **49** was reported by Cramer with the annulation reactions of *N*-sulfonyl ketamines **47** and internal alkynes **43** (Scheme 6).[50]



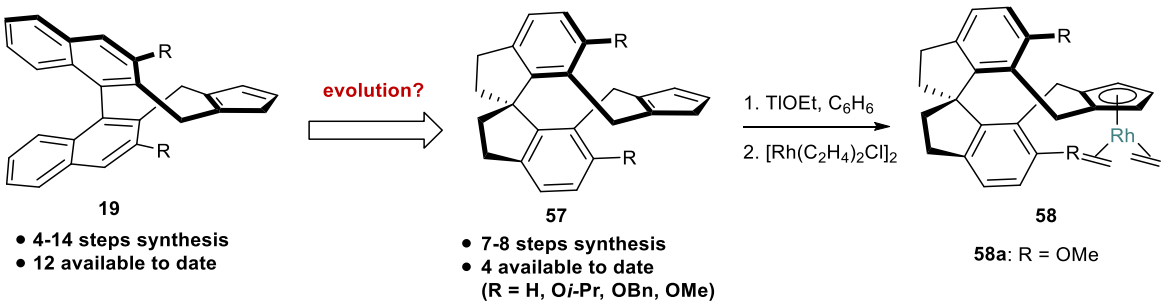
Scheme 6. Enantioselective synthesis of spirocyclic compounds *via* intermolecular (3+2) annulation reactions of alkynes.

With regard to other metal complexes, there is only single report to date for scandium(III)[39], iridium(III)[40] and ruthenium(II)[41], respectively (Scheme 7). This field remains obviously underdeveloped but has shown great potential by these three seminal works. In 2014, Hou discovered an enantioselective C−H functionalization of pyridines **50** with alkenes **51** by employing scandium(III) complex **21a**, giving a variety of 2-alkylated pyridines **52** in up to 98% yield and 96% ee.[39] One year later, Cramer succeeded in the synthesis of reactive iridium(III)[40] and ruthenium(II)[41] complexes (**23** and **25**) derived from ligand **19** by a two-step synthesis, and also their application in intramolecular cycloisomerization of enynes **53** and hetero Diels−Alder reaction of yne-enones **55** respectively. In the first case, iridium(III) complex **23a** was proposed to activate the terminal alkyne moiety, leading to nucleophilic addition of electron-rich tethered alkenes. The following 1,2-H shift process and release of Ir catalyst ultimately delivered the final cyclopropanes **54**. For the latter report, ruthenium(II) complex **25a** was believed to coordinate to substrate by the interaction with carbonyl, alkene and alkyne moiety of **55**, initiating subsequent enantiodetermining oxidative cyclization, isomerization and final reductive elimination to afford pyranes **56** in excellent yields and enantioselectivities.



Scheme 7. Examples of enantioselective reactions catalyzed by Sc(III), Ir(III) and Ru(II) complexes.

Very recently, another type of ligands **57** based on 1,1'-spirobiindane was disclosed by You, which could be regarded as an extension on binaphthyl ligand **19** (Scheme 8).[51] As a proof of concept, the corresponding catalyst **58a** was able to deliver up to 96% ee in contrast to previous 82% ee for the same transformation as shown in Scheme 5. Nevertheless, the generality and superiority of such ligands needs to be identified by more applications in the future.



Scheme 8. The features of chiral Cp ligands **57** compared with binaphthyl ligands **19.**

Based on all the abovementioned reports, an overview on current chiral Cp ligands could be summarized as shown in Fig. 3. In general, there are two categories of Cp ligands to date, including synthetic organic ligands by Cramer and You respectively, as well as protein-based ligands by Ward and Rovis. However, both ligands are significantly limited and actually complementary to each other. On one hand, simple synthetic organic ligands are facing limitation of possible variations in their chemical structure and tedious preparation (up to 14 steps), despite their dramatically growing and broad application in asymmetric metal catalysis in recent years.[15] On the other hand, more complex protein-based ligands can be modified and optimized rapidly without limit, but only one successful example has been reported until now due to unidentified generality and also tedious preparation.[14]

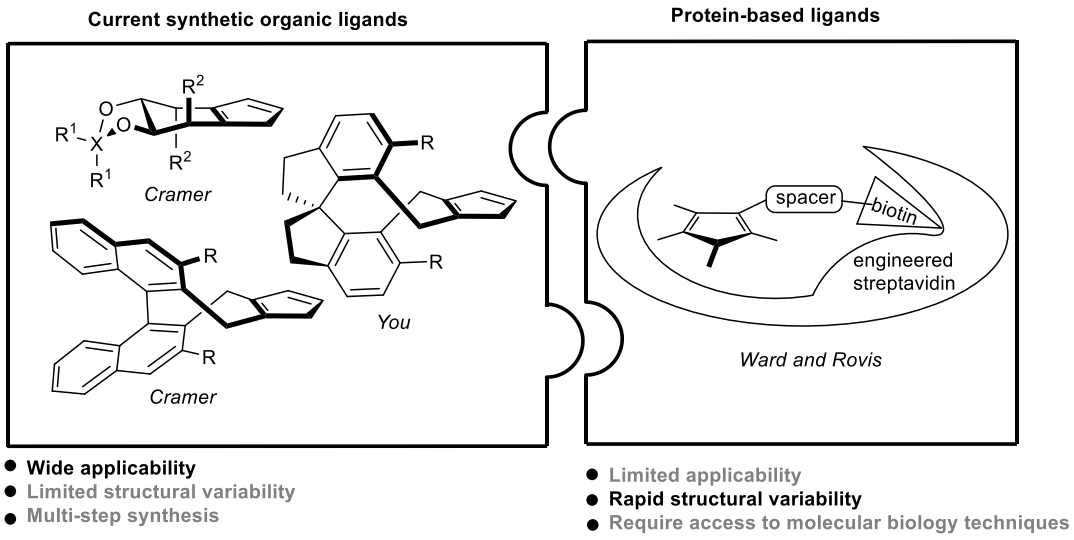
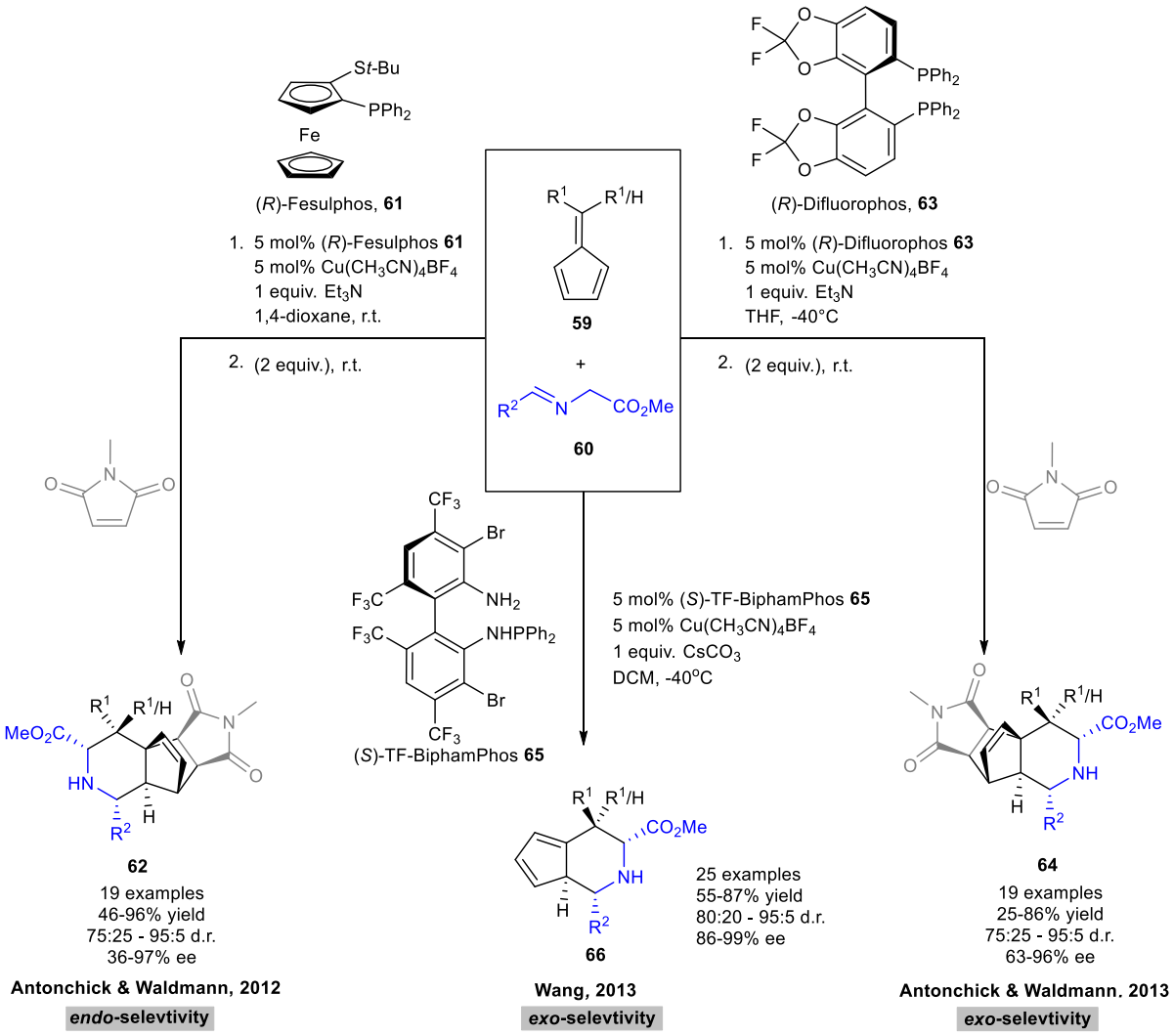


Figure 3. Overview of current chiral Cp ligands.

In conclusion, the development of enantioselective chemistry enabled by chiral Cp ligands is still in its early stages, while the pioneering work in the last half decade have already demonstrated tremendous potential. The potential lies not only in the discovery of new transformations and other metal complexes based on present ligands, but also the design of new Cp ligands with expedient synthesis and improved structural adjustability based on privileged scaffolds for systematic catalyst optimization.

2.1.2 Synthesis of Chiral Cyclopentadiene Derivatives by (6+3) Cycloadditions



Scheme 9. Stereodivergent (6+3) cycloadditions steered by varied ligands.

Recently, the development of catalytic asymmetric 1,3-dipolar cycloadditions has been growing rapidly,[52] in which (6+3) cycloaddition reactions of azomethine ylides and fulvenes[16,17,53] have been disclosed as a highly efficient way to access chiral Cp derivatives (Scheme 9). This type of transformations was initially discovered by Hong in 2003, in which racemic Cp derivatives with piperidines were obtained upon the treatment of base or/and Lewis acid.[54] In 2012, Antonchick and Waldmann described the first highly enantioselective (6+3) cycloaddition of azomethine ylides **60** and fulvenes **59** catalyzed by complex of Cu(I) and (*R*)-Fesulphos ligand **61**, affording highly *endo*-selective chiral cyclopentadiene derivatives in excellent enantioselectivities and yields.[16] Due to the instability of (6+3) cycloadducts, a sequential (4+2) cycloaddition with maleimide was performed to give the products **62**. Later on in 2013, the highly *exo*-selective (6+3) cycloadditions can also be realized by using (*R*)-

Difluorophos **63** as a ligand by the same group[17] and the modified TF-BiphamPhosas ligand **65** by Wang[53], delivering tandem (6+3)/(4+2) products **64** and chiral cyclopentadiene derivatives **66** in high *endo*-selectivity, respectively.

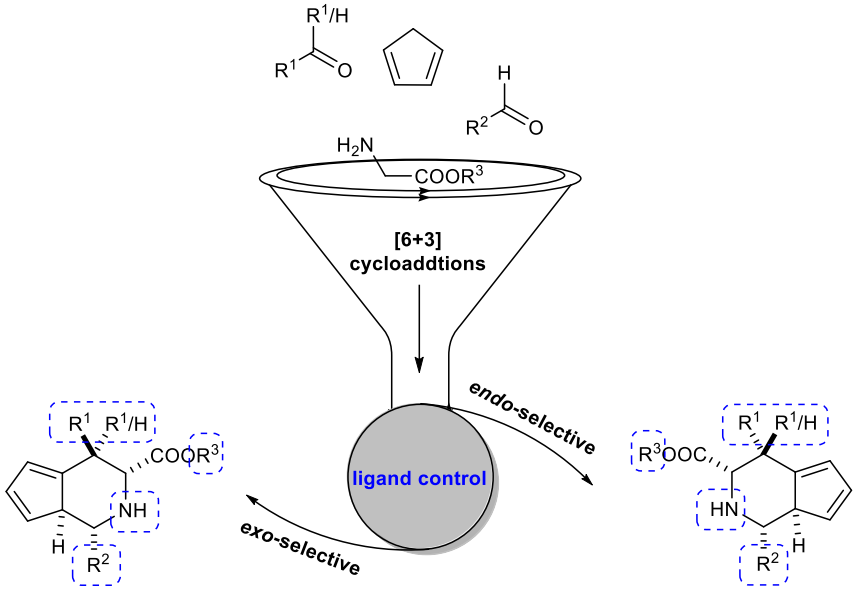


Figure 4. The features of ligand-controlled (6+3) cycloadditions.

There are a couple of prominent features for this transformation as shown in Fig. 4: (i) diverse Cp derivatives are able to be obtained rapidly within 2 steps in a highly enantioselective manner; (ii) there are three highly tunable positions in the Cp scaffold, originating from numerous commercially available aldehydes, ketones and amino acid esters, together with one secondary amine with the potential for further modification. (iii) the stereochemistry of such Cp compounds could be adjusted in terms of enantioselectivity and diastereoselectivity by simple alternation of ligands.

2.1.3 Catalytic Enantioselective Synthesis of Axially Chiral Biaryl Compounds

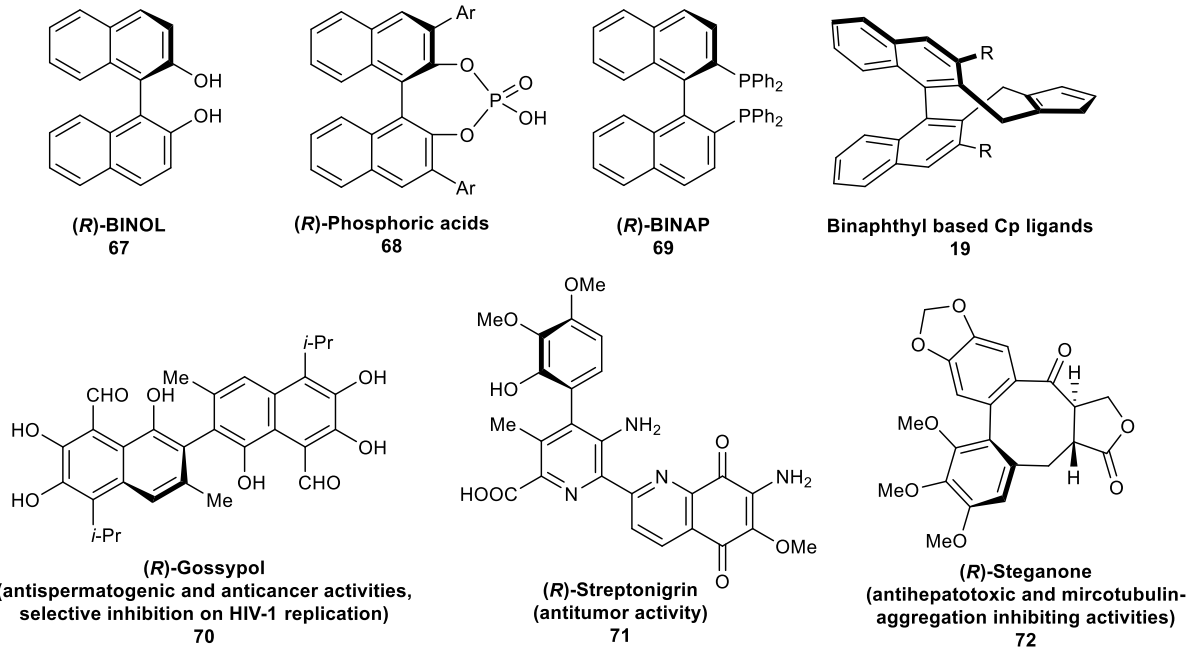
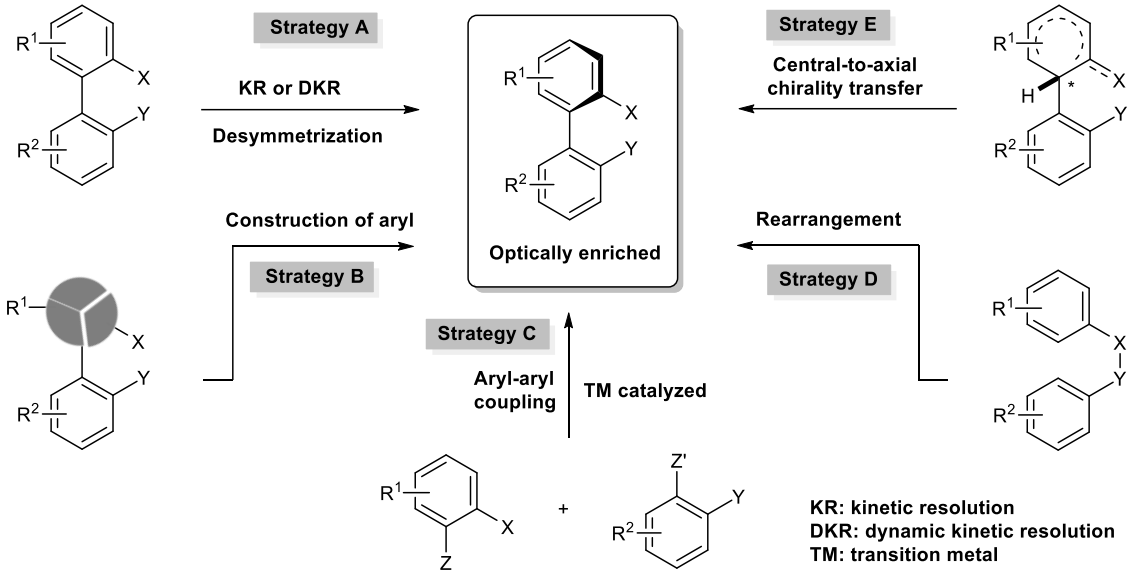


Figure 5. Representative ligands, catalysts, natural products and pharmaceuticals with axially chiral biaryls.

Axially chiral biaryl compounds have been attracting intensive attention in the chemistry community (Fig. 5).[55-57] In asymmetric catalysis, these compounds are extensively exploited as versatile chiral ligands and catalysts,[55,56] especially for BINOL (**67**) and its derivatives which have been recognized as privileged ligands or catalysts coined by Jacobsen.[23,50,51] Due to the structural rigidity and the accessibility of the chiral pool, the ligands or catalysts based on axial chirality have become dominant in a variety of fields in asymmetric catalysis, such as BINOL (**67**), chiral phosphoric acids (**68**), BINAP (**69**), and even the aforementioned binaphthyl based Cp ligands (**19**).[22] Besides applications in catalysis, axially biaryl moiety are widely present in natural products and pharmaceuticals, such as (*R*)-gossypol (**70**), (*R*)-Streptonigrin (**71**), and (*R*)-Steganone (**72**).[57] Notably, in analogy to center-chiral bioactive compounds, atropisomers are also disclosed to have significantly different biological profiles such as (*R*)-gossypol (**70**), highlighting the demands for developing enantioselective synthesis of optically enriched atropisomer for further biological evaluation.

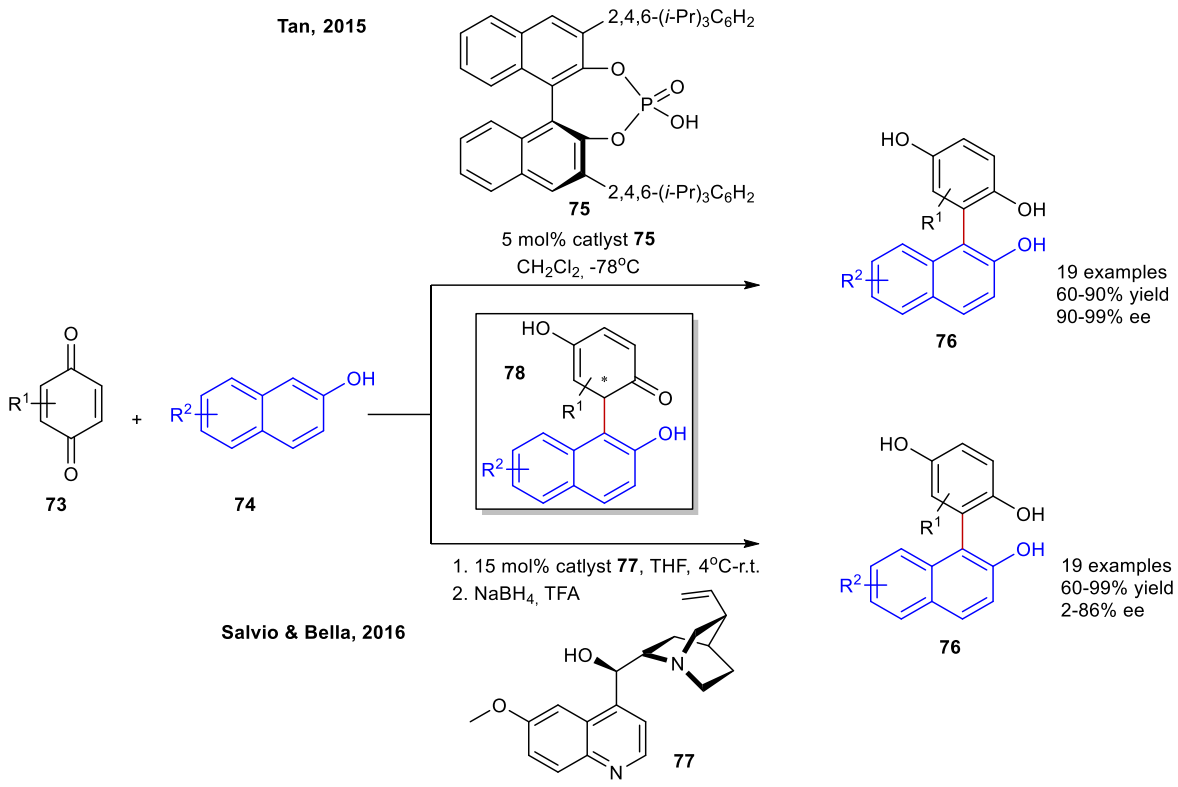
In spite of the importance for such scaffolds, there are only a few methods available to atroposelectively access axially biaryl compounds in a catalytic way, which can be divided into five categories. These strategies involve catalytic kinetic/dynamic kinetic resolution of their racemic precursors or desymmetrization of prochiral biaryls,[58-64] atroposelective construction

of another aryl,[63,65-67] transition metal catalyzed aryl-aryl cross coupling,[68,69] [3,3]-sigmatropic rearrangement,[70,71] and central-to-axial chirality transfer.[72-76] (Scheme 10)



Scheme 10. Current strategies to atroposelective synthesis of axially chiral biaryls in catalysis manner.

Among them, the first strategy involving kinetic resolution (KR), dynamic kinetic resolution (DKR) and desymmetrization is regarded to be the most powerful and straightforward, but the corresponding catalytic processes remain surprisingly scarce.[58-63] For the strategy of *de novo* construction of aromatic ring, albeit with limited number of successful examples, transition-metal-catalyzed enantioselective [2+2+2] cycloadditions have been explored as a general method to access axially chiral biaryls, involving Ni(I), Rh(I), Ir(I) and Co(I).[65] In 2011, Tanaka reported a Pd-catalyzed synthesis of enantioenriched 4-aryl-2-quinolinones by enantioselective intraomolecular hydroarylation.[67] Additionally, the sole example with organocatalysis was reported by Sprr in 2014 by using intramolecular Aldol condensation.[66] As another straightforward way, direct aryl-aryl cross couplings indeed provide axially chiral biaryls in high enantioselectivity, but specific substitution patterns on coupling partners were usually required in such transformations. [3,3]-Sigmatropic rearrangement to realize axial chirality has been known for a long time by using chiral auxiliaries. However, catalytic enantioselective methodologies were only reported very recently in 2013 by Kürti[70] and List[77]. For the last strategy, the concept of central-to-axial chirality transfer was proved by Meyers[78] in 1984, after the initial hypothesis by Berson[79] in 1955. Even throughout another 30 years, the applications of such concept are still limited, especially for the catalytic version.[80]

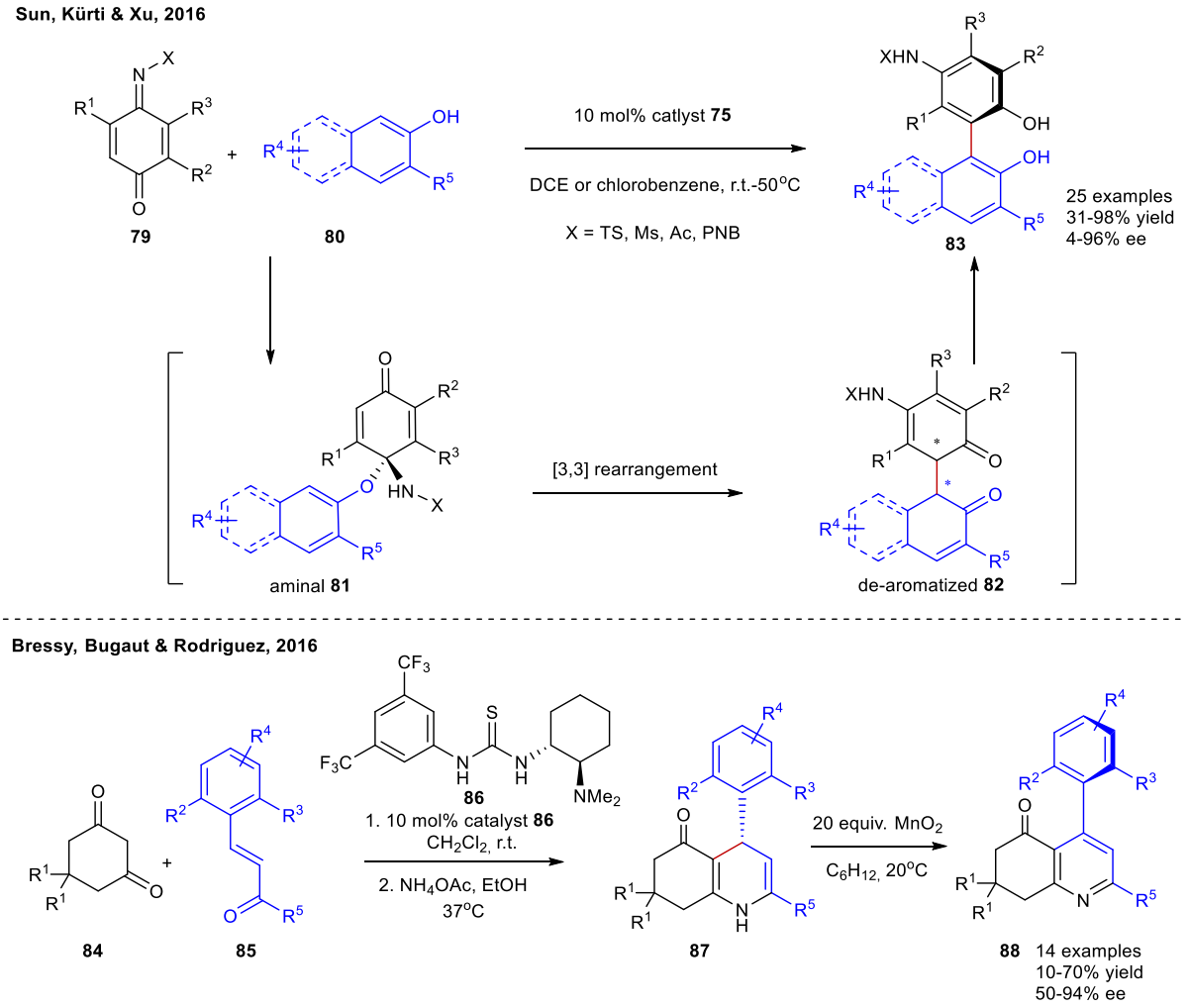


Scheme 11. Enantioselective synthesis of biaryldiols by organocatalysis *via* 1,4-addition.

Very recently, enlightened by the strategy of central-to-axial chirality transfer, there are a few elegant enantioselective catalytic transformations to access axially chiral biaryls by employing organocatalysts.[72-76] In 2015, Tan reported an organocatalytic arylation of 2-naphthols **74** and quinone derivatives **73** to access axially chiral biaryldiols **76** atroposelectively (Scheme 11).[72] Regarding the reaction process, a 1,4-addition was proposed to generate central-chiral intermediate **78** catalyzed by phosphoric acid **75**, followed by a process of central-to-axial chirality transfer to give the final product **76**. Later on in 2016, the same transformation catalyzed by quinine **77** was also demonstrated by Salvio and Bella (Scheme 11).[75]

In 2016, another application in central-to-axial chirality transfer was shown by Sun, Kürti and Xu with phosphoric acid **75** catalyzed reactions of hydroxyarenes **80** and iminoquinones **79** (Scheme 12).[74] The proposed mechanism involved central chirality transfer process from chiral aminal **81** to de-aromatized intermediate **82** *via* [3,3]-sigmatropic rearrangement, and another process of central-to-axial chirality transfer from de-aromatized intermediate **82** to final product **83**. A variety of BINOL derivatives **83** could be obtained in such strategy in high yield and enantioselectivity. In the same year, Bressy, Bugaut and Rodriguez[76] reported a stepwise method involving organocatalyzed Michael addition, Hantzsch-type synthesis and oxidation, to access axially chiral 4-arylpyridines **88** inspired by the prior works of Meyers[78] and Straub[81]

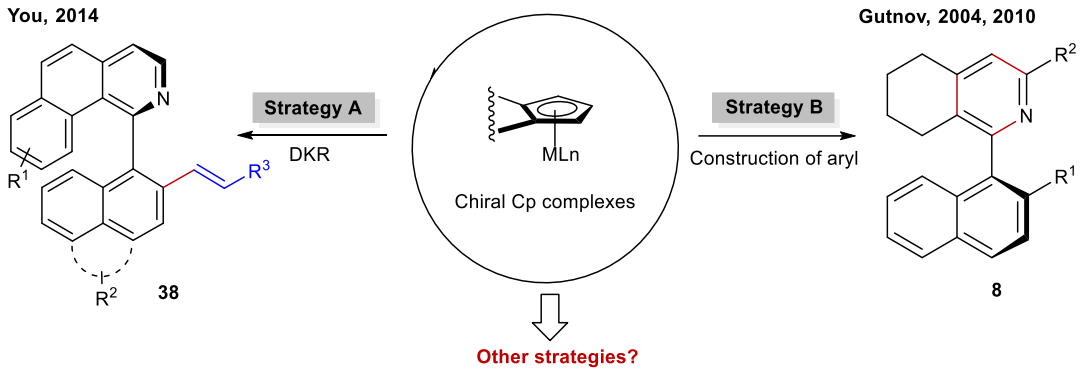
(Scheme 12). In this case, chiral tertiary amine with thiourea **86** played as an efficient catalyst for the enantioselective Michael addition to give chiral Hantzsch-type compound **87**, assisted by the treatment of NH_4OAc. Sequentially, a central-to-axial chirality transfer process enabled the formation of axially chiral 4-Arylpyridines **88**, in which the utilization of MnO_2 as oxidant proved to be critical for the efficiency of chirality transfer.



Scheme 12. Other examples of enantioselective synthesis of biaryldiols by organocatalysis.

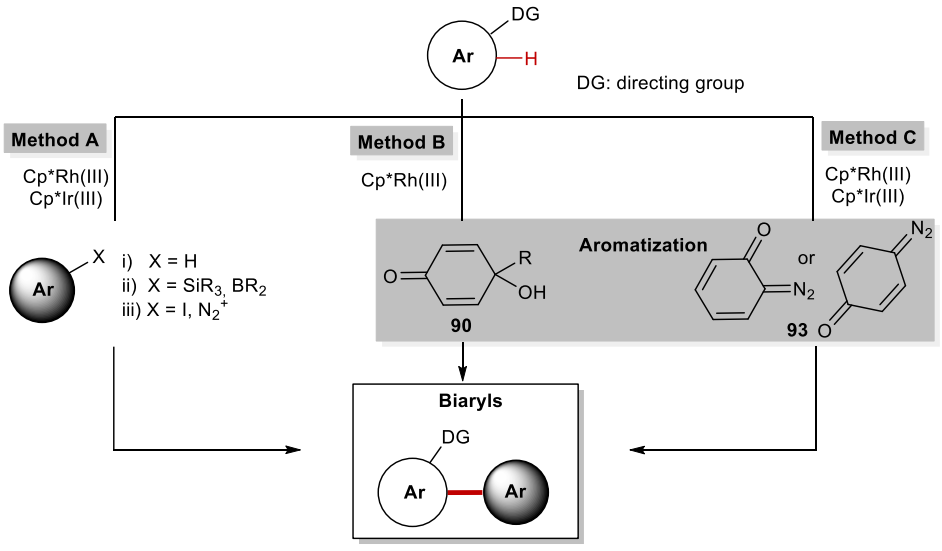
In sharp contrast, only two examples have been reported as efficient methods to synthesize axially chiral biaryls in the field of asymmetric catalysis harnessed by chiral Cp-metal complexes. The earlier example is [2+2+2] cycloadditions catalyzed by chiral Co(I) complexes guided by strategy **B** as shown Scheme 1. A recent example demonstrated in Scheme 5 is dehydrogenative Heck coupling of prochiral biaryl precursors by chiral Rh(I) complexes, which can be ascribed into dynamic kinetic resolution (DKR) of prochiral precursor in strategy **A**. Therefore, there is no example involving central-to-axial chirality transfer in this field to

date (Scheme 13). To conclude, even though there have been quite a few successful applications of chiral Cp ligands in central chirality as shown in **1.1.1**, the realm of axially chirality remains fairly unexplored, especially with the strategy central-to-axial chirality transfer.



Scheme 13. Current strategies enabled by chiral Cp ligands to access axially chiral biaryls.

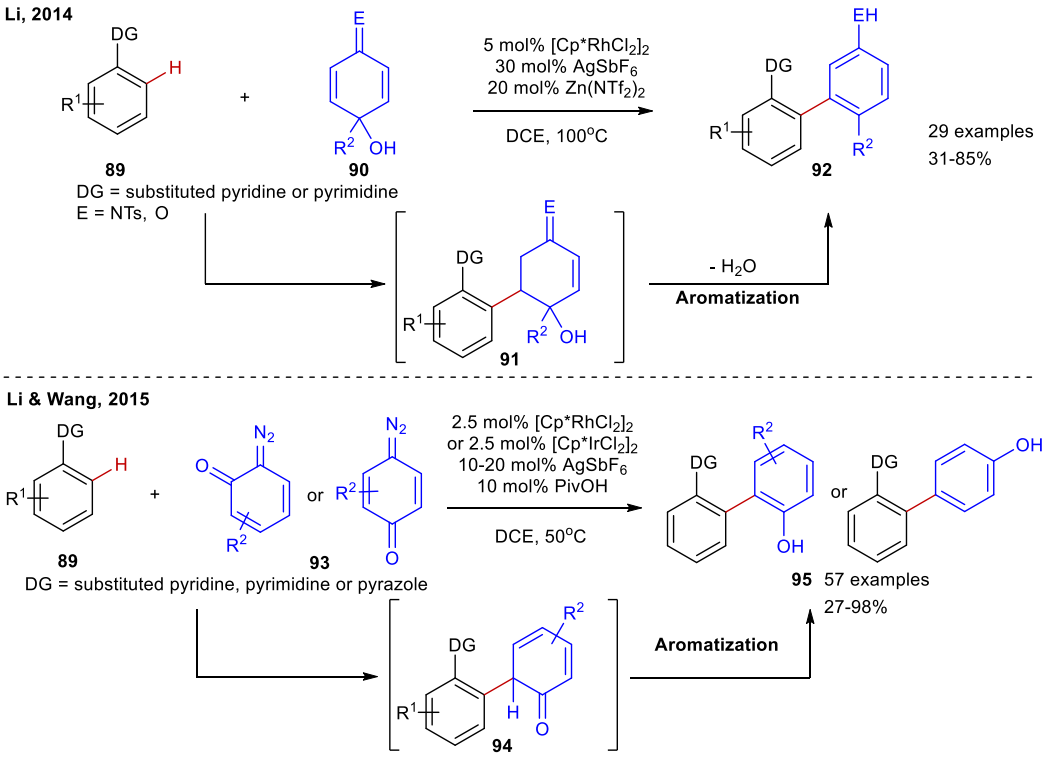
On the other hand, the racemic reactions especially catalyzed by transition metal complexes with Cp* usually act as a starting point to discover application of chiral Cp ligands in asymmetric catalysis. In the field of biaryls synthesis, Cp*Rh(III) and Cp*Ir(III) have been recognized as efficient and attractive catalysts for direct arylation *via* C−H activation to construct versatile aryl-aryl bonds in the last decade.[10,11,82]



Scheme 14. Current methods to access biaryls by Cp* transition metal complexes.

In general, there are three different methods to construct biaryls compounds by using Cp*Rh(III) and Cp*Ir(III) as catalyst (Scheme 14). As the majority of current methods, aryl-aryl coupling assisted by directing group has become the most powerful strategy to construct

biaryls, but with limited examples to date. Among these examples, dehydrogenative coupling (X = H) with two arenes usually requires harsh reaction conditions which is not beneficial for the control of enantioselectivity, although it represents the most convenient and atom-efficient method in biaryl synthesis.[83-90] There are also some examples of oxidative C−H coupling with aryl organometallic reagents such as arylboronic acids and arylsilanes (X = SiR_3, BR_2).[91-93] Very recently, aryl iodides[94] and aryldiazonium salts[95] were identified to be suitable partners for arylations of arenes and even alkenes with proper directing groups. In these cases, relatively milder reaction conditions are required due to the prefunctionalisation of inert C−H bonds. However, in most examples, substitutions in *ortho* position adjacent to aryl-aryl bond are usually not tolerated, which are crucial for the stabilization of axial chiral biaryls. Recently, two methods (**B** and **C**, Scheme 14) were developed by employing 4-hydroxycyclohexa-2,5-dieneones[96] **90** and quinone diazides[97] **93** as arylating reagents, providing an alternative strategy to access biaryl compounds in mild conditions. Notably, both cases involve an aromatization process, which can be regarded as a mechanistically basis for the aforementioned central-to-axial chirality transfer in asymmetric catalysis.



Scheme 15. Two transformations catalyzed by Cp* metal complexes involving aromatization process.

In 2014, Li reported a C−H arylation reaction through a formal Michael reaction/aromatization pathway by employing 4-hydroxycyclohexa-2,5-dieneones **90** as arylating reagents.[96] (Scheme

15) A large spectrum of arylated phenols and anilines **92** could be obtained in moderate to good yield through dehydration of intermediate **91**. In 2015, inspired by the previous reports of Cp*Rh(III) catalyzed C−H functionalization with diazo partners,[98-101] Li and Wang realized a milder C−H arylation reaction with quinone diazides **93** catalyzed by Cp*Rh(III) and Cp*Ir(III), affording varied arylated phenols **95** (Scheme 15).[97] The similar aromatization process of intermediate **94** is also involved in the proposed mechanism. Given the interesting mechanism and mild reaction conditions, these two transformations provide suitable candidates for the application of chiral Cp ligands in the enantioselective synthesis of axially chiral biaryls.

2.2 Design Principle and Aim of the Project

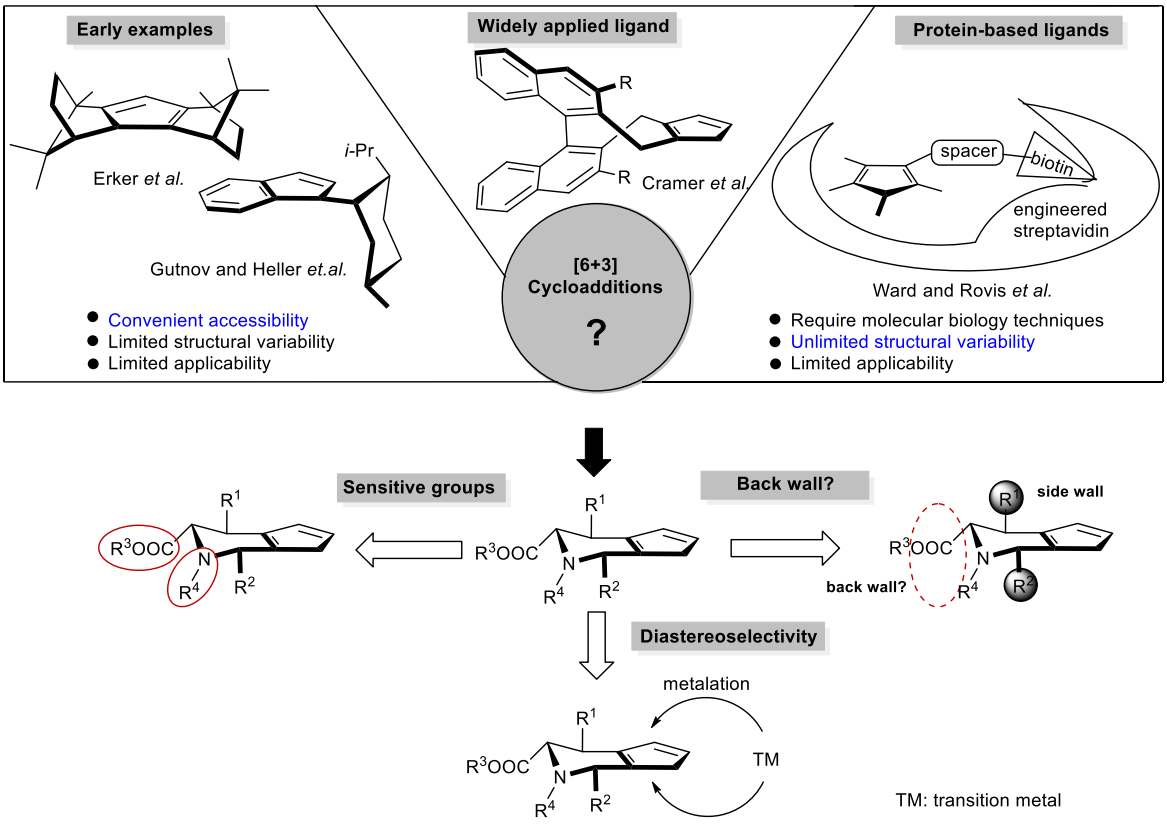


Figure 6. Overview of the current Cp ligands and the application of chiral (6+3) cycloadducts to be ligands.

Throughout the history of chiral Cp derivative synthesis for ligand development, the balance between convenient accessibility and sufficient structural variability is recognized as a long-standing challenge (Fig 6). In the early examples, chiral Cp derivatives derived from the chiral pool such as pulegone, camphor and tartrate indeed can be accessed rapidly. However, for this very reason they are generally lacking structural variability, which severely constrains their potential application as ligands.[24] On the other end, the structures of protein-based Cp

derivatives can be varied rapidly due to the protein nature, but the access to molecular biology techniques is required.[14] Between the two extremes, the Cp derivatives developed by Cramer can be regarded to a compromise with acceptable structural variability and accessibility, leading to considerable progress in this field over the last few years.[38,50] However, for a more general approach to enantioselective catalysis with chiral Cp ligands, novel ligand types would be required which are able to combine the strengths of current approaches.

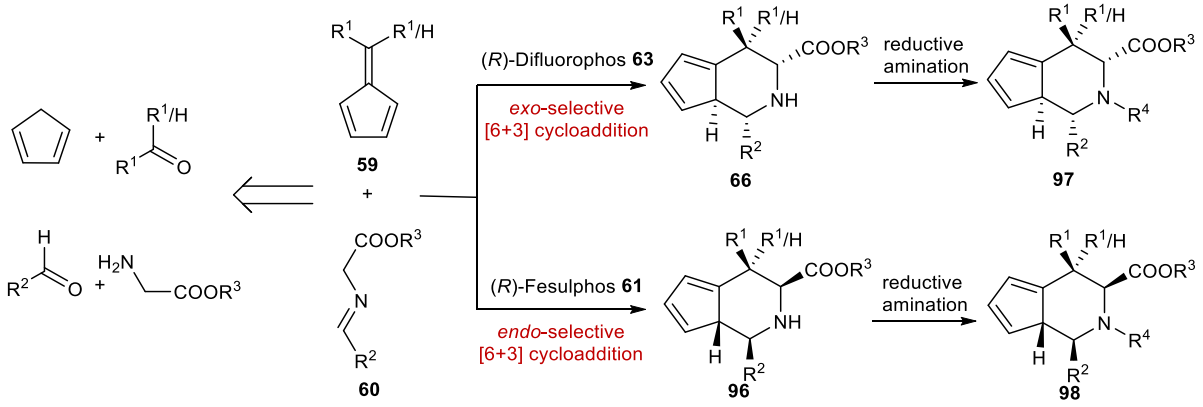
In fact, the enantioselective (6+3) cycloadditions mentioned in **1.1.2** provide a possibility to solve the long-standing challenge abovementioned by providing an approach for the synthesis of chiral Cp derivatives combining the strengths of both accessibility and structural variability. In spite of the obvious advantages compared with the current small molecule Cp derivatives, a few challenges await to be solved as shown in Fig 6: i) some sensitive functional groups embodied in the (6+3) cycloadducts, such as ester, amine, might influence the metal complexation or the catalytic process; ii) diastereomers could be generated during the metal complexation of the non-*C*2-symmetric (6+3) cycloadducts due to face-selectivity; iii) according to the back/side wall hypothesis proposed by Cramer, no functional group in (6+3) cycloadducts can define the back wall, although the side wall can be characterized by the proper functional groups R^1 and R^2.

In this project, to develop and demonstrate (6+3) cycloadducts as efficient ligands, a library of corresponding Rh(I) complexes was planned, considering that chiral Cp-Rh(I) complexes are the most robust and widely applied catalysts in diverse enantioselective reactions to date. At this stage, the possible issues derived from sensitive groups and the lack of *C2*-symmetry need to be investigated and addressed. Sequentially, the applicability and generality of such chiral Rh(I) complexes should be identified first by testing two reported reactions (Scheme 2 and the first example in Scheme 4). If these two reported reactions could be steered in an enantioselective manner, the subsequent aim of this project would be the discovery of unprecedented transformations to demonstrate the flexible applicability of this approach further.

2.3 Results and Discussions

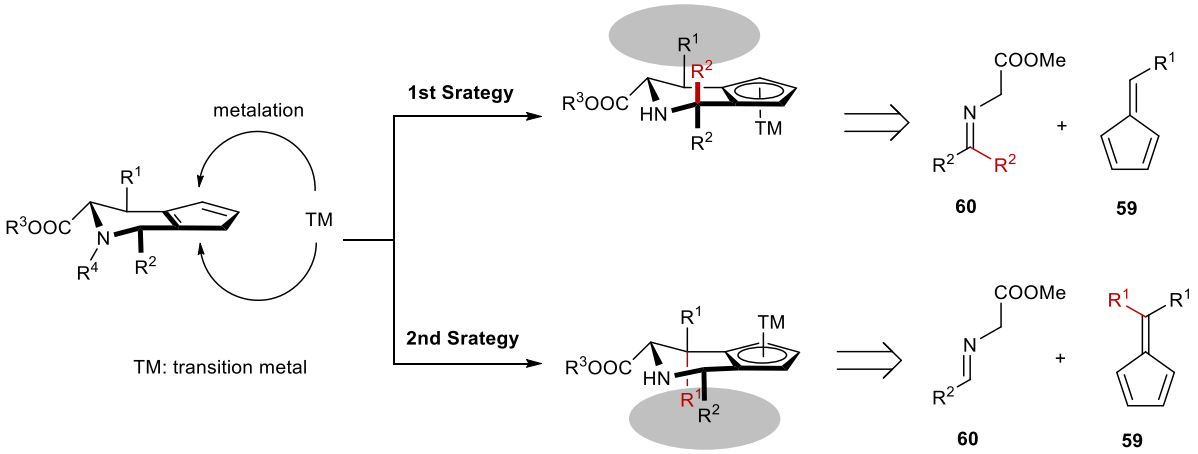
2.3.1 Synthesis of Ligands and Corresponding Rh(I) Complexes

Considering the availability of chiral ligands for (6+3) cycloadditions, two methodologies by employing commercially available ligands **61** and **63** were chosen to access *endo*- and *exo*-selective chiral Cp derivatives (Scheme 16). Starting from simple amino acids, aldehydes, ketones and cyclopentadiene, these enantioenriched Cp derivatives **66** and **96** can be synthesized rapidly with a diverse range of structural variation. As mentioned in **2.1.2**, there are four highly tunable positions in this Cp scaffold including one secondary amine. For modification of the secondary amine, a reductive amination was chosen as a mild and efficient way to obtain alkylated Cp derivatives **97** and **98**, since these Cp derivatives are not stable in transformations with harsher reaction conditions such as alkylation with iodomethane.



Scheme 16. Rapid synthesis of chiral Cp derivatives *via* enantioselective (6+3) cycloadditions.

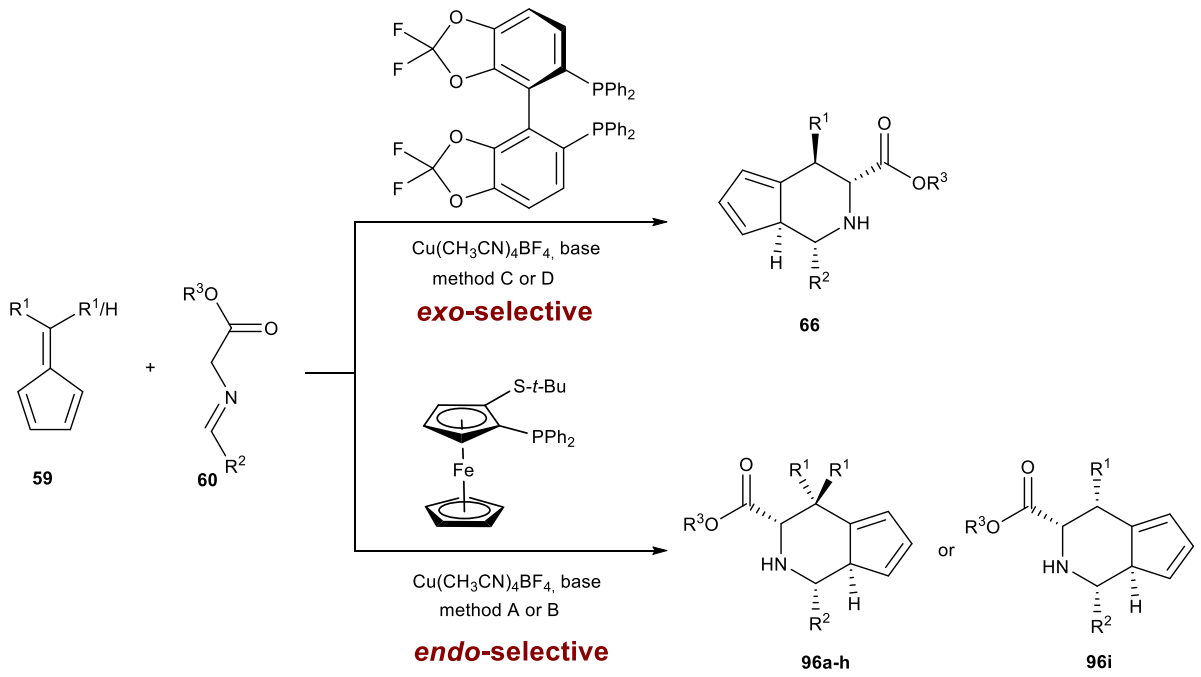
In addition, to address the possible issue of diastereoselectivity in the metalation process, two strategies were envisioned based on the hypothesis that the installation of additional substitution on α position of cyclopentadiene moiety might block the metal complexation to one face of (6+3) cycloadducts to some extent or completely (Scheme 17). For the first strategy, additional R^2 substitution can be generated from disubstituted imine **60**. However, the corresponding disubstituted imines failed to give isolable (6+3) cycloadducts even after intensive condition optimization. Gratifyingly, the desired (6+3) cycloadducts from diverse disubstituted fulvenes **59** could be accessed smoothly in moderate ee by using commercial ligands (*R*)-Fesulphos through *endo*-selective (6+3) cycloadditions.



Scheme 17. Two strategies to address possible diastereoselectivity of metalation.

Based on all the aforementioned considerations, two categories of Cp derivatives (**66** and **96**) were prepared by *endo*- and *exo*-selective (6+3) cycloadditions under various optimized conditions (*see 7.2.1*). Collectively, 22 Cp derivatives without modification of secondary amine were synthesized (Table 1).

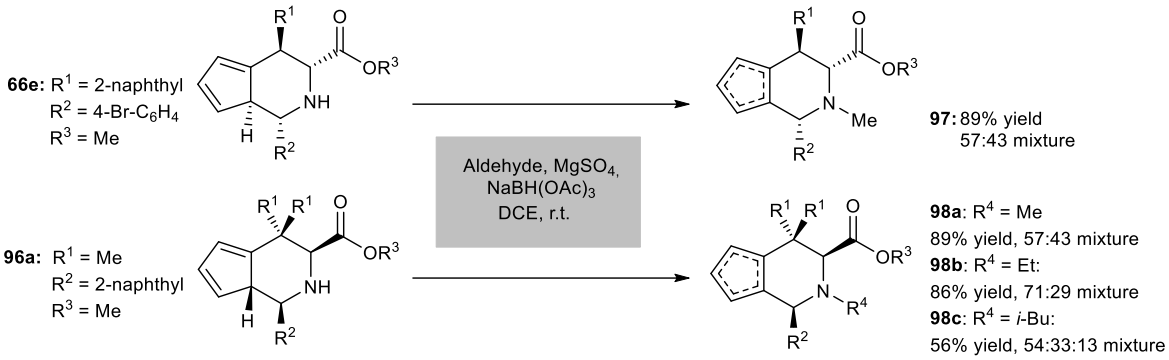
Table 1. Synthesis of chiral Cp ligands by asymmetric (6+3) cycloadditons.



Ligands	Method[a]	R^1	R^2	R^3	yield(%)	ee(%)[b]
96a[c]	A	Me	2-naphthyl	Me	73	70
96b	A	Et	2-naphthyl	Me	57	60
96c	B	-$(CH_2)_3$-	2-naphthyl	Me	89	29
96d	B	-$(CH_2)_5$-	2-naphthyl	Me	90	66
96e	A	Me	4-Br-C_6H_4	Me	83	62
96f	A	Me	4-Me-C_6H_4	Me	77	67
96g	A	Me	2-Me-C_6H_4	Me	78	66
96h	A	Me	2-naphthyl	Et	83	71
96i	B	2-naphthyl	4-Br-C_6H_4	Me	57	96
66a	C	4-Br-C_6H_4	4-Me-C_6H_4	Et	61	92
66b	C	4-Br-C_6H_4	4-Br-C_6H_4	Et	82	96
66c	C	4-Br-C_6H_4	4-F-C_6H_4	Et	82	96
66d	C	4-Br-C_6H_4	2-Me-C_6H_4	Et	50	72
66e	C	2-naphthyl	4-Br-C_6H_4	Me	82	96
66f	C	4-Me- C_6H_4	4-CF_3-C_6H_4	Et	82	97
66g	C	4-Br-C_6H_4	4-CF_3-C_6H_4	Et	70	96
66h	C	4-Cl-C_6H_4	4-CF_3-C_6H_4	Et	67	96
66i	C	*i*-Pr	4-CF_3-C_6H_4	Et	31	89
66j	C	2-naphthyl	4-CF_3-C_6H_4	Et	82	98
66k[d]	D	4-Br-C_6H_4	4-F-C_6H_4	Me	74	>99
66l	C	4-Br-C_6H_4	4-F-C_6H_4	Bn	50	96
66m	C	4-Br-C_6H_4	4-Me-C_6H_4	Me	66	95

[a] Using Method A-D as shown in experimental part. [b] Determined by HPLC analysis. [c] The optical pure form of this ligand could be prepared in gram scale by preparative HPLC of its racemate. Conditions: CHIRAPAK IC column, *iso*-propanol / heptane = 15/85, flow rate = 4 mL min^{-1}, t = 6.8 min, 9.8 min. [d] The optical pure form of ligand was prepared by the recrystallization of corresponding asymmetric (6+3) cycloadduct with 95% ee.

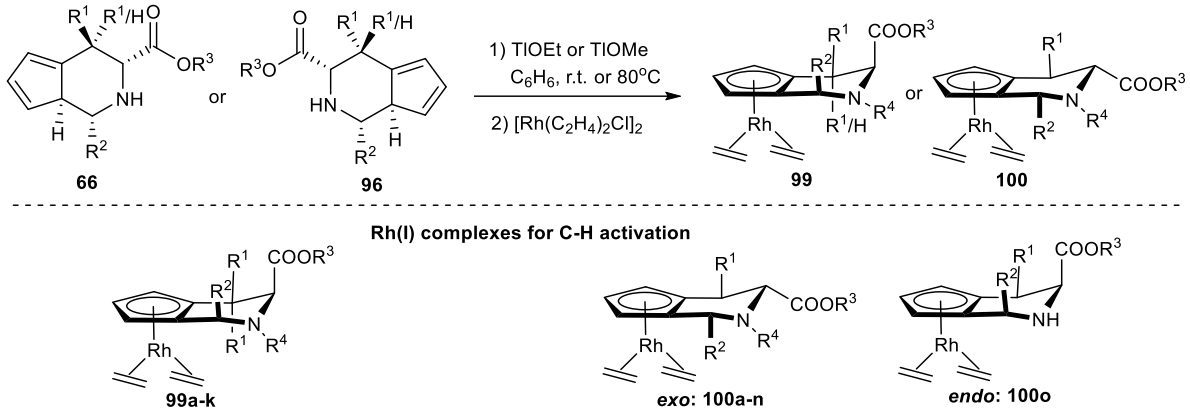
Additionally, alkylated Cp derivatives (**97** and **98**) were also synthesized by reductive amination to investigate the possible influence of secondary amine on catalytic process and enantioselectivity (Scheme 18). Notably, mixtures of isomers were found for alkylated Cp derivatives due to the isomerization of Cp moiety during reductive amination.



Scheme 18. Synthesis of alkylated Cp ligands by reductive amination with aliphatic aldehydes.

With the enantioriched Cp derivatives in hand, intensive optimization of Rh(I) complexation was performed. Four different methods (*see 7.2.2*) were developed for corresponding Rh(I) complexes based on a few considerations. At first, the acidity of proton on Cp moiety differentiates dramatically according to substitutions on R^1 and R^2. Hence, the deprotonation process by thallium alkoxides turned out to be quite sensitive to reaction temperature. Another consideration is based on the observation of transesterification between sensitive ester group of (6+3) cycloadducts and different alkoxides to various degrees. Additionally, Rh(I) complexes are rather unstable in the process of purification, especially on silica. The utilization of neutral Al_2O_3 and Ar pressure proved to be beneficial for the reactivity and yield of Rh(I) complexes. Notably, a special design of chromatography combining neutral Al_2O_3 and neutralized silica is critical to isolate the individual diastereomer of Rh(I) complexes (*see 7.2.2*). After the establishment of robust metalation and purification methods for Cp derivatives, a total of 30 chiral Rh(I) complexes were obtained, which can be divided into two categories (**99** and **100**) based on di- or monosubstitution of R^1 (Table 2). As expected, most catalysts were obtained as mixtures of diastereomers due to the lack of face-selectivity upon metalation. The aforementioned strategy to address face-selectivity of metalation of non-*C2*-symmetric (6+3) cycloadducts with di-substitution of R^1 turned out to be feasible, leading to better diastereoselectivity in the formation of Rh(I) complexes upon metalation (**99a-h**) compared with (6+3) cycloadducts with mono-substitution of R^1 (**100a-n**).

Table 2. Synthesis of Rh(I) complexes.



catalys	method[a]	R^1	R^2	R^3	R^4	yield(%)	d.r.	ee(%)[b]
99a	E	Me	2-naphthyl	Me	H	71	>95:5	70
99b	E	Et	2-naphthyl	Me	H	71	72:28	60
99c	E	-$(CH_2)_3$-	2-naphthyl	Me	H	74	76:24	29
99d	E	-$(CH_2)_5$-	2-naphthyl	Me	H	63	90:10	66
99e	E	Me	4-Br-C_6H_4	Me	H	54	>95:5	62
99f	E	Me	4-Me-C_6H_4	Me	H	62	85:15	67
99g	E	Me	2-Me-C_6H_4	Me	H	78	86:14	66
99h	H	Me	2-naphthyl	Et	H	67	84:16	71
99i	E[c]	Me	2-naphthyl	Me	Me	81	>95:5	100
99j	E[c]	Me	2-naphthyl	Me	Et	45	>95:5	100
99k	E[c]	Me	2-naphthyl	Me	*i*-Bu	82	55:45	100
100a	F	4-Br-C_6H_4	4-Me-C_6H_4	Et	H	78	60:40	92
100b	F	4-Br-C_6H_4	4-Br-C_6H_4	Et	H	60	57:43	96
100c	F	4-Br-C_6H_4	4-F-C_6H_4	Et	H	76	58:42	96
100d	F	4-Br-C_6H_4	2-Me-C_6H_4	Et	H	66	56:44	72
100e	G	2-naphthyl	4-Br-C_6H_4	Me	H	65	50:50	96
100f	G	2-naphthyl	4-Br-C_6H_4	Me	Me	81	55:45	96
100g	F	4-Me-C_6H_4	4-CF_3-C_6H_4	Et	H	80	62:38	97
100h	F	4-Br-C_6H_4	4-CF_3-C_6H_4	Et	H	79	59:41	96
100i	F	4-Cl-C_6H_4	4-CF_3-C_6H_4	Et	H	59	57:43	96

Continuation of Table 2

100j	F	*i*-Pr	4-CF_3-C_6H_4	Et	H	65	67:33	89
100k	F	2-naphthyl	4-CF_3-C_6H_4	Et	H	83	59:41	98
100l	G[d]	4-Br-C_6H_4	4-F-C_6H_4	Me	H	79	60:40	>99
100m	G	4-Br-C_6H_4	4-F-C_6H_4	Bn	H	74	50:50	96
100n	G	4-Br-C_6H_4	4-Me-C_6H_4	Me	H	82	57:43	95
100o	G	2-naphthyl	4-Br-C_6H_4	Me	H	88	>95:5	96

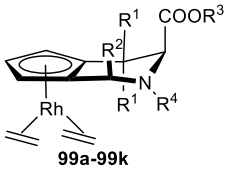
[a] Using Method E-H as shown in experimental part. [b] Determined by ee of corresponding ligands through HPLC analysis. [c] The optical pure form of ligand was prepared by preparative HPLC on chiral phase. [d] The optical pure form of ligand was prepared by recrystallization of corresponding asymmetric (6+3) cycloadduct with 95% ee.

Initially, ligands with moderate to excellent enantioselecetivity were synthesized through catalytic enantioselective methodologies due to relatively simplified preparation. Since Cp ligands are not optically pure, a concept of chirality transfer (CT) was proposed to evaluate the efficiency of chirality induction of a specific ligand. Based on its definition, chirality transfer (CT) = $ee_{prod}/ee_{cat} = ee_{max}$. The ee_{max} also represents the ee of product when ee_{cat} is 100%.[102] However, chirality transfer (CT) as an indicator to screen catalysts can only be feasible under the assumption of linear relationship between ee of catalyst and ee of products for the target reaction. Fortunately, this assumption has been substantially proven by the first model reaction involving enantioselective synthesis of isoquinolinones (*see 7.2.3.1, Fig. S1*).

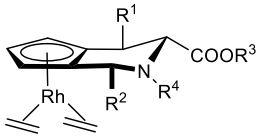
2.3.2 Enantioselective Synthesis of Isoquinolinones as a Model Reaction

To explore the potential of obtained Rh(I) complexes, the C–H functionalization of hydroxamates with alkenes catalyzed by Cp*Rh(III) as shown in Scheme 2 was investigated. As menthioned above, Ward and Rovis as well as Cramer developed two complementary strategies to design and synthesize chiral Cp ligands by using the same transformation in 2012, respectively (Scheme 2).[13,14]

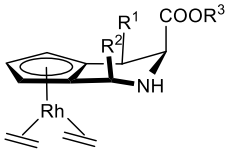
Table 3. Catalysts optimization.[a]



99a, R^1 = Me, R^2 = 2-Naphthyl, R^3 = Me, R^4 = H
99b, R^1 = Et, R^2 = 2-Naphthyl, R^3 = Me, R^4 = H
99c, R^1 = -$(CH_2)_3$-, R^2 = 2-Naphthyl, R^3 = Me, R^4 = H
99d, R^1 = -$(CH_2)_5$-, R^2 = 2-Naphthyl, R^3 = Me, R^4 = H
99e, R^1 = Me, R^2 = 4-Br-C_6H_4, R^3 = Me, R^4 = H
99f, R^1 = Me, R^2 = 4-Me-C_6H_4, R^3 = Me, R^4 = H
99g, R^1 = Me, R^2 = 2-Me-C_6H_4, R^3 = Me, R^4 = H
99h, R^1 = Me, R^2 = 2-Naphthyl, R^3 = Et, R^4 = H
99i, R^1 = Me, R^2 = 2-Naphthyl, R^3 = Me, R^4 = Me
99j, R^1 = Me, R^2 = 2-Naphthyl, R^3 = Me, R^4 = Et
99k, R^1 = Me, R^2 = 2-Naphthyl, R^3 = Me, R^4 = *i*-Bu



100f, R^1 = 4-Br-C_6H_4
R^2 = 2-Naphthyl
R^3 = Me
R^4 = Me



100o, R^1 = 2-Naphthyl
R^2 = 4-Br-C_6H_4
R^3 = Me
R^4 = H

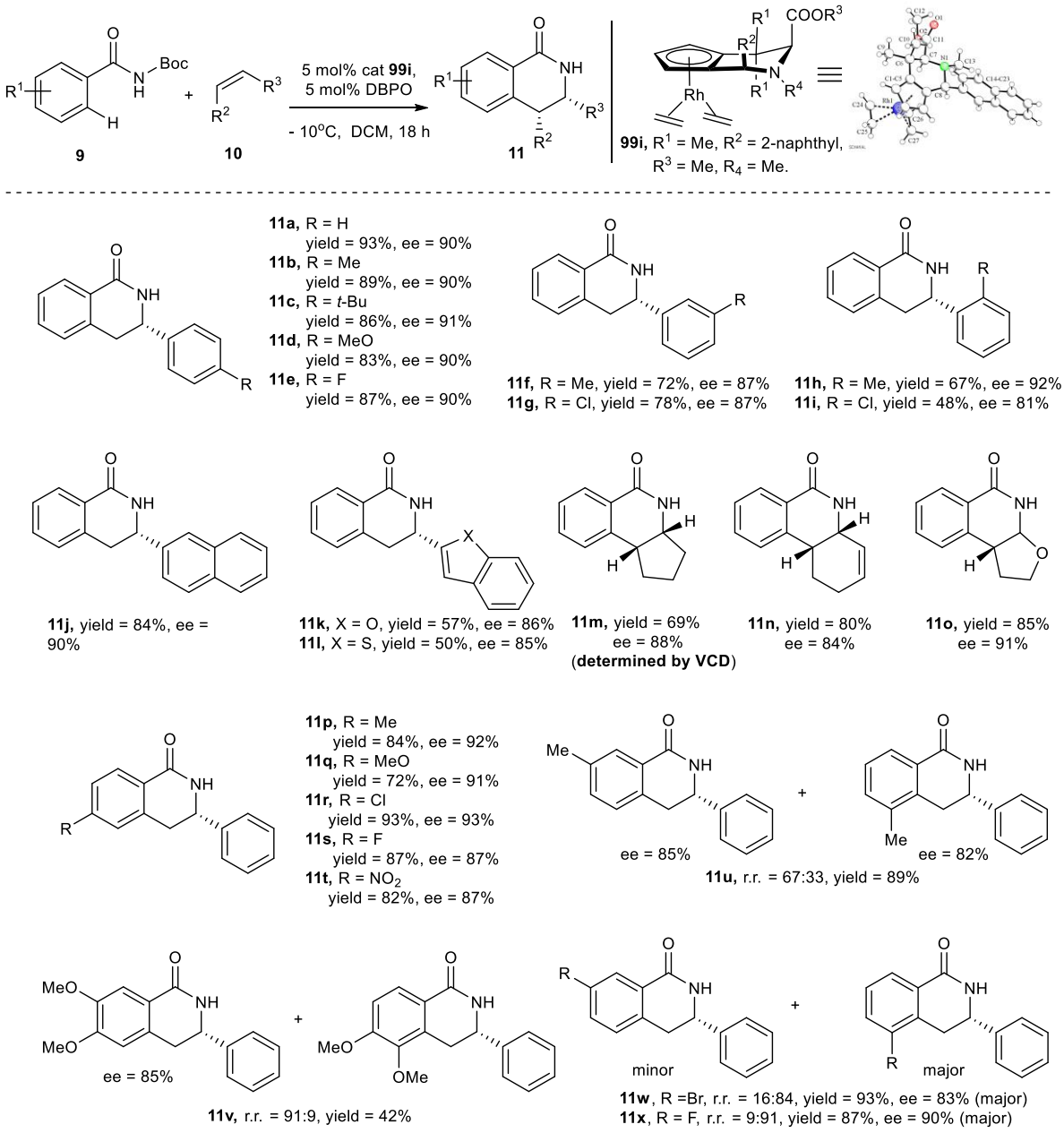
Entry	cat[c]	ee of cat (%)	ee of product (%)	CT	t (h)	yield (%)
1	**100f**[d]	96	60	63	1	67
2	**100o**[d]	96	21	22	1	81
3	**99a**	100	68	68	1	90
4	**99b**	60	38	63	1	67
5	**99c**	29	18	62	1	90
6	**99d**	66	24	36	1	58
7	**99e**	62	43	69	1	76
8	**99f**	67	41	61	1	72
9	**99g**	66	44	67	1	67
10	**99h**[c]	71	46	65	1	52
11	**99i**	**100**	**83**	**83**	**4**	**90**
12	**99j**	100	76	76	18	49
13	**99k**[c]	100	78	78	18	54

[a] General procedure: Rh(I) catalyst (5.00 μmol, 0.05 equiv.), $(BzO)_2$ (75 wt%, 5.00 μmol, 0.05 equiv.), hydroxamate **9** (0.10 mmol, 2.00 equiv.) were dissolved into 1 mL DCM. After stirring at r.t. for 10 mins, corresponding alkenes **10** (0.20 mmol, 2.00 equiv.) was added and the reaction was stirred for specific time. [b] Chirality transfer (CT) = $ee_{prod}/ee_{cat} = ee_{max}$, ee_{max}: the ee of product when ee_{cat} is 100%. [c] Unless otherwise noted, catalyst was used as single isomer or major isomer. [d] Catalyst was used as mixture of two isomers.

Preliminary study revealed that sensitive groups of Cp ligands had no detrimental influence on the catalytic process, and the desired isoquinolinone **11a** could be obtained smoothly in high

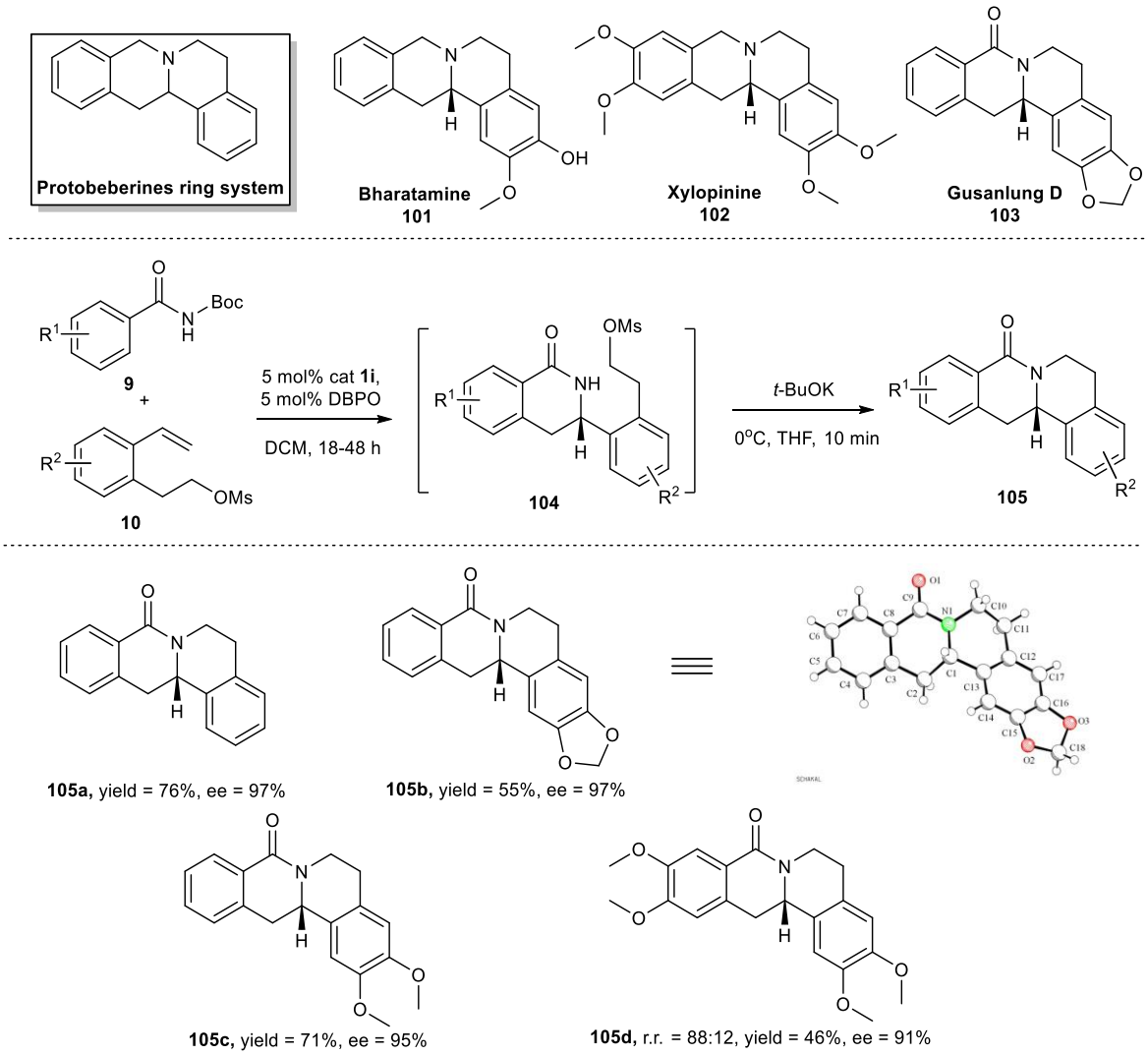
yield (Table 3). The optimization of catalyst was initiated from R^1 substituents originating from different ketones or aldehydes (Table 3, entries 1-6). The methyl group proved to be optimal for disubstituted R^1, with which the corresponding Rh(I) complex **99a** gave the desired product with 68% CT in 90% yield. Other groups on R^1 resulted in either lower reactivity or enantioselectivity. Then, an intensive screening of R^2 was performed (Table 3, entries 7-9). R^2 was identified to be critical for the enantioselectivity and the 2-naphthyl group turned out to be optimal. In addition, the possible effect of R^3 was also investigated, and bulkier groups than methyl such as benzyl led to lower reactivity but with similar enantioselectivity (Table 3, entry 10). At this stage, the optimal Cp ligand **96a** was obtained in optically pure form by separation of enantiomers of racemic **96a** by preparative HPLC on chiral phase in gram scale. After optimization of R^1, R^2 and R^3, the protecting group on secondary amine was identified to be crucial for both enantioselectivity and reactivity. Finally, the ligand with methyl as protective group on the nitrogen (catalyst **99i**) produced the desired product in 90% yield and with 83% ee. Larger groups such as ethyl and isopropyl resulted in the decrease of both reactivity and enantioselectivity. (Table 3, entries 11-13) The absolute configuration of catalyst **99i** was determined by X-ray crystallographic analysis (by Dr. Constantin G. Daniliuc).

With optimal catalyst (**99i**) in hand, the optimization of reaction conditions was carried out (*see 7.2.3.1, Table S1*). Solvents showed obvious effects on reactivity but no influence on enantioselectivity. Moreover, reducing the temperature to -10°C promoted the ee to 90%. After establishing the optimal reaction conditions, the substrate scope was subsequently explored. As outlined in Scheme 19, various styrenes even with various hetero aromatic substitutions were tolerated in this reaction, affording desired products **11a-11l** in excellent enantioselectivity and yield. Cyclic alkenes were suitable for this catalysis sysmtem (**11m-11o**). Surprisingly, *ortho*–substituted styrenes afforded the desired products **11h** and **11i**, which has not been reported for this transformation in chiral or racemic manner.[13,14,35,36] For aryl hydroxamates, substrates with varied electronic and steric properties of substitutions were compatible with this reaction, affording the desired products **11p-11x**. Notably, different electronic properties of substitutions on *meta* position resulted in the reversed regioselectivity of products.



Scheme 19. Substrate scope for the enantioselective synthesis of isoquinolinones.

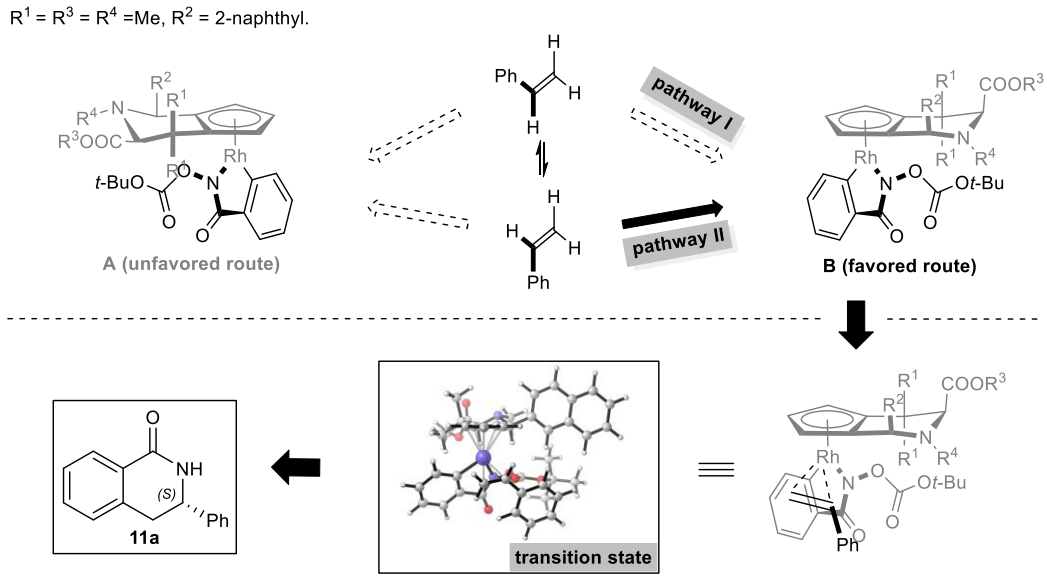
Protoberberines are an important class of naturally occuring tetracyclic isoquinoline alkaloids with diverse biological activities, such as Bharatamine (**101**), Xylopinine (**102**) and Gusanlung (**103**).[103,104] Facilitated by the unique catalytic property of catalyst for *ortho*-substituted styrenes, the synthesis of protoberberines analogs **105a-105d** was achieved by a cascade reaction with a sequence of C–H functionalization followed by intramolecular S_N2 reaction of **104** in one-pot manner (Scheme 20).



Scheme 20. Synthesis of protoberberines analogs in one-pot manner.

To support the rationale of regioselectivity and enantioselectivity of this transformation, preliminary computational studies were performed by Dr. Christian Merten. In theory, there are four possible stereoisomers based on two regioisomers with the phenyl group at 3- and 4-positions, of which only the *S* configuration of the 3-substituted regioisomer **11a** was found experimentally. The excellent regioselectivity can be rationalized by the calculations as all pathways to the 4-substituted regioisomers feature transition state barriers which are approximately 2 kcal/mol higher than those leading to the 3-substituted regioisomers. Hence, from a kinetic perspective, and in agreement with the experimental findings, the pathways leading to the 4-substituted regioisomer can be excluded from the analysis. As for the enantioselectivity of 3-substituted regioisomers, previous mechanistic considerations suggested a preferred structure of the rhodacycle intermediate in which the Boc protective group is located on the sterically less hindered side, and styrene approaches the rhodacycle

intermediate with phenyl pointing away from Cp ligand to avoid unfavorable steric interaction.[13] Accordingly, in the present case, Boc would point towards the 2-naphthyl group (substituent R^2) bearing side of the ligand (intermediate **B**, Scheme 21). On the other hand, styrene should approach in the same way (pathway II, Scheme 21), while the other orientation of styrene would be less favorable (pathway I, Scheme 21). For the calculations, it's also considered that the hydroxamate is in its presumably less favored orientation with respect to the Boc group pointing towards the methyl groups (substituents R^1, intermediate **A**, Scheme 21). In addition, two different orientations of the Boc carbonyl group were taken into account, so that in total four conformers of the rhodacycle intermediate were investigated. Besides, two opposite ways of styrene to approach the rhodacycle intermediate were also taken into consideration. Through analyzing the free energy profiles of all pathways, previous stereochemical model proposed by Cramer group was strongly supported.

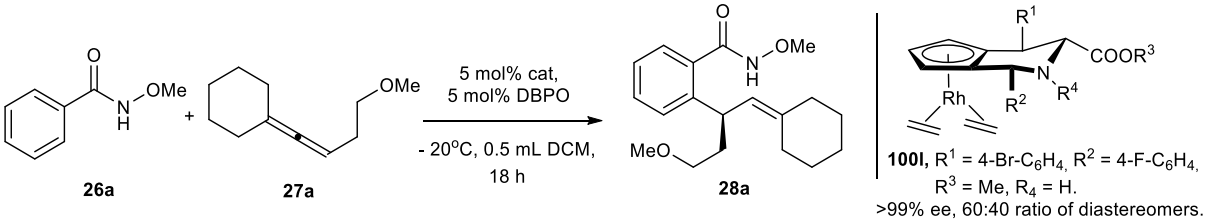


Scheme 21. Computation study on reaction mechanism for the isoquinolinone derivative synthesis.

2.3.3 Enantioselective C−H Allylations of Benzamides as a Model Reaction

In order to further investigate the generality and the flexible applicability of this Cp ligands library, asymmetric C–H allylation of benzamides was investigated as the second model reaction, previously reported by Cramer using chiral binaphthyl-substituted Cp ligands[37] as shown in Scheme 4. In the seminal work, cyclohexyl-substituted chiral Cp ligands successfully applied in the asymmetric synthesis of isoquinolinones could not induce high enantioselectivity in this transformation. By analogy, only 24% ee could be obtained by using optimal catalyst **99i** in the asymmetric synthesis of isoquinolinones (Table 4, entry 3). Delightfully, screening of ligand library revealed that catalyst **100a** derived from a chiral Cp ligand equipped with two aryl groups in *trans* manner is efficient for this enantioselective transformation, delivering up to 86% CT without diminishing the reactivity (Table 4, entry 6). Systematic optimization of substituents R^1 and R^2 in ligands revealed that for this specific transformation *ortho* substituted aryl or aliphatic groups led to decreased enantioselectivity (Table 4, entries 9 and 15), whereas ligands with *para*- or *meta*- substituted aryl groups had no significant influence on enantioselectivity. Furthermore, R^3 had no significant effect on enantioselectivity, but other esters bulkier than methyl ester led to decreased reactivity (Table 4, entries 8, 17 and 18). Contrary to optimal catalyst **99i** in the isoquinolinone synthesis, *N*-methylation of secondary amine resulted in a sluggish reaction and decreased enantioselectivity (Table 4, entry 11). Eventually, catalyst **100l** turned out to be optimal. The corresponding ligand of catalyst **100l** can be readily prepared with > 99% ee on gram scale by recrystallization of chiral (6+3) cycloadduct.

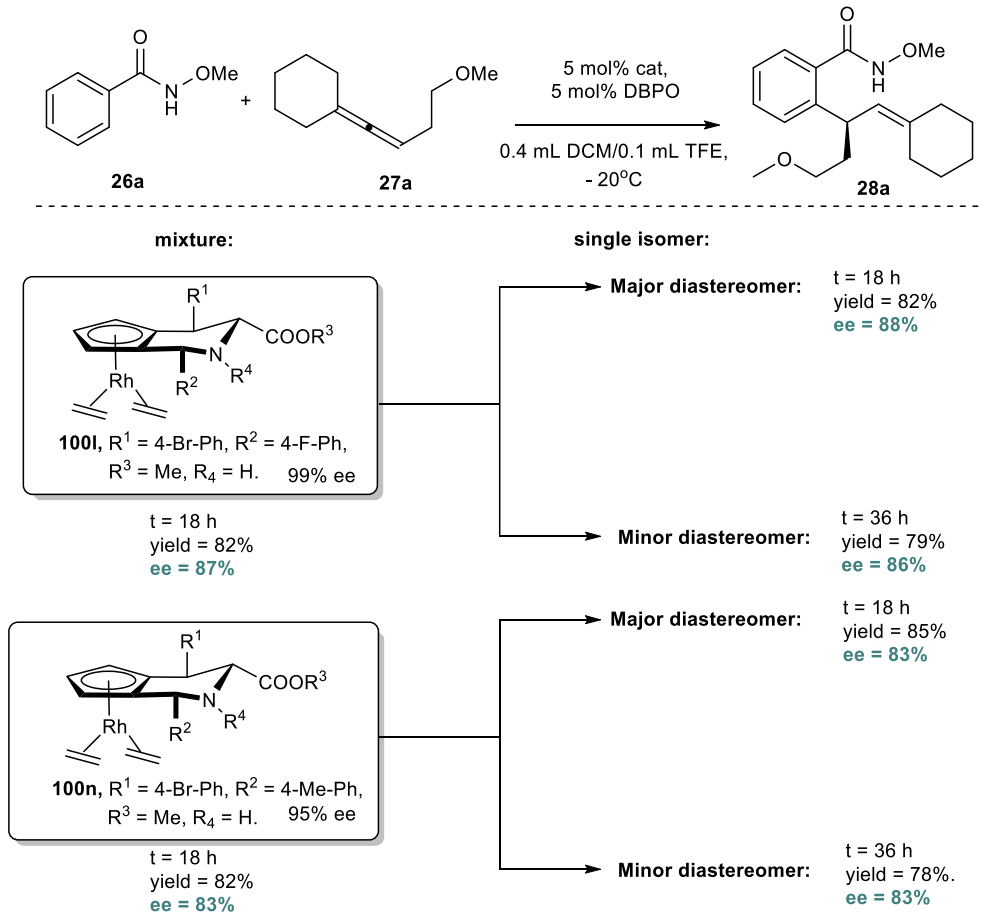
Table 4. Catalysts optimization.[a]



Entry	cat[c]	ee of cat (%)	ee of product (%)	CT (%)[b]	yield (%)
1	**99a**[d]	100	21	21	76
2	**99d**[d]	66	32	48	66
3	**99i**[d]	100	24	63	82
4	**99j**[d]	100	<5	<5	76
5	**99k**	100	13	13	79
6	**100a**	92	79	86	78
7	**100b**	96	84	88	85
8	**100c**	96	84	88	85
9	**100d**	72	59	82	85
10	**100e**	96	82	85	79
11	**100f**	96	80	83	51
12	**100g**	97	85	88	85
13	**100h**	96	85	88	82
14	**100i**	96	85	88	82
15	**100j**	89	64	72	50
16	**100k**	98	86	88	82
17	**100l**	**99**	**87**	**88**	**87**
18	**100m**	96	85	89	67
19	**100n**	95	83	87	82
20	**100o**	96	0	0	63

[a] Catalyst (5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.) and **26a** (0.12 mmol, 1.20 equiv.) were dissolved into 0.5 mL DCM. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to -20°C, corresponding allenes **27a** (0.1 mmol, 1.00 equiv.) was added and the reaction was stirred for 18 hours. [b] Chirality transfer (CT) = $ee_{prod}/ee_{cat} = ee_{max}$, ee_{max}: the ee of product when ee_{cat} is 100%. [c] Unless otherwise noted, catalyst was used as mixture of two isomers. [d] Catalyst was used as single isomer or major isomer.

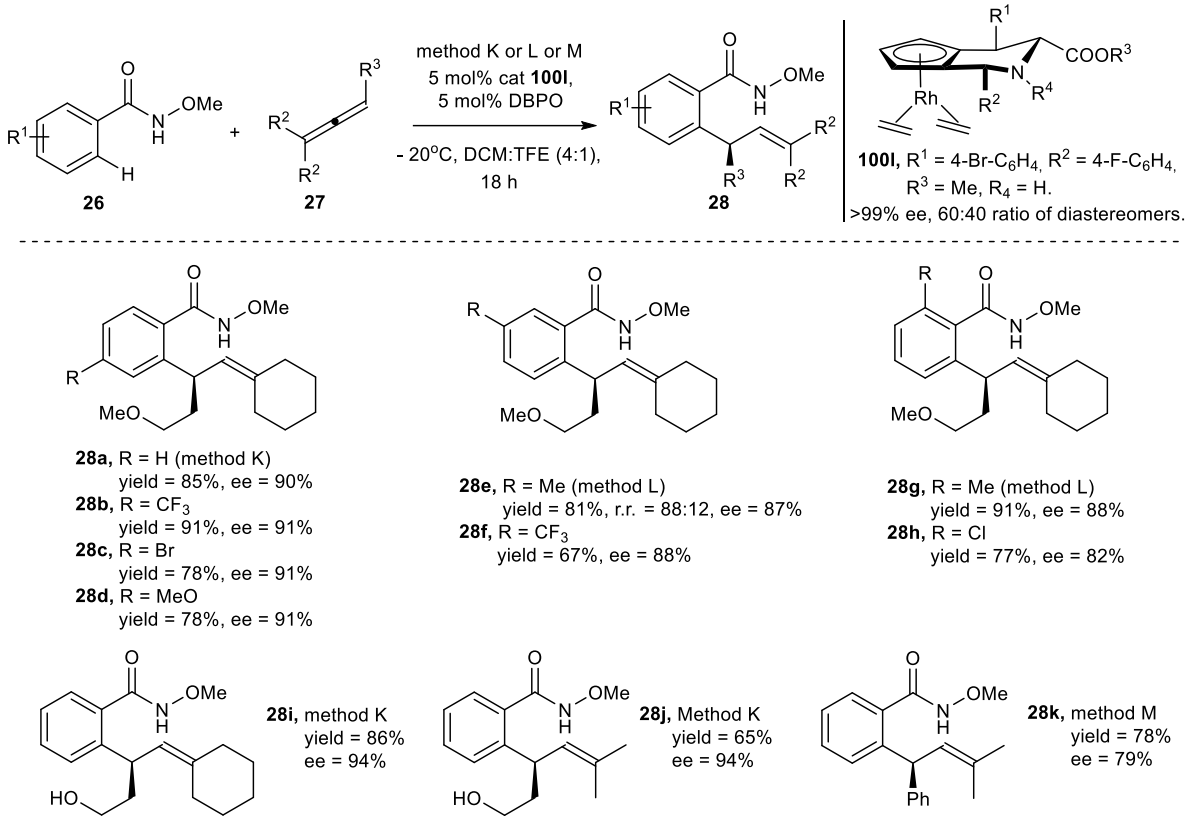
The subsequent optimization of reaction conditions disclosed that the reactivity could be influenced dramatically by solvent, but not for enantioselectivity (*see 7.2.4.1, Table S2*). A 4:1 combination of dichloromethane (DCM) and trifluoroethanol (TFE) proved to be optimal, giving the desired product in 85% yield and with 90% ee within 18 h at -20°C. Since Rh(I) complex **100** is a mixture of diastereomers (Table 2), investigation of the possible difference between two diastereomers of the Rh(I) complex was carried out under optimized reaction conditions, revealing that there was no significant difference between two diastereomers of optimal catalyst **100l** in terms of stereoselectivity (Scheme 22). This observation was confirmed by the same experiment on catalyst **100n**. Hence, Rh(I) complex **100l** was utilized as a mixture of two diastereomers in the further transformations.



Scheme 22. Investigation of difference between two diastereomers of Rh(I) complexes **2l** and **2n**.

Evaluation of the substrate scope (Scheme 23) showed that different substitution patterns on benzamides were suitable, affording products **28a-28h** with good to excellent ee and yield. Additionally, this transformation was also compatible with various allenes (**28i-28k**). Methods **K-M** were employed according to specific benzamides and allenes, either to avoid double

allylation of bezamides or to enhance reactivity by means of increasing concentration (*see 7.2.3.3*).



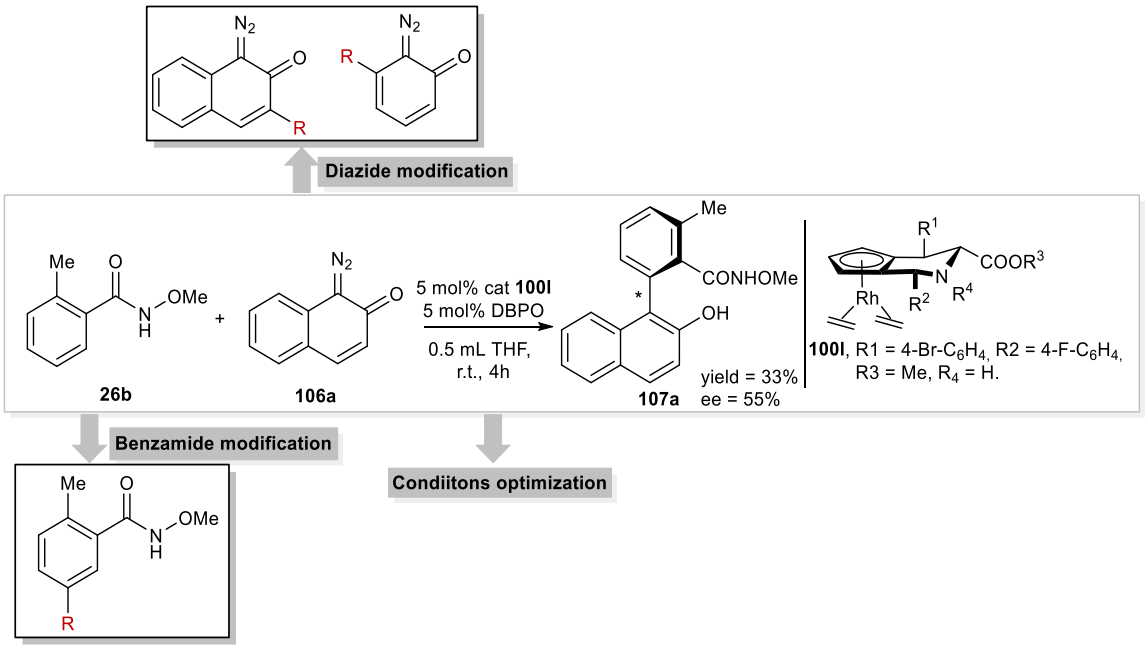
Scheme 23. Substrate scope for enantioselective C−H allylations of benzamides.

2.3.4 Application of Newly Developed Cyclopentadienyl Ligands in Enantioselective Synthesis of Axially Chiral Biaryls

Besides the successful applications in reported reactions, an unprecedented asymmetric reaction was developed to further demonstrate the flexible applicability of this Cp ligands library. As presented in **2.1.3**, asymmetric catalysis to access axially chiral biaryls is still relatively underdeveloped compared with central chirality in spite of the importance of chiral biaryls in NPs, chiral auxiliaries, ligands and catalysts (Fig. 5). To date, there are only a few available strategies to construct axially chiral biaryls in catalytic manner (Scheme 10). Among them, central-to-axial chirality transfer represents an elegant strategy involving destruction of a stereogenic element and a simultaneous formation of different stereogenic element. Even though it has been proposed for more than 60 years, successful catalytic examples by this strategy are still scarce. In the last two years, the strategy of central-to-axial chirality transfer has shown tremendous potential to be a highly efficient way for synthesizing such valuable compounds in the field of organocatalysis (Scheme 11 and 12). However, there is no successful

application of this promising strategy in the transformations steered by chiral Cp ligands (Scheme 13).

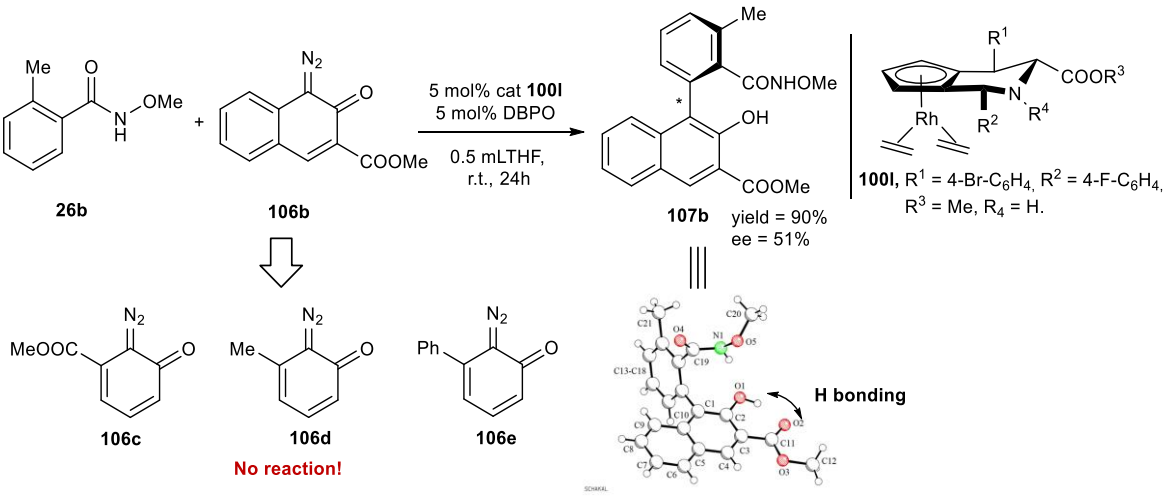
Recently two independent groups reported alternative synthesis of biaryls catalyzed by Cp* transition metal complexes with 4-hydroxycyclohexa-2,5-dieneones and quinone diazides as coupling partners (Scheme 15). These two reports provide the mechanistic basis for possible application of central-to-axial chirality transfer strategy enabled by chiral Cp ligands. Between them, quinone diazides were chosen as substrates for the possible application in asymmetric catalysis, since the corresponding reaction is more efficient and milder.



Scheme 24. Preliminary result and future plan for optimization.

Preliminary study was carried out with benzamide **26a** and diazonaphthoquinone **106a** as standard substrates. The reason for choosing benzamide **26a** is the *ortho*-methyl group can inhibit possible bi-arylated product, simplifying the process of purification and analysis. There are two main considerations for employing diazonaphthoquinone **106a**. On one hand, diazonaphthoquinone **106a** is capable of providing two *ortho*-substitutions adjacent to aryl-aryl bond, leading to stabilized axial chirality. In addition, diazonaphthoquinone is one of the most reactive quinone diazides. After initial reaction conditions optimization, catalyst **100l** could afford the desired product **107a** with up to 55% ee, albeit with poor yield (Scheme 24). Screening of solvents, temperature and even catalysts did not improve enantioselectivity (*see 7.2.5.1, Table S3*). Based on the preliminary result, three approaches were proposed to solve

the issues of reactivity and enantioselectivity, including the modification on the diazo part and benzamide part, and the optimization of reaction conditions (Scheme 24).

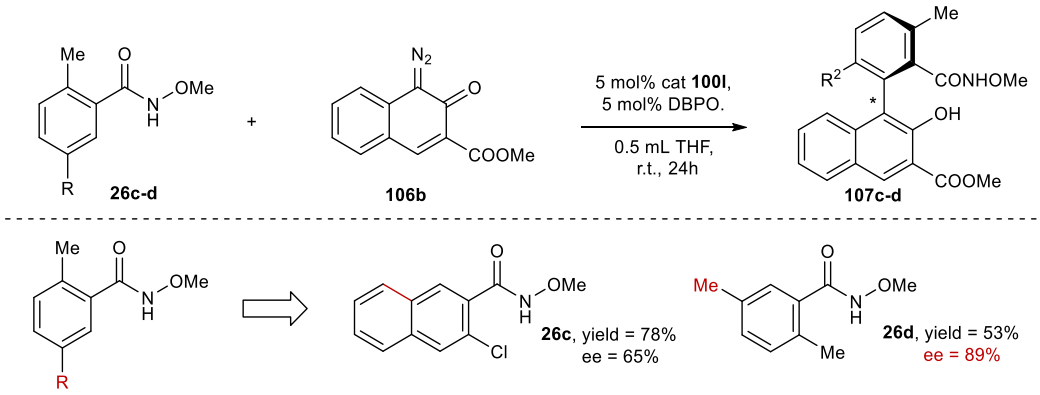


Scheme 25. Investigation on the modification of diazo compounds and benzamides.

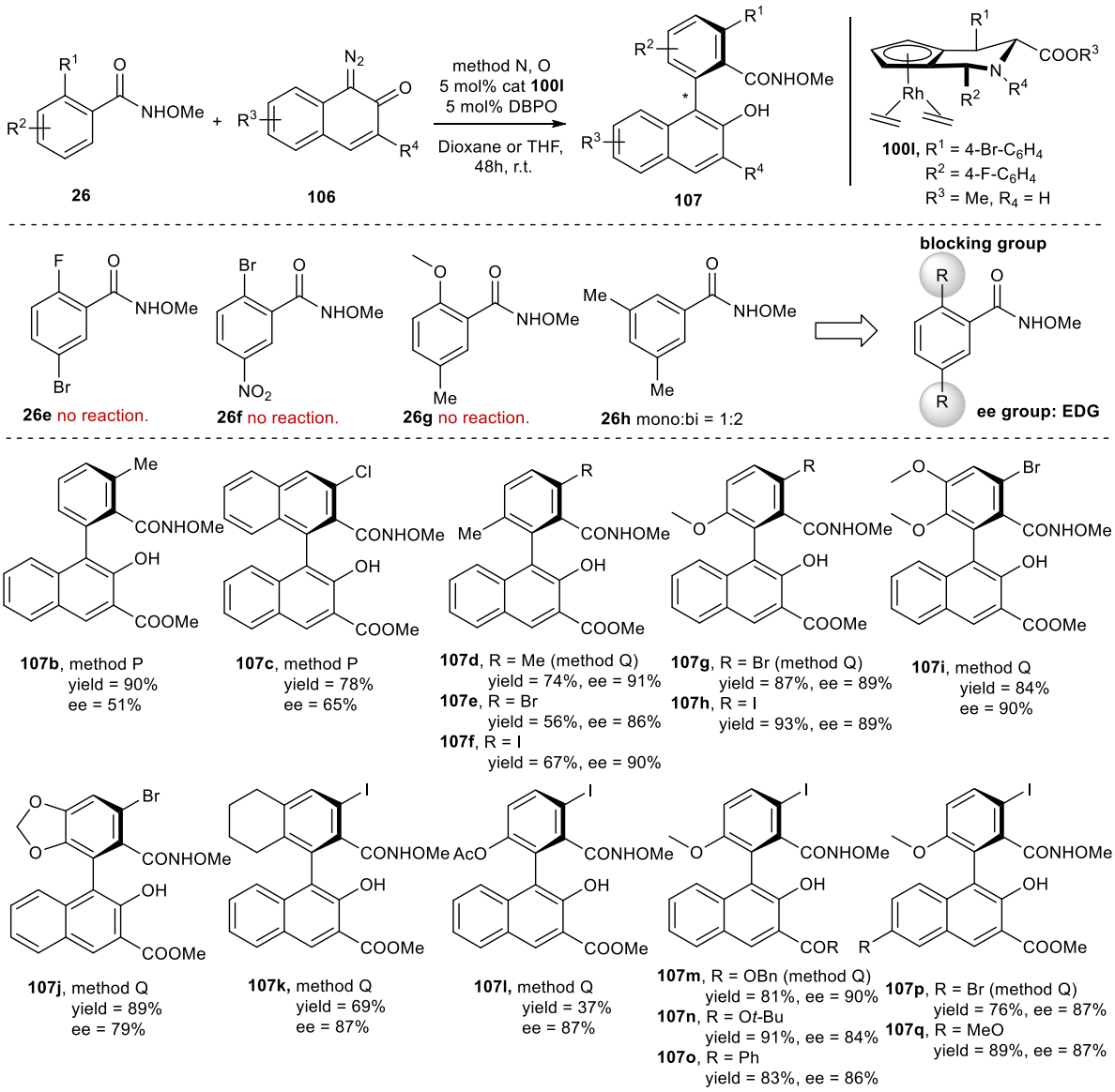
With regard to the modification of diazo compound, easily accessible diazo compound **106b** with additional ester group was employed in this transformation, surprisingly producing the desired product in up to 90% yield within 24 hours (Scheme 25). After obtaining the X-ray structure of **107b** (by Dr. Constantin G. Daniliuc), the presence of strong H-bonding was found between ester group and hydroxyl group. When the diazo compound **106a** without ester group was employed, the reaction stopped to a certain degree, leading to limited conversion. Taken together, the possible reason for enhanced reactivity might lie in the elimination of negative influence of hydroxyl group in catalytic cycle by the installation of ester group as H-acceptor. However, further experiments are needed for elucidating the proposed mechanism. Furthermore, there was no desired product from other diazo compounds except diazonaphthoquinone substrates such as **106c-e**, which proved the initial consideration regarding to reactivity of diazo compound.

On the other hand, the modification on benzamide part was carried out mainly on the installation of another substitution on *meta* position in the presence of *ortho*-substitution (Scheme 26). Delightfully, *meta*-substitutions turned out to be beneficial for enantioselectivity in spite of leading to acceptably decreased reactivity. Benzamide **26d** bearing *meta*-methyl afforded the desired product with up to 89% ee, whereas **26c** derived from 3-chloro-2-naphthoic acid gave 65% ee. Subsequent conditions screening for the reaction involving

benzamide **26e** disclosed that up to 91% ee was obtained by using 1,4-dioxane as solvent (*see 7.2.5.1, Table S4*).

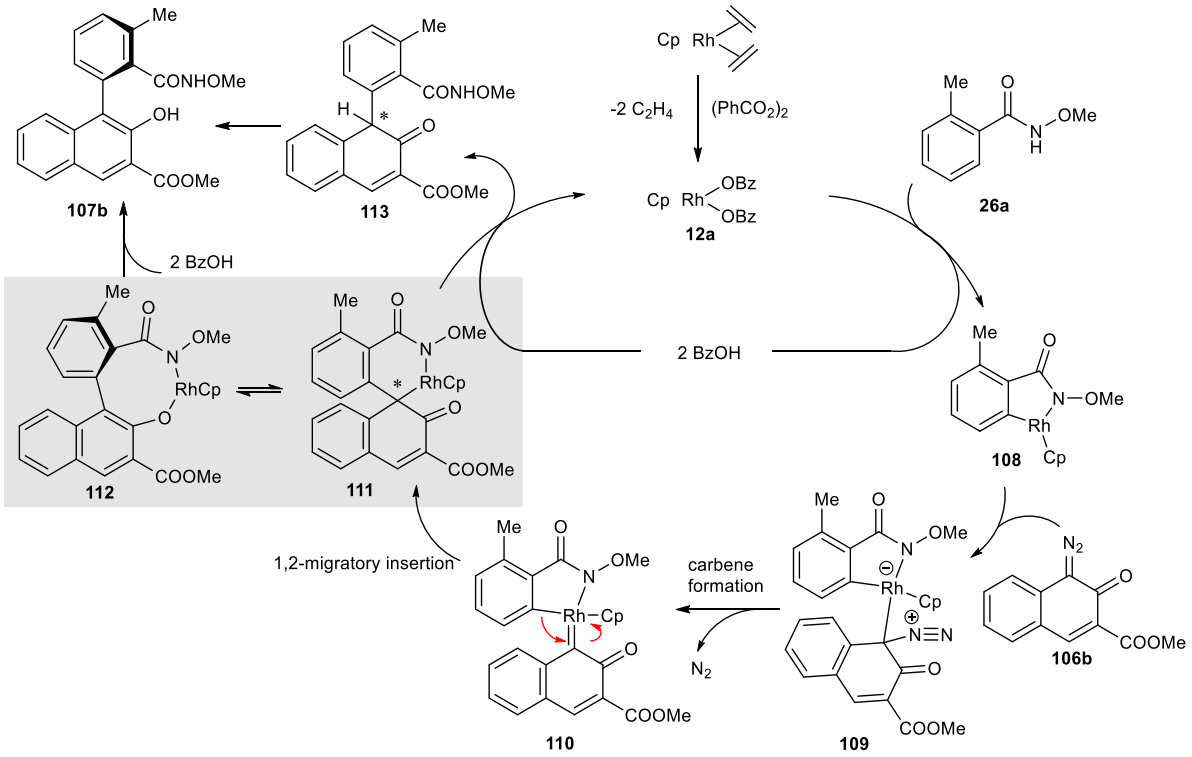


Scheme 26. Investigation on the modification of diazo compounds.



Scheme 27. Substrate scope investigation.

With optimized conditions in hand, substrate scope study was performed. In general, this reaction is not compatible with highly electron-deficient benzamides such as **26e** and **26f**. Electron-rich benzamide with *ortho*-methoxyl (**26g**) also failed to give the desired product. Additionally, benzamide **26h** without *ortho*-substitution gives biarylated compound as major product (Scheme 27). In conclusion, to obtain biaryls in high enantioselectivity and regioselectivity, benzamides should bear 'blocking group' on *ortho*-position except methoxyl and electron-donating 'ee group' on *meta*-position simultaneously. Varied non-C_2-symmetrical biaryl compounds **107** were achieved in excellent enantioselectivity. Besides X-ray crystallographic analysis of **107b** (by Dr. Constantin G. Daniliuc), the absolute configuration of **107d** was also confirmed by vibrational circular dichroism (VCD) spectroscopy (by Dr. Christian Merten, *see 7.2.6.2*).



Scheme 28. Proposed mechanism for the unprecedented reaction.

According to previous reports,[99,105] a plausible mechanism was proposed (Scheme 28). The reactive Rh(III) complex **12a** generated from Rh(I) complex by treatment with dibenzoyl peroxide, and reacts with **26a** *via* N−H insertion followed by sequential concerted-metalation-deprotonation (CMD) process to give intermediate **108**. A subsequent nucleophilic attack by diazo compound **106b** forms rhodium carbene **110** through intermediate **109** with simultaneous

release of nitrogen. Rhodium carbene **110** is subject to a 1,2-migratory insertion to give central chiral intermediate **111**, followed by protodemetalation to recycle Rh(III) catalyst and generate key intermediate **113**. The intermediate **113** with central chirality gives final product **107b** through a central-to-axial chirality transfer process. Another possible pathway is the generation of Rh-enolate **112** through isomerization of intermediate **111**, followed by a protonation process to give the product **107b**.

2.4 Summary and Perspective

The development of chiral Cp ligands had been hampered for a long period due to their inherent difficulties in terms of design and synthesis, in spite of the broad application of Cp* in transition metal catalysis in the past. Inspired by the dramatic progress in the realm of asymmetric (6+3) cycloadditions catalyzed by Lewis acid, a novel approach to chiral Cp ligand discovery had been disclosed as depicted in this chapter. The chiral ligands can readily be synthesized on gram scale by either recrystallization of enantioenriched (6+3) cycloadducts or preparative HPLC on chiral phase of racemic (6+3) cycloadducts. Besides convenient accessibility, more importantly both structure and configuration of such Cp derivatives can efficiently be adjusted by means of flexible ligand-controlled enantioselective (6+3) cycloaddition reactions.

The generality and applicability of these chiral Cp ligands was substantially proved by successful applications of their corresponding Rh(I) complexes in three different reactions. The high enantioselectivity achieved in the first two reported transformations revealed that these easily accessed Cp ligands could actually rival previously developed ligands. Furthermore, an unprecedented C–H activation reaction was realized to afford valuable axially chiral biaryl compounds with excellent enantioselectivity. Notably, through this reaction was the strategy of central-to-axial chirality transfer applied into chiral Cp ligands enabled transformation for the first time.

By integrating the advantages of convenient accessibility, rapid structural variability, as well as wide applicability demonstrated by three different reactions, this library of Cp ligands unites the strengths of previously developed ligand classes reported by Cramer, Ward and Rovis together with You. The findings shown in this chapter suggest that this approach should enable the discovery of efficient chiral Cp ligands for further enantioselective transformations.

Chapter 3. Enantioselective Synthesis of Pyrrolizidines by Lewis Acid Catalysis

3.1 Introduction

3.1.1 Pyrrolizidine Moiety in Natural Products and Its Synthesis

Pyrrolizidine alkaloids (PAs) are a large family of natural products, such as platynecine (**114**), loline (**115**), 9-angeloylplatynecine (**116**), and USC1025A (**117**)[106] (Fig. 7). A broad spectrum of bioactivity has been identified involving insecticidal, anti-bacterial, anti-viral, anti-tumor, anti-diabetic and anti-inflammatory properties, along with diverse toxicity.[107-109] For example, USC1025A (**117**) was isolated form the fungus *Acremonium* sp. KY4917 in 2002, exhibiting antimicrobial activity and antiproliferative activity against human tumor cell lines.[110]

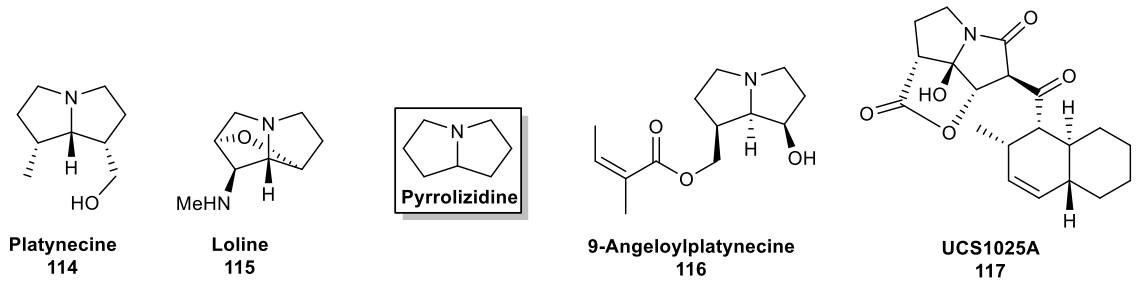
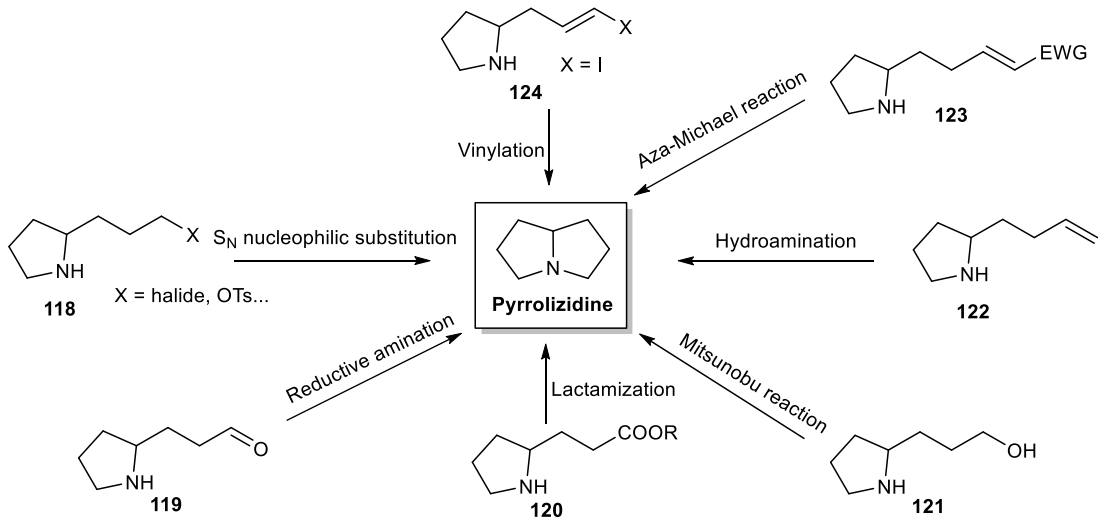


Figure 7. Representative natural products based on pyrrolizidine scaffold.

Due to their biological importance, these bicyclic ring systems have been receiving considerable attention. There had been plenty of methods to construct pyrrolizidine moiety efficiently in the last few decades, in which intramolecular cyclization based on flexile transformations of secondary amine in substituted pyrrolidine core is one of the most straightforward strategies (Scheme 29).[106,111] Various transformations were developed to access pyrrolizidine scaffold by this strategy, involving S_N nucleophilic substitution, reductive amination, lactamization, Mitsunobu reaction, hydroamination, aza-Michael reaction, vinylation, and so on.[111] Besides construction of pyrrolizidine scaffold, another major challenge originates from the prevalence of stereocenters in PAs. In general, multistep synthesis based on chiral pool is usually required to construct such moiety in enantioselective manner.[111] In the chiral pool, proline usually serves as the major starting material due to its accessibility and presence of multiple functional groups especially secondary amine for further transformation. However, catalytic asymmetric preparation of pyrrolizidines for the synthesis of compound library remains scarce to date.[112]



Scheme 29. Versatile methods based on intramolecular cyclization of secondary amine in pyrrolidine core.

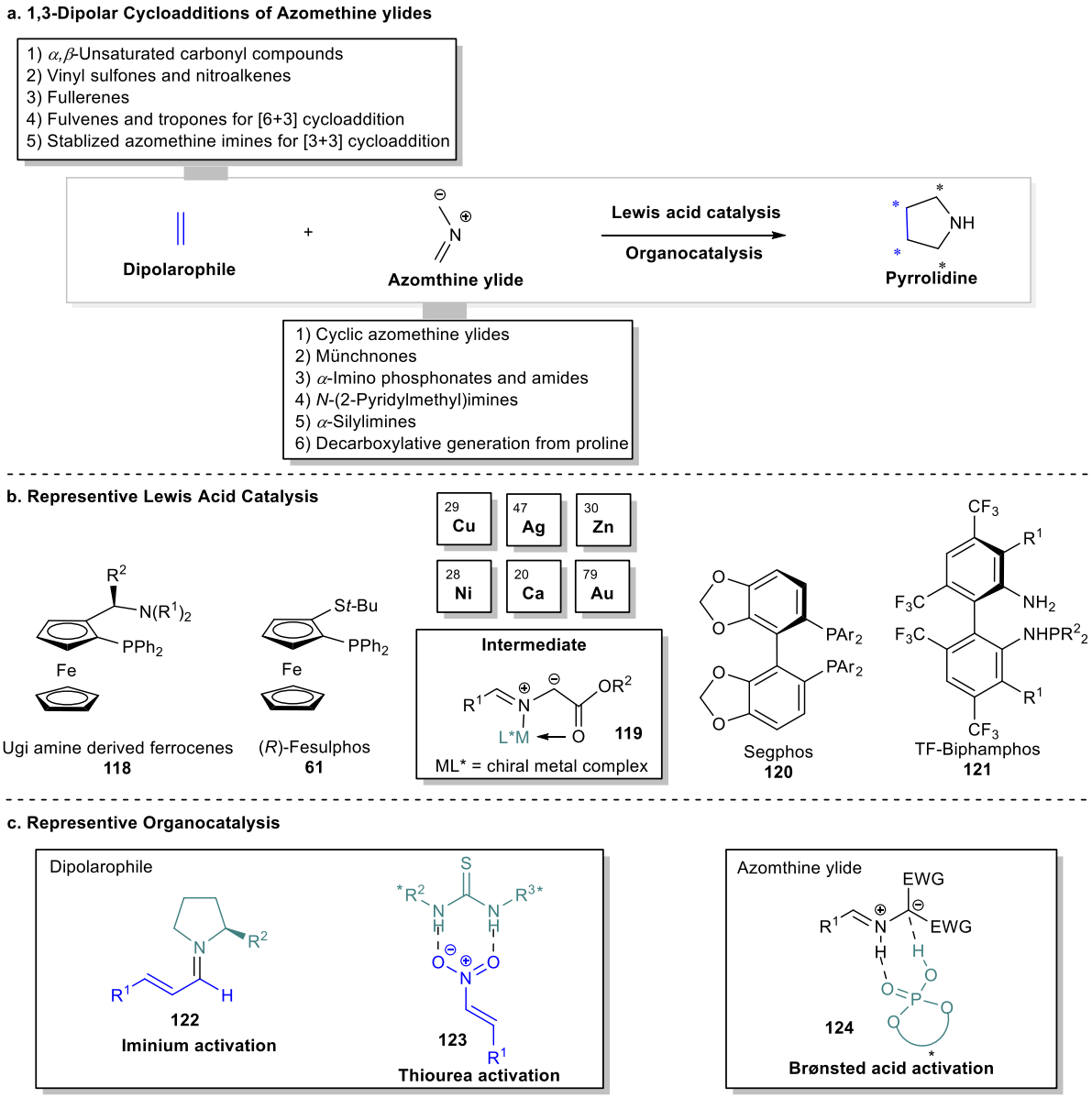
Furthermore, due to the lack of robust methodology, there is no chiral PAs-inspired compound collection to enable systematic investigation in chemical biology and medicinal chemistry. According to BIOS, to define the chemical space based on pyrrolizidine scaffold for potential target protein, the development of enantioselective methodology to build a large library of pyrrolizidines is highly desirable.

3.1.2 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

The cycloaddition reaction represents one of the most prominent reactions in modern organic synthesis owing to its inherent efficiency and atom economy. Especially, 1,3-dipolar cycloaddition reaction (1,3-DC) has become one of the most efficient methods to access heterocycles, due to its unique feature of one sole step to construct heterocycles with up to four stereocenters.[52,113-119] Over the last few decades, versatile dipoles have been successfully applied into catalytic asymmetric 1,3-DC, including nitrone, azomethine imine, azomethine ylide, nitrile oxide, nitrile imine, nitrile ylide, carbonyl ylide, diazo compound, and azide.[52] Among them, the 1,3-DC of azomethine ylide has been intensively explored with a broad range of activated dipolarophiles for the synthesis of enantioriched nitrogen-contained heterocycles.[18,114,118,120]

As the seminal work in this field, Grigg used stoichiometric $CoCl_2$ as Lewis acid together with ephedrine derivative as ligand to realize the asymmetric synthesis of pyrrolidine derivatives in 1991.[121] Inspired by this pioneering work, Zhang[122] and Jørgensen[123] independently reported the first catalytic asymmetric 1,3-DC by employing chiral Ag(I) complex and chiral Zn(II)

complex as catalyst respectively in 2002. Through extensive investigation over the last decade, a great variety of catalytic systems and substrate types had been developed in this field (Scheme 30).[52]



Scheme 30. Catalytic enantioselective 1,3-dipolar cycloaddition reaction and its activation modes.

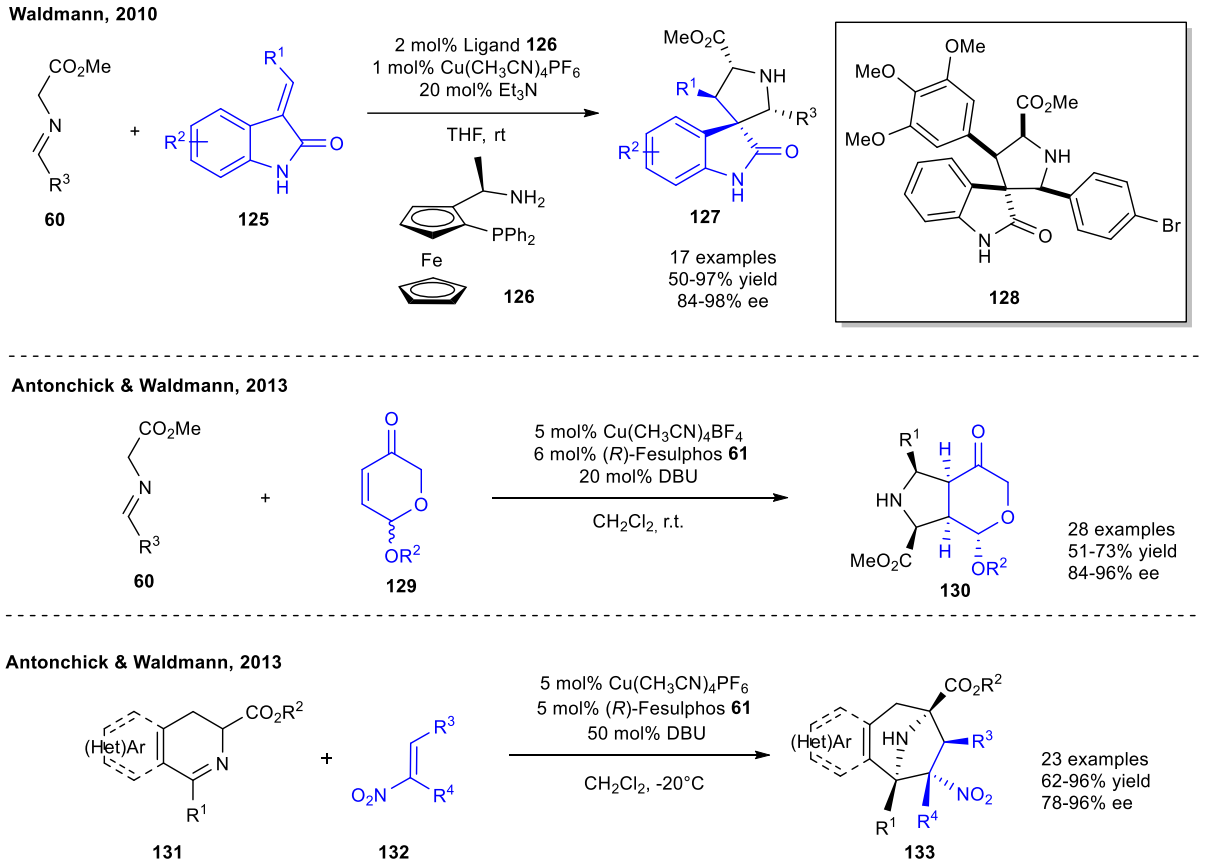
Regarding to substrate types of dipolarophile, the scope of commonly used *α,β*-unsaturated alkenes with electron-deficient property haven been extended, such as sterically demanding and fluorinated alkenes,[120] as well as fullerenes[124-128] (Scheme 30a). Furthermore, higher order 1,3-DC were also realized enabled by utilization of specific substrate as dipolarophiles. For example, (6+3) cycloadditions were reported by using fulvenes[16,17,53] and tropones[129,130], and the use of stabilized azomethine imines led to realization of (3+3) cycloadditions[131]. Besides

the rapid exploration of dipolarophile, various types of azomethine ylides were also exploited to afford versatile functionalized pyrrolizidines, such as cyclic azomethine ylides, Münchnones, α-Imino phosphonates and amides, *N*-(2-pyridylmethyl) imines, α-silylimines, and ylides generated by decarboxylation from proline (Scheme 30a).[52,120]

With regard to activation modes (Scheme 30b), Lewis acid catalysis has become the most efficient way to steer catalytic asymmetric 1,3-DC. Its effectiveness builds on the generation of rigid *N*-metalated azomethine ylides **119** from imines catalyzed by Lewis acid through deprotonation, and the origin of enantioselectivity is from chiral ligands coordinating with Lewis acid. A variety of catalytic systems has been described in the last decade, consisting of varied metals and structurally versatile ligands. Despite the use of Cu and Ag are still the mainstream in current literature, Zn, Ni, Ca and Au were also reported to be effective. As the origin of enantioselective induction, diverse chiral ligands have been designed and successfully applied into substrate-specific reactions. Especially, some of ligands are regarded to be 'privileged'[22,23] with the feature of delivering excellent enantioselectivity for a wide range of substrates, such as Ugi amine derived ferrocenes **118**, Fesulphos **61**, Segphos **120**, and TF-Biphamphos **121**. In addition, the rise and maturity of organocatalysis over the last decade provides an alternative approach to the aforementioned metal catalyzed process (Scheme 30c). Currently, there are three major activations in organocatalyzed 1,3-DC.[52,120] Iminium activation (**122**) is through covalent interaction of chiral amine with α,β-unsaturated aldehyde, while thiourea activation (**123**) usually cooperates with chiral base intramolecularly through H-bonding interaction with nitro or other carbonyl group to induce enantioselectivity effectively. Chiral Brønsted acid activation (**124**) can also induce excellent enantioselectivity mainly for some specific azomethine ylides derived from 2-aminomalonate. Besides the major activation modes mentioned above, chiral *N*-heterocyclic carbene through azolium mechanism[132] and chiral guanidine as strong base and H-bonding donor[133] also emerged as effective approaches to steer 1,3-DC enantioselectively, albeit with scarce examples. In spite of the significant limitations compared with effective Lewis acid catalysis, such as the relatively narrow substrate scope and the need for high amount of catalyst loading, organocatalyzed 1,3-DC still represents one attractive approach due to environmental friendliness, easy handling and compatibility with sensitive substrates.

Considering the power of catalytic enantioselective 1,3-DC to access chiral pyrrolizidine, a few methods guided by BIOS have been developed to build compound collections. These compound collections provided the basis for further investigation in chemical biology and

medicinal chemistry, in which high rates of active hits with various biological activity were identified. An early example is the first Lewis acid catalyzed enantioselective synthesis of 3,3'-pyrrolidinyl spirooxindoles by Waldmann (Scheme 31).[134]

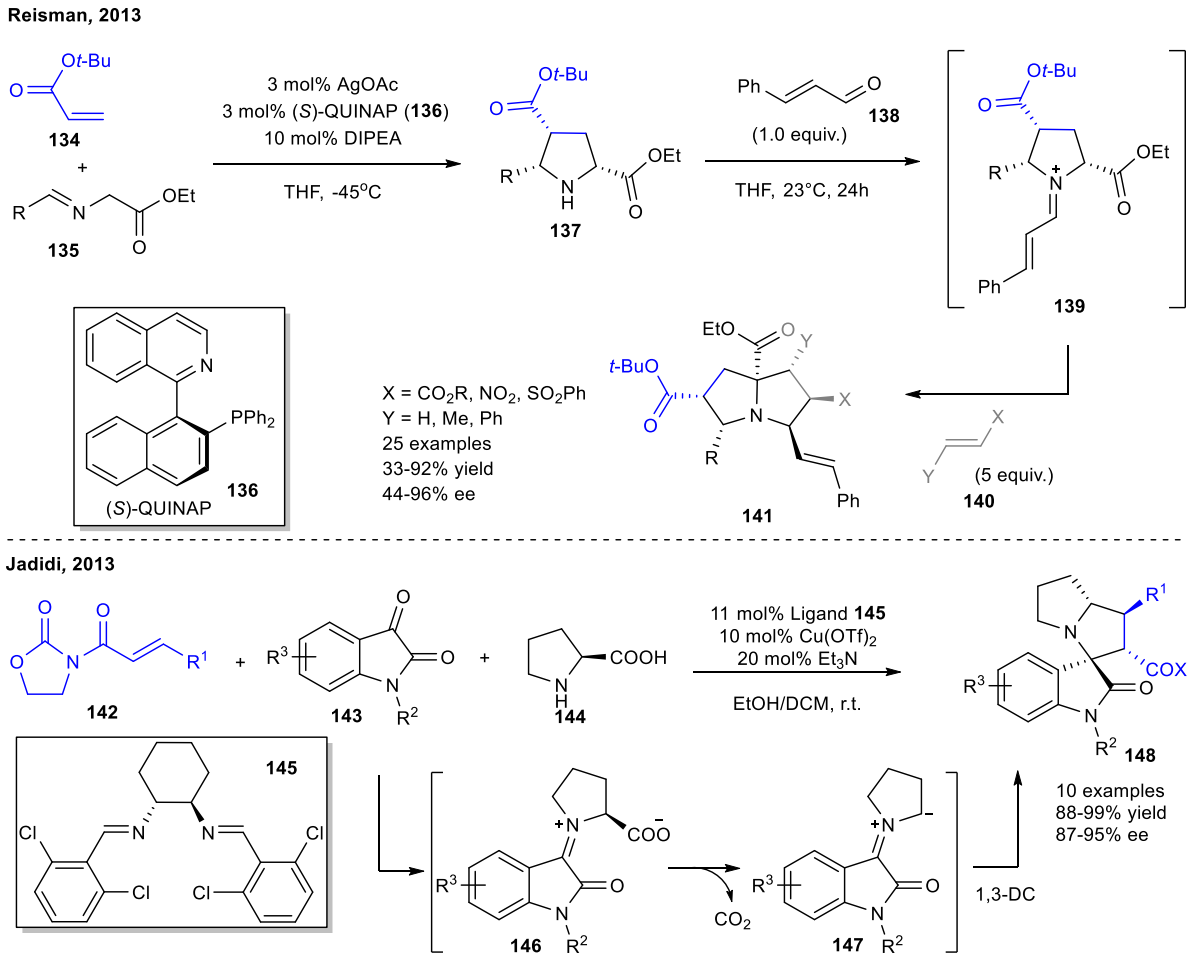


Scheme 31. Catalytic enantioselective 1,3-dipolar cycloaddition reaction developed in light of BIOS.

Using Ugi amine derived ferrocene **126** as chiral ligand, varied spirooxindoles **127** could be obtained by 1,3-DC of 3-methylene-2-oxindoles **125** and imino esters **60** in up to 98% ee. A compound collection with 39 members was subjected to phenotypic screening associated with mitotic arrest in BSC-1 cells, inspired by known principle that 3,3'-pyrrolidinyl spirooxindoles induce mitotic arrest by interference with p53-MDM2 interaction. Among them, only compound **128** with different relative configuration induced significant phenotypic changes. Further study in depth revealed that only (−)-**128** out of two enantiomers is active and it actually interferes microtubule polymerization other than inhibiting p53-MDM2 interaction. In 2013, another iridoid-inspired compound collection (**130**) of 115 compounds was achieved by 1,3-DC of pyranones **129** through a process of kinetic resolution.[135] Several hits were identified to be inhibitors in low micromolar range towards Wnt and Hedgehog pathways. In the same year, a focused compound collection of 84 tropanes (**133**) was reported though 1,3-DC of special

cyclic imines **131** wih nitroalekenes **132**, providing efficient inhibitors for Hedgehog pathway in the low mircomolar range.[136]

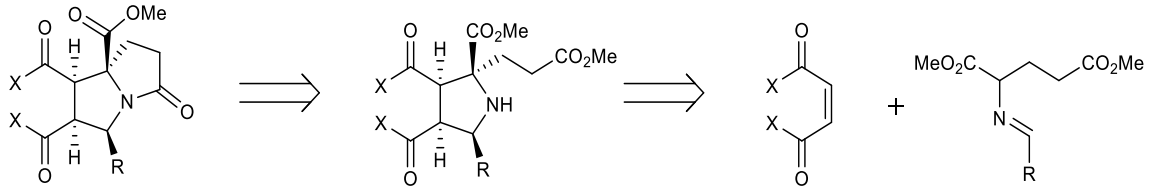
In spite of such efficiency in the synthesis of pyrrolidines, catalytic asymmetric 1,3-DC of azomethine ylide is barely applied in constructing pyrrolizidine scaffold (Scheme 32). Recently, Reisman described a highly enantioselective synthesis of pyrrolizidine (**141**) by a one-pot tandem reaction involving two folds of 1,3-DC.[112] The first step is an enantioselective 1,3-DC by using an AgOAc/(*S*)-QUINAP(**136**) catalytic system. Another subsequent 1,3-DC proceeds in a diastereoselective manner with alkene **140** to afford pyrrolizidines **141** with high enantioselectivity (up to 96% ee) and yield (up to 92%). Another example is 1,3-DC of azomethine ylide **147** generated *in situ* from proline **144** and isatin **143** through a process of condensation followed by decarboxylation.[137] The enantioselectivity was induced by the interaction between classic 1,3-dicarbonyl moiety (**142**) and chiral Lewis acid complex generated from Salen **145** and Cu(II).



Scheme 32. Current examples to access pyrrolizidine by means of 1,3-DC.

3.2 Design Principle and Aim of the Project

Due to the biologically importance of pyrrolizidines, a library of such compounds is highly desirable for further biological evaluation. As mentioned in **3.1.1**, versatile intramolecular cyclization of pyrrolidines with proper substitution has been proven to be an effective approach to access pyrrolizidines. Another inspiration is that catalytic asymmetric 1,3-DC is a powerful method to access chiral pyrrolidines, as stated in **3.1.2**. Hence, a strategy was envisioned to combine 1,3-DC and a subsequent intramolecular lactamization for the enantioselective synthesis of compound collection based on pyrrolizidine scaffold (Scheme 33). To obtain properly substituted pyrrolidines **150**, azomethine ylides generated from *N*-alkylidene glutamic acid esters **152** were utilized for 1,3-DC. The resulting functionalized pyrrolidinyl propionic acid esters **150** could facilitate a sequential intramolecular lactamization to afford pyrrolizidines **149**.



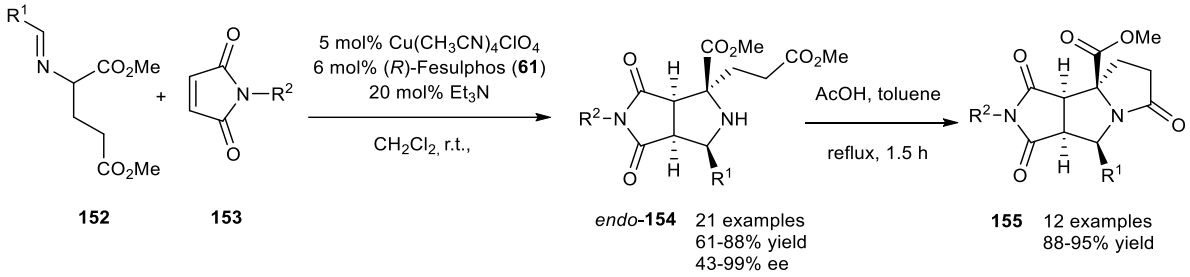
Scheme 33. Retrosynthetic proposal for the compound collection.

In this project, the reactivity of diverse dipolarophiles needs to be investigated for 1,3-DC of azomethine ylides generated from *N*-alkylidene glutamic acid esters. In principle, both tricyclic and bicyclic pyrrolizidines could be obtained by employing cyclic dipolarophiles and linear dipolarophiles respectively. After identifying the suitable dipolarophile, the realization of corresponding enantioselective 1,3-DC would be the next aim by means of intensive screening catalysis system including metals, ligands and other proper reaction conditions. Once establishing robust methodology, a library of pyrrolizidines, together with pyrrolidines as intermediates, would be prepared for the follow-up systematic investigation of biological activity.

3.3 Result and Discussion

3.3.1 Pioneering Work to Access Tricyclic Pyrrolizidines Enantioselectively

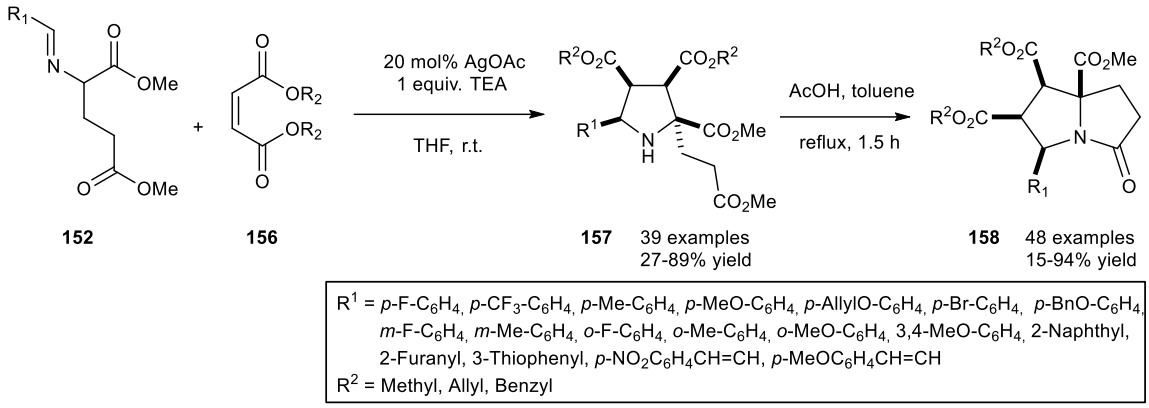
Dr. Hiroshi Takayama had developed a highly enantioselective 1,3-DC of maleimides **153** as dipolarophiles and azomethine ylides **152** generated from *N*-alkylidene glutamic acid esters (Scheme 34). After obtaining optimized reaction conditions for subsequent intramolecular lactaminzation, varied tricyclic pyrrolizidines **155** could be obtained from pyrrolidine intermediates **154** in excellent diastereo- and enantioselectivity by using (*R*)-Fesulphos (**61**) as ligand. Additionally, a 63-member compound collection including pyrrolidine intermediates and pyrrolizidines in either racemic and chiral form was obtained and subjected to biological evaluation. However, preliminary investigation on cell-based assay found no significant bioactivity in both Wnt and Hedgehog pathways signaling.



Scheme 34. The enantioselective synthesis of tricyclic pyrrolizidines.

3.3.2 Synthesis of Compound Collection Based on Other Dipolarophiles

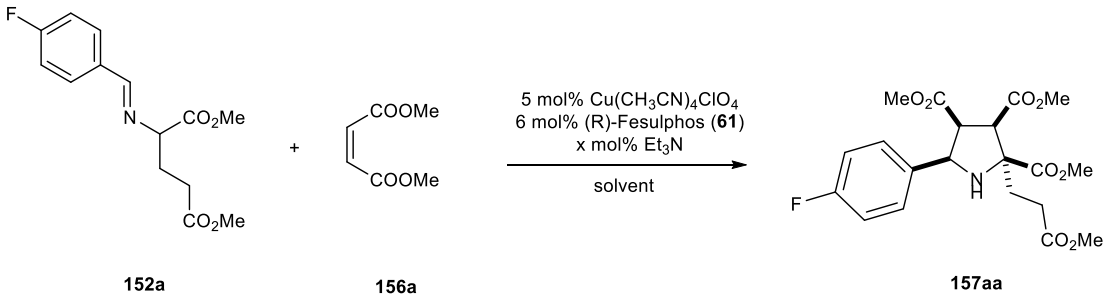
Since there was no significant bioactivity found in the compound collection based on 1,3-DC of maleimides, intensive screening of other dipolarophiles was conducted in order to expand this compound library. Instead of cyclic dipolarophiles, a broad range of linear dipolarophiles was screened. Maleates turned out to be suitable for this transformation by using AgOAc as catalyst, giving pyrrolidines and subsequent pyrrolizidines in satisfactory yields (Scheme 35). With optimized conditions in hands, this robust transformation was subsequently applied in the rapid synethsis of 87-member compound collection containing pyrrolidine intermediates and corresponding pyrrolizidines in racemic form. With regard to substrate scope, versatile substituted aryl and even alkenyl groups as R^1, as well as varied R^1 such as methyl, allyl and benzyl were compatible with 1,3-DC and sequential intramolecular lactamization. When R^1 is aliphatic group, no desired product was found. The relative configuration of **158** was substantially identified by NOE experiment and proved to be identical to racemic **155**.



Scheme 35. Synthesis of compound collection derived from maleate.

However, the corresponding asymmetric 1,3-DC of azomethine ylide **152a** and methyl maleate **156a** under the previously established conditions failed to afford the desired pyrrolidine **157aa** in considerable yield (Table 5, entry 1). Further optimization of solvent together with higher catalyst loading only gave 26% yield, albeit with excellent diastereo- and enantioselectivity (Table 5, entries 2 and 3). Higher temperature resulted in decreased enantioselectivity (Table 5, entry 4). The possible reason might lie in the relatively low reactivity of maleates compared with maleimides.

Table 5. Optimization of reaction conditions.

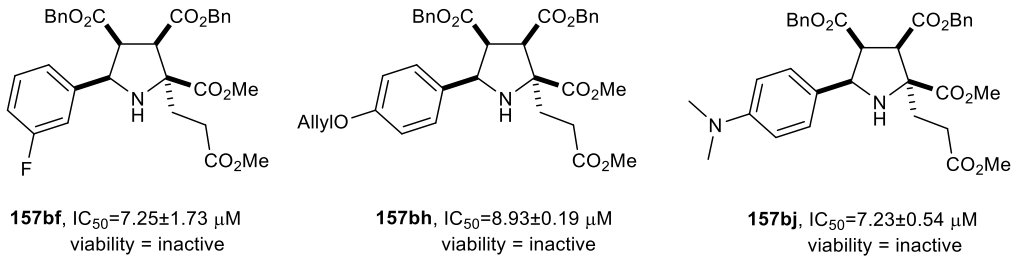


Entry	solvent	base (mol%)	Temp (°C)	yield (%)	d.r.	ee (%)
1	DCM	20	r.t	9%	n.d	n.d
2	THF	20	r.t	7%	n.d	n.d
3*	Toluene	20	r.t	16%	> 20:1	92%
4*	Toluene	100	40	26%	> 20:1	71%

* 10 mol% catalyst and 12 mol% ligand.

3.3.3 Preliminary Biological Study

Although there was no significant bioactivity for tricyclic pyrrolizidines library described in the prior work, the compound library derived from maleates resulted in the discovery of novel inhibitors of Hedgehog pathway signaling in mouse embryonic mesoderm fibroblast C3H10T1/2 cells. As illustrated in Fig. 8, several inhibitors of the Hedgehog pathway signaling were identified with IC_{50} values <10 μM.



157bf, IC_{50}=7.25±1.73 μM viability = inactive

157bh, IC_{50}=8.93±0.19 μM viability = inactive

157bj, IC_{50}=7.23±0.54 μM viability = inactive

Figure 8. Representative inhibitors of Hedgehog pathway signaling.

Later on, selected 119 compounds out of 150 compounds were subjected to specific assays performed by RIKEN in Japan to evaluate anti-proliferative activities against cancer cell lines, bacterium, fungi, and malaria. Delightfully, one third of compounds exhibited anti-malarial activities at 100 μM, while no significant activity was observed in other activities (Table 6).

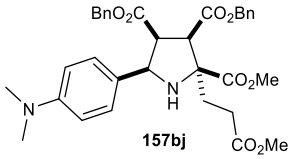
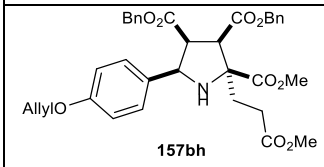
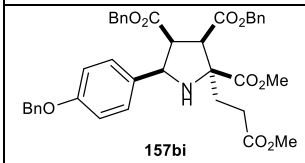
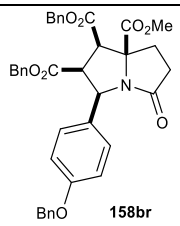
Table 6. Summary for the number of active compounds in each assay system.

	mammalian cancer cells				gram+	gram-	fungi		malaria
Assessment	HeLa	HL-60	TsFT210	tsNRK	*S.a.*	*E.c.*	*M.o.*	*C.a.*	*P.f.*
-	105	101	58	107	113	119	118	113	56
+	13	6	50	12	6	0	1	5	17
++	1	3	9	0	0	0	0	1	8
+++	0	9	2	0	0	0	0	0	38
total	119	119	119	119	119	119	119	119	119

Notation: 100 μM of compound treatment; -; 0-20% inhibition, +; 20-50% inhibition, ++; 50-80% inhibition, +++; > 80% inhibition. The following microorganisms were used as test strains in the assay; *Staphylococcus aureus (S.a.)* 209, *Escherichia coli (E.c.)* HO141, *Candida albicans (C.a.)* JCM1542, and *Magnaporthe oryzae (M.o.)* kita-1.

Among them, four compounds demonstrated relatively selective and potent activities at IC_{50} values of 10 μM or lower (Table 7). Notably, compounds **157bj** and **157bh** also showed activity in Hedgehog pathway signaling as inhibitors. Additionally, both pyrrolizidine **157bi** and corresponding pyrrolidine **158br** were identified to be anti-malarial compounds. Further biological evaluation is still in progress.

Table 7. Summary for the number of active compounds in each assay system.

Concentration (μM)	1	10	100
 **157bj**	+	++	+++
 **157bh**	-	++	+++
 **157bi**	-	++	+++
 **158br**	+	++	+++

Notation: -; 0-20% inhibition, +; 20-50% inhibition, ++; 50-80% inhibition, +++; > 80% inhibition

3.4 Summary and Perspective

In conclusion, an efficient catalytic approach for the synthesis of a PAs-inspired compound collection has been developed by using 1,3-DC of azomethine ylides as the key step. Despite the enantioselective 1,3-DC of maleimides proved to be robust and highly efficient by prior work, the less reactive maleates as dipolarophile failed to afford enantioriched pyrrolidines in considerable yields. Nevertheless, facilitated by the racemic catalytic 1,3-DC of maleates catalyzed by AgOAc, a 87-member library of pyrrolizidines and pyrrolidines had been obtained efficiently. Together with the prior work by Hiroshi Takayama, 150 compounds had been synthesized and subjected to biological evaluation. Although there was no significant bioactivity observed in tricyclic pyrrolizidines and their pyrrolidine precursors derived from

maleimides, extended compound collection derived from maleates indeed provided hits not only in the inhibition of Hedgehog pathway signaling but also with anti-malarial activity. Interestingly, some compounds exhibited both aforementioned activities.

In future, more intensive biological evaluation enabled by this PAs-inspired compound collection will be taken into consideration. With regard to 1,3-DC of azomethine ylides in chemistry, diverse dipolarophiles and dipoles, as well as catalytic systems have been extensively explored in the last decade, leading to the rapid maturation of this field. However, the applications of 1,3-DC in cascade reactions and the intramolecular 1,3-DC are still limited. Furthermore, more endeavor needs to be devoted to the application of 1,3-DC into chemical biology and medicinal chemistry.

Chapter 4. Enantioselective Synthesis of Cycloheptanoids Enabled by Rh(II)/Lewis acid/Amine Catalysis

4.1 Introduction

4.1.1 Cycloheptanoids in Natural Products and Their Synthesis

The seven-membered carbocycle moiety as a privileged scaffold, that defines the core of cycloheptanoids, is widely present in numerous NPs with a broad range of bioacitivity. Some representative examples include Ingenol (**159**), Phorbol (**160**), Cartorimine (**161**), Englerin A (**162**), Alstonisine (**163**) and other macroline-related oxindole alkaloids with a common tropane moiety (**164**-**166**), as well as *Gardneria* alkaloids **167** and **168** (Fig. 9). Two important variations of cycloheptanoid NPs are 8-oxabicyclo[3.2.1]octane and 8-azabicyclo[3.2.1]octane (tropane) scaffolds, embodied in more than 200 NPs respectively.[138]

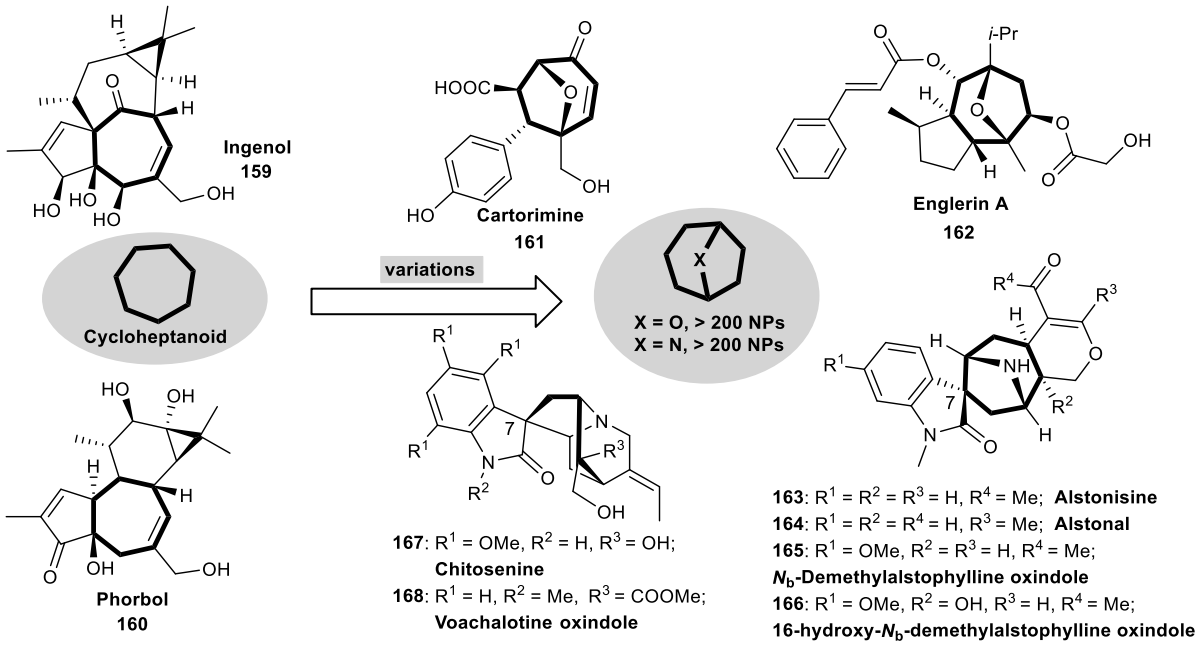
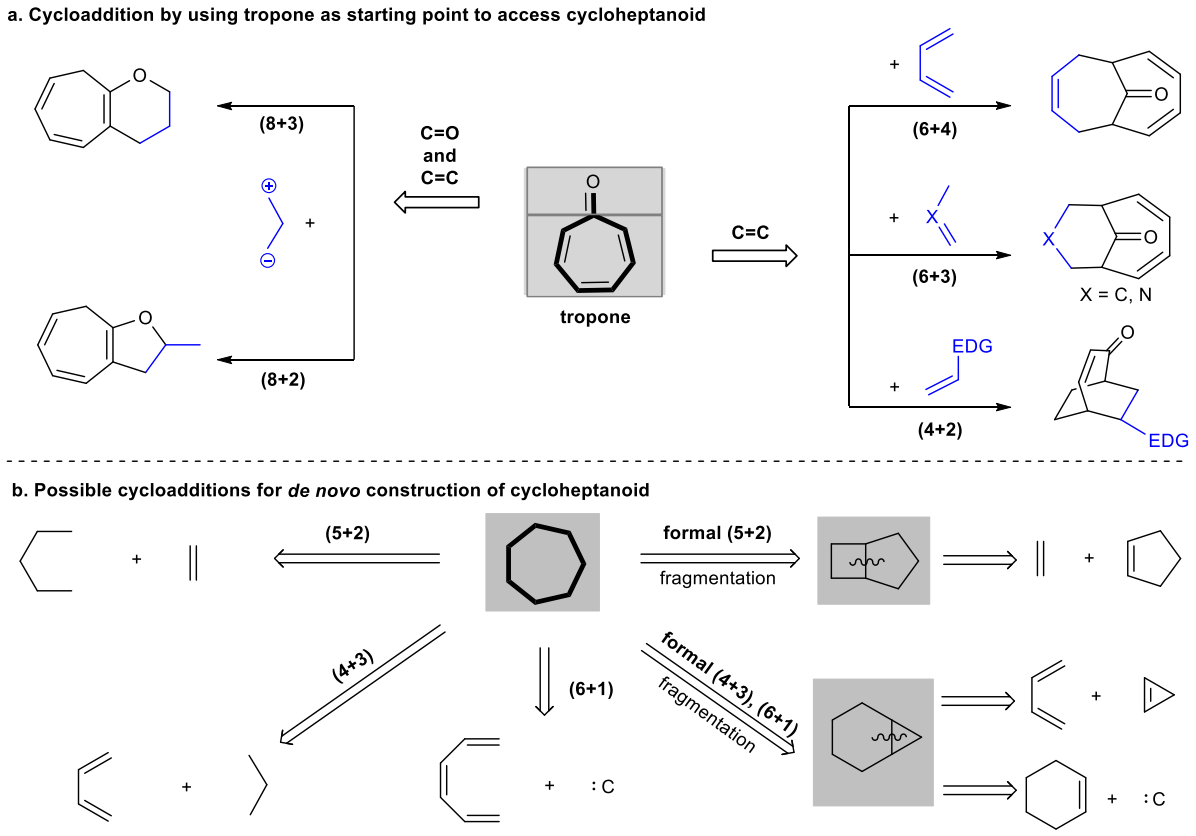


Figure 9. Representative cycloheptanoids in natural products.

Among them, Englerin A (**162**) has attracted interest from both biology[139-143] and chemistry[144-150] communities recently due to its highly selective activity against renal cancer at nanomolar level. Recently, further chemical biological investigation in depth by Waldmann disclosed the rapid and selective inhibition of renal cancer cells by Englerin A could be ascribed to the activation of calcium-permeable nonselective transient receptor potential canonical (TRPC) calcium channels.[19] Notably, in contrast to highly potency of **162**, its enantiomer *ent*-**162** is inactive even at up to micromolar level,[142] highlighting the importance of stereochemistry in BIOS. Another type of interesting cylcoheptanoid NPs is macroline-related oxindole alkaloids (**163**-**166**), with the features of both spirocyclic oxindole moiety and tropane scaffold. Despite

spirocyclic oxindole alkaloids are usually associated with significant bioactivity,[151,152] no investigation was reported in detail for oxindole alkaloids **163-166** due to their paucity in nature. Interestingly, there are also naturally occurring alkaloids Chitosenine **167** and Voachalotine oxindole **168** with similar scaffold to **163-166**, but bearing opposite configuration at spirocyclic C7 atom. Considerable effort has been devoted to the total synthesis of such spirocyclic oxindole alkaloids mainly starting from tryptophan through a mulit-step linear synthesis.[153-157]

In spite of the high occurrence in bioactive NPs, synthetic methods for cycloheptanoids are much less developed compared with five- and six-membered rings, constraining the rapid construction of such compound collection for further investigation in medicinal chemistry and chemical biology.[158-162] From a synthetic chemistry point of view, the construction of seven-membered carbocycles is rather challenging due to unfavorable ring-strain and entropic reasons. Through the continuous effort in this field, a few strategies have been developed, in which cycloaddition represents one of the most efficient strategies compared with stepwise cyclization strategy.[158]



Scheme 36. Cycloadditions to achieve cycloheptanoid.

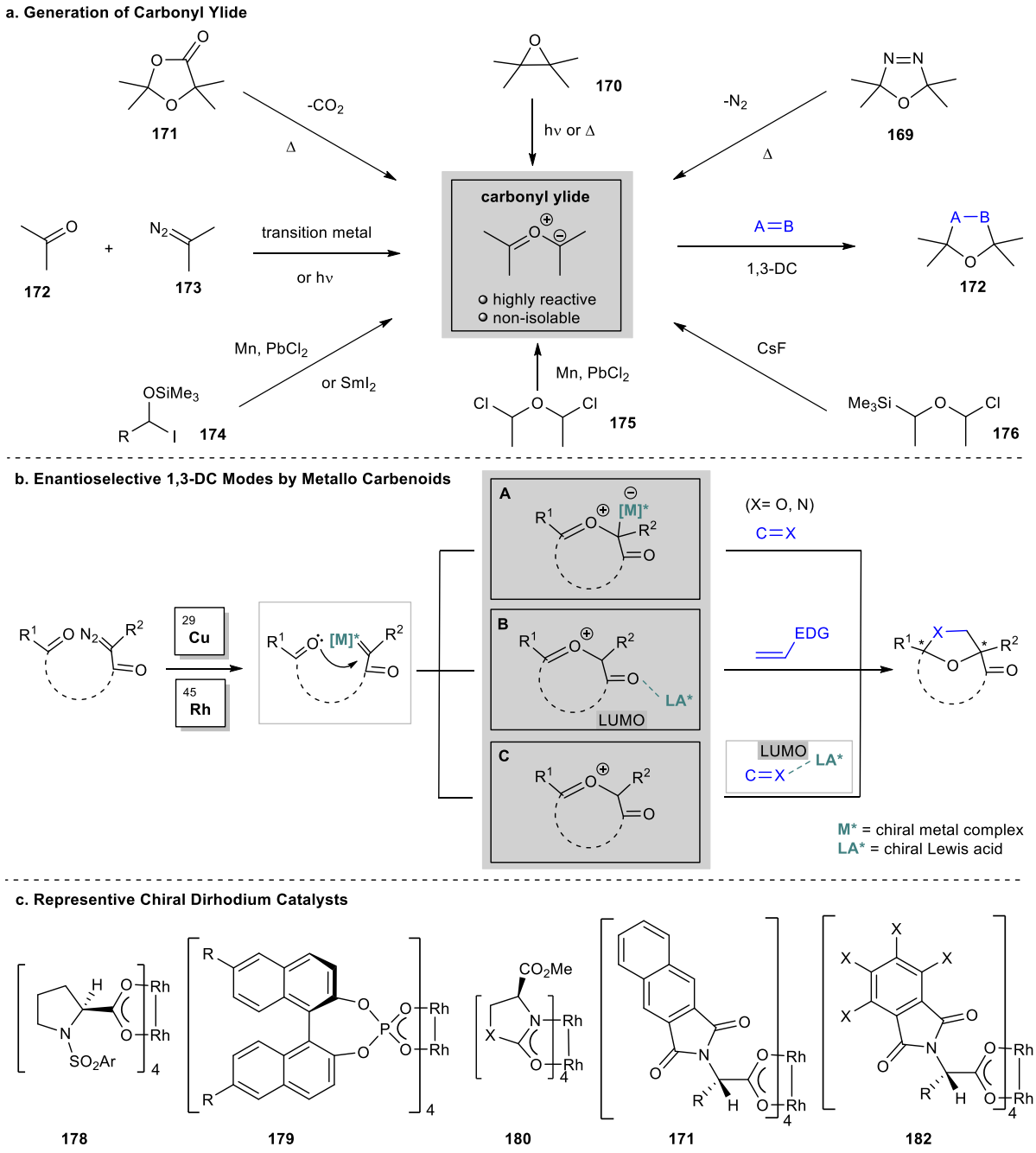
In the cycloaddition strategy, the most straightforward approach is to start from commercially available seven-membered carbocycles. One of valuable feedstocks is tropone, which has proven to exhibit a wide spectrum of reactivity especially towards high order cycloadditions (Scheme 36a). Representative examples comprise (8+3)[163-166] and (8+2)[167,168] cycloadditions involving carbonyl group, as well as (6+4)[169-172], (4+2)[173,174] and (6+3)[129,130,175-177] cycloadditions without the participation of carbonyl group. Facilitated by the efficiency of this strategy and the diverse reactivity of tropone, quite a few elegant synthetic studies towards cycloheptanoid NPs have been reported based on the cylcloaddition reactions of tropone.[170,174,175,178]

In the *de novo* synthesis of cycloheptanoids, various cycloadditions have also been developed.[179] Resulting from the dissection principle of odd-numbered ring, the use of zwitterionic or diradicaloid intermediates is necessary to access seven-membered cycloheptanoids. In theory, there are three pathways involving (6+1), (5+2), (4+3) cycloadditions, along with some formal variations involving fragmentation process (Scheme 36b).[179] Among them, (6+1) cycloaddition is the most challenging from a synthetic chemistry point of view, and no example has been reported in the last decade.[179] In contrary, (5+2)[159,160] and (4+3)[161,162] cycloadditions have attracted considerable interest and are broadly applied into the synthesis of cycloheptanoids. Belonging to (5+2) cycloadditions, the 1,3-dipolar cycloaddition reactions (1,3-DC) of diverse dipoles, such as six-membered cyclic carbonyl ylides and azomethine ylides, together with pyryliums, will be discussed in detail in **4.1.2-4.1.4**, with a main focus on their asymmetric version.

4.1.2 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Carbonyl Ylides Generated from Diazo Compounds by Rh(II) Catalysis

Carbonyl ylides are a family of highly instable and reactive 1,3-dipoles, and their corresponding 1,3-DC have been broadly applied to synthesize tetrahydrofuran rings and other oxygen-contained heterocycles. Due to the high instability, most of carbonyl ylides are usually generated *in situ* as transient species. Conventional methods for the generation of carbonyl ylides consist of thermal extrusion of nitrogen from 1,3,4-oxadiazolines (**169**), thermolysis or photolysis of epoxides (**170**), loss of carbon dioxide from 1,3-dioxolan-4-ones (**171**), as well as transition metal-catalyzed reaction of carbonyl compounds (**172**) and diazo compounds (**173**).[180] Besides, some simple carbonyl ylides are also formed from 1-iodoalkyl trialkyl

ethers[181,182] (**174**) 1,3-elimiation of silyl compounds[183] (**175**) or halogenated ether (**176**) (Scheme 37a).[181,184,185]



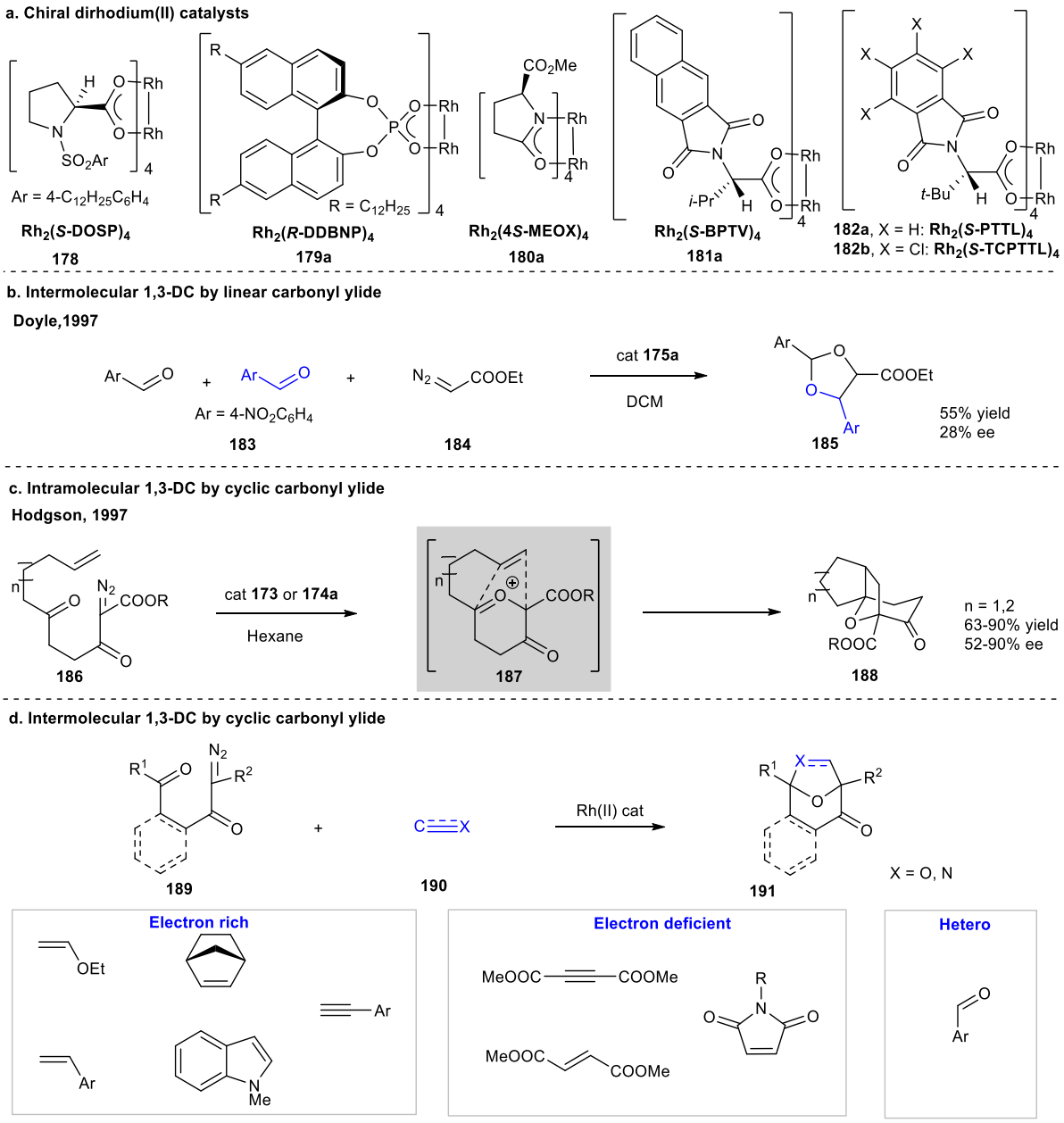
Scheme 37. Carbonyl ylide and its application in catalytic enantioselective 1,3-DC.

However, most of abovementioned methods to generate carbonyl ylides are not suitable for asymmetric catalysis due to either the requirement of harsh reaction conditions or the lack of versatility of substrate types. In contrast, transition metal-catalyzed reaction of carbonyl compounds (**172**) with diazo compounds (**173**) has been largely explored in asymmetric catalysis, especially with Rh(II) catalysts.[180,186-189] The major reason can be attributed to the

ease and mildness properties in the generation of carbonyl ylides by such method (Scheme 37b). This field had grown rapidly to its mature stage over the last two decades, with the appreciable contribution from Padwa.[180,186-189] Additionally, copper is also used in carbonyl ylide generation but with relatively limited application due to its lower efficiency.[190]

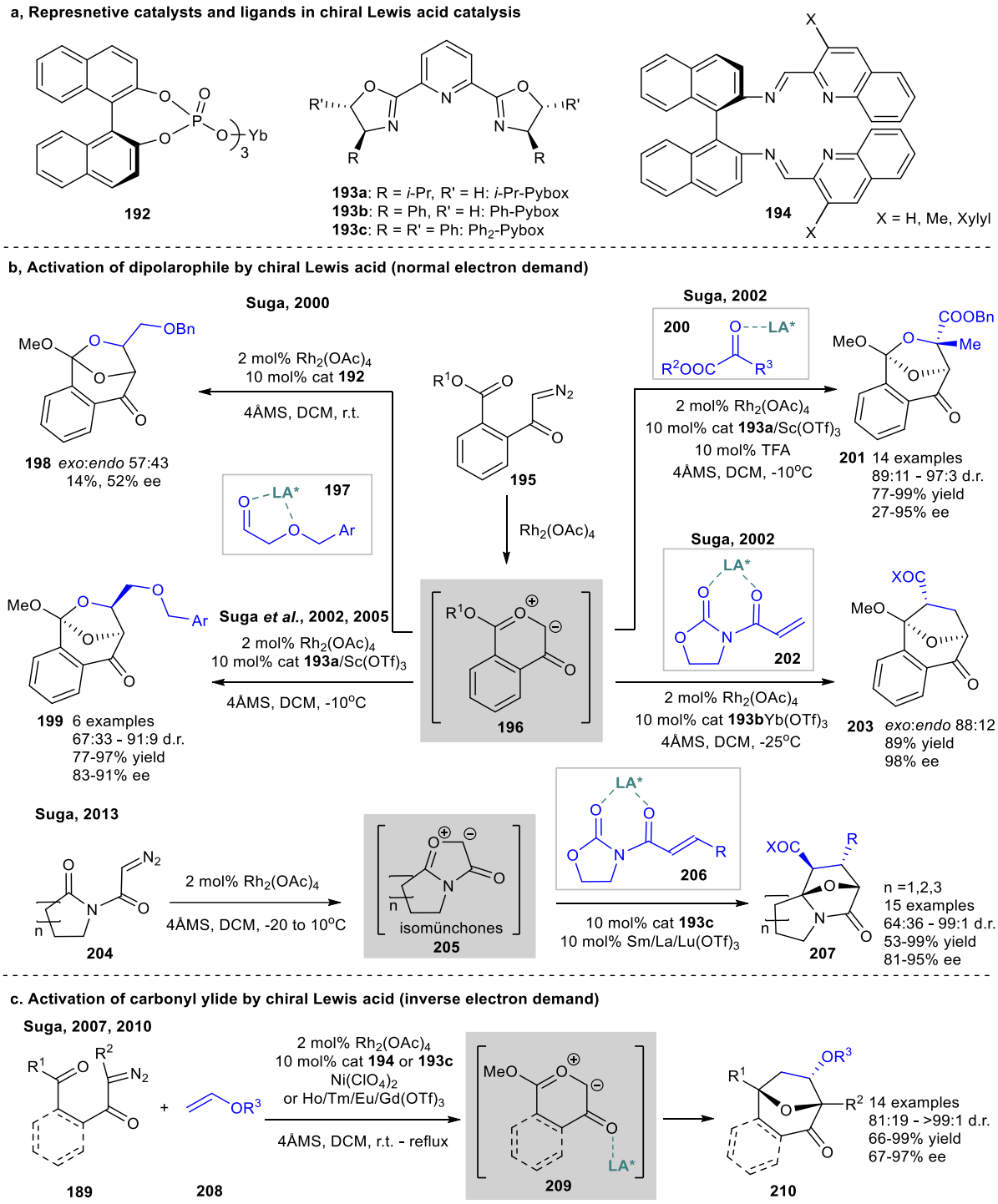
To date, there are three major methods to induce enantioselectivity in the process of 1,3-DC of carbonyl ylides derive from diazo compounds by Rh(II) catalyst (Scheme 37b).[52] First, the utilization of chiral Rh(II) catalysts is the most straightforward method, but a requisite condition is that transition metal with chiral ligand still associates with carbonyl ylide in the process of 1,3-DC (intermediate A, Scheme 37b). In the past two decades, various chiral dirhodium(II) catalysts had been designed and synthesized to steer the enantioselective transformations involving carbonyl ylides (Scheme 37c).[191-193] Another complementary strategy is to employ chiral Lewis acids in a relay-catalysis manner. Depending on the electronic property of substrates, the chiral Lewis acids can activate either dipolarophiles (intermediate B) or dipoles (intermediate C) (Scheme 37b).

As for the enantiocontrol by chiral dirhodium(II) catalysts, Doyle demonstrated such asymmetric catalytic transformation involving carbonyl ylide as an unpublished work in 1997.[191] By using Rh_2(4*S*-MEOX)$_4$ (**180a**) as catalyst, carbonyl ylide generated from aromatic aldehyde **183** and diazoacetate **184** reacted with another molecule of **183** to give dioxolane **185** in rather poor enantioselectivity (Scheme 38b). It should be noted that there is no successful example to date that 1,3-DC of linear carbonyl ylide is able to be realized in high enantioselectivity by solely using chiral dirhodium(II) catalyst. In the same year, the first catalytic 1,3-DC of carbonyl ylides with considerable enantioselectivity was reported by Hodgson.[194] The substrates **186** was synthesized to enable a cascade reaction involving cyclic carbonyl ylide formation and subsequent intramolecular 1,3-DC, affording the chiral cycloheptanoids **188**. In the following study, intermolecular asymmetric 1,3-DC was also developed with cyclic carbonyl ylides (Scheme 38c). As representatively illustrated in Scheme 38d, various dipolarophiles **190** with different electronic property and even with heteroatom were investigated in the reactions of diazo compounds **189** and dipolarophiles **190** catalyzed by dirhodium(II) catalysts (Scheme 38a).



Scheme 38. Catalytic enantioselective 1,3-DC of carbonyl ylide by chiral dirhodium catalysts.

Although quite successful by using chiral dirhodium(II) catalysts, the significant limitations on substrate types of both dipoles and carbonyl ylides were found due to the high tendency of disassociation of chiral Rh(II) from ylide intermediates. Complementarily, Suga developed a relay catalysis system combing chiral Lewis acid and achiral dirhodium(II) catalyst (Scheme 39b). In this strategy, the enatioselectivity of 1,3-DC was introduced by the interaction between chiral Lewis acid and dipolarophile after the generation of carbonyl ylide by achiral dirhodium catalyst.



Scheme 39. Catalytic enantioselective 1,3-DC of carbonyl ylide by chiral Lewis acid.

In their preliminary report, the employment of chiral Yb(III) Lewis acid **192** afforded the cycloadduct **198** in moderate enantioselectivity through 1,3-DC between benzyloxylacetaldehyde **197** and benzopyrylium **196** derived from diazo compound **195**.[195] The successive studies revealed that *i*-Pr-Pybox **193a**/Sc(III) delivered a high enantioselectivity for the same 1,3-DC with much broader substrate scope.[196,197] Facilitated by

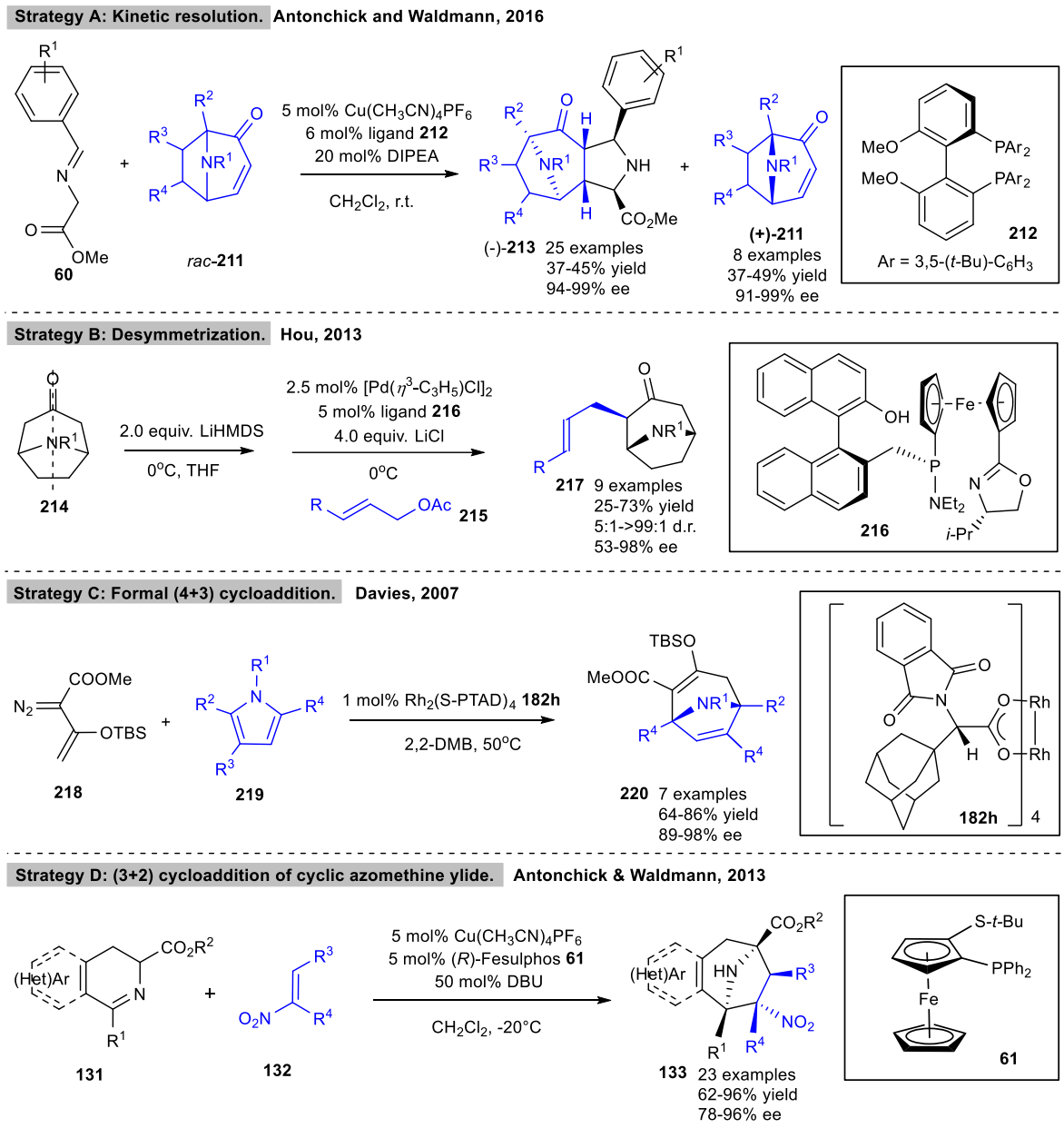
the same structurally rigid intermediate **196**, pyruvate **200** and traditional 1,3-dicarbonyl compound 3-acryloyl-2-oxazolidinone **202** also proved to be suitable for this transformation under specific reaction conditions.[196] Later on, further investigations focusing on the extension of dipolarophile scope for the abovementioned transformations were also conducted by the same group.[198] In 2013, another type of structurally rigid carbonyl ylide **205** generated from diazo **204** was reported, with which a highly enantioselective 1,3-DC was realized by using a complexes of Ph_2-Pybox **193c** with different metals (Scheme 39b).[199] Additionally, Suga also developed catalytic asymmetric 1,3-DC facilitated by the LUMO activation of carbonyl ylide by chiral Lewis acid (Scheme 39c).[200,201] The choice of different combination of metal such as Ni(II), Ho(III), Tm(III), Eu(III), Gd(III), and ligand (**194**/**193c**) is critical for the high enantioselectivity of this transformation.

As described above, most of carbonyl ylides applied in asymmetric catalysis are six-membered cyclic species, resulting in the synthesis of enantioenriched 8-oxabicyclo[3.2.1]octanes and derivatives. This highly efficient method has been applied successfully into a few total synthesis of NPs including Englerin A.[180,187,188,202] Recently, instead of traditional diazo-based carbene strategy, electrophilic activation of alkyne by transition metals followed by nucleophilic attack of carbonyl moiety intramolecularly emerged as a more atom-efficient and safe alternative to generated cyclic carbonyl ylides.[203-210] To date, transition metals such as Cu(II), Ag(I), Pd(I), Pt(II), Au(I), and Rh(II) have been demonstrated as efficient electrophilic catalysts. However, the successful applications in cycloaddition in asymmetric form are still scare.[203]

4.1.3 Catalytic Asymmetric Reactions to Access Tropanes and Cyclic Azomethine Ylides Generated from Diazo Compounds by Rh(II) Catalysis

In spite of the high occurrence of tropane moiety in NPs with diverse bioactivity especially on neurological and psychiatric diseases, the development of tropane synthesis in enantioselective manner still stays limited.[138] To date, the main source of chiral tropanes is from chiral pool, such as sugar, amino acids, or other commercially available or synthesized chiral building blocks. Besides, prochiral substrates are also able to provide chiral tropanes through one single step of transformation, which can be facilitated by traditional chiral auxiliaries, chiral reagent, and chiral catalysts. Other strategies are also available but much less developed, such as kinetic resolution of racemates of tropanes. As the most efficient and economic strategy, the catalytic asymmetric methodologies to access enantioriched tropanes are particularly rare. To date, four

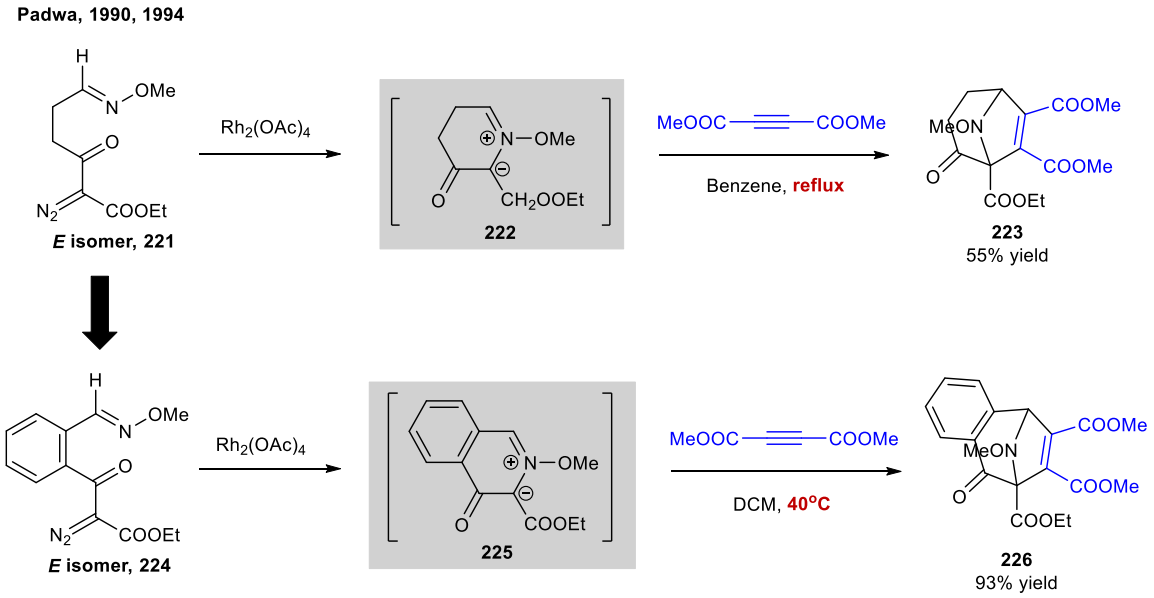
strategies with a handful of examples have been depicted in literature, including kinetic resolution (KR),[211] desymmetrization,[212,213] formal (4+3) cycloaddition,[214,215] and (3+2) cycloaddition of cyclic azomethine ylides[136] (Scheme 40).



Scheme 40. Current catalytic enantioselective examples for the synthesis of enantioriched tropanes.

In the strategy of kinetic resolution, only a few examples by enzyme catalysis[138] were reported before (3+2) cycloadditions of tropane racemates depicted by Antonchick and Waldmann in 2016 (Strategy A, Scheme 40).[211] The tropanes *rac*-**211** synthesized through (5+2) cycloadditions of 3-oxidopyridiniums and alkenes can be resolved by means of asymmetric (3+2) cycloadditions of azomethine ylides (**60**). By using Cu(I) and ligand **212**, tropanes (+)-**211** and a hybrid compound collection (**213**) incorporating both tropane and pyrrolidine

fragments were obtained in highly enantioselective manner. With regard to desymmetrization, one of representative examples[212,213] is a palladium-catalyzed asymmetric allylic alkylation of tropinone derivatives **214** by Hou in 2013 (Strategy B, Scheme 40). The use of ligand **216** proved to be critical for the synthesis of tropane derivatives **217** with moderate to excellent ee. In 2007, Davies developed a highly enantioselective formal (4+3) cycloadditions of pyrroles **219** and vinyldiazoacetate **218** catalyzed by chiral dirhodium catalyst **182h** (Strategy C, Scheme 40).[215] The tropanes **220** were supposed to be generated through a sequential reaction of asymmetric cyclopropanation/Cope rearrangement. Notably, the elegant work from Antonchick and Waldmann in 2013 demonstrated the asymmetric synthesis of fused tropanes **133** by (3+2) cycloadditions of cyclic azomethine ylides **131** (Strategy D, Scheme 40).[136]

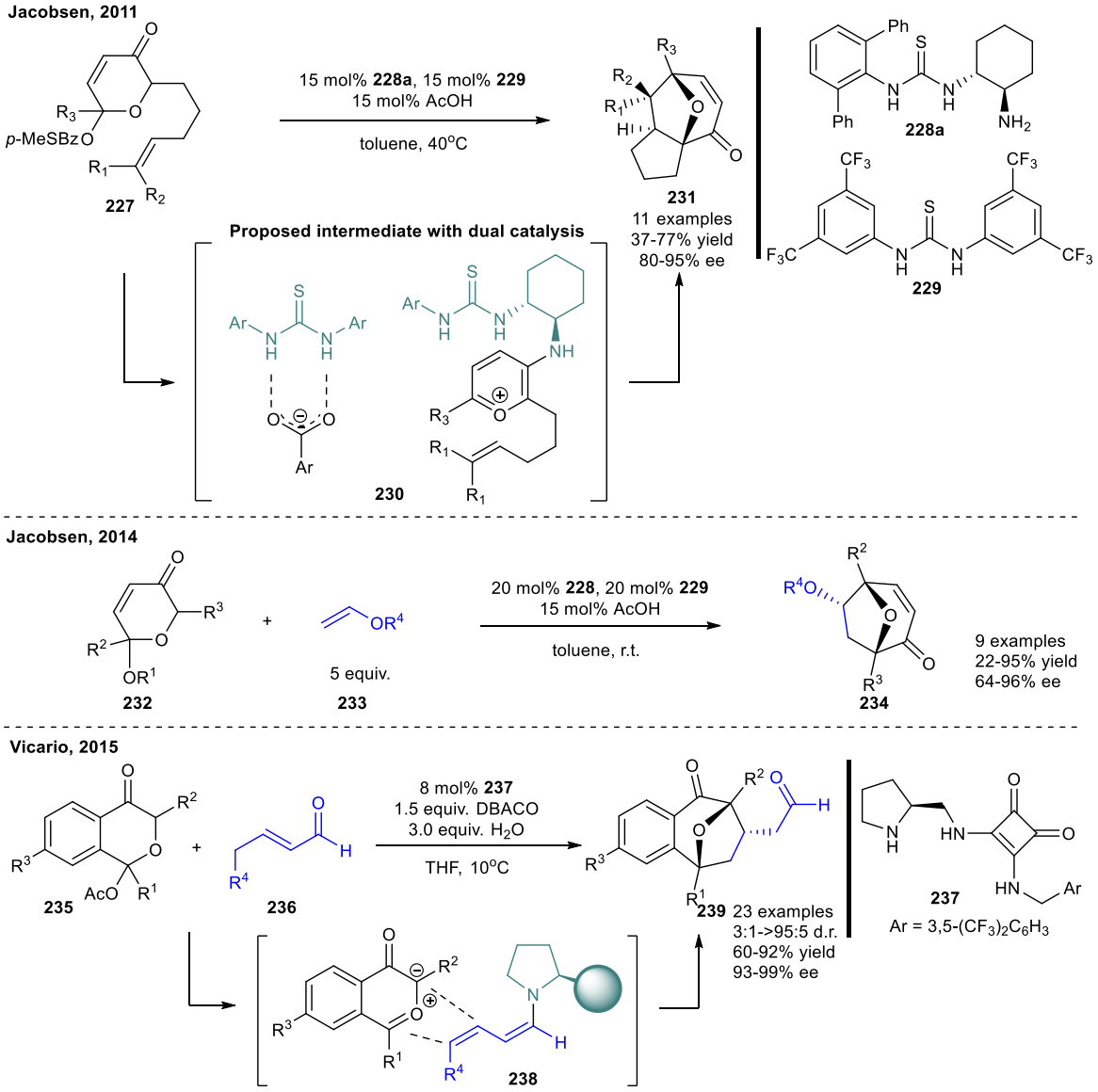


Scheme 41. Cyclic azomethine ylides generated by diazo compounds described by Padwa.

Although Antonchick and Waldmann indeed provided a novel strategy to access tropanes enantiomerically, the presence of aromatic functionalities is critical to stabilize the cyclic ketoimine **131**, therefore only fused tropanes **133** could be obtained. In fact, some aliphatic cyclic azomethine ylides such as **222** were already described by Padwa in 1990s by using diazo compound with a tethered oxime moiety **221** (Scheme 41). However, this species of azomethine ylide intermediates had only been reported in two reports in 1990 and 1994 with extremly limited substrate scope, and never applied in enantioselective transformation.[216,217] One of the main reasons can be attributed to the low reactivity of such intermediates. In the seminal reports, only highly reactive dipolarophiles such as DMAD under refluxing condition is suitable for such transformation. Another reason is the high instability of such intermediates.

Padwa also depicted azomthine ylide **225** with higher reactivity and stability could be generated from benzo fused diazo compound **224**, so that tropane **226** could be achieved in higher yield (94%) and milder condition (40°C) compared with the synthesis of tropane **223**. In conclusion, the methods described by Padwa can provide both aliphatic tropanes and fused counterparts, but suffer from limited application due to the low reactivity and the instability properties of cyclic azomethine ylide intermediates. Notably, in both case was only *E*-isomer of oxime able to afford the desired tropane product due to its proper direction of nitrogen lone pair for azomethine ylide formation.

4.1.4 Organocatalysis to Access 8-Oxabicyclo[3.2.1]octanes Enantioselectively



Scheme 42. Organocatalysis to access 8-oxabicyclo[3.2.1]octanes.

In the last decade, oranocatalysis using small organic molecules as catalysts had thrived to a powerful method in organic synthesis. As a general strategy to construct 8-oxabicyclo[3.2.1]octanes, (5+2) cycloadditions of pyryliums or even pyridiniums has been broadly applied in organic synthesis.[158-160] Nevertheless, the corresponding catalytic asymmetric variant was not reported until 2011 by Jacobson in an intramolecular manner (Scheme 42).[218] Enabled by dual catalysis integrating amine catalyst **228a** and anion-binding catalyst **229**, the desired product **231** could be obtained in excellent eantioselectivity, albeit with rather limited substrate scope. An intermediate **230** was proposed to rationalize the outcome of stereochemistry. Later, by employing the same catalysis system, the intermolecular version was realized, suffering the same problem of limited substrate cope (Scheme 42).[219] In contrast to Jacobsen's work, Vicario demonstrated a highly enantioselective (5+2) cycloaddition of aldehydes **236** and benzopyrylium ylides generated from benzopyranones **235** through enamine activation by secondary amine **237** (Scheme 42).[220]

To conclude, similar to the incapability in metal catalysis to access 8-oxabicyclo[3.2.1]octanes in catalytic enantioselective manner as described in **4.1.2**, although two strategies with regard to (5+2) cycloaddition of pyrylium were conceived in organocatalysis, the further application and especially the substrate scope of these methods are significantly limited.

4.2 Design Principle and Aim of the Project

In light of BIOS, the chemical space defined by NPs not only relies on the privileged scaffolds, but also is complementarily characterized with the sufficient substitutions and the stereogenic centers. To cover adequate chemical space based on seven-membered carbocycles, the exploration of highly enantioselective methodology to build the compound library of cycloheptanoids, especially 8-azabicyclo[3.2.1]octane variant (tropane) and 8-oxabicyclo[3.2.1]octane variant, is highly desirable and valuable. To this end, four different approaches have been designed and will be discussed in this chapter.

For the first approach, the most straightforward way to construct cycloheptanoids is starting directly from commercial available seven-membered carbocycles, as discussed in **4.1.1**. In this regard, tropone was chosen to be the very starting point due to its easy accessibility and versatile reactivity. Although a large spectrum of dipoles such as azomethine ylide had been tested for reactions of tropone, the reactivity of carbonyl ylide has never been investigated, especially in an enantioselective manner. In this thesis, various diazo compounds as precursors

of carbonyl ylides will be synthesized to explore the possible reactivity of tropone by using chiral dirhodium(II) catalysts. This part of work will be summarized in **4.3.2**.

As for the second approach, 1,3-DC of six-membered cyclic carbonyl ylides with all-carbon partners represents one of the most efficient methods to access cyclopentanoid 8-oxabicyclo[3.2.1]octanes, as shown in **4.1.2**. In spite of extensive exploration of this field for more than one decade, the catalytic enantioselective 1,3-DC of carbonyl ylides still suffers from severe limitation of dipolarophile types (Scheme 38d). On the other hand, as possible 2π-, 4π-, 6π-, and even three-carbon components in annulation process, versatile reactivity of fulvene have been explored for the rapid construction of polycyclic systems.[221] In continuation of the effort in this thesis on pentafulvene (Chapter 2), the reactivity of pentafulvene towards carbonyl ylides will be intensively investigated in an enantioselective manner. This part of work will be summarized in **4.3.3**.

The third approach involves 1,3-DC of six-membered cyclic azomethine ylides. In contrast to intensive investigation of cyclic carbonyl ylides generated from diazo compounds by Rh(II) catalysis, cyclic azomethine ylides generated in the same way were reported only in two seminal works by Padwa in 1990s, as described in **4.1.3**. The corresponding catalytic enantioselective transformation remains unprecedented. Considering their promising application in the synthesis of tropanes, it would be highly valuable to perform systematic investigation of such azomethine ylide intermediates. To achieve this target, two issues should be addressed, including the enhancement of reactivity of such intermediates and the efficiency of enantioselectivity induction. To overcome the low reactivity of the aforementioned intermediates, it's assumed that the rational design of diazo precursors is critical. Regarding to the enantioselectivity, in analogy to carbonyl ylides, chiral dirhodium catalysts will be tested at first. As alternatives, additional asymmetric catalysis systems can also be tested in a relay catalysis manner, such as chiral Lewis acid catalysis described in **4.1.2**. This part of work will be summarized in **4.3.4**.

Inspired by the pioneering works of Jacobsen[218] and Chain[222], the fourth approach consists of two different strategies to build 8-oxabicyclo[3.2.1]octane compound collection, involving intermolecular (5+2) cycloaddition of pyrylium salt and stepwise cyclization. This section will be summarized in **4.3.5**.

4.3 Result and Discussion

4.3.1 Synthesis of a Library of Chiral Dirhodium(II) Catalysts

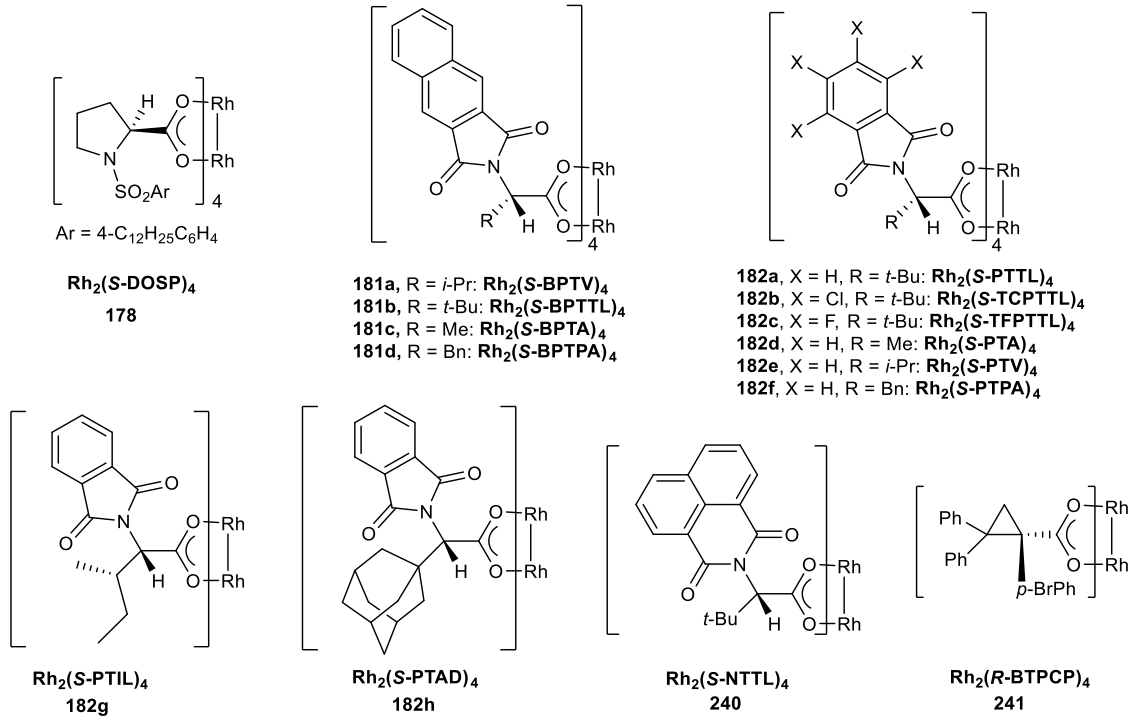
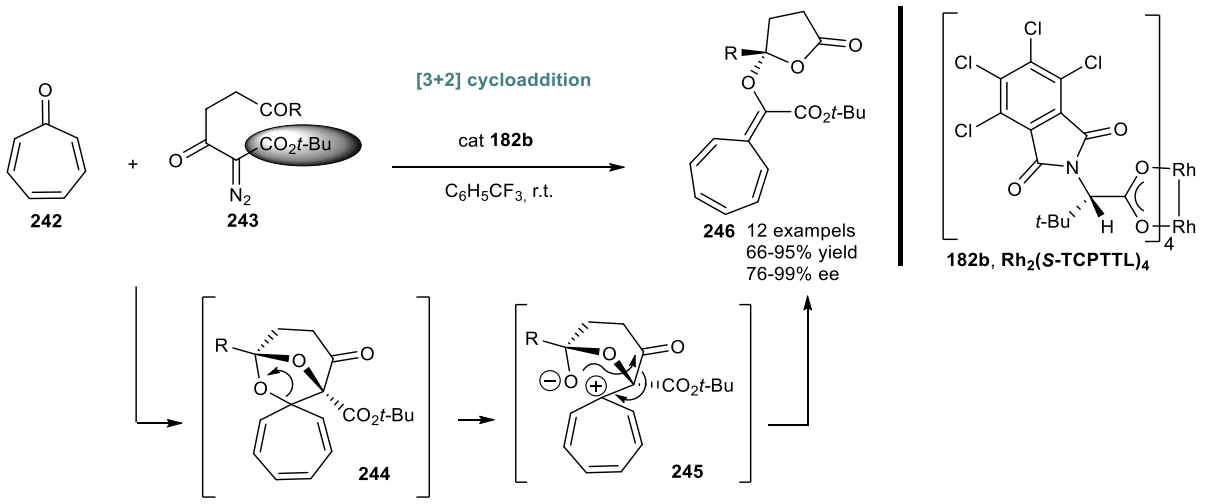


Figure 10. Library of chiral dirhodium catalysts.

Except commercially available chiral dirhodium(II) cataylsts (**178**, **182b**, **182c**, **182h**, **241**), other types of catalysts were synthesized according to literature (Fig. 10).[223]

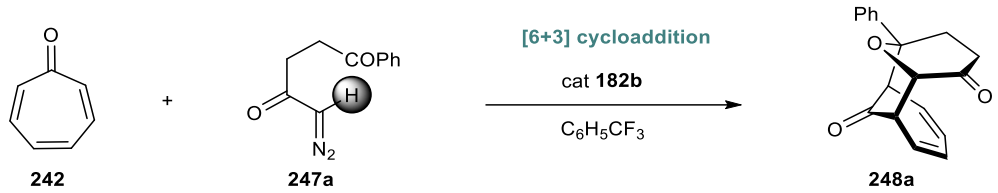
4.3.2 Investigation on Reactivity of Tropone in 1,3-Dipolar Cycloaddition Reactions of Cyclic Carbonyl Ylides



Scheme 43. 1,3-DC of carbonyl moiety of tropone with carbonyl ylide.

In collaboration with Dr. Sandip Murarka, the reactivity of tropone with various carbonyl ylides was intensively investigated. In literature, the catalytic enantioselective 1,3-DC of carbonyl ylides with carbonyl group is rare. Only some specific aldehydes proved to be suitable for such transformation as described in three publications[191,197,224], and the corresponding ketone is unprecedented. Dr. Sandip Murarka discovered that cyclic carbonyl ylides derived from diazodiketoesters **243** underwent (3+2) cycloadditions with the carbonyl group embodied in tropone **242**, representing the first case involving carbonyl group in ketone (Scheme 43).[225] Under the optimized conditions, catalyst **182b** yielded various 5-alkoxylactone derivatives **246** instead of spirocyclic compound **244** in good to excellent enantioselectivity, with the substrate scope from aliphatic to diverse aromatic patterns. Based on the observations, a plausible mechanism involving a cascade process was proposed. Spirocyclic compound **244** generated from 1,3-DC of carbonyl functionality of tropone is converted into zwitterion **245**, which sequentially undergoes cyclization and rearrangement to afford the observed product **246**.

Table 8. Screening of reaction conditions for the synthesis of **214a**.[a]



242 247a 248a

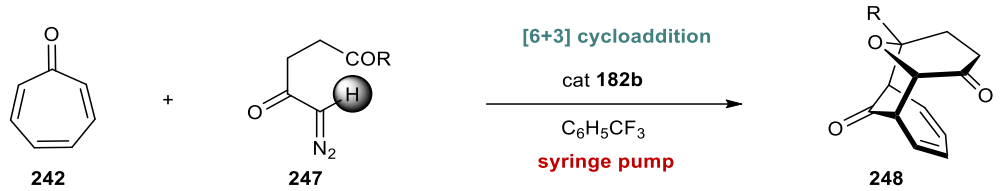
Entry	Temp (°C)	yield (%)	ee (%)
1	r.t	60	94
2[b]	r.t	92	94
3	50	50	92
4[c]	r.t.	75	94

[a] Unless otherwise noted, a flame dried *Schlenk* tube was charged with catalyst **182b** (2.00 μmol, 0.02 equiv.), **242** (0.10 mmol, 1.00 equiv.) and 0.5 mL $C_6H_5CF_3$ under the protection of Ar. Then the solution of diazo compound **247a** (0.15 mmol, 1.50 equiv.) in 0.5 mL $C_6H_5CF_3$ was added slowly into the reaction mixture. [b] The solution of diazo compound **247a** in 0.5 mL $C_6H_5CF_3$ was added over 1 hour by syringe pump. [c] 20 mg 4Å MS was added.

Independently, a (6+3) cycloaddition reaction was discovered by using diazoketone **247a** under the same reaction conditions, to afford corresponding cycloheptaoid **248a** in moderate yield and with excellent enantioselectivity. After optimization of reaction conditions (Table 8), the use of a syringe pump to add diazo compound **247a** over 1 hour was found critical for high yield of this transformation, which is also a standard procedure to reduce background reaction

resulting from 'free' carbonyl ylide without Rh. Additionally, lower temperature and the addition of molecular sieves had a negative effect on yield but no significant influence on enantioselectivity. The absolute configuration of **248a** was unambiguously identified by vibrational circular dichroism (VCD) spectroscopy (by Dr. Christian Merten, *see 7.4.1.2*).

Table 9. Substrate scope of (6+3) cycloaddition reaction.



242 247 248

Entry	Product	R	yield (%)	ee (%)
1	**248a**	C_6H_5	78	94
2	**248b**	4-*n*-HexC_6H_4	55	92
3	**248c**	4-*i*-PrC_6H_4	56	89
4	**248d**	4-FC_6H_4	30	92
5	**248e**	4-BrC_6H_4	66	87
6	**248f**	4-MeOC_6H_4	n.r.	n.r.

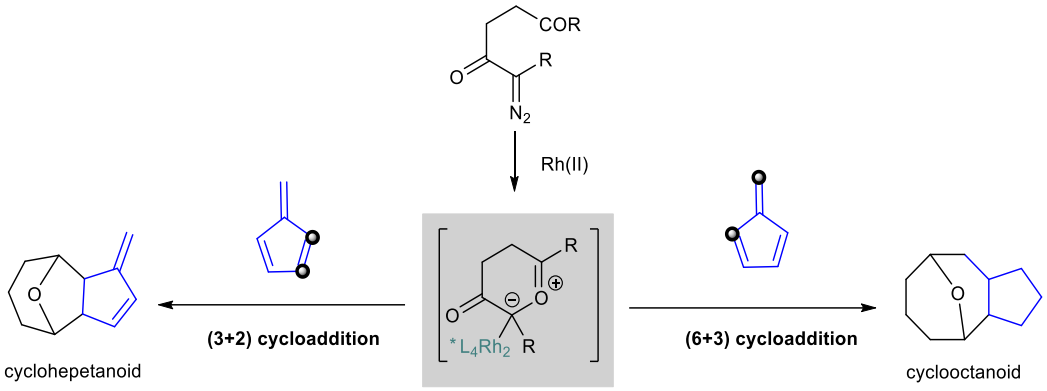
Reaction conditions: a flame dried *Schlenk* tube was charged with catalyst **182b** (2.00 μmol, 0.02 equiv.), **242** (0.10 mmol, 1.00 equiv.) and 0.5 mL $CF_3C_6H_5$ under the protection of Ar. Then the solution of diazo compound **248a** (0.20 mmol, 2.00 equiv.) in 0.5 mL $C_6H_5CF_3$ was added added over 1 hour by syringe pump. n.r.: no reaction.

With the optimized reaction conditions in hand, the substrate scope for diazo compound **247** was investigated. For diazo compounds **247**,[226] substitutions with different electronic and steric properties were tolerated on *para*-position of aromatic group to give cycloheptanoids **248a**-**248e** in moderate to good yield and with excellent enantioselectivity (Table 9). No desired product was found when 4-methoxyl substituted diazo compound **248f** was employed probably due to the possible competition of C−H insertion process which is well known in Rh(II) carbenoid chemistry.[226]

4.3.3 Investigation on Reactivity of Pentafulvenes in 1,3-Dipolar Cycloaddition Reactions of Cyclic Carbonyl Ylides

Towards 1,3-dipole, pentafulvene has been reported to be suitable in both (6+3) cycloaddition and (3+2) cycloaddition.[221] By analogy, there will be two possible pathways in 1,3-DC of carbonyl ylide and fulvene, affording 5-8 fused cyclooctanoids and 5-7 fused cycloheptanoids respectively (Scheme 44). Notably, both 5-8 fused cyclooctanoids[185] and 5-7 fused

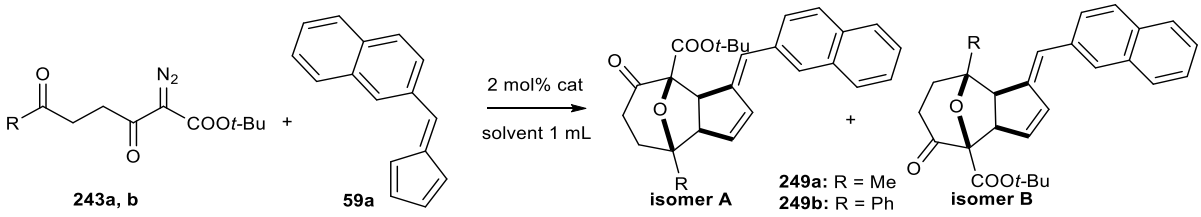
cycloheptanoids[158] are common structural units in a variety of polycyclic NPs. In the sole work involving five-membered cyclic carbonyl ylide and fulvene, the process of (3+2) cycloaddition was exclusively favored with substrate-controlled regioselectivity.[227]



Scheme 44. Possible pathway for 1,3-DC of pentafulvene with carbonyl ylide.

In the preliminary study, chiral dirhodium(II) catalysts (Fig. 8) were tested in the model reaction (Table 10). By analyzing NMR spectra of separable **249a**, (3+2) cycloadducts of fulvene **59a** and carbonyl ylide derived from **243** were identified with *endo*-selectivity (*see 7.4.2*). As outlined in Table 10, in a typical procedure, various dirhodium(II) catalysts were investigated for the model reaction, but almost 1:1 mixture of separable isomers was observed and the highest ee was only 60% (entries 1-11, Table 10). Out of two optimal catalysts, Rh_2(*S*-NTTL)$_4$ (**240**) was chosen as model catalyst for further optimization. In light of previous experience, the use of syringe pump to add diazo compound slowly is usually beneficial for enantioselectivity. However, decreased enantioselectivity was found when adding diazo compound by syringe pump over 1 hour (entry 12, Table 10). Surprisingly, reverse enantioselectivity and limited conversion were observed by decreasing temperature to -20^{o}C (entry 13, Table 10). Further screening on solvents also failed to improve the regio- and enantioselectivity (entries 14-20, Table 10). No desired product was found when using THF as solvent, probably owing to fast decomposition of carbonyl ylides in polar solvent (entry 17, Table 10). Additionally, significant decrease on enantioselectivity was observed by employing the diazo compound with phenyl substitution, albeit with better regioselectivity. (entry 21, Table 10)

Table 10. Condition optimization of (3+2) cycloaddition reaction of pentafulvene and carbonyl ylide.[a]

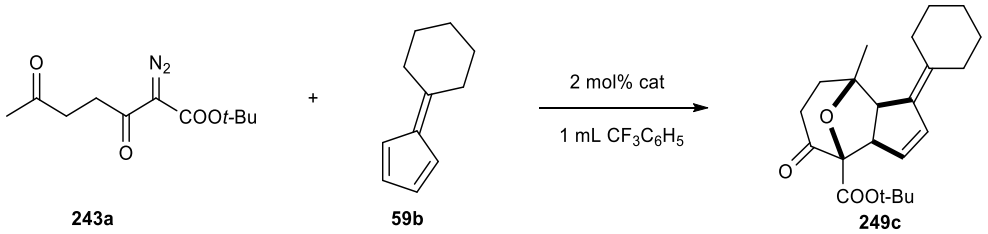


Entry	R	cat	solvent	yield (%)	Ratio (**A**:**B**)	ee (%)	
						A	**B**
1	Me	Rh_2(*S*-PTA)$_4$ **182d**	$CF_3C_6H_5$	55	43:57	47	9
2	Me	Rh_2(*S*-PTV)$_4$ **182e**	$CF_3C_6H_5$	72	47:53	53	11
3	Me	Rh_2(*S*-PTIL)$_4$ **182g**	$CF_3C_6H_5$	77	47:53	29	-5
4	Me	Rh_2(*S*-PTTL)$_4$ **182a**	$CF_3C_6H_5$	65	54:46	60	11
5	Me	Rh_2(*S*-TCPTTL)$_4$ **182b**	$CF_3C_6H_5$	72	47:53	36	52
6	Me	Rh_2(*S*-TFPTTL)$_4$ **182c**	$CF_3C_6H_5$	84	54:46	20	32
7	Me	Rh_2(*S*-PTAD)$_4$ **182h**	$CF_3C_6H_5$	77	53:47	37	-3
8	Me	Rh_2(*S*-PTPA)$_4$ **182f**	$CF_3C_6H_5$	81	53:47	45	14
9	Me	Rh_2(*S*-DOSP)$_4$ **178**	$CF_3C_6H_5$	84	51:49	47	33
10	Me	Rh_2(*R*-BTPCP)$_4$ **241**	$CF_3C_6H_5$	72	40:60	-5	-13
11	Me	Rh_2(*S*-NTTL)$_4$ **240**	$CF_3C_6H_5$	75	48:52	57	32
12[b]	Me	Rh_2(*S*-NTTL)$_4$ **240**	$CF_3C_6H_5$	75	48:52	45	31
13[c]	Me	Rh_2(*S*-NTTL)$_4$ **240**	$CF_3C_6H_5$	29	50:50	-32	-37
14	Me	Rh_2(*S*-NTTL)$_4$ **240**	Hexane	65	44:56	15	-8
15	Me	Rh_2(*S*-NTTL)$_4$ **240**	Toluene	70	52:48	50	17
16	Me	Rh_2(*S*-NTTL)$_4$ **240**	DCM	53	45:55	3	-14
17	Me	Rh_2(*S*-NTTL)$_4$ **240**	THF	n.r.	-	-	-
18	Me	Rh_2(*S*-NTTL)$_4$ **240**	FC_6H_5	72	53:47	53	21
19	Me	Rh_2(*S*-NTTL)$_4$ **240**	Ethyl acetate	36	33:67	11:	-13
20	Me	Rh_2(*S*-NTTL)$_4$ **240**	$CF_3C_6H_5$: Hexane (1:1)	50	43:57	49	23
21	Ph	Rh_2(*S*-NTTL)$_4$ **240**	$CF_3C_6H_5$	82	15:85	35	23

[a] Unless otherwise noted, a flame dried *Schlenk* tube was charged with catalyst Rh(II) catalyst (2.00 μmol, 0.02 equiv.), **59a** (0.10 mmol, 1.00 equiv.) and 0.5 mL solvent under the protection of Ar. Then the solution of diazo compound **243** (0.15 mmol, 1.50 equiv.) in 0.5 mL solvent was added slowly into the reaction mixture. [b] The solution of diazo compound **243** in 0.5 mL $CF_3C_6H_5$ was added over 1 hour by syringe pump. [c] The reaction was performed under -20°C.

To address the issue of regioselectivity, a disubstituted fulvene **59b** was employed, inspired by the improvement of regioselectivity in the seminal work by using the same fulvene.[227] As expected, only one regioisomer was found in the model reaction (Table 11). However, the enantioselectivity remained moderate after screening of catalysts. Notably, the addition of 4Å MS in this case was able to promote conversion and yield. In conclusion, the optimization on reaction conditions and modification of substrate all failed to give cycloheptanoid **249** in considerable enantioselectivity.

Table 11. Condition optimization of (3+2) cycloaddition reaction of pentafulvene and carbonyl ylide.[a]



243a **59b** **249c**

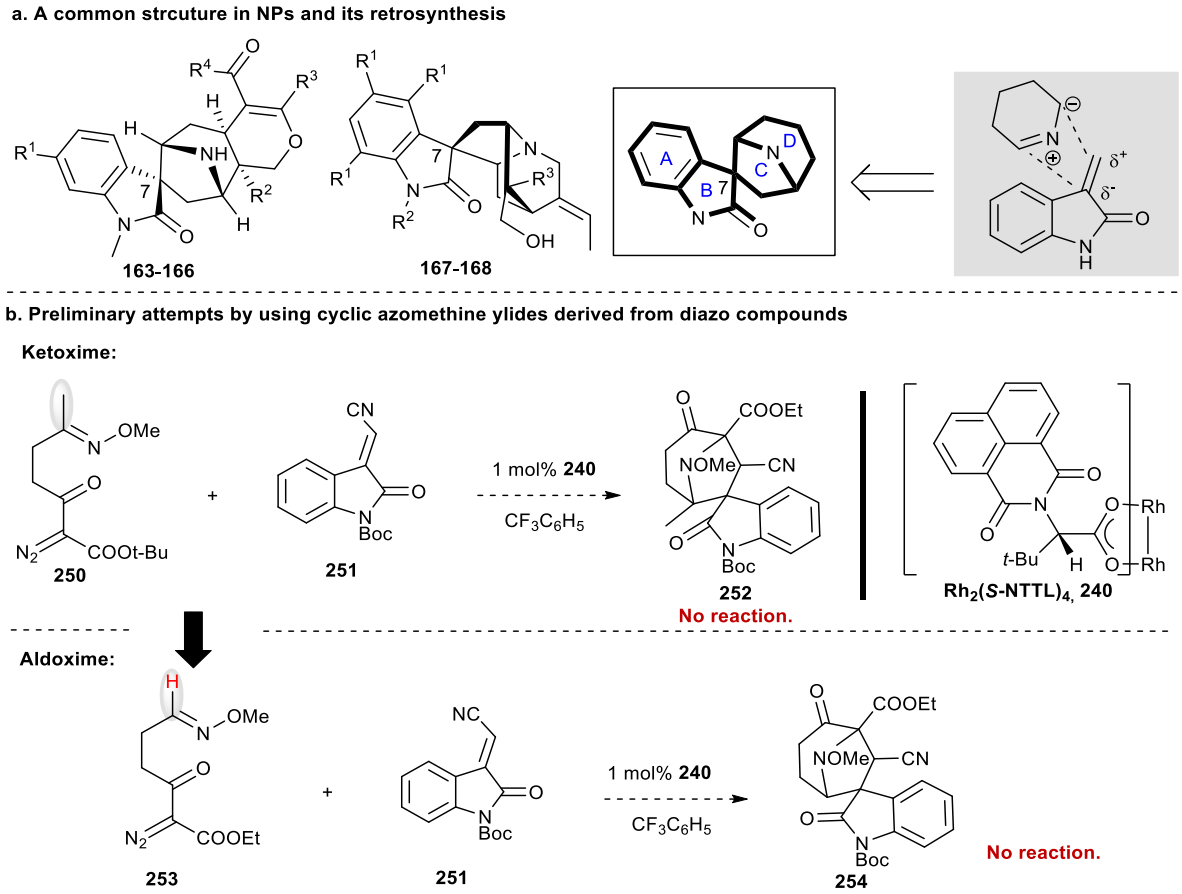
Entries	cat	yield (%, for major)	ratio	ee (%)
1	Rh_2(*S*-PTTL)$_4$	42	>90:10	15
2 [b]	Rh_2(*S*-PTTL)$_4$	70	>90:10	17
3[b]	Rh_2(*S*-TFPTTL)$_4$	75	>90:10	32
4[b]	Rh_2(*S*-DOSP)$_4$	73	>90:10	48
5[b]	Rh_2(*S*-TCPTTL)$_4$	94	>90:10	57

[a] Unless otherwise noted, a flame dried *Schlenk* tube was charged with catalyst Rh(II) catalyst (2.00 μmol, 0.02 equiv.), **59b** (0.10 mmol, 1.00 equiv.) and 0.5 mL $CF_3C_6H_5$ under the protection of Ar. Then the solution of diazo compound **209a** (0.15 mmol, 1.50 equiv.) in 0.5 mL $CF_3C_6H_5$ was added slowly into the reaction mixture. [b] 20 mg 4Å MS was added.

4.3.4 Enantioselective Synthesis of Tropanes by 1,3-Dipolar Cycloaddition Reactions of Cyclic Azomethine Ylides Derived from Diazo Compounds

Besides the potential application in tropane synthesis by cyclic azomethine ylides generated from diazo compound (as stated in **4.2**), another inspiration for this project is the common structure unit embodied in spirooxindole alkaloids **163**-**168** (Scheme 45a). Due to the paucity in natural sources of NPs **163**-**168**, it would be highly valuable to develop methodology to construct such privileged scaffold rapidly for further chemical biology study. To date, a linear synthesis from tryptophan in 6 steps is the major method to synthesize such core,[153-155,228] as well as one sole diastereoselective methodology[229] with less than 20% yield. There is no catalytic asymmetric reaction to access such structure unit. In retrosynthesis analysis, 1,3-DC

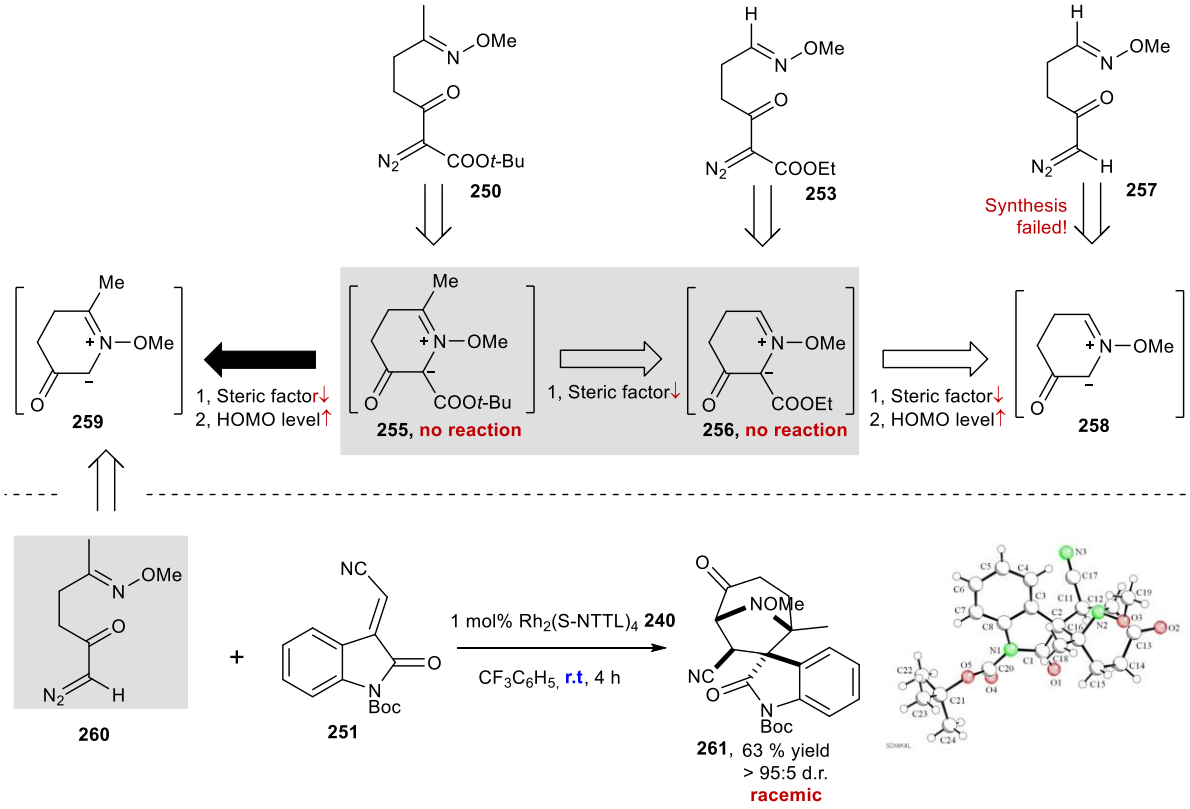
of six-membered cyclic azomethine ylide and 3-methylene-2-oxindole could be one feasible strategy (Scheme 45a). Hence, as one of the most reactive dipolarophiles, 3-methylene-2-oxindole with cyano group **251** was chosen as standard dipolarophile. For the precursors of corresponding azomethine ylide intermediates, diazoketoesters with a tailed oxime functionality **250** and **253** were synthesized according to Padwa's pioneering work (Scheme 45b).[216,217] However, by using Rh(II) catalyst **240**, no desired product was found in both cases.



Scheme 45. Preliminary results of 1,3-DC of 3-methylene-2-oxindole with cyclic azomethine ylide.

Through rational analysis and design, two different strategies were conceived to address the issue of inadequate reactivity (Scheme 46). Starting from intermediates **255** and **256**, the reactivity of intermediate might be enhanced by the removal of ester group from intermediate **256**, due to the raising HOMO level and reduced steric hindrance. However, the precursor **257** for intermediate **258** could not be synthesized. On the other hand, intermediate **259** without ester group compared with **255** might also possess higher reactivity due to the same reasons. Delightfully, the precursor **260** could be synthesized. In its subsequent 1,3-DC with **251**, the desired product **261** could be isolated in 63% yield in a single diastereomer form, albeit with no enantioselectivity by using chiral Rh(II) catalysts. In this reaction, the diazo compound **260**

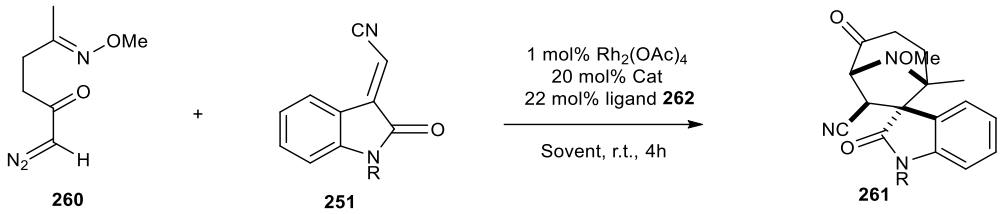
can be fully consumed immediately after the addition of chiral Rh(II) catalysts, but the reaction needs 4h to reach full conversion. Based on this observation, the failure on enantioinduction by chiral Rh(II) catalysts was ascribed to the rapid dissociation of Rh(II) from the azomethine ylide **259** before being trapped by dipolarophile **251**.



Scheme 46. Rational design of azomethine ylide precusors.

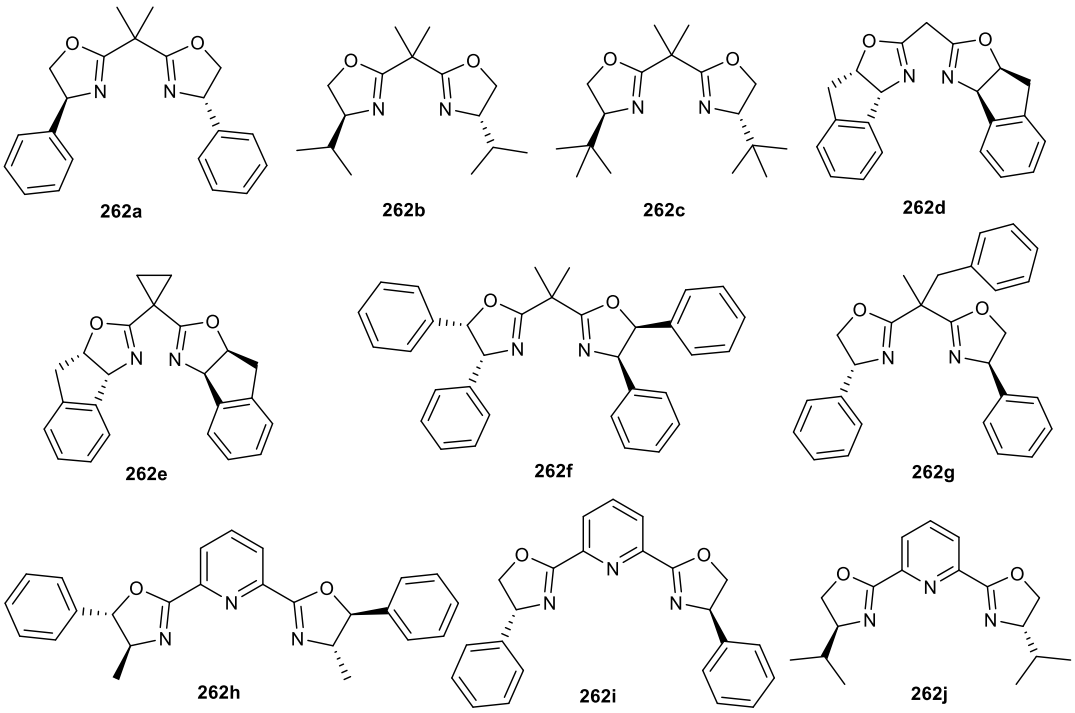
As discussed in asymmetric catalytic reaction of carbonyl ylides (in **4.1.2**), chiral Lewis acid catalysis usually was introduced as a complementary strategy to chiral Rh(II) catalysis. By analogue, chiral Lewis acid catalysis should also be feasible due to the presence of 1,3-dicarbonyl moiety embedded in 3-methylene-2-oxindole **251**. Inspired by the prior works, diverse substrates and chiral Lewis acid complexes were tested (Table 12).[230-232]

Table 12. Condition optimization of 1,3-DC of 3-methylene-2-oxindole with cyclic azomethine ylide..



Entries	R	cat	ligand	solvent	procedure	yield (%)	d.r.	ee (%)
1	Boc	$Mg(NTf_2)_2$	**262a**	DCM	A	68	>95:5	66
2	Boc	$Mg(ClO_4)_2$	**262a**	DCM	A	63	3:1	34
3	Boc	$Cu(OTf)_2$	**262a**	DCM	A	34	>95:5	5
4	Boc	CuOTf	**262a**	DCM	A	58	>95:5	2
5	Boc	$Mg(NTf_2)_2$	**262a**	DCM	B	68	>95:5	67
6	Boc	$Mg(NTf_2)_2$	**262a**	DCM	C	78	>95:5	60
7	Boc	$Mg(NTf_2)_2$	**262a**	THF	B	n.r.	-	-
8	Boc	$Mg(NTf_2)_2$	**262a**	Et_2O	B	24	>95:5	31
9	Boc	$Mg(NTf_2)_2$	**262a**	$C_6H_5CF_3$	B	44	>95:5	59
10	Boc	$Mg(NTf_2)_2$	**262a**	$CHCl_3$	B	49	>95:5	58
11	Boc	$Mg(NTf_2)_2$	**262b**	DCM	B	53	>95:5	12
12	Boc	$Mg(NTf_2)_2$	**262c**	DCM	B	53	>95:5	0
13	Boc	$Mg(NTf_2)_2$	**262d**	DCM	B	58	>95:5	0
14	Boc	$Mg(NTf_2)_2$	**262e**	DCM	B	53	>95:5	8
15	Boc	$Mg(NTf_2)_2$	**262f**	DCM	B	28	>95:5	-53
16	Boc	$Mg(NTf_2)_2$	**262g**	DCM	B	49	>95:5	63
17	Boc	$Mg(NTf_2)_2$	**262h-j**	DCM	A	n.r.	-	-
18	Boc	$Sc(OTf)_3$	**262i**	DCM	A	n.r.	-	-
19	Boc	$Yb(OTf)_3$	**262i**	DCM	A	n.r.	-	-
20	Piv	$Mg(NTf_2)_2$	**262a**	DCM	B	n.r.	-	-
21	Cbz	$Mg(NTf_2)_2$	**262a**	DCM	B	73	>95:5	33
22	Ac	$Mg(NTf_2)_2$	**262a**	DCM	B	40	>95:5	40

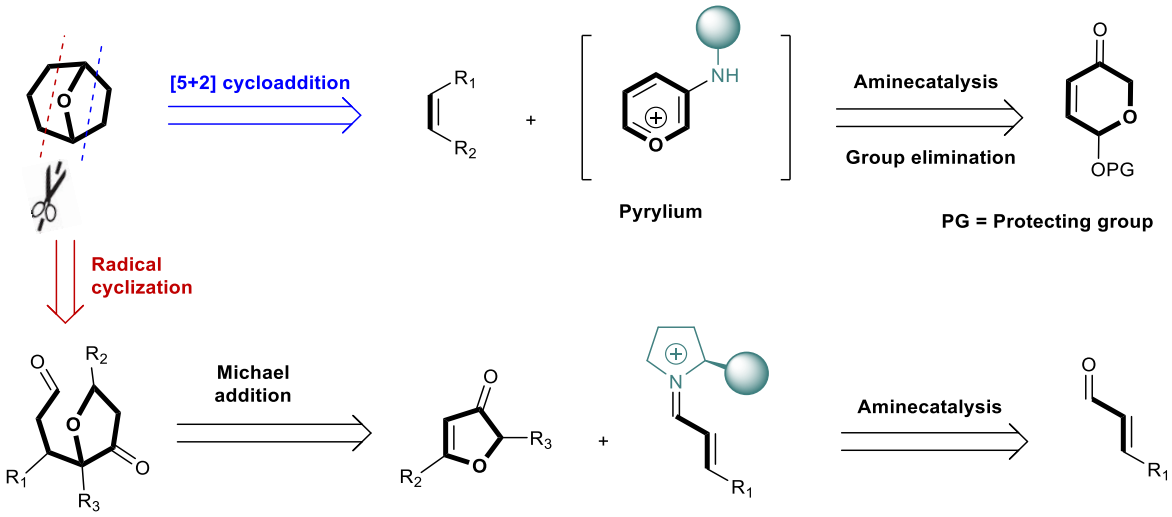
Reaction conditions: **Procedure A**, under the protection of Ar, chiral ligand (0.22 equiv., 0.011 mmol) and corresponding Lewis acid (0.2 equiv., 0.01 mmol) in 0.5 mL of solvent were stirred vigorously in a flame dried *Schlenk* tube at room temperature for 30 min. Then the 3-methylene-2-oxindole **251** (1 equiv., 0.05 mmol), $Rh_2(OAc)_4$ (0.01 equiv., 0.0005 mmol), and 20 mg 4AMS were added for another 15 min stirring. After that, the diazo compound **260** (1.1 equiv., 0.05 mmol) in 0.5 mL of DCM was added in dropwise. The reaction was allowed to proceed in 4 h; **Procedure B**, the same with procedure A, except Mg was heated to 150°C under *vacuum* for 30 min; **Procedure C**, the same with procedure A, except Mg was heated to 150°C under vacuum for 30 min, and syringe pump was used to add diazo compound in 1 h, followed by further 3 h stirring.



As outlined in Table 12, different Lewis acids were tested by using **262a** as ligand, and $Mg(NTf_2)_2$ proved to be the optimal, affording the desired product **261** in 68% yield and 66% ee (entries 1-4). However, poor reproduciblity was found due to highly hydroscopic nature of $Mg(NTf_2)_2$. Intensive optimization on procedure revealed that a constantly reliable result could be obtained by heating $Mg(NTf_2)_2$ to 150°C for 0.5 hour under high *vacuum* (entry 5). The utilization of syringe pump to add diazo compound **260** over 1 hour led to higher yield but reduced ee (entry 6). Subsequent solvent screening disclosed that DCM was optimal (entries 7-10). Furthermore, no improvement on enantioselectivity was achieved by screening of ligands (entries 11-17) and classic combinations of Pybox with either $Sc(OTf)_3$ or $Yb(OTf)_3$ (entries 18 and 19). Besides the condition optimization, protecting groups were also investigated, in which Boc was the optimal (entries 20-24). In conclusion, the reaction conditions indicated in entry 5 proved to be the optimal, but only moderate ee (67%) was obtained.

4.3.5 Enantioselective Synthesis of 8-Oxabicyclo[3.2.1]octanes by Amine Catalysis

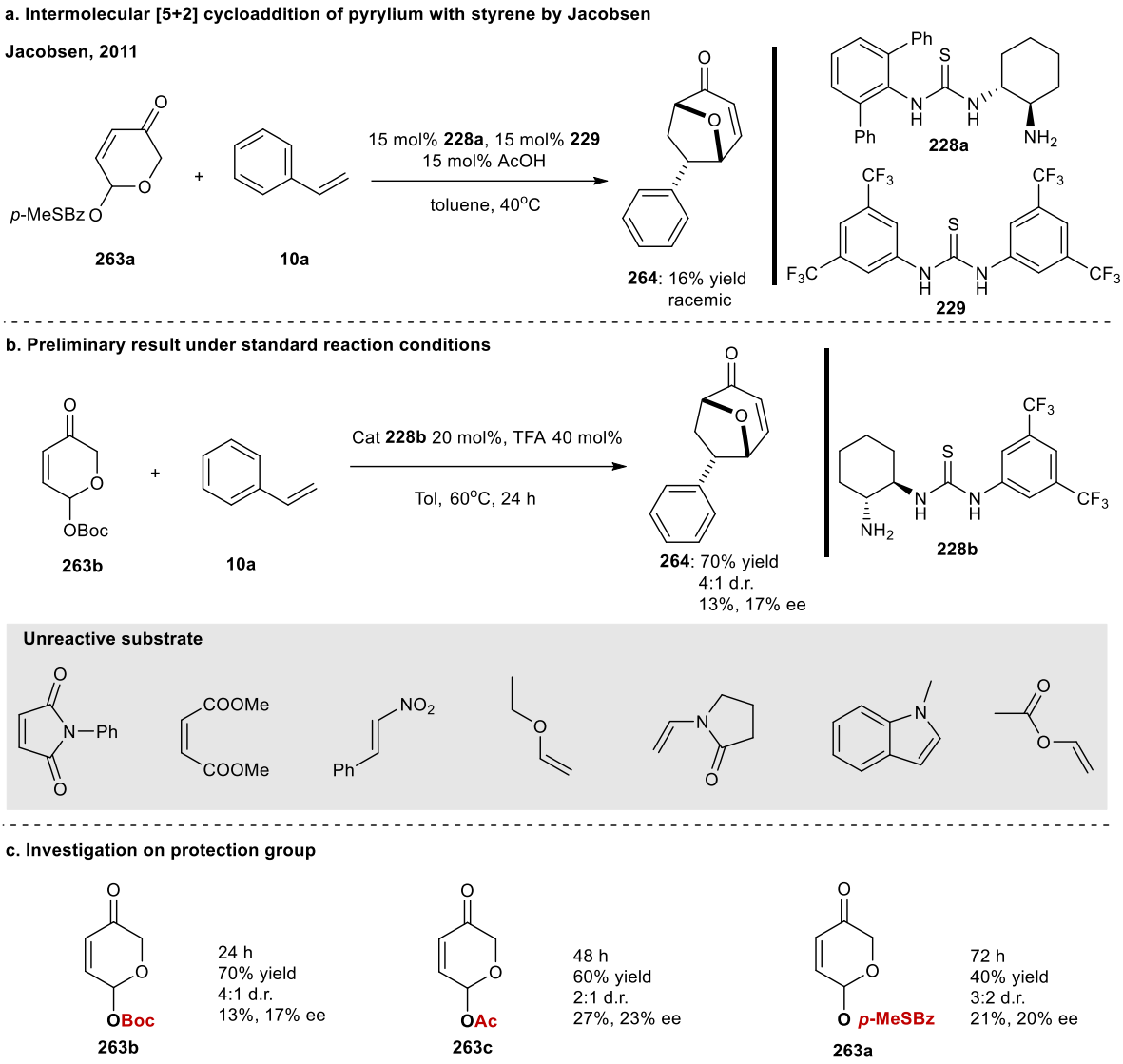
To access 8-oxabicyclo[3.2.1]octane compound collection rapidly, two retrosynthesis strategies were conceived based on aminecatalysis (Scheme 47). On one hand, inspired by the intramolecular (5+2) cycloaddition by Jacobsen in 2011 (Scheme 42),[218] the first strategy involves an intermolecular (5+2) cycloaddition of pyrylium generated from protected pyranones through group elimination. The other strategy is a stepwise chiral-amine-catalyzed Michael reaction followed by reductive radical cyclization mediated by SmI_2, inspired by the total synthesis of Englerin A by Chain.[222]



Scheme 47. Two strategies to access 8-oxabicyclo[3.2.1]octanes based on aminecatalysis.

4.3.5.1 Intermolecular (5+2) Cycloaddition by Amine Catalysis

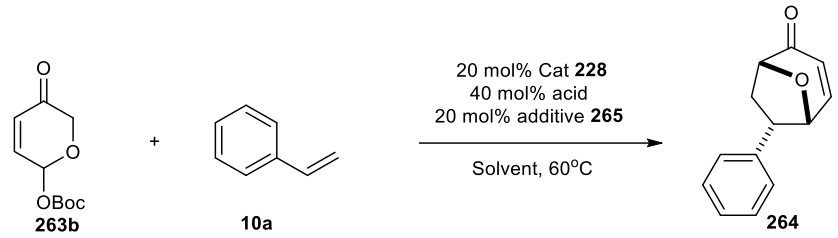
Initially, extensive screening of substrate was performed in the intermolecular (5+2) cycloaddition of pyrylium derived from Boc protected pyranone **263b**, by using amine **228b** as catalyst and TFA as additive (Scheme 48). In contrast to Jacobsen's work in which no enantioselectivity and low yield were observed by using styrene **10a** as dipolarophile (Scheme 48a),[218] it was found that the desired (5+2) cycloadduct could be obtained from styrene **10a** in 24 hours with 70% yield and up to 13% ee for the major diastereomer (Scheme 48b). With this starting point, the investigation on protection group of pyranones was conducted (Scheme 48c). Compared with Boc protected pyranone **263b**, acetyl protected pyranone **263c** could afford the desired (5+2) cycloadduct in similar yield (60%), decreased d.r. (2:1), and higher ee (27%, 23%) by prolonging reaction time. The substrate **263a** with *p*-thiomethylbenzoyl gave decreased yield (40%) and d.r. (3:2), but with higher ee (21%). Considering the efficiency of optimization process, Boc protected pyranone **263b** was used as the standard substrate.



Scheme 48. Preliminary result of the intermolecular (5+2) cycloaddition.

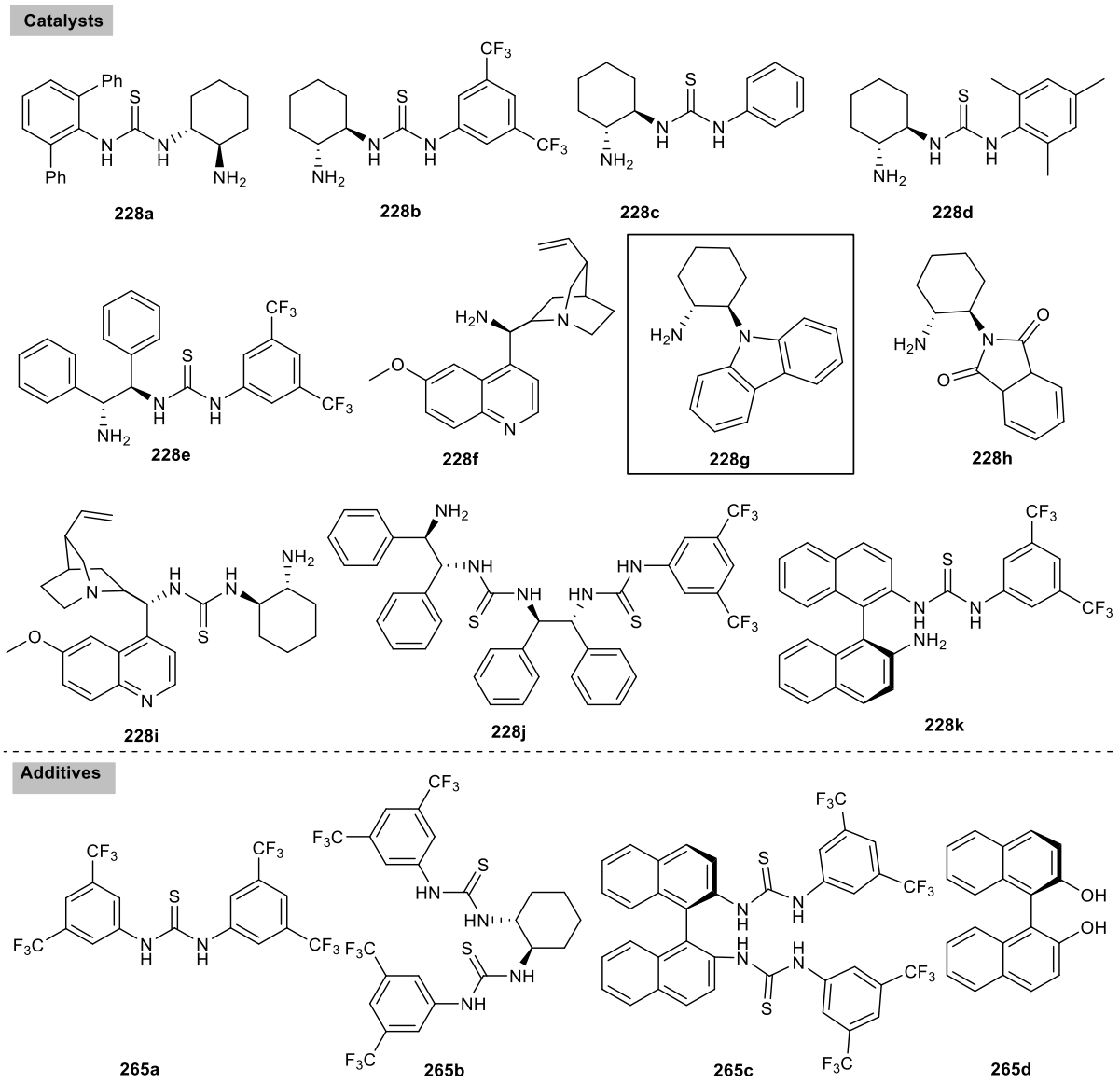
After the determination of model reaction, intensive investigations on solvent, acid, catalyst, and additive were conducted (Table 13). At first, solvent screening disclosed toluene was optimal, while polar solvent such as EtOH, 1,4-dioxane failed to give the desired product (entries 1-4). In addition, no product was observed by employing acids except TFA (entries 5-7). Subsequent extensive screening on catalysts revealed primary amine catalyst without hydrogen-bonding donor **228g** was optimal, giving 40% ee for the major diastereomer, albeit with only 30% yield (entry 13). Screening of **265** as additives indicated that hydrogen-bonding doners were beneficial for enantioselectivity, but the highest ee was still limited to 67% (entry 21).

Table 13. Condition optimization of (5+2) cycloaddition reaction of styrene and pyrylium.[a]



Entries	solvent	acid	cat	additive	yield (%)	t (h)	d.r.	ee (%)	
								major	minor
1	Toluene	TFA	**228b**	none	70	24	4:1	13	17
2	$CHCl_3$	TFA	**228b**	none	50	48	2:1	<5	20
3	1,4-Dioxane	TFA	**228b**	none	n.r.	-	-	-	-
4	EtOH	TFA	**228b**	none	n.r.	-	-	-	-
5	Toluene	TsOH	**228b**	none	mess	-	-	-	-
6	Toluene	AcOH	**228b**	none	n.r.	-	-	-	-
7	Toluene	BzOH	**228b**	none	n.r.	-	-	-	-
8	Toluene	TFA	**228a**	none	35	48	4:1	23	<5
9	Toluene	TFA	**228c**	none	55	96	3:2	23	50
10	Toluene	TFA	**228d**	none	45	96	6:5	27	49
11	Toluene	TFA	**228e**	none	25	96	7:1	15	20
12	Toluene	TFA	**228f**	none	n.r.	-	-	-	-
13	Toluene	TFA	**228g**	none	30	24	4:1	40	<5
14	Toluene	TFA	**228h**	none	60	18	3:1	19	21
15	Toluene	TFA	**228i**	none	30	96	4:1	<5	25
16	Toluene	TFA	**228j**	none	30	96	3:1	<5	13
17	Toluene	TFA	**228k**	none	25	18	12:1	<5	35
18	Toluene	TFA	**228g**	**265a**	40	32	4:1	46	30
19[b]	Toluene	TFA	**228g**	**265a**	45	72	2:1	59	57
20[b]	Toluene	TFA	**228g**	**265b**	40	96	4:1	53	52
21[b]	Toluene	TFA	**228g**	**265c**	40	32	5:2	67	40
22[b]	Toluene	TFA	**228g**	**265d**	35	72	4:1	55	43

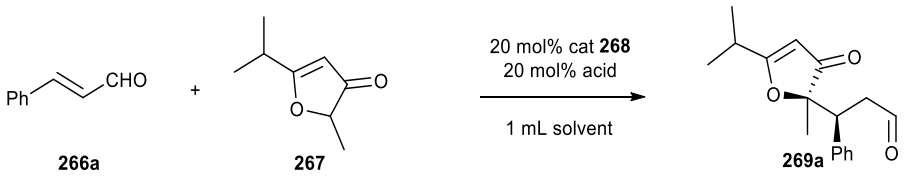
[a] Unless otherwise noted, to the solution of **263b** (0.10 mmol, 1.00 equiv.), styrene **10a** (0.30 mmol, 3.00 equiv.), catalyst **228** (0.02 mmol, 0.20 equiv.), additive **265** (0.02 mmol, 0.20 equiv.) in 1.0 mL solvent was added acid (0.04 mmol, 0.40 equiv.) slowly. Then the mixture was allowed to be stirred for specific time at 60°C. [b] Acid (0.02 mmol, 0.20 equiv.) was used.



4.3.5.2 Stepwise Strategy with Asymmetric Amine-catalyzed Michael Reaction

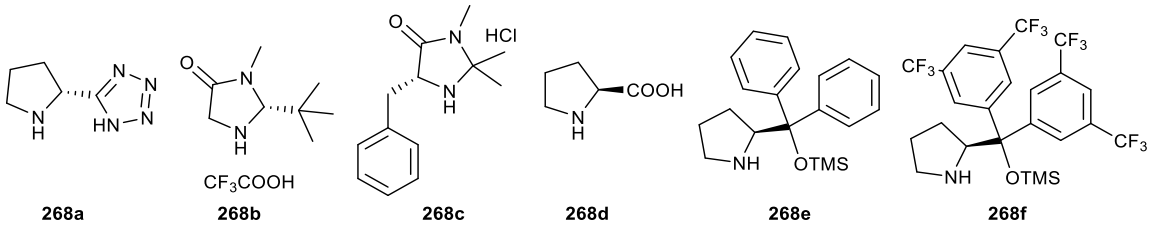
The asymmetric amine-catalyzed Michael reaction has been well documented in the last decade.[233-235] By covalent activation of α,β-unsaturated aldehydes through iminium mechanism, enantioselectivity can be induced efficiently. Although various Michael donors prove to be suitable, no example involving 3-furone has been reported before proposing this project.[236,237] By employing cinnamaldehyde **266a** as Michael acceptor, the optimization of reaction conditions was performed (Table 14). Catalyst **268f** could afford the desired product efficiently with 86:14 d.r. and up to 97% ee, by using toluene as solvent and OFBA as additive (entry 6). Subsequent screening on acid and solvent failed to improve either yield or stereoselectivity (entries 7-10). The absolute configuration of **269a** was assigned according to the known literature.[237]

Table 14. Condition optimization of asymmetric amine-catalyzed Michael reaction.[a]

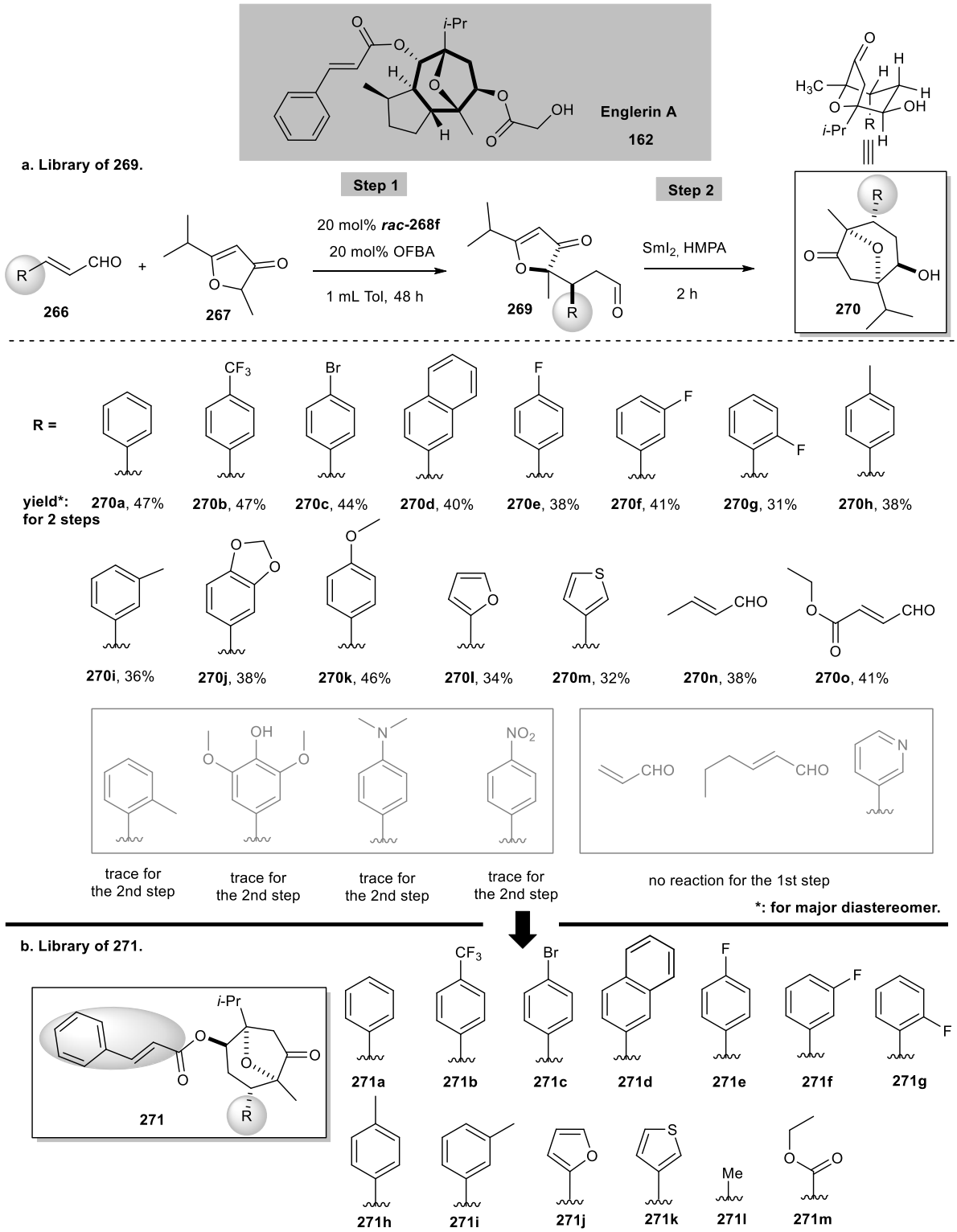


Entries	cat	acid	solvent	t (h)	yield (%)	d.r.	ee (%)[b]	
							Isomer **A**	Isomer **B**
1	**268a**	-	Toluene	48	trace	-	-	-
2	**268b**	-	Toluene	28	92	40:60	<5	<5
3	**268c**	-	Toluene	40	81	58:42	<5	73
4	**268d**	-	Toluene	96	55	76:24	<5	<5
5	**268e**	OFBA	Toluene	32	89	73:27	96	71
6	**268f**	OFBA	Toluene	48	89	86:14	97	90
7	**268f**	BA	Toluene	72	85	85:15	96	89
8	**268f**	OFBA	$CHCl_3$	96	77	78:22	97	95
9	**268f**	OFBA	THF	n.r	-	-	-	-
10	**268f**	OFBA	CH_3CN	n.r	-	-	-	-

[a] Unless otherwise noted, **266a** (0.15 mmol, 1.50 equiv.), 3-furone **267** (0.10 mmol, 1.00 equiv.), catalyst **268** (0.02 mmol, 0.20 equiv.), acid (0.02 mmol, 0.20 equiv.) were added into 1.0 mL solvent. Then the mixture was allowed to be stirred for specific time at r.t.. [b] ee was determined by chiral HPLC after **269a** was reduced to its alcohol by $NaBH_4$ in MeOH. OFBA: 2-fluorobenzoic acid; BA: benzoic acid.



Inspired by the SmI_2-mediated cyclization strategy in the total synthesis of Englerin A by Chain,[222] the Michael adduct **269a** was tested in the same conditions (Scheme 49a). Delightfully, the desired 8-oxabicyclo[3.2.1]octane **270** was obtained in moderate yield, and the relative configuration of additional chiral center in **270** was proposed in analogue to Chain's work.[222] Although the robust methodology had been established for the enantioselective synthesis of 8-oxabicyclo[3.2.1]octanes, a racemic compound library based on 8-oxabicyclo[3.2.1]octanes was firstly attained for preliminary biological evaluation.



Scheme 49. Compound library towards Englerin A.

Following the same procedure described in Chain's paper,[222] a library of 28 members was synthesized towards Englerin A structure, involving two major categories of compounds as demonstrated in Scheme 49. However, no bioactivity was observed for cell-based assays of Hedgehog pathway signaling, Wnt pathway signaling and autophagy by COMAS.

4.4 Summary and Perspective

In conclusion, diverse catalysis systems were investigated to access the biologically important cycloheptanoids, with a focus on 8-azabicyclo[3.2.1]octanes (tropane) and 8-oxabicyclo[3.2.1]octanes.

In **4.3.2**, the 1,3-DC of cyclic carbonyl ylides and tropone catalyzed by chiral Rh(II) catalysts was intensively investigated to provide efficient methods for the synthesis of enantioriched cyclopentanoid. By employing diazodiketoesters, (3+2) cycloaddition reactions of carbonyl ylides and carbonyl functionality on ketone was realized for the first time. Besides, through the variation of diazo substrate, the chemoselectivity of tropone could be switched to a (6+3) cycloaddition process to afford a distinct pattern of bridged cyclopentanoids with high molecular complexity and enantioselectivity.

In **4.3.3**, 1,3-DC of pentafulvene was also investigated by employing the same type of cyclic carbonyl ylides to access enantioriched 5-7 fused cycloheptanoids. First, the utilization of mono-substituted fulvene raised the issue of poor regioselectivity, and no significant improvement on regio- and enantioselectivity was achieved by optimization of reaction conditions. Subsequently, the employment of di-substituted fulvene indeed led to enhanced regioselectivity, but further screening of catalysts still failed to give higher enantioselectivity.

In **4.4.4**, a novel synthesis strategy of enantioriched tropanes was preliminarily investigated by a relay catalysis combining Rh(II)-catalyzed azomethine ylides generation and chiral Lewis acid catalysis. Although only moderate enantioselectivity had been realized for the standard reaction, the unique advantage of flexibly synthesizing varied tropane scaffolds indicates the tremendous potential of this methodology. Further optimizations on both catalyst and substrate are necessary.

In **4.4.5**, two strategies were designed to synthesize 8-oxabicyclo[3.2.1]octanes. In spite of considerable effort, the intermolecular (5+2) cycloaddition of pyrylium and styrene failed to give satisfactory stereoselectivity and yield. In addition, during this project, a similar reaction by using vinyl ether as dipolarophile was reported by Jacobsen in 2014 (Scheme 42). On the other hand, through reliable stepwise strategy, a 28-member compound library inspired by Englerin A was synthesized. However, no bioactivity was observed to date.

Chapter 5. Synthesis of Pyrroloisoquinolines by Phosphine Catalysis

5.1 Introduction

5.1.1 Pyrroloisoquinolines in Natural Products and Their Synthesis

Pyrroloisoquinoline moiety occurs in a diverse range of bioactive NPs and synthetic pharmaceutical compounds. For example, (+)-crispine A (**272**) possesses cytotoxic activity against SKOV3, KB, and HeLa human cancer cell lines;[238] (–)-Trolline (**273**) exhibits antibacterial activity against respiratory bacteria and antiviral activity against influenza virus A and B;[239] JNJ-7925476 (**274**) is a novel triple monoamine uptake inhibitor under development by Johnson & Johnson as an antidepressant drug candidate;[240] The biological study of (–)-Cryptaustoline (**275**) is limited except paralytic activity; (+)-Erysotramidine (**276**) is one member of natural erythrina alkaloids, and this family of NPs usually exhibits hypotensive, sedative, and anticonvulsive properties (Fig. 10).[241]

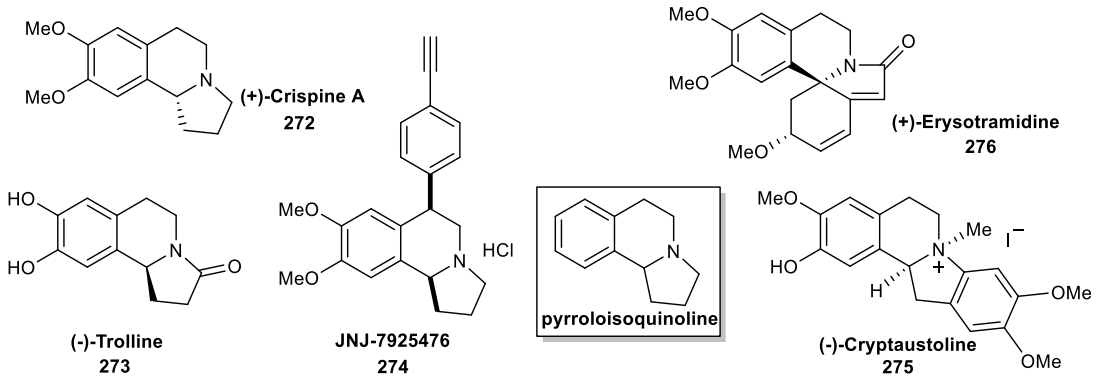


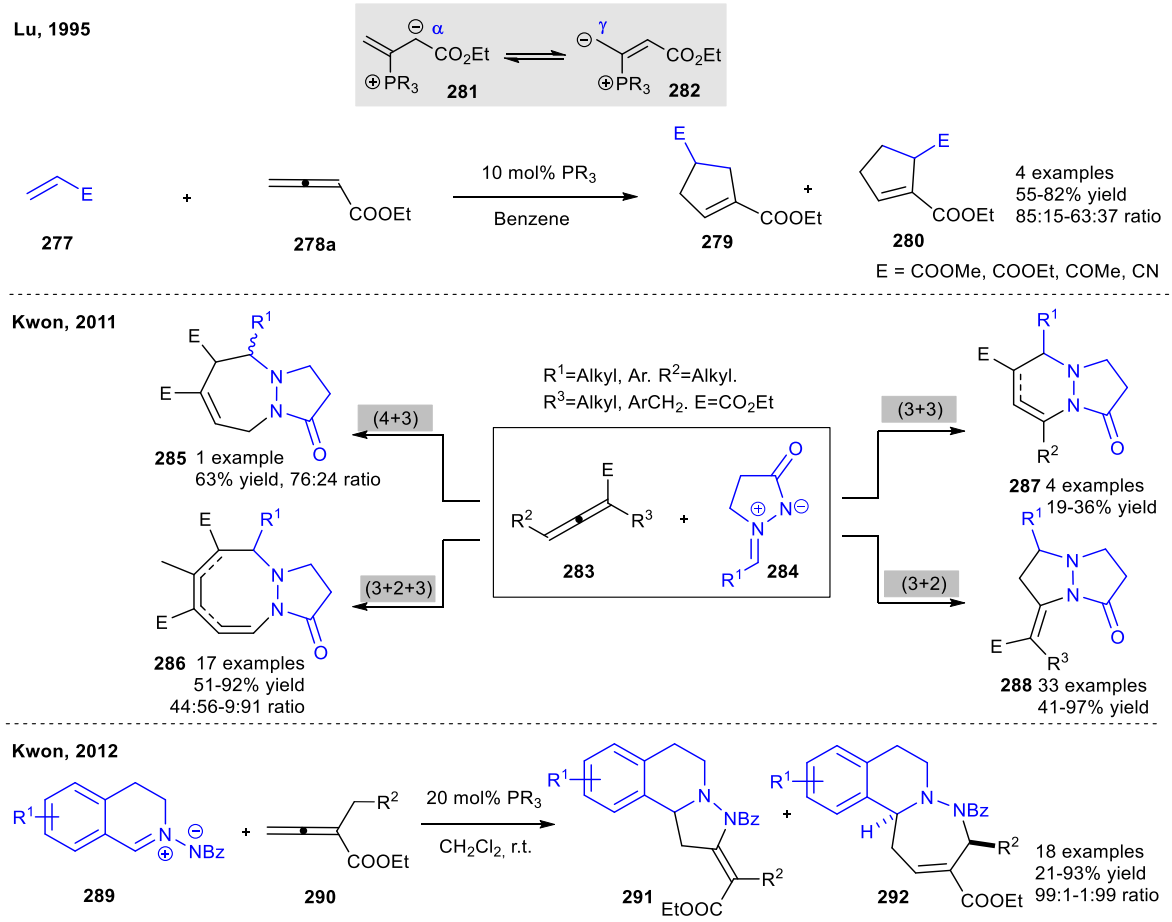
Figure 10. Representative naturally occurring pyrroloisoquinolines.

Owing to the diverse bioactivity of pyrroloisoquinolines, the development of corresponding methodology remains highly desirable.[2] Diverse strategies have been developed for the synthesis of pyrroloisoquinolines. On one hand, as a reliable approach, varied intramolecular cyclization strategies have been broadly applied, such as *N*-acyliminium mediated cyclization,[242-244] imide carbonyl activation,[245] coupling reactions,[246] and so on. Another major approach is 1,3-dipolar cycloaddition reactions (1,3-DC) of azomethine ylides due to its inherent advantages to access pyrrolidine.[247-249]

5.1.2 Phosphine-catalyzed Annulations of Allenes

Although the use of trivalent phosphines as nucleophilic catalysts can be traced back to the 1960s, it was not until 1995 that their first application in annulations of allenes was reported by Lu (Scheme 50).[250] In this work, a novel (3+2) annulation of ethyl 2,3-butadienoate **278**

with electron-deficient alkenes **277** was demonstrated, affording the cyclopentenes **279** and **280**. The observed regioselectivity was proposed to result from the presence of two reactive intermediates **281** and **282**, with negative charge on α position and γ position respectively. Inspired by this seminal work, considerable interest and effort have been devoted into this field. Throughout more than two decades, phosphine-catalyzed annulations of allenes have become one of the most efficient synthetic strategies for the synthesis of highly functionalized carbocycle or heterocycle motif.[20,21] Currently, besides the original (3+2) annulation discovered by Lu, (4+2) annulation also emerged as the other major reaction pattern, together with some rarely reported patterns such as (8+2), (4+3), (3+3) and (3+2+3).[246,247] With regard to substrate types, more than eight types of allenes with varied substitutions have been explored. The substrate scope of electrophiles has also been largely expanded, such as electron-deficient alkenes, imines, carbonyl moieties, aziridines, azomethine imines, and so on, dramatically increasing the molecular complexity and structural variety of the resulting annulation products.



Scheme 50. The first phosphine-catalyzed annulation reaction of allene and diverse reactivity of allenes towards azomethine imines.

Among diverse electrophiles, the investigation of 1,3-dipoles as electrophiles is still scarce due to the complicated reactivity resulting from the nature of 1,3-dipole. To date, only two examples involving stabilized azomethine imines were reported in racemic from by Kwon (Scheme 50).[251,252] In 2011, Kwon reported a phosphine-catalyzed (3+2), (3+3), (4+3) and (3+2+3) annulation of different allenes **283** and azomethine imines **284**.[251] The diverse reaction pathways could be influenced by substrate pattern and substitution type on phosphine catalyst. Later on, the same group demonstrated (3+2) and (3+4) annulations by the employment of another type of azomethine imines **289**.[252] Similarly, substrate types and phosphine catalysts have a critical influence on the ratio of isomers **291** and **292**.

5.2 Design Principle and Aim of the Project

Although the reactivity of azomethine imines in phosphine-catalyzed annulation of allenes has been investigated, azomthine ylides remain surprisingly unexplored. Considering the prevalence of isoquinoline moieties in bioactive NPs and synthetic pharmaceutical molecules, isoquinolinium methylides, a type of stable azomethine ylides, were chosen as standard substrates. The aim of this project is to explore the possible reactivity pathways of isoquinolinium methylides in the phosphine-catalyzed annulations of allenes. The subsequent aim would be the synthesis of compound library based on isoquinoline motif for further chemical biology study. Additionally, the asymmetric version of such transformation was also taken into consideration.

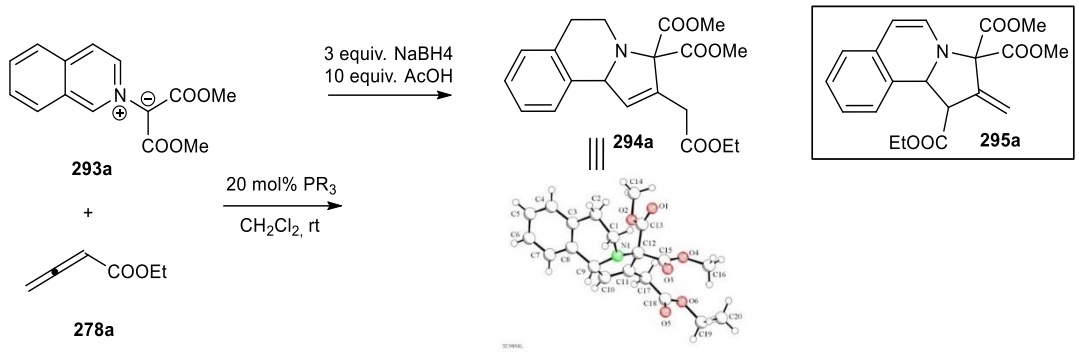
5.3 Result and Discussion

5.3.1 Racemic Phosphine-catalyzed Annulation Reactions of Isoquinolinium Methylides

The reaction of isoquinolinium methylide **293a** and ethyl 2,3-butadienoate **278a** was chosen as the model reaction. As summarized in Table 15, without treatment of any phosphine catalyst, only **295a** was isolated in 51% yield after 6 h as the consequence of background reaction. (entry 1) The addition of PPh_3 as catalyst gave a new product together with trace background product **295a** in 6 h. However, the new product was quite instable, probably due to the presence of enamine motif. Hence, a sequential reduction by $NaBH_4$ under acidic condition was performed in one pot manner, affording another moderately stable product **294a** in 57% yield for two steps (entry 2). The structure of **294a** was subsequently identified by X-ray crystallography analysis (by Dr. Constantin G. Daniliuc). Notably, an unusual alkene translocation occurred after (3+2) annulation process, resulting in the more thermally stable product **294a**. The following

screening of tertiary phosphine catalysts revealed that PBu_3 proved to be the optimal catalyst giving 75% yield in 10 minutes (Table 1, entry 3).

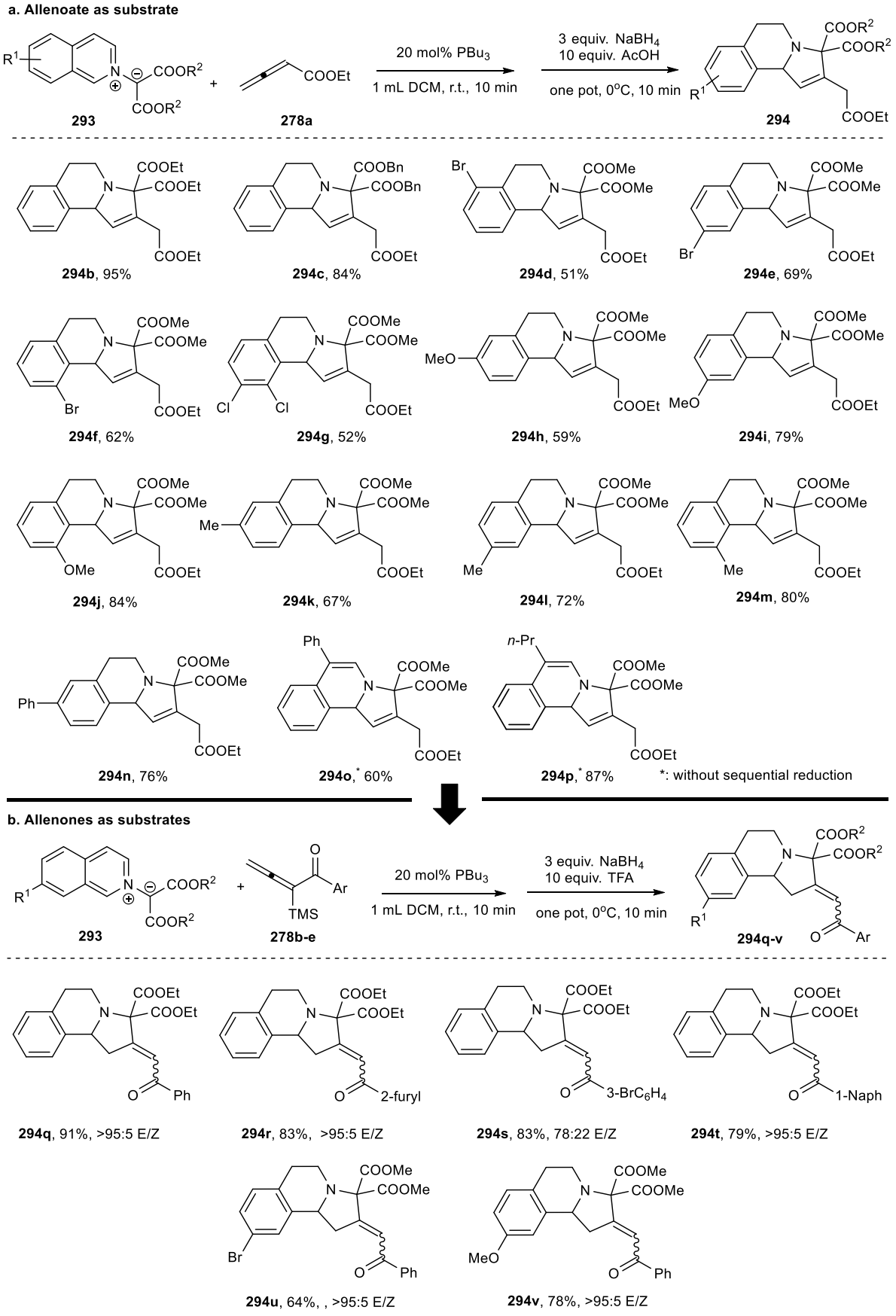
Table 15. Screening of reaction conditions.[a]



Entry	PR_3	Time	Yield[b](%)	
			295a	**294a**
1[c]	-	6 h	51	0
2	PPh_3	6 h	8	57
3	PBu_3	10 min	<5	75
4	$MePPh_2$	10 min	<5	62
5	Me_2PPh	10 min	<5	68
6	PCy_3	2 h	<5	62

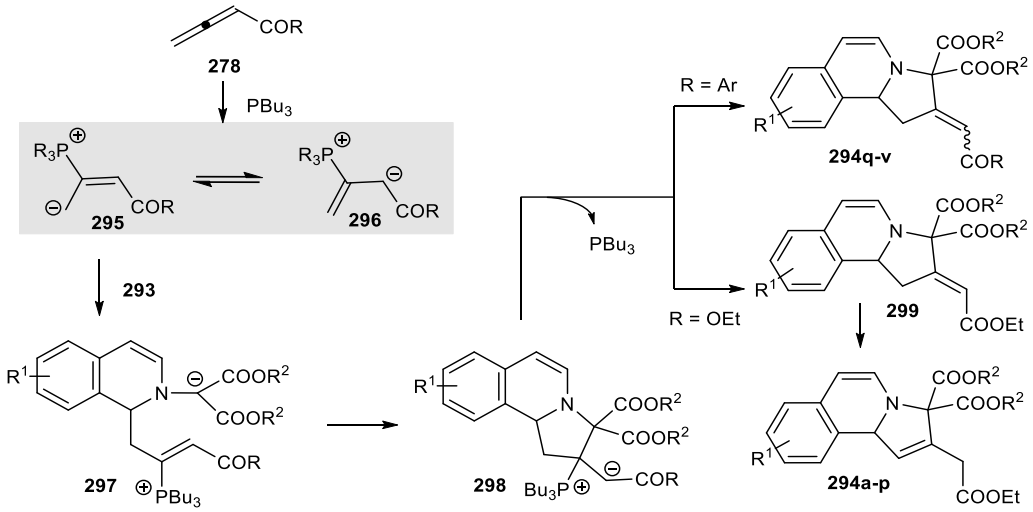
[a]. Unless otherwise noted, reactions were performed with **293a** (0.1 mmol, 1 equiv.), **278a** (0.15 mmol, 1.5 equiv.), PR_3 (0.02 mmol, 0.2 equiv.) in CH_2Cl_2 (1 mL) at room temperature. After reactions completed, $NaBH_4$ (0.3 mmol, 3 equiv.) and acetic acid (1 mmol, 10 equiv.) were added sequentially at 0 ℃. [b]. Isolated yield after column chromatography. [c]. Reaction was performed without phosphine catalyst and sequential reduction in one pot.

With the optimized reaction conditions in hand, the substrate scope of this transformation was investigated (Scheme 51). When allenoate **278a** was used, isoquinolinium methylide with ethyl and benzyl esters were also tolerated well in this reaction, providing the desired products **294b** and **294c**. With respect to variation of R^1, substitutions with different electronic properties on diverse positions of aromatic ring proved to be suitable, furnishing the products **294d-n** in satisfactory yield. In addition, without sequential reduction, the relative stable products **294o** and **294p** could be obtained from isoquinolinium methylides with either aromatic or aliphatic substitutions on 4-position of isoquinoline.



Scheme 51. Substrate scope of (3+2) annulation of isoquinolinium methylides and allenoates.

In contrast to allenoate, the reactivity of allenones were less explored in phosphine catalysis. Inspired by Loh's work in 2009,[253] α-trimethylsilyl substituted aryl allenones were synthesized and subjected to the annulations of isoquinolinium methylides. Delightfully, both aromatic and hetero aromatic group on allenones could be well tolerated, providing the desired γ-selective cycloadducts **294q-t**, in which **294c** was isolated as a 78:22 mixture of *E*/*Z* isomers. Furthermore, the products **294u** and **294v** were also obtained from isoquinolinium methylides with either electron drawing group or electron donating group. Interestingly, there was no alkene translocation when allenones were employed as dipoles.



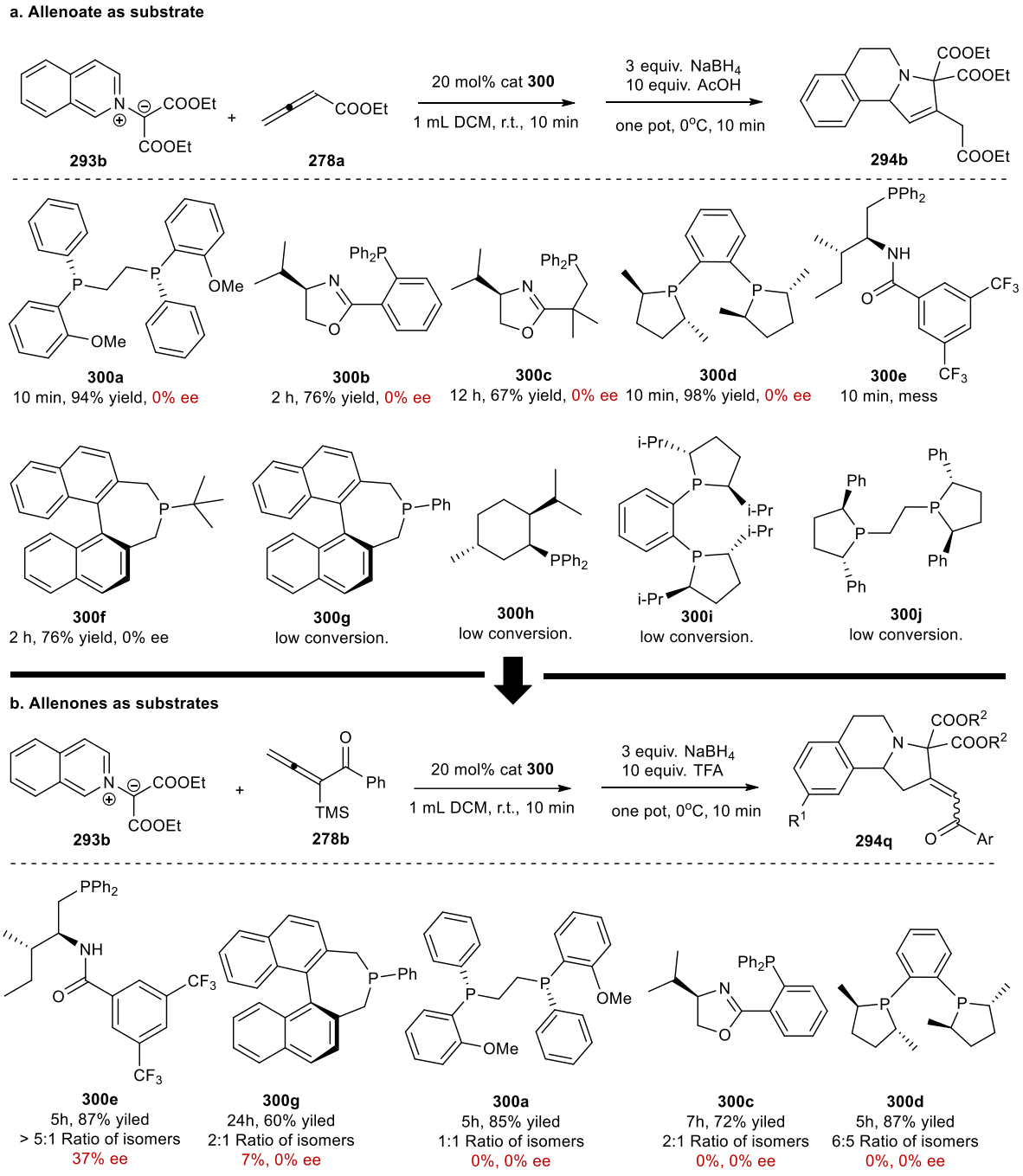
Scheme 52. Proposed mechanism for (3+2) annulations of isoquinolinium methylides and allenes.

A plausible mechanism was proposed based on prior mechanistic studies of nucleophilic phosphine catalysis (Scheme 52). The reactive intermediates **295** and **296** can be generated from the nucleophilic addition of phosphine to allenes **278**. However, only γ-selective intermediates **295** can react with the isoquinolinium methylides **293** to form intermediates **297**. The following intramolecular conjugate addition of **297** give intermediates **298**, followed by sequential β-elimination to provide the desired products **294q-v**, when R is the aromatic group. When R is ethoxy, the more thermally stable products **294a-p** are generated due to sequential isomerizations after the generation of **299**.

Figure 10. Representative compounds for inhibiting hedgehog signaling pathway.

This compound collection based on pyrroloisoquinolines was subjected to cell-based assays, including hedgehog signaling pathway, Wnt signaling pathway and autophage. Delightfully, several pyrroloisoquinoline-inspired compounds inhibited the hedgehog signaling pathway in the low micromolar range (Fig. 10).

5.3.2 Attempts to Asymmtric Phosphine-catalyzed Annulation Reactions of Isoquinolinium Methylides



Scheme 53. Chiral catalysts screening for the (3+2) annulations of isoquinolinium methylides and allenes.

As shown in Scheme 53, different chiral phosphine catalysts were tested in the (3+2) annulations of isoquinolinium methylides with two types of allenes. However, when allenoate **278a** was employed, no eantioselectivity was observed in the treatment of different chiral phosphine catalysts (Scheme 53a). In addition, only poor enantioselectivity (up to 37%) was achieved by catalyst **300e** when allenone **278b** was applied (Scheme 53b). To conclude, preliminary attempts failed to achieve considerable enantioselectivity for the asymmetric reactions of isoquinolinium methylides with allenes.

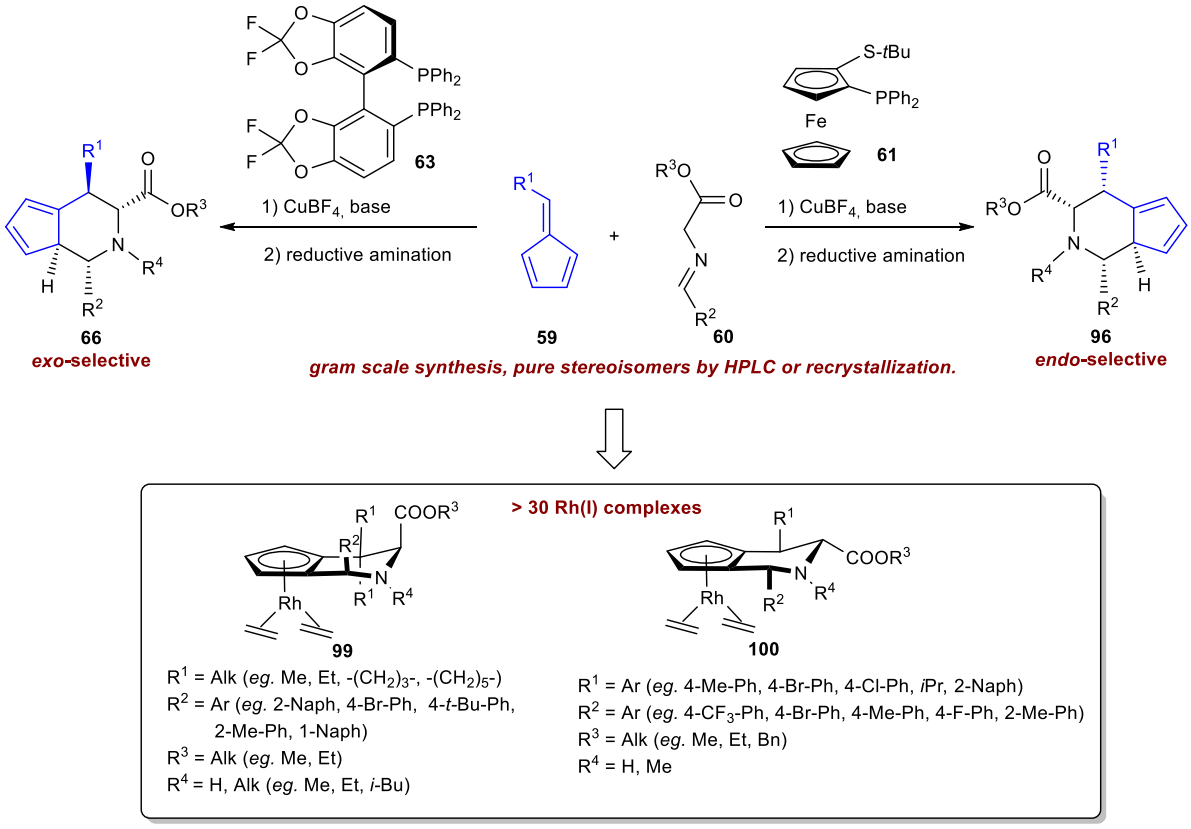
5.4 Summary and Perspective

To conclude, the reactivity of isoquinolinium methylides has been exploited in the annulation reactions of allenes enabled by nucleophilic phosphine catalysis. With this methodology, the valuable pyrroloisoquinolines can be accessed regio- and diastereoselectively under the optimized reaction conditions. However, only poor enantioselectivity was observed in the attempts to realize asymmetric version of this transformation, after intensive screening of chiral phosphine catalysts. The follow-up biological evaluation of such racemic pyrroloisoquinolines revealed several inhibitors in the hedgehog signaling pathway in the low micromolar range.

For the phosphine-catalyzed annulation reactions of allenes and 1,3-dipoles, only few examples were reported, although the reactivity of such transformations had been shown to be considerable diverse by Kwon (Scheme 50). In the future, one of the directions in this field might be the application of other types of 1,3-dipoles into versatile annulation patterns chemoselectively. Additionally, the realization of corresponding transformations in a catalytic enantioselective manner would also be highly valuable.

Chapter 6. Summary

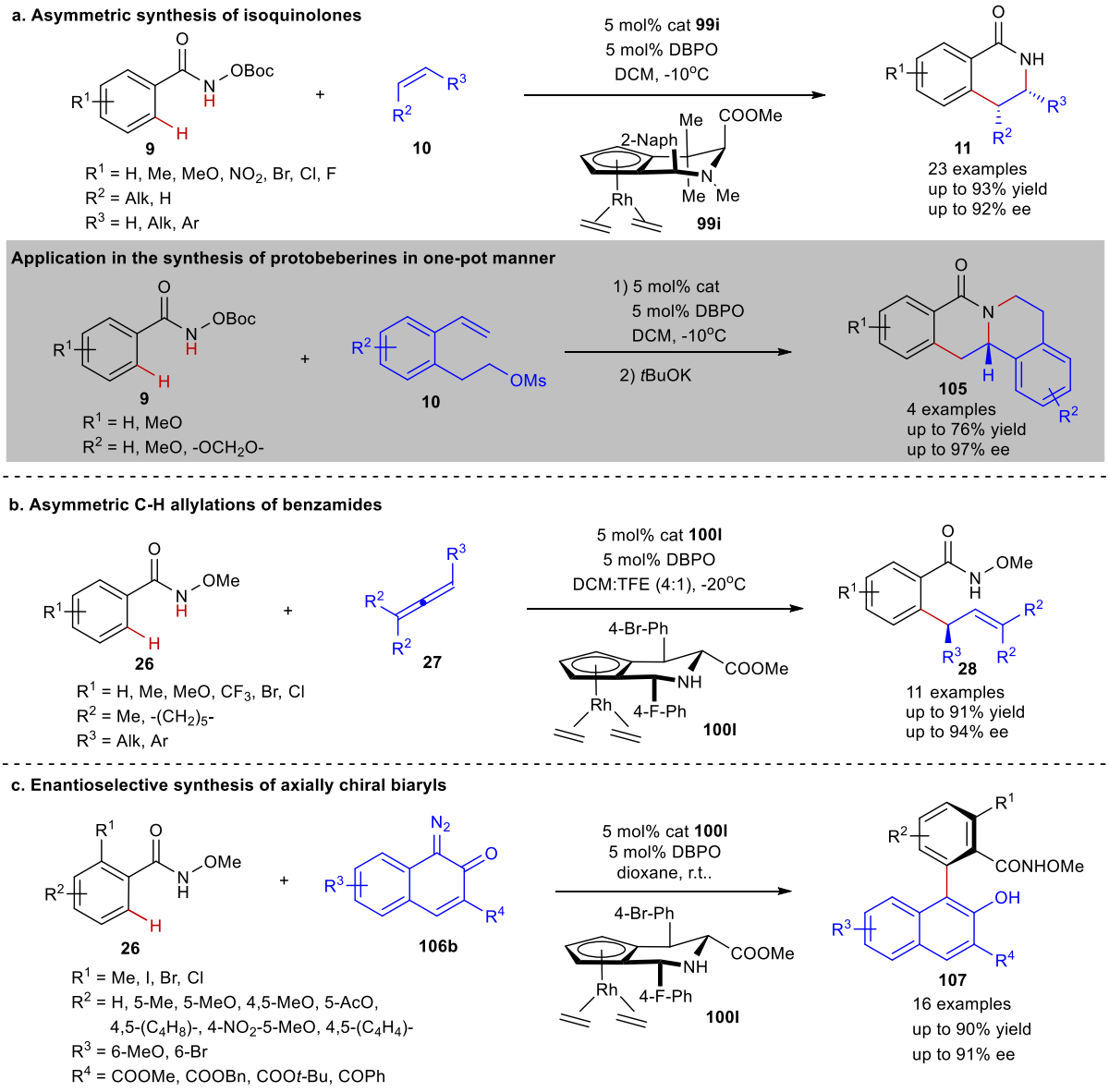
In this thesis, to harness and evolve chemistry tools for biology-orientated synthesis (BIOS), various catalysis systems were explored to access compound collections inspired by bioactive natural products (NPs). On one hand, a novel type of cyclopentadienyl ligands for asymmetric C−H activation was developed to provide a more efficient chemistry tool for the exploration of chemical space defined by small molecules (Chapter 2). On the other hand, diverse compounds collections were synthesized expediently by harnessing the power of known catalysis systems (Chapter 3-5). Such known catalysis systems include chiral dirhodium(II) catalysis, chiral Lewis acids catalysis, chiral amine catalysis, and nucleophilic phosphine catalysis. Remarkably, versatile bioactivities were identified by the follow-up biological evaluation of such compound collections in different cell-based assays.



Scheme 54. The synthesis of cyclopentadienyl ligands through (6+3) cycloadditions and their Rh(I) complexes.

Chapter 2 described the development of chiral Cp ligands for asymmetric C−H activation. As proofs of concept, three C−H activation reactions were realized in highly enantioseletive manner by using the corresponding Rh(I) complexes as catalysts. As shown in Scheme 54, the chiral ligands (**66**, **96**) can readily be synthesized on gram scale by either recrystallization of the enantioenriched (6+3) cycloadducts or preparative HPLC on chiral phase of the racemic (6+3) cycloadducts. Notably, both structure and configuration of such Cp derivatives can be

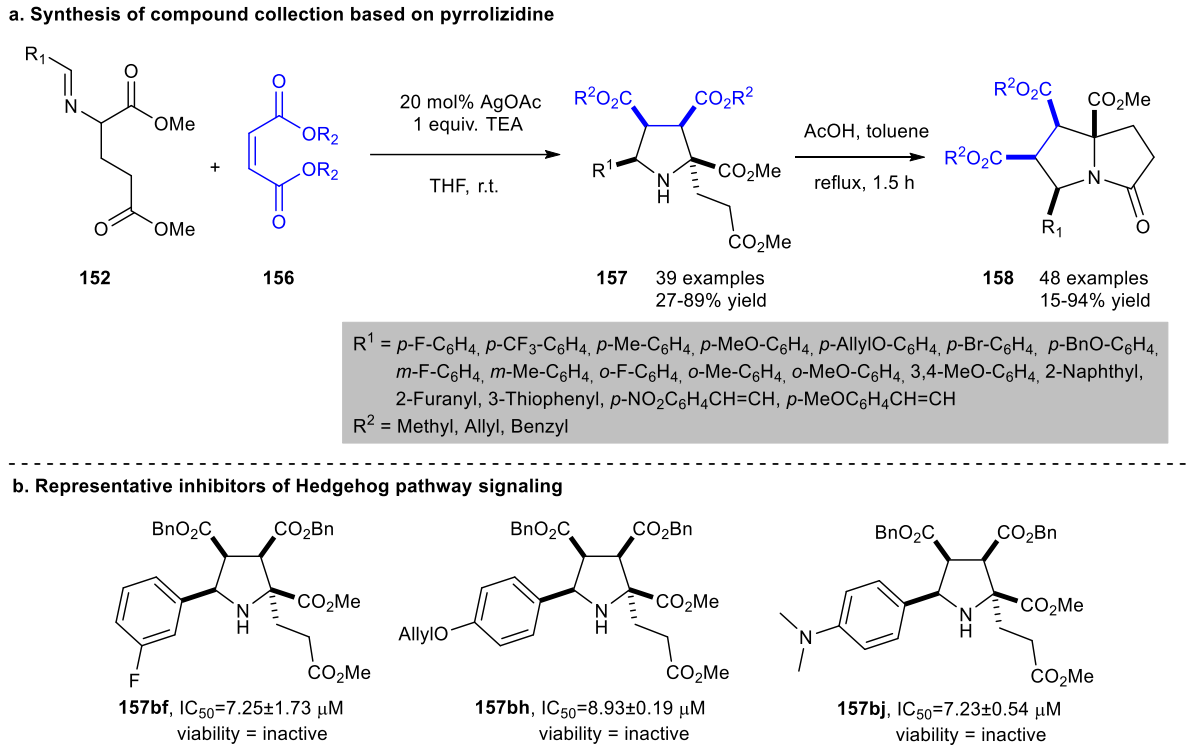
efficiently adjusted by means of flexible ligand-controlled enantioselective (6+3) cycloaddition reactions. Facilitated by the rapid synthesis of chiral Cp ligands through this highly efficient approach, a 30-member library of corresponding Rh(I) complexes (**99**, **100**) was constructed.



Scheme 55. Three reactions as proofs of concept to demonstrate the generality of newly developed Cp ligands.

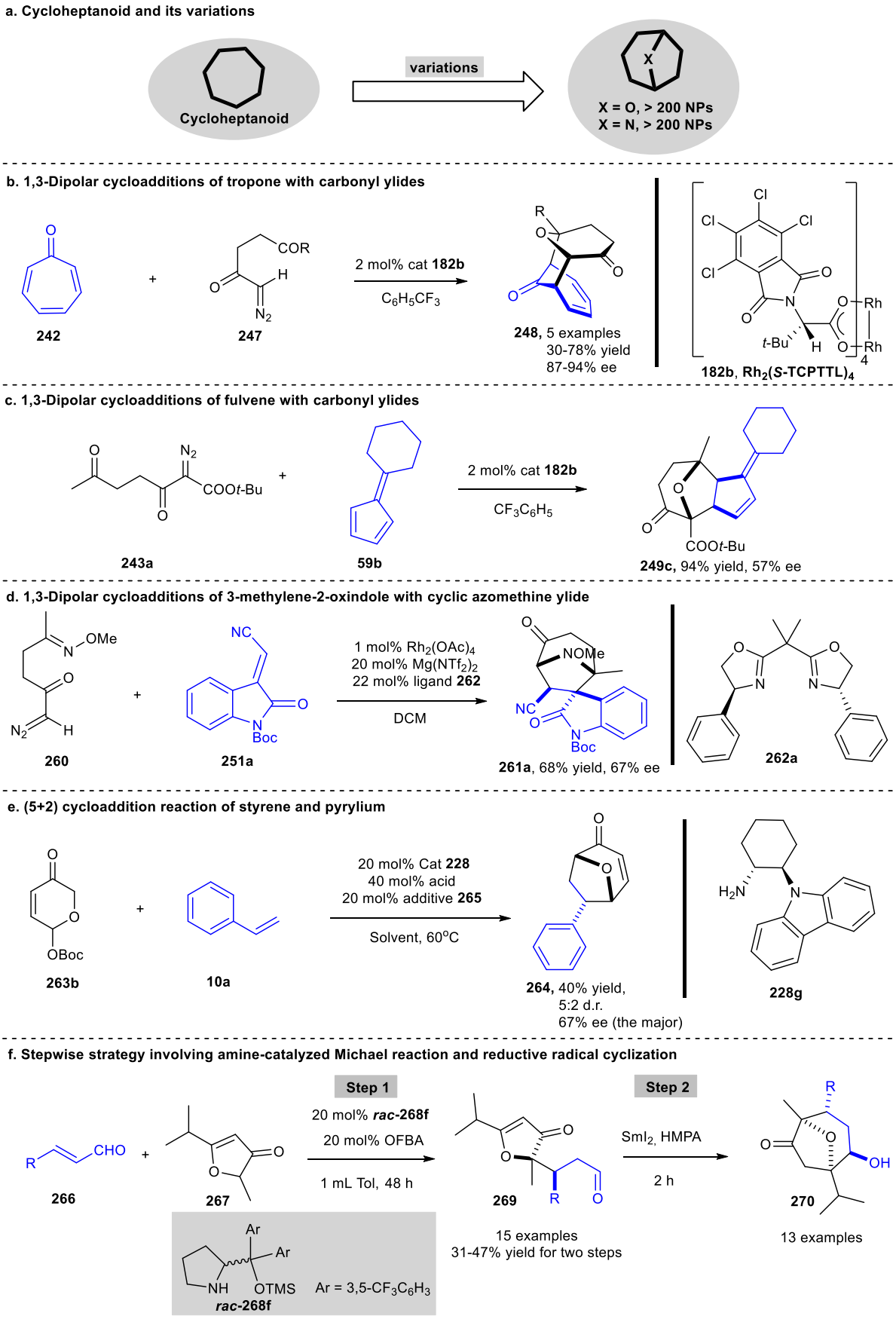
The generality and applicability of these chiral Cp ligands was substantially proved by successful applications of their corresponding Rh(I) complexes in three asymmetric C–H activation reactions (Scheme 55). First, two transformations including the asymmetric synthesis of isoquinolones and the asymmetric C–H allylation of benzamides were realized in highly enantioselective manner, which were previously steered enantioselectively by two types of known Cp ligands (Scheme 55a, b). These successful applications indicate the newly developed Cp ligands can actually rival the previously developed Cp ligands. Notably,

ortho-substituted styrenes also proved to be suitable in the enantioselective synthesis of isoquinolones enabled by the newly developed Cp ligands, which had not been reported for this transformation in chiral or racemic manner before. Facilitated by the unique catalytic property for *ortho*–substituted styrenes, the synthesis of protoberberines analogs **105** was achieved by a cascade reaction with a sequence of C–H functionalization followed by intramolecular S_N2 reaction in one-pot manner (Scheme 55a). Furthermore, an unprecedented C–H activation reaction was realized to afford valuable axially chiral biaryl compounds **107** with excellent enantioselectivity (Scheme 55c).



Scheme 56. The synthesis of compound collection based on pyrrolizidine by 1,3-dipolar cycloadditions.

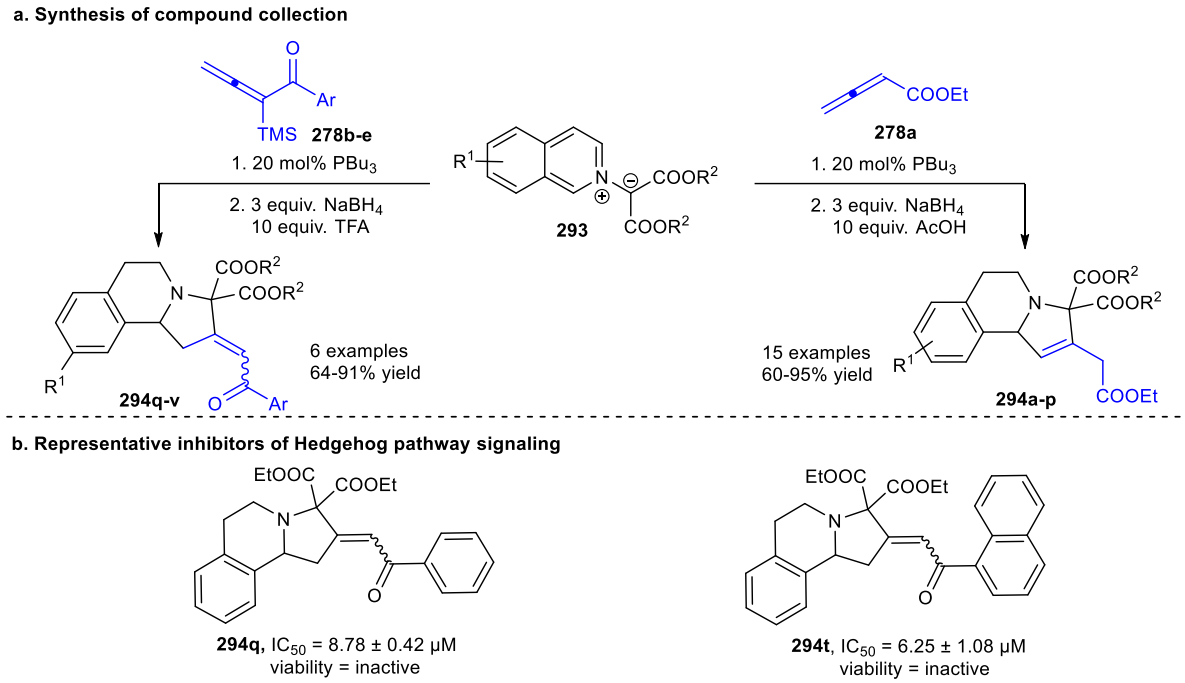
Chapter 3 described an efficient catalytic strategy for the synthesis of pyrrolizidine alkaloids (PAs) inspired compound collection by 1,3-dipolar cycloaddition reaction (1,3-DC) of azomethine ylides **152** and maleates **156** (Scheme 56a). By the employment of AgOAc as catalyst, a 87-member library of pyrrolizidines (**158**) and pyrrolidines (**157**) was obtained rapidly. Through subsequent biological evaluation, the bioactivities such as inhibition of Hedgehog pathway signaling were disclosed (Scheme 56b).



Scheme 57. Different strategies to access cycloheptanoids especially in enantioselective manner.

Chapter 4 demonstrated four different strategies to access biologically important cycloheptanoids, with a focus on 8-azabicyclo[3.2.1]octanes (tropane) and 8-oxabicyclo[3.2.1]octanes (Scheme 57). As shown in Scheme 57a, the first strategy involves the 1,3-DC of tropone **242** and cyclic carbonyl ylides derived from diazodiketones **247** catalyzed by chiral Rh(II) catalyst **182b** (Scheme 57b). The bridged cyclopentanoids **248** with high molecular complexity and enantioselectivity were obtained efficiently. The second strategy is 1,3-DC of pentafulvenes and the same type of cyclic carbonyl ylides to afford the enantioriched 5-7 fused cycloheptanoids (Scheme 57c). The employment of di-substituted fulvene such as **59b** proved to be critaical for the diastereoselectivity, but the enantioselectivity remained moderate (up to 57% ee) even after the intensive optimization of reaction conditions and catalysts. As for the third strategy, a novel synthesis approach to access enantioriched tropanes was preliminarily investigated by a relay catalysis combing Rh(II) catalysis for generation of azomethine ylides and chiral Lewis acid catalysis (Scheme 57d). After intensive optimization of substrates, catalysts and reaction conditions, only moderate enantioselectivity (up to 67% ee) had been achieved for the standard reaction of 3-methylene-2-oxindole **251** and diazo compound **260** by using $Mg(NTf_2)_2$ as Lewis acid and **262a** as ligand. At last, the fourth strategy consists of two approaches to synthesize 8-oxabicyclo[3.2.1]octanes by amine catalysis (Scheme 57e, f). Regarding the first approach, the optimization of intermolecular (5+2) cycloaddition of styrene **10a** and pyrylium salts generated from pyranone **263b** failed to give the desired cycloheptanoids **264** with satisfactory stereoselectivity (up to 67% ee) and yield (Scheme 57e). On the other hand, the second stepwise approach comprises a amine-catalyzed Michael addition of 3-furones **267** and α,β-unsaturated aldehydes **266**, and a subsequent reductive radical cyclization mediated by SmI_2 (Scheme 57f). A 28-member compound library (**270**) inspired by Englerin A was synthesized. However, no bioactivity was found in the subsequent biological evaluation.

Chapter 5 depicted the synthesis of pyrroloisoquinolines **294** by a phosphine-catalyzed annulation reaction of isoquinolinium methylides **293** and allenes **278** (Scheme 58a). Trialkyl phosphine PBu_3 proved to be the efficient catalyst for this transformation. Interestingly, allenoate **278a** and allenones **278b-e** gave different products due to alkene translocation. Unfortunately, only poor enantioselectivity was achieved for this transformation after screening of various chiral phosphine catalysts. Nevertheless, the follow-up biological evaluation of the racemic pyrroloisoquinolines revealed several inhibitors of the hedgehog signaling pathway (Scheme 58b).



Scheme 58. The synthesis of compound collection based on pyrroloisoquinoline through phophine catalysis.

Chapter 7. Experimental Part

7.1 General Methods and Materials

Unless otherwise noted, all commercially available compounds were used as provided without further purifications. Solvents for chromatography were technical grade.

Analytical thin-layer chromatography (TLC) was performed on *Merck silica gel aluminium plates* with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using *silica gel Merck 60* (particle size 0.040-0.063 mm) or aluminum oxide (activated, neutral, Brockmann I, Sigma-Aldrich).

^{1}H-NMR and ^{13}C-NMR were recorded on a *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz), *INOVA500* (500 MHz) and *Bruker DRX700* using CD_2Cl_2, $CDCl_3$, benzene-d_6 or methanol-d_4 as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard (CD_2Cl_2: δ = 5.32 ppm for ^{1}H, δ = 54.00 ppm for ^{13}C; $CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; benzene-d_6: δ = 7.16 ppm for ^{1}H, δ = 128.06 ppm for ^{13}C; methanol-d_4: δ = 4.87 ppm for ^{1}H, δ = 49.00 ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz).

High resolution mass spectra were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Accela HPLC*-System (HPLC column: *Hypersyl GOLD*, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a *Bruker Tensor 27* spectrometer (ATR, neat) and were reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured in a *Schmidt + Haensch Polartronic HH8* polarimeter.

The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (CHIRALCEL IC, CHIRALCEL IA; eluent: (CH2Cl2/EtOH = 100/2) / *iso*-hexane, *i*-PrOH / *iso*-hexane; 4.6 mm x 250 mm, particle size 5 µm). The chiral HPLC methods were calibrated with the corresponding racemic mixtures. The ratio of regioisomers and diastereomers was determined by ^{1}H-NMR analysis via integration of characteristic signals of methyl esters. Chemical yields refer to isolated substances. Yields and enantiomeric excesses, diastereoselectivity and regioselectivity are given in the tables.

7.2 Experimental Part for Development of Tunable Cyclopentadienyl Ligands

7.2.1 Synthesis of Ligands 96a-96i and 66a-66m

Method A for Synthesis of Chiral Cp Ligands 96a, 96b, 96e-h:

(*Rp*)-2-(*tert*-Butylthio)-1-(diphenylphosphino)ferrocene (0.02 mmol, 0.05 equiv.) and tetrakis-(acetonitrile)copper(I) tetrafluoroborate (0.02 mmol, 0.05 equiv.) were dissolved in DCM:MeOH (2mL:10uL) and stirred at ambient temperature for 5 min. To the resulting solution α-iminoesters (0.40 mmol, 1 equiv.), $CsCO_3$ (0.40 mmol, 1 equiv.) and fulvenes (0.60 mmol, 1.5 equiv.) were added. The mixture was allowed to be stirred at ambient temperature for specific time until full conversion monitored by TLC. The solvent was removed *in vacuo* and column chromatography on silica gel afforded the pure products.

Method B for Synthesis of Chiral Cp Ligands 96c, 96d, 96i:

(*Rp*)-2-(*tert*-Butylthio)-1-(diphenylphosphino)ferrocene (0.012 mmol, 0.03 equiv.) and tetrakis-(acetonitrile)copper(I) tetrafluoroborate (0.012 mmol, 0.03 equiv.) were dissolved in 2 mL 1,4-dioxane and stirred at ambient temperature for 5 min. To the resulting solution α-iminoesters (0.40 mmol, 1 equiv), Et_3N (0.40 mmol, 1 equiv) and fulvenes (0.60 mmol, 1.5 equiv.) were added. The mixture was allowed to be stirred at ambient temperature for 1 h. The solvent was removed *in vacuo* and column chromatography on silica gel afforded the pure products.

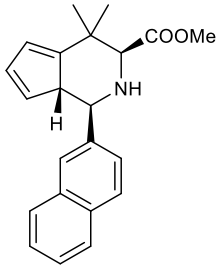
Method C for Synthesis of Chiral Cp Ligands 66a-66j, 66l, 66m:

R-(–)-5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4-4'-bi-1,3-benzodioxole (0.02 mmol, 0.05 equiv.) and tetrakis-(acetonitrile)copper(I) tetrafluoroborate (0.02 mmol, 0.05 equiv.) were dissolved in 4 mL THF and stirred at -40°C for 5 min. To the resulting solution α-iminoesters (0.40 mmol, 1 equiv), Et_3N (0.40 mmol, 1 equiv) and fulvenes (0.60 mmol, 1.5 equiv.) were added and the mixture was allowed to be stirred at -40°C for specific time until full conversion monitored by TLC. The reaction was quenched by saturated NH_4Cl solution, and solvent was removed *in vacuo* and column chromatography on silica gel afforded the pure products.

Method D for Synthesis of Chiral Cp Ligands 66k in gram scale:

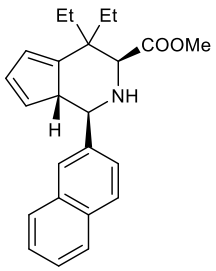
R-(–)-5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4-4'-bi-1,3-benzodioxole (0.04 mmol, 0.01 equiv.) and tetrakis-(acetonitrile)copper(I) tetrafluoroborate (0.04 mmol, 0.01 equiv.) were dissolved in 6 mL THF and stirred at -40°C for 5 min. To the resulting solution α-iminoesters (4 mmol, 1 equiv), Et_3N (4 mmol, 1 equiv) and fulvenes (6 mmol, 1.5 equiv.) were added and the mixture was allowed to be stirred at -40°C for specific time until full conversion monitored by TLC. The reaction was quenched by saturated NH_4Cl solution, and solvent was removed *in vacuo* and column chromatography on silica gel affords the pure product **66k** with 95% ee. The optical pure form of ligand was prepared by recrystallization in dichloromethane/petroleum ether from mother liquor.

Methyl (1*S*,3*R*,7a*S*)-4,4-dimethyl-1-(naphthalen-2-yl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridine-3-carboxylate



96a: Using Method A, 73% yield; The spectral data are identical to those reported;[16,17,53] 70% ee. The optical pure form of this ligand could be prepared in gram scale by chiral preparative HPLC of its racemate. Conditions for preparative HPLC: CHIRAPAK IC column, *iso*-propanol / heptane = 15/85, flow rate = 4 mL min^{-1}, t = 6.8 min, 9.8 min. Procedure for synthesis of racemic **96a**:[54] To the solution of 6,6-dimethylfulvene (7.2 mmol, 1.2 equiv), α-iminoesters (6 mmol, 1 equiv) in toluene (20 mL) was added Ag_2O (0.6 mmol, 0.1 equiv) and Et_3N (7.2 mmol, 1.2 equiv) at r.t., the solution was allowed to be stirred until full conversion monitored by TLC. The solution was filtered through celite, concentrated in *vacuo* and the crude residue was purified by column chromatography to give racemic **96a** (1.62 g, 81% yield).

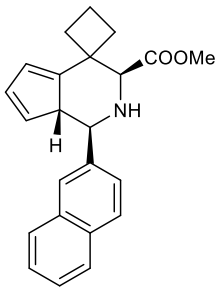
Methyl (1*S*,3*R*,7a*S*)-4,4-diethyl-1-(naphthalen-2-yl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridine-3-carboxylate



96b: Using Method A, 57% yield; ^1H NMR (400 MHz, CD_2Cl_2): δ 7.94 – 7.85 (m, 4H), 7.60 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.54 – 7.46 (m, 2H), 6.56 – 6.46 (m, 1H), 6.20 (s, 1H), 6.00 (d, *J* = 5.3 Hz, 1H), 3.73 (s, 3H), 3.59 (s, 1H), 3.12 (s, 2H), 2.18 – 2.07 (m, 2H), 1.74 – 1.58 (m, 1H), 1.39 – 1.27 (m, 1H), 1.11 (t, *J* = 7.4 Hz, 3H), 0.70 ppm (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.61, 153.08, 141.20, 134.07, 133.93, 133.71, 132.89,

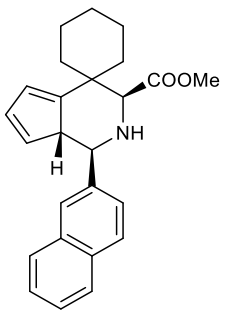
128.70, 128.46, 128.18, 126.68, 126.41, 126.33, 126.26, 126.06, 65.65, 65.50, 57.24, 52.02, 46.08, 29.59, 26.54, 9.08, 8.66 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{28}NO_2$: 362.21200, found: 362.21271; CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.7 min; minor enantiomer: t_R = 33.8 min, 60% ee.

Methyl (1'*S*,3'*R*,7a'*S*)-1'-(naphthalen-2-yl)-1',2',3',7a'-tetrahydrospiro[cyclobutane-1,4'-cyclopenta[*c*]pyridine]-3'-carboxylate



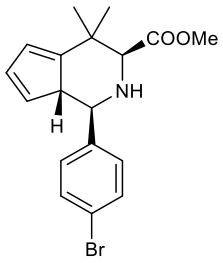
96c: Using Method A, 83% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.92 – 7.85 (m, 4H), 7.56 (dd, 1H), 7.52 – 7.48 (m, 2H), 6.54 – 6.50 (m, 1H), 6.29 – 6.24 (m, 1H), 6.06 – 6.02 (m, 1H), 3.82 (s, 3H), 3.26 (s, 1H), 3.15 (d, *J* = 10.3 Hz, 1H), 3.07 (d, *J* = 10.3 Hz, 1H), 2.52 – 2.42 (m, 3H), 1.99 – 1.90 (m, 2H), 1.78 – 1.65 ppm (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.85, 157.12, 140.98, 134.22, 134.04, 133.68, 133.11, 128.71, 128.46, 128.16, 126.69, 126.43, 126.23, 126.01, 122.07, 68.62, 66.35, 56.85, 52.40, 45.59, 30.27, 26.61, 15.75 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{24}NO_2$: 346.18016, found: 346.17989; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.9 min; minor enantiomer: t_R = 43.7 min, 29% ee.

Methyl (1'*S*,3'*R*,7a'*S*)-1'-(naphthalen-2-yl)-1',2',3',7a'-tetrahydrospiro[cyclohexane-1,4'-cyclopenta[*c*]pyridine]-3'-carboxylate



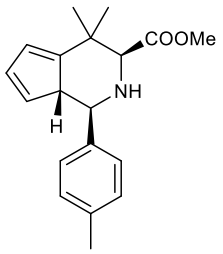
96d: Using Method A, 90% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.96 – 7.83 (m, 4H), 7.59 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.54 – 7.43 (m, 2H), 6.57 – 6.49 (m, 1H), 6.39 (s, 1H), 6.09 – 6.01 (m, 1H), 3.74 (s, 3H), 3.31 (d, *J* = 10.0 Hz, 1H), 3.13 (s, 1H), 2.96 (d, *J* = 10.0 Hz, 1H), 2.29 – 2.16 (m, 2H), 2.10 – 2.02 (m, 1H), 1.97 – 1.86 (m, 1H), 1.81 – 1.55 (m, 4H), 1.48 (td, *J* = 13.0, 3.3 Hz, 1H), 1.30 – 1.11 ppm (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.17, 154.97, 141.25, 134.50, 134.05, 133.68, 132.93, 128.75, 128.45, 128.17, 126.70, 126.43, 126.23, 126.16, 126.02, 72.21, 68.39, 56.64, 52.01, 44.22, 33.33, 32.49, 27.57, 23.20, 23.05 ppm; HRMS: calc. for $[M+H]^+$ $C_{25}H_{28}NO_2$: 374.21146, found: 374.21167; HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 26.8 min; minor enantiomer: t_R = 37.5 min, 66% ee.

Methyl (1*S*,3*R*,7a*S*)-1-(4-bromophenyl)-4,4-dimethyl-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



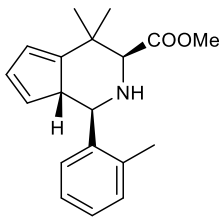
96e: Using Method A, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.46 (m, 2H), 7.39 – 7.30 (m, 2H), 6.53 – 6.39 (m, 1H), 6.15 (d, *J* = 0.6 Hz, 1H), 5.96 (dt, *J* = 5.4, 1.3 Hz, 1H), 3.75 (s, 3H), 3.17 (s, 1H), 3.07 (d, *J* = 10.4 Hz, 1H), 2.86 (d, *J* = 10.4 Hz, 1H), 2.13 (br s, 1H), 1.43 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.76, 157.66, 141.91, 133.56, 132.87, 131.86, 128.96, 122.42, 121.68, 69.98, 65.48, 56.29, 51.84, 38.51, 24.36, 24.34 ppm; HRMS: calc. for $[M+H]^+$ $C_{18}H_{21}NO_2{}^{79}Br$: 362.07502, found: 362.07495; calc. for $[M+H]^+$ $C_{18}H_{21}NO_2{}^{81}Br$: 364.07297, found: 364.07251; HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.0 min; minor enantiomer: t_R = 31.7 min, 62% ee.

Methyl (1*S*,3*R*,7a*S*)-4,4-dimethyl-1-(4-methylphenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridine-3-carboxylate



96f: Using Method A, 77% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.34 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.47 – 6.43 (m, 1H), 6.16 – 6.13 (m, 1H), 5.98 (dt, *J* = 5.3, 1.4 Hz, 1H), 3.72 (s, 3H), 3.17 – 3.10 (m, 2H), 2.84 (d, *J* = 10.3 Hz, 1H), 2.37 (s, 3H), 2.06 (br s, 1H), 1.43 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.28, 158.71, 140.74, 138.00, 134.38, 132.84, 129.72, 127.49, 122.38, 70.59, 66.34, 56.93, 51.99, 38.92, 24.58, 24.56, 21.43 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{24}NO_2$: 298.18016, found: 298.17983; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 31.0 min; minor enantiomer: t_R = 26.5 min, 67% ee.

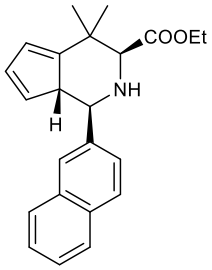
Methyl (1*S*,3*R*,7a*S*)-4,4-dimethyl-1-(2-methylphenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridine-3-carboxylate



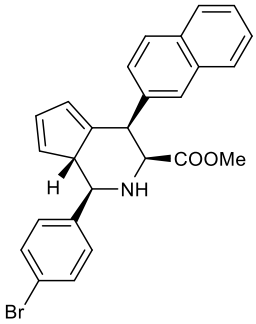
96g: Using Method A, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.23 (m, 1H), 7.25 – 7.13 (m, 2H), 6.50 – 6.43 (m, 1H), 6.16 (s, 1H), 6.03 – 5.92 (m, 1H), 3.74 (s, 3H), 3.24 (d, *J* = 10.4 Hz, 1H), 3.17 (s, 1H), 3.12 (d, *J* = 10.4 Hz, 1H), 2.26 (s, 3H), 2.03 (br s, 1H), 1.44 (s, 3H), 1.23 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.88, 157.80, 140.73, 136.03, 134.04, 132.56, 130.81, 127.53, 126.52, 125.72, 122.13, 69.94, 61.42, 56.13, 51.76, 38.59, 24.45, 24.36, 19.52 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{24}NO_2$: 298.18016, found: 298.18012; HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH =

100/2) / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 30.6 min; minor enantiomer: t_R = 26.5 min, 66% ee.

Ethyl (1*S*,3*R*,7a*S*)-4,4-dimethyl-1-(naphthalen-2-yl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridine-3-carboxylate

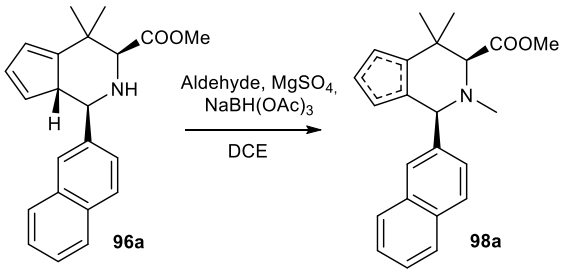


96h: Using Method A, 83% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.93 (s, 1H), 7.92 – 7.86 (m, 3H), 7.62 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.55 – 7.46 (m, 2H), 6.50 – 6.46 (m, 1H), 6.19 (s, 1H), 6.04 – 5.98 (m, 1H), 4.27 – 4.14 (m, 2H), 3.28 (d, *J* = 10.3 Hz, 1H), 3.20 (s, 1H), 3.06 (d, *J* = 10.3 Hz, 1H), 2.26 (br s, 1H), 1.48 (s, 3H), 1.33 – 1.26 ppm (m, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 171.83, 158.80, 141.24, 134.28, 134.06, 133.71, 132.98, 128.72, 128.47, 128.17, 126.68, 126.42, 126.26, 126.09, 122.48, 70.58, 66.73, 61.24, 56.93, 39.00, 24.68, 24.59, 14.73 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{26}NO_2$: 348.19581, found: 348.19565; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 40.2 min; minor enantiomer: t_R = 49.3 min, 71% ee.



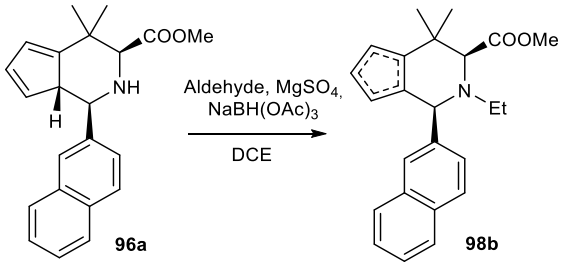
Methyl (1*S*,3*R*,4*S*,7a*S*)-1-(4-bromophenyl)-4-(naphthalen-2-yl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate

96i: Using Method B, The spectral data are identical to those reported;[16] 96% ee.



Mixture of isomers

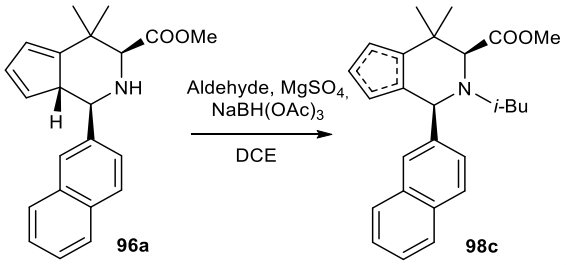
98a: optical pure **96a** (1 equiv., 0.2 mmol) was dissolved in 2 mL DCE. To the resulting solution $MgSO_4$ (10 equiv., 2 mmol), HCHO solution 35 wt. % in H_2O (8 equiv., 1.6 mmol) and $NaBH(OAc)_3$ (3 equiv., 0.6 mmol) were added in sequential way and the mixture was allowed to be stirred at ambient temperature for specific time until full conversion monitored by TLC. Column chromatography on silica gel affords the pure product directly without removal of solvent, 89% yield; three inseparable isomers with 57:43 ratio; For mixture, ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.01 – 7.66 (m, 7.02H), 7.57 – 7.37 (m, 5.26H), 6.47 (d, *J* = 5.2 Hz, 1H), 6.39 (d, *J* = 5.0 Hz, 0.75H), 6.19 (d, *J* = 4.8 Hz, 1H), 6.09 (s, 0.75H), 5.79 (d, *J* = 5.1 Hz, 0.75H), 5.31 (s, 1H), 4.14 (s, 1H), 3.75 (s, 3H), 3.74 (s, 2.26H), 3.32 (d, *J* = 10.8 Hz, 0.75H), 3.22 (s, 1H), 2.77 – 2.64 (m, 1.75 H), 2.47 (d, *J* = 10.8 Hz, 0.75H), 2.25 – 2.13 (m, 4H), 1.92 (s, 2.26H), 1.44 (s, 2.26H), 1.38 (s, 3H), 1.29 (s, 2.26H), 1.21 ppm (s, 3H); For mixture, ^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.33, 172.24, 157.60, 145.41, 141.71, 141.35, 137.80, 134.90, 133.85, 133.70, 133.63, 132.96, 132.84, 130.51, 128.85, 128.29, 128.17, 128.16, 127.72, 126.75, 126.60, 126.50, 126.30, 126.18, 121.22, 80.56, 75.87, 75.31, 70.85, 51.82, 51.74, 42.08, 41.76, 41.38, 37.99, 36.03, 25.61, 25.42, 25.34, 24.75 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{26}NO_2$: 348.19581, found: 348.19578.



Mixture of isomers

98b: optical pure **96a** (1 equiv., 0.2 mmol) was dissolved in 2 mL DCE. To the resulting solution $MgSO_4$ (10 equiv., 2 mmol), acetaldehyde (8 equiv., 1.6 mmol) and $NaBH(OAc)_3$ (3 equiv., 0.6 mmol) were added in sequential way and the mixture was allowed to be stirred at ambient temperature for specific time until full conversion monitored by TLC. Column chromatography on silica gel affords the pure product directly without removal of solvent, 86% yield; two inseparable isomers with 71:29 ratio; For mixture, ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.95 – 7.75 (m, 5.6H), 7.56 – 7.42 (m, 4.2H), 6.50 – 6.45 (m, 0.40H), 6.41 – 6.37 (m, 1H), 6.21 – 6.17 (m, 0.40H), 6.07 (s, 1H), 5.82 – 5.75 (m, 1H), 4.74 (s, 0.40H), 3.76 (s, 1.20H), 3.75 (s, 3H), 3.61 (s, 0.40H), 3.34 – 3.28 (m, 1H), 3.16 (s, 1H), 2.96 (d, 1H), 2.87 – 2.75 (m, 0.80H), 2.78 – 2.70 (m, 0.40H), 2.66 – 2.58 (m, 2H), 2.27 – 2.16 (m, 0.40H), 1.45 (s, 3H), 1.40 (s, 1.20H), 1.29 (s, 3H), 1.22 (s, 1.20H), 0.92 (t, *J* = 7.2 Hz, 1.20H), 0.70 ppm (t, *J* = 7.1 Hz, 3H);

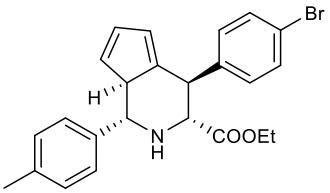
For mixture, ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.24, 157.93, 145.23, 142.27, 140.98, 138.42, 135.09, 134.00, 133.95, 133.76, 133.70, 132.84, 132.80, 130.61, 128.88, 128.82, 128.35, 128.20, 127.49, 127.26, 126.95, 126.61, 126.49, 126.44, 126.34, 126.16, 120.87, 75.13, 71.15, 69.65, 64.43, 57.23, 51.75, 51.65, 44.66, 44.47, 42.22, 38.20, 36.26, 25.42, 25.37, 25.27, 24.79, 7.71, 6.36 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{28}NO_2$: 362.21146, found: 362.21140.



Mixture of isomers

98c: optical pure **96a** (1 equiv., 0.2 mmol) was dissolved in 2 mL DCE. To the resulting solution $MgSO_4$ (10 equiv., 2 mmol), isobutyraldehyde (8 equiv., 1.6 mmol) and $NaBH(OAc)_3$ (3 equiv., 0.6 mmol) were added in sequential way and the mixture was allowed to be stirred at ambient temperature for specific time until full conversion monitored by TLC. Column chromatography on silica gel affords the pure product directly without removal of solvent, 56% yield; three inseparable isomers with 54:33:13 ratio; the resulting mixture was directly subjected to Rhodium complex preparation without resolution of ^{1}H NMR and ^{13}C NMR; HRMS: calc. for $[M+H]^+$ $C_{26}H_{32}NO_2$: 390.24276, found: 390.24350.

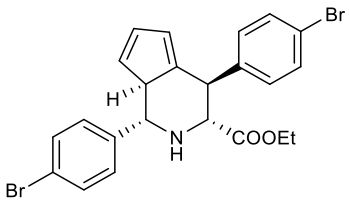
Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-methylphenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66a: Using Method C, 61% yield; For major isomer, ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.20 (m, 4H), 6.46 – 6.40 (m, 1H), 6.08 – 6.02 (m, 1H), 5.72 (s, 1H), 3.97 – 3.86 (m, 3H), 3.53 (d, *J* = 10.4 Hz, 1H), 3.17 (d, *J* = 10.4 Hz, 1H), 3.12 – 3.04 (m, 1H), 2.38 (s, 3H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.13, 151.91, 140.21, 138.66, 138.22, 134.39, 133.19, 131.94, 131.36, 129.79, 127.49, 125.69, 121.22, 67.46, 66.29, 61.37, 59.54, 50.67, 21.44, 14.20 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{25}NO_2{}^{79}Br$: 438.10632, found: 438.10571; calc. for $[M+H]^+$ $C_{18}H_{21}NO_2{}^{81}Br$: 440.10427, found: 440.10338; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions:

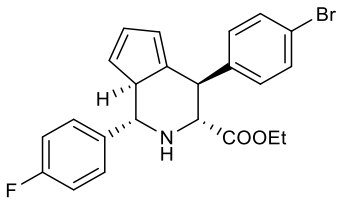
CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 47.5 min; minor enantiomer: t_R = 55.1 min, 92% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-1,4-bis(4-bromophenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*] pyridine-3-carboxylate



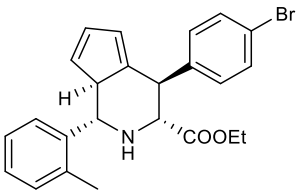
66b: Using Method C, 82% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.45 (dt, *J* = 5.4, 1.6 Hz, 1H), 6.03 (dd, *J* = 5.4, 1.1 Hz, 1H), 5.72 (s, 1H), 3.96 – 3.86 (m, 3H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.18 (d, *J* = 10.4 Hz, 1H), 3.04 (dd, *J* = 10.4, 1.1 Hz, 1H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 171.98, 151.61, 142.29, 138.48, 133.91, 133.56, 132.25, 131.96, 131.35, 129.52, 126.00, 122.05, 121.29, 67.28, 65.90, 61.45, 59.35, 50.48, 14.19 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{22}NO_2{}^{79}Br_2$: 502.00118, found: 502.00072; calc. for $[M+H]^+$ $C_{23}H_{22}NO_2{}^{79}Br{}^{81}Br$: 503.99913, found: 503.99807; calc. for $[M+H]^+$ $C_{23}H_{22}NO_2{}^{81}Br_2$: 505.99709, found: 505.99588; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IA column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 25/75, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.7 min; minor enantiomer: t_R = 27.5 min, 96% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-fluorophenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate

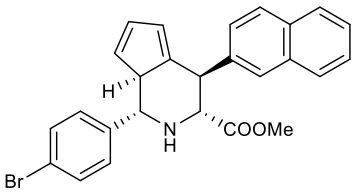


66c: Using Method B, 82% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.53 – 7.44 (m, 4H), 7.24 – 7.20 (m, 2H), 7.15 – 7.08 (m, 2H), 6.44 (d, *J* = 5.2 Hz, 1H), 6.03 (d, *J* = 4.6 Hz, 1H), 5.72 (s, 1H), 4.01 – 3.87 (m, 3H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.20 (d, *J* = 10.4 Hz, 1H), 3.06 (d, *J* = 10.4 Hz, 1H), 1.92 (br s, 1H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.05, 162.90 (d, *J* = 245.1 Hz), 151.73, 139.15 (d, *J* = 3.1 Hz), 138.54, 134.05, 133.47, 131.96, 131.36, 129.37 (d, *J* = 8.1 Hz), 125.92, 121.28, 115.89 (d, *J* = 21.4 Hz), 67.35, 65.78, 61.44, 59.54, 50.53, 14.19 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{22}NO_2{}^{79}BrF$: 442.08125, found: 442.08058; calc. for $[M+H]^+$ $C_{23}H_{22}NO_2{}^{81}BrF$: 444.07920, found: 444.07826; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 18.7 min; minor enantiomer: t_R = 15.1 min, 96% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(2-methylphenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate

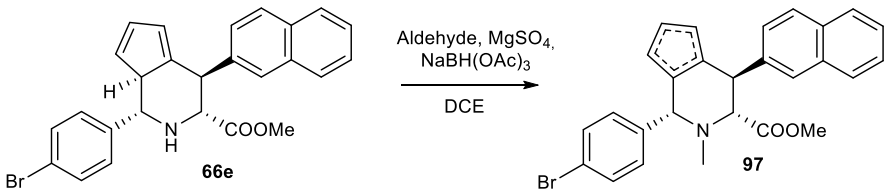


66d: Using Method B, 50% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.28 (m, 1H), 7.27 – 7.21 (m, 4H), 6.45 (d, *J* = 5.4 Hz, 1H), 6.08 – 5.98 (m, 1H), 5.80 – 5.72 (m, 1H), 3.97 – 3.84 (m, 3H), 3.53 (d, *J* = 10.4 Hz, 1H), 3.42 (d, *J* = 10.4 Hz, 1H), 3.22 (d, *J* = 10.4 Hz, 1H), 2.32 (s, 3H), 1.89 (br s, 1H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.2, 151.82, 140.91, 138.62, 136.76, 134.29, 133.34, 131.97, 131.33, 131.21, 128.05, 126.89, 126.12, 125.65, 121.24, 67.33, 61.82, 61.36, 59.04, 51.07, 19.67, 14.20 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{25}NO_2{}^{79}Br$: 438.10632, found: 438.10549; calc. for $[M+H]^+$ $C_{24}H_{25}NO_2{}^{81}Br$: 440.10427, found: 440.10303; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 16.3 min; minor enantiomer: t_R = 15.1 min, 72% ee.



Methyl (1*S*,3*R*,4*R*,7a*S*)-1-(4-bromophenyl)-4-(naphthalen-2-yl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate

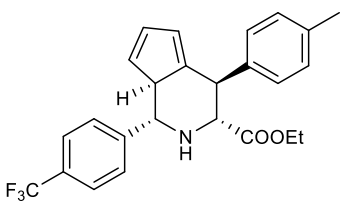
66e: Using Method C, 82% yield; The spectral data are identical to those reported;[17] 96% ee.



Mixture of isomers

97: Ligand **66e** (1 equiv., 0.2 mmol) was dissolved in 2 mL DCE. To the resulting solution $MgSO_4$ (10 equiv., 2 mmol), HCHO solution 35 wt. % in H_2O (8 equiv., 1.6 mmol) and $NaBH(OAc)_3$ (3 equiv., 0.6 mmol) were added in sequential way and the mixture was allowed to be stirred at ambient temperature for specific time until full conversion monitored by TLC. Column chromatography on silica gel affords the pure product directly without removal of solvent, 41% yield; two inseparable isomers with 78:22 ratio; For mixture, ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.89 – 7.76 (m, 5.12H), 7.69 – 7.63 (m, 1.28H), 7.56 – 7.43 (m, 5.12H), 7.37 – 7.29 (m, 2.56H), 7.29 – 7.22 (m, 1.28H), 6.21 – 6.11 (m, 1.28H), 5.94 – 5.90 (m, 0.28H), 5.89 – 5.84 (m, 1H), 4.44 – 4.33 (m, 1.28H), 4.26 – 4.15 (m, 1.28H), 3.49 – 3.41 (m, 5.12H), 2.79 – 2.73 (m, 1.28H), 2.16 (s, 3H), 2.15 (s, 0.66H); For mixture, ^{13}C NMR (101 MHz, CD_2Cl_2): δ 173.04, 143.09, 141.75, 141.20, 140.94, 139.02, 138.98, 138.91, 137.88, 134.08, 133.33, 132.63, 132.59, 132.34, 132.18, 132.12, 131.72, 131.23, 130.81, 128.76, 128.70, 128.26, 128.23, 128.17, 128.16, 127.07, 126.94, 126.70, 126.66, 126.38, 121.77, 121.64, 74.44, 74.20, 69.62, 68.36, 52.08, 48.30, 47.13, 42.23, 41.13, 41.04 ppm; HRMS: calc. for $[M+H]^+$ $C_{27}H_{25}NO_2{}^{79}Br$: 474.10632, found: 474.10574; calc. for $[M+H]^+$ $C_{27}H_{25}NO_2{}^{81}Br$: 476.10427, found: 476.10329; 96% ee.

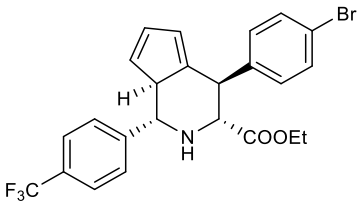
Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-methylphenyl)-1-(4-(trifluoromethyl)phenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66f: Using Method C, 82% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.13 (m, 4H), 6.46 (d, *J* = 5.3 Hz, 1H), 6.02 (d, *J* = 5.3 Hz, 1H), 5.77 (s, 1H), 3.99 – 3.82 (m, 3H), 3.56 (d, *J* = 10.4 Hz, 1H), 3.28 (d, *J* = 10.4 Hz, 1H), 3.07 (dd, *J* = 10.4 Hz, 1H), 2.36 (s, 3H), 0.94 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.24, 152.32, 147.41, 137.35, 135.98, 133.78, 133.47, 129.53, 129.86 (q, *J* = 32.3 Hz), 129.36, 128.24, 126.11 (q, *J* = 3.8 Hz), 125.91, 124.88 (q, *J* = 271.7 Hz), 67.67, 66.21, 61.32, 59.34, 50.78, 21.40, 14.16 ppm; HRMS: calc. for $[M+H]^+$ $C_{25}H_{25}NO_2F_3$: 428.18319, found: 428.18193; e.e. was determined by Diels–Alder

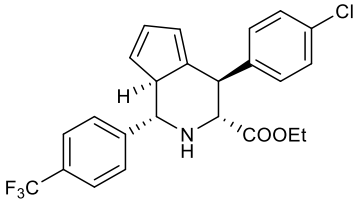
cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 32.5 min; minor enantiomer: t_R = 53.9 min, 97% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-(trifluoromethyl)phenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66g: Using Method C, 70% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.46 (dt, *J* = 5.4, 1.4 Hz, 1H), 6.03 (dd, *J* = 5.4, 0.9 Hz, 1H), 5.75 (s, 1H), 4.05 – 3.84 (m, 3H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.28 (d, *J* = 10.4 Hz, 1H), 3.08 (dd, *J* = 10.4, 0.9 Hz, 1H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 171.94, 151.55, 147.23, 138.43, 133.73, 133.70, 131.99, 131.36, 130.42 (d, *J* = 32.5 Hz), 128.23, 126.14 (q, *J* = 3.8 Hz), 126.08, 124.85 (q, *J* = 270.6 Hz), 121.33, 67.25, 66.09, 61.50, 59.28, 50.48, 14.19 ppm; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}NO_2{}^{79}BrF_3$: 492.07805, found: 492.07758; calc. for $[M+H]^+$ $C_{24}H_{22}NO_2{}^{81}BrF_3$: 494.07601, found: 494.07511; HPLC conditions: CHIRAPAK IA column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 25/75, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.7 min; minor enantiomer: t_R = 27.5 min, 96% ee.

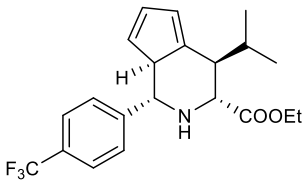
Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66h: Using Method C, 67% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.51 – 6.44 (m, 1H), 6.03 (dd, *J* = 5.4, 1.0 Hz, 1H), 5.74 (s, 1H), 4.02 – 3.86 (m, 3H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.28 (d, *J* = 10.4 Hz, 1H), 3.08 (dd, *J* = 10.4, 1.0 Hz, 1H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 171.97, 151.65, 147.22, 137.92, 133.73, 133.69, 133.25, 130.99, 130.42 (q, *J* = 32.3 Hz), 129.02, 128.23, 126.14, 126.13 (q, *J* = 3.8 Hz), 124.85 (q, *J* = 270.6 Hz), 67.32, 66.10, 61.49, 59.30, 50.43, 14.19 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}NO_2ClF_3$: 448.12857, found: 448.12771; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane =

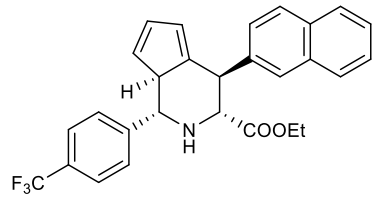
20/80, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 24.0 min; minor enantiomer: t_R = 37.5 min, 96% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-isopropyl-1-(4-(trifluoromethyl)phenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



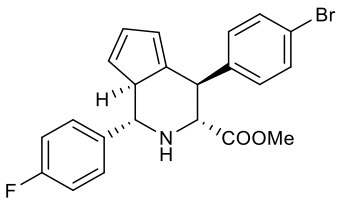
66i: Using Method C, 31% yield; Only for (6+3) cycloadduct, ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 6.54 – 6.50 (m, 1H), 6.30 – 6.26 (m, 1H), 5.97 – 5.92 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.22 (d, *J* = 10.4 Hz, 1H), 3.02 (d, *J* = 10.4 Hz, 1H), 2.94 (d, *J* = 10.4 Hz, 1H), 2.73 (d, *J* = 10.4 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 2H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.10 ppm (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 173.62, 149.93, 133.71, 133.02, 130.22 (q, *J* = 32.2 Hz), 129.20, 128.15, 126.05 (q, *J* = 3.8 Hz), 124.88 (d, *J* = 271.8 Hz), 124.66, 66.35, 64.91, 61.62, 60.68, 49.74, 28.66, 19.72, 19.51, 14.45 ppm; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 20.1 min; minor enantiomer: t_R = 36.6 min, 89% ee.

Ethyl (1*S*,3*R*,4*R*,7a*S*)-4-(naphthalen-2-yl)-1-(4-(trifluoromethyl)phenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



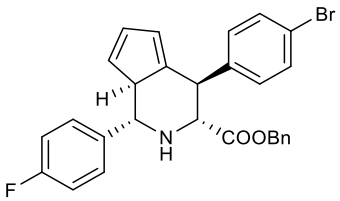
66j: Using Method C, 82% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.90 – 7.82 (m, 3H), 7.79 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.46 (m, 3H), 6.47 (dt, *J* = 5.3, 1.6 Hz, 1H), 6.09 – 6.02 (m, 1H), 5.77 (s, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 3.87 (q, *J* = 7.1 Hz, 2H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.36 (d, *J* = 10.4 Hz, 1H), 3.14 (dd, *J* = 10.4, 1.1 Hz, 1H), 2.21 (br s, 1H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.18, 152.07, 147.35, 136.86, 134.13, 133.81, 133.56, 133.36, 130.40 (d, *J* = 32.3 Hz), 128.30, 128.27, 128.24, 128.15, 127.69, 126.55, 126.29, 126.25, 126.15 (q, *J* = 3.8 Hz), 124.85 (q, *J* = 271.6 Hz), 123.54, 67.36, 66.18, 61.35, 59.40, 51.18, 14.08 ppm; HRMS: calc. for $[M+H]^+$ $C_{28}H_{25}NO_2F_3$: 464.18319, found: 464.18256; e.e. was determined by Diels–Alder cycloadduct of chiral cyclopentadiene and *N*-methylmaleimide, HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2)/ *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 32.5 min; minor enantiomer: t_R = 46.7 min, 98% ee.

Methyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-fluorophenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



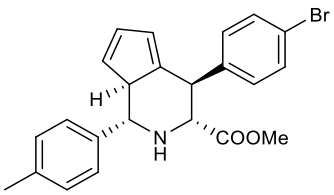
66k: Using Method D, 74% yield, the product with >99% ee was obtained from mother liquor through recrystallization of cycloadduct with 95% ee in petroleum ether and ethyl acetate; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.54 – 7.43 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.05 (m, 2H), 6.45 (d, *J* = 5.4 Hz, 1H), 6.04 (d, *J* = 5.4 Hz, 1H), 5.72 (s, 1H), 3.93 (d, *J* = 10.4 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 1H), 3.49 (s, 3H), 3.21 (d, *J* = 10.4 Hz, 1H), 3.07 (d, *J* = 10.4 Hz, 1H), 2.11 ppm (br s, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.40, 162.90 (d, *J* = 245.2 Hz), 151.63, 139.11 (d, *J* = 3.1 Hz), 138.51, 134.05, 133.48, 132.03, 131.25, 129.36 (d, *J* = 8.1 Hz), 126.06, 121.33, 115.89 (d, *J* = 21.4 Hz), 67.24, 65.79, 59.52, 54.54, 54.27, 54.00, 54.00, 53.73, 53.46, 52.37, 50.20 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}NO_2{}^{79}BrF$: 428.06560, found: 428.06474; calc. for $[M+H]^+$ $C_{22}H_{20}NO_2{}^{81}BrF$: 430.06355, found: 430.06210; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 16.2 min; minor enantiomer: t_R = 14.0 min.

Benzyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-fluorophenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66l: Using Method C, 50% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.53 – 7.41 (m, 4H), 7.33 – 7.24 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 8.7 Hz, 2H), 6.99 – 6.89 (m, 2H), 6.44 (d, *J* = 5.3 Hz, 1H), 6.06 – 6.01 (m, 1H), 5.72 (s, 1H), 4.97 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 12.2 Hz, 1H), 3.90 (d, *J* = 10.4 Hz, 1H), 3.67 – 3.56 (m, 1H), 3.27 – 3.16 (m, 1H), 3.07 (d, *J* = 10.5 Hz, 1H), 2.11 ppm (s, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.13, 162.90 (d, *J* = 245.1 Hz), 151.58, 139.08 (d, *J* = 2.9 Hz), 138.33, 135.83, 134.10, 133.47, 132.11, 131.32, 129.36 (d, *J* = 8.1 Hz), 128.97, 128.74, 128.62, 126.03, 121.44, 115.90 (d, *J* = 21.4 Hz), 67.36, 67.27, 65.70, 59.47, 50.65 ppm; HRMS: calc. for $[M+H]^+$ $C_{28}H_{24}NO_2{}^{79}BrF$: 504.09690, found: 504.09655; calc. for $[M+H]^+$ $C_{28}H_{24}NO_2{}^{81}BrF$: 506.09485, found: 506.09415; HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 21.7 min; minor enantiomer: t_R = 16.9 min, 96% ee.

Methyl (1*S*,3*R*,4*R*,7a*S*)-4-(4-bromophenyl)-1-(4-methylphenyl)-2,3,4,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate



66m: Using Method C, 66% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.20 (m, *J* = 8.4, 2.4 Hz, 4H), 6.43 (d, *J* = 5.1 Hz, 1H), 6.04 (d, *J* = 5.1 Hz, 1H), 5.71 (s, 1H), 3.91 (d, *J* = 10.5 Hz, 1H), 3.57 (d, *J* = 10.5 Hz, 1H), 3.48 (s, 3H), 3.17 (d, *J* = 10.5 Hz, 1H), 3.10 (d, *J* = 10.5 Hz, 1H), 2.38 (s, 3H), 1.98 ppm (br s, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 172.52, 151.80, 140.17, 138.63, 138.25, 134.40, 133.20, 132.01, 131.25, 129.80, 127.49, 125.85, 121.28, 67.35, 66.30, 59.51, 52.33, 50.38, 21.44 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{23}NO_2{}^{79}BrF$: 424.09067, found: 424.09042; calc. for $[M+H]^+$ $C_{23}H_{23}NO_2{}^{81}BrF$: 426.08862, found: 426.08805; HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 5/95, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 22.3 min; minor enantiomer: t_R = 25.5 min, 95% ee.

7.2.2 Synthesis and Analytic Data of Rh(I) Complexes 99a-k and 100a-o

Method E for Synthesis of Rh(I) Complexes 99a-99g, 99i-99l:

Under Ar flow, thallium (I) ethoxide (1.2 equiv., 0.36 mmol, 89.8 mg) was added to 1 mL dry methanol in 10 mL *Schlenk* flask. A white precipitate of thallium (I) methoxide formed immediately. After stirring for 5 mins, methanol was decanted and the thallium (I) methoxide was washed again with 1 mL dry methanol. Then 4 mL dry and degassed benzene was added. Under Ar, to the mixture was added a solution of cyclopetadiene (1 equiv., 0.3 mmol) in 1 mL benzene. The mixture was stirred for 1 hour at 80°C with protection from light. After cooling down, $[Rh(C_2H_4)_2Cl]_2$ (0.6 equiv., 0.18 mmol, 70 mg) was added. After stirring for another 1 hour, the reaction mixture was directly subjected to column chromatography on neutral aluminum oxide (activated, Brockmann I, Sigma-Aldrich) under Ar using EtOAc/hexane as the eluent, affording the desired Rh complexes.

Method F for Synthesis of Rh(I) Complexes 100a-d, 100g-k:

Under Ar, to a solution of cyclopetadiene (0.3 mmol) in degassed 4 mL benzene at room temperature was added a solution of thallium(I) ethanolate (0.18 mmol) in 1 mL benzene. The mixture was stirred for 1 hour at room temperature protected from light. $[Rh(C_2H_4)_2Cl]_2$ (0.6 equiv., 0.18 mmol, 70 mg) was added. After stirring for another 1 hour, the reaction mixture was directly subjected to column chromatography on neutral aluminum oxide (activated, Brockmann I, Sigma-Aldrich) under Ar using EtOAc/hexane as the eluent, affording the desired Rh complexes.

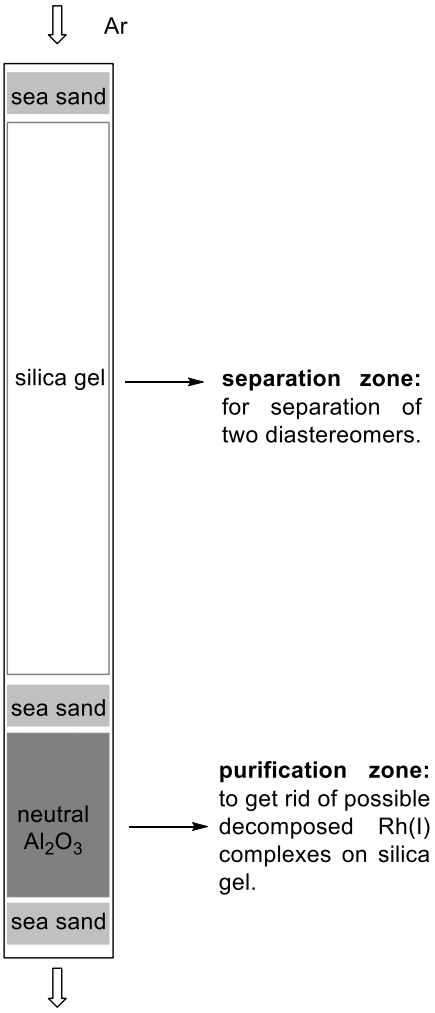
Method G for Synthesis of Rh(I) Complexes 100e, 100f, 100l-2o:

Under Ar flow, thallium (I) ethoxide (1.2 equiv., 0.36 mmol, 89.8 mg) was added to 1 mL dry methanol in 10 mL Schlenk flask. A white precipitate of thallium (I) methoxide formed immediately. After stirring for 5 mins, methanol was decanted and the thallium (I) methoxide was washed again with 1 mL dry methanol. Then 4 mL dry and degassed benzene was added. Under Ar, to the mixture was added a solution of cyclopetadiene (1 equiv., 0.3 mmol) in 1 mL benzene. The mixture was stirred for 1 hour at room temperature with protection from light. $[Rh(C_2H_4)_2Cl]_2$ (0.6 equiv., 0.18 mmol, 70 mg) was added. After stirring for another 1 hour, the reaction mixture was directly subjected to column chromatography on neutral aluminum oxide (activated, Brockmann I, Sigma-Aldrich) under Ar using EtOAc/hexane as the eluent, affording the desired Rh complexes.

Method H for Synthesis of Rh(I) Complexes 99h:

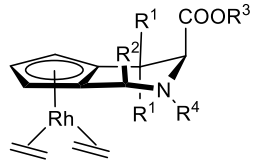
Under Ar, to a solution of cyclopetadiene (0.3 mmol) in degassed 4 mL benzene at room temperature was added a solution of thallium(I) ethanolate (0.18 mmol) in 1 mL benzene. The mixture was stirred for 1 hour at 80°C protected from light. $[Rh(C_2H_4)_2Cl]_2$ (0.6 equiv., 0.18 mmol, 70 mg) was added. After stirring for another 1 hour, the reaction mixture was directly subjected to column chromatography on neutral aluminum oxide (activated, Brockmann I, Sigma-Aldrich) under Ar using EtOAc/hexane as the eluent, affording the desired Rh complex.

For separation of diastereomers of **100l, 100n**:



The column was prepared as shown in the left, sea sand, neutral Al_2O_3 as purification zone, sea sand, silica gel as separation zone and sea sand were added sequentially. Column was neutralized by 1% (v/v) of triethylamine in n-pentane: ethyl acetate (1:1) for 1 hour. Using Ar as pressure source, ethyl acetate was used to wash away extra trimethylamine, followed by n-pentane. (be sure there is no air in column) A precooling solvent to -40°C of n-pentane and ethyl acetate was used as eluent. The purification process should be always under -40°C and argon. Rh(I) complexes are stable in solid form.

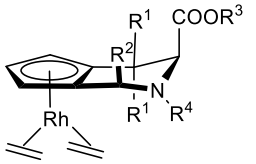
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-3-(methoxycarbonyl)-4,4-dimethyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99a, R^1 = Me, R^2 = 2-naphthyl, R^3 = Me, R^4 = H.

99a: Using Method E, 71% yield; single isomer; ^{1}H NMR (400 MHz, C_6D_6): δ 7.67 (s, 1H), 7.65 – 7.55 (m, 3H), 7.49 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.31 – 7.22 (m, 2H), 4.69 – 4.66 (m, 1H), 4.66 – 4.63 (m, 1H), 4.32 – 4.27 (m, 1H), 4.04 (s, 1H), 3.79 (s, 1H), 3.36 (s, 3H), 2.88 – 2.75 (m, 2H), 2.73 – 2.57 (m, 2H), 1.76 (s, 3H), 1.52 (s, 3H), 1.49 – 1.38 (m, 2H), 1.14 – 1.02 ppm (m, 2H); ^{13}C NMR (101 MHz, C_6D_6): δ 171.85, 141.32, 133.94, 133.81, 128.80, 128.52, 127.93, 127.21, 126.75, 126.31, 126.16, 117.20 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 102.20 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 85.61 (d, $J_{Rh\text{-}C}$ = 4.4 Hz), 84.48 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 82.84 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 66.61, 57.16, 51.13, 40.70 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 36.74 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 36.36, 29.96, 26.70 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2985, 1731, 1506, 1433, 1360, 1183, 1128 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{26}H_{31}O_2NRh$: 492.14043, found: 492.14041; $[\alpha]_D^{RT}$ = -164.4 (CH_2Cl_2, *c* = 1.00).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-4,4-diethyl-3-(methoxycarbonyl)-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

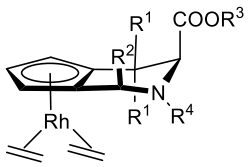


99b, R^1 = Et, R^2 = 2-naphthyl, R^3 = Me, R^4 = H.

99b: Using Method E, 71% yield; two separable isomers with 72:28 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.96 (s, 0.4 H), 7.68 – 7.63 (m, 1.8H), 7.62 – 7.57 (m, 3.4H), 7.52 – 7.48 (m, 1.4H), 7.28 – 7.22 (m, 2.8H), 5.12 (s, 0.4H), 4.83 (s, 1H), 4.78 – 4.74 (m, 0.4H), 4.64 (d, *J* = 2.8 Hz, 0.4H), 4.62 – 4.57 (m, 1H), 4.28 (s, 1.4H), 3.92 – 3.90 (m,1H), 3.84 (d, *J* = 4.0 Hz, 1H), 3.58 (s, 0.4H), 3.39 (s, 1.2H), 3.36 (s, 3H), 3.00 (t, *J* = 10.0 Hz, 0.8H), 2.78 (t, *J* = 10.0 Hz, 2H), 2.68 (t, *J* = 10.0 Hz, 2H), 2.45 – 2.37 (m, 1H), 2.27 – 2.19 (m, 1.4H), 2.15 – 2.10 (m, 0.4H), 2.07 (s, 1H), 2.01 – 1.91 (m, 2.4H), 1.76 – 1.69 (m, 1H), 1.70 – 1.65 (m, 0.4H), 1.57 (t, *J* = 7.4 Hz, 3H), 1.47 – 1.41 (m, 2H), 1.32 (t, *J* = 7.4 Hz, 1.2H), 1.13 – 1.06 (m, 2H), 1.04 – 0.97 (m, 3.4H), 0.92 (t, *J* = 7.4 Hz, 1.2H), 0.78 – 0.71 ppm(m, 0.8H); ^{13}C NMR (176 MHz, C_6D_6): δ 172.52, 172.28, 141.17, 138.32, 133.94, 133.79, 133.68, 133.30, 128.84, 128.58, 128.41, 128.35, 128.31, 128.12, 128.10, 127.99, 127.36, 126.77, 126.36, 126.32, 126.18, 126.00, 125.88, 125.31, 113.43 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 111.46 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 106.07 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 101.68 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 86.03 (d, $J_{Rh\text{-}C}$ = 3.8 Hz), 85.67 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 85.28 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 85.21 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 84.40 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 81.69 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 63.84, 63.82, 60.07, 59.69, 56.98, 51.20, 51.19, 42.69, 41.94,

41.27 (d, J_{Rh-C} = 13.4 Hz), 39.62 (d, J_{Rh-C} = 13.4 Hz), 39.44 (d, J_{Rh-C} = 13.3 Hz), 37.18 (d, J_{Rh-C} = 13.0 Hz), 34.65, 31.70, 30.93, 29.66, 20.56, 14.23, 9.93, 9.55, 9.22, 9.21 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2961, 1731, 1601, 1433, 1359, 1183, 1128, 1032 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{28}H_{35}O_2NRh$: 520.17173, found: 520.17175; $[\alpha]_D^{RT}$ = +32.6 ($CHCl_3$, *c* = 0.19).

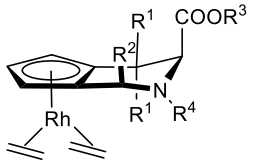
(–)-Bis(*η*^{2}-ethylene){*η*^{5}-(1'*R*,3'*R*)-3'-(methoxycarbonyl)-1'-(naphthalen-2-yl)-2',3'-dihydro-1'*H*-spiro[cyclobutane-1,4'-cycloocta[*c*]pyridin]-yl)}rhodium(I)



99c, R^1 = -$(CH_2)_3$-, R^2 = 2-naphthyl, R^3 = Me, R^4 = H.

99c: Using Method E, 74% yield; two separable isomers with 76:24 ratio; For major isomer, ^{1}H NMR (400 MHz, C_6D_6): δ 7.67 (s, 1H), 7.65 – 7.55 (m, 3H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.31 – 7.21 (m, 2H), 4.85 – 4.79 (m, 1H), 4.76 (t, *J* = 2.7 Hz, 1H), 4.74 (d, *J* = 5.2 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.99 (d, *J* = 4.1 Hz, 1H), 3.40 (s, 3H), 2.94 – 2.65 (m, 6H), 2.29 – 2.15 (m, 1H), 2.14 – 2.10 (m, 1H), 1.91 – 1.79 (m, 1H), 1.79 – 1.68 (m, 1H), 1.36 – 1.22 ppm(m, 4H); ^{13}C NMR (101 MHz, C_6D_6): δ 172.51, 141.66, 133.93, 133.77, 128.81, 127.08, 126.57, 126.29, 126.14, 115.47, 115.44, 104.82 (d, J_{Rh-C} = 3.4 Hz), 84.84 (d, J_{Rh-C} = 4.5 Hz), 84.19 (d, J_{Rh-C} = 4.0 Hz), 82.47 (d, J_{Rh-C} = 4.1 Hz), 64.34, 57.97, 51.47, 42.17, 40.20 (d, J_{Rh-C} = 13.8 Hz), 38.75 (d, J_{Rh-C} = 13.6 Hz), 33.24, 29.46, 15.30 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2986, 2947, 1734, 1432, 1347, 1196, 1125 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{31}O_2NRh$: 504.14043, found: 504.14044; $[\alpha]_D^{RT}$ = -33.4 (CH_2Cl_2, *c* = 0.38).

(–)-Bis(*η*^{2}-ethylene){*η*^{5}-(1'*R*,3'*R*)-3'-(methoxycarbonyl)-1'-(naphthalen-2-yl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-cycloocta[*c*]pyridin]-yl)}rhodium(I)

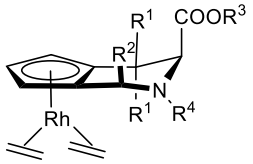


99d, R^1 = -$(CH_2)_5$-, R^2 = 2-naphthyl, R^3 = Me, R^4 = H.

99d: Using Method E, 63% yield; two separable isomers with 90:10 ratio; For major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.66 (s, 1H), 7.61 – 7.55 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.22 (m, 2H), 4.75 (s, 1H), 4.72 – 4.69 (m, 1H), 4.58 (s, 1H), 4.05 (d, *J* = 5.3 Hz, 1H), 3.92 (d, *J* = 4.3 Hz, 1H), 3.38 (s, 3H), 2.86 (t, *J* = 10.5 Hz, 2H), 2.65 (t, *J* = 10.5 Hz, 2H), 2.43 – 2.38 (m, 2H), 2.27 (d, *J* = 13.5 Hz, 1H), 2.05 (t, *J* = 4.8 Hz, 1H), 1.89 (td, *J* = 12.8, 4.4 Hz, 1H), 1.71 – 1.66 (m, 2H), 1.64 – 1.53 (m, 3H), 1.49 – 1.42 (m, 2H), 1.11 – 1.03 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 172.28, 141.38, 133.93, 133.76, 128.83, 128.34, 127.34, 126.75, 126.33, 126.19, 115.41 (d, J_{Rh-C} = 4.3 Hz), 102.66 (d, J_{Rh-C} = 3.3 Hz), 86.50 (d, J_{Rh-C} = 3.8 Hz), 85.57 (d, J_{Rh-C} = 4.3 Hz), 84.88 (d, J_{Rh-C}

= 3.7 Hz), 68.17, 57.31, 51.18, 41.13 (d, $J_{Rh\text{-}C}$ = 13.5 Hz), 39.19, 38.39, 36.18 (d, $J_{Rh\text{-}C}$ = 13.2 Hz), 33.13, 26.41, 23.33, 21.86 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2987, 2927, 1733, 1506, 1432, 1352, 1246, 1198, 1165 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{29}H_{35}O_2NRh$: 532.17173, found: 532.17175; $[\alpha]_D^{RT}$ = -68.9 (CH_2Cl_2, c = 0.47).

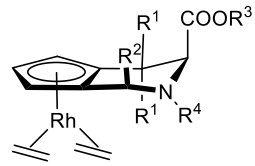
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-1-(4-bromophenyl)-3-(methoxycarbonyl)-4,4-dimethyl-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99e, R^1 = Me, R^2 = 4-Br-C_6H_4, R^3 = Me, R^4 = H.

99e: Using Method E, 54% yield; single isomer; ^{1}H NMR (700 MHz, C_6D_6): δ 7.28 – 7.20 (m, 2H), 6.97 – 6.89 (m, 2H), 4.63 (t, J = 2.7 Hz, 1H), 4.61 – 4.56 (m, 1H), 4.26 – 4.19 (m, 1H), 3.68 (d, J = 4.2 Hz, 1H), 3.64 (d, J = 2.5 Hz, 1H), 3.34 (s, 3H), 2.73 (t, J = 10.3 Hz, 2H), 2.57 (t, J = 10.3 Hz, 2H), 1.69 (s, 3H), 1.47 – 1.37 (m, 5H), 1.10 – 1.00 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.74, 142.83, 131.93, 130.15, 121.84, 116.97 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 101.62 (d, $J_{Rh\text{-}C}$ = 3.4 Hz), 85.64 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 84.11 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 82.83 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 66.37, 56.21, 51.15, 40.67 (d, $J_{Rh\text{-}C}$ = 13.6 Hz), 36.69 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 36.20, 29.89, 26.57 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2986, 1734, 1484, 1433, 1195, 1010 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{28}O_2N^{79}BrRh$: 520.03530, found: 520.03534; calc. for $[M+H]^+$ $C_{22}H_{28}O_2N^{81}BrRh$: 522.03325, found: 522.03333; $[\alpha]_D^{RT}$ = -56.8 (CH_2Cl_2, c = 0.22).

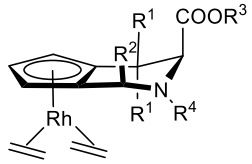
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-3-(methoxycarbonyl)-4,4-dimethyl-1-(4-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99f, R^1 = Me, R^2 = 4-Me-C_6H_4, R^3 = Me, R^4 = H.

99f: Using Method E, 62% yield; two separable isomers with 85:15 ratio; For major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.22 (d, J = 7.7 Hz, 2H), 6.98 (d, J = 7.7 Hz, 2H), 4.76 (s, 1H), 4.67 (s, 1H), 4.27 (s, 1H), 3.89 (d, J = 4.5 Hz, 1H), 3.73 (d, J = 3.1 Hz, 1H), 3.34 (s, 3H), 2.78 (t, J = 10.5 Hz, 2H), 2.61 (t, J = 10.3 Hz, 2H), 2.12 (s, 3H), 1.72 (s, 3H), 1.46 – 1.41 (m, 5H), 1.08 – 1.02 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.48, 140.71, 137.02, 129.14, 128.07, 116.69 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 102.18 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 85.08 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 84.04 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 82.36 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 66.21, 56.25, 50.70, 40.30 (d, $J_{Rh\text{-}C}$ = 13.6 Hz), 36.17 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 35.82, 29.56, 26.26, 20.77 ppm; FT-IR: $\tilde{\nu}$ = 3053, 2986, 2959, 1735, 1512, 1433, 1360, 1195, 1182, 1019 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{23}H_{31}O_2NRh$: 456.14043, found: 456.14044; $[\alpha]_D^{RT}$ = -37.3 (CH_2Cl_2, c = 0.45).

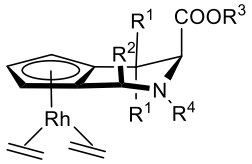
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-3-(methoxycarbonyl)-4,4-dimethyl-1-(2-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99g, R^1 = Me, R^2 = 2-Me-C_6H_4, R^3 = Me, R^4 = H.

99g: Using Method E, 78% yield; two separable isomers with 86:14 ratio; For major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.08 – 6.94 (m, 4H), 4.69 (s, 1H), 4.66 (s, 1H), 4.27 (s, 1H), 3.31 (s, 3H), 2.75 (t, *J* = 10.4 Hz, 2H), 2.59 (t, *J* = 10.4 Hz, 2H), 2.27 (s, 3H), 1.68 (s, 3H), 1.40 (s, 3H), 1.38 – 1.31 (m, 2H), 1.13 – 1.05 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ ^{13}C NMR (176 MHz, C_6D_6): δ 171.78, 140.80, 134.54, 130.08, 127.28, 126.53, 117.11, 116.10 (d, J_{Rh-C} = 3.4 Hz), 108.72 (d, J_{Rh-C} = 3.9 Hz), 85.17 (d, J_{Rh-C} = 4.6 Hz), 83.48 (d, J_{Rh-C} = 3.8 Hz), 81.92 (d, J_{Rh-C} = 4.0 Hz), 69.75, 56.04, 51.06, 39.01 (d, J_{Rh-C} = 13.5 Hz), 38.66 (d, J_{Rh-C} = 13.3 Hz), 35.35, 30.17, 28.31, 19.66 ppm; FT-IR: $\tilde{\nu}$ = 3344, 3055, 2960, 1734, 1433, 1361, 1124, 1018 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{23}H_{31}O_2NRh$: 456.14043, found: 456.14041; $[\alpha]_D^{RT}$ = -69.0 (CH_2Cl_2, *c* = 0.30).

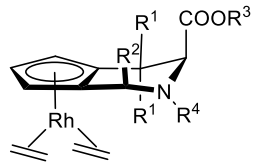
(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-3-(ethoxycarbonyl)-4,4-dimethyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99h, R^1 = Me, R^2 = 2-naphthyl, R^3 = Et, R^4 = H.

99h: Using Method H, 67% yield; two inseparable isomers with 84:16 ratio; For major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.69 – 7.64 (m, 1H), 7.62 – 7.58 (m, 3H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.24 (m, 2H), 4.68 – 4.67 (m, 1H), 4.66 – 4.65 (m, 1H), 4.30 (s, 1H), 4.05 (d, *J* = 4.1 Hz, 1H), 4.03 – 3.94 (m, 2H), 3.81 (d, *J* = 2.3 Hz, 1H), 2.81 (t, *J* = 10.4 Hz, 2H), 2.64 (t, *J* = 10.4 Hz, 2H), 1.79 (s, 3H), 1.56 (s, 3H), 1.47 – 1.42 (m, 2H), 1.11 – 1.04 (m, 2H), 0.97 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.52, 141.34, 133.92, 133.79, 128.79, 128.35, 128.10, 127.21, 126.76, 126.29, 126.15, 117.26 (d, J_{Rh-C} = 4.5 Hz), 102.26 (d, J_{Rh-C} = 3.7 Hz), 85.61 (d, J_{Rh-C} = 4.7 Hz), 84.49 (d, J_{Rh-C} = 4.3 Hz), 82.82 (d, J_{Rh-C} = 4.3 Hz), 66.51, 60.63, 57.13, 40.70 (d, J_{Rh-C} = 14.5 Hz), 36.67 (d, J_{Rh-C} = 14.1 Hz), 36.37, 30.11, 26.69, 14.34 ppm; FT-IR: $\tilde{\nu}$ = 3340, 3054, 2984, 1729, 1433, 1338, 1184, 1029 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{33}O_2NRh$: 506.15608, found: 506.15604; $[\alpha]_D^{RT}$ = +87.4 (CH_2Cl_2, *c* = 0.50).

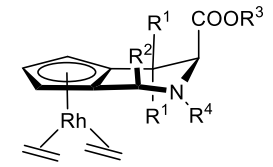
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-3-(methoxycarbonyl)-2,4,4-trimethyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



99i, R^1 = Me, R^2 = 2-naphthyl, R^3 = Me, R^4 = Me.

99i: Using Method E, 81% yield; single isomer; ^{1}H NMR (700 MHz, C_6D_6): δ 7.65 – 7.57 (m, 5H), 7.29 – 7.21 (m, 2H), 4.68 (s, 1H), 4.51 (s, 1H), 4.20 (s, 1H), 3.78 (s, 1H), 3.61 (s, 1H), 3.39 (s, 3H), 2.85 (t, J = 10.5 Hz, 2H), 2.64 (t, J = 10.4 Hz, 2H), 2.25 (s, 3H), 1.81 (s, 3H), 1.51 (s, 3H), 1.48 – 1.43 (m, 2H), 1.14 – 1.03 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.22, 141.44, 133.86, 133.80, 129.17, 128.35, 128.16, 127.59, 126.63, 126.34, 126.14, 115.66 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 101.53 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 85.79 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 85.23 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 81.39 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 75.25, 66.75, 50.81, 41.56 (d, $J_{Rh\text{-}C}$ = 13.6 Hz), 41.08, 36.57 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 36.05, 28.72, 28.01 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2986, 2850, 2770, 1744, 1461, 1311, 1193, 1044 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{33}O_2NRh$: 506.15608, found: 506.15582; $[\alpha]_D^{RT}$ = -184.2 (CH_2Cl_2, c = 0.50).

(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-2-ethyl-3-(methoxycarbonyl)-4,4-dimethyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

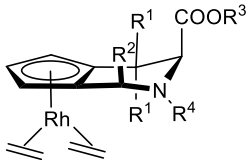


99j, R^1 = Me, R^2 = 2-naphthyl, R^3 = Me, R^4 = Et.

99j: Using Method E, 45% yield; single isomer; ^{1}H NMR (700 MHz, C_6D_6): δ 7.70 (s, 1H), 7.66 – 7.57 (m, 4H), 7.29 – 7.24 (m, 2H), 4.71 (t, J = 2.6 Hz, 1H), 4.56 (s, 1H), 4.27 (s, 1H), 4.21 – 4.15 (m, 2H), 3.39 (s, 3H), 3.06 (dd, J = 15.3, 7.3 Hz, 1H), 2.89 (t, J = 10.5 Hz, 2H), 2.75 – 2.63 (m, 3H), 1.81 (s, 3H), 1.50 (s, 3H), 1.48 – 1.41 (m, 2H), 1.13 – 1.06 (m, 2H), 0.92 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.23, 141.83, 133.89, 133.80, 129.16, 128.35, 127.99, 127.33, 126.77, 126.34, 126.11, 115.50 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 101.98 (d, $J_{Rh\text{-}C}$ = 3.2 Hz), 85.73 (d, $J_{Rh\text{-}C}$ = 4.3 Hz), 85.44 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 81.22 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 70.94, 60.31, 50.79, 44.80, 41.38 (d, $J_{Rh\text{-}C}$ = 13.5 Hz), 36.44 (d, $J_{Rh\text{-}C}$ = 13.3 Hz), 36.21, 28.68, 27.64, 7.96 ppm; FT-IR: $\tilde{\nu}$ = 3055, 2967, 1743, 1433, 1376, 1135, 1053 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{28}H_{35}O_2NRh$: 520.17173, found: 520.17163; $[\alpha]_D^{RT}$ = -83.0 (CH_2Cl_2, c = 1.00).

(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*)-2-isobutyl-3-(methoxycarbonyl)-4,4-dimethyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

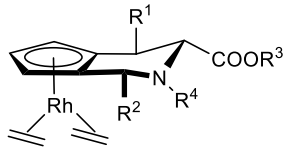
99k: Using Method E, 82% yield; two inseparable isomers with 55:45 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.68 – 7.65 (m, 1.82H), 7.63 – 7.60 (m, 1.82H), 7.59 – 7.51 (m, 5.45H), 7.26 – 7.17 (m, 3.64H), 5.23 (s, 1H), 4.76 (s, 0.82H), 4.75 (s, 1H), 4.51 (s, 1H), 4.46 (s, 0.82H), 4.24 (s, 1H), 4.20 (s, 0.82H), 4.16 (s, 0.82H), 4.02 (s, 0.82H), 3.98 (s, 1H), 3.84 (s,



99k, R^1 = Me, R^2 = 2-naphthyl, R^3 = Me, R^4 = *i*-Bu.

1H), 3.37 (s, 2.45H), 3.32 (s, 3H), 2.96 – 2.84 (m, 3.64H), 2.70 – 2.64 (m, 3.64H), 2.58 (d, *J* = 7.1 Hz, 1.82H), 1.92 (s, 3H), 1.72 (s, 3H), 1.51 (s, 3H), 1.49 (s, 2.45H), 1.48 – 1.39 (m, 6.09H), 1.22 (s, 3H), 1.17 – 1.07 (m, 3.64H), 0.74 (d, *J* = 6.6 Hz, 2.45H), 0.58 ppm (d, *J* = 6.6 Hz, 2.45H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.98, 170.49, 142.27, 141.11, 135.25, 133.74, 133.69, 133.60, 133.52, 131.86, 128.76, 128.35, 128.31, 128.23, 128.13, 127.99, 127.61, 127.59, 127.56, 126.34, 126.20, 126.14, 126.05, 116.24 (d, J_{Rh-C} = 4.2 Hz), 115.46 (d, J_{Rh-C} = 4.2 Hz), 103.18 (d, J_{Rh-C} = 3.4 Hz), 101.44 (d, J_{Rh-C} = 3.4 Hz), 85.81 (d, J_{Rh-C} = 4.3 Hz), 85.62 (d, J_{Rh-C} = 3.7 Hz), 85.38 (d, J_{Rh-C} = 3.7 Hz), 85.22 (d, J_{Rh-C} = 4.4 Hz), 81.51 (d, J_{Rh-C} = 3.9 Hz), 81.36 (d, J_{Rh-C} = 3.9 Hz), 74.59, 73.66, 65.71, 65.31, 64.01, 50.72, 50.68, 41.76 (d, J_{Rh-C} = 13.0 Hz), 41.69 (d, J_{Rh-C} = 13.0 Hz), 36.58 (d, J_{Rh-C} = 13.3 Hz), 36.44 (d, J_{Rh-C} = 13.3 Hz), 36.40, 36.08, 29.75, 28.41, 27.82, 27.30, 27.11, 21.61, 21.35, 21.26, 18.37 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2959, 1747, 1727, 1433, 1382, 1269, 1193 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{30}H_{39}O_2NRh$: 548.20303, found: 548.20270; $[\alpha]_D^{RT}$ = -96.9 (CH_2Cl_2, *c* = 2.00).

(+)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(ethoxycarbonyl)-1-(4-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

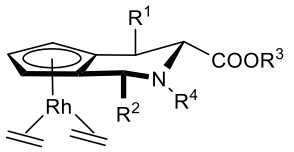


100a, R^1 = 4-Br-C_6H_4, R^2 = 4-Me-C_6H_4, R^3 = Et, R^4 = H.

100a: Using Method F, 78% yield; two separable isomers with 60:40 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1.33H), 7.42 (d, *J* = 8.1 Hz, 1.33H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.11 (m, 3.33H), 6.97 (d, *J* = 7.8 Hz, 1.33H), 6.79 (d, *J* = 8.1 Hz, 2H), 4.96 (s, 0.67H), 4.85 (s, 1H), 4.81 (d, *J* = 6.7 Hz, 1H), 4.64 (t, *J* = 2.4 Hz, 1H), 4.58 (t, *J* = 2.4 Hz, 0.67H), 4.13 (d, *J* = 10.4 Hz, 0.67H), 4.07 (dd, *J* = 10.3, 6.4 Hz, 0.67H), 3.99 (s, 1H), 3.91 (d, *J* = 6.7 Hz, 0.67H), 3.77 – 3.66 (m, 4H), 3.60 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.29 (d, *J* = 10.3 Hz, 1H), 2.82 (t, *J* = 9.7 Hz, 2H), 2.61 – 2.54 (m, 1.33H), 2.54 – 2.47 (m, 2H), 2.47 – 2.41 (m, 1.33H), 2.27 (t, *J* = 6.8 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 2H), 2.02 (t, *J* = 6.7 Hz, 0.67H), 1.37 – 1.25 (m, 3.33H), 1.18 – 1.11 (m, 2H), 1.04 – 0.97 (m, 1.33H), 0.69 – 0.63 ppm (m, 5H); ^{13}C NMR (176 MHz, C_6D_6) δ 171.49, 171.43, 141.47, 140.41, 139.82, 139.64, 137.60, 137.42, 132.04, 131.90, 131.25, 131.16, 129.64, 128.98, 128.57, 128.44, 121.14, 110.65 (d, J_{Rh-C} = 4.7 Hz), 109.83 (d, J_{Rh-C} = 4.6 Hz), 100.89 (d, J_{Rh-C} = 3.3 Hz), 100.09 (d, J_{Rh-C} = 3.5 Hz), 86.62 (d, J_{Rh-C} = 4.0 Hz), 86.57 (d, J_{Rh-C} = 4.1 Hz), 86.19 (d, J_{Rh-C} = 3.7 Hz), 85.35 (d, J_{Rh-C} = 3.7 Hz),

85.07 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 84.19 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 66.10, 63.31, 60.82, 60.66, 59.16, 56.07, 45.87, 42.12, 41.46 (d, $J_{Rh\text{-}C}$ = 13.5 Hz), 41.32 (d, $J_{Rh\text{-}C}$ = 13.6 Hz), 37.56 (d, $J_{Rh\text{-}C}$ = 12.4 Hz), 21.27, 21.12, 13.88, 13.83 ppm; FT-IR: $\tilde{\nu}$ = 3055, 2987, 2932, 1734, 1486, 1183, 1010 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{28}H_{29}O_2N^{79}BrRh$: 596.06660, found: 596.06628; calc. for $[M+H]^+$ $C_{28}H_{29}O_2N^{81}BrRh$: 598.06455, found: 598.06439; $[\alpha]_D^{RT}$ = +11.2 (CH_2Cl_2, *c* = 0.42).

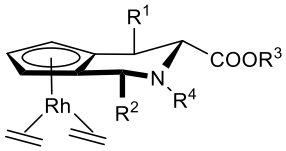
(+)-Bis(η²-ethylene)[η⁵-(1*R*,3*R*,4*R*)-1,4-bis(4-bromophenyl)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100b, R^1 = 4-Br-C_6H_4, R^2 = 4-Br-C_6H_4, R^3 = Et, R^4 = H.

100b: Using Method F, 60% yield; two separable isomers with 57:43 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.62 (d, *J* = 8.2 Hz, 1.50H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.40 (m, 3.50H), 7.23 (d, *J* = 8.2 Hz, 3.50H), 6.84 (d, *J* = 8.2 Hz, 1.50H), 6.76 (d, *J* = 8.2 Hz, 2H), 4.83 (s, 1H), 4.77 (s, 0.75H), 4.61 – 4.56 (m, 2H), 4.55 (t, *J* = 2.6 Hz, 0.75H), 4.08 (d, *J* = 10.3 Hz, 0.75H), 3.99 (dd, *J* = 10.3, 5.8 Hz, 0.75H), 3.77 (s, 1H), 3.75 – 3.66 (m, 4.25H), 3.52 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.19 (d, *J* = 10.3 Hz, 1H), 2.74 (t, *J* = 9.7 Hz, 2H), 2.57 – 2.51 (m, 1.50H), 2.38 (t, *J* = 9.5 Hz, 2H), 2.10 (t, *J* = 6.4 Hz, 1H), 1.88 (t, *J* = 6.2 Hz, 0.75H), 1.37 – 1.28 (m, 2H), 1.26 – 1.19 (m, 1.50H), 1.10 – 1.03 (m, 2H), 1.03 – 0.96 (m, 1.50H), 0.70 – 0.63 ppm (m, 5.25H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.28, 171.25, 142.14, 141.59, 141.22, 139.63, 132.06, 131.99, 131.93, 131.40, 131.28, 131.11, 130.37, 130.16, 128.41, 122.06, 121.91, 121.38, 121.23, 109.77 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 109.72 (d, $J_{Rh\text{-}C}$ = 4.7 Hz), 99.98 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 99.91 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 86.91 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 86.75 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 86.30 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 85.15 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 85.08 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 83.97 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 65.80, 63.08, 60.92, 60.77, 58.69, 55.68, 45.70, 41.96, 41.57 (d, $J_{Rh\text{-}C}$ = 13.5 Hz), 41.33 (d, $J_{Rh\text{-}C}$ = 13.0 Hz), 37.70 (d, $J_{Rh\text{-}C}$ = 12.7 Hz), 37.51 (d, $J_{Rh\text{-}C}$ = 12.7 Hz), 13.86, 13.81 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2986, 1730, 1485, 1184, 1010 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{29}O_2N^{79}Br_2Rh$: 659.96146, found: 659.96204; calc. for $[M+H]^+$ $C_{27}H_{29}O_2N^{79}Br^{81}BrRh$: 661.95996, found: 661.96014; calc. for $[M+H]^+$ $C_{27}H_{29}O_2N^{81}Br_2Rh$: 663.95737, found: 663.95734; $[\alpha]_D^{RT}$ = +49.8 (CH_2Cl_2, *c* = 1.00).

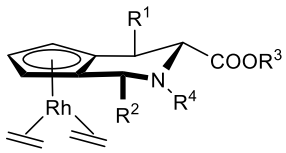
(+)-Bis(η²-ethylene)[η⁵-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(ethoxycarbonyl)-1-(4-fluorophenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100c, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R^3 = Et, R^4 = H.

100c: Using Method F, 76% yield; two separable isomers with 58:42 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.64 (d, *J* = 8.0 Hz, 1.44H), 7.62 – 7.59 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1.44H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.98 – 6.93 (m, 3.44H), 6.79 – 6.74 (m, 3.44H), 4.85 (s, 1H), 4.81 (s, 0.72H), 4.65 (d, *J* = 6.5 Hz, 1H), 4.61 (s, 1H), 4.56 (s, 0.72H), 4.10 (d, *J* = 10.3 Hz, 0.72H), 4.01 (dd, *J* = 10.3, 6.0 Hz, 0.72H), 3.79 (s, 1H), 3.78 – 3.66 (m, 4.88H), 3.54 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.21 (d, *J* = 10.3 Hz, 1H), 2.76 (t, *J* = 9.6 Hz, 2H), 2.59 – 2.52 (m, 1.44H), 2.44 – 2.36 (m, 3.44H), 2.13 (t, *J* = 6.3 Hz, 1H), 1.91 (t, *J* = 6.3 Hz, 0.72H), 1.37 – 1.30 (m, 1.44H), 1.28 – 1.21 (m, 2H), 1.12 – 1.04 (m, 2H), 1.04 – 0.97 (m, 1.44H), 0.70 – 0.62 ppm (m, 5.16H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.31, 171.30, 162.86 (d, *J* = 245.5 Hz), 162.77 (d, *J* = 246.0 Hz), 141.26, 139.67, 139.01 (d, *J* = 3.1 Hz), 138.49 (d, *J* = 3.0 Hz), 132.00, 131.92, 131.28, 131.14, 130.23 (d, *J* = 7.8 Hz), 130.08 (d, *J* = 8.0 Hz), 121.37, 121.22, 115.70 (d, *J* = 21.3 Hz), 115.01 (d, *J* = 21.2 Hz), 110.34 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 109.80 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 100.38 (d, $J_{Rh\text{-}C}$ = 3.2 Hz), 99.95 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 86.88 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 86.70 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 86.25 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 85.15 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 85.13 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 84.02 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 65.89, 63.18, 60.90, 60.75, 58.62, 55.55, 45.75, 41.99, 41.52 (d, $J_{Rh\text{-}C}$ = 13.2 Hz), 41.31 (d, $J_{Rh\text{-}C}$ = 13.4 Hz), 37.67 (d, $J_{Rh\text{-}C}$ = 12.5 Hz), 37.40 (d, $J_{Rh\text{-}C}$ = 13.0 Hz), 13.87, 13.82 ppm; FT-IR: $\tilde{\nu}$ = 3318, 3055, 2987, 2926, 1732, 1603, 1508, 1223, 1185, 1156 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{29}O_2N^{79}BrFRh$: 600.04153, found: 600.04169; calc. for $[M+H]^+$ $C_{27}H_{29}O_2N^{81}BrFRh$: 602.03948, found: 602.03967; $[\alpha]_D^{RT}$ = +60.3 (CH_2Cl_2, *c* = 0.35).

(+)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(ethoxycarbonyl)-1-(2-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

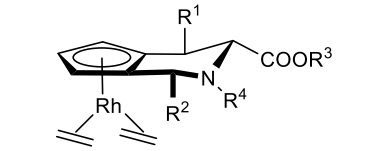


100d, R^1 = 4-Br-C_6H_4, R^2 = 2-Me-C_6H_4, R^3 = Et, R^4 = H.

100d: Using Method F, 66% yield; two inseparable isomers with 56:44 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 8.45 (d, *J* = 7.8 Hz, 0.79H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.20 (m, 1.58H), 7.16 – 7.14 (m, 1H), 7.08 – 7.00 (m, 3.37H), 7.00 – 6.96 (m, 1H), 6.78 (d, *J* = 7.8 Hz, 1.58H), 5.14 (d, *J* = 7.4 Hz, 0.79H), 4.90 (s, 1H), 4.87 (s, 0.79H), 4.66 (s, 0.79H), 4.62 (s, 1H), 4.17 – 4.11 (m, 1H), 4.11 – 4.05 (m, 0.79H), 3.81 (s, 0.79H), 3.78 – 3.62 (m, 6.37H), 3.28 (d, *J* = 10.3 Hz, 0.79H), 2.85 – 2.74 (m, 1.58H), 2.56 (d, *J* = 9.7 Hz, 2H), 2.50 – 2.38 (m, 3.58H), 2.29 (s, 2.37H), 2.28 (s, 3H), 2.26 (s, 0.79H), 1.94 –

1.85 (m, 1H), 1.17 – 1.09 (m, 1.58H), 1.08 – 0.99 (m, 2H), 0.94 – 0.88 (m, 3.58H), 0.68 (t, J = 7.1 Hz, 2.37H), 0.63 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.53, 171.43, 141.43, 141.06, 139.58, 135.27, 131.98, 131.93, 131.29, 131.11, 130.01, 128.42, 128.35, 128.31, 128.12, 127.59, 126.57, 121.36, 121.18, 110.29 (d, J_{Rh-C} = 4.7 Hz), 109.95, 100.85, 100.15 (d, J_{Rh-C} = 3.5 Hz), 86.69 (d, J_{Rh-C} = 4.0 Hz), 86.56 (d, J_{Rh-C} = 3.4 Hz), 86.27 (d, J_{Rh-C} = 3.7 Hz), 85.27, 84.81 (d, J_{Rh-C} = 3.3 Hz), 83.95 (d, J_{Rh-C} = 3.7 Hz), 66.39, 63.24, 60.84, 60.65, 54.92, 45.95, 42.10, 41.68 (d, J_{Rh-C} = 13.9 Hz), 41.57 (d, J_{Rh-C} = 13.4 Hz), 37.78 (d, J_{Rh-C} = 12.3 Hz), 37.48 (d, J_{Rh-C} = 12.7 Hz), 19.39, 13.90, 13.80 ppm; FT-IR: $\tilde{\nu}$ = 3055, 2924, 1723, 1488, 1185, 1010 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{28}H_{32}O_2N^{79}BrRh$: 596.06660, found: 596.06622; calc. for $[M+H]^+$ $C_{28}H_{32}O_2N^{81}BrRh$: 598.06455, found: 598.06439; $[\alpha]_D^{RT}$ = +40.5 (CH_2Cl_2, c = 0.20).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-1-(4-bromophenyl)-3-(ethoxycarbonyl)-4-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

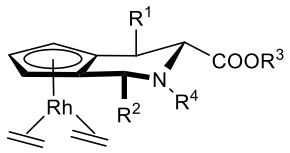


100e, R^1 = 2-naphthyl, R^2 = 4-Br-C_6H_4, R^3 = Me, R^4 = H.

100e: Using Method G, 65% yield; two inseparable isomers with 50:50 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 8.31 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.72 – 7.66 (m, 2H), 7.63 – 7.57 (m, 3H), 7.53 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.33 – 7.21 (m, 7H), 6.89 (d, J = 8.1 Hz, 2H), 4.93 (s, 1H), 4.82 (s, 1H), 4.67 (d, J = 6.9 Hz, 1H), 4.62 (t, J = 2.5 Hz, 1H), 4.55 (t, J = 2.5 Hz, 1H), 4.41 (d, J = 10.3 Hz, 1H), 4.29 – 4.24 (m, 1H), 3.85 – 3.78 (m, 3H), 3.76 (s, 1H), 3.55 (d, J = 10.3 Hz, 1H), 3.04 (s, 3H), 3.00 (s, 3H), 2.83 – 2.76 (m, 2H), 2.66 – 2.60 (m, 2H), 2.51 – 2.39 (m, 4H), 2.12 (t, J = 6.7 Hz, 1H), 1.89 (t, J = 6.5 Hz, 1H), 1.47 – 1.41 (m, 2H), 1.30 – 1.22 (m, 2H), 1.16 – 1.05 ppm (m, 4H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.97, 171.91, 142.27, 141.69, 139.49, 138.01, 134.05, 133.94, 133.57, 133.24, 132.06, 131.38, 130.42, 130.23, 129.19, 128.80, 128.41, 128.35, 128.30, 127.71, 126.93, 126.51, 126.25, 126.19, 126.07, 122.03, 121.86, 110.32 (d, J_{Rh-C} = 4.5 Hz), 109.76 (d, J_{Rh-C} = 4.7 Hz), 100.35 (d, J_{Rh-C} = 3.5 Hz), 99.96 (d, J_{Rh-C} = 3.3 Hz), 86.92 (d, J_{Rh-C} = 4.0 Hz), 86.71 (d, J_{Rh-C} = 4.1 Hz), 86.67 (d, J_{Rh-C} = 3.8 Hz), 85.54 (d, J_{Rh-C} = 3.5 Hz), 85.05 (d, J_{Rh-C} = 3.7 Hz), 84.01 (d, J_{Rh-C} = 3.6 Hz), 65.93, 63.37, 60.07, 58.74, 55.81, 51.39, 51.32, 46.40, 42.62, 41.57 (d, J_{Rh-C} = 13.7 Hz), 41.36 (d, J_{Rh-C} = 13.2 Hz), 37.91 (d, J_{Rh-C} = 12.2 Hz), 37.53 (d, J_{Rh-C} = 12.8 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3053, 2988, 2951, 1736, 1484, 1402, 1198, 1168 cm^{-1}; HRMS: calc. for $[M+H]^+$

$C_{30}H_{30}O_2N^{79}BrRh$: 618.05095, found: 618.05048; calc. for $[M+H]^+$ $C_{30}H_{30}O_2N^{81}BrRh$: 620.04890, found: 620.04865; $[\alpha]_D^{RT}$ = +59.0 (CH_2Cl_2, *c* = 0.21).

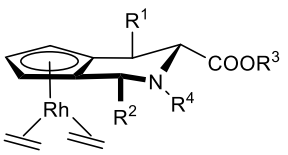
(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-1-(4-bromophenyl)-3-(ethoxycarbonyl)-2-methyl-4-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100f, R^1 = 2-naphthyl, R^2 = 4-Br-C_6H_4, R^3 = Me, R^4 = Me.

100f: Using Method G, 81% yield; two inseparable isomers with 55:45 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 8.30 (s, 0.82H), 8.24 (d, *J* = 8.1 Hz, 0.82H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.70 – 7.66 (m, *J* = 7.1 Hz, 1.82H), 7.63 – 7.50 (m, 4.64 H), 7.44 (d, *J* = 8.3 Hz, 1.64H), 7.32 – 7.25 (m, 5.46 H), 7.25 – 7.20 (m, 1.64H), 7.00 (d, *J* = 8.2 Hz, 2H), 4.97 (s, 0.82H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.69 (s, 1H), 4.61 (t, *J* = 2.6 Hz, 0.82H), 4.53 (t, *J* = 2.6 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.92 (s, 0.82H), 3.71 – 3.64 (m, 2.64H), 3.40 (d, *J* = 10.4 Hz, 0.82H), 3.17 (s, 1H), 2.99 (s, 2.46H), 2.98 (s, 3H), 2.90 (t, *J* = 9.6 Hz, 1.64H), 2.68 – 2.60 (m, 2H), 2.54 – 2.47 (m, 2H), 2.41 (t, *J* = 9.6 Hz, 1.64H), 2.10 (s, 2.46H), 2.09 (s, 3H), 1.49 – 1.42 (m, 2H), 1.24 – 1.18 (m, 1.64H), 1.17 – 1.05 ppm (m, 3.64H); ^{13}C NMR (176 MHz, C_6D_6) δ 171.82, 171.69, 170.03, 142.77, 142.46, 138.09, 136.88, 134.02, 133.89, 133.71, 133.38, 132.13, 131.34, 131.23, 130.44, 129.52, 128.86, 128.53, 127.79, 127.64, 126.90, 126.55, 126.33, 126.29, 126.21, 121.82, 121.68, 110.72 (d, J_{Rh-C} = 4.6 Hz), 108.79 (d, J_{Rh-C} = 4.5 Hz), 99.94 (d, J_{Rh-C} = 3.4 Hz), 98.59 (d, J_{Rh-C} = 3.4 Hz), 87.57 (d, J_{Rh-C} = 3.9 Hz), 87.07 (d, J_{Rh-C} = 4.1 Hz), 85.62 (d, J_{Rh-C} = 3.5 Hz), 85.47 (d, J_{Rh-C} = 3.7 Hz), 84.84 (d, J_{Rh-C} = 3.6 Hz), 84.56 (d, J_{Rh-C} = 3.5 Hz), 75.05, 72.22, 67.85, 64.57, 51.21, 51.16, 46.08, 43.62, 42.46 (d, J_{Rh-C} = 13.3 Hz), 41.40 (d, J_{Rh-C} = 13.0 Hz), 41.17, 41.06, 37.78 (d, J_{Rh-C} = 12.6 Hz), 37.53 (d, J_{Rh-C} = 12.9 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3053, 2988, 2951, 1741, 1484, 1402, 1198, 1167 cm^{-1}; HRMS: calc. for $C_{31}H_{32}O_2N^{79}BrRh$: 632.06660, found: 632.06702; calc. for $[M+H]^+$ $C_{31}H_{32}O_2N^{81}BrRh$: 634.06455, found: 634.06494; $[\alpha]_D^{RT}$ = +60.0 (CH_2Cl_2, *c* = 0.26).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-3-(ethoxycarbonyl)-4-(4-methylphenyl)-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

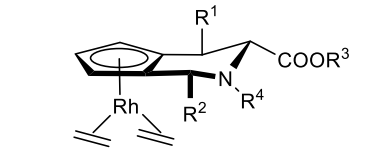


100g, R^1 = 4-Me-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = Et, R^4 = H.

100g: Using Method F, 80% yield; two inseparable isomers with 62:38 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.82 (d, *J* = 7.7 Hz, 1.23H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 11.4

Hz, 1.23H), 7.13 (d, *J* = 7.7 Hz, 1.23H), 7.07 (d, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1.23H), 6.96 (d, *J* = 7.7 Hz, 2H), 5.01 (s, 1H), 4.71 (s, 0.61H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.61 (t, *J* = 2.5 Hz, 1H), 4.57 (t, *J* = 2.5 Hz, 0.61H), 4.27 – 4.24 (m, 0.61H), 4.20 – 4.16 (m, 0.61H), 3.89 (s, 0.61H), 3.85 (d, *J* = 6.9 Hz, 0.61H), 3.80 – 3.75 (m, 2H), 3.75 – 3.70 (m, 1.22H), 3.70 (s, 1H), 3.35 (d, *J* = 10.3 Hz, 1H), 2.75 (t, *J* = 9.8 Hz, 2H), 2.61 (d, *J* = 9.6 Hz, 1.22H), 2.51 (d, *J* = 10.3 Hz, 1.22H), 2.36 (t, *J* = 9.9 Hz, 2H), 2.17 (d, *J* = 7.0 Hz, 1.83H), 2.15 (t, *J* = 6.8 Hz, 1H), 2.10 (s, 3H), 1.89 (t, *J* = 6.7 Hz, 0.61H), 1.45 – 1.38 (m, 1.22H), 1.25 – 1.17 (m, 2H), 1.13 – 1.00 (m, 3.22H), 0.73 – 0.67 ppm (m, 4.83H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.65, 171.59, 147.22, 146.79, 139.15, 137.33, 136.93, 136.79, 130.14, 130.10 (q, *J* = 32.2 Hz), 130.00 (q, *J* = 32.1 Hz), 129.57, 129.29, 128.95, 128.93, 128.91, 128.41, 128.35, 128.31, 128.12, 127.99, 125.94, 125.81 (q, *J* = 3.6 Hz), 125.09 (q, *J* = 3.7 Hz), 124.40, 110.72 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 109.28 (d, $J_{Rh\text{-}C}$ = 4.7 Hz), 100.86 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 99.68 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 86.92 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 86.68 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 86.59 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 85.38 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 84.88 (d, $J_{Rh\text{-}C}$ = 3.8 Hz), 83.86 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 66.11, 63.39, 60.84, 60.69, 58.86, 56.01, 46.04, 42.08, 41.61 (d, $J_{Rh\text{-}C}$ = 13.6 Hz), 41.36 (d, $J_{Rh\text{-}C}$ = 13.7 Hz), 37.72 (d, $J_{Rh\text{-}C}$ = 13.4 Hz), 37.29 (d, $J_{Rh\text{-}C}$ = 12.9 Hz), 21.19, 21.05, 13.91, 13.85 ppm; FT-IR: $\tilde{\nu}$ = 3054, 2987, 1731, 1513, 1322, 1163, 1121, 1066 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{29}H_{32}O_2NF_3Rh$: 586.14347, found: 586.14386; $[\alpha]_D^{RT}$ = +40.4 ($CHCl_3$, *c* = 0.48).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(ethoxycarbonyl)-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

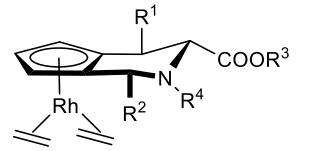


100h, R^1 = 4-Br-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = Et, R^4 = H.

100h: Using Method F, 79% yield; two inseparable isomers with 59:41 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.66 – 7.60 (m, 3.39H), 7.50 (d, *J* = 8.0 Hz, 12H), 7.43 (d, *J* = 8.0 Hz, 1.39H), 7.32 (d, *J* = 8.0 Hz, 1.39H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1.39H), 6.77 (d, *J* = 8.0 Hz, 2H), 4.83 (s, 1H), 4.70 (s, 0.69H), 4.62 (d, *J* = 6.4 Hz, 1H), 4.60 (t, *J* = 2.4 Hz, 1H), 4.56 – 4.54 (m, 0.69H), 4.10 (d, *J* = 10.3 Hz, 0.69H), 4.00 (dd, *J* = 10.3, 5.6 Hz, 0.69H), 3.78 – 3.70 (m, 3.39H), 3.69 (s, 1.69H), 3.52 (dd, *J* = 10.3, 5.9 Hz, 1H), 3.19 (d, *J* = 10.3 Hz, 1H), 2.72 (t, *J* = 9.7 Hz, 2H), 2.57 – 2.52 (m, *J* = 1.39H), 2.41 – 2.36 (m, 1.39H), 2.31 (t, *J* = 9.8 Hz, 2H), 2.13 (t, *J* = 6.2 Hz, 1H), 1.91 (t, *J* = 6.0 Hz, 0.69H), 1.37 – 1.30 (m, 1.39H), 1.23 – 1.16 (m, 2H), 1.09 – 0.97 (m, 2.39H), 0.70 – 0.64 ppm (m, 5.07H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.24, 171.22, 147.01, 146.66, 141.15, 139.56, 131.96, 131.95, 131.31, 131.10, 130.20 (d, *J* = 32.2 Hz),

130.11 (d, *J* = 32.1 Hz), 128.84, 128.41, 128.35, 128.31, 128.20, 128.12, 128.06, 128.06, 127.99, 127.92, 125.90, 125.83 (q, *J* = 3.6 Hz), 125.13 (q, *J* = 3.6 Hz), 124.36, 121.43, 121.29, 109.78 (d, J_{Rh-C} = 4.5 Hz), 109.28 (d, J_{Rh-C} = 4.6 Hz), 99.94 (d, J_{Rh-C} = 3.5 Hz), 99.60 (d, J_{Rh-C} = 3.2 Hz), 87.09 (d, J_{Rh-C} = 4.0 Hz), 86.85 (d, J_{Rh-C} = 4.0 Hz), 86.41 (d, J_{Rh-C} = 3.7 Hz), 85.23 (d, J_{Rh-C} = 3.5 Hz), 84.98 (d, J_{Rh-C} = 3.7 Hz), 83.91 (d, J_{Rh-C} = 3.6 Hz), 65.64, 62.99, 60.98, 60.84, 58.81, 55.87, 45.65, 41.94, 41.68 (d, J_{Rh-C} = 13.2 Hz), 41.36 (d, J_{Rh-C} = 12.9 Hz), 37.78 (d, J_{Rh-C} = 12.8 Hz), 37.40 (d, J_{Rh-C} = 12.7 Hz), 13.86, 13.81 ppm; FT-IR: $\tilde{\nu}$ = 3056, 2988, 1731, 1487, 1322, 1162, 1121, 1065 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{28}H_{29}O_2N^{79}BrF_3Rh$: 650.03833, found: 650.03931; $[\alpha]_D^{RT}$ = +29.9 (CH_2Cl_2, *c* = 0.78).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-4-(4-chlorophenyl)-3-(ethoxycarbonyl)-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

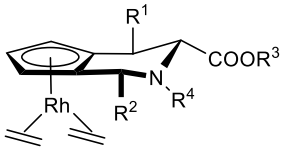


100i, R^1 = 4-Cl-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = Et, R^4 = H.

100i: Using Method F, 59% yield; two inseparable isomers with 57:43 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.68 (d, *J* = 8.1 Hz, 1.51H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 1.51H), 7.27 (d, *J* = 8.1 Hz, 1.51H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 1.51H), 6.83 (d, *J* = 8.1 Hz, 2H), 4.85 (s, 1H), 4.71 (s, 0.75H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.60 (s, 1H), 4.55 (s, 0.75H), 4.12 (d, *J* = 10.3 Hz, 0.75H), 4.01 (dd, *J* = 10.4, 5.7 Hz, 0.75H), 3.78 – 3.71 (m, 3.51H), 3.70 (s, 1.75H), 3.53 (dd, *J* = 10.3, 5.9 Hz, 1H), 3.21 (d, *J* = 10.3 Hz, 1H), 2.72 (t, *J* = 9.7 Hz, 2H), 2.59 – 2.51 (m, 1.51H), 2.40 (d, *J* = 9.7 Hz, 1.51H), 2.31 (t, *J* = 9.8 Hz, 2H), 2.14 (t, *J* = 6.2 Hz, 1H), 1.91 (t, *J* = 6.1 Hz, 0.75H), 1.38 – 1.31 (m, 1.51H), 1.25 – 1.15 (m, 2H), 1.08 – 0.99 (m, 2H), 0.95 – 0.87 (m, 1.51H), 0.70 – 0.63 ppm (m, 5.25H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.26, 171.23, 147.01, 146.67, 140.66, 139.07, 133.31, 133.18, 131.61, 130.75, 130.20 (d, *J* = 32.2 Hz), 130.11 (q, *J* = 32.1 Hz), 128.99, 128.91, 128.84, 128.41, 128.35, 128.34, 128.31, 128.12, 127.99, 125.90, 125.86, 125.83 (q, *J* = 3.6 Hz), 125.80, 125.68, 125.13 (q, J_{Rh-C} = 3.6 Hz), 124.36, 109.89 (d, J_{Rh-C} = 4.5 Hz), 109.29 (d, J_{Rh-C} = 4.6 Hz), 100.03 (d, J_{Rh-C} = 3.5 Hz), 99.63 (d, J_{Rh-C} = 3.2 Hz), 87.09 (d, J_{Rh-C} = 4.0 Hz), 86.84 (d, J_{Rh-C} = 4.0 Hz), 86.41 (d, J_{Rh-C} = 3.7 Hz), 85.23 (d, J_{Rh-C} = 3.5 Hz), 84.98 (d, J_{Rh-C} = 3.7 Hz), 83.91 (d, J_{Rh-C} = 3.6 Hz), 65.71, 63.05, 60.98, 60.83, 58.82, 55.88, 45.59, 41.86, 41.68 (d, J_{Rh-C} = 12.8 Hz), 41.36 (d, J_{Rh-C} = 12.8 Hz), 37.75 (d, J_{Rh-C} = 12.5 Hz), 37.40 (d, J_{Rh-C} = 13.1 Hz), 14.39, 13.87, 13.81 ppm; FT-IR: $\tilde{\nu}$ = 3059, 2988, 1732, 1491, 1322, 1162, 1122, 1065 cm^{-1};

HRMS: calc. for $[M+H]^+$ $C_{28}H_{29}O_2NClF_3Rh$: 606.08885, found: 606.08893; $[\alpha]_D^{RT}$ = +51.4 (Toluene, *c* = 0.29).

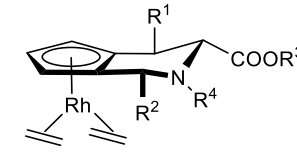
(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-3-(ethoxycarbonyl)-4-isopropyl-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100j, R^1 = *i*-Pr, R^2 = 4-CF_3-C_6H_4, R^3 = Et, R^4 = H.

100j: Using Method F, 65% yield; two inseparable isomers with 67:33 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 5.29 (s, 1H), 4.73 (s, 1H), 4.70 (s, 0.5H), 4.57 (s, 0.5H), 4.40 (d, *J* = 8.7 Hz, 1H), 4.37 (s, 0.5H), 4.00 – 3.94 (m, 3H), 3.69 (t, *J* = 9.1 Hz, 0.5H), 3.64 (s, 1H), 3.59 (d, *J* = 8.5 Hz, 0.5H), 3.51 (t, *J* = 9.2 Hz, 1H), 3.20 (d, *J* = 10.0 Hz, 0.5H), 2.78 (t, *J* = 10.0 Hz, 2H), 2.70 – 2.57 (m, 2H), 2.37 (d, *J* = 9.7 Hz, 1H), 2.32 (t, *J* = 10.0 Hz, 2H), 2.12 – 2.04 (m, 1.5H), 1.92 – 1.84 (m, 1H), 1.55 (t, *J* = 8.3 Hz, 0.5H), 1.46 (d, *J* = 7.0 Hz, 1.5H), 1.39 – 1.26 (m, 2.5H), 1.26 – 1.17 (m, 2H), 1.11 – 1.02 (m, 3H), 0.97 – 0.92 (m, 4.5H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.86 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, C_6D_6): δ 173.05, 172.99, 146.67, 146.10, 129.99 (q, *J* = 32.2 Hz), 129.85 (q, *J* = 32.1 Hz), 128.87, 128.68, 128.41, 128.35, 128.31, 128.12, 127.99, 125.91, 125.73 (q, *J* = 3.7 Hz), 124.99 (q, *J* = 3.7 Hz), 124.37, 111.06 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 106.55 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 100.33 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 99.40 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 86.09 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 85.82 (d, $J_{Rh\text{-}C}$ = 4.2 Hz), 85.70 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 85.02 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 84.69 (d, $J_{Rh\text{-}C}$ = 3.9 Hz), 84.44 (d, $J_{Rh\text{-}C}$ = 3.8 Hz), 61.11, 60.97, 60.55, 59.95, 57.85, 56.14, 43.76, 41.11 (d, $J_{Rh\text{-}C}$ = 13.5 Hz), 40.75 (d, $J_{Rh\text{-}C}$ = 13.7 Hz), 39.00, 37.50 (d, $J_{Rh\text{-}C}$ = 13.0 Hz), 37.30 (d, $J_{Rh\text{-}C}$ = 13.1 Hz), 31.36, 31.31, 21.30, 19.90, 18.56, 18.49, 14.07, 14.03 ppm; FT-IR: $\tilde{\nu}$ = 3057, 2961, 1734, 1322, 1132, 1122, 1065 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{25}H_{32}O_2NF_3Rh$: 538.14347, found: 538.14319; $[\alpha]_D^{RT}$ = +32.9 (CH_2Cl_2, *c* = 0.14).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-3-(ethoxycarbonyl)-4-(naphthalen-2-yl)-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

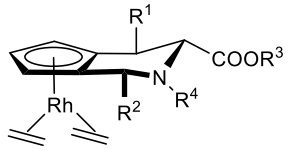


100k, R^1 = 2-naphthyl, R^2 = 4-CF_3-C_6H_4, R^3 = Et, R^4 = H.

100k: Using Method F, 83% yield; two inseparable isomers with 59:41 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 8.27 (s, 0.69H), 8.23 (d, *J* = 8.4 Hz, 0.69H), 7.79 (t, *J* = 7.7 Hz, 1.69H), 7.71 (d, *J* = 7.9 Hz, 0.69H), 7.70 – 7.66 (m, 3H), 7.64 – 7.58 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.22

(m, 5.45H), 7.08 (d, *J* = 7.9 Hz, 1.38H), 4.94 (s, 1H), 4.76 (s, 0.69H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.62 (t, *J* = 2.6 Hz, 1H), 4.56 (t, *J* = 2.5 Hz, 0.69H), 4.42 (d, *J* = 10.3 Hz, 0.69H), 4.28 (dd, *J* = 10.3, 6.0 Hz, 0.69H), 3.87 (d, *J* = 6.7 Hz, 0.69H), 3.83 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.77 (s, 0.69H), 3.74 (s, 1H), 3.73 – 3.60 (m, 3.38H), 3.55 (d, *J* = 10.3 Hz, 1H), 2.79 (t, *J* = 9.8 Hz, 2H), 2.69 – 2.61 (m, *J* = 9.3 Hz, 1.38H), 2.49 – 2.43 (m, 1.38H), 2.40 (t, *J* = 9.9 Hz, 2H), 2.23 (t, *J* = 6.6 Hz, 1H), 1.99 (t, *J* = 6.4 Hz, 0.69H), 1.49 – 1.41 (m, 1.38H), 1.27 – 1.19 (m, 2H), 1.16 – 1.11 (m, 1.38H), 1.11 – 1.04 (m, 2H), 0.57 (t, *J* = 7.1 Hz, 3H), 0.50 ppm (t, *J* = 7.1 Hz, 2.07H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.65, 171.56, 147.19, 146.77, 139.47, 137.98, 134.00, 133.90, 133.56, 133.22, 130.15 (q, *J* = 32.2 Hz), 130.04 (q, *J* = 32.1 Hz), 129.33, 128.95, 128.91, 128.77, 128.56, 128.41, 128.35, 128.31, 128.30, 128.12, , 127.99, 127.62, 126.93, 126.55, 126.28, 126.21, 126.08, 125.94, 125.84 (q, *J* = 3.6 Hz), 125.72, 125.13 (q, *J* = 3.6 Hz), 124.40, 110.39 (d, $J_{Rh\text{-}C}$ = 4.4 Hz), 109.36 (d, $J_{Rh\text{-}C}$ = 4.6 Hz), 100.48 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 99.66 (d, $J_{Rh\text{-}C}$ = 3.2 Hz), 87.08 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 86.79 (d, $J_{Rh\text{-}C}$ = 2.9 Hz), 85.57 (d, $J_{Rh\text{-}C}$ = 3.4 Hz), 84.99 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 83.96 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 65.78, 63.27, 60.86, 60.69, 58.85, 55.97, 46.62, 42.77, 41.67 (d, $J_{Rh\text{-}C}$ = 13.4 Hz), 41.41 (d, $J_{Rh\text{-}C}$ = 13.4 Hz), 37.96 (d, $J_{Rh\text{-}C}$ = 12.2 Hz), 37.40 (d, $J_{Rh\text{-}C}$ = 12.9 Hz), 13.81, 13.71 ppm; FT-IR: $\tilde{\nu}$ = 3319, 3057, 2990, 1733, 1324, 1164, 1121, 1067 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{32}H_{32}O_2NF_3Rh$: 622.14347, found: 622.14410; $[\alpha]_D^{RT}$ = +77.7 (CH_2Cl_2, *c* = 0.60).

(+)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-fluorophenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

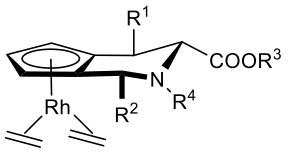


100l, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R^3 = Me, R^4 = H.

100l: Using Method G, 79% yield; two separable isomers with 60:40 ratio; HRMS: calc. for $[M+H]^+$ $C_{26}H_{27}O_2N^{79}BrFRh$: 586.02588, found: 586.02582; calc. for $[M+H]^+$ $C_{26}H_{27}O_2N^{81}BrFRh$: 588.02383, found: 588.02374; $[\alpha]_D^{RT}$ = +65.8 (CH_2Cl_2, *c* = 0.26).

(+)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-fluorophenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

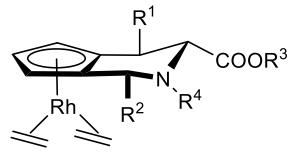
100l-major: Major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.60 (dd, *J* = 8.1, 5.7 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.95 (t, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 2H), 4.84 (s, 1H), 4.61 (d, *J* =



100l-major, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R^3 = Me, R^4 = H.

10.3 Hz, 2H), 3.79 (s, 1H), 3.52 (d, *J* = 10.3 Hz, 1H), 3.20 (d, *J* = 10.3 Hz, 1H), 3.08 (s, 3H), 2.75 (t, *J* = 9.7 Hz, 2H), 2.40 (t, *J* = 9.8 Hz, 2H), 2.06 (s, 1H), 1.28 – 1.19 (m, 2H), 1.12 – 1.02 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.61, 162.87 (d, *J* = 245.6 Hz), 141.18, 138.47 (d, *J* = 3.0 Hz), 131.98, 131.05, 130.23 (d, *J* = 7.8 Hz), 121.30, 115.01 (d, *J* = 21.2 Hz), 110.31 (d, J_{Rh-C} = 4.5 Hz), 99.83 (d, J_{Rh-C} = 3.5 Hz), 86.89 (d, J_{Rh-C} = 4.0 Hz), 86.24 (d, J_{Rh-C} = 3.7 Hz), 84.01 (d, J_{Rh-C} = 3.7 Hz), 65.91, 58.63, 51.43, 41.84, 41.53 (d, J_{Rh-C} = 13.2 Hz), 37.41 (d, J_{Rh-C} = 13.0 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3053, 2988, 2951, 1739, 1507, 1485, 1434, 1198, 1168 cm^{-1}; $[\alpha]_D^{RT}$ = +84.1 (CH_2Cl_2, *c* = 0.22).

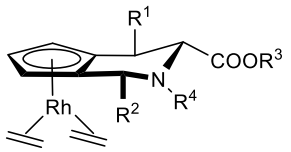
(–)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-fluorophenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100l-minor, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R^3 = Me, R^4 = H.

100l-minor: Minor isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 7.5, 5.9 Hz, 2H), 6.78 – 6.71 (m, 2H), 4.80 (s, 1H), 4.54 (s, 1H), 4.11 (d, *J* = 10.3 Hz, 1H), 4.00 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.75 (d, *J* = 6.6 Hz, 1H), 3.68 (s, 1H), 3.07 (s, 3H), 2.60 – 2.49 (m, 2H), 2.45 – 2.32 (m, 2H), 1.83 (t, *J* = 6.1 Hz, 1H), 1.36 – 1.28 (m, 2H), 1.04 – 0.96 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6) δ 171.59, 162.78 (d, *J* = 246.0 Hz), 139.58, 138.96 (d, *J* = 3.1 Hz), 131.86, 131.38, 130.07 (d, *J* = 8.0 Hz), 121.46, 115.69 (d, *J* = 21.3 Hz), 109.69 (d, J_{Rh-C} = 4.5 Hz), 100.31 (d, J_{Rh-C} = 3.2 Hz), 86.71 (d, J_{Rh-C} = 4.1 Hz), 85.20 (d, J_{Rh-C} = 3.5 Hz), 85.09 (d, J_{Rh-C} = 3.7 Hz), 63.17, 55.59, 51.39, 45.50, 41.30 (d, J_{Rh-C} = 13.2 Hz), 37.70 (d, J_{Rh-C} = 12.8 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3319, 3054, 2987, 1731, 1604, 1509, 1486, 1435, 1229, 1177 cm^{-1}; $[\alpha]_D^{RT}$ = -30.5 (CH_2Cl_2, *c* = 0.22).

(+)-Bis(*η*^{2}-ethylene)[*η*^{5}-(1*R*,3*R*,4*R*)-3-((benzyloxy)carbonyl)-4-(4-bromophenyl)-1-(4-fluorophenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

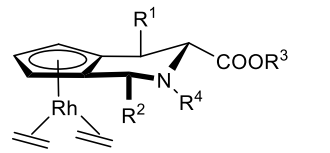


100m, R^1 = 4-Br-C_6H_4, R^2 = 4-F-C_6H_4, R^3 = Bn, R^4 = H.

100m: Using Method G, 74% yield; two separable isomers with 50:50 ratio; For mixture, ^{1}H NMR (700 MHz, C_6D_6): δ 7.59 (dd, *J* = 8.0, 5.7 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 4.0 Hz, 1H), 7.12 – 7.00 (m, 7H), 6.95 (dd, *J* = 15.6, 7.2 Hz, 4H), 6.81 (d, *J* = 7.4 Hz, 2H),

6.80 – 6.73 (m, 4H), 6.66 (d, *J* = 8.1 Hz, 2H), 4.87 – 4.82 (m, 2H), 4.82 (s, 1H), 4.80 (s, 1H), 4.73 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.59 (s, 1H), 4.55 (s, 1H), 4.08 (d, *J* = 10.4 Hz, 1H), 4.03 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.78 (s, 1H), 3.73 (d, *J* = 6.7 Hz, 1H), 3.65 (s, 1H), 3.55 (dd, *J* = 10.4, 6.2 Hz, 1H), 3.16 (d, *J* = 10.4 Hz, 1H), 2.75 (t, *J* = 9.6 Hz, 2H), 2.58 – 2.47 (m, 2H), 2.42 – 2.31 (m, 4H), 2.14 – 2.06 (m, 1H), 1.91 (t, *J* = 6.2 Hz, 1H), 1.34 – 1.28 (m, 2H), 1.26 – 1.21 (m, 2H), 1.10 – 1.04 (m, 2H), 1.01 – 0.95 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.41, 171.36, 162.85 (d, *J* = 245.5 Hz), 162.77 (d, *J* = 246.0 Hz), 140.93, 139.50, 138.95 (d, *J* = 3.1 Hz), 138.44 (d, *J* = 3.0 Hz), 135.65, 132.00, 131.95, 131.39, 131.00, 130.19 (d, *J* = 7.8 Hz), 130.05 (d, *J* = 8.0 Hz), 128.68, 128.66, 128.59, 128.56, 128.55, 128.45, 128.43, 121.44, 121.22, 115.70 (d, *J* = 21.3 Hz), 115.01 (d, *J* = 21.2 Hz), 110.20 (d, J_{Rh-C} = 4.5 Hz), 109.77 (d, J_{Rh-C} = 4.5 Hz), 100.31 (d, J_{Rh-C} = 3.1 Hz), 99.85 (d, J_{Rh-C} = 3.5 Hz), 86.87 (d, J_{Rh-C} = 4.0 Hz), 86.71 (d, J_{Rh-C} = 4.0 Hz), 86.20 (d, J_{Rh-C} = 3.7 Hz), 85.11, 84.04 (d, J_{Rh-C} = 3.6 Hz), 66.81, 66.73, 65.86, 63.15, 58.49, 55.46, 45.84, 42.26, 41.52 (d, J_{Rh-C} = 13.3 Hz), 41.34 (d, J_{Rh-C} = 13.2 Hz), 37.65 (d, J_{Rh-C} = 12.5 Hz), 37.39 (d, J_{Rh-C} = 12.8 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3321, 3051, 2989, 1734, 1603, 1508, 1223, 1156 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{32}H_{31}O_2N^{79}BrFRh$: 662.05718, found: 662.05713; calc. for $[M+H]^+$ $C_{32}H_{31}O_2N^{81}BrFRh$: 664.05513, found: 664.05505; $[\alpha]_D^{RT}$ = +63.8 (CH_2Cl_2, *c* = 0.21).

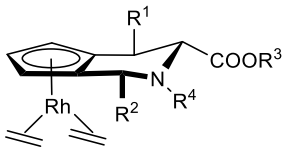
(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100n, R^1 = 4-Br-C_6H_4, R^2 = 4-Me-C_6H_4, R^3 = Me, R^4 = H.

100n: Using Method G, 82% yield; two separable isomers with 57:43 ratio; HRMS: calc. for $[M+H]^+$ $C_{27}H_{30}O_2N^{79}BrRh$: 582.05095, found: 582.05115; calc. for $[M+H]^+$ $C_{27}H_{30}O_2N^{81}BrRh$: 584.04890, found: 584.04889; $[\alpha]_D^{RT}$ = +31.6 (CH_2Cl_2, *c* = 0.23).

(+)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)

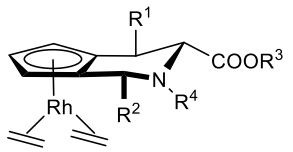


100n-major, R^1 = 4-Br-C_6H_4, R^2 = 4-Me-C_6H_4, R^3 = Me, R^4 = H.

100n-major: Major isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 7.9 Hz, 2H), 4.84 (s, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.63 (s, 1H), 3.98 (s, 1H), 3.58 (dd, *J* = 10.2, 6.5 Hz, 1H), 3.28 (d, *J* = 10.3 Hz,

1H), 3.08 (s, 3H), 2.81 (t, *J* = 9.5 Hz, 2H), 2.49 (t, *J* = 9.6 Hz, 2H), 2.24 – 2.18 (m, 4H), 1.34 – 1.27 (m, 2H), 1.18 – 1.12 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.80, 141.39, 139.61, 137.45, 131.96, 131.07, 128.97, 128.56, 121.22, 110.62 (d, $J_{Rh\text{-}C}$ = 4.6 Hz), 99.97 (d, $J_{Rh\text{-}C}$ = 3.5 Hz), 86.63 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 86.19 (d, $J_{Rh\text{-}C}$ = 3.8 Hz), 84.17 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 66.11, 59.18, 51.39, 41.97, 41.47 (d, $J_{Rh\text{-}C}$ = 13.1 Hz), 37.56 (d, $J_{Rh\text{-}C}$ = 13.0 Hz), 21.26 ppm; FT-IR: $\tilde{\nu}$ = 3051, 2989, 1738, 1513, 1403, 1185, 1105 cm^{-1}; $[\alpha]_D^{RT}$ = +143.1 (CH_2Cl_2, *c* = 0.16).

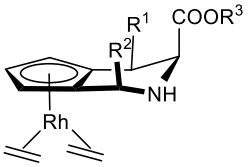
(–)-Bis(η^2-ethylene)[η^5-(1*R*,3*R*,4*R*)-4-(4-bromophenyl)-3-(methoxycarbonyl)-1-(4-methylphenyl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100n-minor, R^1 = 4-Br-C_6H_4, R^2 = 4-Me-C_6H_4, R^3 = Me, R^4 = H.

100n-minor: Minor isomer, ^{1}H NMR (700 MHz, C_6D_6): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.15 (m, 2H), 6.97 (d, *J* = 7.7 Hz, 2H), 4.96 (s, 1H), 4.57 (s, 1H), 4.14 (d, *J* = 10.4 Hz, 1H), 4.07 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.90 (d, *J* = 6.7 Hz, 1H), 3.70 (s, 1H), 3.07 (s, 3H), 2.61 – 2.54 (m, 2H), 2.44 (t, *J* = 9.5 Hz, 2H), 2.12 (s, 3H), 1.96 (t, *J* = 6.5 Hz, 1H), 1.39 – 1.27 (m, 2H), 1.05 – 0.98 ppm (m, 2H); ^{13}C NMR (176 MHz, C_6D_6): δ 171.72, 140.36, 139.74, 137.64, 131.90, 131.35, 129.64, 128.43, 121.38, 109.74 (d, $J_{Rh\text{-}C}$ = 4.6 Hz), 100.83 (d, $J_{Rh\text{-}C}$ = 3.3 Hz), 86.59 (d, $J_{Rh\text{-}C}$ = 4.1 Hz), 85.32 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 85.12 (d, $J_{Rh\text{-}C}$ = 3.6 Hz), 63.31, 56.13, 51.34, 45.62, 41.31 (d, $J_{Rh\text{-}C}$ = 13.1 Hz), 37.61 (d, $J_{Rh\text{-}C}$ = 12.7 Hz), 21.12 ppm; FT-IR: $\tilde{\nu}$ = 3319, 3054, 2987, 1733, 1485, 1433, 1199, 1172 cm^{-1}; $[\alpha]_D^{RT}$ = -18.0 (CH_2Cl_2, *c* = 0.15).

(+)-Bis(η^2-ethylene)[η^5-(1*S*,3*S*,4*R*)-1-(4-bromophenyl)-3-(methoxycarbonyl)-4-(naphthalen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*c*]pyridinyl]rhodium(I)



100o, R^1 = 2-naphthyl, R^2 = 4-Br-C_6H_4, R^3 = Me, R^4 = H.

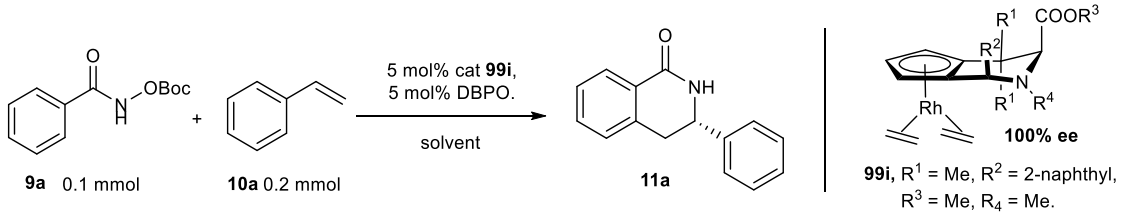
100o: Using Method G, 88% yield; One single isomer; ^{1}H NMR (400 MHz, C_6D_6): δ 7.86 (s, 1H), 7.73 – 7.68 (m, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.36 – 7.29 (m, 2H), 7.29 – 7.20 (m, 2H), 7.15 – 7.12 (m, 2H), 4.88 – 4.79 (m, 1H), 4.73 (d, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 1.4 Hz, 1H), 4.39 – 4.28 (m, 2H), 4.21 (s, 1H), 3.14 (s, 3H), 2.82 – 2.63 (m, 4H), 2.27 (s, 1H), 1.51 – 1.35 ppm (m, 4H); ^{13}C NMR (101 MHz, C_6D_6): δ 171.15, 142.79, 139.46, 133.76, 133.28, 132.13, 129.90, 128.58, 128.17, 128.14, 127.95, 126.24, 126.01, 121.95, 106.71 (d, $J_{Rh\text{-}C}$ = 3.4 Hz), 106.37 (d, $J_{Rh\text{-}C}$ = 3.7 Hz), 85.61 (d, $J_{Rh\text{-}C}$ = 4.0 Hz), 85.44 (d, $J_{Rh\text{-}C}$ = 4.5 Hz), 83.75 (d, $J_{Rh\text{-}C}$ = 4.0 Hz),

61.77, 58.05, 51.25, 43.39, 41.44 (d, $J_{Rh\text{-}C}$ = 13.5 Hz) ppm; FT-IR: $\tilde{\nu}$ = 3332, 3053, 2951, 1736, 1484, 1433, 1199, 1182 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{30}H_{30}O_2N^{79}BrRh$: 618.05095, found: 618.05210; calc. for $[M+H]^+$ $C_{27}H_{30}O_2N^{81}BrRh$: 620.04890, found: 620.05016; $[\alpha]_D^{RT}$ = +13.0 (CH_2Cl_2, c = 0.50).

7.2.3 Experiment Details and Analytic Data for Asymmetric Synthesis of Isoquinolones

7.2.3.1 Reaction Conditions Optimization with Catalyst 99i

Table S1. Reaction Conditions Optimization with Catalyst **99i**.

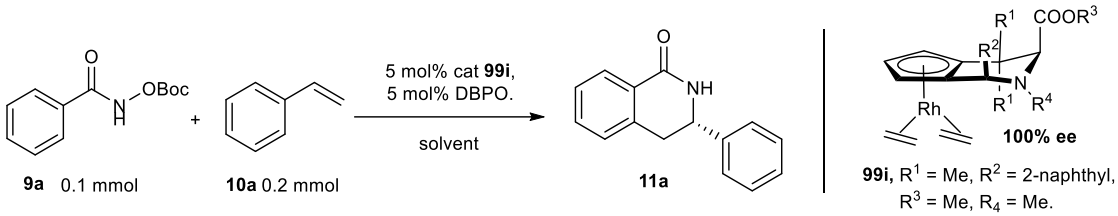


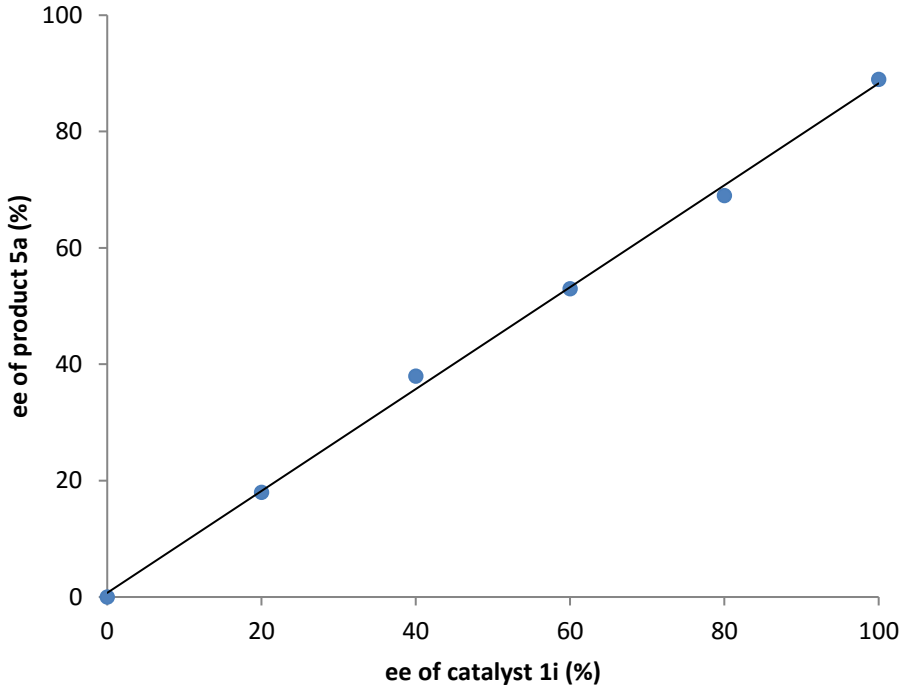
Entry	concentration	temperature	t (h)	solvent	yield(%)	ee(%)
1	0.1	r.t.	4	DCM	90	82
2	1	r.t.	1	DCM	90	83
3	**1**	**-10°C**	**12**	**DCM**	**93**	**90**
4	1	-10°C	24	$CHCl_3$	72	89
5	1	-10°C	24	DCE	72	90
6	1	-10°C	24	EtOH	85	87
7	1	-10°C	24	CH_3CN	22	84
8	1	-10°C	24	Tol	58	87
9	1	-10°C	24	THF	76	88
10	1	-10°C	24	Acetone	67	87
11	1	-10°C	24	Et2O	76	88

General procedure: optical pure catalyst **99i** (2.53 mg, 5.00 μmol, 0.05 equiv.), DBPO (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), hydroxamate **9a** (0.10 mmol, 2.00 equiv.) were dissolved into 100 μL or 1 mL solvent. After stirring at r.t. for 10 mins and/or sequentially cooling to -10°C, corresponding alkenes **10a** (0.20 mmol, 2.00 equiv.) was added and the reaction was stirred for specific time.

7.2.3.2 Investigation of Linear Relationship

Figure S1. Investigation of linear relationship between ee of catalyst and ee of products.





Different ee of catalysts were prepared by mixing two enantiomers of catalyst in certain ratio. The result reveals its linear relationship, which means chirality transfer (CT) we proposed could be regarded to be equal to ee of product when catalyst is optical pure.

General procedure: catalyst **99i** with different ee (2.53 mg, 5.00 μmol, 0.05 equiv.), DBPO (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), hydroxamates **9a** (0.10 mmol, 2.00 equiv.) were dissolved into 100 μL DCM. After stirring at r.t. for 10 mins and sequentially cooling to -10°C, corresponding alkenes **10a** (0.20 mmol, 2.00 equiv.) was added and the reaction was stirred for 12 hours.

7.2.3.3 General Methods and Analytic Data for Synthesis of 11a-11x and 100a-d

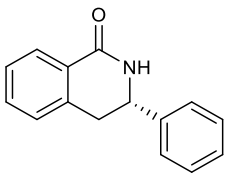
Method I for 11a-11x:

Without protective precaution from air and moisture, catalyst **99i** (2.53 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), hydroxamates **9** (0.10 mmol, 1 equiv.) were dissolved into100 μL DCM. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to -10°C, corresponding alkene **10** (0.20 mmol, 2.00 equiv.) was added and the reaction was stirred for 12-48 hours. The resulting mixture was purified on a silica gel to afford desired product **11a-11n, 11p-11x**. For **11o**, 1 mL DCM was used as solvent.

Method J for 105a-105d:

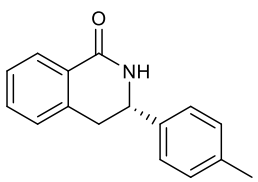
Procedure for C–H activation reactions step is the same with method I. After completion of C–H activation reactions, 2 mL THF was added and the mixture was allowed to cool to 0°C, then *t*-BuOK (2 equiv., 0.20 mmol) was added. The resulting mixture was purified on a silica gel to afford desired product **105a-1005d** after 10 min stirring.

(*S*)-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



11a: Using Method I, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.32 (m, 6H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.06 (s, 1H), 4.86 (ddd, *J* = 10.9, 4.8, 1.1 Hz, 1H), 3.21 (dd, *J* = 15.7, 10.9 Hz, 1H), 3.12 ppm (dd, *J* = 15.6, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.47, 141.03, 137.71, 132.70, 129.16, 128.57, 128.40, 128.22, 127.47, 127.45, 126.56, 56.34, 37.59 ppm; FT-IR: $\tilde{\nu}$ = 3204, 3065, 2924, 1652, 1461, 1318 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{14}NO$: 224.10699, found: 224.10738; $[\alpha]_D^{RT}$ = -159.4 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 50.9 min; minor enantiomer: t_R = 46.5 min, 90% ee.

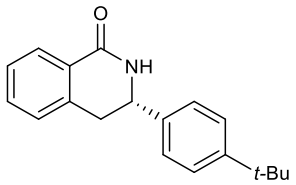
(*S*)-3-(4-methylphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



11b: Using Method I, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.22 – 7.15 (m, 3H), 6.09 (s, 1H), 4.82 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.24 – 3.04 (m, 2H), 2.36 ppm (s, 3H); ^{13}C

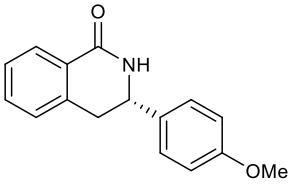
NMR (101 MHz, $CDCl_3$): δ 166.49, 138.35, 138.07, 137.82, 132.61, 129.78, 128.47, 128.19, 127.45, 127.38, 126.46, 56.05, 37.65, 21.24 ppm; FT-IR: $\tilde{\nu}$ = 3194, 3077, 2919, 1653, 1460, 1386, 1319 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO$: 238.12264, found: 238.12298; $[\alpha]_D^{RT}$ = -133.0 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 50.3 min; minor enantiomer: t_R = 43.4 min, 90% ee.

(*S*)-3-(4-(*tert*-butyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



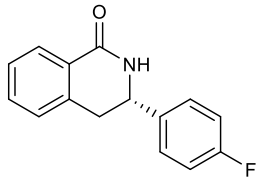
11c: Using Method I, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.43 – 7.35 (m, 3H), 7.35 – 7.31 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.10 (s, 1H), 4.84 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.21 (dd, *J* = 15.7, 11.4 Hz, 1H), 3.10 (dd, *J* = 15.7, 4.5 Hz, 1H), 1.33 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.52, 151.68, 137.91, 137.79, 132.69, 128.35, 128.22, 127.48, 127.41, 126.28, 126.07, 56.04, 37.56, 34.76, 31.44 ppm; FT-IR: $\tilde{\nu}$ = 3189, 3061, 2960, 1657, 1461, 1387, 1318 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{19}H_{22}NO$: 280.16959, found: 280.16990; $[\alpha]_D^{RT}$ = -103.9 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 37.4 min; minor enantiomer: t_R = 33.6 min, 91% ee.

(*S*)-3-(4-methoxyphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



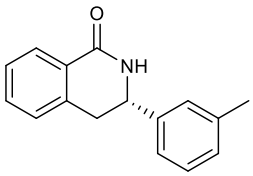
11d: Using Method I, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.02 (s, 1H), 4.80 (dd, *J* = 11.2, 4.5 Hz, 1H), 3.81 (s, 3H), 3.19 (dd, *J* = 15.7, 11.2 Hz, 1H), 3.07 ppm (dd, *J* = 15.7, 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.42, 159.75, 137.86, 133.07, 132.60, 128.50, 128.19, 127.78, 127.45, 127.38, 114.47, 55.78, 55.47, 37.70 ppm; FT-IR: $\tilde{\nu}$ = 3187, 3064, 1659, 1510, 1383, 1247 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO_2$: 254.11756, found: 254.11823; $[\alpha]_D^{RT}$ = -115.5 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 47.6 min; minor enantiomer: t_R = 53.8 min, 90% ee.

(*S*)-3-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



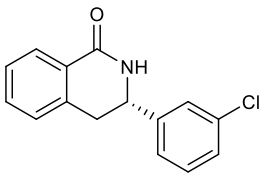
11e: Using Method I, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.14 (s, 1H), 4.85 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.22 – 3.03 ppm (m,2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.40, 162.70 (d, *J* = 247.3 Hz), 137.45, 136.89 (d, *J* = 3.2 Hz), 132.74, 128.37, 128.33, 128.25, 127.85 (d, *J* = 76.5 Hz), 127.52, 116.05 (d, *J* = 21.6 Hz), 55.64, 37.62 ppm; FT-IR: $\tilde{\nu}$ = 3194, 3066, 1652, 1602, 1508, 1387, 1223 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOF$: 242.09757, found: 242.09803; $[\alpha]_D^{RT}$ = -130.5 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 54.6 min; minor enantiomer: t_R = 61.6 min, 90% ee.

(*S*)-3-(3-methylphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



11f: Using Method I, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.24 – 7.13 (m, 4H), 5.99 (s, 1H), 4.82 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.20 (dd, *J* = 15.6, 11.4 Hz, 1H), 3.10 (dd, *J* = 15.6, 4.5 Hz, 1H), 2.37 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.42, 141.03, 138.95, 137.82, 132.64, 129.30, 129.05, 128.48, 128.22, 127.44, 127.42, 127.25, 123.60, 56.36, 37.69, 21.58 ppm; FT-IR: $\tilde{\nu}$ = 3204, 3068, 1660, 1600, 1463, 1384, 1326, 1155 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO$: 238.12264, found: 238.12304; $[\alpha]_D^{RT}$ = -127.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 52.2 min; minor enantiomer: t_R = 43.2 min, 87% ee.

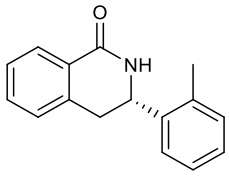
(*S*)-3-(3-chlorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



11g: Using Method I, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.05 (s, 1H), 4.88 – 4.81 (m, 1H), 3.23 – 3.12 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.35, 143.15, 137.22, 135.08, 132.85, 130.49, 128.77, 128.30, 127.62, 127.54, 127.50, 126.88, 124.69, 55.83, 37.42 ppm; FT-IR: $\tilde{\nu}$ = 3185, 3059, 1657, 1602, 1463, 1385, 1322 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOCl$: 258.06802, found: 258.06850; $[\alpha]_D^{RT}$ = -102.7 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-

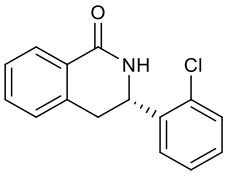
hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 70.5 min; minor enantiomer: t_R = 57.8 min, 87% ee.

(*S*)-3-(2-methylphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



11h: Using Method I, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.18 (m, 4H), 5.95 (s, 1H), 5.14 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.17 (dd, *J* = 15.5, 11.3 Hz, 1H), 3.08 (dd, *J* = 15.5, 4.6 Hz, 1H), 2.39 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.71, 138.90, 137.85, 135.12, 132.70, 131.10, 128.44, 128.27, 128.23, 127.49, 127.02, 125.81, 119.03, 52.40, 36.21, 19.28 ppm; FT-IR: $\tilde{\nu}$ = 3195, 3064, 2919, 1661, 1603, 1461, 1383, 1334, 1154 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO$: 238.12264, found: 128.12318; $[\alpha]_D^{RT}$ = -149.0 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 46.6 min; minor enantiomer: t_R = 56.4 min, 92% ee.

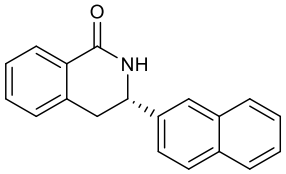
(*S*)-3-(2-chlorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one



11i: Using Method I, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.43 – 7.36 (m, 2H), 7.29 – 7.23 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 6.05 (s, 1H), 5.36 (ddd, *J* = 9.1, 5.1, 2.0 Hz, 1H), 3.35 (dd, *J* = 15.7, 5.1 Hz, 1H), 3.13 ppm (dd, *J* = 15.7, 9.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.59, 138.45, 137.12, 132.83, 132.66, 130.18, 129.41, 128.34, 128.21, 127.71, 127.64, 127.53, 127.40, 52.28, 34.96 ppm; FT-IR: $\tilde{\nu}$ = 3191, 3079, 2925, 1666, 1604, 1465, 1391, 1337, 1039 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOCl$: 258.06802, found: 258.06855; $[\alpha]_D^{RT}$ = -123.0 (CH_2Cl_2, *c* = 0.50); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 46.9 min; minor enantiomer: t_R = 43.3 min, 81% ee.

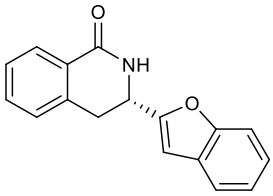
(*S*)-3-(naphthalen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one

11j: Using Method I, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.90 – 7.79 (m, 4H), 7.54 – 7.43 (m, 4H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.33 (s, 1H), 5.02 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.29 (dd, *J* = 15.7, 10.6 Hz, 1H), 3.20 ppm (dd, *J* = 15.7, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.51, 138.37, 137.60, 133.40, 133.29, 132.68, 129.06, 128.47, 128.22, 128.06, 127.85, 127.48, 127.44, 126.70, 126.49, 125.57, 124.18, 56.30,



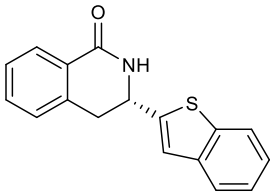
37.43 ppm; FT-IR: $\tilde{\nu}$ = 3195, 3064, 2919, 1661, 1603, 1461, 1383, 1334, 1154 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{19}H_{16}NO$: 274.12264, found: 274.12327; $[\alpha]_D^{RT}$ = -101.7 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 75.6 min; minor enantiomer: t_R = 57.6 min, 90% ee.

(*S*)-3-(benzofuran-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one



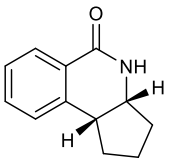
11k: Using Method I, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.51 – 7.41 (m, 3H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.17 (m, 3H), 6.62 – 6.59 (m, 1H), 6.54 (s, 1H), 5.06 (td, *J* = 6.4, 1.7 Hz, 1H), 3.44 ppm (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.92, 156.24, 155.02, 136.78, 132.89, 128.31, 128.18, 127.96, 127.76, 127.60, 124.66, 123.18, 121.27, 111.34, 103.80, 49.73, 32.96 ppm; FT-IR: $\tilde{\nu}$ = 3191, 3085, 2922, 1672, 1603, 1454, 1387, 1251, 1171 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{14}NO_2$: 264.10191, found: 264.10195; $[\alpha]_D^{RT}$ = -6.4 (CH_2Cl_2, *c* = 0.50); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 70/30, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 39.4 min; minor enantiomer: t_R = 27.9 min, 86% ee.

(*S*)-3-(benzo[*b*]thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one



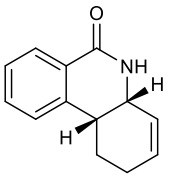
11l: Using Method I, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.72 – 7.68 (m, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.27 – 7.24 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 6.52 (s, 1H), 5.25 – 5.16 (m, 1H), 3.44 – 3.27 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.93, 144.98, 139.39, 139.26, 137.00, 132.91, 128.32, 128.24, 127.73, 127.66, 124.84, 124.76, 123.79, 122.60, 122.01, 52.21, 37.10 ppm; FT-IR: $\tilde{\nu}$ = 3247, 1658, 1636, 1462, 1434, 1381, 1311, 1154 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{14}NOS$: 280.07906, found: 280.07957; $[\alpha]_D^{RT}$ = -14.3 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 70/30, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 38.1 min; minor enantiomer: t_R = 28.4 min, 85% ee.

(3a*R*,9b*R*)-1,2,3,3a,4,9b-hexahydro-5*H*-cyclopenta[*c*]isoquinolin-5-one



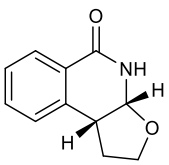
11m: Using Method I, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 (td, *J* = 7.5, 1.3 Hz, 1H), 7.23 – 7.19 (m, 1H), 5.95 (s, 1H), 4.19 (td, *J* = 5.4, 1.3 Hz, 1H), 3.11 (td, *J* = 9.1, 5.4 Hz, 1H), 2.23 – 1.98 (m, 2H), 1.99 – 1.88 (m, 1H), 1.87 – 1.69 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.52, 141.74, 132.45, 128.32, 127.63, 127.02, 126.57, 56.16, 43.20, 34.58, 33.58, 23.15 ppm; FT-IR: $\tilde{\nu}$ = 3184, 2955, 1659, 1603, 1460, 1402, 1329 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_{14}NO$: 188.10669, found: 188.10731; $[\alpha]_D^{RT}$ = -62.7 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 49.0 min; minor enantiomer: t_R = 75.2 min, 88% ee.

(4a*R*,10b*R*)-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one



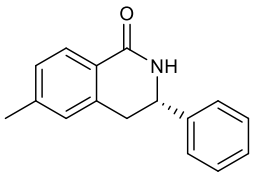
11n: Using Method I, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.02 (m, 1H), 7.53 – 7.44 (m, 1H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.27 – 7.20 (m, 1H), 6.03 (dt, *J* = 9.8, 3.7 Hz, 1H), 5.93 (s, 1H), 5.84 – 5.73 (m, 1H), 4.27 (t, *J* = 4.4 Hz, 1H), 2.94 (dt, *J* = 12.2, 3.8 Hz, 1H), 2.26 – 2.13 (m, 2H), 2.09 – 1.90 (m, 1H), 1.79 – 1.62 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.07, 142.90, 132.65, 132.50, 128.17, 127.66, 127.35, 127.24, 124.54, 48.13, 37.98, 25.33, 25.17 ppm; FT-IR: $\tilde{\nu}$ = 3177, 3026, 2917, 1661, 1602, 1466, 1401, 1293, 1168 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{13}H_{14}NO$: 200.10699, found: 200.10794; $[\alpha]_D^{RT}$ = -53.2 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 70/30, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 39.9 min; minor enantiomer: t_R = 45.8 min, 84% ee.

(3a*R*,9b*R*)-1,3a,4,9b-tetrahydrofuro[2,3-*c*]isoquinolin-5(2*H*)-one



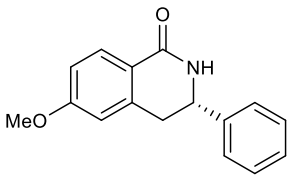
11o: Using Method I, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.4 Hz, 1H), 7.58 (td, *J* = 7.4, 1.5 Hz, 1H), 7.53 – 7.45 (m, 2H), 6.62 (s, 1H), 4.84 (d, *J* = 4.6 Hz, 1H), 4.36 (d, *J* = 4.6 Hz, 1H), 4.13 – 3.96 (m, 2H), 2.50 – 2.38 (m, 1H), 2.22 – 2.12 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.67, 135.50, 132.90, 129.51, 129.14, 128.20, 127.34, 75.33, 66.73, 54.46, 35.17 ppm; FT-IR: $\tilde{\nu}$ = 3194, 3073, 2925, 1657, 1638, 1412, 1334, 1038 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{11}H_{12}NO_2$: 190.08626, found: 190.08693; $[\alpha]_D^{RT}$ = +9.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 41.5 min; minor enantiomer: t_R = 82.0 min, 91% ee.

(*S*)-6-methyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



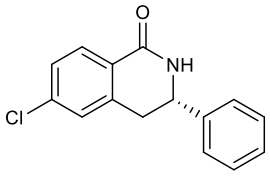
11p: Using Method I, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.31 (m, 6H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 6.07 (s, 1H), 4.84 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.16 (dd, *J* = 15.7, 10.8 Hz, 1H), 3.08 (dd, *J* = 15.7, 4.9 Hz, 1H), 2.38 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): 166.69, 143.38, 141.14, 137.69, 129.13, 128.50, 128.27, 128.09, 126.54, 125.70, 56.38, 37.56, 21.75 ppm; FT-IR: $\tilde{\nu}$ = 3182, 3067, 2920, 1655, 1610, 1454, 1382, 1332, 1309 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO$: 238.12264, found: 238.12305; $[\alpha]_D^{RT}$ = -117.8 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 58.8 min; minor enantiomer: t_R = 54.0 min, 92% ee.

(*S*)-6-methoxy-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



11q: Using Method I, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.30 (m, 5H), 6.88 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.93 (s, 1H), 4.84 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.84 (s, 3H), 3.17 (dd, *J* = 15.6, 10.9 Hz, 1H), 3.08 ppm (dd, *J* = 15.6, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.50, 163.09, 141.16, 139.85, 130.38, 129.13, 128.51, 126.55, 121.23, 112.81, 112.61, 56.35, 55.56, 37.92 ppm; FT-IR: $\tilde{\nu}$ = 3175, 3063, 2925, 1650, 1600, 1454, 1384, 1320, 1253, 1085, 1025 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO_2$: 254.11756, found: 254.11800; $[\alpha]_D^{RT}$ = -108.4 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 70/30, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 38.9 min; minor enantiomer: t_R = 37.2 min, 91% ee.

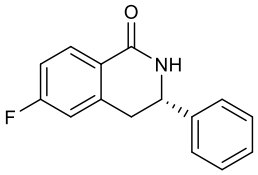
(*S*)-6-chloro-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



11r: Using Method I, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.42 – 7.31 (m, 6H), 7.18 (d, *J* = 1.1 Hz, 1H), 6.16 (s, 1H), 4.85 (dd, *J* = 10.4, 5.1 Hz, 1H), 3.18 (dd, *J* = 15.8, 10.4 Hz, 1H), 3.11 ppm (dd, *J* = 15.8, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.61, 140.57, 139.34, 138.80, 129.83, 129.23, 128.70, 127.83, 127.55, 126.90, 126.50, 56.10, 37.27 ppm; FT-IR: $\tilde{\nu}$ = 3204, 3080, 1652, 1594, 1459, 1422, 1334, 1294 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOCl$: 258.06802, found: 258.06842; $[\alpha]_D^{RT}$ = -116.4 (CH_2Cl_2, *c* =

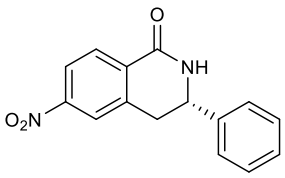
1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 36.8 min; minor enantiomer: t_R = 38.8 min, 93% ee.

(*S*)-6-fluoro-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



11s: Using Method I, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.6, 5.8 Hz, 1H), 7.46 – 7.29 (m, 5H), 7.05 (td, *J* = 8.7, 2.5 Hz, 1H), 6.88 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.08 (s, 1H), 4.86 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.20 (dd, *J* = 15.9, 10.7 Hz, 1H), 3.12 ppm (dd, *J* = 15.9, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.61, 165.37 (d, *J* = 253.6 Hz), 140.66, 140.54 (d, *J* = 9.0 Hz), 131.06 (d, *J* = 9.6 Hz), 129.23, 128.70, 126.52, 124.79 (d, *J* = 2.8 Hz), 114.72 (d, *J* = 21.8 Hz), 114.36 (d, *J* = 22.1 Hz), 56.19, 37.57 ppm; FT-IR: $\tilde{\nu}$ = 3210, 3067, 1651, 1605, 1490, 1455, 1380, 1309, 1248 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOF$: 242.09757, found: 242.09797; $[\alpha]_D^{RT}$ = -130.8 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 44.8 min; minor enantiomer: t_R = 42.8 min, 87% ee.

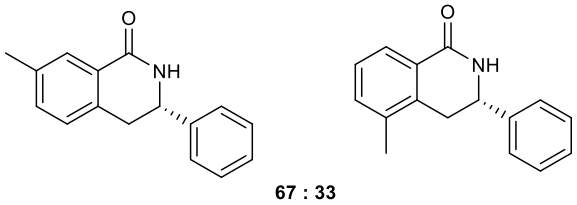
(*S*)-6-nitro-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one



11t: Using Method I, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.25 – 8.19 (m, 1H), 8.07 (d, *J* = 1.9 Hz, 1H), 7.47 – 7.34 (m, 5H), 6.23 (s, 1H), 4.92 (t, *J* = 7.7 Hz, 1H), 3.30 ppm (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.23, 150.27, 139.98, 139.18, 133.71, 129.75, 129.40, 129.00, 126.47, 122.71, 122.45, 55.94, 37.31 ppm; FT-IR: $\tilde{\nu}$ = 3198, 3062, 1668, 1616, 1520, 1457, 1393, 1346, 1159 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}N_2O_3$: 269.09207, found: 269.09237; $[\alpha]_D^{RT}$ = -99.5 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IA column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 34.0 min; minor enantiomer: t_R = 39.8 min, 87% ee.

(*S*)-7-methyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (major),

(*S*)-5-methyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (minor).

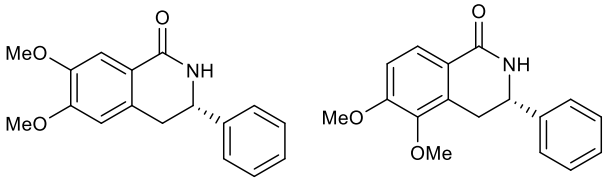


67 : 33

11u: Using Method I, 82% yield; two inseparable isomers with r.r. = 67:33, determined by NMR; For major product, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.49 – 7.27 (m, 6H), 7.06 (t, *J* = 9.4 Hz, 1H), 6.01 (s, 1H), 4.83 (dd, *J* = 10.8, 5.0 Hz, 1H), 3.19 – 3.07 (m, 1H), 2.39 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.70, 141.16, 137.23, 134.72, 133.47, 129.14, 128.57, 128.52, 128.13, 127.39, 126.56, 56.47, 37.25, 21.20 ppm; FT-IR: $\tilde{\nu}$ = 3193, 3059, 2917, 1657, 1613, 1494, 1409, 1333, 1314, 1144 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}NO$: 238.12264, found: 238.12315; $[\alpha]_D^{RT}$ = -132.4 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, for major regioisomer: major enantiomer: t_R = 54.9 min; minor enantiomer: t_R = 52.5 min; For minor regioisomer: major enantiomer: t_R = 61.7 min; minor enantiomer: t_R = 58.6 min, 85% ee for major isomer, 82% ee for minor isomer.

(*S*)-6,7-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (major),

(*S*)-5,6-dimethoxy-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (minor).

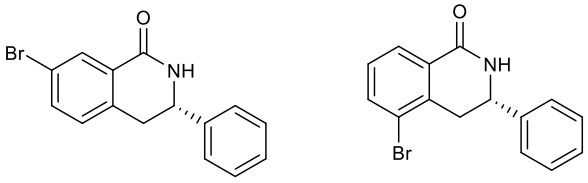


91 : 9

11v: Using Method I, 42% yield; two separable isomers with r.r. = 91:9, determined by NMR; For major product, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.42 – 7.33 (m, 5H), 6.63 (s, 1H), 6.09 (s, 1H), 4.85 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.13 (d, *J* = 10.4 Hz, 1H), 3.08 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.72, 152.82, 148.41, 141.08, 131.56, 129.15, 128.54, 126.55, 120.64, 110.33, 109.79, 56.61, 56.30, 56.22, 37.17 ppm; FT-IR: $\tilde{\nu}$ = 3203, 2939, 1655, 1601, 1510, 1454, 1373, 1332, 1261, 1217, 1070 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{18}NO_3$: 284.12812, found: 284.12850; $[\alpha]_D^{RT}$ = -6.4 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 69.4 min; minor enantiomer: t_R = 85.7 min, 85% ee for major isomer.

(*S*)-7-bromo-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (minor),

(*S*)-5-bromo-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (major).

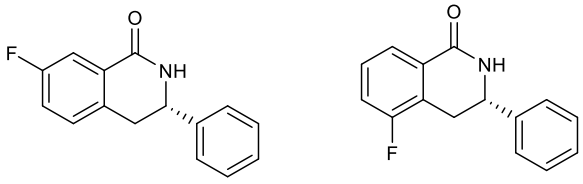


16 : 84

11w: Using Method I, 93% yield; two separable isomers with r.r. = 16:84, determined by NMR; For major product, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 – 7.32 (m, 5H), 7.30 – 7.21 (m, 1H), 6.05 (s, 1H), 4.85 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.42 (dd, *J* = 16.3, 4.5 Hz, 1H), 3.12 ppm (dd, *J* = 16.3, 11.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.50, 140.64, 137.45, 136.58, 130.45, 129.30, 128.82, 128.54, 127.64, 126.64, 123.18, 55.65, 37.42 ppm; FT-IR: $\tilde{\nu}$ = 3180, 3068, 1667, 1592, 1560, 1452, 1386, 1314, 1105 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{33}{}^{79}BrNO$: 302.01750, found: 302.01807; calcd. for $[M+H]^+$ $C_{15}H_{13}{}^{81}BrNO$: 304.01546, found: 304.01591; $[\alpha]_D^{RT}$ = -93.8 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 54.5 min; minor enantiomer: t_R = 56.7 min, 83% ee for major isomer.

(*S*)-7-fluoro-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (minor),

(*S*)-5-fluoro-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (major).

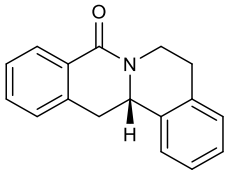


9 : 91

11x: Using Method I, 87% yield; two separable isomers with r.r. = 9:91, determined by NMR; For major product, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.28 (m, 6H), 7.25 – 7.13 (m, 2 6261H), 6.07 (s, 1H), 4.85 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.34 (dd, *J* = 16.2, 4.5 Hz, 1H), 3.04 ppm (dd, *J* = 16.2, 11.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.61, 165.37 (d, *J* = 253.6 Hz), 140.64, 130.36, 129.27, 128.78, 128.27 (d, *J* = 7.9 Hz), 126.56, 124.76 (d, *J* = 18.2 Hz), 123.92 (d, *J* = 3.3 Hz), 119.38 (d, *J* = 21.7 Hz), 55.85, 30.02 ppm; FT-IR: $\tilde{\nu}$ = 3196, 3070, 1655, 1615, 1579, 1469, 1380, 1321, 1239, 1062 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{13}NOF$: 242.09757, found: 242.09815; $[\alpha]_D^{RT}$ = -139.8 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 35.5 min; minor enantiomer: t_R = 33.9 min, 90% ee for major isomer.

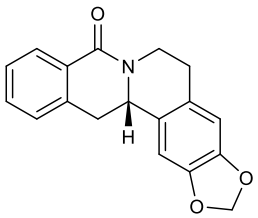
(*S*)-5,6,13,13a-tetrahydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one

105a: Using Method J, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.20 (m, 5H), 5.03 – 4.90 (m, 2H), 3.26 (dd, *J* = 15.7, 3.7 Hz, 1H), 3.08 – 2.96 (m, 3H), 2.93 – 2.82 ppm (m, 1H); ^{13}C



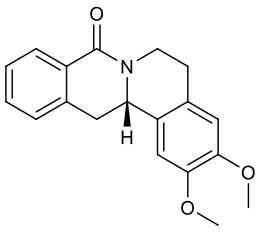
NMR (101 MHz, $CDCl_3$): δ 164.70, 137.47, 136.08, 135.22, 131.93, 129.21, 129.13, 128.72, 127.46, 127.01, 126.99, 126.87, 126.08, 55.35, 38.83, 38.02, 29.87 ppm; FT-IR: $\tilde{\nu}$ = 2933, 2886, 1637, 1600, 1579, 1463, 1402, 1363, 1287, 1149 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{16}NO$: 250.12264, found: 250.12292; $[\alpha]_D^{RT}$ = -440.4 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 32.6 min; minor enantiomer: t_R = 31.6 min, 97% ee.

(*S*)-5,6,13,13a-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]isoquinolino[3,2-*a*]isoquinolin-8-one



105b: Using Method J, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 5.96 (s, 2H), 4.97 – 4.90 (m, 1H), 4.83 (dd, *J* = 13.3, 3.6 Hz, 1H), 3.18 (dd, *J* = 15.7, 3.6 Hz, 1H), 3.02 – 2.86 (m, 3H), 2.81 – 2.68 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.68, 146.89, 146.71, 137.37, 131.96, 129.19, 129.00, 128.73, 128.69, 127.49, 127.02, 108.82, 106.02, 101.25, 55.44, 38.93, 38.27, 29.83 ppm; FT-IR: $\tilde{\nu}$ = 2889, 2865, 1633, 1602, 1577, 1484, 1461, 1413. 1238, 1028 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{16}NO_3$: 294.11247, found: 294.11306; $[\alpha]_D^{RT}$ = -200.2 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 47.6 min; minor enantiomer: t_R = 41.0 min, 97% ee.

(*S*)-2,3-dimethoxy-5,6,13,13a-tetrahydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one

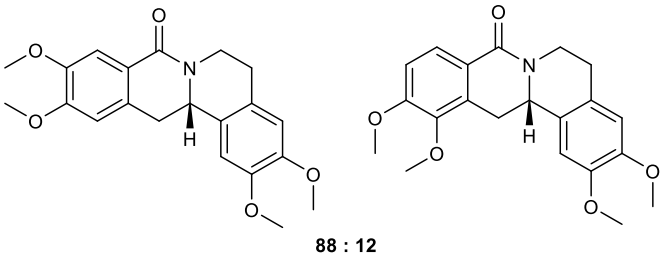


105c: Using Method J, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.46 (td, *J* = 7.4, 1.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29 – 7.22 (m, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 5.03 – 4.95 (m, 1H), 4.86 (dd, *J* = 13.4, 3.7 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.21 (dd, *J* = 15.7, 3.6 Hz, 1H), 3.02 – 2.90 (m, 3H), 2.81 – 2.72 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.75, 148.20, 148.15, 137.42, 131.91, 129.24, 128.73, 127.80, 127.47, 127.46, 126.97, 111.66, 109.06, 56.33, 56.09, 55.14, 38.88, 38.27, 29.36 ppm; FT-IR: $\tilde{\nu}$ = 2927, 2858, 1644, 1602, 1580, 1516, 1460, 1399, 1285, 1202, 1112, 1022 cm^{-1}; HRMS:

calc. for $[M+H]^+$ $C_{19}H_{20}NO_3$: 310.14377, found: 310.14441; $[\alpha]_D^{RT}$ = -353.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 34.6 min; minor enantiomer: t_R = 30.5 min, 95% ee.

(*S*)-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (major),

(*S*)-2,3,11,12-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (minor).

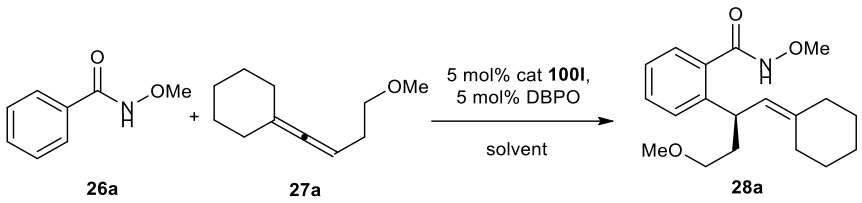


105d: Using Method J, 46% yield in one pot; two inseparable isomers with r.r. = 88:12, determined by NMR; Major product, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 6.72 (s, 1H), 6.71 (s, 1H), 6.69 (s, 1H), 4.98 (dd, J = 8.0, 2.6 Hz, 1H), 4.84 (dd, J = 13.7, 3.9 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.14 (dd, J = 15.6, 3.9 Hz, 1H), 2.97 – 2.90 (m, 3H), 2.81 – 2.73 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.87, 152.09, 148.42, 148.18, 148.14, 131.12, 127.95, 127.55, 121.86, 111.67, 110.96, 109.36, 109.01, 56.31, 56.22, 56.10, 55.45, 38.88, 37.86, 29.43 ppm; FT-IR: $\tilde{\nu}$ = 2932, 2837, 1644, 1602, 1514, 1455, 1429, 1256, 1221, 1098 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{24}NO_5$: 370.16490, found: 370.16608; $[\alpha]_D^{RT}$ = -191.4 (CH_2Cl_2, c = 0.50); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / iso-hexane = 70/30, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 30.2 min; minor enantiomer: t_R = 41.9 min, 91% ee.

7.2.4 Experiment Details and Analytic Data for Asymmetric C–H Allylations of Benzamides

7.2.4.1 Reaction Conditions Optimization with Catalyst 100l

Table S2. Reaction Conditions Optimization with Catalyst **100l**.



26a **27a** **28a**

Entry	solvent	temperature(°C)	t(h	yield(%)	ee(%)
1	0.5 mL DCM	-20	18	79	87
2	0.1 mL DCM	-20	18	82	88
3	0.1 mL DCM	-40	18	28	87
4	0.1 mL MeOH	-20	18	44	90
5	0.1 mL Tol	-20	18	19	85
6	0.1 mL MeOH	-20	36	79	90
7	0.1 mL MeOH	-10	18	60	90
8	0.1 mL EtOH	-20	18	79	91
9	0.1 mL iPrOH	-20	18	66	90
10	0.48 mL DCM/0.02 mL EtOH	-20	18	82	87
11	0.4 mL DCM/0.1 mL EtOH	-20	18	63	89
12	0.25 mL DCM/0.25 mL EtOH	-20	18	65	91
13	0.48 mL DCM/0.02 mL TFE	-20	18	85	89
14	0.48 mL DCM/0.02 mL HFIP	-20	18	85	87
15	0.2 mL TFE	-20	18	63	88
16	0.45 mL DCM/0.05 mL TFE	-20	18	57	89
17	**0.4 mL DCM/0.1 mL TFE**	**-20**	**18**	**85**	**90**
18	0.35 DCM/0.15 mL TFE	-20	18	63	89
19	0.3 mL DCM/0.2 mL TFE	-20	18	72	89
20	0.48 mL DCM/0.02 mL EtOH	-20	18	82	87

General method: Catalyst **100l** (5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 5.00 μmol, 0.05 equiv.) and **26a** (0.12 mmol, 1.20 equiv.) were dissolved into solvent. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to certain temperature, corresponding allene **27a** (0.1 mmol, 1.00 equiv.) was added.

7.2.4.2 General Methods and Analytic Data for Synthesis of 28a-28k

Method K for Synthesis of Compounds 28a-28d, 28i, 28j:

Without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.) and **26** (0.12 mmol, 1.20 equiv.) were dissolved into 0.4 mL DCM: 0.1 mL TFE. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to -20°C, corresponding allenes **27** (0.1 mmol, 1.00 equiv.) was added and the reaction was stirred for 18 hours. The resulting mixture was subjected on a silica gel to afford desired products.

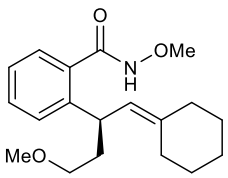
Method L for Synthesis of Compounds 28e-28h:

Without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.) and **26** (0.10 mmol, 1.00 equiv.) were dissolved into 0.4 mL DCM: 0.1 mL TFE. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to -20°C, corresponding allene **27** (0.12 mmol, 1.20 equiv.) was added and the reaction was stirred for 18 hours. The resulting mixture was subjected on a silica gel to afford desired product **28e-28h**.

Method M for Synthesis of Compounds 28k:

Without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.) and **7** (0.12 mmol, 1.20 equiv.) were dissolved into 0.08 mL DCM: 0.02 mL TFE. The mixture was allowed to be stirred at r.t. for 10 mins. After cooling to -20°C, corresponding allene (0.10 mmol, 1.00 equiv.) was added and the reaction was stirred for 18 hours. The resulting mixture was subjected on a silica gel to afford desired product **28k**.

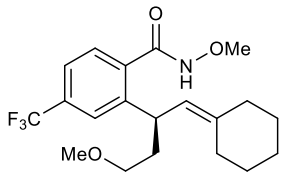
(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxybenzamide



28a: Using method K, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (br s, 1H), 7.46 – 7.36 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 5.15 (d, *J* = 9.3 Hz, 1H), 4.22 – 4.05 (m, 1H), 3.89 (s, 3H), 3.38 – 3.30 (m, 1H), 3.27 (s, 3H), 3.26 – 3.19 (m, 1H), 2.28 – 1.85 (m, 6H), 1.59 – 1.40 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.83, 142.68, 140.77, 133.29, 130.80, 128.89, 127.31, 126.18, 125.20, 70.42, 64.45, 58.27, 37.30, 36.72, 35.68, 29.30, 28.66, 27.85, 26.87 ppm; FT-IR: $\tilde{\nu}$ = 3191, 2925, 2852, 1653, 1599, 1445, 1387, 1303, 1114, 1033 cm^{-1};

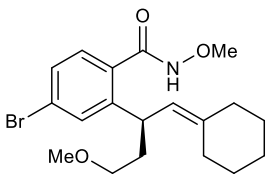
HRMS: calc. for $[M+H]^+$ $C_{19}H_{28}O_3N$: 318.20637, found: 318.20670; $[\alpha]_D^{RT}$ = +10.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 43.1 min; minor enantiomer: t_R = 40.0 min, 90% ee.

(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxy-4-(trifluoromethyl) benzamide



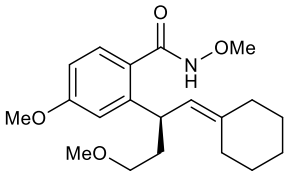
28b: Using method K, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (br s, 1H), 7.59 – 7.52 (m, 2H), 7.51 – 7.45 (m, 1H), 5.12 (d, *J* = 9.2 Hz, 1H), 4.20 (dd, *J* = 15.7, 9.2 Hz, 1H), 3.91 (s, 3H), 3.38 (dt, *J* = 10.1, 5.1 Hz, 1H), 3.28 (s, 3H), 3.20 (td, *J* = 9.5, 4.2 Hz, 1H), 2.23 – 2.17 (m, 1H), 2.14 – 1.96 (m, 4H), 1.96 – 1.85 (m, 1H), 1.50 – 1.46 ppm (m, *J* = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.57, 143.71, 141.93, 136.70, 132.75 (q, *J* = 32.1 Hz), 129.71, 124.28 (q, *J* = 3.4 Hz), 124.21, 123.88 (q, *J* = 272.6 Hz), 123.09 (q, *J* = 3.4 Hz), 70.15, 64.55, 58.28, 37.25, 36.60, 35.81, 29.37, 28.62, 27.82, 26.79 ppm; FT-IR: $\tilde{\nu}$ = 3189, 2928, 1657, 1447, 1328, 1167, 1122, 1077 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{27}O_3NF_3$: 386.19375, found: 386.19481; $[\alpha]_D^{RT}$ = +5.8 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 11.4 min; minor enantiomer: t_R = 12.3 min, 91% ee.

(*R*)-4-bromo-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxybenzamide



28c: Using method K, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (br s, 1H), 7.41 (d, *J* = 1.4 Hz, 1H), 7.38 – 7.29 (m, 2H), 5.09 (d, *J* = 9.2 Hz, 1H), 4.24 – 4.05 (m, 1H), 3.88 (s, 3H), 3.43 – 3.32 (m, 1H), 3.28 (s, 3H), 3.27 – 3.19 (m, 1H), 2.27 – 2.14 (m, 1H), 2.11 – 1.94 (m, 4H), 1.93 – 1.79 (m, 1H), 1.62 – 1.37 ppm (m, *J* = 20.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.78, 144.96, 141.64, 132.21, 130.73, 130.51, 129.50, 125.28, 124.40, 70.20, 64.46, 58.31, 37.25, 36.61, 35.66, 29.35, 28.62, 27.82, 26.81 ppm; FT-IR: $\tilde{\nu}$ = 3185, 2925, 2852, 1653, 1584, 1391, 1115, 1034 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{19}H_{27}O_3N^{79}Br$: 396.11688, found: 396.11713; calcd. for $[M+H]^+$ $C_{19}H_{27}O_3N^{81}Br$: 398.11484, found: 398.11499; $[\alpha]_D^{RT}$ = -50.8 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 29.0 min; minor enantiomer: t_R = 18.1 min, 91% ee.

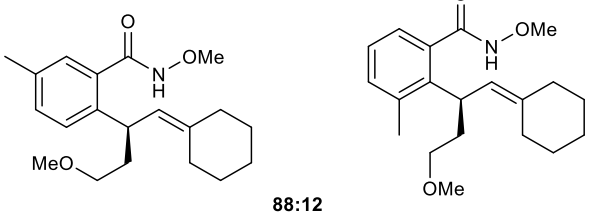
(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*,4-dimethoxybenzamide



28d: Using method K, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.12 (d, *J* = 9.3 Hz, 1H), 4.25 – 4.13 (m, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.38 – 3.30 (m, 1H), 3.28 (s, 3H), 3.27 – 3.20 (m, 1H), 2.28 – 1.82 (m, 6H), 1.58 – 1.36 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.62, 161.44, 145.02, 140.90, 130.73, 125.86, 125.11, 113.11, 111.18, 70.42, 64.37, 58.31, 55.38, 37.26, 36.77, 35.56, 29.32, 28.65, 27.83, 26.85 ppm; FT-IR: $\tilde{\nu}$ = 3190, 2925, 2851, 1651, 1601, 1570, 1446, 1237, 1103, 1027 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{30}O_4N$: 348.21693, found: 348.21759; $[\alpha]_D^{RT}$ = -26.9 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 26.5 min; minor enantiomer: t_R = 24.0 min, 91% ee.

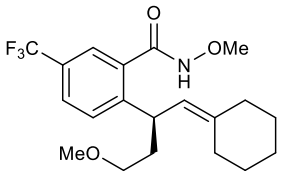
(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxy-5-methylbenzamide (major),

(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxy-3-methylbenzamide (minor).



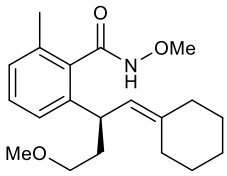
28e: Using method L, 81% yield; r.r. = 88:12; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 7.27 – 7.23 (m, 1H), 7.23 – 7.16 (m, 2H), 5.12 (d, *J* = 9.3 Hz, 1H), 4.18 – 4.02 (m, 1H), 3.89 (s, 3H), 3.33 (dt, *J* = 10.2, 5.3 Hz, 1H), 3.28 (s, 3H), 3.26 – 3.19 (m, 1H), 2.31 (s, 3H), 2.24 – 1.82 (m, 6H), 1.56 – 1.37 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.91, 140.44, 139.42, 135.86, 133.13, 131.69, 129.34, 127.18, 125.45, 70.42, 64.42, 58.25, 37.29, 36.64, 35.26, 29.28, 28.65, 27.85, 26.88, 20.91 ppm; FT-IR: $\tilde{\nu}$ = 3200, 2925, 2852, 1652, 1446, 1114, 1038 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{30}O_3N$: 332.22202, found: 332.22293; $[\alpha]_D^{RT}$ = +6.3 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 39.7 min; minor enantiomer: t_R = 34.5 min, 87% ee for major isomer.

(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxy-5-(trifluoromethyl) benzamide



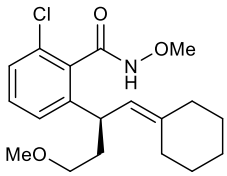
28f: Using method L, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br s, 1H), 7.71 (s, 1H), 7.63 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.27 – 4.14 (m, 1H), 3.90 (s, 3H), 3.42 – 3.32 (m, 1H), 3.27 (s, 3H), 3.20 (td, *J* = 9.6, 4.5 Hz, 1H), 2.25 – 1.85 (m, 6H), 1.56 – 1.40 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.35, 146.81, 141.93, 133.89, 128.64 (q, *J* = 33.0 Hz), 128.07, 127.35 (q, *J* = 3.4 Hz), 126.21 (q, *J* = 3.4 Hz), 124.16, 123.85 (q, *J* = 272.0 Hz), 70.15, 64.49, 58.29, 37.27, 36.57, 35.84, 29.34, 28.59, 27.79, 26.77 ppm; FT-IR: $\tilde{\nu}$ = 3183, 2928, 2853, 1654, 1447, 1336, 1271, 1120 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{27}O_3NF_3$: 386.19375, found: 386.19501; $[\alpha]_D^{RT}$ = +10.9 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 16.9 min; minor enantiomer: t_R = 15.7 min, 88% ee.

(*R*)-2-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxy-6-methylbenzamide



28g: Using method L, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (br s, 1H), 7.29 – 7.22 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 3.91 (s, 3H), 3.88 – 3.79 (m, 1H), 3.40 – 3.16 (m, 5H), 2.35 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 1.82 (m, 5H), 1.63 – 1.37 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.18, 142.26, 140.36, 136.33, 133.41, 129.89, 127.93, 125.12, 124.18, 70.39, 64.33, 58.12, 37.39, 36.78, 36.54, 29.16, 28.66, 27.90, 26.91, 19.47 ppm; FT-IR: $\tilde{\nu}$ = 3174, 2927, 2850, 1642, 1594, 1497, 1463, 1150, 1032 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{30}O_3N$: 332.22202, found: 332.22253; $[\alpha]_D^{RT}$ = +2.6 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 30.2 min; minor enantiomer: t_R = 25.5 min, 88% ee.

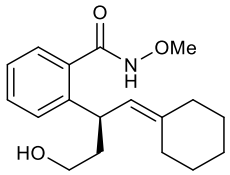
(*R*)-2-chloro-6-(1-cyclohexylidene-4-methoxybutan-2-yl)-*N*-methoxybenzamide



28h: Using method L, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 7.34 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 5.10 (d, *J* = 9.4 Hz, 1H), 3.93 (s, 3H), 3.89 – 3.78 (m, 1H), 3.39 – 3.26 (m, 2H), 3.25 (s, 3H), 2.29 – 2.17 (m, 1H), 2.15 – 1.97 (m, 3H), 1.95 – 1.82 (m, 2H), 1.59 – 1.39 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.10, 145.56, 141.39, 132.62, 132.16, 131.03, 127.23, 125.50, 124.09, 70.35, 64.46, 58.22, 37.41, 37.00, 36.92, 29.21, 28.67, 27.84, 26.86 ppm; FT-IR: $\tilde{\nu}$ = 3176, 2928, 2850, 1649, 1501, 1438, 1116 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{19}H_{27}O_3NCl$: 352.16740, found: 352.16818; $[\alpha]_D^{RT}$ = +12.2 (CH_2Cl_2, *c* = 2.00); HPLC

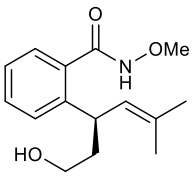
conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 44.4 min; minor enantiomer: t_R = 35.7 min, 82% ee.

(*R*)-2-(1-cyclohexylidene-4-hydroxybutan-2-yl)-*N*-methoxybenzamide



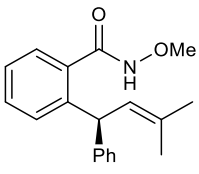
28i: Using method K, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.39 (m, 1H), 7.38 – 7.29 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.24 (d, *J* = 9.4 Hz, 1H), 4.27 – 4.18 (m, 1H), 3.89 (s, 3H), 3.52 (dt, *J* = 11.5, 4.1 Hz, 1H), 3.24 (td, *J* = 11.5, 2.9 Hz, 1H), 2.25– 2.20 (m, 1H), 2.12 – 1.86 (m, 4H), 1.89 – 1.74 (m, 1H), 1.61 – 1.33 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.46, 144.36, 140.32, 132.51, 131.35, 128.23, 127.61, 126.00, 125.59, 64.62, 59.86, 41.06, 37.28, 35.12, 29.34, 28.63, 27.93, 26.87 ppm; FT-IR: $\tilde{\nu}$ = 3154, 2927, 2851, 1639, 1531, 1440, 1315, 1038 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{26}O_3N$: 304.19072, found: 304.19122; $[\alpha]_D^{RT}$ = +33.2 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 61.6 min; minor enantiomer: t_R = 57.7 min, 94% ee.

(*R*)-2-(1-hydroxy-5-methylhex-4-en-3-yl)-*N*-methoxybenzamide



28j: Using method K, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (br s, 1H), 7.47 – 7.41 (m, 1H), 7.37 – 7.31 (m, 2H), 7.24 – 7.18 (m, 1H), 5.31 (d, *J* = 9.3 Hz, 1H), 4.23 – 4.11 (m, 1H), 3.55 (dt, *J* = 11.4, 4.0 Hz, 1H), 3.27 (t, *J* = 9.8 Hz, 1H), 2.51 (br s, 1H), 1.98 (ddd, *J* = 14.8, 9.8, 4.4 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.65 (s, 3H), 1.63 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.51, 144.17, 132.59, 132.34, 131.42, 128.84, 128.28, 127.63, 126.09, 64.75, 59.88, 40.84, 36.18, 25.95, 18.29ppm; FT-IR: $\tilde{\nu}$ = 3153, 2962, 2925, 2853, 1639, 1540, 1439, 1319, 1034 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{22}O_3N$: 264.15942, found: 264.15942; $[\alpha]_D^{RT}$ = +9.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 19.3 min; minor enantiomer: t_R = 18.2 min, 94% ee.

(*S*)-*N*-methoxy-2-(3-methyl-1-phenylbut-2-en-1-yl)benzamide



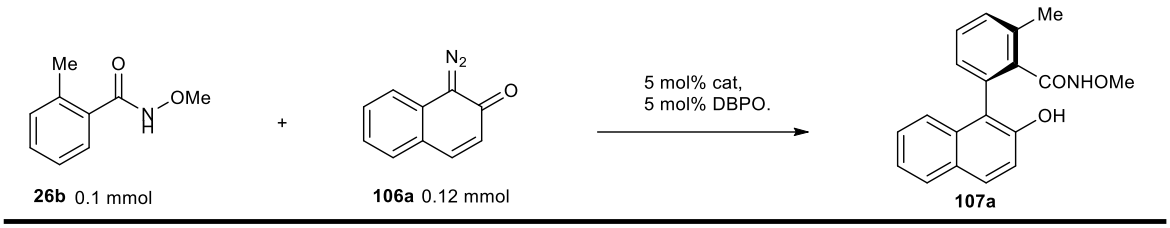
28k: Using method M, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (br s, 1H), 7.43 – 7.35 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.28 – 7.20 (m, 2H), 7.20 – 7.11 (m, 3H), 5.60 – 5.52 (m, 1H), 5.47 (d, *J* = 9.3 Hz, 1H), 3.72 (s, 3H), 1.79 (s, 3H), 1.72 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.11,

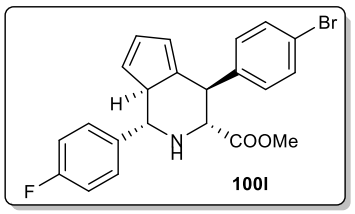
144.94, 144.11, 134.13, 132.95, 130.90, 129.39, 128.51, 128.43, 127.79, 126.91, 126.22, 126.19, 64.60, 45.47, 26.00, 18.40 ppm; FT- IR: $\tilde{\nu}$ = 3179, 2930, 1645, 1492, 1441, 1303, 1033 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{19}H_{22}O_2N$: 296.16451, found: 296.16501; $[\alpha]_D^{RT}$ = -18.0 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 26.1 min; minor enantiomer: t_R = 20.3 min, 79% ee.

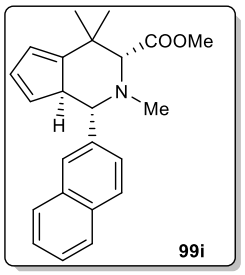
7.2.5 Experiment Details and Analytic Data for Asymmetric Synthesis of Axially Chiral Biaryl Compounds

7.2.5.1 Optimization of Reaction Conditions

Table S3. Optimization of Reaction of of Diazonaphthoquinone **106a** and Benzamide **26b**.



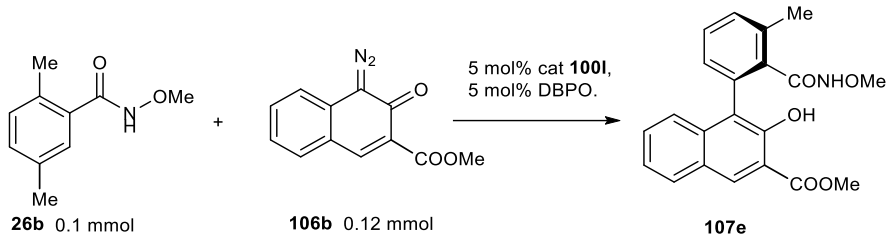




Entr	Solvent	CA	Additives	Temp	T (h)	Yield	ee
1	0.5 mL MeOH	**100l**	-	r.t.	4 h	29	29
2	0.5 mL DCM	**100l**	-	r.t.	4 h	49	27
3	0.5 mL CH3CN	**100l**	-	r.t.	4 h	<10	30
4	0.5 mL THF	**100l**	-	r.t.	4 h	33	55
5	0.5 mL Dioxane	**100l**	-	r.t.	4 h	15	43
6	0.5 mL Tol	**100l**	-	r.t.	4 h	<10	48
7	0.5 mL Acetone	**100l**	-	r.t.	4 h	26	40
8	0.5 mL TFE	**100l**	-	r.t.	4 h	59	20
9	0.4 mL THF/0.1 mL TFE	**100l**	-	r.t.	4 h	39	42
10	0.4 mL THF	**100l**	0.05 mmol PivOH	r.t.	4 h	36	53
11	0.5 mL THF	**99i**		r.t.	4 h	37	14
12	0.5 mL THF	**100l**		0°C	24 h	46	55

General procedure: without protective precaution from air and moisture, catalyst (5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), diazoquinone **106a** (0.12 mmol, 1.20 equiv.) and **26b** (0.10 mmol, 1.00 equiv.) were dissolved into solvent. The mixture was allowed to be stirred at r.t. for 18 hours. The resulting mixture was directly subjected on a silica gel to afford desired product **107a**.

Table S4. Optimization of Reaction of Diazonaphthoquinone **106b** and Benzamide **26b**



Entry	concentration	temperature	t (h)	solvent	yield(%)	ee(%)
1	0.5 M	r.t.	24	THF	53	89
2	0.2 M	50°C	24	THF	63	89
3	0.5 M	r.t.	24	Dioxane	74	91
4	0.5 M	r.t.	24	MeOH	26	82
5	0.5 M	r.t.	24	TFE	37	75
6	0.5 M	r.t.	24	DCM	47	84
7	0.5 M	r.t.	24	CH_3CN	26	73
8	0.5 M	r.t.	24	$CF_3C_6H_5$	52	85

General procedure: without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), diazoquinone **106b** (0.12 mmol, 1.20 equiv.) and **26b** (0.10 mmol, 1.00 equiv.) were dissolved into solvent. The resulting mixture was directly subjected on a silica gel to afford desired product **107e**.

7.2.5.2 General Methods and Analytic Data for the Synthesis of Diazonaphthoquinones 106a-j and Axially Chiral Biaryl Compounds 107a-q

Method N for Synthesis of Diazonaphthoquinones 106a, 106b, 106f-j:

Diazonaphthoquinones were prepared according to the reported procedure. To a solution of 2-chloro-1,3-dimethylimidazolinium chloride (228 mg, 1.35 mmol) in MeCN (2 mL), NaN_3 (99.4 mg, 1.5 mmol), and 15-crown-5 ether (0.06 mL, 0.3 mmol) was added at -20°C, and the mixture was stirred for 30 min. Specific substituted 2-naphthol (0.90 mmol, 1.00 equiv.) and Et_3N (0.25 mL, 1.8 mmol, 2.00 equiv.) in THF (4 mL) was added to the mixture, which was stirred for 2 h. The reaction was quenched with H_2O, and organic materials were extracted three times with CH_2Cl_2. The combined extracts were washed with H_2O and brine, and then, dried over anhyd Na_2SO_4. The solvent was removed in *vacuo* to afford crude compounds. The crude materials

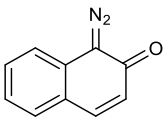
were purified by flash column chromatography to give diazonaphthoquinone **106a, 106b, 106f-j**.

Method O for Synthesis of Diazonaphthoquinones 106c-e:

Diazonaphthoquinones were prepared according to the reported procedure. To a stirred solution of aminophenols (10.0 mmol, 1.0 equiv) in EtOH (60 mL) was slowly added HCl (8.4 mL, 12 N, 100 mmol, 10.0 equiv) at 0 ºC. This mixture was stirred at 0 ºC for 10 min, then an ice-cold solution of $NaNO_2$ (2.07 g, 30 mmol, 3.0 equiv) in H_2O (4 mL) was added dropwise over 10 min. The resulting mixture was stirred for another 2 h at 0 ºC, then diluted with cold CH2Cl2 (200 mL) followed by addition 30 g of ice. The mixture was stirred vigorously while a cold solution of K_2CO_3 (9.2 g, 67 mmol, 6.7 equiv) in H_2O (10 mL) was added. The organic layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layer was washed with brine (100 mL), and dried over Na_2SO_4. Evaporation *in vacuo* resulted in a black solid. This solid was kept anhydrous at -25ºC and used without further purification.

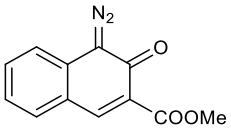
Benzamides 26 were synthesized by Dr. Rajesh Gontla

1-Diazonaphthalen-2(1*H*)-one



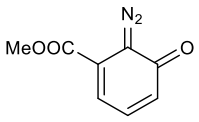
106a: Using Method N, 81% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.66 (d, *J* = 9.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.33 – 7.25 (m, *J* = 11.0, 8.4, 4.5 Hz, 2H), 6.60 ppm (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 180.35, 140.69, 130.49, 130.24, 127.87, 126.29, 126.17, 125.13, 120.36 ppm; HRMS: calc. for $[M+H]^+$ $C_{10}H_7ON_2$: 171.05529, found: 171.05510.

Methyl 4-diazo-3-oxo-3,4-dihydronaphthalene-2-carboxylate



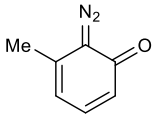
106b: Using Method N, 72% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.34 (s, 1H), 7.75 – 7.68 (m, 1H), 7.66 – 7.56 (m, 1H), 7.35 – 7.26 (m, 2H), 3.88 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 175.94, 165.59, 145.41, 132.37, 132.23, 129.87, 126.80, 125.48, 124.37, 120.05, 52.76 ppm; FT-IR: $\tilde{\nu}$ = 2098, 1693, 1606, 1208, 792 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_9O_3N_2$: 229.06077, found: 229.06072.

Methyl 6-diazo-5-oxocyclohexa-1,3-diene-1-carboxylate



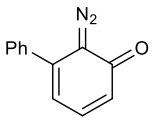
106c: Using Method O, 71% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.31 (dd, *J* = 9.4, 7.0 Hz, 1H), 7.03 (dd, *J* = 7.0, 0.7 Hz, 1H), 6.81 (dd, *J* = 9.4, 0.7 Hz, 1H), 3.92 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 178.41, 163.74, 136.61, 129.72, 126.07, 120.04, 53.47 ppm; HRMS: calc. for $[M+H]^+$ $C_8H_7O_3N_2$: 179.04512, found: 179.04500.

6-Diazo-5-methylcyclohexa-2,4-dien-1-one



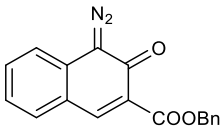
106d: Using Method O, 61% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.27 – 7.18 (m, 1H), 6.51 (dd, *J* = 9.3, 0.7 Hz, 1H), 6.25 – 6.15 (m, 1H), 2.33 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 176.49, 138.25, 134.88, 119.88, 116.47, 18.61 ppm; HRMS: calc. for $[M+H]^+$ $C_7H_7ON_2$: 135.05529, found: 135.05501.

2-Diazo-[1,1'-biphenyl]-3(2*H*)-one



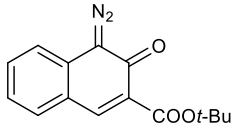
106e: Using Method O, 76% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.56 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.54 – 7.40 (m, 4H), 6.79 (d, *J* = 9.2 Hz, 1H), 6.57 ppm (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 173.46, 138.18, 137.14, 135.97, 129.53, 129.35, 127.92, 119.12, 116.96, 97.08 ppm; HRMS: calc. for $[M+H]^+$ $C_{12}H_9ON_2$: 197.07094, found: 197.07093.

Benzyl 4-diazo-3-oxo-3,4-dihydronaphthalene-2-carboxylate



106f: Using Method N, 51% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.36 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.38 – 7.27 (m, 3H), 5.35 ppm (s, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 175.94, 164.92, 145.45, 136.64, 132.41, 132.26, 129.93, 129.10, 128.73, 128.68, 126.78, 125.48, 124.36, 120.08, 67.43 ppm; FT-IR: $\tilde{\nu}$ = 2124, 1724, 1604, 1201, 1138, 1071, 746 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{18}H_{12}O_3N_2$: 305.09207, found: 305.09204.

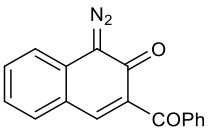
***tert*-butyl 4-diazo-3-oxo-3,4-dihydronaphthalene-2-carboxylate**



106g: Using Method N, 59% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.19 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.35 – 7.26 (m, 2H), 1.58 ppm (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 176.12, 164.21, 143.79, 131.92, 129.52, 128.76, 125.40, 124.59, 120.09, 82.37, 28.49 ppm; FT-IR: $\tilde{\nu}$ = 2086,

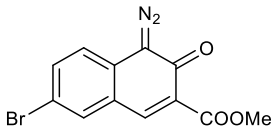
1716, 1613, 1368, 1144, 744 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{15}H_{15}O_3N_2$: 271.10772, found: 271.10794.

3-Benzoyl-1-diazonaphthalen-2(1*H*)-one



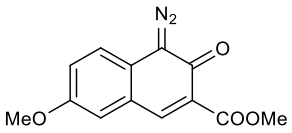
106h: Using Method N, 53% yield; ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.91 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.51 – 7.45 (m, 2H), 7.41 – 7.30 ppm (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 194.56, 177.47, 141.87, 137.72, 135.91, 133.89, 131.83, 131.71, 130.02, 129.10, 128.95, 125.56, 124.94, 120.27 ppm; FT-IR: $\tilde{\nu}$ = 2088, 1655, 1609, 1214, 732 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{17}H_{11}O_2N_2$: 275.08150, found: 275.08154.

Methyl 7-bromo-4-diazo-3-oxo-3,4-dihydronaphthalene-2-carboxylate



106i: Using Method N, 70% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.24 (s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 3.89 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.38, 165.25, 143.74, 135.03, 134.27, 128.59, 128.06, 125.77, 121.58, 118.35, 52.92 ppm; FT-IR: $\tilde{\nu}$ = 2085, 1691, 1611, 1548, 1244, 793 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{12}H_8O_3N_2{}^{79}Br$: 306.97128, found: 306.97155; calc. for $[M+H]^+$ $C_{12}H_8O_3N_2{}^{81}Br$: 308.96923, found: 308.96935.

Methyl 4-diazo-7-methoxy-3-oxo-3,4-dihydronaphthalene-2-carboxylate



106j: Using Method N, 76% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.29 (s, 1H), 7.27 – 7.21 (m, 2H), 7.21 – 7.15 (m, 1H), 3.89 (s, 3H), 3.86 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 175.95, 165.69, 157.77, 144.76, 127.02, 125.44, 122.45, 121.50, 114.12, 56.18, 52.78 ppm; FT-IR: $\tilde{\nu}$ = 1719, 1599, 1648, 1372, 1253, 1144, 844 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}O_4N_2$: 259.07133, found: 259.07134.

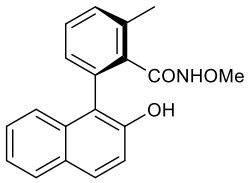
Method P:

Without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), diazoquinones **106** (0.12 mmol, 1.20 equiv.) and **26** (0.10 mmol, 1.00 equiv.) were dissolved into 0.5 mL THF. The mixture was allowed to be stirred at r.t. for 18 hours. The resulting mixture was directly subjected on a silica gel to afford desired product **107a-107c**.

Method Q:

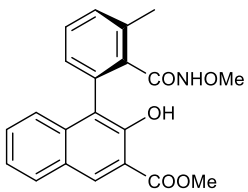
Without protective precaution from air and moisture, catalyst **100l** (2.93 mg, 5.00 μmol, 0.05 equiv.), dibenzoylperoxide (75 wt%, 1.62 mg, 5.00 μmol, 0.05 equiv.), diazoquinones **106** (0.12 mmol, 1.20 equiv.) and **26** (0.10 mmol, 1.00 equiv.) were dissolved into 0.2 mL dioxane. The mixture was allowed to be stirred at r.t. for 18 hours. The resulting mixture was directly subjected on a silica gel to afford desired product **107d-q**.

(*R*)-2-(2-hydroxynaphthalen-1-yl)-N-methoxy-6-methylbenzamide



107a: According to Method P, 33% yield; ^{1}H NMR (600 MHz, methanol-d_4): δ 7.77 – 7.69 (m, 2H), 7.46 – 7.40 (m, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.17 (m, 2H), 7.18 – 7.11 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 2.98 (s, 3H), 2.40 ppm (s, 3H); ^{13}C NMR (600 MHz, methanol-d_4): δ 168.36, 153.02, 137.02, 136.80, 136.00, 135.73, 130.86, 130.53, 130.44, 130.20, 129.78, 128.65, 127.24, 126.19, 123.91, 120.88, 118.80, 63.53, 19.27 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{18}O_3N$: 308.12812, found: 308.12816.

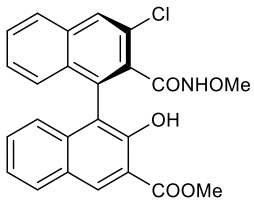
Methyl (*R*)-3-hydroxy-4-(2-(methoxycarbamoyl)-3-methylphenyl)-2-naphthoate



107b: According to Method P, 90% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.03 (s, 1H), 8.81 (s, 1H), 8.63 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.42 – 7.34 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 4.05 (s, 3H), 3.19 (s, 3H), 2.45 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.14, 166.47, 152.83, 137.62, 137.38, 135.36, 133.91, 133.41, 130.46, 130.28, 130.18, 129.97, 128.86, 127.45, 125.41, 124.90, 122.18, 114.07, 63.88, 53.45, 19.45 ppm; FT-IR: $\tilde{\nu}$ = 3148, 2935, 1667, 1505, 1436, 1317, 1217, 1154, 1034 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{20}O_5N$: 366.13360, found: 366.13437; $[\alpha]_D^{RT}$ = +8.9 (CH_2Cl_2, c = 1.00); HPLC

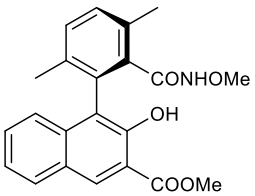
conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 26.9 min; minor enantiomer: t_R = 31.8 min; 51% ee.

Methyl (*R*)-3'-chloro-2-hydroxy-2'-(methoxycarbamoyl)-[1,1'-binaphthalene]-3-carboxylate



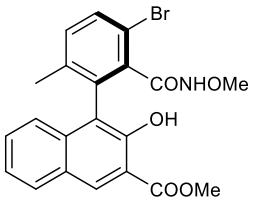
107c: According to Method P, 78% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.94 (s, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 8.00 (s, 1H), 7.89 – 7.85 (m, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.94 – 6.81 (m, 1H), 3.99 (s, 3H), 3.19 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.07, 163.71, 153.72, 137.59, 134.89, 134.43, 134.41, 132.72, 131.38, 130.68, 130.23, 129.16, 128.92, 128.74, 128.10, 127.84, 127.57, 126.59, 125.22, 118.20, 114.32, 64.10, 53.57 ppm; FT-IR: $\tilde{\nu}$ = 3674, 3335, 2987, 2901, 1683, 1665, 1446, 1434, 1340, 1296, 1232, 1066 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{24}H_{19}O_5NCl$: 436.09463, found: 436.09447; $[\alpha]_D^{RT}$ = +6.9 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 45.5 min; minor enantiomer: t_R = 37.2 min; 65% ee.

Methyl (*R*)-3-hydroxy-4-(2-(methoxycarbamoyl)-3,6-dimethylphenyl)-2-naphthoate



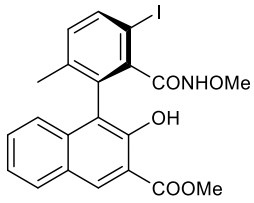
107d: According to Method Q, 74% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 10.95 (s, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.42 – 7.36 (m, 1H), 7.36 – 7.31 (m, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.13 – 7.09 (m, 1H), 4.06 (s, 3H), 3.14 (s, 3H), 2.38 (s, 3H), 1.84 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 171.22, 166.83, 152.87, 137.23, 135.80, 135.34, 134.43, 133.46, 133.03, 131.67, 130.55, 130.44, 130.19, 127.70, 125.01, 124.95, 121.08, 114.32, 63.86, 53.46, 19.54, 19.10 ppm; FT-IR: $\tilde{\nu}$ = 3197, 2954, 1675, 1626, 1504, 1435, 1314, 1270, 1218, 1054 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{22}O_5N$: 380.14925, found: 380.14981; $[\alpha]_D^{RT}$ = -29.4 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 21.8 min; minor enantiomer: t_R = 29.1 min; 91% ee.

Methyl (*R*)-4-(3-bromo-2-(methoxycarbamoyl)-6-methylphenyl)-3-hydroxy-2-naphthoate



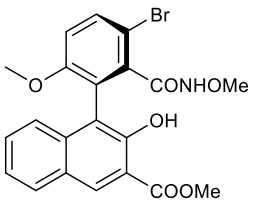
107e: According to Method Q, 56% yield; ^{1}H NMR (700 MHz, CD_2Cl_2) δ 10.96 (s, 1H), 8.64 (s, 1H), 8.59 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.43 – 7.38 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.05 (s, 3H), 3.21 (s, 3H), 1.86 ppm (s, 3H); ^{13}C NMR (176 MHz, CD_2Cl_2) δ 171.11, 164.62, 152.99, 138.49, 136.82, 136.67, 135.73, 133.97, 133.16, 132.88, 130.67, 130.28, 127.60, 125.13, 124.69, 119.80, 118.36, 114.31, 63.97, 53.50, 19.56 ppm; FT-IR: $\tilde{\nu}$ = 3315, 3159, 1687, 1664, 1436, 1332, 1229, 1078, 1048 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}O_5N^{79}Br$: 444.04411, found: 444.04398; calc. for $[M+H]^+$ $C_{21}H_{19}O_5N^{81}Br$: 446.04207, found: 446.04184; $[\alpha]_D^{RT}$ = +9.6 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 33.3 min; minor enantiomer: t_R = 42.6 min; 86% ee.

Methyl (*R*)-4-(3-iodo-2-(methoxycarbamoyl)-6-methylphenyl)-3-hydroxy-2-naphthoate



107f: According to Method Q, 67% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.98 (s, 1H), 8.69 – 8.57 (m, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.44 – 7.36 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 3H), 3.22 (s, 3H), 1.85 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.08, 166.17, 152.87, 140.48, 139.38, 139.24, 136.73, 135.25, 133.91, 133.29, 130.63, 130.24, 127.53, 125.09, 124.65, 120.02, 114.22, 91.05, 63.90, 53.49, 19.57 ppm; FT-IR: $\tilde{\nu}$ = 3673, 3315, 2987, 1686, 1664, 1435, 1405, 1309, 1276, 1077 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}O_5NI$: 492.03024, found: 492.02970; $[\alpha]_D^{RT}$ = +4.7 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 33.6 min; minor enantiomer: t_R = 47.8 min; 90% ee.

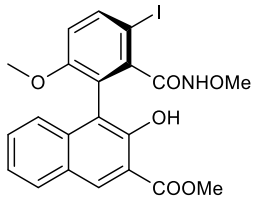
Methyl (*S*)-4-(3-bromo-6-methoxy-2-(methoxycarbamoyl)phenyl)-3-hydroxy-2-naphthoate



107g: According to Method Q, 87% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.00 (s, 1H), 8.72 (s, 1H), 8.63 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.42 – 7.35 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 4.04 (s, 3H), 3.64 (s, 3H), 3.23 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.09, 164.03, 157.50,

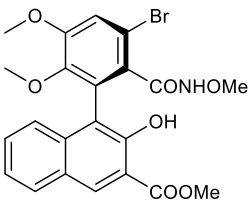
153.30, 137.67, 137.29, 134.11, 133.88, 130.36, 130.13, 127.40, 124.97, 124.89, 117.21, 114.30, 114.21, 111.52, 63.97, 56.64, 53.46 ppm; FT-IR: $\tilde{\nu}$ = 3674, 2255, 2987, 1683, 1501, 1434, 1341, 1312, 1211, 1069, 1038 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}O_6N^{79}Br$: 460.03903, found: 460.03877; calc. for $[M+H]^+$ $C_{21}H_{19}O_6N^{81}Br$: 462.03698, found: 462.03667; $[\alpha]_D^{RT}$ = -11.7 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 75.2 min; minor enantiomer: t_R = 51.6 min; 89% ee.

Methyl (*S*)-4-(3-iodo-6-methoxy-2-(methoxycarbamoyl)phenyl)-3-hydroxy-2-naphthoate



107h: According to Method Q, 93% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.00 (s, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.04 (s, 3H), 3.63 (s, 3H), 3.25 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.09, 165.62, 158.35, 153.23, 141.48, 140.64, 137.27, 133.85, 130.35, 130.11, 127.40, 124.96, 124.90, 124.67, 117.49, 114.71, 114.19, 82.97, 63.94, 56.56, 53.46 ppm; FT-IR: $\tilde{\nu}$ = 3673, 3151, 2987, 1668, 1436, 1314, 1213, 1072, 1026 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}O_6NI$: 508.02516, found: 508.02459; $[\alpha]_D^{RT}$ = -12.8 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 60/40, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 25.9 min; minor enantiomer: t_R = 14.6 min; 89% ee.

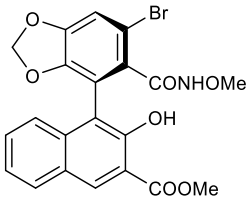
Methyl (*S*)-4-(3-bromo-5,6-dimethoxy-2-(methoxycarbamoyl)phenyl)-3-hydroxy-2-naphthoate



107i: According to Method Q, 84% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.01 (s, 1H), 8.64 (s, 1H), 8.60 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.45 (m, *J* = 7.5 Hz, 1H), 7.44 – 7.36 (m, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 4.05 (s, 3H), 3.94 (s, 3H), 3.49 (s, 3H), 3.19 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.10, 163.95, 155.09, 153.24, 147.28, 137.30, 133.94, 130.39, 130.17, 130.12, 129.42, 127.40, 125.02, 117.36, 117.24, 115.75, 114.14, 63.88, 60.97, 56.70, 53.47 ppm; FT-IR: $\tilde{\nu}$ = 3673, 3236, 2987, 2901, 1672, 1433, 1317, 1287, 1010, 1073, 1029 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{21}O_7N^{79}Br$: 490.04959, found: 490.04917; calc. for $[M+H]^+$ $C_{22}H_{21}O_7N^{81}Br$: 492.04754, found: 492.04710; $[\alpha]_D^{RT}$ = +4.3 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column,

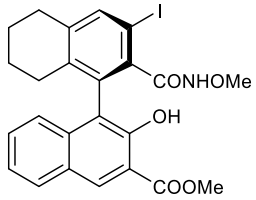
(CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 60/40, flow rate = 1.0 mL min^{-1}, major enantiomer: t_R = 13.3 min; minor enantiomer: t_R = 7.9 min; 90% ee.

Methyl (*S*)-4-(6-bromo-5-(methoxycarbamoyl)benzo[*d*][1,3]dioxol-4-yl)-3-hydroxy-2-naphthoate



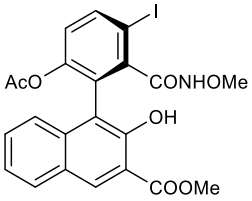
107j: According to Method Q, 89% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 11.08 (s, 1H), 8.65 (s, 2H), 7.92 – 7.86 (m, 1H), 7.59 – 7.49 (m, 1H), 7.44 – 7.39 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.21 – 7.14 (m, 1H), 5.99 – 5.96 (m, 1H), 5.95 (dd, *J* = 1.1, 0.7 Hz, 1H), 4.05 (s, 3H), 3.27 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 171.01, 164.00, 153.78, 149.87, 146.69, 136.88, 134.57, 130.79, 130.33, 127.51, 125.24, 124.80, 116.96, 114.70, 114.33, 113.32, 113.01, 103.17, 64.01, 53.46 ppm; FT-IR: $\tilde{\nu}$ = 3166, 2923, 1676, 1447, 1312, 1228, 1089 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{17}O_7N^{79}Br$: 474.01829, found: 474.01795; calc. for $[M+H]^+$ $C_{21}H_{17}O_7N^{81}Br$: 476.01624, found: 476.01577; $[\alpha]_D^{RT}$ = +7.0 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IA column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 50/50, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 15.9 min; minor enantiomer: t_R = 12.0 min; 79% ee.

Methyl (*R*)-2-hydroxy-3'-iodo-2'-(methoxycarbamoyl)-5',6',7',8'-tetrahydro-[1,1'-binaphthalene]-3-carboxylate



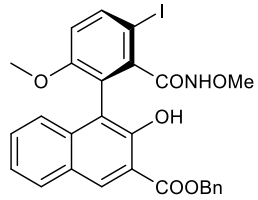
107k: According to Method Q, 69% yield; ^{1}H NMR (700 MHz, CD_2Cl_2): δ 10.87 (s, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.41 – 7.37 (m, 1H), 7.33 – 7.28 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 3.12 (s, 3H), 2.79 – 2.73 (m, 2H), 2.14 – 2.07 (m, 1H), 1.90 – 1.82 (m, 1H), 1.67 – 1.59 (m, 2H), 1.56 – 1.48 ppm (m, 2H); ^{13}C NMR (176 MHz, CD_2Cl_2): δ 171.14, 166.31, 152.80, 142.31, 140.17, 137.99, 137.79, 136.85, 135.05, 133.78, 130.62, 130.23, 127.61, 125.09, 124.72, 120.07, 114.28, 90.63, 63.89, 53.49, 30.12, 27.09, 23.22, 22.85 ppm; FT-IR: $\tilde{\nu}$ = 3673, 3181, 2987, 2920, 1681, 1655, 1505, 1433, 1319, 1209, 1055 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{24}H_{23}O_5NI$: 532.06154, found: 532.06106; $[\alpha]_D^{RT}$ = -10.4 (CH_2Cl_2, *c* = 0.50); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 60/40, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 25.1 min; minor enantiomer: t_R = 13.8 min.

Methyl (*S*)-4-(6-acetoxy-3-iodo-2-(methoxycarbamoyl)phenyl)-3-hydroxy-2-naphthoate



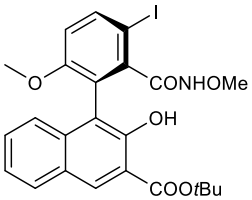
107l: According to Method Q, 37% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.03 (s, 1H), 8.70 (s, 1H), 8.64 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 4.05 (s, 3H), 3.26 (s, 3H), 1.66 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 170.99, 168.73, 165.11, 153.37, 150.19, 142.31, 140.57, 136.84, 134.47, 130.52, 130.08, 129.00, 127.33, 126.63, 125.16, 125.02, 116.02, 114.04, 90.84, 64.03, 53.54, 20.61 ppm; FT-IR: $\tilde{\nu}$ = 3670, 3195, 2987, 1765, 1676, 1435, 1314, 1187, 1072 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{19}O_7NI$: 536.02007, found: 536.01955; $[\alpha]_D^{RT}$ = +8.2 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 60/40, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 20.7 min; minor enantiomer: t_R = 12.9 min; 87% ee.

Benzyl (*S*)-3-hydroxy-4-(3-iodo-6-methoxy-2-(methoxycarbamoyl)phenyl)-2-naphthoate



107m: According to Method Q, 81% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.99 (s, 1H), 8.69 (s, 1H), 8.66 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.50 – 7.34 (m, 5H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 5.51 (d, *J* = 12.2 Hz, 1H), 5.46 (d, *J* = 12.2 Hz, 1H), 3.63 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 170.51, 165.60, 158.36, 153.33, 141.49, 140.66, 137.35, 135.64, 133.91, 130.42, 130.12, 129.26, 129.23, 129.00, 127.40, 125.00, 124.91, 124.67, 117.56, 114.72, 114.18, 82.98, 68.31, 63.94, 56.57 ppm; FT-IR: $\tilde{\nu}$ = 3674, 3324, 2987, 1697, 1661, 1435, 1411, 1305, 1280, 1208, 1066, 1029 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{27}H_{23}O_6NI$: 584.05646, found: 584.05606; $[\alpha]_D^{RT}$ = -7.5 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 69.9 min; minor enantiomer: t_R = 49.8 min; 90% ee.

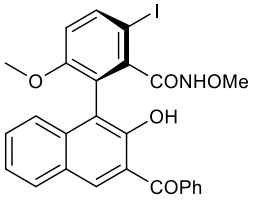
***tert*-Butyl (*S*)-3-hydroxy-4-(3-iodo-6-methoxy-2-(methoxycarbamoyl)phenyl)-2-naphthoate**



107n: According to Method Q, 91% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.34 (s, 1H), 8.72 (s, 1H), 8.54 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.40 – 7.34 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.64 (s, 3H), 3.23 (s, 3H), 1.69 ppm (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 170.34, 165.65, 158.39,

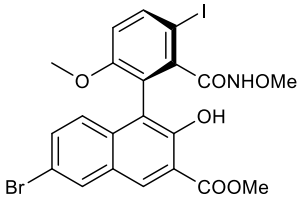
153.67, 141.55, 140.60, 137.05, 133.81, 130.09, 130.00, 127.32, 124.86, 124.82, 117.27, 115.63, 114.69, 84.75, 83.03, 63.86, 56.59, 28.47 ppm; FT-IR: $\tilde{\nu}$ = 3674, 2975, 1668, 1505, 1456, 1434, 1331, 1282, 1242, 1148 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{24}H_{25}O_6NI$: 550.07211, found: 550.07167; $[\alpha]_D^{RT}$ = +5.8 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 46.1 min; minor enantiomer: t_R = 28.4 min; 84% ee.

(*S*)-2-(3-Benzoyl-2-hydroxynaphthalen-1-yl)-6-iodo-*N*,3-dimethoxybenzamide



107o: According to Method Q, 72% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.74 (s, 1H), 8.77 (s, 1H), 8.32 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.85 – 7.77 (m, 3H), 7.74 – 7.68 (m, 1H), 7.64 – 7.56 (m, 2H), 7.55 – 7.47 (m, 1H), 7.43 – 7.36 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.67 (s, 3H), 3.30 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 202.62, 165.70, 158.39, 154.29, 141.56, 140.72, 138.35, 138.11, 137.39, 133.15, 131.03, 130.50, 130.16, 129.13, 127.12, 125.12, 124.94, 124.60, 120.78, 118.19, 114.76, 83.04, 63.96, 56.62, ppm; FT-IR: $\tilde{\nu}$ = 3670, 2987, 2901, 1683, 1628, 1504, 1456, 1339, 1281, 1099 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{26}H_{21}O_5NI$: 554.04589, found: 554.04542; $[\alpha]_D^{RT}$ = +2.7 (CH_2Cl_2, *c* = 1.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 88.5 min; minor enantiomer: t_R = 69.9 min; 86% ee.

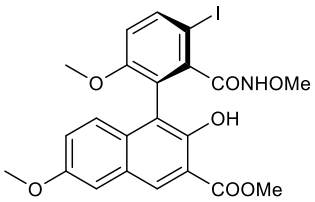
Methyl (*S*)-7-bromo-3-hydroxy-4-(3-iodo-6-methoxy-2-(methoxycarbamoyl)phenyl)-2-naphthoate



107p: According to Method Q, 72% yield; ^{1}H NMR (500 MHz, DMSO-*d*6): δ 11.06 (s, 1H), 10.45 (s, 1H), 8.61 (s, 1H), 8.35 – 8.25 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.54 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.00 (s, 3H), 3.60 (s, 3H), 2.95 ppm (s, 3H); ^{13}C NMR (126 MHz, DMSO): δ 169.90, 163.79, 157.89, 141.92, 139.95, 135.21, 132.37, 132.03, 131.32, 127.82, 127.66, 124.20, 118.05, 117.17, 115.35, 114.92, 83.72, 62.36, 56.39, 53.64 ppm; FT-IR: $\tilde{\nu}$ = 3674, 3370, 2987, 1688, 1458, 1337, 1282, 1190, 1066, 1034 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{21}H_{18}O_6N^{79}BrI$: 585.93567, found: 585.93542; calc. for $[M+H]^+$ $C_{21}H_{18}O_6N^{81}BrI$: 587.93362, found: 587.93333; $[\alpha]_D^{RT}$ = +3.9 (CH_2Cl_2, *c* = 2.00);

HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 60/40, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 42.0 min; minor enantiomer: t_R = 32.6 min; 87% ee.

Methyl (*S*)-3-hydroxy-4-(3-iodo-6-methoxy-2-(methoxycarbamoyl)phenyl)-7-methoxy-2-naphthoate



107q: According to Method Q, 93% yield; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.84 (s, 1H), 8.76 (s, 1H), 8.49 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.10 (d, *J* = 9.1 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.03 (s, 3H), 3.89 (s, 3H), 3.64 (s, 3H), 3.26 ppm (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 171.15, 165.66, 158.32, 157.04, 151.76, 141.46, 140.62, 132.85, 131.99, 128.36, 126.45, 124.77, 123.50, 117.75, 114.69, 114.39, 107.30, 82.97, 63.94, 56.57, 55.88, 53.40 ppm; FT-IR: $\tilde{\nu}$ = 3674, 3271, 2988, 1670, 1438, 1389, 1341, 1222, 1073 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{22}H_{21}O_7NI$: 538.03572, found: 538.03524; $[\alpha]_D^{RT}$ = -28.3 (CH_2Cl_2, *c* = 2.00); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 75/25, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 48.8 min; minor enantiomer: t_R = 31.9 min; 87% ee.

7.2.6 X-Ray Crystallographic Data and VCD Spectra Data.

7.2.6.1 X-Ray Crystallographic Data of 99i, 105b and 107b (by C.-G.D)

X-Ray diffraction: For compound **105b** data sets were collected with a Bruker APEX II Kappa CCD diffractometer. For compound **99i, 107b** were collected with a D8 Venture Dual Source 100 CMOS diffractometer. Programs used: data collection: APEX2 V2014.5-0 (Bruker AXS Inc., 2014); cell refinement: SAINT V8.34A (Bruker AXS Inc., 2013); data reduction: SAINT V8.34A (Bruker AXS Inc., 2013); absorption correction, SADABS V2014/2 (Bruker AXS Inc., 2014); structure solution SHELXT-2014 (Sheldrick, 2014); structure refinement SHELXL-2014 (Sheldrick, 2014) and graphics, XP (Bruker AXS Inc., 2014). *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

Exceptions and special features: For compound **99i** two disordered over two positions ethene groups were found in the asymmetrical unit. Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability of the compound.

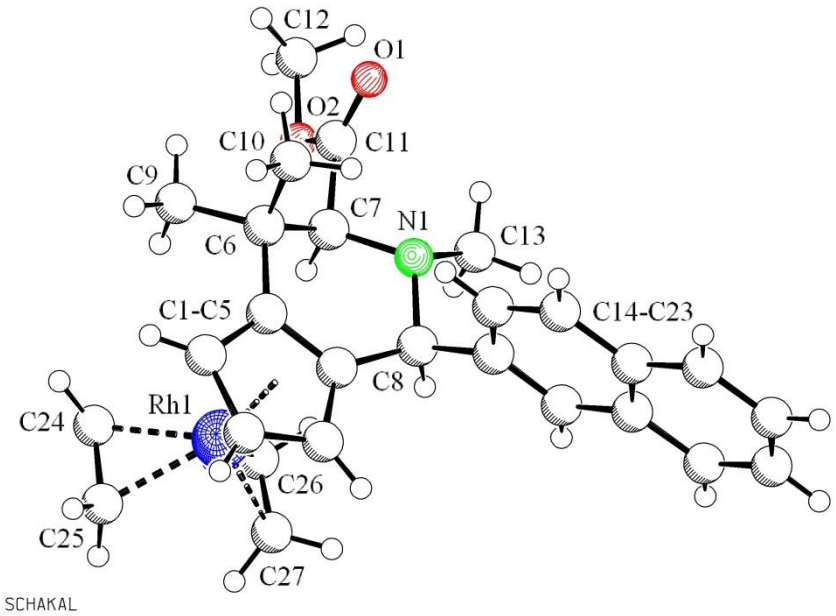
X-ray crystal structure analysis of 99i (CDCC 1450765): A yellow needle-like specimen of $C_{27}H_{32}NO_2Rh$, approximate dimensions 0.059 mm x 0.097 mm x 0.253 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 4.11 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 17185 reflections to a maximum θ angle of 27.10° (0.78 Å resolution), of which 5380 were independent (average redundancy 3.194, completeness = 99.9%, R_{int} = 4.39%, R_{sig} = 4.59%) and 4875 (90.61%) were greater than $2\sigma(F^2)$. The final cell constants of a = 8.8642(3) Å, b = 12.6939(5) Å, c = 10.9689(5) Å, β = 98.9220(10)°, volume = 1219.30(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 9677 reflections above 20 σ(I) with 4.942° < 2θ < 54.96°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.910. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8380 and 0.9590. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 2 for the formula unit, $C_{27}H_{32}NO_2Rh$. The final anisotropic full-matrix least-squares refinement on F^2 with 321 variables converged at R1 = 2.84%, for the observed data and wR2 = 5.29% for all data. The goodness-of-fit was 1.084. The largest peak in the final difference electron density synthesis was 0.378 $e^-/Å^3$ and the largest hole was -0.577 $e^-/Å^3$ with an RMS deviation of 0.072 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.377 g/cm^3 and F(000), 524 e^-.

X-ray crystal structure analysis of 105b (CDCC 1450766): A colorless prism-like specimen of $C_{18}H_{15}NO_3$, approximate dimensions 0.171 mm x 0.226 mm x 0.299 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 815 frames were collected. The total exposure time was 14.29 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 6857 reflections to a maximum θ angle of 68.03° (0.83 Å resolution), of which 2339 were independent (average redundancy 2.932, completeness = 96.5%, R_{int} = 2.47%, R_{sig} = 2.49%) and 2279 (97.43%) were greater than $2\sigma(F^2)$. The final cell constants of a = 7.30910(10) Å, b = 9.2636(2) Å, c = 19.9469(4) Å, volume = 1350.58(4) $Å^3$, are based upon the refinement of the XYZ-centroids of 5456 reflections above 20 σ(I) with 8.866° < 2θ < 136.0°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.900. The calculated minimum and maximum transmission coefficients

(based on crystal size) are 0.7950 and 0.8750. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{18}H_{15}NO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 199 variables converged at R1 = 2.66%, for the observed data and wR2 = 6.69% for all data. The goodness-of-fit was 1.081. The largest peak in the final difference electron density synthesis was 0.128 $e^-/Å^3$ and the largest hole was -0.185 $e^-/Å^3$ with an RMS deviation of 0.041 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.442 g/cm^3 and F(000), 616 e^-.

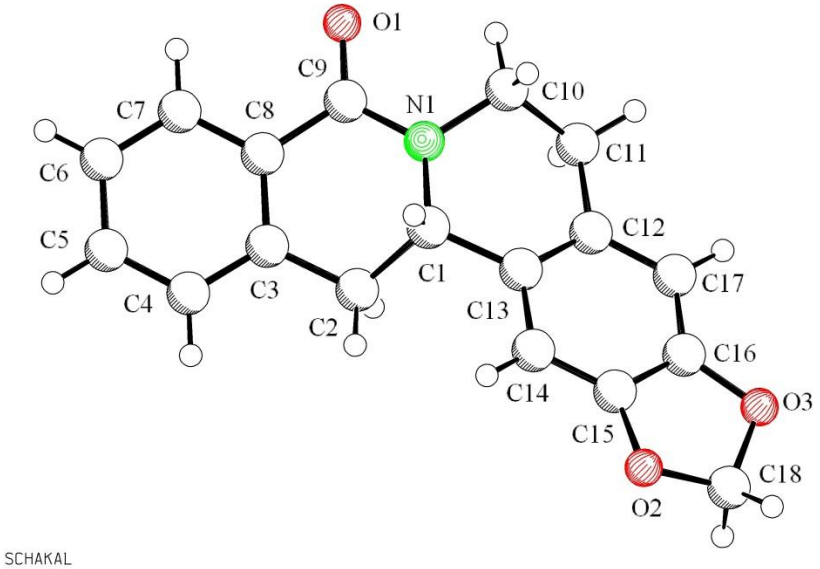
X-ray crystal structure analysis of 107b: A colorless prism-like specimen of $C_{21}H_{19}NO_5$, approximate dimensions 0.156 mm x 0.338 mm x 0.378 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 2367 frames were collected. The total exposure time was 19.18 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 36215 reflections to a maximum θ angle of 68.44° (0.83 Å resolution), of which 6754 were independent (average redundancy 5.362, completeness = 99.5%, R_{int} = 3.27%, R_{sig} = 2.29%) and 6592 (97.60%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 11.3781(3) Å, $\underline{b}$ = 7.7075(2) Å, $\underline{c}$ = 21.5908(6) Å, β = 102.5900(10)°, volume = 1847.91(9) $Å^3$, are based upon the refinement of the XYZ-centroids of 9843 reflections above 20 σ(I) with 7.961° < 2θ < 136.8°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.899. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7580 and 0.8880. The final anisotropic full-matrix least-squares refinement on F^2 with 509 variables converged at R1 = 2.90%, for the observed data and wR2 = 7.48% for all data. The goodness-of-fit was 1.058. The largest peak in the final difference electron density synthesis was 0.134 $e^-/Å^3$ and the largest hole was -0.224 $e^-/Å^3$ with an RMS deviation of 0.042 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.313 g/cm^3 and F(000), 768 e^-.

Crystal structure of compound 99i. (CDCC 1450765)



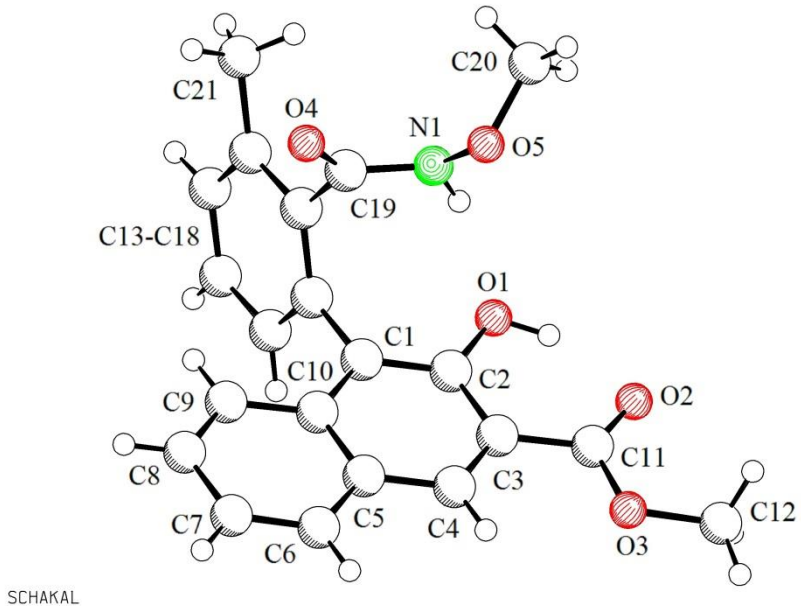
(Thermals ellipsoids are shown with 50% probability.)

Crystal structure of compound 105b. (CDCC 1450766)



(Thermals ellipsoids are shown with 50% probability.)

Crystal structure of compound 107b.

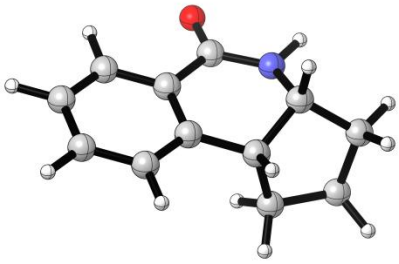


(Thermals ellipsoids are shown with 50% probability.)

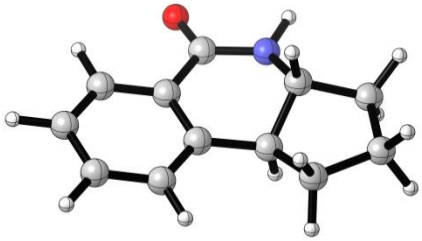
7.2.6.2 VCD Spectra Data of 11m, 107b (by C.M.)

Determination absolute configuration of 11m: Experimental IR and VCD spectra were obtained for a 0.27 M solution of **11m** in $CDCl_3$ (50 mg/ml) at 100 µm path length. The spectra were recorded on a Bruker Vertex 70v equipped with a PMA 50 module for VCD measurements accumulating 26000 scans for the VCD spectrum. The baseline was corrected by subtraction of the solvent spectrum.

In order to analyse experimental IR and VCD spectra, theoretical spectra were simulated for **11m** in both a cis and a trans form. In contrast to the calculations of the reactions pathways, the vibrational spectra calculations were performed at the B3LYP/6-311+G(2d,p) level of theory using Gaussian 09 Rev. D.01. Solvent effects were accounted for by applying a polarizable continuum model (IEFPCM). Brief conformational analysis yielded one conformer for the trans and two for the cis isomer, with one of the cis-conformations being significantly more favoured (ΔE_{ZPC}=2.1 kcal/mol).

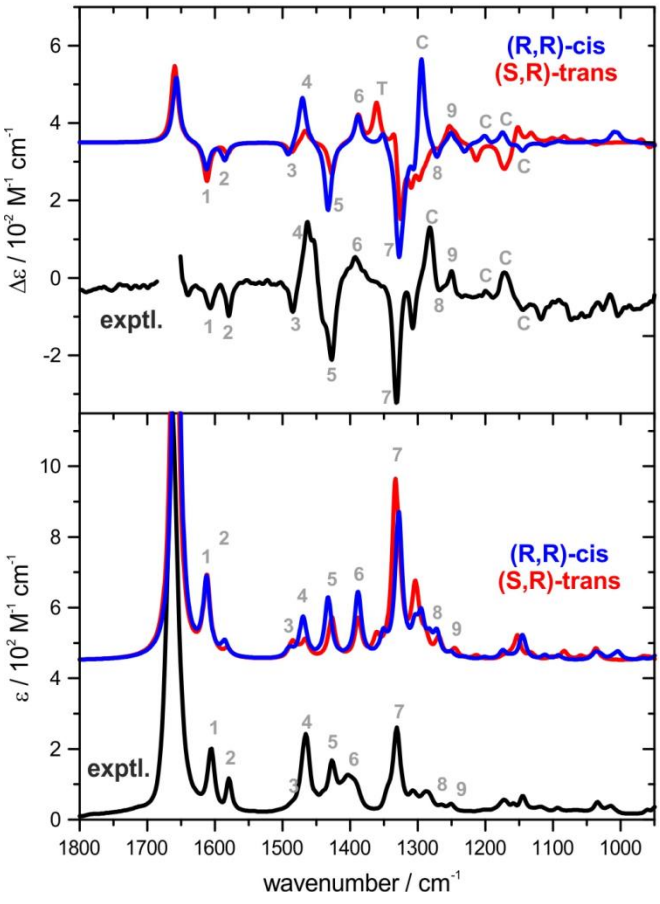


(*R*,*R*)-cis isomer



(*S*,*R*)-trans isomer

For these two major isomers, IR and VCD spectra were calculated for each isomer. In order to account for line broadening, a Lorentzian band shape of 8 cm^{-1} half-width at half-height was assigned to the calculated dipole and rotational strengths. For a better visual comparison of the spectra, the calculated frequencies were scaled by a factor of 0.98.

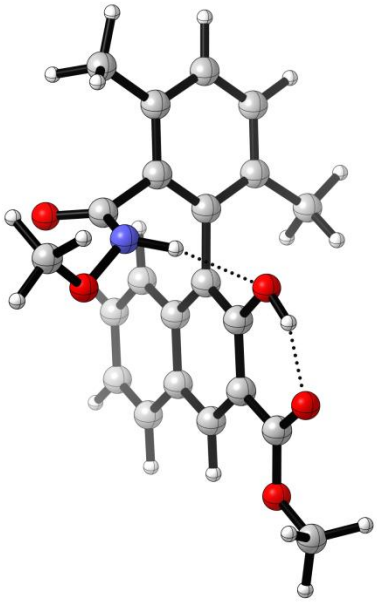


Numbers indicate band assignments; T and C mark diastereomer-specific VCD bands.

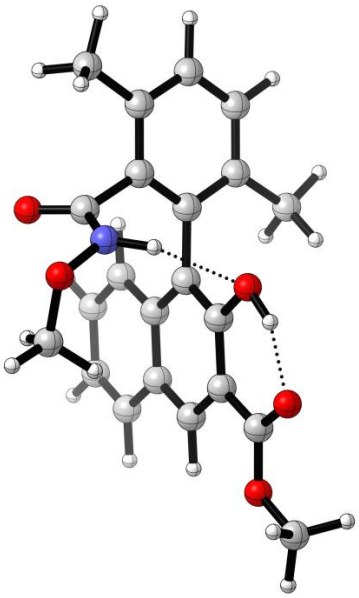
Figure S2. Comparison of experimental IR and VCD spectra of 11m with calculated spectra of the possible cis- and trans-isomer.

In Fig. S1, the experimental and theoretical spectra are compared. As the band assignments indicate, visual comparison does not allow any unambiguous differentiation between the diastereomers from the IR spectra. In the VCD spectra, both stereoisomers feature quite some similarities as well. However, there are also differences in the predicted spectra which can be used to distinguish the isomers. They are marked with T (from trans) and C (for cis). From these diastereomer-specific bands, **11m** can clearly be assigned an (R,R)-cis configuration.

Determination absolute configuration of 107d:



Lowest energy conformer



Second-lowest conformer

(ΔG_{298K}=0.7 kcal/mol)

The IR and VCD spectra of **107d** were measured for a 0.18 M (70mg/ml) solution in chloroform-d_1. Calculations were carried out as mentioned above for the (aR)-configured stereoisomer. The two lowest energy conformations of **107d** are shown above and the corresponding experimental and theoretical spectra are presented in Fig.S3. The absolute configuration of the reaction product is therefore confirmed to be (aR).

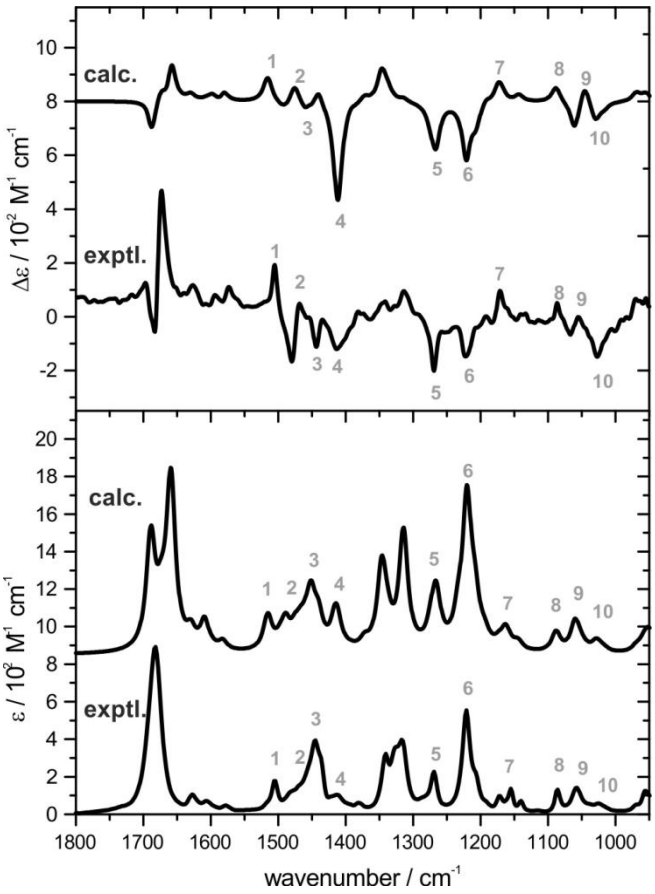


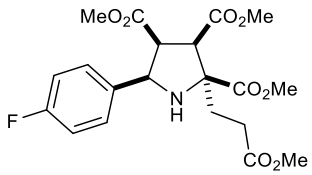
Figure S3. Comparison of the experimental IR and VCD spectra of **107d** (0.18 M, 100 μm, CDCl3) with the calculated spectra of the (aR)-stereoisomer. Numbers indicate band assignments.

7.3 Experimental Part for Enantioselective Synthesis of Pyrrolizidines

7.3.1 Experimental Detail and Analytic Data for Synthesis of Pyrrolidines 157aa-bm

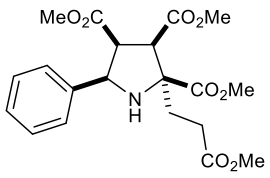
General Method: To CH_2Cl_2 (1 mL) were sequentially added imine (0.30 mmol, 1.50 equiv.), maleate (0.20 mmol, 1.00 equiv.), AgOAc (0.02 mmol, 10 mmol%) and Et_3N (0.20 mmol, 1.00 equiv.). The mixture was stirred for 24 h. The crude mixture was directly purified by silica gel flash without removal of solvent to give desired product.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(4-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



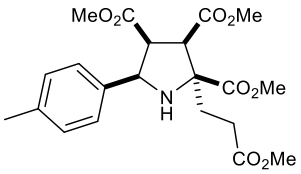
157aa: 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.17 (m, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 4.41 (d, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.38 (t, *J* = 6.7 Hz, 1H), 3.26 (d, *J* = 7.0 Hz, 1H), 3.24 (s, 3H), 2.59 – 2.46 (m, 1H), 2.43 – 2.32 (m, 1H), 2.21 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.06 ppm (ddd, *J* = 13.5, 10.0, 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.66, 173.09, 171.08, 170.95, 163.36, 161.40, 133.17, 128.66, 128.60, 115.49, 115.32, 71.70, 63.40, 57.38, 53.04, 52.92, 52.30, 51.82, 51.51, 35.35, 30.07 ppm; HRMS: calc. for $[M+H]^+$ $C_{20}H_{25}FNO_8$: 426.15587, found 426.15552.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-phenylpyrrolidine-2,3,4-tricarboxylate**



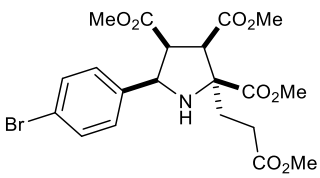
157ab: 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.43 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 3.39 (t, *J* = 6.5 Hz, 1H), 3.31 – 3.29 (m, 4H), 2.65 – 2.54 (m, 1H), 2.49 – 2.38 (m, 1H), 2.29 (s, 3H), 2.27 – 2.22 (m, 1H), 2.16 – 2.05 ppm (m, 1H); HRMS: calc. for $[M+H]^+$ $C_{20}H_{26}NO_8$: 408.16529, found 408.16479.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate**



157ac: 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.43 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 3.39 (t, *J* = 6.5 Hz, 1H), 3.31-3.29 (m, 4H), 2.65 – 2.54 (m, 1H), 2.49 – 2.38 (m, 1H), 2.29 (s, 3H), 2.24 (dd, *J* = 15.8, 5.3 Hz, 1H), 2.16 – 2.05 ppm (m, 1H); HRMS: calc. for $[M+H]^+$ $C_{21}H_{28}NO_8$: 422.18094, found 422.18020.

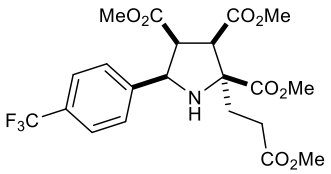
***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(4-bromophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



157ad: 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.42 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.57 – 3.56 (m, 1H), 3.43 (t, *J* = 6.6 Hz, 1H), 3.32 – 3.30 (d, *J* = 6.2 Hz, 4H), 2.65 – 2.50 (m, 1H), 2.42 (dd, *J* = 7.4, 5.9 Hz, 1H), 2.31 – 2.18 (m, 1H), 2.11 ppm (dd, *J* = 11.5, 3.6 Hz, 1H); ^{13}C NMR (101

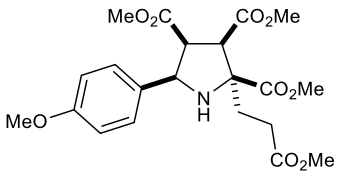
MHz, $CDCl_3$) δ = 173.63, 173.02, 170.99, 170.86, 136.48, 131.57, 128.57, 121.75, 71.59, 63.36, 57.48, 52.92, 52.79, 52.31, 51.82, 51.56, 35.38, 30.06 ppm; HRMS: calc. for $[M+H]^+$ $C_{20}H_{25}O_8N^{79}Br$: 486.07581, found 486.07506; calc. for $[M+H]^+$ $C_{20}H_{25}O_8N^{81}Br$: 488.07376, found 488.07268.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(4-(trifluoromethyl)phenyl) pyrrolidine-2,3,4-tricarboxylate**



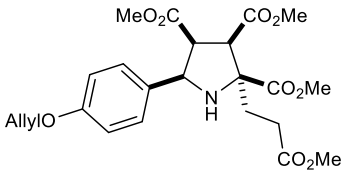
157ae: 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 4.52 (d, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.70 – 3.64 (m, 1H), 3.63 (s, 3H), 3.50 (t, *J* = 6.6 Hz, 1H), 3.34 (d, *J* = 7.0 Hz, 1H), 3.27 (s, 3H), 2.62 – 2.50 (m, 1H), 2.49 – 2.36 (m, 1H), 2.34 – 2.19 (m, 1H), 2.17 – 2.04 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate**



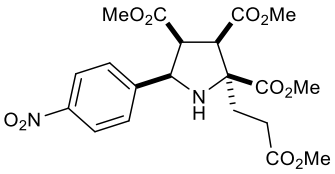
157af: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.43 (d, *J* = 6.2 Hz, 1H), 3.77 (s, 6H), 3.72 (s, 3H), 3.68 (dd, *J* = 12.2, 7.5 Hz, 1H), 3.63 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 1H), 3.32 – 3.28 (m, 4H), 2.65 – 2.54 (m, 1H), 2.48 – 2.36 (m, 1H), 2.31 – 2.21 (m, 1H), 2.16 – 2.05 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(4-(allyloxy)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



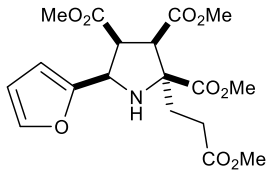
157ag: 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.15 – 5.93 (m, 1H), 5.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.54 – 4.46 (m, 2H), 4.43 (d, *J* = 6.2 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.68 (dd, *J* = 12.3, 7.5 Hz, 1H), 3.63 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 1H), 3.31 – 3.29 (m, 4H), 2.59 (ddd, *J* = 15.5, 10.0, 5.2 Hz, 1H), 2.43 (ddd, *J* = 13.4, 10.0, 5.3 Hz, 1H), 2.26 (ddd, *J* = 15.7, 10.2, 5.3 Hz, 1H), 2.11 ppm (ddd, *J* = 13.4, 10.2, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.72, 173.28, 171.34, 171.06, 158.19, 133.22, 129.39, 127.99, 117.83, 114.66, 71.52, 68.83, 63.62, 57.32, 53.09, 52.88, 52.27, 51.82, 51.49, 35.51, 30.07 ppm; ESI-HRMS: calcd. for $C_{21}H_{27}NO_9$+H: 464.19151, found 464.19143.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(4-nitrophenyl)pyrrolidine-2,3,4-tricarboxylate**



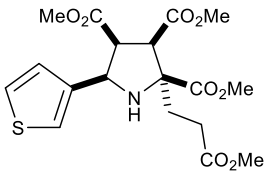
157ah: 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 4.57 (s, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.69 – 3.66 (m, 1H), 3.64 (s, 3H), 3.55 (t, *J* = 6.7 Hz, 1H), 3.37 (d, *J* = 7.1 Hz, 1H), 3.31 (s, 3H), 2.63 – 2.52 (m, 1H), 2.46 (ddd, *J* = 14.6, 8.7, 4.1 Hz, 2H), 2.33 – 2.21 (m, 1H), 2.13 ppm (ddd, *J* = 13.6, 9.6, 5.5 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(furan-2-yl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**

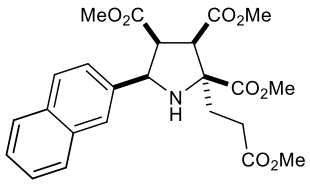


157ai: 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.27 (d, *J* = 3.3 Hz, 1H), 4.46 (d, *J* = 6.1 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.67 – 3.60 (m, 4H), 3.47 (s, 3H), 3.36 (t, *J* = 6.5 Hz, 1H), 3.24 (d, *J* = 6.8 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.41 (ddd, *J* = 13.4, 10.1, 5.4 Hz, 1H), 2.23 (ddd, *J* = 15.8, 10.2, 5.4 Hz, 1H), 2.05 ppm (ddd, *J* = 13.4, 10.2, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.63, 172.95, 171.19, 170.63, 150.86, 142.19, 110.51, 107.35, 71.12, 58.25, 56.99, 52.91, 52.27, 51.80, 51.57, 35.57, 29.99 ppm.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(thiophen-3-yl)pyrrolidine-2,3,4-tricarboxylate**



157aj: 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.18 (m, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 6.96 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.58 (s, 3H), 3.53-3.48 (m, 1H), 3.35 (t, *J* = 6.5 Hz, 1H), 3.31 (s, 3H), 3.23 (d, *J* = 6.9 Hz, 1H), 2.60 – 2.48 (m, 1H), 2.36 (ddd, *J* = 13.4, 9.9, 5.4 Hz, 1H), 2.20 (ddd, *J* = 15.7, 10.1, 5.4 Hz, 1H), 2.04 ppm (ddd, *J* = 13.4, 10.2, 5.2 Hz, 1H).

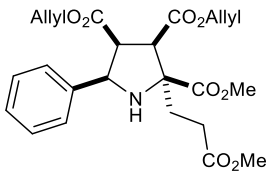


***Rel*-(2*S*,3*R*,4*S*,5*R*)-trimethyl 2-(3-methoxy-3-oxopropyl)-5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate**

157ak: 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 – 7.76 (m, 4H), 7.50 – 7.38 (m, 3H), 4.63 (d, *J* = 5.9 Hz, 1H), 3.80 (s, 3H), 3.74

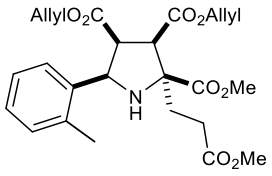
(s, 3H), 3.72 – 3.67 (m, 1H), 3.64 (s, 3H), 3.56 – 3.51 (m, 1H), 3.38 (d, *J* = 6.9 Hz, 1H), 3.21 (s, 3H), 2.66 (ddd, *J* = 15.4, 9.9, 5.2 Hz, 1H), 2.50 (ddd, *J* = 13.4, 9.9, 5.3 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.22 – 2.13 ppm (m, 1H).

Rel-(2_S_,3_R_,4_S_,5_R_)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-phenylpyrrolidine-2,3,4-tricarboxylate



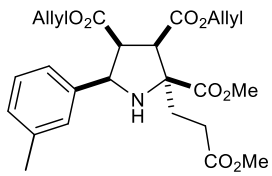
157al: 71% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 – 7.12 (m, 5H), 5.87 (dq, *J* = 10.6, 5.9 Hz, 1H), 5.37 (dq, *J* = 10.7, 5.8 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.96 – 4.85 (m, 2H), 4.54 (d, *J* = 5.8 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 1H), 4.13 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.69 (s, 3H), 3.64 – 3.59 (m, 1H), 3.56 (s, 3H), 3.44 (t, *J* = 6.7 Hz, 1H), 3.29 (d, *J* = 7.1 Hz, 1H), 2.53 (ddd, *J* = 15.4, 9.6, 5.4 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.22 (ddd, *J* = 15.7, 9.8, 5.5 Hz, 1H), 2.14 – 2.01 ppm (m, 1H).

Rel-(2_S_,3_R_,4_S_,5_R_)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(*o*-tolyl)pyrrolidine-2,3,4-tricarboxylate



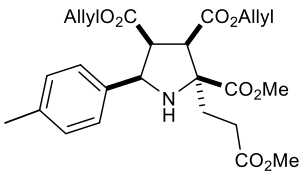
157am: 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 – 7.31 (m, 1H), 7.20 – 7.03 (m, 3H), 5.93 (ddt, *J* = 16.4, 10.5, 5.9 Hz, 1H), 5.44 – 5.29 (m, 2H), 5.24 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.98 – 4.87 (m, 2H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.66 – 4.53 (m, 2H), 4.19 – 4.05 (m, 1H), 3.99 – 3.90 (m, 1H), 3.78 (s, 3H), 3.75 – 3.65 (m, 1H), 3.62 (s, 3H), 3.56 (t, *J* = 6.9 Hz, 1H), 3.38 (d, *J* = 7.2 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.46 (ddd, *J* = 13.6, 9.7, 5.5 Hz, 1H), 2.33 (s, 3H), 2.32 – 2.26 (m, 1H), 2.16 ppm (ddd, *J* = 13.6, 9.9, 5.4 Hz, 1H).

Rel-(2_S_,3_R_,4_S_,5_R_)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(*m*-tolyl)pyrrolidine-2,3,4-tricarboxylate



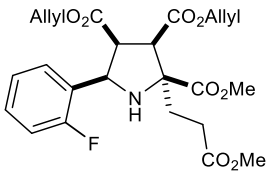
157an: 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 6.1 Hz, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 5.93 (ddd, *J* = 16.4, 10.6, 5.7 Hz, 1H), 5.45 (ddd, *J* = 16.6, 8.3, 5.3 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.04 – 4.94 (m, 2H), 4.65 – 4.57 (m, 2H), 4.47 – 4.45 (m, 1H), 4.21 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.13 (dd, *J* = 13.0, 5.8 Hz, 1H), 3.76 (s, 3H), 3.71 – 3.67 (m, 1H), 3.64 (s, 3H), 3.35 (d, *J* = 7.1 Hz, 1H), 2.61 (ddd, *J* = 15.5, 9.7, 5.4 Hz, 1H), 2.44 (ddd, *J* = 13.9, 9.7, 5.6 Hz, 1H), 2.31 (s, 3H), 2.30 – 2.24 (m, 1H), 2.14 ppm (ddd, *J* = 13.9, 9.9, 5.4 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate**



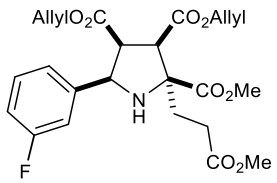
157ao: 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.93 (ddt, *J* = 22.5, 10.5, 5.9 Hz, 1H), 5.46 (ddt, *J* = 16.5, 10.6, 6.0 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.30 – 5.19 (m, 1H), 5.05 – 4.92 (m, 2H), 4.61 (dd, *J* = 5.8, 1.0 Hz, 2H), 4.47 (d, *J* = 6.2 Hz, 1H), 4.21 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.11 (dd, *J* = 13.0, 5.9 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 4H), 3.47 (t, *J* = 6.7 Hz, 1H), 3.34 (d, *J* = 7.1 Hz, 1H), 2.60 (ddd, *J* = 15.5, 9.7, 5.4 Hz, 1H), 2.43 (ddd, *J* = 13.7, 9.7, 5.6 Hz, 1H), 2.30 (s, 3H), 2.26 (dd, *J* = 10.1, 5.7 Hz, 1H), 2.13 ppm (ddd, *J* = 13.7, 9.9, 5.5 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(2-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



157ap: 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (t, *J* = 7.2 Hz, 1H), 7.34 – 7.20 (m, 1H), 7.11 (dd, *J* = 11.0, 4.1 Hz, 1H), 7.02 (dd, *J* = 14.1, 4.6 Hz, 1H), 5.93 (ddt, *J* = 16.3, 10.5, 5.8 Hz, 1H), 5.53 – 5.39 (m, 1H), 5.34 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.01 (d, *J* = 0.8 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.74 – 4.72 (s, 1H), 4.67 – 4.54 (m, 2H), 4.18 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.10 (dd, *J* = 13.0, 5.8 Hz, 1H), 3.79 – 3.77 (s, 3H), 3.70 – 3.54 (m, 4H), 3.41 (d, *J* = 7.2 Hz, 1H), 2.60 (ddd, *J* = 15.2, 9.7, 5.2 Hz, 1H), 2.52 – 2.39 (m, 1H), 2.30 (ddd, *J* = 15.3, 9.9, 5.1 Hz, 1H), 2.16 ppm (ddd, *J* = 13.5, 10.0, 5.2 Hz, 1H).

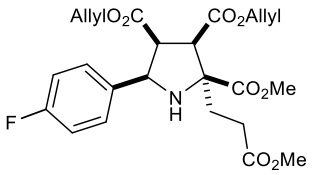
***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(3-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



157aq: 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.15 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 10.0 Hz, 1H), 6.88 (td, *J* = 8.3, 2.1 Hz, 1H), 5.87 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.43 (ddt, *J* = 16.7, 10.8, 6.0 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.98 (d, *J* = 1.3 Hz, 1H), 4.95 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.55 (dd, *J* = 5.8, 0.9 Hz, 2H), 4.43 (d, *J* = 4.0 Hz, 1H), 4.17 (dd, *J* = 12.9, 6.1 Hz, 1H), 4.10 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.70 (s, 3H), 3.64 – 3.49 (m, 4H), 3.46 (t, *J* = 6.7 Hz, 1H), 3.30 (d, *J* = 7.1 Hz, 1H), 2.60 – 2.44 (m, 1H), 2.45 – 2.31 (m, 1H), 2.27 – 2.14 (m, 1H), 2.07 (ddd, *J* = 13.6, 9.7, 5.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.65, 172.85, 170.08, 169.98, 164.01, 161.56, 140.06,

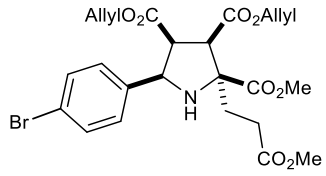
139.99, 131.92, 131.67, 130.03, 129.95, 122.59, 122.56, 118.77, 118.53, 114.81, 114.60, 114.29, 114.06, 77.48, 77.16, 76.84, 71.60, 66.07, 65.39, 63.40, 57.72, 53.06, 52.82, 51.80, 35.26, 30.08.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(4-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



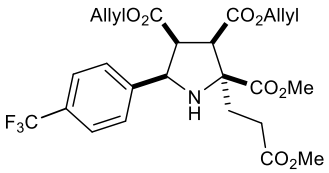
157ar: 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 8.5, 5.3 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.92 (ddt, *J* = 16.3, 10.4, 5.9 Hz, 1H), 5.46 (ddt, *J* = 16.6, 10.5, 6.0 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.07 – 4.93 (m, 2H), 4.60 (dd, *J* = 4.7, 1.2 Hz, 2H), 4.48 (d, *J* = 6.1 Hz, 1H), 4.25 – 4.15 (m, 1H), 4.14 – 4.03 (m, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 3.56 – 3.54 (m, 1H), 3.49 (t, *J* = 6.9 Hz, 1H), 3.34 (d, *J* = 7.2 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.41 (ddd, *J* = 13.5, 9.5, 5.5 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.11 ppm (ddd, *J* = 13.5, 9.7, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.69, 173.03, 170.21, 170.20, 163.60, 161.15, 133.19, 133.16, 131.97, 131.71, 128.80, 128.72, 118.80, 118.51, 115.46, 115.24, 71.70, 66.10, 65.39, 63.34, 57.49, 53.26, 52.85, 51.84, 35.14, 30.05 ppm; HRMS: calc. for $[M+H]^+$ $C_{24}H_{29}FNO_8$: 478.18717, found 478.18727.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(4-bromophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



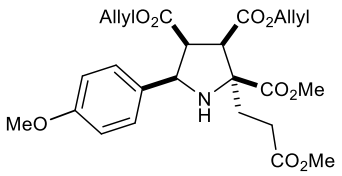
157as: 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.91 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.45 (ddt, *J* = 16.6, 10.5, 6.1 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.09 – 4.93 (m, 2H), 4.59 (d, *J* = 5.9 Hz, 2H), 4.45 (d, *J* = 5.9 Hz, 1H), 4.20 (dd, *J* = 12.9, 6.1 Hz, 1H), 4.13 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.73 (s, 3H), 3.61 (s, 3H), 3.57 – 3.55 (m, 1H), 3.49 (t, *J* = 6.8 Hz, 1H), 3.34 (d, *J* = 7.2 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.46 – 2.35 (m, 1H), 2.34 – 2.18 (m, 1H), 2.11 ppm (ddd, *J* = 13.6, 9.6, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.61, 172.90, 170.05, 170.02, 136.47, 131.90, 131.61, 131.51, 128.73, 121.71, 118.76, 118.58, 71.64, 66.05, 65.38, 63.32, 57.55, 53.06, 52.81, 51.79, 35.11, 30.03 ppm.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2,3,4-tricarboxylate**



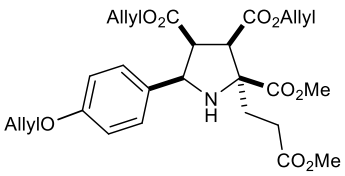
157at: 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 5.92 (ddt, *J* = 16.4, 10.6, 5.9 Hz, 1H), 5.39 (ddd, *J* = 17.1, 8.3, 3.8 Hz, 1H), 5.36 – 5.29 (m, 1H), 5.24 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.01 – 4.87 (m, 2H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.56 (d, *J* = 5.4 Hz, 1H), 4.14 (qd, *J* = 12.9, 6.1 Hz, 2H), 3.75 (s, 3H), 3.67 – 3.65 (m, 1H), 3.61 (d, *J* = 14.3 Hz, 3H), 3.55 (t, *J* = 6.8 Hz, 1H), 3.38 (d, *J* = 7.2 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.49 – 2.34 (m, 1H), 2.33 – 2.22 (m, 1H), 2.14 ppm (ddd, *J* = 13.8, 9.4, 5.7 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate**



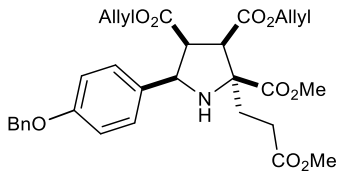
157au: 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.93 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.47 (ddt, *J* = 16.7, 10.7, 6.0 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.99 (ddd, *J* = 11.7, 6.5, 1.2 Hz, 2H), 4.60 (d, *J* = 5.8 Hz, 2H), 4.47 (d, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.14 – 3.99 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 3.45 (t, *J* = 6.8 Hz, 1H), 3.33 (d, *J* = 7.1 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.42 (ddd, *J* = 13.5, 9.7, 5.4 Hz, 1H), 2.26 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.19 – 2.03 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(4-(allyloxy)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



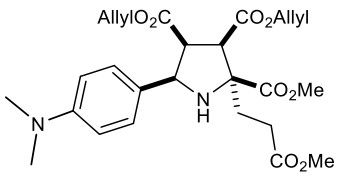
157av: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.13 (m, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.03 – 5.92 (m, 1H), 5.92 – 5.81 (m, 1H), 5.42 (ddt, *J* = 16.7, 10.7, 6.0 Hz, 1H), 5.30 (td, *J* = 17.1, 1.5 Hz, 2H), 5.20 (ddd, *J* = 10.2, 7.3, 1.3 Hz, 2H), 5.01 – 4.87 (m, 2H), 4.55 (d, *J* = 5.8 Hz, 2H), 4.44 (dd, *J* = 3.9, 1.3 Hz, 2H), 4.41 (d, *J* = 6.4 Hz, 1H), 4.17 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.05 (dd, *J* = 13.0, 5.8 Hz, 1H), 3.69 (s, 3H), 3.66 – 3.59 (m, 1H), 3.57 (s, 3H), 3.40 (t, *J* = 6.8 Hz, 1H), 3.28 (d, *J* = 7.1 Hz, 1H), 2.65 – 2.45 (m, 1H), 2.45 – 2.29 (m, 1H), 2.21 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.13 – 1.95 ppm (m, 1H); HRMS: calc. for $[M+H]^+$ $C_{27}H_{34}NO_9$: 516.22281, found 516.22322.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(4-(benzyloxy)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



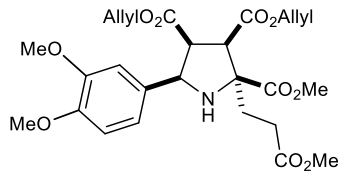
157aw: 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.13 (m, 8H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.94 – 5.80 (m, 1H), 5.40 (ddd, *J* = 16.9, 8.9, 5.6 Hz, 1H), 5.28 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.01 – 4.86 (m, 4H), 4.55 (d, *J* = 5.8 Hz, 2H), 4.41 (d, *J* = 6.3 Hz, 1H), 4.16 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.03 (dd, *J* = 13.0, 5.9 Hz, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.51 – 3.49 (m, 1H), 3.40 (t, *J* = 6.8 Hz, 1H), 3.27 (d, *J* = 7.1 Hz, 1H), 2.62 – 2.45 (m, 1H), 2.45 – 2.26 (m, 1H), 2.21 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.06 ppm (ddd, *J* = 13.5, 9.9, 5.3 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(4-(dimethylamino)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



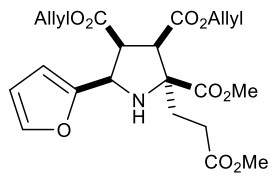
157ax: 43% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 5.99 – 5.89 (m, 1H), 5.55 – 5.43 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.99 (dd, *J* = 9.9, 6.4 Hz, 2H), 4.62 (d, *J* = 5.8 Hz, 2H), 4.43 (d, *J* = 6.2 Hz, 1H), 4.24 (ddd, *J* = 13.0, 6.1, 0.9 Hz, 1H), 4.14 (ddd, *J* = 13.1, 5.8, 1.0 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.61 – 3.46 (m, 1H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.32 (d, *J* = 7.1 Hz, 1H), 2.90 (s, 6H), 2.62 – 2.57 (m, 1 H), 2.44 – 2.39 (m, 1H), 2.30 – 2.24 (m, 1H), 2.16 – 2.12 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



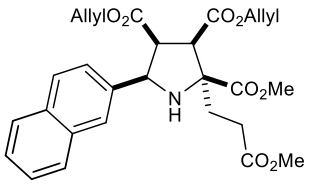
157ay: 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 – 6.83 (m, 2H), 6.77 (d, *J* = 8.9 Hz, 1H), 5.99 – 5.84 (m, 1H), 5.53 – 5.39 (m, 1H), 5.39 – 5.19 (m, 2H), 5.06 – 4.93 (m, 2H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.46 (d, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 13.0, 6.0 Hz, 1H), 4.16 – 4.04 (m, 1H), 3.83 (d, *J* = 2.8 Hz, 6H), 3.73 (s, 3H), 3.62 (s, 3H), 3.55 – 3.50 (m, 1H), 3.50 (t, *J* = 7.0 Hz, 1H), 3.32 (d, *J* = 7.3 Hz, 1H), 2.67 – 2.50 (m, 1H), 2.39 (ddd, *J* = 13.4, 9.5, 5.5 Hz, 1H), 2.34 – 2.17 (m, 1H), 2.11 ppm (ddd, *J* = 13.4, 9.8, 5.4 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 5-(furan-2-yl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



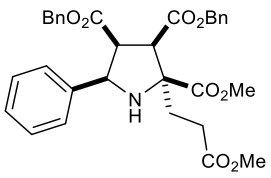
157az: 79% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.27 (m, 1H), 6.35 – 6.21 (m, 2H), 5.92 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.67 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.37 – 5.29 (m, 1H), 5.23 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.18 – 5.06 (m, 2H), 4.59 (ddd, *J* = 5.6, 2.8, 1.3 Hz, 2H), 4.49 (d, *J* = 6.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.31 (ddt, *J* = 13.1, 5.9, 1.2 Hz, 1H), 3.73 (s, 3H), 3.68 – 3.56 (m, 4H), 3.44 (t, *J* = 6.7 Hz, 1H), 3.27 (d, *J* = 7.0 Hz, 1H), 2.64 – 2.48 (m, 1H), 2.39 (ddd, *J* = 13.6, 9.7, 5.6 Hz, 1H), 2.24 (ddd, *J* = 15.8, 9.9, 5.6 Hz, 1H), 2.07 ppm (ddd, *J* = 13.7, 9.9, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.59, 172.78, 170.20, 169.78, 151.06, 142.03, 132.06, 118.65, 118.36, 110.49, 107.44, 71.29, 66.02, 65.57, 58.28, 57.15, 52.75, 51.98, 51.73, 35.32, 29.98 ppm.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-diallyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate**



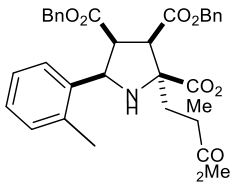
157ba: 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 – 7.72 (m, 4H), 7.51 – 7.35 (m, 3H), 5.95 (ddt, *J* = 22.4, 10.5, 5.9 Hz, 1H), 5.30 (dddd, *J* = 23.9, 19.7, 15.9, 7.5 Hz, 3H), 4.79 (ddd, *J* = 13.8, 11.5, 1.3 Hz, 2H), 4.75 – 4.52 (m, 3H), 4.19 – 4.07 (m, 1H), 4.06 – 3.95 (m, 1H), 3.94 – 3.81 (m, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.61 (t, *J* = 6.7 Hz, 1H), 3.42 (d, *J* = 7.1 Hz, 1H), 2.65 (ddd, *J* = 15.4, 9.6, 5.5 Hz, 1H), 2.49 (ddd, *J* = 13.7, 9.6, 5.5 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.25 – 2.07 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-phenylpyrrolidine-2,3,4-tricarboxylate**



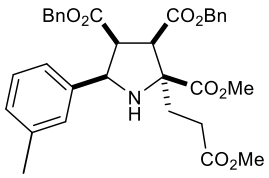
157bb: 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.07 (m, 14H), 6.85 – 6.77 (m, 2H), 5.06 (s, 2H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 2H), 3.75 – 3.61 (m, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 3.47 (t, *J* = 6.7 Hz, 1H), 3.32 (d, *J* = 7.1 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.43 – 2.30 (m, 1H), 2.27 – 2.14 (m, 1H), 2.12 – 2.00 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(*o*-tolyl)pyrrolidine-2,3,4-tricarboxylate**



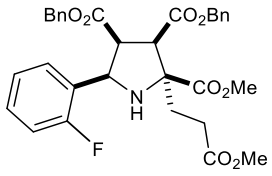
157bc: 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.18 (m, 6H), 7.18 – 6.95 (m, 6H), 6.75 (dd, *J* = 7.4, 1.8 Hz, 2H), 5.04 (t, *J* = 6.6 Hz, 2H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.59 (s, 3H), 3.53 (s, 3H), 3.50 (d, *J* = 6.8 Hz, 1H), 3.34 (d, *J* = 7.1 Hz, 1H), 2.60 – 2.45 (m, 1H), 2.44 – 2.35 (m, 1H), 2.26 – 2.16 (m, 4H), 2.09 ppm (ddd, *J* = 13.5, 9.7, 5.1 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(*m*-tolyl)pyrrolidine-2,3,4-tricarboxylate**



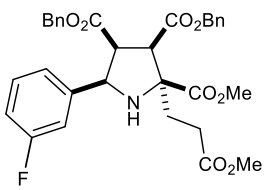
157bd: 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 8H), 7.10 – 6.93 (m, 4H), 6.79 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.05 (d, *J* = 1.3 Hz, 2H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.48 (d, *J* = 12.2 Hz, 1H), 4.39 (s, 1H), 3.64 – 3.62 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 1H), 3.30 (d, *J* = 7.1 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.45 – 2.29 (m, 1H), 2.28 – 2.10 (m, 4H), 2.10 – 2.01 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(2-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



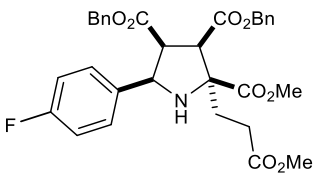
157be: 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.30 (m, 6H), 7.32 – 7.18 (m, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.93 (m, 3H), 5.13 (s, 2H), 4.75 (d, *J* = 3.9 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 3.80 (d, *J* = 6.7 Hz, 1H), 3.72 – 3.66 (m, 4H), 3.65 (s, 3H), 3.46 (d, *J* = 7.2 Hz, 1H), 2.61 (ddd, *J* = 15.3, 9.5, 5.4 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.32 (ddd, *J* = 15.5, 9.7, 5.4 Hz, 1H), 2.18 ppm (ddd, *J* = 13.9, 9.8, 5.4 Hz, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(3-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



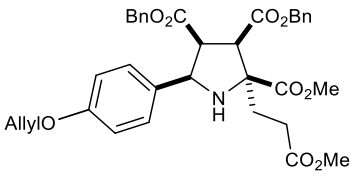
157bf: 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.14 (m, 8H), 7.12 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.00 (dd, *J* = 15.0, 8.9 Hz, 2H), 6.85 (ddd, *J* = 10.3, 7.5, 1.8 Hz, 3H), 5.05 (s, 2H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.40 (d, *J* = 4.9 Hz, 1H), 3.68 – 3.51 (m, 7H), 3.48 (t, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 7.1 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.42 – 2.27 (m, 1H), 2.27 – 2.12 (m, 1H), 2.12 – 2.00 ppm (m, 1H); HRMS: calc. for $[M+H]^+$ $C_{32}H_{33}FNO_8$: 578.21847, found 578.21735.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(4-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



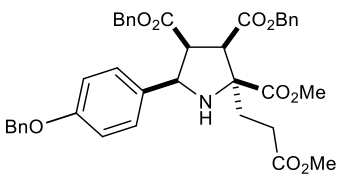
157bg: 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.09 (m, 10H), 6.92 – 6.78 (m, 4H), 5.05 (d, *J* = 12.8 Hz, 2H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.42 (d, *J* = 5.9 Hz, 1H), 3.56 (s, 3H), 3.56 (s, 3H), 3.47 (t, *J* = 6.9 Hz, 1H), 3.31 (d, *J* = 7.2 Hz, 1H), 2.58 – 2.43 (m, 1H), 2.43 – 2.27 (m, 1H), 2.27 – 2.14 (m, 1H), 2.14 – 1.96 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.62, 172.94, 170.37, 170.27, 163.35, 161.39, 135.58, 135.30, 133.06, 128.80, 128.74, 128.71, 128.59, 128.51, 128.43, 128.26, 115.47, 115.30, 71.82, 67.33, 66.52, 63.39, 57.62, 53.25, 52.73, 51.81, 35.10, 30.08 ppm; HRMS: calc. for $[M+H]^+$ $C_{32}H_{33}FNO_8$: 578.21847, found 578.21911.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(4-(allyloxy)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



157bh: 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 – 7.21 (m, 10H), 6.98 – 6.91 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.07 (ddd, *J* = 11.8, 10.5, 5.2 Hz, 1H), 5.43 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.35 – 5.26 (m, 1H), 5.16 (s, 2H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.55 – 4.44 (m, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.53 (t, *J* = 6.8 Hz, 1H), 3.40 (d, *J* = 7.1 Hz, 1H), 2.65 – 2.55 (m, 1H), 2.51 – 2.38 (m, 1H), 2.36 – 2.23 (m, 1H), 2.21 – 2.12 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.67, 173.11, 170.63, 170.35, 158.31, 135.67, 135.46, 133.34, 129.42, 128.71, 128.68, 128.49, 128.44, 128.35, 128.20, 128.11, 117.81, 114.72, 71.72, 68.87, 67.25, 66.44, 63.67, 57.53, 53.38, 52.67, 51.78, 35.25, 30.09 ppm; HRMS: calc. for $[M+H]^+$ $C_{35}H_{38}NO_9$: 616.25411, found 616.25515.

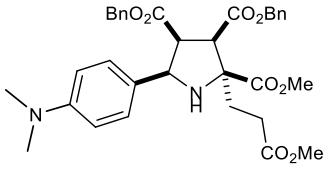
***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(4-(benzyloxy)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



157bi: 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.02 (m, 16H), 6.90 – 6.74 (m, 4H), 5.06 (s, 2H), 4.94 (s, 2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.42 – 4.38 (m, 1H), 3.55 (s, 3H), 3.55 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.29 (d, *J* = 7.1 Hz, 1H), 2.59 – 2.43 (m, 1H), 2.43 – 2.28 (m, 1H), 2.19 (ddd, *J* = 15.5, 9.7, 5.5 Hz, 1H), 2.04 ppm

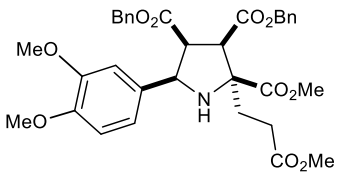
(ddd, *J* = 26.5, 15.9, 11.1 Hz, 1H); HRMS: calc. for $[M+H]^+$ $C_{39}H_{40}NO_9$: 666.26976, found 666.26928.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(4-(dimethylamino)phenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



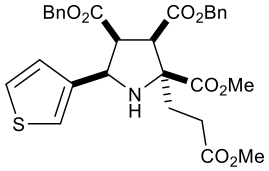
157bj: 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.05 (m, 11H), 6.83 (dd, *J* = 7.5, 1.7 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.19 – 5.01 (m, 2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.37 (s, 1H), 3.63 – 3.44 (m, 7H), 3.45 – 3.35 (m, 1H), 3.29 (t, *J* = 5.7 Hz, 1H), 2.85 (s, 6H), 2.63 – 2.44 (m, 1H), 2.44 – 2.27 (m, 1H), 2.20 (ddd, *J* = 15.6, 9.8, 5.5 Hz, 1H), 2.14 – 1.95 ppm (m, 1H); HRMS: calc. for $[M+H]^+$ $C_{34}H_{39}N_2O_8$: 603.27009, found 603.26802.

***Rel*-(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 5-(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate**



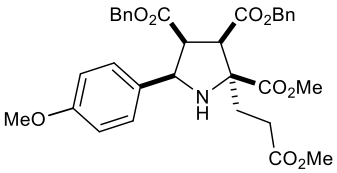
157bk: 53% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 – 7.22 (m, 11H), 7.22 – 7.06 (m, 7H), 6.89 – 6.73 (m, 8H), 6.66 (d, *J* = 8.9 Hz, 2H), 5.14 – 4.98 (m, 4H), 4.63 (d, *J* = 12.2 Hz, 2H), 4.54 (d, *J* = 12.2 Hz, 2H), 4.41 (d, *J* = 6.7 Hz, 2H), 3.78 (s, 6H), 3.70 (s, 6H), 3.56 (d, *J* = 1.5 Hz, 12H), 3.50 (t, *J* = 7.0 Hz, 3H), 3.31 (d, *J* = 7.3 Hz, 2H), 2.62 – 2.42 (m, 2H), 2.34 (ddd, *J* = 13.7, 9.4, 5.7 Hz, 2H), 2.28 – 2.14 (m, 2H), 2.13 – 1.96 ppm (m, 2H).

(2*S*,3*R*,4*S*,5*R*)-3,4-dibenzyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-(thiophen-3-yl)pyrrolidine-2,3,4-tricarboxylate



157bl: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.09 (m, 10H), 6.94 (dd, *J* = 5.6, 3.4 Hz, 3H), 5.06 (s, 2H), 4.70 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.47 (d, *J* = 5.8 Hz, 1H), 3.56 (d, *J* = 7.1 Hz, 3H), 3.54 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.28 (d, *J* = 7.1 Hz, 1H), 2.56 – 2.43 (m, 1H), 2.42 – 2.26 (m, 1H), 2.26 – 2.11 (m, 1H), 2.11 – 1.98 ppm (m, 1H).

***Rel*-(2*S*,3*R*,4*S*,5*S*)-3,4-dibenzyl 2-methyl 2-(3-methoxy-3-oxopropyl)-5-((*E*)-4-methoxystyryl)pyrrolidine-2,3,4-tricarboxylate**

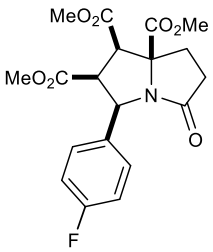


157bm: 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.22 (m, 5H), 7.22 – 7.09 (m, 5H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 15.7 Hz, 1H), 5.89 (dd, *J* = 15.7, 8.3 Hz, 1H), 5.04 (q, *J* = 12.2 Hz, 2H), 4.90 (q, *J* = 12.1 Hz, 2H), 3.96 (t, *J* = 7.8 Hz, 1H), 3.76 – 3.62 (m, 4H), 3.56 (s, 3H), 3.51 (s, 3H), 3.41 (t, *J* = 7.3 Hz, 1H), 3.20 (d, *J* = 7.4 Hz, 1H), 2.51 – 2.36 (m, 1H), 2.30 – 2.03 (m, 2H), 2.03 – 1.90 ppm (m, 1H).

7.3.2 Experimental Detail and Analytic Data for Synthesis of Pyrrolizidines 158aa-bv

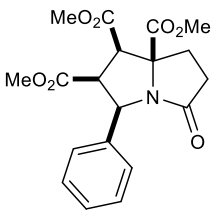
General Method: The specific pyrrolidine was disovled into 5 mL solvent of toluene/AcOH (4:1). The mixture was allowed to be stirred under reflux until full conversion indicated by TLC.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



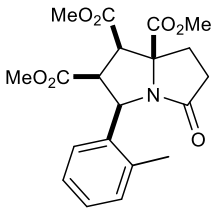
158aa: 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.20 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.83 – 3.79 (m, 1H), 3.77 (s, 3H), 3.22 (d, *J* = 6.9 Hz, 1H), 3.18 (s, 3H), 3.02 (d, *J* = 3.0 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.54 – 2.40 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.84, 171.91, 170.38, 168.24, 163.51, 161.07, 131.84, 131.81, 128.34, 128.26, 115.19, 114.98, 74.19, 60.09, 55.70, 53.21, 53.03, 52.51, 51.63, 36.23, 34.04 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{21}FNO_7$: 394.12966, found 394.12872.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-phenylhexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



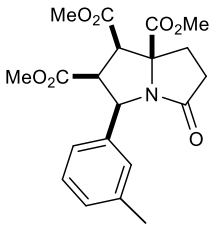
158ab: 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.09 (m, 5H), 5.18 (d, *J* = 8.0 Hz, 1H), 3.76 (dd, *J* = 20.8, 10.9 Hz, 7H), 3.17 (d, *J* = 6.9 Hz, 1H), 3.07 (s, 3H), 3.06 – 2.89 (m, 1H), 2.55 (dd, *J* = 12.1, 8.7 Hz, 1H), 2.45 ppm (dt, *J* = 7.8, 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.86, 171.97, 170.42, 168.34, 135.98, 128.14, 127.66, 126.46, 74.25, 60.72, 55.67, 53.24, 52.98, 52.48, 51.52, 36.33, 34.10 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{22}NO_7$: 376.13908, found 376.13900.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-(o-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



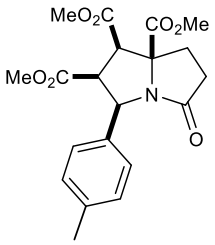
158ac: 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.56 (m, 1H), 7.21 – 6.98 (m, 3H), 5.29 (d, *J* = 7.8 Hz, 1H), 4.04 – 3.89 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.25 (d, *J* = 6.8 Hz, 1H), 3.08 (s, 3H), 3.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.62 (dd, *J* = 12.2, 8.7 Hz, 1H), 2.56 – 2.41 (m, 2H), 2.33 ppm (s, 3H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-(m-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



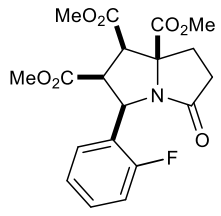
158ad: 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 16.0, 9.0 Hz, 3H), 7.01 (d, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.82 (d, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 3.21 (d, *J* = 6.9 Hz, 1H), 3.15 (s, 3H), 3.04 (dt, *J* = 18.7, 11.7 Hz, 1H), 2.61 (dd, *J* = 12.1, 8.7 Hz, 1H), 2.51 (dt, *J* = 8.0, 6.3 Hz, 2H), 2.31 ppm (s, 3H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-(p-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



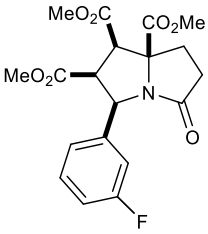
158ae: 95% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 5.14 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.77 – 3.72 (m, 1H), 3.71 (s, 3H), 3.15 (d, *J* = 6.9 Hz, 1H), 3.10 (s, 3H), 3.00 – 2.87 (m, 1H), 2.53 (dd, *J* = 12.1, 8.8 Hz, 1H), 2.43 (dt, *J* = 7.9, 6.4 Hz, 2H), 2.21 ppm (s, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-trimethyl 3-(2-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



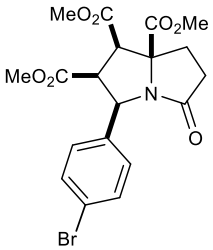
158af: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 – 7.53 (m, 1H), 7.23 (td, *J* = 7.4, 1.6 Hz, 1H), 7.11 (dd, *J* = 10.9, 4.1 Hz, 1H), 6.99 (dd, *J* = 14.0, 4.6 Hz, 1H), 5.42 (d, *J* = 7.8 Hz, 1H), 4.05 – 3.93 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.28 (d, *J* = 6.9 Hz, 1H), 3.18 (s, 3H), 3.06 (dd, *J* = 8.3, 3.1 Hz, 1H), 2.64 (dd, *J* = 12.1, 8.6 Hz, 1H), 2.58 – 2.41 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.74, 171.92, 170.58, 168.23, 160.97, 158.53, 129.51, 129.43, 128.67, 128.63, 124.22, 124.18, 123.58, 123.45, 114.66, 114.45, 73.98, 55.76, 55.72, 55.43, 52.99, 52.47, 51.95, 51.62, 36.29, 34.10 ppm.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(3-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



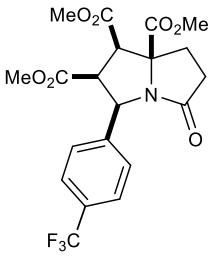
158ag: 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.20 (m, 3H), 7.20 – 7.07 (m, 4H), 7.01 – 6.81 (m, 2H), 5.23 (d, *J* = 8.1 Hz, 2H), 3.94 – 3.82 (m, 8H), 3.79 (s, 6H), 3.25 (d, *J* = 7.0 Hz, 2H), 3.21 (s, 6H), 3.04 (ddd, *J* = 16.1, 11.8, 8.3 Hz, 2H), 2.63 (dd, *J* = 12.3, 8.8 Hz, 2H), 2.59 – 2.41 ppm (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.83, 171.81, 170.21, 168.17, 163.88, 161.44, 138.90, 138.83, 129.69, 129.60, 122.19, 122.16, 114.70, 114.48, 113.97, 113.74, 74.14, 60.08, 60.06, 55.68, 53.01, 52.98, 52.49, 51.61, 36.14, 33.95 ppm.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-bromophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



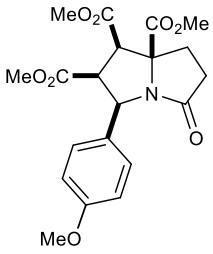
158ah: 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.5 Hz, 4H), 7.25 – 7.09 (m, 5H), 5.11 (d, *J* = 8.1 Hz, 2H), 3.79 – 3.74 (m, 8H), 3.71 (s, 6H), 3.17 (d, *J* = 7.0 Hz, 2H), 3.14 (s, 6H), 2.96 (dt, *J* = 18.8, 11.6 Hz, 2H), 2.54 (dd, *J* = 12.1, 8.7 Hz, 2H), 2.44 ppm (dt, *J* = 7.9, 6.5 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.80, 171.84, 170.32, 168.17, 135.24, 131.28, 128.31, 121.67, 74.14, 60.08, 55.67, 53.03, 52.95, 52.51, 51.68, 36.13, 33.98 ppm.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-(4-(trifluoromethyl)phenyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



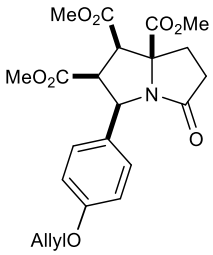
158ai: 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.26 (d, *J* = 8.1 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.26 (d, *J* = 7.0 Hz, 1H), 3.14 (s, 3H), 3.10 – 2.94 (m, 1H), 2.61 (dd, *J* = 12.3, 8.8 Hz, 1H), 2.51 ppm (qd, *J* = 8.8, 3.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.84, 171.77, 170.23, 168.09, 140.35, 129.99, 129.67, 126.97, 125.50, 125.15, 125.11, 125.07, 122.80, 74.14, 60.15, 55.68, 53.05, 52.98, 52.52, 51.60, 36.10, 33.92 ppm.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-methoxyphenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



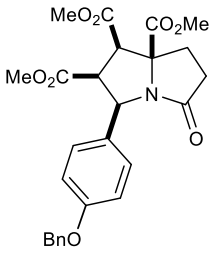
158aj: 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.18 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.19 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.82 – 3.78 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.21 (d, *J* = 6.9 Hz, 1H), 3.18 (s, 3H), 3.02 (dt, *J* = 18.5, 11.7 Hz, 1H), 2.59 (dd, *J* = 12.2, 8.7 Hz, 1H), 2.49 ppm (dt, *J* = 8.2, 6.3 Hz, 2H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-(allyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



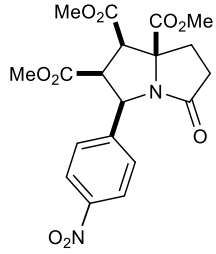
158ak: 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 9.7 Hz, 5H), 6.77 (d, *J* = 8.8 Hz, 4H), 6.02 – 5.88 (m, 2H), 5.31 (dd, *J* = 17.3, 1.5 Hz, 2H), 5.24 – 5.08 (m, 4H), 4.47 – 4.38 (m, 4H), 3.78 (s, 6H), 3.73 (d, *J* = 7.8 Hz, 2H), 3.71 (s, 6H), 3.15 (d, *J* = 6.9 Hz, 2H), 3.11 (s, 6H), 3.04 – 2.89 (m, 2H), 2.53 (dd, *J* = 12.1, 8.7 Hz, 2H), 2.43 ppm (dt, *J* = 7.8, 6.5 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.80, 172.01, 170.52, 168.37, 158.03, 133.36, 128.17, 127.64, 117.70, 114.41, 74.21, 68.82, 60.29, 55.60, 53.28, 52.97, 52.46, 51.59, 36.29, 34.12 ppm; HRMS: calc. for $[M+H]^+$ $C_{22}H_{26}NO_8$: 432.16529, found 432.16540.

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-(benzyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158al: 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 – 7.09 (m, 7H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.12 (d, *J* = 8.0 Hz, 1H), 4.96 (s, 2H), 3.77 (s, 3H), 3.72 (d, *J* = 7.3 Hz, 1H), 3.71 (s, 3H), 3.13 (d, *J* = 6.9 Hz, 1H), 3.09 (s, 3H), 2.95 (dt, *J* = 18.2, 11.1 Hz, 1H), 2.58 – 2.49 (m, 1H), 2.47 – 2.36 (m, 2H).

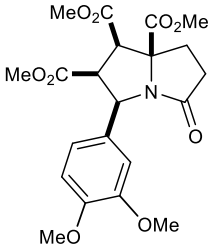
^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.79, 171.99, 170.49, 168.35, 158.25, 137.15, 128.63, 128.35, 127.99, 127.71, 127.54, 114.63, 74.24, 70.02, 60.35, 55.66, 53.33, 52.95, 52.44, 51.57, 36.31, 34.11.



***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-nitrophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**

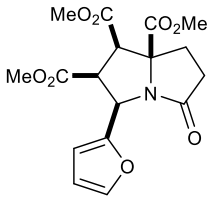
158am: 64% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 5.28 (d, *J* = 8.2 Hz, 1H), 3.98 – 3.85 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.28 (d, *J* = 7.0 Hz, 1H), 3.20 (s, 3H), 3.12 – 2.95 (m, 1H), 2.63 (dd, *J* = 12.3, 8.9 Hz, 1H), 2.54 ppm (qd, *J* = 9.0, 2.7 Hz, 2H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(3,4-dimethoxyphenyl)-5-oxohexahydro-1H-pyrrolizine-1,2,7a-tricarboxylate**



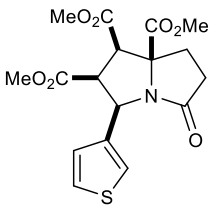
158an: 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 – 6.88 (m, 2H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.19 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 – 3.79 (m, 1H), 3.78 (s, 3H), 3.21 (d, *J* = 7.9 Hz, 4H), 3.09 – 2.85 (m, 1H), 2.58 (s, 1H), 2.54 – 2.35 ppm (m, 2H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(furan-2-yl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



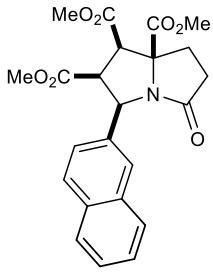
158ao: 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (s, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 6.32 – 6.24 (m, 1H), 5.24 (d, *J* = 8.2 Hz, 1H), 3.85 (t, *J* = 7.7 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.41 (s, 3H), 3.17 (d, *J* = 7.2 Hz, 1H), 2.96 (dd, *J* = 8.8, 3.7 Hz, 1H), 2.57 (dd, *J* = 12.0, 9.0 Hz, 1H), 2.52 – 2.39 (m, 2H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 5-oxo-3-(thiophen-3-yl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



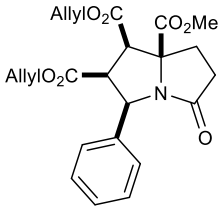
158ap: 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.19 (dd, *J* = 4.9, 3.1 Hz, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 5.26 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.81 – 3.77 (m, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 3.19 (d, *J* = 7.0 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.58 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.53 – 2.42 ppm (m, 2H).

***Rel*-(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(naphthalen-2-yl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



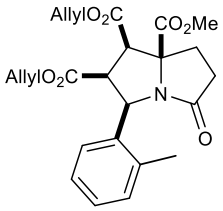
158aq: 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.81 (dd, *J* = 6.2, 3.0 Hz, 1H), 7.77 (dd, *J* = 8.8, 3.9 Hz, 2H), 7.47 – 7.36 (m, 3H), 5.41 (d, *J* = 8.1 Hz, 1H), 3.94 (dd, *J* = 7.9, 7.2 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.27 (d, *J* = 7.0 Hz, 1H), 3.17 – 3.04 (m, 1H), 3.02 (s, 3H), 2.64 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.59 – 2.47 ppm (m, 2H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 5-oxo-3-phenylhexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



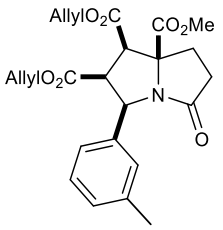
158ar: 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.4 Hz, 2H), 7.27 – 7.10 (m, 3H), 5.87 (ddd, *J* = 11.4, 10.5, 5.3 Hz, 1H), 5.37 – 5.23 (m, 2H), 5.20 (dd, *J* = 7.6, 4.2 Hz, 2H), 5.02 – 4.89 (m, 2H), 4.62 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.06 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.82 (ddd, *J* = 14.9, 12.7, 6.9 Hz, 2H), 3.77 (s, 3H), 3.21 (d, *J* = 6.9 Hz, 1H), 3.05 – 2.90 (m, 1H), 2.63 – 2.50 (m, 1H), 2.50 – 2.38 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.77, 171.86, 169.65, 167.43, 135.96, 131.85, 131.70, 128.16, 127.63, 126.62, 118.66, 118.47, 74.24, 66.10, 65.54, 60.76, 55.77, 53.22, 52.85, 36.32, 34.06 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 5-oxo-3-(o-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



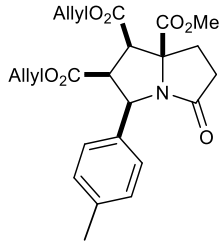
158as: 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.4 Hz, 1H), 7.12 (dt, *J* = 16.4, 7.3 Hz, 2H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.00 – 5.86 (m, 1H), 5.39 – 5.21 (m, 4H), 5.04 – 4.93 (m, 2H), 4.67 (ddd, *J* = 30.0, 13.2, 5.8 Hz, 2H), 4.05 (dd, *J* = 12.9, 6.3 Hz, 1H), 3.93 (t, *J* = 7.3 Hz, 1H), 3.88 – 3.78 (m, 4H), 3.28 (d, *J* = 6.8 Hz, 1H), 3.13 – 2.96 (m, 1H), 2.66 – 2.57 (m, 1H), 2.56 – 2.44 (m, 2H), 2.32 ppm (s, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 5-oxo-3-(m-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158at: 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.07 (m, 3H), 7.01 (d, *J* = 6.6 Hz, 1H), 5.95 (ddd, *J* = 16.3, 11.0, 5.8 Hz, 1H), 5.43 – 5.17 (m, 5H), 5.02 (dd, *J* = 13.6, 2.1 Hz, 1H), 4.71 (dd, *J* = 13.2, 5.9 Hz, 1H), 4.65 (dd, *J* = 13.2, 5.7 Hz, 1H), 4.11 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.94 (dd, *J* = 12.9, 5.9 Hz, 1H), 3.88 – 3.77 (m, 4H), 3.25 (d, *J* = 6.9 Hz, 1H), 3.13 – 2.94 (m, 1H), 2.61 (dd, *J* = 19.5, 11.5 Hz, 1H), 2.57 – 2.43 (m, 2H), 2.30 ppm (s, 3H).

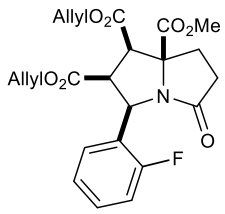
***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 5-oxo-3-(*p*-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158au: 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 12.0, 4.3 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.87 (ddt, *J* = 16.9, 11.4, 5.8 Hz, 1H), 5.38 – 5.22 (m, 2H), 5.17 (dd, *J* = 19.6, 9.2 Hz, 2H), 4.99 – 4.88 (m, 2H), 4.60 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.06 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.87 (dd, *J* = 12.9, 5.9 Hz, 1H), 3.79 – 3.71 (m, 4H), 3.18 (d, *J* = 6.8 Hz, 1H), 3.01

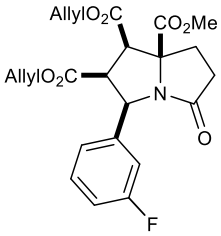
– 2.88 (m, 1H), 2.48 (dddd, *J* = 22.5, 19.7, 13.3, 9.0 Hz, 3H), 2.21 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.70, 171.88, 169.72, 167.45, 137.18, 132.98, 131.93, 131.87, 128.85, 126.53, 118.62, 118.28, 74.26, 66.07, 65.51, 60.68, 55.82, 53.26, 52.79, 36.34, 34.08, 21.16 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(2-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



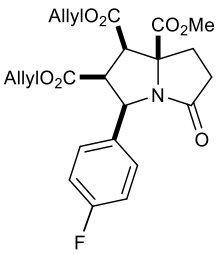
158av: 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.6, 7.0 Hz, 1H), 7.19 (dt, *J* = 7.4, 3.8 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.97 – 6.84 (m, 1H), 5.92 (tdd, *J* = 11.5, 8.2, 3.2 Hz, 1H), 5.44 – 5.29 (m, 3H), 5.28 – 5.19 (m, 1H), 5.08 – 4.95 (m, 2H), 4.66 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.12 (dd, *J* = 13.0, 6.1 Hz, 1H), 3.95 (ddd, *J* = 18.9, 14.5, 6.6 Hz, 2H), 3.81 (d, *J* = 0.6 Hz, 3H), 3.29 (d, *J* = 6.8 Hz, 1H), 3.10 – 2.92 (m, 1H), 2.68 – 2.57 (m, 1H), 2.59 – 2.43 ppm (m, 2H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(3-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158aw: 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.12 (m, 1H), 7.12 – 6.97 (m, 2H), 6.83 (dd, *J* = 13.2, 4.9 Hz, 1H), 5.87 (ddt, *J* = 16.4, 10.7, 5.8 Hz, 1H), 5.48 – 5.31 (m, 1H), 5.31 – 5.22 (m, 1H), 5.21 – 5.10 (m, 2H), 5.04 – 4.88 (m, 2H), 4.71 – 4.48 (m, 2H), 4.09 (ddd, *J* = 12.9, 6.2, 1.1 Hz, 1H), 3.93 (ddd, *J* = 12.9, 6.1, 1.1 Hz, 1H), 3.83 – 3.70 (m, 4H), 3.20 (d, *J* = 6.9 Hz, 1H), 3.03 – 2.87 (m, 1H), 2.54 (dd, *J* = 17.6, 9.6 Hz, 1H), 2.45 ppm (ddd, *J* = 19.6, 13.5, 6.6 Hz, 2H).

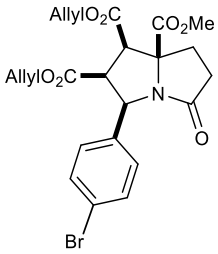
***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(4-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158ax: 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 5.93 (ddt, *J* = 16.5, 10.7, 5.8 Hz, 1H), 5.41 (ddt, *J* = 18.0, 10.1, 6.1 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.25 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.21 (d, *J* = 8.1 Hz, 1H), 5.05 (d, *J* = 0.8 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.66 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.14 (dd, *J* = 12.9, 6.1 Hz, 1H), 3.96 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 3.26 (d, *J* = 6.9 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.64 – 2.56 (m, 1H), 2.56 – 2.43 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$):

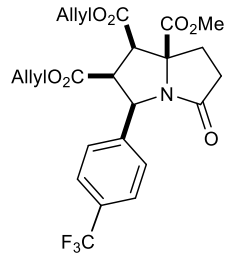
δ 176.78, 171.83, 169.60, 167.32, 163.40, 161.44, 131.88, 131.85, 131.58, 128.55, 128.49, 118.77, 118.72, 115.19, 115.02, 74.24, 66.19, 65.67, 60.23, 55.93, 53.28, 52.90, 36.29, 34.02 ppm; HRMS: calc. for $[M+H]^+$ $C_{23}H_{25}FNO_7$: 446.16096, found 446.16119.

Rel-(2_S_,3_R_,7a_S_)-1,2-diallyl 7a-methyl 3-(4-bromophenyl)-5-oxohexahydro-1_H_-pyrrolizine-1,2,7a-tricarboxylate

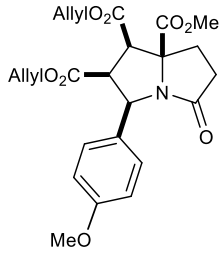


158ay: 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.14 (m, 2H), 5.99 – 5.75 (m, 1H), 5.41 – 5.24 (m, 2H), 5.20 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.12 (d, *J* = 8.0 Hz, 1H), 5.06 – 4.92 (m, 2H), 4.70 – 4.51 (m, 2H), 4.09 (ddd, *J* = 11.7, 4.2, 1.1 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.84 – 3.70 (m, 4H), 3.22 (d, *J* = 6.9 Hz, 1H), 3.02 – 2.83 (m, 1H), 2.64 – 2.49 (m, 1H), 2.49 – 2.33 ppm (m, 2H).

Rel-(1_R_,2_S_,3_R_,7a_S_)-1,2-diallyl 7a-methyl 5-oxo-3-(4-(trifluoromethyl)phenyl)hexahydro-1_H_-pyrrolizine-1,2,7a-tricarboxylate



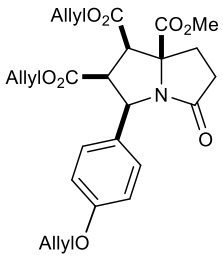
158az: 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 19.1, 8.3 Hz, 4H), 5.99 – 5.86 (m, 1H), 5.39 – 5.21 (m, 4H), 4.97 (dd, *J* = 14.4, 5.4 Hz, 2H), 4.66 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.09 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.98 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.81 (s, 3H), 3.29 (d, *J* = 6.9 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.67 – 2.43 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.79, 171.70, 169.42, 167.19, 140.35, 131.78, 131.23, 130.30, 130.04, 129.78, 129.53, 127.43, 127.22, 125.27, 125.22, 125.19, 125.16, 125.13, 123.10, 118.89, 118.77, 74.18, 66.19, 65.74, 60.30, 55.88, 53.04, 52.88, 36.17, 33.90 ppm.



Rel-(1_R_,2_S_,3_R_,7a_S_)-1,2-diallyl 7a-methyl 3-(4-methoxyphenyl)-5-oxohexahydro-1_H_-pyrrolizine-1,2,7a-tricarboxylate

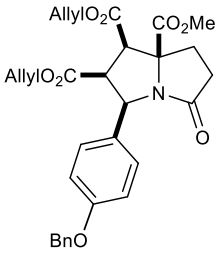
158ba: 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 10.3, 4.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.87 (dq, *J* = 11.2, 5.8 Hz, 1H), 5.42 – 5.31 (m, 1H), 5.28 (dd, *J* = 17.2, 0.8 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.60 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.08 (dd, *J* = 12.7, 6.1 Hz, 1H), 3.89 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.76 – 3.73 (m, 4H), 3.69 (s, 3H), 3.17 (d, *J* = 6.8 Hz, 1H), 3.06 – 2.89 (m, 1H), 2.59 – 2.37 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(4-(allyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



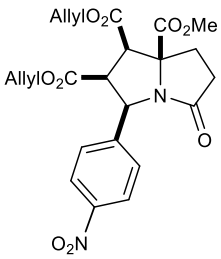
158bb: 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.08 – 5.80 (m, 2H), 5.48 – 5.11 (m, 6H), 5.11 – 4.92 (m, 2H), 4.78 – 4.52 (m, 2H), 4.47 (d, *J* = 5.2 Hz, 2H), 4.13 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.93 (dd, *J* = 12.9, 5.9 Hz, 1H), 3.84 – 3.52 (m, 4H), 3.23 (d, *J* = 6.8 Hz, 1H), 3.12 – 2.86 (m, 1H), 2.68 – 2.24 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.75, 171.93, 169.77, 167.47, 158.15, 133.40, 131.88, 131.80, 128.16, 127.82, 118.70, 118.49, 117.69, 114.47, 74.24, 68.86, 66.12, 65.58, 60.38, 55.78, 53.33, 52.87, 36.33, 34.12 ppm; HRMS: calc. for $[M+H]^+$ $C_{26}H_{30}NO_8$: 484.19659, found 484.19709.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(4-(benzyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



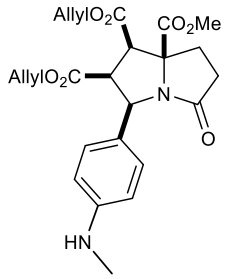
158bc: 86% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.10 (m, 7H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.86 (ddd, *J* = 16.4, 10.9, 5.5 Hz, 1H), 5.46 – 5.06 (m, 4H), 4.95 (t, *J* = 8.1 Hz, 4H), 4.73 – 4.41 (m, 2H), 4.07 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.86 (dd, *J* = 12.9, 5.9 Hz, 1H), 3.79 – 3.70 (m, 4H), 3.17 (d, *J* = 6.8 Hz, 1H), 3.10 – 2.80 (m, 1H), 2.64 – 2.24 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(4-nitrophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



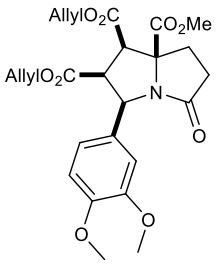
158bd: 27% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 5.94 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.47 – 5.21 (m, 4H), 5.04 (dd, *J* = 13.1, 5.7 Hz, 2H), 4.68 (qd, *J* = 13.2, 5.9 Hz, 2H), 4.15 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.96 (ddd, *J* = 15.1, 10.4, 6.7 Hz, 2H), 3.83 (s, 3H), 3.31 (d, *J* = 6.9 Hz, 1H), 3.16 – 2.95 (m, 1H), 2.65 (t, *J* = 10.6 Hz, 1H), 2.56 ppm (dt, *J* = 15.8, 8.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.83, 171.64, 169.34, 167.05, 147.64, 143.81, 131.80, 131.23, 127.93, 123.51, 119.19, 118.99, 74.20, 66.38, 65.91, 60.17, 56.15, 53.05, 52.99, 36.16, 33.85 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(4-(methylamino)phenyl)-5-oxohexahydro-1H-pyrrolizine-1,2,7a-tricarboxylate**



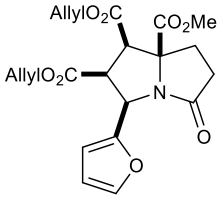
158be: 27% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 2H), 6.02 – 5.86 (m, 1H), 5.53 – 5.14 (m, 4H), 5.13 – 4.96 (m, 2H), 4.66 (dd, *J* = 14.5, 7.2 Hz, 2H), 4.17 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.98 (dd, *J* = 12.8, 5.8 Hz, 1H), 3.89 – 3.70 (m, 4H), 3.22 (d, *J* = 6.8 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.78 (s, 2H), 2.77 – 2.28 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(3,4-dimethoxyphenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



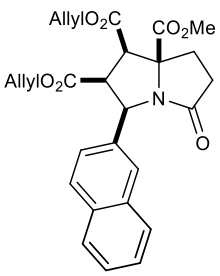
158bf: 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 6.9 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.92 (dd, *J* = 11.1, 5.8 Hz, 1H), 5.30 (ddd, *J* = 26.5, 15.2, 7.8 Hz, 4H), 5.03 (d, *J* = 11.8 Hz, 2H), 4.67 (t, *J* = 6.1 Hz, 2H), 4.16 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.97 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 – 3.78 (m, 1H), 3.24 (d, *J* = 6.8 Hz, 1H), 3.17 – 2.92 (m, 1H), 2.70 – 2.36 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(furan-2-yl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



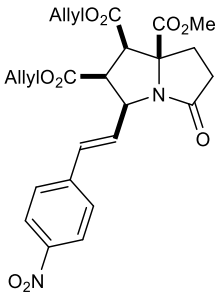
158bg: 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (s, 1H), 6.33 (d, *J* = 3.2 Hz, 1H), 6.21 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.87 (ddd, *J* = 22.9, 11.0, 5.8 Hz, 1H), 5.59 (ddt, *J* = 16.6, 10.5, 6.0 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.22 – 5.16 (m, 2H), 5.16 – 5.03 (m, 2H), 4.60 (qd, *J* = 13.2, 5.8 Hz, 2H), 4.27 (dd, *J* = 13.0, 6.1 Hz, 1H), 4.15 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.82 (t, *J* = 7.7 Hz, 1H), 3.73 (s, 3H), 3.16 (d, *J* = 7.2 Hz, 1H), 2.98 – 2.82 (m, 1H), 2.57 – 2.36 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.02, 171.63, 169.50, 167.16, 149.76, 141.93, 131.87, 131.85, 118.68, 118.57, 110.75, 108.48, 73.84, 66.13, 65.86, 55.70, 54.79, 52.84, 51.76, 35.54, 33.77 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-diallyl 7a-methyl 3-(naphthalen-2-yl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



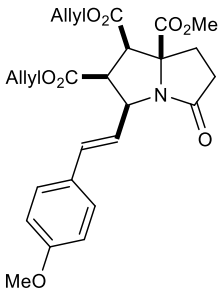
158bh: 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.82 – 7.68 (m, 3H), 7.52 – 7.35 (m, 3H), 5.95 (ddt, *J* = 16.6, 10.9, 5.8 Hz, 1H), 5.42 (d, *J* = 8.1 Hz, 1H), 5.35 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.26 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.18 – 5.02 (m, 1H), 4.78 (dd, *J* = 17.2, 1.0 Hz, 1H), 4.73 – 4.56 (m, 3H), 4.04 – 3.90 (m, 2H), 3.86 (s, 3H), 3.76 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.30 (d, *J* = 6.9 Hz, 1H), 3.16 – 2.99 (m, 1H), 2.71 – 2.60 (m, 1H), 2.59 – 2.50 ppm (m, 2H).

***Rel*-(1*R*,2*S*,3*S*,7a*S*)-1,2-diallyl 7a-methyl 3-((*E*)-4-nitrostyryl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



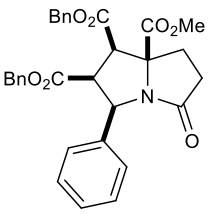
158bi: 15% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.29 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.94 (ddd, *J* = 16.4, 11.1, 5.2 Hz, 1H), 5.77 – 5.65 (m, 1H), 5.36 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.28 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.85 (t, *J* = 7.5 Hz, 1H), 4.68 (t, *J* = 6.1 Hz, 2H), 4.48 (dd, *J* = 9.7, 6.1 Hz, 2H), 3.83 (d, *J* = 4.4 Hz, 3H), 3.76 (t, *J* = 7.9 Hz, 1H), 3.20 (d, *J* = 7.5 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.74 – 2.44 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*S*,7a*S*)-1,2-diallyl 7a-methyl 3-((*E*)-4-methoxystyryl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



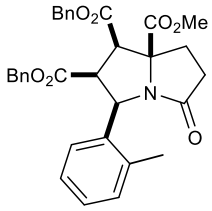
158bj: 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 – 7.16 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 15.9 Hz, 1H), 5.97 – 5.80 (m, 2H), 5.66 (ddd, *J* = 17.1, 6.0, 4.3 Hz, 1H), 5.28 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.4 Hz, 1H), 4.98 (dd, *J* = 10.3, 1.1 Hz, 1H), 4.72 (t, *J* = 7.7 Hz, 1H), 4.69 – 4.53 (m, 2H), 4.42 (dd, *J* = 7.5, 6.3 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.64 (t, *J* = 7.9 Hz, 1H), 3.08 (d, *J* = 7.5 Hz, 1H), 2.84 (dd, *J* = 8.7, 4.0 Hz, 1H), 2.50 (dd, *J* = 12.1, 8.8 Hz, 1H), 2.52 – 2.41 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.94, 171.98, 169.85, 167.62, 159.42, 133.26, 131.91, 129.15, 128.11, 121.63, 119.01, 118.73, 113.81, 74.22, 66.17, 65.85, 58.38, 55.61, 55.35, 52.93, 52.04, 35.21, 33.83 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 5-oxo-3-phenylhexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



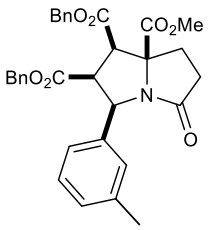
158bk: 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 – 7.17 (m, 10H), 7.14 (d, *J* = 9.4 Hz, 3H), 6.86 (dd, *J* = 6.2, 2.7 Hz, 2H), 5.24 – 5.01 (m, 3H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.21 (d, *J* = 12.1 Hz, 1H), 3.78 (t, *J* = 7.4 Hz, 1H), 3.64 (s, 3H), 3.14 (d, *J* = 6.8 Hz, 1H), 2.94 (dd, *J* = 11.7, 6.6 Hz, 1H), 2.61 – 2.22 ppm (m, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 5-oxo-3-(o-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



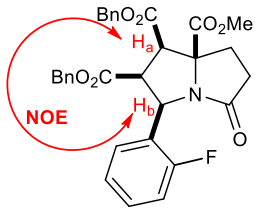
158bl: 90% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.23 (m, 5H), 7.21 – 7.14 (m, 3H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 10.5, 4.1 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 6.4, 2.9 Hz, 2H), 5.22 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.18 (d, *J* = 12.1 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.66 (s, 3H), 3.22 (d, *J* = 6.8 Hz, 1H), 3.05 – 2.88 (m, 1H), 2.53 (t, *J* = 10.7 Hz, 1H), 2.41 (dt, *J* = 14.2, 10.2 Hz, 2H), 2.19 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.54, 171.90, 169.70, 167.59, 135.52, 135.17, 134.39, 134.10, 130.13, 128.71, 128.61, 128.55, 128.53, 128.36, 128.16, 127.80, 127.17, 126.22, 74.19, 67.43, 66.73, 59.21, 55.88, 52.74, 51.40, 36.59, 34.19, 19.40 ppm.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 5-oxo-3-(*m*-tolyl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158bm: 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 5H), 7.23 – 6.97 (m, 6H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.91 – 6.72 (m, 2H), 5.26 – 5.00 (m, 3H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.28 (d, *J* = 12.1 Hz, 1H), 3.78 (t, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 3.17 (d, *J* = 6.8 Hz, 1H), 2.96 (dd, *J* = 12.0, 6.2 Hz, 1H), 2.61 – 2.22 (m, 3H), 2.20 ppm (s, 3H).

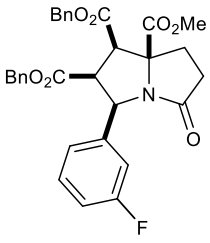
***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(2-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158bn: 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (t, *J* = 7.2 Hz, 1H), 7.29 (s, 5H), 7.22 – 7.14 (m, 3H), 7.03 (ddd, *J* = 23.2, 14.6, 4.5 Hz, 4H), 6.83 – 6.68 (m, 1H), 5.34 (d, *J* = 7.8 Hz, 1H), 5.12 (q, *J* = 12.2 Hz, 2H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.29 (d, *J* = 12.3 Hz, 1H), 3.95 (t, *J* =

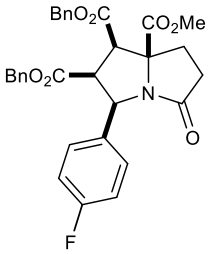
7.2 Hz, 1H), 3.66 (s, 3H), 3.23 (d, *J* = 6.8 Hz, 1H), 3.04 – 2.81 (m, 1H), 2.64 – 2.26 ppm (m, 3H).

Rel-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(3-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate



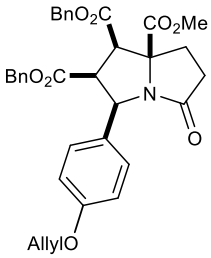
158bo: 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 5H), 7.24 – 7.15 (m, 3H), 7.14 – 6.99 (m, 3H), 6.97 – 6.87 (m, 2H), 6.81 (t, *J* = 8.3 Hz, 1H), 5.25 – 5.00 (m, 3H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.34 (d, *J* = 12.1 Hz, 1H), 3.81 (t, *J* = 7.5 Hz, 1H), 3.67 (s, 3H), 3.15 (d, *J* = 6.9 Hz, 1H), 3.03 – 2.79 (m, 1H), 2.61 – 2.22 ppm (m, 3H).

Rel-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(4-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate



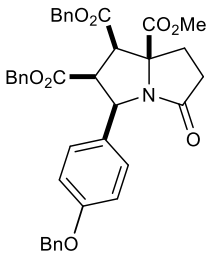
158bp: 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.13 (m, 11H), 6.95 – 6.74 (m, 4H), 5.26 – 5.08 (m, 4H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 12.1 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.67 (s, 3H), 3.20 (d, *J* = 6.8 Hz, 1H), 2.96 (ddd, *J* = 20.8, 16.4, 8.4 Hz, 1H), 2.59 – 2.33 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.82, 171.90, 169.90, 167.47, 163.56, 161.11, 135.38, 134.99, 131.71, 128.75, 128.70, 128.66, 128.63, 128.50, 128.46, 128.42, 128.37, 115.31, 115.09, 74.27, 67.52, 66.81, 60.19, 55.99, 53.13, 52.90, 36.27, 34.05 ppm; HRMS: calc. for $[M+H]^+$ $C_{31}H_{29}FNO_7$: 546.19226, found 546.19312.

Rel-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(4-(allyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate



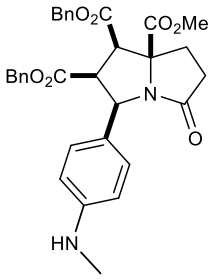
158bq: 86% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 5H), 7.25 – 7.04 (m, 6H), 6.90 (d, *J* = 3.3 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 5.96 (ddd, *J* = 15.9, 10.6, 5.4 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.14 (ddd, *J* = 16.3, 11.3, 8.0 Hz, 4H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.37 (dd, *J* = 21.0, 8.7 Hz, 3H), 3.78 (t, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 3.19 (d, *J* = 6.7 Hz, 1H), 3.11 – 2.83 (m, 1H), 2.62 – 2.28 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.75, 171.97, 170.08, 167.58, 158.14, 135.43, 135.15, 133.40, 128.69, 128.59, 128.54, 128.36, 128.20, 128.14, 127.85, 117.72, 114.49, 74.28, 68.78, 67.40, 66.71, 60.42, 55.83, 53.22, 52.80, 36.28, 34.11 ppm; HRMS: calc. for $[M+H]^+$ $C_{34}H_{34}NO_8$: 584.22789, found 584.22875.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(4-(benzyloxy)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



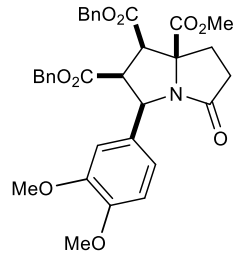
158br: 82% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.02 (m, 15H), 6.88 (d, *J* = 3.4 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.26 – 5.01 (m, 3H), 4.92 (s, 2H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.31 (d, *J* = 12.1 Hz, 1H), 3.75 (t, *J* = 7.4 Hz, 1H), 3.65 (s, 3H), 3.14 (d, *J* = 6.8 Hz, 1H), 2.99 – 2.77 (m, 1H), 2.61 – 2.17 ppm (m, 3H); HRMS: calc. for $[M+H]^+$ $C_{38}H_{36}NO_8$: 634.24354, found 634.24337.

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(4-(methylamino)phenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



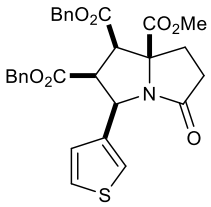
158bs: 54% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.14 (m, 10H), 6.97 (s, 2H), 6.50 (d, *J* = 8.5 Hz, 2H), 5.35 – 5.07 (m, 3H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.44 (d, *J* = 12.2 Hz, 1H), 3.99 – 3.70 (m, 4H), 3.23 (d, *J* = 6.8 Hz, 1H), 2.99 (dd, *J* = 23.3, 13.4 Hz, 1H), 2.79 (s, 3H), 2.53 ppm (dt, *J* = 16.2, 11.8 Hz, 3H).

***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 3-(3,4-dimethoxyphenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158bt: 76% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 5H), 7.19 (s, 3H), 7.00 – 6.77 (m, 4H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.27 – 5.04 (m, 3H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 3.94 – 3.76 (m, 4H), 3.70 (s, 3H), 3.68 (s, 3H), 3.20 (d, *J* = 6.8 Hz, 1H), 2.95 (d, *J* = 15.2 Hz, 1H), 2.49 ppm (dt, *J* = 17.6, 11.8 Hz, 3H).

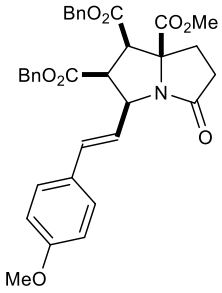
***Rel*-(1*R*,2*S*,3*R*,7a*S*)-1,2-dibenzyl 7a-methyl 5-oxo-3-(thiophen-3-yl)hexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate**



158bu: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.24 (m, 9H), 7.18 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.07 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.01 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.32 – 5.14 (m, 3H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.43 (d, *J* = 12.1 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.72 (s, 3H), 3.22 (d, *J* = 6.9 Hz, 1H), 3.08 – 2.92 (m, 1H), 2.64 – 2.39 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.41, 171.92, 170.03,

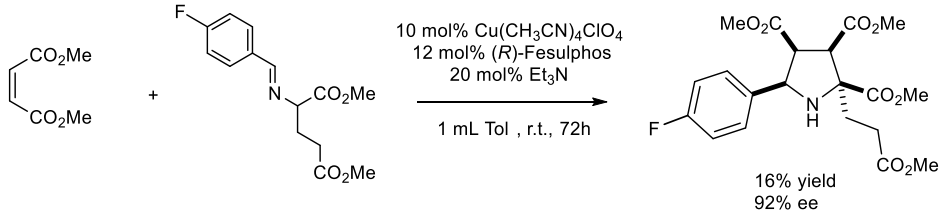
167.46, 137.06, 135.40, 135.14, 128.69, 128.67, 128.59, 128.55, 128.47, 128.29, 126.50, 125.51, 122.88, 74.11, 67.42, 66.95, 57.06, 55.81, 52.82, 52.65, 35.94, 33.99 ppm.

Rel-(1_R_,2_S_,3_S_,7a_S_)-1,2-dibenzyl 7a-methyl 3-((_E_)-4-methoxystyryl)-5-oxohexahydro-1_H_-pyrrolizine-1,2,7a-tricarboxylate



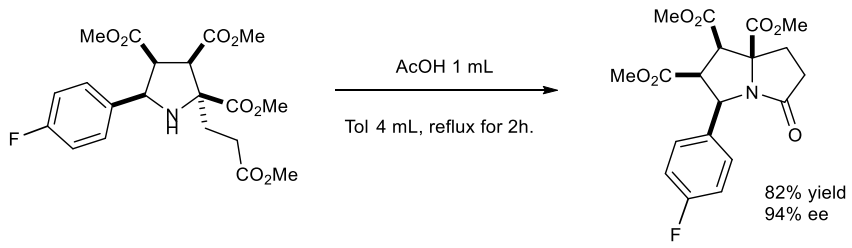
158bv: 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H), 7.21 – 7.02 (m, 7H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 15.8 Hz, 1H), 5.88 (dd, *J* = 15.9, 7.3 Hz, 1H), 5.14 (q, *J* = 12.2 Hz, 2H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.85 (d, *J* = 12.1 Hz, 1H), 4.71 (t, *J* = 7.8 Hz, 1H), 3.74 (s, 3H), 3.72 – 3.61 (m, 4H), 3.09 (d, *J* = 7.5 Hz, 1H), 2.92 – 2.79 (m, 1H), 2.54 – 2.15 ppm (m, 3H).

7.3.3 Experimental Detail and Analytic Data for Enantioselective Synthesis of Pyrrolizidine 157aa



(2_S_,3_R_,4_S_,5_R_)-trimethyl 5-(4-fluorophenyl)-2-(3-methoxy-3-oxopropyl)pyrrolidine-2,3,4-tricarboxylate

Chiral-**157aa**: 16% yield; $[\alpha]_D^{20}$ = +25.5 (*c* = 1.00 in CH_2Cl_2); 92% ee, determined by HPLC analysis [Daicel CHIRALPAK IA, *iso*-hexane/(DCM/EtOH = 100/2) = 80/20, 0.5 mL/min, λ = 235 nm, t (major) = 37.26 min, t (minor) = 23.49 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.17 (m, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 4.41 (d, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.38 (t, *J* = 6.7 Hz, 1H), 3.26 (d, *J* = 7.0 Hz, 1H), 3.24 (s, 3H), 2.59 – 2.46 (m, 1H), 2.43 – 2.32 (m, 1H), 2.21 (ddd, *J* = 15.6, 9.9, 5.4 Hz, 1H), 2.06 ppm (ddd, *J* = 13.5, 10.0, 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.66, 173.09, 171.08, 170.95, 163.36, 161.40, 133.17, 128.66, 128.60, 115.49, 115.32, 71.70, 63.40, 57.38, 53.04, 52.92, 52.30, 51.82, 51.51, 35.35, 30.07 ppm; HRMS: calc. for $[M+H]^+$ $C_{20}H_{25}FNO_8$: 426.15587, found 426.15552.



(1*S*,2*S*,3*R*,7a*S*)-trimethyl 3-(4-fluorophenyl)-5-oxohexahydro-1*H*-pyrrolizine-1,2,7a-tricarboxylate

Chiral-**158baa**: 82% yield; $[\alpha]_D^{20}$ = +93.0 (*c* = 0.50 in CH_2Cl_2); 94% ee, determined by HPLC analysis [Daicel CHIRALPAK IA, *iso*-hexane/(DCM/EtOH = 100/2) = 70/30, 0.5 mL/min, λ = 254 nm, t (major) = 13.21 min, t (minor) = 32.47 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.20 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.83 – 3.79 (m, 1H), 3.77 (s, 3H), 3.22 (d, *J* = 6.9 Hz, 1H), 3.18 (s, 3H), 3.02 (d, *J* = 3.0 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.54 – 2.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.84, 171.91, 170.38, 168.24, 163.51, 161.07, 131.84, 131.81, 128.34, 128.26, 115.19, 114.98, 74.19, 60.09, 55.70, 53.21, 53.03, 52.51, 51.63, 36.23, 34.04 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{21}FNO_7$: 394.12966, found 394.12872.

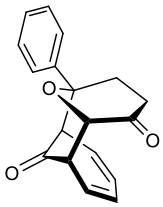
7.4 Experimental Part for Enantioselective Synthesis of Cycloheptanoids

7.4.1 Experimental Detail and Analytic Data for (6+3) Cycloadditions of Tropone

7.4.1.1 General Method and Analytic Data of 248a-e

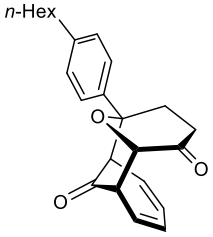
General Method: A flame dried *Schlenk* tube was charged with Rh_2(*S*-TCPTTL)$_4$ (3.94 mg, 0.002 mmol, 2mol%), tropone **242** (10 μL, 0.1 mmol, 1 equiv) and 0.5 mL of α,α,α-trifluorotoluene as solvent. Then a solution of the corresponding diazo compound **247** (2.0 equiv) in 0.5 mL α,α,α-trifluorotoluene was added *via* syringe pump (1 h) to the reaction mixture and was allowed to stir for an additional hour at room temperature. After completion, the reaction reaction mixture was directly loaded on the silica gel column and was purified using 20-30% ethyl acetate/petroleum ether mixture as an eluent to afford desired compounds **248**.

(1*S*,2*S*,6*S*,7*R*)-6-Phenyl-13-oxatricyclo[5.4.1.1^{2,6}]trideca-8,10-diene-3,12-dione



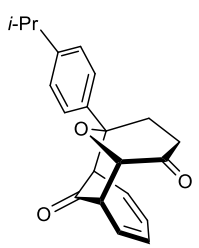
248a: 78% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.51 – 7.38 (m, 4H), 7.36 – 7.27 (m, 1H), 6.34 – 6.15 (m, 2H), 6.02 (dd, *J* = 11.2, 8.0 Hz, 1H), 5.85 (dd, *J* = 10.6, 9.1 Hz, 1H), 5.04 (d, *J* = 11.4 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.73 (dd, *J* = 8.1, 3.8 Hz, 1H), 2.60 – 2.47 (m, 3H), 2.32 – 2.23 ppm (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 205.04, 202.10, 148.85, 128.86, 127.91, 127.59, 126.99, 124.96, 124.61, 123.39, 81.32, 81.27, 63.08, 53.00, 33.42, 31.56 ppm; FT-IR: $\tilde{\nu}$ = 2927, 1720, 1419, 1447, 1279, 1188, 1078 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{18}H_{17}O_3^+$: 281.11777, found: 281.11685; $[\alpha]_D^{RT}$ = +31.2 (c = 0.5 in CH_2Cl_2); HPLC conditions: CHIRALPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 27.40 min; major enantiomer: t_R = 24.93 min; 94% ee.

(1*S*,2*S*,6*S*,7*R*)-6-(4-hexylphenyl)-13-oxatricyclo[5.4.1.1^{2,6}]trideca-8,10-diene-3,12-dione



248b: 55% yield; ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.37 – 7.31 (m, 2H), 7.24 – 7.18 (m, 2H), 6.25 (ddt, *J* = 11.5, 7.5, 0.7 Hz, 1H), 6.22 – 6.18 (m, 1H), 6.02 – 5.95 (m, 1H), 5.87 – 5.80 (m, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.70 (dd, *J* = 8.0, 3.8 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.56 – 2.46 (m, 3H), 2.29 – 2.22 (m, 1H), 1.66 – 1.56 (m, 2H), 1.38 – 1.27 (m, 6H), 0.89 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, CD2Cl2): δ 205.49, 202.65, 146.48, 142.91, 129.18, 128.14, 127.38, 125.32, 125.05, 123.64, 81.72, 81.64, 63.54, 53.46, 36.03, 33.81, 32.29, 32.04, 31.95, 29.59, 23.19, 14.44 ppm; FT-IR: $\tilde{\nu}$ = 2926, 2855, 1724, 1681, 1512, 1280, 1181, 1116, 1058, 986 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{24}H_{29}O_3$:365.21112, found: 365.21131; $[\alpha]_D^{RT}$ = +34.5 (c = 0.6 in CH2Cl2); HPLC conditions: CHIRALPAK IC column, (CH_2Cl_2/EtOH = 100/2) / heptane = 20/80, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 35.0 min; minor enantiomer: t_R = 46.4 min; 92% ee.

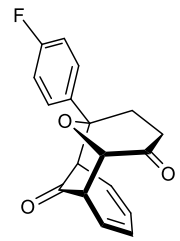
(1*S*,2*S*,6*S*,7*R*)-6-(4-Isopropylphenyl)-13-oxatricyclo[5.4.1.1^{2,6}]trideca-8,10-diene-3,12-dione



248c: 56% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.42 – 7.34 (m, 2H), 7.30 – 7.21 (m, *J* = 2.0, 1.2 Hz, 2H), 6.33 – 6.15 (m, 2H), 6.05 – 5.96 (m, 1H), 5.85 (ddd, *J* = 11.0, 9.1, 0.7 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.71 (dd, *J* = 8.0, 3.8 Hz, 1H), 2.99 – 2.87 (m, 1H), 2.58 – 2.45 (m, 3H), 2.32 – 2.23 (m, 1H), 1.27 ppm (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 205.06, 202.24, 148.39, 146.26, 127.77, 127.02, 126.85, 124.96, 124.66, 123.35,

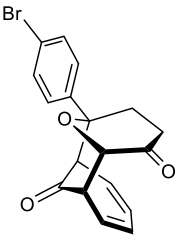
81.34, 81.28, 63.15, 53.12, 33.95, 33.44, 31.58, 23.91 ppm; FT-IR: $\tilde{\nu}$ = 2958, 1721, 1509, 1460, 1410, 1283, 1188, 1079, 865 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{23}O_3$: 323.16472, found: 323.16421; $[\alpha]_D^{RT}$ = +29.0 (c = 0.5 in CH_2Cl_2); HPLC conditions: CHIRALPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 52.41 min; major enantiomer: t_R = 40.93 min; 89% ee.

(1*S*,2*S*,6*S*,7*R*)-6-(4-Fluorophenyl)-13-oxatricyclo[5.4.1.1^{2,6}]trideca-8,10-diene-3,12-dione



248d: 30% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.41 – 7.31 (m, 2H), 7.07 – 6.97 (m, 2H), 6.23 – 6.08 (m, 2H), 5.89 (dd, *J* = 11.3, 8.0 Hz, 1H), 5.76 (dd, *J* = 10.5, 8.8 Hz, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 3.94 – 3.84 (m, 1H), 3.58 (dd, *J* = 8.0, 3.8 Hz, 1H), 2.51 – 2.36 (m, 3H), 2.21 – 2.11 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 204.66, 201.90, 162.09 (d, *J* = 245.60 Hz, 1C), 144.75 (d, *J* = 3.1 Hz, 1C), 128.03, 127.05, 125.37 (d, *J* = 8.10 Hz, 1C), 125.00, 124.29, 115.56 (d, *J* = 21.57 Hz, 1C), 81.25, 81.03, 63.01, 52.99, 33.33, 31.63 ppm; FT-IR: $\tilde{\nu}$ = 2926, 1720, 1604, 1509, 1409, 1281, 1222, 1189, 1161, 1080, 865 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{18}H_{16}O_3F$: 299.10835, found: 299.10747; $[\alpha]_D^{RT}$ = +15.1 (c = 0.3 in CH_2Cl_2); HPLC conditions: CHIRALPAK IA column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 47.42 min; major enantiomer: t_R = 51.58 min; 92% ee.

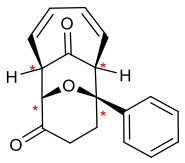
(1*S*,2*S*,6*S*,7*R*)-6-(4-Bromophenyl)-13-oxatricyclo[5.4.1.1^{2,6}]trideca-8,10-diene-3,12-dione



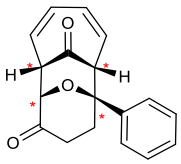
248e: 66% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.59 – 7.53 (m, 2H), 7.41 – 7.28 (m, 2H), 6.34 – 6.17 (m, 2H), 5.99 (dd, *J* = 11.3, 8.0 Hz, 1H), 5.85 (dd, *J* = 10.7, 9.0 Hz, 1H), 5.03 (d, *J* = 11.4 Hz, 1H), 4.03 – 3.93 (m, 1H), 3.67 (dd, *J* = 7.9, 3.8 Hz, 1H), 2.60 – 2.45 (m, 3H), 2.30 – 2.17 ppm (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 204.60, 201.73, 147.86, 131.92, 128.16, 127.03, 125.41, 125.00, 124.21, 121.42, 81.23, 81.02, 62.76, 52.92, 33.30, 31.42 ppm; FT-IR: $\tilde{\nu}$ = 2928, 1721, 1486, 1396, 1283, 1187, 1074, 1008 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{18}H_{16}O_3{}^{79}Br$: 359.02828 and $C_{18}H_{16}O_3{}^{81}Br$: 361.02828, found: 359.02771 and 361.02561; $[\alpha]_D^{RT}$ = +18.9 (c = 0.7 in CH_2Cl_2); HPLC conditions: CHIRALPAK IC column, (CH_2Cl_2/EtOH = 100/2) / *iso*-hexane = 25/75, flow rate = 0.5 mL min^{-1}, minor enantiomer: t_R = 46.09 min; major enantiomer: t_R = 42.32 min; 87% ee.

7.4.1.2 VCD Spectra Data of 248a (by C.M.)

Determination of absolute configurations of 248a



endo-248a



exo-248a

General approach

Experimental IR and VCD spectra were obtained for a solution of **248a** in $CDCl_3$ (50mg/ml) at 100 µm path length. The spectra were recorded on a Bruker Vertex 70v equipped with a PMA 50 module for VCD measurements accumulating 26000 scans for the VCD spectrum. The baseline was corrected by subtraction of the solvent spectrum.

In order to analyse experimental IR and VCD spectra, a thorough conformational analysis followed by spectra calculations for all conformers is necessary. For both compounds, this analysis has been performed manually by systematically generating the input structures, followed by an geometry optimization at the B3LYP/6-311+G(2d,p) level of theory using Gaussian 09 Rev. D.01. Solvent effects were accounted for by applying a polarizable continuum model (IEFPCM).[254] Following the geometry optimization, the IR and VCD spectra were calculated for each conformer. In order to account for line broadening, a Lorentzian band shape of 8 cm^{-1} half-width at half-height was assigned to the calculated dipole and rotational strengths. For a better visual comparison of the spectra, the calculated frequencies were scaled by a factor of 0.98. Finally, the energy differences within the set of conformations of each compound were computed based on the zero-point corrected electronic (ΔE) as well as Gibbs free energy (ΔG) and used to generate population-weighted IR and VCD spectra. During the calculations of VCD spectra, magnetic shielding constants are computed as well. The computed values are references against TMS calculated at the same level of theory.

Absolute configuration of 248a.

Compound **248a** features two sets of stereocenters. First, there are the bridge-atoms of the oxobridge which can either be both (*R*)- or (*S*)-configured. Furthermore, the orientation of the tropone moiety can be either endo or exo with respect to the oxobridge. The scheme above

shows the endo- and exo-form of **248a** with (*S*)-configuration at the oxo bridge atoms which have been considered for the calculations.

For both diastereomers of **248a**, the conformational analysis is straightforward. The seven-membered ring is very rigid due to the C=C bonds, and it can only adopt one planar conformation. In both isomers, a ring-flip of the ketone-containing six-membered ring is possible, i.e. the α-CH_2 can point away or towards the oxobridge. Thus, only two conformations were found for each exo and endo-**248a**. The relative energies of the conformers of exo-**248a** are summarized in Table S6 and the respective lowest-energy structures are shown below.

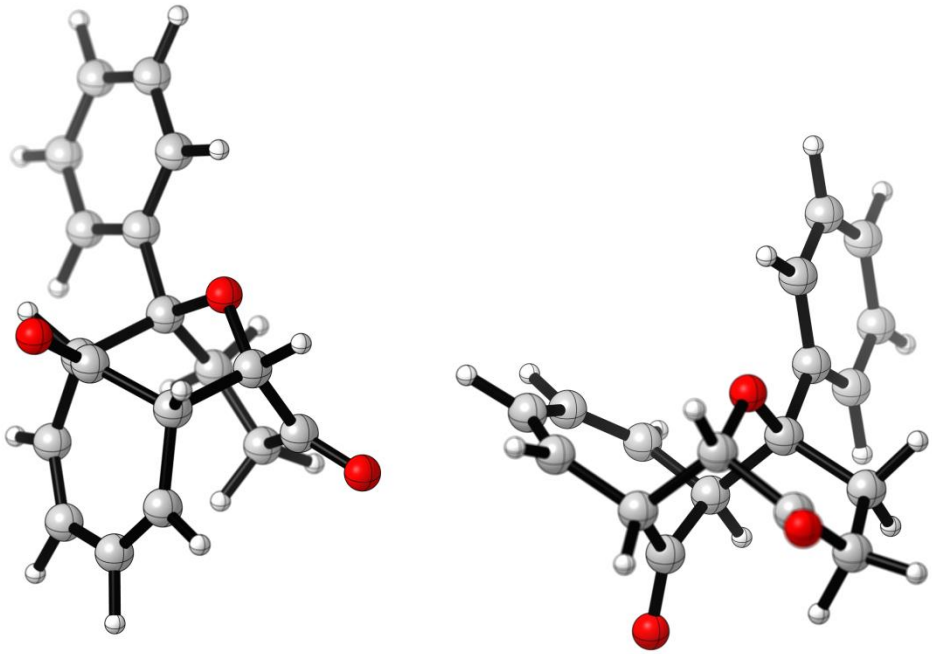


Figure S4. Lowest energy structures of exo-(*S*,*S*)-**248a** (left) and endo-(*S*,*S*)-**248a** (right).

Table S5. Relative energies the two conformers of exo-(*S*,*S*)-**248a.**

	#	ΔE[1]	ΔG[1]	Pop-ΔE[2]	Pop-ΔG[2]
exo	c0	0.00	0.00	74.46	65.57
	c1	0.63	0.38	25.54	34.43

[1] in kcal/mol

[2] population based on ΔE or ΔG in %

[a] with respect to E_{ZPC}=-921.132232hartree and G=-921.17587 hartree

The experimental ^{1}H-NMR chemical shifts of the protons at the two chiral centers suggest the preference of the exo-form. Both protons can easily be identified in the ^{1}H-NMR spectrum based on the coupling pattern, as shown in Figure S4 below. From the calculated chemical shifts of the lowest-energy conformers of endo- and exo-**248a**, which are given in the figure as well, it can be seen that only for the exo-form the resonance frequencies are predicted in the correct order.

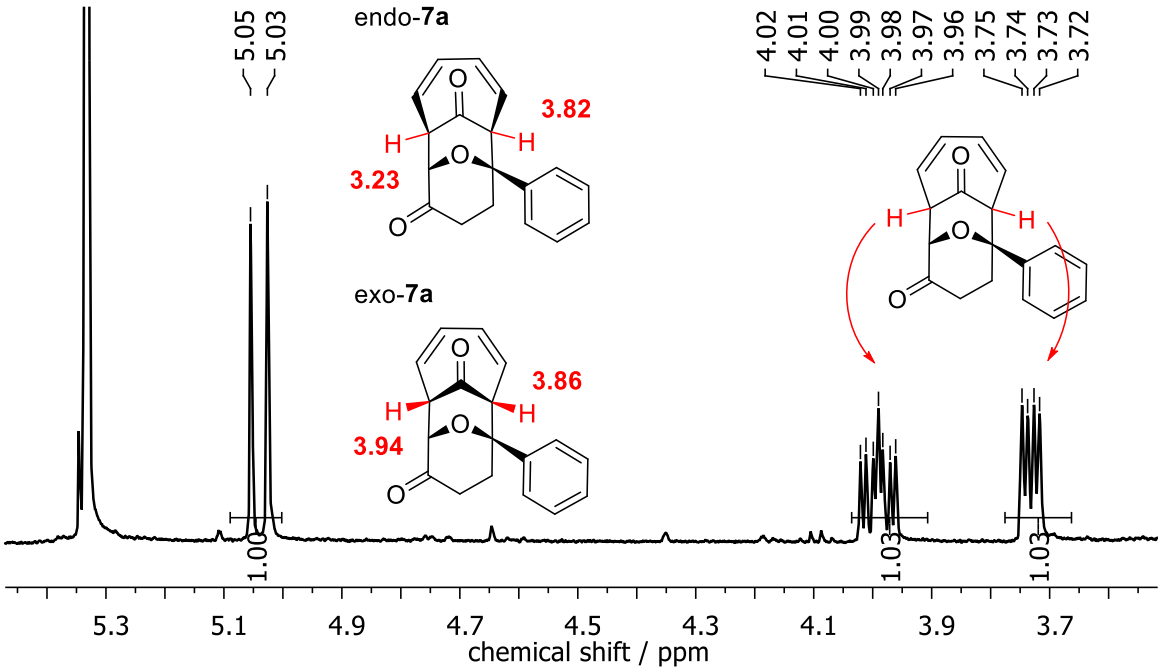


Figure S5. Section of the ^{1}H-NMR spectrum of **248a** showing the two chiral protons of the tropone bridge head, and the theoretically derived values for *endo*- and *exo*-**248a**.

Figure S5 shows a comparison of the experimental IR and VCD spectra with those computed for *exo*-(*S*,*S*)-**248a**. Again, good agreement between the calculated and measured IR spectrum is found. Only the band at ~1140 cm-1 of the experimental spectrum is missing in the simulation. Clear band assignments can be made based on the calculated IR which subsequently allows an assignment of experimental VCD bands to the predicted ones. From the visual comparison, the (*S*,*S*)-configuration of the bridge heads can clearly be established.

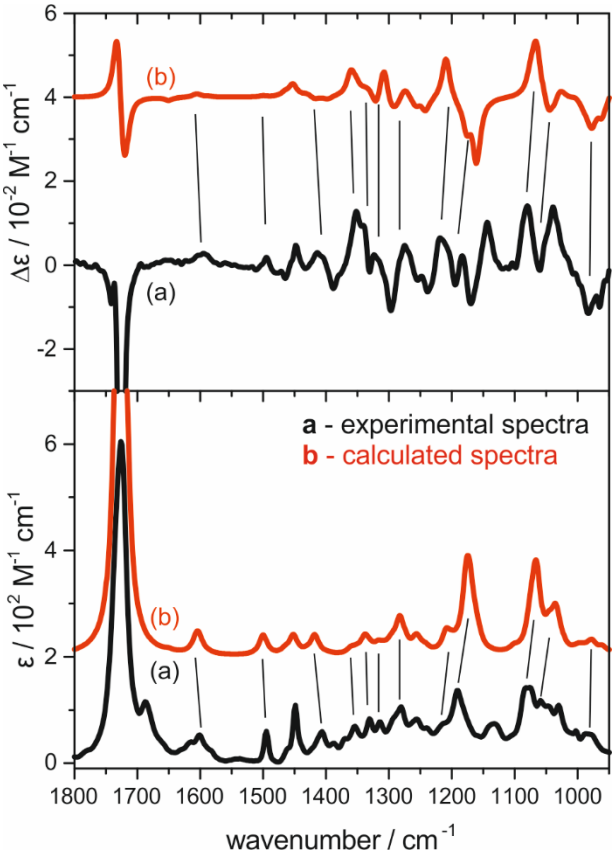
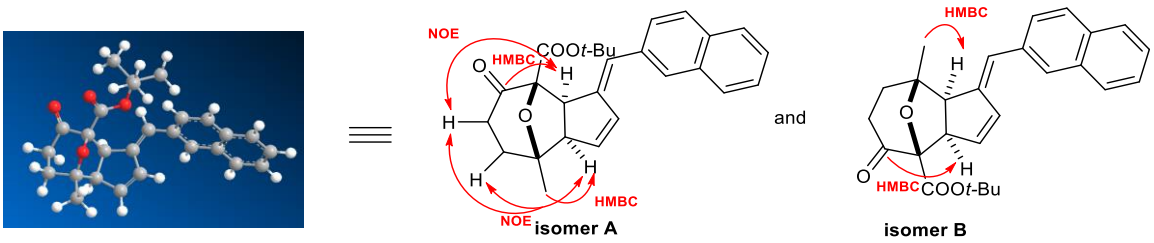


Figure S6. Comparison of experimental and simulated IR and VCD spectra. Band assignments are indicated by thin lines connecting the experimental and simulated band positions.

7.4.2 Experimental Detail and Analytic Data for 1,3-Dipolar Cycloaddition Reactions of Cyclic Carbonyl Ylides and of Pentafulvenes (249a-c)

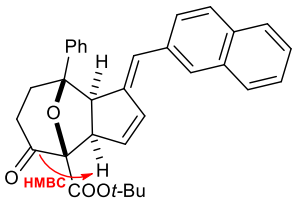


***Rel-tert*-butyl (3a*R*,4*S*,8*S*,8a*R*,*E*)-8-methyl-3-(naphthalen-2-ylmethylene)-5-oxo-3a,5,6,7,8,8a-hexahydro-4,8-epoxyazulene-4(3*H*)-carboxylate and *Rel*-*tert*-butyl (*3aR,4R,8R,8aR,E*)-8-methyl-1-(naphthalen-2-ylmethylene)-5-oxo-3a,5,6,7,8,8a-hexahydro-4,8-epoxyazulene-4(1*H*)-carboxylate**

249a. For isomer **A**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.84 – 7.75 (m, 4H), 7.55 – 7.43 (m, 3H), 6.75 (s, 1H), 6.47 (dd, *J* = 5.4, 1.9 Hz, 1H), 5.98 (dd, *J* = 5.4, 2.3 Hz, 1H), 4.20 (d, *J* = 6.4

Hz, 1H), 3.97 – 3.88 (m, 1H), 2.84 (ddd, *J* = 16.6, 11.7, 8.2 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.33 – 2.26 (m, 1H), 2.23 – 2.14 (m, 1H), 1.56 (d, *J* = 4.7 Hz, 9H), 1.22 ppm (s, *J* = 4.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 202.34, 165.68, 146.93, 140.88, 135.31, 133.72, 133.31, 132.41, 128.38, 127.99, 127.77, 127.38, 126.66, 126.25, 125.88, 124.89, 90.15, 83.74, 83.08, 59.14, 50.07, 39.85, 34.01, 28.32, 22.28 ppm; HRMS: calc. for $[M+H]^+$ $C_{27}H_{29}O_4$: 417.20604, found: 417.20597. For isomer **B**: ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.85 – 7.70 (m, 4H), 7.52 – 7.42 (m, 3H), 6.99 (d, *J* = 5.5 Hz, 1H), 6.41 (s, 1H), 6.13 (d, *J* = 5.5 Hz, 1H), 3.83 (d, *J* = 6.5 Hz, 1H), 3.48 (d, *J* = 6.5 Hz, 1H), 2.80 – 2.67 (m, 1H), 2.55 (dd, *J* = 16.4, 6.6 Hz, 1H), 2.33 (td, *J* = 12.6, 6.8 Hz, 1H), 2.10 (dd, *J* = 13.1, 7.9 Hz, 1H), 1.56 (s, 9H), 1.50 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 202.29, 165.72, 146.00, 137.51, 135.37, 134.57, 133.62, 132.41, 128.15, 127.99, 127.76, 127.09, 126.65, 126.45, 126.01, 124.24, 90.94, 83.77, 83.07, 56.67, 53.99, 40.49, 33.79, 28.32, 23.41 ppm; HRMS: calc. for $[M+H]^+$ $C_{27}H_{29}O_4$: 417.20604, found: 417.205967.

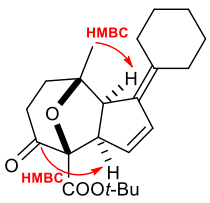
***Rel-tert*-butyl (3a*R*,4*R*,8*R*,8a*R*,*E*)-1-(naphthalen-2-ylmethylene)-5-oxo-8-phenyl-3a,5,6,7,8,8a-hexahydro-4,8-epoxyazulene-4(1*H*)-carboxylate**



isomer B

249b, for the major product: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.36 (m, 4H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.24 – 7.17 (m, 2H), 6.88 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.73 (dd, *J* = 5.7, 1.0 Hz, 1H), 6.13 – 6.07 (m, 1H), 5.55 (s, 1H), 3.96 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.85 (dd, *J* = 13.0, 8.0 Hz, 1H), 2.70 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.62 – 2.46 (m, 1H), 1.59 ppm (d, *J* = 3.2 Hz, 9H); ^{13}C NMR (126 MHz, , $CDCl_3$): δ = 201.99, 165.52, 145.57, 140.26, 135.98, 135.57, 134.76, 133.36, 132.17, 128.01, 127.86, 127.66, 127.62, 127.58, 126.60, 126.55, 126.18, 126.02, 125.74, 125.65, 90.88, 87.77, 83.11, 57.05, 55.55, 38.09, 33.64, 28.45, 28.37 ppm; HRMS: calc. for $[M+H]^+$ $C_{32}H_{31}O_4$: 479.22169, found: 479.22133.

***Rel-tert*-butyl (3a*R*,4*R*,8*R*,8a*R*)-1-cyclohexylidene-8-methyl-5-oxo-3a,5,6,7,8,8a-hexahydro-4,8-epoxyazulene-4(1*H*)-carboxylate**

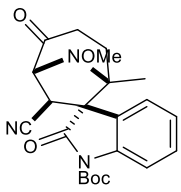


249c, for the major product: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.57 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.74 (dd, *J* = 5.7, 2.2 Hz, 1H), 3.73 (d, *J* = 6.8 Hz, 1H), 3.44 (d, *J* = 6.9 Hz, 1H), 2.70 (ddd, *J* = 16.7, 11.7, 8.2 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.37 (d, *J* = 13.0 Hz, 1H), 2.30 – 2.19 (m, 2H), 2.14 (dd, *J* = 11.9,

7.9 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.68 – 1.56 (m, 4H), 1.56 – 1.45 (m, 12H), 1.32 ppm (s, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 202.81, 165.93, 135.89, 134.83, 134.71, 130.77, 90.59, 84.12, 82.76, 57.46, 49.60, 39.69, 33.93, 33.31, 31.78, 28.29, 27.98, 27.69, 26.69, 22.58 ppm; HRMS: calc. for $[M+H]^+$ $C_{22}H_{31}O_4$: 359.22169, found: 359.22179.

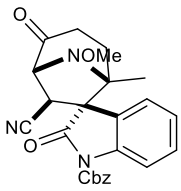
7.4.3 Experimental Detail and Analytic Data for Enantioselective Synthesis of Tropanes (261a-c)

***Rel-tert*-butyl (1*R*,5*R*,6*S*,7*R*)-7-cyano-8-methoxy-5-methyl-2,2'-dioxo-8-azaspiro[bicycle [3.2.1]octane-6,3'-indoline]-1'-carboxylate**



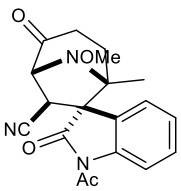
261a, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.20 (s, 1H), 3.68 (d, *J* = 1.4 Hz, 1H), 3.65 (s, 3H), 3.22 – 3.12 (m, 1H), 2.49 – 2.37 (m, 2H), 2.16 – 2.08 (m, 1H), 1.67 (s, 9H), 0.82 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.72, 173.75, 148.49, 139.23, 130.12, 127.48, 127.04, 124.90, 116.68, 115.09, 85.74, 70.00, 69.67, 62.44, 59.32, 36.14, 33.22, 29.20, 28.23, 21.35 ppm; HRMS: calc. for $[M+H]^+$ $C_{22}H_{26}O_5N_3$: 412.18725, found: 412.18755.

***Rel*-Benzyl (1*R*,5*R*,6*S*,7*R*)-7-cyano-8-methoxy-5-methyl-2,2'-dioxo-8-azaspiro[bicycle [3.2.1]octane-6,3'-indoline]-1'-carboxylate**

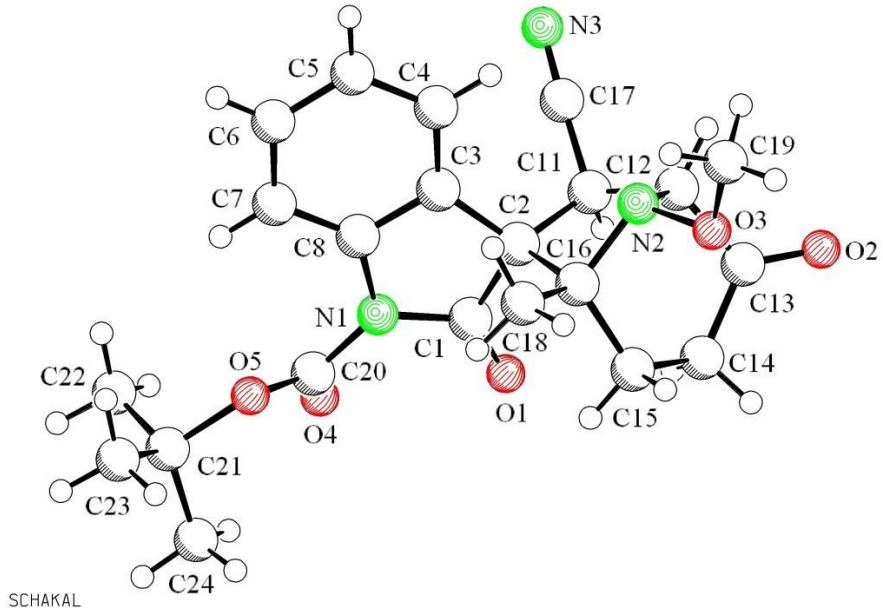


261b, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.36 – 7.28 (m, 1H), 5.51 (d, *J* = 12.2 Hz, 1H), 5.44 (d, *J* = 12.2 Hz, 1H), 4.20 (s, 1H), 3.64 (s, 3H), 3.23 – 3.06 (m, 1H), 2.51 – 2.33 (m, 2H), 2.15 – 2.03 (m, 1H), 0.80 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.51, 173.56, 150.16, 138.77, 134.56, 130.30, 129.01, 128.96, 128.62, 127.48, 127.06, 125.29, 116.52, 115.30, 69.97, 69.77, 69.46, 62.47, 59.42, 36.11, 33.16, 29.20, 21.35 ppm; HRMS: calc. for $[M+H]^+$ $C_{25}H_{24}O_5N_3$: 446:17105, found: 446:17079.

***Rel*- (1*R*,5*R*,6*S*,7*R*)-1'-acetyl-8-methoxy-5-methyl-2,2'-dioxo-8-azaspiro[bicycle [3.2.1]octane -6,3'-indoline]-7-carbonitrile**



261c, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.44 (td, *J* = 8.1, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 0.9 Hz, 1H), 4.22 (s, 1H), 3.65 (s, 3H), 3.19 – 3.03 (m, 1H), 2.71 (s, 3H), 2.53 – 2.38 (m, 2H), 2.08 – 1.97 (m,1H), 0.81 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.31, 176.13, 170.16, 144.96, 139.64, 130.31, 127.19, 125.67, 116.62, 116.48, 69.97, 69.80, 62.52, 36.04, 33.11, 29.85, 29.32, 27.00, 21.39 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{20}O_4N_3$: 354.14483, found: 354.14499.



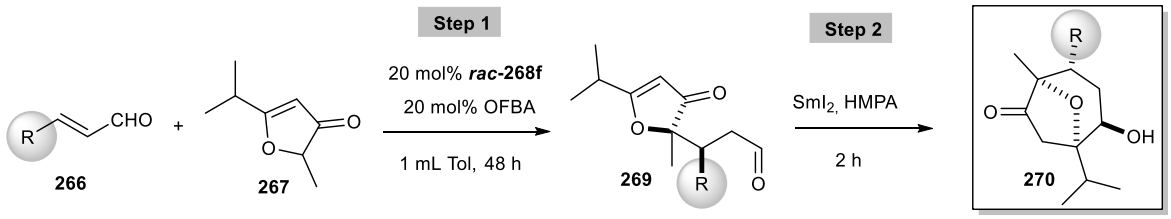
Crystal data and structure refinement for 261a. (by C.-G.D)

Identification code	DAN7627
Empirical formula	$C_{22}\ H_{25}\ N_3\ O_5$
Formula weight	411.45
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1/n$ (No. 14)
Unit cell dimensions	a = 10.0396(2) Å
	b = 8.5802(2) Å β = 92.593(1)°
	c = 24.6644(6) Å
Volume	2122.46(8) $Å^3$

Z, Calculated density	4, 1.288 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	872
Crystal size	0.24 x 0.22 x 0.20 mm
Theta range for data collection	4.32 to 26.37°
Limiting indices	-12<=h<=12, -9<=k<=10, -30<=l<=30
Reflections collected / unique	14660 / 4306 [R(int) = 0.042]
Completeness to theta = 26.37	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9818 and 0.9782
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4306 / 0 / 276
Goodness-of-fit on F^2	1.060
Final R indices [I>2σ(I)]	R1 = 0.0531, wR^2 = 0.1169
R indices (all data)	R1 = 0.0688, wR^2 = 0.1267
Largest diff. peak and hole	0.342 and -0.201 $e.Å^{-3}$

7.4.4 Experimental Detail and Analytic Data for Synthesis of Oxabicyclo[3.2.1]octanes by Aminecatalysis (269a, 270a-o, and 271a-m)

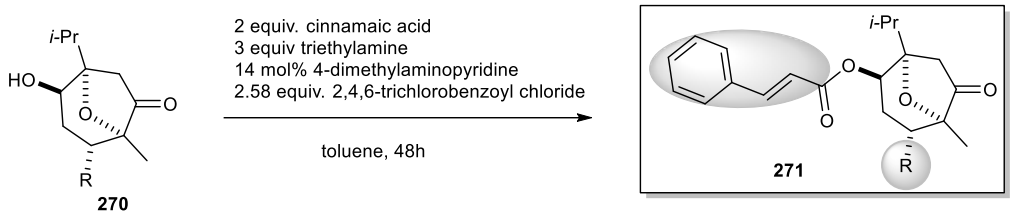
General method for the synthesis of 270:



Cinnamaldehyde **266** (0.15 mmol, 1.50 equiv.), 3-furone **267** (0.10 mmol, 1.00 equiv.), catalyst ***rac*-268f** (0.02 mmol, 0.20 equiv.), OFBA (0.02 mmol, 0.20 equiv.) were added into 1.0 mL toluene. Then the mixture was allowed to be stirred for specific time under room temperature. Direct purification by the silica gel column afforded the Michael adduct **269**.

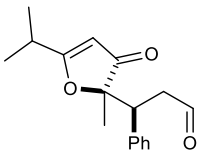
A solution of samarium(II) iodide in THF (0.1 M, 4,00 mL, 400 μmol, 4.00 equiv) was added dropwise to a solution of the Michael adduct **269** (100 μmol, 1 equiv) and HMPA (321 μL,1.85 mmol, 18.5 equiv) in deoxygenated THF (5 mL). The resultant deep purple mixture was stirred at 23°C for 3 h, then was cooled to 0 °C and quenched by the addition aqueous hydrochloric acid solution (1 N, 5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (10 mL), dried over anhydrous sodium sulfate, and the dried solution was concentrated. Purification of the residue by the silica gel column gave the **270**.

General method for the synthesis of 271:



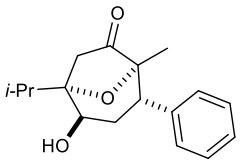
Cinnamic acid (18.0 mg, 120 μmol, 2.00 equiv), triethylamine (25.0 μL, 180 μmol, 3.00 equiv), 2,4,6-trichlorobenzoyl chloride (25.0 μL, 155 μmol, 2.58 equiv) and 4-dimethylaminopyridine (1.0 mg, 8.2 μmol, 0.14 equiv) were added sequentially to a solution of 8 (16.0 mg, 60.0 μmol, 1 equiv) in toluene (2 mL). The resultant mixture was stirred at 23 °C for 2 d, then quenched with aqueous hydrochloric acid solution (1 N, 5 mL). The organic layer of reaction reaction mixture was directly loaded on the silica gel column.

***Rel*-(*S*)-3-((*R*)-5-isopropyl-2-methyl-3-oxo-2,3-dihydrofuran-2-yl)-3-phenylpropanal**



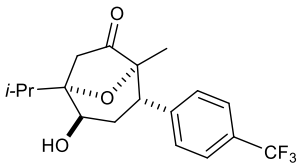
***rac*-269a**, for major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.24 – 7.13 (m, 5H), 5.08 (s, 3H), 3.77 – 3.66 (m, 1H), 3.12 – 3.05 (m, 1H), 2.64 – 2.55 (m, 1H), 1.39 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.12 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.44, 200.77, 197.39, 137.48, 129.66, 128.50, 127.89, 101.31, 91.19, 44.46, 43.61, 30.58, 20.52, 19.93, 19.88 ppm; HRMS: calc. for $[M+H]^+$ $C_{17}H_{21}O_3$: 273.14852, found: 273.14815.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-phenyl-8-oxabicyclo[3.2.1]octan-6-one**



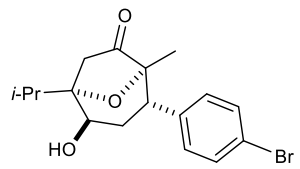
270a, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 – 7.24 (m, 3H), 7.13 – 7.11 (m, 2H), 4.24 (dd, *J* = 10.4, 5.8 Hz, 1H), 2.90 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.45 (d, *J* = 18.8 Hz, 1H), 2.30 – 2.18 (m, 1H), 2.17 – 2.04 (m, 1H), 1.92 – 1.77 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.04 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.69, 138.76, 128.50, 128.47, 127.56, 83.61, 82.83, 69.15, 50.22, 40.65, 35.64, 32.86, 18.78, 17.49, 16.84 ppm; HRMS: calc. for $[M+H]^+$ $C_{17}H_{23}O_3$: 275.16417, found: 275.16428.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-(4-(trifluoromethyl)phenyl)-8-oxabicyclo[3.2.1]octan-6-one**



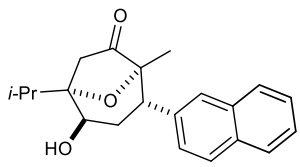
270b, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.26 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.97 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.73 (d, *J* = 18.9 Hz, 1H), 2.47 (d, *J* = 18.9 Hz, 1H), 2.32 – 2.17 (m, 1H), 2.18 – 2.05 (m, 1H), 1.93 – 1.75 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.03 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.46, 142.64, 129.81, 128.72, 125.29 (q, *J* = 3.7 Hz), 83.08, 82.87, 68.74, 49.88, 40.50, 35.30, 32.67, 18.60, 17.32, 16.66 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(4-bromophenyl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo [3.2.1]octan-6-one**



270c, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 4.23 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.87 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.70 (d, *J* = 18.8 Hz, 1H), 2.45 (d, *J* = 18.8 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.17 – 2.01 (m, 1H), 1.86 – 1.71 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.02 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.67, 137.77, 131.61, 130.17, 121.56, 83.30, 82.93, 68.98, 49.64, 40.65, 35.54, 32.83, 18.73, 17.48, 16.83 ppm.

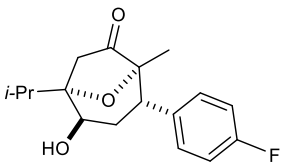
***Rel*-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-(naphthalen-2-yl)-8-oxabicyclo [3.2.1]octan-6-one**



270d, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 – 7.73 (m, 3H), 7.60 (s, 1H), 7.52 – 7.41 (m, 2H), 7.25 (d, *J* = 8.5 Hz, 1H), 4.29 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.08 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.78 (d, *J* = 18.7 Hz, 1H), 2.49 (d, *J* = 18.7 Hz,1H), 2.34 – 2.21 (m, 1H),

2.14 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.03 – 1.88 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.08 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.76, 136.34, 133.42, 132.92, 128.03, 128.02, 127.68, 127.42, 126.60, 126.20, 125.97, 83.75, 82.91, 69.18, 50.36, 40.71, 35.80, 32.90, 18.90, 17.52, 16.87 ppm.

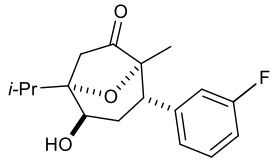
***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(4-fluorophenyl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo [3.2.1]octan-6-one**



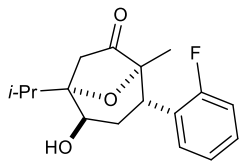
270e, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 – 7.04 (m, 2H), 7.02 – 6.92 (m, 2H), 4.22 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.87 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 2.50 – 2.34 (m, 1H), 2.25 – 2.14 (m, 1H), 2.13 – 1.98 (m, 1H), 1.85 – 1.70 (m, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.00 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.78, 162.29 (d, *J* = 245.8 Hz), 134.53, 129.95 (d, *J* = 8.0 Hz), 115.32 (d, *J* = 21.2 Hz), 83.48, 82.88, 69.07, 49.42, 40.67, 35.84, 32.85, 18.73, 17.49, 16.84 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(3-fluorophenyl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo [3.2.1]octan-6-one**

270f, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 – 7.23 (m, 1H), 7.00 – 6.94 (m, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.88 – 6.81 (m, 1H), 4.23 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.90 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.45 (dd, *J* = 18.8, 0.7 Hz, 1H), 2.30 – 2.16 (m, 1H), 2.16 – 2.03 (m, 1H), 1.85 – 1.73 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.05 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.55, 162.79 (d, *J* = 245.8 Hz), 141.31 (d, *J* = 7.0 Hz), 129.89 (d, *J* = 8.3 Hz), 124.20 (d, *J* = 2.8 Hz), 115.50 (d, *J* = 21.0 Hz), 114.47 (d, *J* = 21.0 Hz), 83.34, 82.93, 68.98, 49.92, 49.91, 40.63, 35.63, 32.84, 18.75, 17.47, 16.82 ppm.



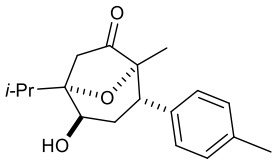
***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(2-fluorophenyl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo [3.2.1]octan-6-one**



270g, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 – 7.20 (m, 1H), 7.16 – 7.07 (m, 2H), 7.07 – 6.99 (m, 1H), 4.27 (dd, *J* = 10.3, 5.9 Hz, 1H), 3.43 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.45 (d, *J* = 18.8 Hz, 1H), 2.23 – 2.03 (m, 2H), 1.88 – 1.76 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.68, 161.07 (d, *J* = 241.7 Hz), 128.79 (d, *J* = 8.6 Hz), 128.56 (d, *J* = 3.3 Hz), 125.75 (d, *J* = 14.0

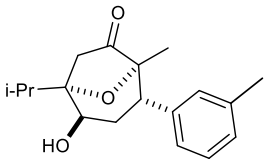
Hz), 124.22 (d, *J* = 3.7 Hz), 115.45 (d, *J* = 23.5 Hz), 83.67, 82.89, 68.99, 40.62, 34.62, 32.86, 17.91, 17.87, 17.49, 16.83 ppm.

Rel-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-(*p*-tolyl)-8-oxabicyclo[3.2.1]octan-6-one



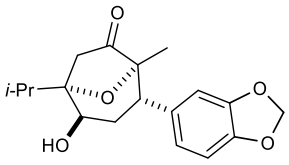
270h, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 4.23 (dd, *J* = 10.2, 5.6 Hz, 1H), 2.87 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.44 (d, *J* = 19.0 Hz, 1H), 2.33 (s, 3H), 2.27 – 2.16 (m, 1H), 2.16 – 2.04 (m, 1H), 1.92 – 1.77 (m, *J* = 13.7, 10.5 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.80, 137.20, 135.70, 129.14, 128.33, 83.69, 82.79, 69.15, 49.76, 40.63, 35.63, 32.83, 21.16, 18.76, 17.47, 16.83 ppm.

Rel-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-(*m*-tolyl)-8-oxabicyclo[3.2.1]octan-6-one



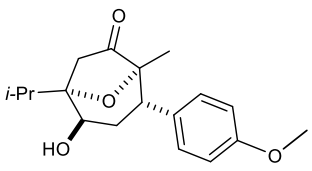
270i, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 – 7.14 (m, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.96 – 6.86 (m, 1H), 4.23 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.86 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.44 (d, *J* = 18.8 Hz, 1H), 2.38 – 2.28 (m, 2H), 2.27 – 2.15 (m, 1H), 2.11 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.04 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.69, 138.71, 137.97, 129.27, 128.32, 128.30, 125.57, 83.64, 82.80, 69.16, 50.13, 40.63, 35.69, 32.86, 21.61, 18.80, 17.48, 16.84 ppm.

Rel-(1*S*,2*R*,4*S*,5*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo[3.2.1]octan-6-one



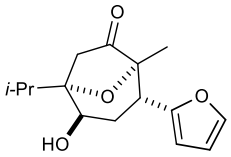
270j, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.54 (m, 2H), 5.95 (s, 2H), 4.21 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.82 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 2.43 (d, *J* = 19.2 Hz, 1H), 2.24 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 1.82 – 1.68 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.05 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.83, 147.67, 146.97, 132.63, 121.93, 108.63, 108.18, 101.14, 83.65, 82.81, 69.12, 49.86, 40.65, 35.95, 32.83, 18.76, 17.47, 16.83 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-4-(4-methoxyphenyl)-5-methyl-8-oxabicyclo [3.2.1]octan-6-one**



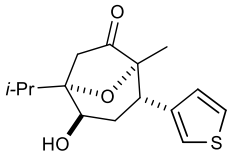
270k, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.23 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.80 (s, 3H), 2.85 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.69 (d, *J* = 18.8 Hz, 1H), 2.44 (d, *J* = 18.8 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.17 – 2.02 (m, 1H), 1.86 – 1.72 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.88, 159.03, 130.87, 129.44, 113.84, 83.77, 82.78, 69.20, 55.36, 49.33, 40.67, 35.81, 32.86, 18.76, 17.49, 16.85 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(furan-2-yl)-2-hydroxy-1-isopropyl-5-methyl-8-oxabicyclo[3.2.1] octan-6-one**



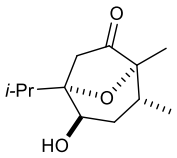
270l, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.30 (m, 1H), 6.37 – 6.28 (m, 1H), 6.12 – 6.03 (m, 1H), 4.20 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.04 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.63 (d, *J* = 18.8 Hz, 1H), 2.40 (d, *J* = 18.8 Hz, 1H), 2.27 (dt, *J* = 13.6, 5.4 Hz, 1H), 2.09 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.75 (td, *J* = 13.7, 10.8 Hz, 1H), 1.19 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.10 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 214.40, 152.72, 141.75, 110.41, 106.73, 83.28, 82.80, 68.61, 43.10, 40.23, 33.51, 32.85, 18.67, 17.47, 16.84 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-(thiophen-3-yl)-8-oxabicyclo[3.2.1] octan-6-one**



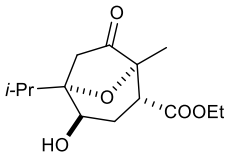
270m, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 – 7.24 (m, 1H), 7.06 – 6.99 (m, 1H), 6.95 – 6.83 (m, 1H), 4.30 – 4.15 (m, 1H), 3.05 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.43 (d, *J* = 18.9 Hz, 1H), 2.26 (dt, *J* = 13.6, 5.3 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.74 (td, *J* = 13.6, 10.6 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz,3H), 1.09 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.79, 139.59, 127.57, 125.37, 122.23, 83.54, 82.82, 68.97, 45.43, 40.64, 36.38, 32.86, 18.82, 17.49, 16.84 ppm.

***Rel*-(1*S*,2*R*,4*R*,5*R*)-2-hydroxy-1-isopropyl-4,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-one**



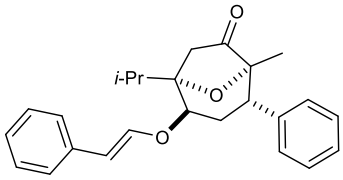
270n, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.07 (dd, *J* = 10.7, 5.9 Hz, 1H), 2.46 (d, *J* = 18.7 Hz, 1H), 2.30 (d, *J* = 18.7 Hz,1H), 2.09 – 1.93 (m, 2H), 1.82 – 1.66 (m, 1H), 1.19 (s, 3H), 1.09 – 1.04 (m, 7H), 0.84 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 216.30, 84.22, 82.64, 69.05, 40.33, 37.92, 37.52, 32.88, 17.97, 17.52, 16.91, 15.15 ppm.

***Rel*-ethyl (1*R*,2*R*,4*R*,5*S*)-4-hydroxy-5-isopropyl-1-methyl-7-oxo-8-oxabicyclo[3.2.1] octane-2-carboxylate**



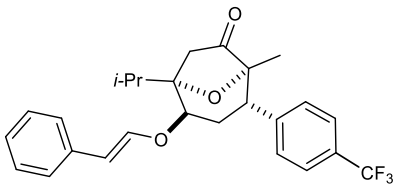
270o, for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.25 – 4.05 (m, 3H), 2.69 (dd, *J* = 13.1, 5.2 Hz, 1H), 2.63 (d, *J* = 18.9 Hz, 1H), 2.36 (dd, *J* = 18.9, 0.8 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.06 (dd, *J* = 13.9, 6.9 Hz, 1H), 1.91 – 1.77 (m, 1H), 1.28 (dd, *J* = 14.0, 6.9 Hz, 6H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.07 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 212.92, 170.04, 83.11, 81.41, 67.93, 61.18, 48.83, 39.74, 32.95, 31.04, 18.73, 17.39, 16.74, 14.23 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-4-phenyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1] octan-6-one**



271a, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.48 – 7.37 (m, 3H), 7.33 – 7.23 (m, 3H), 7.18 – 7.10 (m, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.48 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.01 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.86 (d, *J* = 18.7 Hz, 1H), 2.59 (d, *J* = 18.7 Hz, 1H), 2.49 (dt, *J* = 13.5, 5.4 Hz, 1H), 2.07 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.90 (td, *J* = 13.7, 10.6 Hz, 1H), 1.13 – 1.06 ppm (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.14, 165.72, 145.79, 138.39, 134.27, 130.72, 129.09, 128.48, 128.31, 127.63, 117.70, 84.05, 81.91, 70.43, 49.98, 42.16, 33.63, 32.39, 18.85, 17.59, 16.72 ppm; HRMS: calc. for $[M+H]^+$ $C_{19}H_{20}O_4$: 405.20604, found: 405.20583.

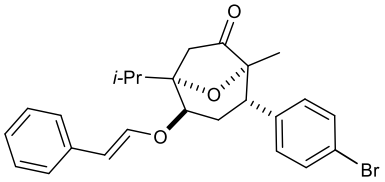
***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-4-(4-(trifluoromethyl) phenyl)-8-oxabicyclo[3.2.1]octan-6-one**



271b, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.46 (m, 3H), 7.46 – 7.33 (m, 3H), 7.28 – 7.22 (m, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.45 (dd, *J* = 10.3, 5.9 Hz,

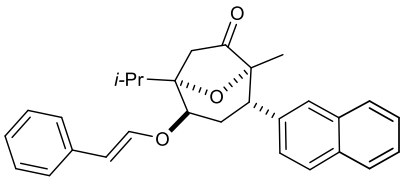
1H), 3.06 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.85 (d, *J* = 18.7 Hz, 1H), 2.59 (d, *J* = 18.7 Hz, 1H), 2.47 (dt, *J* = 13.4, 5.2 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.93 – 1.76 (m, 1H), 1.14 – 0.97 ppm (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.10, 165.63, 146.03, 134.32, 130.82, 129.12, 128.87, 128.34, 125.47, 118.66, 117.51, 83.78, 82.13, 70.14, 49.80, 42.19, 33.61, 32.03, 18.83, 17.57, 16.71 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(4-bromophenyl)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1]octan-6-one**



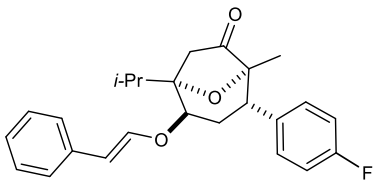
271c, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.53 (dd, *J* = 6.7, 2.8 Hz, 2H), 7.44 – 7.36 (m, 4H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.43 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.95 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.82 (d, *J* = 18.6 Hz, 1H), 2.57 (d, *J* = 18.6 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.10 – 1.99 (m, 1H), 1.81 (td, *J* = 13.7, 10.5 Hz, 1H), 1.14 – 1.00 ppm (m, 9H).

***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-4-(naphthalen-2-yl)-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1]octan-6-one**



271d, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 – 7.78 (m, 2H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.57 – 7.50 (m, 2H), 7.49 – 7.42 (m, 2H), 7.42 – 7.35 (m, 3H), 7.26 – 7.21 (m, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.51 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.17 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.90 (d, *J* = 18.6 Hz, 1H), 2.61 (d, *J* = 18.7 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.11 – 2.03 (m, *J* = 14.4, 7.5 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.13 – 1.04 ppm (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.23, 165.75, 145.85, 135.95, 134.27, 133.41, 132.94, 130.73, 129.09, 128.32, 128.05, 127.67, 127.46, 126.53, 126.20, 125.98, 117.69, 84.20, 82.01, 70.45, 50.11, 42.23, 33.66, 32.50, 18.97, 17.62, 16.75 ppm.

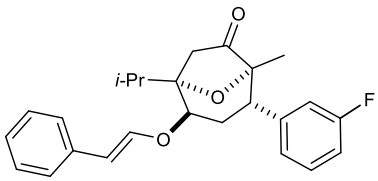
***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(4-fluorophenyl)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1]octan-6-one**



271e, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.45 – 7.34 (m, 3H), 7.09 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.03 – 6.85 (m, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.44 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.98 (dd, *J* = 13.9, 4.8 Hz,

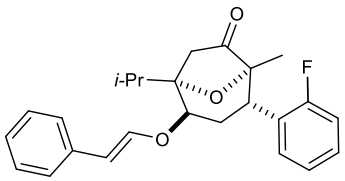
1H), 2.82 (d, *J* = 18.7 Hz, 1H), 2.57 (d, *J* = 18.7 Hz, 1H), 2.46 (dt, *J* = 13.6, 5.4 Hz, 1H), 2.05 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.81 (td, *J* = 13.7, 10.5 Hz, 1H), 1.16 – 0.96 ppm (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.26, 165.73, 162.32 (d, *J* = 245.9 Hz), 145.90, 134.18 (d, *J* = 3.3 Hz), 130.76, 129.96 (d, *J* = 8.0 Hz), 129.10, 128.32, 117.61, 115.35 (d, *J* = 21.2 Hz), 83.94, 81.98, 70.33, 49.19, 42.19, 33.61, 32.59, 18.80, 17.58, 16.71ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(3-fluorophenyl)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1]octan-6-one**



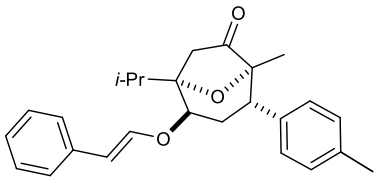
271f, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.43 – 7.36 (m, 3H), 7.25 – 7.20 (m, 1H), 6.98 – 6.92 (m, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 10.1 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.44 (dd, *J* = 10.3, 6.1 Hz, 1H), 2.99 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.83 (d, *J* = 18.7 Hz, 1H), 2.57 (d, *J* = 18.7 Hz, 1H), 2.47 (dt, *J* = 13.5, 5.2 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.82 (td, *J* = 13.7, 10.6 Hz, 1H), 1.13 – 1.00 ppm (m, 9H).

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(2-fluorophenyl)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1]octan-6-one**



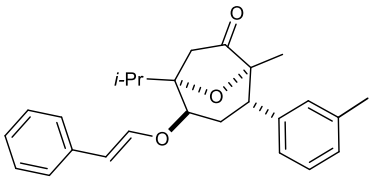
271g, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.45 – 7.36 (m, 3H), 7.24 – 7.17 (m, 1H), 7.15 – 6.96 (m, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.46 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.51 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.83 (d, *J* = 18.7 Hz, 1H), 2.57 (d, *J* = 18.6 Hz, 1H), 2.42 (dt, *J* = 13.3, 5.4 Hz, 1H), 2.14 – 1.98 (m, 1H), 1.92 – 1.79 (m, *J* = 10.7 Hz, 1H), 1.14 – 1.01 ppm (m, 9H).

***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-4-(*p*-tolyl)-8-oxabicyclo [3.2.1]octan-6-one**



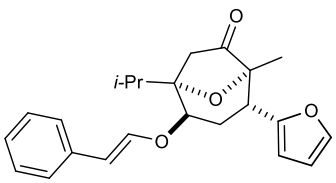
271h, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.45 – 7.30 (m, 3H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.44 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.95 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.82 (d, *J* = 18.7 Hz, 1H), 2.56 (d, *J* = 18.7 Hz, 1H), 2.44 (dt, *J* = 13.5, 5.4 Hz, 1H), 2.31 (s, 3H), 2.12 – 1.98 (m, 1H), 1.95 – 1.75 (m, 1H), 1.12 – 0.97 ppm (m, 9H).

***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-4-(*m*-tolyl)-8-oxabicyclo [3.2.1]octan-6-one**



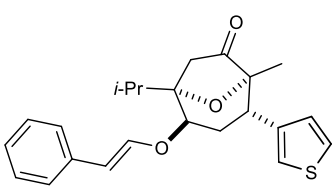
271i, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.44 – 7.35 (m, 3H), 7.20 – 7.13 (m, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.91 (s, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.45 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.95 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.83 (d, *J* = 18.7 Hz, 1H), 2.56 (d, *J* = 18.7 Hz, 1H), 2.45 (dt, *J* = 13.5, 5.3 Hz, 1H), 2.33 (s, 3H), 2.04 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.87 (td, *J* = 13.9, 10.6 Hz, 1H), 1.11 – 1.04 ppm (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.13, 165.72, 145.76, 138.34, 137.99, 134.29, 130.71, 129.23, 129.09, 128.38, 128.33, 128.31, 125.56, 117.74, 110.14, 84.10, 81.88, 70.48, 49.90, 42.15, 33.64, 32.43, 21.60, 18.88, 17.60, 16.74 ppm.

***Rel*-(1*S*,2*R*,4*S*,5*R*)-4-(furan-2-yl)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo [3.2.1]octan-6-one**



271j, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.43 – 7.37 (m, 3H), 7.33 – 7.29 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.40 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.12 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.76 (d, *J* = 18.7 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.03 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.80 (td, *J* = 13.7, 10.6 Hz, 1H), 1.21 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.04 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.84, 165.73, 152.25, 145.89, 141.88, 134.26, 130.76, 129.11, 128.33, 117.64, 110.38, 106.95, 83.69, 81.91, 69.86, 42.89, 41.74, 33.62, 30.18, 18.74, 17.56, 16.72 ppm.

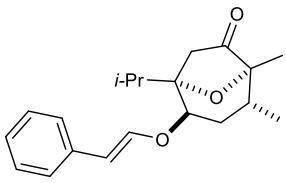
***Rel*-(1*S*,2*R*,4*S*,5*R*)-1-isopropyl-5-methyl-2-(((*E*)-styryl)oxy)-4-(thiophen-3-yl)-8-oxabicyclo[3.2.1]octan-6-one**



271k, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.43 – 7.35 (m, 3H), 7.23 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.04 (dd, *J* = 2.7, 1.0 Hz, 1H), 6.88 (dd, *J* = 5.0, 1.1 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.41 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.14 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.80 (d, *J* = 18.7 Hz, 1H), 2.56 (d, *J* = 18.6 Hz, 1H), 2.50 (dt, *J* = 13.6, 5.4 Hz, 1H), 2.04 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.76 (td, *J* = 13.7, 10.6 Hz, 1H), 1.12 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.06 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ =

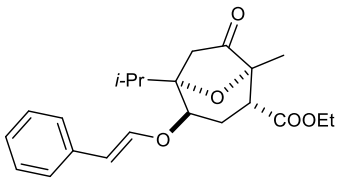
215.28, 165.71, 145.82, 139.17, 134.26, 130.73, 129.09, 128.31, 127.48, 125.42, 122.34, 117.66, 83.97, 81.91, 70.23, 45.21, 42.15, 33.62, 33.13, 18.88, 17.58, 16.72 ppm.

***Rel*-(1*S*,2*R*,4*R*,5*R*)-1-isopropyl-4,5-dimethyl-2-(((*E*)-styryl)oxy)-8-oxabicyclo[3.2.1] octan-6-one**



271l, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.43 – 7.33 (m, 3H), 6.38 (d, *J* = 16.0 Hz, 1H), 5.30 (dd, *J* = 10.6, 6.0 Hz, 1H), 2.61 (d, *J* = 18.6 Hz, 1H), 2.44 (d, *J* = 18.6 Hz, 1H), 2.27 (dt, *J* = 13.5, 5.6 Hz, 1H), 2.07 – 1.89 (m, 1H), 1.91 – 1.78 (m, 1H), 1.25 (s, 3H), 1.12 (td, *J* = 13.3, 10.8 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.86 ppm (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.71, 165.83, 145.62, 134.31, 130.68, 129.08, 128.30, 117.85, 84.67, 81.73, 70.47, 41.88, 37.73, 33.96, 33.63, 18.04, 17.61, 16.78, 15.02 ppm.

***Rel*-ethyl (1*R*,2*R*,4*R*,5*S*)-5-isopropyl-1-methyl-7-oxo-4-(((*E*)-styryl)oxy)-8-oxabicyclo [3.2.1]octane-2-carboxylate**



271m, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.47 – 7.39 (m, 3H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.32 (dd, *J* = 10.8, 6.1 Hz, 1H), 4.27 – 4.01 (m, 2H), 2.82 – 2.66 (m, 2H), 2.48 (d, *J* = 18.8 Hz, 1H), 2.41 (dt, *J* = 13.8, 5.7 Hz, 1H), 2.06 – 1.95 (m, 1H), 1.88 (td, *J* = 13.6, 10.9 Hz, 1H), 1.33 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.01 ppm (d, *J* = 7.2 Hz, 3H).

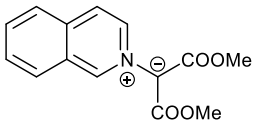
7.5 Experimental Part for Synthesis of Pyrroloisoquinolines

7.5.1 Experimenal Details and Analytic Data for Synthesis of Isoquinolinium Methylides 293a-p

General Method:

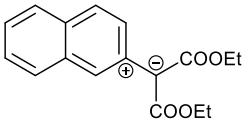
To the mixture of 2-bromomalonate and acetone 30 mL was added isoquinoline. The mixture was stirred for 24 h under r.t., and the resulting precipitate was filtered out and recrystalized in *i*-PrOH and ether to give colorless solid. Then the solid was disolved in water and basified with KCO_3(aq) and extracted with $CHCl_3$. Recrystalization gives yellow needle.

2-(Isoquinolin-2-ium-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-ide



293a, 65% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.28 (s, 1H), 8.30 (d, *J* = 6.8 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.00 – 8.01 (m, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 6.9 Hz, 1H), 7.83 (ddd, *J* = 8.1, 5.3, 2.8 Hz, 1H), 3.73 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.49, 141.41, 136.37, 135.64, 130.21, 129.75, 127.74, 126.85, 123.55, 97.35, 54.93, 50.74 ppm; FT-IR: $\tilde{\nu}$ = 3067, 2948, 1702, 1589, 1440, 1368, 1075 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{14}NO_4$: 260.09173, found: 260.09195.

1,3-Diethoxy-2-(isoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide

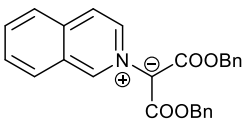


293b, 73% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.28 (s, 1H), 8.31 (d, *J* = 6.9 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.00 – 7.88 (m, 2H), 7.94 (d, *J* = 6.9 Hz, 1H), 7.88 – 7.77 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 4H), 1.29 ppm (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.26, 141.40, 136.22, 135.46, 130.11, 129.68, 127.69, 126.81, 123.32, 97.59, 64.64, 59.12, 14.95 ppm; FT-IR: $\tilde{\nu}$ = 3081, 2976, 1655, 1605, 1409, 1372, 1330, 1170, 1049 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{16}H_{18}NO_4$: 288.12303, found: 288.12299.

General Method:

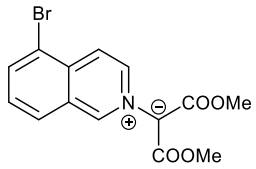
To a solution of the $Cu(acac)_2$ (1 mol %) in 5 mL of CH_2Cl_2 were added the corresponding isoquinolines (1.0 mmol) and iodonium ylides (1.2 mmol). The reaction was stirred at room temperature to 40°C. After reaction completion monitored by TLC, the solution was then concentrated and purified by chromatography on silica gel to give the corresponding isoquinolinium methylides.

1,3-Bis(benzyloxy)-2-(isoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



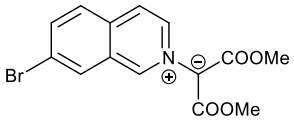
293c, 78% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.37 (d, *J* = 6.8 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.03 – 7.99 (m, 2H), 7.96 (d, *J* = 6.9 Hz, 1H), 7.83 (dt, *J* = 8.2, 4.0 Hz, 1H), 7.44 – 7.36 (m, 4H), 7.33 – 7.23 (m, 6H), 5.28 ppm (s, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.38, 141.32, 137.98, 136.29, 135.57, 130.15, 129.73, 128.41, 127.78, 127.69, 127.41, 126.81, 123.43, 64.97 ppm; FT-IR: $\tilde{\nu}$ = 3031, 2949, 1709, 1575, 1384, 1282, 1052 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{22}NO_4$: 412.15433, found: 412.15440.

2-(5-Bromoisoquinolin-2-ium-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-ide



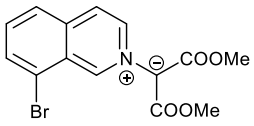
293d, 52% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 8.42 (d, *J* = 6.2 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.87 – 7.76 (m, 1H), 3.76 ppm (s, 6H); FT-IR: $\tilde{\nu}$ = 3023, 2943, 1701, 1590, 1440, 1377, 1359, 1080 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00255; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00045;

2-(7-Bromoisoquinolin-2-ium-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-ide



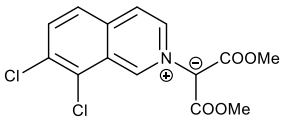
293e, 80% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1H), 8.47 – 8.21 (m, 2H), 8.15 – 8.00 (m, 1H), 8.00 – 7.78 (m, 2H), 3.76 ppm (s, 6H); FT-IR: $\tilde{\nu}$ = 3112, 2947, 1701, 1587, 1442, 1374, 1083, 1077 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00268; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00052;

2-(8-Bromoisoquinolin-2-ium-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-ide



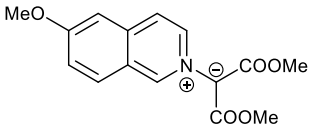
293f, 62% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 8.40 (d, *J* = 6.8 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.81 (t, *J* = 7.9 Hz, 1H), 3.76 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.60, 153.44, 142.27, 137.90, 135.69, 134.21, 127.26, 126.39, 124.30, 123.68, 50.93 ppm; FT-IR: $\tilde{\nu}$ = 3064, 2948, 1626, 1597, 1439, 1337, 1187, 1075 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00257; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00050;

2-(7,8-Dichloroisoquinolin-2-ium-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-ide



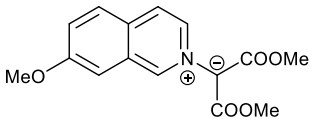
293g, 51% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 8.43 (dd, *J* = 6.8, 1.0 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 3.76 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.56, 150.42, 142.40, 136.66, 135.75, 135.30, 131.80, 127.04, 126.22, 123.35, 50.94 ppm; FT-IR: $\tilde{\nu}$ = 3039, 2944, 1585, 1436, 1337, 1183, 1111, 1054 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{12}Cl_2NO_4$: 328.01379, found: 328.01438.

1,3-Dimethoxy-2-(6-methoxyisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



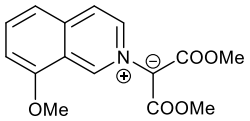
293h, 55% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.04 (s, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.25 – 7.20 (m, 1H), 4.04 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.88, 165.48, 152.34, 141.80, 139.40, 131.57, 123.48, 123.21, 122.09, 104.86, 56.36, 50.68 ppm; FT-IR: $\tilde{\nu}$ = 2944, 2847, 1588, 1434, 1337, 1266, 1184, 1091 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10282.

1,3-Dimethoxy-2-(7-methoxyisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



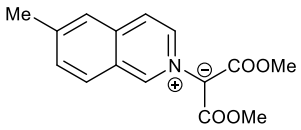
293i, 58% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.18 (d, *J* = 6.8 Hz, 1H), 7.97 – 7.78 (m, 2H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.33 (s, 1H), 3.97 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.82, 160.56, 151.68, 139.68, 132.28, 129.56, 129.19, 128.27, 123.29, 106.17, 56.09, 50.72 ppm; FT-IR: $\tilde{\nu}$ = 3084, 2946, 1705, 1587, 1436, 1375, 1263, 1078 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10236.

1,3-Dimethoxy-2-(8-methoxyisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



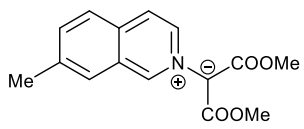
293j, 61% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 8.21 (d, *J* = 6.9 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.92, 157.75, 150.07, 141.73, 137.38, 137.14, 122.99, 120.39, 118.28, 107.90, 56.39, 50.64 ppm; FT-IR: $\tilde{\nu}$ = 3045, 2938, 1596, 1428, 1344, 1213, 1085 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10268.

1,3-Dimethoxy-2-(6-methylisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



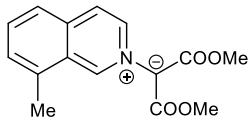
293k, 55% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 8.23 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 6.8 Hz, 1H), 7.82 – 7.71 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 3.73 (s, 6H), 2.66 ppm (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.96, 153.09, 147.64, 141.46, 136.81, 132.53, 129.52, 126.12, 125.92, 122.87, 96.87, 50.72, 22.80 ppm; FT-IR: $\tilde{\nu}$ = 3033, 2943, 1585, 1334, 1189, 1090 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10747.

1,3-Dimethoxy-2-(7-methylisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



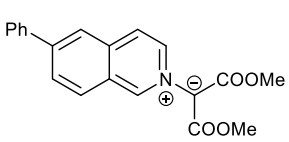
293l, 58% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.23 (d, *J* = 6.7 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.85 – 7.78 (m, 1H), 3.72 (s, 6H), 2.61 ppm (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.79, 152.91, 140.91, 140.67, 138.02, 134.77, 130.08, 128.31, 128.05, 126.56, 123.30, 50.68, 21.90 ppm; FT-IR: $\tilde{\nu}$ = 3093, 2948, 1702, 1588, 1438, 1372, 1071 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10748.

1,3-Dimethoxy-2-(8-methylisoquinolin-2-ium-2-yl)-1,3-dioxopropan-2-ide



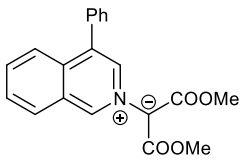
293m, 60% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H), 8.29 (d, *J* = 6.7 Hz, 1H), 7.95 (d, *J* = 6.7 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.62 (d, *J* = 6.7 Hz, 1H), 3.74 (s, 6H), 2.80 ppm (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.71, 151.10, 141.11, 138.33, 137.08, 135.59, 130.88, 127.44, 124.97, 123.97, 50.73, 18.57 ppm; FT-IR: $\tilde{\nu}$ = 3042, 2940, 1592, 1432, 1346, 1198, 1091 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10751.

1,3-Dimethoxy-1,3-dioxo-2-(6-phenylisoquinolin-2-ium-2-yl)propan-2-ide



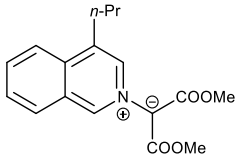
293n, 67% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.30 (s, 1H), 8.25 – 8.13 (m, 2H), 8.13 – 8.03 (m, 1H), 8.03 – 7.94 (m, 1H), 7.83 – 7.68 (m, 2H), 7.65 – 7.44 (m, 3H), 3.76 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.80, 153.06, 152.00, 141.68, 140.83, 138.61, 130.26, 130.01, 129.76, 129.56, 127.91, 126.75, 124.16, 123.55, 50.81 ppm; FT-IR: $\tilde{\nu}$ = 3017, 2952, 1574, 1439, 1350, 1186, 1080 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{18}BrNO_4$: 336.12303, found: 336.12326.

1,3-Dimethoxy-1,3-dioxo-2-(4-phenylisoquinolin-2-ium-2-yl)propan-2-ide



293o, 72% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 8.33 – 8.16 (m, 2H), 8.04 (d, 1H), 8.00 – 7.93 (m, 1H), 7.90 – 7.78 (m, 1H), 7.61 – 7.46 (m, 5H), 3.76 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.87, 165.84, 152.15, 140.40, 137.39, 136.96, 135.64, 134.28, 133.60, 130.07, 129.59, 129.25, 128.06, 125.51, 50.86 ppm; FT-IR: $\tilde{\nu}$ = 2945, 1611, 1434, 1364, 1176, 1074 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{18}BrNO_4$: 336.12303, found: 336.12375.

1,3-Dimethoxy-1,3-dioxo-2-(4-propylisoquinolin-2-ium-2-yl)propan-2-ide

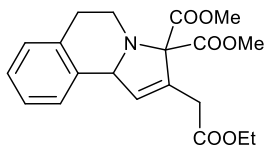


293p, 72% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.14 (s, 1H), 8.18 – 8.10 (m, 3H), 8.06 – 7.96 (m, 1H), 7.87 – 7.76 (m, 1H), 3.73 (s, 6H), 3.06 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.71 (m, 3H), 1.07 ppm (t, *J* = 7.3 Hz, 3H).; ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 151.84, 140.04, 136.26, 135.97, 135.28, 130.57, 129.72, 127.88, 123.48, 50.71, 32.06, 23.04, 14.05 ppm; FT-IR: $\tilde{\nu}$ = 2943, 1707, 1624, 1434, 1367, 1171, 1072 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{17}H_{20}NO_4$: 302.13868, found: 302.13920.

7.5.2 Experimenal Details and Analytic Data for Synthesis of Pyrroloisoquinolines 294a-v

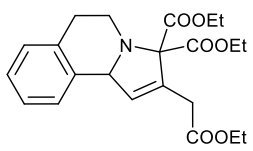
General Method: Reactions were performed with **293a** (0.1 mmol), **278** (0.15 mmol), PBu_3 (0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature. After reactions completed, $NaBH_4$ (0.3 mmol) and acetic acid or trifluoroacetic acid (1 mmol) were added sequentially at 0°C, and the reaction mixture was stirred for 10 minutes. Then the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 ml). The combined organic phase was dried over with $MgSO_4$ and solvent was removed under reduced pressure. The crude residue was purified by silica gel flash chromatography to give the desired product.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



294a: 75% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.19 – 7.07 (m, 4H), 6.51 (d, *J* = 1.3 Hz, 1H), 5.17 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 3.45 – 3.34 (m, 2H), 3.33 (d, *J* = 1.3 Hz, 2H), 2.95 – 2.83 (m, 1H), 2.70 (dd, *J* = 12.2, 8.0 Hz, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.57, 169.31, 169.26, 137.08, 134.77, 133.21, 133.05, 129.01, 126.43, 126.04, 124.39, 81.51, 65.53, 60.94, 52.64, 52.52, 42.47, 33.98, 28.34, 14.32 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2841, 1731, 1452, 1235, 1138, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{24}NO_6$: 374.15981, found: 374.15949.

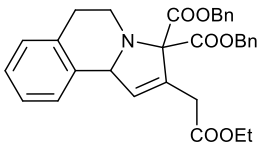
Diethyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



294b: 95% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.20 – 7.07 (m, 4H), 6.54 (s, 1H), 5.23 (s, 1H), 4.33 – 4.22 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.01 (m, 2H), 3.48 (s, 1H), 3.41 – 3.30 (m, 3H), 2.98 – 2.87 (m,

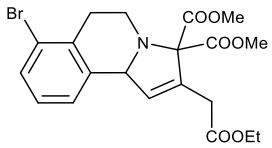
1H), 2.83 – 2.71 (m, *J* = 15.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.06 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.55, 168.59, 136.40, 134.94, 133.20, 132.47, 128.70, 126.68, 126.20, 124.40, 81.81, 65.60, 61.90, 60.96, 43.10, 33.99, 28.54, 14.31, 14.25, 13.79 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2932, 1728, 1447, 1369, 1225, 1147, 1027 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{22}H_{28}NO_6$: 402.19111, found: 402.19064.

Dibenzyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



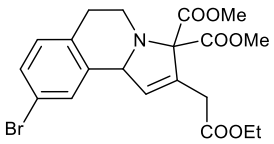
294c: 84% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.38 – 7.31 (m, 5H), 7.31 – 7.24 (m, 3H), 7.20 – 7.13 (m, 2H), 7.14 – 7.06 (m, 4H), 6.56 (d, *J* = 1.4 Hz, 1H), 5.28 – 5.24 (m, 1H), 5.21 (s, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.08 (qd, *J* = 7.1, 3.5 Hz, 2H), 3.39 (ddd, *J* = 8.7, 5.3, 3.5 Hz, 2H), 3.34 (d, *J* = 8.7 Hz, 2H), 2.89 – 2.76 (m, 1H), 2.65 (dt, *J* = 16.1, 4.4 Hz, 1H), 1.22 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.54, 137.17, 135.49, 135.03, 134.92, 133.01, 132.97, 128.99, 128.66, 128.59, 128.38, 128.34, 128.23, 128.18, 126.47, 126.03, 124.31, 81.81, 67.47, 67.39, 65.62, 60.88, 42.56, 33.91, 28.44, 14.25 ppm; FT-IR: $\tilde{\nu}$ = 2979, 1731, 1454, 1368, 1139, 1026 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{32}H_{32}NO_6$: 526.22241, found: 526.22278.

Dimethyl 7-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



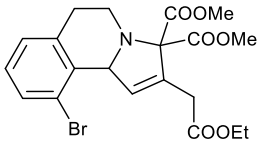
294d: 51% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.5 Hz, 1H), 7.11 – 6.99 (m, 2H), 6.47 (d, *J* = 1.2 Hz, 1H), 5.13 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.82 (dd, *J* = 7.8, 2.3 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.55 (ddd, *J* = 12.8, 6.7, 2.8 Hz, 1H), 3.37 – 3.28 (m, 3H), 2.81 (dd, *J* = 9.9, 6.9 Hz, 1H), 2.74 (d, *J* = 3.4 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.50, 169.05, 139.35, 134.34, 133.60, 132.87, 130.57, 127.26, 125.69, 123.62, 81.05, 65.64, 61.02, 52.86, 52.63, 42.21, 33.93, 29.31, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1562, 1437, 1240, 1143, 1030 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06829; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06794.

Dimethyl 9-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



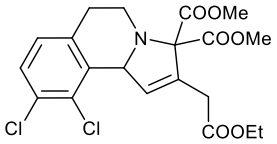
294e: 69% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28 – 7.24 (m, 1H), 7.24 – 7.21 (m, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.46 (d, *J* = 1.4 Hz, 1H), 5.13 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.82 (dd, *J* = 6.6, 3.0 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 3.47 – 3.28 (m, 3H), 2.86 – 2.73 (m, 1H), 2.63 (dt, *J* = 16.3, 4.3 Hz, 1H), 1.26 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.44, 169.12, 139.17, 133.74, 133.60, 132.49, 130.69, 129.51, 127.50, 119.61, 81.37, 65.13, 61.06, 52.77, 52.65, 42.14, 33.94, 27.69, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2986, 1731, 1568, 1234, 1173, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06919; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06799.

Dimethyl 10-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



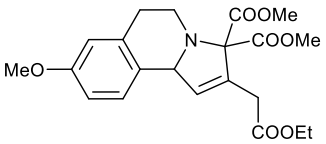
294f: 62% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.3 Hz, 1H), 7.08 – 6.94 (m, 2H), 6.88 (s, 1H), 5.45 (s, 1H), 4.24 – 4.04 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.60 – 3.45 (m, 1H), 3.39 – 3.21 (m, 2H), 3.17 (ddd, *J* = 14.7, 11.4, 3.7 Hz, 1H), 2.72 (ddd, *J* = 16.5, 11.5, 5.4 Hz, 1H), 2.51 (d, *J* = 16.5 Hz, 1H), 1.27 ppm (dt, *J* = 14.3, 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.53, 169.80, 169.72, 137.82, 134.91, 133.64, 132.29, 131.28, 129.07, 127.67, 122.08, 82.15, 66.65, 60.99, 52.96, 52.79, 41.67, 33.96, 27.52, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1558, 1434, 1226, 1138, 1027 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06934; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06767.

Dimethyl 9,10-dichloro-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



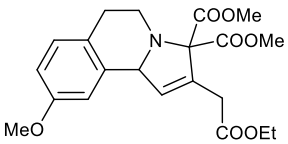
294g: 52% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.27 – 7.24 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 1.1 Hz, 1H), 5.49 (s, 1H), 4.16 – 4.09 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.56 (ddd, *J* = 14.2, 5.5, 2.2 Hz, 1H), 3.34 – 3.24 (m, 2H), 3.21 – 3.12 (m, 1H), 2.70 (ddd, *J* = 17.0, 11.4, 5.7 Hz, 1H), 2.53 (d, *J* = 17.0 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.42, 169.62, 169.44, 135.70, 135.64, 132.89, 132.84, 131.05, 130.31, 128.96, 128.12, 81.87, 65.63, 61.05, 53.02, 52.85, 41.40, 33.95, 27.10, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1731, 1432, 1225, 1138, 1028 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{22}Cl_2NO_6$: 442.08187, found: 442.08248.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



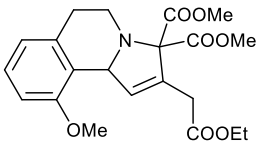
294h: 59% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.48 (s, 1H), 5.13 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 3.41 – 3.33 (m, 2H), 3.32 (d, *J* = 1.2 Hz, 2H), 2.94 – 2.79 (m, 1H), 2.67 (dd, *J* = 11.9, 4.2 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.58, 169.22, 158.15, 136.09, 133.40, 132.80, 129.42, 125.42, 114.01, 112.04, 81.57, 65.14, 60.95, 55.39, 52.70, 52.56, 42.47, 33.98, 28.62, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2930, 2840, 1761, 1719, 1609, 1434, 1306, 1018 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16921.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



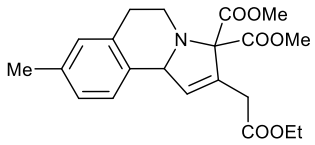
294i: 79% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.3 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.48 (s, 1H), 5.16 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.74 (m, 6H), 3.65 (s, 3H), 3.43 (ddd, *J* = 12.4, 6.2, 3.6 Hz, 1H), 3.38 – 3.27 (m, 3H), 2.86 – 2.73 (m, 1H), 2.68 – 2.52 (m, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.56, 169.31, 157.90, 137.91, 133.15, 133.05, 129.96, 126.66, 112.21, 109.96, 81.45, 65.67, 60.95, 55.43, 52.68, 52.53, 42.54, 33.95, 27.28, 14.31 ppm; FT-IR: $\tilde{\nu}$ = 3004, 2954, 2928, 1726, 1606, 1500, 1350, 1064 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16866.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-10-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



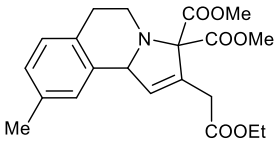
294j: 84% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.15 – 7.03 (m, *J* = 7.9 Hz, 1H), 6.75 – 6.59 (m, 3H), 5.31 (s, 1H), 4.12 (dd, *J* = 14.1, 7.0 Hz, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.54 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.32 – 3.23 (m, 2H), 3.25 – 3.11 (m, 1H), 2.79 – 2.63 (m, 1H), 2.58 – 2.45 (m, 1H), 1.25 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.80, 170.04, 156.24, 136.06, 134.91, 130.95, 126.97, 124.82, 121.88, 107.74, 81.44, 63.48, 60.84, 55.21, 52.77, 52.56, 41.67, 34.04, 27.32, 14.30 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2838, 1730, 1581, 1468, 1248, 1088 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16929.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



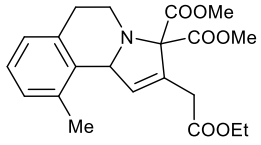
294k: 67% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.02 – 6.94 (m, 2H), 6.94 – 6.88 (m, 1H), 6.48 (s, 1H), 5.15 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.45 – 3.33 (m, 2H), 3.33 – 3.26 (m, 2H), 2.89 – 2.77 (m, 1H), 2.64 (dt, *J* = 16.2, 4.2 Hz, 1H), 2.28 (s, 3H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.58, 169.26, 135.89, 134.54, 134.06, 133.41, 132.77, 129.62, 126.81, 124.30, 81.54, 65.40, 60.92, 52.65, 52.51, 42.48, 33.98, 28.21, 21.17, 14.32 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1550, 1433, 1235, 1140, 1030 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17670.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-9-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



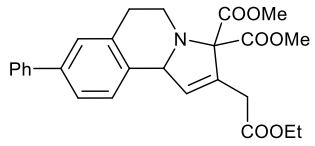
294l: 72% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.03 – 6.85 (m, 3H), 6.50 (s, 1H), 5.16 (s, 1H), 4.19 – 4.04 (m, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.46 – 3.38 (m, 1H), 3.36 – 3.23 (m, 3H), 2.83 – 2.79 (m, 1H), 2.65 – 2.60 (m, 1H), 2.30 (s, 3H), 1.26 ppm (td, *J* = 7.1, 2.7 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.48, 169.26, 135.40, 133.24, 132.71, 131.37, 128.83, 127.10, 124.94, 122.02, 81.37, 65.45, 60.82, 52.55, 52.41, 42.38, 33.84, 27.61, 21.13, 14.19 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2918, 1731, 1433, 1217, 1150, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17688.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-10-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



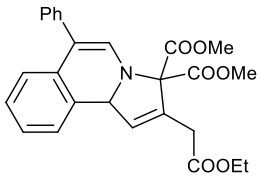
294m: 80% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.50 (s, 1H), 5.45 (s, 1H), 4.18 – 4.09 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.50 (ddd, *J* = 13.6, 5.4, 2.6 Hz, 1H), 3.34 – 3.27 (m, 2H), 3.17 (ddd, *J* = 13.6, 11.1, 3.8 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.62 – 2.51 (m, *J* = 18.3 Hz, 1H), 2.34 (s, 3H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.63, 169.76, 135.05, 134.47, 134.23, 133.35, 132.28, 128.75, 127.53, 126.23, 81.90, 65.36, 60.92, 52.85, 52.68, 41.96, 33.88, 28.18, 20.17, 14.31 ppm; FT-IR: $\tilde{\nu}$ = 2980, 2953, 1730, 1433, 1224, 1133, 1031 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17725.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



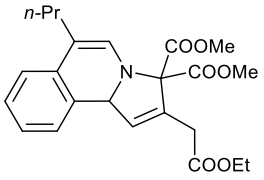
294n: 76% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.58 – 7.53 (m, 2H), 7.45 – 7.37 (m, 3H), 7.37 – 7.29 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 1.4 Hz, 1H), 5.23 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 3.52 – 3.44 (m, 1H), 3.45 – 3.36 (m, 1H), 3.36 – 3.30 (m, 2H), 2.95 (ddd, *J* = 15.9, 9.2, 6.8 Hz, 1H), 2.76 (dt, *J* = 15.9, 3.9 Hz, 1H), 1.27 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.58, 169.34, 141.14, 139.45, 136.11, 135.11, 133.19, 133.06, 128.82, 127.83, 127.24, 127.15, 124.94, 124.90, 81.47, 65.44, 60.98, 52.73, 52.57, 42.41, 33.97, 28.37, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1731, 1433, 1234, 1148, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{28}NO_6$: 450.19111, found: 450.19098.

Dimethyl 2-(2-ethoxy-2-oxoethyl)-6-phenylpyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



294o: 60% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.20 – 7.04 (m, 4H), 6.81 – 6.73 (m, 2H), 5.58 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.47 (s, 2H), 1.29 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.42, 168.39, 167.90, 138.83, 133.30, 132.50, 130.72, 129.83, 129.27, 128.63, 128.59, 127.03, 126.41, 126.38, 123.02, 122.85, 118.08, 80.41, 65.62, 61.16, 53.24, 53.15, 33.66, 14.34 ppm; FT-IR: $\tilde{\nu}$ = 2954, 1732, 1607, 1443, 1244, 1178, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{26}NO_6$: 448.17546, found: 448.17365.

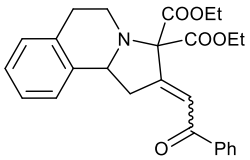
Dimethyl 2-(2-ethoxy-2-oxoethyl)-6-propylpyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate



294p: 87% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21 – 7.10 (m, 3H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 0.5 Hz, 1H), 6.40 (s, 1H), 5.45 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 3.44 – 3.34 (m, 2H), 2.56 (ddd, *J* = 13.7, 8.2, 5.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.67 – 1.58 (m, 1H), 1.56 – 1.44 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.43, 168.61, 168.20, 133.25, 132.44, 131.08, 130.42, 127.76, 126.97, 126.00, 122.76, 121.16, 115.22, 80.79, 65.62, 61.08, 53.01, 52.92, 33.70, 32.18, 22.52,

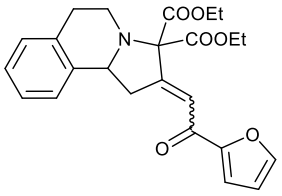
14.33, 14.06 ppm; FT-IR: $\tilde{\nu}$ = 2956, 1735, 1686, 1441, 1244, 1173, 1129, 1031 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{23}H_{28}NO_6$: 414.19111, found: 414.19033.

Diethyl (*E* or *Z*)-2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*] isoquinoline-3,3(2*H*)-dicarboxylate



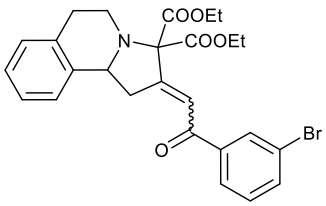
294q: 91% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.92 (m, 2H), 7.61 – 7.53 (m, 1H), 7.51 – 7.44 (m, 2H), 7.45 – 7.39 (m, 1H), 7.21 – 7.10 (m, 4H), 4.39 – 4.22 (m, 4H), 4.19 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.96 (ddd, *J* = 18.2, 6.2, 1.9 Hz, 1H), 3.59 (dd, *J* = 11.1, 5.9 Hz, 1H), 3.30 – 3.18 (m, 1H), 2.98 – 2.79 (m, 3H), 1.35 (t, *J* = 6.1 Hz, 3H), 1.31 ppm (t, *J* = 6.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.56, 168.03, 167.64, 156.95, 138.73, 137.98, 134.29, 132.98, 128.92, 128.78, 128.40, 126.65, 126.06, 125.55, 120.33, 79.07, 62.28, 61.95, 60.32, 44.54, 37.80, 30.19, 14.62, 14.25 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1671, 1368, 1228, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{28}NO_5$: 434.19620, found: 434.19605.

Diethyl (*E* or *Z*)-2-(2-(furan-2-yl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate



294r: 83% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 – 7.54 (m, 1H), 7.31 – 7.28 (m, 1H), 7.23 – 7.21 (m, 1H), 7.18 – 7.11 (m, 4H), 6.60 – 6.48 (m, 1H), 4.42 – 4.21 (m, 4H), 4.23 – 4.12 (m, 1H), 4.03 (ddd, *J* = 18.5, 6.3, 1.9 Hz, 1H), 3.57 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.32 – 3.16 (m, 1H), 2.97 – 2.76 (m, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.30 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 178.52, 167.87, 167.44, 157.59, 154.24, 146.47, 137.97, 134.27, 128.91, 126.66, 126.09, 125.57, 119.36, 117.26, 112.58, 79.10, 62.28, 61.94, 60.34, 44.53, 37.89, 30.17, 14.60, 14.23 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1667, 1621, 1466, 1232, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{24}H_{26}NO_6$: 424.17546, found: 424.17525.

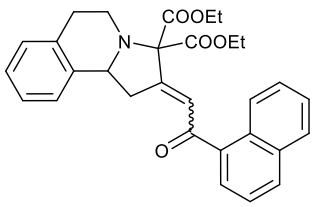
Diethyl (*E* or *Z*)-2-(2-(3-bromophenyl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo [2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate



294s: 83% yield; Ratio of isomer, 78:22; For major product: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 – 8.04 (m, 1H), 7.91 – 7.84 (m, 1H), 7.68 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.22 – 7.06 (m, 4H), 4.37 – 4.24 (m, 4H), 4.18 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.93 (ddd, *J* = 18.4, 6.3, 1.8 Hz, 1H), 3.59 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.30 – 3.15 (m, 1H), 2.96

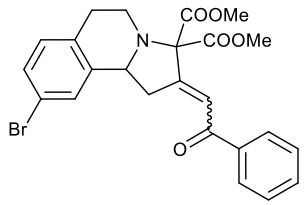
– 2.78 (m, 3H), 1.40 – 1.29 ppm (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 189.01, 167.91, 167.49, 158.26, 140.50, 137.87, 135.79, 134.28, 131.44, 130.38, 128.94, 126.89, 126.69, 126.08, 125.51, 123.12, 119.74, 79.10, 62.37, 62.03, 60.26, 44.51, 37.94, 30.18, 14.63, 14.26 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1673, 1368, 1220, 1038 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{27}{}^{79}BrNO_5$: 512.10671, found: 512.10677; calcd. for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrNO_6$: 514.10467, found: 514.10462; For minor isomer, ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 – 8.07 (m, 1H), 7.91 – 7.87 (m, 1H), 7.68 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.35 (dd, *J* = 10.4, 5.4 Hz, 1H), 7.20 – 7.11 (m, 4H), 7.09 – 7.05 (m, 1H), 4.31 – 4.24 (m, 3H), 4.18 – 4.12 (m, 1H), 4.06 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.77 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.33 (dd, *J* = 15.6, 5.4 Hz, 1H), 3.25 – 3.14 (m, 1H), 2.91 – 2.72 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.09 ppm (t, *J* = 7.1 Hz, 3H).

Diethyl (*E* or *Z*)-2-(2-(naphthalen-1-yl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo [2,1-a]isoquinoline-3,3(2H)-dicarboxylate



294t: 79% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.26 – 7.23 (m, 1H), 7.21 – 7.10 (m, 4.9 Hz, 4H), 4.38 – 4.22 (m, 5H), 4.00 (dd, *J* = 18.3, 6.2 Hz, 1H), 3.62 (dd, *J* = 11.4, 6.2 Hz, 1H), 3.34 – 3.22 (m, 1H), 3.06 – 2.81 (m, 3H), 1.31 ppm (q, *J* = 7.2 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = ^{13}C NMR (101 MHz, cdcl$_3$) δ 194.17, 167.69, 167.39, 137.67, 134.25, 134.10, 132.65, 128.99, 128.70, 128.16, 127.85, 126.87, 126.66, 126.24, 125.88, 125.64, 124.80, 124.62, 79.13, 62.49, 62.18, 60.58, 44.74, 37.70, 30.13, 14,68, 14.28 ppm; FT-IR: $\tilde{\nu}$ = 2978, 2924, 1727, 1673, 1368, 1230, 1039 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{30}H_{30}NO_5$: 484.21185, found: 484.21150.

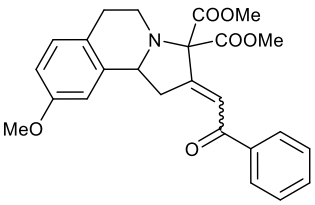
Dimethyl (*E* or *Z*)-9-bromo-2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo [2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate



294u: 64% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.93 (m, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.46 (m, 2H), 7.40 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.92 (ddd, *J* = 11.7, 8.0, 2.7 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.54 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.14 (dd, *J* = 14.7, 8.0 Hz, 1H), 2.91 – 2.74 ppm (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.37, 168.45, 167.92, 155.98, 139.88, 138.53, 133.17, 133.12, 130.59, 129.78, 128.83, 128.52, 128.45, 120.56, 119.65, 78.99, 59.98, 53.43, 52.66, 44.25, 37.56, 29.61 ppm; FT-IR: $\tilde{\nu}$ = 2955, 1755, 1728, 1672, 1443, 1220, 1118, 1033 cm^{-1};

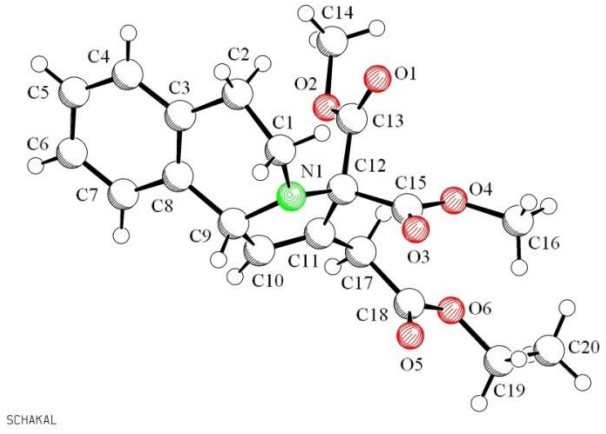
HRMS: calcd. for $[M+H]^+$ $C_{24}H_{23}{}^{79}BrNO_5$: 484.07541, found: 484.07507; calcd. for $[M+H]^+$ $C_{24}H_{23}{}^{81}BrNO_5$: 486.07337, found: 486.07296.

Dimethyl (*E* or *Z*)-9-methoxy-2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo [2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylatedimethyl



294v: 78% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 – 7.92 (m, 2H), 7.59 – 7.55 (m, 1H), 7.51 – 7.42 (m, 2H), 7.40 (dd, *J* = 3.2, 1.9 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.94 (ddd, *J* = 8.1, 6.1, 3.0 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.53 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.22 – 3.11 (m, 1H), 2.94 – 2.82 (m, 2H), 2.81 – 2.74 ppm (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.52, 168.64, 168.02, 158.04, 156.57, 138.67, 138.61, 133.06, 129.88, 128.81, 128.43, 126.16, 120.46, 113.27, 110.21, 79.22, 60.48, 55.55, 53.38, 52.54, 44.69, 37.64, 29.27 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1730, 1672, 1614, 1503, 1443, 1226, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{25}H_{26}NO_6$: 436.17546, found: 436.17547.

7.5.3 X-Ray Crystallographic Data of 294a (by C.-G.D)



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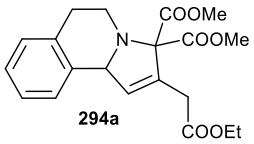

Empirical formula	$C_{20}H_{23}NO_6$
Formula weight	373.39
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1/c$ (No. 14)
Unit cell dimensions	a = 8.7052(2) Å
	b = 7.8790(2) Å β = 93.841(1)°

	c = 27.3581(9) Å
Volume	1872.23(9) $Å^3$
Z, Calculated density	4, 1.325 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	792
Crystal size	0.30 x 0.15 x 0.03 mm
Theta range for data collection	4.48 to 26.37°
Limiting indices	-10<=h<=10, -9<=k<=8, -34<=l<=34
Reflections collected / unique	16357 / 3784 [R(int) = 0.073]
Completeness to theta = 26.37	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9971 and 0.9712
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3784 / 0 / 247
Goodness-of-fit on F^2	1.060
Final R indices [I>2σ(I)]	R1 = 0.0643, wR^2 = 0.1242
R indices (all data)	R1 = 0.1122, wR^2 = 0.1476
Largest diff. peak and hole	0.192 and -0.220 $e.Å^{-3}$

I. References

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II. Abbreviations

Ac	Acyl
aq	aqueous
Ar	Aryl
BA	Benzoic acid
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
Binol	1,1’-Bi-2-napthol
BIOS	Biology-oriented synthesis
Bu	Butyl
Box	Bisoxazoline
Bz	Benyoate
$(BzO)_2$	Benzoyl peroxide
Calcd	Calculated
cat	catalyst
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CMD	Concerted metalation deprotonation
CSA	Camphor sulphonic acid
COMAS	Compound management and screening center
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
DBPO	Benzoyl peroxide
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DG	Directing group
DKR	Dynamic kinetic resolution
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide

DNP	Dictionary of natural products
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EDG	Electron donating group
Equiv.	Equivalent
ESI	Electron spray inonisation
Et_2O	Diethylether
Et	Ethyl
Et_3N	triethylamine
EWG	Electron withdrawing group
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectroscopy
i-Bu	isobutyl
IC_{50}	Half maximal inhibitory concentration
i-Pr	isopropyl
J	Coupling constant
KR	Kinetic resolution
L	Ligand
LA	Lewis acid
M	Metal
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
M*Hz*	Megahertz
MOM	Methoxymethyl
Ms	Mesyl
NMR	Nuclear manetic resonance
NOE	Nucler Overhauser effect

NPs	Natural producs
n.r.	No reaction
OFBA	2-fluorobenzoic acid
PAs	Pyrrolizidine alkaloids
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
PSSC	Protein Structure Similarity Clustering
Py	Pyridine
r.t.	Room temperature
SCONP	Structural Classification of Natural Products
S_N	Nucleophilic substitution
T	Temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyl dimethylsilyl
t-Bu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TM	Transition meal
TMS	Trimethylsilyl
Ts	Tosyl
VCD	Vibrational circular dichroism
Xyl	Xylene
1,3-DC	1,3-dipolar cycloaddition reaction

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